Peptidomimetics, Propargylamide-Based Isosteres of Peptide Structures

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Abbreviations

3D	three dimensional
ACN	Acetonitrile
All	Allyl
ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
BuS	*tert*-Butylsulfinyl
CD	Circular Dichroism
cy	cyclohexyl
d	doublet
DCM	Dichlormethane
DIPEA	Di *iso*-Propylethylamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric Ratio
ee	Enantiomeric Excess
eq	Equivalents
ESI	Electrospray Ionization
Et	Ethyl
Et_2O	Diethyl Ether
EtOAc	Ethylacetate
FT	Fourier Transform
h	Hours
HATU	1-[Bis(dimethylamino) methyliumyl]-1*H*-1,2,3-triazolo[4,5-b]pyridine-3-oxide Hexafluorophosphate
HOAt	1-Hydroxy-7-azabenzotriazole
HPLC	High Performance Liquid Chromatography
IBCF	Chloroformic Acid Isobutylester
IR	Infrared
m	Multiplett
M	Molar [mol L^{-1}]
Me	Methyl
MeOH	Methanol
MD	Molecular Dynamics
MHz	Megahertz
MMFF	Merck Molecular Force-Field
mp	Melting Point
MS	Mass Spectrometry
NMM	*N*-Methyl Morpholine
NMR	Nuclear Magnetic Resonance
PE	petrolether
Ph	Phenyl
PPI	Protein-Protein Interaction
q	Quartet
R*f*	Retention Factor
RGD	Amino Acid sequence, Arg-Gly-Asp
rt	Room Temperature
s	Singlet
tert	tertiary
SAR	Structure Affinity Relationship
TFA	Trifluoracetic Acid
TFE	trifluoroethanol
THF	Tetrahydrofurane
TIPS	Triisopropylsilane
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
t	Triplet
UV	Ultra Violet
Vis	Visible

Table of Contents

I Structure and Objectives

I-1. Abstract

In medicinal chemistry, the importance of peptidomimetics as small-molecular, orally bioavailable PPI disruptors increases with the structural elucidation of PPI interfaces. However, the design of peptidomimetics, which accurately represent the peptide-template requires a sophisticated diversity of structural devices and reactions. In this thesis, a versatile peptidomimetic scaffold consisting of 3-amino-prop-1-yn-1-yl-benzoates is contributed. This structure is obtained by connection of enantiomerically pure propargylamides with halo-benzoates by *Sonogashira* cross-coupling. To access a variety of side chains, an array of propargylamides is prepared asymmetrically, comprising all kinds of functional groups (Chapter II).

Variation of the aromatic substitution pattern, application of heteroarenes and olefins (by hydroalkynylation of propynoates) in the *C*-terminal moiety enables the introduction of versatile side chains and a well-defined curvature in the backbone. Conformational preferences are analyzed by NMR- and CD spectroscopy, MD simulations and X-ray crystal structure analysis. Oligomerization of the peptidomimetic scaffolds is performed to investigate their properties as structural helix mimetics. Additionally, interesting dipeptide analogous peptidomimetics with unique properties are presented (Chapter III).

Particularly rigid peptidomimetic structures based on naphthalene-, biphenyl-, azobenzene- and hydrazine scaffolds direct *N*- and *C*-termini into the same direction and are therefore applied as sterically enforced turn motif mimetics. Their introduction in peptide chains to induce a hairpin formation is studied by ^{1}H NMR spectroscopy, temperature coefficient, CD spectra and X-ray structure analysis (Chapter IV).

para-Substituted peptidomimetics are applied as isosteres of the natural HDAC substrate (e.g. acetylated lysine). By functionalization with a hydroxamic acid, potent HDAC inhibitors can be generated. From a SAR study, interesting information on the influence of the aromatic, the side chain and its configuration on the affinity are derived (Chapter V).

An arginine analogous propargylamide is linked to different carboxylate moieties by *Click* reactions giving alkynylarene-, triazole- and amide-based spacers with a similar size as the RGD sequence. These novel RGD isosteres are evaluated by docking experiments, as well as a competitive ELISA based assay (Chapter VI).

I-2. Published Chapters

II Asymmetric Synthesis of Propargylamines as Amino Acid Surrogates [1].

V SAR of Propargylamine-Based HDAC Inhibitors [2].

II Asymmetric Synthesis of Propargylamines as Amino Acid Surrogates

This chapter is a summary of the results, published in 2017 in the article "*Asymmetric synthesis of propargylamines as amino acid surrogates in peptidomimetics*" (appendix) [1].

While amino acids with a terminal alkyne in the side chain are well-known due to their antibiotic effects [3], the synthesis of analogs with a terminal alkyne instead of the carboxy group is still tedious. This scaffold is called propargylamines. Propargylamines play an important role as substructure of diverse active pharmaceutical agents. Exemplarily, selective MAO-B inhibitors with neuroprotective properties (Selegilin) have been developed [4] and used in the clinical treatment of *Alzheimer*'s disease [5], as well as to target mitochondrial pathogenic processes in the treatment of ageing and age-related neurodegenerative diseases [6]. In other propargylamine derivatives, psychoactive properties have been reported [7]. Additionally, a very important feature of such terminal alkynes is their unique versatility as building blocks in organic and medicinal chemistry. Their chemistry involves various highly selective reactions, e.g. [3+2]-cycloadditions with nitrile oxides [8], azides and other isoelectronic functional groups [9,10], *Sonogashira* cross-coupling [2], thiol-yne reactions [11], *Diels-Alder* reactions [12], intramolecular *Pauson-Khand* reactions [13] and gold-catalized azetidine-3-one formations [14]. All these reactions can be performed with achiral *N*-Boc-propargylamide **1**.

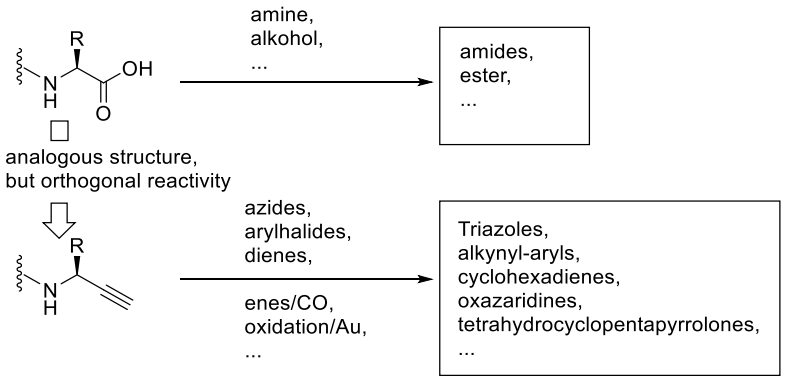

Figure 1. Comparison of the reactivity of amino acids with structurally related designed propargylamines.

The unique reactivity of propargylamines allows the preparation of various potentially bioactive scaffolds. Hence, the enantioselective synthesis of versatile amino-C$^{\alpha}$HR-alkyne building blocks in analogy to natural amino acids has stimulated various drug-design projects.

In preliminary works, propargylamines have been synthesized using the *Corey-Fuchs* or the *Seyferth-Gilbert* homologation of enantiomerically pure α-amino acids [15,16]. However, racemization and incompatibility with various functional groups limited the broad application of these strategies.

In this work, a *de-novo* approach for the synthesis of enantiomerically pure propargylamines is reported as recently published in the course of this work [1]. The synthesis of *N*-propargylsulfinamides **6** started with the *Lewis-Acid* mediated condensation of *Ellman*'s chiral sulfinamide **2** with an aldehyde **3a-u** under typical imine-formation conditions [17–20]. Diastereoselective addition of trimethylsilylethynyl lithium to the purified imines **4a-u** under optimized conditions [13,21–25] gave the TMS-alkynes **5a-u**, which were desilylated in common procedures [26–28] to form diastereomerically pure *N*-propargylsulfinamides **6a-x** (Figure 2).

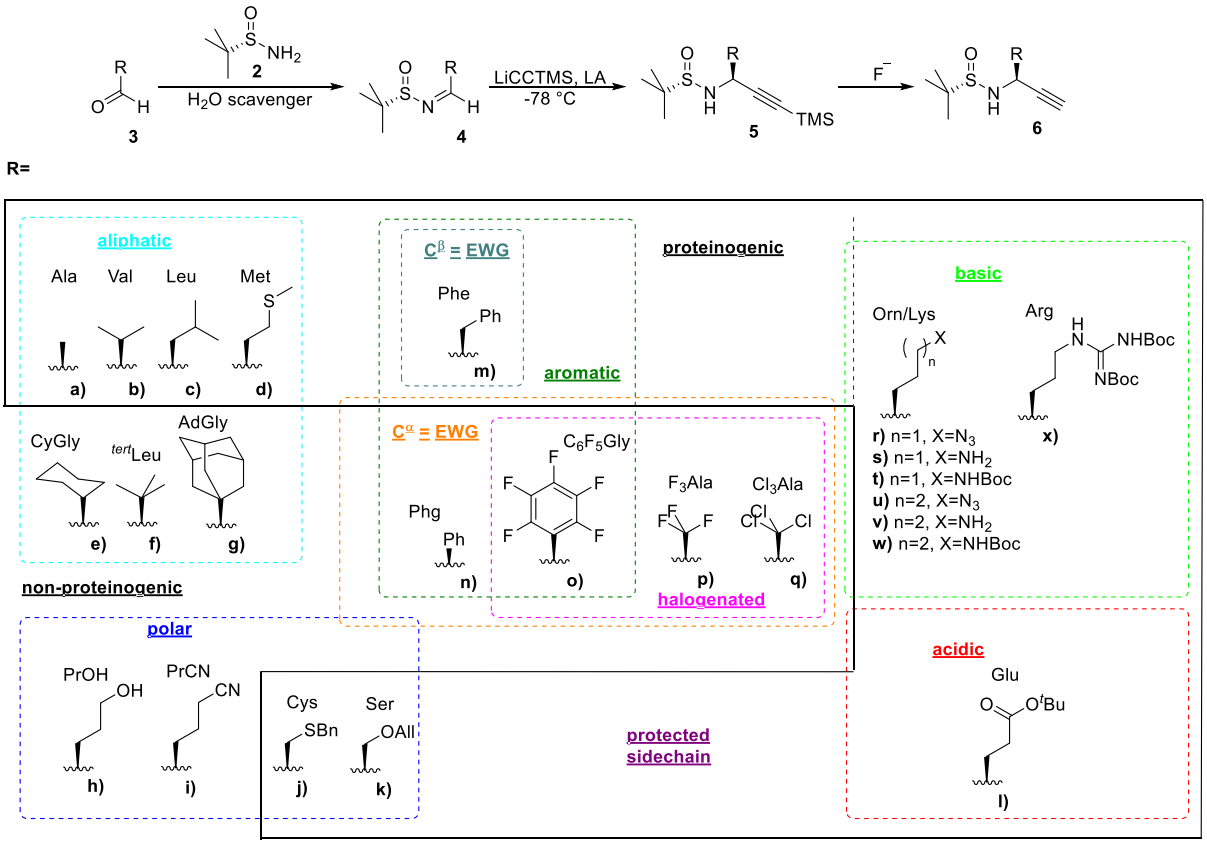

Figure 2. Asymmetric synthesis of *N*-protected propargylamides **6a-x**. The side chains are classified according to their reactivity, properties and functional groups into aliphatic, polar, acidic, electron withdrawing substituents in C^{β}-position, aromatic, electron withdrawing substituents in C^{α}-position, halogenated, basic, (non-)proteinogenic and side chain protected groups. Annotations show the analogy to proteinogenic amino acids. Side chains shown in Figure 2 refer to synthesized *N*-propargylsulfinamides **6**. However, the substituent of a few precursors **3-5** differ in exceptional cases: **3h-5h**, the alcohol function was TBDMS-protected. Precursors **3r-5r** were converted into propargylamides **6r-t** and **6x**. Precursors **3-5u** were converted into propargylamides **6u-w**.

While propargylamides **6a-g** with aliphatic residues are directly accessible by this approach, polar and acidic substituents in the side chain of compounds **6h-l** have to be carefully protected or masked to prevent side reactions.

Electron withdrawing groups adjacent to the imine acidify the respective proton of sulfinylimines **4** and result in a competition between nucleophilic addition and C^{β}-deprotonation during the reaction of imine **4m** and trimethylsilylethynyl lithium. As a result, the reported method is not appropriate for the synthesis of propargylamides **6** with electron withdrawing substituents in C^{β}-position. However, if an electron withdrawing substituent is located at the C^{α}-atom of **5**, extremely mild desilylation-conditions have to be employed to prevent the irreversible base-catalyzed enimine rearrangement

(Chapter III-20) of propargylamides **6n-q** in alkaline milieu. As electron withdrawing groups also increase the electrophilicity of the imino moiety **4n-q**, addition of water as well as a ligand transfer from the *Lewis* acids $AlMe_3$ and $Ti(O^iPr)_4$ to the imine **4p** has been observed.

To introduce basic substituents into the side chain, azides **4r** and **4u** were used as central intermediate, which are stable under the conditions of the nucleophilic addition. Unexpectedly, an intramolecular *Huisgen* reaction (Figure 3) occurred without any catalyst at room temperature even in the presence of the TMS group. The azides **5r,u** and **6r,u** reacted to form bicyclic triazoles **7r,u** and **8r,u** as side products, which dramatically reduced the yields of propargylamides **6r** and **6u**.

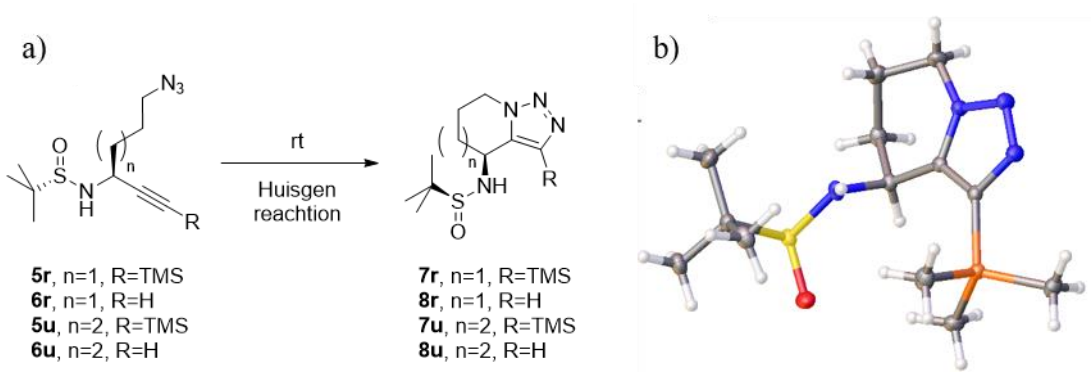

Figure 3. Side reaction, occurring in the synthesis of propargylamides **6r**,**u** with an azide in the side chain. a) Observation of a remarkable non-catalyzed low-temperature *Huisgen* reaction. b) X-ray crystal structure of cyclization product **7r**.

The intramolecular Huisgen reaction can be completely suppressed, if azides **5r** and **5u** were reduced with PPh_3 immediately after the nucleophilic addition of trimethylsilylethynyl lithium. Surprisingly, this reduction also lead to complete removal of the TMS group affording propargylamides **6s** and **6v**. Cleavage of the TMS group could never be realized under these reaction conditions with silylalkynes **5** bearing aliphatic side chains (e.g. **5f**). Therefore it is assumed, that an intramolecular interaction of the TMS group and the intermediate phosphorus ylide, which is formed as intermediate in the *Staudinger* reaction, induces this cycloaddition.

In this chapter, the asymmetric *de-novo* synthesis of a set of 24 *N*-propargylsulfinamides **6a-x** is described. The synthesized propargylamides **6** contain aliphatic, polar, acidic, aromatic and basic functional groups in the side chain. Some side reactions occurring during the synthesis of compounds with particular residues were analyzed in detail. The

side reactions include the competing deprotonation of imine **4m**, the base-catalyzed enamine rearrangement of propargylamides **5n-q** and **6n-q**, the ligand transfer from Lewis acids to imine **4p** and the intramolecular Huisgen reaction of **5r,u** and **6r,u**. Propargylamides **6** were designed as analog of proteinogenic and non-natural amino acids and represent the basis of the peptidomimetic scaffolds described in the following Chapters III-VI.

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III Peptidomimetics

The propargylamides, presented in Chapter II, inaugurate the design of versatile molecular scaffolds, based on the unique reactivity of the alkyne moiety. Using the *Sonogashira* cross-coupling or the copper-catalyzed 1,3-dipolar cycloaddition facilitates the converging composition of complex structures. In this chapter, the propargylamine moiety is regarded as the *N*-terminus of a peptidomimetic. The additional aromatic or olefinic moiety of the molecule bearing a carboxylic acid at various positions represents the *C*-terminus of the peptidomimetic. As both the propargylamine- and the carboxy moiety are formed independently, a considerable diversity of peptidomimetic entities can be achieved. In the following, the newly designed peptidomimetics will be grouped according to their structural elements bearing the carboxy moiety: alkynylarenes with different substitution patterns, alkynylalkenes and triazoles. Side reactions, rearrangements and reasonable conformational preferences of the new structures are discussed, as well as possible applications as photosensitive backbone, aspartam analogues or hydrogel inducer.

III-1. Concept and Definition

Peptide-based active compounds have frequently proven their high affinity and selectivity towards all kinds of peptides, serving as antagonists, agonists or protein-protein interaction (PPI) disruptors. However, the big size and high polarity of peptide-based drugs are unlikely to comply with Lipinski's guidelines for oral application [29]. Furthermore, their numerous amide bonds imply inconvenient pharmacodynamic properties, as they are flexible and prone to digestion by proteases. The application of peptidomimetics is still the most common concept to circumvent drawbacks and maintain the activity of peptide-based drugs. Therefore, structural elements are introduced to increase proteolytic stability, to reduce the degrees of freedom, to lock convenient conformations and to reduce size and polarity to enable cell-permeation.

As several different design approaches are pursued in Medicinal Chemistry [30], the definition and classification of peptidomimetics is inconsistent in literature over the past 40 years [31]. Early definitions rather focus on small molecular scaffolds, which arrange their functional groups in 3D space analog to the topology of the active conformation of a peptide [32]. More recent considerations distinguish between small-molecule peptidomimetics, which only mimic a local part of a protein and proteomimetics, which imitate larger parts

of a protein [33]. As functional peptidomimetics (type II mimetics, see chapter III-3) interact with their target structure differently than native peptide ligands [32], their rational design is rather difficult. Therefore, functional peptidomimetics lost their impact in the early 21st century, remaining completely unmentioned in most publications and even excluded from some recommended definitions [34,35]. As the relevance of peptidomimetics in the field of influencing protein-protein interaction (PPI) increased, Azzarito *et al.* emphasized the imitation of secondary structural elements, like helix mimetics, turn mimetics and foldamers [36]. Taking all approaches in peptidomimetic design and classification into account, current definitions are very broad, covering all molecules, that are designed to mimic the interaction potential of natural peptides [31,37,38]. Due to different structural features, interaction mechanisms and design principles, it is rather difficult to come up with a consistent definition and classification of peptidomimetics.

III-2. Rational Design Principles

The large pool of established lead structures allows various approaches to design peptidomimetics [30]. The benefit of each design approach complies with the desired mechanism of action. Akram *et al*. recently formulated a rational strategy for the identification of lead structures [37], which was completed by the hierarchical principle for chemical modifications and abstractions by Trabocchi and Guarna [38] (illustrated in Figure 4).

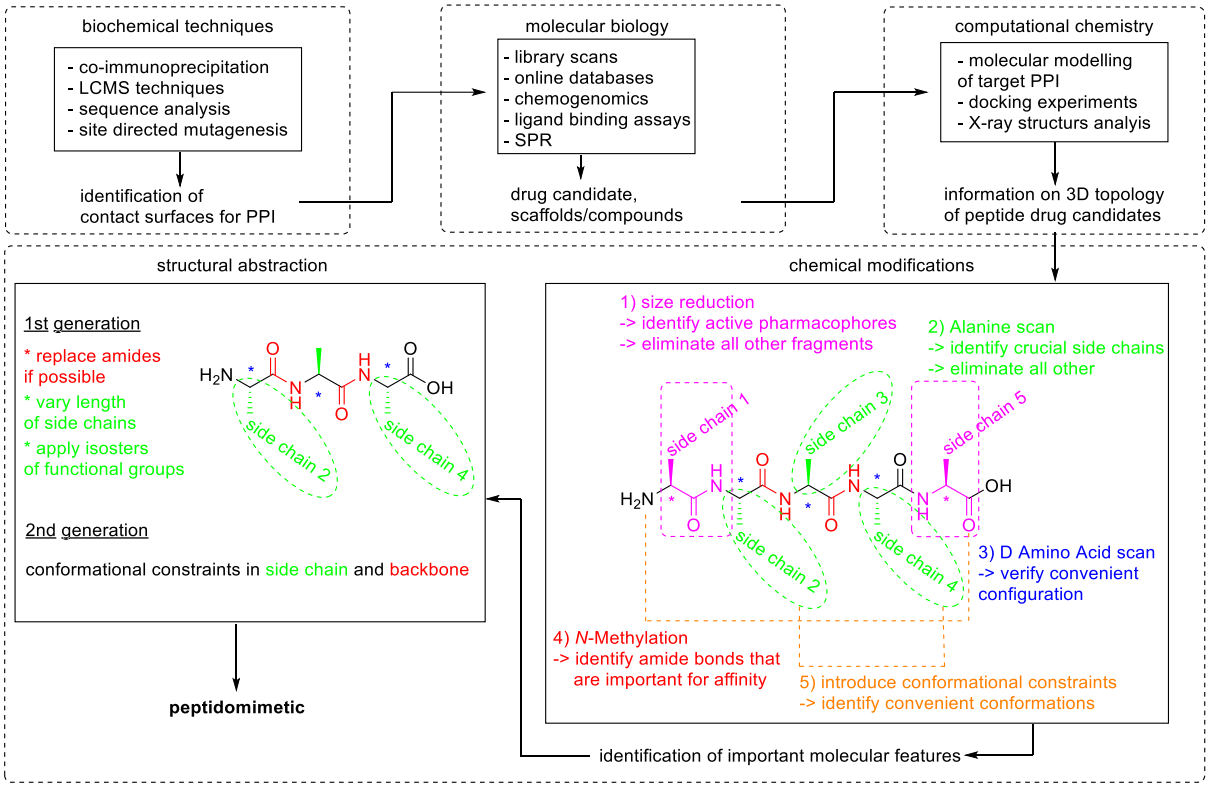


Figure 4. Systematic approach for the rational design of peptidomimetics as active compounds. The concept for lead structure identification was outlined by Akram *et al*. [37]. The chemical modifications have been summarized by Trabocchi and Guarna [38]. The workflow is chronological and classified by the operating scientific fields. The result of each operation defines the next work step.

The acquired PPI contact region can be identified using biomolecular techniques, like protein arrays, two-protein hybrid interaction systems, tandem-affinity purification coupled mass spectrometry, pull-down assays with bait proteins or co-immunoprecipitation experiments [37]. High-throughput screening of peptide libraries for possible lead structures is helpful to find effector candidates, which are further characterized by ligand binding assays like Surface Plasmon Resonance (SPR). In current approaches, the employment of chemogenomics helps to organize the scanning of chemical libraries much more efficiently [39]. Computational methods, like molecular modelling or docking experiments allow an evaluation of the interaction potential of the new lead structures with the PPI interfaces [40]. If available, X-ray crystal structures of drug-protein complexes add valuable information on the desired pharmacophores of the lead structure.

To construct peptidomimetics with improved stability and pharmacodynamic properties, an identified peptide-based lead compound is processed in a series of chemical modifications [38]:

1) Size Reduction: Individual amino acids are eliminated, if this doesn't affect the peptides affinity. Size reduction often leads to a loss of selectivity.
2) Alanine Scan: Single amino acids are replaced by alanine. This procedure leads to the identification of key amino acids which are essential for the biological activity.
3) D-Amino Acid Scan: Replacement of natural L-amino acids by D-amino acids will give information about biological activity and proteolytic stability.
4) *N*-Methylation: *N*-methylation of the backbone amides will give information about the importance of a particular H-bond donor property of a particular peptide. The nonessential amides are substituted by isosteres.
5) Conformational constraints: Cyclization by disulfide bridges, lactams or connection of *N*- and *C*-terminus are possibilities to lock certain conformations. If such a constraint results in promising biological activity, further non-peptidic structural elements leading to similar conformations will be incorporated in order to further improve the activity.

In 1st generation peptidomimetics, the flexibility of all segments is preserved. They are accessed by either chemical modifications of the peptide template, or small fragments like D-amino acids, non-proteinogenic side chains or flexible amide bond isosteres are introduced [30]. The 2nd generation peptidomimetics comprise rigid structural elements, that are introduced in the side chains, as well as in the backbone of the existing scaffold [41]. These conformational constraints are chosen on the basis of the available knowledge about the spatial 3D topology of the bioactive conformation using X-ray crystal structures of protein-ligand complexes as well as preliminary SAR studies [38]. The more abstract new molecular scaffolds become, the more elaborate is their *de novo* synthesis. Fortunately, current literature compiles a plethora of useful frameworks, structural elements and isosteres of functional groups. Moreover, several selective chemical operations are reported to form the designed scaffolds and connect them with the peptide framework in order to end up with the desired conformation.

This chapter contributes convenient structural devices as well as corresponding synthesis concepts to the established pool of molecular fragments that are fit for the chemical abstraction of peptide-based effectors.

III-3. Fusion of current Peptidomimetic-Classifications

The growing diversity of peptidomimetics in drug design resulted in classification according to their structural features, design strategies, abstraction from the native peptide interaction with the target protein. Most publications still use the historic chronological typification defined by Ripka *et al.* in 1998 [32]. Pelay-Gimeno *et al*. recently considered this typification too general to assign the current approaches or to visualize the abstraction from the parent peptide sufficiently. Consequently, they proposed an updated classification [31]. The overlaps of both grouping approaches suggest distribution of Ripka's types into the subclasses introduced by Pelay-Gimeno *et al*. (Figure 5).

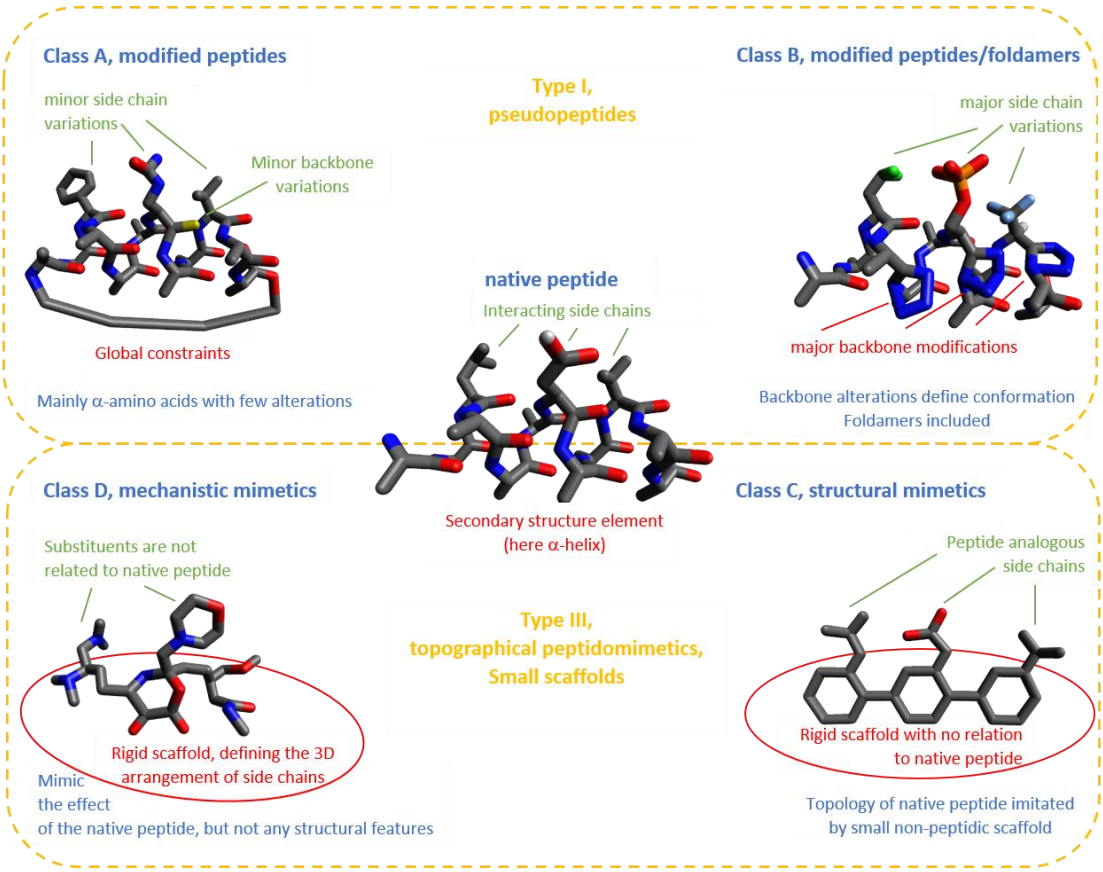


Figure 5. Fusion of Ripka's historical (yellow) and Pelay-Gimeno's (blue) updated classification of peptidomimetics. Exemplary structures are selected to illustrate the concept systematically. Comments in green refer to the side chains and modifications. Comments in red refer to the backbone and its modifications.

Type I, Structural- or Peptide Backbone Mimetics

Class A, Modified Peptides are short amino acid sequences, which differ from the parent peptides only by exchanged functional groups in the side chains, amino acid configuration, replacement of single atoms in the backbone as well as alkylation of the secondary amide or the C^{α}. Peptidomimetics with such modifications are able to replicate the 3D topology of the native peptide and stabilize conformations analog to their secondary structure by cyclization via side chains or backbone [31].

Class B, Modified Peptides and Foldamers are Class A peptidomimetics with major structural abstractions in the side chain and the backbone is no longer related to an amide. Class B peptidomimetics are rigidified by constraints to align the side chains in orientations similar to those of the native peptide. Foldamers such as β- and α/β-peptides and peptoids are also included in Class B peptidomimetics [31].

Type II, Functional Peptidomimetics are small non-peptide compounds characterized predominantly by their effects on the target protein [36]. Therefore, a structural classification and a rational design are unpractical. Usually, functional peptidomimetics interact with the same target protein as the natural peptide, but in a different manner. It is not necessary that all PPI are featured by the functional type II peptidomimetic. Even allosteric ligands of a target protein belong to the type II peptidomimetics, as confirmed by site-directed mutagenesis of the receptor [35]. As type II peptidomimetics cannot be structurally defined or categorized, they are excluded from the updated classification of Pelay-Gimeno (Figure 5).

Type III, Ideal or Topographical Peptidomimetics

Class C, Structural Mimetics are novel, nonpeptidic compounds, with an arrangement of side chains participating in the PPI, in an analogous manner to the native peptide. Secondary structural elements such as helices are imitated partially by Class C peptidomimetics [31].

Class D, Mechanistic Mimetics are small nonpeptidic compounds, with functional groups not related to proteinogenic side chains. Despite different side chains, the PPIs of the native peptide are imitated accurately [31]. Usually, mechanistic peptidomimetics are detected by screening of compound libraries, in silico screening of virtual libraries or by SAR optimizations of Class C peptidomimetics [42].

Type IV, Non-Peptide Mimetics

The type of non-peptide mimetics has been added by Kharb *et al*. [35] and comprises type I peptidomimetics with additional PPIs not covered by the native peptide. They can be designed by Group Replacement Assisted Binding (GRAB). As Type IV peptidomimetics are only characterized by their interaction potential with the target protein, they can be derived from all four classes A-D of structural devices.

Whereas Class A peptidomimetics are based on peptide templates, the design of Class B-D peptidomimetics requires an extensive pool of structural devices, containing functional groups imitating the peptide side chains. Moreover, the building blocks should allow an easy coupling to the peptidomimetic framework. In order to select appropriate building blocks to imitate the secondary structure of the parent peptide, a deep knowledge about their conformation is essential. In this chapter, a novel concept for the preparation of Class B-D peptidomimetics is presented in order to expand the options to imitate secondary structure elements for a Medicinal Chemist.

III-4. Modification of Amino Acids

Incorporation of particularly modified amino acids into the active part of a peptide is a simple option to optimize PPIs. Such Class A peptidomimetics can be quickly prepared by solid phase organic synthesis or biochemically by using engineered DNA with installed mutated codons for the non-proteinogenic amino acids [43]. Amino acids **9** with non-proteinogenic side chains can be grouped according to their features (Figure 6).

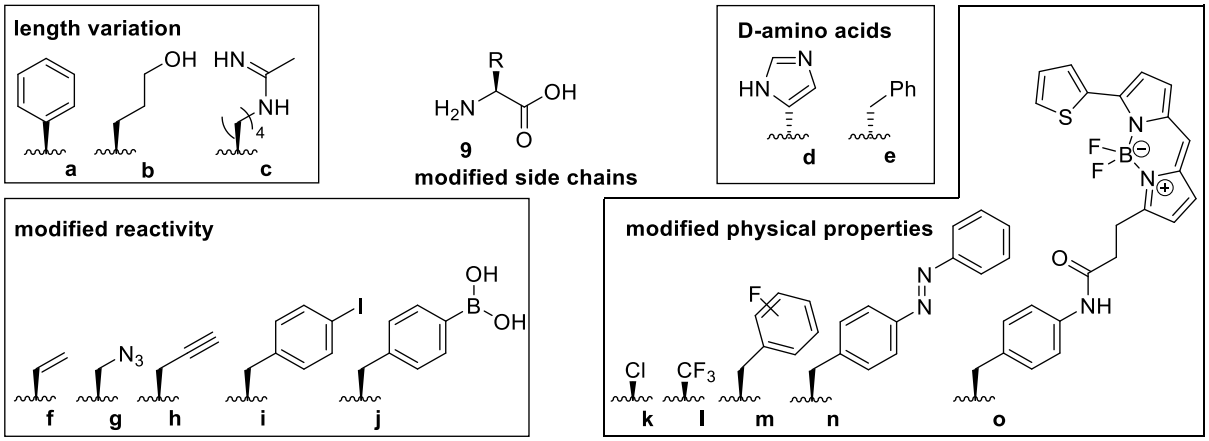


Figure 6. Four groups of side chains of Class A peptidomimetics. The different groups are illustrated with prototypes.

Length variation: To reduce or increase the flexibility of a peptide, variation of the side chain length but preserving the natural functional group is a reasonable approach for SAR studies. Even though the $C^{\alpha}H$ acidity renders phenylglycine derivatives **9a** susceptible to epimerization, its reduced flexibility is a common feature to replace phenylalanine, e.g. in Dengue Virus protease inhibitors [44] or β-lactam antibiotics, e.g. ampicillin, cephalixin [45]. Examples for peptidomimetics with enhanced side chain lengths are pentahomoserine (or 5-hydroxynorvaline, **9b**), a biosynthetic precursor of glutamate, which accumulates in plants as defensive agent to be mis-incorporated by herbivores [46]. Non-proteinogenic amino acids with enhanced side chains are used in drug design, if the molecular scaffold is too rigid for a good interaction, as demonstrated in the SAR study of the immunosuppressive 5-hydroxynorvaline-2-cyclosporin [47]. Synthetic amino acids containing side chains with substituted or protected functional groups are used in peptide synthesis, as well as to bind side chain converting enzymes. For example, lysine analogs such as **9c** are promising antibiotics, binding to riboswitches of Bacillus subtilis resulting in the suppression of lysine biosynthesis [48].

D-Amino acids: Incorporation of D-amino acids, like **9d-e** enhances the stability of peptides against degradation by ribosomes [49] and facilitates cyclization (e.g. in Cilengitide®) [50].

Modified reactivity: A reasonable approach for the selective conversion of peptides is the incorporation of amino acids with unique functional groups in the side chain. Appropriately selected substituents in the side chain can undergo orthogonal conversions including Heck

reactions (e.g. **9f,i**) [51], [3+2]-cycloadditions (e.g. **9g,h**) [52], transition metal catalyzed cross-coupling reactions (e.g. **9h-j**) [53] to mention only few well investigated representatives.

Modified physical properties: Amino acids with halogen atoms in the side chains (e.g. **9k-m**) can be used as tools to enhance the stability of a peptide. F atoms in the side chain allow the investigation of conformational properties of the peptides in solution or even in vivo by HOESY or ^{19}F NMR spectroscopy [54]. Smart materials are accessed by the incorporation of photosensitive groups. Peptides including azobenzene (e.g. **9n**) have been reported to form smart hydrogels, which collapse upon irradiation [55]. Fluorescent-labeled amino acids, such as the BODIPY558-AF labeled amino acid **9o** was incorporated into calmodulin to monitor its conformational changes via FRET [56].

Propargylamide **6** based peptidomimetics of all four groups of unnatural amino acid side chains are discussed in Chapters III-9 to III-20.

A further concept of Class A peptidomimetics comprises the introduction of additional substituents at various positions of the amino acid backbone as a conformational constraint or secondary side chain.

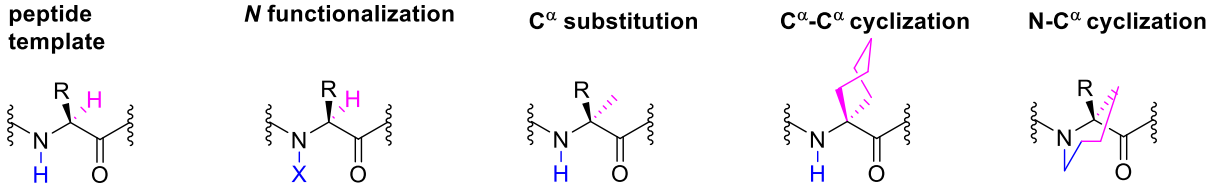


Figure 7. Class A peptidomimetics with additional substituents at the *N*-atom and/or the C$^{\alpha}$-atom of an amino acid. X=CH_3, NH_2 or OH.

Alkylation of the backbone amide eliminates one H-bond donor increasing the bioavailability, restricting the rotational freedom around the amide bond [57] and supporting secondary structures. This concept has been realized in the turn motif of cilengitide® [50,58]. Electrophilic amination the backbone amide is an approach to increase the number of H-bond donors leading to improved solubility and rigidity of the backbone. A strategy to convert most of the canonical amino acids into hydrazine acids for solid phase organic synthesis has been recently reported [59]. Epimerization can be

completely prevented by alkylation or fluorination of the C^{α}-atom. Helix motifs are stabilized in dependence on the constrained dihedral angles ϕ and ψ [60]. While connection of two C^{α}-substituents forming a cycle only locks the orientation of the side chain and defines the angle χ, prolin analogs with a bridge between C^{α}-atom and the amide N-atom also lock the backbone angle ϕ [38].

III-5. Peptide backbone modifications

Partial substitution of backbone elements is usually performed by the incorporation of a dipeptide analog into the peptide. Expected effects of such modifications are enhanced proteolytic stability, conformational variance and optimization of protein-inhibitor interactions. Larger substituted units constitute an elevated degree of abstraction, constituting Class B peptidomimetics.

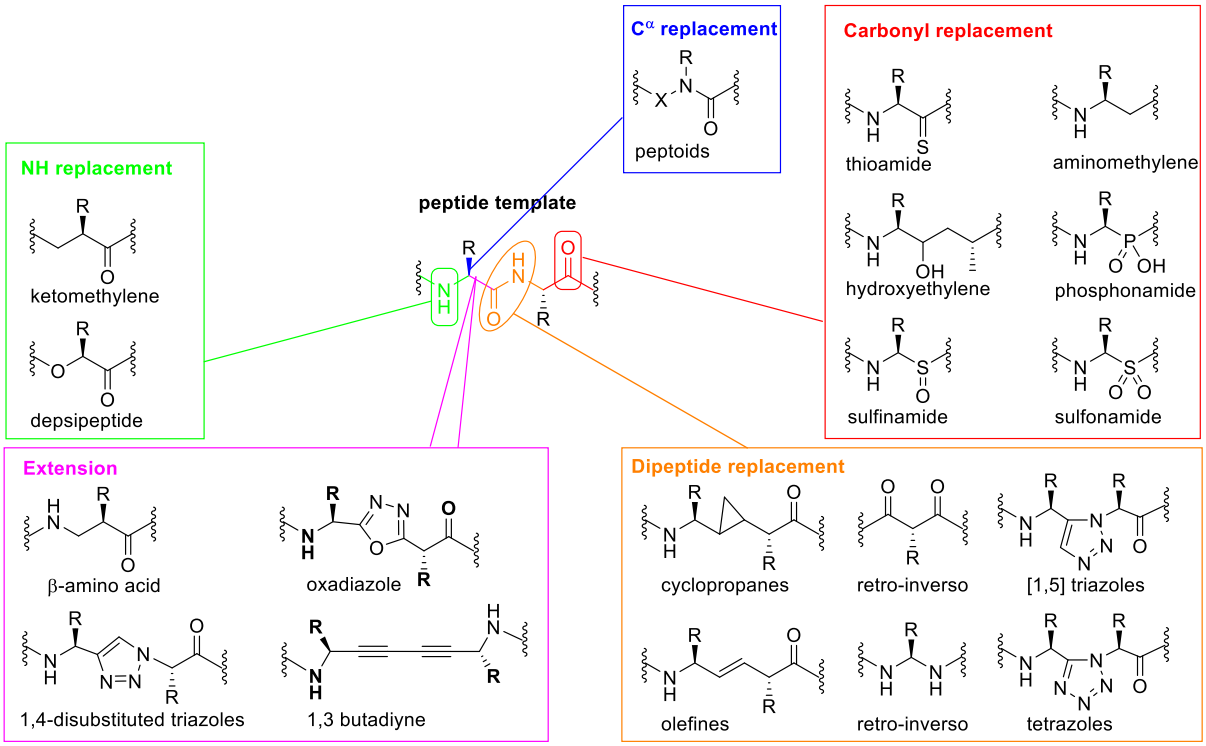


Figure 8. Options for the exchange of single peptide moieties illustrated by well documented representatives [35,38,61,62]. C^{α} replacement: Peptoids ($X=CH_2$), α-Aminoxypeptoids ($X=O$), Azapeptoids ($X=NH$).

Reduction of some functional groups in the backbone leads to an increased backbone flexibility. Among the isosteric groups of the NH moiety, O atoms resulting in depsipeptides or CH_2 moieties forming ketomethylene groups are best documented and often found in cyclopeptides [35].

During enzymatic amide hydrolysis the carbonyl moiety is converted into a tetrahedral intermediate. Thus, proteolysis can be suppressed by replacement of the carbonyl moiety by stable tetrahedral isosteres, imitating the tetrahedral hydrolysis intermediate. Since the tetrahedral peptide isoster is tightly bound within the active site of the enzyme but cannot be hydrolyzed, the catalytic activity of the enzyme is blocked. This concept of transition state mimetics was exploited in e.g. aspartyl protease inhibitors, and comprises numerous surrogates, including aminomethylene, hydroxyethylene, dihydroxyethylene, phosphinate, thioamide, phosphonamide, sulfinamide and sulfonamide components [63,64]. Hydroxyethylurea derivatives were applied as lead compounds for the development of γ-Secretase inhibitors as anti-cancer drugs (e.g. neuroblastoma) [65]. Sulfonamide derivatives were oligomerized to form β-peptidosulfonamide peptide hybrids. Although such oligomers were characterized as potent helix breakers and transition state mimetics, their application is limited due to fast racemization and diffraction [64].

The side chain of an amino acid within a peptide can be attached to the amino moiety instead of the C^{α} atom, giving achiral peptidomimetics which can fold into chiral helices [66] or sheet-structural elements of (*N*-hydroxy) peptoids (Figure 7) [67]. α-Aminoxypeptoids exhibit an even stronger preference for *cis*-amide bonds [68], forming probably more stable helices. The macrodipole of a peptoid helix is oriented opposite to that of a peptide helix. Combining high stability against proteases with improved cell permeability peptoids are promising PPI disruptors. The biologically active oligomers of azapeptoids in proteasome inhibitor mimetics [69] represent interesting examples for tumor therapy [70]. Moreover, diverse flexible, amphipathic peptoid-oligomers have been reported to be effective antimicrobials [71].

Numerous approaches for the replacement of the complete amide structure have been reported. Cyclopropane and alkene moieties are used to lock the dihedral angle ψ in Ras Farnesyltransferase inhibitors [72,73]. In retro-inverso peptidomimetics, formally the stereochemistry is inverted and *C*- and *N*-termini are exchanged, enhancing their *in vivo* half-life [74]. Aromatic heterocycles including 1,5-disubstituted 1,2,3-triazoles and

tetrazoles resemble the amide in size and length and are used as *cis* configured amide bond replacement, enforcing a reverse turn on a peptide [75,76].

The most abstract isosteres of peptidic amides are extended amino acids, which allow the introduction of peptide-like side chains in a three-dimensionally defined orientation into the linker between the amino- and carboxy moiety. Usually, extended amide isosteres are classified according to the number n of bonds between two N-atoms: α: n=3, β: n=4, γ: n=5, δ: n=6, etc. Polymeric β-amino acids are closely related to the native peptides consisting of α-amino acids. They are able to form well defined secondary structures. 1,4-Disubstituted 1,2,3-triazoles, 2,5-disubstituted 1,3,4-oxadiazoles and disubstituted butadiynes do not feature any peptide related functional group. Yet, Ko and coworkers managed to mimic the spatial 3D topology of native peptides with oligomers of these scaffolds [15]. Oligomers of this type are termed foldamers.

III-6. Foldamers

Oligomeric Class B peptidomimetics with modified $C^{\alpha}H$ moiety or replaced or extended amide moiety form predictable secondary structures, which are called foldamers. Creative modifications of the backbone of foldamers result in many new hydrolytically stable secondary structural elements rendering foldamers a promising approach for the development of diverse antimicrobials and anti-tumor agents [36]. In the following part, foldamers are categorized according to the size of their monomers and the driving force of their folding process.

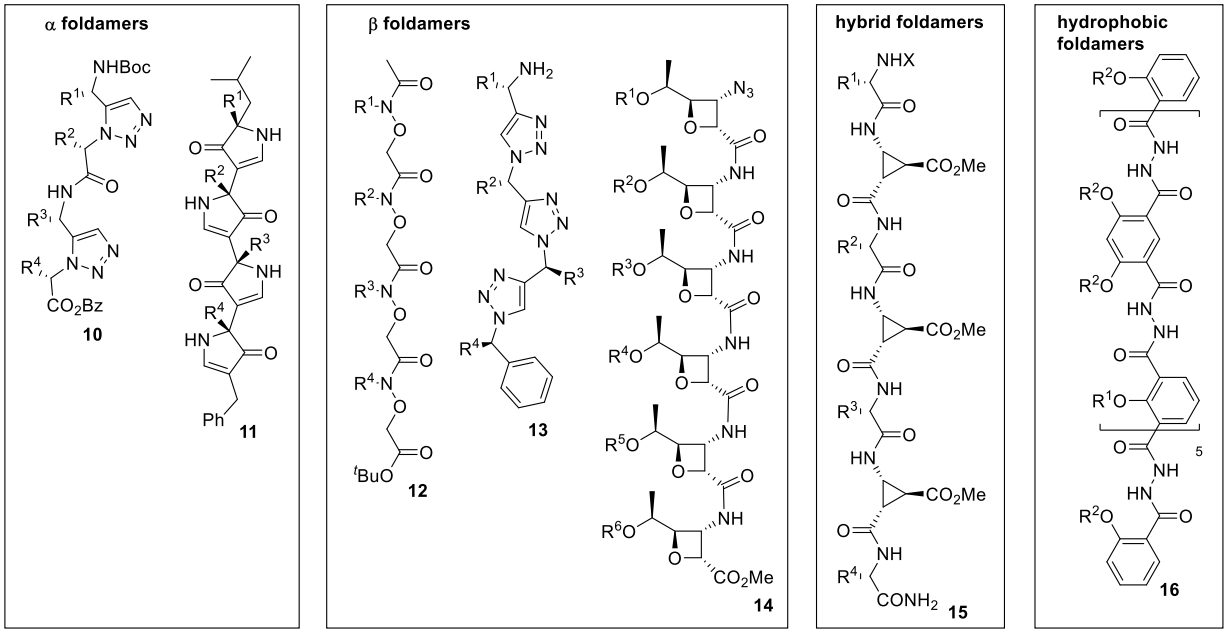


Figure 9. A selection of representative foldamers: 1,5-Disubstituted 1,2,3-triazolamer **10**, R^1=^{i}Pr, R^2=Me, R^3=^{i}Bu, R^4=^{i}Pr [75]. Pyrrolinone **11**, R^1=CH_2Ph, R^2=CH_2indole, R^3=$(CH_2)_4NH_2$, R^4=^{i}Pr [77]. α-Aminoxy peptoid **12**, R^1=$CH_2CH{=}CH_2$, R^2=CH(Me)Ph, R^3=CH_2-3,5-dimethoxybenzene, R^4=CH(Me)Ph [68]. 1,4-Disubstituted 1,2,3-triazolamer **13**, R^1=^{i}Pr, R^2=CH_2Ph, R^3=CH_2Ph, R^4=Me [78]. Oxetane **14**, $R^{1\text{-}6}$=Bn [79]. α-Amino acid/β-Cyclopropane amino acid hybrid **15**, X=Ac-Arg-His-Tyr-Ile-Asn-Leu, R^1=CH(Me)Et, R^2=R^3=$(CH_2)_4NHC(NH)NH_2$, R^4=CH_2(4-OH-Phenyl) [80]. Oligohydrazide **16**, R^1=CH_3, R^2=C_8H_{17} [81].

In **α-foldamers** three bonds are between the $C^{\alpha i}$ and $C^{\alpha i+1}$ atoms of adjacent monomeric units. Usually, this distance induces an α-helix with a 13-atom-circle, closed by an H-bond and 3.6 monomers per turn. The 1,5-disubstituted 1,2,3-triazolamers like **10** are constructed of alternating amide isosteres and amides. The 1,5-disubstituted 1,2,3-triazole mimics a *cis* amide moiety bending the backbone and stabilizing a helical turn even in short chains, as exemplified by the homochiral tetramer **10**. Analogously to α-helices, the conserved amide moieties form H-bonds between the CO^i and NH^{i+4} moieties, which was confirmed by X-ray structure analysis [75]. Homochiral pyrrolinone chains are rather rigid and compensate the angle of each monomer by antiparallel arrangement forming β-strand and β-sheet secondary structures. Oligopyrrolinones, e.g. tetrapyrrolinone **11** are considered as potential inhibitors for the aspartyl proteases renin and HIV-1 protease. Heterochiral oligopyrrolinones, like **11**, consist of alternating *R*- and *S*-configured monomers. The angles of parallel arranged monomers add up to a turn and even to helix-like structure. Crystal structure analysis of oligomers revealed a cavity in the middle of the helix, which

can be described as a nanotube. Tetrapyrrolinone derivatives are currently investigated as inhibitors of somatostatin receptors hsst4 an hsst5 [77].

An increased length of four bonds between $C^{\alpha i}$ and $C^{\alpha i+1}$ of adjacent monomeric units in **β foldamers** increases the flexibility. As a result, various secondary structures are available comprising 6- and 8-ribbons, 10-, 12- and 14-helices as well as miscellaneous 12/14-helices with 1.7-3.1 residues per turn. With the amplified pool of secondary structural elements, PPIs can be addressed more precisely, enhancing selectivity and affinity of foldamer-based PPI disruptors. In contrast to the flexible β-peptides and peptoids, NBO, X-ray and NOESY experiments prove a preferred *cis* configuration around the amide bond of α-aminoxy peptoids like **12**. Consequently, α-aminoxy peptoids are able to stabilize a helical structure with an H-bond between CH_2^i and CO^{i+1}. Furthermore, the facile synthetic access to versatile functional groups in the side chain makes α-aminoxy peptoids a promising alternative to peptoids and β-peptides [68]. The antiparallel orientation of the dipole moments of the planar monomers of homochiral 1,4-disubstituated 1,2,3-triazolamers align their dipole moments antiparallel, compensat the angle of each monomer. Thus, this type of oligomers is able to form stable β-strand structures, especially if the side chains consist of bulky residues [78]. As HIV protease cleaves 4-5 amino acids in β-strand conformation, X-ray crystal structures of co-crystallized HIV1-protease and the established ligands L-700,417 and A-74704 were used as template to design 1,4-disubstituted 1,2,3-triazolamer **13**, a peptidomimetic with a HIV inhibiting activity in micromolar range [82]. NMR and MD studies show that the chirality of *cis*-substituted oxetane β-amino acids such as **14** induces a well-defined left-handed 10-helix, which is stabilized by an H-bond between NH^i and CO^{i+1} [79].

Hybrid foldamers combine different building blocks like α- and β-peptidomimetics. The combination of two structural elements adds further secondary structural elements to the variety of secondary structures produced by homogeneous foldamers, like the 11- and 14/15-helix, consisting of 3 or 4.5 monomers per turn, respectively. As the kind and number of functional groups in the side chain of Class B peptidomimetics are limited, in most cases for synthetic reasons, hybrid foldamers allow the combination of two or more side chain pools, enhancing the options for the design of PPI disruptors. For instance, β-cycloaminopropane hybrid **15** consing of α-amino acids and peptidomimetics in an alternating fashion forms a stable 13-helix in solution, which combines the proteinogenic

side chain diversity of α-amino acids with the proteolytic and conformational stability of the peptidomimetic [83]. Hybrid **15** has been applied as mimetic of neuropeptide NPY with high affinity on Y_1 and Y_5 receptors [80].

Whereas the secondary structure of foldamers **10-15** discussed above are stabilized by intramolecular H-bonds, the secondary structure arrangement of **hydrophobic foldamers** is arranged by solvophobic forces like π-stacking. Even though oligohydrazide **16** forms intramolecular H-bonds between Ar-OR^i, N^iH and CO^i, these H-bonds are only established within a single monomer. These H-bonds induce the backbone curvature in the monomers, but do not contribute to the overall folding process of the oligomer. Formation of the helix structure is navigated by the parallel arrangement of the hydrophobic aliphatic- and aromatic entities. Similar to tetrapyrrolinone **11**, a polar, hydrophilic cavity emerges within the helix, in which disaccharides perfectly fit. With NOESY spectroscopy, H-bonds between the hydroxy-groups of α-D-glucose and the carbonyl moiety of the foldamer were observed. Moreover, temperature resolved CD spectroscopy indicates an immense stabilization of the helix in the presence of α-D-glucose in chloroform [81].

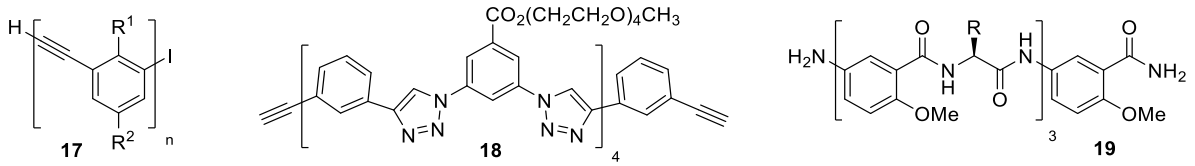


Figure 10. Additional hydrophobic foldamers **17**-**18** designed from extended amide isosteres: oligo ethynylarenes **17a**, n=2-18, R^1=H, R^2=$CO_2(CH_2CH_2O)_3CH_3$ [84]. **17b**, n=18, R^1=Me, R^2=$CO_2(CH_2CH_2O)_3CH_3$ [85]. Clickamer **18** [86]. Strongly hydrophilic oligo 5-amino-salicylates **19**, R=$(CH_2)_4NHC(NH)NH_2$ [87].

Due to their high lipophilicity, the achiral oligo ethynylarenes **17** require a short polyoxyethylene side chain to remain in solution when prolonged. In polar solvents, **17** folds controlled solely by hydrophobic π-stacking forces into a helix, enclosing a cavity as described in oligohydrazide **16**. The hydrophobic cavity of oligo ethynylarenes like **17a** can host appropriately sized nonpolar guests in stoichiometric ratio. Nonpolar solvents or elevated temperature induce a transition of the helix into a random coil structure [84]. Insertion of chiral bicycloheptane- or pinene derivatives into the helix cavity of oligo ethynylarenes **17b** conducts a defined helix-direction [85]. Similarly, the amphiphilic clickamer **18** forms a helix of 8.5 aromatic units per turn in polar solvents [86]. Driving force for helix formation are π-π interactions between the aromatics. Halide ions are

stoichiometrically coordinated by an H-bond to the triazole-CH, bending clickamer **18** to a half circle around the halide ion and thus inverting the helix. An enhanced chain length increases the number of triazoles and thus the positive polarity inside the cavity. Consequently, the coordination of halides is strengthened [88]. Basic research on the selective hosting of (non-)polar, anionic and cationic molecules in helical cavities has been performed in the past years to investigate the potential of foldamers as substrate specific catalysts [89].

The high polarity and thus solvophilicity of the basic side chains of oligo 5-amino-salicylat **19** has the opposite effect. It inhibits the folding to afford a helix, but induces the formation of a β-sheet like structure, which inhibits spontaneous fibrilization of amyloids Aβ42 and Aβ43. Therefore, foldamers of type **19** are considered as promising approach for the treatment of Alzheimer's disease [87]. As the secondary structure of oligo 5-amino-salicylates is still under investigation, an unequivocal categorization is not yet possible.

III-7. Structural Helix Mimetics

The α-helix motif occurs in protein-membrane interfaces, DNA binding motifs and in 62 % of all PPI interfaces [90], making it a fundamental mimicry-target. While foldamers mimic a complete secondary structural element, structural helix mimetics only recapitulate the topology of a certain face of the helix template. Their rod-like scaffold aligns in a parallel manner to the helix template and presents residues only on one side analogously to the helix. Thus, helix mimetics are comparatively small and nonpolar molecules, complying possibly with Lipinski's criteria for oral bioavailability. Design of appropriate structural helix mimetics represents a valuable approach for the development of innovative PPI disruptors or synthetic antibodies [91]. The concept of helix-mimicry was also observed in nature. The natural compounds Sekikaic- and Lobaric acid were identified to interact with the dynamic interface of the coactivator complex CBP/p300 in low micromolar concentrations [92].

Thorough investigation of helical PPIs by analysis of X-ray crystal structures from the PDB revealed that most helices (60 %) interact with only one face with the complementary protein. Simultaneous interactions of two helix-faces was also frequently observed (33 %), whereas interactions with three faces is rather seldom (7 %) and mainly occurs in membrane proteins. The location of helical hot spot residues reflects the interaction side:

i+1 (12%), i+2 (4%), i+3 (10%), i+4 (27%), i+5 (5%), i+6 (4%), i+7 (15%), i+8 (9%), i+9 (3%), i+10 (4%), i+11 (7%) [90]. The side chains in positions i, i+3/4, i+7 are assembled on the same helix side. Therefore, the nature and orientation of these side chains are easy to reproduce using non-peptidic scaffolds. In contrast, two-faced helix mimetics require a correct arrangement of appropriate residues on opposing sides of the scaffold. In both cases, sophisticated conformational constraints are necessary for an accurate orientations of the residues [93]. Structural helix mimetics can be assigned to three groups, according to their align mechanisms [31].

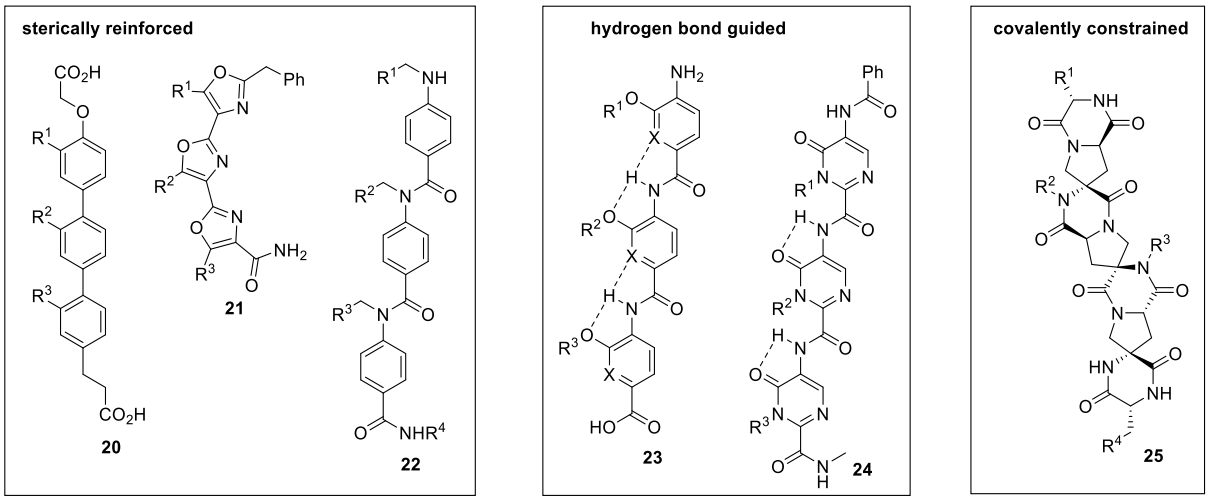


Figure 11. Types of structural helix mimetics organized according to their align mechanism. Exemplary representatives with defined side chains R are given here: **Sterically reinforced**, terphenyls **20**, R^1=$CH_2{}^i$Pr, R^2=CH_2Ph, R^3= $CH_2{}^i$Pr [94]. Teroxazoles **21**, R^1= Me, R^2=$CH_2{}^i$Pr, R^3=Et [95]. *N*-Alkylated oligobenzamides **22**, R^1=Ph, R^2=naphthyl, R^3=^{i}Pr [96]. **Hydrogen bond guided**, 3-alcoxy oligobenzamide ethers **23a**, X=CH, R^1=Bn, R^2= -CH_2-2-naphthyl, R^3=^{i}Pr [97]. Trispyridylamides **23b**, X=N, R^1=^{i}Pr, R^2= R^3=Bn [98]. Trispyrimidonamides **24**, R^1=$(CH_2)_4NH_2$, R^2=$CH_2{}^i$Pr, R^3=CH_2CH_2indole [99]. **Covalently constrained**, spiroligomers **25**, R^1=CH_2CH_2Ph, R^2=CH_2-(3,4-dichlorophenyl), R^3=$CH_2{}^i$Pr, R^4=CO_2H [100].

Sterically reinforced helix mimetics are characterized by a low energy barrier between different conformations, that allows fast conformational interconversion at room temperature. Despite the high flexibility, this type of helix mimetics adopts a defined conformation by *induced fit*, i.e. by adaptation of the helix mimetic at the template. Design of such helix mimetics requires only information about key residues, but not on their spatial 3D topology [101]. Terphenyl derivatives (e.g. **20**) belong to the earliest helix mimetics. The π-delocalization of the phenyl rings leads to a parallel alignment of the monomers, while steric repulsion results in dihedral angles [102]. As example, rather flexible terphenyl **20** disrupts the Bcl-x_L/Bak interaction (IC_{50}=1.5 μM). The side chains of terphenyl **20** are

oriented in such a manner to mimic the side chains in position i, i+3/4, i+7 of an α-helix. Whereas free Bcl-x_L is removed by interaction with helix mimetic **20**, the unbound pro-apoptotic Bak-protein induces the programmed cell death. Although terphenyl derivatives represent promising lead compounds for the development of anti-tumor drugs, their tedious synthesis and low log P value limits their broad application [94]. The more polar teroxazoles like **21** were prepared on solid phase. MD studies confirm a planar arrangement of the side chains in helix position i, i+3, i+6, as well as a curve in the backbone. Libraries of such scaffolds are currently under evaluation as PPI disruptors [95]. A much greater diversity of side chains can be achieved by solid phase organic synthesis of *N*-alkylated oligobenzamides such as **22** [103,104]. Oligobenzamides of type **22** orient their side chains on one face (α-helix residues i, i+3/4, i+7). Representative **22** was designed as anti-cancer agent by disruption of the interactions between P53 and HDM2 in low micromolar range [96]. However, increase of solubility by addition of polar substituents led to reduced activity [102].

Hydrogen bond constrained helix mimetics with the monomers arranged in a parallel manner require much higher energy conformational interconversion [93]. The residues of 3-alcoxy oligobenzamide ethers **23a** are oriented analogously to the α-helix side chains in i, i+3/4 and i+7 position [97]. Large side chain diversity and oligomerization by amide bond formation allow a quick composition of compound libraries by solid phase organic synthesis [105,106]. However, 3-alcoxy oligobenzamide ether **23a** is a far less active inhibitor of P53/HDM2 interactions than therphenyl **20** [97]. Investigation of the preorganized H-bonds stabilizing trispyridylamides **23b** indicates an altered backbone curvature than in 3-alcoxy oligobenzamide ether **23a** [98]. Target helices could be reproduced very well by oligomers composed of a combination of both monomers, affording Bak mimetics which inhibit Bcl-x_L in nanomolar range [107]. Extensive investigation of the conformation of the closely related trispyrimidonamide **24** showed that side chain orientation on alternating sides of the backbone by 180° rotation has to be expected if no H-bonds link the monomers [99].

The backbone of **covalently constrained helix mimetics** does not show any conformational freedom. As it is difficult to match such a structure to a helix template, only few examples are conversant. Schafmeister *et al*. synthesized flexible oligomers on resin, which were rigidified by formation of diketopiperazine spiroligomers [108]. The mere backbone was first used as a spacer in metal-ligand complexes [108]. However, an α-helix face (i, i+4, i+8) could be imitated by attachement of nonpolar side chains [109]. Passive diffusion of fluorescein-bound spiroligomers into human liver cells was visualized by confocal microscopy and fluorescent imaging. These convenient cell permeation properties stimulated the design of further spiroligomer. Thus, spiroligomer **25** reacted as mimetic of the p53 activation domain to bind to HDM2. Renoval of HDM2 represents a promising tumor treatment approach [100]. The probable reproduction of stereochemical PPI aspects by chiral helix mimetics is still under investigation [93].

III-8. A Geometric Contemplation of Structure-Design

In this chapter, novel structural devices for the design of peptidomimetics are developed. According to the novel concept, propargylamides **6** (see Chapter II [1]) should be coupled with appropriately substituted aromatic halides via *Sonogashira* cross-coupling. The propargylamide represents the *N*-terminus and the carboxylic acid at the aromatic system imitates the *C*-terminus of a dipeptide. Various side chains can be introduced at the aromatic ring (resulting in a locked χ angle) and at the propargylic C^{α}-atom. While diverse amino acid like side chains are introduced into the propargylic moiety geometric properties, such as size, distance, angles and conformational degrees of freedom of the peptidomimetic scaffold are defined by the kind of the aromatic system and the position of the carboxylic acid.

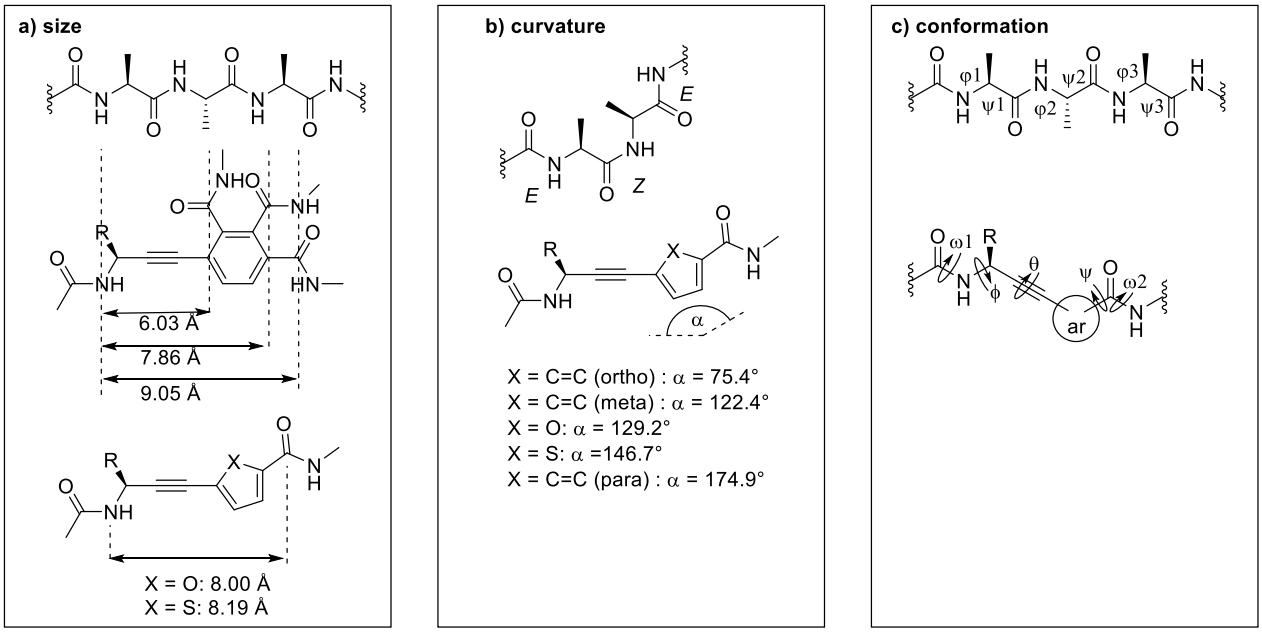


Figure 12. Comparison of geometric properties of aminopropynylarenecarboxylic acids with analog peptides. a) Size of one segment in comparison to the peptide. b) Introduction of a defined bending into the backbone in dependence of the substitution pattern of the aromatic ring. c) Amino acids based on the arylalkyne framework show certain conformational constraints and decreased rotational degrees of freedom.

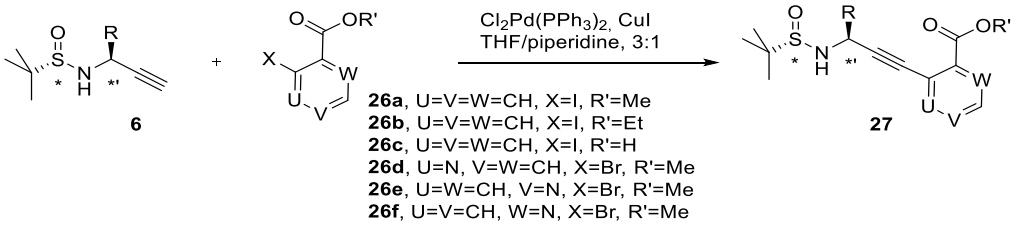
The peptidomimetic aminopropynylarene scaffold of this work represents a rather rigid spacer. The length and backbone bending depend on the substitution pattern of the aromatic ring. Some energetically favored conformations can be predicted, as the rotation around several bonds is restricted. Free rotation is only possible around the axis between C^{α} and aryl, referred to as θ. Aminopropynylarenecarboxylic acid dipeptide analogs comply with Lipinski's rules with respect to lipophilicity (logP < 5) and molecular weight (mw < 500) for oral application [29]. Furthermore, hydrolysis of the designed dipeptide analogs is no longer possible, since due to the great degree of abstraction from the native peptide backbone hydrolysable functional groups are absent. The designed structures belong to the Class B dipeptidomimetics with extended amide isoster. Typically, prolongation of such monomers by orthogonal *Click* reactions (here amide formation and the *Sonogashira* cross-coupling) leads to defined secondary structure elements, as observed for Class C foldamers. Moreover, rigid scaffolds like these aminopropynylarenecarboxylic acids are required in the design of topographical type III peptidomimetics, like helix- and mechanistic mimetics.

Synthetic aspects, compound library formation and properties are discussed for each geometric entity.

III-9. Synthesis of Peptidomimetics with *ortho*-Substituted Arenes

Sonogashira cross-coupling of *N*-propargylamides **6** with 2-haloarenecarboxylic acid derivatives **26a-f** gave the dipeptidomimetics **27** in varying yields. This strategy was used to synthesize a small compound library of 17 peptidomimetics **27a-q** including a great diversity of side chains and heteroarenes. Since the palladium catalyst $PdCl_2(PPh_3)_2$ led to higher yields of coupling products than the catalysts $Pd(PPh_3)_4$, Pd(dppf) and $Pd(OAc)_2$ it was used as standard catalyst throughout this work.

Table 1. Synthesis of a set of diverse peptidomimetics **27a-q** by cross-coupling of various propargylamides **6** and haloarenecarboxylates **26a-f**.



entry	propargylamide	*/*'	R	**26**	**27**, Yield
a)	**6b**	(*S/S*)	$CH(CH_3)_2$	**26b**	**27a**, 68%
b)	**6b**	(*S/S*)	$CH(CH_3)_2$	**26a**	**27b**, 85%
c)	**6c**	(*R/R*)	$CH_2CH(CH_3)_2$	**26b**	**27c**, 97%
d)	**6c**	(*S/S*)	$CH_2CH(CH_3)_2$	**26a**	**27d**, 78%
e)	**6c**	(*R/R*)	$CH_2CH(CH_3)_2$	**26d**	**27e**, 0%
f)	**6c**	(*R/R*)	$CH_2CH(CH_3)_2$	**26e**	**27f**, 18%
g)	**6c**	(*R/R*)	$CH_2CH(CH_3)_2$	**26f**	**27g**, 10%
h)	**6e**	(*S/S*)	cyclohexyl	**26a**	**27h**, 82%
i)	**6f**	(*S/S*)	$C(CH_3)_3$	**26a**	**27i**, 66%
j)	**6f**	(*S/R*)	$C(CH_3)_3$	**26a**	**27j**, 19%
k)	**6l**	(*S/S*)	$CH_2CH_2CO_2C(CH_3)_3$	**26a**	**27k**, 78%
l) [a]	**6o**	(*S/R*)	C_6F_5	**26a**	**27l**, 62%
m) [a]	**6o**	(*S/R*)	C_6F_5	**26c**	**27m**, 0%
n) [a]	**6p**	(*S/S*)	CF_3	**26a**	**27n**, 32%
o) [a]	**6p**	(*S/R*)	CF_3	**26a**	**27o**, 52%
p)	**6w**	(*S/S*)	$CH_2CH_2CH_2CH_2NHBoc$	**26a**	**27p**, 20%
q)	**6x**	(*S/S*)	$CH_2CH_2CH_2NHC(=NBoc)NHBoc$	**26a**	**27q**, 60%

[a] The milder base DIPEA was used instead of piperidine.

As the iodo substituent is only slightly shielded by the ester moiety in *o*-position [110], the *o*-substituted benzoates **27a-d** with aliphatic side chains were obtained in high yields. In order to introduce a dipole moment to peptidomimetics **27** an H-bond accepting heteroatom should be introduced into the aromatic system. Thus, propargylamide **6c** was reacted with the bromopyridines **26d-f**. The lower reactivity of bromides is compensated by the increased electron withdrawing character of the pyridine ring of **26d-f** [111]. However, the coordinating character of electron poor pyridine derivatives to Pd^0 in alkaline medium can poison the catalyst resulting in low yields of 18 % (**27f**) and 10 % (**27g**). Although several experiments under varied conditions were performed, the bromopyridine **26e** did not react with the alkynes **6** to yield arylalkynes **27**. This result is in good accordance with literature, reporting the extraordinarily low reactivity of 2,6-disubstituted aryl halides in *Sonogashira* reactions [110].

Sterically demanding substituents at the alkyne are considered to be the most serious factor to reduce the reaction rate of *Sonogashira* reactions [110]. As small phosphine ligands are recommended to accelerate the conversion rate [110], electron donating PPh_3 [112] with a low Tolman cone angle of 145° [113] was chosen for the synthesis of the sterically demanding compounds **27h-q**. Propargylamides **6f** and **6p** with *unlike* configuration (*S,R*) of the centers of chirality gave lower yields than the *like*-configured diastereomers **6f** and **6p** with (*S,S*)-configuration. It is postulated that the *unlike* diastereomers form more shielded complexes with the phosphine ligands.

III-10. A Surprising Intramolecular Hydrocarboxylation Reaction

Surprisingly, cross-coupling product **27m** could not be isolated after the reaction of propargylamide **6o** with 2-iodobenzoate (**26c**). Instead, the alkylidenelactone **28** was isolated in 27 %. Apparently, the *Sonogashira* cross-coupling had been successful, but was followed by an unexpectedly intramolecular hydrocarboxylation. The free carboxylic acid had reacted with the adjacent alkyne to provide lactone **28**.

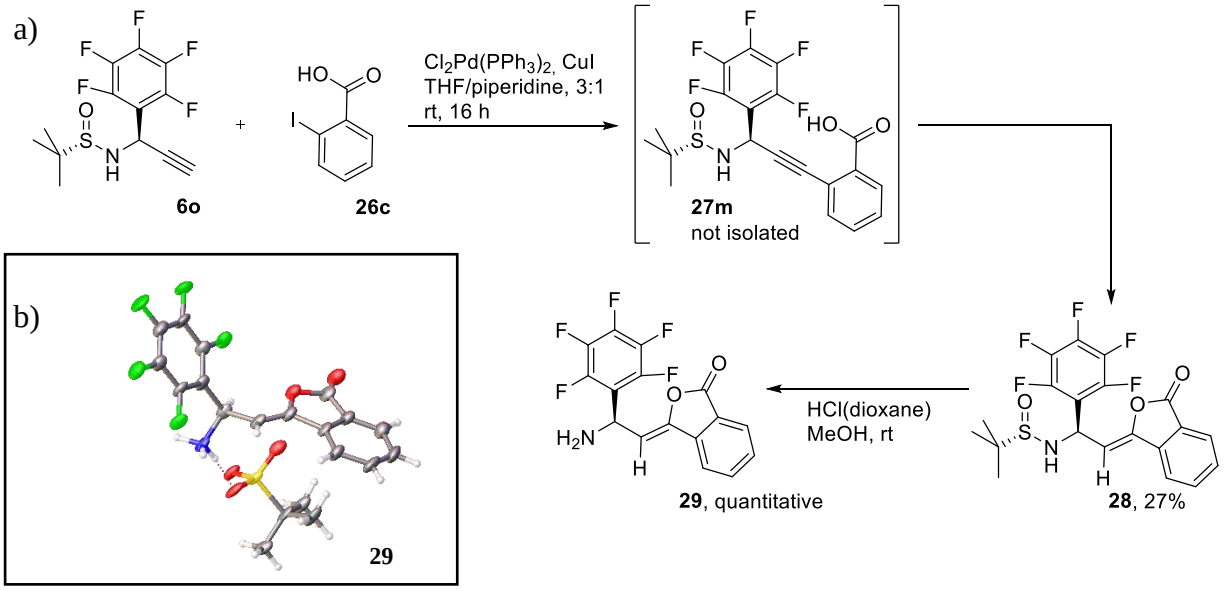


Figure 13. a) A *Sonogashira* cross-coupling reaction of propargylamide **6o** with 2-iodo carboxylate **26c**, *in situ* succeeded by a hydrocarboxylation reaction. b) X-ray crystal structure of deprotected hydrocarboxylation product **29**.

The X-ray crystal structure of the deprotected amine **29** confirmed the 5-*exo*-dig cyclization forming the benzofurane derivative. Analogous hydrocarboxylation reactions catalyzed by Cu^{I} and Pd^{0} on carbon nanotubes have been reported under harsh conditions (100 °C in DMF, 3-15 h), giving mixtures of benzofuranone- and coumarin derivatives [114]. As the electronic properties of the catalyst determine the regioselectivity, the AuCl catalysis selectively induces 5-*exo*-dig cyclization forming benzofuranones [115], while the $ReCl(CO)_5$ catalyst selectively initiates 6-*endo*-dig cyclization forming coumarins [116]. This unexpected domino reaction comprising of a *Sonogashira* cross-coupling and a subsequent hydrocarboxylation reaction under mild conditions is unprecedented.

III-11. *ortho*-Substituted Peptidomimetics as Foldamers

Usually, oligomerized Class B dipeptidomimetics with extended amide isosteres fold in a predictable manner to adopt a secondary structure [15]. The narrow angle in the backbone of scaffold **27** of 75.4° already enforces a turn to the backbone, enhancing the formation of a particular foldamer conformation. As dipeptidomimetic **27** has orthogonal protective groups at both the *N*- and *C*-termini, selective oligomerization by peptide-bond formation was performed. Thus, hybrid peptidomimetics **32-35** with different length had been prepared and discussed in my preliminary master thesis [117] (Figure 14).

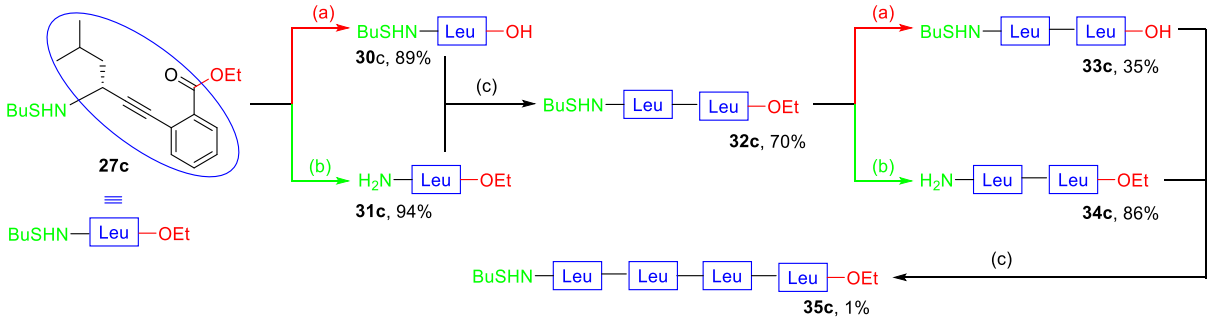


Figure 14. Oligomerization of dipeptidomimetic **27** with a narrow angle. (a) Aqueous LiOH (1 M, 3 eq)/MeOH (1:2), 0 °C, 12 h. (b) HCl (dioxane, 4 M, 4 eq), MeOH (15 mL), 4-8 h, rt. (c) TBTU or HATU (3 eq), HOBt or HOAt (2 eq), DIPEA (6 eq), DMF (2-6 mL), rt, 16 h.

The solubility of non-polar scaffolds such as **27** decreases with increased number of monomers (e.g. proceeding prolongation), reducing the yield of subsequent reactions. Therefore, further elongation of tetramer **35** turned out to be impossible under the given conditions. The aggregation, which lead to precipitation of the tetramer resulted from intermolecular interaction rather than intramolecular folding. Nevertheless, CD spectra of monomer **27c** and dimer **32c** at different concentrations indicate a folding which is not associated with aggregation (Diagram EP8a,b Experimental Part). Nelson *et al.* [84] and Prince *et al.* [85] reported a promising approach to circumvent similar aggregations by introduction of a polyoxethylene unit at the aromatic ring. The amphiphilic foldamers maintain solubility, while solvophobic interactions of the nonpolar scaffolds led to nanotube formation [84] with a cavity for nonpolar guest molecules [85]. Conversion of peptidomimetic scaffolds **27** into solvophobic foldamers with amphiphilic properties induced by polyoxyethylene substituents at the aromatic rings will be the subject of successive investigations.

III-12. Conformational Preference

Although the conformation of oligomers **32-35** could not be determined unequivocally, the torsion angles of monomers should induce a secondary structure of the oligomers as observed for peptides [118]. The dihedral angles of dipeptidomimetics L-**27n** and D-**31o** in the solid state were determined by X-ray crystal structure analysis. These dihedral angles were used to validate MD simulations resulting in energy profiles of each torsion. The energy profiles were used to detect convenient dihedral angles and deduce constraints analogously to the work of Krieger *et al*. [68].

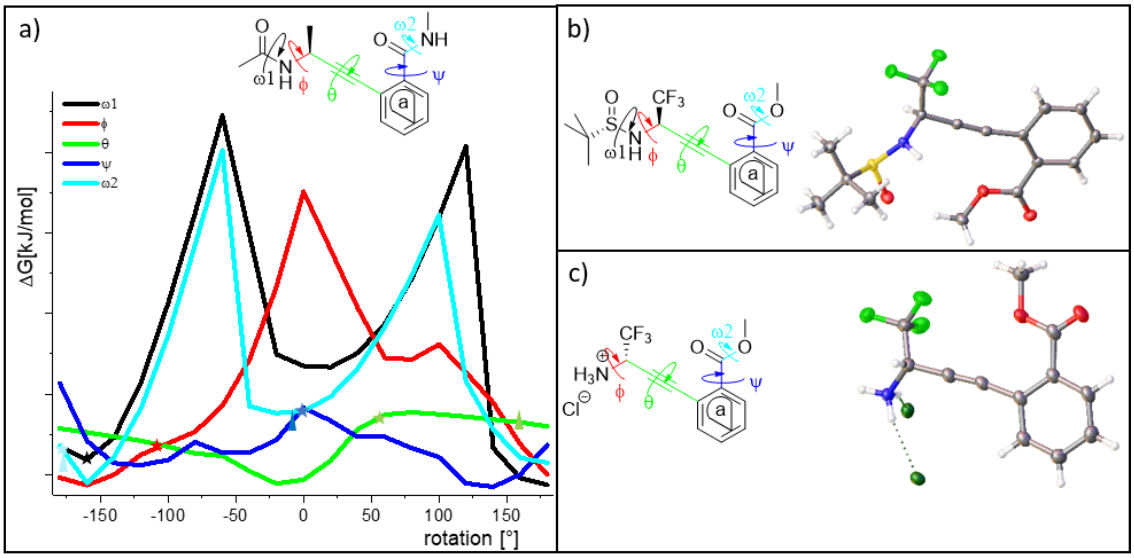


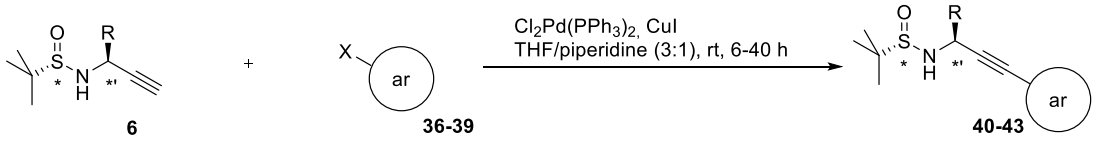
Figure 15. Comparison of the torsion angles of peptidomimetics **27**. a) Model compound, used for the MD calculation of the energy profiles of the respective torsion angles. The angles observed in the X-ray crystal structures are marked with an asterisk (L-**27n**) and a triangle (D-**31o**) in the colors, corresponding to the respective angles. b) X-ray crystal structure of compound L-**27n** (ω1 = -156°, ϕ = -107°, θ = 57°, α = 75°, ψ = −2°, and ω2 = -180°) and c) X-ray crystal structure of *N*-terminal deprotected D-**31o** (ω1 n.d., ϕ n.d., θ = 156.9°, α = 75°, ψ = −8°, and ω2 = -178°) (for more details, see Diagram EP14 and Table EP1 Experimental Part).

As expected, the energy profiles of ω1 and ω2 suggest a preference of *trans*-configured amides, as well as a stretched arrangement of the *N*-terminal moiety (large ϕ). As steric repulsions exceed electronic interactions in the MMFF94, calculation of ψ was not very accurate. However, the orientation of the ester moiety in the crystal structure increases the backbone bending giving hints for solvophobic folding. The narrow backbone angle of dipeptidomimetic **27** induces a turn motif into the chain. Since the axis between the C^{α} and the arene moiety is rotatable without any restriction, the dipeptidomimetic backbone contains at least one flexible substructure.

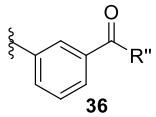
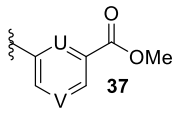
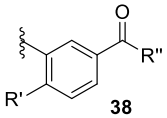
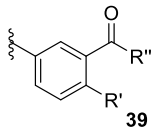
III-13. Synthesis of *meta*-substituted Aminopropynylbenzoates

Versatile substitution patterns are possible, when the carboxy moiety is in *meta*-position of the arene ring in the peptidomimetic. Under analogous *Sonogashira* cross-coupling conditions, a compound library could be prepared (Table 2) comprising compounds with diverse side chains at the propargylamide moiety, heteroarenes as well as side chains at the (hetero)arene opening a new dimension of diversity.

Table 2. Newly prepared peptidomimetics, based on *meta*-substituted arenes. The library includes compounds **40a-i** with diverse protective groups at the *C*-terminus, disubstituted pyridine derivatives **41a-c** and benzoates **42a-d** and **43a-c** with different substituents in 4- and 6-position, respectively.



6 + **36-39** → **40-43**

entry	(*,*')	**6**, R	ar	**36-39**	**40-43**, yield
a)	(*S*,*S*)	**6b**, -CH(CH$_3$)$_2$	 **36**	**36b**, X = I, R'' = OEt	**40a**, 81%
b)	(*R*,*R*)	**6c**, -CH$_2$CH(CH$_3$)$_2$		**36b**, X = I, R'' = OEt	**40b**, 98%
c)	(*R*,*R*)	**6d**, -CH$_2$CH$_2$SCH$_3$		**36b**, X = I, R'' = OEt	**40c**, 85%
d)	(*R*,*R*)	**6e**, -cyclohexyl		**36a**, X = I, R'' = OMe	**40d**, 44%
e)	(*S*,*S*)	**6c**, -CH$_2$CH(CH$_3$)$_2$		**36c**, X = I, R'' = OH	**40e**, 52%
f) [a]	(*S*,*R*)	**6o**, -C$_6$F$_5$		**36a**, X = I, R'' = OMe	**40f**, 65%
g) [a]	(*S*,*R*)	**6p**, -CF$_3$		**36a**, X = I, R'' = OMe	**40g**, 45%
h) [a]	(*S*,*R*)	**6o**, -C$_6$F$_5$		**36d**, X = I, R'' = NHCH$_2$-(3,5)F$_2$Ph	**40h**, 70%
i) [a]	(*S*,*R*)	**6p**, -CF$_3$		**36d**, X = I, R'' = NHCH$_2$-(3,5)F$_2$Ph	**40i**, 17%
j)	(*S*,*S*)	**6b**, -CH(CH$_3$)$_2$	 **37**	**37a**, X = Br, U = CH, V = N	**41a**, 58%
k)	(*R*,*R*)	**6c**, -CH$_2$CH(CH$_3$)$_2$		**37a**, X = Br, U = CH, V = N	**41b**, 79%
l)	(*R*,*R*)	**6c**, -CH$_2$CH(CH$_3$)$_2$		**37b**, X = Br, U = N, V = CH	**41c**, 90%
m)	(*S*,*S*)	**6i**, -CH$_2$CH$_2$CH$_2$CN	 **38**	**38a**, X = I, R' = -CO$_2$Me, R'' = OH	**42a**, 29%
n)	(*R*,*R*)	**6b**, -CH(CH$_3$)$_2$		**38b**, X = I, R' = -NH$_2$, R'' = OMe	**42b**, 83%
o)	(*R*,*R*)	**6b**, -CH(CH$_3$)$_2$		**38c**, X = I, R' = -N=N-Ph-4-NMe$_2$, R'' = OMe	**42c**, 7%
p)	(*R*,*R*)	**6c**, -CH$_2$CH(CH$_3$)$_2$		**38d**, X = I, R' = -N=N-Ph, R'' = OMe	**42d**, 16%
q)	(*R*,*R*)	**6e**, -cyclohexyl	 **39**	**39a**, X = I, R' = -NH$_2$, R'' = OMe	**43a**, 63%
r)	(*R*,*R*)	**6b**, -CH(CH$_3$)$_2$		**39b**, X = I, R' = -NH$_2$, R'' = OH	**43b**, 13%
s)	(*S*,*S*)	**6b**, -CH(CH$_3$)$_2$		**39c**, X = I, R' = -N=N-Ph, R'' = OH	**43c**, 11%

[a] Standard base piperidine was substituted by mild DIPEA.

In accordance to the hypothesis of Schlitz and Plenio on the size dependence of alkyne substituents on *Sonogashira* reactions [110], β-dibranched propargylamides **6b**,**e** reacted with aromatic halides **36a**,**b** in slightly lower yields than β-monobranched propargylamides **6c**,**d**. Despite the prevailing opinion the sulfur-containing side chain of propargylamide **6d** did not reduce the conversion by catalyst poisoning. In contrast to 2-iodobenzoic acid **26c**, 3-iodobenzoic acid **36c** reacted as expected without subsequent lactone formation to provide peptidomimetic **40e** in 52 % yield. This yield is lower compared to the yield of ester **40b** (98 %).

Fluorinated amino acid analogs have been incorporated in foldamers as ^{19}F NMR probes to investigate their folding and helix inversion behavior [119]. Moreover, enhanced stability, lipophilicity and dipolar moment at comparable size render fluorinated amino acid analogs important tools in drug design [120]. Consequently, considerable effort was spent on the synthesis of fluorinated dipeptidomimetic building blocks **40f-i**. The *Sonogashira* reaction of alkyne **6p** containing a trifluoromethyl moiety with ester **36a** (45 %) and amide **36d** (17 %) showed that aromatic amides obstruct conversion. Catalyst coordination or reduced solubility may account for the lower yield of amide **40i**.

Nicotinate and picolinate-based peptidomimetics **41a-c** were designed to enhance the dipole moment of the hydrophobic scaffold. In particular, nicotinate based compounds **41a**,**b** contain a dipole moment antiparallel to the amide moiety. The rather high yields (58-90 %) of the coupling products **41a-c** indicate a compensation of the lower reactivity of aromatic bromides **37a**,**b** by the reduced electron density in the pyridine rings.

In order to further modify the electronic properties of the peptidomimetics, additional functional groups were introduced in 4- (**42**) or 6-position (**43**) as side chain isosteres with a locked orientation χ. In particular, ester (**42a**) and amino moieties (**42b**, **43a,b**) were selected, as these groups allow the introduction of further versatile substituents by amide coupling. The coupling products can be further developed in the direction of helix mimetics **20**, **22** and **23** (see Chapter III-18.). As example of the versatility of this concept, side chains with modified physical properties were installed. Smart peptidomimetic **42d** represents a photoswitchable compound changing the orientation of it's terminal phenyl moiety upon irradiation with UV light. Protonation of azobenzene **42c** with an additional amino moiety in *para*-position leads to a bathochromic shift of UV absorption, rendering peptidomimetic **42c** an UV/*Vis* active pH indicator (Figure EP1, Experimental Part). Titration experiments and UV/*Vis* spectra (Diagram EP1, Experimental Part) verify a narrow pH sensitivity in physiological milieu (λ_{max}(pH<7.8) = 448 nm, λ_{max}(pH>8.2) = 469 nm). Incorporation of peptidomimetic **42c** into short peptides could give valuable information on the pH value of the environment of the corresponding peptide area. Although substituents in *ortho*-position of the halide are generally well tolerated in *Sonogashira* reactions [110], reactions with azobenzenes **38c**,**d** led to considerably reduced yields of 7-16 %.

Introduction of substituents in *ortho*-position of the ester, directing towards the *C*-terminus, of the complete peptide influences the conformation of the adjacent amide and therefore the backbone orientation. Therefore, amino moieties were attached to the benzoate, as exemplified with peptidomimetics **43a**,**b**. The introduced amino groups will enable connection of the peptidomimetic to versatile further structural elements. The yield of the *Sonogashira* reaction depends only on the protective group of the carboxylate.

III-14. Smart sterically enforced Helix Mimetics

Photoisomerizing azobenzene groups in peptide side chains were used to control the hydrogel-sol transition of amphiphilic Class A peptidomimetics by irradiation, as only the *E*-configured isomer is able to self-assemble [55]. The introduction of azobenzene units into the is a new approach to control the 3D-structure of the backbone by irradiation, as the terminal bulky phenyl group of the azobenzene **43c** is located close to the *C*-terminus. To investigate the effects of this isomerization, L-proline was linked to the dipeptidomimetic **43c** and the *N*-terminus was deprotected by acidic methanolysis to obtain the tripeptide analog **44**.

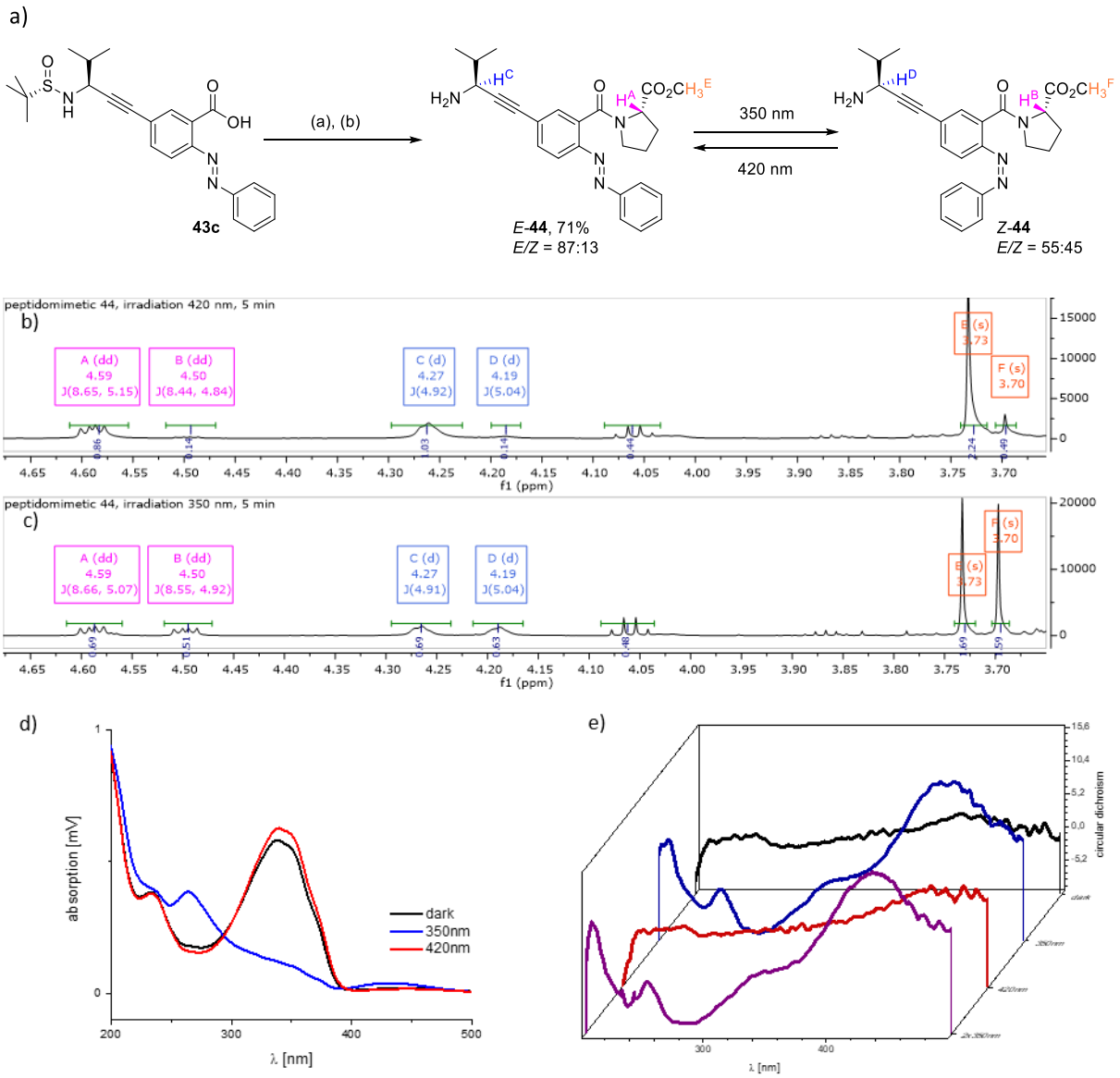


Figure 16. Introduction and effects of a photo-isomerizing side chain adjacent to the *C*-terminal amide. a) Synthesis of peptidomimetic **44**. (a) Methyl L-prolinate (2 eq), HOAt (3 eq), HATU (2 eq), DMF/DIPEA (2:1), rt, 16 h, 98 %. (b) HCl (4 M, dioxane)/MeOH (1:3), rt, 90 min, 81 % (71 % over two steps). Structures of *E*- and *Z*-**44** with marked protons. b) Part of the ^{1}H NMR spectrum (4.7-3.6 ppm) of **44** after irradiation for 5 min at 420 nm. The multipletts refer to the marked protons of *E*-**44** and *Z*-**44** in reaction scheme 17a) Integration of these signals leads to a ratio *E*/*Z*-**44** of 87:13. c) Part of the ^{1}H NMR spectrum of the same sample of **44** after irradiation for 5 min at 350 nm. Integration of the marked signals shows a ratio *E*/*Z*-**44** of 55:45. d) UV/*Vis* spectra of a sample of **44** in the dark (black curve), after irradiation for 5 min at 420 nm (blue curve) and after irradiation for 5 min at 420 nm (red curve). e) CD spectra of a sample of **44** in the dark (black curve), after irradiation for 5 min at 350 nm (blue curve), after irradiation for 5 min at 420 nm (red curve) and after a second irradiation for 5 min at 350 nm (violet curve) (More experimental details are given in Diagram EP2-6 Experimental Part).

Although UV/*Vis* spectra (Figure 16d) indicate complete and reversible *E/Z* isomerization of peptidomimetic **44** (Figure 16a), investigation by ^{1}H NMR spectroscopy (Figure 16b,c) proved only *E/Z* ratio of 87:13 (420 nm) and 55:45 (350 nm). The irradiation cycle was repeated 6 times to demonstrate the reversibility of the isomerization. The change of the azobenzene configuration was examined by CD spectroscopy (Figure 16e). A significant CD was observed in the backbone relevant region (180-300 nm) of the *E*-azobenzene *E*-**44**, indicating a distinct backbone conformation. However, a CD could not be observed for the *Z*-isomer *Z*-**44** pointing towards a loss of structure. It is assumed, that the bulky *E*-azobenzene *E*-**44** restricts conformational interconversions of the adjacent proline, while *Z*-azobenzene allows free rotation rendering dipeptidomimetic **43c** with the azobenzene scaffold a promising building block for smart sterically enforced helix mimetics.

III-15. Conformational Preference in *meta*-substituted Peptidomimetics

Reports about hydrophobic folding of 3-alkynylbenzene oligomers **17** [84,85] led to the idea, that hybrid oligomers of peptidomimetic scaffolds **40-43** are capable of similar folding. In order to analyze the geometrical properties of the scaffolds **40-43** MD simulations were performed. These simulations led to the detection of rotational constraints, which were confirmed by X-ray crystal structures of (*R*)-**40d** and (*S*)-**41a** (Figure 17).

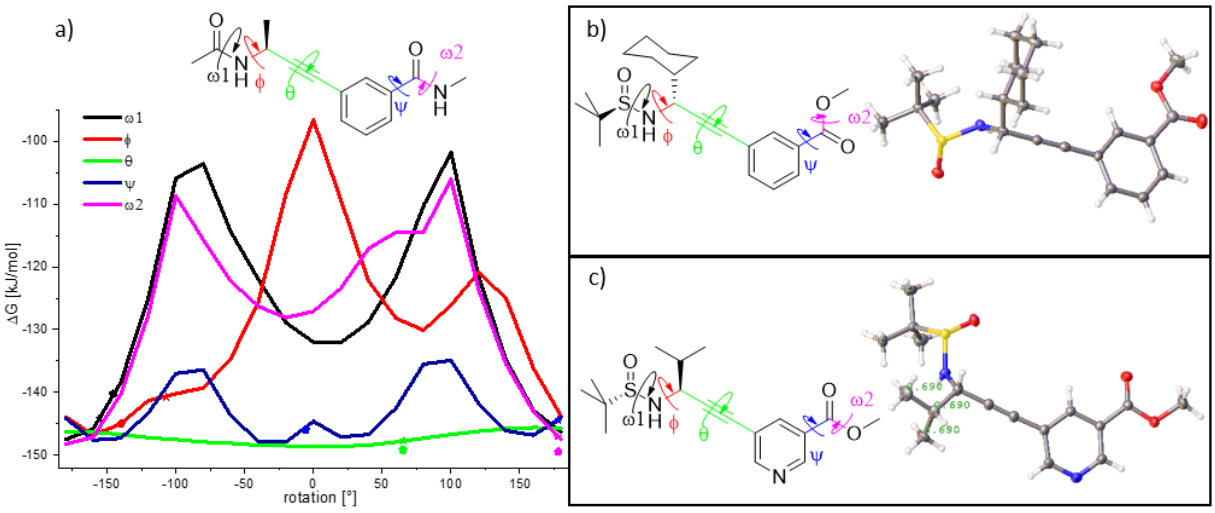


Figure 17. Comparison of the torsion angles of peptidomimetics **40d** and **41a**. a) Model compound used for the calculation of the energy profiles resulting by rotation around particular single bonds. The angles observed in the X-ray crystal structures are marked with a pentagon for D-**40d** and an asterisk for L-**41a** in the colors, corresponding to the respective angles. b) X-ray crystal structure of compounds D-**40d** (mirrored angles: ω1 = -145°, ϕ

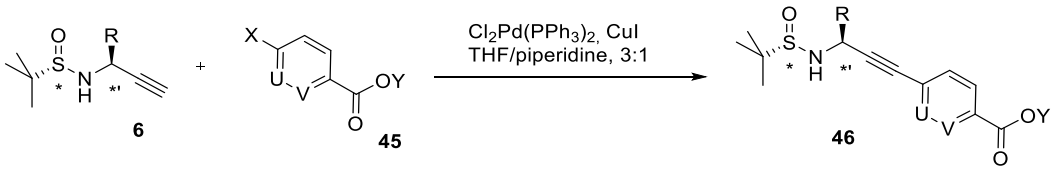
= -140°, θ = -65°, α = 122°, ψ = −5°, and ω2 = 178°). c) X-ray crystal structure of L-**41a** (ω1 = -156°, ϕ = -107°, θ = 66°, α = 120°, ψ = 180°, and ω2 = -178°) (for more details, see Table EP2 Experimental Part).

All dihedral angles (except for ψ) measured in the crystal structures are in good agreement with the energetic minima of the calculations supporting the quality of the force field calculations. Only the accurate prediction of ψ is limited due to overinterpretation of the steric repulsion effects. As expected, rotation around the single bonds θ of the alkyne is completely unobstructed enabling independent orientation of the *N*- and *C*-terminal moieties. The dihedral angles ω and ψ are estimated to be 0° or 180° defining the curve of the backbone. According to this angle hydrophobic folding (ω=ψ=0°) or a stretched orientation (ω=ψ=180°) like a helix mimetic are possible. Although the crystal structure of **40d** indicates a folding of the backbone (ψ=0°), the stretched conformation (see **41a**) is energetically favored. Interestingly, the impact of the stereocenter can be observed in the asymmetry of the energy profile resulting from rotation ϕ around the bond between amine and C^{α}-atom. The impact of chirality in helix mimetics on PPIs is subject to current investigations [93].

III-16. *para*-Substituted Arenes

In 4-(3-aminoprop-1-yn-1-yl)-benzoate based peptidomimetics **46** the C^{α}-atom and the carbonyl group are linked in a linear manner. A compound library of building blocks **46** comprising diverse side chains at the propargylamide moiety (**46a-j**) as well as (hetero)arenes in the backbone (**40k,l**) were synthesized under the same *Sonogashira* cross-coupling conditions as described above.

Table 3. Synthesis of a compound library of compounds **46** by *Sonogashira* cross-coupling of propargylamides **6** with haloarenes **45**.



entry	*/*'	propargylamide, R=		arene **45**	**46**, yield
a) [a]	-	**1**	-H	**45a**, X=I, Y=Me, U=V=CH	**46a**, 58%
b)	(*S/S*)	**6b**	$-CH(CH_3)_2$	**45a**, X=I, Y=Me, U=V=CH	**46b**, 83%
c)	(*R/R*)	**6b**	$-CH(CH_3)_2$	**45a**, X=I, Y=Me, U=V=CH	**46c**, 64%
d)	(*S/S*)	**6c**	$-CH_2CH(CH_3)_2$	**45b**, X=I, Y=Et, U=V=CH	**46d**, 94%
e)	(*R/R*)	**6c**	$-CH_2CH(CH_3)_2$	**45b**, X=I, Y=Et, U=V=CH	**46e**, 95%
f)	(*S/S*)	**6e**	-cyclohexyl	**45a**, X=I, Y=Me, U=V=CH	**46f**, 66%
g)	(*R/R*)	**6e**	-cyclohexyl	**45a**, X=I, Y=Me, U=V=CH	**46g**, 74%
h)	(*R/R*)	**6j**	$-CH_2SCH_2Ph$	**45a**, X=I, Y=Me, U=V=CH	**46h**, 11%
i)	(*R/R*)	**6m**	$-CH_2Ph$	**45b**, X=I, Y=Et, U=V=CH	**46i**, 59%
j) [b]	(*S/S*)	**6n**	-Ph	**45a**, X=I, Y=Me, U=V=CH	**46j**, 54%
k)	(*R/R*)	**6e**	-cyclohexyl	**45c**, X=Br, Y=Me, U=N, V=CH	**46k**, 2%
l)	(*R/R*)	**6e**	-cyclohexyl	**45d**, X=Br, Y=Me, U=CH, V=N	**46l**, 41%

[a] The protective group was Boc instead of *tert*-Butylsulfinyl.

[b] Mild base DIPEA was used instead of piperidine.

Aliphatic propargylamides **6b-c**,**e** were linked to the aromatic iodides **45a**,**b** to give the hydrophobic peptidomimetics **46b-j** in high yields of 64-95 %. In contrast to the hypothesis that the steric demands of the alkyne define the reactivity of *Sonogashira* reactions, conversion of Boc protected, glycine analogous propargylamide **1** provided only 58 % yield of the coupling product **46a**. The catalyst poisoning sulfur of the cysteine analogue propargylamide **6j** apparently hinders the cross-coupling reaction dramatically decreasing

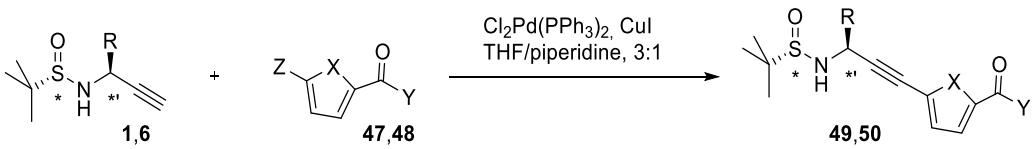
the yield of **46h** to 11 %. Bulky, electron withdrawing aromatic substituents in α- or β-position (**6m**,**n**) do not seem to interfere with the reaction procedure. The position of the *N*-atom in the arene ring has a considerable effect on the yield of coupling compounds. The more reactive nicotinic derivative **45c**, which is isoelectronic to an acetyl bromide afforded the cross-coupling product **46k** in only 2 % yield. On the other hand, less reactive picolinate **45d** gave 41 % yield of the coupling product **46l**. The direction of the induced dipole moment of the pyridine derivatives **46k** and **46l** is not predefined due to free rotation of the backbone around the linear axis. However, the additional *N*-atom represents a coordination site to influence the conformation of the adjacent carbonyl moiety in analogy to the hydrogen bond guided helix mimetics **23** [97,98] and **24** [99].

The locked backbone angle of 180° caused by the substitution pattern of the arene, reduces the rotational degree of freedom of the peptidomimetics **46** by one assembling θ and ψ on one axis. Preferred dihedral angles were identified by MD simulations and X-ray crystal structures of **46j**, **52b** and **55c** (Figure EP2 and Table EP3, Experimental Part) and suggest a straight, unbent conformation. Certainly, formation of foldamers cannot be expected by oligomerization of this type of building blocks. However, formation of helix type superstructures might be possible. Very recently, the peptidomimetics **46** were used to prepare HDAC inhibitors by mimicking the acetylated lysine moiety (see Chapter V, SAR of Propargylamine-Based HDAC Inhibitors [2]).

III-17. Heteroaromatic Derivatives

Whereas the backbone curvature of benzoate based scaffolds is limited to three angles of 75° (*ortho* substituted benzoates **27a-q**), 122° (*meta*-substituted benzoates **40-43**) and 175° (*para*-substituted benzoates **46a-l**), asymmetric, distorted heteroaromatic five-membered rings access multiple different angles. This work focuses on 2,5-disubstituted furan- (129°) and thiophene derivatives (147°). For this purpose, the furan- and thiophenecarboxylic derivatives were brominated to obtain aromatic halides **47a** and **48a,b** (Table 4).

Table 4: Preparation of furan- and thiophene-based peptidomimetics.



entry	(*/*')	propargylamide		aromatic	yield
a)	(*S*/*S*)	**6b**	$CH(CH_3)_2$	**47a**, X=O, Z=Br, Y=OMe	**49a**, 63%
b) [a]	-	**1**	H	**48a**, X=S, Z=Br, Y=OMe	**50a**, 64%
c)	(*S*/*S*)	**6b**	$CH(CH_3)_2$	**48a**, X=S, Z=Br, Y=OMe	**50b**, 21%
d)	(*R*/*R*)	**6c**	$CH_2CH(CH_3)_2$	**48a**, X=S, Z=Br, Y=OMe	**50c**, 44%
e)	(*R*/*R*)	**6e**	cyclohexane	**48a**, X=S, Z=Br, Y=OMe	**50d**, 23%
f)	(*R*/*R*)	**6b**	$CH(CH_3)_2$	**48c**, X=S, Z=I, Y=OH	**50e**, 50%

[a] The protective group was Boc instead of *tert*-Butylsulfinyl.

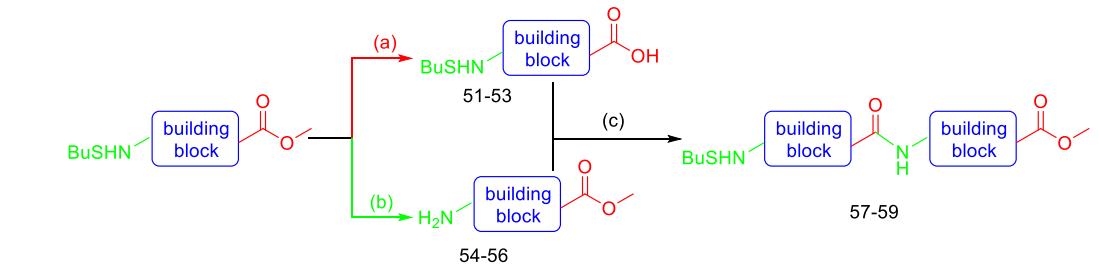
In the subsequent *Sonogashira* reaction, the conversion of bromo thiophenes **48a,b** resulted in considerably lower yields of coupling products **50** (21-63 %) than the conversion of the corresponding bromo furane **47a** (64 %). It is possible, that the *S*-atom of the thiophene derivatives **48** reduces the activity of the Pd catalyst leading to lower yields of peptidomimetic **50**.

The dipole moment, which is added by the furan moiety of **49a** to the backbone is likely to be parallel to the adjacent carbonyl enhancing the backbone curvature similar to the 3D structure of Teroxazoles **21** (Figure 11) [95]. The conformational preference of **49** and **50** is supported by MD simulations of the dihedral angles and the X-ray crystal structure of **49a** and **56b** (Figure EP3, EP4 and Table EP4, EP5, Experimental Part). The rotation of the structure determining dihedral angle ψ is predicted accurately in accordance to the X-ray crystal structures. The energy minimum conformations suggest a turn and a

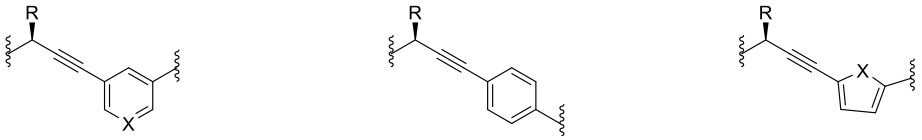
cumulation of hydrogen acceptors on one face of the backbone. Similar to *meta*-substituted benzoate derivatives **27**, a hydrophobic folding of oligomers from scaffolds **49** and **50** can be expected as reported in 3-alkynylbenzene oligomers **17** [84,85].

III-18. Prop-1-yn-1-yl Benzoates as Helix Mimetics

Combining a stretched, rigid backbone scaffold with low bending tendency, the prop-1-yn-1-yl benzoate based peptidomimetics of this work qualify for applications in helix mimetics. In order to investigate relevant parameters, like the distance between side chains and their relative orientation towards each other, hybrid dimers were formed by connecting different peptidomimetics described in previous passages (Chapter III-9,13,16,17). The designed oligomers should contain amides and alkynyl aryl moieties in an alternating fashion. The orthogonal protective groups of the *N*- and *C*-termini were cleaved off by acidic methanolysis (*tert*-butylsulfinyl group) and saponification with LiOH (ester) prior to peptide coupling, using uronium coupling agents TBTU or HATU (Figure 18).



building block =



carboxylic acid	**51a**, X=CH, R=(*R*)-CH_2CHMe_2, 94%	**52a**, R=(*S*)-$CHMe_2$, n.d.	**53a**, X=O, R=(*S*)-$CHMe_2$, 68%
	51b, X=N, R=(*S*)-$CHMe_2$, 70%	**52b**, R=(*R*)-CH_2CHMe_2, 94%	
amine	**54a**, X=CH, R=(*R*)-CH_2CHMe_2, 93%	**55a**, R=(*S*)-$CHMe_2$, 93%	**56a**, X=O, R=(*S*)-$CHMe_2$, quant
	54b, X=N, R=(*S*)-$CHMe_2$, quant	**55b**, R=(*R*)-CH_2CHMe_2, quant	**56b**, X=S, R=(*R*)-CH_2CHMe_2, quant
dimer	**57a**, X=CH, R=(*R*)-CH_2CHMe_2, 71%	**58a**, R=(*S*)-$CHMe_2$, 87%	**59a**, X=O, R=(*S*)-$CHMe_2$, 35%
	57b, X=N, R=(*S*)-$CHMe_2$, 58%	**58b**, R=(*R*)-CH_2CHMe_2, 19%	

Figure 18. Oligomerization of wide angled dipeptidomimetics **27**. (a) Aqueous LiOH (1 M, 3 eq)/MeOH (1:2), 0 °C, 12 h. (b) HCl(dioxane, 4 M, 4 eq), MeOH (15 mL), 4-8 h, rt. (c) TBTU or HATU (3 eq), HOBt or HOAt (2 eq), DIPEA (6 eq), DMF (2-6 mL), rt, 16 h.

Homochiral dimers of *meta*- (**57a**,**b**) and *para*-substituted benzoates (**58a**,**b**) as well as the furan-based dimer **59a** were prepared in acceptable to high yields (19-87 %). However, most attempts on a dimerization of dimers **58** and **59** repeating the synthesis cycle of Figure 18 failed. The low conversion rate of the dimers compared to the monomers **40**-**43**, **46** and **50** is attributed to their decreased polarity causing aggregation and precipitation. Only 4-(3-aminoprop-1-yn-1-yl) benzoate **46e** could be oligomerized into tetramer **60** in a remarkable yield of 23 %, referred to dimer **57a** which had been obtained in 71 %.

Comparison of the CD spectra of the monomers and the dimers visualized significant differences (Diagram EP9-EP13, Experimental Part). All (*S*)-configured monomers show only a small local minimum at 190-210 nm. However, the corresponding dimers led to more complex CD spectra with an additional 5- to 10-fold more intensive local minimum at 220-250 nm and a local maximum of similar intensity at 250-280 nm. (*R*)-Configured peptidomimetics generate mirror-image CD spectra. Independent on the concentration, the CD effects of the dimers are enhanced in polar solvents (e.g. TFE) and weakened in nonpolar solvents (e.g. CH_3CN), suggesting intermolecular solvophobic interaction similar to the aggregation reported for arylethynenes **17** [84,85] and clickamer **18** [86]. Elongation of the chain length leads to stronger interactions and thus reduced solubility, which requires the introduction of polar groups. Nicotinates, like **57b**, possess a dipole moment, oriented antiparallel to the amide, which increases the polarity but eliminates completely the CD effects. It is assumed, that intermolecular hydrophobic interactions occur between nonpolar substructures of the backbone. Due to free rotation around the alkyne axis, the side chains can assemble on one or more faces of the helix axis. In contrast, the dipole moment of the furan based peptidomimetics such as **59a** is oriented parallel to the amide, which enhances the CD effect in both polar and nonpolar solvents. Presumably, the increased polarity contrast between the two faces of helix mimetic **59a** assist the amphiphilic agglomeration behavior.

The most important parameter for the evaluation of helix mimetics is the distance between two side chains $C^{\alpha i}$-$C^{\alpha i+1}$. This distance defines the number of amino acids bypassed by the mimetic (Figure 19).

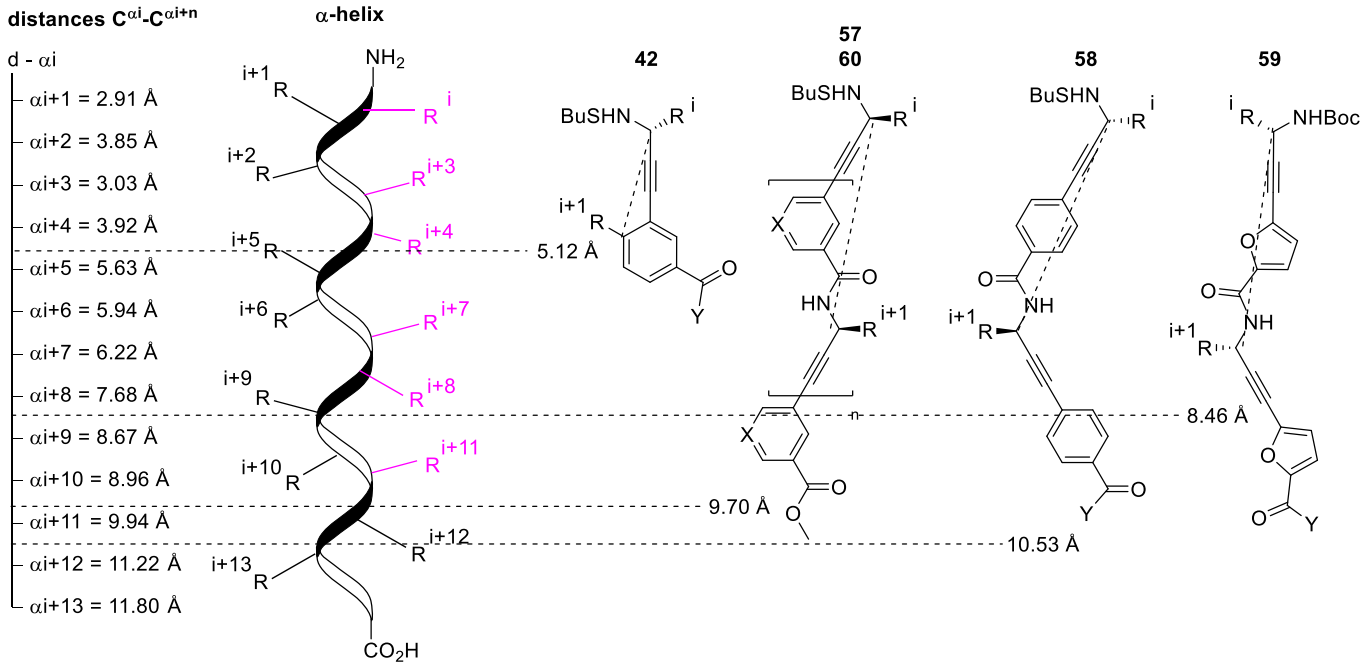


Figure 19. Comparison of the distances between different side chains, $C^{\alpha i}$-$C^{\alpha i+n}$ of the helix mimetic scaffolds of this work with a canonical α-helix (parallel aligned residues are marked). From left to right: **42a**, R^i=(*S*)-$(CH_2)_3CN$, R^{i+1}=CO_2Me, Y=OH. **42b**, R^i=$CHMe_2$, R^{i+1}=NH_2, Y=OMe. **42c**, R^i=$CHMe_2$, R^{i+1}=NN-Ph-4-NMe_2, Y=OMe. **42d**, R^i=CH_2CHMe_2, R^{i+1}=NN-Ph, Y=OMe. **57a**, X=CH, R^i=R^{i+1}=(*R*)-CH_2CHMe_2, n=1. **57b**, X=N, R^i=R^{i+1}=(*S*)-$CHMe_2$, n=1. **60**, X=CH, R^i=R^{i+1}=(*R*)-CH_2CHMe_2, n=3. **58a**, R^i=R^{i+1}=$CHMe_2$, Y=OH. **58b**, R^i=R^{i+1}=CH_2CHMe_2, Y=OEt. **58c**, R^i=R^{i+1}=CH_2CHMe_2, Y=OH. **59a**, R^i=R^{i+1}=$CHMe_2$, Y=OMe. **59b**, R^i=R^{i+1}=$CHMe_2$, Y=OH. The given distances were calculated using MMFF94 and are correlated with the distances measured in available X-ray crystal structures.

The residues R^i, R^{i+1}, $R^{i+3/4}$, $R^{i+7/8}$ and R^{i+11} of an α-helix which are oriented on the same face enabling PPI are marked in Figure 19. Scaffold **42** comprises two side chains in one monomer, imitating one helix turn. The distance of the two side chains ($C^{\alpha i}$-$C^{\alpha i+1}$ 5.12 Å) is slightly longer than in the helix ($C^{\alpha i}$-$C^{\alpha i+4}$ 3.92 Å). The shorter distance in the helix is compensated by the locked angle χ directing residue R^{i+1} towards the *N*-terminus. In dimers **57** and the tetramer **60** only one benzene moiety of the backbone can be correlated with the R^{i+3} position of the helix as they do not contain an aromatic side chain. The $C^{\alpha i}$-$C^{\alpha i+1}$ distance between the propargylic side chains of two monomers in **57** equals the distance of R^i-R^{i+11} of an α-helical undecapeptide, representing three helix turns. Altogether, *meta*-substituted benzoate scaffolds **57** and **60** represent promising α-helix mimetics. The $C^{\alpha i}$-$C^{\alpha i+1}$ distance of the stretched *para*-substituted scaffolds **58** also correlates with the distance between residues R^i and R^{i+11} of an α-helix. Despite its favored dipole moment, leading to the desired amphiphilic backbone character, the side chain arrangement of furan-

based scaffold **59** do not reproduce the side chains for the PPI of one α-helix face. Their $C^{\alpha i}$-$C^{\alpha i+1}$ distance is only comparable to the R^{i}-R^{i+6} distance of a 3_{10}-helix (7.53 Å), which is in good accordance to two turns.

Although free rotation around the alkyne axis enables the adoption of each relative orientation of the helix mimetic side chains, the chirality of the C^{α} has a local impact on the conformation. The asymmetric energy profile of the dihedral rotation around ϕ suggests constraints in the conformation of ϕ and χ which control the interaction potential of the side chain. This approach of helix imitation combines the free rotation of unselective sterically enforced mimetics (see Chapter III-7) with the rare character of chirality, which is expected to severely influence the PPI of helix mimetics [93]. An important advantage of the presented structures is the direct connection of the versatile building blocks by *Click* reactions.

III-19. Propargylamine-Based Mimetics of α,α- and α,β-Dipeptides

The aromatic moiety of the discussed peptidomimetics is optimal for the adjustment of almost any desired angle in the backbone by application of different (hetero)aromatic substitution patterns. Unfortunately, the preparation of aromatic precursors with amino acid side chain analogous residues is elaborate. Propargylamine derived olefins or triazoles offer versatile options to introduce a second substituent, representing innovative analogues to α,α- or α,β-dipeptides (overview in Figure 20).

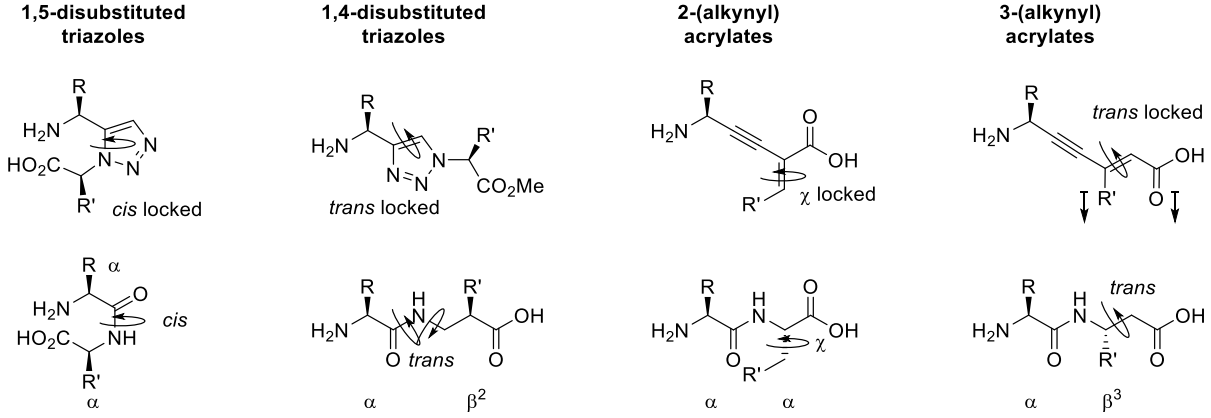
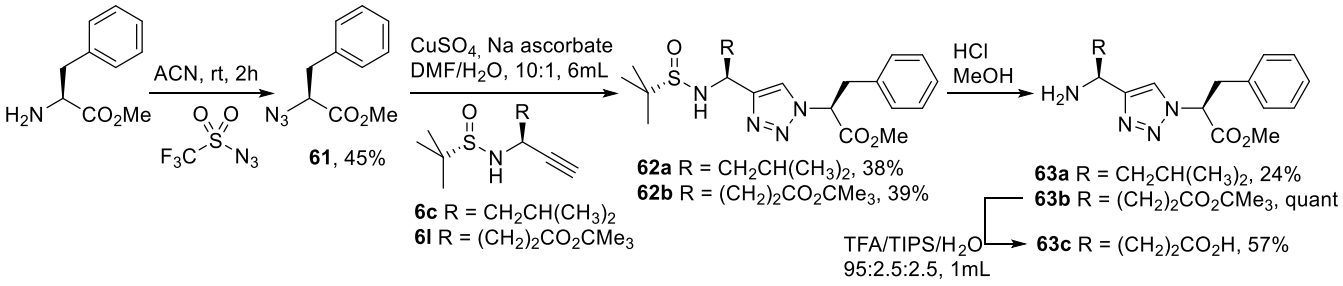


Figure 20. Propargylamine based triazoles and propargylamine substituted olefins as peptidomimetics of α,α- and $\alpha,\beta^{2/3}$-dipeptides.

The *cis*-configuration of the amide moiety and its dipole moment are well imitated by 1,5-disubstituted triazoles inducing a helix turn to the backbone, as very recently reported by Kracker *et al*. [75]. 1,4-Disubstituted triazoles reproduce the dipole moment, planarity and alignement of a *trans*-configured amide. The additional backbone atom evokes accurate analogy to α,β^2-dipeptides. Oligomerization of such scaffolds on solid phase is a well-established approach to generate versatile triazolamers [121]. Investigation of their secondary structure by ROESY experiments revealed an *anti*-conformation of the triazoles, leading to a zigzag structure with parallel axial orientation of side chains R^i and R^{i+2} forming an ideal β-strand mimetic [122]. As HIV-1 protease preferably converts such β-strand motifs, oligo phenylalanine analogous triazolamers have been explored as potent HIV-1 protease inhibitors with IC_{50}-values in the low μM range [78]. The side chain diversity of this type of triazole-based peptidomimetics as well as oligomers were extensively expanded by Tanja Fröhr [123]. Dipeptidomimetics **63** (Scheme 1) contribute to the side chain diversity of the important triazole-based peptidomimetic structure, imitating important natural dipeptides.



Scheme 1. Synthesis of triazole-based peptidomimetic **63** as analogs of a potential hydrogelation inducer (**63a**) and of the synthetic sweetener aspartam (**63c**).

Azide-transfer to methyl (*S*)-phenylalanine gave the *C*-terminal moiety **61**, which underwent a [3+2]-cycloaddition with the propargylamide analogs of leucine **6c** (38 %) and glutamic acid **6l** (39 %). Acidic methanolysis successfully cleaved off the *N*-terminal *tert*-butyl sulfinyl group of α,β^2-dipeptide analogs **62a** and **b**. Further cleavage of the *tert*-butyl ester of **63b**, however required harsher conditions (Scheme 1).

The dipeptide H_2N-Leu-Phe-OMe has been reported to self-assemble to a nanofiber network inducing hydrogelation at extraordinaryly low concentrations (2.3 mM, 0.07 % w/v) [124]. Using this nanofiber network led to a method to remove dyes and heavy metal ions from water by diffusion and hydrogel-sol transition [124]. Peptidomimetic **63a** was

designed to mimic the properties of the dipeptide. Therefore, the reported gelation experiments were recapitulated with peptidomimetic **63a**. However, the rigidity and increased hydrophobicity of **63a** led to a much higher minimum gelation concentration of 22-32 mM (50-75 mg mL^{-1}) and frequent precipitation. When the solvent was changed to CH_2Cl_2 or ^{i}PrOH, gelation was observed at concentrations lower than 2 mM (<5 mg mL^{-1}), while in other organic solvents solutions (MeOH) or suspensions (Et_2O, $CHCl_3$, CH_3CN, EtOAc, acetone) were formed. Apparently, the nanostructures responsible for the gelation differ from the nanofibers, which the peptide-based template forms in aqueous environment (see Picture EP2, Experimental Part).

Peptidomimetic **63c** was designed as analogue to the natural dipeptide H_2N-Asp-Phe-OMe (aspartame), which is an FDA-approved synthetic sweetener E951 tasting about 200-fold sweeter than saccharose. The impact of the structural abstraction on the taste receptor has to be examined by a recently published assay, which investigates in vitro the interaction of sweeteners with the Class C G protein-coupled receptor subunits TAS1R2 and TAS1R3 [125].

Connection of propargylamides to acrylates affords versatile α,α-dipeptidomimetics with considerably (50 %) reduced rotational freedom in the backbone and a locked angle χ fixing the side chains in a particular orientation (see Figure 20). *Sonogashira* type cross-coupling of alkynes with 2-bromo acrylates was reported for inert substrates, i.e. alkynes and acrylates with stabilizing substituents [126–128].

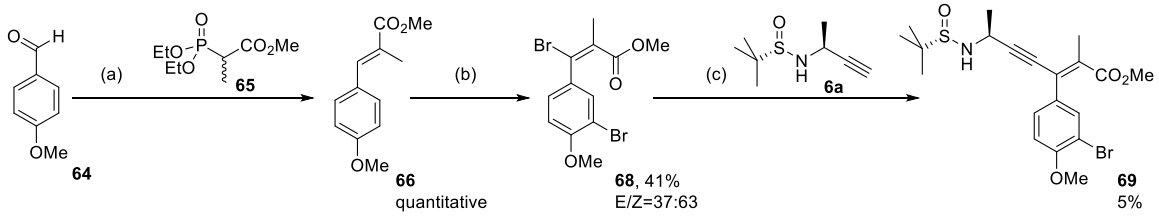
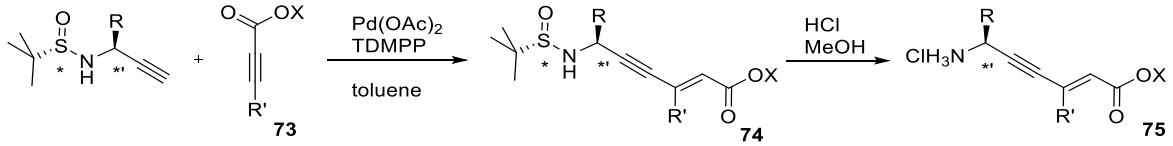


Figure 21. First approach on the preparation of 3-(alkynyl)acrylates as α,$β^3$-dipeptidomimetics. (a) ^{n}BuLi, THF, -78 °C, overnight. (b) 1.) Br_2, CH_2Cl_2, -78 °C, 2-6 h. 2.) KO^{t}Bu, THF, 0 °C, overnight. (c) $PdCl_2(PPh_3)_2$, CuI, THF/piperidine (3:1), rt.

The β-halogenated acrylates **68** were prepared by addition of Br_2 to methyl acrylate **66** affording 2,3-dibromopropanoates **67** and subsequent HBr elimination. The aromatic of **66** was also brominated under these conditions. Cross-coupling reactions of propargylamides

6 with α-bromoacrylates under the described *Sonogashira* conditions do not result in the desired 2-(alkynyl)acrylates since fast comproportionation occurs [129]. Only the coupling of alanine analogous propargylamide **6a** and brominated olefin **68** provided dipeptidomimetic **69** in a very low yield of 5 %. Recently, Trost *et al.* [130] reported the synthesis of 3-(alkynyl)acrylates by hydroalkynylation of propynoates. Employing our propargylamides **6** in this reaction will result in 3-(alkynyl)acrylates **74**, which can be considered as mimetics of α,β^3-dipeptides as displayed in Figure 20. In Table 5, α,β^3-dipeptidopeptidomimetics prepared in this thesis are summarized.

Table 5: Synthesis of 3-(alkynyl)acrylates **74** by hydroalkynylation of propynoates **73** as α,β^3-dipeptidomimetics. Cleavage of the *tert*-butylsulfinyl protective group by acidic methanolysis usually proceeded quantitatively.



entry	(*/*')	Propargylamide, R=	acceptor alkyne **73**	**74**, yield
a) [a]	-	**1**, H	**73b**, R'=Ph, X=Me	**74a**, 87%
b)	(*S,S*)	**6c**, $CH_2CH(CH_3)_2$	**73b**, R'=Ph, X=Me	**74b**, 45%
c)	(*S,S*)	**6e**, cyclohexyl	**73b**, R'=Ph, X=Me	**74c**, 64%
d)	(*S,S*)	**6l**, $CH_2CH_2CO_2C(CH_3)_3$	**73b**, R'=Ph, X=Me	**74d**, 40%
e)	(*S,S*)	**6c**, $CH_2CH(CH_3)_2$	**73a**, R'=Me, X=Et	**74e**, 76%
f)	(*S,S*)	**6e**, cyclohexyl	**73a**, R'=Me, X=Et	**74f**, 69%
g)	(*R,R*)	**6n**, Ph	**73a**, R'=Me, X=Et	**74g**, 0%
h)	(*S,S*)	**6c**, $CH_2CH(CH_3)_2$	**73c**, R'=$(CH_2)_5CH_3$, X=Me	**74h**, 18%
i)	(*S,S*)	**6e**, cyclohexyl	**73d**, R'=$CH_2OCO_2CH_3$, X=Me	**74i**, 47%
j)	(*S,S*)	**6b**, $CH(CH_3)_2$	**73e**, R'=CO_2CH_3, X=Me	**74j**, 8%
k)	(*S,S*)	**6c**, $CH_2CH(CH_3)_2$	**73e**, R'=CO_2CH_3, X=Me	**74k**, 11%

[a] The protective group was Boc instead of *tert*-butylsulfinyl.

Propynoate precursors **73** with side chains analogously to substituents of proteinogenic amino acids were accessed by reaction of respective lithiated alkynes with methyl chloroformate [130]. Under the reaction conditions developed by Trost *et al.*, aromatic propynoate **73b** gave stable dipeptidomimetics **74a-d** in yields of 40-87 % in dependence on the reactivity of propargylamides **1** and **6**. The hydroalkynylation reaction of the

propargylamide **6n** with an electron withdrawing phenyl substituent in C^{α}-position led to the desired product, which subsequently underwent a non-base-induced enimine-rearrangement (Chapter III-20). The reactivity of propynoates **73a** and **c** with aliphatic side chains and propynoates **73d** with an additional polar functional group in the side chain seems to depend on the size of the substituent. Thus, propynoate **73d** with the large aliphatic ^{n}hexyl group in the side chain afforded only 18 % of **74h**. The low yield may be attributed to the size of the ^{n}hexyl substituent and agglomeration and reduced solubility of the starting material **73c**. Butynedioate **73e** with two ester moieties at the triple bond did not give a clear transformation. The desired addition products **74j** and **74k** were obtained in only 8-11 % yields out of a complex mixture of reaction products. In order to prepare dipeptidomimetics **75** with a free amino moiety capable of peptide coupling, the *tert*-butylsulfinyl protective group was cleaved off by acidic methanolysis to afford aminoesters **75** in quantitative yields. Moreover, the methyl ester of the glycine analog **74a** was hydrolyzed with LiOH to give the free acid for an amide coupling. Due to the structural similarity of **75b** to **63a** and the superhydrogel dipeptide H-Leu-Phe-OMe the formation of a hydrogel was investigated. However, despite the structural relationships, the formation of a hydrogel could not be observed, yet. After cleavage of the *tert*-butyl ester of **75d** with TFA, the aspartam (H-Asp-Phe-OMe) analogous peptidomimetic **75l** was achieved as potential artificial sweetener in a yield of 24 %.

In order to detect energetically favored conformations of dipeptidomimetics **75**, MD simulations were performed for a model compound and X-ray crystal structures of **75e** and **75f** were recorded (Figure 22).

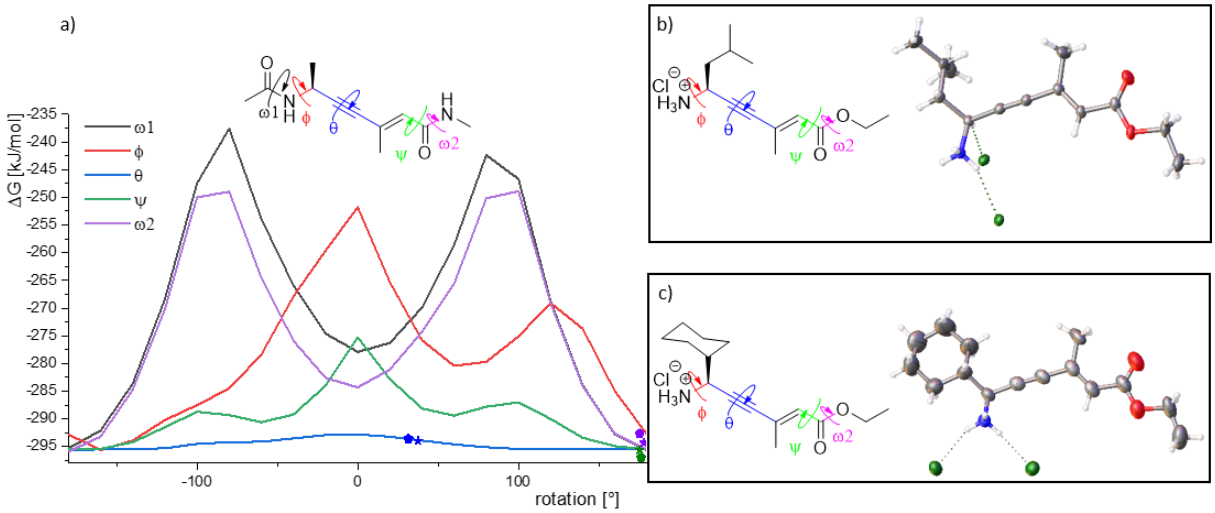


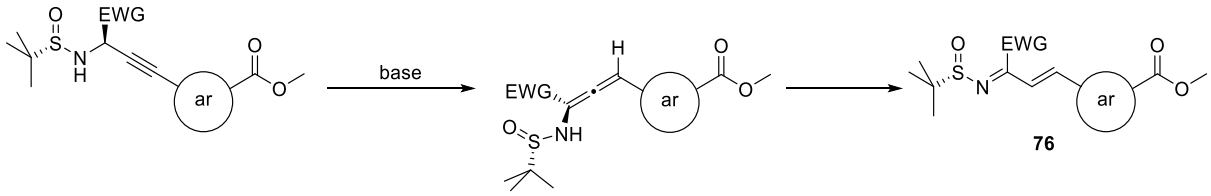
Figure 22. Comparison of the torsion angles of dipeptidomimetics **75e** and **75f**. a) Calculated energy profiles resulting from rotation of the given model compound around various single bonds. The angles observed in the X-ray crystal structures are marked with a pentagon (**75e**) and an asterisk (**75f**) in the colors corresponding to the respective bonds. b) X-ray crystal structure of compound **75e** (ω1 n.a., ϕ n.a., θ = 29°, α = 176°, ψ = 180°, and ω2 = 179°). c) X-ray crystal structure of compound **75f** (ω1 n.a., ϕ n.a., θ = 37°, α = 175°, ψ = 176°, and ω2 = 176°) (for more details, see Table EP6 Experimental Part).

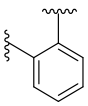
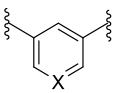
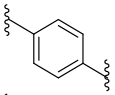
The X-ray crystal structures of both **75e** and **75f** reveal a short distance between the carbonyl *O*-atom and one proton of the CH_3-group in C^{β}-position. The distances in the isobutyl- and cyclohexyl derivatives **75e** and **75f** are 2.25 Å and 2.68 Å, respectively. This H-bond additionally stabilizes the energetically favored *trans*-configuration of the double bond with a defined backbone torsion angle ψ. Although the free rotation around the alkyne axis θ allows each relative orientation of the side chains, the X-ray crystal structures suggest an almost parallel arrangement of the isobutyl or cyclohexyl side chain and the methyl group with dihedral angles of -30° for **75e** and -18° for **75f**. In contrast to the zigzag shaped β-strand preferably formed by triazolamers [122], 3-(alkynyl)acrylates arrange their nonpolar regions on one face inducing an amphiphilic character to the molecule. Moreover, the parallel alignment of side chains led to the orientations of *C*- and *N*-termini in the same direction imposing a bend to the backbone. Compared to one face of an α-helix (see Figure 19), the distances between the side chains R^i and R^{i+1} are 4.10 Å for **75e** and 4.08 Å for **75f**, which is in good accordance to one helical turn ($d_{(C\alpha i\text{-}C\alpha i+4)}$: 3.92 Å). These structural features render scaffolds **74** and **75** promising structural helix mimetics. A convenient feature of the presented approach are the versatile options to combine various functional groups in the side chains of both moieties, independently.

III-20. Propargylamides rearrange to Enimines

First observations of an enimine rearrangement have been published as part of this work under the title "Asymmetric synthesis of propargylamines as amino acid surrogates in peptidomimetics" [1]. Propargylamides substituted with an electron withdrawing group in C^{α}-position are able to rearrange under basic conditions into α,β-unsaturated sulfinylimines. At first, deprotonation in $C^{\alpha}H$ position initiates the rearrangement into a sulfinamido substituted allene, which further rearranges into α,β-unsaturated sulfinylimine **76** (concrete examples in Table 6). Similar rearrangements have been observed in propargyl alcohols [131].

Table 6. Rearrangement of various propargylamides with an electron withdrawing group (EWG) in C^{α}-position into α,β-unsaturated sulfinylimines **76a-f**. Yields refer to isolated rearranged products.



entry	propargylamide, side chain	*C*-terminal moiety	conditions	enimines 76, yield
a)	**27l**, EWG=C_6F_5	ar= 	base=piperidine	**76a**, 43%
b)	**27o**, EWG=CF_3	ar=	base=piperidine	**76b**, 24%
c)	**40g**, EWG=CF_3, X=CH	ar= 	base=piperidine	**76c**, 84%
d)	**41d**, EWG=CF_3, X=N	ar=	base=DIPAH	**76d**, 3%
e)	**46j**, EWG=Ph	ar= 	base=piperidine	**76e**, 98%
f)	**74g**, EWG=Ph	ar= 	no base	**76f**, 13%

Various sulfinamides with electron withdrawing groups such as phenyl, trifluoromethyl or pentafluorophenyl in C^{α}-position underwent an enimine rearrangement upon treatment with piperidine. The conversion was complete within 10 min (checked by TLC and analytical HPLC). Sometimes, decomposition during workup and purification reduced the yields to 24-98 %. In the absence of acidifying substituents in C^{α}-position (e.g. cyclohexyl in **46f**), even strong bases such as KOH, KO^{t}Bu or LDA could not induce the enimine rearrangement. Activated olefin based peptidomimetics with EWG substituted C^{α} (e.g. **74g**) even underwent the rearrangement under neutral conditions at rt making the isolation

of hydroalkynylation product **74g** impossible. Cleavage of the *N*-terminal *tert*-butylsulfinyl group by acidic methanolysis resulted in the α,β-unsaturated imines **77c,f**. Since imines **77c** and **77f** underwent further hydrolysis, the α,β-unsaturated ketones **78c,f** were isolated by crystallization. The X-ray crystal structures of conjugated ketones **78c,f** are presented in the Experimental Part. The extended π-system of the α,β-unsaturated sulfinylimines **76** allows monitoring the progress of the enimine rearrangement by UV/*Vis* spectroscopy or optically with the naked eye (Figure 23).

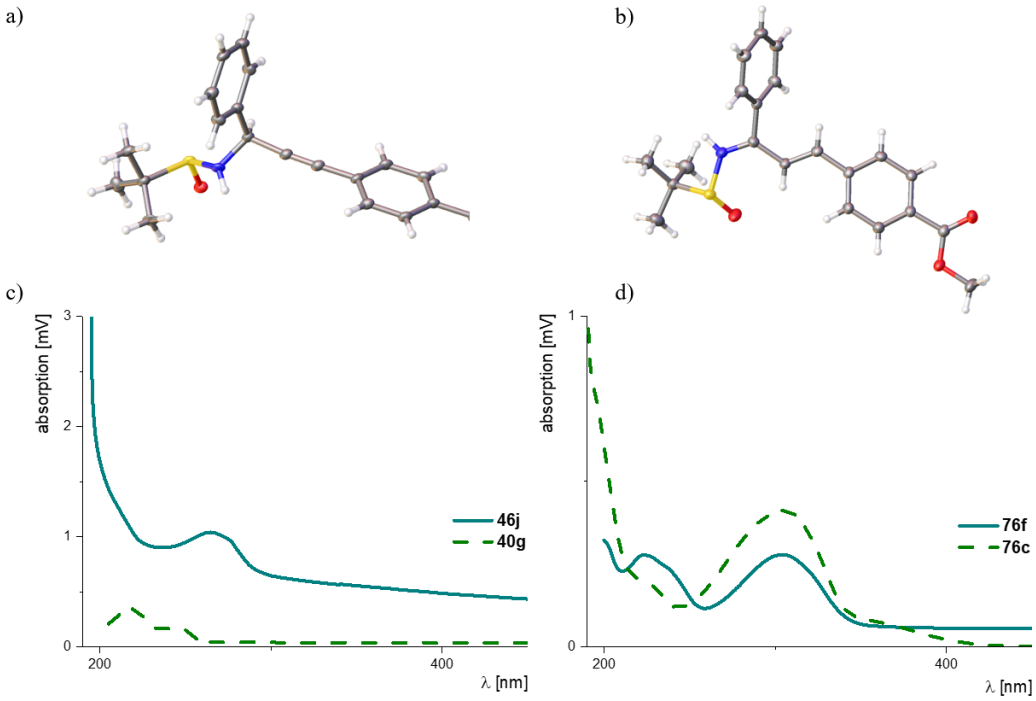


Figure 23. Visualization of the enimine rearrangement. a) X-ray crystal structure of propargylamide **46j**. b) UV/*Vis* spectra of propargylamides **40g** and **46j** (see also Diagram EP2 Experimental Part). c) X-ray crystal structure of rearrangement product **76e**. d) Exemplary UV/*Vis* spectra of α,β-unsaturated sulfinylimines **76c** and **76e** (also see Diagram EP7 Experimental Part).

The locked antiparallel orientation of side chains R^i (EWG) and R^{i+1} (arene) in the α,β-unsaturated sulfinylimines **76** is confirmed by X-ray crystal structures of **76e** and **78c,f**. This structure corresponds to the zigzag structure adopted by β-strand analogous 1,4-disubstituted triazolamers [122]. Both, the rearrangement of the alkyne into the allene and the subsequent tautomerism to the α,β-unsaturated sulfinylimine are irreversible. A reversible enimine rearrangement would lead to epimerization in C^{α}-position. Thus, due to the irreversibility, epimerization could be excluded.

III-21. Conclusion

In this part of the thesis, several peptidomimetics with great diversity were prepared and characterized. Variations have been realized with respect to the total length and the angle associated with the arene moiety. Conformational preferences were elucidated by MD simulations and X-ray crystal structure analysis. The peptidomimetics were classified as foldamers and helix mimetics. The conformational preferences could be influenced by the photoswitchable configuration of an azobenzene unit introduced into the backbone. α,β-Dipeptide analogues were realized in the form of triazoles and alkynes linked to olefins. In the course of 3-(alkynyl)acrylate synthesis, the substrate scope of the recently reported hydroalkynylation reaction was enhanced. Special dipeptide sequences were selected as model compounds for the design and synthesis of functional analogues, such as the synthetic sweetener aspartame or the super hydrogel forming leucine-phenylalanine dimer. An enimine rearrangement was observed and investigated. This reaction occurred in the course of the synthesis of peptidomimetics with electron withdrawing substituents in C^{α}-position of propargylamides. The presented dipeptidomimetics are elementary for the preparation of β-turn mimetics, HDAC inhibitors and RGD mimetics, which will be subject to chapters IV, V and VI.

III-22. References (29-131)

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IV Propynyl-Aryl Scaffolds as Turn Motif Mimetics

The low flexibility of the Class B peptidomimetics introduced in Chapter III can be exploited to define the orientation of the side chains and the *N*- and *C*-termini. Herein, novel turn motif mimetics were developed by expanding the monocyclic aromatic moiety to a naphthalene system, a flexible biphenyl unit and a photoswitchable azobenzene moiety. Additionally, the propargylamide moiety was aminated to afford hydrazine and hydrazone derivatives. Orientation of *N*- and *C*- termini of the novel scaffolds was examined by ^{1}H NMR spectroscopy, temperature coefficient $\Delta\delta/\Delta T$, CD spectroscopy and X-ray crystal structure analysis.

IV-1. The Concept of Turn Motif Inducers

Peptide turn motifs usually terminate β-sheet structures, leading to H-bonds between antiparallel peptide strands as well as spatial proximity between the *C*-atoms in α-position [132]. Therefore, they are usually located at the protein surface exposed to the solvent, which requires the presence of hydrophilic side chains (e.g. Ser, Asn) and a flexible backbone element with a preference of a *cis*-configured amide bond (e.g. Gly, Pro) [133]. The location at the surface combined with their major influence on protein folding makes turn motifs a distinctive feature, which is involved in various molecular recognition events as observed in the X-ray crystal structures of peptide-antibody complexes [134,135]. Participation of turn motifs in the peptide induced activation of G-protein coupled receptors by PPI is well investigated [136]. Therefore, the responsible turn motifs are promising pharmacological targets. As turn motifs frequently participate in PPIs, they are popular structural elements for the design of protein epitope mimetics [137]. Well investigated targets of current research comprise serine protease inhibitors based on the *Bowman-Birk* motif, mimetics of protegrine I as novel antibacterials and inhibitors of CXCR4 [138]. In contrast to β-sheets and α-helices, turn motifs lack the preference of a defined torsion angle ϕ, ψ and are therefore termed irregular structures [133]. They are classified according to their direction into forward- ($NH^{N\text{-term}}$-$CO^{C\text{-term}}$) and reverse turns ($CO^{C\text{-term}}$-$NH^{N\text{-term}}$). A further sub-classification is performed according to the loop size represented by the number of ring members defined by the H-bond. Forward turns: δ-Turn, 8-ring, NH^{i}-CO^{i+1}. ε-Turn, 11-ring, NH^{i}-OC^{i+2}. Reverse turns: γ-Turn, 7-ring, CO^{i}-HN^{i+2}. β-Turn, 10-ring, CO^{i}-HN^{i+3}.

α-Turn, 13-ring, CO^{i}-HN^{i+4}. π-Turn, 16-ring, CO^{i}-HN^{i+4}. Ω-Turn, >18-ring, CO^{i}-HN^{i+6+n} [139] (Figure 24a).

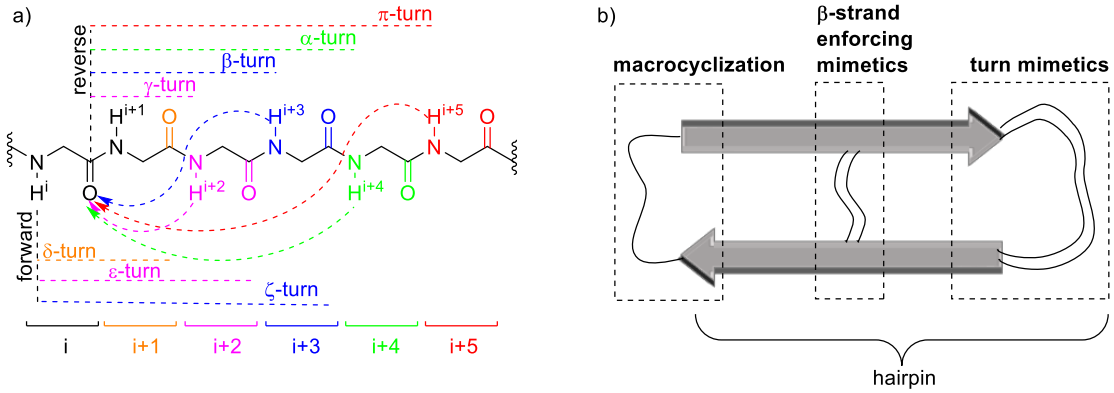


Figure 24. Concept of turn motif induction. a) Different classes of forward and reverse turns in peptides [133]. b) Approaches to enforce antiparallel alignment of peptide strands [31].

Whereas forward turns typically do not occur in natural peptides, β-turns are the most common turn structures in peptides. Therefore, they are further subtypified by their backbone conformation and side chain orientation [61]. Attachment of amino acids aligning to a β-sheet that may be assisted by inter side chain interactions builds a hairpin. This structure represents the template for the design of complementary peptidomimetics [140]. Hairpin mimetics are distinguished by the subdomains subjected to chemical modifications (Figure 24b).

Macrocyclization is an option to support the formation of a turn motif, directing *N*- and *C*-termini into the same direction and avoiding terminal unfolding. Usually, Class A modified peptides are used as global constraints connecting the backbone ($N^{N\text{-term}}H$-$C^{C\text{-term}}O$) or the side chains by lactams (Lys-Glu/Asp), disulfide bridges (Cys-Cys), π-stacking (Phe/Trp) and tethers based on non-natural amino acids [31]. A famous example is the induction of γ-turns [141] or type II' β-turn [142] conformations of the RGD sequence by backbone cyclization enhancing its affinity to integrine αvβIII by 146 fold [143].

β-Strand enforcing mimetics or **β-strand mimetics** are Class B modified peptides with nonpeptide elements that assist β-sheet formation. They either reproduce the typical interstrand H-bond pattern [144] or connect the β-strands covalently [145]. However, peptidomimetics of this type have not yet been used as PPI disruptors.

Turn mimetics are discussed in Chapter IV.2.

IV-2. Structural Turn Motif Mimetics

Structural turn motif mimetics (Figure 24b) contain strongly constrained backbone elements orienting *N*- and *C*-termini into the same direction and in appropriate spatial proximity for antiparallel alignment of the β-strands. The rigid scaffolds induce stable hairpin structures in much shorter peptides than in their peptide templates (1-3 instead of >20) [146]. While the side chains of peptide turn motifs are usually hydrophilic as they are located on the protein surface exposed to water, the substituents of turn mimetics are not restricted to polar groups. In conclusion, small molecules comprising a turn mimetic can be designed as stable, versatile substituted hairpin analogues. In internal turn motif mimetics (Class A peptidomimetics), the backbone constraint is realized by exchanging an H-bond of the turn by a covalent bond [147]. The group of Class B turn mimetics consists of abstract scaffolds designed as constrained dipeptide isosteres [133]. These Class B peptidomimetics are referred to as external turn motifs. They are subclassified according to their sterical constraints (Figure 25) in analogy to the characterization of helix mimetics (Chapter III-7) [133].

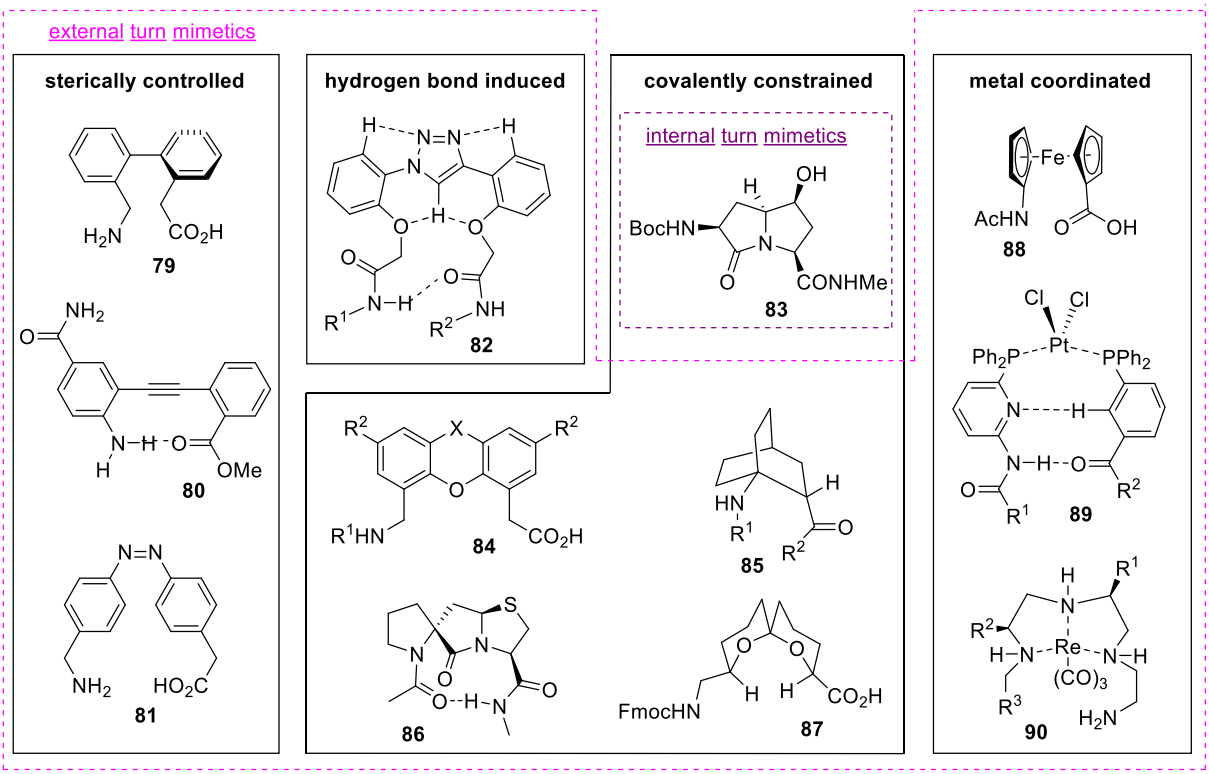


Figure 25. Established structural turn motif mimetics organized by their mechanism to induce β-folds. **Sterically controlled**: Biphenyls **79** [148]. Tolanes **80** [149]. *Z*-Azobenzenes **81** [150]. **Hydrogen bond induced**: 1,4-Diphenyl-1,2,3-Triazoles **82**, R^1=-Val-NH^{i}Pr, R^2=-Gly-NH^{n}Bu [151]. **Covalently constrained**: Pyrrolizidinone amino acids **83** [152].

2,8-Dimethylphenoxathiine **84a**, X=SO_2, R^1=H, R^2=Me [153]. Dibenzofurane **84b**, X=-, R^1=Boc [154]. Bicyclooctanes **85a** R^1=Boc, R^2=OH, **85b** R^1=Ala-CO^{i}Pr, R^2=Phe-OMe [155]. Spiro-bicycles **86** [156]. Spiroketale **87** [157]. **Metal coordinated**: Ferrocenes **88** [158]. *cis*-Platinates **89**, R^1=R^2=CH_2Ph [159]. Rhenium complexes **90**, R^1=CH_2Ph, R^2=R^3=Me [160].

Sterically controlled Turn Motifs keep the peptide strands in a defined distance, but contain a single bond allowing free rotation and thus various relative orientations of the β-strands can be adopted. Interstrand interactions stabilize the hairpin motif. The axial rotation of *ortho*-substituted biphenyl derivatives **79** is free in the limits of the steric constraints. MD-simulations revealed a preferred dihedral angle of 90° between the aromatic rings [148]. Still, **79** turned out to be an appropriate β-sheet inducer forming a 15-membered ring stabilized by an appropriate H-bond (π-turn) when incorporated into a peptide [148]. Peptide strands terminated by aromatic boronates and halides could be connected via *Suzuki* coupling in yields of 15-38 % [148]. Extension of the axis led to tolane derivatives **80** with completely unconstrained axial rotation around the triple bond. Diarylalkynes of type **80** have been used as disulfide bridge isosteres. They can be obtained after establishing the corresponding peptide by final intramolecular *Sonogashira* cross coupling on solid phase forming a macrocycle [149]. The exposed Ω-loop of the Cε3 domain in human IgE could be successfully stabilized by tolane derivative **80** affording a promising agent against hypersensitivity responses [149]. Smart turn mimetics like azobenzene **81** have been developed to control the backbone conformation and therefore the interstrand distance by light. Azobenzene derivative **81** has been linked by an Ala-Ala dipeptide to the binding β-sheet motif Phe-Trp-Lys-Thr as a somatostatin analogue. MD simulations suggest a hairpin conformation for *Z*-configured azobenzene **81** and more extended conformations for *E*-configured azobenzene. Biological evaluation confirmed the change of conformation rendering the light-induced *Z*-isomer twice as active as the thermodynamically preferred *E*-isomer [150]. When the substituents of the aromatic rings of **81** were in *meta* position, a hairpin formation could only be observed for the light-induced *Z*-isomer. Attachment of the substituents in *ortho* position can lead to an H-bond between the NH and C=O moieties of different strands in the *E*-isomer of the azobenzene [161]. Reisomerization of an analog of (*Z*)-configured azobenzenes **81** with attached peptide chains proceeded 30 % slower than that of amino acid **81**. As the reduced

reisomerization tendency depends on the stability of the β-fold, incorporation of **81** into β-sheets enables the evaluation of its stability [162].

Hydrogen Bond induced Turn Motifs

Additional H-bonds in the turn mimetic support the orientation of peptide strands by enhancing the stability of particular conformations. In diphenyl-triazoles **82**, the axial rotation around the single bonds connecting the triazole ring with the phenyl rings is constrained by several H-bonds (Figure 25). 1,4-Diphenyl-1,2,3-triazoles **82** were obtained by a copper catalyzed 1,3-dipolar cycloaddition after preparation of appropriately substituted peptides. As this turn mimetic additionally contains the features of a retro-inverso amide isostere, the peptide strands R^1 and R^2 align to a parallel β-sheet [151].

Covalently constrained Turn Motifs

Covalently constrained turn motifs are completely rigid scaffolds without any conformational degrees of freedom. The subdivision into aromatic and spirocyclic skeletons as proposed by Nair *et al.* [133] is not considered herein because it does not cover all representatives belonging to this group. Internal turn motif mimetics are Class A modified peptides containing a turn-generating ring formed by covalent bonds instead of H-bonds. The covalent tethers in internal γ- and β-turn mimetics lead to rigid scaffolds justifying their assignment to the covalently constrained turn motifs. A type II' β-turn conformation is fixed in pyrrolizidinones **83**. The low temperature coefficients of the amide protons confirm the induced β-sheet [152]. Modification of the peptide template adaptation and the turn class is realized by a variation of the configuration of the center of chirality and the ring size of azabicycloalkanes like **83** [163]. The macrocyclic system consisting of the tripeptide -Ile-Val-Gly-, which is connected at its *N*- and *C*-termini by 2,8-dimethylphenoxathiine **84a** forms H-bonds leading to a γ-loop in the amino acids and a β-turn with its methyl groups at the heterocycle representing the side chains of the amino acids i+1 and i+2 in a peptide β-turn [153]. However, the X-ray crystal structure of a peptide incorporating the closely related dibenzofuran **84b** reveals an H-bond resulting in a 15-membered ring, referred to as π-turn. Interestingly, interactions of nonpolar side chains with the hydrophobic turn inducing scaffold **84b** could be deduced from ROESY

experiments [154]. This hydrophobic cluster is expected to support β-sheet formation [154]. The conformation of bicyclooctane **85a** mimicking a β-amino acid is highly constrained. The X-ray crystal structure of hairpin mimetic **85b**, a peptide with incorporated bicyclooctane **85a**, confirms the narrow γ-turn conformation [155].

Two of the best investigated representatives of spirocyclic turn mimetics are bicyclic **86** and spiroketal **87**. Three of their four dihedral angles ϕ, ψ characterizing a peptide conformation are locked. The conformational analogy of the spirocyclic compound **86** to a type II β-turn was confirmed by determination of the temperature coefficient, MD simulations and NOESY experiments [156]. Different hairpin motifs derived from **86** by variation of the lactam and thiazolidine ring sizes were active in the 6-hydroxydopamine-lesioned animal model of *Parkinson's* disease in nanomolar range [164]. The solid phase synthesis compatible spiroketal **87** arranges in analogy to a π-turn [157].

Turn Motifs by Metal Coordination

The most recently established group of turn motif mimetics resulting from a coordination of the backbone to a metal ion like Fe, Pt, Rh or Ni. X-ray crystal structures of oligopeptides of different length containing ferrocene based amino acid **88** were recorded. Depending on the number of additional amino acids, different turn structures can be adopted. In short oligomers, a forward δ-turn was found, while longer oligomers form interstrand H-bonds which rather indicate a helix structure (NH^{i+2}-CO^{i+4} and CO^{i}-NH^{i+3}) [158]. Therefore, turn motif mimetic **88** does not necessarily induce hairpin formation. Introduction of *cis*-platinate **89** as warhead for DNA interaction terminating a hairpin structure represents an innovative approach for the development of anti-cancer drugs. The driving forces for the self-assembly of the Pt-complex **89** combines metal coordination, weak H-bonds and π-stacking. X-ray crystal structure analysis and thermodynamic investigations confirmed the resulting exceptional stability of the X_2M complex [159]. A similar self-assembly provided Re-complex **90** [160], which is related to a crown ether. The distance between two adjacent α-C-atoms in the Re-chelat is proportional to the metal ion radius [165]. Consequently, the turn motif can be modified by introduction of different metal cations.

IV-3. Propargyl-aryl Architectures as Turn Motif Mimetics

The scaffolds discussed above differ in their lipophilicity, rigidity, degrees of conformational freedom and modification options. These features make them promising tools to generate structural turn motif mimetics. In analogy to the peptidomimetics described in Chapter III, the compounds of this part are based on propargylamides **6**, linked via *Sonogashira* cross coupling to an aromatic moiety. The alkyne in the backbone leads to a linear structure, which only allows rotation around the alkyne axis. Therefore, the corresponding compounds are referred to as sterically controlled turn mimetics.

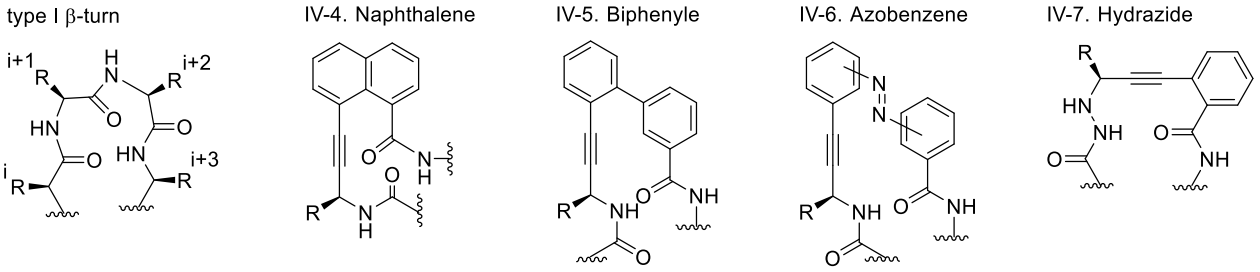
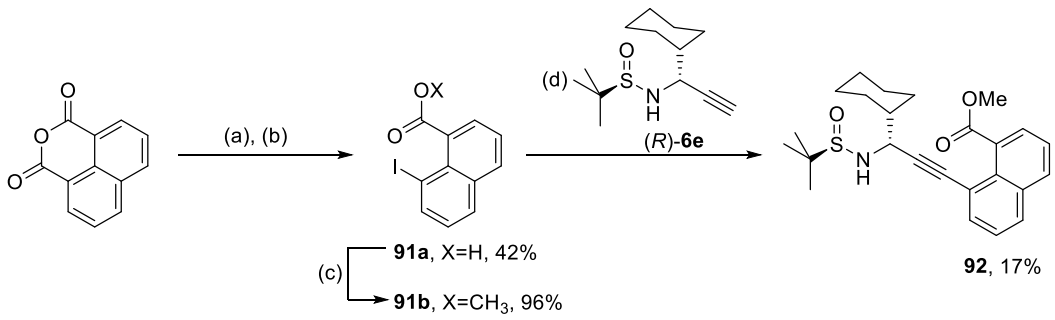


Figure 26. Overview of the turn motif mimetics presented in this work. As all scaffolds are based on a connection of propargylamides to aromatic systems, the discussion is structured in analogy to Chapter III according to the aromatic system (compare the captions of the scaffolds).

IV-4. Naphthoate-Based Turn Mimetics

Reports of the selective mercuration of 1,8-naphthoic anhydride in 8 position by Chen *et al.* allowed the versatile functionalization of naphthalene-1-carboxylates in 8-position [166]. Wiley *et al.* further developed a procedure for the synthesis of 8-iodonaphthalene-1-carboxylate **91a** [167], which can be used in various transition metal catalyzed cross coupling reactions. Therefore, **91** represents a promising aromatic scaffold for novel peptidomimetics.



Scheme 2. Preparation of naphthoate-based turn motif mimetic **92**. (a) Iodination of naphthoate was performed as described by Wiley *et al.* [167]. 1. NaOH, H_2O, 100 °C, 1 h. 2. $Hg(OAc)_2$, $HOAc/H_2O$ (2:1), 120 °C, 48 h. (b) I_2, KI, H_2O, 100 °C, 24 h. (c) $TMSCHN_2$, DIPEA, THF, rt, 1 h. (d) *Sonogashira* cross coupling: THF/piperidine (3:1), $PdCl_2(PPh_3)_2$, CuI, rt, overnight.

First attempts to react iodonaphthoate **91a** with propargylamide **6e** by a *Sonogashira* cross coupling reaction failed possibly due to various side reactions including intramolecular hydrocarboxylation (compare Chapter III-10). Additionally, coordination of palladium species by the carboxy group could inhibit the transformation especially in proximity to the aromatic halide. However, the methyl ester **91b** was converted into peptidomimetic **92** in a yield of at least 17 %.

The rigid naphthalene scaffold leads to a parallel orientation of *N*- and *C*-termini. Nevertheless, the free rotation around the alkyne axis and the steric interactions possibly separate the peptide strands spatially. Hints for hairpin formation can be derived from the chemical shifts in the ^{1}H NMR spectra (Figure 27).

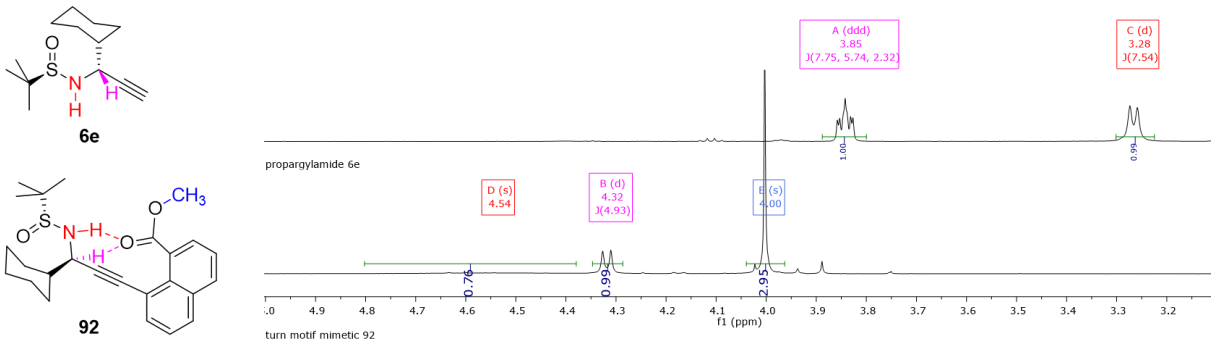


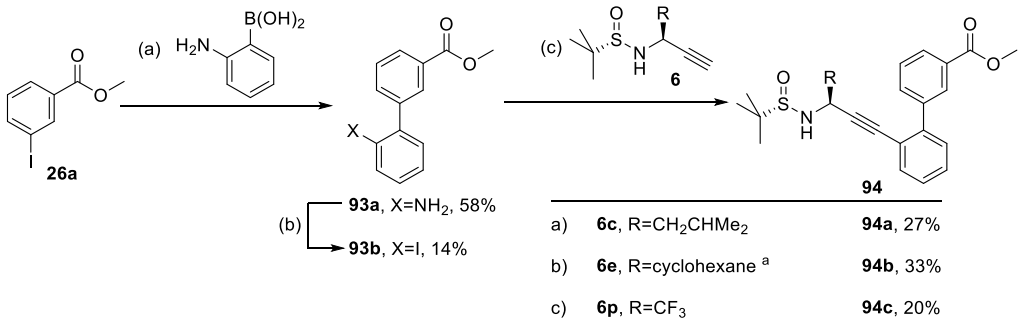
Figure 27. Comparison of ^{1}H NMR chemical shifts of propargylamide **6e** and peptidomimetic **92** in the range of 5.0-3.0 ppm. The magenta signals at 3.85 ppm (A for **6e**) and 4.32 (B for **92**) are caused by the protons in α-position. The purple signals at 3.28 ppm (C for **6e**) and 4.54 ppm (D for **92**) are caused by the protons of the amide NH group. The methyl ester protons resonate as singlet at 4.00 ppm (E for **92**, blue).

Remarkably, the resonance of the amide proton of **92** is downfield shifted by Δ 1.26 ppm compared to the NH-signal of **6e**. Moreover, the signal of the amide proton of **92** is extraordinarily broad. Both phenomena usually indicate strong intramolecular H-bonds. A lower downfield shift of Δ 0.47 ppm for the signal of the α-proton of **92** compared to **6e** indicates a weaker intramolecular H-bond. Due to the parallel orientation of the substituents in 1- and 8-position of the naphthalene ring, a coordination of both protons to the carbonyl *O*-atom is very probable. These H-bonds lead to a 10-membered ring with a similar structure as found in non-natural forward ε-turns. To confirm this hairpin structure, peptidomimetic **92** was incorporated into a larger peptide by *Sonogashira* reaction of H-Pro-Tyr-Thr-**6e** with **91a**-Leu-Thr-Val-OH. The resulting hairpin mimetic H-Pro-Tyr-Thr-**92**-Leu-Thr-Val-OH was isolated in very low amounts and a yield of 27 %. Investigation by NMR spectroscopy is not yet completed, but temperature resolved CD spectroscopy indicates the existence of a distinct secondary structure, which is stable even at elevated temperatures of >70 °C (Diagram EP24, Experimental Part).

Nonpolar naphthoate scaffolds such as **92** were reported to diffuse through cell walls and intercalate into DNA provoking cancer. On the other hand, **92** was suggested as lead scaffold for the development of various patented active agents [168]. In the presented hairpin mimetics H-Pro-Tyr-Thr-**92**-Leu-Thr-Val-OH the naphthoate moiety terminates a β-sheet and thus acts as a DNA intercalating warhead in analogy to *cis*-platinate **89** (Figure 25) [159].

IV-5. Biphenyl-Based Hairpin Mimetics

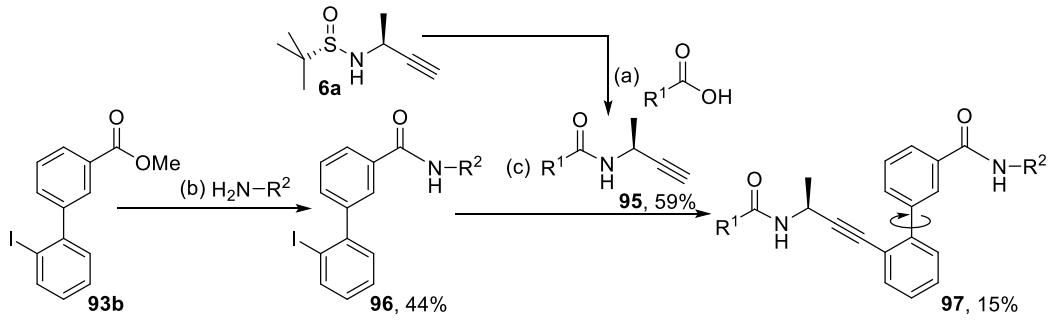
Biphenyl derivatives are closely related to the presented naphthalene species. A 3,2'-substitution pattern of the biphenyl scaffold was used to maintain rotation around the Ph-Ph single bond. These biphenyls can adopt conformations with parallel orientation of *C*- and *N*-termini bringing a carbonyl and an amino moiety in close proximity to form a strong H-bond. Various substitution patterns of the aromatic system can be accessed by the *Suzuki* reaction of iodo-benzoates **26**, **36**-**39**, **45**, **47** and **48** with 2-aminophenyl-boronic acid (Scheme 3).



Scheme 3. Preparation of biphenyl-based turn mimetics. (a) *Suzuki* coupling: K_3PO_4, 1,4-dioxane/H_2O (4:1), $PdCl_2(PPh_3)_2$, sonication, rt, overnight. (b) *Sandmeyer*-type reaction: 1) $NaNO_2$, NaI, HCl (6 M), 0 °C, 5 min. 2) I_2, rt, 14 h. (c) *Sonogashira* reaction: $PdCl_2(PPh_3)_2$, CuI, THF/DIPEA (3:1), rt, overnight.

[a] Both stereocenters of propargylamide **6e** and turn mimetic **94b** were (*R*) configured.

The obtained aminobiphenyl **93a** was converted by a *Sandmeyer*-type reaction into iodo arene **93b**. Hydroxylation competed with the iodination and reduced the yield to only 14 %. Alkynes **6** and aromatic halide **93b** were connected by a *Sonogashira* reaction, affording peptidomimetics **94a-c**. Steric repulsion of the connected phenyl rings as well as high electron density of the aromatic system inhibited the oxidative addition reducing the yields to 20-33 %. The amide protons of peptidomimetics **94a-c** resonate in a very similar range as the amide protons of the corresponding propargylamides **6c,e,p** (Diagram EP15, Experimental Part). Therefore, it was concluded that intramolecular H-bonds do not exist in **94a-c**. Indeed, previous MD-simulations confirm a preferred dihedral angle of 90° between the phenyl rings [148]. In order to induce a possible hairpin conformation peptidomimetic **94** was incorporated into a short peptide (Scheme 4).



Scheme 4. Incorporation of turn mimetic **94** in a short peptide. R^1=-Gly-Phe-Tyr-NHBoc, R^2=-Ala-Val-Leu-OMe. (a) 1. HCl (4 M in dioxane), MeOH, rt, overnight. 2. HATU, HOAt, CH_2Cl_2, DIPEA, rt, 3 d. (b) 1. LiOH x H_2O, MeOH/H_2O (2:1). 2. HATU, HOAt, CH_2Cl_2, DIPEA, rt, 3 d. (c) $PdCl_2(PPh_3)_2$, CuI, dioxane/DIPAH/DMSO (15:4:1), microwave, 60 °C, 2 h.

After hydrolysis of the *tert*-butylsulfinamide **6a**, the resulting primary amine was coupled with the tripeptide BocHN-Tyr-Phe-Gly-OH using HATU and HOAt to form the peptidomimetic **95** with an *N*-terminal alkyne moiety. Ester **93b** was hydrolyzed and the resulting acid was linked to the tripeptide H_2N-Ala-Val-Leu-OMe also using HATU and HOAt to give peptidomimetic **96** with an iodobiphenyl at the *C*-terminus. Both peptidomimetics were connected by a *Sonogashira* reaction at elevated temperatures to give peptidomimetic **97**. Interstrand H-bonds were identified by temperature gradient determination (Figure 28).

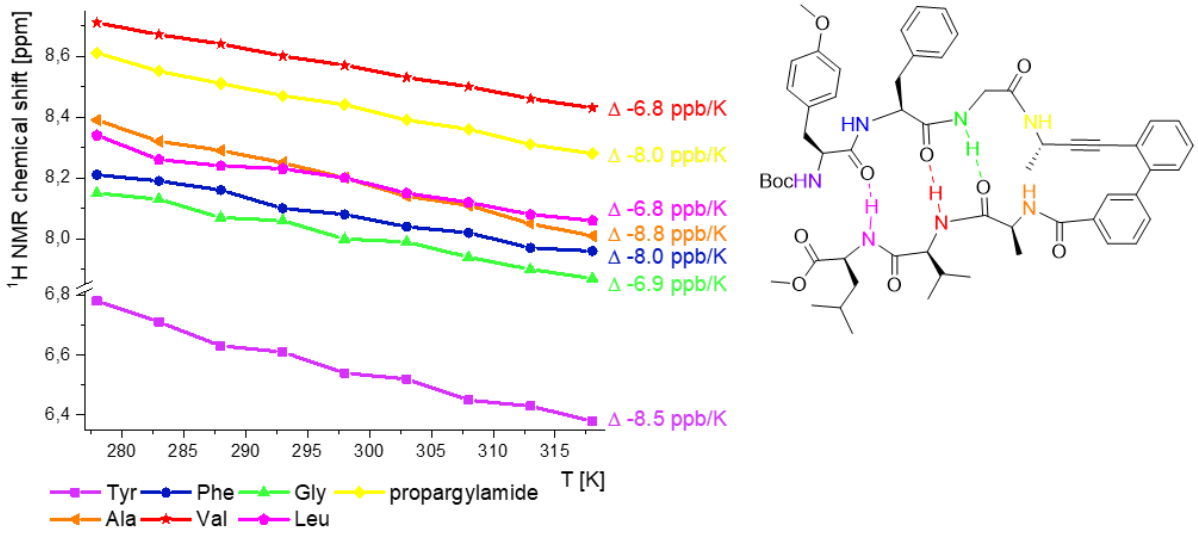


Figure 28: Detection of intramolecular H-bonds in hairpin mimetic **97** by temperature coefficient Δδ/ΔT determination. Left side: ^{1}H NMR shift of amide protons in dependence on the temperature in CD_3OH. A low chemical shift is typical for a strong intramolecular H-bond. Right side: Assumed conformation of hairpin mimetic **97** with H-bonds assigned to protons with low temperature dependence of the chemical shifts (see also Diagram EP16, Experimental Part).

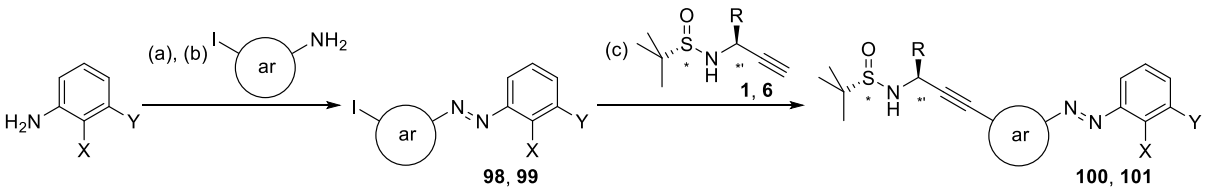
The chemical shift of each amide proton was plotted against the corresponding temperature. Determination of the gradient allows an evaluation, whether the proton is surrounded by solvent (high gradient) or coordinated intramolecularly to a carbonyl moiety (low gradient). Using this technique led to the identification of three interstrand H-bonds (Figure 28) stabilizing the two β-strands in an antiparallel manner. The H-bonds result in an 18-membered ring classifying the motif as forward ζ-turn. Apparently, the dihedral angle of 90° between the phenyl rings of the biphenyl system does not align the peptide strands

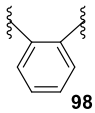
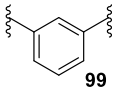
in a parallel manner and renders the biphenyl scaffold a poor hairpin inducer. Although temperature resolved CD spectroscopy indicates a secondary structure with high stability (Diagram EP26, Experimental Part), a comparison of hairpin **97** and turn motif **94b** shows that the observed CD effect is generated mainly by the turn motif mimetic and not by the β-strand (Diagram EP25, Experimental Part).

IV-6. Smart Azobenzene-Based Turn Mimetics

The distance between two peptide strands and therefore the initiation of β-sheet formation can be optically controlled if their linker is an azobenzene derivative [150]. The stability of such smart hairpin motifs depends on the substitution pattern [161], as well as the inherent tendency of the strands to form β-sheets [162]. For the incorporation of such structural motifs into peptidomimetics the synthesis of versatile iodo-diazenylbenzoates as aromatic scaffold is a central task. In first attempts, 4-methylaniline was substituted with methyl 2-diazonium-benzoate to afford the azobenzene derivative in 94 % yield. Subsequently, the aromatic amine was converted into an iodo substituted by a *Sandmeyer*-type reaction (17 %). Unfortunately, purification of the iodo compound was difficult and only *ortho* iodinated azobenzene derivatives could be isolated using this procedure. A far more versatile approach to access azobenzene derivatives **98** and **99** with diverse substitution patterns was the oxidation of methyl benzoates with amino groups in 2- or 3-position to obtain the corresponding nitroso derivatives and subsequent condensation with 2- or 3-iodo-anilines (Table 7).

Table 7. Preparation of azobenzene-based turn motif mimetics **100** and **101**. (a) Oxone®, CH_2Cl_2/H_2O (2:8), rt, 20 h. (b) 2- or 3-iodo-aniline, AcOH, 0 °C-rt, 14 h. (c) Propargylamide **1**, **6**, $PdCl_2(PPh_3)_2$, CuI, THF/piperidine (3:1), rt, overnight.



entry	aniline derivative	iodo aniline	azobenzene **98**, **99**	propargylamide **1**, **6**	turn mimetics
a)	X=CO_2Me, Y=H	 **98**	**98a**, 25%	**1** [a], R=H	**100a**, 41%
b)	X=CO_2Me, Y=H		**98a**, 25%	**6e**, (*R,R*), R=cyclohexyl	**100b**, 8%
c)	X=H, Y=CO_2Me		**98b**, 38%		
d)	X=H, Y=CO_2Me	 **99**	**99**, 76%	**6c**, (*S,S*), R=CH_2CHMe_2	**101**, 48%

[a] The *tert*-butylsulfinyl protective group of the amide was replaced by Boc.

Sonogashira reaction of iodinated azobenzenes **98-99** with propargylamides **1** and **6** gave the smart peptidomimetics **100-101**. The sterically hindered 2-iodo-anilines were much less reactive in the diazotation reaction than the 3-iodo-anilines giving **98** in yields of only 25-38 % instead of 76 % yield obtained for **99**. The subsequent *Sonogashira* reaction is hindered in a similar manner by the adjacent diazobenzenecarboxylate resulting in a yield of 8 % for 2-substituted azobenzene **100b** instead of 48 % for the 3-substituted azobenzene **101**.

UV/*Vis* spectroscopic investigation of *ortho*-substituted azobenzene derivatives showed reversible isomerization for precursor **98a** (Diagram EP21, Experimental Part), but not for peptidomimetic **100b** (Diagram EP22, Experimental Part). The photoisomerization of *meta*-substituted peptidomimetic **101** could be confirmed by UV/*Vis*- as well as ^{1}H NMR spectroscopy (Figure 29).

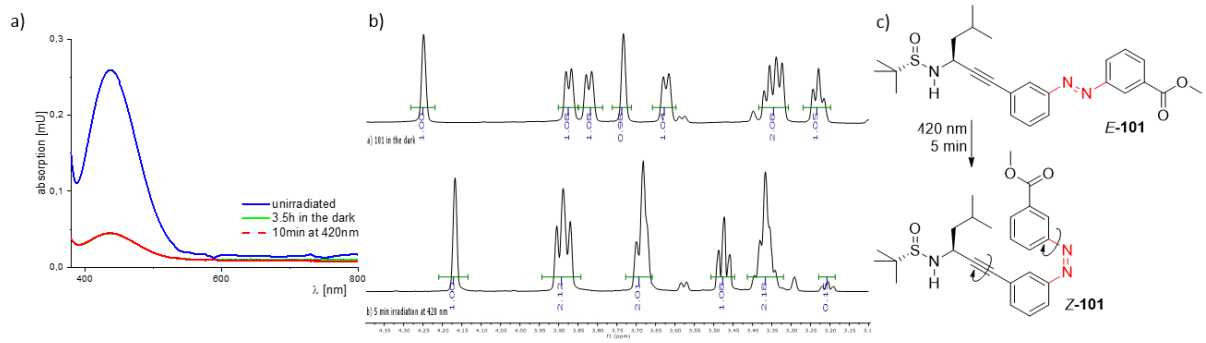


Figure 29. Photoisomerization of azobenzene-based peptidomimetic **101**. a) UV/*Vis* spectra of *E*-**101** (blue) and *Z*-**101** (red and green, also compare Diagram EP23, Experimental Part). Reisomerization could not be observed. b) ^{1}H NMR spectra in the range of 3.40-3.10 ppm of *E*-**101** (top) and *Z*-**101** (bottom) in $CDCl_3$ (also compare Diagram EP17, Experimental Part). c) Chemical structures of *E*-**101** (top) and *Z*-**101** (bottom) corresponding to the ^{1}H NMR spectra in Figure 29b with marked azobenzene isomers and remaining rotational degrees of freedom.

In the dark, the *E/Z* ratio of peptidomimetic **101** was 100:0 as confirmed by ^{1}H NMR spectroscopy. Irradiation of **101** for 5 min at 420 nm led to almost complete isomerization, i.e. an *E/Z* ratio of 4:96 (Figure 29b and Diagram EP17, Experimental Part). Still, reisomerization could not be observed even within 3 weeks in the dark. The presence of internal H-bonds was confirmed ^{1}H NMR spectroscopically by comparison of the chemical shifts of propargylamide **6c** with those of the *E*- and *Z*-isomers of peptidomimetic **101** (Figure 30).

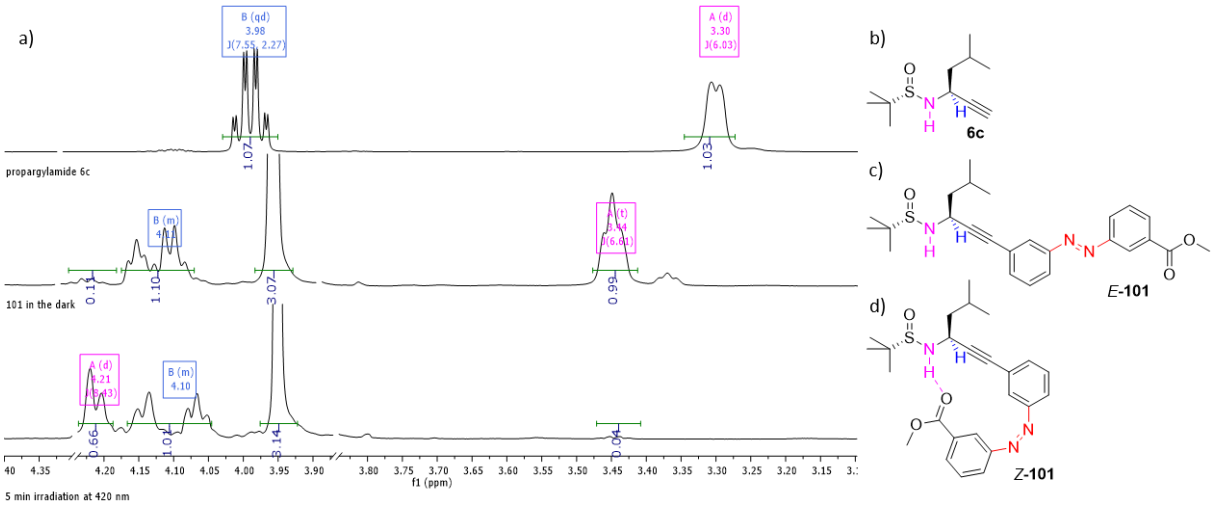


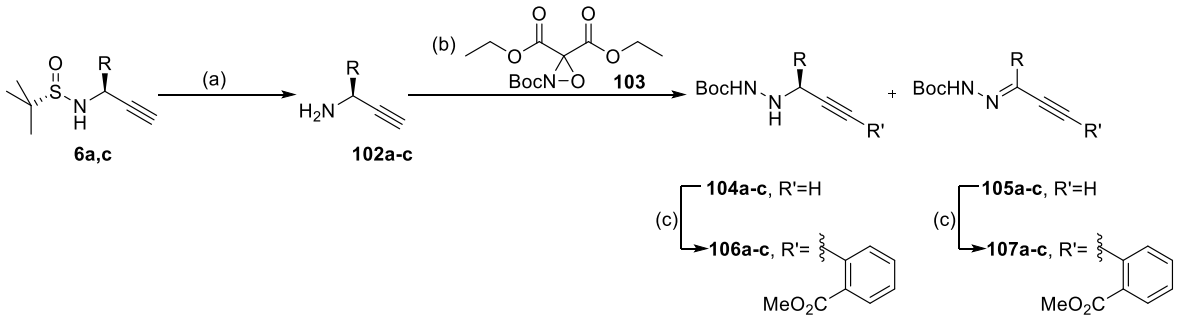
Figure 30. Identification of intramolecular H-bonds by comparing the chemical shifts of the amide protons. a) Parts of the ^{1}H NMR spectra (4.40-3.10 ppm) measured in $CDCl_3$ of b) propargylamide **6c**, c) *E*-isomer of **101** and d) *Z*-isomer of **101** (the postulated H-bond is visualized with a dotted line).

In comparison to propargylamide **6c** and *E*-**101**, the signal of the amide proton of *Z*-**101** is significantly shifted to the downfield by Δ 0.8-0.9 ppm. Such a downfield shift Δ is typical for the existence of an H-bond and, therefore indicates an intramolecular H-bond between the amide proton and the carbonyl moiety in the *Z*-isomer *Z*-**101**. This H-bond encloses a 15-membered ring in *Z*-**101**, which cannot be observed for the *E*-isomer *E*-**101**. In conclusion, peptidomimetic **101** forms a forward ζ-turn motif when exposed to irradiation at 420 nm and a more extended conformation in the dark and is therefore referred to as a smart turn mimetic.

IV-7. Hydrazines and Hydrazones induce Backbone Bending

In the last application of the peptidomimetic scaffolds of this work as turn mimetics, the *N*-terminal moiety was expanded instead of the aromatic part. The propargylamine was converted into a propargylhydrazide to spatially enable the formation of an H-bond between the terminal NH group of the hydrazide and the carbonyl moiety of an *ortho*-substituted benzoate. Therefore, the propargylamides **6** described in Chapter II had to be deprotected and converted into propargylhydrazides **104**. According to a reported method, an excess of propargylamine **102a** (>5 eq) was aminated with hydroxylamine-*O*-sulfonic acid (1 eq) and the propargylhydrazide **104a** was isolated by distillation [169]. However, most propargylamides **6** and their derivatives are not volatile and wasting four out of fife equivalents of propargylamine was not efficient. In a very new approach recently reported by Kang *et al.* [59], the electrophilic amination reagent **103** was used to transfer an NHBoc moiety to an amine. Reaction of propargylamines **102a-c** with **103** afforded Boc protected hydrazides **104**, which were subsequently linked to 2-iodo-benzoate **26a** by the *Sonogashira* reaction (Table 8).

Table 8. Preparation of hydrazine- and hydrazone-based turn motifs. Reaction conditions: (a) HCl (4 M in dioxane, 4 eq), MeOH (5-15 mL), rt, 4-7 h. (b) Aqueous, saturated $NaHCO_3$ solution/THF (1:1, 40 mL), diethyl 2-Boc-1,2-oxaziridine-3,3-dicarboxylate (**103**, 1.2 eq), rt, overnight [59]. (c) Methyl 2-iodobenzoate (**26a**, 1.6 eq), $PdCl_2(PPh_3)_2$ (1 mol%) CuI (2 mol%), THF/piperidine (3:1). All given yields refer to isolated compounds.



entry	propargylamide	propargylamine	propynyl hydrazine	hydrazine-turn	hydrazone-turn
a)	-	**102a**, R=H[a]	**104a/105a**, R'=H, 51%	**106a**, R'= -Ph-2-CO_2Me, 48%	**107a**, 40%
b)	**6a**, R=Me	**102b**, R=Me, quantitatively	**104b/105b**, R'=H, 86%	**106c**, R'= -Ph-2-CO_2Me, 31%	**107b**, 24%
c)	**6c**, R=CH_2CHMe_2	**102c**, R=CH_2CHMe_2, quantitatively	**104c/105c**, R'=H, 62%	**106c**, R'= -Ph-2-CO_2Me, 13%	**107c**, n.d.

[a] Propargylamine **102a** was commercially available.

The amination of propargylamines **102** using the Boc-amine transfer reagent **103** proceeded in yields of 51-86 %. Formation of a byproduct could be observed by TLC of the crude product. NMR spectroscopic investigation revealed that the amine of **104** had been partially oxidized to provide propynal hydrazones **105**. According to the ^{1}H NMR spectra, the ratio of hydrazines **104** : hydrazones **105** was 66:44. It is assumed that amine transfer reagent **103** was contaminated by the oxidant Oxone®, which was used for the preparation of **103** and does not produce any signals during NMR spectroscopy. Coupling of hydrazines **104** and hydrazones **105** to iodoarene **26a** by *Sonogashira* cross coupling provided peptidomimetics **106** and **107** in equimolar ratio. The yields decreased with extension of the side chain of the alkyne moiety with **104a>104b>104c** and **105a**>**105b>105c** under the given conditions.

The readily crystallizing hydrazone **107a** allowed the recording of an X-ray crystal structure giving information about the conformation of **107a** in the solid state (Figure 31).

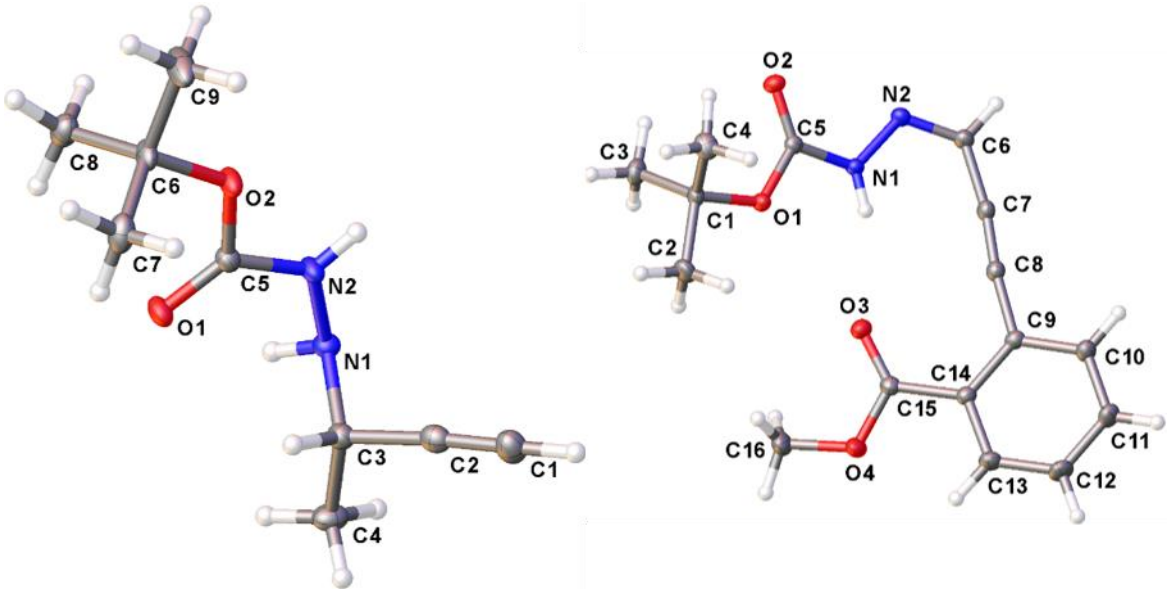


Figure 31. X-ray crystal structures of the alanine analogous propargylhydrazide **104b** (left) and of propynal hydrazone **107a** (right).

The short interatomic distance of only 2.246 Å as visualized in the X-ray crystal structure indicates a strong intramolecular H-bond between the hydrazone proton and the carbonyl moiety of the ester. In a $CDCl_3$-solution, the chemical shift in the ^1H NMR spectrum of the amide proton confirms the stability of this H-bond (for a complete and detailed visualization of the NMR studies, please see Diagrams EP18-20 in the Experimental Part). Whereas the downfield shift in hydrazides **106** in comparison to **104** is already significant (Δ**a** 0.93 ppm, Δ**b** 0.39 ppm, Δ**c** 0.86 ppm), the downfield shift in hydrazones **107** versus **105** is immense (Δ**a** 4.03 ppm, Δ**b** 3.19 ppm, Δ**c** n.a.). Apparently, H-bonds between the amide proton and the carbonyl moiety are much stronger in hydrazones **107** than in hydrazines **106**. Yet, both compounds arrange in a forward ε-turn analogous motif and are likely to form hairpin mimetics.

IV-8. Conclusion

Based on the pool of peptidomimetics presented in Chapter III, several nonpolar small molecules were designed as sterically induced turn mimetics. Thus, naphthoate-based turn mimetic **92** was designed as DNA-intercalating warhead of a hairpin mimetic. While biphenyl-based peptidomimetic **94** did not form a turn motif, the analogous hairpin mimetic **97** induced a β-sheet by an extended loop. Furthermore, the access to smart azobenzene-

based peptidomimetics **100** and **101** was reported. Their irradiation-induced complete isomerization to the turn forming *Z*-azobenzene derivatives renders these scaffolds smart turn mimetics. Although hydrazines **106** and hydrazones **107** contain the highest number of rotationally unconstrained single bonds, they form the most stable turn mimetics. The conformational preferences of the novel scaffolds have been investigated by ^{1}H NMR spectroscopy, determination of temperature coefficients and X-ray crystal structure analysis. Analysis of intramolecular H-bonds showed that all turn mimetics arranged in an analogue manner to the non-natural forward ε- or ζ-turn. In future works, these turn mimetics can be incorporated into di- or tripeptides by adding only one or two amino acids to the *N*- and *C*-termini. The investigation of such short hairpin mimetics will contribute to the comprehension and directed application of the discussed scaffolds. As the structures of this work differ from peptide-based turns by lower polarity, an application of these turn motifs as hydrophobic interaction partners will be another reasonable approach for future works.

IV-9. References (132-169)

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V Structure-Activity Relationship of Propargylamine-Based HDAC Inhibitors

This chapter is a summary of the results, published in 2017 in the article "*Structure-Activity Relationship of Propargylamine-Based HDAC Inhibitors*" (see appendix) [2].

V-1. Peptidomimetics as HDAC Inhibitors

Histone Deacetylases (HDACs) control cellular functions like transcription and thus are valuable therapeutic targets in epigenetic regulation including autoimmunity [170], neurological processes [171] and tumor growth suppression [172–174]. The eleven HDAC members are divided into four classes according to their function, localization and sequence homology [175]. Knockout experiments suggest, that suppression of class I-IIA HDACs may lead to serious side effects like cardiac defects, which were not observed in class IIB-IV HDACs [176–178]. A particularly interesting drug target is HDAC6 belonging to class IIB, which also deacetylates α-tubulin [179]. Defects in its regulation are related to Alzheimer's disease [171], Huntington's disease [180–182] and cancer cell metastasis [172]. Therefore, we became interested in the development of novel selective HDAC inhibitors (in particular HDAC6 inhibitors). In this part, some peptidomimetics inhibiting selectively HDAC6 are reported.

The active site of an HDAC consists of a hydrophobic channel that is terminated by a bound Zn^{2+} ion catalyzing the deacetylation of lysine residues [183–185]. Therefore, potent inhibitors consist of a Zn^{2+} binding group that is linked by a rather rigid, rod-like linker with a selectivity inducing cap group [186,187] (Figure 32).

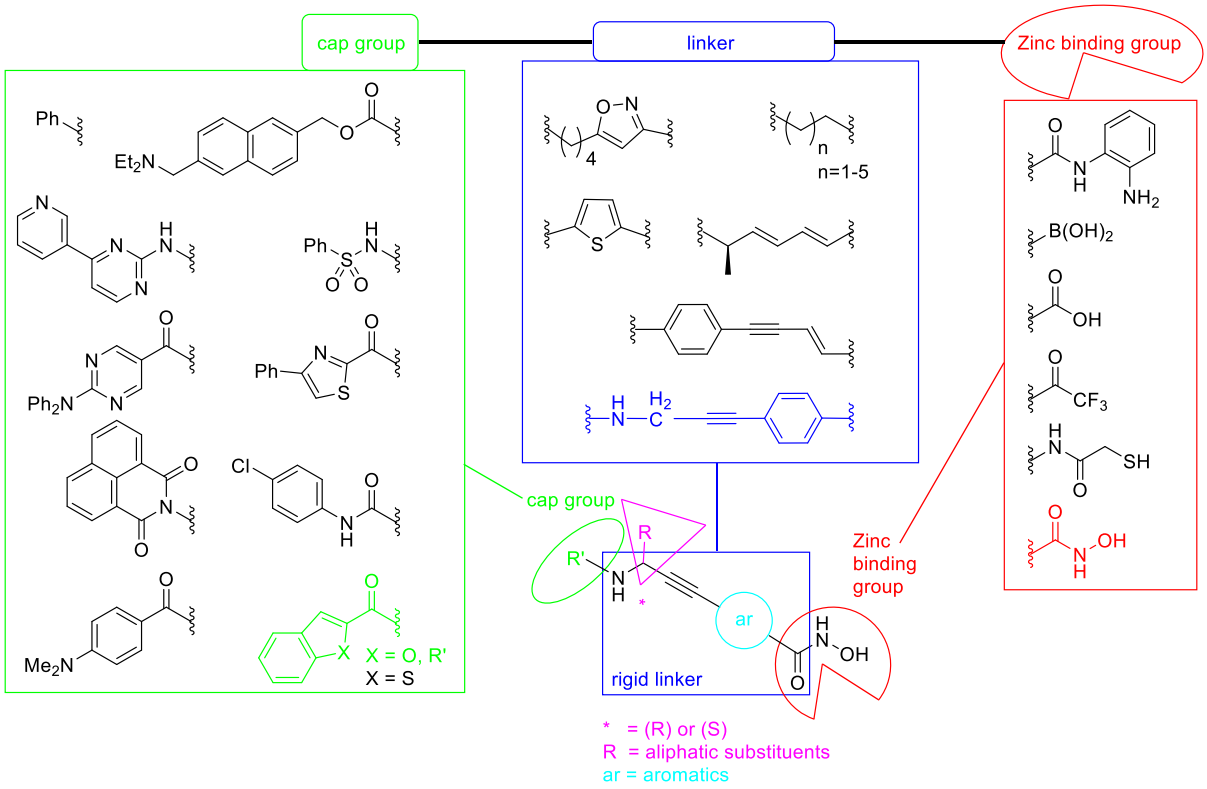


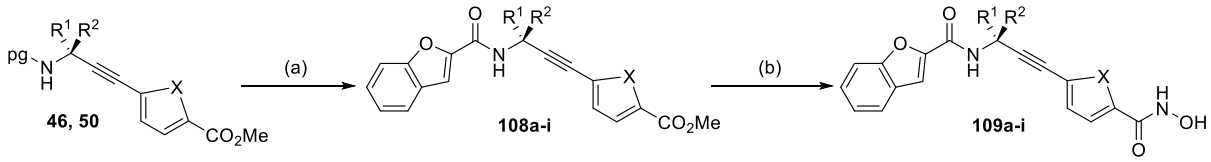
Figure 32. HDAC inhibitors composed of a cap group, linked to a Zn^{2+} binding group. Structural elements for each segment of the scaffold are summarized in the boxes below the general structures [175,180,188]. The moieties, selected for the composition of the model compound of this SAR are marked. Combination of the segments gives the lead structure (molecule below) [189] whose derivatives are discussed in this work.

The bulky, mainly aromatic cap groups interact with the surface of HDACs, allowing discrimination between different enzymes. Nonpolar aliphatics, olefins, alkynes or aromatics facilitate the entrance of the linker into the hydrophobic channel. The Zn^{2+} complexing group, e.g. a benzamide, boronic- or carboxylic acid, ketone, thiol or hydroxamic acid terminates the linker. Sendzik *et al.* have combined three moieties as depicted in Figure 32 extensively varying the cap group [189]. In this work, the linker was functionalized with residues of different size (Figure 32, marked magenta) and chirality. Furthermore, the aromatic ring was varied, as well (Figure 32, marked light blue).

V-2. Synthesis of Inhibitors from Peptidomimetics

The peptidomimetics inaugurated in chapter III contain the scaffold of the discussed inhibitors. They were converted into hydroxamic acids **109a-i** in two reaction steps (Table 9).

Table 9. Synthesis of hydroxamic acids **109** as HDAC inhibitors. (a) 1) HCl (4 M in dioxane, 4 eq). 2) 2-Benzofuranoyl chloride (1.5 eq), NEt_3 (6 eq), CH_2Cl_2, 0 °C, 6-14 h. (b) H_2NOH/H_2O/MeOH/THF (1:1:4:4), NaOH (pH 10-11), rt, 16 h. The given yields refer to peptidomimetic **46**, **50**. Order of the entries: a-c) (*S*)-Configured peptidomimetics with decreasing size. d) Reference compound **109d** has been described by Sendzik *et al.* [189]. e-g) (*R*)-Configured peptidomimetics with increasing size. h-i) Heteroarenes.

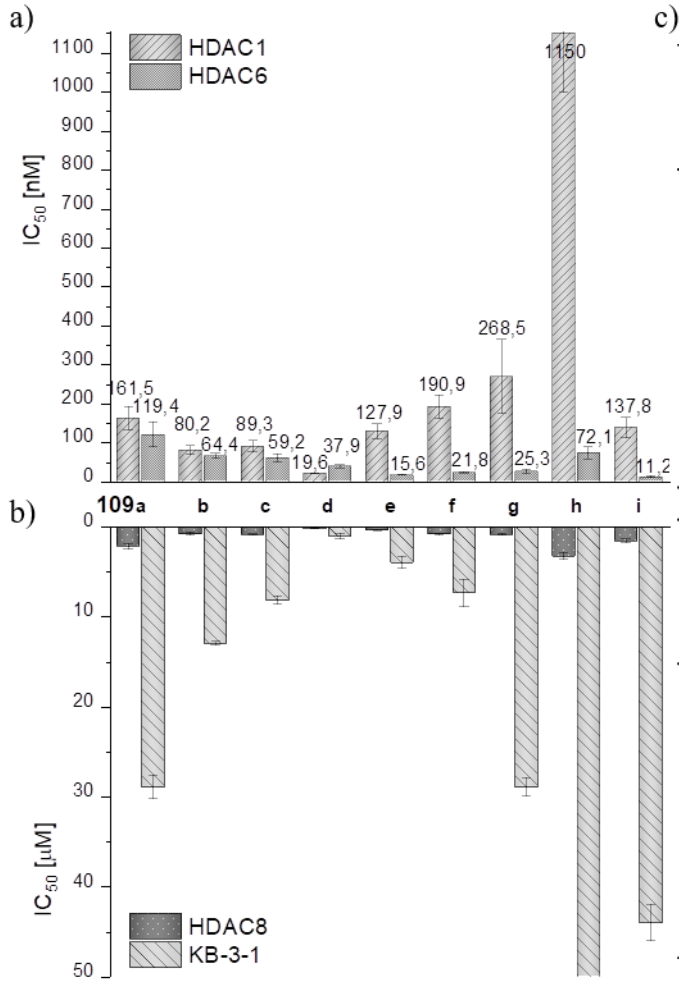


entry	peptidomimetic	pg	R^1	R^2	X	**109**, yield
a)	**46f**		H	cyclohexane	-CH=CH-	**109a**, 24%
b)	**46c**		H	$CH_2CH(CH_3)_2$	-CH=CH-	**109b**, 43%
c)	**46b**		H	$CH(CH_3)_2$	-CH=CH-	**109c**, 16%
d)	**46a**	Boc	H	H	-CH=CH-	**109d**, 3%
e)	**46c**		$CH(CH_3)_2$	H	-CH=CH-	**109e**, 37%
f)	**46e**		$CH_2CH(CH_3)_2$	H	-CH=CH-	**109f**, 9%
g)	**46g**		cyclohexyl	H	-CH=CH-	**109g**, 6%
h)	**46l**		cyclohexyl	H	-CH=N-	**109h**, 25%
i)	**50d**		cyclohexyl	H	-S-	**109i**, 16%

After acidic methanolysis of sulfinamides **46** and **50** with diluted HCl, the free amines were reacted with 2-benzofuranoyl chloride to give carboxamides **108a-i**. Under basic conditions, the methyl esters **108a-i** were converted with an excess of hydroxylamine into hydroxamic acids **109a-i**. Hydrolysis of the esters was observed as byproduct of the reaction via LCMS. Low solubility in water, acetonitrile or any other solvent except for DMSO led to significant losses during the purification process giving total yields of 6-43 %.

V-3. SAR of HDAC Inhibitors

The inhibitory activity of the synthesized compounds was determined in an enzyme inhibiting assay developed by Schwienhorst *et al.* [190,191]. Application of a fluorescent substrate developed by Jung *et al.* allowed monitoring of the HDAC inhibition by fluorescence quantification [192]. The results of the SAR study are summarized in Figure 33c and visualized in Figure 33a,b.



c)

Compound	HDAC1 [a] IC_{50} ± SEM [nM]	HDAC6 [a] IC_{50} ± SEM [nM]	Selectivity HDAC1/ HDAC6
109a	161.5±30.6	119.4 ± 30.4	1.35
109b	80.2±10.2	64.4 ± 6.7	1.25
109c	89.3±14.6	59.2 ± 9.2	1.51
109d	19.6±1.4	37.9 ± 4.1	0.52
109e	127.9±19.3	15.6 ± 0.9	8.20
109f	190.9±30.5	21.8 ± 1.6	7.40
109g	268.5±95.3	25.3 ± 5.1	8.76
109h	1150±150	72.1 ± 15.2	16.00
109i	137.8±26.2	11.2 ± 1.1	12.30

Compound	HDAC8 [a] IC_{50} ± SEM [nM]	Selectivity HDAC8/ HDAC6	Cyto-toxicity EC_{50} [mM] [b]
109a	2200 ± 300	18.4	29±1.3
109b	803 ± 111	43232	13±0.2
109c	916 ± 93	43235	8.2±0.4
109d	232 ± 22	43106	1.08±0.3
109e	417 ± 53	43307	4±0.7
109f	862 ± 107	39.5	7.4±1.5
109g	876 ± 125	34.6	29
109h	3300 ±400	45.8	100
109i	1600 ± 200	142.9	44

Figure 33. Results of the SAR study of compounds **109a-i**. a) Comparison of inhibition of HDAC1 and HDAC6. IC_{50}(±SEM) values are given in nM. b) Comparison of inhibition of HDAC8 and cytotoxicity values on KB-3-1 cell line. IC_{50}(±SEM) values are given in µM. c) Table with all test results and their corresponding selectivity.

[a] The inhibition at each inhibitor concentration was determined as triplicates for HDAC1 and HDAC6 and as technical and biological duplicates for HDAC8.

[b] Cytotoxicity values refer to cell line KB-3-1 and were determined as sixfold replicates.

While (*S*)-configured hydroxamic acids **109a-c** are not very active against HDAC1,6 and 8, their potency toward HDAC6 even decreases with increasing bulkiness of the substituent in the C^{α} position. The (*R*)-configured compounds **109e-i** are potent inhibitors of HDAC6 without significant influence of the R^1 substituent size. However, selectivity on HDAC6 is largely enhanced for *R*-configured compounds **109e-i** relative to the achiral parent compound **109d**. Inhibition of HDAC8 by hydroxamic acids **109a-i** is significantly weaker (Figure 33b). A correlation between cytotoxicity and HDAC1 inhibition could be observed. Unexpectedly, the picolinate-based peptidomimetic **109h** was inactive. Probably, due to an intramolecular H-bond between the hydroxamic acid and the pyridine *N*-atom, the Zn^{2+} binding is weakened. Thiophene-based peptidomimetic **109i** on the other hand shows an extraordinarily high HDAC6-inhibitory activity affinity and selectivity. Both features are probably related to the slight curvature in the backbone of **109i**.

The observed structure-activity relationships, in particular with respect to the influence of the configuration, are clearly supported by molecular docking studies with the recently elucidated X-ray crystal structure of the complex of HDAC6 and trichostatin A [193,194].

The peptidomimetics described in Chapter III were applied as a linker segment for potent HDAC inhibitors. (*R*)-Configured propargylamides mimic (*S*)-configured lysine-based substrates and display high activity and selectivity toward HDAC6. In particular, thiophene derivative **109i** emerged as a selective low-nanomolar HDAC6 inhibitor with good HDAC6 selectivity while retaining low cytotoxicity.

V-4. References (170-194)

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VI Peptidomimetics as RGD-Mimetics

In this chapter, the application of the discussed peptidomimetic scaffolds as integrin αvβ3 antagonists is described. Therefore, the recognition amino acid sequence arginine-glycine-aspartate will be imitated linking an arginine analogous propargylamide to different aspartic acid surrogates. The glycine-spacer will be replaced by a rigid ethynyl-based spacer. The geometry of the novel class B peptidomimetics will be compared to established mechanistic class D peptidomimetics and class A modified peptides reported in literature.

VI-1. Design of mechanistic Peptidomimetics

The tripeptide sequence RGD (-Arg-Gly-Asp-) is the recognition epitope of extracellular matrix proteins to interact with diverse transmembrane cell adhesion receptors [195], which are associated with adhesion [196,197] and signal transduction [198]. Mimicry of this recognition sequence is a promising approach to disrupt protein-protein-interaction [199,200]. Thus, effective antithrombotic agents based on RGD containing peptides have been developed to inhibit aggregation of fibronectin to GPIIβ/IIIα [200,201]. Radiolabeled RGD mimetics have been used for integrin imaging [202] and aggressive cytotoxic agents have been successfully linked to RGD mimetics to induce selective drug targeting [203].

In particular, the conformation of RGD mimetics determines the spatial arrangement of the functional groups and consequently its affinity for a particular receptor. γ-Turns [58] and type II' β-turn motifs [204] have been discussed as appropriate conformational constraints to induce a kink around the glycine moiety and the appropriate distance between the basic and acidic functional groups, which support the interaction with integrins [58,204].

The development of highly potent inhibitors like *Cilengitide*® proved, that cyclization is a convenient constraint to fix such types of conformation and to achieve proteolytic stability [50,205]. X-ray crystal structures of the αvβ3 integrin together with the peptide-based inhibitor, reveal a stretched and almost linear spatial arrangement of the arginine- and the aspartate side chain in the bound conformation [206]. The most important functional groups and their three-dimensional arrangement for possible interactions between integrin αvβ3 and its inhibitors can be deduced from the X-ray crystal structure.

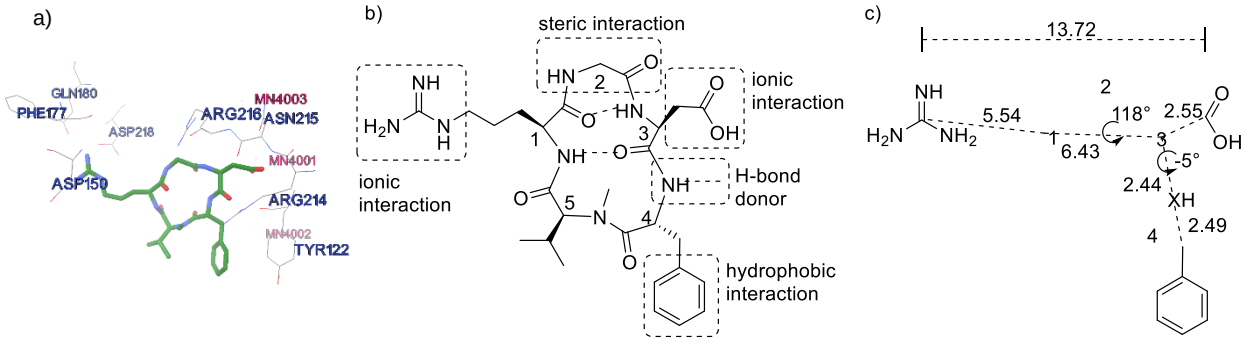


Figure 34. Interaction potential of *cyclo*(RGDfX) (X = V, L, A, …), derived from the X-ray crystal structure of integrin αvβ3 co-crystallized with *Cilengitide*® [206]. a) Interactions of *Cilengitide*® in the binding pocket of integrin αvβ3 found in the X-ray crystal structure. b) *Cilengitide*®: Important functional groups for the interaction are emphasized and labeled. c) Most significant distances and angles of *Cilengitide*® as representative of RGD-based agents.

A different approach to improve bioavailability, selectivity and the recognition of the active site of the receptor is the development of small mechanistic class D peptidomimetics, with the required functional groups arranged in an appropriate manner within a non-peptidic scaffold.

These mechanistic peptidomimetics represent promising PPI disruptors, since they follow Lipinski's criteria for drug admission and show high stability against proteases [29]. Moreover, investigations of the binding pocket of integrins showed, that only the guanidine- and the carboxylate moieties of RGD peptides are enlaced in the crevice between α- and β-subunit [206]. The rest of the molecule is exposed to the water surface associated with hydrolysis, rendering topographical mimetics more stable than peptide structures. Extensive analysis of the topology of bioactive conformations of the RGD motif is required to develop potent RGD mimetics. Typically, such mechanistic peptidomimetics consist of a basic (guanidine, amidine) and an acidic (carboxylate) functional group, which are arranged on a rigid scaffold. Some examples of class D peptidomimetics are displayed in Figure 35.

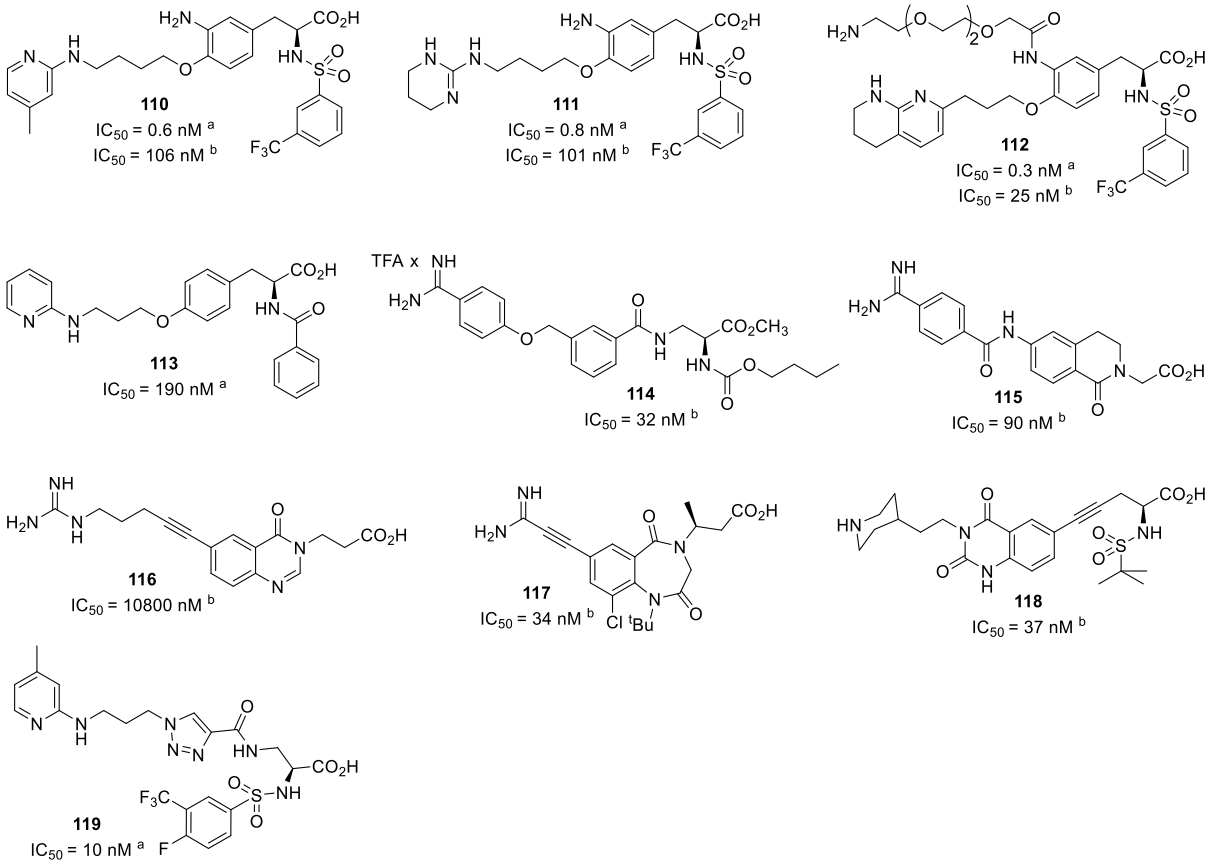


Figure 35. Topographical peptidomimetics of the RGD sequence. Compound **110**, **111**, **112** [207], compound **113** [208], compound **114** [209], compound **115** [210], compound **116**, **117** [211], compound **118** [200], compound **119** [202].

[a] IC_{50} values refer to integrin αvβ3 determined in a cell adhesion assay [202,207,208].

[b] IC_{50} values refer to glycoprotein αIIbβ3 determined in a platelet-rich plasma assay [200,207,209–211].

Whereas an ester [212] or hydroxamic acid [212] instead of the carboxylic acid of aspartate are rare (e.g. compound **114**) [209], diverse surrogates of the guanidine of arginine are reported in literature, like 2-aminopyridine moieties (compounds **110**, **112**, **113** and **119**) [202,207,208], amidines (compounds **114**, **115**, **117**) [209–211] or piperidines (compound **118**) [200]. As in arginine, the basic group usually terminates an aliphatic side chain, but connects onto an alkyne (e.g. compound **117**) [211] or a benzene ring (e.g. compounds **114** and **115**) [209,210] are also conversant. The glycine spacer in the model peptide RGD has been replaced by various rigid structural elements, such as 1,3- (e.g. **114**) [209] or 1,4-disubstituted aromatics (e.g. compounds **110-112**) [207], quinazolinone systems (e.g. compounds **115-118**) [200,210,211], combined with alkynes (e.g. compounds **116**, **118**) [200,211] and triazoles (e.g. **119**) [202], which typically represent the core unit of the

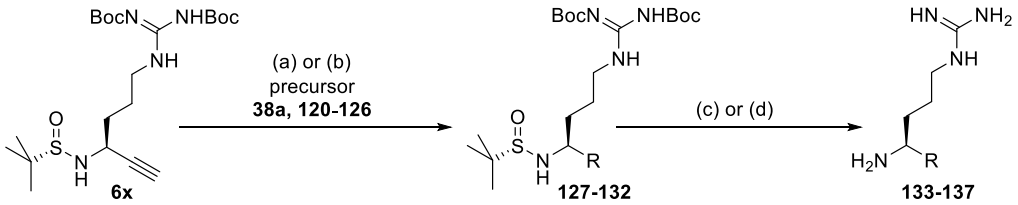
mimetics. As the elevated scaffolds of the glycine surrogates allow the introduction of versatile components including cytotoxins [203], radiolabels [202] or surface recognition elements to adhere to cells [199], the development of functionalized RGD mimetics has become subject to various current works. Successful approaches comprise polyethylenglycol linker units at the *N*-terminal part of the topographical mimetic [207] or β-alanine substituents at the *C*-terminal part of the backbone structure [202,208,209].

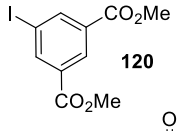
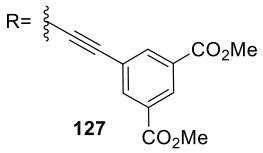
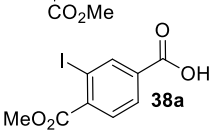
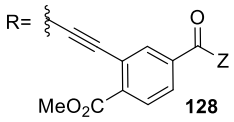
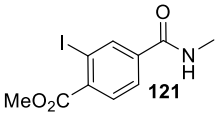
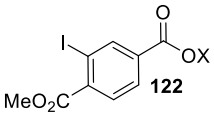
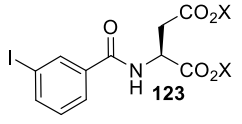
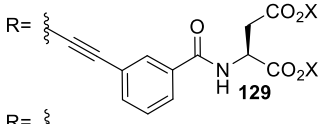
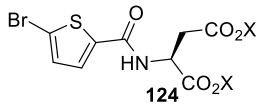
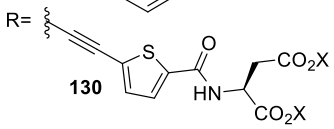
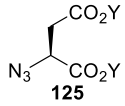
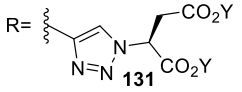
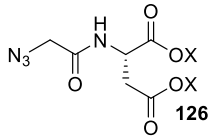
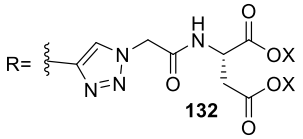
In this work class B peptidomimetics, referred to the definition of Pelay-Gimeno [31], with rigid scaffolds and orthogonal substitutable *N*- and *C*-terminus are applied to mimic the RGD sequence.

VI-2. Preparation of RGD analogous Class B modified Peptides

The synthesis of the RGD mimetics started with the arginine analogue propargylamide **6x**, which has been prepared in Chapter II using Ellman's chiral sulfonamide [1]. In analogy to the RGD sequence, the inhibitors of this work contain an arginine related side chain, which is connected via a rigid alkyne-based linker with an aspartate related side chain. The rigid linker moieties consist of alkyne-aryl units or 1,2,3-triazoles, which can be formed by reliable Click reactions.

Table 10. Synthesis of RGD mimetics **133-137** by conversion of the arginine analogous propargylamide **6x** with aspartate analogous aromatic halides **38a** and **120-124** via *Sonogashira* cross-coupling or with azides **125**, **126** via copper catalyzed [3+2]cycloaddition.



entry	precursor [a]	conditions [b]	protected peptidomimetic [a]	yield	conditions [b]	RGD mimetic, yield
a)	 **120**	(a)	R=  **127**	**127**	43%	
b)	 **38a**	(a)	R=  **128**	**128a**, Z=OH	0%	
c)	 **121**	(a)		**128b**, Z=NHCH$_3$	0%	
d)	 **122**	(a)		**128c**, Z=OX	52%	(c) **133**, 37%
e)	 **123**	(a)	R=  **129**	**129**	74%	(c) **134**, 3%
f)	 **124**	(a)	R=  **130**	**130**	64%	(c) **135**, 22%
g)	 **125**	(b)	R=  **131**	**131**	39%	(d) **136**, 38%
h)	 **126**	(b)	R=  **132**	**132**	59%	(c) **137**, 80%

[a] In compounds **122-132**, X = *tert*-Butyl and Y = Me. In compounds **133-137**, X = Y = H.

[b] Reaction conditions: (a) $PdCl_2(PPh_3)_2$, CuI, piperidine/THF, 1:3. (b) $CuSO_4$, sodium ascorbate, DMF/H_2O, 10:1. (c) TFA/Triisopropylsilane/H_2O 190:5:5, rt, 36 h. (d) 1. LiOH, MeOH/H_2O, 2:1, 0 °C, 12 h; 2. TFA/Triisopropylsilane/H_2O 190:5:5, rt, 36 h.

The aromatic halides **120** and **38a** were obtained by a *Sandmeyer* type reaction. Dimethyl 5-aminoisophthalate and 3-amino-4-(methoxycarbonyl)benzoate were reacted with $NaNO_2$ in half-concentrated HCl and subsequent addition of KI and I_2 gave the desired

aromatic iodides **120** and **38a** in yields of 30 % and 87 %, respectively. As the benzoates are supposed to resemble the *C*-terminus of a peptide, carboxylic acid **38a** was converted into an acid chloride, which was reacted with methylamine to afford methylamide **121** in a yield of 43 %. However, neither benzoate **38a** nor amide **121** could be successfully coupled with propargylamide **6x** under *Sonogashira* conditions. Most probably, the palladium catalyst was coordinated by the carboxylic acid of **38a** or the amide of **121**, respectively.

To improve the reactivity of halide **38a** for the following *Sonogashira* cross-coupling, the carboxy group was protected as *tert*-butyl ester to provide diester **122** in a yield of 50 %. Aryl iodide **122** was coupled in a *Sonogashira* reaction with the arginine analogous propargylamide **6x** to provide peptidomimetic **128** in 52 % yield. Under acidic conditions, the *tert*-butylsulfinyl protective group, both Boc protective groups and the *tert*-butyl ester were cleaved simultaneously to form inhibitor **133**.

Geometric considerations of ligand **133** suggest that the size of the phenylethynyl-linker unit between the side chains is only 4.9 Å, resulting in a distance of 13.0 Å between the guanidino and carboxylate moieties, which was estimated to be rather short. Therefore, the size was extended by linking an aspartic acid derivative via an amide bond to 3-iodobenzoic acid and 5-bromothiophene-2-carboxylic acid, providing the aromatic halides **123** and **124** in 48 % and 30 % yield, respectively. Both aromatic halides could be readily coupled with alkyne **6x** in a *Sonogashira* cross-coupling reaction leading to **129** and **130** in 74 % and 64 % yield, respectively. The cleavage of all protective groups was performed simultaneously under acidic conditions. Diester **129** was dissolved in HCl (2 M, CH_2Cl_2/dioxane, 1:1), which led to an incomplete cleavage of the protective groups, resulting in low yield 3 %. Complete cleavage was accomplished with TFA, triisopropylilane and H_2O (95:2.5:2.5).

For the synthesis of RGD-mimetics with a triazole ring, (*S*)-2-azidosuccinic acid **125** was required as *C*-terminal moiety. Starting from (*S*)-aspartic acid, methylation and subsequent azide transfer yielded the desired precursor **125** in only 11 % yield, whilst the reverse order of reaction worked even worse (4 % overall yield). However, conversion of dimethyl (*R*)-malate with NaN_3 under *Mitsunobu* conditions led to azide **125** in 18 % yield (see also Scheme EP3, Experimental part). [3+2]-Cycloaddition of azide **125** with propargylamine **6x** and subsequent cleavage of the ester groups with LiOH and of all other protective groups under acidic conditions yielded peptidomimetic **136** in 15 % overall yield.

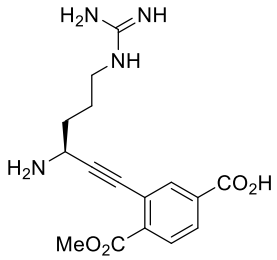
As the linker unit of RGD mimetic **136** appeared to be comparatively short, as in **133**, a triazole-based mimetic with an extended linker unit was prepared.

Therefore, *tert*-butyl protected aspartic acid was acylated with azidoacetic acid, which was obtained by nucleophilic substitution of bromoacetic acid with NaN_3. [3+2]-Cycloaddition of azide **126** with propargylamine **6x**, followed by simultaneous cleavage of all protective groups under acidic conditions yielded triazole **137** in an overall yield of 47 %.

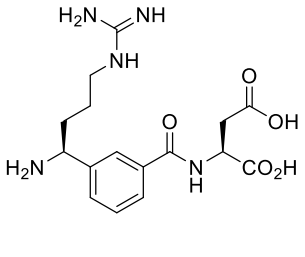
VI-3. Biological Evaluation of novel RGD Mimetics

The affinity of the RGD analogous peptidomimetics **133**-**137** to integrin αvβ3 was determined in a standardized, competitive ELISA, developed by Frank *et al*.[213] and evaluated by Kapp *et al*. [143]. In the assay, the inhibition of αvβ3 binding to immobilized vitronectin by the competing test compound is measured. As the peroxidase on IgG-POD, which is linked via anti-αvβ3 to integrin αvβ3, only converts a colorless substrate into a colored one when it's immobilized on vitronectin, the intensity of the color correlates with the amount of integrin, that does not bind the test compound.

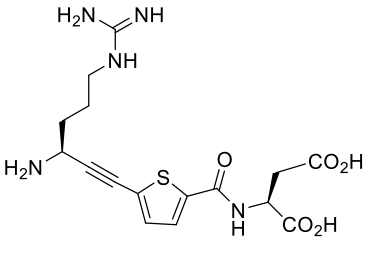
Table 11. IC_{50}-values of the peptidomimetics **133**-**137** on integrin αvβ3, using the competitive ELISA, developed by Frank *et al*.[213] and evaluated by Kapp *et al*.[143] All IC_{50}-values were referenced to *Cilengitide*® (0.54 nM) [143]. For Sigmoidal Curves of ELISA- and cell adhesion assays, see Figures EP5 and EP6, Experimental Part.



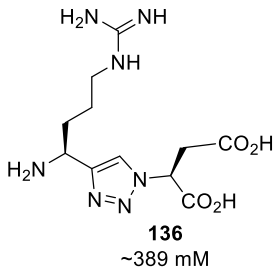
133
~73 mM



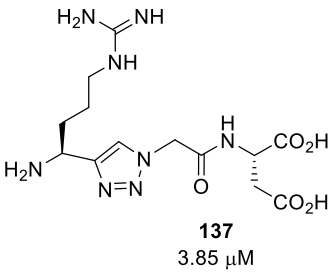
134
173.8 μM



135
41.91 μM



136
~389 mM



137
3.85 μM

The aromatic carboxylate **133** has a very low affinity, which could be increased 400-fold by an extension of the backbone, like in compound **134**. Substitution of the aromatic by a thiophene ring in compound **135** surprisingly led to another 4-fold increase of the affinity. The triazole based compound **136** has hardly any affinity. However, when the scaffold was elongated in compound **137**, the most active compound under investigation was obtained (IC_{50} = 3.85 μM).

Docking studies of all compounds to available crystal structures of αvβ3 were performed to understand the observed in vitro inhibition data and correlate them with Craig *et al.*'s discussion of the binding site of αvβ3 (also see Figure EP7-11 and Table EP33, EP34, Experimental Part) [214]. As expected, the benzoic acid of compound **133** is able to contact the MIDAS site of the β-subunit, but is too bulky and hydrophobic to enter the corresponding crevice (Figure 36, see also Figure EP9, Experimental Part). Yet, the guanidino group can reach one side of the highly polar pocket of the αv-subunit, forming hydrogen bonds to Asp218 and Gln180.

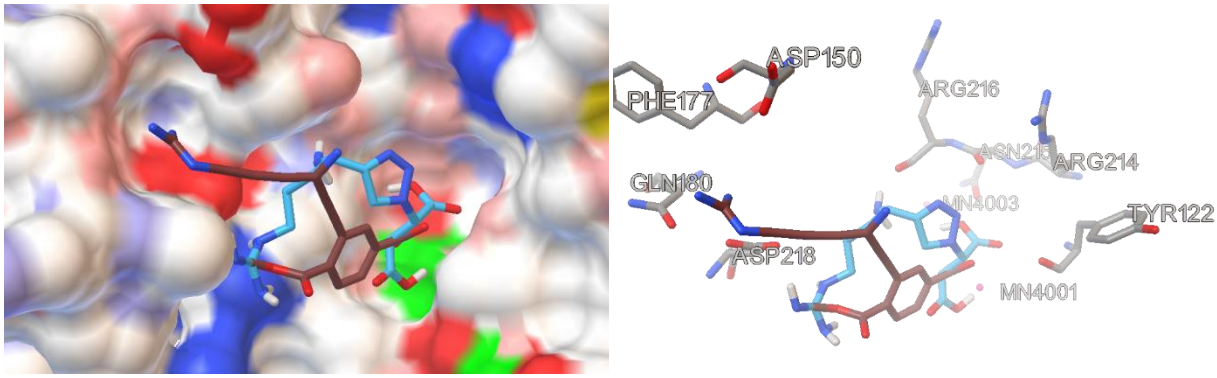


Figure 36. Binding modes of the short RGD mimetics **133** (brown) and **136** (cyan), docked into the binding pocket of integrin αvβ3. Left side: Demonstration of the crevices between the αv- and the β3-segment. Polar regions are colored in red, hydrophobic regions are colored in blue and Mn^{2+} ions are colored in green. Right side: Most important amino acid residues of the binding pocket of integrin αvβ3. The Mn^{2+} ions are shown as pink dots.

The interaction potential of the smaller triazole-based compound **136** appears to be even smaller (see also Figure EP9 and Table EP34, Experimental Part). Although its carboxylic acid has an appropriate geometry to enter the crevice of the MIDAS site, the whole molecule is too short for the guanidino group to reach the polar binding pocket of the αv-segment, allowing only a weak interaction with Asp218. Both RGD mimetics **133** and **136** appear to be too short for appropriate interaction of the terminal basic and acid functional groups with integrin αvβ3. In order to increase the interaction with integrin αvβ3 the size

of the ligands and thus the distance between the acidic and basic functional groups was increased. The ligands with extended linkers including **134**, **135** and **137** showed increased affinity towards integrin αvβ3 (Figure 37, see also Figure EP10, 11 and Table EP34, Experimental Part).

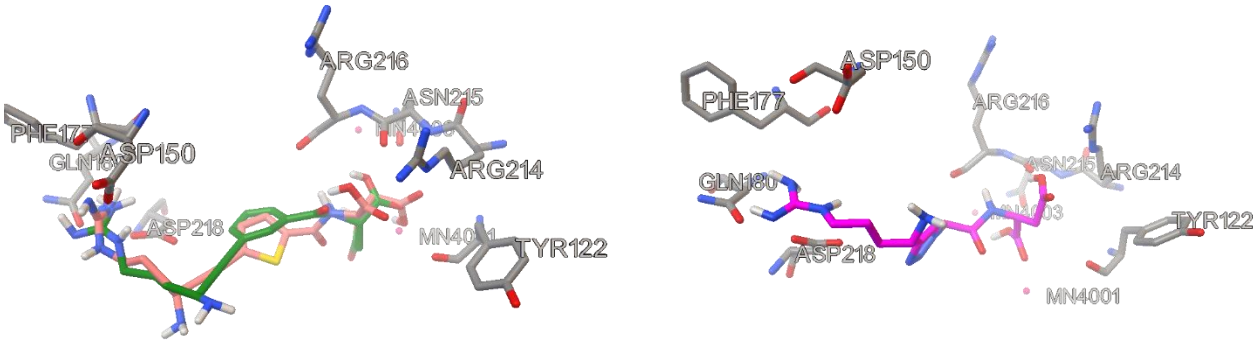


Figure 37. Binding modes of the RGD mimetics **134** (green, left side), **135** (rose, left side) with an arylethynyl spacer as well as the triazole-based mimetic **137** (magenta, right side) docked into the binding pocket of integrin αvβ3. The Mn^{2+} ions are shown as pink dots.

Introduction of a spacer between the benzene ring and the carboxy moiety of **133** led to a ca. 400-fold increased affinity of **134** towards integrin αvβ3. The higher affinity of **134** is explained by stronger interaction in the binding pocket. In particular, H-bonds between the guanidine group of **134** and carbonyl moieties of Asp150, Gln180 and Asp218 are found and the carboxy group of **134** coordinates the Mn^{2+} ion within the MIDAS site. Both ends are able to enter the polar crevices between the αv- and β3-subunits. The additional amide group of **134** can contact the backbone-carbonyl moiety of Arg216. Replacement of the benzene ring by a thiophene ring (**135**) does not alter the docking result, but increases the affinity 4-fold.

Introduction of a similar spacer into triazole **136** led to 10000-fold increased affinity. Both crevices between αv- and β3-subunits can be addressed by the guanidino group and the carboxy moiety. The guanidine group can form H-bonds to Gln180 and Asp218 and the carboxy group of the aspartic acid can coordinate the MIDAS site. Furthermore, a H-bond between the amide NH of the RGD mimetic and the backbone carbonyl moiety of Arg216, as well as between the triazole and the backbone carbonyl moiety of Asp218 can be detected.

Notably, all investigated compounds are far less active than the reference compound, *Cilengitide*®, or any of the topographical class C peptidomimetics compiled in Figure 35. Although all compounds are hydrophilic and small (less than 400 g mol^{-1}), they contain a lot of H-bond acceptor (10-16) and H-bond donator groups (6-9). So, they inconveniently do not comply with Lipinski's rule of five [29]. Nevertheless, as class B peptidomimetics, they retain a *N*- and *C*-terminus, maintaining the option of cyclization. The linear tripeptide RGD (IC_{50} = 89±12 nM) [143] shows the highest similarity to the mimetics **133**-**137** of this work. Still, the linear RGD tripeptide has a 43-fold higher affinity to integrin αvβ3 than the most active mimetic **137** of this work.

VI-4. Conclusion

In this chapter, a novel concept to imitate the RGD sequence with versatile class B peptidomimetics is presented. In the RGD mimetics, the glycine residue is replaced by an arylalkynyl moiety or a triazole ring. Attachment of an aspartic acid moiety to the central core unit resulted in a 400- to 10000-fold increased affinity (**134**, **135**, **137**). Although the presented compounds show moderate αvβ3 affinity, they offer versatile potential for further modifications, like the replacement of the amide moiety in compounds **134**, **135** and **137**, attachment of cap-groups to the *C*- and *N*-terminus of the ligands or cyclization. Despite their comparatively low affinity, the newly designed compounds combine the proteolytic stability of topographical peptidomimetics with the versatile substitution pattern of the linear RGD sequence.

VI-5. References (195-214)

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VII Summary and Perspectives

In this thesis, novel devices for the design of peptidomimetics were explored. The amino acid isosteric propargylamides were established as elementary building blocks. In a three step *de novo* synthesis 24 propargylamides **6** with diverse functional groups in the side chain including aliphatic, aromatic, non-proteinogenic, polar, acidic and basic groups were prepared in high diastereomeric purity (Figure 38).

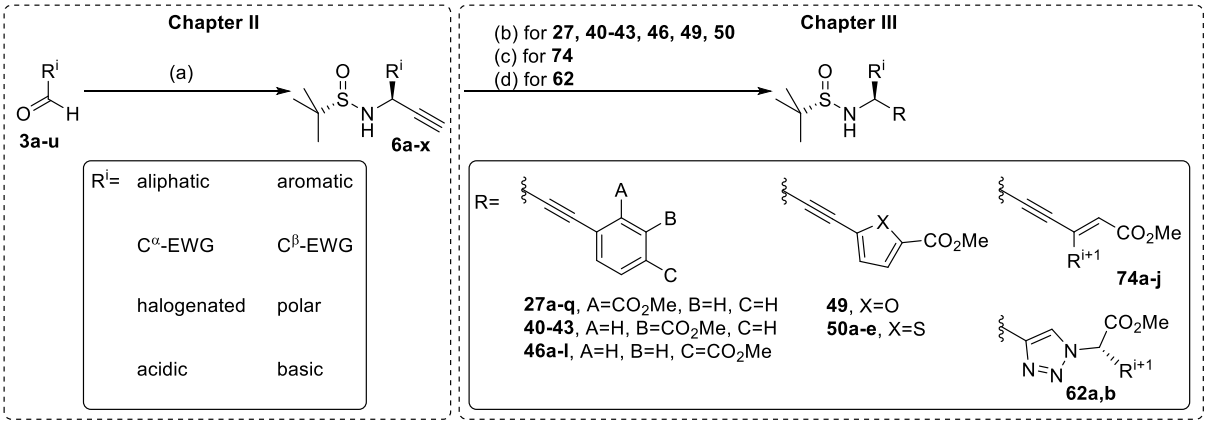


Figure 38. *De novo* preparation of diastereomerically pure propargylamides **6** and their conversion into peptidomimetics. (a) 1. (*S*)-*tert*-Butylsulfinamide (**2**), $CuSO_4$, CH_2Cl_2, 3 d. 2. Trimethylsilylethynyl lithium, $AlMe_3$, toluene, -78 °C, 2-4 h. 3. KF, 18-crown-6, THF/H_2O (98:2), 0 °C, 4-8 h. (b) Haloarenes (**26** gave **27**, **36-39** gave **40-43**, **45** gave **46**, **47** gave **49**, **48** gave **50**), $PdCl_2(PPh_3)_2$, CuI, THF/piperidine (3:1), overnight, rt. (c) Methyl propynoate **73**, $Pd(OAc)_2$, TDMPP, toluene, rt, 2 h. (d) Azide **61**, $CuSO_4$, sodium ascorbate, DMF/H_2O (10:1), rt, 2d.

Aldehydes **3a-u** were condensed with Ellman's chiral sulfinamide **2**. Diastereoselective *Re*-face addition of trimethylsilylethynyl lithium to the (*S*)-configured sulfinylimines **4** and subsequent removal of the TMS group gave propargylamides **6a-x**. An electron withdrawing group (EWG) in α-position resulted in susceptibility of the propargylamides towards bases, while an EWG in β-position increased the acidity of the adjacent methylene moiety leading to a competition between deprotonation and nucleophilic addition during the reaction with trimethylsilylethynyl lithium. Surprisingly an azide present in the side chain led to an intramolecular non-catalyzed *Huisgen* [3+2] cycloaddition at ambient temperature. This side reaction could be completely suppressed by reduction of the azide via *Staudinger* reaction directly after nucleophilic addition of trimethylsilylethynyl lithium at -78 °C. During the reduction of the azide with PPh_3 simultaneous cleavage of the TMS group was observed (Chapter II).

A large set of peptidomimetics **27**, **40-43**, **46**, **49** and **50** with diverse structural elements was obtained by connection of the enantiomerically pure propargylamides **6a-x** with halo-benzoates **26**, **36-39**, **45**, **47** and **48** via *Sonogashira* cross-coupling (Figure 38).

The backbone curvature of these peptidomimetics was defined by the substitution pattern of the arenes. Preferences of particular conformations were analyzed by combination of molecular dynamics (MD) simulations with X-ray crystal structure analysis. Remarkably, during the preparation of the *ortho*-substituted benzoic acid derivative **27m** an intramolecular 5-exo-dig cyclization with the alkyne forming benzofuran **28** was observed under *Sonogashira* conditions. Another investigated side reaction was the Propargylamide-Enimine rearrangement, which occurred when peptidomimetics with EWGs such as CF_3, Ph, C_6F_5 in α-position were exposed to alkaline conditions. The discovered tautomerism converting propargylamides into α,β-unsaturated *N*-sulfinylimines **76** was thoroughly studied.

Further peptidomimetic scaffolds were obtained by Pd-catalyzed hydroalkynylation of methyl propynoates **73** with propargylamides **6** giving versatile α,β^3-dipeptide isosteres **74**. Due to the rigid system of **74**, the side chain R^{i+1} is locked in a particular orientation χ. Copper catalyzed [3+2] cycloaddition of propargylamides **6** with azide **61** gave 1,4-disubstituted triazoles **62**. The backbone of these peptidomimetics accurately represents a *trans*-configured α,β^2-dipeptide.

Based on the design-concept of the inaugurated peptidomimetics, enhanced aromatic systems were introduced to predefine the relative 3D orientation of *N*- and *C*-termini with the aim to form structural turn motif mimetics and to thereby influence the secondary structure of a peptide (Figure 39).

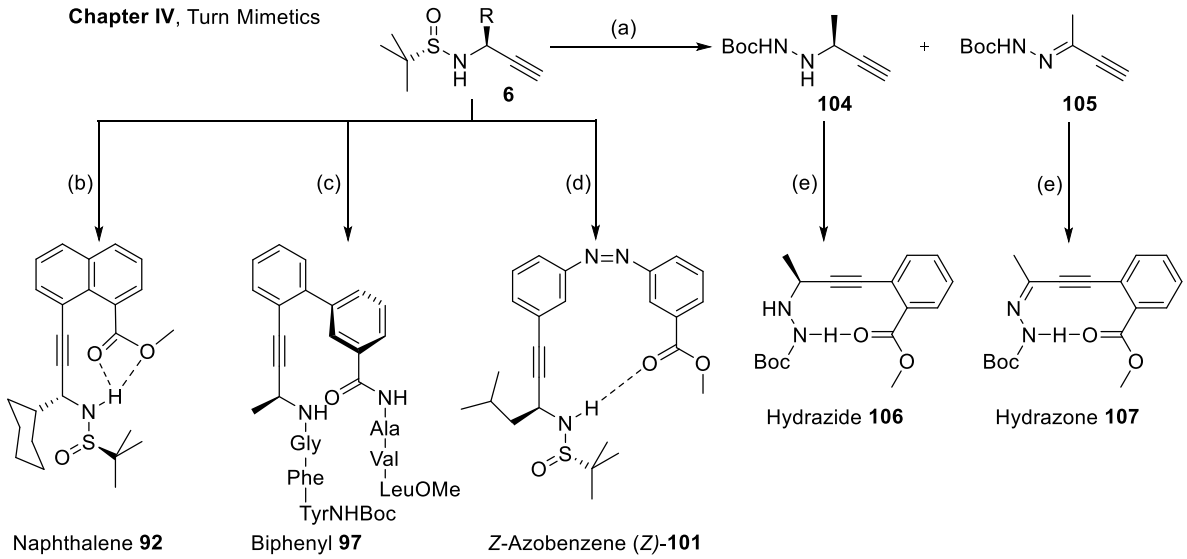


Figure 39. Various structural turn mimetics based on the amino-propynyl-benzoate scaffold. (a) 1. (*S*)-**6a**, HCl (4 M in dioxane), MeOH, rt, overnight. 2. Amine transfer reagent **103**, saturated $NaHCO_3$ solution/THF (1:1, 40 mL), rt, overnight. (b) (*R*)-**6e**, naphthalene **91b**, $PdCl_2(PPh_3)_2$, CuI, THF/piperidine (3:1), rt, overnight (=standard conditions). (c) 1. (*S*)-**6a**, HCl (4 M in dioxane), MeOH, rt, overnight. 2. HO-Gly-Phe-Tyr(*tert*Bu)-NHBoc, HATU, HOAt, CH_2Cl_2, DIPEA, rt, 3 d. 3. Peptide-haloarene **96**, $PdCl_2(PPh_3)_2$, CuI, dioxane/DIPAH/DMSO (15:4:1), microwave, 60 °C, 2 h. (d) (*S*)-**6c**, iodoazobenzoate **99**, standard conditions. (e) 2-Iodobenzoate **26a**, standard conditions.

^{1}H NMR spectroscopy, the temperature coefficient Δδ/ΔT, CD spectroscopy and X-ray crystal structure analysis were used to identify intramolecular H-bonds indicating the adoption of non-natural forward ε- or ζ-turn motifs. The hydrophobic naphthoate-based turn mimetic **92** was designed as DNA-intercalating warhead of a hairpin mimetic. However, its incorporation into a short peptide and the subsequent biological evaluation are not yet completed. Whereas the twisted biphenyl scaffold of peptidomimetic **94** precluded an alignment as a turn motif, the analogous hairpin mimetic **97** with two short peptide chains at the *N*- and *C*-termini nucleated a β-sheet by an extended loop. When exposed to irradiation, smart (*E*)-configured azobenzene-based peptidomimetics (*E*)-**100** and (*E*)-**101** completely isomerized into (*Z*)-configured isomers, which in contrast to the (*E*)-isomers formed a turn mimetic. Using the electrophilic amine transfer reagent **103** propargylamines **102** were converted into hydrazines **104** and hydrazones **105**. *Sonogashira* cross-coupling reactions of **104** and **105** with 2-iodobenzoates **26a** provided the strong turn motif mimetics **106** and **107**. Introduction of one or two amino acids at the *N*- and *C*-termini of all discussed turn mimetics would be a promising approach to obtain valuable information on their properties as hairpin mimetics.

At last, some remarkable peptidomimetics of this work are compiled, which were designed in analogy to interesting natural templates (Figure 40). The superhydrogelator dipeptide H-Leu-Phe-OMe was exactly imitated by the alkynylalkene **75b** and the triazole **63d**. While the minimum hydrogel forming concentration of triazole **63b** was very high in water (22-32 mM), stable gels were formed from ^{i}PrOH and CH_2Cl_2 solutions at low concentrations (< 2 mM). Structurally related peptidomimetics **63c** and **75d** were designed to imitate the natural dipeptide aspartame, a potent synthetic sweetener. However, the evaluation of their sweetness has not been performed. Introduction of additional side chains at the phenyl moiety of the *meta*-substituted aminopropynylbenzoate scaffolds was achieved by using appropriately substituted haloarenes prepared by electrophilic aromatic substitution. In analogy to the photoswitchable side chain of 4-(phenyldiazenyl)-phenylalanine, compound **44** was prepared with a phenyldiazenyl substituent in the backbone. The ratio of *E:Z*-isomers was altered upon irradiation of **44** from 87:13 to 45:55. A remarkable influence of the isomerization on the backbone conformation was observed. Substituents in 4-position were introduced as additional side chains (**42**) to imitate one α-helical turn with constrained preorientation χ of the side chain R^{i+1}. Three helix turns of a natural peptide could be accurately mimicked by **57** consisting of a dimer of *meta*-substituted aminopropynylbenzoate.

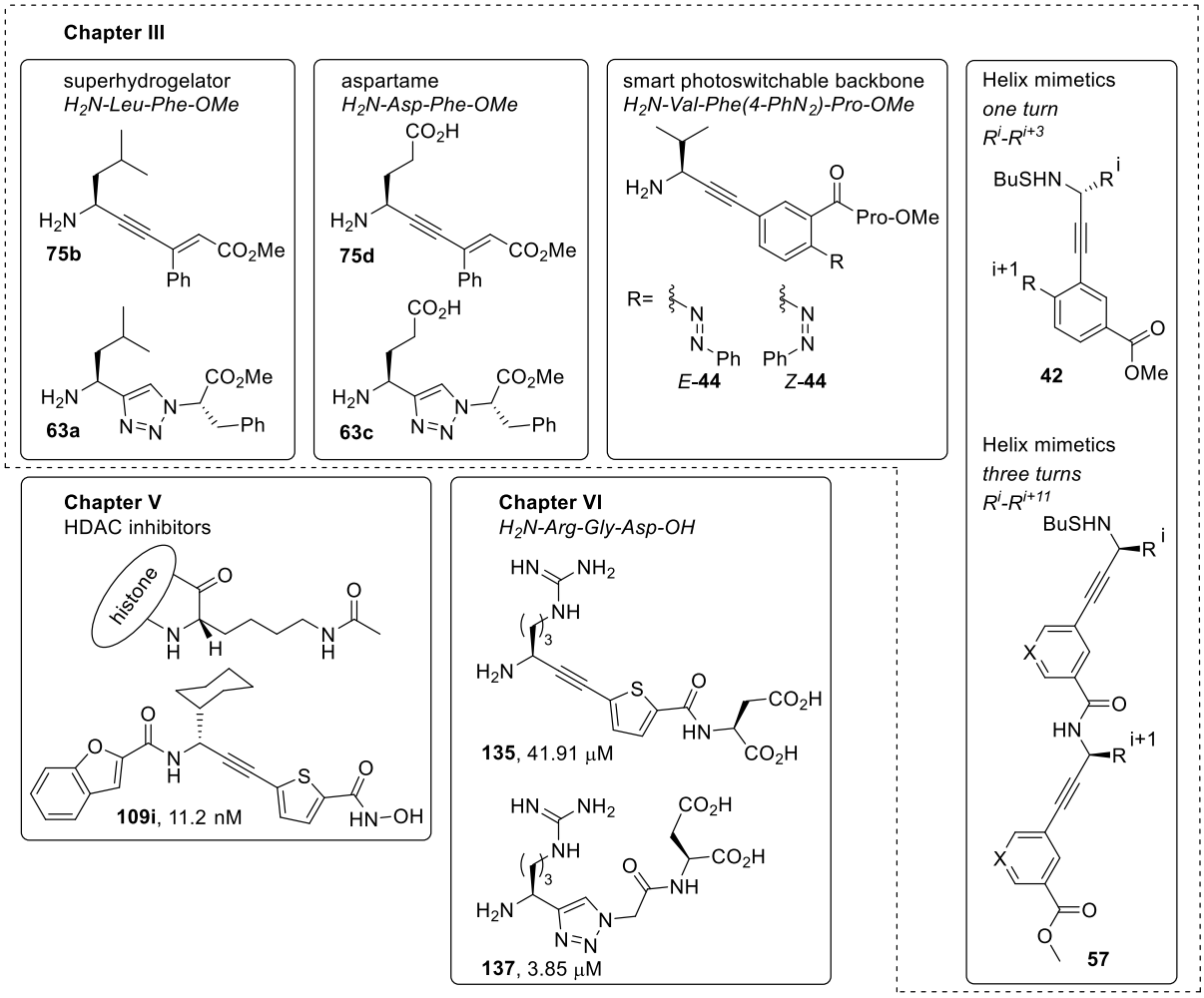


Figure 40. Remarkable representatives of peptidomimetics as isosteres of natural templates. The headlines represent the natural compartement imitated by the depicted peptidomimetics. The IC_{50} value of compound **109i** refers to HDAC6 and the IC_{50} value of compounds **135** and **137** refer to αvβ3. **42**, R^i=$(CH_2)_3CN$, $CHMe_2$, CH_2CHMe_2, R^{i+1}=CO_2Me, NH_2, N=NPh, N=NPh-4-NMe_2. **57**, X=CH, N, R^i/R^{i+1}=CH_2CHMe_2, $CHMe_2$.

Linear peptidomimetics **46** and **50** were used as isosteres of ω-acetylated lysine, the natural substrate of histone deacetylases (HDACs). Conversion of peptidomimetics **46** and **50** into hydroxamic acids **109** resulted in potent and selective HDAC6 inhibitors. A docking supported SAR study confirmed that (*R*)-configured peptidomimetics with aliphatic side chains increased HDAC6 inhibitory activity compared to the HDAC inhibition of the achiral, unsubstituted model compound up to 2.4-fold. Moreover, the selectivity over other HDACs was increased at least 15.8-fold. Replacement of the benzene ring by a thiophene ring led to inhibitor **109i** with remarkably enhanced affinity (2.3-fold), selectivity (>1.4-fold) and reduced cytotoxicity (1.5-fold) in comparison to the analogous *para*-substituted

phenyl derivative **109g**. The herein discussed modifications of the linker moiety shall contribute to the rational design of novel HDAC inhibitors.

Imitation of the RGD sequence was approached by connection of arginine analogous propargylamide **6x** with different carboxylate moieties. The glycine moiety between arginine and aspartate of the tripeptide RGD was reproduced by the rigid backbone of the benzene-, thiophene- and triazole-based peptidomimetics **133-137**. A competitive ELISA based assay (supported by docking studies) attested the novel RGD mimetics a low micromolar affinity. Although the IC_{50} values of the novel leads are quite high in comparison to the linear RGD sequence, the arginine analogous propargylamide **6x** offers promising options for the discovery of new RGD mimetics and subsequent SAR studies.

The diversity of natural products mimicked by the herein reported novel peptidomimetics indicates the versatility of the discussed building blocks as devices for the design and synthesis of new bioactive lead compounds.

IIX Experimental Part

IIX-1. General Methods and Materials

If not mentioned differently, all reagents and solvents were purchased from commercial sources and applied without further purification. THF and Et_2O were kept over KOH before being dried with sodium/benzophenone under reflux and were freshly distilled before use. Toluene was predried over $CaCl_2$, then dried over sodium under reflux and distilled freshly before use. CH_2Cl_2 used for synthesis was predried over $CaCl_2$, dried over CaH_2 under reflux and distilled freshly before use. MeOH and EtOH were heated under reflux conditions over 2 h with magnesium and iodine, before distillation and storage over molsieves (3 Å). NEt_3 was refluxed and distilled first over KOH and then over NaH. After absolutation, NEt_3 was stored over molsieves (4 Å). DMSO was dried under reflux over CaH_2, distilled and stored over molsieves (4 Å) until use. CH_2Cl_2, EtOAc, PE and Et_2O used for aqueous work-ups or column chromatography were purchased in technical grade and distilled prior to application.

Schlenk-conditions: If not mentioned differently, the reactions were carried out under exclusion of moisture and oxygen in dried glassware under argon atmosphere. The argon gas was supplied from Linde (quality 4.0) and led through a column filled with phosphorpentoxide (sicapent®, *Merck*) before use.

Solvents were removed on a rotational evaporator at 40 °C and appropriately reduced pressure. Solvent residues were removed at rt and 0.001-0.1 mbar.

For column chromatography, Silica gel 60, 40-63 μm (*Merck*) was used. The eluents and their proportions are individually noted. Thin layer chromatography (TLC) was executed using silica gel 60 coated aluminium sheets with fluorescence indicator F254 (*Merck*). Spots were identified using different stains, such as $KMnO_4$, iodine, ninhydrin or UV light with a wavelength of λ = 254 nm or λ = 366 nm.

Preparative HPLC (Thermo Seperation Products): Equipment: UV detector: UV1000; pump: Thermo Seperation Products P4000; Method: column: Thermo Scientific Hypersil Gold (8 μm), 250 x 21.2 mm cartridge; flow rate: 10.00 mL min^{-1}; injection volume: 1.00 mL; detection at λ = 254 nm; solvents: A: water/acetonitrile/trifluoroacetic acid (94.9:5:0.1); B: water/acetonitrile/trifluoroacetic acid (5:94.9:0.1). gradient elution: (A %):

0-1 min: 100 %, 1-30 min: gradient from 100 % to 0 %, 30-44 min: 0 %, 44-45 min: gradient from 100 % to 0 %.

Melting point: Melting points were determined using a Büchi 540 melting point apparatus and are uncorrected.

Optical rotation was measured on a DIP-360 (Jasco) polarimeter with a sodium vapour light source at a specific given temperature. A quartz cell with a path length of 10 cm was used. The average of ten single measurements divided by the concentration in units of g/mL and the pathlength (1 dm). The sample concentration and solvent is given in c = g/100 mL in parentheses.

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance 300 (300.13 MHz for ^{1}H, 282.38 MHz for ^{19}F, 75.48 MHz for ^{13}C) or DRX 500 (499.87 MHz for ^{1}H, 470.43 MHz for ^{19}F, 125.70 MHz for ^{13}C) or Avance 500 (500.01 MHz for ^{1}H, 125.74 MHz for ^{13}C) or Avance 500 HD (500.20 MHz for ^{1}H, 125.79 MHz for ^{13}C) or Avance 600 (600.13 MHz for ^{1}H, 564.63 MHz for ^{19}F, 150.92 MHz for ^{13}C). chemical shifts (δ), given in the experimental section, are reported in ppm relative to TMS (δ_{TMS} = 0 ppm) and referenced to the solvent residue signals as internal standard: δ_i [ppm]: $CHCl_3$ (δ 7.26 ppm (^{1}H NMR) and δ 77.2 ppm (^{13}C NMR)) and CHD_2OD (δ 3.31 ppm (^{1}H NMR) and δ 49.0 ppm (^{13}C NMR)) and $D_2HCSOCD_3$ (δ 2.50 ppm (^{1}H NMR) and δ 39.5 ppm (^{13}C NMR)). Coupling constants (J) are reported in Hertz (Hz) with 0.05 Hz resolution. Multiplicities are described as singlet (s), doublet (d), triplet (t) quartet (q) or multiplet (m). The assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques (COSY, HMQC, HMBC).

MS: Nano-ESI mass spectra were recorded using an Esquire 3000 ion trap mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a standard nano-ESI source. Samples were introduced by static nano-ESI using *in-house* pulled glass emitters. Nitrogen served both as the nebuliser gas and the dry gas. Nitrogen was generated by a Bruker nitrogen generator NGM 11. Helium served as cooling gas for the ion trap and collision gas for MS^n experiments.

ESI mass spectra were recorded using an Agilent 6220 time-of-flight mass spectrometer (Agilent Technologies, Santa Clara, CA, USA) in extended dynamic range mode equipped with a Dual-ESI source, operating with a nitrogen generator NGM 11. Samples were

introduced with a 1200 HPLC system consisting of an autosampler, degasser, binary pump, column oven and diode array detector (Agilent Technologies, Santa Clara, CA, USA) using a C18 Hypersil Gold column (length: 50 mm, diameter: 2.1 mm particle size: 1.9 μm) with a short gradient (in 4 min from 0 % B to 98 % B, back to 0 % B in 0.2 min, total run time 7.5 min) at a flow rate of 250 μL min^{-1} and column oven temperature of 40 °C. HPLC solvent A consisted of water, acetonitrile and formic acid (94.9:5:0.1), solvent B of water, acetonitrile and formic acid (5:94.9:0.1). The mass axis was externally calibrated with ESI-L Tuning Mix (Agilent Technologies, Santa Clara, CA, USA) as calibration standard.

Elemental analysis was performed on an Element Analyser EURO EA.

IR: IR spectra were recorded as neat samples on a FT-IR spectrophotometer Nicolet 380 (Thermo Scientific) equipped with ATR technique (smart orbit).

Analytical HPLC (Thermo Scientific Accela): Equipment; UV detector: Thermo Seperation Products UV6000LP; pump: Thermo Seperation Products P4000; autosampler: Thermo Seperation Products AS100, Method: column: Jupiter 5 C18 Fa. Phenomenex, 250 x 4.60 mm cartridge; flow rate: 1.00 mL/min; injection volume: 0.2 μL; detection at λ = 254 nm; solvents: A: water/acetonitrile/trifluoroacetic acid (95.9:5:0.1); B: water/acetonitrile/trifluoroacetic acid (5:95.9:0.1). Gradient elution: (A, method 1): 0-9 min: gradient from 100 % to 0 %, 9-12 min: 0 %, 12-13 min: gradient from 0 % to 100 %. (A, method 1): 0-4.5 min: gradient from 100 % to 0 %, 4.5-7 min: 0 %, 7-8 min: gradient from 100 % to 0 %.

Crystal data were collected on an Agilent SuperNova diffractometer with Cu Kα radiation (**27n**, **29**, **31o**, **40d**, **46j**, **49a**, **50f**, **55c**, **76f**, **77g**, **104b**, **120**) or Mo Kα radiation (**41a**, **52b**, **66g**, **71**, **75e**, **75f**, **77c**, **107a**) was used. The crystals were kept at 100.0(3) K during data collection. Using Olex2 [215] the structures were solved and refined with the ShelX program package [216] using direct methods and least-squares minimization. The experimental part of each chapter contains the supplementary crystallographic data of all respective compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

IIX-2. Propargylamides

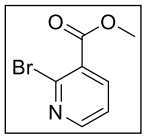
A detailed description of the propargylamide **6a-x** synthesis of Chapter II, side reactions like the intramolecular *Huisgen*-reaction forming triazoles **7-8**, as well as the corresponding NMR spectra and X-ray crystal structures have been recently published in the Beilstein JOC "*Asymmetric Synthesis of Propargylamines as Amino Acid Surrogates*" [1]. This experimental part is not attached to the Appendix.

IIX-3. Peptidomimetics

IIX-3. a) *ortho*-Substituted Peptidomimetics (26-27)

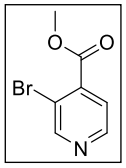
2-Iodobenzoate **26a-c** were purchased from Fisher Scientific.

Methyl 2-Bromonicotinate (26d). 2-Bromonicotinate was esterified in accordance to the description of Setliff & Huie [217]. Under argon atmosphere, thionylchloride (0.5 mL, 6.9 mmol, 1.4 eq) was added over a period of 30 min to a solution of 2-bromonicotinic acid (1.02 g, 5.06 mmol, 1.0 eq) in CH_2Cl_2 (30 mL) at -30 °C. The reaction mixture was slowly warmed up to rt and stirred for 3 h at ambient temperature, before anhydrous methanol (4 mL) was added in one portion. The solution was stirred for another 18 h, the solvent removed under reduced pressure and the residue was filtered through a short pad of silica gel to yield nicotinate **26d** in pure form.



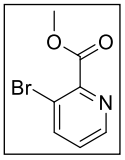
Slightly yellow fluid. Yield: 426 mg, 1.97 mmol, 39 % (Lit. 89 % [217]). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.53 (dd, ^3J = 4.79 Hz, ^4J = 2.00 Hz, 1H, ar-6-**H**), 8.18 (dd, ^3J = 7.72 Hz, ^4J = 1.99 Hz, 1H, ar-4-**H**), 7.34 (dd, ^3J = 7.68 Hz, ^3J = 4.77 Hz, 1H, ar-5-**H**), 3.97 (s, 3H, $CO_2C\mathbf{H_3}$). $C_7H_6BrNO_2$ (216.03 g mol^{-1}). TLC: R*f* (EtOAc/PE, 1:1) = 0.71.

Methyl 3-Bromoisonicotinate (26e). The esterification of 3-bromoisonicotinate was performed as suggested by Conde et al. [218]. Concentrated sulfuric acid (0.1 mL) was carefully dropped into a solution of 3-bromoisonicotinic acid (268 mg, 1.33 mmol) in MeOH (6.0 mL). The reaction mixture was heated under reflux conditions for 4 d. The solvent was removed under reduced pressure and the residue was filtered through a short pad of silica gel to yield the isonicotinate **26e** in pure form.



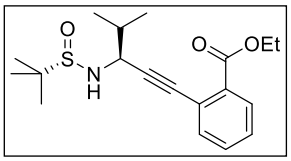
Red, viscous oil. Yield: 44.6 mg, 103 mmol, 8 % (Lit. 78 % [218]). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.85 (s, 1H, ar-2-**H**), 8.61 (d, ^{3}J = 5.0 Hz, 1H, ar-6-**H**), 7.62 (d, ^{3}J = 4.9 Hz, 1H, ar-5-**H**), 3.96 (s, 3H, $CO_2C\mathbf{H_3}$). $C_7H_6BrNO_2$ (216.03 g mol^{-1}). TLC: R*f* (PE/EtOAc, 1:1) = 0.56.

Methyl 3-Bromopicolinate (26f). 3-Bromopicolinate was esterified under the conditions described by Oballa et al. [219]. Under a nitrogen atmosphere, diazomethane (0.1 M, 19.0 mL, 1.90 mmol, 1.3 eq) was added dropwise to a non-stirred solution of 3-bromopicolinic acid (289.7 mg, 1.434 mmol, 1.0 eq) in dry THF (10 mL) at 0 °C. The reaction mixture was slowly warmed up to rt and stirred for 20 h at ambient temperature. The red solution was dilluted with water (40 mL) and acetic acid (1 M, 1 mL, 1 mmol) and the aqoueous layer was extracted with Et_2O (5 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was filtered through a short pad of silica gel to yield picolinate **26f** in pure form.



Slightly yellow fluid. Yield: 292 mg, 1.35 mmol, 94 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.57 (m, 1H, ar-6-**H**), 7.97 (m, 1H, ar-4-**H**), 7.23 (m, 1H, ar-5-**H**), 3.97 (s, 3H, $CO_2C\mathbf{H_3}$). $C_7H_6BrNO_2$ (216.03 g mol^{-1}). TLC: R*f* (EtOAc/PE, 1:1) = 0.59.

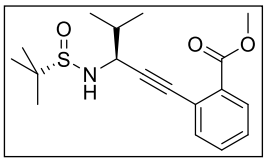
Ethyl 2-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)benzoate (27a). Piperidine (0.3 mL) was added to a solution of L-valine analogous propargylamide **6b** (46.6 mg, 231 μmol, 1 eq) and ethyl 2-iodobenzoate (**26b**, 102 mg, 370 μmol, 1.6 eq) in THF (1.0 mL). The reaction mixture was degassed by freeze pump thaw method, until no more gas atmosphere could be detected by the manometer (3 x). The catalysts, $PdCl_2(PPh_3)_2$ (1 mg) and CuI (2 mg) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After 30-120 min, a colorless precipitate formed in the clear solution, indicating the procedure of the reaction. At least 2-8 h later, the suspension was diluted with a saturated aqueous NH_4Cl solution and $KHSO_4$ (aq, 5 %) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O, the organic layer was separated and the organic layer extracted to more



times with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. The crude product of peptidomimetic **27a** was purified by column chromatography (EtOAc/PE, 1:1).

Colorless oil. Yield: 119 mg, 340 μmol, 68 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.90 (dd, ^3J = 7.8 Hz, ^4J = 1.3 Hz, 1H, ar-6-**H**), 7.57 (dd, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1H, ar-3-**H**), 7.43 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, ar-4-**H**), 7.34 (td, ^3J = 7.6 Hz, ^4J = 1.4 Hz, 1H, ar-5-**H**), 4.37 (q, ^3J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.19 (dd, ^3J = 5.4 Hz, ^3J = 6.0 Hz, 1H, $C^{\alpha}\mathbf{H}$), 3.66 (d, ^3J = 6.0 Hz, 1H, $C^{\alpha}HN\mathbf{H}$), 2.05 (m, 1H, $C\mathbf{H}(CH_3)_2$), 1.39 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.26 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.10 (d, ^3J = 6.8 Hz, 3H, $CH_3CHC\mathbf{H_3}$), 1.07 (d, ^3J = 6.7 Hz, 3H, $CH_3CHC\mathbf{H_3}$). $C_{19}H_{27}NO_3S$ (349.49 g mol^{-1}). TLC: R*f* (PE/EtOAc, 1:1) = 0.51.

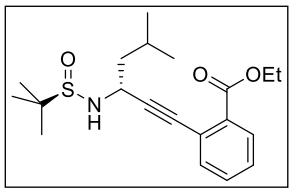
Methyl 2-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yne-1-yl)benzoate (27b). A solution of L-valine analogous propargylamide **6b** (500 mg, 2.48 mmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 0.49 mL, 3.23 mmol, 1.3 eq) in a mixture of THF/piperidine (6 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (1 mol%) and CuI (2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (5:4, 90 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 10-15 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product of **27b** was purified by column chromatography (PE/EtOAc, 1:1).



Highly viscous, pale green oil. Yield: 716 mg, 2.13 mmol, 85 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.64 (d, ^3J = 7.8 Hz, 1H, ar-2-**H**), 7.32 (d, ^3J = 7.6 Hz, 1H, ar-5-**H**), 7.17 (t, ^3J = 7.5 Hz, 1H, ar-4-**H**), 7.07 (t, ^3J = 7.6 Hz, 1H, ar-3-**H**), 3.91 (dd, ^3J = 6.5 Hz, ^3J = 6.0 Hz, 1H, $C^{\alpha}\mathbf{H}$), 3.71 (d, ^3J = 6.5 Hz, 1H, $C^{\alpha}HN\mathbf{H}$), 3.64 (s, 3H, $CO_2C\mathbf{H_3}$), 1.76 (m, 1H, $C^{\alpha}HC\mathbf{H}(CH_3)_2$), 1.00 (s, 9H, $SC(C\mathbf{H_3})_3$), 0.84 (d, ^3J = 6.8 Hz, 6H, $C^{\alpha}HCH(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.9 ($\mathbf{C}O_2CH_3$), 133.7 (ar-**C**-4), 131.3 (ar-**C**-5),

131.1 (ar-**C**-6), 129.7 (ar-**C**-2), 127.4 (ar-**C**-3), 122.7 (ar-**C**-1), 92.7 ($C^{\alpha}H\mathbf{C}\equiv$Car), 83.8 ($C^{\alpha}HC\equiv\mathbf{C}$ar), 55.7 ($S\mathbf{C}(CH_3)_3$), 53.9 ($\mathbf{C}^{\alpha}H$), 51.6 ($CO_2\mathbf{C}H_3$), 33.4 ($C^{\alpha}H\mathbf{C}H(CH_3)_2$), 22.2 ($SC(\mathbf{C}H_3)_3$), 18.6 ($C^{\alpha}HCH(\mathbf{C}H_3)_2$), 17.2 ($C^{\alpha}HCH(\mathbf{C}H_3)_2$). $C_{18}H_{25}NO_3S$ (335.46 g mol^{-1}). LCMS(ESI): t*r* = 9.9 min, *m/z* = 336.16170 (calcd. 336.16279 $[M+H]^+$), 358.1427 (calcd. 358.1447 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.19.

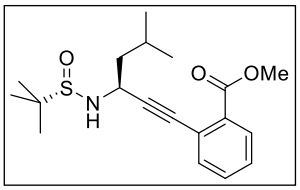
Ethyl 2-((*R*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoate (27c). Piperidine (0.4 mL) was added to a solution of D-leucine analogous propargylamide **6c** (163 mg, 757 μmol, 1.0 eq) and the ethyl benzoate **26b** (162 μL, 1.23 mmol, 1.6 eq) in THF (1.2 mL). The reaction mixture was degassed by freeze pump thaw method, until no more gas atmosphere could be detected by the manometer. The catalysts, $PdCl_2(PPh_3)_2$ (1.8 mg) and CuI (0.9 mg) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After 30-120 min, a colorless precipitate formed in the clear solution, indicating the procedure of the reaction. At least 2-8 h later, the suspension was diluted with a saturated aqueous NH_4Cl solution and $KHSO_4$ (aq, 5%) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O, the organic layer separated and the organic layer extracted to more times with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. Crude product **27c** was purified by column chromatography (EtOAc/PE, 1:1).



Colorless, highly viscous oil. Yield: 649 mg, 1.79 mmol, 97 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.89 (dt, ^3J = 7.9 Hz, ^4J = 1.1 Hz, 1H, ar-6-**H**), 7.56 (dd, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H, ar-3-**H**), 7.42 (tt, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 1H, ar-5-**H**), 7.33 (tt, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H, ar-4-**H**), 4.37 (q, ^3J = 7.2 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.32 (m, 1H, $C^{\alpha}\mathbf{H}$), 3.69 (d, ^3J = 6.4 Hz, 1H, $C^{\alpha}HN\mathbf{H}$), 1.96 (m, 1H, $C^{\alpha}HCH_2C\mathbf{H}(CH_3)_2$), 1.75-1.66 (m, 2H, $C^{\alpha}HC\mathbf{H_2}CH(CH_3)_2$), 1.39 (t, ^3J = 7.2 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.24 (s, 9H, $SC(C\mathbf{H_3})_3$), 0.97 (d, ^3J = 6.6 Hz, 6H, $CH(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.3 ($\mathbf{C}O_2CH_2CH_3$), 133.5 (ar-**C**-4), 131.6 (ar-**C**-5), 130.9 (ar-**C**-6), 129.5 (ar-**C**-2), 127.3 (ar-**C**-3), 122.5 (ar-**C**-1), 94.0 ($C^{\alpha}H\mathbf{C}\equiv$C-ar), 82.9 ($C^{\alpha}HC\equiv\mathbf{C}$-ar), 60.4 ($CO_2\mathbf{C}H_2CH_3$), 56.3 ($S\mathbf{C}(CH_3)_3$), 46.2 ($HN\mathbf{C}^{\alpha}HCH_2CH(CH_3)_2$), 46.0 ($C^{\alpha}H\mathbf{C}H_2CH(CH_3)_2$), 25.0 ($C^{\alpha}HCH_2\mathbf{C}H(CH_3)_2$), 24.3 ($C^{\alpha}HCH_2HC(\mathbf{C}H_3)_2$), 22.0 ($SC(\mathbf{C}H_3)_3$), 13.7 ($CO_2CH_2\mathbf{C}H_3$). $C_{20}H_{29}NO_3S$ (363.52 g mol^{-1}), MS(ESI): *m/z* = 386.17499 (calcd. 386.17604 $[M+Na]^+$).

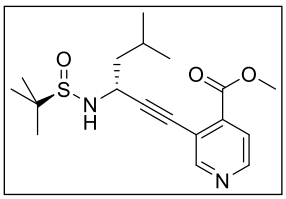
TLC: R*f* (EtOAc/PE, 1:1) = 0.66. $[\alpha]_{589}^{21}$ = -8.4 (*c* = 0.73, $CHCl_3$). IR(ATR): ϑ [cm^{-1}] = 3251 (-NH-); 2955, 2925, 2866 (C-CH_3, CH_2); 1712 (CO2Et); 1597, 1623 (ar, C=C); 1288, 1271, 1246, 1175, 1126, 1011 (C-H).

Methyl 2-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoate (27d). A solution of L-leucine analogue propargylamide **6c** (484 mg, 2.25 mmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 0.44 mL, 2.91 mmol, 1.3 eq) in a mixture of THF/piperidine (4.8 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (1 mol%) and CuI (2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (5:4, 90 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 10-15 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **27d** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless crystalline solid. Yield: 503 mg, 1.44 mmol, 78 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.78 (d, ^3J = 7.5 Hz, 1H, ar-6-**H**), 7.45 (d, ^3J = 5.3 Hz, 1H, ar-3-**H**), 7.31 (t, ^3J = 6.2 Hz, 1H, ar-4-**H**), 7.21 (t, ^3J = 7.2 Hz, 1H, ar-5-**H**), 4.21 (ddd, ^3J = 8.4 Hz, ^3J = 7.8 Hz, ^3J = 4.6 Hz, 1H, C^{α}**H**$CH_2CH(CH_3)_2$), 3.78 (s, 3H, ar-1-CO_2C**H₃**), 3.67 (d, ^3J = 6.7 Hz, 1H, N**H**$C^{\alpha}HCH_2CH(CH_3)_2$), 1.86 (m, 1H, $C^{\alpha}HCH_2C$**H**$(CH_3)_2$), 1.57-1.63 (m, 2H, $C^{\alpha}HC$**H₂**$CH(CH_3)_2$), 1.13 (s, 9H, SC(C**H₃**)$_3$), 0.86 (d, ^3J = 5.9 Hz, 6H, $C^{\alpha}HCH_2CH(C$**H₃**$)_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.4 (ar-1-**C**O_2CH_3), 134.0 (ar-**C**-3), 131.7 (ar-**C**-2), 131.5 (ar-**C**-4), 130.1 (ar-**C**-6), 127.8 (ar-**C**-5), 123.0 (ar-**C**-1), 94.4 (C^{α}H**C**≡Car), 83.3 (C^{α}HC≡**C**ar), 56.0 (S**C**$(CH_3)_3$), 51.9 (ar-1-CO_2**C**H_3), 46.8 (**C**$^{\alpha}$H), 45.9 (C^{α}H**C**$H_2CH(CH_3)_2$), 24.8 ($C^{\alpha}HCH_2$**C**$H(CH_3)_2$), 22.4 (SC(**C**$H_3)_3$), 22.0 ($C^{\alpha}HCH_2CH($**C**$H_3)_2$). $C_{19}H_{27}NO_3S$ (349.49 g mol^{-1}). LCMS(ESI): t*r* = 10.4 min, *m/z* = 350.17730 (calcd. 350.17844 $[M+H]^+$), 372.1666 (calcd. 372.1604 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.29. $[\alpha]_{589}^{20}$ = -0.21 (*c* 1.794, $CHCl_3$).

Methyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)isonicotinate (27f). To a solution of D-leucine analogous propargylamide **6c** (27.5 mg, 128 μmol, 1 eq) in a mixture of dry THF and piperidine (3:1, 0.8 mL, 6 eq piperidine), the

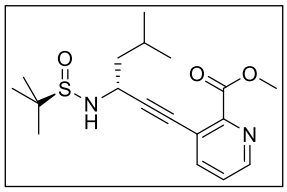


aromatic methyl 3-bromoisonicotinate (**26e**, 44.2 mg, 204 μmol, 1.6 eq) was added and the mixture was thoroughly degassed by freeze pump thaw method (3 x 10^{-2} mbar). Afterwards the catalysts $Pd(PPh_3)_4$ (2 mg) and CuI (1 mg) were added and the solution warmed to rt. While the slightly yellow solution was stirred for 14 h at ambient temperature, a colorless precipitate formed. The suspension was diluted with saturated NH_4Cl solution (ca. 8 mL) and neutralized with aqueous HCl (2 M, ca. 2 mL). After seperation of the phases, the aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phases dried over Na_2SO_4. Crude product **27f** was purified by column chromatography. In this attempt, *Glaser* homocoupling occurred. *Sonogashira/Glaser* = 25:75 (determined by isolated yield).

Slightly brown oil. Yield: 8.1 mg, 23 μmol, 18 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.65 (s, 1H, pyridine-2-**H**), 7.74 (d, ^3J = 4.9 Hz, 1H, pyridine-6-**H**), 7.49 (m, 1H, pyridine-5-**H**), 4.34 (q, ^3J = 7.5 Hz, 1H, C^{α}**H**), 3.96 (s, 3H, CO_2C**H$_3$**), 3.55 (d, ^3J = 6.9 Hz, 1H, C^{α}HN**H**), 1.95 (m, 1H, $C^{\alpha}HCH_2C$**H**$(CH_3)_2$), 1.68-1.77 (m, 2H, $C^{\alpha}HC$**H$_2$**$CH(CH_3)_2$), 1.25 (s, 9H, $SC(C$**H$_3$**$)_3$), 0.99 (d, ^3J = 6.6 Hz, 6H, $CH(C$**H$_3$**$)_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.2 (**C**O_2CH_3), 154.9 (ar-**C**-4), 148.9 (ar-**C**-5), 138.7 (ar-**C**-3), 133.1 (ar-**C**-2), 123.0 (ar-**C**-6), 97.7 ($C^{\alpha}HC{\equiv}$**C**-ar), 80.6 ($C^{\alpha}H$**C**≡C-ar), 56.4 ($SC($**C**$H_3)_3$), 52.9 (CO_2**C**H_3), 47.2 (**C$^{\alpha}$**H), 46.2 ($C^{\alpha}H$**C**$H_2CH(CH_3)_2$), 25.1 ($C^{\alpha}HCH_2$**C**$H(CH_3)_2$), 22.7 ($SC($**C**$H_3)_3$), 22.3 ($C^{\alpha}HCH_2CH($**C**$H_3)_2$). $C_{18}H_{26}N_2O_3S$ (350.48 g mol^{-1}). MS (ESI): *m/z* = 373.2 (calcd. 373.16 $[M+Na]^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.15.

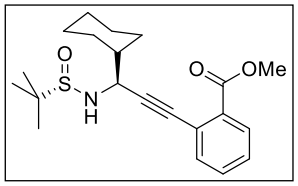
Methyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)picolinate (27g). To a solution of D-leucine analogous propargylamide **6c** (21.5 mg, 100 μmol, 1 eq) in a mixture of dry THF and piperidine (3:1, 1.0 mL, 6 eq piperidine), the aromatic methyl 3-bromopicolinate (**26f**, 34.6 mg, 160 μmol, 1.6 eq) was added and the mixture was thoroughly degassed by freeze pump thaw method (3 x 10^{-2} mbar). Afterwards the catalysts $Pd(PPh_3)_4$ (2 mg) and CuI (1 mg) were added and the solution warmed to rt. While the slightly yellow solution was stirred for 14 h at ambient temperature, a colorless

precipitate formed. The suspension was diluted with saturated NH_4Cl solution (ca. 10 mL) and neutralized with aqueous HCl (2 M, ca. 2 mL). After seperation of the phases, the aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phases dried over Na_2SO_4. Crude product **27g** was purified by preparative HPLC.



Yellow, viscous oil. Yield: 3.5 mg, 10 μmol, 10 %. ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 8.62 (dd, ^3J = 4.6 Hz, ^4J = 1.3 Hz, 1H, ar-6-**H**), 8.02 (dd, ^3J = 8.2 Hz, ^4J = 1.4 Hz, 1H, ar-4-**H**), 7.57 (dd, ^3J = 7.4 Hz, ^3J = 4.7 Hz, 1H, ar-5-**H**), 4.45 (m, 1H, C^{α}**H**$CH_2CH(CH_3)_2$), 4.01 (s, 3H, CO_2C**H**$_3$), 3.48 (d, ^3J = 7.0 Hz, 1H, $C^{\alpha}HN$**H**), 1.89 (m, 1H, $C^{\alpha}HCH_2C$**H**$(CH_3)_2$), 1.63-1.58 (m, 2H, $C^{\alpha}HC$**H**$_2CH(CH_3)_2$), 1.22 (s, 9H, $SC(C$**H**$_3)_3$), 0.96 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha}HCH_2CH(C$**H**$_3)_2$), 0.93 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha}HCH_2CH(C$**H**$_3)_2$). $C_{18}H_{26}N_2O_3S$ (350.48 g mol^{-1}). MS(ESI): *m/z* = 373.3 (calcd. 373.16 $[M+Na]^+$).

Methyl 2-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)benzoate (27h). A solution of L-cyclohexylglycine analogous propargylamide **6e** (134 mg, 555 μmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 129 μL, 851 μmol, 1.5 eq) in a mixture of THF/piperidine (2.33 mL, 6:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (1:1, 80 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 10-15 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **27h** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless, highly viscous oil. Yield: 170.8 mg, 454.8 μmol, 82 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.91 (d, ^3J = 7.9 Hz, 1H, ar-6-**H**), 7.58 (d, ^3J = 7.7 Hz, 1H, ar-3-**H**), 7.44 (t, ^3J = 7.7 Hz, 1H, ar-4-**H**), 7.35 (t, ^3J = 7.7 Hz, 1H, ar-5-**H**), 4.15 (dd, ^3J = 8.0 Hz, ^3J = 6.5 Hz, 1H, C^{α}**H**), 3.91 (s, 3H, ar-1-CO_2C**H**$_3$), 3.58 (d, ^3J = 6.5 Hz, 1H, N**H**C^{α}H), 1.94

(d br., ^{3}J = 8.0 Hz, 1H, cy-1-**H**), 1.89 (d br., ^{2}J = 12.4 Hz, 1H, cy-4-**H**), 1.83-1.77 (m br., 3H, cy-2-**H**, cy-4-**H**, cy-6-**H**), 1.73-1.67 (m br., 3H, cy-2-**H**, cy-3-**H**, cy-6-**H**), 1.27 (s, 9H, SC(C**H**$_3$)$_3$), 1.24-1.16 (m br., 3H, cy-3-**H**, cy-5-**H**, cy-5-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.8 (ar-1-**C**O$_2$CH$_3$), 134.5 (ar-**C**-3), 132.1 (ar-**C**-2), 131.8 (ar-**C**-4), 130.4 (ar-**C**-6), 128.0 (ar-**C**-5), 123.4 (ar-**C**-1), 93.6 (C$^{\alpha}$H**C**≡Car), 84.6 (C$^{\alpha}$HC≡**C**ar), 56.5 (S**C**(CH$_3$)$_3$), 54.0 (**C$^{\alpha}$**H), 52.3 (ar-1-CO$_2$**C**H$_3$), 43.6 (cy-**C**-1), 29.7 (cy-**C**-2), 28.4 (cy-**C**-6), 26.5 (cy-**C**-4), 26.2 (cy-**C**-5), 26.1 (cy-**C**-3), 22.9 (SC(**C**H$_3$)$_3$). $C_{21}H_{29}NO_3S$ (375.53 g mol^{-1}). LCMS(ESI): t*r* = 11.1 min, *m/z* = 376.19360 (calcd. 376.19409 [M+H]$^+$), 398.1780 (calcd. 398.1760 [M+Na]$^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.03, R*f* (PE/EtOAc, 1:1) = 0.06.

Methyl 2-(3-(((*S*)-*tert*-Butylsulfinyl)amino)-4,4-dimethylpent-1-yn-1-yl)benzoate (27i,j). A solution of L- and D-*tert*-leucine analogous propargylamide **6f** (80:20, 122 mg, 566 μmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 129 μL, 851 μmol, 1.5 eq) in a mixture of THF/piperidine (1.33 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (1:1, 80 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 10-15 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with aqueous $KHSO_4$ (5 %, 20 mL) brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The mixture of (*S*,*S*) and (*S*,*R*) configured diastereomers **27i** and **27j** was separated by automatic column chromatography (PE/EtOAc, 1:1).

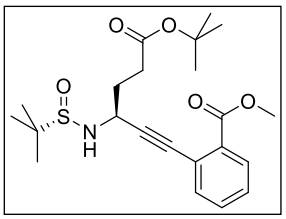
Colorless, crystalline solid. Yield: 130 mg, 372.0 μmol, 66 %. dr: (*S*,*S*):(*S*,*R*) = 79:21 (determined by HPLC), 71:29 (determined by isolated yield of both diastereomers). $C_{19}H_{27}NO_3S$ (349.49 g mol^{-1}). HRMS(ESI): *m/z* = 350.17770 (calcd. 350.17844 [M+H]$^+$).

Methyl 2-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4,4-dimethylpent-1-yn-1-yl)benzoate (27i). Colorless, crystalline solid. Yield: 92.7 mg, 265 μmol, 47 %. dr > 99 % (determined by ^{1}H NMR spectroscopy). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.86 (d, ^{3}J = 7.9 Hz, 1H, ar-6-**H**), 7.56 (d, ^{3}J = 7.7 Hz, 1H, ar-3-**H**), 7.38 (t, ^{3}J = 7.5 Hz, 1H, ar-4-**H**), 7.29 (t, ^{3}J = 7.7 Hz, 1H, ar-5-**H**), 3.89 (d, ^{3}J = 8.5 Hz, 1H, C$^{\alpha}$**H**), 3.86 (s, 3H, ar-1-CO_2C**H₃**), 3.55 (d, ^{3}J = 8.5 Hz, 1H, N**H**C$^{\alpha}$H), 1.23 (s, 9H, SC(C**H₃**)$_3$), 1.04 (s, 9H, C$^{\alpha}$HC$^{\beta}$(C**H₃**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (ar-1-**C**O_2CH_3), 134.4 (ar-**C**-3), 131.8 (ar-**C**-2), 131.6 (ar-**C**-4), 130.2 (ar-**C**-6), 127.9 (ar-**C**-5), 123.3 (ar-**C**-1), 93.7 (C$^{\alpha}$H**C**≡Car), 84.6 (C$^{\alpha}$HC≡**C**ar), 59.1 (**C$^{\alpha}$**HC$^{\beta}$$(CH_3)_3$), 56.7 (S**C**$(CH_3)_3$), 52.2 (ar-1-$CO_2$**C**$H_3$), 36.6 (C$^{\alpha}$H**C$^{\beta}$**$(CH_3)_3$), 26.2 (C$^{\alpha}HC^{\beta}$(**C**$H_3)_3$), 22.9 (SC(**C**$H_3)_3$). $C_{19}H_{27}NO_3S$ (349.49 g mol^{-1}). HRMS(ESI): *m/z* = 350.17770 (calcd. 350.17844 [M+H]$^{+}$). LCMS: t*r* = 10.2 min. TLC: R*f* (PE/EtOAc, 2:1) = 0.09, R*f* (PE/EtOAc, 1:1) = 0.21.

Methyl 2-((*R*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4,4-dimethylpent-1-yn-1-yl)benzoate (27j). Colorless, crystalline solid. Yield: 37.3 mg, 107 μmol, 19 %. dr > 99 % (determined by ^{1}H NMR spectroscopy). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.90 (d, ^{3}J = 7.8 Hz, 1H, ar-6-**H**), 7.54 (d, ^{3}J = 7.8 Hz, 1H, ar-3-**H**), 7.44 (t, ^{3}J = 7.7 Hz, 1H, ar-4-**H**), 7.35 (t, ^{3}J = 7.7 Hz, 1H, ar-5-**H**), 4.07 (d, ^{3}J = 5.8 Hz, 1H, C$^{\alpha}$**H**), 3.89 (s, 3H, ar-1-CO_2C**H₃**), 3.54 (d, ^{3}J = 5.7 Hz, 1H, N**H**C$^{\alpha}$H), 1.26 (s, 9H, SC(C**H₃**)$_3$), 1.11 (s, 9H, C$^{\alpha}$HC$^{\beta}$(C**H₃**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.7 (ar-1-**C**O_2CH_3), 134.5 (ar-**C**-3), 132.1 (ar-**C**-2), 131.7 (ar-**C**-4), 130.4 (ar-**C**-6), 128.0 (ar-**C**-5), 123.3 (ar-**C**-1), 92.5 (C$^{\alpha}$H**C**≡Car), 85.1 (C$^{\alpha}$HC≡**C**ar), 58.9 (**C$^{\alpha}$**HC$^{\beta}$$(CH_3)_3$), 56.3 (S**C**$(CH_3)_3$), 52.4 (ar-1-$CO_2$**C**$H_3$), 36.4 (C$^{\alpha}$H**C$^{\beta}$**$(CH_3)_3$), 26.2 (C$^{\alpha}HC^{\beta}$(**C**$H_3)_3$), 22.7 (SC(**C**$H_3)_3$). $C_{19}H_{27}NO_3S$ (349.49 g mol^{-1}). HRMS(ESI): *m/z* = 350.17770 (calcd. 350.17844 [M+H]$^{+}$). LCMS: t*r* = 10.6 min. TLC: R*f* (PE/EtOAc, 2:1) = 0.21, R*f* (PE/EtOAc, 1:1) = 0.43.

Methyl 2-((*S*)-6-(*tert*-Butoxy)-3-(((*S*)-*tert*-butylsulfinyl)amino)-6-oxohex-1-yn-1-yl)benzoate (27k). A solution of L-glutamate analogous propargylamide **6l** (80.8 mg, 281 μmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 100 μL, 660 μmol, 2.3 eq) in a mixture of THF/piperidine (1.2 mL, 5:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (1 mol%) and CuI (2 mol%) was

added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The

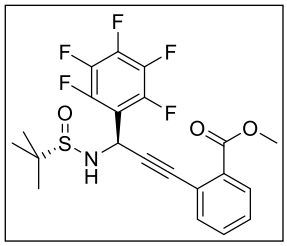


reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (3:2, 25 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 3-5 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **27k** was purified by column chromatography (PE/EtOAc, 1:1).

Colorless, crystalline needles. Yield: 92.7 mg, 220 μmol, 78 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.89 (d, ^3J = 7.8 Hz, 1H, ar-6-**H**), 7.54 (d, ^3J = 7.7 Hz, 1H, ar-3-**H**), 7.42 (t, ^3J = 7.5 Hz, 1H, ar-4-**H**), 7.33 (t, ^3J = 7.6 Hz, 1H, ar-5-**H**), 4.38 (ddd, ^3J = 6.5 Hz, ^3J = 4.6 Hz, ^3J = 6.0 Hz, 1H, C^{α}**H**), 3.89 (s, 3H, CO_2C**H**$_3$), 3.73 (d, ^3J = 6.0 Hz, 1H, N**H**C^{α}H), 2.54-2.46 (m, 2H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}$**H**$_2CO_2$), 2.12 (m, 1H, $C^{\alpha}HC^{\beta}$**H**$_2C^{\gamma}H_2CO_2$), 2.05 (m, 1H, $C^{\alpha}HC^{\beta}$**H**$_2C^{\gamma}H_2CO_2$), 1.42 (s, 9H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2CO_2C(C$**H**$_3)_3$), 1.23 (s, 9H, $SC(C$**H**$_3)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 172.3 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2$**C**$O_2$), 166.5 (ar-1-**C**$O_2CH_3$), 134.3 (ar-**C**-3), 132.1 (ar-**C**-2), 131.8 (ar-**C**-4), 130.4 (ar-**C**-6), 128.2 (ar-**C**-5), 123.0 (ar-**C**-1), 93.3 ($C^{\alpha}H$**C**≡Car), 84.3 ($C^{\alpha}HC$≡**C**ar), 80.6 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2CO_2$**C**$(CH_3)_3$), 56.3 (S**C**$(CH_3)_3$), 52.2 (ar-1-$CO_2$**C**$H_3$), 47.6 (**C**$^{\alpha}HC^{\beta}H_2C^{\gamma}H_2CO_2$), 31.9 ($C^{\alpha}HC^{\beta}H_2$**C**$^{\gamma}H_2CO_2$), 31.5 ($C^{\alpha}H$**C**$^{\beta}H_2C^{\gamma}H_2CO_2$), 28.2 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2CO_2C($**C**$H_3)_3$), 22.7 ($SC($**C**$H_3)_3$). $C_{22}H_{31}NO_5S$ (421.55 g mol^{-1}). MS(ESI): *m/z* = 422.20090 (calcd. 422.19957 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.09, R*f* (PE/EtOAc, 1:1) = 0.34.

Methyl 2-((*R*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-3-(perfluorophenyl)prop-1-yn-1-yl)benzoate (27l). A solution of L-pentafluoro phenylglycine analogous propargylamide **6o** (106 mg, 326 μmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 100 μL, 660 μmol, 1.3 eq) in a mixture of THF/DiPEA (2.34 mL, 6:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (1:1, 80 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 10-15 mL, until pH 6). The phases were

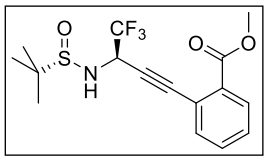
separated and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **27l** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless, crystalline solid. Yield: 134 mg, 290 µmol, 62 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.93 (d, ^3J = 7.8 Hz, 1H, ar-6-**H**), 7.53 (d, ^3J = 7.7 Hz, 1H, ar-3-**H**), 7.46 (t, ^3J = 7.5 Hz, 1H, ar-4-**H**), 7.39 (t, ^3J = 7.6 Hz, 1H, ar-5-**H**), 5.88 (d, ^3J = 5.3 Hz, 1H, C$^\alpha$**H**N), 4.30 (d, ^3J = 5.4 Hz, 1H, C$^\alpha$HN**H**), 3.87 (s, 3H, CO_2C**H**$_3$), 1.20 (s, 9H, SC(C**H**$_3$)$_3$). ^{19}F NMR (471 MHz, Chloroform-*d*) δ = -141.8 (dd, ^3J = 21.1 Hz, ^4J = 6.8 Hz, F_5C_6-2-**F**, F_5C_6-6-**F**), -153.5 (t, ^3J = 20.8 Hz, F_5C_6-4-**F**), -161.1 (td, ^3J = 21.4 Hz, ^4J = 7.3 Hz, F_5C_6-3-**F**, F_5C_6-5-**F**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.3 (**C**O_2CH_3), 144.95 (d, ^1J = 251.7 Hz, F_5C_6-**C**-3, F_5C_6-**C**-5), 141.5 (d, ^1J = 255.5 Hz, F_5C_6-**C**-4), 137.8 (dt, ^1J = 253.2 Hz, ^2J = 12.7 Hz, F_5C_6-**C**-2, F_5C_6-**C**-6), 134.2 (benzoate-**C**-3), 132.4 (benzoate-**C**-2), 131.9 (benzoate-**C**-4), 130.6 (benzoate-**C**-6), 128.8 (benzoate-**C**-5), 122.1 (benzoate-**C**-1), 113.8 (td, ^2J = 15.2 Hz, ^3J = 4.1 Hz, F_5C_6-**C**$^\beta$-1), 89.1 (C$^\alpha$H-**C**≡C-ar), 84.9 (C$^\alpha$H-C≡**C**-ar), 56.8 (S**C**$(CH_3)_3$), 52.3 (CO_2**C**H_3), 41.8 (**C**$^\alpha$HN), 22.4 (SC(**C**$H_3)_3$). $C_{21}H_{18}F_5NO_3S$ (459.43 g mol^{-1}). LCMS: t*r* = 10.8 min, *m/z* = 482.0840 (calcd. 482.0820 [M+Na]$^+$). HRMS(ESI): *m/z* = 460.10090 (calcd. 460.10003 [M+H]$^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.22, R*f* (PE/EtOAc, 1:1) = 0.60, R*f* (PE/EtOAc, 2:1) = 0.42. IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 3200 (N-H), 2955 (CH_3), 2800 (O-CH_3), 2363 (C≡C), 1723 (CO_2CH_3), 1524-1508 (ar-H), 1121 (S=O). $[\alpha]_{589}^{22}$ = 22.8 (*c* = 1.79, $CHCl_3$).

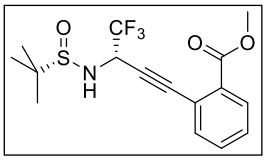
Methyl 2-((*R*)-3-(((*S*)-Butylsulfinyl)amino)-4,4,4-trifluorobut-1-yne-1-yl)benzoate (27n). A solution of L-trifluoro-alanine analogous propargylamide **6p** (61.1 mg, 273 µmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 100 µL, 660 µmol, 2.4 eq) in a mixture of THF/DIPEA (1.29 mL, 78:22) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (4:5, 9 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 3-5 mL, until pH 6). The phases

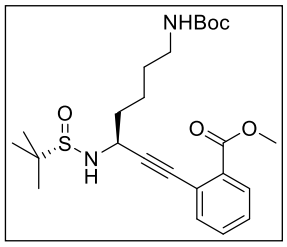
were separated and the aqueous layer was extracted with Et_2O (3 x 6 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **27n** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless crystalline needles. Yield: 51.6 mg, 142 μmol, 52 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.99 (d, $^3J_{HH}$ = 7.8 Hz, 1H, ar-2-**H**), 7.59 (d, $^3J_{HH}$ = 7.8 Hz, 1H, ar-5-**H**), 7.49 (t, $^3J_{HH}$ = 7.5 Hz, 1H, ar-4-**H**), 7.44 (t, $^3J_{HH}$ = 7.6 Hz, 1H, ar-3-**H**), 4.81 (p, $^3J_{HF}$ = 6.4 Hz, 1H, C$^{\alpha}$**H**CF_3), 4.12 (d, $^3J_{HH}$ = 6.0 Hz, 1H, C$^{\alpha}$HN**H**), 3.92 (s, 3H, CO_2C**H**$_3$), 1.29 (s, 9H, SC(C**H**$_3$)$_3$). ^{19}F NMR (471 MHz, Chloroform-*d*) δ = -76.2 (d, $^3J_{FH}$ = 6.1 Hz, 3F, C**F**$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.3 (**C**O_2CH_3), 134.3 (ar-**C**-5), 132.6 (ar-**C**-1), 132.0 (ar-**C**-4), 130.8 (ar-**C**-2), 129.3 (ar-**C**-3), 121.6 (ar-**C**-6), 119.1 (q, $^1J_{CF}$ = 280.1 Hz, C$^{\alpha}$H**C**F_3), 96.0 (C$^{\alpha}$H**C**≡C-ar), 84.6 (C$^{\alpha}$HC≡**C**-ar), 57.5 (S**C**$(CH_3)_3$), 52.5 (CO_2**C**H_3), 51.8 (q, $^2J_{CF}$ = 34.9 Hz, **C$^{\alpha}$**HCF_3), 22.6 (SC(**C**$H_3)_3$). $C_{16}H_{18}F_3NO_3S$ (361.38 g mol^{-1}). HRMS(ESI): *m/z* = 362.10400 (calcd. 362.10323 $[M+H]^+$), 384.0828 (calcd. 384.0852 $[M+Na]^+$), 745.1850 (calcd. 745.1811 $[2M+Na]^+$). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3300 (N-H), 2914 (CH_3), 2844 (O-CH_3), 2366-2334 (C≡C), 1717 (CO_2Me), 1140 (S=O). $[\alpha]_{589}^{21}$ = 20.7 (*c* = 0.21, $CHCl_3$). TLC: R*f* (PE/EtOAc, 10:1) = 0.02, R*f* (PE/EtOAc, 4:1) = 0.05, R*f* (PE/EtOAc, 2:1) = 0.21, R*f* (PE/EtOAc, 1:1) = 0.45. X-ray crystal structure in Chapter IIX-3. n.

Methyl 2-((*S*)-3-(((*S*)-Butylsulfinyl)amino)-4,4,4-trifluorobut-1-yne-1-yl)benzoate (27o). A solution of D-trifluoroalanine analogous propargylamide **6p** (36.5 mg, 160 μmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 80 μL, 530 μmol, 3.2 eq) in a mixture of THF/DIPEA (2.33 mL, 6:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (2.4 mg, 3 μmol, 1 mol%) and CuI (1.4 mg, 7 μmol, 2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred 15 h at ambient temperature. The orange solution was diluted with a mixture of Et_2O and aqueous NH_4Cl (5:1, 18 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 3-5 mL, until pH 6). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **27o** was purified by column chromatography (PE/EtOAc, 1:1).

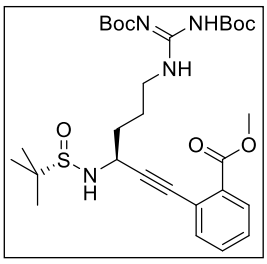
Colorless, crystalline solid. Yield: 18.2 mg, 50 µmol, 32 %. ^{1}H NMR (300 MHz, 
Chloroform-*d*) δ = 7.98 (dd, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.6 Hz, 1H, ar-6-**H**), 7.64 (dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.3 Hz, 1H, ar-3-**H**), 7.50 (td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H, ar-5-**H**), 7.43 (td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.6 Hz, 1H, ar-4-**H**), 4.90 (qd, $^{3}J_{HF}$ = 6.4 Hz, $^{3}J_{HH}$ = 5.6 Hz, 1H, C$^{\alpha}$**H**CF$_3$), 4.34 (m, 1H, N**H**C$^{\alpha}$HCF$_3$), 3.91 (s, 3H, CO$_2$C**H$_3$**), 1.28 (s, 9H, SC(C**H$_3$**)$_3$). ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -75.7 (d, $^{3}J_{FH}$ = 6.3 Hz, C$^{\alpha}$HC**F$_3$**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.4 (ar-1-**C**O$_2$CH$_3$), 134.8 (ar-**C**-3), 132.5 (ar-**C**-1), 132.0 (ar-**C**-5), 130.7 (ar-**C**-6), 129.2 (ar-**C**-4), 123.2 (q, ^{1}J = 281.7 Hz, C$^{\alpha}$H**C**F$_3$), 121.6 (ar-**C**-2), 87.7 (C$^{\alpha}$H**C**≡C-ar), 83.4 (C$^{\alpha}$HC≡**C**-ar), 57.2 (S**C**(CH$_3$)$_3$), 52.4 (CO$_2$**C**H$_3$), 50.9 (q, ^{2}J = 35.1 Hz, **C$^{\alpha}$**HCF$_3$), 22.5 (SC(**C**H$_3$)$_3$). $C_{16}H_{18}F_3NO_3S$ (361.38 g mol^{-1}), MS(ESI): *m/z* = 362.218 (calcd. 362.1032 [M+H]$^{+}$), 384.167 (calcd. 384.0852 [M+Na]$^{+}$). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 3167 (N-H), 2955 (CH$_3$), 2869 (O-CH$_3$), 2363-2331 (C≡C), 1720 (CO$_2$Me), 1128 (S=O). $[\alpha]_{589}^{22}$ = 79.8 (*c* = 0.91, CHCl$_3$). TLC: R*f* (PE/EtOAc, 2:1) = 0.07.

Methyl 2-((*S*)-7-((*tert*-Butoxycarbonyl)amino)-3-(((*S*)-*tert*-butylsulfinyl)amino)hept-1-yn-1-yl)benzoate (27p). A solution of L-lysine analogous propargylamide **6w** (94 mg, 284 µmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 100 µL, 660 µmol, 2.3 eq) in a mixture of THF/piperidine (0.67 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw 
method. While still frozen, the solid catalyst PdCl$_2$(PPh$_3$)$_2$ (1 mol%) and CuI (2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et$_2$O and aqueous NH$_4$Cl (3:2, 25 mL), neutralized with aqueous KHSO$_4$ solution (5 %, 3-5 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et$_2$O (3 x 15 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. Crude product **27p** was purified by column chromatography (PE/EtOAc, 1:1).

Clear yellow oil. Yield: 26.7 mg, 57.5 µmol, 20 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.92 (d, ^{3}J = 7.8 Hz, 1H, ar-6-**H**), 7.56 (d, ^{3}J = 7.7 Hz, 1H, ar-3-**H**), 7.44 (t, ^{3}J = 7.6 Hz, 1H, ar-4-**H**), 7.34 (t, ^{3}J = 7.6 Hz, 1H, ar-5-**H**), 4.81 (s, 1H, N**H**Boc), 4.32 (ddd, ^{3}J = 6.5 Hz,

^{3}J = 6.0 Hz, ^{3}J = 5.6 Hz, 1H, NHC$^{\alpha}$**H**C$^{\beta}$H$_2$C$^{\gamma}$H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$H$_2$NHBoc), 3.90 (s, 3H, CO$_2$C**H$_3$**), 3.66 (d, ^{3}J = 5.7 Hz, 1H, N**H**C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$H$_2$NHBoc), 3.15 (q, ^{3}J = 6.6 Hz, 2H, NHC$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$**H$_2$**NHBoc), 1.91-1.75 (m, 2H, NHC$^{\alpha}$HC$^{\beta}$**H$_2$**C$^{\gamma}$H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$H$_2$NHBoc), 1.69-1.53 (m, 4H, NHC$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$**H$_2$**C$^{\delta}$**H$_2$**C$^{\varepsilon}$H$_2$NHBoc), 1.41 (s, 9H, NHCO$_2$C(C**H$_3$**)$_3$), 1.24 (s, 9H, SC(C**H$_3$**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.5 (ar-1-**C**O$_2$CH$_3$), 156.2 (NHC$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$H$_2$NH**C**O$_2$C(CH$_3$)$_3$), 134.4 (ar-**C**-3), 131.9 (ar-**C**-2), 131.9 (ar-**C**-4), 130.4 (ar-**C**-6), 128.1 (ar-**C**-5), 123.3 (ar-**C**-1), 94.2 (NHC$^{\alpha}$H**C**≡Car), 83.9 (NHC$^{\alpha}$HC≡**C**ar), 79.1 (NHCO$_2$**C**(CH$_3$)$_3$), 56.3 (C$^{\alpha}$NHSO**C**(CH$_3$)$_3$), 52.3 (ar-1-CO$_2$**C**H$_3$), 48.3 (NH**C$^{\alpha}$**HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$H$_2$NH), 40.4 (NHC$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$C$^{\delta}$H$_2$**C$^{\varepsilon}$**H$_2$NH), 36.5 (NHC$^{\alpha}$H**C$^{\beta}$**H$_2$C$^{\gamma}$H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$H$_2$NH), 29.6 (NHC$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$**C$^{\delta}$**H$_2$C$^{\varepsilon}$H$_2$NH), 28.6 (NHCO$_2$C(**C**H$_3$)$_3$), 22.8 (NHC$^{\alpha}$HC$^{\beta}$H$_2$**C$^{\gamma}$**H$_2$C$^{\delta}$H$_2$C$^{\varepsilon}$H$_2$NH), 22.7 (C$^{\alpha}$HNHSOC(**C**H$_3$)$_3$). $C_{24}H_{36}N_2O_5S$ (464.6210 g mol^{-1}). LCMS(ESI): t*r* = 10.04 min, *m/z* = 465.24240 (calcd. 465.24177 [M+H]$^{+}$), 487.2185 (calcd. 487.2237 [M+Na]$^{+}$). TLC: R*f* (PE/EtOAc, 2:1) = 0.05, R*f* (PE/EtOAc, 1:1) = 0.16.

Methyl 2-((*S*)-6-((*E*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)-3-(((*S*)-*tert*-butylsulfinyl)amino)hex-1-yn-1-yl)benzoate (27q). A solution of L-arginine analogous propargylamide **6x** (753 mg, 1.64 mmol, 1.0 eq) and methyl 2-iodobenzoate (**26a**, 320 µL,

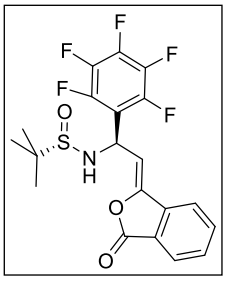


2.1 mmol, 1.3 eq) in a mixture of THF/piperidine (4.0 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (1 mol%) and CuI (2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (1:1, 100 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 10-15 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc, 1:1).

Colorless, highly viscous oil. Yield: 585 mg, 986 μmol, 60 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 11.68 (s, 1H, N_2CN**H**Boc), 8.49 (t, ^{3}J = 5.5 Hz, 1H, $C^{\delta}H_2N$**H**CN_2), 8.00 (d, ^{3}J = 7.9 Hz, 1H, ar-2-**H**), 7.66 (d, ^{3}J = 7.8 Hz, 1H, ar-5-**H**), 7.54 (t, ^{3}J = 7.6 Hz, 1H, ar-4-**H**), 7.44 (t, ^{3}J = 7.7 Hz, 1H, ar-3-**H**), 4.47 (ddd, ^{3}J = 6.2 Hz, ^{3}J = 5.8 Hz, ^{3}J = 4.6 Hz, 1H, C^{α}**H**), 4.38 (d, ^{3}J = 6.3 Hz, 1H, C^{α}HN**H**), 3.99 (s, 3H, CO_2C**H**$_3$), 3.63-3.58 (m, 2H, $C^{\alpha}H(CH_2)_2C$**H**$_2$N), 2.16-1.84 (m, 4H, $C^{\alpha}H(C$**H**$_2)_2CH_2N$), 1.58 (s, 9H, $NCO_2C(C$**H**$_3)_3$), 1.57 (s, 9H, $NHCO_2C(C$**H**$_3)_3$), 1.34 (s, 9H, $SC(C$**H**$_3)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.6 (ar**C**O_2CH_3), 162.9 ($C^{\delta}NH$**C**N_2), 155.5 ($C^{\delta}NHC$=N**C**O_2), 152.5 ($C^{\delta}NHCHN$**C**O_2), 133.5 (ar-**C**-4), 131.2 (ar-**C**-5), 131.1 (ar-**C**-6), 129.6 (ar-**C**-2), 127.4 (ar-**C**-3), 122.5 (ar-**C**-1), 93.5 ($C^{\alpha}H$**C**≡Car), 83.1 ($C^{\alpha}HC$≡**C**ar), 82.2 (NCO_2**C**$(CH_3)_3$), 78.2 ($NHCO_2$**C**$(CH_3)_3$), 55.4 (S**C**$(CH_3)_3$), 51.4 (arCO_2**C**H_3), 47.3 (**C**$^{\alpha}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2$), 39.7 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2$**C**$^{\boldsymbol{\delta}}H_2$), 33.4 ($C^{\alpha}HC^{\beta}H_2$**C**$^{\gamma}H_2C^{\delta}H_2$), 27.6 ($NCO_2C($**C**$H_3)_3$), 27.3 ($NHCO_2C($**C**$H_3)_3$), 24.6 ($C^{\alpha}H$**C**$^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2$), 22.0 ($SC($**C**$H_3)_3$). $C_{29}H_{44}N_4O_7S$ (592.75 g mol^{-1}). LCMS(ESI): t*r* = 11.1 min, *m/z* = 593.30190 (calcd. 593.30035 $[M+H]^+$), 615.2868 (calcd. 615.2823 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.23.

Catalyzed Hydrocarboxylation of Propargylic Derivatives (28-29)

(*S*)-2-Methyl-*N*-((*R*)-2-((*Z*)-3-Oxoisobenzofuran-1(3H)-ylidene)-1-(perfluorophenyl)ethyl)propane-2-sulfinamide (28). 2-Iodobenzoate (**26c**, 61.2 mg, 250 μmol, 2 eq) and DIPEA (120 μL, 690 μmol, 5.5 eq) was added in one portion to a



solution of L-pentafluoro-phenylglycine analogue propargylamine **6o** (39.9 mg, 120 μmol, 1.0 eq) in THF (0.34 mL) and the reaction mixture was degassed by freeze-pump-thaw method (3 cycles). $PdCl_2(PPh_3)_2$ (2 mg, 2.8 μmol, 1 mol%) and CuI (0.9 mg, 4 μmol, 3 mol%) was added and the mixture was stirred at rt for 16 h. Aqueous NH_4Cl solution (sat., 2 mL) was added to the depply red solution, followed by water (1 mL) and hydrochloric acid (1 M, 1 mL) until the pH value was 7. The mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and benzofuranon **28** was isolated by preparative HPLC.

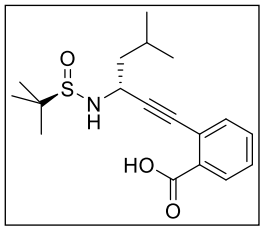
Pale yellow, crystalline solid. Yield: 14.4 mg, 30 μmol, 27 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.91 (dt, ^{3}J = 7.7 Hz, ^{4}J = 1.0 Hz, 1H, ar-6-**H**), 7.72 (dt, ^{3}J = 7.9, ^{4}J =

0.9 Hz, 1H, ar-3-**H**), 7.69 (tt, ^{3}J = 7.9 Hz, ^{4}J = 1.0 Hz, 1H, ar-4-**H**), 7.59 (ddd, ^{3}J = 7.9 Hz, ^{3}J = 7.1 Hz, ^{4}J = 1.1 Hz, 1H, ar-5-**H**), 6.12 (dd, ^{3}J = 9.3 Hz, ^{3}J = 4.5 Hz, 1H, C^{α}**H**), 5.99 (dt, ^{3}J = 8.9 Hz, ^{4}J = 1.7 Hz, 1H, C^{α}H**C**H=C(O_2C)ar), 4.29 (d, ^{3}J = 7.4 Hz, 1H, C^{α}HN**H**), 3.78 (s, br., 2H, **H_2**O coordinated), 1.22 (s, 9H, SC(C**H_3**)$_3$). ^{19}F NMR (565 MHz, Chloroform-*d*) δ = -141.7 (dd, $^{3}J_{FF}$ = 21.6 Hz, $^{4}J_{FF}$ = 7.0 Hz, C_6F_5-2-**F**, C_6F_5-6-**F**), -153.6 (t, $^{3}J_{FF}$ = 20.9 Hz, C_6F_5-4-**F**), -160.6 (td, $^{3}J_{FF}$ = 21.1 Hz, $^{4}J_{FF}$ = 6.7 Hz, C_6F_5-3-**F**, C_6F_5-5-**F**). ^{13}C NMR (75 MHz, Chloroform-*d*) δ = 165.7 (ar-1-**C**O_2), 147.2 (C^{α}HCH=**C**(O_2C)ar), 138.5 (ar-**C**-2), 134.9 (ar-**C**-3), 131.2 (ar-**C**-5), 125.9 (ar-**C**-6), 125.0 (ar-**C**-1), 120.8 (ar-**C**-4), 104.1 (C^{α}H**C**H=C(O_2C)ar), 57.1 (S**C**(CH_3)$_3$), 47.7 (**C$^{\alpha}$**HCH=C(O_2C)ar), 22.5 (SC(**C**H_3)$_3$). $C_{20}H_{16}F_5NO_3S$ (445.40 g mol^{-1}). MS(EI): *m/z* = 446.117 (calcd. 446.0844 $[M+H]^+$), 468.112 (calcd. 468.0663 $[M+Na]^+$), 443.955 (calcd. 443.955 $[M-H]^-$), 479.913 (calcd. 480.0465 $[M+Cl]^-$), 461.965 (calcd. 462.0804 $[M+OH]^-$). TLC: R*f* (PE/EtOAc, 2:1) = 0.40.

Hydrochloric acid (4 M in dioxane, 0.2 mL, 400 μmol) was added dropwise to an icecold solution of peptidomimetic **28** (14.4 mg, 30 μmol) in MeOH (3 mL). The reaction mixture was kept at rt overnight. The solvent evaporated at ambient pressure. The crude product was digerated with $CHCl_3$ and the solvent was again evaporated at ambient pressure. Compound **29** crystallized as *tert*-butylsulfonate salt in form of colorless needles from a concentrated $CHCl_3$ solution. X-ray crystal structure in Chapter IIX-3. n.

IIX-3. b) Oligomerization (30-35)

2-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoic Acid (30c). At 0 °C, an aqueous solution of LiOH x H_2O (133.7 mg, 3.19 mmol, 3.3 eq in 4.5 mL H_2O) was added dropwise to a vigorously stirred solution of ethylester **27c** (353.3 mg, 971.9 μmol, 1.0 eq). The reaction mixture was stirred at 0 °C overnight. After full conversion of the starting material (checked by TLC), the mixture was diluted with aqueous HCl (1 M, 20 mL, pH 1-2) and extracted with Et_2O (5 x 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to yield benzoate **30c** in pure form.

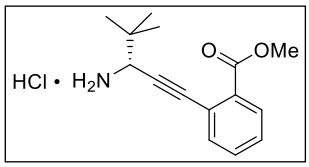


Colorless, amorphous solid. Yield: 289 mg, 861 μmol, 89 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.62 (s, 1H, CO_2**H**), 7.60 (d, ^{3}J = 7.9 Hz, 1H, ar-6-**H**), 7.46 (d, ^{3}J = 7.7 Hz, 1H, ar-3-**H**), 7.27 (t, ^{3}J = 7.7 Hz, 1H, ar-4-**H**), 7.05 (t, ^{3}J = 7.6 Hz, 1H, ar-5-**H**), 5.33 (d, ^{3}J = 9.2 Hz, 1H, C^{α}HN**H**), 4.24 (ddd, ^{3}J = 8.1 Hz, ^{3}J = 7.2 Hz, ^{3}J = 6.9 Hz, 1H, C^{α}**H**), 2.06 (m, 1H, $C^{\alpha}HCH_2C$**H**$(CH_3)_2$), 1.83 (dd, ^{2}J = 13.2 Hz, ^{3}J = 6.9 Hz, 1H, $C^{\alpha}HC$**H**$_2CH(CH_3)_2$), 1.74 (dd, ^{2}J = 13.2 Hz, ^{3}J = 7.2 Hz, 1H, $C^{\alpha}HC$**H**$_2CH(CH_3)_2$), 1.30 (s, 9H, $SC(C$**H**$_3)_3$), 0.97 (d, ^{3}J = 6.6 Hz, 6H, $C^{\alpha}HCH_2CH(C$**H**$_3)_2$). $C_{18}H_{25}NO_3S$ (335.46 g mol^{-1}). $[\alpha]_{589}^{20}$ = -28.88 (*c* 0.134, $CHCl_3$).

The preparation and charactierization of amine **31c** has been detailedly reported in the master thesis [117].

Methyl (*R*)-2-(3-Amino-4,4-dimethylpent-1-yn-1-yl)benzoate Hydrochloride (31j).

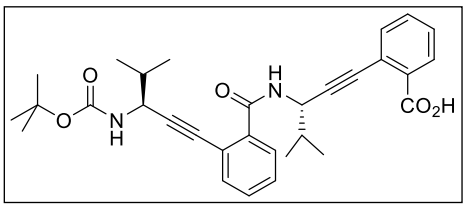
Hydrochloride (4 M in dioxane, 0.1 mL, 400 μmol) was added dropwise to a vigorously stirred solution of peptidomimetic **27j** (37.3 mg, 107 μmol) in MeOH (15 mL) at 0 °C. The reaction mixture was stirred overnight and the solvent was evaporated under reduced pressure. The crude product was digerated with $CHCl_3$ and the solvent was evaporated under reduced pressure.



Colorless, amorphous solid. Quantitative yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.89 (d, ^{3}J = 7.9 Hz, 1H, ar-6-**H**), 7.52 (d, ^{3}J = 7.7 Hz, 1H, ar-3-**H**), 7.43 (t, ^{3}J = 7.6 Hz, 1H, ar-4-**H**), 7.33 (t, ^{3}J = 7.6 Hz, 1H, ar-5-**H**), 3.91 (s, 3H, ar-1-CO_2C**H**$_3$), 3.53 (s, 1H, C^{α}**H**$C(CH_3)_3$), 1.62 (s, 3H, Cl**H**$_3NC^{\alpha}HC(CH_3)_3$), 1.08 (s, 9H, $C^{\alpha}HC(C$**H**$_3)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.0 (ar-1-**C**O_2CH_3), 134.3 (ar-**C**-3), 132.1 (ar-**C**-1), 131.6 (ar-**C**-4), 130.3 (ar-**C**-6), 127.6 (ar-**C**-5), 124.0 (ar-**C**-2), 97.3 (C^{α}H**C**≡Car), 82.2 ($C^{\alpha}HC$≡**C**ar), 54.7 (**C**$^{\alpha}HC(CH_3)_3$), 52.3 (ar-1-CO_2**C**H_3), 35.5 (C^{α}H**C**$(CH_3)_3$), 26.2 ($C^{\alpha}HC($**C**$H_3)_3$). $C_{15}H_{20}ClNO_2$ (281.78 g mol^{-1}).

2-((*S*)-3-(2-((*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)benzamido)-4-methylpent-1-yn-1-yl)benzoic Acid (33b). A mixture of acid **30c** (71.0 mg, 224 μmol, 1.0 eq), amine **31c** (59.4 mg, 222 μmol, 1.0 eq), HATU (255.2 mg, 671 μmol, 3 eq) and HOAt (120.9 mg, 896 μmol, 4 eq) was dissolved under argon atmosphere in a mixture of DMF and DIPEA (5.25 mL, 95:5). The reaction mixture was stirred for 48 h at ambient temperature. After complete consumption of acid **30c** (checked by TLC), the clear solution was diluted in CH_2Cl_2 (40 mL) and extractec with aqueous $NaHCO_3$ solution (saturated, 15 mL), water (20 mL), aqueous $KHSO_4$ solution (5 %, 20 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Amide **32b** was isolated by column chromatography (PE/EtOAc, 1:1).

An aqueous solution of LiOH (1 M, 1 mL) was added dropwise to a vigorously stirred solution of complete peptidomimetic **32b** at 0 °C. After complete consumption of the peptidomimetic (checked by TLC, ca. 8 h), the reaction mixture was diluted with an aqueous $KHSO_4$ solution (5 %, 20 mL) and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated under reduced pressure and the crude product was purified by preparative HPLC.



Colorless, highly viscous oil. Yield: 40.1 mg, 77.7 μmol, 35 %. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 8.82 (d, ^3J = 8.4 Hz, 1H, CON**H**C$^{\alpha i+1}$H), 7.82 (d, ^3J = 7.8 Hz, 1H, ar^{i+1}-6-**H**), 7.56-7.51 (m, 2H, ar^{i}-3-**H**, ar^{i+1}-3-**H**), 7.47-7.44 (m, 3H, ar^{i}-6-**H**, ar^{i}-4-**H**, ar^{i+1}-4-**H**), 7.44-7.39 (m, 2H, ar^{i}-5-**H**, ar^{i+1}-5-**H**), 7.29 (d, ^3J = 8.9 Hz, 1H, CON**H**C$^{\alpha I}$H), 4.84 (dd, ^3J = 8.4 Hz, ^3J = 6.3 Hz, 1H, C$^{\alpha i+1}$**H**), 4.28 (dd, ^3J = 8.9 Hz, ^3J = 6.5 Hz, 1H, C$^{\alpha I}$**H**), 2.03 (dhept, ^3J = 6.3 Hz, ^3J = 6.7 Hz, 1H, C$^{\alpha i+1}$HC$^{\beta}$**H**(CH$_3$)$_2$), 1.81 (dhept, ^3J = 6.5 Hz, ^3J = 6.7 Hz, 1H, C$^{\alpha I}$HC$^{\beta}$**H**(CH$_3$)$_2$), 1.39 (s, 9H, CO$_2$C(C**H$_3$**)$_3$), 1.10 (d, ^3J = 6.6 Hz, 3H, C$^{\alpha i+1}$HC$^{\beta}$H(C**H$_3$**)$_2$), 1.05 (d, ^3J = 6.7 Hz, 3H, C$^{\alpha i+1}$HC$^{\beta}$H(C**H$_3$**)$_2$), 0.94 (d, ^3J = 6.7 Hz, 3H, C$^{\alpha I}$HC$^{\beta}$H(C**H$_3$**)$_2$), 0.90 (d, ^3J = 6.7 Hz, 3H, C$^{\alpha I}$HC$^{\beta}$H(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 167.3 (**C**O$_2$H), 166.9 (**C**ONHC$^{\alpha i+1}$), 155.1 (O$_2$**C**NH), 139.1 (ar^{i}-**C**-1), 134.1 (ar^{i}-**C**-3), 133.4 (ar^{i+1}-**C**-3), 132.9 (ar^{i+1}-**C**-4), 131.6 (ar^{i}-**C**-4), 129.9 (ar^{i+1}-**C**-6), 129.6 (ar^{i+1}-**C**-5), 128.3 (ar^{i}-**C**-2), 128.2 (ar^{i+1}-**C**-2), 127.7 (ar^{i}-**C**-6), 122.4 (ar^{i}-**C**-5), 120.2 (ar^{i+1}-**C**-1), 93.0 (C$^{\alpha i+1}$H**C**≡C-ar), 92.6 (C$^{\alpha I}$H**C**≡C-ar), 81.7 (C$^{\alpha i+1}$HC≡**C**-ar), 80.9 (C$^{\alpha I}$HC≡**C**-ar), 78.2 (CO$_2$**C**(CH$_3$)$_3$), 49.0 (**C$^{\alpha I}$**HC$^{\beta}$H(CH$_3$)$_2$), 47.8 (**C$^{\alpha i+1}$**HC$^{\beta}$H(CH$_3$)$_2$), 33.2 (C$^{\alpha I}$H**C$^{\beta}$**H(CH$_3$)$_2$), 32.9

($C^{\alpha i+1}H\mathbf{C}^{\beta}H(CH_3)_2$), 28.3 ($CO_2C(\mathbf{C}H_3)_3$), 19.3 ($C^{\alpha i+1}HC^{\beta}H(\mathbf{C}H_3)_2$), 19.0 ($C^{\alpha I}HC^{\beta}H(\mathbf{C}H_3)_2$), 18.4 ($C^{\alpha I}HC^{\beta}H(\mathbf{C}H_3)_2$), 18.3 ($C^{\alpha i+1}HC^{\beta}H(\mathbf{C}H_3)_2$). $C_{31}H_{36}N_2O_5$ (516.64 g mol^{-1}). MS(ESI): *m/z* = 517.3 (calcd. 517.2697 $[M+H]^+$), 539.3 (calcd. 539.2516 $[M+Na]^+$).

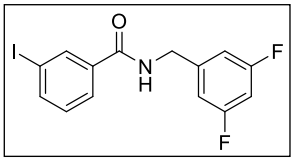
The preparation and charactierization of dimer **33c**, the *N*- and *C*-terminal cleavage of protective groups giving amine **34c** and acid **33c**, as well as their dimerization forming tetramer **35c** has been detailedly reported in the master thesis [117].

IIX-3. c) Peptidomimetics from *meta*-Substituted Aromatics (36-44)

Aromatic halides **36a-c** were purchased from Fisher Scientific.

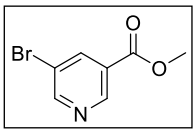
***N*-(3,5-Difluorobenzyl)-3-iodobenzamide (36d).** No information on compound **36d** has been published, yet. However, the FCH Group has assigned CAS nr. 1280343-82-9 to it. A solution of EDC (0.6 mL, 2.8 mmol, 1.3 eq) in dry CH_2Cl_2 (3 mL) was added dropwise to an ice-cold solution of of 3-iodobenzoate (**36c**, 630 mg, 2.54 mmol, 1.2 eq) in CH_2Cl_2 (6 mL). After 5 min, 3,5-difluorobenzylamine (0.27 mL, 2.10 mmol, 1.0 eq) and DMAP (64 mg, 530 µmol, 0.25 eq) was added. The reaction mixture was stirred for 3 d at ambient temperature. The reaction mixture was diluted with an aqueous $KHSO_4$ solution (5 %, 15 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to yield amide **36d** in pure form.

Colorless crystalline solid. Yield: 930 mg, 2.49 mmol, 99 %. ^{1}H NMR (300 MHz, Methanol-d_4) δ = 8.18 (t, ^4J = 1.8 Hz, 1H, ar-2-**H**), 7.80 (dd, ^3J = 8.1 Hz, ^4J = 1.8 Hz, 1H, ar-6-**H**), 7.80 (dd, ^3J = 6.6 Hz, ^4J = 1.2 Hz, 1H, ar-4-**H**), 7.15 (t, ^3J = 7.9 Hz, 1H, ar-5-**H**), 6.88 (dd, $^3J_{HF}$ = 6.3 Hz, $^4J_{HH}$ = 2.1 Hz, 2H, F_2Ph-2-**H**, F_2Ph-6-**H**), 6.72 (tt, $^3J_{HF}$ = 9.1 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, F_2Ph-4-**H**), 4.50 (s, 2H, CONHC**H₂**PhF_2). ^{19}F NMR (282 MHz, Methanol-d_4) δ = -111.00 (dd, $^3J_{FH}$ = 9.1 Hz, $^3J_{FH}$ = 6.3 Hz, F_2Ph-3-**F**, F_2Ph-5-**F**). ^{13}C NMR (151 MHz, Methanol-d_4) δ = 168.2 (F_2Ph-1-**C**ONH), 164.2 (dd, ^1J = 247.6 Hz, ^3J = 12.7 Hz, F_2Ph-**C**-3, F_2Ph-**C**-5),



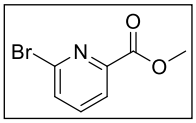
144.4 (t, ^{3}J = 8.8 Hz, F_2Ph-**C**-1), 141.6 (ar-**C**-1), 137.3 (ar-**C**-4), 136.9 (ar-**C**-2), 131.2 (ar-**C**-5), 127.5 (ar-**C**-6), 111.1 (d, ^{2}J = 25.0 Hz, F_2Ph-**C**-2, F_2Ph-**C**-6), 103.1 (t, ^{2}J = 25.8 Hz, F_2Ph-**C**-4), 94.9 (ar-**C**-3), 43.8 (CONH**C**H_2PhF_2). $C_{14}H_{10}F_2INO$ (373.14 g mol^{-1}). MS(EI): *m/z* = 374.066 (calcd. 373.9848 $[M+H]^+$), 396.008 (calcd. 395.9667 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.65. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3373 (NH), 3063 (ar-H), 1698 (CONH), 1619, 1597 (C=C), 1556 (CONH), 1435 (CH_2), 1268(C-F), 1112 (C-I), 973, 853 (ar-H).

Methyl 5-Bromonicotinate (37a). The esterification of 5-bromonicotinate was performed in accordance to the description of Do-Thanh et al. [220]. 5 Drops of H_2SO_4 (97 %) were carefully added to a solution of 5-bromonicotinic acid (1.12 g, 4.5 mmol) in MeOH (15 mL). The reaction mixture was heated for 43 h under reflux conditions and afterwards cooled to -18 °C. Colorless crystals of nicotinate **37c** formed in the reaction mixture, which were isolated by filtration, washed with some mL of ice-cold MeOH and dried under fine vacuum (0.499 g, 2.3 mmol, 51 %). The mother liquor was concentrated up at 80 °C, until more colorless crystals formed, which were isolated like the first fraction and added to the yield.



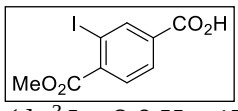
Colorless, crystals. Total yield: 721 mg, 3.34 mmol, 74 % (Lit. 88 % [220]). ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 9.13 (d, ^{4}J = 1.5 Hz, 1H, ar-2-**H**), 8.84 (dd, ^{4}J = 2.3 Hz, ^{4}J = 1.2 Hz, 1H, ar-6-**H**), 8.44 (d, ^{4}J = 1.8 Hz, 1H, ar-4-**H**), 3.97 (s, 3H, CO_2C**H**$_3$). $C_7H_6BrNO_2$ (216.03 g mol^{-1}). TLC: R*f* (PE/EtOAc 1:1) = 0.58.

Methyl 6-Bromopicolinate (37b). 6-Bromopicolinate was esterified as described by Oballa et al. [219]. Under a nitrogen atmosphere, diazomethane (0.1 M, 18.8 mL, 1.88 mmol, 1.3 eq) was added dropwise to a non-stirred solution of 3-bromopicolinic acid (312 mg, 1.44 mmol, 1.0 eq) in dry THF (10 mL) at 0 °C. The reaction mixture was slowly warmed up to rt and stirred for 20 h at ambient temperature. The red solution was dilluted with water (40 mL) and acetic acid (1 M, 1 mL, 1 mmol) and the aqoueous layer was extracted with Et_2O (5 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was filtered through a short pad of silica gel to yield methyl ester **37b** in pure form.



Slightly yellow fluid. Yield: 253 mg, 1.17 mmol, 81 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.07 (dd, ^3J = 7.1 Hz, ^4J = 1.5 Hz, 1H, ar-3-**H**), 7.69 (t, ^3J = 7.1 Hz, 1H, ar-4-**H**), 7.66 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, ar-5-**H**), 3.97 (s, 3H, $CO_2C\mathbf{H_3}$). $C_7H_6BrNO_2$ (216.03 g mol^{-1}).

3-Iodo-4-(methoxycarbonyl)benzoic Acid (38a). *Sandmeyer* reactions were performed in analogy to the work of Aiken, Gabbutt, Heron, Instone, Horton and Hursthouse [221]. Compound **38a** has been first described by Kiick, Saxon, Tirrell and Bertozzi [222]. 3-Amino-4-(methoxycarbonyl)benzoic acid (1.05 g, 5.39 mmol, 1 eq) was dissolved in aqueous hydrochloric acid (6 M, 5 mL 1 mL/mmol) and the solution was cooled to -40 °C. An aqueous solution of $NaNO_2$ (400 mg, 5.79 mmol, 1.1 eq, in 3 mL) was added dropwise under vigorous stirring. The solution was warmed up to rt and solid KI (1.79 g, 10.78 mmol, 2 eq) and I_2 (137 mg, 0.1 mmol, 0.1 eq) was added in one portion, which lead to the precipitation of a black solid. The reaction mixture was diluted with a $KHSO_4$ solution (5 %, 10 mL) and extracted with CH_2Cl_2 (5 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure.

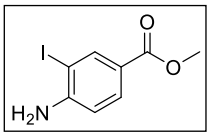


Slightly brown solid. Yield: 1.44 g, 4.71 mmol, 87 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.34 (d, ^4J = 1.7 Hz, 1H, ar-2-**H**), 7.83 (d, ^3J = 8.0 Hz, 1H, ar-5-**H**), 7.77 (dd, ^3J = 8.0 Hz, ^4J = 1.7 Hz, 1H, ar-6-**H**), 3.95 (s, 3H, $CO_2C\mathbf{H_3}$). $C_9H_7IO_4$ (306.06 g mol^{-1}). MS(ESI): *m/z* = 306.900 (calcd. 306.9462 $[M+H]^+$). TLC: R*f* (EtOAc/PE, 1:10) = 0.2. Mp = 104 °C (+/- 2 K).

When the reaction was carried out at 0 °C in a test tube, cooled by an ice bath, hydroxylation was observed as side reaction, giving the title compound **38a** (30 %) and 3-amino-4-(methoxycarbonyl)benzoic acid (6 %) in a ratio 75:25 (determined by ^{1}H NMR spectroscopy).

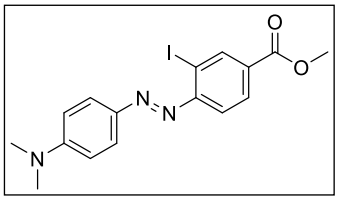
Methyl 4-Amino-3-iodobenzoate (38b). The iodination of methyl 4-aminobenzoate was performed in accordance with the description of Spivey et al. [149]. A solution of iodochloride (1 M in CH_2Cl_2, 3.35 mL, 3.35 mmol, 1.0 eq) was added dropwise to a solution of methyl 4-aminobenzoate (500 mg, 3.31 mmol, 1.0 eq) in glacial acetic acid (15 mL) at 0 °C. The deeply purple reaction mixture was stirred for 100 min at ambient

temperature. The solvent was evaporated under reduced pressure and the brown residue was diluted in a mixture of saturated $NaHCO_3$ and water (1:1, 30 mL), until a clear solution was formed. Addition of some solid Na_2CO_3 made the brown colour of the solution vanish. The phases were separated and the organic layer was washed with another portion of $NaHCO_3$ solution (5 mL), brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated and aromatic halide **38b** was purified by column chromatography PE/EtOAc (4:1).



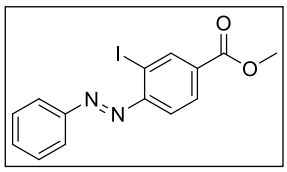
Pale, yellow crystals. Yield: 517 mg, 1.87 mmol, 56 % (Lit: 74 % [149]). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.32 (d, ^4J = 1.9 Hz, 1H, ar-2-**H**), 7.80 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1H, ar-6-**H**), 6.69 (d, ^3J = 8.4 Hz, 1H, ar-5-**H**), 4.52 (s, 2H, ar-N**H₂**), 3.84 (s, 3H, CO_2C**H₃**). $C_8H_8INO_2$ (277.06 g mol^{-1}). MS(ESI): *m/z* = 276.030 (calcd. 275.9527 [M-H$^+$]$^-$). TLC: R*f* (EtOAc/PE, 1:4) = 0.30.

Methyl (*E*)-4-((4-(Dimethylamino)phenyl)diazenyl)-3-iodobenzoate (38c). A cooled solution of $NaNO_2$ (27.4 mg, 397 μmol, 1.1 eq) in water (0.3 mL) was added dropwise to a solution of aniline derivative **38b** (100 mg, 361 μmol, 1.0 eq) in hydrochloric acid (half concentrated, 6 M, 0.5 mL) at 0 °C. After 5 min, the green mixture was slowly dropped into an icecold, vigorously stirred solution of *N*,*N*-dimethyl aniline (50.4 mg, 541 μmol, 1.5 eq) in hydrochloric acid (0.8 mL, 1 M). The reaction mixture immediately turned brightly red and was stirred for another 15 min at 0 °C. Afterwards, the reaction mixture was diluted with a NaOH solution (1 M, ca. 5 mL) until pH>8 and the solution was kept overnight at -20 °C. A red precipitate formed, which was centrifuged, filtered off and purified by column chromatography (PE/EtOAc, 2:1).



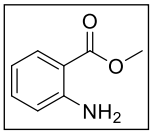
Purple solid. Yield: 85.5 mg, 209 μmol, 58 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.33 (d, ^4J = 1.9 Hz, 1H, benzoate-2-**H**), 7.95 (d, ^3J = 9.2 Hz, 2H, aniline-2-**H**, aniline-6-**H**), 7.80 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1H, benzoate-6-**H**), 6.75 (d, ^3J = 9.2 Hz, 2H, aniline-3-**H**, aniline-5-**H**), 6.70 (d, ^3J = 8.4 Hz, 1H, benzoate-5-**H**), 3.85 (s, 3H, CO_2C**H₃**), 3.12 (s, 6H, N(C**H₃**)$_2$). $C_{16}H_{16}IN_3O_2$ (409.23 g mol^{-1}). MS(ESI): *m/z* = 409.929 (calcd. 410.0360 [M+H]$^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.52.

Methyl (*E*)-3-Iodo-4-(phenyldiazenyl)benzoate (38d). No information on synthesis and characteristics of azobenzene **38d** have been published, yet. However, ChemSpider has assigned CAS nr. 1027164-11-9 to the compound. Nitrosylbenzene (2 x 37 mg, 0.72 mmol, 2.0 eq) was added in two portions to a solution of aniline derivative **38b** (100 mg, 0.361 mmol, 1.0 eq) in AcOH (18 mL). The reaction mixture was heated for 5 d under reflux conditions to 120 °C. It turned a dark red colour. After complete conversion of aniline **38b**, the solution was diluted with H_2O (30 mL), lyophilized and purified by column chromatography (PE/EtOAc, 4:1) to yield azobenzene **38d** in pure form.



Dark red solid. Yield: 12.0 mg, 25.9 mmol, 7 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.68 (d, ^4J = 1.4 Hz, 1H, benzoate-2-**H**), 8.08 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 1H, benzoate-5-**H**), 8.02 (dd, ^3J = 8.1 Hz, ^4J = 1.3 Hz, 1H, benzoate-6-**H**), 7.90 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 7.57-7.51 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 3.96 (s, 3H, $CO_2C\mathbf{H_3}$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 165.4 ($\mathbf{C}O_2CH_3$), 152.5 (benzoate-**C**-2), 141.2 (Ph-**C**-1), 133.0 (benzoate-**C**-6), 132.4 (benzoate-**C**-4), 130.4 (Ph-**C**-4), 129.4 (Ph-**C**-3), 124.8 (Ph-**C**-5), 124.0 (benzoate-**C**-3), 122.9 (Ph-**C**-2), 117.3 (Ph-**C**-6), 101.1 (benzoate-**C**-1), 52.7 ($CO_2\mathbf{C}H_3$). $C_{14}H_{11}IN_2O_2$ (366.16 g mol^{-1}). LCMS(ESI): *m/z* = 367.119 (calcd. 366.9938 $[M+H]^+$).

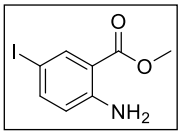
Methyl 2-Amino-5-iodobenzoate (39a). Methyl 2-aminobenzoate was synthesized by methylation of anthranilate as described by Arifuzzaman et al. [223]. Concentrated sulfuric acid (98 %, 0.1 mL) was added to a solution of 2-amino benzoic acid (686 mg, 5 mmol) in



MeOH (35 mL) and the solution was heated for 4 d under reflux conditions to 90 °C. The solvent was removed under reduced pressure and crude product was dried to give a red solid.

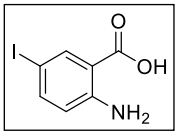
^{1}H NMR (300 MHz, Methanol-d_4) δ = 8.15 (dd, ^3J = 8.08 Hz, ^4J = 1.44 Hz, 1H, ar-6-**H**), 7.66 (ddd, ^3J = 8.03 Hz, ^3J = 7.44 Hz, ^4J = 1.61 Hz, 1H, ar-5-**H**), 7.44-7.32 (m, 2H, ar-3-**H**, ar-4-**H**), 3.70 (s, 3H, $CO_2C\mathbf{H_3}$). $C_8H_9NO_2$ (151.17 g mol^{-1}). MS(ESI): *m/z* = 174.06 (calcd. 174.0525 $[M+Na]^+$).

Methyl 2-Amino-5-iodobenzoate (39a) was prepared by iodination of methyl anthranilate in accordance to the description of Adepu et al. [224]. A solution of iodchloride (1 M in CH_2Cl_2, 6 mL, 6 mmol, 1.2 eq) was added dropwise to a solution of methyl 2-aminobenzoic acid (5 mmol, 1 eq) in acetic acid/CH_2Cl_2 (5:2, 70 mL). The reaction mixture was stirred for 1 h at rt. After complete conversion (monitored by TLC), some drops of a saturated $Na_2S_2O_3$ solution were added at 0 °C and the mixture was neutralized with a saturated Na_2CO_3 solution (90 mL). The forming precipitate was filtered off and the filtrate was extracted with CH_2Cl_2 (2 x 30 mL), EtOAc (1 x 30 mL) and Et_2O (2 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the crude product of aromatic halide **39a** in pure form.



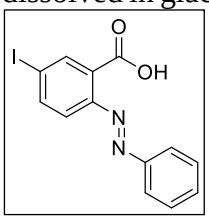
Red solid. Yield: 345 mg, 1.25 mmol, 25 % (over two steps, referred to anthranilate, Lit: 80 % [224]). ^{1}H NMR (Chloroform-*d*, 300 MHz): δ = 8.13 (d, ^4J = 2.19 Hz, 1H, ar-6-**H**), 7.47 (dd, ^3J = 8.69 Hz, ^4J = 2.18 Hz, 1H, ar-4-**H**), 6.46 (d, ^3J = 8.70 Hz, 1H, ar-3-**H**), 3.86 (s, 3H, $CO_2C\mathbf{H}_3$). $C_8H_8INO_2$ (277.06 g mol^{-1}). MS(ESI): *m/z* = 277.98 (calcd. 277.9672 $[M+H]^+$).

2-Amino-5-((*R*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)benzoic Acid (39b). Anthranilate was iodinated as described by Wallingford et al. [225]. A iodochloride solution (1 M in CH_2Cl_2, 4.4 mL, 4.4 mmol, 1.0 eq) was added dropwise within 3 min to a solution of 2-aminobenzoic acid (600 mg, 4.38 mmol, 1.0 eq) in glacial acetic acid (20 mL) at 0 °C. The reaction mixture immediately turned deeply red and a colorless precipitate formed, which was separated by filtration. After extensive drying, the colorless solid **39b** was recrystallized from EtOH.



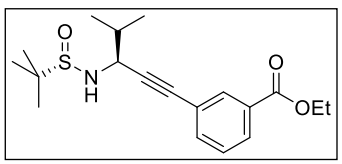
Colorless, crystalline solid. Yield: 599 mg, 2.28 mmol, 52 % (Lit: 90 % [225]). ^{1}H NMR (600 MHz, methanol-d_4) δ = 8.05 (d, ^4J = 2.2 Hz, 1H, ar-6-**H**), 7.44 (dd, ^3J = 8.8 Hz, ^4J = 2.2 Hz, 1H, ar-4-**H**), 6.56 (d, ^3J = 8.7 Hz, 1H, ar-3-**H**). $C_7H_6INO_2$ (263.03 g mol^{-1}). LCMS (ESI): t_r = 6.8 min, *m/z* = 264.050 (calcd. 263.9516 $[M+H]^+$).

(*E*)-5-Iodo-2-(phenyldiazenyl)benzoic Acid (39c). Methyl 5-iodo-2-aminobenzoate (179 mg, 0.65 mmol, 1.0 eq) and nitrosylbenzene (83 mg, 0.78 mmol, 1.1 eq) were dissolved in glacial acid (8.5 mL) and the solution was stirred for 5 h at rt, heated for 80 min at 65 °C and stirred for another 12 h at rt. As the starting material had not been completely converted, yet, another portion of nitrosylbenzene (55 mg, 0.51 mmol, 0.8 eq) was added the solution was heated for 3 more h to 65 °C. After cooling down to 0 °C, the solution was neutralized with a saturated Na_2CO_3 solution and extracted with Et_2O (5 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was dried under vacuum.



Brown solid. Yield: 159 mg, 0.45 mmol, 70 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.80 (d, ^4J = 2.03 Hz, 1H, ar-6-**H**), 8.31 (dd, ^3J = 8.44 Hz, ^4J = 1.59 Hz, 1H, ar-4-**H**), 7.65-7.59 (m, 2H, Ph-2-**H**, Ph-6-**H**), 7.56-7.48 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 6.47 (d, ^3J = 8.74 Hz, 1H, ar-3-**H**). $C_{13}H_9IN_2O_2$ (352.13 g mol^{-1}). MS (ESI): *m/z* = 352.99 (calcd. 352.9781 $[M+H]^+$).

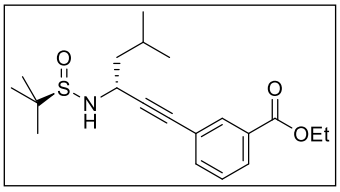
Ethyl 3-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)benzoate (40a). A solution of L-valine analogous propargylamide **6b** (100 mg, 498 μmol, 1.0 eq) and ethyl 3-iodobenzoate (**36b**, 120 μL, 838 μmol, 1.4 eq) in a mixture of THF/piperidine (1.3 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) was added in one portion and the mixture was allowed to warm up to rt and stirred over 18 h at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (1:1, 60 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 5-10 mL, until pH 6). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **40a** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless oil. Yield: 141 mg, 403 μmol, 81 %. ^{1}H NMR (300 MHz, Chloroform-*d*): δ = 8.09 (t, ^4J = 1.49 Hz, 1H, ar-2-**H**), 7.97 (dt, ^3J = 7.90 Hz, ^4J = 1.46 Hz, 1H, ar-6-**H**), 7.62 (dt, ^3J = 7.77 Hz, ^4J = 1.45 Hz, 1H, ar-4-**H**), 7.37 (t, ^3J = 7.63 Hz,

1H, ar-5-**H**), 4.38 (q, ^{3}J = 7.13 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.13 (m, 1H, $C^{\alpha}\mathbf{H}CH(CH_3)_2$), 3.41 (d, ^{3}J = 6.62 Hz, 1H, $C^{\alpha}N\mathbf{H}$), 2.06 (m, 1H, $C^{\alpha}HC\mathbf{H}(CH_3)_2$), 1.40 (t, ^{3}J = 7.12 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.25 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.07 (d, ^{3}J = 6.70 Hz, 3H, $C^{\alpha}HCH(C\mathbf{H_3})_2$), 1.06 (d, ^{3}J = 6.70 Hz, 3H, $C^{\alpha}HCH(C\mathbf{H_3})_2$). ^{13}C NMR (75 MHz, Chloroform-*d*) δ = 166.1 ($\mathbf{C}O_2CH_2CH_3$), 136.1 (ar-**C**-4), 132.9 (ar-**C**-2), 130.8 (ar-**C**-1), 129.5 (ar-**C**-6), 128.5 (ar-**C**-5), 123.2 (ar-**C**-3), 88.6 ($C^{\alpha}H\mathbf{C}\equiv$C-ar), 84.8 ($C^{\alpha}HC\equiv\mathbf{C}$-ar), 61.4 ($CO_2\mathbf{C}H_2CH_3$), 56.5 ($S\mathbf{C}(CH_3)_3$), 54.3 ($\mathbf{C^{\alpha}}HCH(CH_3)_2$), 33.9 ($C^{\alpha}H\mathbf{C}H(CH_3)_2$), 22.8 ($S(C(\mathbf{C}H_3)_3$), 19.2 ($C^{\alpha}HCH(\mathbf{C}H_3)_2$), 17.7 ($C^{\alpha}HCH(\mathbf{C}H_3)_2$), 14.5 ($CO_2CH_2\mathbf{C}H_3$). $C_{19}H_{27}NO_3S$ (349.49 g mol^{-1}). TLC: R*f* (PE/EtOAc, 1:1) = 0.52. $[\alpha]_{589}^{20}$ = +13.75 (*c* 0.708, $CHCl_3$).

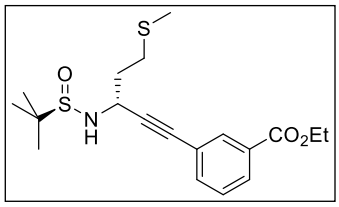
Ethyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoate (40b).
A solution of D-leucine analogous propargylamide **6c** (375 mg, 1.74 mmol, 1.0 eq) and ethyl 3-iodobenzoate (**36b**, 500 µL, 2.90 mmol, 1.7 eq) in a mixture of THF/piperidine (4 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (1:1, 60 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 10-20 mL, until pH 6). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **40b** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless, highly viscous oil. Yield: 621.7 mg, 1.710 mmol, 98 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.06 (t, ^{4}J = 1.7 Hz, 1H, ar-2-**H**), 7.95 (dt, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz, 1H, ar-6-**H**), 7.60 (dt, ^{3}J = 7.6 Hz, ^{4}J = 1.5 Hz, 1H, ar-4-**H**), 7.35 (t, ^{3}J = 7.8 Hz, 1H, ar-5-**H**), 4.35 (q, ^{3}J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.26 (ddd, ^{3}J = 4.6 Hz, ^{3}J = 7.4 Hz, ^{3}J = 7.9 Hz, $C^{\alpha}\mathbf{H}CH_2CH(CH_3)_2$), 3.45 (s br., 1H, $C^{\alpha}HN\mathbf{H}$), 1.90 (m, 1H, $C^{\alpha}HCH_2C\mathbf{H}(CH_3)_2$), 1.82-6.54 (m, 2H, $C^{\alpha}HC\mathbf{H_2}CH(CH_3)_2$), 1.37 (t, ^{3}J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.22 (s, 9H, $SC(C\mathbf{H_3})_3$), 0.95 (d, ^{3}J = 6.6 Hz, 6H, $C^{\alpha}HCH_2CH(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.9 ($\mathbf{C}O_2CH_2CH_3$), 136.0 (ar-**C**-4), 132.7 (ar-**C**-2), 130.6 (ar-**C**-6), 129.3 (ar-**C**-3), 128.3 (ar-**C**-5), 123.1 (ar-**C**-1), 90.3 ($C^{\alpha}H\mathbf{C}\equiv$C-ar),

83.7 ($C^{\alpha}HC{\equiv}\mathbf{C}$-ar), 61.2 ($CO_2\mathbf{C}H_2CH_3$), 56.2 ($S\mathbf{C}(CH_3)_3$), 46.9 ($\mathbf{C^{\alpha}}HCH_2CH(CH_3)_2$), 46.2 ($C^{\alpha}H\mathbf{C}H_2CH(CH_3)_2$), 25.0 ($C^{\alpha}HCH_2\mathbf{C}H(CH_3)_2$), 22.6 ($SC(\mathbf{C}H_3)_3$), 22.1 ($C^{\alpha}HCH_2CH(\mathbf{C}H_3)_2$), 21.4 ($C^{\alpha}HCH_2CH(\mathbf{C}H_3)_2$), 14.3 ($CO_2CH_2\mathbf{C}H_3$). $C_{20}H_{29}NO_3S$ (363.52 g mol^{-1}). MS(ESI): *m/z* = 386.17499 (calcd. 386.17604 $[M+Na]^+$). $[\alpha]_{589}^{22}$ = -11.0 (*c* 0.73, $CHCl_3$), $[\alpha]_{589}^{20}$ = +13.90 (*c* 0.854, MeOH). R*f* (EtOAc/PE, 1:1) = 0.48. IR (ATR): ϑ [cm^{-1}] = 3272 (-NH-), 2953, 2866 (C-CH_3, -CH_2-), 1719 (CO_2Et), 1604, 1581 (ar, C=C), 1281, 1217, 1100, 1053 (C-H). Mp = 160.7 °C (± 1.7 K).

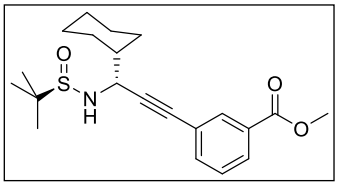
Ethyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-(methylthio)pent-1-yn-1-yl)benzoate (40c). A solution of the D-methionine analogous propargylamide **6d** (100 mg, 430 µmol, 1.0 eq) and ethyl 3-iodobenzoate (**36b**, 1.3 mL, 0.77 mmol, 1.8 eq) in a mixture of THF/piperidine (7:3, 1.0 mL) was thoroughly degassed by the freeze-pump-thaw method. Afterwards, the catalysts $PdCl_2(PPh_3)_2$ (30 mg, 43 µmol, 0.1 eq) and CuI (17 mg, 86 µmol, 0.2 eq) were added in one portion to the cold solution and the mixture was stirred at rt. 12 h later, a colorless precipitate had formed. The reaction mixture was diluted with an aqueous NH_4Cl solution (saturated, 10 mL) neutralized with hydrochloric acid (1 M, about 3 mL) and extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. After purification by column chromatography (PE/EtOAc, 1:1), title compound **40c** was isolated in form of a very pale brown solid.



Pale brown highly viscous oil. Yield: 138 mg, 362 µmol, 85 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.08 (t, ^4J = 1.8 Hz, 1H, ar-2-**H**), 7.98 (dt, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, ar-6-**H**), 7.61 (dt, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, ar-4-**H**), 7.37 (td, ^3J = 7.8 Hz, ^4J = 0.6 Hz, 1H, ar-5-**H**), 4.47 (ddd, ^3J = 6.6 Hz, ^3J = 6.7 Hz, ^3J = 5.4 Hz, 1H, $C^{\alpha}\mathbf{H}C^{\beta}H_2C^{\gamma}H_2SCH_3$), 4.37 (q, ^3J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 3.55 (d, ^3J = 6.6 Hz, 1H, $C^{\alpha}HN\mathbf{H}$), 2.74 (ddt, ^2J = 11.3 Hz, ^3J = 6.7 Hz, ^3J = 5.8 Hz, 1H, $C^{\alpha}HC^{\beta}\mathbf{H}_2C^{\gamma}H_2SCH_3$), 2.67 (ddt, ^2J = 11.9 Hz, ^3J = 5.4 Hz, ^3J = 6.3 Hz, 1H, $C^{\alpha}HC^{\beta}\mathbf{H}_2C^{\gamma}H_2SCH_3$), 2.13 (s, 3H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2SC\mathbf{H_3}$), 2.12-2.06 (m, 2H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}\mathbf{H_2}SCH_3$), 1.39 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.24 (s, 9H, $SC(C\mathbf{H_3})_3$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 166.0 ($\mathbf{C}O_2CH_2CH_3$), 136.0 (ar-**C**-4), 132.9 (ar-**C**-2), 130.8 (ar-**C**-1), 129.6 (ar-**C**-6), 128.5 (ar-**C**-5), 122.9 (ar-**C**-3), 89.2 ($C^{\alpha}H\mathbf{C}{\equiv}$C-ar), 84.6 ($C^{\alpha}HC{\equiv}\mathbf{C}$-ar), 61.3 ($CO_2\mathbf{C}H_2CH_3$), 56.4 ($S\mathbf{C}(CH_3)_3$), 47.4

(**C$^{\alpha}$**HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$SCH$_3$), 36.2 (C$^{\alpha}$HC$^{\beta}$H$_2$**C$^{\gamma}$**H$_2$SCH$_3$), 30.3 (C$^{\alpha}$H**C$^{\beta}$**H$_2$C$^{\gamma}$H$_2$SCH$_3$), 22.7 (SC(**C**H$_3$)$_3$), 15.7 (C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$S**C**H$_3$), 14.4 (CO$_2$CH$_2$**C**H$_3$). $C_{19}H_{27}NO_3S_2$ (381.55 g mol^{-1}). MS(EI): *m/z* = 382.219 (calcd. 382.1505 [M+H]$^+$), 404.198 (calcd. 404.1325 [M+Na]$^+$). TLC: R*f* (EtOAc/PE, 1:2) = 0.14. IR (ATR): ῦ [cm^{-1}] = 3205 (NH), 2974, 2958, 2914 (CH$_3$, CH$_2$, ar-CH), 2359 (C≡C), 1714 (C=O), 1600, 1578 (ar C=C), 1473, 1429, 1385, 1365 (δ CH$_3$, δ CH$_2$), 1290, 1223 (CO-O-C), 1059 (S=O), 913, 865 755, 685 (ar C-H). $[\alpha]_{589}^{20}$ = -15.84 (*c* 5.532, MeOH).

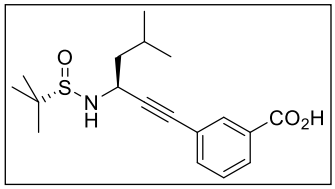
Methyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)benzoate (40d). Piperidine (0.3 mL) was added to a solution of D-cyclohexylglycine analogous propargylamide **6e** (46.4 mg, 192.4 μmol, 1.3 eq) and methyl 3-iodobenzoate (**36a**, 38.8 mg, 192 μmol, 1.3 eq) in THF (0.9 mL). The reaction mixture was degassed by freeze pump thaw method, until no more gas atmosphere could be detected by the manometer (usually 3 x). The catalysts, $PdCl_2(PPh_3)_2$ (1 mg) and CuI (2 mg) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After 2 h, a colorless precipitate formed in the clear solution, indicating the procedure of the reaction. 14 h Later, the suspension was diluted with a saturated aqueous NH_4Cl (10 mL) solution and $KHSO_4$ (aq, 5%, 7 mL) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O (20 mL), the organic layer was separated and extracted to more times with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. Crude product **40d** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless crystals. Yield: 24.5 mg, 65.2 μmol, 44 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.08 (d, ^4J = 1.8 Hz, 1H, ar-2-**H**), 7.95 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, ar-6-**H**), 7.62 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, ar-4-**H**), 7.37 (t, ^3J = 7.8 Hz, 1H, ar-5-**H**), 4.08 (dd, ^3J = 7.1 Hz, ^3J = 6.4 Hz, 1H, C$^{\alpha}$**H**cy), 3.91 (s, 3H, CO$_2$C**H$_3$**), 3.38 (d, ^3J = 7.1 Hz, 1H, C$^{\alpha}$HN**H**), 1.90 (d br., ^2J = 11.7 Hz, 1H, cy-2-**H**), 1.88 (d br., ^2J = 11.7 Hz, 1H, cy-6-**H**), 1.79 (d br., ^2J = 12.6 Hz, 2H, cy-2-**H**, cy-6-**H**), 1.72-1.62 (m br., 2H, cy-1-**H**, cy-4-**H**), 1.33-1.26 (m br., 2H, cy-3-**H**, cy-5-**H**), 1.25 (s, 9H, SC(C**H$_3$**)$_3$), 1.22-1.10 (m br., 3H, cy-3-**H**, cy-4-**H**, cy-5-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (**C**O$_2$CH$_3$), 136.2 (ar-**C**-4), 132.9 (ar-**C**-4), 130.4 (ar-**C**-1), 129.4 (ar-**C**-6), 128.5 (ar-**C**-5), 123.4 (ar-**C**-3),

89.3 (C^{α}H**C**≡Car), 84.8 (C^{α}HC≡**C**ar), 56.5 (S**C**$(CH_3)_3$), 53.8 (**C$^{\alpha}$**H), 52.4 (**C**O_2CH_3), 43.6 (cy-**C**-1), 29.7 (cy-**C**-2), 28.5 (cy-**C**-6), 26.4 (cy-**C**-4), 26.1 (cy-**C**-5), 26.0 (cy-**C**-3), 22.8 (SC(**C**$H_3)_3$). $C_{21}H_{29}NO_3S$ (375.53 g mol^{-1}). MS(ESI): *m/z* = 376.1998 (calcd. 376.1941 $[M+H]^+$), 398.1814 (calcd. 398.1760 $[M+Na]^+$). Mp = 101 °C (+/- 3 K).

3-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoic Acid (40e). A

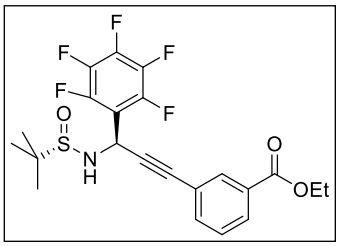


solution of L-leucine analogous propargylamide **6c** (64 mg, 320 µmol, 1 eq) and 3-iodo benzoate (**36c**, 122 mg, 480 µmol, 1.5 eq) in a mixture of THF/piperidine (2:1, 1 mL) was thoroughly degassed by the freeze pump thaw method. The solid catalyst, $PdCl_2(PPh_3)_2$ (22 mg, 32 µmol, 0.1 eq) and CuI (12 mg, 64 µmol, 0.2 eq) was added in one portion. The reaction mixture was stirred for 16 h at ambient temperature, before it was diluted with a mixture of aqueous NH_4Cl and Et_2O (2:5, 45 mL) and neutralized with aqueous HCl (1 M, 3-5 mL, pH 6). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (8 mL) and dried over Na_2SO_4. After evaporation of the solvent, crude product **40e** was purified by column chromatography (CH_2Cl_2/MeOH, 95:5).

Pale, orange solid. Yield: 56 mg, 167 µmol, 52 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.16 (t, ^4J = 1.7 Hz, 1H, ar-2-**H**), 7.77 (ddd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, ^4J = 1.4 Hz, 1H, ar-6-**H**), 7.41 (ddd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, ^4J = 1.4 Hz, 1H, ar-4-**H**), 7.16 (t, ^3J = 7.8 Hz, 1H, ar-5-**H**), 5.39 (s, 1H, C^{α}HN**H**), 4.19 (ddd, ^3J = 7.6 Hz, ^3J = 7.4 Hz, ^3J = 6.9 Hz, 1H, C^{α}**H**), 1.90 (m, 1H, $C^{\alpha}HCH_2C$**H**$(CH_3)_2$), 1.70 (dt, ^2J = 15.0 Hz, ^3J = 7.6 Hz, 1H, $C^{\alpha}HC$**H**$_2CH(CH_3)_2$), 1.62 (dt, ^2J = 14.6 Hz, ^3J = 7.4 Hz, 1H, $C^{\alpha}HC$**H**$_2CH(CH_3)_2$), 1.32 (s, 9H, SC(C**H**$_3)_3$), 0.96 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha}HCH_2CH(C$**H**$_3)_2$), 0.94 (d, ^3J = 6.5 Hz, 3H, $C^{\alpha}HCH_2CH(C$**H**$_3)_2$). $C_{18}H_{25}NO_3S$ (335.46 g mol^{-1}). TLC: R*f* (CH_2Cl_2/MeOH, 95:5) = 0.09.

Ethyl 3-((*R*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-3-(perfluorophenyl)prop-1-yn-1-yl)benzoate (40f). A solution of L-pentafluorphenyl-glycine analogous propargylamide **6o** (50 mg, 154 µmol, 1 eq) and ethyl 3-iodobenzoate (**36c**, 100 mg, 362 µmol, 2 eq) in a mixture of THF/DIPEA (10:1, 1.1 mL) was thoroughly degassed, before adding the catalysts $PdCl_2(PPh_3)_2$ (1.1 mg, 1.5 µmol, 1 mol%) and CuI (0.7 mg, 3.8 µmol, 2 mol%).

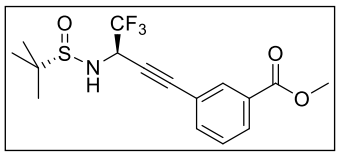
The reaction mixture was stirred for 24 h at rt. The now darkly green suspension was diluted with an aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. The brown crude product was purified by column chromatography (EtOAc/PE, 1:2) to yield peptidomimetic **40f** in pure form.



Pale yellow, highly viscous oil. Yield: 47 mg, 99 μmol, 65 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.08 (t, ^4J = 1.7 Hz, 1H, ar-2-**H**), 8.00 (dt, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, ar-6-**H**), 7.60 (dt, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, ar-4-**H**), 7.38 (t, ^3J = 7.8 Hz, 1H, ar-5-**H**), 5.82 (dt, $^3J_{HH}$ = 6.2 Hz, $^4J_{HF}$ = 1.3 Hz, 1H, C$^{\alpha}$**H**C$_6$F$_5$), 4.37 (q, ^3J = 7.1 Hz, 2H, CO$_2$C**H$_2$**CH$_3$), 4.13 (d, ^3J = 5.9 Hz, 1H, N**H**C$^{\alpha}$H), 1.38 (t, ^3J = 7.1 Hz, 3H, CO$_2$CH$_2$C**H$_3$**), 1.20 (s, 9H, SC(C**H$_3$**)$_3$). ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -142.0 (dd, $^3J_{FF}$ = 20.5 Hz, $^4J_{FH}$ = 6.7 Hz, 2F, F$_5$Ph-2-**F**, F$_5$Ph-6-**F**), -153.1 (tt, $^3J_{FF}$ = 20.9 Hz, $^4J_{FF}$ = 2.2 Hz, 1F, F$_5$Ph-4-**F**), -160.7 (dd, $^3J_{FF}$ = 20.8 Hz, $^4J_{FF}$ = 13.9 Hz, 2F, F$_5$Ph-3-**F**, F$_5$Ph-5-**F**). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 165.8 (ar-1-**C**O$_2$CH$_2$CH$_3$), 144.9 (d, $^1J_{CF}$ = 259.8 Hz, F$_5$Ph-**C**-3, F$_5$Ph-**C**-5), 141.6 (d, $^1J_{CF}$ = 255.1 Hz, F$_5$Ph-**C**-4), 137.9 (d, $^1J_{CF}$ = 248.5 Hz, F$_5$Ph-**C**-2, F$_5$Ph-**C**-6), 136.1 (ar-**C**-4), 133.0 (ar-**C**-2), 131.0 (ar-**C**-1), 130.2 (ar-**C**-6), 128.6 (ar-**C**-5), 122.1 (ar-**C**-3), 113.8 (F$_5$Ph-**C**-1), 85.2 (C$^{\alpha}$H**C**≡C-ar), 85.0 (C$^{\alpha}$HC≡**C**-ar), 61.4 (CO$_2$**C**H$_2$CH$_3$), 56.9 (S**C**(CH$_3$)$_3$), 41.9 (**C$^{\alpha}$**HC$_6$F$_5$), 22.4 (SC(**C**H$_3$)$_3$), 14.4 (CO$_2$CH$_2$**C**H$_3$). $C_{22}H_{20}F_5NO_3S$ (473.46 g mol^{-1}). MS(EI): *m/z* = 496.1 (calcd. 496.0976 [M+Na]$^+$). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3227 (w, ν, -NH), 2977 (w, ν, aryl-H), 2360 (w, ν, -C≡C-), 1717 (s, ν, -C=O), 1518 (s, δ, EtO-C=O), 1502 (vs, δ, -S-NH-), 1296 (s, ν, -CF), 1078 (vs, ν, S=O).

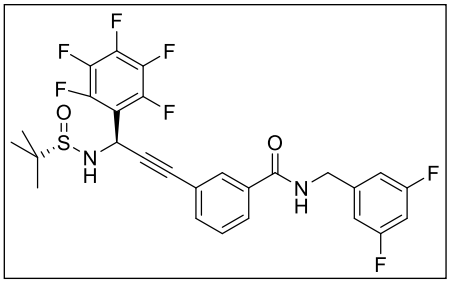
Methyl 3-((*R*)-3-(((*S*)-*tert*-Butylsulfinyl)amido)-4,4,4-trifluorobut-1-yn-1-yl)benzoate (40g). A solution of L-trifluoro-alanine analogous propargylamide **6p** (132 mg, 582 μmol, 1.0 eq) and methyl 3-iodobenzoate (**36a**, 183 mg, 698 μmol, 1.2 eq) in a mixture of THF/DIPEA (2.33 mL, 6:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (5 mg, 6 μmol, 1 mol%) and CuI (2.6 mg, 12 μmol, 2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred 15 h at ambient temperature. The orange solution was diluted with a mixture of Et_2O and aqueous NH_4Cl (5:1, 18 mL), neutralized with aqueous $KHSO_4$

solution (5 %, 5-10 mL, until pH 6). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product **40g** was purified by column chromatography (PE/EtOAc, 1:1).



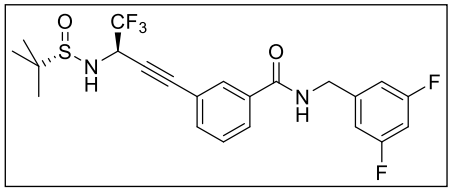
Faintly yellow oil. Yield: 94.7 mg, 262 µmol, 45 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.10 (t, ^4J = 1.7 Hz, 1H, ar-2-**H**), 8.01 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, ar-6-**H**), 7.62 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, ar-4-**H**), 7.39 (t, ^3J = 7.8 Hz, 1H, ar-5-**H**), 4.77 (dq, $^3J_{HH}$ = 7.6 Hz, $^3J_{HF}$ = 6.3 Hz, 1H, C$^{\alpha}$**H**CF_3), 4.04 (d, ^3J = 7.6 Hz, 1H, C$^{\alpha}$HN**H**), 3.90 (s, 3H, CO_2C**H$_3$**), 1.25 (s, 9H, $SC(C$**H$_3$**$)_3$). ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -76.3 (d, $^3J_{FH}$ = 6.3 Hz, C$^{\alpha}$HC**F$_3$**). ^{13}C NMR (75 MHz, Chloroform-*d*) δ = 166.2 (**C**$O_2(CH_3)$), 136.2 (ar-**C**-4), 133.2 (ar-**C**-2), 130.6 (ar-**C**-1), 130.5 (ar-**C**-6), 128.7 (ar-**C**-5), 121.5 (ar-**C**-3), 121.3 (q, $^1J_{CF}$ = 280.7 Hz, C$^{\alpha}$H**C**F_3), 86.7 (C$^{\alpha}$HC≡**C**ar), 80.6 (q, $^3J_{CF}$ = 2.2 Hz, C$^{\alpha}$H**C**≡Car), 57.6 (S**C**$(CH_3)_3$), 52.4 (CO_2**C**H_3), 51.5 (q, $^2J_{CF}$ = 35.1 Hz, **C$^{\alpha}$**HCF_3), 22.5 ($SC($**C**$H_3)_3$). $C_{16}H_{18}F_3NO_3S$ (361.38 g mol^{-1}). MS(ESI): *m/z* = 362.1022 (calcd. 362.1032 $[M+H]^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.63. UV/*Vis*: λ_{max} = 252 nm (Diagram EP2b Experimental Part).

3-((*R*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-3-(perfluorophenyl)prop-1-yn-1-yl)-*N*-(3,5-difluorobenzyl)benzamide (40h). A solution of L-pentafluorphenyl-glycine analogous propargylamide **6o** (100 mg, 307 µmol, 1 eq) and *N*-(3,5-Difluorobenzyl)-3-iodobenzamide (**36d**, 116 mg, 445 µmol, 1.5 eq) in a mixture of THF/DIPEA (6:1, 2.3 mL) was thoroughly degassed, before adding the catalysts $PdCl_2(PPh_3)_2$ (2.2 mg, 3.1 µmol, 1 mol%) and CuI (1.2 mg, 6.2 µmol, 2 mol%). The reaction mixture was stirred for 24 h at rt. The now darkly green suspension was diluted with an aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. The brown crude product was purified by column chromatography (EtOAc/PE, 1:2) to yield peptidomimetic **40h** in pure form.

Pale brown solid. Yield: 123 mg, 215 μmol, 70 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 
7.82 (d, ^{4}J = 1.4 Hz, 2H, ar-2-**H**), 7.81 (dt, ^{3}J = 7.1 Hz, ^{4}J = 1.5 Hz, 1H, ar-4-**H**), 7.51 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.4 Hz, 1H, ar-6-**H**), 7.48 (t, ^{3}J = 6.8 Hz, 1H, CON**H**CH$_2$), 7.35 (dd, ^{3}J = 8.6 Hz, ^{3}J = 7.6 Hz, 1H, ar-5-**H**), 6.85 (d, $^{3}J_{FH}$ = 4.5 Hz, 2H, F$_2$Ph-2-**H**, F$_2$Ph-6-**H**), 6.67 (tt, $^{3}J_{HF}$ = 8.9 Hz, $^{4}J_{HH}$ = 2.3 Hz, 1H, F$_2$Ph-4-**H**), 5.72 (d, ^{3}J = 7.0 Hz, 1H, C$^{\alpha}$**H**), 4.57 (d, ^{3}J = 5.9 Hz, 2H, CONHC**H$_2$**PhF$_2$), 4.19 (d, ^{3}J = 7.2 Hz, 1H, N**H**C$^{\alpha}$H), 1.17 (s, 9H, SC(C**H$_3$**)$_3$). ^{19}F NMR (470 MHz, Chloroform-*d*) δ = -109.5 (t, $^{3}J_{FH}$ = 7.9 Hz, 2F, F$_2$Ph-3-**F**, F$_2$Ph-5-**F**), -142.1 (dd, $^{3}J_{FF}$ = 20.6 Hz, $^{4}J_{FF}$ = 6.6 Hz, 2F, F$_6$Ph-2-**F**, F$_6$Ph-6-**F**), -153.0 (t, $^{3}J_{FF}$ = 20.9 Hz, 1F, F$_6$Ph-4-**F**), -160.6 (td, $^{3}J_{FF}$ = 21.1 Hz, $^{4}J_{FF}$ = 7.0 Hz, 2F, F$_6$Ph-3-**F**, F$_6$Ph-5-**F**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.8 (**C**ONH), 163.2 (dd, $^{1}J_{CF}$ = 248.9 Hz, $^{3}J_{CF}$ = 12.6 Hz, F$_2$Ph-**C**-3, F$_2$Ph-**C**-5), 144.7 (d, $^{1}J_{CF}$ = 250.1 Hz, F$_6$Ph-**C**-3, F$_6$Ph-**C**-5), 142.6 (t, $^{3}J_{CF}$ = 8.8 Hz, F$_2$Ph-**C**-1), 141.4 (d, $^{1}J_{CF}$ = 235.3 Hz, F$_6$Ph-**C**-4), 137.8 (d, $^{1}J_{CF}$ = 258.1 Hz, F$_6$Ph-**C**-2, F$_6$Ph-**C**-6), 135.0 (ar-**C**-6), 134.4 (ar-**C**-1), 130.4 (ar-**C**-2), 128.8 (ar-**C**-5), 128.2 (ar-**C**-4), 122.0 (ar-**C**-3), 113.7 (td, $^{2}J_{CF}$ = 14.7 Hz, $^{3}J_{CF}$ = 4.0 Hz, F$_6$Ph-**C**-1), 110.5 (dd, $^{2}J_{CF}$ = 19.5 Hz, $^{4}J_{CF}$ = 6.0 Hz, F$_2$Ph-**C**-2, F$_2$Ph-**C**-6), 102.9 (t, $^{2}J_{CF}$ = 25.3 Hz, F$_2$Ph-**C**-4), 85.3 (C$^{\alpha}$H**C**≡C-ar), 85.0 (C$^{\alpha}$HC≡**C**-ar), 57.0 (S**C**(CH$_3$)$_3$), 43.3 (CONH**C**H$_2$PhF$_2$), 42.1 (**C$^{\alpha}$**H), 22.4 (SC(**C**H$_3$)$_3$). C$_{27}$H$_{21}$F$_7$N$_2$O$_2$S (570.53 g mol^{-1}). MS(EI): *m/z* = 593.145 (calcd. 593.1104 [M+Na]$^{+}$). TLC: R*f* (PE/EtOAc, 2:1) = 0.23. IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3307 (w, ν, -NH), 2962 (w, ν, Aryl-H), 2360 (w, ν, -C≡C-), 1648 (m, ν, -C=O), 1622 (m, ν, -C=C- Aryl), 1521 (s, δ, -C-NH-), 1505 (vs, δ, -S-NH-), 1256 (s, ν, -CF), 1052 (vs, ν, S=O).

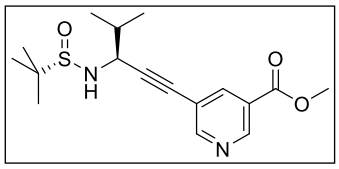
3-((*R*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4,4,4-trifluorobut-1-yn-1-yl)-*N*-(3,5-difluorobenzyl)benzamide (40i). A mixture of L-trifluoralanin analogous propargylamide (**6p**, 105 mg, 462 μmol, 1.0 eq) and *N*-(3,5-difluorbenzyl)-3-iodobenzamide (**36d**, 172 mg, 462 μmol, 1.0 eq) in THF/DIPEA (1.3 mL, 3:1) was thoroughly degassed by the *freeze-pump-thaw* method. Then, the solid catalyst, PdCl$_2$(PPh$_3$)$_2$ (3.2 mg, 4.6 μmol, 1 mol%) and CuI (1.8 mg, 9.4 μmol, 2 mol%), was added and the reaction mixture was stirred for 24 h at ambient temperature. The dark green solution was diluted with an aqueous solution of NH$_4$Cl, neutralized with KHSO$_4$ (5 %, 1-3 mL, pH 6) and extracted with Et$_2$O (3 x 10 mL).

The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by preparative HPLC to yield peptidomimetic **40i** in pure form.



Pale yellow solid. Yield: 38 mg, 80 µmol, 17 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.90 (t, ^4J = 1.7 Hz, 1H, ar-2-**H**), 7.85 (dt, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, ar-6-**H**), 7.65 (dt, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, ar-4-**H**), 7.44 (t, ^3J = 7.7 Hz, 1H, ar-5-**H**), 6.87 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 2.2 Hz, 2H, F_2Ph-2-**H**, F_2Ph-6-**H**), 6.72 (tt, $^3J_{HF}$ = 8.9 Hz, $^4J_{HH}$ = 2.3 Hz, 1H, F_2Ph-4-**H**), 4.81 (dq, $^3J_{HF}$ = 6.4 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, C$^\alpha$**H**CF_3), 4.61 (d br., ^3J = 6.0 Hz, 2H, CONHC**H**$_2$PhF_2), 4.09 (d, ^3J = 7.3 Hz, 1H, N**H**C$^\alpha$H), 1.27 (s, 9H, SC(C**H**$_3$)$_3$). ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -75.7 (d, $^3J_{FH}$ = 6.3 Hz, 3F, C$^\alpha$HC**F**$_3$), -109.2 (dd, $^3J_{FH}$ = 8.0 Hz, $^3J_{FH}$ = 7.7 Hz, 2F, F_2Ph-3-**F**, F_2Ph-5-**F**). $C_{22}H_{21}F_5N_2O_2S$ (472.47 g mol^{-1}). MS(EI): *m/z* = 473.112 (calcd. 473.1317 $[M+H]^+$), 495.137 (calcd. 495.1136 $[M+Na]^+$).

Methyl 5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)nicotinate (41a).

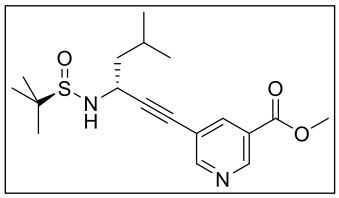


Piperidine (0.3 mL) was added to a solution of the L-valine analogous propargylamide **6b** (302 mg, 1.50 mmol, 1 eq) and methyl 5-bromonicotinate (454 mg, 2.10 mmol, 1.4 eq) in THF (0.9 mL). The reaction mixture was degassed by freeze pump thaw method, until no more gas atmosphere could be detected by the manometer (3 x). The catalysts, $PdCl_2(PPh_3)_2$ (2 mg, 4.8 µmol, 0.3 mol%) and CuI (1 mg, 5.3 µmol, 0.3 mol%) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After 30 min, a colorless precipitate formed in the clear solution, indicating the procedure of the reaction. 5 h Later, the suspension was diluted with a saturated aqueous NH_4Cl solution (13 mL) and $KHSO_4$ (aq, 5%, ca. 5 mL) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O (20 mL), the organic layer was separated and the organic layer extracted to more times with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. The crude product of peptidomimetic **41a** was purified by column chromatography (EtOAc/PE, 1:1) and recrystallizytion from Et_2O.

Colorless crystals. Yield: 293.5 mg, 872.3 µmol, 58 %, dr = 97 % (determined via integration of ^{1}H NMR signals of C$^{\alpha}$**H**, 4.12 ppm), ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 9.10 (s, 1H, ar-6-**H**), 8.80 (s, 1H, ar-2-**H**), 8.31 (s, 1H, ar-4-**H**), 4.12 (ddd, ^{3}J = 9.4 Hz, ^{3}J = 7.3 Hz, ^{3}J = 4.6 Hz, 1H, C$^{\alpha}$**H**), 3.95 (s, 3H, CO_2C**H**$_3$), 3.40 (d, ^{3}J = 7.3 Hz, 1H, C$^{\alpha}$HN**H**), 2.04 (m, 1H, C$^{\alpha}$HC**H**$(CH_3)_2$), 1.25 (s, 9H, SC(C**H**$_3)_3$), 1.08 (d, ^{3}J = 6.8 Hz, 3H, C$^{\alpha}$HCH(C**H**$_3)_2$), 1.07 (d, ^{3}J = 6.6 Hz, 3H, C$^{\alpha}$HCH(C**H**$_3)_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.2 (**C**O_2CH_3), 155.8 (ar-**C**-2), 149.7 (ar-**C**-6), 139.7 (ar-**C**-4), 125.6 (ar-**C**-5), 120.0 (ar-**C**-3), 92.6 (C$^{\alpha}$H**C**≡C-ar), 81.5 (C$^{\alpha}$HC≡**C**-ar), 56.6 (S**C**$(CH_3)_3$), 54.5 (**C**$^{\alpha}$H), 52.7 (CO_2**C**H_3), 34.0 (C$^{\alpha}$H**C**H$(CH_3)_2$), 22.8 (SC(**C**$H_3)_3$), 19.2 (C$^{\alpha}$HCH(**C**$H_3)_2$), 17.9 (C$^{\alpha}$HCH(**C**$H_3)_2$). $C_{17}H_{24}N_2O_3S$ (336.45 g mol^{-1}). EA: C 60.281 (calcd. 60.69), H 7.149 (calcd. 7.19), N 8.356 (calcd. 8.33), S 9.543 (calcd. 9.53). $[\alpha]_{589}^{21}$ = 20.3 (*c* = 0.71, $CHCl_3$). TLC: R*f* (PE:EE 1:1) = 0.26. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3183 (w, NH-VS), 2955, 2920, 2901, 2866 (m, w, w, w, CH-VS), 2357, 2235 (m, m, C≡C), 1730 (s, $COOCH_3$), 1587 (w, NH-DS), 1562 (w), 1448 (m), 1410 (m), 1388 (w), 1362 (w), 1302 (s), 1233 (s), 1163 (w), 1109 (m), 1055(s, S=O), 1021 (m), 1011 (w), 910 (w), 764 (m), 698 (w), 666 (w). X-ray crystal structure in Chapter IIX-3. n.

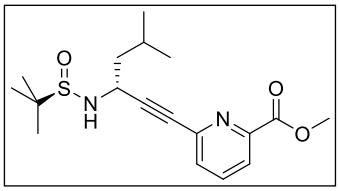
Methyl 5-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)nicotinate (41b). DIPEA (0.25 mL) was added to a solution of the L-leucine analogous propargylamide **6c** (40.3 mg, 187 µmol, 1 eq) and methyl 5-bromonicotinate (**37a**, 52.5 mg, 243 µmol, 1.3 eq) in THF (0.75 mL). The reaction mixture was degassed by freeze pump thaw method (3 x). The catalysts, $Pd(PPh_3)_4$ (2 mg, 4.8 µmol, 3 mol%) and CuI (1 mg, 5.3 µmol, 3 mol%) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After 50 min, a colorless precipitate formed in the clear solution, indicating the procedure of the reaction. 18 h Later, the suspension was diluted with a saturated aqueous NH_4Cl solution (13 mL) and $KHSO_4$ (aq, 5%, ca. 5 mL) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O (20 mL), the organic layer was separated and the organic layer extracted to more times with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. Crude product **41b** was purified by column chromatography (EtOAc/PE, 1:1).

Yellow viscous oil. Yield: 52 mg, 148 μmol, 79 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ



= 9.10 (s, 1H, ar-2-**H**), 8.79 (s, 1H, ar-6-**H**), 8.30 (t, ^{4}J = 2.1 Hz, 1H, ar-4-**H**), 4.27 (ddd, ^{3}J = 7.8 Hz, ^{3}J = 7.7 Hz, ^{3}J = 7.4 Hz, 1H, C$^{\alpha}$**H**), 3.94 (s, 3H, $CO_2C\mathbf{H_3}$), 3.52 (d, ^{3}J = 7.8 Hz, 1H, C$^{\alpha}$HN**H**), 1.91 (m, 1H, C$^{\alpha}$HCH$_2$C**H**(CH$_3$)$_2$), 1.69 (t, ^{3}J = 7.4 Hz, 2H, C$^{\alpha}$HC**H$_2$**CH(CH$_3$)$_2$), 1.24 (s, 9H, SC(C**H$_3$**)$_3$), 0.97 (d, ^{3}J = 6.6 Hz, 6H, CH(C**H$_3$**)$_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.2 (**C**O$_2$CH$_3$), 155.8 (ar-**C**-6), 149.6 (ar-**C**-2), 139.7 (ar-**C**-4), 132.3 (ar-**C**-5), 128.7 (ar-**C**-3), 94.1 (C$^{\alpha}$HC≡**C**-ar), 80.6 (C$^{\alpha}$H**C**≡C-ar), 56.6 (S**C**(CH$_3$)$_3$), 52.7 (CO$_2$**C**H$_3$), 47.2 (**C$^{\alpha}$**H), 46.1 (C$^{\alpha}$H**C**H$_2$), 31.1 (C$^{\alpha}$HCH$_2$**C**H(CH$_3$)$_2$), 22.7 (SC(**C**H$_3$)$_3$), 22.6 (C$^{\alpha}$HCH$_2$CH(**C**H$_3$)$_2$), 22.3 (C$^{\alpha}$HCH$_2$CH(**C**H$_3$)$_2$). $C_{18}H_{26}N_2O_3S$ (350.48 g mol^{-1}). MS(ESI): *m/z* = 373.15581 (calcd. 373.15563 [M+Na]$^{+}$). TLC: R*f* (EtOAc/PE, 1:1) = 0.1.

Methyl 6-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)picolinate (41c). A solution of D-leucine analogous propargylamide **6c** (52 μmol, 1.0 eq) and methyl 6-bromopicolinate (**37b**, 14.6 mg, 67.6 μmol, 1.3 eq) in a mixture of THF/piperidine (1 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method.

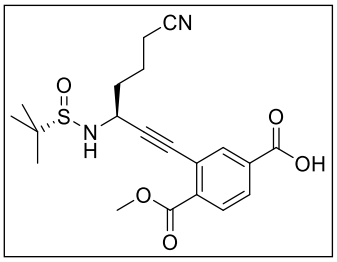


While still frozen, the solid catalyst Pd(PPh$_3$)$_4$ (2 mg, 4.8 μmol, 9 mol%) and CuI (1 mg, 5.4 μmol, 10 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. The reaction mixture was diluted with a mixture of Et$_2$O and aqueous NH$_4$Cl (1:1, 6 mL), neutralized with aqueous KHSO$_4$ solution (5 %, 3 mL, until pH 6). The phases were separated and the aqueous layer was extracted with Et$_2$O (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. Crude product **41c** was purified by preparative HPLC.

Slightly orange oil. Yield: 16.4 mg, 46.8 μmol, 90 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.06 (d, ^{3}J = 7.8 Hz, 1H, ar-3-**H**), 7.82 (t, ^{3}J = 7.8 Hz, 1H, ar-4-**H**), 7.61 (dd, ^{3}J = 7.9 Hz, ^{4}J = 1.2 Hz, 1H, ar-5-**H**), 4.24 (d, ^{3}J = 7.8 Hz, 1H, C$^{\alpha}$HN**H**), 4.11 (ddd, ^{3}J = 7.8 Hz, ^{3}J = 7.3 Hz, ^{3}J = 7.2 Hz, 1H, C$^{\alpha}$**H**), 3.98 (s, 3H, $CO_2C\mathbf{H_3}$), 1.90 (m, 1H, C$^{\alpha}$HCH$_2$C**H**(CH$_3$)$_2$), 1.70 (t, ^{3}J = 7.3 Hz, 2H, C$^{\alpha}$HC**H$_2$**CH(CH$_3$)$_2$), 1.26 (s, 9H, SC(C**H$_3$**)$_3$), 0.96 (d, ^{3}J = 7.0 Hz, 3H, C$^{\alpha}$HCH$_2$CH(C**H$_3$**)$_2$), 0.94 (d, ^{3}J = 6.9 Hz, 3H, C$^{\alpha}$HCH$_2$CH(C**H$_3$**)$_2$). ^{13}C NMR

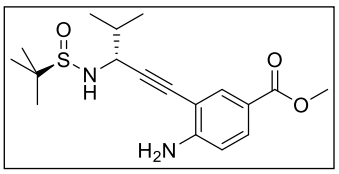
(126 MHz, Chloroform-*d*) δ = 164.8 (ar-2-**C**O_2CH_3), 147.7 (ar-**C**-2), 142.7 (ar-**C**-6), 138.0 (ar-**C**-4), 130.7 (ar-**C**-5), 124.5 (ar-**C**-3), 91.8 ($C^{\alpha}H$**C**≡C-ar), 82.7 ($C^{\alpha}HC$≡**C**-ar), 57.3 (S**C**$(CH_3)_3$), 53.2 (ar-2-CO_2**C**H_3), 47.9 (**C**$^{\alpha}HCH_2CH(CH_3)_2$), 45.3 ($C^{\alpha}H$**C**$H_2CH(CH_3)_2$), 24.8 ($C^{\alpha}HCH_2$**C**$H(CH_3)_2$), 22.8 (SC(**C**$H_3)_3$), 22.4 ($C^{\alpha}HCH_2CH$(**C**$H_3)_2$), 22.1 ($C^{\alpha}HCH_2CH$(**C**$H_3)_2$). $C_{18}H_{26}N_2O_3S$ (350.48 g mol^{-1}). MS(ESI): *m/z* = 373.15581 (calcd. 373.15563 $[M+Na]^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.11. IR (ATR): ϑ [cm^{-1}] = 2955, 2927, 2866 (C-CH_3, -CH_2-), 2615 (C≡C), 2360, 2339, 2318 (C-CH_3, -CH_2-), 1726 (CO_2Et), 1578, 1574, 1559 (ar, C=C), 1309,1288, 1243, 1199, 1164, 1138, 1117 (C-H).

3-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-6-cyanohex-1-yn-1-yl)-4-(methoxycarbonyl)benzoic Acid (42a). The catalysts $PdCl_2(PPh_3)_2$ (2.8 mg, 6.8 μmol, 4 mol%) and CuI (0.9 mg, 4.7 μmol, 3 mol%) were added to a thoroughly degassed solution of L-Glutamine analogon precursor nitrile **6i** (40.5 mg, 178.9 μmol, 1 eq) and 1-Methyl-2-iodoterephthalat (**38a**, 82.1 mg, 268.4 μmol, 1.5 eq) in HN(^{i}Pr)$_2$/THF (1:3, 5 mL). The reaction mixture was stirred overnight at ambient temperature. After complete conversion of the starting material (checked by TLC), the mixture was diluted with aqueous NH_4Cl solution (saturated, 2 mL) and hydrochloric acid (1 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Peptidomimetic **42a** was isolated by column chromatography (PE/EtOAc, 4:1).



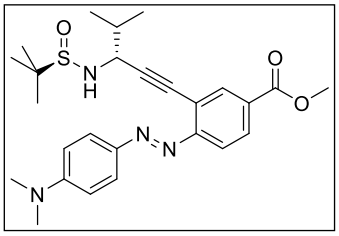
Pale yellow crystalline solid. Yield: 20.6 mg, 50.9 μmol, 29 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.99 (d, ^4J = 1.5 Hz, 1H, ar-2-**H**), 7.81 (d, ^3J = 7.9 Hz, 1H, ar-5-**H**), 7.40 (dd, ^3J = 7.9 Hz, ^4J = 1.6 Hz, 1H, ar-6-**H**), 3.94 (s, 3H, ar-4-CO_2C**H**$_3$), 3.69 (s br., 1H, C^{α}**H**$C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2CN$), 3.29 (s br., 1H, $C^{\alpha}HN$**H**), 3.14 (dt, ^2J = 12.5 Hz, ^3J = 5.0 Hz, 1H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}$**H**$_2$CN), 3.00 (dt, ^2J = 12.5 Hz, ^3J = 5.2 Hz, 1H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}$**H**$_2$CN), 1.73-1.64 (m, 2H, $C^{\alpha}HC^{\beta}$**H**$_2C^{\gamma}H_2C^{\delta}H_2CN$), 1.63-1.54 (m, 2H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}$**H**$_2C^{\delta}H_2CN$), 1.16 (s, 9H, SC(C**H**$_3)_3$). $C_{20}H_{24}N_2O_5S$ (404.48 g mol^{-1}), MS(ESI): *m/z* = 405.127 (calcd. 405.1479 $[M+H]^+$), 809.335 (calcd. 809.2885 $[2M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.29.

Methyl 4-Amino-3-((*R*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)benzoate (42b). A solution of D-valine analogous propargylamide **6b** (100 mg, 497 µmol, 1.0 eq) and methyl 4-amino-3-iodobenzoate (**38b**, 158 mg, 570 µmol, 1.1 eq) in a mixture of THF/piperidine (4:1, 1.25 mL) was thoroughly degassed using the freeze-pump-thaw method. The catalyst $PdCl_2(PPh_3)_2$ (3.0 mg, 4.3 µmol, 0.9 mol%) and CuI (1.7 mg, 8.9 µmol, 2 mol%) was added under argon atmosphere and the reaction mixture was stirred 14 h at ambient temperature. A colourless precipitate formed, indicating the procedure of the reaction. After dilution with Et_2O (4 mL) and NH_4Cl solution (2 mL), the phases were separated and the aqueous layer was extracted with Et_2O (2 x 4 mL). The combined organic layers were washed with water (2 x 10 ml) and brine (1 x 4 mL) and dried over $MgSO_4$. After evaporation, the crystalline peptidomimetic **42b** was purified by column chromatography (PE/EtOc, 1:1) and recrystallized from Et_2O.



Pale orange, crystalline solid. Yield: 144 mg, 411 µmol, 83 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.89 (d, ^4J = 2.0 Hz, 1H, ar-2-**H**), 7.74 (dd, ^3J = 8.6 Hz, ^4J = 2.1 Hz, 1H, ar-6-**H**), 6.58 (d, ^3J = 8.6 Hz, 1H, ar-5-**H**), 5.26 (s, 2H, ar-4-N**H₂**), 3.99 (dd, ^3J = 10.5 Hz, ^3J = 6.2 Hz, 1H, C$^\alpha$**H**), 3.84 (s, 3H, ar-1-CO_2C**H₃**), 3.29 (d, ^3J = 10.6 Hz, 1H, C$^\alpha$HN**H**), 1.98 (dh, ^3J = 6.2 Hz, ^3J = 6.7 Hz, 1H, C$^\alpha$HC**H**$(CH_3)_2$), 1.24 (s, 9H, SC(C**H₃**)₃), 1.10 (d, ^3J = 6.7 Hz, 3H, C$^\alpha$HCH(C**H₃**)₂), 1.08 (d, ^3J = 6.8 Hz, 3H, C$^\alpha$HCH(C**H₃**)₂). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.9 (ar-1-**C**O_2CH_3), 153.7 (ar-**C**-1), 134.1 (ar-**C**-2), 131.6 (ar-**C**-6), 118.2 (ar-**C**-4), 113.2 (ar-**C**-5), 106.0 (ar-**C**-3), 93.9 (C$^\alpha$H**C**≡C-ar), 82.7 (C$^\alpha$HC≡**C**-ar), 56.7 (S**C**$(CH_3)_3$), 55.9 (**C$^\alpha$**H$CH(CH_3)_2$), 51.7 (CO_2**C**H_3), 34.2 (C$^\alpha$H**C**$H(CH_3)_2$), 22.7 (SC(**C**$H_3)_3$), 19.1 (C$^\alpha$HCH(**C**$H_3)_2$), 18.7 (C$^\alpha$HCH(**C**$H_3)_2$). $C_{18}H_{26}N_2O_3S$ (350.48 g mol^{-1}). LCMS (ESI): t_r = 6.0 min, *m/z* = 351.309 (calcd. 351.1737 [M+H]$^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.36. $[\alpha]_{589}^{21}$ = 12.0 (*c* 0.47, MeOH). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 3430 (-N-H), 3329 (-N-H), 3212 (-N-H), 2955, 2924, 2870 (-C-H), 1708 (-C=O), 1622 (-N-H), 1603 (-N-H), 1505 (ar, -C=C-), 1438 (-CH_3, -CH_2), 1261, 1226, 1147, 1103 (-C-H).

Methyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)-4-((*E*)-(4-(dimethylamino)phenyl)diazenyl)benzoate (42c). The catalysts $PdCl_2(PPh_3)_2$ (1.5 mg, 2.1 μmol, 1 mol%) and CuI (1.1 mg, 5.8 μmol, 3 mol%) were added to a thoroughly degassed solution of D-valine analogous propargylamide **6b** (35.1 μmol, 174 μmol, 1 eq) and azobenzene **38c** (85.5 mg, 209 μmol, 1.2 eq) in piperidine/THF (1:3, 0.4 mL). The reaction mixture was stirred for 16 h at ambient temperature. After complete conversion of the starting material (checked by LCMS), the mixture was diluted with aqueous NH_4Cl solution (saturated, 4 mL) and hydrochloric acid (1 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Title compound **42c** was isolated by preparative HPLC.



Purple oil. Yield: 5.8 g, 12 μmol, 7 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.20 (d, ^4J = 1.9 Hz, 1H, benzoate-2-**H**), 8.06-7.99 (m, 3H, benzoate-6-**H**, anilin-2-**H**, anilin-6-**H**), 7.75 (d, ^3J = 8.6 Hz, 1H, benzoate-5-**H**), 6.94 (d, ^3J = 9.1 Hz, 2H, anilin-3-**H**, anilin-5-**H**), 4.17 (d br., ^3J = 5.8 Hz, 1H, C$^{\alpha}$**H**), 3.94 (s, 3H, $CO_2C\mathbf{H_3}$), 3.27 (s, 6H, $N(C\mathbf{H_3})_2$), 2.09 (hd, ^3J = 6.6 Hz, ^3J = 5.8 Hz, 1H, C$^{\alpha}$HC**H**$(CH_3)_2$), 1.29 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.12 (d, ^3J = 6.7 Hz, 3H, C$^{\alpha}$HCH$(C\mathbf{H_3})_2$), 1.11 (d, ^3J = 6.6 Hz, 3H, C$^{\alpha}$HCH$(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.1 (**C**O_2CH_3), 154.8 (benzoate-**C**-4), 143.0 (anilin-**C**-1), 135.0 (benzoate-**C**-2), 130.6 (benzoate-**C**-1), 129.8 (benzoate-**C**-5), 129.0 (anilin-**C**-2, anilin-**C**-6), 119.2 (benzoate-**C**-6), 116.7 (anilin-**C**-1), 115.7 (benzoate-**C**-3), 114.1 (anilin-**C**-3, anilin-**C**-5), 95.0 (C$^{\alpha}$H**C**≡C-ar), 82.2 (C$^{\alpha}$HC≡**C**-ar), 57.2 (S**C**$(CH_3)_3$), 55.6 (**C$^{\alpha}$**H), 52.5 ($CO_2\mathbf{C}H_3$), 41.6 ($N(\mathbf{C}H_3)_2$), 34.0 (**C**$H(CH_3)_2$), 22.8 ($SC(\mathbf{C}H_3)_3$), 19.3 (C$^{\alpha}$HCH(**C**$H_3)_2$), 18.2 (C$^{\alpha}$HCH(**C**$H_3)_2$). $C_{26}H_{34}N_4O_3S$ (482.64 g mol^{-1}). MS(ESI): *m/z* = 379.339 (calcd. 379.2134 [M-C_4H_9OS+H]$^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.37. $[\alpha]_{589}^{22}$ = 75.3 (*c* 0.29, CH_3CN). pH (c=0.1 μM in H_2O) = 2.3. UV/*Vis*: λ_{max} (pH < 7.8) = 448 nm, λ_{max} (pH > 8.2) = 469 nm.

A sample of azobenzoate **42c** was investigated at different pH values (Figure EP1 Experimental Part). An aqueous solution of NaOH (0.1 μM) was added dropwise via burette to a vigorously stirred aqueous solution of azobenzoate **42c** (0.1 μM, pH 2.3) until the color of the solution changed from purple to dark yellow (monitored with the naket eye). The pH value was monitored by a pH electrode. The color change was determined at pH 7.8-8.2 (Diagram EP1 Experimental Part).

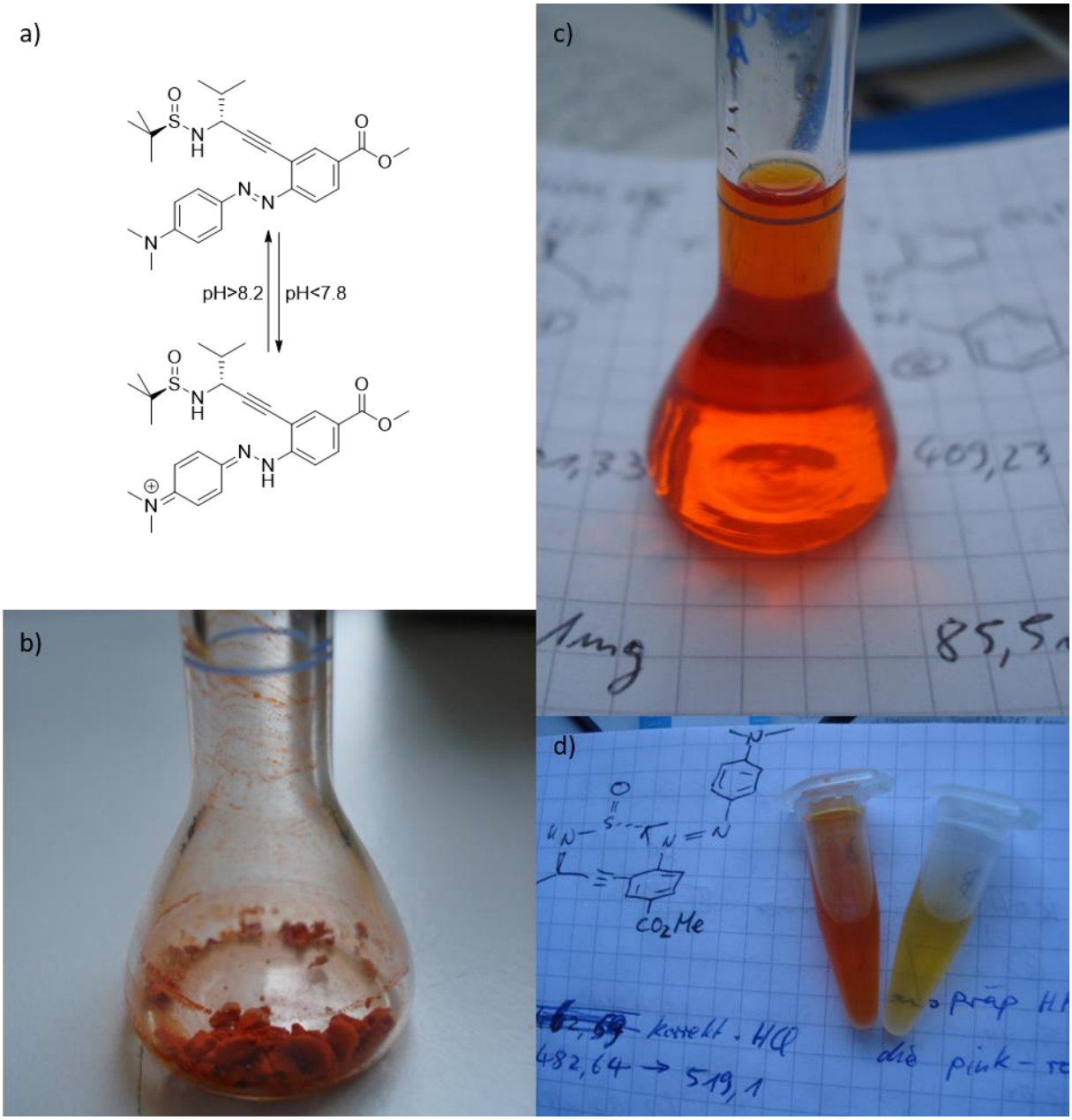
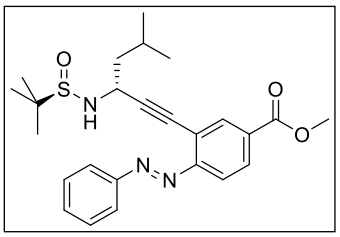


Figure EP1. pH-Dependent colours of peptidomimetic **42c**. a) Protonation of azobenzoate derivative **42c** in acidic milieu (pH<7.8) and deprotonation in alkaline milieu (pH>8.2). b) Solid peptidomimetic **42c**. c) 0.1 µM Solution of **42c** in water. d) Comparison of the 0.1 µM aqueous **42c** solution at pH 11.0 (left side) and pH 2.7 (right side).

Methyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)-4-((*E*)-phenyldiazenyl)benzoate (42d). The catalysts $PdCl_2(PPh_3)_2$ (2 mg, 4.8 µmol, 1.5 mol%) and CuI (1 mg, 5.2 µmol, 1.7 mol%) were added to a thoroughly degassed solution of D-leucine analogous propargylamide **6c** (68.2 mg, 317 µmol, 1.0 eq) and azobenzene **38d** (139 mg, 318 µmol, 1.2 eq) in piperidine/THF (1:3, 0.4 mL). The pink reaction mixture was stirred for 30 h at ambient temperature. After complete conversion of the starting

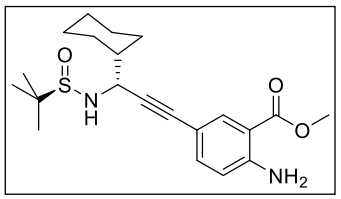
material (checked by LCMS), the mixture was diluted with aqueous NH_4Cl solution (saturated, 4 mL), water (10 mL) and hydrochloric acid (1 mL) and extracted with Et_2O (3 x 15 mL) until the aqueous phase had completely lost its pink colour. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Peptidomimetic **42d** was isolated by preparative HPLC.

Dark red solid. Yield: 23 mg, 51 μmol, 16 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.28 (d, ^4J = 1.5 Hz, 1H, ar-2-**H**), 8.05 (dt, ^3J = 8.5 Hz, ^4J = 1.4 Hz, 1H, ar-6-**H**), 7.99 (dd, ^3J = 6.7 Hz, ^4J = 1.4 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 7.69 (d, ^3J = 8.5 Hz, 1H, ar-5-**H**), 7.63-7.41 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 4.39 (dd, ^3J = 8.3 Hz, ^3J = 6.9 Hz, 2H, NHC$^{\alpha}$**H**), 3.95 (s, 3H, $CO_2C\mathbf{H_3}$), 2.24 (s br., 1H, C$^{\alpha}$HN**H**), 1.99 (m, 1H, C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$**H**(CH$_3$)$_2$), 1.76 (ddd, ^2J = 14.3 Hz, ^3J = 8.7 Hz, ^3J = 5.8 Hz, 1H, C$^{\alpha}$HC$^{\beta}$**H**$_2$C$^{\gamma}$H(CH$_3$)$_2$), 1.70 (ddd, ^2J = 12.9 Hz, ^3J = 8.4 Hz, ^3J = 6.7 Hz, 1H, C$^{\alpha}$HC$^{\beta}$**H**$_2$C$^{\gamma}$H(CH$_3$)$_2$), 1.26 (s, 9H, SC(C**H₃**)$_3$), 0.96 (d, ^3J = 6.7 Hz, 3H, C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H(C**H₃**)$_2$), 0.95 (d, ^3J = 6.7 Hz, 3H, C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H(C**H₃**)$_2$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 166.1 (**C**O$_2$CH$_3$), 155.6 (Ph-**C**-1), 135.2 (ar-**C**-4), 133.7 (ar-**C**-2), 132.0 (Ph-**C**-4), 131.6 (ar-**C**-1), 130.1 (ar-**C**-5), 129.3 (Ph-**C**-5, Ph-**C**-3), 123.7 (Ph-**C**-2, Ph-**C**-6), 122.8 (ar-**C**-6), 116.1 (ar-**C**-3), 95.8 (C$^{\alpha}$H**C**≡C-ar), 81.5 (C$^{\alpha}$HC≡**C**-ar), 56.6 (S**C**(CH$_3$)$_3$), 52.6 (CO$_2$**C**H$_3$), 47.5 (**C**$^{\alpha}$NH), 31.1 (C$^{\alpha}$H**C**$^{\beta}$H$_2$C$^{\gamma}$H(CH$_3$)$_2$), 25.2 (C$^{\alpha}$HC$^{\beta}$H$_2$**C**$^{\gamma}$H(CH$_3$)$_2$), 22.7 (SC(**C**H$_3$)$_3$), 22.0 (C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H(**C**H$_3$)$_2$), 21.7 (C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H(**C**H$_3$)$_2$). $C_{25}H_{31}N_3O_3S$ (453.60 g mol^{-1}). MS (ESI): *m/z* = 454.421 (calcd. 454.2159 [M+H]$^+$). UV/*Vis*: λ_{max} 355 nm (Diagram EP2a).



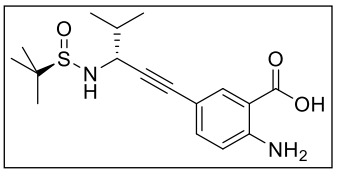
Methyl 2-Amino-5-((*R*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)benzoate (43a). A solution of D-cyclohexylglycine analogous propargylamide **6e** (32.2 mg, 132 μmol, 1.0 eq) and Methyl-2-((2-iodo-5-methylphenyl)diazenyl)benzoate (**39a**, 108 mg, 280 μmol, 2.2 eq) in a mixture of THF/DIPEA (2 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (1 mol%) and CuI (2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (4:5, 12 mL), neutralized with aqueous $KHSO_4$

solution (5 %, 3-5 mL, until pH 6). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **43a** was purified by column chromatography (PE/EtOAc, 1:1).



Pale yellow oil. Yield: 32.5 mg, 83.2 µmol, 63 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.90 (d, ^3J = 8.2 Hz, 1H, ar-3-**H**), 7.83 (s, 1H, ar-6-**H**), 7.19 (d, ^3J = 8.2 Hz, 1H, ar-4-**H**), 4.04 (dd, ^3J = 7.4 Hz, ^3J = 5.9 Hz, 1H, C$^{\alpha}$**H**cy), 3.92 (s, 3H, $CO_2C\mathbf{H_3}$), 3.37 (d, ^3J = 7.5 Hz, 1H, C$^{\alpha}$HN**H**), 1.87 (m, 2H, cy-**H**), 1.83-1.75 (m, 3H, cy-**H**), 1.72-1.60 (m, 2H, cy-**H**), 1.24 (s, 9H, SC($C\mathbf{H_3}$)$_3$), 1.21-1.09 (m, 4H, cy-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.4 (ar-1-**C**O_2CH_3), 141.4 (ar-**C**-3), 135.5 (ar-**C**-4), 135.2 (ar-**C**-1), 134.0 (ar-**C**-6), 123.2 (ar-**C**-2), 93.9 (ar-**C**-5), 90.8 (C$^{\alpha}$H**C**≡Car), 83.9 (C$^{\alpha}$HC≡**C**ar), 56.6 (S**C**(CH_3)$_3$), 54.0 (**C$^{\alpha}$**Hcy), 52.8 (ar-2-CO_2**C**H_3), 43.6 (cy-**C**-1), 29.7 (cy-**C**-2), 28.6 (cy-**C**-6), 26.4 (cy-**C**-4), 26.1 (cy-**C**-5), 26.0 (cy-**C**-3), 22.8 (SC(**C**H_3)$_3$). $C_{21}H_{30}N_2O_3S$ (390.54 g mol^{-1}).

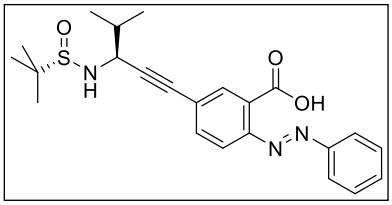
2-Amino-5-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)benzoic Acid (43b). A solution of D-valine analogous propargylamide **6b** (106 mg, 527 µmol, 1 eq) and 4-iodoanthranilate **39a** (207 mg, 786 µmol, 1.5 eq) in a mixture of THF and piperidine (3:1, 1.3 mL) was thoroughly degassed by the freeze pump thaw method. After 3 cycles, the catalysts CuI (2.2 mg, 12 µmol, 2 mol%) and $PdCl_2(PPh_3)_2$ (3.6 mg, 5.1 µmol, 1 mol%) was added in one portion and the reaction mixture was stirred for 15 h at rt. A colorless precipitate formed, which had formed dissolved upon dilution with a saturated NH_4Cl solution (5 mL) and $KHSO_4$ solution (3 mL). The clear solution was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Peptidomimetic **43b** was isolated by preparative HPLC.



Yellow, highly viscous oil. Yield: 23.7 mg, 70.4 µmol, 13 %. ^{1}H NMR (600 MHz, methanol-d_4) δ = 7.89 (d, ^4J = 2.0 Hz, 1H, ar-6-**H**), 7.27 (dd, ^3J = 8.6 Hz, ^4J = 2.1 Hz, 1H, ar-4-**H**), 6.68 (d, ^3J = 8.6 Hz, 1H, ar-3-**H**), 3.96 (d br., ^3J = 6.4 Hz, 1H, C$^{\alpha}$**H**CH(CH_3)$_2$),

1.97 (dh, ^{3}J = 6.4 Hz, ^{3}J = 6.7 Hz, 1H, $C^{\alpha}HC\mathbf{H}(CH_3)_2$), 1.26 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.10 (d, ^{3}J = 6.7 Hz, 3H, $C^{\alpha}HCH(C\mathbf{H_3})_2$), 1.07 (d, ^{3}J = 6.7 Hz, 3H, $C^{\alpha}HCH(C\mathbf{H_3})_2$). ^{13}C NMR (151 MHz, methanol-d_4) δ = 198.3 ($\mathbf{C}O_2H$), 170.8 (ar-**C**-1), 157.0 (ar-**C**-5), 135.3 (ar-**C**-3), 134.5 (ar-**C**-6), 125.7 (ar-**C**-4), 117.3 (ar-**C**-2), 110.1 ($C^{\alpha}H\mathbf{C}$≡Car), 60.9 ($C^{\alpha}HC$≡**C**ar), 57.5 ($S\mathbf{C}(CH_3)_3$), 41.8 ($\mathbf{C^{\alpha}}HCH(CH_3)_2$), 33.7 ($C^{\alpha}H\mathbf{C}H(CH_3)_2$), 23.3 ($SC(\mathbf{C}H_3)_3$), 19.8 ($C^{\alpha}HCH(\mathbf{C}H_3)_2$), 18.5 ($C^{\alpha}HCH(\mathbf{C}H_3)_2$). $C_{17}H_{24}N_2O_3S$ (336.45 g mol^{-1}). HRMS (ESI): *m/z* = 335.14448 (calcd. 335.14349 [M-H$^+$]$^-$). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 3471 (-O-H), 3360 (-N-H); 2965 (-C-H); 1619 (-N-H); 1584 (ar, -C=C-); 1299, 1245, 1211, 1169 (C-H). $[\alpha]_{589}^{22}$ = -51.8 (*c* 1.04, MeOH).

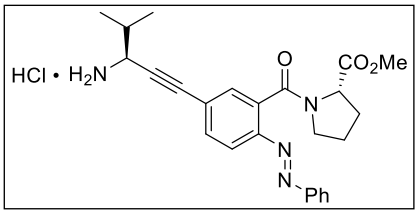
5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)-2-((*E*)-phenyldiazenyl)benzoic Acid (43c). A solution of L-valine analogous propargylamide **6b** (75.5 mg, 380 μmol, 1.0 eq) and azobenzene **39c** (159 mg, 450 μmol, 1.2 eq) in THF (0.7 mL) and piperidine (0.25 mL) was thoroughly degassed by freeze-pump-thaw. The catalyst $PdCl_2(PPh_3)_2$ (2.6 mg, 6.3 μmol, 1.7 mol%) and CuI (1.4 mg, 7.4 μmol, 1.9 mol%) was added under argon atmosphere and the reaction mixture was stirred 4 h at ambient temperature. After complete conversion of the propargylamide (checked by TLC), the reaction mixture was diluted with aqueous NH_4Cl solution (saturated, 30 mL). The aqueous phase was extracted with Et_2O (2 x 30 mL) and EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude brown oil was purified by column chromatography (CH_2Cl_2/MeOH, 10:1) and preparative HPLC.



Red, amorphous solid. Yield: 17.1 mg, 40 μmol, 11 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.44 (d, ^{4}J = 1.9 Hz, 1H, ar-6-**H**), 7.95 (d, ^{3}J = 8.5 Hz, 1H, ar-4-**H**), 7.93-7.83 (m, 2H, Ph-2-**H**, Ph-6-**H**), 7.72 (dd, ^{3}J = 8.5 Hz, ^{4}J = 1.9 Hz, 1H, ar-3-**H**), 7.68-7.55 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 4.14 (dd, ^{3}J = 4.5 Hz, ^{3}J = 4.0 Hz, 1H, $C^{\alpha}\mathbf{H}C^{\beta}H(CH_3)_2$), 3.74 (d, ^{3}J = 4.0 Hz, 1H, $C^{\alpha}HN\mathbf{H}$), 2.05 (m, 1H, $C^{\alpha}HC^{\beta}\mathbf{H}(CH_3)_2$), 1.28 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.10 (d, ^{3}J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H(C\mathbf{H_3})_2$), 1.08 (d, ^{3}J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H(C\mathbf{H_3})_2$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 165.8 (ar-1-$\mathbf{C}O_2H$), 151.8 (ar-**C**-2), 148.8 (Ph-**C**-1), 136.8 (ar-**C**-3), 136.3 (ar-**C**-6), 133.8 (Ph-**C**-4), 130.0 (Ph-**C**-3, Ph-**C**-5), 127.7 (ar-**C**-1), 127.3 (ar-**C**-5), 123.8 (Ph-**C**-2, Ph-**C**-6), 116.2

(ar-**C**-4), 93.0 ($C^{\alpha}H\mathbf{C}{\equiv}Car$), 84.4 ($C^{\alpha}HC{\equiv}\mathbf{C}ar$), 56.8 ($S\mathbf{C}(CH_3)_3$), 54.8 ($\mathbf{C}^{\boldsymbol{\alpha}}HC^{\beta}H(CH_3)_2$), 34.1 ($C^{\alpha}H\mathbf{C}^{\boldsymbol{\beta}}H(CH_3)_2$), 22.8 ($SC(\mathbf{C}H_3)_3$), 19.2 ($C^{\alpha}HC^{\beta}H(\mathbf{C}H_3)_2$), 18.0 ($C^{\alpha}HC^{\beta}H(\mathbf{C}H_3)_2$). $C_{23}H_{27}N_3O_3S$ (425.55 g mol^{-1}). MS(ESI): *m/z* = 426.6 (calcd. 426.1846 $[M+H]^+$), 448.9 (calcd. 448.1665 $[M+Na]^+$). TLC: R*f* (CH_2Cl_2/MeOH/TFA, 89:10:1) = 0.40. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3205 (w, NH-VS), 2961 (s, CH-VS), 2920 (m, CH-VS), 2866 (m, CH-VS), 2359 (s, C≡C), 2341 (s, C≡C), 1698 (s, $(C{=}O)OCH_3$), 1597 (w, NH), 1577 (w, N=N), 1464 (m, C=C-VS), 1306 (w), 1220 (m), 1026 (m, S=O), 922 (m), 685 (w). $[\alpha]_{589}^{22}$ = -74.3 (*c* 0.45, $CHCl_3$). UV/*Vis*: ε = 33708 cm^{-1} M^{-1} (in CH_3CN at λ_{max} = 355 nm, c = 26.4 μM, d = 1 cm).

Methyl (5-((*S*)-3-Amino-4-methylpent-1-yn-1-yl)-2-((*E*)-phenyldiazenyl)benzoyl)-L-prolinate Hydrochloride (44). A mixture of peptidomimetic **43c** (17.1 mg, 40 μmol, 1.0 eq), L-methyl prolinate (10.3 mg, 80 μmol, 2.0 eq), HOAt (16.2 mg, 120 μmol, 3.0 eq) and HATU (30.4 mg, 80 μmol, 2.0 eq) was dissolved in a mixture of DMF (0.8 mL) and



DIPEA (0.4 mL, 0.25 mmol, 6.3 eq) and stirred for 16 h at ambient temperature. After complete conversion of the peptidomimetic (checked by LCMS), the solution was diluted in CH_2Cl_2 (7 mL) and washed with aqueous $NaHCO_3$ solution (saturated, 10 mL) and hydrochloric acid (1 M, 10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and purified by column chromatography (PE/EtOAc, 1:1). Yield: brown, amorpheous solid, 19 mg, 35 μmol, 89 %.

Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a solution of the coupling product (19 mg, 35 μmol) in MeOH (2 mL) at 0 °C. The reaction mixture was stirred 90 min at ambient temperature, until the complete starting material was converted. The solvent was evaporated under reduced pressure and azobenzamide **44** was isolated by preparative HPLC.

Amorpheous orange solid. Yield: 13.3 mg, 28.4 μmol, 81 % (71 % over two steps, referred to peptidomimetic **43c**). ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.70 (s, 3H, $C^{\alpha I}HN\mathbf{H_3}Cl$), 7.97 (s, 1H, ar-3-**H**), 7.84 (m, 1H, ar-4-**H**), 7.77 (t, ^3J = 8.1 Hz, 1H, Ph-3-**H**, Ph-5-**H**), 7.63 (s, 1H, ar-6-**H**), 7.56-7.48 (m, 6H, Ph-2-**H**, Ph-4-**H**, Ph-6-**H**), 4.59 (dd, ^3J = 8.5 Hz, ^3J = 5.2 Hz, 1H, $C^{\alpha II}\mathbf{H}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2N$), 4.27 (d br., ^3J = 5.3 Hz, 1H, $C^{\alpha I}\mathbf{H}C^{\beta}H(CH_3)_2$), 3.79

(s, 3H, $CO_2C\mathbf{H_3}$), 3.34 (m, 1H, $C^{\alpha II}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}\mathbf{H}_2N$), 3.19 (m, 1H, $C^{\alpha II}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}\mathbf{H}_2N$), 2.29 (dt, ^2J = 15.7 Hz, ^3J = 7.9 Hz, 1H, $C^{\alpha II}HC^{\beta}\mathbf{H}_2C^{\gamma}H_2C^{\delta}H_2N$), 2.22 (m, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}(CH_3)_2$), 2.05 (dq, ^2J = 12.5 Hz, ^3J = 6.2 Hz, 1H, $C^{\alpha II}HC^{\beta}\mathbf{H}_2C^{\gamma}H_2C^{\delta}H_2N$), 1.95 (dp, ^2J = 13.9 Hz, ^3J = 7.1 Hz, 1H, $C^{\alpha II}HC^{\beta}H_2C^{\gamma}\mathbf{H}_2C^{\delta}H_2N$), 1.82 (dt, ^2J = 12.9 Hz, ^3J = 6.6 Hz, 1H, $C^{\alpha II}HC^{\beta}H_2C^{\gamma}\mathbf{H}_2C^{\delta}H_2N$), 1.12 (d, ^3J = 6.3 Hz, 3H, $C^{\alpha I}HC^{\beta}H(C\mathbf{H_3})_2$), 1.08 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha I}HC^{\beta}H(C\mathbf{H_3})_2$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 172.5 (ar**C**ONC$^{\alpha II}$), 168.3 ($C^{\alpha II}H\mathbf{C}O_2CH_3$), 152.6 (Ph-**C**-1), 147.6 (ar-**C**-2), 133.6 (ar-**C**-4), 132.1 (ar-**C**-6), 131.6 (Ph-**C**-4), 129.4 (Ph-**C**-2, Ph-**C**-6), 129.4 (Ph-**C**-3, Ph-**C**-5), 125.1 (ar-**C**-3), 123.7 (ar-**C**-5), 123.4 (ar-**C**-1), 87.0 ($C^{\alpha I}H\mathbf{C}\equiv$C-ar), 85.5 ($C^{\alpha I}HC\equiv\mathbf{C}$-ar), 59.2 ($\mathbf{C^{\alpha II}}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2N$), 52.5 ($CO_2\mathbf{C}H_3$), 50.0 ($\mathbf{C^{\alpha I}}HC^{\beta}H(CH_3)_2$), 49.0 ($C^{\alpha II}HC^{\beta}H_2C^{\gamma}H_2\mathbf{C^{\delta}}H_2N$), 31.5 ($C^{\alpha I}H\mathbf{C^{\beta}}H(CH_3)_2$), 29.9 ($C^{\alpha II}H\mathbf{C^{\beta}}H_2C^{\gamma}H_2C^{\delta}H_2N$), 24.9 ($C^{\alpha II}HC^{\beta}H_2\mathbf{C^{\gamma}}H_2C^{\delta}H_2N$), 19.5 ($C^{\alpha I}HC^{\beta}H(\mathbf{C}H_3)_2$), 17.1 ($C^{\alpha I}HC^{\beta}H(\mathbf{C}H_3)_2$). $C_{25}H_{28}N_4O_3$ (432.52 g mol^{-1}), MS(ESI): *m/z* = 433.2 (calcd. 433.2234 $[M+H]^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.15. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3452 (w, -CO-NH-), 3056 (s, CH-VS), 2967 (m, CH-VS), 2879 (m, CH-VS), 2664 (s), 2369 (s, C≡C), 1749 (m, (C=O)OCH), 1676 (s, (C=O)NH), 1622 (m, NH_2), 1438 (m, C=C), 1375 (w), 1201 (s), 1179 (s), 1135 (m), 837 (s, arH). $[\alpha]_{589}^{21}$ = -52.4 (*c* 0.67, $CHCl_3$). UV/*Vis*: $\varepsilon_{(E\text{-isomer})}$ = 19005 cm^{-1} M^{-1} (in CH_3CN at λ_{max}=338 nm, c=30.6 μM, d=1 cm), $\varepsilon_{(Z\text{-isomer})}$=657 cm^{-1} M^{-1} (in CH_3CN at λ_{max}=442 nm, c=30.6 μM, d=1 cm), see also UV/*Vis* spectra EP3,4 and NMR spectra EP5,6 in the Experimental Part.

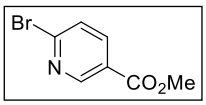
IIX-3. d) *para*-Substituted Peptidomimetics (45-46)

Halogenated benzoates methyl 4-iodobenzoate (**45a**) and ethyl 4-iodobenzoate (**45b**) were purchased at Fisher Scientific.

Methyl 6-Bromonicotinate (45c). The methylation of 6-bromonicotinate has been first reported by Wang et al. under acidic conditions [226]. However, the application of thionylchloride, as demonstrated here, has not been reported yet.

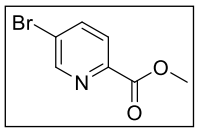
Under argon atmosphere, thionylchloride (0.3 mL, 4 mmol, 1.6 eq) was carefully added to a solution of 5-bromo nicotinic acid (500 mg, 2.48 mmol, 1.0 eq) in MeOH (40 mL) at

0 °C. The clear reaction mixture was stirred overnight at 80 °C under reflux conditions. A colorless solid precipitated when the solvent was evaporated to concentrate up the solution. The colorless, amorpheous precipitate was dissolved in EtOAc (10 mL), neutralized with a saturated, aqueous bicarbonate solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Methyl ester 45c was isolated by column chromatography (PE/EtOAc, 4:1).



Colorless, crystalline solid. Yield: 167.4 mg, 775 µmol, 34 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.16 (dd, ^4J = 2.1 Hz, ^5J = 0.9 Hz, 1H, ar-2-**H**), 8.33 (dd, ^3J = 8.2 Hz, ^4J = 2.1 Hz, 1H, ar-4-**H**), 7.58 (dd, ^3J = 8.2 Hz, ^5J = 0.9 Hz, 1H, ar-5-**H**), 3.96 (s, 3H, $CO_2C\mathbf{H_3}$). $C_7H_6BrNO_2$ (216.03 g mol^{-1}). MS(ESI): *m/z* = 217.143 (calcd. 217.9634 $[M+H]^+$).

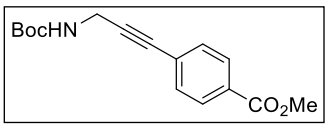
Methyl 5-Bromopicolinate (45d). The methylation of 5-bromopicolinate was carried out analog to the description of Voronkov et al. [227] with minor modifications:



Thionylchloride (0.3 mL, 4 mmol, 1.6 eq) was added dropwise to a solution of 5-bromopicolinic acid (500 mg, 2.48 mmol, 1.0 eq) in dry methanol (40 mL) and the reaction mixture was heated to 70 °C under reflux for 16 h. Afterwards, the clear solution was cooled to room temperature and the solvent was evaporated under reduced pressure. The remainder, a white solid, was dissolved in ethyl acetate (10 mL) and neutralized with aqueous bicarbonate. After seperation of the phases, the aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic phases were dried over Na_2SO_4. Filtration through a short column of silica gel (EtOAc/PE, 1:2) lead to the isolated title compound.

Colorless crystalline solid. Yield: 256 mg, 1.185 mmol, 53 % (Lit: 87 % [227]). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.80 (dd, ^4J = 2.1 Hz, ^5J = 0.9 Hz, 1H, ar-6-**H**), 8.03 (dd, ^3J = 8.4 Hz, ^5J = 0.9 Hz, 1H, ar-4-**H**), 7.98 (dd, ^3J = 8.3 Hz, ^4J = 2.1 Hz, 1H, ar-3-**H**), 4.01 (s, 3H, $CO_2C\mathbf{H_3}$). $C_7H_6BrNO_2$ (216.03). MS(ESI): *m/z* = 242.2 (calcd. 242.9 $[M+Na^+]$). TLC: R*f* (PE/EtOAc, 2:1) = 0.68.

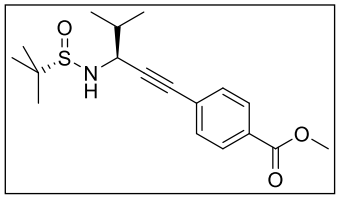
Methyl 4-(3-((*tert*-Butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate (46a). The synthesis of peptidomimetic 46a has been first described by Martin Sendzik [189] and has been reproduced with minor modifications: In one portion, a mixture of the catalyst $PdCl_2(PPh_3)_2$ (2 mg, 4.8 μmol, 0.1 mol%) and CuI (1 mg, 5.2 μmol, 0.1 mol%) was added to a thoroughly degassed solution of glycine analogous propargylamide **1** (578.2 mg, 3.726 mmol, 1.0 eq) and methyl 2-iodobenzoate **45a** (1.562 g, 5.960 mmol, 1.6 eq) in a mixture of THF/piperidine (3:1, 9.2 mL) under argon atmosphere. After 20 min at rt, precipitation of a colorless solid could be observed. The suspension was stirred at ambient temperature for 18 h. After complete conversion of propargylamide **1** (checked by TLC), the suspension was diluted with Et_2O (20 mL) and washed with an aqueous solution of $KHSO_4$ (5 %, 2 x 10 mL) and water (1 x 10 mL). The combined aqueous layers were extracted with Et_2O (2 x 20 mL) and all organic layers were combined, washed with brine (10 mL) and dried over Na_2SO_4. After evaporation oft he solvent under reduced pressure, the crude coupling product **46a** was purified by column chromatography (PE/EtOAc, 1:1).



Colorless, crystalline solid. Yield: 335.4 mg, 2.161 mmol, 58 % (Lit: Yield not determined [189]). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.87 (d, ^3J = 8.3 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.36 (d, ^3J = 8.3 Hz, 2H, ar-3-**H**, ar-5-**H**), 5.23 (s br., 1H, $C^{\alpha}H_2N$**H**), 4.10 (d, ^3J = 5.6 Hz, 2H, C^{α}**H$_2$**NHBoc), 3.82 (s, 3H, CO_2C**H$_3$**), 1.38 (s, 9H, $C(C$**H$_3$**$)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.5 (ar-1-**C**O_2CH_3), 156.3 ($C^{\alpha}HNH$**C**$O_2C(CH_3)_3$), 131.6 (ar-**C**-3, ar-**C**-5), 129.7 (ar-**C**-1-CO_2CH_3), 129.5 (ar-**C**-2, ar-**C**-6), 127.4 (ar-**C**-4), 88.5 ($C^{\alpha}H$**C**≡C-ar), 82.4 ($C^{\alpha}HC≡$**C**-ar), 80.2 ($C^{\alpha}HNCO_2$**C**$(CH_3)_3$), 52.2 (ar-1-CO_2**C**H_3), 28.4 ($C^{\alpha}HNCO_2C(C$**H$_3$**$)_3$), 28.4 (**C**$^{\alpha}$H). $C_8H_{13}NO_2$ (155.2 g mol^{-1}). TLC: R*f* (EtOAc/PE, 1:1) = 0.64.

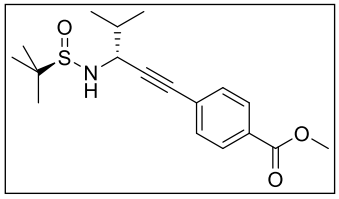
Methyl 4-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)benzoate (46b). A solution of L-valine analogous propargylamide **6b** (50.0 mg, 248 μmol, 1.0 eq) and aromatic halide **45a** (104 mg, 397 μmol, 1.6 eq) in THF (1.0 mL) and piperidine (0.3 mL) was thoroughly degassed by freeze-pump-thaw. The catalyst $PdCl_2(PPh_3)_2$ (2 mg, 4.8 μmol, 2 mol%) and CuI (1 mg, 5.3 μmol, 2 mol%) was added under argon atmosphere and the reaction mixture was stirred 10 h at ambient temperature. After complete conversion of propargylamide **6b** (checked by TLC), the reaction mixture

was diluted with aqueous NH_4Cl solution (saturated, 5 mL) and $KHSO_4$ (5 %, 10 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude coupling product **46b** was purified by column chromatography (PE/EtOAc, 1:1) and recrystallized from CH_2Cl_2.



Colorless crystalline solid. Yield: 69.0 mg, 206 μmol, 83 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.93 (d, ^3J = 8.3 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.46 (d, ^3J = 8.3 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.09 (dd, ^3J = 7.0 Hz, ^3J = 5.2 Hz, 1H, HNC$^\alpha$**H**CH$(CH_3)_2$), 3.87 (s, 3H, CO_2C**H$_3$**), 3.41 (d, ^3J = 7.0 Hz, 1H, **H**NC$^\alpha$HCH$(CH_3)_2$), 2.00 (m, 1H, HNC$^\alpha$HC**H**$(CH_3)_2$), 1.22 (s, 9H, C(C**H$_3$**)$_3$), 1.04 (d, ^3J = 6.8 Hz, 3H, HNC$^\alpha$HCH(C**H$_3$**)$_2$), 1.04 (d, ^3J = 6.8 Hz, 3H, HNC$^\alpha$HCH(C**H$_3$**)$_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (ar-1-**C**O_2CH_3), 131.8 (ar-**C**-3), 129.6 (ar-**C**-1), 129.4 (ar-**C**-2), 127.5 (ar-**C**-4), 90.9 (C$^\alpha$H**C**≡Car), 85.0 (C$^\alpha$HC≡**C**ar), 56.4 (S**C**$(CH_3)_3$), 54.4 (**C$^\alpha$**HCH$(CH_3)_2$), 52.3 (ar-1-CO_2**C**H_3), 33.9 (C$^\alpha$H**C**H$(CH_3)_2$), 22.7 (SC(**C**$H_3)_3$), 19.1 (C$^\alpha$HCH(**C**$H_3)_2$), 17.7 (C$^\alpha$HCH(**C**$H_3)_2$). $C_{18}H_{25}NO_3S$ (335.46 g mol^{-1}). MS(ESI): *m/z* = 358.1452 (calcd. 358.1447 [M+Na]$^+$). $[\alpha]_{589}^{20}$ = 13.7 (*c* 0.325, $CHCl_3$). IR(ATR): $\tilde{\nu}$[cm^{-1}] = 2958 (CH_3/CH_3), 2927-2873 (CH_3/CH_2), 1720 (CO_2Me), 1603 (N-H), 1280 (S=O), 1442/1306/1173 (ar, C=C), 770 (S-C).

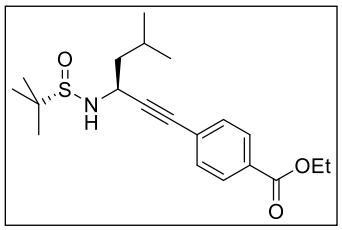
Methyl 4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)benzoate (46c). The *Sonogashira* cross coupling reaction of D-valine analogous propargylamide **6b** (98.9 mg, 492 μmol) with methyl 4-iodobenzoate (**45a**, 193 mg, 738 μmol, 1.5 eq) was performed as reported in the synthesis of **46b**.



Colorless crystalline solid. Yield: 105.7 mg, 315 μmol, 64 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.96 (d, ^3J = 8.3 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.50 (d, ^3J = 8.3 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.13 (dd, ^3J = 6.9 Hz, ^3J = 5.7 Hz, 1H, NHC$^\alpha$**H**), 3.91 (s, 3H, CO_2C**H$_3$**), 3.38 (d, ^3J = 6.9 Hz, 1H, C$^\alpha$HN**H**), 2.04 (dqq, ^3J = 6.6 Hz, ^3J = 6.7 Hz, ^3J = 6.7 Hz, 1H, C$^\alpha$HC**H**$(CH_3)_2$), 1.26 (s, 9H, C(C**H$_3$**)$_3$), 1.07 (d, ^3J = 6.8 Hz, 3H, C$^\alpha$HCH(C**H$_3$**)$_2$), 1.07 (d, ^3J = 6.7 Hz, 3H, C$^\alpha$HCH(C**H$_3$**)$_2$). ^{13}C NMR (126 MHz,

Chloroform-*d*) δ = 166.6 (ar-1-**C**O_2CH_3), 131.8 (ar-**C**-3, ar-**C**-5), 129.6 (ar-**C**-1-CO_2CH_3), 129.4 (ar-**C**-2, ar-**C**-6), 127.5 (ar-**C**-4), 90.9 ($C^{\alpha}H$**C**≡Car), 85.0 ($C^{\alpha}HC$≡**C**ar), 56.4 (S**C**$(CH_3)_3$), 54.4 (HN**C$^{\alpha}$**H), 52.3 (ar-1-CO_2**C**H_3), 33.9 ($C^{\alpha}H$**C**H$(CH_3)_2$), 22.7 (SC(**C**$H_3)_3$), 19.1 (C^{α}HCH(**C**$H_3)_2$), 17.7 (C^{α}HCH(**C**$H_3)_2$). MS(ESI): *m/z* = 358.2 (calcd. 358.15 $[M+Na]^+$). IR(ATR): $\tilde{\nu}$[cm^{-1}] = 2958 (CH_3/CH_3), 2927-2873 (CH_3/CH_2), 1720 (CO_2Me), 1603 (N-H), 1280 (S=O), 1442/1306/1173 (ar, C=C), 770 (S-C).

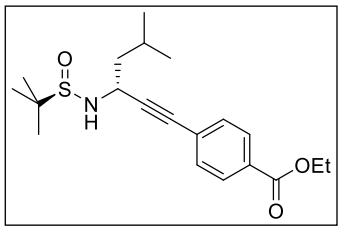
Ethyl 4-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoate (46d). The *Sonogashira* cross coupling reaction of L-leucine analogous propargylamide **6c** (14.5 mg, 67.3 µmol, 1.0 eq) with ethyl 4-iodobenzoate (**45b**, 22.9 mg, 87.5 µmol, 1.3 eq) was performed as reported in the synthesis of **46b**.



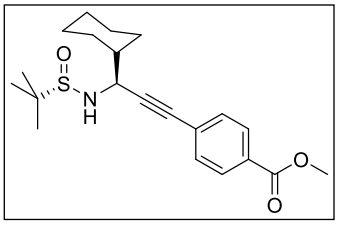
Colorless, crystalline solid. Yield: 23.0 mg, 63.3 µmol, 94 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.94 (d, ^3J = 8.4 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.47 (d, ^3J = 8.4 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.35 (q, ^3J = 7.1 Hz, 2H, CO_2C**H$_2$**CH_3), 4.27 (ddd, ^3J = 7.5 Hz, ^3J = 7.5 Hz, ^3J = 7.3 Hz, 1H, C^{α}**H**$CH_2CH(CH_3)_2$), 3.36 (d br., ^3J = 7.3 Hz, 1H, C^{α}HN**H**), 1.92 (m, 1H, $C^{\alpha}HCH_2C$**H**$(CH_3)_2$), 1.67 (m, 2H, $C^{\alpha}HC$**H$_2$**$CH(CH_3)_2$), 1.37 (t, ^3J = 7.13 Hz, 3H, CO_2CH_2C**H$_3$**), 1.22 (s, 9H, SC(C**H$_3$**$)_3$), 0.95 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HCH_2CH(C$**H$_3$**$)_2$), 0.95 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HCH_2CH(C$**H$_3$**$)_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.2 (ar-1-**C**$O_2CH_2CH_3$), 131.7 (ar-**C**-3, ar-**C**-5), 130.0 (ar-**C**-1), 129.4 (ar-**C**-2, ar-**C**-6), 127.4 (ar-**C**-4), 92.4 (C^{α}H**C**≡C-ar), 84.2 (C^{α}HC≡**C**-ar), 61.2 (CO_2**C**H_2CH_3), 56.4 (S**C**$(CH_3)_3$), 47.1 (**C$^{\alpha}$**$HCH_2CH(CH_3)_2$), 46.2 (C^{α}H**C**$H_2CH(CH_3)_2$), 25.1 ($C^{\alpha}HCH_2$**C**$H(CH_3)_2$), 22.6 (SC(**C**$H_3)_3$), 22.3 ($C^{\alpha}HCH_2CH(C$**H$_3$**$)_2$), 22.2 ($C^{\alpha}HCH_2CH(C$**H$_3$**$)_2$), 14.4 (CO_2CH_2C**H**$_3$). $C_{20}H_{29}NO_3S$ (363.52 g mol^{-1}). MS(ESI): *m/z* = 386.17499 (calcd. 386.17604 $[C_{20}H_{29}NO_3S+Na]^+$).

Ethyl 4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoate (46e). The *Sonogashira* cross coupling reaction of D-leucine analogous propargylamide **6c** (418.0 mg, 1944 µmol, 1.0 eq) with ethyl 4-iodobenzoate (**45b**, 814.9 mg, 3.110 mmol, 1.6 eq) was performed as reported in the synthesis of **46b**.

Slightly green, viscous oil. Yield: 671.3 mg, 1.847 mmol, 95 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.97 (d, ^{3}J = 8.3 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.49 (d, ^{3}J = 8.4 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.37 (q, ^{3}J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.29 (ddd, ^{3}J = 7.5 Hz, ^{3}J = 7.4 Hz, ^{3}J = 7.4 Hz, 1H, HNC$^{\alpha}$**H**), 3.39 (d, ^{3}J = 7.3 Hz, 1H, C$^{\alpha}$HN**H**), 1.92 (m, 1H, C$^{\alpha}$HCH$_2$C**H**(CH$_3$)$_2$), 1.70 (dd, ^{3}J = 7.4 Hz, ^{3}J = 7.5 Hz, 2H, C$^{\alpha}$HC**H$_2$**CH(CH$_3$)$_2$), 1.39 (t, ^{3}J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.25 (s, 9H, C(C**H$_3$**)$_3$), 0.98 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha}$HCH$_2$CH(C**H$_3$**)$_2$), 0.98 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha}$HCH$_2$CH(C**H$_3$**)$_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.2 (ar-1-**C**O$_2$CH$_2$CH$_3$), 131.7 (ar-**C**-3, ar-**C**-5), 130.0 (ar-**C**-1-CO$_2$), 129.4 (ar-**C**-2, ar-**C**-6), 127.4 (ar-**C**-4), 92.4 (C$^{\alpha}$H**C**≡C-ar), 84.2 (C$^{\alpha}$HC≡**C**-ar), 61.2 (CO$_2$**C**H$_2$CH$_3$), 56.4 (S**C**(CH$_3$)$_3$), 47.1 (**C$^{\alpha}$**HCH$_2$CH(CH$_3$)$_2$), 46.2 (C$^{\alpha}$H**C**H$_2$CH(CH$_3$)$_2$), 25.1 (C$^{\alpha}$HCH$_2$**C**H(CH$_3$)$_2$), 22.6 (SC(**C**H$_3$)$_3$), 22.3 (C$^{\alpha}$HCH$_2$CH(**C**H$_3$)$_2$), 22.2 (C$^{\alpha}$HCH$_2$CH(**C**H$_3$)$_2$), 14.4 (CO$_2$CH$_2$**C**H$_3$). $C_{20}H_{29}NO_3S$ (363.52 g mol^{-1}). MS(ESI): *m/z* = 386.17645 (calcd. 386.17604 [M+Na]$^{+}$). CHN: 62.905 % C, 7.822 % H, 3.67 % N, 7.786 % S. TLC: R*f* (EtOAc/PE, 1:1) = 0.26.



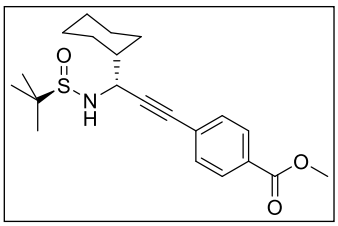
Methyl 4-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)benzoate (46f). The *Sonogashira* cross coupling reaction of L-cyclohexylglycine analogous propargylamide **6e** (99.5 mg, 412.4 µmol, 1.0 eq) with methyl 4-iodobenzoate (**45a**, 129.7 mg, 494.9 µmol, 1.2 eq) was performed as reported in the synthesis of **46b**.



Colorless, crystalline solid. Yield: 102.2 mg, 272.2 µmol, 66 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.93 (d, ^{3}J = 8.2 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.47 (d, ^{3}J = 8.1 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.06 (dd, ^{3}J = 7.5 Hz, ^{3}J = 5.8 Hz, 1H, C$^{\alpha}$**H**NH), 3.88 (s, 3H, CO$_2$C**H$_3$**), 3.36 (d, ^{3}J = 7.4 Hz, 1H, C$^{\alpha}$HN**H**), 1.93-1.82 (m, 2H, cy-**H**), 1.83-1.72 (m, 2H, cy-**H**), 1.70-1.61 (m, 2H, cy-**H**), 1.22 (s, 9H, C(C**H$_3$**)$_3$), 1.19-1.06 (m, 5H, cy-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (ar-1-**C**O$_2$), 131.8 (ar-**C**-3, ar-**C**-5), 129.6 (ar-**C**-2, ar-**C**-6), 129.4 (ar-1-**C**), 127.6 (ar-**C**-4), 91.4 (C$^{\alpha}$H**C**≡C-ar), 85.0 (C$^{\alpha}$HC≡**C**-ar), 56.5 (S**C**(CH$_3$)$_3$), 53.8 (ar-1-CO$_2$**C**H$_3$), 52.3 (**C$^{\alpha}$**Hcy), 43.5 (cy-**C**-1), 29.7 (cy-**C**-2), 28.6 (cy-**C**-6), 26.4 (cy-**C**-4), 26.0 (cy-**C**-5), 25.9 (cy-**C**-3), 22.7 (SC(**C**H$_3$)$_3$). $C_{21}H_{29}NO_3S$

(375.53 g mol^{-1}). MS(ESI): *m/z* = 398.2 (calcd. 398.18 [M+Na]$^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.69.

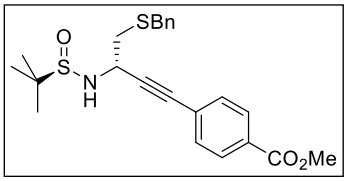
Methyl 4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)benzoate (46g). The *Sonogashira* cross coupling reaction of D-cyclohexylglycine analogous propargylamide **6e** (99.8 mg, 413.5 μmol, 1.0 eq) with methyl 4-iodobenzoate (**45a**, 129.8 mg, 537.6 μmol, 1.3 eq) was performed as reported in the synthesis of **46b**.

Colorless, crystalline solid. Yield: 114.8 mg, 306 μmol, 74 %. ^{1}H NMR (500 MHz, 
Chloroform-*d*) δ = 7.93 (d, ^3J = 8.2 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.47 (d, ^3J = 8.1 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.06 (dd, ^3J = 7.5 Hz, ^3J = 5.8 Hz, 1H, HNC$^{\alpha}$**H**), 3.88 (s, 3H, CO_2C**H**$_3$), 3.36 (d, ^3J = 7.4 Hz, 1H, N**H**C$^{\alpha}$H), 1.93-1.82 (m, 2H, cy-**H**), 1.83-1.72 (m, 2H, cy-**H**), 1.70-1.61 (m, 2H, cy-**H**), 1.22 (s, 9H, C(C**H**$_3$)$_3$), 1.19-1.06 (m, 5H, cy-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (ar-1-**C**O_2), 131.8 (ar-**C**-3, ar-**C**-5), 129.6 (ar-**C**-1-CO_2), 129.4 (ar-**C**-2, ar-**C**-6), 127.6 (ar-**C**-4), 91.4 (C$^{\alpha}$H**C**≡C-ar), 85.0 (C$^{\alpha}$HC≡**C**-ar), 56.5 (S**C**$(CH_3)_3$), 53.8 (ar-1-CO_2**C**H_3), 52.3 (HN**C$^{\alpha}$**H), 43.5 (cy-**C**-1), 29.7 (cy-**C**-2), 28.6 (cy-**C**-6), 26.4 (cy-**C**-4), 26.0 (cy-**C**-5), 25.9 (cy-**C**-3), 22.7 (SC(**C**$H_3)_3$). $C_{21}H_{29}NO_3S$ (375.53 g mol^{-1}). MS(ESI): *m/z* = 398.2 (calcd. 398.18 [M+Na]$^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.69.

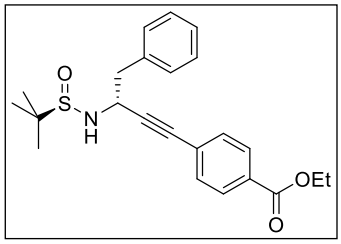
Methyl 4-((*S*)-4-(Benzylthio)-3-(((*R*)-*tert*-butylsulfinyl)amino)but-1-yn-1-yl)benzoate (46h). A mixture of D-cycstein analogous propargylamide **6j** (28.6 mg, 122 μmol, 1 eq) and aromatic halide **45a** (47.4 mg, 191 μmol, 1.6 eq) was dissolved in THF/piperidine (0.8 mL, 3:1) and the solution was thoroughly degassed viy freeze pump thaw (3 x 10^{-2} mbar). Under argon atmosphere, the catalyst $PdCl_2(PPh_3)_2$ (0.86 mg, 1.2 μmol, 1 mol%) and CuI (0.46 mg, 0.24 μmol, 2 mol%) was added in one portion and the reaction mixture was warmed up to rt. At ambient temperature, the solution was stirred for 2 h, before diluting it with saturated aqueous NH_4Cl solution (10 mL). After addition of aqueous HCl (1 M, 5 mL), the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The

solvent was evaporated under reduced pressure and the crude cross coupling product **46h** was purified by preparative HPLC.

Yellow, foul smelling, highly viscous oil. Yield: 6.0 mg, 14 mmol, 11 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.97 (d, ^{3}J = 8.4 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.50 (d, ^{3}J = 8.4 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.54-7.12 (m, 5H, Ph-**H**), 4.36 (ddd, ^{3}J = 6.4 Hz, ^{3}J = 6.1 Hz, ^{3}J = 3.1 Hz, 1H, C$^{\alpha}$**H**), 3.91 (s, 3H, $CO_2C\mathbf{H_3}$), 3.86 (d, ^{3}J = 3.1 Hz, 1H, C$^{\alpha}$HN**H**), 2.89 (dd, ^{2}J = 13.7 Hz, ^{3}J = 6.4 Hz, 1H, C$^{\alpha}$HC$^{\beta}$$\mathbf{H_2}$S), 2.83 (dd, ^{2}J = 13.7 Hz, ^{3}J = 6.1 Hz, 1H, C$^{\alpha}$HC$^{\beta}$$\mathbf{H_2}$S), 2.16 (s, 2H, SC$\mathbf{H_2}$Ph), 1.24 (s, 9H, SC(C$\mathbf{H_3}$)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (**C**O_2CH_3), 138.0 (ar-**C**-4), 131.9 (ar-**C**-3, ar-**C**-5), 130.0 (Ph-**C**-1), 129.6 (ar-**C**-2, ar-**C**-6), 129.1 (Ph-**C**-3, Ph-**C**-5), 128.8 (Ph-**C**-2, Ph-**C**-6), 127.5 (Ph-**C**-4), 127.0 (ar-**C**-1), 90.9 (C$^{\alpha}$H**C**≡C-ar), 85.2 (C$^{\alpha}$HC≡**C**-ar), 56.9 (S**C**(CH$_3$)$_3$), 52.4 (CO_2**C**H$_3$), 48.4 (**C$^{\alpha}$**H), 38.3 (C$^{\alpha}$**C$^{\beta}$**H$_2$), 37.0 (S**C**H$_2$Ph), 22.7 (SC(**C**H$_3$)$_3$). $C_{23}H_{27}NO_3S_2$ (429.59 g mol^{-1}). MS(ESI): *m/z* = 452.1 (calcd. 452.1325 [M+Na]$^{+}$). $[\alpha]_{589}^{22}$ = -23.6 (*c* 0.30, $CHCl_3$). IR(ATR): $\tilde{\nu}$[cm^{-1}] = 2920.3 (CH), 2359.9 (C-C alkyne), 1603.2 (C=C, ar).



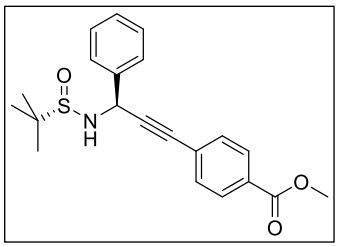
Ethyl 4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-4-phenylbut-1-yn-1-yl)benzoate (46i). Iodobenzoate **45b** (33.8 µL, 200 µmol, 1.0 eq) and piperidine (1.0 mL) was added to a stirred solution of D-phenylalanine analogous propargylamide **6m** (50 mg, 200 µmol, 1.0 eq) in THF (3.0 mL) and the mixture was degassed by the freeze pump thaw method (3x). $PdCl_2(PPh_3)_2$ (1 mg, 2.4 µmol, 1.2 mol%) and CuI (1 mg, 5.3 µmol, 2.7 mol%) was added and the reaction mixture was stirred for 14 h at rt. After 2 h, a colorless precipitate was observed. The solution was diluted with an aqueous NH_4Cl solution (saturated, 20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography (PE/EtOAc, 2:1) yielded the title compound in pure form.



Yellow, highly viscous oil. Yield: 47 mg, 118 µmol, 59 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.96 (d, ^{3}J = 8.4 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.45 (d, ^{3}J = 8.4 Hz, 2H, ar-3-**H**, ar-5-**H**), 7.36-7.29 (m, 5H, Ph-**H**), 4.50 (ddd, ^{3}J = 7.0 Hz, ^{3}J = 6.8 Hz, ^{3}J = 6.7 Hz, 1H, C$^{\alpha}$**H**), 4.37 (q, ^{3}J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$),

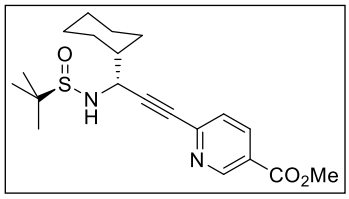
3.46 (d, ^{3}J = 7.0 Hz, 1H, C$^{\alpha}$HN**H**), 3.15 (dd, ^{2}J = 13.5 Hz, ^{3}J = 6.7 Hz, 1H, C$^{\alpha}$HC$^{\beta}$**H**$_2$Ph), 3.10 (dd, ^{2}J = 13.5 Hz, ^{3}J = 6.7 Hz, 1H, C$^{\alpha}$HC$^{\beta}$**H**$_2$Ph), 1.39 (t, ^{3}J = 7.1 Hz, 3H, CO_2CH_2C**H**$_3$), 1.18 (s, 9H, SC(C**H**$_3$)$_3$). $C_{23}H_{27}NO_3S$ (397.53 g mol^{-1}). MS(ESI) *m/z* = 420.002 (calcd. 420.1604 [M+Na]$^{+}$). TLC: R*f* (PE/EtOAc, 2:1) = 0.20.

Methyl 4-((*S*)-3-(((*S*)-*tert*-Butylsulfinylamido)-3-phenylprop-1-yn-1-yl)benzoate (46j). 4-Iodobenzoate **45a** (192 mg, 733 µmol, 1.8 eq) and DIPEA (0.8 mL) was added to a stirred solution of D-phenylalanine analogous propargylamide **6n** (95.8 mg, 407 µmol, 1.0 eq) in THF (2.4 mL) and the mixture was degassed by the freeze pump thaw method (3x). $PdCl_2(PPh_3)_2$ (1 mg, 2.4 µmol, 0.6 mol%) and CuI (1 mg, 5.3 µmol, 1.3 mol%) was added and the reaction mixture was stirred overnight at rt. The solution was diluted with an aqueous NH_4Cl solution (saturated, 20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$. After evaporation of the solvent and purification by column chromatography (PE/EtOAc, 2:1) and recrystallization from Et_2O, peptidomimetic **46j** was achieved in pure form.



Colourless crystalline solid. Yield: 83 mg, 225 µmol, 54 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.98 (d, ^{3}J = 8.4 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.56 (d, ^{3}J = 6.9 Hz, 1H, Ph-2-**H**, Ph-6-**H**), 7.53 (d, ^{3}J = 8.4 Hz, 2H, ar-3-**H**, ar-5-**H**), 7.41 (t, ^{3}J = 7.3 Hz, 2H, Ph-3-**H**, Ph-5-**H**), 7.37 (m, 1H, Ph-4-**H**), 5.47 (m, 1H, C$^{\alpha}$**H**Ph), 3.92 (s, 3H, CO_2C**H**$_3$), 1.27 (s, 9H, SC(C**H**$_3$)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (**C**O_2CH_3), 138.3 (Ph-**C**-1), 131.9 (ar-**C**-3, ar-**C**-5), 130.1 (ar-**C**-1), 129.6 (ar-**C**-2, ar-**C**-6), 129.0 (Ph-**C**-3, Ph-**C**-5), 128.8 (Ph-**C**-1), 127.8 (Ph-**C**-2, Ph-**C**-6), 127.0 (Ph-**C**-4), 90.2 (C$^{\alpha}$H**C**≡Car), 86.3 (C$^{\alpha}$HC≡**C**ar), 57.3 (S**C**$(CH_3)_3$), 52.4 (CO_2**C**H_3), 52.3 (**C**$^{\alpha}$), 22.7 (SC(**C**$H_3)_3$). $C_{21}H_{23}NO_3S$ (369.48 g mol^{-1}). MS(ESI): *m/z* = 392.975 (calcd. 392.129 [M+Na]$^{+}$). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 2977 (CH), 2948 (CH), 2920 (CH), 2328 (C≡C), 2353 (C-C), 1720 (C=O), 1543 (ar, C=C), 1280 (C-N). TLC: R*f* (EtOAc/PE, 1:2) = 0.44. $[\alpha]_{589}^{19}$ = 10.4 (*c* 0.72, $CHCl_3$). X-ray crystal structure in Chapter IIX-3. n.

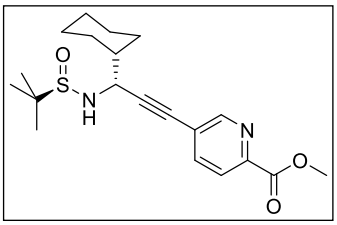
Methyl 6-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)nicotinate (46k). The catalysts $PdCl_2(PPh_3)_2$ (2.9 mg, 4.1 µmol, 1 mol%) and CuI (1.6 mg, 8.3 µmol, 2 mol%) were added under argon atmosphere to a thoroughly degassed solution of D-cyclohexylglycine analogous propargylamide **6e** (100.0 mg, 414 µmol, 1.0 eq) and aromatic bromide **45c** (107.4 mg, 497.2 µmol, 1.2 eq) in THF/piperidine (1.0 mL, 3:1). The reaction mixture was warmed up to rt and stirred overnight at ambient temperature. A colorless precipitate formed during the procedure of the reaction. After complete conversion of propargylamde **6e** (checked by TLC), the mixture was diluted with an aqueous NH_4Cl solution (saturated, 10 mL) and neutralized with aqueous HCl (1 M, 6 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude cross coupling product **46k** was purified by column chromatography (PE/EtOAc, 2:1).

Colorless, amorphous solid. Yield: 3.4 mg, 9.0 µmol, 2 %. ^{1}H NMR (300 MHz, 

Chloroform-*d*) δ = 9.16 (dd, ^4J = 2.2 Hz, ^5J = 0.8 Hz, 1H, ar-2-**H**), 8.33 (dd, ^3J = 8.2 Hz, ^4J = 2.1 Hz, 1H, ar-4-**H**), 7.58 (dd, ^3J = 8.2 Hz, ^5J = 0.9 Hz, 1H, ar-5-**H**), 4.07 (d, ^3J = 5.9 Hz, 1H, C$^{\alpha}$**H**), 3.96 (s, 3H, $CO_2C\mathbf{H_3}$), 3.53 (s br., 1H, C$^{\alpha}$HN**H**), 1.92 (d br., ^2J = 11.4 Hz, 2H, cy-2-**H**, cy-6-**H**), 1.79 (d br., ^2J = 10.8 Hz, 2H, cy-2-**H**, cy-6-**H**), 1.77-1.63 (m, 3H, cy-1-**H**, cy-4-**H**, cy-4-**H**), 1.28 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.26-1.04 (m, 4H, cy-3-**H**, cy-3-**H**, cy-5-**H**, cy-5-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 164.8 (ar-3-$\mathbf{C}O_2CH_3$), 149.9 (ar-**C**-2), 145.3 (ar-**C**-6), 138.6 (ar-**C**-4), 127.5 (ar-**C**-5), 125.6 (ar-**C**-3), 93.8 (C$^{\alpha}$H**C**≡Car), 83.5 (C$^{\alpha}$HC≡**C**ar), 57.3 ($S\mathbf{C}(CH_3)_3$), 54.6 (**C$^{\alpha}$**Hcy), 52.9 ($CO_2\mathbf{C}H_3$), 43.5 (cy-**C**-1), 29.6 (cy-**C**-2), 29.0 (cy-**C**-6), 27.1 (cy-**C**-4), 26.3 (cy-**C**-5), 25.9 (cy-**C**-3), 22.8 ($SC(\mathbf{C}H_3)_3$). $C_{20}H_{28}N_2O_3S$ (376.51 g mol^{-1}). MS(EI): *m/z* = 377.180 (calcd. 377.5225 $[M+H]^+$), 399.155 (calcd. 399.5042 $[M+Na]^+$). $[\alpha]_{589}^{21}$ = -13.3 (*c* 0.17, $CHCl_3$). TLC: R*f* (PE/EtOAc, 2:1) = 0.67.

Methyl 5-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)picolinate (46l). The catalysts $PdCl_2(PPh_3)_2$ (2.9 mg, 4.1 µmol, 1 mol%) and CuI (1.6 mg, 8.3 µmol, 2 mol%) were added under argon atmosphere to a thoroughly degassed solution of D-cyclohexylglycine analogous propargylamide **6e** (98.7 mg, 419.5 µmol,

1.0 eq) and aromatic bromide **45d** (108 mg, 503 µmol, 1.2 eq) in THF/piperidine (1.0 mL, 3:1). The reaction mixture was warmed up to rt and stirred over 16 h at 60 °C under reflux conditions. A colorless precipitate formed during the procedure of the reaction. After complete conversion of propargylamde **6e** (checked by TLC), the mixture was diluted with an aqueous NH_4Cl solution (saturated, 10 mL) and neutralized with aqueous HCl (1 M, 6 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude cross coupling product **46l** was purified by column chromatography (PE/EtOAc, 2:1).



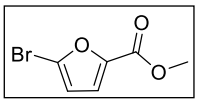
Pale green, highly viscous oil. Yield: 64.6 mg, 172 µmol, 41 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.71 (dd, ^4J = 2.1 Hz, ^5J = 0.9 Hz, 1H, py-6-**H**), 8.04 (dd, ^3J = 8.1 Hz, ^5J = 0.9 Hz, 1H, py-3-**H**), 7.86 (dd, ^3J = 8.1 Hz, ^4J = 2.1 Hz, 1H, py-4-**H**), 4.07 (dd, ^3J = 7.9 Hz, ^3J = 5.9 Hz, 1H, HNC$^{\alpha}$**H**), 3.98 (s, 3H, CO_2C**H**$_3$), 3.37 (d, ^3J = 7.9 Hz, 1H, N**H**C$^{\alpha}$H), 1.94-1.83 (m, 3H, cy-**H**), 1.81-1.72 (m, 3H, cy-**H**), 1.71-1.62 (m, 2H, cy-**H**), 1.22 (s, 9H, SC(C**H**$_3$)$_3$), 1.18-1.07 (m, 3H, cy-**H**). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 165.3 (py-2-**C**O_2CH_3), 152.1 (py-**C**-6), 146.3 (py-**C**-2), 139.9 (py-**C**-4), 124.5 (py-**C**-3), 123.5 (py-**C**-5), 95.1 (C$^{\alpha}$H**C**≡Car), 82.0 (C$^{\alpha}$HC≡**C**ar), 56.7 (S**C**$(CH_3)_3$), 54.0 (py-2-CO_2**C**H_3), 53.1 (**C$^{\alpha}$**), 43.5 (cy-**C**-1), 29.6 (cy-**C**-2), 28.8 (cy-**C**-6), 26.3 (cy-**C**-4), 26.0 (cy-**C**-5), 25.9 (cy-**C**-3), 22.7 (SC(**C**H_3)$_3$). $C_{20}H_{28}N_2O_3S$ (376.51 g mol^{-1}). MS(ESI): *m/z* = 399.1 (calcd. 399.17 $[C_{20}H_{28}N_2O_3S+Na]^+$). IR(ATR): $\tilde{\nu}$[cm^{-1}] = 2927 (CH_2), 2854 (CH_2, NH), 1724 (CO_2Me), 1448 (ar, C=C), 1302 (ar, C=C). TLC: R*f* (EtOAc/PE, 1:2) = 0.05.

IIX-3. e) Heteroaromatic Peptidomimetics (47-50)

Methyl 5-Bromofuran-2-carboxylate (47a). A similar bromination procedure of methyl furan-2-carboxylate has been described by Yu-Sheng and coworkers using $AlCl_3$ instead of $KClO_4$ as catalyst, giving 86 % yield of **47a** [228]. Bromine (5.76 mL, 18.0 g, 12.3 mmol, 1.2 eq) was added in one portion to a solution of methyl furan-2-carboxylate (10.00 mL, 93.57 mmol, 1.0 eq) in chloroform (100 mL). To the brown solution, solid $KClO_4$ (2.59 g, 18.7 mmol, 0.2 eq) was added in one portion and the mixture was heated under reflux for 36 h. Afterwards, the mixture was cooled to rt, diluted with a $KHSO_4$

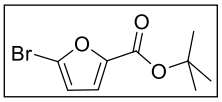
solution (5 %, 20 mL) and solid Na_2SO_3 was added under vigorous stirring until the brown solution turned colorless. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product, a brown oil, contained a mixture of brominated **47a** and unbrominated species (76 % conversion, determined by ^{1}H NMR spectroscopy), was filtered through silica gel (EtOAc/PE, 1:4) and sublimated under reduced pressure.

Colorless crystals. Yield: 8.875 g, 43.29 mmol, 46 %. ^{1}H NMR (600 MHz, Chloroform-*d*)



δ = 7.15 (d, ^3J = 3.5 Hz, 1H, furan-4-**H**), 6.52 (d, ^3J = 3.5 Hz, 1H, furan-3-**H**), 3.90 (s, 3H, $CO_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 157.4 (furan-2-**C**O_2CH_3), 145.8 (furan-**C**-2), 126.9 (furan-**C**-4), 119.7 (furan-**C**-3), 113.6 (furan-**C**-5), 51.6 (furan-2-CO_2**C**H_3). $C_6H_5BrO_3$ (205.01 g mol^{-1}). TLC: R*f* (PE/EtOAc, 1:1) = 0.75.

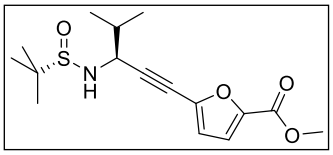
***tert*-Butyl 5-Bromofuran-2-carboxylate (47b).** Transesterification of 5-bromo fuoroate



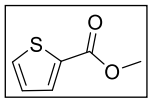
47b has been reported before using Boc_2O instead of the herein described *Steglich* esterification [229]. Solid DCC (9.94 g, 48.4 mmol, 1.3 eq) was added at 0 °C to a solution of 5-bromofuran-2-carboxylic acid (6.944 g, 36.36 mmol, 1.0 eq) in dry CH_2Cl_2 (60 mL). After 5 min, a solution of *tert*-butanol (4.043 g, 54.54 mmol, 1.5 eq) in dry CH_2Cl_2 (20 mL) was added together with DMAP (1.11 g, 9.09 mmol, 0.25 eq). The reaction mixture was stirred overnight at ambient temperature. The solution had now turned orange and was diluted with H_2O (36 ml), filtered and the phases were separated. The organic layer was dried over Na_2SO_4, filtered again and the solvent was evaporated. The crude brown oil was digerated with PE. The developing white precipitate was centrifuged (5000 rpm, 6 min), filtered off and *tert*-Butyl ester **47b** was isolated by column chromatography (gradient PE, PE/EtOAc 4:1, PE/EtOAc 2:1) of the filtrate.

Colorless fluid. Yield: 4.460 g, 18.05 mmol, 50 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.01 (d, ^3J = 3.4 Hz, 1H, furan-3-**H**), 6.41 (d, ^3J = 3.4 Hz, 1H, furan-4-**H**), 1.56 (s, 9H, $CO_2C(C\mathbf{H_3})_3$). $C_9H_{11}BrO_3$ (247.09 g mol^{-1}). MS(ESI): *m/z* = 247.048 (calcd. 246.9964 $[M+H]^+$). 248.996 (calcd. 248.9944 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.95.

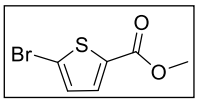
Methyl 5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)furan-2-carboxylate (49a). A solution of L-valine analogous propargylamide **6b** (520.1 mg, 2.587 mmol, 1.0 eq) and methyl 5-bromofuran-2-carboxylate (**47a**, 849 mg, 4.14 mmol, 1.6 eq) in a mixture of THF/piperidine (2.7 mL, 3:1) was thoroughly degassed by the freeze-pump-thaw method. While still frozen, the solid catalyst $PdCl_2(PPh_3)_2$ (1 mol%) and CuI (2 mol%) was added in one portion and the mixture was allowed to warm up to rt and stirred overnight at ambient temperature. A colorless precipitate formed in the course of the reaction. The reaction mixture was diluted with a mixture of Et_2O and aqueous NH_4Cl (3:2, 25 mL), neutralized with aqueous $KHSO_4$ solution (5 %, 3-5 mL, until pH 7). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product of **49a** was isolated by column chromatography (PE/EtOAc, 1:1) and purified by recrystallisation from Et_2O.

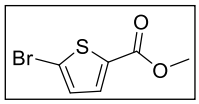


Colorless crystals. Yield: 530.5 mg, 1.63 mmol, 63 %. dr ≥ 99 % (determined via integration of ^{1}H NMR signals of C$^\alpha$**H**, 4.09 ppm), ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.10 (d, ^3J = 3.6 Hz, 1H, ar-3-**H**), 6.61 (d, ^3J = 3.6 Hz, 1H, ar-4-**H**), 4.09 (ddd, ^3J = 6.8 Hz, ^3J = 5.4 Hz, ^4J = 1.0 Hz, 1H, C$^\alpha$**H**CH(CH$_3$)$_2$), 3.86 (s, 3H, CO$_2$C**H$_3$**), 3.44 (d, ^3J = 7.0 Hz, 1H, C$^\alpha$HN**H**), 2.00 (m, 1H, C$^\alpha$HC**H**(CH$_3$)$_2$), 1.21 (s, 9H, SC(C**H$_3$**)$_3$), 1.02 (d, ^3J = 6.8 Hz, 3H, C$^\alpha$HCH(C**H$_3$**)$_2$), 1.01 (d, ^3J = 6.7 Hz, 3H, C$^\alpha$HCH(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 158.5 (**C**O$_2$(CH$_3$)), 144.3 (ar-**C**-2), 139.8 (ar-**C**-5), 118.8 (ar-**C**-3), 117.0 (ar-**C**-4), 94.1 (C$^\alpha$H**C**≡Car), 75.2 (C$^\alpha$HC≡**C**ar), 56.6 (S**C**(CH$_3$)$_3$), 54.3 (**C$^\alpha$**HCH(CH$_3$)$_2$), 52.2 (CO$_2$**C**H$_3$), 33.8 (C$^\alpha$H**C**H(CH$_3$)$_2$), 22.7 (SC(**C**H$_3$)$_3$), 19.0 (C$^\alpha$HCH(**C**H$_3$)$_2$), 17.8 (C$^\alpha$HCH(**C**H$_3$)$_2$). $C_{16}H_{23}NO_4S$ (325.42 g mol^{-1}). LCMS(ESI): t*r* = 9.5 min, *m/z* = 326.14290 (calcd. 326.14206 [M+H]$^+$), 651.2888 (calcd. 651.2768 [2M+H]$^+$). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 3230 (w, NH), 2958, 2930, 2870 (m, w, w, CH), 1723 (s, CO$_2$CH$_3$), 1581 (w, NH), 1505 (s), 1464 (m), 1432 (w), 1385 (w), 1363 (m), 1299 (s), 1239 (w), 1211 (s), 1192 (w), 1141(s), 1062 (s, S=O), 1017 (w), 989 (w), 926 (w), 808 (m), 761(s). TLC: R*f* (PE/EtOAc, 1:1) = 0.29. $[\alpha]_{589}^{23}$ = 1.0 (*c* 0.63, CHCl$_3$). X-ray crystal structure in Chapter IIX-3. n.

Methyl 5-Bromothiophene-2-carboxylate (48a). Methyl Thiophene-2-carboxylate. The methylation of thiophene carboxylate was performed as described by Cardoso et al.  [230]. Thionylchloride (0.6 mL, 8.3 mmol, 1.1 eq) was added dropwise to a cooled solution of thiophene 2-carboxylic acid (1.00 g, 7.034 mmol, 1 eq) in dry methanol (15 mL). The clear solution was heated under reflux for 36 h. After cooling down to rt, the solvent was evaporated. The crude product was diluted with water and an aqueous solution of NaOH (2 M) was added until pH 9-10 before extraction with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated to yield methyl thiophene-2-carboxylate in pure form.

Colorless, thin liquid. Yield: 1.027 g, 7.22 mmol, 93 % (Lit: 98 % [230]). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.80 (dt, ^3J = 3.8 Hz, ^4J = 0.9 Hz, 1H, thiophene-3-**H**), 7.55 (dt, ^3J = 5.0 Hz, ^4J = 1.0 Hz, 1H, thiophene-5-**H**), 7.10 (dd, ^3J = 4.8 Hz, ^3J = 3.7 Hz, 1H, thiophene-4-**H**), 3.89 (s, 3H, thiophene-2-$CO_2C\mathbf{H}_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 162.9 (thiophene-2-$\mathbf{C}O_2CH_3$), 133.7 (thiophene-**C**-2), 133.6 (thiophene-**C**-3), 132.5 (thiophene-**C**-4), 127.9 (thiophene-**C**-5), 52.3 ($CO_2\mathbf{C}H_3$). $C_6H_6O_2S$ (142.17 g mol^{-1}). TLC: R*f* (EtOAc/PE, 1:1) = 0.89.

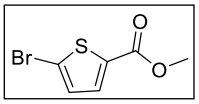
Methyl 5-Bromothiophene-2-carboxylate (48a). Alternative 1: Esterification using the  Mukaiyama reagent was performed as described by Irina Novosjolova [231]. Bromothiophene-2-carboxylic acid (**48b**, 1.61 g, 7.8 mmol, 1 eq) was dissolved in a mixture of CH_2Cl_2/THF (30 mL, 1:2). 2-Chloro-1-methylpyridin-1-iumiodide (3.98 g, 15.6 mmol, 2 eq) was added in one portion and the reaction mixture was stirred at rt. After 2 h, MeOH (20 mL) was added and the mixture was stirred for another 2 h at rt. The mixture was diluted with a saturated NH_4Cl solution (30 mL), the phases were separated and the aqueous layer was extracted with Et_2O (6 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/PE, 1:1). Yield: 649 mg, 2.93 mmol, 38 %.

Alternative 2: The methylation of **48b** using thionylchloride was performed similarly to the description of [232]. Thionylchloride (0.565 mL, 7.804 mmol, 1 eq) was added dropwise  to a solution of 5-bromothiophene-2-carboxylate (1.616 g, 7.804 mmol, 1 eq) in dry methanol (20 mL) and the reaction mixture was heated to 70 °C. The procedure of the reaction was surveyed by TLC. After 14 h the yellow solution

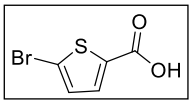
was cooled to room temperature. Aqueous NH_4Cl solution (sat, 10 mL) was added and the methanol was evaporated under reduced pressure. The aqueous solution was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4. The crude product was dissolved in warm EtOAc and precipitated with PE at 4 °C. After centrifugation, the remaining clear solvent was decanted and the purified ester **48a** was isolated in pure form. Yield: 607 mg, 2.7 mmol, 35 % (2 steps, referred to thiophene-2-carboxylic acid).

Alternative: Bromine (0.74 mL, 14.4 mmol, 2.0 eq) was added dropwise to a solution of methyl thiophene-2-carboxylate (1.027 g, 14.44 mmol, 1.0 eq) in chloroform (10 mL). To the brown solution, solid $KClO_4$ (300 mg, 2.17 mmol, 0.3 eq) was added in one portion and the mixture was heated under reflux for another 36 h. Afterwards, the mixture was cooled to rt, diluted with a $KHSO_4$ solution (5 %, 20 mL) and solid Na_2SO_3 was added under vigorous stirring until the brown solution turned colorless. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product, a brown oil, contained a mixture of brominated and unbrominated species (76 % conversion, determined by ^{1}H NMR spectroscopy). was filtered through silica gel (EtOAc/PE, 1:4) and precipitated by addition of a big portion of PE at 0 °C. The colorless solid was filtered of, washed with a few milliliters of ice cold PE and dried under vacuum. Yield: 1.017 g, 4.601 mmol, 64 %.

Colorless, crystalline solid. Yield 649 mg, 2.93 mmol, 38 %. ^{1}H NMR (300 MHz, Methanol-d_4) δ = 7.59 (d, ^3J = 4.0 Hz, 1H, thiophene-4-**H**), 7.20 (d, ^3J = 4.0 Hz, 1H, thiophene-3-**H**), 3.86 (s, 3H, thiophene-5-$CO_2C\mathbf{H_3}$). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.65 (d, ^3J = 4.0 Hz, 1H, thiophene-4-**H**), 7.37 (d, ^3J = 4.1 Hz, 1H, thiophene-3-**H**), 3.81 (s, 3H, $CO_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 161.7 (thiophene-5-$\mathbf{C}O_2CH_3$), 134.8 (thiophene-**C**-5), 133.8 (thiophene-**C**-4), 131.0 (thiophene-**C**-3), 120.4 (thiophene-**C**-2), 52.5 ($CO_2\mathbf{C}H_3$). $C_6H_5BrO_2S$ (221.07 g mol^{-1}). MS(ESI): *m/z* = 242.2 (calcd. 242.9 $[M+Na]^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.83, R*f* (EtOAc/PE, 1:2) = 0.69, R*f* (EtOAc/PE, 1:4) = 0.50.



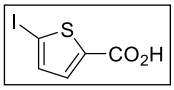
5-Bromothiophene-2-carboxylic Acid (48b). A similar bromination procedure of thiophene 2-carboxylic acid has been described by Sun and coworkers using bromine in glacial acetic acid [233]. A mixture of thiophene 2-carboxylic acid (1.00 g, 7.034 mmol, 1 eq) and *N*-bromosuccinimide (2.003 g, 11.25 mmol, 1.6 eq) was dissolved in DMF



(50 mL) and heated to 75 °C. After 12 h, the solvent was evaporated under reduced pressure. The crude product was diluted with Et_2O (30 mL) and washed with an aqueous solution of NaOH (1 M, 15 mL) and Na_2SO_3 (sat, 10 mL). The combined aqueous phases were acidified with HCl (10 M, pH = 1) and extracted with Et_2O (3 x 30 mL). Drying of the organic layers over Na_2SO_4 and evaporation of the solvent yielded 5-bromothiophene-2-carboxylate in pure form.

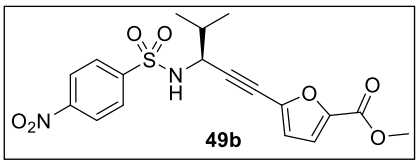
Colorless crystalline solid. Yield: 508 mg, 2.45 mmol, 35 %. ^{1}H NMR (300 MHz, Methanol-d_4) δ = 7.15 (d, ^3J = 4.0 Hz, 1H, thiophene-4-**H**), 7.52 (d, ^3J = 4.1 Hz, 1H, thiophene-3-**H**). $C_5H_3BrO_2S$ (207.04 g mol^{-1}).

5-Iodothiophene-2-carboxylic Acid (48c). Iodochloride (1 M in CH_2Cl_2, 3.9 mL, 1.0 eq) was added dropwise to a solution of thiophene-2-carboxylate (500 mg, 3.90 mmol, 1.0 eq) in glacial acetic acid (15 mL) at rt over a period of 10 min. The reaction mixture was heated for 3 h to 80 °C under reflux conditions. After cooling down to rt, the volatile parts of the mixture were evaporated under reduced pressure. The crude pale brown solid was washed with CH_3CN (3 x 3 mL) and purified by column chromatography (CH_2Cl_2/MeOH, 98:2).



Colorless solid. Yield: 67.8 mg, 266 μmol, 7 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 9.94 (s, 1H, CO_2**H**), 7.52 (d, ^3J = 3.9 Hz, 1H, thiophene-3-**H**), 7.30 (d, ^3J = 3.9 Hz, 1H, thiophene-4-**H**). $C_5H_3IO_2S$ (254.04 g mol^{-1}). LCMS(ESI): t_r = 7.8 min, *m/z* = 255.129 (calcd. 254.8971 $[M+H]^+$).

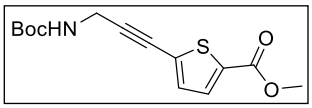
Methyl (*S*)-5-(4-Methyl-3-((4-nitrophenyl)sulfonamido)pent-1-yn-1-yl)furan-2-carboxylate (49b). To a suspension of hydrochloride salt **56a** (37.4 mg, 145 μmol) in THF (3 mL), 4-nitrobenzyle sulfuric chloride (47.4 mg, 217 μmol, 1.5 eq) and Triethylamine



(0.2 mL, 1.56 mmol, 10 eq) was added. The suspension immediately became a clear solution, which was stirred for 21 h at ambient temperature. After complete

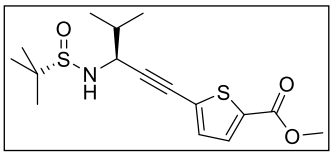
conversion (checked by LCMS), an aqueous solution of NH_4Cl (saturated, 3.5 mL) and HCl (aqueous, 1 M, 2 mL) was added to adjust the pH value to 6-7. The resulting solution was extracted with Et_2O (4 x 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography to yield the desired peptidomimetic **49b** in form of a yellow oil (53.4 mg, 131 μmol, 91 %). TLC: R*f* (PE/EtOAc, 1:1) = 0.55. Compound **49b** was directly converted to **53b** without further characterization.

Methyl 5-(3-((*tert*-Butoxycarbonyl)amino)prop-1-yn-1-yl)thiophene-2-carboxylate (50a). The catalyst $PdCl_2(PPh_3)_2$ (3.2 mg, 4.6 μmol, 1 mol%) and CuI (1.8 mg, 9.1 μmol, 2 mol%) was added under argon atmosphere to a thoroughly degassed solution of glycine analogous propargylamide **1** (70.7 mg, 455 μmol, 1.0 eq) and methyl 5-bromo-thiophencarboxylate (**48a**, 100.7 mg, 455 μmol, 1.0 eq) in a mixture of THF/piperidine (1.6 mL, 3:1) and the reaction mixture was stirred overnight at ambient temperature. Formation of a colorless precipitate indicated the reaction procedure. The reaction mixture was diluted with an aqueous solution of NH_4Cl (saturated, 15 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **50a** was purified by column chromatography (PE/EtOAc, 2:1).



Colorless, amorphous solid. Yield: 86.5 mg, 293 μmol, 64 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.63 (d, ^3J = 3.9 Hz, 1H, thiophene-3-**H**), 7.12 (d, ^3J = 3.9 Hz, 1H, thiophene-4-**H**), 4.78 (s br., 1H, N**H**C$^{\alpha}$H$_2$), 4.18 (d, ^3J = 5.7 Hz, 2H, C$^{\alpha}$**H$_2$**C≡C-thiophene), 3.88 (s, 3H, thiophene-2-CO$_2$C**H$_3$**), 1.47 (s, 9H, CO$_2$C(C**H$_3$**)$_3$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 162.1 (thiophene-2-**C**O$_2$CH$_3$), 134.0 (thiophene-**C**-2), 133.2 (thiophene-**C**-3), 132.6 (thiophene-**C**-4), 129.5 (thiophene-**C**-5), 92.3 (C$^{\alpha}$H$_2$**C**≡C-thiophene), 80.4 (C$^{\alpha}$H$_2$C≡**C**-thiophene), 76.0 (CO$_2$**C**(CH$_3$)$_3$), 52.5 (thiophene-2-CO$_2$**C**H$_3$), 41.8 (**C$^{\alpha}$**H$_2$C≡C-thiophene), 28.5 (CO$_2$C(**C**H$_3$)$_3$). $C_{14}H_{17}NO_4S$ (295.35 g mol^{-1}). MS(ESI): *m/z* = 296.353 (calcd. 296.0951 [M+H]$^+$), 318.366 (calcd. 318.3422 [M+Na]$^+$). TLC: R*f* (EtOAc/PE, 1:2) = 0.11.

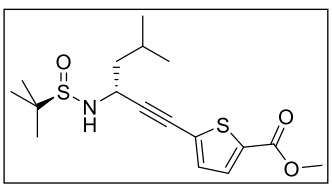
Methyl 5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)thiophene-2-carboxylate (50b). The catalyst $PdCl_2(PPh_3)_2$ (1 mg, 4.6 μmol, 1 mol%) and CuI (1.8 mg, 9.1 μmol, 2 mol%) was added under argon atmosphere to a thoroughly degassed solution of L-valine analogous propargylamide **6b** (73.8 mg, 366.7 μmol, 1.0 eq) and



methyl 5-bromo thiophencarboxylate (**48a**, 113.5 mg, 513.4 μmol, 1.4 eq) in a mixture of THF/piperidine (1.0 mL, 3:1) and the reaction mixture was stirred overnight at ambient temperature. Formation of a colorless precipitate indicated the reaction procedure. The reaction mixture was diluted with an aqueous solution of NH_4Cl (saturated, 15 mL) and $KHSO_4$ (5 %, 10 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Crude product **50b** was purified by column chromatography (PE/EtOAc, 2:1).

Colorless, crystalline solid. Yield: 26.2 mg, 77 μmol, 21 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.62 (d, ^3J = 4.0 Hz, 1H, thiophene-3-**H**), 7.13 (d, ^3J = 4.0 Hz, 1H, thiophene-4-**H**), 4.12 (dd, ^3J = 6.8 Hz, ^3J = 5.3 Hz, 1H, C^{α}**H**), 3.86 (s, 3H, CO_2C**H₃**), 3.42 (d, ^3J = 6.9 Hz, 1H, C^{α}N**H**), 2.02 (m, 1H, $C^{\alpha}HC$**H**$(CH_3)_2$), 1.24 (s, 9H, $SC(C$**H₃**$)_3$), 1.05 (d, ^3J = 6.2 Hz, 3H, $C^{\alpha}HCH(C$**H₃**$)_2$), 1.03 (d, ^3J = 6.2 Hz, 3H, $C^{\alpha}HCH(C$**H₃**$)_2$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 162.0 (**C**O_2CH_3), 133.9 (thiophene-**C**-5), 133.2 (thiophene-**C**-4), 132.6 (thiophene-**C**-2), 129.4 (thiophene-**C**-3), 94.5 ($C^{\alpha}H$**C**≡C-ar), 78.4 ($C^{\alpha}HC$≡**C**-ar), 56.6 (S**C**$(CH_3)_3$), 54.5 (CO_2**C**H_3), 52.4 (**C$^{\alpha}$**H), 34.0 ($C^{\alpha}H$**C$^{\beta}$**$H(CH_3)_2$), 22.8 ($SC($**C**$H_3)_3$), 19.1 ($C^{\alpha}HC^{\beta}H($**C**$H_3)_2$), 17.8 ($C^{\alpha}HC^{\beta}H($**C**$H_3)_2$). $C_{16}H_{23}NO_3S_2$ (341.48 g mol^{-1}). $[\alpha]_{589}^{20}$ = +27.07 (*c* 4.46, $CHCl_3$). X-ray crystal structure in Chapter IIX-3. n.

Methyl 5-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)thiophene-2-carboxylate (50c). A solution of D-leucine analogous propargylamide **6c** (38 mg, 180 μmol, 1.0 eq) and thiophene derivative **48a** (58 mg, 210 μmol, 1.2 eq) in a mixture of THF (12 mL) and piperidine (4 mL) was thoroughpy degassed. The catalyst $PdCl_2(PPh_3)_2$ (6 mg, 13 μmol) and CuI (4 mg, 26 μmol) was added under argon atmosphere and the reaction mixture was stirred for 5 h at ambient temperature. After



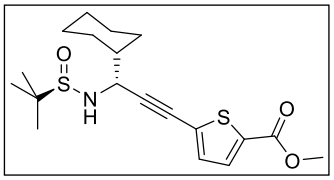
complete conversion of the propargylamide (checked by TLC), the reaction mixture was diluted with an aqueous NH_4Cl solution (halfsaturated, 8 mL). The mixture was extracted with Et_2O (4 x 10 mL) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, crude product **50c** was purified by column chromatography (PE/EtOAc, 1:1).

Pale yellow, highly viscous oil. Yield: 28 mg, 79 μmol, 44 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7 .62 (d, ^3J = 3.9 Hz, 1H, thiophene-3-**H**), 7.13 (d, ^3J = 3.9 Hz, 1H, thiophene-4-**H**), 4.29 (ddd, ^3J = 7.5 Hz, ^3J = 7.3 Hz, ^3J = 7.3 Hz, 1H, C^{α}**H**), 3.87 (s, 3H, CO_2C**H**$_3$), 3.40 (d, ^3J = 7.3 Hz, 1H, $C^{\alpha}HN$**H**), 1.88 (m, 1H, $C^{\alpha}HC^{\beta}H_2C$**H**$(CH_3)_2$), 1.69 (t, ^3J = 7.3 Hz, 2H, $C^{\alpha}HC^{\beta}$**H**$_2CH(CH_3)_2$), 1.24 (s, 9H, $SC(CH_3)_3$), 0.96 (d, ^3J = 6.6 Hz, 6H, $C^{\alpha}HC^{\beta}H_2CH(CH_3)_2$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 162.1 (thiophene-2-**C**O_2CH_3), 133.9 (thiophene-**C**-5), 133.2 (thiophene-**C**-4), 132.7 (thiophene-**C**-2), 129.4 (thiophene-**C**-3), 96.0 ($C^{\alpha}H$**C**≡C-thiophene), 77.6 ($C^{\alpha}HC$≡**C**-thiophene), 56.5 (S**C**$(CH_3)_3$), 52.4 (CO_2**C**H_3), 47.2 (**C**$^{\alpha}HC^{\beta}H_2CH(CH_3)_2$), 46.1 ($C^{\alpha}H$**C**$^{\beta}H_2CH(CH_3)_2$), 25.1 ($C^{\alpha}HC^{\beta}H_2$**C**$H(CH_3)_2$), 22.7 ($SC$(**C**$H_3)_3$), 22.6 ($C^{\alpha}HC^{\beta}H_2CH$(**C**$H_3)_2$), 22.3 ($C^{\alpha}HC^{\beta}H_2CH$(**C**$H_3)_2$). $C_{17}H_{25}NO_3S_2$ (355.51 g mol^{-1}). MS(ESI): *m/z* = 378.1157 (calcd. 378.1168 $[M+Na]^+$), 733.2452 (calcd. 733.2444 $[2M+Na]^+$). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3281 (-N-H), 2951 (=C-H), 2920 (-C-H), 2847 (-O-C-H), 2331 (-C≡C-), 2359 (-C-C-), 1714 (-C=O), 1545 (-C=C-, arom.), 1284 (C-N). $[\alpha]_{589}^{20}$ = -6.9 (*c* 0.12, $CHCl_3$). TLC: R*f* (PE/EtOAc, 1:1) = 0.60.

Methyl 5-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)thiophene-2-carboxylate (50d). A solution of D-cyclohexylglycine analogous propargylamide **6e** (100.7 mg, 417.0 μmol, 1.0 eq) and thiophene derivative **48a** (138.3 mg, 625.4 μmol, 1.5 eq) in a mixture of THF (2 mL) and piperidine (0.6 mL) was thoroughly degassed. The catalyst $PdCl_2(PPh_3)_2$ (2 mg, 4.8 μmol, 1 mol%) and CuI (3 mg, 16 μmol, 3 mol%) was added under argon atmosphere and the reaction mixture was stirred for 5 h at ambient temperature. After complete conversion of the propargylamide (checked by TLC), the reaction mixture was diluted with an aqueous NH_4Cl solution (halfsaturated, 8 mL) and neutralized with aqueous HCl (1 M, 3-5 mL). The mixture was extracted with Et_2O (4 x 10 mL) and the combined organic layers were dried over $MgSO_4$. After

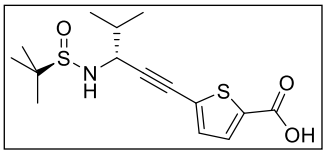
evaporation of the solvent, crude product **50c** was purified by column chromatography (PE/EtOAc, 1:1).

Colorless, crystalline solid. Yield: 36.6 mg, 95.9 μmol, 23 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.62 (d, ^{3}J = 3.9 Hz, 1H, thiophene-2-**H**), 7.12 (d, ^{3}J = 3.9 Hz, 1H, thiophene-3-**H**), 4.06 (d br., ^{3}J = 6.2 Hz, 1H, C$^{\alpha}$**H**), 3.87 (s, 3H, $CO_2C\mathbf{H_3}$), 1.91-1.84 (m, 2H, cy-**H**), 1.83-1.74 (m, 2H, cy-**H**), 1.73-1.62 (m, 2H, cy-**H**), 1.29 (s, 9H, $C(C\mathbf{H_3})_3$), 1.26-1.02 (m, 5H, cy-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 162.1 (thiophene-$\mathbf{C}O_2CH_3$), 133.9 (thiophene-**C**-5), 133.3 (thiophene-**C**-4), 132.7 (thiophene-**C**-2), 129.1 (thiophene-**C**-3), 94.1 (C$^{\alpha}$H**C**≡C-thiophene), 78.8 (C$^{\alpha}$HC≡**C**-thiophene), 57.6 ($S\mathbf{C}(CH_3)_3$), 55.1 (thiophene-$CO_2\mathbf{C}H_3$), 52.5 (**C$^{\alpha}$**Hcy), 43.6 (cy-**C**-1), 29.6 (cy-**C**-2), 28.9 (cy-**C**-6), 26.3 (cy-**C**-4), 25.9 (cy-**C**-5), 25.8 (cy-**C**-3), 22.8 ($SC(\mathbf{C}H_3)_3$). $C_{19}H_{27}NO_3S_2$ (381.55 g mol^{-1}). MS(ESI): *m/z* = 404.1 (calcd. 404.13 $[C_{19}H_{27}NO_3S_2 + Na]^+$). $[\alpha]_{589}^{21}$ = -11.3 (*c* 0.40, MeOH). IR(ATR): $\tilde{\nu}$[cm^{-1}] = 2927 (cy, CH_2), 2844 (CH_3), 1711 (CO_2Me), 1448 (HNS=O), 1258 (ar, C=C), 1173 (ar, C=C), 1097 (ar, C=C).



5-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)thiophene-2-carboxylic Acid (50e). A mixture of D-valine analogous propargylamide **6b** (57.3 mg, 285 μmol, 1.0 eq) and iodo thiophene derivative **48c** (81.0 mg, 318 μmol, 1.1 eq) was dissolved in a mixture of THF/piperidine (0.63 mL, 4:1) under argon atmosphere. After thoroughly degassing the reaction solution, the solid catalysts $PdCl_2(PPh_3)_2$ (1.7 mg, 2.4 μmol, 0.8 mol%) and CuI (0.9 mg, 5 μmol, 2 mol%) were added in one portion under argon atmosphere. The brown solution was stirred 15 h at ambient temperature. Precipitation of a colorless solid could be observed. The volatile parts of the mixture were evaporated under reduced pressure and peptidomimetic **50e** was isolated by preparative HPLC.

Colorless solid. Yield: 46.5 mg, 142 μmol, 50 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 9.39 (s, 1H, $CO_2\mathbf{H}$), 7.42 (d, ^{3}J = 3.9 Hz, 1H, thiophene-3-**H**), 7.00 (d, ^{3}J = 3.9 Hz, 1H, thiophene-4-**H**), 5.06 (d, ^{3}J = 8.6 Hz, 1H, C$^{\alpha}$HN**H**), 4.03 (dd, ^{3}J = 8.5 Hz, ^{3}J = 5.5 Hz, 1H, C$^{\alpha}$**H**), 1.93 (m, 1H, C$^{\alpha}$HC**H**$(CH_3)_2$), 1.31 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.04 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha}$HCH$(C\mathbf{H_3})_2$),

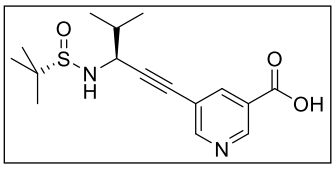


1.01 (d, ^{3}J = 6.8 Hz, 3H, C$^{\alpha}$HCH(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 164.2 (**C**O$_2$H), 135.8 (thiophene-**C**-5), 133.2 (thiophene-**C**-4), 132.9 (thiophene-**C**-2), 129.4 (thiophene-**C**-3), 93.7 (C$^{\alpha}$H**C**≡C-thiophene), 79.0 (C$^{\alpha}$HC≡**C**-thiophene), 57.7 (S**C**(CH$_3$)$_3$), 56.4 (**C$^{\alpha}$**H), 35.0 (C$^{\alpha}$H**C**H(CH$_3$)$_2$), 23.3 (SC(**C**H$_3$)$_3$), 19.1 (C$^{\alpha}$HCH(**C**H$_3$)$_2$), 18.4 (C$^{\alpha}$HCH(**C**H$_3$)$_2$). $C_{15}H_{21}NO_3S_2$ (327.46 g mol^{-1}). HRMS(ESI): *m/z* = 350.08647 (calcd. 350.08551 [M+Na]$^{+}$). $[\alpha]_{589}^{22}$ = 50.3 (*c* 0.72, MeOH).

IIX-3. f) Oligomerization to access Helix Mimetics (51-60)

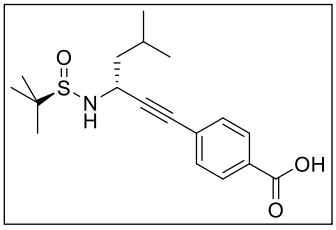
The preparation and charactierization of benzoate **51a** has been detailedly reported in the master thesis [117].

5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)nicotinate (51b). An aqueous solution of LiOH x H$_2$O (61.5 mg, 1.47 mmol in 3.8 mL water, 1 M) was added dropwise to a solution of peptidomimetic **41a** (159.7 mg, 480 μmol, 1.0 eq) in MeOH (7.8 mL) at



0 °C. The reaction mixture was stirred for 16 h at 0 °C. After complete consumption of **41a** (checked by TLC), the pH was adjusted to 1-2 by adding aqueous HCl (1 M). The solution was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give benzoate **51b** (258.7 mg, 0.80 mmol) in pure form. Carboxylate **51b** was directly used for the following dimerization reaction forming dimer **57b** without further characterization.

4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoic Acid (52b). An aqueous solution of NaOH (185 mg, 4.63 mmol, 5.4 eq) was added dropwise to a solution of peptidomimetic (**46e**, 311 mg, 856 μmol, 1.0 eq) in THF/EtOH (3:1, 8 mL). The

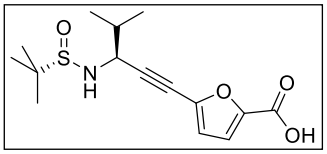


reaction mixture was stirred overnight at rt, until the starting material was completely consumed (checked by TLC). The solvent was evaporated and the residue was diluted in water (50 mL). At 0 °C, the pH value was adjusted to 2-3 by adding an aqueous HCl solution (1 M), which lead to the formation of a colorless precipitate. The solution was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were

washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent gave acid **52b** in pure form.

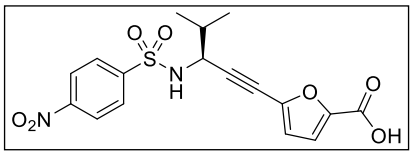
Colorless, amorphous solid. Yield: 269 mg, 803 µmol, 94 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.52 (d, ^3J = 8.1 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.16 (d, ^3J = 8.1 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.88 (d, ^3J = 9.0 Hz, 1H, $C^{\alpha}HN$**H**), 4.21 (ddd, ^3J = 9.0 Hz, ^3J = 7.7 Hz, ^3J = 6.5 Hz, 1H, C^{α}**H**), 1.89 (m, 1H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}$**H**$(CH_3)_2$), 1.69 (dd, ^2J = 14.1 Hz, ^3J = 7.7 Hz, ^3J = 4.6 Hz, 1H, $C^{\alpha}HC^{\beta}$**H**$_2$), 1.64 (dd, ^2J = 14.9 Hz, ^3J = 6.5 Hz, ^3J = 6.2 Hz, 1H, $C^{\alpha}HC^{\beta}$**H**$_2$), 1.32 (s, 9H, SC(C**H**$_3)_3$), 0.96 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}$H(C**H**$_3)_2$), 0.95 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}$H(C**H**$_3)_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 168.4 (**C**O_2H), 131.6 (ar-**C**-3, ar-**C**-5), 130.1 (ar-**C**-1), 129.4 (ar-**C**-2, ar-**C**-6), 126.6 (ar-**C**-4), 91.4 (C^{α}H**C**≡Car), 84.5 (C^{α}HC≡**C**ar), 57.3 (S**C**$(CH_3)_3$), 48.9 (**C**$^{\boldsymbol{\alpha}}$H), 47.2 (C^{α}H**C**$^{\boldsymbol{\beta}}H_2$), 24.9 ($C^{\alpha}HC^{\beta}H_2$**C**$^{\boldsymbol{\gamma}}$H$(CH_3)_2$), 23.1 (SC(**C**$H_3)_3$), 22.4 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}$H(**C**$H_3)_2$), 22.3 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}$H(**C**$H_3)_2$). $C_{18}H_{25}NO_3S$ (335.46 g mol^{-1}). LCMS(ESI): t*r* = 10.0 min, *m/z* = 336.240 (calcd. 336.1628 [M+H$^+$]), 358.357 (calcd. 358.1447 [M+Na$^+$]), 671.134 (calcd. 671.3183 [2M+H$^+$]). $[\alpha]_{589}^{22}$ = -13.6 (*c* 0.124, TFE). X-ray crystal structure in Chapter IIX-3. n.

5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)furan-2-carboxylate (53a). An aqueous solution of LiOH x H_2O (95.8 mg, 2.28 mmol, 3 eq in 5.5 mL H_2O, 1 M) was added dropwise to a solution of peptidomimetic **49a** (248.2 mg,



760 µmol, 1.0 eq) in MeOH (11 mL) at 0 °C and the reaction mixture was stirred for 17 h at 0 °C. An HCl solution (1 M, ca. 3.5 mL) was added to adjust the pH value to 5-6. The solution was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL) dried over $MgSO_4$, the solvent evaporated under reduced pressure to give acid **53b** in form of a slightly yellow, highly viscous oil, which was directly converted in the following dimerization reaction to form **59a** (172.5 mg, 0.55 mg, 68 %).

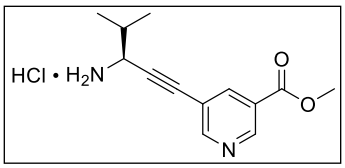
(*S*)-5-(4-Methyl-3-((4-nitrophenyl)sulfonamido)pent-1-yn-1-yl)furan-2-carboxylate (53b). An aqueous solution of LiOH (1 M, 1.0 mL, 1.0 mmol, 8 eq) was added dropwise to a solution of peptidomimetic **49b** (53 mg, 131 μmol, 1.0 eq) in MeOH (2 mL) at 0 °C and the reaction mixture was stirred for 11 h at 0 °C. An HCl solution (1M, ca. 1 mL) was added to adjust the pH value to 1-2. The solution was extracted with Et_2O (4 x 8 mL). The combined organic layers were dried over Na_2SO_4, the solvent evaporated under reduced pressure and the crude product was purified by preparative HPLC to isolate acid **53b** in pure form.



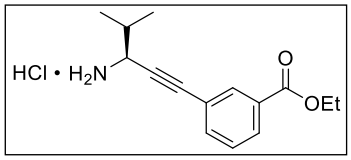
Slightly yellow, highly viscous oil. Yield: 35 mg, 89 μmol, 68 %. ^{1}H NMR (600 MHz, Methanol-d_4) δ = 8.33 (d, ^3J = 8.8 Hz, 2H, ar-2-**H**, ar-6-**H**), 8.14 (d, ^3J = 8.8 Hz, 2H, ar-3-**H**, ar-5-**H**), 7.05 (d, ^3J = 3.5 Hz, 1H, furan-3-**H**), 6.42 (d, ^3J = 3.5 Hz, 1H, furan-4-**H**), 4.14 (d br., ^3J = 6.5 Hz, 1H, C^{α}**H**), 1.96 (m, 1H, $C^{\alpha}HC^{\beta}$**H**$(CH_3)_2$), 1.07 (d, ^3J = 6.8 Hz, 3H, $C^{\alpha}HC^{\beta}H(C$**H**$_3)_2$), 1.06 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H(C$**H**$_3)_2$). ^{13}C NMR (151 MHz, Methanol-d_4) δ = 160.6 (**C**O_2H), 151.4 (ar-**C**-4), 148.0 (ar-**C**-1), 146.6 (furan-**C**-2), 140.0 (furan-**C**-5), 129.9 (ar-**C**-3, ar-**C**-5), 125.2 (ar-**C**-2, ar-**C**-6), 119.3 (furan-**C**-3), 117.5 (furan-**C**-4), 93.6 (C^{α}H**C**≡C-furan), 75.9 (C^{α}HC≡**C**-furan), 53.4 (**C**$^{\alpha}$H), 34.8 (C^{α}**C**$^{\beta}$H$(CH_3)_2$), 19.1 (C^{β}H(**C**$H_3)_2$), 18.8 (C^{β}H(**C**$H_3)_2$). $C_{17}H_{16}N_2O_7S$ (392.38 g mol^{-1}).

The preparation and characterization of amine **54a** has been detailedly reported in the master thesis [117].

Methyl (*S*)-5-(3-Amino-4-methylpent-1-yn-1-yl)nicotinate Hydrochloride (54b). Hydrogen chloride (4 M in 1,4-dioxane, 0.2 mL, 0.8 mmol, 3 eq) was added dropwise to a vigorously stirred solution of *N*-protected peptidomimetic **41a** (87.8 mg, 260 μmol, 1 eq) in MeOH (12 mL) at ambient temperature. After 6 h, the solvent was evaporated under reduced pressure. The residue was digerated with CH_2Cl_2 and the solvent was evaporated under reduced pressure again. The title compound was achieved as hydrochloride salt **54b** (49.6 mg, 0.18 mmol, 70 %) in pure form. Amine **54b** was directly used for the dimerization reaction to give **57b** without further characterization.

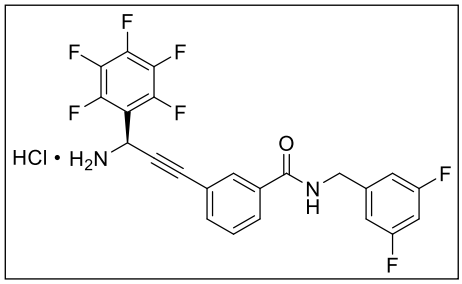


Ethyl (*S*)-3-(3-Amino-4-methylpent-1-yn-1-yl)benzoate Hydrochloride (54c). Hydrochloric acid (4 M in 1,4-dioxane, 0.5 mL) was added dropwise to a stirred solution of *N*-protected peptidomimetic **40a** (123 mg, 352 μmol) in MeOH (25 mL) at 0 °C. After 6 h, the solvent was evaporated at 40 °C. The residue was digerated with CH_2Cl_2 and the solvent was evaporated under reduced pressure again. The title compound was achieved as hydrochloride salt in pure form.

Colorless, amorphous solid. Yield: quantitative. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 

9.01 (s, 3H, $C^{\alpha}HN\mathbf{H_3}Cl$), 8.04 (m, 1H, ar-2-**H**), 7.94 (dt, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, ar-6-**H**), 7.64 (dt, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1H, ar-4-**H**), 7.29 (t, ^3J = 7.8 Hz, 1H, ar-5-**H**), 4.34 (q, ^3J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.14 (d, ^3J = 5.2 Hz, 1H, $C^{\alpha}\mathbf{H}C^{\beta}H(CH_3)_2$), 2.35 (m, 1H, $C^{\alpha}HC^{\beta}\mathbf{H}(CH_3)_2$), 1.37 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.16 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha}HC^{\beta}H(C\mathbf{H_3})_2$), 1.10 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H(C\mathbf{H_3})_2$). $C_{15}H_{20}ClNO_2$ (281.78 g mol^{-1}).

(*R*)-3-(3-Amino-3-(perfluorophenyl)prop-1-yn-1-yl)-*N*-(3,5-difluorobenzyl)benzamid Hydrochloride (54d). Hydrochloric acid (4 M in dioxane, 0.2 mL) was added dropwise to an ice-cold solution of the *N*-protected peptidomimetic **40h** (571 mg, 215 μmol) in MeOH (15 mL). After 5 h, the organic solvent was evaporated at 40 °C. The residue was resuspended with CH_2Cl_2 and then dried under fine vacuum.

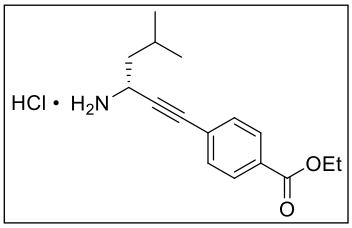
Pale yellow solid. Yield: 108 mg, 215 μmol, quantitative. ^{1}H NMR (300 MHz, Methanol- 

d$_4$) δ = 8.01 (t, ^4J = 1.8 Hz, 1H, ar-2-**H**), 7.93 (dt, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, ar-6-**H**), 7.69 (dt, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, ar-4-**H**), 7.54 (t, ^3J = 7.8 Hz, 1H, ar-5-**H**), 6.97 (dd, $^3J_{HF}$ = 6.3 Hz, $^4J_{HH}$ = 2.2 Hz, 1H, F_2Ph-2-**H**), 6.92 (dd, $^3J_{HF}$ = 6.3 Hz, $^4J_{HH}$ = 2.2 Hz, 1H, F_2Ph-6-**H**), 6.84 (tt, $^3J_{HF}$ = 9.1 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, F_2Ph-4-**H**), 6.01 (m, 1H, C^{α}**H**), 4.56 (s, 2H, $CONHC\mathbf{H_2}PhF_2$). ^{19}F NMR (282 MHz, Methanol-*d*$_4$) δ = -111.9 (dd, $^3J_{FH}$ = 9.0 Hz, $^3J_{FH}$ = 8.5 Hz, F_5Ph-3-**F**, F_5Ph-5-**F**), -142.3 (dt, $^3J_{FF}$ = 16.9 Hz, $^4J_{FF}$ = 2.8 Hz, F_5Ph-2-**F**, F_5Ph-6-**F**), -153.4 (t, $^3J_{FF}$ = 20.2 Hz, 1F, F_5Ph-4-**F**), -163.1 (dd, $^3J_{FF}$ = 20.0 Hz, $^3J_{FF}$ = 13.3 Hz, F_5Ph-3-**F**, F_5Ph-5-**F**). ^{13}C NMR (75 MHz, Methanol-*d*$_4$) δ = 168.8 (**C**ONH),

164.6 (dd, $^{1}J_{CF}$ = 247.3 Hz, $^{3}J_{CF}$ = 12.8 Hz, F_2Ph-**C**-3, F_2Ph-**C**-5), 144.8 (t, $^{3}J_{CF}$ = 8.8 Hz, F_2Ph-**C**-1), 136.0 (ar-**C**-1), 135.9 (ar-**C**-6), 132.1 (ar-**C**-2), 130.3 (ar-**C**-5), 129.6 (ar-**C**-4), 122.5 (ar-**C**-3), 111.2 (d, $^{2}J_{CF}$ = 25.3 Hz, F_2Ph-**C**-2, F_2Ph-**C**-6), 103.23 (t, $^{2}J_{CF}$ = 25.8 Hz, F_2Ph-**C**-4), 88.2 ($C^{\alpha}H$**C**≡C-ar), 81.6 ($C^{\alpha}HC$≡**C**-ar), 43.8 (**C$^{\alpha}$**HC_6F_5), 37.6 (CONH**C**H_2PhF_2). $C_{23}H_{14}ClF_7N_2O$ (502.82 g mol^{-1}).

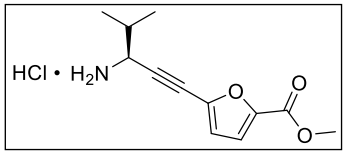
Ethyl (*R*)-4-(3-Amino-5-methylhex-1-yn-1-yl)benzoate Hydrochloride (55b). Hydrochloride (4 M in dioxane, 0.4 mL) was added dropwise to an ice-cold solution of the *N*-protected peptidomimetic **46e** (399 mg, 1.05 mmol, 1.0 eq) in MeOH (15 mL). After 5 h, the organic solvent was evaporated at 40 °C. The residue was digerated with CH_2Cl_2 and then dried under fine vacuum.

Colorless solid. Yield: 289 mg, 977 µmol, 93 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.81



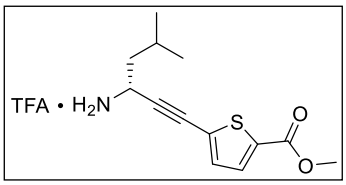
(s, 3H, $C^{\alpha}N$**H$_3$**Cl), 7.98 (d, ^{3}J = 8.4 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.60 (d, ^{3}J = 8.4 Hz, 2H, ar-3-**H**, ar-5-**H**), 4.35 (ddd, ^{3}J = 6.5 Hz, ^{3}J = 5.7 Hz, ^{3}J = 3.9 Hz, 1H, C^{α}**H**), 4.32 (q, ^{3}J = 7.1 Hz, 2H, CO_2C**H$_2$**CH_3), 1.87 (m, 1H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}$**H**$(CH_3)_2$), 1.68-1.79 (m, 2H, $C^{\alpha}HC^{\beta}$**H$_2$**$C^{\gamma}H(CH_3)_2$), 1.32 (t, ^{3}J = 7.1 Hz, 3H, CO_2CH_2C**H$_3$**), 0.97 (d, ^{3}J = 6.6 Hz, 3H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H(C$**H$_3$**$)_2$), 0.93 (d, ^{3}J = 6.5 Hz, 3H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H(C$**H$_3$**$)_2$). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 165.0 (**C**$O_2CH_2CH_3$), 131.8 (ar-**C**-3, ar-**C**-5), 130.1 (ar-**C**-1), 129.5 (ar-**C**-2, ar-**C**-6), 125.8 (ar-**C**-4), 88.5 ($C^{\alpha}H$**C**≡Car), 85.0 ($C^{\alpha}HC$≡**C**ar), 61.1 (CO_2**C**H_2CH_3), 41.5 ($C^{\alpha}H$**C$^{\beta}$**H_2), 41.2 (**C$^{\alpha}$**H), 24.7 ($C^{\alpha}HC^{\beta}H_2$**C$^{\gamma}$**$H(CH_3)_2$), 22.9 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}H$(**C**$H_3)_2$), 21.3 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}H$(**C**$H_3)_2$), 14.1 ($CO_2CH_2$**C**$H_3$). $C_{16}H_{22}ClNO_2$ (295.81 g mol^{-1}).

Methyl (*S*)-5-(3-Amino-4-methylpent-1-yn-1-yl)furan-2-carboxylate Hydrochloride (56a). Hydrochloric acid (4 M in dioxane, 0.1 mL, 40 µmol, 3 eq) was added dropwise to a solution of peptidomimetic **49a** (47.2 mg, 145 µmol) in MeOH (6 mL). After stirring for 20 h at rt, the solvent was evaporated to yield the hydrochloride salt of peptidomimetic **56a** quantitatively in form of a faintly yellow solid (37.4 mg, 145 µmol,



quantitative), which was directly converted to compound **49b** without further characterization.

Methyl (*R*)-5-(3-Amino-5-methylhex-1-yn-1-yl)thiophene-2-carboxylate trifluoroacetate (56b). HCl (4 M in dioxane, 0.2 mL) was added dropwise to a solution of peptidomimetic **50c** (24 mg, 70 μmol, 1.0 eq) in MeOH (5 mL) at 0 °C. The reaction



mixture was stirred for 24 h at ambient temperature. After complete consumption of **50c** (checked by TLC), the solvent was evaporated under reduced pressure. The crude product was suspended in CH_2Cl_2 and volatile sideproducts were coevaporated under reduced pressure (3 x 10 mL). The crude amine **56b** was purified by preparative HPLC.

Colorless crystalline solid. Yield: quantitative. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.37 (s, 3H, C$^\alpha$HN**H$_3$**), 7.59 (d, ^3J = 3.9 Hz, 1H, thiophene-3-**H**), 7.16 (d, ^3J = 3.9 Hz, 1H, thiophene-4-**H**), 4.17 (dd br., ^3J = 9.7 Hz, ^3J = 5.2 Hz, 1H, C$^\alpha$**H**), 3.87 (s, 3H, CO_2C**H$_3$**), 1.92-1.73 (m, 2H, C$^\alpha$HC**H$_2$**CH(CH$_3$)$_2$), 1.65 (m, 1H, C$^\alpha$HCH$_2$C**H**(CH$_3$)$_2$), 0.95 (d, ^3J = 6.3 Hz, 3H, C$^\alpha$HCH$_2$CH(C**H$_3$**)$_2$), 0.91 (d, ^3J = 6.3 Hz, 3H, C$^\alpha$HCH$_2$CH(C**H$_3$**)$_2$). $C_{15}H_{18}F_3NO_4S$ (365.37 g mol^{-1}). X-ray crystal structure in Chapter IIX-3. n.

The preparation and charactierization of amine **57a** has been detailedly reported in the master thesis [117].

Methyl 5-((*S*)-3-(5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)nicotinamido)-4-methylpent-1-yn-1-yl)nicotinate (57b). A mixture of amine **54b** (49.6 mg, 180 μmol, 1.0 eq), acid **51b** (86.2 mg, 266 μmol, 1.5 eq), HOAt (75.8 mg, 560 μmol, 3 eq) and HATU (237.7 mg, 630 μmol, 4 eq) was combined under argon atmosphere and dissolved in DMF (3.5 mL). DIPEA (0.2 mL, 1.2 mmol) was added and the clear orange solution was stirred for 5 h at ambient temperature. After 5 h, CH_2Cl_2 (3.5 mL), NH_4Cl solution (5 ml, saturated aqueous) and bicarbonate (5 mL, saturated aqueous) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with aqueous HCl (1 M, 5 mL) and brine (5 mL). The organic solution was dried over Na_2SO_4 and the solvent was evaporated under reduced

pressure. The crude productwas purified by column chromatography (PE/EtOAc, 1:1) to give dimer **57b** in pure form.

Pale yellow, highly viscous oil. Yield: 56.1 mg, 105 µmol, 58 %. ^{1}H NMR (600 MHz, Chloroform-*d*): δ = 9.26 (s, 1H, nic^{i}-2-**H**), 9.13 (s, 1H, nic^{i+1}-2-**H**), 8.89 (s, 1H, nic^{i+1}-6-**H**), 8.68 (s, 1H, nic^{i}-6-**H**), 8.52 (s, 1H, nic^{i+1}-4-**H**), 8.42 (s, 1H, nic^{i}-4-**H**), 8.04 (d, ^{3}J = 7.2 Hz, 1H, C$^{\alpha i+1}$HN**H**CO), 5.09 (dd, ^{3}J = 7.9 Hz, ^{3}J = 6.8 Hz, 1H, C$^{\alpha i+1}$**H**), 4.12 (dd, ^{3}J = 7.6 Hz, ^{3}J = 5.4 Hz, 1H, C$^{\alpha i}$**H**), 3.99 (s, 1H, C$^{\alpha i}$HN**H**), 3.98 (s, 3H, ar^{i+1}-3-CO$_2$C**H$_3$**), 2.18 (m, 1H, C$^{\alpha i+1}$HC**H**(CH$_3$)$_2$), 2.00 (m, 1H, C$^{\alpha i}$HC**H**(CH$_3$)$_2$), 1.29 (s, 9H, SC(C**H$_3$**)$_3$), 1.14 (d, ^{3}J = 6.6 Hz, 3H, C$^{\alpha i+1}$HCH(C**H$_3$**)$_2$), 1.11 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha i+1}$HCH(C**H$_3$**)$_2$), 1.05 (d, ^{3}J = 6.6 Hz, 6H, C$^{\alpha i}$HCH(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, Chloroform-*d*): δ = 163.9 (nic^{i+1}-3-**C**O$_2$CH$_3$), 162.3 (nic^{i}-3-**C**ONH), 152.8 (nic^{i+1}-**C**-6), 149.7 (nic^{i}-**C**-6), 146.8 (nic^{i+1}-**C**-2), 143.8 (nic^{i}-**C**-2), 142.3 (nic^{i}-**C**-3), 42.1 (nic^{i}-**C**-4), 131.4 (nic^{i+1}-**C**-3), 127.3 (nic^{i+1}-**C**-4), 121.8 (nic^{i}-**C**-5), 121.7 (nic^{i+1}-**C**-5), 95.6 (C$^{\alpha i}$H**C**≡Car), 93.6 (C$^{\alpha i+1}$H**C**≡Car), 79.8 (C$^{\alpha i+1}$HC≡**C**ar), 79.0 (C$^{\alpha i+1}$HC≡**C**ar), 57.7 (SO**C**(CH$_3$)$_3$), 55.9 (**C$^{\alpha i}$**H), 53.2 (nic^{i+1}-3-CO$_2$**C**H$_3$), 49.0 (**C$^{\alpha i+1}$**H), 34.4 (C$^{\alpha i}$H**C**H(CH$_3$)$_2$), 33.1 (C$^{\alpha i+1}$H**C**H(CH$_3$)$_2$), 22.8 (SOC(**C**H$_3$)$_3$), 19.3 (C$^{\alpha i+1}$HCH(**C**H$_3$)$_2$), 18.9 (C$^{\alpha i}$HCH(**C**H$_3$)$_2$), 18.5 (C$^{\alpha i}$HCH(**C**H$_3$)$_2$), 18.4 (C$^{\alpha i+1}$HCH(**C**H$_3$)$_2$). $C_{29}H_{36}N_4O_4S$ (536.69 g mol^{-1}). MS(ESI): *m/z* = 537.7 (calcd. 537.2530 [M+H]$^{+}$), 559.9 (calcd. 559.2349 [M+Na]$^{+}$). $[\alpha]_{589}^{24}$ = + 6.06 (*c* 0.34, $CHCl_3$).

4-((*S*)-3-(4-((*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)benzamido)-4-methylpent-1-yn-1-yl)benzoate (58a). Boc$_2$O (56.1 mg, 257 µmol, 2.0 eq) was added to a vigorously stirred solution of amine **54c** (34.4 mg, 128 µmol 1.0 eq) in aqueous bicarbonate/THF (1:1, 5 mL). The solution was stirred overnight at ambient temperature. After complete conversion of amine **54c** (checked by TLC), imidazole (350 mg, 514 µmol, 4 eq) was added to the reaction mixture and the now clear solution was stirred for another 2 h at rt. The mixture was diluted with Et$_2$O (10 mL) and aqueous KHSO$_4$ (5 %, 10 mL). The phases were separated and the aqueous layer was extracted with Et$_2$O (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered and the solvent was evaporated to achieve Methyl (*S*)-4-(3-((*tert*-Butoxycarbonyl)amino)-4-

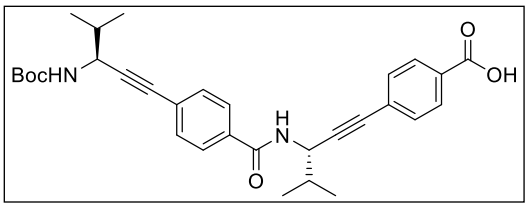
methylpent-1-yn-1-yl)benzoate (39.5 mg, 119 μmol, 93 %) in pure form. It was directly converted without further characterization.

An aqueous solution of LiOH (1 M, 1.0 mL, 1.0 mmol) was added dropwise to a solution of Methyl (*S*)-4-(3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)benzoate (39.5 mg, 119 μmol, 1.0 eq) in MeOH (2 mL) at 0 °C and the reaction mixture was stirred for 6 h at 0 °C. An HCl solution (1M, ca. 5 mL) was added to adjust the pH value to 1-2. The solution was extracted with Et_2O (4 x 10 mL). The combined organic layers were dried over Na_2SO_4, the solvent evaporated under reduced pressure and (*S*)-4-(3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)benzoate (33.6 mg, 106 μmol 89 %) was achieved in pure form. It was directly reacted with amine **54c** without further characterization.

A mixture of amine **54c** (51.1 mg, 191 μmol, 1.8 eq), (*S*)-4-(3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)benzoate (33.6 mg, 106 μmol 1.0 eq), HOAt (86.5 mg, 637 μmol, 4 eq) and HATU (182.6 mg, 479 μmol, 3 eq) was combined under argon atmosphere and dissolved in DMF (5 mL). DIPEA (0.25 mL, 1.47 mmol, 9.2 eq) was added and the clear orange solution was stirred for 24 h at ambient temperature. After 24 h, CH_2Cl_2 (15 mL), NH_4Cl solution (10 ml, saturated aqueous) and bicarbonate (10 mL, saturated aqueous) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with aqueous HCl (1 M, 5 mL) and brine (5 mL). The organic solution was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude productwas purified by column chromatography (PE/EtOAc, 1:1) to give Methyl 4-((*S*)-3-(4-((*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)benzamido)-4-methylpent-1-yn-1-yl)benzoate (24.8 mg, 46.6 μmol, 44 %) in pure form.

An aqueous solution of LiOH (1 M, 1.0 mL, 1.0 mmol) was added dropwise to a solution of Methyl 4-((*S*)-3-(4-((*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)benzamido)-4-methylpent-1-yn-1-yl)benzoate (24.8 mg, 46.6 μmol, 1.0 eq) in MeOH (2 mL) at 0 °C and the reaction mixture was stirred for 6 h at 0 °C. An HCl solution (1M, ca. 5 mL) was added to adjust the pH value to 1-2. The solution was extracted with Et_2O (4 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent

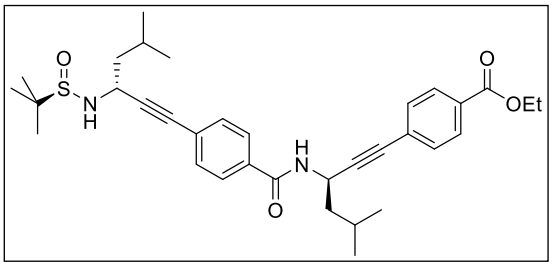
evaporated under reduced pressure. Dimer **58a** (15.4 mg, 29.8 µmol 64 %) was isolated by preparative HPLC.



Colorless, amorpheous solid. Yield: 15.4 mg, 29.8 µmol, 19 %. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.03 (d, ^{3}J = 8.4 Hz, 1H, CON**H**C$^{\alpha i+1}$H), 7.92 (d, ^{3}J = 8.3 Hz, 2H, ar^{i+1}-2-**H,** ar^{i+1}-6-**H**), 7.89 (d, ^{3}J = 8.4 Hz, 2H, ar^{i}-2-**H**, ar^{i}-6-**H**), 7.55 (d, ^{3}J = 8.4 Hz, 2H, ar^{i+1}-3-**H**, ar^{i+1}-5-**H**), 7.50 (d, ^{3}J = 8.4 Hz, 2H, ar^{i}-3-**H**, ar^{i}-5-**H**), 7.43 (d, ^{3}J = 9.0 Hz, 1H, O_2CN**H**C$^{\alpha I}$H), 4.87 (dd, ^{3}J = 8.4 Hz, ^{3}J = 7.8 Hz, 1H, C$^{\alpha i+1}$**H**C$^{\beta}$H(CH$_3$)$_2$), 4.30 (dd, ^{3}J = 9.0 Hz, ^{3}J = 7.7 Hz, 1H, C$^{\alpha I}$**H**C$^{\beta}$H(CH$_3$)$_2$), 2.06 (hd, ^{3}J = 6.8 Hz, ^{3}J = 7.8 Hz, 1H, C$^{\alpha i+1}$HC$^{\beta}$**H**(CH$_3$)$_2$), 1.86 (hd, ^{3}J = 6.7 Hz, ^{3}J = 7.7 Hz, 1H, C$^{\alpha I}$HC$^{\beta}$**H**(CH$_3$)$_2$), 1.40 (s, 9H, CO$_2$C(C**H$_3$**)$_3$), 1.09 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha i+1}$HC$^{\beta}$H(C**H$_3$**)$_2$), 1.00 (d, ^{3}J = 6.7 Hz, 6H, C$^{\alpha I}$HC$^{\beta}$H(C**H$_3$**)$_2$, C$^{\alpha i+1}$HC$^{\beta}$H(C**H$_3$**)$_2$), 0.95 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha I}$HC$^{\beta}$H(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 166.8 (**C**O$_2$H), 165.2 (**C**ONHC$^{\alpha i+1}$), 155.2 (O$_2$**C**NHC$^{\alpha I}$), 133.5 (ar^{i+1}-**C**-4), 131.7 (ar^{i+1}-**C**-3, ar^{i+1}-**C**-5), 131.3 (ar^{i}-**C**-3, ar^{i}-**C**-5), 130.5 (ar^{i+1}-**C**-1), 129.6 (ar^{i+1}-**C**-2, ar^{i+1}-**C**-6), 128.0 (ar^{i}-**C**-2, ar^{i}-**C**-6), 126.8 (ar^{i+1}-**C**-4), 125.5 (ar^{i}-**C**-1), 91.7 (C$^{\alpha i+1}$H**C**≡C-ar), 91.5 (C$^{\alpha I}$H**C**≡C-ar), 82.3 (C$^{\alpha i+1}$HC≡**C**-ar), 82.1 (C$^{\alpha I}$HC≡**C**-ar), 78.4 (CO$_2$**C**(CH$_3$)$_3$), 48.9 (**C$^{\alpha I}$**HC$^{\beta}$H(CH$_3$)$_2$), 47.8 (**C$^{\alpha i+1}$**HC$^{\beta}$H(CH$_3$)$_2$), 33.0 (C$^{\alpha i+1}$H**C$^{\beta}$**H(CH$_3$)$_2$), 32.8 (C$^{\alpha I}$H**C$^{\beta}$**H(CH$_3$)$_2$), 28.3 (CO$_2$C(**C**H$_3$)$_3$), 19.3 (C$^{\alpha i+1}$HC$^{\beta}$H(**C**H$_3$)$_2$), 19.1 (C$^{\alpha I}$HC$^{\beta}$H(**C**H$_3$)$_2$), 18.8 (C$^{\alpha i+1}$HC$^{\beta}$H(**C**H$_3$)$_2$), 18.6 (C$^{\alpha I}$HC$^{\beta}$H(**C**H$_3$)$_2$). $C_{31}H_{36}N_2O_5$ (516.64 g mol^{-1}). MS(ESI): *m/z* = 517.8 (calcd. 517.2697 [M+H]$^{+}$), 539.7 (calcd. 539.6272 [M+Na]$^{+}$). TLC: R*f* (EtOAc/PE, 1:1) = 0.16.

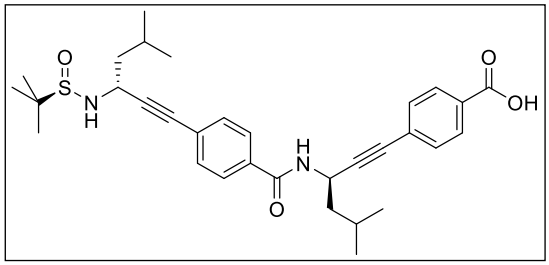
Ethyl 4-((*R*)-3-(4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzamido)-5-methylhex-1-yn-1-yl)benzoate (58b). Under argon atmosphere, solid HOBt (8 mg, 60 µmol, 0.3 eq) and TBTU (98 mg, 0.30 mmol, 1.5 eq) were added in one portion to a vigorously stirred solution of amine **55b** (69 mg, 0.20 mmol, 1.0 eq) and acid **52b** (67 mg, 0.20 mmol, 1.0 eq) in a mixture of DMF/CH_2Cl_2 (1:1, 18 mL) and DIPEA (0.10 mL, 0.6 mmol, 3 eq). The reaction mixture was stirred over 18 h at ambient temperature. The solution was diluted with water (150 mL) and extracted with CH_2Cl_2 (5 x 100 mL). The combined organic layers were washed with an aqueous solution of K_2CO_3

(saturated, 30 mL), HCl (1 M, 30 mL) and brine (15 mL). The solvent was evaporated and the crude product was purified by column chromatography (PE/EtOAc, 1:1) to yield dimer **58b** in pure form.



Yellow, highly viscous oil. Yield: 98 mg, 170 µmol, 87 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.96 (d, ^{3}J = 8.4 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.72 (d, ^{3}J = 8.5 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.46 (d, ^{3}J = 8.1 Hz, 4H, ar-3-**H**, ar-5-**H**, ar-3-**H**, ar-5-**H**), 6.44 (d, ^{3}J = 8.5 Hz, 1H, $C^{\alpha}N\mathbf{H}CO$), 5.25 (ddd, ^{3}J = 7.9 Hz, ^{3}J = 7.1 Hz, ^{3}J = 8.5 Hz, 1H, $C^{\alpha II}\mathbf{H}$), 4.36 (q, ^{3}J = 7.1 Hz, 2H, $C^{\alpha}HCOC\mathbf{H_2}CH_3$), 4.27 (ddd, ^{3}J = 7.5 Hz, ^{3}J = 7.2 Hz, ^{3}J = 5.4 Hz, 1H, $C^{\alpha I}\mathbf{H}$), 3.41 (d, ^{3}J = 7.4 Hz, 1H, $C^{\alpha}HN\mathbf{H}SC(CH_3)_3$), 1.95-1.85 (m, 2H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}\mathbf{H}(CH_3)_2$), 1.75 (t, ^{3}J = 7.4 Hz, 2H, $C^{\alpha}HC^{\beta}\mathbf{H_2}$), 1.68 (t, ^{3}J = 7.4 Hz, 2H, $C^{\alpha}HC^{\beta}\mathbf{H_2}$), 1.38 (t, ^{3}J = 7.1 Hz, 3H, $C^{\alpha}HCOCH_2C\mathbf{H_3}$), 1.24 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.01 (d, ^{3}J = 6.6 Hz, 3H, $CH(C\mathbf{H_3})_2$), 0.99 (d, ^{3}J = 6.6 Hz, 3H, $CH(C\mathbf{H_3})_2$), 0.96 (d, ^{3}J = 6.7 Hz, 6H, $CH(C\mathbf{H_3})_2$). $C_{34}H_{44}N_2O_4S$ (576.80 g mol^{-1}). TLC: R*f* (PE/EtOAc, 1:1) = 0.33. $[\alpha]_{589}^{21}$ = -2.61 (*c* 2.26, $CHCl_3$).

4-((*R*)-3-(4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzamido)-5-methylhex-1-yn-1-yl)benzoate (58c). An aqueous solution of LiOH (1 M, 1.0 mL, 1.0 mmol, 8 eq) was added dropwise to a solution of peptidomimetic **58b** (33.8 mg, 58.6 µmol, 1.0 eq) in MeOH (2 mL) at 0 °C and the reaction mixture was stirred for 8 h at 0 °C. An HCl solution (1 M, ca. 1 mL) was added to adjust the pH value to 1-2. The solution was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, the solvent evaporated under reduced pressure and the crude product was purified by preparative HPLC to isolate acid **58c** in pure form.

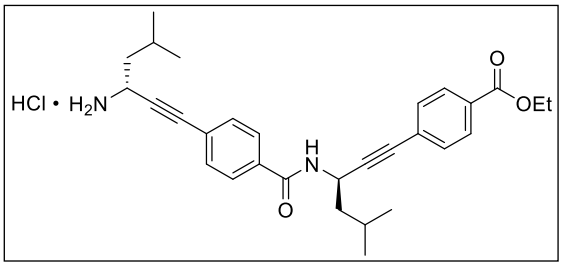


Highly viscous, colorless oil. Yield: 11.9 mg, 21.7 µmol, 36 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.91 (d, ^{3}J = 8.4 Hz, 2H, ar^{i+1}-2-**H**, ar^{i+1}-6-**H**), 7.63 (d, ^{3}J = 8.3 Hz, 2H, ar^{I}-2-**H**, ar^{I}-6-**H**), 7.43 (d, ^{3}J = 8.5 Hz, 2H, ar^{i+1}-3-**H**, ar^{i+1}-5-**H**), 7.39 (d, ^{3}J = 8.3 Hz, 2H, ar^{I}-3-**H**, ar^{I}-5-**H**), 6.36 (d br., ^{3}J = 8.5 Hz,

1H, $C^{\alpha i+1}HN\mathbf{H}CO$), 5.65 (s br., 1H, $CO_2\mathbf{H}$), 5.24 (ddd, ^3J = 8.5 Hz, ^3J = 7.8 Hz, ^3J = 7.4 Hz, 1H, $C^{\alpha i+1}\mathbf{H}NCO$), 4.58 (s br., 1H, $C^{\alpha I}HN\mathbf{H}BuS$), 4.24 (ddd, ^3J = 7.4 Hz, ^3J = 7.6 Hz, ^3J = 5.4 Hz, 1H, $C^{\alpha I}\mathbf{H}NHBuS$), 1.96-1.83 (m, 2H, $C^{\alpha I}HCH_2C\mathbf{H}(CH_3)_2$, $C^{\alpha I}HCH_2C\mathbf{H}(CH_3)_2$), 1.74 (dd, ^3J = 7.4 Hz, ^3J = 7.6 Hz, 2H, $C^{\alpha i+1}HC\mathbf{H_2}CH(CH_3)_2$), 1.69 (dd, ^3J = 7.4 Hz, ^3J = 7.8 Hz, 2H, $C^{\alpha I}HC\mathbf{H_2}CH(CH_3)_2$), 1.29 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.01 (d, ^3J = 6.5 Hz, 3H, $C^{\alpha I}HCH_2CH(C\mathbf{H_3})_2$), 1.00 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha I}HCH_2CH(C\mathbf{H_3})_2$), 0.97 (d, ^3J = 6.5 Hz, 3H, $C^{\alpha i+1}HCH_2CH(C\mathbf{H_3})_2$), 0.96 (d, ^3J = 6.6 Hz, 3H, $C^{\alpha i+1}HCH_2CH(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 169.5 (ar^{i+1}-C-1-$\mathbf{C}O_2H$), 165.9 (ar^{I}-C-1-**C**ONH), 133.3 (ar^{I}-**C**-1), 132.0 (ar^{I}-**C**-3, ar^{I}-**C**-5), 131.7 (ar^{i+1}-**C**-3, ar^{i+1}-**C**-5), 130.0 (ar^{i+1}-**C**-2, ar^{i+1}-**C**-6), 129.7 (ar^{i+1}-**C**-1), 127.7 (ar^{i+1}-**C**-4), 126.9 (ar^{I}-**C**-2, ar^{I}-**C**-6), 126.4 (ar^{I}-**C**-4), 92.0 ($C^{\alpha i+1}H\mathbf{C}$≡Car), 91.8 ($C^{\alpha I}H\mathbf{C}$≡Car), 84.1 ($C^{\alpha I}HC$≡**C**ar), 82.6 ($C^{\alpha i+1}HC$≡**C**ar), 57.1 ($S\mathbf{C}(CH_3)_3$), 48.0 ($\mathbf{C^{\alpha I}}HCH_2CH(CH_3)_3$), 46.1 ($C^{\alpha i+1}H\mathbf{C}H_2CH(CH_3)_3$), 45.2 ($C^{\alpha i+1}H\mathbf{C}H_2CH(CH_3)_3$), 41.2 ($\mathbf{C^{\alpha i+1}}HCH_2CH(CH_3)_3$), 25.5 ($C^{\alpha i+1}HCH_2\mathbf{C}H(CH_3)_3$), 25.0 ($C^{\alpha I}HCH_2\mathbf{C}H(CH_3)_3$), 22.8 ($SC(\mathbf{C}H_3)_3$), 22.4 ($C^{\alpha i+1}HCH_2CH(\mathbf{C}H_3)_3$), 22.4 ($C^{\alpha i+1}HCH_2CH(\mathbf{C}H_3)_3$), 22.2 ($C^{\alpha I}HCH_2CH(\mathbf{C}H_3)_3$), 22.2 ($C^{\alpha I}HCH_2CH(\mathbf{C}H_3)_3$). $C_{32}H_{40}N_2O_4S$ (548.74 g mol^{-1}). MS(ESI): *m/z* = 549.195 (calcd. 549.2782 $[M+H]^+$). $[\alpha]_{589}^{21}$ = -19.13 (*c* 0.60, $CHCl_3$).

Ethyl 4-((*R*)-3-(4-((*R*)-3-Amino-5-methylhex-1-yn-1-yl)benzamido)-5-methylhex-1-yn-1-yl)benzoate Hydrochloride (58d). Dimer **58b** (197.0 mg, 341.6 µmol) was dissolved in EtOH (11.5 mL). After addition of HCl (4 M in dioxane, 0.35 mL, 1.4 mmol, 4 eq), the reaction mixture was stirred overnight at ambient temperature. The solvent was evaporated, digerated with CH_2Cl_2 and volatile parts were coevaporated. Colorless solid. Dissolved in an aqueous solution of K_2CO_3 (1M, 10 mL) and extracted with Et_2O (3 x 20 mL). Evaporation of the solvent achieved the free amine **58d**.

Colorless fluid. Yield: 141.9 mg, 300.2 µmol, 88 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ

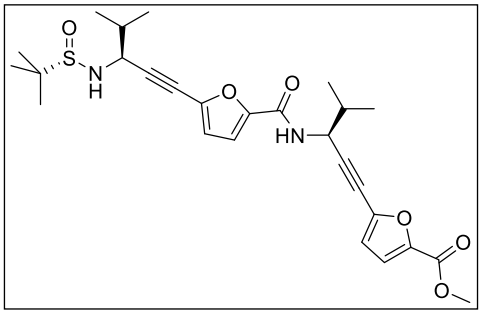


= 8.58 (s, 2H, $C^{\alpha I}N\mathbf{H_2}$), 7.91 (d, ^3J = 8.3 Hz, 2H, ar^{i+1}-2-**H**, ar^{i+1}-6-**H**), 7.60 (d, ^3J = 8.1 Hz, 2H, ar^{i}-2-**H**, ar^{i}-6-**H**), 7.41 (d, ^3J = 8.3 Hz, 2H, ar^{i+1}-3-**H**, ar^{i+1}-5-**H**), 7.31 (d, ^3J = 8.1 Hz, 2H, ar^{i}-3-**H**, ar^{i}-5-**H**), 7.02 (d, ^3J = 8.5 Hz, 1H, $C^{\alpha i+1}N\mathbf{H}CO$), 5.25 (ddd, ^3J = 7.9 Hz, ^3J = 7.8 Hz, ^3J = 5.4 Hz, 1H, $C^{\alpha I}\mathbf{H}$), 4.35 (q, ^3J =

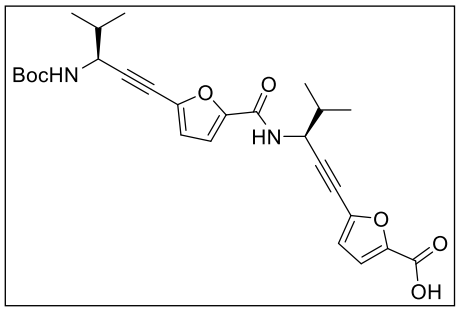
7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.18 (ddd, ^3J = 10.0 Hz, ^3J = 7.8 Hz, ^3J = 5.3 Hz, 1H, $C^{\alpha i+1}\mathbf{H}$), 1.93-1.84 (m, 2H, $C^{\alpha I}HCH_2C\mathbf{H}(CH_3)_2$, $C^{\alpha i+1}HCH_2C\mathbf{H}(CH_3)_2$), 1.83 (m, 1H, $C^{\alpha I}HC\mathbf{H}_2CH(CH_3)_2$), 1.77 (t, ^3J = 7.4 Hz, 2H, $C^{\alpha i+1}HC\mathbf{H_2}CH(CH_3)_2$), 1.67 (m, 1H, $C^{\alpha I}HC\mathbf{H}_2CH(CH_3)_2$), 1.37 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.00 (d, ^3J = 6.6 Hz, 6H, $C^{\alpha i+1}HCH_2CH(C\mathbf{H_3})_2$), 0.92 (d, ^3J = 6.4 Hz, 3H, $C^{\alpha I}HCH_2CH(C\mathbf{H_3})_2$), 0.89 (d, ^3J = 6.4 Hz, 3H, $C^{\alpha I}HCH_2CH(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.3 ($C^{\alpha I}NH\mathbf{C}O$), 166.2 ($ar^{i+1}\mathbf{C}O_2CH_2CH_3$), 134.3 ($ar^i$-**C**-1), 132.1 ($ar^i$-**C**-3, ar^i-**C**-5), 131.7 (ar^{i+1}-**C**-3, ar^{i+1}-**C**-5), 130.0 (ar^{i+1}-**C**-1), 129.5 (ar^{i+1}-**C**-2, ar^{i+1}-**C**-6), 127.4 (ar^{i+1}-**C**-4), 127.2 (ar^i-**C**-2, ar^i-**C**-6), 124.8 (ar^i-**C**-4), 91.8 ($C^{\alpha I}$H-**C**≡C-ar), 86.6 ($C^{\alpha I}$H-C≡**C**-ar), 85.1 ($C^{\alpha i+1}$H-**C**≡C-ar), 82.5 ($C^{\alpha i+1}$H-C≡**C**-ar), 61.3 ($CO_2\mathbf{C}H_2CH_3$), 45.0 ($C^{\alpha i+1}H\mathbf{C}H_2CH(CH_3)_2$), 42.8 ($\mathbf{C^{\alpha I}}$H), 42.3 ($C^{\alpha I}H\mathbf{C}H_2CH(CH_3)_2$), 41.2 ($\mathbf{C^{\alpha i+1}}$H), 25.5 ($C^{\alpha I}HCH_2\mathbf{C}H(CH_3)_2$), 25.2 ($C^{\alpha i+1}HCH_2\mathbf{C}H(CH_3)_2$), 22.9 ($C^{\alpha i+1}HCH_2CH(\mathbf{C}H_3)_2$), 22.9 ($C^{\alpha i+1}HCH_2CH(\mathbf{C}H_3)_2$), 22.3 ($C^{\alpha I}HCH_2CH(\mathbf{C}H_3)_2$), 21.2 ($C^{\alpha I}HCH_2CH(\mathbf{C}H_3)_2$), 14.4 ($CO_2CH_2\mathbf{C}H_3$). $C_{30}H_{36}N_2O_3$ (472.63 g mol^{-1}). MS(ESI): *m/z* = 473.222 (calcd. 473.278 $[M+H]^+$). $[\alpha]_{589}^{21}$ = -2.81 (*c* 1.71, $CHCl_3$). Replacement of EtOH by MeOH leads to a partial formation of methylester.

Methyl 5-((*S*)-3-(5-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)furan-2-carboxamido)-4-methylpent-1-yn-1-yl)furan-2-carboxylate (59a). Under argon atmosphere, solid HOAt (150 mg, 1.1 mmol, 1 eq) and HATU (418 mg, 1.1 mmol, 1 eq) were added in one portion to a vigorously stirred solution of amine **56a** (247.3 mg, 0.96 mmol, 2 eq) and acid **53a** (172.5 mg, 0.55 mmol, 1.0 eq) in DMF (15 mL) and DIPEA (0.55 mL, 3.2 mmol, 3 eq). The reaction mixture was stirred over 16 h at ambient temperature. After 16 h, CH_2Cl_2 (50 mL) and an aqueous solution of bicarbonate (saturated, 30 mL) was added. After separation of the phases, the organic phase was washed with a $KHSO_4$ solution (5 % in water, 20 mL) and brine (8 mL). The solvent of the organic phase was evaporated under reduced pressure and the crude dipeptidomimetic **59a** was purified by column chromatography (PE/EtOAc, 1:1).

Pale yellow, viscous oil, 100.3 mg, 195 µmol, 35 %. de ≥ 99% (determined by ^{1}H NMR integration: 4.93 (dd, ^{3}J = 8.9 Hz, ^{3}J = 6.3 Hz, 1H) and 4.00 ppm (dd, ^{3}J = 7.2 Hz, ^{3}J = 5.4 Hz, 1H). ^{1}H NMR (600 MHz, Chloroform-*d*): δ = 7.04 (d, ^{3}J = 3.6 Hz, 1H, furan^{i+1}-3-**H**), 7.02 (d, ^{3}J = 3.6 Hz, 1H, furan^{i}-3-**H**), 6.90 (d, ^{3}J = 9.0 Hz, 1H, C$^{\alpha i+1}$HN**H**), 6.52 (d, ^{3}J = 3.7 Hz, 1H, furan^{i+1}-4-**H**), 6.52 (d, ^{3}J = 3.7 Hz, 1H, furan^{i}-4-**H**), 4.93 (dd, ^{3}J = 8.9 Hz, ^{3}J = 6.3 Hz, 1H, C$^{\alpha i+1}$**H**C$^{\beta i+1}$H(CH$_3$)$_2$), 4.00 (dd, ^{3}J = 7.2 Hz, ^{3}J = 5.4 Hz, 1H, C$^{\alpha i}$**H**C$^{\beta i}$H(CH$_3$)$_2$), 3.78 (s, 3H, furan^{i+1}-2-CO$_2$C**H$_3$**), 3.59 (d, ^{3}J = 7.6 Hz, 1H, C$^{\alpha i}$HN**H**), 2.01 (m, 1H, C$^{\alpha i+1}$HC$^{\beta i+1}$**H**(CH$_3$)$_2$), 1.92 (m, 1H, C$^{\alpha i}$HC$^{\beta i}$**H**(CH$_3$)$_2$), 1.14 (s, 9H, SC(C**H$_3$**)$_3$), 1.00 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha i+1}$HC$^{\beta i+1}$H(C**H$_3$**)$_2$), 0.97 (d, ^{3}J = 6.8 Hz, 3H, C$^{\alpha i+1}$HC$^{\beta i+1}$H(C**H$_3$**)$_2$), 0.95 (d, ^{3}J = 6.7 Hz, 6H, C$^{\alpha i}$HC$^{\beta i}$H(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, Chloroform-*d*): δ = 158.2 (furan^{i+1}-2-**C**O$_2$CH$_3$), 156.6 (furan^{i}-2-**C**ONH) 147.1 (furan^{i}-**C**-2), 144.2 (furan^{i+1}-**C**-2), 139.6 (furan^{i+1}-**C**-5), 137.7 (furan^{i}-**C**-5), 118.6 (furan^{i+1}-**C**-3), 117.3 (furan^{i}-**C**-3), 116.6 (furan^{i+1}-**C**-4), 115.7 (furan^{i}-**C**-4), 93.8 (C$^{\alpha i}$H**C**≡C-furan^{i}), 93.4 (C$^{\alpha i+1}$H**C**≡C-furan^{i+1}), 74.9 (C$^{\alpha i}$HC≡**C**-furan^{i}), 73.4 (C$^{\alpha i+1}$HC≡**C**-furan^{i+1}), 56.4 (S**C**(CH$_3$)$_3$), 54.4 (**C$^{\alpha i}$**HC$^{\beta i}$H(CH$_3$)$_2$), 52.0 (furan^{i+1}-2-CO$_2$**C**H$_3$), 47.4 (**C$^{\alpha i+1}$**HC$^{\beta i+1}$H(CH$_3$)$_2$), 33.9 (C$^{\alpha i}$H**C$^{\beta i}$**H(CH$_3$)$_2$), 33.1 (C$^{\alpha i+1}$H**C$^{\beta i+1}$**H(CH$_3$)$_2$), 22.5 (SC(**C**H$_3$)$_3$), 18.9 (C$^{\alpha i}$HC$^{\beta i}$H(**C**H$_3$)$_2$, C$^{\alpha i+1}$HC$^{\beta i+1}$H(**C**H$_3$)$_2$), 18.2 (C$^{\alpha i+1}$HC$^{\beta i+1}$H(**C**H$_3$)$_2$), 17.8 (C$^{\alpha i+1}$HC$^{\beta i+1}$H(**C**H$_3$)$_2$). C$_{27}$H$_{34}$N$_2$O$_6$S (514.64 g mol^{-1}). MS(ESI): *m/z* = 515.6 (calcd. 515.22 [M+H]$^{+}$), 537.7 (calcd. 537.20 [M+Na]$^{+}$). TLC: R*f* (PE/EtOAc, 1:1) = 0.38.



5-((*S*)-3-(5-((*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-methylpent-1-yn-1-yl)furan-2-carboxamido)-4-methylpent-1-yn-1-yl)furan-2-carboxylate (59b). An aqueous solution of LiOH (1 M, 5.0 mL, 5.0 mmol) was added dropwise to a solution of dimer **59a** (24.8 mg, 46.6 µmol, 1.0 eq) in MeOH (10 mL) at 0 °C and the reaction mixture was stirred for 6 h at 0 °C. An aqueous KHSO$_4$ solution (5 %, ca. 10 mL) was added to adjust the pH value to 1-2. The solution was extracted with Et$_2$O (4 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent evaporated under reduced pressure. Dimer **59b** (15.4 mg, 29.8 µmol 64 %) was isolated by preparative HPLC.



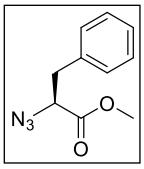
Colorless, highly viscous oil. Yield: 17.1 mg, 34.5 mmol, 34 %. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.07 (d, ^{3}J = 8.5 Hz, 1H, CON**H**C$^{\alpha i+1}$H), 7.49 (d, ^{3}J = 8.9 Hz, 1H, CON**H**C$^{\alpha I}$H), 7.24 (d, ^{3}J = 3.6 Hz, 1H, furan^{i}-3-**H**), 7.23 (d, ^{3}J = 3.6 Hz, 1H, furan^{i+1}-3-**H**), 6.92 (d, ^{3}J = 3.6 Hz, 1H, furan^{i+1}-4-**H**), 6.88 (d, ^{3}J = 3.6 Hz, 1H, furan^{i}-4-**H**), 4.77 (dd, ^{3}J = 8.2 Hz, ^{3}J = 6.8 Hz, 1H, C$^{\alpha i+1}$**H**), 4.32 (dd, ^{3}J = 8.0 Hz, ^{3}J = 6.5 Hz, 1H, C$^{\alpha I}$**H**), 2.05 (m, 1H, C$^{\alpha i+1}$HC$^{\beta}$**H**(CH$_3$)$_2$), 1.86 (dh, ^{3}J = 7.6 Hz, ^{3}J = 6.8 Hz, 1H, C$^{\alpha I}$HC$^{\beta}$**H**(CH$_3$)$_2$), 1.39 (s, 9H, CO$_2$C(C**H$_3$**)$_3$), 1.05 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha i+1}$HC$^{\beta}$H(C**H$_3$**)$_2$), 0.98 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha I}$HC$^{\beta}$H(C**H$_3$**)$_2$), 0.95 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha i+1}$HC$^{\beta}$H(C**H$_3$**)$_2$), 0.93 (d, ^{3}J = 6.9 Hz, 3H, C$^{\alpha I}$HC$^{\beta}$H(C**H$_3$**)$_2$). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 158.7 (**C**O$_2$H), 156.5 (**C**ONH), 155.2 (NH**C**O$_2$C(CH$_3$)$_3$), 147.3 (furan^{i}-**C**-2), 145.2 (furan^{i+1}-**C**-2), 138.5 (furan^{i+1}-**C**-5), 137.4 (furan^{i}-**C**-5), 118.7 (furan^{i+1}-**C**-3), 117.3 (furan^{i+1}-**C**-4), 117.1 (furan^{i}-**C**-4), 115.4 (furan^{i}-**C**-3), 95.3 (C$^{\alpha I}$H**C**≡C-furan), 94.8 (C$^{\alpha i+1}$H**C**≡C-furan), 78.6 (CO$_2$**C**(CH$_3$)$_3$), 72.6 (C$^{\alpha I}$HC≡**C**-furan), 72.6 (C$^{\alpha i+1}$HC≡**C**-furan), 49.0 (**C$^{\alpha I}$**HC$^{\beta}$H(CH$_3$)$_2$), 47.2 (**C$^{\alpha i+1}$**HC$^{\beta}$H(CH$_3$)$_2$), 32.7 (C$^{\alpha I}$H**C$^{\beta}$**H(CH$_3$)$_2$), 32.4 (C$^{\alpha i+1}$H**C$^{\beta}$**H(CH$_3$)$_2$), 28.3 (CO$_2$C(**C**H$_3$)$_3$), 19.1 (C$^{\alpha i+1}$HC$^{\beta}$H(**C**H$_3$)$_2$), 19.0 (C$^{\alpha I}$HC$^{\beta}$H(**C**H$_3$)$_2$, C$^{\alpha i+1}$HC$^{\beta}$H(**C**H$_3$)$_2$), 18.7 (C$^{\alpha I}$HC$^{\beta}$H(**C**H$_3$)$_2$). $C_{27}H_{32}N_2O_7$ (496.56 g mol^{-1}). MS(MALDI): *m/z* = 497.7 (calcd. 497.2282 [M+H]$^{+}$), 519.8 (calcd. 519.2102 [M+Na]$^{+}$). TLC: R*f* (PE/EtOAc, 1:1) = 0.2.

The dimerization of dimer **57a** giving tetramer **60** has been reported in detail in the master thesis [117].

IIX-3. g) Triazole-Based Peptidomimetics (61-63)

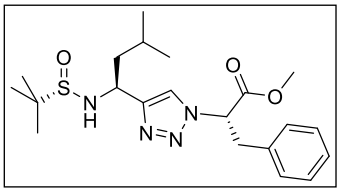
Methyl (*S*)-2-Azido-3-phenylpropanoate (61). The synthesis of the phenylalanine-based azide **61** was performed as reported by Ri-Bai et al. [234]: Trifluormethanesulfonic anhydride (0.36 mL, 604 mg, 2.14 mmol, 1.5 eq) was added to a vigorously stirred solution of NaN_3 (140.4 mg, 2.160 mmol, 1.5 eq) in CH_3CN (5.5 mL). The reaction mixture was stirred for 2 h at room temperature, before methyl (*S*)-phenylalaninate hydrochloride (300 mg, 1.391 mmol, 1.0 eq) was added in one portion. After another 2 h, the starting

material was consumed completely (checked by TLC) and an aqueous solution of $KHSO_4$ (5 %, 30 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 30 mL), the organic layers were combined, dried over Na_2SO_4 and filtered. After evaporation of the solvent, azide **61** was adsorbed on silica and purified by filtration through a short column of silica gel (PE/EtOAc, 10:1).



Pale green oil. Yield: 129.1 mg, 629 μmol, 45 % (Lit: 95 % [234]). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.32 (t, ^3J = 7.7 Hz, 2H, ar-3-**H**, ar-5-**H**), 7.26 (t, ^3J = 7.0 Hz, 1H, ar-4-**H**), 7.22 (d, ^3J = 7.6 Hz, 2H, ar-2-**H**, ar-6-**H**), 4.07 (dd, ^3J = 8.8 Hz, ^3J = 5.5 Hz, 1H, $N_3C^{\alpha}\mathbf{H}C^{\beta}H_2Ph$), 3.77 (s, 3H, $CO_2C\mathbf{H_3}$), 3.18 (dd, ^2J = 13.9 Hz, ^3J = 5.5 Hz, 1H, $N_3C^{\alpha}HC^{\beta}\mathbf{H}_2Ph$), 3.00 (dd, ^2J = 13.9 Hz, ^3J = 8.7 Hz, 1H, $N_3C^{\alpha}HC^{\beta}\mathbf{H}_2Ph$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.6 ($N_3C^{\alpha}H\mathbf{C}O_2CH_3$), 136.0 (Ph-**C**-1), 129.3 (Ph-**C**-2, Ph-**C**-6), 128.8 (Ph-**C**-3, Ph-**C**-5), 127.4 (Ph-**C**-4), 63.4 ($N_3\mathbf{C^{\alpha}}HC^{\beta}H_2Ph$), 52.8 ($N_3C^{\alpha}HCO_2\mathbf{C}H_3$), 37.8 ($N_3C^{\alpha}H\mathbf{C^{\beta}}H_2Ph$). $C_{10}H_{11}N_3O_2$ (205.22 g mol^{-1}). TLC: R*f* (PE/EtOAc, 4:1) = 0.77.

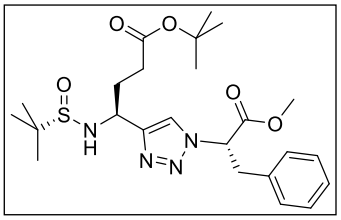
Methyl (*S*)-2-(4-((*S*)-1-(((*S*)-*tert*-Butylsulfinyl)amino)-3-methylbutyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropanoate (62a). $CuSO_4$ x 5 H_2O (77 mg, 308 μmol, 0.5 eq) and sodium ascorbate (123 mg, 621 μmol, 1.0 eq) were added in one portion to a vigorously stirred solution of leucine analogous propargylamide **6c** (132 mg, 613 μmol, 1.0 eq) and phenylalanine analogous azide **61** (198 mg, 965 μmol, 1.5 eq) in DMF/H_2O (10:1, 6 mL). The reaction mixture was stirred for 18 h at ambient temperature, diluted with brine (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with H_2O (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Triazole **62b** was isolated by column chromatography (PE/EtOAc, 1:1).



Conversion: 62 % of propargylamine **6c**. Colorless, highly viscous oil. Yield: 97.2 mg, 231 μmol, 38 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.70 (s, 1H, triazol-5-**H**), 7.25-7.17 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 7.04 (d, ^3J = 7.2 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 5.51 (ddd, ^3J = 8.9 Hz, ^3J = 6.4 Hz, ^3J = 8.1 Hz, 1H, Phe-C^{α}**H**), 4.51 (dd, ^3J = 7.5 Hz, ^3J = 7.4 Hz, 1H, Leu-C^{α}**H**), 3.74 (s, 3H, $CO_2C\mathbf{H_3}$), 3.60 (d, ^3J = 8.1 Hz, 1H, Phe-C^{α}HN**H**), 3.50 (dd, ^2J = 14.0 Hz, ^3J = 6.4 Hz, 1H, Phe-$C^{\alpha}HC^{\beta}\mathbf{H}_2Ph$), 3.44 (dd, ^2J

= 13.8 Hz, ^3J = 8.9 Hz, 1H, Phe-C$^{\alpha}$HC$^{\beta}$**H**$_2$), 1.83 (dd, ^3J = 7.5 Hz, ^3J = 7.2 Hz, 2H, Leu-C$^{\alpha}$HC$^{\beta}$**H**$_2$), 1.69-1.57 (m, 1H, Leu-C$^{\alpha}$HC$^{\beta}$HC$^{\gamma}$**H**(CH$_3$)$_2$), 1.21 (s, 9H, SC(C**H**$_3$)$_3$), 0.92 (d, ^3J = 6.7 Hz, 3H, C$^{\gamma}$H(C**H**$_3$)$_2$), 0.90 (d, ^3J = 6.4 Hz, 3H, C$^{\gamma}$H(C**H**$_3$)$_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 168.8 (Phe-C$^{\alpha}$H**C**O$_2$CH$_3$), 150.0 (triazol-**C**-4), 134.9 (Ph-**C**-1), 129.2 (Ph-**C**-3, Ph-**C**-5), 128.9 (Ph-**C**-2, Ph-**C**-6), 127.6 (Ph-**C**-4), 122.2 (triazol-**C**-5), 64.2 (Phe-**C$^{\alpha}$**H), 56.4 (S**C**(CH$_3$)$_3$), 53.2 (CO$_2$**C**H$_3$), 51.4 (Leu-**C$^{\alpha}$**H), 45.3 (Leu-C$^{\alpha}$H**C$^{\beta}$**H$_2$), 39.0 (Phe-C$^{\alpha}$H**C$^{\beta}$**H$_2$), 24.3 (Leu-C$^{\alpha}$HC$^{\beta}$H**C$^{\gamma}$**H(CH$_3$)$_2$), 22.8 (SC(**C**H$_3$)$_3$), 22.6 (C$^{\gamma}$H(**C**H$_3$)$_2$), 22.0 (C$^{\gamma}$H(**C**H$_3$)$_2$). C$_{21}$H$_{32}$N$_4$O$_3$S (420.57 g mol^{-1}). LCMS(ESI): t*r* = 9.7 min, *m/z* = 421.22590 (calcd. 421.22679 [M+H]$^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.19.

***tert*-Butyl (*S*)-4-(((*S*)-*tert*-Butylsulfinyl)amino)-4-(1-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)-1H-1,2,3-triazol-4-yl)butanoate (62b).** CuSO$_4$ x 5 H$_2$O (40 mg, 160 µmol, 0.5 eq) and sodium ascorbate (66 mg, 333 µmol, 1.1 eq) were added in one portion to a vigorously stirred solution of glutamic acid analogous propargylamide **6l** (86.6 mg, 301 µmol, 1.0 eq) and phenylalanine analogous azide **61** (100 mg, 487 µmol, 1.6 eq) in DMF/H$_2$O (10:1, 3 mL). The reaction mixture was stirred for 18 h at ambient temperature, diluted with brine (40 mL) and extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined organic layers were washed with water (40 mL), dried over MgSO$_4$ and the solvent was evaporated under reduced pressure. The crude triazole **62b** was purified by column chromatography (PE/EtOAc, 1:1, then CH$_2$Cl$_2$/MeOH, 10:1).



Recovered propargylamide **6l** (33.7 mg, 39 %), conversion: 61 %. Colorless solid. Yield: 32.6 mg, 66.2 µmol, 22 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.70 (s, 1H, triazol-5-**H**), 7.35-7.09 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 7.02 (d, ^3J = 7.2 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 5.51 (dd, ^3J = 8.4 Hz, ^3J = 6.3 Hz, 1H, Phe-C$^{\alpha}$**H**), 4.53 (ddd, ^3J = 7.0 Hz, ^3J = 5.6 Hz, ^3J = 7.7 Hz, 1H, Glu-C$^{\alpha}$**H**), 3.92 (d, ^3J = 7.7 Hz, 1H, Glu-C$^{\alpha}$HN**H**), 3.73 (s, 3H, Phe-C$^{\alpha}$HCO$_2$C**H**$_3$), 3.50 (dd, ^2J = 14.2 Hz, ^3J = 6.4 Hz, 1H, Phe-C$^{\alpha}$HC$^{\beta}$**H**$_2$Ph), 3.43 (dd, ^2J = 14.2 Hz, ^3J = 8.7 Hz, 1H, Phe-C$^{\alpha}$HC$^{\beta}$**H**$_2$Ph), 2.32-2.22 (m, 2H, Glu-C$^{\alpha}$HC$^{\beta}$**H**$_2$), 2.20-2.11 (m, 2H, Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$**H**$_2$), 1.43 (s, 9H, Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$CO$_2$C(C**H**$_3$)$_3$), 1.22 (s, 9H, SC(C**H**$_3$)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 172.5 (Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$**C**O$_2$C(CH$_3$)$_3$), 168.7 (Phe-C$^{\alpha}$H**C**O$_2$CH$_3$), 149.0 (triazol-**C**-

4), 134.9 (Ph-**C**-1), 129.1 (Ph-**C**-3, Ph-**C**-5), 128.9 (Ph-**C**-2, Ph-**C**-6), 127.6 (Ph-**C**-4), 122.3 (triazol-**C**-5), 80.7 ($CO_2\mathbf{C}(CH_3)_3$), 64.2 (Phe-$\mathbf{C}^{\alpha}$H), 56.4 (S$\mathbf{C}(CH_3)_3$), 53.2 ($CO_2\mathbf{C}H_3$), 52.3 (Glu-$\mathbf{C}^{\alpha}$H), 38.9 (Phe-$C^{\alpha}H\mathbf{C}^{\beta}H_2Ph$), 31.7 (Glu-$C^{\alpha}HC^{\beta}H_2\mathbf{C}^{\gamma}H_2$), 31.3 (Glu-$C^{\alpha}H\mathbf{C}^{\beta}H_2C^{\gamma}H_2$), 28.2 ($CO_2C(\mathbf{C}H_3)_3$), 22.8 ($SC(\mathbf{C}H_3)_3$). $C_{24}H_{36}N_4O_5S$ (492.64 g mol^{-1}). LCMS(ESI): t*r* = 9.8 min, *m/z* = 493.24740 (calcd. 493.24792 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.33, R*f* (CH_2Cl_2/MeOH, 10:1) = 0.70.

Methyl (*S*)-2-(4-((*S*)-1-Amino-3-methylbutyl)-1H-1,2,3-triazol-1-yl)-3-phenylpropanoate Trifluoroacetate (63a). A hydrochloride solution (4 M in dioxane, 0.1 mL) was added dropwise to a solution of triazole **62a** in MeOH (2.5 mL). After stirring the reaction mixture at room temperature overnight, the solvent was evaporated under reduced pressure at 40 °C. The colorless solid residue was dissolved in MeOH (1 mL) and purified by preparative HPLC. Colorless, amorpheous solid. Yield: 24.16 mg, 56.1 µmol, 24 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.39 (s, 3H, $[C^{\alpha}HN\mathbf{H_3}]^+$), 8.24 (s, 1H, triazol-5-**H**), 7.20-7.13 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 7.09 (d, ^3J = 6.5 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 5.93 (dd, ^2J = 11.0 Hz, ^3J = 4.4 Hz, 1H, Phe-$C^{\alpha}\mathbf{H}CH_2$), 4.37 (dd br., ^3J = 9.9 Hz, ^3J = 5.0 Hz, 1H, Leu-$C^{\alpha}\mathbf{H}CH_2$), 3.72 (s, 3H, $CO_2C\mathbf{H_3}$), 3.58 (dd, ^2J = 14.1 Hz, ^3J = 4.5 Hz, 1H, Phe-$C^{\alpha}HC\mathbf{H}_2Ph$), 3.46 (dd, ^2J = 14.1 Hz, ^3J = 11.5 Hz, 1H, Phe-$C^{\alpha}HC\mathbf{H}_2Ph$), 1.78 (m, 1H, Leu-$C^{\alpha}HC\mathbf{H}_2$), 1.62 (m, 1H, Leu-$C^{\alpha}HC\mathbf{H}_2$), 1.12 (m, 1H, Leu-$C^{\alpha}HCH_2C\mathbf{H}(CH_3)_2$), 0.81 (d, ^3J = 6.8 Hz, 3H, $C^{\gamma}H(C\mathbf{H_3})_2$), 0.76 (d, ^3J = 6.3 Hz, 3H, $C^{\gamma}H(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 168.6 (Phe-$C^{\alpha}H\mathbf{C}O_2CH_3$), 158.1 (q, $^2J_{CF}$ = 30.97 Hz, $[CF_3\mathbf{C}O_2]^-$), 143.5 (triazol-**C**-4), 135.6 (Ph-**C**-1), 128.9 (Ph-**C**-3, Ph-**C**-5), 128.3 (Ph-**C**-2, Ph-**C**-6), 126.9 (Ph-**C**-4), 124.3 (triazol-**C**-5), 117.3 (q, $^1J_{CF}$ = 300.31 Hz, $[\mathbf{C}F_3CO_2]^-$), 63.1 (Phe-$\mathbf{C}^{\alpha}$H), 53.0 (Phe-$C^{\alpha}HCO_2\mathbf{C}H_3$), 45.0 (Leu-$\mathbf{C}^{\alpha}$H), 41.8 (Leu-$C^{\alpha}H\mathbf{C}^{\beta}H_2$), 36.8 (Phe-$C^{\alpha}H\mathbf{C}^{\beta}H_2$), 23.9 (Leu-$\mathbf{C}^{\gamma}H(CH_3)_2$), 22.9 (Leu-$C^{\gamma}H(\mathbf{C}H_3)_2$), 21.2 (Leu-$C^{\gamma}H(\mathbf{C}H_3)_2$). $C_{19}H_{25}F_3N_4O_4$ (430.63 g mol^{-1}). LCMS(ESI): t*r* = 6.0 min, *m/z* = 317.2004 (calcd. 317.1972 $[M+H]^+$), 339.1856 (calcd. 339.1791 $[M+Na]^+$).

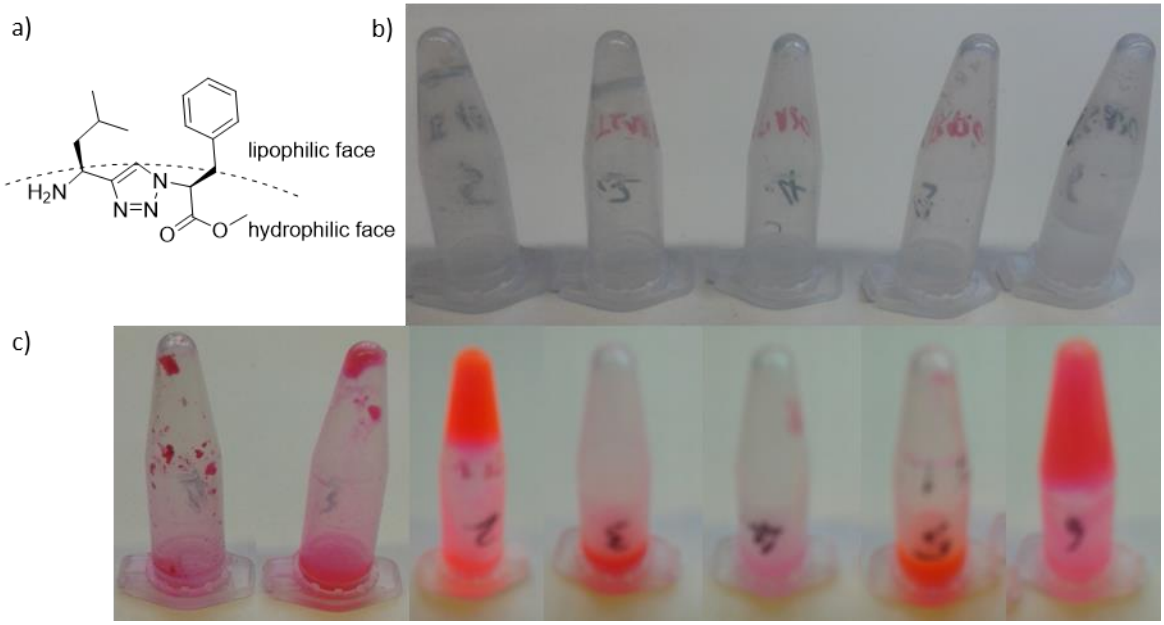
Gelation experiments with H-Leu-Phe-OMe analogue **63a**.

Buffer solution. 14.8 mL of KH_2PO_4 (907.8 mg in 100 mL H_2O) + 85.2 mL of Na_2HPO_4 x 2 H_2O (1.4890 g in 100 mL H_2O) -> 100 mL buffer at pH 7.4.

Samples: 100 mg mL^{-1} (10 % w/v): 4.83 mg in 48.3 µL buffer solution. 75 mg mL^{-1} (7.5 % w/v): 4.55 mg in 113.8 µL buffer solution. 50 mg mL^{-1} (5 % w/v): 3.97 mg in 198.5 µL buffer solution. 25 mg mL^{-1} (2.5 % w/v): 2.97 mg in 222.8 µL buffer solution. 10 mg mL^{-1} (1 % w/v): 7.15 mg in 715 µL buffer solution.

Procedure: 1) Vortex. 2) Sonication at 40 °C, 5 min. 3) store in fridge -20 °C, 30 min, then 4 °C overnight. 4) 40 °C for 20 min. 5) -20 °C for 1 h and ice stored overnight at 4 °C. 30 min rt. The procedure was repeated once with all samples, in which no hydrogelation had occurred. Results are visualized in picture EP2b. Hydrogelation only occurred at high concentrations. Minium gel concentration (MGC) was between 75 and 50 mg.

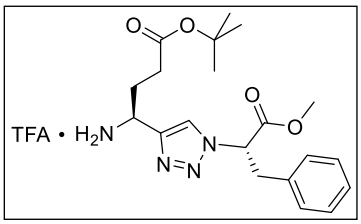
Other solvents: All samples were prepared with a concentration of 10 mg mL^{-1} in varied solvents. Rhodamin B (10 µL, 280 nM, 2.8 nmol) was added to each sample for visualization. Results are summed up in picture EP2c. Gel formation was observed in solutions of CH_2Cl_2 (MGC < 0.5 % w/v) and ^{i}PrOH (MGC < 0.5 % w/v).



Picture EP2. Gelation experiments with superhydrogelinducing H-Leu-Phe-OMe mimetic **63a**. a) Visualization of amphiphilicity in the appropriate conformation for an alignment of polar- and nonpolar regions on one side, each. b) Photography of inverted-tube method. Samples in aqueous buffer solution at pH 7.4 are ordered in increasing dilution from left to right: 100 mg mL^{-1} hydrogel, 75 mg mL^{-1} hydrogel, 50 mg mL^{-1} precipitate, 25 mg mL^{-1} precipitate, 10 mg mL^{-1} precipitate. c) Photography of inverted tube method with a

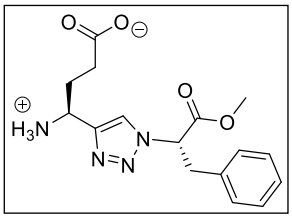
concentration of 10 mg mL^{-1} in different solvents, ordered with increasing polarity from left to right: CH_3CN precipitate, Et_2O precipitate, CH_2Cl_2 hydrogel, $CHCl_3$ solution, EtOAc suspension, MeOH solution, ^{i}PrOH hydrogel. Samples have been visualized by addition of Rhodamin B (10 µL, 280 nM, 2.8 nmol in each vial).

***tert*-Butyl (*S*)-4-Amino-4-(1-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)-1H-1,2,3-triazol-4-yl)butanoate Trifluoroacetate (63b).** A solution of hydrochloric acid (4 M in dioxane, 0.1 mL, 0.4 mmol) was added dropwise to a vigorously stirred, icecold solution of triazole **62b** (97.2 mg, 231 µmol) in MeOH (2.5 mL). The reaction mixture was stirred overnight at ambient temperature, before evaporating the solvent under reduced pressure. The crude amine **63b** was diluted with MeOH and the residual solvent was coevaporated.

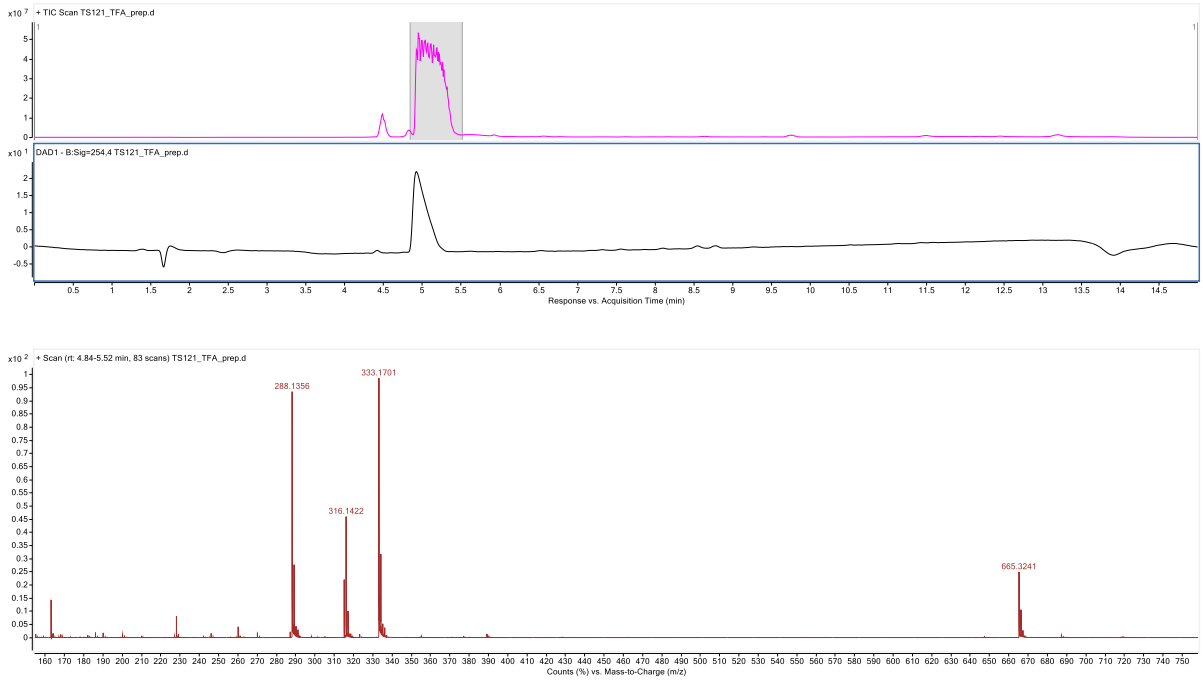


Colorless solid. Yield: quantitative. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 8.08 (s, 1H, triazol-5-**H**), 7.35-7.03 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 7.09 (d, ^{3}J = 7.3 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 5.81 (dd, ^{3}J = 11.1 Hz, ^{3}J = 4.9 Hz, 1H, Phe-C$^{\alpha}$**H**), 4.53 (dd br., ^{3}J = 9.7 Hz, ^{3}J = 5.3 Hz, 1H, Glu-C$^{\alpha}$**H**), 3.79 (s, 3H, $CO_2C\mathbf{H_3}$), 3.67 (dd, ^{2}J = 14.3 Hz, ^{3}J = 5.0 Hz, 1H, Phe-C$^{\alpha}$HC$^{\beta}$C**H**$_2$Ph), 3.52 (dd, ^{2}J = 13.1 Hz, ^{3}J = 11.5 Hz, 1H, Phe-C$^{\alpha}$HC$^{\beta}$C**H**$_2$Ph), 2.28-2.17 (m, 2H, Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$**H$_2$**CO$_2$C(CH$_3$)$_3$), 2.12-2.06 (m, 2H, Glu-C$^{\alpha}$HC$^{\beta}$**H$_2$**C$^{\gamma}$H$_2$CO$_2$C(CH$_3$)$_3$), 1.45 (s, 9H, Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$CO$_2$C(C**H$_3$**)$_3$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 172.9 (Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$**C**O$_2$C(CH$_3$)$_3$), 169.9 (Phe-C$^{\alpha}$H**C**O$_2$CH$_3$), 143.7 (triazol-**C**-4), 136.8 (Ph-**C**-1), 130.0 (Ph-**C**-3, Ph-**C**-5), 129.7 (Ph-**C**-2, Ph-**C**-6), 128.3 (Ph-**C**-4), 125.8 (triazol-**C**-5), 82.2 (Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$CO$_2$**C**(CH$_3$)$_3$), 65.4 (Phe-**C$^{\alpha}$**H), 53.6 (CO$_2$**C**H$_3$), 47.8 (Glu-**C$^{\alpha}$**H), 38.8 (Phe-C$^{\alpha}$H**C$^{\beta}$**H$_2$Ph), 31.8 (Glu-C$^{\alpha}$H**C$^{\beta}$**H$_2$C$^{\gamma}$H$_2$CO$_2$), 29.5 (Glu-C$^{\alpha}$HC$^{\beta}$H$_2$**C$^{\gamma}$**H$_2$CO$_2$), 28.3 (Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$CO$_2$C(**C**H$_3$)$_3$). $C_{20}H_{29}ClN_4O_4$ (424.93 g mol^{-1}). LCMS(ESI): $tr_{(\text{polar method})}$ = 11.2 min, *m/z* = 389.2284 (calcd. 389.2183 $[M\text{-}Cl+H]^{+}$).

(*S*)-4-Amino-4-(1-((*S*)-1-methoxycarbonyl-3-phenylpropan-2-yl)-1H-1,2,3-triazol-4-yl)butanoic Acid (63c). Triazole **63b** (231 µmol) was dissolved in a mixture of TFA/TIPS/H_2O (95:2.5:2.5, 2 mL) and stirred overnight at ambient temperature. After complete conversion (checked by LCMS), the crude amine **63c** was precipitated with icecold Et_2O (10 mL), centrifuged and isolated in form of a colorless solid, which was purified by preparative HPLC.



Colorless crystalline solid. Yield: 12.45 mg, 37.46 µmol, 57 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.33 (s, 1H, Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$CO$_2$**H**), 8.44 (s, 3H, Glu-C$^{\alpha}$HN**H$_3$**$^{+}$), 8.26 (s, 1H, triazol-5-**H**), 7.33-7.03 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 7.09 (d, ^{3}J = 7.2 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 5.94 (dd, ^{3}J = 11.2 Hz, ^{3}J = 4.9 Hz, 1H, Phe-C$^{\alpha}$**H**), 4.44 (m, 1H, Glu-C$^{\alpha}$**H**), 3.72 (s, 3H, Phe-C$^{\alpha}$HCO$_2$C**H$_3$**), 3.59 (dd, ^{2}J = 14.3 Hz, ^{3}J = 4.9 Hz, 1H, Phe-C$^{\alpha}$HC$^{\beta}$**H**$_2$Ph), 3.47 (dd, ^{2}J = 14.4 Hz, ^{3}J = 10.9 Hz, 1H, Phe-C$^{\alpha}$HC$^{\beta}$**H**$_2$Ph), 2.15-1.98 (m, 4H, Glu-C$^{\alpha}$HC$^{\beta}$**H$_2$**C$^{\gamma}$**H$_2$**CO$_2$). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 173.3 (Glu-C$^{\alpha}$HC$^{\beta}$H$_2$C$^{\gamma}$H$_2$**C**O$_2$H), 168.5 (Phe-C$^{\alpha}$HCO$_2$**H**), 142.9 (triazol-**C**-4), 135.6 (Ph-**C**-1), 128.9 (Ph-**C**-3, Ph-**C**-5), 128.3 (Ph-**C**-2, Ph-**C**-6), 126.9 (Ph-**C**-4), 124.3 (triazol-**C**-5), 63.2 (Phe-**C$^{\alpha}$**H), 53.0 (Phe-C$^{\alpha}$HCO$_2$**C**H$_3$), 45.8 (Glu-**C$^{\alpha}$**H), 36.8 (Phe-C$^{\alpha}$H**C$^{\beta}$**H$_2$), 29.3 (Glu-C$^{\alpha}$HC$^{\beta}$H$_2$**C$^{\gamma}$**H$_2$CO$_2$), 28.2 (Glu-C$^{\alpha}$H**C$^{\beta}$**H$_2$C$^{\gamma}$H$_2$CO$_2$). C$_{16}$H$_{20}$N$_4$O$_4$ (332.36 g mol^{-1}). LCMS(ESI): $tr_{(\text{polar method})}$ = 333.1701 (calcd. 333.1557 [M+H]$^{+}$), 355.1491 (calcd. 355.1377 [M+Na]$^{+}$).

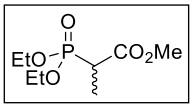


Scheme EP1. Analytical chromatogram and mass spectra of aspartame analogue 63c to prove its purity.

IIX-3. h) Synthesis of Olefin Halides (64-72)

4-Methoxybenzaldehyde (**64**) was purchased from Fisher Scientific.

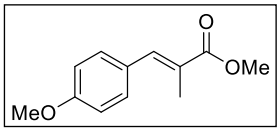
Methyl-2-(diethoxyphosphoryl)propanoate (65). The *Michaelis-Arburzov* reaction was performed following the description in the Organikum [235]: $P(OEt)_3$ (21.66 mL, 179 mmol) was added to a solution of methyl 2-bromopropanoate (20.0 mL, 179 mmol) in dry toluene (300 mL) at 0 °C. The reaction mixture was heated for 3 d to 120 °C under reflux conditions. Afterwards, the solvent was evaporated and the crude product was isolated by distillation (p = 5.3 mbar, T_k = 125 °C).



Colorless fluid. Yield: 12.93 g, 57.68 mmol, 32 %, dr = 1:1. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 4.19-4.06 (m, 4H, POC**H**$_2$CH$_3$), 3.74 (s, 3H, CO_2C**H**$_3$), 3.03 (dq, $^2J_{HP}$ = 23.5 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, POC**H**CH$_3$), 1.43 (dd, $^3J_{HP}$ = 18.0 Hz, $^3J_{HH}$ = 7.3 Hz, 3H, POCHC**H**$_3$), 1.32 (td, $^3J_{HH}$ = 7.1 Hz, $^4J_{HP}$ = 2.6 Hz, 6H, $POCH_2C$**H**$_3$). ^{31}P NMR (202 MHz, Chloroform-*d*) δ = 23.6. ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.4 (d, $^2J_{CP}$ = 4.8 Hz, CH**C**O_2CH_3), 62.8 (d, $^2J_{CP}$ = 6.7 Hz, PO**C**H_2CH_3), 52.6 (s, CO_2**C**H_3), 39.4 (d, $^1J_{CP}$ = 133.6 Hz, PO**C**HCH_3), 16.5 (d, $^3J_{CP}$ = 4.9 Hz, $POCH_2$**C**H_3), 11.9 (d, $^2J_{CP}$ = 6.3 Hz, $POCH_2$**C**H_3). $C_8H_{17}O_5P$ (224.19 g mol^{-1}). T_k = 125 °C (p = 5.3 mbar).

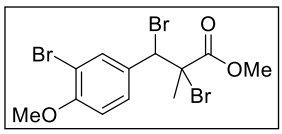
Methyl (*E*)-3-(4-Methoxyphenyl)-2-methylacrylate (66). The preparation of **66** has been described before by Li Ze-Yu *et al.* under different conditions [236]. An ^{n}BuLi solution (1.6 M in hexanes, 4.1 mL, 6.6 mmol, 1.2 eq) was added dropwise to a solution of methyl-2-(diethoxyphosphoryl)propanoate (1.5 g, 6.6 mmol, 1.2 eq) in THF (10 mL) at -78 °C. After 15 min stirring at -78 °C, 4-methoxy-benzaldehyde (0.70 mL, 5.5 mmol, 1.0 eq) was carefully added and the reaction mixture was stirred for another 15 min at -78 °C bevore warming up to rt. The slightly yellow suspension was stirred for 12 h at ambient temperature, then diluted with an aqueous NH_4Cl solution (saturated, 10 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give olefin **66** in pure form.

Colorless fluid. Yield: 1.4 g, quantitative. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.62 (s, 1H, ar-C**H**=C(CH_3)CO_2CH_3), 7.35 (d, ^3J = 8.1 Hz, 2H, ar-3-**H**, ar-5-**H**), 6.89 (d, ^3J = 8.8 Hz, 2H, ar-2-**H**, ar-6-**H**), 3.79 (s, 3H, ar-



OC**H**$_3$), 3.77 (s, 3H, ar-CH=C(CH$_3$)CO$_2$C**H**$_3$), 2.10 (s, 3H, ar-CH=C(C**H**$_3$)CO$_2$CH$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 169.4 (ar-CH=C(CH$_3$)**C**O$_2$CH$_3$), 159.7 (ar-**C**-1), 138.7 (ar-**C**H=C(CH$_3$)CO$_2$CH$_3$), 131.5 (ar-**C**-3, ar-**C**-5), 128.4 (ar-CH=**C**(CH$_3$)CO$_2$CH$_3$), 126.0 (ar-**C**-4), 113.9 (ar-**C**-2, ar-**C**-6), 55.3 (ar-1-O**C**H$_3$), 52.0 (ar-CH=C(CH$_3$)CO$_2$**C**H$_3$), 14.1 (ar-CH=C(**C**H$_3$)CO$_2$CH$_3$). C$_{12}$H$_{14}$O$_3$ (206.24 g mol^{-1}).

Methyl 2,3-Dibromo-3-(3-bromo-4-methoxyphenyl)-2-methylpropanoate (67). A



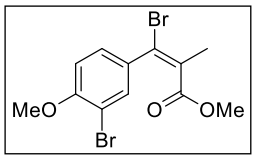
solution of bromine (0.8 mL, 15.3 mmol, 2.0 eq) in CH$_2$Cl$_2$ (5 mL) was added dropwise to a solution of olefin **66** (1.58 g, 7.66 mmol, 1.0 eq) in CH$_2$Cl$_2$ (20 mL) at -78 °C, until the brown color of the reaction mixture stopped vanishing. The purple solution was stirred for 2 h at -78 °C and then 30 min at ambient temperature. Water (20 mL) and an aqueous Na$_2$SO$_3$ solution was added until the the red color had completely disappeared. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL) dried over Na$_2$SO$_4$ and the solvent was evaporated under reduced pressure. The crude dibromide **67** was purified by column chromatography (PE/EtOAc, 25:1).

Colorless, crystalline solid. Yield: 3.05 g, 6.86 mmol, 90 %. dr = 37:63. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.66 (d, ^4J = 2.4 Hz, 1H, ar-6-**H**), 7.40 (dd, ^3J = 8.7 Hz, ^4J = 2.4 Hz, 1H, ar-4-**H**), 6.81 (d, ^3J = 8.6 Hz, 1H, ar-3-**H**), 5.55 (s, 1H, ar-C**H**Br-C(Br)CH$_3$), 3.89 (s, 3H, ar-C**H**Br-C(Br)C**H**$_3$), 3.76 (s, 3H, ar-2-OC**H**$_3$), 2.02 (s, 3H, ar-CHBr-C(Br)C**H**$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 169.1 (ar-CHBr-C(Br)**C**O$_2$CH$_3$), 156.4 (ar-**C**-2), 134.7 (ar-**C**-6), 130.2 (ar-**C**-4), 129.7 (ar-**C**-5), 113.3 (ar-**C**-1), 111.2 (ar-**C**-3), 64.8 (ar-CHBr-**C**(Br)CO$_2$CH$_3$), 59.3 (ar-**C**HBr-C(Br)CO$_2$CH$_3$), 56.4 (ar-2-O**C**H$_3$), 53.6 (ar-CHBr-C(Br)CO$_2$**C**H$_3$), 25.7 (ar-CHBr-C(Br)**C**H$_3$). C$_{12}$H$_{13}$Br$_3$O$_3$ (444.95 g mol^{-1}). TLC: R*f* (PE/EtOAc, 25:1) = 0.22. X-ray crystal structure in Chapter IIX-3. n.

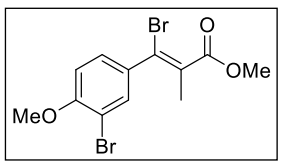
Methyl 3-Bromo-3-(3-bromo-4-methoxyphenyl)-2-methylacrylate (68). A solution of KO^{t}Bu (430 mg, 3.84 mmol, 1.5 eq) in dry THF (15 mL) was slowly added over a period of 30 min to a solution of dibromide **67** (927 mg, 2.54 mmol, 1.0 eq) in dry THF (25 mL) at -78 °C. The reaction mixture was stirred for 30 min at the same temperature before warming up to rt. After stirring the yellow suspension for 12 more hours at rt, water (10 mL)

and Na_2SO_3 (aq., sat., 5 mL) were added. The mixture was extracted with Et_2O (3 x 10 mL), washed with brine (5 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude *E/Z* mixture of **68** was separated by column chromatography (PE/EtOAc, 25:1). Yield: 163.4 mg, 450 µmol, 41%, *E/Z* = 37:63.

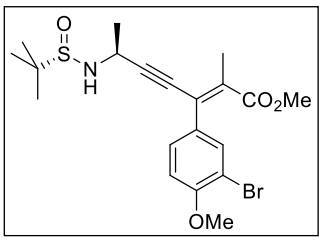
***E*-68**: Colorless, highly viscous oil. Yield: 98.1 mg, 270 µmol, 15 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.51 (d, ^4J = 2.3 Hz, 1H, ar-6-**H**), 7.23 (dd, ^3J = 8.5 Hz, ^4J = 2.3 Hz, 1H, ar-4-**H**), 6.83 (d, ^3J = 8.5 Hz, 1H, ar-3-**H**), 3.91 (s, 3H, ar-2-OC**H**$_3$), 3.52 (s, 3H, CO_2C**H**$_3$), 2.21 (d, ^4J = 1.7 Hz, 3H, BrC=CC**H**$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.8 (**C**O_2CH_3), 156.1 (ar-**C**-2), 134.3 (ar-**C**-), 133.2 (ar-**C**-), 131.4 (ar-**C**-), 131.0 (Br**C**=CCH_3), 128.6 (ar-**C**-), 113.9 (BrC=**C**CH_3), 111.0 (ar-**C**-), 56.3 (ar-2-O**C**H_3), 52.1 (CO_2**C**H_3), 21.6 (BrC=C**C**H_3). $C_{12}H_{12}Br_2O_3$ (364.03 g mol^{-1}).



***Z*-68**: Colorless, highly viscous oil. Yield: 65.3 g, 180 µmol, 26 %. ^{1}H NMR (600 MHz, Chloroform-*d*) δ = 7.55 (d, ^4J = 2.2 Hz, 1H, ar-2-**H**), 7.28 (d, ^4J = 2.2 Hz, 1H, ar-6-**H**), 6.89 (d, ^3J = 8.6 Hz, 1H, ar-5-**H**), 3.92 (s, 3H, COC**H**$_3$), 3.86 (s, 3H, CO_2C**H**$_3$), 1.90 (s, 3H, =CC**H**$_3$). ^{13}C NMR (151 MHz, Chloroform-*d*) δ = 169.2 (**C**O_2CH_3), 156.3 (ar-**C**-4), 133.8 (ar-**C**-2), 132.5 (ar-**C**-1), 132.1 (Br**C**=$C(CH_3)CO_2$), 129.4 (ar-**C**-6), 120.2 (BrC=**C**CH_3), 111.6 (ar-**C**-5), 56.5 (ar-2-CO**C**H_3), 52.5 (CO_2**C**H_3), 18.9 (BrC=C**C**H_3). $C_{12}H_{12}Br_2O_3$ (364.03 g mol^{-1}). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 2946 sh/m, 2838 w, 2366 w, 2337 w, 1714 s, 1590 m, 1492 s, 1483 s, 1454 m, 1438 m, 1283 s, 1249 s, 1213 m, 1128 m, 1055 m, 1024 m, 964 w, 916 w, 805 m, 761 m, 682 m.



Methyl (*S*,*E*)-3-(3-Bromo-4-methoxyphenyl)-6-(((*S*)-*tert*-butylsulfinyl)amino)-2-methylhept-2-en-4-ynoate (69). A solution of alanine analogous propargylamide **6a** (50 mg, 270 µmol, 1.0 eq) and vinylbromide ***E*-68** (98.1 mg, 270 µmol, 1.0 eq) in THF/piperidine (3:1, 0.66 mL) was thoroughly degassed by freeze pump thaw method. After adding the catalysts $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) to the solution, the reaction mixture was stirred 2 hours at rt and 2 more hours at 40 °C. Afterwards, the pale yellow solution was diluted with Et_2O (10 mL), washed with NH_4Cl solution (half concentrated, 6 mL) and aqueous HCl (1 M,



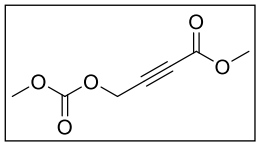
10 mL). The combined aqueous layers were extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (EtOAc/PE, 1:1).

Pale yellow, highly viscous oil. Yield: 6.2 mg, 14 μmol, 5 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.48 (d, ^4J = 2.2 Hz, 1H, ar-6-**H**), 7.23 (dd, ^3J = 8.5 Hz, ^4J = 2.2 Hz, 1H, ar-4-**H**), 6.83 (d, ^3J = 8.5 Hz, 1H, ar-3-**H**), 4.40 (dq, ^3J = 5.9 Hz, ^3J = 6.8 Hz, 1H, C$^{\alpha}$**H**), 3.89 (s, 3H, ar-OC**H$_3$**), 3.56 (s, 3H, CO_2C**H$_3$**), 3.37 (d, ^3J = 5.9 Hz, 1H, C$^{\alpha}$N**H**), 2.25 (s, 3H, C=CC**H$_3$**), 1.52 (d, ^3J = 6.8 Hz, 3H, C$^{\alpha}$HC**H$_3$**), 1.22 (s, 9H, SC(C**H$_3$**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 169.8 (**C**O_2CH_3), 155.8 (ar-**C**-2), 136.2 (ar-C=**C**-CO_2CH_3), 132.9 (ar-**C**-6), 132.0 (ar-**C**=C-CO_2CH_3), 128.4 (ar-**C**-4), 126.2 (ar-**C**-5), 111.4 (ar-**C**-3), 111.3 (ar-**C**-1), 100.0 (C$^{\alpha}$H**C**≡C), 82.7 (C$^{\alpha}$HC≡**C**), 56.4 (S**C**$(CH_3)_3$), 56.2 (ar-O**C**H_3), 52.0 (CO_2**C**H_3), 43.7 (**C$^{\alpha}$**H), 23.5 (C$^{\alpha}$**C**H_3), 22.6 (SC(**C**H_3)$_3$), 19.7 (C=C**C**H_3). $C_{20}H_{26}BrNO_4S$ (456.40 g mol^{-1}). MS(ESI): *m/z* = 456.173/458.979 (calcd. 456.0839/458.979 $[M+H]^+$), 478.163/480.125 (calcd. 478.0658/480.0638 $[M+Na]^+$). TLC: R*f* (EtOAc/PE 1:1) = 0.29.

IIX-3. i) Hydroalkynylation of Propynoates (73-75)

Propynoates **73a-c,e** were purchased from Fisher Scientific.

Methyl 4-((Methoxycarbonyl)oxy)but-2-ynoate (73d). The di-formiation of propargylic alcohol to form alkyne 73d as precursor for hydroalkinylation reactions has been previously reported by Trost et al. [130]. ^{n}Buthyllithium (1.6 M in hexanes, 5.7 mL 9.1 mmol, 2.1 eq) was added dropwise to a solution of propargylalcohol (250 μL, 243 mg, 4.33 mmol, 1.0 eq) in dry THF (10 mL) at -78 °C. After 30 min, methyl chloroformate (0.70 mL, 859 mg, 9.1 mmol, 2.1 eq) was carefully added to the vigorously solution at -78 °C. After complete conversion, the reaction mixture was allowed to warm up to rt and stirred for 2 h at ambient temperature. The solution was washed with water (3 x 10 mL) and brine (10 mL). After drying over Na_2SO_4, filtration end evaporation of the solvent, the crude alkyne **73d** was purified by column chromatography (PE/EtOAc, 4:1).

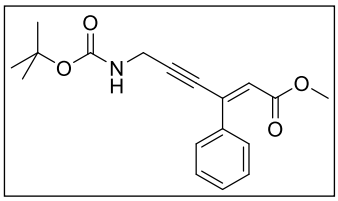


Colorless fluid. 306.7 mg, 1.782 mmol, 41 % (Lit: 49 % [130]). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 4.84 (s, 2H, C**H$_2$**), 3.83 (s, 3H, CH_2OCO_2C**H$_3$**), 3.78 (s, 3H, $CH_2C{\equiv}CCO_2C$**H$_3$**). ^{13}C NMR

(126 MHz, Chloroform-*d*) δ = 155.1 (O**C**CO_2CH_3), 153.3 (CH_2-C≡C**C**O_2CH_3), 80.6 (CH_2-C≡**C**CO_2CH_3), 78.4 (CH_2**C**≡CCO_2CH_3), 55.6 (OCO_2**C**H_3), 54.7 (**C**H_2), 53.1 (CH_2C≡CCO_2**C**H_3). $C_7H_8O_5$ (172.14 g mol^{-1}). MS(ESI): *m/z* = 195.0276 (calcd. 195.0264 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.59.

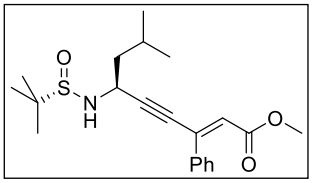
Methyl (*Z*)-2-Benzylidene-5-((*tert*-butoxycarbonyl)amino)pent-3-ynoate (74a).

Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. To build the catalyst, a mixture of $Pd(OAc)_2$ (21.2 mg, 94 µmol, 3 mol%) and the ligand Tris(2,6-dimethoxyphenyl)phosphan (TDMPP, 42.0 mg, 95 µmol, 3 mol%) were dissolved in dry toluene (3.1 mL) and stirred for 15 min at rt under argon atmosphere, giving a deeply purple solution. Glycin analogous propargylamide **1** (727 mg, 4.68 mmol, 1.5 eq) and phenylglycin analogous propynoate **73b** (460 µL, 3.1 mmol, 1 eq) were added in one portion. Immediately, the reaction mixture turned a black colour. After stirring the black solution for 51 h at rt, it was filtered through a pad of charcoal (0.5 cm) and silica (1 cm) with vacuum. The pad was washed with Et_2O/CH_2Cl_2 (1:1, 5 mL) and then Et_2O (5 mL) and the solvent was evaporated. The crude product was purified by column chromatography (PE/EtOAc, 2:1).



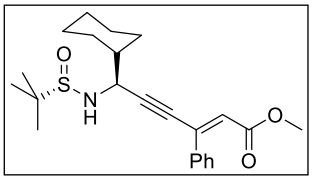
Pale green fluid. Yield: 854.8 mg, 2.711 mmol, 87 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.42-7.38 (m, 2H, ar-2-**H**, ar-6-**H**), 7.37-7.33 (m, 3H, ar-3-**H**, ar-4-**H**, ar-5-**H**), 6.28 (s, 1H, Ph-C**H**=C-CO_2CH_3), 4.71 (s br., 1H, CH_2N**H**Boc), 4.11 (d, ^3J = 5.8 Hz, 2H, C**H**$_2$NHBoc), 3.61 (s, 3H, CO_2C**H**$_3$), 1.45 (s, 9H, CH_2NHCO_2C(C**H**$_3$)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.7 (Ph-CH=C-**C**O_2CH_3), 138.1 (Ph-CH=**C**-CO_2CH_3), 136.3 (ar-**C**-1), 129.1 (ar-**C**-2, ar-**C**-6), 128.5 (ar-**C**-3, ar-**C**-5), 128.0 (ar-**C**-4), 124.7 (Ph-**C**H=C-CO_2CH_3), 91.9 (CH_2C≡**C**(CO_2CH_3)=), 83.9 (CH_2**C**≡C(CO_2CH_3)=), 80.3 ($NHCO_2$**C**$(CH_3)_3$), 60.5 (**C**H_2NHBoc), 51.6 (CO_2**C**H_3), 28.5 (CH_2NHCO_2C(**C**$H_3)_3$). $C_{18}H_{21}NO_4$ (315.37 g mol^{-1}), LCMS(ESI): t*r* = 10.0 min, *m/z* = 316.1535 (calcd. 316.1543 $[M+H]^+$), 338.1371 (calcd. 338.1363 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.67.

Methyl (*S*,*E*)-6-(((*S*)-*tert*-Butylsulfinyl)amino)-8-methyl-3-phenylnon-2-en-4-ynoate (74b). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. A mixture of $Pd(OAc)_2$ (3 mol%) and the ligand Tris(2,6-dimethoxyphenyl)phosphan (TDMPP, 3 mol%) was dissolved in dry toluene (3 mL) and stirred for 15 min at rt under argon atmosphere. After formation of the catalytist complex, leucine analogous propargylamide **6c** (100.6 mg, 467.1 µmol, 0.94 eq) and phenylglycine analogous propynoate **73b** (61 µL, 500 µmol, 1.0 eq) were added in one portion to the deeply purple solution, which turned immediately black. After stirring the reaction mixture overnight, it was filtered through a pad of charcoal (1 cm) on silica (1 cm). The pad was washed with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL), the solvent was evaporated and the crude product was purified by column chromatography (PE/EtOAc, 2:1).



Pale yellow highly viscous oil. Yield: 82.2 mg, 218.9 µmol, 45 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.43-7.37 (m, 2H, Ph-2-**H**, Ph-6-**H**), 7.33-7.29 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 6.27 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}C\mathbf{H}CO_2$), 3.84 (ddd, ^3J = 7.4 Hz, ^3J = 7.5 Hz, ^3J = 6.4 Hz, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 3.57 (s, 3H, $CO_2C\mathbf{H_3}$), 3.32 (t br., ^3J = 7.4 Hz, 1H, $C^{\alpha I}HN\mathbf{H}$), 1.81 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}(CH_3)_2$), 1.56 (dd, ^3J = 7.5 Hz, ^3J = 7.2 Hz, 2H, $C^{\alpha I}HC^{\beta}\mathbf{H_2}C^{\gamma}H(CH_3)_2$), 1.19 (s, 9H, $SC(C\mathbf{H_3})_3$), 0.89 (d, ^3J = 6.7 Hz, 6H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.7 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}CH\mathbf{C}O_2$), 137.8 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}{=}CHCO_2$), 136.0 (Ph-**C**-1), 129.0 (Ph-**C**-3, Ph-**C**-5), 128.6 (Ph-**C**-4), 127.9 (Ph-**C**-2, Ph-**C**-6), 124.6 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}\mathbf{C}HCO_2$), 95.4 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 84.1 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}{=}CHCO_2$), 56.2 ($S\mathbf{C}(CH_3)_3$), 53.6 ($CO_2\mathbf{C}H_3$), 51.4 ($\mathbf{C^{\alpha I}}HC{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 46.1 ($C^{\alpha I}H\mathbf{C^{\beta}}H_2C^{\gamma}H(CH_3)_2$), 33.5 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C^{\gamma}}H(CH_3)_2$), 24.8 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 22.6 ($SC(\mathbf{C}H_3)_3$), 22.1 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$). $C_{21}H_{29}NO_3S$ (375.53 g mol^{-1}), MS (ESI): *m/z* = 376.19490 (calcd. 376.1941 $[M+H]^+$), 751.3791 (calcd. 751.3809 $[2M+H]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.22, R*f* (PE/EtOAc, 1:1) = 0.50.

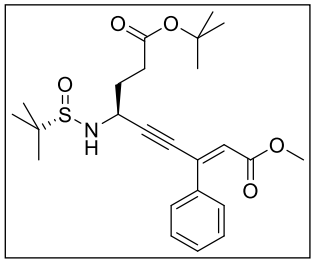
Methyl (*S*,*E*)-6-(((*S*)-*tert*-Butylsulfinyl)amino)-6-cyclohexyl-3-phenylhex-2-en-4-ynoate (74c). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. After forming the catalyst complex of $Pd(OAc)_2$ (3 mol%) and the ligand Tris(2,6-dimethoxyphenyl)phosphan (TDMPP, 3 mol%),



stirring the mixture for 15 min in dry toluene (3 mL) under argon atmosphere, cyclohexylglycine analogous propargylamide **6e** (120.7 mg, 500.0 μmol, 1.0 eq) and phenylglycine analogous propynoate **73b** (74 μL, 500 μmol, 1.0 eq) were added in one portion to the purple solution. The black reaction mixture was stirred overnight at ambient temperature and then filtered through a pad of charcoal (1 cm) and silica (1 cm). After washing the pad with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL) and evaporation of the solvent, the crude product was purified by column chromatography (PE/EtOAc, 2:1).

Pale yellow oil. Yield: 127.8 mg, 318.3 μmol, 64 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.47-7.42 (m, 2H, Ph-2-**H**, Ph-6-**H**), 7.36-7.34 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 6.32 (s, 1H, $C^{\alpha I}$HC≡C-$C^{\alpha II}$=C**H**CO_2), 4.04 (dd, ^3J = 6.4 Hz, ^3J = 7.1 Hz, 1H, $C^{\alpha I}$**H**C≡C-$C^{\alpha II}$=CHCO_2), 3.62 (s, 3H, CO_2C**H**$_3$), 3.29 (d, ^3J = 7.1 Hz, 1H, $C^{\alpha I}$HN**H**), 1.82 (d br., ^2J = 12.4 Hz, 2H, cy-1-**H**, cy-4-**H**), 1.76 (d br., ^2J = 13.1 Hz, 2H, cy-2-**H**, cy-6-**H**), 1.72-1.62 (m, 2H, cy-2-**H**, cy-6-**H**), 1.25 (m, 1H, cy-4-**H**), 1.22 (s, 9H, SC(C**H**$_3$)$_3$), 1.18-1.03 (m, 4H, cy-3-**H**, cy-5-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.8 ($C^{\alpha I}$HC≡C-$C^{\alpha II}$=CH**C**O_2), 138.0 ($C^{\alpha I}$HC≡C-**C**$^{\alpha II}$=CHCO_2), 136.2 (Ph-**C**-1), 129.1 (Ph-**C**-3, Ph-**C**-5), 128.7 (Ph-**C**-2, Ph-**C**-6), 128.0 (Ph-**C**-4), 124.7 ($C^{\alpha I}$HC≡C-$C^{\alpha II}$=**C**HCO_2), 94.4 ($C^{\alpha I}$H**C**≡C-$C^{\alpha II}$=CHCO_2), 86.5 ($C^{\alpha I}$HC≡**C**-$C^{\alpha II}$=CHCO_2), 56.6 (S**C**$(CH_3)_3$), 53.8 (**C**$^{\alpha I}$HC≡C-$C^{\alpha II}$=CHCO_2), 51.6 (CO_2**C**H_3), 43.6 (cy-**C**-1), 29.7 (cy-**C**-2), 28.5 (cy-**C**-6), 26.4 (cy-**C**-4), 26.0 (cy-**C**-5), 26.0 (cy-**C**-3), 22.8 (SC(**C**$H_3)_3$). $C_{23}H_{31}NO_3S$ (401.57 g mol^{-1}), MS(ESI): *m/z* = 402.21020 (calcd. 402.20974 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.61, R*f* (PE/EtOAc, 2:1) = 0.28.

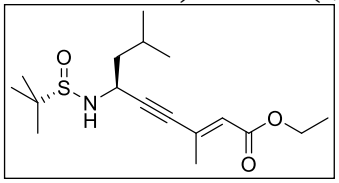
8-(*tert*-Butyl) 1-Methyl (*S*)-2-((*Z*)-Benzylidene)-5-(((*S*)-*tert*-butylsulfinyl)amino)oct-3-ynedioate (74d). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. A mixture of $Pd(OAc)_2$ (6 mg, 27 μmol, 18 mol%) and the ligand Tris(2,6-dimethoxyphenyl)phosphan (TDMPP, 12 mg, 27 μmol, 18 mol%) was dissolved in dry toluene (3 mL) and stirred for 15 min at rt under argon atmosphere. To the red catalyst solution, glutamic acid analogous propargylamide **6l** (43.5 mg, 151 μmol, 1.0 eq) and phenylglycine analogous propynoate **73b** (36 mg, 225 μmol, 1.5 eq) were added in one portion and the mixture was stirred overnight at ambient temperature. The black solution was filtered through a pad of charcoal (1 cm) and silica (1 cm), the pad was washed with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL) and the solvent was evaporated. The title compound was isolated by column chromatography (PE/EtOAc, 2:1).



Brightly yellow oil. Yield: 26.9 mg, 60.1 μmol, 40 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.45-7.39 (m, 2H, Phe-2-**H**, Phe-6-**H**), 7.38-7.34 (m, 3H, Phe-3-**H**, Phe-4-**H**, Phe-5-**H**), 6.32 (s, 1H, Ph-C=C**H**CO_2CH_3), 4.30 (ddd, ^{3}J = 6.2 Hz, ^{3}J = 6.7 Hz, ^{3}J = 5.4 Hz, 1H, C^{α}**H**), 3.61 (s, 3H, CO_2C**H**$_3$), 3.47 (d, ^{3}J = 6.7 Hz, 1H, $C^{\alpha}HN$**H**), 2.49-2.26 (m, 2H, $C^{\alpha}CH_2C$**H**$_2CO_2$), 2.13-1.89 (m, 2H, $C^{\alpha}HC$**H**$_2CH_2CO_2$), 1.44 (s, 9H, $CO_2C(C$**H**$_3)_3$), 1.21 (s, 9H, $SC(C$**H**$_3)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 172.1 (C^{γ}**C**$O_2C(CH_3)_3$), 165.7 (**C**O_2CH_3), 137.6 (**C**(Ph)=$CHCO_2$), 136.0 (Ph-**C**-1), 129.2 (Ph-**C**-3, Ph-**C**-5), 128.6 (Ph-**C**-4), 128.0 (Ph-**C**-2, Ph-**C**-6), 125.1 (C(Ph)=**C**HCO_2), 94.1 (C^{α}H**C**≡C-C(Ph)=), 86.0 ($C^{\alpha}HC$≡**C**-C(Ph)=), 81.0 (CO_2**C**$(CH_3)_3$), 56.5 (S**C**$(CH_3)_3$), 51.6 (CO_2**C**H_3), 47.6 (**C**$^{\alpha}$), 32.0 (C^{α}H**C**$^{\beta}H_2C^{\gamma}H_2CO_2$), 31.6 ($C^{\alpha}HC^{\beta}H_2$**C**$^{\gamma}H_2CO_2$), 28.2 ($CO_2C($**C**$H_3)_3$), 22.7 ($SC($**C**$H_3)_3$). $C_{24}H_{33}NO_5S$ (447.59 g mol^{-1}), MS(ESI): t*r* = 10.6 min, *m/z* = 448.2283 (calcd. 448.2152 $[M+H]^+$), 470.2093 (calcd. 470.1972 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.17.

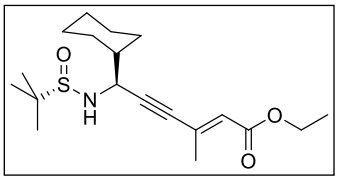
Ethyl (*S*,*E*)-6-(((*S*)-*tert*-Butylsulfinyl)amino)-3,8-dimethylnon-2-en-4-ynoate (74e).
Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. A mixture of $Pd(OAc)_2$ (3 mol%) and the ligand TDMPP (3 mol%) was dissolved in dry toluene (3 mL) and stirred for 15 min at rt under argon atmosphere. L-Leucine analogous propargylamide **6c** (101.2 mg, 469.9 μmol, 0.94 eq) and alanine analogous propynoate **73a** (58 μL, 500 μmol, 1.00 eq) were added in one portion and the reaction mixture was stirred overnight at ambient temperature. The blak solution was filtered through a pad of charcoal (1 cm) and silica (1 cm). After washing the pad with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL), the solvent was evaporated and the crude product was purified by column chromatography (PE/EtOAc, 2:1).

Colorless crystalline needles. Yield: 116.4 mg, 355.4 μmol, 76 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.02 (s, 1H, $C^{\alpha I}HC$≡C-$C^{\alpha II}(CH_3)$=C**H**CO_2), 4.17 (ddd, ^{3}J = 8.1 Hz, ^{3}J = 7.4 Hz, ^{3}J = 7.2 Hz, 1H, $C^{\alpha I}$**H**C≡C-$C^{\alpha II}(CH_3)$=$CHCO_2$), 4.13 (q, ^{3}J = 7.6 Hz, 2H, CO_2C**H**$_2CH_3$), 3.27 (d br., ^{3}J = 7.2 Hz, 1H, $C^{\alpha I}HN$**H**), 2.24 (s, 3H, $C^{\alpha I}HC$≡C-$C^{\alpha II}$(C**H**$_3$)=$CHCO_2$), 1.82 (hd, ^{3}J = 6.8 Hz, ^{3}J = 7.4 Hz, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}$**H**$(CH_3)_2$), 1.59 (dd, ^{3}J = 7.5 Hz, ^{3}J = 7.4 Hz, 2H, $C^{\alpha I}HC^{\beta}$**H**$_2C^{\gamma}H(CH_3)_2$), 1.24 (t, ^{3}J = 7.2 Hz, 3H, CO_2CH_2C**H**$_3$), 1.19 (s, 9H, $SC(C$**H**$_3)_3$),



0.92 (d, ^{3}J = 6.8 Hz, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$), 0.90 (d, ^{3}J = 6.8 Hz, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.0 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CH\mathbf{C}O_2$), 137.3 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}(CH_3){=}CHCO_2$), 124.7 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}\mathbf{C}HCO_2$), 93.7 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 86.7 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 60.1 ($CO_2\mathbf{C}H_2CH_3$), 56.3 ($S\mathbf{C}(CH_3)_3$), 46.9 ($\mathbf{C^{\alpha I}}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 46.0 ($C^{\alpha I}H\mathbf{C^{\beta}}H_2C^{\gamma}H(CH_3)_2$), 25.1 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C^{\gamma}}H(CH_3)_2$), 22.6 ($SC(\mathbf{C}H_3)_3$), 22.5 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 22.2 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 19.8 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(\mathbf{C}H_3){=}CHCO_2$), 14.3 ($CO_2CH_2\mathbf{C}H_3$). $C_{17}H_{29}NO_3S$ (327.48 g mol^{-1}). MS(ESI): *m/z* = 328.19450 (calcd. 328.19409 $[M+H]^+$), 350.1811 (calcd. 350.1760 $[M+Na]^+$), 655.3905 (calcd. 655.3809 $[2M+H]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.25, R*f* (PE/EtOAc, 1:1) = 0.48. $[\alpha]_{589}^{20}$ = +32.80 (*c* 0.399, $CHCl_3$).

Ethyl (*S*,*E*)-6-(((*S*)-*tert*-Butylsulfinyl)amino)-6-cyclohexyl-3-methylhex-2-en-4-ynoate (74f). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. A mixture of $Pd(OAc)_2$ (3 mol%) and the ligand TDMPP (3 mol%) was dissolved in dry toluene (3 mL) and stirred for 15 min at rt under argon atmosphere. In one portion, cycloheylglycine analogous propargylamide **6e** (121.7 mg, 504.2 μmol, 1.01 eq) and alanine analogous propynoate **73a** (61 μL, 500 μmol, 1.00 eq) were added to the red solution, which immediately turned black. After stirring the solution for 24 h at ambient temperature, the solution was filtered through a pad of charcoal (1 cm) and silica (1 cm) and the pad was purged with CH_2Cl_2/Et_2O (6 mL) and Et_2O (6 mL). The filtrate was concentrated up to dryness and purified by column chromatography (PE/EtOAc, 2:1).

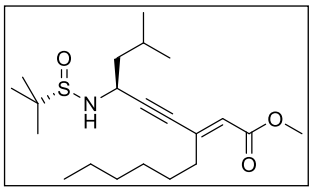


Colorless, highly viscous oil. Yield: 122.3 mg, 345.9 μmol, 69 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.06 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}C\mathbf{H}CO_2$), 4.16 (q, ^{3}J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 4.00 (dd, ^{3}J = 6.5 Hz, ^{3}J = 7.2 Hz, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 3.26 (d, ^{3}J = 7.2 Hz, 1H, $C^{\alpha I}HN\mathbf{H}$), 2.28 (s, 3H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(C\mathbf{H_3}){=}CHCO_2$), 1.82 (d br., ^{3}J = 13.8 Hz, 2H, cy-2-**H**, cy-6-**H**,), 1.77 (d br., ^{2}J = 13.2 Hz, 2H, cy-2-**H**, cy-6-**H**), 1.69 (d br., ^{2}J = 12.6 Hz, 1H, cy-4-**H**), 1.65-1.55 (m, 1H, cy-1-**H**, cy-4-**H**), 1.27 (t, ^{3}J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.23 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.18-1.03 (m, 4H, cy-3-**H**, cy-5-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.1 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CH\mathbf{C}O_2$), 137.5 ($C^{\alpha I}HC{\equiv}C$-

C$^{\alpha II}$(CH_3)=$CHCO_2$), 124.7 ($C^{\alpha I}HC{\equiv}C$-$C^{\alpha II}$(CH_3)=**C**HCO_2), 92.7 ($C^{\alpha I}$H**C**≡C-$C^{\alpha II}$(CH_3)=$CHCO_2$), 87.6 ($C^{\alpha I}HC{\equiv}$**C**-$C^{\alpha II}$(CH_3)=$CHCO_2$), 60.1 (CO_2**C**H_2CH_3), 56.6 (S**C**(CH_3)$_3$), 53.7 (**C**$^{\alpha I}$HC≡C-$C^{\alpha II}$(CH_3)=$CHCO_2$), 43.5 (cy-**C**-1), 29.7 (cy-**C**-2), 28.5 (cy-**C**-6), 26.4 (cy-**C**-4), 26.1 (cy-**C**-5), 26.0 (cy-**C**-3), 22.8 (SC(**C**H_3)$_3$), 19.9 ($C^{\alpha I}HC{\equiv}C$-$C^{\alpha II}$(**C**H_3)=$CHCO_2$), 14.4 (CO_2CH_2**C**H_3). $C_{19}H_{31}NO_3S$ (353.52 g mol^{-1}). MS(ESI): *m/z* = 354.20950 (calcd. 354.20974 $[M+H]^+$), 707.4102 (calcd. 707.4122 $[2M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.63, R*f* (PE/EtOAc, 2:1) = 0.33.

Methyl (*S*,*E*)-6-(((*S*)-*tert*-Butylsulfinyl)amino)-3-hexyl-8-methylnon-2-en-4-ynoate (74h). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. $Pd(OAc)_2$ (3 mol%) and TDMPP (3 mol%) were mixed in dry toluene (3 mL) and stirred for 15 min at rt under argon atmosphere. L-Leucine analogous propargylamide **6c** (101.4 mg, 470.8 µmol, 0.94 eq) and *n*-hexylglycine analogous propynoate **73c** (92 µL, 500 µmol, 1.00 eq) were added in one portion and the reaction mixture was stirred overnight at ambient temperature. The black solution was filtered through a pad of charcoal (1cm) and silica (1 cm). After purging the pad with CH_2Cl_2/Et_2O (1:1, 6 mL), Et_2O (6 mL), the solvent was evaporated and the title compound was isolated by column chromatography (PE/EtOAc, 2:1).

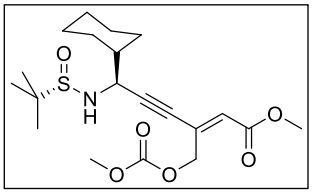
Colorless, highly viscous oil. Yield: 31.1 mg, 84.2 µmol, 18 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.04 (s, 1H, $C^{\alpha I}HC{\equiv}C$-$C^{\alpha II}$=C**H**CO_2), 4.20 (ddd, ^3J = 7.4 Hz, ^3J = 6.7 Hz, ^3J = 7.8 Hz, 1H, $C^{\alpha I}$**H**C≡C-$C^{\alpha II}$=$CHCO_2$), 3.68 (s, 3H, CO_2C**H$_3$**), 3.31 (d br., ^3J = 6.7 Hz, 1H, $C^{\alpha I}$HN**H**), 2.71 (t, ^3J = 7.8 Hz, 2H, $C^{\alpha II}C^{\beta}$**H$_2$**), 1.84 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}$**H**($CH_3$)$_2$), 1.63 (dd, ^3J = 7.4 Hz, ^3J = 7.8 Hz, 2H, $C^{\alpha I}HC^{\beta}$**H$_2$**C^{γ}H(CH_3)$_2$), 1.55 (tt, ^3J = 7.5 Hz, ^3J = 7.4 Hz, 2H, $C^{\alpha II}C^{\beta}H_2C^{\gamma}$**H$_2$**$C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$), 1.36-1.23 (m, 6H, $C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}$**H$_2$**$C^{\varepsilon}$**H$_2$**$C^{\zeta}$**H$_2$**$C^{\eta}H_3$), 1.21 (s, 9H, SC(C**H$_3$**)$_3$), 0.93 (t, ^3J = 5.8 Hz, 6H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}$H(C**H$_3$**)$_2$), 0.86 (t, ^3J = 7.2 Hz, 3H, $C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}$**H$_3$**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.3 ($C^{\alpha I}HC{\equiv}C$-$C^{\alpha II}$=CH**C**O_2), 143.0 ($C^{\alpha I}HC{\equiv}C$-**C**$^{\alpha II}$=$CHCO_2$), 124.0 ($C^{\alpha I}HC{\equiv}C$-$C^{\alpha II}$=**C**HCO_2), 94.4 (**C**$^{\alpha I}HC{\equiv}C$-$C^{\alpha II}$=$CHCO_2$), 85.7 ($C^{\alpha I}HC{\equiv}$**C**-$C^{\alpha II}$=$CHCO_2$), 56.4 (S**C**(CH_3)$_3$), 51.3 (CO_2**C**H_3), 46.9 (**C**$^{\alpha I}HC{\equiv}C$-$C^{\alpha II}$=$CHCO_2$), 46.1 ($C^{\alpha I}$H**C**$^{\beta}H_2C^{\gamma}$H(CH_3)$_2$), 32.3 ($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2$**C**$^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$),



31.8 ($C^{\alpha II}\mathbf{C^{\beta}}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$), 29.0 ($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2\mathbf{C^{\delta}}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$), 28.4 ($C^{\alpha II}C^{\beta}H_2\mathbf{C^{\gamma}}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$), 25.2 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C^{\gamma}}H(CH_3)_2$), 22.7 ($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2\mathbf{C^{\zeta}}H_2C^{\eta}H_3$), 22.7 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 22.6 ($SC(\mathbf{C}H_3)_3$), 22.1 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 14.2 ($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2\mathbf{C^{\eta}}H_3$). $C_{21}H_{37}NO_3S$ (383.59 g mol^{-1}), MS (ESI): *m/z* = 384.25790 (calcd. 384.25669 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.66, R*f* (PE/EtOAc, 2:1) = 0.32.

Methyl (*S*,*Z*)-6-(((*S*)-*tert*-Butylsulfinyl)amino)-6-cyclohexyl-3-(((methoxycarbonyl)oxy)methyl)hex-2-en-4-ynoate (74i). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. $Pd(OAc)_2$ (6 mg, 27 μmol, 5 mol%) and TDMPP (12 mg, 27 μmol, 5 mol%) were mixed in dry toluene (1.5 mL) and stirred for 15 min at rt under argon atmosphere. Cyclohexylglycine analogous propargylamide **6e** (100 mg, 415 μmol, 1.0 eq) and serine analogous propynoate **73d** (102 mg, 580 μmol, 1.4 eq) were added in one portion. The reaction mixture was stirred overnight at rt, before filtering the black solution through a pad of charcoal (1 cm) on silica (1 cm). The pad was purged with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL). The solvent was evaporated and the crude product was purified by column chromatography (PE/EtOAc, 2:1).

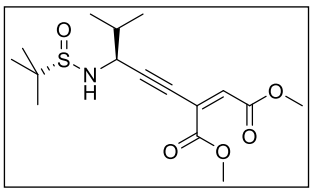
Faintly yellow, highly viscous oil. Yield: 81.0 mg, 196 μmol, 47 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.17 (t, ^4J = 1.9 Hz, 1H, $NHC^{\alpha I}HC{\equiv}CC^{\alpha II}{=}C\mathbf{H}\text{-}CO_2CH_3$), 5.21 (d, ^4J = 1.9 Hz, 3H, $C^{\alpha II}C\mathbf{H_2}OCO_2CH_3$), 4.00 (dd, ^3J = 6.2 Hz, ^3J = 6.9 Hz, 1H, $C^{\alpha I}\mathbf{H}$), 3.78 (s, 3H, $NHC^{\alpha I}HC{\equiv}CC^{\alpha II}{=}CH\text{-}CO_2C\mathbf{H_3}$), 3.70 (s, 3H, $C^{\alpha II}CH_2OCO_2C\mathbf{H_3}$), 3.37 (d, ^3J = 6.9 Hz, 1H, $N\mathbf{H}C^{\alpha I}H$), 1.80 (d br., ^2J = 9.6 Hz, 2H, cy-2-**H**, cy-6-**H**), 1.74 (d br., ^2J = 14.5 Hz, 3H, cy-2-**H**, cy-4-**H**, cy-6-**H**), 1.65 (d br., ^2J = 12.2 Hz, 1H, cy-4-**H**), 1.57 (m, 1H, cy-1-**H**), 1.20 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.16-0.99 (m, 4H, cy-3-**H**, cy-5-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.6 ($C^{\alpha II}CH_2O\mathbf{C}O_2CH_3$), 155.6 ($NHC^{\alpha I}HC{\equiv}CC^{\alpha II}{=}CH\text{-}\mathbf{C}O_2CH_3$), 136.9 ($NHC^{\alpha I}HC{\equiv}C\mathbf{C^{\alpha II}}{=}CH\text{-}CO_2CH_3$), 125.4 ($NHC^{\alpha I}HC{\equiv}CC^{\alpha II}{=}\mathbf{C}H\text{-}CO_2CH_3$), 96.7 ($NHC^{\alpha I}H\mathbf{C}{\equiv}CC^{\alpha II}{=}CH\text{-}CO_2CH_3$), 82.5 ($NHC^{\alpha I}HC{\equiv}\mathbf{C}C^{\alpha II}{=}CH\text{-}CO_2CH_3$), 64.9 ($C^{\alpha II}\mathbf{C}H_2OCO_2CH_3$), 56.5 ($S\mathbf{C}(CH_3)_3$), 55.1 ($C^{\alpha II}CH_2OCO_2\mathbf{C}H_3$), 53.6 ($NH\mathbf{C^{\alpha I}}HC{\equiv}CC^{\alpha II}{=}CH\text{-}CO_2CH_3$), 51.8 ($C^{\alpha II}CH_2OCO_2\mathbf{C}H_3$), 43.3 (cy-**C**-1), 29.5 (cy-**C**-2), 28.2 (cy-**C**-6), 26.2 (cy-**C**-4), 26.0 (cy-**C**-5), 25.9 (cy-**C**-3),



22.7 (SC(**C**H_3)$_3$). $C_{20}H_{31}NO_6S$ (413.53 g mol^{-1}). MS(ESI): *m/z* = 414.2011 (calcd. 414.1945 $[M+H]^+$), 436.1677 (calcd. 436.1764 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.14. $[\alpha]_{589}^{20}$ = +17.30 (*c* 0.334, $CHCl_3$).

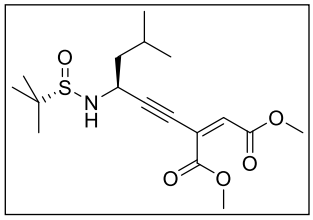
Dimethyl 2-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)maleate (74j). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. A mixture of $Pd(OAc)_2$ (6 mg, 27 μmol, 5 mol%), TDMPP (12 mg, 27 μmol, 5 mol%) in dry toluene (3 mL) was stirred 15 min at ambient temperature under argon atmosphere to give a brightly red catalyst solution. Valine analogous propargylamide **6b** (99.0 mg, 492 μmol, 1.0 eq) and aspartic acid analogous propynoate **73e** (90 μL, 732 μmol, 1.5 eq) were added in one portion and the dark reaction mixture was stirred overnight at rt. After complete reaction (checked by TLC), the mixture was filtered through a pad of charcoal (1 cm) on silica (1 cm), the pad was purged with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL) and the solvent was evaporated. The title compound was isolated by column chromatography (PE/EtOAc, 2:1). During the purification, starting material **6b** was retrieved (45.8 mg, 228 μmol, 46 %), indicating a conversion of only 54 %.

Colorless oil. Yield: 13.9 mg, 40.5 μmol, 8 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.33 (s, 1H, NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=C**H**-CO_2CH_3), 4.06 (dd, ^3J = 6.8 Hz, ^3J = 5.4 Hz, 1H, C$^{\alpha I}$**H**), 3.85 (s, 3H, NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=CH-CO_2C**H$_3$**), 3.75 (s, 3H, C$^{\alpha II}$$CO_2$C**H$_3$**), 3.39 (d, ^3J = 6.2 Hz, 1H, C$^{\alpha I}$HN**H**), 2.03-1.96 (m, 1H, C$^{\alpha I}$HC$^{\beta}$**H**), 1.23 (s, 9H, SC(C**H$_3$**)$_3$), 1.01 (d, ^3J = 6.6 Hz, 3H, C$^{\alpha}$HC$^{\beta}$(C$^{\gamma}$H$_3$)HC$^{\gamma}$**H$_3$**), 0.99 (d, ^3J = 6.5 Hz, 1H, C$^{\alpha}$HC$^{\beta}$(C$^{\gamma}$H$_3$)HC$^{\gamma}$**H$_3$**).



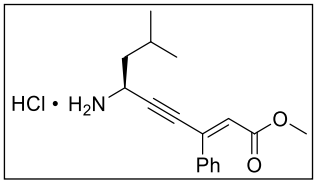
^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.0 (C$^{\alpha II}$**C**O_2CH_3), 164.7 (NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=CH-**C**O_2CH_3), 129.5 (NHC$^{\alpha I}$HC≡C**C$^{\alpha II}$**=CH-CO_2CH_3), 129.0 (NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=**C**H-CO_2CH_3), 97.0 (NHC$^{\alpha I}$H**C**≡CC$^{\alpha II}$=CH-CO_2CH_3), 80.4 (NHC$^{\alpha I}$HC≡**C**C$^{\alpha II}$=CH-CO_2CH_3), 56.7 (S**C**$(CH_3)_3$), 54.3 (NH**C$^{\alpha I}$**HC≡CC$^{\alpha II}$=CH-CO_2CH_3), 53.3 (NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=CH-CO_2**C**H_3), 52.4 (C$^{\alpha II}$$CO_2$**C**$H_3$), 33.9 (C$^{\alpha I}$H**C$^{\beta}$**H$(CH_3)_2$), 22.7 (SC(**C**$H_3$)$_3$), 19.1 (C$^{\alpha}HC^{\beta}$(C$^{\gamma}H_3$)H**C$^{\gamma}$**H$_3$), 17.7 (C$^{\alpha}HC^{\beta}$(C$^{\gamma}H_3$)H**C$^{\gamma}$**H$_3$). $C_{16}H_{25}NO_5S$ (343.44 g mol^{-1}), MS(ESI): *m/z* = 344.1607 (calcd. 344.1526 $[M+H]^+$), 366.1376 (calcd. 366.1346 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.19, R*f* (PE/EtOAc, 4:1) = 0.09. $[\alpha]_{589}^{20}$ = -39.13 (*c* 0.104, $CHCl_3$).

Dimethyl 2-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)maleate (74k). Hydroalkynylation reactions were carried out as described by Trost *et al.* [130]. A mixture of $Pd(OAc)_2$ (3 mol%), TDMPP (3 mol%) in dry toluene (3 mL) was stirred 15 min at ambient temperature under argon atmosphere to give a brightly red catalyst solution. Leucine analogous propargylamide **6c** (100.6 mg, 467.1 μmol, 0.94 eq) and aspartic acid analogous propynoate **73e** (61 μL, 500 μmol, 1.00 eq) were added in one portion and the reaction mixture was stirred overnight at rt. The mixture was filtered through a pad of charcoal (1 cm) on silica (1 cm) and the pad was purged with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL). The title compound was isolated by column chromatography (PE/EtOAc, 2:1).



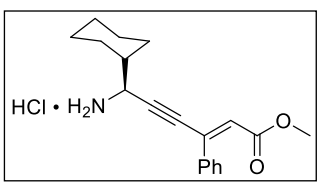
Yellow, highly viscous oil. Yield: 18.0 mg, 50.4 μmol, 11 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.30 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CO_2CH_3){=}C\mathbf{H}CO_2$), 3.85 (s, 3H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CO_2C\mathbf{H_3}){=}CHCO_2$), 3.74 (s, 3H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CO_2CH_3){=}CHCO_2C\mathbf{H_3}$), 3.47 (ddd, ^3J = 7.0 Hz, ^3J = 7.4 Hz, ^3J = 7.2 Hz, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}(CO_2CH_3){=}CHCO_2$), 3.33 (d, ^3J = 7.2 Hz, 1H, $C^{\alpha I}HN\mathbf{H}$), 1.83 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}(CH_3)_2$), 1.64 (t, ^3J = 7.4 Hz, 2H, $C^{\alpha I}HC^{\beta}\mathbf{H_2}C^{\gamma}H(CH_3)_2$), 1.21 (s, 9H, $SC(C\mathbf{H_3})_3$), 0.93 (d, ^3J = 6.7 Hz, 6H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 164.9 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(\mathbf{C}O_2CH_3){=}CHCO_2$), 164.7 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CO_2CH_3){=}CH\mathbf{C}O_2$), 129.3 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}(CO_2CH_3){=}CHCO_2$), 103.7 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CO_2CH_3){=}\mathbf{C}HCO_2$), 98.5 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}(CO_2CH_3){=}CHCO_2$), 79.5 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}(CO_2CH_3){=}CHCO_2$), 56.5 ($S\mathbf{C}(CH_3)_3$), 53.2 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CO_2CH_3){=}CHCO_2\mathbf{C}H_3$), 52.4 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CO_2\mathbf{C}H_3){=}CHCO_2CH_3$), 45.8 ($C^{\alpha I}H\mathbf{C^{\beta}}H_2C^{\gamma}H(CH_3)_2$), 25.0 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C^{\gamma}}H(CH_3)_2$), 22.6 ($SC(\mathbf{C}H_3)_3$), 22.5 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 22.3 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$). $C_{17}H_{27}NO_5S$ (357.47 g mol^{-1}). MS(ESI): *m/z* = 358.16750 (calcd. 358.16827 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.37, R*f* (PE/EtOAc, 2:1) = 0.15.

Methyl (*S*,*E*)-6-Amino-8-methyl-3-phenylnon-2-en-4-ynoate Hydrochloride (75b). Hydrochloric acid (4 M in dioxane, 0.2 mL) was added dropwise to a solution of peptidomimetic **74b** (82.2 mg, 218.9 μmol) in MeOH (4 mL). After stirring the solution overnight, the solvent was evaporated under reduced pressure. The desired amine was achieved quantitatively with minor impurities as hydrochloric salt. Brightly yellow amorphous solid.



Yield: 67.4 mg, 219 μmol, quantitative. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 7.29-6.97 (m, 5H, Ph-**H**), 6.12 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}C\mathbf{H}CO_2$), 4.06 (m, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 3.83 (s, 3H, $CO_2C\mathbf{H_3}$), 1.82 (s, 3H, $C^{\alpha I}HN\mathbf{H_3}Cl$), 1.47 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}(CH_3)_2$), 1.10 (d, ^{2}J = 21.3 Hz, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 1.04 (d, ^{2}J = 21.1 Hz, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 0.80 (d, ^{3}J = 6.6 Hz, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$), 0.75-0.62 (m, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 166.9 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}CH\mathbf{C}O_2$), 137.1 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}{=}CHCO_2$), 136.8 (Ph-**C**-3, Ph-**C**-5), 130.3 (Ph-**C**-1), 129.4 (Ph-**C**-2, Ph-**C**-6), 129.1 (Ph-**C**-1), 127.1 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}\mathbf{C}HCO_2$), 79.3 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 78.0 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}{=}CHCO_2$), 52.2 ($CO_2\mathbf{C}H_3$), 42.7 ($\mathbf{C^{\alpha I}}HC{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 32.3 ($C^{\alpha I}H\mathbf{C^{\beta}}H_2C^{\gamma}H(CH_3)_2$), 26.2 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C^{\gamma}}H(CH_3)_2$), 23.3 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 21.5 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$). $C_{17}H_{22}ClNO_2$ (307.82 g mol^{-1}). LCMS(ESI): t*r* = 6.7 min, *m/z* = 272.1725 (calcd. 272.1645 $[M+H]^+$), 294.1352 (calcd. 294.1465 $[M+Na]^+$). $[\alpha]_{589}^{20}$ = +129.0 (*c* 3.00, MeOH).

Methyl (*S*,*E*)-6-Amino-6-cyclohexyl-3-phenylhex-2-en-4-ynoate Hydrochloride (75c). Hydrochloric acid (4 M in dioxane, 0.2 mL) was added dropwise to a solution of peptidomimetic **74c** (127.8 mg, 318.3 μmol) in MeOH (4 mL). After stirring the solution overnight, the solvent was evaporated under reduced pressure. The desired amine was achieved quantitatively with minor impurities as hydrochloric salt. Brightly yellow amorphous solid.

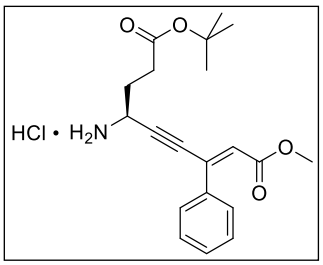


Yield: 106.2 mg, 318.3 μmol, quantitative. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 7.47-7.41 (m, 2H, Ph-2-**H**, Ph-6-**H**), 7.40-7.35 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 6.42 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}C\mathbf{H}CO_2$), 4.22 (d br., ^{3}J = 5.2 Hz, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 3.61 (s, 3H, $CO_2C\mathbf{H_3}$), 1.90 (d br., ^{2}J = 13.6 Hz, 1H, cy-4-**H**), 1.86-1.78 (m,

3H, cy-1-**H**, cy-2-**H**, cy-6-**H**), 1.71 (d br., ^{2}J = 13.2 Hz, 1H, cy-4-**H**), 1.40-1.27 (m, 3H, cy**H**), 1.21 (dt, ^{2}J = 18.8 Hz, ^{3}J = 6.5 Hz, 2H, cy**H**), 1.15 (s, 3H, $C^{\alpha I}HN\mathbf{H_3}Cl$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 166.9 ($\mathbf{C}O_2CH_3$), 137.1 (Ph-**C**-1), 136.8 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}{=}CHCO_2$), 130.3 (Ph-**C**-4), 129.5 (Ph-**C**-3, Ph-**C**-5), 129.1 (Ph-**C**-2, Ph-**C**-6), 127.0 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}\mathbf{C}HCO_2$), 89.1 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 89.0 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}{=}CHCO_2$), 52.2 ($CO_2\mathbf{C}H_3$), 49.5 ($\mathbf{C^{\alpha I}}HC{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 41.9 (cy-**C**-1), 30.5 (cy-**C**-2), 28.6 (cy-**C**-6), 26.9 (cy-**C**-4), 26.6 (cy-**C**-5), 26.4 (cy-**C**-3). $C_{19}H_{24}ClNO_2$ (333.86 g mol^{-1}). MS(ESI): t*r* = 6.9 min, *m/z* = 298.1894 (calcd. 298.1802 $[M+H]^+$). $[\alpha]_{589}^{20}$ = +3.78 (*c* 6.14, $CHCl_3$).

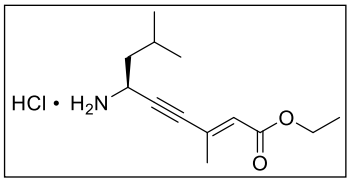
9-(*tert*-Butyl) 1-Methyl (*S*,*E*)-6-Amino-3-phenylnon-2-en-4-ynedioate Hydrochloride (75d). Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a vigorously stirred solution of propargyl-3-acrylate **74d** (26.9 mg, 60.1 μmol) in MeOH (4 mL). The reaction mixture was stirred overnight at rt before evaporating the solvent under reduced pressure.

Pale yellow oil. Yield: 22.8 mg, 60.1 μmol, quantitative. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 7.49-7.43 (m, 2H, ar-2-**H**, ar-6-**H**), 7.41 (m, 1H, ar-4-**H**), 7.45-7.29 (m, 2H, ar-3-**H**, ar-5-**H**), 6.45 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}C\mathbf{H}CO_2$), 4.46 (ddt, ^{3}J = 8.4 Hz, ^{3}J = 5.5 Hz, ^{3}J = 2.8 Hz, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 3.62 (s, 3H, $CO_2C\mathbf{H_3}$), 2.67-2.51 (m, 2H, $C^{\alpha I}HC\mathbf{H_2}CH_2CO_2$), 2.24 (m, 1H, $C^{\alpha I}HCH_2C\mathbf{H}_2CO_2$), 2.07 (m, 1H, $C^{\alpha I}HCH_2C\mathbf{H}_2CO_2$), 1.15 (s, 9H, $CO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 174.0 ($C^{\alpha I}HCH_2CH_2\mathbf{C}O_2$), 166.8 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}CH\mathbf{C}O_2$), 135.8 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}{=}CHCO_2$), 130.4 (Ph-**C**-1), 129.5 (Ph-**C**-3, Ph-**C**-5), 129.2 (Ph-**C**-2, Ph-**C**-6), 128.7 (Ph-**C**-4), 127.5 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}\mathbf{C}HCO_2$), 89.1 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}{=}CHCO_2$), 88.1 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 72.4 ($CO_2\mathbf{C}(CH_3)_3$), 62.2 ($CO_2\mathbf{C}H_3$), 44.0 ($\mathbf{C^{\alpha I}}HCH_2CH_2CO_2$), 30.6 ($C^{\alpha I}H\mathbf{C}H_2CH_2CO_2$), 29.5 ($C^{\alpha I}HCH_2\mathbf{C}H_2CO_2$), 21.5 ($CO_2C(\mathbf{C}H_3)_3$). $C_{20}H_{26}ClNO_4$ (379.88 g mol^{-1}). LCMS(ESI): t*r* = 6.7 min, *m/z* = 344.0866 (calcd. 344.1856 $[M+H]^+$). $[\alpha]_{589}^{20}$ = +27.88 (*c* 0.294, $CHCl_3$).



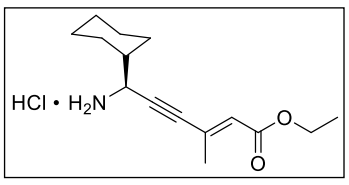
Ethyl (*S*,*E*)-6-Amino-3,8-dimethylnon-2-en-4-ynoate Hydrochloride (75e).

Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a vigorously stirred solution of propargyl-3-acrylate **74e** (116.4 mg, 355.4 μmol) in MeOH (4 mL). The reaction mixture was stirred overnight at rt before evaporating the solvent under reduced pressure.



Colorless crystals. Yield: 88.7 mg, 355.4 μmol, quantitative. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 6.12 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}C\mathbf{H}CO_2$), 4.34 (dd, ^{3}J = 9.5 Hz, ^{3}J = 3.7 Hz, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 4.17 (q, ^{3}J = 6.9 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 2.28 (s, 3H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(C\mathbf{H_3}){=}CHCO_2$), 1.89 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}(CH_3)_2$), 1.80 (m, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 1.71 (m, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 1.27 (t, ^{3}J = 6.9 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.15 (s, 3H, $C^{\alpha I}HN\mathbf{H_3}Cl$), 1.03 (d, ^{3}J = 6.4 Hz, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$), 0.99 (d, ^{3}J = 6.3 Hz, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 166.7 ($\mathbf{C}O_2CH_2CH_3$), 136.9 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}(CH_3){=}CHCO_2$), 126.8 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}\mathbf{C}HCO_2$), 89.4 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 88.7 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 61.4 ($CO_2\mathbf{C}H_2CH_3$), 43.3 ($\mathbf{C^{\alpha I}}HC^{\beta}H_2C^{\gamma}H(CH_3)_2$), 43.0 ($C^{\alpha I}H\mathbf{C^{\beta}}H_2C^{\gamma}H(CH_3)_2$), 26.4 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C^{\gamma}}H(CH_3)_2$), 23.3 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 21.6 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 19.6 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(\mathbf{C}H_3){=}CHCO_2$), 14.6 ($CO_2CH_2\mathbf{C}H_3$). $C_{13}H_{22}ClNO_2$ (259.77 g mol^{-1}). MS(ESI): t*r* = 6.4 min, *m/z* = 224.1805 (calcd. 224.1645 $[M\text{-}Cl^-]^+$), 246.1580 (calcd. 246.1465 $[M\text{-}HCl\text{+}Na]^+$). $[\alpha]_{589}^{20}$ = +5.91 (*c* 2.70, $CHCl_3$). X-ray crystal structure in Chapter IIX-3. n.

Ethyl (*S*,*E*)-6-Amino-6-cyclohexyl-3-methylhex-2-en-4-ynoate Hydrochloride (75f).



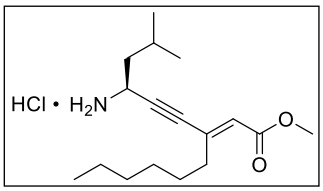
Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a vigorously stirred solution of propargyl-3-acrylate **74f** (122.3 mg, 345.9 μmol) in MeOH (4 mL). The reaction mixture was stirred overnight at rt before evaporating the solvent under reduced pressure. Colorless, crystalline needles.

Yield: 98.9 mg, 346 μmol, quantitative. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 6.06 (s, 1H, $C^{\alpha II}{=}C\mathbf{H}CO_2$), 4.12 (d br., ^{3}J = 5.3 Hz, 1H, $C^{\alpha I}\mathbf{H}$), 4.09 (q, ^{3}J = 6.8 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 2.23 (s, 3H, $C^{\alpha II}C^{\beta}\mathbf{H_3}$), 1.86 (d br., ^{2}J = 12.7 Hz, 1H, cy-1-**H**), 1.82-1.74 (m, 4H, $C^{\alpha I}N\mathbf{H_3}Cl$,

cy-**H**), 1.67 (d br., ^{2}J = 12.9 Hz, 1H, cy-4-**H**), 1.29-1.26 (m, 2H, cy-**H**), 1.21 (t, ^{3}J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$), 1.19-1.11 (m, 3H, cy-**H**), 1.09 (m, 3H, cy-**H**). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 166.7 ($\mathbf{C}O_2CH_2CH_3$), 137.0 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}(CH_3){=}CHCO_2$), 126.8 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(CH_3){=}\mathbf{C}HCO_2$), 90.3 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 87.8 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}(CH_3){=}CHCO_2$), 61.4 ($CO_2\mathbf{C}H_2CH_3$), 41.8 ($\mathbf{C^{\alpha I}}H$), 30.5 (cy-**C**-1), 28.6 (cy-**C**-2), 26.9 (cy-**C**-6), 26.7 (cy-**C**-4), 26.5 (cy-**C**-5), 21.5 (cy-**C**-3), 19.6 ($C^{\alpha II}\mathbf{C^{\beta}}H_3$), 14.6 ($CO_2CH_2\mathbf{C}H_3$). $C_{15}H_{24}ClNO_2$ (285.81 g mol^{-1}). MS(ESI): t*r* = 6.5 min, *m/z* = 250.1917 (calcd. 250.1802 [M-Cl$^-$]$^+$), 272.1711 (calcd. 272.1621 [M-HCl+Na]$^+$). $[\alpha]_{589}^{20}$ = +0.09 (*c* 3.20, $CHCl_3$). X-ray crystal structure in Chapter IIX-3. n.

Methyl (*S*,*E*)-6-Amino-3-hexyl-8-methylnon-2-en-4-ynoate Hydrochloride (75h).
Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a vigorously stirred solution of propargyl-3-acrylate **74h** (31.1 mg, 84.2 μmol) in MeOH (4 mL). The reaction mixture was stirred overnight at rt before evaporating the solvent under reduced pressure.

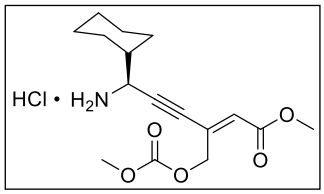
Yellow oil. Yield: 21.0 mg, 84.2 μmol, quantitative. ^{1}H NMR (500 MHz, Methanol-d_4) δ



= 6.13 (s, 1H, $C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}C\mathbf{H}CO_2$), 4.34 (dd br., ^{3}J = 11.0 Hz, ^{3}J = 4.9 Hz, 1H, $C^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 3.71 (s, 3H, $CO_2C\mathbf{H_3}$), 2.77 (t, ^{3}J = 7.7 Hz, 2H, $C^{\alpha II}C^{\beta}\mathbf{H_2}$), 1.89 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}(CH_3)_2$), 1.80 (m, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 1.68 (m, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 1.59 (tt, ^{3}J = 7.6 Hz, ^{3}J = 7.4 Hz, 2H, $C^{\alpha II}C^{\beta}H_2C^{\gamma}\mathbf{H_2}$), 1.40-1.28 (m, 6H, $C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}\mathbf{H_2}C^{\varepsilon}\mathbf{H_2}C^{\zeta}\mathbf{H_2}C^{\eta}H_3$), 1.15 (s, 3H, $C^{\alpha I}HN\mathbf{H_3}Cl$), 1.04 (d, ^{3}J = 6.8 Hz, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$), 1.00 (d, ^{3}J = 6.4 Hz, 3H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$), 0.92 (t, ^{3}J = 6.28 Hz, 3H, $C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}\mathbf{H_3}$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 167.0 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}CH\mathbf{C}O_2$), 142.3 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}{=}CHCO_2$), 126.4 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}{=}\mathbf{C}HCO_2$), 89.3 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}{=}CHCO_2$), 88.6 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}{=}CHCO_2$), 51.9 ($CO_2\mathbf{C}H_3$), 43.3 ($\mathbf{C^{\alpha I}}HC^{\beta}H_2C^{\gamma}H(CH_3)_2$), 43.2 ($C^{\alpha I}H\mathbf{C^{\beta}}H_2C^{\gamma}H(CH_3)_2$), 32.8 ($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2\mathbf{C^{\varepsilon}}H_2C^{\zeta}H_2C^{\eta}H_3$), 32.7 ($C^{\alpha II}\mathbf{C^{\beta}}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$), 29.9 ($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2\mathbf{C^{\delta}}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$), 29.4 ($C^{\alpha II}C^{\beta}H_2\mathbf{C^{\gamma}}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2C^{\eta}H_3$), 26.6 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C^{\gamma}}H(CH_3)_2$), 23.6 ($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2\mathbf{C^{\zeta}}H_2C^{\eta}H_3$), 23.3 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 21.5 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 14.4

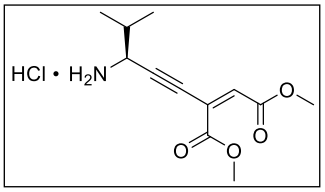
($C^{\alpha II}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2C^{\varepsilon}H_2C^{\zeta}H_2\mathbf{C}^{\eta}H_3$). $C_{17}H_{30}ClNO_2$ (315.88 g mol^{-1}). MS(ESI): t*r* = 8.2 min, *m/z* = 280.2325 (calcd. 280.2271 $[M\text{-}Cl^-]^+$), 302.2138 (calcd. 302.2091 $[M\text{-}HCl+Na]^+$).

Methyl (*S*,*Z*)-6-Amino-6-cyclohexyl-3-(((methoxycarbonyl)oxy)methyl)hex-2-en-4-ynoate Hydrochloride (75i). Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a vigorously stirred solution of propargyl-3-acrylate **74i** (81.0 mg, 196 μmol) in MeOH (4 mL). The reaction mixture was stirred overnight at rt before evaporating the solvent under reduced pressure.



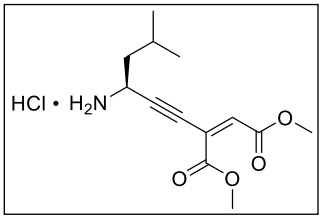
Colorless crystalline solid. Yield: 67.6 mg, 196 μmol, quantitative. ^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ = 6.30 (t, ^4J = 2.0 Hz, 1H, $H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2OCO_2CH_3){=}C^{\alpha II}\mathbf{H}CO_2CH_3$), 5.25 (dd, ^2J = 15.2 Hz, ^4J = 1.9 Hz, 1H, $H_2NC^{\alpha I}HC{\equiv}C\text{-}C(C\mathbf{H}_2OCO_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 5.22 (dd, ^2J = 15.2 Hz, ^4J = 1.9 Hz, 1H, $H_2NC^{\alpha I}HC{\equiv}C\text{-}C(C\mathbf{H}_2OCO_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 4.19 (d, ^3J = 5.6 Hz, 1H, $H_2NC^{\alpha I}\mathbf{H}C{\equiv}C\text{-}C(CH_2OCO_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 3.80 (s, 3H, $H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2OCO_2CH_3){=}C^{\alpha II}HCO_2C\mathbf{H_3}$), 3.75 (s, 3H, $H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2OCO_2C\mathbf{H_3}){=}C^{\alpha II}HCO_2CH_3$), 1.92 (d br., ^2J = 13.5 Hz, 1H, cy-2-**H**), 1.89-1.81 (m, 6H, cy-1-**H**, cy-2-**H**, cy-4-**H**, cy-5-**H**, cy-6-**H**, cy-6-**H**), 1.78 (d br., ^2J = 12.4 Hz, 1H, cy-4-**H**), 1.73 (d br., ^2J = 13.4 Hz, 1H, cy-3-**H**), 1.30-1.17 (m, 2H, cy-3-**H**, cy-5-**H**). ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 166.4 ($H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2O\mathbf{C}O_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 157.0 ($H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2OCO_2CH_3){=}C^{\alpha II}H\mathbf{C}O_2CH_3$), 147.6 ($H_2NC^{\alpha I}HC{\equiv}C\text{-}\mathbf{C}(CH_2OCO_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 128.0 ($H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2OCO_2CH_3){=}\mathbf{C}^{\alpha II}HCO_2CH_3$), 90.9 ($H_2NC^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C(CH_2OCO_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 85.6 ($H_2NC^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C(CH_2OCO_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 65.5 ($H_2NC^{\alpha I}HC{\equiv}C\text{-}C(\mathbf{C}H_2OCO_2CH_3){=}C^{\alpha II}HCO_2CH_3$), 55.7 ($H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2OCO_2CH_3){=}C^{\alpha II}HCO_2\mathbf{C}H_3$), 52.4 ($H_2NC^{\alpha I}HC{\equiv}C\text{-}C(CH_2OCO_2\mathbf{C}H_3){=}C^{\alpha II}HCO_2CH_3$), 42.0 (cy-**C**-1), 30.3 (cy-**C**-2), 28.8 (cy-**C**-6), 28.4 (cy-**C**-4), 26.7 (cy-**C**-5), 26.5 (cy-**C**-3). $C_{16}H_{24}ClNO_5$ (345.82 g mol^{-1}).

Dimethyl (*S*)-2-(3-Amino-4-methylpent-1-yn-1-yl)maleate Hydrochloride (75j).
Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a vigorously stirred solution of propargyl-3-acrylate **74j** (13.9 mg, 40.5 µmol) in MeOH (4 mL). The reaction mixture was stirred overnight at rt before evaporating the solvent under reduced pressure.



Deeply yellow highly viscous oil. Yield: 11.1 mg, 40.5 µmol, quantitative. ^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ = 6.59 (s, 1H, NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=C**H**-CO$_2$CH$_3$), 4.25 (d, ^{3}J = 5.7 Hz, 1H, NHC$^{\alpha I}$**H**C≡CC$^{\alpha II}$=CH-CO$_2$CH$_3$), 3.82 (s, 3H, C$^{\alpha II}$C$^{\beta}$O$_2$C**H$_3$**), 3.77 (s, 3H, NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=CH-CO$_2$C**H$_3$**), 2.15 (m, 1H, C$^{\alpha I}$HC**H**(CH$_3$)$_2$), 1.12 (d, ^{3}J = 6.7 Hz, 3H, C$^{\alpha I}$HCH(C**H$_3$**)$_2$), 1.10 (d, ^{3}J = 6.8 Hz, 3H, C$^{\alpha I}$HCH(C**H$_3$**)$_2$). ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 165.9 (**C**O$_2$CH$_3$), 165.3 (**C**O$_2$CH$_3$), 133.1 (NHC$^{\alpha I}$HC≡CC$^{\alpha II}$=**C**H-CO$_2$CH$_3$), 127.9 (NHC$^{\alpha I}$HC≡C**C$^{\alpha II}$**=CH-CO$_2$CH$_3$), 91.1 (NHC$^{\alpha I}$H**C**≡CC$^{\alpha II}$=CH-CO$_2$CH$_3$), 83.4 (NHC$^{\alpha I}$HC≡**C**C$^{\alpha II}$=CH-CO$_2$CH$_3$), 53.7 (CO$_2$**C**H$_3$), 52.9 (CO$_2$**C**H$_3$), 50.2 (**C$^{\alpha I}$**HCH(CH$_3$)$_2$), 32.8 (C$^{\alpha I}$H**C**H(CH$_3$)$_2$), 19.4 (C$^{\alpha I}$HCH(**C**H$_3$)$_2$), 17.3 (C$^{\alpha I}$HCH(**C**H$_3$)$_2$). C$_{12}$H$_{18}$ClNO$_4$ (275.73 g mol^{-1}). LCMS(ESI): t$_r$ = 5.1 min, *m/z* = 240.1275 (calcd. 240.1230 [M+H]$^+$), 262.0925 (calcd. 262.1050 [M+Na]$^+$), 479.2488 (calcd. 479.2388 [2M+H]$^+$).

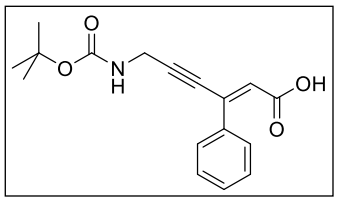
Dimethyl (*S*)-2-(3-Amino-5-methylhex-1-yn-1-yl)maleate Hydrochloride (75j).
Hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a solution of the peptidomimetic in MeOH (4 mL). After stirring the solution overnight, the solvent was evaporated under reduced pressure. The desired amine was achieved quantitatively with minor impurities as hydrochloric salt. Brightly yellow oil. Yield: 17.4 mg, 50.4 µmol, quantitative.



^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ = 6.57 (s, 1H, C$^{\alpha I}$HC≡C-C$^{\alpha II}$(CO$_2$CH$_3$)=C**H**CO$_2$), 4.37 (m, 1H, C$^{\alpha I}$**H**C≡C-C$^{\alpha II}$(CO$_2$CH$_3$)=CHCO$_2$CH$_3$), 3.81 (s, 3H, C$^{\alpha I}$HC≡C-C$^{\alpha II}$(CO$_2$CH$_3$)=CHCO$_2$C**H$_3$**), 3.76 (s, 3H, C$^{\alpha I}$HC≡C-C$^{\alpha II}$(CO$_2$C**H$_3$**)=CHCO$_2$CH$_3$), 2.02 (s, 3H, C$^{\alpha I}$HN**H$_3$**Cl), 1.86 (m, 1H, C$^{\alpha I}$HC$^{\beta}$H$_2$C$^{\gamma}$**H**(CH$_3$)$_2$), 1.52-1.43 (m, 2H, C$^{\alpha I}$HC$^{\beta}$**H$_2$**C$^{\gamma}$H(CH$_3$)$_2$), 1.05-0.94 (m, 6H, C$^{\alpha I}$HC$^{\beta}$H$_2$C$^{\gamma}$H(C**H$_3$**)$_2$). ^{13}C NMR (126 MHz, Methanol-*d*$_4$) δ = 165.9 (C$^{\alpha I}$HC≡C-

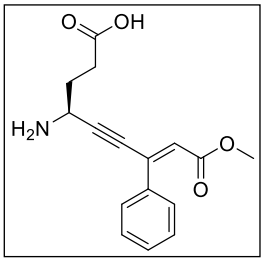
$C^{\alpha II}(\mathbf{C}O_2CH_3)=CHCO_2CH_3$), 165.2 ($C^{\alpha I}HC\equiv C\text{-}C^{\alpha II}(CO_2CH_3)=CH\mathbf{C}O_2CH_3$), 137.4 ($C^{\alpha I}HC\equiv C\text{-}\mathbf{C}^{\boldsymbol{\alpha II}}(CO_2CH_3)=CHCO_2CH_3$), 133.0 ($C^{\alpha I}HC\equiv C\text{-}C^{\alpha II}(CO_2CH_3)=\mathbf{C}HCO_2CH_3$), 92.6 ($C^{\alpha I}H\mathbf{C}\equiv C\text{-}C^{\alpha II}(CO_2CH_3)=CHCO_2CH_3$), 82.5 ($C^{\alpha I}HC\equiv\mathbf{C}\text{-}C^{\alpha II}(CO_2CH_3)=CHCO_2CH_3$), 53.7 ($C^{\alpha I}HC\equiv C\text{-}C^{\alpha II}(CO_2CH_3)=CHCO_2\mathbf{C}H_3$), 52.9 ($C^{\alpha I}HC\equiv C\text{-}C^{\alpha II}(CO_2\mathbf{C}H_3)=CHCO_2CH_3$), 43.3 ($\mathbf{C}^{\boldsymbol{\alpha I}}HC^{\beta}H_2C^{\gamma}H(CH_3)_2$), 42.9 ($C^{\alpha I}H\mathbf{C}^{\boldsymbol{\beta}}H_2C^{\gamma}H(CH_3)_2$), 26.4 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C}^{\boldsymbol{\gamma}}H(CH_3)_2$), 23.2 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 21.6 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$). $C_{13}H_{20}ClNO_4$ (289.76 g mol^{-1}), MS(ESI): t*r* = 5.9 min, *m/z* = 254.1436 (calcd. 254.1387 $[M\text{-}Cl^-]^+$), 276.1234 (calcd. 276.1206 $[M\text{-}HCl+Na]^+$).

(*E*)-6-((*tert*-Butoxycarbonyl)amino)-3-phenylhex-2-en-4-ynoic Acid (75a). An aqueous solution of LiOH (1 M, 5.0 mL) was carefully dropped into a vigorously stirred solution of propargyl-3-acrylate **74a** (507 mg, 1.61 mmol) in MeOH (10 mL) at 0 °C. The reaction mixture was continued stirring at 0 °C until the starting material was completely consumed (checked by TLC, about 3 h). The mixture was poured into an aqueous $KHSO_4$ solution (5 %, 20 mL) and immediately extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude acid **75a** was purified by preparative HPLC.

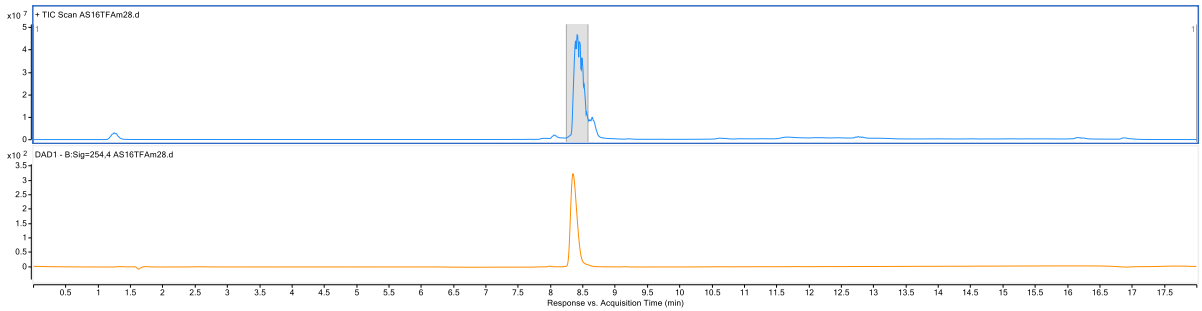


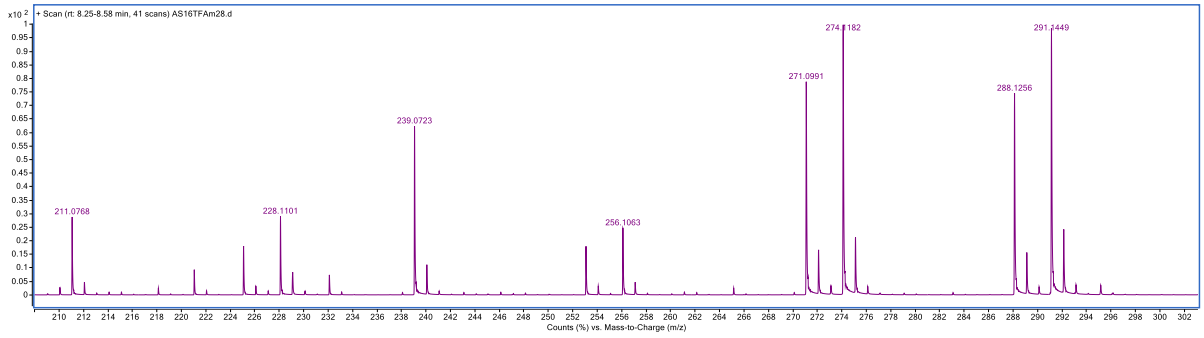
Slightly brown highly viscous oil. Yield: 392 mg, 1.30 mmol, 81 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.06 (t, ^3J = 7.8 Hz, 1H, $C^{\alpha I}H_2N\mathbf{H}Boc$), 7.45-7.38 (m, 2H, ar-2-**H**, ar-6-**H**), 7.35-7.31 (m, 3H, ar-3-**H**, ar-4-**H**, ar-5-**H**), 6.27 (s, 1H, $C^{\alpha I}H_2C\equiv C\text{-}C^{\alpha II}=C\mathbf{H}CO_2H$), 4.11 (s, 2H, $C^{\alpha I}\mathbf{H}_2C\equiv C\text{-}C^{\alpha II}=CHCO_2H$), 1.44 (s, 9H, $NHCO_2C(C\mathbf{H}_3)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 169.0 ($C^{\alpha I}H_2C\equiv C\text{-}C^{\alpha II}=CH\mathbf{C}O_2H$), 157.6 ($NH\mathbf{C}O_2C(CH_3)_3$), 136.0 ($C^{\alpha I}H_2C\equiv C\text{-}\mathbf{C}^{\boldsymbol{\alpha II}}=CHCO_2H$), 130.2 (Ph-**C**-1), 129.2 (Ph-**C**-4), 128.7 (Ph-**C**-3, Ph-**C**-5), 128.1 (Ph-**C**-2, Ph-**C**-6), 124.4 ($C^{\alpha I}H_2C\equiv C\text{-}C^{\alpha II}=\mathbf{C}HCO_2H$), 92.7 ($C^{\alpha I}H_2\mathbf{C}\equiv C\text{-}C^{\alpha II}=CHCO_2H$), 84.0 ($NHCO_2\mathbf{C}(CH_3)_3$), 80.4 ($C^{\alpha I}H_2C\equiv\mathbf{C}\text{-}C^{\alpha II}=CHCO_2H$), 31.4 ($\mathbf{C}^{\boldsymbol{\alpha I}}H_2C\equiv C\text{-}C^{\alpha II}=CHCO_2H$), 28.4 ($NHCO_2C(\mathbf{C}H_3)_3$). $C_{17}H_{19}NO_4$ (301.34 g mol^{-1}). MS(ESI): *m/z* = 246.0724 (calcd. 246.0761 $[M\text{-}C(CH_3)_3+H]^+$).

(*S*,*E*)-4-Amino-9-methoxy-9-oxo-7-phenylnon-7-en-5-ynoate (75l). Crude ester **75d** (22.8 mg, 60.1 µmol) was carefully dissolved in a mixture of TFA/H_2O/TIPS (95:2.5:2.5, 1 mL) and stirred overnight at ambient temperature. The clear yellow solution was poured into icecold Et_2O (20 mL). This lead to precipitation of a fine, colorless solid which was separated by centrifugation. After removing the solvent with a cannula, the crude product was purified by preparative HPLC.



Colorless, amorphous solid. Yield: 4.15 mg, 14.4 µmol, 24 %. ^{1}H NMR (500 MHz, Methanol-d_4) δ = 7.42-7.39 (m, 2H, Ph-2-**H**, Ph-6-**H**), 7.39-7.36 (m, 3H, Ph-3-**H**, Ph-4-**H**, Ph-5-**H**), 6.44 (s, 1H, $H_2NC^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}Ph{=}C\mathbf{H}CO_2CH_3$), 4.45 (dd, ^3J = 9.4 Hz, ^3J = 5.3 Hz, 1H, $C^{\alpha I}\mathbf{H}C^{\beta}H_2C^{\gamma}H_2CO_2H$), 3.62 (s, 3H, $H_2NC^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}Ph{=}CHCO_2C\mathbf{H_3}$), 2.60 (dd, ^2J = 17.3 Hz, ^3J = 6.4 Hz, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}_2CO_2H$), 2.54 (dd, ^2J = 17.3 Hz, ^3J = 7.4 Hz, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}_2CO_2H$), 2.21 (dtd, ^2J = 13.0 Hz, ^3J = 7.6 Hz, ^3J = 5.3 Hz, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H_2CO_2H$), 2.06 (ddt, ^2J = 13.5 Hz, ^3J = 9.4 Hz, ^3J = 6.7 Hz, 1H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H_2CO_2H$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 175.4 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2\mathbf{C}O_2H$), 167.0 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(Ph){=}CH\mathbf{C}O_2CH_3$), 166.8 ($C^{\alpha I}HC{\equiv}C\text{-}\mathbf{C^{\alpha II}}(Ph){=}CHCO_2CH_3$), 136.8 (Ph-**C**-1), 130.4 (Ph-**C**-4), 129.4 (Ph-**C**-3, Ph-**C**-5), 129.2 (Ph-**C**-2, Ph-**C**-6), 127.6 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(Ph){=}\mathbf{C}HCO_2CH_3$), 89.0 ($C^{\alpha I}H\mathbf{C}{\equiv}C\text{-}C^{\alpha II}(Ph){=}CHCO_2CH_3$), 88.9 ($C^{\alpha I}HC{\equiv}\mathbf{C}\text{-}C^{\alpha II}(Ph){=}CHCO_2CH_3$), 52.2 ($C^{\alpha I}HC{\equiv}C\text{-}C^{\alpha II}(Ph){=}CHCO_2\mathbf{C}H_3$), 44.0 ($\mathbf{C^{\alpha I}}HC^{\beta}H_2C^{\gamma}H_2CO_2H$), 30.6 ($C^{\alpha I}HC^{\beta}H_2\mathbf{C}^{\gamma}H_2CO_2H$), 29.6 ($C^{\alpha I}H\mathbf{C^{\beta}}H_2C^{\gamma}H_2CO_2H$). $C_{16}H_{17}NO_4$ (287.32 g mol^{-1}). LCMS(ESI): *tr* = 8.4 min, *m/z* = 288.1256 (calcd. 288.1230 $[M+H]^+$).

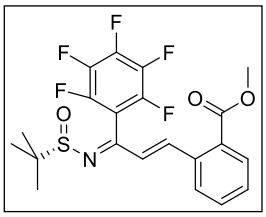




IIX-3. j) Propargylamide-Enimine Rearrangement (76-78)

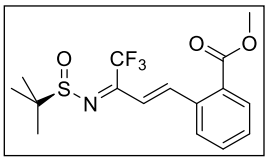
Description and characterization of α,β-unsaturated imines **76c,f** and **77c** has been previously published [1].

Methyl 2-((1*E*,3*Z*)-3-(((*S*)-*tert*-Butylsulfinyl)imino)-3-(perfluorophenyl)prop-1-en-1-yl)benzoate (76a). Piperidine (0.2 mL, 2.0 mmol) was added to a solution of peptidomimetic **27l** (4.2 mg, 9.1 μmol) in THF (0.5 mL). The reaction mixture was stirred 30 min at ambient temperature. After dilution of the crude solution with an aqueous $KHSO_4$ solution (5 %, 0.5 mL) and extraction with Et_2O (3 x 5 mL), the solvent of the combined organic layers was evaporated under reduced pressure. The crude product was purified by preparative HPLC.



Brightly yellow oil. Yield: 1.8 mg, 3.9 μmol, 43 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.15 (d, ^3J = 16.0 Hz, 1H, N=C(C_6F_5)-CH=C**H**-ar), 7.96 (d, ^3J = 8.0 Hz, 1H, ar-6-**H**), 7.66 (d, ^3J = 7.1 Hz, 1H, ar-3-**H**), 7.54 (t, ^3J = 7.6 Hz, 1H, ar-5-**H**), 7.43 (t, ^3J = 7.6 Hz, 1H, ar-3-**H**), 6.97 (d, ^3J = 16.0 Hz, 1H, N=C(C_6F_5)-C**H**=CH-ar), 3.82 (s, 3H, CO_2CH_3), 1.31 (s, 9H, SC(CH_3)$_3$). ^{19}F NMR (470 MHz, Chloroform-*d*) δ = -170.9 (t, ^3J = 20.2 Hz, C_6F_5-3-**F**, C_6F_5-5-**F**), -171.1 (dd, ^3J = 22.3 Hz, ^3J = 6.3 Hz, C_6F_5-4-**F**), -171.5 (dd, ^3J = 22.1 Hz, ^3J = 7.3 Hz, C_6F_5-2-**F**, C_6F_5-6-**F**). $C_{21}H_{18}F_5NO_3S$ (459.43 g mol^{-1}). MS(ESI): *m/z* = 460.10090 (calcd. 460.10003 $[M+H]^+$).

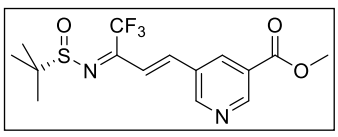
Methyl 2-((1*E*,3*Z*)-3-(((*R*)-*tert*-Butylsulfinyl)imino)-4,4,4-trifluorobut-1-en-1-yl)benzoate (76b). Piperidine (0.2 mL, 2.0 mmol) was added to a solution of



peptidomimetic **27o** (4.4 mg, 10 μmol) in THF (0.5 mL). The reaction mixture was stirred 30 min at ambient temperature. After dilution of the crude solution with an aqueous $KHSO_4$ solution (5 %, 0.5 mL) and extraction with Et_2O (3 x 5 mL), the solvent of the combined organic layers was evaporated under reduced pressure. The crude product was purified by preparative HPLC.

Brightly yellow oil. Yield: 1.0 mg, 2.7 μmol, 24 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.79 (d, ^3J = 16.0 Hz, 1H, N=C(CF_3)-CH=C**H**-ar), 8.04 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, ar-6-**H**), 7.68 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, ar-3-**H**), 7.60 (td, ^3J = 7.6 Hz, ^4J = 1.7 Hz, 1H, ar-5-**H**), 7.54 (td, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, ar-4-**H**), 6.84 (d, ^3J = 16.0 Hz, 1H, N=C(CF_3)-C**H**=CH-ar), 3.95 (s, 2H, $CO_2C\mathbf{H_3}$), 1.23 (s, 9H, SC($C\mathbf{H_3}$)$_3$). ^{19}F NMR (282 MHz, Chloroform-*d*) δ = -82.8 (s, 3F, $C\mathbf{F_3}$). $C_{16}H_{18}F_3NO_3S$ (361.38 g mol^{-1}). MS(ESI): *m/z* = 362.218 (calcd. 362.1032 $[M+H]^+$), 384.167 (calcd. 384.0852 $[M+Na]^+$).

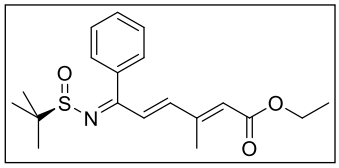
Methyl 5-((1*E*,3*Z*)-3-(((*S*)-*tert*-Butylsulfinyl)imino)-4,4,4-trifluorobut-1-en-1-yl)nicotinate (76d). Under argon atmosphere, $PdCl_2(PPh_3)_2$ (1.2 mg) and CuI (1.8 mg) was added in one portion to a thoroughly degassed solution of propargylamide **6p** (51.0 mg, 224 μmol, 1.0 eq) and arBr **37a** (91.5 mg, 424 μmol, 1.9 eq) in a mixture of THF/DIPAH, (3:1, 1 mL). The reaction mixture was stirred over 3 d at rt. The clear brightly yellow solution was diluted with an aqueous NH_4Cl- (saturated, 5 mL) and $KHSO_4$ solution (5 %, 5 mL) and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude brightly yellow oil was purified by column chromatography (PE/EtOAc, 4:1).



Yellow oil. Yield: 2.3 mg, 6.3 μmol, 3 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 9.28 (s, 1H, ar-2-**H**), 8.98 (s, 1H, ar-6-**H**), 8.56 (s, 1H, ar-4-**H**), 7.99 (d, ^3J = 16.1 Hz, 1H, C(CF_3)C**H**=CHar), 7.16 (d, ^2J = 16.1 Hz, 1H, C(CF_3)CH=C**H**ar), 4.01 (s, 3H, $CO_2C\mathbf{H_3}$), 1.25 (s, 9H, SC($C\mathbf{H_3}$)$_3$). $C_{15}H_{17}F_3N_2O_3S$ (362.37 g mol^{-1}). LCMS(ESI): t*r* = 8.7 min, *m/z* =

363.0987 (calcd. 363.0985 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.6, R*f* (PE/EtOAc, 2:1) = 0.37. $[\alpha]_{589}^{20}$ = +26.35 (*c* 0.39, MeOH).

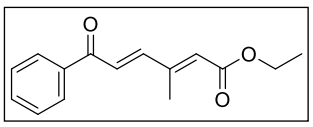
Ethyl (2*E*,4*E*,6*Z*)-6-(((*R*)-*tert*-Butylsulfinyl)imino)-3-methyl-6-phenylhexa-2,4-dienoate (76f). A mixture of $Pd(OAc)_2$ (6 mg, 27 μmol, 11 mol%), TDMPP (12 mg, 27 μmol, 11 mol%) in dry toluene (3 mL) was stirred 15 min at ambient temperature under argon atmosphere to give a brightly red catalyst solution. D-Glycine analogous propargylamide **6n** (55.9 mg, 238 μmol, 1.0 eq) and alanin analogous propynoate **73a** (41 μL, 350 μmol, 1.5 eq) were added in one portion, turning the solution a black colour. After stirring the reaction mixture overnight, it was filtered through a pad of charcoal (1 cm) on silica (1 cm). The pad was purged with CH_2Cl_2/Et_2O (1:1, 6 mL) and Et_2O (6 mL) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc, 4:1).



Brightly yellow oil. Yield: 11.1 mg, 32.0 μmol, 13 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.84 (d, ^3J = 7.7 Hz, 2H, Ph-2-**H**, Ph-6-**H**), 7.48 (t, ^3J = 7.6 Hz, 1H, Ph-4-**H**), 7.40 (t, ^3J = 6.8 Hz, 2H, Ph-3-**H**, Ph-5-**H**), 6.69 (dd, ^3J = 12.7 Hz, ^4J = 2.4 Hz, 1H, N=C$^{\alpha I}$(Ph)CHC**H**C$^{\alpha II}$(CH_3)$CHCO_2$), 6.46 (d, ^2J = 12.9 Hz, 1H, N=C$^{\alpha I}$(Ph)C**H**CHC$^{\alpha II}$(CH_3)$CHCO_2$), 5.80 (s, 1H, N=C$^{\alpha I}$(Ph)CHCHC$^{\alpha II}$(CH_3)C**H**CO_2), 4.08 (q, 6.88 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 2.03 (s, 3H, N=C$^{\alpha I}$(Ph)CHCHC$^{\alpha II}$(C**H₃**)$CHCO_2$), 1.35 (s, 9H, SC(C**H₃**)₃), 1.22 (t, ^3J = 6.9 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 175.6 (N=C$^{\alpha I}$(Ph)CHCHC$^{\alpha II}$(CH_3)CH**C**O_2), 166.3 (N=**C$^{\alpha I}$**(Ph)CHCHC$^{\alpha II}$(CH_3)$CHCO_2$), 151.0 (N=C$^{\alpha I}$(Ph)CHCH**C$^{\alpha II}$**(CH_3)$CHCO_2$), 137.3 (Ph-**C**-1), 137.0 (N=C$^{\alpha I}$(Ph)**C**HCHC$^{\alpha II}$(CH_3)$CHCO_2$), 132.4 (Ph-**C**-4), 128.8 (N=C$^{\alpha I}$(Ph)CH**C**HC$^{\alpha II}$(CH_3)$CHCO_2$), 128.7 (Ph-**C**-3, Ph-**C**-5), 128.5 (Ph-**C**-2, Ph-**C**-6), 122.5 (N=C$^{\alpha I}$(Ph)CHCHC$^{\alpha II}$(CH_3)**C**HCO_2), 60.0 ($CO_2\mathbf{C}H_2CH_3$), 57.8 (S**C**(CH_3)₃), 22.7 (SC(**C**H_3)₃), 16.8 (N=C$^{\alpha I}$(Ph)CHCHC$^{\alpha II}$(**C**H_3)$CHCO_2$), 14.4 ($CO_2CH_2\mathbf{C}H_3$). $C_{19}H_{25}NO_3S$ (347.16 g mol^{-1}). LCMS(ESI): t*r* = 10.3 min, *m/z* = 348.1759 (calcd. 348.1628 $[M+H]^+$), 370.1556 (calcd. 370.1447 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.39. UV/*Vis*: ε = 126136 cm^{-1} M^{-1} (in MeOH at λ_{max} = 287 nm, c = 17.6 μM, d = 1 cm). $[\alpha]_{589}^{20}$ = -38.37 (*c* 0.020, $CHCl_3$).

Ethyl (2*E*,4*E*)-3-Methyl-6-oxo-6-phenylhexa-2,4-dienoate (78f). A solution of hydrochloric acid (4 M in dioxane, 0.2 mL, 0.8 mmol) was added dropwise to a vigorously stirred, icecold solution of rearrangement product **76g** (11.1 mg, 32.0 µmol) in MeOH (4 mL). The reaction mixture was stirred overnight at ambient temperature, before evaporating the solvent under reduced pressure. The crude product was diluted with MeOH and the residual solvent was coevaporated.

Orange crystals. Yield: 11.1 mg, 32.0 µmol, 13 %. ^{1}H NMR (500 MHz, Methanol-d_4) δ =



8.68 (d, ^{3}J = 15.8 Hz, 1H, PhCOCH=C**H**-C(CH_3)=CH-CO_2), 8.04 (d, ^{3}J = 7.2 Hz, 2H, ar-2-**H**, ar-6-**H**), 7.56-7-52 (m, 3H, ar-3-**H**, ar-5-**H**, ar-4-**H**), 7.40 (dd, ^{3}J = 15.6 Hz, ^{4}J = 0.8 Hz, 1H, PhCOC**H**=CH-C(CH_3)=CH-CO_2), 6.20 (s, 1H, PhCOCH=CH-C(CH_3)=C**H**-CO_2), 4.20 (q, ^{3}J = 7.1 Hz, 2H, $CO_2C\mathbf{H_2}CH_3$), 2.42 (t, ^{4}J = 1.5 Hz, 3H, PhCOCH=CH-C(C**H₃**)=CH-CO_2), 1.30 (t, ^{3}J = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Methanol-d_4) δ = 190.5 (Ph**C**OCH=CH-C(CH_3)=CH-CO_2), 166.2 (PhCOCH=CH-C(CH_3)=CH-**C**O_2), 149.7 (PhCOCH=**C**H-C(CH_3)=CH-CO_2), 146.4 (PhCOC**H**=CH-C(CH_3)=CH-CO_2), 133.1 (ar-**C**-1), 128.5 (ar-**C**-3, ar-**C**-5), 128.3 (ar-**C**-2, ar-**C**-6), 127.9 (ar-**C**-4), 125.9 (PhCOCH=CH-C(CH_3)=**C**H-CO_2), 60.8 ($CO_2\mathbf{C}H_2CH_3$), 13.2 ($CO_2CH_2\mathbf{C}H_3$), 12.6 (PhCOCH=CH-C(**C**H_3)=CH-CO_2). $C_{15}H_{16}O_3$ (244.29 g mol^{-1}). LCMS(ESI): *m/z* = 245.1178 (calcd. 245.1172 $[M+H]^+$), 267.0454 (calcd. 267.0992 $[M+Na]^+$). $[\alpha]_{589}^{20}$ = -13.35 (*c* 0.120, $CHCl_3$). X-ray crystal structure in Chapter IIX-3. n.

IIX-3. k) UV/*Vis* Spectra, pH-Dependence and Photoisomerization Experiments

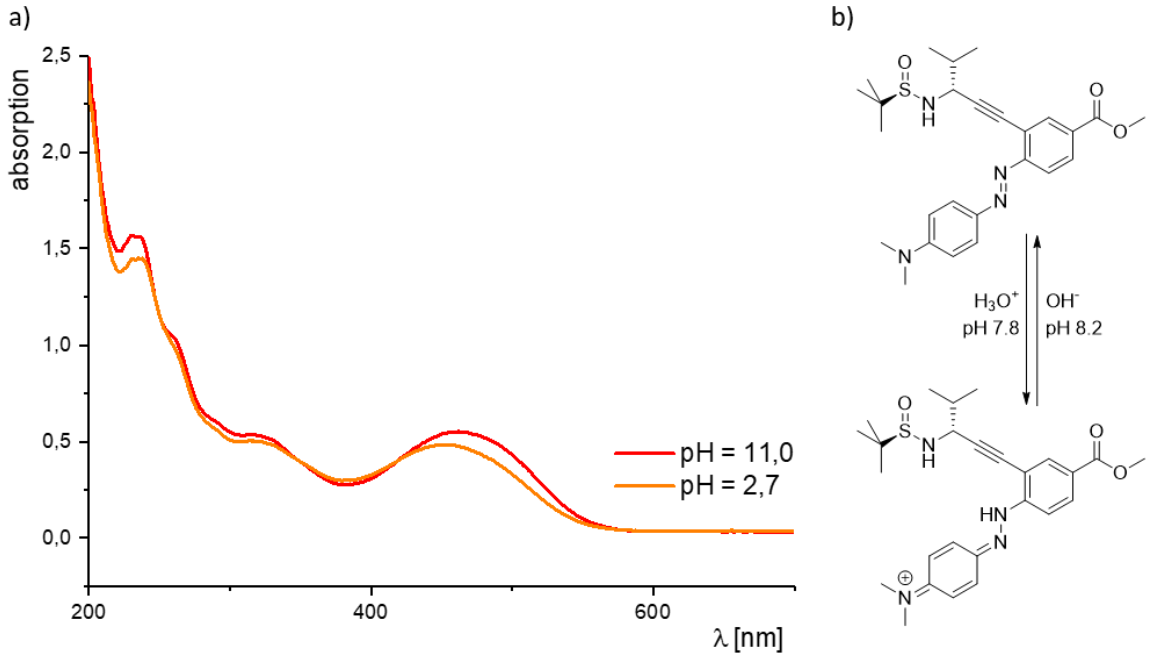


Diagram EP1. a) UV/*Vis* Spectra of peptidomimetic **42c** (0.1 µM) in aqueous solution at pH 11.0 (red curve) and at pH 2.7 (orange curve). b) Chemical structures of neutral- and protonated peptidomimetic **42c**.

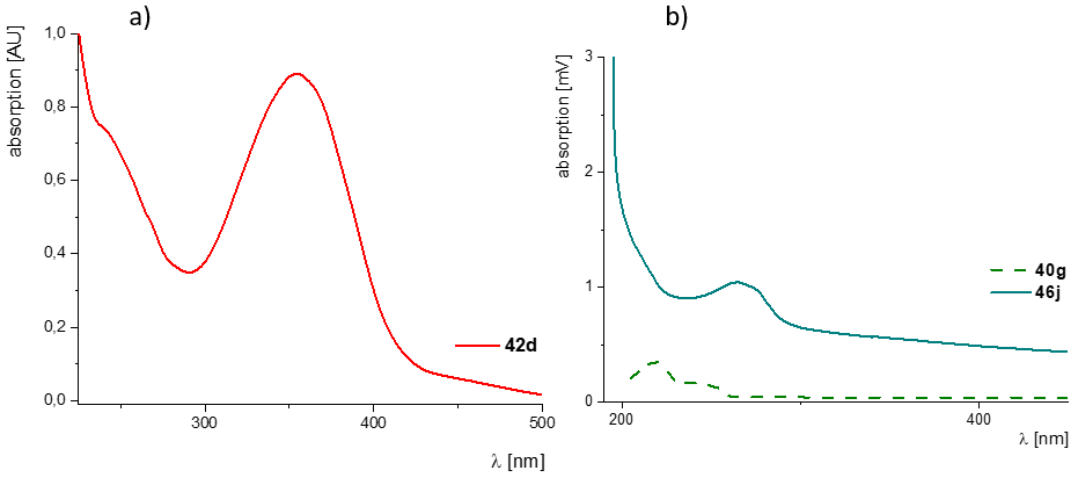


Diagram EP2: UV/*Vis* Spectra of azobenzene based peptidomimetic **42d** in comparison to other peptidomimetics. a) **42d** (c = 26.4 µM) in CH_3CN and a pathlength of 1 cm. b) Peptidomimetics with EWG CF_3-glycine analogous propargylamide moiety **40g** and phenylglycine analogous propargylamide moiety **46j** in CH_3CN.

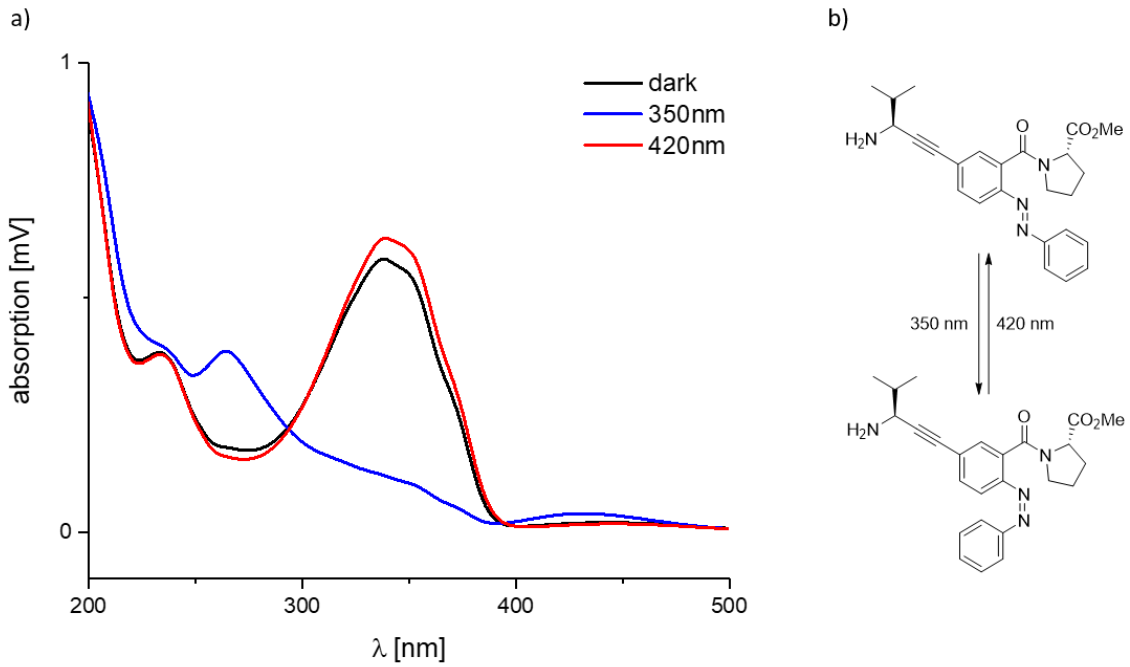


Diagram EP3: Photoisomerisation of compound **44**. a) UV/*Vis* Spectra of one sample of peptidomimetic **44**, measured at a concentration of 30.6 µM in CH_3CN and a pathlength of 1 cm. Black line: UV/Vis spectra of compound **44**. Blue line: UV/*Vis* Spectra of compound **44** after 15 min irradiation at 350 nm. Red line: UV/*Vis* Spectra of compound **44** after 15 min irradiation at 420 nm. All measurements were performed at a concentration of 30.6 µM in CH_3CN and a pathlength of 1 cm. b) Chemical structures of **44** with *E* and *Z* configurated azobenzene isomer.

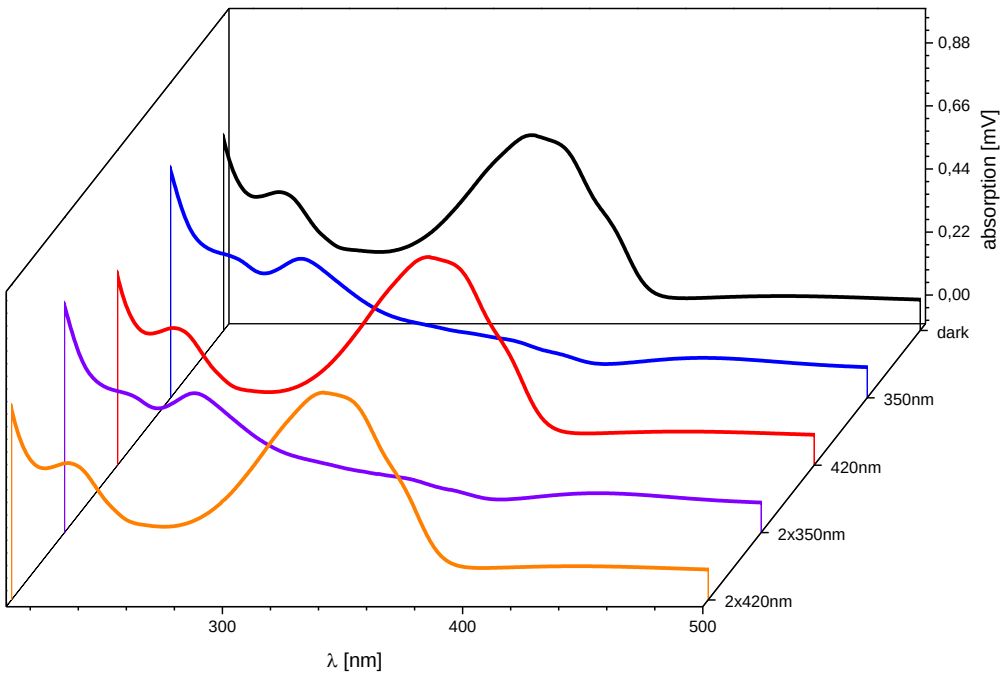


Diagram EP4: Reversibility of the photoisomerization of peptidomimetic **44**. Black line: UV/*Vis* Spectra of compound **44**. Blue line: UV/*Vis* Spectra of compound **44** after 15 min irradiation at 350 nm. Red line: UV/*Vis* Spectra of isomerized compound **44** after 15 min irradiation at 420 nm. Violet line: UV/*Vis* Spectra of isomerized compound **44** after another

15 min irradiation at 350 nm. Orange line: UV/*Vis* Spectra of isomerized compound **44** after 15 min irradiation at 420 nm. All measurements were performed with the same sample on the same day in a sequence at a concentration of 30.6 µM in CH_3CN and a pathlength of 1 cm.

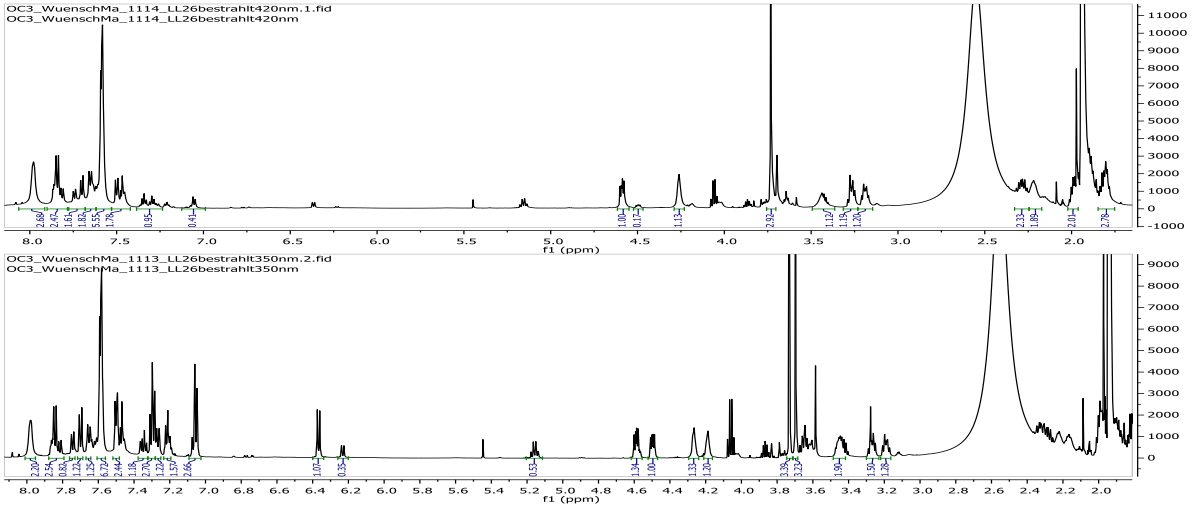


Diagram EP5: Influence of light irradiation on the ^{1}H NMR spectra of compound **44**. Above: after 15 min irradiation at 420 nm shows *E*:*Z* = 8.93:1.00 (11.2 % isomerization). Below: after 15 min irradiation at 350 nm shows *E*:*Z* = 2.16:1.00 (46.3 % isomerization).

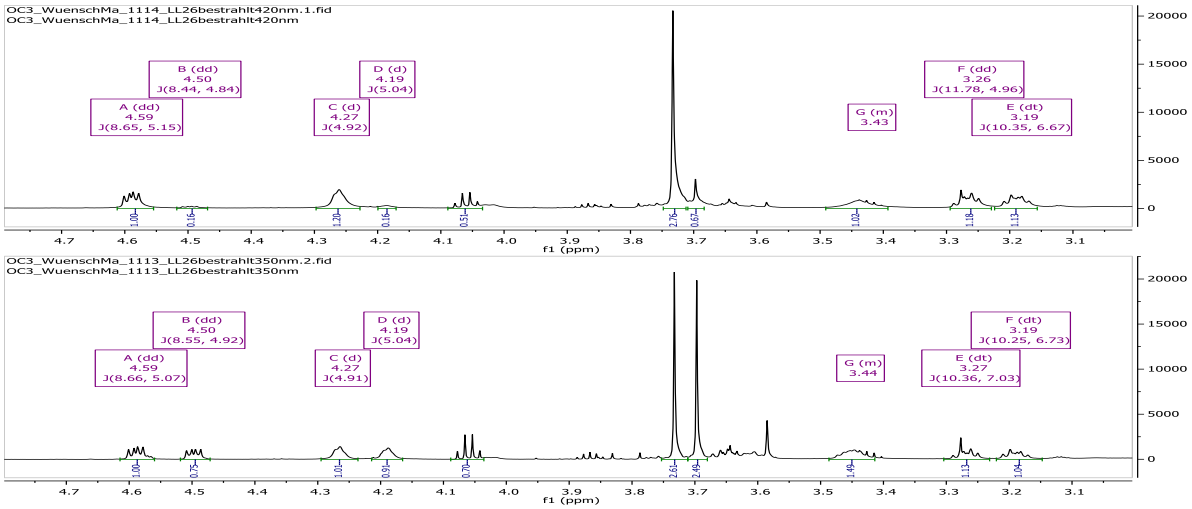


Diagramm EP6: Influence of irradiation on compound **44**, observed by ^{1}H NMR spectroscopy. Comparison of the region of the C$^\alpha$-proton in the ^{1}H NMR spectra (4.8-3.0 ppm). Above: after 15 min irradiation at 420 nm shows *E*:*Z* = 8.93:1.00 (11.2 % isomerization). Below: after 15 min irradiation at 350 nm shows *E*:*Z* = 2.16:1.00 (46.3 % isomerization).

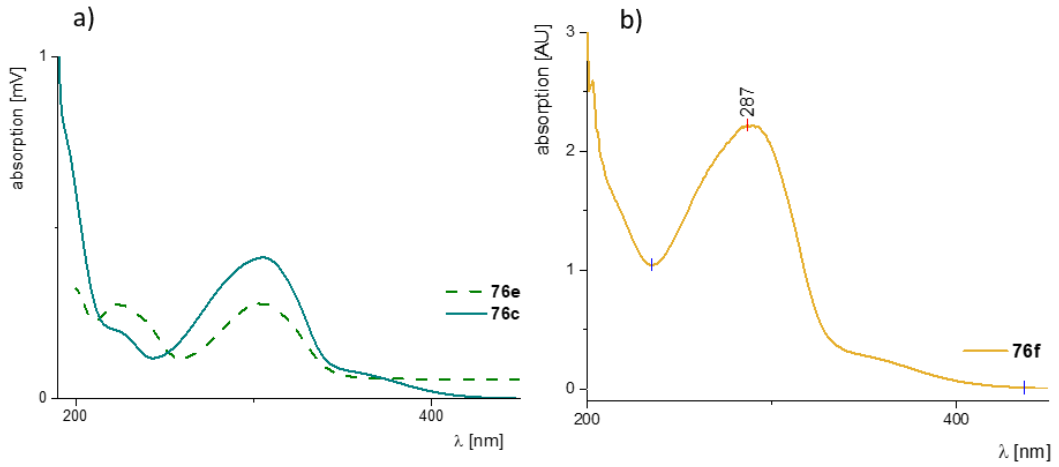


Diagram EP7: UV/*Vis* Spectra of diverse rearranged propargylamides. a) The EWG of the C^{α} was CF_3 in **76c** and Ph in **76e**. b) Analogue of H-Phe-Ala-OMe (**76f**). ε = 126136 cm^{-1} M^{-1} (in MeOH at λ_{max} = 287 nm, c = 17.6 µM, d = 1 cm, rt).

IIX-3. l) CD Spectroscopy

CD measurements were performed on a J-810 Jasco (Gross-Umstadt) in a range of at least 190-300 nm and at most 180-450 nm. A quartz tube with a pathlength of 1 mm was applied. CH_3CN and TFE solutions of the samples were diluted until the H(T) parameter was below 750 V. Each measurement was repeated with a dilution of 1:10 and compared qualitatively to the first measurement to detect intermolecular interaction. All spectra were baseline corrected and smoothed by Gauss approximation (f=25, 1x).

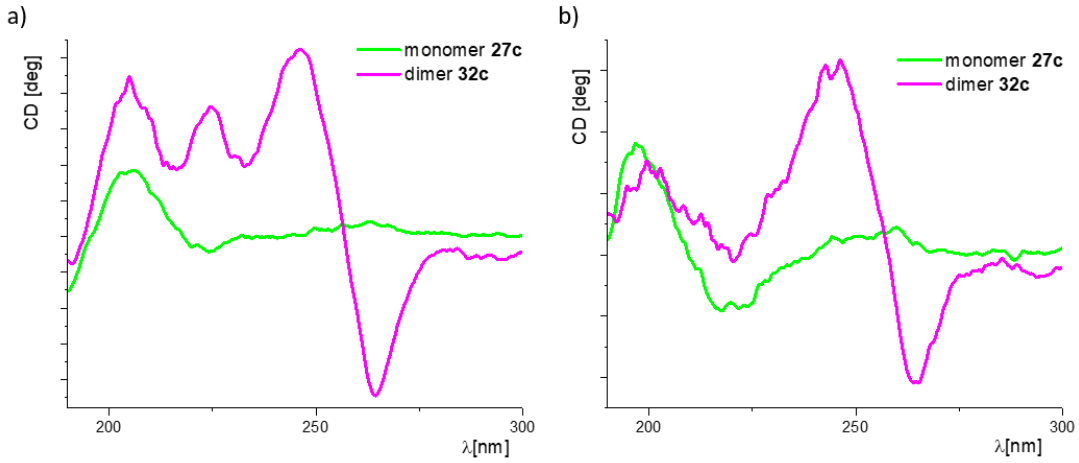


Diagram EP8. Comparison of CD spectra of 2-benzoate based peptidomimetic monomer **27c** and dimer **32c**, measured in a) CH_3CN and b) in TFE.

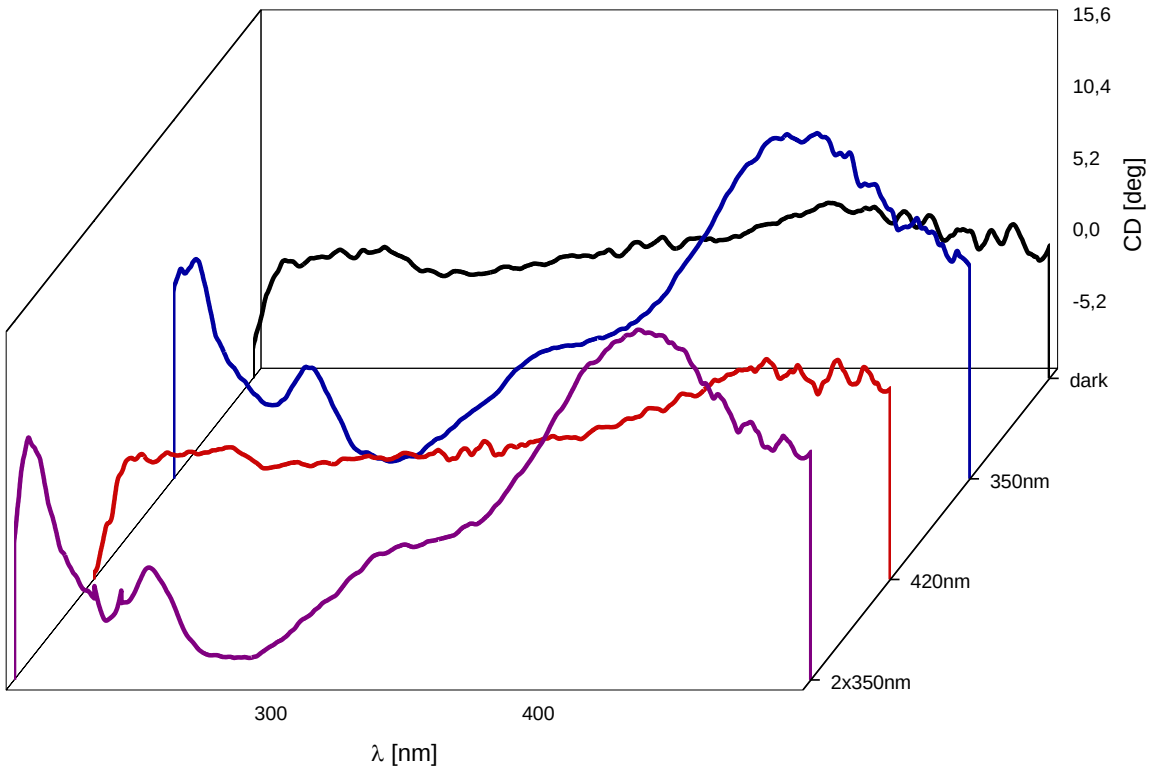


Diagram EP9: Photoisomerization of the conformation of peptidomimetic **44**. Black line: CD spectrum of compound **44**. Blue line: CD spectra of compound **44** after 15 min irradiation at 350 nm. Red line: CD spectra of isomerized compound **44** after 15 min irradiation at 420 nm. Violet line: CD spectra of isomerized compound **44** after another 15 min irradiation at 350 nm. All measurements were performed with the same sample on the same day in a sequence at a concentration of 765 µM in CH_3CN and a pathlength of 1 mm.

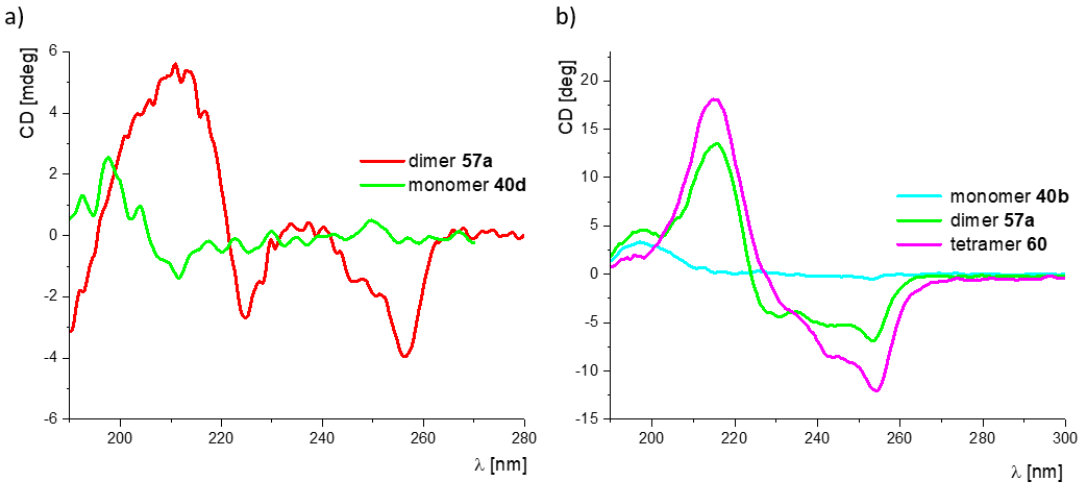


Diagram EP10. Comparison of CD spectra of 3-benzoate based peptidomimetic monomer **40d**, dimer **57a** and **60**, measured in a) CH_3CN and b) in TFE.

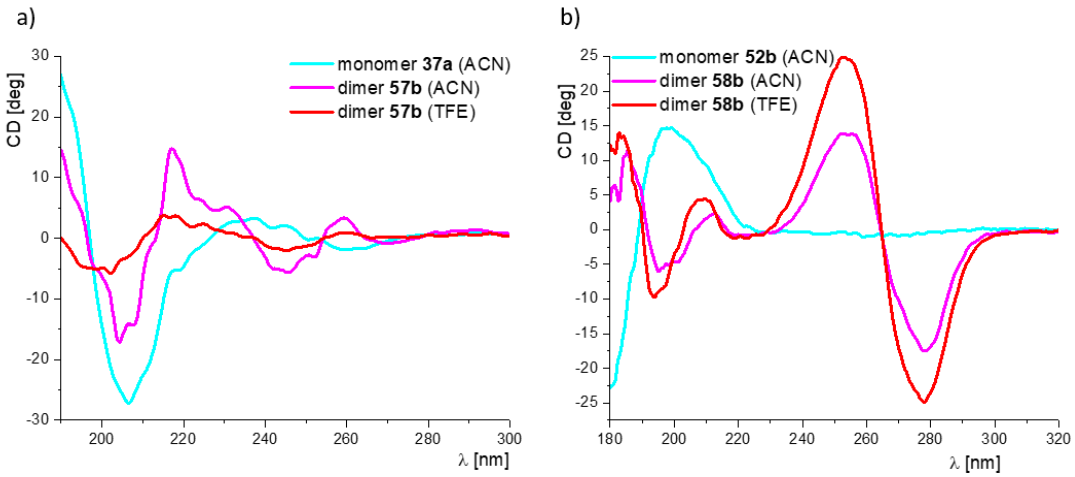


Diagram EP11. Comparison of CD spectra of a) nicotinate based peptidomimetic monomer **37a** and dimer **57b** measured in CH_3CN and in TFE and of b) 4-benzoate based peptidomimetic monomer **52b** and dimer **58b**.

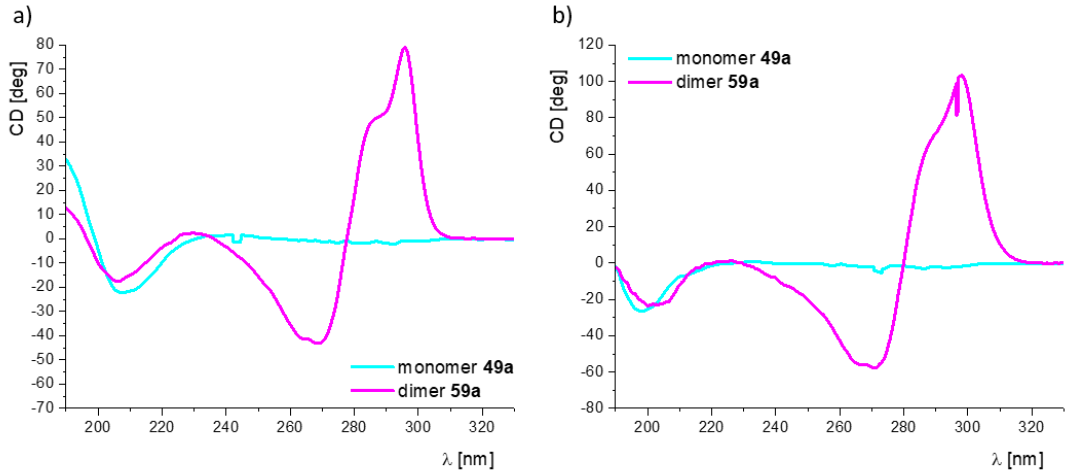


Diagram EP12. Comparison of CD spectra of furan based peptidomimetics **49a** and **59a**, measured in a) CH_3CN and b) in TFE.

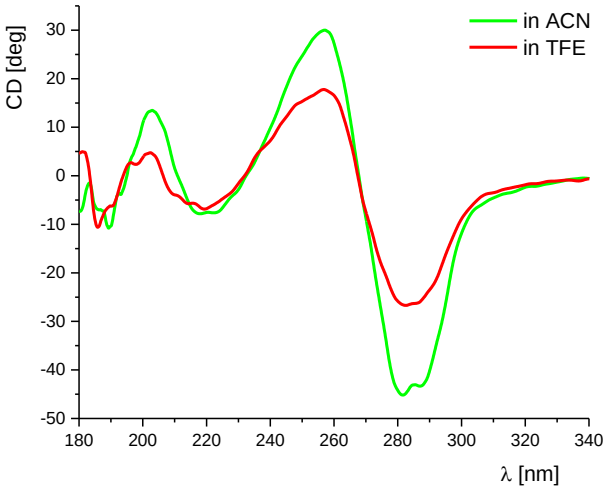


Diagram EP13. CD spectra of furan based peptidomimetic **53b**, measured in CH_3CN and TFE.

IIX-3. m) Molecular Dynamics (MD) Simulations

Accurate potentials of the backbone torsion angles ω1, ϕ, θ, ψ and ω2 are critical for a proper description of the conformational properties of the peptidomimetic scaffolds and were determined as described in the work of Krieger et al. [68]. Conformations of the peptidomimetics were optimized using the Merck Molecular Force Field (MMFF94) within Avogadro (number of steps: 5000, algorithm: steepest descent, convergence: $10e^{-7}$) with the torsion angles ω1, ϕ, θ, ψ and ω2 constrained at intervals of 20° over a range of 360°. The conformational energy (table 1) and the distance of ($C^{\alpha(n)}$-$C^{\alpha(n+1)}$) (table 2) was calculated after optimization. The energy profiles, derived from the calculations were validated by assignement of the dihedral angles, measured in the X-ray crystal structure. The dihedral angles of all D-configured peptidomimetics were mirrored prior to the assignment.

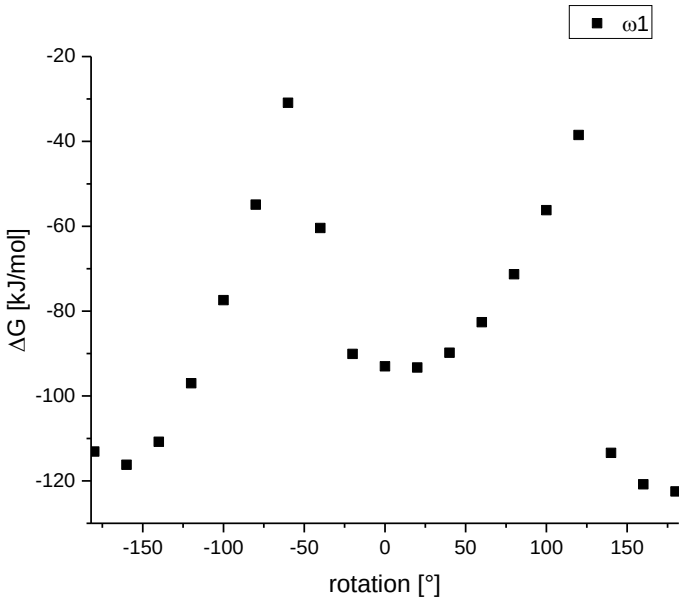
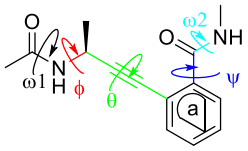


Diagram EP14. Exemplary energy profile of dihedral angle ω1 in the model compound of the *ortho*-substituted peptidomimetics. The points represent the relative (molecular mechanics) energy of the molecule, calculated using the *Merck* Molecular Force Field (MMFF94). The rotation of 6the discussed angle was constrained at angles in the range [-180°, 180°] at intervals of 20° prior to the structure optimization and energy calculation. The model has been designed in order to derive an energy profile which depends only on the examined angle.

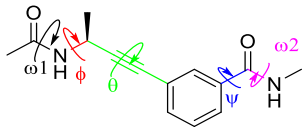
Table EP1. Energy values of the *ortho*-substituted peptidomimetic model compound for energy profile determination.



rotation °	ω1 ΔG [kJ/mol]	ϕ ΔG [kJ/mol]	θ ΔG [kJ/mol]	ψ ΔG [kJ/mol]	ω2 ΔG [kJ/mol]
-180	-113,1	-120,7	-108,5	-97,3	-112,8
-160	-116,2	-122,6	-109,5	-111,6	-122
-140	-110,8	-120	-110,5	-117,1	-115,6
-120	-97	-115	-111,6	-117,6	-103,4
-100	-77,4	-112,2	-113	-116,3	-85,5
-80	-54,9	-109,3	-114,7	-111,9	-62,8
-60	-30,9	-102,9	-115,3	-114,5	-39,5
-40	-60,4	-91,5	-119,1	-114,5	-103
-20	-90,1	-73,4	-122,2	-111,4	-104,7
0	-93	-49,8	-121,2	-103,3	-104,2
20	-93,3	-64,1	-116,5	-106,6	-100,6
40	-89,8	-78,6	-108,7	-110,6	-93,6

60	-82,6	-91	-105,1	-110,6	-83,4
80	-71,3	-91,4	-104,5	-113,4	-70,5
100	-56,2	-87,7	-105	-115,6	-55,6
120	-38,5	-94,6	-105,6	-122,1	-96,8
140	-113,4	-102,1	-106,3	-123	-108,8
160	-120,8	-112,4	-107	-119,9	-115,8
180	-122,5	-120	-108	-112,6	-117

Table EP2. Energy values of the *meta*-substituted peptidomimetic model compound for energy profile determination.



rotation °	ω1 ΔG [kJ/mol]	ϕ ΔG [kJ/mol]	θ ΔG [kJ/mol]	ψ ΔG [kJ/mol]	ω2 ΔG [kJ/mol]
-180	-147,5	-143,9	-146,3	-144,1	-148,2
-160	-145,8	-146,8	-146,3	-147,6	-147,1
-140	-138,4	-145	-146,7	-147,3	-140,3
-120	-125	-141,3	-147,2	-143,3	-127,7
-100	-105,9	-140,2	-147,5	-137	-108,7
-80	-103,6	-139,3	-147,9	-136,4	-115,7
-60	-114,4	-134,6	-148,1	-143,7	-122,3
-40	-122	-125,6	-148,4	-147,8	-126,3
-20	-128,9	-108,4	-148,5	-147,9	-128,1
0	-132	-96,6	-148,7	-144,6	-127,1
20	-132,1	-109,4	-148,6	-147,1	-123,4
40	-128,8	-122,2	-148,4	-146,7	-117,1
60	-121,7	-128,2	-147,9	-142,5	-114,5
80	-110,3	-130,1	-147,3	-135,5	-114,4
100	-101,8	-126,1	-146,7	-134,9	-106,1
120	-121,5	-120,9	-146,2	-141,7	-123,6
140	-134,8	-125	-145,8	-146,1	-135,5
160	-142,9	-136,2	-145,6	-146,8	-143,1
180	-146,3	-143,8	-145,7	-144	-147,4

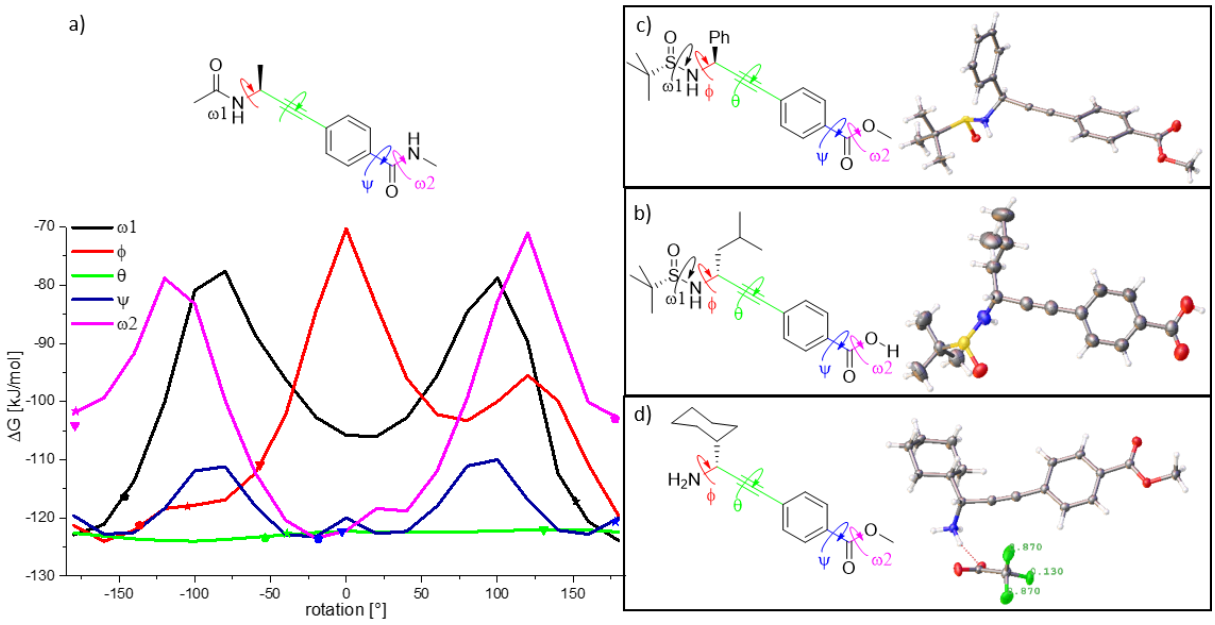
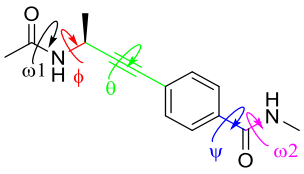


Figure EP2. Comparison of the torsion angles of peptidomimetics **46j**, **52b** and **55c**. a) Model compound, used for the calculation of the energy profiles corresponding to the torsion angles. The angles observed in the X-ray crystal structures are flagged with a pentagon (L-**46j**), a star (D-**52b**) and a triangle (D-**55c**) in the colors, corresponding to the respective angles. b) X-ray crystal structures of compounds L-**46j** (ω1 = -146°, ϕ = -136°, θ = -53°, α = 180°, ψ = 176°, and ω2 = 179°), c) D-**52b** (mirrored angles: ω1 = -150°, ϕ = -104°, θ = 38°, α = 175°, ψ = 179°, and ω2 = -174°) and d) D-**55c** (mirrored angles: ω1 n.a., ϕ = -56°, θ = -130°, α = 175°, ψ = −3°, and ω2 = -176°) (for more details, see Table EP3).

Table EP3. Energy values of the *para*-substituted peptidomimetic model compound for energy profile determination.



rotation °	ω1 ΔG [kJ/mol]	ϕ ΔG [kJ/mol]	θ ΔG [kJ/mol]	ψ ΔG [kJ/mol]	ω2 ΔG [kJ/mol]
-180	-122,9	-121,3	-122,6	-119,6	-102
-160	-121,1	-124	-123,1	-122,8	-99,4
-140	-113,6	-122,1	-123,6	-122,5	-91,7
-120	-100,1	-118,4	-123,9	-118,4	-78,8
-100	-80,9	-117,8	-124	-111,9	-83,2
-80	-77,6	-116,9	-123,7	-111,2	-99,8
-60	-88,6	-112,3	-123,3	-118	-112,3
-40	-96,2	-102,3	-122,9	-122,9	-120,4
-20	-102,7	-84,5	-122,5	-123,2	-123,5
0	-105,8	-70,3	-122,3	-120	-122,2

20	-106	-83,5	-122,4	-122,7	-118,4
40	-102,8	-96	-122,5	-122,3	-118,8
60	-95,6	-102,2	-122,5	-118	-112
80	-84,6	-103,3	-122,4	-111,1	-99,4
100	-78,8	-100	-122,2	-110	-82,8
120	-89,8	-95,5	-122,1	-116,9	-71
140	-112,4	-99,9	-122	-122,1	-86
160	-120,6	-110,8	-122,1	-122,8	-100,1
180	-123,9	-119,6	-122,4	-120	-102,9

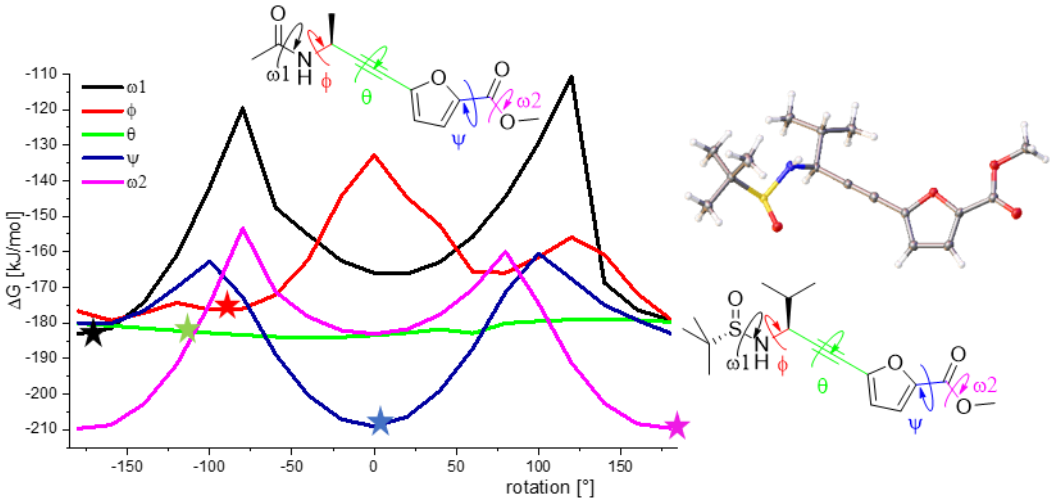


Figure EP3. Comparison of the torsion angles of the peptidomimetics with the results from MD calculations. Left side: Model compound, used for the calculation of the energy profiles corresponding to the torsion angles. The angles observed in the X-ray crystal structures are flagged with a star (L-**49a**) in the colors, corresponding to the respective angles. Right side: X-ray crystal structure of compound L-**49a** (ω1 = -162°, ϕ = -92°, θ = -112°, α = 129°, ψ = −8°, and ω2 = 178°). (For more details, see Table EP4).

Table EP4: Energy values of the furan-based peptidomimetic model compound for energy profile determination.

rotation	ω1	ϕ	θ	ψ	ω2
°	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]
-180	-183,1	-176,7	-180,1	-180	-209,7
-160	-181,5	-179,3	-180,8	-180,1	-208,7
-140	-174,2	-177,2	-181,5	-176,6	-202,8
-120	-160,9	-174,3	-182,2	-169,9	-191,6
-100	-141,8	-176,3	-182,8	-162,7	-174,6
-80	-119,6	-176	-183,4	-172,7	-153,4
-60	-147,6	-172,1	-183,9	-188,8	-171,3

-40	-155,3	-162,2	-184,1	-200,4	-178,3
-20	-162,5	-144,4	-184	-207,1	-182,1
0	-166	-132,8	-183,5	-209,1	-183,1
20	-166,2	-144,7	-182,8	-206,4	-181,8
40	-162,9	-152,6	-181,8	-199,1	-177,7
60	-155,7	-165,7	-182,9	-187,2	-170,5
80	-144,5	-165,9	-180,1	-171,3	-160
100	-129,4	-161,5	-179,5	-160,5	-174,5
120	-110,6	-155,9	-179,1	-167,6	-191,2
140	-168,7	-160,8	-179	-175	-202,6
160	-176,3	-171,7	-179,2	-179,2	-208,4
180	-179,2	-178,9	-179,7	-182,9	-209,6

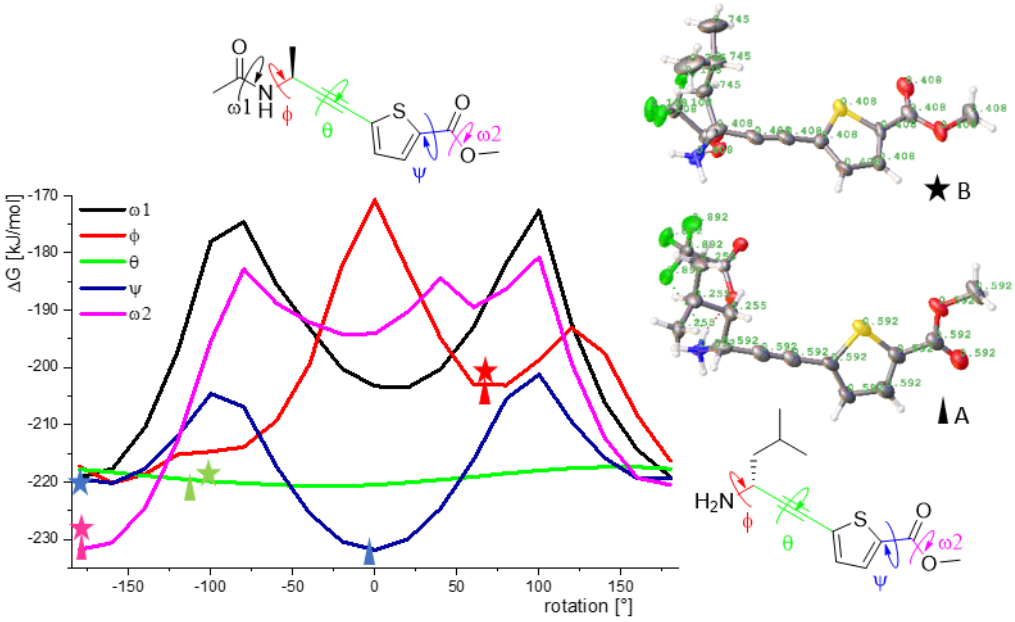
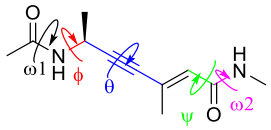


Figure EP4. Comparison of the torsion angles of the two conformers of peptidomimetic **x** with the results from MD calculations. Left side: Model compound, used for the calculation of the energy profiles corresponding to the torsion angles. The angles observed in the X-ray crystal structures are flagged with a triangle (**56b** A) and a star (**56b** B) in the colors, corresponding to the respective angles. Right side: X-ray crystal structures of both conformers of compound D-**56b** A (mirrored angles: ω1 n.a., ϕ = 65°, θ = -112°, α = 151°, ψ = −5°, and ω2 = -178°) and D-Leux **56b** (mirrored angles: ω1 n.a., ϕ = 55°, θ = -109°, α = 142°, ψ = −171°, and ω2 = -179°). (for more details, see Table EP5).

Table EP5. Energy values of the thiophene-based peptidomimetic model compound for energy profile determination.

rotation	ω1	ϕ	θ	ψ	ω2
°	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]
-180	-219,2	-217,3	-217,8	-219,5	-231,8
-160	-217,7	-220,2	-218,3	-220,2	-230,6
-140	-210,4	-218,6	-218,9	-217,7	-224,4
-120	-197,1	-215,2	-219,4	-211,9	-212,7
-100	-178	-214,7	-219,9	-204,6	-195,4
-80	-174,6	-213,9	-220,2	-206,9	-182,8
-60	-185,5	-209,3	-220,5	-217,3	-188,8
-40	-193,1	-199,5	-220,7	-225,4	-192,1
-20	-200,2	-182,2	-220,7	-230,4	-194,2
0	-203,3	-170,8	-220,5	-231,9	-194,1
20	-203,5	-183	-220,1	-230	-190,3
40	-200,3	-194,9	-219,6	-224,6	-184,4
60	-193	-202,9	-219,1	-216,2	-189,5
80	-181,8	-203,1	-218,5	-205,5	-186,3
100	-172,6	-198,7	-218	-201,2	-180,7
120	-192,5	-193,1	-217,6	-209,5	-199,4
140	-206,1	-197,5	-217,4	-215,8	-212,3
160	-214,4	-208,4	-217,4	-219,4	-219,3
180	-219,1	-216,3	-217,7	-219,4	-220,5

Table EP6. Energy values of the olefin-based peptidomimetic model compound for energy profile determination.



rotation	ω1	ϕ	θ	ψ	ω2
°	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]	ΔG [kJ/mol]
-180	-295,3	-292,8	-295,6	-295,4	-295,9
-160	-292,1	-295,6	-295,5	-295,4	-293,2
-140	-283,6	-293,9	-295,4	-294,2	-284,7
-120	-268,4	-290,2	-295,3	-291,5	-270,2
-100	-247,5	-287,5	-294,5	-288,7	-250
-80	-237,6	-284,5	-294,2	-289,3	-249
-60	-253,9	-278,4	-294,1	-290,6	-264,5
-40	-265,9	-267,9	-293,5	-289,2	-275,9
-20	-274,6	-259,6	-292,9	-284	-282,6
0	-277,9	-251,8	-292,8	-275,3	-284,3

20	-276,3	-265,3	-293,2	-282,8	-281,1
40	-269,9	-275,8	-293,9	-288,1	-274,3
60	-258,6	-280,4	-294,6	-289,4	-265,6
80	-242,4	-279,7	-295,1	-287,8	-250,2
100	-246,7	-275,1	-295,4	-287	-248,9
120	-268,7	-269,1	-295,5	-290	-269,1
140	-283,9	-273,7	-295,5	-293,4	-284,1
160	-292,8	-285	-295,4	-294,9	-292,7
180	-295,6	-292,8	-295,4	-295,5	-295,6

IIX-3. n) X-ray Crystal Structure Analysis

Details of crystal and refinement data can be found in Table EP7-EP29, which contain the supplementary crystallographic data for this paper.

Table EP7. Crystal data and structure refinement for the *ortho*-substituted peptidomimetics **27n**, **29** and **31o**.

compound	**27n**	**29**	**31o**
Diffractometer	SuperNova, Dual, Cu at zero, Atlas	Rigaku Supernova diffractometer	SuperNova, Dual, Cu at zero, Atlas
Radiation Source	CuKα (λ = 1.54184)	CuKα (λ = 1.54184 Å)	CuKα (λ = 1.54184)
Identification code	wuensch25	Wuensch28	wuensch12
Empirical formula	$C_{16}H_{18}F_3NO_3S$	$C_{20}H_{18}F_5NO_5S$	$C_{12}H_{11}ClF_3NO_2$
Formula weight	361.37	479.41	293.67
Temperature/K	100.01(10)	100.0(1)	100.01(10)
Crystal system	triclinic	orthorhombic	monoclinic
Space group	P1	$P2_12_12_1$	$P2_1$
a/Å	6.6342(2)	6.2681(3)	6.95431(14)
b/Å	9.9578(6)	12.7729(9)	9.75251(17)
c/Å	13.8970(8)	25.830(2)	19.1760(3)
α/°	72.512(5)	90	90
β/°	83.885(4)	90	95.3554(16)
γ/°	79.078(4)	90	90
Volume/Å^3	858.57(8)	2068.0(3)	1294.88(4)
Z	2	4	4
ρ_{calc}mg/mm^3	1.398	1.540	1.506
μ/mm^{-1}	2.096	2.120	2.966
F(000)	376.0	984.0	600.0
Crystal size/mm^3	0.163 × 0.098 × 0.024	0.192 × 0.047 × 0.01	0.187 × 0.05 × 0.027
2Θ range for data collection	6.678 to 144.108	6.844 to 135.054	9.264 to 143.942°
Index ranges	-8 ≤ h ≤ 8, -12 ≤ k ≤ 12, -17 ≤ l ≤ 17	-7 ≤ h ≤ 6, -15 ≤ k ≤ 11, -29 ≤ l ≤ 30	-7 ≤ h ≤ 8, -12 ≤ k ≤ 12, -23 ≤ l ≤ 23
Reflections collected	14748	8878	21714
Independent reflections	5946 [R_{int} = 0.0244, R_{sigma} = 0.0285]	3580 [R_{int} = 0.0588, R_{sigma} = 0.0734]	5106[R(int) = 0.0414]
Data/restraints/parameters	5812	3580/0/304	5106/1/347
Goodness-of-fit on F^2	1.044	1.095	1.098
Final R indexes [I>=2σ (I)]	R_1 = 0.0265, wR_2 = 0.0673	R_1 = 0.0684, wR_2 = 0.1707	R_1 = 0.0486, wR_2 = 0.1305
Final R indexes [all data]	R_1 = 0.0274, wR_2 = 0.0683	R_1 = 0.0810, wR_2 = 0.1787	R_1 = 0.0510, wR_2 = 0.1325
Largest d. peak/hole / e Å^{-3}	0.17/-0.20	0.90/-0.41	0.33/-0.21
Flack parameter	-0.013(7)	-0.03(3)	0.03(2)

Table EP8. Crystal data and structure refinement for the furan-based structures and the *meta*-substituted peptidomimetics **40d**, **41a** and **46j**.

compound	**40d**	**41a**	**46j**
Diffractometer	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Dual, Cu at zero, Atlas
Radiation Source	CuKα (λ = 1.54184)	(Mo Ka) X-ray Source	CuKα (λ = 1.54184)
Identification code	wuensch26	wuensch03	wuensch09
Empirical formula	$C_{21}H_{29}NO_3S$	$C_{17}H_{24}N_2O_3S$	$C_{21}H_{23}NO_3S$
Formula weight	375.51	336.44	369.46
Temperature/K	100.01(10)	100.00(10)	100.00(10)
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	$P2_1$	$P2_12_12_1$	$P2_1$
a/Å	10.4953(5)	8.82565(14)	10.3754(9)
b/Å	5.9572(3)	10.48674(13)	5.8828(3)
c/Å	16.4920(7)	19.8727(3)	15.9341(16)
α/°	90	90	90
β/°	99.901(5)	90	101.162(8)
γ/°	90	90	90
Volume/Å^3	1015.76(8)	1839.26(4)	954.17(14)
Z	2	4	2
ρ_{calc}mg/mm^3	1.228	1.215	1.288
μ/mm^{-1}	1.568	0.191	1.668
F(000)	404.0	720.0	392.0
Crystal size/mm^3	0.181 × 0.043 × 0.02	0.3 × 0.3 × 0.2754	0.358 × 0.071 × 0.02
2Θ range for data collection	5.44 to 144.256	5.648 to 64.608°	5.654 to 143.896°
Index ranges	-12 ≤ h ≤ 12, -7 ≤ k ≤ 7, -20 ≤ l ≤ 20	-12 ≤ h ≤ 13, -15 ≤ k ≤ 15, -29 ≤ l ≤ 29	-12 ≤ h ≤ 11, -7 ≤ k ≤ 7, -19 ≤ l ≤ 19
Reflections collected	16407	111421	5148
Independent reflections	3961 [R_{int} = 0.0466, R_{sigma} = 0.0358]	6285[R(int) = 0.0655]	5148[R(int) = ?]
Data/restraints/parameters	3961/1/243	6285/7/244	5148/1/244
Goodness-of-fit on F^2	1.107	1.084	1.128
Final R indexes [I>=2σ (I)]	R_1 = 0.0415, wR_2 = 0.1139	R_1 = 0.0321, wR_2 = 0.0885	R_1 = 0.0574, wR_2 = 0.1628
Final R indexes [all data]	R_1 = 0.0445, wR_2 = 0.1182	R_1 = 0.0335, wR_2 = 0.0900	R_1 = 0.0613, wR_2 = 0.1651
Largest d. peak/hole / e Å^{-3}	0.51/-0.48	0.37/-0.33	0.72/-0.45
Flack parameter	-0.003(13)	0.004(12)	-0.03(3)

Table EP9. Crystal data and structure refinement for the thiophene-based structures and the *para*-substituted peptidomimetics **49a**, **50f** and **52b**.

compound	**49a**	**50f**	**52b**
Diffractometer	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Dual, Cu at zero, Atlas
Radiation Source	SuperNova (Cu Ka) X-ray Source	SuperNova (Cu Ka) X-ray Source	SuperNova (Mo Ka) X-ray Source
Identification code	wuensch04	wuensch06	wuensch02

Empirical formula	$C_{16}H_{23}NO_4S$	$C_{15}H_{18}F_3NO_4S$	$C_{18}H_{25}NO_3S$
Formula weight	325.41	365.36	335.45
Temperature/K	100.0(1)	100.0(1)	291(4)
Crystal system	monoclinic	orthorhombic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a/Å	9.85826(13)	6.38314(9)	8.56680(14)
b/Å	5.86078(10)	13.1674(2)	11.7350(3)
c/Å	14.6079(2)	21.3573(3)	19.5702(4)
α/°	90	90	90
β/°	97.4233(13)	90	90
γ/°	90	90	90
Volume/Å^3	836.93(2)	1795.08(5)	1967.43(7)
Z	2	4	4
ρ_{calc}mg/mm^3	1.291	1.352	1.132
μ/mm^{-1}	1.867	2.053	0.177
F(000)	348.0	760.0	720.0
Crystal size/mm^3	0.2753 × 0.1293 × 0.0858	0.2985 × 0.0613 × 0.0436	0.3919 × 0.354 × 0.2328
2Θ range for data collection	9.046 to 144.258°	7.888 to 152.728°	5.19 to 59.998°
Index ranges	-12 ≤ h ≤ 12, -7 ≤ k ≤ 6, -18 ≤ l ≤ 18	-7 ≤ h ≤ 7, -16 ≤ k ≤ 16, -26 ≤ l ≤ 26	-12 ≤ h ≤ 12, -16 ≤ k ≤ 16, -27 ≤ l ≤ 27
Reflections collected	13609	31815	115409
Independent reflections	3048[R(int) = 0.0342]	3739[R(int) = 0.0362]	5734[R(int) = 0.0402]
Data/restraints/parameters	3048/1/291	3739/19/364	5734/0/221
Goodness-of-fit on F^2	1.051	1.028	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0232, wR_2 = 0.0590	R_1 = 0.0279, wR_2 = 0.0718	R_1 = 0.0305, wR_2 = 0.0831
Final R indexes [all data]	R_1 = 0.0235, wR_2 = 0.0592	R_1 = 0.0294, wR_2 = 0.0730	R_1 = 0.0333, wR_2 = 0.0849
Largest d. peak/hole / e Å^{-3}	0.18/-0.23	0.19/-0.24	0.15/-0.19
Flack parameter	0.002(7)	-0.005(7)	0.000(10)

Table EP10. Crystal data and structure refinement for the *para*-substituted peptidomimetic **55c** and the olefin-based peptidomimetics **75e,f** generated by the hydroalkinylation reaction.

compound	**55c**	**75e**	**75f**
Diffractometer	Rigaku Supernova diffractometer	Rigaku Supernova diffractometer	Rigaku Supernova diffractometer
Radiation Source	CuKα (λ = 1.54184 Å)	MoKα (λ = 0.71073 Å)	MoKα (λ = 0.71073 Å)
Identification code	Wuensch31	Wuensch29	Wuensch30
Empirical formula	$C_{19}H_{22}F_3NO_4$	$C_{13}H_{22}ClNO_2$	$C_{30}H_{48}Cl_2N_2O_4$
Formula weight	385.37	259.76	571.60
Temperature/K	100.00(10)	100.0(2)	100.0(2)
Crystal system	orthorhombic	monoclinic	orthorhombic
Space group	$P2_12_12_1$	C2	$C222_1$
a/Å	6.4600(2)	28.7444(4)	20.4594(14)
b/Å	14.0712(6)	6.81340(10)	22.3693(13)
c/Å	21.0520(7)	15.9919(2)	14.3402(8)
α/°	90	90	90

β/°	90	99.0930(10)	90
γ/°	90	90	90
Volume/Å^3	1913.62(12)	3092.61(7)	6563.0(7)
Z	4	8	8
ρ_{calc}mg/mm^3	1.338	1.116	1.157
μ/mm^{-1}	0.963	0.239	0.232
F(000)	808.0	1120.0	2464.0
Crystal size/mm^3	0.163 × 0.067 × 0.03	0.223 × 0.181 × 0.126	0.58 × 0.037 × 0.02
2Θ range for data collection	7.556 to 151.392	3.542 to 60.064	3.642 to 50.7
Index ranges	-7 ≤ h ≤ 7, -17 ≤ k ≤ 9, -18 ≤ l ≤ 26	-40 ≤ h ≤ 40, -9 ≤ k ≤ 9, -22 ≤ l ≤ 22	-22 ≤ h ≤ 24, -26 ≤ k ≤ 23, -17 ≤ l ≤ 17
Reflections collected	6929	91051	25863
Independent reflections	3824 [R_{int} = 0.0374, R_{sigma} = 0.0650]	9077 [R_{int} = 0.0298, R_{sigma} = 0.0156]	6010 [R_{int} = 0.0530, R_{sigma} = 0.0543]
Data/restraints/parameters	3824/15/342	9077/1/380	6010/4/338
Goodness-of-fit on F^2	1.021	1.086	1.040
Final R indexes [I>=2σ (I)]	R_1 = 0.0422, wR_2 = 0.0888	R_1 = 0.0296, wR_2 = 0.0791	R_1 = 0.0825, wR_2 = 0.2082
Final R indexes [all data]	R_1 = 0.0591, wR_2 = 0.0966	R_1 = 0.0316, wR_2 = 0.0803	R_1 = 0.1231, wR_2 = 0.2395
Largest d. peak/hole / e Å^{-3}	0.18/-0.20	0.30/-0.17	0.53/-0.31
Flack parameter	-0.16(14)	-0.003(11)	0.04(4)

Table EP12. Crystal data and structure refinement for peptidomimetics, after undergoing the Propargylamide-Enimine rearrangement, **76f** and **77c,g**.

compound	**76f**	**77c**	**77g**
Diffractometer	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Single source at offset, Eos	Rigaku Supernova diffractometer
Radiation Source	CuKα (λ = 1.54184)	Mo Kα (0.71073 Å)	CuKα (λ = 1.54184)
Identification code	wuensch07	Wuensch17	wuensch32b
Empirical formula	$C_{21}H_{24}NO_3S$	$C_{11}H_7F_3O_3$	$C_{15}H_{16}O_3$
Formula weight	370.47	244.17	244.28
Temperature/K	100.01(10)	100.0(1)	100.01(10)
Crystal system	orthorhombic	monoclinic	triclinic
Space group	$P2_12_12_1$	C2/c	P-1
a/Å	6.03357(10)	15.9688(11)	6.3379(3)
b/Å	10.31093(18)	10.3072(7)	7.9472(3)
c/Å	31.0591(6)	13.6073(13)	13.9013(4)
α/°	90	90	104.048(3)
β/°	90	104.846(8)	92.626(3)
γ/°	90	90	112.032(4)
Volume/Å^3	1932.24(6)	2164.9(3)	622.30(4)
Z	4	8	2
ρ_{calc}mg/mm^3	1.274	1.498	1.304
μ/mm^{-1}	1.648	0.141	0.730

F(000)	788.0	992.0	260.0
Crystal size/mm^3	0.2716 × 0.123 × 0.028	0.393 × 0.307 × 0.193	0.285 × 0.24 × 0.047
2Θ range for data collection	9.036 to 143.992°	4.8 to 52.0°	12.416 to 144.25
Index ranges	-7 ≤ h ≤ 7, -12 ≤ k ≤ 12, -38 ≤ l ≤ 38	-17 ≤ h ≤ 19, -12 ≤ k ≤ 7, -16 ≤ l ≤ 13	-7 ≤ h ≤ 7, -9 ≤ k ≤ 9, -17 ≤ l ≤ 17
Reflections collected	47179	4376	9772
Independent reflections	3806[R(int) = 0.0443]	2089[R(int) = 0.0339]	2432 [R_{int} = 0.0201, R_{sigma} = 0.0158]
Data/restraints/parameters	3806/0/239	2089/0/182	2432/0/198
Goodness-of-fit on F^2	1.039	1.060	1.098
Final R indexes [I>=2σ (I)]	R_1 = 0.0382, wR_2 = 0.0996	R_1 = 0.0509, wR_2 = 0.1105	R_1 = 0.0603, wR_2 = 0.1621
Final R indexes [all data]	R_1 = 0.0391, wR_2 = 0.1005	R_1 = 0.0798, wR_2 = 0.1307	R_1 = 0.0629, wR_2 = 0.1642
Largest d. peak/hole / e Å^{-3}	0.82/-0.41	0.28/-0.30	0.32/-0.50

Methyl 2-((*R*)-3-(((*S*)-Butylsulfinyl)amino)-4,4,4-trifluorobut-1-yne-1-yl)benzoate (27n)

Single crystals of $C_{16}H_{18}F_3NO_3S$ were achieved by evaporation of the solvent of a concentrated MeOH solution at rt.

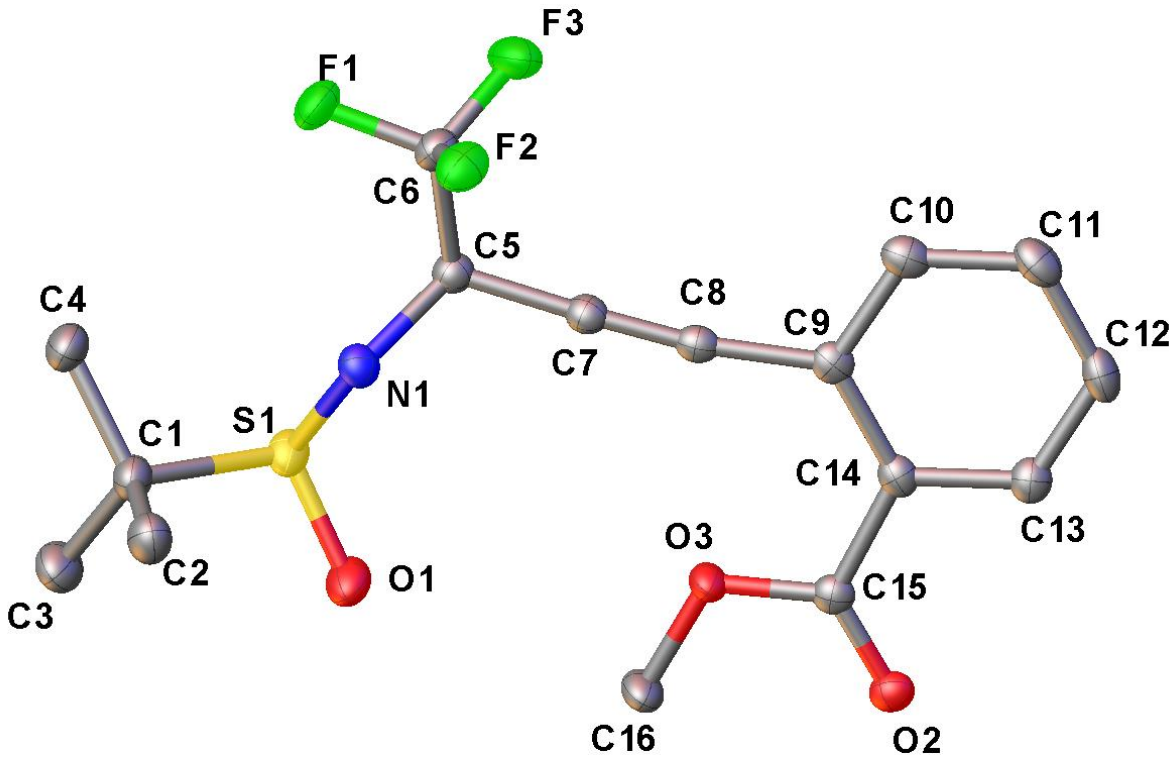


Table EP13. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for peptidomimetic **27n**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	7136.5(8)	2316.1(6)	2907.8(5)	24.12(14)
F1	6362(2)	5077.9(19)	4485.9(12)	31.0(3)
F2	8524(2)	6263.8(18)	3486.2(12)	29.7(3)
F3	5277(3)	7072.7(19)	3382.9(13)	35.0(4)
O1	7957(3)	2018(2)	1940.6(15)	33.3(5)
O2	8020(2)	6149.4(19)	-2023.1(13)	21.9(4)
O3	7595(3)	5234.2(19)	-345.2(13)	22.9(4)
N1	7987(3)	3740(2)	3021.3(16)	21.8(4)
C1	8596(4)	929(3)	3904(2)	25.6(5)
C2	10887(4)	972(3)	3726(2)	31.2(6)
C3	8101(5)	-485(3)	3838(2)	35.7(7)
C4	7725(4)	1183(3)	4910(2)	30.1(6)
C5	6540(4)	5085(3)	2768.7(19)	20.6(5)
C6	6683(4)	5879(3)	3537(2)	24.1(5)
C7	6813(3)	6028(3)	1747.0(19)	19.8(5)
C8	6970(3)	6836(3)	916.2(19)	18.8(5)
C9	7049(3)	7941(3)	-19.5(19)	18.7(5)
C10	6698(3)	9349(3)	45(2)	22.9(5)
C11	6646(4)	10502(3)	-812(2)	25.9(6)
C12	6979(4)	10284(3)	-1766(2)	26.0(5)
C13	7356(3)	8907(3)	-1843.8(19)	21.5(5)
C14	7378(3)	7731(3)	-989.8(19)	18.5(5)
C15	7711(3)	6305(3)	-1179.3(19)	18.8(5)
C16	7743(4)	3842(3)	-493(2)	27.6(6)
S2	3006.1(7)	3682.8(6)	7199.8(4)	20.24(13)
F4	3958(3)	7320.3(19)	5413.3(12)	36.3(4)
F5	1492(2)	8397.2(18)	6182.2(12)	32.3(4)
F6	4635(3)	8494.0(18)	6375.7(13)	33.0(4)
O4	2445(3)	2860(2)	8242.7(14)	27.4(4)
O5	2016(3)	4680(2)	12028.2(14)	24.6(4)
O6	2519(3)	4666(2)	10408.2(14)	25.8(4)
N2	2088(3)	5422(2)	6996.4(16)	19.0(4)
C17	1328(4)	3312(3)	6361.6(19)	20.0(5)
C18	1922(4)	4082(3)	5281(2)	28.8(6)
C19	1855(4)	1694(3)	6554(2)	31.0(6)
C20	-924(4)	3764(3)	6642(2)	27.2(6)
C21	3487(3)	6290(3)	7172.9(18)	18.6(5)
C22	3393(4)	7631(3)	6279.9(19)	24.0(5)
C23	3020(3)	6683(3)	8118.3(19)	19.3(5)
C24	2645(3)	7027(3)	8880.7(19)	19.0(5)
C25	2196(3)	7653(3)	9704.8(18)	18.4(5)
C26	1977(3)	9145(3)	9425(2)	22.5(5)

C27	1522(4)	9886(3)	10145(2)	24.4(5)
C28	1309(4)	9137(3)	11160(2)	26.7(6)
C29	1541(3)	7661(3)	11449(2)	22.8(5)
C30	1976(3)	6900(3)	10729.7(19)	19.2(5)
C31	2168(3)	5316(3)	11133.9(19)	21.1(5)
C32	2714(5)	3126(3)	10738(2)	30.4(6)

(*R,Z*)-3-(2-Amino-2-(perfluorophenyl)ethylidene)isobenzofuran-1(3H)-one (29)

Single crystals of $C_{20}H_{18}F_5NO_5S$ were achieved by evaporation of the solvent of a concentrated MeOH solution at rt.

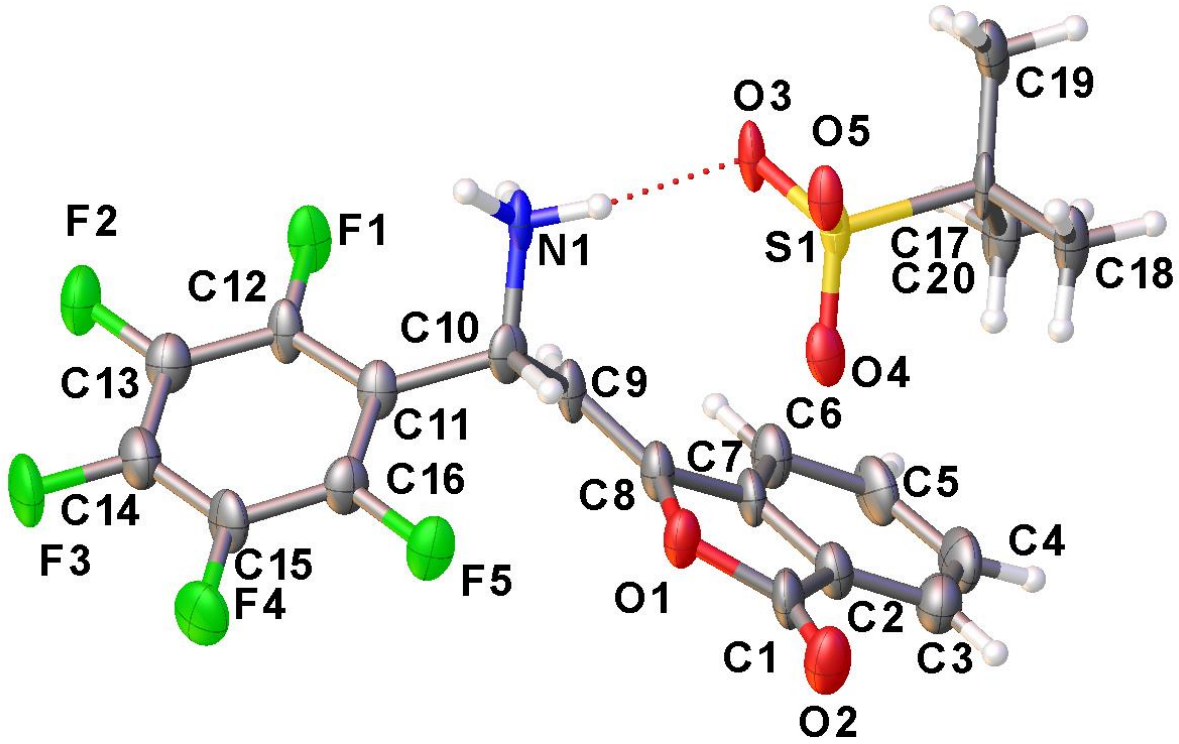


Table EP15. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for benzofuran **29**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	9982(3)	5536.1(14)	5440.0(8)	28.9(4)
O3	7839(9)	5671(4)	5221(3)	35.6(14)
O4	10093(9)	5730(4)	5985(2)	35.0(13)
O5	11545(8)	6146(4)	5135(2)	32.0(13)
C17	10685(12)	4171(6)	5351(4)	33(2)
C18	13074(12)	4060(7)	5479(4)	41(2)
C19	10265(14)	3881(7)	4796(4)	40(2)
C20	9300(14)	3537(7)	5723(4)	44(2)
F1	1153(7)	8180(4)	5728(2)	36.8(11)

F2	-444(8)	10108(4)	5893(2)	44.1(13)
F3	1749(9)	11507(4)	6479(2)	50.2(15)
F4	5647(9)	10998(4)	6863(2)	49.1(14)
F5	7330(8)	9097(4)	6672(2)	39.7(12)
O1	7889(9)	6600(4)	6870(2)	33.8(13)
O2	10802(10)	6081(5)	7311(3)	48.2(17)
N1	5160(12)	7267(5)	5507(3)	29.5(14)
C1	9047(14)	5885(7)	7156(4)	37(2)
C2	7743(14)	4948(7)	7210(3)	33.4(19)
C3	8190(16)	3995(8)	7438(4)	43(2)
C4	6618(18)	3225(7)	7421(4)	47(2)
C5	4656(17)	3427(7)	7198(4)	44(2)
C6	4197(15)	4377(7)	6961(4)	37(2)
C7	5777(14)	5135(6)	6972(3)	31.6(19)
C8	5922(13)	6175(6)	6728(3)	32.3(18)
C9	4653(12)	6632(6)	6386(3)	31.9(18)
C10	5404(11)	7541(6)	6067(3)	30.6(18)
C11	4316(13)	8583(6)	6185(3)	29.4(18)
C12	2307(12)	8862(6)	6006(4)	30.9(18)
C13	1451(14)	9837(7)	6098(4)	34.9(19)
C14	2559(15)	10555(7)	6388(4)	40(2)
C15	4549(14)	10307(6)	6583(4)	36(2)
C16	5394(12)	9321(7)	6476(3)	33.1(18)

Methyl (*S*)-2-(3-Amino-4,4,4-trifluorobut-1-yn-1-yl)benzoate (31o)

Single crystals of $C_{12}H_{11}ClF_3NO_2$ were achieved by evaporation of the solvent of a concentrated $CHCl_3$ solution at rt.

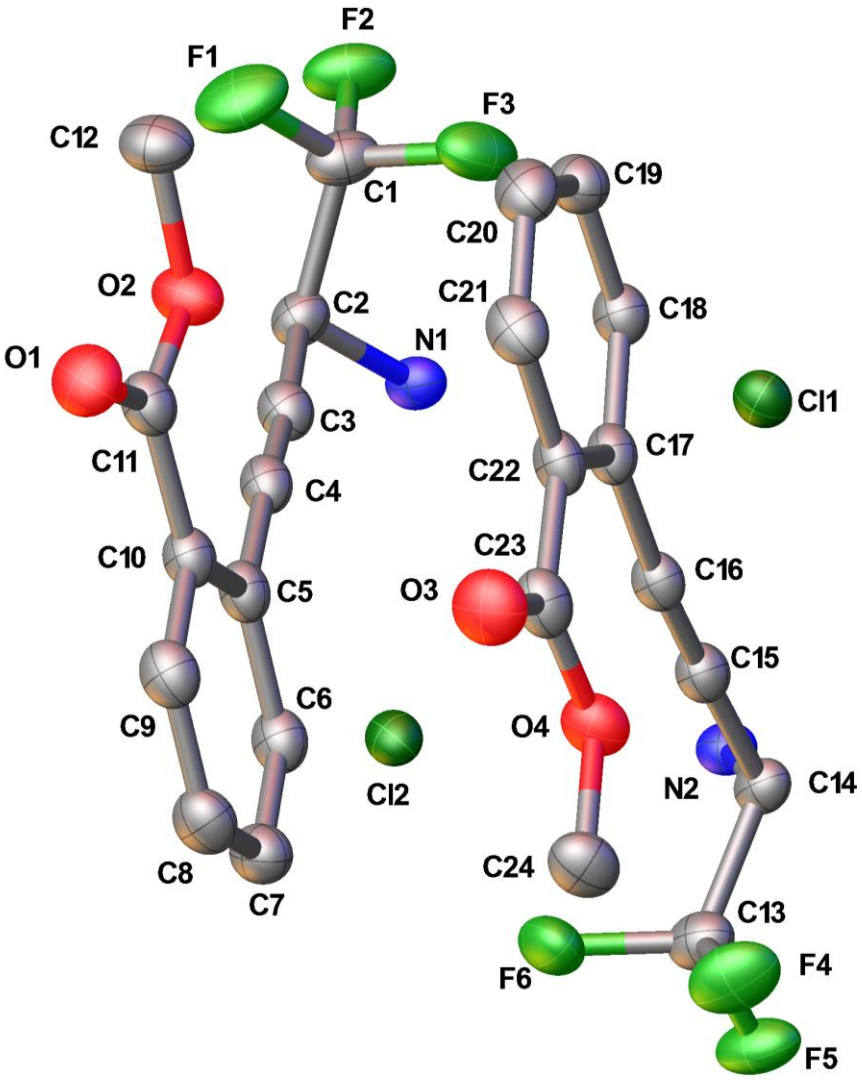


Table EP14. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for amine **31o**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1	5078.1(14)	6507.5(9)	5619.1(5)	27.0(2)
F1	-316(6)	9044(3)	7125.5(16)	51.5(9)
F2	-48(6)	9466(3)	6038.5(17)	45.4(8)
F3	2351(5)	8617(3)	6679.3(18)	46.0(7)
O1	398(5)	6030(4)	9663.4(17)	37.4(8)
O2	595(5)	6982(4)	8611.3(16)	34.0(7)
N1	573(6)	6666(4)	5731.9(18)	25.9(7)
C1	433(7)	8591(6)	6555(2)	33(1)
C2	-293(7)	7155(5)	6373(2)	27.2(8)

C3	153(6)	6211(5)	6956(2)	27.3(9)
C4	431(6)	5453(5)	7444(2)	25.9(9)
C5	714(6)	4382(5)	7958(2)	26.3(9)
C6	931(7)	3059(5)	7695(2)	29.7(10)
C7	1182(7)	1946(5)	8139(2)	33.2(9)
C8	1201(7)	2124(5)	8861(3)	35(1)
C9	985(7)	3427(6)	9126(2)	31.5(9)
C10	756(6)	4572(5)	8690(2)	26.7(9)
C11	564(7)	5922(5)	9046(2)	29.3(9)
C12	493(8)	8317(5)	8932(3)	36.7(10)
Cl2	237.7(14)	3436.8(9)	5628.3(5)	27.0(2)
F4	6453(6)	944(4)	7140.3(16)	50.4(8)
F5	5618(6)	504(3)	6053.5(17)	44.1(8)
F6	3531(5)	1332(3)	6699.6(18)	44.6(7)
O3	5830(6)	3913(4)	9671.7(18)	41.4(9)
O4	6122(5)	3016(4)	8611.4(16)	32.6(7)
N2	4796(5)	3288(4)	5736.1(18)	26.2(7)
C13	5386(8)	1384(6)	6572(3)	33.7(10)
C14	5976(7)	2827(4)	6384(2)	26.0(8)
C15	5775(6)	3770(5)	6961(2)	26.6(9)
C16	5682(6)	4527(5)	7446(2)	25.0(9)
C17	5592(6)	5606(5)	7957(2)	25.5(9)
C18	5390(6)	6931(5)	7685(2)	28.4(9)
C19	5266(7)	8053(5)	8123(3)	32.6(9)
C20	5354(8)	7862(6)	8847(3)	35.2(10)
C21	5548(7)	6548(6)	9119(2)	32.6(10)
C22	5669(7)	5407(5)	8685(2)	28.5(9)
C23	5873(7)	4054(6)	9047(2)	31.6(10)
C24	6339(8)	1678(5)	8932(3)	36.2(10)

Methyl 3-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)benzoate (40d)

Single crystals of $C_{21}H_{29}NO_3S$ were achieved by evaporation of the solvent of a concentrated $CHCl_3$ solution at rt.

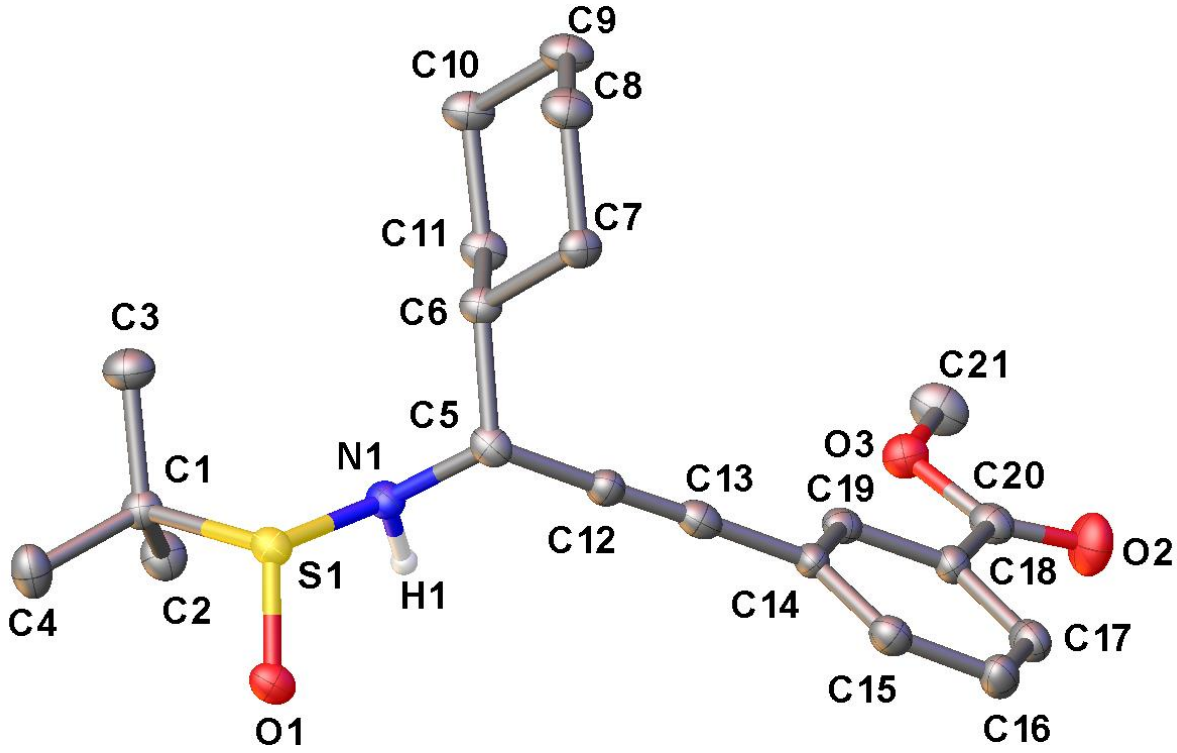


Table EP17. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{21}H_{29}NO_3S$ **40d**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	3503.7(6)	1314.6(11)	4801.1(4)	17.41(19)
O1	4634(2)	1693(3)	4375.2(12)	21.1(5)
O2	8021(3)	9971(5)	10142.7(15)	35.1(6)
O3	6071(2)	9933(4)	9330.8(13)	23.8(5)
N1	3734(2)	2611(4)	5704.3(15)	18.7(5)
C1	2179(3)	3078(5)	4246.5(18)	19.0(6)
C2	2486(3)	5568(5)	4355(2)	24.4(7)
C3	970(3)	2430(6)	4596(2)	27.0(7)
C4	2054(3)	2370(6)	3347.5(19)	27.7(7)
C5	4101(3)	1111(5)	6430.2(16)	17.8(6)
C6	2899(3)	508(5)	6803.4(18)	18.3(6)
C7	3208(3)	-1230(5)	7491.7(19)	21.3(6)
C8	1995(3)	-1878(6)	7840(2)	25.6(7)
C9	1338(3)	184(6)	8130(2)	26.5(7)
C10	1032(3)	1913(5)	7444(2)	24.0(7)
C11	2252(3)	2564(5)	7109.5(19)	20.4(6)

C12	5099(3)	2221(6)	7034.2(18)	19.5(6)
C13	5897(3)	3118(6)	7533.9(17)	20.7(6)
C14	6879(3)	4189(5)	8124.8(17)	18.5(6)
C15	8120(3)	3267(6)	8298.5(17)	21.8(6)
C16	9079(3)	4302(6)	8864.7(19)	24.6(7)
C17	8798(3)	6238(7)	9269.0(17)	23.3(6)
C18	7556(3)	7153(6)	9104.6(17)	19.3(6)
C19	6600(3)	6155(6)	8525.1(16)	18.3(5)
C20	7277(3)	9171(6)	9582.4(19)	22.9(6)
C21	5715(4)	11838(5)	9784(2)	30.9(8)

Methyl 5-((*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)nicotinate (41a)

Single crystals of $C_{17}H_{24}N_2O_3S$ were achieved by evaporating an Et_2O solution. The fine needles were placed in a saturated solution of $C_{17}H_{24}N_2O_3S$ in Et_2O at -18 °C to let them grow.

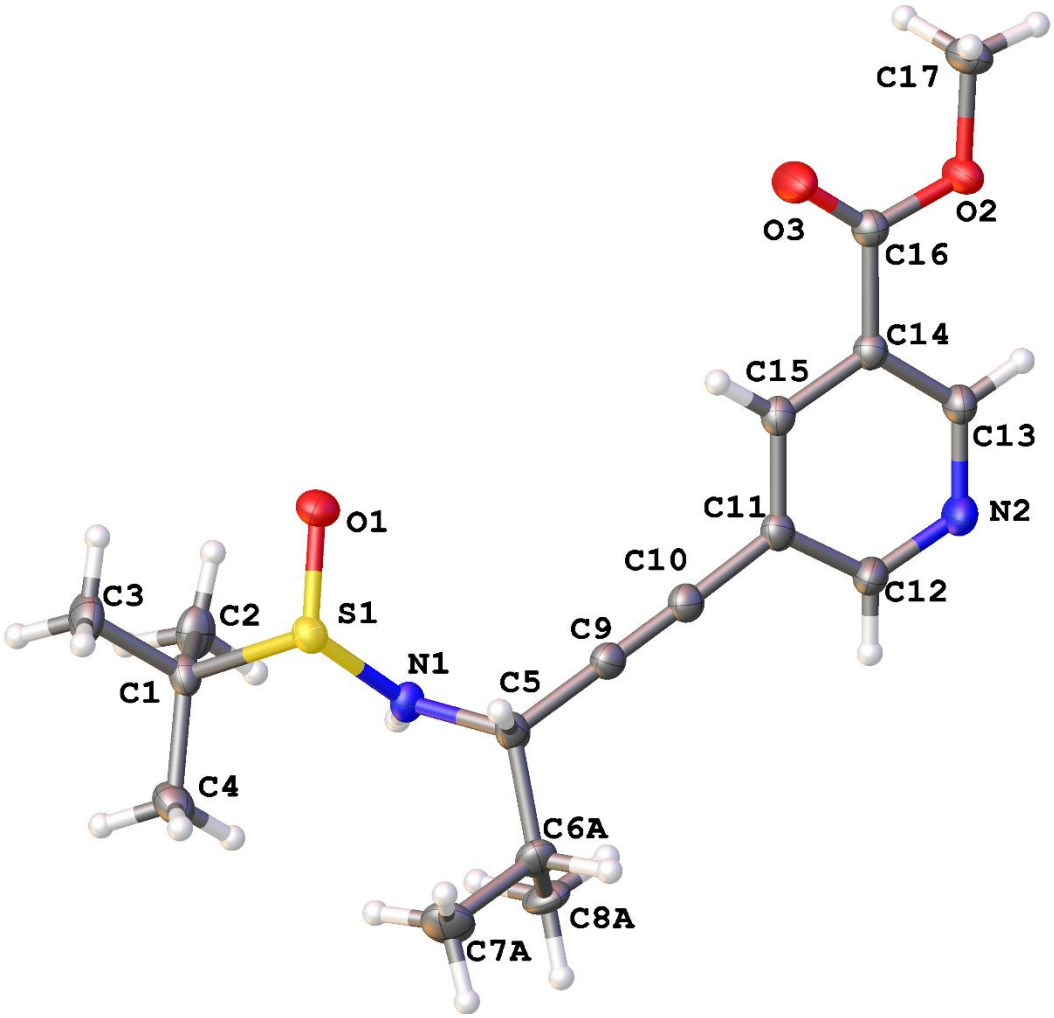


Table EP18. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for nicotinate derivative **41a**. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	5173.0(4)	2082.6(3)	4376.0(2)	20.13(8)
O1	5672.5(14)	1912.0(12)	5090.8(6)	29.0(2)
O2	5184.0(14)	8144.1(11)	7973.3(5)	26.5(2)
O3	6406.9(19)	6469.6(14)	7533.2(7)	41.3(3)
N1	3822.8(14)	3150.0(11)	4293.6(6)	20.7(2)
N2	2527.8(18)	8617.2(13)	6299.6(7)	29.8(3)
C1	4069.9(17)	639.4(13)	4178.4(8)	22.2(3)
C2	2800(2)	459.4(16)	4684.0(9)	31.1(3)

C3	5220(2)	-441.9(15)	4229.6(10)	34.2(4)
C4	3480(2)	763.9(18)	3461.6(9)	30.9(3)
C5	4290(2)	4466.8(13)	4140.5(7)	23.5(3)
C6A	3584(6)	4963(6)	3492(3)	26.4(10)
C6B	3150(16)	5025(13)	3562(6)	33(3)
C7A	4155(5)	4231(4)	2889.4(15)	39.0(7)
C7B	3285(18)	4337(10)	2906(5)	60(3)
C8A	1849(3)	4922(3)	3562.4(13)	31.0(6)
C8B	3586(9)	6404(6)	3392(4)	47(2)
C9	4087.2(18)	5312.6(13)	4724.1(7)	22.1(3)
C10	3935.6(18)	6008.0(14)	5200.2(7)	22.7(3)
C11	3783.3(17)	6819.7(13)	5776.6(7)	21.3(3)
C12	2715.5(19)	7813.3(14)	5784.5(8)	26.7(3)
C13	3407.1(18)	8452.8(14)	6841.5(8)	24.2(3)
C14	4476.2(15)	7475.8(13)	6891.1(7)	19.6(2)
C15	4665.5(17)	6645.5(13)	6349.6(7)	20.8(2)
C16	5457.7(17)	7290.7(13)	7491.6(7)	22.4(3)
C17	6137(2)	8037.3(19)	8563.8(8)	34.6(4)

Methyl 4-((*S*)-3-(((*S*)-*tert*-Butylsulfinylamido)-3-phenylprop-1-yn-1-yl)benzoate (46j)

Single crystals of $C_{21}H_{23}NO_3S$ were achieved by evaporation of the solvent of a concentrated Et_2O solution at -20 °C.

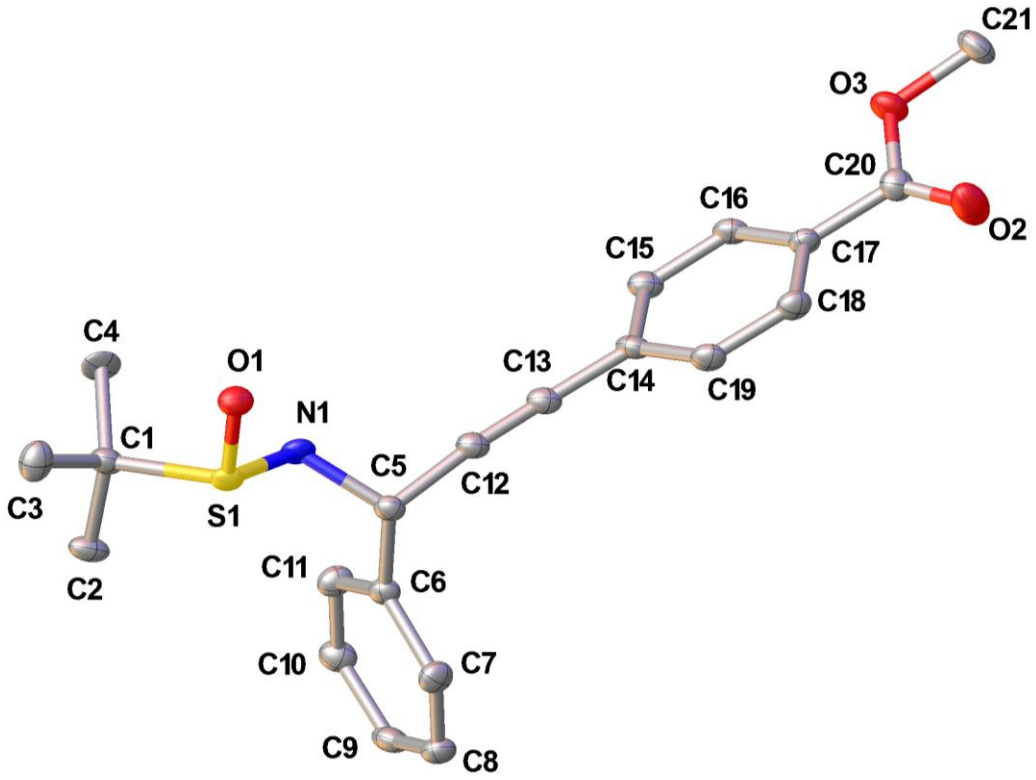


Table EP21. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{21}H_{23}NO_3S$ **46j**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	3625.0(14)	1722(3)	5182.7(8)	17.6(3)
O1	5017(4)	2166(8)	5617(3)	21.3(10)
O2	8272(6)	5050(11)	-390(4)	39.8(14)
O3	7635(5)	8606(9)	-177(3)	25.5(11)
N1	3295(6)	3101(10)	4254(3)	20.3(11)
C1	2594(6)	3384(12)	5789(4)	21.5(13)
C2	1180(6)	2645(13)	5458(4)	24.9(14)
C3	3065(7)	2617(14)	6717(4)	28.3(16)
C4	2786(7)	5923(12)	5694(4)	25.4(14)
C5	3283(6)	1620(13)	3498(3)	18.0(11)
C6	1901(6)	1006(11)	3050(3)	18.7(13)
C7	1676(7)	-1122(13)	2655(4)	23.8(14)
C8	445(7)	-1634(13)	2184(4)	24.6(14)
C9	-573(7)	-43(13)	2103(4)	25.1(14)
C10	-351(6)	2018(14)	2513(4)	24.7(15)
C11	885(7)	2566(12)	2984(4)	22.4(13)
C12	3964(6)	2721(13)	2873(4)	20.1(13)

C13	4477(6)	3494(13)	2324(4)	20.2(13)
C14	5203(6)	4279(12)	1692(4)	20.5(14)
C15	5001(6)	6405(13)	1306(4)	22.0(14)
C16	5779(6)	7106(12)	736(4)	21.1(14)
C17	6741(6)	5669(12)	536(3)	19.0(13)
C18	6922(7)	3527(13)	897(4)	21.6(13)
C19	6160(6)	2839(12)	1477(4)	21.4(14)
C20	7613(6)	6354(13)	-59(4)	22.9(15)
C21	8496(7)	9386(15)	-739(4)	29.8(16)

Methyl 5-((*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-4-methylpent-1-yn-1-yl)furan-2-carboxylate (49a)

Single crystals of $C_{16}H_{23}NO_4S$ were achieved by evaporation of the solvent of a concentrated Et_2O solution at rt.

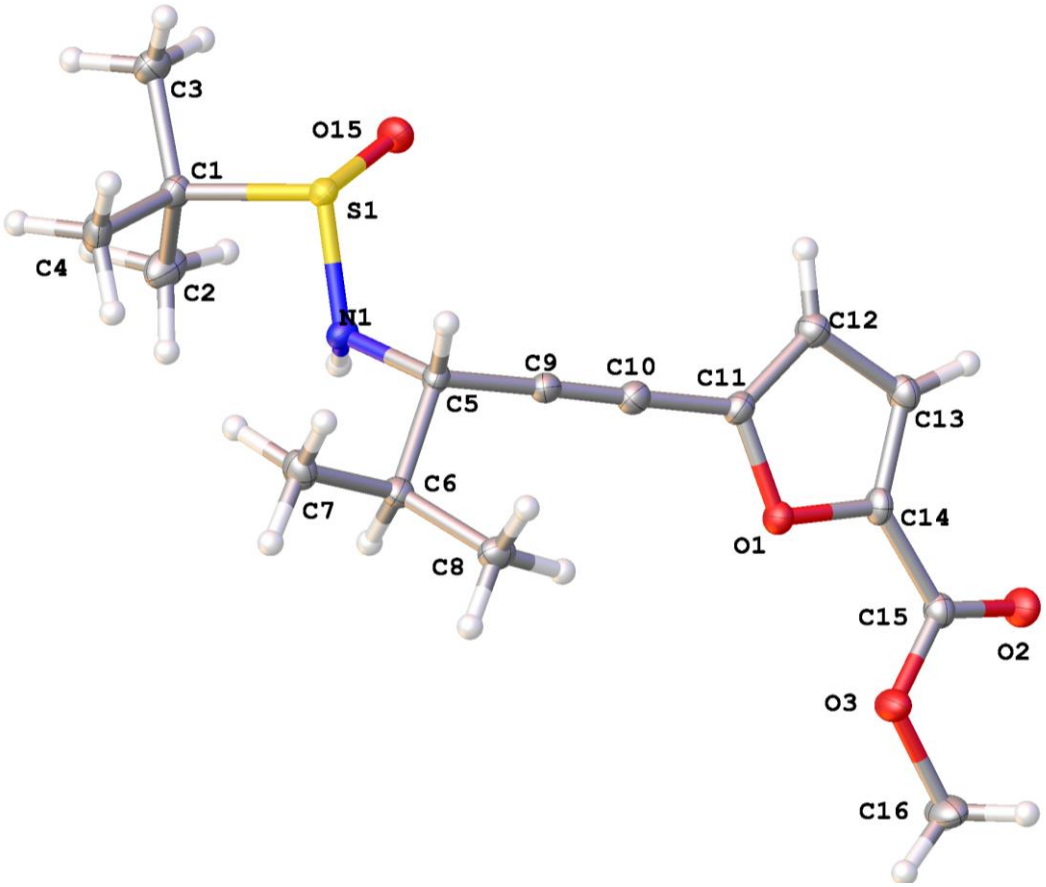


Table EP16. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for furan derivative **49a**. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	3951.2(4)	4957.6(8)	6571.9(2)	14.59(11)
O1	-1272.7(12)	5231(2)	9043.6(8)	16.6(3)
O2	-3094.0(15)	7092(3)	10854.6(9)	24.1(3)
O3	-2999.5(14)	3700(3)	10136.3(9)	21.4(3)
O15	4060.6(14)	7002(3)	7174.8(9)	22.6(3)
N1	3030.6(15)	2884(3)	6972.3(10)	15.7(3)
C1	5638.1(17)	3526(4)	6770.7(12)	17.2(4)
C2	5920(2)	2585(4)	7751.2(15)	27.0(5)
C3	6657.2(19)	5396(4)	6610.1(14)	22.8(4)
C4	5616(2)	1649(4)	6045.2(15)	23.6(4)
C5	1540.3(17)	2960(3)	6694.7(11)	15.2(4)
C6	1001.6(17)	498(3)	6548.4(12)	16.2(4)
C7	1562(2)	-541(4)	5715.3(14)	21.7(4)
C8	-562.6(18)	394(4)	6408.6(13)	20.0(4)
C9	827.3(18)	4245(3)	7359.8(12)	16.5(4)
C10	244.9(17)	5260(4)	7903.6(12)	17.7(4)
C11	-448.1(17)	6492(4)	8544.3(12)	16.4(4)
C12	-474.4(19)	8729(4)	8783.7(13)	19.2(4)
C13	-1356.5(19)	8904(4)	9476.7(12)	19.0(4)
C14	-1806.0(18)	6760(4)	9612.5(12)	16.7(4)
C15	-2697.2(19)	5896(3)	10267.2(13)	17.2(4)
C16	-3832(3)	2728(4)	10792.2(16)	28.9(5)

Methyl (*R*)-5-(3-Amino-5-methylhex-1-yn-1-yl)thiophene-2-carboxylate x TFA (50f)

Single crystals of $C_{15}H_{18}F_3NO_4S$ were achieved out of a saturated solution in MeOH/$CHCl_3$ (1:4) at rt. The concentration was gradually increased by evaporation of the solvent.

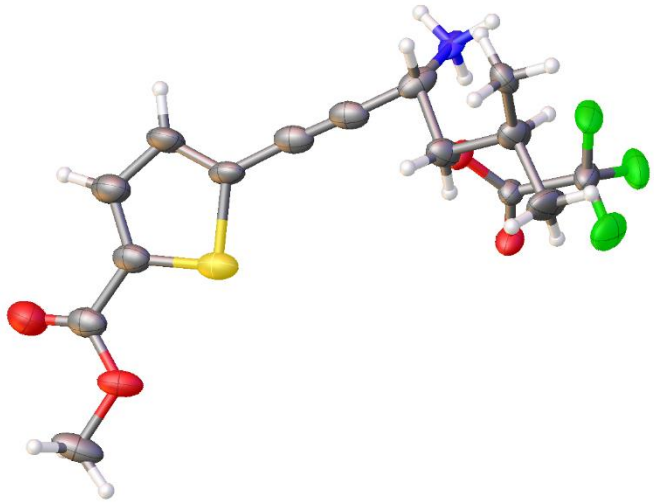


Table EP19. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for thiophene derivative **50f**. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1A	3561(2)	3606.8(19)	6998.6(9)	44.4(5)
S1B	3304(3)	4056(3)	6875.2(8)	37.3(5)
F1A	1420(3)	5704.9(11)	3882.5(11)	58.3(5)
F1B	1660(20)	5118(15)	3378(6)	54.5(5)
F2A	1682(2)	4578.4(17)	3169.4(7)	54.5(5)
F2B	-860(30)	4773(16)	4000(9)	45.7(5)
F3A	-900(3)	4518.3(16)	3810.9(9)	45.7(5)
F3B	1120(20)	5793(9)	4272(9)	58.3(5)
O1A	7200(5)	2130(3)	8163.3(15)	64.7(10)
O1B	7330(6)	4423(4)	7529.8(18)	46.8(12)
O2A	7253(7)	3723(4)	7789(2)	47.1(12)
O2B	7283(7)	2966(4)	8079(2)	45.7(12)
O3	1536(2)	3570.1(9)	4621.7(6)	31.4(3)
O4	4389.1(19)	4142.7(10)	4119.8(6)	34.4(3)
N1A	-2790(20)	3381(14)	4939(7)	29.5(14)
N1B	-2460(30)	3340(20)	4865(12)	29.5(14)
C1A	-3813(14)	5732(5)	5232(4)	42(2)
C1B	-3772(6)	5771(2)	5788.9(18)	56(1)
C2A	-6180(30)	5671(12)	5478(5)	35(2)
C2B	-2905(10)	6845(3)	5733(3)	83.5(17)
C3A	-3110(20)	6858(7)	5264(8)	62(3)
C3B	-6132(13)	5766(6)	5713(5)	98(3)
C4A	-2346(15)	5108(6)	5633(6)	39(2)

C4B	-2736(5)	5088(2)	5299.7(19)	38.9(8)
C5A	-2960(60)	3970(30)	5525(10)	41.4(14)
C5B	-2930(80)	3930(40)	5444(15)	41.4(14)
C6A	-1452(16)	3610(20)	5993(4)	40.2(6)
C6B	-1480(20)	3560(30)	5916(5)	40.2(6)
C7A	-129(12)	3233(7)	6333(9)	40.2(6)
C7B	-198(18)	3417(10)	6311(13)	40.2(6)
C8A	1420(20)	2873(8)	6782(5)	37(2)
C8B	1480(30)	3167(11)	6702(9)	34(3)
C9A	1502(15)	1951(7)	7069(5)	48.8(18)
C9B	1828(19)	2284(9)	7010(6)	41(2)
C10A	3252(9)	1847(5)	7474(2)	52.6(13)
C10B	3691(13)	2305(7)	7382(3)	37.7(16)
C11A	4504(9)	2673(6)	7475(2)	44.0(12)
C11B	4636(9)	3228(6)	7355(2)	34.3(13)
C12A	6466(8)	2795(3)	7845(2)	45.1(10)
C12B	6549(14)	3606(9)	7655(4)	41.2(19)
C13A	9118(7)	3907(4)	8166(3)	57.1(13)
C13B	9158(10)	3316(7)	8405(3)	56.2(17)
C14	2497(3)	4076.6(13)	4217.7(8)	27.5(3)
C15A	1150(4)	4719(2)	3765.5(12)	35.7(5)
C15B	1140(30)	4948(16)	3965(9)	35.7(5)

Single crystals of $C_{15}H_{18}F_3NO_4S$ **50f** were analyzed several times. All crystals show entirely disordered molecules. Except C14, O3 and O4 all atoms are disordered showing different conformers. Same distance restraints were used for: C-F bonds, C-N bonds, C5-C6, C6-C7, C7-C8. ADP's were constrained to be equivalent for the four atoms of the acetylene bridge and pairwise for C5, C6, all F and N atoms. A suitable crystal was selected and mounted on a SuperNova, Dual, Cu at zero, Atlas diffractometer. The crystal was kept at 100.0(1) K during data collection.

4-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)benzoic Acid (52b)

Single crystals of $C_{18}H_{25}NO_3S$ were achieved out of a saturated solution in MeOH/EtOAc (2:1) at -18 °C.

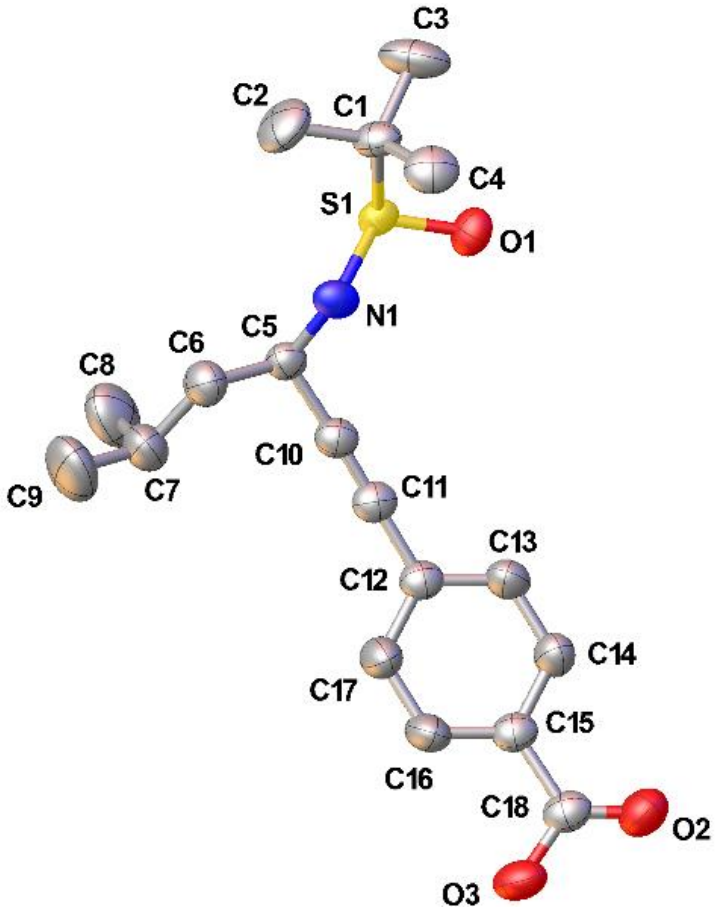


Table EP20. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{18}H_{25}NO_3S$ **52b**. U_{eq} is defined as 1/3 of of the trace of the orthogonalized U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	3097.1(4)	2722.9(3)	4253.5(2)	38.08(9)
O1	2585.8(13)	2011.4(11)	4852.8(6)	49.7(3)
O2	4952(2)	5074.2(14)	9220.3(8)	72.7(4)
O3	6117(2)	6711.9(15)	8940.6(8)	68.0(4)
N1	4537.8(15)	3566.6(12)	4456.2(7)	45.2(3)
C1	4135(2)	1724.9(15)	3687.2(8)	48.5(4)
C2	4764(3)	2414(3)	3087.2(10)	79.6(7)
C3	2871(3)	894(2)	3455.0(15)	85.4(8)
C4	5410(2)	1103.1(18)	4070.8(11)	62.3(5)
C5	4190.9(19)	4768.8(13)	4614.5(8)	43.6(3)
C6	5406(2)	5516.8(17)	4262.3(11)	60.3(4)
C7	5215(3)	6800.6(19)	4374.9(12)	75.3(6)
C8	3681(4)	7245(2)	4103.3(19)	102.9(9)

C9	6595(5)	7416(3)	4038(2)	120.5(13)
C10	4151(2)	4976.4(14)	5357.0(9)	46.0(3)
C11	4185(2)	5170.9(14)	5950.5(8)	47.4(3)
C12	4338.0(19)	5377.4(14)	6671.2(8)	44.4(3)
C13	3797(3)	4600.7(16)	7144.4(10)	57.6(4)
C14	4095(3)	4748.2(17)	7835.6(10)	58.5(4)
C15	4932(2)	5676.2(15)	8062.0(8)	46.5(3)
C16	5433(3)	6465.9(18)	7590.7(10)	68.9(6)
C17	5120(3)	6331.8(19)	6901.3(10)	68.8(6)
C18	5326(2)	5771.8(17)	8802.0(9)	51.1(4)

Methyl (*R*)-4-(3-Amino-3-cyclohexylprop-1-yn-1-yl)benzoate (55c)

Single crystals of $C_{19}H_{22}F_3NO_4$ were achieved by evaporation of the solvent of a concentrated $CHCl_3$ solution at rt.

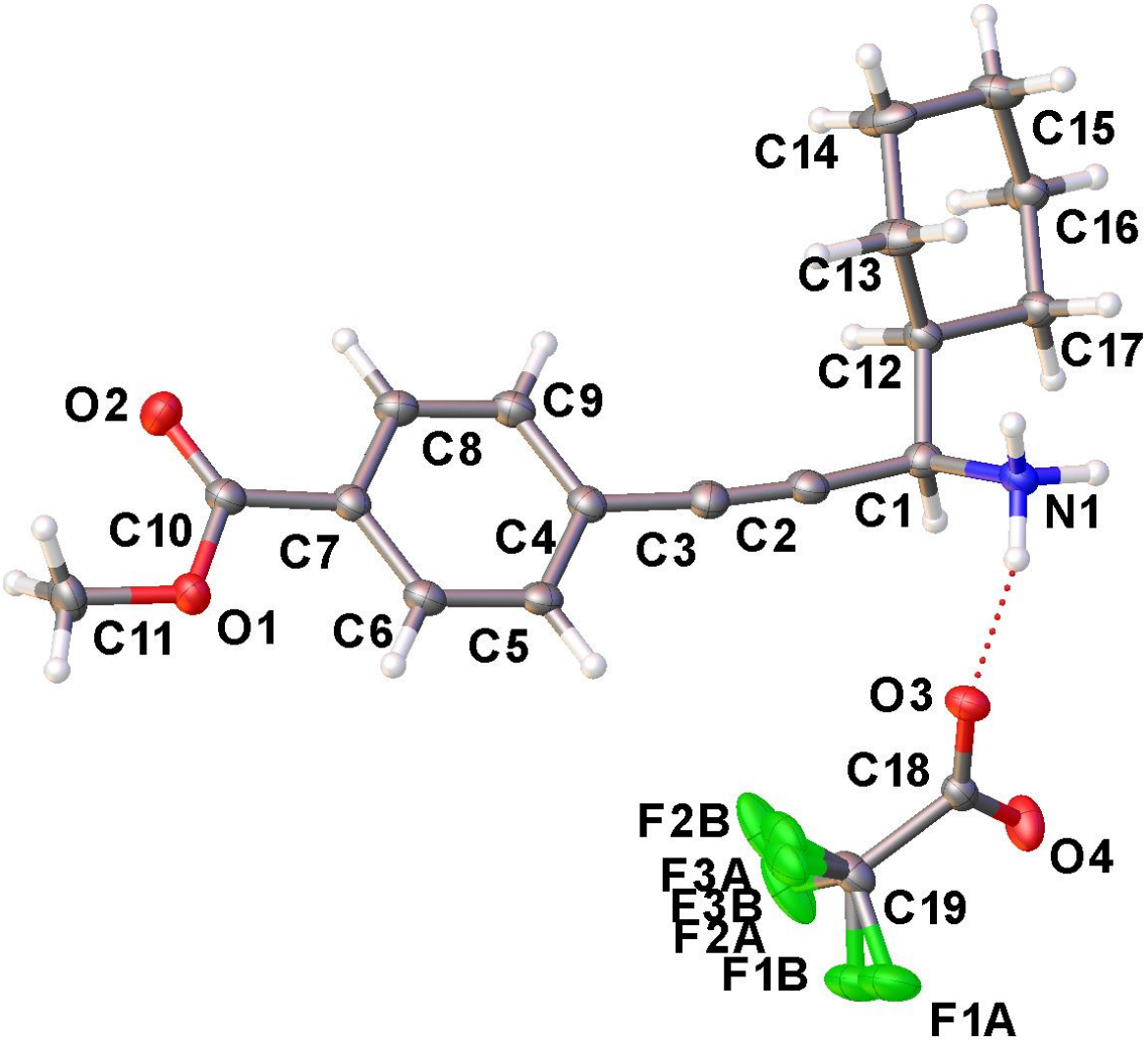


Table EP22. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{19}H_{22}F_3NO_4$ **55c**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
F1A	5747(5)	2083(3)	7249.6(13)	42.2(10)
F1B	5400(40)	2550(20)	7354(8)	42.2(10)
F2A	5487(6)	3581(3)	7067(2)	47.9(12)
F2B	6210(40)	3760(12)	6822(13)	47.9(12)
F3A	8104(5)	2778(6)	6704(3)	33.6(11)
F3B	8120(30)	2630(50)	6820(20)	33.6(11)
O3	5838(4)	2407.7(17)	5705.2(10)	23.2(5)
O4	2927(4)	2536(2)	6278.6(12)	31.7(6)
C18	4803(5)	2542(2)	6202.7(14)	19.9(6)
C19	6072(5)	2764(3)	6806.7(14)	26.7(7)
O1	16586(4)	6209.3(17)	6657.1(11)	25.0(5)
O2	16437(4)	7302.0(19)	5880.8(11)	31.4(6)
N1	4908(5)	3198(2)	4538.7(12)	20.1(6)
C1	4873(5)	4238(2)	4706.6(14)	21.0(6)
C2	6787(5)	4496(3)	5037.6(14)	22.8(7)
C3	8324(5)	4808(3)	5278.8(15)	23.8(7)
C4	10157(5)	5251(2)	5522.5(14)	20.7(6)
C5	11257(5)	4870(2)	6037.7(14)	22.1(7)
C6	13054(5)	5304(2)	6245.8(14)	21.7(6)
C7	13787(5)	6124(2)	5945.7(14)	21.2(6)
C8	12687(5)	6508(3)	5432.6(16)	23.2(7)
C9	10889(5)	6076(3)	5226.0(15)	23.3(7)
C10	15724(5)	6613(2)	6145.7(14)	22.3(7)
C11	18399(6)	6690(3)	6902.3(18)	29.7(8)
C12	4503(5)	4892(3)	4132.7(14)	21.5(7)
C13	6218(6)	4854(3)	3638.7(17)	31.4(8)
C14	5837(6)	5594(3)	3117.6(18)	37.6(10)
C15	3721(6)	5478(3)	2811.9(16)	29.7(8)
C16	1996(6)	5468(3)	3304.9(16)	26.2(7)
C17	2399(5)	4721(3)	3815.0(15)	22.6(7)

Methyl 2,3-Dibromo-3-(3-bromo-4-methoxyphenyl)-2-methylpropanoate (67)

Single crystals of $C_{12}H_{13}Br_3O_3$ were achieved by evaporation of the solvent of a concentrated EtOAc solution at rt. SuperNova, Single source at offset, Eos. Micro-focus sealed X-ray tube, Mo Kα/0.71073 Å. Wuensch18, $C_{12}H_{13}Br_3O_3$, M=444.95 g mol^{-1}. T=100.00(10) K. Monoclinic, $P2_1$, a=8.4652(3) Å, b=7.16932(18) Å, c=12.2165(4) Å, α=90°, β=102.518(3)°, γ=90°, Volume=723.79(4) $Å^3$, Z=2, crystal size=0.293 × 0.235 ×

0.18. 2Θ range for data collection=3.4 to 60.1°. Index ranges: -11 ≤ h ≤ 11, -9 ≤ k ≤ 9, -17 ≤ l ≤ 17. 11113 Reflections. Goodness-of-fit on F^2=1.043.

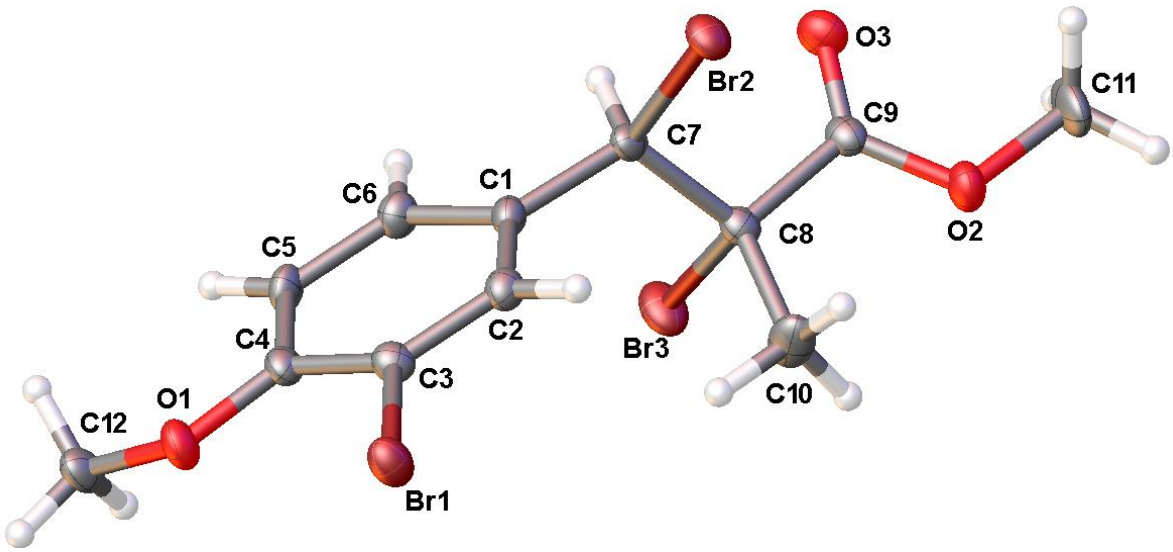


Table EP24. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for $C_{12}H_{13}Br_3O_3$ **67**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Br1	6722.2(7)	4695.7(9)	-319.2(4)	24.68(13)
Br2	4363.8(7)	7708.8(7)	3403.3(5)	23.19(13)
Br3	2162.9(7)	1781.2(8)	3117.9(5)	29.42(15)
O1	8210(5)	1283(6)	896(3)	24.6(9)
O2	-51(5)	5903(6)	3221(4)	25.6(9)
O3	1884(5)	5299(7)	4743(3)	27.0(9)
C1	5305(6)	4104(7)	2714(4)	18.3(10)
C2	5500(6)	4752(9)	1673(4)	20.3(10)
C3	6494(7)	3800(8)	1100(4)	19.5(10)
C4	7303(6)	2172(7)	1537(5)	19.2(10)
C5	7166(6)	1583(8)	2596(5)	20.5(10)
C6	6174(6)	2542(8)	3169(4)	21.4(10)
C7	4161(6)	4958(8)	3357(4)	17.9(10)
C8	2369(6)	4538(8)	2923(4)	18.0(9)
C9	1401(7)	5303(8)	3742(4)	19.7(10)
C10	1645(8)	4929(12)	1687(5)	31.6(14)
C11	-1059(8)	6566(12)	3968(6)	36.6(16)
C12	8745(8)	-558(8)	1225(5)	26.1(12)

Ethyl (*S*,*E*)-6-Ammonium-3,8-dimethylnon-2-en-4-ynoate Hydrochloride (75e)

Single crystals of $C_{13}H_{22}ClNO_2$ were achieved by evaporation of the solvent of a concentrated MeOH solution at rt.

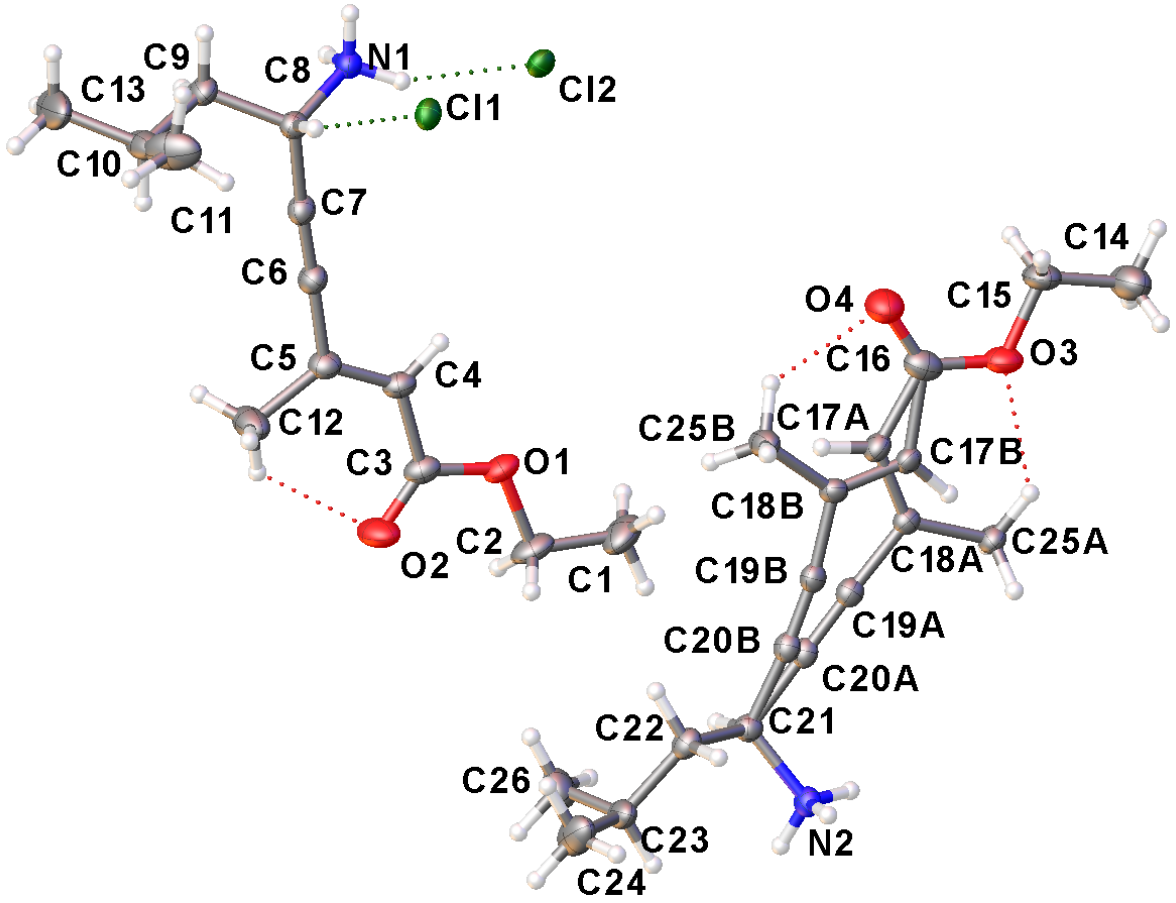


Table EP25. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for $C_{13}H_{22}ClNO_2$ **75e**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1	5770.9(2)	6949.0(7)	9844.4(2)	23.31(8)
Cl2	4747.5(2)	1965.9(7)	8633.9(2)	22.51(8)
O1	5808.7(4)	1989(3)	5276.5(6)	29.5(2)
O2	6600.2(5)	1971(4)	5476.1(8)	45.6(3)
N1	5753.3(5)	1544(2)	9760.1(9)	23.1(3)
C1	5306.2(9)	2081(6)	3939.2(11)	50.6(6)
C2	5809.6(7)	2013(5)	4366.2(9)	36.6(4)
C3	6235.5(6)	1977(4)	5761.8(9)	27.7(3)
C4	6181.4(6)	1993(3)	6667.2(9)	25.0(3)
C5	6538.1(5)	1981(4)	7316.9(9)	26.5(3)
C6	6427.1(5)	2037(4)	8166.5(9)	25.3(3)
C7	6347.3(5)	2130(3)	8875.6(9)	23.7(3)
C8	6228.5(6)	2398(2)	9729.2(10)	21.6(3)
C9	6584.6(6)	1494(3)	10434.1(10)	26.5(4)
C10	7075.5(7)	2399(4)	10503.4(11)	42.5(6)

C11	7067.9(11)	4616(5)	10686.0(17)	59.3(8)
C12	7054.4(6)	1951(7)	7256.0(11)	47.3(5)
C13	7413.1(9)	1320(6)	11183.2(16)	72.2(13)
O3	3212.4(5)	7104(3)	4041.1(7)	34.9(3)
O4	3726.4(5)	6951(4)	5244.4(8)	44.5(3)
N2	5198.3(5)	7294(2)	1375.0(8)	22.9(3)
C14	2380.2(8)	7276(5)	3957.7(14)	50.1(7)
C15	2833.3(7)	7153(5)	4549.8(11)	38.4(5)
C16	3646.5(6)	7016(4)	4482.9(11)	33.3(3)
C21	5313.3(6)	6564(2)	2268.1(10)	21.9(3)
C22	5746.4(6)	7637(3)	2726.9(10)	24.7(3)
C23	6206.4(6)	7121(4)	2403.2(10)	32.1(4)
C24	6588.4(9)	8570(4)	2779.0(16)	50.0(6)
C26	6357.1(8)	5014(4)	2637.1(16)	43.3(5)
C17A	4062.5(10)	6970(7)	4036.6(19)	23.9(5)
C18A	4060.5(7)	6993(4)	3193.9(12)	19.5(4)
C19A	4509.9(9)	6918(5)	2902.5(17)	22.2(4)
C20A	4871.4(17)	6798(12)	2628(3)	21.7(7)
C25A	3642.4(7)	7033(5)	2497.8(12)	23.4(5)
C17B	3926(2)	7006(13)	3729(4)	20.6(11)
C18B	4392.1(17)	7047(11)	3938(3)	21.3(10)
C19B	4678.6(19)	6958(12)	3271(4)	21.1(9)
C20B	4957(5)	6860(30)	2800(7)	21.7(7)
C25B	4669.1(18)	7127(14)	4814(3)	31.3(13)

Ethyl (*S*,*E*)-6-Ammonium-6-cyclohexyl-3-methylhex-2-en-4-ynoate Hydrochloride (75f)

Single crystals of $C_{30}H_{48}Cl_2N_2O_4$ were achieved by evaporation of the solvent of a concentrated MeOH solution at rt.

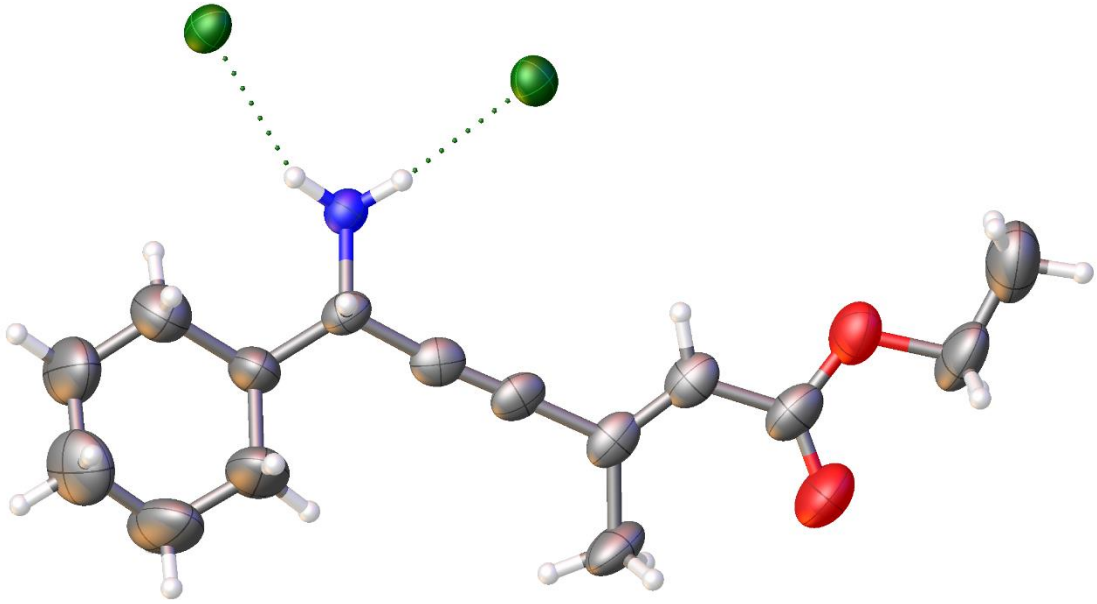


Table EP26. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for olefin **75f**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1	5848.6(9)	5734.6(7)	3832.6(14)	45.1(5)
Cl2	4208.7(9)	4407.6(8)	3824.1(15)	46.5(5)
O1	3318(3)	2052(3)	3921(5)	72.3(19)
O2	4060(4)	1328(3)	3758(7)	94(2)
N1	5734(3)	4330(2)	3967(4)	38.9(14)
C1	2186(6)	1905(6)	3981(11)	108(5)
C2	2804(6)	1588(4)	3905(9)	85(3)
C3	3935(5)	1852(4)	3818(7)	61(2)
C4	4392(5)	2353(3)	3770(6)	52(2)
C5	5041(5)	2305(3)	3720(5)	50(2)
C6	5416(4)	2844(3)	3642(5)	46(2)
C7	5738(4)	3291(4)	3558(5)	46(2)
C8	6066(4)	3854(3)	3399(6)	44.4(19)
C9	6794(4)	3843(4)	3566(8)	66(3)
C10	7098(5)	4464(5)	3288(10)	85(3)
C11	7805(6)	4453(6)	3303(11)	108(5)
C12	8067(7)	3982(6)	2662(9)	99(4)
C13	7816(7)	3377(6)	2952(12)	119(6)
C14	7112(6)	3358(5)	2955(11)	102(5)
C15	5421(5)	1738(3)	3714(8)	68(3)
N33	4295(3)	4190(3)	6009(5)	51.8(17)

C20	4960(5)	2177(4)	6203(6)	60(2)
C21	4580(4)	2703(4)	6294(6)	53(2)
C22	4268(5)	3153(4)	6376(5)	49(2)
C23	3917(5)	3717(4)	6514(6)	51(2)
C24	3196(5)	3707(4)	6222(9)	71(3)
C25	3051(5)	3468(5)	5291(7)	74(3)
C26	2312(5)	3464(5)	5124(8)	87(4)
C27	1999(6)	4068(6)	5286(8)	89(4)
C28	2131(5)	4276(5)	6241(9)	89(4)
C29	2869(5)	4301(4)	6447(8)	76(3)
C30	5679(5)	2276(7)	6155(8)	100(4)
O3B	4805(13)	751(12)	6897(17)	156(8)
O4B	5673(8)	1045(7)	6126(12)	83(4)
C16B	5294(18)	-138(15)	7450(30)	161(15)
C17B	5130(40)	110(20)	6570(40)	320(40)
C18B	5143(16)	1118(12)	6370(20)	101(8)
C19B	4588(12)	1652(8)	6027(16)	68(4)
O3A	4399(8)	622(7)	5854(12)	95(5)
O4A	5397(11)	855(9)	5735(14)	108(6)
C16A	3960(20)	-180(40)	5020(70)	260(30)
C17A	4560(20)	-60(20)	5510(30)	190(20)
C18A	4866(13)	997(11)	5858(18)	85(7)
C19A	4736(12)	1633(8)	6307(16)	68(4)

Methyl 4-((1*E*,3*Z*)-3-(((*R*)-*tert*-Butylsulfinyl)imino)-3-phenylprop-1-en-1-yl)benzoate (76e).

Single crystals of $C_{21}H_{24}NO_3S$ were achieved by evaporation of the solvent of a concentrated $CHCl_3$ solution at -20 °C.

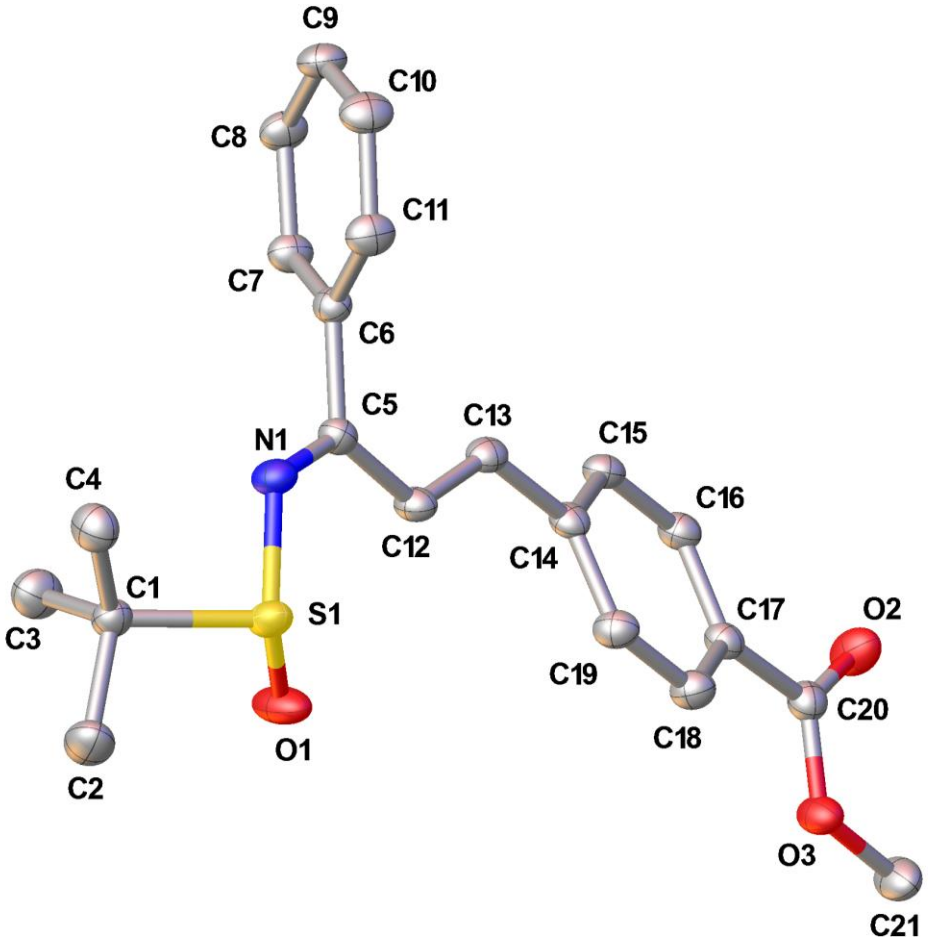


Table EP28. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for enimin **76e**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	5313.5(11)	5191.5(6)	3501.6(2)	26.65(17)
O1	3568(4)	6178(2)	3586.6(8)	40.6(6)
O2	-7437(3)	5126(2)	5629.0(7)	33.0(5)
O3	-5236(3)	6883.7(17)	5585.6(6)	28.8(4)
N1	4352(4)	3670(2)	3444.7(7)	24.7(5)
C1	6103(4)	5394(3)	2929.1(8)	23.5(5)
C2	7134(6)	6752(3)	2910.6(10)	37.5(7)
C3	4073(5)	5320(3)	2643.6(10)	35.3(7)
C4	7818(5)	4369(3)	2822.5(10)	32.6(6)
C5	2672(4)	3189(3)	3652.1(8)	21.8(5)
C6	2266(4)	1784(2)	3565.6(8)	20.8(5)

C7	296(5)	1351(2)	3386.1(8)	24.2(5)
C8	-3(5)	38(3)	3299.2(9)	26.5(5)
C9	1650(5)	-848(3)	3403.3(9)	28.0(6)
C10	3592(5)	-420(3)	3591.3(10)	30.6(6)
C11	3923(5)	892(3)	3668.3(9)	27.3(6)
C12	1280(4)	3866(2)	3967.0(8)	22.5(5)
C13	-305(4)	3275(2)	4199.4(8)	22.0(5)
C14	-1651(4)	3914(2)	4530.8(8)	21.1(5)
C15	-3746(4)	3405(2)	4629.2(8)	22.4(5)
C16	-5087(4)	3993(2)	4932.5(8)	22.9(5)
C17	-4345(4)	5092(2)	5150.5(8)	21.0(5)
C18	-2247(5)	5597(3)	5062.6(9)	25.5(6)
C19	-924(4)	5005(3)	4755.1(9)	24.3(5)
C20	-5837(5)	5680(3)	5480.5(8)	23.9(6)
C21	-6645(6)	7512(3)	5898.5(10)	35.2(7)

Methyl (*E*)-3-(4,4,4-Trifluoro-3-oxobut-1-en-1-yl)benzoate (78c)

Single crystals of $C_{11}H_7F_3O_3$ were achieved by evaporation of the solvent of a concentrated MeOH solution at rt.

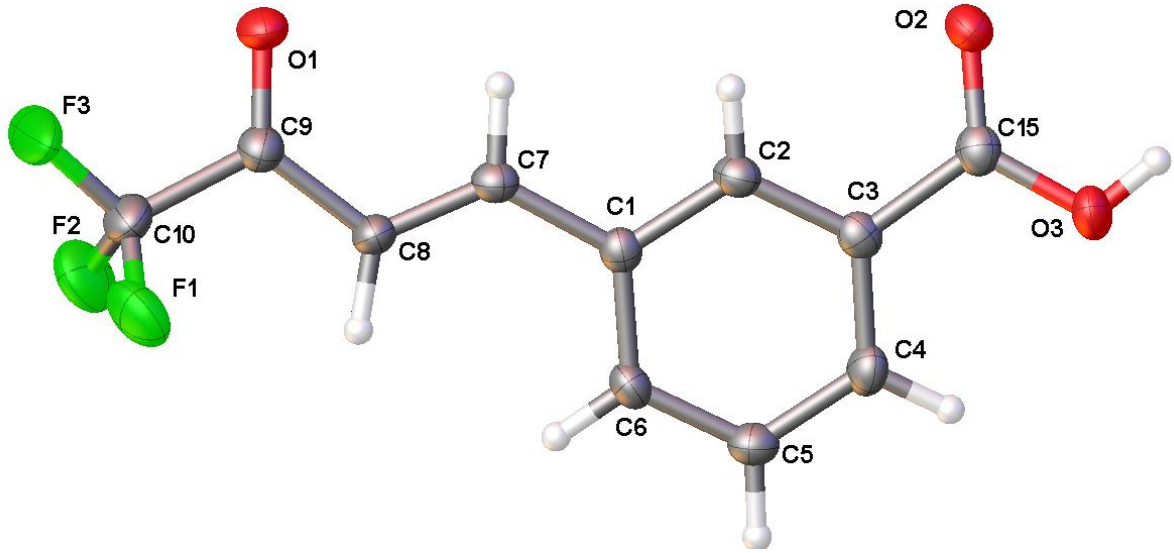
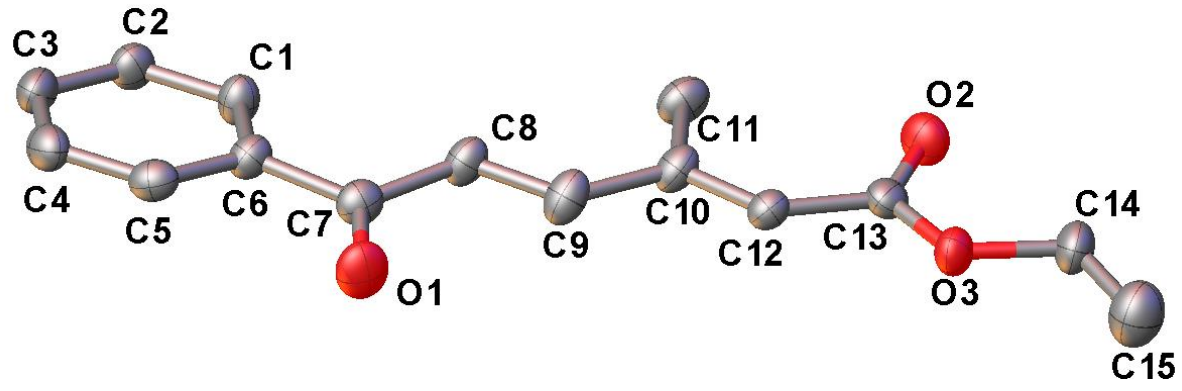


Table EP27. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for keton **77c**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
F1	1467.9(9)	6458.8(17)	1152.3(11)	49.7(5)
F2	1058(1)	6633.7(18)	2521.6(13)	56.5(5)
F3	583.9(10)	5069.4(19)	1493.9(16)	82.2(8)
O1	1913(1)	3810.2(18)	2611.1(13)	37.3(5)
O2	6460.9(10)	2704.4(18)	4669.3(12)	33.6(5)
O3	7476.2(10)	4218(2)	4694.8(13)	34.1(5)
C1	4484.7(13)	5390(2)	3557.0(15)	21.7(5)
C2	5145.0(14)	4473(3)	3864.5(17)	24.0(6)
C3	6004.6(13)	4855(3)	4202.6(16)	22.9(5)
C4	6213.4(14)	6167(3)	4242.9(17)	26.6(6)
C5	5567.0(15)	7082(3)	3956.6(17)	26.9(6)
C6	4707.5(14)	6706(3)	3608.7(17)	24.8(6)
C7	3593.3(14)	4922(3)	3204.7(17)	24.5(6)
C8	2877.7(13)	5612(3)	2801.6(17)	24.7(6)
C9	2046.3(14)	4945(3)	2468.1(18)	27.8(6)
C10	1276.7(15)	5782(3)	1898(2)	39.0(7)
C15	6668.0(14)	3833(3)	4538.2(16)	25.9(6)

Ethyl (2*E*,4*E*)-3-Methyl-6-oxo-6-phenylhexa-2,4-dienoate (78f)

Single crystals of $C_{15}H_{16}O_3$ were achieved by evaporation of the solvent of a concentrated MeOH solution at rt.



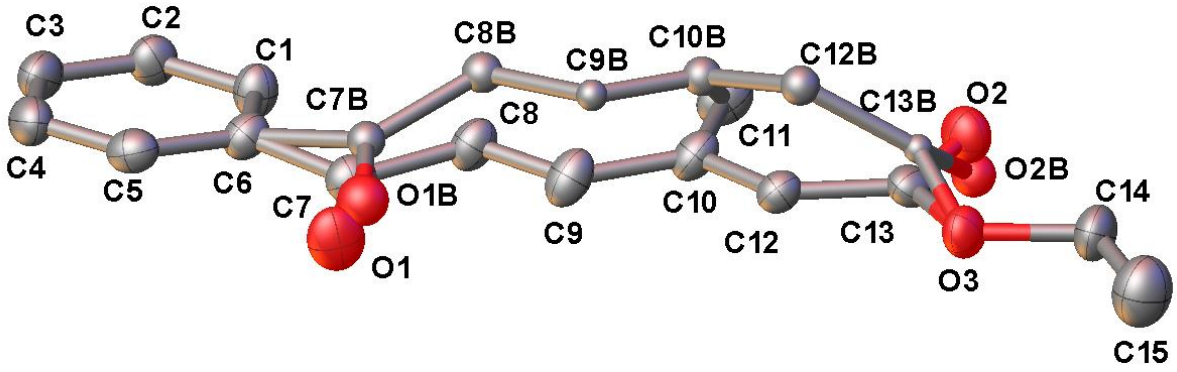


Table EP29. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for keton **77f**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor. Disorder B was 15 %.

Atom	*x*	*y*	*z*	U(eq)
O1	7540(4)	6064(4)	6105.8(17)	43.7(6)
O1B	7160(20)	5355(18)	6097(10)	35(3)
O2	3873(4)	-2668(3)	2154.0(19)	39.3(5)
O2B	4260(20)	-2375(18)	1903(9)	26(3)
O3	1317(2)	-1451.9(19)	1862.4(10)	33.2(4)
C1	12300(3)	5201(3)	7117.2(15)	32.0(4)
C2	14109(3)	6044(3)	7913.0(15)	32.8(4)
C3	14226(4)	7605(3)	8657.3(15)	34.7(5)
C4	12552(4)	8319(3)	8607.6(15)	34.9(5)
C5	10746(3)	7482(3)	7820.7(15)	31.0(4)
C6	10607(3)	5911(3)	7067.2(13)	28.6(4)
C7	8705(5)	5172(5)	6205(2)	30.4(6)
C7B	8380(30)	4600(20)	6281(12)	20(4)
C8	8233(4)	3312(4)	5489.6(17)	30.7(6)
C8B	7908(19)	2475(17)	5759(9)	22(3)
C9	6499(4)	2569(4)	4725.5(17)	34.2(6)
C9B	5690(16)	1492(14)	4968(7)	13(2)
C10	5938(4)	804(4)	3936.0(16)	30.3(6)
C10B	5393(18)	-69(16)	4264(8)	21(2)
C11	7504(3)	-258(3)	3892.5(15)	35.4(5)
C12	4059(4)	258(3)	3254.2(15)	25.2(5)
C12B	2972(18)	-1033(15)	3624(8)	21(2)
C13	3215(5)	-1383(4)	2367(2)	29.3(6)
C13B	2770(20)	-1842(19)	2497(10)	11(3)
C14	350(4)	-3024(3)	946.9(15)	40.2(5)
C15	-1597(5)	-2865(4)	442(2)	56.9(7)

IIX-3. o) References (215-236)

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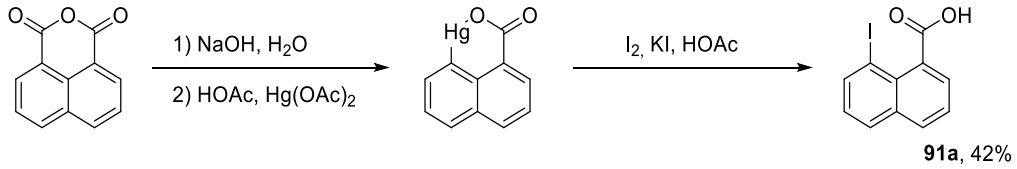
IIX-4. Propynyl-Aryl Scaffolds as Turn Motif Mimetics

IIX-4. a) Halogenated Naphthoate Derivatives (91-92)

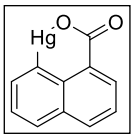
8-Iodo-1-naphthoic Acid (91a).



Scheme EP2. Synthesis of iodo nachthoat derivative **91a** via mercury-organyle.

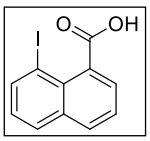
The synthesis was carried out in analogy to the description of Wiley *et al.* [167].

1,8-Naphthoic acid anhydride (3.95 g, 19.9 mmol, 1.0 eq) was dissolved in aqueous NaOH



(2.85 g in 120 mL) at 100 °C under reflux conditions. The clear solution was cooled down to rt and neutralized by adding glacial acetic acid (2 mL). A solution of $Hg(OAc)_2$ (6.35 g, 19.9 mmol, 1.0 eq) in water/glacial acetic acid (2:1, 30 mL) was very carefully added and the reaction mixture was heated under reflux conditions for 30 min to 120 °C. More glacial acetic acid (3.6 mL) was added and the suspension was heated for 48 h under reflux conditions to 120 °C. A colorless solid precipitated in the course of the reaction, which was filtered off, washed with water and dried over 5 days in an exsikkator over P_4O_{10}.

Iodine (4.9 g, 19.7 mmol, 1.0 eq) was added to a vigorously stirred aqueous solution of anhydro-8-(hydroxymercury)-1-naphthalic acid anhydrid (7.29 g, 19.7 mmol, 1.0 eq) and

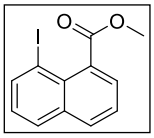


KI (14.00 g, 84.58 mmol, 4.3 eq) and the solution was heated to 110 °C for 24 h under reflux conditions. Afterwards, remaining solid was filtered off and the filtrate was washed with an aqueous $Na_2S_2O_3$ solution. By careful addition of concentrated HCl, the iodo naphthoate **91a** was precipitated, isolated by filtration and purified by recrystallization from $CHCl_3$.

Colorless, crystalline solid. Yield: 2.48 g, 8.35 mmol, 42 % (Lit: 52 % [167]). ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.28 (dd, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 1H, naphthoate-2-**H**), 7.96-7.89 (m, 3H, naphthoate-4-**H**, naphthoate-6-**H**, naphthoate-8-**H**), 7.52 (dd, ^3J = 8.2 Hz, ^3J = 7.1 Hz, 1H, naphthoate-3-**H**), 7.23 (t, ^3J = 7.9 Hz, 1H, naphthoate-3-**H**). ^{13}C NMR (75 MHz, Chloroform-*d*) δ = 174.1 (naphthoate-1-**C**O_2H), 155.1 (naphthoate-**C**-

5), 153.8 (naphthoate-**C**-10), 142.1 (naphthoate-**C**-8), 135.5 (naphthoate-**C**-1), 133.3 (naphthoate-**C**-9), 132.8 (naphthoate-**C**-4), 129.7 (naphthoate-**C**-6), 129.6 (naphthoate-**C**-2), 127.6 (naphthoate-**C**-7), 125.2 (naphthoate-**C**-3). $C_{11}H_7IO_2$ (298.08 g mol^{-1}). LCMS (ESI): *tr* = 6.9 min, *m/z* = 298.937 (calcd. 298.9563 $[M+H]^+$).

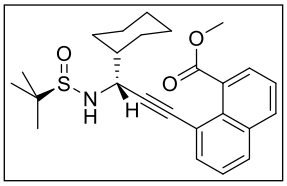
Methyl 8-Iodo-1-naphthoate (91b). Similar methylation reactions, as well as the characterization of naphthoate **91b** have been reported by Bailey *et al.* [237]. A solution of trimethylsilyl diazomethane (2 M in THF, 0.25 mL, 0.50 mmol, 1.0 eq) and DIPEA (0.16 mL, 124 mg, 0.96 mmol, 2.0 eq) was added dropwise to a vigorously stirred solution of iodo naphthoic acid (143 mg, 0.48 mmol, 1.0 eq) in THF (10 mL). The reaction mixture was stirred for 1 h at ambient temperature. After complete consumption of the acid (checked by TLC), the reaction mixture was diluted with acetic acid (1 M, 20 mL) and extracted with Et_2O (4 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, methyl naphthoate **91b** was afforded in pure form.



Colorless crystalline solid. Yield: 150 mg, 0.48 mmol, 96 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 8.21 (dd, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 1H, naphthoate-2-**H**), 7.88 (dd, ^3J = 8.1 Hz, ^4J = 1.3 Hz, 1H, naphthoate-6-**H**), 7.85 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1H, naphthoate-8-**H**), 7.69 (dd, ^3J = 7.1 Hz, ^4J = 1.4 Hz, 1H, naphthoate-4-**H**), 7.46 (dd, ^3J = 8.2 Hz, ^3J = 7.1 Hz, 1H, naphthoate-3-**H**), 7.16 (t, ^3J = 7.8 Hz, 1H, naphthoate-7-**H**), 4.00 (s, 3H, $CO_2C\mathbf{H_3}$). $C_{12}H_9IO_2$ (312.12 g mol^{-1}). LCMS (ESI): *m/z* = 313.531 (calcd. 312.9720 $[M+H]^+$).

Methyl 8-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yne-1-yl)-1-naphthoate (92). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2.4 mg, 3.6 μmol, 1.0 mol%) and CuI (1.4 mg, 7.2 μmol, 2.0 mol%) were added in one portion to a thoroughly degassed solution of propargylamide **6e** (86 mg, 360 μmol, 1.0 eq) and iodo naphthoate **91b** (169 mg, 540 μmol, 1.5 eq) in a mixture of THF/piperidine (2:1, 0.7 mL). The reaction mixture was stirred overnight at ambient temperature. After complete consumption of propargylamide **6e** (checked by TLC), the mixture was diluted with water (5 mL), aqueous NH_4Cl (saturated, 10 mL) and aqueous hydrochloric acid (1 M, 3-4 mL

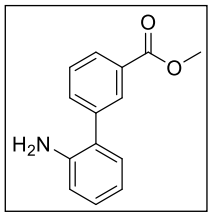
until pH was 7). The aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude naphthoate **92** was purified by preparative HPLC.



Colorless, highly viscous oil. Yield: 36.7 mg, 90 mmol, 17 %. ^{1}H NMR (300 MHz, Chloroform-*d*) δ = 7.92 (dd, ^3J = 8.4 Hz, ^4J = 1.4 Hz, 1H, naphthoate-2-**H**), 7.86 (dd, ^3J = 8.3 Hz, ^4J = 1.3 Hz, 1H, naphthoate-6-**H**), 7.75 (dd, ^3J = 7.2 Hz, ^4J = 1.3 Hz, 1H, naphthoate-7-**H**), 7.61 (dd, ^3J = 7.1 Hz, ^3J = 1.4 Hz, 1H, naphthoate-4-**H**), 7.49 (dd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, 1H, naphthoate-3-**H**), 7.46 (dd, ^3J = 8.2 Hz, ^3J = 7.3 Hz, 1H, naphthoate-8-**H**), 4.32 (d br., ^3J = 4.9 Hz, 1H, C$^{\alpha}$**H**), 4.00 (s, 3H, $CO_2C\mathbf{H_3}$), 2.03-1.64 (m, 6H, cy-**H**), 1.35 (s, 9H, $SC(C\mathbf{H_3})_3$), 1.30-1.11 (m, 5H, cy-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 171.8 ($\mathbf{C}O_2CH_3$), 134.2 (naphthoate-**C**-10), 133.8 (naphthoate-**C**-8), 131.7 (naphthoate-**C**-2), 131.4 (naphthoate-**C**-5), 129.7 (naphthoate-**C**-6), 128.9 (naphthoate-**C**-1), 127.7 (naphthoate-**C**-4), 126.0 (naphthoate-**C**-7), 125.3 (naphthoate-**C**-3), 118.8 (naphthoate-**C**-9), 93.3 (C$^{\alpha}$H**C**≡Car), 85.2 (C$^{\alpha}$HC≡**C**ar), 57.1 ($S\mathbf{C}(CH_3)_3$), 53.6 (**C$^{\alpha}$**H), 52.9 ($CO_2\mathbf{C}H_3$), 43.0 (cy-**C**-1), 29.8 (cy-**C**-2), 28.0 (cy-**C**-6), 26.5 (cy-**C**-4), 26.2 (cy-**C**-5), 26.0 (cy-**C**-3), 23.0 ($SC(\mathbf{C}H_3)_3$). $C_{25}H_{31}NO_3S$ (425.59 g mol^{-1}). MS(ESI): *m/z* = 426.326 (calcd. 426.2097 $[M+H]^+$), 448.299 (calcd. 448.1917 $[M+Na]^+$). IR(ATR): ῡ [cm^{-1}] = 3262 (NH), 2923, 2850 (CH_3, CH_2), 1720 (CO_2Me), 1042 (S=O).

IIX-4. b) Biphenyl-Based Turn Motifs (93-94)

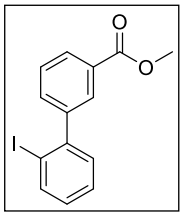
Methyl 2'-Amino-[1,1'-biphenyl]-3-carboxylate (93a). A similar Suzuki reaction using 3-chlorobenzoat instead of **26a**, as well as the characterization of **93a** has been reported by Anderson *et al.* [238]. (2-Aminophenyl)boronic acid hydrochloride (100 mg, 577 μmol, 1 eq), methyl 3-iodobenzoate (**26a**, 0.15 g 58 μmol, 1 eq) and K_3PO_4 (0.37 g, 1.7 mmol, 3 eq) was placed under an argon atmosphere and suspended in a mixture of dioxane/H_2O (2 mL, 4:1). $PdCl_2(PPh_3)_2$ (1 mol%) was added in one portion and the suspension was sonicated for a short time at 40 °C, until a fine, colorless suspension formed. The reaction mixture was stirred under nitrogen overnight at rt, which lead to a slightly yellow solution with a colloidal colorless precipitate. The solution was diluted with a solution of $NaHCO_3$



(saturated, 20 mL) and extracted with Et_2O (5 x 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Purification of the crude product by column chromatography (EtOAc/PE, 2:1) lead to the title compound in pure form.

Colorless fluid. Yield: 76.2 mg, 335 μmol, 58 % (Lit: 94 % [238]). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.16 (d, ^4J = 1.8 Hz, 1H, ar-2-**H**), 8.03 (dt, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, ar-6-**H**), 7.67 (dt, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, ar-4-**H**), 7.52 (t, ^3J = 7.7 Hz, 1H, ar-5-**H**), 7.18 (td, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 1H, ar'-5-**H**), 7.13 (d, ^3J = 7.5 Hz, 1H, ar'-3-**H**), 6.84 (td, ^3J = 7.4, ^4J = 1.1 Hz, 1H, ar'-4-**H**), 6.78 (d, ^3J = 8.0 Hz, 1H, ar'-6-**H**), 3.93 (s, 3H, ar-3-$CO_2C\mathbf{H_3}$), 3.67 (s, 2H, ar'-2-$N\mathbf{H_2}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.0 (ar-3-**C**O_2CH_3), 143.6 (ar'-**C**-1), 139.9 (ar-**C**-3), 133.7 (ar-4-**H**), 130.8 (ar'-**C**-3), 130.5 (ar-**C**-2), 130.3 (ar-5-**H**), 129.0 (ar'-**C**-5), 128.9 (ar-**C**-1), 128.4 (ar-6-**H**), 126.5 (ar'-**C**-2), 118.8 (ar'-**C**-4), 115.8 (ar'-**C**-6), 52.3 (ar-3-$CO_2\mathbf{C}H_3$). $C_{14}H_{13}NO_2$ (227.26 g mol^{-1}). LCMS(ESI): t*r* = 8.8 min, *m/z* = 228.1064 (calcd. 228.1019 $[M+H]^+$). TLC: R*f* (EtOAc/PE, 1:4) = 0.59, R*f* (EtOAc/PE, 1:10) = 0.44.

Methyl 2'-Iodo-[1,1'-biphenyl]-3-carboxylate (93b). Rickhaus et al. have reported before the characterization of **93b**, which they accessed by a completely different synthesis strategy [239]. $NaNO_2$ (110 mg, 1.59 mmol, 1.2 eq) was added to a vigorously stirred solution of methyl 2'-amino-[1,1'-biphenyl]-3-carboxylate (301 mg, 1.32 mmol, 1.0 eq) and NaI (594 mg, 3.96 mmol, 3.0 eq) in half concentrated, aqueous HCl (6 M, 20 mL) at 0 °C in one portion. After stirring the reaction mixture for 5 min, solid iodine (33.5 mg, 264 μmol, 0.2 eq) was added in one portion. The reaction mixture was allowed to warm up to room temperature overnight. After 14 h, an aqueous solution of Na_2SO_3 (saturated, 10 mL) was added until the red color of the solution had completely vanished. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with aqueous $NaHCO_3$ (saturated, 10 mL) and brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc, 4:1) to yield the title compound in pure form.

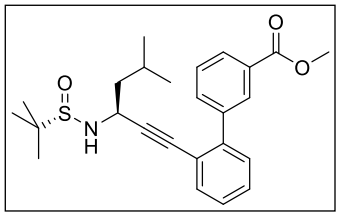


Colorless, highly viscous oil. Yield: 63.9 mg, 189 μmol, 14 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.08 (d, ^3J = 7.6 Hz, 1H, ar-6-**H**), 8.03 (s, 1H, ar-2-**H**), 7.97 (d, ^3J = 7.9 Hz, 1H, ar'-6-**H**), 7.56 (d, ^3J = 7.5 Hz, 1H, ar'-4-**H**), 7.50 (t, ^3J = 7.5 Hz, 1H, ar-5-**H**),

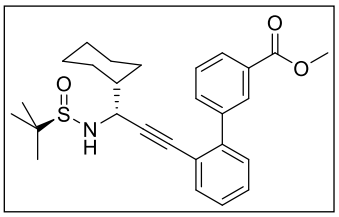
7.41 (t, ^{3}J = 7.5 Hz, 1H, ar'-4-**H**), 7.31 (d, ^{3}J = 7.6 Hz, 1H, ar'-3-**H**), 7.06 (t, ^{3}J = 7.6 Hz, 1H, ar'-5-**H**), 3.93 (s, 3H, ar-1-$CO_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.0 (ar-1-$\mathbf{C}O_2CH_3$), 145.7 (ar'-**C**-2), 144.4 (ar-**C**-3), 139.7 (ar'-**C**-6), 134.0 (ar-**C**-4), 130.5 (ar-**C**-2), 130.1 (ar'-**C**-3), 130.1 (ar'-**C**-5), 129.3 (ar-**C**-1), 129.0 (ar-**C**-6), 128.4 (ar'-**C**-4), 128.2 (ar-**C**-5), 98.5 (ar'-**C**-1), 52.3 (ar-1-$CO_2\mathbf{C}H_3$). $C_{14}H_{11}IO_2$ (338.14 g mol^{-1}). LCMS (ESI): t*r* = 11.3 min, *m/z* = 338.9969 (calcd. 338.9876 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.69.

Methyl 2'-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)-[1,1'-biphenyl]-3-carboxylate (94a). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (4 mg, 6 μmol, 2 mol%) and CuI (3 mg, 16 μmol, 4 mol%) were added in one portion to a thoroughly degassed solution of propargylamide **6c** (76 mg, 370 μmol, 1.0 eq) and iodo biphenyl **93b** (127 mg, 376 μmol, 1.0 eq) in a mixture of THF/piperidine (3:1, 1.2 mL). The reaction mixture was stirred over 16 h at ambient temperature. After complete consumption of propargylamide **6c** (checked by TLC), the mixture was diluted with Et_2O (20 mL) and washed with aqueous $KHSO_4$ (5 %, 2 x 15 mL). The aqueous layers were extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude biphenyl derivative **94a** was purified by column chromatography (PE/EtOAc, 2:1).

Colorless, highly viscous oil. Yield: 43.6 mg, 102 μmol, 27 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.24 (s, 1H, ar-2-**H**), 8.02 (d, ^{3}J = 7.8 Hz, 1H, ar-6-**H**), 7.78 (d, ^{3}J = 7.7 Hz, 1H, ar-4-**H**), 7.58 (d, ^{3}J = 7.6 Hz, 1H, ar'-6-**H**), 7.49 (t, ^{3}J = 7.8 Hz, 1H, ar-5-**H**), 7.39-7.33 (m, 2H, ar'-4-**H**, ar'-3-**H**), 7.30 (t, ^{3}J = 7.3 Hz, 1H, ar'-5-**H**), 4.12 (ddd, ^{3}J = 7.6 Hz, ^{3}J = 7.2 Hz, ^{3}J = 4.6 Hz, 1H, $C^{\alpha}\mathbf{H}$), 3.92 (s, 3H, ar-3-$CO_2C\mathbf{H_3}$), 3.29 (d, ^{3}J = 6.7 Hz, 1H, $C^{\alpha}HN\mathbf{H}$), 1.58 (m, 1H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}\mathbf{H}(CH_3)_2$), 1.54-1.40 (m, 2H, $C^{\alpha}HC^{\beta}\mathbf{H_2}C^{\gamma}H(CH_3)_2$), 1.18 (s, 9H, $SC(C\mathbf{H_3})_3$), 0.80 (d, ^{3}J = 6.5 Hz, 6H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$). $C_{25}H_{31}NO_3S$ (425.59 g mol^{-1}). TLC: R*f* (EtOAc/PE, 1:1) = 0.51.

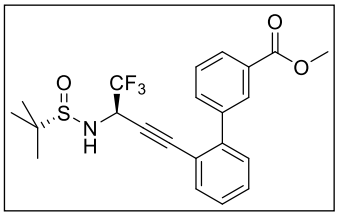


Methyl 2'-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yn-1-yl)-[1,1'-biphenyl]-3-carboxylate (94b). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (4 mg, 6 μmol, 2 mol%) and CuI (3 mg, 16 μmol, 4 mol%) were added in one portion to a thoroughly degassed solution of propargylamide **6e** (23.7 mg, 99 μmol, 1.0 eq) and iodo biphenyl **93b** (65.7 mg, 198 μmol, 2.0 eq) in a mixture of THF/DIPAH (3:1, 1.5 mL). The reaction mixture was stirred overnight at ambient temperature. After complete consumption of propargylamide **6e** (checked by TLC), the mixture was diluted with Et_2O (30 mL) and washed with aqueous $KHSO_4$ (5 %, 2 x 20 mL). The aqueous layers were extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude biphenyl derivative **94b** was purified by column chromatography (PE/EtOAc, 2:1).



Pale yellow, crystalline very thin needles. Yield: 14.7 mg, 32.6 μmol, 33 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.07 (dd, ^3J = 7.1 Hz, ^4J = 1.7 Hz, 1H, ar-6-**H**), 7.98 (s, 1H, ar-2-**H**), 7.88 (d, ^3J = 8.2 Hz, 1H, ar-6-**H**), 7.54-7.46 (m, 3H, ar-5-**H**, ar'-3-**H**, ar'-5-**H**), 7.37 (m, 1H, ar'-4-**H**), 7.12 (dd, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 1H, ar'-6-**H**), 4.05 (dd, ^3J = 7.3 Hz, ^3J = 6.5 Hz, 1H, C$^{\alpha}$**H**cy), 3.93 (s, 3H, ar-1-CO_2C**H**$_3$), 3.36 (d br., ^3J = 7.3 Hz, 1H, N**H**C$^{\alpha}$Hcy), 1.91-1.84 (m, 2H, cy-**H**), 1.80-1.72 (m, 3H, cy-**H**), 1.72-1.62 (m, 6H, cy-**H**), 1.24 (s, 9H, SC(C**H**$_3$)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.9 (ar-1-**C**O_2CH_3), 145.8 (ar'-**C**-1), 143.7 (ar-**C**-3), 139.6 (ar-**C**-4), 133.9 (ar'-**C**-3), 133.0 (ar'-**C**-4), 132.3 (ar'-**C**-6), 130.4 (ar-**C**-2), 130.2 (ar'-**C**-5), 129.2 (ar-**C**-6), 128.3 (ar-**C**-5), 123.3 (ar-**C**-1), 98.4 (ar'-**C**-2), 90.1 (C$^{\alpha}$H**C**≡Car), 84.6 (C$^{\alpha}$HC≡**C**ar), 56.1 (S**C**$(CH_3)_3$), 52.4 (ar-1-CO_2**C**H_3), 42.8 (cy-**C**-1), 29.1 (cy-**C**-2), 28.7 (cy-**C**-6), 28.4 (cy-**C**-4), 26.7 (cy-**C**-5), 26.5 (cy-**C**-3), 22.9 (SC(**C**$H_3)_3$). $C_{27}H_{33}NO_3S$ (451.63 g mol^{-1}). MS(ESI): *m/z* = 452.2254 (calcd. 452.2242 $[M+H]^+$).

Methyl 2'-((*R*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-4,4,4-trifluorobut-1-yn-1-yl)-[1,1'-biphenyl]-3-carboxylate (94c). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$



(2 mg, 3 μmol, 2 mol%) and CuI (1 mg, 5 μmol, 4 mol%) were added in one portion to a thoroughly degassed solution of propargylamide **6p** (32 mg, 141 μmol, 1.0 eq) and iodo biphenyl **93b** (63.9 mg, 189 μmol, 1.3 eq) in a mixture of

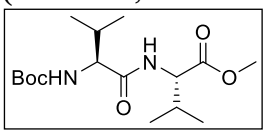
THF/DIPEA (3:1, 2.8 mL). The reaction mixture was stirred overnight at ambient temperature. After complete consumption of propargylamide **6p** (checked by TLC), the mixture was diluted with aqueous NH_4Cl (saturated, 20 mL), CH_2Cl_2 (20 mL) and aqueous $KHSO_4$ (5 %, 20 mL). The phases were separated and the aqueous layers were extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude biphenyl derivative **94c** was purified by column chromatography (PE/EtOAc, 2:1).

Pale yellow oil. Yield: 11.9 mg, 27.8 μmol, 20 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.26 (s, 1H, ar-2-**H**), 8.03 (d, ^3J = 7.5 Hz, 1H, ar-6-**H**), 7.76 (d, ^3J = 7.6 Hz, 1H, ar-4-**H**), 7.62 (d, ^3J = 7.7 Hz, 1H, ar‘-6-**H**), 7.52 (t, ^3J = 7.7 Hz, 1H, ar-5-**H**), 7.45 (t, ^3J = 7.9 Hz, 1H, ar‘-5-**H**), 7.42 (d, ^3J = 7.5 Hz, 1H, ar‘-3-**H**), 7.34 (t, ^3J = 7.4 Hz, 1H, ar‘-4-**H**), 4.63 (dq, ^3J = 7.8 Hz, ^3J = 6.4 Hz, 1H, C$^{\alpha}$**H**CF_3), 3.93 (s, 3H, ar-1-CO_2C**H**$_3$), 3.72 (d br., ^3J = 7.8 Hz, 1H, N**H**C$^{\alpha}$H), 1.22 (s, 9H, SC(C**H**$_3$)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.3 (ar-1-**C**O_2CH_3), 143.5 (ar’-**C**-1), 140.1 (ar-**C**-3), 133.8 (ar’-**C**-6), 133.7 (ar-**C**-4), 130.5 (ar-**C**-2), 130.2 (ar-**C**-1), 129.9 (ar‘-**C**-3), 129.5 (ar‘-**C**-5), 128.8 (ar-**C**-6), 128.5 (ar-**C**-5), 127.7 (ar‘-**C**-4), 123.0 (q, $^1J_{CF}$ = 282.0 Hz, C$^{\alpha}$H**C**F_3), 119.6 (ar‘-**C**-2), 87.2 (C$^{\alpha}$HC≡**C**ar), 82.9 (C$^{\alpha}$H**C**≡Car), 57.5 (S**C**$(CH_3)_3$), 51.7 (q, $^2J_{CF}$ = 34.9 Hz, **C$^{\alpha}$**HCF_3), 22.5 (SC(**C**$H_3)_3$). $C_{22}H_{22}F_3NO_3S$ (437.48 g mol^{-1}). MS(ESI): *m/z* = 438.13490 (calcd. 438.1345 $[M+H]^+$). TLC: R*f*(PE/EtOAc, 2:1) = 0.39.

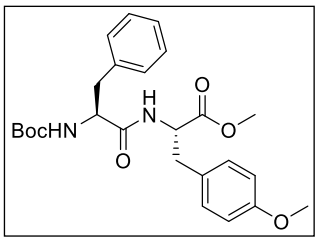
IIX-4. c) Introduction of Peptidomimetics into Peptides (95-97)

Methyl (*tert*-Butoxycarbonyl)-L-valyl-L-valinate. The dimerization of valine under analogous conditions has been reported by Jana *et al.* [240]. A mixture of *tert*-butoxycarbonyl-L-valine (1.08 g, 4.97 mmol, 1.0 eq) and methyl L-valinate hydrochloride (1.09 g, 6.50 mmol, 1.3 eq), TBTU (4.79 g, 14.9 mmol, 3.0 eq) and HOBt (201 mg, 1.49 mmol, 0.3 eq) was dissolved under argon atmosphere in a mixture of DMF/DIPEA (12.5 mL, 4:1) and stirred for three days at ambient temperature. The reaction mixture was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by column chromatography (PE/EtOAc, 2:1).

Colorless crystalline solid. Yield: 1.52 g, 4.60 mmol, 92 % (Lit: 84 % [240]). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.94 (d, ^{3}J = 8.4 Hz, 1H, CON**H**-Val), 5.43 (d, ^{3}J = 9.0 Hz, 1H, Val-N**H**Boc), 4.38 (dd, ^{3}J = 8.5 Hz, ^{3}J = 5.2 Hz, 1H, Val-C$^{\alpha}$**H**), 3.93 (dd, ^{3}J = 8.1 Hz, ^{3}J = 8.1 Hz, 1H, Val-C$^{\alpha}$**H**), 3.57 (s, 3H, $CO_2C\mathbf{H_3}$), 2.02 (dh, ^{3}J = 7.3 Hz, ^{3}J = 6.7 Hz, 1H, Val-C$^{\alpha}$HC**H**$(CH_3)_2$), 1.92 (dh, ^{3}J = 6.8 Hz, ^{3}J = 5.2 Hz, 1H, Val-C$^{\alpha}$C**H**$(CH_3)_2$), 1.28 (s, 9H, $CO_2C(C\mathbf{H_3})_3$), 0.82 (d, ^{3}J = 6.9 Hz, 3H, Val-(CH_3)CHC**H**$_3$), 0.79 (d, ^{3}J = 6.9 Hz, 6H, Val-CH$(C\mathbf{H_3})_2$), 0.76 (d, ^{3}J = 7.0 Hz, 3H, Val-(CH_3)CHC**H**$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 172.1 (Val-**C**O_2CH_3, Val-**C**ONH), 155.8 (NH**C**$O_2C(CH_3)_3$), 79.2 (CO_2**C**$(CH_3)_3$), 59.7 (Val-**C**$^{\alpha}$H), 57.1 (Val-**C**$^{\alpha}$H), 51.8 (CO_2**C**H_3), 30.8 (Val-C$^{\alpha}$HCH_2C**H**$(CH_3)_2$), 30.7 (Val-C$^{\alpha}$HC**H**$(CH_3)_2$), 28.2 ($CO_2C($**C**$H_3)_3$), 19.0 (Val-(CH_3)CH**C**H_3), 18.8 (Val-(CH_3)CH**C**H_3), 18.0 (Val-(CH_3)CH**C**H_3), 17.8 (Val-(CH_3)CH**C**H_3). $C_{16}H_{30}N_2O_5$ (330.43 g mol^{-1}). MS(ESI): *m/z* = 353.2011 (calcd. 353.2047 $[M+Na]^+$). TLC: R*f* (EtOAc/PE, 1:2) = 0.55.



Methyl ((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-phenylalaninate. This dipeptide has been first characterized by Chapman *et al.*, who accessed it in a completely different way [241]. A mixture of *tert*-butoxycarbonyl L-4-methoxyphenylalanine (1.08 g, 3.66 mmol, 1.0 eq) and methyl L-phenylalaninate hydrochloride (1.09 g, 5.05 mmol, 1.4 eq), TBTU (3.53 g, 11.0 mmol, 3.0 eq) and HOBt (150 mg, 1.48 mmol, 0.3 eq) was dissolved under argon atmosphere in DMF (10 mL). DIPEA (2.6 mL, 1.94 g, 15 mmol, 3.0 eq) was added and the reaction mixture was stirred for three days at ambient temperature. The reaction mixture was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by column chromatography (PE/EtOAc, 2:1). The title compound was obtained as EtOAc adduct in form of a gel.

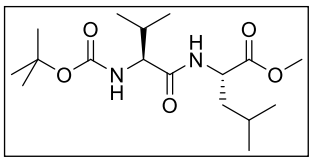


Colorless gel. Yield: 1.697 g, 3.116 mmol, 85 %, ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.13 (t, ^{3}J = 7.3 Hz, 2H, Phe-ar-3-**H**, Phe-ar-5-**H**), 7.09 (t, ^{3}J = 7.0 Hz, 1H, Phe-ar-4-**H**), 7.00 (d, ^{3}J = 8.2 Hz, 2H, Tyr-ar-3-**H**, Tyr-ar-5-**H**), 6.96 (d, ^{3}J = 7.3 Hz, 2H, Phe-ar-2-**H**, Phe-ar-6-**H**), 6.84 (d, ^{3}J = 7.7 Hz, 1H, CON**H**-Phe), 6.68 (d, ^{3}J = 8.1 Hz, 2H, Tyr-ar-2-**H**, Tyr-ar-6-**H**), 5.38 (d, ^{3}J = 8.2 Hz, 1H, Tyr-N**H**Boc), 4.71 (ddd, ^{3}J = 6.8 Hz, ^{3}J = 8.2 Hz, ^{3}J = 5.7 Hz, 1H, Phe-C$^{\alpha}$**H**), 4.33 (ddd, ^{3}J = 8.3 Hz, ^{3}J =

4.6 Hz, ^{3}J = 6.5 Hz, 1H, Tyr-C$^{\alpha}$**H**), 4.00 (q, ^{3}J = 7.1 Hz, 2H, $CH_3CO_2C\mathbf{H_2}CH_3$), 3.62 (s, 3H, Tyr-ar-OC**H₃**), 3.53 (s, 3H, Phe-$CO_2C\mathbf{H_3}$), 2.98 (dd, ^{2}J = 13.8 Hz, ^{3}J = 6.1 Hz, 1H, Phe-C$^{\alpha}$HC**H**$_2$), 2.93 (m, 1H, Tyr-C$^{\alpha}$C**H**$_2$), 2.90 (d, ^{2}J = 13.5 Hz, ^{3}J = 5.7 Hz, 1H, Phe-C$^{\alpha}$HC**H**$_2$), 2.82 (m, 1H, Tyr-C$^{\alpha}$HC**H**$_2$), 1.91 (s, 3H, $C\mathbf{H_3}CO_2CH_2CH_3$), 1.30 (s, 9H, Phe-$CO_2C(C\mathbf{H_3})_3$), 1.14 (t, ^{3}J = 7.1 Hz, 3H, $CH_3CO_2CH_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 171.3 (Tyr-**C**ONH), 171.1 (Phe-**C**O$_2$Me), 170.7 ($CH_3\mathbf{C}O_2CH_2CH_3$), 158.2 (Tyr-ar-**C**-1), 155.1 (Tyr-NH**C**O$_2$^{t}Bu), 135.7 (Phe-ar-**C**-1), 130.1 (Tyr-ar-**C**-3, Tyr-ar-**C**-5), 129.0 (Phe-ar-**C**-2, Phe-ar-**C**-6), 128.5 (Phe-ar-**C**-3, Phe-ar-**C**-5), 128.2 (Tyr-ar-**C**-4), 126.7 (Phe-ar-**C**-4), 113.6 (Tyr-ar-**C**-2, Tyr-ar-**C**-6), 79.4 (Phe-$CO_2\mathbf{C}(CH_3)_3$), 60.0 ($CH_3CO_2\mathbf{C}H_2CH_3$), 55.5 (Tyr-**C**$^{\alpha}$H), 54.8 (Tyr-ar-O**C**H$_3$), 53.2 (Phe-**C**$^{\alpha}$H), 51.8 (Phe-$CO_2\mathbf{C}H_3$), 37.7 (Tyr-C$^{\alpha}$H**C**H$_2$), 37.2 (Phe-C$^{\alpha}$H**C**H$_2$), 28.0 (Tyr-$CO_2C(\mathbf{C}H_3)_3$), 20.6 ($\mathbf{C}H_3CO_2CH_2CH_3$), 13.9 ($CH_3COOCH_2\mathbf{C}H_3$). $C_{29}H_{40}N_2O_8$ (544.65 g mol^{-1}). MS(ESI): *m/z* = 457.2235 (calcd. 457.2333 $[C_{25}H_{32}N_2O_6+H]^{+}$). TLC: R*f* (PE/EtOAc, 2:1) = 0.38.

Methyl (*tert*-Butoxycarbonyl)-L-valyl-L-leucinate. The preparation of this dipeptide was performe das described by Styers *et al.* [242]. A mixture of *tert*-butoxycarbonyl L-valine (460 mg, 2.53 mmol, 1.2 eq) and methyl L-Leucinate hydrochloride (460 mg, 2.12 mmol, 1.0 eq), TBTU (2.04 g, 6.36 mmol, 3.0 eq) and HOBt (86 mg, 0.64 mmol, 0.3 eq) was dissolved under argon atmosphere in a mixture of CH_2Cl_2/DIPEA (12.5 mL, 4:1) and the reaction mixture was stirred for three days at ambient temperature. The solution was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by column chromatography (PE/EtOAc, 2:1).

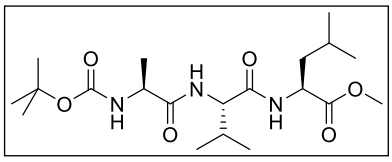
Colorless crystalline solid. Yield: 718.3 mg, 2.085 mmol, 76 % (Lit: 94 % [242]). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.14 (d br., ^{3}J = 7.6 Hz, 1H, Leu-C$^{\alpha}$HN**H**), 6.60 (d br., ^{3}J = 9.1 Hz, 1H, Val-C$^{\alpha}$HN**H**), 4.31 (ddd, ^{3}J = 10.0 Hz, ^{3}J = 7.6 Hz, ^{3}J = 4.9 Hz, 1H, Leu-C$^{\alpha}$**H**), 3.79 (dd, ^{3}J = 8.2 Hz, ^{3}J = 9.1 Hz, 1H, Val-C$^{\alpha}$**H**), 3.60 (s, 3H, Leu-$CO_2C\mathbf{H_3}$), 1.91 (dh, ^{3}J = 8.2 Hz, ^{3}J = 6.9 Hz, 1H, Val-C**H**$(CH_3)_2$), 1.66 (m, 1H, Leu-C**H**$(CH_3)_2$), 1.57 (ddd, ^{2}J = 15.0 Hz, ^{3}J = 10.3 Hz, ^{3}J = 5.0 Hz, 1H, Leu-C$^{\alpha}$H-C**H**$_2$), 1.47 (ddd, ^{2}J = 13.8 Hz, ^{3}J = 9.1 Hz, ^{3}J = 4.8 Hz, 1H, Leu-C$^{\alpha}$H-C**H**$_2$), 1.37 (s, 9H, Val-OC$(C\mathbf{H_3})_3$), 0.88 (d, ^{3}J = 6.6 Hz, 3H, Leu-C$^{\alpha}$HCH$_2$CH$(C\mathbf{H_3})_2$, 0.85 (d, ^{3}J = 6.8 Hz, 3H, Val-C$^{\alpha}$HCH$(C\mathbf{H_3})_2$, 0.82 (d, ^{3}J = 6.6 Hz, 6H,



Val-$C^{\alpha}HCH_2CH(C\mathbf{H_3})_2$, Leu-$C^{\alpha}HCH_2CH(C\mathbf{H_3})_2$. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.8 (Leu-$\mathbf{C}O_2CH_3$), 171.6 (Val-$C^{\alpha}H\mathbf{C}ONH$), 155.3 (Val-$C^{\alpha}HNH\mathbf{C}O_2C(CH_3)_3$), 77.9 (Val-$NHCO_2\mathbf{C}(CH_3)_3$), 59.5 (Val-$\mathbf{C}^{\alpha}H$), 51.7 (Leu-$CO_2\mathbf{C}H_3$), 50.0 (Leu-$\mathbf{C}^{\alpha}H$), 39.7 (Leu-$C^{\alpha}H\mathbf{C}H_2$), 30.3 (Val-$C^{\alpha}H\mathbf{C}H(CH_3)_2$), 28.1 (Val-$C^{\alpha}HNHCO_2C(\mathbf{C}H_3)_3$), 24.0 (Leu-$C^{\alpha}HCH_2\mathbf{C}H(CH_3)_2$), 22.8 (Leu-$C^{\alpha}HCH_2CH(\mathbf{C}H_3)_2$), 21.1 (Val-$C^{\alpha}HCH(\mathbf{C}H_3)_2$), 19.1 (Leu-$C^{\alpha}HCH_2CH(\mathbf{C}H_3)_2$), 18.2 (Val-$C^{\alpha}HCH_2CH(\mathbf{C}H_3)_2$). $C_{17}H_{32}N_2O_5$ (344.45 g mol^{-1}). MS(ESI): *m/z* = 367.2143 (calcd. 367.2203 $[M+Na]^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.82.

Methyl (*tert*-Butoxycarbonyl)-L-alanyl-L-valyl-L-leucinate. This tripeptide has been first described and characterized by Abiko and Sekino. Their synthesis was completely different [243]. A mixture of H_2N-Val-Leu-OMe (540 mg, 1.93 mmol, 1.0 eq) and BocH-Ala-OH x HCl (480 mg, 2.51 mmol, 1.3 eq), TBTU (1.86 g, 5.79 mmol, 3.0 eq) and HOBt (78 mg, 0.58 mmol, 0.3 eq) was dissolved under argon atmosphere in a mixture of CH_2Cl_2/DIPEA (12.5 mL, 4:1) and the reaction mixture was stirred for three days at ambient temperature. The solution was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by column chromatography (PE/EtOAc, 2:1).

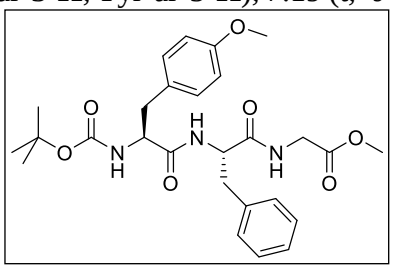
Pale yellow, highly viscous oil. Yield: 819 mg, 1.93 mmol, quantitative. ^1H NMR (500 MHz, Chloroform-*d*) δ = 7.45-6.96 (m, 2H, Val-$C^{\alpha}HN\mathbf{H}COC^{\alpha}H$-Ala, Leu-$C^{\alpha}HN\mathbf{H}COC^{\alpha}H$-Val), 5.52 (m, 1H, Ala-$C^{\alpha}HN\mathbf{H}CO_2C(CH_3)_3$), 4.48 (dd, ^3J = 8.7 Hz, ^3J = 4.7 Hz, 1H, Leu-$C^{\alpha}\mathbf{H}CH_2CH(CH_3)_2$), 4.22 (dh, ^3J = 6.5 Hz, ^3J = 7.5 Hz, 1H, Val-$C^{\alpha}\mathbf{H}CH(CH_3)_2$), 4.03 (qd, ^3J = 7.6 Hz, ^3J = 5.6 Hz, ^3J = 4.1 Hz, 1H, Ala-$C^{\alpha}\mathbf{H}CH_3$), 3.62 (s, 3H, Leu-$CO_2C\mathbf{H_3}$), 2.02 (m, 1H, Val-$C^{\alpha}HC\mathbf{H}(CH_3)_2$), 1.95 (m, 1H, Leu-$C^{\alpha}HCH_2C\mathbf{H}(CH_3)_2$), 1.59-1.45 (m, 2H, Leu-$C^{\alpha}HC\mathbf{H_2}CH(CH_3)_2$), 1.34 (s, 9H, Ala-$C^{\alpha}HNHCO_2C(C\mathbf{H_3})_3$), 1.28-1.21 (m, 3H, Ala-$C^{\alpha}HC\mathbf{H_3}$), 0.90-0.75 (m, 12H, Val-$C^{\alpha}HCH(C\mathbf{H_3})_2$, Leu-$C^{\alpha}HCH_2CH(C\mathbf{H_3})_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 175.5 (Ala-$C^{\alpha}H\mathbf{C}ONHC^{\alpha}H$-Val), 173.1 (Val-$C^{\alpha}H\mathbf{C}O_2CH_3$), 171.4 (Val-$C^{\alpha}H\mathbf{C}ONHC^{\alpha}H$-Leu), 155.5 (Ala-$C^{\alpha}HNH\mathbf{C}O_2C(CH_3)_3$), 79.7 (Ala-$C^{\alpha}HNHCO_2\mathbf{C}(CH_3)_3$), 60.3 (Ala-$\mathbf{C^{\alpha}}HCH_3$), 52.1 (Leu-$\mathbf{C^{\alpha}}HCH_2CH(CH_3)_2$), 50.8 (Leu-$C^{\alpha}HCO_2\mathbf{C}H_3$), 50.1 (Val-$\mathbf{C^{\alpha}}HCH(CH_3)_2$), 40.8 (Leu-$C^{\alpha}H\mathbf{C}H_2CH(CH_3)_2$), 31.0 (Val-$C^{\alpha}H\mathbf{C}H(CH_3)_2$), 28.3 (Ala-$C^{\alpha}HNHCO_2C(\mathbf{C}H_3)_3$),



24.7 (Leu-C$^{\alpha}$HCH$_2$CH(**C**H$_3$)$_2$), 22.7 (Leu-C$^{\alpha}$HCH$_2$CH(**C**H$_3$)$_2$), 21.7 (Val-C$^{\alpha}$HCH(**C**H$_3$)$_2$), 19.0 (Val-C$^{\alpha}$HCH(**C**H$_3$)$_2$), 14.1 (Ala-C$^{\alpha}$H**C**H$_3$). $C_{20}H_{37}N_3O_6$ (415.53 g mol^{-1}). LCMS(ESI): t*r* = 9.0 min, *m/z* = 416.2725 (calcd. 416.2755 $[M+H]^+$), 438.2550 (calcd. 438.2575 $[M+Na]^+$).

Methyl ((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-phenylalanylglycinate. A mixture of ((*S*)-2-(*tert*Butoxycarbonylamino)-3-(4-methoxyphenyl)propanoyl)-L-phenylalanine (700 mg, 1.58 mmol, 1.0 eq) and methyl L-Glycinate hydrochloride (300 mg, 2.37 mmol, 1.5 eq), TBTU (1.52 g, 4.74 mmol, 3.0 eq) and HOBt (64 mg, 0.47 mmol, 0.3 eq) was dissolved under argon atmosphere in a mixture of CH_2Cl_2/DIPEA (8 mL, 4:1) and the reaction mixture was stirred for three days at ambient temperature. The solution was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by column chromatography (PE/EtOAc, 2:1).

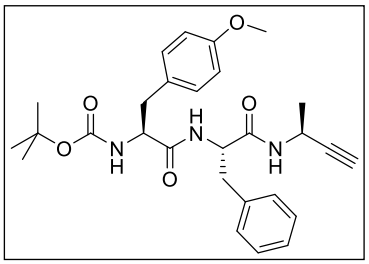
Colorless crystalline solid. Yield: 807 mg, 1.57 mmol, 99 %. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ = 8.48 (t, ^3J = 6.0 Hz, 1H, Gly-C$^{\alpha}$HN**H**), 8.01 (d, ^3J = 8.6 Hz, 1H, Phe-C$^{\alpha}$HN**H**), 7.28 (d, ^3J = 7.9 Hz, 2H, Phe-ar-2-**H**, Phe-ar-6-**H**), 7.25 (d, ^3J = 7.6 Hz, 2H, Tyr-ar-3-**H**, Tyr-ar-5-**H**), 7.19 (t, ^3J = 6.8 Hz, 2H, Phe-ar-3-**H**, Phe-ar-5-**H**), 7.09 (d, ^3J = 8.1 Hz, 2H, Phe-ar-2-**H**, Phe-ar-6-**H**), 6.82 (d, ^3J = 8.9 Hz, 1H, Tyr-C$^{\alpha}$HN**H**), 6.79 (d, ^3J = 8.3 Hz, 2H, Tyr-ar-2-**H**, Tyr-ar-6-**H**), 4.64 (ddd, ^3J = 8.7 Hz, ^3J = 4.8 Hz, ^3J = 6.5 Hz, 1H, Phe-C$^{\alpha}$**H**), 4.10 (ddd, ^3J = 9.3 Hz, ^3J = 7.2 Hz, ^3J = 4.3 Hz, 1H, Tyr-C$^{\alpha}$**H**), 3.91 (dd, ^2J = 17.8 Hz, ^3J = 5.6 Hz, 1H, Gly-C$^{\alpha}$**H**$_2$), 3.86 (dd, ^2J = 17.8 Hz, ^3J = 6.0 Hz, 1H, Gly-C$^{\alpha}$**H**$_2$), 3.69 (s, 3H, Tyr-ar-OC**H**$_3$), 3.63 (s, 3H, Gly-CO$_2$C**H**$_3$), 3.07 (dd, ^2J = 14.0 Hz, ^3J = 4.7 Hz, 1H, Phe-C$^{\alpha}$HC**H**$_2$), 2.86 (dd, ^2J = 13.9 Hz, ^3J = 9.0 Hz, 1H, Phe-C$^{\alpha}$HC**H**$_2$), 2.81 (dd, ^2J = 13.9 Hz, ^3J = 4.3 Hz, 1H, Tyr-C$^{\alpha}$HC**H**$_2$), 2.61 (dd, ^2J = 13.9 Hz, ^3J = 10.1 Hz, 1H, Tyr-C$^{\alpha}$HC**H**$_2$), 1.29 (s, 9H, Tyr-C(C**H**$_3$)$_3$). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ = 171.5 (Phe-C$^{\alpha}$H**C**ON), 171.4 (Tyr-C$^{\alpha}$H**C**ON), 170.1 (Gly-C$^{\alpha}$H**C**O$_2$), 157.8 (Tyr-ar-**C**-1), 155.1 (Tyr-NH**C**O$_2$C(CH$_3$)$_3$), 137.6 (Tyr-ar-**C**-4), 130.2 (Phe-ar-**C**-1), 129.4 (Phe-ar-**C**-3, Phe-ar-**C**-5), 128.1 (Tyr-ar-**C**-3, Tyr-ar-**C**-5), 126.3 (Phe-ar-**C**-4), 113.5 (Tyr-ar-**C**-2, Tyr-ar-**C**-6), 78.2 (Tyr-CO$_2$**C**(CH$_3$)$_3$), 56.2 (Tyr-**C**$^{\alpha}$H), 54.9 (Tyr-ar-O**C**H$_3$), 53.5 (Phe-**C**$^{\alpha}$H), 51.7 (Gly-CO$_2$**C**H$_3$), 40.6 (Gly-**C**$^{\alpha}$H$_2$),



37.9 (Phe-C$^{\alpha}$H**C**H$_2$), 36.8 (Tyr-C$^{\alpha}$H**C**H$_2$), 28.1 (Tyr-C(**C**H$_3$)$_3$). $C_{27}H_{35}N_3O_7$ (513.59 g mol^{-1}). MS(ESI): *m/z* = 514.2642 (calcd. 514.2548 [M+H]$^+$). TLC: R*f* (EtOAc/PE, 1:1) = 0.14.

***tert*-Butyl ((*S*)-1-(((*S*)-1-(((*S*)-But-3-yn-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate**. A mixture of ((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-phenylalanylglycine (200 mg, 0.46 mmol, 1 eq) and (*S*)-but-3-yne-2-amine hydrochloride (50 mg, 0.46 mmol, 1 eq), TBTU (443 mg, 1.38 mmol, 3.0 eq) and HOBt (19 mg, 0.14 mmol, 0.3 eq) was dissolved under argon atmosphere in a mixture of DMF/DIPEA (6 mL, 4:1) and the reaction mixture was stirred for three days at ambient temperature. The solution was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and purified by preparative HPLC.

Colorless amorphous solid. Yield: 8.1 mg, 16.4 μmol, 4 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.23 (d, ^3J = 7.6 Hz, 2H, Phe-Ph-2-**H**, Phe-Ph-6-**H**), 7.20 (t, ^3J = 7.0 Hz, 1H, Phe-Ph-4-**H**), 7.07 (d, ^3J = 8.2 Hz, 2H, Tyr-ar-3-**H**, Tyr-ar-5-**H**), 7.04 (t, ^3J = 5.3 Hz, 2H, Phe-Ph-3-**H**, Phe-Ph-5-**H**), 6.83 (d, ^3J = 8.2 Hz, 2H, Tyr-ar-2-**H**, Tyr-ar-6-**H**), 6.45 (s br., 2H, Phe-C$^{\alpha}$HN**H**COC$^{\alpha}$H-Tyr, C$^{\alpha}$HN**H**COC$^{\alpha}$H-Phe), 4.86 (d br., ^3J = 6.4 Hz, 1H, Tyr-C$^{\alpha}$HN**H**CO$_2$C(CH$_3$)$_3$), 4.68 (ddd, ^3J = 7.2 Hz, ^3J = 6.5 Hz, ^4J = 2.3 Hz, 1H, C$^{\alpha}$**H**CH$_3$), 4.62 (ddd, ^3J = 7.4 Hz, ^3J = 6.5 Hz, ^3J = 5.4 Hz, 1H, Phe-C$^{\alpha}$**H**CH$_2$Ph), 4.24 (ddd, ^3J = 6.4 Hz, ^3J = 7.2 Hz, ^3J = 4.7 Hz, 1H, Tyr-C$^{\alpha}$**H**CH$_2$ar), 3.77 (s, 3H, Tyr-ar-OC**H$_3$**), 3.18 (d, ^2J = 13.7 Hz, 1H, Phe-C$^{\alpha}$HC**H**$_2$Ph), 2.97 (dd, ^2J = 14.0 Hz, ^3J = 6.1 Hz, 1H, Tyr-C$^{\alpha}$HC**H**$_2$ar), 2.94-2.86 (m, 2H, Tyr-C$^{\alpha}$HC**H**$_2$ar, Phe-C$^{\alpha}$HC**H**$_2$Ph), 2.21 (d, ^4J = 2.2 Hz, 1H, C$^{\alpha}$HC≡C**H**), 1.33 (s, 9H, Tyr-C$^{\alpha}$HNHCO$_2$C(C**H$_3$**)$_3$), 1.29 (d, ^3J = 6.9 Hz, 3H, C$^{\alpha}$HC**H$_3$**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 171.1 (Tyr-C$^{\alpha}$H**C**ONH), 169.4 (Phe-C$^{\alpha}$H**C**ONH), 158.9 (Tyr-C$^{\alpha}$HNH**C**O$_2$C(CH$_3$)$_3$), 155.7 (Tyr-ar-**C**-1-OCH3), 136.2 (Phe-**C**-1), 130.4 (Tyr-**C**-3, Tyr-**C**-5), 129.5 (Phe-**C**-3, Phe-**C**-5), 128.8 (Phe-**C**-4), 128.1 (Tyr-**C**-4), 127.2 (Phe-**C**-2, Phe-**C**-6), 114.4 (Tyr-**C**-2, Tyr-**C**-6), 83.6 (Ala-C$^{\alpha}$H**C**≡CH), 80.7 (Tyr-C$^{\alpha}$HNHCO$_2$**C**(CH$_3$)$_3$), 70.6 (Ala-C$^{\alpha}$HC≡**C**H), 56.3 (Tyr-**C$^{\alpha}$**HCH$_2$ar), 55.4 (Tyr-ar-1-O**C**H$_3$), 53.8 (Phe-

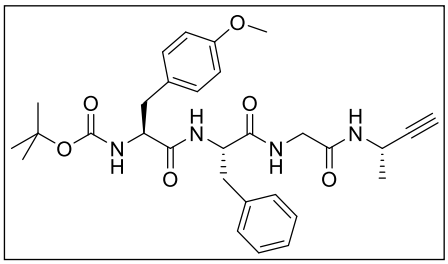


C$^{\alpha}$HCH$_2$Ph), 37.8 (Phe-C$^{\alpha}$H**C**H$_2$Ph), 37.2 (Ala-**C$^{\alpha}$**HCH$_3$), 37.0 (Tyr-C$^{\alpha}$H**C**H$_2$Ph), 28.3 (Tyr-C$^{\alpha}$HNHCO$_2$C(**C**H$_3$)$_3$), 22.0 (Ala-C$^{\alpha}$HC**H$_3$**). $C_{28}H_{35}N_3O_5$ (493.60 g mol^{-1}). MS(ESI): *m/z* = 494.2650 (calcd. 494.2649 [M+H]$^+$).

***tert*-Butyl ((*S*)-1-(((*S*)-1-((2-(((*S*)-But-3-yn-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate (95)**.

A mixture of ((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanoyl)-L-phenylalanylglycine (710 mg, 1.42 mmol, 1 eq) and (*S*)-but-3-yne-2-amine hydrochloride (180 mg, 1.70 mmol, 1.2 eq), TBTU (1.37 mg, 4.26 mmol, 3.0 eq) and HOBt (58 mg, 0.43 mmol, 0.3 eq) was dissolved under argon atmosphere in a mixture of DMF/DIPEA (6 mL, 4:1) and the reaction mixture was stirred for three days at ambient temperature. The solution was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and the crude product **95** was purified by preparative HPLC.

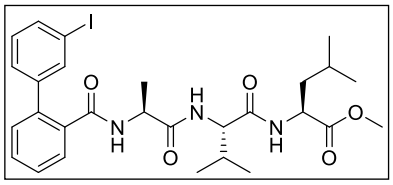
Pale yellow, crystalline solid. Yield: 454 mg, 830 µmol, 59 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.31-7.21 (m, 5H, Phe-Ph-**H**), 7.09 (d, ^3J = 8.2 Hz, 2H, Tyr-ar-3-**H**, Tyr-ar-5-**H**), 7.05 (d br., ^3J = 7.0 Hz, 1H, Tyr-C$^{\alpha}$HN**H**Boc), 6.95 (t br., ^3J = 9.5 Hz, 1H, C$^{\alpha}$HN**H**COC$^{\alpha}$H-Gly), 6.86 (d, ^3J = 8.3 Hz, 2H, Tyr-ar-2-**H**, Tyr-ar-6-**H**), 6.61 (m, 1H, Phe-C$^{\alpha}$HN**H**COC$^{\alpha}$H-Tyr), 6.37 (s br., 1H, Gly-C$^{\alpha}$HN**H**COC$^{\alpha}$H-Phe), 5.00 (ddd, ^3J = 6.2 Hz, 5.0 Hz, ^3J = 7.0 Hz, 1H, Tyr-C$^{\alpha}$**H**CH$_2$ar), 4.79 (qd, ^3J = 7.0 Hz, ^3J = 3.7 Hz, 1H, Ala-C$^{\alpha}$**H**CH$_3$), 4.56 (ddd, ^3J = 6.6 Hz, ^3J = 4.8 Hz, ^3J = 7.2 Hz, 1H, Phe-C$^{\alpha}$**H**CH$_2$Ph), 4.22 (m, 1H, Gly-C$^{\alpha}$**H**$_2$), 4.14 (m, 1H, Gly-C$^{\alpha}$**H**$_2$), 3.98-3.90 (m, 2H, Tyr-C$^{\alpha}$HC**H$_2$**ar), 3.80 (s, 3H, Tyr-ar-1-OC**H$_3$**), 3.16 (m, 2H, Phe-C$^{\alpha}$HC**H**$_2$Ph), 3.02 (m, 1H, Phe-C$^{\alpha}$HC**H**$_2$Ph), 2.27 (d, ^4J = 2.3 Hz, 1H, C$^{\alpha}$HC≡C**H**), 1.44 (d, ^3J = 7.0 Hz, 3H, C$^{\alpha}$HC**H$_3$**), 1.33 (s, 9H, Tyr-C$^{\alpha}$HNHCO$_2$C(C**H$_3$**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 172.0 (Tyr-C$^{\alpha}$H**C**ONHC$^{\alpha}$H-Phe), 171.1 (Phe-C$^{\alpha}$H**C**ONHC$^{\alpha}$H-Ala), 167.9 (Gly-C$^{\alpha}$H**C**ONHC$^{\alpha}$H-Ala), 159.0 (Tyr-ar-**C**-1-OCH$_3$), 156.2 (Tyr-C$^{\alpha}$HNH**C**O$_2$C(CH$_3$)$_3$), 136.2 (Phe-**C**-1), 130.4 (Tyr-**C**-3, Tyr-**C**-5), 130.3 (Tyr-**C**-4), 129.2 (Phe-**C**-3, Phe-**C**-5), 129.0 (Phe-**C**-2, Phe-**C**-6), 127.4 (Phe-**C**-4), 114.4 (Tyr-**C**-2, Tyr-**C**-



6), 84.2 ($C^{\alpha}H\mathbf{C}{\equiv}CH$), 81.1 (Tyr- $C^{\alpha}HNHCO_2\mathbf{C}(CH_3)_3$), 70.4 ($C^{\alpha}HC{\equiv}\mathbf{C}H$), 56.6 (Tyr-$\mathbf{C^{\alpha}}HCH_2ar$), 55.4 (Tyr-ar-1-O$\mathbf{C}H_3$), 54.7 (Phe-$\mathbf{C^{\alpha}}HCH_2Ph$), 45.5 ($\mathbf{C^{\alpha}}HCH_3$), 43.4 (Gly-$\mathbf{C^{\alpha}}H_2$), 36.9 (Tyr-$C^{\alpha}H\mathbf{C}H_2ar$), 36.5 (Phe-$C^{\alpha}H\mathbf{C}H_2Ph$), 28.3 (Tyr-$C^{\alpha}HNHCO_2C(\mathbf{C}H_3)_3$), 22.1 ($C^{\alpha}H\mathbf{C}H_3$). $C_{30}H_{38}N_4O_6$ (550.66 g mol^{-1}). MS(ESI): t*r* = 9.3 min, *m/z* = 551.290 (calcd. 551.28600 $[M+H]^+$), 573.269 (calcd. 573.26841 $[M+Na]^+$).

Methyl (2'-Iodo-[1,1'-biphenyl]-3-carbonyl)-L-alanyl-L-valyl-L-leucinate (96). A mixture of methyl L-alanyl-L-valyl-L-leucinate (0.16 mg, 0.39 mmol, 1.0 eq) and 2'-iodo-[1,1'-biphenyl]-3-carboxylate (**93c**, 0.17 g, 0.53 mmol, 1.4 eq), HATU (445 mg, 1.17 mmol, 3.0 eq) and HOAt (16 mg, 0.12 mmol, 0.3 eq) was dissolved under argon atmosphere in a mixture of CH_2Cl_2/DIPEA (18 mL, 10:1) and the reaction mixture was stirred for three days at ambient temperature. The solution was diluted with aqueous NH_4Cl (saturated, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and isolated by column chromatography (PE/EtOAc, 4:1). Afterwards, the crude product **96** was purified by preparative HPLC.

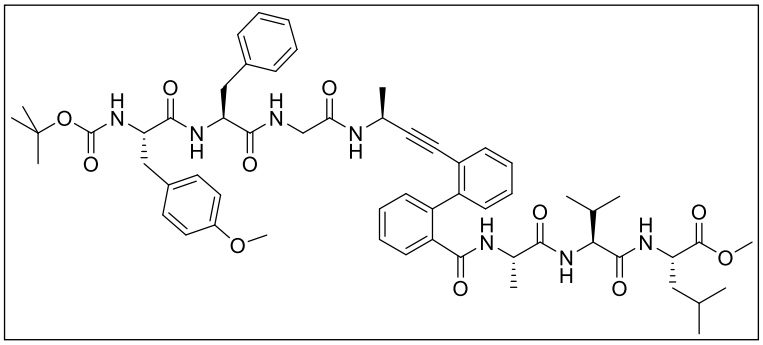
Pale yellow, highly viscous oil. Yield: 105 mg, 170 μmol, 44 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.87 (d, ^3J = 7.9 Hz, 1H, ar'-6-**H**), 7.82 (d, ^3J = 7.4 Hz, 1H, ar-6-**H**), 7.75 (s, 1H, ar-2-**H**), 7.56 (d br., ^3J = 8.7 Hz, 1H, Ala-$C^{\alpha}HN\mathbf{H}CO$), 7.45 (d br., ^3J = 9.2 Hz, 1H, Val-$C^{\alpha}HN\mathbf{H}CO$), 7.40 (t, ^3J = 6.5 Hz, 1H, ar-5-**H**), 7.37 (d, ^3J = 7.3 Hz, 1H, ar-4-**H**), 7.32 (d, ^3J = 7.3 Hz, 1H, ar'-4-**H**), 7.29 (d br., ^3J = 8.8 Hz, 1H, Leu-C^{α}-N**H**CO), 7.21 (d, ^3J = 7.4 Hz, 1H, ar'-3-**H**), 6.97 (t, ^3J = 7.5 Hz, 1H, ar'-5-**H**), 4.87 (dq, ^3J = 6.2 Hz, ^3J = 7.1 Hz, 1H, Ala-C^{α}**H**), 4.50 (m, 1H, Leu-C^{α}**H**), 4.37 (dd, ^3J = 8.0 Hz, ^3J = 7.1 Hz, 1H, Val-C^{α}**H**), 3.61 (s, 3H, Leu-$CO_2C\mathbf{H_3}$), 2.08 (dh, ^3J = 7.5 Hz, ^3J = 6.9 Hz, 1H, Val-$C^{\alpha}HC\mathbf{H}(CH_3)_2$), 1.60-1.54 (m, 2H, Leu-$C^{\alpha}HC\mathbf{H_2}CH(CH_3)_2$), 1.50 (m, 1H, Leu-$C^{\alpha}HCH_2C\mathbf{H}(CH_3)_2$), 1.41 (d, ^3J = 7.0 Hz, 3H, Ala-$C^{\alpha}HC\mathbf{H_3}$), 0.87 (d, ^3J = 7.4 Hz, 3H, Val-$C^{\beta}C\mathbf{H_3}$), 0.86 (d, ^3J = 7.5 Hz, 3H, Leu-$C^{\gamma}HC\mathbf{H_3}$), 0.81-0.74 (m, 6H, Val-$C^{\beta}C\mathbf{H_3}$, Leu-$C^{\gamma}HC\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 173.2 (Leu-$C^{\alpha}H\mathbf{C}O_2CH_3$), 172.8 (Ala-$C^{\alpha}H\mathbf{C}ONH$), 171.2 (Val-$C^{\alpha}H\mathbf{C}ONH$), 166.9 (Leu-NH**C**Oar), 145.6 (ar'-**C**-2), 144.3 (ar-**C**-3), 139.5 (ar'-**C**-6), 133.8 (ar-**C**-5), 132.6 (ar'-**C**-3), 130.1 (ar'-**C**-5), 129.1 (ar-**C**-2), 128.2 (ar'-**C**-4), 128.0 (ar-**C**-4), 126.6 (ar-**C**-6), 120.8 (ar-**C**-1), 98.3 (ar'-**C**-1), 58.6 (Val-



C$^{\alpha}$), 52.1 (Leu-CO_2**C**H_3), 50.8 (Leu-**C$^{\alpha}$**), 49.3 (Ala-**C$^{\alpha}$**), 40.9 (Leu-C$^{\alpha}$H**C$^{\beta}$**H_2), 31.0 (Val-**C$^{\beta}$**), 24.8 (Leu-**C$^{\gamma}$**), 22.8 (Val-C$^{\beta}$**C**H_3), 21.8 (Val-C$^{\beta}$**C**H_3), 19.2 (Leu-C$^{\gamma}$H**C**H_3), 18.5 (Leu-C$^{\gamma}$H**C**H_3), 18.2 (Ala-C$^{\alpha}$H**C**H_3). $C_{28}H_{36}IN_3O_5$ (621.52 g mol^{-1}). LCMS(ESI): t*r* = 10.5 min, *m/z* = 622.1773 (calcd. 622.1772 $[M+H]^+$), 644.1553 (calcd. 644.1592 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.11.

Methyl (2'-((*S*)-3-(2-((*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-methoxyphenyl)propanamido)-3-phenylpropanamido)acetamido)but-1-yn-1-yl)-[1,1'-biphenyl]-3-carbonyl)-L-alanyl-L-valyl-L-leucinate (97). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2 mg, 3 µmol, 2 mol%) and CuI (1 mg, 5 µmol, 4 mol%) were added in one portion to a thoroughly degassed solution of BocHN-4-methoxyPhe-Phe-Gly-propargylamide **95** (68.2 mg, 120 µmol, 1.0 eq) and iodo biphenyl-Ala-Val-Leu-OMe **96** (76.7 mg, 120 µmol, eq) in a mixture of 1,4-dioxane/DIPEA (3:1, 1.9 mL). The reaction mixture was stirred for 3 h at 60 °C. After complete consumption of propargylamide **6p** (checked by LCMS), the mixture was diluted with aqueous NH_4Cl (saturated, 20 mL), CH_2Cl_2 (20 mL) and aqueous $KHSO_4$ (5 %, 20 mL). The phases were separated and the aqueous layers were extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude hairpin mimetic **97** was purified by preparative HPLC.

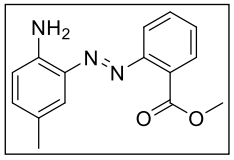
Colorless, amorphous solid. Yield: 19.8 mg, 19.0 µmol, 15 %. ^{1}H NMR (600 MHz, Methanol-d_3) δ = 8.15 (s br., 1H, Val-N**H**), 7.98 (d br., ^3J = 8.7 Hz, 1H, propargylamine-N**H**), 7.91 (d br., ^3J = 7.9 Hz, 1H, Ala-N**H**), 7.87 (d br., ^3J = 7.4 Hz, 1H, Leu-N**H**), 7.83 (d br., ^3J = 7.7 Hz, 1H, Phe-N**H**), 7.76 (d br., ^3J = 7.7 Hz, 1H, Gly-N**H**), 7.74 (d, ^3J = 7.9 Hz, 1H, ar-6-**H**), 7.64 (d, ^3J = 7.9 Hz, 1H, ar'-6-**H**), 7.48 (d, ^3J = 7.8 Hz, 1H, ar-4-**H**), 7.45 (t, ^3J = 7.7 Hz, 1H, ar-5-**H**), 7.37 (d, ^4J = 1.9 Hz, 1H, ar-2-**H**), 7.35 (td, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 1H, ar'-4-**H**), 7.26 (td, ^3J = 7.4 Hz, ^4J = 1.7 Hz, 1H, ar'-5-**H**), 7.18 (t, ^3J = 7.5 Hz, 2H, Phe-Ph-3-**H**, Phe-Ph-



5-**H**), 7.12 (t, ^{3}J = 7.4 Hz, 1H, Phe-Ph-4-**H**), 7.09 (d, ^{3}J = 7.8 Hz, 2H, Phe-Ph-2-**H**, Phe-Ph-6-**H**), 7.02 (td, ^{3}J = 7.8 Hz, ^{4}J = 1.8 Hz, 1H, ar'-3-**H**), 6.99 (d, ^{3}J = 8.1 Hz, 2H, Tyr-ar-3-**H**, Tyr-ar-5-**H**), 6.73 (d, ^{3}J = 8.6 Hz, 2H, Tyr-ar-2-**H**, Tyr-ar-6-**H**), 5.64 (d br., ^{3}J = 7.7 Hz, 1H, Tyr-N**H**Boc), 4.80-4.72 (m, 2H, Ala-C$^{\alpha}$**H**, propargylamine-C$^{\alpha}$**H**), 4.55 (dd, ^{3}J = 7.3 Hz, ^{3}J = 4.6 Hz, 1H, Val-C$^{\alpha}$**H**), 4.49 (m, 1H, Leu-C$^{\alpha}$**H**), 4.08 (m, 1H, Tyr-C$^{\alpha}$**H**), 3.87 (dd, ^{2}J = 17.0 Hz, ^{3}J = 5.7 Hz, 1H, Gly-C$^{\alpha}$**H**), 3.77 (dd, ^{2}J = 16.9 Hz, ^{3}J = 5.3 Hz, 1H, Gly-C$^{\alpha}$**H**), 3.72 (m, 1H, Phe-C$^{\alpha}$**H**), 3.70 (s, 3H, Tyr-O-C**H$_3$**), 3.66 (s, 3H, Leu-CO$_2$C**H$_3$**), 3.08 (dd, ^{2}J = 13.9 Hz, ^{3}J = 6.3 Hz, 1H, Phe-C$^{\beta}$**H$_2$**), 2.92 (dd, ^{2}J = 13.9 Hz, ^{3}J = 8.0 Hz, 1H, Phe-C$^{\beta}$**H$_2$**), 2.87 (dd, ^{2}J = 14.1 Hz, ^{3}J = 5.8 Hz, 1H, Tyr-C$^{\beta}$**H$_2$**), 2.68 (dd, ^{2}J = 14.0 Hz, ^{3}J = 8.2 Hz, 1H, Tyr-C$^{\beta}$**H$_2$**), 2.04 (m, 1H, Val-C$^{\beta}$**H**), 1.59 (dt, ^{2}J = 13.3 Hz, ^{3}J = 7.1 Hz, 2H, Leu-C$^{\alpha}$C$^{\beta}$**H$_2$**), 1.54 (m, 1H, Leu-C$^{\gamma}$**H**(CH$_3$)$_2$), 1.39 (d, ^{3}J = 7.1 Hz, 3H, Ala-C$^{\beta}$**H$_3$**), 1.29 (s, 9H, Tyr-NHCO$_2$C(C**H$_3$**)$_3$), 1.23 (d, ^{3}J = 6.8 Hz, 3H, propargylamine-C$^{\beta}$**H$_3$**), 0.92 (d, ^{3}J = 6.6 Hz, 3H, Val-C$^{\beta}$C**H$_3$**), 0.90 (d, ^{3}J = 6.8 Hz, 3H, Val-C$^{\beta}$C**H$_3$**), 0.87 (d, ^{3}J = 6.1 Hz, 3H, Leu-C$^{\gamma}$C**H$_3$**), 0.84 (d, ^{3}J = 5.9 Hz, 3H, Leu-C$^{\gamma}$C**H$_3$**). ^{13}C NMR (151 MHz, Methanol-d_3) δ = 173.7 (Phe-**C**ONH), 173.5 (Leu-**C**O$_2$CH$_3$), 172.6 (Tyr-**C**ONH), 171.9 (Ala-**C**ONH), 171.8 (Val-**C**ONH), 168.5 (Gly-**C**ONH), 168.3 (ar-**C**ONH), 158.6 (Tyr-ar-**C**-1), 156.1 (Tyr-NH**C**O$_2$^{t}Bu), 142.7 (Phe-Ph-**C**-1), 140.7 (ar-**C**-3), 136.7 (ar'-**C**-6), 133.2 (ar-**C**-4), 132.6 (ar-**C**-1), 130.4 (Tyr-ar-**C**-3, Tyr-ar-**C**-5), 130.3 (Tyr-ar-**C**-4), 129.3 (Phe-Ph-**C**-3, Phe-Ph-**C**-5), 129.3 (ar'-**C**-3), 129.2 (ar-**C**-2), 128.9 (ar'-**C**-4), 128.7 (Phe-Ph-**C**-2, Phe-Ph-**C**-6), 128.6 (ar-**C**-5), 128.5 (Phe-Ph-**C**-4), 127.6 (ar'-**C**-5), 127.0 (ar'-**C**-1), 125.9 (ar-**C**-6), 121.0 (ar'-**C**-2), 114.0 (Tyr-ar-**C**-2, Tyr-ar-**C**-6), 92.6 (C$^{\alpha}$H**C**≡C-ar), 81.9 (C$^{\alpha}$HC≡**C**-ar), 80.2 (Tyr-NHCO$_2$**C**(CH$_3$)$_3$), 59.0 (Val-**C$^{\alpha}$**H), 56.1 (Tyr-**C$^{\alpha}$**H), 55.2 (Tyr-O-**C**H$_3$), 54.9 (Phe-**C$^{\alpha}$**H), 52.2 (Leu-CO$_2$**C**H$_3$), 51.1 (Leu-**C$^{\alpha}$**), 49.8 (Ala-**C$^{\alpha}$**H), 42.7 (Gly-**C$^{\alpha}$**H$_2$), 42.1 (Val-**C$^{\alpha}$**), 40.7 (Leu-**C$^{\beta}$**H$_2$), 37.8 (**C$^{\alpha}$**HC≡C-ar), 37.6 (Phe-**C$^{\beta}$**), 37.5 (Tyr-**C$^{\beta}$**), 31.1 (Val-**C$^{\beta}$**), 28.2 (Tyr-NHCO$_2$C(**C**H$_3$)$_3$), 24.9 (Leu-**C$^{\gamma}$**(CH$_3$)$_2$), 22.7 (Val-C$^{\beta}$**C**H$_3$), 21.9 (Leu-C$^{\gamma}$**C**H$_3$), 21.6 (C$^{\alpha}$(-**C$^{\beta}$**H$_3$)HC≡C-ar), 19.1 (Leu-C$^{\gamma}$**C**H$_3$), 18.2 (Val-C$^{\beta}$**C**H$_3$), 18.2 (Ala-**C$^{\beta}$**H$_3$). $C_{58}H_{73}N_7O_{11}$ (1044.26 g mol^{-1}). MS(ESI): *m/z* = 1044.5356 (calcd. 1044.5441 $[M+H]^+$).

IIX-4. d) Smart Azobenzene-Based Turn Mimetics (98-101)

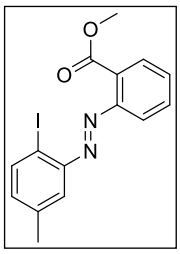
Methyl (*E*)-2-((2-Amino-5-methylphenyl)diazenyl)benzoate. An aqueous solution of $NaNO_2$ (489 mg, 7.08 mmol, 1.1 eq in 9 mL HCl, 4 M) was carefully dropped into a vigorously stirred colorless suspension of methyl anthranilate (1.00 g, 6.62 mmol, 1.0 eq) in aqueous hydrochloric acid (6 M, 4.5 mL) at 0 °C. The suspension was stirred at 0 °C, until it became a clear solution (5 min). After 5 min, the reaction mixture was poured in a solution of *para*-toluidine (722 mg, 6.74 mmol, 1.0 eq) in aqueous hydrochloric acid (6 M, 7 mL) at 0 °C. This reaction mixture was allowed to warm up to rt and stirred for 6 h at ambient temperature. After 6 h, the mixture was neutralized with an aqueous solution of NaOH. When the pH was in the range of 7, the aqueous solution turned a deep purple color and was extracted with CH_2Cl_2 until it had completely lost its color (6 x 60 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc, 10:1).



Deeply purple liquid. Yield: 1.675 g, 6.22 mmol, 94 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 12.33 (s, 2H, benzoate-CO-**H**-N_2), 8.01 (d, ^3J = 8.2 Hz, 1H, benzoate-6-**H**), 7.93 (d, ^3J = 8.4 Hz, 1H, benzoate-3-**H**), 7.63-7.43 (m, 3H, benzoate-5-**H**, N_2Ph-4-**H**, N_2Ph-6-**H**), 7.23 (d, ^3J = 8.0 Hz, 1H, N_2Ph-3-**H**), 7.00 (t, ^3J = 7.7 Hz, 1H, benzoate-4-**H**), 3.94 (s, 3H, benzoate-1-CO_2C**H**$_3$), 3.55 (s, 2H, N_2Ph-2-N**H**$_2$), 2.40 (s, 3H, N_2Ph-5-C**H**$_3$). $C_{15}H_{15}N_3O_2$ (269.30 g mol^{-1}). LCMS(ESI): *m/z* = 270.1315 (calcd. 270.1237 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.66, R*f* (PE/EtOAc, 10:1) = 0.36.

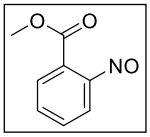
Methyl (*E*)-2-((2-Iodo-5-methylphenyl)diazenyl)benzoate. An aqueous hydroiodine solution (50 %, 1.7 mL) was slowly added to a solution of Methyl (*E*)-2-((2-Amino-5-methylphenyl)diazenyl)benzoate (795 mg, 2.95 mmol, 1.0 eq) and KI (975 mg, 5.87 mmol, 2 eq) in H_2O (20 mL). At 0 °C, an aqueous solution of $NaNO_2$ (243 mg, 3.52 mmol, 1.2 eq in 1.6 mL) was added dropwise. The reaction mixture was stirred at 80 °C for 2 h. Then, another portion of $NaNO_2$ (451 mg, 6. 54 mmol, 2.2 eq) was added and the solution was heated once more to 80 °C for 1 h. The red mixture was cooled to rt, extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with an aqueous Na_2SO_3 solution (2 x 15 mL), brine (1 x 10 mL) and dried over Na_2SO_4. After evaporation of the

solvent, the brown crude product was purified by column chromatography (PE/EtOAc, 10:1).



Deep purple, amorphous solid. Yield: 193 mg, 510 µmol, 17 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.10 (d, ^{4}J = 1.7 Hz, 1H, N_2Ph-6-**H**), 7.99 (d, ^{3}J = 8.1 Hz, 1H, benzoate-6-**H**), 7.80 (d, ^{3}J = 7.8 Hz, 1H, benzoate-3-**H**), 7.67 (d, ^{3}J = 8.2 Hz, 1H, N_2Ph-3-**H**), 7.42 (dd, ^{3}J = 8.3 Hz, ^{4}J = 1.7 Hz, 1H, N_2Ph-4-**H**), 7.39 (t, ^{3}J = 7.6 Hz, 1H, benzoat-4-**H**), 7.14 (t, ^{3}J = 7.7 Hz, 1H, benzoat-5-**H**), 3.93 (s, 3H, benzoat-1-$CO_2C\mathbf{H_3}$), 2.28 (s, 3H, N_2Ph-5-$C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.0 (benzoat-1-$\mathbf{C}O_2CH_3$), 142.8 (N_2Ph-**C**-1), 141.6 (benzoat-**C**-2), 141.4 (benzoat-**C**-6), 139.7 (N_2Ph-**C**-6), 137.5 (N_2Ph-**C**-4), 136.7 (N_2Ph-**C**-5), 135.1 (N_2Ph-**C**-3), 132.7 (benzoat-**C**-5), 131.0 (benzoat-**C**-3), 127.9 (benzoat-**C**-4), 122.8 (benzoat-**C**-1-CO_2CH_3), 90.3 (N_2Ph-**C**-2-I), 52.6 (benzoat-1-$CO_2\mathbf{C}H_3$), 21.1 (N_2Ph-5-$\mathbf{C}H_3$). $C_{15}H_{13}IN_2O_2$ (380.19 g mol^{-1}). LCMS(ESI): t*r* = 10.8, *m/z* = 381.0027 (calcd. 381.0094 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.76.

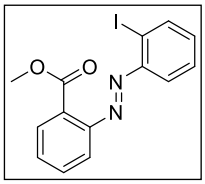
Methyl (*E*)-2-((2-Iodophenyl)diazenyl)benzoate (98a).



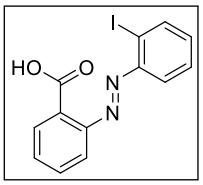
Methyl 2-Nitrosobenzoate. The synthesis of the azobenzene derivatives was performed following the detailed descriptions of Osorio-Planes, Rodríguez-Escrich and Pericàs [161]. An aqueous solution of oxone (7.36 g, 12.0 mmol, 3.6 eq in 72 mL, 0.17 M) was slowly added to a solution of methyl 2-amino benzoate (1.00 g, 6.62 mmol, 2.0 eq) in CH_2Cl_2 (18 mL, 0.5 M). The resulting two-phase system was vigorously stirred for 20 h, turning brightly green. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with aqueous HCl (1 M, 20 mL), aqueous $NaHCO_3$ (saturated, 20 mL), water (15 mL) and brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product has been described to be a mixture of nitrosyl- and nitro benzoate (1:1) by the group of Pericàs. Furthermore, they reported the aromatic nitrosyl derivatives to be prone to disproportionation [161]. Thus, further purifications of the nitrosyl compound were not attempted. The crude product was directly applied for the subsequent reaction, as proposed by Osorio-Planes et al. $C_8H_7NO_3$ (165.15 g mol^{-1}).

Methyl (*E*)-2-((2-Iodophenyl)diazenyl)benzoate (98a). A solution of the complete crude methyl 3-nitrosobenzoate in AcOH (7.5 mL, 0.5 M) was added dropwise in two portions over a period of 1 h to a stirred solution of 2-iodoanilin (510 mg, 2.44 mmol, 1.0 eq) in AcOH (5 mL, 0.6 M) at 0 °C. The reaction mixture was allowed to warm up to room temperature overnight. After 14 h, the green color of the solution had vanished and a deeply purple solution had developed. An aqueous solution of $NaHCO_3$ (saturated, ca. 50 mL) was added dropwise, until no more gas developed. Then, the aqueous phase was carefully extracted with EtOAc (3 x 50 mL). After the combined organic layers had been washed with aqueous $NaHCO_3$ (saturated, 30 mL), water (40 mL) and brine (20 mL), they were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. A deeply purple oil remained as crude product of **98a**, which was purified by a short column chromatography (PE, the first fraction to elute is the title compound).

Deeply purple oil. Yield: 227 mg, 620 μmol, 25 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.99 (d, ^3J = 7.9 Hz, 1H, N_2Ph-6-**H**), 7.85 (d, ^3J = 7.7 Hz, 1H, benzoate-6-**H**), 7.72 (d, ^3J = 8.0 Hz, 1H, benzoate-3-**H**), 7.65 (d, ^3J = 8.0 Hz, 1H, N_2Ph-3-**H**), 7.58 (d, ^3J = 7.9 Hz, 1H, N_2Ph-5-**H**), 7.47 (t, ^3J = 7.5 Hz, 1H, benzoate-5-**H**), 7.39 (t, ^3J = 7.6 Hz, 1H, benzoate-4-**H**), 7.12 (t, ^3J = 7.5 Hz, 1H, N_2Ph-4-**H**), 4.11 (br. s, 1H, benzoate-CO-**H**-N_2), 3.93 (s, 3H, benzoate-1-$CO_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.2 (benzoate-1-**C**O_2CH_3), 151.3 (N_2Ph-**C**-1), 151.1 (benzoate-**C**-2), 139.6 (N_2Ph-**C**-6), 132.5 (N_2Ph-**C**-4), 132.0 (N_2Ph-**C**-5), 130.3 (benzoate-**C**-5), 129.7 (benzoate-**C**-6), 128.9 (benzoate-**C**-4), 119.6 (benzoate-**C**-1), 118.5 (benzoate-**C**-3), 117.9 (N_2Ph-**C**-3), 102.4 (N_2Ph-**C**-2), 52.4 (benzoate-1-$CO_2\mathbf{C}H_3$). $C_{14}H_{11}IN_2O_2$ (366.16 g mol^{-1}). MS(ESI): *m/z* = 366.9941 (calcd. 366.9938 $[M+H]^+$), 388.9735 (calcd. 388.9757 $[M+Na]^+$).



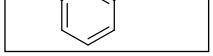
(*E*)-2-((2-Iodophenyl)diazenyl)benzoic Acid (98c). An aqueous LiOH solution (1 M, 2.5 mL) was added dropwise to a solution of benzoate **98a** (432 mg, 1.18 mmol) in MeOH (5.0 mL) at 0 °C. The reaction mixture was allowed to warm up to rt overnight. After complete consumption of ester **98a**, the solution was diluted with aqueous $KHSO_4$ (5 %, 20 mL). After extraction of the aqueous phase with CH_2Cl_2 (3 x 30 mL) the organic layers were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc, 1:1). A photoisomerization of 19 % was observed by ^{1}H NMR spectroscopy.



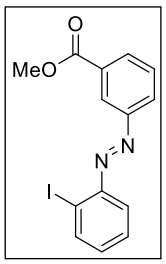
Deeply purple amorphous solid. Yield: 148 mg, 420 µmol, 36 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.48 (d, ^{3}J = 7.4 Hz, 1H, benzoate-3-**H**), 8.13 (d, ^{3}J = 7.8 Hz, 2H, N_2Ph-6-**H**, benzoate-6-**H**), 7.78-7.72 (m, 2H, benzoate-5-**H**, benzoate-4-**H**), 7.52 (t, ^{3}J = 7.6 Hz, 1H, N_2Ph-4-**H**), 7.47 (d, ^{3}J = 7.9 Hz, 1H, N_2Ph-3-**H**), 7.30 (t, ^{3}J = 7.5 Hz, 1H, N_2Ph-5-**H**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 159.4 (benzoate-C-1-**C**O_2H), 150.9 (N_2Ph-**C**-1), 149.4 (benzoate-**C**-2-N_2), 146.9 (N_2Ph-**C**-3), 140.9 (benzoate-**C**-4), 139.1 (N_2Ph-**C**-4), 133.4 (benzoate-**C**-5), 129.7 (N_2Ph-**C**-5), 129.5 (benzoate-**C**-6), 120.1 (N_2Ph-**C**-6), 117.3 (benzoate-**C**-3), 116.8 (benzoate-**C**-1), 114.9 (N_2Ph-**C**-2). $C_{13}H_9IN_2O_2$ (352.13 g mol^{-1}).

Methyl (*E*)-3-((3- and 2-Iodophenyl)diazenyl)benzoate (98b, 99).

Methyl 3-Nitrosobenzoate. The synthesis of the azobenzene derivatives was performed following the detailed descriptions of Osorio-Planes, Rodríguez-Escrich and Pericàs [161]. An aqueous solution of oxone (4.25 g, 13.8 mmol, 4.0 eq in 72 mL, 0.2 M) was slowly added to a solution of methyl 3-amino benzoate (1.00 g, 6.62 mmol, 2.0 eq) in CH_2Cl_2 (18 mL, 0.5 M). The resulting two-phase system was vigorously stirred for 20 h, turning brightly green. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with aqueous HCl (1 M, 20 mL), aqueous $NaHCO_3$ (saturated, 20 mL), water (15 mL) and brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product has been described to be a mixture of nitrosyl- and nitro benzoate (1:1) by the group of Pericàs. Furthermore, they reported the aromatic nitrosyl derivatives to be prone to disproportionation [161]. Thus, further purifications of the nitrosyl compound were not attempted. The crude product was directly applied for the subsequent reaction, as proposed by Osorio-Planes et al. [161].



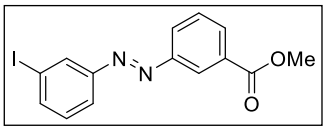
Methyl (*E*)-3-((2-Iodophenyl)diazenyl)benzoate (98b). A solution of the complete crude methyl 3-nitrosobenzoate in AcOH (7.5 mL, 0.5 M) was added dropwise in two portions over a period of 1 h to a stirred solution of 2-iodoanilin (722.8 mg, 3.30 mmol, 1.0 eq) in AcOH (5 mL, 0.7 M) at 0 °C. The reaction mixture was allowed to warm up to room temperature overnight. After 14 h, the green color of the solution had vanished and a deeply purple solution had developed. An aqueous solution of $NaHCO_3$ (saturated, ca. 50 mL) was



added dropwise, until no more gas developed. Then, the aqueous phase was carefully extracted with EtOAc (3 x 50 mL). After the combined organic layers had been washed with aqueous $NaHCO_3$ (saturated, 30 mL), water (40 mL) and brine (20 mL), they were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. A deeply purple oil remained as crude product, which was purified by a short column chromatography (PE, the first fraction to elute is the title compound).

Deeply purple, crystalline needles. Yield: 457.6 mg, 1.250 mmol, 38 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.65 (s, 1H, benzoate-2-**H**), 8.18 (d, ^3J = 7.2 Hz, 1H, benzoate-6-**H**), 8.16 (d, ^3J = 7.2 Hz, 1H, benzoate-4-**H**), 8.05 (d, ^3J = 7.9 Hz, 1H, N_2Ph-6-**H**), 7.66 (d, ^3J = 8.2 Hz, 1H, N_2Ph-3-**H**), 7.61 (d, ^3J = 7.9 Hz, 1H, benzoate-5-**H**), 7.44 (t, ^3J = 7.7 Hz, 1H, N_2Ph-4-**H**), 7.20 (t, ^3J = 7.7 Hz, 1H, N_2Ph-5-**H**), 3.98 (s, 3H, benzoate-1-CO_2C**H**$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (benzoate-1-**C**O_2CH_3), 152.4 (N_2Ph-**C**-1), 151.3 (benzoate-**C**-3), 140.1 (N_2Ph-**C**-3), 132.8 (N_2Ph-**C**-4), 132.4 (benzoate-**C**-6), 129.5 (N_2Ph-**C**-5), 129.1 (benzoate-**C**-5), 126.4 (benzoate-**C**-4), 126.1 (N_2Ph-**C**-6), 120.1 (benzoate-**C**-1), 117.5 (benzoate-**C**-2), 103.0 (N_2Ph-**C**-2), 52.6 (benzoate-1-CO_2**C**H_3). $C_{14}H_{11}IN_2O_2$ (366.16 g mol^{-1}). TLC: R*f* (PE) = 0.50.

Methyl (*E*)-3-((3-Iodophenyl)diazenyl)benzoate (99). A solution of the complete crude methyl 3-nitrosobenzoate in AcOH (7.5 mL, 0.5 M) was added dropwise in two portions



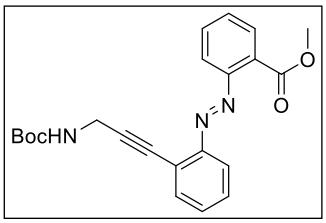
over a period of 1 h to a stirred solution of 3-iodoanilin (0.40 mL, 728 mg, 3.33 mmol, 1.0 eq) in AcOH (5 mL, 0.7 M) at 0 °C. The reaction mixture was allowed to warm up to room temperature overnight. After 14 h, the green color of the solution had vanished and a deeply purple solution had developed. An aqueous solution of $NaHCO_3$ (saturated, ca. 50 mL) was added dropwise, until no more gas developed. Then, the aqueous phase was carefully extracted with EtOAc (3 x 50 mL). After the combined organic layers had been washed with aqueous $NaHCO_3$ (saturated, 30 mL), water (40 mL) and brine (20 mL), they were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. A deeply purple oil remained as crude product, which was purified by a short column chromatography (PE, the first fraction to elute is the title compound).

Deeply purple, crystalline needles. Yield: 921.1 mg, 2.516 mmol, 76 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.57 (s, 1H, benzoate-2-**H**), 8.28 (s, 1H, N_2Ph-2-**H**), 8.18 (d,

^{3}J = 7.8 Hz, 1H, benzoate-6-**H**), 8.11 (d, ^{3}J = 8.0 Hz, 1H, benzoate-4-**H**), 7.95 (d, ^{3}J = 8.0 Hz, 1H, N_2Ph-6-**H**), 7.83 (d, ^{3}J = 7.9 Hz, 1H, N_2Ph-4-**H**), 7.61 (t, ^{3}J = 8.4 Hz, 1H, benzoate-5-**H**), 7.29 (t, ^{3}J = 8.1 Hz, 1H, N_2Ph-5-**H**), 3.98 (s, 3H, benzoate-1-$CO_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (benzoate-1-$\mathbf{C}O_2CH_3$), 152.4 (N_2Ph-**C**-1), 140.1 (benzoate-**C**-3), 132.3 (N_2Ph-**C**-4), 131.6 (N_2Ph-**C**-2), 130.9 (benzoate-**C**-6), 130.9 (N_2Ph-**C**-5), 129.4 (benzoate-**C**-5), 127.3 (benzoate-**C**-2), 124.3 (benzoate-**C**-4), 123.9 (N_2Ph-**C**-6), 111.0 (benzoate-**C**-1), 94.7 (N_2Ph-**C**-3), 52.6 (benzoate-1-$CO_2\mathbf{C}H_3$). $C_{14}H_{11}IN_2O_2$ (366.16 g mol^{-1}). TLC: R*f* (PE) = 0.52, R*f* (PE/EtOAc, 2:1) = 0.74.

Methyl (*E*)-2-((2-(3-((*tert*-Butoxycarbonyl)amino)prop-1-yn-1-yl)phenyl)diazenyl)benzoate (100a). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2 mg, 3 μmol, 2 mol%) and CuI (1 mg, 5 μmol, 3 mol%) were added in one portion to a thoroughly degassed solution of glycine analogous propargylamide **1** (51 mg, 329 μmol, 1.8 eq) and iodo azobenzene **98a** (65.4 mg, 179 μmol, 1.0 eq) in a mixture of THF/piperidine (5:2, 0.7 mL). The reaction mixture was stirred overnight at ambient temperature. After complete consumption of propargylamide **1** (checked by TLC), the mixture was diluted with aqueous NH_4Cl (saturated, 10 mL), Et_2O (20 mL) and aqueous $KHSO_4$ (5 %, 10 mL). The phases were separated and the aqueous layers were extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude peptidomimetic **100a** was purified by column chromatography (PE/EtOAc, 2:1).

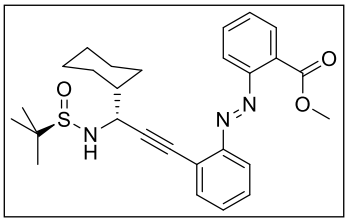
Purple oil. Yield: 30.0 mg, 73 μmol, 41 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.03 (d, ^{3}J = 7.9 Hz, 1H, benzoate-6-**H**), 7.86 (d, ^{3}J = 7.4 Hz, 1H, benzoate-3-**H**), 7.72 (d, ^{3}J = 8.0 Hz, 1H, N_2Ph-6-**H**), 7.64 (d, ^{3}J = 7.8 Hz, 1H, N_2Ph-3-**H**), 7.62 (t, ^{3}J = 7.5 Hz, 1H, N_2Ph-4-**H**), 7.52 (t, ^{3}J = 7.5 Hz, 1H, benzoate-4-**H**), 7.44 (t, ^{3}J = 7.6 Hz, 1H, N_2Ph-5-**H**), 7.19 (t, ^{3}J = 7.4 Hz, 1H, benzoate-5-**H**), 5.71 (s br., 1H, $C^{\alpha}H_2N\mathbf{H}$Boc), 3.95 (s, 3H, benzoate-1-$CO_2C\mathbf{H_3}$), 3.87 (s br., 2H, $C^{\alpha}\mathbf{H_2}$NHBoc), 1.26 (s, 9H, $C^{\alpha}H_2NCO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 167.7 (benzoate-1-$\mathbf{C}O_2CH_3$), 155.1 ($C^{\alpha}H_2NH\mathbf{C}O_2C(CH_3)_3$), 151.7 (benzoate-**C**-2), 151.5 (N_2Ph-**C**-1), 140.0 (benzoate-**C**-6), 132.7 (benzoate-**C**-5), 132.3 (N_2Ph-**C**-3), 130.5 (benzoate-**C**-4), 130.0 (benzoate-**C**-3), 129.2 (N_2Ph-**C**-5), 120.1 (benzoate-**C**-1), 118.9



(N_2Ph-**C**-6), 118.2 (N_2Ph-**C**-4), 114.8 (N_2Ph-**C**-2), 102.4 ($C^{\alpha}H_2$**C**≡Car), 92.2 ($C^{\alpha}H_2NHCO_2$**C**$(CH_3)_3$), 84.3 ($C^{\alpha}H_2C$≡**C**ar), 52.7 (benzoate-1-CO_2**C**H_3), 32.1 (**C**$^{\alpha}H_2C$≡Car), 29.9 ($C^{\alpha}H_2NHCO_2C$(**C**$H_3)_3$). $C_{22}H_{23}N_3O_4$ (393.44 g mol^{-1}). LCMS(ESI): t*r* = 9.9 min, *m/z* = 394.1757 (calcd. 394.17613 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.22.

Methyl 2-((*E*)-(2-((*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-cyclohexylprop-1-yne-1-yl)phenyl)diazenyl)benzoate (100b). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2 mg) and CuI (1 mg) were added in one portion to a thoroughly degassed solution of D-cyclohexylglycine analogous propargylamide **6e** (36.0 mg, 149 μmol, 1.0 eq) and iodo azobenzene **98a** (65.7 mg, 179 μmol, 1.2 eq) in a mixture of THF/DIPAH (3:1, 1.0 mL). The reaction mixture was stirred overnight at ambient temperature. After complete consumption of propargylamide **6e** (checked by TLC), the mixture was diluted with aqueous NH_4Cl (saturated, 10 mL), Et_2O (20 mL) and sulfuric acid (0.5 M, ca. 10 mL until pH 2). The phases were separated and the aqueous layers were extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL) dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude peptidomimetic **100b** was purified by column chromatography (PE/EtOAc, 2:1).

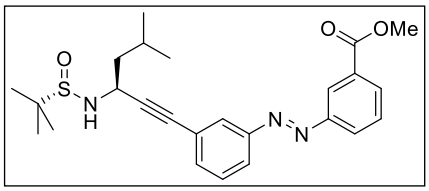
Deeply purple oil. Yield: 5.46 mg, 11.3 μmol, 8 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ



= 7.80 (d, ^3J = 7.5 Hz, 1H, benzoate-6-**H**), 7.73 (d, ^3J = 8.0 Hz, 1H, benzoate-3-**H**), 7.69 (d, ^3J = 8.0 Hz, 1H, N_2Ph-6-**H**), 7.64 (d, ^3J = 7.4 Hz, 1H, N_2Ph-3-**H**), 7.58 (t, ^3J = 7.6 Hz, 1H, benzoate-5-**H**), 7.49 (t, ^3J = 7.6 Hz, 1H, benzoate-4-**H**), 7.430-7.35 (m, 2H, N_2Ph-4-**H**, N_2Ph-5-**H**), 4.17 (dd br., ^3J = 6.2 Hz, ^3J = 5.4 Hz, 1H, C^{α}**H**), 3.89 (s, 3H, CO_2C**H**$_3$), 3.80 (d br., ^3J = 6.6 Hz, 1H, $C^{\alpha}N$**H**), 1.92 (d br., ^3J = 10.5 Hz, 1H, cy-1-**H**), 1.87 (d br., ^3J = 10.9 Hz, 1H, cy-2-**H**), 1.75-1.66 (m, 4H, cy-6-**H**$_2$, cy-2-**H**), 1.63 (d br., ^2J = 13.5 Hz, 1H, cy-4-**H**), 1.25 (s, 9H, SC(C**H**$_3)_3$), 1.23-1.19 (m, 3H, cy-5-**H**$_2$, cy-4-**H**), 1.19-1.14 (m, 3H, cy-3-**H**$_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 168.2 (**C**O_2CH_3), 153.2 (N_2Ph-**C**-1), 152.1 (benzoate-**C**-2), 133.9 (N_2Ph-**C**-3), 131.9 (benzoate-**C**-5), 131.2 (N_2Ph-**C**-5), 130.1 (benzoate-**C**-4), 129.8 (benzoate-**C**-6), 129.0 (N_2Ph-**C**-4), 128.9 (benzoate-**C**-1), 124.2 (N_2Ph-**C**-2), 119.9 (benzoate-**C**-3), 116.2 (N_2Ph-**C**-6), 94.9 (C^{α}H**C**≡C-ar), 82.7 (C^{α}HC≡**C**-ar), 56.5 (S**C**$(CH_3)_3$), 54.1 (**C**$^{\alpha}$H), 52.7 (benzoate-1-CO_2**C**H_3), 43.7 (cy-**C**-1), 29.8 (cy-**C**-6), 28.4 (cy-**C**-2), 26.4 (cy-**C**-4), 26.1 (cy-**C**-5), 26.0

(cy-**C**-3), 22.9 (SOC(**C**H_3)$_3$). $C_{27}H_{33}N_3O_3S$ (479.64 g mol^{-1}). MS(ESI): *m/z* = 480.2319 (calcd. 480.2315 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.21.

Methyl 3-((*E*)-(3-((*S*)-3-(((*S*)-*tert*-Butylsulfinyl)amino)-5-methylhex-1-yn-1-yl)phenyl)diazenyl)benzoate (101). Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2 mg, 3 µmol, 2 mol%) and CuI (1 mg, 5 µmol, 3 mol%) were added in one portion to a thoroughly degassed solution of L-leucin analogous propargylamide **6c** (40 mg, 186 µmol, 1.0 eq) and iodo azobenzene **99** (101 mg, 276 µmol, 1.5 eq) in a mixture of



THF/piperidine (3:1, 4.0 mL). The reaction mixture was stirred for 20 h at ambient temperature. After complete consumption of propargylamide **6c** (checked by TLC), the mixture was diluted with aqueous NH_4Cl (saturated, 20 mL), Et_2O (20 mL) and aqueous $KHSO_4$ (0.5 M, ca. 20 mL until pH 7). The phases were separated and the aqueous layers were extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with water (30 mL) and brine (10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude peptidomimetic **101** was purified by column chromatography (PE/EtOAc, 2:1).

Deeply purple oil. Yield: 60.1 mg, 132 µmol, 48 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.54 (s, 1H, benzoate-2-**H**), 8.14 (d, ^3J = 7.7 Hz, 1H, benzoate-6-**H**), 8.08 (d, ^3J = 8.0 Hz, 1H, benzoate-4-**H**), 7.99 (s, 1H, N_2Ph-2-**H**), 7.87 (d, ^3J = 8.0 Hz, 1H, N_2Ph-6-**H**), 7.59 (d, ^3J = 8.0 Hz, 1H, benzoate-5-**H**), 7.55 (d, ^3J = 8.7 Hz, 1H, N_2Ph-4-**H**), 7.44 (t, ^3J = 8.0 Hz, 1H, N_2Ph-5-**H**), 4.29 (ddd, ^3J = 7.5 Hz, ^3J = 6.6 Hz, ^3J = 5.4 Hz, 1H, C$^\alpha$**H**C$^\beta$H$_2$C$^\gamma$H(CH$_3$)$_2$), 3.95 (s, 3H, benzoate-1-CO$_2$C**H$_3$**), 3.44 (d br., ^3J = 6.6 Hz, 1H, N**H**C$^\alpha$H), 1.94 (ddh, ^3J = 7.1 Hz, ^3J = 7.5 Hz, ^3J = 6.8 Hz, 1H, C$^\alpha$HC$^\beta$H$_2$C$^\gamma$**H**(CH$_3$)$_2$), 1.70 (t, ^3J = 7.5 Hz, 1H, C$^\alpha$HC$^\beta$**H$_2$**C$^\gamma$H(CH$_3$)$_2$), 1.27-1.19 (m, 9H, SC(C**H$_3$**)$_3$), 1.08 (d, ^3J = 6.7 Hz, 3H, C$^\alpha$HC$^\beta$H$_2$C$^\gamma$H(C**H$_3$**)$_2$), 0.97 (d, ^3J = 6.6 Hz, 3H, C$^\alpha$HC$^\beta$H$_2$C$^\gamma$H(C**H$_3$**)$_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (benzoate-1-**C**O$_2$CH$_3$), 152.5 (N_2Ph-**C**-1), 152.2 (benzoate-**C**-3), 134.5 (N_2Ph-**C**-4), 132.0 (benzoate-**C**-1), 131.4 (benzoate-**C**-6), 129.3 (benzoate-**C**-5), 129.2 (N_2Ph-**C**-5), 127.1 (benzoate-**C**-4), 126.1 (N_2Ph-**C**-2), 124.2 (benzoate-**C**-2), 123.9 (N_2Ph-**C**-3), 123.2 (N_2Ph-**C**-4), 90.3 (C$^\alpha$H**C**≡Car), 84.0 (C$^\alpha$HC≡**C**ar), 56.3 (S**C**(CH$_3$)$_3$), 52.4 (benzoate-3-CO$_2$**C**H$_3$), 47.0 (**C$^\alpha$**HC$^\beta$H$_2$C$^\gamma$H(CH$_3$)$_2$), 46.3 (C$^\alpha$H**C$^\beta$**H$_2$C$^\gamma$H(CH$_3$)$_2$), 25.1 (C$^\alpha$HC$^\beta$H$_2$**C$^\gamma$**H(CH$_3$)$_2$), 22.7 (SC(**C**H$_3$)$_3$), 19.2

($C^{\alpha}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$), 17.7 ($C^{\alpha}HC^{\beta}H_2C^{\gamma}H(\mathbf{C}H_3)_2$). $C_{25}H_{31}N_3O_3S$ (453.60 g mol^{-1}). LCMS(ESI): t*r* = 11.0 min, *m/z* = 454.2088 (calcd. 454.2159 $[M+H]^+$), TLC: R*f* (PE/EtOAc, 1:1) = 0.24, R*f* (PE/EtOAc, 2:1) = 0.15. $[\alpha]_{589}^{20}$ = +9.73 (*c* 3.86, $CHCl_3$).

IIX-4. e) Propargyl Hydrazides (102-106)

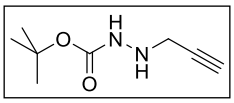
Prop-2-yn-1-amine (102a) was purchased commercially from Fisher Scientific.

(*S*)-But-3-yn-2-amine Hydrochloride (102b). Compound **102b** has been synthesized following the instructions of Beierle *et al.*, who also published a full characterization [244]. Hydrochloric acid (4 M, 1.2 mL, 4.7 mmol, 3 eq) was added dropwise to a solution of *N*-protected propargylamide **6a** (273 mg, 1.58 mmol, 1.0 eq) in MeOH (5 mL) at 0 °C. The reaction mixture was allowed to warm up to rt and stirred for 5-6 h at ambient temperature. After complete consumption of propargylamide **6a** (checked by TLC), the solvent was evaporated under reduced pressure. The crude material **102b** was suspended in toluene and the solvent was removed under reduced pressure. This procedure was repeated, until color and odor of the material had vanished and the title compound was afforded in pure form. Yield: 167 mg, 1.58 mmol, quantitative.

(*S*)-5-Methylhex-1-yn-3-amine Hydrochloride (102c). Compound **102c** has been synthesized following the instructions of Chen *et al.*, who also published a full characterization [245]. Hydrochloric acid (4 M, 170 µL, 680 µmol, 3 eq) was added dropwise to a solution of *N*-protected propargylamide **6c** (49.2 mg, 229 µmol, 1.0 eq) in MeOH (2 mL) at 0 °C. The reaction mixture was allowed to warm up to rt and stirred for 5-6 h at ambient temperature. After complete consumption of propargylamide **6c** (checked by TLC), the solvent was evaporated under reduced pressure. The crude material **102c** was suspended in toluene and the solvent was removed under reduced pressure. This procedure was repeated, until color and odor of the material had vanished and the title compound was afforded in pure form. Yield: 33.9 mg, 229 µmol, quantitative.

2-(*tert*-Butyl) 3,3-Diethyl 1,2-Oxaziridine-2,3,3-tricarboxylate (103). The Boc-amine transfer reagent **103** was prepared following the instructions of Kang *et al.* [59].

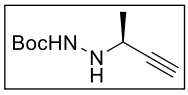
***tert*-Butyl 2-(Prop-2-yn-1-yl)hydrazine-1-carboxylate (104a)**. The synthesis of hydrazides was performed in analogy to the reports of Kang *et al.* [59]. Compound **104a** has been first characterized by Bonnet et al., who prepared it by conversion of propargylbromide with Boc protected hydrazine [246]. A solution of propargylamine **102a** (0.3 mL, 0.34 g 6.2 mmol, 1.3 eq) in THF (0.3 mL) was added dropwise to a vigorously stirred solution of transfer reagent **103** (1.39 g, 4.80 mmol, 1.0 eq) in a mixture of THF/saturated aqueous $NaHCO_3$ solution (1:1, 10 mL) at 0 °C. A pale yellow suspension formed which was stirred overnight at ambient temperature. After about 12 h, the solvents in the flask separated, forming a two-phase system of clear solutions. The phases were separated and the aqueous phase was extracted with Et_2O (4 x 15 mL). The combined organic layers were washed with an aqueous $KHSO_4$ solution (5 %, 20 mL), water (20 mL) and brine (10 mL). Afterwards, they were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude hydrazide **104a** was purified by column chromatography (PE/EtOAc, 1:1).

Pale yellow, crystalline solid. Yield: 413 mg, 2.43 mmol, 51 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.19 (s br., 1H, BocN**H**NHC$^{\alpha}$H$_2$C≡CH), 3.96 (s br., 1H,  BocNHN**H**C$^{\alpha}$H$_2$C≡CH), 3.63 (d, ^4J = 2.4 Hz, 2H, BocNHNHC$^{\alpha}$**H$_2$**C≡CH), 2.25 (t, ^4J = 2.4 Hz, 1H, BocNHNHC$^{\alpha}$H$_2$C≡C**H**), 1.47 (s, 9H, NHCO$_2$C(C**H$_3$**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 156.4 (NH**C**O$_2$C(CH$_3$)$_3$), 81.0 (BocNHNHC$^{\alpha}$H$_2$**C**≡CH), 80.0 (NHCO$_2$**C**(CH$_3$)$_3$), 72.5 (BocNHNHC$^{\alpha}$H$_2$C≡**C**H), 41.4 (BocNHNH**C$^{\alpha}$**H$_2$C≡CH), 28.5 (NHCO2C(**C**H$_3$)$_3$). $C_8H_{14}N_2O_2$ (170.21 g mol^{-1}).

***tert*-Butyl (*S*)-2-(But-3-yn-2-yl)hydrazine-1-carboxylate (104b)**. The synthesis of hydrazides was performed in analogy to the reports of Kang *et al.* [59]. Compound **104b** has been first characterized by Bare et al., who prepared it by *Mitsunobu* reaction of but-3-yn-2-ol with Boc protected hydrazine [247]. A solution of propargylamine **102b** (167 mg, 1.58 mmol, 1.0 eq) in THF (0.2 mL) was added dropwise to a vigorously stirred solution of transfer reagent **103** (684 mg, 2.40 mmol, 1.5 eq) in a mixture of THF/saturated aqueous $NaHCO_3$ solution (1:1, 5 mL) at 0 °C. A pale yellow suspension formed which was stirred overnight at ambient temperature. After about 12 h, the solvents in the flask separated, forming a two-phase system of clear solutions. The phases were separated and the aqueous

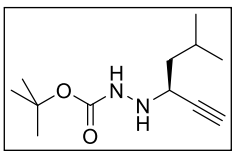
phase was extracted with Et_2O (4 x 15 mL). The combined organic layers were washed with an aqueous $KHSO_4$ solution (5 %, 20 mL), water (20 mL) and brine (10 mL). Afterwards, they were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude hydrazide **104b** was purified by column chromatography (PE/EtOAc, 1:1).

Colorless, crystalline needles. Yield: 339 mg, 1.84 mmol, 86 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.72 (s br., 1H, C$^\alpha$HNHN**H**Boc), 4.15 (m, 1H, C$^\alpha$HN**H**NHBoc), 3.67



(dq, ^4J = 2.0 Hz, ^3J = 7.0 Hz, 1H, C$^\alpha$**H**CH$_3$), 2.13 (d, ^4J = 2.0 Hz, 1H, C$^\alpha$HC≡C**H**), 1.26 (s, 9H, $CO_2C(C\mathbf{H_3})_3$), 1.11 (d, ^3J = 6.6 Hz, 3H, C$^\alpha$HC**H$_3$**). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 156.3 (NH**C**O$_2$C(CH$_3$)$_3$), 84.1 (C$^\alpha$H**C**≡CH), 80.0 ($CO_2\mathbf{C}(CH_3)_3$), 71.2 (C$^\alpha$HC≡**C**H), 47.1 (**C$^\alpha$**HCH$_3$), 27.9 ($CO_2C(\mathbf{C}H_3)_3$), 18.9 (C$^\alpha$H**C**H$_3$). $C_9H_{16}N_2O_2$ (184.24 g mol^{-1}). TLC: R*f* (PE/EtOAc, 1:1) = 0.62. X-ray crystal structure in Chapter IIX-4. i.

***tert*-Butyl (*S*)-2-(5-Methylhex-1-yn-3-yl)hydrazine-1-carboxylate (104c)**. The synthesis of hydrazides was performed in analogy to the reports of Kang *et al.* [59]. A solution of propargylamine **102c** (33.9 mg, 229 μmol, 1.0 eq) in THF (0.2 mL) was added dropwise to a vigorously stirred solution of transfer reagent **103** (197 mg, 680 μmol, 3.0 eq) in a mixture of THF/saturated aqueous $NaHCO_3$ solution (1:1, 5 mL) at 0 °C. A pale yellow suspension formed which was stirred overnight at ambient temperature. After about 12 h, the solvents in the flask separated, forming a two-phase system of clear solutions. The phases were separated and the aqueous phase was extracted with Et_2O (4 x 15 mL). The combined organic layers were washed with an aqueous $KHSO_4$ solution (5 %, 20 mL), water (20 mL) and brine (10 mL). Afterwards, they were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude hydrazide **104c** was purified by column chromatography (PE/EtOAc, 1:1).

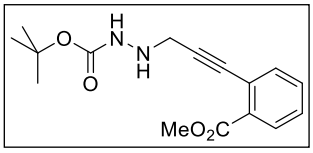


Colorless, crystalline, superfine needles. Yield: 83.9 mg, 371 μmol, 62 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 6.28 (s br., 1H, C$^\alpha$HNHN**H**CO$_2$C(CH$_3$)$_3$), 3.92 (s br., 1H, C$^\alpha$HN**H**NHCO$_2$C(CH$_3$)$_3$), 3.73 (dd, ^3J = 6.2 Hz, ^3J = 5.6 Hz, 1H, C$^\alpha$**H**NHNHCO$_2$C(CH$_3$)$_3$), 2.25 (d, ^4J = 1.9 Hz, 1H, C$^\alpha$HC≡C**H**), 1.82 (m, 1H, C$^\alpha$HC$^\beta$H$_2$C$^\gamma$**H**(CH$_3$)$_2$), 1.42 (s, 9H, C$^\alpha$HNHNHCO$_2$C(C**H$_3$**)$_3$),

1.28-1.21 (m, 1H, $C^{\alpha}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 1.22-1.18 (m, 1H, $C^{\alpha}HC^{\beta}\mathbf{H}_2C^{\gamma}H(CH_3)_2$), 0.92 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$), 0.87 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H_2C^{\gamma}H(C\mathbf{H_3})_2$). $C_{12}H_{22}N_2O_2$ (226.32 g mol^{-1}). MS(ESI): *m/z* = 227.1186 (calcd. 227.1754 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 1:1) = 0.71.

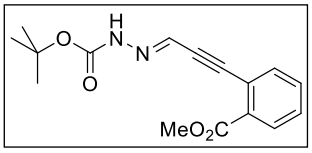
***tert*-Butyl 2-(3-(2-(Methoxycarbonyl)phenyl)prop-2-yne-1-yl)hydrazine-1-carboxylate (106a)**. Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2 mg, 3 μmol, 0.3 mol%) and CuI (1 mg, 5 μmol, 0.4 mol%) were added in one portion to a thoroughly degassed solution of glycine analogous propargylhydrazide **104a** (220 mg, 1.18 mmol, 1.0 eq, containing 44 % hydrazone **105a**) and iodo benzoate **26a** (200 μL, 356 mg, 1.36 mmol, 1.2 eq) in a mixture of THF/piperidine (3:1, 3.2 mL). The reaction mixture was stirred for 18 h at ambient temperature. After complete consumption of propargylhydrazide **104a** (checked by TLC), the mixture was diluted with aqueous NH_4Cl (saturated, 20 mL), Et_2O (20 mL) and aqueous $KHSO_4$ (0.5 M, ca. 20 mL until pH 7). The phases were separated and the aqueous layers were extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with water (30 mL) and brine (10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Propargylhydrazide **106a** and hydrazone **107a** were separated by column chromatography (PE/EtOAc, 2:1).

Pale yellow, highly viscous oil. Yield: 173.0 mg, 568.4 μmol, 48 %. ^{1}H NMR (500 MHz,



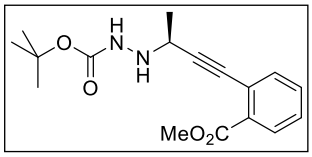
Chloroform-*d*) δ = 7.91 (d, ^3J = 7.9 Hz, 1H, ar-2-**H**), 7.49 (d, ^3J = 8.0 Hz, 1H, ar-5-**H**), 7.42 (t, ^3J = 7.9 Hz, 1H, ar-3-**H**), 7.32 (t, ^3J = 7.7 Hz, 1H, ar-4-**H**), 7.00 (s br., 1H, $C^{\alpha}H_2NH$-N**H**Boc), 3.89 (s, 3H, $CO_2C\mathbf{H_3}$), 3.83 (s, 2H, $C^{\alpha}\mathbf{H_2}$NH-NHBoc), 3.67 (s br., 1H, $C^{\alpha}H_2N\mathbf{H}$-NHBoc), 1.44 (s, 9H, $NHCO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.5 ($\mathbf{C}O_2CH_3$), 156.4 ($NH\mathbf{C}O_2C(CH_3)_3$), 133.8 (ar-**C**-5), 131.9 (ar-**C**-4), 131.7 (ar-**C**-6), 130.4 (ar-**C**-2), 127.9 (ar-**C**-3), 123.6 (ar-**C**-1), 91.4 ($C^{\alpha}H_2\mathbf{C}$≡C-ar), 83.5 ($C^{\alpha}H_2C$≡**C**-ar), 80.3 ($NHCO_2\mathbf{C}(CH_3)_3$), 52.3 ($CO_2\mathbf{C}H_3$), 42.3 ($\mathbf{C^{\alpha}}H_2NH$), 28.4 ($NHCO_2C(\mathbf{C}H_3)_3$). $C_{16}H_{20}N_2O_4$ (304.35 g mol^{-1}). LCMS(ESI): t*r* = 8.98 min, *m/z* = 305.1489 (calcd. 305.14958 $[M+H]^+$), 327.1313 (calcd. 327.1315 $[M+Na]^+$). IR(ATR): ϑ [cm^{-1}] = . TLC: R*f* (PE/EtOAc, 2:1) = 0.31.

***tert*-Butyl (*E*)-2-(3-(2-(Methoxycarbonyl)phenyl)prop-2-yne-1-ylidene)hydrazine-1-carboxylate (107a)**. Colorless crystals. Yield: 144.0 mg, 476.3 mmol, 40 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 10.20 (s, 1H, C**H**N), 8.11 (d, ^{3}J = 7.9 Hz, 1H, ar-2-**H**), 7.61 (d, ^{3}J = 7.7 Hz, 1H, ar-5-**H**), 7.56 (t, ^{3}J = 7.5 Hz, 1H, ar-3-**H**), 7.48 (t, ^{3}J = 7.6 Hz, 1H, ar-4-**H**), 6.76 (s br., 1H, C=N-N**H**Boc), 3.98 (s, 3H, $CO_2C\mathbf{H_3}$), 1.58 (s, 9H, $NHCO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.8 ($CO_2\mathbf{C}H_3$), 152.7 ($NH\mathbf{C}O_2C(CH_3)_3$), 134.2 (ar-**C**-5), 132.6 (ar-**C**-4), 131.3 (ar-**C**-6), 131.0 (ar-**C**-2), 129.6 (ar-**C**-3), 122.4 (**C**=NNHNoc), 121.0 (ar-**C**-1), 100.4 (CN**C**≡C-ar), 84.7 (CNC≡**C**-ar), 52.7 (ar-1-$CO_2\mathbf{C}H_3$), 28.5 ($NHCO_2C(\mathbf{C}H_3)_3$). $C_{16}H_{18}N_2O_4$ (302.33 g mol^{-1}). LCMS(ESI): t*r* = 9.19 min, *m/z* = 303.1336 (calcd. 303.13393 $[M+H]^+$), 325.1182 (calcd. 325.1159 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.48. X-ray crystal structure in Chapter IIX-4. i.



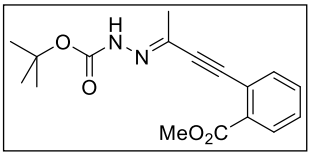
***tert*-Butyl (*S*)-2-(4-(2-(Methoxycarbonyl)phenyl)but-3-yne-2-yl)hydrazine-1-carboxylate (106b)**. Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2 mg, 3 μmol, 0.2 mol%) and CuI (1 mg, 5 μmol, 0.4 mol%) were added in one portion to a thoroughly degassed solution of glycine analogous propargylhydrazide **104b** (380 mg, 1.26 mmol, 1.0 eq, containing 44 % hydrazone **105b**) and iodo benzoate **26a** (400 μL, 702 mg, 2.6 mmol, 2.1 eq) in a mixture of THF/piperidine (3:1, 6.0 mL). The reaction mixture was stirred for 18 h at ambient temperature. After complete consumption of propargylhydrazide **104b** (checked by TLC), the mixture was diluted with aqueous NH_4Cl (saturated, 20 mL), Et_2O (20 mL) and aqueous $KHSO_4$ (0.5 M, ca. 20 mL until pH 7). The phases were separated and the aqueous layers were extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with water (30 mL) and brine (10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Propargylhydrazide **106b** and hydrazone **107b** were separated by column chromatography (PE/EtOAc, 2:1).

Pale yellow oil. Yield: 123 mg, 386 μmol, 31 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.93 (d, ^{3}J = 7.9 Hz, 1H, ar-2-**H**), 7.50 (d, ^{3}J = 7.8 Hz, 1H, ar-5-**H**), 7.44 (t, ^{3}J = 7.7 Hz, 1H, ar-3-**H**), 7.33 (t, ^{3}J = 7.7 Hz, 1H, ar-4-**H**), 7.10 (m, 1H, C^{α}HNHN**H**Boc), 4.29 (m, 1H, C^{α}HN**H**NHBoc), 4.05 (dq, ^{3}J = 5.4 Hz, ^{3}J = 6.6 Hz, 1H, C^{α}**H**), 3.91 (s, 3H, $CO_2C\mathbf{H_3}$), 1.45 (s,



9H, $NHCO_2C(C\mathbf{H_3})_3$), 1.40 (d, ^3J = 6.8 Hz, 3H, $C^{\alpha}HC\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.6 (ar-$\mathbf{C}O_2CH_3$), 156.5 ($NH\mathbf{C}O_2C(CH_3)_3$), 133.9 (ar-**C**-5), 131.9 (ar-**C**-4), 131.8 (ar-**C**-6), 130.5 (ar-**C**-2), 127.9 (ar-**C**-3), 123.7 (ar-**C**-1), 95.6 ($C^{\alpha}H\mathbf{C}$≡C-ar), 82.5 ($C^{\alpha}HC$≡**C**-ar), 80.2 ($NHCO_2\mathbf{C}(CH_3)_3$), 52.3 (ar-$\mathbf{C}O_2CH_3$), 48.9 (**C$^{\alpha}$**), 28.5 ($NHCO_2C(C\mathbf{H_3})_3$), 19.1 ($C^{\alpha}HC\mathbf{H_3}$). $C_{17}H_{22}N_2O_4$ (318.37 g mol^{-1}). MS(ESI): *m/z* = 319.1887 (calcd. 319.1652 $[M+H]^+$). IR(ATR): ϑ [cm^{-1}] = 3316, 3060, 2974, 2933, 2867, 2357, 2341, 1714, 1366, 1274, 1242, 1141, 1078, 752. TLC: R*f* (PE/EtOAc, 2:1) = 0.45. $[\alpha]_{589}^{20}$ = -56.56 (*c* 3.45, MeOH).

***tert*-Butyl (*E*)-2-(4-(2-(Methoxycarbonyl)phenyl)but-3-yne-2-ylidene)hydrazine-1-carboxylate (107b)**. Pale yellow oil. Yield: 96.6 mg, 305 µmol, 24 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 9.89 (s br., 1H, C=NN**H**Boc), 8.08 (d, ^3J = 7.9 Hz, 1H, ar-2-**H**), 7.61 (d, ^3J = 7.7 Hz, 1H, ar-5-**H**), 7.54 (t, ^3J = 7.6 Hz, 1H, ar-3-**H**), 7.46 (t, ^3J = 7.8 Hz, 1H, ar-4-**H**), 3.95 (s, 3H, ar-$CO_2C\mathbf{H_3}$), 2.22 (s, 3H, $CNC\mathbf{H_3}$), 1.54 (s, 9H, $NHCO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.7 (ar-$\mathbf{C}O_2CH_3$), 152.9 ($NH\mathbf{C}O_2C(CH_3)_3$), 134.4 (ar-**C**-5), 132.5 (ar-**C**-4), 131.2 (ar-**C**-6), 130.9 (ar-**C**-2), 130.2 ($CH_3\mathbf{C}$=N), 129.5 (ar-**C**-3), 122.3 (ar-**C**-1), 99.3 ($C^{\alpha}H\mathbf{C}$≡C-ar), 85.8 ($C^{\alpha}HC$≡**C**-ar), 80.8 ($NHCO_2\mathbf{C}(CH_3)_3$), 52.6 ($CO_2\mathbf{C}H_3$), 28.4 ($NHCO_2C(\mathbf{C}H_3)_3$), 22.3 ($\mathbf{C}H_3C$=N). $C_{17}H_{20}N_2O_4$ (316.36 g mol^{-1}). MS(ESI): *m/z* = (calcd. 317.1496 $[M+H]^+$). IR(ATR): ϑ [cm^{-1}] = 3259, 2977, 2924, 2867, 2360, 2338, 1793, 1736, 1711, 1565, 1502, 1432, 1258, 1141, 1081, 755. TLC: R*f* (PE/EtOAc, 2:1) = 0.55. $[\alpha]_{589}^{20}$ = -13.0 (*c* 2.17, MeOH).



***tert*-Butyl (*S*)-2-(1-(2-(Methoxycarbonyl)phenyl)-5-methylhex-1-yn-3-yl)hydrazine-1-carboxylate (106c)**. Under argon atmosphere, the solid catalysts $PdCl_2(PPh_3)_2$ (2 mg, 3 µmol, 0.4 mol%) and CuI (1 mg, 5 µmol, 0.7 mol%) were added in one portion to a thoroughly degassed solution of glycine analogous propargylhydrazide **104c** (197 mg, 680 µmol, 1.0 eq, containing 44 % hydrazone **105c**) and iodo benzoate **26a** (150 µL, 260 mg, 980 µmol, 2.1 eq) in a mixture of THF/piperidine (3:1, 2.5 mL). The reaction mixture was stirred for 18 h at ambient temperature. After complete consumption of propargylhydrazide **104c** (checked by TLC), the mixture was diluted with aqueous NH_4Cl (saturated, 20 mL), Et_2O (20 mL) and aqueous $KHSO_4$ (0.5 M, ca. 20 mL until pH 7). The phases were separated and the aqueous layers were extracted with Et_2O (3 x 40 mL). The

combined organic layers were washed with water (30 mL) and brine (10 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. Propargylhydrazide **106c** was purified by column chromatography (PE/EtOAc, 4:1). Hydrazone **107c** could be observed by LCMS, but not be isolated due to its low amount.

Pale yellow, viscous oil. Yield: 31.8 mg, 88.2 µmol, 13 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.94 (d, ^3J = 7.9 Hz, 1H, ar-6-**H**), 7.51 (d, ^3J = 7.8 Hz, 1H, ar-3-**H**), 7.45 (t, ^3J = 7.5 Hz, 1H, ar-4-**H**), 7.35 (t, ^3J = 7.7 Hz, 1H, ar-5-**H**), 7.14 (s br., 1H, C^{α}-NH-N**H**Boc), 3.97 (ddd, ^3J = 7.0 Hz, ^3J = 5.7 Hz, ^3J = 3.6 Hz, 1H, C^{α}**H**$C^{\beta}H_2CH(CH_3)_2$), 3.92 (s, 3H, CO_2C**H**$_3$), 1.97 (m, 1H, $C^{\alpha}HC^{\beta}H_2C$**H**$(CH_3)_2$), 1.80 (s br., 1H, $C^{\alpha}HN$**H**-NHBoc), 1.58 (m, 2H, $C^{\alpha}HC^{\beta}$**H**$_2CH(CH_3)_2$), 1.47 (s, 9H, $CO_2C(C$**H**$_3)_3$), 0.99 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H_2CH(C$**H**$_3)_2$), 0.95 (d, ^3J = 6.7 Hz, 3H, $C^{\alpha}HC^{\beta}H_2CH(C$**H**$_3)_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.7 (ar-**C**O_2CH_3), 156.5 (NH**C**$O_2{}^t$Bu), 134.0 (ar-**C**-2), 132.0 (ar-**C**-4), 131.8 (ar-**C**-3), 130.5 (ar-**C**-6), 127.9 (ar-**C**-5), 123.9 (ar-**C**-1), 95.2 ($C^{\alpha}H$**C**≡C-ar), 83.4 ($C^{\alpha}HC$≡**C**-ar), 80.1 (CO_2**C**$(CH_3)_3$), 52.6 (CO_2**C**H_3), 52.4 (**C**$^{\alpha}HC^{\beta}H_2CH(CH_3)_2$), 41.9 ($C^{\alpha}H$**C**$^{\beta}H_2CH(CH_3)_2$), 28.4 ($CO_2C(C$**H**$_3)_3$), 25.3 ($C^{\alpha}HC^{\beta}H_2$**C**$H(CH_3)_2$), 23.0 ($C^{\alpha}HC^{\beta}H_2CH($**C**$H_3)_2$), 22.3 ($C^{\alpha}HC^{\beta}H_2CH($**C**$H_3)_2$). $C_{20}H_{28}N_2O_4$ (360.45 g mol^{-1}). MS(ESI): *m/z* = 361.2123 (calcd. 361.2122 $[M+H]^+$). TLC: R*f* (PE/EtOAc, 2:1) = 0.53. IR(ATR): $\tilde{\nu}$[cm^{-1}] = 3322 (br, NH), 2952 (s, CH), 2936 (s, CH), 2867 (s, CH), 2360 (s, C≡C), 2338 (s, C≡C), 1726 (s, CO), 1720 (s, CO), 1432(s, arH), 1367 (s, arH), 1293 (s, arH), 1255 (s, arH), 1157 (s, arH), 1081 (s, arH), 764 (CC).

IIX-4. f) Conformationally relevant ^{1}H NMR Shifts

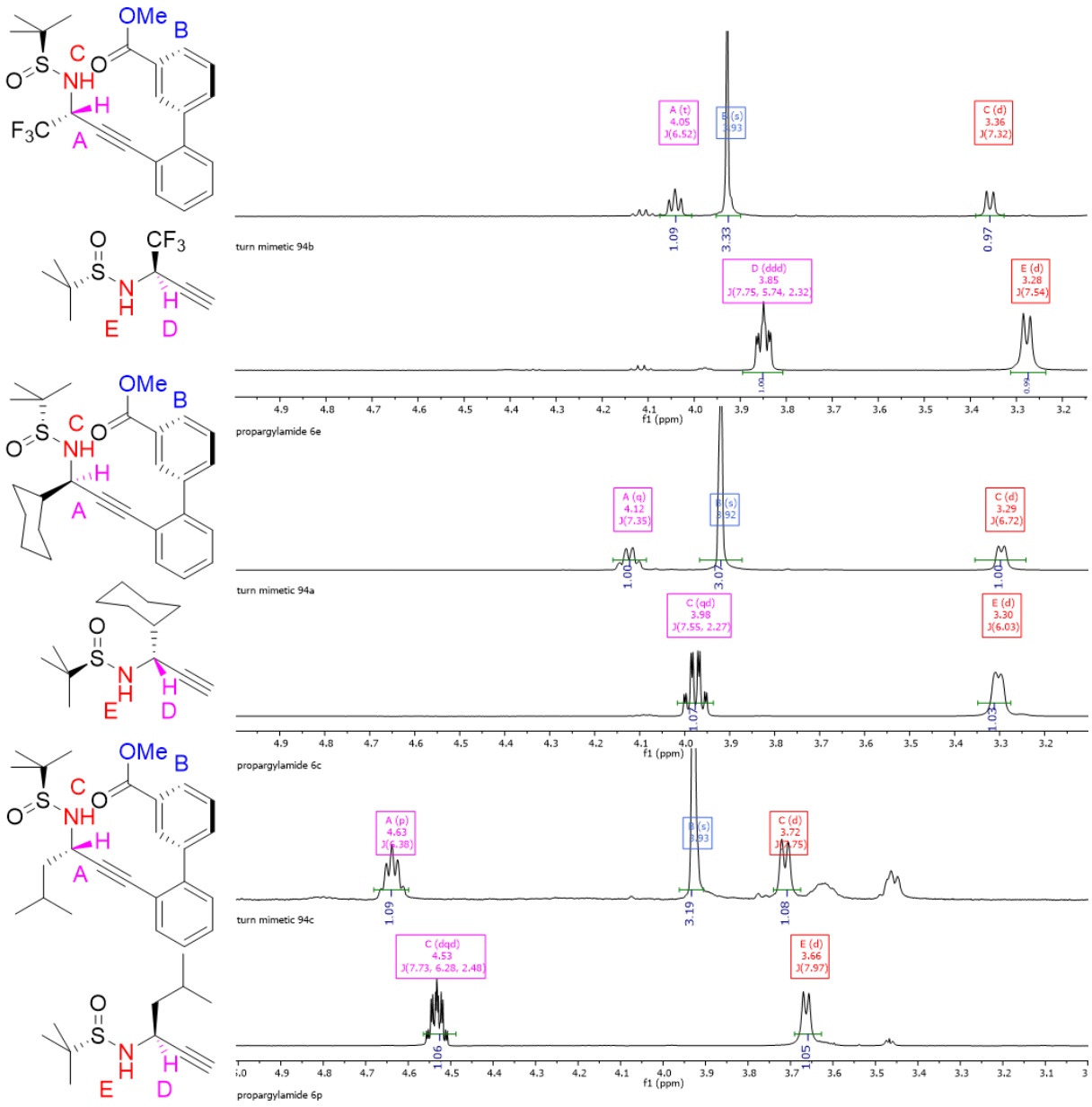
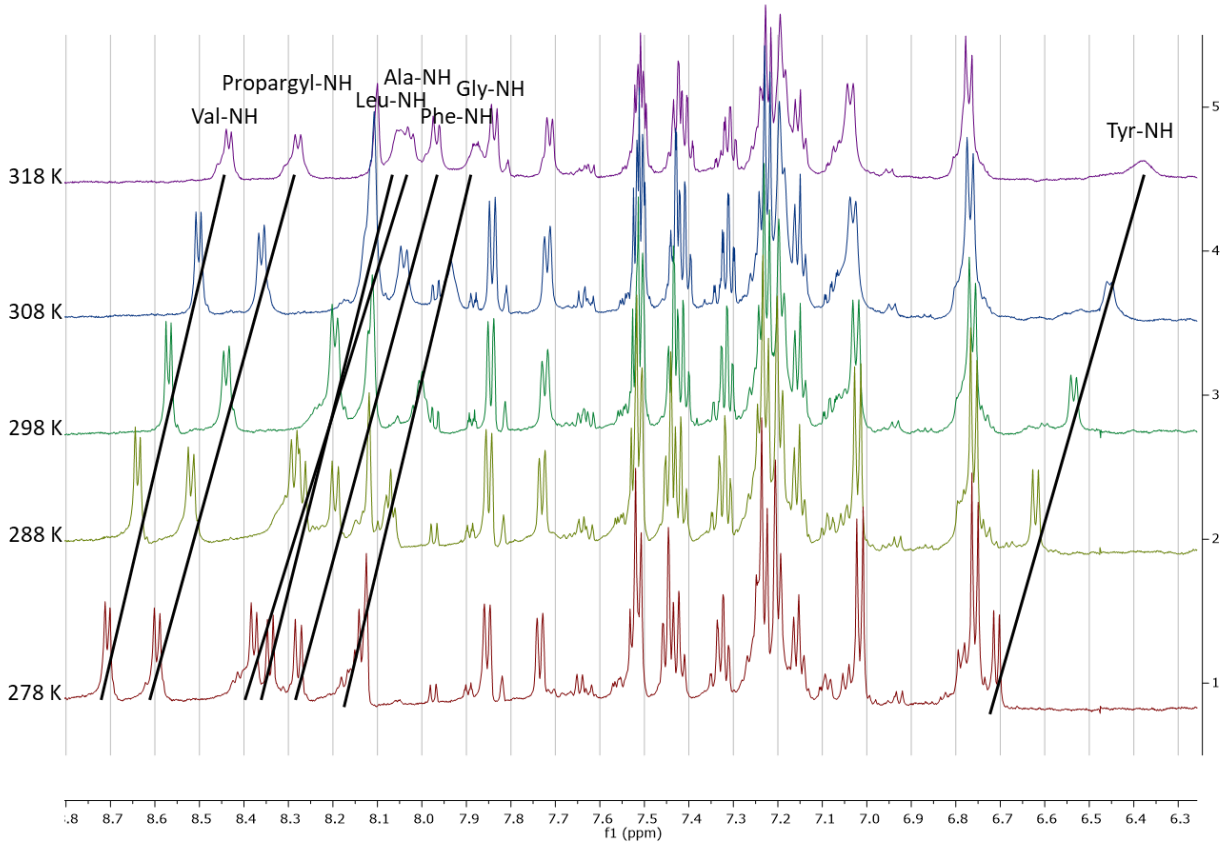


Diagram EP15. Comparison of the ^{1}H NMR shifts of propargylamides **6** to turn mimetics **94** in chloroform-*d*. From top to bottom: **94c**, **6p**, **94b**, **6e**, **94a**, **6c**. Magenta: C$^{\alpha}$H, multipletts A, D. Blue: Methyl ester protons, singlet B. Red: Amide protons, doublets C, E.



Amino Acid	Val	Proparg	Ala	Leu	Phe	Gly	Tyr
δ[ppm]	8,57	8,44	8,22	8,20	8,12	8,01	6,54
Δ[0,001 ppm/K]	-6,80	-8,00	-8,80	-6,80	-8,00	-6,90	-8,50

Diagram EP16. Visualization of temperature coefficients of turn mimetic **94** incorporated in a short peptide giving hairpin mimetic **97**. Temperature coefficients were derived from the gradient of ^{1}H NMR shifts in dependence of the temperature.

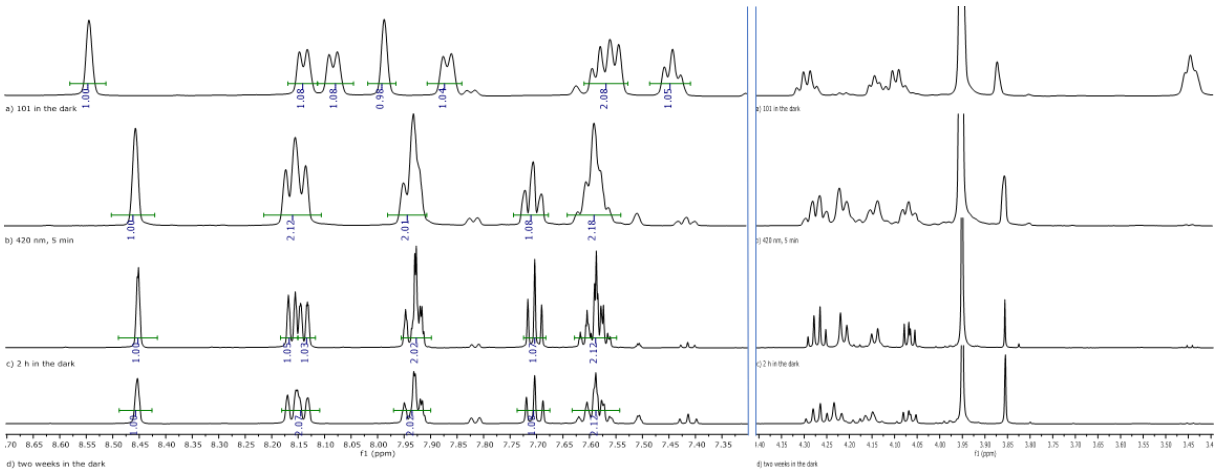


Diagram EP17. ^{1}H NMR spectroscopic observation of the photoisomerization of compound **101** in chloroform-*d*. The aromatic region (9.0-7.0 ppm, left side), as well as the amide region (4.5-3.5 ppm, right side) of the same sample is shown in dependence of irradiation a) Aromatic region of the ^{1}H NMR spectra just after the isolation. Compound **101** was kept in the dark until the measurement was performed. b) 5 min irradiation at 420 nm. c) Irradiated

sample kept in the dark for relaxation for 2 h. d) Irradiated sample kept in the dark for relaxation for three weeks.

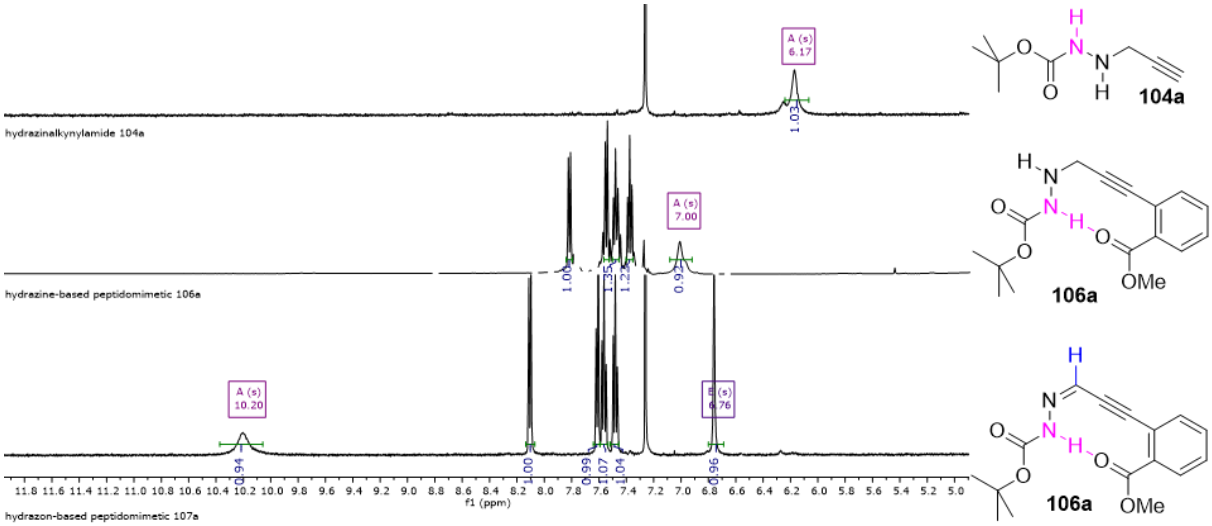


Diagram EP18. ^{1}H NMR spectroscopic observation of the amide shift of glycine analogous derivatives to deduce intramolecular H-bonds. Singletts A are assigned to the protons flagged in the chemical structures on the right. Top, hydrazine **104a**, δ(NH)=6.17 ppm. Middle, peptidomimetic **106a**, δ(NH)=7.00 ppm. Bottom, hydrazone **107a**, δ(NH)=10.20 ppm.

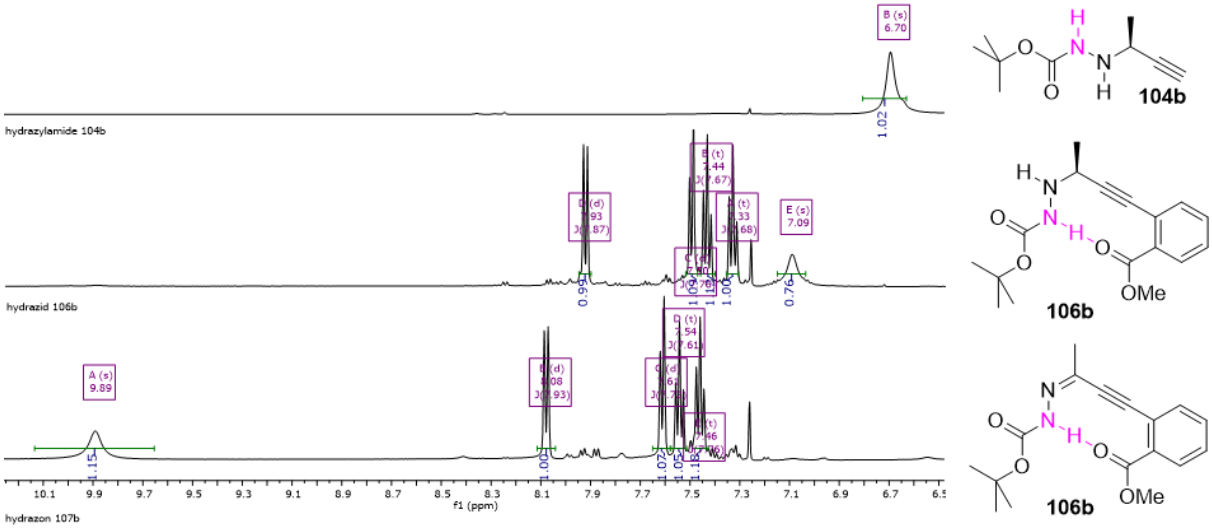


Diagram EP19. ^{1}H NMR spectroscopic observation of the amide shift of alanine analogous derivatives to deduce intramolecular H-bonds. Singletts A are assigned to the protons flagged in the chemical structures on the right. Top, hydrazine **104b**, δ(NH)=6.70 ppm. Middle, peptidomimetic **106b**, δ(NH)=7.09 ppm. Bottom, hydrazone **107b**, δ(NH)=9.89 ppm.

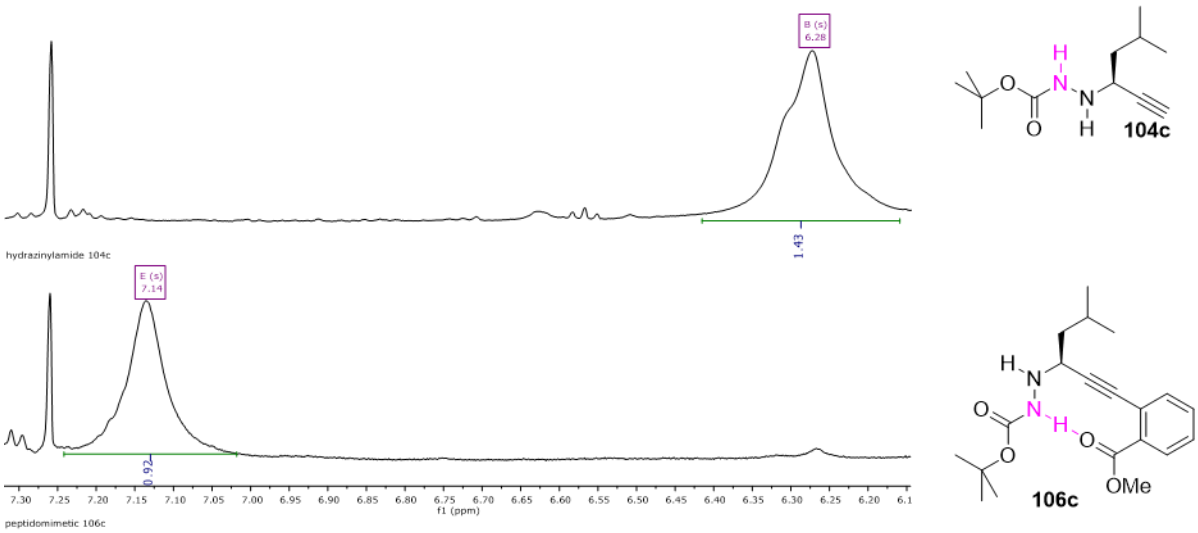


Diagram EP20. ^{1}H NMR spectroscopic observation of the amide shift of leucine analogous derivatives to deduce intramolecular H-bonds. Singletts A are assigned to the protons flagged in the chemical structures on the right. Top, hydrazine **104c**, δ(NH)=6.29 ppm. Bottom, peptidomimetic **106c**, δ(NH)=7.34 ppm.

IIX-4. g) UV/*Vis* Spectra

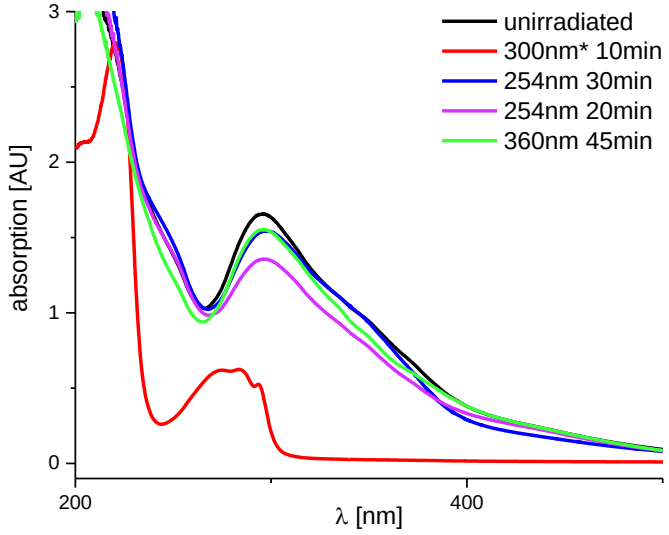


Diagram EP21. UV/*Vis* spectroscopic observation of the photoisomerization of **98b** (in CH_3CN, c = 160 nM, d = 1 cm). Black curve: Pure sample in relaxed state, ε = 10375000 cm^{-1} M^{-1} (λ_{max} = 296 nm). Green curve: Same sample after 45 min irradiation at 360 nm, ε = 9687500 cm^{-1} M^{-1} (λ_{max} = 296 nm). Red curve: Same sample after 10 min irradiation at 300 nm and 200 W, ε = 3875000 cm^{-1} M^{-1} (λ_{max} = 274 nm). Violet curve: Same sample after 20 min irradiation at 254 nm, ε = 8562500 cm^{-1} M^{-1} (λ_{max} = 296 nm). Blue curve: Same sample after 30 min irradiation at 254 nm, ε = 9675000 cm^{-1} M^{-1} (λ_{max} = 296 nm).

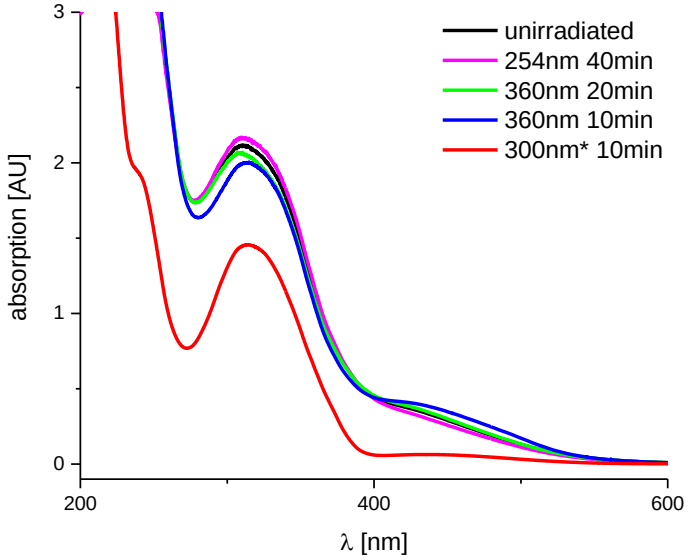


Diagram EP22. UV/*Vis* spectroscopic observation of the photoisomerization of **100b** (in CH_3CN, c=300 nM, d=1 cm). Black curve: Pure sample in relaxed state, ε = 7033333 cm^{-1} M^{-1} (λ_{max} = 311 nm). Green curve: Same sample after 20 min irradiation at 360 nm, ε = 6888889 cm^{-1} M^{-1} (λ_{max} = 309 nm). Red curve: Same sample after 10 min irradiation at 300 nm and 200 W, ε = 4833333 cm^{-1} M^{-1} (λ_{max} = 314 nm). Blue curve: Same sample after 10 min irradiation at 360 nm, ε = 6666666 cm^{-1} M^{-1} (λ_{max} = 314 nm). Violet curve: Same sample after 40 min irradiation at 254 nm, ε = 7230000 cm^{-1} M^{-1} (λ_{max} = 311 nm).

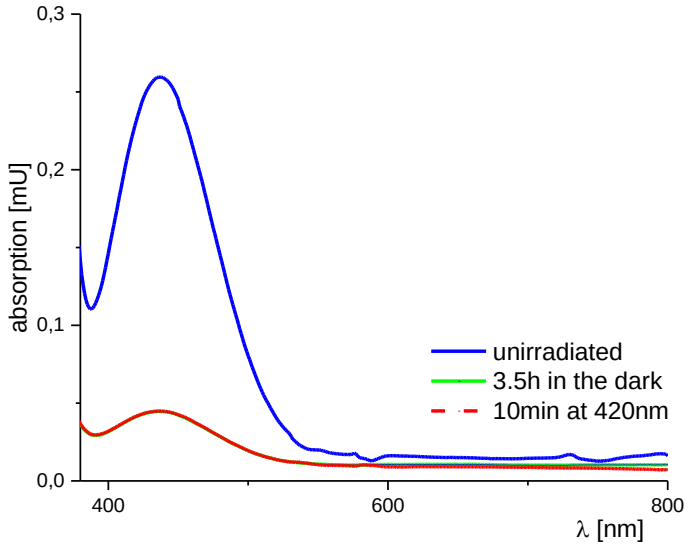


Diagram EP23. UV/*Vis* spectroscopic observation of the photoisomerization of **101** (in CH_3CN, c = 500 nM, d = 1 cm). Blue curve: Pure sample in relaxed state, ε = 520000 cm^{-1} M^{-1} (λ_{max} = 437 nm). Red curve: Same sample after 10 min irradiation at 420 nm, ε = 90200 cm^{-1} M^{-1} (λ_{max} = 434 nm). Green curve: Irradiated sample after 3.5 h in the dark at rt, ε = 90200 cm^{-1} M^{-1} (λ_{max} = 434 nm).

IIX-4. h) Circular Dichroism Spectra

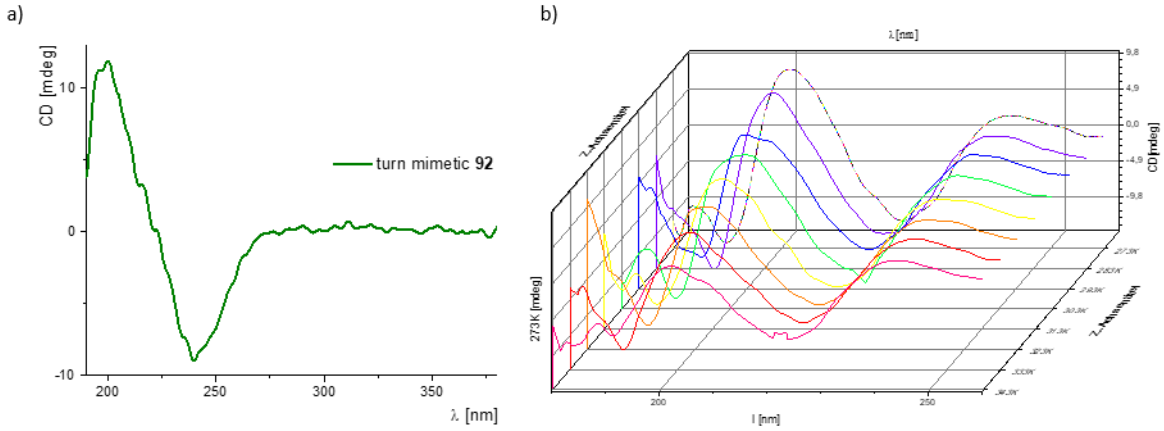


Diagram EP24. Investigation of naphthoate-based turn mimetics via CD spectroscopy. Left side: CD spectra of turn mimetic **92** (c=120 µM in TFE). Right side: Temperature-resolved CD spectra of turn motif mimetic **92** incorporated in a peptide giving H-Pro-Tyr-Thr-**92**-Leu-Thr-Val-OH (c=71 µM in TFE). Peptide strands connected by *Sonogashira* cross coupling: iodo naphthoate (20 mg, 26 µmol), propargylamide (23.8 mg, 30 µmol), 1,4-dioxane/DIPAH (10:1), CuI/ $PdCl_2(PPh_3)_2$, 60 °C, microwave, 2 h. H-Pro-Tyr-Thr-**92**-Leu-Thr-Val-OH 7.81 mg, 7.07 µmol, 27 %. MS(ESI): *m/z* = 1105.541 $[M+H]^+$, 1127.609 $[M+Na]^+$.

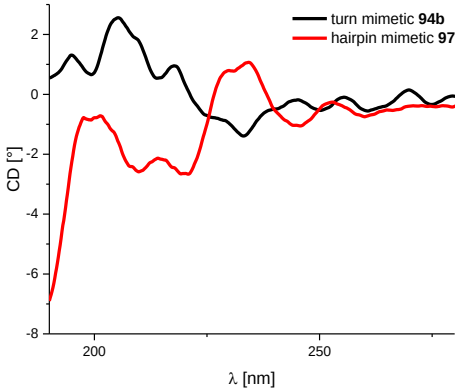


Diagram EP25. Comparison of CD spectra of turn mimetic **94b** (c=130 µM) to hairpin mimetic **97** (c=67 µM) in CH_3CN.

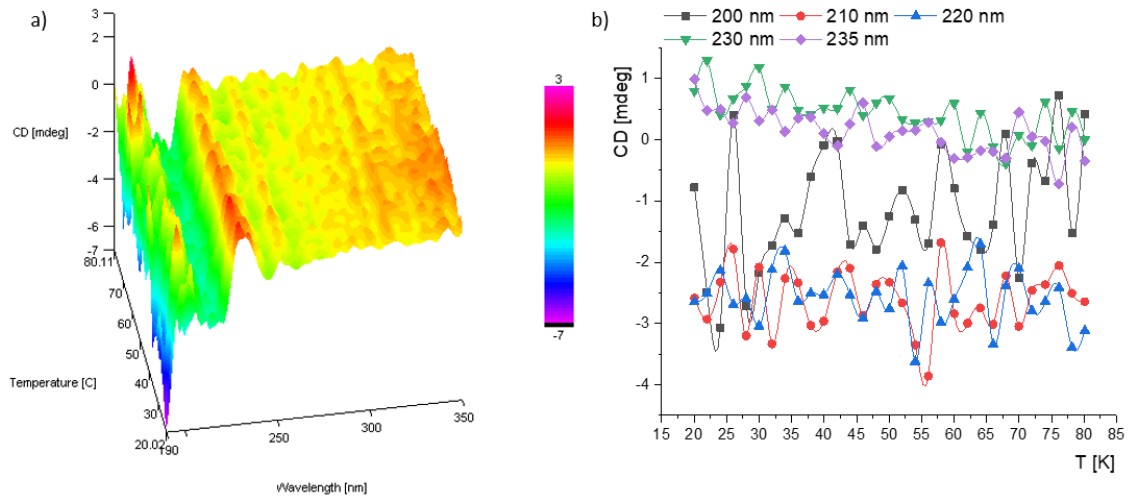


Diagram EP26. Temperature-dependent development of the CD-effect to determine the stability of β-strand alignment in hairpin mimetic **97**. a) CD-Spectra of hairpin mimetic **97** (c = 67 µM in CH_3CN) at temperatures of 20-80 °C. Every 2 K one spectra was measured with only 2 accumulations. b) CD(T) at relative maxima/minima of Diagram EP26a to visualize the development.

IIX-4. i) X-ray Structure Analysis

Table EP30. Crystal data and structure refinement for hydrazides **104b** and hydrazone **107a**.

compound	**104b**	**107a**
Identification code	wuensch24	wuensch23
Empirical formula	$C_9H_{16}N_2O_2$	$C_{16}H_{18}N_2O_4$
Formula weight	184.24	302.32
Temperature/K	100.0(1)	100.00(10)
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1/c$
a/Å	5.15904(6)	8.27678(19)
b/Å	10.30935(12)	9.6836(2)
c/Å	19.4194(3)	19.5096(4)
α/°	90	90
β/°	90	91.720(2)
γ/°	90	90
Volume/Å^3	1032.85(2)	1562.97(6)
Z	4	4
ρ_{calc}g/cm^3	1.185	1.285
µ/mm^{-1}	0.687	0.093
F(000)	400.0	640.0
Crystal size/mm^3	0.303 × 0.108 × 0.038	0.465 × 0.247 × 0.157
Radiation/Å	CuKα (λ = 1.54184)	MoKα (λ = 0.71073)
2Θ range for data collection/°	9.108 to 151.966	5.93 to 60.16

Index ranges	-6 ≤ h ≤ 6, -12 ≤ k ≤ 12, -24 ≤ l ≤ 23	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13, -27 ≤ l ≤ 27
Reflections collected	15511	43744
Independent reflections	2155 [R_{int} = 0.0160, R_{sigma} = 0.0075]	4582 [R_{int} = 0.0218, R_{sigma} = 0.0097]
Data/restraints/parameters	2155/0/183	4582/0/271
Goodness-of-fit on F^2	1.041	1.099
Final R indexes [$I > 2\sigma(I)$]	R_1 = 0.0203, wR_2 = 0.0509	R_1 = 0.0351, wR_2 = 0.0971
Final R indexes [all data]	R_1 = 0.0203, wR_2 = 0.0509	R_1 = 0.0369, wR_2 = 0.0983
Largest diff. peak/hole / e $Å^{-3}$	0.15/-0.12	0.39/-0.24
Flack parameter	0.03(2)	

tert-Butyl (_S_)-2-(But-3-yn-2-yl)hydrazine-1-carboxylate (104b).

Single crystals of hydrazine **104b** were achieved by evaporation of the solvent of a concentrated $CHCl_3$ solution at ambient temperature. Single crystals were collected and put in a concentrated solution of **104b** at -20 °C to increase their size.

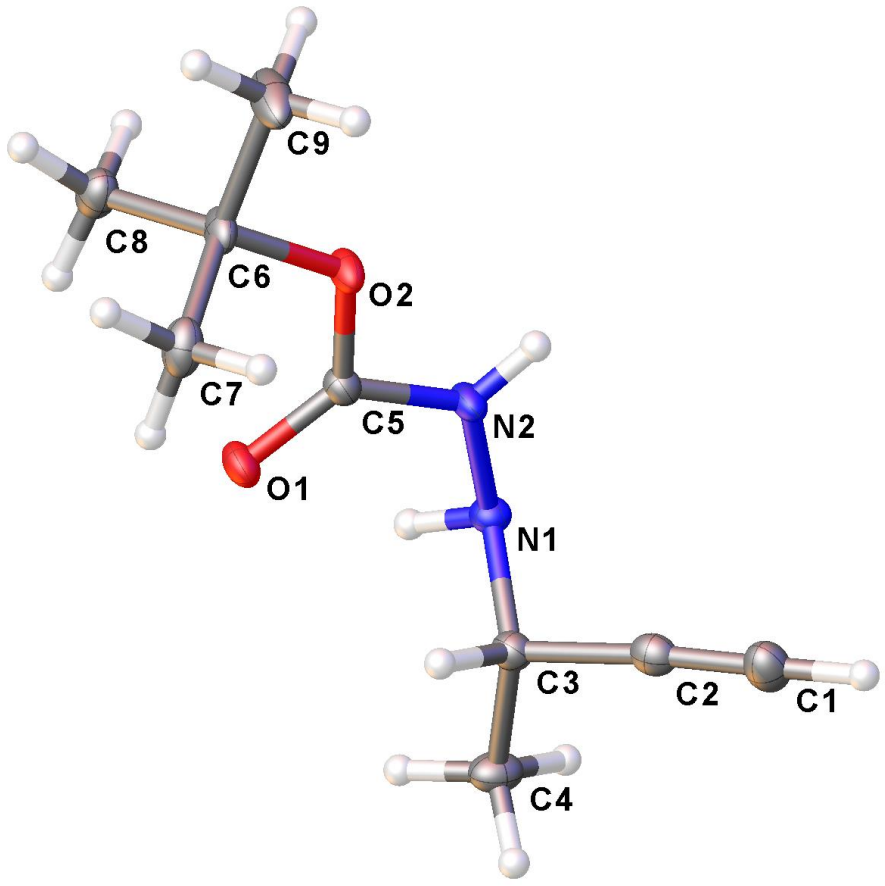


Table EP31. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å2×103) for hydrazide **104b**. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	2702.4(16)	6923.0(8)	6278.1(4)	19.51(19)
O2	5680.4(14)	7141.1(9)	7143.5(4)	18.9(2)
N1	6747.1(19)	6659.4(9)	5358.4(5)	15.7(2)
N2	7031.5(19)	6838.4(10)	6076.1(5)	17.0(2)
C1	9910(3)	3655.3(12)	5348.7(7)	24.1(3)
C2	8202(2)	4422.7(11)	5295.2(6)	18.9(2)
C3	5984(2)	5306.7(11)	5198.9(6)	16.4(2)
C4	5024(3)	5251.8(12)	4457.1(6)	23.0(3)
C5	4928(2)	6960.9(10)	6487.0(5)	14.9(2)
C6	3724(2)	7306.2(12)	7693.3(6)	18.6(2)
C7	2059(3)	6099.2(12)	7751.9(7)	23.8(3)
C8	2110(3)	8517.9(12)	7567.6(7)	22.8(3)
C9	5392(3)	7476.0(19)	8331.1(7)	34.1(4)

tert-Butyl (_E_)-2-(3-(2-(Methoxycarbonyl)phenyl)prop-2-yne-1-ylidene)hydrazine-1-carboxylate (107a).

Single crystals of hydrazone **107a** were achieved by evaporation of the solvent of a concentrated EtOAc solution at ambient temperature. Similar crystals were achieved from other organic solvents like Et_2O, CH_2Cl_2, chloroform, MeOH and EtOH.

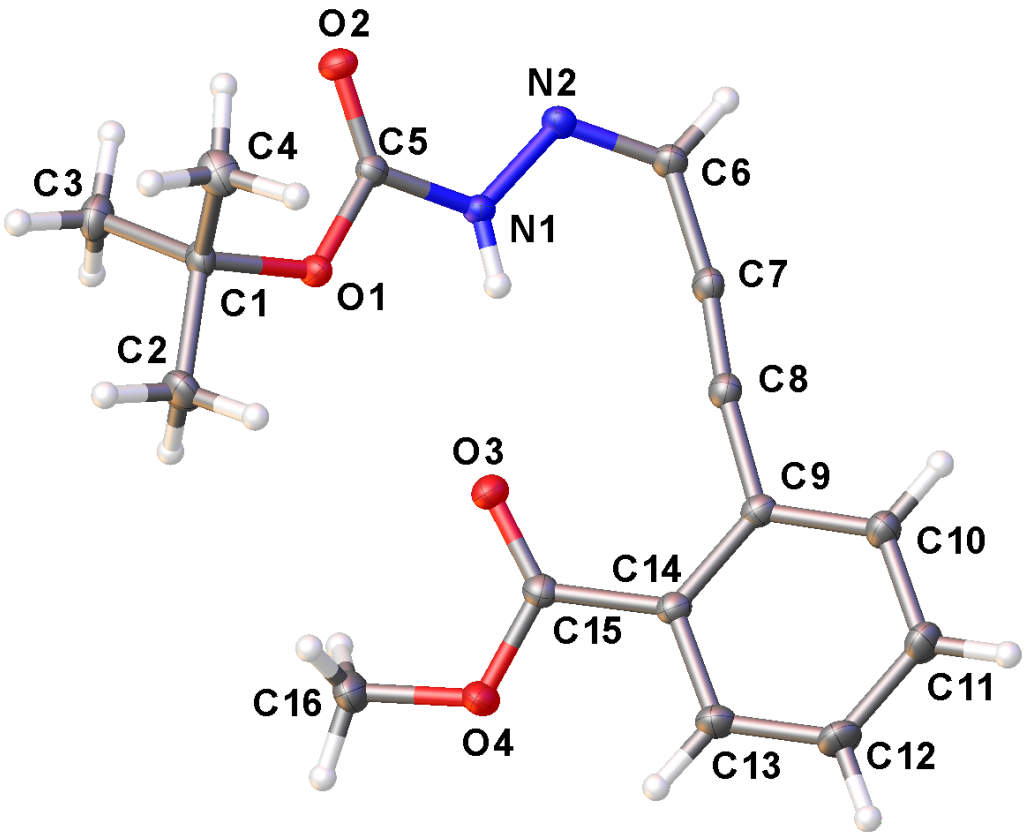


Table EP32. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for hydrazone **107a**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	6305.7(8)	6348.8(7)	7783.4(3)	17.01(13)
O2	7420.6(8)	5711.7(7)	8821.4(3)	18.61(14)
O3	7885.6(9)	5999.8(7)	6293.5(3)	21.37(14)
O4	7141.7(10)	6658.2(8)	5228.2(4)	26.43(17)
N1	8603.5(9)	5235.5(8)	7797.3(4)	14.73(14)
N2	9807.2(9)	4472.2(8)	8103.3(4)	15.85(14)
C1	4827(1)	6952.2(9)	8061.5(4)	16.70(16)
C2	3847.6(13)	7278.6(11)	7409.6(5)	25.3(2)
C3	5258.6(13)	8254.3(10)	8460.0(5)	23.52(19)
C4	3938.1(12)	5900.4(11)	8490.2(6)	23.78(19)
C5	7427.8(10)	5771.5(8)	8203.2(4)	14.10(15)
C6	10640.2(11)	3720.0(9)	7693.7(4)	17.45(17)
C7	10295.8(10)	3628.1(9)	6974.4(4)	17.12(16)
C8	9755.5(10)	3620.2(9)	6394.4(4)	16.70(16)
C9	9138(1)	3434.1(9)	5706.8(4)	15.84(16)
C10	9507.8(12)	2185.2(10)	5382.1(5)	20.89(18)
C11	8934.5(13)	1915.0(11)	4720.7(5)	24.6(2)
C12	8004.2(14)	2896.2(11)	4371.6(5)	26.6(2)
C13	7632.7(13)	4139(1)	4683.5(5)	22.76(19)

C14	8181(1)	4422.3(9)	5354.2(4)	16.22(16)
C15	7742.8(11)	5751.2(9)	5685.8(4)	17.15(16)
C16	6707.6(17)	7994.0(11)	5499.4(6)	31.3(2)

IIX-4. j) References (237-247)

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IIX-5. Peptidomimetics as HDAC Inhibitors

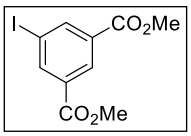
The syntheses of all compounds associated with Chapter V are published in ChemMedChem "*SAR of Propargylamine-Based HDAC Inhibitors*" [2] and are attached to the Appendix.

IIX-6. Peptidomimetics as RGD-Mimetics

IIX-6. a) Synthesis of Aromatic Halides (120-124)

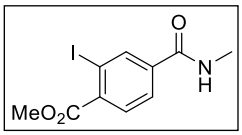
Dimethyl 5-Iodoisophthalate (120). The *Sandmeyer* reactions were performed in analogy to the work of Aiken, Gabbutt, Heron, Instone, Horton and Hursthouse [221]. Compound **120** has been first described by Sundberg and Heintzelman, who prepared it in a different way [248]. Dimethyl 5-aminoisophthalate (1.02 g, 4.88 mmol, 1 eq) was dissolved in aqueous hydrochloric acid (6 M, 5 mL, 1 mL/mmol) and the solution was cooled to -40 °C. An aqueous solution of $NaNO_2$ (408 mg, 5.91 mmol, 1.2 eq in 2.2 mL H_2O) was added dropwise under vigorous stirring. The solution was warmed to rt and solid KI (1.62 g, 9.76 mmol, 2 eq) and I_2 (122 mg, 480 μmol, 0.1 eq) was added in one portion, which lead to the precipitation of a black solid. Heating to 60 °C for 1 h completed the reaction (checked by TLC). The reaction mixture was diluted with a $KHSO_4$ solution (5 %, 10 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product of halogenated isophthalate **120** was filtered through a pad of silica gel with a mixture of EtOAc/PE (1:10).

Slightly yellow, crystalline solid. Yield: 767 mg, 2.39 mmol, 49 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.63 (t, ^4J = 1.5 Hz, 1H, ar-2-**H**), 8.54 (d, ^4J = 1.5 Hz, 2H, ar-4-**H**, ar-6-**H**), 3.95 (s, 6H, ar-1-$CO_2C\mathbf{H_3}$, ar-3-$CO_2C\mathbf{H_3}$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.0 (ar-1-$\mathbf{C}O_2CH_3$, ar-3-$\mathbf{C}O_2CH_3$), 142.6 (ar-**C**-4, ar-**C**-6), 132.3 (ar-**C**-3, ar-**C**-1), 130.0 (ar-**C**-2), 93.6 (ar-**C**-5), 52.8 (ar-1-$CO_2\mathbf{C}H_3$, ar-3-$CO_2\mathbf{C}H_3$). $C_{10}H_9IO_4$ (320.08 g mol^{-1}). MS(ESI): *m/z* = 320.908 (calcd. 320.9618 $[M+H]^+$). TLC: R*f* (EtOAc/PE, 1:10) = 0.2.



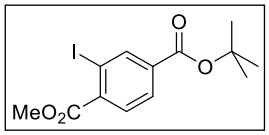
When the addition of $NaNO_2$ was attempted with insufficient cooling, hydroxylation was observed as side reaction, giving dimethyl 5-hydroxyisophthalate in a yield of 30 %. X-ray crystal structure in Chapter IIX-6. i.

***N,O*-Dimethyl 2-Iodoterephthalamate (121)**. Under argon atmosphere, a solution of 1-methyl 2-iodo terephthalat (**38a**, 694 mg, 2.27 mmol, 1.0 eq) in dry THF (10 mL) was cooled to -30 °C. IBCF (0.3 mL, 2.31 mmol, 1.0 eq) and NMM (0.15 mL, 1.36 mmol, 0.6 eq) was simultaneously added dropwise. The formation of a thin, colorless precipitate was observed. After 30 min, methylamine (0.75 mL, 16.7 mmol, 7.3 eq) was slowly added and the reaction mixture was stirred for another 4 h at -30 °C. After complete conversion of the terephthalate (checked by TLC), the reaction mixture was diluted with aqueous HCl (1 M, 30 mL) and the solution was stirred for 3 days at ambient temperature, while it turned a brightly orange emulsion. EtOAc (10 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The dark brown crude product was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) to yield the title compound **121** in pure form.



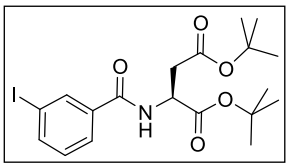
Faintly orange solid. Yield: 308 mg, 0.97 mmol, 43 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.34 (d, ^4J = 1.6 Hz, 1H, ar-3-**H**), 7.84 (dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, 1H, ar-5-**H**), 7.77 (d, ^3J = 8.0 Hz, 1H, ar-6-**H**), 6.11 (s br., 1H, ar-4-CON**H**CH_3), 3.95 (s, 3H, ar-1-CO_2C**H**$_3$), 3.03 (d, ^3J = 5.0 Hz, 3H, ar-4-CONHC**H**$_3$). $C_{10}H_{10}INO_3$ (319.10 g mol^{-1}).

4-(*tert*-Butyl) 1-Methyl 2-Iodoterephthalate (122). The preparation of ester **122** was performed in analogy to the work of Pintér, Haberhauer, Hyla-Krypsin and Grimme [249]. Compound **122** has been mentioned before by Hangauer and Bertozzi, who prepared it in a different way [250]. 1-Methyl 2-iodo terephthalate (**38a**, 748 mg, 2.45 mmol, 1.0 eq) was dissolved under an argon atmosphere in dry THF (18 mL). 4-Dimethylaminopyridine (88 mg, 0.72 mmol, 0.3 eq) and Boc_2O (586 mg, 2.69 mmol, 1.1 eq) was added in one portion under vigorous stirring. While the reaction mixture was stirred overnight at room temperature, it turned into a brightly orange color. After complete conversion of the starting material (checked by TLC), the solvent was evaporated under reduced pressure. The crude product was diluted with aqueous hydrochloric acid (1 M) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) to yield title



compound **122** in form of a light orange solid. Yield: 442 mg, 1.22 mmol, 50 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.54 (s, 1H, ar-3-**H**), 7.98 (d, ^{3}J = 8.1 Hz, 1H, ar-6-**H**), 7.78 (d, ^{3}J = 8.1 Hz, 1H, ar-5-**H**), 3.95 (s, 3H, ar-1-$CO_2C\mathbf{H_3}$), 1.60 (s, 9H, ar-4-$CO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 166.8 (ar-1-$\mathbf{C}O_2CH_3$), 163.5 (ar-4-$\mathbf{C}O_2C(CH_3)_3$), 142.1 (ar-**C**-3), 138.8 (ar-**C**-1), 135.6 (ar-**C**-4), 130.5 (ar-**C**-6), 128.9 (ar-**C**-5), 93.5 (ar-**C**-2), 82.5 (ar-4-$CO_2\mathbf{C}(CH_3)_3$), 52.9 (ar-1-$CO_2\mathbf{C}H_3$), 28.3 (ar-4-$CO_2C(\mathbf{C}H_3)_3$). $C_{13}H_{15}IO_4$ (362.16 g mol^{-1}).

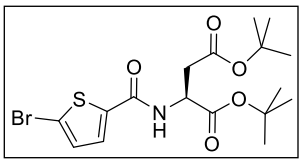
Di-*tert*-butyl (3-Iodobenzoyl)-L-aspartate (123). Oxalylchloride (0.11 mL, 1.28 mmol, 2.0 eq) was slowly added to a suspension of 3-iodobenzoate (317 mg, 1.28 mmol, 2.0 eq) in a mixture of CH_2Cl_2/DMF (15 mL, 2:1) at 0 °C over a period of 10 min. The reaction mixture was stirred for 2 h at rt, until the conversion of the starting material was complete (checked by TLC). A solution of di-*tert*-butyl aspartate (182 mg, 0.64 mmol, 1.0 eq) in THF (5 mL), DIPEA (1.3 mL, 0.96 g, 7.44 mmol, 9.2 eq) was added dropwise, followed by DMAP (10 mg, 82 μmol, 0.1 eq) and the reaction mixture was stirred on at rt. After another 24 h, the solution was diluted with water (30 mL) and a saturated NH_4Cl-solution (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic layers were washed with water (50 mL), brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvent lead to the slightly brown crude product of **123**, which was purified by column chromatography (PE/EtOAc, 4:1).



Colorless, crystalline solid. Yield: 146.5 mg, 308 μmol, 48 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.15 (s, 1H, ar-2-**H**), 7.84 (d, ^{3}J = 7.9 Hz, 1H, ar-6-**H**), 7.75 (d, ^{3}J = 7.8 Hz, 1H, ar-4-**H**), 7.17 (t, ^{3}J = 7.9 Hz, 1H, ar-5-**H**), 7.15 (d br., ^{3}J = 7.2 Hz, 1H, ar-1-CON**H**C^{α}H), 4.84 (ddd, ^{3}J = 8.1 Hz, ^{3}J = 4.2 Hz, ^{3}J = 4.3 Hz, 1H, NHC^{α}**H**$C^{\beta}H_2CO_2$), 2.98 (dd, ^{2}J = 17.1 Hz, ^{3}J = 4.2 Hz, 1H, NH$C^{\alpha}HC^{\beta}$**H**$_2CO_2$), 2.84 (dd, ^{2}J = 17.1 Hz, ^{3}J = 4.3 Hz, 1H, NH$C^{\alpha}HC^{\beta}$**H**$_2CO_2$), 1.49 (s, 9H, $CO_2C(C\mathbf{H_3})_3$), 1.45 (s, 9H, $CO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.6 (NH$C^{\alpha}HC^{\beta}H_2$**C**O_2), 169.9 (NHC^{α}**H**CO_2), 165.5 (ar-1-**C**ONHC^{α}H), 140.7 (ar-**C**-6), 136.4 (ar-**C**-2), 136.2 (ar-**C**-1), 130.4 (ar-**C**-5), 126.3 (ar-**C**-4), 94.4 (ar-**C**-3), 82.8 ($CO_2\mathbf{C}(CH_3)_3$), 81.9 ($CO_2\mathbf{C}(CH_3)_3$), 49.7 (NH$\mathbf{C^{\alpha}}HC^{\beta}H_2$), 37.6 (NH$C^{\alpha}H\mathbf{C^{\beta}}H_2$), 28.2 ($CO_2C(\mathbf{C}H_3)_3$), 28.1 ($CO_2C(\mathbf{C}H_3)_3$). $C_{19}H_{26}INO_5$ (475.32 g mol^{-1}).

MS(ESI): *m/z* = 476.0906 (calcd. 476.0928 $[M+H]^+$), 498.0730 (calcd. 498.0748 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.55.

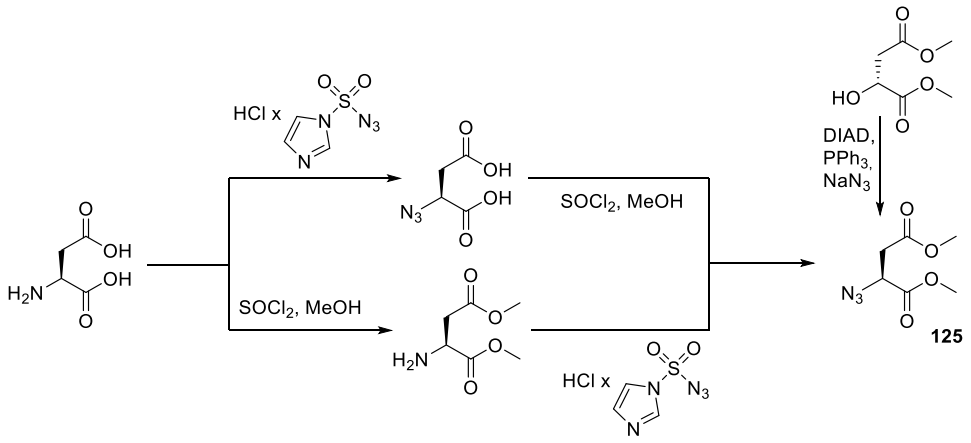
Di-*tert*-butyl (5-Bromothiophene-2-carbonyl)-L-aspartate (124). Oxalylchloride (0.11 mL, 1.28 mmol, 2.0 eq) was slowly added to a suspension of 5-bromothiophene-2-carboxylic acid (265 mg, 1.28 mmol, 2.0 eq) in a mixture of CH_2Cl_2/DMF (5 mL, 99:1) at 0 °C over a period of 10 min. The reaction mixture was stirred for 2 h at rt, until the conversion of the starting material was complete (checked by TLC). A solution of di-*tert*-butyl aspartate (182 mg, 0.64 mmol, 1.0 eq) in THF (5 mL), DIPEA (1.3 mL, 0.96 g, 7.44 mmol, 9.2 eq) was added dropwise, followed by DMAP (10 mg, 82 µmol, 13 mol%) and the reaction mixture was stirred on at rt. After another 24 h, the solution was diluted with water (20 mL) and a saturated NH_4Cl solution (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (5 x 30 mL). The combined organic layers were washed with water (30 mL), brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent lead to the slightly brown crude product of **124**, which was purified by column chromatography (PE/EtOAc, 4:1).



Colorless, crystalline solid. Yield: 85.0 mg, 195 µmol, 30 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.28 (d, ^3J = 3.8 Hz, 1H, thiophene-3-**H**), 7.04 (d, ^3J = 3.9 Hz, 1H, thiophene-4-**H**), 6.99 (d, ^3J = 7.9 Hz, 1H, $C^{\alpha}HN\mathbf{H}CO$), 4.78 (ddd, ^3J = 7.8 Hz, ^3J = 4.3 Hz, ^3J = 4.1 Hz, 1H, $C^{\alpha}\mathbf{H}$), 2.95 (dd, ^2J = 17.2 Hz, ^3J = 4.4 Hz, 1H, $C^{\alpha}HC^{\beta}\mathbf{H}_2$), 2.82 (dd, ^2J = 17.1 Hz, ^3J = 4.3 Hz, 1H, $C^{a}HC^{b}\mathbf{H}_2$), 1.47 (s, 9H, $CO_2C(C\mathbf{H_3})_3$), 1.45 (s, 9H, $CO_2C(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.5 ($C^{\alpha}HC^{\beta}H_2\mathbf{C}O_2C(CH_3)_3$), 160.5 ($C^{\alpha}H\mathbf{C}O_2C(CH_3)_3$), 159.0 ($C^{\alpha}NH\mathbf{C}O$), 140.1 (thiophene-**C**-2), 130.8 (thiophene-**C**-3), 128.5 (thiophene-**C**-4), 118.5 (thiophene-**C**-5), 82.9 ($C^{\alpha}HC^{\beta}H_2CO_2\mathbf{C}(CH_3)_3$), 81.9 ($C^{\alpha}HCO_2\mathbf{C}(CH_3)_3$), 49.6 ($\mathbf{C^{\alpha}}HC^{\beta}H_2$), 37.6 ($C^{\alpha}H\mathbf{C^{\beta}}H_2CO_2C(CH_3)_3$), 28.2 ($C^{\alpha}HC^{\beta}H_2CO_2C(\mathbf{C}H_3)_3$), 28.1 ($C^{\alpha}HCO_2C(\mathbf{C}H_3)_3$). $C_{17}H_{24}BrNO_5S$ (434.35 g mol^{-1}). MS(ESI): *m/z* = 456.04570 (calcd. 456.0451 $[M+Na]^+$). TLC: R*f* (PE/EtOAc, 4:1) = 0.59.

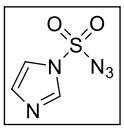
IIX-6. b) Azides in Aspartic Acid Derivatives (125-126)

Dimethyl (*S*)-2-Azidosuccinate (125).



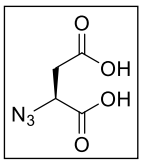
Scheme EP3. Different synthesis pathways for the preparation of azide **125**.

1H-Imidazol-1-sulfurylazide Hydrochloride. The synthesis and application of the azide transfer reagent was carried out according to Wang *et al.* [251]. Sulfurylchloride (5.0 mL, 61.8 mmol, 1.0 eq) was added at 0 °C to a solution of NaN_3 (4.10 g, 62.9 mmol, 1.0 eq) in dry CH_3CN (30 mL). After stirring the reaction mixture 16 h at ambient temperature, imidazole 88.43 g, 124 mmol, 2.0 eq) was added at 0 °C and the solution was allowed to warm up to room temperature. The mixture was diluted in EtOAc and washed with water (2 x 30 mL) and saturated aqueous $NaHCO_3$ (30 mL) and dried over Na_2SO_4. A Solution of HCl (6.5 mL of acetylchloride in 25 mL of absolute EtOH) was added to the solution of crude material in EtOAc at 0 °C. Immediately, a colorless precipitate formed, which was filtered off, washed with a few milliliters of ice cold EtOAc and dried under vacuum. 1H-Imidazol-1-sulfurylazide was isolated in form of a colorless solid.



Yield: 8.81 g, 50.9 mmol, 82 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.53 (m, 1H, imidazole-2-**H**), 7.95 (d, ^4J = 1.5 Hz, 1H, imidazole-4-**H**), 7.30 (d, ^4J = 2.3 Hz, 1H, imidazole-5-**H**). $C_3H_3N_5O_2S$ (173.15 g mol^{-1}).

(*S*)-2-Azidosuccinic Acid. This synthesis was performed analogously to the procedure of

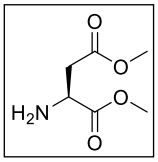


Bachl *et al.*, who prepared a glutamic acid based azide [252]. (*S*)-2-Azidosuccinic acid has been first described by Li *et al.* [141]. Imidazol-1-sulfonylazide hydrochloride (1.88 g, 9 mmol, 1.2 eq), K_2CO_3 (2.8 g, 20 mmol,

2.7 eq) and $CuSO_4$ x 5 H_2O (19 mg, 75 µmol, 1 mol%) was added in small portions to a solution of (*S*)-aspartic acid (1.0 g, 7.5 mmol, 1.0 eq) in MeOH (10 mL). After stirring for 15 h at room temperature, the solvent was evaporated under reduced pressure. The residue was diluted with water (15 mL) the pH value was adjusted to 2 by the addition of aqueous HCl (1 M) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to yield (*S*)-2-azidosuccinic acid in pure form.

Yellow solid. Yield: 336 mg, 2.1 mmol, 28 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 10.97 (s, 2H, CO_2**H**), 4.42 (dd, ^3J = 7.5 Hz, ^3J = 5.0 Hz, 1H, C$^\alpha$**H**), 2.91 (dd, ^2J = 17.2 Hz, ^3J = 5.2 Hz, 1H, C$^\alpha$C**H**$_2$), 2.78 (dd, ^2J = 17.3 Hz, ^3J = 7.5 Hz, 1H, C$^\alpha$C**H**$_2$). $C_4H_5N_3O_4$ (159.10 g mol^{-1}). $[\alpha]_{589}^{20}$ = -137 (*c* 0.57, $CHCl_3$). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 3249 (OH), 2961 (CH), 2106 (N_3), 1720 (CO), 1359 (CH_2), 1182 (OH).

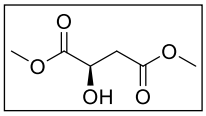
Dimethyl L-Aspartate. The synthesis was carried out according to Jung and Fletcher [253]. Under argon atmosphere, thionyl chloride (5.62 g, 47.3 mmol, 2.1 eq) was added dropwise to a solution of (*S*)-aspartic acid (3.00 g, 22.5 mmol, 1.0 eq) in MeOH (30 mL). The reaction mixture was stirred for 15 h at 60 °C. After cooling down to room temperature, the pH value of the solution was adjusted to 8 by adding a saturated solution of $NaHCO_3$. Extracted with Et_2O (3 x 20 mL), combination of the organic layers, drying over Na_2SO_4 and evaporation of the solvent lead to the isolation of dimethyl (*S*)-aspartic acid. Slightly yellow oil. Yield: 1.432 g, 8.88 mmol, 39 % (Lit: 100 % [253]). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 3.83 (dd, ^3J = 7.4 Hz, ^3J = 4.7 Hz, 1H, C$^\alpha$**H**), 3.75 (s, 3H, CO_2C**H**$_3$), 3.71 (s, 3H, CO_2C**H**$_3$), 2.81 (dd, ^2J = 16.5 Hz, ^3J = 4.6 Hz, 1H, C$^\alpha$C**H**$_2$), 2.71 (dd, ^2J = 16.5 Hz, ^3J = 7.4 Hz, 1H, C$^\alpha$C**H**$_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 174.8 (**C**O_2CH_3), 171.8 (**C**O_2CH_3), 52.5 (CO_2**C**H_3), 52.1 (CO_2**C**H_3), 51.3 (**C**$^\alpha$), 38.9 (C$^\alpha$**C**H_2). $C_6H_{11}NO_4$ (161.16 g mol^{-1}). TLC: R*f* (EtOAc/PE, 1:4) = 0.36.



Dimethyl Malate. The methylation of Äpfelsäure was performed according to Hao Bao-Yu *et al.* [254]. Thionylchloride (7.5 mL, 104 mmol, 3.1 eq) was added dropwise to a solution of D-Äpfelsäure (4.46 g, 33.3 mmol, 1.0 eq) in dry methanol. The reaction mixture was stirred for 5 h at rt. Afterwards, the solvent was evaporated. The residue was dissolved in

an aqueous solution of NH_4Cl (saturated, 30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na2SO4 and the solvent was evaporated to yield the dimethyl malate in pure form.

Pale, yellow liquid. Yield: 3.547 g, 21.9 mmol, 66 %. ^{1}H NMR (500 MHz, Chloroform-*d*)

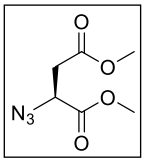


δ = 4.50 (ddd, ^3J = 5.8 Hz, ^3J = 5.5 Hz, ^3J = 4.4 Hz, 1H, C^{α}**H**OH), 3.81 (s, 3H, $C^{\alpha}HCO_2C$**H**$_3$), 3.71 (s, 1H, $C^{\alpha}HCH_2CO_2C$**H**$_3$), 3.23 (d, ^3J = 5.6 Hz, 1H, $C^{\alpha}HO$**H**), 2.93-2.72 (m, 2H, $C^{\alpha}HC$**H**$_2CO_2CH_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 173.8 ($C^{\alpha}H$**C**O_2CH_3), 171.1 ($C^{\alpha}HCH_2$**C**O_2CH_3), 67.4 (**C**$^{\alpha}$HOH), 53.0 ($C^{\alpha}HCO_2$**C**H_3), 52.2 ($C^{\alpha}HCH_2CO_2$**C**H_3), 38.6 ($C^{\alpha}H$**C**$H_2CO_2CH_3$). $C_6H_{10}O_5$ (162.14 g mol^{-1}).

Dimethyl (*S*)-2-Azidosuccinate (125). The azide transfer was carried out as proposed by Wang *et al.* [251], as well as by Bachl *et al.*, who prepared a glutamic acid based azide in an analogous manner [252]. To a solution of dimethyl-(*S*)-aspartic acid (1.43 g, 8.88 mmol, 1.0 eq) in methanol (15 mL), imidazol-1-sulfonylazide hydrochloride (2.23 g, 10.7 mmol, 1.2 eq), K_2CO_3 (3.31 g, 24.0 mmol, 2.7 eq) and $CuSO_4$ x 5 H_2O (22 mg, 88 µmol, 1 mol%) were added one after another. After stirring the reaction mixture 15 h at rt, the solvent was evaporated. The residue was dissolved in aqueous HCl (20 mL, pH = 2) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Dimethyl (*S*)-2-azidosuccinate (**125**, 336 mg, 2.1 mmol, 28 %, total: 11 %, over two steps) was obtained in form of a slightly orange, crystalline solid.

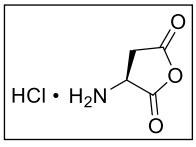
Thionylchloride (403 mg, 3.38 mmol, 2.1 eq) was added dropwise to a solution of (*S*)-2-azidosuccinic acid (257 mg, 1.61 mmol, 1.0 eq) in dry methanol (5 mL) at 0 °C. After 15 h of stirring the reaction mixture at rt, the solvent was evaporated. The residue was dissolved in an aqueous solution of NH_4Cl (saturated, 10 mL) and an aqueous solution of NaOH (1 M) was added dropwise to adjust the pH value to 8. The solution was extracted with Et_2O (3 x 20 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to yield dimethyl (*S*)-2-azidosuccinate (**125**, 56.6 mg, 1.07 mmol, 16 %, total: 4 %, over two steps) in form of a slightly orange, crystalline solid.

The *Mitsunobu* reaction was carried out according to Castro *et al.* [142]. The (*R*)-configured analogue of azide **125** has been described by Hoffman and Kim [255]. Simultaneously, a solution of DPPA (9.5 mL, 44.1 mmol, 2.0 eq) in THF (10 mL) and a solution of dimethyl malate (3.55 g, 21.9 mmol, 1 eq) in THF (10 mL) were added dropwise into a suspension of DIAD (4.2 mL, 22.2 mmol, 1 eq) and triphenylphosphane (5.75 g, 21.9 mmol, 1 eq) in THF (40 mL) at 0 °C. After stirring the reaction mixture for 17 h at rt, the reaction mixture was poured into an aqueous NH_4Cl solution (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After evaporating the solvent under reduced pressure, the crude material was dissolved in PE and filtered. Silica gel was added to the filtrate to adsorb crude product **125** and dimethyl-(*S*)-2-azidsuccinat and separate them by column chromatography.



Pale yellow, highly viscous oil. Yield: 754.4 mg, 4.03 mmol, 18 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 4.32 (dd, ^3J = 7.8 Hz, ^3J = 5.3 Hz, 1H, $N_3C^{\alpha}\mathbf{H}$), 3.73 (s, 3H, $C^{\alpha}HCO_2C\mathbf{H_3}$), 3.63 (s, 3H, $C^{\alpha}HCH_2CO_2C\mathbf{H_3}$), 2.78 (dd, ^2J = 16.7 Hz, ^3J = 5.3 Hz, 1H, $C^{\alpha}HC\mathbf{H}_2$), 2.64 (dd, ^2J = 16.8 Hz, ^3J = 7.8 Hz, 1H, $C^{\alpha}HC\mathbf{H}_2$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.0 ($C^{\alpha}\mathbf{C}O_2CH_3$), 169.5 ($C^{\alpha}HCH_2\mathbf{C}O_2CH_3$), 58.2 ($N_3\mathbf{C}^{\alpha}H$), 52.8 ($CO_2\mathbf{C}H_3$), 52.0 ($CO_2\mathbf{C}H_3$), 35.8 ($C^{\alpha}H\mathbf{C}H_2$). $C_6H_9N_3O_4$ (187.16 g mol^{-1}). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 2977 (CH), 2107 (N_3), 1733 (CO_2Me), 1711 (CO_2CH_3), 1613, 1454, 1366, 1299, 1245, 1144, 919, 846, 733, 669. $[\alpha]_{589}^{20}$ = -38.58 (*c* 1.244, $CHCl_3$).

(*S*)-3-Aminosuccinic anhydride. This synthesis was performed in accordance with the

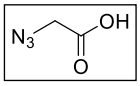


description of Yan *et al.* [256]. Under argon atmosphere, PCl_3 (2.75 g, 15.87 mmol, 0.4 eq) was added dropwise to a solution of (*S*)-aspartic acid (5.00 g, 37.57 mmol, 1 eq) in THF (15 mL). A colorless precipitate formed, which was filtered off after 15 h and washed with cold THF. The colorless, crystalline solid was dried under reduced pressure and stored under argon atmosphere.

Colorless crystalline solid. Yield: 6.01 g, 36.32 mmol, 97 % (Lit: 100 % [256]). $C_4H_6ClNO_3$ (151.55 g mol^{-1}). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 2967 (CH), 2863 (CH_2), 1802 (C=O), 1774 (C=O).

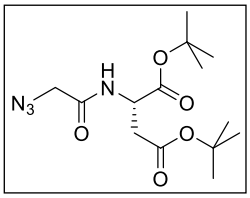
Di-*tert*-butyl (2-Azidoacetyl)-L-aspartate (126)

2-Azidoacetic Acid. The synthesis of 2-azidoacetic acid has been performed as described by Liu *et al.* [257]. In one portion, NaN_3 (1.38 g, 18.0 mmol, 5 eq) was added at 0 °C to an aqueous solution of 2-bromoacetic acid (500 mg, 3.60 mmol, 0.72 M, 1 eq). The faintly yellow reaction mixture was stirred for 48 h at room temperature. After complete conversion of the starting material (checked by TLC), the solution was acidified with aqueous HCl (2 mL) to pH 2 and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure.



Highly viscous, colorless oil. Yield: 350 mg, 3.46 mmol, 96 % (Lit: 95 % [257]). ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 10.86 (s, 1H, CO_2**H**), 3.97 (s, 2H, N_3C**H$_2$**). $C_2H_3N_3O_2$ (101.07 g mol^{-1}). IR(ATR): $\tilde{\nu}$ [cm^{-1}] = 2965 (OH), 2936 (CH), 2876 (CH), 2103 (N_3), 1708 (CO_2H), 1451, 1229, 945.

Di-*tert*-butyl (2-Azidoacetyl)-L-aspartate (126). A mixture of 2-azidoacetic acid (184 mg, 1.82 mmol, 1.0 eq), di-*tert*-butyl aspartate (515 mg, 1.83 mmol, 1.0 eq), HOAt (75.2 mg, 0.55 mmol, 0.3 eq) and HATU (1.390 mg, 3.66 mmol, 2.0 eq) was placed under argon atmosphere in a *Schlenk*-flask. A mixture of CH_2Cl_2/DMF/DIPEA (17 mL, 59:30:11) was added until the mixture was completely dissolved. After stirring the reaction mixture for 2 days at rt, brine (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water (50 mL), brine (10 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude product of **126** was purified by column chromatography (PE/EtOAc, 4:1).

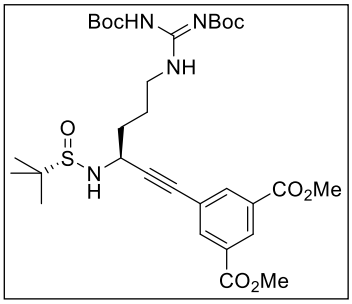


Colorless, crystalline solid. Yield: 458.4 mg, 1.396 mmol, 77 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 7.24 (d br., ^3J = 8.3 Hz, 1H, CON**H**), 4.66 (ddd, ^3J = 8.6 Hz, ^3J = 4.3 Hz, ^3J = 4.4 Hz, 1H, C$^{\alpha}$**H**), 3.99-3.95 (m, 2H, N_3C**H$_2$**CONH), 2.88 (dd, ^2J = 16.9 Hz, ^3J = 4.3 Hz, 1H, C$^{\alpha}$HC**H**$_2$CO$_2$), 2.69 (dd, ^2J = 17.2 Hz, ^3J = 4.2 Hz, 1H, C$^{\alpha}$HC**H**$_2$CO$_2$), 1.44 (s, 9H, C$^{\alpha}$HCO$_2$C(C**H$_3$**)$_3$), 1.43 (s, 9H, C$^{\alpha}$HCH$_2$CO$_2$C(C**H$_3$**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.0 (C$^{\alpha}$H**C**O$_2$C(CH$_3$)$_3$), 169.3 (C$^{\alpha}$HCH$_2$**C**O$_2$C(CH$_3$)$_3$), 166.5 (N$_3$CH$_2$**C**ONH),

82.7 ($C^{\alpha}HCO_2\mathbf{C}(CH_3)_3$), 81.9 ($C^{\alpha}HCH_2CO_2\mathbf{C}(CH_3)_3$), 52.6 ($N_3\mathbf{C}H_2CO$), 49.1 ($\mathbf{C}^{\alpha}H$), 37.4 ($C^{\alpha}H\mathbf{C}H_2$), 28.1 ($C^{\alpha}HCO_2C(\mathbf{C}H_3)_3$), 28.0 ($C^{\alpha}HCH_2CO_2C(\mathbf{C}H_3)_3$). $C_{14}H_{24}N_4O_5$ (328.37 g mol^{-1}). MS(ESI): *m/z* = 351.1675 (calcd. 351.1639 $[M+Na]^+$). Mp = 56.1 °C (+/- 0.6 K). $[\alpha]_{589}^{20}$ = +10.67 (*c* 1.28, $CHCl_3$).

IIX-6. c) Synthesis of Peptidomimetics 127-132 by *Click*-Reactions

Dimethyl 5-((*S*)-6-((*Z*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)-3-(((*S*)-*tert*-butylsulfinyl)amino)hex-1-yn-1-yl)isophthalate (127). *Sonogashira* cross-coupling: Under *Schlenk*-conditions, piperidine (0.3 mL) was added to a solution of propargylamide **6x** (109 mg, 239 µmol, 1.0 eq) and dimethyl 5-iodo isophthalat (**120**, 157 mg, 491 µmol, 2.1 eq) in THF (1.0 mL). The reaction mixture was thoroughly degassed by freeze pump thaw method. The catalysts, $PdCl_2(PPh_3)_2$ (21 mg, 30 µmol, 0.1 eq) and CuI (14 mg, 74 µmol, 0.3 eq) were added to the frozen reaction mixture and the solution slowly warmed up to room temperature. After 45 min, a colorless precipitate formed in the clear solution, indicating the progress of the reaction. 21 h later, the suspension was diluted with a saturated aqueous NH_4Cl solution (10 mL) and $KHSO_4$ (aq, 5 %, 4 mL) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O (20 mL), the organic layer separated and the aqueous layer extracted to more times with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product of **127** was purified by column chromatography (PE/EtOAc, 1:1).

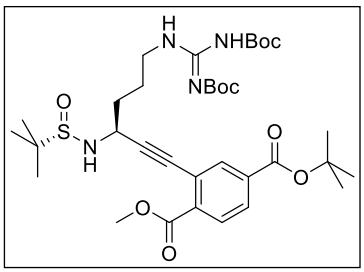


Colorless, highly viscous oil. Yield: 66.5 mg, 102 µmol, 43 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 11.48 (s br., 1H, N**H**Boc), 8.58 (d, ^4J = 1.8 Hz, 1H, ar-2-**H**), 8.35 (t br., ^3J = 5.3 Hz, 1H, CN**H**CH_2), 8.23 (t, ^4J = 1.8 Hz, 2H, ar-4-**H**, ar-6-**H**), 4.32 (ddd, ^3J = 6.6 Hz, ^3J = 6.2 Hz, ^3J = 5.3 Hz, 1H, C^{α}**H**), 3.92 (s, 6H, $(CO_2C\mathbf{H_3})_2$), 3.50 (m, 1H, ^{t}BuSN**H**), 3.49-3.44 (m, 2H, NHC$\mathbf{H_2}$), 1.89-1.82 (m, 2H, $C^{\alpha}HC\mathbf{H_2}$), 1.82-1.76 (m, 2H, $C^{\alpha}HCH_2C\mathbf{H_2}$), 1.47 (s, 9H, $C{=}NCO_2C(C\mathbf{H_3})_3$), 1.46 (s, 9H, $CHNCO_2C(C\mathbf{H_3})_3$), 1.23 (s, 9H, $SC(C\mathbf{H_3})_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.6 ($ar(\mathbf{C}O_2CH_3)_2$), 163.7 ($N{=}\mathbf{C}N_2$), 156.3 ($C{=}N\mathbf{C}O_2C(CH_3)_3$), 153.4 ($CHN\mathbf{C}O_2C(CH_3)_3$), 136.8 (ar-**C**-4, ar-**C**-6), 131.0 (ar-**C**-1, ar-**C**-3), 130.4 (ar-**C**-2), 123.6 (ar-**C**-5), 90.6 ($C{=}NCO_2\mathbf{C}(CH_3)_3$), 83.3 ($C^{\alpha}HC{\equiv}\mathbf{C}$-ar), 83.2

($CHNCO_2\mathbf{C}(CH_3)_3$), 79.4 ($C^{\alpha}H\mathbf{C}{\equiv}C$-ar), 56.4 ($S\mathbf{C}(CH_3)_3$), 52.6 ($CO_2\mathbf{C}H_3$), 47.9 ($\mathbf{C}^{\alpha}$), 40.3 ($CHN\mathbf{C}H_2$), 34.1 ($C^{\alpha}\mathbf{C}H_2$), 28.4 ($C{=}NCO_2C(\mathbf{C}H_3)_3$), 28.2 ($CHNCO_2C(\mathbf{C}H_3)_3$), 25.4 ($C^{\alpha}CH_2\mathbf{C}H_2$), 22.7 ($SC(\mathbf{C}H_3)_3$). $C_{31}H_{46}N_4O_9S$ (650.79 g mol^{-1}). MS(ESI): *m/z* = 651.3047 (calcd. 651.30583 $[M+H]^+$).

The synthesis of peptidomimetics **128a,b** was attempted in an analog way to **128c**, using halogenides **38a** and **121** as starting material. However, none of the products **128a,b** could be isolated.

4-(*tert*-Butyl) 1-Methyl 2-((*S*)-6-((*E*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)-3-(((*S*)-*tert*-butylsulfinyl)amino)hex-1-yn-1-yl)terephthalate (128c). *Sonogashira* cross-coupling: Under *Schlenk*-conditions, piperidine (0.6 mL) was added to a solution of arginine analogous propargylamide **6x** (262 mg, 572 μmol, 1.0 eq) and 4-(*tert*-butyl)-1-methyl 2-iodoterephthalate (**122**, 350 mg, 966 μmol, 1.7 eq) in THF (2.0 mL). The reaction mixture was thoroughly degassed by freeze pump thaw method. The catalysts, $PdCl_2(PPh_3)_2$ (15 mg, 21 μmol, 4 mol%) and CuI (17 mg, 91 μmol, 0.2 eq) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After 60 min, a colorless precipitate formed in the clear solution, indicating the progress of the reaction. 30 h Later, the suspension was diluted with a saturated aqueous NH_4Cl solution (10 mL) and $KHSO_4$ (aq, 5 %, 6 mL) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O (20 mL), the organic layer separated and the aqueous layer extracted to more times with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. The crude product of **128c** was purified by column chromatography (PE/EtOAc, 1:1).

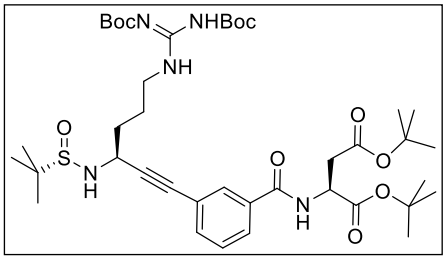


Colorless oil, Yield: 200 mg, 289 μmol, 52 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 11.44 (s br., 1H, N**H**Boc), 8.32 (t br., ^3J = 5.3 Hz, 1H, N**H**CN_2), 8.04 (d, ^4J = 1.6 Hz, 1H, ar-3-**H**), 7.89 (d, ^3J = 8.2 Hz, 1H, ar-6-**H**), 7.86 (dd, ^3J = 8.2 Hz, ^4J = 1.6 Hz, 1H, ar-5-**H**), 4.36 (ddd, ^3J = 5.6 Hz, ^3J = 4.8 Hz, ^3J = 5.2 Hz, 1H, C^{α}**H**), 3.86 (s, 3H, ar-1-$CO_2C\mathbf{H_3}$),

3.71 (d, ^{3}J = 5.4 Hz, 1H, $C^{\alpha}HN\mathbf{H}S$), 3.48-3.41 (m, 2H, $C^{\alpha}CH_2CH_2C\mathbf{H_2}$), 1.86-1.79 (m, 4H, $C^{\alpha}C\mathbf{H_2}CH_2$, $C^{\alpha}CH_2C\mathbf{H_2}$), 1.53 (s, 9H, ar-4-$CO_2C(C\mathbf{H_3})_3$), 1.43 (s, 9H, C=N$CO_2C(C\mathbf{H_3})_3$), 1.41 (s, 9H, CHN$CO_2C(C\mathbf{H_3})_3$), 1.20 (s, 9H, $SC(C\mathbf{H_3})_3$).^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.8 (ar-1-$\mathbf{C}O_2CH_3$), 164.1 (ar-4-$\mathbf{C}O_2C(CH_3)_3$), 163.6 (N=$\mathbf{C}N_2$), 156.2 (C=N$\mathbf{C}O_2C(CH_3)_3$), 153.2 (CHN$\mathbf{C}O_2C(CH_3)_3$), 135.1 (ar-**C**-4), 134.8 (ar-**C**-2), 134.8 (ar-**C**-3), 130.2 (ar-**C**-6), 128.7 (ar-**C**-5), 123.1 (ar-**C**-1), 94.3 ($C^{\alpha}H\mathbf{C}\equiv$C-ar), 83.3 ($C^{\alpha}HC\equiv\mathbf{C}$-ar), 83.0 (CHN$CO_2\mathbf{C}(CH_3)_3$), 82.1 (ar-4-$CO_2\mathbf{C}(CH_3)_3$), 79.2 (C=N$CO_2\mathbf{C}(CH_3)_3$), 56.2 ($S\mathbf{C}(CH_3)_3$), 52.4 (ar-1-$CO_2\mathbf{C}H_3$), 47.7 ($\mathbf{C}^{\alpha}$), 40.4 ($C^{\alpha}CH_2CH_2\mathbf{C}H_2$), 33.8 ($C^{\alpha}\mathbf{C}H_2$), 28.3 (CHN$CO_2C(\mathbf{C}H_3)_3$), 28.1 (C=N$CO_2C(\mathbf{C}H_3)_3$), 28.0 (ar-4-$CO_2C(\mathbf{C}H_3)_3$), 25.0 ($C^{\alpha}CH_2\mathbf{C}H_2$), 22.6 ($SC(\mathbf{C}H_3)_3$). $C_{34}H_{52}N_4O_9S$ (692.87 g mol^{-1}). MS(ESI): *m/z* = 693.1764 (calcd. 693.3528 $[M+H]^+$), 715.0878 (calcd. 715.3347 $[M+Na]^+$).

Di-*tert*-butyl (3-((*S*)-6-((*E*)-2,3-bis(*tert*-butoxycarbonyl)guanidino)-3-(((*S*)-*tert*-butylsulfinyl)amino)hex-1-yn-1-yl)benzoyl)-L-aspartate (129). *Sonogashira* cross-coupling: Under *Schlenk*-conditions, piperidine (183 µL, 1.85 mmol, 6.0 eq) was added to a solution of arginine analogous propargylamide **6x** (143 mg, 312 µmol, 1.0 eq) and di-*tert*-butyl (3-iodobenzoyl)-L-aspartate (**123**, 146.5 mg, 308 µmol, 1.0 eq) in dry THF (3.0 mL). The reaction mixture was thoroughly degassed by freeze pump thaw method. The catalysts, $PdCl_2(PPh_3)_2$ (7 mg, 10 µmol, 3 mol%) and CuI (5 mg, 30 µmol, 10 mol%) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After about 60 min, a colorless precipitate formed in the clear solution, indicating the progress of the reaction. Three days later, the suspension was diluted with a saturated aqueous NH_4Cl solution (10 mL) and Et_2O (10 mL), before the pH-value was brought to about 7 by the addition of an aqueous $KHSO_4$ solution (5 %, 2-3 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product of **129** was purified by column chromatography (PE/EtOAc, 1:1).

Colorless oil. Yield: 183.4 mg, 227.5 µmol, 74 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ =

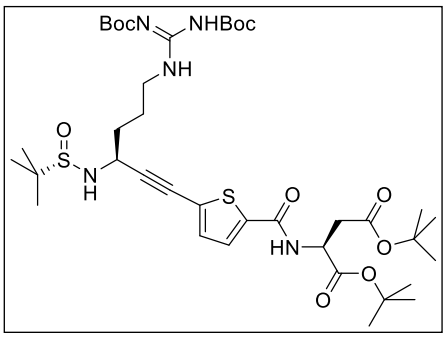


11.49 (s br., 2H, C(NBoc)N**H**Boc), 8.37 (t br., ^{3}J = 3.9 Hz, 1H, $C^{\delta}H_2N$**H**), 7.86 (s, 1H, ar-2-**H**), 7.75 (d, ^{3}J = 7.9 Hz, 1H, ar-6-**H**), 7.58 (d, ^{3}J = 7.7 Hz, 1H, ar-4-**H**), 7.38 (t, ^{3}J = 7.7 Hz, 1H, ar-5-**H**), 7.19 (d br., ^{3}J = 7.9 Hz, 1H, CO**H**N$C^{\alpha II}$H), 4.86 (ddd, ^{3}J = 7.8 Hz, ^{3}J = 7.2 Hz, ^{3}J = 4.3 Hz, 1H, $C^{\alpha II}$**H**), 4.35 (dd, ^{3}J = 6.1 Hz, ^{3}J = 7.1 Hz, ^{3}J = 4.5 Hz, 1H, $C^{\alpha I}$**H**), 3.23 (td, ^{3}J = 6.8 Hz, ^{3}J = 3.9 Hz, 2H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}$**H₂**NH), 3.07 (d br., ^{3}J = 6.8 Hz, 1H, N**H**$C^{\alpha I}$H), 2.97 (dd, ^{2}J = 17.4 Hz, ^{3}J = 4.3 Hz, 1H, $C^{\alpha II}HC^{\beta}$**H₂**CO_2), 2.85 (dd, ^{2}J = 16.9 Hz, ^{3}J = 4.3 Hz, 1H, $C^{\alpha II}HC^{\beta}$**H₂**CO_2), 1.85-1.78 (m, 2H, $C^{\alpha I}HC^{\beta}$**H₂**$C^{\gamma}H_2C^{\delta}H_2$NH), 1.75-1.67 (m, 2H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}$**H₂**$C^{\delta}H_2$NH), 1.50 (s, 9H, $C^{\alpha II}HC^{\beta}H_2CO_2C$(C**H₃**)₃), 1.49 (s, 9H, $C^{\alpha II}HCO_2C$(C**H₃**)₃), 1.44 (s, 18H, N=CO_2C(C**H₃**)₃, NHCO_2C(C**H₃**)₃), 1.21 (s, 9H, SC(C**H₃**)₃). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.6 ($C^{\alpha II}HC^{\beta}H_2$**C**$O_2$), 170.0 ($C^{\alpha II}$H**C**$O_2$), 166.2 (**C**OHN$C^{\alpha II}$H), 163.8 (NH**C**(=NBoc)NHBoc), 156.3 (N**C**$O_2C(CH_3)_3$), 153.4 (NH**C**$O_2C(CH_3)_3$), 135.1 (ar-**C**-6), 134.4 (ar-**C**-1), 130.5 (ar-**C**-2), 128.8 (ar-**C**-5), 128.2 (ar-**C**-3), 127.2 (ar-**C**-4), 89.6 ($C^{\alpha I}$H**C**≡Car), 84.4 (NCO_2**C**$(CH_3)_3$), 83.2 (NHCO_2**C**$(CH_3)_3$), 82.7 (CO_2**C**$(CH_3)_3$), 81.8 (CO_2**C**$(CH_3)_3$), 79.4 ($C^{\alpha I}$HC≡**C**ar), 56.6 (S**C**$(CH_3)_3$), 56.0 (**C$^{\alpha II}$**H), 49.7 (**C$^{\alpha I}$**H), 47.8 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2$**C$^{\delta}$**$H_2$NH), 40.9 ($C^{\alpha II}$H**C$^{\beta}$**$H_2CO_2$), 35.7 ($C^{\alpha I}$H**C$^{\beta}$**$H_2C^{\gamma}H_2C^{\delta}H_2$NH), 33.4 ($C^{\alpha I}HC^{\beta}H_2$**C$^{\gamma}$**$H_2C^{\delta}H_2$NH), 28.5 (N$CO_2C$(**C**$H_3)_3$), 28.2 ($C^{\alpha II}HC^{\beta}H_2CO_2C$(**C**$H_3)_3$, $C^{\alpha II}HCO_2C$(**C**$H_3)_3$), 28.1 (NHCO_2C(**C**$H_3)_3$), 22.9 (SC(**C**$H_3)_3$). $C_{40}H_{63}N_5O_{10}S$ (806.03 g mol^{-1}). MS(ESI): *m/z* = 806.43940 (calcd. 806.4368 $[M+H]^+$).

Di-*tert*-butyl (5-((*S*)-6-((*E*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)-3-(((*S*)-*tert*-butylsulfinyl)amino)hex-1-yn-1-yl)thiophene-2-carbonyl)-L-aspartate (130). *Sonogashira* cross-coupling: Under *Schlenk*-conditions, piperidine (116 µL, 1.17 mmol, 6.0 eq) was added to a solution of arginine analogous propargylamide **6x** (90 mg, 196 µmol, 1.0 eq) and di-*tert*-butyl (5-bromothiophene-2-carbonyl)-L-aspartate (**124**, 350 mg, 966 µmol, 1.7 eq) in THF (3.0 mL). The reaction mixture was thoroughly degassed by freeze pump thaw method. The catalysts, $PdCl_2(PPh_3)_2$ (7 mg, 10 µmol, 5 mol%) and CuI (5 mg, 30 µmol, 15 mol%) were added to the frozen reaction mixture and the solution slowly warmed to room temperature. After 60 min, a colorless precipitate

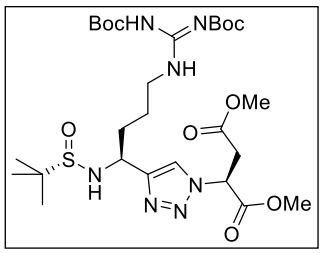
formed in the clear solution, indicating the progress of the reaction. After 30 h, the suspension was diluted with a saturated aqueous NH_4Cl solution (10 mL) and $KHSO_4$ (aq, 5 %, 6 mL) was added, until the organic layer started to turn faintly red (pH 5-6). The emulsion was diluted with Et_2O (20 mL), the organic layer separated and the aqueous layer extracted to more times with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuum. The crude product of **130** was purified by column chromatography (PE/EtOAc, 1:1).

Pale yellow oil. Yield: 101.8 mg, 125.4 μmol, 64 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 11.47 (s br., 1H, N=CN**H**Boc), 8.30 (s br., 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2N$**H**), 7.35 (d, ^3J = 3.8 Hz, 1H, thiophene-3-**H**), 7.12 (d, ^3J = 3.7 Hz, 1H, thiophene-4-**H**), 7.01 (d br., ^3J = 7.9 Hz, 1H, $C^{\alpha II}N$**H**CO), 4.77 (ddd, ^3J = 8.2 Hz, ^3J = 7.5 Hz, ^3J = 4.4 Hz, 1H, $C^{\alpha II}$**H**-CO_2), 4.32 (ddd, ^3J = 6.4 Hz, ^3J = 4.4 Hz, ^3J = 4.3 Hz, 1H, $C^{\alpha I}$**H**-C≡C), 3.55 (d br., ^3J = 6.3 Hz, 1H, $C^{\alpha I}$HN**H**), 3.45 (dt, ^3J = 7.8 Hz, ^3J = 8.0 Hz, 2H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}$**H₂**NH), 2.92 (dd, ^2J = 17.2 Hz, ^3J = 4.3 Hz, 1H, $C^{\alpha II}HC^{\beta}$**H₂**CO_2), 2.79 (dd, ^2J = 17.1 Hz, ^3J = 4.4 Hz, 1H, $C^{\alpha II}HC^{\beta}$**H₂**CO_2), 1.86-1.81 (m, 2H, $C^{\alpha I}HC^{\beta}$**H₂**$C^{\gamma}H_2C^{\delta}H_2$NH), 1.80-1.74 (m, 2H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}$**H₂**$C^{\delta}H_2$NH), 1.47 (s, 18H, $C^{\beta}H_2CO_2C(CH_3)_3$, $C^{\alpha}HCO_2C(CH_3)_3$), 1.44 (s, 9H, N=$CO_2C(CH_3)_3$), 1.41 (s, 9H, NH$CO_2C(CH_3)_3$), 1.21 (s, 9H, S$C(CH_3)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 171.3 ($C^{\beta}H_2$**C**$O_2C(CH_3)_3$), 169.7 ($C^{\alpha}H$**C**$O_2C(CH_3)_3$), 163.7 ($C^{\alpha II}$HNH**C**O-thiophene), 160.7 ($C^{\delta}H_2$NH**C**(NBoc)NHBoc), 156.3 (C=N**C**$O_2C(CH_3)_3$), 153.4 (CHN**C**$O_2C(CH_3)_3$), 139.2 (thiophene-**C**-2), 132.9 (thiophene-**C**-3), 128.1 (thiophene-**C**-4), 127.2 (thiophene-**C**-5), 94.7 ($C^{\alpha I}$H-**C**≡C-thiophene), 83.3 (NCO_2**C**$(CH_3)_3$), 83.2 (NHCO_2**C**$(CH_3)_3$), 82.8 ($C^{\alpha I}$H-C≡**C**-thiophene), 81.9 ($C^{\beta}H_2CO_2$**C**$(CH_3)_3$), 79.4 ($C^{\alpha}HCO_2$**C**$(CH_3)_3$), 56.0 (S**C**$(CH_3)_3$), 49.6 (**C$^{\alpha II}$**$HC^{\beta}H_2CO_2$), 48.0 (**C$^{\alpha I}$**$HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2$NH), 40.9 ($C^{\alpha II}$H**C$^{\beta}$**$H_2CO_2$), 35.6 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2$**C$^{\delta}$**$H_2$NH), 33.4 ($C^{\alpha I}$H**C$^{\beta}$**$H_2C^{\gamma}H_2C^{\delta}H_2$NH), 28.4 ($C^{\beta}H_2CO_2C$(**C**$H_3)_3$, $C^{\alpha}HCO_2C$(**C**$H_3)_3$), 28.2 (C=NCO_2C(**C**$H_3)_3$), 28.0 (CHNCO_2C(**C**$H_3)_3$), 27.8 ($C^{\alpha I}HC^{\beta}H_2$**C$^{\gamma}$**$H_2C^{\delta}H_2$NH), 22.8 (SC(**C**$H_3)_3$). $C_{38}H_{61}N_5O_{10}S_2$ (812.05 g mol^{-1}). MS(ESI): *m/z* = 812.39340 (calcd. 812.3933 $[M+H]^+$).



Dimethyl (*S*)-2-(4-((*S*)-4-((*E*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)-1-(((*S*)-*tert*-butylsulfinyl)amino)butyl)-1H-1,2,3-triazol-1-yl)succinate (131). Copper catalyzed [3+2] cycloaddition (*Click* reaction): $CuSO_4$ x 5 H_2O (165 mg, 0.7 mmol, 0.6 eq) and Sodium ascorbate (243.8 mg, 1.2 mmol, 1.0 eq) were simultaneously added in one portion to a heavily stirred solution of arginine analogous propargylamide **6x** (545 mg, 1.2 mmol, 1.0 eq) and dimethyl (*S*)-2-azidosuccinate (**125**, 288 mg, 1.5 mmol, 1.3 eq) in DMF/H_2O (10:1, 11 mL). The reaction mixture was stirred for 23 h at rt and the procedure checked by TLC. After complete conversion, the solution was concentrated up under reduced pressure, diluted with a saturated NH_4Cl solution (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product of **131** was purified by column chromatography CH_2Cl_2/MeOH (10:1).

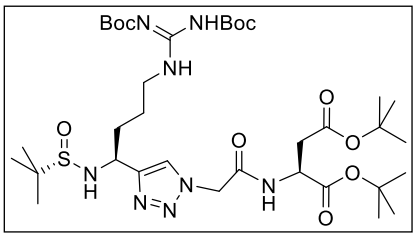
Yield: 303 mg, 470 µmol, 39 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 11.47 (s br., 1H,



N**H**Boc), 8.32 (t br., ^3J = 5.3 Hz, 1H, C$^\alpha$CH$_2$CH$_2$CH$_2$N**H**), 7.84 (s, 1H, C=C**H**), 5.64 (dd, ^3J = 6.6 Hz, ^3J = 7.4 Hz, 1H, CH$_3$O$_2$CC$^\alpha$'**H**), 4.54 (ddd, ^3J = 7.4 Hz, ^3J = 4.6 Hz, ^3J = 6.4 Hz, 1H, NHC$^\alpha$**H**), 3.84 (d br., ^3J = 7.4 Hz, 1H, C$^\alpha$HN**H**), 3.77 (s, 3H, C$^\alpha$'HCO$_2$C**H$_3$**), 3.70 (s, 3H, C$^\alpha$'HCH$_2$CO$_2$C**H$_3$**), 3.43 (td, ^3J = 6.8 Hz, ^3J = 6.3 Hz, 2H, C$^\alpha$HCH$_2$CH$_2$C**H$_2$**), 3.36 (dd, ^2J = 17.4 Hz, ^3J = 6.2 Hz, 1H, CH$_3$O$_2$CC**H**$_2$C$^\alpha$'H), 3.30 (dd, ^2J = 17.3 Hz, ^3J = 7.1 Hz, 1H, CH$_3$O$_2$CC**H**$_2$C$^\alpha$'H), 2.12 (m, 1H, C$^\alpha$HC**H$_2$**), 1.94 (m, 1H, C$^\alpha$HC**H**$_2$), 1.69 (m, 1H, C$^\alpha$HCH$_2$C**H**$_2$), 1.61 (m, 1H, C$^\alpha$HCH$_2$C**H**$_2$), 1.49 (s, 9H, C=NCO$_2$C(C**H$_3$**)$_3$), 1.48 (s, 9H, CHNCO$_2$C(C**H$_3$**)$_3$), 1.23 (s, 9H, SC(C**H$_3$**)$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 169.9 (C$^\alpha$'HCH$_2$**C**O$_2$CH$_3$), 167.9 (C$^\alpha$'H**C**O$_2$CH$_3$), 163.7 (N=**C**N$_2$), 156.3 (C=N**C**O$_2$C(CH$_3$)), 153.4 (CHN**C**O$_2$C(CH$_3$)), 149.5 (C$^\alpha$H**C**=CH), 123.1 (C$^\alpha$HC=**C**H), 83.2 (CHNCO$_2$**C**(CH$_3$)$_3$), 79.4 (C=NCO$_2$**C**(CH$_3$)$_3$), 58.8 (CH$_3$O$_2$C**C**$^\alpha$'HN), 56.5 (S**C**(CH$_3$)$_3$), 53.6 (C$^\alpha$'HCO$_2$**C**H$_3$), 52.9 (NH**C$^\alpha$**-C=CH), 52.6 (C$^\alpha$'HCH$_2$CO$_2$**C**H$_3$), 40.6 (C$^\alpha$CH$_2$CH$_2$**C**H$_2$), 36.4 (CH$_3$O$_2$C-**C**H$_2$HC$^\alpha$'N), 33.5 (NHC$^\alpha$H**C**H$_2$), 28.4 (C=NCO$_2$C(**C**H$_3$)$_3$), 28.2 (CHNCO$_2$C(**C**H$_3$)$_3$), 25.4 (C$^\alpha$HCH$_2$**C**H$_2$), 22.8 (SC(**C**H$_3$)$_3$). $C_{27}H_{47}N_7O_9S$ (645.77 g mol^{-1}). MS(ESI): *m/z* = 646.3243 (calcd. 646.3229 [M+H]$^+$). IR(ATR): $\tilde{\upsilon}$ [cm^{-1}] = 3329, 3291, 3142, 2977, 2955, 2936, 2870, 1739, 1720, 1635, 1610, 1575, 1413, 1366, 1328, 1226, 1154, 1128, 1046, 1024, 913, 808, 729. TLC: R*f* (CH_2Cl_2/MeOH, 10:1) = 0.59.

Di-*tert*-butyl (2-(4-((*S*)-4-((*E*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)-1-(((*S*)-*tert*-butylsulfinyl)amino)butyl)-1H-1,2,3-triazol-1-yl)acetyl)-L-aspartate (132). Copper catalyzed [3+2] cycloaddition (*Click* reaction): Di-*tert*-butyl (2-Azidoacetyl)-L-aspartate (**126**, 85 mg, 260 µmol, 1.2 eq) and arginine analogous propargylamide **6x** (102 mg, 222 µmol, 1.0 eq) were dissolved in a mixture of DMF/H_2O (10:1, 3 mL). Under vigorous stirring, solid $CuSO_4$ x 5 H_2O (28 mg, 112 µmol, 0.5 eq) and sodium ascorbate (48 mg, 242 µmol, 1.1 eq) was added in one portion. The reaction mixture was stirred over 56 h at rt. After complete conversion of alkyne **6x** (checked by TLC), the solution was concentrated under reduced pressure, diluted with brine (75 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with water (2 x 75 mL), brine (40 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude product of the desired triazole. Purification by column chromatography (CH_2Cl_2/MeOH, 10:1) allowed the isolation of triazole **132**.

Colorless fluid. Yield: 103.4 mg, 131.4 µmol, 59 %. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 11.47 (s br., 1H, Arg-N_2CN**H**Boc), 8.31 (t br., ^3J = 4.9 Hz, 1H, Arg-$C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2N$**H**), 7.83 (s, 1H, triazol-5-**H**), 6.94 (t br., ^3J = 6.6 Hz, 1H, Gly-$C^{\alpha II}CON$**H**$C^{\alpha III}$-Asp), 5.08 (d, ^2J = 16.8 Hz, 1H, Gly-$C^{\alpha II}$**H**$_2$), 5.04 (d, ^2J = 16.8 Hz, 1H, Gly-$C^{\alpha II}$**H**$_2$), 4.66 (ddd, ^3J = 8.9 Hz, ^3J = 6.2 Hz, ^3J = 4.9 Hz, 1H, Asp-$C^{\alpha III}$**H**), 4.53 (ddd, ^3J = 7.4 Hz, ^3J = 6.3 Hz, ^3J = 4.5 Hz, 1H, Arg-$C^{\alpha I}$**H**), 3.84 (d br., ^3J = 8.1 Hz, 1H, Arg-$C^{\alpha I}$HN**H**), 3.46-3.40 (m, 2H, Arg-$C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}$**H**$_2$NH), 2.82 (dd, ^2J = 17.1 Hz, ^3J = 4.7 Hz, 1H, Asp-$C^{\alpha III}HC^{\beta}$**H**$_2CO_2$), 2.68 (dd, ^2J = 17.1 Hz, ^3J = 4.5 Hz, 1H, Asp-$C^{\alpha III}HC^{\beta}$**H**$_2CO_2$), 2.14 (m, 1H, Arg-$C^{\alpha I}HC^{\beta}$**H**$_2C^{\gamma}H_2C^{\delta}H_2$NH), 1.96 (m, 1H, Arg-$C^{\alpha I}HC^{\beta}$**H**$_2C^{\gamma}H_2C^{\delta}H_2$NH), 1.73 (m, 1H, Arg-$C^{\alpha I}HC^{\beta}H_2C^{\gamma}$**H**$_2C^{\delta}H_2$NH), 1.64 (m, 1H, Arg-$C^{\alpha I}HC^{\beta}H_2C^{\gamma}$**H**$_2C^{\delta}H_2$NH), 1.48 (s, 9H, $C^{\beta}H_2CO_2C(C$**H**$_3)_3$), 1.47 (s, 9H, $C^{\alpha}HCO_2C(C$**H**$_3)_3$), 1.42 (s, 9H, $NCO_2C(C$**H**$_3)_3$), 1.41 (s, 9H, $NHCO_2C(C$**H**$_3)_3$), 1.21 (s, 9H, $SC(C$**H**$_3)_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ = 170.0 ($C^{\beta}H_2$**C**$O_2C(CH_3)_3$), 169.2 ($C^{\alpha}H$**C**$O_2C(CH_3)_3$), 165.0 (Gly-$C^{\alpha II}H_2$**C**$ONHC^{\alpha III}$-Asp), 163.7 (NH**C**(N)NH), 156.3 (N**C**$O_2C(CH_3)_3$), 153.4 (NH**C**$O_2C(CH_3)_3$), 150.2 (triazol-**C**-4), 123.9 (triazol-**C**-5), 83.2 ($NHCO_2$**C**$(CH_3)_3$), 82.8 ($C^{\beta}H_2CO_2$**C**$(CH_3)_3$), 81.9 ($C^{\alpha}HCO_2$**C**$(CH_3)_3$), 79.4 ($N{=}CO_2$**C**$(CH_3)_3$), 56.5 (S**C**$(CH_3)_3$), 53.2 (Asp-**C**$^{\alpha III}HC^{\beta}H_2CO_2$), 52.7 (Gly-**C**$^{\alpha II}H_2$), 49.5 (Arg-**C**$^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2$NH), 40.6 (Arg-



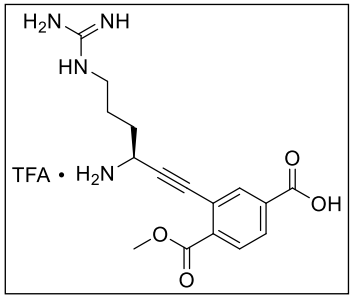
$C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2\mathbf{C}^{\delta}H_2NH$), 37.2 (Asp-$C^{\alpha III}H\mathbf{C}^{\beta}H_2CO_2$), 33.1 (Arg-$C^{\alpha I}H\mathbf{C}^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2NH$), 28.4 (Asp-$C^{\alpha III}HC^{\beta}H_2CO_2C(\mathbf{C}H_3)_3$), 28.2 (Asp-$C^{\alpha III}HCO_2C(\mathbf{C}H_3)_3$), 28.1 ($NCO_2C(\mathbf{C}H_3)_3$), 28.0 ($NHCO_2C(\mathbf{C}H_3)_3$), 25.5 (Arg-$C^{\alpha I}HC^{\beta}H_2\mathbf{C}^{\gamma}H_2C^{\delta}H_2NH$), 22.8 ($SC(\mathbf{C}H_3)_3$). $C_{35}H_{62}N_8O_{10}S$ (786.99 g mol^{-1}). MS(ESI): *m/z* = 787.4354 (calcd. 787.43824 $[M+H]^+$). TLC: R*f* (CH_2Cl_2/MeOH, 10:1) = 0.48.

IIX-6. d) Cleavage of Protective Groups to obtain RGD Mimetics 133-137

(*S*)-3-(3-Amino-6-guanidinohex-1-yn-1-yl)-4-(methoxycarbonyl)benzoic Acid (133).

Hydrochloric acid (4 M in dioxane, 3 mL) was added dropwise to an ice-cold solution of peptidomimetic **128** (200 mg, 298 μmol, 1.0 eq) in CH_2Cl_2 (3 mL). The reaction mixture was warmed up to rt and stirred 12 h at ambient temperature until the starting material was completely consumed (checked by LCMS) before evaporating the solvent at 40 °C. Inhibitor **133** was isolated by preparative HPLC as TFA adduct.

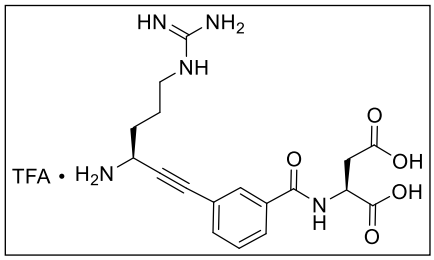
Colorless solid. Yield: 37.0 mg, 111 μmol, 37 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.66



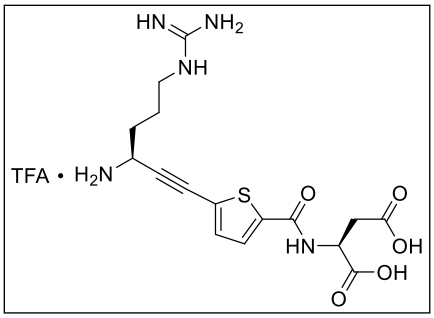
(s br., 3H, $C^{\alpha}N\mathbf{H_3}^+$), 8.12 (d, ^4J = 1.6 Hz, 1H, ar-2-**H**), 8.05 (dd, ^3J = 8.2 Hz, ^4J = 1.7 Hz, 1H, ar-6-**H**), 8.01 (d, ^3J = 8.2 Hz, 1H, ar-5-**H**), 7.35 (s br., 4H, $N\mathbf{H_2}C{=}N\mathbf{H_2}^+$), 4.44 (dd, ^3J = 8.9 Hz, ^3J = 5.2 Hz, 1H, $C^{\alpha}\mathbf{H}$), 3.89 (s, 3H, ar-4-$CO_2C\mathbf{H_3}$), 3.21 (td, ^3J = 6.5 Hz, ^3J = 4.8 Hz, 2H, $N_2CNC^{\delta}\mathbf{H_2}$), 1.86 (dt, ^2J = 12.2 Hz, ^3J = 5.8 Hz, 1H, $C^{\alpha}C\mathbf{H}_2$), 1.82-1.75 (m, 2H, $C^{\alpha}HC\mathbf{H}_2$, $C^{\alpha}HCH_2C\mathbf{H}_2$), 1.68 (m, 1H, $C^{\alpha}HCH_2C\mathbf{H}_2$). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 165.8 (ar-4-$\mathbf{C}O_2CH_3$), 165.3 (ar-1-$\mathbf{C}O_2H$), 156.9 (HN=$\mathbf{C}N_2$), 134.9 (ar-**C**-1), 134.7 (ar-**C**-4), 134.5 (ar-**C**-2), 130.6 (ar-**C**-5), 129.8 (ar-**C**-6), 121.3 (ar-**C**-3), 90.4 ($C^{\alpha}HC{\equiv}\mathbf{C}$-ar), 84.0 ($C^{\alpha}H\mathbf{C}{\equiv}C$-ar), 52.6 (ar-4-$\mathbf{C}O_2CH_3$), 42.4 ($\mathbf{C}^{\alpha}H$), 40.1 ($N_2CNH\mathbf{C}^{\delta}H_2$), 30.2 ($C^{\alpha}H\mathbf{C}H_2$), 24.8 ($C^{\alpha}HCH_2\mathbf{C}H_2$). $C_{18}H_{21}F_3N_4O_6$ (446.38 g mol^{-1}). MS(ESI): *m/z* = 333.1544 (calcd. 333.1557 $[C_{16}H_{20}N_4O_4+H]^+$).

(3-((*S*)-3-Amino-6-guanidinohex-1-yn-1-yl)benzoyl)-L-aspartic Acid Trifluoroacetate (134). Peptidomimetic **129** (183.4 mg, 227.5 μmol) was dissolved in a mixture of TFA/TIPS/H_2O (190:5:5, 2 mL) and stirred vigorously overnight. After complete conversion (checked by LCMS), the crude product was precipitated with ice-cold Et_2O and sucked off through a frit. The colorless precipitate of **134** was dissolved in MeOH and purified by preparative HPLC.

Pale yellow oil. Yield: 2.39 mg, 6.14 μmol, 3 % (the main part of the product was lost during a previous deprotection attempt under the conditions described in the cleavage of the protective groups of **128** to form **133**. The method described above did not complete the cleavage, leading to the loss of a great part of the material). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.90 (d br., ^3J = 7.9 Hz, 1H, $C^{\alpha II}HN\mathbf{H}CO$), 8.53-8.44 (s br., 4H, $C^{\delta}H_2N\mathbf{H}C(N\mathbf{H})\text{-}N\mathbf{H_2}$), 7.94 (t, ^3J = 2.2 Hz, 1H, ar-2-**H**), 7.92 (d, ^3J = 7.7 Hz, 1H, ar-6-**H**), 7.64 (dt, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1H, ar-4-**H**), 7.56 (t, ^3J = 7.7 Hz, 1H, ar-5-**H**), 4.75 (td, ^3J = 8.0 Hz, ^3J = 5.4 Hz, 1H, $C^{\alpha II}\mathbf{H}C^{\beta}H_2CO_2H$), 4.42 (dt, ^3J = 9.8 Hz, ^3J = 5.1 Hz, 1H, $C^{\alpha I}\mathbf{H}C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2NH$), 3.19 (dt, ^3J = 7.0 Hz, ^3J = 6.7 Hz, 2H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}\mathbf{H_2}NH$), 2.85 (dd, ^2J = 16.5 Hz, ^3J = 5.5 Hz, 1H, $C^{\alpha II}HC^{\beta}\mathbf{H}_2CO_2H$), 2.72 (dd, ^2J = 16.5 Hz, ^3J = 8.3 Hz, 1H, $C^{\alpha II}HC^{\beta}\mathbf{H}_2CO_2H$), 1.87-1.71 (m, 2H, $C^{\alpha I}HC^{\beta}\mathbf{H_2}C^{\gamma}H_2C^{\delta}H_2NH$), 1.75-1.59 (m, 2H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H_2}C^{\delta}H_2NH$). $C_{18}H_{23}N_5O_5$ (389.41 g mol^{-1}). LCMS(ESI): *m/z* = 390.1828 (calcd. 390.1772 $[M+H]^+$).



(5-((*S*)-3-Amino-6-guanidinohex-1-yn-1-yl)thiophene-2-carbonyl)-L-aspartic Acid Trifluoroacetate (135). Peptidomimetic **130** (101.8 mg, 125.4 μmol) was dissolved in a mixture of TFA/TIPS/H_2O (190:5:5, 2 mL) and stirred vigorously overnight. After complete conversion (checked by LCMS), the crude product was precipitated with ice-cold Et_2O and sucked off through a frit. The colorless precipitate of **135** was dissolved in MeOH and purified by preparative HPLC.

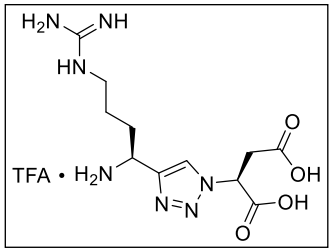


Pale yellow highly viscous oil. Yield: 10.87 mg, 27.49 µmol, 22 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.99 (d br., ^{3}J = 8.0 Hz, 1H, CON**H**$C^{\alpha II}HC^{\beta}H_2CO_2$), 8.51 (s br., 4H, NHC(N**H**$_2$)$_2$), 7.79 (d, ^{3}J = 3.9 Hz, 1H, thiophene-3-**H**), 7.64 (t br., ^{3}J = 6.4 Hz, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2N$**H**), 7.40 (d, ^{3}J = 3.8 Hz, 1H, thiophene-4-**H**), 4.69 (dd, ^{3}J = 7.1 Hz, ^{3}J = 6.0 Hz, 1H, $C^{\alpha II}$**H**$C^{\beta}H_2CO_2$), 4.46 (m, 1H, $C^{\alpha I}$**H**$C^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2NH$), 3.18 (td, ^{3}J = 6.6 Hz, ^{3}J = 5.8 Hz, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}$**H**$_2$NH), 2.85 (dd, ^{2}J = 16.8 Hz, ^{3}J = 5.5 Hz, 1H, $C^{\alpha II}HC^{\beta}$**H**$_2CO_2H$), 2.68 (dd, ^{2}J = 16.4 Hz, ^{3}J = 8.4 Hz, 1H, $C^{\alpha II}HC^{\beta}$**H**$_2CO_2H$), 1.89-1.73 (m, 2H, $C^{\alpha I}HC^{\beta}$**H**$_2C^{\gamma}H_2C^{\delta}H_2NH$), 1.72-1.59 (m, 2H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}$**H**$_2C^{\delta}H_2NH$). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.2 ($C^{\alpha II}HC^{\beta}H_2$**C**$O_2H$), 171.6 ($C^{\alpha II}$H**C**$O_2H$), 160.0 (NH**C**$(NH_2)_2$), 156.9 (thiophene-**C**O$HNC^{\alpha II}$H), 141.3 (thiophene-**C**-2), 134.3 (thiophene-**C**-3), 128.7 (thiophene-**C**-4), 124.5 (thiophene-**C**-5), 93.0 (C^{α}H**C**≡C-thiophene), 82.1 (C^{α}HC≡**C**-thiophene), 50.3 (**C**$^{\alpha II}HC^{\beta}H_2CO_2$), 49.4 (**C**$^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2NH$), 40.4 ($C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2$**C**$^{\delta}H_2NH$), 35.7 ($C^{\alpha II}$H**C**$^{\beta}H_2CO_2$), 31.7 ($C^{\alpha I}$H**C**$^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2NH$), 22.0 ($C^{\alpha I}HC^{\beta}H_2$**C**$^{\gamma}H_2C^{\delta}H_2NH$). $C_{16}H_{21}N_5O_5S$ (395.43 g mol^{-1}), LCMS (ESI): *m/z* = 396.0498 (calcd. 396.1336 $[M+H]^+$), 418.0259 (calcd. 418.1156 $[M+Na]^+$).

(*S*)-2-(4-((*S*)-1-Amino-4-guanidinobutyl)-1H-1,2,3-triazol-1-yl)succinic Acid Trifluoroacetate (136). An aqueous solution of LiOH (1 M, 3.8 mL) was added dropwise to an icecold solution of peptidomimetic **131** (303 mg, 0.47 mmol, 1 eq) in MeOH (8 mL). After complete addition, the reaction mixture was warmed up to rt and stirred for 2.3 h, until the starting material was completely consumed (checked by LCMS). The solution was concentrated up under reduced pressure, diluted with an aqueous $KHSO_4$ solution (5 %, 10 mL) to adjust the pH value to 1-2 and extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure.

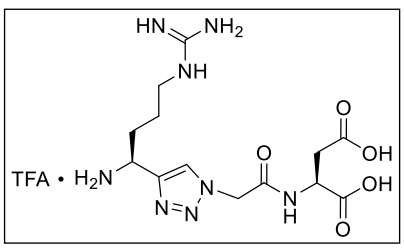
The crude product was dissolved in a mixture of TFA/TIPS/H_2O (9 mL, 95:2.5:2.5) and stirred overnight at ambient temperature. After complete consumption of the starting material (checked by LCMS), the crude product was precipitated with ice-cold Et_2O and

sucked off through a frit. The colorless precipitate of **136** was dissolved in MeOH and purified by preparative HPLC.



Colorless solid, yield: 75.7 mg, 177 μmol, 38 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 13.03 (s br., 1H, CO_2**H**), 8.52 (s br., 3H, $C^{\alpha}HN$**H**$_3^+$), 8.31 (s, 1H, $C^{\alpha}HC$=C**H**), 7.96 (t, ^{3}J = 5.8 Hz, 1H, $C^{\alpha}HCH_2CH_2CH_2N$**H**), 7.37 (s br., 5H, **H**$_2$N-C=N**H**$_2^+$), 5.73 (dd, ^{3}J = 7.8 Hz, ^{3}J = 5.9 Hz, 1H, CO_2C**H**N-CH_2CO_2), 4.50 (dd, ^{3}J = 7.3 Hz, ^{3}J = 4.8 Hz, 1H, $^{+}H_3N$-C^{α}**H**), 3.25 (dd, ^{2}J = 17.0 Hz, ^{3}J = 6.5 Hz, 2H, $CO_2C^{\alpha}HC$**H**$_2CO_2$), 3.19 (dd, ^{2}J = 17.0 Hz, ^{3}J = 8.0 Hz, 1H, CO_2CHN-C**H**$_2CO_2$), 3.11 (dt, ^{3}J = 6.7 Hz, ^{3}J = 7.3 Hz, 2H, $C^{\alpha}CH_2CH_2C$**H**$_2$NH), 1.92 (dd, ^{3}J = 7.7 Hz, ^{3}J = 6.5 Hz, 2H, $C^{\alpha}HC$**H**$_2CH_2CH_2$NH), 1.49 (m, 1H, $C^{\alpha}CH_2C$**H**$_2CH_2$NH), 1.38 (m, 1H, $C^{\alpha}CH_2C$**H**$_2CH_2$NH). ^{19}F NMR (471 MHz, DMSO-d_6) δ = -73.85 (C**F**$_3CO_2$H). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 170.9 (CH_2-**C**O_2), 169.2 (CHN-**C**O_2), 159.0 (q, $^{2}J_{CF}$ = 31.9 Hz, F_3C-**C**O_2), 157.1 (N=**C**N_2), 143.4 ($C^{\alpha}H$**C**=CH), 124.5 (C=C**H**), 117.1 (q, ^{1}J = 295.7 Hz, **C**F_3CO_2H), 59.1 (CO_2-**C**HN-CH_2CO_2), 46.4 (**C**$^{\alpha}NH_3^+$), 40.1 ($C^{\alpha}HCH_2CH_2$**C**H_2NH), 36.0 (CO_2CHN-**C**H_2CO_2), 30.2 ($C^{\alpha}H$**C**$H_2CH_2CH_2$NH), 24.8 ($C^{\alpha}HCH_2$**C**H_2CH_2NH). $C_{13}H_{20}F_3N_7O_6$ (427.34 g mol^{-1}). MS(ESI): *m/z* = 314.1564 (calcd. 314.1571 $[M+H]^+$).

(2-(4-((*S*)-1-Amino-4-guanidinobutyl)-1H-1,2,3-triazol-1-yl)acetyl)-L-aspartic Acid Trifluoroacetate (137). Peptidomimetic **132** (103.4 mg, 131.4 μmol) was dissolved in a mixture of TFA/TIPS/H_2O (190:5:5, 2 mL) and stirred vigorously overnight. After complete conversion (checked by LCMS), the crude product was precipitated with ice-cold Et_2O and sucked off through a frit. The colorless precipitate of **137** was dissolved in MeOH and purified by preparative HPLC.



Colorless amorphous solid. Yield: 38.90 mg, 105.0 μmol, 80 %. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.81 (d br., ^{3}J = 7.9 Hz, 1H, Gly-$C^{\alpha II}HCO$**H**$NC^{\alpha III}HC^{\beta}H_2CO_2$), 8.38 (s br., 4H, NHC(N**H**$_2$)$_2$), 8.22 (s br., 1H, Arg-$C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2$N**H**), 8.14 (s, 1H, triazol-5-**H**), 7.53 (ddd, ^{3}J = 5.8 Hz, ^{3}J = 7.0 Hz, ^{3}J = 6.8 Hz, 1H, Asp-$C^{\alpha III}$**H**), 5.22 (d, ^{2}J = 17.4 Hz, 1H, Gly-$C^{\alpha II}$**H**$_2$CONH), 5.18 (d, ^{2}J = 16.9 Hz, 1H, Gly-

$C^{\alpha II}\mathbf{H}_2CONH$), 4.53 (ddd, ^3J = 6.8 Hz, ^3J = 5.4 Hz, ^3J = 6.9 Hz, 1H, Arg-$C^{\alpha I}\mathbf{H}$), 3.08 (d, ^3J = 6.9 Hz, 3H, Arg-$C^{\alpha I}HN\mathbf{H_3}$), 2.70 (dd, ^2J = 17.0 Hz, ^3J = 5.8 Hz, 1H, Asp-$C^{\alpha III}HC^{\beta}\mathbf{H}_2CO_2H$), 2.64 (dd, ^2J = 16.9 Hz, ^3J = 7.0 Hz, 1H, Asp-$C^{\alpha III}HC^{\beta}\mathbf{H}_2CO_2H$), 1.91 (ddd, ^3J = 7.9 Hz, ^3J = 7.7 Hz, ^3J = 5.9 Hz, 2H, $C^{\alpha I}HC^{\beta}\mathbf{H}_2C^{\gamma}H_2C^{\delta}H_2NH$), 1.46 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}_2C^{\delta}H_2NH$), 1.35 (m, 1H, $C^{\alpha I}HC^{\beta}H_2C^{\gamma}\mathbf{H}_2C^{\delta}H_2NH$). ^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.2 (Asp-$C^{\alpha III}HC^{\beta}H_2\mathbf{C}O_2H$), 171.3 (Asp-$C^{\alpha III}H\mathbf{C}O_2H$), 170.2 (Gly-$C^{\alpha II}H_2\mathbf{C}ONH$), 165.5 ($NH\mathbf{C}(=NH)NH_2$), 156.9 (triazol-**C**-4), 143.5 (triazol-**C**-5), 51.7 (Asp-$\mathbf{C}^{\alpha III}HC^{\beta}H_2CO_2H$), 50.9 (Arg-$\mathbf{C}^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2NH$), 49.1 (Gly-$\mathbf{C}^{\alpha II}H_2$), 46.6 (Asp-$C^{\alpha III}H\mathbf{C}^{\beta}H_2CO_2H$), 36.2 (Arg-$C^{\alpha I}HC^{\beta}H_2C^{\gamma}H_2\mathbf{C}^{\delta}H_2NH$), 30.3 (Arg-$C^{\alpha I}H\mathbf{C}^{\beta}H_2C^{\gamma}H_2C^{\delta}H_2NH$), 24.9 (Arg-$C^{\alpha I}HC^{\beta}H_2\mathbf{C}^{\gamma}H_2C^{\delta}H_2NH$). $C_{13}H_{22}N_8O_5$ (370.37 g mol^{-1}), LCMS (ESI): *m/z* = 371.1800 (calcd. 371.1786 $[M+H]^+$).

IIX-6. e) Chromatograms of Samples 133-137 for the Affinity Assays

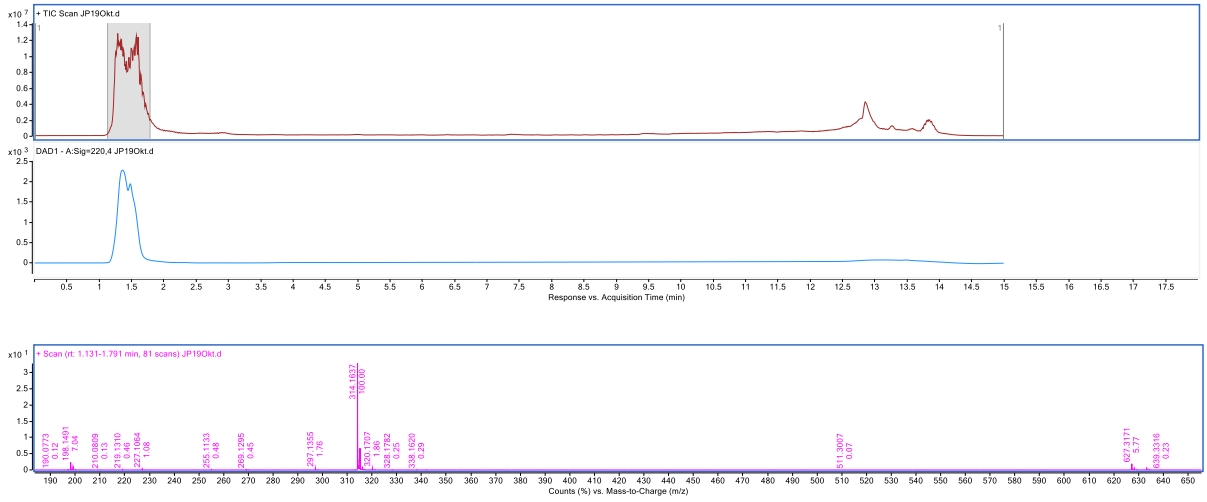


Diagram EP27. Analytical chromatogram of (*S*)-3-(3-Amino-6-guanidinohex-1-yn-1-yl)-4-(methoxycarbonyl)benzoic Acid (**133**). Purity >99 %.

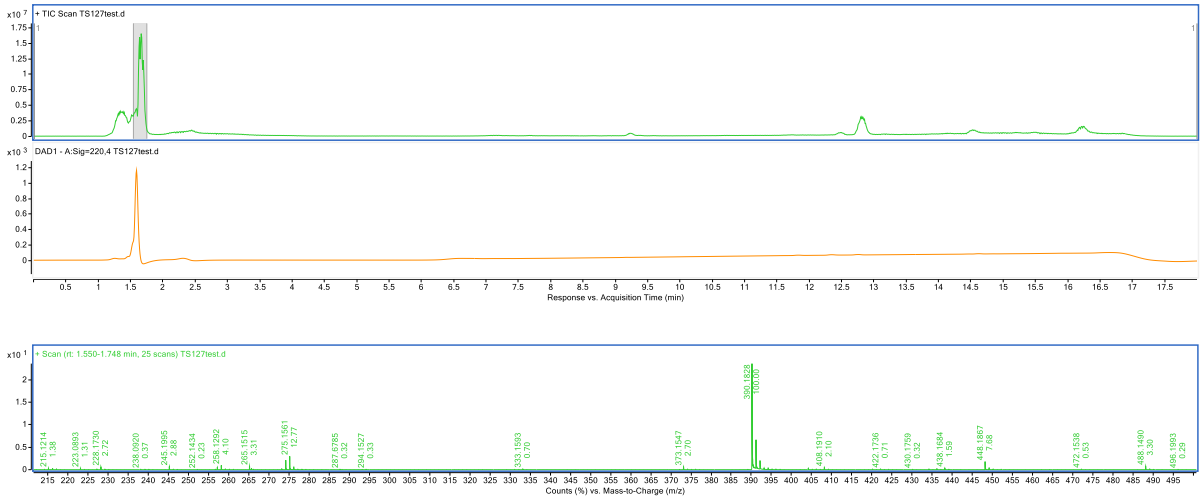


Diagram EP28. Analytical chromatogram of (3-((*S*)-3-Amino-6-guanidinohex-1-yn-1-yl)benzoyl)-L-aspartic Acid (**134**). Purity >99 %.

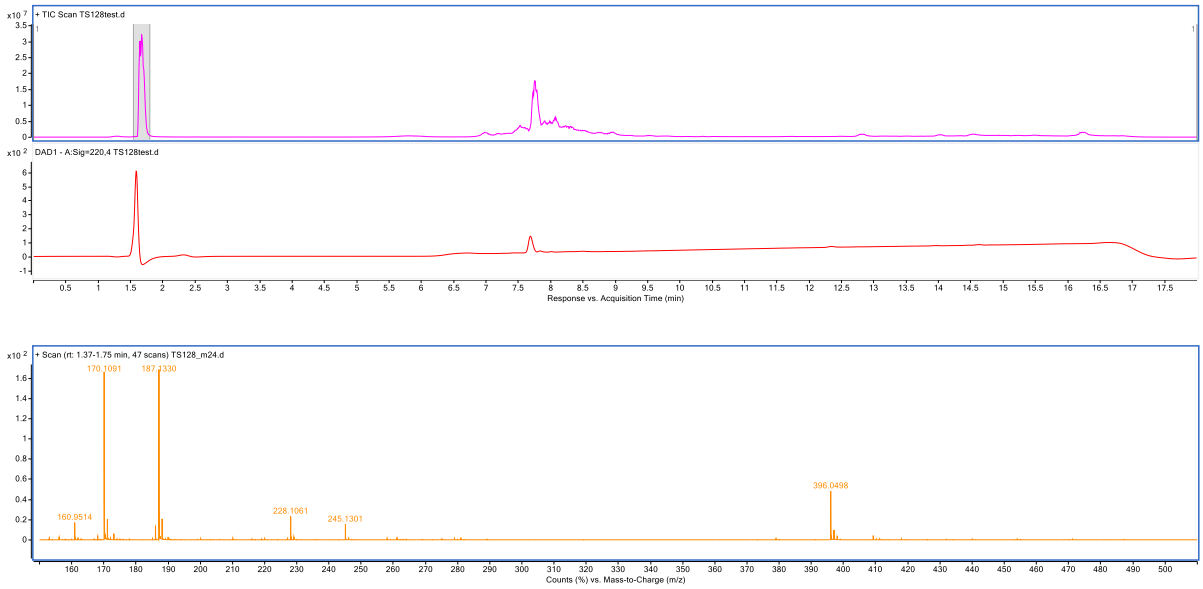


Diagram EP29. Analytical chromatogram of (5-((*S*)-3-Amino-6-guanidinohex-1-yn-1-yl)thiophene-2-carbonyl)-L-aspartic Acid (**135**). Purity >95 %.

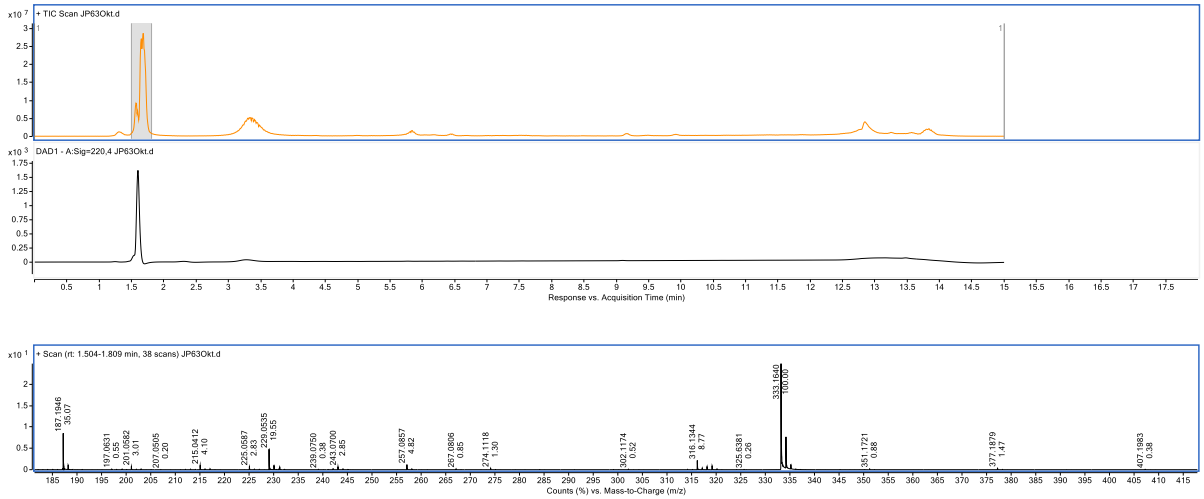


Diagram EP30. Analytical chromatogram of (*S*)-2-(4-((*S*)-1-Amino-4-guanidinobutyl)-1H-1,2,3-triazol-1-yl)succinic Acid (**136**). Purity >99 %.

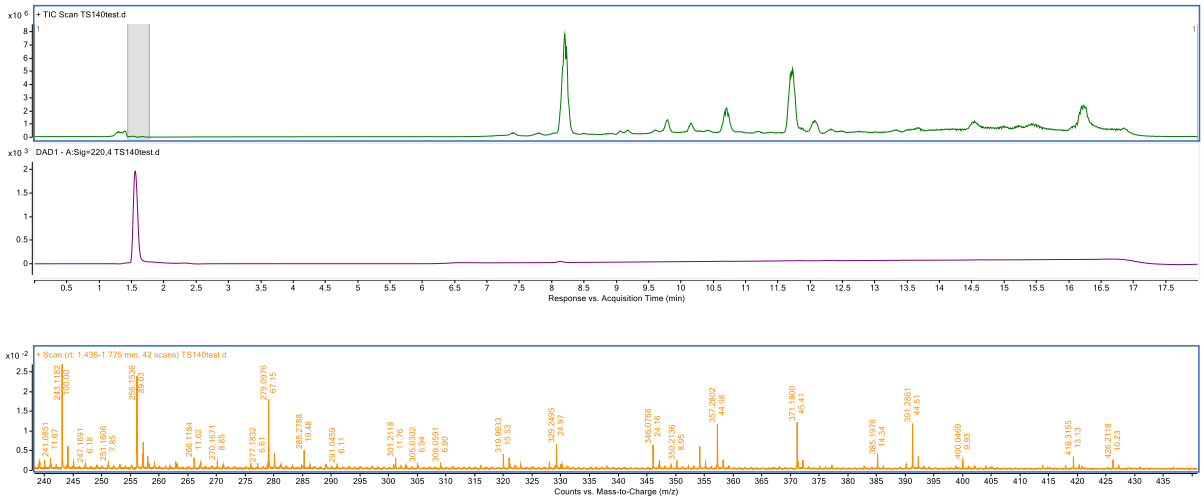


Diagram EP31. Analytical chromatogram of (2-(4-((*S*)-1-Amino-4-guanidinobutyl)-1H-1,2,3-triazol-1-yl)acetyl)-L-aspartic Acid (**137**). Purity >99 %.

IIX-6. f) Integrin Binding Assay

The activity and selectivity of integrin ligands were determined by a solid-phase binding assay according to the previously reported protocol [213] as adapted by Kapp *et al.* [143], using coated extracellular matrix proteins and soluble integrins. *Cilengitide*® (*c*(RGDf(*N*Me)V) was used as internal standard for αvβ3 (0.54 nM). Flat-bottom 96-well Immuno Plates (BRAND, Wertheim, Germany) were coated overnight at 4 °C with human vitronectin (1.0 μg mL^{-1}, 100 μL per well, R&D) in carbonate buffer (15 mM Na_2CO_3, 35 mM $NaHCO_3$, pH 9.6). Each well was then washed with PBS-T-buffer (phosphate-buffered saline/Tween20, 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 2 mM KH_2PO_4, 0.01 % Tween20, pH 7.4; 3 x 200 μL) and blocked for 1 h at room temperature with TS-B-buffer (Tris-saline/BSA buffer, 150 μL/well, 20 mM Tris-HCl, 150 mM NaCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 1 mM $MnCl_2$, pH 7.5, 1 % BSA). In the meantime, a dilution series of the compound and internal standard was prepared in an extra plate, starting from 2000 μM to 7.1 nM (reference compound 20 μM to 0.43 nM) in 1:5 dilution steps. After washing the assay plate three times with PBS-T (200 μL), 50 μl of the dilution series was transferred to each well from B‑G. Well A was filled with 100 μl TSB-solution (blank) and well H was filled with 50 μl TS-B-buffer. 50 μl of a solution of human αvβ3-integrin (2.0 μg ml^{-1}, R&D) in TS-B-buffer was transferred to wells H‑B and incubated for 1 h at rt. The plate was washed three times with PBS-T buffer, and then the primary antibody (2.0 μg mL, mouse anti-human CD51/61, BD Biosciences, 100 μL per well) was added to the plate. After incubation for 1 h at rt, the plate was washed three times with PBS-T. Then, the secondary peroxidase-labeled antibody (1.0 μg mL^{-1}, anti-mouse IgG-POD, Sigma-Aldrich, 100 μL $well^{-1}$) was added to the plate and incubated for 1 h at rt. After washing the plate three times with PBS-T, the plate was developed by quick addition of SeramunBlau (50 μL $well^{-1}$, Seramun Diagnostic GmbH, Heidesee, Germany) and incubation until a colour gradient was visible. The reaction was stopped with 3 M H_2SO_4 (50 μL $well^{-1}$), and the absorbance was measured at 450 nm with a plate reader (Tecan Reader). The IC_{50} of each compound was tested in duplicate, and the resulting inhibition curves were analyzed using OriginPro 2017G (32-bit) SR1 software. The inflection point describes the IC_{50} value. All determined IC_{50} were referenced to the activity of the internal standard *Cilengitide*® (0.54 nM) [143].

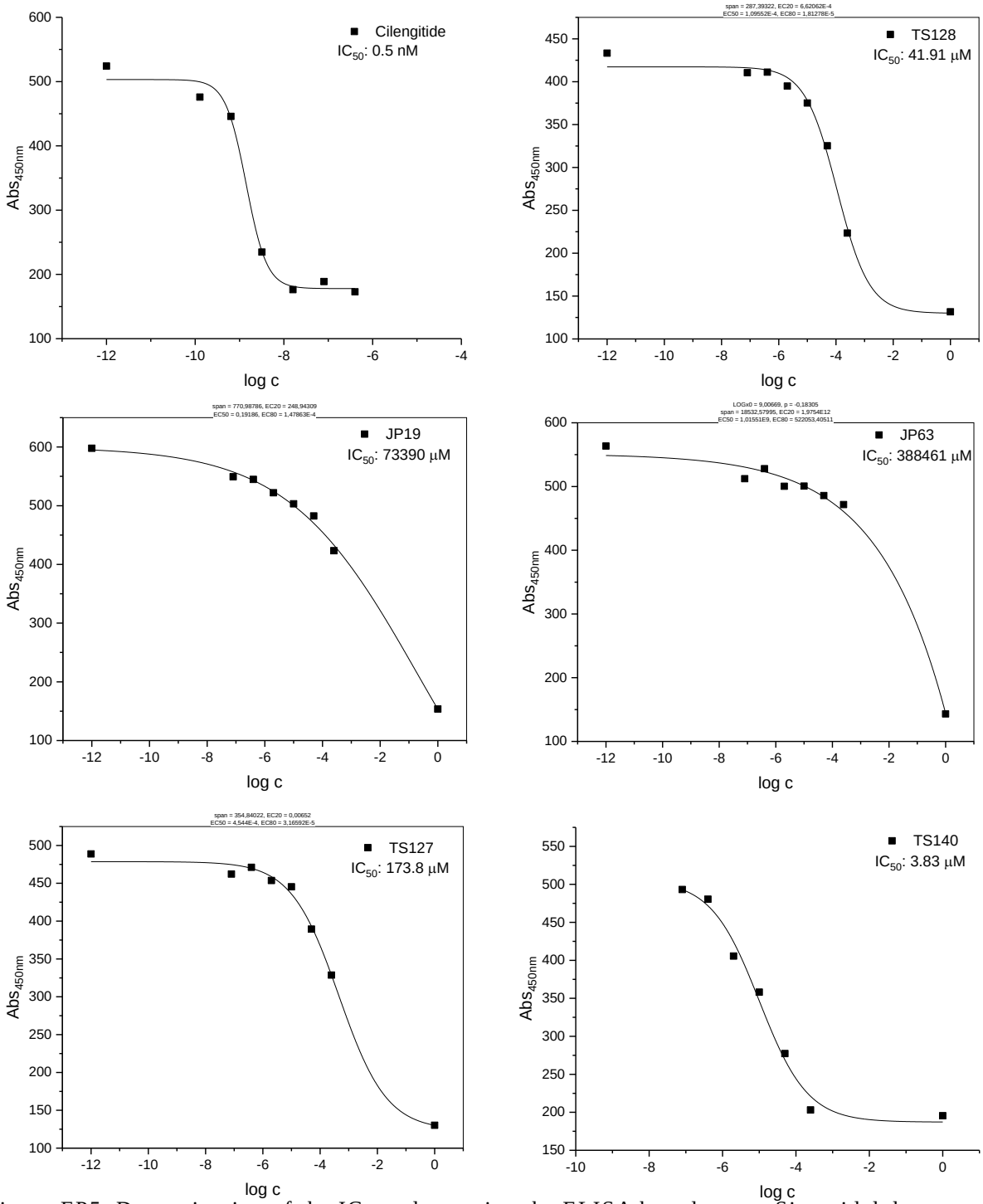


Figure EP5. Determination of the IC_{50} values using the ELISA based assay. Sigmoidal dose-response curves of the compounds **133** (JP19), **134** (TS127), **135** (TS128), **136** (JP63), **137** (TS140) and *Cilengitide*®.

IIX-6. g) Cell Adhesion Assay

The cell adhesion tests were performed as previously described by Conradi *et al.* [258]. Competition assays were performed with WM-115 human epithelial cancer cells. Therefore, WM-115 cells were cultivated to a confluence of 70 %, detached with Trypsin-EDTA (0.05 % / 0.02 % in D-PBS) (PAA, Pasching, Austria), washed with MEM medium, resuspended in MEM medium with 1 mg mL^{-1} fluorescein diacetate (Sigma-Aldrich, St. Louis, USA) to a cell density of 1 x 10^5 cells mL^{-1}, and incubated at 37 °C under steady shaking for 30 min. Subsequently, cells were washed two times with MEM medium, resuspended with MEM medium containing divalent cations Ca^{2+} and Mg^{2+} (2 mM) to obtain a cell density of 1 x 10^5 cells mL^{-1} and incubated in the dark on ice for 30 min. For the cell adhesion assay $CagL^{WT}$ was immobilized on a Nunc Maxisorp™ surface and WM-115 cells pre-incubated with varying concentrations of vitronectin were dispensed to the immobilized $CagL^{WT}$. Likewise, WM-115 cells were pre-incubated with different $CagL^{WT}$ concentrations before adding to immobilized vitronectin (1 μg mL^{-1}). The cell suspension was added to the peptide solutions to give concentrations ranging from milimolar to nanomolar and incubated 30 min at 37 °C. It was then dispensed on the coated microtiter plate (5 x 10^4 cells $well^{-1}$) and incubated for 1 h at 37 °C. Unbound cells were aspirated and bound cells were washed twice with MEM medium. Fluorescence was measured (λ_{ex} = 485 nm; λ_{em} = 514 nm) in an Infinite™ 200 Microplate Reader (Tecan, Männedorf, Switzerland). IC_{50} values (50 % cell binding inhibition) of the tested peptides were evaluated with the GraphPad Prism 4.03 software (GraphPad, San Diego, USA). In cell adhesion assays the murine monoclonal antibodies LM609 (EMD Millipore, Billerica, USA) against human integrin αVβ3, 3S3 (AbD Serotec, MorphoSys AG, Germany) against b1 integrin, and P1F6 (EMD Millipore, Billerica, USA) against αVβ5 were used in final concentrations of 25 μg mL^{-1}. The assay was performed as described above. Instead of staining the cells with fluorescein diacetate, they were washed with Puck's salt solution (5.4 mM KCl, 0.4 mM KH_2PO_4, 5.6 mM D-glucose, 136 mM NaCl, 2 mM $MgCl_2$, 2 mM $MnCl_2$), fixed for 30 min at rt using 5 % (w/v) glutaraldehyde, and stained with crystal violet 1 % (w/v) in 100 mM MES (pH 6.0) over 60 min at rt. After a second washing step with Puck's salt solution, 100 mM citric acid in ethanol was added and the cells were incubated 30 min at rt for visualization. Absorption at 485 nm and emission at 514 nm was measured using the Tecan M200 Microplate Reader and the data was processed with Origin (Dose-Response).

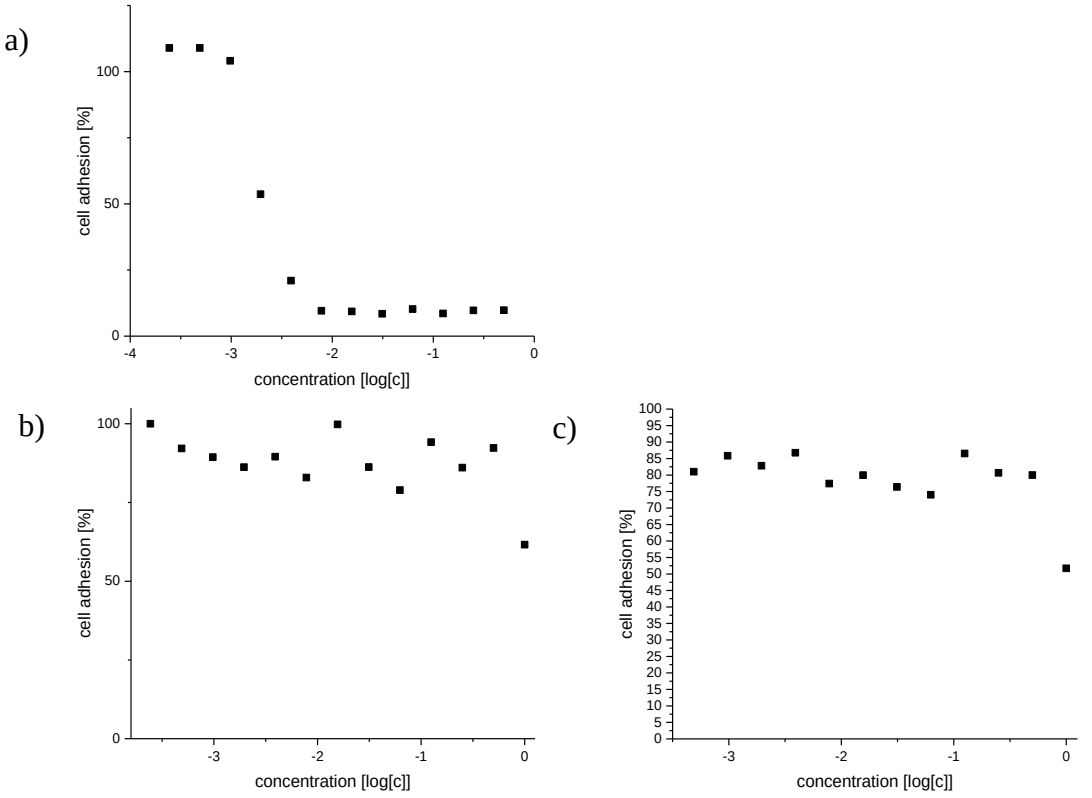


Figure EP6. Sigmoidal dose-response plots of the competitive cell adhesion assays for peptidomimetics **133** and **137**, inhibiting the binding of WM-115 cells to the $CagL^{WT}$ proteins. a) Reference inhibitor was *Cilengitide*®, IC_{50} 1.9 µM. b) Therephthalate **133**, referenced to *Cilengitide*® IC_{50} > 250 µM. c) triazole **136**, referenced to *Cilengitide*®. IC_{50} > 1000 µM.

IIX-6. h) Docking Studies

Docking studies were performed with the AutoDock Vina software tool using default parameters (exhaustiveness = 8) [259]. The crystal structure of the complex of αvβ3 and *Cilengitide*®, which has been presented by Xiong *et al.* [206] and published in the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank under the ID 15LG, was chosen. The cocrystallized RGD peptide and water molecules in the binding pocket were detached using the AutoDock Tools software [260]. Polar hydrogen atoms were added at heteroatoms only. The 3D structures of test compounds **133-137** were constructed using Avogadro software [261] and optimized with the MMFF94s force-field method option [262]. Degrees of freedom and rotatable bonds were defined by the AutoDock Tools software [260]. The binding pocket was defined as the location of the co-crystallized *Cilengitide*® as the grid (x = 19.0, y = 44.6, z = 43.0) with a size of 16 × 22 × 16 $Å^3$ and a distance of points of 1 Å. The evaluation of the docking results and the visualization were performed using PyMOL viewer software [263].

Cilengitide® was re-modelled into the binding pocket of integrin αvβ3 using the AotoDock Vina software tool [259]. The results were compared to the crystal structure in order to evaluate the results (Figure EP7).

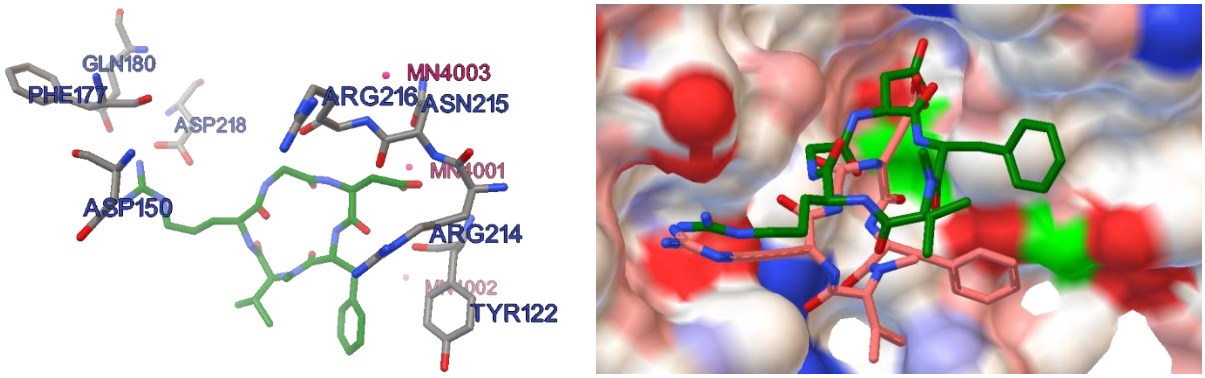


Figure EP7. Evaluation of the docking method by comparison of the X-ray structure analysis of *Cilengitide*®, co-crystallized with integrin αvβ3 [206]. Left side: Co-crystallized binding pocket of αvβ3 and *Cilengitide*®. Right side: Superimposition of co-crystalline *Cilengitide*® (colored green) and *Cilengitide*® computed as described above (colored rose). Regions of the binding pocket of integrin αvβ3 were colored according to their polarity (blue = hydrophobic, red = hydrophilic, green = metal ions).

Coumpounds **110-119** were computed into the binding pocket of integrin αvβ3 as described above in order to define the bioactive conformation of the ligands. The bond lengths and angles, which have been used to characterize the class D peptidomimetics and their affinity

potential to the binding pocket have been measured in the results of the docking experiments and summarized in Table EP33.

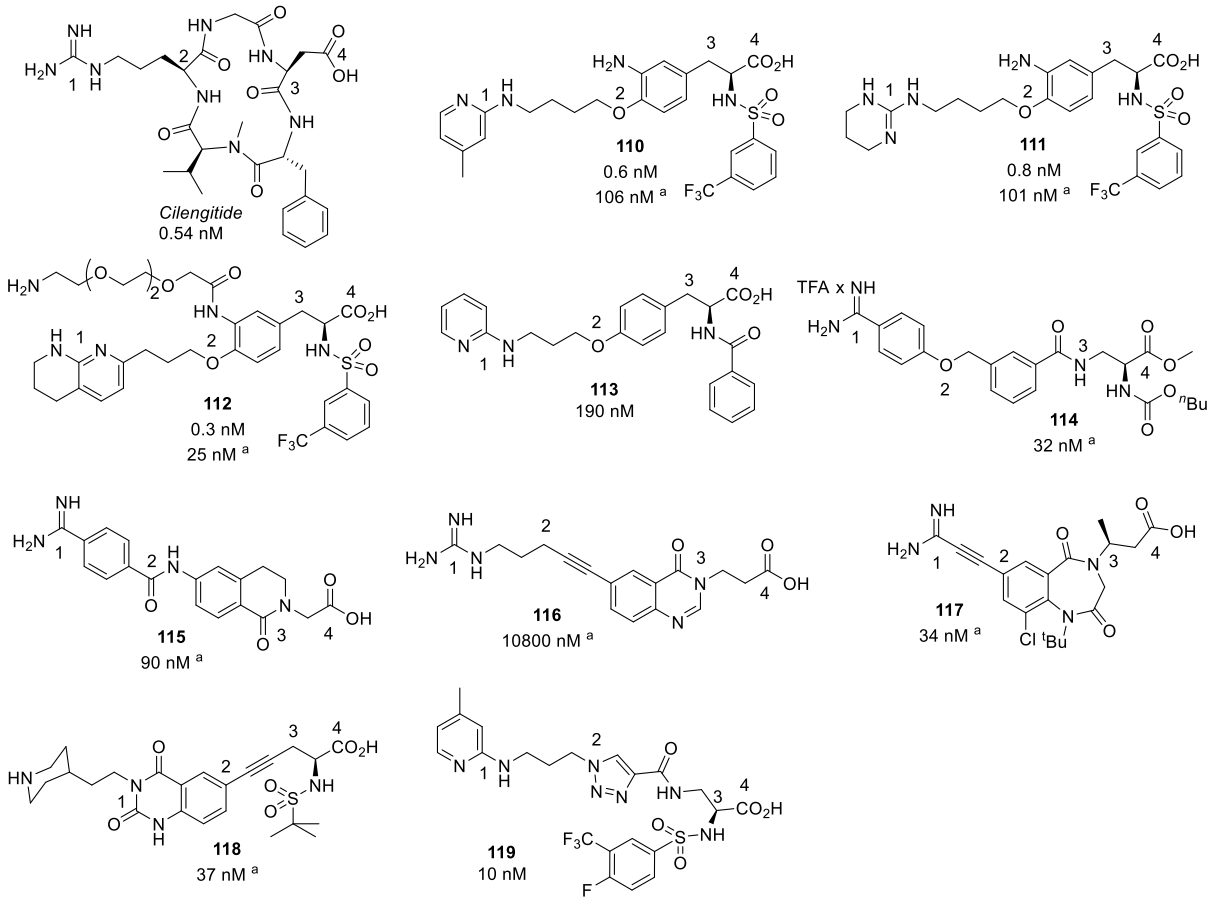


Figure EP8. Mechanistic class D peptidomimetics, used for docking experiments in order to deduce information about convenient bond lengths and dihedral angles. Crucial atoms for the conformation are labeled.

[a] IC_{50} values refer to GP IIβ/IIIα determined in a platelet-rich plasma assay.

Table EP33. Important conformational parameters of topographical peptidomimetic scaffolds **110**-**119** model peptide *Cilengitide*® for comparison with the scaffolds investigated in this work. Atom numbers refer to Figure EP8. Torsion angles and distances of the peptidomimetics have been measured in convenient conformations, which were derived from docking experiments. Torsion angle and distances of the bioactive conformation of *Cilengitide*® has been measured in its X-ray crystal structure of the complex with αvβ3 [206].

Compound	d(atom1-2) [Å]	d(atom2-3) [Å]	d(atom3-4) [Å]	α-torsion [°]	d(atom1-4) [Å]	IC_{50} [nM]
Cilengitide®	5.54	6.43	2.55	118	13.72	0.54
110	6.73	5.68	2.49	109	11.83	0.6
111	6.23	6.46	1.51	140	12.74	0.8
112	5.86	5.68	2.49	102	13.03	0.3
113	4.89	5.68	2.50	159	12.14	190
114	5.67	9.13	1.53	-100	14.78	32 [a]

115	5.79	7.60	2.48	-104	14.19	90 [a]
116	4.64	8.70	3.40	40	14.50	10800 [a]
117	4.07	4.88	3.01	78	11.34	34 [a]
118	5.03	9.83	2.48	155	16.19	37 [a]
119	4.58	6.24	2.51	-105	12.32	100

[a] IC_{50} values refer to glycoprotein GP IIβ/IIIα. Values for integrin αvβ3 were not available.

The shown pictures of the compounds, modeled into the respective binding pocket of integrin αVβ3 have been made using PMV and ADT software [260]. Visualisation was realised using a Visual Programming Environment for Python [263], programmed by *Sanner et al.*.

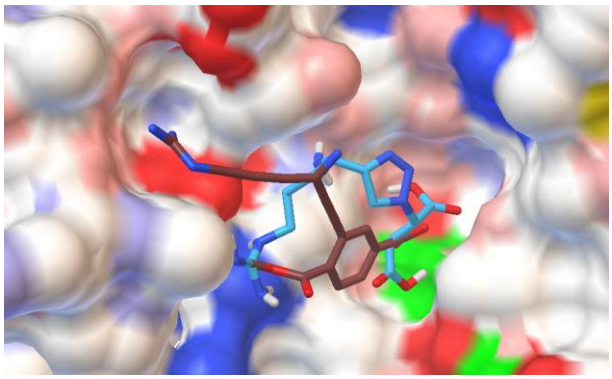


Figure EP9. Integrin αvβ3 docking results. Docking poses of the first, shorter integrin αvβ3 inhibitors **133** (colored brown) and **136** (colored cyan). The molecular surface of integrin αvβ3 is displayed and colored according to the hydrophobicity (blue = hydrophobic, red = hydrophilic, green = metal ions).

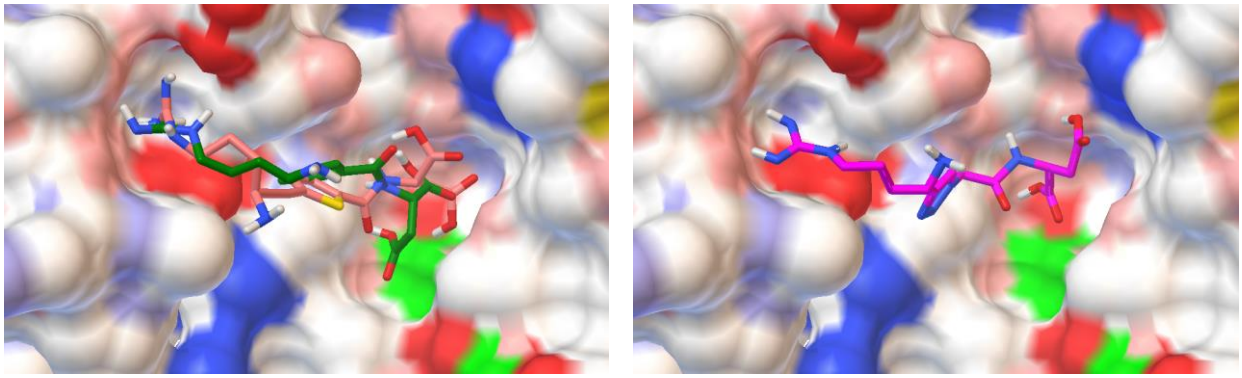


Figure EP10. Integrin αvβ3 docking results. Left side: docking poses of the aromatic integrin αvβ3 inhibitors **134** (colored green) and **135** (colored rose). Right side: docking pose of the triazole based inhibitor **137** (colored magenta), which is the most potent inhibitor under study. The molecular surface of integrin αvβ3 is displayed and colored according to the hydrophobicity (blue = hydrophobic, red = hydrophilic, green = metal ions).

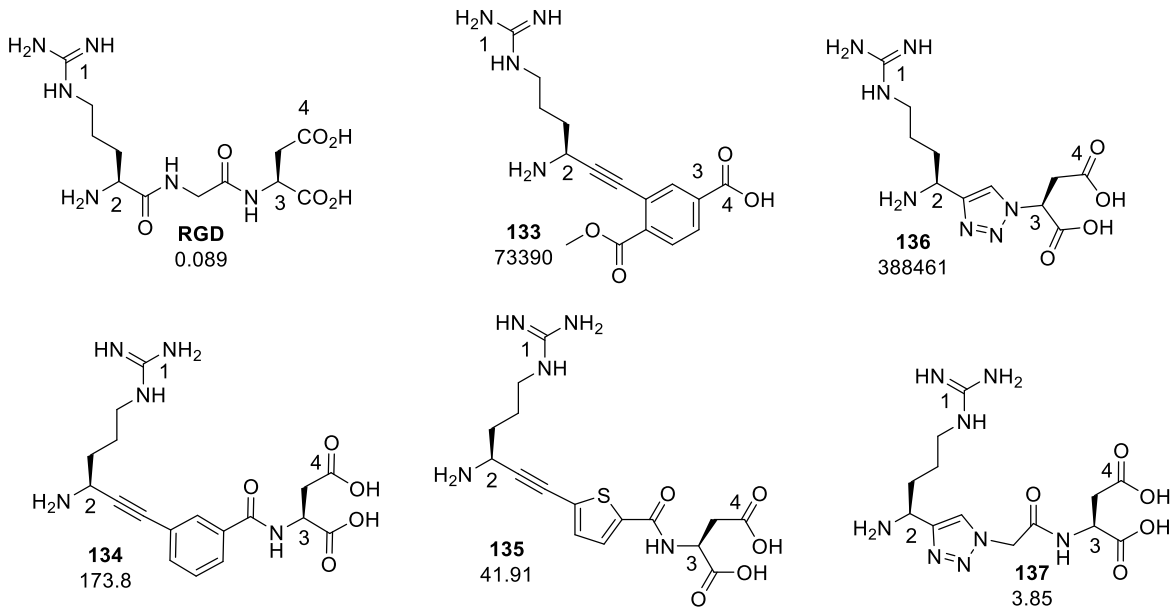


Figure EP11: Class B peptidomimetics **133-137** as analogues of the RGD sequence (also depicted). All compounds were used for docking experiments in order to deduce information about bond lengths and dihedral angles in convenient conformations for interaction with integrin αvβ3. The linear RGD sequence was used as reference compound [143]. Crucial atoms for the conformation are labeled.

Table EP34: Bond lengths and dihedral angles in compounds **133-137**. Distances and angles were derived from conformations, convenient for the interaction with integrin αvβ3. Appropriate conformations were determined by docking experiments. Atom numbers refer to Figure EP11.

Compound	d(atom1-2) [Å]	d(atom2-3) [Å]	d(atom3-4) [Å]	α-torsion [°]	d(atom1-4) [Å]	IC_{50} [μM]
133	6.61	4.89	2.95	180	12.98	73390
134	5.90	9.35	2.57	-84	13.48	173.8
135	5.13	9.88	2.49	-124	15.21	41.91
136	6.61	4.05	3.81	141	13.33	388461
137	5.78	7.98	2.45	121	12.81	3.85

IIX-6. i) X-ray Structure Analysis

Dimethyl 5-Hydroxyisophthalate, the side product in the synthesis of aromatic halide **120**. Colorless crystals, appropriate for X-ray structure analysis were obtained by concentrating slowly up a solution of dimethyl 5-hydroxyisophthalat in a mixture of PE/EtOAc (2:1) at ambient temperature and pressure.

Crystal Data for $C_{10}H_{10}O_5$ (M = 210.18 g mol^{-1}): orthorhombic, space group Fdd2 (no. 43), a = 41.5876(15) Å, b = 23.9061(9) Å, c = 3.78390(10) Å, V = 3761.9(2) Å^3, Z = 16, T = 100.01(10) K, μ(CuKα) = 1.032 mm^{-1}, *Dcalc* = 1.484 g/cm^3, 9822 reflections measured (8.504° ≤ 2Θ ≤ 152.12°), 1731 unique (R_{int} = 0.0244, R_σ = 0.0158) which were used in all calculations. The final R_1 was 0.0256 for 1648 reflections with $I > 2\sigma(I)$ and wR_2 was 0.0732 for all data.

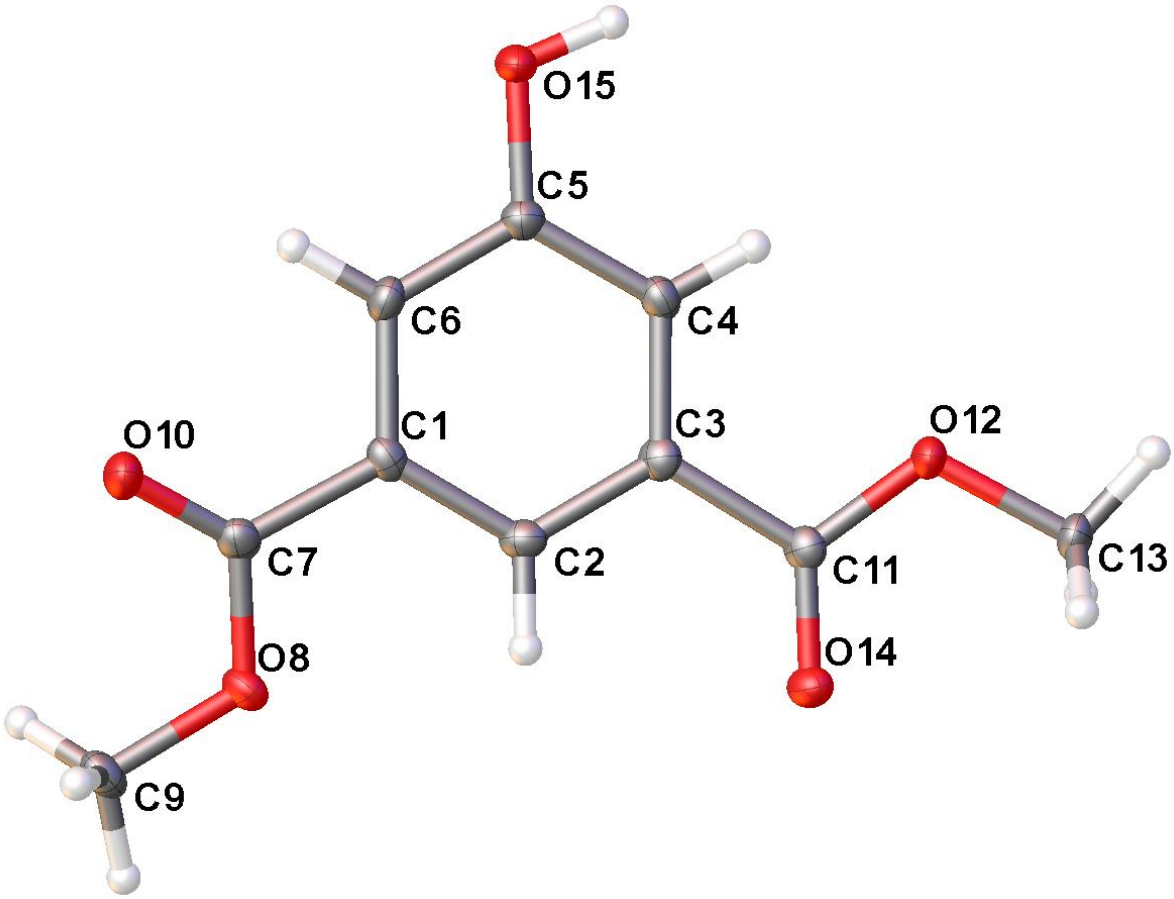


Table EP35. Fractional Atomic Coordinates (×104) and Equivalent Isotropic Displacement Parameters (Å²×103) for Dimethyl 5-Hydroxyisophthalat. Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

Atom	*x*	*y*	*z*	U(eq)
O8	5370.7(4)	5266.9(6)	-676(5)	19.2(4)
O14	5203.2(3)	3349.7(6)	3845(5)	20.7(4)
O12	5630.2(4)	2908.4(6)	6175(5)	18.8(4)
O15	6554.8(4)	4226.8(7)	5102(5)	22.0(4)
O10	5821.3(4)	5730.9(6)	739(5)	23.6(4)
C2	5587.1(5)	4303.8(9)	2523(7)	16.1(5)
C3	5711.0(5)	3814.6(9)	3958(7)	15.6(5)
C11	5485.0(5)	3340.9(9)	4618(7)	15.6(5)
C1	5789.7(5)	4760.5(9)	2040(6)	15.4(5)
C5	6236.6(5)	4236.3(9)	4290(7)	16.9(5)
C6	6113.3(5)	4730.3(9)	2929(7)	16.9(5)
C7	5666.9(5)	5300.0(9)	649(7)	16.8(5)
C4	6036.7(5)	3777.8(9)	4827(7)	16.1(5)
C13	5423.5(6)	2436.8(10)	7001(8)	19.0(5)
C9	5236.4(6)	5782.6(10)	-2062(7)	20.3(5)

IIX-6. j) References (248-263)

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Appendix