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Peptide–Heterocycle Chimera: New Classes of More Drug-Like Peptidomimetics by Ligations of Peptide–Bis(electrophiles) with Various Bis(nucleophiles)

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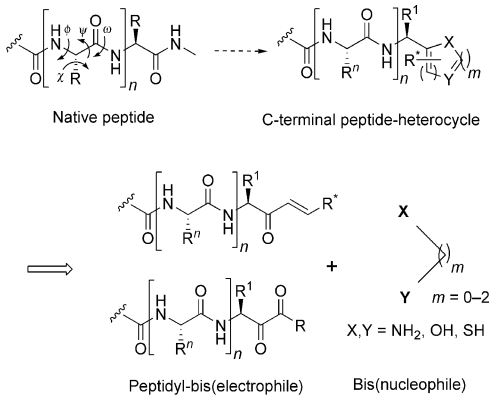
Several C-terminal peptidyl-substituted bis- and tris(electrophiles) were prepared by starting from polymeric phosphoranylidenacetates as acyl anion equivalents. After *C*-acylations with amino acids and peptide elongation, the obtained peptidyl-phosphoranylideneacetate resins were either cleaved oxidatively, delivering peptidyl-diketo esters, or saponified, leading to immediate decarboxylation. The generated peptidyl-phosphorane could be treated with aldehydes to yield peptidyl vinyl ketones or could be cleaved oxidatively to yield peptidyl keto aldehydes. Ligation with various bis(nucleophiles) including hydrazines, hydroxylamine, diamines, amino-thiols, amidines, and guanidines were investigated in the formation of peptide-heterocycle chimera containing pyrazoline, pyrazole, isoxazole, isoxazoline, thiazepine, quinoxaline, and imidazolone heterocycles.

Introduction

Most functions within biological systems are exerted by proteins and are based on the enormous diversity of their secondary, tertiary and quaternary structures, which are encoded in sequences composed of a limited set of 20 amino acids.[1]

Protein binders are of primordial importance for the study of functions and structures of proteins in chemical biology and can in many cases be used as drug molecules.[2] Methods to develop novel protein-binding molecules are therefore of general interest. In many cases the native protein binders are other proteins or peptides derived thereof.[3] Peptides are especially well suited as protein binders because they provide the hydrogen-bonding patterns of proteins and their complete side chain diversity. The use of peptide ligands in chemical biology and medicinal chemistry, however, is limited severely for several reasons.[3,4] Most of the shorter peptides are conformationally flexible: they do not possess rigid solution structures, which leads to decreased binding affinities and biological activities. Moreover, peptidic ligands are prone to proteolytic degradation under physiological conditions, often possess no significant bioavailability and in most instances do not permeate through biological membranes.[5]

For these reasons, small, nonpeptidic interfering molecules can be a powerful complementation to peptides. Heterocycles are especially suitable as drugs, due to their limited flexibility and the low numbers of rotating bonds found in these molecules (Scheme 1).[6] Moreover, many heterocycles contain both hydrogen bond acceptor and donor sites. Heterocycles often possess high polarizabilities for efficient interactions with hydrophobic pockets and the release of water from them, and many of these molecules are highly membrane permeable and metabolically stable.



Scheme 1. Synthesis of peptidyl-substituted heterocycles from peptidyl-bis(electrophiles) and bis(nucleophiles).

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Molecular combinations of peptides and heterocycles have been investigated with the goal of blending the desirable properties of peptides with those of heterocycles to obtain powerful, bioactive and still bioavailable, metabolically stable and membrane-permeable molecules.[4c] Such combinations have been especially successful in those cases in which peptides are the native substrates of ligands of the targeted protein, such as in the field of protease inhibitors. Novel structural combinations of heterocycles and peptides are therefore highly desirable.[6] Because many novel structures of this type can be envisioned, however, a rationale for the selection of newly synthesized molecules is required. Recently we have conducted a substructure analysis of the World Drug Index (WDI) and have identified 561 privileged substructures found with high probability in bioactive molecules.[7] As expected, the majority of these substructures contain aromatic rings and heterocycles. The presence of these heterocyclic substructures is highly characteristic for newly admitted drugs, and also for those that contain new chemical entities (NCEs), which in the predominant number of cases are novel combinations of the 561 privileged substructures.

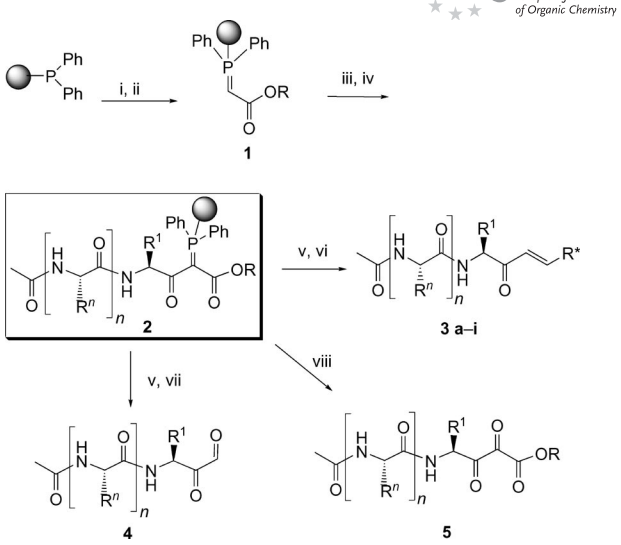
This maximum common substructure concept should be useful as well for the design of novel, potentially bioactive peptide–heterocycle chimera. Hitherto the standard approach to combine heterocycles and peptide has been to incorporate heterocycles in the side chains of amino acid building blocks or/and to integrate heterocycles through standard acylations of amino groups of the peptide and the heterocycles.[8] Only a few examples have been accomplished in which heterocycles are integrated in the peptide backbone itself, because this in most cases requires specific, C-terminal derivatization of peptides.[9]

Over recent years we have developed a set of methods for the C-terminal variation of peptides through polymer-supported synthesis on reagent linkers of type **1** (Scheme 2).[10] As a result, several novel peptidyl-substituted bis- and tris(electrophiles) – namely the peptidyl vinyl ketones **3**, the peptidyl-substituted α-keto aldehydes **4**, and the peptidyl diketo esters **5**[10d] – have become accessible. In this contribution we have now investigated the potential of these starting materials to provide novel peptide–heterocycle chimera.

Results and Discussion

Synthesis of Peptide Bis- and Triselectrophiles

We have recently reported that the *C*-acylation of polymer-supported 2-phosphoranylidene acetates of type **1** and subsequent peptide elongation yields the 3-oxo-4-(peptidylamino)-2-phosphoranylidenebutanoates **2** ("peptidyl-phosphoranylidenacetates", see Scheme 2).[10d] Oxidative cleavage with, for example, dimethyldioxirane (DMDO) or Wittig-type linker cleavage provided access to a wide variety of C-terminally modified peptide derivatives.



Scheme 2. Synthesis of peptidyl-substituted bis(electrophiles): i. $BrCH_2COOR$ (5 equiv.), toluene, 100 °C (MW), 15 min; ii. TEA (5 equiv.), CH_2Cl_2, room temp., 2 h; iii. Fmoc-AA (5 equiv.), 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT, 5 equiv.), 2,6-lutidine (5 equiv.), CH_2Cl_2, room temp., 12 h; iv. piperidine/DMF (20%), acylation/coupling steps (SPPS; Fmoc-AA, DIC, HOBT); v. for R = $C_2H_4Si(CH_3)_3$: tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F, 5 equiv.), DMF, room temp., 3 h; vi. R*CHO (3 equiv.), THF, room temp. (R* aliphatic) or 60 °C (R* aromatic), 12 h; vii. DMDO/acetone/CH_2Cl_2, 0 °C, 30 min; viii. DMDO/acetone/CH_2Cl_2, room temp., 1 h.

Decarboxylative saponification followed by treatment with an aldehyde furnished the peptidyl-1-aminobut-3-en-4-ones (peptidyl vinyl ketones) **3a**–**i** (Scheme 2, Table 1). Decarboxylative saponification and oxidative cleavage of **2** provided the 2-oxo-3-(peptidylamino)propanals (peptidyl-substituted α-keto aldehydes) **4**, whereas immediate oxidation provided the peptidyl-substituted 4-amino-2,3-dioxobutanoates (peptidyl-substituted 2,3-diketo esters) **5**. In this work we now have investigated applications of the newly prepared peptidyl bis- and triselectrophiles **3**, **4** and **5** for the preparation of peptide–heterocycle chimera.

Table 1. Synthesis of the peptidyl vinyl ketones **3a**–**3i**.

	Ac-peptidyl	R^1	R*	Yield[a]
3a	Ac-Phe	benzyl	isobutyl	80
3b	Ac-Phe	benzyl	2-chloro-6-fluorophenyl	62
3c	Ac-Phe	isopropyl	2-thienyl	85
3d	Ac-Leu	benzyl	2-chloro-6-fluorophenyl	64
3e	Ac-Phe	isopropyl	2-chloro-6-fluorophenyl	61
3f	Ac-Phe	isopropyl	tribromomethyl	80
3g	Ac-Phe-Ala	benzyl	methyl	90
3h	Ac-Phe-Ala	benzyl	isobutyl	80
3i	Ac-Val	benzyl	ethyl	80

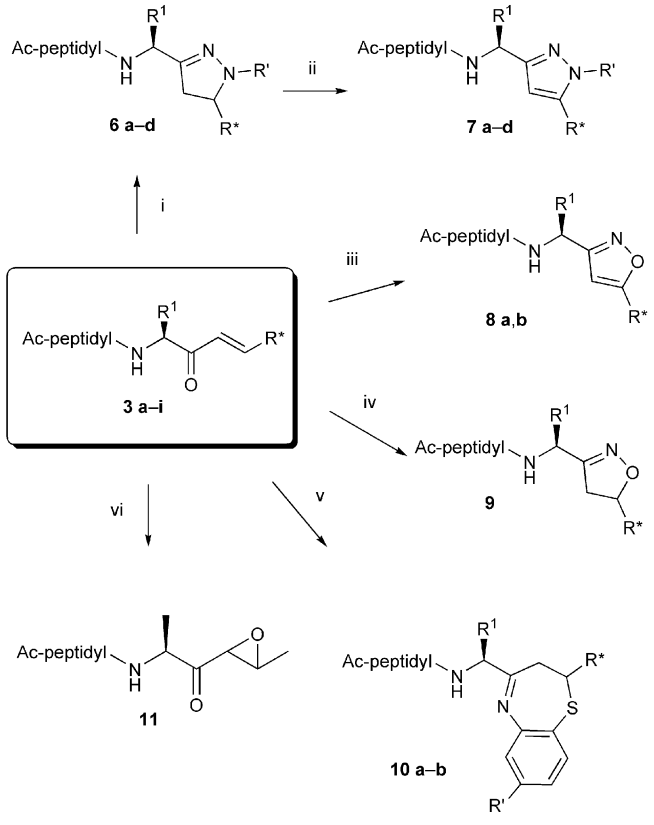
[a] Isolated yields, purities of isolated products >95%.

Peptidyl-Pyrazolines 6a–d and Peptidyl-Pyrazoles 7a–d

Pyrazoles were selected as our primary heterocyclic goals. They have been reported to display a wide range of biological activities and are commonly obtained from hy-

drazines as bis(nucleophiles) and various 1,3-bis(electrophiles). Accordingly, the peptidyl vinyl ketones **3a**–**i** (Scheme 2, Table 1) appeared to be realistic starting points for the preparation of peptidyl-pyrazoles.[11]

Reaction conditions yielding the desired peptidyl-pyrazolines were investigated with respect to regioselective and diastereoselective ring formation; in addition, the oxidation state of the resulting heterocyclic product had to be controlled. The presence of a strong base such as sodium methoxide led to rapid cyclization at room temperature. Presumably the hydrazines are deprotonated under these conditions and react by Michael addition followed by allowed 5-*exo*-*tet* ring closure. The products were obtained as diastereomeric mixtures of pyrazolines with pyrazoles. In order to reduce epimerization, the reaction was conducted in the absence of a strong base, yielding exclusively 1,3,5-trisubstituted heterocycles. Formation of these regioisomers can be explained by the initial formation of hydrazone intermediates followed by formal 5-*endo*-*trig* cyclization. The occurrence of this formally disfavoured cyclization step can be explained by assuming a 6π-electron electrocyclic mechanism.[12]



Scheme 3. Synthesis of three- to seven-membered peptidyl-substituted heterocycles from peptidyl vinyl ketones: i. NH_2-NHR′ (3 equiv.), THF, 60 °C, 8 h; ii. DDQ (1.2 equiv.), toluene, room temp., 12 h; iii. hydroxylamine (1.2 equiv.), CH_3COOH (5 mol-%)/CH_3COONa (few crystals), 80 °C, 8 h; iv) hydroxylamine (1.2 equiv.), CH_3COOH (5 mol-%)/CH_3COONa (few crystals), 80 °C, 8 h, under N_2; v) 2-aminothiophenol (3 equiv.), acetic acid (5 mol-%), 80 °C, 12 h, under N_2; vi) DMDO/acetone (3–4 equiv.), CH_2Cl_2, –20 °C to room temp., 8 h.

Under air, mixtures of the pyrazolines **6** and the pyrazoles **7** (Scheme 3) were obtained from the peptidyl vinyl ketones **3a**–**i** with use of several aliphatic or aromatic hydrazines in DMSO at 80 °C. On switching to nitrogen, the pyrazolines **6** were obtained in good purities and yields in THF at only 60 °C. The peptidyl-pyrazolines were stable towards oxidation when stored for several months under nitrogen at 4 °C.

Consequently, the desired peptidyl-pyrazoles **6a**–**d** were prepared by oxidation of the peptidyl-pyrazolines. Oxidation was best accomplished with 2,3-dichloro-4,5-dicyanoquinone (DDQ) as oxidant and was complete in 8 h at room temp. The 1,3,5-substituted peptidyl-pyrazoles **7a**–**d** were obtained regioselectively and in high purities and yields from both aliphatic and aromatic hydrazines (Table 2). All compounds could be characterized by HPLC, high-resolution mass spectrometry and NMR spectroscopy. The spectra of the prevalent diastereomers have been fully assigned. Epimeric products in the heterocyclic position were quantified in the ^{1}H NMR spectra and were found in the following ratios: **7b** 1:3, **7c** 1:4, and **7d** 1:2.

Table 2. Synthesis of peptidyl-pyrazolines **6a**–**6d**, pyrazoles **7a**–**7d**, isoxazoles **8a**, **8b**, isoxazolines **9**, thiazepines **10a**, **10b**, and oxiranes **11**.

	Ac-peptidyl	R^1	R*	R′	Yield[a]
6a	Ac-Phe-Ala	benzyl	methyl	H	65
6b	Ac-Phe-Ala	benzyl	methyl	methyl	61
6c	Ac-Phe-Ala	benzyl	isobutyl	H	67
6d	Ac-Phe-Ala	benzyl	isobutyl	methyl	78
7a	Ac-Phe-Ala	benzyl	methyl	H	>90
7b	Ac-Phe-Ala	benzyl	methyl	methyl	>90
7c	Ac-Phe-Ala	benzyl	methyl	isobutyl	>90
7d	Ac-Phe-Ala	benzyl	methyl	phenyl	>90
8a	Ac-Val	benzyl	ethyl	–	80
8b	Ac-Phe	benzyl	2-chloro-6-fluorophenyl	–	85
9	Ac-Phe	benzyl	isobutyl	–	68
10a	Ac-Phe	benzyl	isobutyl	chloro	55
10b	Ac-Phe	benzyl	2-chloro-6-fluorophenyl	chloro	71
11	Ac-Phe-Ala	benzyl	methyl	–	40

[a] Isolated yields, purities of isolated products >95%.

Peptidyl-Isoxazoles 8a, 8b and Isoxazolines 9

Isoxazoles and isoxazolines were targeted as a second family of heterocycles with interesting biological activities.[13] From the readily available starting peptidyl vinyl ketones **3**, isoxazole synthesis was conducted with hydroxylamine in EtOH together with a catalytic amount of acetic acid (5 mol-%) and a few crystals of sodium acetate under air (Scheme 3, Table 2).[14] Under these conditions, the oxidized isoxazoles **8a** and **8b** were obtained in cases of an aliphatic substituent in the vinylic position (**8a**: R* = ethyl) or of an aromatic vinyl ketone (**8b**: R* = 2-chloro-6-fluorophenyl). When the same reaction was carried out under nitrogen the non-oxidized isoxazoline **9** (R* = isobutyl) was isolated. For both products, LC-MS and NMR experiments indicated the predominant formation of a single enantiomer that could be isolated by preparative HPLC.

Peptidyl-Benzodiazepines

In our ongoing investigations into the preparation of peptidyl-substituted heterocycles based on the peptidyl vinyl ketones **3** (Scheme 3), we decided to investigate the synthesis of peptidyl-benzodiazepines. 1,4-Benzodiazepines are privileged protein ligands with high pharmacological relevance.[15] At first, the peptidyl vinyl ketones **3** were treated with *o*-phenylenediamine at 80 °C without base. No desired condensation product was detected under these conditions. Instead, addition of Et_3N at 80 °C led to the formation of mixtures of compounds with the masses of the expected dihydrobenzodiazepines detected by LC-MS, but chromatography did not deliver pure diazepine derivatives.[16]

Peptidyl-Thiazepines 10a, 10b

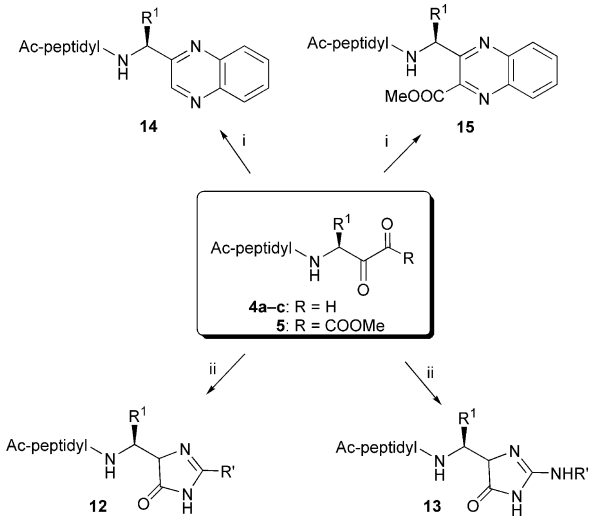
The peptidyl-thiazepines **10a** and **10b**, representing another class of peptidyl-substituted heterocycles, were accessible through [4+3] annulations of the peptidyl vinyl ketones **3** with *o*-aminothiophenol. The literature suggested their synthesis at elevated temperatures under acid catalysis conditions (80 °C, 12 h, N_2, AcOH).[17] The desired products **10a** and **10b** were formed, isolated by HPLC and characterized by ^{1}H NMR and LC-MS experiments. Attempts to reduce the reaction times by elevating the temperature under microwave irradiation conditions were unsuccessful. After 15 min MW at 120 °C only traces of the products (3–5%) were detected, with no starting materials left. The reactivity of the vinyl ketones varied with the vinyl substituents; the aromatic vinyl ketone **3b** reacted more smoothly than the aliphatic vinyl ketone **3a**.

Peptidyl-Oxiranes 11

In an extension of this approach to novel peptidyl-substituted heterocycles we investigated the syntheses of the peptidyl-oxiranes **11** (Scheme 2, Table 2). DMDO is known as an efficient and rapidly developing oxidant and operates under strictly neutral conditions,[18] so we used DMDO for the conversion of peptidyl vinyl ketones into their epoxides. The epoxidation was conducted by adding freshly prepared DMDO to the peptidyl vinyl ketone **3g** at room temp. in acetone under N_2. The conversion of electron-rich olefins should normally be complete within two hours according to the reported literature.[19,18a] Because the peptidyl vinyl ketone **3g** is electron-poor in relation to the reported olefins, 12 h were therefore required for its complete conversion into the peptidyl-oxirane **11**, with the workup simply consisting of evaporation of excess DMDO and acetone. The epoxide was obtained in good yield (80%) as a 1:1 ratio of epoxide diastereomers according to the ^{1}H-^{1}H COSY-NMR spectrum.

Peptidyl-Imidazolones 12, 13

Prompted by the positive results obtained from the peptidyl vinyl ketone bis(electrophiles) we decided to extend this concept to peptidyl keto aldehydes and peptidyl diketo esters as bis(electrophiles) (Scheme 4). The peptidyl keto aldehydes **4** were found to react smoothly with both amidines and guanidines as bis(nucleophiles).



Scheme 4. Synthesis of peptidylheterocycles from the peptidyl keto aldehydes **4a**–**c** and the peptidyl diketo ester **5**; i) 1,2-phenylenediamine (1.5 equiv.), CH_2Cl_2, room temp., N_2, 12 h (**14** was formed within 8 h); ii) amidine or guanidine derivative (3 equiv.), DMF/0.1% AcOH, room temp., 8 h.

In both cases, 2-substituted imidazol-4-ones were identified and isolated as single products, the 2-phenyl-substituted imidazolones **12a** and **12b** from phenyl amidine and the 2-phenyl-amino-imidazolone **13** from phenyl guanidine.

Peptidyl-Quinoxalines 14, 15

Analogous reactions of the peptidyl α-keto aldehyde **4** or the peptidyl 2,3-diketo ester **5** were investigated with 1,2-diamines as bis(nucleophiles) (Scheme 4, Table 3) Cyclocondensation of **5** with *o*-phenylenediamine was accomplished in EtOH at 60 °C in 3 h or in CH_2Cl_2 at room temperature in 12 h, leading to the peptidyl-quinoxaline **14** in very good yield and high purity (Scheme 4, Table 3).[20] Characterization by NMR spectroscopy confirmed the stereospecificity of this reaction. The peptidyl-substituted keto aldehyde **4** was even more reactive under these conditions. The reaction with 1,2-phenylenediamine in CH_2Cl_2 proceeded smoothly at room temp. After 8 h the starting material had been consumed, yielding the quinoxaline **15** again without epimerization of the peptide part.

Table 3. Synthesis of the peptidyl-imidazolones **12** and **13** and the peptidyl-quinoxalines **14** and **15**.

	Ac-peptidyl	R^1	R′	Yield[a]
12a	Ac-Val	benzyl	phenyl	67
12b	Ac-Ala	isopropyl	phenyl	70
13	Ac-Ala	isopropyl	2-imidazolyl	75
14	Ac-Phe-Ala	benzyl	–	75
15	Ac-Phe-Ala	isobutyl	–	64

[a] Isolated yields, purities of isolated products >95%.

Conclusions

We have reported a flexible synthesis of the C-terminal peptide bis- and tris(electrophiles) **3**, **4** and **5** (Scheme 1). All of these attractive peptide mimetics were successfully converted into novel peptide–heterocycle chimera under mild conditions. The peptidyl vinyl ketones served as starting materials for the synthesis of C-terminal peptidyl-pyrazolines **6**, pyrazoles **7**, isoxazoles **8** and isoxazolines **9**, which were formed by gentle heating or with mild acid catalysis. All five-membered ring heterocycles were formed regioselectively and in good yields. The peptidyl-thiazepines **10** and oxiranes **11** were also obtained in high yields but as diastereomeric mixtures.

The peptidyl diketo esters and keto aldehydes were ligated smoothly with bis(nucleophiles) at room temperature. Peptidyl-imidazolones were readily formed from the peptidyl α-keto aldehydes **4**, phenylamidine delivered the 2-phenyl-substituted imidazolones **12**, whereas the corresponding guanidine furnished the 2-amino-substituted imidazolone **13**. The peptidyl-quinoxalines **14** and **15** based on the starting materials **4** and **5** were prepared without epimerization as well.

In general, the peptidyl keto aldehydes were found to be the most reactive bis(electrophiles), followed by the peptidyl diketo esters and the peptidyl vinyl ketones. The reactions with the peptidyl keto aldehydes especially proceed smoothly at room temperature both in nonpolar and in polar or protic solvents and so can be regarded as ligation reaction. Although only amino acids without side chain functionalities were used in all examples considered in this article, one can already predict the reactivity of arginine residues with peptidyl keto aldehydes and peptidyl diketo esters.

The chemistry presented here should be of specific value if heterocycles are to be integrated in peptidic ligands. In order to select the best-fitting heterocycle for a given protein target, however, further studies considering the preferred conformations of peptide–heterocycle chimera will be required.

Experimental Section

General Methods: Unless otherwise stated, all reagents were obtained from commercial suppliers and were used without further purification. Dry solvents were purchased and stored over molecular sieves. Solid-phase chemistry was performed in polypropylene syringes with Teflon® filters. Triphenylphosphane–polystyrene resin was purchased from Fluka. Microwave-assisted solid-phase reactions were performed with a Biotage Initiator monomodal microwave reactor. Resins were washed with DMF, THF, toluene and CH_2Cl_2 unless otherwise stated. Resin loadings were determined by photometric determination after Fmoc cleavage. Solid-phase reactions were monitored by FT-ATR-IR spectra of the resins recorded with a Bruker Tensor 27 FT-IR spectrometer. Purification of products was performed with a semipreparative HPLC column (10 μm, 250 × 20 mm, Grom-SIL 300 ODS-5 ST RP-C18) with use of individual gradients derived from analytical runs. LC-MS was conducted with an Agilent 1100 Series HPLC system with an ESI-MS and single quadrupole detector. HRMS measurements were conducted with an Agilent 6220 accurate mass ESI-ToF-MS. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 300 MHz instrument and chemical shifts were measured in parts per million (ppm).

General Procedure for the Preparation of the Peptidylvinyl Ketones 3a–3i: The aldehyde (2 equiv., 0.76 mmol) was added to a suspension of a peptidyl-substituted α-keto methylenetriphenylphosphorane generated from **2** after the saponification of the protecting group (200 mg, 1.27 mmol g^{-1}, 0.254 mmol) in dry THF (1 mL) and the mixture was stirred for 8 h either at room temp. (aliphatic aldehydes) or at 60 °C (aromatic aldehydes). Solvent was removed under reduced pressure with a rotary evaporator. The residue was subjected to purification by preparative HPLC to afford the product. The pure compounds were characterized by LC-MS and NMR spectroscopy.

(1*S*,3*E*)-1-[(*N*-Acetyl-L-phenylalanyl)amino]-1-benzyl-6-methylhept-3-en-2-one (3a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, J = 9.8 Hz, 3 H, CH_3, isobutyl), 0.95, (d, J = 8.5 Hz, 3 H, CH_3, isobutyl), 1.65–1.81 (m, 1 H, *CH*, isobutyl), 1.94 (s, 3 H, CH_3CO), 2.07 (bt, J = 6.1 Hz, 2 H, CH_2, isobutyl), 2.9–3.2 (m, 4 H, $C^{\beta1,\beta1',\beta2,\beta2'}H$, Phe, benzyl), 4.64–4.78 (m, 1 H, $C^{\alpha}H$, Phe), 4.85–5.05 (m, 1 H, $C^{\alpha}H$, benzyl), 6.05 (d, J = 15.9 Hz, 1 H, *CH*, olefin), 6.15 (d, J = 7.3 Hz, 1 H, NH^{I}), 6.56 (d, J = 7.3 Hz, 1 H, NH^{II}), 6.86–7.06 (m, 10 H arom. Phe 1, Phe 2, *CH*, olefin) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 22.7, 27.3, 37.6, 37.8, 41.4, 53.9, 56.6, 126.5, 126.5, 127.6, 127.9, 128.1, 128.7, 128.9, 135.3, 135.9, 148.9, 169.3, 169.9, 195.6 ppm. HRMS: calcd. $[M + H]^+ = [C_{26}H_{33}N_2O_3]$ 421.2481; found 421.2456; (85 mg, 80%).

(1*S*,3*E*)-1-[(*N*-Acetyl-L-phenylalanyl)amino]-1-benzyl-4-(2-chloro-6-fluorophenyl)but-3-en-2-one (3b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (s, 3 H, CH_3CO), 2.98–3.19 (m, 4 H, $C^{\beta1,\beta2}H_2$, benzyl, $C^{\beta1,\beta2}H_2$, Phe), 4.65–4.74 (m, 1 H, $C^{\alpha}H$, Phe), 4.99–5.06 (m, 1 H, $C^{\alpha}H$, benzyl), 6.14–6.17 (d, J = 8.55 Hz, 1 H), 6.56–6.59 (d, J = 7.33 Hz, 1 H), 6.95–7.33 (m, 13 H, 2-chloro-6-fluorophenyl, benzyl, Phe, $C^{\alpha}H$, $C^{\beta}H$, vinyl), 7.80–7.81 (d, J = 4.88 Hz, 1 H, NH^{I}), 7.85–7.86 (d, J = 4.88 Hz, 1 H, NH^{II}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7, 37.1, 37.9, 53.9, 57.9, 114.3, 114.7, 120.9, 121.1, 125.7, 126.7, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128, 128.9, 130.9, 133.9, 135.0, 135.9, 135.9, 136.2, 136.3, 169.5, 170.0, 195.7 ppm. HRMS: calcd. $[M + H]^+ = [C_{28}H_{27}ClFN_2O_3] + Et_3N$ 595.2926; found 595.2939; (77.5 mg, 62%).

(1*S*,3*E*)-1-[(*N*-Acetyl-L-phenylalanyl)amino]-1-isopropyl-4-(2-thienyl)but-3-en-2-one (3c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, J = 8.95 Hz, 3 H, $C^{\gamma1}H_3$, isopropyl), 0.96 (d, ^3J = 8.94 Hz, 3 H, $C^{\gamma2}H$, isopropyl), 2.0 (s, 3 H, CH_3CO), 2.90–2.95 (m, 1 H, $C^{\beta1,\beta2}H_2$, isopropyl), 3.08–3.11 (m, 2 H, $C^{\beta1,\beta2}H_2$, Phe), 4.64 (m, 1 H, $C^{\alpha}H$, Phe), 4.74 (m, 1 H, $C^{\alpha}H$, isopropyl), 7.08–7.55 (m, 7 H, *Phe*, *thiophene*, $C^{\alpha}H$, $C^{\beta}H$, vinyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 23.3, 32.0, 34.2, 50.1, 56.4, 121.3, 126.5, 127.6, 128.1, 128.5, 128.7, 130.4, 132.4, 135.6, 143.5 ppm. HRMS: calcd. $[M + H]^+ = [C_{22}H_{27}N_2O_3S] + Et_3N$ 500.2959; found 500.2967; (85 mg, 85%).

(1*S*,3*E*)-1-[(*N*-Acetyl-L-leucinyl)amino]-1-benzyl-4-(2-chloro-6-fluorophenyl)but-3-en-2-one (3d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, J = 7.3 Hz, 3 H, $C^{\delta}H_3$, Leu), 0.98, (d, J = 6.1 Hz, 3 H, $C^{\delta2}H3$, Leu), 1.14–1.28 (m, 2 H, $C^{\beta1,\beta2}H_2$, Leu), 1.32–1.50 (m, 1 H, $C^{\gamma}H$, Leu), 1.76 (s, 3 H, CH_3CO), 2.85 (dd, J_1 = 15.0, J_2 = 9.7 Hz, 1 H, $C^{\beta1}H$, benzyl), 3.15 (dd, J_1 = 15, J_2 = 8.5 Hz, 1 H, $C^{\beta2}H$, Phe), 4.27 (m, 1 H, $C^{\alpha}H$, benzyl), 4.71 (m, 1 H, $C^{\alpha}H$, Leu), 7.13 (d, J = 15.8 Hz, 1 H, $C^{\alpha}H$, vinyl), 7.15–7.50 (m, 5 H, benzyl, 2-chloro-6-fluorophenyl), 7.6 (d, J = 14.7 Hz, 1 H, $C^{\beta}H$, vinyl), 7.68 (dd, J = 8.5, J = 4.9 Hz, 1 H, 2-chloro-6-fluorophenyl), 7.95

(d, J = 8.6 Hz, 1 H, NH^{I}), 8.54 (d, J = 8.6 Hz, 1 H, NH^{II}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 22.3, 22.6, 23.9, 37.9, 40.9, 50.8, 58.6, 115.9, 116.2, 121.1, 121.5, 126.2, 126, 127.9, 128, 129.2, 129.3, 136.1, 136.2, 137.5, 137.7, 160.6, 168.7, 168.8, 172.3, 172.5, 178.2 ppm. HRMS: calcd. $[M + H]^+ = [C_{25}H_{29}ClFN_2O_3] + Et_3N$ 561.3082; found 561.3110; (73.6 mg, 64%).

(1*S*,3*E*)-1-[(*N*-Acetyl-L-phenylalanyl)amino]-1-isopropyl-4-(2-chloro-6-fluorophenyl)but-3-en-2-one (3e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, J = 7.3 Hz, 3 H, $C^{\gamma 1}H_3$ isopropyl), 0.89 (d, J = 7.3 Hz, 3 H, $C^{\gamma 2}H_3$ isopropyl), 1.74 (s, 3 H, CH_3CO), 1.27 (m, 1 H, $C^{\beta}H$, isopropyl), 2.71 (dd, J_1 = 14.6, J_2 = 9.7 Hz, 1 H, $C^{\beta 1}H$, Phe), 2.95 (dd, J_1 = 13.4, J_2 = 4.9 Hz, 1 H, $C^{\beta 2}H$, Phe), 4.37 (t, J = 7.3 Hz, 1 H, $C^{\alpha}H$, isopropyl), 4.64 (ddd, J = 9.8, J = 9.8, 4.9 Hz, 1 H, $C^{\alpha}H$, Phe), 7.07–7.24 (m, 5 H Phe, 2-chloro-6-fluorophenyl), 7.32 (dd, J_1 = 7.3, J_2 = 2.4 Hz, 1 H, 2-chloro-6-fluorophenyl), 7.40 (d, J = 16.1 Hz, 1 H, $C^{\alpha}H$, vinyl), 7.45–7.51 (m, 2 H, Phe), 7.65 (d, J = 15.9 Hz, 1 H, $C^{\beta}H$, vinyl), 8.14 (d, J = 8.5 Hz, 1 H, NH^{I}), 8.39 (d, J = 7.3 Hz, 1 H, NH^{II}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 19.4, 22.4, 29.1, 37.5, 36.0, 53.4, 60.8, 115.4, 115.7, 120.9, 121.1, 126.1, 126.3, 126.4, 127.9, 129.1, 129.5, 129.7, 131.6, 131.7, 132.1, 132.3, 135.1, 135.2, 137.8, 159.6, 162.9, 169.0, 172.0, 197.2 ppm. HRMS: calcd. $[M]^+ = [C_{24}H_{27}ClFN_2O_3] + Et_3N$ 546.2893; found 546.2912; (70.1 mg, 61%).

(1*S*,3*E*)-1-[(*N*-Acetyl-L-phenylalanyl)amino]-5,5,5-tribromo-1-isopropylpent-3-en-2-one (3f): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.83 (d, J = 3.60 Hz, 3 H, $C^{\gamma 1}H_3$ isopropyl), 0.86 (d, J = 3.44 Hz, 3 H, $C^{\gamma 2}H_3$, isopropyl), 2.73 (s, 3 H, CH_3CO), 2.52–2.56 (br. s, 1 H, $C^{\beta}H$, isopropyl), 2.72 (br. s, 2 H, $C^{\beta 1\beta 2}H_2$, Phe), 4.3 (m, 1 H, $C^{\alpha}H$, Phe), 4.60–4.62 (m, 1 H, $C^{\alpha}H$, isopropyl), 6.9–7.24 (m, 7 H, *Phe*., $C^{\alpha}H$, $C^{\beta}H$, vinyl), 8.12, 8.93 (br. s, 2 H, NH^{I}, NH^{II}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 19.2, 22.4, 34.1, 36.2, 58.4, 93.8, 125.8, 126.5, 128.2, 136.3, 140.1, 167.2, 171, 178.4, 196.1; (116 mg, 80%) ppm.

(1*S*,3*E*)-1-[(*N*-Acetyl-L-phenylalanyl-L-alanyl)amino]-1-benzylpent-3-en-2-one (3g): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.14–1.16 (d, J = 7.33 Hz, 3 H, $C^{\beta}H_3$, Ala), 1.71 (s, 3 H, CH_3, vinyl), 1.84 (s, 3 H, CH_3CO), 2.66–2.77 (m, 2 H, $C^{\beta 1,\beta 2}H_2$, Phe), 2.94–3.06 (m, 2 H, $C^{\beta 1,\beta 2}H_2$, benzyl), 4.21–4.26 (m, 1 H, C$^{\alpha}$H, benzyl), 4.44–4.47 (m, 1 H, $C^{\alpha}H$, Phe), 4.66–4.68 (m, 1 H, C$^{\alpha}$H, Ala), 6.30–6.35 (d, J = 15.87 Hz, 1 H, $C^{\alpha}H$, vinyl), 6.81–6.89 (m, 1 H, $C^{\beta}H$, vinyl), 7.1–7.25 (m, 10 H, benzyl, Phe), 8.14–8.16 (d, J = 8.55 Hz, 1 H, NH^{I}, Phe), 8.28–8.24 (d, J = 7.33 Hz, 1 H, NH^{II}, Ala), 8.34–8.37 (d, J = 7.32 Hz, 1 H, NH^{II}, Phe-Ac) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 18.1, 22.4, 30.4, 34.3, 48.3, 57.4, 124.8, 126.0, 126.2, 128.0, 127.9, 129.0, 129.1, 137.5, 137.6, 137.1, 138.1, 138.0, 139.1, 143.8, 169.1, 171.1, 172.1, 196.7 ppm. HRMS: calcd. $[M + H]^+ = [C_{26}H_{32}N_3O_4]$ 450.2350; found 450.2347; (103 mg, 90%).

(1*S*,3*E*)-1-[(*N*-Acetyl-L-phenylalanyl-L-alanyl)amino]-1-benzyl-6-methylhept-3-en-2-one (3h): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.82–0.85 (d, J = 4.88 Hz, 6 H, CH_3CHCH_2), 1.13–1.15 (d, J = 7.32 Hz, 3 H, $C^{\beta}H_3$, Ala), 1.71 (s, 3 H, CH_3CO), 1.88 (m, 1 H, $C^{\delta}H$, vinyl), 2.03–2.17 (m, 2 H, $C^{\beta}H_2$, vinyl), 2.65–3.55 (m, 4 H, $C^{\beta 1,\beta 2}H_2$, benzyl, $C^{\beta 1,\beta 2}H_2$, Phe), 4.21–4.26 (t, J_1 = 14.65, J_2 = 7.32 Hz, 1 H, C$^{\alpha}$H, benzyl), 4.44–4.5 (m, 1 H, $C^{\alpha}H$, Phe), 4.67–4.7 (m, 1 H, $C^{\alpha}H$, Ala), 6.26–6.31 (d, J = 15.87 Hz, 1 H, $C^{\alpha}H$, vinyl), 6.7–6.86 (m, 1 H, $C^{\beta}H$, vinyl), 7.1–7.28 (m, 10 H benzyl, Phe), 8.22–8.25 (d, J = 8.55 Hz, 1 H, NH^{I}, Phe), 8.47–8.52 (d, J = 7.33 Hz, 1 H, NH^{II}, Ala), 8.63–8.66 (d, J = 7.32 Hz, 1 H, NH^{III}, Phe-Ac) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 22.1, 22.4, 22.8, 25.6, 27.2, 30.4, 34.4, 46.4, 53.9, 124.9, 126.0, 126.2, 127.9, 128.0, 128.1, 129.1, 137.6, 138.2, 139.2, 169.1, 171.1, 172.2, 196.9 ppm. HRMS: calcd. $[M + H]^+ = [C_{29}H_{38}N_3O_4]$ 492.2818; found 492.2830; (100 mg, 80%).

(1*S*,3*E*)-1-[(*N*-Acetyl-L-valinyl)amino]-1-benzylhex-3-en-2-one (3i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88–0.92 (dd, J_1 = 1.83, J_2 = 1.83 Hz, 6 H, $C^{\gamma 1}H_3$, $C^{\gamma 1}H_3$, Val), 1.00–1.05 (t, J_1 = 7.32, J_2 = 7.32 Hz, 3 H,CH_3-CH_2-vinyl), 2.02 (s, 3 H, CH_3CO), 2.20–2.25 (m, 3 H, $C^{\beta}H$ and CH_2CH_3, Val), 2.98–3.14 (m, 2 H, $C^{\beta}H_2$, benzyl), 4.26–4.31 (t, J_1 = 7.32, J_2 = 7.48 Hz, 1 H, C$^{\alpha}$H, benzyl), 4.88–4.90 (d, J = 7.33 Hz, 1 H, NH^{I}, benzyl), 5.06–5.13 (m, 1 H, $C^{\alpha}H$, Val), 6.08–6.13 (m, 1 H, CH, vinyl), 6.58–6.60 (d, J = 7.93 Hz, 1 H, CH, vinyl), 6.99–7.00 (d, J = 7.33 Hz, 1 H, NH^{II}, Val) 7.02–7.26 (m, 5 H, benzyl) ppm. HRMS: calcd. $[M + H]^+ = [C_{20}H_{29}N_2O_3]$ 345.2173; found 345.2170; (100 mg, 80%).

General Procedure for the Preparation of Peptidyl-Substituted α-Keto Aldehydes (4): Peptidyl-substituted α-keto methylenetriphenylphosphoranes (200 mg, 1.27 mmol g^{-1}, 0.254 mmol) were pre-swollen in dry CH_2Cl_2 (6 mL) in a 50 mL round-bottomed flask. Cold DMDO solutions (12 mL each, approx. 0.072 mmol mL^{-1}, 0.864 mmol, 3–4 equiv., –20 °C) were carefully added and the mixture was stirred for 30 min at 0 °C, during which the yellow-coloured resins turned pale (*Note*: cleavage from the resin can be accomplished by the use of only an equimolar amount of DMDO: i.e., 2 equiv.). The remaining DMDO, acetone and CH_2Cl_2 were removed in vacuo. The resulting white solids were characterized by LC-MS and used directly as starting material for the preparation of the peptidyl-imidazolinones **12** and the peptidyl-quinoxaline **14**.

(3*S*)-3-[(*N*-Acetyl-L-valinyl)amino]-3-benzyl-2-oxopropanal (4a): HRMS: calcd. {$[M + H]^+ = [C_{17}H_{23}N_2O_4]$ 319.1652; found 319.1659; 36 mg, 45%}.

(3*S*)-3-[(*N*-Acetyl-L-alaninyl)amino]-5-methyl-2-oxohexanal (4b): HRMS: calcd. {$[M + H]^+ = [C_{11}H_{19}N_2O_4]$ 243.13186; found 243.1389; 42 mg, 67%}.

(3*S*)-3-[(*N*-Acetyl-L-phenylalanyl-L-alanyl)amino]-3-benzyl-2-oxopropanal (4c): HRMS: calcd. {$[M + H]^+ = [C_{24}H_{28}N_3O_5]$ 438.5113; found 438.5118; 60 mg, 54%}.

Methyl (4*S*)-[(*N*-Acetyl-L-phenylalanyl)amino]-6-methyl-2,3-dioxoheptanoate (5): The resin **2** was pre-swollen in minimal dry CH_2Cl_2 in 50 mL round-bottom flask. Freshly prepared cold DMDO solutions (12 mL each, approx. 0.072 mmol mL^{-1}, 0.864 mmol, 3–4 equiv., –20 °C) were added and the mixtures were stirred for 1 h at room temp., during which the yellow-coloured resins turned pale. (Note: cleavage from the resin can be accomplished by the use of only an equimolar amount of DMDO: i.e., 2 equiv.). DMDO, acetone and CH_2Cl_2 were removed in vacuo. The obtained compounds were characterized by LC-MS and NMR. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.78 (d, J = 7.84 Hz, 3 H, $C^{\delta 1}H_3$, isopropyl), 0.82, (d, J = 7.81 Hz, 3 H, $C^{\delta 2}H_3$, isobutyl), 1.13 (d, J = 6.95 Hz, 3 H, $C^{\beta}H_3$, Ala), 1.27 (m, 1 H, $C^{\gamma}H$, isobutyl), 1.57 (m, 2 H, $C^{\beta 1,\beta 2}H_2$, isobutyl), 1.66 (s, 3 H, CH_3CO), 2.63 (dd, J_1 = 11.47, J_2 = 7.50 Hz, 1 H, $C^{\beta 1}H$, Phe), 2.90 (dd, J_1 = 11.23, J_2 = 7.40 Hz, 1 H, $C^{\beta 2}H$, Phe), 3.56 (s, 3 H, CH_3O), 4.23 (m, 1 H, $C^{\alpha}H$, isobutyl), 4.43 (m, 1 H, $C^{\alpha}H$, Phe), 4.88 (m, 1 H, $C^{\alpha}H$, Ala), 7.08–7.22 (m, 5 H, Phe), 7.87 (d, J = 7.51 Hz, 1 H, NH^{I}), 8.01 (d, J = 7.58 Hz, 1 H, NH^{II}), 8.10 (d, J = 7.87 Hz, 1 H, NH^{III}) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 17.7, 20.7, 22.1, 23.1, 24.0, 37.2, 47.6, 51.3, 52.0, 53.5, 125.9, 127.7, 128.8, 137.8, 168.8, 169.2, 170.8, 171.5, 204.4 ppm. HRMS: calcd. {$[M + H]^+ = [C_{23}H_{31}N_3O_7]$ 462.2240; found 462.2248; 90.1 mg, 77%}.

Procedure for the Preparation of the Peptidyl-Pyrazolines 6a–d: Hydrazine (3 equiv., 0.96 mg, 0.03 mmol) or methylhydrazine

(3 equiv., 1.38 mg, 0.03 mmol) in THF was added under N_2 to a stirred solution of the peptidyl vinyl ketone **3g** (1 equiv., 5 mg, 0.010 mmol), in THF. The reaction mixture was stirred at 60 °C for 8 h. By the same procedure, hydrazine (3 equiv., 1.0 mg, 0.033 mmol) or methylhydrazine (3 equiv., 1.5 mg, 0.033 mmol) was added to a stirred solution of the peptidyl vinyl ketone **3h** (1 equiv., 5 mg, 0.011 mmol). The solvent was removed under reduced pressure with a rotary evaporator. The resulting crude product was subjected to purification by preparative HPLC to afford the pyrazoline as a white solid. The obtained compounds were characterized by LC-MS and NMR spectroscopy.

Pyrazoline 6a: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.14–1.16 (d, J = 6.11 Hz, 3 H, CH_3-pyrazoline), 1.19–1.22 (d, J = 9.77 Hz, 3 H, C$^{\beta}H_3$, Ala), 1.73 (s, 3 H, CH_3CO), 2.53–2.54 (d, J = 4.89 Hz, 2 H, CH_2-pyrazoline), 2.63–2.71 and 2.93–3.11 (m, 4 H, $C^{\beta1,\beta2}H_2$, benzyl, $C^{\beta1,\beta2}H_2$, Phe), 4.16–4.20 (m, 1 H, *CH*, pyrazoline), 4.45–4.50 (m, 1 H, $C^{\alpha}H$, Ala), 4.65–4.75 (m, 1 H, $C^{\alpha}H$, benzyl), 5.0–5.10 (m, 1 H, $C^{\alpha}H$, Phe), 5.86 (s, 1 H, NH^{I}, pyrazoline), 7.16–7.27 (m, 10 H, *arom.* benzyl, Phe), 8.05–8.16 (d, J = 7.33 Hz, 1 H, NH^{I}, Phe), 8.19–8.21 (d, J = 8.55 Hz, 1 H, NH^{II}, Ala) ppm. HRMS: calcd. [M + H]$^+$ = [$C_{26}H_{34}N_5O_3$] 464.2508; found 464.2501; (3.6 mg, 65%).

Pyrazoline 6b: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.14–1.22 (m, 6 H, CH_3-pyrazoline, C$^{\beta}H_3$, Ala), 1.73 (s, 3 H, CH_3CO), 2.09–2.16 (m, 2 H, CH_2-pyrazoline), 2.55–3.0 (m, 8 H, C*H*-pyrazoline, CH_3-*N*-pyrazoline, $C^{\beta1,\beta2}H_2$ benzyl, $C^{\beta1,\beta2}H_2$, Phe), 4.16–4.20 (m, 1 H, $C^{\alpha}H$, Ala), 4.45–4.50 (m, 1 H, $C^{\alpha}H$, benzyl), 7.15–7.23 (m, 10 H, benzyl, Phe), 8.05–8.16 (d, J = 8.55 Hz, 1 H, NH^{I}, Phe), 8.19–8.21 (d, J = 7.33 Hz, 1 H, NH^{II}, Ala) ppm. HRMS: calcd. [M + H]$^+$ = [$C_{27}H_{36}N_5O_3$] 478.2673; found 478.2693; (3.0 mg, 61%).

Pyrazoline 6c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.79–0.85 [m, 6 H, $(CH_3)_2$, isobutyl], 1.12–1.34 (br. s, 5 H, CH_2-CH-isobutyl, C$^{\beta}H_3$, Ala), 1.51–1.58 (m, 1 H, *CH*-isobutyl), 1.73 (s, 3 H, CH_3CO), 1.76–1.78 (m, 2 H, CH_2-pyrazoline), 2.68–2.72, 2.84–3.01 (m, 4 H, $C^{\beta1,\beta2}H_2$, benzyl, $C^{\beta1,\beta2}H_2$, Phe), 3.49–3.53 (m, 1 H, *CH*-pyrazoline), 4.16–4.21 (m, 1 H, $C^{\alpha}H$, Ala), 4.43–4.50 (m, 1 H, $C^{\alpha}H$, benzyl), 4.65–4.70 (m, 1 H, $C^{\alpha}H$, Phe), 6.39 (s, 1 H, *NH*-pyrazoline), 7.13–7.25 (m, 10 H, benzyl, Phe), 8.08–8.11 (d, J = 8.55 Hz, 1 H, NH^{I}, Phe), 8.19–8.22 (d, J = 8.45 Hz, 1 H, NH^{II}, Ala), 8.30–8.33 (d, J = 8.54 Hz, 1 H, NH^{III}, Phe) ppm. HRMS: calcd. [M + H]$^+$ = [$C_{29}H_{40}N_5O_3$] 506.3086; found 506.3099; (4.0 mg, 67%).

Pyrazoline 6d: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.81–0.82 (d, J = 2.44 Hz, 3 H, CH_3, isobutyl), 0.85–0.86 (d, J = 4.88 Hz, 3 H, CH_3, isobutyl), 1.11–1.14 (d, J = 7.33 Hz, 3 H, C$^{\beta}H_3$, Ala), 1.22–1.28 (m, 2 H, CH_2, isobutyl), 1.59–1.66 (m, 1 H, *CH*, isobutyl), 1.72 (s, 3 H, CH_3CO), 1.93–1.94 (d, J = 2.44 Hz, 2 H, CH_2, pyrazoline), 2.19–3.24 (m, 8 H, *CH3* pyrazoline, $C^{\beta1,\beta2}H_2$, $C^{\beta1,\beta2}H_2$ Phe, *CH*, pyrazoline), 4.14–4.18 (m, 1 H, $C^{\alpha}H$, Ala), 4.43–4.50 (m, 1 H, $C^{\alpha}H$, Phe), 4.63–4.67 (m, 1 H, $C^{\alpha}H$, benzyl), 6.85 (br. s, 1 H, NH^{I}, benzyl), 7.15–7.22 (m, 10 H, benzyl, Phe), 8.14–8.17 (d, J = 8.55 Hz, 1 H, NH$^{\mathrm{II}}$), 8.31–8.33 (d, J = 7.33 Hz, 1 H, NH$^{\mathrm{III}}$) ppm. HRMS: calcd. [M + H]$^+$ = [$C_{30}H_{42}N_5O_3$] 520.3148; found 520.3133; (4.7 mg, 67%).

General Procedure for the Preparation of the Peptidyl-Pyrazoles 7a–7d: 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 1.2 equiv., 0.012 mmol) in toluene was added to a stirred solution of a peptidyl-pyrazoline (1 equiv., 0.01 mmol) in toluene. The reaction mixture was stirred at room temp. for 12 h. The mixture was filtered through a plug of celite with diethyl ether. The filtrate was concentrated in vacuo. The residue was subjected to purification by preparative HPLC to afford the peptidyl-pyrazole as a white solid. The purified compounds were characterized by LC-MS and NMR spectroscopy.

Pyrazole 7a: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.22 (br. s, 3 H, C$^{\beta}H_3$, Ala), 1.73 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3-pyrazole), 2.65–2.73 (m, 2 H, $C^{\beta1,\beta2}H_2$, Phe), 2.91–2.95 (m, 2 H, $C^{\beta1,\beta2}H_2$, benzyl), 4.20–4.24 (m, 1 H, $C^{\alpha}H$, Ala), 4.46–5.49 (m, 1 H, $C^{\alpha}H$, benzyl), 4.99–5.05 (m, 1 H, $C^{\alpha}H$, Phe), 5.31 (s, 1 H, *CH*-pyrazole), 5.86 (s, 1 H, NH^{I}, pyrazole), 6.64 (d, J = 8.45 Hz, 1 H, NH^{I}, Phe), 7.12–7.25 (m, 10 H benzyl, Phe), 8.02 (d, J = 8.45 Hz, 1 H, NH^{II}, Phe), 8.19–8.21 (d, J = 8.45 Hz, 1 H, NH^{III}, Ala) ppm. HRMS: calcd. [M + H]$^+$ = [$C_{26}H_{32}N_5O_3$] 462.2508; found 462.2505; (3.24 mg, 90%).

Pyrazole 7b: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.12–1.13 (d, J = 7.33 Hz, 3 H, C$^{\beta}H_3$, Ala), 1.72 (s, 3 H, CH_3CO), 2.16 (s, 3 H, CH_3-pyrazole), 2.64–2.68 (m, 2 H, $C^{\beta1,\beta2}H_2$, Phe), 2.92–2.94 (m, 2 H, $C^{\beta1,\beta2}H_2$, benzyl), 3.60 (s, 3 H, CH_3-*N*-pyrazole), 4.20–4.26 (m, 1 H, $C^{\alpha}H$, Ala), 4.47–4.49 (m, 1 H, $C^{\alpha}H$, Phe), 4.92–4.98 (m, 1 H, $C^{\alpha}H$, benzyl), 5.87 (s, 1 H, *CH*-pyrazole), 7.12–7.22 (m, 10 H, benzyl, Phe), 7.96–7.97 (d, J = 8.45 Hz, 1 H, NH^{I}, Phe), 8.04–8.08 (d, J = 7.66 Hz, 1 H, NH^{II}, Ala), 8.10–8.12 (d, J = 7.31 Hz, 1 H, NH^{II}, Ala) ppm. HRMS: calcd. [M + H]$^+$ = [$C_{27}H_{34}N_5O_3$] 476.2700; found 462.2692; (2.7 mg, 90%).

Pyrazole 7c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.85–0.87 [m, 6 H, $(CH_3)_2$, isobutyl], 1.12–1.14 (d, J = 7.35 Hz, 3 H C$^{\beta}H_3$, Ala), 1.72 (s, 3 H, CH_3CO), 1.80–1.95, [brs, 1 H, $CH(CH_3)_2$], 2.39–2.41 [d, J = 6.10 Hz, 2 H $CH_2CH(CH_3)_2$], 2.61–2.71 (m, 2 H, $C^{\beta1,\beta2}H_2$, Phe), 2.89–2.97 (m, 2 H, $C^{\beta1,\beta2}H_2$, Phe), 3.60 (s, 3 H, CH_3-N pyrazole), 4.17–4.28 (m, 1 H, $C^{\alpha}H$, Ala), 4.42–4.50 (m, 1 H, $C^{\alpha}H$ Phe), 4.92–5.02 (m, 1 H, $C^{\alpha}H$, benzyl), 5.84 (s, 1 H, *CH*-pyrazole), 7.09–7.23 (m, 10 H, benzyl, Phe), 7.93 (d, J = 8.55 Hz, 1 H, NH^{I}, Phe), 7.96 (d, 1 H, NH^{II}, Ala), 8.03–8.06 (d, J = 8.54 Hz, 1 H, NH^{III}, Phe) ppm. HRMS: calcd. [M + Na]$^+$ = [$C_{26}H_{32}N_5O_3$] 540.2955; found 540.2950; (4.23 mg, 90%).

Pyrazole 7d: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.16–1.18 (d, J = 7.32 Hz, 3 H, C$^{\beta}H_3$, Ala), 1.74 (s, 3 H, CH_3CO), 2.28 (s, 3 H, CH_3-pyrazole), 2.62–2.71 (m, 2 H, $C^{\beta1,\beta2}H_2$ benzyl), 2.91–3.04, 3.12–3.21 (m, 2 H, $C^{\beta1,\beta2}H_2$, Phe), 4.21–4.28 (m, 1 H, $C^{\alpha}H$, Ala), 4.43–4.52 (m, 1 H, $C^{\alpha}H$, Phe), 5.05–5.13 (m, 1 H, $C^{\alpha}H$ benzyl), 6.16 (s, 1 H, *CH*-pyrazole), 7.14–7.25 and 7.36–7.50 (m, 15 H, aromatic), 8.04 (d, J = 8.55 Hz, 1 H, NH^{I}, Phe), 8.12 (d, J = 8.54 Hz, 1 H, $NH^{\mathrm{I}}{}_{\mathrm{l}}$, Phe) ppm. HRMS: calcd. [M + H]$^+$ = [$C_{26}H_{32}N_5O_3$] 538.2821; found 538.2810; (5.4 mg, 90%).

General Procedure for the Preparation of the Peptidyl-Isoxazoles 8a and 8b and the Isoxazoline 9: Hydroxylamine hydrochloride (3 equiv.) was added under air to a stirred solution of a peptidyl vinyl ketone **3** (1 equiv.) in EtOH, together with a catalytic amount of acetic acid (5 mol-%) and a few crystals of sodium acetate. The reaction mixture was heated at reflux at 80 °C for 8 h. The solvent was removed under reduced pressure with a rotary evaporator. The residue was subjected to purification by preparative HPLC to afford the isoxazole **8** as a white solid. The resulting compound was characterized by LC-MS and NMR spectroscopy. The peptidyl-isoxazoline **9** was obtained by the same procedure but under N_2.

Isoxazole 8a: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.68–0.73 (t, J_1 = 6.71, J_2 = 6.72 Hz, 6 H, C$^{\gamma1}H_3$, C$^{\gamma2}H_3$, Val), 1.01–1.08 (t, J_1 = 7.94, J_2 = 7.32 Hz, 3 H, CH_3, 5-ethyl), 1.82 (s, 3 H, CH_3CO), 2.23–2.27 (m, 1 H, C$^{\beta}H$, Val), 2.66–2.74 (m, 2 H, CH_2, 5-ethyl), 3.00–3.06 (m, 2 H, C$^{\beta}H_2$, benzyl), 4.06–4.11 (t, J_1 = 9.15, J_2 = 8.55 Hz, 1 H, C$^{\alpha}H$, Val), 5.11–5.17 (m, 1 H, C$^{\alpha}H$, benzyl), 6.15 (s, 1 H, C*H*, isoxazole), 7.15–7.21 (m, 5 H C$_6H_5$, benzyl), 7.76–7.79 (d, J = 9.15 Hz, 1 H, N^1H), 8.46–8.49 (d, J = 8.55 Hz, 1 H, N$^{\mathrm{II}}H$) ppm.

HRMS: calcd. $[M + H]^+ = [C_{20}H_{27}N_3O_3]$ 358.2125; found 358.2130; (4.2 mg, 80%).

Isoxazole 8b: ^{1}H NMR (300 MHz, [D$_4$]MeOH): δ = 1.84 (s, 3 H, CH_3CO), 2.68–2.76 (m, 2 H, C$^{\beta1,\beta2}H$ benzyl, Phe), 2.93–3.04 (m, 2 H, C$^{\beta1,\beta2}H$ Phe), 4.52 (dd, J_1 = 15.9, J_2 = 7.3 Hz, 1 H, C$^{\alpha}H$ Phe), 5.38 (dd, J_1 = 15.9, J_2 = 7.3 Hz, 1 H,C$^{\alpha}H$ benzyl), 6.71 (s, 1 H, *arom.*), 6.92 (s, 1 H, *arom.*), 7.03–7.22 (m, 12 H, *arom.*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 30.6, 53.6, 53.6, 64.9, 64.9, 115.1, 115.4, 125.9, 126.1, 126.3, 127.5, 127.5, 127.9, 128.0, 128.1, 128.9, 128.9, 128.9, 129.0, 129.2, 137.8, 137.8, 168.9, 170.6, 170.8, 206.4, 207.1 ppm. LCMS: calcd. $[M + H]^+ = [C_{28}H_{28}ClFN_3O_3]$ 507.0; found 507.1; (8.9 mg, 85%).

Isoxazoline 9: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, J = 7.3 Hz, 3 H, CH_3, isobutyl), 0.95 (d, J = 7.3 Hz, 3 H, CH_3, isobutyl), 1.40–1.56 [m, 3 H, *CH*-(CH$_3$)$_2$, *CH*$_2$-CH-(CH$_3$)$_2$], 2.16 (s, 3 H, CH_3CO), 2.9–3.1 (m, 4 H, C$^{\beta1,\beta1',\beta2,\beta2'}H$, benzyl, Phe), 4.1 (dd, J_1 = 9.8, J_2 = 3.7 Hz, 1 H, C$^{\alpha}H$, Phe), 4.09 (dd, J_1 = 14.6, J_2 = 4.9 Hz, 1 H,C$^{\alpha}H$, benzyl), 7.11–7.39 (m, 11 H, benzyl, Phe), 6.3 (s, 1 H, N$H^{\rm I}$), 7.6 (s, 1 H, N$H^{\rm II}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 22.1, 28.9, 35.9, 37.2, 48.6, 60.1, 85.7, 126.2, 127.9, 128.0, 128.1, 129.0, 129.1, 135.9, 137.0, 164.9, 173.3, 173.6 ppm. HRMS: calcd. $[M + H]^+ = [C_{26}H_{34}N_3O_3] + Et_3N$ 433.2831; found 433.2832; (6.8 mg, 68%).

General Procedure for the Preparation of the Peptidyl-Thiazepines 10a and 10b: 1,2-Amino-4-chlorothiophenol (3 equiv.) was added under N_2 to a stirred solution of a peptidyl vinyl ketone (1 equiv.) in EtOH, together with catalytic amounts of acetic acid (5 mol-%). The reaction mixture was stirred at 80 °C for 12 h. The solvent was removed under reduced pressure with a rotary evaporator. The residue was subjected to purification by preparative HPLC to afford the benzothiazepines as off-white to pale yellow solids.

2,3-Dihydro-1,5-benzothiazepine 10a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, J = 7.3 Hz, 3 H, CH_3, isobutyl), 0.93 (d, J = 7.3 Hz, 3 H, CH_3, isobutyl), 1.42–1.60 (m, 1 H, *CH*$_2$, isobutyl), 1.81–2.20 [m, 5 H, *CH*(CH$_3$)$_2$, *CH*$_2$CH(CH$_3$)$_2$, *CH*$_3$CO], 2.82–3.18 (m, 6 H, C$^{\beta1,\beta2}H_2$, benzyl, C$^{\beta1,\beta2}H_2$ Phe, *CH*$_2$CH–S), 4.70 (m, 1 H, *CH*–S), 4.03 (dd, J_1 = 14.6, J_2 = 6.1 Hz, 1 H, C$^{\alpha}H$ Phe), 5.60 (dd, J_1 = 15.9, J_2 = 7.3 Hz, 1 H, C$^{\alpha}H$, benzyl), 7.04–7.37 (m, 13 H, *arom. CH*), 7.82 (d, J = 7.3 Hz, arom. *CH*), 4.16 (d, J = 6.1 Hz, 1 H, N$H^{\rm I}$), 8.32 (br. s, 1 H, N$H^{\rm II}$) ppm. HRMS: calcd. $[M - H]^+ = [C_{32}H_{36}N_3O_2S] + Et_3N$ 624.2409; found 624.2421; (8.2 mg, 55%).

2,3-Dihydro-1,5-benzothiazepine 10b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, *CH*$_3$CO), 2.90–3.18 (m, 5 H, C$^{\beta1,\beta2}H_2$, benzyl, C$^{\beta1,\beta2}H_2$, Phe, *CH*$_2$CH–S), 4.70–4.82 (m, 2 H, *CH*$_2$CH–S, *CH*–S), 5.04 (dd, J_1 = 13.4, J_2 = 7.3 Hz, 1 H, C$^{\alpha}H$, Phe), 5.39 (dd, J = 14.6, 7.3 Hz, 1 H, C$^{\alpha}H$, benzyl), 7.06–7.58 (m, 16 H, *arom.*), 7.85 (d, J = 7.3 Hz, 1 H, *arom.*), 6.18 (br. s, 1 H, N$H^{\rm I}$), 8.08 (s, 1 H, N$H^{\rm II}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 35.3, 35.3, 37.7, 39.2, 48.9, 54.8, 54.9, 59.5, 114.4, 114.8, 117.9, 118.2, 121.2, 122.1, 125.8, 125.8, 126.5, 126.9, 128.3, 128.3, 128.4, 128.5, 128.5, 128.6, 128.7, 128.8, 129.0, 129.1, 129.8, 129.9, 131.3, 136.4, 151.4, 155.3, 158.5, 163.2, 173.2, 173.3 ppm. HRMS: calcd. $[M + H]^+ = [C_{34}H_{32}ClFN_3O_2S]$ 600.1845; found 600.1852; (9.3 mg, 71%).

Preparation of the Peptidyl-Oxirane 11: A solution of freshly prepared and cooled DMDO in acetone (12 mL, 0.86 mmol, 8 equiv., –20 °C) was added dropwise to a stirred solution of the peptidyl vinyl ketone (50 mg, 0.11 mmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 8 h. Solvent and residual DMDO were removed under reduced pressure with a rotary evaporator. The crude product was subjected to purification by preparative HPLC to afford the peptidyl-oxirane as a white solid. The resultant compound was characterized by LC-MS and NMR spectroscopy.

Oxirane 11: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.03 (d, J = 7.32 Hz, 3 H, C$^{\beta}H_3$, Ala), 1.23–1.24 (d, J = 4.88 Hz, 3 H, *CH*$_3$, oxirane), 1.72–1.73 (s, 3 H, *CH*$_3$CO), 2.6–2.7 (m, 2 H, C$^{\beta1,\beta2}H_2$, benzyl), 2.84–2.90 (m, 2 H, C$^{\beta1,\beta2}H_2$, Phe), 2.92–2.93 (m, 1 H, *CH*-oxirane), 3.12–3.13 (m, 1 H, *CH*CH$_3$-oxirane), 4.26–4.27 (m, 1 H, C$^{\alpha}H$, benzyl), 4.48–4.49 (m, 1 H, C$^{\alpha}H$, Phe), 4.6–4.65 (m, 1 H, C$^{\alpha}H$, Ala), 7.14–7.24 (m, 10 H, benzyl, Phe), 8.02–8.06 (d, J = 8.54 Hz, 1 H, N$H^{\rm I}$), 8.12–8.13 (d, J = 7.33 Hz, 1 H, N$H^{\rm II}$), 8.33–8.39 (d, J = 7.32 Hz, 1 H, N$H^{\rm III}$) ppm. HRMS: calcd. $[M + H]^+ = [C_{26}H_{32}N_3O_5]$ 466.2285; found 466.2291; (20 mg, 40%).

General Procedure for the Preparation of the Peptidyl-Imidazolinones 12a, 12b, and 13: The desired amidine derivative (3 equiv., 0.03 mmol), dissolved in DMF/AcOH (0.1%), was added to a stirred solution of the peptidyl α-keto aldehyde (1 equiv., 0.01 mmol) in DMF/AcOH (0.1%). The reaction mixture was stirred at room temp. for 8 h. The solvent was removed under reduced pressure with a rotary evaporator. The crude product was purified by preparative HPLC to afford the peptidyl-imidazolone. The resulting compounds were characterized by LC-MS and NMR spectroscopy.

Imidazol-5-one 12a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.85 (d, J = 3.05 Hz, 3 H, C$^{\gamma1}H_3$, Val), 0.87–0.88 (d, J = 3.05 Hz, 3 H, C$^{\gamma2}H_3$, Val), 1.95 (s, 3 H, CH_3CO), 1.99–2.04 (m, 2 H, C$^{\beta1,2}H_2$, Val), 3.02–3.04 (d, J = 6.72 Hz, 1 H, C$^{\alpha}H$, Val), 4.02–4.07 (t, J_1 = 7.91, J_2 = 8.55 Hz, 1 H, C$^{\alpha}H$, benzyl), 4.16–4.25 (m, 1 H, C$^{\beta1,2}H_2$, benzyl), 5.92–5.98 (d, J = 9.14 Hz, 1 H, N^1H), 7.19–7.30 (m, 10 H, benzyl, benzylimidazolinone) ppm. HRMS: calcd. $[M + H]^+ = [C_{24}H_{28}N_4O_3]$ 421.605; found 421.2608; (4.5 mg, 66.6%).

Imidazol-5-one 12b: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.78–0.83 (t, J_1 = 7.33, J_2 = 6.71 Hz, 6 H, C$^{\gamma1}H_3$, C$^{\gamma2}H_3$, isopropyl), 1.21–1.24 (d, J = 7.32 Hz, 3 H, C$^{\beta}{}_3H$, Ala), 1.86 (s, 3 H, CH_3CO), 2.72–2.82 (m, 1 H, C$^{\beta}H$, isopropyl), 3.64–3.66 (m, 1 H, C$^{\alpha}H$, Ala), 4.27–4.31 (t, J_1 = 6.71, J_2 = 7.32 Hz, 1 H, C$^{\alpha}H$), 7.433–7.64 (d, J = 6.10 Hz, 1 H, N^1H), 7.61–7.64 (m, 3 H, *phenyl*), 7.91–7.92 (d, J = 1.83 Hz, 1 H, CH, *phenyl*), 7.94–7.95 (d, J = 2.44 Hz, 1 H, CH, *phenyl*), 8.15–8.18 (d, J = 7.32 Hz, 1 H, N$^{\rm II}H$) ppm. HRMS: calcd. $[M + H]^+ = [C_{18}H_{27}N_4O_3]$ 347.2078; found 347.2075; (6 mg, 70%).

Imidazol-5-one 13: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.78–0.81 (d, J = 6.71 Hz, 3 H, C$^{\gamma1}H_3$, isopropyl), 0.87–0.89 (d, J = 6.72 Hz, 3 H, C$^{\gamma2}H_3$, isopropyl), 1.07–1.10 (d, J = 7.32 Hz, 3 H, C$^{\beta}H_3$, Val, isopropyl), 1.79 (s, 3 H, CH_3CO), 2.25–2.27 (m, 1 H, C$^{\beta}H$, isopropyl), 3.83–3.89 (m, 1 H, C$^{\alpha}H$, Ala), 4.19–4.21 (t, J_1 = 1.83, J_2 = 2.44 Hz, 1 H, C$^{\alpha}H$, isopropyl), 7.51–7.55 (d, J = 7.93 Hz, 1 H, CH, imidazolinone), 7.83 (s, 1 H, N^1H), 7.90–7.93 (d, J = 7.93 Hz, 1 H, CH, imidazolinone), 8.03 (s, 1 H, CH, imidazolinone), 10.5 (s, 1 H, OH, imidazolinone) ppm. HRMS: calcd. $[M + H]^+ = [C_{15}H_{24}N_6O_3]$ 337.0222; found 337.0232; (5 mg, 75%).

General Procedure for the Preparation of the Peptidyl-Quinoxalines 14 and 15: 1,2-Phenylenediamine (1.5 equiv., 0.034 mmol, 2.98 mg) dissolved in dry CH_2Cl_2 was added carefully to a stirred solution of a peptidyl α,β-keto aldehyde (1 equiv., 0.023 mmol, 10 mg) in dry CH_2Cl_2. The reaction mixture was stirred under N_2 at room temp. for 12 h. The solvent was removed under reduced pressure with a rotary evaporator. The crude product was purified by preparative HPLC to afford the peptidyl-quinoxaline as a white or yellow solid. The resulting compounds were characterized by LC-MS and NMR spectroscopy.

Quinoxaline 14: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.17 (d, J = 7.50 Hz, 3 H, C$^{\beta}H_3$, Ala), 1.72 (s, 3 H, *CH*$_3$CO), 2.95–3.0 (m, 2

H, $C^{\beta1,\beta2}H_2$, benzyl), 3.35–3.55 (m, 1 H, $C^{\beta1,\beta2}H_2$, Phe), 4.27–4.30 (m, 1 H, $C^{\alpha}H$, Ala), 4.46–4.50 (m, 1 H, $C^{\alpha}H$, Phe), 5.35–5.39 (m, 1 H, $C^{\alpha}H$, benzyl), 7.1–7.28 (m, 10 H, benzyl, Phe), 7.82–783 (d, J = 8.55 Hz, 1 H, NH^{I}), 8.01–8.14 (m, 4 H, 1,2-phenylenediamine), 8.50–8.52 (d, J = 7.33 Hz, 1 H, NH^{II}), 8.84 (s, 1 H, CH-N, 1,2-phenylenediamine) ppm. HRMS: calcd. $[M + H]^+ = [C_{30}H_{32}N_5O_3]$ 510.2460; found 510.2458; (8.4 mg, 75%).

Quinoxaline 15: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.92–0.96 (t, J = 6.10 Hz, 6 H, $C^{\delta1}H_3$, $C^{\delta2}H_3$, isobutyl), 1.13–1.15 (d, J = 7.33 Hz, 3 H, $C^{\beta}H_3$, Ala), 1.19–1.29 (m, 3 H, $C^{\beta1,\beta2}H_2$, isobutyl, $C^{\gamma}H$, isobutyl), 1.71 (s, 3 H, CH_3CO), 2.62–2.70 and 2.96–2.99 (br. s, 2 H, $C^{\beta1,\beta2}H_2$, Phe), 3.99 (s, 3 H, CH_3COOMe), 4.26–4.33 (m, 1 H, $C^{\alpha}H$, Ala), 4.45–5.0 (m, 1 H, $C^{\alpha}H$, Phe), 5.56–5.63 (t, 1 H, $C^{\alpha}H$, isobutyl), 7.1–7.23 (m, 5 H, Phe), 7.90–8.78 (m, 4 H, *arom.*, 1,2-phenylenediamine), 8.14–8.18 (d, J = 8.55 Hz, 1 H, NH^{I}), 8.34–8.36 (d, J = 7.33 Hz, 1 H, NH^{II}) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 17.9, 21.4, 22.4, 23.2, 24.6, 37.5, 43.0, 47.9, 49.2, 53.1, 53.7, 126.1, 127.9, 129.1, 132.3, 138.0, 139.3, 143.7, 155.7, 165.4, 169.1, 171.9 ppm. HRMS: calcd. $[M + Na]^+ = [C_{18}H_{26}N_4O_3]$ 387.2001; found 387.2008; (6.8 mg, 64%).

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