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Backbone-Fluorinated 1,2,3-Triazole-Containing Dipeptide Surrogates

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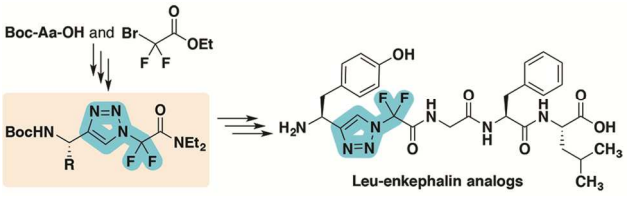
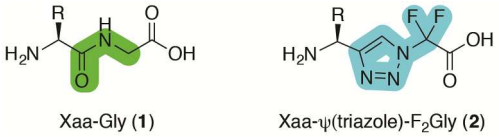


ABSTRACT: The 1,2,3-triazole moiety can be incorporated as a peptide bond bioisostere to provide protease resistance in peptidomimetics. Herein, we report the synthesis of peptidomimetic building blocks containing backbone fluorinated, 1,4-disubstituted-1,2,3-triazole moieties. Synthetic protocols for preparation of various Xaa-Gly dipeptide surrogates in the form of Xaa-ψ[triazole]-F_2Gly building blocks were established and selected examples were introduced into the endogenous peptide opiod receptor ligand Leu-enkephalin as a model compound.

Peptides are pharmacologically active compounds that play vital roles in cellular regulation. Naturally occurring peptides have generally been evolved to exhibit high target affinity and specificity, and may therefore offer attractive starting points for development of novel therapeutics. However, peptides suffer from poor metabolic stability as a result of proteolytic susceptibility *in vivo* and are often poorly cell permeable. Efforts to circumvent these disadvantages related to peptides and proteins as drug candidates have resulted in extensive research within unnatural oligomers mimicking biological function.[1] Substitution of amide bonds with bioisosteres in biologically active peptides may provide access to new peptidomimetic structures with improved physicochemical and pharmacokinetic properties. Examples of these modifications include functional groups such as esters, thioesters, thioamides, hydrazides, and ureas[2] as well as heterocycles such as tetrazoles, oxazoles, and 1,2,4-triazoles.[3] Over the last decade, the application of 1,2,3-triazoles have attracted increased attention, following the discovery of regioselective Cu(I)-[4] or Ru(II)-catalyzed[5] azide–alkyne cycloaddition, to furnish 1,4- or 1,5-disubstituted 1,2,3-triazoles, respectively. Although distances between side chains are slightly longer than for a peptide bond, the 1,2,3-triazoles have shown promise as amide bond bioisosteres.[6] with efficient synthesis of their azide and alkyne precursors from commercial amino acids by diazo transfer[7] and Seyferth-Gilbert homologation[8] using the Ohira-Bestmann reagent,[6j, 9] respectively. Furthermore, macrocyclization of peptidomimetics by "click chemistry" has gained interest due to its synthetic efficiency.[6j, 10]

It has been acknowledged that hydrogen to fluorine substitution in organic compounds can provide useful pharmacokinetic properties such as enhanced stability and altered lipophilicity.[11] Furthermore, fluorine is the most electronegative element in the periodic table and thus, the C–F bond is highly polarized and displays significant ionic character. The large dipole moment of the C–F bond has a considerable effect on the conformational behavior of organofluorine compounds.[12] Fluorine has been introduced extensively into drug molecules,[13] here it can engage in dipole–dipole and charge–dipole interactions[14] in addition to the potential benefits of the altered physicochemical properties.[11c] Substitution of hydrogen atoms with fluorine have also been reported for proteins[15] and *β*-peptide peptidomimetics.[16]

We envisioned that triazole-based amide bond isosteres could be combined with a *gem*-difluoromethylene moiety in peptide backbones to combine their features and extend the current arsenal of peptidomimetic architectures.[17] While this manuscript was in preparation, a communication describing the same backbone modification was published.[18] However, the synthetic strategy developed in the current work is fundamentally different, since we rely on synthesis of dimer building blocks, rather than assembly of fragments via the click reaction. Our protocols therefore complement the previous work by extending the structural diversity to include amino acid side chains.



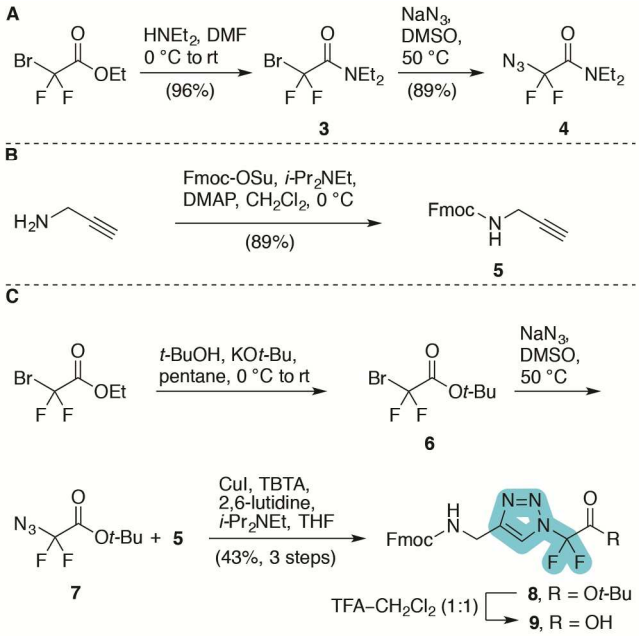
Xaa-Gly (**1**) Xaa-ψ(triazole)-F_2Gly (**2**)

Figure 1. Generic structure of Xaa-Gly dipeptide (**1**) and a backbone fluorinated 1,2,3-triazole-containing dipeptide surrogate (**2**).

Thus, we report the synthesis of a series of *gem*-difluorinated 1,2,3-triazole building blocks manifested as Xaa-

Gly dipeptide surrogates that may be incorporated to modify the properties of bioactive peptides (Figure 1). Finally, we demonstrate the solid-phase peptide synthesis (SPPS) of analogs of the endogenous opioid receptor ligand Leu-enkephalin.

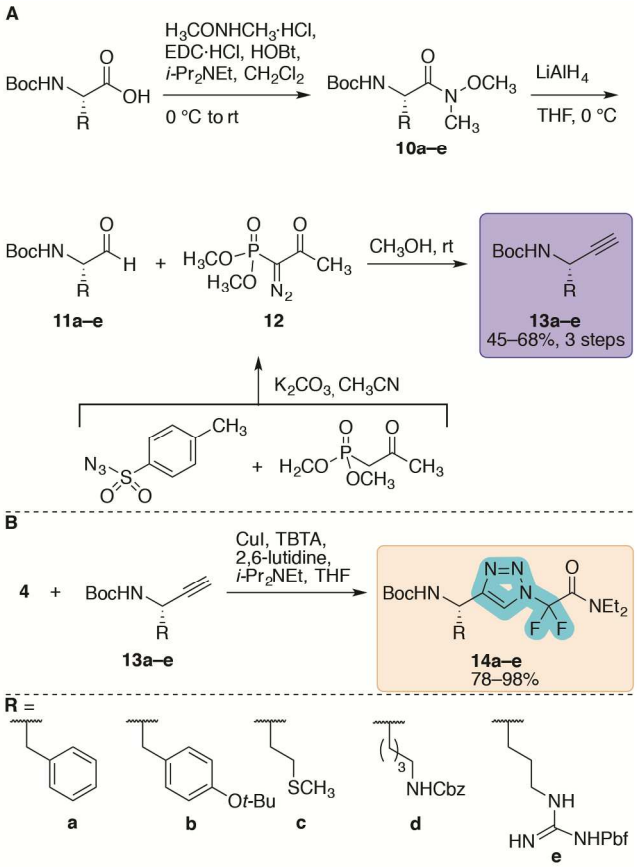
The synthesis of *gem*-difluoromethylene-containing 1,2,3-triazoles is scarcely described in literature.[18-19] However, in 2011 Zhao *et al.* described the synthesis of 1,4-disubstituted 1,2,3-triazoles by Cu(I)-catalyzed azide–alkyne click chemistry (CuAAC) from ethyl 2-azido-2,2-difluoroacetate,[19d] which potentially could be directly applied for the synthesis of Xaa-ψ[triazole]-F_2Gly building blocks. The azide substrate was prepared by azidation of the commercially available ethyl 2-bromo-2,2-difluoroacetate. However, in our hands this azidation reaction provided poor yields of a product containing impurities that were difficult to separate, presumably due to the reactivity of the ethyl ester. Instead, the *N,N*-diethylamide-protected derivative (**3**)[20] provided compound **4** in good yield (Scheme 1A). For initial testing of the cycloaddition, the Fmoc-protected alkyne derivative of glycine (**5**) was selected, which is readily available by Fmoc protection of propargyl amine (Scheme 1B). Subjecting compounds **4** and **5** to the conditions reported by Zhao *et al.* provided the fully protected dipeptide surrogate in 27% yield.[17d] The subsequent hydrolysis of the *N,N*-diethylamide was previously accomplished in refluxing 12 M aqueous HCl,[21] and we hypothesized that milder conditions could be applied due to the electron withdrawing effect of the two alpha fluorine atoms. Unfortunately, milder acidic conditions (1–6 M HCl) failed to hydrolyze the amide, and basic hydrolysis was inappropriate because of the base labile Fmoc group. Instead, we chose to prepare the *t*-Bu ester derivative **8**, which was synthesized by cycloaddition of building blocks **5** and **7** (Scheme 1C).



Scheme 1. Synthesis of Fmoc protected Gly-Gly dipeptide surrogate 9

In this reaction, we added the ligand TBTA (tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine)[22] for the Cu(I) catalyst, which resulted in an improved yield of **8**, compared to the initial reaction. Albeit, the isolated efficiency of the modified reaction conditions was difficult to determine due to the volatile nature of intermediates **6** and **7**, which precluded their isolation. Thus, azide **7** was reacted with alkyne **5** directly without purification or evaporation to dryness to give **8** in a three-step procedure. Finally, the C-terminal *t*-Bu ester was hydrolyzed by 50% trifluoroacetic acid (TFA) in CH_2Cl_2 to give building block **9** (Scheme 1C).

Next, a series of dipeptide surrogates containing proteinogenic amino acid side chains in the alkyne half of the molecule were prepared. The alkynes corresponding to phenylalanine (**a**), tyrosine (**b**), methionine (**c**), lysine (**d**), and arginine (**e**) were prepared from their corresponding Boc-protected amino acids to demonstrate functional group compatibility with the building block synthesis (Scheme 2A). First, carbodiimide-mediated reaction with *N,O*-dimethylhydroxylamine afforded Weinreb amides **10a**–**e**, which were reduced using $LiAlH_4$ to give Boc-protected amino aldehydes **11a**–**e**. Preformed Ohira-Bestmann reagent (**12**) in acetonitrile was mixed with crude aldehyde in methanol solution to provide the desired alkynes **13a**–**e** (Scheme 2A).

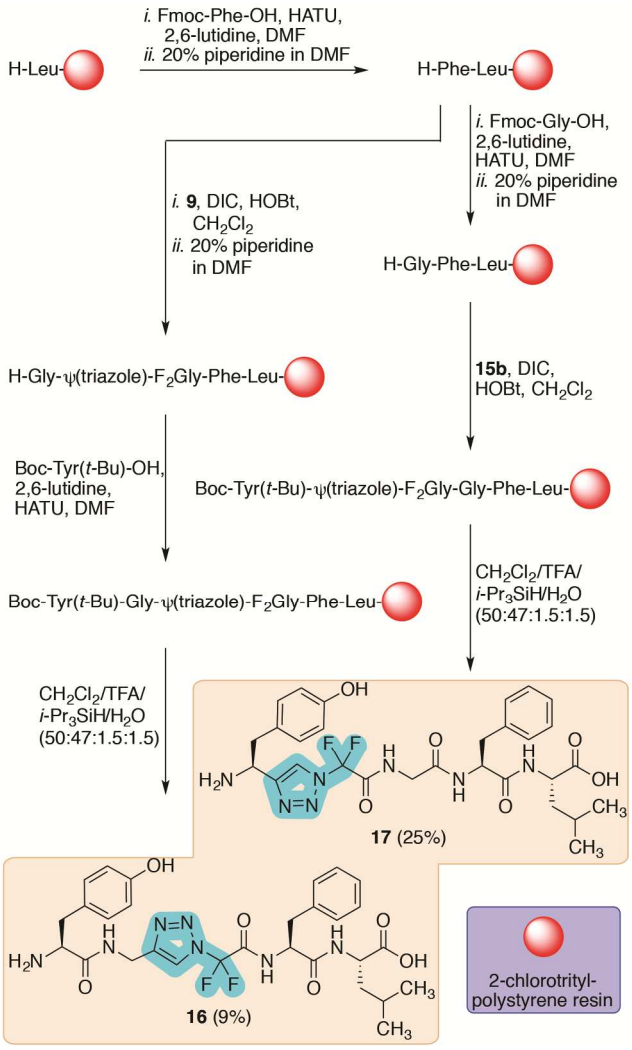


Scheme 2. Synthesis of protected Xaa-Gly dipeptide surrogates 14a–e

This method has been employed previously for selected amino acids where the stereochemical integrity was investigated by Mosher's method.[23] It was therefore gratifying that optical rotations of our products were in agreement with literature in the cases of known compounds (**13a**,**b**,**d**). The Boc protecting group was chosen because Fmoc is not compatible with $LiAlH_4$, and depending on the desired protecting groups in one's final building block, manipulation may be considered at the amino alkyne stage. We decided to prepare Boc-

protected building blocks **14a–e**, which can undergo C-terminal deprotection under basic conditions or acidic cleavage of the Boc group for solution-phase peptide synthesis (Scheme 2B).

The yields of compounds **14a–e** ranged from good to excellent, which illustrate the compatibility of the fluorinated azide **4** with the Cu(I)-catalyzed azide–alkyne cycloaddition (Scheme 2B). At this stage, the stereochemical integrities of the building blocks were investigated by removal of the Boc group and subsequent functionalization with Marfey's reagent. Analytical HPLC traces showed that the compounds contained 85–98% of the major stereoisomer (Supporting Figure S1). We suspect that the partial epimerization occurred at the amino aldehyde stage (**11a–e**) and therefore underline the importance of careful handling of these intermediates to minimize potential epimerization.



Scheme 3. Solid-phase peptide synthesis of Leu-enkephalin analogs 16 and 17

Finally, we wanted to evaluate the Xaa-ψ[triazole]-F_2Gly dipeptide mimic as a suitable building block for incorporation into peptides. As a model peptide, we chose Leu-enkephalin – an endogenous opioid receptor ligand – which has the amino acid sequence Tyr-Gly-Gly-Phe-Leu and has previously been modified by substituting amide bonds with 1,2,3-triazole moieties.[24] Because it comprises two glycine residues, we could prepare analogs containing either the Gly-Gly or Tyr-Gly dipeptide surrogate, **9** and **14b**, respectively. Standard Fmoc-based SPPS was applied for coupling the canonical amino acids using HATU (1-[bis-(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate) as the coupling reagent and 2,6-lutidine as base. In the Leu-enkephalin analog, containing the Gly-Gly dipeptide surrogate (**16**), building block **9** was introduced using DIC (1,3-diisopropylcarbodiimide) and HOBt (1-hydroxybenzotriazole), followed by coupling of Boc/*t*-Bu-protected tyrosine, which enabled concomitant cleavage from the resin and deprotection (Scheme 3).

For synthesis of the analog containing the Tyr-Gly surrogate (**17**), compound **14b** was treated with LiOH in ethanol to deprotect the C-terminal carboxylic acid (**15b**, see the Experimental Section for details). This building block was coupled to 2-chlorotrityl resin-bound Gly-Phe-Leu using DIC and HOBt, and again, simultaneous cleavage and deprotection furnished crude Leu-enkephalin analog **17** (Scheme 3). Both compounds were isolated by reversed-phase preparative HPLC to give 9% and 25% of pure peptide, respectively.

In summary, we describe the design and synthesis of a series of dipeptide surrogates encompassing a central 1,4-disubstituted 1,2,3-triazole as amide bond bioisostere, combined with a difluoromethylene group in its 4-position. Substitution of the amide bond with a 1,2,3-triazole bioisostere was a key feature because difluoroglycine itself is unstable and readily eliminates fluoride.[25] Given the continued interest in incorporation of fluorine atoms into the side chains of peptides and proteins, the present work should be of pertinent interest as it provides a means to introduce fluorine into the backbones of peptidomimetics. This has previously been achieved for β-peptides and recently for architectures mimicking the α-amino acid topology by introduction of Gly-F_2Gly surrogates.[18] Our study complements this work by including proteinogenic side chains in the N-terminal residue of the dipeptide surrogates.

We demonstrate the synthesis of examples of dipeptide surrogates containing either Fmoc or Boc groups at their N-termini and apply selected building blocks for incorporation into analogs of the endogenous peptide Leu-enkephalin. We envision that the novel peptidomimetic backbone motif introduced in this communication may find applications in alteration and fine tuning of the properties of biologically active peptides.

EXPERIMENTAL SECTION

General methods and materials. All reagents and solvents were of analytical grade and used without further purification as obtained from commercial suppliers. All reactions under nitrogen or argon atmosphere were performed in dry solvents. Dichloromethane, *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene were retrieved from a solvent purification system. All reactions were monitored by thin-layer chromatography (TLC) using silica gel coated plates (analytical SiO_2-60, F-254). Vacuum liquid chromatography (VLC) purification was performed on silica gel 60 (particle size 0.015−0.040 μm). Ultra-high-performance liquid chromatography mass spectrometry (UPLC-MS) analyses were performed using a gradient with eluent I (0.1% HCOOH in water) and eluent II (0.1% HCOOH in MeCN) rising linearly from 0% to 95% of II during t = 0.00–2.50 min applied at a flow rate of 0.6 mL/min (gradient A) or during t = 0.00–5.20 min (gradient B). Compounds which were not obtained in sufficient purity by VLC, were purified by preparative HPLC performed on a C18 column [250 mm × 20 mm, 5 µm, 100 Å]

using a diode array UV detector. A gradient C with eluent III (95:5:0.1, water−MeCN−trifluoroacetic acid(TFA)) and eluent IV (0.1% TFA in MeCN) rising linearly from 0% to 95% of IV during t = 5−45 min was applied at a flow rate of 20 mL/min. All final compound purities were determined by analytical HPLC analysis to be >95% pure on a C18 column [150 mm × 4.6 mm, 3 μm)] using a multi wavelength UV detector. The gradient consisted of eluent III (95:5:0.1, water−MeCN−TFA) and eluent IV (0.1% TFA in MeCN) rising linearly from 0% to 95% of IV during t = 2−20 min at a flow rate of 1 mL/min (gradient C). 1D and 2D NMR spectra were recorded on a 400 MHz spectrometer at 298 K. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz, respectively. NMR chemical shifts are reported in ppm relative to deuterated solvent peaks as internal standards (δ_H: CD_3OD 3.31 ppm, $CDCl_3$ 7.26 ppm, and DMSO-d_6 2.50 ppm, δ_C: CD_3OD 49.00 ppm, $CDCl_3$ 77.16 ppm, and DMSO-d_6 39.50 ppm). Coupling constants (J) are given in hertz (Hz). Multiplicities of NMR signals are reported as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet. The HRMS spectra were recorded using either matrix assisted laser desorption/ionization (MALDI) or electrospray ionization (ESI) as indicated for each compound with Fourier transform ion cyclotron resonance (FT-ICR) as mass analyzer.

*2-Azido-N,N-diethyl-2,2-difluoroacetamide (**4**).* Ethyl bromodifluoroacetate (2.5 g, 12.5 mmol) was added to a solution of Et_2NH (3.65 g, 50 mmol) in DMF (15 mL) at 0 °C under argon. The mixture was allowed to reach room temperature and stirred 18 h. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (3 × 40 mL). The organic phase was washed with water (2 × 100 mL) and 1 M HCl (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to give compound **3**[20] as a light yellow oil (2.75 g, 96%). Caution: this product is volatile! Without further purification, a solution of **3** (460 mg, 2 mmol) in DMSO (2 mL) was stirred under argon and NaN_3 (195 mg, 3 mmol) was added in small portions over 10 min. The mixture was heated to 50 °C for 5 h before it was cooled to room temperature, quenched with water (10 mL), and extracted with Et_2O (3 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield a colorless oil (343 mg, 89%). Caution: this product is volatile and was used without further purification. An IR-signal at 2100 cm^{-1} confirms the presence of an azide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54–3.24 (m, 4H), 1.23–1.01 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (t, J = 32.9 Hz), 115.6 (t, J = 270.1 Hz), 42.3, 41.9, 14.1, 12.3. MS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_6H_{11}F_2N_4O^+$ 192; Found 192.

*N-Fmoc propargyl amine (**5**).* Fmoc-OSu (1.35 g, 4 mmol) followed by 4-dimethylaminopyridine (50 mg, 0.4 mmol) and *i*-Pr_2NEt (0.71 mL, 4 mmol) was added to a solution of propargylamine (0.26 mL, 4 mmol) in CH_2Cl_2 (13 mL) at 0 °C under argon. After stirring for 4 h at room temperature the mixture was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4), flitered, and concentrated *in vacuo* to give a white solid (1.03 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (td, J = 7.5, 1.0 Hz, 2H), 4.98 (s, 1H), 4.44 (d, J = 6.9 Hz, 2H), 4.23 (t, J = 6.9 Hz, 1H), 4.00 (m, 2H), 2.26 (t, J = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 143.8, 141.3, 127.7, 127.1, 125.0, 120.0, 79.60, 71.7, 67.0, 47.1, 30.8. UPLC-MS gradient A, t_R = 2.12 min, *m/z:* $[M+Na]^+$ Calcd for $C_{18}H_{15}NNaO_2^+$ 300.1; Found 300.0). The data is in agreement with literature.[26]

*tert-Butyl 2-azido-2,2-difluoroacetate (**7**).* Potassium *tert*-butoxide (393 mg, 3.5 mmol) was added in two portions over 5 min to a solution of ethyl bromodifluoroacetate (5 g, 25 mmol) in pentane (200 mL) and *t*-BuOH (35 mL) at 0 °C under argon. After stirring for 1 h at room temperature the reaction was quenched with concentrated aqueous HCl and washed with water (2 × 50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and filtered through a pad of silica gel (4 × 5 cm) followed by elution with 20% Et_2O in pentane (100 mL). Most solvent was carefully removed by distillation to give compound **6**[27] as a colorless oil, which was used without further purification. To a solution of **6** (462 mg, 2 mmol) in DMSO (4 mL), NaN_3 (195 mg, 3 mmol) was added under argon. The reaction was stirred for 16 h, quenched with water, and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with water (2×) and brine, dried over $MgSO_4$, and filtered. Most of the solvent was carefully removed *in vacuo* and the material was used as a solution in the next step. CAUTION: this compound has not been reported previously but due to the ratio of nitrogen to carbon/oxygen, it may be a potential explosive. We therefore performed the reaction behind a blast shield in the fume hood and stopped evaporation of the solvent before complete dryness was reached. An IR-signal at 2100 cm^{-1} confirms the presence of an azide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (t, J = 38.3 Hz), 112.3 (t, J = 269.1 Hz), 87.0, 27.8.

*Fmoc-Gly-ψ[triazole]-F$_2$Gly-Ot-Bu (**8**).* 2,6-Lutidine (2 equiv) and *i*-Pr_2NEt (2 equiv) were added to a solution of **5** (416 mg, 1.5 mmol) was reacted with **7** (193 mg, 1 mmol) in THF (0.2 M with respect to alkyne) and argon was bubbled through the solution for 2 min. CuI (0.2 equiv) and TBTA (0.2 equiv) was added and argon bubbling was repeated for 2 min. The mixture was stirred at room temperature for 2 h under argon and the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (×3) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by VLC to yield a colorless oil (190 mg, 43% over three steps). VLC eluent: 0–20% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.49 (d, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.4 Hz, 2H), 5.37 (s, 1H), 4.42 (d, J = 6.0 Hz, 2H), 4.37 (d, J = 6.8 Hz, 2H), 4.12 (t, J = 6.7 Hz, 1H), 1.50 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9 (t, J = 33.2 Hz), 156.3, 145.7, 143.7, 141.3, 127.7, 127.0, 125.0, 120.2, 120.1, 109.1 (t, J = 267.7 Hz), 87.8, 66.8, 47.2, 36.20, 27.6 ppm. UPLC-MS gradient A, t_R = 2.45 min, *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{25}F_2N_4O_4^+$ 471.2; Found 471.2. HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{25}F_2N_4O_4^+$ 471.1838; Found 471.1846.

*Fmoc-Gly-ψ[triazole]-Gly-OH (**9**).* Compound **8** was dissolved in CH_2Cl_2–TFA (1:1; 0.05 M) and the solution was stirred for 1 h. The solvent was removed *in vacuo* and residual TFA co-evaporated with CH_2Cl_2 (3×). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by VLC and the product obtained as a colorless amorphous solid (92 mg, 94%). VLC eluent: CH_2Cl_2–MeOH–AcOH (95:4.5:0.5–90:9:1). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.88 (d, J = 7.6 Hz, 3H), 7.69 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 4.31 (d, J = 7.0 Hz, 2H), 4.28 (d, J = 5.9 Hz, 2H), 4.22 (t, J = 7.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.4 (t, J = 25.9 Hz), 156.2, 144.9, 143.8, 140.7, 127.6, 127.1, 125.2, 121.8, 120.1, 110.6 (t, J = 274.1 Hz), 65.6, 46.7, 35.6. HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{17}F_2N_4O_4^+$ 415.1212; Found 415.1222.

General procedure for Synthesis of Boc-protected alkyne derivatives 13a–e. *i*-Pr_2NEt (2.0 equiv) was added to a solution of the amino acid (1.0 equiv), *N,O*-dimethylhydroxylamine·HCl (1.1 equiv) and HOBt (1.1 equiv) in CH_2Cl_2 (0.3 M with respect to amino acid) under nitrogen. EDC•HCl (1.1 equiv) was added to the mixture at 0 °C and stirring was continued for 3 h, after which it was allowed to reach room temperature. The mixture was diluted with EtOAc (2 × volume of CH_2Cl_2), washed with 5% aq. $KHSO_4$ (2×), 5% aq. $NaHCO_3$ (2×), and brine (2×). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude Weinreb amide. The crude product was dissolved in dry THF (0.25 M) and $LiAlH_4$ (1.25 equiv) was added in one portion at 0 °C under nitrogen. After stirring at 0 °C for 1 h the reaction was quenched with 5% aq. $KHSO_4$ (SLOW ADDITION!). The mixture was diluted with EtOAc and washed with 5% aq. $KHSO_4$ (2×), 5% aq. $NaHCO_3$ (2×), and brine (2×). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude aldehyde, which was used directly without further purification. K_2CO_3 (3.0 equiv) and *p*-toluenesulfonylazide (1.2 equiv) were suspended in MeCN (0.5 M with respect to *p*-toluenesulfonylazide) under nitrogen. Dimethyl-(2-oxopropyl)-phosphonate (1.2 equiv) was added and the mixture was stirred for 4–8 h. A solution of the crude aldehyde in dry MeOH (1.6 M) was added. After stirring for 16 h, the solvents were removed *in vacuo* and the crude residue was dissolved in EtOAc, washed with

water (2×) and brine (2×), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by VLC.

*Boc-Phe-alkyne (**13a**).* The product was isolated as colorless solid (206 mg, 45% over three steps). Mp: 106–111 °C. VLC eluent: 0–20% EtOAc in heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H, Ar-*H*), 4.68 (br s, 2H, N*H*/α-C*H*), 3.03–2.91 (m, 2H, β-CH_2), 2.27 (s, 1H, CC*H*), 1.43 (s, 9H, Boc-(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 136.5, 129.9, 128.4, 127.0, 82.9, 80.2, 72.3, 44.0, 41.9, 28.5. UPLC-MS gradient B, t_R = 2.23 min, *m/z:* $[M+H]^+$ Calcd for $C_{15}H_{20}NO_2^+$ 246.1; Found 246.3). $[\alpha]_{589.3}$: –20° (*c* = 0.1, 293 K, $CHCl_3$), literature –10.6° (*c* = 1.01, $CHCl_3$).[28]

*Boc-Tyr(t-Bu)-alkyne (**13b**).* The product was isolated as a colorless gel (557 mg, 59% over 3 steps). VLC eluent: 20–40% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.67 (2 × br s, 1H), 2.93 – 2.89 (m, 2H), 2.26 (d, *J* = 2.1 Hz, 1H), 1.42 (s, 9H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 154.5, 131.3, 130.3, 124.0, 83.1, 80.1, 78.4, 72.1, 44.0, 41.2, 29.0, 28.5. UPLC-MS gradient A, t_R = 2.51 min, *m/z:* $[M+H]^+$ Calcd for $C_{19}H_{28}NO_3^+$ 318.2, found 318.1. HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{28}NO_3^+$ 318.2064; Found 318.2065. $[\alpha]_{589.3}$: –4° (*c* = 1.0, 293 K, $CHCl_3$), literature –0.44° (*c* = 3.18, $CHCl_3$).[24]

*Boc-Met-alkyne (**13c**).* The product was isolated as a colorless oil (230 mg, 50% over three steps). VLC eluent: 0–10% EtOAC in heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (br s, 1H, N*H*), 4.55 (br s, 1H, α-C*H*), 2.67–2.55 (m, 2H, γ-CH_2), 2.30 (d, *J* = 2.3 Hz, 1H, CC*H*), 2.11 (s, 3H, ε-CH_3), 2.00–1.89 (m, 2H, β-CH_2), 1.45 (s, 9H, Boc-(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 82.9, 80.2, 71.9, 42.3, 35.5, 30.2, 28.5, 15.6. UPLC-MS gradient B, t_R = 2.05 min, *m/z:* $[M+H]^+$ Calcd for $C_{11}H_{20}NO_2S^+$ 230.1; Found 230.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{20}NO_2S^+$ 230.1209; Found 230.1216. $[\alpha]_{589.3}$: –60° (*c* = 0.1, 293 K, $CHCl_3$).

*Boc-Lys(Cbz)-alkyne (**13d**).* The product was isolated as a colorless solid (533 mg, 46%). Mp: 84–87°C. VLC eluent: 0–20% EtOAC in heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 5H, Ar-*H*), 5.09 (s, 2H, CBz-CH_2), 4.81 (br s, 1H, ε-N*H*), 4.73 (br s, 1H, α-N*H*), 4.38 (br s, 1H, α-C*H*), 3.20 (q, *J* = 6.3 Hz, 2H, ε-CH_2), 2.25 (d, *J* = 2.3 Hz, 1H, CC*H*), 1.74–1.62 (m, 2H, β-CH_2), 1.58–1.51 (m, 2H, δ-CH_2) 1.49–1.44 (m, 11H, γ-CH_2/Boc-(CH_3)$_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 155.0, 136.8, 128.6, 128.2, 128.2, 83.5, 80.1, 71.3, 66.7, 42.7, 40.9, 35.8, 29.5, 28.5, 22.8. UPLC-MS gradient B, t_R = 2.35 min, *m/z:* $[M + H]^+$ Calcd for $C_{20}H_{29}N_2O_4^+$ 361.2; Found 361.2. $[\alpha]_{589.3}$: –25° (*c* = 0.1, 293 K, $CHCl_3$) literature –23.1° ($CHCl_3$).[23]

*Boc-Arg(Pbf)-alkyne (**13e**).* The product was isolated as a colorless solid (1.71 g, 68% over 3 steps). Mp: 85 °C. VLC eluent: CH_2Cl_2–MeOH–NH_4OH (99.5:0.45:0.05–98.5:1.35:0.15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 2H), 4.91 (d, *J* = 8.6 Hz, 1H), 4.34 (br s, 1H), 3.35–3.09 (m, 2H), 2.95 (s, 2H), 2.57 (s, 3H), 2.51 (s, 3H), 2.26 (d, *J* = 2.2 Hz, 1H), 2.09 (s, 3H), 1.75 (s, 1H), 1.73- 1.53 (m, 4H), 1.45 (s, 6H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 156.1, 155.5, 138.6, 132.6, 124.8, 117.71, 86.6, 83.0, 80.4, 71.7, 43.3, 40.9, 33.6, 28.7, 28.4, 28.3, 25.4, 19.5, 18.0, 12.6. UPLC-MS gradient A, t_R = 2.25 min, *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{39}N_4O_5S^+$ 507.3; Found 507.3. HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{39}N_4O_5S^+$ 507.2636, found 507.2668. $[\alpha]_{589.3}$: –8° (*c* = 1.03, 293 K, $CHCl_3$).

General procedure for Synthesis of 14a–e through Cu(I)-catalyzed azide–alkyne cycloaddition. The alkyne and the azide were dissolved in dry THF (0.1 M with respect to alkyne). 2,6-Lutidine (2.0 equiv) and *i*-Pr_2NEt (2.0 equiv) were added and nitrogen was bubbled through the solution for 5 min while stirring. CuI (0.2 equiv) and TBTA (0.2 equiv) were added and nitrogen bubbling was repeated for 5 min. The mixture was stirred under nitrogen at room temperature for 2 h. Subsequently, the reaction was quenched with water and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated and the resulting residue was purified by VLC.

*Boc-Phe-ψ[triazole]-F_2Gly-NEt$_2$ (**14a**).* Compound **13a** (100 mg, 0.4 mmol) was reacted with **4** (118 mg, 0.6 mmol) according to the general procedure. The product was purified by VLC and obtained as a colorless oil (140 mg, 78%). VLC eluent: 0–20% EtOAc in heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.25–7.22 (m, 2H), 7.22–7.19 (m, 1H), 7.09–7.06 (m, 2H), 5.20 (br s, 1H), 5.16–5.08 (m, 1H), 3.49 (q, *J* = 7.1 Hz, 2H), 3.30–3.23(m, 3H), 2.21–2.14 (m, 1H), 1.40 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 156.9, 155.2, 149.0, 136.9, 129.6, 128.6, 126.9, 119.5, 111.3, 80.1, 48.7, 42.7 (t, *J* = 4 Hz), 42.5, 41.5, 28.4, 14.0, 12.1. HRMS (MALDI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{30}F_2N_5O_3^+$ 438.2311; Found 438.2317. $[\alpha]_{589.3}$: –15° (*c* = 0.1, 293 K, $CHCl_3$).

*Boc-Tyr(t-Bu)-ψ[triazole]-F_2Gly-NEt$_2$ (**14b**).* Compound **13b** (190 mg, 0.6 mmol) was reacted with **4** (173 mg, 0.9 mmol) according to the general procedure. The product was purified by VLC and obtained as a colorless solid (304 mg, 99%). Mp: 93–97 °C. VLC eluent: 0–20% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.16 (s, 1H), 5.02 (d, *J* = 7.4 Hz, 1H), 3.42 (q, *J* = 7.4 Hz, 2H), 3.19 (m, 3H), 3.03 (m, 1H), 1.34 (s, 9H), 1.24 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 (t, *J* = 29.1 Hz), 155.0, 154.1, 148.9, 131.6, 129.8, 124.1, 119.2, 111.1 (t, *J* = 266.6 Hz). 79.9, 78.3, 48.5, 42.6 (t, *J* = 4 Hz), 42.3, 40.7, 28.8, 28.3, 13.8, 11.9. UPLC-MS gradient A, t_R = 2.51 min, *m/z:* $[M+H]^+$ Calcd for $C_{25}H_{38}F_2N_5O_4^+$ 510.3; Found 510.3. HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{38}F_2N_5O_4^+$ 510.2886; Found 510.2895. $[\alpha]_{589.3}$: –4° (*c* = 1.0, 293 K, $CHCl_3$).

*Boc-Met-ψ[triazole]-F_2Gly-NEt$_2$ (**14c**).* Compound **13c** (150 mg, 0.65 mmol) was reacted with **4** (209 mg, 0.98 mmol) according to the general procedure. The product was purified by VLC and obtained as a colorless oil (270 mg, 98%). VLC eluent: 0–20% EtOAc in heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 5.19 (br s, 1H), 5.03 (q, *J* = 7.7 Hz, 1H), 3.48 (q, *J* = 7.1 Hz, 2H), 3.34 (q, *J* = 7.1 Hz, 2H), 2.59–2.46 (m, 2H), 2.31–2.16 (m, 2H), 2.09 (s, 3H), 1.42 (s, 9H), 1.25–1.16 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (t, *J* = 29.1 Hz), 155.3, 149.4, 119.6, 114.1, 111.5, 80.1, 46.2, 42.8 (t, *J* = 4.2 Hz), 42.5, 34.3, 30.4, 28.5, 15.5, 14.0, 12.0. UPLC-MS gradient B, t_R = 2.34 min, *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{30}F_2N_5O_3S^+$ 422.2; Found 422.2. HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{30}F_2N_5O_3S^+$ 422.2032, found 422.2037. $[\alpha]_{589.3}$: –45° (*c* = 0.1, 293 K, $CHCl_3$).

*Boc-Lys(Cbz)-ψ[triazole]-F_2Gly-NEt$_2$ (**14d**).* Compound **13d** (150 mg, 0.4 mmol) was reacted with **4** (133 mg, 0.6 mmol) according to the general procedure. The product was purified by VLC and obtained as a colorless oil (223 mg, 96%). VLC eluent: 55% EtOAc in heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.37–7.27 (m, 5H), 5.12 (br s, 1H), 4.85 (br s, 2H), 3.48 (q, *J* = 7.1 Hz, 2H), 3.34 (q, *J* = 7.2 Hz, 2H), 3.24–3.13 (m, 2H), 2.01–1.93 (m, 1H), 1.89 (br s, 1H), 1.59–1.48 (m, 2H), 1.42 (s, 9H), 1.25–1.14 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (t, *J* = 29.2 Hz), 156.6, 155.5, 150.1, 136.8, 128.6, 128.2, 128.2, 119.3, 111.5 (t, *J* = 266.7 Hz), 80.0, 66.8, 47.0, 42.8 (t, *J* = 4.2 Hz), 42.5, 40.7, 34.7, 29.6, 28.5, 22.9, 14.0, 12.0. UPLC-MS gradient B, t_R = 2.52 min, *m/z:* $[M+H]^+$ Calcd for $C_{26}H_{39}F_2N_6O_5^+$ 553.3; Found 533.2. HRMS (MALDI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{39}F_2N_6O_5^+$ 553.2945; Found 553.2950. $[\alpha]_{589.3}$: –50° (c = 0.1, 293 K, $CHCl_3$).

*Boc-Arg(Pbf)-ψ(triazole)-F_2Gly-NEt$_2$ (**14e**).* Compound **13e** (304 mg, 0.6 mmol) was reacted with **4** (96 mg, 0.5 mmol) according to the general procedure. The product was purified by VLC and the product obtained as a colorless gel (281 mg, 80%). VLC eluent: CH_2Cl_2–MeOH–NH_4OH (99.5:0.45:0.05–97:2.7:0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 5.47 (br s, 1H), 4.93–4.84 (m, 1H), 3.69 (s, 1H), 3.48 (q, *J* = 7.1 Hz, 2H), 3.36 (q, *J* = 7.1 Hz, 2H), 3.32-3.15 (m, 2H), 2.94 (s, 2H), 2.56 (s, 3H), 2.50 (s, 3H), 2.08 (s, 3H), 1.97–1.86 (m, 2H), 1.66–1.54 (m, 2H), 1.45 (s, 6H), 1.41 (s, 9H), 1.23–1.18 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 157.5 (t, *J* = 28.6 Hz), 156.3, 155.9, 150.1, 138.5, 133.1, 132.4, 129.2, 124.7, 119.6, 117.6, 111.6 (t, *J* = 266.8 Hz), 86.5, 80.2, 43.4, 42.9 (t, *J* = 4.0 Hz), 42.6, 41.0, 32.9, 28.7, 28.5, 25.6, 19.4, 18.0, 14.0, 12.6, 12.1. UPLC–MS gradient A, t_R = 2.35 min, *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{49}F_2N_8O_6S^+$ 699.3; Found 699.3. HRMS (MALDI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{31}H_{49}F_2N_8O_6S^+$ 699.3468, found 699.3496. $[\alpha]_{589.3}$: –10° (*c* = 0.98, 293 K, $CHCl_3$).

*Boc-Tyr(tBu)-ψ[triazole]-F_2Gly-OH (**15b**).* 1 M LiOH (10 equiv) was added to a solution of **14b** in EtOH (0.1 M). After stirring for 16 h the reaction was acidified with 2 M HCl (2.5 mL) and extracted with CH_2Cl_2 (3×). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo.* The crude was purified by VLC and the product obtained as a colorless amorphous solid (143 mg, 78%). VLC eluent: CH_2Cl_2–MeOH–AcOH (99:0.9:0.1–90:9:1). ^{1}H NMR (600 MHz, CD_3OD) δ 8.09 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 5.05 (dd, *J* = 9.3, 5.9 Hz, 1H), 3.20 (dd, *J* = 13.8, 5.9 Hz, 1H), 3.00 (dd, *J* = 13.8, 9.3 Hz, 1H), 1.36 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (151 MHz, CD_3OD) δ 153.9 (t, *J* = 26.8 Hz), 148.0, 145.6, 141.1 124.8, 121.5, 115.6, 112.0, 102.7 (t, *J* = 271.3 Hz), 70.8, 70.0, 40.6, 32.1, 19.7, 19.2, 14.2. HRMS (MALDI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{28}F_2N_4NaO_5^+$ 477.1920; Found 477.1929. $[\alpha]_{589.3}$: –6° (*c* = 1.0, 293 K, $CHCl_3$).

General procedure for SPPS on 2-chlorotrityl polysterene resin. *Loading of first residue and capping:* Resin (1 equiv.) was washed with CH_2Cl_2 (2×) and swelled in CH_2Cl_2 for 20 min. The resin was drained and treated with Fmoc protected amino acid (4 equiv) and *i*-Pr_2NEt (8 equiv) in CH_2Cl_2 (0.4 M with respect to amino acid). The mixture was shaken for 4 h, drained, and washed (3 × CH_2Cl_2, 3 × MeOH, 3 × DMF). The unreacted sites on the resin were capped with *i*-Pr_2NEt (10 equiv) in MeOH (10 min) and the resin washed (3 × CH_2Cl_2, 3 × MeOH, 3 × DMF). *Fmoc deprotection and amino acid coupling:* A solution of piperidine–DMF (1:4, 2 mL per 100 mg resin) was added to the resin and shaken for 20 min. The resin was drained and the deprotection wasrepeated for 20 min. The resin was drained and washed (3 × CH_2Cl_2, 3 × MeOH, 3 × DMF). Fmoc protected amino acid (4 equiv) was preincubated with HATU (4 equiv) and 2,6-lutidine (8 equiv) in DMF (0.4 M with respect to the amino acid) for 10 min. The solution was added to the resin and shaken for 2 h. The resin was then drained and washed (3 × CH_2Cl_2, 3 × MeOH, 3 × DMF).

*Tyr-Gly-ψ[triazole]-F_2Gly-Phe-Leu (**16**).* Dipeptide Phe-Leu was synthesized on resin according to the general SPPS procedure. A mixture of **9** (53 mg, 0.128 mmol), HOBt (20 mg, 0.128 mmol) and DIC (16 mg, 0.128 mmol) in DMF (1.5 mL) was shaken for 10 min and added to the resin-bound Phe-Leu (0.09 mmol). After shaking overnight the resin was drained and washed (3 × CH_2Cl_2, 3 × MeOH, 3 × DMF). Fmoc deprotection and coupling to Boc-Tyr(*t*-Bu)-OH was performed according to the general SPPS procedure. The resulting product was cleaved from the resin by treatment with a CH_2Cl_2–TFA–*i*-Pr_3SiH–H_2O (50:47:1.5:1.5) mixture (2 × 20min). The cleavage solution was concentrated and the product precipitated from Et_2O, dried *in vacuo*, and purified by preparative HPLC to give a white powder (4.1 mg, 9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (d, *J* = 8.4 Hz, 1H, Phe amide N*H*), 9.35 (s, 1H, Tyr O*H*), 8.98 (t, *J* = 5.5 Hz, 1H, Gly-ψ[triazole] amide N*H*), 8.48 (d, *J* = 7.8 Hz, 1H, Leu amide N*H*), 8.15 (s, 1H, triazole 5-C*H*), 8.10 (br s, 2H, Tyr amine NH_2), 7.39–7.15 (m, 5H, Phe Ar*H*), 6.98 (d, *J* = 8.4 Hz, 2H, Tyr Ar*H*), 6.68 (d, *J* = 8.4 Hz, 2H, Tyr Ar*H*), 4.72–4.67 (m, 1H, Phe α-C*H*), 4.40 (2 × dd, *J* = 15.4, 5.5 Hz, 2H, Gly-ψ[triazole] α-CH_2), 4.31–4.20 (m, 1H, Leu α-C*H*), 3.88 (m, 1H, Tyr α-C*H*), 3.15 (dd, *J* = 13.9, 3.5 Hz, 1H, Phe β-CH_2), 2.97 (dd, *J* = 13.9, 3.5 Hz, 1H, Phe β-CH_2), 2.95 (dd, *J* = 14.1, 7.6 Hz, 1H), 2.83 (dd, *J* = 14.1, 7.6 Hz, 1H), 1.79–1.45 (m, 3H, Leu β-CH_2 and γ-C*H*), 0.91 (d, *J* = 6.5 Hz, 3H, Leu δ-CH_3), 0.86 (d, *J* = 6.4 Hz, 3H, Leu δ-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 169.8, 168.2, 158.1, 156.6, 144.7, 137.4, 130.4, 129.1, 128.2, 126.5, 124.7, 121.8, 115.3 (t, *J* = 297.7 Hz), 54.8, 53.8, 50.5, 39.7, 36.5, 36.2, 33.8, 24.3, 22.8, 21.3. UPLC–MS gradient A, t_R = 2.28 min, *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{36}F_2N_7O_6^+$ 616.3; Found 616.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{36}F_2N_7O_6^+$ 616.2690; Found 616.2699.

*Tyr-ψ[triazole]-F_2Gly-Gly-Phe-Leu (**17**).* Tripeptide Gly-Phe-Leu was synthesized on resin according to the general SPPS procedure. A mixture of **15b** (90.9 mg, 0.2 mmol), HOBt (27 mg, 0.2 mmol) and DIC (31 μL, 0.2 mmol) in DMF was shaken for 10 min and added to the resin-bound Gly-Phe-Leu (0.15 mmol). After shaking for 18 h the resin was drained and washed (3 × MeOH, 3 × DMF, 3 × CH_2Cl_2). The peptidomimetic was cleaved from the resin by treatment with a CH_2Cl_2–TFA–*i*-Pr_3SiH–H_2O (50:47:1.5:1.5) mixture (2 × 20 min). The solution was concentrated and the product precipitated from Et_2O, vacuum-dried, and purified by preparative HPLC to give a white powder (23 mg, 25%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (br s, 1H, Leu COO*H*), 9.79 (t, *J* = 6.0 Hz, 1H, Gly amide N*H*), 9.33 (br s, 1H, Tyr O*H*), 8.70 (s, 1H, triazole 5-C*H*), 8.58–8.47 (m, 2H, Tyr amine NH_2), 8.37 (d, *J* = 8.0 Hz, 1H, Leu amide N*H*), 8.30 (d, *J* = 8.4 Hz, 1H, Phe amide N*H*), 7.33–7.13 (m, 5H, Phe Ar*H*), 6.94 (d, *J* = 8.4 Hz, 2H, Tyr Ar*H*), 6.64 (d, *J* = 8.4 Hz, 2H, Tyr Ar*H*), 4.75–4.68 (m, 1H, Tyr α-C*H*), 4.60 (td, *J* = 9.7, 4.0 Hz, 1H, Phe α-C*H*), 4.25–4.18 (m, 1H, Leu α-C*H*), 3.94–3.86 (m, 1H, Gly α-CH_2), 3.80–3.72 (m, 1H, Gly α-CH_2), 3.15 (d, *J* = 8.2 Hz, 2H, Tyr β-CH_2), 3.05 (dd, *J* = 13.8, 4.0 Hz, 1H, Phe β-CH_2), 2.75 (dd, *J* = 13.8, 9.7 Hz, 1H, Phe β-CH_2), 1.70-1.50 (m, 3H, Leu β-CH_2 and γ-C*H*), 0.90 (t, *J* = 5.7 Hz, 3H, Leu δ-CH_3), 0.84 (t, *J* = 5.7 Hz, 3H, Leu δ-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.9, 171.0, 166.7, 157.7, 156.3, 156.8, 144.2, 137.8, 137.6, 130.3, 129.3, 128.0, 126.3, 125.3, 123.5, 115.3, 110.1 (t, *J* = 268.0 Hz), 53.7, 50.3, 47.7, 41.9, 37.8, 37.5, 24.3, 22.9, 21.3. UPLC–MS gradient A, t_R = 1.09 min, *m/z:* $[M+H]^+$ Calcd for $C_{29}H_{36}F_2N_7O_6^+$ 616.3; Found 616.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{36}F_2N_7O_6^+$ 616.2690; Found 616.2704.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting Figure S1 as well as copies of ^{1}H and ^{13}C NMR spectra (PDF)

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The manuscript was written through contributions from all authors. All authors have given approval to the final version of the manuscript. Part of this work was performed by J.E.-A. at the Technical University of Denmark, Kgs. Lyngby, Denmark.

Notes

The authors declare no competing financial interest.

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