Tetrahedron 67 (2011) 7042–7049

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Amino acids as building blocks for the synthesis of substituted 1,2,4-triazoles

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ARTICLE INFO

Article history:
Received 12 May 2011
Received in revised form 4 July 2011
Accepted 6 July 2011
Available online 14 July 2011

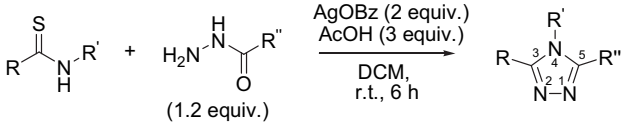
Keywords:
1,2,4-Triazole
Thioamide
Building block
Heterocycle
Lawesson's reagent

ABSTRACT

We report on the synthesis of 1,2,4-triazoles substituted with 2 or 3 amino acid side chains, using silver benzoate as a key reagent for the cyclization step. A complete study of the optical purity retention during the synthetic process leading to these compounds is described. In addition an improved work-up after the addition-cyclization step was also established leading to better yields and metal-free products.

1. Introduction

We recently reported on the synthesis of 3,4,5-trisubstituted-1,2,4-triazoles using silver benzoate as a key reagent (Scheme 1).[1] This methodology was useful for the synthesis of optically pure compounds, bearing a chiral moiety in position 3 (Scheme 1), as intermediates for the synthesis of GHS–R1a ligands.[2] In our ongoing efforts to develop original compounds with potential biological activities, we decided to work on the synthesis of more complex structures, based on the 1,2,4-triazole scaffold substituted with **1**, **2** or even **3** amino acid side chains. We thus attempted to apply the silver benzoate methodology to the synthesis of these derivatives. Because α-amino acids possess an asymmetric carbon atom, the synthesis of such compounds required a complete study of the optical purity retention during the synthetic process.



Scheme 1. Synthesis of 3,4,5-trisubstituted 1,2,4-triazole using silver benzoate.

2. Results and discussion

Using chiral HPLC, we previously demonstrated that the use of silver benzoate allowed us to introduce a chiral moiety on position 3 of the ring, maintaining the optical purity of this center unchanged.[1] The same strategy was used to study the introduction of chiral centers in positions 4 and 5. We synthesized two analogs of 3,4,5-trisubstituted 1,2,4-triazole enantiomers that were then analyzed by chiral HPLC analysis.

We first studied epimerization when introducing a chiral substituent in position 5 of the triazole (Scheme 2). For this purpose we produced the corresponding hydrazides starting from optically pure Boc-L-Trp-OH and Boc-D-Trp-OH. We used a recently described pathway for the synthesis of these chiral hydrazides.[3] This approach for the synthesis of hydrazides bearing a large variety of chemical groups without epimerization, degradation or deprotection problems, which can occur with classical methods. Hydrazides **4** and **7** were reacted with an achiral thioamide **6** (obtained as previously described via Lawesson's reagent).[4] Silver benzoate-mediated coupling–cyclization afforded triazoles **5** and **8**.

Using chiral HPLC analysis we observed that the synthetic scheme did not induce epimerization when a chiral group was placed in position 5 (ee ≥98%).

Secondly, we studied epimerization when a chiral group is introduced at position 4 of the triazole ring (Scheme 3). For this purpose we synthesized amides **9** and **12** by coupling picolinic acid with HCl·H-L-Phe-OMe and HCl·H-D-Phe-OMe, respectively. Without further purification these amides were reacted with the Lawesson's reagent to obtain thioamides **10** and **13**. The

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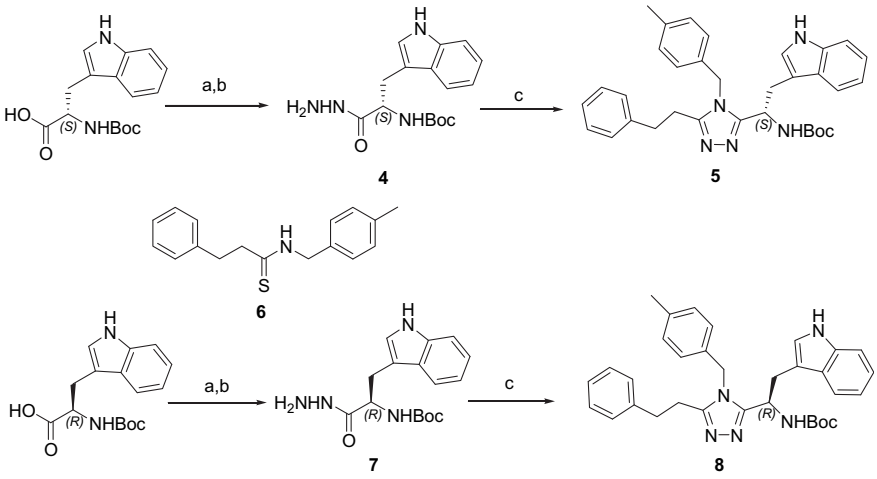
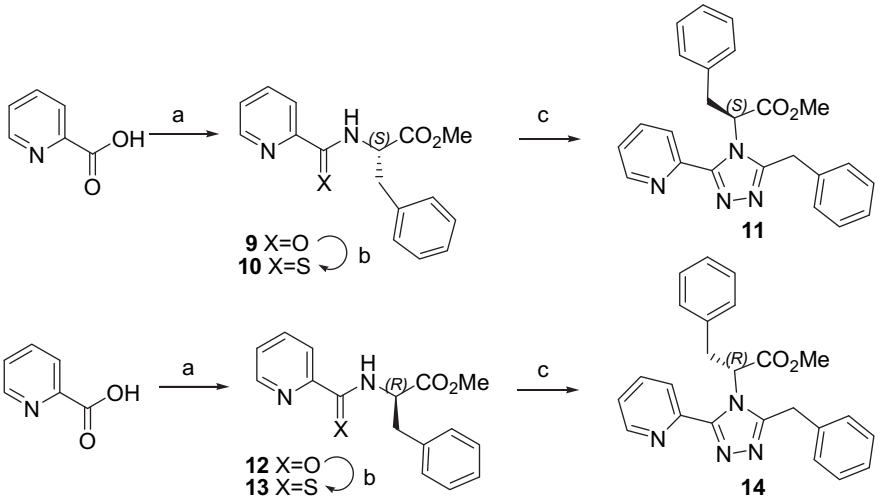
doi:10.1016/j.tet.2011.07.011



Scheme 2. Synthesis of triazoles **5** and **8**. Experimental conditions: (a) EDC·HCl (1.4 equiv), DCM, 2 h, 0 °C then *N*-aminophthalimide 1 h, 0 °C and overnight rt (b) Aminomethyl polystyrene resin, 1.1 mmol/g, DCM, 24 h, rt (c) **6** (1 equiv), **4** (1.2 equiv), AgOBz (2 equiv), AcOH (3 equiv), DCM, 6 h, rt.



Scheme 3. Synthesis of triazoles **11** and **14**. Experimental conditions: (a) BOP (1 equiv), benzylamine (1.1 equiv), DIEA (2 equiv), 30 min, rt (b) Lawesson reagent (0.55 equiv), DME, 2 h, 80 °C (c) phenylacetic hydrazide (2 equiv), AgOBz (2 equiv), AcOH (3 equiv), DCM, 6 h, rt.

coupling–cyclization step with phenylacetic hydrazide in the presence of silver benzoate proceeded very slowly to yield triazoles **11** and **14** in low yields (about 20% after 14 days).

Following isolation by silica gelcompounds **11** and **14** were analyzed by chiral HPLC. No epimerization was detected during the procedure (ee $\geq$98%).

From these experiments, we could conclude that the silver benzoate-mediated coupling–cyclization reaction did not induce epimerization in any asymmetric carbon atom present in α position of the triazole ring.

We then attempted to apply our methodology to the synthesis of the 1,2,4-triazole scaffold, substituted with 2 or 3 amino acid side chains. Three types of diastereoisomers could be synthesized: trisubstituted triazoles bearing chiral groups in positions 3 and 5 of the triazole ring, trisubstituted triazoles bearing chiral groups in positions 3 and 4 of the triazole ring, trisubstituted triazoles bearing chiral groups in positions 3, 4 and 5 of the triazole ring.

In the following section, we describe the synthesis of optically pure diastereoisomers bearing chiral groups in positions 3 and 5. Fmoc, Z or Boc *N*-protected amino acids were coupled to various amines to yield amides that were converted into thioamides **15a**–**q**. The resulting thioamides were allowed to react with different *N*-protected amino acid hydrazides **16a**–**q** to produce the 1,2,4-triazoles **17a**–**q**. Hydrazides **16a**–**o** were prepared according to Ref. 3. Hydrazide **16p** was synthesized by overnight hydrazinolysis of the corresponding methyl ester with hydrazine monohydrate (6 equiv) in MeOH at room temperature, to avoid the epimerization of acylated amino acids that occurs during activation with EDC. Results are summarized in Table 1.

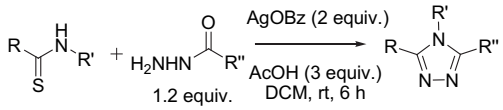
These results indicate that this method in scope is robust, being compatible with usual peptide synthesis protecting groups (Boc, Cbz, and Fmoc) and amino acids functionalized on their side chain can be introduced. Yields ranged from poor to good and were irrespective both of the electron withdrawing or donating effects and of the nature of side chains. In addition, the protecting groups used in these examples were stable under these reaction conditions.

All compounds described in Table 1 were obtained by silica gel purification of the crudes. Usually a very polar eluent was required for elution of triazole derivatives (5% MeOH/95% Ethyl acetate) and low yields were obtained in some cases (**17f** and **17h**, for example).

For the synthesis of 1,2,4-triazoles trisubstituted by amino acid side chains in positions 3, 4, and 5, the same protocol was followed (Scheme 4).

This reaction yielded, after purification, triazole **20** trisubstituted in position 3, 4, and 5 by amino acid side chains in an

Table 1
Synthesis of 1,2,4-triazoles bearing amino acid side chains in positions **3** and **5** of the ring



15(a-q) **16(a-q)** **17(a-q)**

17	Starting material for R	R′	Starting material for R″	Yield (%)
a	Fmoc-L-Trp	Benzyl	Boc-L-Phe	42
b	Fmoc-L-Trp	*p*-OMeBenzyl	Boc-L-Phe	77
c	*Z*-L-Phe	Benzyl	Boc-L-Phe	59
d	*Z*-L-Phe	*p*-OMeBenzyl	Boc-L-Phe	49
e	Fmoc-L-Phe	*p*-ClBenzyl	Boc-L-Phe	51
f	*Z*-L-Trp	*p*-ClBenzyl	Boc-L-Phe	32
g	Fmoc-L-Trp	Benzyl	Boc-L-Trp	34
h	*Z*-L-Trp	*p*-ClBenzyl	Boc-L-Trp	29
i	*Z*-L-Phe	*p*-OMeBenzyl	Boc-L-Lys(Z)	79
j	Boc-L-Nle	Benzyl	Z-L-Asp(OBzl)	76
k	Boc-L-Nle	Benzyl	Z-D-Asp(OBzl)	62
l	Boc-L-Nle	Phenethyl	Fmoc-L-Asp(O*t*-Bu)	70
m	Boc-L-Nle	Benzyl	Fmoc-L-Glu(O*t*-Bu)	77
n	Boc-L-Trp	Pentyl	Z-L-Asp(OBzl)	33
o	Boc-L-Nle	Benzyl	Fmoc-L-Asp(O*t*-Bu)	60
p	Boc-L-Nle	Ethyl 2-acetate	Ac-L-Phe	84
q	Boc-L-Nle	Ethyl 2-acetate	Ac-D-Phe	77

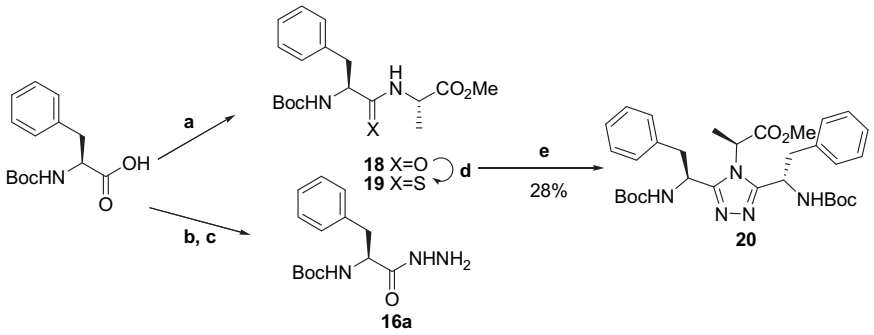
This new procedure was applied to the synthesis of two compounds **17e** and **17f**. A comparison of the yields that were obtained are shown in Table 2.

Table 2
Influence of the treatment on the yields

Compounds	Yields (%) and silver concentration (ppm) (direct purification by chromatography)	Yields (%)and silver concentration (ppm) (precipitation treatment and chromatography)
17e	51—ND	79—ND
17f	32—13.3	59—2.3

Indeed, the apparent polarity of the products was changed after removal of silver salts. As a comparison, the eluent for elution of the desired compound on silica gel chromatography, in the presence of silver salts, was 5% MeOH in EtOAc, whereas in the absence of silver salts only a 9/1 (v/v) EtOAc/hexane mixture was needed. Yields were clearly improved under this new procedure (Table 2).

As part of our ongoing effort to obtain metal-free final compounds, we synthesized and purified a compound by the two methods described above. Then we measured the silver salts concentration using ICPMS (Inductively Coupled Plasma—Mass Spectroscopy) analysis. As we can see in Table 2, the silver concentrations were very low in both cases. However treatment by silver salts precipitation allowed us to mostly eliminate silver contained in the crude. This result confirmed the superiority of the silver salt precipitation treatment over the direct purification by chromatography on silica gel.



Scheme 4. Synthesis of a triazole ring starting from amino acids. Experimental conditions: (a) AlaOMe (1.1 equiv), DIEA, BOP (1 equiv), 30 min, rt (b) EDC·HCl (1.4 equiv), DCM, 2 h, 0 °C then *N*-aminophthalimide 1 h at 0 °C and overnight rt (c) Aminomethyl Polystyrene resin, 1.1 mmol/g, DCM, 24 h, rt (d) Lawesson's reagent (0.55 equiv), DME, 2 h, 80 °C (e) **19** (1.0 equiv), **16a** (1.2 equiv), AgOBz (2 equiv), AcOH (3 equiv), DCM, 3 days, rt.

optically pure form as assessed by ^{1}H NMR. In this case, the reaction proceeded slowly. This example indicated that we are able to produce rigid tripeptide analogs. The biological study of this class of compounds is currently under investigation.

We tried to optimize the treatment and purification of our triazole compounds. To solve problems related to the presence of silver salts, we did not succeed in eliminating them using the different methods described in the literature (aqueous barium sulfide washing,[5] filtration of the crude on a Celite pad, aqueous NaCl washing). We thus developed a new strategy, employing the formation of a silver salt, that is, insoluble in organic media and compatible with the protecting groups that were used. The simplest example used was silver chloride, which is insoluble in water and organic media. The treatment was optimized to minimize the risk of acid labile group deprotection. Typically after evaporation of dichloromethane, a 50/50 (v/v) solution of DCM and MeOH was added. After vigorous stirring, 2 equiv of HCl (1 N solution in water) were added. Stirring was continued for 2 min and a black powder precipitated. *N*,*N*-Diisopropylethylamine (2 equiv) was added to neutralize the remaining HCl. After evaporation of the solvent, the residue was filtered on Celite and eluted with methanol. After solvent evaporation, dilution in ethyl acetate and washing twice with $KHSO_4$ (1 M solution in water) and $NaHCO_3$ (saturated water solution) afford the product as a colorless solid or oil. The product was isolated by silica gel in good yield.

To conclude, in this paper we described the first synthesis of 1,2,4-triazoles bearing at least two amino acid side chains. This synthetic procedure is epimerization free as demonstrated by chiral HPLC analysis. This study allowed the synthesis of compounds that can mimic small peptides. We will now focus on the synthesis of potentially bioactive compound libraries. We aim to prove that the triazole moiety can be a good scaffold to rigidify small peptides structures with possible improvement in their pharmacological properties.

3. Experimental section

3.1. General

Commercially available reagents and solvents were used without further purification. Aminomethyl polystyrene resin was purchased from Iris Biotech GmbH (Marktredwitz, Germany).

LC/MS analyses—samples were prepared in acetonitrile/water (50/50 v/v) mixture, containing 0.1% TFA. All the analyses were

carried out using a Merck Chromolith Speed rod C18, 25×4.6 mm reversed-phase column. A flow rate of 3 mL/min and a gradient of (0–100)% B over 3 min (or over 5 min) were used. Eluent A: water/0.1% HCO_2H; eluent B: acetonitrile/0.1% HCO_2H. Nitrogen was used for both the nebulizing and drying gas. The data were obtained in a scan mode ranging from 100 to 1000 *m*/*z* in 0.1 s intervals; 10 scans were summed up to get the final spectrum.

NMR spectroscopy—chemical shifts were reported as δ values (ppm) indirectly referenced to the solvent signal; *J* values are in hertz, and splitting patterns are designated as follows: br s (broad singlet), s (singlet), d (doublet), t (triplet), m (multiplet).

Chiral HPLC—for compounds **11** and **14**, analysis were performed on a Chiracel OD column (normal phase), with a flow rate of 1 ml/min in an isocratic mode 70/30 hexane/isopropanol (v/v) 1‰ Et_2NH and monitoring at 280 nm. For compounds **5** and **8**, analysis was performed on a Welck 01 column (normal phase), with a flow rate of 1 ml/min in an isocratic mode 70/30 hexane/isopropanol (v/v) and monitoring at 280 nm.

Flash chromatography—purifications were performed with Kieselguhr Merck G silica gel Si 60 (40–63 μm) with hexane/AcOEt as eluent.

Preparation of amides, thioamides, and hydrazides have been previously described in Refs. 1,3.

3.2. General procedure for preparation of compounds 17a–q

Thioamide (1 equiv) and hydrazide (1.2 equiv) were diluted in dichloromethane (10 ml/mmol). Silver benzoate (2 equiv) was then added immediately followed by acetic acid (3 equiv). The mixture was stirred 6 h at room temperature. Distillation of the solvent under reduced pressure gave a black oil, which was diluted in a solution of dichloromethane. A flash chromatography on silica gel, with AcOEt/hexane 5/5 to MeOH 5% in AcOEt as eluent, afforded the triazoles in 32–90% yield.

3.3. General procedure for preparation of 1,2,4-triazoles with silver salts precipitation work-up

Thioamide (1 equiv) and hydrazide (1.2 equiv) were diluted in dichloromethane (10 ml/mmol). Silver benzoate (2 equiv) was then added immediately followed by acetic acid (3 equiv). The mixture was stirred for 6 h at room temperature. Distillation of the solvent under reduced pressure gave a black oil, which was diluted in 50/50 (v/v) solution of DCM and MeOH solution (10 ml/mmol). Under vigorous stirring, 2 equiv of HCl (1 N solution in water) were added. After 2 min of stirring a black powder precipitated. Diisopropylethylamine (2 equiv) was then added. After evaporation under reduced pressure, the reaction mixture was filtered on filter paper and eluted with methanol. After solvent evaporation, dilution in ethyl acetate and washing twice with $KHSO_4$ (1 M solution in water) and $NaHCO_3$ (saturated water solution) a colorless compound was obtained. A flash chromatography on silica gel, with AcOEt/hexane 5/5 to pure AcOEt eluents, afforded the pure triazoles in 60–90% yield.

3.4. Compounds characterization

*3.4.1. tert-Butyl 1-(4-(4-methylbenzyl)-5-phenethyl-4H-1,2,4-triazol-3-yl)-2-(1H-inden-3-yl)ethylcarbamate **5**.* Brown powder, 185 mg, 70% and **8** brown powder, 185 mg, 70% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.22 (s, 9H, CH_3 Boc), 2.23 (3H, s, CH_3 *p*-methylbenzyl), 2.67–2.69 (4H, m, CH_2CH_2 phenethyl), 3.22–3.43 (m, 2H, $CH_2\beta$ tryptophan), 4.91 (dd, 1H, 9 and 14 Hz, CHα tryptophan), 5.06 (s, 2H, CH_2 *p*-methylbenzyl), 6.72 (d, 7 Hz, NH Boc and H_5 tryptophan), 6.89 (t, 1H, H_6 tryptophan), 6.99–7.33 (m, 11H, CH aromatics phenethyl and *p*-methylbenzyl, and H_2H_7 tryptophan), 7.55 (d, 1H, 9 Hz, H_4 tryptophan), 10.72 (s, 1H, NH indole). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 20.5 (CH_3 *p*-methylbenzyl), 26.2 ($CH_2\beta$ phenethyl), 28.0 (CH_3 Boc), 28.9 (CH_2 α phenethyl), 32.4 ($CH_2\beta$ tryptophan), 45.0 (CH_2 *p*-methylbenzyl), 45.3 (CHα tryptophan), 78.3 (C quat. Boc), 110.2 (C_3 tryptophan), 111.2 (C_7 tryptophan), 118.1 (C_4 tryptophan), 118.2 (C_5 tryptophan), 120.7 (C_6 tryptophan), 123.8 (C_2 tryptophan), 125.9 and 126.0 (C_4 phenethyl and *p*-methylbenzyl), 127.1 (C_9 tryptophan), 128.2 and 129.1 (CH aromatics and *p*-methylbenzyl), 132.9 (C_4 *p*-methylbenzyl), 135.9 and 136.6 (C_1 *p*-methylbenzyl and C_8 tryptophan), 140.6 (CO Boc), 153.8 and 155.1 (C_3C_5 triazole). MS (ES), *m*/*z*: 536.3 $[M+H]^+$.

*3.4.2. (S)-Methyl 3-phenyl-2-(pyridine-2-carbothioamido)propanoate **10**.* Yellow oil, 2.83 g, 94%.

*3.4.3. (R)-Methyl 3-phenyl-2-(pyridine-2-carbothioamido)propanoate **13**.* Yellow oil, 2.52 g, 84% ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.38 (dd, 1H, 8 and 14 Hz, $CH_2\beta$ phenylalanine), 3.40 (dd, 1H, 6 and 14 Hz, $CH_2\beta$ phenylalanine), 3.68 (s, 3H, OMe), 5.44 (m, 1H, CHα phenylalanine), 7.20–7.29 (m, 5H, CH aromatics phenylalanine), 7.63 (ddd, 1H, 1 and 5 and 8 Hz, H_5 pyridine), 8.00 (td, 1H, 2 and 8 Hz, H_3 pyridine), 8.44 (dt, 1H, 8 Hz, H_4 pyridine), 8.62 (m, 1H, H_6 pyridine), 10.83 (d, 1H, 8 Hz, NH thioamide). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 36.1 ($CH_2\beta$ phenylalanine), 52.8 (OMe), 59.4 (CHα phenylalanine), 125.0 (C_3 pyridine), 127.3 and 127.3 (C_4 phenylalanine and C_5 pyridine), 128.9 (C_2 and C_6 phenylalanine), 129.5 (C_3 and C_5 phenylalanine), 137.1 (C_1 phenylalanine), 138.3 (C_4 pyridine), 148.1 (C_6 pyridine), 151.3 (C_2 pyridine), 170.7 (CO carbonyl), 191.9 (CS thioamide). MS (ES), *m*/*z*: 301.1 $[M+H]^+$.

*3.4.4. (S)-Methyl 2-(3-benzyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-4-yl)-3-phenylpropanoate **11**.* Colorless oil, 80 mg (20%).

*3.4.5. (R)-Methyl 2-(3-benzyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-4-yl)-3-phenylpropanoate **14**.* Colorless oil, 82 mg (20%) ^{1}H NMR (400 MHz, DMSO-d_6, 303 K): δ (ppm) 3.27 (dd, 1H, *J*=10 and 14 Hz, $CH_2\beta$ phenylalanine), 3.49 (s, 3H, OMe), 3.60 (br s, 1H, CH_2 benzyl), 3.64 (dd, 1H, *J*=4 and 14 Hz, $CH_2\beta$ phenylalanine), 5.68 (m, 1H, CHα phenylalanine), 6.84 (d, 2H, *J*=8Hz, H_2H_6 benzyl), 7.02 (d, 2H, *J*=7 Hz, H_2H_6 phenylalanine), 7.14–7.28 (m, 6H, $H_3H_4H_5$ benzyl and $H_3H_4H_5$ phenylalanine), 7.50 (ddd, 1H, *J*=1 and 5 and 7 Hz, H_5 pyridine), 8.00 (td, 1H, *J*=2 and 8 Hz, H_4 pyridine), 8.20 (d, 1H, *J*=8 Hz, H_3 pyridine), 8.58 (br d, 1H, *J*=5 Hz, H_6 pyridine). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 30.5 (CH_2 benzyl), 37.2 ($CH_2\beta$ phenylalanine), 52.7 (OMe), 59.8 (CHα phenylalanine), 123.0 (C_3 pyridine), 124.9 (C_5 pyridine), 127.1 and 127.4 (C_4 phenylalanine and C_4 benzyl), 128.8–129.5 ($C_2C_3C_5C_6$ phenylalanine and $C_2C_3C_5C_6$ benzyl), 136.0 (C_1 benzyl), 136.9 (C_4 pyridine), 138.2 (C_1 phenylalanine), 147.3 (C_3 or C_5 triazole), 148.4 (C_6 pyridine), 151.6 (C_2 pyridine), 156.2 (C_3 or C_5 triazole), 169.0 (CO ester). MS (ES), *m*/*z*: 399.0 $[M+H]^+$.

*3.4.6. (9H-Fluoren-9-yl)methyl (S)-1-(benzylthiocarbamoyl)-2-(1H-indol-3-yl)ethylcarbamate **15a** and **15g**.* Yellow oil, 1.46 g, 60% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 3.11 (dd, 1H, 9 and 14 Hz, $CH_2\beta$ tryptophan), 3.26 (dd, 1H, 5 and 14 Hz, $CH_2\beta$ tryptophan), 4.20 (m, 3H, CH–CH_2 Fmoc), 4.74 (m, 1H, CHα tryptophan), 4.80 (d, 2H, 5Hz, CH_2 benzyl), 7.00 (m, 1H, H_5 tryptophan), 7.08 (t, 1H, 8 Hz, H_6 tryptophan), 7.18 (d, 2H, 7 Hz, H_2 tryptophan and H_4 benzyl), 7.23–7.30 (m, 6H, $H_2H_3H_5H_6$ benzyl and H_2H_7 Fmoc), 7.35–7.41 (m, 3H, H_7 tryptophan and H_3H_6 Fmoc), 7.59 (d, 1H, 8 Hz, H_4 tryptophan), 7.64–7.73 (m, 3H, H_1H_8 Fmoc and NH Fmoc), 7.87 (d, 2H, 7Hz, H_4 H_5 Fmoc), 10.48 (br s, 1H, NH thioamide), 10.85 (s, 1H, NH indole tryptophan). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 30.9 ($CH_2\beta$ tryptophan), 46.6 (CH Fmoc), 48.3 (CH_2 benzyl), 61.9 (CHα tryptophan), 65.7 (CH_2 Fmoc), 109.9 (C_3 tryptophan), 111.3 (C_7 tryptophan), 118.2 (C_4 tryptophan), 118.5 (C_5 tryptophan), 120.0

(C_4C_5 Fmoc), 120.8 (C_6 tryptophan), 124.1 (C_2 tryptophan), 125.3 (C_1 C_8 Fmoc), 127.0 (C_4 benzyl and C_2 C_7 Fmoc), 127.2 (C_9 tryptophan), 127.4 (C_2 C_6 benzyl), 127.7 (C_3 C_5 benzyl), 128.2 (C_3 C_6 Fmoc), 136.1 (C_1 benzyl), 136.9 (C_8 tryptophan), 140.6 (C_4 a/b Fmoc), 143.8 (C_8 a/b Fmoc), 155.5 (CO Fmoc), 204.8 (CS thioamide). MS (ES), *m*/*z*: 532.0 $[M+H]^+$.

3.4.7. (9H-Fluoren-9-yl)methyl (S)-1-(4-methoxybenzylthiocarbamoyl)-2-(1H-indol-3-yl)ethylcarbamate ***15b***. Yellow oil, ^1H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 3.12 (dd, 1H, 9 and 14 Hz, $CH_2\beta$ tryptophan), 3.21 (dd, 1H, 5 and 14 Hz, $CH_2\beta$ tryptophan), 3.71 (s, 3H, O–CH_3), 4.18 (m, 3H, $CHCH_2$–Fmoc), 4.72 (m, 3H, CHα tryptophan and CH_2 4-methoxybenzyl), 6.82 (d, 2H, 8 Hz, H_3 H_5 4-methoxybenzyl), 7.01 (t, 1H, 8 Hz, H_5 tryptophan), 7.05–7.13 (m, 3H, H_6 tryptophan and H_2H_6 4-methoxybenzyl), 7.24 (d, 1H, 2Hz, H_2 tryptophan), 7.29 (m, 2H, H_2H_7 Fmoc), 7.32–7.43 (m, 2H, H_3H_6 Fmoc and H_7 tryptophan), 7.56 (d, 1H, 8 Hz, H_4 tryptophan),7.70 (m, 3H, H_1H_8 Fmoc and NH Fmoc), 7.87 (d, 2H, 8Hz, H_4H_5 Fmoc), 10.39 (br s, 1H, NH thioamide), 10.85 (s, 1H, NH indole tryptophan). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 30.8 ($CH_2\beta$ tryptophan), 46.6 (CH Fmoc), 47.8 (CH_2 4-methoxybenzyl), 55.0 (O–CH_3), 61.8 (CHα tryptophan), 65.7 (CH_2 Fmoc), 109.9 (C_3 tryptophan), 111.3 (C_7 tryptophan), 113.6 (C_3 C_5 4-methoxybenzyl), 118.2 (C_4 tryptophan), 118.5 (C_5 tryptophan), 120.0 (C_4C_5 Fmoc), 120.8 (C_6 tryptophan), 124.1 (C_2 tryptophan), 125.3 (C_1C_8 Fmoc), 127.0 (C_2C_7 Fmoc), 127.3 (C_9 tryptophan), 127.6 (C_2C_6 4-methoxybenzyl or C_3C_6 Fmoc), 128.9 (C_2C_6 4-methoxybenzyl or C_2C_6 Fmoc), 128.7 (C_1 4-methoxybenzyl), 136.1 (C_8 tryptophan), 140.6 (C_4 a/b Fmoc), 143.6 (C_8 a/b Fmoc), 155.4 (CO Fmoc), 158.4 (C_4 4-methoxybenzyl), 204.3 (CS thioamide). MS (ES), *m*/*z*: 562.1 $[M+H]^+$.

3.4.8. Benzyl (S)-1-(benzylthiocarbamoyl)-2-phenylethylcarbamate ***15c***. Yellow oil, 1.25 g, 65% ^1H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 2.92 (dd, 2H, 9 and 14 Hz, $CH_2\beta$ phenylalanine), 3.04 (dd, 2H, 5 and 14 Hz, $CH_2\beta$ phenylalanine), 4.71 (m, 1H, CHα phenylalanine), 4.77 (d, 2H, 5 Hz, CH_2 benzyl), 4.98 (s, 2H, CH_2 Z), 7.20 (t, 3H, 7 Hz, H_4 benzyl and H_4 Z and H_4 phénylalanine), 7.27 (m, 12H, H_2 H_3 H_5 H_6 benzyl and H_2 H_3 H_5 H_6 Z and H_2 H_3 H_5 H_6 phenylalanine), 7.56 (d, 1H, 8Hz, NH Z), 10.50 (t, 1H, 7 Hz, NH thioamide). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 40.4 ($CH_2\beta$ phenylalanine), 48.2 (CH_2 benzyl), 62.2 (CHα phenylalanine), 65.2 (CH_2 Z), 126.3–129.3 (C_2 C_3 C_4 C_5 C_6 benzyl, C_2 C_3 C_4 C_5 C_6 Z, C_2 C_3 C_4 C_5 C_6 phenylalanine), 136.8 and 136.9 and 137.6 (C_1 benzyl and C_1 Z and C_1 phenylalanine), 155.5 (CO Z), 204.2 (CS thioamide) MS (ES), *m*/*z*: 405.0 $[M+H]^+$.

3.4.9. Benzyl (S)-1-(4-methoxybenzylthiocarbamoyl)-2-phenylethylcarbamate ***15d*** *and* ***15i***. Yellow oil, 1.44 g, 90% ^1H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 2.90 (dd, 1H, 9 and 14 Hz, $CH_2\beta$ phenylalanine), 3.02 (dd, 1H, 5 and 14 Hz, $CH_2\beta$ phenylalanine), 3.74 (s, 3H, O–*CH*$_3$), 4.67 (m, 3H, CHα phenylalanine and CH_2 4-methoxybenzyl), 4.87 (s, 2H, CH_2 Z), 6.87 (d, 2H, 8 Hz, H_3 H_5 4-methoxybenzyl), 7.22 (d, 2H, 8 Hz, H_2 H_6 4-methoxybenzyl), 7.22–7.30 (m, 10H, H_2 H_3 H_4 H_5 H_6 Z and H_2 H_3 H_4 H_5 H_6 phenylalanine), 7.53 (d, 1H, 8 Hz, NH Z), 10.42 (br s, 1H, NH thioamide). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 38.3 ($CH_2\beta$ phenylalanine), 47.8 (CH_2 4-methoxybenzyl), 55.0 (O–*CH*$_3$), 62.2 (CHα phenylalanine), 65.2 (CH_2 Z), 113.7 (C_3 C_5 4-methoxybenzyl), 126.3–129.3 (C_2 C_3 C_4 C_5 C_6 Z and C_2 C_3 C_4 C_5 C_6 phenylalanine and C_2 C_6 4-methoxybenzyl), 132.3 (C_1 p-méthoxybenzyl), 136.9 (C_1 Z), 137.7 (C_1 phenylalanine), 155.5 (CO Z), 158.5 (C_4 4-methoxybenzyl), 203.7 (CS thioamide). MS (ES), *m*/*z*: 435.0 [M+H].

3.4.10. (9H-Fluoren-9-yl)methyl (S)-1-(4-chlorobenzylthiocarbamoyl)-2-phenylethylcarbamate ***15e***. White solid, 1.79 g, 68% ^1H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 2.97 (dd, 1H, 9 and 14 Hz, $CH_2\beta$ phenylalanine), 3.05 (dd, 1H, 5 and 14 Hz, $CH_2\beta$ phenylalanine), 4.17 (m, 3H, CH_2CH Fmoc), 4.70 (m, 1H, CHα phenylalanine), 4.76 (d, 2H, 5Hz, CH_2 4-chlorobenzyl), 7.18 (d, 2H, 8Hz, H_2 H_6 4-chlorobenzyl), 7.27 (d, 2H, 7Hz, H_3 H_5 4-chlorobenzyl), 7.31–7.32 (m, 7H, H_2 H_7 Fmoc and H_2 H_3 H_4 H_5 H_6 phenylalanine), 7.41 (t, 2H, 7 Hz, H_3 H_6 Fmoc), 7.67 (d, 2H, 8 Hz, H_1 H_8 Fmoc), 7.73 (d, 1H, 8 Hz, NH Fmoc), 7.87 (d, 2H, 8 Hz, H_4 H_5 Fmoc), 10.53 (t, 1H, 5 Hz, NH thioamide). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 40.3 ($CH_2\beta$ phenylalanine), 46.5 (CH Fmoc), 47.4 (CH_2 4-chlorobenzyl), 62.3 (CHα phenylalanine), 65.7 (CH_2 Fmoc), 120.0 (C_4C_5 Fmoc), 125.3 (C_1C_8 Fmoc), 126.3 (C_4 phenylalanine), 127.0 (C_2C_7 Fmoc), 127.6 (C_3C_6 Fmoc), 128.0 and 128.1 ($C_2C_3C_5C_6$ 4-chlorobenzyl), 129.3 (CH Ar phenylalanine), 135.8 (C_1 phenylalanine), 137.6 (C_1 4-chlorobenzyl), 140.6 (C_4 a/b Fmoc), 143.7 (C_8 a/b Fmoc), 155.5 (CO Fmoc), 204.5 (CS thioamide). MS (ES), *m*/*z*: 527.0 $[M+H]^+$.

3.4.11. Benzyl (S)-1-(4-chlorobenzylthiocarbamoyl)-2-(1H-indol-3-yl)ethylcarbamate ***15f*** *and* ***15h***. Yellow 3.07 g, 100% ^1H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 3.07 (dd, 1H, 9 and 14 Hz, $CH_2\beta$ tryptophan), 3.24 (dd, 1H, 5 and 14 Hz, $CH_2\beta$ tryptophan), 4.74 (m, 3H, CH_2 4-chlorobenzyl and CHα tryptophan), 4.95 (br s, 2H, CH_2 Z), 7.00 (t, 2H, 7 Hz, H_5 tryptophan), 7.00 (d, 1H, 7Hz, NH Z), 7.11 (t, 1H, 8 Hz, H_6 tryptophan), 7.12 (d, 2H, 8 Hz, H_2 H_6 4-chlorobenzyl), 7.20 (s, 1H, H_2 tryptophan), 7.31 (d, 5H, 6 Hz, H_2 H_3 H_4 H_5 H_6 Z), 7.37 (d, 1H, 8 Hz, H_7 tryptophan), 7.36 (d, 2H, 8 Hz, H_3 H_5 4-chlorobenzyl), 7.66 (d, 1H, 8 Hz, H_4 tryptophan), 10.47 (t, 1H, 5 Hz, NH thioamide), 10.84 (s, 1H, NH indole tryptophan). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 30.8 ($CH_2\beta$ tryptophan), 47.4 (CH_2 4-chlorobenzyl), 61.9 (CHα tryptophan), 65.3 (CH_2 Z), 109.7 (C_3 tryptophan), 111.3 (C_7 tryptophan), 118.2 (C_4 tryptophan), 118.5 (C_5 tryptophan), 120.9 (C_6 tryptophan), 124.1 (C_2 tryptophan), 127.2 (C_9 tryptophan), 127.4 (C_4 Z), 128.1 (C_2 C_3 C_5 C_6 Z), 128.2 (C_2 C_6 4-chlorobenzyl), 129.2 (C_3 C_5 4-chlorobenzyl), 131.4 (C_4 4-chlorobenzyl), 136.1 (C_8 tryptophan and C_1 Z), 136.9 (C_1 4-chlorobenzyl), 155.5 (CO Z), 204.9 (CS thioamide). MS (ES), *m*/*z*: 478.1 [M+H].

3.4.12. tert-Butyl (S)-1-(5-((S)-1-Fmoc-amino-2-(1H-indol-3-yl)ethyl)-4-benzyl-4H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate ***17a***. Brown oil, 180 mg (42%) ^1H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.08 (s, 9H, CH_3 Boc), 3.15–3.41 (m, 4H, $CH_2\beta$ phenylalanine and tryptophan), 3.93–4.13 (m, 3H, C*H*$_2$C*H* Fmoc), 4.81–4.95 (m, 2H, CHα phenylalanine and tryptophan), 5.27 (dd, *J*=17 Hz, CH_2 benzylamine), 6.88 (m, 4H, H_4 benzylamine and H_4 phenylalanine and H_5 tryptophan and NH Boc), 7.01 (m, 2H, H_2H_6 tryptophan), 7.12–7.21 (m, 8H, $H_2H_3H_5H_6$ benzylamine and $H_2H_3H_5H_6$ phenylalanine), 7.25–7.31 (m, 3H, H_7 tryptophan and H_2H_7 Fmoc), 7.36–7.43 (dd, 2H, H_3H_6 Fmoc), 7.49 (d, 1H, *J*=9Hz, H_4 tryptophan), 7.58 (t, 2H, *J*=8 Hz, H_1H_8 Fmoc), 7.86 (d, 2H, *J*=7 Hz, H_4H_5 Fmoc), 8.17 (d, 2H, *J*=8 Hz, NH Fmoc), 10.77 (s, 1H, NH tryptophan). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 27.8 (CH_3 Boc), 38.0 ($CH_2\beta$ tryptophan and phenylalanine), 45.8 (CH_2 benzylamine), 46.4 (CHα phenylalanine and tryptophan), 46.6 (*C*HCH_2 Fmoc), 65.7 (CH*C*H$_2$ Fmoc), 78.0 (C quat. Boc), 109.6 (C_3 tryptophan), 111.2 (C_7 tryptophan), 117.8 (C_4 tryptophan), 118.2 (C_5 tryptophan), 120.0 (C_4C_5 Fmoc), 120.7 (C_6 tryptophan), 125.2 (C_2 tryptophan), 125.7 (C_1C_8 Fmoc), 126.1 (C_4 phenylalanine), 126.9 (C_9 tryptophan and C_4 benzylamine), 126.9 (C_2C_7 Fmoc), 127.5 (C_3C_6 Fmoc), 127.9 (C_2C_6 phenylalanine and benzylamine), 128.5–129.3 (C_3C_5 phenylalanine and benzylamine), 135.7 (C_1 phenylalanine), 135.9 (C_1 benzylamine), 137.6 (C_8 tryptophan), 140.6 ($C_{4a/b}$ Fmoc), 143.6 ($C_{8a/b}$ Fmoc), 154.8 and 155.2 (CO Fmoc and Boc), 155.7 and 156.1 (C_3 and C_5 triazole). HRMS (ESI) calcd for $C_{47}H_{47}N_6O_4$, 759.3659; found 759.3652.

3.4.13. tert-Butyl (S)-1-(5-((S)-1-Fmoc-amino-2-(1H-indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate ***17b***. Beige oil, 534 mg, 77% ^1H NMR (300 MHz, DMSO-d_6,

303 K): δ (ppm) 1.12 (s, 9H, CH_3 Boc), 3.18 and 3.36 (m, 4H, $CH_2\beta$ phenylalanine and tryptophan), 3.64 (s, 3H, 4-methoxybenzyl), 4.05 (m, 3H, $CHCH_2$—Fmoc), 4.90 (m, 2H, CHα phenylalanine and tryptophan), 5.17 (dd, 2H, 8 and 17Hz, CH_2 benzyl), 6.72 (d, 2H, 8Hz, H_3H_5 4-methoxybenzyl), 6.84 (m, 3H, H_2H_6 4-methoxybenzyl and NH Boc), 7.02 (m, 3H, H_2 H_5 H_6 tryptophan), 7.11–7.23 (m, 5H, CH aromatics phenylalanine), 7.29 (t, 3H, 8Hz, H_2H_7 Fmoc and H_7 tryptophan), 7.40 (m, 2H, H_3H_6 Fmoc), 7.46 (d, 1H, 9Hz, H_4 tryptophan), 7.60 (t, 2H, 8 Hz, H_1 H_8 Fmoc), 7.86 (d, 2H, 7Hz, H_4H_5 Fmoc), 8.19 (d,1H, 8Hz, NH Fmoc), 10.78 (s, 1H, NH indole tryptophan). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 27.8 (CH_3 Boc), 38.2 ($CH_2\beta$ phenylalanine and tryptophan), 45.3 (CH_2 4-methoxybenzyl), 46.5 (CHα tryptophan and phenylalanine), 46.7 ($CHCH_2$ Fmoc), 55.0 (4-methoxybenzyl), 65.8 (CH_2CHFmoc), 78.0 (C quat Boc), 109.7 (C_3 tryptophan), 111.2 (C_7 tryptophan), 113.9 (C_3C_5 4-methoxybenzyl), 117.9 (C_4 tryptophan), 118.2 (C_5 tryptophan), 120.0 (C_4C_5 Fmoc), 120.8 (C_6 tryptophan), 125.3 (C_1C_8 Fmoc), 126.1 (C_2 tryptophan), 127.0 (C_4 phenylalanine), 127.1 (C_2C_7 Fmoc), 127.6 (C_3C_6 Fmoc), 127.9 (C_2C_6 phenylalanine and 4-methoxybenzyl), 129.3 (C_3C_5 phenylalanine), 136.0 (C_1 4-methoxybenzyl and C_8 tryptophan), 137.6 (C_1 phenylalanine), 140.6 (C_4 a/b Fmoc), 143.6 (C_8a/b Fmoc), 155.2 (C_4 4-methoxybenzyl), 155.7 (CO Boc or Fmoc), 156.0 (CO Boc or Fmoc), 158.6 (C_3 and C_5 triazole). HRMS (ESI) calcd for $C_{48}H_{49}N_6O_5$, 789.3764; found 789.3763.

3.4.14. tert-Butyl (S)-1-(5-((S)-1-Cbz-amino-2-(phenyl)ethyl)-4-benzyl-4H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate ***17c***. White powder, 367 mg, 59% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.13 (s, 9H, CH_3 Boc), 3.07 (m, 4H, $CH_2\beta$ phenylalanine), 4.72–4.90 (m, 4H, CH_2 benzylamine and CH_2 Z), 5.2 (dd, 2H, 17Hz and 20 Hz CHα phenylalanine), 6.94–7.33 (m, 20H, CH aromatics), 7.54 (d, 1H, 9Hz, NH Boc), 8.05 (d, 1H, 9Hz, NH Z) ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 27.8 (CH_3 Boc), 38.3 ($CH_2\beta$ phenylalanine), 45.7 (CH_2 benzylamine), 46.6 (CHα phenylalanine), 47.3 (CHα phenylalanine), 65.3 (CH_2 Z), 78.0 (C quat. Boc), 126.0 and 126.1 and 126.3 (C_4 benzylamine and C_4 phenylalanine and C_4 Z), 127.3–129.2 ($C_2C_3C_5C_6$ phenylalanine and Z and benzylamine), 135.7 and 136.7 and 137.4 and 137.6 (C_1 phenylalanine and C_1 benzyl and C_1Z), 154.9 (CO Boc or Z), 155.4 (CO Boc or Z), 155.6 (C_3 and C_5 triazole). HRMS (ESI) calcd for $C_{38}H_{42}N_5O_4$, 632,3237; found 632,3224.

3.4.15. tert-Butyl (S)-1-(5-((S)-1-Cbz-amino-2-(phenyl)ethyl)-4-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate ***17d***. White powder, 374 mg, 49% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.17 (s, 9H, CH_3 Boc), 3.09 (m, 4H, $CH_2\beta$ phenylalanine), 3.72 (s, 3H, O—Me), 4.83 (m, 4H, CH_2 4-methoxybenzyl and CH_2 Z), 5.11 (dd, 2H, CHα phenylalanine), 6.82 (d, 2H, 9 Hz, H_2H_6 4-methoxybenzyl), 6.90 (d, 2H, 8 Hz, H_3H_5 4-methoxybenzyl), 7.00–7.31 (m, 15H, CH Ar. Z and phenylalanine), 7.55 (d, 1H, 9 Hz, NH Boc), 8.06 (d, 1H, 9 Hz, NH Z). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 27.9 (CH_3Boc), 38.2 and 38.3 ($CH_2\beta$ phenylalanine), 45.4 (CH_2 4-methoxybenzyl), 46.6 ($CH_2\beta$ phenylalanine), 47.3 (CHα phenylalanine), 55.1 (CH_3 4-methoxybenzyl), 65.4 (CH_2 Z), 78.1 (C quat. Boc), 114.0 (C_3 C_5 4-methoxybenzyl), 126.2–129.2 (C_2 C_3 C_4 C_5 C_6 phenylalanine and C_2 C_3 C_4 C_5 C_6 Z and C_2 C_6 4-methoxybenzyl), 136.7 and 137.3 and 137.5 (C_1 Z and phenylalanine and 4-methoxybenzyl), 154.9 (C═O Boc or Z), 155.4 (C_4 4-methoxybenzyl), 155.6 (C═O Boc or Z), 158.6 (C_3 and C_5 triazole). HRMS (ESI) calcd for $C_{39}H_{44}N_5O_5$,: 662,3342; found 662,3334.

3.4.16. tert-Butyl (S)-1-(5-((S)-1-Fmoc-amino-2-(phenyl)ethyl)-4-(4-chlorobenzyl)-4H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate ***17e***. White powder, 290 mg, 51%, ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.14 (s, 9H, CH_3 Boc), 3.19 (m, 4H, $CH_2\beta$ phenylalanine), 3.89 (t, 1H, 8 Hz, CH Fmoc), 4.02 (t, 1H, 7 Hz, CH_2 Fmoc), 4.09 (t, 1H, 8 Hz, CH_2 Fmoc), 4.83 (m, 2H, CHα phenylalanine), 5.16 (d, 1H, 17 Hz, CH_2 4-chlorobenzyl), 5.24 (d, 1H, 17 Hz, CH_2 4-chlorobenzyl), 6.84 (d, 2H, 9 Hz, H_2H_6 4-chlorobenzyl), 7.05 (d, 2H, 7 Hz, H_2H_6 phenylalanine), 7.10 (d, 2H, 7 Hz, H_2H_6 phenylalanine), 7.17 (m, 8H, H_3 H_4 H_5 phenylalanine and H_3 H_5 4-chlorobenzyl), 7.30 (dd, 2H, 7 and 9 Hz, H_2 H_7 Fmoc), 7.42 (d, 2H, 7 and 8 Hz, H_3 H_6 Fmoc), 7.56 (d, 1H, 9 Hz, NH Fmoc), 7.60 (dd, 2H, 9 Hz, H_1 H_8 Fmoc), 7.89 (dd, 2H, 8 Hz, H_4 H_5 Fmoc), 8.21 (d, 1H, 8 Hz, NH Boc). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 28.4 (CH_3 Boc), 38.6 ($CH_2\beta$ phenylalanine), 38.8 ($CH_2\beta$ phenylalanine), 45.6 (CH_2 4-chlorobenzyl), 46.9 (CHα phenylalanine), 47.1 (CH Fmoc), 47.8 (CHα phenylalanine), 66.3 (CH_2 Fmoc), 78.6 (C quat. Boc), 120.6 (C_4 C_5 Fmoc), 125.7 and 125.8 (C_1 C_8 Fmoc), 126.7 and 126 .8 (C_2 C_7 Fmoc), 127.4 and 127.5 (C_4 phenylalanine), 128.1 (C_3 C_5 phenylalanine), 128.4 and 128.5 and 128.5 and 128.8 (C_2 C_3 C_5 C_6 4-chlorobenzyl), 129.7 and 129.7 (C_2 C_6 phenylalanine), 132.4 (C_4 4-chlorobenzyl), 135.4 (C_1 4-chlorobenzyl), 138.0 and 138.1 (C_1 phenylalanine), 141.1 ($C_{4a/b}$ Fmoc), 144.0 and 144.1 ($C_{8a/b}$ Fmoc), 155.3 (CO Fmoc), 155.9 and 155.8 (C_3 and C_5 triazole), 156.0 (CO Boc). HRMS (ESI) calcd for $C_{45}H_{45}ClN_5O_4$, 734.3160; found 734.3161.

3.4.17. tert-Butyl (S)-1-(5-((S)-1-Cbz-amino-2-(1H-indol-3-yl)ethyl)-4-(4-chlorobenzyl)-4H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate ***17f***. White powder, 237 mg, 32%, ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.07 (s, 9H, CH_3 Boc), 3.18–3.31 (m, 4H, CH_2 β phenylalanine and $CH_2\beta$ tryptophan), 4.76–4.90 (m, 4H, CHα phenylalanine and CHα tryptophan and CH_2 4-chlorobenzyl), 5.25 (s, 2H, CH_2 Z), 6.83 (m, 2H, 7 and 8 Hz, H_4 and H_5 tryptophan), 6.95 (d, 1H, 7 Hz, NH Boc), 7.03 (m, 2H, H_2H_6 trytophane), 7.14–7.32 (m, 13H, CH Ar phenylalanine and Z, $H_2H_3H_5H_6$ 4-chlorobenzyl), 7.46 (d, 1H, 9Hz, H_7 tryptophan), 8.04 (d, 2H, 8 Hz, NH Z), 10.78 (s, 1H, NH indole). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 27.7 (CH_3 Boc), 37.6 and 38.0 ($CH_2\beta$ tryptophan and phenylalanine), 45.1 (CH_2 4-chlorobenzyl), 46.4 and 46.6 (CHα tryptophan and phenylalanine), 65.4 (CH_2 Z), 78.0 (C quat. Boc), 109.5 (C_3 tryptophan), 111.2 (C_7 tryptophan), 117.8 (C_4 tryptophan), 118.2 (C_5 tryptophan), 120.8 (C_6 tryptophan), 126.2 (C_2 tryptophan), 126.9 (C_9 tryptophan), 127.4–128.3 (CH Ar. Z and phenylalanine and $C_2C_3C_5C_6$ 4-chlorobenzyl), 132.0 (C_4 4-chlorobenzyl), 134.7 and 135.9 and 137.6 (C_1 phenylalanine and C_1 4-chlorobenzyl and C_1 Z), 136.6 (C_8 tryptophan), 154.7 and 155.2 (CO Z and Boc), 155.7 (C_3 and C_5 triazole). HRMS (ESI) calcd for $C_{40}H_{42}ClN_6O_4$, 705.2956; found 705.2955.

3.4.18. tert-Butyl(S)-1-(5-((S)-1-Fmoc-amino-2-(1H-indol-3-yl)ethyl)-4-benzyl-4H-1,2,4-triazol-3-yl)-2-(1H-indol-3-yl)ethylcarbamate ***17g***. Beige oil, 153 mg, 34%, ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.22 (s, 9H, CH_3 Boc), 3.27 (m, 4H, $CH_2\beta$ tryptophan), 4.11 (m, 3H, CH_2CH Fmoc), 4.79 (m, 2H, CHα tryptophan), 5.26 (s, 2H, CH_2 benzyl), 6.64 (d, 2H, H_2H_6 benzyl), 6.83 (m, 2H, H_5 tryptophan), 6.98–7.15 (m, 9H, H_2 H_4 H_6 tryptophan and H_3 H_4 H_5 benzyl), 7.28 (m, 4H, H_2H_7 Fmoc and H_7 tryptophan), 7.40 (dd, 2H, 7 and 11 Hz, H_3H_6 Fmoc), 7.59 (m, 3H, H_1 H_8 Fmoc and NH Fmoc), 7.86 (d, 2H, 7 Hz, H_4 H_5 Fmoc), 8.20 (d, 1H, 8 Hz, NH Boc), 10.76 (s, 2H, NH indole). HRMS (ESI) calcd for $C_{49}H_{48}N_7O_4$, 798.3768; found 798.3775.

3.4.19. tert-Butyl (S)-1-(5-((S)-1-Cbz-amino-2-(1H-indol-3-yl)ethyl)-4-(4-chlorobenzyl)-4H-1,2,4-triazol-3-yl)-2-(1H-indol-3-yl)ethylcarbamate ***17h***. Beige oil, 179 mg, 29%, ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.24 (s, 9H, CH_3 Boc), 3.28 (m, 4H, $CH_2\beta$ tryptophan), 4.77 (m, 2H, CHα tryptophan), 4.82 (m, 1H, CH_2 Z), 4.89 (m, 1H, CH_2 Z), 5.26 (m, 2H, CH_2 4-chlorobenzyl), 6.56 (d, 2H, 8 Hz, H_2H_6 4-chlorobenzyl), 6.86 (m, 2H, H_5 tryptophan), 7.02–7.10 (m, 6H, H_2 H_4 H_6 tryptophan), 7.16 (d, 1H, 8 Hz, H_4 Z), 7.19 (d, 2H, 6 Hz, H_3 H_5 4-chlorobenzyl), 7.30–7.35 (m, 5H, H_7 tryptophan and H_2 H_3 H_5 H_6 Z), 7.61 (d, 1H, 9 Hz, NH Z), 8.11 (d, 1H, 8 Hz, NH Boc), 10.80 (s, 2H, NH indole). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 28.5 (CH_3 Boc), 29.2 ($CH_2\beta$ tryptophan), 45.4 (CH_2 4-chlorobenzyl), 46.9

and 47.3 (CHα tryptophan), 66.0 (CH_2 Z), 78.8 (C quat. Boc), 110.1 and 110.3 (C_3 tryptophan), 111.7 and 111.8 (C_7 tryptophan), 118.3 and 118.4 (C_4 tryptophan), 188.8 (C_5 tryptophan), 121.3 and 121.3 (C_6 tryptophan), 124.5 and 124.7 (C_2 tryptophan), 127.3 (C_4 Z), 127.5 and 127.6 (C_9 tryptophan), 128.0 (C_2 C_6 4-chlorobenzyl), 128.2 (C_3 C_5 4-chlorobenzyl), 128.8 ($C_2C_3C_5$ C_6 Z), 132.4 (C_4 4-chlorobenzyl), 136.4 (C_8 tryptophan and C_1 Z), 137.1 (C_1 4-chlorobenzyl), 155.6 (CO Z), 155.8 and 156.0 (C_3 C_5 triazole), 156.2 (CO Boc). HRMS (ESI) calcd for $C_{42}H_{43}ClN_7O_4$, 744.3065; found 744.3074.

3.4.20. tert-Butyl (S)-1-(5-((S)-1-Cbz-amino-2-(phenyl)ethyl)-4-(4-methoxybenzyl)-4H-1,2,4-triazol-3-yl)-1-(5-Cbz-amino)pentylcarbamate ***17i***. Colorless oil, 390 mg, 79%, ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.14–1.37 (m, 13H, CH_3 Boc and CH_2 γ δ lysine), 1.76 (m, 2H, CH_2β lysine), 2.90 (dd, 1H, 7 and 14 Hz, CH_2 ε lysine), 2.97–3.18 (m, 2H, CH_2 β phenylalanine), 3.71 (s, 3H, OMe), 4.64 (m, 1H, CHα lysine), 4.78 (d, 1H, 13 Hz, CH_2 Z), 4.89 (m, 2H, CH_2 Z and CHα phenylalanine), 5.00 (s, 2H, CH_2 4-methoxybenzyl), 5.10 (d, 1H, 16 Hz, CH_2 Z), 5.24 (br d, 1H, 18 Hz, CH_2 Z), 6.84 (d, 2H, 8 Hz, H_3H_5 4-methoxybenzyl), 7.00 (m, 3H, H_2H_6 4-methoxybenzyl), 7.10–7.47 (m, 16 H, $C_2C_3C_5C_6$ phenylalanine and $C_2C_3C_4C_5C_6$ Z and NH Boc and NH lysine), 8.08 (d, 1H, 10Hz, NH Z phenylalanine). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 22.7 (CH_2 γ lysine), 27.9 (CH_3 Boc), 28.8 (CH_2 δ lysine), 32.0 (CH_2 β lysine), 38.4 (CH_2β phenylalanine and CH_2 ε lysine), 45.5 (CH_2 4-methoxybenzyl), 47.4 (CHα phenylalanine), 55.1 (CHα lysine and OMe), 65.1 and 65.4 (CH_2 Z), 78.2 (C quat. Boc), 114.0 (C_3C_5 4-methoxybenzyl), 127.65–129.2 (CH Ar. phenylalanine and Z and C_2C_6 4-methoxybenzyl), 136.7 and 137.3 (C_1 phenylalanine and Z), 155.4 and 155.7 and 156.0 (CO Z and CO Boc and C_4 4-methoxybenzyl), 158.7 (C_3 and C_5 triazole). HRMS (ESI) calcd for $C_{44}H_{53}ClN_6O_7$, 777.3976; found 777.3981.

3.4.21. tert-Butyl (S)-1-(5-((S)-(1-Cbz-amino)-(2-((benzyloxy)carbonyl)ethyl))-4-benzyl-4H-1,2,4-triazol-3-yl)pentylcarbamate ***17j***. Colorless oil, 1.0 g, 76% ^{1}H NMR (400 MHz, DMSO-d_6, 303 K): δ (ppm) 0.74 (t, 3H, CH_3 alkyl), 1.10 (m, 4H, CH_2 γ δ norleucine), 1.26 (s, 9H, CH_3 Boc), 1.74 (m, 2H, CH_2β norleucine), 2.94 (dd, 1H, 8 and 16 Hz, CH_2β aspartic acid), 3.13 (dd, 1H, 7 and 16 Hz, CH2β aspartic acid), 4.55 (m, 1H, CHα norleucine), 4.78 (d, 1H, 11 Hz, CH_2 benzyl), 4.78 (d, 1H, 11 Hz, CH_2 benzyl), 4.89 (d, 1H, 11 Hz, CH_2 benzyl), 5.03 (s, 2H, CH_2 benzyl), 5.11 (m, 1H, CHα aspartic acid), 5.20 (d, 1H, 18 Hz, CH_2 benzyl), 5.39 (d, 1H, 17Hz, CH_2 benzyl), 6.98–7.39 (m, 16 H, CH aromatics and NH Boc), 8.01 (d, 1H, 9 Hz, NH Z). ^{13}C NMR (100 MHz, DMSO-d_6, 303 K): δ (ppm) 13.7 (CH_3 norleucine), 21.4 (CH_2 δ norleucine), 27.5 (CH_2γ norleucine), 28.0 (CH_3 Boc), 32.3 (CH_2β norleucine), 37.3 (CH_2β aspartic acid), 42.8 and 45.0 (CHα norleucine and CHα aspartic acid), 45.7 (CH_2 benzyl), 65.5 (CH_2 Z), 65.6 (CH_2 benzyl), 78.0 (C quat. Boc), 125.0–128.3 (CH aromatics), 135.8 and 135.9 and 136.6 (C_1 aromatics), 153.8 (CO Boc), 155.2 and 155.3 (C_3 and C_5 triazole), 156.3 (CO Z), 169.6 (CO Bzl). HRMS (ESI) calcd for $C_{37}H_{46}N_5O_6$, 656.3448; found 656.3458.

3.4.22. tert-Butyl (S)-1-(5-((R)-(1-Cbz-amino)-(2-((benzyloxy)carbonyl)ethyl))-4-benzyl-4H-1,2,4-triazol-3-yl)pentylcarbamate ***17k***. Colorless oil, 0.84 g, 62% ^{1}H NMR (400 MHz, DMSO-d_6, 303 K): δ (ppm) 0.71 (t, 3H, 7 Hz, CH_3 norleucine), 1.01–1.11 (m, 4H, CH_2γδ norleucine), 1.31 (s, 9H, CH_3 Boc), 1.69 (m, 2H, CH_2β norleucine), 3.00 (dd, 1H, 7 and 17 Hz, CH_2 β aspartic acid), 3.25 (dd, 1H, 9 and 16 Hz, CH_2β aspartic acid), 4.52 (m, 1H, CHα norleucine), 4.91 (d, 1H, 13 Hz, CH_2 benzyl), 4.97 (d, 1H, 13 Hz, CH_2 benzyl), 5.02 (d, 1H, 13 Hz, CH_2 benzyl), 5.09 (d, 1H, 13 Hz, 13 Hz, CH_2 benzyl), 5.16 (m, 1H, CHα aspartic acid), 5.26 (d, 1H, 17 Hz, CH_2 benzyl), 5.32 (d, 1H, 17 Hz, CH_2 benzyl), 7.00 (m, 2H, NH Boc and H_4 benzyl[4]), 7.27–7.35 (m, 13H, CH aromatics benzyl), 7.41 (d, 1H, 9 Hz, NH Z). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 14.2 (CH_3 norleucine), 21.9 (CH_2 δ norleucine), 28.0 (CH_2 γ norleucine), 28.6 (CH_3 Boc), 32.8 (CH_2 β norleucine), 39.4 (CH_2 β aspartic acid), 43.2 and 45.7 (CHα norleucine and CHα aspartic acid), 46.0 (O–*CH_2*–benzyl), 66.0 (CH_2 Z), 66.2 (N–*CH_2*–benzyl), 78.7 (C quat. Boc), 126.5 and 128.0 and 128.3 and 128.8 and 129.1 (CH aromatics), 136.4 and 137.2 (C_1 benzyl), 154.2 (CO Boc), 155.8 and 156.0 (C_3 and C_5 triazole), 156.7 (CO Z), 170.2 (CO benzyl). HRMS (ESI) calcd for $C_{37}H_{46}N_5O_6$, 656.3448; found 656.3458.

3.4.23. tert-Butyl (S)-1-(5-((S)-(1-Fmoc-amino)-(2-((tert-butyloxy)carbonyl)ethyl))-4-phenethyl-4H-1,2,4-triazol-3-yl)pentylcarbamate ***17l***. White powder, 0.61 g, 70% ^{1}H NMR (400 MHz, DMSO-d_6, 303 K): δ (ppm) 1H NMR, DMSO-d_6, 400 MHz: 0.85 (t, 3H, 7 Hz, CH_3 norleucine), 1.27 (m, 4H, CH_2δγ norleucine), 1.31 (s, 9H, CH_3 Boc), 1.36 (s, 9H, CH_3 *tert*-butyl), 1.66 (m, 1H, CH_2β norleucine), 1.83 (m, 1H, CH_2β norleucine), 2.67–3.06 (m, 4H, CH_2β aspartic acid and CH_2 β phenethyl), 4.14 (m, 3H, $CHCH_2$ Fmoc), 4.29 (m, 2H, CH_2α phenethyl), 4.58 (m, 1H, CHα norleucine), 5.10 (m, 1H, CHα aspartic acid), 7.19–7.45 (m, 10H, CH aromtics phenethyl and NH Boc and H_2H_7 and H_3H_6 Fmoc), 7.64 and 7.67 (d, 2H, 7 Hz, H_1H_8 Fmoc), 7.86 (m, 3H, H_4H_5 Fmoc and NH norleucine), 8.19 (d, 1H, 9 Hz, NH Fmoc). HRMS (ESI) calcd for $C_{42}H_{54}N_5O_6$, 724.4074; found 724.4075.

3.4.24. tert-Butyl (S)-1-(5-((S)-(1-Fmoc-amino)-(3-((tert-butyloxy)carbonyl)propyl))-4-benzyl-4H-1,2,4-triazol-3-yl)pentylcarbamate ***17m***. White powder, 0.67 g, 77% ^{1}H NMR (400 MHz, DMSO-d_6, 303 K): δ (ppm) 0.72 (t, 3H, 7 Hz, CH_3 norleucine), 1.06 (m, 4H, CH_2 γ δ norleucine), 1.26 (s, 9H, CH_3 *tert*-butyl or Boc), 1.34 (s, 9H, CH_3 *tert*-butyl or Boc), 1.73 (m, 2H, CH_2β norleucine), 2.06 (m, 2H, CH_2γ glutamic acid), 2.16 (m, 2H, CH_2β glutamic acid), 4.03 (m, 2H, CH_2 Fmoc), 4.17 (dd, 1H, 7 and 9 Hz, CH Fmoc), 4.53 (m, 1H, CHα norleucine), 4.72 (m, 1H, CHα glutamic acid), 5.18 (d, 1H, 17 Hz, CH_2 benzyl), 5.36 (d, 1H, 17 Hz, CH_2 benzyl), 7.00 (d, 2H, H_3H_5 benzyl), 7.20 (m, 3H, $H_2H_4H_6$ benzyl), 7.30 (m, 2H, H_2H_7 Fmoc), 7.66 (t, 2H, 8 Hz, H_1H_8 Fmoc), 7.88 (d, 2H, 8 Hz, H_4H_5 Fmoc), 8.03 (d, 1H, 9 Hz, NH Fmoc). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 13.8 (CH_3 norleucine), 21.5 (CH_2δ norleucine), 27.6 (CH_2γ norleucine), 27.7 (CH_3 Boc or CH_3 *tert*-butyl), 28.0 (CH_3 Boc and CH_3 *tert*-butyl), 28.2 (CH_2δ glutamic acid), 31.3 (CH_2β glutamic acid), 32.3 (CH_2β norleucine), 45.0 (CHα norleucine and CHα glutamic acid), 45.7 (CH_2 benzyl), 46.5 (CH Fmoc), 65.72 (CH_2 Fmoc), 78.1 and 78.7 (C quat. Boc and *tert*-butyl), 120.1 (C_1C_8 Fmoc and C_4C_5 Fmoc), 126.1 (C_2C_7 Fmoc), 127.0 (C_3C_6 Fmoc and C_4 benzyl), 127.6 (C_3C_5 benzyl), 128.4 (C_2C_6 benzyl), 136.1 (C_1 benzyl), 140.7 ($C_{4a/b}$ Fmoc), 143.6 and 143.7 ($C_{8a/b}$ Fmoc), 154.7 and 155.7 (C_3C_5 triazole), 155.2 and 155.9 (CO Boc and CO Fmoc), 171.4 (CO ester). HRMS (ESI) calcd for $C_{42}H_{54}N_5O_6$, 724.4074; found 724.4064.

3.4.25. tert-Butyl (S)-1-(5-((S)-(1-Cbz-amino)-(2-((benzyloxy)carbonyl)ethyl))-4-pentyl-4H-1,2,4-triazol-3-yl)-2-(1H-indol-3-yl)ethylcarbamate ***17n***. White powder, 0.61 g, 33% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 0.75 (br s, 3H, CH_3 alkyl), 1.08 (m, 4H, CH_2 γ δ alkyl), 1.28 (s, 9H, CH_3 Boc), 1.35 (m, 2H, CH_2 β alkyl), 3.01 (dd, 1H, 6 and 10 Hz, CH_2β aspartic acid), 3.26 (m, 2H, CHα alkyl), 3.39 (m, 1H, CH_2β aspartic acid), 3.81 (m, 2H, CH_2β tryptophan), 4.96–5.10 (m, 5H, CH_2 benzyl and CH_2 Z and CHα tryptophan), 5.20 (m, 1H, CHα aspartic acid), 6.97 (t, 1H, 7 Hz, H_5 tryptophan), 7.02 (m, 1H, H_6 tryptophan), 7.07 (s, 1H, H_2 tryptophan), 7.32 (m, 11H, CH aromatics benzyl and H_7 tryptophan), 7.53 (t, 2H, H_4 tryptophan and NH Z), 8.00 (d, 1H, NH Boc), 10.76 (s, 1H, NH indole). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 13.6 (CH_3 alkyl), 21.5 (CH_2δ alkyl), 28.0 (CH_3 Boc), 28.2 (CH_2 γ alkyl), 29.2 (CH_2β tryptophan), 29.6 (CH_2β alkyl), 37.7 (CH_2α alkyl), 38.7 (CH_2β aspartic acid), 42.6 (CHα aspartic acid), 46.2 (CHα tryptophan), 65.6 and 65.7 (CH_2 Z and CH_2 benzyl), 78.1 (C quat. Boc), 110.2 (C_3 tryptophan), 111.2 (C_7 tryptophan), 118.2 (C_4 tryptophan and C_5 tryptophan), 120.8 (C_6 tryptophan), 127.2 (C_9 tryptophan and C_4 benzyl and C_4 Z),

127.6–128.3 (C_2 C_3 C_5 C_6 Z and C_2 C_3 C_5 C_6 benzyl), 135.8 and 136.0 (C_1 benzyl and Z), 136.7 (C_8 tryptophan), 153.2 (CO Boc and CO Z), 155.1 and 155.4 (C_3 C_5 triazole), 169.7 (CO ester). HRMS (ESI) calcd for $C_{40}H_{49}N_6O_6$, 709.3714; found 709.3704.

3.4.26. tert-Butyl (S)-1-(5-((S)-(1-Fmoc-amino)-(2-((tert-butyloxy) carbonyl)ethyl))-4-benzyl-4H-1,2,4-triazol-3-yl)pentylcarbamate ***17o***. White powder, 0.54 g, 84% ^{1}H NMR (400 MHz, DMSO-d_6, 303 K): δ (ppm) ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 0.87 (t, 3H, 7 Hz, CH_3 norleucine), 1.21 (t, 3H, 7 Hz, CH_3 ester), 1.25–1.34 (m, 4H, $CH_2\gamma\delta$ norleucine), 1.37 (s, 9H, CH_3 Boc), 1.64 (s, 3H, CH_3 acetyl), 1.91 (m, 2H, $CH_2\beta$ norleucine), 3.19 (dd, 1H, 10 and 14 Hz, $CH_2\beta$ phenylalanine), 3.26 (dd, 1H, 5 and 14 Hz, $CH_2\beta$ phenylalanine), 4.11 (m, 2H, CH_2 ester), 4.58 (m, 1H, CHα norleucine), 4.87 (d, 1H, 18 Hz, CH_2 glycine), 4.94 (d, 1H, 18 Hz, CH_2 glycine), 5.16 (m, 1H, CHα phenylalanine), 7.18 (m,1H, H_4 phenylalanine), 7.27 (m, 4H, $H_2H_3H_5H_6$ phenylalanine), 7.40 (d, 1H, 9 Hz, NH Boc), 8.53 (d, 1H, 9 Hz, NH acetyl). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 14.4 (CH_3 norleucine and CH_3 ester), 22.2 ($CH_2\delta$ norleucine), 22.4 (CH_3 acetyl), 28.2 ($CH_2\gamma$ norleucine), 28.6 (CH_3 Boc), 32.4 ($CH_2\beta$ norleucine), 38.5 ($CH_2\beta$ phenylalanine), 44.5 (CH_2 glycine), 44.8 (CHα phenylalanine), 45.4 (CHα norleucine), 61.9 (CH_2 ester), 78.8 (C quat Boc), 126.8 (C_4 phenylalanine), 128.5 (C_2C_6 phenylalanine), 129.7 (C_3C_5 phenylalanine), 138.4 (C_1 phenylalanine), 155.7 and 156.0 (C_3 and C_5 triazole and CO Boc), 167.9 (CO ester), 169.3 (CO acetyl). HRMS (ESI) calcd for $C_{26}H_{40}N_5O_5$, 502.3029; found 502.3034.

3.4.27. tert-Butyl (S)-1-(4-((ethoxycarbonyl)methyl)-5-((S)-1-acetamido-2-phenylethyl)-4H-1,2,4-triazol-3-yl)pentylcarbamate ***17p***. White powder, 0.58 g, 77% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 0.81 (t, 3H, 13 Hz, CH_3 norleucine), 1.14 (t, 3H, 7 Hz, CH_3 ester), 1.23 (m, 4H, CH_2 γ δ norleucine), 1.32 (s, 9H, CH_3 Boc), 1.62 (s, 3H, CH_3 acetyl), 1.81 (m, 2H, CH_2 β norleucine), 3.17 (m, 2H, CH_2 β phenylalanine), 4.06 (q, 2H, 8 Hz, CH_2 ester), 4.56 (dd, 8 and 15 Hz, CHα norleucine), 4.84 (d, 1H, 19 Hz, CH_2 glycine), 4.96 (d, 1H, 1H, 18 Hz, CH_2 glycine), 5.08 (m, 1H, CHα phenylalanine), 7.11–7.29 (m, 8H, NH Boc and CH aromatics), 8.47 (d, 1H, 9Hz, NH acetyl). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 14.2 (CH_3 norleucine and CH_3 ester), 22.1 (CH_2 γ norleucine), 22.4 (CH_3 acetyl), 28.0 (CH_2 δ norleucine), 28.5 (CH_3 Boc), 32.6 (CH_2 β norleucine), 38.6 ($CH_2\beta$ phenylalanine), 44.4 (CH_2 glycine), 44.8 (CHα norleucine), 45.7 (CHα phenylalanine), 61.8 (CH_2 ester), 78.6 (C quat. Boc), 126.7 (C_4 phenylalanine), 128.4 (C_2 and C_6 phenylalanine), 129.6 (C_3 and C_5 phenylalanine), 138.2 (C_1 phenylalanine), 155.6 (C_3 and C_5 triazole and CO Boc), 167.6 (CO ester), 169.3 (CO acetyl). MS (ES), HRMS (ESI) calcd for $C_{26}H_{40}N_5O_5$, 502.3029; found: 502.3029.

3.4.28. tert-Butyl (S)-1-(4-((ethoxycarbonyl)methyl)-5-((R)-1-acetamido-2-phenylethyl)-4H-1,2,4-triazol-3-yl)pentylcarbamate ***17q***. Colorless solid, 0.80 g, 60% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 0.72 (t, 3H, 7 Hz, CH_3 norleucine), 1.06 (m, 4H, CH_2 $\delta\gamma$ norleucine), 1.27 (s, 9H, CH_3 Boc or CH_3 *t*-Bu), 1.29 (s, 9H, CH_3 Boc or CH_3 *t*-Bu), 1.71 (m, 2H, $CH_2\beta$ norleucine), 2.78 (m, 1H, 7 and 16 Hz, $CH_2\beta$ aspartic acid), 2.87 (m, 1H, 8 and 15 Hz, $CH_2\beta$ aspartic acid), 4.00 (m, 2H, CH_2 Fmoc), 4.14 (dd, 1H, 6 and 9 Hz, CH Fmoc), 4.54 (m, 1H, CHα norleucine), 5.07 (m, 1H, CHα aspartic acid), 5.23 (d, 1H, 17 Hz, CH_2 benzyl), 5.41 (d, 1H, 17 Hz, CH_2 benzyl), 7.01 (d, 2H, 7 Hz, H_3H_5 benzyl), 7.21 (m, 3H, $H_2H_4H_6$ benzyl), 7.30 (m, 2H, H_2H_7 Fmoc), 7.41 (td, 3H, 1 and 8 Hz, H_3 H_6 Fmoc and NH Boc), 7.61 (m, 2H, H_1H_8 Fmoc), 7.87 (d, 2H, 8 Hz, H_4H_5 Fmoc), 8.08 (d, 1H, 9 Hz, NH Fmoc). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 13.7 (CH_3 norleucine), 21.4 ($CH_2\delta$ norleucine), 27.5 (CH_3 Boc and CH_2 γ norleucine), 28.0 (CH_3 *tert*-butyl), 32.1 ($CH_2\beta$ norleucine), 42.7 ($CH_2\beta$ aspartic acid), 45.0 (CHα norleucine), 45.9 (CHα aspartic acid), 46.4 (CH Fmoc and CH_2 benzyl), 65.8 (CH_2 Fmoc), 78.1 (C quat Boc), 80.1 (C quat *tert*-butyl), 120.0 (C_4C_5 Fmoc), 125.2 (C_1C_8 Fmoc), 126.1 (C_2C_7 Fmoc), 127.0 (C_2C_6 benzyl), 127.3 (C_4 benzyl), 127.6 (C_3C_5 benzyl), 128.4 (C_3C_6 Fmoc), 135.7 (C_1 benzyl), 140.6 (C_4 a/b Fmoc), 143.6 (C_8 a/b Fmoc), 154.0 and 155.3 (C_3 and C_5 triazole and CO Boc), 156.3 (CO Fmoc), 168.6 (CO aspartic acid). MS (ES), *m*/*z*: 710.2 $[M+H]^+$.

3.4.29. tert-Butyl (S)-1-(4-((S)-1-(methoxycarbonyl)ethyl)-5-((S)-1-Boc-amino-2-phenylethyl)-4H-1,2,4-triazol-3-yl)-2-phenylethylcarbamate ***20***. White powder, 0.09 g, 28% ^{1}H NMR (300 MHz, DMSO-d_6, 303 K): δ (ppm) 1.22 (s, 18H, CH_3 Boc), 1.62 (d, 3H, 7Hz, $CH_3\beta$ alanine), 3.20 (d, 4H, 7Hz, $CH_2\beta$ phenylalanine), 3.65 (s, 3H, O–Me alanine), 4.87 (m, 2H, CHα phenylalanine), 5.61 (m, 1H, CHα alanine), 7.18–7.27 (m, 10H, CH Ar.), 7.52 (d, 2H, 9 Hz, NH Boc). ^{13}C NMR (75 MHz, DMSO-d_6, 303 K): δ (ppm) 16.7 ($CH_3\beta$ alanine), 27.9 (CH_3 Boc), 38.7 ($CH_2\beta$ phenylalanine), 47.1 (CHα alanine), 51.9 (O–Me alanine), 52.9 (CHα phenylalanine), 78.2 (C quaternaire Boc), 126.2 (C_4 phenylalanine), 128.0 (C_2 C_6 phenylalanine), 129.3 (C_3 C_5 phenylalanine), 137.8 (C_1 phenylalanine), 154.9 (C_3 and C_5 triazole), 155.0 (CO Boc), 170.0 (CO ester). HRMS (ESI) calcd for $C_{32}H_{44}N_5O_6$, 594.3292; found 594.3282.

Acknowledgements

The authors like to thank Dr. O. Bruguier from UMR Géosciences (University Montpellier 2, France) for ICPMS analysis and Dr. P. Chevallet for his invaluable help in nomenclature determination.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.011.

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