DOI: 10.1002/ejoc.201100611

Synthesis of Various Chiral 1,2,4-Triazole-Containing α-Amino Acids from Aspartic or Glutamic Acids

Anne-Laure Blayo,[a] Frédéric Brunel,[a] Jean Martinez,[a] and Jean-Alain Fehrentz*[a]

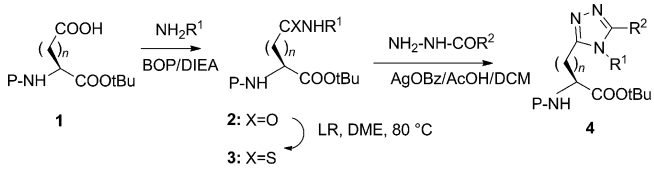
Keywords: Amino acids / Heterocycles / Heterocycles

Starting from N- and C-protected aspartic or glutamic acids, new unnatural α-amino acids containing 3,4,5-trisubstituted 1,2,4-triazole heterocycles on their side chains have been synthesized. Two points of diversity could easily be achieved on the heterocyclic moiety, which could easily be incorporated in peptide sequences to modify or improve their pharmacokinetic properties.

Introduction

In our effort to develop original chiral nonproteinogenic α-amino acids that could be incorporated into biologically relevant peptides, we focused our work on the synthesis of heterocycle-containing α-amino acids. The choice of the heterocycle is crucial in such an approach. Indeed, it is supposed to improve pharmacokinetic properties of the modified peptides and can be used as a scaffold bearing various substituents. These substituents could interact with the biological target, providing better specificity. These unnatural amino acids also prevent enzymatic degradation of the peptides.

One interesting heterocyclic moiety is the well-known 1,2,4-triazole. The first amino acid bearing a 1,2,4-triazole moiety on its side chain was 1,2,4-triazole-3-alanine, which was used to replace a histidine residue.[1] This heterocycle displays a wide range of biological activities and can be used as an amide bioisostere for the design of receptor ligands with enhanced pharmacokinetic properties[2,3]or to mimic the *cis* configuration of the amide function observed in several peptides.[4–6] The chemistry we previously described for the preparation of 3,4,5-trisubstituted 1,2,4-triazoles from a modified procedure developed by Hitotsuyanagi et al.[4] is robust, nontoxic and allows the introduction of various substituents on this scaffold. Our synthetic strategy for the formation of a trisubstituted 1,2,4-triazole started with the formation of an amide bond, followed by a thionation with the Lawesson's reagent (LR)[7] and finally reaction of the resulting thioamide with a hydrazide to form the heterocycle.[8,9] We used this synthetic scheme mainly from N-protected α-amino acids to design potent ligands of the ghrelin receptor with a large variety of substituents.[10–12] Here, we applied the developed strategy to the synthesis of unnatural amino acids bearing a 3,4-substituted 1,2,4-triazole on their side chain. A series of unnatural amino acid derivatives were prepared starting from N- and C-protected aspartic or glutamic acids. To show the stability of the N-protecting groups under the experimental conditions that we used, we started from Fmoc-Asp-O*t*Bu and Z-Glu-O*t*Bu (Scheme 1). The bulky *tert*-butyl ester group was chosen to avoid a side reaction during the dehydration–cyclization step for the formation of acylamidrazones into triazoles. Two points of diversity could easily be introduced as shown in Scheme 1.



Scheme 1. Synthesis of unnatural amino acids bearing a 3,4-substituted 1,2,4-triazole in their side chains.

Results and Discussion

When starting from Fmoc-Asp-O*t*Bu (**1**) (n = 1, P = Fmoc), different amines were introduced by a coupling step by using BOP: ethylamine, isopropylamine, methyl 4-aminobutanoate and (4-bromobenzyl)amine. After thionation of the corresponding amides **2**, four different hydrazides, acetyl hydrazide, benzoic hydrazide, phenylacetic hydrazide and ethyl 3-hydrazino-3-oxopropionate, were allowed to react with thioamides **3** to form triazoles **4**. The cyclization step was performed as already described[9] in the presence of silver benzoate as a thiophile reagent and in acetic acid

[a] Institut des Biomolécules Max Mousseron, CNRS UMR 5247, Université Montpellier I, Université Montpellier II, Faculté de Pharmacie,
15 avenue Charles Flahault, B. P. 14491, 34093 Montpellier Cedex 5, France
Fax: 33-4-67548654
E-mail: jean-alain.fehrentz@univ-montp1.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100611.

in dichloromethane. After purification, nine new nonproteinogenic amino acids were obtained in acceptable to good yields (Table 1, compounds **4a**–**i**).

Table 1. Various 1,2,4-triazole containing α-amino acids.

4	P	*n*	R^1	R^2	$[\alpha]_D^{20}$[a]	Yield [%][b]
a	Fmoc	1	isopropyl	methyl	–6.8	42
b	Fmoc	1	isopropyl	benzyl	–22.7	52
c	Fmoc	1	isopropyl	ethyl acetate	–13.6	46
d	Fmoc	1	methyl butanoate	benzyl	–18.7	61
e	Fmoc	1	methyl butanoate	phenyl	–13.4	58
f	Fmoc	1	4-bromobenzyl	ethyl acetate	–14.7	77
g	Fmoc	1	4-bromobenzyl	methyl	–15.3	67
h	Fmoc	1	4-bromobenzyl	phenyl	–16.3	54
i	Fmoc	1	ethyl	benzyl	–8.5	65
j	Z	2	ethyl	methyl	–14.1	11
k	Z	2	ethyl	benzyl	–15.2	52
l	Z	2	ethyl	ethyl acetate	–12.2	55
m	Z	2	4-methoxybenzyl	methyl	–9.8	58
n	Z	2	4-methoxybenzyl	benzyl	–7.8	78
o	Z	2	4-methoxybenzyl	ethyl acetate	–6.3	56

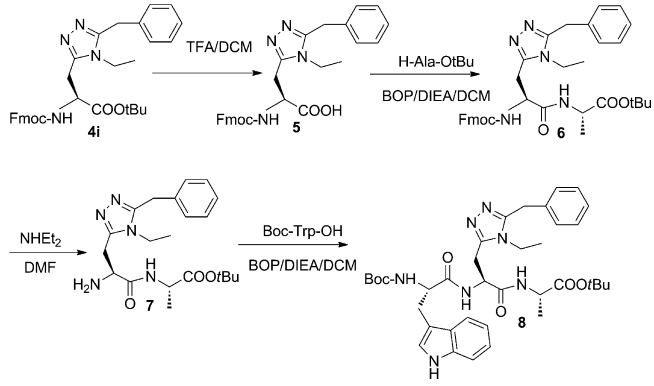
[a] (*c* 1, MeOH). [b] From **3**.

When starting from Z-Glu-O*t*Bu **1** (*n* = 2, P = Z), the side chain carboxylic acid was coupled with two amines, ethylamine and (4-methoxybenzyl)amine. Amides **2** were thionated with Lawesson's reagent, and the obtained thioamides **3** were treated with three hydrazides, acetylhydrazide, phenylacetic hydrazide and ethyl 3-hydrazino-3-oxopropionate, under the same experimental conditions to yield six original amino acids **4** bearing a 1,2,4-triazole moiety on their side chain (Table 1, compounds **4j**–**o**).

Stereochemical Aspect

Optical purity is an essential characteristic of amino acids. Synthesis from enantiopure aspartyl or glutamyl derivatives should lead to triazole compounds without any significant epimerization. We recently demonstrated that, when performed on the carboxylic acid of an α-amino acid, this three-step sequence (coupling, thionation and triazole formation) did not induce any epimerization.[9] There is therefore no reason to suspect that epimerization can occur when performed on the β position of an asymmetric carbon.

To show that these new 1,2,4-triazole-containing amino acids can easily be incorporated into a peptide sequence, we synthesized a tripeptide including an unnatural amino acid in the middle of the sequence (Scheme 2). Starting from compound **4i**, the *tert*-butyl ester was deprotected in acidic medium (TFA/DCM), and the corresponding carboxylic acid **5** was directly coupled to L-alanine *tert*-butyl ester with BOP[13] as coupling reagent. After classical workup used in peptide chemistry and purification by column chromatography on silica gel, dipeptide **6** was obtained in 81% yield. The N-terminal Fmoc protection was then removed by diethylamine in DMF, and after evaporation of the solvents, amine **7** was acylated with Boc-L-tryptophan in the presence of BOP. After coupling and classical washings, the crude was purified by preparative reversed-phase HPLC to give, after lyophilization, the tripeptide **8** as a white solid in 79% yield. This compound was characterized by ^{1}H and ^{13}C NMR spectroscopy and MS.



Scheme 2. Synthesis of a tripeptide containing compound **4i** in its sequence.

Conclusions

In summary, we have shown that it was possible, in a few steps, to generate nonproteinogenic amino acids from protected aspartic or glutamic acids, which incorporate different 3,4,5-trisubstituted 1,2,4-triazole heterocycles. These compounds represent an original addition to the list of available unnatural amino acids. Their preparation as Fmoc- or Z-protected derivatives may allow their use in peptide and peptidomimetic synthesis, as well as in solution- and solid-phase combinatorial syntheses. Although a limited number of different and representative substituents are presented here, a much larger diversity may be achieved.

Experimental Section

All final compounds were characterized by LC/MS, ^{1}H and ^{13}C NMR spectroscopy and HRMS, and their purity was found to be >98% by monitoring by HPLC at 214 nm. Analytical HPLC chromatographs were performed on a Beckman Gold apparatus composed of the 126 solvent module, the 168 detector and the 32 Karat software; runs were performed on a VWR Chromolith column (50 × 3.9 mm) at a flow rate of 5 mL/min from solution A (water, 0.1% TFA) to solution B (acetonitrile, 0.1% TFA) in a 3-min gradient.

Synthesis of Amides 2: In a solution of DCM, the amine (1.1 equiv.), amino acid (1.0 equiv.), DIEA (2.2 equiv.) and BOP (1.0 equiv.) were successively added. After stirring for 1 h at room temperature, the mixture was concentrated in vacuo and dissolved in AcOEt. The organic layer was successively washed with aqueous solutions of 1 M $KHSO_4$, saturated $NaHCO_3$ and brine. The organic layer was then dried with Na_2SO_4, filtered, and concentrated in vacuo to yield amide **2**, which was used without purification.

General Procedure for Thionation: To 1.0 equiv. of amide in DME (10 mmol/mL) was added Lawesson's reagent (0.5 equiv.). The reaction was heated to 85 °C for 2 h and then concentrated in vacuo. The residue was filtered through aluminium oxide standardized, eluted with DCM and then purified by chromatography on silica

gel with a mixture of AcOEt/hexane as eluent. Thioamide **3** was obtained as a white powder (yields between 60 and 90% for the two steps).

General Procedure for the Conversion of Thioamides to Trisubstituted 1,2,4-Triazoles: Thioamide **2** (1 equiv.) and hydrazide (1.2 equiv.) were diluted in the minimum volume of dichloromethane. Silver benzoate (2 equiv.) was then added immediately followed by acetic acid (3 equiv.). The reaction was monitored by RP-HPLC, and after completion (usually within 6 h), it was filtered through a pad of Celite. Flash chromatography on silica gel, eluted with AcOEt/hexane (5/5) to MeOH (5% in AcOEt), afforded the desired triazole derivative.

4a: HPLC: t_R = 1.89 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.31 (s, 9 H, CH$_3$ *t*Bu), 1.38 [d, *J* = 6.9 Hz, 6 H, CH(C*H*$_3$)$_2$], 2.40 (s, 3 H, C*H*$_3$-triazole), 3.07 (dd, *J* = 15.6, 7.9 Hz, 1 H, CH$_2$ β Asp), 3. 17 (dd, *J* = 15.6, 6.6 Hz, 1 H, CH$_2$ β Asp), 4.17–4.36 (m, 3 H, CH and CH$_2$ Fmoc), 4.36–4.51 [m, 2 H, CH α Asp and C*H*(CH$_3$)$_2$], 7.32 (t, *J* = 7.3 Hz, 2 H, H^2 and H^7 Fmoc), 7.41 (t, *J* = 7.3 Hz, 2 H, H^3 and H^6 Fmoc), 7.69 (d, *J* = 7.3 Hz, 2 H, H^1 and H^8 Fmoc), 7.78 (d, *J* = 8.3 Hz, 1 H, NH Fmoc), 7.89 (t, *J* = 7.3 Hz, 2 H, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 12.3 (*C*H$_3$-triazole), 21.1 and 21.2 [CH(*C*H$_3$)$_2$], 27.3 (CH$_2$ β Asp), 27.5 (CH$_3$ *t*Bu), 46.6 (CH Fmoc), 46.7 [*C*H(CH$_3$)$_2$], 52.8 (CH α Asp), 65.7 (CH$_2$ Fmoc), 80.9 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 125.2 (C^1 and C^8 Fmoc), 127.1 (C^2 and C^7 Fmoc), 127.7 (C^3 and C^6 Fmoc), 140.8 (C^{11} and C^{12} Fmoc), 143.8 (C^{10} and C^{13} Fmoc), 150.2 and 150.6 (Cq triazole), 155.9 (CO Fmoc), 170.1 (*C*O$_2$*t*Bu) ppm. HRMS (ESI+): calculated for $C_{28}H_{35}N_4O_4$, 491.2658; found 491.2638.

4b: HPLC: t_R = 2.12 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.29–1.37 [m, 15 H, CH$_3$ *t*Bu and CH(C*H*$_3$)$_2$], 3.28 (dd, *J* = 16.1, 8.0 Hz, 1 H, CH$_2$ β Asp), 3. 41 (dd, *J* = 16.1, 6.2 Hz, 1 H, CH$_2$ β Asp), 4.18–4.25 (m, 1 H, CH Fmoc), 4.28–4.40 (m, 2 H, CH$_2$ Fmoc), 4.43 (s, 2 H, triazole-C*H*$_2$-phenyl), 4.49–4.59 (m, 1 H, CH α Asp), 4.70 [quintuplet, *J* = 7.0 Hz, 1 H, C*H*(CH$_3$)$_2$], 7.22–7.37 (m, 7 H, H^2 and H^7 Fmoc, H^2, H^3, H^4, H^5 and H^6 phenyl), 7.42 (t, *J* = 7.3 Hz, 2 H, H^3 and H^6 Fmoc), 7.68 (d, *J* = 7.3 Hz, 2 H, H^1 and H^8 Fmoc), 7.89 (d, *J* = 7.3 Hz, 3 H, NH Fmoc, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 20.7 [CH(*C*H$_3$)$_2$], 27.5 (CH$_2$ β Asp and CH$_3$ *t*Bu), 30.3 (triazole-*C*H$_2$-phenyl), 46.6 (CH Fmoc), 49.3 [*C*H(CH$_3$)$_2$], 52.1 (CH α Asp), 65.8 (CH$_2$ Fmoc), 81.5 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 125.2 (C^1 and C^8 Fmoc), 127.1 (C^2 and C^7 Fmoc), 127.4 (C^4 phenyl), 127.7 (C^3 and C^6 Fmoc), 128.7 and 128.8 (C^2, C^3, C^5 and C^6 phenyl), 134.6 (C^1 phenyl), 140.8 (C^{11} and C^{12} Fmoc), 143.8 (C^{10} and C^{13} Fmoc), 152.1 and 153.3 (Cq triazole), 155.9 (CO Fmoc), 169.3 (*C*O$_2$*t*Bu) ppm. HRMS (ESI+): calculated for $C_{34}H_{39}N_4O_4$, 567.2971; found 567.2971.

4c: HPLC: t_R = 2.10 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.19 (t, *J* = 7.1 Hz, 3 H, O-CH$_2$-C*H*$_3$), 1.33 (s, 9 H, CH$_3$ *t*Bu), 1.42 [d, *J* = 6.8 Hz, 6 H, CH(C*H*$_3$)$_2$], 3.24 (dd, *J* = 15.8, 7.7 Hz, 1 H, CH$_2$ β Asp), 3. 36 (dd, *J* = 15.8, 6.4 Hz, 1 H, CH$_2$ β Asp), 4.08–4.64 [m, 9 H, triazole-C*H*$_2$-CO$_2$Et, O-C*H*$_2$-CH$_3$, CH and CH$_2$ Fmoc, CH α Asp, C*H*(CH$_3$)$_2$], 7.21 (t, *J* = 7.3 Hz, 2 H, H^2 and H^7 Fmoc), 7.41 (t, *J* = 7.3 Hz, 2 H, H^3 and H^6 Fmoc), 7.69 (d, *J* = 7.3 Hz, 2 H, H^1 and H^8 Fmoc), 7.83 (d, *J* = 8.3 Hz, 1 H, NH Fmoc), 7.89 (t, *J* = 7.3 Hz, 2 H, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 14.0 (O-CH$_2$-*C*H$_3$), 20.9 and 21.0 [CH(*C*H$_3$)$_2$], 27.5 (CH$_3$ *t*Bu), 27.6 (CH$_2$ β Asp), 31.6 (triazole-*C*H$_2$-CO$_2$Et), 46.6 (CH Fmoc), 48.7 [*C*H(CH$_3$)$_2$], 52.3 (CH α Asp), 61.4 (O-*C*H$_2$-CH$_3$), 65.8 (CH$_2$ Fmoc), 81.3 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 125.2 (C^1 and C^8 Fmoc), 127.1 (C^2 and C^7 Fmoc), 127.7 (C^3 and C^6 Fmoc), 140.8 (C^{11} and C^{12} Fmoc), 143.7 and 143.8 (C^{10} and C^{13} Fmoc), 148.5 and 151.7 (Cq triazole), 155.9 (CO Fmoc), 167.8 (*C*O$_2$Et), 169.6 (*C*O$_2$*t*Bu) ppm. HRMS (ESI+): calculated for $C_{31}H_{39}N_4O_6$, 563.2870; found 563.2867.

4d: HPLC: t_R = 2.13 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.33 (s, 9 H, CH$_3$ *t*Bu), 1.72 (quintuplet, *J* = 7.1 Hz, 2 H, N-CH$_2$-C*H*$_2$-CH$_2$-CO$_2$Me), 2.39 (t, *J* = 7.1 Hz, 2 H, N-CH$_2$-CH$_2$-C*H*$_2$-CO$_2$Me), 3.17 (dd, *J* = 16.0, 8.6 Hz, 1 H, CH$_2$ β Asp), 3. 31 (dd, *J* = 16.0, 5.7 Hz, 1 H, CH$_2$ β Asp), 3.58 (s, 3 H, CO$_2$*Me*), 3.97–4.08 (m, 2 H, N-C*H*$_2$-CH$_2$-CH$_2$-CO$_2$Me), 4.17–4.38 (m, 3 H, triazole-C*H*$_2$-phenyl, CH and CH$_2$ Fmoc), 4.47–4.58 (m, 1 H, CH α Asp), 7.22–7.36 (m, 7 H, H^2 and H^7 Fmoc, H^2, H^3, H^4, H^5 and H^6 phenyl), 7.42 (t, *J* = 7.3 Hz, 2 H, H^3 and H^6 Fmoc), 7.67 (d, *J* = 7.3 Hz, 2 H, H^1 and H^8 Fmoc), 7.84–7.92 (m, 3 H, NH Fmoc, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 24.3 (N-CH$_2$-*C*H$_2$-CH$_2$-CO$_2$Me), 26.2 (CH$_2$ β Asp), 27.5 (CH$_3$ *t*Bu), 29.5 (N-CH$_2$-CH$_2$-*C*H$_2$-CO$_2$Me), 29.9 (triazole-*C*H$_2$-phenyl), 42.8 (N-*C*H$_2$-CH$_2$-CH$_2$-CO$_2$Me), 46.6 (CH Fmoc), 51.5 (CO$_2$*Me*), 52.1 (CH α Asp), 65.8 (CH$_2$ Fmoc), 81.5 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 125.2 (C^1 and C^8 Fmoc), 127.1 (C^2 and C^7 Fmoc), 127.3 (C^4 phenyl), 127.7 (C^3 and C^6 Fmoc), 128.8 (C^2, C^3, C^5 and C^6 phenyl), 134.6 (C^1 phenyl), 140.8 (C^{11} and C^{12} Fmoc), 143.8 (C^{10} and C^{13} Fmoc), 152.5 and 153.6 (Cq triazole), 155.9 (CO Fmoc), 169.6 (*C*O$_2$*t*Bu), 172.6 (*C*O$_2$Me) ppm. HRMS (ESI+): calculated for $C_{36}H_{41}N_4O_6$, 625.3026; found 625.3025.

4e: HPLC: t_R = 2.11 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.37 (s, 9 H, CH$_3$ *t*Bu), 1.77 (quintuplet, *J* = 6.9 Hz, 2 H, N-CH$_2$-C*H*$_2$-CH$_2$-CO$_2$Me), 2.27 (t, *J* = 6.9 Hz, 2 H, N-CH$_2$-CH$_2$-C*H*$_2$-CO$_2$Me), 3.23 (dd, *J* = 15.9, 8.3 Hz, 1 H, CH$_2$ β Asp), 3. 34 (dd, *J* = 15.9, 5.9 Hz, 1 H, CH$_2$ β Asp), 3.48 (s, 3 H, CO$_2$*Me*), 4.03–4.16 (m, 2 H, N-C*H*$_2$-CH$_2$-CH$_2$-CO$_2$Me), 4.20–4.26 (m, 1 H, CH Fmoc), 4.26–4.40 (m, 2 H, CH$_2$ Fmoc), 4.53–4.62 (m, 1 H, CH α Asp), 7.27–7.36 (m, 2 H, H^2 and H^7 Fmoc), 7.41 (t, *J* = 7.4 Hz, 2 H, H^3 and H^6 Fmoc), 7.55–7.67 (m, 5 H, H^2, H^3, H^4, H^5 and H^6 phenyl), 7.70 (d, *J* = 7.4 Hz, 2 H, H^1 and H^8 Fmoc), 7.84–7.92 (m, 3 H, NH Fmoc, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO, 303 K): δ = 24.5 (N-CH$_2$-*C*H$_2$-CH$_2$-CO$_2$Me), 26.6 (CH$_2$ β Asp), 27.6 (CH$_3$ *t*Bu), 29.8 (N-CH$_2$-CH$_2$-*C*H$_2$-CO$_2$Me), 43.0 (N-*C*H$_2$-CH$_2$-CH$_2$-CO$_2$Me), 46.6 (CH Fmoc), 51.4 (CO$_2$*Me*), 52.4 (CH α Asp), 65.8 (CH$_2$ Fmoc), 81.3 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 125.2 (C^1 and C^8 Fmoc), 125.7 (C^1 phenyl), 127.1 (C^2 and C^7 Fmoc), 127.7 (C^3 and C^6 Fmoc), 128.8 and 129.2 (C^2, C^3, C^5 and C^6 phenyl), 130.8 (C^4 phenyl), 140.8 (C^{11} and C^{12} Fmoc), 143.8 (C^{10} and C^{13} Fmoc), 152.5 and 153.4 (Cq triazole), 155.9 (CO Fmoc), 169.8 (*C*O$_2$*t*Bu), 172.4 (*C*O$_2$Me) ppm. HRMS (ESI+): calculated for $C_{35}H_{39}N_4O_6$, 611.2870; found 611.2871.

4f: HPLC: t_R = 2.18 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.09 (t, *J* = 7.1 Hz, 3 H, O-CH$_2$-C*H*$_3$), 1.31 (s, 9 H, CH$_3$ *t*Bu), 2.92 (dd, *J* = 15.8, 8.1 Hz, 1 H, CH$_2$ β Asp), 3.01 (dd, *J* = 15.8, 6.1 Hz, 1 H, CH$_2$ β Asp), 3.88–3.98 (m, 4 H, triazole-C*H*$_2$-CO$_2$Et and O-C*H*$_2$-CH$_3$), 4.17–4.31 (m, 3 H, CH and CH$_2$ Fmoc), 4.36–4.44 (m, 1 H, CH α Asp), 5.23 (s, 2 H, CH$_2$ *p*-bromobenzyl), 7.04 (d, *J* = 8.4 Hz, 2 H, H^2 and H^6 *p*-bromobenzyl), 7.31 (t, *J* = 7.2 Hz, 2 H, H^2 and H^7 Fmoc), 7.41 (t, *J* = 7.2 Hz, 2 H, H^3 and H^6 Fmoc), 7.53 (d, *J* = 8.4 Hz, 2 H, H^3 and H^5 *p*-bromobenzyl), 7.69 (dd, *J* = 7.2, 1.4 Hz, 2 H, H^1 and H^8 Fmoc), 7.77 (d, *J* = 8.3 Hz, 1 H, NH Fmoc), 7.89 (t, *J* = 7.2 Hz, 2 H, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 13.9 (O-CH$_2$-*C*H$_3$), 26.8 (CH$_2$ β Asp), 27.5 (CH$_3$ *t*Bu), 30.9 (triazole-*C*H$_2$-CO$_2$Et), 45.5 (CH$_2$ *p*-bromobenzyl), 46.6 (CH Fmoc), 52.5 (CH α Asp), 60.9 (O-*C*H$_2$-CH$_3$), 65.8 (CH$_2$ Fmoc), 81.1 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 120.9 (C^4 *p*-bromobenzyl), 125.2 (C^1 and C^8 Fmoc), 127.1

(C^2 and C^7 Fmoc), 127.7 (C^3 and C^6 Fmoc), 128.8 (C^2 and C^6 *p*-bromobenzyl), 131.6 (C^3 and C^5 *p*-bromobenzyl), 135.0 (C^1 *p*-bromobenzyl), 140.8 (C^{11} and C^{12} Fmoc), 143.7 and 143.8 (C^{10} and C^{13} Fmoc), 148.9 and 151.9 (Cq triazole), 155.8 (CO Fmoc), 168.0 (*C*O_2Et), 169.9 (*C*O_2*t*Bu) ppm. HRMS (ESI+): calculated for $C_{35}H_{38}BrN_4O_6$, 689.1975; found 689.1985.

4g: HPLC: t_R = 2.15 min. ^{1}H NMR (300 MHz, [D_6]DMSO, 303 K): δ = 1.31 (s, 9 H, CH_3 *t*Bu), 2.23 (s, 3 H, C*H*$_3$-triazole), 2.96 (dd, J = 15.7, 8.1 Hz, 1 H, CH_2 β Asp), 3. 06 (dd, J = 15.7, 6.1 Hz, 1 H, CH_2 β Asp), 4.15–4.32 (m, 3 H, CH and CH_2 Fmoc), 4.33–4.43 (m, 1 H, CH α Asp), 5.19 (s, 2 H, CH_2 *p*-bromobenzyl), 7.01 (d, J = 8.4 Hz, 2 H, H^2 and H^6 *p*-bromobenzyl), 7.31 (t, J = 7.3 Hz, 2 H, H^2 and H^7 Fmoc), 7.41 (t, J = 7.3 Hz, 2 H, H^3 and H^6 Fmoc), 7.54 (d, J = 8.4 Hz, 2 H, H^3 and H^5 *p*-bromobenzyl), 7.68 (d, J = 7.3 Hz, 2 H, H^1 and H^8 Fmoc), 7.75 (d, J = 8.3 Hz, 1 H, NH Fmoc), 7.89 (t, J = 7.3 Hz, 2 H, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 303 K): δ = 10.5 (*C*H_3-triazole), 26.6 (CH_2 β Asp), 27.5 (CH_3 *t*Bu), 45.1 (CH_2 *p*-bromobenzyl), 46.6 (CH Fmoc), 52.7 (CH α Asp), 65.7 (CH_2 Fmoc), 81.0 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 120.9 (C^4 *p*-bromobenzyl), 125.2 (C^1 and C^8 Fmoc), 127.1 (C^2 and C^7 Fmoc), 127.7 (C^3 and C^6 Fmoc), 128.6 (C^2 and C^6 *p*-bromobenzyl), 131.8 (C^3 and C^5 *p*-bromobenzyl), 135.4 (C^1 *p*-bromobenzyl), 140.8 (C^{11} and C^{12} Fmoc), 143.7 and 143.8 (C^{10} and C^{13} Fmoc), 151.2 and 151.3 (Cq triazole), 155.8 (CO Fmoc), 170.0 (*C*O_2*t*Bu) ppm. HRMS (ESI+): calculated for $C_{32}H_{34}BrN_4O_4$, 617.1763; found 617.1755.

4h: HPLC: t_R = 2.43 min. ^{1}H NMR (300 MHz, [D_6]DMSO, 303 K): δ = 1.34 (s, 9 H, CH_3 *t*Bu), 3.04 (dd, J = 15.7, 8.2 Hz, 1 H, CH_2 β Asp), 3. 15 (dd, J = 15.7, 5.9 Hz, 1 H, CH_2 β Asp), 4.16–4.33 (m, 3 H, CH and CH_2 Fmoc), 4.42–4.52 (m, 1 H, CH α Asp), 5.32 (s, 2 H, CH_2 *p*-bromobenzyl), 6.94 (d, J = 8.3 Hz, 2 H, H^2 and H^6 *p*-bromobenzyl), 7.24–7.34 (m, 2 H, H^2 and H^7 Fmoc), 7.41 (t, J = 7.4 Hz, 2 H, H^3 and H^6 Fmoc), 7.44–7.54 (m, 7 H, H^3 and H^5 *p*-bromobenzyl, H^2, H^3, H^4, H^5 and H^6 phenyl), 7.69 (d, J = 7.4 Hz, 2 H, H^1 and H^8 Fmoc), 7.84 (d, J = 8.3 Hz, 1 H, NH Fmoc), 7.89 (t, J = 7.3 Hz, 2 H, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 303 K): δ = 26.7 (CH_2 β Asp), 27.5 (CH_3 *t*Bu), 46.2 (CH_2 *p*-bromobenzyl), 46.6 (CH Fmoc), 52.4 (CH α Asp), 65.8 (CH_2 Fmoc), 81.2 (Cq *t*Bu), 120.2 (C^4 and C^5 Fmoc), 121.0 (C^4 *p*-bromobenzyl), 125.2 (C^1 and C^8 Fmoc), 126.2 (C^1 phenyl), 127.1 (C^2 and C^7 Fmoc), 127.7 (C^3 and C^6 Fmoc), 128.3 (C^2 and C^6 *p*-bromobenzyl), 128.5 and 129.1 (C^2, C^3, C^5 and C^6 phenyl), 130.4 (C^4 phenyl), 131.8 (C^3 and C^5 *p*-bromobenzyl), 134.9 (C^1 *p*-bromobenzyl), 140.8 (C^{11} and C^{12} Fmoc), 143.7 and 143.8 (C^{10} and C^{13} Fmoc), 152.7 and 154.1 (Cq triazole), 155.8 (CO Fmoc), 169.7 (*C*O_2*t*Bu) ppm. HRMS (ESI+): calculated for $C_{37}H_{36}BrN_4O_4$, 679.1920; found 679.1918.

4i: HPLC: t_R = 2.00 min. ^{1}H NMR (300 MHz, [D_6]DMSO, 303 K): δ = 0.91 (t, 3 H, C*H*$_3$), 1.29 (s, 9 H, CH_3 *t*Bu), 3.03 (dd, J = 16.1, 8.0 Hz, 1 H, CH_2 β Asp), 3. 09 (dd, J = 16.1, 6.2 Hz, 1 H, CH_2 β Asp), 3.85 (q, 2 H, C*H*$_2$), 4.05–4.40 (m, 5 H, CH Fmoc, CH_2 Fmoc, triazole-C*H*$_2$-phenyl), 4.49–4.59 (m, 1 H, CH α Asp), 7.22–7.33 (m, 7 H, H^2 and H^7 Fmoc, H^2, H^3, H^4, H^5 and H^6 phenyl), 7.41 (t, J = 7.3 Hz, 2 H, H^3 and H^6 Fmoc), 7.67 (d, J = 7.3 Hz, 2 H, H^1 and H^8 Fmoc), 7.68 (d, 1 H, NH Fmoc), 7.89 (d, J = 7.3 Hz, 2 H, H^4 and H^5 Fmoc) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 303 K): δ = 14.9 (*C*H_3), 26.40 (CH_2 β Asp), 27.4 (CH_3 *t*Bu), 30.2 (triazole-*C*H_2-phenyl), 37.6 (*C*H_2-ethyl), 46.5 (CH Fmoc), 52.6 (CH α Asp), 65.6 (CH_2 Fmoc), 80.9 (Cq *t*Bu), 120.1 (C^4 and C^5 Fmoc), 125.1 (C^1 and C^8 Fmoc), 126.6 and 127.1 (C^2 and C^7 Fmoc), 127.6 (C^4 phenyl), 128.2 (C^3 and C^6 Fmoc), 128.5 (C^2, C^3, C^5 and C^6 phenyl), 136.6 (C^1 phenyl), 140.7 (C^{11} and C^{12} Fmoc), 143.8 and 143.7 (C^{10} and C^{13} Fmoc), 150.9 and 152.6 (Cq triazole), 155.8 (CO Fmoc), 170.1 (*C*O_2*t*Bu) ppm. HRMS (ESI+): calculated for $C_{33}H_{37}N_4O_4$, 553.2815; found 553.2813.

4j: HPLC: t_R = 1.55 min. ^{1}H NMR (300 MHz, [D_6]DMSO, 303 K): δ = 1.28 (t, J = 7.31 Hz, 3 H, N-CH_2-*C*H_3), 1.40 (s, 9 H, CH_3 *t*Bu), 1.89–2.21 (m, 2 H, CH_2 β), 2.61 (s, 3 H, methyl), 2.81–3.07 (m, 2 H, CH_2 γ), 4.03–4.3 (m, 3 H, N-*C*H_2-CH_3 and CH α), 5.04 (d, J = 12.4 Hz, 1 H, CH_2 Z), 5.10 (d, J = 12.4 Hz, 1 H, CH_2 Z), 7.37 (m, 5 H, Har phenyl Z), 7.78 (d, J = 8 Hz, 1 H, NH Z) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 303 K): δ = 9.4 (methyl), 13.9 (N-CH_2-*C*H_3), 20.5 (CH_2 β), 27.2 (CH_2 γ), 27.6 (CH_3 *t*Bu), 39.2 (N-*C*H_2-CH_3), 53.7 (CH α), 65.5 (CH_2 Z), 80.9 (Cq *t*Bu), 127.1 (C^4 phenyl Z), 127.8 (C^3 and C^5 phenyl Z), 128.3 (C^2 and C^6 phenyl Z), 138 (C^1 phenyl Z), 152 (C^5 triazole), 154.1 (C^3 triazole), 156.2 (CO Z), 170.8 (CO-O*t*Bu) ppm. HRMS (ESI+): calculated for $C_{21}H_{31}N_4O_4$ [MH^+], 403.2345; found 403.2335.

4k: HPLC: t_R = 1.83 min. ^{1}H NMR (300 MHz, [D_6]DMSO, 303 K): δ = 0.91 (t, J = 7.22 Hz, 3 H, N-CH_2-*C*H_3), 1.39 (s, 9 H, CH_3 *t*Bu), 1.89–2.25 (m, 2 H, CH_2 β), 2.62–2.78 (m, 2 H, CH_2 γ), 3.78–3.80 (d, J = 7.1 Hz, 2 H, N-*C*H_2-CH_3), 4.01–4.14 (m, 3 H, CH_2-phenyl and CH α), 5.04 (d, J = 12.5 Hz, 1 H, CH_2 Z), 5.10 (d, J = 12.5 Hz, 1 H, CH_2 Z), 7.17–7.42 (m, 10 H, Har phenyl and phenyl Z), 7.75 (d, J = 7.76 Hz, 1 H, NH Z) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 303 K): δ = 14.9 (N-CH_2-*C*H_3), 20.8 (CH_2 β), 27.6 (CH_3 *t*Bu), 28.0 (CH_2 γ), 37.4 (N-*C*H_2-CH_3), 54.0 (CH α), 65.4 (CH_2 Z), 80.6 (Cq *t*Bu), 126.6 (C^4 phenyl), 127.7 (C^4 phenyl Z), 128.3 (C^3 and C^5 phenyl), 128.5 (C^2 and C^6 phenyl), 128.6 (C^2 and C^6 phenyl Z), 136.7 (C^1 phenyl Z), 137.0 (C^1 phenyl), 152.5 (C^5 triazole), 153 (C^3 triazole), 156.1 (CO Z), 171.3 (CO-O*t*Bu) ppm. HRMS (ESI+): calculated for $C_{27}H_{35}N_4O_4$ [MH^+], 479.2658; found 479.2654.

4l: HPLC: t_R = 1.73 min. ^{1}H NMR (300 MHz, [D_6]DMSO, 303 K): δ = 1.09–1.24 (m, 6 H, N-CH_2-*C*H_3 and COO-CH_2-*C*H_3), 1.41 (s, 9 H, CH_3 *t*Bu), 1.92–2.23 (m, 2 H, CH_2 β), 2.68–2.84 (m, 2 H, CH_2 γ), 3.84–3.92 (m, 2 H, COO-*C*H_2-CH_3), 3.94 (s, 2 H, *C*H_2-COOEt), 4.09–4.16 (m, 3 H, N-*C*H_2-CH_3 and CH α), 5.03 (d, J = 12.6 Hz, 1 H, CH_2 Z), 5.08 (d, J = 12.6 Hz, 1 H, CH_2 Z), 7.18 (m, 5 H, Har phenyl Z), 7.76 (d, J = 7.85 Hz, 1 H, NH Z) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 303 K): δ = 13.91 (N-CH_2-*C*H_3), 14.98 (COO-CH_2-*C*H_3), 20.83 (CH_2 β), 27.57 (CH_3 *t*Bu), 27.96 (CH_2 γ), 30.77 (N-*C*H_2-CH_3), 37.65 (COO-*C*H_2-CH_3), 54.05 (CH α), 60.90 (*C*H_2-COOEt), 65.41 (CH_2 Z), 80.63 (Cq *t*Bu), 127.11 (C^4 phenyl Z), 127.72 (C^3 and C^5 phenyl Z), 128.28 (C^2 and C^6 phenyl Z), 136.97 (C^1 phenyl Z), 148.00 (C^5 triazole), 153.26 (C^3 triazole), 156.14 (CO Z), 168.46 (CO-OEt), 171.23 (CO-O*t*Bu) ppm. HRMS (ESI+): calculated for $C_{24}H_{35}N_4O_6$[MH^+], 475.2557; found 475.2558.

4m: HPLC: t_R = 1.79 min. ^{1}H NMR (300 MHz, [D_6]DMSO, 303 K): δ = 1.35 (s, 9 H, CH_3 *t*Bu), 1.87–2.11 (m, 2 H, CH_2 β), 2.24 (s, 3 H, methyl), 2.61 (m, 2 H, CH_2 γ), 3.72 (s, 3 H, CH_3-O), 3.99–4.21 (m, 1 H, CH α), 4.80–5.19 (m, 4 H, CH_2 Z and CH_2-4-methoxybenzyl), 6.90 (d, J = 8.7 Hz, 2 H, H^3 and H^5 4-methoxybenzyl), 6.97 (d, J = 8.7 Hz, 2 H, H^2 and H^6 4-methoxybenzyl), 7.33 (m, 5 H, Har phenyl Z), 7.73 (d, J = 7.75 Hz, 1 H, NH Z) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 303 K): δ = 10.43 (methyl), 21.07 (CH_2 β), 27.52 (CH_3 *t*Bu), 28.17 (CH_2 γ), 45.03 (*C*H_2-4-methoxybenzyl), 54.00 (CH α), 55.1 (*C*H_3-O), 65.42 (CH_2 Z), 80.58 (Cq *t*Bu), 114.22 (C^3 and C^5 4-methoxybenzyl), 127.62 (C^4 phenyl Z), 127.70 (C^2 and C^6 4-methoxybenzyl), 127.75 (C^3 and C^5 phenyl Z), 128.28 (C^2 and C^6 phenyl Z, C^1 4-methoxybenzyl), 136.94 (C^1 phenyl Z), 150.90 (C^5 triazole), 153.17 (C3 triazole), 156.11 (CO Z), 158.68 (C^4 4-methoxybenzyl), 171.16 (CO-O*t*Bu) ppm. HRMS

(ESI+): calculated for $C_{27}H_{35}N_4O_5$ [MH^+], 495.2607; found 495.2602.

4n: HPLC: t_R = 2.01 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.33 (s, 9 H, CH_3 *t*Bu), 1.83–2.08 (m, 2 H, CH_2 β), 2.56–2.76 (m, 2 H, CH_2 γ), 3.69 (s, 3 H, CH_3-O), 3.88–4.12 (m, 3 H, CH_2-phenyl and CH α), 5.03 (m, 4 H, CH_2 Z and CH_2 4-methoxybenzyl), 6.80 (s, 4 H, H^2 H^3 H^5 and H^6 4-methoxybenzyl), 7.15–7.41 (m, 10 H, Har phenyl and phenyl Z), 7.69 (d, *J* = 7.8 Hz, 1 H, NH Z) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 21.1 (CH_2 β), 27.5 (CH_3 *t*Bu), 28.0 (CH_2 γ), 30.3 (*C*H_2-phenyl), 45.1 (CH_2- 4-methoxybenzyl), 53.9 (CH α), 55.0 (CH_3-O), 65.4 (CH_2 Z), 80.6 (Cq *t*Bu), 114.1 (C^3 and C^5 4-methoxybenzyl), 126.6 (C^4 phenyl), 127.5 (C^4 phenyl Z), 127.7 (C^3 and C^5 phenyl) 127.8 (C^2 and C^6 4-methoxybenzyl), 128.3 (C^2 and C^6 phenyl), 128.4 (C^3 and C^5 phenyl Z), 128.5 (C^2 and C^6 phenyl Z), 129.1 (C^1 4-methoxybenzyl), 136.3 (C^1 phenyl), 136.9 (C^1 phenyl Z), 153.1 (C^3 triazole), 153.7 (C^5 triazole), 156.1 (CO Z), 158.6 (C^4 4-methoxybenzyl), 171.1 (CO-O*t*Bu) ppm. HRMS (ESI+): calculated for $C_{33}H_{39}N_4O_5$ [MH^+], 571.2920; found 571.2925.

4o: HPLC: t_R = 1.93 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.12 (t, *J* = 7.09 Hz, 3 H, COO-CH_2-*C*H_3), 1.35 (s, 9 H, CH_3 *t*Bu), 1.87–2.12 (m, 2 H, CH_2 β), 2.65 (m, 2 H, CH_2 γ), 3.71 (s, 3 H, CH_3-O), 3.86 (s, 2 H, *C*H_2-COOEt), 3.92–4.09 (m, 3 H, COO-*C*H_2-CH_3 and CH α), 4.93–5.18 (m, 4 H, CH_2 Z and CH_2 4-methoxybenzyl), 6.88 (d, *J* = 8.74 Hz, 2 H, H^3 and H^5 4-methoxybenzyl), 6.95 (d, *J* = 8.74 Hz, 2 H, H^2 and H^6 4-methoxybenzyl), 7.24–7.41 (m, 5 H, Har phenyl Z), 7.69 (d, *J* = 7.86 Hz, 1 H, NH Z) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 13.8 (COO-CH_2-*C*H_3), 21.2 (CH_2 β), 27.5 (CH_3 *t*Bu), 28.0 (CH_2 γ), 31.0 (COO-*C*H_2-CH_3), 45.4 (*C*H_2- 4-methoxybenzyl), 54.0 (CH α), 55.1 (*C*H_3-O-), 60.9 (*C*H_2-COOEt), 65.4 (CH_2 Z), 80.6 (Cq *t*Bu), 114.1 (C^3 and C^5 4-methoxybenzyl), 127.3 (C^1 4-methoxybenzyl), 127.7 (C^2 and C^6 4-methoxybenzyl, C^1 phenyl Z), 127.8 (C^3 and C^5 phenyl Z), 128.3 (C^2 and C^6 phenyl Z), 136.9 (C^1 phenyl Z), 148.6 (C^5 triazole), 153.9 (C3 triazole), 156.1 (CO Z), 158.8 (C^4 4-methoxybenzyl), 168.0 (CO-OEt), 171.1 (CO-O*t*Bu) ppm. HRMS (ESI+): calculated for $C_{30}H_{39}N_4O_7$ [MH^+], 567.2819; found 567.2823.

8: HPLC: t_R = 1.97 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 303 K): δ = 1.10 (t, *J* = 7.23 Hz, 3 H, N-CH_2-*C*H_3), 1.18–1.57 (m, 21 H, CH_3 Ala, CH_3 Boc and CH_3 *t*Bu), 2.79–3.30 (m, 4 H, CH_2 β triazole and CH_2 β Trp), 4.08–4.21 (m, 3 H, N-*C*H_2-CH_3 and CH α triazole), 4.36 (s, 2 H, *C*H_2-phenyl), 4.77–4.92 (m, 1 H, CH α Trp), 6.84 (d, *J* = 7.50 Hz, 1 H, NH Boc), 6.98 (t, *J* = 7.50 Hz, 1 H, H^5 Trp), 7.05 (t, *J* = 7.56 Hz, 1 H, H^6 Trp), 7.14 (d, *J* = 2.02 Hz, 1 H, H^2 Trp), 7.2–7.35 (m, 6 H, H^7 Trp and Har phenyl), 7.56 (d, *J* = 7.7 Hz, 1 H, H^4 Trp), 8.34 (m 2 H, NH amides), 10.82 (s, 1 H, NH indole Trp) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 303 K): δ = 14.3 (CH_3 Ala), 16.8 (N-CH_2-*C*H_3), 26.9 (CH_2 β triazole), 27.3 (CH_2 β Trp), 27.6 (CH_3 *t*Bu), 28.1 (CH_3 Boc), 29.5 (CH_2-phenyl), 39.0 (N-*C*H_2-CH_3), 48.5 (CH α triazole), 50.0 (CH α Ala), 55.5 (CH α Trp), 78.3 (Cq Boc), 80.6 (Cq *t*Bu), 110.0 (Cq$_3$ Trp), 111.3 (C^7 Trp), 118.1 (C^4 Trp), 118.3 (C^5 Trp), 120.8 (C^6 Trp), 123.7 (C^2 Trp), 127.3 (C^9 Trp), 128.7 (C^2, C^3, C^4, C^5 and C^6 phenyl), 134.4 (C^1 phenyl), 136.0 (Cq$_8$ Trp), 151.9 (C^5 triazole), 153.2 (C^3 triazole), 155.3 (CO Boc), 169.1 (CO-O*t*Bu), 171.2 (CO amide Ala), 172.1 (CO amide Trp) ppm. HRMS (ESI+) calculated for $C_{37}H_{50}N_7O_6$ [MH^+], 688.3823; found 688.3822.

Supporting Information (see footnote on the first page of this article): NMR and mass spectra and HPLC chromatograms are presented.

Acknowledgment

We are grateful to Mr. Pierre Sanchez for his indispensable help in obtaining mass spectrometry data.

[1] R. G. Jones, C. Ainsworth, *J. Am. Chem. Soc.* **1955**, *77*, 1538.
[2] S. K. Thompson, A. M. Eppley, J. S. Frazee, M. G. Darcy, R. T. Lum, T. A. Tomaszek Jr., L. A. Ivanoff, J. F. Morris, E. J. Sternberg, D. M. Lambert, A. V. Fernandez, S. R. Petteway, T. D. Meek, B. W. Metcalf, J. G. Gleason, *Bioor. Med. Chem. Lett.* **1994**, *4*, 2441.
[3] S. A. Boyd, A. K. L. Fung, W. R. Baker, R. A. Mantei, H. H. Stein, J. Cohen, J. L. Barlow, V. Klinghofer, J. L. Wessale, K. M. Verburg, J. S. Polakowski, A. L. Adler, S. V. Calzadilla, P. Kovar, Z. L. Yao, C. W. Hutchins, J. F. Denissen, B. A. Grabowski, S. Cepa, D. J. Hoffman, K. W. Garren, H. D. Kleinert, *J. Med. Chem.* **1994**, *37*, 2991
[4] Y. Hitotsuyanagi, S. Motegi, H. Fukaya, K. Takeya, *J. Org. Chem.* **2002**, *67*, 3266.
[5] Y. Hitotsuyanagi, S. Motegi, T. Hasuda, K. Takeya, *Org. Lett.* **2004**, *6*, 1111–1114.
[6] K. Ersmark, M. Nervall, E. Hamelink, K. Janka, L. J. C. Clemente, M. Dunn, B. M. J. Blackman, B. Samuelsson, J. Aqvist, A. Hallberg, *J. Med. Chem.* **2005**, *48*, 6090.
[7] K. Clausen, M. Thorsen, S. O. Lawesson, *Tetrahedron* **1981**, *37*, 3635.
[8] D. Boeglin, S. Cantel, A. Heitz, J. Martinez, J.-A. Fehrentz, *Org. Lett.* **2003**, *5*, 4465.
[9] M. Bibian, A.-L. Blayo, A. Moulin, J. Martinez, J.-A. Fehrentz, *Tetrahedron Lett.* **2010**, *51*, 2660.
[10] L. Demange, D. Boeglin, A. Moulin, D. Mousseaux, J. Ryan, G. Bergé, D. Gagne, A. Heitz, D. Perrissoud, V. Locatelli, A. Torsello, J.-C. Galleyrand, J.-A. Fehrentz, J. Martinez, *J. Med. Chem.* **2007**, *50*, 1939.
[11] A. Moulin, L. Demange, G. Bergé, D. Gagne, J. Ryan, D. Mousseaux, A. Heitz, D. Perrissoud, V. Locatelli, A. Torsello, J.-C. Galleyrand, J.-A. Fehrentz, J. Martinez, *J. Med. Chem.* **2007**, *50*, 5790.
[12] A. Moulin, L. Demange, J. Ryan, D. Mousseaux, P. Sanchez, G. Bergé, D. Gagne, D. Perrissoud, V. Locatelli, A. Torsello, J.-C. Galleyrand, J.-A. Fehrentz, J. Martinez, *J. Med. Chem.* **2008**, *51*, 689.
[13] B. Castro, J. R. Dormoy, G. Evin, C. Selve, *Tetrahedron Lett.* **1975**, *16*, 1219.

Received: May 2, 2011
Published Online: June 6, 2011

