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On the Manner of Cyclization of *N*-Acylated Aspartic and Glutamic Acid Derivatives

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Abstract When synthesizing arylpiperazine library modified with *N*-acylated amino acid derivatives (e.g., cyclized aspartic acid, cyclized glutamic acid, proline) we wished to rapidly determine the way of cyclization of *N*-acylated glutamic acid derivatives. During concomitant cleavage and cyclization two alternative routes were possible—either formation of six-member imide (glutarimide) or five-member lactam. Application of MS/MS and ^{1}H NMR method allowed us to establish that cyclization of *N*-acylated glutamic acid derivatives preceded to lactams—*N*-acylated pyroglutamic acid derivatives.

Keywords Solid-phase synthesis · Aspartic acid cyclization · Glutamic acid cyclization · Pyroglutamic acid · Mass spectrometry · SynPhase Lanterns

Introduction

Synthesis of amino acid-derived small organic compounds for biological studies and drug discovery is an attractive research field. Especially, amino acids-derived cyclic compounds, e.g., imides, lactones, lactams are interesting templates for combinatorial/parallel synthesis developments.

Although, solution-phase synthesis of imide derivatives is quite well established, (Miller and Long 1951; Zajdel et al. 2009; Chilmonczyk et al. 1995) few approaches for solid-phase have been described. (Girdwood and Shute 1997; Barn and Morphy 1999). A common feature of solid-supported approaches is the attachment of the α-amino acid derivatives to the support through an amide or ester linkage, thus resulting in a carboxylic acid or simple amide residue on the final product upon cleavage. Alvarez-Gutierrez et al. (2000a) described the synthesis of 1,3-disubstituted succinimide on *p*-methylbenzhydrylamine (MBHA) resin. Cyclization of aspartic acid was accomplished at elevated temperature in the presence of diphenylphosphorylazide (DPPA) and TEA in THF. Interestingly, a similar strategy involving intramolecular cyclization of glutamic acid derivative was applied for the solid-phase synthesis of 1,5-disubstituted-2-pyrrolidinones (Alvarez-Gutierrez et al. 2000b). One of the inconveniences of the latter approach was the use of strong acidic conditions of HF to perform cleavage from the resin and cyclization of glutamic acid derivatives requiring highly basic conditions. Moreover, cyclization was performed between the carboxylic function of the side chain and the free or alkylated *N*-terminus of glutamic acid.

As an alternative, we have previously presented efficient solid-phase strategy for the synthesis of *N*-acylated amino acid derivatives, connected via an alkylen linker with arylpiperazines (Zajdel et al. 2004, 2006), on BAL linker functionalized SynPhase Lanterns (Jensen et al. 1998). The amino acids were *N*-acylated aspartic and glutamic acids. In the last stage of the synthesis, compounds bearing these dicarboxylic amino acid fragments

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underwent concomitant cleavage and cyclization in the acidic conditions.

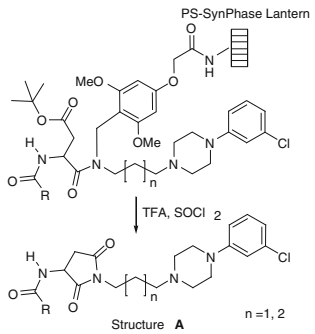
It is generally accepted that cyclization of sequences including an aspartic acid regioselectively yields aspartimide moiety (3-amino-pyrrolidine-2,5-dione), while in the case of glutamic acid possessing an additional methylene group in the lateral chain, two alternative cyclization routes, namely six-member imide (glutarimide) and five-member lactam (pyrrolidine-5-on-2-carboxylic acid, pyroglutamic acid), might occur. The possible ways of cyclization for aspartic acid derivatives and glutamic acid are presented in Schemes 1 and 2, respectively.

In this report, we will demonstrate application of MS/MS and ^{1}H NMR techniques for the elucidation of the type of *N*-acylated glutamic acid derivatives cyclization.

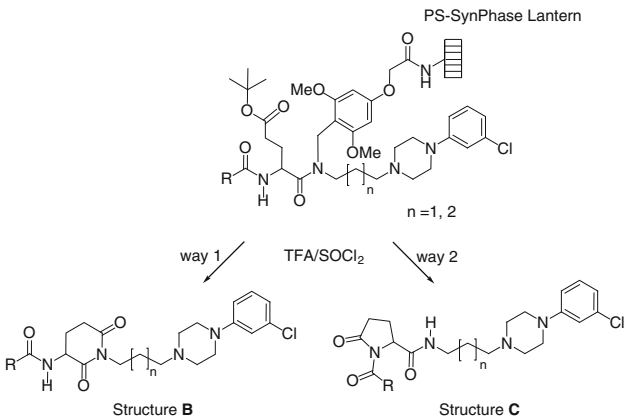
Results and Discussion

Chemistry

Compound **7** was synthesized according to the standard methods used in peptide chemistry and outlined in Scheme 3.



Scheme 1 Cyclization of the aspartic acid derivatives to the 3-*N*-acyl-amino-pyrrolidine-2,5-dione—Structure **A**



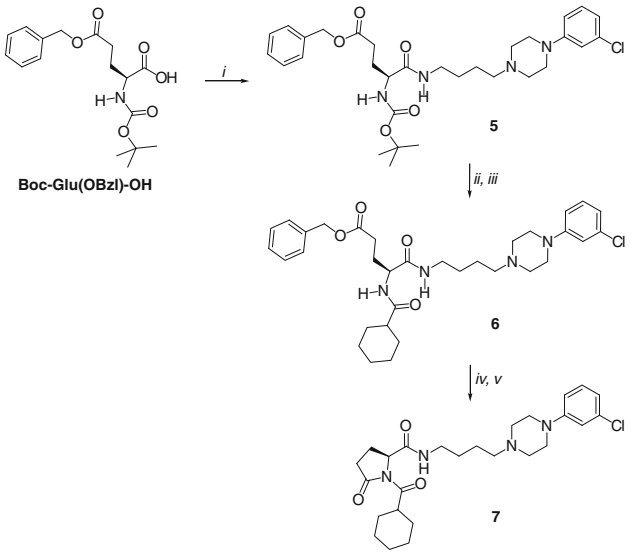
Scheme 2 Possible routes of cyclization of the glutamic acid derivatives: glutarimide—Structure **B**, and pyroglutamic acid—Structure **C**

First, *N*-α-*tert*-butoxycarbonyl-L-glutamic acid γ-benzyl ester was directly coupled with 4-[4-(3-chlorophenyl)piperazin-1-yl]butylamine, in the presence of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU). It was then coupled with cyclohexane carboxylic acid to yield compound **6**. After removal of benzyl protection a corresponding acid derivative of compound **6** was submitted to cyclization in the presence of $SOCl_2$ in chloroform. The final pyroglytamyl derivative was purified by column chromatography to yield pure **7** as white solid.

Mass Spectrometry

The goal of this study was to determine the manner of intramolecular cyclization of *N*-acylated glutamic acids during cleavage from the BAL linker (Scheme 2). In the first stage, mass spectrometry techniques were applied. Of the available spectroscopic methods, mass spectrometry is particularly well suited for probing combinatorial libraries, since it provides rapid and sensitive measurements of the cleaved mixtures of compounds. It is worth noting that this technique has been successfully adapted for direct analysis of the products attached to a solid support (MALDI, S-SIMS) (Enjalbal et al. 2000).

Taking into account a structural similarity, four compounds from the initial library were selected (Zajdel et al. 2004). Two of them were *N*-acylated aspartic acid derivatives—compounds **1** and **2** (Scheme 4) and two were the



Scheme 3 Synthesis routes to the 1-*N*-cyclohexanoyl-{4-[4-(3-chlorophenyl)piperazin-1-yl]-butyl}-pyrrolidine-5-one-2-carboxamide (**7**). (*i*) 4-[4-(3-chlorophenyl)piperazin-1-yl]butylamine, HBTU, TEA, CH_2Cl_2, rt, 8 h; (*ii*) TFA; (*iii*) cyclohexane carboxylic acid, HBTU, TEA, CH_2Cl_2, rt, 8 h; (*iv*) 30% HBr/AcOH; (*v*) $SOCl_2$, $CHCl_3$

studied *N*-acylated glutamic acid derivatives—compounds **3** and **4** (Scheme 5).

The model compounds were submitted to ESI + MS. In MS spectra of compounds **1** and **2** apart from molecular ions, isotopic ions $(M + 2)^+$ were observed. Their intensity equated to 33% of the molecular ion peak which proved the presence of a chlorine ion. During spectra investigation it was found that two routes of fragmentation of Structure **A** occur simultaneously (Scheme 4). The first one is the result of a loss of an acyl-amino moiety in compound **2**, forming a succinimide carbocation—348.2/350.2 Da (way 1).

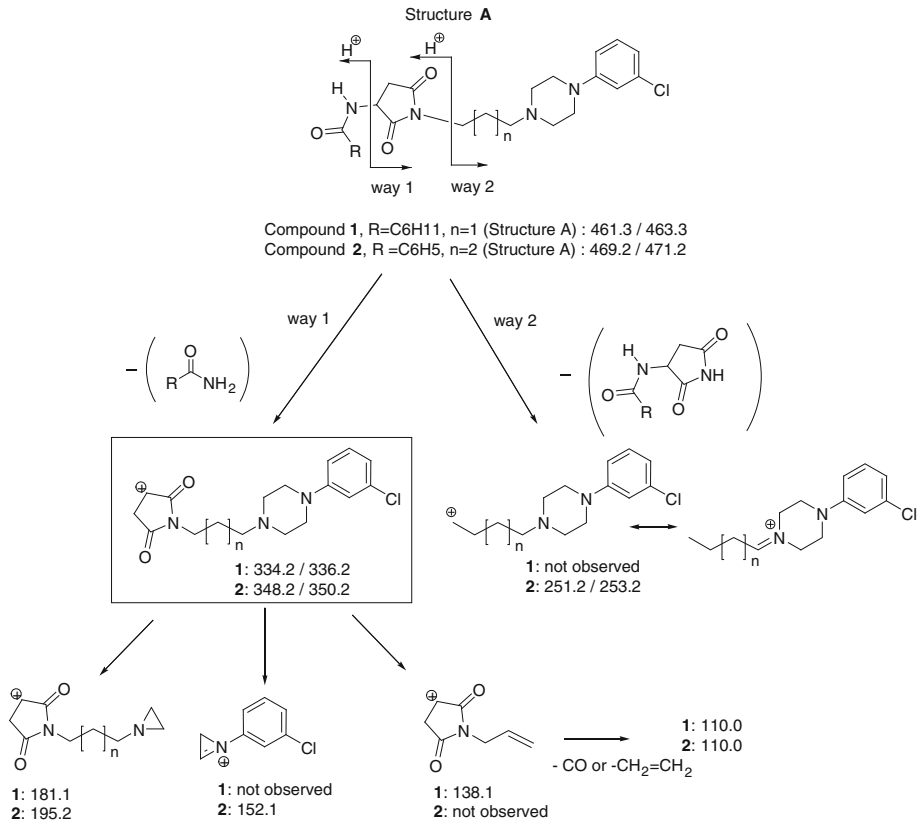
Further fragmentation caused by piperazine ring disturbance resulted in the creation of succinimides carbocations (compound **1**: 181.1, compound **2**: 195.2), and a characteristic iminium cation containing a *m*-chlorophenyl moiety of 152.1 Da observed for compound **2**. The second way of fragmentation involved selective cleavage between an imide nitrogen atom and the tetramethylene aliphatic spacer, resulting in a 251.2/253.2 Da ion for compound **2.**

During cyclative cleavage from the solid-support, an activated lateral carboxylic group of the glutamic acid carboxamide derivative may attack two amide bond localized in its proximity. This may result in creation of two kinds of cyclic derivatives: a six-membered 3-aminoglutarimide ring and a five-membered pyroglutamyl moiety (Scheme 5, Structures **B** and **C**, respectively).

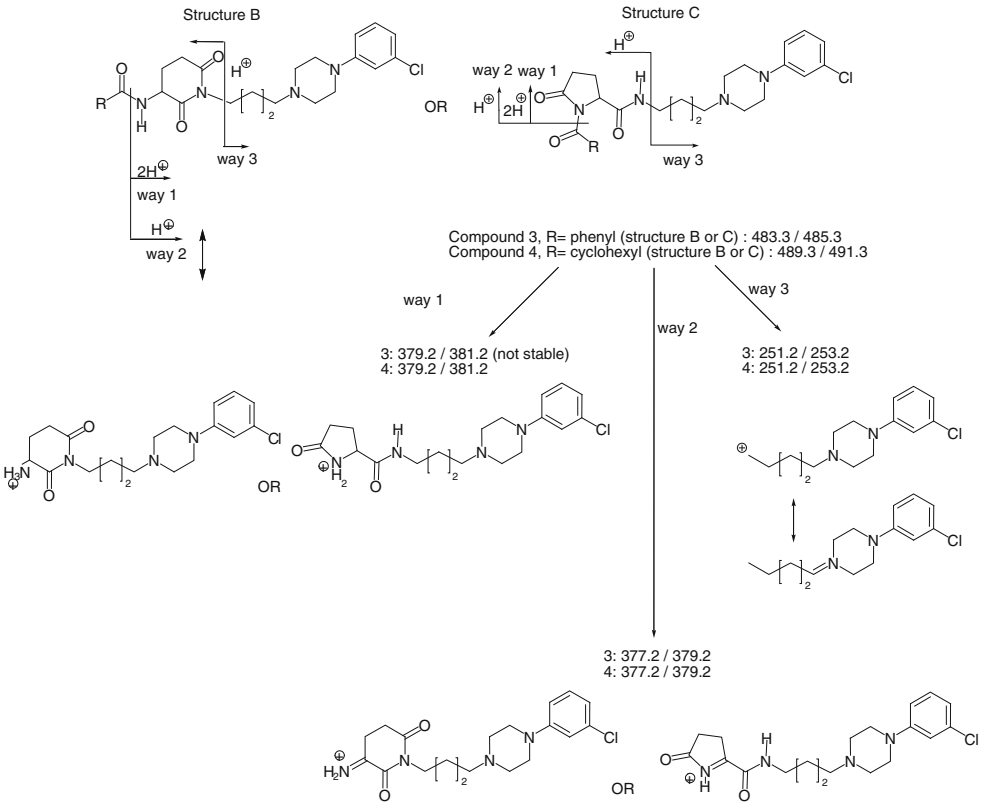
Even though, the five-member ring is favored due to the less significant tensive interaction, six-membered glutarimides were also described in literature (Xiao et al. 2002). In the mass spectra analysis of cyclized glutamic acid derivatives three types of ions were observed. The cleavage of an amide bond between the acyl residue and an amine group at position 3 of a glutarimide led to formation of two types of ions: ammonium ions—379.2/381.2 (way 1) and iminium ions—377.2/379.2 (way 2). Furthermore, fission between an imide nitrogen atom of Structure **B** and the alkyl chain, or between a nitrogen atom of an amide bond linking the pyroglutamyl residue with alkyl spacer in the case of Structure **C** led to characteristic isotopic carbocations for the halogen derivative—251.2/253.2 (way 3).

Determination of the manner of cyclization of glutamic acid was problematic because the same fragmentation ions were observed in two cases. Thus, at the next stage, compound **4** was subjected to a Collisionally Activated Decomposition (CAD) experiment. The spectrum analysis proved the existence of protonated molecular ions (489.4/491.4 Da), and the fragmentation ions presented in Table 1.

It could be noticed that fragment ions characterized by masses higher than 200 Da contained chlorine atoms,



Scheme 4 Fragmentation routes of the compounds **1** and **2** bearing aspartic acid residue



Scheme 5 Fragmentation routes of the compounds **3** (R = phenyl) and **4** (R = cyclohexyl), bearing cyclized glutamic acid residue

Table 1 Fragmentation ions obtained for cyclized *N*-acylated glutamic acid derivative compound **3**

Fragmentations ions for **3** (Da)
489.4/491.4
379/381
278/280
251/253
183
111
83

contrary to fragment ions with masses lower or equal to 200 Da. Additional information concerning the genealogy of the fragment ions, namely of 379/381 and 251/253 Da, was obtained. A proposed fragmentation is thus presented in Scheme 6. The lines mark the fragment ions observed in the CAD spectra of the parent molecule.

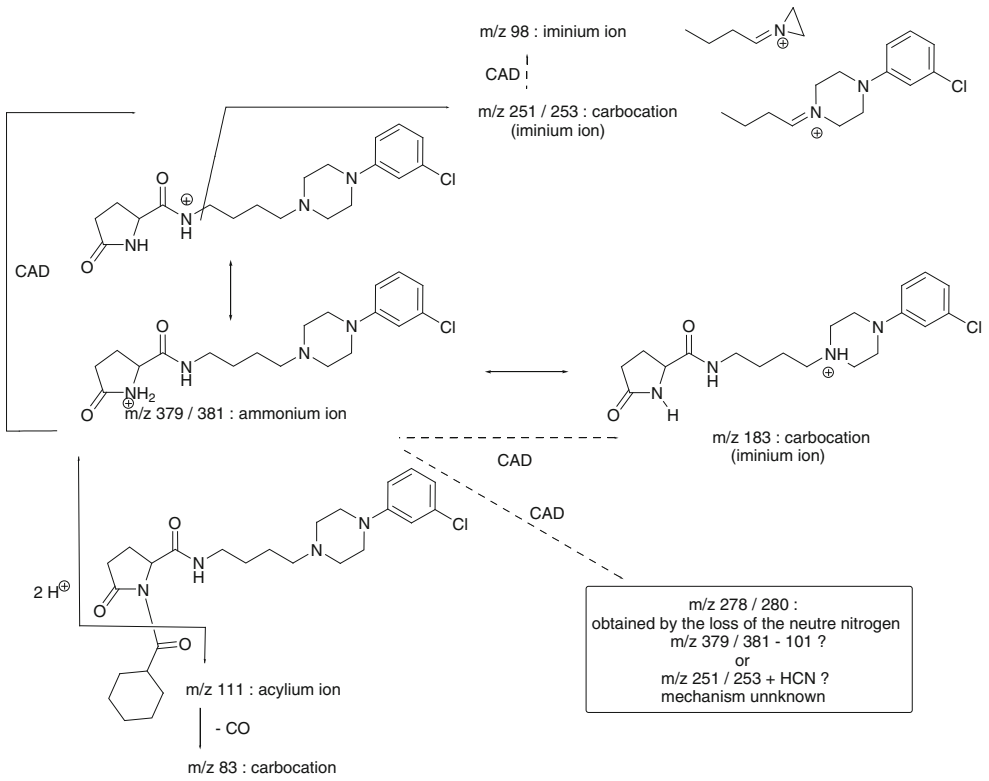
It was difficult to determine the mechanism of creation of the fragment ion possessing a chlorine atom with the mass of 278/280 Da. Its parent fragment ion was 379/381 Da. When we compared those two ions (parent and fragment), the second one turned out to contain an odd number of nitrogen atoms. This observation may suggest possible loss of the HCN nitrile in the fragment ion 379/381, but the mechanism remains unclear.

In the LC/MS/MS it appeared that the pyroglutamyl cycle (lactone) was the most favored isomer. The most abundant fragment ion—ammonium 379/381 Da, if of glutarimide origin, would very easily lose an NH_3 moiety, resulting in an unobserved carbocation 362/364 Da (Fig. 1). The above illustrated fragmentation was, however, observed in the case of succinimide derivatives (Structure **A**, Scheme 1).

^{1}H NMR Structure Analysis

To evidence a creation of lactam derivative, a structure of model pyroglutamic acid derivative was investigated by ^{1}H NMR technique. For this purpose, compound **4** was re-synthesized on solid support in larger quantity (6 Lanterns) according to the previously described strategy (Zajdel et al. 2004), and purified by RP-HPLC. It was also synthesized in liquid phase according to the standard Boc/Bzl peptide (compound **7**, Scheme 3).

As it was anticipated, the classic one-dimensional ^{1}H NMR spectra for compounds synthesized on solid support (compound **4**) and in a solution phase (compound **7**) were similar. Thus, in the next stage two-dimensional spectra were prepared. Standard Varian pulse sequence was used for the COSY 2D experiment (Fig. 2). The



Scheme 6 Fragmentation routes of the compound **4**

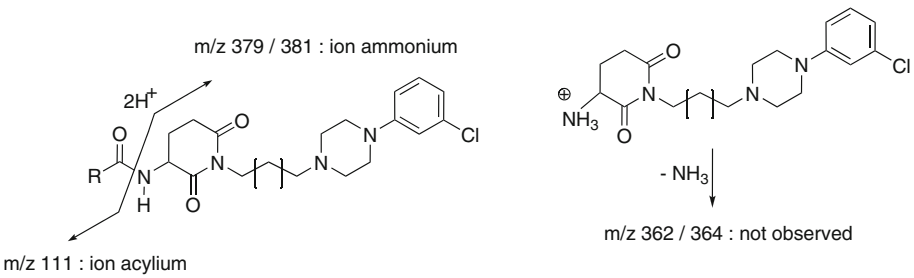


Fig. 1 Proposed fragmentation of glutarimide derivatives

spectrum was measured with 16 repetitions each 256 increments each. For data processing purpose the spectrum was zerofilled up to 2 K and sine bell apodization was used.

In the 2D COSY spectrum of compound **4**, the amide proton observed at resonance 6.6 ppm exhibited a cross-peak with the multiplet at resonance range 3.22–3.29 ppm. The latter was attributed to 2 carbon protons from alkyl spacer ($C_{1\text{-spacer}}$) and 4 protons of the piperazine moiety. Other observations indicated that the proton coming from C_α, observed as a doublet of doublets at 4.61–4.64 ppm, was coupled with two protons localized in the aliphatic range of 2.17–2.24 ppm, which could be attributed to carbon β of the pyroglutamyl moiety. Furthermore, the C_α proton did not couple with the amide proton. This is of particular importance, since such coupling should have been observed for 6 member cycle—glutarimide (Structure **B**, Scheme 2).

Conclusions

Summing up, application of mass spectrometry and 2D ^{1}H NMR has allowed determining the manner of cyclization of the *N*-acylated glutamic acid derivatives. It was found that both on solid support and in solution cyclization of *N*-acylated glutamic acid derivatives yielded a five-member lactams—pyrrolidine-5-on-2-carboxylic acid (pyroglutamic acid) derivatives.

Experimental

Chemistry

All reagents and solvents were from Aldrich and Alfa Aesar and were used without further purification. Protected amino acids and HBTU were purchased from Iris.

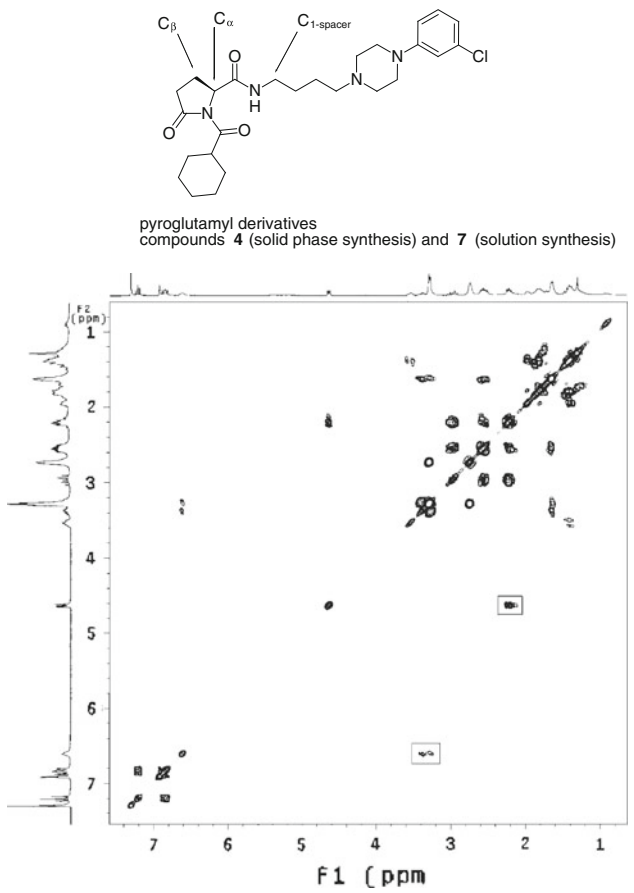


Fig. 2 The COSY ^{1}H NMR spectrum of the compounds **4** or **7**. The interaction between the amide protons and the protons of an aliphatic spacer is shown in *rectangle*

Analytical HPLC were run on a Waters Alliance HPLC instrument, equipped with a Chromolith SpeedROD column (4.6 × 50 mm). Standard conditions were eluent system A (water/0.1% TFA), system B (acetonitrile/0.1% TFA). A flow rate of 5 ml/min and a gradient of (0–100)% B over 5 min were used, detection 214 nm. Retention times (t_R) are given in minutes. All melting points were determined with Büchi 353 capillary apparatus and remain uncorrected. Elemental analyses were carried out using an Elementar Vario EL III, and were within ±0.4% of the theoretical values. Silica gel 60 230–400 mesh, purchased from Merck, was used for preparative chromatographic purification.

LC/MS Analysis

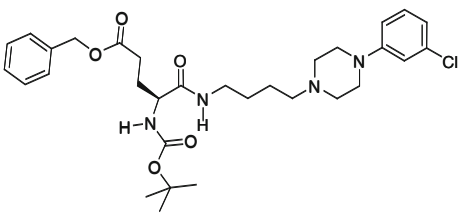
Samples were prepared in acetonitrile/water (50:50 v/v), containing a 0.1% TFA. The LC/MS system consisted of a Waters Alliance 2690 HPLC, coupled to a Micromass (Manchester, UK) Platform II spectrometer (electrospray ionization mode, ESI+). All the analyses were carried out using a C18 Xterra MS, 21 × 3.0 mm column. A flow rate of 500 µl/min and a gradient of (0–100)% B over 5 min were used. Eluent A: water/0.1% TFA; eluent B: acetonitrile/0.1% TFA. Positive ion electrospray mass spectra were acquired at a solvent flow rate of 100–500 µl/min. Nitrogen was used for both the nebulizing gas and the drying gas. The data were obtained in a scan mode ranging from 400 to 1400 m/z in 0.1 s intervals; 10 scans were summed up to get the final spectrum.

Collision activated dissociations (CAD) analyses were carried out with the energy of 70 V, and all the fragmentations were observed in the source.

^{1}H NMR Experiments

NMR spectra were obtained using a Varian BB 200 (300 MHz) spectrometer at 28°C; chemical shifts (δ) are expressed in ppm downfield from the internal TMS as a reference; J values are in hertz, and splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). The samples were dissolved in $CDCl_3$.

(S)-2-*N*-*Tert*-Butoxycarbonyl-4-{4-[4-(3-Chlorophenyl)piperazin-1-yl]-Butyl}-Glutamyl Amide 5-Benzyl Ester (5)

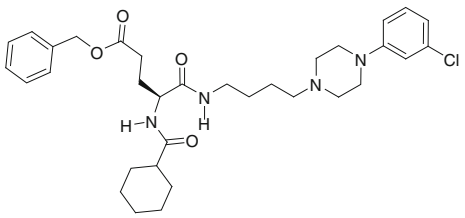


A solution of *N*-2-*tert*-butoxycarbonyl-L-glutamic acid 5-benzyl ester (0.67 g, 2 mmol), HBTU (0.83 g, 2.2 mmol) in CH_2Cl_2 (25 ml) was stirred at room temperature for 2 min and then 4-[4-(3-chlorophenyl)piperazin-1-yl]butylamine (0.49 g, 1.8 mmol) in CH_2Cl_2 (2 ml) was added followed by the addition of TEA (0.84 ml, 6 mmol). After the reaction has been stirred for 8 h, the solvent was removed under reduced pressure. The oily residue was dissolved in AcOEt (50 ml) and washed with saturated $NaHCO_3$ (3 × 30 ml), water (3 × 30 ml), brine, dried over Na_2SO_4, and finally concentrated in vacuum. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH: 9/1) gave **5** (0.94 g, 81% yield) as white solid.

Melting point: 106–108°C. HPLC: $t_R = 2.73$. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.42 (s, 9H, $C(CH_3)_3$), 1.54–1.56 (m, 4H, $NCH_2CH_2CH_2$), 1.90–1.95 (m, 1H, H_β Glu), 2.09–2.13 (m, 1H, H_β Glu), 2.40–2.54 (m, 4H, $CH_2CH_2N(CH_2)_2$, H_γ Glu),

2.56–2.60 (m, 4H, N(CH_2)$_2$), 3.18–3.28 (m, 6H, (CH_2)$_2$N, NCH_2), 4.11–4.20 (m, 1H, H_α Glu), 5.06–5.16 (q, 2H, CH_2Ph), 5.21–5.23 (m, 1H, N*H*CH), 6.45 (b, 1H, N*H*CH_2) 6.76–6.81 (m, 2H, Ph), 6.86–6.85 (m, 1H, Ph), 7.12–7.18 (t, 1H, Ph, $J = 8.1$ Hz), 7.32–7.37 (m, 5H, Ph). ESI ($M + H^+$) calcd for $C_{31}H_{43}ClN_4O_5$ (monoisotope): 586.3; found 587.5. Elemental analysis—Found (%): C, 63.66; H, 7.33; N, 9.60. Calcd (%) for $C_{31}H_{43}ClN_4O_5$: C, 63.41; H, 7.38; N, 9.54.

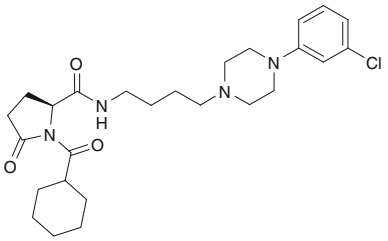
(S)-2-*N*-Cyclohexanoyl-4-{4-[4-(3-Chlorophenyl)piperazin-1-yl]-Butyl}-Glutamyl Amide 5-Benzyl Ester (6)



Compound **1** (0.9 g, 1.5 mmol) was stirred in a mixture TFA/CH_2Cl_2 (9/1, v/v) at room temperature for 60 min. The volatiles were removed under reduced pressure to yield the corresponding TFA salt as orange oil (0.92 g, 100% yield). It was then dissolved in CH_2Cl_2 (20 ml) and added to the mixture of cyclohexane carboxylic acid (0.21 g, 1.65 mmol), HBTU (0.62 g, 1.65 mmol), and TEA (0.69 ml, 4.95 mmol) in 20 ml of CH_2Cl_2. The reaction was stirred at room temperature for 8 h. After concentration the resulting crude was dissolved in AcOEt (50 ml), washed with saturated $NaHCO_3$ (2 × 40 ml), water (1 × 40 ml), brine, dried over $MgSO_4$, and finally concentrated. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH: 9/1) gave **6** (0.69 g, 75% yield) as a white powder.

Melting point: 142–143°C. HPLC: $t_R = 2.81$. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.16–1.84 (m, 14H, cluster-cHex, NCH_2CH_2CH_2), 1.89–2.18 (m, 3H, H_β Glu, CH_2C*H*CH_2), 2.34–2.44 (m, 3H, CH_2CH_2N(CH_2)$_2$, H_γ Glu), 2.53–2.63 (m, 5H, N(CH_2)$_2$, H_γ Glu), 3.19–3.49 (m, 6H, (CH_2)$_2$N, NCH_2), 4.36–4.43 (m, 1H, H_α Glu), 5.06–5.12 (q, 2H, CH_2Ph), 6.33–6.37 (d, 1H, N*H*CH, $J = 7.70$ Hz), 6.65 (b, 1H, N*H*CH_2), 6.76–6.81 (m, 2H, Ph), 6.86–6.87 (m, 1H, Ph), 7.12–7.18 (t, 1H, Ph, $J = 8.1$ Hz), 7.30–7.39 (m, 5H, Ph), ESI ($M + H^+$) calcd for $C_{33}H_{45}ClN_4O_4$ (monoisotope): 596.3; found 597.3. Elemental analysis—Found (%): C, 66.66; H, 7.54; N, 9.43. Calcd (%) for $C_{33}H_{45}ClN_4O_4$: C, 66.37; H, 7.60; N, 9.38.

(S)-1-*N*-Cyclohexanoyl-{4-[4-(3-Chlorophenyl)piperazin-1-yl]-Butyl}-Pyrrolidin-5-on-2-Carboxamide (7)



Compound 2 was dissolved in 5 ml of a 30% solution of HBr in acetic acid in a round bottom flask. The mixture was stirred at 40°C for 3 h. After complete deprotection (TLC control), the solution was concentrated under reduced pressure, and residue co-evaporated several times with CH_2Cl_2 and ether to give a slightly yellow foam. The obtained acid was left to dry in desiccator over P_2O_5 overnight. Carboxylic acid was used without further analytical identification. It was (0.63 g, 1.25 mmol) dissolved in chloroform (4 ml) and thionyl chloride (0.1 g, 1.25 mmol) was added at 0°C. The mixture was allowed to warm in room temperature for 60 min, and then the mixture was heated under reflux for 6 h while stirring. Then, the mixture was concentrated under reduced pressure and the residue was dissolved in AcOEt (40 ml). The organic phase was washed with saturated $NaHCO_3$ (2 × 30 ml), water (2 × 30 ml), dried over $MgSO_4$, and finally concentrated in vacuum to give a crude product as a yellow oil. It was purified by column chromatography over silica gel (CH_2Cl_2/MeOH: 9/1) to give **7** as a white solid (yield: 47%).

Melting point: 131–133°C. HPLC: $t_R = 2.47$. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.14–2.00 (m, 14H, cluster-cHex, NHCH_2CH_2CH_2), 2.09–2.30 (m, 2H, H–C_β Pyr), 2.46–2.63 (m, 3H, CH_2CH_2N(CH_2)$_2$, H–C_γ Pyr), 2.65–2.80 (m, 4H, N(CH_2)$_2$), 2.97 (dt, 1H, H–C_γ Pyr, $J = 17.60$, 10.18 Hz), 3.21–3.45 (m, 6H, (CH_2)$_2$N, NCH_2), 3.47–3.61 (m, 1H, cHex), 4.63 (dd, 1H, H–C_α Pyr, $J = 7.84$, 2.89 Hz), 6.60 (m, 1H, N*H*CH_2), 6.78–6.88 (m, 2H, Ar), 6.88–6.94 (m, 1H, Ar), 7.20 (t, 1H, Ar). ESI ($M + H^+$) calcd for $C_{26}H_{37}ClN_4O_3$ (monoisotope): 488.3; found 489.4. Elemental analysis—Found (%): C, 63.64; H, 7.96; N, 11.24. Calcd (%) for $C_{26}H_{37}ClN_4O_3$: C, 63.85; H, 7.63; N, 11.46.

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