Eur J Med Chem (1996) 31, 215–220

Synthesis and receptor-binding affinity of dipeptoid cholecystokinin ligands

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(Received 16 October 1995; accepted 21 November 1995)

Summary — This paper describes the synthesis of novel derivatives **4a–i**, which are structurally related to PD134308 and in which the indole moiety is replaced by other aromatic groups. Cholecystokinin-A and -B (CCK-A and CCK-B) receptor binding affinities of these analogues are described and the contribution of the various rings is discussed. Several of the compounds prepared have CCK-B receptor binding values similar to that reported for PD134308 and are highly selective over the CCK-A receptor. They represent potential therapeutic agents for anxiety.

peptoid / CCK-B antagonist / PD134308 derivative

Introduction

The importance of selective cholecystokinin-B (CCK-B) antagonists as potential anxiolytic agents is well known. One of the most potent and selective CCK-B antagonists reported to date is the peptoid PD134308 (CI-988) [1, 2], which has been shown to be a potent anxiolytic agent in a number of animal models [3, 4]. Extensive SAR studies have been carried out on related 'dipeptoids' [5–11], also revealing that the chirality at each of the three centers is critical for binding affinity. The principal structural feature of CI-988 is the α-methyl-substituted Trp residue, considered essential for receptor affinity. Thus a large number of compounds have been synthesized which incorporate the Trp residue. Our objective was to determine whether the indole moiety of the Trp residue could be replaced by a variety of aromatic rings. This was suggested by a report in the literature [12] that the replacement of this ring by naphthalene in CCK-4 gives an interesting mimic of this CCK fragment. To our knowledge, few examples are known in this series of peptoids of the indole moiety being replaced by other aromatic rings [13, 14]. Such considerations led us to design compounds of structure **4a–i** and this paper reports a facile and efficient method for the synthesis of some aryl analogues and their biological properties. Because of the importance of stereochemistry in differentiating between CCK-A and CCK-B receptor subtypes, we chose to have a determined *R* configuration at the phenyl alanine site, whereas an *R,S* mixture was initially maintained at the Trp moiety. These compounds were found to act as potent CCK-B ligands. Moreover, one of them (compound **4c**) was found to be more selective than PD 134308, indicating that the indole ring is not essential for high affinity and can be replaced by an appropriate substituent.

Chemistry

Although the synthesis of the parent compound PD134308 is well known [15], to our knowledge there is no complete report of the synthesis of its aryl counterparts, which were only generally embraced in a patent published during our investigation [16].

Schemes 1 and 2 summarize the synthetic pathways used to obtain the compounds **4a–i** listed in table I. The key step is the coupling reaction between the unnatural amino acids **1a–i** and the amine **2** to give the methyl ester intermediates **3a–i**. All the coupling reactions between acids **1a–i** and the amine **2** were performed using 1,3-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole hydrate (HOBT) in ethyl acetate at room temperature and yielded methyl esters

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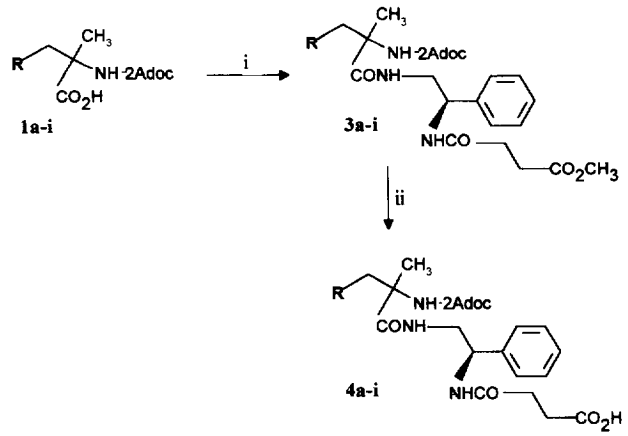
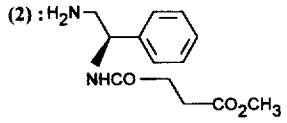
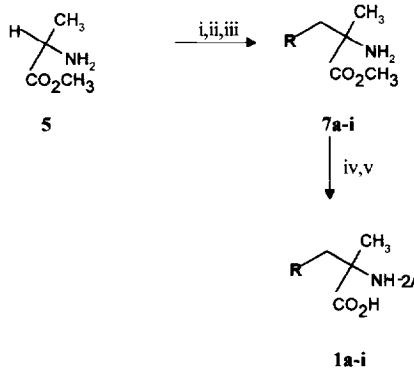




Scheme 1. i) DCC, HOBt (**2**); ii) 0.1 M LiOH, THF. For definition of **a–i** see table I.

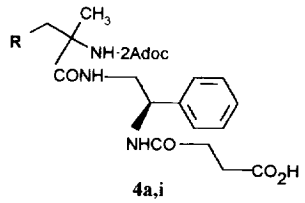
3a–i in fairly good yield [1]. The target acid derivatives **4a–i** were obtained after hydrolysis of the corresponding esters by treatment with LiOH in THF. The synthesis of the chiral amine **2** has been described previously [1].



Scheme 2. i) Benzaldehyde, Et_3N, Na_2SO_4, CH_2Cl_2; ii) *t*-BuOK, THF/DMSO, **6** or KOH, TEBA, CH_2Cl_2, **6**; iii) HCl (1 N), Et_2O; iv) 2-Adoc-Cl, Et_3N, THF; v) LiOH, dioxane. **6** = RCH_2Cl.

As regards the preparation of α-methyl amino acids **1a–i**, a convenient approach is reported in scheme 2. Alanine methyl ester hydrochloride **5** was converted into its Schiff base through reaction with benzaldehyde and alkylated with the required halides **6a–i** in THF/DMSO to give the intermediate **7a–i** [17, 18] under catalytic solid-liquid phase-transfer conditions. The aryl halides **6**, if not commercially available, were prepared by converting the aldehydes (compounds **f,g**) [19] or the acyl chloride precursors into the corresponding alcohol (compound **h**) [20] through

Table I. Potencies of CCK ligands **4a–i** in inhibiting [^{3}H]-pCCK8 specific binding.



4a,i

Compound	*R*	*CCK-A** (pK_i)	*CCK-B** (pK_i)	*Affinity ratio B/A*
PD134308	3-Indolyl	6.16	8.73	220
4a	Ph	5.53 ± 0.02	6.88 ± 0.06	22
4b	1-Naphthyl	5.69 ± 0.12	7.44 ± 0.03	56
4c	2-Naphthyl	5.79 ± 0.10	8.51 ± 0.03	525
4d	2-Quinolyl	5.80 ± 0.03	7.11 ± 0.02	20
4e	1-(*p*-Ph-Ph)	5.61 ± 0.02	6.27 ± 0.04	5
4f	5,6,7,8-Tetrahydro-2-naphthyl	5.70 ± 0.16	8.28 ± 0.05	380
4g	9-Phenanthryl	5.48 ± 0.01	6.67 ± 0.06	15
4h	2-Benzo[*b*]thienyl	5.72 ± 0.07	7.94 ± 0.05	166
4i	3-Py	5.05 ± 0.05	5.50 ± 0.04	4

$n = 3$.

reduction with sodium borohydride or diisobutylaluminum hydride. The alcohols were subsequently reacted with $POCl_3$ or $SOCl_2$ to give the corresponding halides **6f,g,h**. Preparation of compound **7i**, in which the indole moiety was replaced by pyridine, required the use of its *N*-oxide derivative to be reduced at the final step to the α-methyl amino acid [21].

Finally, the *N*-(2-adamantyloxycarbonyl)-2-methylamino acids **1a–i** were obtained from the corresponding methyl esters **7** by condensation with 2-adamantyl chloroformate and subsequent hydrolysis of the methyl ester intermediate with lithium hydroxide [1].

Results and discussion

All the compounds were evaluated as competitors in the binding of [^{3}H]-CCK8s on guinea-pig brain CCK-B receptors and on rat pancreas CCK-A receptors to determine selectivity. As shown in table I, all the compounds exhibited a weak affinity with K_i values ranging roughly from 1 to 10 μM for CCK-A sites. The affinity for CCK-B receptors varied much more widely, with K_i values ranging from 3 μM to 2 nM. As a result, the condensed polycyclic nucleus turned out to be more selective than PD 134308 (B/A = 220). The best results were obtained with the 2-naphthalene derivative **4c** (B/A = 525). Interestingly, it proved to be ten-fold more selective than the corresponding 1-naphthalene derivative **4b**. Also 5,6,7,8-tetrahydronaphthalene **4f** was much more selective than PD 134308, whereas its 2-quinoline counterpart **4d** was 30-fold less selective than **4c** and 2-benzo[*b*]thienyl **4h** gave a ten-fold lower affinity for CCK-B, while retaining a good selectivity (B/A = 166).

In our case, the condensed polycyclic nucleus turned out to be much more potent and selective than compounds with a single aromatic ring (**4a,i**) or two separated aromatic rings (**4e**). All the compounds in this series are substituted phenethylamide derivatives with the optimal through-bond distance from the -COOH group to the phenethylamide backbone as shown by PD 134308. All were prepared with an *R* configuration at the β-carbon of the phenethylamide, since it has been previously shown [2] that an *R* configuration at this center is required to achieve optimal CCK-B receptor-binding affinity. Although it is well known that the *R* configuration is also crucial at the tryptophan moiety, we chose to begin with diastereomeric mixture at this level. Nevertheless, some interesting conclusions may be drawn from the binding affinities of this series of compounds. It is evident that the indole ring is not essential and if replaced by an appropriate substituent, high CCK-B/A selectivity can be reached. It is likely that the preparation of the single *R* isomer will enhance the affinity and selectivity shown by racemic 4c.

Conclusions

In this paper we have described the synthesis and the SAR of the indole-replaced ligands **4**. Several novel compounds **4c,f,h** in this series have CCK-B receptor binding affinities similar to PD 1343308 with a consistent improvement in B/A selectivity. This paper demonstrates that the indole moiety can be replaced by some aromatic groups without loss of CCK-B receptor binding affinity.

Experimental protocols

Receptor-binding assays

[^{3}H]-CCK8s competition binding experiments were carried out in a total volume of 1 mL, containing 0.2 nM radioligand for both CCK-B and CCK-A receptors with various concentrations of unlabeled drugs, dissolved in DMSO (maximum concentration 0.1% in test tubes). Incubations were started by the addition of 250 μg/mL for CCK-B and 70 μg/mL for CCK-A to membrane preparations and continued for 60 min at 25 °C for CCK-B and at 37 °C for CCK-A binding. The B_{max} and the K_D for the [^{3}H]-CCK8s were determined beforehand in saturation experiments by incubating increasing concentrations (up to ten times the estimated K_D) of the radioligand. Non-specific binding was defined in the presence of 1 μM L-365 260 for CCK-B and 0.1 μM L-364 718 for CCK-A receptors. For both CCK-A and CCK-B receptors, the K_D measured for [^{3}H]-CCK8s was 0.2 nM. The bound was separated from the free radioactivity by rapid filtration over Whatman GF/C filters on a Brandel M-48 harvester. Filters were washed and counted by liquid scintillation detection (Filter-count cocktail, in a TriCarb 1900CA, Packard, β-counter). Membranes for CCK-B binding were prepared according to Van Dijk et al [22], with minor modifications; pancreatic membranes were prepared according to Innis et al [23]. Data from saturation and competition experiments were analyzed using WinLig, a Windows version (developed in-house) of the fitting program LIGAND [24]. Protein was measured with the Pierce Protein Assay Reagent (BCA Method), using BSA as a standard.

Chemistry

Infrared spectra (IR) were recorded on a FT-IR instrument in chloroform-d_1 solution. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz as solution in chloroform-d_1 with tetramethylsilane as an internal reference. Silica-gel TLC was performed on precoated sheets (E Merck, Darmatadt) and column chromatography was carried out on silica gel. MS spectra were recorded on V-G4 Fisons Instruments. Analyses indicated by elemental symbol were performed on CHNS-O [Carlo Erba].

DL-α-Methylphenylalanine methyl ester **7a**, DL-α-methyl-3-(1-naphthyl)alanine methyl ester **7b**, DL-α-methyl-3-(2-naphthyl)alanine methyl ester **7c**, *N*-[(2-adamantyloxy)carbonyl]-DL-α-methyl-3-phenylalanine **1a**, *N*-[(2-adamantyloxy)carbonyl]-DL-α-methyl-3-(1-naphthyl)alanine **1b** and *N*-[(2-adamantyloxy)carbonyl]-DL-α-methyl-3-(2-naphthyl)alanine **1c** were known compounds and were prepared according to published procedures [26].

4-[[2-[[3-Aryl-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester derivatives ***3a–i***

Compounds **3a–i** were obtained by condensation of the corresponding amino acids with DCC and HOBT. A typical reaction procedure is as follows:

4-[[2-[[3-Phenyl-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester ***3a***. *N,N'*-Dicyclohexylcarbodiimide (0.263 g, 1.28 mmol) and 1-hydroxybenzotriazole (0.187 g, 1.2 mmol) were added to a solution of the intermediate **1a** (0.4 g, 1.12 mmol) in ethyl acetate (30 mL). The solution was stirred at 25 °C for 2 h, and then a solution of the amine **2** in ethyl acetate (30 mL) was added. The resulting solution was stirred for 2 h at 25 °C, then filtered and concentrated in vacuo. The residue was purified by neutral aluminium oxide column chromatography using ethyl acetate/cyclohexane 1:1 as eluents, to afford the title compound **3a** as a white foam (0.413 g, 64% yield).

IR (cm^{-1}): 3310, 1740, 1717, 1682, 1650. ^1H NMR: (DMSO): 0.9–1.3 and 1.4–2.1 (m, m 17H), 2.3–2.5 (m, 4H), 2.97 and 3.2–3.4 (bd, m, 4H), 4.66 (m, 1H), 4.94 (m, 1H), [4.78 (d), 6.98 (m), 7.1–7.4 (m), 7.79 (t), 12H], 8.21–8.24 (m, 1H).

4-[[2-[[3-(1-Naphthyl)-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester ***3b***. *m/z*: 640, 608, 462, 251, 184, 135. IR (cm^{-1}): 3319, 1740, 1738, 1713,1655. ^1H NMR (DMSO): 1.9 (s, 3H), 1.4–2.1 (14H), 2.35–2.6 (m, 4H), 3.3 (s, 3H), 3.2–3.64 (m, 4H), 4.71 (bs, 1H), 4.9–5.04 (m, 1H), 6.92 (bs, 1H), 7.14–7.54 (m, 9H), 7.78–7.84 (m, 2H), 7.89 (m, 1H), 8.06 (bd, 1H), 8.18 (m,1H).

4-[[2-[[3-(2-Naphthyl)-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester ***3c***. IR (cm^{-1}): 3325, 1738, 1715,1653. ^1H NMR (DMSO): 0.8–2.0 (m), 2.10 (m), 2.35–2.5 (m, 4H), 3.1–3.6 (m, 4H), 3.53 (s, 3H), 4.71 (m, 1H), 4.9–5.0 (m, 1H), 6.78 and 6.84 (bs, bs, 1H), 7.1–7.4 (m, 9H), 7.64–7.9 (m), 8.1–8.24 (m, 1H).

4-[[2-[[3-(2-Quinolyl)-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester ***3d***. *m/z*: 641, 391, 363, 257. IR (cm^{-1}): 3317, 3184, 1734, 1668,1663. ^1H NMR (DMSO): 1.23 (s, 3H), 1.4–2.1 (m, 14H), 2.5–3.4 (m, 4H), 3.53 (s, 3H), 3.25–3.45 (m, 1H), 4.23 (d, 1H), 4.64–4.7 (m, 1H), 4.9–5.02 (m, 1H), 7.2–7.4 (m, 6H), 7.08 (s, 1H), 7.55 (t, 1H), 7.73 (t, 1H), 7.8–8.0 (m, 3H), 8.21 (bd, 2H).

4-[[2-[[3-(1-(4-Phenyl)phenyl)-2-methyl-1-oxo-2-adamantyl-oxycarbonylamino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester ***3e***. *m/z*: 667, 484, 210, 135. IR (cm^{-1}): 3321, 3190, 1738, 1653, 1585. ^1H NMR (DMSO): 1.4–2.1 (m, 17H), 2.4–2.54 (m, 4H), 3.54 (s, 3H), 3.2–3.4 (m, 4H), 4.6–4.7 (m, 1H), 4.9–5.0 (m, 1H), 6.88 (bd, 1H), 7.09 (t, 2H), 7.2–7.4 (m, 6H), 7.4–7.52 (m, 4H), 7.61 (d, 2H), 7.82 (bt, 1H), 8.21 (bd, 12H).

4-[[2-[[3-(2-(5,6,7,8)-Tetrahydronaphthyl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]propyl]amino]-1-(R)-phenylethyl]-amino-4-oxobutanoic acid methyl ester ***3f***. *m/z*: 644, 499, 366, 232. IR (cm^{-1}): 3315, 3184, 1736–1720, 1680, 1653. ^1H NMR (DMSO): 1.4–2.1 (m, 18H), 2.3–2.5 (m, 4H), 2.5–2.7 (m, 4H), 2.88 (bd, 1H), 3.22 and 3.24–3.46 (d, m, 3H), 3.54 (s, 3H), 4.69 (bs, 1H), 4.95 (m, 1H), [6.67 (bs), 6.7 (m), 6.76 (s), 6.81(s), 6.88 (m), 4H], 7.2–7.34 (m, 5H), 7.76 (m, 1H), 8.1–8.24 (2d, 1H).

4-[[2-[[3-(9-Phenanthryl)-2-methyl-1-oxo-2-adamantyloxycar-bonylamino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxo-butanoic acid methyl ester ***3g***. *m/z*: 691, 690, 559, 320, 251, 234, 135. IR (cm^{-1}): 3323, 1750–1628. ^1H-NMR (DMSO): 1.0–2.2 (m, 17H), 2.4–2.6 (m, 4H), 3.51 (s, 3H), 3.2–3.5 (m, 4H), 4.7 (m, 1H), 4.95 (m, 1H), 6.98 (bs), 7.0–7.5 (m), 7.54–7.9 (m), 8.18 (m, 2H), 8.75–8.86 (m, 2H).

4-[[2-[[3-(2-Benzo[b]thienyl)-2-methyl-1-oxo-2-adamantyl-oxycarbonylamino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester ***3h***. *m/z*: 646, 614, 428, 225. IR (cm^{-1}): 3323, 1750–1628. ^1H NMR (DMSO): 1.4–2.1 (m, 17H), 2.4–2.5 (m, 4H), 3.2–3.4 (m, 3H), 3.54 (s, 3H), 3.66 (d, 1H), 4.7 (s, 1H), 4.8–5.0 (m, 1H), 6.9–7.1 (bs, 1H), 6.99 (s, 1H), 7.2–7.4 (m, 7H), 7.70 (d, 1H), 7.8–7.94 (m, 2H), 8.22 (d, 1H).

4-[[2-[[3-(3-Pyridyl)-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid methyl ester ***3i***. *m/z*: 591, 484, 439 234, 207. IR (cm^{-1}): 3314, 1734–1717, 1682. ^1H NMR (DMSO): 1.5–2.2 (m, 17H), 2.4–2.8 (m, 4H), 3.66 (s, 3H), 3.1–3.5 (m, 4H), 4.8–5.3 (m, 2H), 6.5–7.1 (m, 2H), 7.16–7.5 (m, 8H), 8.35 (dd, 1H), 8.49 (m, 1H).

4-[[2-[[3-Aryl-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid derivatives ***4a–i***.

Compounds **4a–i** were obtained by hydrolysis of the corresponding methyl esters lithium hydroxide. A typical reaction procedure is as follows:

4-[[2-[[3-Phenyl-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid ***4a***. 0.1 M solution of lithium hydroxide (7.3 mL, 0.72 mmol) was added dropwise to a solution of the intermediate **3a** (0.4 g, 0.69 mmol) in tetrahydrofuran (40 mL) at 0 °C. The resulting solution was stirred at 0 °C for 3 h, then acidified with 1 M citric acid solution (0.8 mL) and concentrated in vacuo to give an oil which was dissolved in ethyl acetate (50 mL) washed with brine (50 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography using dichloromethane/methanol (90:10) as eluent, to give the title compound **4a** as an amorphous solid (0.2 g, 52%). *m/z*: 614, 598, 577, 576, 532, 460, 371 (found: C, 68.00; H, 6.88; N, 7.40; calc $C_{32}H_{39}N_3O_6$ requires C, 68.42; H, 7.00; N, 7.48%). IR (cm^{-1}): 3306, 1700–1640. ^1H NMR (DMSO): 1.0–2.1(m, 17H), 2.1–2.4 (m, 4H), 2.99 and 3.2–3.5 (bd, m, 4H), 4.64 (bs, 1H), 4.93 (m, 1H), [6.8–6.9 (m), 6.98 (m), 7.14–7.36 (m), 12H], 8.0–8.2 (bs, 1H), 8.36–8.56 (m, 1H).

4-[[2-[[3-(1-Naphthyl)-2-methyl-1-oxo-2-adamantyloxycarbonyl-amino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid ***4b***. *m/z*: 664, 648, 626, 460 (found: C, 71.10; H, 6.96; N, 6.70; calc $C_{37}H_{43}N_3O_6$ requires C, 71.01; H, 6.93; N, 6.72%). IR (cm^{-1}): 3500–3100, 3294, 1653. ^1H NMR (DMSO): 1.4–2.1 (m, 17H), 2.1–2.4 (m, 4H), 3.0–3.4 (m, 2H), 3.64 (bs, 2H), 4.68 (bs, 1H), 4.94 (m, 1H), 7.16 (bs, 1H), 7.19 (bs, 1H), 7.14–7.5 (m, 10H), 7.78 (d, 1H), 7.87 (dd, 1H), 8.09 (bs, 1H), 8.54 (bs 1H).

4-[[2-[[3-(2-Naphthyl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]-propyl]amino]-1(R)-phenylethyl]amino-4-oxobutanoic acid ***4c***. *m/z*: 664, 648, 626, 582, 448 (found: C, 71.00; H, 6.91; N, 6.69; calc $C_{37}H_{43}N_3O_6$ requires C, 71.01; H, 6.93; N, 6.72%). IR (cm^{-1}): 3314, 3184, 1653. ^1H NMR (DMSO): 1.1–2.1 (m, 17H), 2.2–2.4 (m, 4H), 3.1–3.5 (m, 4H), 4.72 (m, 1H), 4.97 (m, 1H), 6.84 and 6.92 (bs, bs, 1H), 7.14–7.34 (m, 6H), 7.4–7.56 (m, 3H), 7.7–7.9 (m, 3H), 8.0–8.02 (m, 2H), 8.36–8.56 (m, 1H).

4-[[2-[[3-(2-Quinolyl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]propyl]amino]-1(R)-phenylethyl]amino-4-oxobutanoic acid ***4d***. *m/z*: 649, 627, 475, 391, 363, 289, 176 (found: C, 68.95; H, 6.70; N, 8.90; calc $C_{36}H_{42}N_4O_6$ requires C, 69.03; H, 6.75; N, 8.95%) IR (cm^{-1}): 3292, 1699, 1663. ^1H NMR (DMSO): 1.27–1.56 (bs and m, 5H), 1.6–2.1 (m, 12H), 2.1–2.4 (m, 4H), 2.6–3.7 (m, 4H), 4.65 (bs, 1H), 4.94 (m, 1H), 7.16–7.4 (m, 6H), 7.54 (t, 1H), 7.72 (t, 1H), 7.92 (m, 2H), 8.19 (bd, 1H), 8.2–8.36 (bm, 1H), 8.73 (bm, 1H).

4-[[2-[[3-(1-(4-Phenyl)phenyl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid ***4e***. *m/z*: 690, 674, 6.52, 608, 474, 210, 167, 135 (found: C, 71.95; H, 6.98; N, 6.49; calc $C_{39}H_{45}N_3O_6$ requires C, 71.91; H, 6.96; N, 6.45%). IR (cm^{-1}): 3319–3200, 1715, 1653. ^1H NMR (DMSO): 2.29–2.33 (m, 4H), 3.03 (d, 1H), 4.67 (bs, 1H), 4.8–5.0 (m, 1H), 6.8–6.9 (bs and bs, 1H), 7.08 (t, 2H), 7.22 (m, 1H), [7.2–7.3 (m), 7.33 (t), 5H], 7.44 (t, 2H), 7.48 (t, 2H), 7.60 (d, 2H), 7.9–8.0 (bs, 1H), 8.3–8.44 (bs, 1H).

4-[[2-[[3-(2-(5,6,7,8)-Tetrahydronaphthyl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]-propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid ***4f***. *m/z*: 630, 188 (found: C, 70.50; H, 7.50; N, 6.65; calc $C_{37}H_{47}N_3O_6$ requires C, 70.56; H, 7.52; N, 6.67%). IR (cm^{-1}): 3500–3100, 3323, 1653, 1553. ^1H NMR (DMSO): 1.13 (s, 3H), 1.4–1.86 (m, 14H), 1.9–2.1 (m, 4H), 2.2–2.3 (m, 4H), 2.5–2.7 (m, 4H), 2.9–3.2 (d, 2H), 4.67 (s, 1H), 4.96 (m, 1H), 6.6–6.7 (m, 2H), 6.80 (s, 1H), 6.86 (dd, 1H), 7.18–7.24(m, 1H), 7.26–7.33 (m, 4H), 8.08 (bs, 1H), 8.48 (bd, 1H).

4-[[2-[[3-(9-Phenanthryl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]-propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid ***4g***. *m/z*: 676, 575, 560, 545 (found: C, 71.95; H, 6.57; N, 6.00; calc $C_{41}H_{45}N_3O_6$ requires C, 72.90; H, 6.72; N, 6.227%) IR (cm^{-1}): 3315–3192, 1684–1653. ^1H NMR (DMSO): 1.0–2.2 (m, 17H), 2.3 (m, 4H), 3.4–3.7 (m, 2H), 4.75 (bs, 1H), 5.0 (m, 1H), 7.04 (m, 1H), 7.2–7.3 (m, 5H), 7.47 (bs, 1H), 7.6–7.7 (m, 4H), 7.78 (m, 1H), 7.9–8.3 (bm, 2H), 8.38 (bd, 1H), 8.78–8.87 (m, 2H).

4-[[2-[[3-(2-Benzo[b]thienyl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid ***4h***. *m/z*: 670, 654, 632, 588, 532 (found: C, 65.80; H, 6.50; N, 6.22; calc $C_{35}H_{41}N_3O_6S$ requires C, 66.58; H, 6.54; N, 6.66%). IR (cm^{-1}): 3587–3200, 3315, 1688, 1657, 1547. ^1H NMR (DMSO): 1.2–2.2 (m, 17H), 2.2–2.4 (m, 4H), 3.0–3.5 (m, 3H), 3.70 (d, 1H), 4.68 (s, 1H), 4.8–5.1 (m, 1H), 6.9–7.2 (m, 2H), 7.2–7.4 (m, 7H), 7.70 (d, 1H), 7.82 (bs, 1H), 8.13 (bs, 1H), 8.43 (bm, 1H).

4-[[2-[[3-(3-Pyridyl)-2-methyl-1-oxo-2-adamantyloxycarbonylamino]propyl]amino]-1-(R)-phenylethyl]amino-4-oxobutanoic acid ***4i***. *m/z*: 577, 462, 371, 313, 135 (found: C, 66.45; H, 6.94; N, 9.70; calc $C_{32}H_{40}N_4O_6$ requires C, 66.58; H, 6.54; N, 6.66%). IR (cm^{-1}): 3500–3200, 2700, 1695. ^1H NMR (DMSO): 1.11 (bs, 3H), 1.5 (t, 2H), 1.6–1.9 (m, 8H), 1.9–2.1 (m, 4H), 2.2–2.4 (m, 4H), 3.02 (bd, 1H) ,4.65 (bs, 1H), 4.95 (m, 1H), 6.9–7.0 (bs, 1H), 7.2–7.4 (m, 7H), 8.0–8.01 (bs, 1H), 8.21 (bs, 1H), 8.35–8.5 (bs, 1H), 8.39 (m, 1H).

DL-α-Methyl-3-(aryl)alanine methyl ester ***7a–i***

These were synthesized according to literature procedure [25, 26]. The analytical and spectral data were as follows:

D,L-α-Methyl-3-(2-quinolyl)alanine methyl ester **7d**. ^1H NMR (DMSO): 1.47 (s, 3H); 2.05 (bs, 2H), 3.18 (d, 1H), 3.57 (d, 1H), 3.68 (s, 3H), 7.24 (d, 1H), 7.48 (m, 1H), 7.66 (m, 1H), 7.76 (dd, 1H), 7.97 (d, 1H), 8.05 (d, 1H). IR (cm^{-1}): 1734, 1618, 1601.

DL-α-Methyl-3-(1-diphenyl)alanine methyl ester ***7e***. *m/z*: 270, 210, 192, 167. IR (cm^{-1}): 3400, 1734, 1599. ^1H NMR (DMSO): 1.42 (s, 3H), 1.61 (bs, 2H), 2.84 (d, 1H), 3.17 (d, 1h), 3.72 (s, 3H), 7.22 (d, 2H), 7.33 (t, 1H), 7.42 (t, 2H); 7.51 (d, 2H), 7.57 (d, 4H).

DL-α-Methyl-3-[2-(5,6,7,8)-tetrahydronaphthyl]alanine methyl ester ***7f***. *m/z*: 248, 188. IR (cm^{-1}): 3380–3300, 1734, 1599. ^1H NMR ($CDCl_3$): 1.39 (s, 3H), 1.72–1.84 (m, 7H), 2.66–2.80 (m), 2.79 (m, 5H), 3.07 (d, 1H), 3.72 (s, 3H), 6.84 (m, 2H), 6.97 (m, 1H).

DL-α-Methyl-3-(9-phenanthryl)alanine methyl ester ***7g***. IR (cm^{-1}): 1726 ^1H NMR (DMSO): 1.52 (s, 3H), 3.42–3.62 (dd, 2H), 3.54 (s, 3H), 7.56–7.70 (m, bs, 5H), 7.80 (dd, 1H), 8.20 (dd, 1H), 8.65 (d, 1H), 8.72 (dd, 1H).

DL-α-Methyl-3-(2-benzo[b]thienyl)alanine methyl ester ***7h***. *m/z*: 250, 190, 102. IR (cm^{-1}): 3381, 3254, 1734 ^1H NMR (DMSO): 1.69 (bs, 2H), 1.44 (s, 3H), 3.1 (d, 1H), 3.44 (d, 1H), 3.78 (s, 3H), 7.08 (s, 1H), 7.27 (td, 1H), 7.69 (dd, 1H), 7.76 (dd, 1H).

DL-α-Methyl-3-(3'-pyridyl)alanine methyl ester ***7i***. IR (cm^{-1}): 3377–3308, 1732. ^1H NMR (DMSO): 1.40 (s, 3H), 2.82 (d, 1H), 3.09 (d, 1H), 3.72 (s, 3H), 7.22 (m, 1H), 7.52 (m, 1H), 8.43 (d, 1H), 8.50 (dd, 1H).

N-[(2-Adamantyloxy)carbonyl]-DL-α-methyl-3-(aryl)alanine ***1a–i***

These were synthesized according to literature procedure [26]. The analytical and spectral data were as follows:

N-[(2-Adamantyloxy)carbonyl]-DL-α-methyl-3-(2-quinolyl)-alanine ***1d***. IR (cm^{-1}): 3400, 3385, 1707, 1697. ^1H NMR (DMSO): 1.5 (s, 3H), 1.4–2.0 (m, 14H), 3.43 (d, 1H), 3.56 (d, 1h), 4.59 (s, 1H), 6.45 (s, 1H), 7.37 (t, 1H), 7.49 (t, 1H), 7.66 (t, 1H), 7.81 (d, 1H), 7.85 (d, 1H), 8.09 (d, 1H).

N-[(2-Adamantyloxy)carbonyl]-DL-α-methyl-3-(1-diphenyl)-alanine ***1e***. IR (cm^{-1}): 3500–3200, 1691, 1607 ^1H NMR (DMSO): 1.5–2.1 (m, 17H), 3.32 (d, 1H), 3.38 (d, 1h), 4.61 (s, 1H), 6.49 (s, 1H), 7.16 (d, 2H), 7.30 (t, 1H), 7.41 (dt, 2H), 7.43 (d, 2H), 7.56 (d, 2H).

N-[(2-Adamantyloxy)carbonyl]-DL-α-methyl-3[2(5,6,7,8)-tetrahydronaphthyl]alanine ***1f***. *m/z*: 410, 366, 232. IR (cm^{-1}): 3416–3333, 1717. ^1H NMR (DMSO): 1.30 (bs, 3H), 1.5 (m, 2H), 1.6–2.1 (m, 16H), 2.5–2.7 (m, 4H), 3.04 (m, 2H), 4.64 (bs, 1H), 6.66 and 6.71 and 6.74–6.94 (bs, s, m, 4H), 12.70 (bs, 1H).

N-[(2-Adamantyloxy)carbonyl]-DL-α-methyl-3-(9-phenanthryl)-alanine ***1g***. IR (cm^{-1}): 3410, 1707–1686, 1599 ^1H NMR (DMSO): 1.51 (bs, 3H), 1.2–2.0 (m, 14H), 3.5–3.8 (m, 2H), 4.65 (m, 1H), 6.76 (bs, 2H), 7.4–7.8 (m, 6H), 8.35 (m, 1H), 8.77 (m, 2H).

N-[(2-Adamantyloxy)carbonyl]-DL-α-methyl-3-(2-benzo[b]-thiophenyl)alanine ***1h***. IR (cm^{-1}): 3398, 1684, 1583 ^1H NMR (DMSO): 1.41 (s, 3H), 1.4–1.54 (m, 2H), 1.6–1.96 (m, 10H), 2.07 (m, 2H), 3.4–3.6 (2d, 2H), 4.64 (bs, 1H), 6.63 (bs, 1H), 6.99 (s, 1H), 7.24 (m, 2H), 7.63 (d, 1H), 7.76 (d, 1H).

N-[(2-Adamantyloxy)carbonyl]-DL-α-methyl-3-(3'-pyridyl)-alanine ***1i***. IR (cm^{-1}): 3500–3080, 1717, 1653. ^1H NMR (DMSO): 1.43 (s, 3H), 1.48 (bs, 2H), 1.6–2.0 (m, 12H), 3.27 (m, 2H), 4.60 (bs, 1H), 6.44 (bs, 1H), 7.16 (d + d, 1H), 7.41 (d, 1H), 8.25 (d, 1H), 8.31 (dd, 1H).

Acknowledgments

The authors thank members of the Analytical Sciences Department for determination of the spectral and micro-analytical data for the compounds reported herein. We are particularly grateful to C Marchioro and S Davalli from the Spectroscopy Laboratory and M Hamdan from the Mass Spectrometry Laboratory and we also thank R Pellicciari for his support and advice during the course of these studies.

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