Bioorganic & Medicinal Chemistry, Vol. 1, No. 1, pp. 45-58, 1993
Printed in Great Britain

0968-0896/93 $6.00 + .00
© 1993 Pergamon Press Ltd

Modification Of "Peptoid" CCK-B Antagonists To Probe Requirements For CCK-B Agonist Activity

Andrew E. Davey and David C. Horwell
Parke-Davis Neurosciences Research Centre, Addenbrooke's Hospital Site, Hills Road, Cambridge CB2 2QB, U.K.

(*Received* 12 *January* 1993)

Abstract–This paper describes the use of the non-peptidal *N*-(2-adamantyloxycarbonyl)-α-methyl tryptophan phenylethylamide template of the "peptoid" CCK B antagonist compounds **1** as a basis to probe the functional group requirements of the CCK B receptor in order to produce an agonist response. Comparison of the peptoid template with inter-group distances in a fully extended conformation of the endogenous CCK-B agonist CCK 30-33 led to the design of a series of compounds **2** containing additional Ph, COOH and $CONH_2$. functions at distances from the Trp indole ring that are able to mimic those in the natural ligand. The effect of these modifcations was then assessed by measurement of CCK B binding affinities and potential agonist efficacy was investigated by comparison with contraction of guinea-pig isolated stomach corpus muscle strip stimulated by the CCK-B agonist pentagastrin. All compounds showed sub-micromolar binding affinities with each series displaying discernible dependence on intermediate chain length. All compounds (except **2f**) were shown to be good CCK B antagonists; no compounds showed significant agonist activity up to a concentration of 1 μM.

Introduction

The C-terminal octapeptide of cholecystokinin (CCK 26-33) is present in the periphery where it acts as a hormonal regulator of various gut functions[1–3] and in the brain where its role is less clear, but seems to be that of a neurotransmitter.[4] Furthermore, it is now well known that pancreatic ("peripheral type" or CCK A) and brain/gastrin ("central type" or CCK B) receptors differ in structure and ligand specificity,[5–6] although the respective roles of both types of receptors in many CCK-induced responses such as satiety, analgesia and neuroleptic effects remain to be elucidated. It is therefore of interest to design non-peptide agonist and antagonist analogues or mimetics of CCK with high potency and selectivity for the CCK-A and CCK-B receptors which are metabolically stable and hence useful as robust pharmacological probes. Numerous examples of modified peptides exhibiting varying degrees of receptor subtype selectivity and functional response as agonists and antagonists of both CCK A and CCK B exist.[7–20] There are now also several well recognised classes of non-peptide CCK A and CCK B antagonists.[7,8,20] However no examples of robust, selective non-peptide agonists of either subtype exist.

Our interest in this field developed from the discovery of potent "dipeptoid" antagonists of CCK B of type **1** (Figure 1) which possessed binding affinities (IC_{50}) in the region of 10^{-7} to 10^{-9} M.[21,22] For example, compound CI-988 (**1**, R = $NHCOCH_2CH_2CO_2H$) has K_i = 1.7 nM at the CCK-B receptor. This paper describes our studies which attempt to use the template of these non-peptide molecules as a basis relative importance of the backbone amide linkages,[11,18,23] the Asp[15,16,23] and Phe[10,12,15,19] side chains and the primary amide function[9,13,14,17] in determining agonist properties in peptide analogues of CCK 30-33 has been investigated by several groups. We wished to test the feasibility of extrapolating these findings to derivatives containing our "peptoid" structure **1**, whilst specifically addressing:

(i) the effect of introducing an aromatic ring (to mimic the Phe residue) at a calculated through bond distance from the Trp indole ring and whether the phenyl ring of structures **1** corresponds to the phenyl ring of the Phe residue of CCK 30-33, and

(ii) the effect of introducing a primary amide function in these molecules.

It would be possible to address the measurement of interatomic or inter-group distances in these compounds in two ways; either by

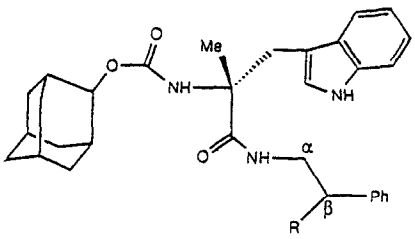
(i) molecular modelling/conformational analysis and design of more rigid analogues based on measurement of through-space distance in selected conformations, or

(ii) measurement of through-bond distance of the most extended conformation.

We adopted the second method since this would provide compounds with sufficiently flexible side-chains to search for the available accessory binding sites on the receptor.

Abbreviations— **CCK:** cholecystokinin; **Boc:** *t*-butyloxy-carbonyl; **2-Adoc:** 2-adamantyloxycarbonyl; **PFP:** pentafluorophenol; **DCC:** *N,N'*-dicyclohexylcarbodiimide; **DCU:** *N,N'*-dicyclohexylurea; **HOBt:** 1-hydroxybenzo-triazole; **DMAP:** 4-(*N,N*-dimethylamino)pyridine; **TFA:** trifluoroacetic acid.

Keywords— CCK B agonism: Sub-micromolar"peptoid" antagonists: *N*-(2-Adamantyloxycarbonyl)-α-methyltrypt-ophan phenylethylamides: Through-bond distance measurements: "Molecular components strategy": Ariens' "three-ligand concept": Variable length phenylalkyl chain.



1 (R = H or -(spacer)-COOH)

Figure 1 "Non-peptide" binding moiety **1**.

Trigonometrical or Dreiding model analysis of a fully extended conformation of the tetrapeptide CCK 30-33 shows values of ca. 15.9 Å and 12.3 Å for distances between the Trp indole and Phe phenyl rings and between the Trp indole ring and the Asp carboxylate carbon respectively. Both these groups have been suggested as essential for agonism in the tetrapeptide and that the inter-group distances are critical.[15,24] We wished therefore to build these interatomic distances into our compounds to determine whether binding sites for these side chain functions could be accessed in these peptoid templates.

We have already shown that the introduction of a carboxylate function in these molecules at similar fully extended distances from the indole ring to that in the natural ligand (**1**, R = $NHCO(CH_2)_{2-3}COOH$) results in analogues with an increase of ca. 10-fold receptor affinity over the simpler phenylethylamides (**1**, R = H).[22] However the phenyl ring of **1** lies at a through bond distance of only 8.4Å from the indole (cf. ca. 15.9Å for the natural tetrapeptide) when similarly measured. Assuming identical binding domains for these compounds and the natural ligands, it is not entirely clear from analysis of binding data[21,25] whether the phenyl ring is accessing the Phe binding site of the CCK-B receptor specifically or merely locating an alternative closer hydrophobic pocket. We sought therefore to add a phenyl ring at a fully extended distance approximating to that in the natural ligand while retaining conformational flexibility. We envisaged this to be attached via the α-position by an amide linkage. A series of ω-phenylbutyl-, pentyl- and hexyl-amides would then provide indole-phenyl ring through bond distances in the range 14.7–17.2Å. The importance of the original peptoid C-terminal phenyl ring (Ph in Fig. 1) could then be assessed by comparison with the analogue with modified structures where the original Ph group is removed. These considerations led to the design of compounds **2a–i** as initial synthetic targets (Scheme I).

It has also been postulated that Phe^{33} of CCK 30-33 exhibits a binding role through the aromatic moiety and a functional role through the C-terminal primary amide group.[13] Consequently we sought to further elaborate the target compounds by introduction of a primary amide function. We chose to retain the topographical relationship of the amide function and phenyl ring, leading us to target for synthesis the more synthetically complex analogues **2j-l**.

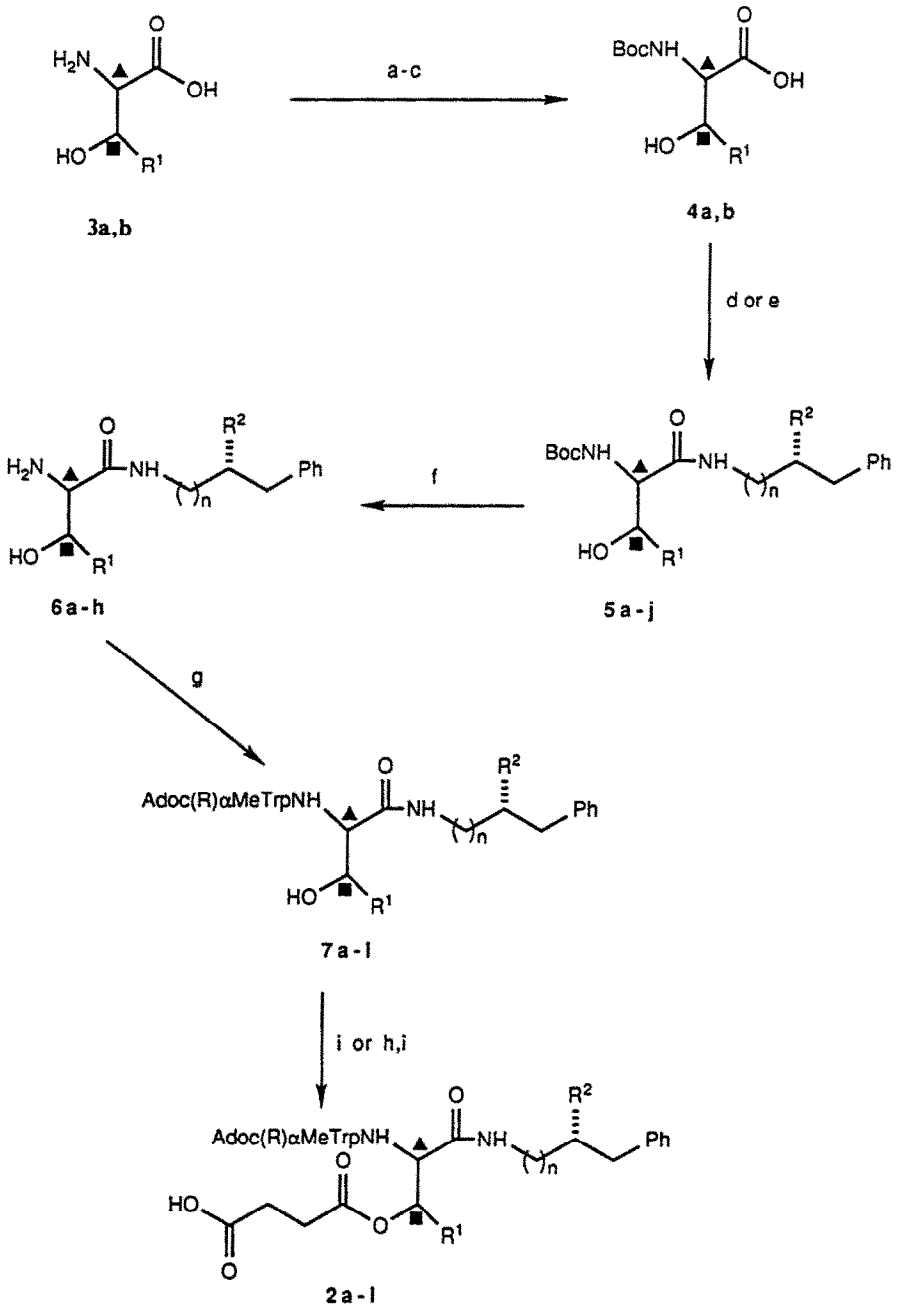
Chemistry

N-(2-Adoc)-(*R*)-α-methyltryptophan, the moiety common to all compounds reported here was synthesised as reported previously.[22]

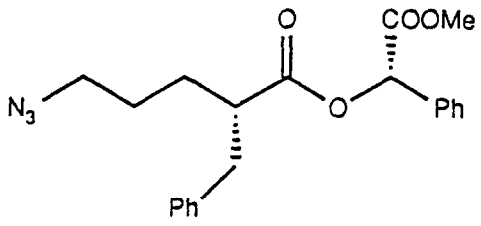
Compounds **2a–f** were prepared as detailed in Scheme I from the common precursor (±) *threo*-3-phenylserine **3a**. Esterification via the acid chloride ($SOCl_2$/MeOH) gave the methyl ester[26] in good yield. Subsequent N-protection with di-*t*-butyl dicarbonate followed by ester hydrolysis provided the N-Boc-protected acid **4a** in 62% overall yield from the free amino-acid. ^1H NMR analysis of these compounds could reveal no epimerization of the α-position in any of these steps. Coupling of this racemic acid to 4-phenylbutylamine, 5-phenylpentylamine and 6-phenylhexylamine via the active pentafluorophenol (PFP) ester under standard conditions gave the ω-phenylalkylamides **5** whose N-protective Boc functionality could be cleaved in TFA at room temperature, providing the free amino-amides **6a-d** in moderate-to-good yields. Active ester methodology was employed to couple *N*-(2-Adoc)-(*R*)-α-methyltryptophan to these amines, but here the 1-hydroxybenzotriazole (Bt) ester routinely gave higher yields of the diastereomeric products **7a–f** than the PFP intermediate. After chromatographic separation, each isomer was *O*-acylated with succinic anhydride under DMAP catalysis to afford the products **2a-f** as single isomers.

The synthesis of analogues **2g–i**, simplified by the removal of one phenyl ring, followed a similar course from the commercially available (*S*)-*N*-*t*-butoxycarbonylserine **3b** (Scheme I).

Target compounds **2j–l** containing additional primary amide functionality ($R_2 = CONH_2$) were synthesised by similar coupling methods, but here the presence of a chiral centre in the alkyl chain necessitated an asymmetric synthesis of ω-amino-acid **12**. For this we employed Evans' asymmetric alkylation of *N*-acyloxazolidinones[27] outlined in Scheme II. Thus 5-azidopentanoyl chloride **8** was prepared by literature methods[28] in a three step process from ethyl 5-bromopentanoate. We found that the subsequent two step process of Evans chiral auxiliary coupling and asymmetric benzylation could best be accomplished without intermediate purification to give the *N*-acyloxazolidinone **10** in overall 50% yield. Standard hydroperoxide hydrolysis[29] of the oxazolidinone then revealed the chiral azido-acid **11**. The enantiomeric purity of this acid was determined as follows; diastereomeric derivatisation by (*S*)-methyl mandelate[30] produced ester **13** whose ^1H NMR spectrum showed only a single methoxy signal (δ 3.68, $CDCl_3$). Comparative derivatisation using the racemic mandelate gave a diastereomeric mixture of esters in a 1:1 ratio whose methoxy signals were easily distinguishable (δ 3.68, 3.71) indicating that the acid **11** is produced in >95% e.e. (i.e. pure to the detection limits of the analytical method).



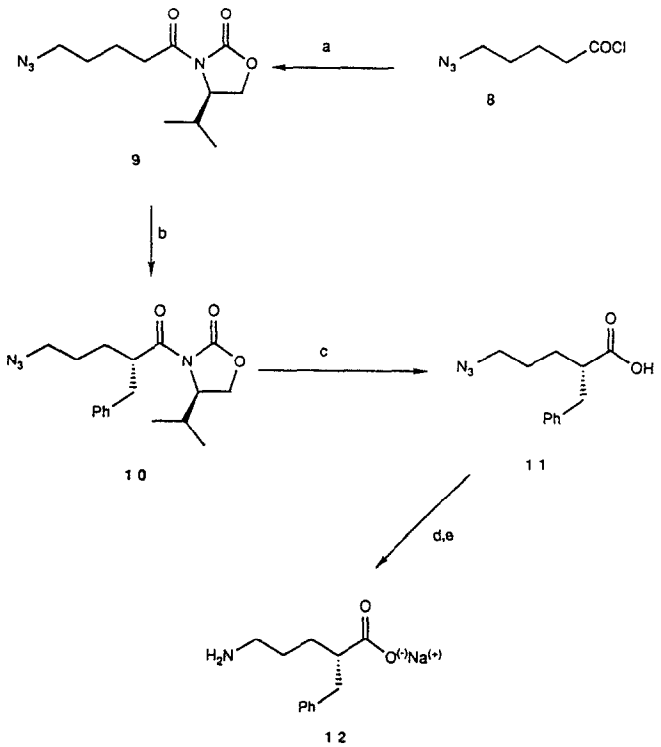
Scheme I. General synthetic scheme for compounds **2**. (a) $SOCl_2$/MeOH; (b) Boc_2O/Na_2CO_3; (c) LiOH; (d) PFP/DCC, then $Ph(CH_2)_{4-6}NH_2$; (e) PFP/DCC/14, then DCC/HOBt/aq. NH_3; (f) TFA; (g) Adoc-α-MeTrpOBt; (h) separate isomers; (i) DMAP/succinic anhydride; **4a**, R^1=Ph, ■▲ = *RS* + *SR*; **b**, R^1=H, ▲ = *S*; **5a**, n=2, R^1=Ph, R^2=H, ■▲ = *RS* + *SR*; **b**, n=3, R^1=Ph, R^2=H, ■▲ = *RS* + *SR*; **c**, n=4, R^1=Ph, R^2=H, ■▲ = *RS* + *SR*; **d**, n=2, R^1=H, R^2=H, ▲ = *S*; **e**, n=3, R^1=H, R^2=H, ▲ = *S*; **f**, n=4, R^1=H, R^2=H, ▲ = *S*; **g**, n=3, R^1=Ph, R^2=COOH, ■▲ = *RS* + *SR*; **h**, n=3, R^1=H, R^2=COOH, ▲ = *S*; **i**, n=3, R^1=Ph, R^2=$CONH_2$, ■▲ = *RS* + *SR*; **j**, n=3, R^1=H, R^2=$CONH_2$, ▲ = *S*; **6a**, n=2, R^1=Ph, R^2=H, ■▲ = *RS* + *SR*; **b**, n=3, R^1=Ph, R^2=H, ■▲ = *RS* + *SR*; **c**, n=4, R^1=Ph, R^2=H, ■▲ = *RS* + *SR*; **d**, n=2, R^1=H, R^2=H, ▲ = *S*; **e**, n=3, R^1=H, R^2=H, ▲ = *S*; **f**, n=4, R^1=H, R^2=H, ▲ = *S*; **g**, n=3, R^1=Ph, R^2=$CONH_2$, ■▲ = *RS* + *SR*; **h**, n=3, R^1=H, R^2=$CONH_2$, ▲ = *S*; **7a**, n=2, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer A); **b**, n=2, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer B); **c**, n=3, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer A); **d**, n=3, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer B); **e**, n=4, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer A); **f**, n=4, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer B); **g**, n=2, R^1=H, R^2=H, ▲ = *S*; **h**, n=3, R^1=H, R^2=H, ▲ = *S*; **i**, n=4, R^1=H, R^2=H, ▲ = *S*; **j**, n=3, R^1=Ph, R^2=$CONH_2$, ■▲ = *RS* or *SR* (isomer A); **k**, n=3, R^1=Ph, R^2=$CONH_2$, ■▲ = *RS* or *SR* (isomer B); **l** n=3, R^1=H, R^2=$CONH_2$, ▲ = *S*; **2a**, n=2, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer A); **b**, n=2, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer B); **c**, n=3, R^1=Ph, R^2=H, ■▲ = *RS* or SR (isomer A); **d**, n=3, R^1=Ph, ■▲ = *RS* or *SR* (isomer B); **e**, n=4, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer A); **f**, n=4, R^1=Ph, R^2=H, ■▲ = *RS* or *SR* (isomer B); **g**, n=2, R^1=H, R^2=H, ▲ = *S*; **h**, n=3, R^1=H, R^2=H, ▲ = *S*; **i**, n=4, R^1=H, R^2=H, ▲ = *S*; **j**, n=3, R^1=Ph, R^2=$CONH_2$, ■▲ = *RS* or *SR* (isomer A); **k**, n=3, R^1=Ph, R^2=$CONH_2$, ■▲ = *RS* or *SR* (isomer B); **l**, n=3, R^1=H, R^2=$CONH_2$, ▲ = *S*.



13

Figure 2 Mandelate derivative of azido-acid **13**.

Azido-acid **11** was then incorporated into the synthesis of compounds **2j–l** as before (Scheme I); the sodium salt of acid **11** underwent smooth hydrogenation to the amino-acid sodium salt **12** which was coupled without purification to the PFP ester of the respective acid **4a** or **4b** to give the Boc-protected amino-acids **5g,h**. These acids were subsequently converted to their primary amides **5i,j** under mild conditions[31] and converted to final products **2j–l** in a three step process directly analogous to the synthesis of analogues **2a–i**.



Scheme II. Synthesis of enantiomerically pure (*S*)-5-amino-2-benzyl-pentanoic acid sodium salt via Evans' asymmetric alkylation. (a) BuLi/(4*R*)-(+)-4-isopropyl-2-oxazolidinone; (b) $NaN(SiMe_3)_2/PhCH_2Br$; (c) LiOOH; (d) NaH; (e) H_2/Pd-C.

Results and Discussion

The approach used here to design compounds **2** follows closely that of Farmer's "molecular components strategy"[32] with modifications to accommodate a moiety (**1**) already known to provide high CCK B receptor affinity. Using this strategy, ligands containing functional groups to mimic the amino-acid side chains thought to be involved in binding interactions in the natural peptide are attached to a central pivotal atom via flexible side chains to allow for potential conformational shifts on binding. In these modifications, compounds **2** retain the complete configurational integrity of moiety **1** while additional groups are connected to this sub-structure at variable chain lengths from the indole ring.

A working hypothesis for the mode of binding of compounds **1**, which assumes a common receptor site with CCK 30-33, holds that the essential indole ring of **1** is able to locate the same CCK 30-33 Trp^{30} indole recognition site on the receptor. It would then be possible for the phenyl ring and adamantyl group of **1** to interact with two hydrophobic pockets. Due to the non-rigid nature of these molecules they may possibly access those pockets in an accessible low energy conformation in a folded form that recognises the Met and Phe side chains of CCK 30-33. Ariens' three-ligand concept[32] suggests that the binding affinities displayed by compounds **1**[22] and **2** (Table 1) could be easily achieved by three such groups appropriately located. Furthermore the relatively modest increase in binding affinity conferred by the succinate carboxylate group (≤1.4 kcal/mol) in compounds **1**[25] suggests that a tight ion-pair interaction is not involved, despite the fully extended distances between the indole and succinate carboxylate groups in compounds **1** and the Trp^{30} indole and Asp^{32} carboxylate groups in CCK 30-33 being similar in through bond distance (13.3Å vs 12.3Å). This is further supported by evidence which attests to the importance of the Asp^{32} residue of CCK 30-33 for an agonist response.[15,16,23] That compounds **1** bind with high affinity but are antagonists is commensurate with a model where the succinate carboxylate group cannot locate the corresponding Asp^{30} receptor site. However, the presence of such a group could induce a favourable conformation in the molecules via inter- or intramolecular hydrogen bonding, possibly bringing the hydrophobic groups closer to their respective binding sites. Binding of the phenyl ring of **1** may then prevent participation of the carboxylate group in a functional response. Addition to or replacement of this phenyl ring by another phenyl ring attached at a calculated distance from the indole ring system may allow both the new phenyl ring and the carboxylate function to locate their recognition sites without such a mutual hindrance.

The model produced by Pincus *et al.*[33] of an energy minimised conformation of *N*-acetyl CCK 30-33 derived by computational conformational analysis, indicates that the peptide can adopt an α-helical conformation where the

Trp indole and Phe phenyl rings are in close proximity. Superimposition of Dreiding models of compounds **1** and **2** show good overlap of the Trp-indole and Phe-phenyl ring with the peptide. Furthermore the flexibility of these structures also allows superimposition of the primary amide function of compounds **2j–l** with that of the peptide, which may be important for the molecule to be able to elicit an agonist functional response.[9,13,14,17]

Table 1. CCK B receptor data for compounds **2**

	R1	(a)	n	R2	IC50 (b)	pKb (c)
2a	Ph	isomer A	2	H	86(78-96)	NT
2b	Ph	isomer B	2	H	217(156-303)	6.8
2c	Ph	isomer A	3	H	78(65-94)	6.6
2d	Ph	isomer B	3	H	109(96-124)	7.9
2e	Ph	isomer A	4	H	344(306-387)	5.5
2f	Ph	isomer B	4	H	644(531-782)	d
2g	H	S	2	H	331(311-354)	NT
2h	H	S	3	H	118(94-150)	NT
2i	H	S	4	H	450(384-529)	NT
2j	Ph	isomer A	3	$CONH_2$	320(240-400)	NT
2k	Ph	isomer B	3	$CONH_2$	23 (19 - 29)	e
2l	H	S	3	$CONH_2$	320(240-400)	NT

[a] ■▲ relative configuration *RS* or *SR* (absolute unknown).
[b] IC_{50} represents the concentration (nM) producing half maximal inhibition of specific binding of [^{125}I] Bolton Hunter CCK-8 to CCK receptors in the mouse cerebral cortex. The values given are the geometric mean and the range from at least two separate experiments.
[c] pK_b represents the logarithmic affinity constant as calculated from the function log{(dose ratio - 1)/[antagonist]} in the guinea-pig isolated stomach corpus muscle strip preparation, measuring dose–response curves to pengastrin ± test compound.[34] All compounds dissolved in 100% DMSO and tested at 1 μM organ bath concentration. No compounds tested showed significant agonist activity up to a concentration of 1 μM.
[d] No significant antagonism.
[e] No significant dose dependent agonist activity up to a concentration of 1 μM.
NT = not tested.

Inspection of these data reveals a discernible trend in binding affinity with respect to length of alkyl chain within the three series **2a,c,e, 2b,d,f** and **2g,h,i**. Each series shows maximum affinity in compounds where n = 3, whose fully extended indole–phenyl distance corresponds most closely to that found in the natural peptide. Whilst the affinity differences between n = 2 and n = 3 are similar, increasing the chain length to n = 4 causes a more marked drop in affinity (ca. 1 kcal/mol).

Comparison of these series also reveals that little or no extra binding energy is lost by removal of the original phenyl rings (**2g** vs **2a,b**; **2h** vs **2c,d**; **2i** vs **2e,f**). This may indicate that the ω–phenylalkyl ring in compounds **2** provides a hydrophobic binding interaction of a similar magnitude to the phenylethylamide Ph of structures **1**, rendering the latter superfluous. The observation that the members of the isomer A series (**2a,c,e**) apparently have a generally slightly higher affinity for the receptor than their respective counterparts (**2b,d,f**) may indicate a general but minor conformational feature of the series as a whole.

Results from the functional assay guinea-pig isolated stomach corpus muscle strip (Table 1) for these compounds (**2a–i**) shows them all (except **2f**, where n = 4) to be competitive antagonists with different potencies. The reported logarithmic affinity constants (pK_b) parallel the IC_{50} binding data. No agonist response was seen for any members of the series. A possible explanation for lack of agonist properties is that while the hydrophobic binding requirements of the receptor are at least partially fulfilled in these compounds, the triggering event, possibly mediated in the natural ligand by the Asp^{30} carboxylate[15,16,23] or Phe^{33} residue,[9,13,14,17] cannot take place due to the conformational restrictions imposed by the template used which prevents correct positioning of the succinate carboxylate function. Alternatively the absence of agonist properties could be due to the lack of a primary amide function. Compounds **2j–l** containing a primary amide did not show agonist properties either. However, the higher affinity isomer **2k** did produce some potentiation of stimulation but in a non-dose related manner in this assay. Taking the antagonism elicited by these compounds into consideration, the possibility remains that one or more of the binding functions in compounds **2** is locating a specific local *accessory* site on the receptor or associated lipid, either preventing access of the functional group ('participation' model) or preventing the specific conformational change ('allosteric' model) responsible for triggering the agonist response.[34]

Conclusion

The derivatives of the template in Fig. 1 that have been chosen as probes to introduce pharmacological agonism into the peptoid CCK-B antagonists **1** still retain weak antagonist properties but with no evidence of agonist activity on the guinea-pig isolated corpus muscle strip assay, a tissue containing both CCK-A and CCK-B receptors. The chemical modification of small molecule non-peptide hormones and neurotransmitters to produce their corresponding pharmacological antagonist has historical precedent, e.g. adrenaline/noradrenaline → β-blockers (dichloroisoproterenol, propranolol); histamine → H_2 antagonists (cimetidine, ranitidine). However, modification of such an antagonist to convert it back into the corresponding agonist has less precedent. A notable example however, has been the discovery of the potent and selective H_2 agonist impromidine (SKF 92676).[35] In this case, the core template of the parent guanidine moiety of the H_2 antagonist cimetidine had been chain extended by a propylimidazole moiety to restore potent agonist properties. This restoration of agonist properties appears not to have been paralleled in our peptoid template. This

may suggest that rotation of the peptide bonds in the flexible tetrapeptide CCK 30-33 may well be critical in allowing an agonist producing conformation to be adopted. However, due to the low affinity of these compounds (Table 1) compared with the efficacious agonists pentagastrin and CCK 30-33, agonism may not be apparent at the doses used. It appears that the tetrapeptide CCK 30-33 remains the minimum fragment of CCK that can be modified to show agonist properties at the CCK-B receptor.[11,12,14,15,17,19,20]

Experimental Section

Biological Assays

(1) CCK-B Receptor binding assay. These were performed as previously described.[22]

(2) Guinea-pig isolated corpus muscle strip assay.[36]
Tissue preparation. Adult male Dunkin–Hartley guinea-pigs (wt 330–400g) with free access to food and water were sacrificed by cervical dislocation and the stomach rapidly removed. The fundus was discarded and the stomach was opened along the greater curvature, pinned out on a petri-dish with the mucosa uppermost. The mucosal and submucosal layers were removed by dissection to reveal the underlying smooth muscle layer. Strips of circular muscle (2 x 25 mm) from the corpus region of the stomach were mounted in siliconised 3 mL organ baths containing Krebs–Henseleit solution of the following composition (mm); NaCl, 118; KCl, 5.9; $MgSO_4$, 1.2; $CaCl_2$, 2,5; NaH_2PO_4, 1.2; $NaHCO_3$, 25.5; glucose, 5.5. The solution was maintained at 37°C and was gassed continuously with a mixture of O_2:CO_2; 95:5. After preliminary experiments the buffer was modified to include 5 μM indomethacin. Isometric contractile responses were measured with Grass FT.03 force displacement transducers and recorded on Graphtec Linearcorders (Mk VII).

Experimental procedure. Tissues were placed under 1 g tension and allowed to equilibrate for 30 min, after which time they were contracted with a submaximal dose of carbamylcholine (10 nM). Using a 12 min dose cycle, dose–response curves were established for a range of agonists that included CCK 26-33 (sulphated), CCK 26-33, gastrin 1, CCK (30-33) and pentagastrin. Drugs were added in volumes not exceeding 10 μL. No contractile response was observed for any compound in Table 1, except for compound **2k**, but the small contractile response was not dose related in concentrations up to 1 μM and was not considered significant or indicative of agonist activity with this compound. For Schild plot studies tissues were exposed to antagonists for 15 min before re-exposure to agonists. Contractile responses to exogenously applied agonists were expressed as absolute changes in tension and then transformed to a percentage of the maximal response achieved for that agonist. Responses obtained to agonists in the presence of antagonists were expressed as a percentage of the control maximum response obtained in the same tissue preparation.

Chemistry

Melting points were determined with a Mettler FP80 or a Reichert Thermovar hotstage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker AM300 spectrometer; chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane. IR spectra were recorded with the compound either neat (oils and liquids) or as a Nujol mull on a sodium chloride disc on a Perkin-Elmer 1750 Fourier transform spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Finnegan 4500 or ZAB-E VG Analytical. Elemental analyses indicated by the symbols of the elements were within ± 0.4% of theoretical values and were determined by Medac Ltd., Uxbridge, U.K. Normal phase silica gel used for chromatography was Merck No. 9385 (230–400 mesh); reverse-phase silica gel used was Lichroprep RP-18 (230-400 mesh); both were supplied by E. Merck, A.G., Darmstadt, Germany. Anhydrous solvents were purchased in septum-capped bottles from Fluka Chemicals Ltd., Glossop, U.K., and dispensed by syringe. *N*-(2-Adoc)-(*R*)-α-methyltryptophan was prepared as previously described.[22] All other chemicals were purchased from the Aldrich Chemical Co. Ltd., Gillingham, U.K., and were used without further purification. Standard extractive workup (solvent specified) refers to the following sequence of operations; the material was dissolved in or extracted with the specified organic solvent and this extract washed with the specified aqueous reagent solution(s), dried over magnesium sulphate, filtered and concentrated to dryness.

(+)-threo-3-Phenylserine methyl ester. Thionyl chloride (45.0 9,28 mL,375 mmol,5 equiv.) was added dropwise to a methanolic (150 mL) solution of the acid (15.0 9, 75 mmol) at -15°C (ice/salt) and the mixture allowed to warm slowly to room temperature. The clear solution was then heated at 60°C (oil bath temperature) under nitrogen for 20 h and allowed to cool. After solvent removal (40°C), the resulting solid was subjected to standard extractive workup (EtOAc, $NaHCO_3$), giving the **title compound** as an oil which crystallised on standing to an almost colourless solid (10.5 9, 70%) which could be recrystallised from ether, giving needles, m.p. 59.3°C (lit. 26, m.p. 62°C); ^{1}H NMR ($CDCl_3$) 2.33 (3H, br s, O<u>H</u> and N<u>H</u>$_2$), 3.65 (1 H, d, 4.4Hz, H$_2$NC<u>H</u>COOMe), 3.68 (3H, s, OC<u>H</u>$_3$), 4.91 (1H, d, 4.4Hz, PhC<u>H</u>OH), 7.26–7.38 (5H, m, Ph<u>H</u>); IR 2600–3600 (including 2 sharp peaks; 3330, 3273), 1738 cm^{-1}; Anal. $C_{10}H_{13}NO_3$ (C,H,N). This material was used without further purification.

(+)-threo-N-t-Butyloxycarbonyl-3-phenylserine methyl ester. The methyl ester (crude from above, 17.0 9, 87.2 mmol) and sodium carbonate (11.1 9, 105 mmol, 1.2 equiv.) were stirred together in a THF:H_2O mixture (1:1, 600 mL). To this mixture was added di-*t*-butyl dicarbonate (20.9 9, 95.9 mmol, 1.1 equiv.) and the suspension stirred at room temperature for 18 h. The THF was removed and the residue acidified to pH 4 with 1M HCl. Standard extractive workup (EtOAc) then gave the **title compound** as a colourless oil (25.7 9, 100%); ^{1}H NMR

($CDCl_3$) 1.33 (9H, s, *t*-butylH), 2.86 (1H, br s, OH), 3.75 (3H, s, OCH_3), 4.53 (1H, br d, BocNHCHCOOMe), 5.23 (1H, s, BocNH), 5.35 (1H, br d, PhCHOH), 7.26–7.38 (5H, m, PhH); IR 3436 (br), 1760-1680 (br, max 1722), 1505cm^{-1} Anal. $C_{15}H_{21}NO_5$ (C,H,N); having similar chromato-graphic properties to those reported.[37] This material was used without further purification.

(+)-threo-N-t-*Butyloxycarbonyl-3-phenylserine* ***4a.*** To a solution of the N-protected methyl ester above (9.57 g, 32.4 mmol) in THF (300 mL) was added an aqueous solution of $LiOH{\cdot}H_2O$ (1.43 g, 34.0 mmol, 1.05 equiv. in 250 mL) over 60 min. and the mixture stirred at room temperature for 16 h. The THF was removed at 30°C and the basic mixture extracted with ether (150 mL). Acidification to pH 2 (conc. HCl dropwise) and standard extractive workup (EtOAc) gave racemate **4a** as an amorphous powder (8.64 9, 95%), which could be recrystallised from $EtOH/H_2O$, giving colourless needles; m.p. 122–124°C; ^1H NMR (DMSO d_6) 1.35 (9H, s, *t*-butylH), 3.40 (1H, br s, OH under HOD), 4.02 (1H, br s, BocNHCHCOOH), 5.08 (1H, d, 3.4Hz, PhCHOH), 5.76 (1H, d, 7.5Hz, BocNH), 7.23–7.37 (5H, m, PhH), (COOH not visible); IR 3390 (br), 1685 (br), 1582 cm^{-1}; Anal. $C_{14}H_{19}NO_5{\cdot}0.25H_2O$ (C,H,N);. This material was used without further purification.

(+)-threo-N-t-*Butyloxycarbonyl-3-phenylserine ω-phenylalkylamides* ***5a–c.*** General method; A mixture of (+)-*threo-N-t*-butoxycarbonyl-3-phenylserine (1.00 equiv.), DCC (1.03 equiv.) and pentafluorophenol (1.03 equiv.) was stirred together as a ca. 1M solution in ethyl acetate for 4 h, and the resultant thick suspension filtered to remove the precipitated DCU. The filtrate was added to the ω-phenylalkylamine (1.03 equiv.) and this mixture stirred at room temperature for 24 h. Standard extractive workup (EtOAc, (1) . 0.1 M HCl, (2) $NaHCO_3$) and crystallisation or chromatography then gave the amides **5a–c** as follows:

5a; yield 65%; purified by crystallisation (Et_2O/hexane); colourless crystalline solid, m.p. 111.2–111.5°C; ^1H NMR ($CDCl_3$) 1.31 (9H, s, *t*-butylH), 1.51–1.65 (4H, m, $CH_2CH_2CH_2CH_2$), 2.61 (2H, t, 7.4Hz, $PhCH_2$), 3.23–3.31 (2H, m, $CONHCH_2$), 3.74 (1H, br s, OH), 4.30 (1H, dd, 2.6Hz and 8.5Hz, BocNHCH-), 5.34 (2H, br s, PhCHOH and BocNH), 6.47 (1 H, br s, CONH), 7.14-7.36 (1OH, m, PhH); IR 1704, 1656, 1532 cm^{-1}; Anal. $C_{24}H_{32}N_2O_4$ (C,H,N).

5b; yield 73%; purified by reverse phase chromatography ($MeOH:H_2O$; 3:1); colourless crystalline solid, m.p. 113°C (EtOAc/hexane); ^1H NMR ($CDCl_3$) 1.32 (9H, br s, *t*-butylH), 1.37–1.68 (6H, m, central $(CH_2)_3$), 2.60 (2H, t, 7.6Hz, $PhCH_2$), 3.20 (2H, m, $CONHCH_2$), 3.70 (1H, br s, OH), 4.30 (1H br d, 8.5Hz, BocNHCH-), 5.33 (2H, br s, PhCHOH, BocNH) 6.46 (1H, br s, CONH), 7.14–7.35 (10H, m, PhH); IR 1681, 1652, 1525 cm^{-1}; MS m/e (Cl) 427 (M+H, 8%); Anal. $C_{25}H_{34}N_2O_4$ (C,H,N).

5c; yield 65%; purified by flash chromatography (EtOAc:hexane, 3:2), then recrystallisation ($MeOH/H_2O$); colourless crystalline solid, m.p. 96.8°C; ^1H NMR ($CDCl_3$) 1.22–1.59 (18H, m, *t*-butylH, central $(CH_2)_4$ and OH), 2.59 (2H, t, 7.7Hz, CH_2Ph), 3.21 (2H, m, $CONHCH_2$), 4.32 (1H, br d, 8.2Hz, BocNHCH), 5.32 (1H, s) and 5.41 (1H, br s, PhCHOH and BocNH), 6.57 (1H, br s, CONH), 7.14–7.36 (1OH, m, PhH); IR 1682, 1655, 1520 cm^{-1}; MS m/e (Cl) 441 (M + H, 25%); Anal. $C_{26}H_{36}N_2O_4$ (C,H,N).

(S)-N-t-*Butyloxycarbonylserine ω-phenylalkylamides* ***5d–f.*** These were prepared by the same method as amides **5a–c**, giving products as follows:

5d; yield 83%; purified by reverse phase chromatography ($MeOH:H_2O$; 65:35); colourless crystalline solid, m.p. 62–66°C; ^1H NMR ($CDCl_3$) 1.43 (9H, s, *t*-butylH), 1.48–1.69 (4H, m, $-(CH_2)_2-$), 2.61 (2H, t, 7.1Hz, $-CH_2Ph$), 3.26 (2H, m, $CONHCH_2-$), 3.63 and 4.08 (3H, 2m, CH_2OH and BocNHCHCO-), 5.62 (1H, d, 7.1Hz, BocNH), 6.77 (1H, s, amide CONH), 7.13–7.29 (5H, m, PhH), (OH not visible); IR 3333, 3269, 1708, 1651, 1573 cm^{-1}; MS m/e (Cl) 337 (M+H, 83%); α_D-13.4° (MeOH, 21°C, c = 0.73); Anal. $C_{18}H_{28}N_2O_4{\cdot}0\ 5H_20$ (C,H,N).

5e; yield 66%; purified by reverse phase chromatography ($MeOH:H_2O$; 60:40–70:30); colourless crystalline solid, m.p. 45.8–47.7°C; ^1H NMR ($CDCl_3$) 1.45 (9H, s, *t*-butylH), 1.29-1.69 (6H, m, $(CH_2)_3-$), 1.84 (1H, br s, OH), 2.59 (2H, t, 7.6Hz, CH_2Ph), 3.23 (2H, m, $CONHCH_2-$), 3.62 and 4.02–4.11 (3H, 2m, CH_2OH and BocNHCHCO-), 5.59 (1H, d, 5.9Hz, BocNH), 6.71 (1H, s, amide CONH), 7.14–7.29 (5H, m, PhH); IR 3326 (br), 1701, 1652, 1537 cm^{-1}; MS m/e (Cl) 351 (M + H, 42%); α_D-47.3° ($CHCl_3$, 20°C, c = 0.73); Anal. $C_{19}H_{30}N_2O_4$ (C,H,N).

5f; yield 50%; purified by reverse phase chromatography ($MeOH:H_2O$; 60:40–70:30); colourless crystalline solid, m.p. 72.7–74.4°C; ^1H NMR ($CDCl_3$) 1.45 (9H, s, *t*-butylH), 1.32–1.65 (8H, m, $(CH_2)_4-$), 2.59 (2H, t, 7.4Hz, CH_2Ph), 3.21–3.47 (3H, m, $CONHCH_2-$ and OH), 3.63 and 4.08 (3H, 2m, CH_2OH and BocNHCHCO-), 5.56 (1H, br s, BocNH), 6.67 (1H, s, amide CONH), 7.14–7.29 (5H, m, PhH); IR 3323 (br), 1700, 1651, 1536 cm^{-1}; MS m/e (Cl) 365 (M + H, 41 %); α_D -44.4° ($CHCl_3$, 20°C, c = 0.65); Anal. $C_{20}H_{32}N_2O_4$ (C,H,N).

(+)-threo-*3-Phenylserine ω-phenylalkylamides* ***6a-c.*** General method; A TFA (0.1M) solution of the Boc protected amine **5a–c** was stirred at room temperature for 20 min and then the solvent removed. The residue was poured into saturated aqueous $NaHCO_3$, and then standard extractive workup (EtOAc, brine) gave an oil which crystallised either on standing or on trituration with ether. Recrystallisation then gave pure **6a–c** as follows:

6a; yield 86%; colourless crystalline solid, m.p. 67.8–68.4°C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) 1.42–1.64 (4H, m, CH_2CH_2), 2.12 (3H, br s, NH_2 and OH), 2.59 (2H, t, 7.6Hz, CH_2Ph), 3.17–3.31 (2H, m, $CONHCH_2$), 3.41 (1H, d, 3.3Hz, CHCONHR), 5.30 (1H, m, 3.3Hz, PhCHOH), 7.13–7.36 (11H, m, PhH, CONH); IR 1652, 1585, 1540 cm^{-1}; Anal. $C_{19}H_{24}N_2O_2$ (C,H,N).

6b; yield 70%; colourless crystalline solid, m.p. 77.4–79.0°C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) 1.31, 1.47 and 1.62 (6H, 3m, central $(CH_2)_3$), 1.80 (3H, br s, NH_2 and OH), 2.59 (2H, t, 7.8Hz, CH_2Ph), 3.22 (2H, 2d, 6.6Hz, $CONHCH_2$), 3.42 (1H, br s, $CHNH_2$), 5.29 (1H, d, 3.1 Hz, PhCHOH), 7.14–7.36 (11H, m, PhH and CONH); IR 1656, 1585, 1534 cm^{-1}; MS m/e (FAB) 327 M+H, 100%); Anal. $C_{20}H_{26}N_2O_2$ (C,H,N).

6c; yield 71 %; colourless crystalline product, m.p. 77–78°C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) 1.22–1.62 (8H, central $(CH_2)_4$), 1.90 (3H, br s, NH_2 and OH), 2.59 (2H, t, 7.5Hz, $PhCH_2$), 3.19 (2H, m, $CONHCH_2$), 3.41 (1H, d, 1 Hz, $CHNH_2$), 5.30 (1H, d, 3.1 Hz, PhCHOH), 7.14–7.35 (11H, m, PhH and CONH); IR 1656, 1583, 1541 cm^{-1}; MS m/e (Cl) 341 (M + H, 47%), 235 (M + H-PhCHO (McLafferty), 100%); Anal. $C_{21}H_{28}N_2O_2 \cdot 0.25$ EtOAc (C,H,N).

(S)-*Serine ω-alkylamides* ***6d–f***. These were prepared in the same manner as compounds **6a-c** and purified by silica chromatography (MeOH:CH_2Cl_2, 15:85) giving the products as follows:

6d; yield 70%; colourless waxy solid, m.p. 44–46°C; ^{1}H NMR (DMSO-d_6) 1.39–1.60 (4H, m, -$(CH_2)_2$-), 2.56 (2H, t, 7.6Hz, CH_2Ph), 3.06–3.16 (2H, m, $CONHCH_2$-), 3.35 and 3.58 (4H, 3m, CH_2OH, H_2NCH and OH), 4.56 (2H, br s, NH_2), 7.13–7.28 (5H, m, PhH), 8.00 (1H, br s, amide CONH); IR 3311 (br), 1673 (br), 1207, 1132 cm^{-1}; MS found m/e (Cl), 237.1610. $C_{13}H_{21}N_2O_2$ (M + H) requires 237.16029; α_D + 3.0° (MeOH, 20°C, c = 0. 59).

6e; yield 87%; colourless waxy solid, m.p. 41 .5–44°C; ^{1}H NMR ($CDCl_3$) 1.29–1.66 (6H, m, -$(CH_2)_3$-), 2.58 (2H, t, 7.7Hz, CH_2Ph), 3.10 (3H, br s, OH, NH_2), 3.18 (2H, m, $CONHCH_2$-), 3.52 (1H, br s, H_2NCH), 3.74 (2H, br s, CH_2OH), 7.12–7.27 (5H, m, PhH), 7.50 (1H, br s, amide CONH); IR 3300 (br), 1684, 1651, 1562, 1203, 1135, 1057 cm^{-1}; MS found m/e (Cl), 251.1760. $C_{14}H_{23}N_2O_2$ (M + H) requires, 251.17594; α_D-1.4° (MeOH, 20°C, c = 0.91).

6f; yield 83%; colourless waxy solid, m.p. 74.7–79.2°C; ^{1}H NMR ($CDCl_3$) 1.31–1.63 (8H, m, -$(CH_2)_4$-), 2.58 (2H, t, 7.7Hz, CH_2Ph), 2.75 (3H, br s, OH and NH_2), 3.15–3.27 (2H, m, $CONHCH_2$-), 3.47 (1H, br s, H_2NCH), 3.71 (1H, dd, 5.3 and 10.9Hz) and 3.80 (1 H, dd, 5.3 and 10.8Hz, CH_2OH), 7.13–7.28 (5H, m, PhH), 7.47 (1H, br s, amide CONH); IR 3282 (br), 1651, 1560, 1203, 1070 cm^{-1}; MS found m/e (Cl), 265.1920. $C_{15}H_{25}N_2O_2$ (M+H) requires 265.19159; α_D-1.6° (MeOH, 20°C, c = 0.86).

N-[α-methyl-N-{Tricyclo[3.3.1.1^{3,7}]dec-2-yloxy-carbonyl}-(R)-tryptophyl]-3-phenylserine [ω-phenylalkyl]-amides ***7a-f***. General method; A 0.2M solution of *(R)-N*-[2-Adoc]-2-methyltryptophan (1.00 equiv.), DCC (1.03 equiv.) and HOBt (1.03 equiv.) in dry ethyl acetate was stirred at room temperature for 3 h, after which time a thick precipitate of DCU had settled. The solid was filtered off and the filtrate added to a solution of amine **6a–f** in EtOAc. This mixture was then stirred at 20–50°C for 6–24 h under nitrogen and allowed to cool. Standard extractive workup (EtOAc; (1) dil. HCl; (2) saturated aqueous $NaHCO_3$; (3) brine) and crystallisation from hot methanol effectively provided reasonably pure samples of each diastereomer on cooling (isomer A remaining in solution, isomer B crystallising as rods). These could be further purified by recrystallisation or reverse phase chromatography. Reaction with **6a** gave the following diastereomeric pair:

7a; yield 39%; purified by chromatography (MeOH:H_2O; 85:15); white powder m.p. 91–94°C; ^{1}H NMR ($CDCl_3$) 1.45–1.90 (21H, m, 14 x adamantyl H, α-CH_3 and $CH_2CH_2CH_2Ph$), 2.58 (2H, t, 7.6Hz, CH_2Ph), 2.92, 3.01 (2H, 2d, 14.7Hz, CH_2-indole), 3.16 (2H, m, $CONHCH_2$), 4.30 (1H, br s, OH), 4.63 (1H, s, adamantyl C(2)H), 4.72 (1H, dd, 3.5Hz and 8.8Hz, CHCONHR), 5.01 (1H, m, PhCHOH), 5.23 (1H, s, AdocNH), 6.52 (1H, d, 8.7Hz, TrpCONH), 6.81 (1H, d, 2.3Hz, indole C(2)H), 7.08–7.28 (13H, m, PhH, CONH, indole C(5,6)H), 7.37 (1H, d, 7.4Hz, indole C(7)H), 7.55 (1H, d, 7.8Hz, indole C(4)H), 8.23 (1H, s, indole NH); IR 1698,1650 cm^{-1}; MS m/e (FAB) 691 (M+H, 66%); α_D +62.5° ($CHCl_3$, 20°C, c = 0.48); Anal. $C_{42}H_{50}N_4O_5 \cdot 0.5H_20$ (C,H,N).

7b; yield 33%; purified by recrystallisation (MeOH); colourless crystalline solid, m.p. 228–232°C; ^{1}H NMR ($CDCl_3$) 1.04 (3H, s, α-CH_3), 1.56–2.01 (18H, m, 14 x adamantyl H, $CH_2CH_2CH_2Ph$), 2.64 (2H, t, 7.6Hz, CH_2Ph), 3.28 and 3.48 (5H, 2m, OH, $CONHCH_2$, CH_2-indole), 4.79–4.84 (3H, m, adamantyl C(2)H, CHCONH and PhCHOH), 5.50 (1H, s, AdocNH), 6.64 (1H, d, 9.4Hz, TrpCONH), 6.81 (1H, d, 2Hz, indole C(2)H), 7.04–7.35 (14H, m, PhH, indole C(5,6,7)H, CONH), 7.49 (1H, d, 7.9Hz, indole C(4)H), 8.04 (1H, s, indole NH); IR 1700, 1652 cm^{-1}; MS m/e (FAB) 691 (M+H, 43%); α_D +30.0° ($CHCl_3$, 20°C, c = 0.16); Anal. $C_{42}H_{50}N_4O_5$ (C,H,N).

Reaction with **6b** gave the following diastereomeric pair:

7c; yield 30%; purified by chromatography (MeOH:H_2O; 85:15); white powder, m.p. 90–94°C; ^{1}H NMR ($CDCl_3$) 1.25–1.90 (23H, m, 14 x adamantyl H, α-CH_3, -$(CH_2)_3$-), 2.58 (2H, t, 7.7Hz, CH_2Ph), 2.90 and 2.99 (2H, 2d, 14.6Hz, CH_2-indole), 3.08–3.22 (2H, m, $CONHCH_2$), 4.17 (1H, d, 5.5Hz, OH), 4.63 (1H, s, adamantyl C(2)H), 4.72 (1 H, dd, 3.4Hz and 8.9Hz, NHCHCONHR), 5.00

(1H, m, PhCHOH), 5.20 (1H, s, AdocNH), 6.50 (1H, d, 9.1 Hz, TrpCONH), 6.81 (1H, d, 2.3Hz, indole C(2)H), 7.08–7.27 (13H, m, PhH, indole C(5,6)H and CONH), 7.38 (1H, d, 7.4Hz, indole C(7)H), 7.54 (1H, d, 8.2Hz, indole C(4)H), 8.19 (1H, s, indole NH); IR 1700, 1651 cm^{-1}; MS m/e (FAB) 705 (M+H, 11 %); α_D + 63.1° ($CHCl_3$, 20°C, c = 0.18); Anal. $C_{43}H_{52}N_4O_5$ (C,H,N).

7d; yield 30%; purified by recrystallisation (MeOH/H_2O); colourless crystalline solid, m.p. 201–204°C; ^1H NMR ($CDCl_3$) 1.03 (3H, s, α-CH_3), 1.33–2.01 (21H, m, 14 x adamantylH, -$(CH_2)_3$- and OH), 2.61 (2H, t, 7.7Hz, CH_2Ph), 3.23 (2H, m, $CONHCH_2$), 3.27 and 3.43 (2H, 2d, 14.8Hz, CH_2-indole), 4.80–4.83 (3H, m, NHCHCONHR, adamantyl C(2)H and PhCHOH), 5.49 (1H, s, AdocNH), 6.63 (1H, d, 8.8Hz, TrpCONH), 6.80 (1H, d, 2.2Hz, indole C(2)H), 7.03–7.35 (14H, m, PhH, indole C(5,6,7)H, CONH), 7.48 (1H, d, 8.2Hz, indole C(4)H), 8.03 (1H, s, indole NH); IR 1686, 1672, 1652 cm^{-1}; MS m/e (FAB) 705 (M+H, 7%); α_D + 26.4° ($CHCl_3$, 20°C, c = 0.17); Anal. $C_{43}H_{52}N_4O_5$ (C,H,N).

Reaction with **6c** gave the following diastereomeric pair:

7e; yield 26%; purified by chromatography (MeOH:H_2O; 87:13); white powder, m.p. 110.7–112°C (m.p. of recrystallised material; MeOH/H_2O); ^1H NMR ($CDCl_3$) 1.28–1.90 (26H, m, OH, 14 x adamantylH, α-CH_3, and -$(CH_2)_4$-), 2.58 (2H, t, 7.4Hz, CH_2Ph), 2.90 and 3.00 (2H, 2d, 1 4.7Hz, CH_2-indole), 3.16 (2H, m, $CONHCH_2$), 4.62 (1H, s, adamantyl C(2)H), 4.73 (1H, dd, 8.7Hz, 2Hz, CHCONH), 4.99 (1H, d, 2Hz, PhCHOH), 5.20 (1H, s, AdocNH), 6.48 (1H, d, 9.0Hz, TrpCONH), 6.82 (1H, d, 2.2Hz, indole C(2)H), 7.06–7.27 (13H, m, PhH, indole C(5,6)H, CONH), 7.38 (1H, d, 7.4Hz, indole C(7)H), 7.55 (1H, d 7.4Hz, indole C(4)H), 8.23 (1H, s, indole NH); IR 1700, 1652 cm^{-1}; MS m/e (FAB) 719 (M + H, 2%); α_D + 57.5° ($CHCl_3$, 21°C, c = 0.30); Anal. $C_{44}H_{54}N_4O_5 \cdot 0.25H_2O$ (C,H,N).

7f; yield 28%; purified by crystallisation (MeOH/H_2O); colourless crystalline solid, m.p. 193.5–196°C; ^1H NMR ($CDCl_3$) 1.03 (3H, s, α-CH_3), 1.30–2.10 (23H, m, 14 x adamantylH, -$(CH_2)_4$- and OH), 2.60 (2H, t, 7.6Hz, CH_2Ph), 3.28 (2H, m, $CONHCH_2$-), 3.25 (1H, d, 4.8Hz) and 3.42 (1H, d, 4.8Hz, CH_2-indole), 4.80 (3H, m, NHCHCONHR, PhCHOH, adamantyl C(2)H), 5.50 (1 H, d, 1 Hz, AdocNH), 6.62 (1H, d, 9.1Hz, TrpCONH), 6.80 (1H, d, 1Hz, indole C(2)H), 7.00–7.35 (14H, m, PhH, indole C(5,6,7)H and 1 x CONH), 7.49 (1H, d, 7.8Hz, indole C(4)H), 8.03 (1H, s, indole NH); IR 1692, 1671, 1653 cm^{-1}; MS m/e (FAB) 719 (M+H, 2.6%); α_D +27.7° ($CHCl_3$, 22°C, c = 0.12); Anal. $C_{44}H_{54}N_4O_5$ (C,H,N).

N-*[α-methyl*-N-*(Tricyclo[3.3.1.1^{3,7}]dec-2-yloxycarbonyl}*-(R)-*tryptophyl]*-(S)-*serine ω-phenylalkylamides* ***7a-i.*** These were prepared by the same method as compounds **7a–f** and purified by reverse phase chromatography (MeOH:H_2O, 85:15–90:10) to give compounds **7g–i** as follows:

7g; yield 65%; colourless powder; ^1H NMR ($CDCl_3$) 1.46–2.02 (21H, m,14 x adamantylH, $(CH_2)_2$, TrpCH$_3$), 2.62 (2H, t, 7.5Hz, CH_2Ph), 2.72 (1H, br s, OH), 3.22 (2H, m, $CONHCH_2$), 3.38 (1H, d, 14.7Hz) and 3.48 (1H, d, 14.7Hz, indole CH_2), 3.45 (1H, m) and 4.13 (1H, m, CH_2OH), 4.46 (1H, m, Ser α-H), 4.81 (1H, s, adamantyl C(2)H), 5.09 (1H, s, AdocNH), 6.82 (1H, d, 8.0Hz, amide CONH),6.97 (1H, d, 2.1 Hz, indole C(2)H),7.07–7.27 (8H, m, PhH, amide CONH and indole C(5,6)H), 7.35 (1H, d, 8.0 Hz, indole C(7)H), 7.57 (1H, d, 7.8Hz, indole C(4)H), 8.20 (1H, s, indole NH); IR 3319, 1695, 1655, 1498 cm^{-1}; MS m/e (FAB) 637.5 (M + Na, 100%), 615.5 (M + H, 85%); α_D +63.0° (MeOH, 20°C, c = 0.26); Anal $C_{36}H_{46}N_4O_5 \cdot 0\ 5H_2O$ (C,H,N).

7h; yield 61 %; colourless powder; ^1H NMR ($CDCl_3$) 1.32–2.02 (23H, m, 14 x adamantylH, $(CH_2)_3$, TrpCH$_3$),2.59 (2H, t, 7.7Hz, CH_2Ph), 2.76 (1H, br s, OH), 3.18 (2H, m, $CONHCH_2$), 3.38 (1H, d) and 3.48 (1H, d, 14.6Hz, indole CH_2), 3.45 (1H, m) and 4.10 (1H, m, CH_2OH), 4.46 (1H, m, Ser α-H), 4.82 (1H, s, adamantyl C(2)H), 5.10 (1H, s, AdocNH), 6.82 (1H, d, 8.0Hz, amide CONH), 6.97 (1H, d, 2.1Hz, indole C(2)H), 7.07–7.27 (8H, m, PhH, amide CONH and indole C(5,6)H), 7.36 (1H, d, 8.1Hz, indole C(7)H), 7.57 (1H, d, 7.8Hz, indole C(4)H), 8.25 (1H, s, indole NH); IR 3324, 1695, 1656, 1498 cm^{-1}; MS m/e (FAB) 651.5 (M + Na, 100%), 629.5 (M + H, 70%); α_D + 64.6° (MeOH, 20°C, c = 0.67); Anal. $C_{37}H_{48}N_4O_5$ (C,H,N).

7i; yield 59%; colourless powder; ^1H NMR ($CDCl_3$) 1.34–2.02 (25H, m, 14 x adamantylH, $(CH_2)_4$, TrpCH$_3$), 2.58 (2H, t, 7.8Hz, CH_2Ph), 2.72 (1H, br s, OH), 3.18 (2H, m, $CONHCH_2$), 3.38 (1H, d, 14.6Hz) and 3.48 (1H, d, 14.6Hz, indole CH_2), 3.46 (1H, m) and 4.13 (1H, m, CH_2OH), 4.46 (1H, m, Ser α-H), 4.82 (1H, s, adamantyl C(2)H), 5.08 (1H, s, AdocNH), 6.82 (1H, d, 8.3Hz, amide CONH), 6.97 (1 H, d, 2.3Hz, indole C(2)H), 7.07–7.27 (8H, m, PhH, amide CONH and indole C(5,6)H), 7.35 (1H, d, 8.0Hz, indole C(7)H), 7.57 (1H, d, 7.9Hz, indole C(4)H), 8.20 (1H, s, indole NH); IR 3313, 1695, 1651, 1496 cm^{-1}; MS m/e (FAB) 665.5 (M+Na, 100%), 643.5 (M+H, 94%); α_D +64.5° (MeOH, 20°C, c = 0.61); Anal. $C_{38}H_{50}N_4O_5$ (C,H,N).

*4-{N-[α-methyl-*N'*-(Tricyclo[3.3.1.1^{3,7}]dec-2-yloxy-carbonyl)-*(R)*-tryptophyl]-(2S)-2-[ω-phenylalkylamino-carbonyl]-2-aminoethoxy}-4-oxobutanoic acids* ***2a-i.*** General method; To a ca. 0.02M solution of the benzylic alcohol **7a–i** in DMF was added succinic anhydride (3 equiv.) and DMAP (1 equiv.) and the mixture stirred at 20°C for 5–48 h. After cooling and standard extractive workup (EtOAc, (1) 1M HCl, (2) brine) the crude product was purified by recrystallisation or reverse phase

chromatography (eluant as detailed below), giving the title compounds **2a–i** as follows:

2a; yield 75%; eluant MeOH:H_2O (4:1–6:1); white powder, m.p. 93–95°C; ^1H NMR ($CDCl_3$) 1.47–1.93 (21H, m, α-CH_3, -$(CH_2)_2CH_2Ph$, 14 x adamantyl$H$), 2.61 (6H, m, CH_2Ph, C(O)CH_2CH_2CO), 2.97 (2H, s, CH_2-indole), 3.17 (2H, m, CONHCH_2), 2.2–3.8 (v br signal, CO_2H/H_2O), 4.76 (1H, br s, adamantyl C(2)H), 4.84 (1 H, dd, ca. 4Hz and 8Hz, -NHCHCONH-), 5.44 (1H, s, AdocNH), 6.44 (1H, d, 3.8Hz, PhCHO-succinate), 6.76 (1H, d, 2Hz, indole C(2)H), 6.90 (2H, m, 2 x CONH), 7.12–7.27 (12H, m, PhH, indole C(5,6)H), 7.35 (1H, d, 7.8Hz, indole C(7)H), 7.53 (1H, d, 8.0Hz, C(4)H), 8.30 (1H, s, indole NH); IR 1709, 1660 (broad, coalesced) cm^{-1}; MS m/e (FAB) 791 (M+H, 65%); α_D +53 7° ($CHCl_3$, 19.5°C, c = 0.42); Anal. $C_{46}H_{54}N_4O_8 \cdot 0.5H_2O$ (C,H,N).

2b; yield 70%; recrystallised from MeOH; needles, m.p. 169.3°C; ^1H NMR ($CDCl_3$) 1.10 (3H, s, Trp α-CH_3), 1.52–1.96 (18H, m, 14 x adamantyl$H$, -$CH_2CH_2CH_2Ph$), 2.48–2.68 (6H, m, CH_2Ph, C(O)CH_2CH_2CO), 2.80–3.60 (1H, br s, CO_2H/H_2O), 3.18–3.30 (2H, m, CONHCH_2), 3.23 and 3.46 (2H, 2d, 1 4.7Hz, CH_2-indole), 4.78–4.91 (2H, m, adamantyl C(2)H, CHC(O)NHR), 5.20 (1H, s, AdocNH), 6.50 (1H, d, 4Hz, PhCHO-succinate), 6.79 (1H, d, 9.2Hz, CONH), 6.83 (1H, s, indole C(2)H), 7.04–7.33 (14H, m, PhH, indole C(5,6,7)H, CONH), 7.50 (1H, d, 7.9Hz, indole C(4)H), 8.13 (1H, s, indole NH); IR 1757, 1733, 1705, 1676 (strong), 1644 cm^{-1}; MS m/e (FAB) 791 (M + H, 10%); α_D + 39 7° ($CHCl_3$, 20°C, c = 0.33); Anal. $C_{46}H_{54}N_4O_8$ (C,H,N).

2c; yield 47%; eluant MeOH:H_2O, (4:1–6:1); white microcrystalline solid, m.p. 90–94°C; ^1H NMR ($CDCl_3$) 1.20–2.00 (23H, m, 14 x adamantyl$H$, α-CH_3, -$(CH_2)_3$-), 2.56 (2H, t, 7.6Hz, CH_2Ph), 2.66 (4H, m, C(O)CH_2CH_2CO), 2.98 (2H, br s, CH_2-indole), 3.05–3.25 (2H, m, CONHCH_2), 4.77 (1H, s, adamantyl C(2)H), 4.82 (1 H, dd, 4Hz, 8Hz, NHCHCONHR), 5.44 (1H, br s, AdocNH), 6.42 (1H, d, 4Hz, PhCHO-succinate), 6.78 (1H, s, indole C(2)H), 6.90 (2H, br s, 2 x CONH), 7.12–7.30 (12H, m, PhH, indole C(5,6)H), 7.35 (1H, d, 8Hz, indole C(7)H), 7.53 (1H, d, 7.9Hz, indole C(4)H), 8.33 (1H, s, indole NH), (COOH not visible); IR 1740, 1709, 1658 (broad) cm^{-1}; MS m/e (FAB) 805 (M+H, 89%); α_D +48.0 ($CHCl_3$, 22°C, c = 0.2); Anal. $C_{47}H_{56}N_4O_8 \cdot 0.5H_2O$ (C,H,N).

2d; yield 48%; recrystallised from MeOH/H_2O; colourless needles, m.p. 171.0–172.6°C; ^1H NMR ($CDCl_3$) 1.10 (3H, s, α-CH_3), 1.32–2.01 (20H, m, 14 x adamantyl H, -$(CH_2)_3$-), 2.56–2.63 (6H, m, CH_2Ph, C(O)CH_2CH_2CO), 2.70–3.60 (v br signal, CO_2H/H_2O), 3.18–3.22 (2H, m, CONHCH_2), 3.25–3.46 (2H, 2d, 15Hz, CH_2-indole), 4.81 (1H, dd, 4Hz and 8Hz, NHCHCONHR), 4.86 (1H, s, adamantyl C(2)H), 5.20 (1H, br s, AdocNH), 6.49 (1H, d, 4Hz, PhCHO-succinate), 6.79 (1H, d, 8.8Hz, CONH), 6.83 (1H, s, indole C(2)H), 7.03–7.34 (14H, m, PhH, indole C(5,6,7)H, CONH), 7.50 (1H, d, 7.9Hz, indole C(4)H), 8.16 (1H, s, indole NH); IR 1761, 1718, 1680, 1639 cm^{-1}; MS m/e (FAB) 805 (M+H, 100%); α_D +40.0° ($CHCl_3$, 20°C, c = 0 16); Anal. $C_{47}H_{56}N_4O_8 \cdot 0.5H_2O$ (C,H,N).

2e; yield 70%; eluant MeOH:H_2O (85:15); white microcrystalline solid, m.p. 91–95°C; ^1H NMR ($CDCl_3$) 1.26–1.93 (25H, 14 x adamantyl H, α-CH_3, -$(CH_2)_4$-), 2.54–2.67 (6H, m, CH_2Ph, C(O)CH_2CH_2), 2.96 (2H, s) and 3.12 (2H, br dd, 6Hz, 8Hz, CH_2-indole, CONHCH_2), 3.00–4.50 (broad s, CO_2H/H_2O), 4.76 (1H, br s, adamantyl C(2)H), 4.83 (1H, dd, 3.9Hz and 8.7Hz, NHCHCONHR), 5.43 (1H, s, AdocNH), 6.43 (1H, d, 3.9Hz, PhCHO-succinate), 6.77 (1H, d, 2Hz, indole C(2)H), 6.93 (2H, br d, 8Hz, 2 x CONH), 7.10–7.27 (12H, m, indole C(5,6)H and PhH), 7.35 (1H, d, 7.8Hz, indole C(7)H), 7.53 (1H, d, 7.9Hz, indole C(4)H), 8.38 (1H, s, indole NH); IR 1740, 1710, 1658 cm^{-1}; MS m/e (FAB) 819 (M+H, 5%); α_D +51.5° ($CHCl_3$, 20°C, c = 0.16); Anal. $C_{48}H_{58}N_4O_8 \cdot H_2O$ (C,H,N).

2f; yield 79%; recrystallised from MeOH/H_2O; colourless needles, m.p. 168.0–170.0°C; ^1H NMR ($CDCl_3$) 1.08 (3H, s, α-CH_3), 1.25–2.05 (22H, m, adamantyl H, -$(CH_2)_4$-), 2.56–2.62 (6H, m, CH_2Ph, C(O)CH_2CH_2CO), 3.17 (2H, m, CONHCH_2), 3.24 and 3.46 (2H, 2d, 15.4Hz, CH_2-indole), 3.60 (v br signal, CO_2H/H_2O), 4.83 (1H, dd, 12.2Hz and 3.1 Hz, NHCHCONHR), 4.86 (1H, s, adamantyl C(2)H), 5.20 (1H, br s, AdocNH), 6.50 (1H, d, 3.1Hz, PhCHO-succinate), 6.78 (1H, d, 8.9Hz, TrpCONH), 6.82 (1H, s, indole C(2)H), 7.03–7.30 (13H, m, PhH, indole C(5,6)H, CONH), 7.33 (1H, d, 8.0Hz, indole C(7)H) 7.49 (1H, d, 8.0Hz, indole C(4)H), 8.19 (1H, s, indole NH); IR 1740, 1691, 1677, 1665 cm^{-1}; MS m/e (FAB) 819 (M+H, 48%); α_D +36.0° ($CHCl_3$, 23°C, c = 0.17); Anal. $C_{48}H_{58}N_4O_8 \cdot 0.5H_2O$ (C,H,N).

2g; yield 65%; purified by reverse phase chromatography (MeOH:H_2O; 82:18); m.p.119–121°C; ^1H NMR ($CDCl_3$) 1.43–2.02 (21H, m, 14 x adamantyl H, -$(CH_2)_2$-, α-CH_3), 2.44–2.61 (6H, m, CH_2Ph, C(O)CH_2CH_2CO), 2.50 (v br signal, CO_2H/H_2O), 3.20 (2H, m, CONHCH_2), 3.37 and 3.50 (2H, 2d, 14.5Hz, CH_2-indole), 4.25 (1H, dd, 2.0Hz and 10.4Hz) and 4.54 (1H, dd, 3.0Hz and 10.4Hz, CH_2OH), 4.66 (1H, m, NHCHCONHR), 4.84 (1H, s, adamantyl C(2)H), 5.34 (1H, br s, AdocNH), 6.92 (1H, d, 8.0Hz, CONH), 6.96 (1H, s, indole C(2)H), 7.08–7.25 (8H, m, CONH, indole C(5,6)H, PhH), 7.34 (1H, d, 8.0Hz, indole C(7)H) 7.56 (1H, d, 7.8Hz, indole C(4)H), 8.28 (1H, s, indole NH); IR 2400–3400, 1728, 1693, 1657 cm^{-1}; MS m/e (FAB) 737.5 (M + Na, 100%), 715.5 (M + H, 45%); α_D +44.0° (MeOH, 20°C, c = 0.57); Anal. $C_{40}H_{50}N_4O_8$ (C,H,N).

2h; yield 61%; purified by reverse phase chromatography (MeOH:H_2O; 85:15); m.p. 92–94°C; ^{1}H NMR ($CDCl_3$) 1.33–2.01 (23H, m, 14 x adamantyl H, -(CH_2)$_3$-, α-CH_3), 2.44–2.61 (6H, m, CH_2Ph, C(O)CH_2CH_2CO), 3.13 (2H, m, CONHCH_2), 3.37 and 3.50 (2H, 2d, 14.7Hz, CH_2-indole), 3.60 (v br signal, CO_2H/H_2O),4.25 (1H, dd, 2.0Hz and 10.5Hz) and 4.47 (1 H, dd, 3.0Hz and 10.5Hz, CH_2OH), 4.64 (1H, m, NHCHCONHR), 4.84 (1H, s, adamantyl C(2)H), 5.39 (1H, br s, AdocNH), 6.92–7.25 (10H, m, TrpCONH, SerCONH, indole C(2,5,6)H and PhH), 7.33 (1H, d, 7.9Hz, indole C(7)H) 7.56 (1H, d, 7.8Hz, indole C(4)H), 8.44 (1H, s, indole NH); IR 2400–3400, 1729, 1694, 1658 cm^{-1}; MS m/e (FAB) 751.5 (M+Na, 20%), 729.5 (M+H, 7%); α_D +46.1° (MeOH, 20°C, c = 0.80); Anal. $C_{41}H_{52}N_4O_8$ (C,H,N).

2i; yield 67%; purified by reverse phase chromatography (MeOH:H_2O; 80:20–82:18); m.p. 84–87°C; ^{1}H NMR ($CDCl_3$) 1.32–2.01 (25H, m,14 x adamantyl H, -(CH_2)$_4$-, α-CH_3),2.45–2.61 (6H, m, CH_2Ph, C(O)CH_2CH_2CO), 3.15 (2H, m, CONHCH_2), 3.37 and 3.50 (2H, 2d, 14.6Hz, CH_2-indole), 3.40 (v br signal, CO_2H/H_2O), 4.26 (1H, dd, 2.5Hz and 10.5Hz) and 4.49 (1H, dd,3.0Hz and 10.5Hz, CH_2OH), 4.64 (1H, m, NHCHCONHR), 4.84 (1H, s, adamantyl C(2)H),5.29 (1H, br s, AdocNH), 6.92 (1H, d, 8.0Hz, CONH), 6.96 (1H, s, indole C(2)H), 7.07–7.25 (8H, m, CONH, indole C(5,6)H, PhH), 7.33 (1H, d, 7.9Hz, indole C(7)H) 7.56 (1H, d, 7.9Hz, indole C(4)H), 8.39 (1H, s, indole NH); IR 2400–3400, 1729, 1693, 1658, 1511 cm^{-1}; MS m/e (FAB) 765.5 (M+Na, 100%), 743.5 (M+H, 45%); α_D +50.3° (MeOH, 20°C, c = 0.31); Anal. $C_{42}H_{54}N_4O_8$ (C,H,N).

N-(5-azidopentanoyl)-(4R)-4-isopropyl-2-oxazolidinone ***9***. n-BuLi in hexane (1.41M, 100 mL, 141 mmol, 1.05 equiv.) was added dropwise to a solution of (4*R*)-(+)-4-isopropyl-2-oxazolidinone (17.50 g, 135 mmol) in dry THF (150 mL) at -78°C, keeping the internal temperature below -55°C. The opaque mixture was then stirred at -70°C for a further 30 min. After this time 5-azidopentanoyl chloride[54] (24.00 g, 148.5 mmol, 1.1 equiv.) was added as a solution in THF (75 mL) dropwise over 20 min, keeping the internal below -55°C. This viscous solution was allowed to warm to 20°C, poured into water (2L) and acidified (pH 3, HCl). Standard extractive workup (Et_2O, brine) gave the crude product as a viscous oil (70.5 g) which could be used in the following Evans alkylation without further purification. Final purification could however be accomplished by silica chromatography (EtOAc:hexane, 3:7); yield 79%; ^{1}H NMR ($CDCl_3$) 0.87 (3H, d, 6.9 Hz) and 0.92 (3H, d, 7.0 Hz, (CH_3)$_2$), 1.61–1.81 (4H, m, -(CH_2)-, 2.32–2.41 (1H, m, CHMe$_2$), 2.85–3.07 (2H, m, -CH_2CO), 3.31 (2H, t, 6.4 Hz, -CH_2N_3), 4.18–4.30 (2H, m, oxazolidinone C(5)H_2), 4.40–4.45 (1H, m, oxazolidinone C(4)H); IR 2098, 1780, 1703 cm^{-1}; MS m/e (Cl) 255 (M+H, 100%); α_D -16.7° ($CHCl_3$, 20°C, c = 1.22); Anal. $C_{11}H_{18}N_4O_3$ (C,H,N).

N-[5-azido-(2S)-2-benzylpentanoyl]-(4R)-4-isopropyl-2-oxazolidinone ***10***. Crude oxazolidinone **9** (5.08 g, approx 15–20 mmol) was added dropwise as a solution in THF (80 mL) to a 1 .OM solution of sodium bis(trimethylsilyl)amide (22.0 mL, 22.0 mmol, approx. 1.1 equiv.) in THF at -78°C, keeping the temperature below -65°C. After stirring at this temperature for a further 10 min, a solution of benzyl bromide (20.52 g, 14.2 mL, 120 mmol, approx. 6 equiv.) in THF (10 mL) was added in one portion, the mixture allowed to reach 20°C and poured into 0.1M HCl. Standard extractive workup (Et_2O, brine) gave the crude product contaminated with excess benzyl bromide. This was removed on a rotary evaporator (75°C, 2 Torr) and the yellow residue crystallised from MeOH:H_2O (9:1) giving oxazolidinone **10** as colourless cuboids (3.37 g, 2 step yield from the acid chloride; 50%); m.p. 58.0–58.6°C; ^{1}H NMR ($CDCl_3$) 0.51 (3H, d, 6.9Hz) and 0.81 (3H, d, 7.1 Hz, (CH_3)$_2$), 1.50–1.63 and 1.74–1.83 (4H, m, -(CH_2)$_2$-), 2.06–2.16 (1H, m, CHMe$_2$), 2.73 (1H, dd, 7.1 Hz and 13.3Hz) and 3.05 (1H, dd, 8.0Hz and 13.3Hz, CH_2Ph), 3.23 (2H, t, 6.7Hz, -CH_2N_3), 4.10–4.31 (3H, m, oxazolidinone C(5)H_2 and COCHRR'), 4.40–4.45 (1H, m, oxazolidinone C(4)H), 7.15–7.42 (5H, m, PhH); IR 2098, 1780, 1698 cm^{-1}; MS m/e (Cl) 345 (M+H, 43%); α_D -29.1° ($CHCl_3$, 20°C, c = 1.2); Anal. $C_{18}H_{24}N_4O_3$ (C,H,N).

(2S)-5-Azido-2-benzylpentanoic acid ***11***. Hydrogen peroxide (27.5% solution in water, 93 mL, 25.5 g of contained H_2O_2, 750 mmol, 8.0 equiv.) and LiOH·H_2O (7.87g, 187.4 mmol, 2.0 equiv.) were added sequentially to an ice-cooled solution of oxazolidinone **10** (32.3g, 93.7 mmol) in THF:H_2O (3:1, 600 mL) and the mixture allowed to reach 20°C. After stirring at ambient temperature for a further 4h, aqueous Na_2SO_3 (1.5M, 500 mL, approx. 750 mmol) was added dropwise over 2h, keeping the internal temperature below 15°C (CAUTION: extremely exothermic reaction). Saturated aqueous $NaHCO_3$ (400 mL) was then added to buffer the solution and the THF was removed on a rotary evaporator. The residual aqueous mixture was repeatedly extracted with CH_2Cl_2 to remove the chiral auxiliary and then acidified to pH 3 (HCl). Standard extractive workup (EtOAc, brine) then gave acid **11** as a colourless oil (18.0 g, 86%); ^{1}H NMR ($CDCl_3$) 1.54–1.76 (4H, m, -CH_2CH_2-), 2.64–2.79 (2H, m incorporating dd, 1 x CH2Ph and -CHRCOOH), 3.01 (1 H, dd, 6.9Hz and 1 3.0Hz, 1 x CH_2Ph), 3.25 (2H, t, 6.4Hz, -CH_2N_3), 7.15–7.41 (5H, m, PhH), (COOH not visible); IR 2400–3400, 2098, 1704, 1278 cm^{-1}; MS m/e (Cl) 251 (M+NH_4, 30%), 234 (M+H, 11%), 206 (M+H-N_2, 100%); α_D + 1.4° ($CHCl_3$, 1 9°C, c = 2.9); Anal. $C_{12}H_{15}N_3O_2$ (C,H,N).

N-[N'-t-butoxycarbonylserin]-yl-(2S)-5-amino-2-benzylpentanoic acids ***5g–h***. The azido-acid **11** (1.1 equiv.) was added as a THF (0.3M) solution to a stirred suspension of sodium hydride (60% dispersion in oil, 1.1 equiv. of contained NaH) in dry THF (1M). The resulting thick suspension was allowed to stir for a further 10 min, added

to water, washed with EtOAc to remove impurities and concentrated to dryness. The resulting sodium salt **12** was dissolved in EtOH (0.2M) containing 10% Pd on carbon (**12** :Pd/C; 10:1 by wt) and shaken under hydrogen (Parr apparatus, 50 psi) for 2h. The suspension was filtered through a plug of Celite to remove Pd residues and the filtrate concentrated to a white powder. This was dissolved in DMF (0.2M) containing the freshly prepared PFP ester of acid **4** (1.0 equiv.) and the mixture stirred at 20°C for 24h. After this time the solvent was removed and the residue poured into saturated aqueous $NaHCO_3$. This was washed repeatedly with EtOAc to remove non-acidic impurities and then acidified to pH 1.5 (HCl). Standard extractive workup (EtOAc, brine) gave crude product which was purified as described to give the acids **5g–h** as follows:

5g; purified by reverse phase chromatography (MeOH:H_2O; 60:40–62:38); white powder (50%, 1:1 diastereomeric mixture); m.p. 62–64°C; ^{1}H NMR ($CDCl_3$) 1.10–1.70 (14H, m, *t*-butylH -CH_2CH_2- and OH), 2.60–2.80 and 2.98–3.10 (3H, 2m, CH_2Ph and -CHRCOOH), 3.05–3.35 (2H, m, -CONHCH_2-), 4.35 (1H, m, BocNHCHRCO), 5.29 and 5.37 (1H, 2s, BocNH), 5.50 and 5.61 (1H, 2 br d, PhCHOH), 6.80 and 6.91 (1H, 2 br s, amide CONH), 7.11–7.35 (10H, m, PhH), (COOH not visible); IR 2400–3600, 1707, 1651, 1540 cm^{-1}; MS m/e (FAB) 493 (M + Na, 76%), 471 (M + H, 37),371 (M + H-Boc, 100); Anal. $C_{26}H_{34}N_2O_6$ (C,H,N).

5h; purified by reverse phase chromatography (MeOH:H_2O; 50:50–65:35); white powder (64%); m.p. 43–45°C; ^{1}H NMR ($CDCl_3$) 1.43 (9H, s, *t*-butylH), 1.50–1.64 (5H, m, -CH_2CH_2- and OH), 2.60–2.74 and 2.95–3.05 (3H, 2m, CH_2Ph and -CHRCOOH), 3.20 (2H, m, -CONHCH_2-), 3.64 (1H, m, BocNHCHRCO), 3.95 (1H, dd, 3.5Hz and 11.2Hz) and 4.12 (1H, m, CH_2OH), 5.77 (1H, br s, BocNH), 6.95 (1H, br t, amide CONH), 7.15–7.29 (5H, m, PhH), (COOH not visible); IR 2400–3600, 1709, 1650, 1540 cm^{-1}; MS m/e (FAB) 417 (M+Na,100%), 395 (M+H, 58%); α_D -9.5° (MeOH, 19°C, c = 0.66); Anal. $C_{20}H_{30}N_2O_6$ (C,H,N).

*(2S)-5-[*N'-t-*butoxycarbonylserin]-ylamino-2-benzylpentanoic acid amides **5i,j**.* The acids **5g** or **h** (1.0 equiv.) was added as an EtOAc (0.1M) solution to a mixture of DCC (1.0 equiv.) and 1-hydroxybenzotriazole hydrate (1.6 equiv.) in EtOAc (0.2M) and the mixture stirred at 20°C for 16h. After this time the DCU was filtered off and the filtrate concentrated, dissolved in DMF (0.1M) and cooled to 0°C. Aqueous ammonia (25% w/v, 1.1 equiv.) was added and the solution stirred at ambient temperature for a further 24 h. Standard extractive workup (EtOAc, (1) $NaHCO_3$; (2) HCl; (3) brine) and purification by reverse phase chromatography (MeOH:H_2O, 50:50–60:40) gave products **5i,j** as follows:

5i; white powder (46%); m.p. 115–118°C; ^{1}H NMR (CD_3OD) 1.36–1.70 (14H, m, *t*-butylH and -CH_2)$_2$ and OH), 2.59 (1H, br s, -CHRCONH$_2$), 2.72 (1H, br dd, 1 x CH_2Ph), 2.86 (1H, m, 1x CH_2Ph), 3.20 (2H, m, -CONHCH_2), 4.25 (1H, br s, BocNHCHCO-), 5.12 (1H, br s, PhCHOH), 5.58–5.80 (3H, m, BocNH and CONH$_2$), 6.90 (1H, br s, amide CONH), 7.19–7.44 (10H, m, PhH); IR 3000–3400, 1682, 1657, 1627, 1530 cm^{-1}; MS m/e (FAB) 492 (M + Na, 30%), 470 (M + H, 29), 370 (M + H-Boc,100); Anal. $C_{26}H_{35}N_3O_5$ (C,H,N).

5j; white powder (47%); m.p. 101–105°C; ^{1}H NMR ($CDCl_3$) 1.44 (9H, s, *t*-butylH), 1.50–1.72 (5H, m, -CH_2CH_2- and OH), 2.45 (1H, m, -CHRCONH$_2$), 2.68 (1H, dd, 6.0Hz and 13.6Hz, 1 x CH_2Ph), 2.89 (1H, dd, 8.8Hz and 13.6Hz, 1 x CH_2Ph), 3.15–3.31 (2H, m, -CONHCH_2-), 3.65 (1H, m, BocNHCHRCO), 3.98 (1H, br d, 11.2Hz) and 4.12 (1H, m, CH_2OH), 5.60–5.73 (3H, m, BocNH and CONH$_2$), 6.87 (1H, br s, amide CONH), 7.15–7.29 (5H, m, PhH); IR 3317 (br), 1690, 1661, 1562, 1526 cm^{-1}; MS m/e (Cl) 394 (M + H, 3%), 294 (M + H-Boc, 100%); α_D + 0.8° (MeOH, 19°C, c = 1.1); Anal. $C_{20}H_{31}N_3O_5 \cdot 0\ 5H_2O$ (C,H,N).

*(2S)-5-serinylamino-2-benzylpentanoic acid amides **6g,h**.* A TFA (0.1M) solution of the Boc protected amine **5i** or **j** was stirred at ambient temperature for 20 min and then the solvent removed. The residue was poured into saturated aqueous $NaHCO_3$ and this aqueous solution extracted repeatedly (continuous extraction necessary for 6h) with EtOAc. The extract was dried ($MgSO_4$), filtered, concentrated and purified by silica chromatography eluting with the specified solvent mixtures to give the products as follows:

6g; column eluant MeOH:CH_2Cl_2 (1:4); yield 74%; white powder; m.p. 70–73°C; ^{1}H NMR (DMSO-d_6) 1.28–1.39 (4H, m, -CH_2CH_2-), 1.89 (2H, br s, NH_2), 2.40 (1H, m, CHCONH$_2$), 2.52 (1H) and 2.75 (1H, 2dd, 9.1Hz and 13.2Hz, CH_2Ph), 2.82–3.08 (2H, m, CONHCH_2-), 3.17 (1H, d, 4.2Hz, H_2NCHCONH-), 4.83 (1 H, br s, PhCHOH), 5.37 (1H, br s, OH), 6.67 (1H, s, 1 x CONH$_2$), 7.15–7.31 (11H, m, PhH and 1 x CONH$_2$), 7.79 (1H, br t, -CONH-); IR 3296 (br), 1657 cm^{-1}; MS m/e (FAB) 392 (M+Na; 74%), 370 (M+H, 100%); Anal. $C_{21}H_{27}N_3O_3 \cdot 0.5H_2O$ (C,H,N).

6h; column eluant MeOH:CH_2Cl_2 (3:7–2:3); yield 60%; hygroscopic white powder; becomes glassy 45–50°C; ^{1}H NMR (DMSO-d_6) 1.28–1.47 (4H, m, -CH_2CH_2-), 2.36–2.45 (1H, m, CHCONH$_2$), 2.53 (1H, dd, 5.9Hz and 13.3Hz) and 2.78 (1H, dd,8.5Hz and 13.3Hz, CH_2Ph), 2.97–3.08 (2H, m, CONHCH_2-), 3.10–3.35 (m, OH, NH_2, H_2NCHCONH- and H_2O), 3.38 (1H, dd, 6.3Hz and 10.4Hz) and 3.50 (1H, dd, 4.6Hz and 10.4Hz, CH_2OH), 6.67 (1H, s, 1 x CONH$_2$), 7.15–7.26 (6H, m, PhH and 1 x CONH$_2$), 7.88 (1H, br t, -CONH-); IR 3000–3600, 1662cm^{-1}; MS found m/e (Cl) 294.1820. $C_{15}H_{24}N_3O_3$ (M+H) requires 294.18176.

*5-(2-[[α-methyl-*N*-(Tricyclo[3.3.1.1^{3,7}]dec-2-yloxycarbonyl)-(R)-tryptophanyl] amino]-2-[hydroxymethyl]-*

acetylamino)-2(S)-2-benzylpentanamides 7j–l. These were prepared by the same method as compounds **7a–i** from amines **6g** and **6h** giving the coupled products **7j–l** as follows (isomeric separation of **7j** and **7k** was achieved by reverse phase chromatography as described):

7j; eluant: MeOH:H_2O; 80:20–85:15; 34% yield after isomer separation; white powder; m.p. 120–122°C; ^{1}H NMR ($CDCl_3$) 1.45–1.95 (22H, m, 14 x adamantyl H, $(CH_2)_2$, OH and α-CH_3), 2.47 (1H, m, $CHCONH_2$), 2.68 (1H, dd, 5.1 and 14.5Hz, 1 x $PhCH_2$) and 2.83–2.98 (3H, m, 1 x CH_2Ph and indole CH_2), 3.06 and 3.31 (2H, 2m, $CONHCH_2$), 4.62 (1H, dd, 2.0 and 8.2Hz, NHCHCONH-), 4.68 (1H, s, adamantyl C(2)H), 5.31 (2H, m, PhCHOH and AdocNH), 5.38 (1H, s) and 5.79 (1H, s, $CONH_2$), 6.65 (1H, br s, indole C(2)H), 6.82 (1H, d, 6.5Hz, $TrpCONH_2$), 7.15–7.37 (14H, m, indole C(5,6,7)H, PhH and 1 x -CONH-), 7.51 (1H, d, 7.7Hz, indole C(4)H), 8.25 (1H, s, indole NH); IR 3330, 1663, 1549, 1496 cm^{-1}; MS m/e (FAB) 748.5 (M+H, 100%); α_D -11.6° (MeOH, 19°C, c = 0.41); Anal. $C_{44}H_{53}N_5O_6$ (C,H,N).

7k; eluant: MeOH:H_2O; 80:20–85:15; 35% yield after isomer separation and crystallisation (CH_2Cl_2; colourless octagonal plates; m.p. 125.8–127.8°C; ^{1}H NMR ($CDCl_3$) 1.04 (3H, s, α-CH_3), 1.55–1.99 (18H, m, 14 x adamantyl H, $(CH_2)_2$), 2.52 (1H, m, $CHCONH_2$), 2.69 (1H, dd, 6.0 and 13.5Hz) and 2.91 (1H, dd, 8.5 and 13.5Hz, CH_2Ph), 3.30 (2H, m, $CONHCH_2$),3.22 (1H, d, 14.9Hz) and 3.40 (1H, d, 14.9Hz, indole CH_2), 3.85 (1H, br signal, OH), 4.67 (1H, dd, 2.0 and 8.5Hz, NHCHCONH-), 4.78 (1H, s, adamantyl C(2)H), 5.00 (1H, PhCHOH), 5.42 (1H, s) and 5.92 (1H, s, $CONH_2$), 5.47 (1H, s, AdocNH), 6.79–6.82 (2H, m, Trp CONH and indole C(2)H), 7.02–7.34 (13H, m, indole C(5,6,7)H and PhH), 7.45–7.50 (2H, m, indole C(4)H and 1 x -CONH-), 8.30 (1H, s, indole NH); IR 3310, 1657, 1542, 1495 cm^{-1}; MS m/e (FAB) 748.5 (M+H, 60%); α_D +41.0° (MeOH, 19°C, c = 0.60); Anal. $C_{44}H_{53}N_5O_6$.

7l; eluant: MeOH:H_2O; 7:3–8:2; 59% yield; white powder; m.p. 122–124°C; ^{1}H NMR ($CDCl_3$) 1.40–2.04 (21H, m, 14 x adamantyl H, $(CH_2)_2$, $TrpCH_3$), 2.10 (1H, br signal, OH), 2.48 (1H, m, $CHCONH_2$), 2.68 (1H, dd, 5.9 and 13.5Hz) and 2.89 (1H, dd, 8.6 and 13.5Hz, CH_2Ph), 3.10 and 3.24 (2H, 2m, $CONHCH_2$), 3.36 (1H, d, 14.6Hz) and 3.45 (1H, d, 14.6Hz, indole CH_2), 3.50 (1H, dd, 15.9 and 4.0Hz) and 4.05 (1H, br d, CH_2OH), 4.37 (1H, m, Ser α-H), 4.80 (1H, s, adamantyl C(2)H), 5.24 (1H, s, AdocNH), 5.45 (1H, s) and 5.88 (1H, s, $CONH_2$), 6.98–7.27 (9H, m, indole C(2,5,6)H, PhH and 1 x -CONH-), 7.36 (2H, d, 7.9Hz, indole C(7)H and 1 x -CONH-), 7.56 (1H, d, 7.8Hz, indole C(4)H), 8.50 (1H, s, indole NH); IR 3323, 1658, 1497 cm^{-1}; MS m/e (FAB) 672 (M+H, 23%); α_D +64.9° (MeOH, 20°C, c = 0.57); Anal. $C_{38}H_{49}N_5O_6 \cdot 0.5H_2O$ (C,H,N).

4-{N-[α-methyl-N'-{Tricyclo[3.3.1.1^{3,7}]dec-2-yloxy-carbonyl}-(R)-tryptophyl]-(2S)-2-[(4S)-4-aminocarbonyl-5-phenylpentylamino]-2-aminoethoxy} -4-oxobutanoic acids 2j–l. These were prepared by the same method as compounds 2a-i, giving products as follows:

2j; eluant MeOH:H_2O (65:35–75:25); yield 74%; white powder, m.p. 120–123°C; ^{1}H NMR 1.40–2.05 (21H, m,14 x adamantyl H, α-CH_3 and -$(CH_2)_2$-), 2.50–2.72 (6H, m, $CO(CH_2)_2COOH$, -$CHCONH_2$ and 1 x CH_2Ph), 2.86–3.05 (4H, m, CH_2-indole, 1 x CH_2Ph and 1 x -$CONHCH_2$-), 3.35–3.46 (1H, m, 1 x $CONHCH_2$-), 2.30–4.20 (v br signal, COOH/H_2O), 4.78 (1H, s, adamantyl C(2)H), 4.82 (1H, dd, 9.7Hz and ca. 2Hz, -NHCHCONH-), 5.46 (1H, s, AdocNH), 6.02 and 6.27 (2H, 2s, $CONH_2$), 6.55 (1H, br. d, ca. 2Hz, PhCHO-succinate), 6.72 (1H, br s, indole C(2)H),7.00 (1H, d, 8.3Hz, TrpCONH), 7.11–7.52 (15H, m, PhH, indole C(4,5,6,7)H and 1 x -CONH-), 8.46 (1H, s, indole NH), IR 2400–3600 (max. 3308), 1658 (br), 1494 cm^{-1}; MS m/e (FAB) 848.5 (M+H,100%); α_D +19.6° (MeOH, 20°C, c = 0.47); Anal. $C_{48}H_{57}N_5O_9 \cdot 0.5H_2O$ (C,H,N).

2k; eluant MeOH:H_2O (65:35–75:25); yield 73%; white powder, m.p. 123–125°C; ^{1}H NMR ($CDCl_3$ + 1 drop DMSO-d_6) 1.10 (3H, s, α-CH_3), 1.55–2.05 (18H, m, adamantyl H and -$(CH_2)_2$-), 2.00–3.00 (v br signal, COOH/H_2O), 2.54–2.71 (6H, m, $CO(CH_2)_2COOH$, $CHCONH_2$ and 1 x CH_2Ph), 2.94 (1H, dd, 9.3Hz and 12.0Hz, 1 x CH_2Ph), 3.08–3.18 and 3.27–3.39 (2H, 2m, -$CONHCH_2$-), 3.20–3.52 (2H, 2d, 15.0Hz, indole CH_2), 4.88 (2H, superimposed s and dd, adamantyl C(2)H and NHCHCONH), 5.46 (1H, br s, AdocNH), 5.89 (1H, s) and 6.16 (1H, br s, $CONH_2$), 6.58 (1H, d, ca. 2.0Hz, PhCHO-succinate), 6.87 (1H, br s, indole C(2)H), 6.95–7.36 (14H, m, PhH, indole C(5,6,7)H and 1 x CONH), 7.49 (1H, d, 8.0Hz, indole C(4)H), 7.52 (1H, br s, -CONH-), 9.19 (1H, s, indole NH); IR 2400–3600 (br), 1660, 1495 cm^{-1}; MS m/e (FAB) 848 (M + H,15%); α_D +24.8° (MeOH, 20°C, c = 0.37); Anal. $C_{48}H_{57}N_5O_9$ (C,H,N).

2l; eluant MeOH:H_2O (65:35–75:25); yield 75%; white powder, m.p. 115–117°C; ^{1}H NMR 1.25–2.05 (21H, m, 14 x adamantyl H, α-CH_3 and -$(CH_2)_2$-), 2.30–2.72 (7H, m, $CO(CH_2)_2COOH$, $PhCH_2$ and $CHCONH_2$), 2.92–3.05 (1H, m, 1 x $CONHCH_2$-), 3.28–3.42 (1H, m, 1 x $CONHCH_2$), 3.30 (1H, d, 14.4Hz) and 3.54 (1H, d, 14.4Hz, indole-CH_2), 4.40 (1H, br d, ca. 8Hz) and 4.50 (1H, br d, ca. 8Hz, -CH_2O-succinate), 4.60–4.68 (1H, m, -NHCHCONH-), 4.81 (1H, s, adamantyl C(2)H), 5.63 (1H, s), 6.00 (1H, s) and 6.17 (1H, s, AdocNH and $CONH_2$), 6.95–7.40 (10H, m, PhH, indole C(2,5,6,7)H and 1 x -CONH-), 7.51 (1H, d, 7.9Hz, indole C(4)H), 7.60 (1H, br s, -CONH-), 8.98 (1H, s, indole NH), (COOH not visible); IR 2400–3600 (max. 3343), 1725, 1661 cm^{-1}; MS m/e (FAB) 772 (M + H, 100%); α_D +44.7° (MeOH, 20°C, c = 0.44); Anal. $C_{42}H_{53}N_5O_9$ (C,H,N).

Acknowledgements

We thank Dr D. R. Hill for the CCK-B binding assay and Dr S. J. Boyle and Mr K.-W. Tang for performing the guinea pig isolated stomach corpus muscle strip assay.

References

1. Mutt, V.; Jorpes J. E. (1971) *Biochem. J.* **125,** 57–60.

2. Peikin, S. R.; Rottmann, A. J.; Batzri, S.; Gardner, J. D. (1978) *Am. J. Physiol.* **235,** E743–749.

3. Jensen, R. T.; Lemp, G. F.; Gardner, J. D. (1982) *J. Biol. Chem.* **257,** 5554–5559.

4. Vanderhaeghen, J. J.; Lotslra, F.; De Mey, J.; Gilles, C. (1980) *Proc. Natl Acad. Sci. U.S.A.* **77,** 1190–1194.

5. Sakamoto, C.; Williams, J. A.; Goldfine, I. D. (1984) *Biochem. Biophys. Res. Commun.* **124,** 49.

6. Innis, R. B.; Snyder, S. H. (1980) *Proc. Natl Acad. Sci. U.S.A.* **77,** 6917–6921.

7. Woodruff, G. N.; Hughes, J. (1991) *Annu. Rev. Pharmacol. Toxicol.* **31,** 469–501.

8. Freidinger, R. M. (1989) *Med. Res. Rev.* **9,** 271–290.

9. Lignon, M.-F.; Galas, M.-C.; Rodriguez, M.; Laur, J.; Aumelas, A.; Martinez, J. (1987) *J. Biol. Chem.* **262,** 7226–7231.

10. Yasui, A.; Douglas, A. J.; Walker, B.; Magee, D. F.; Murphy, R. F. (1990) *Int. J. Pept. Protein Res.* **3–5,** 301–307.

11. Rodriguez, M.; Lignon, M.-F.; Galas, M.-C.; Amblard, M.; Martinez, J. In *Peptides; Chemistry, Structure and Biology* , pp. 108–110 (Proceedings of the 11th American Peptide Symposium, La Jolla, U.S.A., 1989; Eds Rivier J. E., Marshall G. R.) ESCOM, Leiden, 1990.

12. Martinez, J.; Bali, J. P.; Magous, R.; Laur, J.; Lignon, M.-F.; Briet, C.; Nisato, D.; Castro, B. (1985) *J. Med. Chem.* **28,** 273–278.

13. Martinez, J.; Rodriguez. M.; Bali. J.-P.; Laur, J. (1986) *J. Med. Chem.* **29,** 2201–2206.

14. Martinez, J.; Magous, R.; Lignon, M.-F.; Laur, J.; Castro, B.; Bali, J.-P. (1984) *J. Med. Chem.* **27,** 1597–1601.

15. Morley, J. S. (1986) *Proc. Roy. Soc. B.* **170,** 97–111.

16. Zarandi, M.; Penke, B.; Varga, J.; Kovacs, K. (1982) *Peptides* 577–581.

17. Lin, C. W; Holladay, M. W.; Barrett, R. W.; Wolfram, C. A. W.; Miller, T. R.; Witte, D.; Kerwin, J. F.; Wagenaar, F.; Nadzan, A. (1990) *Mol. Pharmacol.* **36,** 881–886.

18. Martinez, J.; Bali, J.-P.; Rodriguez, M.; Castro, B.; Magous, R.; Laur, J.; Lignon, M.-F. (1985) *J. Med. Chem.* **28,** 1874–1879.

19. Spanarkel, M.; Martinez, J.; Briet, C.; Jensen, R. T.; Gardner, J. D. (1983) *J. Biol. Chem.* **258,** 6746–6749.

20. Holladay, M. W.; Lin, C.-W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A. W.; Nadzan, A. M. (1991) *J. Med. Chem.* **34,** 455–457.

21. Horwell, D. C.; Birchmore, B.; Boden, P. R.; Higginbottom, M.; Ping, H.-Y.; Hughes, J.; Hunter, J. C.; Richardson, R. S. (1990) *Eur. J. Med. Chem.* **25,** 53–60.

22. Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N. (1991) *J. Med. Chem.* **34,** 404–414.

23. Morley, J. S. *First International Symposium on Hormonal Peceptors in Digestive Tract Physiology, INSERM Symp. No.3,* pp. 3–11 (Eds Bonfils *et al.*) Elsevier/North Holland, Biomedical Press, 1977.

24. Rodriguez, M.; Fulcrand, P.; Laur, J.; Aumelas, A; Bali, J. P.; Martinez, J. (1989) *J. Med. Chem.* **32,** 522–528.

25. Horwell D. C., unpublished results.

26. Shaw, K. N. F.; Fox, S. W. (1953) *J. Am. Chem. Soc.* **75,** 3421–3424.

27. Evans, D. A.; Ennis, M. D.; Mathre, D. J. (1982) *J. Am. Chem. Soc.* **104,** 1737–1739.

28. Khouki, N.; Vaultier, M.; Carrie, R. (1987) *Tetrahedron* **43,** 1811–1822.

29. Evans, D. A.; Britton, T. C.; Ellman, J. A. (1987) *Tetrahedron Lett.* **28,** 6141–6144.

30. Parker, D. J. (1983) *Chem. Soc. Perkin Trans. 2,* 83–88.

31. Chen, S.-T.; Wu, S.-H.; Wang, K.-T. (1989) *Synthesis,* 37–38.

32. Farmer, P. S. In *Drug Design, Vol. X* (Ed. Ariens, E.), Academic Press, London, 1980.

33. Pincus, M. R.; Randall, M. B.; Carty, R. P.; Chen, J.; Shah, D.; Scheraga, H. A. (1988) *Peptides,* **9**(Suppl. 1), 145–152.

34. De Lean, A.; Munson, P. J.; Rodbard, D. (1979) *Mol. Pharmacol.* **15,** 60–70.

35. Ganellin, R. C. In *Recent Advances in Drug Research,* pp. 31–67 (Eds Cleave, M. J., Ganellin, C. R. *et al.*) Symposium Press, London, 1979.

36. Boyle, S. J.; Tang, K. W.; McKnight, A. T.; Woodruff, G. N. (1992) *Brit. J. Pharmacol.,* in press.

37. Gregory, H.; Jones, D. S.; Morley, J. S. (1986) *J. Chem. Soc. C.,* 531–540.