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Rational Design of High Affinity Tachykinin NK_1 Receptor Antagonists

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Abstract—The rational design of a non-peptide tachykinin NK_1 receptor antagonist, [(2-benzofuran)-CH_2OCO]-(*R*)-α-MeTrp-(*S*)-NHCH(CH_3)Ph (**28**, PD 154075) is described. Compound **28** has a K_i = 9 and 0.35 nM for the NK_1 receptor binding site in guinea-pig cerebral cortex membranes and human IM9, cells respectively (using [^{125}I] Bolton–Hunter-SP as the radioligand). It is a potent antagonist *in vitro* where it antagonises the contractions mediated by SPOMe in the guinea-pig ileum (K_B = 0 3 nM). Compound **28** is active *in vivo* in the guinea-pig plasma extravasation model, where it is able to block the SPOMe-induced protein plasma extravasation (monitored by Evans Blue) in the bladder with an ID_{50} of 0.02 mg kg^{-1} iv.

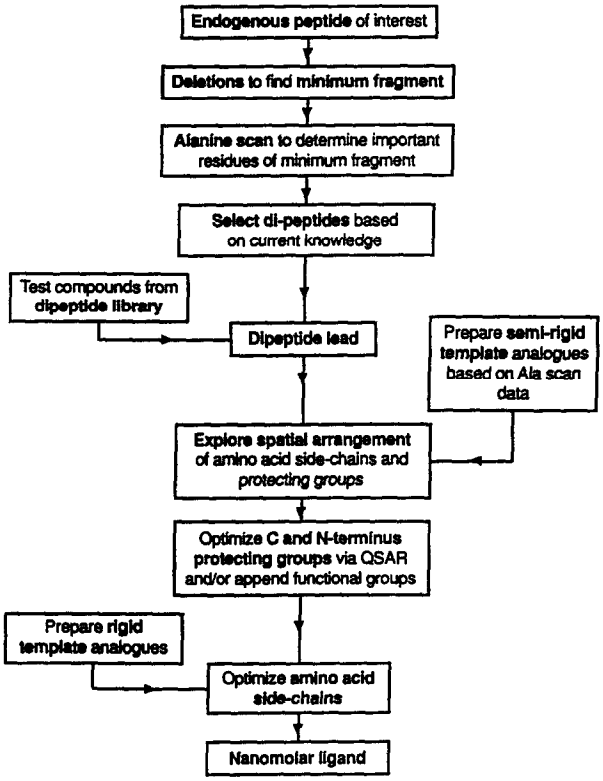
Introduction

Substance P (**1**) is the best known of the mammalian tachykinins and has been shown to display preferential affinity for the NK_1 tachykinin receptor.[1] Substance P and the other tachykinins are suggested to play a major role in a variety of biological processes including pain transmission, vasodilation, bronchoconstriction, activation of the immune system and neurogenic inflammation.[2]

A number of high affinity, non-peptide NK_1 tachykinin receptor antagonists have been identified primarily as a result of the screening of large compound collections using high throughput radioligand binding assays,[3] these include the following: the quinuclidine derivative, CP-96345 (**2**),[3a] the piperidine derivative, CP-99994,[3b] the perhydroisoindolone derivative, RP-67580 (**3**),[3c] the steroid derivative, WIN 51708 (**4**),[3d] the piperidine derivative, SR-140333,[3c] and a tryptophan derivative.[3f]

FK888 (**5**), a di-peptide with high affinity for the NK_1 receptor was rationally designed from the octapeptide [D-Pro,[4] D-Trp,[7,9,10] Phe[11]]SP(4-11).[4] Schilling *et al.* have described a series of piperidines as NK_1 receptor antagonists derived from a peptide/template approach.[5]

Here we describe the rational design of low molecular weight, non-peptide NK_1 receptor antagonists. Our approach is similar to that reported by Horwell which led to the first rationally designed non-peptide antagonist at cholecystokinin receptors.[6] This strategy[7] has been further refined during the course of this work and is outlined in Scheme I.

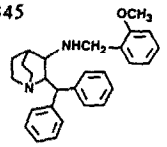
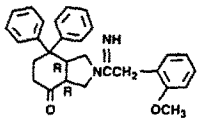
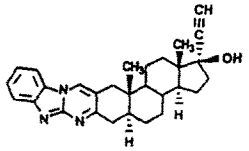
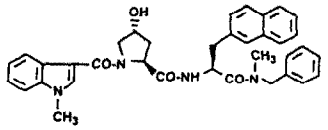


Scheme I. A strategy for peptoid design.

Chemistry

The structures of the compounds prepared can be found in Tables 1 and 2 together with their binding affinity for the tachykinin NK_1 receptor (guinea-pig cerebral cortex membranes).

Table 1. NK_1 tachykinin receptor binding affinities: standards and deletions

Compound No	Structure	NK_1 receptor binding affinity, K_i(nM)
1	Substance P: ArgProLysProGlnGlnPhePheGlyLeuMetNH_2[a]	0.05 (-0 01, +0 01)[b]
2	racemic CP-96345 	1.4
3	RP-67580 	130 (-15, +17)
4	WIN 51708 	>10,000
5	FK 888 	6.4 (-1.5, +1 8)
6	Z-TrpPheNH_2	4200 (-480, +550)
7	CH_3OCO-TrpPheNH_2	>10,000
8	TrpPheNH_2	>10,000
9	desNH_2-TrpPheNH_2	>10,000
10a	Z-TrpNH$(CH_2)_2$Ph	1400 (-460, 690)
10b	Z-TrpNHCH_2Ph	750 (-180, +230)
10c	Z-TrpNHPh	>10,000

[a]All aminoacids have (*S*)-stereochemistry unless indicated.
[b]Ki values are given as geometric means (-, +sem) from at least 3 separate experiments using [^{125}I]-BHSP in the Guinea-pig cerebral cortex assay.

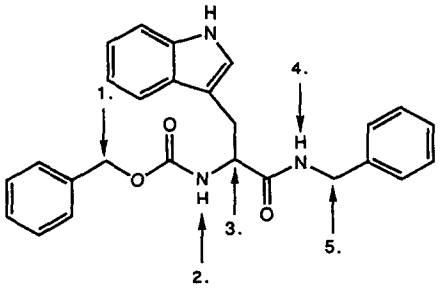
The compounds **1–5** where purchased from commercial sources or prepared as previously reported.[8] The dipeptide **6** was prepared as described by Boyle *et al.*,[7] while the methylurethane analogue **7** was obtained by reacting (*S*)-tryptophyl-(*S*)-phenylalaninamide (**8**)[7] with methylchloroformate. The des-amino analogue of **8**, compound **9**, was synthesized by the condensation of 3-indolepropionic acid with (*S*)-phenylalaninamide. The C-terminal deleted derivatives of **6**, compounds **10a–c**, were prepared by the reaction of *N*-(benzyloxycarbonyl)-(U)-tryptophan pentafluorophenyl ester (U = *S*) with the appropriate primary amine, while the enantiomer of **10b**, compound **10d**, was obtained in a similar manner from (U)-tryptophan (U = *R*), see Scheme II.

The N-terminal α-methylbenzyl analogues of **10b**, compounds **11a–d**, were synthesized by the method shown in Scheme III. *N*-[(9H-Fluoren-9-ylmethoxy)carbonyl]-(V)-tryptophan pentafluorophenyl ester (V = *R* or *S*) were treated with benzylamine to give the amides **12** (V = *R* or *S*). Deprotection of the Fmoc group furnished the amines **13** (V = *R* or *S*) which were reacted with (W)-1-phenethyloxychloroformate (W = *R* or *S*) to give the four isomers **11a–d**.

The preparation of the (*R*)-*N*-Me-Trp derivative **14** was more complex (Scheme IV): (*R*)-tryptophan methyl ester was treated with 4-toluenesulphonyl chloride, followed by KOH and MeI to give the N-methylated analogue **15**. The acid **15** was subsequently activated as the pentafluorophenyl ester and reacted with benzylamine to give amide **16**. The 4-toluenesulphonyl group of **16** was then removed with sodium naphthalenide to give the secondary amine **17**, which was treated with benzylchloroformate resulting in the desired compound **14**. The (*S*)-*N*-Me-Trp derivative **18** was obtained by reacting the pentafluorophenyl ester of *N*-methyl-*N*-(benzyloxycarbonyl)-(*S*)-tryptophan[7] with benzylamine.

The α-Me-Trp derivatives, **19a** and **b**, were obtained by reacting (X)-α-methyl tryptophan methyl ester (X = *R* or *S*)[9] with benzylchloroformate to give the urethanes **20** (X = *R* or *S*). Hydrolysis of the methyl ester followed by activation with DCCI and pentafluorophenol furnished the

Table 2. NK_1 tachykinin receptor binding affinities: conformationally restricted analogues



Compound	Site of methylation					Stereochemistry			NK1 receptor
No	R^1	R^2	R^3	R^4	R^5	1	3	5	Binding affinity K_i (nM) [a]
10b	H	H	H	H	H	-	S	-	750 (-180, +230)
10d	H	H	H	H	H	-	R	-	1000(-260, +350)
11a	CH_3	H	H	H	H	R	R	-	550
11b	CH_3	H	H	H	H	S	R	-	10,000
11c	CH_3	H	H	H	H	R	S	-	850
11d	CH_3	H	H	H	H	S	S	-	1600
14	H	CH_3	H	H	H	-	R	-	2300
18	H	CH_3	H	H	H	-	S	-	120 (-25, +31)
19a	H	H	CH_3	H	H	-	R	-	780
19b	H	H	CH_3	H	H	-	S	-	>10,000
22a	H	H	H	CH_3	H	-	R	-	1400
22b	H	H	H	CH_3	H	-	S	-	170
23a	H	H	H	H	CH_3	-	R	R	2500
23b	H	H	H	H	CH_3	-	S	R	1000
23c	H	H	H	H	CH_3	-	R	S	58
23d	H	H	H	H	CH_3	-	S	S	240
24a	H	H	CH_3	H	CH_3	-	R	R	1400
24b	H	H	CH_3	H	CH_3	-	S	R	10,000
24c	H	H	CH_3	H	CH_3	-	R	S	35 (-5, +6)
24d	H	H	CH_3	H	CH_3	-	S	S	530
25			-				-		11
28			-				-		9

[a]see footnote b, Table 1.

pentafluorophenyl esters **21** (X = *R* or *S*). Treatment of **21** (X=*R* or *S*) with benzylamine gave the amides **19a** and **b** (see Scheme V).

The *N*-Me-benzamide analogues, **22a** and **b**, were prepared by reacting *N*-(benzyloxycarbonyl)-(U)-tryptophan pentafluorophenyl ester (U = *R* or *S*) with *N*-methylbenzylamine (Scheme II).

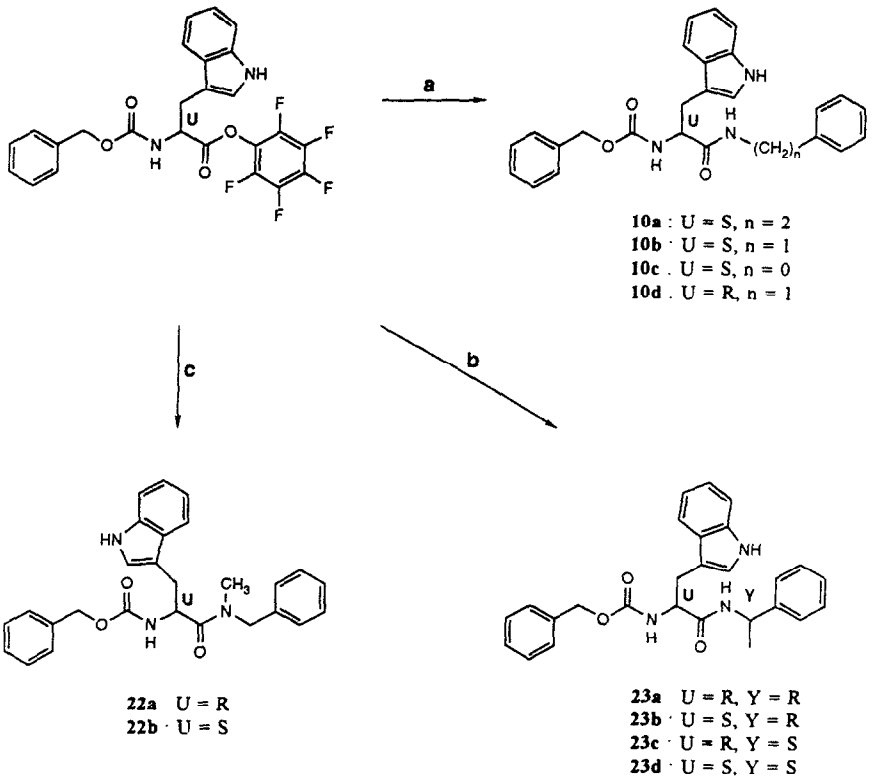
The C-terminal α-methylbenzyl analogues of **10b**, compounds **23a–d**, were synthesized by treating the pentafluorophenyl ester of *N*-(benzyloxycarbonyl)-(U)-tryptophan (U = *R* or *S*) with (Y)-α-methyl-benzylamine (Y = *R* or *S*) to fumish the four desired stereoisomers (Scheme II).

The dimethylated analogues of **10b**, compounds **24a–d**, were obtained by treatment of the pentafluorophenyl esters **21**(X = *R* or *S*) with (Y)-α-methyl-benzylamine (Y = *R* or *S*) to give the four desired stereoisomers (Scheme V).

Compound **25**, was prepared from **24c** by removal of the Z-protecting group to give the amine **26**, and subsequent reaction with the appropriate mixed carbonate **27** (Scheme V). Compound **28** was obtained in a similar manner from the mixed carbonate **29**.

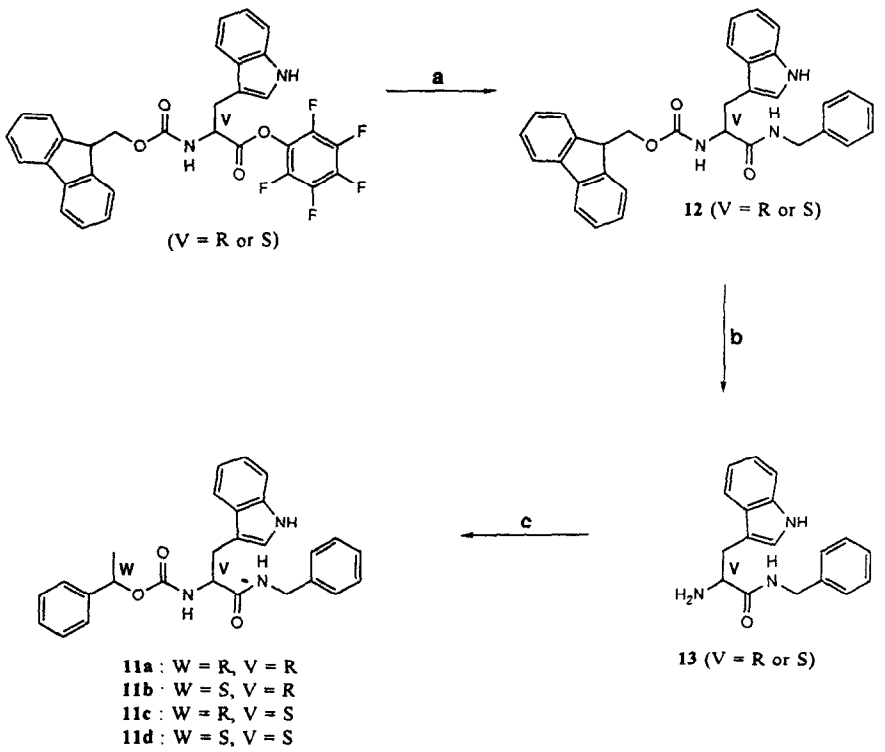
Results and Discussions

The results of NK_1 receptor binding (guinea-pig cerebral cortex membranes, [^{125}I]- Bolton–Hunter-SP) are collated in Tables 1 and 2, together with those obtained for reference compounds **1–5**.



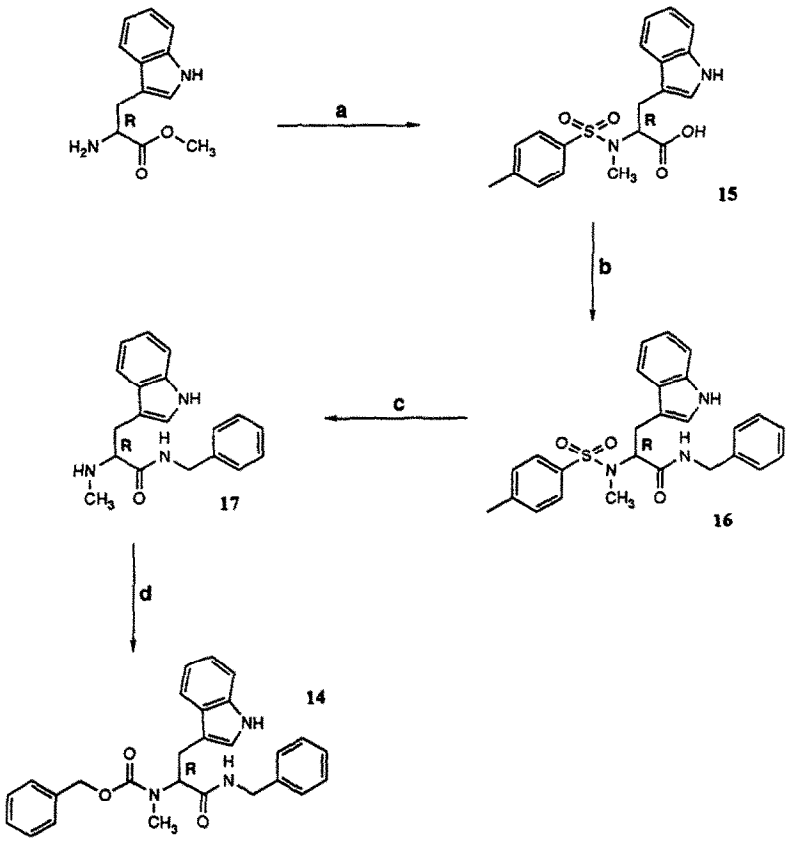
a: $NH_2(CH_2)_nPh$, EtOAc; **b**: (Y)-$NH_2CH(CH_3)Ph$, EtOAc; **c**: $NH(CH_3)CH_2Ph$, EtOAc

Scheme II. Synthetic scheme for compounds **10a–d**; **22a,b**; **23a–d**.



a: NH_2CH_2Ph, EtOAc; **b**: piperidine/DMF; **c**: Ph-(W)-$CH(CH_3)OCO_2(4\text{-}NO_2\text{-}C_6H_4)$, DMF

Scheme III. Synthetic scheme for compounds **11a–d**.



a: i. TsCl, Pyridine, ii. KOH, MeI, MeOH, H_2O; **b**: i. DCCI, PfpOH, EtOAc, ii. NH_2CH_2Ph; **c**: Sodium Naphthalenide, DME; **d**: $PhCH_2OCOCl$, Na_2CO_3, dioxane, H_2O

Scheme IV. Synthetic scheme for compound **14**.

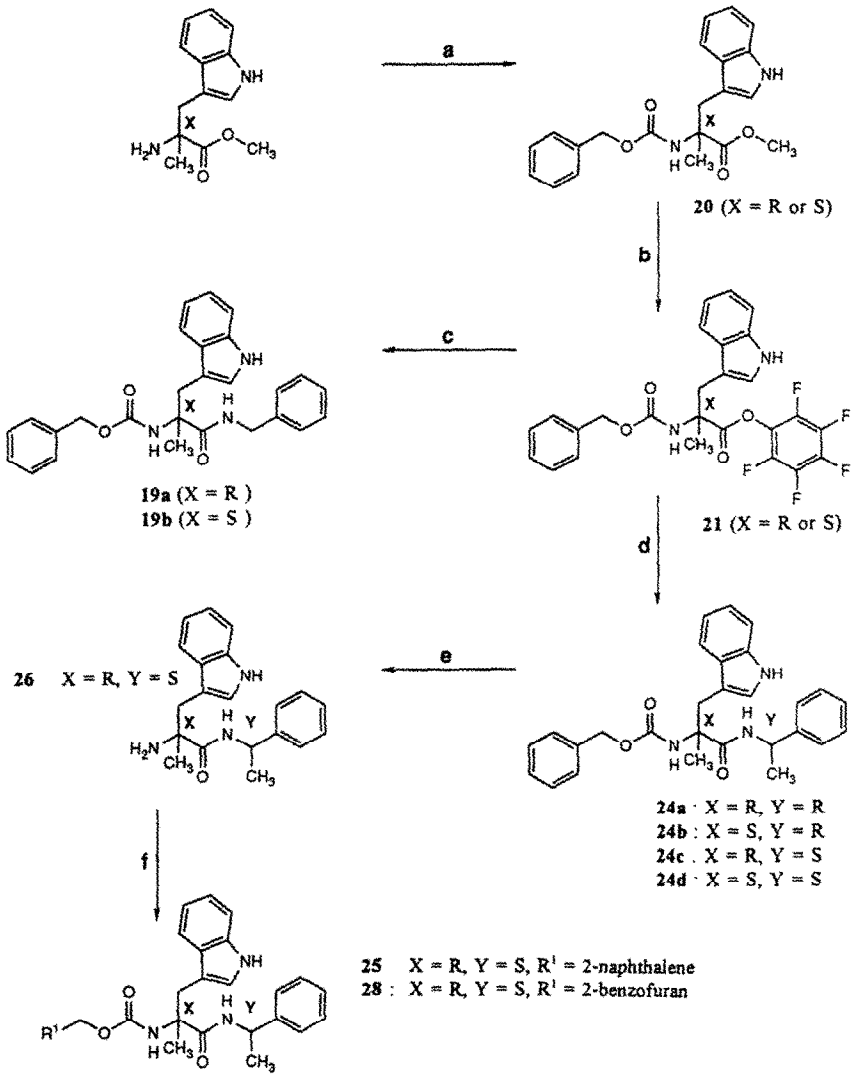
The protected dipeptide, Z-TrpPheNH$_2$ (**6**), has previously been shown to have micromolar affinity for the NK_2 receptor binding sites present in hamster urinary bladder membranes, but no significant affinity for the NK_1 and NK_3 receptor binding sites present in rat cerebral cortex membranes.[7] Interestingly compound **6** also has micromolar affinity for the guinea-pig cerebral cortex NK_1 receptor (K_i = 4200 nM) and was thus selected as a chemical lead for the search for a high affinity NK_1 receptor ligand using the guinea-pig NK, receptor assay.

Explore spatial arrangement of the amino acid side-chains and N- *and* C-*terminus groups*

a) Deletions. Having identified the micromolar affinity dipeptide lead **6** the next step in the strategy (Scheme I) is to explore the spatial arrangement of the amino acid side-chains and N- and C-terminus groups; the first part of this step involves a series of deletions. Preparation and evaluation of analogues where the N-terminal moiety or part of it were deleted led to a significant loss of affinity (K_i > 10,000 nM) in all cases (compounds **7**–**9**). Interestingly, removal of the C-terminal amide to give **10a** (K_i = 1400 nM) led to an improvement in affinity which was optimized in this series (compounds **10a**–**c**) by the deletion of a methylene to give **10b** (K_i = 750 nM). Compound **10b** is a diprotected amino-acid derivative, i e. a non-peptide and shows no significant affinity (K_i> 10,000 nM) for the NK_2 and NK_3 receptors present in hamster urinary bladder and rat cerebral cortex membranes respectively.[10]

b) Conformationally restricted analogues. The second part of this step in our strategy (Scheme I) involved preparing conformationally restrained analogues of the low affinity lead **10b**. The rationale for this is that compound **10b** has eight bonds which determine its conformation and are expected to be freely rotating under normal blood temperature conditions. The high conformational entropy associated with these degrees of freedom is expected to make a negative contribution to the overall binding affinity of **10b**.[11]

To introduce conformational restraint into Z-(*S*)-Trp-NHCH$_2$Ph (**10b**) a single methyl group was incorporated at key positions along the 'peptide' backbone. A methyl group was selected for the following reasons. Firstly, it provides a balance between decreasing conformational entropy sufficient to change the receptor binding affinity whilst still allowing sufficient conformational flexibility for the ligand to adopt the conformation(s) required for molecular recognition. Introduction of a single methyl



a: $PhCH_2OCOCl$, THF, NEt_3; **b**: i. LiOH, THF, MeOH, H_2O, ii. DCCI, PfpOH, EtOAc; **c**: NH_2CH_2Ph, EtOAc; **d**: (Y)-$NH_2CH(CH_3)Ph$, EtOAc; **e**: **24c**, H_2, $Pd(OH)_2$, EtOH; **f**: **27** or **29**, DMAP, DMF

Scheme V. Synthetic scheme for compounds **19a,b**; **24a–d**; **25**; **28**.

group into the C-α-position of related Trp derivatives has previously been shown to increase their CCK-B receptor binding by 3.5 kcal mol^{-1} (ΔK_i >100-fold).[12] This significant effect of methylation may be ascribed to the reduction in conformational entropy between the Trp and the corresponding α-MeTrp derivative.[12] Secondly, the incorporation of methyl groups into small peptides/protected amino acid derivatives confers resistance to enzymatic hydrolysis.[13] Thirdly, compared to its steric effects, a methyl group in this context has relatively little effect on lipophilicity, molecular mass or electronic properties. Fourthly, even if the methyl group introduces unfavourable steric interactions leading to a decreased binding affinity, then alternative conformational restrictions leading to improved affinity can be rationally designed.[14]

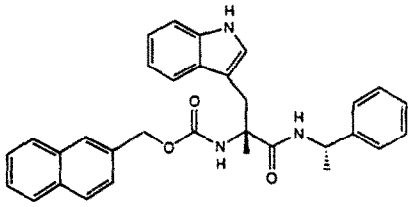
The initial synthetic targets were the monomethylated analogues (**11a–23d**). The NK_1 receptor binding data shown in Table 2 indicates that C-methylation at the N-terminal benzylic (R^1, **11a–d**) or C-α (R^3, **19a** and **b**) position has no significant effect or is detrimental. However, when compared with the non-methylated compound **10b** (K_i = 750 nM), increases in the binding affinity are observed after N-methylation of the carbonate (**18**, K_i = 120 nM), or amide (**22b**, K_i = 170 nM), or C-methylation of the C-terminal benzylic (R^5) position (**23c**, K_i = 58 nM) although the Trp-stereochemistry is reversed in this case. Thus, the introduction of a single methyl group increases the NK_1 receptor binding affinity 13-fold compared to the non-methylated derivative **10b**.

A second methyl group was then incorporated into the 'backbone' of the molecule. The most active members of the mono-methyl series were selected for evaluation. In only compound **24c** (K_i = 35 nM) was a further enhancement in the affinity achieved. This compound has a methyl group appended and (*R*)-stereochemistry at the C-α (R^3) position and a second methyl group attached and (*S*)-stereochemistry at the C-terminus benzylic (R^5) position. The other stereoisomers all possess lower affinity, in particular its enantiomer (**24b**, K_i= 10,000 nM) has 300-fold lower affinity for the NK_1 receptor.

N-terminus optimization

The affinity of **24c** (K_i = 35 nM) was improved by replacing the N-terminus phenyl with a 2-naphthalene moiety to give compound 25 (K_i = 11 nM). Replacement of the 2-naphthalene with the less lipophilic 2-benzofuran moiety to give **28** (K_i = 9 nM) led to a further increase in affinity. Compound **28** (PD 154075, Figure 1) contains no peptide amide bonds and is therefore a non-peptide. Compound **28** is selective for the NK_1 receptor (NK_2 or NK_3, K_i > 10,000 nM, hamster urinary bladder and guinea-pig cortex binding assays respectively[10]), binding to the NK_1 receptor present on human IM9 cells with a K_i = 0.35 nM. Compound **28** is a powerful tachykinin NK_1 receptor antagonist *in vitro* in the guinea-pig ileum bioassay (K_B = 0.3 nM). It is also active *in vivo* in the guinea-pig plasma extravasation model,[15] where it is able to block the SPOMe-induced protein plasma extravasation in the bladder in a dose dependent manner (ID_{50} = 0.02 mg kg^{-1} iv).

Compound **25**



Compound **28**

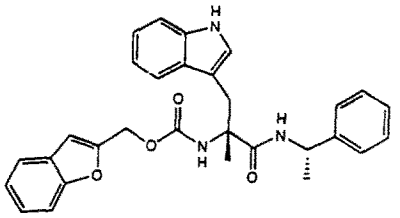


Figure 1. Chemical structure of compounds **25** and **28**.

Conclusion

Compound **28** has been identified as a non-peptide, low molecular weight, high affinity, selective NK_1 receptor antagonist. Three key steps in the design strategy which led to this compound are i) the identification of a dipeptide ligand with micromolar affinity; ii) the simplification of the chemical structure of this lead to give a conformationally flexible micromolar affinity ligand, and iii) the incorporation of conformational restraint by appending methyl groups to the peptide 'backbone' to enhance receptor affinity. This ligand based design strategy which has previously led to CCK_A, CCK_B and NK_2 antagonists (see reference 7 for example) and here has been used for the development of NK_1 antagonists, may have general application for the design of small molecule, non-peptide, receptor antagonists.

Experimental Section

Biological assays

(1) *NK_1 receptor binding assays.Guinea-pig cerebral cortex membranes.* Compounds were tested for affinity at NK_1 tachykinin binding sites by measurement of [^{125}I]Bolton–Hunter-SP (0.1 nM) binding to NK_1 sites in guinea-pig cerebral cortex membranes in the presence of 1 μM senktide (to occlude binding to NK_3 sites). Non-specific binding was defined with 1 μM [Sar^9, Met $(O_2)^{11}$] SP(1-11), see reference 10 for more details.

Human IM9 cells. IM9 cells were grown in RPMI 1640 culture medium supplemented with 10 % foetal calf serum and 2 mM glutamine and maintained under an atmosphere of 5 % CO_2. Cells were harvested for experiments by centrifugation at 1000 *g* for 3 min. Pelleted cells were washed once by resuspension into assay buffer (50 mM Tris HCl pH 7.4, 3 mM $MnCl_2$, 0.02 % BSA, 40 μg mL^{-1} bacitracin, 2 μg mL^{-1} chymostatin, 2 μM phosphoramidon, 4 μg mL^{-1} leupeptin) and repeating the centrifugation step, before resuspending at a concentration of 2.5 x 10^6 cells mL^{-1} assay buffer. Cells (200 μL) were incubated with [^{125}I]Bolton–Hunter Substance P (0.05–0.1 nM) in the presence and absence of varying concentrations of test compounds for 50 min at 21°C. Non-specific binding (10 % of the total binding observed under these conditions) was defined by 1 μM [Sar^9, Met $(O_2)^{11}$] SP(1-11). Reactions were terminated by rapid filtration under vacuum onto GF\C filters presoaked in 0.2 % PEI for 1–2 h, using a Brandel cell harvester. Filters were washed with 6 x 1 mL with ice-cold Tris HCl (50 mM, pH 7.4), and radioactivity bound determined using a gamma counter. Results were analysed using computerized curve-fitting procedures in RS1 or Inplot.

(2) *NK_2 and NK_3 receptor binding assays.* These were performed as previously described.[10]

(3) *Guinea-pig isolated ileum. Tissue preparation.* Segments of ileum from 300–400 g male Dunkin–Hartley guinea-pigs were cleared of their contents and mounted on a glass pipette of maximum outer diameter 5 mm. The longitudinal muscle layer of the ileum was carefully stripped off using moist cotton wool and the remainder discarded. Preparations of the longitudinal muscle approximately 25 mm in length, were set up under a resting tension of 1 gf (9.8 mN) for isometric recording of smooth muscle contraction (Grass FT.03C force-displacement transducer, Graphtec MKVII Linearcorder) in 3 mL silanized-glass organ baths, containing a modified 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, 11; indomethacin, 0.005; atropine, 0.01; mepyramine, 0.01; methysergide, 0.01. The solution was maintained at 37 °C and was continuously gassed with a mixture of oxygen/carbon dioxide: 95/5.

Experimental procedure. Non-cumulative concentration–response curves to the selective NK_1 agonist [Met-O-Me^{11}]substance P (substance P–methyl ester, SPOMe) were constructed by addition of increasing doses (≤10 μL) to the organ bath. To assess the affect of putative antagonists, concentration–response curves to the agonist were obtained in the absence, and then the presence of known concentrations of the presumptive antagonist. Contractile responses to SPOMe were expressed as a percentage of the maximum response for the one preparation, arld concentration–response data fitted by a least-squares iterative method in Inplot (Graphpad Software Inc.) to the logistic function $R = 100\ x^n/(EC_{50}{}^n + x^n)$, where R is the response, x is the agonist concentration, EC_{50} is the 'location parameter' for the curve (approximates to the value for EC_{50}, the concentration of agonist producing 50 % of the maximum response), and n is the 'slope factor' of the curve. The effect of the antagonist was observed as a rightward shift of the log(concentration) - response curve, and generally this was quantified in terms of the 'dose ratio' (DR) between $[EC_{50}]_A$ and $[EC_{50}]_C$, these parameters being the measures made in the presence and absence of antagonist, respectively. By repeating estimates for DR using at least three observations at any one concentration of antagonist, and not less than three concentrations of antagonist, the affinity of the antagonist was derived by Schild analysis by plotting log(DR-l) against -log[antagonist].[16] The plots were analysed by regression analysis, and if the slope of the line of best fit was not significantly different from unity, the intercept on the abscissa from the regression analysis with the slope constrained to unity was taken as the negative logarithm of K_B (pK_B), the estimate of the antagonist dissociation constant.

(4) *Extravasation of plasma protein in the guinea-pig.*[15] *Preparation.* Male Dunkin–Hartley guinea-pigs (250–350 g) were anaethetized with equithesin (35 mL kg^{-1} ip), and following tracheostomy were respired artificially with room air. The left jugular vein was cannulated for drug administration; body temperature was maintained at 37°C using a homeothermic blanket.

Experimental procedure. Evans Blue dye (30 mg kg^{-1} iv) was administered 5 min prior to administration of antagonist or vehicle (DMSO). A further 5 min elapsed before administration of the NK_1 agonist SPOMe (or vehicle) at a dosc of 3 nmol kg^{-1} iv, and 5 min later the animal was killed and the urinary bladder, and other tissues were removed. Tissues were roughly chopped and treated for extraction of Evans Blue bound to plasma protein by incubation overnight at 60°C in 4 ml formamide. Extracts were centrifuged at 3000 r.p.m. for 15 min and the concentration of dye in the supernatant quantified by absorption spectrometry at 620 nm, against a standard curve of Evans Blue in the range 0–10 μg mL^{-1}. Animals treated with vehicle alone were used to obtain values for basal levels of extravasation of bound dye (and to account for residual dye in blood vessels in the tissue), and the basal value was subtracted from the response obtained in groups ($n \geq 4$) given SPOMe. The activity of the antagonist was quantifled in terms of the estimated value for ID_{50} obtained from the best fit to the dose–response data for block of the SPOMe-evoked extravasation response, using an iterative (least-squares) curve-fitting programme (InPlot) with the logistic function: R = basal + (max-basal)/$\{1+(x/ID_{50})^n\}$, where max is the effect with SPOMe alone, basal is the response (R) in the vehicle-treated animal, x is the dose of antagonist, and n is the slope factor.

Chemistry

Melting points were determined with a Mettler FP80 or a Reichert Thermovar hotstage apparatus. Proton NMR spectra were recorded on a Bruker AM300 spectrometer; chemical shifts were recorded in 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 VG Analytical ZAB-E. 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. All other chemicals were purchased from Aldrich Chemical Co. Ltd, Gillingham, U.K. and were used without further purification, unless stated.

N-(Methoxycarbonyl)-(S)-tryptophyl-(S)-phenylalaninamide (7). Methylchloroformate (0.15 mL, 2 mmol) in dioxane (10 mL) was added to a stirred suspension of (*S*)-tryptophyl-(*S*)-phenylalaninamide (**8**,[7] 0.7 g, 2 mmol) and 10 % Na_2CO_3 solution (60 mL) and dioxane (15 mL). The mixture was stirred at room temperature for 24 h and the solvent removed *in vacuo* to give a white solid. This was suspended in H_2O (150 mL) and extracted with CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give crude product. This was purified by flash chromatography on silica eluting with a mixture of CH_2Cl_2 /MeOH (95:5) to give **7** as a white solid (0.4 g, 49 %) mp 193.1–193.9 °C; ^1H NMR (DMSO-d_6) δ 2.78–3.05 (4 H, m, 2 x β-CH_2), 3.44 (3H, s, CH_3), 4.20 (1H, m, α-H), 4.47 (1H, m, α-H), 6.94–7.95 (14H, m, ArH, $CONH_2$, CONH, OCONH), 10.78 (1H, s, indoleNH); IR 3307, 1661 cm^{-1}; MS m/z (FAB) 409 (M+H), Anal. $C_{22}H_{24}N_4O_4$ 0.1 H_2O (C,H,N)

(S)-N-[2-Amino-2-oxo-1-(phenylmethyl)ethyl]-1H-indole-3-propanamide (9). 1H-Indole-3-propionic acid (368 mg, 2 mmol), ethylchloroformate (0.17 mL, 2 mmol) and triethylamine (0.28 mL, 2 mmol) were stirred in THF (10 mL) at room temperature for 15 min. Then (*S*)-phenylalaninamide (220 mg, 1.3 mmol) was added and the reaction mixture stirred for 1 h. Water was then added and the precipitate filtered and dried to give **9** as a white solid (500 mg, 75 %), mp 188.5–190.5 °C; ^1H NMR (DMSO-

d_6) δ 2.42 (2H, dd, 7.0, 8.5 Hz, CH_2CO), 2.72–2.80 (3H, m, CH_2, CH^1HCH_2CO), 2.99 (1H, dd, 13.6, 4.8 Hz, CH^1HCH_2CO), 4.48 (1H, m, α-H), 6.94–7.07 (4H, m, ArH, CONH), 7.16–7.27 (3H, m, ArH), 7.31 (1H), d, 8.1 Hz, ArH), 7.41 (1H, d, 13.7 Hz, ArH), 8.00 (1H, d, 8.6 Hz, ArH), 10.70 (1H, s, indoleNH); IR 1633 cm^{-1}; MS m/z (FAB) 336 (M+H); $[\alpha]_D$ -16.7 ° (MeOH, 20 °C, *c* = 0.09); Anal. $C_{20}H_{21}N_3O_2$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(2-phenylethyl)amino]ethyl]-phenylmethyl ester, (S) ***10a***. To a stirred solution of *N*-[(phenylmethoxy)carbonyl]-(*S*)-tryptophan (15 g, 44.3 mmol) and pentafluorophenol (8.97 g, 48.8 mmol) in CH_2Cl_2 (250 mL) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (9.35 g, 28.8 mmol). The solution was stirred for 15 h at room temperature and the mixture then washed with H_2O, 10 % $NaHCO_3$ solution, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting yellow oil was triturated with pet.-ether (40–60 °C boiling range) to give the crude product as a white solid (21.25 g 42 mmol), which was used without further purification; ^1H NMR ($CDCl_3$) δ 3.38–3.56 (2H, m, β-CH_2), 5.11 (2H, m, CH_2OCO), 5.26 (1H, m, α-H), 7.08–7.39 (10H, m, ArH, OCONH), 7.59 (1H, d, 8 Hz, ArH), 8.10 (1H, s, indole NH).

Phenylethylamine (24 mg, 0.2 mmol) dissolved in EtOAc (2 mL) was added dropwise to a stirred solution of *N*-[(phenylmethoxy)carbonyl]-(*S*)-tryptophyl-pentafluorophenyl ester (103 mg, 0.2 mmol) in EtOAc (5 mL). The reaction mixture was stirred for 18 h at room temperature, the solvent was removed *in vacuo* and the residue triturated with Et_2O to give the product **10a** as a white solid (77 mg, 0.17 mmol); mp 149–151 °C; ^1H NMR ($CDCl_3$) δ 2.44–2.59 (2H, m, $CONHCH_2$), 3.07–3.14 (1H, m, β-CH_2),3.26–3.49 (3H, m, β-CH_2, CH_2Ar), 4.40 (1H, m, α-H), 5.09 (2H, s, CH_2OCO), 5.41 (1H, m, OCONH), 5.53 (1H, m, CONH), 6.88–6.92 (4H, m, ArH), 7.12–7.36 (9H, m, ArH), 7.69 (1H, m, ArH), 7.97 (1H, m, indole NH); IR 3305, 1707, 1658 cm^{-1}; MS m/z (FAB) 442 (M+H); $[\alpha]_D$ -5.5 ° (MeOH, 20 °C, *c* = 0.35); Anal. $C_{27}H_{27}N_3O_3$ $0.25H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]-, phenylmethyl ester (S) ***10b***. Compound **10b** was prepared in a similar manner to **10a** utilizing benzylamine instead of phenylethylamine. The crude material was recrystallized from EtOAc to yield **10b** as a white solid (59 mg, 0.14 mmol), mp 154–157 °C; ^1H NMR (DMSO-d_6) δ 2.91–2.99 (1H, m, β-CH_2), 3.10–3.17 (1H, m, β-CH_2), 4.28–4.34 (3H, m, α-H, CH_2N), 4.96 (2H, s, CH_2OCO), 6.94–7.43 (15H, m, ArH, OCONH), 7.63 (1H, d, 8 Hz, ArH), 8.54 (1H, m, CONH), 10.84 (1H, s, indoleNH); IR 3306, 1705, 1657 cm^{-1}; MS m/z (FAB) 428 (M+H), 450 (M+Na); $[\alpha]_D$ -1.5 ° (MeOH, 20 °C, *c* = 0.13); Anal. $C_{26}H_{25}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-(phenylamino)ethyl]-, phenylmethyl ester, (S) ***10c***. Aniline (20 mg, 0.22 mmol) dissolved in EtOAc (2 mL) was added dropwise to a stirred solution of *N*-[(phenylmethoxy)carbonyl]-(*S*)-tryptophyl-pentafluorophenyl ester (103 mg, 0.2 mmol) in EtOAc (5 mL). The reaction mixture was stirred at room temperature for 18 h; the resulting yellow precipitate was then recrystallized from EtOAc to give the product as a white solid (82 mg, 0.16 mmol), mp 157–158 °C; ^1H NMR (DMSO-d_6) δ 2.98–3.05 (1H, m, β-CH_2), 3.13–3.19 (1H, m, β-CH_2), 4.48 (1H, m, α-H), 4.98 (2H, s, CH_2OCO), 6.95–7.33 (12H, m, ArH, OCONH), 7.53–7.69 (4H, m, ArH), 10.10 (1H, s, CONH), 10.80 (1H, s, indole NH); IR 3307, 1670 cm^{-1}; MS m/z (FAB) 414 (M+H), 436 (M+Na); $[\alpha]_D$ +39.2 ° (MeOH, 20 °C, *c* = 0.24); Anal. $C_{25}H_{23}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]-, phenylmethyl ester, (R) ***10d***. Compound **10d** was prepared in a similar manner to **10a** utilizing benzylamine instead of phenylethylamine, and *N*-[phenylmethoxycarbonyl]-(*R*)-tryptophan. The crude material was recrystallized from EtOAc to yield **10d** as a white solid (59 mg, 0.14 mmol), mp 165–167 °C; ^1H NMR (DMSO-d_6) δ 2.88–3.20 (2H, m, β-CH_2), 4.24–4.41 (3H, m, α-H, CH_2N), 4.98 (2H, s, CH_2OCO), 6.90–7.48 (15H, m, ArH, OCONH), 7.65 (1H, d, 7.8 Hz, ArH), 8.52 (1H, m, CONH), 10.80 (1H, s, indoleNH); IR 3313, 1703,1656 cm^{-1}; MS m/z (FAB) 428 (M+H); $[\alpha]_D$ +1.6 ° (MeOH, 23 °C, *c* = 0.2); Anal. $C_{26}H_{25}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]-, phenylethyl ester, [R-,(R,S*)]* ***11c***. To a solution of *N*-[(9*H*-fluoren-9-ylmethoxy)-carbonyl]-(*S*)-tryptophan pentafluorophenyl ester (5.0 g, 8.4 mmol) in EtOAc (50 mL) was added benzylamine (1.5 mL,1.5 g, 14mmol) and the mixture stirred for 2 h. The reaction mixture was then washed in 2 M HCl solution, dried ($MgSO_4$) and concentrated *in vacuo* to give crude amide **12** (V = *S*). This was taken up in DMF (50 mL) and treated with piperidine/DMF (50 mL, 20 % solution). After stirring for 20 min the volatiles were removed *in vacuo* and the residue purified by flash column chromatography on silica eluting with mixtures of CH_2Cl_2:MeOH (100:0–90:10 gradient). This gave 1.9 g (77 %) of crude amine **13** (V = *S*) as a white solid; IR 3294, 1651 cm^{-1}.

To a stirred solution of (*R*)-1-phenylethyl alcohol (1.0 mL, 1.0 g, 8.3 mmol) in acetone (10 mL) at 0°C was added 4-nitrophenylchloroformate (1.8 g, 9.2 mmol), followed by triethylamine (1.4 mL, 1.0 g, 9.9 mmol) over a 10 min period. The mixture was stirred for 30 min at this temperature and allowed to warm to room temperature. Subsequently, it was triturated with Et_2O and the precipitated triethylamine hydrochloride was filtererd off. The filtrate was concentrated *in vacuo* (without heating) and the residue purified by flash column chromatography on silica eluting with hexane:ether (90:10) to give crude mixed carbonate (1.94 g, 82 %) as a clear oil; IR 1766 cm^{-1}.

To a solution of the crude amine **13** (V = *S*) (0.1 g, 0.3 mmol) in DMF (20 mL) was added the mixed carbonate (0.13 g, 0.4 mmol) and the reaction mixture was stirred for

19 h. The reaction mixture was then taken up in EtOAc (80 mL), washed with 2 M HCl solution, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by reverse phase chromatography eluting with MeOH:H_2O (80:20) to give **11c** as a white foam (78 mg, 55 %), mp 158–161 °C, ^{1}H NMR (DMSO-d_6) δ 1.38 (3H, d, 6.6 Hz, CH_3), 2.99 (1H, dd, 8.6, 14.5 Hz, β-C^{1}HH), 3.16 (1H, dd, 5.3, 14.6 Hz, β-C^{1}H*H*), 4.26 (2H, d, 5.8 Hz, CH_2), 4.36 (1H, m, H), 5.63 (1H, dd, 6.5, 13.0 Hz, CH), 6.96 (1H, t, 7.8 Hz, indole H-5), 7.00–7.36 (14H, m, ArH, $NHCO_2$), 7.39 (1H, d, 7.8 Hz, indole H-4), 8.16 (1H, br, NHCO), 10.63 (1H, br, indole NH); IR 1705, 1661 cm^{-1}; MS m/z (CI) 442 (M+H); $[\alpha]_D$ +26 ° (MeOH, 20 °C, *c* = 0.2); Anal. $C_{27}H_{27}N_3O_3.0.1H_2O$ (C,H,N)

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]-, 1-phenylethyl ester, [R-(R,R *)]* ***11a***. Prepared as described for **11c**, but starting with (*R*)-tryptophan, to yield **11a** as a white foam (97 mg, 68 %); mp 149–150 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (3H, br, CH_3), 2.98 (1H, dd, 8.5, 14.5 Hz, β-C^1*H*H), 3.15 (obscured, β-C^{1}H*H*), 4.29 (2H, d, 5.6 Hz, CH_2), 4.33 (1H, m, Hα), 5.64 (1H, m, CH), 6.95 (1H, t, 7.7 Hz, indole H-5), 7.02–7.34 (14H, m, ArH, $NHCO_2$), 7.57 (1H, d, 7.6 Hz, indole H-4), 8.21 (1H, br, CONH), 10.63 (1H, br, indoleNH); IR 1705, 1660 cm^{-1}; MS m/z (CI) 441 (M); α_D +26 ° (MeOH, 20 °C, *c* = 0.2); Anal. $C_{27}H_{27}N_3O_3.0.1H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]-, 1-phenylmethyl ester, [S-(R,S*)]* ***11b***. Prepared as described for **11c**, but starting with (*S*)-1-phenylethyl alcohol and (*R*)-tryptophan, to give **11b** as a white foam (79 mg, 55 %); chromatography eluent MeOH:H_2O (80:20); mp 159–161 °C; ^{1}H NMR (DMSO-d_6) δ 1.37 (3H, d, 6.6 Hz, CH_3), 2.96–3.25 (2H, m, β-CH_2), 4.26 (2H, d, 5.7 Hz, CH_2), 4.35 (1H, m, α-H), 5.63 (1H, m, CH), 6.97 (1H, t, 6.9 Hz, indole H-5), 7.00–7.38 (14H, m, ArH, $NHCO_2$), 7.60 (1H, d, 7.7 Hz, indole H-4), 8.17 (1H, br, CONH), 10.65 (1H, br, indoleNH); IR 1699, 1652 cm^{-1}; MS m/z (CI) 441 (M); $[\alpha]_D$ -28 ° (MeOH, 20 °C, *c* = 0.25); Anal. $C_{27}H_{27}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]-, 1-phenylmethyl ester, [S-(R,R*)]* ***11d***. Prepared as described for **11c**, but starting with (*S*)-1-phenylethyl alcohol, to yield **11d** as a white foam (106mg, 74 %); chromatography eluent MeOH:H_2O (80:20); mp 150–151 °C; ^{1}H NMR (DMSO-d_6) δ 1.41 (3H, br, CH_3), 2.98 (1H, dd, 8.7, 14.6 Hz, β-C^1*H*H), 3.13 (obscured, β-C^{1}H*H*), 4.29 (2H, d, 5.9 Hz, CH_2), 4.31 (1H, m, α-H), 5.63 (1H, m, CH), 6.95 (1H, t, 7.7 Hz, indole H-5), 7.00–7.34 (14H, m, ArH, $NHCO_2$), 7.57 (1H, d, 7.8 Hz, indole H-4), 8.21 (1H, br, CONH), 10.62 (1H, br, indoleNH); IR 1705, 1660 cm^{-1}; MS m/z (CI) 441 (M); $[\alpha]_D$ -25 ° (MeOH, 20 °C, *c* = 0.2); Anal $C_{27}H_{27}N_3O_3.0.25H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]methyl-, phenylmethyl ester, (R) ***14*** *and N-Methyl-N-[(4-methylphenyl)sulfonyl]-(R)-tryptophan (15).* To a vigorously stirred solution of (*R*)-tryptophan methyl ester, hydrochloride (0.4 g, 1.7 mmol) in pyridine (15 mL) at room temperature was added 4-toluenesulfonylchloride (0.4 g, 2.0 mmol) over a 15 min period. After 10 min the reaction mixture was taken up in EtOAc (50 mL), washed with 2 M HCl solution, H_2O, 1 M $NaHCO_3$ solution, dried ($MgSO_4$) and the solvents removed *in vacuo*. The residue was taken up in MeOH (20 mL) and treated with H_2O (5 mL), KOH (0.5 g, 8.9 mmol) and MeI (0.5 ml, 1.1 g, 8.0 mmol). The reaction was stirred at room temperature for 48 h, then was poured into 2 M HCl solution (100 mL) and the product extracted with EtOAc (2 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica eluting with mixtures of CH_2Cl_2:MeOH (100:0 to 80:20 gradient) to give **15** as a white foam (0.27 g, 44 %); mp 131–135 °C, ^{1}H NMR (DMSO-d_6) δ 2.32 (3H, s, CH_3), 2.82 (3H, s, CH_3N) 2.96 (1H, dd, 9.3, 14.9 Hz, β-C^1*H*H), 3.26 (1H, dd, 6.2, 14.9 Hz, β-C^{1}H*H*), 4.77 (1H, dd, 6.3, 9.2 Hz, α-H), 6.96–7.47 (9H, m, ArH), 10.82 (1H, brs, indoleNH), 12.84 (1H, brs, CO_2H); IR 1722, 1324, 1158 cm^{-1}; MS m/z (CI) 373 (M+H); $[\alpha]_D$ +44 ° (MeOH, 20 °C, *c* = 1.1); Anal. $C_{19}H_{20}N_2O_4S$ (C,H,N).

*1H-Indole-3-propanamide, α-[methyl[(4-methylphenyl)sulfonyl]amino]-*N*-(phenylmethyl)-, (R)* ***16***. Compound **15** was taken up in EtOAc (50 mL), treated with DCCI (0.15 g, 0.73 mmol) and pentafluorophenol (0.14 g, 0.76 mmol) and stirred at room temperature for 30 min. A white precipitate of dicyclohexylurea was removed by filtration. The filtrate was treated with benzylamine (0.1 mL, 0.1 g, 0.9 mmol) and stirred for a further 30 min. The reaction mixture was washed with 2 M HCl solution and H_2O, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica eluting with hexane:Et_2O (90:10), CCl_4 was then added and the solvent removed *in vacuo* to give **16** as a white foam, (230 mg, 66 %); mp 55–58 °C; ^{1}H NMR (DMSO-d_6) δ 2.34 (3H, s, CH_3), 2.86 (1H, dd, 8.1, 14.5 Hz, β-C^1*H*H), 2.95 (3H, s, CH_3N), 3.18 (1H, dd, 7.5, 14.9 Hz, β-C^{1}H*H*), 4.12 (2H, m, CH_2) 4.77 (1H, m, α-H), 6.95–7.55 (14H, m, ArH), 8.55 (1H, t, 5.8 Hz, CONH), 10.80 (1H, brs, indoleNH); IR 1666, 1338, 1160 cm^{-1}; MS m/z (CI) 462 (M+H); $[\alpha]_D$ +19 ° (MeOH, 20 °C, *c* = 0.5); Anal. $C_{26}H_{27}N_3O_3S.0.25CCl_4$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]methyl-, phenylmethyl ester, (R) ***14***. Compound **16** (122 mg, 0.26 mmol) was dissolved in DME (10 mL) and cooled to -78°C. To this was added a solution of sodium naphthalenide (2 M) in DME, dropwise with stirring, until the green colour was persistent. The reaction was quenched with saturated $NaHCO_3$ solution (1 mL), then dry K_2CO_3 (2 g, 14 mmol) was added and stirring was continued for 3 h. The solid was removed by filtration, washed (Et_2O, 3 x 20 mL) and discarded. The organics were combined, concentrated *in vacuo*, and purified by flash column chromatography on silica eluting with mixtures of CH_2Cl_2:MeOH (100:0 to 80:20 gradient) to give crude **17** (61 mg, 75 %).

This was taken up in dioxane (20 mL) containing H_2O (I mL) and Na_2CO_3 (1.0 g, 9.4 mmol), and treated with benzylchloroformate (0.1 ml, 0.1 g, 0.7 mmol) and stirred for 30 min. The reaction mixture was then taken up in EtOAc (100 mL) and washed in 1 M HCl solution, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by reverse phase chromatography eluting with MeOH:H_2O (70:30) to give **14** as a white foam (62 mg, 71 %); mp 45–49 °C; ^1H NMR (DMSO-d_6) δ 2.86 (3H, br, CH_3N), 3.07 (1H, br, β-C^1*H*H), 3.30 (obscured, β-C^{1}H*H*), 4.29 (2H, d, 5.9 Hz, CH_2), 4.80–5.10 (3H, br, CO_2CH_2, α-H), 6.90–7.40 (14H, m, ArH), 7.62 (1H, br, indole H-4), 8.57 (1H, br, CONH), 10.80 (1H, br indoleNH); IR 1681, 1660 cm^{-1}; MS m/z (CI) 442 (M+H); $[\alpha]_D$ +54 ° (MeOH, 20 °C, *c* = 0.5); Anal. $C_{27}H_{27}N_3O_3.0.33H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(phenylmethyl)amino]ethyl]methyl-,phenylmethyl ester, (S) ***18.*** *N*-Methyl-*N*-[(phenylmethoxy)carbonyl]-(*S*)-tryptophan[7] (0.85 g, 24 mmol), DCCI (0.56 g, 24 mmol) and pentafluorophenol (0.44 g, 27 mmol) were dissolved in EtOAc (20 mL) and the reaction mixture stirred at room temperature for 1 h. The mixture was then filtered to remove dicyclohexylurea. Benylamine (0.3 mL, 26 mmol) was then added to the filtrate and the mixture stirred for 10 h at room temperature. The solvent was then removed *in vacuo* and the crude product purified by column chromatography on silica eluting with CH_2Cl_2:MeOH (9:1) to give **18** as a white solid (0.66 g, 63 %); mp 48–54 °C; ^1H NMR (DMSO-d_6) δ 2.88 (3H, brs, CH_3N), 3.10 (1H, brm, β-C^1*H*H), 3.33 (1H, m, β-C^{1}H*H*), 4.32 (2H, d, 5.9 Hz, CH_2), 4.80–5.20 (3H, br, CO_2CH_2, α-H), 6.80–7.70 (15H, m, ArH, OCONH), 8.65 (1H, brs, CONH), 10.85 (1H, brs, indoleNH); IR 1695, 1662 cm^{-1}; MS m/z (CI) 442 (M+H); $[\alpha]_D$ -52 ° (MeOH, 24.5 °C, *c* = 1); Anal $C_{27}H_{27}N_3O_3.0.2H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(phenylmethyl)amino]ethyl]-, phenylmethyl ester, (R) ***19a.*** A solution of (*R*)-α-methyltryptophan methyl ester[9] (Y = *R*; 37.16 g, 160 mmol) in dry THF (800 mL) and triethylamine (19.43 g, 192 mmol) was cooled to 0°C and treated with benzylchloroformate (30.0 g, 176 mmol) in dry THF (200 mL) dropwise. This was allowed to warm to room temperature slowly, then the solvent removed *in vacuo*. The residue was redissolved in EtOAc (500 mL), washed with H_2O (500 mL), 2 N HCl solution (500 mL), saturated $NaHCO_3$ solution (500 mL), then H_2O (500 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The residue was purified by chromatography on silica using Et_2O: *n*-hexane (3:2) as eluant to give the urethane **20** (X = *R*).

The crude *N*-[(phenylmethoxy)carbonyl]-α-methyl-(*R*)-tryptophan methyl ester (**20**) (X = *R*; 69.15 g, 150 mmol) was dissolved in THF (800 mL), cooled to 0 °C, and treated with LiOH (30 g in 250 mL H_2O). MeOH was added (150 mL) and the mixture stirred for 3 h. The solvent was removed *in vacuo*. The residue was diluted with H_2O (500 mL) and washed with CH_2Cl_2, (2 x 300 mL). The aqueous phase was acidified to pH = 2 using 2 M citric acid solution and extracted with CH_2Cl_2 (2 x 500 mL). The organic phase was washed with H_2O, dried ($MgSO_4$), and filtered and evaporated to dryness to give the crude acid (57.5 g), which was used in the next step . The crude carboxylic acid was redissolved in EtOAc (320 mL) and treated with pentafluorophenol (21 g, 114 mmol), followed by the dropwise addition of a solution of DCCI (23.5 g, 114 mmol) in EtOAc (150 mL). This was stirred for 18 h at room temperature. The reaction mixture was then filtered, and the filtrate evaporated to dryness. The solid residue was redissolved in CH_2Cl_2 (200 mL) and absorbed on to silica, and purified by chromatography eluting with EtOAc: *n*-hexane (1:1) to give the pentafluorophenyl ester **21** (X = *R*), 49.77 g (64 %) from α-methyl-(*R*)-tryptophan methyl ester. ^1H NMR ($CDCl_3$) δ 1.72 (3H, s, CH_3) 3.44 (1H, d, 14.7 Hz, β-C^1*H*H), 3.66 (1H, d, 14.7 Hz, β-C^{1}H*H*), 5.15 (2H, CH_2), 5.22 (1H, brs), 6.97–8.11 (12H, m, ArH, OCONH, indoleNH); IR 1785, 1709 cm^{-1}. A solution of *N*-[(phenylmethoxy)carbonyl]-α-methyl-(*R*)-tryptophan pentafluorophenyl ester **21** (X = *R*; 0.75 g, 1.5 mmol) in EtOAc (50 mL) was treated with benzylamine (0.5 ml, 0.5 g, 4.5 mmol) and stirred at room temperature for 1 h. The reaction mixture was then washed with 1M HCl solution, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was purified by flash column chromatography on silica eluting with hexane:Et_2O (50:50) to give **19a** as a white foam. (0.52 g, 76 %); mp 57–60 °C, ^1H NMR (DMSO-d_6) δ 1.36 (3H, s, α-CH_3), 3.23 (1H, d, 14.5 Hz, β-C^1*H*H), 3.40 (1H, d, 14.7 Hz, β-C^{1}H*H*), 4.27 (2H, d, 5.2 Hz, CH_2N), 5.04 (2H, dd, 12.7, 17.6 Hz, CH_2O), 6.92–7.34 (15H, m, ArH, $NHCO_2$), 7.48 (1H, d, 7.8 Hz, indole H-4), 8.28 (1H, brs, CONH), 10.82 (1H, brs, indole NH); IR 1713, 1657 cm^{-1}; MS m/z (CI) 442 (M+H); $[\alpha]_D$ +35 ° (MeOH, 20 °C, *c* = 0.5); Anal. $C_{27}H_{27}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(phenylmethyl)amino]ethyl]-, phenylmethyl ester, (S) ***19b.*** Prepared as described above for **19a** but starting from *N*-[(phenylmethoxy)carbonyl]-α-methyl-(*S*)-tryptophan to give **19b** as a white solid (0.58 g, 85 %); mp 148–149 °C; ^1H NMR (DMSO-d_6) δ 1.36 (3H, s, α-CH_3), 3.23 (1H, d, 14.5 Hz, β-C^1*H*H), 3.40 (1H, d, 14.8 Hz, β-C^{1}H*H*), 4.27 (2H, d, 5.2 Hz, CH_2N), 5.04 (2H, dd, 12.7, 17.6 Hz, CH_2O), 6.92–7.34 (15H, m, ArH, $NHCO_2$), 7.18 (1H, d, 7.8 Hz, indole H-4), 8.28 (1H, brs, NHCO), 10.82 (1H, br, indoleNH); IR 1716, 1652 cm-^{1}; MS m/z (CI) 442 (M+H); $[\alpha]_D$ -34 ° (MeOH, 20 °C, *c* = 0.5); Anal. $C_{27}H_{27}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-[methyl-(phenylmethyl)amino]-2-oxoethyl]-, phenylmethyl ester, (S) ***22b.*** *N*-[(Phenylmethoxy)carbonyl]-(*S*)-tryptophyl-pentafluorophenyl ester (0.50 g, 1 mmol) was prepared *in situ* (as described for **10a**) and reacted with N-benzylmethylamine (0.13 mL, 1 mmol) in EtOAc (5 mL). The reaction mixture was stirred overnight at room temperature then washed with 2 M HCl solution (1 x 10 mL), H_2O (4 x 10 mL), and dried ($MgSO_4$). Removal of the solvent *in vacuo* resulted in a clear oil which was purified by flash chromatography on silica eluting with

mixtures of Et_2O:hexane (1:4 to 7:3) to give **22b** as a white solid (0.175 g, 40 %); mp 48–50 °C; ^1H NMR (DMSO-d_6) δ 2.50 (3H, s, CH_3), 3.01 (1H, dd, 7.3, 13.8 Hz, β-C^1*H*H), 4.43 (2H, s, NCH_2), 4.72 (1H, m, α-CH), 5.00 (2H, s, OCH_2), 7.02–7.35 (15H, m, ArH), 7.57 (1H, brs, CO_2NH), 10.65 (1H, s, indole NH); IR 1710, 1635, 1530 cm^{-1}; MS m/z (CI) 442 (M); $[\alpha]_D$ +30.4 ° (MeOH, 23 °C, *c* = 0.25); Anal. $C_{27}H_{27}N_3O_3.0.5H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-[methyl(phenylmethyl)amino]-2-oxoethyl]-, phenylmethyl ester, (R) **22a**. Method as described for **22b**, but using *N*-[(phenylmethoxy)carbonyl]-(*R*)-tryptophan to give **22a** as a white solid (0.08 g, 35 %); mp 50–53°C; ^1H NMR (DMSO-d_6) δ 2.75 (3H, s, CH_3), 3.01 (1H, dd, 7.7, 13.9 Hz, β-C^{1}H*H*), 4.44 (2H, s, CH_2), 4.54 (1H, m, α-CH), 5.01 (2H, s, CH_2O); 6.97–7.37 (15H, m, ArH), 7.57 (1H, d, 7.7 Hz, CO_2NH), 10.7 (1H, s, indole NH); IR 1712, 1636, 1525 cm^{-1}; MS m/z (CI) 442 (M); $[\alpha]_D$ -27.2 ° (MeOH, 23 °C, *c* = 0.25); Anal. $C_{27}H_{27}N_3O_3.0.25H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [R-(R,R*)]* **23a**. *N*-[(Phenylmethoxy)carbonyl]-(*R*)-tryptophyl-pentafluorophenyl ester (0.25 g, 0.5 mmol) was prepared *in situ* (as described for **10a**), dissolved in EtOAc (2.5 mL) and (*R*)-α-methylbenzylamine (0.06 mL, 0.5 mmol) was added. The reaction mixture was stirred at room temperature until no starting material remained. The white precipitate was collected by filtration and recrystallized from EtOAc to give **23a** (0.10 g, 44 %); mp 169–170 °C, ^1H NMR (DMSO-d_6) δ 1.35 (3H, d, 6.7 Hz, C*H*$_3$CH), 2.87 (1H, dd, 9.2, 14.3 Hz, β-C^1*H*H), 3.06 (1H, dd, 4.8, 14.3 Hz, β-C^{1}H*H*), 4.36 (1H, m, *CH*(CH$_3$)Ph), 4.90–4.96 (3H, m, C*H*$_2$Ph, α-CH), 6.94–7.35 (15H, m, ArH), 7.63 (1H, d, 7.8 Hz, OCONH), 8.41 (1H, d, 7.8 Hz, CONH), 10.80 (1H, s, indoleNH); IR 3306, 1705, 1657, 1531 cm^{-1}; MS m/z (CI) 442 (M); $[\alpha]_D$ +12.8 ° (MeOH, 23 °C, *c* = 0.5); Anal. $C_{27}H_{27}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [S-(R,S*)]* **23b**. Method as described for **23a**, but using *N*-[(phenylmethoxy)carbonyl]-(*S*)-tryptophylpentafluorophenyl ester to give **23b** as a white solid (0.077 g, 17 %); mp 160–163 °C; ^1H NMR (DMSO-d_6): δ 1.24 (3H, d, 7.0 Hz, CH_3), 2.95 (1H, dd, 9.4, 14.3 Hz, β-C^1*H*H), 3.08 (1H, dd, 5.4,14.3 Hz, β-C^{1}H*H*), 4.32 (1H, m, C*H*(CH$_3$)Ph), 4.86–4.94 (3H, m, PhC*H*$_2$, α-CH), 6.95–7.34 (15H, m, ArH), 7.63 (1H, d, 7.7 Hz, OCONH), 8.32 (1H, d, 7.8 Hz, CONH), 10.80 (1H, s, indoleNH); IR 3307, 1704, 1657, 1517 cm^{-1}; MS m/z (CI) 442 (M); $[\alpha]_D$ +24.4 ° (MeOH, 23 °C, *c* = 0.5); Anal. $C_{27}H_{27}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [S-(R,S*)]* **23c**. Method as described for **23a**, but using (*S*)-α-methylbenzylamine to give **23c** as a white solid (0.09 g, 21 %); mp 160–161°C; ^1H NMR (DMSO-d_6): δ 1.23 (3H, d, 6.8 Hz, CH_3), 2.95 (1H, dd, 9.4, 14.3 Hz, β-C^1*H*H), 3.08 (1H, dd, 5.4, 14.3 Hz, β-C^{1}H*H*), 4.32 (1H, m, C*H*(CH$_3$)Ph), 4.86–4.94 (3H, m, PhC*H*$_2$, α-CH), 6.95–7.34 (15H, m, ArH), 7.63 (1H, d, 7.7 Hz, OCONH), 8.33 (1H, d, 7.5 Hz, CONH), 10.8 (1H, s, indoleNH); IR 3330, 1709, 1658, 1514 cm^{-1}; MS m/z (CI) 442 (M); $[\alpha]_D$ -26.0 ° (MeOH, 23 °C, *c* = 0.5); Anal. $C_{27}H_{27}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [S-(R,S*)]* **23d**. Method as described for **23a**, but using (*S*)-α-methylbenzylamine and *N*-[(phenylmethoxy)carbonyl]-(*S*)-tryptophyl-pentafluorophenyl ester. Recrystallization from EtOAc gave **23d** as a white solid (0.057 g, 13 %); mp 168-170 °C; ^1H NMR (DMSO-d_6) δ 1.35 (3H, d, 6.9 Hz, CH_3); 2.86 (1H, dd, 9.2, 14.3 Hz, β-C^1*H*H), 3.06 (1H, dd. 4.8, 14.3 Hz, β-C^{1}H*H*), 4.36 (1H, m, C*H*(CH$_3$)Ph), 4.90–4.96 (3H, m, PhC*H*$_2$, α-CH), 6.94–7.35 (15H, m, ArH), 7.63 (1H, d, 7.9 Hz, OCONH), 8.41 (1H, d, 7.7 Hz, CONH), 10.80 (1H, s, indoleNH); IR 3294, 1704, 1656, 1536 cm^{-1}; MS m/z (CI) 442 (M); $[\alpha]_D$ -11.6 ° (MeOH, 23 °C, *c*= 0.5); Anal. $C_{27}H_{27}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [S-(R,S*)]* **24c**. A solution of *N*-[(phenylmethoxy)-carbonyl]-α-methyl-(*R*)-tryptophan pentafluorophenyl ester **21** (X = *R*, 730 mg, 1.40 mmol) in EtOAc (15 mL) was treated with (*S*)-α-methylbenzylamine (940 mg, 7.76 mmol) and left stirring at room temperature for 1 h. The mixture was washed with 2 M HCl (20 mL) then H_2O (20 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The residue was then subject to reverse phase chromatography using 80 % MeOH; 20 % H_2O as eluant to give **24c** as a white foam (150 mg, 24 %); mp 107–109 °C; ^1H NMR (DMSO-d_6) δ 1.32 (3H, d, 7 Hz, C*H*$_3$CH), 1.38 (3H, s, CH_3), 3.20–3.40 (2H, m, β-CH_2), 4.90 (1H, m, CH), 5.00 (2H, s, CH_2O), 6.80 (1H, s), 6.90 (1H, t, 7 Hz), 7.00 (1H, t, 7 Hz), 7.01–7.40 (12H, m, ArH), 7.50 (1H, d, 8 Hz), 8.00 (1H, d, 8 Hz), 10.80 (1H, s, indoleNH); IR 3460–3400, 1711, 1658 cm^{-1}; MS m/z (CI) 456 (M+H); $[\alpha]_D$ +13.0 ° (MeOH, 20 °C, *c* = 0.5); Anal. $C_{28}H_{29}N_3O_3 \cdot 0.5H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [R-(R,R*)]* **24a**. Method as for **24c** but using (*R*)-α-methylbenzylamine to give **24a** as a white solid (150 mg, 24 %); mp 63–68 °C; ^1H NMR (DMSO-d_6) δ 1.28 (3H, d, 6.8 Hz, C*H*$_3$CH), 1.34 (3H, s, CH_3), 3.16–3.30 (2H, m, β-CH_2), 4.89 (1H, m, CH), 5.04 (2H, s, CH_2O), 6.89 (1H, s), 7.00 (1H, t, 7.9 Hz), 7.20–7.45 (13H, m, ArH), 7.48 (1H, d, 7.8 Hz), 7.88 (1H, d, 7.5 Hz), 10.80 (1H, s, indoleNH); IR 1719, 1658 cm^{-1}; MS m/z (CI) 456 (M+H); $[\alpha]_D$ +9.4 ° (MeOH, 28 °C, *c* = 0.5); Anal. $C_{28}H_{29}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [S-(R,S*)]* **24b**. Method as for **24c** but using *N*-[(phenylmethoxy)carbonyl]-α-methyl-(*S*)-tryptophan pentafluorophenyl ester **21** (Y=*S*) and (*R*)-α-methylbenzylamine

to give **24b** as a white solid (190 mg, 30 %); mp 109–111 °C; ^{1}H NMR (DMSO-d_6) δ 1.34 (3H, d, 7.9 Hz, C*H*$_3$CH), 1.39 (3H, s, CH_3), 3.28–3.36 (2H, m, β-CH_2), 4.92 (1H, m, CH), 5.04 (2H, s, CH_2O), 6.82 (1H, s), 6.87 (1H, br), 6.93 (1H, t, 7.6 Hz), 7.02 (1H, t, 7.0 Hz), 7.22–7.47 (11H, m, ArH), 7.50 (1H, d, 7.8 Hz), 8.02 (1H, d, 8.2 Hz), 10.80 (1H, s, indoleNH); IR 1719, 1654 cm^{-1}; MS m/z (CI) 456 (M+H); $[\alpha]_D$ -13.2 ° (MeOH, 24 °C, *c* = 0.5); Anal. $C_{28}H_{29}N_3O_3 \cdot 0.25H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, phenylmethyl ester, [S-(R,S*)] **24d**.* Method as for **24c** except using *N*-[(phenylmethoxy)carbonyl]-α-methyl-(*S*)-tryptophan pentafluorophenyl ester **21** (Y=*S*) to give **24d** as a white solid (142 mg, 23 %); mp 107–110 °C; ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (6H, m, 2 x CH_3), 3.10–3.40 (2H, m, β-CH_2), 4.90 (1H, m, CH), 5.00 (2H, s, CH_2O), 6.80–7.50 (16H, m, ArH, OCONH), 7.90 (1H, d, 8 Hz, CONH), 10.80 (1H, brs, indoleNH); IR 3327, 1716, 1653 cm^{-1}; $[\alpha]_D$ -9.0 ° (MeOH, 26 °C, *c* = 0.5) Anal. $C_{28}H_{29}N_3O_3 \cdot 0.25H_2O$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 2-naphthalenylmethyl ester, [R-(R,S*)] **25**. 1H-Indole-3-propanamide, α-amino-α-methyl-N-(1-phenylethyl)-, [R-(R *,S*)] **26**.* A solution of **24c** (17 g, 37 mmol) in EtOH (200 mL) was treated with 20 % $Pd(OH)_2$ (1 g, 6 % w/w) and shaken under an atmosphere of hydrogen at 30 °C at a pressure of 45 psi for 3 h. The reaction mixture was then filtered and evaporated to dryness *in vacuo*, the residue was purified by chromatography on silica eluting with NH_4OH:MeOH:CH_2Cl_2,(1:10:189) to give **26** as a white solid (8.1 g, 62 %); mp 124.5–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, d, 6.9 Hz, C*H*$_3$CH), 1.46 (3H, s, CH_3), 1.53 (2H, brs, NH_2), 2.81 (1H, d, 14.2 Hz, β-C^1*H*H), 3.46 (1H, d, 14.2 Hz, β-C^{1}H*H*), 5.02 (1H, dq, 7 Hz, CH), 6.71 (1H, d, 2.2 Hz), 7.17 (7H, m, ArH), 7.33 (1H, d, 8.0 Hz), 7.59 (1H, d, 7.8 Hz), 7.82 (1H, d, 8 Hz), 8.02 (1H, s); IR 1643, 1512, 1454 cm^{-1}, MS m/z (CI) 322 (M+H); $[\alpha]_D$ +7.0 ° (MeOH, 20 °C, *c* = 1); Anal. $C_{20}H_{23}N_3O$ (C,H,N).

Carbonic acid, 2-naphthalenylmethyl-, 4-nitrophenyl ester *(27).* To a stirred solution of 2-naphthalenemethanol (1.58g, 10 mmol) and 4-nitrophenylchloroformate (2.01g, 10 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise a solution of pyridine (0.79 g, 10 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and the residue taken up between EtOAc (50 mL) and 10 % citric acid solution (50 mL). The product was then filtered off and washed with 10 % citric acid solution followed by H_2O until the filtrate was neutral to give pure product **27** (2.37 g, 73 %); mp 150.5–152.5 °C; ^{1}H NMR (DMSO-d_6) δ 5.48 (2H, s, CH_2O), 7.50–7.65 (3H, m, ArH), 7.59 (2H, d, 9.2 Hz, ArHs *meta* to NO_2), 7.90–8.05 (4H, m, ArH); 8.32 (2H, d, 9.1 Hz, ArHs *ortho* to NO_2); IR 1752, 1615, 1595 cm^{-1}; MS m/z (CI) 323; Anal. $C_{18}H_{13}NO_5$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 2-naphthalenylmethyl ester, [R-(R,S*)] **25**.* To a stirred solution of carbonate **27** (178 mg, 0.55 mmol) and amine **26** (160 mg, 0.5 mmol) in DMF (5 mL) was added 4-dimethylaminopyridine (61 mg, 0.5 mmol) and the reaction mixture left to stir overnight at room temperature. The solvent was removed at 60 °C under reduced pressure, the residue taken up in EtOAc (30 mL) and washed successively with 10 % citric acid solution (2 x 30 mL), H_2O (30 mL), 1 N NaOH (5 x 30 mL), brine (2 x 50 mL), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica eluting with 3 % MeOH in CH_2Cl_2. Crystallisation from Et_2O gave pure **25** (220 mg, 87 %); mp 121–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, 6.9 Hz, CHC*H*$_3$); 1.63 (3H, s, CCH_3), 3.26 (1H, d, 14.7 Hz, C*H*H-indole), 3.48 (1H, d, 14.7 Hz, CH*H*-indole), 4.95–5.05 (1H, m, NHC*H*CH$_3$), 5.18–5.30 (2H, m, CH_2O), 5.40 (1H, s, OCONH), 6.30–6.40 (1H, brd, CON*H*CH), 6.74 (1H, s, indole C_2H), 7.05–7.30 (7H, m, ArH), 7.31 (1H, d, 8.0 Hz, indole C7-H), 7.40–7.52 (3H, m, ArH), 7.58 (1H, d, 8.4 Hz, indole C4-H), 7.75–7.85 (5H, m, ArH and indole NH); IR 3342, 3052, 2974, 2926, 1717, 1653 cm^{-1}; MS m/z (CI) 506.3 (M^++H); $[\alpha]_D$ +21.2 ° (MeOH, 20 °C, *c* = 0.5); Anal. $C_{32}H_{31}N_3O_3$ (C,H,N).

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-, 2-benzofuranylmethyl ester, [R-(R,S*)] **28**. Carbonic acid, 2-benzofuranylmethyl, 4-nitrophenyl ester (29).* To a stirred solution of 2-benzofuranylmethanol[17] (1.48 g, 10 mmol) and 4-nitrophenylchloroformate (2.01 g, 10 mmol) in CH_2Cl_2 (50 mL, a) at 0 °C was added dropwise a solution of pyridine (0.79 g, 10 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to room temperature ovemight. The solvent removed under reduced pressure and the residue taken up between EtOAc (50 mL) and 10 % citric acid solution (50 mL). The organic phase was washed successively with 10 % citric acid solution (2 x 50 mL), H_2O (50 mL), saturated $NaHCO_3$ solution (5 x 50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. The product was then recrystallised from Et_2O to give pure **29** (1.80 g, 58 %); mp 90.5–92.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.41 (2H, s, CH_2O), 6.90 (1H, s, benzofuran C3-H), 7.21–7.42 (2H, m, ArH), 7.39 (2H, d, 9.2 Hz, ArHs *meta* to NO_2), 7.52 (1H, d, 7.8 Hz, ArH), 7.60 (1H, d, 7.1 Hz, ArH), 8.28 (2H, d, 9.2 Hz, ArHs *ortho* to NO_2); IR 3119, 1770, 1617, 1594, 1524 cm^{-1}; MS m/z (CI) 313; Anal. $C_{16}H_{11}NO_6$ (C,H,N).

N-[[(2-Benzofuranyl)methoxy]carbonyl] -(R)-α-methyl-tryptophyl-(S)-α-methyl-benzylamide (28). To a stirred solution of carbonate **29** (185 mg, 0.6 mmol) and amine **26** (160 mg, 0.5 mmol) in DMF (5 mL) was added 4-dimethylaminopyridine (61 mg, 0.5 mmol) and the mixture left to stir overnight at room temperature. The solvent was removed at 60 °C under reduced pressure, the residue taken up in EtOAc (100 mL) and washed successively with 10 % citric acid solution (3 x 30 mL),

H_2O (30 mL), 1 N NaOH (5 x 30 mL), brine (2 x 50 mL), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was then purified by chromatography on reverse phase silica eluting with 65 % MeOH in H_2O. Crystallisation from Et_2O gave pure **28** (140 mg, 56 %); mp 103–111 °C; ^1H NMR ($CDCl_3$) δ 1.31 (3H, d, 6.9 Hz, $CHCH_3$), 1.63 (3H, s, CCH_3), 3.25 (1H, d, 14.8 Hz, C*H*H-indole), 3.47 (1H, d, 14.8 Hz, CH*H*-indole), 4.95–5.05 (1H, m, $NHCHCH_3$), 5.14 and 5.21 (each 1H, d, 13.2 Hz, $CHHO$), 5.41 (1H, s, OCONH), 6.30–6.35 (1H, brd, CONHCH), 6.74 (1H, s, benzofuran C3-H), 6.78 (1H, d, 2.3 Hz, indole C2-H), 7.05–7.33 (10H, m, ArH), 7.45 (1H, d, 8.4 Hz); 7.52–7.58 (2H, m, ArH), 7.85 (1H, s, indole NH); IR 3334, 1715, 1651cm^{-1}; MS m/z (FAB) 496.3 (M^++H); $[\alpha]_D$ +17.6 ° (MeOH, 21 °C, *c* = 0.5); Anal. $C_{30}H_{29}N_3O_4$ (C,H,N).

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