Pergamon

Tetrahedron 54 (1998) 4591–4606

TETRAHEDRON

The Use of Heterocycles for the Conformational Restriction of Biologically Active Peptoids.

David C. Horwell, Russell A. Lewthwaite*, Martyn C. Pritchard, Giles S. Ratcliffe and J. Ronald Rubin[†].

Parke-Davis Neuroscience Research Centre, Cambridge University Forvie Site, Robinson Way, Cambridge, CB2 2QB, UK.

[†] Department of Chemistry, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105, USA.

Received 11 December 1997; revised 27 January 1998; accepted 29 January 1998

Abstract : A series of piperazinone ring systems have been synthesised as a means of evaluating the effect of conformational restriction on high affinity non-peptide NK_1, NK_3 and CCK-B receptor ligands. The synthesis of the targeted heterocycles is described along with a discussion of their affinities for their respective receptor types.

INTRODUCTION

We have reported on the successes of a rational peptoid 'Drug Design Strategy' [1] and a dipeptide chemical library [2] as approaches to the discovery of non-peptide antagonists for peptidic receptors projects, *eg* cholecystokinin [3] and tachykinin .[2, 4] Representative compounds from these studies include the CCK-B receptor antagonist **1** (**PD 156885**, mCCK-B IC_{50} 74 nM), a NK_1 receptor antagonist **2** (**PD 154075**, hNK_1 IC_{50} 0.55 nM) and a NK_3 receptor antagonist **3** (**PD 132461**, hNK_3 IC_{50} 6.4 nM). The computer generated representations [5] of the X-ray derived crystal structures of these compounds show remarkable similarities to each other despite their distinct pharmacologies. It can be seen from Figure 1 that the main backbone, -OCONHC(α-Me)Trp/PheCONH-, has in each case an almost identical conformation. The amide and urethane hydrogens point in the same direction, and the two carbonyls of the amide and urethane groups point in the opposing direction, the only differences in the structures being the orientation and structure of the appended pharmacophoric groups.

The use of constrained heterocycles has been successful for the generation of higher affinity binding compounds compared with their acyclic analogues. This strategy was developed to study such effects with the selected leads **1**, **2** and **3**. The cyclisation of the peptoid backbone should result in a more conformationally restricted 'backbone' unit, and if chosen correctly, a compound which exhibits, a similar X-ray structure of the acyclic lead. Assuming the premise that the X-ray structure is the binding conformer at the receptor binding site, then higher affinity binding could be affected by these more rigid conformers.

With the aid of computer assisted modelling of various heterocycles (5-8 membered rings incorporating the -NCTrp/PheCON- backbone unit, cyclising *via* the two nitrogen atoms) the piperazinone ring system was selected for synthesis as this offered the optimal template from those studied, see Figure 2 (the compound

0040-4020/98/$19.00
PII: S0040-4020(98)00092-1

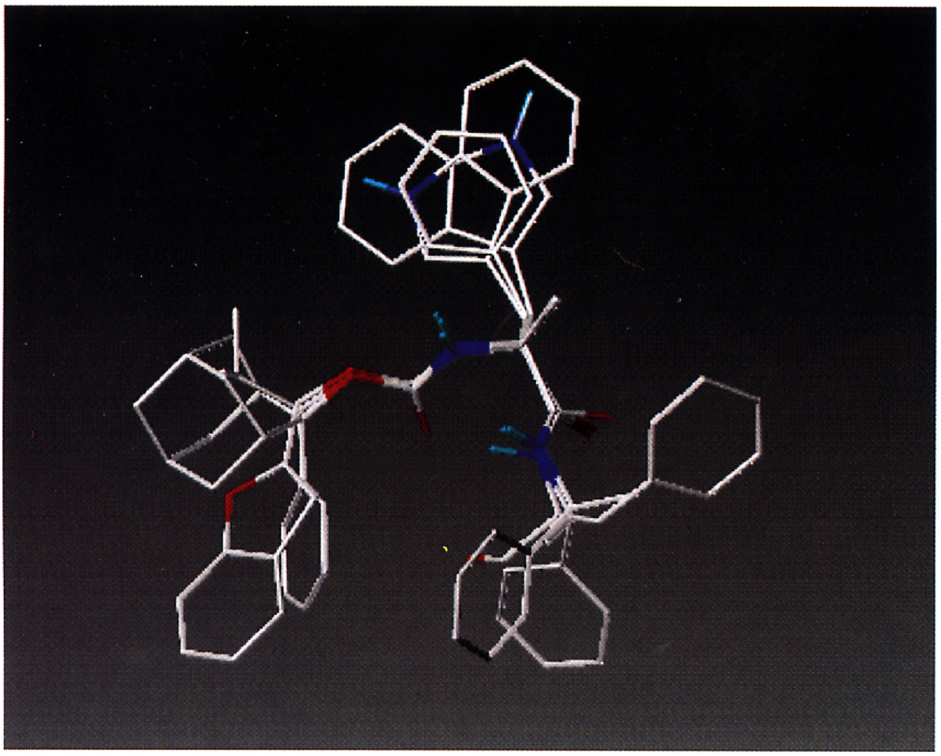


Figure 1, X-ray crystal structures of compounds 1,2 and 3.

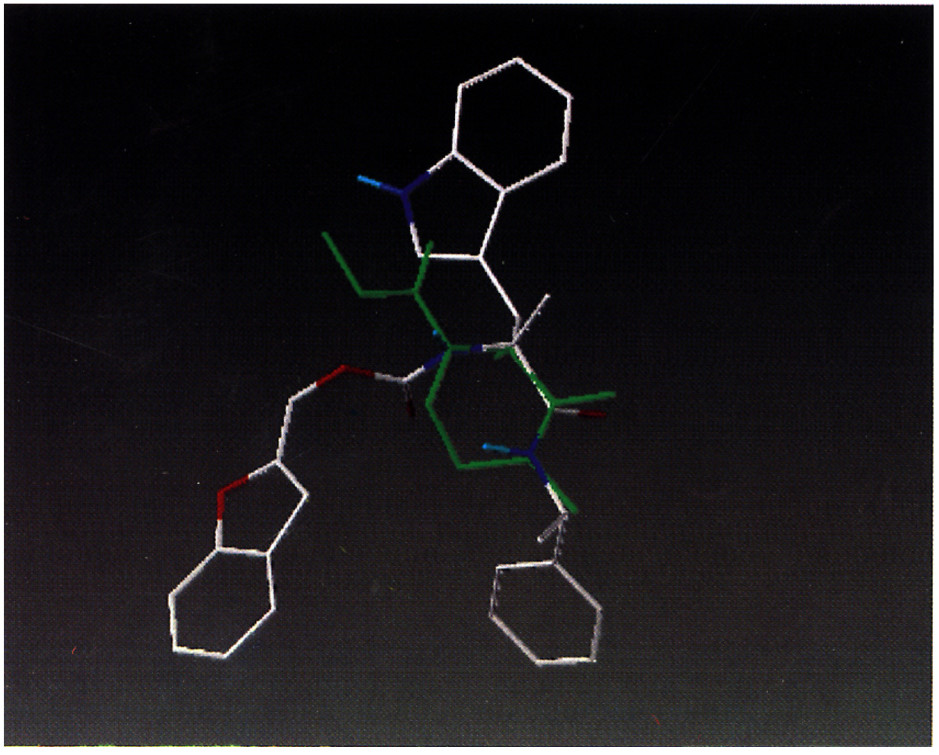
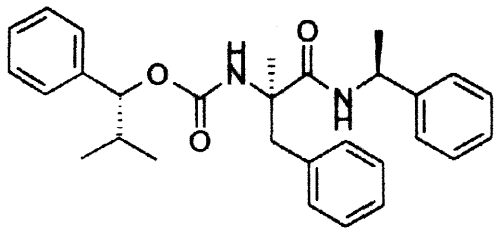
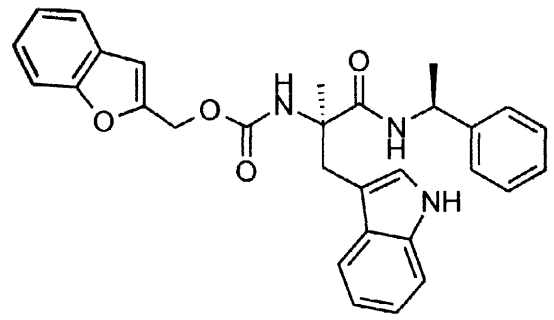


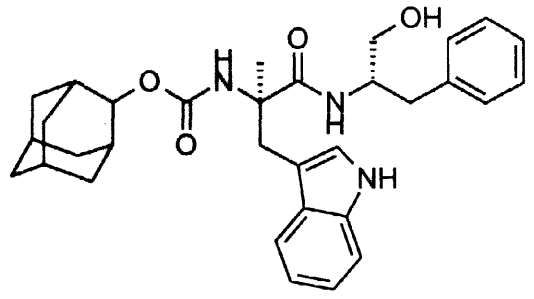
Figure 2, Compound 2 and general piperazinone (green).



1



2

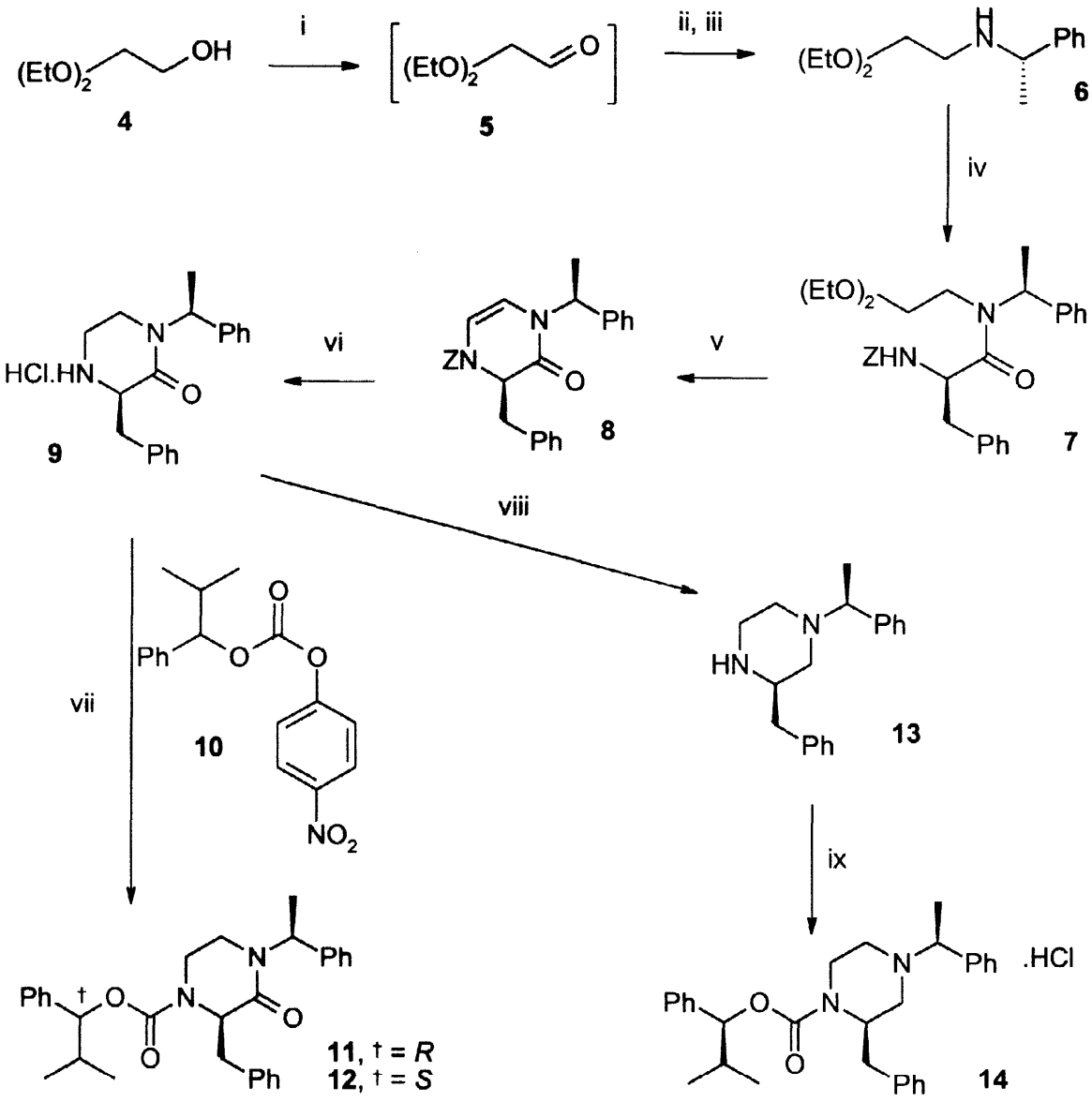


3

depicted in green is 1-methyl-4-methoxycarbonyloxypiperazin-2-one). The piperazinone compound mimics the backbone conformation of peptoid **2** where the α-substituent and *C*-terminus show excellent overlay on the X-ray structure of **2**, the *N*-terminus does not however overlay to the same extent, though this could be due to the small representative group (methoxy urethane) chosen at this terminus. The conformationally restricting α-methyl group present in all of the peptoid leads would not be required as the piperazinone ring should impart the desired restrictions. This heterocycle was shown to give the conformational restriction of the 'backbone' unit, whilst still allowing the same spatial arrangement of the pharmacophoric groups [6]. The use of piperazinones as antagonists has been applied for other peptides such as Leu-enkephalin [7], tachykinins (NK_1) [8, 9] and endothelin [10]. The strategy selected was to use the same template for all three classes of compounds namely the NK_1, NK_3 and CCK-B classes of receptor ligands, and deduce the structure-activity-relationship (SAR) of the conformational restriction.

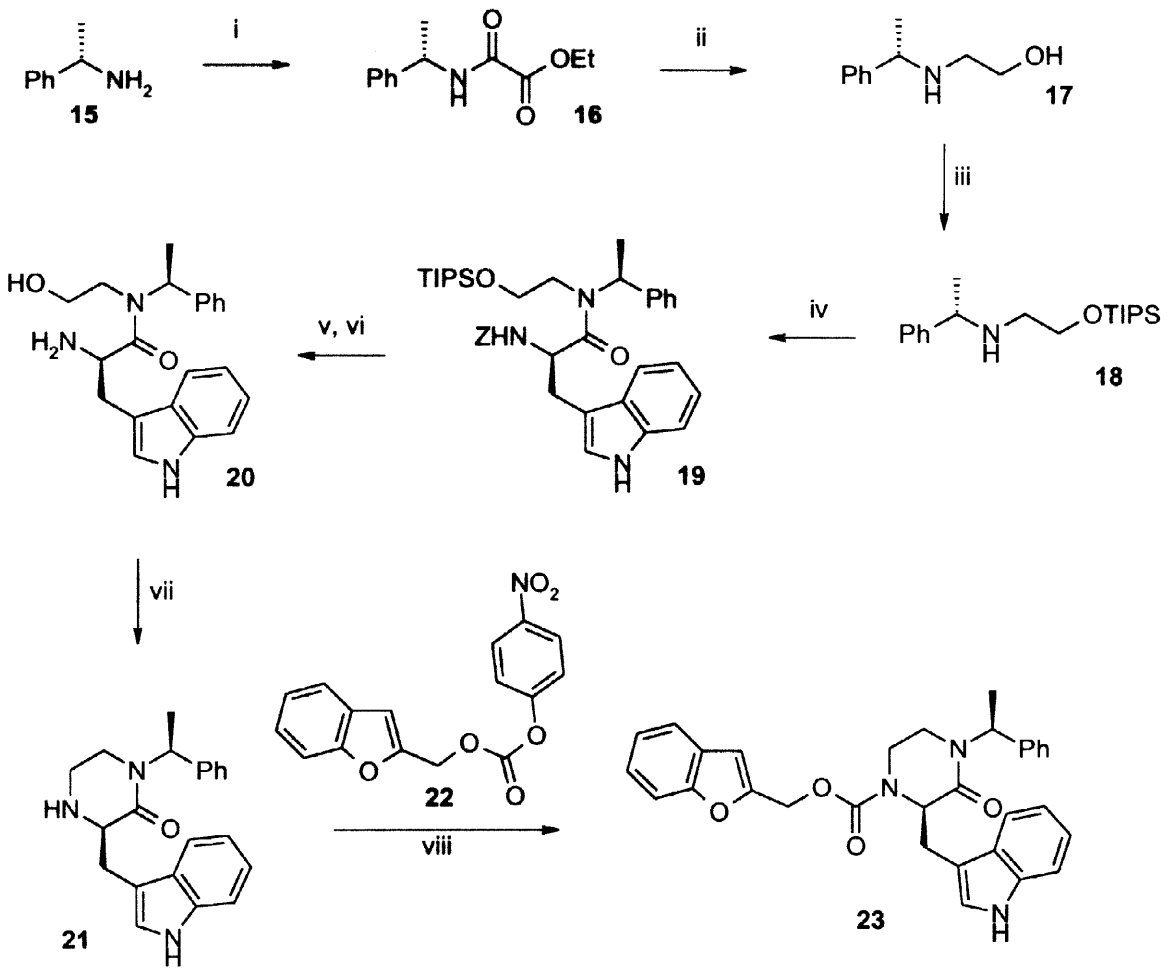
CHEMISTRY

The main concern for the proposed synthesis was with stereochemistry, *ie* the use of single enantiomers/diastereomers to avoid racemates or attempting separations of diastereomeric mixtures; thus a direct comparison with the selected lead compounds can be achieved. This criterion limited the choice of syntheses available because of the enantiomeric centre appended to the amide nitrogen. This was achieved (see Scheme 1, for the NK_3 receptor ligands) initially by a reductive amination using the enantiomerically pure (*S*)-1-phenylethylamine. Diethoxyethanol, **4**, was oxidised to the corresponding aldehyde using Swern conditions [11] then reductively aminated *in situ* to the masked amino-aldehyde, **6**, using sodium cyanoborohydride as the selective reducing agent. The yield of this compound was not optimised at 29 % over the two steps. The resulting amine was immediately coupled to benzyloxycarbonyl (Z) protected phenylalanine using standard basic coupling conditions to afford the amide, **7**, in moderate 50 % yield. It was reported that these types of compounds will undergo cyclic condensations in the presence of aqueous trifluoroacetic acid in good yield at room temperature [7]. This cyclisation step proceeded in good yield to give the product **8** (**PD 164838**). The proton NMR spectrum of **8**, and the preceding compound were hard to



Scheme 1. *Reagents* : i, DMSO, $COCl_2$, TEA, THF; ii, Amine, 4A sieves; iii, $NaCNBH_3$, 29 %; iv, ZPheOH, HBTU, DIPEA, DMF, 50 %; v, TFA (aq), 72 %; vi, $Pd(OH)_2$-C, EtOH, cHCl, 52 %; vii, (*R*)-Alcohol, triphosgene, Py, DIPEA, EtOAc or (*S*)-**10**, DMF, DMAP, 15 %; viii (a), $NaHCO_3$, EtOAc; (b), BMS, THF, 61 %; ix, (a) (*S*)-**10**, DMF, DMAP, 67 %, (b) HCl.

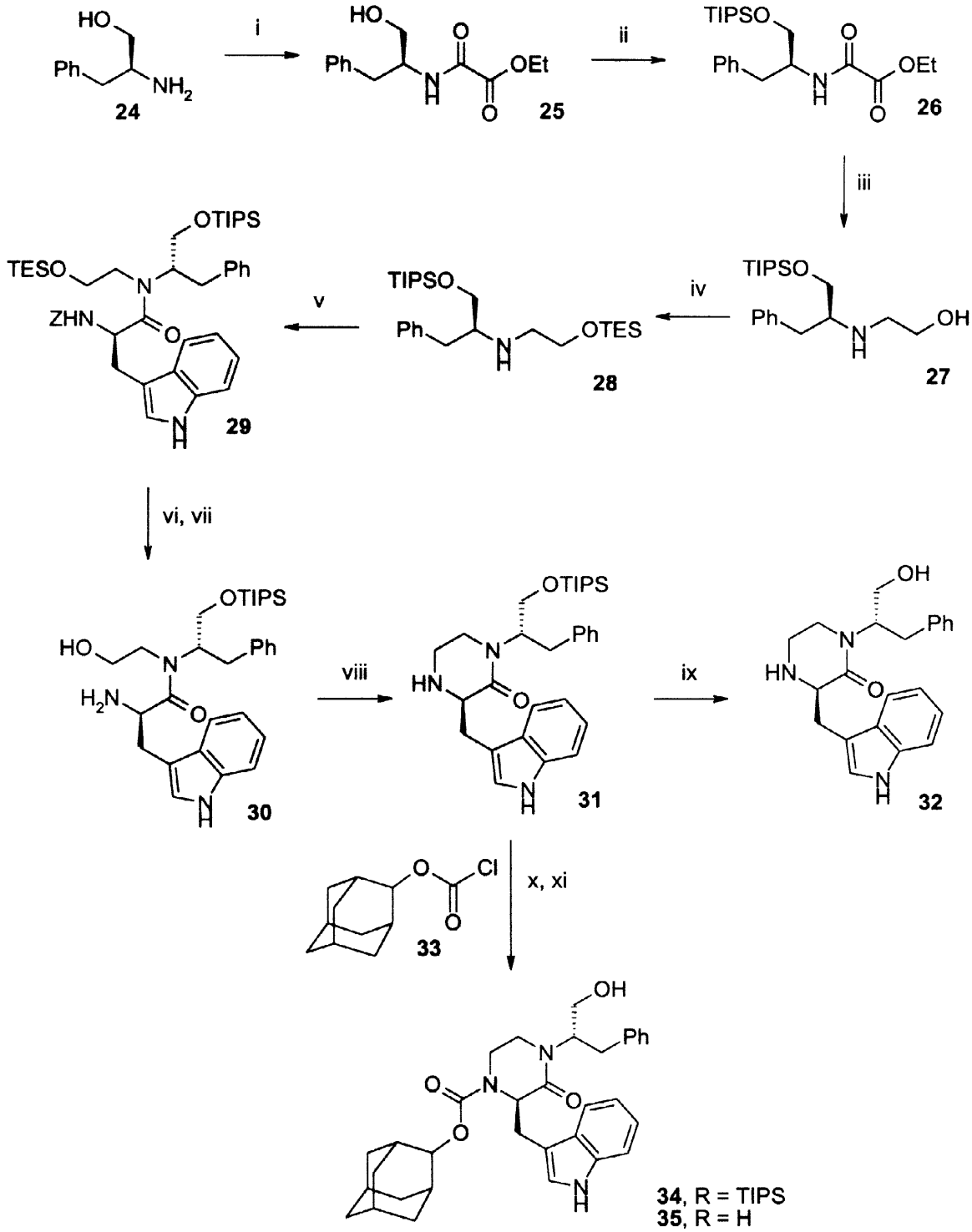
interpret due to rotomeric structures derived from the tertiary amide, but at elevated temperatures in DMSO-d_6 the proton spectrum of the cyclised product could be resolved. Hydrogenation of **8**, removed both the Z protecting group as well as reducing the internal alkene to give the piperazinone structure, **9** (**PD 164837**), in reasonable isolated yield (52 %) as its hydrochloride salt. The free amino function of this compound was acylated to give the urethane to give the desired compounds **11** and **12** (**PD 181603** and **PD 165076** respectively); the (*R*, *R*, *S*) isomer, **11**, being the analogue of **1**. The acylations were achieved by the use of *in situ* chloroformate formation from the corresponding (*R*)-1-phenyl-2-methylpropanol or *via* activated carbonate (*S*)-**10**, the chloroformate route was preferred because the reaction was quicker, cleaner and higher yielding. Also, the free-base of **9** was liberated using aqueous saturated sodium bicarbonate and then the amidic carbonyl reduced using borane dimethylsulfide (BMS) complex to give the de-oxo derivative **13**. The secondary amine function was acylated with activated carbonate (*S*)-**10** to give **14** (**PD 177241**) as its hydrochloride salt. This successful strategy was employed for the structurally similar NK_1 receptor ligand, the only significant difference being the use of tryptophan (Trp) instead of phenylalanine. However, this



Scheme 2. *Reagents :* i, EtO_2CCOCl, Py, CH_2Cl_2, 99%; ii, LAH, THF, 81 %; iii, TIPSCl, Im, DMF 89 %; iv, ZTrpOH, HBTU, DIPEA, DMF, 59 %; v, TBAF, THF, 88 %; vi, $Pd(OH)_2$-C, MeOH, 100 %; vii, DEAD, PPh_3, THF, 62 %; viii, DMF, DMAP, 77 %.

seemingly subtle change proved to be important at the acid promoted cyclisation step and an unidentified compound was returned.

An alternative synthesis was therefore required for the incorporation of the indole-(Trp)nucleus. This lead to the use of a reported synthesis of piperazinones, where the construction of the piperazinone ring system was effected using Mitsunobu ring closure conditions [12]. This synthetic approach (Scheme 2) required a 6-hydroxy-amine which gives rise to the amino-function in the piperazinone ring system by the loss of the hydroxy-group. The synthesis of the required intermediate **20**, was fairly straightforward using standard protection procedures. Thus hydroxyethyl function was incorporated into the system by the addition of chloroethyl oxalate to (*S*)-1-phenylethylamine, the isolated amide was reduced using $LiAlH_4$ to give desired amino-alcohol **17** in excellent overall yield (81 % over 2 steps). The coupling of this amino-alcohol to ZTrpOH gave the corresponding ester rather than the desired amide, presumably the secondary amine being too sterically hindered to react in preference. Therefore, the hydroxy function of **17** was protected using the robust triisopropylsilyl (TIPS) ether. The coupling reaction of the protected alcohol and ZTrpOH then proceeded to give the desired amide, **19**, in reasonable yield (59 %). The TIPS ether protecting group was removed using tetrabutylammonium fluoride (TBAF) to afford the hydroxy function, which was followed by the catalytic hydrogenolysis of the Z group to release the free amine. The aforementioned Mitsunobu cyclisation procedure worked well to give the 'parent' piperazinone ring, **21** (**PD 172684**) in an acceptable



Scheme 3. *Reagents :* i, EtO_2CCOCl, TEA, DMF/THF, 74 %; ii, TIPSCl, Im, DMF, 87 %; iii, BMS, THF, 54 %; iv, TESCl, Im, DMF, 96 %; v, ZTrpOH, HBTU, DIPEA, DMF; vi, TFA, THF/H_2O; vii, $Pd(OH)_2$-C, MeOH, 42 %; viii, DEAD, PPh_3, THF, 21 %; ix, TBAF, THF, 42 %; x, TEA, THF, 76 %; xi, TBAF, THF, 86 %.

yield (62 %). The free amine was then acylated with activated carbonate **22** to give the NK_1 receptor ligand **23 (PD 172770)**.

The synthesis of the CCK-B receptor ligand **35**, was very similar to **23**, the NK_1 piperazinone compound. The same general synthetic strategy was employed (Scheme 3), though an extra protecting group was required for the extra hydroxy function in the compound. The first step was the selective acylation of phenylalaninol with chloroethyl oxalate to give the amide, this reaction gave a good yield of amide **25** when the co-base was triethylamine (the use of pyridine as co-base gave mainly the bis-acylated product). The hydroxy function of this molecule was then protected with a TIPS ether prior to the reduction of the carbonyls using BMS to give the amino-alcohol; lithium aluminium hydride reduction resulted in desilylation. The protection of the second hydroxy function was achieved using a triethylsilyl (TES) ether, this ether was chosen as it only needs to be present for the subsequent amide forming step, whereas the TIPS ether has to be present for the duration of the synthesis. The different stabilities of these two silyl ethers means that the TES ether can be selectively removed in the presence of the TIPS ether by the use of aqueous trifluoroacetic acid in tetrahydrofuran [13]. After the coupling step with ZTrpOH to give amide **29**, the TES ether was hydrolysed to yield the mono-hydroxy protected product. The Z group was removed by catalytic hydrogenolysis leaving amino-alcohol **30**. Once again the Mitsunobu ring-closure reaction was performed this time however a disappointing yield of the piperazinone product, **31** was obtained. The TIPS group was removed in the presence of TBAF to give **32 (PD 174248)**. The desired CCK-B receptor ligand was prepared by acylation of the amine using 2-adamantyl chloroformate [3], and finally deprotection of the silyl protecting group ether using TBAF once again to give target compound **35 (PD 174249)**.

RESULTS and DISCUSSION

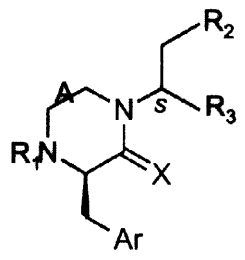
Compounds **11, 23** and **35** were submitted for their respective receptor binding assays. In all three cases the effect of cyclisation led to a considerable loss in receptor binding affinity; now being in the micromolar range in contrast to the nanomolar affinity achieved by their corresponding acyclic parents (**1**, **2**, and **3**).

The NK_3 receptor compounds (compounds **8**, **9**, **11**, **12** and **14** in Table 1) are conformationally restricted analogues of **1**; **11** being the closest compound (*ie* the analogous cyclic equivalent). The Z protected compound **8** was not expected to exhibit good binding affinity for the NK_3 receptor because of its constrained ring (incorporating an internal alkene) and the unoptimised *N*-terminal (Z) group. The deprotected/reduced intermediate, **9**, shows similar efficacy to the Z-protected compound at the NK_3 receptor. This could be due to the removal of the unoptimised (but functional) urethane unit compensated by the reduced rigidity within the ring system due to alkene reduction.

The introduction of the preferred *N*-terminal group to give compound **11** gave an inactive (at 10 μmol) compound at both the NK_1 and NK_3 receptors. However the opposite stereochemistry at the *N* terminus (*ie* *SRS*-**12** compared to *RRS*-**11**) gave modest binding at both the NK_1 and NK_3 receptors; these receptor binding affinities are about 400 times lower than their respective acyclic parent compounds. Interestingly the corresponding (*SRS*)-isomer of **1** is inactive at both receptor types. Removal of the annular carbonyl in **12** gave tertiary amine **14**. This target has greater flexibility than the analogous piperazinone due to the omission of the planar amide group. This greater freedom however does not transcend to give a higher binding ligand at the designated receptor site as can be seen from the binding affinity data - obviously the annular carbonyl is required for binding at the receptor.

The NK_1 receptor ligands (compounds **21** and **23** in Table 1) exhibit a flat structure-affinity relationship in the micro molar range. That is to say that the incorporation of the preferred benzofuranyl group at the *N*-terminus has very little effect on the binding affinity at the NK_1 receptor. The lead compound **2** has a binding affinity of 0.55 nM; 10^4 times more active than the piperazinone compounds at the same receptor. The free amine, **21**, though not envisaged to be a strongly binding compound does show similar activity to its chain-opened analogue **36 (PD 152104)**, but is obviously of little use due to its poor affinity for the NK_1 receptor.

The CCK-B compounds **32** and **35** show similar loss in binding results to those of the structurally related NK_1 and NK_3 compounds. Both these compounds have micro-molar affinity for the CCK-B receptor again a 10^3 decrease in activity over their lead open chain compound **3**.



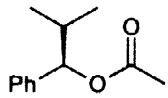
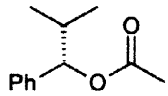
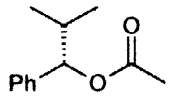
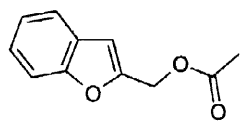
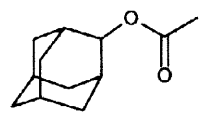
N°.	A	R_1	R_2	R_3	Ar	X	IC_{50} (μM)[a]		
							NK_1[b]	NK_3[c]	CCK-B[d]
8	-CH=CH-	$PhCH_2OCO$-	H	Ph	Ph	O	6.31	7.20	-
9	$-CH_2CH_2$-	H	H	Ph	Ph	O	IA	6.16	-
11	$-CH_2CH_2$-		H	Ph	Ph	O	IA	IA	-
12	$-CH_2CH_2$-		H	Ph	Ph	O	1.96	3.09	-
14[e]	$-CH_2CH_2$-		H	Ph	Ph	H_2	IA	5.50	-
21	$-CH_2CH_2$-	H	H	Ph	Ind[f]	O	5.16	-	-
23	$-CH_2CH_2$-		H	Ph	Ind	O	1.17	-	-
32	$-CH_2CH_2$-	H	OH	CH_2Ph	Ind	O	-	-	IA
35	$-CH_2CH_2$-		OH	CH_2Ph	Ind	O	-	-	9.12

Table 1, Receptor binding affinities of synthesised cyclic products.

[a] IC_{50} is the concentration producing half-maximal inhibition of specific binding at the receptor, and is a geometric mean of three separate experiments. IA denotes no inhibition at 10 μmol.
[b] [^{125}I]-Bolton Hunter-Substance P to NK_1 receptors in IM9 cells.
[c] [^{125}I]-[MePhe^7]NKB to NK_3 receptors in cloned human NK_3 receptors stably expressed in CHO cells.
[d] [^{125}I]-Bolton Hunter CCK-26-33 to CCK receptors in the mouse cerebral cortex.
[e] HCl salt.
[f] Ind refers to 3-indolyl.

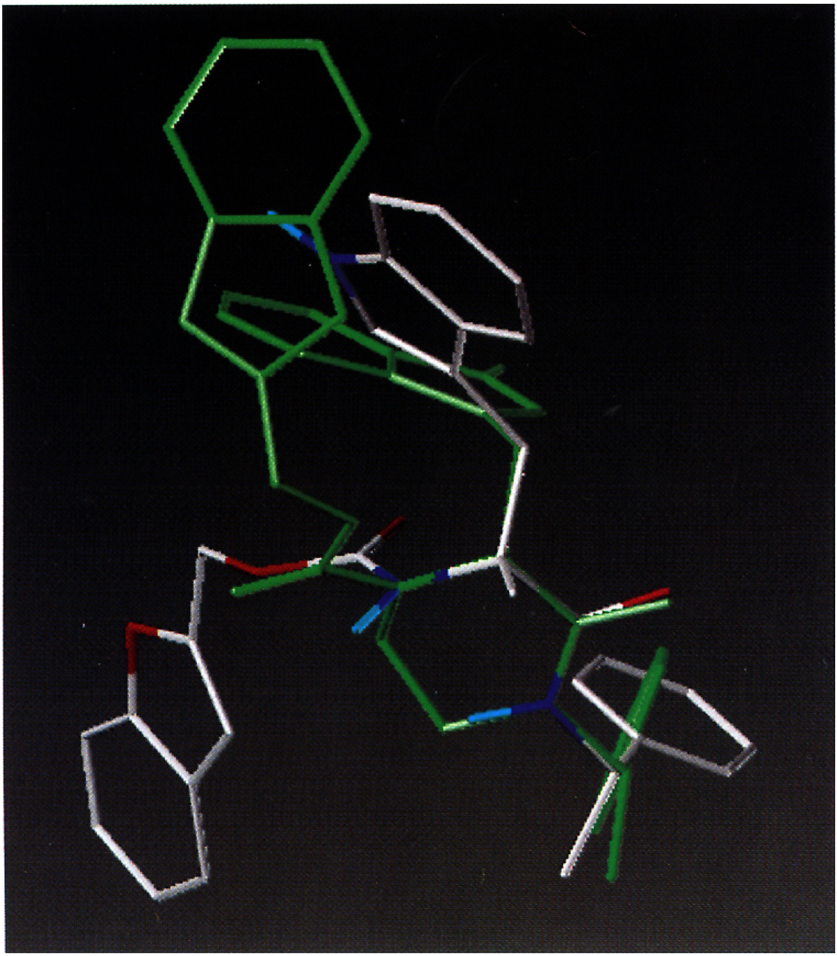
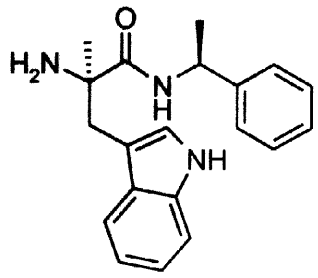


Figure 3, X-ray crystal structures of compounds 2 and 23 (green).



36 (NK_1 4.11 μmol, NK_3 IA)

The X-ray crystal structure of compound **23** seen in Figure 3 shows that the piperazinone ring is an excellent template for overlap of the open-chain backbone of the lead compound **2** (and presumably also compounds **1** and **3**). The major deviation from the X-ray structure of **2** is that the benzofuranylmethyl urethane group is not occupying the same space. This is due to the fact the urethane nitrogen atom is now rigidly constrained (presumably due to the presence of unfavourable transannular interactions) within the piperazinone ring system and therefore cannot present the appended (benzofuranylmethyl) group as depicted in the acyclic analogue; there are also rotational changes causing the indole and phenylethyl groups to be out of conformation.

These conformational changes could be the reason that compound **23**, and presumably also **11** and **35**, have poor binding activity affinity for their respective receptors compared with the open chain analogues **1**, **2** and **3**. Or, alternatively the poor binding could be due to the fact the amide and urethane NH's are missing in the cyclic compound which could potentially result in the loss of H-bonding centres necessary for strong affinity binding at the receptor. Also the structure could have become too constrained, *ie* the binding conformer at the receptor may require more flexibility than is allowed by the piperazinone ring system. This may suggest that the X-ray crystal structure of the lead compounds (**1**, **2** and **3**) is not the binding conformer of the ligand *in vitro*.

CONCLUSIONS

This study has shown that substituted piperazinones can be prepared, as single diastereomers from amino acid precursors, relatively quickly and efficiently. This strategy has used two different synthetic methods for the cyclisation reactions and in each case the enantiomeric integrity of the compounds was retained (analysed by ^{1}H NMR and HPLC). The piperazinone ring system proved to be an excellent choice for the conformationally restricting the 'backbone' of the peptoid parents as shown by the overlap of the X-ray crystal structure of cyclic **23** onto its acyclic parent **2**. The 'backbone' shows good alignment with only the pharmacophoric groups being subjected to rotational changes, however these compounds were perhaps too conformationally constrained as shown by the poor binding affinities at the CCK-B, NK_1 and NK_3 receptors

ACKNOWLEDGEMENTS

The authors would like to thank the group of N. Suman-Chauhan for the generation of the biological data and J. A. Bikker for technical assistance.

EXPERIMENTAL SECTION

General Procedures : Melting points were determined on a Mettlar FP80 or a Reichert Thermovar hot-stage apparatus. Proton NMR spectra were recorded on a Varian Unity +400 MHz spectrometer using deuterochloroform as the solvent at 298 K unless otherwise stated; chemical shifts are recorded in ppm downfield from tetramethylsilane. IR spectra are recorded with the compound neat on a sodium chloride disk on a Perkin-Elmer System 2000 Fourier transform spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Finnigan MAT TSQ70 or Fisons VG trio-2A instrument. Accurate mass spectra were obtained from EPSRC Nation Mass Spectrometry Service Centre, Swansea, UK. Elemental analysis are within ± 0.4 % of theoretical values and were determined by Medac Ltd, Uxbridge, UK. Normal phase silica gel used for chromatography was Merck No. 9385 (230 - 400 mesh) and reverse phase silica gel was Lichroprep RP-18 (230 - 400 mesh); both supplied by E. Merck, A. G. Darmstadt, Germany. Anhydrous solvents were purchased in septum-capped bottles from Fluka Chemicals Ltd., Glossop, UK. All final compounds were analysed by reverse phase analytical high performance liquid chromatography and were > 99.5 % pure.

(S)-2,2-Diethoxyethyl-(1-phenylethyl)amine (**6**)
2,2-Diethoxyethanal [11] (assumed 3.0 mmol) in anhydrous THF (120 ml) at 0 °C under a nitrogen atmosphere was treated with (*S*)-1-phenylethylamine (727 mg, 6.0 mmol). The resulting solution was allowed to stir for 2 h with 4A molecular sieves. Sodium cyanoborohydride (1 M in THF, 4.6 ml, 6.0 mmol) was then added and the resulting mixture left to stir overnight. The mixture was filtered and 0.5 M NaOH solution added, the crude product was extracted into ethyl acetate and the organic phase was washed with brine and dried ($MgSO_4$). Purification by chromatography (33 % EtOAc in heptane) yielded a slightly yellow oil (414 mg, 29 %); δ_H 1.19 (3H, t, CH_3, *J* 7.2 Hz), 1.21 (3H, t, CH_3, *J* 7.2 Hz), 1.35 (3H, d, $CHCH_3$, *J* 6.4 Hz), 1.58 (1H, bs, NH), 2.61 (2H, 2x dd, CH_2N, *J* 5.6, 6.4 Hz), 3.46-3.70 (4H, m, 2x CH_2), 3.76 (1H, dq, $CHCH_3$, *J* 7.2, 7.2 Hz), 4.56 (1H, t, CH, *J* 5.6 Hz), 7.24-7.32 (5H, m, Ph); ν_{max} 2975, 1452, 1373, 1125, 1067, 762 cm^{-1}; *m/z* 238 (M^+, 14 %), 192 (91 %), 105 (86 %), 103 (100 %).

(1R, 1'S)-{1-[(2,2-Diethoxyethyl)-(1-phenylethyl)carbamoyl]-2-phenylethyl}carbamic acid benzyl ester (**7**)
(*R*)-*N*-CBZ-PheOH (1.32 g, 4.42 mmol), HBTU (1.68 g, 4.42 mmol) and diisopropylethylamine (570 mg, 4.42 mmol) were dissolved in DMF (10 ml). The solution was stirred for 30 min amine **6** was added along with diisopropylethylamine (570 mg, 4.42 mmol) and the resulting solution allowed to stir overnight. The solvent was then removed *in vacuo* and the crude material taken up in EtOAc and washed with 10 % citric acid, sat. $NaHCO_3$, brine and dried ($MgSO_4$). The product was purified by chromatography (10 % EtOAc in heptane) to yield a straw coloured oil (1.15 g, 50 %); δ_H of little use due to rotamers and peak broadening; ν_{max} 3294, 2976, 1716, 1634, 1455, 1129, 1058, 748 cm^{-1}; *m/z* 473.5 (M^+ -EtO, 100 %).

(2R, 4S)-2-Benzyl-3-oxo-4-(1-phenylethyl)-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester (**8**)
Compound **7** (1.12 g, 2.16 mmol) and 70 % aqueous TFA were stirred at RT for 2 h [7]. The solvent was removed *in vacuo*, the residue taken up in EtOAc and washed with sat. $NaHCO_3$, brine and dried ($MgSO_4$). The product was purified by chromatography (67 % EtOAc in heptane) to give a solid which was recrystallised (heptane) to yield white crystal/powder (660 mg, 72 %); mp 104.5-106 °C; δ_H (DMSO-d_6, 398 K) 1.50 (3H, d, $CHCH_3$, *J* 7.1 Hz), 2.85 (2H, m, CH_2Ph), 4.84 (1H, dd, α-H, *J* 6.1, 7.3 Hz), 4.97 (2H, dd, CH_2O, *J* 12.5, 27.5 Hz), 5.60 (1H, d, CH, *J* 5.6 Hz), 5.69 (1H, q, $CHCH_3$, *J* 7.2 Hz), 6.23 (1H, d, CH, *J* 6.1 Hz), 7.00 (2H, m, arom), 7.15 (3H, m, arom), 7.24-7.57 (10H, m, arom); ν_{max} 1713, 1677, 1422, 1395, 1311 cm^{-1}; *m/z* 426 (M^+, 19 %), 323 (19 %), 105 (59 %), 91 (100 %); Anal. calc. for $C_{27}H_{26}N_2O_3$ C 76.03, H 6.14, N 6.57 % found C 76.27, H 6.09, N 6.54 %; $[\alpha]_D^{24}$ -225° (c = 0.19, MeOH).

(1S, 3R)-3-Benzyl-1-(1-phenylethyl)piperazin-2-one hydrochloride (**9**)
Compound **8** (600 mg, 1.41 mmol), conc. HCl (0.5 ml) and palladium hydroxide on charcoal (10 %) in ethanol (30 ml) were subjected to a hydrogen atmosphere (50 psi) at RT for 3.5 h. After filtration through 'filter-aid' the solvent was removed *in vacuo* and the salt triturated with Et_2O. The crude product was recrystallised (EtOH/Et_2O) to give white crystals (241 mg, 52 %); mp 179-185 °C; δ_H (DMSO-d_6) 1.48 (3H, d, CHCH_3, *J* 6.8 Hz), 3.02-3.46 (6H, m, CH_2Ph, 2x CH_2N), 4.29 (1H, dd, C*H*CH_2, *J* 3.6, 4.4 Hz), 5.81 (1H, q, C*H*CH_3, *J* 7.2 Hz), 7.30-7.40 (10H, m, 2x Ph); ν_{max} 3418, 2633, 1652, 1455 cm^{-1}; *m/z* 295 (M^+, 39 %), 203 (100 %) 191 (25 %); Anal. calc. for $C_{19}H_{23}N_2O_1Cl$ 0.2H_2O C 68.22, H 7.05, N 8.38 % found C 68.40, H 6.83, N 8.31 %.

(1'R, 2R, 4''S)-2-Benzyl-3-oxo-4-(1-phenylethyl)piperazine-1-carboxylic acid 2-methyl-1-phenyl-propyl ester (**11**)
A solution of compound **9** (100 mg, 303 μmol), (*R*)-**10** [2] (95 mg, 303 μmol), DMAP (74 mg, 605 μmol) in DMF was stirred over the weekend. The solution was diluted with EtOAc, washed with 10 % HCl, 10 % K_2CO_3, brine and dried ($MgSO_4$). The product was purified by chromatography (25 % EtOAc in heptane) to afford a white solid (21 mg, 15 %); mp 139-142 °C; δ_H (DMSO-d_6, 398 K) rotamers 0.77 (6H, 3x d, 2x CHCH_3, *J* 6.4, 6.8 Hz), 1.40 (3H, 2x d, CHCH_3, *J* 6.8, 7.2 Hz), 2.00 (1H, m, C*H*$(CH_3)_2$), 2.60-3.30 (5H, m, 2.5x CH_2), 3.70 (1H, m, 0.5x CH_2), 4.65 (1H, m, α-H), 5.38 (1H, dd, CHO, *J* 5.2, 6.4 Hz), 5.78 (1H, dq, C*H*CH_3, *J* 6.8, 7.2 Hz), 7.08 (2H, m, arom), 7.18-7.38 (13H, m, arom); ν_{max} 2965, 1703, 1645, 1417 cm^{-1}; HRMS for $C_{30}H_{34}N_2O_3$ requires 470.2569 found 470.2569 (M^+).

(1'S, 2R, 4''S)-2-Benzyl-3-oxo-4-(1-phenylethyl)piperazine-1-carboxylic acid 2-methyl-1-phenyl-propyl ester (**12**)
A solution of (*S*)-1-Phenyl-2-methylpropanol (64 mg, 428 μmol) in EtOAc (2 ml) at 0 °C was treated with triphosgene (41 mg, 137 μmol), then pyridine (34 mg, 428 μmol). After 30 min. the mixture was filtered and the filtrate treated with a cooled (~0 °C) solution of compound **9** (100 mg, 342 μmol) and diisopropylamine (44 mg, μmol) in EtOAc (2 ml). The resulting mixture was allowed to warm to RT over 2h, then diluted with EtOAc, washed with 10 % HCl, brine and dried ($MgSO_4$). The product was purified by chromatography (20 % EtOAc in heptane) to yield a white solid (56 mg, 35 %); mp 139-141 °C; δ_H (DMSO-d_6, 378 K) rotamers 0.77 (3H, d, CHCH_3, *J* 6.8 Hz), 0.84 (3H, d, CHCH_3, *J* 6.8 Hz) 1.42 (3H, d, CHCH_3, *J* 7.2 Hz), 2.05 (1H, m, C*H*$(CH_3)_2$), 2.59 (2H, m, C*H*), 3.23 (3H, m, C*H*), 3.77 (1H, bd, CH, *J* 13.6 Hz), 4.67 (1H, bs, α-H), 5.39 (1H, d, CHO, *J* 6.4 Hz), 6.83 (1H, q, C*H*CH_3, *J* 6.8, 7.2 Hz), 7.01 (2H, bs, arom), 7.17-7.38 (13H, m, arom); ν_{max} 2964, 1700, 1645, 1417 cm^{-1}; HRMS for $C_{30}H_{35}N_2O_3$ requires 471.2648 found 471.2648 (MH^+).

(1S, 3R)-3-Benzyl-1-(1-phenylethyl)piperazine (**13**)
Compound **9** (204 mg, 617 μmol) was stirred with Et_2O (10 ml) and sat. $NaHCO_3$ (10 ml) for 5 mins. The etheral layer was washed with brine and dried ($MgSO_4$) and the solvent removed. The free base was dissolved in anhydrous THF (5 ml) and BMS (0.68 ml, 1.36 mmol, 2M in THF) slowly added, the resulting solution was heated to reflux for 30 min. A further aliquot of BMS (1.38 ml, 2.72 mmol) was added and heating continued for 1 h. Methanol (5 ml) was slowly added followed by conc. hydrochloric acid (0.2 ml) and the resulting mixture heated under reflux for 1 h. The solvents were removed *in vacuo* and the mixture diluted with EtOAc, the organics were washed with sat. $NaHCO_3$, brine and dried ($MgSO_4$). Removal of the solvent left a yellow oil which solidified on standing (106 mg, 61 %); δ_H 1.36 (3H, d, CHCH_3, *J* 6.4 Hz), 1.57 (1H, bs, NH), 1.87 (1H, t, CH*H*, *J* 10.8 Hz), 1.99 (1H, dt, C*H*H, *J* 2.8, 10.8 Hz), 2.53-2.64 (4H, m, 2x CH_2), 2.82 (1H, dt, CH, *J* 2.8, 11.6 Hz), 3.01 (2H, m, CH_2), 3.37 (1H, q, C*H*CH_3, *J* 6.0 Hz), 7.20-7.32 (10H, m, arom); ν_{max} 3325, 2810, 1492, 1451, 1325, 1137 cm^{-1}; HRMS for $C_{19}H_{25}N_2$ requires 281.2018 found 281.2018 (MH^+).

(1'S, 2R, 4''S)-2-Benzyl-4-(1-phenylethyl)piperazine-1-carboxylic acid 2-methyl-1-phenyl-propyl ester hydrochloride (**14**)
Compound **13** (100 mg, 357 μmol), carbonate **10** (113 mg 357 μmol), DMAP (catalytic) and DMF (1 ml) were stirred at RT for 3 days. The DMF was removed *in vacuo* and the crude material taken up in EtOAc, the

organics were washed with 10 % K_2CO_3, brine and dried ($MgSO_4$). The product was purified by chromatography (20 % EtOAc in heptane) to yield a clear oil (109 mg, 67 %). The free base was treated with HCl in Et_2O (~ 0.5 M) and the resulting solid crystallised ($MeOH/Et_2O$) to yield fine white needles; mp 167-180 °C; δ_H (DMSO-d_6, 298 K) 0.77 (3H, t, $CHCH_3$, *J* 6.0 Hz), 0.84 (3H, d, $CHCH_3$, *J* 6.8 Hz), 1.76 (3H, d, $CHCH_3$, *J* 6.8 Hz), 2.03 (1H, m, $CH(CH_3)_2$), 2.67 (1H, m, CH), 2.93 (3H, m, CH), 3.42 (1H, q, $CHCH_3$, *J* 10.8 Hz), 3.75 (0.5H, t, CH, *J* 12.6 Hz), 4.88 (1H, d, CH, *J* 11.6 Hz), 4.12 (0.5H, d, CH, *J* 14.0 Hz), 4.37 (3H, m, 3x CH), 5.29 (1H, bs, PhCH), 7.04 (1H, d, arom, *J* 6.8 Hz), 7.17-7.32 (9H, m, arom), 7.44 (3H, dt, arom, *J* 6.8, 11.2 Hz), 7.66 (2H, bs, arom), 11.07 (1H, bd, NH^+, *J* 5.6 Hz); ν_{max} 3436, 2426, 1704, 1418 cm^{-1}; *m/z* 457 (MH^+, 100 %); Anal. calc. for $C_{30}H_{37}N_2O_2$ 0.1 H_2O C 72.81, H 7.58, N 5.66 % found C 72.61, H 7.35, N 5.93 %.

(S)-1-Phenylethylamino ethyl oxalate (16)

Ethyl oxalyl chloride (3.00 g, 22 mmol) was added to a solution of (*S*)-1-phenylethylamine (2.42 g, 20 mmol) and pyridine (1.66 g, 21 mmol) in CH_2Cl_2 (20 ml) at 0 °C. After 30 min the mixture was diluted with CH_2Cl_2, washed with 10 % HCl, sat. $NaHCO_3$, brine and dried ($MgSO_4$). The resulting clear oil was used without further purification (4.42 g, 100 %); δ_H 1.37 (3H, t, CH_2CH_3, *J* 7.2 Hz), 1.56 (3H, d, $CHCH_3$, *J* 6.8 Hz), 4.33 (2H, q, CH_2CH_3, *J* 7.2 Hz), 5.15 (1H, dq, $CHCH_3$, *J* 1.2, 6.8 Hz), 7.27-7.38 (6H, m, Ph, NH); ν_{max} 3297, 2982, 1736, 1688, 1527, 1278, 1216, 1022 cm^{-1}; *m/z* 222 (MH^+, 40 %), 221 (M^+, 13 %), 105 (100 %).

(S)-(1-Phenylethyl)aminoethan-2-ol (17)

A solution of compound **16** (6.49 g, 30 mmol) in THF (100 ml) was slowly added to a suspension of LAH (6.70 g, 0.176 mol) in THF (50 ml) under nitrogen. The resulting mixture was then heated to reflux for 8 h and left for 64 h at RT. The mixture was slowly treated with 0.5 M NaOH (50 ml) and the resulting suspension stirred for 1 h before filtering through a filter-aid. The organics were extracted with EtOAc and washed with 0.5 M NaOH, brine and dried ($MgSO_4$). Purification of the product by chromatography (0-8 % MeOH in CH_2Cl_2) left a clear oil (3.91 g, 81 %); δ_H 1.42 (3H, d, $CHCH_3$, *J* 6.4 Hz), 2.08 (2H, bs, OH, NH), 2.66 (2H, m, CH_2N), 3.63 (2H, m, CH_2O), 3.82 (1H, q, $CHCH_3$, *J* 6.8 Hz), 7.24-7.34 (5H, m, Ph) ; ν_{max} 3299, 2928, 14352, 1071, 1051, 763 cm^{-1}; *m/z* 166 (MH^+, 22 %), 105 (100 %); Anal. calc. for $C_{10}H_{15}NO.0.1H_2O$ C 71.90, H 9.17, N 8.39 % found C 71.68, H 8.97, N 8.69 %.

(S)-(1-Phenylethyl)-(2-triisopropylsilyloxyethyl)amine (18)

Compound **17** (2.00 g, 12.1 mmol) in DMF (5 ml) was added to a solution of chlorotriisopropylsilane (2.92 g, 15.2 mmol) and imidazole (1.65 g, 24.2 mmol) in DMF (10 ml) [14]. After stirring at RT for 64 h the solvent was removed *in vacuo*, the residue taken up in EtOAc, washed with brine and dried ($MgSO_4$). Purification by chromatography (10 % EtOAc in heptane) left a clear oil (3.46 g, 89 %); δ_H 1.05 (21H, bs, 6x $CHCH_3$, 3x $CH(CH_3)_2$), 1.36 (3H, d, $CHCH_3$, *J* 6.8 Hz), 1.81 (1H, s, NH), 2.58 (2H, m, CH_2N), 3.78 (3H, m, CH_2O, OH), 7.22-7.32 (5H, m, Ph); ν_{max} 2959, 2943, 2866, 1464, 1105, 883, 759 cm^{-1}; *m/z* 322 (MH^+, 92 %), 105 (100 %) ; Anal. calc. for $C_{19}H_{35}NOSi$, C 70.96, H 10.97, N 4.36 % found C 70.95, H 10.90, N 4.78 %; $[\alpha]_D^{20}$ -21.1 ° (c = 0.80, MeOH).

(1R, 1'S)-{2-(3-Indolyl)-1-[(1-phenylethyl)-(2-triisopropylsilanyloxyethyl)-carbamoyl]-ethyl}-carbamic acid benzyl ester (19)

Procedure as for the preparation of compound **7**, purified by chromatography (20 % EtOAc in heptane) to yield a straw coloured gum (2.22 g, 59 %); δ_H of little use due to rotamers; ν_{max} 3304, 2943, 2866, 1716, 1628, 1456, 1103, 741 cm^{-1}; HRMS for $C_{38}H_{52}N_3O_4Si$ requires 642.3727 found 642.373 (MH^+); $[\alpha]_D^{20}$-49.3 ° (c = 0.94, MeOH).

(2R, 1'S)-2-Amino-N'-(2-hydroxyethyl)-3-(3-indolyl)-N-(1-phenylethyl)propionamide (20)

(i) A solution of compound **19** (2.22 g, 3.46 mmol) in THF (25 ml) under a nitrogen atmosphere was treated with TBAF (1 M in THF, 6.93 ml, 6.93 mmol) and the resulting solution left to stir for 2 h. The solution was then diluted with EtOAc, washed with brine and dried ($MgSO_4$). Purification by chromatography (20-80 %

EtOAc in heptane) gave a solid white foam (1.47 g, 88 %); mp 50-54 °C; δ_H of little use due to rotamers; ν_{max} 3408, 3298, 1699, 1622, 1456, 1047, 739 cm^{-1}; *m/z* 486 (MH^+), 148 (100 %); $[\alpha]_D^{20}$-74.8 ° (c = 0.73, MeOH). **(ii)** The foam (500 mg, 1.03 mmol) and palladium hydroxide on charcoal (10 %) in methanol (10 ml) were subjected to a hydrogen atmosphere (50 psi) at RT for 1 h. After filtration through 'filter-aid' the solvent was removed *in vacuo* to give a white foam in quantitative yield. δ_H of little use due to rotamers; ν_{max} 3290, 1620, 1456, 1050, 734 cm^{-1}; HRMS for $C_{21}H_{26}N_3O_2$ requires 352.2025 found 352.2025 (M^+).

(1S, 3R)-3-(3-Indolylmethyl)-1-(1-phenylethyl)piperazin-2-one (**21**)
A cooled (0 °C) solution of compound **20** (362 mg, 1.03 mmol), and triphenylphosphine (364 mg, 1.39 mmol) in THF (10 mol) was treated with DEAD (233 mg, 1.34 mmol). After 30 min at this temp. the solution was allowed to warm to RT over 2h [12]. The solvent was the removed *in vacuo* and the product partially purified by chromatography (25-100 % EtOAc in heptane, followed by 1-3 % MeOH in CH_2Cl_2). The yellow foam was crystallised (EtOAc/heptane) to yield fine white needles (21 mg, 62 %); mp 149-150 °C; δ_H 1.51 (3H, d, $CHCH_3$, *J* 7.1 Hz), 1.60 (1H, bs, NH), 2.67, 2.83 (2H, 2x m, CH_2N), 2.96 (2H, m, CH_2N), 3.25 (1H, dd, IndCH*H*, *J*, 8.7, 14.4 Hz), 3.56 (1H, dd, IndC*H*H, *J* 3.7, 14.4 Hz), 3.81 (1H, dd, α-H, *J* 3.7, 8.7 Hz), 6.08 (1H, q, C*H*CH_3, *J* 7.1 Hz), 7.10-7.29 (8H, m, arom), 7.38 (1H, d, arom, *J* 7.6 Hz), 7.76 (1H, d, arom, *J* 8.0 Hz), 8.06 (1H, s, NH); ν_{max} 3282, 1615, 1455, 1319, 744 cm^{-1}; *m/z* 334 (MH^+, 52 %), 204 (100 %) ; Anal. calc. for $C_{21}H_{23}N_3O.0.05$EtOAc C 75.37, H 6.98, N 12.44 % found C 75,68, H 7.11 N 12.10 % ; $[\alpha]_D^{20}$-21.6 ° (c = 0.68, MeOH).

(2R, 4'S)-2-(3-Indolylmethyl)-3-oxo-4-(1-phenylethyl)piperazine 1-carboxylic acid benzofuran-2-ylmethyl ester (**23**)
Compound **21** (85 mg, 255 μmol), (2-benzofuranyl)methyl 4-nitrophenylcarbonate [4] (80 mg, 255 μmol), DMAP (catalytic) and DMF (1 ml) were stirred at RT for 3 h. A further portion of carbonate (80 mg, 255 μmol) was added and the mixture stirred for 16 h. the solvent was removed *in vacuo*, the residue taken up in EtOAc, washed with 10 % K_2CO_3, brine and dried ($MgSO_4$). The product was purified by chromatography (20-33 % EtOAc in heptane) to give a solid foam which was crystallised (EtOH) to yield slightly off-white crystals (99 mg , 77 %); mp 168-170 °C; δ_H (DMSO-d_6, 398 K) 1.40 (3H, d, $CHCH_3$, *J* 7.2 Hz), 2.56 (2H, m, CH*H*N), 3.28, 3.40 (2H, dd, IndCH_2, *J* 5.2, 14.4 Hz), 3.66 (1H, m, C*H*HN), 4.68 (1H, t, α-H, *J* 5.2 Hz), 5.16 (2H, dd, CH_2O, *J* 13.6, 42.4 Hz), 5.77 (1H, q, C*H*CH_3, *J* 7.2 Hz), 6.81 (2H, m, arom), 6.99 (4H, m, arom), 7.17-7.32 (6H, m, arom), 7.39 (1H, d, arom, *J* 8.0 Hz), 7.52 (1H, d, arom, *J* 8.4 Hz), 7.62 (1H, d, arom, *J* 6.8 Hz), 10.57 (1H, s, NH) ; ν_{max} 3313, 1702, 16331, 1455, 1314, 741 cm^{-1}; *m/z* 508 (MH^+, 100 %); Anal. calc. for $C_{31}H_{29}N_3O_4$ C 73.35, H 5.76, N 8.28 found C 73.07, H 5.75, N 8.16 % ; $[\alpha]_D^{20}$-146.8 ° (c = 0.50, MeOH).

(S)-(2-Phenyl-1-hydroxymethyl)ethylamino ethyl oxalate (**25**)
A solution of ethyl oxalyl chloride (4.52 g, 33.1 mmol) in THF (10 ml) was slowly added to a cooled (0 °C) solution of (*S*)-(+)-2-phenylalaninol (5.00 g, 33.1 mmol) and triethylamine (3.34 g, 3.31 mmol) in THF/DMF (60/20 ml). After 15 min the solution was allowed to warm to RT and stirred for 30 min. The solvents were removed *in* vacuo and the residue taken up in EtOAc and filtered, the concentrated filtrates were purified by chromatography (20-60 % EtOAc in heptane) to give a clear oil (6.13 g, 74 %); δ_H 1.38 (3H, t, CH_3, *J* 7.2 Hz), 2.10 (1H, t, OH, *J* 5.6 Hz), 2.93 (2H, m, CH_2Ph), 3.68 (2H, 2x m, CH_2O), 4.21 (1H, m, CH), 4.33 (2H, q, CH_2CH_3, *J* 7.2 Hz), 7.22-7.35 (6H, m, Ph, NH); ν_{max} 3367, 1739, 1683, 1538, 1213, 1018, 745 cm^{-1}; *m/z* 252 (MH^+, 100 %), 234 (59 %), 134 (37 %); Anal. calc. for $C_{13}H_{17}N_1O_4.0.4H_2O$ C 60.41, H 6.94, N 5.42 % found C 60.45, H 6.65, N 5.37 %; $[\alpha]_D^{20}$-46.2 ° (c = 0.58, MeOH).

(S)-(2-Phenyl-1-triisopropylsilyoxymethyl)ethylamino ethyl oxylate (**26**)
Procedure as for the preparation of compound **18**, purified by chromatography (5-15 % EtOAc in heptane) to yield a clear oil (7.22 g, 87 %); NMR 1.07-1.13 (21H, m, 3x CH, 6x CH_3), 1.37 (3H, t, CH_2CH_3, *J* 7.2 Hz), 2.96 (2H, m, CH_2Ph), 3.68 (2H, m, CH_2O), 4.20 (1H, m, CH), 4.33 (2H, q, CH_2CH_3, *J* 7.2 Hz), 7.20-7.32 (5H, m, Ph), 7.44 (1H, d, NH, *J* 7.6 Hz); ν_{max} 3413, 3314, 2943, 2867, 1762, 1733, 1705, 1119, 883 cm^{-1}; *m/z* 408.7

(MH^+, 100 %); Anal. calc. for $C_{22}H_{37}NO_4Si$ C 64.82, H 9.15, N 3.44 % found C 64.71, H 8.86, N 3.31 %; $[\alpha]_D^{20}$-39.8 ° (c = 0.59, MeOH).

(S)-(2-Phenyl-1-triisopropylsilyoxymethyl)ethylaminoethan-2-ol (**27**)
BMS (2M in toluene, 13.3 ml, 26.6 mmol) was added to a solution of compound **26** (7.22 mg, 17.7 mmol) in THF (50 ml) and the resulting solution heated to reflux for 3 h. Another aliquot of BMS was added and heating continued for a further 2 h. NaOH (0.5 M, 10 ml) was then slowly added to the mixture and heating continued for 1h. The mixture was then diluted with EtOAc, washed with sat. $NaHCO_3$, brine and dried ($MgSO_4$). Purification by chromatography (30-50 % EtOAc in heptane) gave a clear oil (3.34 g, 54 %); δ_H 1.05-1.09 (21 H, m, s, 3x CH, 6x CH_3), 2.20 (2H, bs, NH, OH), 2.73-2.84 (5H, m, CH_2Ph, CH_2N, CHN), 3.52 (2H, dt, CH_2O, *J* 1.2, 5.6 Hz), 3.59 (1H, dd, CH*H*O, *J* 4.8, 10.0 Hz), 3.62 (1H, dd, C*H*HO, *J* 4.8, 9.6 Hz), 7.19-7.31 (5H, m, Ph); ν_{max} 3388, 2943, 2866, 1463, 1103, 1069, 882 cm^{-1}; *m/z* 352.6 (MH^+, 100 %) ; Anal. calc. for $C_{20}H_{37}NO_2Si.0.1H_2O$ C 67.97, H 10.61, N 3.96 % found C 67.81, H 10.47, N 4.34 %; $[\alpha]_D^{20}$+21.8 ° (c = 0.79, MeOH).

(S)-(2-Phenyl-1-triisopropylsilyoxymethyl)ethyl-(2-triethylsilyloxyethyl)amine (**28**)
Procedure as for the preparation of compound **18** and the clear oil obtained was used without further purification (4.24 g, 96 %); δ_H 0.55 (6H, q, 3x CH_2Si, *J* 8.4 Hz), 0.92 (9H, t, 3x CH_2CH_3, *J* 8.0 Hz), 1.63 (18H, m, 6x $CHCH_3$), 1.27 (3H, bs, 3x CHSi), 2.74-2.85 (5H, m, CH_2Ph, CH_2N, CHN), 3.59 (2H, 2x dd, CH_2O, *J* 5.6, 10.0 Hz), 3.68 (2H, t, CH_2O, *J* 5.6 Hz), 7.18-7.27 (5H, m, Ph); ν_{max} 3418, 2944, 2867, 1463, 1104 cm^{-1}; *m/z* 466.6 (MH^+, 100 %).

(1R, 1'S)-2-Amino-N-(1-benzyl-2-triisopropylsilanyloxyethyl)-N-(2-hydroxyethyl)-3-(3-indolyl)-propionamide (**30**)
(i) Procedure as for the preparation of compound **7** to give the amide. TFA (2.60 g, 22.8 mmol) was added to a solution of the TES ether (assumed 7.15 g, 9.11 mmol) in THF/H_2O (85/15 ml). The resulting mixture was stirred at RT for 90 min before $NaHCO_3$ (s) was added [13]. The products were extracted into EtOAc and washed with sat. $NaHCO_3$, brine and dried ($MgSO_4$). Partial purification by chromatography (10-40 % EtOAc in heptane) gave a straw coloured gum (4.40 g, 72 %); δ_H of little use due to rotamers.; ν_{max} 3412, 3335, 2943, 2866, 1713, 1634, 1456, 1053, 742 cm^{-1}; HRMS for $C_{39}H_{54}N_3O_5Si$ requires 672.3833 found 672.383 (MH^+).
(ii) Procedure as for the preparation of compound **20(ii)**, partial purification by reverse phase chromatography (MeOH/H_2O) gave a straw coloured gum (1.55 g, 58 %); δ_H of little use due to rotamers; ν_{max} 3291, 2943, 2866, 1634, 1457, 1112, 1066, 883, 741 cm^{-1}; HRMS for $C_{31}H_{48}N_3O_3Si$ requires 538.3465 found 538.3465 (MH^+).

(1S, 3R)-3-(3-Indolylmethyl)-1-[2-(1-triisopropylsilyloxy-3-phenylpropyl)]piperazin-2-one (**31**)
Procedure as for the preparation of compound **21**, purification by chromatography (20-70 % EtOAc in heptane) and crystallisation (EtOAc/heptane), and recrystallisation (MeOH/IPA) gave fine white needles (206 mg, 21 %); mp 94-97 °C; δ_H 1.06 (21H, bs, 3x CH, 6x CH_3), 1.59 (1H, bs, NH), 2.64 (1H, m, CH*H*N), 3.92 (1H, m, C*H*HN), 3.00 (3H, m, IndCH*H*, CH_2Ph), 3.18 (2H, m, CH_2N), 3.54 (2H, m, α-H, IndC*H*H), 3.88 (2H, m, CH_2O), 4.60 (1H, bs, CHN), 7.09 (1H, m, arom), 7.18-7.28 (6H, m, Ph, arom), 7.35 (1H, d, arom, *J* 8.0 Hz), 7.70 (1H, d, arom, *J* 8.0 Hz), 8.04 (1H, bs, NH); ν_{max} 3398, 3288, 3942, 2805, 1627, 1456, 1112, 742 cm^{-1}; *m/z* 520.5 (MH^+, 100 %); Anal. calc. for $C_{31}H_{45}N_3O_2Si.0.3H_2O$ C 70.89, H 8.75, N 8.00 % found C 71.63, H 8.73, N 8.08 %; $[\alpha]_D^{21}$ +32.7 ° (c = 0.52, MeOH).

(1'S, 3R)-1-(1-Hydroxymethyl-2-phenylethyl)-3-(3-indolylmethyl)-1-piperazin-2-one (**32**)
Procedure as for the preparation of compound **20(i)**, purification by chromatography (0-10 % MeOH in CH_2Cl_2) gave a solid foam (22 mg, 42 %); mp 68-71 °C; δ_H 1.59 (2H, bs, NH, OH), 2.71 (1H, m, CH*H*N), 2.99 (5H, m, CH_2N, CH_2Ph, C*H*HN), 3.16 (1H, dd, IndCH*H*, *J* 8.8 14.4 Hz), 3.51 (1H, dd, IndC*H*H, *J* 8.8, 14.4 Hz), 3.66 (1H, dd, α-H, *J* 3.4, 8.8 Hz), 3.80 (2H, m, CH_2O), 4.11 (1H, t, CHN, *J* 7.2 Hz), 7.12-7.26 (8H, m, arom), 7.37 (1H, d, arom, *J* 7.6 Hz), 7.72 (1H, d, arom, *J* 6.8 Hz), 8.08 (1H, s, NH); ν_{max} 3290, 1622, 1456,

743 cm^{-1}; HRMS for $C_{22}H_{26}N_3O_2$ requires 364.2025 found 364.2025 (MH^+, 100 %); $[\alpha]_D^{19}$ +51.5 ° (c = 0.40, MeOH).

(2R, 4'S)-4-(1-Hydroxymethyl-2-phenylethyl)-2-(3-indolylmethyl)-3-oxo-piperazine-1-carboxylic acid adamant-2-yl ester **(34)**

(i) 2-Adamantyl chloroformate [3] (77 mg, 360 μmol) was added to a solution of compound **31** (170 mg, 328 mmol) in THF (2 ml), followed by the addition of triethylamine (44 mg, 360 μmol) and the resulting solution stirred for 2 h at RT. Then diluted with EtOAc, washed with 10 % HCl, brine and dried ($MgSO_4$). Purification by chromatography (10-15 % EtOAc in heptane) yielded a white solid foam (174 mg, 76 %); mp 80-85 °C; δ_H (DMSO-d_6, 398 K) 1.02 (21H, bs, 3x CH, 6x $CHCH_3$), 1.34-1.79 (14H, m, adam), 2.93 (4H, m, CH_2N, CH_2Ph), 3.20 (3H, m, IndC*H*H, CH_2N), 3.68 (2H, dd, IndC*H*H, C*H*HO, *J* 5.2, 10.2 Hz), 3.93 (1H, dd, C*H*HO, *J* 7.2, 10.0 Hz), 4.40 (1H, t, α-H, *J* 6.8 Hz), 4.51 (1H, t, CHN, *J* 5.6 Hz), 4.55 (1H, s, CHO), 6.91 (1H, t, arom, *J* 7.2 Hz), 6.97 (1H, s, arom), 7.01 (1H, t, arom, *J* 7.2 Hz), 7.11-7.22 (5H, m, arom), 7.29 (1H, d, arom, *J* 8.0 Hz), 7.43 (1H, d, arom, *J* 8.0 Hz), 10.53 (1H, s, NH); ν_{max} 3334, 2926, 2865, 1682, 1634, 1453, 1424, 1121, 737 cm^{-1}; *m/z* 698 (MH^+, 100 %); Anal. calc. for $C_{42}H_{59}N_3O_4Si$ C 72.27, H 8.52, N 6.02 % found C 72.63, H 8.47 N 6.07 %; $[\alpha]_D^{19}$ -70.8 ° (c = 0.47, MeOH).

(ii) Procedure as for the preparation of compound **20(i)**, purification by chromatography (40-80 % EtOAc in heptane) gave a white solid foam (107 mg, 86 %); mp 94-98 °C; δ_H (DMSO-d_6, 398 K) 1.35-1.82 (14H, m, adam), 2.75-3.02 (4H, m, CH_2N, CH_2Ph), 3.21 (3H, m, $IndCH_2$, CH*H*N), 3.46 (1H, m, C*H*HO), 3.57 (2H, m, CH*H*O, C*H*HN), 4.28 (1H, t, CH_2OH, *J* 5.6 Hz), 4.48 (1H, t, α-H, *J* 5.6 Hz), 4.53 (1H, m, CHN), 4.57 (1H, bs, CHO), 6.91 (1H, m, arom), 6.99-7.20 (7H, m, arom), 7.29 (1H, d, arom, *J* 8.0 Hz), 7.44 (1H, d, arom, *J* 8.0 Hz), 10.52 (1H, s, NH); ν_{max} 3338, 2909, 1679, 1633, 1425, 735 cm^{-1}; *m/z* 542 (MH^+, 100 %); Anal. calc. for $C_{33}H_{39}N_3O_4$ C 73.17, H 7.26, N 7.76 % found C 72.80, H 7.18, N 7.70 %; $[\alpha]_D^{20}$-82.3 ° (c = 0.49, MeOH).

REFERENCES

1. Horwell, D. C., *Trends Biotechnol.*, 1995, **13**, 132.; Horwell, D. C.; Pritchard, M. C.; Raphy, J.; Ratcliffe, G., *Immunopharm.*, 1996, **33** 68.
2. Boden, P.; Eden, J. M.; Hodgson, J.; Horwell, D. C.; Hughes, J; McKnight, A. T.; Lewthwaite, R. A.; Pritchard, M. C.; Raphy, J.; Meecham, K; Ratcliffe, G. S.; Suman-Chauhan, N.; Woodruff, G. N., *J. Med. Chem.*, 1996, **39**, 1664.
3. Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N., *J. Med. Chem.*, 1991, **34**, 404.
4. Boyle, S.; Guard, S.; Higginbottom, M.; Horwell, D. C.; Howson, W.; McKnight, A. T.; Martin, K.; Pritchard, M. C.; O'Toole, J.; Raphy, J.; Rees, D. C.; Roberts, E.; Watling, K. J., Woodruff, G. N.; Hughes, J., *Bioorg. Med. Chem.*, 1994, **2**, 357.
5. Sybil 6.3, Tripos Associates, 1699 South Hanley Road, Suite 303, St. Louis, Missouri 63144, USA.
6. Gante, J., *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 1699.
7. DiMaio, J.; Belleau, B. *J. Chem. Soc. Perkin Trans. I*, 1989, 1687.
8. Ofner, S.; Hauser, K., Schilling, W.; Vassout, A.; Veenstra, S. J., *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1623.
9. Burkholder, T. P.; Kudlacz, E. M. and Le, T.-B., *US Patent* 1996, 404788.
10. Doherty, A. M., *Drug Disc. Today*, 1996, **1**, 60.
11. Bernard, D; Doutheau, A; Goré, J., *Synth. Comm.*, 1987, **17**, 1807.
12. Mickelson, J. W.; Belonga, K. L.; Jacobsen, E. J., *J. Org. Chem.*, 1995, **60**, 4177.
13. Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G., *J. Am. Chem. Soc.*, 1990, **112**, 2998.
14. Cunico, R. F.; Bedell, L., *J. Org. Chem.*, 1980, **45**, 4797.