Tryptophan-Derived NK_1 Antagonists: Conformationally Constrained Heterocyclic Bioisosteres of the Ester Linkage

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The 3,5-bis(trifluoromethyl)benzyl ester of *N*-acetyl-L-tryptophan **1** (L-732,138) has been identified previously as a potent and selective substance P receptor antagonist. A series of analogs which introduced a 6-membered heterocyclic ring into the backbone of this structure were prepared for evaluation as bioisosteric replacements of the ester linkage of **1**. The 2,5-dioxopiperazine **2** had very weak receptor affinity, but 2-oxopiperazine **5** exhibited modest activity. Examination of the conformations accessible to the substituents on these templates led to exploration of the corresponding 5-membered heterocyclic rings. This study culminated in the identification of oxazolidinedione **14** as a suitable ester mimic in terms of the retention of good NK_1 binding affinity.

Introduction

The role of the ubiquitous neuropeptide substance P in the endogenous responses associated with pain and inflammation has received considerable attention in recent years.[1] A clear link between the transmission of pain, the induction of inflammatory responses as a result of noxious stimuli, and the release of substance P has been established. These observations have suggested that suitable substance P receptor antagonists may be of significant therapeutic use in the treatment of a wide range of clinical conditions, ranging from arthritis,[2a] migraine,[2b] and asthma[3] to postoperative pain and nausea.[4] As a result of the intense interest in this field, a number of structurally diverse series of NK_1 antagonists have been discovered.[5] A variety of structures derived from peptidomimetic studies of substance P in its entirety, or from the Phe-Phe-Gly-Leu-Met N-terminal region (also highly conserved in the related neurokinins A and B), have been reported.[6] However, considerable interest has been generated by the recent disclosure of nonpeptide antagonists CP-96,345[7] and RP-67580[8] and related compounds such as CP-99,994[9] (Figure 1).

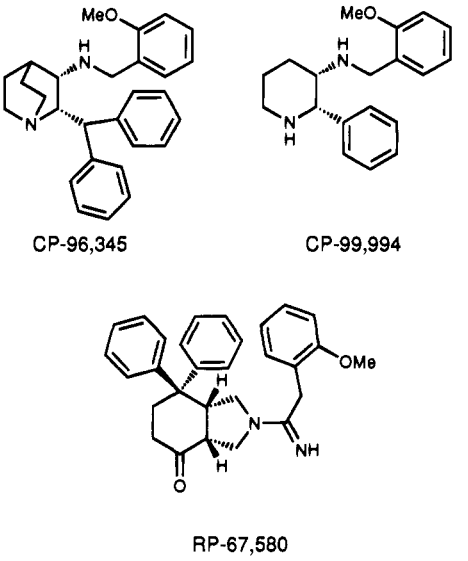

Figure 1.

The cyclic cores of these compounds may be considered as serving the role of molecular scaffolding, deploying a pair of suitably functionalized aromatic rings which are key elements for high-affinity receptor binding.[7-10] Site-directed mutagenesis studies of the NK_1 receptor indicate important receptor–aromatic interactions with residues His-197[11] and His-265.[12] We recently published preliminary work[13] on the discovery of (*S*)-tryptophan benzyl esters such as L-732,138 (**1**), a new structural class of potent and selective NK_1 antagonists. Binding studies with NK_1 receptor mutants indicate similar receptor–ligand interactions to be important with this class.[14] It is plausible that these conformationally flexible ligands bind in a conformation

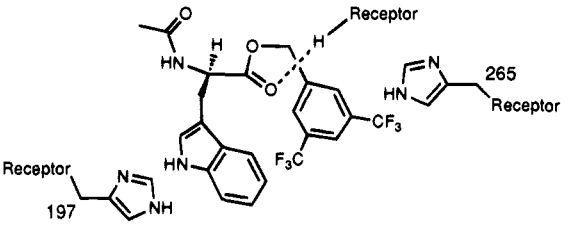

Figure 2. Proposed pharmacophoric receptor interaction of tryptophan ester NK_1 antagonists based on SAR data obtained from site-directed mutagenesis of the NK_1 receptor.[14]

which is analogous to those available to ligand classes exemplified by CP-99,994 or CP-96,345.[14] In addition to the aromatic interactions, the ester linkage appears to contribute significantly to the receptor binding of this series,[15] presumably via hydrogen bonding, thus establishing a putative three-point pharmacophoric interaction, (Figure 2).

We have sought to replace the ester moiety of these compounds with more robust linking groups, with a

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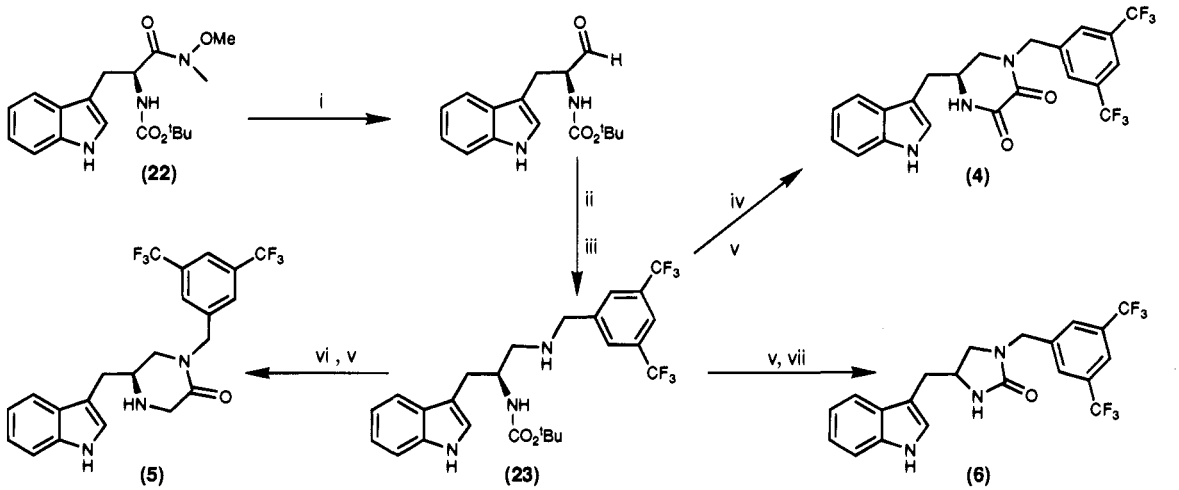
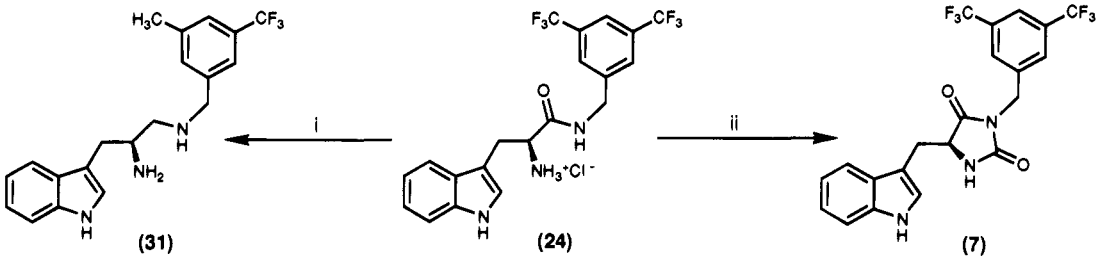
Scheme 1



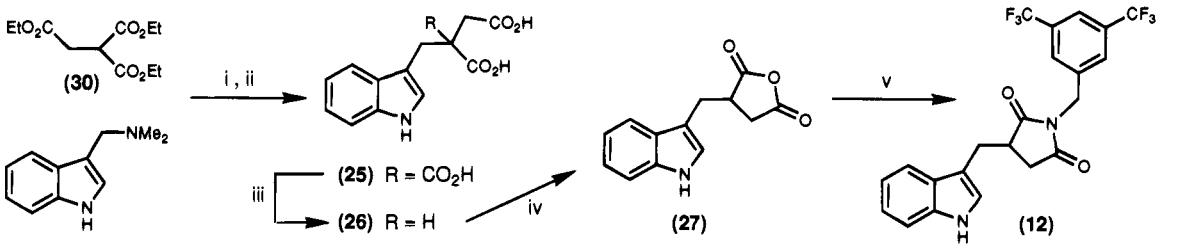
[a] Reagents: (i) $LiAlH_4$; (ii) $ArCH_2NH_2/MgSO_4/CH_2Cl_2$; (iii) $NaBH_4$; (iv) MeOCOCOCl; (v) (a) MeOH/HCl, (b) K_2CO_3; (vi) $BrCH_2COBr$; (vii) Et_3N/carbonyldiimidazole.

Scheme 2



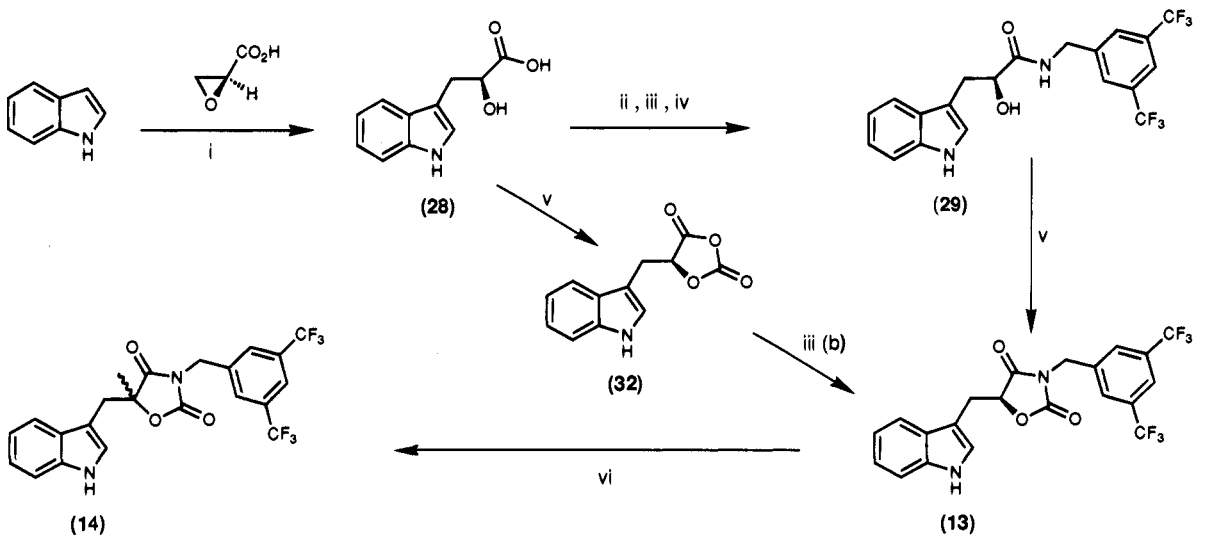
[a] Reagents: (i) $LiAlH_4$/25 °C; (ii) Et_3N/carbonyldiimidazole.

Scheme 3



[a] Reagents: (i) Na/toluene/Δ; (ii) EtOH/KOH; (iii) Cu(0)/quinoline; (iv) Ac_2O; (v) $ArCH_2NH_2$/xylene/Δ.

Scheme 4



[a] Reagents: (i) $SnCl_4/CCl_4$; (ii) TBDMSiOTf/Et_3N; (iii) (a) *i*-BuOCOCl, (b) $ArCH_2NH_2$; (iv) TBAF; (v) carbonyldiimidazole/THF; (vi) NaH/THF, 25 °C/MeI.

view to improving their *in vivo* stability. In this paper we describe our studies on the introduction of a range of heterocyclic templates into the tryptophan backbone of our lead ester series. In addition to an expected improvement in stability, we hoped that the attendant increase in conformational restraints would benefit affinity for the NK_1[16] receptor, by virtue of a more favorable entropy of binding. Studies of available X-ray crystallographic data, and molecular modeling of the Pfizer NK_1 antagonists, have led to postulation of the existence of an intramolecular $\pi-\pi$ interaction between the pendant aromatic moieties.[7,10,14,17] In selecting the heterocyclic templates for investigation, a primary objective was that a $\pi-\pi$ interaction between the indole and bis(trifluoromethyl)phenyl rings should be potentially accessible.

Chemistry

Tryptophan methyl ester was reacted with chloroacetyl chloride under Schotten–Baumann conditions and the resulting 2-chloroacetamide heated with bis(trifluoromethyl)benzylamine to give the 2,5-dioxo-1,4-piperazine **2**[18] (Figure 3). Borane reduction of **2** followed by acidic workup to cleave the intermediate borane–amine complex afforded the piperazine **3** (Table 1). The 2,3-dioxo-1,4-piperazine **4** was obtained by reaction of the amine **23** with methyl oxalyl chloride followed by N-deprotection with *in situ* cyclization (Scheme 1). Similarly, acylation of **23** with bromoacetyl bromide followed by removal of the *tert*-butoxycarbonyl (Boc) protecting group allowed cyclization to 2-oxopiperazine **5**. Treatment of the diamine derived from **23** with carbonyldiimidazole[19] provided cyclic urea **6**. The Boc-protected diamine **23** was most conveniently prepared by $LiAlH_4$ reduction of the Weinreb–Namh[20] amide **22** to the aldehyde followed by reductive amination with 3,5-bis(trifluoromethyl)benzylamine. Exploration of an alternative route to this intermediate via the $LiAlH_4$ reduction of amide **24** led to the discovery of an interesting facet of the chemistry of bis(trifluoromethyl)-phenyl rings. Reduction of the amide **24** with either $LiAlH_4$ or DIBAl-H at temperatures above 0 °C is accompanied by clean reduction of one of the trifluoromethyl groups to a methyl to give diamine **31** (Scheme 2). This reaction is presumably a reflection of the powerful inductive electron-withdrawing effects of the second CF_3 substituent. BH_3-THF complex does not appear to be sufficiently reactive to cause this transformation, even when heated at reflux.[21] Defluorination does not occur to a significant extent at temperatures below 0 °C and thus may be avoided by careful monitoring of reaction temperature. The hydantoin **7** was accessed from amide **24** by treatment with carbonyl diimidazole[22] (Scheme 2).

Succinimide **12** was prepared as shown in Scheme 3. Reaction of gramine with malonate derivative **30**, followed by saponification, gave tricarboxylic acid **25**. Copper–quinoline-induced decarboxylation and reaction of the derived cyclic anhydride **27** with 3,5-bis(trifluoromethyl)benzylamine afforded succinimide **12**. The oxazolidinediones were prepared (Scheme 4) from indolelactic acid (**28**), which is commercially available as the racemate. Protection of the alcohol as its *tert*-butyldimethylsilyl ether allowed amide formation via isobutyl carbonate activation of the acid. Deprotection afforded the 2-hydroxy amide **29** which was then treated with carbonyldiimidazole. More conveniently, it was found that direct reaction of **28** with carbonyldiimidazole followed by addition of the chosen benzylamine afforded the oxazolidinedione in a single step. Initial expectation was that reaction would proceed via the *O*-carboxy anhydride **32**. It was observed, however, that employment of 2 equiv of carbonyldiimidazole led to a doubling (to 60%) of the yield. It is therefore possible that the reaction occurs via independent activation of both functional groups. The *S*-enantiomer of indolelactic acid (**28**) was prepared from (*S*)-glycidic acid, available in optically pure form from D-serine,[23] by Lewis acid-induced ring opening of the oxirane in the presence of indole.[24] Alkylation at C-5 (**14**) was accomplished by deprotonation of **13** with either sodium hydride or potassium hexamethyldisilazide. Some alkylation of the indole nitrogen was also observed under these conditions, but the products were readily separated by flash chromatography.

Biology

A stable CHO cell line expressing the human NK_1 receptor was used to determine binding affinities by displacement of [^{125}I]Tyr8-substance P as radioligand, as previously reported.[25] All binding affinities are reported with standard deviations resulting from three or more independent determinations.

Results and Discussion

(a) Piperazine Analogs. The 2,5-dioxopiperazine **2** (Table 1) appeared, *a priori*, to be a suitable choice for preliminary studies, since all the connectivity of the backbone of the original ester lead is preserved, including the important *S*-stereochemistry of the α-chiral center. This ring system also offered potential sites for further exploration by the subsequent attachment of substituents. Moreover, on the basis of molecular modeling[26] and available literature precedence,[27] it was plausible that the diketopiperazine heterocycle would allow access to a $\pi-\pi$ interaction between the indole and bis(trifluoromethyl)phenyl rings. However, 2,5-dioxopiperazine **2** proved to have poor affinity, a loss of more than 3 orders of magnitude in binding when compared with the parent ester[28] **1** (Table 1). Reduction of the carbonyl groups to give the less conformationally rigid piperazine **3** regained some NK_1 activity. The 8-fold improvement over parent diketopiperazine **2** was encouraging but compromised by loss of the potential to locate the important receptor–carbonyl binding interaction. The 2,3-dioxopiperazine **4** was equipotent with **3**, presumably having also failed to locate this additional binding site. However, the 2-oxopiperazine **5** exhibited a 2-fold improvement (IC_{50} = 243 nM). We have examined the solution conformations of **2**, **4**, and **5** by NMR in conjunction with molecular modeling in an attempt to rationalize these observations.

Solution Conformations of 2, 4, and 5. Proton, COSY45 and NOE difference spectra were acquired for **2**, **4**, and **5** using standard methods (DMSO-d_6, 300 K, 360 MHz). This data, which is reported in the Experimental Section, permitted complete spectral assignment and measurement of the relevant ^3J coupling constants for each compound. Molecular modeling was then used to generate a series of accessible conformations for each molecule.[26] Comparison of experimentally obtained coupling constants and NOE measurements with the dihedral angles and interproton distances derived from

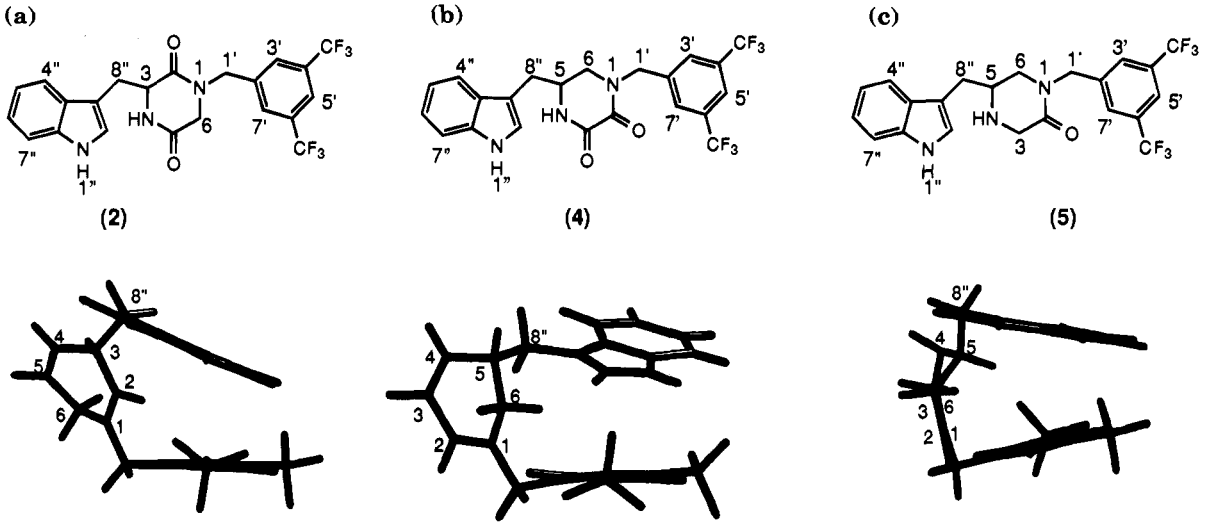
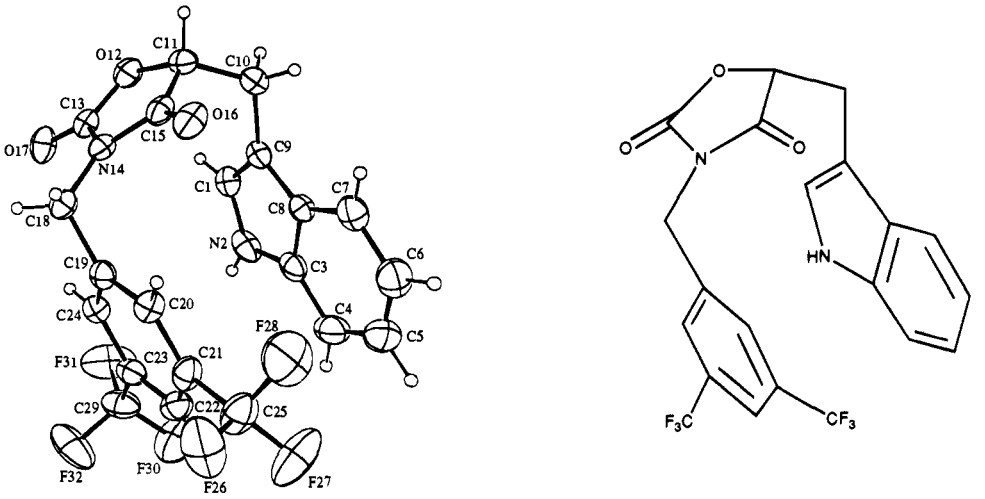


Figure 3. (a) Preferred conformation of **2**. (b) Preferred conformation of **4**. (c) Preferred conformation of **5**.



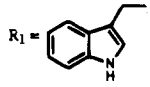
L-732,244 (**13**)

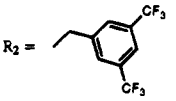
Figure 4. Ortep X-ray structure of L-732,244 ((±)**13**). The structural determination was performed on racemic material, but only the *R*-enantiomer is shown. The U-shaped conformation suggests a face-to-face $\pi-\pi$ interaction, with a 3.94 Å separation between the planes of the aromatic systems.

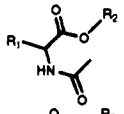
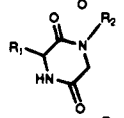
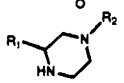
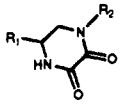
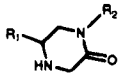
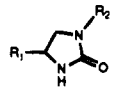
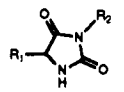
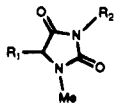
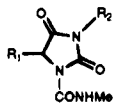
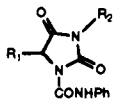
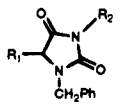
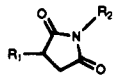
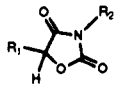
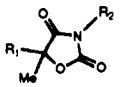
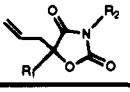
molecular modeling of **2**, **4**, and **5** permitted the major solution conformation populations to be defined within relatively narrow limits for each molecule. Thus a solution conformation was identified which effectively reconciled the experimental data with a conformation obtained from molecular modeling for each of the three compounds. The structures of **2**, **4**, and **5** (Figure 3) possess relatively rigid central rings which restrict the conformational possibilities, and the coupling constants and NOEs allow definition of the orientation of the tryptophan side chain. In each case π-stacking of the indole and phenyl rings is consistently favored over an extended arrangement in the modeling,[26] and the conformation of the *N*-benzyl group is therefore inferred. For each of the structures **2**, **4**, and **5**, the indole and phenyl rings may be successfully overlaid, with the major differences occurring in the vicinity of the piperazine rings. Most revealing is the comparison between **2** and **5**, where the difference in receptor affinity is greatest. It is apparent that the central piperazine rings of these two molecules occupy planes which are almost orthogonal. These observations suggested the possibility of deleterious interactions between the receptor and part of the piperazine ring system as a cause of the differences in binding affinity of these molecules. We were thus encouraged to explore further modification of the central ring and focused on 5-membered ring analogs for which modeling predicted conformations similar to that adopted by **5** (*vide infra*).

(b) 5-Membered Ring Analogs. Contraction of the ring as in the cyclic urea **6** did not significantly alter binding (by comparison with **5**) (Table 1). In consequence the corresponding hydantoin **7** was prepared, in the hope of locating the carbonyl binding site utilized by the tryptophan ester series, but disappointingly failed to improve receptor affinity. A brief exploration of substitution at the available hydantoin nitrogen revealed that small groups such as methyl (**8**) or methylurea (**9**) significantly enhanced affinity but larger groups such as phenylurea (**10**) or benzyl (**11**) offered no advantage (Table 1). Succinimide **12** was prepared and proved to be equipotent with hydantoin **7**. However, on replacement of the ring methylene of **12** with oxygen to give oxazolidinedione **13**, a 10-fold improvement in binding affinity was observed, prompting a more detailed examination of this lead. The *S*-(−)-enantiomer was prepared in optically pure form and

Table 1. SAR of 5- and 6-Membered Ring Heterocyclic Templates

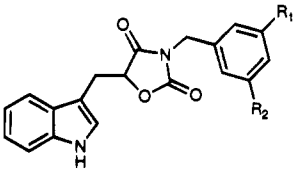




Structure	No.	IC50 / nM ± S.D (a)
	**1**	2.5
	**2**	4333 ± 471
	**3**	567 ±125
	**4**	400 ± 82
	**5**	243 ± 33
	**6**	267 ± 47
	**7**	317 ±62
	**8**	153 ± 5
	**9**	63 ± 15
	**10**	220 ± 136
	**11**	310 ± 226
	**12**	203 ± 38
	(±)**13** (-)**13**	22 ± 7 26 ± 6
	**14**	11 ± 2
	**15**	31 ± 12

[a] Human NK_1 receptor binding affinity, measured[25] by displacement of [^{125}I]Tyr8-substance P.

Table 2. SAR of Benzyl Ring Substitution on the Oxazolidinediones



no.	R_1	R_2	IC_{50} (nM)[a]
13	CF_3	CF_3	22 ± 7
16	CF_3	H	2666 ± 471
17	H	H	6000 ± 100
18	CH_3	CH_3	683 ± 256
19	CH_3O	CH_3O	7366 ± 450
20	F	F	4275 ± 3290
21	Cl	Cl	273 ± 250

[a] Human NK_1 receptor binding affinity, measured[25] by displacement of [^{125}I]Tyr8-substance P.

found to be as active as the racemate, which is consistent[29] with observations from the tryptophan ester series.[13,28] Compound **13** gave crystals suitable for X-ray structural determination[31] (Figure 4). The U-shaped conformation adopted is clearly visible, with the planes of the phenyl and indole rings separated by 3.94 Å and almost parallel, subtending an angle of 11.9°, which is indicative of a face-to-face arrangement with the possiblity of $\pi-\pi$ interactions, at least in the solid state. The oxazolidinedione ring lies in an orthogonal plane, which bears comparison with the solution conformation determined for piperazine **5** (Figure 3). We also sought evidence for the solution conformation of **13** from NOE difference spectroscopy in the aromatic region of the proton spectrum, but results were inconclusive, possibly due to rapid relaxation of the aromatic protons by the neighboring fluorine atoms. Geminal substitution at the chiral center was explored in an attempt to bias the solution conformation in favor of this $\pi-\pi$ interaction by virtue of the Thorpe–Ingold effect[32] of steric compression. Alkylation at the chiral center with a methyl group (**14**) afforded a 2-fold improvement in affinity. However, the larger allyl substituent of **15** was not as well tolerated, resulting in a 3-fold decrease in affinity. This result ties in with the premise of limited receptor tolerance to substitution in this region being responsible for the poor affinity of the diketopiperazine **2**.

The effect of substitution on the phenyl ring was also explored (Table 2). Deletion of one trifluoromethyl group to give **16** caused a substantial loss in binding, while compounds bearing electron-donating substituents such as 3,5-dimethyl (**18**) or 3,5-dimethoxy (**19**) were also substantially less active. These results correlate well with the ester series[13,28] where 3,5-dimethylphenyl substitution was 10–30-fold less active than the 3,5-bis(trifluoromethyl) analog. The 3,5-difluoro substituents of **20** also conferred poor affinity, but the 3,5-dichloro substitution in **21** exhibited a slight improvement over 3,5-dimethyl analog **18**. These observations suggest that a combination of lipophilicity with an overall electron deficient ring is required for optimum binding. The trends are consistent with those established for the ester series[13] but demonstrate a greater degree of sensitivity to substitution than previously observed, presumably due to an inability to attain optimal binding geometry with this series.

Summary

We have sought to replace the ester linkage of our tryptophan ester NK_1 antagonists with more robust linking groups, with a view to improving their *in vivo* stability.[30] Introduction of a range of piperazines resulted in a substantial loss in binding affinity. However, careful analysis of the solution conformations of these compounds led us to investigate a variety of 5-membered ring analogs. These studies culminated in the identification of the oxazolidinedione moiety as a useful replacement for the ester linkage of **1**, albeit with some sacrifice of NK_1 activity, which we postulate may be ascribed principally to the loss of optimal binding geometry in conjunction with limited steric tolerance at the receptor. An alternative strategy, which avoids these problems, is described in the accompanying paper.[15]

Experimental Section

NMR spectra were recorded at 360 MHz on a Bruker AM360 instrument or at 250 MHz on a Bruker AC250 instrument. ^{1}H NMR chemical shifts are expressed in ppm downfield from tetramethylsilane. Nuclear Overhauser enhancements were measured by the NOE difference method on degassed samples. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Flash column chromatography was carried out on silica gel (E. Merck Art 7734) or Woelm grade III alumina (ICN 02087). Petroleum ether refers to petroleum ether with bp 60–80 °C. Reagents and dry solvents were purchased from Fluka or Aldrich and used without further purification. Organic solvents were evaporated on a Büchi rotary evaporator at reduced pressure. Elemental analyses were determined by Butterworth Laboratories Ltd., Teddington, England.

1-[3,5-Bis(trifluoromethyl)benzyl)]-2,5-dioxo-3-[(3-indolyl)methyl]-1,4-piperazine (2). To L-tryptophan methyl ester hydrochloride (3.58 g, 14 mmol) and dichloromethane (35 mL) at 0 °C was added aqueous sodium hydroxide (1.4 g, 35 mmol dissolved in 35 mL of water). To the vigorously stirred mixture at 0 °C was added chloroacetyl chloride (2.4 g, 21 mmol). The mixture was allowed to warm to room temperature and stirred for a further 18 h. After dilution with dichloromethane (30 mL), the aqueous layer was removed and the organic layer washed with 1 M aqueous hydrochloric acid and water and then dried ($MgSO_4$). The solvents were evaporated and the residual oil treated with ethoxyethanol (35 mL) and 3,5-bis(trifluoromethyl)benzylamine (3.37 g, 14 mmol). The resulting solution was heated at reflux for 24 h. On cooling, the solvent was evaporated at reduced pressure and the residue chromatographed on silica gel (eluent, ethyl acetate) to give **2** (4.68 g, 71%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.18 (1H, s), 7.81 (1H, s), 7.60 (3H, m), 7.38 (1H, d, J = 7.2 Hz), 7.22 (1H, t, J = 7.2 Hz), 7.14 (1H, t, J = 7.5 Hz), 7.04 (1H, d, J = 2.1 Hz), 6.16 (1H, s), 4.84 (1H, d, J = 15.1 Hz), 4.41 (1H, m), 3.88 (1H, d, J = 15.1 Hz), 3.47 (1H, d, J = 17 Hz), 3.37 (2H, m), 2.93 (1H, d, J = 16.9 Hz); MS *m/e* (CI^+) 470 (M^+H). Anal. ($C_{22}H_{17}N_3F_6O_2$) C, H, N.

1-[3,5-Bis(trifluoromethyl)benzyl]-3-[(3-indolyl)methyl]-1,4-piperazine (3). To diketopiperazine **2** (1.16 g, 2.47 mmol), in dry THF (10 mL), was added borane·THF (25 mL of a 1.0 M solution in THF), and the mixture was heated at reflux for 24 h. The solvent was evaporated at reduced pressure, and the residue, cooled in ice, was treated with a methanolic solution of hydrogen chloride added dropwise with caution. When gas evolution ceased, the mixture was stirred at room temperature for a further 2 h and the volatiles were evaporated at reduced pressure. The residue was partitioned between saturated aqueous K_2CO_3 and ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and evaporated and the residue chromatographed on grade III alumina (eluent, 5% methanol/ethyl acetate) to give **3** (0.90 g, 83%): ^{1}H NMR (360 MHz, DMSO-d_6) δ 10.80 (1H, bs), 7.94 (3H, bs), 7.50 (1H, d, J = 7.8 Hz), 7.32 (1H, d, J = 8.0 Hz), 7.10 (1H, d, J = 2.1 Hz), 7.05 (1H, t, J = 7.0 Hz), 6.96 (1H, t, J = 7.4 Hz), 3.66 (1H, d, J = 14.0 Hz), 3.56 (1H, d, J = 14.0 Hz), 3.17 (2H, s), 2.94 (1H, m), 2.84 (1H, m), 2.74–2.49 (4H, m), 2.01 (1H, m), 1.85 (1H, t, J = 10.1 Hz); MS *m/e* (ES^+) 442 (M^+H). The dihydrochloride salt was prepared by treatment with 1 N aqueous hydrochloric acid and freeze-dried. Anal. ($C_{22}H_{23}N_3F_6Cl_2{\cdot}0.5H_2O$) C, H, N.

***N*-[3,5-Bis(trifluoromethyl)benzyl]-2-[(*tert*-butyloxycarbonyl)amino]propylamine (23).** *N*-α-Boc-L-tryptophan (15.2 g, 100 mmol) in dichloromethane (400 mL) with triethylamine (20 mL, 144 mmol) was cooled to −30 °C and treated with isobutyl chloroformate (6.9 g, 50 mmol). The mixture was stirred at −30 °C for 15 min and allowed to warm to 0 °C, and then *N,O*-dimethylhydroxylamine hydrochloride (5.37 g, 100 mmol) was added in one portion. The reaction mixture was stirred for 1 h and then washed with water (50 mL), 10% citric acid solution (50 mL), water (50 mL), saturated sodium bicarbonate solution (50 mL), and water (50 mL). The organic solution was dried ($MgSO_4$), filtered through a small pad of silica gel, and evaporated to yield the Weinreb amide **22** as white solid (9.5 g, 49%).

The Weinreb amide **22** (5.07 g, 26 mmol) in tetrahydrofuran (200 mL) was cooled to −10 °C and treated dropwise with lithium aluminum hydride (1 M in ether, 15 mL). The reaction mixture was stirred for 2 h at −50 °C and then the reaction cautiously quenched with 20% citric acid solution. The reaction mixture was poured into ethyl acetate and washed with water, saturated sodium bicarbonate, and then water. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in dichloromethane, and magnesium sulfate (10 g) and 3,5-bis(trifluoromethyl)-benzylamine (6.3 g, 26 mmol) were added. The reaction mixture was stirred for 16 h before filtering and evaporating. The residue was dissolved in methanol and treated with excess sodium borohydride at 5 °C. The reaction mixture was stirred for 1 h, before evaporating the solvent and partitioning the residue between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate to yield the amine **23** (5.2 g, 55%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.04 (1H, s), 7.75 (3H, s), 7.62 (1H, d, J = 7 Hz), 7.35 (1H, d, J = 7 Hz), 7.18 (1H, t, J = 7 Hz), 7.10 (1H, t, J = 7 Hz), 7.01 (1H, s), 4.68 (1H, bs), 4.11 (1H, bs), 3.83 (2H, ABQ), 3.00–2.92 (2H, m), 2.73 (1H, dd, J = 5 and 12 Hz), 2.65 (1H, dd, J = 6 and 13 Hz), 1.42 (9H, s).

1-[3,5-Bis(trifluoromethyl)benzyl]-2,3-dioxo-5-[(3-indolyl)methyl]-1,4-piperazine (4). The amine **23** (2.0 g, 3.9 mmol) was dissolved in dichloromethane (200 mL) with triethylamine (1.0 g, 10 mmol) and treated with methyl oxalyl chloride (400 μL, 4.3 mmol). The reaction mixture was stirred for 1 h before evaporating the solvent and dissolving the residue in methanolic hydrogen chloride solution. The reaction mixture was stirred for 16 h, the solvent was removed, and the residue was partitioned between ethyl acetate and aqueous potassium carbonate. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by chromatography on silica gel to yield **4** (1.16 g, 64%): ^{1}H NMR (360 MHz, DMSO-d_6) δ 10.89 (1H, s), 8.77 (1H, d, J = 2 Hz), 8.01 (1H, s), 7.98 (2H, s), 7.44 (1H, d, J = 7 Hz), 7.33 (1H, d, J = 7 Hz), 7.08 (1H, t, J = 7 Hz), 6.97 (1H, t, J = 7 Hz), 7.70 (2H, ABQ), 3.91 (1H, bs), 3.56 (1H, dd, J = 4 and 13 Hz), 3.54–3.31 (1H, m), 2.95 (1H, dd, J = 5 and 14 Hz), 2.78 (1H, dd, J = 8 and 15 Hz); MS *m/e* (CI^+) 470 (MH^+). Anal. ($C_{22}H_{17}F_6N_3O_2$) C, H, N.

1-[3,5-Bis(trifluoromethyl)benzyl]-2-oxo-5-[(3-indolyl)methyl]-1,4-piperazine (5). The amine **23** (2.0 g, 3.9 mmol) was dissolved in dichloromethane (200 mL) and stirred with with potassium carbonate (2.0 g) and bromoacetyl bromide (807 mg, 4 mmol). The reaction mixture was stirred for 16 h before filtering and evaporating the solvent. The residue was dissolved in methanolic hydrogen chloride solution and stirred for 16 h, the solvent was removed, and the residue was partitioned between ethyl acetate and aqueous potassium carbonate. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by chromatography on silica gel (eluent, 5% methanol/dichloromethane) to give **5** (1.15 g, 65%). The hydrochloride salt was prepared by treatment

with ethereal hydrogen chloride: ^{1}H NMR (360 MHz, DMSO-d_6) δ 8.01 (1H, s), 7.95 (2H, s), 7.59 (1H, d, J = 7 Hz), 7.36 (1H, d, J = 7 Hz), 7.22 (1H, s), 7.09 (1H, t, J = 7 Hz), 6.99 (1H, t, J = 7 Hz), 4.83 (1H, d, J = 14 Hz), 4.58 (1H, d, J = 14 Hz), 3.99 (1H, m), 3.97 (1H, d, J = 14 Hz), 3.81 (1H, d, J = 14 Hz), 3.52–3.46 (2H, m), 3.27–3.22 (1H, m), 3.10–3.03 (1H, m); MS m/e (CI$^+$) 456 (MH$^+$). Anal. ($C_{22}H_{19}F_6N_3O$·HCl·0.5H_2O) C, H, N.

3-[3,5--Bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)imidazolidin-2-one (6). The amine **23** (1.0 g, 1.9 mmol) was dissolved in methanolic hydrogen chloride solution and stirred for 16 h, the solvent was removed, and the residue was dissolved in dichloromethane (20 mL) with triethylamine (1.0 g, 10 mmol) and treated with carbonyldiimidazole (400 mg, 2.5 mmol). The reaction mixture was stirred for 16 h; the solvent was removed, and the residue was partitioned between ethyl acetate and aqueous potassium carbonate. The organic layer was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by chromatography on silica gel to yield compound **6** (0.6 g, 71%): ^{1}H NMR (360 MHz, DMSO-d_6) δ 10.86 (1H, s), 8.01 (1H, s), 7.90 (2H, s), 7.39 (1H, d, J = 7 Hz), 7.31 (1H, d, J = 7 Hz), 7.13 (1H, d, J = 2 Hz), 7.04 (1H, dt, J = 7 and 2 Hz), 6.93 (1H, t, J = 7 Hz), 6.85 (1H, s), 4.44–4.34 (2H, m), 3.90–3.88 (1H, m), 3.33–3.25 (1H, m), 2.99–2.90 (2H, m), 2.77–2.71 (1H, m); MS m/e (CI$^+$) 442 (MH$^+$). Anal. ($C_{21}H_{17}F_6N_3O$) C, H, N.

L-Tryptophan 3,5-Bis(trifluoromethyl)benzylamide Hydrochloride (24). To a stirred solution of *N*-Boc-L-tryptophan (5.0 g,16.4 mmol) and 1-hydroxybenzotriazole (2.48 g, 18.4 mmol) in dimethylformamide (85 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.15 g, 16.4 mmol) at 0 °C. After 30 min 3,5-bis(trifluoromethyl)-benzylamine (4.43 g, 18.2 mmol) was added, and stirring was continued for 16 h at 25 °C. The reaction mixture was diluted with dichloromethane, washed with sodium bicarbonate solution and water, and dried (Na_2SO_4). The solvents were evaporated *in vacuo* to give a white solid which was dissolved in methanolic hydrogen chloride and allowed to stand for 16 h. Concentration under reduced pressure afforded **24** as a solid.

3-[3,5-Bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)imidazolidine-2,4-dione (7). The amine hydrochloride **24** (1.0 g, 2.1 mmol) in dichloromethane (5 mL) was treated with triethylamine (0.6 mL, 4.2 mmol) and carbonyldiimidazole (0.35 g, 2.2 mmol). After stirring for 16 h the mixture was washed with 10% citric acid solution and then aqueous sodium bicarbonate solution and dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:1). The product was recrystallized from diethyl ether–petroleum ether to give the imidazolidine-2,4-dione **7** (840 mg, 88%): mp 151–153 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 10.80 (1H, s), 8.38 (1H, s), 7.96 (1H, s), 7.77 (2H, s), 7.47 (1H, d, J = 7.8 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.06 (1H, d, J = 2.2 Hz), 7.00 (1H, t, J = 8.3 Hz), 6.89 (1H, t, J = 7.5 Hz), 4.56 (2H, s), 4.50 (1H, t, J = 5.2 Hz), 3.11 (2H, m); MS m/e (CI$^-$) 454 (M – H). Anal. ($C_{21}H_{15}F_6N_3O_2$) C, H, N.

1-Methyl-3-[3,5-bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)imidazolidine-2,4-dione (8). A solution of the imidazolidine-2,4-dione **7** (0.5 g, 1.1 mmol) in dry tetrahydrofuran (20 mL) was cooled to −78 °C, and *n*-butyllithium (0.72 mL of a 1.6 M solution in hexanes) was added with stirring. After 15 min methyl iodide (0.08 mL, 1.3 mmol) was added. The solution was allowed to warm to room temperature and then heated to reflux for 3 h, cooled, and poured into saturated ammonium chloride solution (20 mL). This mixture was extracted with ethyl acetate, and the organic layers were dried ($MgSO_4$). The solvents were evaporated, and the residue was purified by chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:3) and recrystallized from methanol to give compound **8** (17 mg, 3%): mp 145–147 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.88 (1H, bs), 7.70 (1H, s), 7.61 (2H, s), 7.47 (1H, d, J = 7.8 Hz), 7.19 (1H, d, J = 8.0 Hz), 7.10 (1H, t, J = 7.3 Hz), 7.02 (1H, t, J = 7.4 Hz), 6.88 (1H, bs), 4.51 (2H, s), 4.20 (1H, t, J = 4.2 Hz), 3.35 (2H, ABX, J = 15.3 and 4.2 Hz), 3.01 (3H, s); MS m/e (CI$^-$) 468 (M – H). Anal. ($C_{22}H_{17}F_6N_3O_2$) C, H, N.

1-(Methylcarboxamoyl)-3-[3,5-bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)imidazolidine-2,4--dione (9). A solution of the imidazolidinedione **7** (0.5 g, 1.1 mmol) in dry dichloromethane (20 mL) was cooled to −78 °C, and *n*-butyllithium (0.72 mL of a 1.6 M solution in hexanes) was added with stirring. After 15 min methyl isocyanate (0.07 mL, 1.2 mmol) was added. The solution was allowed to warm to room temperature and stirred for a further 1 h. Water (20 mL) was added, the organic layer was separated and dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:3) and the product recrystallized from diethyl ether/petroleum ether to give compound **9** (26 mg, 5%): mp 173–175 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.74 (2H, bs), 7.54 (3H, m), 7.40 (1H, d, J = 7.9 Hz), 7.13 (1H, d, J = 8.1 Hz), 7.06 (1H, t, J = 7.1 Hz), 6.97 (1H, t, J = 7.1 Hz), 6.74 (1H, d, J = 2.3 Hz), 4.86 (1H, dd, J = 4.9 and 2.5 Hz), 4.42 (2H, s), 3.81 (1H, dd, J = 14.8 and 5.0 Hz), 3.45 (1H, dd, J = 14.8 and 2.5 Hz), 2.97 (3H, d, J = 4.8 Hz); MS m/e (CI$^+$) 530 (M·NH$_4^+$), 513 (MH$^+$). Anal. ($C_{23}H_{18}F_6N_4O_3$) C, H, N.

1-(Phenylcarbamoyl)-3-[3,5-bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)imidazolidine-2,4-dione (10). A solution of the imidazolidinedione **7** (0.5 g, 1.1 mmol) in dry dichloromethane (20 mL) was cooled to −78 °C, and *n*-butyllithium (0.72 mL of a 1.6 M solution in hexanes) was added with stirring. After 15 min phenyl isocyanate (0.12 mL, 1.1 mmol) was added. The solution was allowed to warm to room temperature and stirred for a further 1 h. Water (20 mL) was added, the organic layer was separated and dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was purified by chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:3) and the product recrystallized from diethyl ether/petroleum ether to give compound **10** (88 mg, 14%): mp 170–172 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.70 (1H, bs), 7.75 (2H, bs), 7.55 (4H, m), 7.40 (3H, m), 7.17 (2H, m), 7.04 (1H, t, J = 7.1 Hz), 6.90 (1H, t, J = 7.5 Hz), 6.80 (1H, d, J = 2.4 Hz), 4.95 (1H, dd, J = 5.0 and 2.4 Hz), 4.44 (2H, ABq), 3.87 (1H, dd, J = 14.9 and 5.0 Hz), 3.51 (1H, dd, J = 14.9 and 2.4 Hz); MS m/e (CI$^+$) 592 (M·NH$_4^+$), 575 (MH$^+$). Anal. ($C_{28}H_{22}F_6N_4O_3$) C, H, N.

1-Benzyl-3-[3,5-bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)imidazolidine-2,4-dione (11). A solution of the imidazolidine-2,4-dione **7** (0.5 g, 1.1 mmol) in dry tetrahydrofuran (20 mL) was cooled to −78 °C and *n*-butyllithium (0.72 mL of a 1.6 M solution in hexanes) was added with stirring. After 15 min benzyl bromide (0.14 mL, 1.2 mmol) was added. The solution was allowed to warm to room temperature and then heated to reflux for 3 h, cooled, and poured into saturated ammonium chloride solution (20 mL). This mixture was extracted with ethyl acetate, and the organic layers were dried ($MgSO_4$). The residue was purified by chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:3) to give compound 11 (30 mg, 5%): mp 154–156 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.89 (1H, bs), 7.72 (1H, bs), 7.62 (2H, bs), 7.44 (1H, d, J = 7.9 Hz), 7.33–6.99 (8H, m), 6.83 (1H, d, J = 2.4 Hz), 5.17 (1H, d, J = 15.0 Hz), 4.57 (2H, s), 4.10 (1H, m), 4.06 (1H, d, J = 15.0 Hz), 3.31 (2H, ABX, m); MS m/e (CI$^+$) 563 (M·NH$_4^+$), 546 (MH$^+$). Anal. ($C_{28}H_{21}F_6N_3O_2$) C, H, N.

3,3-Dicarboxy-4-(indol-3-yl)butanoic Acid (25). Gramine (17.4 g, 100 mmol) and triethyl 1,1,2-ethanetricarboxylate (24.6 g, 100 mmol) were suspended in dry toluene. Sodium (0.05 g, 2 mmol) was added, and the stirred reaction was heated at reflux for 6 h. The reaction mixture was cooled and washed with 2 N hydrochloric acid (100 mL), and the organic layer was dried ($MgSO_4$) and evaporated. The resulting brown oil was dissolved in ethanol (400 mL), and potassium hydroxide (56 g, 1 mol) was added. The reaction mixture was heated to reflux for 6 h, cooled, poured onto ice, and acidified to pH 1 with 5 N hydrochloric acid. The mixture was saturated with sodium sulfate, extracted with ethyl acetate, dried (Na_2SO_4), filtered, and evaporated. The resulting oil was crystallized from 1,2-dichloroethane (400 mL) to yield compound **25**: mp 184–185 °C. Anal. ($C_{14}H_{13}NO_6$·0.75H_2O) C, H, N.

3-Carboxy-4-(indol-3-yl)butanoic Acid (26). 3,3-Dicarboxy-4-(indol-3-yl)butanoic acid **25** (10.0 g, 34 mmol) was dissolved in freshly distilled quinoline (50 mL) under dry

nitrogen, and copper powder (1.0 g, 40–80 mesh) was added. The reaction mixture was treated with ultrasound for 0.5 h and heated to 125 °C for 0.75 h and 145 °C for 1 h. The reaction mixture was cooled and poured onto ice, acidified with 5 N hydrochloric acid, and saturated with sodium sulfate. The mixture was extracted with ethyl acetate (4 × 100 mL). The combined organic extract was extracted with 5% sodium bicarbonate solution, and the combined aqueous extract was poured onto ice, acidified with 5 N hydrochloric acid, saturated with sodium sulfate, and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The resulting oil was taken up into hot 1,2-dichloroethane and scratched to induce crystallization. Filtration gave compound **26** as white crystals: mp 144–145 °C. Anal. ($C_{13}H_{13}NO_4$) C, H, N.

3-(Indol-3-ylmethylene)succinic Anhydride (27). The succinic acid **26** (5.35 g, 21.6 mmol) was dissolved in acetic anhydride (100 mL) and heated to reflux for 6 h. The reaction mixture was cooled, and the solvent was removed by evaporation under reduced pressure. The residue was azeotroped with xylene and crystallized from dichloromethane and petroleum ether (bp 60–80 °C) to give compound **27**: mp 90–91 °C. Anal. ($C_{13}H_{11}NO_3 \cdot 0.125H_2O$) C, H, N.

1-[3,5-Bis(trifluoromethyl)benzyl]-3-(indol-3-ylmethylene)pyrrolidine-2,5-dione (12). The anhydride **27** (1.5 g, 6.55 mmol) and 3,5-bis(trifluoromethyl)benzylamine (1.9 g, 7.8 mmol) were dissolved in xylene (100 mL) and heated to reflux under Dean–Stark conditions for 16 h. The reaction mixture was cooled and evaporated, and the resulting oil was purified by column chromatography using ethyl acetate–petroleum ether (2:3) on silica gel to yield the title compound as a white solid (981 mg, 33%): mp 68–69 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97 (1H, s), 7.78 (1H, s), 7.74 (2H, s), 7.52 (1H, d, J = 7 Hz), 7.31 (1H, d, J = 7 Hz), 7.15 (1H, dt, J = 7 Hz and 2 Hz), 7.08 (1H, dt, J = 7 Hz and 2 Hz), 6.91 (1H, d, J = 2 Hz), 4.64 (2H, s), 3.31–3.14 (3H, m), 2.76 (1H, dd, J = 7 and 18 Hz), 2.56 (1H, dd, J = 4 and 18 Hz); MS *m/e* (CI^-) 453 (M − H). Anal. ($C_{22}H_{16}F_6N_2O_2$) C, H, N.

L-Indolelactic Acid (S-28). Potassium glycidate prepared from D-serine by the method of Larcheveque and Petit[23a] was dissolved in water which was adjusted to pH 2 with concentrated hydrochloric acid. The solution was extracted with diethyl ether (5×), and the combined extracts were dried and concentrated to give glycidic acid as a colorless oil.

To a mixture of the glycidic acid (1.0 g, 11.4 mmol) and indole (1.35 g, 11.5 mmol) in CCl_4 (25 mL) was added tin tetrachloride (2.1 mL, 17.9 mmol) with stirring, at 0 °C. After 30 min the mixture was diluted with ethyl acetate and 2 N sodium hydroxide. The organic solution was separated and the aqueous phase extracted (2×) with ethyl acetate. The aqueous solution was adjusted to pH 2 with 5 N hydrochloric acid and extracted with ethyl acetate which was then dried (Na_2SO_4) and evaporated *in vacuo*. The residual crude L-indolelactic acid (170 mg, 7%) was converted via **29** to ***S*-(−)-13**.

Indolelactic Acid 3,5-Bis(trifluoromethyl)benzylamide (29). D,L-Indolelactic acid **28** (2.0 g, 9.75 mmol) suspended in dichloromethane (25 mL) was treated with triethylamine (2.8 mL, 20 mmol) and *tert*-butyldimethylsilyl triflate (2.3 mL, 10 mmol) for 16 h. Triethylamine (1.32 mL, 9.5 mmol) was then added followed by isobutylchloroformate (1.5 mL, 11.8 mmol). After stirring for 30 min 3,5-bis(trifluoromethyl)benzylamine (2.5 g, 10.3 mmol) was added and the reaction mixture stirred for a further 2 h. The mixture was washed with 2 N hydrochloric acid, aqueous sodium bicarbonate, and water and then dried (Na_2SO_4) and concentrated. Chromatography on silica gel, eluting with ethyl acetate–petroleum ether (1:3), gave an oil which was treated with tetrabutylammonium fluoride (20 mL of a 1 M solution in tetrahydrofuran) for 16 h. The solution was concentrated, diluted with dichloromethane, washed with water, dried, and concentrated. The residue was purified by chromatography (eluting with ethyl acetate–petroleum ether) followed by crystallization from diethyl ether–petroleum ether to give compound **29** as a white crystalline solid: mp 119 °C. Anal. ($C_{20}H_{16}F_6N_2O_2$) C, H, N.

3-[3,5-Bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)oxazolidine-2,4-dione (13). A solution of the alcohol **29** (230 mg, 0.53 mmol) in tetrahydrofuran (1 mL) was stirred with carbonyldiimidazole (160 mg, 0.98 mmol) for 1 h. The solvent was evaporated and the residue chromatographed on silica gel eluting with ethyl acetate–petroleum ether (1:3) to give the title compound as a colorless solid (241 mg, 99%): mp 145–146 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.70 (1H, s), 7.51 (2H, s), 7.47 (1H, d, J = 7.5 Hz), 7.12–6.70 (4H, m), 5.14 (1H, t, J = 4 Hz), 4.44 (2H, s), 3.45 (1H, dd, J = 11.5 Hz and 4 Hz), 3.40 (1H, dd, J = 11.5 Hz and 4 Hz); IR (CH_2Cl_2, ν_{max}, cm^{-1}) 1747, 1809, 1825; MS *m/e* (CI^+) 474 ($M \cdot NH_4^+$), 457 (MH^+). Anal. ($C_{21}H_{14}F_6N_2O_2$) C, H, N.

X-ray Experimental Data[33] for 13. Formula, $C_{21}H_{14}F_6N_2O_3$; M_r = 456.348; orthorhombic, $P2_12_12_1$; a = 9.495(3) Å, b = 27.003(6) Å, c = 8.165(3) Å, V = 2093(2) Å^3, Z = 4, d = 1.448 g cm^{-3}; monochromatized radiation, λ(Cu $K\alpha$) = 1.541838 Å; μ =1.15 mm^{-1}; $F(000)$ = 928; T = 294 K. Data were collected on a Rigaku AFC5 diffractometer to a θ limit of 72.5° which yielded 2405 measured (2378 unique) reflections. The structure was solved by direct methods (SHELXS-86[33]) and refined using full-matrix least-squares on F^2 (SHELXL-93[34]). The final model was refined using 314 parameters and all 2378 data. Both CF_3 groups are rotationally disordered and were modeled with two staggered sets of positions for the fluorines. All non-hydrogen atoms, with the exception of six of the disordered F atoms, were refined with anisotropic thermal displacements. Hydrogen atoms were positioned at their calculated positions and required to 'ride' with the attached atom. The final agreement statistics are R = 0.057 (based on 1680 reflections with $I \geq 2\sigma(I)$), R_w = 0.154, and S = 1.01 with $(\Delta/\sigma)_{max}$ = −0.53 (associated with an F atom). The maximum peak height in a final difference Fourier map is 0.24 eÅ^{-3}, and this peak is associated with a disordered CF_3 group.

(*S*)-(−)-3-[3,5-Bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)oxazolidine-2,4-dione (*S*-(−)-13). ***S*-(−)-13** was obtained from L-indolelactic acid as a colorless crystalline solid after chromatography on silica gel (eluent, ethyl acetate–petroleum ether, 1:3) and crystallization from diethyl ether–petroleum ether: mp 170 °C; $[\alpha]^{20}_D$ −58.5° (c = 1, CH_2Cl_2); ee 98.6% by chiral HPLC on an Ultron ES-OVM column; eluent 30% ethanol in 10 mM K_2HPO_4 (aqueous), pH 7.0; flow 0.9 mL/min; detection UV at 210 nM. Anal. ($C_{21}H_{14}F_6N_2O_3$) C, H, N.

3-[3,5-Bis(trifluoromethyl)benzyl]-5-methyl-5-(indol-3-ylmethylene)oxazolidine-2,4-dione (14). The oxazolidine-2,4-dione **13**, (147 mg, 0.32 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen was treated with sodium hydride (13 mg of a 60% dispersion in oil, 0.32 mmol) and methyl iodide (0.25 mL, 4 mmol). After stirring for 16 h water was added and the mixture extracted with ethyl acetate. The organic solution was dried (Na_2SO_4) and concentrated and the residue purified by chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:3) to give compound **14** (18 mg, 12%): mp 158–159 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 (1H, s), 7.46–7.40 (3H, m), 7.04–6.94 (4H, m), 4.38 and 4.31 (2H, AB, J = 21.5 Hz), 3.36 and 3.23 (2H, AB, J = 21.5 Hz), 1.74 (3H, s); MS *m/e* (CI^+) 488 ($M \cdot NH_4^+$), 470 (M^+). Anal. ($C_{22}H_{16}F_6N_2O_3$) C, H, N.

3-(2-Propenyl)-3-[3,5-bis(trifluoromethyl)benzyl]-5-(indol-3-ylmethylene)oxazolidine-2,4-dione (15). To a solution of oxazolidine-2,4-dione **13** (452 mg) in dimethylformamide (30 mL) under nitrogen at −78 °C was added potassium hexamethyldisilazide (4 mL of a 0.5 M solution in toluene). After stirring for 5 min allyl bromide (0.12 mL) was added and the solution stirred for 30 min. Water was then added and the mixture extracted (3×) with diethyl ether. The combined extracts were dried and concentrated and the residue purified by chromatography on silica gel (eluent, ethyl acetate–petroleum ether, 1:4) to give the title compound as a crystalline solid (15 mg, 3%): mp 124 °C (diethyl ether–petroleum ether); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.62 (1H, s), 7.42–7.39 (3H, m), 7.05–6.91 (4H, m), 5.61 (1H, m), 5.18 (1H, dd, J = 24.6 and 2.4 Hz), 5.09 (1H, dd, J = 14.5 and 2.4 Hz), 4.30 and 4.21 (2H, AB, J = 25.5 Hz), 3.29 and 3.18 (2H, AB, J = 21.5 Hz), 2.73–2.69 (2H, m); MS *m/e* (CI^+) 514 ($M \cdot NH_4^+$), 497 (MH^+). Anal. ($C_{24}H_{18}F_6N_2O_3$) C, H, N.

Table 3. ^{1}H NMR (360 MHz, DMSO-d_6) Chemical Shifts, Coupling Constants, and NOE Enhancements Observed for Compound **2**[a]

proton	ppm	^3J (Hz)	NOE enhancements on irradiation (strong [s], medium [m], weak [w])
H6u	2.85, 1H, d	17.07	H6d [s], H3′/H7′ [w]
H8″u	3.03, 1H, dd	14.48, 4.75	H8″d [s], H3 [m], H2″ [m], H4″ [m], H4 [m/w]
H8″d	3.27, 1H, dd	14.36, 4.44	H8″u [s], H3 [m], H2″ [m], H4″ [m]
H6d	3.53, 1H, d	16.95	H6u [s], H1′d [w], H3′/H7′ [m]
H1′u	4.14, 1H, d	14.97	H1′d [s], H3′/H7′ [m]
H3	4.23, 1H, m		H4 [m]
H1′d	4.59, 1H, d	14.95	H1′u [s], H3′/H7′ [s/m], H6d [w]

[a] For atom numbering, see Figure 3.

Table 4. ^{1}H NMR (360 MHz, DMSO-d_6) Chemical Shifts, Coupling Constants, and NOE Enhancements Observed for Compound **4**[a]

proton	ppm	^3J (Hz)	NOE enhancements on irradiation (strong [s], medium [m], weak [w])
H8″u	2.77, 1H, dd	14.5, 8.58	H8″d [s], H2″ [m], H4″ [w]
H8″d	2.94, 1H, dd	14.5, 5.2	H8″u [s], H5 [w], H4″ [m]
H6u	3.38, 1H, dd	12.77, 6.7	H6d [s], H2″ [w], H3′/H7′ [w]
H6d	3.55, 1H, dd	12.74, 4.26	H6u [s], H5 [m], H1′u [w], H3′/H7′ [m]
H5	3.90, 1H, m		H6u [w], H6d [w], H2″ [m], H4″ [m], H4 [m]
H1′u	4.66, 1H, d	15.18	H1′d [s], H3′/H7′ [m]
H1′d	4.76, 1H, d	15.2	H1′u [s], H3′/H7′ [m]

[a] For atom numbering, see Figure 3.

Table 5. ^{1}H NMR (360 MHz, DMSO-d_6) Chemical Shifts, Coupling Constants, and NOE Enhancements Observed for Compound **5**[a]

proton	ppm	^3J (Hz)	NOE enhancements on irradiation (strong [s], medium [m], weak [w])
H8″u	3.07, 1H, dd	14.63, 8.43	H8″d [s], H2″ [m], H4″ [m]
H8″d	3.27, 1H, dd	14.58, 4.84	H8″u [s], H2″ [m], H4″ [m]
H6u	3.47, 1H, dd	12.97, 4.75	H6d [s], H5 [m], H1′u [m], H2″ [w], H3′/H7′ [m]
H6d	3.52, 1H, dd	13.09, 9.52	H6u [s], H3′/H7′ [m]
H3u	3.80, 1H, d	16.57	H3d [s]
H3d	3.97, 1H, bd	16.68	H3u [s], H2″ [m], H4″ [m], (NH?)
H5	3.99, 1H, m		H3d/H5 irradiated together!
H1′u	4.59, 1H, d	15.51	H1′d [s], H3′/H7′ [s]
H1′d	4.83, 1H, d	15.52	H1′u [s], H3′/H7′ [s/m], H6d [w]

[a] For atom numbering, see Figure 3.

3-(3,5-Dichlorobenzyl)-5-(indol-3-ylmethylene)oxazolidine-2,4-dione (21). To a solution of indolelactic acid (0.5 g, 2.4 mmol) in CH_2Cl_2 (10 mL) and triethylamine (0.68 mL, 4.9 mmol) was added carbonyldiimidazole (0.78 g, 4.8 mmol). After stirring for 1 h 3,5-dichlorobenzylamine (0.55 g, 3.1 mmol) was added and the solution stirred for a further 1 h. The mixture was eluted through a column of silica gel with ethyl acetate–petroleum ether (1:3) to give the title compound as a crystalline solid (560 mg, 60%): mp 157–158 °C (ethyl acetate–petroleum ether); ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.0 (1H, bs), 7.99 (1H, bs), 7.52 (1H, d, J = 7.8 Hz), 7.24 (1H, d, J = 8.1 Hz), 7.12 (3H, m), 7.01 (1H, d, J = 2.4 Hz), 6.85 (1H, d, J = 1.8 Hz), 5.11 (1H, t, J = 4.0 Hz), 4.28 (2H, ABq), 3.43 (2H, ABX). Anal. ($C_{19}H_{14}Cl_2N_2O_3$) C, H, N.

Compounds **16–20** were similarly prepared.

16: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.89 (1H, bs), 7.58 (1H, d, J = 7.9 Hz), 7.43 (1H, d, J = 7.9 Hz), 7.39 (1H, s), 7.24 (1H, d, J = 9.5 Hz), 7.18–7.08 (3H, m), 6.98 (1H, d, J = 2.4 Hz), 6.82 (1H, d, J = 7.6 Hz), 5.12 (1H, t, J = 4.1 Hz), 4.48 (1H, d, J = 14.7 Hz), 4.37 (1H, d, J = 14.7 Hz), 3.44 (2H, ABX). Anal. ($C_{20}H_{15}F_3N_2O_3$) C, H, N.

17: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.89 (1H, bs), 7.64 (1H, d, J = 7.7 Hz), 7.30 (1H, d, J = 7.9 Hz), 7.22–7.08 (5H, m), 6.97 (1H, d, J = 2.4 Hz), 6.84 (2H, m), 5.09 (1H, t, J = 4.3 Hz), 4.47 (1H, d, J = 14.7 Hz), 4.35 (1H, d, J = 14.7 Hz), 3.44 (2H, ABX); MS m/e (CI^+) 338 ($M{\cdot}NH_4^+$), 320 (M^+). Anal. ($C_{19}H_{16}N_2O_3$) C, H, N.

18: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.90 (1H, bs), 7.62 (1H, d, J = 7.7 Hz), 7.29 (1H, d, J = 7.8 Hz), 7.15 (2H, m), 7.02–6.97 (3H, m), 6.93 (1H, s), 6.64 (1H, m), 5.07 (1H, t, J = 4.4 Hz), 4.42 (1H, d, J = 14.5 Hz), 4.34 (1H, d, J = 14.5 Hz), 3.48 (1H, dd, J = 15.5 and 4.4 Hz), 3.37 (1H, dd, J = 15.5 and 4.7 Hz), 2.25 (3H, s); MS m/e (CI^-) 333 (M – H). Anal. ($C_{20}H_{18}N_2O_3$) C, H, N.

19: ^{1}H NMR (360 MHz, DMSO-d_6) δ 10.90 (1H, s), 7.52 (1H, d, J = 7.9 Hz), 7.33 (1H, d, J = 8.0 Hz), 7.13 (1H, d, J = 2.0 Hz), 7.06 (1H, t, J = 7.5 Hz), 6.96 (1H, t, J = 7.5 Hz), 6.37 (1H, t, J = 2.2 Hz), 6.21 (2H, m), 5.42 (1H, m), 4.36 (2H, s), 3.67 (6H, s), 3.34 (2H, m). Anal. ($C_{21}H_{20}N_2O_5$) C, H, N.

20: ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.03 (1H, bs), 7.50 (1H, d, J = 7.9 Hz), 7.28 (1H, d, J = 8.1 Hz), 7.01 (3H, m), 6.59 (1H, m), 6.30 (2H, m), 5.17 (1H, t, J = 4.1 Hz), 4.38 (1H, AB, J = 15.1 Hz), 4.27 (1H, AB, J = 15.1 Hz), 3.40 (2H, ABX); MS m/e (FAB^+) 357 (MH^+). Anal. ($C_{19}H_{14}F_2N_2O_3$) C, H, N.

Identification of the Solution Conformations of 2, 4, and 5. For each compound conformers were constructed (in the SYBYL[26] modeling package) with the 3-indolylmethyl group oriented either axially or equatorially on the central ring, and the resulting structures were minimized.[26] A random search of the four rotatable bonds was then conducted for each structure generated, and the resulting conformers were minimized again to provide lowest energy conformations. Observed coupling constants and NOEs from ^{1}H NMR data recorded in DMSO-d_6 (300 K, 360 MHz) for each compound were compared with the computer-generated conformations to determine which of these satisfied all of the experimental data.

The low-energy conformers of **2** both have dihedral angles of ca. 60° for the indolemethyl side chain, which agree with the observed coupling constants (Table 3) ($^3J_{H8''-H3}$ = 4.79 and 4.44 Hz). However, the conformer with an axial indolemethyl has interproton distances in accord with the experimental NOEs (Table 3), while the equatorial indolemethyl conformer has a short interproton distance for H3–H5 (2.532 Å) due to the conformation of the 2,5-diketopiperazine ring. The lack of an NOE between H3 and H5 supports the conclusion that the major conformer population is with the indolemethyl group axial and the phenyl and indole rings π-stacked below the plane of the 2,5-diketopiperazine ring.

The low-energy conformers of **4** with either the axially or equatorially disposed indolemethyl group both displayed a π-stacked arrangement, with dihedral angles for the indolemethyl side chain of ca. 180° and 60° ($^3J_{H8''-H5}$ = 8.58 and 5.20 Hz). However, only the axial tryptophan derivative had H5,-

H6 dihedral angles of ca. 60°, consistent with the observed coupling constants (Table 4) (($^3J_{H6-H5}$ = 6.7 and 4.26 Hz). The interproton distances were also consistent with the observed NOEs (Table 4). This conformer has the phenyl and indole rings π-stacked below the plane of the 2,3-diketopiperazine ring.

A low-energy conformer of **5** had dihedral angles for the indolemethyl side chain of ca. 180° and 60° ($^3J_{H8''-H5}$ = 8.43 and 4.84 Hz) and H5,H6 dihedral angles of 180° and 60° ($^3J_{H6-H5}$ = 9.52 and 4.75 Hz) only for the equatorial 3-indolylmethyl case, consistent with the observed coupling constants (Table 5), and with no discrepancies between interproton distances and observed NOEs (Table 5). The phenyl and indole rings were π-stacked, to one side of and in the plane of the lactam ring. The central lactam ring has greater conformational flexibility than either the 2,3- or 2,5-dioxopiperazine rings.

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(26) Molecular modeling was carried out using SYBYL (version 6.0; Tripos Associates Inc.). Minimization was performed utilizing the default settings (method—Powell; initial optimization—Simplex; force field—Tripos; charges—none; maximum iterations—100; dielectric constant—1.0). The random search was conducted with the above default values for minimization, default values for the energy setup, and random search default parameters) (energy cutoff, 70 kcal/mol; maximum cycles, 1000; rms threshold, 0.2 Å). For **2**, **4**, and **5**, the global energy minimum, with the pendant aromatic moieties exhibiting a face-to-face interaction of the aromatic rings, was approximately 3 kcal lower in energy than conformers adopting an edge-to-face arrangement, and the lowest energy extended conformer was approximately 3 kcal higher in energy. For further discussion of the significance of these results, see ref 13.

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(28) In all of the cases which we have examined, the esters are invariably significantly higher affinity NK_1 ligands than the corresponding acyclic amide derivatives. A more detailed discussion of this phenomenon is to be found in the accompanying paper (ref 15).

(29) (±)-**13** possesses an NK_1 affinity of 22 (±7) nM, while *S*-(−) **13** exhibits an NK_1 affinity of 26 (±6) nM. It is important to note that the *R*-(+)-enantiomer of **13** has not been prepared in homochiral form. By analogy with the ester series where NK_1 affinity resides predominantly with the *S*-enantiomer,[13] we would expect the active enantiomer to be 2-fold more potent than the racemate if the distomer is entirely devoid of biological activity; however such small differences in activity are within the error limits of the binding assay.

(30) The heterocyclic compounds described in this manuscript were not evaluated *in vivo* because they failed to reach the level of affinity seen with the ester series and because other related approaches proved to be more fruitful.[15]

(31) The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, U.K.

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