Pergamon

*Bioorganic & Medicinal Chemistry*, Vol. 4, No. 10, pp 1733–1745, 1996

PII: S0968-0896(96)00185-X
0968-0896/96 $15.00 + 0.00

# Cholecystokinin B Antagonists. Synthesis and Quantitative Structure-Activity Relationships of a Series of C-Terminal Analogues of CI-988†

Corinne E. Augelli-Szafran,*[a] David C. Horwell,[c] Clare Kneen,[c] Daniel F. Ortwine,[a] Martyn C. Pritchard,[c] Terri S. Purchase,[a] Bruce D. Roth,[a] Bharat K. Trivedi,[a] David Hill,[c] Nirmala Suman-Chauhan[d] and Louise Webdale[d]

*Departments of [a]Medicinal Chemistry and [b]Pharmacology, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan, 48105, U.S.A.*

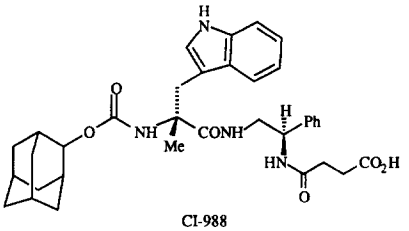
*Departments of [c]Medicinal Chemistry and [d]Pharmacology, Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge CB2 2QB, U.K.*

*[e]Organon Laboratories Ltd., Newhouse, Lanarkshire ML1 5SH, U.K.*

**Abstract**—A study of structure–activity relationships of a series of 'dipeptoid' CCK-B receptor antagonists was performed in which variations of the phenyl ring were examined while the [(2-adamantyloxy)carbonyl]-α-methyl-*R*)-tryptophan moiety of the potent antagonist CI-988 was kept constant. Since the main focus of this study was phenyl substituent variation, series design techniques were employed to insure an adequate spread of physicochemical properties (lipophilic, steric, electronic), as well as positional substitution. A QSAR analysis on sets of 26 and 16 analogues revealed that CCK-B affinity was related to a combination of the overall size and, marginally, lipophilicity of the phenyl ring substituents (i.e., smaller groups were associated with increased potency with an optimum π near zero, respectively). Further exploration revealed that the dimensions and electronics of the para-phenyl substituent could be related to CCK-B affinity. Increased affinity was seen with short, bulky (branched) electron withdrawing groups. Analogs with small *para*-substituents appeared to be about 1000-fold CCK-B selective, indicating that selectivity for CCK-B binding is sensitive to phenyl ring substitution. The 4-F-phenyl dipeptoid, derived from this study, has extraordinary high affinity at the CCK-B receptor ($IC_{50}$ = 0.08 nM) and was also very selective (940-fold CCK-B selective). Consistent with previous reports, (*S*)-configuration at the substituted phenethylamide center, a carboxylic acid and the presence of a phenyl ring were found to be associated with increased affinity at both CCK-A and CCK-B receptors. Copyright © 1996 Elsevier Science Ltd

## Introduction

Cholecystokinin (CCK), a 33 residue polypeptide originally isolated from porcine intestine,[1] is known to stimulate gallbladder contraction and pancreatic enzyme secretion. It is widely distributed in the central nervous system, where it acts as a neurotransmitter. Two receptor subtypes for CCK are presently known.[2] CCK-A receptors are distributed mainly in peripheral tissue such as gallbladder and pancreas, while CCK-B receptors are located mainly in the central nervous system. The role of CCK in anxiety/panic disorders, acting via interactions with the CCK-B receptors, has been explored. Some selective antagonists of this receptor are known to produce anxiolytic-like effects in both animal models[3] and humans.[4] Thus, it has been postulated that CCK-B receptor antagonists could represent a novel treatment for CNS disorders such as anxiety and panic attacks. Recently, the pharmacological profiles of a number of diverse antagonists have been described.[5]



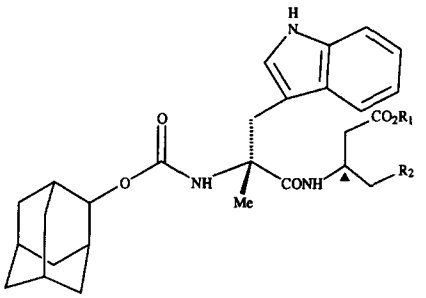
CI-988

Previous work in our laboratories[6] led to the development of dipeptoid CCK-B receptor antagonist, CI-988, which exhibits potent and selective antagonism at the CCK-B receptor[6a] (CCK-B, $IC_{50}$ = 1.7 nM; CCK-A, $IC_{50}$ = 4300 nM, A/B ratio = 2500) as well as marked anxiolytic activity. Continued SAR efforts led to the discovery of a higher affinity (**1**, Table 1, CCK-B, $IC_{50}$ = 0.15 nM; CCK-A, $IC_{50}$ = 22.5 nM), but less selective (A/B ratio = 170) dipeptoid analogue of CI-988.[7] Due to the encouraging biological results found with both CI-988 and **1**, we felt that further exploration of the phenyl ring ($R_2$) of **1** might expand our understanding of the structural requirements for

†Presented in part at the 206th National Meeting, American Chemical Society, Chicago, Illinois, 1993; MEDI 194.

CCK-B receptor affinity and selectivity. Therefore, a series of compounds was synthesized in which the [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan moiety of CI-988 was kept constant and the phenyl ring ($R_2$) of **1** was varied. These modifications led to the identification of a number of dipeptoids with high affinity and increased selectivity for binding to the CCK-B receptor. The effect on affinity at CCK-B receptors was quantified by the use of a QSAR analysis.

**Table 1.** CCK receptor affinities of C-terminal analogues of CI-988




**I**

| Example | $R_1$ | $R_2$ | ▲ | Method of Preparation | $IC_{50}$(nM)[a] | | A/B ratio | Formula[b] |
|---|---|---|---|---|---|---|---|---|
| | | | | | CCK-A | CCK-B | | |
| **1** | H | Ph | *S* | ref 7a | 22.5 | 0.15 | 150 | $C_{33}H_{39}N_3O_5 \cdot 0.1\ H_2O$ |
| **2** | H | Ph-2-Cl | *R,S* (1.3:1)[c] | B | 68 | 0.40 | 170 | $C_{33}H_{38}ClN_3O_5 \cdot 0.61$ EtOAc |
| **3** | Et | Ph-2-Cl | *R,S* (1:1)[c] | B | 796 | 43 | 19 | $C_{35}H_{42}ClN_3O_5 \cdot 0.84$ EtOAc |
| **4** | H | Ph-2,6-$Cl_2$ | *R,S* (1.8:1)[c] | B | 38 | 0.22 | 173 | $C_{33}H_{37}Cl_2N_3O_5$d |
| **5** | Et | Ph-2,6-$Cl_2$ | *R,S* (1:1)[c] | B | 3080 | 62 | 50 | $C_{35}H_{41}Cl_2N_3O_5$e |
| **6** | H | Ph-3-I, 4-$NH_2$ | *S* | A | 158 | 0.523 | 302 | $C_{33}H_{39}IN_4O_5 \cdot 0.5\ H_2O$ |
| **7** | H | Ph-3-I, 4-$N_3$ | *S* | A | 392 | 0.882 | 444 | $C_{33}H_{37}IN_6O_5 \cdot 0.5\ H_2O$ |
| **8** | H | Ph-3-I, 4-OH | *S* | A | 182 | 1.68 | 108 | $C_{33}H_{38}IN_3O_6 \cdot 0.5\ Et_2O$ |
| **9** | H | Ph-3,4-$Cl_2$ | *S* | A | 87 | 0.53 | 164 | $C_{33}H_{37}Cl_2N_3O_5 \cdot 0.25\ H_2O$ |
| **10** | H | Ph-3,4-$Cl_2$ | *R* | A | 327 | 19.3 | 17 | $C_{33}H_{37}Cl_2N_3O_5 \cdot 0.25\ H_2O$ |
| **11** | H | Ph-3,5-$(CF_3)_2$ | *S* | A | 683 | 35.9 | 19 | $C_{35}H_{37}F_6N_3O_5$ |
| **12** | H | Ph-3,5-$(CF_3)_2$ | *R* | A | 1379 | 153 | 9 | $C_{35}H_{37}F_6N_3O_5 \cdot 0.25\ H_2O$ |
| **13** | H | Ph-3,5-$I_2$, 4-$NH_2$ | *S* | A | 188 | 5.45 | 34 | $C_{33}H_{38}I_2N_4O_5$ |
| **14** | H | Ph-3,5-$I_2$, 4-OH | *S* | A | 189 | 5.22 | 36 | $C_{33}H_{37}I_2N_3O_6 \cdot 0.5$ EtOAc |
| **15** | H | Ph-4-$CF_3$ | *S* | A | 367 | 0.91 | 403 | $C_{34}H_{38}F_3N_3O_5 \cdot 0.25\ H_2O$ |
| **16** | H | Ph-4-$CF_3$ | *R* | A | 843 | 40.6 | 21 | $C_{34}H_{38}F_3N_3O_5 \cdot 0.5\ H_2O$ |
| **17** | Et | Ph-4-Ph | *R,S* (1.1:1)[c] | B | 37% @10μM | 800 | f | $C_{41}H_{47}N_3O_5$g |
| **18** | H | Ph-4-Ph | *R,S* (2.6:1)[c] | B | 849 | 41 | 21 | $C_{39}H_{43}N_3O_5$h |
| **19** | H | Ph-4-F | *S* | A | 75 | 0.08 | 938 | $C_{33}H_{38}FN_3O_5$ |
| **20** | Me | Ph-4-F | *S* | A | 613 | 3.23 | 189 | $C_{36}H_{44}FN_3O_5$ |
| **21** | H | Ph-4-I | *S* | A | 250 | 0.27 | 926 | $C_{33}H_{38}IN_3O_5$ |
| **22** | H | Ph-4-$NHCOCH_3$ | *S* | A | 576 | 54.7 | 11 | $C_{35}H_{42}N_4O_6 \cdot 0.5$ EtOAc$\cdot 0.5\ H_2O$ |
| **23** | H | Ph-4-$NH_2$ | *S* | A | 354 | 0.24 | 1475 | $C_{33}H_{40}N_4O_5 \cdot H_2O$ |
| **24** | H | Ph-4-$NO_2$ | *S* | A | 225 | 0.19 | 1184 | $C_{33}H_{38}N_4O_7 \cdot 0.5\ H_2O$ |
| **25** | H | Ph-4-$OCH(CH_3)_2$ | *S* | A | 744 | 24.1 | 31 | $C_{36}H_{45}N_3O_6 \cdot 0.5$ EtOAc |
| **26** | H | Ph-4-OH | *S* | A | 334 | 0.55 | 607 | $C_{33}H_{39}N_{23}O_6 \cdot 0.5$ EtOAc$\cdot 0.5\ H_2O$ |
| **27** | Et | Me | *R,S*[c,i] | C | 3219 | 151 | 21 | $C_{30}H_{41}N_3O_5 \cdot 0.75$ EtOAc |
| **28** | H | Me | *R,S* (1:2.3)[c] | C | 1670 | 154 | 11 | $C_{28}H_{37}N_3O_5$j |

[a] $IC_{50}$ represents the concentration (nM) producing half-maximal inhibition of specific binding of [$^{125}$I] Bolton–Hunter-labeled CCK-8 to CCK receptors in the mouse cerebral cortex (CCK-B) or the rat pancreas (CCK-A). Assays were carried out in duplicate using 10 concentrations of each test compound. Values shown represent geometric means of $IC_{50}$ values obtained from three separate experiments. Complete protocol of both assays is described by Boden et al.[6]

[b] Analytical results are within ±0.4% of theoretical values unless otherwise noted. Some difficulty was found in obtaining combustion analysis on the indicated compounds due to the propensity of these compounds to retain solvents.

[c] HPLC conditions: [Hypersil BDS, 250 × 4.6 mm, 5 μm column; 55:45 $CH_3CN$:buffer (0.05 M $NH_4H_2PO_4$, 0.5% TEA), pH 3.0].

[d] High mass; calcd 626.2188; found 626.2194.

[e] High mass: calcd 654.2501; found 654.2496.

[f] Not determined.

[g] High mass: calcd 662.3594; found 662.3609.

[h] High mass: calcd 634.3281; found 634.3315.

[i] No HPLC separation detected.

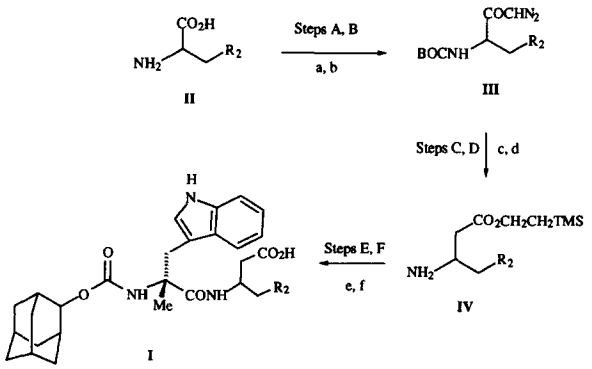
[j] High mass: calcd 496.2811; found 496.2807.

## Chemistry

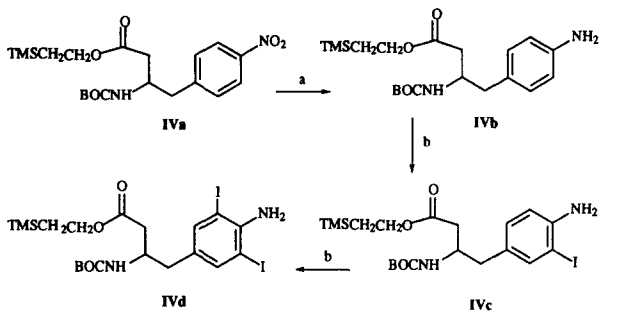
Examples **9–12**, **15**, **16**, **21**, **24**, and **26** were synthesized from readily available racemic β-amino acids via the Arndt–Eistert based synthesis illustrated in Scheme 1 (Method A). Thus, the substituted phenylalanines[8] (**II**) were protected with BOC-anhydride, followed by the formation of the corresponding mixed anhydride with isobutyryl chloride which was reacted with diazomethane to give diazoketone **III**. Treatment of **III** with silver benzoate and 2-(trimethylsilyl)ethanol induced the diazoketone to undergo a Wolff rearrangement to give **IV**. Removal of the BOC-group with *para*-toluenesulfonic acid (*p*-TSOH), followed by coupling of the primary amine to [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan[9] using 1-hydroxybenzotriazole (HOBt) and 1,3-dicyclohexylcarbodiimide (DCC), and subsequent hydrolysis with tetrabutylammonium fluoride (TBAF) yielded the desired phenyl-substituted analogues (**I**).

Examples **6**, **7**, and **13** were prepared from the *p*-nitro-(*S*)-trimethylsilyl BOC-protected **IVa** (Scheme 2). Intermediate **IVa** is obtained from diazoketone **III** (Scheme 1). As mentioned above, treatment of **III** with silver benzoate and 2-(trimethylsilyl)ethanol induced the diazoketone to undergo a Wolff rearrangement to give BOC-protected amine **IVa**. Reduction of the *p*-nitro group with Pearlman's catalyst [$Pd(OH)_2$/C] yielded **IVb**. Intermediate **IVd** was obtained by treating first **IVb**, then **IVc**, with NaI and Chloramine T. Following the general synthetic route outlined in Scheme 1 (i.e. conversion of **IV**→**I**), intermediates **IVc** and **d** yielded **6** and **13**, respectively. Diazotization of **6** followed by treatment with $NaN_3$ yielded **7**.

Examples **8**, **14**, and **25** were synthesized by the synthetic route outlined in Scheme 3. Treatment of the trimethylsilylethyl protected acid (**I**) with sodium iodide and Chloramine T yielded **Ia**, a mixture of the 3-I, 4-OH, and 3,5-$I_2$ analogues that were separated by chromatography. Removal of the trimethylsilylethyl group with TBAF gave **8** and **14**. Treatment of **I** with isopropyl iodide gave **Ib** that was then deprotected with TBAF to yield **25**. Example **23** was obtained by treating




**Scheme 1.** Method A. (a) $(BOC)_2O$, $NaHCO_3$, aq dioxane; (b) i. *i*-BuOCOCl, *N*-Me-morpholine, THF; ii. $CH_2N_2$, $Et_2O$; (c) $PhCO_2Ag$, $NEt_3$, $TMSCH_2CH_2OH$; (d) *p*-TSOH; (e) 2-Adoc-*R*-α-Me-Trp-OH, DCC, HOBt; (f) TBAF, THF.

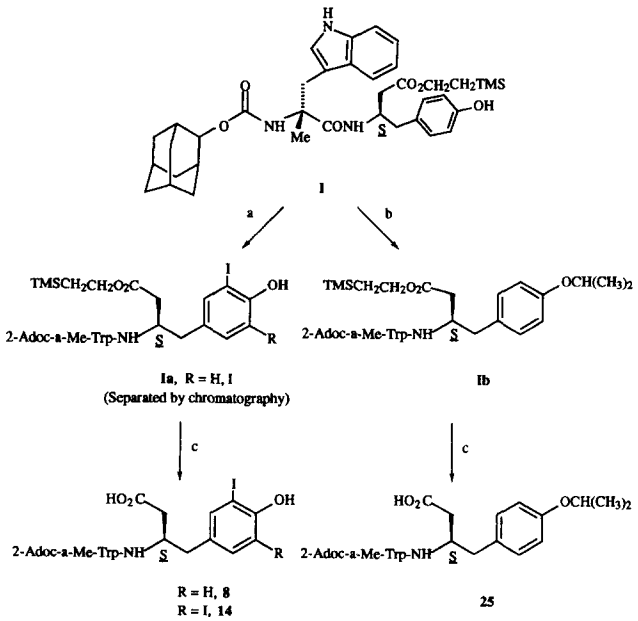



**Scheme 2.** (a) Pd(OH2)/C; (b) Chloramine T. NaI, HOAc.

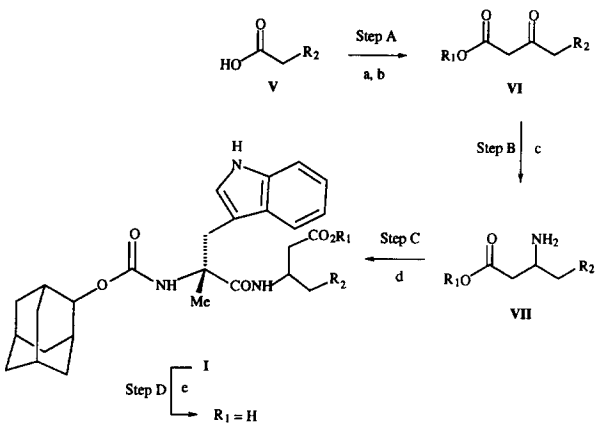
**24** with Pearlman's catalyst ($Pd(OH)_2$/C, EtOH). Acetylation of **23** ($AcCl,NEt_3$) gave **22**. Example **19** was synthesized via intermediate **III** using silver benzoate, methanol, and triethylamine to give the corresponding methyl ester of **IV** (Scheme 1). Removal of the BOC group with trifluoroacetic acid, followed by coupling and hydrolysis yielded **19**.

Examples **2–5**, **17**, and **18** were prepared by the synthetic route shown in Scheme 4 (Method B). Treatment of the appropriate carboxylic acid (**V**) with 1,1′-carbonyldiimidazole, followed by the addition of the magnesium salt of mono-ethyl malonate ($R_1$ = Et) yielded the required β-ketoester (**VI**).[10] Reductive amination[11] of **VI** yielded amine **VII**. Amide formation with 2-Adoc-α-Me-(*R*)-Trp-OH,[9] followed by hydrolysis with lithium hydroxide provided **I**.

In Scheme 5 (Method C), the synthesis of **27** and **28** is outlined. The required α,β-unsaturated ester (**IX**, $R_2$ = Me) was synthesized via a Wittig reaction using (carbethoxymethylene)triphenylphosphorane and propionaldehyde (**VIII**, $R_2$ = Me). The Michael addition[12,13] of (*S*)-α-methyl-benzylamine to **IX**,




**Scheme 3.** (a) Chloramine T, NaI, MeCN; (b) $ICH(CH_3)_2$, 2-butanone, $K_2CO_3$; (c) TBAF, THF.

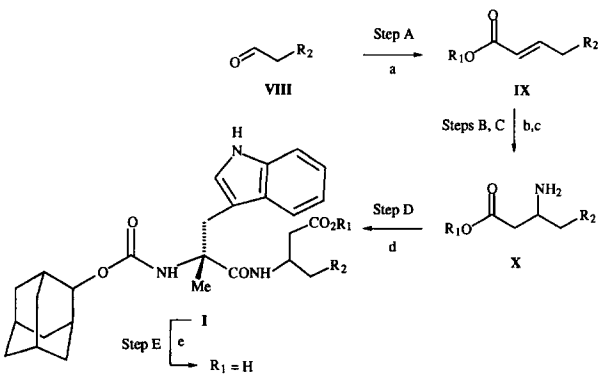


**Scheme 4.** Method B. (a) CDI, 0 °C; (b) $(R_1OCOCH_2CO_2^-)$ $Mg^{2+}$, $CH_3CN$, 25 °C; (c) $NH_4OAc$/MeOH, $NaBH_3CN$, 3 Å sieves; (d) 2-Adoc-R-α-Me-Trp-OH, DCC, HOBt; (e) LiOH, $H_2O$/dioxane.

followed by hydrogenation (10% Pd/C, $H_2$), gave **X**, a mixture of diastereomeric amines. Coupling of **X** to 2-Adoc-α-Me-(*R*)-Trp-OH[9] and subsequent hydrolysis yielded targeted analogues **I**.

## Results and Discussion

Comprehensive structure–activity studies have examined the effects of structural changes in both CI-988[6] and **1**.[7] The present study extends this work by varying the phenyl group ($R_2$) of **1** while keeping the [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan moiety constant. It has previously been shown that the N-terminal carbamate alkyl moiety required a cycloalkyl or bulky substituent rather than a straight chain or aromatic hydrocarbon to achieve micromolar CCK-B receptor affinity.[14] A study of bulky, fused C-10 cyclic systems led to the 2-adamantyl group which has been proven to be the optimal N-terminus necessary for potent CCK-B receptor binding. Also, the [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan-configured derivative has shown a higher affinity than the corresponding α-methyl-(*S*)-tryptophan-configured analogue.[6a,7] Inversion of the substituted phenethylamide center from (*S*) to (*R*) yielded a decrease in CCK-B affinity.[7] Examples of this latter decrease in CCK-B affinity is illustrated by **10**, **12**, and **16** (Table 1, $IC_{50}$ = 19.3, 15.3, and 40.6 nM, respectively), which show lower affinity at the CCK-B receptor than their corresponding enantiomers (**9**, **11**, and **15**, $IC_{50}$ = 0.53, 35.9, and 0.91 nM, respectively). Also observed was at least a twofold decrease on CCK-A receptor binding affinity for these stereoisomeric pairs.



**Scheme 5.** Method C. (a) $R_1OCOCHPPh_3$, THF, 25 °C; (b) $PhNH_2C$, EtOH, Δ; (c) 10% Pd/C, $H_2$; (d) 2-Adoc-R-α-Me-Trp-OH; DCC, HOBt, DMAP; (e) LiOH, $H_2O$/dioxane.

Other previous studies have focused on the terminal carboxylic acid group of **I** ($R_1$ = H). It has been shown that the full tetrapeptide (Trp-Met-Asp-Phe-$NH_2$; CCK 30–33) necessary for nanomolar affinity[15] exists as a folded structure[16] in which the Asp residue is readily available to serve as an accessory binding group, and the terminal COOH group is free to explore a large volume of space.[16,17] SAR studies of mobile chains on the C-terminus that terminate in the COOH group led to the discovery of CI-988[6] and **1** (Table 1).[7] SAR studies of the terminal COOH group have shown that there is a clear specificity of interaction involving this group, which appears to be essential for enhancing affinity and selectivity for the CCK-B receptor.[18] Several ester precursors of the final acid analogues illustrated in Table 1 showed reduced binding affinity for the CCK-B receptor relative to their corresponding acids (**3** vs **2**, **5** vs **4**, **20** vs **19**, and **17** vs **18**, respectively). These results are additional evidence for the importance of a COOH group necessary for enhanced affinity for the CCK-B receptor.

The majority of the modifications in this study involved variations of the phenyl group ($R_2$) of **1**. It appeared that selectivity toward the CCK-B receptor was sensitive to the pattern of phenyl substitution. Most substitution patterns on the phenyl ring (**2**, **4**, **6–10**) were tolerated, with the exception of 3,5-disubstitution (**11**). However, this is the only 3,5-disubstituted analogue that lacks a 4-substituent. The greatest improvement in selectivity was found with 4-substitution (**15**, **19**, **21**, **23**, **24**, and **26**), which resulted in compounds with five- to tenfold greater selectivity than the parent analogue (**1**). Larger groups in the 4-position (**18**, **22**, and **25**) led to compounds with reduced CCK-B binding affinity ($IC_{50}$ = 41, 54.7, and 24.1 nM, respectively), indicating that the size of the 4-substituent appeared to influence the degree of CCK-B affinity. Also, replacement of the phenyl group of **1** with a methyl group (**28**, $R_2$ = Me, $IC_{50}$ = 154 nM) resulted in at least a 1000-fold decrease in CCK-B affinity.

### Quantitative structure–activity relationships

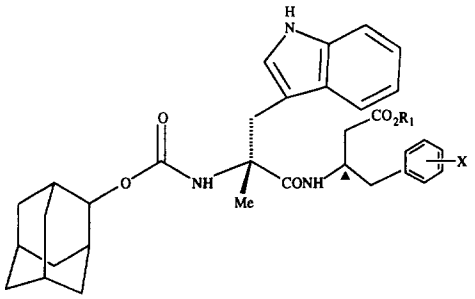
Since the focus of the present study was the exploration of modifications of the phenyl ring of **1**, it was of interest to examine the effect of phenyl substituent modification on potency at CCK receptors. A set of substituents was selected that incorporated systematic variation in lipophilic, electronic, steric, and hydrogen bonding properties.[19] The effect of altering positional substitution on the ring was also tested via the prepara-

tion of analogues incorporating substitution at multiple ring positions. To determine which of these properties might be influencing the affinity and selectivity for the CCK-B receptor, the set of substituted phenyl derivatives (i.e. **1–26**) was analysed using QSAR techniques.[20]

In addition to substituent variation on the phenyl ring, the set of 26 analogues selected for analysis included carboxylic acids and esters at $R_1$, and enantiomeric mixtures at the substituted phenethylamide center (▲, Table 2). The logarithm of $1/K_i$ at CCK-B receptors was used as the measure of affinity; values ranged from 6.1 to 10.1 with a standard error of replicate analyses of $\pm 0.11$. Analyses using affinity at CCK-A receptors was not possible due to insufficient variation in the affinity (1.2 log units) among substituted phenyl derivatives. Parameters used in the initial correlations included $\pi$, $\pi^2$, $\sigma$, and MR as published by Hansch,[21] summed for the phenyl ring substituents, and the positional-dependent $F$ and $R$ values of Norrington.[22] Indicator variables were included to denote acid versus ester at $R_1$ (ESTER), (*R*)- vs (*S*)-stereoisomer (▲, ISOMER), and a single isomer versus an isomeric mixture at this position (MIXTURE). Also, correlations that examined the addition of parameters specific to the *para*-phenyl substituent ($\pi$_4, [$\pi$_4]$^2$, MR_4, and the Sterimol[23] parameters L_4, B1_4, and B5_4) were studied. MR was multiplied by 0.1 to place it on a scale similar to that of the other parameters. Pairwise correlations between all the parameters for the full 26-compound set and a 16-compound subset containing only acids at $R_1$ and (*S*)-isomers are given in Tables 3 and 4, respectively. Values for those parameters included in eqs (1)–(4) can be found in Table 2.

Multiple regression analysis using the initial set of nine parameters on the 26 compound set produced eqs (1) and (2).

**Table 2.** Data used to formulate the QSAR




| Example | X | $R_1$ | Stereo | Isomer | Ester | $\pi^2$ | $F$ | MR | MR_4 | L_4 | B1_4 | $K_i$ (nM) | Log ($1/K_i$) | Calcd (eq 3) | Residual |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | *S* | 0 | 0 | 0.00 | 0.00 | 0.10 | 0.10 | 2.06 | 1.00 | 0.15 | 9.81 | 9.24 | 0.57 |
| 2 | 2-Cl | H | *R,S* | 0 | 0 | 0.50 | 0.86 | 0.60 | 0.10 | 2.06 | 1.00 | 0.40 | 9.40 | 9.08 | 0.32 |
| 3 | 2-Cl | $CH_2CH_3$ | *R,S* | 0 | 1 | 0.50 | 0.86 | 0.60 | 0.10 | 2.06 | 1.00 | 43.00 | 7.37 | 7.42 | −0.05 |
| 4 | 2,6-$Cl_2$ | H | *R,S* | 0 | 0 | 2.02 | 1.72 | 1.21 | 0.10 | 2.06 | 1.00 | 0.22 | 9.66 | 8.88 | 0.78 |
| 5 | 2,6-$Cl_2$ | $CH_2CH_3$ | *R,S* | 0 | 1 | 2.02 | 1.72 | 1.21 | 0.10 | 2.06 | 1.00 | 62.00 | 7.21 | 7.22 | −0.01 |
| 6 | 3-I,4-$NH_2$ | H | *S* | 0 | 0 | 0.01 | 0.70 | 1.94 | 0.54 | 2.78 | 1.35 | 0.52 | 9.28 | 8.87 | 0.41 |
| 7 | 3-I,4-$N_3$ | H | *S* | 0 | 0 | 2.50 | 0.65 | 2.41 | 1.02 | 4.62 | 1.50 | 0.88 | 9.05 | 8.03 | 1.02 |
| 8 | 3-I,4-OH | H | *S* | 0 | 0 | 0.20 | 1.15 | 1.68 | 0.29 | 2.74 | 1.35 | 1.70 | 8.77 | 8.98 | −0.21 |
| 9 | 3,4-$Cl_2$ | H | *S* | 0 | 0 | 2.02 | 1.37 | 1.21 | 0.60 | 3.52 | 1.80 | 0.53 | 9.27 | 9.51 | −0.24 |
| 10 | 3,4-$Cl_2$ | H | *R* | 1 | 0 | 2.02 | 1.37 | 1.21 | 0.60 | 3.52 | 1.80 | 19.00 | 7.71 | 7.50 | 0.21 |
| 11 | 3,5-$(CF_3)_2$ | H | *S* | 0 | 0 | 3.10 | 1.24 | 1.00 | 0.10 | 2.06 | 1.00 | 36.00 | 7.44 | 8.94 | −1.50 |
| 12 | 3,5-$(CF_3)_2$ | H | *R* | 1 | 0 | 3.10 | 1.24 | 1.00 | 0.10 | 2.06 | 1.00 | 150.00 | 6.82 | 6.93 | −0.11 |
| 13 | 3,5-$I_2$,4-$NH_2$ | H | *S* | 0 | 0 | 1.02 | 1.36 | 3.33 | 0.54 | 2.78 | 1.35 | 5.50 | 8.26 | 8.41 | −0.15 |
| 14 | 3,5-$I_2$,4-OH | H | *S* | 0 | 0 | 2.46 | 1.81 | 3.07 | 0.29 | 2.74 | 1.35 | 5.20 | 8.28 | 8.51 | −0.23 |
| 15 | 4-$CF_3$ | H | *S* | 0 | 0 | 0.77 | 0.63 | 0.50 | 0.50 | 3.30 | 1.60 | 0.91 | 9.04 | 9.51 | −0.47 |
| 16 | 4-$CF_3$ | H | *R* | 1 | 0 | 0.77 | 0.63 | 0.50 | 0.50 | 3.30 | 1.60 | 41.00 | 7.39 | 7.50 | −0.11 |
| 17 | 4-$C_6H_5$ | $CH_2CH_3$ | *R,S* | 0 | 1 | 3.84 | 0.14 | 2.54 | 2.54 | 6.28 | 1.71 | 800.00 | 6.10 | 5.85 | 0.25 |
| 18 | 4-$C_6H_5$ | H | *R,S* | 0 | 0 | 3.84 | 0.14 | 2.54 | 2.54 | 6.28 | 1.71 | 41.00 | 7.39 | 7.51 | −0.12 |
| 19 | 4-F | H | *S* | 0 | 0 | 0.02 | 0.71 | 0.09 | 0.09 | 2.65 | 1.35 | 0.08 | 10.08 | 9.55 | 0.53 |
| 20 | 4-F | $CH_3$ | *S* | 0 | 1 | 0.02 | 0.71 | 0.09 | 0.09 | 2.65 | 1.35 | 20.00 | 7.70 | 7.89 | −0.19 |
| 21 | 4-I | H | *S* | 0 | 0 | 1.25 | 0.67 | 1.39 | 1.39 | 4.23 | 2.15 | 0.28 | 9.56 | 9.69 | −0.13 |
| 22 | 4-$NHCOCH_3$ | H | *S* | 0 | 0 | 0.94 | 0.47 | 1.49 | 1.49 | 5.09 | 1.35 | 55.00 | 7.26 | 7.84 | −0.58 |
| 23 | 4-$NH_2$ | H | *S* | 0 | 0 | 1.51 | 0.04 | 0.54 | 0.54 | 2.78 | 1.35 | 0.24 | 9.62 | 9.33 | 0.29 |
| 24 | 4-$NO_2$ | H | *S* | 0 | 0 | 0.08 | 1.11 | 0.74 | 0.74 | 3.44 | 1.70 | 0.19 | 9.71 | 9.54 | 0.17 |
| 25 | 4-$OCH(CH_3)_2$ | H | *S* | 0 | 0 | 0.81 | 0.49 | 1.71 | 1.71 | 4.80 | 1.35 | 24.00 | 7.62 | 7.92 | −0.30 |
| 26 | 4-OH | H | *S* | 0 | 0 | 0.45 | 0.49 | 0.29 | 0.29 | 2.74 | 1.35 | 0.55 | 9.26 | 9.44 | −0.18 |

**Table 3.** Correlation matrix on the full 26-compound set

| | Log(1/K$_i$) | Ester | Mixture | Isomer | π | π$^2$ | σ | *F* | *R* | MR | MR_4 | π_4 | [π_4]$^2$ | L_4 | B1_4 | B5_4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Log(1/*K*$_i$) | 1.00 | | | | | | | | | | | | | | | |
| Ester | −0.52 | 1.00 | | | | | | | | | | | | | | |
| Mixture | −0.29 | 0.53 | 1.00 | | | | | | | | | | | | | |
| Isomer | −0.37 | −0.15 | −0.20 | 1.00 | | | | | | | | | | | | |
| π | −0.45 | 0.14 | 0.37 | 0.24 | 1.00 | | | | | | | | | | | |
| π2 | −0.53 | 0.08 | 0.34 | 0.18 | 0.73 | 1.00 | | | | | | | | | | |
| s | −0.17 | −0.02 | 0.03 | 0.40 | 0.56 | 0.32 | 1.00 | | | | | | | | | |
| *F* | −0.04 | 0.00 | 0.05 | 0.16 | 0.41 | 0.14 | 0.59 | 1.00 | | | | | | | | |
| *R* | −0.19 | 0.08 | 0.18 | 0.35 | 0.30 | 0.23 | 0.71 | −0.10 | 1.00 | | | | | | | |
| MR | −0.31 | −0.08 | 0.11 | −0.15 | 0.48 | 0.52 | −0.07 | 0.22 | −0.41 | 1.00 | | | | | | |
| MR_4 | −0.37 | 0.03 | 0.20 | −0.13 | 0.22 | 0.46 | −0.28 | −0.49 | 0.03 | 0.52 | 1.00 | | | | | |
| π_4 | −0.33 | 0.21 | 0.35 | 0.18 | 0.62 | 0.47 | 0.24 | −0.25 | 0.54 | 0.05 | 0.58 | 1.00 | | | | |
| [π_4]2 | −0.34 | 0.09 | 0.28 | −0.11 | 0.19 | 0.47 | −0.40 | −0.49 | −0.09 | 0.54 | 0.84 | 0.43 | 1.00 | | | |
| L_4 | −0.34 | 0.00 | 0.09 | −0.09 | 0.19 | 0.42 | −0.22 | −0.48 | 0.06 | 0.48 | 0.97 | 0.59 | 0.77 | 1.00 | | |
| B1_4 | 0.07 | −0.17 | −0.27 | 0.09 | 0.10 | 0.12 | −0.02 | −0.21 | 0.06 | 0.23 | 0.59 | 0.48 | 0.49 | 0.66 | 1.00 | |
| B5_4 | −0.18 | −0.19 | −0.19 | −0.09 | −0.00 | 0.16 | −0.25 | −0.43 | −0.10 | 0.46 | 0.77 | 0.31 | 0.49 | 0.84 | 0.53 | 1.00 |

Equation 1

$$\log(1/K_i) = -0.53(\pm 0.16)\mathrm{MR} - 1.8(\pm 0.44)\mathrm{ISOMER} - 1.9(\pm 0.39)\mathrm{ESTER} + 9.6$$

$n = 26 \quad r^2 = 0.66 \quad F = 14.0 \quad s = 0.49$

Equation 2

$$\log(1/K_i) = -0.35(\pm 0.17)\mathrm{MR} - 1.6(\pm 0.45)\mathrm{ISOMER} - 1.8(\pm 0.38)\mathrm{ESTER} - 0.23(\pm 0.14)\pi^2 + 9.6$$

$n = 26 \quad r^2 = 0.70 \quad F = 12.0 \quad s = 0.45.$

The addition of a $\pi^2$ term to eq (1) was statistically marginal (partial *F*-test = 3.49, prob $> F = 0.076$), and the low negative coefficient indicated a shallow parabolic relationship centered around an optimum π of 0. A plot of log (1/*K*$_i$) vs π illustrates this rough correlation (Fig. 1). The 4-NHCOCH$_3$ analogue (**22**) stood out as having a π different from that of the more potent compounds. Deleting it from the compound set and rerunning the correlations resulted in an equation not substantially different from eq (2) (same parameters, similar coefficients) with a somewhat improved fit ($n = 25$, $r^2 = 0.78$, $F = 17.6$, $s = 0.33$).

To test whether inclusion of esters at R$_1$ and isomer mixtures was obscuring a more significant correlation between phenyl substituent parameters and potency, regressions were run on a 16-compound subset containing only (*S*)-isomers and acids at R$_1$. No significant correlations were found.

The 4-NHCOCH$_3$ (**22**), 4-OCH(CH$_3$)$_2$ (**25**), and 3,5-(CF$_3$)$_2$ (**11**) derivatives were poorly fit by eq (2), all being less potent than predicted (residuals $> 1$ log unit). In addition to these three, the 4-phenyl analogue (**18**) was mispredicted by eq (1). Since three of the four outliers contained relatively large 4-substituents, we reasoned that there might be specific effects at this position that were not being adequately characterized by the composite physicochemical parameters used in the correlations. To test this hypothesis, parameters to describe the lipophilicity (π_4, [π_4]$^2$), overall size (MR_4), and specific dimensions (L_4, B1_4, B5_4) of the 4-substituent were added and the regressions rerun on the same compound sets as above.

Multiple regression analysis using the expanded set of 15 parameters on the 26 compound set generated eq (3). This equation demonstrated a significant improve-

**Table 4.** Correlation matrix on 16-compound subset containing *S* isomers at ▲ and acids at R$_1$

| | Log(1/*K*$_i$) | π | π$^2$ | σ | *F* | *R* | MR | MR_4 | π_4 | [π_4]$^2$ | L_4 | B1_4 | B5_4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Log(1/*K*$_i$) | 1.00 | | | | | | | | | | | | |
| π | −0.27 | 1.00 | | | | | | | | | | | |
| π2 | −0.44 | 0.62 | 1.00 | | | | | | | | | | |
| *s* | −0.08 | 0.60 | 0.43 | 1.00 | | | | | | | | | |
| *F* | −0.30 | 0.62 | 0.41 | 0.56 | 1.00 | | | | | | | | |
| *R* | 0.15 | 0.16 | 0.11 | 0.73 | −0.12 | 1.00 | | | | | | | |
| MR | −0.49 | 0.49 | 0.39 | 0.06 | 0.59 | −0.52 | 1.00 | | | | | | |
| MR_4 | −0.36 | −0.01 | 0.05 | −0.16 | −0.22 | −0.05 | 0.27 | 1.00 | | | | | |
| π_4 | 0.12 | 0.55 | 0.18 | 0.40 | −0.06 | 0.54 | −0.24 | 0.32 | 1.00 | | | | |
| [π_4]2 | −0.10 | −0.24 | −0.09 | −0.55 | −0.15 | −0.53 | 0.37 | 0.39 | −0.35 | 1.00 | | | |
| L_4 | −0.32 | 0.03 | 0.10 | −0.02 | −0.16 | 0.04 | 0.24 | 0.94 | 0.37 | 0.21 | 1.00 | | |
| B1_4 | 0.33 | 0.17 | 0.01 | 0.21 | 0.15 | 0.16 | 0.06 | 0.47 | 0.47 | 0.27 | 0.50 | 1.00 | |
| B5_4 | −0.37 | 0.02 | 0.09 | −0.10 | −0.18 | −0.09 | 0.34 | 0.82 | 0.22 | 0.18 | 0.90 | 0.26 | 1.00 |

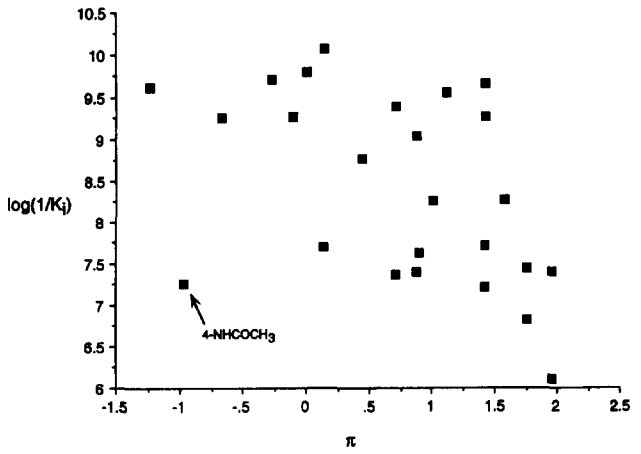



**Figure 1.** Potency at CCK-B receptors vs π of phenyl substituents.

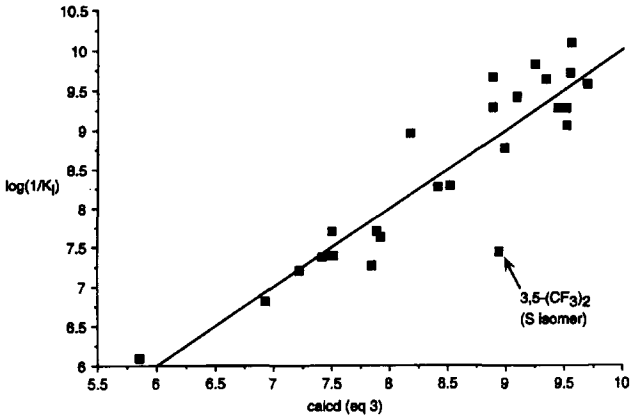



**Figure 2.** Measured vs calculated (eq 3) potency.

ment in fit over eq (2), and incorporated parameters describing specific dimensions of the 4-substituent. Addition of a $\pi^2$ term to eq (3) was not statistically significant. Regression analysis on the 16-compound subset containing (*S*)-isomers and acids at $R_1$ produced eq (4). A slightly inferior correlation resulted when MR_4 in eq (4) was replaced by L_4. Since these two parameters are themselves highly intercorrelated within the 16-compound set (Table 4, correlation coefficient = 0.94), they are describing the same [steric] effect.

Equation 3

$$\log(1/K_i) = -0.33(\pm 0.14)\mathrm{MR} - 2.0(\pm 0.35)\mathrm{ISOMER} - 1.6(\pm 0.31)\mathrm{ESTER} - 0.51(\pm 0.13)\mathrm{L\_4} + 1.8(\pm 0.49)\mathrm{B1\_4} + 8.6$$

$$n = 26 \quad r^2 = 0.81 \quad F = 17.1 \quad s = 0.30$$

Equation 4

$$\log(1/K_i) = -1.6(\pm 0.27)\mathrm{MR\_4} + 2.7(\pm 0.48)\mathrm{B1\_4} - 1.1(\pm 0.25)F + 7.0$$

$$n = 16 \quad r^2 = 0.88 \quad F = 19.5 \quad s = 0.13$$

Calculated affinities and residuals from eq (3) appear in Table 2; a plot of measured versus calculated (eq 3) potency is shown in Figure 2. With the exception of the outlier 3,5-$(CF_3)_2$ analogue (**11**), the dipeptoids fell into two groups — moderately potent compounds [measured $\log(1/K_i)$ less than 8.3] that were well predicted by eq (3), and very potent compounds [measured $\log(1/K_i)$ greater than 8.75] that were generally less well fit. One reason for this may be that affinity in the moderately potent group is dictated by nonspecific factors (transport, overall fit to the receptor) that are well-modeled by the substituent parameters and indicator variables, while affinity in the more potent group is governed by a specific fit to a receptor pocket, a phenomenon that is less well-modeled by the parameters used to derive eq (3).

Thus, CCK-B receptor affinity among substituted phenyl dipeptoids is governed by overall size of the phenyl substituents (smaller substituents are associated with increased affinity), and marginally, lipophilicity, with a optimum π of near 0. Because this series was designed in part to break up the correlation typically encountered between π and MR (Table 3: correlation coefficient of 0.52 between the two), it appears that both properties may be operative in describing affinity. Beyond this, the affinity is related to the dimensions of the 4-phenyl substituent, such that increased affinity is seen with short, bulky (branched, spherical) groups. It is not surprising that the indicator variables ESTER and ACID appeared in eqs (1)–(3), since an inspection of Table 2 shows that esters at $R_1$ and (*R*)-isomers (or isomer mixtures) decreased affinity in every case.

Among the more potent (*S*)-acids, electron withdrawal in a field sense was found to be associated with increased affinity. The appearance of *F* rather than σ in eq (4) makes sense in that the system under study is a phenyl group, with little resonance possible back into the parent structure. Therefore, *F*, L_4, and B1_4 are probably describing specific receptor interaction phenomena rather than some effect on the overall structure. The requirement of small, bulky (spherical-shaped), electron withdrawing groups for increased affinity suggests that large increases in affinity with additional phenyl substituents would not be expected in this series, beyond the potent 4-F derivative (**19**, $IC_{50} = 0.08$ nM), which has extraordinary high affinity. Further insights into specific receptor interactions would involve modeling these compounds in the active site, an analysis that is not possible at this time due to the lack of a three-dimensional structure of the CCK-B receptor.

## Conclusions

Variation of the phenyl ring ($R_2$) of the CCK antagonist **1** has led to a series of substituted-phenyl derivatives with variable affinity and selectivity toward the CCK-B receptor, culminating in extraordinary high affinity (**19**, $IC_{50} = 0.08$ nM) and CCK-B-selective (900-fold) agents. The use of series design techniques to preselect phenyl substituent variation has allowed

the identification and quantification, via QSAR techniques, of specific substituent properties related to CCK-B receptor affinity. The lack of sufficient variation in CCK-A affinity among the analogues tested precluded a QSAR analysis in this area. This suggests that this receptor subtype may have a more open binding site, lacking an interaction between the substituted phenyl ring and a specific pocket within the CCK-B receptor. The requirement for (*S*)-stereochemistry at the substituted phenethylamide center (▲) apparently is directing the phenyl ring to a specificity pocket within the CCK-B receptor. The flanking $CO_2H$ group probably anchors the molecule in the active conformation by forming hydrogen bonds or electrostatic interactions in the binding site. The reduced affinity of the 3,5-substituted analogue **11** supports the possibility that a specific CCK-B receptor interaction exists near the 4-position of the phenyl ring. Support for this observation was the fact that the QSAR fit the analogues with moderate affinity better than the high affinity analogues, since the general nature of the substituent parameters employed did not lend themselves to describing specific receptor interactions. Incorporation of small *para*-phenyl substituents on **1** resulted in increased CCK-B selectivity with no loss in CCK-B affinity. This observation may argue for receptor subtype differences in this area. Based on the above findings, selective and high affinity ligands, such as **19**, should provide useful probes for CCK receptor pharmacology.

## Experimental

High-field NMR spectra were recorded in deuterochloroform ($CDCl_3$) as a solvent on a Varian XL-200 or a Bruker 250 MHz spectrometer. All chemical shifts are reported in ppm downfield from internal tetramethylsilane. IR spectra were determined on a Nicolet MX-1 FT-IR spectrophotometer. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Perkin–Elmer Model 240C elemental analyzer and are within 0.4% of theory unless noted otherwise. Mass spectra were obtained by using a VG Masslab Trio-2A, Finnigan TSQ-70, or VG Analytical 7070E/HF mass spectrometer. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. All chemicals and reagents used were of commercial purity unless otherwise specified.

### Biological assays

Complete protocols for the two biological assays used to evaluate the compounds prepared in this study are described by Boden et al.[7] The ability of each compound to inhibit specific binding of [$^{125}$I]Bolton–Hunter-labeled CCK-8 to CCK receptors in the mouse cerebral cortex (CCK-B) and the rat pancreas (CCK-A) was evaluated. Activity (Table 1) is expressed as the nanomolar concentration of compound required to inhibit enzyme activity by 50% ($IC_{50}$).

### Chemistry

#### Method A

**3-[2-(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methyl-propionylamino]-4-(3,4-dichlorophenyl) butyric acid, [*R,S*]-(9) and [*R,R*]-(10).** Step A: Preparation of 2-*tert*-butyloxycarbonylamino-3-(3,4-dichlorophenyl)propionic acid. To a soln of 2-amino-3-(3,4-dichloro-phenyl)propionic acid (8.91 g, 38 mmol) in 50 mL dioxane, NaOH soln (3.04 g in 50 mL $H_2O$) and $NaHCO_3$ (3.83 g, 1.3 equiv) was added. This mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (8.71 g, 1.03 equiv) in 50 mL dioxane was added dropwise. The reaction mixture was then allowed to gradually warm to room temperature and stir for at least 16 h. The reaction mixture was concd in vacuo to give a residue, which was acidified with citric acid solution to pH 3 and then extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concd in vacuo to yield a foam. Purification by column chromatography (silica gel, 3–6% MeOH:$CHCl_3$, 2.63 g, 21%) followed by crystallization from cyclohexane yielded 2.03 g of the desired product.

Step B: Preparation of 3-diazo-1-(3,4-dichlorobenzyl)-2-oxo-propyl)carbamic acid *tert*-butyl ester (**III**, Scheme 1). To a cooled (−5 °C) soln of 2-*tert*-butyloxycarbonylamino-3-(3,4-dichlorophenyl)-propionic acid (2.0 g, 6.0 mmol) in 75 mL THF, *N*-methyl morpholine (0.60 g, 6.0 mmol) was added, followed by isobutyl chloroformate (0.82 g, 6.0 mmol). After stirring for 15 min, this mixture was filtered using non-quickfit glassware, and the urea was then suspended in 15 mL ether and cooled to −5°C. Aq KOH soln (40%, 4.5 mL) was then added and the cooling both removed. Stirring was continued until the solid was dissolved. The ether was decanted two times each onto 3 KOH pellets and then added to the cooled (0 °C) mixed anhydride. This mixture was allowed to gradually warm to room temperature and stir for at least 16 h. The reaction mixture was concd in vacuo with HOAc in a Buchi trap. The residue was dissolved in ethyl acetate, washed with 10% citric acid solution, $H_2O$, satd $NaHCO_3$ soln and $H_2O$ again, dried ($MgSO_4$), filtered and concd in vacuo to give crude product. Recrystallization from ethyl acetate yielded 1.87 g of desired product. Analysis ($C_{15}H_{17}Cl_2N_3O_3$) C,H,Cl,N.

Step C: Preparation of 3-*tert*-butoxycarbonylamino-4(3,4-dichlorophenyl)butyric acid 2-trimethylsilanyl ethyl ester. To a suspension of 3-diazo-1-(3,4-dichlorobenzyl)-2-oxo-propyl)carbamic acid (1.80 g, 5.0 mmol) in trimethylsilyl ethanol (5 mL), 0.5 mL of silver benzoate (0.10 g) in triethylamine (1.0 mL) was added. After nitrogen evolution had ceased, the remaining silver benzoate/triethylamine solution was added and the resulting mixture was stirred for 15 min at room temperature. The mixture was then diluted with ethyl acetate and treated with charcoal. After filtration, the ethyl acetate solution was washed two times with 10% citric acid solution, two times with $NaHCO_3$ solution and water, dried ($Na_2SO_4$), filtered and concd in vacuo. The product was then dried under high vacuum to

yield 1.90 g of the required compound. Analysis ($C_{20}H_{31}Cl_2NO_4Si$) C,H,Cl,N.

Step D: Preparation of 3-amino-4-(3,4-dichlorophenyl) butyric acid 2-trimethylsilanyl ethyl ester (**IV**, Scheme 1). To a solution of 3-*tert*-butoxycarbonylamino-4-(3,4-dichlorophenyl)butyric acid 2-trimethylsilanyl ethyl ester (1.90 g, 4.24 mmol) in dichloromethane (150 mL) *p*-toluenesulfonic acid (1.45 g, 7.0 mmol) was added and the mixture was stirred at room temperature for at least 48 h. The reaction mixture was washed two times with satd $NaHCO_3$, water, dried ($MgSO_4$), filtered, and concd in vacuo to give crude product. Purification by flash chromatography (silica gel, 10% MeOH:EtOAc) yielded 0.91 g (62%) of the desired product. Analysis ($C_{15}H_{23}Cl_2NO_2Si$) C,H,N.

Step E: Preparation of 3-[2-(adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(3,4-dichlorophenyl)butyric acid 2-trimethylsilanyl ethyl ester. To a soln of [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan[9] (1.02 g, 2.58 mmol) in ethyl acetate (40 mL), 1-hydroxybenzotriazole (0.40 g, 2.61 mmol) was added, followed by 1,3-dicyclohexylcarbodiimide (0.53 g, 2.57 mmol). This reaction mixture was stirred for 2 h at room temperature. The solid was filtered and to the filtrate, a soln of 3-amino-4-(3,4-dichlorophenyl)butyric acid 2-trimethylsilanyl ethyl ester (0.90 g, 2.58 mmol) in ethyl acetate was added and stirred at room temperature for at least 48 h. The reaction mixture was concd in vacuo to afford crude product. Purification by flash chromatography (silica gel, 10% EtOAc:$CH_2Cl_2$) gave 1.61 g of the desired product (86%). Analysis ($C_{38}H_{49}Cl_2N_3O_5Si$) C,H,Cl,N.

Step F: Preparation of 3-[2-(adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(3,4-dichloro-phenyl)butyric acid, [*R,S*]-(**9**) and [*R,R*]-(**10**). To a soln of 3-[2-(adamantan-2-yloxycarbo nylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(3,4-dichlorophenyl)butyric acid 2-trimethylsilanyl ethyl ester (1.20 g, 1.60 mmol) in dry THF (120 mL), tetrabutylammonium fluoride (1.0 M solution in THF, 2 mL, 2.0 mmol) was added and the reaction mixture stirred at room temperature for 4 h. The mixture was then diluted with ethyl acetate, and the organic layer washed with 10% citric acid soln, two times with water, dried ($MgSO_4$), filtered, and concd in vacuo to give 1.2 g of a colorless foam. Purification two times by reverse phase chromatography yielded 0.22 g (22%) of **9** [98.0%, mp 113–116 °C, Analysis $C_{33}H_{37}Cl_2N_3O_5 \cdot 0.25$ $H_2O$) C,H,Cl,N, $[\alpha]_D$ + 7.0° (*c* 1; MeOH) and 0.20 g (20%) of **10** [99.4%, mp 140–145 °C, Analysis ($C_{33}H_{37}Cl_2N_3O_5 \cdot 0.25$ $H_2O$) C,H,Cl,N, $[\alpha]_D$ + 44.6° (*c* 1, MeOH).

**3-[2-(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropronyl-amino]-4-(4-aminophenyl)butyric acid, [*R,S*]-(23).** To a soln of **24** (0.90 g) in ethanol (150 mL), Pearlman's catalyst [$Pd(OH)_2$, 0.094 g] was added and the mixture shaken under 40 psi $H_2$ for at least 16 h. The reaction mixture was filtered through Celite and the filtrate concd in vacuo to afford a residue. The residue was diluted with EtOAc, washed with $H_2O$, dried ($MgSO_4$), filtered, and concd in vacuo to give crude product **23**. Purification by reverse phase chromatography (10% $H_2O$:MeOH) yielded the desired product. Analysis ($C_{33}H_{40}N_4O_5 \cdot H_2O$) C,H,N. $[\alpha]_D$ + 11.2° (*c* 1; MeOH).

**4-(4-Acetylaminophenyl)-3-[2-adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropronylamino]-butyric acid, [*R,S*]-(22).** To a cooled (0 °C) soln of **23** (0.16 g, 0.28 mmol) in 10 mL THF, triethylamine (0.06 g, 0.59 mmol) in 1 mL THF was added, followed by acetyl chloride (0.024 g, 0.31 mmol) in 1 mL THF. After stirring at 0 °C for 1 h, the mixture was then stirred at room temperature for 1 h. The mixture was then filtered and the filtrate was diluted with EtOAc, washed two times with 10% aqueous citric acid solution, six times with $H_2O$, dried ($MgSO_4$), filtered, and concd in vacuo to give crude product. Purification by reverse phase chromatography (10% $H_2O$/MeOH) yielded 0.085 g (49%) of **22**. Analysis [$C_{35}H_{42}N_4O_6 \cdot 0.5$ ($C_4H_8O_2$) $\cdot 0.5$ $H_2O$] C,H,N. $[\alpha]_D 20 + 7.2°$ (*c* 0.5; MeOH).

**3-[2-(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(4-amino-3-iodophenyl)butyric acid, [*R,S*]-(6) and 3-[2-(adamantan-2-yloxycarbonyl-amino)-3-(1*H*-indol-3-yl)-2-methylpropronylamino]-4-(4-amino-3,5-diiodopheyl) butyric acid, [*R,S*]-(13).** To a soln of (*S*)-3-*tert*-butoxycarbonylamino-4-(4-nitrophenyl)butyric acid 2-trimethylsilanylethyl ester (1.14 g, 2.7 mmol) in 150 mL ethanol, Pearlman's catalyst [$Pd(OH)_2$, 0.105 g] was added and the mixture shaken under 50 psi $H_2$ for at least 16 h. The reaction mixture was filtered through Celite and the filtrate concd in vacuo to give crude product. Purification by column chromatography two times (silica gel, 20% EtOAc:hexane and $Et_2O$, respectively) yielded 0.65 g (61%, 1.65 mmol) of (*S*)-4-(4-aminophenyl)-3-*tert*-butoxycarbonylamino butyric acid 2-trimethylsilanyl ethyl ester. $[\alpha]_D^{25}$ −17.8° (*c* 1; MeOH). MS: 395($MH^+$). To a soln of this amine (3.57 g, 9.06 mmol) in 100 mL acetic acid, sodium iodide (2.04 g, 10.87 mmol) was added followed by portionwise addition of Chloramine T (3.06 g, 10.86 mmol). After stirring this reaction mixture at room temperature for 45 min, 10% aq sodium thiosulfate solution was added followed by addition of satd sodium bicarbonate soln. This mixture was extracted with ethyl acetate and the organic layers were washed with water, dried ($MgSO_4$), filtered, and concd in vacuo to give crude product. Purification by column chromatography (silica gel, 25% EtOAc:hexane) yielded 3.50 g (74%) of (*S*)-4-(4-amino-3-iodophenyl)-3-*tert*-butoxy-carbonyl-aminobutyric acid 2-trimethylsilanyl ethyl ester (**IVb**, Scheme 2). Analysis ($C_{20}H_{33}IN_2O_4Si$) C,H,N. $[\alpha]_D^{20}$ −7.8° (*c* 1; MeoH). Treatment of this mono-iodinated amine (0.340 g, 0.65 mmol) with sodium iodide (0.105 g, 0.70 mmol) and chloramine T (0.197 g, 0.70 mmol) in acetic acid (10 mL) yielded (*S*)-4-(4-amino-

3,5-diiodophenyl)-3-*tert*-butoxy-carbonylaminobutyric acid 2-trimethylsilanyl ethyl ester (**IVb**, Scheme 2). Analysis ($C_{20}H_{32}I_2N_2O_4Si$) C,H,N. $[\alpha]_D^{20}$ −10.3° (*c* 1, MeOH). Both the mono- and di-iodinated amines were carried through the general synthetic route outlined in Scheme 1, Method A, to give **6** and **13**, respectively.

**3-[2-(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(4-azido-3-iodophenyl) butyric acid, [*R,S*]-(7).** To a cooled (water bath) soln of **6** (0.350 g, 0.05 mmol) in 90% aq acetic acid (20 mL), sodium azide (0.200 g, 3.08 mmol) was added followed by sodium nitrite (0.150 g, 2.17 mmol). After stirring the reaction mixture at room temperature for 30 min, satd aq $NaHCO_3$ was added, and then extracted with ethyl acetate. The organic layers were combined and washed with $H_2O$, dried ($MgSO_4$), filtered, and concd in vacuo to give crude product. Purification by reverse phase chromatography (MeOH:$H_2O$) yielded 0.1 g (0.13 mmol, 40%) of **7**. Mp 111–116 °C. Analysis ($C_{33}H_{37}IN_6O_5 \cdot 0.5\ H_2O$) C,H,N.

**3-[2(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methyl propionylamino]-4-(4-hydroxy-3-iodo-phenyl)butyric acid, [*R,S*]-(8) and 3-[2(adamantan-2-yloxylcarbonyl-amino)-3-(1*H*-indol-3-yl)-2-methyl propionylamino]-4-(4-hydroxy-3,5-diiodophenyl) butyric acid, [*R,S*]-(14).** To a cooled (0 °C) soln of 3-[2-(adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methyl-priopionylamino]-4-(4-hydroxyphenyl)butyric acid 2-trimethylsilanyl ethyl ester, [*R,S*] (0.585 g, 0.87 mmol) in acetonitrile (20 mL, sodium iodide (0.149 g, 0.99 mmol) was added dropwise followed by the addition of a solution of chloramine T (0.281 g, 1.0 mmol) in 20 mL acetonitrile. After stirring the mixture for 2 h at 0 °C, EtOAc was added and then washed with 10% aq $Na_2S_2O_3$ soln and water. The organic layer was then dried ($MgSO_4$), filtered, and concd to give a crude mixture of the monoiodo and diiodo trimethylsilyl ethyl esters. Purification by flash chromatography (silica gel, 20% $Et_2O/CH_2Cl_2$) yielded pure monoiodo- (0.11 g, 16%) [Analysis ($C_{38}H_{50}IN_3O_6Si$) C,H,N] trimethylsilyl ethyl esters.

To a cooled (0 °C) soln of diiodo-TMS ethyl ester (0.11 g, 0.12 mmol) in 10 mL THF, tetrabutylammonium fluoride (1.0 M in THF, 0.38 mL) was added dropwise and the mixture was allowed to warm to room temperature and stir at least 8 h. The mixture was dild with ethyl acetate and 10% citric acid aq solution. The layers were separated and the organic layer was washed with citric acid solution and water, dried ($MgSO_4$), filtered, and concd in vacuo to give crude diiodo product. Purification by reverse phase chromatography yielded 0.045 g (0.05 mmol, 45%) of pure **14**. Analysis ($C_{33}H_{37}I_2N_3O_6 \cdot 0.5$ EtOAc) C,H,N. $[\alpha]_D^{20}$ + 8.2° (*c* 0.5, MeOH). Compound **8** was obtained in the same manner from its corresponding monoiodo trimethylsilyl ethyl ester as described for the diiodo-analogue. Analysis ($C_{33}H_{38}IN_3O_6 \cdot 0.5\ Et_2O$) C,H,N. $[\alpha]_D^{20}$ +12.4° (*c* 0.5; MeOH).

**3-[2-(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(4-isopropoxyphenyl) butyric acid, [*R,S*]-(25).** To a soln of 3-[2-(adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(hydroxy-phenyl)butyric acid 2-trimethylsilanyl ethyl ester, [*R,S*] (0.20 g, 0.30 mmol) in 10 mL methyl ethyl ketone, a soln of 2-iodopropane (0.51 mmol) in 2 mL methyl ethyl ketone was added followed by potassium carbonate (0.041 g, 0.30 mmol), and heated at 80 °C for 7 days. The mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with aq citric acid soln and water, dried ($MgSO_4$), filtered, and concd in vacuo to give crude product. Purification by flash chromatography (silica gel, 80% $Et_2O$:hexane) yielded 0.11 g (50%) of **25**. Analysis ($C_{41}H_{57}N_3O_6 \cdot 0.5\ H_2O$) C,H,N. $[\alpha]_D^{20}$ + 11.0° (*c* 1; MeOH).

**Method B**

**3-[2-(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(2-chlorophenyl) butyric acid, [*R*-(*R,S*)]-(2).** Step A: Preparation of 4-(2-chlorophenyl)butyric acid ethyl ester. To a cooled (0 °C) solution of 2-chlorophenyl acetic acid (8.0 g, 47 mmol) in 100 mL THF, 1,1′-carbonyldiimidazole (9.2 g, 57 mmol) was added in one portion and the reaction mixture was allowed to gradually warm to room temperature and stir for 16 h under a nitrogen atmosphere. In a separate flask, to a cooled (0 °C) soln of ethyl potassium malonate (12.8 g, 75 mmol) in 100 mL acetonitrile, magnesium chloride (8.5 g, 90 mmol) was added followed by triethylamine (10.5 g, 104 mmol). This mixture was stirred for 2 h at 0 °C and then allowed to warm to room temperature over a 30 min period. The activated ester mixture was then added dropwise to the stirring magnesium salt and the resulting mixture was then stirred for 16 h at room temperature. A solution of $NaHSO_4$ (40.6 g) in $H_2O$ (130 mL) was then added to the reaction mixture and stirred for 5 min. An additional 300 mL of $H_2O$ was added, the layers were sepd, and the aq layer was extracted two times each with 300 mL EtOAc. The combined organic layers were washed with 300 mL 5% NaOH soln, 300 mL brine, dried ($MgSO_4$), filtered, and concd in vacuo to afford 14.9 g of crude product. Purification by flash chromatography (silica gel, EtOAc:hexane) yielded 8.4 g (79%) of **2**. 250 MHz NMR ($CDCl_3$) 1.28 (t, 3H, $J$=7.3 Hz), 3.52 (s, 2H), 3.99 (s, 2H), 4.20 (q, 2H, $J$=7.1 Hz), 7.23–7.28 (m, 3H), 7.37–7.42 (m, 1H).

Step B: Preparation of 3-amino-4-(2-chlorophenyl)butyric acid ethyl ester. To a soln of 4-(2-chlorophenyl)butyric acid ethyl ester (0.40 g, 1.66 mmol) in anhydrous methanol (17 mL), ammonium acetate (1.33 g, 17.3 mmol) was added followed by molecular sieves (3 Å). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for one week. The mixture was then acidified to pH 2 with anhydrous 5 N methanolic hydrogen chloride, treated with sodium cyanoborohydride (0.14 g, 2.19 mmol), and acidified again with 5 N methanolic HCl. This mixture was

stirred for 16 h at room temperature under nitrogen. After concentrating the reaction mixture in vacuo, the residue was diluted with ethyl acetate, basified to pH 11 with 2 N NaOH soln, diluted with $H_2O$, and the layers sepd. The aq layer was washed 3 times with ethyl acetate, combined, dried ($Na_2SO_4$), filtered, and concd in vacuo to give 210 mg (53%) of the desired product. 250 MHz NMR ($CDCl_3$): δ 1.26 (t, 3H, $J=7.1$ Hz), 2.36–2.58 (m, 4H), 2.79–2.98 (m, 2H), 3.52–3.65 (m, 1H), 4.15 (q, 2H, $J=7.1$ Hz), 7.14–7.39 (m, 4H).

Step C: Preparation of 3-[2-(adamantan-2-yl-oxycarbonylamino)-3-(1*H*-indol-3-yl)- 2-methylpropionylamino]-4-(2-chlorophenyl)butyric acid ethyl ester, [*R*,(*R*,*S*)]-(**3**). A mixture of [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan[9] (0.23 g, 0.59 mmol), 1-hydroxybenzotriazole (0.088 g, 0.65 mmol), and 1,3-dicyclohexylcarbodiimide (0.146 g, 0.71 mmol) in 20 mL EtOAc was stirred for 1.5 h at room temperature under a nitrogen atmosphere. After ridding the reaction mixture of dicyclohexyl urea by filtration and rinsing the filter cake 2 times each with 10 mL EtOAc, 3-amino-4-(2-chlorophenyl)butyric acid ethyl ester (0.59 mmol) in EtOAc (20 mL) was added to the filtrate and the mixture was stirred for at least 16 h at room temperature under a nitrogen atmosphere. The reaction mixture was concd in vacuo to give crude product. Purification by flash chromatography (silica gel, acetone:hexane) yielded 0.301 g (82%) of **3**. Analysis ($C_{35}H_{42}ClN_3O_5 \cdot 0.85$ EtOAc) C,H,N.

Step D: Preparation of 3-[2-(adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-4-(2-chlorophenyl)butyric acid, [*R*,(*R*,*S*)]-(**2**). To a cooled (0 °C) soln of **3** (0.29 g, 0.47 mmol) in 30 mL THF, lithium hydroxide (0.1 M soln, 0.78 mmol) was added dropwise. The reaction mixture was allowed to gradually warm to room temperature and stir for at least 16 h under a nitrogen atmosphere. The reaction mixture was then acidified with 0.1 M HCl soln (0.93 mmol) and concd in vacuo to remove THF. The aq residue was then extracted with EtOAc (50 mL), and the organic layer washed with $H_2O$ (25 mL), dried ($MgSO_4$), filtered, and concd in vacuo to give crude product. Purification by flash chromatography (silica gel, acetone/hexane), followed by repeated concentration from ether yielded desired product. Further purification by prep. HPLC ($SiO_2$ column, EtOAc:hexane) afforded 0.10 g (34%) of the desired product. Analysis ($C_{33}H_{38}ClN_3O_5 \cdot 0.61$ EtOAc) C,H,N.

## Method C

**3-[2-(Adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino]-pentanoic acid, [*R*-(*R*,*S*)]-(28).** Step A: Preparation of pen-2-tenoic acid ethyl ester. To a soln of (carbethoxymethylene)triphenylphosphorane (20.3 g, 58 mmol) in 150 mL THF, propionaldehyde (3.0 g, 51.6 mmol) was added and the reaction mixture was stirred for at least 16 h at room temperature under a nitrogen atmosphere. The reaction mixture was dild with a satd aq soln of ammonium chloride and then extracted two times with diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concd in vacuo at room temperature to give crude product. A soln of EtOAc:hexane (30%) was added to the material and then filtered through a pad of silica gel. After flushing the silica gel pad with 500 mL 30% EtOAc:hexane, the mother liquor was concd in vacuo to give 5.04 g (76%) of the desired product. MS: 12.9 ($MH^+$), 128 ($M^+$).

Step B: Preparation of 3-(methylphenylamino)pentanoic acid ethyl ester. A soln of pent-2-enoic acid ethyl ester (2.50 g, 19.5 mmol) and (*S*)-(−)-α-methylbenzylamine (2.36 g, 19.5 mmol) in 50 mL ethanol was heated at 78 °C for at least 16 h.[12,13] The mixture was cooled to room temperature and then concd in vacuo to give crude product. Purification by flash chromatography (silica gel, 20% EtOAc:hexane) yielded 1.28 g (5 mmol, 26%) of pure product. MS: 250 ($MH^+$), 249 ($M^+$).

Step C: Preparation of 3-aminopentanoic acid ethyl ester. Hydrogenation (20% Pd/C, 0.20 g) of 3-(methylphenylamino)pentanoic acid ethyl ester (0.32 g, 1.31 mmol) in ethanol (75 mL) under a hydrogen atmosphere at room temperature for 18 h yielded desired product (0.167 g, 88%). MS 146 ($MH^+$), 145 ($M^+$).

Step D: Preparation of 3-[2-(adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino] pentanoic acid ethyl ester, [*R*,(*R*,*S*)]-(**27**). To a turbid soln of [(2-adamantyloxy)carbonyl]-α-methyl-(*R*)-tryptophan[9] (0.284 g, 0.716 mmol) and 1-hydroxybenzotriazole (0.107 g, 0.788 mmol) in EtOAc (10 mL), 1,3-dicyclohexylcarbodiimide (0.185 g, 0.895 mmol) was added and stirred at room temperature for 1 h. 4-Dimethylaminopyridine (0.0087 g, 0.072 mmol) was added to the reaction mixture followed by the dropwise addition of 3-aminopentanoic acid ethyl ester (0.130 g, 0.895 mmol) in EtOAc (3 mL). This mixture was stirred at room temperature under a nitrogen atmosphere for 72 h. The reaction mixture was filtered and the ethyl acetate layer was washed two times with 5% citric acid solution, two times with satd $NaHCO_3$ soln, 5% citric acid solution, brine, dried ($MgSO_4$), filtered, and concd in vacuo to give crude product. Purification by flash chromatography (silica gel, 30% EtOAc/hexane) yielded 0.240 g (64%) of **27**. Analysis ($C_{30}H_{41}N_3O_5 \cdot 0.75$ EtOAc) C,H,N.

Step E: Preparation of 3-[2-(adamantan-2-yloxycarbonylamino)-3-(1*H*-indol-3-yl)-2-methylpropionylamino] pentanoic acid, [*R*-(*R*,*S*)]-(**28**). To a cooled (0 °C) soln of **27** (0.20 g, 0.382 mmol) in THF (20 mL), 0.1 M LiOH soln (1.2 mL) added dropwise via syringe over a 5 min period. The mixture was allowed to gradually warm to room temperature and stir for at least 72 h. The reaction mixture was then quenched with 10% HCl soln (1.37 mL) and extracted three times with diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concd in vacuo to give 0.14 g

(0.282 mmol, 74%) of **28**. High mass: calcd, 496.2811; found 496.2807.

| Compound | Microanalysis | | | | | |
|---|---|---|---|---|---|---|
| | Carbon | | Hydrogen | | Nitrogen | |
| | Calcd | Found | Calcd | Found | Calcd | Found |
| **1** | 70.84 | 71.12 | 7.06 | 7.45 | 7.51 | 7.13 |
| **2** | 65.91 | 66.01 | 6.69 | 6.70 | 6.51 | 6.38 |
| **3** | 66.37 | 66.38 | 7.07 | 6.68 | 6.05 | 5.86 |
| **6** | 56.01 | 55.96 | 5.70 | 5.73 | 7.92 | 7.85 |
| **7** | 54.03 | 53.78 | 5.08 | 5.11 | 11.46 | 11.13 |
| **8** | 57.07 | 57.02 | 5.88 | 5.91 | 5.70 | 5.49 |
| **9** | 62.80 | 62.83 | 5.99 | 5.79 | 6.66 | 6.62 |
| **10** | 62.80 | 62.71 | 5.99 | 5.81 | 6.66 | 6.53 |
| **11** | 60.60 | 60.33 | 5.38 | 5.38 | 6.06 | 6.05 |
| **12** | 60.21 | 60.02 | 5.41 | 5.41 | 6.02 | 5.95 |
| **13** | 48.07 | 47.94 | 4.65 | 4.67 | 6.80 | 6.85 |
| **14** | 48.34 | 48.42 | 4.75 | 4.89 | 4.83 | 4.64 |
| **15** | 64.34 | 64.44 | 6.19 | 6.14 | 6.62 | 6.67 |
| **16** | 64.34 | 64.25 | 6.19 | 5.98 | 6.62 | 6.61 |
| **19** | 68.85 | 68.71 | 6.65 | 6.75 | 7.30 | 7.00 |
| **20** | 69.25 | 69.11 | 6.84 | 7.03 | 7.13 | 7.00 |
| **21** | 57.98 | 57.82 | 5.60 | 5.76 | 6.15 | 5.89 |
| **22** | 66.54 | 66.63 | 7.10 | 7.08 | 8.39 | 8.27 |
| **23** | 67.09 | 67.21 | 7.17 | 7.46 | 9.49 | 9.44 |
| **24** | 64.79 | 64.58 | 6.43 | 6.40 | 9.16 | 8.94 |
| **25** | 69.17 | 68.92 | 7.48 | 7.50 | 6.37 | 6.32 |
| **26** | 67.07 | 67.44 | 7.08 | 7.33 | 6.70 | 6.64 |
| **27** | 67.21 | 67.52 | 8.03 | 8.40 | 7.12 | 6.75 |

## Data processing

Statistical analyses were run on an IBM 3090-200E mainframe using release 6.07 of the SAS program package.[24] In eqs (1)–(4), the figures in parentheses are the standard errors of the regression coefficients. For a given equation, $n$ is the number of compounds, $r$ is the correlation coefficient, $F$ is a significance test, and $s$ is the standard error.

## Acknowledgments

We thank the analytical departments for spectral and analytical determinations, Mr J. Calvitt for HPLC analysis, Mr T. Stevenson for the high resolution MS data, and Ms. S. Lovelady, Ms. C. Neering, and Ms. B. McMillan for manuscript preparation.

## References

1. Mutt, V.; Jorpeo, J. E. *Eur. J. Biochem.* **1968**, *6*, 156.

2. Innis, R. B.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 6917.

3. (a) Hughes, J.; Boden, P.; Costall, B.; Domeney, A.; Kelly, E.; Horwell, D.; Hunter, J. C.; Pinnock, R. D.; Woodruff, G. N. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 6728. (b) Rataud, J.; Darche, F.; Piot, O.; Stutzmann, J.-M.; Bohme, G. A.; Blanchard, J.-C. *Brain Res.* **1991**, *548*, 315. (c) Singh, L.; Lewis, A. S.; Field, M. J.; Hughes, J.; Woodruff, G. N. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 1130.

4. (a) Bradwejn, J.; Koszycki, D. In *Multiple Cholecystokinin Receptors in the CNS*; Dourish, C. T., *et al.*, Eds.; Oxford University: Oxford, 1992; pp 121–131. (b) Bradwejn, J.; Koszycki, D.; Couetoux du Tertre, A.; Bourin, M.; Palmour, R.; Ervin, F. *J. Psychopharmacol.* **1992**, *6*, 345.

5. (a) Trivedi, B. K. *Curr. Opin. Ther. Patents* **1994**, *4*, 31. (b) Trivedi, B. K. *Curr. Med. Chem.* **1994**, *1*, 313.

6. (a) 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. (b) Bourne, G. T.; Horwell, D. C.; Pritchard, M. C. *Tetrahedron* **1991**, *47*, 4763. (c) Singh, L.; Field, M. J.; Hughes, J.; Menzies, R.; Oles, R. J.; Vass, C. A.; Woodruff, G. N. *Br. J. Pharmacol.* **1991**, *104*, 239. (d) Higginbottom, M.; Kneen, C.; Ratcliffe, G. S. *J. Med. Chem.* **1992**, *35*, 1572. (e) Drysdale, M. J.; Pritchard, M. C.; Horwell, D. C. *J. Med. Chem.* **1992**, *35*, 2573. (f) Drysdale, M. J.; Pritchard, M. C.; Horwell, D. C. *Biorg. Med. Chem. Lett.* **1992**, *2*, 45. (g) Didier, E.; Horwell, D. C.; Pritchard, M. C. *Tetrahedron* **1992**, *48*, 8471. (h) Bolton, G. L.; Roth, B. D.; Trivedi, B. K. *Tetrahedron* **1993**, *49*, 525. (i) Horwell, D. C. *TIBTECH* **1995**, *13*, 132.

7. Boden, P. R.; Higgenbottom, M.; Hill, D. R.; Horwell, D. C.; Hughes, J.; Rees, D. C.; Roberts, E.; Singh, L.; Suman-Chauhan, N.; Woodruff, G. N. *J. Med. Chem.* **1993**, *36*, 552.

8. Either the (*S*) or racemic substituted phenylalanines were used as the starting materials. In the case of the racemic phenylalanines (Examples **6–16**, **19–26**), the diastereomers of **I** at the final step were separated by reverse phase chromatography.

9. The synthesis of (*R*)- or (*S*)-[(2-adamantyloxy)carbonyl]-α-methyltryptophan (2-Adoc-α-Me-Trp-OH) is reported in ref. 6a.

10. Augelli-Szafran, C. E.; Blankley, C. J.; Roth, B. D.; Trivedi, B. K.; Bousley, R. F.; Essenburg, A. D.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *J. Med Chem.* **1993**, *36*, 2943.

11. Crossley, M. J.; Fisher, M. L.; Potter, J. J.; Kuchel, P. W.; York, M. J. *J. Chem Soc., Perkin Trans. 1.* **1990**, 2363.

12. Furukawa, M.; Okawara, T.; Terawaki, Y. *Chem. Phar. Bull.* **1977**, *25*, 1319.

13. Davies, S. G.; Ichihara, O. *Tetrahedron:Asymmetry* **1991**, *2*, 183.

14. Birchmore, B.; Boden, P. R.; Hewson, G.; Higginbottom, M.; Horwell, D. C.; Ho, Y. P.; Hughes, J.; Hunter, J. C.; Richardson, R. S. *Eur. J. Med. Chem.* **1990**, *25*, 53.

15. Horwell, D. C.; Beeby, A.; Clark, C. R.; Hughes, J. *J. Med Chem.* **1987**, *30*, 729.

16. Pincus, M. R.; Carty, R. P.; Chen, J.; Lubowsky, J.; Avitable, M.; Shah, D.; Scheraga, H. A.; Murphy, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 4821.

17. (a) Horwell, D. C. In *Topics in Medicinal Chemistry, 4th SCI-RSC Medicinal Chemistry Symposium*; Leeming P. R., Ed.; Royal Society of Chemistry Special Publication No. 65; Royal Society of Chemistry: Letchworth, 1988; p 62. (b) Chuong, P. P. V. *Horm. Recept. Proc. Int. Symp.*; *Horm. Recept. Dig. Tract Physiol., 2nd*, **1979**, 33.

18. Eden, J. M.; Higginbotton, M.; Hill, D. R.; Horwell, D. C.; Hunter, J. C.; Martin, K.; Pritchard, M. C.; Rahman, S. S.; Richardson, R. S.; Roberts, E. *Eur. J. Med. Chem.* **1993**, *28*, 37.

19. Pleiss, M. A.; Unger, S. H. In *Comprehensive Medicinal Chemistry*, Vol. 4, *Quantitative Drug Design*; Ramsden, C. A., Ed.; Pergamon: New York, 1990; pp 561–587.

20. Martin, Y. C. In *Quantitative Drug Design: A Critical Introduction*, Grunewald G. L., Ed.; Marcel Dekker: New York, 1978.

21. Hansch, C.; Leo, A. *Substituent Constants For Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

22. Norrington, F. E.; Hyde, R. M.; Williams, S. G.; Wootten, R. *J. Med. Chem.* **1975**, *18*, 604.

23. Verloop, A. In *IUPAC Pesticide Chemistry, Human Welfare and the Environment*; Miyamoto, J. *et al.*, Eds; Pergamon: New York, 1983; pp 339–344.

24. SAS Institute Inc., *SAS/STAT User's Guide, Version 6, 4th Ed.*, Vol. 1 and 2, Cary, NC: SAS Institute Inc., 1989.

(*Received in U.S.A.* 6 *June* 1996; *accepted* 28 *June* 1996)