# Amide Bond Replacements Incorporated into CCK-B Selective "Dipeptoids"

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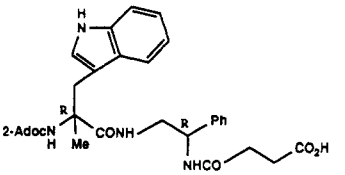
This paper describes the chemical synthesis and CCK-B and CCK-A receptor binding affinities of a series of compounds in which the central amide bond of the CCK-B "dipeptoid" ligand tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*R**,*S**)]-[2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-2-oxoethyl]carbamate (**4**) (CCK-B $IC_{50}$ = 852 nM), and tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(2-phenylethyl)amino]ethyl]carbamate (**23**) (CCK-B $IC_{50}$ = 32 nM) is replaced by 11 different amide replacements. These replacements are the methyleneamino ($CH_2NH$), the reverse amide (NHCO), the ester (COO), the *N*-methylamide (CONMe), the thioamide (CSNH), the *N*-acetylmethyleneamino ($CH_2NAc$), the cis double bond (CHCH), the ethylene ($CH_2CH_2$), the thiolester (COS), the hydroxyethylene ($CHOHCH_2$), and a 4,5-dihydro-1,3-thiazole. Most of the replacements have weaker affinity and reduced selectivity for the CCK-B receptor than the parent amide. However, this affinity can be improved by appending a fumarate side chain to the phenethyl group, e.g. tricyclo[3.3.1.1$^{3,7}$]dec-2-yl-3-(1*H*-indol-3-ylmethyl)-3-methyl-4,9-dioxo-7-phenyl-5,13-dioxa-2,8-diazatetradec-10-enoate (**36**) (CCK-B $IC_{50}$ = 38.8 nM). Replacement of the amide of compound **4** with a 4,5-dihydro-1,3-thiazole gives tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [1-[4,5-dihydro-4-(phenylmethyl)-2-thiazolyl]-2-(1*H*-indol-3-yl)ethyl]carbamate (**5**), which is selective for the CCK-A receptor (CCK-A $IC_{50}$ = 125 nM, CCK-B $IC_{50}$ = 2580 nM, ratio = 21). The methyleneamino and hydroxyethylene replacements, which have been used elsewhere as transition-state inhibitors of enzymes, are poor mimics of the amide in these CCK-B receptor ligands. Some of the steric, lipophilic, and hydrogen bonding properties of amide replacements incorporated into the simple amide, *N*-methylacetamide, have been quantified with the aid of molecular modeling. These data will contribute to the rational selection of amide bond replacements in other substrates.

## Introduction

The amide bonds of peptides constitute a major site of enzymatic metabolism and limit the use of peptides as drugs.[1] This has led to a large amount of work aimed at replacing the amide bond (CONH) of biologically active peptides with a variety of groups. These include a reversed amide (NHCO), a hydroxyethylene ($CHOHCH_2$), a methyleneamino ($NHCH_2$), a ketomethylene ($COCH_2$), or an olefin (HC=CH) in an attempt to identify metabolically stable agonists/antagonists of peptide receptors or proteolytic enzyme inhibitors. These backbone modifications have been reviewed by Spatola[2] and by the Royal Society of Chemistry annually since 1984.[3] These reviews describe modifications (frequently referred to by the term "isosteres") incorporated into one or more of the amide bonds of several neuropeptides and hormones including Met- and Leu-enkephalin, cholecystokinin (CCK), gastrin, and somatostatin in an attempt to mimic the receptor-bound state of the amide. These modifications have also been used extensively in enzyme inhibitors [e.g. the metalloprotease, angiotensin converting enzyme (EC 3.4.15.11), and the aspartic proteinases, renin (EC 3.4.99.19) and HIV proteinase] to mimic an enzyme-bound transition state of the scissile amide bond.[4] General interest in this area continues to grow with several publications describing new types of amide replacements[5] or the chemical synthesis of classical ground or transition state "amide isosteres" into peptide derivatives.[6]

As part of our program to design non-peptide ligands ("peptoids") which modulate the actions of mammalian peptide neurotransmitters or hormones, we have recently described the discovery of a novel series of selective "dipeptoid" cholecystokinin-B (CCK-B) and gastrin receptor antagonists of which the prototype is CI-988 (PD 134308) (**1**).[7] These compounds, which were developed from the neuropeptide CCK-26-33 (sulfated) (**2**) have been shown to have potent anxiolytic and anti-gastrin activity in rodent models.[7]




(1) CI-988 (PD 134308)

CCK 26-33 Asp-Tyr-($SO_3H$)-Met-Gly-Trp-Met-Asp-Phe-$NH_2$

(2)

(1) Humphrey, M. J.; Ringrose, P. S. Peptides and Related Drugs: A Review of their Absorption, Metabolism and Excretion. *Drug Metab. Rev.* **1986**, *17*, 283–310.

(2) Spatola, A. F. Peptide Backbone Modifications: A Structure-Activity Analysis of Peptides containing Amide Bond Surrogates. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Dekker: New York, 1983; Vol. 7, Chapter 5.

(3) (a) Davies, J. S. Analogue and Conformational Studies on Peptide Hormones and Other Biologically Active Peptides. In *Amino Acids and Peptides*; Jones, J. H., Ed.; The Royal Society of Chemistry: London, 1986; Vol. 17, pp 104–125. (b) Ibid. 1987; Vol. 18, pp 140–168. (c) Ibid. 1987; Vol. 19, pp 141–189. (d) Ibid. 1989; Vol. 20, pp 128–174. (e) Ibid. 1990; Vol. 21, pp 129–173.

(4) (a) Rich, D. H. Peptidase Inhibitors. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon: New York, 1990; Vol. 2., Chapter 8.2, pp 391–441. (b) Page, M. I. Enzyme Inhibition. Ibid.; Vol. 2, Chapter 5.4, pp 61–87. (c) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G.; Machin, P. J.; Rational Design of Peptide-Based HIV Proteinase Inhibitors. *Science* **1990**, *248*, 358–361.

(5) (a) Wolf, J-P.; Rapoport, H. Conformationally Constrained Peptides. Chirospecific Synthesis of 4-Alkyl-Substituted γ-Lactam-Bridged Dipeptides from L-Aspartic Acid. *J. Org. Chem.* **1989**, *54*, 3164–3173. (b) Jones, R. C. F.; Ward, G. J.; Amide Bond Isosteres: Imidazolines in Pseudopeptide Chemistry. *Tetrahedron Lett.* **1988**, *29*, 3853–3856. (c) Arrowsmith, R. J.; Davies, D. E.; Fogden, Y. C.; Harris, C. J.; Thompson, C.; Amino-Alcohol Dipeptide Analogues: A Simple Synthesis of a Versatile Isostere for the Development of Proteinase Inhibitors. *Tetrahedron Lett.* **1987**, *28*, 5569–5572.

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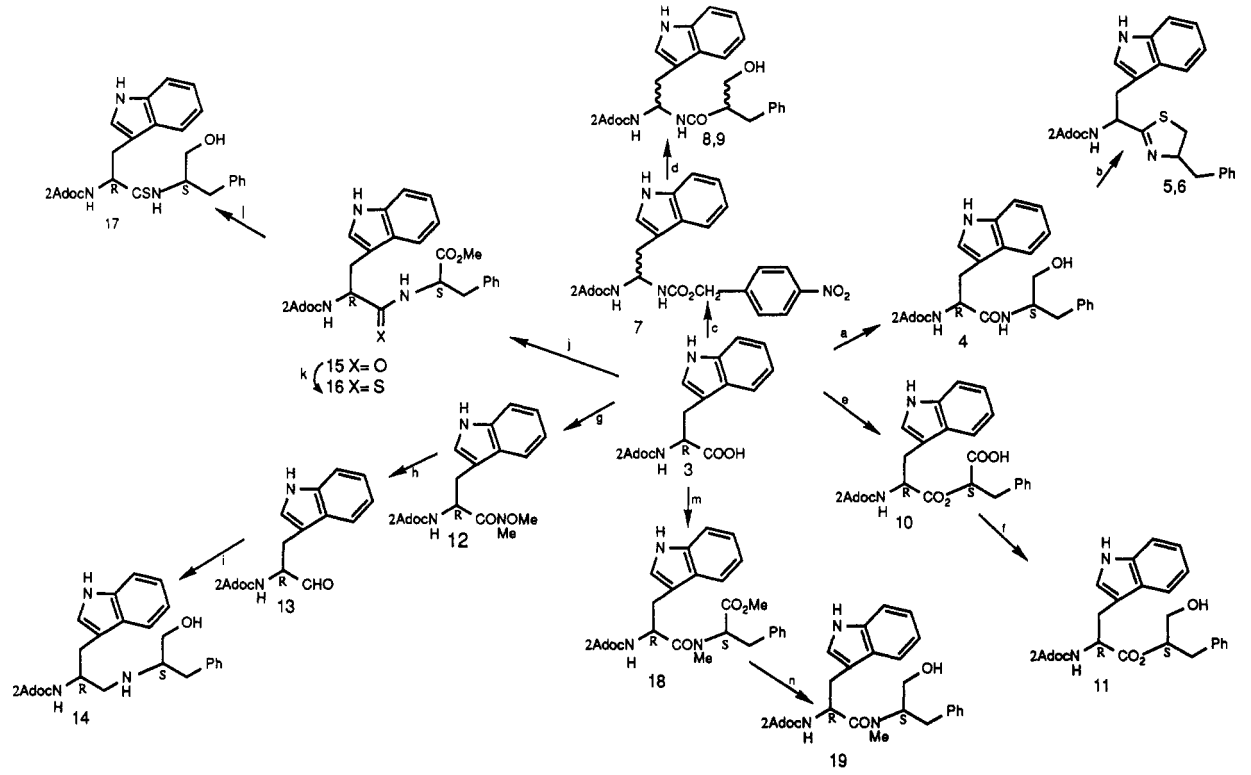
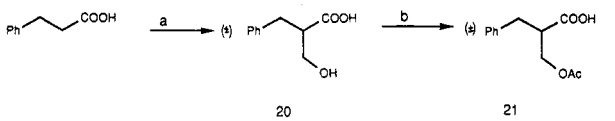
**Scheme I**[a]



[a] (a) (i) DCC, PFP, EtOAc; (ii) (*S*)-2-amino-3-phenyl-1-propanol; (b) Lawesson's reagent; (c) (i) *N*-methylmorpholine, *i*-BuOCOCl; (ii) $Me_3SiN_3$; (iii) 40 °C; (iv) *p*-nitrobenzyl alcohol, DABCO; (d) (i) 20% $Pd(OH)_2/C$, $H_2$, 45 psi, 40 °C; (ii) compound **21**, HOBt, DCC; (iii) LiOH; (e) PFP, DCC, DMAP, (-)-(*S*)-3-phenyllactic acid, DMF; (f) (i) EtOCOCl, $Et_3N$; (ii) $NaBH_4$; (g) (i) *N*-methylmorpholine, *i*-BuOCOCl; (ii) MeNH(OMe)·HCl; (h) $LiAlH_4$; (i) $NaCN(BH_3)$, (*S*)-2-amino-3-phenyl-1-propanol; (j) (i) DCC, HOBt; (ii) (*S*)-H-Phe-Me·HCl, $Et_3N$; (k) 2,4-bis(phenylthio)-1,3-dithia-2,4-diphosphetane-2,4-disulfide; (l) $LiAlH_4$; (m) (i) DCC, HOBt; (ii) *N*-Me-(*S*)-phenylalanine methyl ester; (n) $LiBH_4$.

**Scheme II**[a]



[a] (a) (i) *i*-$Pr_2NH$, *n*-BuLi; (ii) $H_2CO$; (b) AcCl.

A key consideration in the design of peptide mimetic drugs is the synthesis of selective molecules with a pharmaceutically useful duration of action. This has led to the current study of amide bond replacements.

Many publications describe the synthesis and biological evaluation of peptides possessing amide bond surrogates, but very little has been reported on the systematic quantitative rationalization of the physicochemical consequences of main chain amide bond replacement in terms of lipophilicity, hydrogen bonding, or steric properties. Furthermore, there are very few examples in the literature where a single amide bond has undergone multiple replacements to give several derivatives that have been evaluated in the same in vitro bioassay. One such example is the Nle[28]-Gly[29] region of CCK which has been modified by Martinez.[6h]

As part of our long-term strategy aimed at analyzing the structure-activity relationships (SAR) of amide bond mimetics in neuropeptides it was decided to replace the central amide in the series of CCK-B "dipeptoids" wth several known amide surrogates. This paper describes the synthesis and CCK-A and CCK-B receptor binding affinities of these compounds.

(6) (a) Rich, D. H.; Green, J.; Toth, M. V.; Marshall, G. R.; Kent, S. B. H. Hydroxyethylamine Analogues of the p17/p24 Substrate Cleavage Site are Tight-Binding Inhibitors of HIV Protease. *J. Med. Chem.* **1990**, *33*, 1285–1288. (b) Yasui, A.; Douglas, A. J.; Walker, B.; Magee, D. F.; Murphy, R. F. Novel C-Terminal Gastrin Antagonists. *Int. J. Pept. Protein Res.* **1990**, *35*, 301–305. (c) Rodriguez, M.; Aumelas, A.; Martinez, J. A General route to "Carba" Peptide Bond Replacements: Unequivocal Synthesis of Boc-L-Phe-Ψ($CH_2$-$CH_2$)-L-Ala-OH and Boc-L-Phe-Ψ-($CH_2CH_2$)-D-Ala-OH. *Tetrahedron Lett.* **1990**, *31*, 5153–5156. (d) Vara Pasad, J. V. N.; Rich, D. H. Addition of Allylic Metals to Alpha-Aminoaldehydes. Application to the Synthesis of Statine, Ketomethylene and Hydroxyethylene Dipeptide Isosteres. *Tetrahedron Lett.* **1990**, *31*, 1803–1806. (e) Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolades, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. Renin Inhibitors Containing Isosteric Replacements of the Amide Bond Connecting the $P_3$ and $P_2$ Sites. *J. Med. Chem.* **1990**, *33*, 838–845. (f) Mendre, C.; Rodriguez, M.; Lignon, M-F.; Galas, M-C.; Gueudet, C.; Worms, P.; Martinez, J. Pharmacological Activity of Cholecystokinin Analogues Modified in the Met[28]-Gly[29] Region. *Eur. J. Pharmacol.* **1990**, *186*, 213–222. (g) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. Orally Potent Renin Inhibitors Derived from Angiotensinogen Transition State: Design, Synthesis and Mode of Action. *J. Med. Chem.* **1990**, *33*, 2707–2714. (h) Mendre, C.; Rodriguez, M.; Laur, J.; Aumelias, A.; Martinez, J. Peptide and Pseudopeptide Analogues of Cholecystokinin. Chemical Modifications of the Met[28]-Gly[29] Region. *Tetrahedron* **1988**, *44*, 4415–4430.

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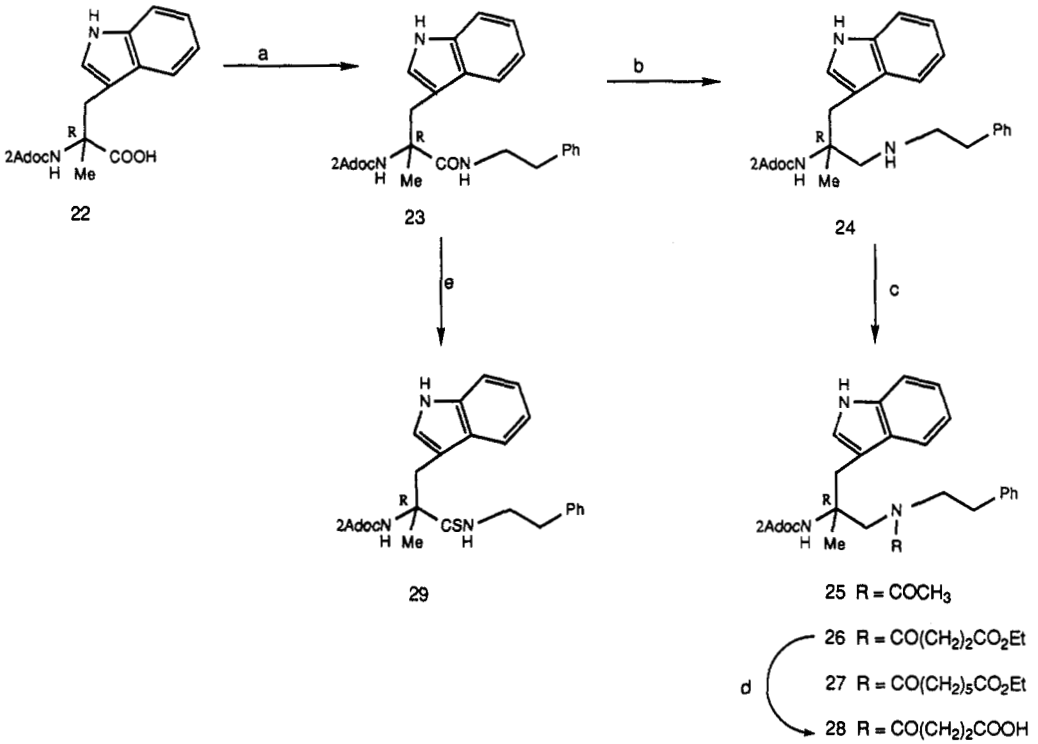
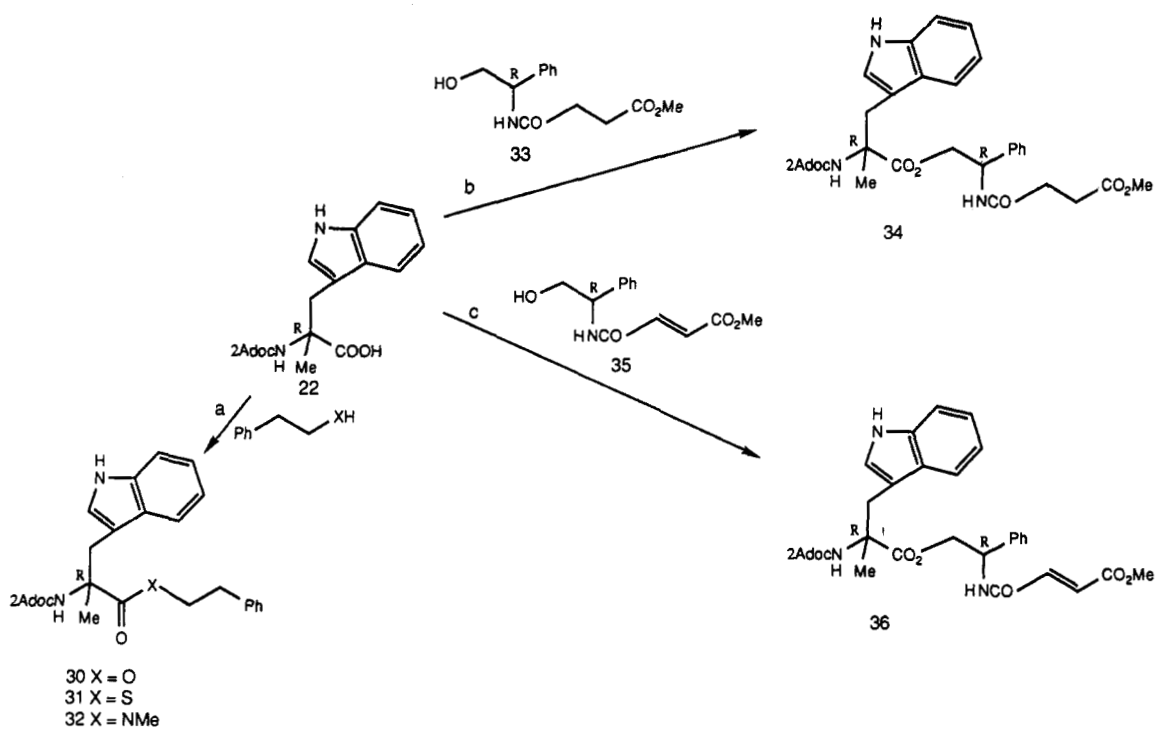
**Scheme III**[a]




[a] (a) Reference 7; (b) $LiBH_4$, $Me_3SiCl$; (c) RCOCl, $Et_3N$; (d) LiOH; (e) Lawesson's reagent.

**Scheme IV**[a]

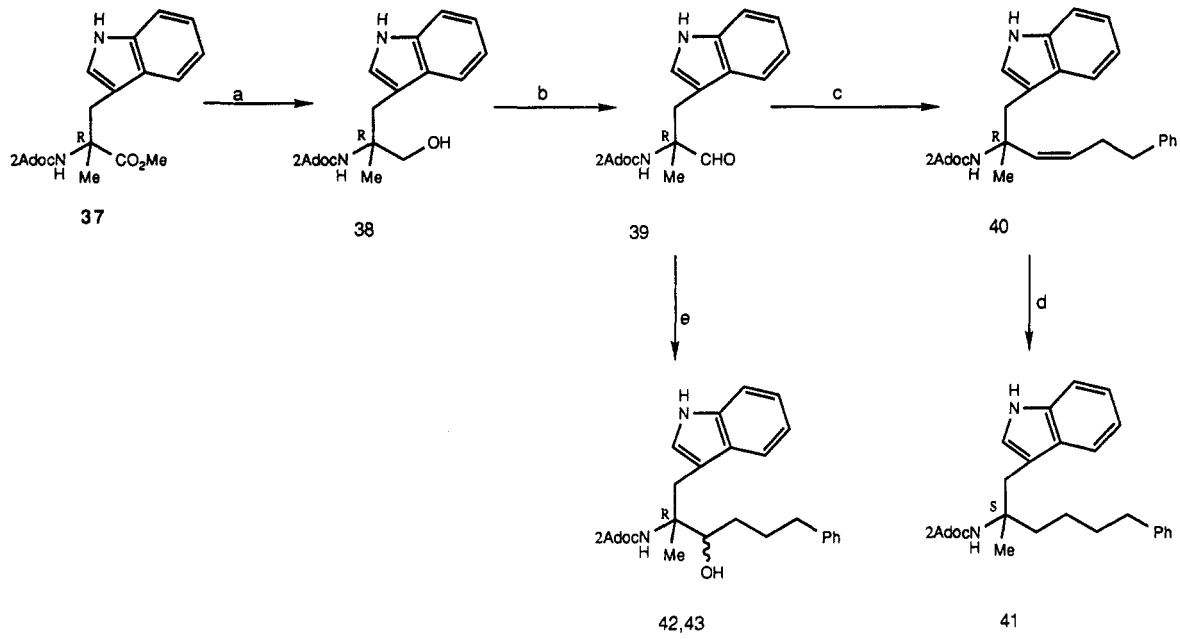



[a] (a) (i) DCC; (ii) $PhCH_2CH_2NH_2$ (for **30**) or $PhCH_2CH_2SH$ (for **31**) or $PhCH_2CH_2NHMe$ (for **32**); (b) (i) DCC, DMAP; (ii) **33**; (c) (i) DCC; (ii) **35**.

## Chemistry

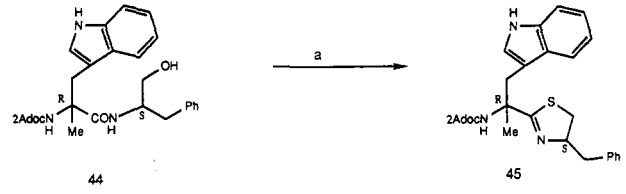
Two compounds from the series of tryptophanylphenethylamide CCK-B dipeptoids have been selected for the amide replacement strategy. These are compound **4** (CCK-B $IC_{50}$ = 852 nM), which contains a hydroxymethylene side chain, and compound **23** (CCK-B $IC_{50}$ = 32 nM),[7a] which contains an $\alpha$-methyl substituent on the tryptophan moiety. These compounds were selected because their CCK-B receptor affinity is such that quantitative binding data can be determined for higher or lower affinity derivatives and because the chemical synthesis of derivatives of the amide groups was considered to be feasible. Both the $\alpha$-methyl and the hydroxymethylene groups have been shown previously to be desirable for CCK-B receptor binding affinity.[7a,8] The substituent

**Scheme V**[a]




[a] (a) $LiAlH_4$; (b) TPAP, *N*-methylmorpholine *N*-oxide; (c) (i) $Ph_3P$, $BrCH_2CH_2CH_2Ph$; (ii) NaH; (d) 10% Pd–C, $H_2$, 40 psi; (e) Mg, $BrCH_2CH_2CH_2Ph$.

**Scheme VI**[a]




[a] (a) Lawesson's reagent.

selected for the N-terminus was (2-adamantyloxy)carbonyl (2-adoc) which has previously been shown to be optimal.[7a,9] The amide bond in compounds **4** and **23** has been replaced as outlined in Schemes I–VI. The reversed amide analogue, $\psi$(NHCO) (**8** and **9**, Scheme I), is prepared from the *R*-Trp derivative **3** via a Curtius rearrangement which gives the racemic bis urethane **7**. Hydrogenolysis of **7** and coupling with an active ester of the carboxylic acid **21** (Scheme II) followed by treatment with LiOH produces the desired reversed amide derivative as a mixture of two racemic diastereoisomers which are separated into **8** and **9** each of which is a single racemic diastereoisomer of undetermined stereochemistry. The intermediate acid **21** is prepared from 3-phenylpropanoic acid via a two-step procedure involving hydroxymethylation with formaldehyde to give **20**, followed by acetylation of the resulting alcohol (Scheme II).

The method used to prepare the ester replacements, $\psi$(COO), **11** (Scheme I), **30**, **34**, and **36** (Scheme IV) involves coupling (*S*)-3-phenyllactic acid, 2-phenylethanol, alcohol **33**, or alcohol **35**, respectively, with the appropriate Trp derivative (**3** or **22**). In the case of **11** the hydroxymethylene side chain is obtained by reduction of the carboxylic acid of compound **10**. Compounds **34** and **36** contain a succinic or fumaric acid derived side chain which has previously been shown to confer high CCK-B binding affinity.[7a] The thiolester, $\psi$(COS), **31** is prepared by an analogous procedure using phenethyl mercaptan.

The methyleneamino replacement, $\psi(CH_2NH)$, **24** (Scheme III) is prepared from compound **23** by direct reduction with $LiBH_4$–$Me_3SiCl$.[10] Acylation of **24** with acetyl chloride, ethyl succinyl chloride, and ethyl pimeloyl chloride gives the amides **25**, **26**, and **27**, respectively. Treatment of **26** with LiOH gives the acid **28**. In the other series the methyleneamino compound **14** (Scheme I) is obtained by reductive amination of the aldehyde **13** with (*S*)-2-amino-3-phenyl-1-propanol. The aldehyde **13** is prepared via **12**.

The *N*-methylamide, $\psi$(CONMe), **32** (Scheme IV) is prepared via direct coupling of *N*-methylphenethylamine to the carboxylic acid **22**. The non-$\alpha$-methyl derivative **19** (Scheme I) is prepared by coupling the acid **3** with *N*-methyl-(*S*)-phenylalanine methyl ester to give **18** followed by reduction with lithium borohydride to give **19**. The NMR spectrum of **19** is complicated by the presence of amide rotamers.

The aldehyde **39** (Scheme V) is obtained by reduction of the methyl ester **37** to the alcohol **38** and subsequent oxidation to **39**. This compound is a key intermediate for the preparation of several of the required amide replacements. The hydroxyethylenes, $\psi(CHOHCH_2)$, **42** and **43** are obtained as optically active diastereoisomers via a Grignard reaction. The cis olefin, $\psi$(HC=CH), **40** is obtained by a Wittig reaction of the aldehyde **39** and 1-bromo-3-phenylpropane. Subsequent hydrogenation gives the ethylene replacement, $\psi(CH_2CH_2)$, **41**.

The thioamide, $\psi$(CSNH), **29** (Scheme III) Is prepared by treatment of the amide **23**[7a] with Lawesson's reagent. Under the same conditions, the hydroxymethyl derivative **44** (Scheme VI) (CCK-B $IC_{50}$ = 6.4 nM)[7a] gives the 4,5-

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Table I. Physical Data of New Compounds

| compd | mol formula | mp, °C | anal. |
|---|---|---|---|
| 3 | $C_{22}H_{26}N_2O_4$ | 208–209 | C,H,N |
| 4 | $C_{31}H_{37}N_3O_4 \cdot 0.5H_2O$ | 90–92 | C,H,N |
| 5 | $C_{31}H_{35}N_3O_2S$ | 59–63 | C,H,N |
| 6 | $C_{31}H_{35}N_3O_2S$ | 56–63 | C,H,N,S |
| 7 | $C_{29}H_{32}N_4O_6$ | 148–149 | C,H,N |
| 8 | $C_{31}H_{37}N_3O_4 \cdot 0.25H_2O$ | 185–187 | C,H,N |
| 9 | $C_{31}H_{37}N_3O_4 \cdot 0.2CCl_4$ | 77–85 | C,H,N |
| 10 | $C_{31}H_{34}N_2O_6$ | 77–84 | C,H,N |
| 11 | $C_{31}H_{36}N_2O_5 \cdot 0.25H_2O$ | 48–58 | C,H,N |
| 12 | $C_{24}H_{31}N_3O_4$ | 72–80 | C,H,N |
| 13 | $C_{22}H_{26}N_2O_3 \cdot 0.5H_2O$ | 50–54 | C,H,N |
| 14 | $C_{31}H_{39}N_3O_3 \cdot 0.2H_2O$ | 59–61 | C,H,N |
| 15 | $C_{32}H_{37}N_3O_5$ | 74–76 | C,H,N |
| 16 | $C_{32}H_{37}N_3O_4S$ | 63–67 | C,H,N,S |
| 17 | $C_{31}H_{37}N_3O_3S \cdot 0.65EtOAc$ | 71–77 | C,H,N |
| 18 | $C_{33}H_{39}N_3O_5$ | 62–67 | C,H,N |
| 19 | $C_{32}H_{39}N_3O_4 \cdot 0.85CHCl_3$ | 97–99 | C,H,N |
| 20 | $C_{10}H_{12}O_3$ | 71–73 | C,H |
| 21 | $C_{12}H_{14}O_4$ | [a] | C,H |
| 24 | $C_{31}H_{39}N_3O_2 \cdot C_7H_8SO_3 \cdot 0.75H_2O$ | 90–93 | C,H,N |
| 25 | $C_{33}H_{41}N_3O_3 \cdot 0.25H_2O$ | 101–103 | C,H,N |
| 26 | $C_{37}H_{47}N_3O_5$ | 67–70 | C,H,N |
| 27 | $C_{40}H_{53}N_3O_5$ | 49–54 | C,H,N |
| 28 | $C_{35}H_{43}N_3O_5 \cdot 0.25H_2O$ | 96–99 | C,H,N |
| 29 | $C_{31}H_{37}N_3O_2S$ | 134–136 | C,H,N |
| 30 | $C_{31}H_{36}N_2O_4$ | 57–63 | C,H,N |
| 31 | $C_{31}H_{36}N_2O_3S$ | 62–65 | C,H,N |
| 32 | $C_{32}H_{39}N_3O_3$ | 90–95 | C,H,N |
| 33 | $C_{13}H_{17}NO_4$ | 59–61 | C,H,N |
| 34 | $C_{36}H_{43}N_3O_7 \cdot 0.5H_2O$ | 69–71 | C,H,N |
| 35 | $C_{13}H_{15}NO_4$ | 75–77 | C,H,N |
| 36 | $C_{36}H_{41}N_3O_7$ | 96–99 | C,H,N |
| 38 | $C_{23}H_{30}N_2O_3 \cdot 0.5H_2O$ | 72–74 | C,H,N |
| 39 | $C_{23}H_{28}N_2O_3$ | 178–179 | C,H,N |
| 40 | $C_{32}H_{38}N_2O_2$ | 49–52 | C,H,N |
| 41 | $C_{32}H_{40}N_2O_2 \cdot 0.25H_2O$ | 43–46 | C,H,N |
| 42 | $C_{32}H_{40}N_2O_3$ | 82–85 | C,H,N |
| 43 | $C_{32}H_{40}N_2O_3 \cdot 0.5H_2O$ | 75–77 | C,H,N |
| 45 | $C_{32}H_{37}N_3O_2S$ | 73–76 | C,H,N |

[a] Compound obtained as a viscous oil.

dihydro-1,3-thiazole **45**.[11] The corresponding compound in the des-$\alpha$-methyl series is obtained by treating the amide **4** with Lawesson's reagent to give the 4,5-dihydro-1,3-thiazole as a mixture of two optically active diastereoisomers with unknown configuration (**5**, **6**) (Scheme I) which are separated by chromatography. The thioamide **17** is prepared in two steps from the amide **15** using 2,4-bis-(phenylthio)-1,3-dithia-2,4-diphosphetane 2,4-disulfide[12] to give the ester **16** which is reduced to the required alcohol **17** by treatment with lithium aluminum hydride.

Physical data for new compounds **3–21**, **24–36**, **38–43**, and **45** are presented in Table I.

## Results and Discussion

The CCK-B and CCK-A in vitro receptor binding data for amide replacements incorporated into compounds **4** and **23** are shown in Tables II and III, respectively. The data obtained with the CCK-B antagonist CI-988 (**1**)[7a] are given for comparison.

In order to probe the physicochemical consequences of replacing an amide bond some molecular modeling using *N*-methylacetamide as a reference compound and the derivatives listed in Table IV has been performed. Three physicochemical parameters of the amide bond and amide replacements were selected for this study, lipophilicity, steric properties, and hydrogen bonding, since these are known to be involved in the molecular recognition phenomena of drug receptor interactions.[13] The data are presented in Table IV. The four columns to the left summarize the steric data generated with the molecular modeling package SYBYL[14] in terms of the distances and angles between the two methyl groups and the volume of space occupied by the entire molecule. These data show that most of the amide replacements are of similar size, and this justifies the use of the term "isostere". Column five contains log *P* data which monitor the lipophilicity of the molecule in the region of the amide bond. These were calculated using the CLOG P[15] program and indicate how the lipophilicity changes "locally" in the region of the amide bond when this is replaced. It should be noted that in this reference compound, *N*-methylacetamide, the reversed amide replacement is identical to the parent compound. In a less symmetrical molecule such as a drug or a peptide this would not be the case. The final two columns of Table IV give an indication of the hydrogen bond donating (log $K_\alpha$) and accepting (log $K_\beta$) abilities. These figures are taken from the work of Morris and Taylor and co-workers[16] who quantified hydrogen bonding by measuring the association constants between test compounds and a standard proton donor, 4-nitrophenol, or a standard acceptor, *N*-methylpyrrolidinone. Thus, an amide (log $K_\beta$ = 3.0) is a much better H-bond acceptor than an ester (log $K_\beta$ = 1.5).

A qualitative comparison of peptide backbone modifications has been published previously,[2] and some of the physicochemical properties of the amino acid side chains have been parametrized.[17] To our knowledge, this is the first time that these properties of the amide bond have been quantified in a single study incorporating such a variety of amide replacements. The data reported in this paper should contribute to a more rational selection of amide bond replacements in other substrates.

The *N*-methylacetamide reference compound is a simpler molecule that most amides in peptides or drugs, and conformational properties have not been considered. However, the data in Table IV do provide a useful aid for considering the SAR of the CCK ligands reported in this study (Tables II and III). For example, the amide bond of compound **4** (CCK-B $IC_{50}$ = 852 nM, CCK-A $IC_{50}$ = 1080 nM, Table II) will tolerate being replaced with a reversed amide, compounds **8** and **9** (CCK-B $IC_{50}$ = 1230, 780 and CCK-A $IC_{50}$ = 317, 976 nM, respectively) or an ester, compound **11** (CCK-B $IC_{50}$ = 1890 nM, CCK-A $IC_{50}$ = 2950 nM) or an *N*-methylamide, compound **19** (CCK-B $IC_{50}$ = 1460 nM, CCK-A $IC_{50}$ 1080 nM) (Table II) with only a 3-fold change in the CCK-B or CCK-A binding affinities. These replacements change significantly the hydrogen bonding properties and/or the CLOG P values and/or the molecular volume of the amide, respectively (Table IV). Another replacement which increases the molecular vol-

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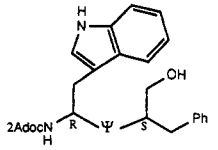
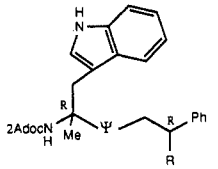
**Table II.** CCK-B and CCK-A Receptor Binding Data for Amide Replacements Incorporated into Compound **4**



| compd | $\psi$ | receptor binding affinity: $IC_{50}$ (nM)[a] CCK-B | CCK-A | A/B ratio |
|---|---|---|---|---|
| **4** | -CONH- | 852 (365–1590) | 1080 (769–2020) | 1.3 |
| **5** | dihydrothiazole[b] | 2580 (2230–3150) | 125 (60.7–241) | 0.048 |
| **6** | dihydrothiazole[b] | 2510 (2140–3190) | 708 (542–1120) | 0.28 |
| **8**[c] | -NHCO- | 1230 (1100–1340) | 317 (228–582) | 0.26 |
| **9**[c] | -NHCO- | 780 (666–853) | 976 (841–1270) | 1.3 |
| **11** | -COO- | 1890 (1260–2430) | 2950 (1310–7290) | 1.6 |
| **14** | $-CH_2NH-$ | 11500 (5290–24100) | 1250 (1190–1320) | 0.11 |
| **17** | -CSNH- | 1590 (506–4430) | 1980 (1560–2250) | 1.2 |
| **19** | -CONMe- | 1460 (1060–1780) | 1080 (732–1810) | 0.74 |
| CI-988[d] | | 1.7 (1.3–2.7) | 4300 (1200–8500) | 2500 |

[a] $IC_{50}$ is the concentration (nM) producing half-maximal inhibition of specific binding of [$^{125}$I]CCK-8 to CCK receptors in the mouse cerebral cortex (CCK-B) or the rat pancreas (CCK-A). The values given are the geometric mean and the range from at least three separate experiments. [b] These 4,5-dihydro-1,3-thiazole derivatives do not possess the $CH_2OH$ group. See Scheme I for full structure. [c] **8** and **9** were separated by column chromatography. Each is a racemic diastereoisomer of unknown stereochemistry [i.e. each is either (*R*,*R* and *S*,*S*) or (*R*,*S* and *S*,*R*)]. [d] Previously reported compound, ref 7a.

**Table III.** CCK-B and CCK-A Receptor Binding Data for Amide Replacements Incorporated into Compound **23**



| compd | $\psi$ | R | receptor binding affinity: $IC_{50}$ (nM)[a] CCK-B | CCK-A | A/B ratio |
|---|---|---|---|---|---|
| **23**[b] | -CONH- | H | 32 (15.9–42.6) | 640 (515–751) | 20 |
| **24** | $-CH_2NH-$ | H | 1080 (973–1270) | 4060 (2600–8400) | 3.8 |
| **26** | $-CH_2N(COCH_2CH_2CO_2Et)-$ | H | 1630 (834–5070) | 3670 (1520–6450) | 2.3 |
| **25** | $-CH_2N(Ac)-$ | H | 1060 (960–1220) | 1310 (1210–1440) | 1.2 |
| **27** | $-CH_2N(CO(CH_2)_5CO_2Et)-$ | H | 863 (794–952) | 3530 (1150–13900) | 4.1 |
| **28** | $-CH_2N(COCH_2CH_2CO_2H)-$ | H | 1270 (972–1530) | 1080 (944–1330) | 0.85 |
| **29** | -CSNH- | H | 808 (700–907) | 1500 (1280–1820) | 1.9 |
| **30** | -COO- | H | 547 (458–620) | 1070 (834–1510) | 2.0 |
| **31** | -COS- | H | 932 (672–1300) | 1190 (861–1590) | 1.3 |
| **32** | -CONMe- | H | 123 (102–136) | 757 (635–961) | 6.2 |
| **34** | -COO- | $NHCOCH_2CH_2CO_2Me$ | 71.2 (68.0–75.7) | 351 (294–482) | 4.9 |
| **36**[f] | -COO- | $NHCOCH{=}CHCO_2Me$ | 38.8 (30.0–45.4) | 394 (283–487) | 10 |
| **40**[c] | -HC=CH- | H | 6340 (5060–7950) | 3620 (1600–8040) | 0.57 |
| **41**[d] | $-CH_2CH_2-$ | H | 8690 (4990–14400) | 19500 (7760–34500) | 2.2 |
| **42**[e] | $-CH(OH)CH_2-$ | H | 595 (450–689) | 1230 (676–2820) | 2.1 |
| **43**[e] | $-CH(OH)CH_2-$ | H | 1970 (1420–2840) | 2620 (1340–4170) | 1.3 |
| **45** | dihydrothiazole[g] | H | 801 (668–910) | 827 (768–869) | 1.0 |
| CI-988[b] | | | 1.7 (1.3–2.7) | 4300 (1200–8500) | 2500 |

[a] Binding affinities defined in footnote *a*, Table II. [b] Previously reported compound, ref 7a. [c] Olefin has *Z* configuration. [d] Stereochemistry of the chiral quaternary carbon atom is designated *S* because priority of the substituents has changed. [e] **42** and **43** are optically active diastereoisomers with different but unknown configuration of the chiral carbon in hydroxyethylene replacement. [f] Olefin has *E* configuration. [g] See Scheme VI for full structure of this 4,5-dihydro-1,3-thiazole derivative.

ume and has similar CCK-B affinity despite its reduced hydrogen bonding acceptor ability is the thioamide **17** (CCK-B $IC_{50}$ = 1590 nM, CCK-A $IC_{50}$ = 1980 nM).

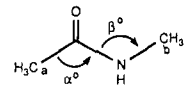
The methyleneamino group is one of the most widely used replacements for peptidic amide bonds.[18] It is found in renin inhibitors[18a] and its incorporation into bombesin,[18b] gastrin,[18c] substance P,[18d] growth hormone releasing factor (GRF),[18e] and secretin[18f] pseudopeptides has led to the identification of receptor antagonists for these peptides. Within our series of CCK-ligands the methyleneamino replacement **14**, which is anticipated to be charged at physiological pH and therefore have very different electronic properties to the amide, has much weaker affinity for the CCK-B receptor than the parent amide **4**, but CCK-A affinity is retained, resulting in a CCK-A/CCK-B selectivity of 9-fold (CCK-B $IC_{50}$ = 11500 nM, CCK-A $IC_{50}$ = 1250 nM).

The 4,5-dihydro-1,3-thiazole derivatives **5** and **6** have little effect on the CCK-B affinity (CCK-B $IC_{50}$ = 2580, 2510 nM), but one of the stereoisomers has significantly enhanced CCK-A affinity (CCK-A $IC_{50}$ = 125, 780 nM, respectively) resulting in a modest A/B selectivity of 21-fold.

The overall conclusion is that in this series of CCK-B ligands the central amide bond can be replaced with groups which significantly change the physicochemical properties shown in Table IV without having much effect on CCK-B binding affinity, indicating that this amide group itself does not participate in a binding interaction with the receptor.

The other compound selected for amide replacement, **23** (CCK-B $IC_{50}$ = 32 nM, CCK-A $IC_{50}$ = 640 nM, Table

**Table IV.** Physiochemical Properties of Amide Replacements in *N*-Methylacetamide (See Text for Details)



| compound $CH_3$–$\psi$–$CH_3$ | distance between $C_a$ and $C_b$ (Å) | $\alpha°$ | $\beta°$ | mol vol (Å$^3$) | CLOG P | hydrogen bonding log $K_\alpha$[a] | hydrogen bonding log $K_\beta$[a] |
|---|---|---|---|---|---|---|---|
| $CH_3$–CONH–$CH_3$ | 3.8 | 119 | 120 | 69.3 | −1.08 | 0.7 | 3.0 |
| $\psi$[NHCO] | 3.8 | 119 | 120 | 69.3 | −1.08 | 0.7 | 3.0 |
| $\psi$[$CH_2O$] | 3.7 | 107 | 113 | 67.0 | 0.34 | – | 1.5 |
| $\psi$[COO] | 3.7 | 116 | 113 | 65.8 | 0.14 | – | 1.4 |
| $\psi$[$CH_2NH$] | 3.8 | 111 | 115 | 71.6 | 0.01 | – | 2.8[b] |
| $\psi$[$COCH_2$] | 3.9 | 118 | 110 | 75.6 | 0.26 | – | 1.6 |
| $\psi$[CHCH][c] | 3.9 | 122 | 122 | 68.2 | 2.27 | – | – |
| $\psi$[CHCH][d] | 3.0 | 125 | 236 | 68.5 | 2.27 | – | – |
| $\psi$[$CH_2CH_2$] | 3.9 | 111 | 112 | 76.0 | 2.81 | – | – |
| $\psi$[$CHOHCH_2$] | 4.0 | 111 | 113 | 83.3 | 0.63 | 1.2 | 1.4 |
| $\psi$[$CH_2S$] | 4.2 | 110 | 98 | 76.2 | 1.37 | – | 0.4[e] |
| $\psi$[CSNH] | 3.8 | 115 | 116 | 82.0 | −0.37 | 1.0 | 1.8 |
| $\psi$[$CONCH_3$] | 3.9 | 119 | 119 | 85.5 | −0.80 | – | 3.0[f] |
| $\psi$[COS] | 4.2 | 118 | 98 | 76.4 | 0.53 | – | – |

[a] Hydrogen bond donating (log $K_\alpha$) and hydrogen bond accepting (log $K_\beta$) parameters are taken from ref 16. [b] Log $K_\beta$ of isopropylamine. [c] Olefin has trans configuration. [d] Olefin has cis configuration. [e] Value estimated from basicity p$K_b$. [f] N-Methylation claimed to leave acceptor strength unchanged in ref 16.

III), has higher CCK-B receptor affinity than **4**. Once again, amide replacement with the thioamide **29** (CCK-B $IC_{50}$ = 808 nM, CCK-A $IC_{50}$ = 1500 nM) or the methyleneamino **24** (CCK-B $IC_{50}$ = 1080 nM, CCK-A $IC_{50}$ = 4060 nM) results in significantly reduced activity compared to the parent amide **23**. The amino group of **24** was acetylated in order to restore the amide character to the nitrogen atom. However, the acetate **25** (CCK-B $IC_{50}$ = 1060 nM, CCK-A $IC_{50}$ = 1310 nM) does not restore CCK-B affinity.

Incorporation of a succinic ester or a succinic acid in the CI-988 series has been shown previously to enhance CCK-B affinity.[7a] The same groups were attached to the aminomethylene replacement to give **26** and **28**, but they do not increase affinity (CCK-B $IC_{50}$ = 1630, 1270 nM and CCK-A $IC_{50}$ = 670, 1080 nM, respectively). The ethyl pimelate side chain was appended to give **27** (CCK-B $IC_{50}$ = 863, CCK-A $IC_{50}$ = 3530) which contains the same number of bonds between the amide nitrogen and the ester as is found in the CI-988 series. Once again, this fails to restore CCK-B affinity.

The amide in **23** is more sensitive to replacement than that of **4** because, unlike the compounds in Table II discussed above, the *N*-methylamide **32**, the 4,5-dihydro-1,3-thiazole **45**, and the ester **30** all have significantly weaker CCK-B receptor affinity (CCK-B $IC_{50}$ = 123, 801, 547 nM and CCK-A $IC_{50}$ = 757, 827, 1070 nM, respectively). The thiolester **31** (CCK-B $IC_{50}$ = 932 nM, A/B ratio = 1.3) has similar binding affinity to the ester **30** despite the differences between them in terms of molecular volume (76.4 and 65.8 Å$^3$ respectively, Table IV), size, and CLOG P values.

The methyl succinate and methyl fumarate side chains found in the CI-988 series[7a] were appended to the ester **30** to give **34** and **36** which have 8- and 14-fold improved affinity for the CCK-B receptor, respectively. This ester replacement is of particular interest here because it should be stabilized toward esterase hydrolysis by steric hindrance of the $\alpha$-methyl group, and it cannot undergo the hydantoin formation which has been shown to occur when the corresponding amides in the CI-988 series are treated with base.[19]

The cis double bond in **40** has different steric, CLOG P, and hydrogen-bonding properties compared to the amide, and it is much less active (CCK-B $IC_{50}$ = 6340 nM, CCK-A $IC_{50}$ = 3620 nM). It is the synthetic precursor for the dimethylene replacement **41** which is a closer mimic of the steric properties of the amide in terms of the parameters in Table IV. However, this does not improve affinity (CCK-B $IC_{50}$ = 8690 nM, CCK-A $IC_{50}$ = 19500 nM), indicating that these steric properties are not the only reason for the inactivity of **40**.

The hydroxyethyl group has been used successfully to replace the amide bond in peptide substrates of proteolytic enzymes[4a,6a,6e] where it is thought to mimic the tetrahedral $sp^3$ transition state of the amide bond hydrolysis that is catalyzed by these enzymes. In this series of CCK-B ligands the hydroxyethyl replacements **42** and **43** are significantly less active than the parent amide (by 19-fold and 62-fold, respectively), and the data in Table IV show that they are poor mimics of the amide bond in terms of lipophilicity, molecular volume, and the bond angles $\alpha$ and $\beta$.

In summary, the amide replacements incorporated into **23** reduce CCK-B binding affinity and CCK-A/CCK-B selectivity. The amide replacements which have been used

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(19) Horwell, D. C.; Ratcliffe, G.; Roberts, E. Stabilities of Tryptophanylphenethylamides to Acid and Alkaline Conditions. *BioMed. Chem. Lett.* **1991**, *1*, 169–172.

as transition-state mimics to increase activity in peptidic enzyme inhibitors (methyleneamino, hydroxyethylene) are particularly inactive (compounds **14**, **24**, **42**, and **43**) presumably because they are poor mimics of the amide ground state which is expected to be the state recognized by the reversible interactions with receptors.

Other replacements which are poor mimics of the amide in terms of steric, hydrogen bonding, and lipophilic properties (cis double bond, ethylene) are also amongst the least active compounds (**40**, **41**). However, some change to the molecular volume of the amide group appears to be tolerated by the CCK-B receptor (e.g. *N*-methylamide compounds **19**, **32**). The CCK-A and CCK-B receptors have different binding preferences for this central amide bond and the 4,5-dihydro-1,3-thiazole replacement **5** has a significantly higher affinity and selectivity for the CCK-A receptor than does the parent amide **4** ($IC_{50}$ = 125 and 1080 nM, respectively).

Although many of these replacements reduce the CCK-B receptor affinity, it has been possible to restore this by appending an auxiliary side chain to the phenethyl group. Thus the ester replacement **30** has a 17-fold weaker CCK-B affinity than the amide **23** ($IC_{50}$ = 547 and 32 nM, respectively) but attaching a fumarate side chain gives compound **36** which is approximately equiactive as **23** ($IC_{50}$ = 38.8 nM).

## Conclusion

The central amide bond of the CCK-B ligands **4** and **23** has been replaced with eleven different amide replacements. This represents one of the most comprehensive studies of amide replacements in a ligand for a membrane bound receptor. It has resulted in a series of compounds which generally have weaker CCK-B receptor affinity than the parent amide. This decrease in affinity indicates that these replacements are poor mimics of the amide bond in terms of CCK-B receptor binding interactions with these ligands. Since no correlation between the binding affinity and the physicochemical properties of the compounds in Table IV has been determined, it is presumed that other factors (e.g. conformation) are of greater importance for this particular ligand-receptor interaction. These results are contrasted with many successful reports in the literature of the replacement of amide bonds in certain enzyme substrates to produce potent enzyme inhibitors (e.g. renin, angiotensin converting enzyme, HIV proteinase). It should be noted that these enzymes are thought to interact with a transition state of amide bond hydrolysis but the receptors presumably bind to a ground state of the amide.

## Experimental Section

**Molecular Modeling.** The models of *N*-methylacetamide, and its amide-replaced analogues, were built using the commercial package SYBYL (version 5.3), running on a Silicon Graphics 4D-310 workstation. Each model was built to mimic the trans configuration of the amide as closely as possible. The geometry was then optimized using MAXIMIN II (A)[20] with the Tripos force field.[21,22] No atomic charges were calculated. The molecular volumes were calculated as that space within one van der Waals radii of the atoms, using the surfaces/volume option. CLOG P values were calculated according to the method of Leo.[15]

Melting points were determined with a Reichart Thermovar hot-stage apparatus and are uncorrected. All NMR spectra were $^1$H NMR recorded on a Bruker AM300 MHz spectrometer or a JEOL PMX60 MHz spectrometer; chemical shifts were recorded in parts per million downfield from tetramethylsilane and coupling constants ($J$) are measured in hertz. IR spectra were recorded with compound (neat) on a sodium chloride disk with a Perkin-Elmer 1750 Fourier transform spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Silica gel used for chromatography was Kieselgel-60 (230–400 mesh); reverse-phase silica gel was Lichroprep RP-18 (230–400 mesh). Both were supplied by E. Merck AG, Darmstadt, Germany. Elemental analyses were determined by CHN Analyses Limited, Leicester, U.K. Mass spectra were recorded with a Finnegan 4500 spectrometer. All experiments using moisture sensitive reagents were performed under a dry nitrogen atmosphere.

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [1-Carboxy-2-(1*H*-indol-3-yl)-ethyl]carbamate (3).** Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl chloroformate[23] (2.97 g, 13.9 mmol) in 1,4-dioxane (10.5 mL) was added dropwise with stirring to a cooled (ice bath) mixture of (*R*)-tryptophan (2.13 g, 10.4 mmol), $NaHCO_3$ (879 mg, 10.5 mmol), and 1 N NaOH (10.5 mL, 10.5 mmol) in 1,4-dioxane (10.5 mL). After the addition was complete, the cooling bath was removed, and the mixture was stirred at room temperature for 18 h. The 1,4-dioxane was removed in vacuo, and the residue was partitioned between 10% citric acid (100 mL) and ethyl acetate (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was crystallized from ethyl acetate to give the acid **3** (2.03 g, 51%): $[\alpha]^{22}_D$ +9.4° ($c$ = 1.2, MeOH); IR (film) 3399 (OH), 2908 and 2854 (CH), 1715 sh (CO acid), and 1693 (CO urethane) cm$^{-1}$; NMR (DMSO-$d_6$) $\delta$ 1.31–2.09 (14 H, m, adamantyl), 3.07 (1 H, dd, $J$ = 14, 9 Hz), 3.18 (1 H, dd, $J$ = 14, 5 Hz), 4.22 (1 H, m), 4.58 (1 H, s), 6.99 (1 H, dd, $J$ = 8, 8 Hz), 7.12 (1 H, dd, $J$ = 8, 8 Hz), 7.17 (1 H, s), 7.25 (1 H, d, $J$ = 9 Hz), 7.34 (1 H, d, $J$ = 8 Hz, indole 7-H), 7.54 (1 H, d, $J$ = 8 Hz, indole 4-H), 10.84 (1 H, s), 12.62 (1 H, br s); MS $m/e$ (CI) 383 ($M^+$ + H, 31%).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*R**,*S**)]-[2-[[1-(Hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-2-oxoethyl]carbamate (4).** The carboxylic acid **3** (380 mg, 1.0 mmol), *N*,*N*'-dicyclohexylcarbodiimide (DCC) (230 mg, 1.1 mmol), and pentafluorophenol (PFP) (200 mg, 1.1 mmol) were suspended in EtOAc (25 mL), stirred for 2 h, and then treated with (*S*)-2-amino-3-phenyl-1-propanol (150 mg, 1.0 mmol) and stirred at 40 °C for 18 h. The mixture was filtered, and the filtrate was washed with saturated aqueous citric acid, followed by saturated aqueous $NaHCO_3$ and then $H_2O$. The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by reverse-phase silica gel chromatography, using MeOH–$H_2O$ (4:1) as eluant to give the product **4** (0.36 g, 71%): $[\alpha]^{20}_D$ = 20.4° ($c$ = 0.25, $CH_2Cl_2$); NMR ($CDCl_3$) $\delta$ 1.5–2.0 (14 H, m), 2.20 (1 H, br s), 2.60 (2 H, d, $J$ = 7 Hz), 3.1–3.5 (4 H, m), 4.0–4.1 (1 H, m), 4.42 (1 H, q, $J$ = 7 Hz), 4.6–4.8 (1 H, m), 5.45 (1 H, br s), 6.15 (1 H, br s), 6.9–7.3 (8 H, m), 7.37 (1 H, d, $J$ = 8 Hz), 7.67 (1 H, d, $J$ = 8 Hz), 8.25 (1 H, br s).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [1-[4,5-Dihydro-4-(phenylmethyl)-2-thiazolyl]-2-(1*H*-indol-3-yl)ethyl]carbamate (5 and 6).** The hydroxyamide **4** (339 mg, 0.657 mmol) and Lawesson's reagent (Aldrich) (250 mg, 0.618 mmol) were refluxed in toluene (10 mL) for 1 h. The solution was cooled to room temperature and purified by column chromatography using ether–hexane (60:40) to give the diastereoisomeric thiazolines **5** and **6**. Isomer I (57 mg, 17%): $[\alpha]^{20}_D$ = 9.1° ($c$ = 0.52, MeOH); IR (film) 2911, 2854, 1702, and 1620 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 1.44–2.11 (14 H, m), 2.42 (1 H, m), 2.96 (2 H, dd, $J$ = 7 and 11 Hz), 3.14 (1 H, dd, $J$ = 8 and 11 Hz), 3.21–3.47 (2 H, m), 4.65 (1 H, m), 4.84 (1 H, s), 4.89 (1 H, br s), 5.57 (1 H, br d, $J$ = 7 Hz), 6.92–7.35 (9 H, m), 7.68 (1 H, d, $J$ = 8 Hz), 8.12 ( 1 H, s); MS $m/e$ (CI) 514 ($M^+$ + H) (100%). Isomer II (170 mg, 50%): $[\alpha]^{20}_D$ = −31° ($c$ = 1.00,

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$CHCl_3$); IR (film) 2909, 2854, 1698, and 1621 $cm^{-1}$; NMR ($CDCl_3$) δ 1.43–2.09 (14 H, m), 2.68 (1 H, dd, $J$ = 9 and 14 Hz), 2.83–3.44 (5 H, m), 4.62 (1 H, m), 4.82 (1 H, s), 4.88 (1 H, br s), 5.44 (1 H, br d, $J$ = 7 Hz), 6.96–7.38 (9 H, m), 7.63 (1 H, d, $J$ = 8 Hz), 8.16 (1 H, s); MS $m/e$ (FAB) 514 ($M^+$ + H) (19%).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (±)-[2-(1*H*-Indol-3-yl)-1-[[[(4-nitrophenyl)methoxy]carbonyl]amino]ethyl]carbamate (7).** To a solution of acid **3** (3.62 g, 9.47 mmol) in THF (36 mL) at −10 °C was added *N*-methylmorpholine (1.15 mL, 10.4 mmol) and isobutyl chloroformate (1.35 mL, 10.4 mmol). This mixture was stirred for 20 min at −10 °C and then filtered. Trimethylsilyl azide (Aldrich) (1.89 mL, 14.2 mmol) was added to the filtrate, and the resulting solution was stirred at −10 °C for 1 h. The solvent was removed in vacuo at 25 °C, and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo at 25 °C. The residue was dissolved in toluene (100 mL) and heated at 40 °C until rearrangement to the isocyanate was complete (30 min). [IR (neat) 2139 ($N_3$); 2249 (NCO) $cm^{-1}$]. *p*-Nitrobenzyl alcohol (2.20 g, 14.3 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (149 mg, 1.33 mmol) were added, and the mixture was left at 40 °C for 15 h. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography using ether–hexane (4:1) as eluant to give **7** as a yellow solid which was recrystallized from ether–hexane (2.12 g, 42%): IR (film) 2908, 2855 (adamantyl C–H), 1703 (br, CO urethane), 1520 ($NO_2$), and 1347 ($NO_2$) $cm^{-1}$; NMR (DMSO-$d_6$) δ 1.39–2.03 (14 H, m), 3.07 (2 H, br s, $CH_2$-indole), 4.64 (1 H, s, adamantyl H-2), 5.14 (2 H, s, $CH_2Ph$), 5.37 (1 H, m, $CH$-($NHCO_2$)$NHCO_2$), 6.90–7.29 (4 H, m, indole H-2, H-5, H-6 NH), 7.34 (2 H, d, $J$ = 8 Hz, PhH-2, PhH-6), 7.46–7.62 (3 H, m, indole H-4, H-7, NH), 8.16 (2 H, d, $J$ = 8 Hz, PhH-3, PhH-5), 10.61 (1 H, s, indole NH).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (±)-[1-[[2-(Hydroxymethyl)-1-oxo-3-phenylpropyl]amino]-2-(1*H*-indol-3-yl)ethyl]carbamate (8 and 9).** The bis urethane **7** (524 mg, 0.984 mmol) was dissolved in EtOAc (36 mL) and treated with 20% palladium hydroxide on carbon (Pearlman's catalyst). The mixture was put under an atmosphere of hydrogen gas at 45 psi at 40 °C for 1 h and then filtered through Celite (to remove the catalyst) into a flask containing an activated ester of **21** which had been generated via the reaction of **21** (226 mg, 1.02 mmol) in EtOAc (5 mL) with 1-hydroxybenzotriazole hydrate (HOBt) (179 mg, 1.17 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (235 mg, 1.14 mmol) at 0 °C for 90 min. The resulting mixture was stirred at room temperature for 18 h, then concentrated in vacuo, cooled to 0 °C, filtered, and evaporated to dryness. The crude product was purified by silica gel chromatography using $CH_2Cl_2$–EtOAc (80:20) as eluant to give the acetate (265 mg, 48%): IR (film) 2916, 2855 (adamantyl), 1740 sh (CO ester), 1698 (CO urethane), and 1658 (CO amide) $cm^{-1}$; NMR ($CDCl_3$) δ 1.47–2.14 (17 H, m, adamantyl, $CH_3$), 2.62 (1 H, m, COC*H*), 2.78 (1 H, m, CH of $CH_2Ph$), 2.90 (1 H, m, CH of $CH_2Ph$), 3.13 (1 H, m, CH of $CH_2$-indole), 3.23 (1 H, m, CH of $CH_2$-indole), 4.18 (2 H, m, $CH_2OCO$), 4.80 (1 H, s, adamantyl H-2), 5.41 (1 H, br d, C*H*NH), 6.25 (0.5 H, br s), 6.77 (0.5 H, s, indole H-2), 6.88 (0.5 H, s, indole H-2), 7.04–7.62 (9.5 H, m, Ph, indole H-4, H-5, H-6, H-7), 8.09 (1 H, s, indole NH); MS $m/e$ (FAB) 558 (3) ($M^+$ + 1), 363 (83) ($M^+ - C_{11}H_{17}NO_2$), 135 (100) ($C_{10}H_{15}$). This acetate (264 mg, 0.473 mmol) was dissolved in THF–MeOH–$H_2O$ (3:2:1) (6 mL) and treated with lithium hydroxide monohydrate (56.6 mg, 1.35 mmol) at room temperature for 30 min. The reaction mixture was poured into 2 N HCl (50 mL) and extracted with EtOAc (3 × 25 mL). The EtOAc fractions were combined and washed with brine, dried ($MgSO_4$), and evaporated to dryness. The crude material was purified by silica gel chromatography using $CH_2Cl_2$–MeOH (95:5) as eluant to give the diastereoisomeric alcohols (**8** and **9**) (150 mg, 62%). Diastereoisomer I, **8**, (80 mg): IR (film) 3540–3140 (br, OH), 2910, 2855 (adamantyl C-H), 1695 (CO urethane), and 1660 (CO amide) $cm^{-1}$; NMR ($CD_3OD$) δ 1.43–2.04 (14 H, br m, adamantyl), 2.42 (1 H, m, NHCOC*H*), 2.67–3.22 (5 H, br m, indole $CH_2$, $PhCH_2$, O*H*), 3.67 (2 H, m, $CH_2OH$), 4.78 (1 H, s, adamantyl H-2), 5.40 (1 H, br s), 5.58 (1 H, br s), 6.26 (1 H, br s, amide NH), 6.82 (1 H, s, indole H-2), 7.02–7.37 (8 H, m, Ph, indole H-5, H-6, H-7), 7.44 (1 H, d, $J$ = 8 Hz, indole H-4), 8.16 (1 H, s, indole NH); MS $m/e$ (FAB) 538 (39), 516 (8) ($M^+$ + H), 321 (100). Diastereoisomer II, **9** (70 mg): IR (film) 3440 (br, OH), 2908, 2856 (adamantyl C–H), 1698 (CO urethane), and 1657 (CO amide) $cm^{-1}$; NMR ($CDCl_3$) δ 1.47–2.14 (14 H, m, adamantyl), 2.44 (1 H, m, COC*H*), 2.74 (1 H, dd, $J$ = 7, 14 Hz, one of $CH_2Ph$), 2.84 (1 H, dd, $J$ = 8, 14 Hz, one of $CH_2Ph$), 2.95 (1 H, br s, OH), 3.19 (2 H, d, $J$ = 5 Hz, $CH_2$-indole), 3.64 (2 H, s, $CH_2OH$), 4.79 (1 H, s, adamantyl H-2), 5.27 (1 H, br d, indole-$CH_2CH$), 5.49 (1 H, br s, urethane NH), 6.42 (1 H, br s, amide NH), 6.91 (1 H, s, indole H-2), 7.02–7.29 (7 H, m, indole H-6, H-5, Ph), 7.35 (1 H, d, $J$ = 8 Hz, indole H-7), 7.56 (1 H, d, $J$ = 8 Hz), 8.30 (1 H, s, indole NH); MS $m/e$ (CI) 516 (0.2) ($M^+$ + H), 321 (94), 180 (100).

**(*S*)-*N*-[(Tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]-(*R*)-tryptophan, 1-Carboxy-2-phenylethyl Ester (10).** The acid **3** (428 mg, 1.12 mmol) was treated with pentafluorophenol (247 mg, 1.34 mmol), *N*,*N*′-dicyclohexylcarbodiimide (254 mg, 1.23 mmol), 4-(dimethylamino)pyridine (DMAP) (14 mg, 0.11 mmol), and (−)-(*S*)-3-phenyllactic acid (208 mg, 1.25 mmol) in DMF (3 mL) and stirred at room temperature for 18 h. Water (21 mL) was added, and the resulting emulsion was extracted with ether (50 mL). The organic phase was washed with $H_2O$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography using EtOAc–*n*-hexane–acetic acid (66:33:1) as eluant to give acid/ester **10** as a white foam (396 mg, 66%): IR (film) 3410 (br, OH), 2913, 2854 (adamantyl C–H), 1736 (br, CO ester/acid), and 1703 (CO urethane) $cm^{-1}$; NMR ($CD_3OD$) δ 1.52–2.17 (14 H, m, adamantyl), 2.95–3.30 (4 H, m, 2 × $CH_2$), 4.63 (1 H, m, ind $CH_2CH$), 4.71 (1 H, s, adamantyl H-2), 5.18 (1 H, m, $OCHCO_2H$), 6.77 (1 H, s, indole H-2), 6.92–7.39 (8 H, m, indole H-7, H-6, H-5, Ph), 7.48 (1 H, d, $J$ = 8 Hz, indole H-4); MS (FAB) $m/e$ 531 (98) ($M^+$ + H), 470 (100), 396 (5), 383 (11).

**(*S*)-*N*-[(Tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]-(*R*)-tryptophan, 1-(Hydroxymethyl)-2-phenylethyl Ester (11).** The acid **10** (208 mg, 0.392 mmol), ethyl chloroformate (41 μL, 0.47 mmol), and triethylamine (66 μL, 0.47 mmol) in THF (1 mL) were stirred at 5 °C for 30 min. The mixture was filtered, and the filtrate was added to a cooled solution (ice bath) of sodium borohydride (46 mg, 1.2 mmol) in $H_2O$ (2 mL). The solution was warmed to room temperature and stirred for 18 h, then acidified with concentrated HCl to pH 2, and extracted with EtOAc (3 × 25 mL). The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography using $CH_2Cl_2$–EtOAc (1:1) as eluant to give hydroxy ester **11** as a white foam (144 mg, 71%): IR (film) 3418 (OH), 2902, 2856 (adamantyl C–H), 1740 (CO ester), and 1697 (CO urethane) $cm^{-1}$; $[\alpha]^{20}_D$ = +7.6° ($c$ = 1.01, $CHCl_3$); NMR ($CDCl_3$) δ 1.44–2.18 (14 H, m, adamantyl), 2.63 (2 H, br s, $PhCH_2$), 3.39 (2 H, br s, indole $CH_2$), 3.77–4.02 (2 H, m, C*H* of $CH_2OH$, $OCHCH_2Ph$), 4.11 (1 H, dd, $J$ = 3 and 11 Hz, C*H* of $CH_2OH$), 4.65–4.75 (1 H, m), 4.82 (1 H, s, adamantyl H-2), 5.28 (1 H, br d, $J$ = 8 Hz, urethane NH), 6.93–7.38 (9 H, m, indole H-7, H-6, H-5, H-2, Ph), 7.57 (1 H, d, $J$ = 8 Hz, indole H-4), 8.16 (1 H, s, indole NH); MS (FAB) $m/e$ 516 (100) ($M^+$).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[1-(1*H*-Indol-3-ylmethyl)-2-(methoxymethylamino)-2-oxoethyl]carbamate (12).** To a solution of acid **3** (859 mg, 2.25 mmol) in $CH_2Cl_2$ (8 mL) was added *N*-methylmorpholine (495 μL, 4.50 mmol). The mixture was cooled to −15 °C, and isobutyl chloroformate (292 μL, 2.25 mmol) was added. The mixture was stirred at −15 °C for 15 min and then treated with *N*,*O*-dimethylhydroxylamine hydrochloride (219 mg, 2.25 mmol). The reaction mixture was stirred at −15 °C for 1 h, then warmed to room temperature, and stirred for a further 15 h. The mixture was filtered, and the filtrate was washed sequentially with aqueous $NaHCO_3$, water, 10% citric acid, and brine, dried ($MgSO_4$), and evaporated to dryness. The crude material was purified by silica gel chromatography using hexane–EtOAc (1:1) as eluant to give the hydroxamate **12** as a white foam (694 mg, 73%): $[\alpha]^{20}_D$ = −9.4° ($c$ = 0.30, $CHCl_3$); IR (film) 2908, 2855, 1695, and 1651 $cm^{-1}$; NMR ($CDCl_3$) δ 1.30–2.01 (14 H, m, adamantyl), 2.99–3.24 (5 H, m, indole $CH_2$, $NCH_3$), 3.58 (3 H, s, $OCH_3$), 4.7 (1 H, s, adamantyl H-2), 5.00 (1 H, br d, C*H*(NHR)CON), 5.36 (1 H, br d, urethane NH), 6.92–7.17 (3 H, m, indole H-2, H-5, H-6), 7.27 (1 H, d, $J$ = 8 Hz, indole H-7), 7.53 (1 H, d, $J$ = 8 Hz, indole H-4), 7.99 (1 H, s, indole NH).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[1-Formyl-2-(1*H*-indol-3-yl)ethyl]carbamate (13).** Lithium aluminum hydride (45 mg, 1.2 mmol) was added portionwise over a period of 30 min to a solution of the hydroxamate **12** (197 mg, 0.460 mmol) in THF (3

mL) at 0 °C. The mixture was stirred for a further 30 min, and then ether (30 mL) was added, followed by an ice-cold solution of 10% citric acid (40 mL). The mixture was stirred vigorously for 30 min, then the layers were separated, and the aqueous phase was extracted with ether (5 × 10 mL). The ether extracts were combined and sequentially washed with saturated aqueous $NaHCO_3$ (25 mL), $H_2O$ (25 mL), 10% citric acid (25 mL), and brine (25 mL), dried ($Na_2SO_4$), and concentrated in vacuo to give the aldehyde **13** as a white foam (140 mg, 83%): $[\alpha]^{20}_D$ = 36.9 ($c$ = 1.14, $CHCl_3$); IR (film) 1725 sh (aldehyde CO) and 1693 (urethane CO) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.47–2.13 (14 H, m, adamantyl), 3.26 (2 H, dd, $J$ = 7, 15 Hz, indole-$CH_2$), 4.58 (1 H, br d, C*H*(NHR)CHO), 4.84 (1 H, s, adamantyl H-2), 5.3 (1 H), 6.98–7.26 (3 H, m), 7.35 (1 H, d, $J$ = 8 Hz, indole H-7), 7.60 (1 H, br d, $J$ = 8 Hz, indole H-4), 8.24 (1 H, br s, indole NH), 9.64 (1 H, s, CHO).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*R**,*S**)]-[2-[[1-(Hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-ethyl]carbamate (14).** Sodium cyanoborohydride (37 mg, 0.59 mmol) was added portionwise over a period of 15 min to a solution of the aldehyde **13** (136 mg, 0.370 mmol) and (*S*)-2-amino-3-phenyl-1-propanol (61 mg, 0.40 mmol) in MeOH–acetic acid (99:1) (5 mL). The mixture was stirred for 2 h at room temperature and then chilled (ice bath). Saturated aqueous $NaHCO_3$ (30 mL) was added with stirring, followed by EtOAc (45 mL). The organic layer was separated, washed with brine (5 mL), dried ($Na_2SO_4$), and evaporated to dryness. The crude product was purified by silica gel chromatography using $CH_2Cl_2$–MeOH (95:5) as eluant to give the amino alcohol **14** as a beige foam (60 mg, 32%): $[\alpha]^{20}_D$ = +1.2° ($c$ = 1.1, $CHCl_3$); IR (film) 3325 (OH), 1690 (CO urethane), 1496 (N–H), 1266 (OH), 1048 (C–O), 740 and 701 (monosubstituted Ph) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.31–2.04 (16 H, m, adamantyl, NH, OH), 2.44–3.01 (7 H, m, indole-$CH_2$, $CH_2NH$, $CH_2Ph$, NHC*H*($CH_2OH$)$CH_2Ph$), 3.21 (1 H, dd, $J$ = 6 and 11 Hz, one of $CH_2OH$), 3.47 (1 H, dd, $J$ = 4 and 11 Hz, one of $CH_2OH$), 3.97 (1 H, m, $CH_2CH(NHCO_2R)CH_2NH$), 4.66 (1 H, br d, urethane NH), 4.73 (1 H, s, adamantyl H-2), 6.87 (1 H, d, $J$ = 2 Hz, indole H-2), 6.96–7.24 (7 H, m, indole H-5, H-6, Ph), 7.29 (1 H, d, $J$ = 8 Hz, indole H-7), 7.55 (1 H, d, $J$ = 7 Hz, indole H-4), 7.97 (1 H, br s, indole NH).

***N*-[*N*-[(Tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]-(*R*)-tryptophyl]-(*S*)-phenylalanine, Methyl Ester (15).** (*S*)-Phenylalanine methyl ester hydrochloride (Aldrich) (361 mg, 1.67 mmol) and triethylamine (233 μL, 1.67 mmol) were stirred at room temperature in ethyl acetate (10 mL) for 10 min and then filtered. The filtrate was added dropwise with stirring to a cooled (ice/salt) solution of the active ester of acid **3** [generated by stirring acid **3** (426 mg, 1.11 mmol), *N*,*N*′-dicyclohexylcarbodiimide (228 mg, 1.11 mmol), and 1-hydroxybenzotriazole monohydrate (HOBt) (182 mg, 1.35 mmol) for 10 min in dichloromethane (10 mL) in an ice/salt bath]. The resulting mixture was warmed to room temperature and stirred for 2 h [at which point TLC ($SiO_2$; toluene–acetic acid 90:10) showed that no starting material remained]. The solvent was removed in vacuo, and the residue was stirred in ethyl acetate (20 mL), chilled (ice/salt), and then filtered. The filtrate was washed with saturated sodium hydrogen carbonate, water, 2 N hydrochloric acid, and brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The crude material was purified by silica gel column chromatography using dichloromethane–ethyl acetate (80:20) as eluant and then recrystallized from ether–hexane to give **15** as a white solid (459 mg, 76%): $[\alpha]^{20}_D$ = +3.0° ($c$ = 1.1, MeOH); IR (film) 2907, 2854, 1739, 1700, and 1665 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.43–2.13 (14 H, m), 2.82 (1 H, dd, $J$ = 6 and 14 Hz), 2.93 (1 H, dd, $J$ = 6 and 14 Hz), 3.08–3.42 (2 H, m), 3.61 (3 H, s), 4.53 (1 H, dd, $J$ = 7 and 14 Hz), 4.67–4.83 (2 H, m), 5.32 (1 H, br s), 6.19 (1 H, br d, $J$ = 6 Hz), 6.74–6.99 (2 H, m), 7.08–7.23 (6 H, m), 7.34 (1 H, d, $J$ = 8 Hz), 7.66 (1 H, d, $J$ = 7 Hz), 8.08 (1 H, s); MS $m/e$ (CI) 544 (100) ($M^+$ + H), 409 (18), 392 (99), 130 (32).

**(*R*)-*N*-[3-(1*H*-Indol-3-yl)-1-thioxo-2-[[(tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl]-(*S*)-phenylalanine, Methyl Ester (16).** The amide **15** (264 mg, 0.486 mmol) and 2,4-bis(phenylthio)-1,3-dithia-2,4-diphosphetane 2,4-disulfide[12] (201 mg, 0.492 mmol) were stirred for 18 h at room temperature in THF (15 mL). The solvent was removed in vacuo, the crude material was placed in a silica gel column, and elution with dichloromethane followed by a dichloromethane–ethyl acetate gradient (2–8%) gave unreacted amide (50 mg, 19%) and the thioamide **16** (194 mg, 71%): $[\alpha]^{20}_D$ = +7.4° ($c$ = 0.97, MeOH); IR (film) 2906, 2855, 1738, 1698, 1499, and 1213 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.44–2.02 (14 H, m), 2.78 (1 H, m), 2.99 (1 H, m), 3.38 (2 H, m), 3.58 (3 H, s), 4.78 (2 H, br s), 5.25 (1 H, m), 5.55 (1 H, br s), 6.58–6.83 (2 H, m), 7.02 (1 H, s), 7.04–7.25 (5 H, m), 7.33 (1 H, d, $J$ = 8 Hz), 7.69 (2 H, m), 8.03 (1 H, s); MS $m/e$ (CI) 560 (100) ($M^+$ + H).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*R**,*S**)]-[2-[[1-(Hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-2-thioxoethyl]carbamate (17).** Lithium aluminum hydride (1.0 M in THF, 750 μL, 0.750 mmol) was added dropwise with stirring to a cooled (ice/salt) solution of **16** (104 mg, 0.186 mmol) in THF (5 mL). After 10 min the reaction was quenched via the cautious addition of 2 N HCl (7.5 mL). The resulting emulsion was extracted with EtOAc (3 × 35 mL). The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by silica gel column chromatography using dichloromethane–ethyl acetate (65:35) as eluant to give **17** (69 mg, 70%) as a white foam; $[\alpha]^{20}_D$ = −42° ($c$ = 0.59, MeOH); IR (film) 2910, 2855, 1694, 1497, and 1214 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.40–2.08 (14 H, m), 2.40 (1 H, m), 2.64 (1 H, m), 3.12–3.64 (5 H, m), 4.58–4.82 (3 H, m), 5.74 (1 H, br s), 7.02 (3 H, m), 7.08–7.27 (5 H, m), 7.35 (1 H, d, $J$ = 8 Hz), 7.64 (1 H, br d, $J$ = 8 Hz), 7.73 (1 H, d, $J$ = 8 Hz), 8.02 (1 H, s); MS $m/e$ (CI) 532 (2%) ($M^+$ + H), 498 (100), 346 (40), 130 (20).

***N*-Methyl-*N*-[*N*-[(tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]-D-tryptophyl]-(*S*)-phenylalanine, Methyl Ester (18).** Acid **3** (808 mg, 2.11 mmol), 1-hydroxybenzotriazole monohydrate (348 mg, 2.58 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (498 mg, 2.41 mmol) were stirred in DMF (2 mL) for 1 h at room temperature, and then *N*-methyl-(*S*)-phenylalanine methyl ester (Bachem) (620 mg, 3.21 mmol) was added. The mixture was stirred for 24 h at room temperature then poured into $H_2O$ (15 mL). The emulsion was extracted with $Et_2O$ (30 mL). The organic phase was washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. The crude material was purified by silica gel chromatography eluting with ether–hexane (70:30) to give **18** as a white foam (720 mg, 61%); $[\alpha]^{20}_D$ = −42° ($C$ = 1.1, $CHCl_3$); IR (film) 2909, 2854, 1741, 1699, and 1641 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.42–2.11 (14 H, m), 2.61 (3 H, s), 2.73–2.98 (3 H, m), 3.29 (1 H, m), 3.70 (3 H, s), 4.77 (1 H, s), 4.95 (1 H, m), 5.34 (1 H, m), 5.55 (1 H, d, $J$ = 8 Hz), 6.54 (1 H, s), 7.01–7.36 (8 H, m), 7.59 (1 H, d, $J$ = 8 Hz), 7.82 (1 H, s); MS $m/e$ (CI) 558 (81%) ($M^+$ + H), 130 (100).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*R**,*S**)]-[2-[[1-(Hydroxymethyl)-2-phenylethyl]methylamino]-1-(1*H*-indol-3-ylmethyl)-2-oxoethyl]carbamate (19).** Lithium borohydride (Aldrich) (2.0 M in THF, 0.50 mL, 1.00 mmol) was added dropwise with stirring to a chilled (ice/salt) solution of **18** (510 mg, 0.915 mmol) in THF (5 mL). After the addition was complete, the cooling bath was removed, and the reaction was stirred at room temperature for 18 h. The solution was then cooled, the reaction was quenched with 2 N HCl (30 mL), and the emulsion was extracted with EtOAc (3 × 30 mL). The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by reverse-phase chromatography using methanol–water (4:1) as eluant to give **19** as an amorphous white solid (100 mg, 20%); $[\alpha]^{23}_D$ = −16° ($c$ = 0.34, MeOH); IR (film) 3311, 2908, 2855, 1694, and 1631 $cm^{-1}$; NMR ($CDCl_3$) (a pair of amide rotamers as determined by saturation transfer experiments: irradiation of $\delta$ 6.67 (s) resulted in transfer of irradiation to $\delta$ 6.93 (s), indicating that these signals arise from rotamers) $\delta$ 1.44–2.14 (14 H, m), 2.41–3.29 (9.5 H, m), 3.60 (1.5 H, m), 4.61 and 4.87 (1 H, 2 m), 4.78 (1 H, s), 5.40 and 5.62 (1 H, 2 d, $J$ = 8 Hz), 6.67 and 6.93 (1 H, 2 s), 6.97–7.48 (8 H, m), 7.59 and 7.81 (1 H, 2 d, $J$ = 7 Hz), 8.18 and 8.53 (1 H, 2 s), MS $m/e$ CI 530 ($M^+$ + H) (100%).

**(±)-α-(Hydroxymethyl)benzenepropanoic Acid (20).** Diisopropylamine (28 mL, 0.20 mol) was dissolved in THF (300 mL), cooled to −70 °C, and treated with *n*-butyllithium (1.6 M in hexane, 125 mL, 0.20 mol). After stirring for 20 min at 0 °C, hydrocinnamic acid (14.3 g, 95.2 mmol) was added and the mixture was stirred for a further 15 min at 20 °C. Then formaldehyde gas [generated by heating paraformaldehyde (10.1 g) at 180–220

°C over 1 h] was passed into the mixture which was kept between 5–15 °C. After a further 10 h, the mixture was acidified with dilute aqueous HCl and extracted with ether (3 × 100 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a solid, which was recrystallized from ether to give **20** (9.2 g, 54%); IR (film) 3600–2400 and 1709 $cm^{-1}$; NMR (DMSO-$d_6$) δ 2.62 (1 H, m, C*H*COOH), 2.78 (2 H, m, PhC$H_2$), 3.40 (2 H, m, C$H_2$OH), 4.0–3.0 (1 H, br, COOH), 7.20 (5 H, m, Ph); MS (FAB) *m/e* 179 (60) and 127 (100).

**(±)-α-[(Acetyloxy)methyl]benzenepropanoic Acid (21).** Acetyl chloride (904 μL, 12.7 mmol) was added dropwise to a cooled (ice bath) solution of racemic 2-benzyl-3-hydroxypropionic acid (1 equiv) (**20**) in THF (10 mL). The solution was allowed to warm to room temperature and stirred for 48 h. The solvent was removed in vacuo, and the crude material was purified by silica gel chromatography using toluene–acetic acid (90:10) as eluant to give **21** as a viscous oil (2.04 g, 86%): IR (film) 1742 and 1714 $cm^{-1}$; NMR (acetone-$d_6$) δ 1.98 (3 H, s), 2.81–2.94 (1 H, m), 2.96–3.09 (2 H, m), 4.10–4.23 (2 H, m), 7.16–7.32 (5 H, m); MS (CI) *m/e* 240 (100%) ($M^+ + NH_4^+$), 223 (42), ($M^+$ + H), 222 (13) ($M^+$), 204 (4), 162 (2), 91 (4).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-[(2-phenylethyl)amino]ethyl]carbamate (24).** To a solution of lithium borohydride (4 mL, 2 M solution, 8 mmol) in THF was added a solution of chlorotrimethylsilane (1.75 g, 16.0 mmol) in THF (5 mL). A white precipitate (of lithium chloride) was observed. After 2 min, a solution of **23**[7a] (1 g, 2 mmol) in THF (15 mL) was added slowly (over 3–4-min period), and the reaction mixture was stirred for 20 h at ambient temperature. The reaction was treated cautiously with MeOH (5 mL), and the volatiles were removed in vacuo at 40 °C. The residue was purified by silica gel chromatography using hexane–EtOAc (80:20) as eluant to give **24** as a colorless oil (0.14 g, 14%) and recovered **23** (0.52 g; yield of **24** was based on recovered starting material 30%). The amine **24** (0.14 g, 0.28 mmol) was dissolved in MeOH (5 mL) and treated with 4-toluenesulfonic acid hydrate (0.054 g, 0.28 mmol). The solution was evaporated to leave a white solid (0.19 g, 0.28 mmol): $[\alpha]^{20}_D$ = +22° (*c* = 0.25, MeOH); IR (film) 2928 and 1708 $cm^{-1}$ (C=O urethane); NMR (DMSO-$d_6$) δ 1.2 (3 H, s, $CH_3$), 1.4–2.1 (14 H, m, adamantyl), 2.3 (3 H, s, PhC$H_3$), 2.9–3.7 (8 H, m, 4 × C$H_2$), 4.7 (1 H, br s, adamantyl H-2), 6.9–7.6 (15 H, m, aromatics, urethane NH), 8.3 (1 H, br, one of $NH_2^+$), 8.5 (1 H, br, one of $NH_2^+$), 11.0 (1 H, s, indole NH); MS *m/e* (FAB) 486 (100) ($M^+$ + H), 136 (52).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*R**,*S**)]-[2-[Acetyl(2-phenylethyl)amino]-1-(1*H*-indol-3-ylmethyl)-1-methylethyl]carbamate (25).** To a solution of **24** (0.1 g, 0.2 mmol) in dichloromethane (20 mL) at 0 °C was added acetyl chloride (0.3 mL, 4 mmol), followed by triethylamine (0.2 mL, 1.4 mmol). Stirring was continued at 0 °C for 20 min, and then the reaction mixture was dissolved in ethyl acetate (50 mL), washed (dilute HCl, then $H_2O$, and then aqueous $NaHCO_3$), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by column chromatography using hexane–ethyl acetate (70:30) as eluant to give an off-white solid (0.092 g, 85%): $[\alpha]^{21}_D$ = +24° (*c* = 0.25, $CHCl_3$); IR (film) 2909, 2855, 1709, and 1610 $cm^{-1}$; NMR ($CDCl_3$) δ 1.3 (3 H, s), 1.4–2.1 (17 H, m), 2.8 (2 H, m), 3.1 (1 H, d, *J* = 14 Hz), 3.3–3.7 (4 H, m), 4.0 (1 H, d, *J* = 14 Hz), 4.8 (1 H, s), 5.5 (1 H, br s), 6.9–7.7 (10 H, m), 8.1 (1 H, br s); MS *m/e* (FAB) 528 (45) ($M^+$ + H), 397 (100), 333 (27).

**Ethyl (*R*)-4-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[(tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl](2-phenylethyl)amino]-4-oxobutanoate (26).** Prepared by a method similar to that for compound **25**. Obtained **26** as a white solid (0.102 g, 81%): $[\alpha]^{21}_D$ = +26° (*c* = 0.5, $CHCl_3$); IR (film) 2905, 2853, 1732, 1711, and 1634 $cm^{-1}$; NMR ($CDCl_3$) δ 1.2 (6 H, m), 1.3–2.1 (14 H, m), 2.6 (4 H, br s), 2.9 (2 H, m), 3.0 (1 H, d, *J* = 14 Hz), 3.3–3.8 (4 H, m), 4.0–4.2 (3 H, m), 4.8 (1 H, br s), 5.3 (1 H, br), 6.9–7.6 (10 H, m), 8.1 (1 H, br s); MS *m/e* (FAB) 614 (36) ($M^+$ + H), 483 (100), 419 (24).

**Ethyl (*R*)-7-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[(tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl](2-phenylethyl)amino]-7-oxoheptanoate (27).** Prepared by a method similar to that for compound **25**. (Ethyl pimelyl chloride was prepared from monoethyl pimelate and oxalyl chloride.) Obtained **27** as a white solid (0.092 g, 68%): $[\alpha]^{20}_D$ = +12° (*c* = 0.25, $CHCl_3$); IR (film) 2929, 2855, 1730 (sh), 1712, and 1631 $cm^{-1}$; NMR ($CDCl_3$) δ 1.2–2.3 (30 H, m), 2.8 (2 H, m), 3.1 (1 H, d, *J* = 14 Hz), 3.3–3.7 (4 H, m), 4.0–4.2 (3 H, m), 4.8 (1 H, br), 5.6 (1 H, br), 6.9–7.4 (9 H, m), 7.6 (1 H, d, *J* = 8 Hz), 8.1 (1 H, br); MS *m/e* (FAB) 656 (40) ($M^+$ + H), 525 (100), 461 (28).

**(*R*)-4-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[(tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]amino]propyl](2-phenylethyl)amino]-4-oxobutanoic Acid (28).** To a stirred solution of **26** (0.04 g, 0.06 mmol) in THF (5 mL) were added methanol (5 mL), water (5 mL), and lithium hydroxide monohydrate (0.1 g, 2.4 mmol). The reaction mixture was stirred for 40 min at ambient temperature and then acidified (2 N HCl, 50 mL), and the products were extracted into ethyl acetate (50 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo (40 °C). The oily residue was purified by column chromatography using dichloromethane/methanol (9:1) as eluant to give **28** (0.031 g, 81%) as a white solid: IR (film) 3400 (br), 2912, 2852, 1714, 1700, and 1635 $cm^{-1}$; NMR (MeOH-$d_4$) δ 1.1–2.2 (17 H, m, $CH_3$, adamantane), 2.6–3.2 (6 H, m, 3 × $CH_2$), 3.4–4.1 (6 H, m, 3 × $CH_2$), 4.8 (1 H, br, adamantane H-2), 7.0–7.6 (10 H, m, aromatics); $[\alpha]^{22}_D$ = +4° (*c* = 0.2, MeOH); MS *m/e* (FAB) 586 (51) ($M^+$ + H), 455 (100), 391 (24).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[1-(1*H*-Indol-3-ylmethyl)-2-methyl-2-[(2-phenylethyl)amino]-2-thioxoethyl]carbamate (29).** To a solution of **23**[7a] (0.1 g, 0.2 mmol) in toluene (10 mL) was added Lawesson's reagent (0.10 g, 0.25 mmol), and the mixture was heated to reflux for 1 h. The mixture was allowed to cool to ambient temperature and was purified by silica gel chromatography using $CH_2Cl_2$ followed by ether as eluant to give **29** as a white foam (0.065 g, 63%): $[\alpha]^{22}_D$ = +40° (*c* = 0.3, $CHCl_3$); IR (film) 2916, 1703 (C=O urethane), and 1520 (C—S) $cm^{-1}$; NMR ($CDCl_3$) δ 1.5 (3 H, s, $CH_3$), 1.6–2.0 (14 H, m, adamantane), 2.6 (2 H, m, $CH_2$Ph), 3.4 (1 H, d, *J* = 14 Hz, one of $CH_2$-indole), 3.6 (1 H, d, *J* = 14 Hz, one of $CH_2$-indole), 3.8 (2 H, m, $CH_2$N), 4.7 (1 H, br, adamantane H-2), 5.3 (1 H, br, urethane NH), 6.9–7.5 (9 H, m, indole H-5, H-6, H-7, H-2, phenyl), 7.6 (1 H, d, *J* = 8 Hz, indole H-4), 7.8 (1 H, br, thioamide NH), 8.1 (1 H, br, indole NH); MS *m/e* (FAB) 516 (25) ($M^+$ + H), 217 (95), 109 (100).

**α-Methyl-*N*-[(tricyclo[3.3.1.1$^{3,7}$]dec-2-yloxy)carbonyl]-(*R*)-tryptophan, 2-phenylethyl ester (30)** was prepared and purified by a method similar to that for compound **36**: yield 103 mg (85%); $[\alpha]^{22}_D$ = +13.6° (*c* = 1, MeOH); IR (film) 3412 (NH), 2907, 2855, 1730 (C=O ester), and 1698 (C=O urethane) $cm^{-1}$; NMR ($CDCl_3$) δ 1.50 (1 H, s, adamantyl CH), 1.56 (4 H, s, $CCH_3$, adamantyl CH), 1.70–2.05 (12 H, m, adamantyl CH), 2.87 (2 H, t, *J* = 7 Hz, $CH_2CH_2$Ph), 3.32 (1 H, d, *J* = 14.5 Hz, one of $CH_2$-indole), 3.45–3.55 (1 H, m, one of $CH_2$-indole), 4.18 (1 H, dt, *J* = 7, 11 Hz, one of $OCH_2$), 4.28–4.38 (1 H, m, one of $OCH_2$), 4.84 (1 H, s, C*H*OCONH), 5.3–5.5 (1 H, br s, OCON*H*), 6.79 (1 H, s, indole H-2), 7.05 (1 H, t, *J* = 7 Hz), 7.10–7.33 (7 H, m), 7.47 (1 H, d, *J* = 8 Hz, indole H-4), 8.00 (1 H, s, indole NH); MS *m/e* (FAB) 501 (30) ($M^+$ + H), 217 (84), 130 (100).

**Tricyclo[3.3.1.1$^{3,7}$]dec-3-yl (*R*)-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(2-phenylethyl)thio]ethyl]carbamate (31)** was prepared and purified by a method similar to that for compound **36**: yield 196 mg (57%); $[\alpha]^{21}_D$ = +47° (*c* = 0.5, MeOH); IR (film) 3500–3300, 2906, 2854, and 1698 $cm^{-1}$; NMR ($CDCl_3$) δ 1.50 (1 H, s, adamantyl CH), 1.53 (4 H, s, $CCH_3$, adamantyl), 1.70–2.05 (12 H, m, adamantyl), 2.84 (2 H, t, *J* = 8 Hz, $CH_2$Ph), 3.08–3.14 (2 H, m, $CH_2CH_2$Ph), 3.30 (1 H, d, *J* = 14 Hz, one of $CH_2$-indole), 3.56 (1 H, d, *J* = 14 Hz, one of $CH_2$-indole), 4.87 (1 H, s, C*H*OCONH), 5.00–5.20 (1 H, br s, OCONH), 6.97 (1 H, d, *J* = 2 Hz, indole CH), 7.10 (1 H, t, *J* = 7 Hz, indole CH), 7.15–7.32 (6 H, m, Ph, indole CH), 7.35 (1 H, d, *J* = 8 Hz, indole CH), 7.59 (1 H, d, *J* = 8 Hz, indole CH), 8.10 (1 H, s, indole NH); MS *m/e* (FAB) 517 (11) ($M^+$ + H), 379 (55), 351 (39), 307 (100).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-[methyl(2-phenylethyl)amino]-2-oxoethyl]carbamate (32)** was prepared and purified by a method similar to that for compound **36**: yield 50 mg (61%); $[\alpha]^{21}_D$ = +67.2° (*c* = 0.5, MeOH); IR (film) 3500–3200, 2907, 2855, 1698 (C=O urethane), and 1625 (C=O amide) $cm^{-1}$; NMR (DMSO-$d_6$) (340 K) δ 1.30 (3 H, s, $CCH_3$), 1.40–1.55 (2 H, m, adamantyl), 1.65–2.05 (12 H, m, adamantyl), 2.70–2.80 (2 H, m, $CH_2$Ph), 2.99 (3 H, s, $NCH_3$), 3.20 (1 H, d, *J* = 15 Hz, one of $CH_2$-indole), 3.44 (1 H, d, *J* = 15 Hz, one of $CH_2$-indole), 3.40–3.70 (2 H, m,

$CH_2CH_2NHCO$), 4.74 (1 H, s, CHOCONH), 6.90–7.05 (4 H, m), 7.15–7.30 (5 H, m), 7.31 (1 H, d, $J$ = 8 Hz, indole 7-H), 7.43 (1 H, d, $J$ = 8 Hz, indole 4-H), 10.65 (1 H, s, indole NH); MS $m/e$ (FAB) 514 (66) ($M^+ + H$), 379 (76), 318 (32), 173 (34), 135 (100).

**Methyl (*R*)-4-[(2-Hydroxy-1-phenylethyl)amino]-4-oxobutanoate (33).** Prepared by a route similar to that for compound **35**. Recovered 3.6 g (65%) of **33**: $[\alpha]^{22}_D$ = −53° ($c$ = 1, $CHCl_3$); IR (film) 3250 (OH), 1737 (C=O ester), and 1651 (C=O amide) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.7 (1 H, br, OH), 2.5–2.8 (6 H, m, 3 × $CH_2$), 3.7 (2 H, s, $CH_3$), 5.1 (1 H, m, CH), 6.4 (1 H, br d, NH), 7.2–7.4 (5 H, m, Ph); MS $m/e$ (FAB) 252 (100) ($M^+ + H$), 225 (23), 115 (26).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl 3-(1*H*-Indol-3-ylmethyl)-3-methyl-4,9-dioxo-7-phenyl-5,13-dioxa-2,8-diazatetradecanoate (34).** To a solution of 1,3-dicyclohexylcarbodiimide (0.3 g, 1.5 mmol) and 4-(dimethylamino)pyridine (0.05 g, 0.40 mmol) in $CH_2Cl_2$ (40 mL) was added **22** (0.50 g, 1.3 mmol). After stirring for 20 min at ambient temperature, **33** (0.30 g, 1.2 mmol) was added and the reaction was heated at reflux for 2 h. The volatiles were removed in vacuo at 40 °C, and the residue was purified by silica gel chromatography, using hexane–EtOAc as eluant to give **34** as a white solid (0.41 g, 52%): $[\alpha]^{22}_D$ = −18° ($c$ = 1, $CHCl_3$); IR (film) 2920, 1739 (C=O ester), 1700 (C=O urethane), and 1660 (C=O amide) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.5–2.1 (17 H, m, adamantane, $CH_3$), 2.5–2.7 (4 H, m, 2 × $CH_2$), 3.4 (2 H, m, $CH_2$-indole), 3.7 (3 H, s, $CH_3$), 4.1 (1 H, m, one of $CH_2O$), 4.8 (2 H, br, adamantane H-2, one of $CH_2O$), 5.2 (1 H, br s, urethane NH), 5.3 (1 H, m, OH), 6.9–7.4 (10 H, m, indole H-5, H-6, H-7, H-2, amide NH, phenyl), 7.5 (1 H, d, $J$ = 8 Hz, indole H-4), 8.3 (1 H, br, indole NH); MS $m/e$ (FAB) 631 (11) ($M^+ + H$), 307 (10), 252 (12), 234 (100).

**Methyl (*R*)-4-[(2-Hydroxy-1-phenylethyl)amino]-4-oxo-2-butenoate (35).** To a solution of monomethyl fumarate (3.0 g, 23 mmol) in EtOAc (40 mL) was added 1-hydroxybenzotriazole hydrate (3.4 g, 22 mmol), followed by *N*,*N*′-dicyclohexylcarbodiimide (4.5 g, 22 mmol), and the reaction was stirred at ambient temperature for 1 h. The solid was filtered off and discarded. To the filtrate was added (*R*)-α-phenylglycinol (3.0 g, 22 mmol), and stirring was continued for 20 min. The volatiles were removed in vacuo at 40 °C, and the residue was purified by silica gel chromatography using hexane–EtOAc (1:1) as eluant to give the amide **35** as a white solid (2.5 g, 46%): $[\alpha]^{24}_D$ = −53° ($c$ = 1, $CHCl_3$); IR (film) 3250 (OH), 1729 (C=O ester), 1666 (C=O amide), and 1640 (C=C) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.3 (1 H, t, $J$ = 5 Hz, OH), 3.8 (3 H, s, $CH_3$), 3.9 (2 H, t, $J$ = 3 Hz, $CH_2$), 5.2 (1 H, m, CH), 6.6 (1 H, br d, NH), 6.8 (1 H, d, $J$ = 15 Hz, trans alkene), 7.0 (1 H, d, $J$ = 15 Hz, trans alkene), 7.3–7.4 (5 H, m, Ph); MS $m/e$ (FAB) 250 (100) ($M^+ + 1$).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl 3-(1*H*-Indol-3-ylmethyl)-3-methyl-4,9-dioxo-7-phenyl-5,13-dioxa-2,8-diazatetradec-10-enoate (36).** To a solution of *N*,*N*′-carbonyldiimidazole (0.15 g, 0.90 mmol) in $CH_2Cl_2$ (40 mL) was added compound **22**[1] (0.25 g, 0.63 mmol). After 20 min of stirring at ambient temperature, **35** (0.2 g, 0.8 mmol) was added and the reaction was heated at reflux for 10 h. After cooling to ambient temperature, the volatiles were removed in vacuo at 40 °C, and the residue was purified by silica gel chromatography using hexane–EtOAc (70:30) as eluant to give **36** as a white solid (0.28 g, 71%): $[\alpha]^{24}_D$ = +25° ($c$ = 0.2, $CHCl_3$); IR (film) 2910, 1730 (C=O ester), 1695 (C=O urethane), and 1670 (C=O amide) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.4–2.1 (18 H, m, adamantane, $CH_3$), 3.3 (1 H, d, $J$ = 14 Hz, one of $CH_2$-indole), 3.5 (1 H, d, $J$ = 14 Hz, one of $CH_2$-indole), 3.8 (3 H, s, $CH_3$), 4.1 (1 H, dd, $J$ = 4, 11 Hz, one of $CH_2O$), 4.8 (1 H, br s, adamantane H-2), 5.0 (1 H, br, CH), 5.1 (1 H, s, urethane NH), 5.3 (1 H, br, one of $CH_2O$), 6.8 (1 H, d, $J$ = 16 Hz, trans alkene CH), 6.9–7.3 (10 H, m, indole H-6, H-7, H-2, phenyl, amide NH, one of alkene CH), 7.4 (1 H, d, $J$ = 8 Hz, indole H-5), 7.5 (1 H, d, $J$ = 8 Hz, indole H-4), 8.3 (1 H, br, indole NH); MS $m/e$ (FAB) 628 (27) ($M^+ - H$), 232 (38), 130 (100).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[2-Hydroxy-1-(1*H*-indol-3-ylmethyl)-1-methylethyl]carbamate (38).** To a solution of **37**[1] (1.0 g, 2.4 mmol) in THF (20 mL) at 0 °C was added a solution of lithium aluminum hydride in ether (3 mL of a 1 M solution, 3 mmol), and the reaction was stirred for 20 min. EtOAc (20 mL) was added slowly, and the resulting solution was washed with acid (2 N HCl, 2 × 100 mL), dried ($MgSO_4$), and evaporated to dryness to give **38** as a white solid (0.85 g, 91%): $[\alpha]^{22}_D$ = +42° ($c$ = 1, $CHCl_3$); IR (film) 2918 and 1693 (C=O urethane) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.2 (3 H, s, $CH_3$), 1.5–2.1 (14 H, m, adamantane), 3.0 (1 H, d, $J$ = 14 Hz, one of $CH_2$-indole), 3.25 (1 H, d, $J$ = 14 Hz, one of $CH_2$-indole), 3.8 (2 H, m, $CH_2O$), 4.0 (1 H, br, OH), 4.8 (1 H, br, adamantane H-2), 4.85 (1 H, br s, urethane NH), 7.0–7.2 (3 H, m, indole H-6, H-7, H-2), 7.35 (1 H, d, $J$ = 8 Hz, indole H-5), 7.6 (1 H, d, $J$ = 8 Hz, indole H-4), 8.1 (1 H, br, indole NH); MS $m/e$ (FAB) 383 (50) ($M^+ + H$) 252 (45) 135 (100).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[1-Formyl-2-(1*H*-indol-3-yl)-1-methylethyl]carbamate (39).** To a solution of **38** (0.03 g, 0.08 mmol) in $CH_2Cl_2$ (40 mL) at ambient temperature was added *N*-methylmorpholine *N*-oxide (0.1 g, 0.9 mmol), molecular sieves (4A activated powder, 0.5 g) and tetra-*n*-propylammonium perruthenate (TPAP) (0.01 g, 0.03 mmol). After stirring for 30 min, the solid was removed by filtration, and then the volatiles were removed in vacuo (40 °C). The residue was dissolved in EtOAc and purified by silica gel chromatography using hexane–EtOAc (95:5) as eluant to give **39** as a white foam (0.2 g, 67%): $[\alpha]^{22}_D$ = +22° ($c$ = 1, $CHCl_3$); IR (film) 2900, 1732 (C=O aldehyde), and 1692 (C=O urethane) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.3–2.1 (17 H, m, adamantane, $CH_3$), 3.3 (2 H, br, $CH_2$-indole), 4.8 (1 H, s, adamantane H-2), 5.2 (1 H, br, urethane NH), 6.9–7.6 (5 H, m, indole), 8.1 (1 H, br s, indole NH), 9.6 (1 H, s, CHO); MS $m/e$ (FAB) 381 (26) (M + H), 363 (45), 264 (100), 229 (74).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*Z*)]-[1-(1*H*-Indol-3-ylmethyl)-1-methyl-5-phenyl-2-pentenyl]carbamate (40).** A mixture of triphenylphosphine (0.35 g, 1.3 mmol) and 1-bromo-3-phenylpropane (0.27 g, 1.3 mmol) was heated to 110 °C at which point the molten reactants solidified. On cooling to ambient temperature and triturating with hexane a white solid was removed (0.4 g, 65%). This was added to a suspension of sodium hydride (50 mg of 50% in oil dispersion, 1 mmol) in toluene (40 mL), and the reaction was heated to reflux for 20 min. The aldehyde **39** (0.2 g, 0.5 mmol) was added, and heating was continued for 1 h. The volatiles were removed in vacuo, and the residue was purified by silica gel chromatography using EtOAc as eluant to give **40** as a white solid (0.20 g, 79%): $[\alpha]^{23}_D$ = +1.5° ($c$ = 1, $CHCl_3$); IR (neat) 2904, 1696 (C=O urethane), 1683 (C=C) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.4 (3 H, s, $CH_3$), 1.4–2.1 (14 H, m, adamantane), 2.4–2.6 (4 H, m, 2 × $CH_2$), 3.1 (1 H, d, $J$ = 14 Hz, one of $CH_2$-indole), 3.3 (1 H, d, $J$ = 14 Hz, one of $CH_2$-indole), 4.8 (2 H, m, urethane NH, adamantane H-2), 5.4 (1 H, dt, $J$ = 5, 12 Hz, CH=C*H*—$CH_2$), 5.6 (1 H, d, $J$ = 12 Hz, C*H*=$CHCH_2$), 6.9 (1 H, s, indole H-2), 7.0–7.3 (8 H, m, indole H-5, H-6, H-7, phenyl), 7.6 (1 H, d, $J$ = 8 Hz, indole H-4), 8.3 (1 H, s, indole NH); MS $m/e$ (FAB) 483 (5) ($M^+$), 352 (99), 288 (99), 135 (100).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl (*R*)-[1-(1*H*-Indol-3-ylmethyl)-1-methyl-5-phenylpentyl]carbamate (41).** A solution of **40** (0.3 g, 0.6 mmol) in EtOH (20 mL) was treated with 10% Pd/C (0.01 g, 1 mmol) and hydrogen gas at 40 psi for 16 h. After removal of the catalyst by filtration through Kieselguhr, the solvent was removed in vacuo and the residue was purified by silica gel chromatography using hexane–ether (90:10) as eluant to give **41** as a white glassy solid (0.25 g, 83%): $[\alpha]^{22}_D$ = +30° ($c$ = 0.5, $CHCl_3$); IR (film) 2916 and 1698 (C=O urethane) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.2 (3 H, s, $CH_3$), 1.4–2.1 (20 H, m, adamantane, 3 × $CH_2$), 2.6 (2 H, t, $J$ = 8 Hz, $CH_2Ph$), 3.0 (1 H, d, $J$ = 14 Hz, one of $CH_2$-indole), 3.2 (1 H, d, $J$ = 14 H, one of $CH_2$-indole), 4.5 (1 H, br, urethane NH), 4.8 (1 H, br, adamantane H-2), 6.9 (1 H, d, $J$ = 2 Hz, indole H-2), 7.0–7.3 (8 H, m, indole H-5, H-6, H-7, phenyl), 7.6 (1 H, d, $J$ = 8 Hz, indole H-4), 8.2 (1 H, br, indole NH); MS $m/e$ (FAB) 485 (3) ($M^+ + H$), 354 (38), 310 (45), 290 (58), 135 (100).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [2-Hydroxy-1-(1*H*-indol-3-ylmethyl)-1-methyl-5-phenylpentyl]carbamate (42, 43).** To a stirred mixture of magnesium turnings (0.5 g, 21 mmol) and dry ether (20 mL) at 0 °C were addded 1-bromo-3-phenylpropane (0.2 mL, 1.3 mmol) and iodine (1 crystal). After a short induction period, a vigorous exothermic reaction was observed. When this reaction had subsided, the supernatant was removed by syringe and was added to a solution of **39** (0.3 g, 0.8 mmol) in ether (40 mL) at 0 °C. After 20 min, the reaction was warmed to ambient temperature and quenched (2 N HCl, 50 mL), and the products were extracted into EtOAc (2 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was

purified by silica gel chromatography using hexane–ether (70:30) as eluant to give **42** and **43**. Diastereoisomer I as a white solid (0.15 g, 38%): $[\alpha]^{22}_D = +69°$ ($c = 0.5$, $CHCl_3$); IR (film) 2910 and 1687 (C=O urethane) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.3 (4 H, m, 2 × $CH_2$), 1.4–2.1 (17 H, m, adamantane, $CH_3$), 2.7 (2 H, m, $CH_2Ph$), 3.1 (1 H, d, $J = 14$ Hz, one of $CH_2$-indole), 3.5 (1 H, d, $J = 14$ Hz, one of $CH_2$-indole), 3.6 (1 H, m, CH), 4.6 (1 H, br, OH), 4.7 (1 H, s, urethane NH), 4.8 (1 H, s, adamantane H-2), 7.0–7.4 (9 H, m, indole H-5, H-6, H-7, H-2, phenyl), 7.6 (1 H, d, $J = 8$ Hz, indole H-4), 8.2 (1 H, s, indole NH), MS $m/e$ (FAB) 501 (17) ($M^+ + H$), 135 (100), 130 (99). Diastereoisomer II as a white solid (0.18 g, 46%): $[\alpha]^{22}_D = +43°$ (22 °C, $c = 0.5$, $CHCl_3$); IR (film) 2912 and 1690 (C=O urethane) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.3 (4 H, m, 2 × $CH_2$), 1.5–2.1 (17 H, m, adamantane, $CH_3$), 2.7 (2 H, m, $CH_2Ph$), 2.9 (1 H, d, $J = 14$ Hz, one of $CH_2$-indole), 3.2 (1 H, d, $J = 14$ Hz, one of $CH_2$-indole), 3.8 (1 H, m, CH), 4.0 (1 H, br, OH), 4.7 (1 H, s, urethane NH), 4.8 (1 H, s, adamantane H-2), 6.9–7.4 (9 H, m, indole H-5, H-6, H-7, H-2, phenyl), 7.6 (1 H, d, $J = 8$ Hz, indole H-4), 8.1 (1 H, br, indole NH); MS $m/e$ (FAB) 501 (12) ($M^+ + H$), 370 (30), 135 (100), 130 (99).

**Tricyclo[3.3.1.1$^{3,7}$]dec-2-yl [*R*-(*R**,*S**)]-[1-[4,5-Dihydro-4-(phenylmethyl)-2-thiazolyl]-2-(1*H*-indol-3-yl)-1-methylethyl]carbamate (45).** To a solution of **44**[7a] (0.1 g, 0.2 mmol) in toluene (10 mL) was added Lawesson's reagent (0.10 g, 0.25 mmol), and the mixture was heated at reflux for 1 h. The reaction mixture was allowed to cool to ambient temperature and was purified by silica gel chromatography using $CH_2Cl_2$–ether as eluant to give **45** as a white solid (0.07 g, 70%): $[\alpha]^{22}_D = -20°$ ($c = 0.5$, $CHCl_3$); IR (film) 2910, 1697 (C=O urethane), and 1620 (C=N) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.3 (3 H, s, $CH_3$), 1.4–2.1 (14 H, m, adamantane), 2.2 (1 H, br, one of $CH_2Ph$), 2.8 (1 H, br, one of $CH_2Ph$), 2.9 (1 H, m, one of $CH_2S$), 3.2 (1 H, m, one of $CH_2S$), 3.4 (1 H, d, $J = 14$ Hz, one of $CH_2$-indole), 3.7 (1 H, d, $J = 14$ Hz, one of $CH_2$-indole), 4.6 (1 H, m, CH), 4.9 (1 H, br, adamantane H-2), 5.8 (1 H, br, urethane NH), 6.9–7.4 (9 H, m, indole H-5, H-6, H-7, H-2, phenyl), 7.7 (1 H, d, $J = 8$ Hz, indole H-4), 8.1 (1 H, br, indole NH); MS $m/e$ (FAB) 529 (47) ($M^+ + H$), 398 (44), 130 (100).

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# *Communications to the Editor*

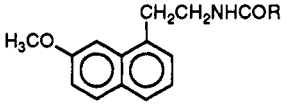
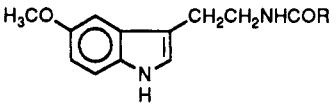
## Novel Naphthalenic Ligands with High Affinity for the Melatonin Receptor

### Introduction

The neurohormone melatonin (5-methoxy-*N*-acetyltryptamine), which is synthesized principally in the pineal gland, is putatively involved in several physiological axes. These include the entrainment of both seasonal (reproduction)[1] and circadian (activity)[2] rhythms. The role of melatonin in the human is still controversial, but it is thought to be involved in the regulation of sleep,[3,4] seasonal disorders,[4] depression,[4] and ageing.[5] The lack of rigorous data in this regard has often led to conflicting and confusing reports.[4] Nevertheless, the localization of 2-[$^{125}$I]-iodomelatonin binding sites in the suprachiasmatic nucleus (SCN) of the human hypothalamus,[6] which is the biological clock of the brain, enhances the argument for a physiological role in man.

The recent development of a radioligand binding assay for melatonin receptors using ovine pars tuberalis membranes of the pituitary enables the rapid screening of melatonin analogues for their receptor binding potency.[7]

**Table I.** Structure Binding Characteristics of 2-(7-Methoxy-1-naphthyl)ethylamides for the Melatonin Receptor

| compd | R | mp, °C | $K_d$:[a] mean ± SEM | order of potency |
|---|---|---|---|---|
| |  | | | |
| **5** | $CH_3$ | 109–110 | $(1.00 \pm 0.353) \times 10^{-10}$ | 7 |
| **6** | $CH_2CH_3$ | 103 | $(2.19 \pm 0.897) \times 10^{-11}$ | 5 |
| **7** | $(CH_2)_2CH_3$ | 96–97 | $(6.15 \pm 0.178) \times 10^{-12}$ | 4 |
| **8** | $(CH_2)_3CH_3$ | 90 | $(3.43 \pm 2.430) \times 10^{-12}$ | 3 |
| **9** | $(CH_2)_4CH_3$ | 84–85 | $(2.83 \pm 0.211) \times 10^{-7}$ | 12 |
| **10** | $(CH_2)_5CH_3$ | 68–70 | $(2.33 \pm 0.815) \times 10^{-6}$ | 15 |
| **11** | isopropyl | 77–78 | $(2.29 \pm 0.745) \times 10^{-9}$ | 8 |
| **12** | $CH{=}CHCH_3$ | 119–120 | $(8.47 \pm 0.793) \times 10^{-9}$ | 9 |
| **13** | cyclopropyl | 91–92 | $(4.18 \pm 0.870) \times 10^{-13}$ | 1 |
| **14** | cyclobutyl | 75–76 | $(2.42 \pm 0.536) \times 10^{-8}$ | 10 |
| **15** | cyclohexyl | 105–106 | $(1.59 \pm 0.792) \times 10^{-7}$ | 11 |
| **16** | benzyl | 101–102 | $(1.95 \pm 0.397) \times 10^{-6}$ | 14 |
| **17** | phenyl | 128–130 | $(4.99 \pm 4.360) \times 10^{-6}$ | 16 |
| **18** | $C_6H_3Cl_2$(*m*) | 138 | $(1.13 \pm 0.856) \times 10^{-5}$ | 17 |
| **19** | 2-indolyl | 198–199 | $(1.17 \pm 0.781) \times 10^{-6}$ | 13 |
| |  | | | |
| melatonin | $CH_3$ | 116–118 | $(9.15 \pm 3.980) \times 10^{-11}$ | 6 |
| **20** | cyclopropyl | 101–102 | $(4.97 \pm 0.928) \times 10^{-13}$ | 2 |

[a] $K_d$'s are the means of three independent experiments, calculated as inverse $K_a$'s from single-site fit of untransformed data to equations describing the law of mass action,[10] using a $K_a$ for 2-[$^{125}$I]iodomelatonin of $3.3 \times 10^{10}$ L/mol. The protocol for the synthesis and purification of the radioligand 2-[$^{125}$I]iodomelatonin and the receptor-binding assay using ovine pars tuberalis membranes were as described previously.[7]

Fifteen naphthalenic bioisosteres of melatonin with variations on the *N*-acylamino group have been synthesized.

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