Rationally Designed "Dipeptoid" Analogues of CCK. Acid Mimics of the Potent and Selective Non-Peptide CCK-B Receptor Antagonist CI-988

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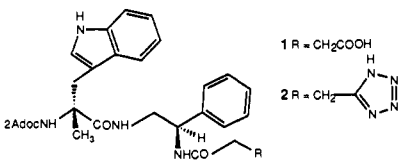
This paper outlines the synthesis of selected acid mimics of the non-peptide CCK-B selective antagonist CI-988, 1. CCK-B and CCK-A binding affinities of these analogues are described and their CCK-B affinity and selectivity rationalized by consideration of the pK_a values, charge distribution, and geometry of the respective acid mimics. Several of the compounds have CCK-B binding affinities similar to the parent carboxylic acid 1 (CCK-B, IC_{50} = 1.7 nM; pK_a = 5.6) and span a pK_a range of <1 (sulfonic acid **27**) to >9.5 (5-thio-1,2,4-triazole **24**). Among the more active compounds synthesized are tricyclo[3.3.1.1^{3,7}]dec-2-yl [*R*-(*R**,*R**)]-[2-[[2-[[(3-hydroxy-5-isoxazolyl)acetyl]-amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate (**15**), tricyclo[3.3.1.1^{3,7}]dec-2-yl [*R*-(*R**,*R**)]-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[(1-oxo-3-sulfopropyl)amino]-2-phenylethyl]amino]-ethyl]carbamate, monosodium salt (**27**), and tricyclo[3.3.1.1^{3,7}]dec-2-yl [*R*-(*R**,*R**)]-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[[(1*H*-1,2,4-triazol-5-ylsulfinyl)acetyl]amino]-2-phenylethyl]amino]ethyl]carbamic acid (**34**) which have CCK-B binding affinities of IC_{50} = 2.6, 1.3, and 1.7 nM, CCK-A/-B ratios of 650, 780, and 550 and pK_a values of 6.5, <1, and 7.0, respectively.

Introduction

Cholecystokinin (CCK) belongs to a group of peptide messengers which are found in the central nervous system as well as in the gastrointestinal tract.[1] Previous approaches to the discovery of non-peptide ligands for CCK as well as other peptide receptors and peptidases have relied on mass screening of compound collections or natural products for the identification of lead compounds.[2] These approaches have led to the development of both CCK-A[3] and CCK-B[4,5] selective antagonists, substance P antagonists,[6,7] angiotensin II antagonists,[8,9] and vasopressin antagonists.[10]

We have recently described the rational design and synthesis of a series of potent and selective non-peptide CCK-B receptor antagonists[11-14] using the structure of the endogenous neuropeptide CCK-26-33 (sulfated) as our lead compound. These "dipeptoid" compounds, e.g. 1 (CI-988), were shown to display both antianxiety[15] and antigastrin[16] properties. Structure–activity relationship studies[14] have shown that the presence of a carboxylic acid moiety in R enhances both affinity and selectivity for the CCK-B receptor. The carboxylic acid group is proposed to mimic the side chain of Asp 32 in the C-terminal octapeptide of cholecystokinin, CCK-26-33 (sulfated).

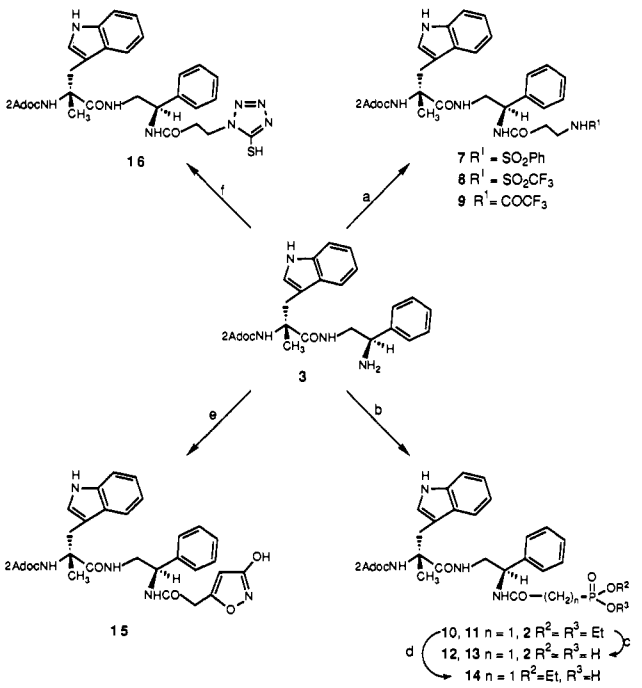


We have previously shown that the carboxylic acid moiety in 1 can be replaced by selected acid mimics[17] to give compounds of similar CCK-B receptor affinity if reduced selectivity, e.g. 2. There appears to be no direct relationship between binding affinity and pK_a of the acid moiety in this series, but it may be that the geometry and/or charge distribution about the acid mimic are important factors for receptor interaction. This paper describes an investigation into the key parameters of the acidic moiety that are important for high CCK-B receptor affinity and selectivity.

Chemistry

The intermediates and compounds described in Table I were prepared as shown in Schemes I–IV. In general,

Scheme I



Reagents: (a) $HO_2CCH_2CH_2NHR^1$ (4 R^1=SO_2Ph; 5 R^1= SO_2CF_3; 6 R^1= $COCF_3$), DCC, HOBt, EtOAc, 7(78%); 8(64%); 9(54%); (b) $HO_2C(CH_2)_nP(O)(OEt)_2$, DCC, PFP, EtOAc, 10(38%); 11(65%); (c) (i) 2eq. TMSBr, CH_2Cl_2; (ii) MeOH, H_2O, 12(74%); 13(43%); (d) (i) 1eq. TMSBr, CH_2Cl_2; (ii) MeOH, H_2O, 14(25%); (e) 3-hydroxy-5-isoxazole acetic acid, DCC, PFP, DMF, 15(53%); (f) 1-(2-carboxyethyl)tetrazol-5-thiol, DCC, PFP, DMF, 16(43%).

a series of carboxylic acids containing the relevant acid mimic in free or protected form were coupled to the amine

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(1) de Belleroche, J.; Dockray, G. J., Eds. *Cholecystokinin in the Nervous System*; Ellis Harwood: Chichester, 1984.
(2) Morgan, B. A.; Gainor, J. A. Approaches to the Discovery of Non-Peptide Ligands for Peptide Receptors and Peptidases. In *Topics in Medicinal Chemistry*; Vinick, F. J., Ed.; Academic Press Inc: New York, 1989; pp 243–252.
(3) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. Design of Potent, Orally Effective, Non-Peptidal Antagonists of the Peptide Hormone Cholecystokinin. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918.
(4) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. Benzodiazepine Gastrin and Brain Cholecystokinin Receptor Ligands - L-365,260. *J. Med. Chem.* **1989**, *32*, 13.

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Table I. Physical and Chemical Data of Compounds and Intermediates

compd	molecular formula	mp, °C	anal.	method of purification[a]
7	$C_{40}H_{47}N_5O_8S$	114.5–115.5	C,H,N	A
8	$C_{35}H_{42}F_3N_5O_8S$	112–116	C,H,N	A
9	$C_{36}H_{42}F_3N_5O_5$	112.5–115	C,H,N	A
10	$C_{37}H_{49}N_4O_7P{\cdot}0.5H_2O$	91–97	C,H,N	B
11	$C_{38}H_{51}N_4O_7P{\cdot}H_2O$	96–99	C,H,N	B
12	$C_{33}H_{41}N_4O_7P{\cdot}1.5H_2O$	145–151	C,H,N	C
13	$C_{34}H_{43}N_4O_7P{\cdot}1.25H_2O$	146–150	C,H,N	C
14	$C_{35}H_{45}N_4O_7P{\cdot}1.5H_2O$	136–142	C,H,N	C
15	$C_{36}H_{41}N_5O_6{\cdot}0.75H_2O$	136–143	C,H,N	C
16	$C_{35}H_{42}N_8O_4S{\cdot}0.5H_2O$	139–144	C,H,N	C
17	$C_{33}H_{39}BrN_4O_4$	–	*b*	A
18	$C_{34}H_{41}BrN_4O_4$	–	*c*	A
19	$C_{36}H_{47}N_4O_6P$	–	*d*	D
20	$C_{37}H_{49}N_4O_7P$	–	*e*	D
21	$C_{34}H_{43}N_4O_6P{\cdot}1.5H_2O$	148–155	C,H,N	C
22	$C_{35}H_{45}N_4O_7P{\cdot}1.5H_2O$	138–144	C,H,N	C
23	$C_{36}H_{42}N_8O_4S{\cdot}0.5H_2O$	112–122	C,H,N	D
24	$C_{35}H_{41}N_7O_4S{\cdot}0.2EtOAc$	102–107.5	C,H,N	D
25	$C_{36}H_{43}N_7O_4S{\cdot}H_2O$	119–126.5	C,H,N	D
26	$C_{39}H_{44}N_4O_5S{\cdot}H_2O$	93–102	C,H,N	A
27	$C_{34}H_{41}N_4NaO_7S{\cdot}0.5H_2O$	168–177	C,H,N	E
19a	$C_5H_7N_3O_2S$	113–115	C,H,N	*f*
19b	$C_5H_7N_3O_2S$	*g*	*g*	F
29c	$C_5H_7N_3O_3S$	157.5	C,H,N	*f*
30	$C_5H_7N_3O_3S$	116.2	C,H,N	*f*
30b	$C_{35}H_{41}N_7O_4S{\cdot}0.7H_2O$	118–120	C,H,N	C
33c	$C_{35}H_{41}N_7O_5S{\cdot}0.75H_2O$	150–155	C,H,N	C
34	$C_{35}H_{41}N_7O_5S{\cdot}H_2O$	143–149	C,H,N	C
35	$C_{36}H_{43}N_9O_5{\cdot}H_2O$	155–160	C,H,N	C
36	$C_{35}H_{43}N_5O_6{\cdot}1.5H_2O$	118–122	C,H,N	C
37	$C_{36}H_{45}N_5O_6{\cdot}0.25H_2O$	109–113	C,H,N	D

[a] Chromatography solvent systems: A, 75% EtOAc/25% hexane; B, EtOAc; C, 75% MeOH/25% H_2O (reverse-phase medium pressure chromatography); D, 10% MeOH/90% EtOAc; E, 60% MeOH/40% H_2O (reverse-phase medium pressure chromatography); F, 5% MeOH/95% CH_2Cl_2. [b] $(M + 1)^+$ requires 635.2224; found 635.2233. [c] $(M + 1)^+$ requires 649.2380; found, 649.2389. [d] $(M + 1)^+$ requires 663.3300; found, 663.3311. [e] $(M + 1)^+$ requires 677.3456; found, 677.3468. [f] Recrystallized from EtOAc. [g] Oil, $(M + 1)^+$ requires 173.0259; found, 173.0259.

3.[13] Where necessary the free acid mimic was liberated by further manipulation.

(5) (a) Howbert, J. J.; Lobb, K. L.; Brown, R. F.; Reel, J. K.; Neel, D. A.; Mason, N. R.; Mendelsohn, L. G.; Hodgkiss, J. P.; Kelly, J. S. A Novel Series of Non-peptide CCK and Gastrin Antagonists; Medicinal Chemistry and Electrophysiological Demonstrations of Antagonism in Multiple Cholecystokinin Receptors. In *Progress Towards CNS Therapeutic Targets*; Dourish, C. T., Cooper, S. J., Iversen, L. L., Iversen, S. C., Eds.; Oxford University Press: Oxford, 1991; in press. (b) Yu, M. J.; Thrasher, J.; McCowan, J. R.; Mason, N. R.; Mendelsohn, L. G. Quinazolinone Cholecystokinin - B Receptor Ligands. *J. Med. Chem.* **1991**, *34*, 1505–1508.

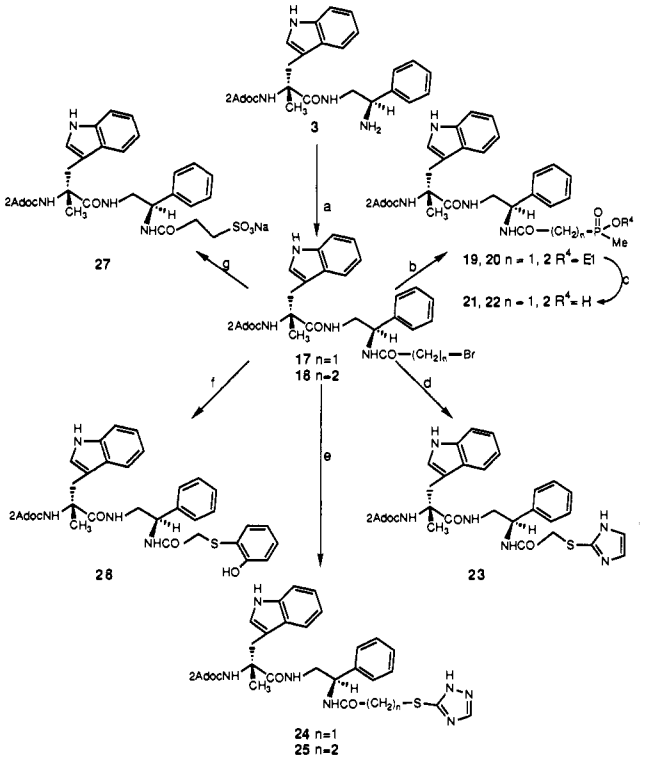
(6) Snider, R. M.; Constantine, J. W.; Lowe, J. A., III; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H-J. A Potent Nonpeptide Antagonist of the Substance P (NK_1) Receptor. *Science* **1991**, *251*, 435–437.

(7) McLean, S.; Ganong, A. H.; Seeger, T. F.; Bryce, D. K.; Pratt, K. G.; Reynolds, L. S.; Siok, C. J.; Lowe, J. A., III; Heym, J. Activity and Distribution of Binding Sites in Brain of a Nonpeptide Substance P (NK_1) Receptor Antagonist. *Science* **1991**, *251*, 437–439.

(8) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calbrese, J. C.; Timmermans, P. B. M. W. M. The Discovery of Potent Non-peptide Angiotensin II Receptor Antagonists: A New Class of Potent Antihypertensives. *J. Med. Chem.* **1990**, *33*, 1312–1329.

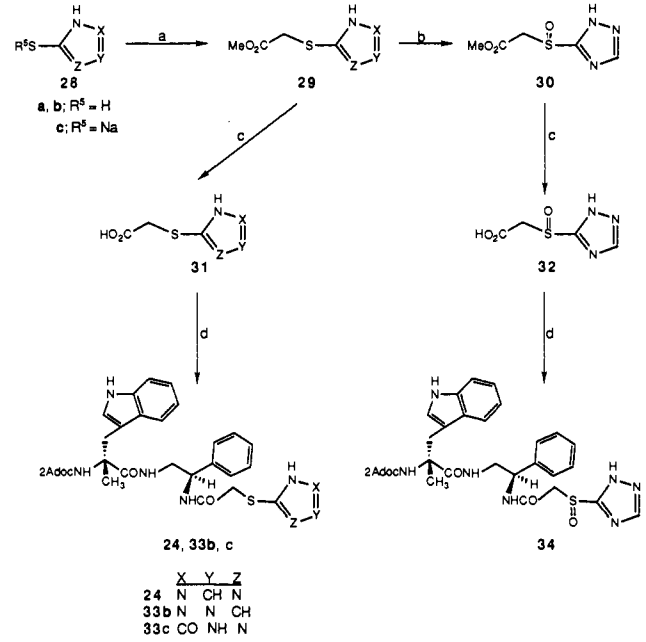
(9) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Gregory, G. B.; Pierce, W. A.; Price, W. A.; Santella III, J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S-E.; Timmermans, P. B. M. W. M. Non-Peptide Angiotensin II Receptor Antagonists: The Discovery of a Series of *N*-(Biphenylmethyl)imidazoles as Potent, Orally Active Antihypertensives. *J. Med. Chem.* **1991**, *34*, 2525–2547.

Scheme II



Reagents : (a) $HO_2C(CH_2)_nBr$, DCC, PFP, EtOAc, **17**(71%); **18**(67%); (b) $MeP(OEt)_2$, toluene, Δ, **19**(58%); **20**(55%); (c) (i) TMSBr, CH_2Cl_2. (ii) MeOH, H_2O, **21**(28%); **22**(37%); (d) 2-mercaptoimidazole, Et_3N, THF, (91%); (e) 5-mercapto-1,2,4-triazole, Et_3N, THF, **24**(90%); **25**(42%); (f) *o*-hydroxythiophenol, Bu^nLi, TMEDA, -60°C → R.T., **26**(51%); (g) Na_2SO_3, EtOH, H_2O, 75°C, **27**(52%).

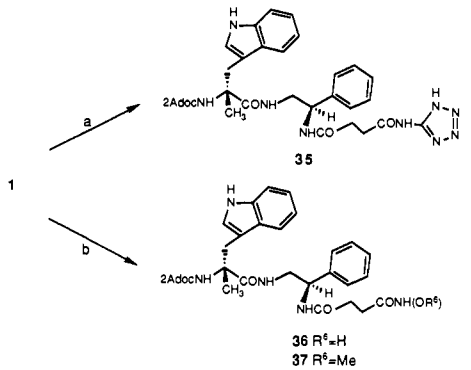
Scheme III



Reagents : (a) MeO_2CCH_2Br, Et_3N, THF, **29a**(52%); **29b**(80%), or MeO_2CCH_2Br, **29c**(18%); (b) *m*-CPBA, CH_2Cl_2, 0–40°C, **30**(70%); (c) KOH, MeOH, H_2O, quantitative; (d) (i) DCC, PFP, DMF, R.T.; (ii) **3**, R.T., **24**(38%); **33b**(76%); **33c**(34%); **34**(32%).

Compounds **7**, **8**, and **9** (Scheme I) were made by coupling the 1-hydroxybenzotriazole (HOBt) esters of the β-alanine-derived intermediates **4**, **5**, and **6** with the amine **3**. The phosphonate esters **10** and **11** were prepared by coupling **3** with the pentafluorophenol (PFP) esters of (diethoxyphosphoryl)acetic acid and 3-(diethoxyphosphoryl)propionic acid, respectively. The free phosphonic acids **12** and **13** were liberated from the esters by treatment with 2 equiv of bromotrimethylsilane (TMSBr) in dichloromethane followed by hydrolysis of the TMS esters in aqueous methanol. Careful treatment of the ester **10** with 1 equiv of TMSBr gave after workup the monoester **14**. Similarly the PFP esters of 3-hydroxy-5-isoxazoleacetic acid[18] and 1-(2-carboxyethyl)tetrazole-5-thiol[19] with the amine **3** gave the 3-hydroxyisoxazole **15** and the tetrazole-5-thiol **16**, respectively.

Scheme IV



Reagents : (a) (i) DCC, PFP, DMF, R.T.; (ii) 5-aminotetrazole, R.T., 4 days, **35**(9%); (b) (i) DCC, PFP, DMF, R.T.; (ii) $NH_2(OH).HCl$ or $NH_2(OMe).HCl$, Et_3N, **36**(35%); **37**(43%).

The versatile bromo derivatives **17** and **18** synthesized from the amine **3** were used to prepare the acid mimics **19**–**27** (Scheme II). An Arbusov reaction on **17** and **18** with diethyl methylphosphonite gave the phosphonate esters **19** and **20**, respectively. Treating the esters **19** and **20** with TMSBr in dichloromethane followed by aqueous methanol liberated the free phosphinic acids **21** from **19** and **22** from **20**. Treatment of **17** with 2-mercaptoimidazole and triethylamine gave the imidazole **23**. Similarly treating **17** and **18** with 5-mercapto-1,2,4-triazole and triethylamine yielded the 1,2,4-triazole derivatives **24** and **25**, respectively. In the case of the phenol **26**, generation of the lithio derivative of the thiol of *o*-hydroxythiophenol in THF in the presence of 2 equiv of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and treatment with the bromide **17** at −60 °C smoothly gave **26**. The sulfonic acid derivative **27** was readily obtained by heating **17** with Na_2SO_3 in aqueous ethanol.

The sulfur-linked azole acid mimics,[20] **24**, **33b**,**c**, and **34**, were synthesized as shown in Scheme III.[21] Methyl bromoacetate was reacted with 5-mercapto-1,2,4-triazole (**28a**) or 5-mercapto-1,2,3-triazole[22] (**28b**) and triethylamine, or the sodium salt of 5-mercapto-1,2,4-triazol-3-one[23] (**28c**) to yield the methyl esters **29a**, **29b**, and **29c**,

(10) Yamamura, Y.; Ogawa, H.; Chihara, T.; Kondo, K.; Onogawa, T.; Nakamura, S.; Mori, T.; Tominaga, M.; Yabuuchi, Y. OPC - 21268, An Orally Effective Nonpeptide Vasopressin V1 Receptor Antagonist. *Science* **1991**, *252*, 572–574.

(11) Horwell, D. C.; Birchmore, B.; Boden, P. R.; Higginbottom, M.; Ping Ho, Y.; Hughes, J.; Hunter, J. C.; Richardson, R. S. α-Methyl Tryptophanylphenylalanines and Their Arylethylamine "Dipeptoid" Analogues of the Tetrapeptide Cholecystokinin (30-33). *Eur. J. Med. Chem.* **1990**, *25*, 53–60.

(12) Hughes, J.; Boden, P.; Costall, B.; Domeney, A.; Kelly, E.; Horwell, D. C.; Hunter, J. C.; Pinnock, R. D.; Woodruff, G. N. Development of a Class of Selective Cholecystokinin Type B Receptor Antagonists Having Potent Anxiolytic Activity. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 6728–6732.

(13) Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N. Rationally Designed "Dipeptoid" Analogues of CCK. α-Methyltryptophan Derivatives as Highly Selective and Orally Active Gastrin and CCK-B Antagonists with Potenet Anxiolytic Properties. *J. Med. Chem.* **1991**, *34*, 404–414.

(14) Eden, J. M.; Higgenbottom, M.; Hill, D. R.; Horwell, D. C.; Hunter, J. C.; Martin, K.; Pritchard, M. C.; Richardson, R. S.; Roberts, E. Rationally Designed "Dipeptoid" Analogues of CCK. C-Terminal Structure-Activity Relationships of α-Methyltryptophan Derivatives. *Eur. J. Med. Chem.* **1992**, submitted for publication.

(15) Singh, L.; Field, M. J.; Hughes, J.; Menzies, R.; Oles, R. J.; Vass, C. A.; Woodruff, G. N. The Behavioural Properties of CI-988, a Selective Cholecystokinin$_B$ Receptor Antagonist. *Br. J. Pharmacol.* **1991**, *104*, 239–245.

(16) Hayward, N. J.; Harding, M.; Lloyd, S. A. C.; McKnight, A. T.; Hughes, J.; Woodruff, G. N. The Effect of CCK$_B$/Gastrin Antagonists on Stimulated Gastric Acid Secretion in the Anaesthetized Rat. *Br. J. Pharmacol.* **1991**, *104*, 973–977.

(17) Drysdale, M. J.; Pritchard, M. C.; Horwell, D. C. The Synthesis and CCK Receptor Affinities of Selected Carboxylic Acid Mimics of CI-988 - A Potent and Selective CCK-B Antagonist. *Bioorg. Med. Chem. Lett.* **1991**, *2*, 45–48.

(18) (a) Iwai, I.; Nakamura, N. Studies on Acetylenic Compounds. XLIV. Synthesis of 3-Aminoisoxazoles and 3-Hydroxyisoxazoles (3-Isoxazolones). *Chem. Pharm. Bull.* **1966**, *14*, 1277–1286; (b) Oster, T. A.; Harris, T. H. Generation and Reactions of the Dianion of 3-Hydroxy-5-methylisoxazole, a Convenient β-Keto Amide Synthon. Total Synthesis of Muscimol. *J. Org. Chem.* **1983**, *48*, 4307–4311.

(19) Berges, D. A. Tetrazol-5-ylthiomethylcephemcarboxylic Acids. Ger. Offen. 2,558,022 CA 86, 1978, 72667w.

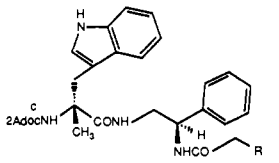
(20) Chenard, B. L.; Lipinski, C. A.; Dominy, B. W.; Mena, E. E.; Ronau, R. T.; Butterfield, G. C.; Marinovic, L. C.; Pagnozzi, M.; Butler, T. W.; Tsang, T. A Unified Approach to Systematic Isosteric Substitution for Acidic Groups and Application to NMDA Antagonists Related to 2-Amino-7-phosphonoheptanoate. *J. Med. Chem.* **1990**, *33*, 1077–1083.

(21) Compounds **23**, **24**, and **25** (Scheme II) are also based on compounds in ref 20.

(22) Goerdeler, J.; Gnad, G.; Über 5-Amino-1,2,3-thiadiazole. *Chem. Ber.* **1966**, *99*, 1618–1631.

(23) Fromm, E.; Nehring, E. Synthesis of 3-Oxy-5-thiotriazole. *Chem. Ber.* **1923**, *56*, 1370–1375.

Table II. Charge Distributed Monoanionic Acid Mimics—CCK Receptor Binding Affinities[a] and pK_a Data[b]



compd	R	IC_{50} (nM) CCK-B	IC_{50} (nM) CCK-A	A/B ratio	pK_a
1	CH_2COOH	1.7 (1.3–3.7)	4500 (1200–8500)	2500	5.6
2	CH_2CHN_4	6.0 (3.6–8.1)	970 (800–1100)	160	5.4
15	3-hydroxyisoxazole	2.6 (2.4–3.0)	1700 (1300–2200)	650	6.5
16	CH_2-tetrazole-5-thiol	2.4 (2.0–2.8)	620 (540–700)	260	4.3
24	$S(C_2H_2N_3)$	2.5 (1.9–3.2)	680 (530–800)	270	>9.5
25	$CH_2S(C_2H_2N_3)$	16 (11–34)	850 (610–1200)	53	>9.5
33c	$S(C_2H_2N_3O)$	4.3 (3.9–4.7)	660 (570–810)	150	7.7
34	$SO(C_2H_2N_3)$	1.7 (1.6–1.8)	940 (820–1100)	550	7.0
35	$CH_2CONH(CHN_4)$	6.3 (5.3–7.7)	1300 (1200–1500)	200	5.2
33b	$S(C_2H_2N_3)$	18 (15–22)	600 (450–740)	33	>8.2
36	$CH_2CONH(OH)$	14 (9–32)	1300 (900–1900)	93	>9.5
L-365,260		5.1 (4.6–5.4)	230 (170–380)	45	
CCK-8S		0.3 (0.2–0.3)	0.1 (0.08–0.2)	0.33	
pentagastrin		0.8 (0.5–0.9)	600 (500–650)	750	

[a] IC_{50} represents the concentration (nM) producing half-maximal inhibition of specific binding of [^{125}I]-Bolton Hunter 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] pK_a measurements are obtained by a titration method using a Radiometer VIT90 video titrator. The solvent used was 20% aqueous DMF. The values given are the arithmetic mean from at least three separate experiments. [c] 2Adoc refers to 2-adamantyloxycarbonyl.

respectively. In the case of **29a**, oxidation with *m*-chloroperbenzoic acid in dichloromethane gave the sulfoxide **30**. Hydrolysis of the methyl esters with methanolic potassium hydroxide gave the free carboxylic acids **31a–c** and **32** in quantitative yield after isolation by ion-exchange chromatography. The PFP esters of these acids were coupled to the amine **3** to give the sulfur-linked azoles **24**, **33b,c**, and **34**, respectively.

The parent carboxylic acid **1**[13] was reacted as its PFP ester with 5-aminotetrazole to give **35** and with hydroxylamine or *O*-methylhydroxylamine to give the hydroxamic acid **36** and the *O*-methylhydroxamate **37**, respectively (Scheme IV).

Results and Discussion

Having established that the presence of a C-terminal carboxylic acid in our "dipeptoid" antagonists enhances affinity and selectivity for the CCK-B receptor,[14] we were interested to further investigate the key parameters of the acidic binding moiety which are important for high binding affinity. To this end we selected a number of known carboxylic acid mimics[20,24] as replacements for the C-terminal carboxylate which would allow us to vary pK_a values as well the geometry and charge distribution about the acid center.

Initial studies indicated that there is no simple correlation between the readily measured pK_a of the C-terminal acidic moiety and CCK-B binding affinity and selectivity.[17] This is in contrast to the example of the angiotensin II antagonists[8,9] where it has been shown that an increase in acidity (i.e. a lowering of pK_a) correlates well with an increase in binding affinity. However, it is known that differences in charge distribution[25] and geometry[26] at the acid center can have profound effects. For example, it has been suggested that the difference between the highly potent $GABA_A$ agonists muscimol and dihydromuscimol and the weak agonist isomuscimol can be explained by the differences in charge distribution of the acid mimic. In muscimol and dihydromuscimol the charge distribution of the acid mimic is similar to that of the parent carboxylic acid in GABA itself, whereas isomuscimol has a much more highly delocalized charge distribution.[25] In the case of the $GABA_B$ agonist baclofen, replacement of the planar carboxylic acid with a tetrahedral sulfonic acid (saclofen) or phosphonic acid (phaclofen) yields compounds which are antagonists.[26] In our study it became apparent that it was indeed charge distribution and geometry about the acid center which are important to retain high binding and good selectivity at the CCK-B receptor (Tables II, III, and IV).

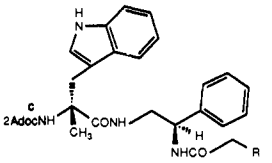
The acid mimics synthesized can be divided up depending upon their respective anionic charge distribution and geometry with respect to the prototype carboxylic acid (see Figure 1). All the heterocyclic azoles, the 3-hydroxyisoxazole, and the hydroxamic acid, like the carboxylic acid, are planar acid moieties with their charge distribution as shown, delocalized over at least three atoms (Figure 1). This class of acid mimics can be further subdivided by charge distribution into two sections. Firstly, those with a central relatively electropositive atom surrounded by two electronegative atoms e.g. compounds **2**, **15**, **16**, **24**, **25**, **33c**, **34**, and **35** (Table II). These compounds all show high binding at the CCK-B receptor with IC_{50} values ranging from 1.7 to 16 nM which compares favorably with the parent carboxylic acid **1** (IC_{50} = 1.7 nM). The only apparently erroneous compound in this subgroup, the 5-thio-1,2,4-triazole **25** (IC_{50} = 16 nM), has an extra methylene group in the side chain rendering the acid too distant from the phenethyl backbone compared to **24** for optimum binding. The other two compounds in this group are the 5-thio-1,2,3-triazole **33b** and the hydroxamic acid

(24) (a) Thornber, C. W. Isosterism and Molecular Modification in Drug Design. *Chem. Soc. Rev.* **1979**, *8*, 563–580. (b) Lipinski, C. A. Bioisosterism in Drug Design. *Annu. Rep. Med. Chem.* **1986**, *21*, 283–291.

(25) Krøgsgaard-Larsen, P.; Hjeds, H.; Curtis, D. R.; Lodge, D.; Johnston, G. A. R. Dihydromuscimol, Thiomuscimol and Related Heterocyclic Compounds as GABA Analogues. *J. Neurochem.* **1979**, *32*, 1717.

(26) Bowery, N. G. $GABA_B$ Receptors and Their Significance in Mammalian Pharmacology. *Trends Pharm. Sci.* **1989**, *10*, 401–417.

Table III. Point Charge Monoanionic Acid Mimics—CCK Receptor Binding Affinities[a] and pK_a Data[b]



compd	R	IC_{50} (nM) CCK-B	IC_{50} (nM) CCK-A	A/B ratio	pK_a
1	CH_2COOH	1.7 (1.3–3.7)	4500 (1200–8500)	2500	5.6
7	CH_2NHSO_2Ph	70 (50–122)	300 (260–340)	4.3	>9.5
8	$CH_2NHSO_2CF_3$	77 (62–98)	680 (620–770)	9	7.9
9	$CH_2NHCOCF_3$	110 (63–170)	790 (680–970)	7	>9.5
26	$S(C_6H_4)$-o-OH	80 (65–99)	510 (480–540)	6.4	>9.5
37	$CH_2CONH(OMe)$	21 (16–28)	1500 (1100–1800)	71	>9.5

[a–c] Footnotes same as in Table II.

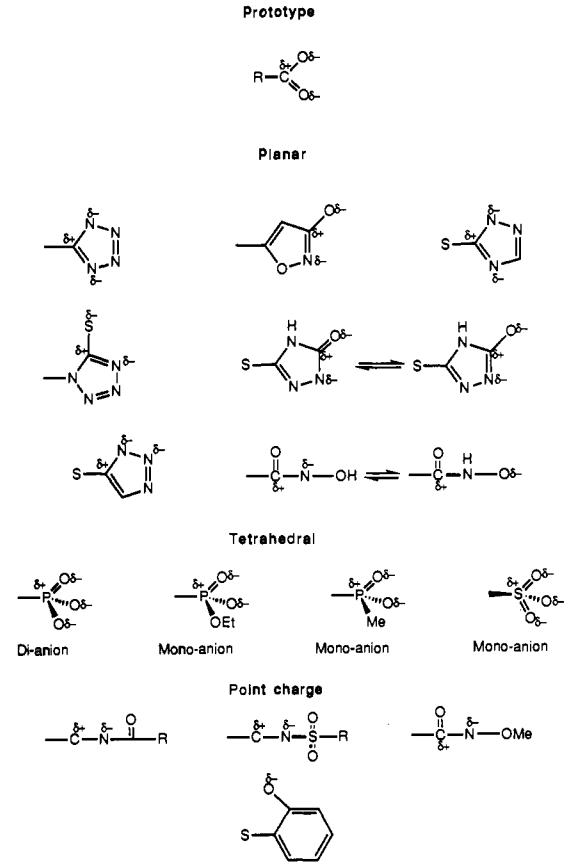


Figure 1. Partial charges for acid mimics.

36. Though these are planar acid moieties, unlike the carboxylic acid they have a linear charge distribution (Figure 1) which is apparently not optimal for high CCK-B binding affinity. These compounds have IC_{50} values an order of magnitude lower than that of the carboxylic acid being 18 and 14 nM, respectively.

A second group of planar acid mimics are shown in Table III. These compounds **7**, **8**, **9**, **26**, and **37** correspond to the point charge acid mimics in Figure 1. This localized charge does not lead to high binding compounds as can be seen from the IC_{50} values ranging from 21 nM for the *O*-methylhydroxamate **37** to 110 nM for the trifluoroacetamide **9**.

The final group of acid mimics differ from the previous compounds in that they have tetrahedral geometry (Figure 1 and Table IV). The phosphonic acids **12** and **13** exist primarily as the dianion at physiological pH which, from the higher IC_{50} values of 27 and 23 nM, respectively, is disfavored. The monoester **14** (IC_{50} = 12 nM) and the phosphinic acids **21** and **22** (IC_{50} = 12 and 23 nM, respectively) have IC_{50} values around 1 order of magnitude higher than that of the carboxylic acid **1** (IC_{50} = 1.7 nM), suggesting that a tetrahedron geometry at the acid center is not optimum for CCK-B binding. However the sulfonic acid **27**, which also has a tetrahedral acid moiety, has an IC_{50} = 1.3 nM and is 780-fold selective for the CCK-B receptor. This makes the sulfonic acid the most active and selective acid mimic for the CCK-B receptor made in this series and indicates that, in certain circumstances, an acid with tetrahedral geometry can be tolerated by the receptor. Though the other tetrahedral acid mimics, the monoester **14**, and the phosphinic acids **21** and **22** are less active, the sulfonic acid is unique in that the charge of its anion is spread over three oxygen atoms compared to only two in the phosphorus monoanions. This may be closer to the optimal charge distribution for interaction at the receptor, thus leading to such an active compound.

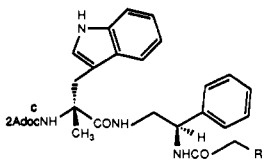
Studies[27] with CCK-related peptides have shown that the Asp-32 residue in these peptides is very sensitive to change and that little latitude is allowed in the requirements for binding at the Asp site. The only replacements for Asp-32 which have given significant activity were the electronically and geometrically similar tetrazol-5-yl in stimulated gastric acid secretion studies with CCK 30-33 analogues,[28] and Ser(SO_3H), Thr(SO_3H), or Hyp(SO_3H) in anticonvulsant studies with Ac-CCK-7 analogues.[29] This is consistent with our work where the most active compounds obtained by replacing the carboxylic acid are those which are electronically and geometrically similar (Figure 1, Table II) or contain the SO_3H moiety (Table IV).

Conclusions

In this paper we have described the synthesis of a number of carboxylic acid mimics of the CCK-B receptor antagonist CI-988, **1**. It is of interest to note that due to the pK_a range of the carboxylic acid mimics herein, some of the groups will be charged and others uncharged at the receptor. It is unusual that the receptor accepts both a charged and uncharged species but as we have previously shown, a carboxylic acid is essential for enhancement of both affinity and selectivity for the CCK-B receptor[14] and

(27) Morley, J. S. Structure-Function Relationships in Gastrin-like Peptides. *Proc. R. Soc. London B* **1968**, *170*, 97–111.
(28) Morley, J. S. Polypeptides. XI. Tetrazole Analogs of the C-Terminal Tetrapeptide Amide Sequence of the Gastrins. *J. Chem. Soc. C* **1969**, 809–813.
(29) Botond, P.; Hajnal, F.; Lonovics, J.; Holzinger, G.; Kadar, T.; Telegdy, G.; Rivier, J. Synthesis of Potent Heptapeptide Analogues of Cholecystokinin. *J. Med. Chem.* **1984**, *27*, 845–849.

Table IV. Charge Distributed Tetrahedral Acid Mimics—CCK Receptor Binding Affinities[a] and pK_a Data[b]



compd	R	IC_{50} (nM) CCK-B	IC_{50} (nM) CCK-A	A/B ratio	pK_a
1	CH_2COOH	1.7 (1.3–3.7)	4500 (1200–8500)	2500	5.6
12	$P(O)(OH)_2$	27 (26–28)	5200 (2300–17000)	190	3.4, 7.7
13	$CH_2P(O)(OH)_2$	23 (22–24)	2700 (2300–3500)	120	3.4, 7.8
14	P(O)(OH)(OEt)	12 (7–16)	480 (380–610)	40	6.5
21	P(O)(OH)Me	12 (11–15)	1700 (1300–2500)	140	3.8
22	$CH_2P(O)(OH)Me$	23 (16–27)	4400 (3900–4900)	190	3.7
27	CH_2SO_3Na	1.3 (1.0–1.6)	1010 (930–1100)	780	–

[a–c] Footnotes same as in Table II.

there is a clear specificity of interaction involving this group. We have shown that in general, for highest binding at the CCK-B receptor the acid moiety should be planar and have a charge distribution similar to that of the carboxylic acid. The only exception to this, appears to be with the case of the sulfonic acid **27**, but this is consistent with what is known about the allowed changes of Asp-32 in CCK-related peptides.[27-29]

Experimental Section

Biological Assays.[30,31] CCK-A receptor binding assays were performed on male rat pancreas. Tissue (250 mg) homogenized in ice-cold Tris-HCl (pH 7.4) (50 mL of a 50-mmol solution) was centrifuged at 20000*g*. The pellet was washed once by resuspension in Tris-HCl followed by recentrifugation and suspended in a standard assay buffer (SAB) comprising 10 mM Hepes (pH 7.2 at 21 °C), 130 mM NaCl, 5 mM $MgCl_2$, 4.7 mM KCl, 1 mM 1,2-bis(2-aminoethoxy)ethane and 0.25 mg/mL of bacitracin at a tissue concentration of 0.5 mg original wet weight per mL of buffer.

CCK-B receptor binding assays were performed on male mouse cerebral cortex. Tissue homogenized in 10 volumes of 50 mM ice-cold Tris-HCl buffer (pH 6.9 at 21 °C) was centrifuged for 15 min at 20000*g*. The pellet was washed by resuspension in ice-cold 50 mM Tris-HCl and recentrifuged as above. The final pellet was then washed and resuspended in a standard assay buffer (SAB) comprising 10 mM Hepes (pH 7.2 at 21 °C), 130 mM NaCl, 5 mM $MgCl_2$, 4.7 mM KCl, 1 mM 1,2-bis(2-aminoethoxy)ethane and 0.25 mg/mL of bacitracin at a tissue concentration of 2 mg original wet weight per mL of SAB.

For each of the binding assays, aliquots of tissue (400 mL) were incubated at 21 °C for 120 min with 35 pM [^{125}I]-Bolton Hunter conjugated CCK (26-33) ([^{125}I]CCK 8S) in the absence and presence of a range of concentrations of the test compound in a final volume of 500 mL. Nonspecific binding was estimated by 1 mM CCK 8S.

After each incubation, the assay was terminated by rapid filtration under vacuum through Whatman GF/B filterstrips followed by washing three times with 4 mL of ice-cold NaCl. Radioactivity was then measured using a Packard Series 5000 gamma counter.

Chemistry. pK_a measurements are obtained by a titration method using an inflection point criteria on a Radiometer VIT90 video titrator. Approximately 2 mg of the test compound was dissolved in 10 mL of 20% aqueous DMF. This was then titrated against 30 mM NaOH solution using an autotitrator via a 1-mL burette. Melting points were determined with a Mettler FP800 or a Reichart Thermovar hot-stage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker AM300 spectrometer; chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane. IR spectra were recorded using the compound (neat) on a sodium chloride disc with a Perkin-Elmer 1750 Fourier transform spectrophotometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Finnegan 4500 or a ZAB-E VG Analytical spectrometer. Elemental analyses were determined by CHN Analysis Ltd., Leicester, UK, Butterworth Laboratories Ltd., Teddington, U.K., or MEDAC limited, Brunel University, U.K. Normal-phase silica gel used was Kieselgel-60 (230–400 mesh); reverse-phase silica gel used was Lichroprep RP-18 (230–400 mesh) both supplied by E. Merck, A. G., Darmstadt, Germany. Anhydrous solvents were used directly as purchased from Aldrich Chemical Co. Ltd., Gillingham, England and Lancaster Chemical Co. Ltd., Lancaster, England.

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[[1-oxo-3-[(phenylsulfonyl)amino]propyl]-amino]-2-phenylethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]-dec-2-yl Ester, [*R*-(*R,*R**)]- (7).** A solution of *N*-(phenylsulfonyl)-β-alanine (**4**) (178 mg, 0.778 mmol) in EtOAc (30 mL) was treated with 1-hydroxybenzotriazole (HOBt) hydrate (105 mg, 0.778 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (161 mg, 0.778 mmol) and stirred at room temperature for 3 h. After this time, the mixture was filtered and tricyclo[3.3.1.1^{3,7}]dec-2-yl [*R*-(*R**,*R**)]-[2-[(2-amino-2-phenethyl)amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate[13] (**3**) (400 mg, 0.778 mmol) added all at once. The resulting mixture was stirred overnight at room temperature, filtered, concentrated in vacuo, and purified by silica gel chromatography to yield the desired sulfonamide **7** as an amorphous solid (442 mg, 78%): $[\alpha]^{20}_D$ −57° (*c* = 0.10, $CHCl_3$); IR (neat) 1730, 1329, 1162, 1027, 912 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.04 (17 H, m), 2.47 (2 H, t, *J* = 6 Hz), 3.18–3.27 (3 H, m), 3.39 (2 H, ABq, *J* = 14.6 Hz), 4.09 (1 H, br s), 4.84 (1 H, s), 5.07 (1 H, br s), 5.15 (1 H, s), 5.97 (1 H, br s), 6.30 (1 H, br s), 7.00 (1 H, d, *J* = 2.3 Hz), 7.07–7.58 (14 H, m), 7.85 (1 H, d, *J* = 6.8 Hz), 8.25 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[[1-oxo-3-[[(trifluoromethyl)sulfonyl]amino]-propyl]amino]-2-phenylethyl]amino]ethyl]-, Tricyclo-[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (8).** Method as for **7** except using *N*-[(trifluoromethyl)sulfonyl]-β-alanine (**5**): yield 356 mg, 64%; $[\alpha]^{20}_D$ −1.9° (*c* = 0.10, $CHCl_3$); IR (neat) 1794, 1722, 1668, 1377, 1193 cm^{-1}; NMR ($CDCl_3$) δ 1.43–2.06 (17 H, m), 2.50–2.70 (2 H, m), 3.21 (1 H, dt, *J* = 13.8, 4.2 Hz)), 3.35 (2 H, ABq, *J* = 14.6 Hz), 3.50–3.70 (2 H, m), 4.12–4.30 (1 H, m), 4.83 (1 H, s), 5.08 (1 H, s), 5.18 (1 H, br s), 6.20 (1 H, br s), 6.96 (1 H, d, *J* = 2.3 Hz), 7.07–7.37 (10 H, m), 7.54 (1 H, d, *J* = 7.7 Hz), 8.13 (1 H, s).

2,5,8,12-Tetraazatetradecanoic Acid, 14,14,14-Trifluoro-3-(1*H*-indol-3-ylmethyl)-3-methyl-4,9,13-trioxo-7-phenyl-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (9).** Method as for **7** except using *N*-(trifluoroacetyl)-β-alanine (**6**): yield 281

(30) Chang, R. S. L.; Lotti, V. J. Biochemical and Pharmacological Characterisation of an Extremely Potent and Selective Nonpeptide Cholecystokinin Antagonist. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4923–4926.

(31) Clark, C. R.; Daum, P.; Hughes, J. A Study of the Cerebral Cortex Cholecystokinin Receptor Using Two Radiolabelled Probes: Evidence for a Common CCK 8 and CCK 4 Cholecystokinin Receptor Binding Site. *J. Neurochem.* **1986**, *46*, 1094–1101.

mg, 54%; $[\alpha]^{20}_D$ -10.5° (c = 0.10, $CHCl_3$); IR (neat) 1794, 1728, 1163, 1027, 908 cm^{-1}; NMR ($CDCl_3$) δ 1.41–2.04 (17 H, m), 2.54–2.59 (2 H, m), 3.21 (1 H, dt, J = 13.8, 4.0 Hz)), 3.36 (2 H, ABq, J = 14.6 Hz), 3.64–3.67 (2 H, m), 4.15–4.30 (1 H, m), 4.82 (1 H, s), 4.99 (1 H, s), 5.19–5.22 (1 H, m), 6.16–6.18 (1 H, m), 6.96 (1 H, d, J = 2.3 Hz), 7.07–7.39 (9 H, m), 7.54 (1 H, d, J = 7.9 Hz), 7.91 (1 H, br s), 8.16 (1 H, s).

12-Oxa-2,5,8-triaza-11-phosphatetradecanoic Acid, 11-Ethoxy-3-(1*H*-indol-3-ylmethyl)-3-methyl-4,9-dioxo-7-phenyl-, 11-Oxide, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (10).** Method as for 7 except using (diethoxyphosphinyl)acetic acid, pentafluorophenol (PFP) and DCC: yield 800 mg, 38%; IR (neat) 3291, 2911, 1662, 1536, 1494, 1242, 1053, 1027 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.31 (3 H, t, J = 7 Hz), 1.46–1.92 (17 H, m), 2.88 (2 H, dd, J = 20.9, 3.5 Hz), 3.31 (1 H, $^1/_2$ × ABq, J = 14.6 Hz), 3.34–3.46 (3 H, m), 3.81–3.88 (1 H, m), 4.03–4.19 (4 H, m), 4.79 (1 H, s), 5.05–5.11 (1 H, m), 5.26 (1 H, s), 6.54 (1 H, t, J = 6 Hz), 6.99 (1 H, d, J = 2.3 Hz), 7.07–7.38 (9 H, m), 7.58 (1 H, d, J = 7.8 Hz), 8.58 (1 H, s).

Carbamic Acid, [2-[[2-[[3-(Diethylphosphono)-1-oxopropyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (11).** Method as for 10 except using 3-(diethoxyphosphinyl)propionic acid: yield 180 mg, 65%; IR (neat) 3306, 2909, 1662, 1531, 1235, 1055, 1028, 967 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 1.32 (3 H, t, J = 7.1 Hz), 1.49–1.95 (17 H, m), 2.01–2.17 (2 H, m), 2.45–2.55 (2 H, m), 3.21–3.29 (1 H, m), 3.28 (1 H, $^1/_2$ × ABq, J = 14.6 Hz), 3.50 (1 H, $^1/_2$ × ABq, J = 14.6 Hz), 3.87–3.94 (1 H, m), 3.99–4.16 (4 H, m), 4.75 (1 H, s), 5.01–5.04 (1 H, m), 5.25 (1 H, s), 6.41–6.45 (1 H, m), 6.74 (1 H, d, J = 7.8 Hz), 7.00–7.22 (8 H, m), 7.40 (1 H, d, J = 8 Hz), 7.60 (1 H, d, J = 7.8 Hz), 9.21 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-phenyl-2-[(phosphonoacetyl)amino]ethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (12).** A mixture of the diethyl phosphonate 10 (400 mg, 0.578 mmol), bromotrimethylsilane (372 mg, 2.24 mmol, 4.4 equiv), and dry CH_2Cl_2 (3 mL) was stirred at room temperature for 36 h. The mixture was concentrated in vacuo, and the pinkish solid was dissolved in MeOH and enough water to just prevent precipitation. This aqueous mixture was stirred at room temperature for 24 h and concentrated in vacuo to a foam. Purification by reverse-phase chromatography gave the desired phosphonic acid 12 as a hygroscopic amorphous solid (204 mg, 74%); $[\alpha]^{20}_D$ +2° (c = 0.10, MeOH); IR (neat) 3307, 2905, 1659, 1529, 1254, 1073 cm^{-1}; NMR (d^6-DMSO) δ 1.10–2.20 (17 H, m), 2.58–2.70 (2 H, m), 2.80–4.00 (4 H, m, obscured by H_2O), 4.69 (1 H, s), 4.90–5.00 (1 H, m), 6.40 (1 H, br s), 6.89–7.34 (9 H, m), 7.44 (1 H, d, J = 7.7 Hz), 7.89–8.00 (1 H, m), 8.20–8.40 (1 H, m), 10.87 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[(1-oxo-3-phosphonopropyl)amino]ethyl]amino]-ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (13).** Method as for 12 except using the diethyl phosphonate 11: yield 25 mg, 43%; $[\alpha]^{20}_D$ -1.8° (c = 0.11, acetone); IR (neat) 3393, 2857, 1689, 1657, 1534, 1254 cm^{-1}; NMR (d^6-acetone) δ 1.49–1.96 (17 H, m), 2.36–2.44 (2 H, m), 3.02–3.22 (2 H, m), 3.50 (2 H, ABq, J = 14.9 Hz), 3.55–3.79 (2 H, m), 4.84 (1 H, s), 5.18–5.22 (1 H, m), 6.94–7.37 (8 H, m), 7.44 (1 H, d, J = 7.2 Hz), 7.60 (1 H, d, J = 7.8 Hz).

Carbamic Acid, [2-[[2-[[(Ethylphosphono)acetyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (14).** Method as for 12 except using only 1 equiv of bromotrimethylsilane: yield 26 mg, 25%; $[\alpha]^{20}_D$ -1.90 (c = 0.10, MeOH); IR (neat) 3305, 2909, 1661, 1533, 1495, 1253, 1101, 1071, 1047, 989, 910, 734 cm^{-1}; NMR ($CDCl_3$ + 1 drop d^4-MeOH) δ 1.20–1.40 (3 H, m), 1.49–2.00 (17 H, m), 2.70–2.90 (2 H, m), 3.25–3.43 (3 H, m), 3.81–3.85 (1 H, m), 4.05 (2 H, br s), 4.84 (1 H, s), 5.01 (1 H, br s), 5.51 (1 H, br s), 6.90 (1 H, br s), 6.98–7.27 (8 H, m), 7.35 (1 H, d, J = 7.2 Hz), 7.56 (1 H, d, J = 7.8 Hz), 7.75 (1 H, br s), 8.88 (1 H, br s); MS (M + 1)$^+$ req 665.3093; found 665.3104.

Carbamic Acid, [2-[[2-[[(3-Hydroxy-5-isoxazolyl)acetyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (15).** A solution of 3-hydroxyisoxazole-5-acetic acid[18] (56 mg, 0.389 mmol) in dry EtOAc (5 mL) was treated with pentafluorophenol (PFP) (72 mg, 0.389 mmol) and DCC (81 mg, 0.389 mmol) and stirred at room temperature for 3 h. After this time, the mixture was filtered and the amine 3 (200 mg, 0.389 mmol) added all at once. The resulting mixture was stirred overnight at room temperature, filtered, concentrated in vacuo, and purified by reverse-phase chromatography to yield the desired 3-hydroxyisoxazole 15 as an amorphous solid (132 mg, 53%): $[a]^{20}_D$ -10° (c = 0.10, MeOH); IR (neat) 3289, 2904, 1666, 1528, 1461, 1258 cm^{-1}; NMR (d^6-DMSO) δ 1.18–1.91 (17 H, m), 3.10–3.50 (3 H, m, obscured by H_2O), 3.55–3.70 (3 H, m), 4.70 (1 H, s), 4.95–5.05 (1 H, m), 5.80 (1 H, s), 6.73 (1 H, br s), 6.89–7.29 (9 H, m), 7.44 (1 H, d, J = 7.7 Hz), 7.80 (1 H, br s), 8.43 (1 H, br s), 10.86 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[[1-oxo-3-(5-mercapto-1*H*-tetrazol-1-yl)propyl]amino]-2-phenylethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (16).** Method as for 15 except using 1-(2-carboxyethyl)tetrazole-5-thiol[19] in DMF: yield 112 mg, 43%; $[\alpha]^{20}_D$ -1.0° (c = 0.10, MeOH); IR (neat) 3312, 2922, 2854, 1661, 1511, 1459, 1378, 1253, 1072 cm^{-1}; NMR (d^6-DMSO) δ 1.22 (3 H, s), 1.51–2.00 (14 H, m), 2.81 (2 H, t, J = 7 Hz), 3.20–3.40 (4 H, m, obscured by H_2O), 4.40 (2 H, t, J = 7.1 Hz), 4.71 (1 H, s), 4.95–5.05 (1 H, m), 5.80 (1 H, s), 6.75 (1 H, br s), 6.92–7.31 (9 H, m), 7.47 (1 H, d, J = 7.8 Hz), 7.75–7.85 (1 H, m), 8.34 (1 H, br s), 10.89 (1 H, s); MS (M + 1)$^+$ req 671.3119; found 671.3130.

Carbamic Acid, [2-[[2-[(2-Bromoacetyl)amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (17).** A solution of bromoacetic acid (54 mg, 0.389 mmol) in EtOAc (10 mL) was treated with PFP (72 mg, 0.389 mmol) and DCC (81 mg, 0.389 mmol) and the mixture allowed to stir at room temperature for 2 h. The precipitate was filtered off and the amine 3 (200 mg, 0.389 mmol) added all at once. The resulting mixture was stirred overnight at room temperature, filtered, and concentrated in vacuo to a white foam. Purification by silica gel chromatography yielded the desired bromo compound 17 as an amorphous solid (175 mg, 71%) which was used without further purification: IR (neat) 3299, 2911, 1657, 1530, 1453, 1254, 1073, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.46–2.00 (17 H, m), 3.32 (1 H, $^1/_2$ × ABq, J = 14.7 Hz), 3.39–3.49 (3 H, m), 3.85 (2 H, ABq, J = 12.2 Hz), 3.85–3.97 (1 H, m), 4.89 (1 H, s), 5.03 (1 H, s), 5.12 (1 H, br s), 6.38 (1 H, br s), 6.97 (1 H, d, J = 2.4 Hz), 7.08–7.38 (8 H, m), 7.57 (1 H, d, J = 7.6 Hz), 7.65 (1 H, d, J = 7.6 Hz), 8.14 (1 H, s).

Carbamic Acid, [2-[[2-[(3-Bromo-1-oxopropyl)amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (18).** Method as for 17 except using 3-bromopropionic acid: yield 168 mg, 67%; IR (neat) 3309, 2908, 1662, 1526, 1453, 1264, 1074, 740, 701 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (3 H, s), 1.62–2.07 (14 H, m), 2.85–2.90 (2 H, m), 3.23–3.30 (1 H, m), 3.34 (1 H, $^1/_2$ × ABq, J = 14.7 Hz), 3.45 (1 H, $^1/_2$ × ABq, J = 14.5 Hz), 3.62–3.69 (2 H, m), 4.08–4.20 (1 H, m), 4.91 (1 H, br s), 5.00 (1 H, s), 5.19–5.29 (1 H, m), 6.20–6.30 (1 H, m), 6.96 (1 H, d, J = 2.3 Hz), 7.08–7.37 (9 H, m), 7.56 (1 H, d, J = 7.9 Hz), 8.16 (1 H, s).

Carbamic Acid, [2-[[2-[[(Ethoxymethylphosphinyl)acetyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (19).** A mixture of the bromo compound 17 (651 mg, 0.940 mmol) and diethyl methylphosphonite (256 mg, 1.88 mmol, 2 equiv) were heated in dry toluene (8 mL) at 110 °C under a nitrogen atmosphere for 2 h. After this time, the solvent and excess diethyl methylphosphonite were removed under water pump vacuum and the resulting glassy solid was purified by silica gel chromatography to yield the desired phosphinite ester 19 as a pair of diastereomers about phosphorus (362 mg, 58%) and used without further purification: IR (neat) 3408, 2900, 1657, 1536, 1215, 1039 cm^{-1}; NMR ($CDCl_3$) δ 1.27 and 1.36 (3 H, t, J = 7.1 Hz, two diastereoisomers), 1.51–1.96 (20 H, m), 2.85–2.94 (2 H, m), 3.24–3.51 (3 H, m), 3.88–3.99 (1 H, m), 4.03–4.15 (2 H, m), 4.78 and 4.81 (1 H, s, two diastereoisomers), 5.07–5.14 (1 H, m), 5.15 and 5.25 (1 H, s, two diastereoisomers), 6.35–6.41 and 6.51–6.59 (1 H, m, two diastereoisomers), 6.98–7.59 (11 H, m), 8.48 and 8.93 (1 H, s, two diastereoisomers); MS (M + 1)$^+$ req 663.3300; found 663.3311.

Carbamic Acid, [2-[[2-[[3-(Ethoxymethylphosphinyl)-1-oxopropyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (20).** Method as for 19 except using the bromo compound 18: yield 200 mg, 55%; NMR ($CDCl_3$) δ 1.23–2.00 (23 H, m), 2.02–2.13 (2 H, m), 2.47–2.60 (2 H, m), 3.17–3.57 (3 H, m), 3.89–4.24 (3 H, m), 4.71 and 4.75 (1 H, s, two diastereoisomers), 5.03 (1 H, br s), 5.24 and 5.31 (1 H, s, two diastereoisomers), 6.44 and 6.48 (1 H, s, two diastereoisomers), 6.81–7.61 (11 H, m), 9.44 and 9.63 (1 H, s, two diastereoisomers).

Carbamic Acid, [2-[[2-[[(Hydroxymethylphosphinyl)-acetyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (21).** Method as for 12 except using phosphinite ester 19: yield 33 mg, 28%; $[\alpha]^{20}_D$ −2.38° (*c* = 0.10, MeOH); NMR (d^6-DMSO) δ 1.27–2.10 (20 H, m), 2.65–2.84 (2 H, m), 3.00–3.40 (4 H, m, obscured by H_2O), 4.73 (1 H, s), 5.01 (1 H, br s), 6.68 (1 H, s), 6.94–7.36 (9 H, m), 7.49 (1 H, d, *J* = 7.7 Hz), 7.88 (1 H, br s), 8.43 (1 H, br s), 10.90 (1 H, s); MS $(M + 1)^+$ req 635.2988; found 635.2998.

Carbamic Acid, [2-[[2-[[3-(Hydroxymethylphosphinyl)-1-oxopropyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (22).** Method as for 12 except using phosphinite ester 20: yield 36 mg, 37%; $[\alpha]^{20}_D$ −5.26° (*c* = 0.09, MeOH); IR (neat) 3303, 2910, 1660, 1531, 1495, 1453, 1376, 1255, 1172, 1101, 1073, 981, 734 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.05 (22 H, m), 2.50–2.65 (2 H, m), 3.20–3.50 (3 H, m, obscured by H_2O), 3.75–3.82 (1 H, m), 4.93 (1 H, br s), 5.37 (1 H, s), 6.65 (1 H, br s), 6.97 (1 H, s), 7.06–7.26 (7 H, m), 7.38 (1 H, d), 7.48 (1 H, d), 7.55 (1 H, d), 9.05 (1 H, s); MS $(M + 1)^+$ req 649.3144; found 649.3155.

Carbamic Acid, [2-[[2-[[(1*H*-Imidazol-2-ylthio)acetyl]-amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (23).** A mixture of the bromo compound 17 (100 mg, 0.157 mmol) and 2-mercaptoimidazole (15.7 mg, 0.157 mmol) in dry THF (10 mL) at room temperature under a nitrogen atmosphere was treated with Et_3N (0.1 mL, 0.714 mmol, 4.5 equiv). After stirring at room temperature for 3 h the mixture was filtered, concentrated in vacuo, and partitioned between EtOAc and H_2O. Drying of the organic layer ($MgSO_4$) and concentration in vacuo gave a white solid which was purified by silica gel chromatography to yield the desired imidazole **23** as an amorphous solid (94 mg, 91%): $[\alpha]^{20}_D$ +7.0° (*c* = 0.10, MeOH); IR (neat) 3240, 2908, 1657, 1521, 1452, 1255, 1073 cm^{-1}; NMR ($CDCl_3$) δ 1.54–2.00 (17 H, m), 3.20–3.29 (1 H, m), 3.32 (1 H, $^1/_2 \times$ ABq, *J* = 14.6 Hz), 3.49 (1 H, $^1/_2 \times$ ABq, *J* = 14.6 Hz), 3.58 (2 H, s), 4.08–4.16 (1 H, m), 4.86 (1 H, br s), 5.06 (1 H, s), 5.08–5.18 (1 H, m), 6.41 (1 H, br s), 6.97–7.38 (10 H, m), 7.56 (1 H, d, *J* = 8.2 Hz), 7.93 (1 H, d, *J* = 7.8 Hz), 8.29 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-phenyl-2-[[(1*H*-1,2,4-triazol-5-ylthio)acetyl]-amino]ethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (24).** Method as for **23** except using 5-mercapto-1,2,4-triazole: yield 93 mg, 90%; $[\alpha]^{20}_D$ +2.0° (*c* = 0.10, MeOH); IR (neat) 3306, 2909, 1657, 1517, 1453, 1264, 1073, 741, 701 cm^{-1}; NMR ($CDCl_3$) δ 1.49–2.01 (17 H, m), 3.20–3.30 (1 H, m), 3.37 (2 H, ABq, *J* = 14.6 Hz), 3.69 (2 H, ABq, *J* = 15.5 Hz), 4.05–4.13 (1 H, m), 4.85 (1 H, s), 5.14 (1 H, br s), 5.19 (1 H, s), 6.50 (1 H, br s), 6.97 (1 H, s), 7.06–7.36 (8 H, m), 7.55 (1 H, d, *J* = 7.8 Hz), 7.94 (1 H, br s), 7.96 (1 H, s), 8.35 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[[1-oxo-3-(1*H*-1,2,4-triazol-5-ylthio)propyl]-amino]-2-phenylethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]-dec-2-yl Ester, [*R*-(*R,*R**)]- (25).** Method as for **24** except using the bromo compound 18: yield 43 mg, 42%; $[\alpha]^{20}_D$ +12° (*c* = 0.10, MeOH); IR (neat) 3306, 2855, 1657, 1529, 1452, 1254, 1073, 774 cm^{-1}; NMR ($CDCl_3$) δ 1.46–1.94 (17 H, m), 2.50–2.63 (2 H, m), 3.15–3.40 (5 H, m), 4.10–4.30 (1 H, m), 4.76 (1 H, s), 5.25 (1 H, br s), 5.36 (1 H, s), 6.22 (1 H, br s), 7.02 (1 H, d, *J* = 2.3 Hz), 7.08–7.50 (9 H, m), 7.56 (1 H, d, *J* = 7.8 Hz), 7.98 (1 H, s), 8.33 (1 H, s).

Carbamic Acid, [2-[[2-[[[(2-Hydroxyphenyl)thio]acetyl]-amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (26).** To a cooled (−60 °C) solution of 2-hydroxythiophenol (19.8 mg, 0.016 mL, 0.157 mmol) in dry THF (10 mL) under a nitrogen atmosphere, was added Bu^nLi (0.098 mL of a 1.6 M solution in hexanes, 0.157 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (36.5 mg, 0.048 mL, 0.314 mmol, 2 equiv). The mixture was warmed to room temperature over 30 min, stirred at room temperature for a further 15 min, then recooled to −60 °C. To the cold mixture was added slowly dropwise, a solution of the bromo compound **17** (100 mg, 0.157 mmol) in dry THF (6 mL). After the addition was complete the mixture was allowed to warm to room temperature overnight and concentrated in vacuo. The residue was partitioned between EtOAc and water, the organic layer dried ($MgSO_4$), concentrated in vacuo, and the residue purified by silica gel chromatography to yield the desired phenol **26** as an amorphous solid (54 mg, 51%); $[\alpha]^{20}_D$ −11° (*c* = 0.10, MeOH); IR (neat) 3305, 2855, 1657, 1531, 1495, 1470, 1450, 1252, 739 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (3 H, s), 1.57–2.00 (14 H, m), 3.23–3.30 (1 H, m), 3.31 (1 H, $^1/_2 \times$ ABq, *J* = 14.4 Hz), 3.42 (1 H, $^1/_2 \times$ ABq, *J* = 14.5 Hz), 3.53 (2 H, s), 4.05 (1 H, br s), 4.86 (1 H, s), 5.03 (1 H, s), 5.13–5.20 (1 H, m), 6.19–6.28 (1 H, m), 6.77–7.66 (15 H, m), 8.13 (1 H, s), 9.04 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[(1-oxo-3-sulfopropyl)amino]-2-phenylethyl]-amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, Monosodium Salt, [*R*-(*R,*R**)]- (27).** A solution of the bromo compound 18 (200 mg, 0.308 mmol) in 95% ethanol (6 mL) and H_2O (2.2 mL) was stirred at room temperature and a solution of Na_2SO_3 (38.8 mg, 0.308 mmol) in H_2O (2.2 mL) was added dropwise. When the addition was complete, the mixture was heated to 80 °C (oil bath temperature) for 2 h. Upon cooling, the alcohol was removed under vacuum and the residue partitioned between EtOAc and H_2O. The aqueous layer was acidified to pH 1 with 1 N HCl, concentrated in vacuo and the residue purified by reverse-phase chromatography to yield the desired monosodium salt of the sulfonic acid **27** as an off-white amorphous solid (104 mg, 52%); $[\alpha]^{20}_D$ −13.6° (*c* = 0.22, MeOH); IR (neat) 3325, 2908, 1695, 1536, 1197, 1048 cm^{-1}; NMR (d^6-DMSO) δ 1.27–1.95 (17 H, m), 2.40–2.55 (2 H, m, obscured by DMSO peak), 2.60–2.75 (2 H, m), 3.20–3.55 (4 H, m, obscured by H_2O), 4.71 (1 H, br s), 4.98–5.01 (1 H, m), 6.71 (1 H, s), 6.96–7.34 (9 H, m), 7.47 (1 H, d, *J* = 7.8 Hz), 7.93 (1 H, br s), 8.36 (1 H, d, *J* = 7.8 Hz), 10.92 (1 H, s).

Methyl Esters 29a–c. The methyl esters **29a–c** were prepared by alkylation of methyl bromoacetate on sulfur with 5-mercapto-1,2,4-triazole,[32] 5-mercapto-1,2,3-triazole,[22] and 5-mercapto-1,2,4-triazol-3-one[23] in dry THF with triethylamine as base.

(1,2,4-Triazol-5-ylthio)acetic acid, Methyl Ester (29a). A solution of 5-mercapto-1,2,4-triazole (7.98 g, 79 mmol) and methyl bromoacetate (12.08 g, 79 mmol) in dry THF (200 mL), stirred at 0 °C under a nitrogen atmosphere, was treated dropwise with a solution of triethylamine (11 mL, 79 mmol) in dry THF (10 mL). When the addition was complete, the mixture was heated at 60 °C for 1 h then stirred at ambient temperature overnight. Filtration and concentration in vacuo gave an orange solid which was recrystallized from EtOAc to yield **29a** (7.12 g, 52%) as colorless crystals mp 113–115 °C (lit. mp[33] 114–116 °C).

(1,2,4-Triazol-5-ylsulfinyl)acetic acid, Methyl Ester (30). A solution of the sulfide **29a** (2 g, 11.6 mmol) in dry CH_2Cl_2 (50 mL) under a nitrogen atmosphere was treated, all at once, with *m*-chloroperbenzoic acid (2.18 g, 12 mmol, 95% wt/wt) and the mixture immediately cooled to 0 °C using an externally applied ice-bath. After 15 min at 0 °C, the mixture was warmed to 40 °C for 1 h and then allowed to stir at room temperature overnight. The resulting white precipitate was filtered and recrystallized from EtOAc to yield **30** (1.55 g, 70%) as fine white needles: NMR (d^6-DMSO) δ 3.66 (3 H, s), 4.41 (2 H, s), 8.85 (1 H, s), 14.9 (1 H, br s).

(32) 5-Mercapto-1,2,4-triazole was bought from Lancaster Chemical Co.

(33) Rudnicka, W.; Sawlewicz, J. 4H-1,2,4-triazole-3-thiol derivatives. II. Synthesis of 4H-1,2,4-triazole-3-acetic acid and some of its derivatives. *Gdansk Tow. Nauk., Rozpr. Wydz. 3* **1967**, *4*, 335–341.

Carboxylic Acids 31a–c and 32. The acids **31a–c** and **32** were prepared by hydrolysis of the esters **29a–c** and **30**, respectively, using methanolic potassium hydroxide.

[(3-Oxo-1,2,4-triazol-5-yl)thio]acetic Acid (31c). To a solution of the ester **29c** (150 mg, 0.794 mmol) in MeOH/H_2O (1/1, 32 mL) was added KOH (159 mg, 2.84 mmol) and the solution stirred overnight at room temperature. After this time, the solution was acidified with glacial acetic acid to pH 4 and concentrated in vacuo. The residue was dissolved in a minimum of water and purified by ion-exchange chromatography (Amberlite IR120H analytical grade) to yield **31c** as a white solid (quantitative yield) [NMR (d^6-DMSO) δ 3.83 (2 H, s), 11.50 (1 H, s), 11.63 (1 H, s)], which was used without further purification.

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-phenyl-2-[[(1*H*-1,2,4-triazol-5-ylthio)acetyl]amino]ethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (24).** A solution of the acid **31a** (62 mg, 0.389 mmol), PFP (72 mg, 0.389 mmol), and DCC (81 mg, 0.389 mmol) in dry DMF (3 mL) was stirred for 3 h at room temperature, then filtered, and the amine **3** (200 mg, 0.389 mmol) added all at once. The resulting mixture was stirred overnight at room temperature, filtered, and partitioned between EtOAc and water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by reverse-phase chromatography to yield the desired 1,2,4-triazole **24** as an amorphous solid (68 mg, 38%); physical data is identical to that described for the alternative synthesis of **24** above.

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-phenyl-2-[[(1*H*-1,2,3-triazol-5-ylthio)acetyl]amino]ethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (33b).** Method as for **24** except using the acid **31b**: yield 72 mg, 76%; $[\alpha]^{20}_D$ −12° (*c* = 0.10, MeOH); IR (neat) 1700, 1657, 1525, 1459, 1377 cm^{-1}; NMR (d^6-DMSO) δ 1.18 (3 H, s), 1.48–1.90 (14 H, m), 3.10–3.50 (4 H, m, obscured by H_2O), 3.64 (2 H, ABq, *J* = 18.1 Hz), 4.68 (1 H, s), 4.92–4.98 (1 H, m), 6.73 (1 H, br s), 6.89–7.28 (9 H, m), 7.43 (1 H, d, *J* = 7.9 Hz), 7.81 (1 H, s), 8.39 (1 H, br s), 10.87 (1 H, s).

Carbamic Acid, [2-[[2-[[[(4,5-Dihydro-5-oxo-1*H*-1,2,4-triazol-3-yl)thio]acetyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (33c).** Method as for **24** except using the acid **31c**: yield 89 mg, 34%; $[\alpha]^{20}_D$ −12° (*c* = 0.10, MeOH); IR (neat) 3358, 2912, 1703, 1665, 1530 cm^{-1}; NMR (d^6-DMSO) δ 1.19 (3 H, s), 1.40–2.00 (14 H, m), 3.10–3.50 (4 H, m, obscured by H_2O), 3.78 (2 H, ABq, *J* = 17.6 Hz), 4.68 (1 H, s), 4.92–4.99 (1 H, m), 6.74 (1 H, br s), 6.90–7.31 (9 H, m), 7.43 (1 H, d, *J* = 7.7 Hz), 7.80 (1 H, br s), 8.47 (1 H, br s), 10.87 (1 H, s), 11.05 (1 H, s), 11.13 (1 H, s).

Carbamic Acid, [1-(1*H*-Indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-phenyl-2-[[(1*H*-1,2,4-triazol-5-ylsulfinyl)acetyl]amino]ethyl]amino]ethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (34).** Method as for **24** except using the acid **32**: yield 83 mg, 32%; $[\alpha]^{20}_D$ +14° (*c* = 0.10, MeOH); IR (neat) 3279, 2907, 2856, 1657, 1535, 1453, 1254, 1051 cm^{-1}; NMR (d^6-DMSO) δ 1.17–2.00 (17 H, m), 3.10–3.50 (3 H, m, obscured by H_2O) 4.01–4.10 (1 H, m), 4.30 (2 H, ABq, *J* = 13.9 Hz), 4.67–4.72 (1 H, m), 4.98–5.03 (1 H, m), 6.74 and 6.78 (1 H, 2 × br s, rotomers), 6.89–7.31 (9 H, m), 7.42 (1 H, d, *J* = 7.5 Hz), 7.76 (1 H, br s), 8.70 (1 H, br s), 8.82 (1 H, s), 10.87 (1 H, s).

Carbamic Acid, [2-[[2-[[1,4-Dioxo-4-(1*H*-tetrazol-5-ylamino)butyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (35).** A solution of the acid 1[13] (468 mg, 0.762 mmol), PFP (154 mg, 0.838 mmol), and DCC (173 mg, 0.838 mmol) was stirred in dry DMF (10 mL) for 3 h at room temperature and filtered, and 5-aminotetrazole monohydrate (94 mg, 0.914 mmol) was added. The resulting mixture was stirred at room temperature for 4 days, filtered, and concentrated in vacuo. The residue was purified by passing through two reverse-phase columns and concentrating the fractions which showed only one peak on an HPLC analytical column to yield the desired amino tetrazole **35** as an amorphous solid (45 mg, 9%); $[\alpha]^{20}_D$ −2.0° (*c* = 0.10, MeOH); IR (neat) 3299, 2907, 1697, 1651, 1595, 1546, 1495, 1453, 1251, 1070, 735 cm^{-1}; NMR (d^6-DMSO) δ 1.19 (3 H, s), 1.45–1.94 (17 H, m), 2.62–2.66 (2 H, m), 3.10–3.45 (5 H, m, obscured by H_2O), 4.07 (1 H, br s), 4.68 (1 H, s), 4.94–5.00 (1 H, m), 6.75 (1 H, s), 6.90–7.32 (9 H, m), 7.43 (1 H, d, *J* = 7.8 Hz), 7.76 (1 H, t, *J* = 5.5 Hz), 8.22 (1 H, br s), 10.89 (1 H, s), 11.59 (1 H, br s).

Carbamic Acid, [2-[[2-[[4-(Hydroxyamino)-1,4-dioxobutyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (36).** Method as for **35** except using hydroxylamine hydrochloride and triethylamine: yield 36 mg, 35%; $[\alpha]^{20}_D$ −1.0° (*c* = 0.10, MeOH); IR (neat) 3322, 2909, 1662, 1532, 1453, 1376, 1256, 1073, 910, 735, 702 cm^{-1}; NMR (d^6-DMSO) δ 1.19 (3 H, s), 1.48–1.95 (14 H, m), 2.15–2.20 (2 H, m), 2.36–2.41 (2 H, m), 3.10–3.50 (4 H, m, obscured by H_2O) 4.69 (1 H, s), 4.95–4.99 (1 H, m), 6.70 (1 H, s), 6.89–7.31 (9 H, m), 7.43 (1 H, d, *J* = 7.8 Hz), 7.76 (1 H, s), 8.17 (1 H, br s), 8.66 (1 H, s), 10.36 (1 H, s), 10.86 (1 H, s); MS (M + 1)$^+$ req 630.3281; found 630.3292.

14-Oxa-2,5,8,13-tetraazapentadecanoic Acid, 3-(1*H*-Indol-3-ylmethyl)-3-methyl-4,9,12-trioxo-7-phenyl-, Tricyclo[3.3.1.1^{3,7}]dec-2-yl Ester, [*R*-(*R,*R**)]- (37).** Method as for **35** except using *O*-methylhydroxylamine hydrochloride and triethylamine: yield 45 mg, 43%; $[\alpha]^{20}_D$ −5.0° (*c* = 0.10, MeOH); IR (neat) 3311, 2909, 1657, 1530, 1375, 1257, 1073, 740, 701 cm^{-1}; NMR (d^6-DMSO) δ 1.24 (3 H, s), 1.50–1.95 (14 H, m), 2.13–2.21 (2 H, m), 2.39–2.45 (2 H, m), 3.10–3.40 (4 H, m, obscured by H_2O) 3.58 (3 H, s), 4.73 (1 H, s), 4.93–5.00 (1 H, m), 6.73 (1 H, br s), 6.94–7.42 (9 H, m), 7.47 (1 H, d, *J* = 7.3 Hz), 7.83 (1 H, br s), 8.23 (1 H, br s), 10.92 (1 H, s), 11.01 (1 H, s).

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