

# 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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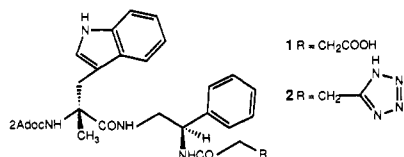
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This paper outlines the synthesis of selected acid mimics of the non-peptide CCK-B selective antagonist CI-988, 1. CCK-B and CCK-A binding affinities of these analogues are described and their CCK-B affinity and selectivity rationalized by consideration 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<sup>3,7</sup>]dec-2-yl [*R*-(*R*\*,*R*\*)]-[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<sup>3,7</sup>]dec-2-yl [*R*-(*R*\*,*R*\*)]-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-[(1-oxo-3-sulfoethyl)amino]-2-phenylethyl]amino]ethyl]carbamate, monosodium salt (27), and tricyclo[3.3.1.1<sup>3,7</sup>]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]carbamate (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.<sup>1</sup> 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.<sup>2</sup> These approaches have led to the development of both CCK-A<sup>3</sup> and CCK-B<sup>4,5</sup> selective antagonists, substance P antagonists,<sup>6,7</sup> angiotensin II antagonists,<sup>8,9</sup> and vasopressin antagonists.<sup>10</sup>

We have recently described the rational design and synthesis of a series of potent and selective non-peptide CCK-B receptor antagonists<sup>11-14</sup> 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<sup>15</sup> and antigestrins<sup>16</sup> properties. Structure-activity relationship studies<sup>14</sup> 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).

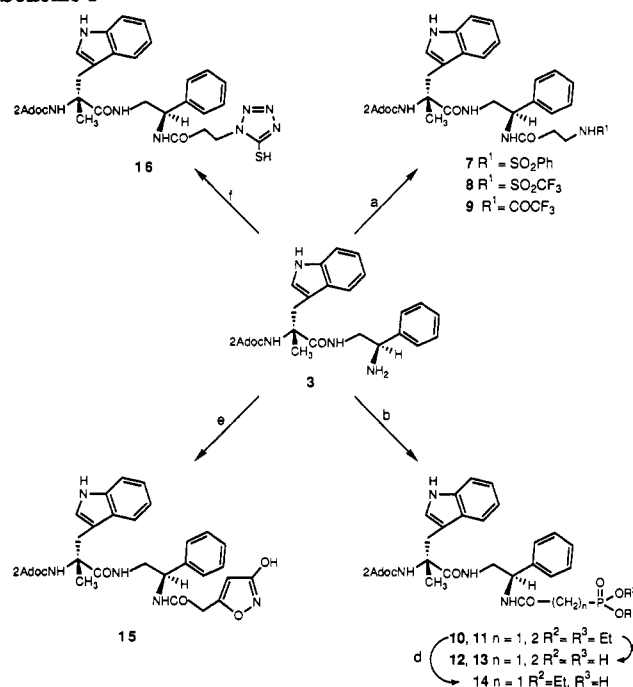


We have previously shown that the carboxylic acid moiety in 1 can be replaced by selected acid mimics<sup>17</sup> to give compounds of similar CCK-B receptor affinity if reduced selectivity, e.g. 2. There appears to be no direct relationship between binding affinity and  $pK_a$  of the acid moiety in 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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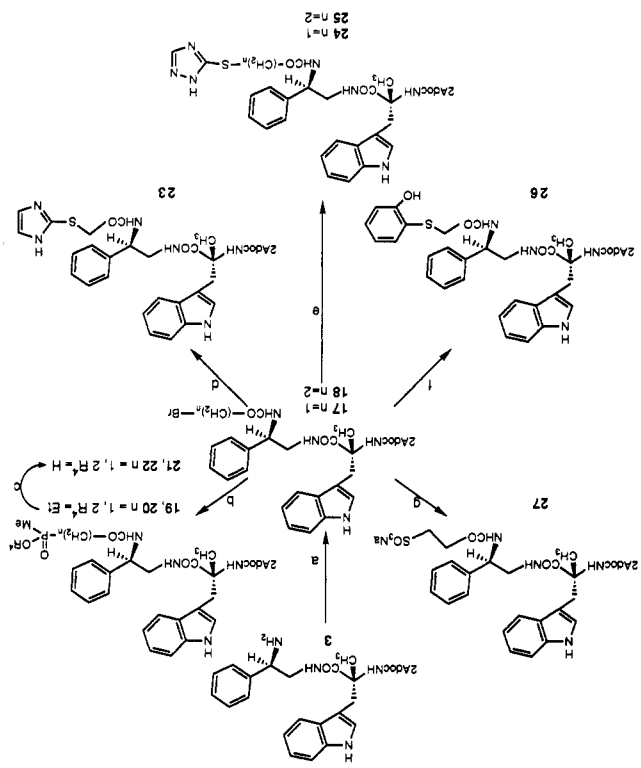
Table I. Physical and Chemical Data of Compounds and Intermediates

compd	molecular formula	mp, °C	anal.	method of purification <sup>a</sup>
7	C <sub>40</sub> H <sub>47</sub> N <sub>5</sub> O <sub>8</sub> S	114.5-115.5	C, H, N	A
8	C <sub>37</sub> H <sub>42</sub> F <sub>3</sub> N <sub>6</sub> O <sub>6</sub> S	112-116	C, H, N	A
9	C <sub>36</sub> H <sub>42</sub> F <sub>3</sub> N <sub>6</sub> O <sub>6</sub> S	112.5-115	C, H, N	A
10	C <sub>37</sub> H <sub>49</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	91-97	C, H, N	B
11	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	96-99	C, H, N	B
12	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	145-151	C, H, N	C
13	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	146-150	C, H, N	C
14	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	136-142	C, H, N	C
15	C <sub>36</sub> H <sub>41</sub> N <sub>6</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	136-143	C, H, N	C
16	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	139-144	C, H, N	C
17	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	139-144	C, H, N	C
18	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	139-144	C, H, N	C
19	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	139-144	C, H, N	C
20	C <sub>37</sub> H <sub>49</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	139-144	C, H, N	C
21	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	139-144	C, H, N	C
22	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	138-144	C, H, N	C
23	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	112-122	C, H, N	D
24	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	102-107.5	C, H, N	D
25	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	119-126.5	C, H, N	D
26	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	93-102	C, H, N	A
27	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	168-177	C, H, N	E
19a	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	113-115	C, H, N	F
19b	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	157.5	C, H, N	F
29c	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	157.5	C, H, N	F
30	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	116.2	C, H, N	f
30b	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	116.2	C, H, N	f
33c	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	118-120	C, H, N	C
34	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	143-149	C, H, N	C
35	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	155-160	C, H, N	C
36	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	118-122	C, H, N	C
37	C <sub>38</sub> H <sub>51</sub> N <sub>7</sub> O <sub>7</sub> P <sub>2</sub> O <sub>6</sub> S <sub>2</sub> H <sub>2</sub> O	109-113	C, H, N	D

<sup>a</sup> Chromatography solvent systems: A, 75% EtOAc/25% hexane; B, EtOAc; C, 75% MeOH/25% H<sub>2</sub>O (reverse-phase medium pressure chromatography); D, 10% MeOH/90% EtOAc; E, 60% MeOH/40% H<sub>2</sub>O (reverse-phase medium pressure chromatography); F, 5% MeOH/95% CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> (M + 1)<sup>+</sup> requires 635.2224; found 635.2233. <sup>c</sup> (M + 1)<sup>+</sup> requires 649.2389; found 649.2389. <sup>d</sup> (M + 1)<sup>+</sup> requires 663.3300; found 663.3311. <sup>e</sup> (M + 1)<sup>+</sup> requires 677.3456; found 677.3468. <sup>f</sup> Recrystallized from EtOAc. <sup>g</sup> Oil, (M + 1)<sup>+</sup> requires 173.0259; found 173.0259.

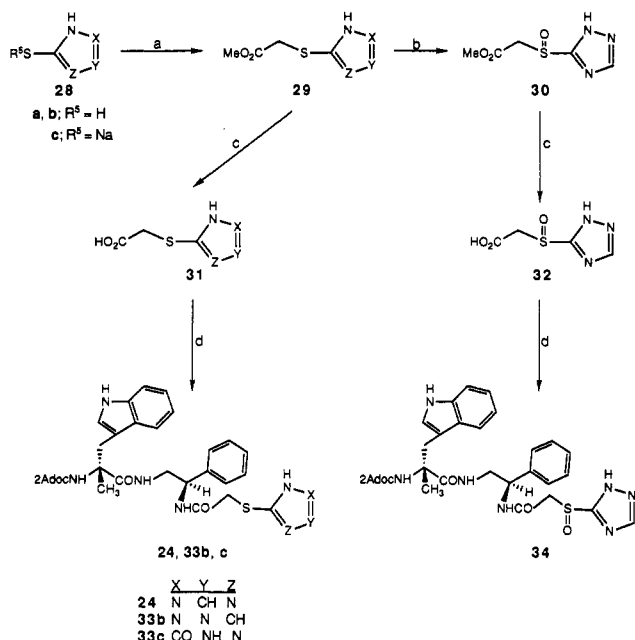
3.13 Where necessary the free acid mimic was liberated by further manipulation.

Scheme II



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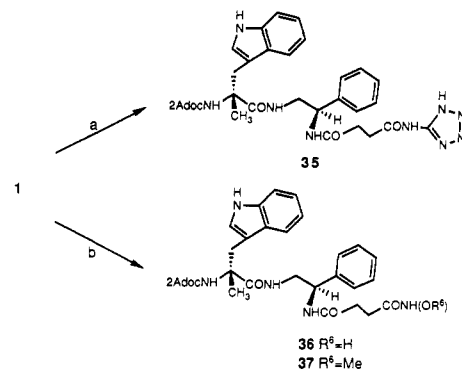
Scheme III



Reagents : (a)  $\text{MeO}_2\text{CCH}_2\text{Br}$ ,  $\text{Et}_3\text{N}$ , THF, 29a(52%); 29b(80%), or  $\text{MeO}_2\text{CCH}_2\text{Br}$ , 29c(18%); (b) *m*-CPBA,  $\text{CH}_2\text{Cl}_2$ , 0–40°C, 30(70%); (c) KOH, MeOH,  $\text{H}_2\text{O}$ , quantitative; (d) (i) DCC, PFP, DMF, R.T.; (ii) 3, R.T., 24(36%); 33b(76%); 33c(34%); 34(32%).

Compounds 7, 8, and 9 (Scheme I) were made by coupling the 1-hydroxybenzotriazole (HOBt) esters of the  $\beta$ -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 phos-

Scheme IV



Reagents : (a) (i) DCC, PFP, DMF, R.T.; (ii) 5-amino-1,2,4-triazole, R.T., 4 days, 35(9%); (b) (i) DCC, PFP, DMF, R.T.; (ii)  $\text{NH}_2(\text{OH})\cdot\text{HCl}$  or  $\text{NH}_2(\text{OMe})\cdot\text{HCl}$ ,  $\text{Et}_3\text{N}$ , 36(35%); 37(43%).

phonic 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 mono-ester 14. Similarly the PFP esters of 3-hydroxy-5-isoxazoleacetic acid<sup>18</sup> and 1-(2-carboxyethyl)tetrazole-5-thiol<sup>19</sup> with the amine 3 gave the 3-hydroxyisoxazole 15 and the tetrazole-5-thiol 16, respectively.

The versatile bromo derivatives 17 and 18 synthesized from the amine 3 were used to prepare the acid mimics 19–27 (Scheme II). An Arbuzov reaction on 17 and 18 with diethyl methylphosphonite gave the phosphonite 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  $\text{Na}_2\text{SO}_3$  in aqueous ethanol.

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

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Table III. Point Charge Monoanionic Acid Mimics—CCK Receptor Binding Affinities<sup>a</sup> and pK<sub>a</sub> Data<sup>b</sup>

compd	R	IC <sub>50</sub> (nM)		A/B ratio	pK <sub>a</sub>
		CCK-B	CCK-A		
1	CH <sub>2</sub> COOH	1.7 (1.3–3.7)	4500 (1200–8500)	2500	5.6
7	CH <sub>2</sub> NHSO <sub>2</sub> Ph	70 (50–122)	300 (260–340)	4.3	>9.5
8	CH <sub>2</sub> NHSO <sub>2</sub> CF <sub>3</sub>	77 (62–98)	680 (620–770)	9	7.9
9	CH <sub>2</sub> NHCOCF <sub>3</sub>	110 (63–170)	790 (680–970)	7	>9.5
26	S(C <sub>6</sub> H <sub>4</sub> )-o-OH	80 (65–99)	510 (480–540)	6.4	>9.5
37	CH <sub>2</sub> CONH(OMe)	21 (16–28)	1500 (1100–1800)	71	>9.5

<sup>a-c</sup> Footnotes same as in Table II.

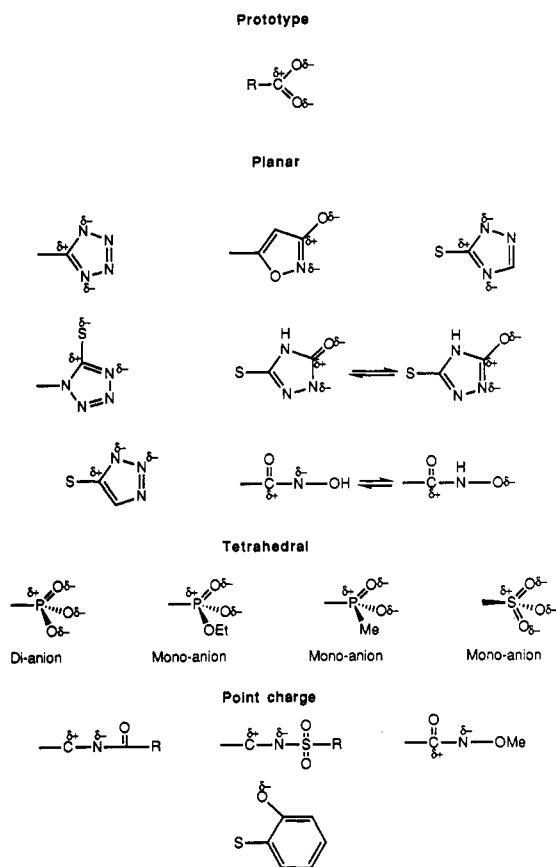


Figure 1. Partial charges for acid mimics.

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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> values of 27 and 23 nM, respectively, is disfavored. The monoester 14 (IC<sub>50</sub> = 12 nM) and the

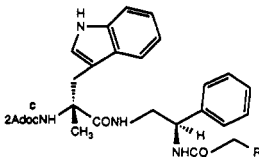
phosphinic acids 21 and 22 (IC<sub>50</sub> = 12 and 23 nM, respectively) have IC<sub>50</sub> values around 1 order of magnitude higher than that of the carboxylic acid 1 (IC<sub>50</sub> = 1.7 nM), suggesting that a tetrahedron geometry at the acid center is not optimum for CCK-B binding. However the sulfonic acid 27, which also has a tetrahedral acid moiety, has an IC<sub>50</sub> = 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<sup>27</sup> 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,<sup>28</sup> and Ser(SO<sub>3</sub>H), Thr(SO<sub>3</sub>H), or Hyp(SO<sub>3</sub>H) in anticonvulsant studies with Ac-CCK-7 analogues.<sup>29</sup> 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<sub>3</sub>H 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<sub>a</sub> 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<sup>14</sup> and

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**Table IV.** Charge Distributed Tetrahedral Acid Mimics—CCK Receptor Binding Affinities<sup>a</sup> and p*K<sub>a</sub>* Data<sup>b</sup>


compd	R	IC <sub>50</sub> (nM)		A/B ratio	p <i>K<sub>a</sub></i>
		CCK-B	CCK-A		
1	CH <sub>2</sub> COOH	1.7 (1.3–3.7)	4500 (1200–8500)	2500	5.6
12	P(O)(OH) <sub>2</sub>	27 (26–28)	5200 (2300–17000)	190	3.4, 7.7
13	CH <sub>2</sub> P(O)(OH) <sub>2</sub>	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 <sub>2</sub> P(O)(OH)Me	23 (16–27)	4400 (3900–4900)	190	3.7
27	CH <sub>2</sub> SO <sub>3</sub> Na	1.3 (1.0–1.6)	1010 (930–1100)	780	–

<sup>a-c</sup> 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.<sup>27–29</sup>

## Experimental Section

**Biological Assays.**<sup>30,31</sup> 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 20000g. 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<sub>2</sub>, 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 20000g. 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<sub>2</sub>, 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 [<sup>125</sup>I]-Bolton Hunter conjugated CCK (26–33) ([<sup>125</sup>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.** p*K<sub>a</sub>* 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<sup>3,7</sup>]-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<sup>3,7</sup>]-dec-2-yl [*R*-(*R*\*,*R*\*)]-[2-[[2-amino-2-phenethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate<sup>13</sup> (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%): [ $\alpha$ ]<sub>D</sub><sup>20</sup> –57° (c = 0.10, CHCl<sub>3</sub>); IR (neat) 1730, 1329, 1162, 1027, 912 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) 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<sup>3,7</sup>]-dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (8).** Method as for 7 except using *N*-[(trifluoromethyl)sulfonyl]-β-alanine (5): yield 356 mg, 64%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –1.9° (c = 0.10, CHCl<sub>3</sub>); IR (neat) 1794, 1722, 1668, 1377, 1193 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) 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<sup>3,7</sup>]-dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (9).** Method as for 7 except using *N*-(trifluoroacetyl)-β-alanine (6): yield 281

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mg, 54%;  $[\alpha]_D^{20}$  -10.5° ( $c = 0.10$ ,  $\text{CHCl}_3$ ); IR (neat) 1794, 1728, 1163, 1027, 908  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  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<sup>3,7</sup>]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  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  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,  $1/2 \times$  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-oxo-propyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1<sup>3,7</sup>]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  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  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,  $1/2 \times$  ABq,  $J = 14.6$  Hz), 3.50 (1 H,  $1/2 \times$  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<sup>3,7</sup>]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  $\text{CH}_2\text{Cl}_2$  (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%);  $[\alpha]_D^{20} +2^\circ$  ( $c = 0.10$ , MeOH); IR (neat) 3307, 2905, 1659, 1529, 1254, 1073  $\text{cm}^{-1}$ ; NMR ( $d^6$ -DMSO)  $\delta$  1.10–2.20 (17 H, m), 2.58–2.70 (2 H, m), 2.80–4.00 (4 H, m, obscured by  $\text{H}_2\text{O}$ ), 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (13).** Method as for 12 except using the diethyl phosphonate 11: yield 25 mg, 43%;  $[\alpha]_D^{20} -1.8^\circ$  ( $c = 0.11$ , acetone); IR (neat) 3393, 2857, 1689, 1657, 1534, 1254  $\text{cm}^{-1}$ ; NMR ( $d^6$ -acetone)  $\delta$  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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (14).** Method as for 12 except using only 1 equiv of bromotrimethylsilane: yield 26 mg, 25%;  $[\alpha]_D^{20} -1.90$  ( $c = 0.10$ , MeOH); IR (neat) 3305, 2909, 1661, 1533, 1495, 1253, 1101, 1071, 1047, 989, 910, 734  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3 + 1$  drop  $d^4$ -MeOH)  $\delta$  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 ( $M + 1$ )<sup>+</sup> 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (15).** A solution of 3-hydroxyisoxazole-5-acetic acid<sup>18</sup>

(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%);  $[\alpha]_D^{20} -10^\circ$  ( $c = 0.10$ , MeOH); IR (neat) 3289, 2904, 1666, 1528, 1461, 1258  $\text{cm}^{-1}$ ; NMR ( $d^6$ -DMSO)  $\delta$  1.18–1.91 (17 H, m), 3.10–3.50 (3 H, m, obscured by  $\text{H}_2\text{O}$ ), 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (16).** Method as for 15 except using 1-(2-carboxyethyl)tetrazole-5-thiol<sup>19</sup> in DMF: yield 112 mg, 43%;  $[\alpha]_D^{20} -1.0^\circ$  ( $c = 0.10$ , MeOH); IR (neat) 3312, 2922, 2854, 1661, 1511, 1459, 1378, 1253, 1072  $\text{cm}^{-1}$ ; NMR ( $d^6$ -DMSO)  $\delta$  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  $\text{H}_2\text{O}$ ), 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 ( $M + 1$ )<sup>+</sup> 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<sup>3,7</sup>]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  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  1.46–2.00 (17 H, m), 3.32 (1 H,  $1/2 \times$  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<sup>3,7</sup>]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  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  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,  $1/2 \times$  ABq,  $J = 14.7$  Hz), 3.45 (1 H,  $1/2 \times$  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<sup>3,7</sup>]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  $\text{cm}^{-1}$ ; NMR ( $\text{CDCl}_3$ )  $\delta$  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 ( $M + 1$ )<sup>+</sup> 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (20).** Method as for 19 except using the bromo compound 18: yield 200 mg, 55%; NMR (CDCl<sub>3</sub>)  $\delta$  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-[[3-(Hydroxymethylphosphinyl)-acetyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (21).** Method as for 12 except using phosphinite ester 19: yield 33 mg, 28%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –2.38° (*c* = 0.10, MeOH); NMR (d<sup>6</sup>-DMSO)  $\delta$  1.27–2.10 (20 H, m), 2.65–2.84 (2 H, m), 3.00–3.40 (4 H, m, obscured by H<sub>2</sub>O), 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)<sup>+</sup> 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (22).** Method as for 12 except using phosphinite ester 20: yield 36 mg, 37%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –5.26° (*c* = 0.09, MeOH); IR (neat) 3303, 2910, 1660, 1531, 1495, 1453, 1376, 1255, 1172, 1101, 1073, 981, 734 cm<sup>–1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  1.40–2.05 (22 H, m), 2.50–2.65 (2 H, m), 3.20–3.50 (3 H, m, obscured by H<sub>2</sub>O), 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)<sup>+</sup> req 649.3144; found 649.3155.

**Carbamic Acid, [2-[[[2-[[3-(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<sup>3,7</sup>]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<sub>3</sub>N (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<sub>2</sub>O. Drying of the organic layer (MgSO<sub>4</sub>) 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%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> +7.0° (*c* = 0.10, MeOH); IR (neat) 3240, 2908, 1657, 1521, 1452, 1255, 1073 cm<sup>–1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (24).** Method as for 23 except using 5-mercapto-1,2,4-triazole: yield 93 mg, 90%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +2.0° (*c* = 0.10, MeOH); IR (neat) 3306, 2909, 1657, 1517, 1453, 1264, 1073, 741, 701 cm<sup>–1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (25).** Method as for 24 except using the bromo compound 18: yield 43 mg, 42%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +12° (*c* = 0.10, MeOH); IR (neat) 3306, 2855, 1657, 1529, 1452, 1254, 1073, 774 cm<sup>–1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>3,7</sup>]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<sup>+</sup>Li (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<sub>4</sub>), concentrated in vacuo, and the residue purified by silica gel chromatography to yield the desired phenol 26 as an amorphous solid (54 mg, 51%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> –11° (*c* = 0.10, MeOH); IR (neat) 3305, 2855, 1657, 1531, 1495, 1470, 1450, 1252, 739 cm<sup>–1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>3,7</sup>]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<sub>2</sub>O (2.2 mL) was stirred at room temperature and a solution of Na<sub>2</sub>SO<sub>3</sub> (38.8 mg, 0.308 mmol) in H<sub>2</sub>O (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<sub>2</sub>O. 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%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> –13.6° (*c* = 0.22, MeOH); IR (neat) 3325, 2908, 1695, 1536, 1197, 1048 cm<sup>–1</sup>; NMR (d<sup>6</sup>-DMSO)  $\delta$  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<sub>2</sub>O), 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,<sup>32</sup> 5-mercapto-1,2,3-triazole,<sup>22</sup> and 5-mercapto-1,2,4-triazol-3-one<sup>23</sup> 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<sup>33</sup> 114–116 °C).

**(1,2,4-Triazol-5-ylsulfonfyl)acetic acid, Methyl Ester (30).** A solution of the sulfide 29a (2 g, 11.6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (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<sup>6</sup>-DMSO)  $\delta$  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. 4*H*-1,2,4-triazole-3-thiol derivatives. II. Synthesis of 4*H*-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<sub>2</sub>O (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*<sup>6</sup>-DMSO)  $\delta$  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<sup>3,7</sup>]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<sub>4</sub>) 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (33b).** Method as for 24 except using the acid 31b: yield 72 mg, 76%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -12° (*c* = 0.10, MeOH); IR (neat) 1700, 1657, 1525, 1459, 1377 cm<sup>-1</sup>; NMR (*d*<sup>6</sup>-DMSO)  $\delta$  1.18 (3 H, s), 1.48–1.90 (14 H, m), 3.10–3.50 (4 H, m, obscured by H<sub>2</sub>O), 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (33c).** Method as for 24 except using the acid 31c: yield 89 mg, 34%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -12° (*c* = 0.10, MeOH); IR (neat) 3358, 2912, 1703, 1665, 1530 cm<sup>-1</sup>; NMR (*d*<sup>6</sup>-DMSO)  $\delta$  1.19 (3 H, s), 1.40–2.00 (14 H, m), 3.10–3.50 (4 H, m, obscured by H<sub>2</sub>O), 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (34).** Method as for 24 except using the acid 32: yield 83 mg, 32%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +14° (*c* = 0.10, MeOH); IR (neat) 3279,

2907, 2856, 1657, 1535, 1453, 1254, 1051 cm<sup>-1</sup>; NMR (*d*<sup>6</sup>-DMSO)  $\delta$  1.17–2.00 (17 H, m), 3.10–3.50 (3 H, m, obscured by H<sub>2</sub>O), 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  $\times$  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-yl-amino)butyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (35).** A solution of the acid 1<sup>13</sup> (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%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> -2.0° (*c* = 0.10, MeOH); IR (neat) 3299, 2907, 1697, 1651, 1595, 1546, 1495, 1453, 1251, 1070, 735 cm<sup>-1</sup>; NMR (*d*<sup>6</sup>-DMSO)  $\delta$  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<sub>2</sub>O), 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-dioxo-butyl]amino]-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, Tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (36).** Method as for 35 except using hydroxylamine hydrochloride and triethylamine: yield 36 mg, 35%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -1.0° (*c* = 0.10, MeOH); IR (neat) 3322, 2909, 1662, 1532, 1453, 1376, 1256, 1073, 910, 735, 702 cm<sup>-1</sup>; NMR (*d*<sup>6</sup>-DMSO)  $\delta$  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<sub>2</sub>O), 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)<sup>+</sup> 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<sup>3,7</sup>]dec-2-yl Ester, [*R*-(*R*\*,*R*\*)]- (37).** Method as for 35 except using *O*-methylhydroxylamine hydrochloride and triethylamine: yield 45 mg, 43%; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -5.0° (*c* = 0.10, MeOH); IR (neat) 3311, 2909, 1657, 1530, 1375, 1257, 1073, 740, 701 cm<sup>-1</sup>; NMR (*d*<sup>6</sup>-DMSO)  $\delta$  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<sub>2</sub>O), 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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