Non-Peptide Cholecystokinin-B/Gastrin Receptor Antagonists Based on Bicyclic, Heteroaromatic Skeletons

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A series of potent and selective cholecystokinin-B/gastrin receptor antagonists based on the dibenzobicyclo[2.2.2]octane (BCO) skeleton which have recently been described were found to show species-dependent behavior when examined in rat and dog models. We now report the discovery of compounds in which the BCO skeleton has been replaced with bicyclic, heteroaromatic frameworks, such as a 5,6-disubstituted indole or benzimidazole. These new ligands maintain the affinity and selectivity profile of the previous compounds *in vitro* but show a much more consistent behavior pattern *in vivo*. Representative examples of this class of compound have been shown to inhibit pentagastrin-stimulated acid secretion when administered intravenously at doses of 0.1 μmol kg^{-1} or less.

Introduction

The hormones gastrin and cholecystokinin are structurally related peptides for which two classes of receptor have been recognized. These are designated cholecystokinin-A (CCK_A), found predominantly in gallbladder[1] and pancreatic tissue,[2] as well as in a number of areas of the brain, such as the posterior hypothalamus,[3] and cholecystokinin-B (CCK_B)/gastrin, found in gastric tissue[4] and in the cortical areas of the brain.[5]

In recent publications[6,7] we have described the design, synthesis, and optimization of a new class of selective CCK_B/gastrin receptor antagonists based on a dibenzobicyclo[2.2.2]octane (BCO) skeleton. We were able to show how the side chains attached to the BCO could be varied so as to produce compounds with affinities for CCK_B/gastrin receptors in the nanomolar range and selectivities, relative to CCK_A receptors, of at least 1000-fold. In this paper we report *in vivo* data which shows that this class of compounds was prone to variability between rat and dog models. Thus, whereas the BCO molecules were reasonably potent in their ability to antagonize pentagastrin-stimulated gastric acid secretion when administered intravenously to Ghosh and Schild anaesthetized rats, they were 700-fold less active as antagonists when given to chronic gastric fistula dogs by a similar route.

This paper will then show that the variability of behavior *in vivo* was overcome by diversifying the chemistry into new skeletal types. The choice of replacements for the BCO framework was influenced by molecular modeling, which identified the essential features of the molecules involved in interactions with the CCK_B/gastrin receptor. A number of the compounds derived in this way displayed comparable CCK_B/gastrin receptor affinity and selectivity to the most potent BCO's and, moreover, were of equivalent activity in both of the models *in vivo*.

Chemistry

The compounds described for the first time in this paper were prepared according to Schemes 1−5. The naphthalene derivative **3** was prepared from naphthalene-2,3-dicarboxylic acid anhydride as shown in Scheme 1 by treatment of the anhydride with 1-adamantanemethylamine in THF. Derivatives **4** and **6** were prepared respectively by reacting compound **3** with either D-proline benzyl ester or 1(*S*)-[[[3,5-bis(benzyloxycarbonyl)phenyl]amino]carbonyl]-2-phenylethylamine (prepared as described previously[7]) followed by hydrogenation using 10% palladium on charcoal.

Scheme 2 firstly shows how indole-5,6-dicarboxylic acid anhydride **24** was prepared in six steps from 4-methylphthalic acid. Nitration with fuming nitric acid followed by esterification[8] gave predominantly the mononitro compound **20** which, after recrystallization, was treated with dimethylformamide dimethyl acetal to give the enamine **21**. On treatment with hydrogen and 10% palladium on charcoal in toluene as solvent, two products could be observed. When the reaction was performed in concentrated solutions, the predominant material was the 10-membered ring dimer **23**, whereas in dilute solutions (<5 g/L) compound **22**, the desired material, was the sole, isolable product. The dimethyl ester **22** was saponified with aqueous sodium hydroxide and the resulting acid converted to the anhydride by heating to 120 °C under vacuum. The same scheme then shows how the anhydride **24** was converted into compounds **7**, **8**, **12**, **15**, and **17**. The anhydride was opened using an appropriately protected 3,5-disubstituted anilide of phenylalanine or a close amino acid analogue. As the ring opening was not regioselective, a mixture of acids was formed by this procedure, but the regioisomer leading to compounds **7**, **12**, **15**, and **17** was insoluble under these reaction conditions and was isolated by filtration. Compounds **7**, **12**, **15**, and **17** were prepared by coupling the appropriate amine ($R\text{-}NH_2$) to the acid using bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBrOP) in dichloromethane and deprotection, either by hydrogenolysis of the benzyl esters or ammonolysis of the POM-protected tetrazoles.

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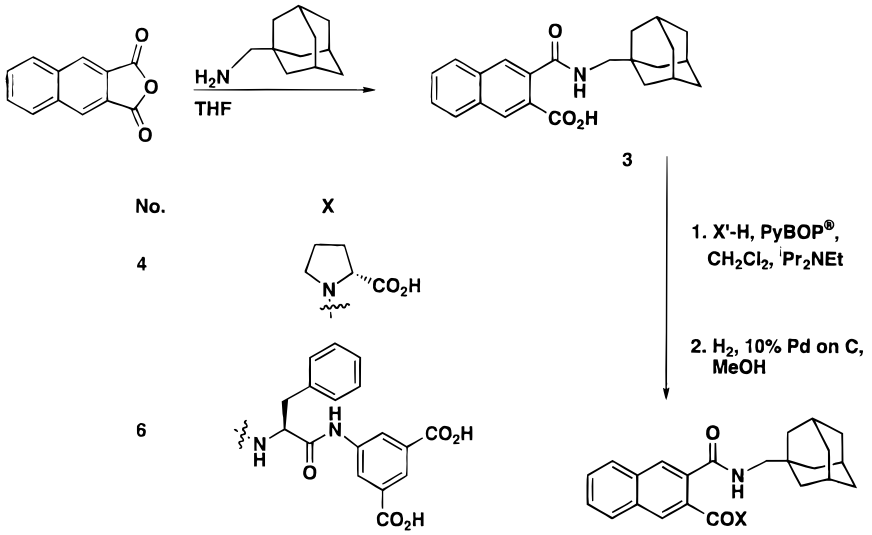
Scheme 1. Synthesis of Compounds **3**, **4**, and **6**



X'-H is the benzyl (4) and di-benzyl (6) ester precursor to the sidechain X

Compound **8**, the regioisomer of compound **7**, was prepared in an analogous fashion using the more soluble regioisomeric acid generated by the anhydride ring opening.

Scheme 3 shows the preparation of the various benzimidazole derivatives described in this paper. Benzimidazole-5,6-dicarboxylic acid[9] was converted to its anhydride **26** by heating to 120 °C under vacuum. The anhydride was opened and the resulting acids elaborated and deprotected in a fashion analogous to that described in Scheme 2 to give compounds **9**, **13**, **16**, **18**, and **19**.

Compound **11** was prepared as shown in Scheme 4. Dimethyl 5,6-benzothiophenedicarboxylate[10] was saponified and the resulting acid converted to its anhydride **28** by heating in acetic anhydride. This was reacted with 1-adamantanemethylamine in THF to give a regioisomeric mixture of amide acids (only one regioisomer **29** shown in scheme). PyBOP coupling of this mixture with 1(*S*)-[[[3,5-bis(*tert*-butyloxycarbonyl)phenyl]amino]carbonyl]-2-phenylethylamine in dichloromethane in the presence of diisopropylethylamine, gave the di-*tert*-butyl ester of compound **11** which was deprotected using TFA.

Scheme 5 shows the synthesis of compound **10**. Dimethyl 4-hydroxy-5-iodophthalate (**30**)[11] was reacted with (trimethylsilyl)acetylene in dioxane at reflux in the presence of bis(triphenylphosphine)palladium(II) chloride and cuprous iodide. This resulted in the 2-TMS-substituted benzofuran derivative **31**, which was treated sequentially with TBAF in THF, sodium hydroxide, and acetic anhydride to give benzofuran-5,6-dicarboxylic acid anhydride (**32**). The anhydride was opened using 1(*S*)-[[[3,5-bis(allyloxycarbonyl)phenyl]amino]carbonyl]-2-phenylethylamine in refluxing acetonitrile to give a mixture of regioisomeric amide acids (only one regioisomer **33** shown in scheme). PyBOP coupling of this mixture with 1-adamantanemethylamine in dichloromethane, in the presence of diisopropylethylamine, gave the diallyl ester of compound **10** which was deprotected using tetrakis(triphenylphosphine)palladium-(0) in diethylamine and THF.

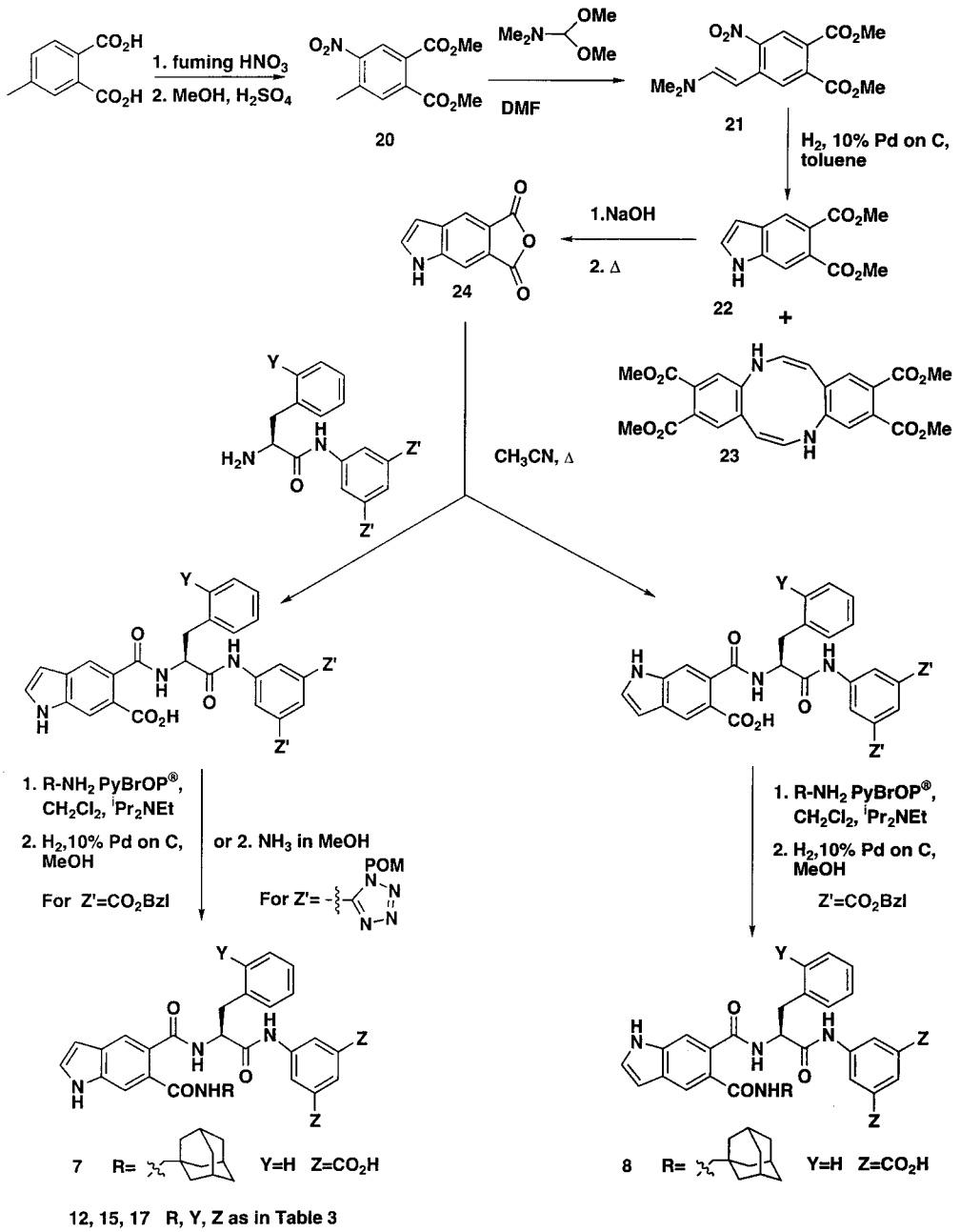
Molecular Modeling

Molecular modeling analyses were carried out using the multiconformational composite molecular potential field method of Vinter and Trollope.[12] This method allows sets of "fieldpoints" to be defined for individual conformations of a molecule equipped with XED (extended electronic distribution) charges,[13] rather than atom-centered charges. The fieldpoints are derived such that the properties of the structure are distilled into three classes of fieldpoint: namely, positive and negative electrostatic fieldpoints, and a third class of "sticky" points that define the van der Waals surface around the molecule. Comparisons between pairs of molecules are then made on the basis of the pattern of fieldpoints, rather than the structural features of the molecule. This provides a rapid method of comparing fieldpoints from sets of conformations, in contrast to comparing single structures which commonly form the basis of most QSAR studies. Hence, fieldpoints were calculated for all the conformations of a structure lying within 3 kcal/mol of the calculated global minimum, typically 10−40 conformations; that, is all the conformations that have a >99% probability of existing at body temperature. Each pair comparison was carried out three times, such that the three types of fieldpoint were compared on an individual basis and the best overall overlays retained. The process took about 18 h to reach completion on a Silicon Graphics Indy 4000 in a typical case involving the comparison of two structures with 20 conformations each.

Results and Discussion

We have previously described compound **5** as a potent CCK_B/gastrin selective receptor antagonist[9] *in vitro* with a pK_i of 8.80 at CCK_B/gastrin sites in mouse cortical membranes[14] and a 1300-fold selectivity over CCK_A binding sites in guinea pig pancreatic cells.[15] Table 4 shows the behavior of this compound when examined *in vivo*, and this was typical of the profile shown for BCO derivatives in general. In an anaesthetized Ghosh and Schild rat preparation, the compound, when administered intravenously at a dose of 0.025 μmol/kg, gave a peak inhibition of 79% of the acid secretory

Scheme 2. Synthesis of Indole Derivatives **7**, **8**, **12**, **15**, and **17**



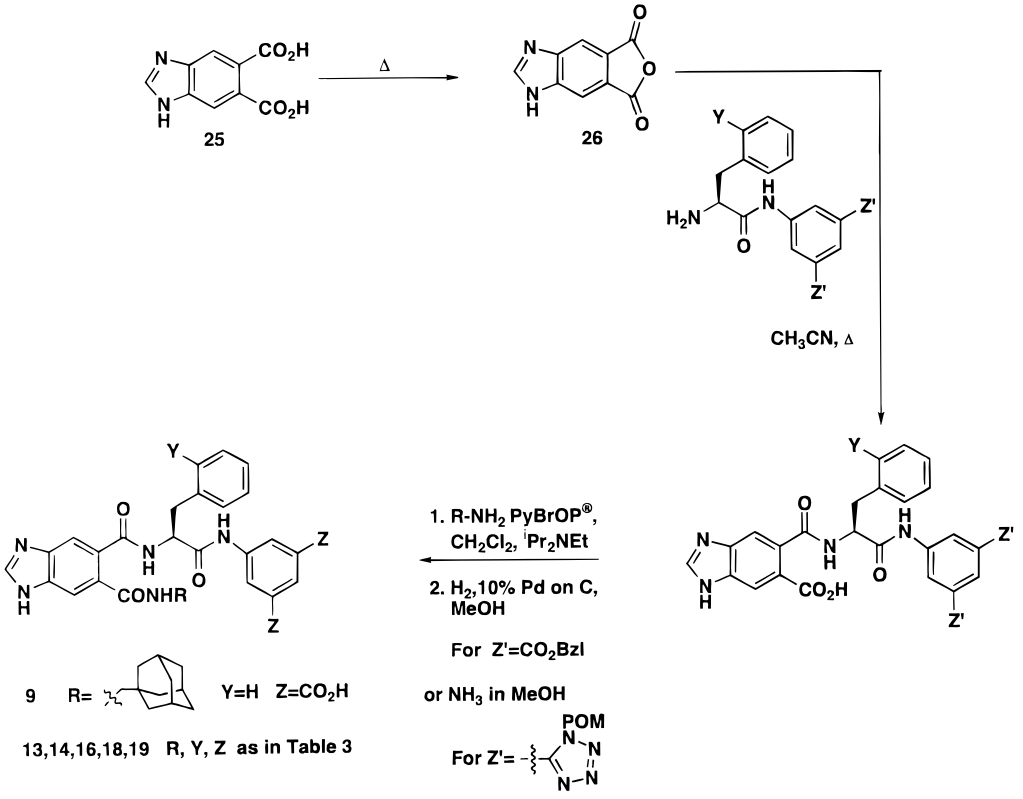
12, 15, 17 R, Y, Z as in Table 3

response observed for a submaximal infusion of pentagastrin. Thus it was at least 40-fold more potent in this assay than the standard CCK_B/gastrin receptor ligand L-365,260. However, when compound **5** was examined in conscious chronic gastric fistula dogs, a very different picture emerged. Whereas L-365,260 was effective in the dog at doses similar to its activity in the rat, the BCO derivative **5** was at least *700-fold* less potent in this model. This was clearly a problem that had to be addressed for at least two reasons. Firstly, a discrepancy of this magnitude between the two species used most frequently in toxicological studies would have led to difficulties in any development work involving compound **5**, or any other BCO with a similar profile. Secondly, given the interspecies nature of the variation, potential activity in human could be considered quantitatively unpredictable.

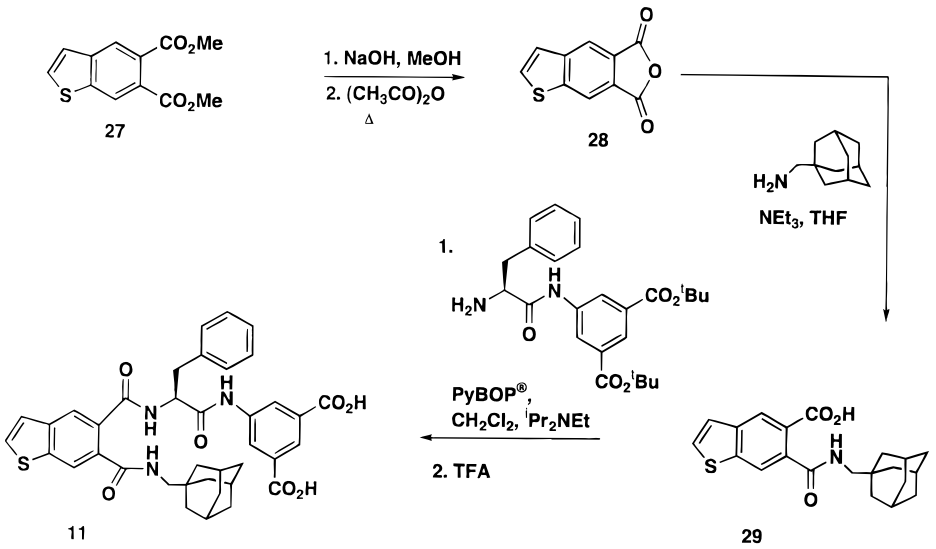
Side chain manipulation in the BCO series failed to improve the consistency between species. Therefore we chose to examine the impact of variations to the skeleton. We were initially guided by the compounds in Table 1 which shows that a 2,3-disubstituted naphthalene could be used as a replacement skeleton. Thus compounds **3** and **4** had activities and selectivities that were comparable with those of their corresponding BCO counterparts. When the optimum compounds in the BCO series, such as compound **5**, were identified from *in vitro* studies, these side chains were also applied to the naphthalene skeleton to give compound **6**. As seen in Table 2 it was about 10-fold less potent at CCK_B/gastrin receptors than compound **5**, and significantly less selective over CCK_A receptors. However, the existence of another group of compounds with reasonable receptor affinity, but with a skeleton structurally dissimilar to the BCO derivatives, provided the opportunity to use molecular modeling to examine the important features within the skeletons that were required for receptor affinity.

Compounds **5** and **6** were subjected to a molecular modeling examination. Typical low-energy conforma-

Scheme 3. Synthesis of Benzimidazole Derivatives **9**, **13**, **14**, **16**, **18**, and **19**



Scheme 4. Synthesis of Benzothiophene Derivative **11**



tions are shown for each structure in Figure 1, and it is apparent that there are significant electrostatic field points which are principally due to the skeletons in each case. Whereas both molecules have a series of electropositive field points of varying magnitude around the periphery of the skeleton, there is in addition a large electronegative field point that results from the focus of the π electron clouds of the isolated aromatic rings in compound **5** which is absent in the low-energy conformations of compound **6**. As the naphthalene derivative was significantly less potent and selective than the corresponding BCO, it was decided to try to design compounds which reproduced the electronegative field point noted in the model of compound **5**. It was felt that this might be achieved by the introduction of a heteroatom into the aromatic bicyclic structure and so an indole derivative, compound **7**, was devised and compared with compound **5** by molecular modeling. A large number of close overlays, as judged by the overlay energy output from the calculation, were obtained, and the one shown in Figure 2 is a typical example.

Compound **7** was prepared, and we were impressed with the results (Table 2) which show that it has a profile in the *in vitro* assays that is indistinguishable from that of compound **5** in line with our modeling expectations. This was clearly a very significant finding and suggested that the modeling approach could be meaningfully applied across these series of compounds.

Compounds **7** and **8** are regioisomers in which the side chains have been exchanged relative to the indole nitrogen. The structures of the two compounds were assigned unambiguously by ^{1}H NOE difference exper-

Scheme 5. Synthesis of Benzofuran Derivative **10**

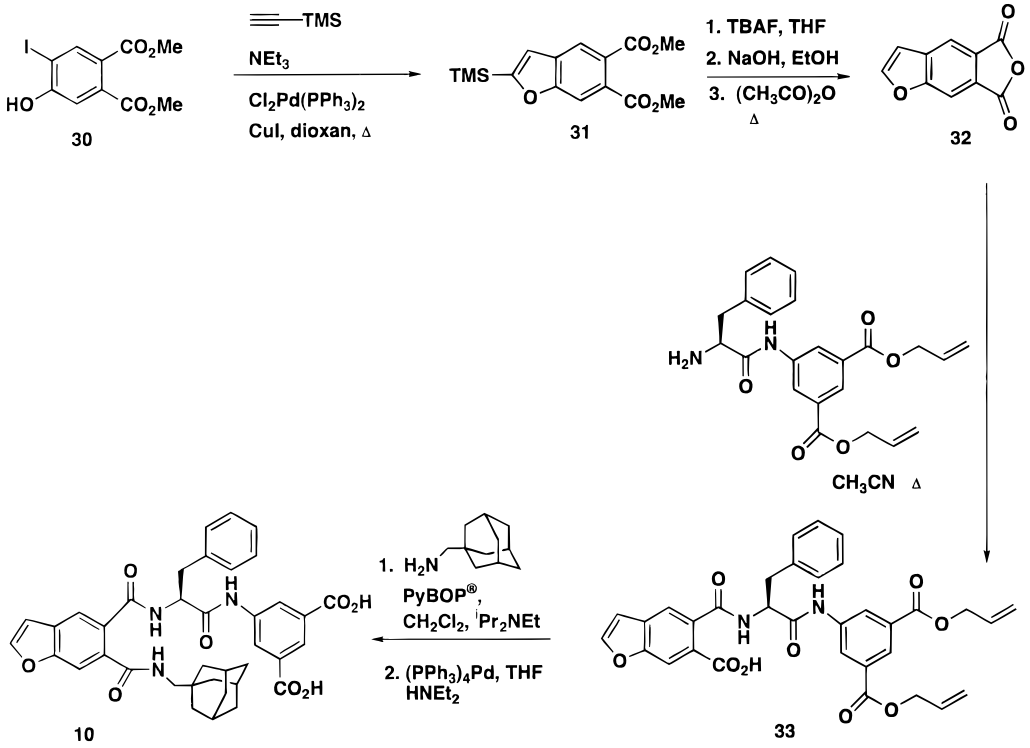
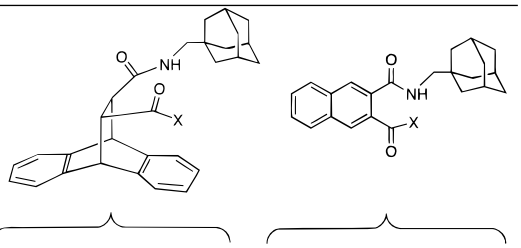
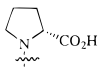


Table 1. Comparison of Receptor Affinity Values for CCK_B/Gastrin Antagonists in Which the Skeleton Has Been Varied

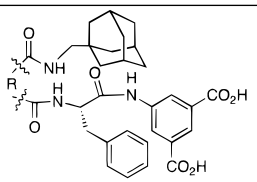


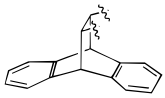
X	no.[a,d]	CCK_B/ gastrin[b]	CCK_A [c]	no.[a]	CCK_B/gastrin[b]	CCK_A [c]
OH	**1**	6.27±0.08	5.08	**3**	5.54±0.04	4.93
	**2**	6.05±0.03	5.09	**4**	6.47±0.08	5.45

[a] Compounds were tested as the *N*-methyl-D-glucamine salts. [b] $pK_i \pm$ SEM competition with 20 pM [^{125}I]BH-CCK-8S for CCK_B/gastrin binding sites in mouse cortical homogenates from at least three separate experiments. [c] pK_i competition with 20 pM [^{125}I]BH-CCK-8S at CCK_A binding sites on guinea pig pancreatic cells from at least two separate experiments. Approximate SEM 0.2 log units. [d] Compound **1** was a mixture of enantiomers, and compound **2** was a mixture of diastereoisomers.

iments and are as shown in Table 2. Compound **8** also had reasonable activity *in vitro*, and this is not entirely unexpected as the two regioisomers can be entirely superimposed sterically except for the position of the nitrogen atom in the five-membered ring. This leads to a situation whereby the negative fieldpoint is in the correct position relative to the rest of the molecule, but the positive fieldpoint distribution is different than that found for compounds **5** and **7**. This may in part account for the modest decrease in affinity observed for this compound relative to its regioisomer. Oxygen and sulfur were introduced into the skeleton instead of nitrogen, giving rise to the benzofuran **10** and the benzothiophene **11**, both of which had the desired fields associated with the skeletons, and both of which, while

Table 2. Comparison of Receptor Affinity Values for CCK_B/Gastrin Antagonists in Which the Skeleton Has Been Varied with the Optimal Side Chains



no.[a,d]	R	CCK_B/gastrin[b]	CCK_A [c]
5		8.80±0.08	5.68
6		7.88±0.05	6.07
7		8.96±0.24	5.44
8		7.87±0.16	5.47
9		8.28±0.13	5.83
10		8.27±0.09	5.42
11		8.91±0.04	5.65

[a] Compounds were tested as the bis(*N*-methyl-D-glucamine) salts. [b,c] See corresponding footnotes to Table 1. [d] Compound **5** was a single diastereoisomer of unknown absolute configuration. Compounds **6**–**9** were single compounds as shown, and compounds **10** and **11** were a mixture of regioisomers with the side chains at positions 5 and 6 reversed.

mixtures of regioisomers, gave affinities and selectivities in line with modeling-based expectations.

The occurrence of regioisomers for these mono-heteroaromatic analogues was a considerable inconve-

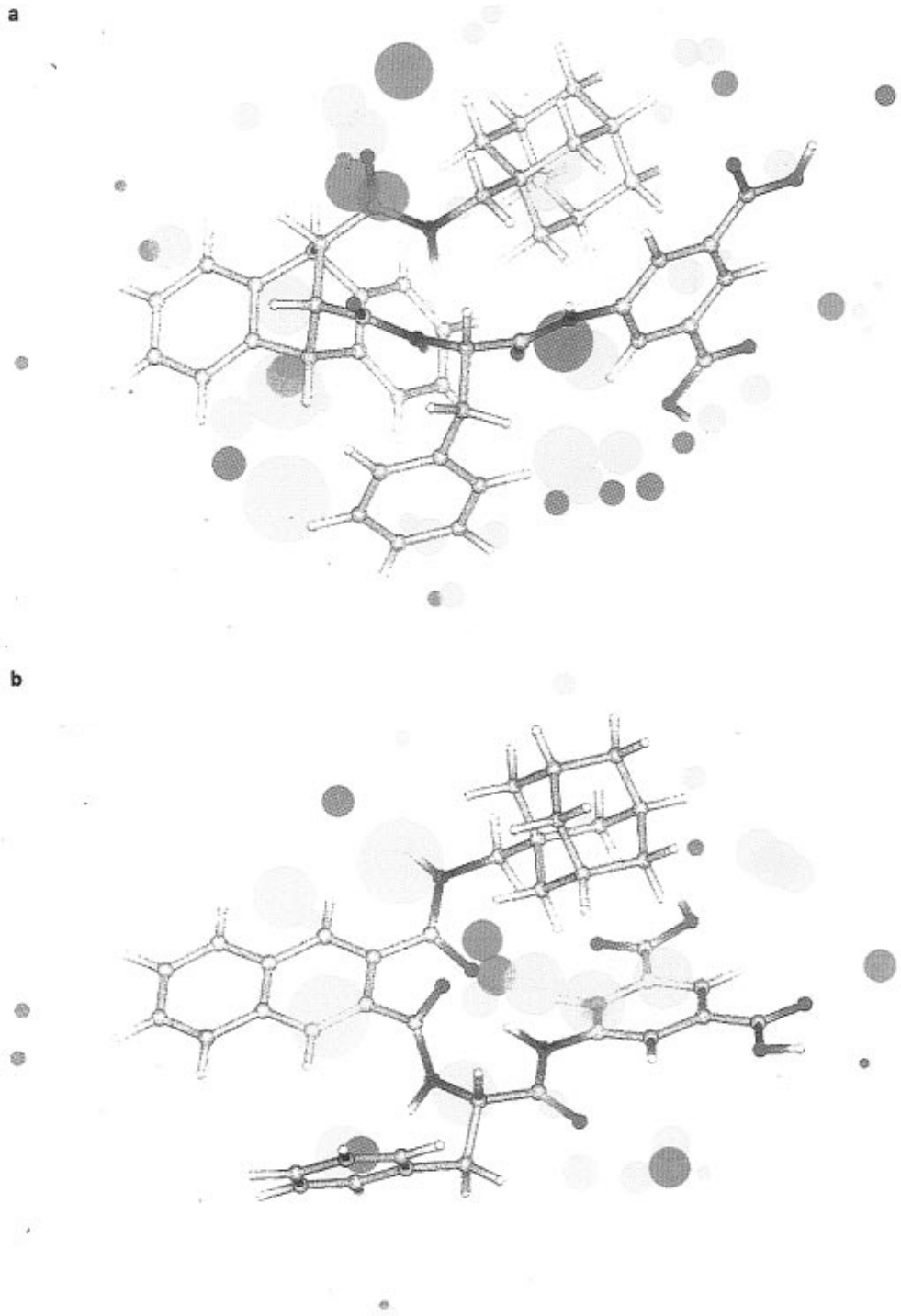


Figure 1. Composite molecular fields of (a) compound **5** and (b) compound **6**. Each depiction is of a typical low-energy conformation. Green spheres represent negative electrostatic fieldpoints, pink spheres represent electropositive fieldpoints, and yellow spheres are "sticky points" that define the van der Waals surface around the molecule. The size of each sphere is directly related to the magnitude of the fieldpoint.

nience, as the compounds either had to be prepared and tested as mixtures, or a separation procedure had to be used, which was often difficult and wasteful of material. Attempts to control and direct the anhydride ring opening by modification of reaction conditions were unsuccessful. This problem was circumvented by the introduction of a second nitrogen into the five-membered ring to give rise to the tautomeric benzimidazole derivative, compound **9**, which generally met the molecular modeling criteria and also expressed high affinity for CCK_B/gastrin binding sites (Table 2).

Table 3 shows the *in vitro* activity of a few of the other indole and benzimidazole derivatives which were prepared. The variations in activity for these materials were broadly in line with our expectations from the BCO series, the results of which have already been reported.[7] Only the tetrazole-containing compounds **16**, **17**, and **19** gave surprising activity in the assays, showing 1.5–2.0 log units more potency at CCK_B/gastrin receptors than the corresponding BCO derivatives.

Of greatest interest, however, was the behavior *in vivo* of these new compounds, and data is shown for two

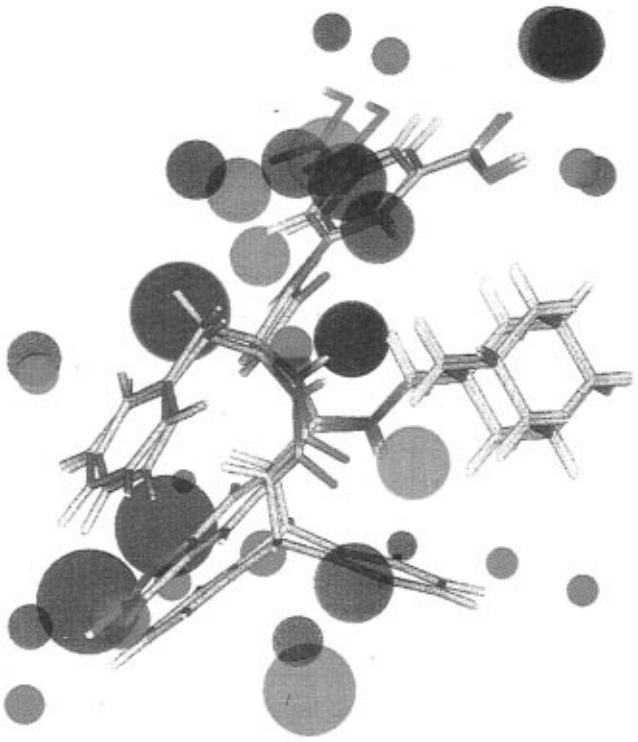
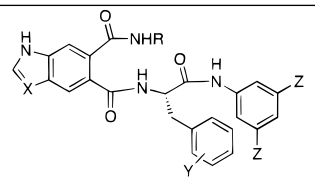


Figure 2. Typical low-energy overlay of compounds **5** and **7** showing positive and negative fieldpoints. Fieldpoints due to compound **5** are depicted in light green (−ve) and pink (+ve). Those due to compound **7** are in dark green (−ve) and brown (+ve). The "sticky points" have been omitted for clarity.

Table 3. Comparison of Receptor Affinity Values for CCK_B/Gastrin Antagonists



no.[a]	R	X	Y	Z	CCK_B/gastrin[b]	CCK_A [c]
12		CH	2-F	CO_2H	9.13±0.05	5.48
13		N	2-F	CO_2H	8.35±0.18	5.59
14		N	4-OH	CO_2H	7.80±0.09	5.55
15		CH	H	CO_2H	7.82±0.07	5.50
16		N	H		8.39±0.06	6.05
17		CH	H		8.92±0.09	5.89
18		N	2-F	CO_2H	8.12±0.03	5.13
19		N	2-F		8.41±0.16	6.04

[a] Compounds **12**−**15** and **17**−**19** were tested as the bis(*N*-methyl-D-glucamine) salts. Compound **16** was tested as the bis(ammonium) salt. [b,c] See corresponding footnotes in Table 1.

representative examples in Table 4. Compounds **7** and **9** in which the BCO skeleton had been replaced with indole and benzimidazole units, respectively, were at least as potent as compound **5** in the anaesthetized rat assay but were more potent when examined in the gastric fistula dog. Indeed, the compounds containing these heterocyclic skeletons were of comparable activity in the rat and the dog assays. Further, where examined, the activities *in vivo* (data not shown) of other heterocyclic ring containing compounds described in Tables 2 and 3 were much as would be expected from the observed affinities *in vitro*. Thus compounds **7** and **9**, along with a number of their derivatives, met our target criteria with respect to both *in vitro* potency and selectivity and *in vivo* consistency.

Table 4. Intravenous Activities of CCK_B/Gastrin Antagonists in Ghosh and Schild Rat and Chronic Gastric Fistula Dog Model

	Ghosh and Schild rat[a]		gastric fistula dog[d]	
no.	dose[b]	inhibition[c]	dose[b]	inhibition[e]
5	0.025	79 ± 14 (4)	17.5	49 ± 10 (10)
7	0.025	97 ± 11 (4)	0.1	79 ± 7 (4)
9	0.025	61 ± 3 (4)	0.1	83 ± 8 (3)
L-365,260	1.0	46 ± 10 (3)	4.0	70 ± 5 (4)
			10.0	95 ± 2 (4)

[a] See experimental section for this anaesthetised rat preparation. [b] Compound dose in μmol/kg. Compounds **5**, **7**, and **9** dosed in 0.9% saline solution and L-365,260 in a 45% aqueous solution of molecusol. Materials dosed by intravenous bolus administration. [c] Peak percentage inhibition ± SEM (*n* in parentheses) relative to an infused, submaximal acid secretory dose of 0.1 μg/kg/min of pentagastrin. Values obtained by comparison with the acid output of the stimulated preparation prior to dosing with test compounds. [d] See Experimental Section for details of this model. [e] Peak percentage inhibition ± SEM (*n* in parentheses) relative to an infused, submaximal acid secretory dose of pentagastrin. This dose varies for each individual animal. Values obtained by comparison with the acid output of the stimulated preparation immediately prior to dosing with test compounds.

The reasons for the discrepancy in the BCO series but not in the heteroaromatic bicyclic compounds is a matter for conjecture. It is possible that the reasons are pharmacokinetic, but in this regard, only limited data on plasma levels could be obtained and this was inconclusive. Instead, it may be necessary to consider interspecies variation in CCK_B/gastrin receptors. It is known that there are species differences in CCK_B/gastrin receptors which do not significantly affect hormone binding but which have been observed to influence the affinities of non-peptide antagonists. For example, Beinborn *et al.*[16] have shown that canine and human CCK_B/gastrin receptors have several amino acid differences. One of these, the amino acid at position 355 in the sequence of the canine CCK_B/gastrin receptor, is apparently responsible for significantly reducing the affinity of L-365,260 at this receptor, while at the same time increasing the affinity of L-364,718, relative to wild type human receptor. The rat receptor is also known to have a slightly different amino acid sequence to human and dog.[17] In the absence of an accurate three-dimensional structure for the CCK_B/gastrin receptor and thus a detailed knowledge of the binding pocket in the receptor protein, we would speculate that the differences we were observing *in vivo* between rat and dog might be an indication that the BCO ligands were interacting, in part at least, with a portion of the receptor protein which was not conserved between these species. Given the excellent overlay of the electrostatic potential fields between compounds **5** and **7**, it is unlikely that they are being attracted to completely separate sites on the receptors, but clearly there are differences in the mo-

lecular volume of the two compounds that may in some circumstances cause unfavorable steric interactions for the BCO in certain species-specific areas within the binding pocket and thus lead to a loss of activity. Prompted by these possibilities, a canine gastric tissue binding assay was set up and some of the compounds were examined. It was found that the affinity of the BCO derivative, compound **5**, at CCK_B/gastrin sites labeled with [^{125}I]BH-CCK-8S was about 1.5 log units lower than that of the indole, compound **7** (data not shown), in contrast to the data in Table 2 for the equivalent binding sites in the mouse cortex. Thus, this low affinity for compound **5** in canine gastric mucosa could account for most of the poor potency observed for this compound, relative to compound **7**, when administered intravenously in the dog model. An account of the canine gastric tissue binding assay and the full results on these and other compounds will be reported in due course.

In conclusion the BCO compounds described previously,[7] despite an excellent affinity and selectivity profile *in vitro*, exhibited species-variable behavior *in vivo*. A new series of compounds was devised with the help of molecular modeling in which the BCO skeleton had been replaced by an *ortho*-disubstituted heteroaromatic bicyclic framework. These materials, exemplified by compounds **7** and **9**, still maintained the excellent *in vitro* properties of the BCO series but in addition gave a far more consistent *in vivo* profile, working potently by iv bolus administration in both rat and dog models.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on either a Nicolet GE300 or a Bruker DRX 300 machine, or using the Bruker AMX400 University of London Intercollegiate Research Service for NMR at Kings College. Elemental analyses were carried out at the London School of Pharmacy, and all compounds gave analytical results of ±0.4% of theoretical values. Flash column chromatography was performed using Merck Kieselgel 60 silica grade 9385.

3-[[(1-Adamantylmethyl)amino]carbonyl]-2-naphthoic Acid (3). 2,3-Naphthalenedicarboxylic anhydride (198 mg, 1.0 mmol) and 1-adamantanemethylamine (176 mg, 1.0 mmol) were dissolved in dry THF (5 mL) and stirred at room temperature for 1 h. A thick white precipitate was formed, and this was isolated by filtration and washed with ether to leave the title compound (229 mg, 69%): ^{1}H NMR (DMSO-d_6) δ 12.9 (1H, s), 8.3 (2H, s), 8.1 (2H, t), 7.9 (1H, s), 7.6 (2H, m), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, q), 1.5 (6H, s); further characterised as the *N*-methyl-D-glucamine salt. Anal. ($C_{23}H_{25}NO_3 \cdot C_7H_{17}NO_5 \cdot H_2O$) C, H, N.

Coupling and Deprotection Method A. 2-[(2(*R*)-Carboxypyrrolidino)carbonyl]-3-[[(1-adamantylmethyl)amino]carbonyl]naphthalene (4). Step a. 3-[[(1-Adamantylmethyl)amino]carbonyl]-2-naphthoic acid (400 mg, 1.1 mmol) (**3**) and PyBOP (530 mg, 1.1 mmol) were taken up in dry dichloromethane (30 mL), and diisopropylethylamine (0.54 mL, 3.3 mmol) was added. The reaction mixture was stirred under an atmosphere of dry argon for 1 h. D-Proline benzyl ester hydrochloride (246 mg, 1.1 mmole) was added and the mixture stirred overnight. The organic layer was washed successively with 5% potassium hydrogen sulfate (5 mL), sodium hydrogen carbonate (5 mL), and saturated brine (5 mL). It was then dried, filtered, and evaporated to leave the crude title compound which was further purified by column chromatography (silica and ethyl acetate). The benzyl ester of the title compound (532 mg, 88%) was isolated as a white solid.

Steb b: The product of step a (525 mg, 0.9 mmol) was dissolved in THF (30 mL), and 10% palladium on charcoal (50 mg) was added. The reaction mixture was stirred overnight under an atmosphere of hydrogen and then filtered through Celite and evaporated to yield the title compound (415 mg, 93%): ^{1}H NMR (DMSO-d_6) δ 12.6 (1H, s), 8.4 (1H, t), 8.2−7.5 (6H, m), 4.3 (1H, m), 3.6−2.2 (6H, m), 2.0 (2H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{28}H_{32}N_2O_4 \cdot C_7H_{17}NO_5 \cdot 2.4H_2O$) C, H, N.

2-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-3-[[(1-adamantylmethyl)-amino]carbonyl]naphthalene (6). The compound was prepared as in method A using the amine described in Scheme 1: ^{1}H NMR (DMSO-d_6) δ 13.3 (2H, s), 10.1 (1H, s), 9.0 (1H, d), 8.7 (3H, m), 8.2 (2H, m), 8.0 (1H, m), 7.9 (1H, m), 7.6 (2H, m), 7.4 (1H, s), 7.3 (5H, m), 4.8 (1H, m), 3.5−2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, m); further characterized as the bis(*N*-methyl-D-glutamine) salt. Anal. ($C_{40}H_{39}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 3.7H_2O \cdot 0.7$dioxane) C, H, N.

Dimethyl 3-[2-(*N*,*N*-Dimethylamino)ethylene]-4-nitrophthalate (21). Dimethyl 4-methyl-5-nitrophthalate (3.14 g, 12.4 mmol) (**20**) was dissolved in DMF (10 mL), and dimethylformamide dimethyl acetal (4.43 g, 37.2 mmol) was added. The reaction mixture was heated at 150 °C for 6 h and then allowed to cool. The solution was diluted with ethyl acetate (500 mL), washed with brine (6 × 100 mL), dried, filtered, and evaporated to leave the title compound as a deep red solid (3.70 g, 97%): ^{1}H NMR ($CDCl_3$) δ 8.4 (1H, s), 7.5 (1H, s), 7.2 (1H, s), 6.0 (1H, d), 3.9 (3H, s), 3.0 (6H, s).

Dimethyl Indole-5,6-dicarboxylate (22). 21 (1.50 g, 4.9 mmol) was dissolved in toluene (300 mL), and 10% palladium on charcoal (150 mg) was introduced. The reaction was stirred under an atmosphere of hydrogen at room temperature for 1 h. The catalyst was removed by filtration and the solvent evaporated to leave the title compound (1.14 g, 99%): ^{1}H NMR ($CDCl_3$) δ 9.0 (1H, br s), 8.1 (1H, s), 7.8 (1H, s), 7.4 (1H, t), 6.6 (1H, m), 3.91 (3H, s), 3.89 (3H, s).

Indole-5,6-dicarboxylic Acid Anhydride (24). To a stirred solution of **22** (1.14 g, 4.9 mmol) in a 5:1 mixture of ethanol:water (12 mL) was added solid sodium hydroxide (0.49 g, 12.4 mmol). The solution was stirred at a gentle reflux for 3 h. The solution was allowed to cool and acidified to pH 2 with hydrochloric acid and then evaporated. The residue was dried by coevaporation with ethanol and then toluene and dried under vacuum. The residue was then extracted with hot acetone (5 × 20 mL), and the combined extracts were evaporated to leave the diacid as a pale yellow solid. This was then heated strongly with a heat gun for 10 min under vacuum to leave the title compound (800 mg, 87%).

Coupling and Deprotection Method B. 5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]-carbonyl]-6-[[(1-adamantylmethyl)amino]carbonyl]-indole (7). Step a. The anhydride **24** (73 mg, 0.39 mmol) and 1(*S*)-[[[3,5-bis(benzyloxycarbonyl)phenyl]amino]carbonyl]-2-phenylethylamine (200 mg, 0.39 mmol) were suspended in dry acetonitrile (10 mL), and the solution was heated to reflux. A precipitate formed within 30 min, and heating was continued for a further 3 h. The mixture was allowed to cool, and diethyl ether was added. The precipitate was collected by filtration, this being 5-[[[1(*S*)-[[(3,5-bis(benzyloxycarbonyl)phenyl]amino]-carbonyl]-2-phenylethyl]amino]carbonyl]indole-6-carboxylic acid, the precursor regioisomer to compound **7** (151 mg, 57%): ^{1}H NMR (DMSO-d_6) δ 12.6 (1H, br s), 11.5 (1H, s), 10.3 (1H, s), 8.6 (1H, m), 8.5 (2H, s), 8.2 (1H, s), 7.9 (1H, m), 7.6 (1H, s), 7.4−7.2 (16H, m), 6.5 (1H, s), 5.4 (4H, s), 4.8 (1H, m), 3.2 (1H, dd), 3.0 (1H, dd). The other regioisomer (70 mg, 26%), the precursor to compound **8**, was isolated from the mother liquors by column chromatography (silica, 5% methanol and 95% dichloromethane).

Step b. 5-[[[1(*S*)-[[[3,5-Bis(benzyloxycarbonyl)phenyl]amino]-carbonyl]-2-phenylethyl]amino]carbonyl]indole-6-carboxylic acid (91 mg, 0.13 mmol) was dissolved in dichloromethane (1 mL), and PyBrOP (61 mg, 0.13 mmol) was added together with diisopropylethylamine (0.045 mL, 0.26 mmol). After 5 min a solution of 1-adamantanemethylamine (24 mg, 0.14 mmol) in dichloromethane (1 mL) was added, and the resulting solution was stirred for 24 h at room temperature. Dichloromethane (10 mL) was added, and the organic layer washed successively with 2 M hydrochloric acid solution (2 × 5 mL), saturated

aqueous sodium hydrogen carbonate solution (5 mL), and brine (5 mL) and dried. Column chromatography (silica, 5% ethyl acetate and 95% dichloromethane) afforded a white solid (76 mg, 69%): ^{1}H NMR (DMSO-d_6) δ 11.5 (1H, s), 10.3 (1H, s), 8.8 (3H, m), 8.5 (1H, t), 8.3 (1H, s), 7.7 (1H, s), 7.6−7.2 (16H, m), 7.2 (1H, s), 6.5 (1H, s), 5.4 (4H, s), 4.7 (1H, m), 3.4 (1H, m), 2.9 (3H, m), 1.8 (3H, s), 1.6−1.3 (12H, m).

Step c. The product of step b (70 mg, 0.08 mmol) was dissolved in a 1:1 mixture of THF and methanol (3 mL), and 10% palladium on charcoal (10 mg) was added. The reaction mixture was stirred overnight under an atmosphere of hydrogen and then filtered through Celite and evaporated to yield the title compound (53 mg, 96%): ^{1}H NMR (DMSO-d_6) δ 11.5 (1H, s), 10.2 (1H, s), 8.7 (1H, d), 8.6 (2H, s), 8.4 (1H, t), 8.2 (1H, s), 7.7 (1H, s), 7.5 (1H, s), 7.2 (6H, m), 6.5 (1H, s), 4.8 (1H, m), 3.5 (1H, m), 3.0 (3H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{38}H_{38}N_4O_7\cdot 2C_7H_{17}NO_5\cdot H_2O$) C, H, N.

6-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-5-[[(1-adamantylmethyl)-amino]carbonyl]indole (8). This was made using the coupling deprotection method B but using the soluble regioisomer purified by column chromatography in step a: ^{1}H NMR (DMSO-d_6) δ 11.5 (1H, s), 10.2 (1H, s), 8.8 (1H, d), 8.6 (2H, s), 8.4 (1H, t), 8.2 (1H, s), 7.9 (1H, s), 7.5 (1H, t), 7.2−7.4 (5H, m), 7.0 (1H, s), 6.6 (1H, s), 4.7 (1H, m), 3.4 and 2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, m), 1.3 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{38}H_{38}N_4O_7\cdot 2C_7H_{17}NO_5\cdot H_2O$) C, H, N.

Indole derivatives **12** and **15** were prepared using method B with the appropriate synthons as described in Scheme 2 and Table 3. Compound **17**, a tetrazole derivative, was prepared using the (pivaloyloxy)methyl (POM) group protection and using the coupling methodology described in method B, steps a and b but with deprotection of the POM group achieved using a solution of ammonia in methanol. In each case the insoluble regioisomer isolated in step a was the precursor of interest. **5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(2-fluorophenyl)ethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)amino]carbonyl]indole (12)**: ^{1}H NMR (DMSO-d_6) δ 13.3 (2H, br s), 11.8 (1H, s), 10.2 (1H, s), 8.74 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.2 (1H, s), 7.8 (1H, s), 7.6-7.2 (6H, m), 6.5 (1H, s), 4.8 (1H, m), 3.6 (1H, m), 3.0 (3H, m), 1.9 (3H, br s), 1.6 (12H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{38}H_{37}FN_4O_7\cdot 2C_7H_{17}NO_5\cdot 2.8H_2O$) C, H, N.

5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-6-[[(cycloheptylmethyl)-amino]carbonyl]indole (15): ^{1}H NMR (DMSO-d_6) δ 11.5 (1H, s), 10.2 (1H, s), 8.7 (3H, m), 8.5 (1H, t), 8.2 (1H, s), 7.8 (1H, s), 7.5−7.0 (7H, m), 6.5 (1H, s), 4.7 (1H, m), 3.2−2.7 (4H, m), 1.7−1.0 (13H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{35}H_{36}N_4O_7\cdot 2C_7H_{17}NO_5\cdot 4.3H_2O$) C, H, N.

5-[[[1(*S*)-[[(3,5-Ditetrazolylphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)-amino]carbonyl]indole (17): ^{1}H NMR (DMSO-d_6) δ 11.5 (1H, s), 10.4 (1H, s), 8.8 (3H, m), 8.5 (2H, m), 7.7 (1H, s), 7.5 (1H, t), 7.4−7.0 (6H, m), 6.5 (1H, s), 4.8 (1H, m), 3.2−2.9 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.3 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{38}H_{38}N_{12}O_3\cdot 2C_7H_{17}NO_5\cdot 3H_2O$) C, H, N.

Benzimidazole-5,6-dicarboxylic Acid Anhydride (26). Benzimidazole-5,6-dicarboxylic acid (18.00 g, 87.4 mmol) was heated strongly with a heat gun under vacuum for 20 min. The yellow solid was extracted with hot acetone (750 mL) using a Soxhlet apparatus to give the title compound (13.79 g, 84%): ^{1}H NMR (DMSO-d_6) δ 8.7 (1H, s), 8.3 (2H, s).

The following benzimidazoles were made using the coupling conditions in method B but using the appropriate synthons shown in Scheme 3 and Table 3. No regioisomers can arise from the chemistry so the product of step a after work up was the single desired precursor. Deprotection of benzyl esters was by hydrogenation as described in method B step c, and POM groups were removed from tetrazoles using a solution of ammonia in methanol.

5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)-amino]carbonyl]benzimidazole (9): ^{1}H NMR (DMSO-d_6) δ 10.2 (1H, m), 8.9 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, m), 7.9 (1H, br s), 7.3 (7H, m), 4.7 (1H, m), 3.5 (1H, m), 3.0 (3H, m), 1.8 (3H, s), 1.5 (6H, m), 1.4 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{37}H_{37}N_5O_7\cdot 2C_7H_{17}NO_5\cdot 3.25H_2O$) C, H, N.

5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(2-fluorophenyl)ethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)amino]carbonyl]benzimidazole (13): ^{1}H NMR (DMSO-d_6) δ 13.0 (3H, br s), 10.2 (1H, s), 8.9 (1H, d), 8.7 (2H, s), 8.6 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, d), 7.4−7.2 (4H, m), 7.1 (1H, s), 4.8 (1H, m), 3.6−2.9 (4H, m), 1.8 (3H, s), 1.6 (6H, m), 1.3 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{37}H_{36}FN_5O_7\cdot 2C_7H_{17}NO_5$) C, H, N.

5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(4-hydroxyphenyl)ethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)amino]carbonyl]benzimidazole (14): ^{1}H NMR (DMSO-d_6) δ 13.0 (3H, br s), 10.2 (1H, s), 9.3 (1H, br s), 8.8 (1H, d), 8.7 (2H, s), 8.5 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.9 (1H, s), 7.2 (1H, s), 7.1 (2H, d), 6.7 (2H, d), 4.6 (1H, m), 3.0−2.3 (4H, m), 1.8 (3H, s), 1.6 (6H, m), 1.4 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{37}H_{37}N_5O_8\cdot 2C_7H_{17}NO_5\cdot 0.2H_2O$) C, H, N.

5-[[[1(*S*)-[[(3,5-Ditetrazolylphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)-amino]carbonyl]benzimidazole (16): isolated as the bis-(ammonium) salt; ^{1}H NMR (DMSO-d_6) δ 10.2 (1H, s), 8.8 (1H, d), 8.6 (2H, d), 8.4 (2H, m), 7.9 (1H, s), 7.4−7.2 (7H, m), 4.8 (1H, m), 3.5−3.0 (4H, m), 1.8 (3H, s), 1.5 (6H, q), 1.4 (6H, s). Anal. ($C_{37}H_{37}N_{13}O_3\cdot 2NH_3\cdot 1.5H_2O$) C, H, N.

5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(2-fluorophenyl)ethyl]amino]carbonyl]-6-[[(cycloheptylmethyl)amino]carbonyl]benzimidazole (18): ^{1}H NMR (DMSO-d_6) δ 3.0 (3H, br s), 10.2 (1H, br s), 8.9 (1H, d), 8.74 (2H, s), 8.7 (1H, t), 8.4 (1H, s), 8.2 (1H, s), 7.8 (1H, s), 7.5−7.1 (5H, m), 4.8 (1H, m), 3.5 (1H, m), 3.3−3.1 (3H, m), 1.6−1.1 (13H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{34}H_{34}FN_5O_7\cdot 2C_7H_{17}NO_5$) C, H, N.

5-[[[1(*S*)-[[(3,5-Ditetrazolylphenyl)amino]carbonyl]-2-(2-fluorophenyl)ethyl]amino]carbonyl]-6-[[(cycloheptylmethyl)amino]carbonyl]benzimidazole (19): ^{1}H NMR (DMSO-d_6) δ 10.4 (1H, s), 8.9 (1H, d), 8.8 (2H, s), 8.7 (1H, t), 8.5 (1H, s), 8.4 (1H, s), 7.9 (1H, s), 7.4 (1H, m), 7.3 (1H, m), 7.2 (2H, m), 7.1 (1H, m), 4.9 (1H, m), 3.6 (1H, dd), 3.1 (2H, m), 2.9 (1H, dd), 1.6−1.0 (13H, m); further characterized as the bis-(*N*-methyl-D-glucamine) salt. Anal. ($C_{34}H_{34}FN_{13}O_3\cdot 2C_7H_{17}NO_5\cdot 4.0H_2O$) C, H, N.

5,6-Bis(methoxycarbonyl)-2-(trimethylsilyl)benzofuran (31). Compound **30** (4.5 g, 13.4 mmol) and (trimethylsilyl) acetylene (1.71 g, 17.4 mmol) were dissolved in a mixture of triethylamine (50 mL) and dioxane (80 mL), and the solution was degassed with argon for 15 min. Copper(I) iodide (152 mg, 0.8 mmol) was added followed by bis(triphenylphosphine)-palladium dichloride (564 mg, 0.8 mmol). The reaction was stirred at 60 °C overnight under an atmosphere of argon. The solvents were removed by evaporation, and the resulting oil was redissolved in dichloromethane and washed sequentially with 10% citric acid solution and brine. The organic layer was dried, filtered, evaporated, and passed through a short silica column (dichloromethane) to give the title compound (4.0 g, 97%): ^{1}H NMR ($CDCl_3$) δ 7.9 (1H, s), 7.8 (1H, s), 7.0 (1H, s), 3.9 (6H, s), 0.3 (9H, s).

Benzofuran-5,6-dicarboxylic Acid Anhydride (32). Step a. Compound **31** (1.2 g, 3.9 mmol) was dissolved in THF (50 mL), and tetrabutylammonium fluoride monohydrate (1.02, 3.9 mmol) was added. The solution immediately turned black and was allowed to stir at room temperature overnight. The reaction mixture was evaporated to leave a brown oil which was purified by column chromatography (silica, 10% ethyl acetate and 90% dichloromethane) to leave the desilylated analogue of compound **31** (720 mg, 79%).

Step b. The saponification and anhydride formation were carried out in an analogous manner to the preparation of compound **24**.

5-[[[1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)-amino]carbonyl]benzofuran (10). This was prepared using coupling method B as outlined in Scheme 5, but no separation of regioisomers could be seen. The final deprotection of the diallyl ester was carried out with diethylamine in THF in the presence of palladium tetrakis(triphenylphosphine). The product was initially isolated as the bis(diethylamine) salt: ^{1}H NMR (DMSO-d_6) δ 10.2 (1H, s), 9.0 (1H, d), 8.8 (2H, s), 8.4 (3H, m), 8.1 (2H, m), 7.9 (1H, 2 × s), 7.4−7.1 (6H, m), 7.0 (1H, m), 4.7 (1H, m), 3.4 (1H, m), 2.9 (3H, m), 1.8 (3H, s), 1.5 (6H, q), 1.3 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{38}H_{37}N_3O_8 \cdot 2C_7H_{17}NO_5$) C, H, N.

Benzothiophene-5,6-dicarboxylic Acid Anhydride (28). Benzothiophene-5,6-dicarboxylic acid (1.5 g, 6.75 mmol) was suspended in acetic anhydride (20 mL) and heated to 130 °C for 1 h. The solvent was evaporated, and the product was triturated with diethyl ether to leave the title compound (1.3 g, 94%): ^{1}H NMR (DMSO-d_6) δ 8.9 (1H, s), 8.6 (1H, s), 8.3 (1H, d), 7.8 (1H, d).

6-[[(1-Adamantylmethyl)amino]carbonyl]benzo-thiophene-5-carboxylic Acid and Its Regioisomer (29). The compound was prepared using the method of compound **3**: ^{1}H NMR (DMSO-d_6) δ 12.8 (1H, br s), 8.4 and 8.3 (1H, 2 × s), 8.2 (1H, m), 8.0 (1H, m), 7.9 (1H, m), 7.6 (1H, m), 2.9 (2H, d), 1.9 (3H, s), 1.6 (12H, m).

5-[[(1(*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-6-[[(1-adamantylmethyl)-amino]carbonyl]benzothiophene (11). This was prepared using the coupling in method A as outlined in Scheme 4, and the *tert*-butyl ester protection was removed using trifluoroacetic acid: ^{1}H NMR (DMSO-d_6) δ 13.2 (2H, br s), 10.2 (1H, s), 8.9 (1H, m), 8.7 (2H, m), 8.4 (1H, m), 8.3 (2H, m), 8.2 (2H, m), 8.0 (1H, m), 7.5−7.0 (5H, m), 4.8 (1H, m), 3.3−2.9 (4H, m), 1.8 (3H, s), 1.6 (6H, q), 1.4 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{38}H_{37}N_3O_7S \cdot 2C_7H_{17}NO_5 \cdot 3.7H_2O$) C, H, N.

***In Vivo* Methods: Anaesthetized Rat Preparation.** Fasted rats were anaesthetized with 20% w/v urethane (1.8 mL/kg) administered ip. The pyloric sphincter and the cardiac sphincters were cannulated using small plastic tubing. The jugular vein was cannulated, and a tracheotomy was also carried out. The rats were maintained at 37−39 °C, and the stomachs were perfused with an unbuffered, physiological solution at 1 mL/min. The pH of the perfusate exiting the stomach was monitored. After approximately 15−20 min a stable baseline pH was noted. Pentagastrin infusion (submaximal acid secretory dose 0.1 μg/kg/min) was administered via a jugular vein. Pentagastrin induced acid secretion took approximately 5 min to begin and usually stabilized within 30 min. A bolus dose of the test compound was administered via the contralateral jugular vein and the pH response monitored for 60 min. Responses were measured as the peak percentage with respect to the change in pH evoked by pentagastrin infusion over the baseline.

Chronic Gastric Fistula Dogs. Dogs with chronic indwelling gastric fistula were fasted overnight with free access to water. The gastric fistula was opened, cleared of food debris, and flushed with up to 30 mL of tepid water. Thereafter the gastric contents were collected under gravity every 15 min, and the total titratable acidity was determined against 0.001 M NaOH. An intravenous cannula with a two-way tap was placed in the foreleg vein for continuous infusion of saline and subsequently pentagastrin to evoke a background, submaximal acid secretory response. One hour after commencing the pentagastrin infusion a bolus dose of the test compound was administered and the response monitored for at least an additional hour. Responses were measured as the peak percentage reduction in total acid secretion with respect to the predose 15 min sample.

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