Improving the Affinity and Selectivity of a Nonpeptide Series of Cholecystokinin-B/Gastrin Receptor Antagonists Based on the Dibenzobicyclo[2.2.2]octane Skeleton

S. Barret Kalindjian,* Ildiko M. Buck, Julia R. Cushnir, David J. Dunstone, Martin L. Hudson, Caroline M. R. Low, Iain M. McDonald, Michael J. Pether, Katherine I. M. Steel, and Matthew J. Tozer

James Black Foundation, 68 Half Moon Lane, London SE24 9JE, U.K.

Received June 16, 1995[⊗]

We have recently described a novel series of nonpeptidic cholecystokinin-B (CCK_B)/gastrin receptor antagonists based on a dibenzobicyclo[2.2.2]octane skeleton. We wish now to report on compounds arising out of our earlier work which have substantially greater affinity as antagonists for the CCK_B/gastrin receptor system and which maintain, or improve on, the already high selectivity with respect to CCK_A receptors. Thus, *cis*-7-[[[(1*S*)-[[(3,5-dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane expressed a pK_i of 8.80 in mouse cortical membranes at CCK_B/gastrin receptors. The selectivity for these receptors over CCK_A receptors was in the order of 1000-fold.

Introduction

The hormones gastrin and cholecystokinin are structurally related peptides which are found both in gastrointestinal tissue and in the central nervous system.[1] Two classes of receptors for these hormones are recognized, namely, cholecystokinin-A (CCK_A) and cholecystokinin-B (CCK_B)/gastrin. A number of selective antagonists of the action of these hormones at both classes of receptors have been discovered. More specifically, several series of nonpeptide ligands for the CCK_B/gastrin receptor have appeared. For example, benzodiazepines, arising from the manipulation of the structure of asperlicin, have been reported by a number of groups.[2-5] In addition, Howbert *et al.*[6] and Yu *et al.*[7] have described series based respectively on diphenylpyrazolidinones and quinazolinones, while benzolactams from Lowe *et al.*[8] and ureido acetamides from Bertrand *et al.*[9] have also been disclosed. The most potent of these compounds are reported to have affinities at CCK_B/gastrin receptors in the nanomolar region.

In a recent publication,[10] we reported the design and synthesis of the first examples of a new class of selective CCK_B/gastrin receptor antagonists based on the dibenzobicyclo[2.2.2]octane (BCO) skeleton and derived from consideration of the shape of tetragastrin. These materials, as exemplified by compound **1** in Table 1, had sub-micromolar affinity and showed at least a 30-fold selectivity for CCK_B/gastrin over CCK_A receptors. Much of the work already described focused on changing the side chain groups attached to the bridgehead positions of the BCO. The initial studies had shown that activity could be obtained with a bulky hydrophobic substituent on one arm of the BCO group and a polar group, typically a carboxylic acid, on the second. The aim of this paper is to show how further modification of the side arm substituents produced compounds which had affinities at CCK_B/gastrin receptors in the nanomolar range and which maintained or improved their selectivity for these receptors over CCK_A receptors.

Chemistry

The compounds described in this paper were made according to Schemes 1–3. The BCO skeleton was prepared in a single step, as in Scheme 1, by the Diels–Alder reaction[11] between maleic anhydride and anthracene in refluxing toluene. The resulting anhydride could be opened either with 1-adamantylmethylamine to lead eventually to compounds **1–28** or with the appropriate amine to give compounds **29–33**. This reaction was carried out in THF. The carboxylic acids unmasked during the amide formation were reacted further with a suitably protected amine fragment. This coupling was performed using PyBOP in dichloromethane and diisopropylethylamine as base for the fragments, ultimately leading to compounds **1–5**. Preparation of the analogous intermediates for compounds **6–33** was carried out using PyBrOP in dichloromethane and diisopropylethylamine with a catalytic quantity of DMAP. The fragments with a terminal glycine moiety were all made using NHS active ester-coupling methodology, whereas those containing anilines were made as illustrated in Scheme 2 again using PyBrOP as the coupling agent.

Separation of diastereomeric mixtures was performed by flash column chromatography following the second coupling step. This gave either the final compound **11** or **14** or their protected precursors. Thus hydrogenation over 10% palladium on charcoal gave compounds **1–10** and **15–33**, treatment of compound **41** with methanolic ammonia gave compound **12**, and reaction of compound **42** with potassium carbonate resulted in compound **13**.

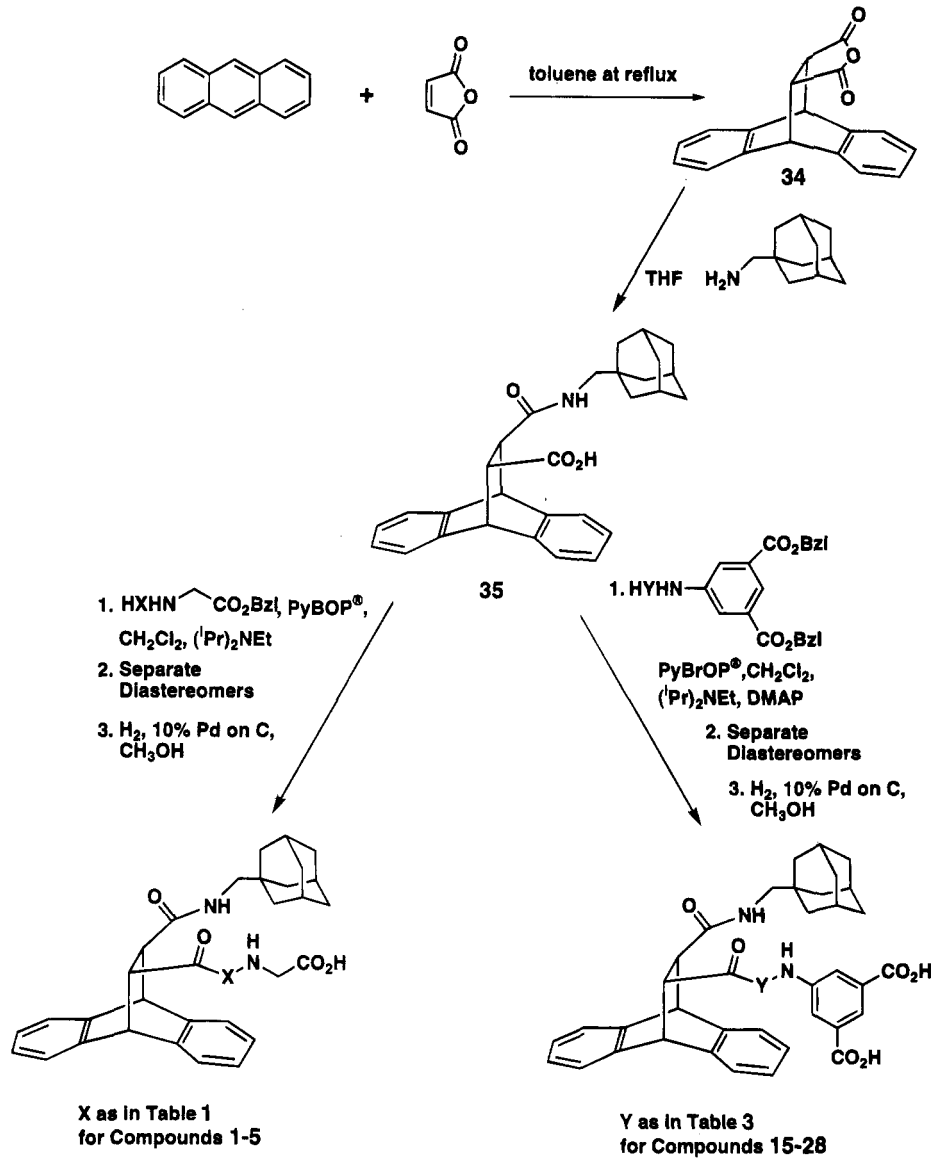
Discussion

Our recent communication describes the discovery of compounds such as **1**, which arose from observations that the activity of this series was dependent on the position of the acidic function relative to the bridgehead carbon atoms of the BCO. Hence, an investigation was undertaken into possible alternatives to the proline and pyrrolidine acetic acid derivatives described earlier[10] as a first stage in making compounds with more affinity at CCK_B/gastrin receptors. It was found that a number

[⊗] Abstract published in *Advance ACS Abstracts*, September 15, 1995.

0022-2623/95/1838-4294$09.00/0

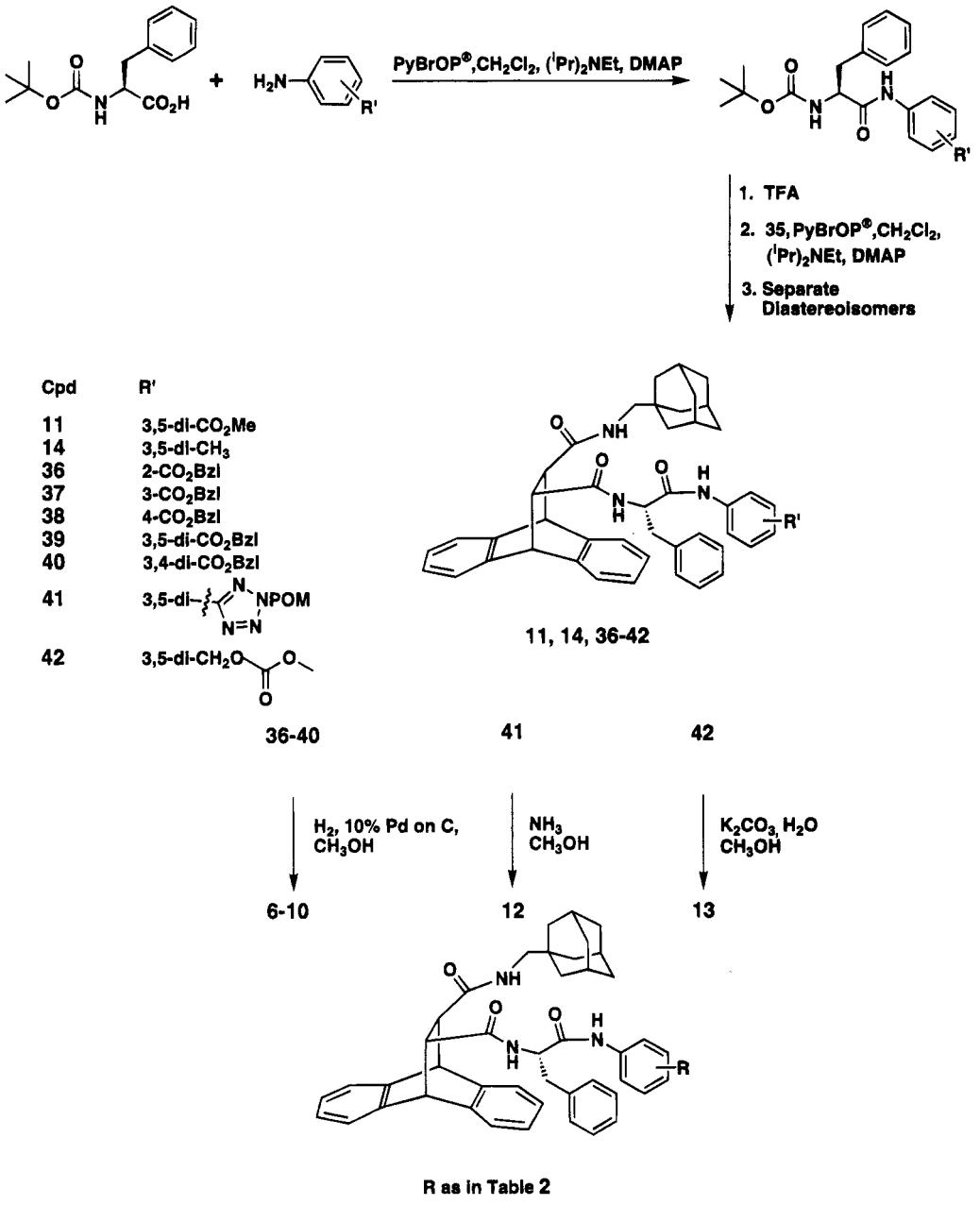
Scheme 1. Synthesis of Compounds **1–5** and **15–28**



of different amino acids could be used to bridge the BCO skeleton and the terminal glycine. Some of these derivatives are shown in Table 1. It can be seen that phenylalanine substitution gave a compound, **4**, which was equipotent with compound **1** in a mouse cerebral cortical radioligand-binding assay.[12] Whereas in the proline series the D-isomer **1** had a slightly greater affinity for CCK_B/gastrin receptors relative to the L-isomer **2**, in the phenylalanine series it was the L-compound **4** which was preferred. Proline had originally been introduced to this part of the BCO molecule in order to constrain sterically the conformational flexibility of the side chain. This led to improved affinity. The phenylalanine substitution presumably leads to a constraint of the side chain in a different way, as the secondary amide NH, introduced with this amino acid, has the potential to be utilized in an internal hydrogen bonding role. Because the constraint due to the phenylalanine is by a different internal interaction from that of the proline, this might provide an explanation for the switch in the preferred stereochemistry between the two series.

It is unlikely in these glycine-extended compounds that there is much interaction between the bridging amino acid side chain and the receptor, as the differences in activity between corresponding pairs of molecules, differing only in the stereochemistry of the side chain (cf. compounds **1** with **2** and **3** with **4**), are relatively small. However, data in Table 1 do suggest that the nature of the amino acid side chain used in this position plays some role with regard to selectivity over CCK_A receptors based on results obtained in a guinea pig pancreatic radioligand-binding assay.[13] Thus, compound **4** was slightly less selective for CCK_B/gastrin receptors over CCK_A receptors in comparison to compound **1**, and compound **5**, the tryptophan derivative, had lost all selectivity. It should be noted that the situation with regards to selectivity considerations in these early molecules is complicated by the fact that not all the compounds described in Table 1 could be separated into their constituent diastereomers. As a result, the possibility that CCK_B/gastrin activity was present in one set of diasteromers and CCK_A activity present in the other could not be excluded, and this should be born in mind when interpretating the selectivity data. However, with the knowledge that CCK_B/gastrin receptor activity could be maintained with other amino acids,

Scheme 2. Synthesis of Compounds **6**–**14**



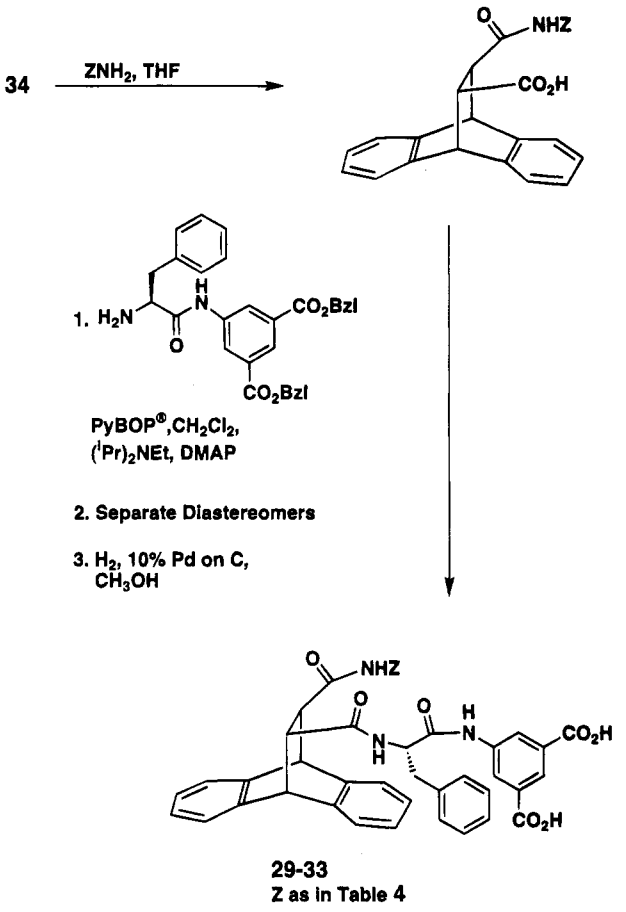
it was possible to broaden significantly the base of our structure–activity relationship (SAR) explorations.

As a second stage in our investigations, we decided to modify the glycine group, and this was done for two reasons. Firstly, we wished to produce compounds of increased affinity by further reducing conformational freedom and altering the location of the acid group. Secondly, literature precedent[14] suggested that the presence of a terminal glycine moiety might predispose these compounds to metabolic instability. This concern arose from consideration of the mechanism by which the C-terminal amides of naturally occurring peptides are generated, which involves enzymatic cleavage of a precursor bearing a glycine residue at the C-terminus.

Having shown that both prolines and phenylalanines could be used to link the BCO ring system and the terminal carboxylic acid, we wanted to investigate whether alternative carboxylic acid moieties could be incorporated into the BCO series. Thus, it was decided to constrain the terminal part of the carboxylic acid side chain by replacing the glycine unit with a carboxylic acid-containing aromatic moiety. The 2-, 3-, and 4-carboxyanilide derivatives of the phenylalanine series were made (compounds **6**–**8**), and as described in Table 2, the 3-isomer **7** showed an enhancement in activity in the mouse cortex assay relative to the glycine derivative **4**, whereas compounds **6** and **8** showed no such improvement. It would seem that the presence of a carboxylic acid in the *meta*-position of the terminal aromatic ring was optimal.

When two carboxylic acids were introduced to the aniline aromatic ring, it was found that both the 3,5- (compound **9**) and 3,4- (compound **10**) substituted materials were active. Most importantly the affinity of compound **9** was some 2 log units greater at CCK_B/gastrin receptors when compared to compound **4**, so that the activity of this molecule was now in the nanomolar range. Furthermore, the affinity of this molecule at CCK_A receptors showed no significant increase over compound **4**, thus indicating that the selectivity profile

Scheme 3. Synthesis of Compounds **29–33**



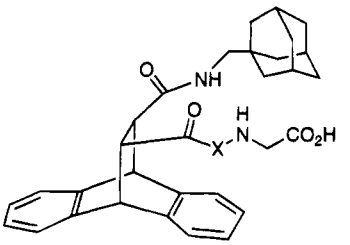
29-33
Z as in Table 4

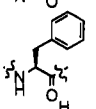
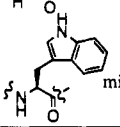
was substantially improved. The potent activity of the 3,5-dicarboxyanilide motif is consistent with results reported by Ewing *et al.*,[15,16] who have shown in a series of β-carboline CCK$_B$/gastrin receptor antagonists that the introduction of a variety of dicarboxylic acid-containing units gives rise to improved activity.

Table 2 also shows that the aniline aromatic ring in this series must be substituted with acidic groups. The dimethyl ester **11** the diol **13**, and the dimethyl compound **14** all possessed very limited activity, whereas the ditetrazole **12**, an acidic compound, maintained an appreciable CCK$_B$/gastrin receptor affinity. Molecular modeling[17] of compound **9** suggests that the molecule is very rigid, in common with all BCO's, and that there are only a few low-energy conformations. Examination of the electrostatic fields of these particular conformations reveal the presence of a pattern of strong electronegative field points which can be mainly attributed to the aromatic 3,5-dicarboxylic acid moiety. Any chemical change, such as removal of some or all acidic character, leads to a loss of activity.

Compound **9** which expressed a CCK$_B$/gastrin receptor affinity in the nanomolar range and selectivity of *ca.* 1000-fold was chosen as the starting point to explore the salient features of the SAR of this series. It was decided to make the 3,5-dicarboxyanilides of both the L- and D-forms of proline and the D-form of phenylalanine and couple these to the BCO skeleton. The resulting compounds (**15–17**) are shown in Table 3 together with their *in vitro* data. With the exception of compound **15**, each of the four dicarboxyanilides prepared to this point showed an increase of about 2 log units in affinity at CCK$_B$/gastrin receptors when compared to their glycine analogues in Table 1 (compounds **1–4**).

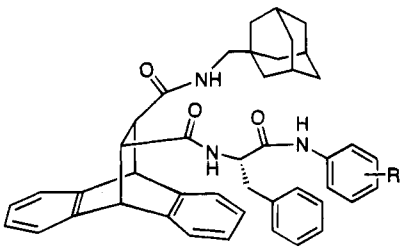
Table 1. Receptor Affinity Values for Glycine-Extended CCK$_B$/Gastrin Antagonists with Variation of Amino Acid



no.[a,d]	X		CCK$_B$/gastrin[b]	CCK$_A$[c]
1			6.86±0.10	5.36
2			6.06±0.03	5.58
3		mix DS	6.13±0.05	5.39
4		mix DS	6.65±0.09	5.84
5		mix DS	6.06±0.09	6.21

[a] Compounds were tested as the *N*-methyl-D-glucamine salts. [b] pK_i ± 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 one or two separate experiments. Approximate variability 0.1 log unit. [d] The compounds were single diastereoisomers unless indicated by use of 'mix DS' in the table and of unknown absolute configuration.

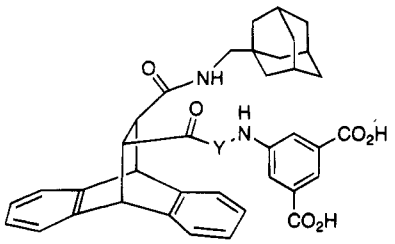
Table 2. Receptor Affinity Values for CCK$_B$/Gastrin Antagonists with Variation of Carboxylic Acid Substitution and Function

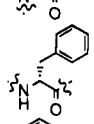
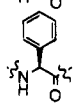
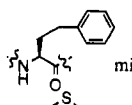
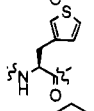
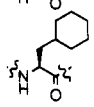
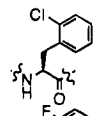
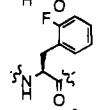
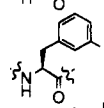
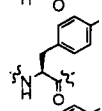
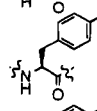
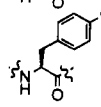


no.[a,d]	R		CCK$_B$/gastrin[b]	CCK$_A$[c,e]
6	2-CO$_2$H	mix DS	6.75 ± 0.09	5.92
7	3-CO$_2$H		7.78 ± 0.12	5.99
8	4-CO$_2$H		6.87 ± 0.15	5.67
9	3,5-di-CO$_2$H		8.80 ± 0.08	5.68
10	3,4-di-CO$_2$H	mix DS	6.98 ± 0.20	5.87
11	3,5-di-CO$_2$Me		4.96 ± 0.10	5.02
12	3,5-ditetrazole	mix DS	7.75 ± 0.10	6.52
13	3,5-di-CH$_2$OH	mix DS	5.89 ± 0.12	NT
14	3,4-di-CH$_3$		5.08 ± 0.10	5.13

[a] Compounds **6–8** were tested as the *N*-methyl-D-glucamine salts. Compounds **9** and **10** were tested as the bis(*N*-methyl-D-glucamine) salts, and compound **12** was tested as the diammonium salt. [b–d] See corresponding footnotes in Table 1. [e] NT indicates that the compound was not tested in this assay.

Table 3. Receptor Affinity Values for CCK_B/Gastrin Antagonists with Variation of Amino Acid

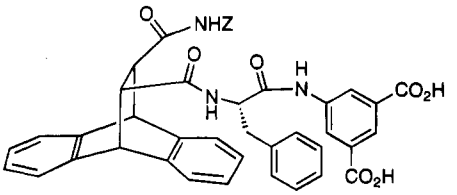


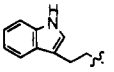
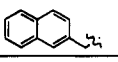
no.[a,d]	Y	CCK_B/gastrin [b]	CCK_A [c]
15		7.15±0.08	5.38
16		8.12±0.09	5.43
17		8.10±0.03	5.57
18	 mix DS	6.28±0.08	5.59
19	 mix DS	7.23±0.01	5.68
20		8.63±0.12	5.74
21	 mix DS	7.55±0.11	5.92
22	 mix DS	7.15±0.15	4.98
23		7.91±0.13	5.67
24		8.49±0.15	5.84
25		8.40±0.23	6.52
26		7.88±0.05	6.03
27		7.06±0.35	5.78
28		8.66±0.08	5.45

[a] The compounds were all tested as their bis(*N*-methyl-D-glucamine) salts. [b-d] See corresponding footnotes in Table 1.

The results obtained from varying the phenylalanine residue further are presented in Table 3. Altering the chain length of the phenyl residue (compounds **18** and **19**) resulted in a loss of affinity, which was most marked in the L-phenylglycine derivative **18**. Evidence for the optimal nature of an aromatic substituent in this position was obtained by making the saturated cyclohexylalanine derivative **21** and the alanine equivalent **22**. Both of these modifications led to some reduction in CCK_B/gastrin receptor affinity, whereas replacement of the phenyl group in compound **9** with a thiophene (**20**) resulted in a compound with equal activity. However, it remains unclear as to whether the aromatic ring of the amino acid side chain is interacting directly with the receptor or whether it is conferring extra conformational stability by some means to the molecule. Halogenation of the aromatic ring in the *ortho*- and *meta*-positions (compounds **23**–**25**) gave compounds that were comparable with the unsubstituted material, although the 3-fluoro derivative **25** showed increased CCK_A receptor affinity. Substitution in the *para*-position of the aromatic ring was well tolerated with smaller substituents (**26** and **28**), but introduction of the slightly more sterically demanding methoxy group, **27**, produced a significant loss of receptor affinity.

Table 4. Receptor Affinity Values for CCK_B/Gastrin Antagonists with Variation of Hydrophobic Portion



no.[a]	Z	CCK_B/gastrin[b]	CCK_A [c]
29		7.98±0.15	6.31
30		7.76±0.05	5.39
31		8.36±0.02	5.69
32		7.82±0.08	6.35
33		8.57±0.27	5.79

[a] Compounds were tested as the bis(*N*-methyl-D-glucamine) salts. [b,c] See corresponding footnotes in Table 1.

In Table 4 the effect of altering the adamantylmethyl group is shown. This had in our previous work[10] been an optimal hydrophobic group, but in this part of the series, there was a greater tolerance in the structure that was compatible with the CCK_B/gastrin receptor affinity. The cycloheptylmethyl analogue **31** had a similar profile to compound **9**, and reasonable affinity was maintained with the other derivatives (**29**, **30**, **32**, and **33**) presented. However, selectivity with respect to CCK_A receptors was reduced to *ca.* 30-fold in the case of the 1-naphthylmethyl, **29**, and 3-indolylethyl, **32**, compounds.

Conclusion

We have improved the CCK_B/gastrin receptor affinity of the BCO series of compounds that we recently

disclosed[10] by altering the position of the acidic grouping by incorporation of an aromatic 3,5-disubstituted dicarboxylic acid. In addition, we have shown that a wide range of aromatic amino acids can be used as spacer groups to link the bridgehead position of the BCO to the acid group. The affinity of compounds such as **9**, **24**, **25**, **28**, **31**, and **33** is in the nanomolar range at CCK_B/gastrin receptors. This has been achieved without increasing the low levels of CCK_A receptor affinity found in the parent series so that the selectivity with respect to CCK_A receptors is in the order of 1000-fold or greater. The SAR of the series was tolerant of small changes to the phenylalanine spacer group, such as ring substitution, and also to some of the modifications to the hydrophobic group, but alterations to the acidic parts of the molecule were, in general, detrimental to activity. The most active compounds of this series are now comparable in terms of affinity and selectivity for CCK_B/gastrin receptors with the other nonpeptidic series of ligands that are available for these receptors. The behavior of these compounds *in vivo* will be described elsewhere.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on either a Nicolet GE300 or Bruker DRX 300 machine. 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.

2,3:5,6-Dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic Anhydride (34). Anthracene (8.9 g, 0.05 mol) and maleic anhydride (4.9 g, 0.05 mol) were dissolved in toluene (200 mL) and heated at reflux for 3 h. On cooling the title compound precipitated and was isolated by filtration as a white crystalline compound (10.2 g, 74%): ^{1}H NMR (DMSO-d_6) δ 7.5 (2H, m), 7.3 (2H, m), 7.2 (4H, m), 4.8 (2H, s), 3.6 (2H, s).

***cis*-(±)-8-[[(1-Adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic Acid (35).** 2,3:5,6-Dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic anhydride (276 mg, 1.0 mmol) **34** was dissolved in THF (5 mL) and 1-adamantylmethylamine (182 mg, 1.1 mmol) was added. The resulting solution was heated at reflux for 1 h. A thick white precipitate was formed, and this was isolated by filtration and washed with THF to yield the title compound (320 mg, 72%): mp 237–9 °C. ^{1}H NMR (DMF-d_7) δ 7.7 (1H, t), 7.4 (3H, m), 7.2 (3H, m), 7.1 (2H, m), 4.7 (1H, d), 4.6 (1H, d), 3.5 (1H, dd), 3.0 (1H, dd), 2.9 (1H, dd), 2.7 (1H, dd), 2.0 (3H, s), 1.7 (6H, m), 1.5 (6H, s). Anal. ($C_{29}H_{31}NO_3$) C, H, N.

Method A. *cis*-7-[[(2*R*)-[[(Carboxymethyl)amino]carbonyl]pyrrolidino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (1). Step a: *cis*-(±)-8-[[(1-Adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid (**35**; 1.22 g, 2.8 mmol) and PyBOP (1.43 g, 2.8 mmol) were taken up in dry dichloromethane (30 mL), and diisopropylethylamine (1.44 mL, 8.3 mmol) was added. When a clear solution was obtained, D-prolylglycine benzyl ester (723 mg, 2.8 mmol) was introduced, and the reaction mixture was stirred at room temperature under an atmosphere of dry argon for 2 h. The solvent was evaporated, and ethyl acetate (30 mL) was added to the residue. The organic layer was washed successively with 5% aqueous potassium hydrogen sulfate (3 × 20 mL), 10% aqueous sodium hydrogencarbonate (2 × 20 mL), and saturated brine (20 mL). The organic phase was then dried (magnesium sulfate), filtered, and evaporated to leave a material that was purified by column chromatography (silica gel, 70% dichloromethane–30% ethyl acetate) to leave the title compound as a mixture of diastereomers (1.73 g, 92%). The material was recrystallized from ethyl acetate to afford crystals of the single diastereomer with lower R_f which was shown by conversion to the acid to be the inactive isomer. The mother liquors were concentrated and purified by column chromatography (silica gel, 50% dichloromethane–50% ethyl acetate) to yield the pure, higher R_f (less polar) diastereomer (704 mg, 30%) which was the desired material: ^{1}H NMR ($CDCl_3$) δ 7.6–7.0 (14H, m), 6.1 (1H, m), 5.2 (2H, m), 4.5 (2H, m), 4.3 (1H, m), 4.1 (2H, m), 3.4 (2H, m), 3.2 (1H, d), 2.8 (1H, dd), 2.3 (2H, m), 2.0 (3H, s), 1.7 (10H, m), 1.5 (6H, s).

Step b: The product of step a (530 mg, 0.77 mmol) was dissolved in methanol (15 mL), and a catalytic quantity of 10% palladium on charcoal was added. The suspension was stirred under an atmosphere of hydrogen gas for 2 h. The solution was filtered, and on evaporation the title compound was isolated as a white solid (436 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 7.6–7.0 (9H, m), 6.1 (1H, m), 5.1 (1H, m), 4.6 (2H, m), 4.2 (2H, m), 4.0–3.4 (2H, m), 2.8 (1H, dd), 2.5 (1H, m), 2.0 (5H, m), 1.7 (10H, m), 1.5 (6H, s); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{36}H_{41}N_3O_5 \cdot C_7H_{17}NO_5$) C, H, N.

The following compounds were prepared using method A as outlined in Scheme 1. Where diastereomers were separated and the more polar diastereomer was used for testing, this is indicated with the compound data.

***cis*-7-[[(2*S*)-[[(Carboxymethyl)amino]carbonyl]pyrrolidino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (2)**: the more polar diastereomer was the benzyl ester isolated in step b; ^{1}H NMR ($CDCl_3$) δ 7.6–7.0 (9H, m), 6.1 (1H, t), 4.8–4.4 (3H, m), 4.2–3.4 (4H, m), 2.9 (2H, m), 2.0 (5H, m), 1.7 (10H, m), 1.5 (6H, s); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{36}H_{41}N_3O_5 \cdot C_7H_{17}NO_5 \cdot 3.3H_2O$) C, H, N.

***cis*-7-[[[(1*R*)-[[(Carboxymethyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (3)**: ^{1}H NMR (DMSO-d_6) δ 8.1 (1H, m), 7.1 and 7.5 (1H, 2m), 7.4–6.9 (14H, m), 4.6–4.2 (3H, m), 3.8–2.4 (8H, m), 1.9 (3H, br s), 1.6 (6H, m), 1.3 (6H, m); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{40}H_{43}N_3O_5 \cdot C_7H_{17}NO_5 \cdot 4.0H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(Carboxymethyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (4)**: ^{1}H NMR (DMSO-d_6) δ 8.1 (1H, m), 7.1 and 7.5 (1H, 2m), 7.4–6.9 (14H, m), 4.6–4.2 (3H, m), 3.8–2.4 (8H, m), 1.9 (3H, br s), 1.6 (6H, m), 1.3 (6H, m); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{40}H_{43}N_3O_5 \cdot C_7H_{17}NO_5 \cdot 2.3H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(Carboxymethyl)amino]carbonyl]-2-(3-indolyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (5)**: ^{1}H NMR (DMSO-d_6) δ 10.9 and 10.8 (1H, 2s), 8.1 (1H, m), 7.7–6.7 (15H, m), 4.5–4.1 (3H, m), 3.8–2.3 (8H, m), 1.9 (3H, br s), 1.6 (6H, m), 1.2 (6H, m); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{42}H_{44}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 3.2H_2O \cdot 1.0CH_2Cl_2$) C, H, N.

Method B. *cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (9). Step a: BOC-L-phenylalanine (8.76 g, 33 mmol) was dissolved in dry dichloromethane (200 mL), and dry diisopropylethylamine (11.48 mL, 66 mmol) was added followed by PyBrOP (15.33 g, 33 mmol). The mixture was stirred at room temperature for 5 min, and 3,5-bis(benzyloxycarbonyl)-aniline (7.22 g, 20 mmol) was added. The solution was stirred at room temperature for a further 5 h, and the solution was washed sequentially with 2 M hydrochloric acid (100 mL), water (100 mL), saturated sodium hydrogen carbonate solution (100 mL), and water (100 mL) and finally dried, filtered, and evaporated to leave an oil. This was purified by column chromatography (90% dichloromethane–10% ethyl acetate) to leave the title compound as a white solid (11.0 g, 90%): ^{1}H NMR (DMSO-d_6) δ 10.5 (1H, s), 8.5 (2H, s), 8.2 (1H, s), 7.3 (15H, m), 5.4 (4H, s), 4.3 (1H, m), 2.9 (2H, m), 1.3 (9H, s).

Step b: Preparation of Compound 39. The product of step a (8.0 g, 13 mmol) was dissolved in trifluoroacetic acid (40 mL) and stirred at room temperature for 30 min. The solvent was removed by evaporation and the residue taken up in dry dichloromethane (50 mL) and basified with diiso-

propylethylamine. Meanwhile compound **35** (5.75 g, 13 mmol) was suspended in dry dichloromethane (150 mL), and diisopropylethylamine (4.6 mL, 26 mmol) was added followed by PyBrOP (6.04 g, 13 mmol). The mixture was stirred at room temperature for 5 min, and the solution of the amine prepared above was added. After stirring at room temperature for 3 h, the solution was washed sequentially with 2 M hydrochloric acid and water, dried, filtered, and evaporated. The residual oil was purified by column chromatography (90% dichloromethane and 10% ethyl acetae), this procedure also separating the two diastereoisomers. The less polar material was the diastereomer of interest (4.65 g, 39%): ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.1 (24H, m), 5.3 (4H, s), 4.5 (2H, s), 4.2 (1H, s), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s).

Step c: The dibenzyl ester prepared in step b above (4.65 g, 5.0 mmol) was dissolved in 1:1 (v/v) methanolic THF (40 mL), 10% palladium on charcoal (400 mg) was added, and the reaction mixture was stirred under an atmosphere of hydrogen overnight. The catalyst was removed by filtration through Celite and the product isolated by evaporation (3.53 g): ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.1 (14H, m), 4.5 (2H, s), 4.2 (1H, s), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{45}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 1.2H_2O$) C, H, N.

The following compounds were prepared using the coupling methodology as described in method B as outlined in Schemes 1 and 2. Where deprotections did not involve hydrogenation, further details are given. Where diastereomers were separated and the more polar diastereomer was used for testing, this is indicated with the compound data.

***cis*-7-[[[(1*S*)-[[(2-Carboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)-amino]carbonyl-2,3:5,6-dibenzobicyclo[2.2.2]octane (6)**: ^{1}H NMR (DMSO-d_6) δ 13.7 (1H, br s), 8.5 (2H, m), 8.2–7.9 (2H, m), 7.6–6.4 (16H, m), 4.5 (1H, s), 4.4 (1H, m), 4.2 (1H, s), 3.5–3.2 (2H, m), 2.9 (2H, m), 2.6 (1H, m), 2.3 (1H, m), 1.7 (3H, m), 1.5 (6H, m), 1.0 (6H, m); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{45}H_{45}N_3O_5 \cdot C_7H_{17}NO_5 \cdot 4.2H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3-Carboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)-amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (7)**: ^{1}H NMR (DMSO-d_6) δ 9.7 (1H, s), 8.2 (1H, s), 8.0 (1H, m), 7.8–6.9 (17H, m), 4.5 (1H, s), 4.4 (1H, s), 4.2 (1H, s), 3.5–3.2 (2H, m), 2.9 (2H, m), 2.6 (1H, m), 2.3 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.4 (6H, s); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{45}H_{45}N_3O_5 \cdot C_7H_{17}NO_5 \cdot 0.7H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(4-Carboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)-amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (8)**: ^{1}H NMR (DMSO-d_6) δ 12.9 (1H, br s), 9.7 (1H, s), 8.2 (1H, s), 7.6–7.0 (17H, m), 6.8 (1H, t), 4.5 (3H, m), 3.2 (1H, m), 3.0 (2H, m), 2.9 (1H, m), 2.6 (1H, m), 2.4 (1H, m), 1.8 (3H, m), 1.5 (6H, m), 1.3 (6H, m); further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{45}H_{45}N_3O_5 \cdot C_7H_{17}NO_5 \cdot 1.9H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,4-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (10)**: ^{1}H NMR (DMSO-d_6) δ 13.0 (2H, br s), 9.8 (1H, d), 8.0 (1H, d), 7.9–6.8 (17H, m), 4.5–4.2 (3H, m), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.3 (1H, m), 1.8 (3H, m), 1.5 (6H, m), 1.1 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{45}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 2.9H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[3,5-Bis(methoxycarbonyl)phenyl]amino]-carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (11)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.1 (14H, m), 4.5 (2H, s), 4.2 (1H, s), 3.9 (6H, s), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s). Anal. ($C_{48}H_{49}N_3O_7$) C, H, N.

***cis*-7-[[[(1*S*)-[[[3,5-Bis[[[(pivaloyloxy)methyl]carbonyl]-tetrazolyl]phenyl]amino]carbonyl]-2-phenylethyl]-amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (41)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, m), 8.4–8.0 (3H, m), 7.1 (14H, m), 6.5 (4H, m), 4.5 (3H, m), 3.0 (4H, m), 2.6 (1H, m), 2.2 (1H, m), 1.8 (3H, m), 1.5 (6H, m), 1.2 (18H, m), 1.1 (6H, s).

***cis*-7-[[[(1*S*)-[[[3,5-Bis[[(methoxycarbonyl)oxy]methyl]-phenyl]amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (42)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, m), 7.3 (18H, m), 5.1 (2H, m), 4.8 (2H, m), 4.4 (5H, m), 3.8 (6H, s), 3.0 (4H, m), 2.6 (1H, m), 2.2 (1H, m), 1.8 (3H, m), 1.5 (6H, m), 1.1 (6H, s).

***cis*-7-[[[(1*S*)-[[(3,5-Dimethylphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)-amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (14)**: ^{1}H NMR ($CDCl_3$) δ 8.4 (1H, s), 7.3 (13H, m), 7.1 (2H, m), 6.7 (1H, s), 5.6 (1H, m), 4.7 (1H, m), 4.3 (2H, m), 3.1 (4H, m), 2.7 (1H, m), 2.4 (1H, m), 2.3 (6H, s), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, s). Anal. ($C_{46}H_{49}N_3O_3$) C, H, N.

***cis*-7-[[(2*R*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-pyrrolidino]carbonyl]-8-[[(1-adamantylmethyl)amino]-carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (15)**: the more polar benzyl ester was the diasteromer used to give the active isomer on hydrogenation; ^{1}H NMR (DMSO-d_6) δ 11.7 (1H, s), 10.2 (1H, s), 8.45 (2H, s), 8.40 (1H, t), 8.1 (1H, s), 7.3 (3H, m), 7.1 (3H, m), 6.9 (2H, m), 4.5 (2H, s), 4.0 (1H, m), 3.5 (2H, m), 3.1 (1H, d), 3.0 (1H, d), 2.8 (1H, m), 2.5 (1H, m), 2.0 (3H, m), 1.5 (10H, m), 1.2 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{42}H_{43}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 2H_2O$) C, H, N.

***cis*-7-[[(2*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-pyrrolidino]carbonyl]-8-[[(1-adamantylmethyl)amino]-carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (16)**: ^{1}H NMR (DMSO-d_6) δ 9.4 (1H, s), 8.4 (2H, s), 8.3 (1H, t), 8.1 (1H, s), 7.3 (3H, m), 7.1 (3H, m), 6.9 (2H, m), 4.6 (2H, s), 4.3 (1H, m), 3.5 (2H, m), 3.1 (1H, d), 3.0 (1H, d), 2.8 (1H, m), 2.6 (1H, m), 2.1 (3H, m), 1.5 (10H, m), 1.2 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{42}H_{43}N_3O_7 \cdot 2C_7H_{17}NO_5$) C, H, N.

***cis*-7-[[[(1*R*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (17)**: the more polar benzyl ester was the diasteromer used to give the active isomer on hydrogenation; ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.3 (2H, s), 8.1 (1H, s), 7.1 (15H, m), 4.4 (3H, m), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.2 (1H, m), 1.8 (3H, s), 1.5 (6H, m), 1.2 (6H, s); further characterized as the bis-(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{45}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 2H_2O$) C, H, N.

***cis*-7-[[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-phenyl]methyl]amino]carbonyl]-8-[[(1-adamantyl-methyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (18)**: ^{1}H NMR (DMSO-d_6) δ 10.5 and 10.3 (1H, 2s), 8.4–8.0 (3H, m), 7.2 (13h, m), 5.3 (1H, d), 4.5 (2H, m), 3.1 (2H, m), 2.5 (2H, m), 1.8 (3H, m), 1.5 (6H, m), 1.2 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{45}H_{43}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 2.2H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-3-phenylpropyl]amino]carbonyl]-8-[[(1-adamantylmeth-yl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (19)**: ^{1}H NMR (DMSO-d_6) δ 13.1 (2H, br s), 10.1–9.7 (1H, 3s), 8.4–7.0 (18H, m), 4.5–4.1 (3H, m), 3.1 (2H, m), 2.8 (2H, m), 2.6 (2H, m), 2.0 (2H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{47}H_{47}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 3.6H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(2-thiopheneyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (20)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.4 (2H, s), 8.1 (2H, s), 7.2 (12H, m), 4.4 (3H, m), 3.0 (4H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{44}H_{43}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 5.0H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-cyclohexylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (21)**: ^{1}H NMR (DMSO-d_6) δ 10.1 and 9.8 (1H, 2s), 8.4 (2H, d), 8.1 (1H, m), 7.7 and 7.4 (1H, 2m), 7.1 (9H, m), 4.5 (2H, m), 4.2 (1H, m), 3.2 (2H, m), 2.9 (1H, m), 2.6 (1H, m), 2.2 (1H, m), 1.8–0.8 (28H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{51}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 2.5H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]-carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (22)**: ^{1}H NMR (DMSO-d_6) δ 10.0 and 9.7 (1H, 2s), 8.4 (2H, m), 8.1 (1H, m), 7.9 (1H, m), 7.2 (8H, m), 4.5 (2H, m), 4.2 (1H, m), 3.2 (2H, m), 2.9 (1H, m), 2.6 (1H, m), 2.2 (1H, m), 1.8–0.8 (18H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{40}H_{41}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 2.5H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(2-chlorophenyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (23)**: ^{1}H NMR (DMSO-d_6) δ 13.2 (2H, br s), 9.8 (1H, s), 8.2 (4H, m), 7.2 (13H, m), 4.5–4.2 (3H, m), 3.2 (2H, m), 2.9 (1H, m), 2.4 (2H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{44}N_3O_7Cl \cdot 2C_7H_{17}NO_5 \cdot 4.1H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(2-fluorophenyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (24)**: ^{1}H NMR (DMSO-d_6) δ 13.2 (2H, br s), 9.8 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.2 (13H, m), 4.5 (2H, m), 4.2 (1H, s), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{44}N_3O_7F \cdot 2C_7H_{17}NO_5 \cdot 4.0H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(3-fluorophenyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (25)**: ^{1}H NMR (DMSO-d_6) δ 13.2 (2H, br s), 9.9 (1H, s), 8.3 (2H, s), 8.1 (1H, s), 7.1 (14H, m), 4.5 (3H, m), 3.1 (1H, m), 2.8 (3H, m), 2.4 (2H, m), 1.8 (3H, s), 1.5 (6H, m), 1.2 (6H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{44}N_3O_7F \cdot 2C_7H_{17}NO_5 \cdot 3.9H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(4-fluorophenyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (26)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.2 (13H, m), 4.5 (2H, m), 4.2 (1H, s), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{44}N_3O_7F \cdot 2C_7H_{17}NO_5 \cdot 3.1H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(4-methoxyphenyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo-[2.2.2]octane (27)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 7.9 (1H, d), 7.2 (13H, m), 4.4 (2H, m), 4.2 (1H, m), 3.7 (3H, s), 3.0 (4H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{47}H_{47}N_3O_8 \cdot 2C_7H_{17}NO_5 \cdot 3.3H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-(4-hydroxyphenyl)ethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo-[2.2.2]octane (28)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 9.2 (1H, br s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.2 (11H, m), 6.6 (2H, d), 4.5 (1H, s), 4.4 (1H, m), 4.2 (1H, s), 3.1 (2H, m), 2.8 (2H, m), 2.6 (1H, m), 2.2 (1H, m), 1.7 (3H, s), 1.5 (6H, m), 1.1 (6H, s); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{45}N_3O_8 \cdot 2C_7H_{17}NO_5 \cdot 4.4H_2O$) C, H, N.

Method C. *cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]-carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(cyclohexylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (30). Step a: 2,3:5,6-Dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic anhydride (**34**; 1.0 g, 3.6 mmol) was dissolved in THF (15 mL), and cyclohexylmethylamine (0.82 g, 7.2 mmol) was added. The resulting solution was stirred at room temperature overnight. The reaction mixture was poured onto a mixture of 2 M hydrochloric acid and ice to leave a white precipitate which was isolated by filtration and washed with water to yield the amide acid (1.41 g, 99%). ^{1}H NMR ($CDCl_3$) δ 7.8 (1H, t), 6.9–7.3 (8H, m), 4.4 (2H, m), 3.2 (2H, m), 2.7 (3H, m), 0.7–1.7 (10H, m).

Step b: The product of step a (778 mg, 2.0 mmol) was dissolved in dichloromethane (50 mL), and diisopropylethylamine (1.04 mL, 6.0 mmol) was added followed by PyBOP (1.04 g, 2 mmol). The mixture was stirred at room temperature for 15 min, and a solution of (1*S*)-[[[bis(benzyloxycarbonyl)phenyl]-amino]carbonyl]-2-phenylethylamine in dichloromethane (30 mL) was added. This was prepared as described in the synthesis of compound **9**, step b, by the action of trifluoroacetic acid on the BOC derivative (1.22 g, 2.0 mmol). After stirring at room temperature for 4 h, the reaction mixture was washed consecutively with 2 M hydrochloric acid (50 mL), 10% sodium hydrogen carbonate (50 mL), and brine (50 mL) and then dried (sodium sulfate), filtered, and evaporated to give the protected bis-amide as a mixture of diastereoisomers. These were separated by column chromatography (silica gel, 50% ethyl acetate and 50% hexane) to leave the required compound, which was the less polar diastereomer, as a white solid (0.59 g, 34%): ^{1}H NMR (DMSO-d_6) δ 10.0 (1H, s), 8.5 (2H, d), 8.2 (1H, s), 8.0 (1H, d), 7.2 (24H, m), 5.3 (4H, s), 4.5 (2H, m), 4.2 (1H, d), 3.0 (4H, m), 2.5 (2H, m), 0.3–1.4 (11H, m).

Step c: The product of step b (590 mg, 0.68 mmol) was dissolved in a 1:1 (v/v) mixture of THF and ethanol (25 mL), and 10% palladium on charcoal (59 mg) was added. The mixture was stirred under an atmosphere of hydrogen overnight. The catalyst was removed by filtration through Celite and the product (454 mg, 94%) isolated by evaporation: ^{1}H NMR (DMSO-d_6) δ 9.2 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.2 (14H, m), 5.3 (4H, s), 4.5 (2H, m), 4.2 (1H, s), 3.3 (2H, m), 3.1 (2H, m), 2.7 (2H, m), 0.5–1.5 (11H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{42}H_{41}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 3.2H_2O$) C, H, N.

The following compounds were prepared using the coupling methodology as described in method C as outlined in Scheme 3.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-naphthylmethyl)-amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (29)**: ^{1}H NMR (DMSO-d_6) δ 13.1 (2H, br s), 9.8 (1H, s), 8.4 (2H, s), 8.3–6.8 (23H, m), 4.7–4.2 (3H, m), 3.2 (4H, m), 2.7 (2H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{46}H_{37}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 3.7H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(cycloheptylmethyl)-amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (31)**: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, s), 8.4 (2H, s), 8.1 (1H, s), 8.0 (1H, d), 7.1 (14H, m), 4.5 (2H, m), 4.2 (1H, s), 3.1 (3H, m), 2.7 (3H, m), 1.4–0.7 (13H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{47}H_{39}N_3O_7 \cdot 2C_7H_{17}NO_5 \cdot 2.9H_2O$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(3-indolylethyl)-amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (32)**: ^{1}H NMR (DMSO-d_6) δ 10.5 (1H, s), 9.9 (1H, s), 8.5 (2H, s), 8.1 (1H, s), 7.9 (1H, d), 7.7 (1H, br t), 7.4–6.7 (18H, m), 4.6 (1H, m), 4.4 (1H, s), 4.1 (1H, s), 3.3 (2H, m), 3.0 (2H, m), 2.9–2.7 (2H, m), 2.6 (2H, m); further characterized as the bis(*N*-methyl-D-glucamine) salt. Anal. ($C_{45}H_{38}N_4O_7 \cdot 2C_7H_{17}NO_5 \cdot 4.0H_2O$).

***cis*-7-[[[(1*S*)-[[(3,5-Dicarboxyphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(2-naphthylmethyl)-amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (33)**: ^{1}H NMR (DMSO-d_6) δ 13.2 (2H, br s), 9.8 (1H, s), 8.4 (2H, s), 8.3 (1H, m), 8.1 (2H, m), 7.7 (3H, m), 7.5 (1H, s), 7.3 (9H, m), 7.2 (2H, m), 7.1 (2H, m), 6.9 (3H, s), 4.6 (1H, s), 4.55 (1H, m), 4.4 (1H, m), 4.3 (1H, s), 4.1 (1H, m), 3.2 (2H, m), 2.9 (1H, m), 2.8 (1H, m). Anal. ($C_{46}H_{37}N_3O_7$) C, H, N.

***cis*-7-[[[(1*S*)-[[(3,5-Ditetrazolylphenyl)amino]carbonyl]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]-octane (12).** Compound **41** (300 mg, 0.3 mmol) was dissolved

in THF (5 mL), and a saturated solution of ammonia in methanol (10 mL) was added. This solution was stirred at room temperature for 5 h and then evaporated to dryness. The residue was suspended in diethyl ether and re-evaporated and the resulting white solid triturated with more diethyl ether. The diammonium salt was isolated by filtration and dried in vacuo (248 mg, 99%): ^{1}H NMR (DMSO-d^6) δ 9.8 (1H, m), 8.4–8.0 (3H, m), 7.1 (14H, m), 4.5 (3H, m), 3.0 (4H, m), 2.6 (1H, m), 2.2 (1H, m), 1.8 (3H, m), 1.5 (6H, m), 1.1 (6H, s). Anal. ($C_{46}H_{45}N_{11}O_3 \cdot 2NH_3$) C, H, N.

***cis*-7-[[[(1*S*)-[[[3,5-Bis(hydroxymethyl)phenyl]phenyl]amino]carbonyl)]-2-phenylethyl]amino]carbonyl]-8-[[(1-adamantylmethyl)amino]carbonyl]-2,3:5,6-dibenzobicyclo[2.2.2]octane (13).** Compound **42** (383 mg, 0.456 mmol) was dissolved in methanol (40 mL), and a 1% aqueous potassium carbonate solution (20 mL) was added slowly with rapid stirring. A fine white suspension resulted which was stirred overnight at room temperature. The methanol was removed by evaporation and the white solid isolated by filtration. This was washed with water and dried to yield the title compound: ^{1}H NMR (DMSO-d_6) δ 9.8 (1H, m), 7.3 (18H, m), 5.1 (2H, m), 4.8 (2H, m), 4.4 (5H, m), 3.0 (4H, m), 2.6 (1H, m), 2.2 (1H, m), 1.8 (3H, m), 1.5 (6H, m), 1.1 (6H, s). Anal. ($C_{46}H_{49}N_3O_5 \cdot H_2O$) C, H, N.

Acknowledgment. We would like to thank Dr. N. P. Shankley and Dr. E. A. Harper for providing the *in vitro* data presented in the tables.

References

(1) *Gastrin and Cholecystokinin: Chemistry, Physiology and Pharmacology*; Bali, J.-P., Martinez, Eds.; Elsevier: Amsterdam, The Netherlands, 1987.

(2) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Garsky, V. M.; Gilbert, K. F.; Leighton, J. L.; Carbon, K. L.; Mellin, E. C.; Veber, D. F.; Chang, R. S. L.; Lotti, V. J.; Freedman, S. B.; Smith, A. J.; Patel, S.; Anderson, P. S.; Freidinger, R. M. Development of 1,4-Benzodiazepine Cholecystokinin Type B Antagonists. *J. Med. Chem.* **1993**, *36*, 4276–92.

(3) Showell, G. A.; Bourrain, S.; Neduvelil, J. G.; Fletcher, S. R.; Baker, R.; Watt, A. P.; Fletcher, A. E.; Freedman, S. B.; Kemp, J. A.; Marshall, G. R.; Patel, S.; Smith, A. J.; Matassa, V. G. High-Affinity and Potent, Water-Soluble 5-Amino-1,4-Benzodiazepine CCKB/Gastrin Receptor Antagonists Containing a Cationic Solubilizing Group. *J. Med. Chem.* **1994**, *37*, 719–21.

(4) Nishida, A.; Miyata, K.; Tsutsumi, R.; Yuki, H.; Akuazawa, S.; Kobayashi, A.; Kamato, T.; Ito, H.; Yamano, M.; Katuyama, Y.; Satoh, M.; Ohta, M.; Honda, K. Pharmacological Profile of (*R*)-1-[2,3-Dihydro-1-(2′-methylphenacyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl]-3-(3-methylphenyl)urea, a New Potent and Selective Gastrin/Cholecystokinin-B Receptor Antagonist, *in Vitro* and *in Vivo*. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 725–31.

(5) See, for example, Glaxo SPA Patent Publication No. WO 95/03285, 1995.

(6) Howbert, J. J.; Lobb, K. L.; Britton, T. C.; Mason, N. R.; Burns, R. F. Diphenylpyrazolidinone and Benzodiazepine Cholecystokinin Antagonists: A Case of Convergent Evolution in Medicinal Chemistry. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 875–80.

(7) Yu, M. J.; Thrasher, K. J.; McCowan, J. R.; Mason, N. R.; Mendelsohn, L. G. Quinazolinone Cholecystokinin-B Receptor Ligands. *J. Med. Chem.* **1991**, *34*, 1508–11.

(8) Lowe, J. A., III; Hageman, D. L.; Drzda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R. T.; Zorn, S.; Morrone, J.; Bordner, J. 5-Phenyl-3-ureidobezazepin-2-ones as Cholecystokinin-B Receptor Antagonists. *J. Med. Chem.* **1994**, *37*, 3789–811.

(9) Bertrand, P.; Bohme, G. A.; Durieux, C.; Guyon, C.; Capet, M.; Jeantaud, B.; Boudeau, P.; Ducos, B.; Pendley, C. E.; Martin, G. E.; Floch, A.; Doble, A. Pharmacological Properties of Ureidoacetamides, New Potent and Selective Non-peptide CCKB/Gastrin Receptor Antagonists. *Eur. J. Pharmacol.* **1994**, *262*, 233–45.

(10) Kalindjian, S. B.; Bodkin, M. J.; Buck, I. M.; Dunstone, D. J.; Low, C. M. R.; McDonald, I. M.; Pether, M. J.; Steel, K. I. M. A New Class of Non-Peptidic Cholecystokinin-B/Gastrin Receptor Antagonists Based on Dibenzobicyclo[2.2.2]octane. *J. Med. Chem.* **1994**, *37*, 3671–3.

(11) Diels, O.; Alder, K. Synthesen in der Hydroaromatrichen Reile. (Synthesis of a Series of Hydroaromatic Compounds.) *Ann. Chem.* **1931**, *486*, 191–202.

(12) (a) Harper, E. A.; Shankley, N. P.; Black, J. W. Competition between L-365,260 and [^{125}I]-BH-CCK8S in Guinea-pig Gastric Glands and Mouse and Rat Cortex Assays; Evidence for Variable Expression of Two CCK/Gastrin Receptors. *Br. J. Pharmacol.* **1995**, *114*, 221P. (b) Harper, E. A.; Shankley, N. P.; Roberts, S. P.; Black, J. W. Variable Expression of Two CCK_B/Gastrin Receptors: Evidence from L-365,260 Competition Curves in Radioligand Binding Assays. *Br. J. Pharmacol.*, submitted for publication. (c) James Black Foundation Patent Publication No. WO Patent Application 93/16982, 1993.

(13) Hull, R. A. D.; Shankley, N. P.; Harper, E. A.; Gerskowitch, V. P.; Black, J. W. 2-Naphthalenesulphonyl-L-aspartyl-(2-phenethyl)amide (2-NAP)-a selective cholecystokinin CCKA-Receptor Antagonist. *Br. J. Pharmacol.* **1993**, *108*, 734–40.

(14) Fauchere, J.-L.; Thurieau, C. Evaluation of the Stability of Peptides and Pseudopeptides as a Tool in Peptide Drug Design. *Adv. Drug Res.* **1992**, *23*, 127–59 and references contained therein.

(15) Rorer International (Holdings), Inc., Patent Publication No. WO 92/00295, 1992.

(16) Ewing, W. R.; Molino, B. F.; Bolton, S. A.; Manetta, V.; Pendley, C.; Capilino, A. Highly Potent and Selective Gastrin Receptor Antagonists based on CCK-4. *Proceedings of the Twenty-Second European Peptide Symposium*; ESCOM: Leiden, The Netherlands, 1993.

(17) Vinter, J. G.; Trollope, K. I. Multi-conformational Composite Molecular Potential Fields in the Analysis of Drug Action. (I) Methodology and First Evaluation using 5-HT and Histamine Action as examples. *J. Comput.-Aid. Drug Des.* **1995**, *9*, 297–307.

JM950438N