Optimization of the in Vitro and in Vivo Properties of a Novel Series of 2,4,5-Trisubstituted Imidazoles as Potent Cholecystokinin-2 (CCK_2) Antagonists

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The systematic optimization of the structure of a novel 2,4,5-trisubstituted imidazole-based cholecystokinin-2 (CCK_2) receptor antagonist afforded analogues with nanomolar receptor affinity. These compounds were now comparable in their potency to the bicyclic heteroaromatic-based compounds **5** (JB93182) and **6** (JB95008), from which the initial examples were designed using a field-point based molecular modeling approach. They were also orally active as judged by their inhibition of pentagastrin stimulated acid secretion in conscious dogs, in contrast to the bicyclic heteroaromatic-based compounds, which were ineffective because of biliary elimination. Increasing the hydrophilicity through replacement of a particular methylene group with an ether oxygen, as in 3-{[5-(adamantan-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazole-4-carbonyl]amino}benzoic acid (**53**), had little effect on the receptor affinity but significantly increased the oral potency. Comparison of the plasma pharmacokinetics and the inhibition of pentagastrin-stimulated acid output following bolus intraduodenal administration of both **53** and **6** indicated that **53** was well absorbed, had a longer half-life, and was not subject to the elimination pathways of the earlier series.

Introduction

Cholecystokinin (CCK) and gastrin are two closely related peptide hormones that mediate a range of peripheral and central biological processes. Cholecystokinin receptors are divided into two subclasses: CCK_1 and CCK_2 receptors. CCK_1 receptors are mainly located in the periphery, while CCK_2 receptors are the predominant subtype in the central nervous system (CNS). In the periphery CCK_2 receptors are located on the ECL cells of the stomach and are activated by the peptide hormone gastrin. The last five residues at the carboxy terminus of both CCK and gastrin are identical, and the C-terminal tetrapeptide (CCK(30−33)) is sufficient to elicit a full biological response at CCK_2 receptors in both the periphery and the CNS.[1,2] However, this fragment has only micromolar affinity for the CCK_1 receptor, which requires the sulfated octapeptide fragment (CCK-8S) for full activation.[3]

The quest for drugs that block the actions of the peptide hormone gastrin that are mediated by CCK_2 receptors has led to the discovery of a wide range of small-molecule ligands.[4−6] Many compounds have been derived from leads obtained through screening of compound libraries. For example, the natural product asperlicin was shown to possess weak affinity for the CCK_1 receptor, leading to the development of the 1,4-benzodiazepine **1** (L-365,260)[7] in the late 1980s (Figure 1). Many subsequent ligands utilized this or related benzodiazepine ring systems. However, the development of many of these compounds has been limited because of their low oral activity. Two notable exceptions are **2** (YF-476),[8] which is a compound with high in vitro affinity and oral potency, and **3** (Z-360),[9] a related 1,5-benzodiazepine (Figure 1). An alternative approach is rational drug design using the endogenous ligand as the starting point. While this approach has been used successfully with small-molecule hormones, such as biogenic amines, examples where the endogenous ligand is a peptide are relatively few.[10] The most significant drawback when applying this strategy to peptides is that the high molecular weight of the starting peptide often results in high molecular weight compounds. Nevertheless, compounds derived using this approach may retain the specificity of the endogenous ligands. CCK_2 receptor ligands designed from the C-terminal fragment of gastrin, the tetrapeptide (CCK(30−33)), include the peptoid **4** (PD-134,308),[11] which behaves as a partial agonist,[12] and the indole and benzimidazole antagonists **5** (JB93182) and **6** (JB95008).[13] However, compared to **2**, these antagonist compounds display low in vivo potency as measured by their effect on pentagastrin-stimulated gastric acid secretion following enteral administration. In the case of **5** this has been ascribed to rapid hepatic elimination of the unchanged compound via the bile duct. In the preceding paper[14] we have described new heterocyclic compounds derived from **5** using a field-point based molecular modeling approach. Although these were less potent and less

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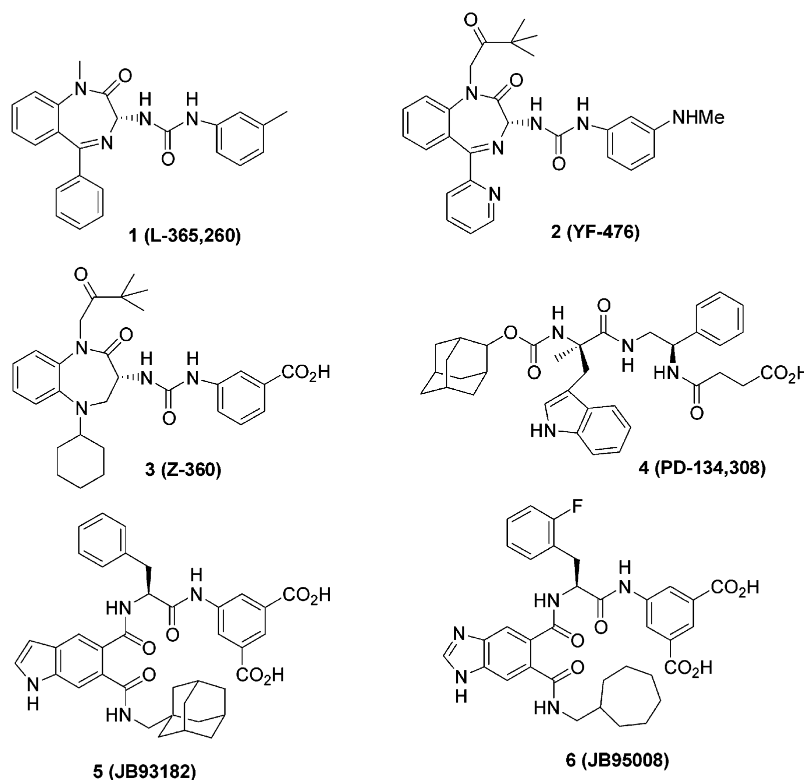


Figure 1. Structures of CCK_2 receptor antagonists.

selective with respect to CCK_1 receptors, their biliary elimination was greatly diminished. The mechanism underlying biliary excretion is not fully understood, but high molecular weight is one factor considered to predispose compounds to clearance by this route. Reducing the molecular weight in going from **5** to the new compounds was not sufficient to achieve a reduction in biliary elimination. Only by additionally changing the polarity through removal of one of the two carboxylic acid groups present was biliary elimination markedly reduced. In this paper, we describe efforts to increase both affinity and selectivity at CCK_2 receptors through further structural modification while restricting the molecular weight to around 500, which is commonly taken as a threshold value for biliary elimination in man. Moreover, we recognized that polarity would also be an important factor in achieving our goal of obtaining orally active CCK_2 receptor antagonists.

Chemistry

The pyrrole derivatives (**12**–**14**) in Table 1 were prepared according to the general route in Scheme 1. The diketoesters (**8**) were obtained by alkylation of β-ketoesters (**7**)[15] with the appropriate haloketone. These were treated with ammonium acetate in acetic acid[16] to form the 2,3,5-trisubstituted pyrroles (**9**). The ethyl esters were hydrolyzed to afford the corresponding carboxylic acids (**10**), and following activation as their acid chlorides, were reacted with 3-aminobenzoic acid benzyl ester (**11a**). The benzyl ester protecting group was removed by hydrogenolysis in the presence of 10% palladium on charcoal to give the desired compounds **12**–**14**.

The imidazoles (**20**–**55**) in Tables 1 and 2 were prepared by the general route outlined in Scheme 2. The substituted acetic acids (**15**) were reacted with acyl

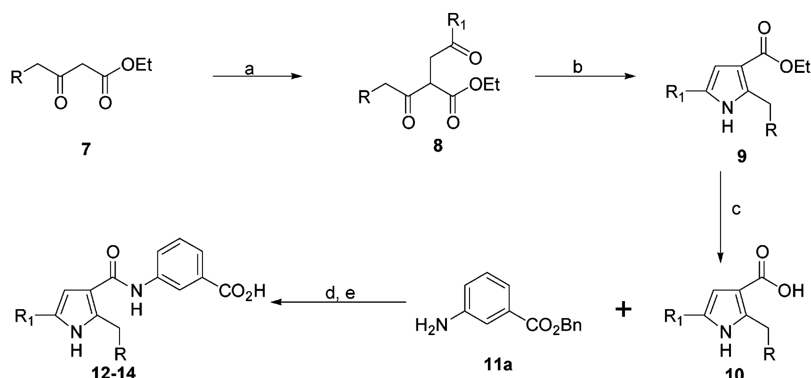
Table 1. Comparison of Pyrroles and Imidazoles

compd	R	R_1	X	CCK_2[a]	CCK_2[b]	CCK_1[c]
12[d]	c-C_7H_{13}	2-$C_{10}H_7$	CH	ia[e]	5.88 ± 0.04	5.52
20[d]	c-C_7H_{13}	2-$C_{10}H_7$	N	ia[e]	6.09 ± 0.11	5.60
13	1-Ad-CH_2	C_6H_5	CH	ia[e]	6.35 ± 0.1	5.68
21	1-Ad-CH_2	C_6H_5	N	6.63 ± 0.33	6.50 ± 0.06	5.88
14	1-Ad-CH_2	2-Me-C_6H_4	CH	ia[e]	6.69 ± 0.04	5.66 ± 0.1
22	1-Ad-CH_2	2-Me-C_6H_4	N	7.23 ± 0.3	6.92 ± 0.01	6.18

[a] pA_2 ± SEM values, estimated from single shifts of pentagastrin concentration–effect curves in the isolated, lumen-perfused immature rat stomach. [b] pK_I ± SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S for CCK_2 binding sites in mouse cortex homogenates from at least three separate experiments. [c] pK_I ± SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S at CCK_1 binding sites on guinea pig pancreatic cells from at least three separate experiments. When errors are not given, the data are obtained from two separate experiments. Approximate SEM is 0.1 log units. [d] Reference 11. [e] Inactive at the concentration tested (between 10^{-4} and 3×10^{-5} M).

phosphoranylidines[17] to afford the keto phosphoranes (**16**). Oxidation of the carbon–phosphorus double bond with potassium peroxymonosulfate (OXONE)[18] gave the tricarbonyl intermediates (**17**). Treatment of **17** with the appropriate aldehydes in the presence of ammonium acetate in acetic acid delivered the imidazole derivatives **18**.[19] Removal of the ester protecting group of intermediates **18** by hydrolysis or hydrogenolysis afforded the corresponding carboxylic acids **19**. These were coupled with the aniline derivatives **11a**–**k** under standard conditions. Where the substituent (X) was a carboxylic acid group this component was introduced as an ester (X′). The desired compounds were obtained on removal of the protecting group by hydrogenolysis with pal-

Scheme 1. Synthesis of Trisubstituted Pyrroles[a]



[a] (a)$BrCH_2COR_1$, K_2CO_3, NaI, acetone; (b) NH_4OAc, AcOH; (c) NaOH, EtOH−H_2O; (d) $SOCl_2$, DMF, CH_2Cl_2, then **11a**, pyr; (e) Pd−C, H_2, THF−MeOH.

Table 2. In Vitro Data from CCK_2 and CCK_1 Bioassays for Trisubstituted Imidazoles

compd	R	R_1	X	Y	CCK_2[a]	CCK_2[b]	CCK_1[c]
23	*i*-Pr-CH_2	2-Me-C_6H_4	CO_2H	H	7.58 ± 0.5	5.08 ± 0.07	6.18 ± 0.05
24	*t*-Bu-CH_2	2-Me-C_6H_4	CO_2H	H	NT[d]	5.42 ± 0.02	NT[d]
25	*c*-$C_6H_{11}CH_2$	2-Me-C_6H_4	CO_2H	H	7.70 ± 0.33	6.21 ± 0.12	6.53 ± 0.07
26	$C_6H_5CH_2$	2-Me-C_6H_4	CO_2H	H	5.93 ± 0.24	5.57 ± 0.04	NT[d]
27	1-Ad	2-Me-C_6H_4	CO_2H	H	ia[e]	5.84 ± 0.12	NT[d]
28	1-Ad-CH_2	2-Me-C_6H_4	Me	H	NT[d]	<4	NT[d]
29	1-Ad-CH_2	2-Me-C_6H_4	CO_2Me	H	NT[d]	<4	NT[d]
30	1-Ad-CH_2	2-Me-C_6H_4	NHMe	H	NT[d]	4.95 ± 0.15	NT[d]
31	1-Ad-CH_2	2-Me-C_6H_4	CH_2CO_2H	H	ia[e]	8.65 ± 0.14	6.40 ± 0.17
32	1-Ad-CH_2	2-Me-C_6H_4	$C_2H_5CO_2H$	H	6.30 ± 0.27	8.16 ± 0.16	6.52 ± 0.06
33	1-Ad-CH_2	2-Me-C_6H_4	CO_2H	Me	7.48 ± 0.12	8.23 ± 0.18	6.38 ± 0.24
34	1-Ad-CH_2	2-Me-C_6H_4	CO_2H	F	7.06 ± 0.24	7.33 ± 0.09	6.25 ± 0.08
35	1-Ad-CH_2	2-Me-C_6H_4	CO_2H	NMe_2	6.13 ± 0.27	6.49 ± 0.05	6.1
36	1-Ad-CH_2	2-Me-C_6H_4	CO_2H	OMe	ia[e]	6.74 ± 0.03	NT[d]
37	1-Ad-CH_2	2,4-Me_2-C_6H_3	CO_2H	H	8.00 ± 0.38	7.08 ± 0.03	6.21 ± 0.01
38	1-Ad-CH_2	2,6-Me_2-C_6H_3	CO_2H	H	7.00 ± 0.34	6.85 ± 0.07	<5
39	1-Ad-CH_2	2,4,6-Me_3-C_6H_2	CO_2H	H	8.06 ± 0.25	7.57 ± 0.05	6.14 ± 0.06
40	1-Ad-CH_2	2,4,6-Me_3-C_6H_2	CO_2H	Me	8.48 ± 0.34	8.52 ± 0.07	6.91 ± 0.01
41	1-Ad-CH_2	Me	CO_2H	H	5.81 ± 0.29	5.63 ± 0.18	NT[d]
42	1-Ad-CH_2	C_3H_7	CO_2H	H	7.28 ± 0.26	6.57 ± 0.16	5.95 ± 0.12
43	1-Ad-CH_2	*i*-C_3H_7	CO_2H	H	7.68 ± 0.26	6.73 ± 0.04	5.84 ± 0.13
44	1-Ad-CH_2	*t*-Bu	CO_2H	H	7.96 ± 0.25	7.17 ± 0.12	5.54 ± 0.08
45	1-Ad-CH_2	*c*-C_3H_5	CO_2H	H	7.15 ± 0.26	6.11 ± 0.06	5.63 ± 0.08
46	1-Ad-CH_2	*c*-C_5H_9	CO_2H	H	8.15 ± 0.35	7.40 ± 0.04	6.28 ± 0.10
47	1-Ad-CH_2	*c*-C_6H_{11}	CO_2H	H	8.31 ± 0.25	7.60 ± 0.07	6.24 ± 0.10
48	1-Ad-CH_2	*c*-C_7H_{13}	CO_2H	H	8.27 ± 0.22	7.93 ± 0.04	6.90 ± 0.24
49	1-Ad-CH_2	bicyclo[2.2.2]octan-1-yl	CO_2H	H	8.61 ± 0.36	7.69 ± 0.02	6.49 ± 0.04
50	1-Ad-CH_2	*c*-$C_{12}H_{23}$	CO_2H	H	ia[e]	5.77 ± 0.05	NT[d]
51	1-Ad-CH_2	1-Me-*c*-C_6H_{10}	CO_2H	H	8.79 ± 0.38	7.75 ± 0.01	6.25 ± 0.21
52	1-Ad-CH_2	1-Me-*c*-C_6H_{10}	CO_2H	Me	9.05 ± 0.29	8.48 ± 0.06	6.60 ± 0.19
53	1-Ad-O	*c*-C_6H_{11}	CO_2H	H	9.06 ± 0.32	7.87 ± 0.04	6.25 ± 0.09
54	1-Ad-O	bicyclo[2.2.2]octan-1-yl	CO_2H	H	9.15 ± 0.25	7.56 ± 0.12	6.11 ± 0.02
55	1-Ad-O	2,4,6-Me_3-C_6H_2	CO_2H	H	7.87 ± 0.26	7.86 ± 0.09	6.27 ± 0.18

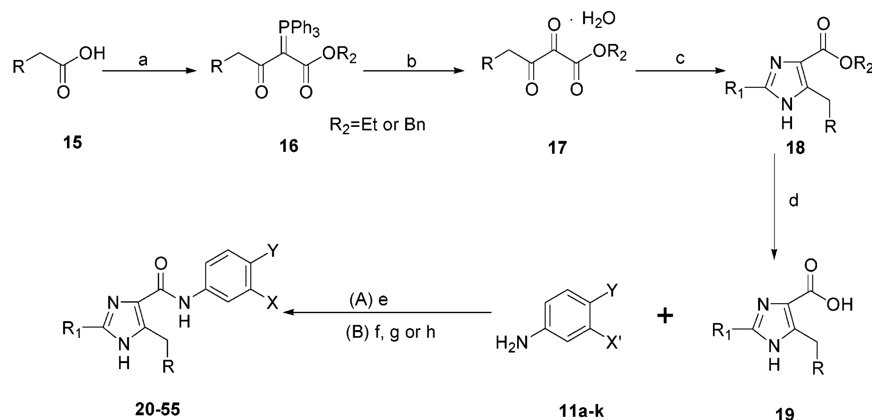
[a] pA_2 ± SEM values, estimated from single shifts of pentagastrin concentration−effect curves in the isolated, lumen-perfused immature rat stomach. [b] pK_I ± SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S for CCK_2 binding sites in mouse cortex homogenates from at least three separate experiments. [c] pK_I ± SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S at CCK_1 binding sites on guinea pig pancreatic cells from at least three separate experiments. When errors are not given, the data are obtained from two separate experiments. Approximate SEM is 0.1 log units. [d] NT = not tested. [e] Inactive at the concentration tested (between 10^{-4} and 3×10^{-5} M).

ladium on charcoal (**20**−**27**, **31**, and **33**−**55**) or acidolysis with trifluoroacetic acid (**26**). When the substituent (X) was an *N*-methylamino group, it was introduced as its *tert*-butoxycarbonyl derivative (X′) and the protecting group was removed by treatment with hydrochloric acid in dioxan (**30**).

Results and Discussion

Molecular modeling, initial structure−activity relationships (SAR), and assessment of biliary elimination identified two lead compounds with micromolar affinity for CCK_2 receptors, as measured by displacement of [^{125}I]BH-CCK-8S in a mouse cortex radioligand binding

Scheme 2. Synthesis of Trisubstituted Imidazoles[a]



[a] (a) $Ph_3Ph{=}CO_2Et$ or $Ph_3PCH{=}CO_2Bn$, EDC, DCM; (b) OXONE, $THF-H_2O$ or $CH_2Cl_2-H_2O$; (c) R_1CHO, NH_4OAc, AcOH; (d) NaOH, $EtOH-H_2O$ when R_2 = Et, or Pd−C, H_2, THF−MeOH when R_2 = Bn; (e) EDC, HOBt, DMF; (f) Pd−C, H_2, THF−MeOH for **20**−**27**, **31**, and **33**−**55**; (g) HCl−dioxan for **30**; (h) TFA for **32**.

assay.[20] These were the pyrrole **12** and the imidazole analogue **20**.[14] Further exploration of the structure−activity of these lead compounds, which is summarized in Table 1, indicated that a 1-adamantylethyl substituent could be used in place of cycloheptylmethyl at C-5 of the imidazole ring and that a smaller aromatic group such as phenyl or *o*-tolyl was superior to 2-naphthyl in the C-2 position. In all cases the compounds showed selectivity over CCK_1 receptors as judged by their competition with [^{125}I]BH-CCK-8S at CCK_1 binding sites on guinea pig pancreatic cells.[21] We chose to further optimize only the imidazole series, since **21** and **22** had marginally higher activity in the mouse cortex assay than the pyrrole analogues **13** and **14**, respectively, and in addition they displayed similar affinity in the rat stomach functional bioassay[22] in contrast to the pyrrole-based compounds. Differences in CCK_2 activity of compounds between the rat stomach and the mouse cortex assays have been known to occur. This has been attributed to CCK_2 receptor heterogeneity,[20,22,23] although it could also be explained by speciation of the CCK_2 receptor.[24] However, it cannot be discounted that the discrepancy in behavior of compounds across these particular assays, as with the pyrroles, is due to low aqueous solubility. In the mouse cortex assay this property is rarely manifest because this assay is more tolerant of the organic solvent used to aid dissolution, whereas in the rat stomach assay the same compound may appear inactive at the concentration tested. Pragmatically, we aimed to obtain more potent compounds having comparable receptor affinities in the two assays.

With **22** as the structure on which to base further systematic changes, the compounds listed in Table 2 were prepared. Initially, the structural requirements of the hydrophobic group attached to the C-5 position of the imidazole ring were explored (**23**−**27**). There appeared to be no benefit in changing the 1-adamantylethyl group with regard to potency, interassay variation, or selectivity over CCK_1 receptors. Although affinity estimates similar to that for **22** were observed in the rat stomach assay for the isoamyl (**23**) and cyclohexylethyl (**25**) derivatives, these were achieved only at a cost of greater interassay differences and reduced selectivity over CCK_1 receptors.

When changes were made to the substituent on the anilide group, a trend to that of **5** and its analogues was observed. Replacing the carboxylic acid with either neutral groups (**28** and **29**) or a basic substituent (**30**) greatly reduced the biological activity, supporting our initial model that the carboxylic acid substituents of the respective series fulfilled an identical role. The homologues of **22**, which contained carboxymethyl and carboxyethyl substituents, **31** and **32**, respectively, were at least 10-fold more potent in the mouse cortex assay but significantly less potent in the rat stomach assay. This discrepancy between assays suggested that these changes offered no advantage over the 3-carboxy analogue (**22**). When an additional substituent was attached at the 4-postion of this ring, the activity appeared to be influenced by steric factors because both the sterically demanding dimethylamino (**35**) and methoxy (**36**) derivatives were less potent than the fluoro-substituted compound (**34**), which was indistinguishable from **22**. On the other hand, the 4-methyl analogue (**33**) did achieve increased activity, but this was only observed in the mouse cortex assay.

Thus far, where structural changes had resulted in increased activity with respect to **22**, this had generally occurred selectively in the mouse cortex assay. However, when the hydrophobic character of the *o*-tolyl substituent was increased through the introduction of further methyl groups, this change had a greater impact on affinity in the rat stomach assay. This was most marked for the 2,4-dimethyl derivative (**37**), whereas when this group was introduced in the 6-position, affording the symmetrically substituted 2,6 analogue (**38**), selectivity over CCK_1 receptors was increased. In the 2,4,6-trimethyl compound (**39**), increased affinity in the rat stomach relative to **22** was also observed in a pattern similar to that of **37**. However the low CCK_1 activity observed for **38** was not maintained. When this substitution pattern was combined with a 4-methyl substituent in the 3-carboxy-anilide ring, a change that we had previously identified as having a positive influence on the CCK_2 activity in the mouse cortex assay (**33**), the resulting compound (**40**) was now active in the nanomolar range in both of the CCK_2 assays. The advantage

Table 3. Inhibition of Pentagastrin-Stimulated Acid Secretion in Conscious Dogs by Bolus Administration

compd	log *D* [a]	pIC$_{50}$ [b]	route of administration	dose, mg/kg	inhibition[c]
40	4.90 ± 0.03	7.40 ± 0.14	iv	3.0	76 ± 7 (3)
47	4.12 ± 0.05	7.53 ± 0.09	iv	1.0	40 ± 15 (3)
47			id	10.0	46 ± 8 (3)
52	4.91 ± 0.09	7.95 ± 0.18	iv	3.0	54 ± 5 (4)
53	2.73 ± 0.03	7.71 ± 0.12	iv	1.0	76 ± 5 (4)
53			id	3.0	63 ± 6 (3)
55	3.02 ± 0.01	7.20 ± 0.14	iv	1.0	61 ± 14 (3)

[a] log *D* measured in octanol/buffer (pH 7.4). [b] Competition with [^{125}I]BH-CCK-8S for CCK$_2$ binding sites in canine gastric mucosa. [c] Peak percentage inhibition ± SEM (number of replicates in parentheses) in the first four collection periods (1 h) after dosing.

of this gain in potency was somewhat offset by a concomitant increase in CCK$_1$ activity.

Compounds were also prepared in which the aromatic group attached to the C-2 position of the imidazole ring was replaced by a series of nonaromatic hydrocarbon substituents. With acyclic groups (**41**−**44**) there was a distinct trend of increased CCK$_2$ activity with increasing number of carbon atoms in the substituent, with the *tert*-butyl-containing compound (**44**) being superior to **22** in terms of CCK$_2$ activity and selectivity over CCK$_1$. In a series of cyclic hydrocarbon groups only the cyclopropyl derivative (**45**) was less potent than **22**, albeit in the mouse cortex assay, whereas larger cyclic groups (**46**−**48**) were uniformly more potent, showing behavior similar to one another in both assays. Further insight into the nature of the receptor binding pocket for the 2-substituent on the imidazole ring was afforded by the observation that while the bulky bicyclooctane group (**49**) was particularly well accommodated, the larger cyclododecyl analogue (**50**) displayed only weak activity. The 1-methylcyclohexyl derivative (**51**) had a profile similar to that of the bicyclooctane analogue (**49**), and when this change was combined with a 4-methyl substituent on the anilide ring, the most potent and selective of the nonaromatic C-2 substituted derivatives was obtained (**52**).

By the process of optimization outlined above, we now had obtained compounds with affinities comparable to that of **6** in terms of their potency and selectivity based on in vitro assays; however, it was unclear whether they were devoid of the shortcomings of the earlier series. In the anesthetized rat, our primary in vivo model of gastric acid secretion, examples of this new series were generally as potent on intravenous administration as **6** relative to their respective CCK$_2$ receptor affinities (as measured in the rat stomach assay) (data not shown).

To establish whether these compounds were orally active, selected examples were further assessed in conscious, chronic gastric fistula dogs. Although these compounds had CCK$_2$ receptor affinity similar to that of **6** in this species as judged by competition with [^{125}I]-BH-CCK-8S in canine gastric mucosa, they were less potent in vivo following intravenous administration (Table 3). However, in contrast to our earlier bicyclic heteroaromatic-based series of CCK$_2$ antagonists (**5** and **6**), **47** did inhibit pentagastrin-stimulated acid secretion when administered by an intraduodenal route in the same model. From a physicochemical point of view, the most potent compounds arising from the SAR studies were particularly lipophilic, with measured log $D_{(oct/pH7.4)}$ values being in excess of 4.0 (Table 3). Encouraged by

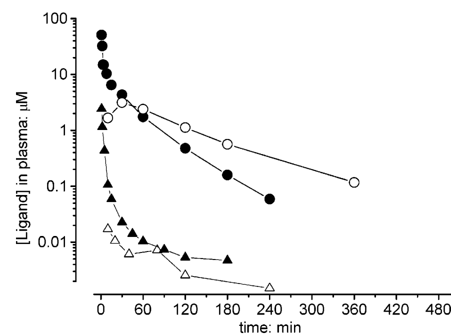


Figure 2. Data showing variation of plasma levels of compounds with time following iv bolus (3 mg/kg) and po (10 mg/kg) administration to dogs: **53** iv (●); **53** po (○); **6** iv (▲); **6** po (△).

the effect of **47** on intraduodenal dosing, indicating that we had made progress toward fulfilling our aim of obtaining orally active compounds, we sought to reduce their lipophilic character to improve their oral potency still further. Toward this general aim, a study was undertaken to see into which parts of the molecule a heteroatom could be introduced without detriment to the CCK$_2$ affinity and selectivity. This was only satisfactorily achieved by replacement of the methylene group directly attached to the adamantyl substituent with an oxygen atom, as in examples **53**−**55**. Furthermore, this did meet our need to obtain more hydrophilic compounds because the log $D_{(oct/pH7.4)}$ value of **53** was significantly lower than for its corresponding carbon analogue (**47**). The influence of lipophilicity on in vivo potency was subsequently confirmed, since **53** not only achieved substantial acid inhibition at 1 mg/kg by intravenous administration but was at least 3-fold more potent by intraduodenal delivery than its more hydrophobic analogue **47**.

Our aim when starting the program of work was to obtain potent CCK$_2$ antagonists that were orally bioavailable and that, once absorbed, did not suffer the biliary elimination encountered by our earlier bicyclic heteroaromatic based series.[13] That these twin goals have been achieved is shown in Figures 2 and 3 in which **6**, a representative of the latter series, and **53** are compared with respect to plasma kinetics and intraduodenal potency. The kinetic data reported in Figure 2 show that the plasma levels of **53**, whether following intravenous or oral administration, are substantially higher at all time points than those obtained following administration of the same dose of **6**. The oral bioavailability of **53** calculated from these data is 27%, which compares favorably with the low estimate for **6** (<1%). To derive a more reliable comparison of their duration of action following enteral administration, the same compounds were assessed for their ability to inhibit a continuous infusion of pentagastrin-stimulated acid secretion using dual fistula dogs (Figure 3). The shorter duration of the inhibitory effect of **6** (40 μmol/kg, intraduodenal bolus) during the course of the experiment is a reflection of the low oral bioavailablity associated with high clearance through biliary elimination of this compound, whereas a 15-fold lower dose of **53** gives a sustained inhibitory effect showing no reversal up to 2 h after dosing.

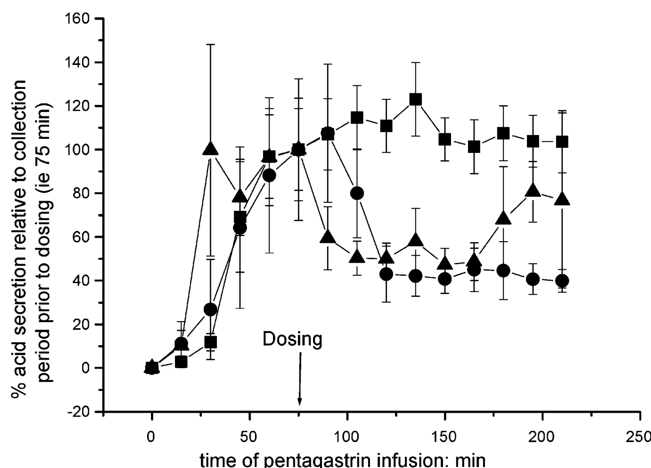


Figure 3. Data showing the effect of control (■), **53** (3 μmol/kg) (●), and **6** (40 μmol/kg) (▲) in inhibiting gastric acid secretion induced by a continuous intravenous infusion of pentagastrin in conscious dual (gastric and duodenal) fistula female beagle dogs. Pentagastrin infusion rates are established for individual dogs by analyzing dose response curves and selecting a rate of infusion that elicits an acid secretary response between 60% and 80% of the maximum response obtained. In each dog, acid secretion is determined by continual collection from the gastric fistula and assessment of the volume and acidity of the collected gastric secretion every 15 min. After five collection periods, the test compound is administered as an intraduodenal bolus (into the duodenal fistula) and gastric secretion is measured for up to 5 h. The data are expressed as percentage acid output relative to the acid output in the collection period immediately prior to dosing. Error bars represent SEM.

Conclusion

A process that began with consideration of the structure of the smallest fragment of gastrin retaining full activity at CCK_2 receptors led to **5**. Faced with the limitations of **5** in vivo, which are often shared by other ligands for G-protein-coupled receptrs (GPCRs) obtained by this approach, other more suitable frameworks were identified using a field point based molecular modeling technique. The small ring heterocyclic-based compounds described herein are one example of such a framework. Through selective optimization of the CCK_2 affinity and careful consideration of parameters such as molecular weight and polarity, it has been possible to obtain a series of potent, orally active CCK_2 receptor antagonists. Their lineage is reflected in the high receptor specificity of **53**.[25] Moreover, this and the preceding paper provide a demonstration of the value of rational drug design based on SAR interpretation coupled with molecular modeling methods. These novel compounds represent an important milestone in our investigations of the therapeutic utility of this class of compound.

Experimental Section

Abbreviations. 1-Ad, adamantan-1-yl; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP, 4-(dimethylamino)pyridine; HOBt, 1-hydroxybenzotriazole; PCC, pyridinium chlorochromate; OXONE, potassium peroxymonosulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).

General. All the compounds except **28**–**30** and **32** were tested as *N*-methyl-D-glucamine salts. The salts were prepared by stirring a mixture of the compound with 1 equiv of *N*-methyl-D-glucamine in dioxan–water 1:1 until a solution was obtained, and the solutions were freeze-dried. The isolated perfused rat stomach assay and the method of analysis were conducted as previously described,[22] and at least six separate tissue preparations were used to obtain pA_2 estimates for each compound. The mouse cerebral cortex[20] and guinea pig pancreas[21] assays were used as previously described. The canine radioligand binding assay methodology will be described in due course.

NMR spectra were recorded on a Bruker DRX 300 spectrometer with chemical shifts reported in ppm (δ) relative to the solvent peak ($CDCl_3$ at 7.26, DMSO-d_6 at 2.52, and MeOH-d_4 at 3.34). Elemental analysis was performed at the London School of Pharmacy, and the results are within 0.4% of the theoretical values. Merck silica gel 60 (40–63μm) was used for column chromatography.

The β-ketoesters (**7**) were prepared from commercially available carboxylic acids and bromoketones.[15]

3-Adamantan-1-ylpropionic acid was prepared from 1-bromoadamantane,[26] and 4,4-dimethylpentanoic acid was synthesized in three steps from trimethylacetaldehyde and triethyl phosphonoacetate. (Adamantan-1-yloxy)acetic acid ethyl ester was prepared from 1-adamantanol and ethyl diazoacetate.[27] Hydrolysis of the ester afforded (adamantan-1-yloxy)acetic acid. The aldehydes, which were not commercially available, were prepared from the corresponding alcohols (where necessary obtained by lithium aluminum hydride reduction of the corresponding carboxylic acids) by PCC[28] or Swern[29] oxidation. Bicyclo[2.2.2]oct-1-ylmethanol was prepared by a literature method.[30] 2,6-Dimethylbenzaldehyde was made from 2-bromo-*m*-xylene.[31]

Anilines *m*-tolylamine (**11b**) and 3-aminobenzoic acid methyl ester (**11c**) are commercially available. 3-Aminobenzoic acid benzyl ester (**11a**), (3-aminophenyl)acetic acid benzyl ester (**11e**), 5-amino-2-methylbenzoic acid benzyl ester (**11g**), 5-amino-2-fluorobenzoic acid benzyl ester (**11h**), 5-amino-2-dimethylaminobenzoic acid benzyl ester (**11i**), and 5-amino-2-methoxybenzoic acid benzyl ester (**11j**) were prepared from the appropriate nitrobenzoic acids in two steps. The benzyl esters were made with benzyl bromide in the presence of cesium carbonate, followed by reduction of the nitro group with tin(II) chloride dihydrate. (3-Aminophenyl)methylcarbamic acid *tert*-butyl ester (**11d**) was prepared by a literature procedure.[32] 3-(3-Aminophenyl)propionic acid *tert*-butyl ester (**11f**) was made by reacting 3-nitrobenzaldehyde with (*tert*-butoxycarbonylmethyl)triphenylphosphonium bromide and sodium hydride followed by hydrogenation of the product in the presence of 10% palladium on charcoal catalyst.

Syntheses of **12** and **20** are reported elsewhere.[14]

The pyrrole derivatives **13** and **14** were prepared by the method described below.

3-{[2-(2-Adamantan-1-ylethyl)-5-phenyl-1*H*-pyrrole-3-carbonyl]amino}benzoic Acid (13). Step a. To a solution of 5-adamantan-1-yl-3-oxopentanoic acid ethyl ester[15] (2.78 g, 10 mmol) in acetone (30 mL) was added sodium iodide (100 mg, 0.67 mmol) and anhydrous potassium carbonate (2.76 g, 20 mmol), then a solution of 2-bromo-1-phenylethanone (1.99 g, 10 mmol) in acetone (10 mL). The mixture was heated at reflux for 16 h, cooled to room temperature, and filtered. The filtrate was evaporated, and the residue was dissolved in diethyl ether (50 mL) and washed with water (2 × 20 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by chromatography on silica gel using hexanes–EtOAc (4:1) as eluant to afford 5-adamantan-1-yl-3-oxo-2-(2-oxo-2-phenylethyl)pentanoic acid ethyl ester as a pale-yellow oil (1.91 g, 48%). ^{1}H NMR ($CDCl_3$) δ 7.97 (2H, m), 7.56 (1H, m), 7.46 (2H, m), 4.25 (3H, m), 3.67 (1H, dd), 3.55 (1H, dd), 2.73 (2H, m), 1.97 (3H, br s), 1.65 (6H, m), 1.48 (8H, m), 1.30 (3H, t).

Step b. 5-Adamantan-1-yl-3-oxo-2-(2-oxo-2-phenylethyl)-pentanoic acid ethyl ester (1.91 g, 4.82 mmol) and ammonium acetate (1.42 g, 18.4 mmol) were stirred in acetic acid (3 mL) at 80 °C for 16 h. The reaction mixture was cooled, then partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallized from

ethanol to afford 2-adamantan-1-ylethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester as a white solid (1.12 g, 62%). ^{1}H NMR ($CDCl_3$) δ 8.40 (1H, br s), 7.48 (2H, m), 7.37 (2H, m), 7.25 (1H, m), 6.85 (1H, d), 4.32 (2H, q), 2.97 (2H, m), 2.00 (3H, br s), 1.70 (6H, m), 1.58 (6H, s), 1.46 (2H, m), 1.38 (3H, t).

Step c. To a solution of 2-adamantan-1-ylethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (1.12 g, 3 mmol) in ethanol (80 mL) was added 6 M sodium hydroxide (9 mL). The mixture was heated at reflux for 16 h. It was allowed to cool to room temperature and was concentrated to a small volume under reduced pressure. The concentrated solution was diluted with 2 M hydrochloric acid (40 mL), and the precipitated solid was filtered, washed with water, and dried to afford 2-adamantan-1-ylethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (980 mg, 94%). ^{1}H NMR ($CDCl_3$) δ 11.50 (1H, br s), 11.40 (1H, s), 7.60 (2H, m), 7.35 (2H, m), 7.16 (1H, m), 6.70 (1H, d), 2.85 (2H, m), 1.94 (3H, br s), 1.66 (6H, m), 1.52 (6H, s), 1.35 (2H, m).

Step d. To a suspension of 2-adamantan-1-ylethyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (274 mg, 0.79 mmol) in CH_2Cl_2 (5 mL) was added thionyl chloride (180 μL, 2.5 mmol) and DMF (20 μL). The mixture was stirred at room temperature for 30 min, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (5 mL), and the solvent was evaporated. 3-Aminobenzoic acid benzyl ester (**5a**) (197 mg, 0.87 mmol) was added to the residue followed by anhydrous pyridine (3 mL). The solution was kept at room temperature for 16 h and diluted with CH_2Cl_2 (30 mL). The organic phase was washed with 2 M hydrochloric acid (2 $\times$ 20 mL) and brine (20 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by chromatography on silica gel using CH_2Cl_2−hexanes−EtOAc (95:95:10) as eluant to afford 3-{[2-(2-adamantan-1-ylethyl)-5-phenyl-1*H*-pyrrole-3-carbonyl]amino}-benzoic acid benzyl ester as a pale-yellow solid (157 mg, 56%). ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, br s), 8.15 (1H, m), 8.01 (1H, d), 7.81 (1H, d), 7.59 (1H, br s), 7.51−7.37 (10H, m), 7.27 (1H, t), 6.64 (1H, d), 5.38 (2H, s), 3.07 (2H, m), 1.98 (3H, br s), 1.75−1.46 (14H, m).

Step e. A mixture of 3-{[2-(2-adamantan-1-ylethyl)-5-phenyl-1*H*-pyrrole-3-carbonyl]amino}benzoic acid benzyl ester (157 mg, 0.27 mmol), 10% palladium on charcoal (50 mg) and THF−methanol (1:1, 20 mL) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate was evaporated to afford **13** as a white solid (123 mg, 93%). ^{1}H NMR (DMSO-d_6) δ 11.38 (1H, s), 9.42 (1H, s), 8.22 (1H, s), 7.91 (1H, d), 7.63 (2H, d), 7.56 (1H, d), 7.37 (2H, t), 7.28 (1H, t), 7.17 (2H, m), 2.96 (2H, m), 1.94 (3H, br s), 1.65 (6H, m), 1.54 (6H, s), 1.38 (2H, m). The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{32}N_2O_3 \cdot C_7H_{17}NO_5 \cdot 1.6H_2O$) C, H, N.

3-{[2-(2-Adamantan-1-ylethyl)-5-*o*-tolyl-1*H*-pyrrole-3-carbonyl]amino}benzoic Acid (14). 14 was prepared by a similar sequence used to obtain **13** except that 2-bromo-1-*o*-tolyethanone replaced 2-bromo-1-phenylethanone in step a. ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{34}N_2O_3 \cdot C_7H_{17}NO_5 \cdot 1.5H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (22). Step a. To a solution of 3-(adamantan-1-yl)propionic acid[26] (14.6 g, 70 mmol) and (carbethoxymethylene)triphenylphosphorane (24.4 g, 70 mmol) in CH_2Cl_2 (300 mL) were added EDC (12.25 g, 64 mmol) and DMAP (5 mg) at 0 °C. The solution was stirred at this temperature for 1 h, then at room temperature for 16 h. The reaction mixture was washed with saturated $NaHCO_3$ (2 $\times$ 100 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography on silica gel using CH_2Cl_2−EtOAc (9:1) as eluant to afford 5-adamantan-1-yl-3-oxo-2-(triphenyl-λ^5-phosphanylidene)pentanoic acid ethyl ester (35.6 g, 94%). ^{1}H NMR ($CDCl_3$) δ 7.65 (6H, m), 7.43 (9H, m), 3.73 (2H, m), 2.85 (2H, m), 1.92 (3H, br s), 1.66 (6H, m), 1.50 (6H, s), 1.39 (2H, m), 0.67 (3H, m).

Step b. To a solution of 5-adamantan-1-yl-3-oxo-2-(triphenyl-λ^5-phosphanylidene)pentanoic acid ethyl ester (35.6 g, 66 mmol) in THF (500 mL) and H_2O (250 mL) was added OXONE (60.9 g, 99 mmol) at 0 °C. The solution was stirred at room temperature for 16 h and diluted with H_2O (300 mL), and the product was extracted with EtOAc (2 $\times$ 200 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The crude product was purified by chromatography on silica gel using CH_2Cl_2−EtOAc (9:1) as eluant, affording 5-adamantan-1-yl-2,3-dioxopentanoic acid ethyl ester hydrate as a pale-yellow oil (14.3 g, 70%). ^{1}H NMR ($CDCl_3$) δ 5.02 (2H, br s), 4.30 (2H, m), 2.54 (2H, m), 1.94 (3H, br s), 1.58 (6H, m), 1.39 (8H, m), 1.25 (3H, m).

Step c. To a slurry of ammonium acetate (2.25 g, 30 mmol) in acetic acid (15 mL) was added 5-adamantan-1-yl-2,3-dioxopentanoic acid ethyl ester hydrate (930 mg, 3 mmol) followed by *o*-tolualdehyde (0.7 mL, 6 mmol). The mixture was heated at 70 °C for 2 h. The solution was cooled to room temperature, and the acetic acid was evaporated. The residue was dissolved in EtOAc (50 mL) and washed with saturated $NaHCO_3$ (2 $\times$ 50 mL), water (20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by chromatography on silica gel using CH_2Cl_2−EtOAc (19:1) as eluant to afford 5-(2-adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carboxylic acid ethyl ester as a white amorphous solid (665 mg, 56%). ^{1}H NMR ($CDCl_3$) δ 10.0 (1H, br s), 7.52 (1H, m), 7.25 (3H, m), 4.32 (2H, m), 2.91 (2H, m), 2.49 (3H, s), 1.97 (3H, br s), 1.74−1.34 (17H, m).

Step d. To a suspension of 5-(2-adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carboxylic acid ethyl ester (660 mg, 1.68 mmol) in ethanol (10 mL) was added a solution of sodium hydroxide (340 mg, 8.4 mmol) in water (2 mL). The reaction mixture was heated under reflux for 24 h, allowed to cool to room temperature, and concentrated under reduced pressure. The aqueous solution was diluted with water (30 mL) and acidified to pH 2 by the addition of 1 M hydrochloric acid. The precipitate formed was collected by filtration, washed with water, and dried to afford 5-(2-adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carboxylic acid as an off-white solid (490 mg, 80%). ^{1}H NMR (DMSO-d_6) δ 7.55 (2H, m), 7.40 (2H, m), 7.64 (2H, m), 2.90 and 2.66 (2H, 2 $\times$ m), 2.43 and 2.40 (3H, 2 $\times$ s), 1.95 (3H, s), 1.70−1.39 (14H, m).

Step e. To a solution of 5-(2-adamantan-1-yethyl)-2-*o*-tolyl-1*H*-imidazole-4-carboxylic acid (290 mg, 0.8 mmol) and 3-aminobenzoic acid benzyl ester (**5a**) (180 mg, 0.8 mmol) in DMF (3 mL) were added HOBt (110 mg, 0.8 mmol), DMAP (5 mg), and EDC (150 mg, 0.8 mmol). The solution was kept at room temperature for 72 h, diluted with water (20 mL), and extracted with EtOAc (2 $\times$ 20 mL). The organic phase was washed with 5% $KHSO_4$ solution (20 mL), saturated $NaHCO_3$ (20 mL), and brine (2 $\times$ 20 mL). The solution was dried over $MgSO_4$ and filtered, and the solvent was evaporated. The crude product was purified by chromatography on silica gel using CH_2Cl_2−EtOAc (9:1) as eluant to afford 3-{[5-(2-adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}benzoic acid benzyl ester as a white amorphous solid (246 mg, 54%). ^{1}H NMR ($CDCl_3$) δ 9.35 (1H, br s), 9.27 (1H, s), 8.16 (2H, m), 7.80 (1H, d), 7.55 (1H, d), 7.47−7.27 (10H, m), 5.37 (2H, s), 3.13 (2H, m), 2.59 (3H, s), 1.98 (3H, s), 1.74−1.45 (14H, m).

Step f. 3-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}benzoic acid benzyl ester (240 mg, 0.42 mmol) was deprotected using the same procedure as in step e in the preparation of **13** to afford **22** as a white solid (168 mg, 84%). ^{1}H NMR (DMSO-d_6) δ 12.70 (1H, br s), 12.55 (1H, br s), 9.76 (1H, s), 8.49 (1H, s), 7.95 (1H, d), 7.61 (2H, m), 7.43 (1H, d), 7.30 (3H, m), 2.98 (2H, m), 2.55 (3H, s), 1.95 (3H, s), 1.71−1.41 (14H, m). The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{33}N_3O_3 \cdot C_7H_{17}NO_5 \cdot 2.1H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-phenyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (21). 21 was prepared by similar sequence used to prepare **22** except that benzaldehyde was used in place of *o*-tolualdehyde in step c. ^{1}H NMR (DMSO-

d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{29}H_{31}N_3O_3·C_7H_{17}NO_5·2.9H_2O$) C, H, N.

Compounds **23**–**27** were prepared by similar sequence used to prepare **22** except that the appropriate carboxylic acid was used in step a instead of 3-(adamantan-1-yl)propionic acid.

3-{[5-(2-Methylbutyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonylamino}benzoic Acid (23). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{23}H_{25}N_3O_3·C_7H_{17}NO_5·2.0H_2O$) C, H, N.

3-{[5-(3,3-Dimethylbutyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (24). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{24}H_{27}N_3O_3·C_7H_{17}NO_5·2.3H_2O$) C, H, N.

3-{[5-(2-Cyclohexylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (25). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{26}H_{29}N_3O_3·C_7H_{17}NO_5·1.7H_2O$) C, H, N.

3-[(5-Phenethyl-2-*o*-tolyl-1*H*-imidazole-4-carbonyl)amino]benzoic Acid (26). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{26}H_{23}N_3O_3·C_7H_{17}NO_5·1.5H_2O$) C, H, N.

3-[(5-Adamantan-1-ylmethyl-2-*o*-tolyl-1*H*-imidazole-4-carbonyl)amino]benzoic Acid (27). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{29}H_{31}N_3O_3·C_7H_{17}NO_5·1.9H_2O$) C, H, N.

Compounds **28** and **29** were prepared according to steps a–e used for the preparation of **22** except that **11b** and **11c** were used respectively in step e instead of **11a**.

5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carboxylic Acid *m*-Tolylamide (28). ^{1}H NMR (CDCl$_3$) experiments were conducted. Anal. ($C_{30}H_{35}N_3O·1H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-*1H*-imidazole-4-carbonyl]amino}benzoic Acid Methyl Ester (29). ^{1}H NMR (CDCl$_3$) experiments were conducted. Anal. ($C_{31}H_{35}N_3O_3$) C, H, N.

5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carboxylic Acid (3-Methylaminophenyl)amide (30). (3-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]-amino}phenyl)carbamic acid *tert*-butyl ester was prepared according to steps a–e used for the preparation of **22** except that **11d** was used in step e instead of **11a**.

Step g. To a solution of (3-{[5-(2-adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}phenyl)carbamic acid *tert*-butyl ester (275 mg, 0.48 mmol) in chloroform (3 mL) was added 4 M HCl–dioxan (1 mL, 4 mmol), and the solution was stirred at room temperature for 1 h. The solvent was evaporated and the residue was triturated with diethyl ether to afford the dihydrochloride salt of **30** as a white solid. ^{1}H NMR (CDCl$_3$) δ 10.91 (1H, br s), 7.94 (1H, br s), 7.67 (2H, m), 7.55–7.39 (4H, m), 7.08 (1H, m), 3.05 (2H, m), 2.85 (3H, s), 2.53 (3H, s), 1.95 (3H, s), 1.71–1.44 (14H, m). Anal. ($C_{30}H_{36}N_4O·2HCl·3H_2O$) C, H, N.

(3-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}phenyl)acetic Acid (31). **31** was prepared by similar sequence used to prepare **22** except that **11e** was used in step e instead of **11a**. ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{35}N_3O_3·C_7H_{17}NO_5·3.5H_2O$) C, H, N.

3-(3-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}phenyl)propionic Acid (32). 3-(3-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]-amino}phenyl)propionic acid *tert*-butyl ester was prepared according to steps a–e used for the preparation of **22** except that **11f** was used in step e instead of **11a**.

Step h. A solution of 3-(3-{[5-(2-adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}phenyl)propionic acid *tert*-butyl ester (355 mg, 0.63 mmol) was dissolved in trifluoroacetic acid (5 mL), and the solution was stirred at room temperature for 16 h. The reaction mixture was diluted with toluene (50 mL), and the solvent was evaporated in vacuo. The residue was suspended in chloroform (2 × 40 mL), and the solvent was evaporated. The same process was repeated from methanol (2 × 30 mL). The residue was dried in vacuo to afford trifluoroacetic acid salt of **32** as a white solid (378 mg, 96%). ^{1}H NMR (DMSO-d_6) δ 13.00 (1H, br s), 9.58 (1H, br s), 8.00–6.00 (2H, br s), 7.59 (3H, m), 7.41–7.30 (3H, m), 7.23 (1H, m), 6.94 (1H, m), 2.95 (2H, m), 2.79 (2H, m), 2.52 (5H, m), 1.95 (3H, s), 1.68–1.44 (14H, m). Anal. ($C_{32}H_{37}N_3O_3·C_2HF_3O_2$) C, H, N.

Compounds **33**–**36** were prepared by a similar sequence used to prepare **22** except that the appropriate aniline derivatives (**11g**–**j**) were used in step e instead of **11a**.

5-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}-2-methylbenzoic Acid (33). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{35}N_3O_3·C_7H_{17}NO_5·2.5H_2O$) C, H, N.

5-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}-2-fluorobenzoic Acid (34). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{32}FN_3O_3·C_7H_{17}NO_5·3H_2O$) C, H, N.

5-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}-2-(dimethylamino)benzoic Acid (35). ^{1}H NMR (DMSO-d_6) experiments were conducted. Anal. ($C_{32}H_{38}N_4O_3·3H_2O$) C, H, N.

5-{[5-(2-Adamantan-1-ylethyl)-2-*o*-tolyl-1*H*-imidazole-4-carbonyl]amino}-2-methoxybenzoic Acid (36). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{35}N_3O_4·C_7H_{17}NO_5·3H_2O$) C, H, N.

Compounds **37**–**52** were prepared by similar sequence used to prepare **22** except that the appropriate aldehydes were used in step c instead of *o*-tolualdehyde and, additionally, in the preparation of **40** and **52**, **11g** replaced **11a** in step e.

3-{[5-(2-Adamantan-1-ylethyl)-2-(2,4-dimethylphenyl)-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (37). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{35}N_3O_3·C_7H_{17}NO_5·2.7H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-(2,6-dimethylphenyl)-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (38). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{35}N_3O_3·C_7H_{17}NO_5·3H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-(2,4,6-trimethylphenyl)-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (39). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{37}N_3O_3·C_7H_{17}NO_5·2.5H_2O$) C, H, N.

5-{[5-(2-Adamantan-1-ylethyl)-2-(2,4,6-trimethylphenyl)-1*H*-imidazole-4-carbonyl]amino}-2-methylbenzoic Acid (40). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{33}H_{39}N_3O_3·C_7H_{17}NO_5·2.3H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-methyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (41). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{24}H_{29}N_3O_3·C_7H_{17}NO_5·5H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-propyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (42). ^{1}H NMR (MeOH-d_4) experiments were conducted. The product was further characterized as the hydrochloride salt. Anal. ($C_{26}H_{33}N_3O_3·HCl·0.5H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-isopropyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (43). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{26}H_{33}N_3O_3·C_7H_{17}NO_5·3.2H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-*tert*-butyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (44). ^{1}H NMR (MeOH-d_4) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{27}H_{35}N_3O_3$·$C_7H_{17}NO_5$·$2.3H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-cyclopropyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (45). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{26}H_{31}N_3O_3$·$C_7H_{17}NO_5$·$1.7H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-cyclopentyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (46). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{28}H_{35}N_3O_3$·$C_7H_{17}NO_5$·$2.2H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-cyclohexyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (47). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{29}H_{37}N_3O_3$·$C_7H_{17}NO_5$·$3.1H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-cycloheptyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (48). ^{1}H NMR (MeOH-d_4) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{39}N_3O_3$·$C_7H_{17}NO_5$·$2.2H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-bicyclo[2.2.2]oct-1-yl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (49). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{39}N_3O_3$·$C_7H_{17}NO_5$·$3.0H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-cyclododecyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (50). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{49}N_3O_3$·$C_7H_{17}NO_5$·$2.5H_2O$) C, H, N.

3-{[5-(2-Adamantan-1-ylethyl)-2-(1-methylcyclohexyl)-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (51). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{39}N_3O_3$·$C_7H_{17}NO_5$·$2H_2O$) C, H, N.

5-{[5-(2-Adamantan-1-ylethyl)-2-(1-methylcyclohexyl)-1*H*-imidazole-4-carbonyl]amino}-2-methylbenzoic Acid (52). ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{41}N_3O_3$·$C_7H_{17}NO_5$·$1.1H_2O$) C, H, N.

3-{[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (53). Step a. To a solution of (adamantan-1-yloxy)acetic acid (45 g, 0.204 mol) in thionyl chloride (200 mL) was added DMF (2 mL). The mixture was gently warmed as required to maintain effervescence for 2 h, then heated at reflux for 15 min. The thionyl chloride was evaporated, and CH_2Cl_2 (100 mL) was added to the residue and then removed in vacuo. This process was repeated three more times. The residue was dissolved in benzene (50 mL), and the solution was slowly added to a solution of benzyl (triphenylphosphoranylidene)acetate (83.6 g, 0.204 mol) and *N,O*-bis(trimethylsilyl)acetamide (62 mL, 0.251 mol) in benzene (350 mL) at room temperature. The mixture was stirred at room temperature for 16 h and the precipitate was collected by filtration, washed with benzene, and dried to afford 4-(adamantan-1-yloxy)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)butyric acid benzyl ester as a white solid (105.6 g, 86%). ^{1}H NMR ($CDCl_3$) δ 7.64−6.94 (20H, m), 4.74 (2H, s), 4.72 (2H, s), 2.08−1.57 (15H, m).

Step b. To a vigorously stirred solution of 4-(adamantan-1-yloxy)-3-oxo-2-(triphenyl-λ^5-phosphanylidene)butyric acid benzyl ester (33.0 g, 55 mmol) in CH_2Cl_2−water (1:1, 800 mL) were added tetrabutylammonium bromide (1.77 g, 5.5 mmol) and OXONE (67.4 g, 110 mmol) at 0 °C. The mixture was stirred at room temperature for 48 h, and the organic layer was separated, washed with water (3 × 300 mL) and brine (300 mL), and dried ($MgSO_4$). The solvent was evaporated. The residue was purified by chromatography on silica gel using hexanes−EtOAc (1:1) as eluant to afford 4-(adamantan-1-yloxy)-2,3-dioxobutyric acid benzyl ester monohydrate as a pale-yellow oil (25.6 g, 80%). ^{1}H NMR ($CDCl_3$) δ 7.33 (5H, m), 5.26 (2H, s), 4.98 (2H, br s), 4.30 (2H, s), 2.14 (3H, br s), 1.72−1.54 (12H, m).

Step c. 4-(Adamantan-1-yloxy)-2,3-dioxobutyric acid benzyl ester monohydrate (3.4 g, 45.4 mmol) was reacted with cyclohexanecarboxaldehyde (1.1 mL, 9.1 mmol) using the same conditions as in step c in the preparation of **22** to afford 5-(adamantan-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazole-4-carboxylic acid benzyl ester. ^{1}H NMR ($CDCl_3$) δ 7.40 (5H, m), 5.30 (2H, s), 4.76 (2H, br s), 2.79 (1H, m), 2.14 (3H, br s), 2.05 (2H, m), 1.85−1.26 (20H, m).

Step d. 5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazole-4-carboxylic acid benzyl ester was deprotected using the same procedure as in step e in the preparation of **13** to afford the acid as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.00 (1H, br s), 4.60 (2H, br s), 2.63 (1H, m), 2.09 (3H, br s), 2.02−1.23 (22H, m).

Step e. 5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazole-4-carboxylic acid was reacted with **11a** (480 mg, 2.12 mmol) using the same conditions as in step e in the preparation of **22** to afford 3-{[5-(adamantan-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazole-4-carbonyl]amino}benzoic acid benzyl ester. ^{1}H NMR ($CDCl_3$) δ 9.50 and 8.90 (1H, 2 × br s), 8.15 (2H, m), 7.81 (1H, d), 7.40 (6H, m), 5.38 (2H, s), 4.98 (2H, br s), 2.71 (1H, m), 2.16 (3H, br s), 2.00 (2H, m), 1.85−1.24 (20H, m).

Step f. 3-{[5-(Adamantan-1-yloxymethyl)-2-cyclohexyl-1*H*-imidazole-4-carbonyl]amino}benzoic acid benzyl ester was hydrogenated using the same procedure as in step e in the preparation of **13** to afford **53** as a white solid. ^{1}H NMR (DMSO-d_6) δ 12.50 (1H, br s), 12.00 (1H, br s), 9.70 (1H, br s), 8.45 (1H, s), 7.92 (1H, dd), 7.62 (1H, d), 7.41 (1H, t), 4.79 (2H, s), 2.70 (1H, m), 2.11 (3H, br s), 1.89 (2H, m), 1.76 (6H. m), 1.60 (10H, m), 1.30 (4H, m). The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{28}H_{35}N_3O_4$·$C_7H_{17}NO_5$·$3H_2O$) C, H, N.

3-{[5-(Adamantan-1-yloxymethyl)-2-bicyclo[2.2.2]oct-1-yl-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (54). 54 was prepared by a sequence similar to that used to prepare **53** except that bicyclo[2.2.2]oct-1-ylcarbaldehyde replaced cyclohexanecarboxaldehyde in step c. ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{37}N_3O_4$·$C_7H_{17}NO_5$·$2H_2O$) C, H, N.

3-{[5-(Adamantan-1-yloxymethyl)-2-(2,4,6-trimethylphenyl)-1*H*-imidazole-4-carbonyl]amino}benzoic Acid (55). 55 was prepared by a sequence similar to that used to prepare **53** except that 2,4,6-trimethylbenzaldehyde replaced cyclohexanecarboxaldehyde in step c. ^{1}H NMR (DMSO-d_6) experiments were conducted. The product was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{35}N_3O_4$·$C_7H_{17}NO_5$·$1.2H_2O$) C, H, N.

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Supporting Information Available: Analytical data for compounds used in biological tests. This material is available free of charge via the Internet at http://pubs.acs.org.

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