Optimization of 1,3,4-Benzotriazepine-Based CCK_2 Antagonists to Obtain Potent, Orally Active Inhibitors of Gastrin-Mediated Gastric Acid Secretion

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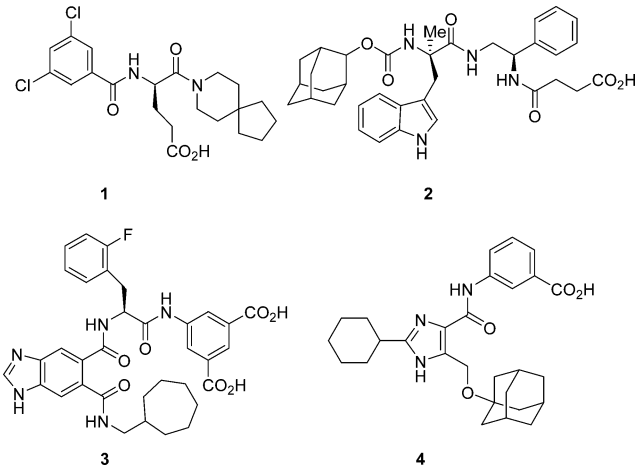
Starting from a novel, achiral 1,3,4-benzotriazepine-based CCK_2 receptor antagonist, a process of optimization has afforded further compounds of this type that maintain the nanomolar affinity for recombinant, human CCK_2 receptors and high selectivity over CCK_1 receptors observed in the initial lead but display more potent inhibition of pentagastrin-stimulated gastric acid secretion in vivo. Moreover, this has largely been achieved without altering their potency at wild-type canine and rat receptors, as judged by their displacement of [^{125}I]-BH-CCK-8S in a radioligand binding assay and by their activity in an isolated, perfused rat stomach bioassay, respectively. 2-(5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-(5-oxo-2,5-dihydro- [1,2,4]oxadiazol-3-yl)-phenyl)-acetamide (**47**) was identified as the most effective compound stemming from this approach, proving to be a potent inhibitor of pentagastrin-stimulated gastric acid secretion in rats and dogs by intravenous bolus as well as by enteral administration.

Introduction

The association of the hormone CCK[a] with the mediation of pain, panic, and anxiety through its stimulation of CCK_2 receptors in the CNS, has focused interest on the discovery of CCK_2 receptor antagonists, long considered to have the potential to provide novel means of controlling these disorders.[1,2] The closely related hormone gastrin also potently stimulates CCK_2 receptors, being a primary stimulant of gastric acid secretion and a key growth factor for the histamine-storing ECL cells of the stomach. Studies have also suggested that gastrin plays a role in the progression of some gastrointestinal tumors, including the premalignant condition of Barrett's oesophagus. Thus, it has been proposed that CCK_2 receptor antagonists may also have a potential role in the treatment of gastric acid-related conditions (such as gastro esophageal reflux disease and proton pump inhibitor-evoked rebound gastric acid hypersecretion)[3] as well as some cancers.[4−6]

Despite the availability of a number of CCK_2 receptor antagonists that have generally demonstrated high CCK_2 receptor affinity as well as selectivity over the CCK_1 receptor subtype,[7,8] their further progress and clinical efficacy has been hampered for different reasons. Amino acid (e.g., **1** (CR2194)) and peptoid-based CCK_2 antagonists have been described. In the latter case, these compounds have been devised by a rational approach starting from the peptide hormone (Chart 1). Compound **1** achieved inhibition of gastrin-stimulated gastric acid output in man when administered by continuous intravenous infusion.[9] The peptoid-based compound **2** (CI-988) failed to affect CCK-4 induced symptoms in patients with panic disorder[10] and was shown subsequently to be an agonist in certain animal in vivo assays.[11] We obtained **3** (JB95008), also by a rational approach,[12] and although it suffered from low oral bioavailability, when delivered by continuous intravenous infusion, it lead to an increase in survival time in a small, placebo-controlled clinical trial in pancreatic cancer patients.[6] Advancement of this rational process led to imidazole-based compounds such as **4** (JB99157). Although **4** was orally active, it was insufficiently potent in its inhibitory effect on pentagastrin-stimulated gastric acid secretion in vivo.[13]

Chart 1. Amino Acid-Based CCK_2 Receptor Antagonist **1** and Other CCK_2 Receptor Antagonists Devised by a Rational Approach



A quite different approach led workers at Merck to the 1,4-BDZ-based CCK_2 receptor antagonist **5** (L-365,260; Chart 2).[14] Compound **5** progressed to human studies in which it proved capable of reversing the anxiogenic effects produced by tetragastrin,[15] but it was ineffective in patients with panic disorder.[16] In a separate study, **5** inhibited gastrin-stimulated gastric acid secretion when given orally.[17] Its low potency in this trial was ascribed partly to its poor oral bioavailability. Other CCK_2 receptor antagonists based on a BDZ ring system have all followed the disclosure of **5**, including compounds that lacked charged functionality (e.g., **6** (GR 199114X))[18] and those that contain acidic (e.g., **7** (L-736,380),[19] **8** (Z-360))[20] or basic (e.g., **9** (L-740,093),[21] **10** (YF476))[22] substituents. The efficacy of these molecules and their superiority or otherwise to **5** has been

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[a] Abbreviations: CCK, cholecystokinin; ECL, enterochromaffin-like; BDZ, benzodiazepine.

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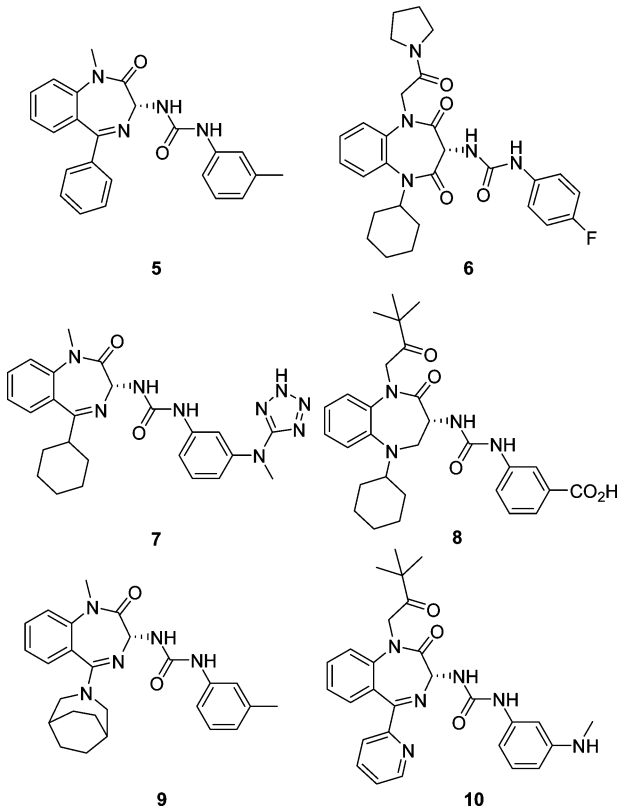
Chart 2. BDZ-Based CCK_2 Receptor Antagonists



established mostly in animal models of gastrin-stimulated gastric acid secretion, such as Ghosh and Schild rat or gastric fistula dog. Compound **10** is the most significant compound that stemmed from this approach, and it was subsequently shown, on oral dosing in an acute study in healthy volunteers, to have a profound inhibitory effect upon intragastric pH,[23] but this effect was not maintained on repeat dosing for 7 days.[24] However, in a subsequent study, **10** was shown to inhibit pentagastrin-stimulated gastric acid secretion effectively, following an acute as well as a chronic dosing regimen,[25] indicating that its capacity for CCK_2 receptor antagonism remained undiminished during this period. Thus, the potential utility of CCK_2 receptor antagonists remains unresolved, but encouraged by the effect of **3** in pancreatic cancer patients, we have aimed to help clarify their possible role by devising potent, orally active CCK_2 receptor antagonists.

We have shown previously that 1,3,4-benzotriazepine-based analogues of 1,4-BDZ CCK_2 receptor antagonists display high affinity for CCK_2 receptors.[26] However, in contrast to the latter compounds, where ligand stereochemistry has a strong bearing on CCK receptor subtype selectivity, the 1,3,4-benzotriazepine-based derivatives are achiral (and as such, they can be synthesized in a relatively straightforward manner), yet they are highly selective for CCK_2 over CCK_1 receptors. The structural aspects and in vitro biological activity of initial examples of this novel class of CCK_2 receptor antagonists gave a clue to their relationship to the 1,4-BDZ-based compounds and identified some of the chemical features that influence their pharmacological and physicochemical properties. In particular, compound **11** (Figure 1), which contained a carboxylic acid substituent, not only displayed high CCK_2 affinity in a radioligand binding assay and potent antagonism in a functional bioassay, but was also sufficiently soluble to enable its satisfactory evaluation in in vivo assays. In this paper, we describe the results of these experiments and the characterization of

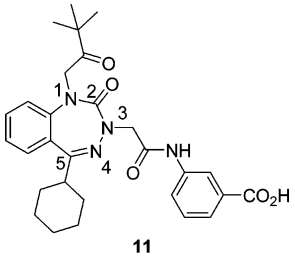


Figure 1. 1,3,4-Benzotriazepine-based CCK_2 receptor antagonist obtained following optimization of initial lead.

further examples of this class of compounds with respect to their affinity for CCK_2 receptors and in relation to their inhibition of pentagastrin-stimulated gastric acid secretion in in vivo assays.

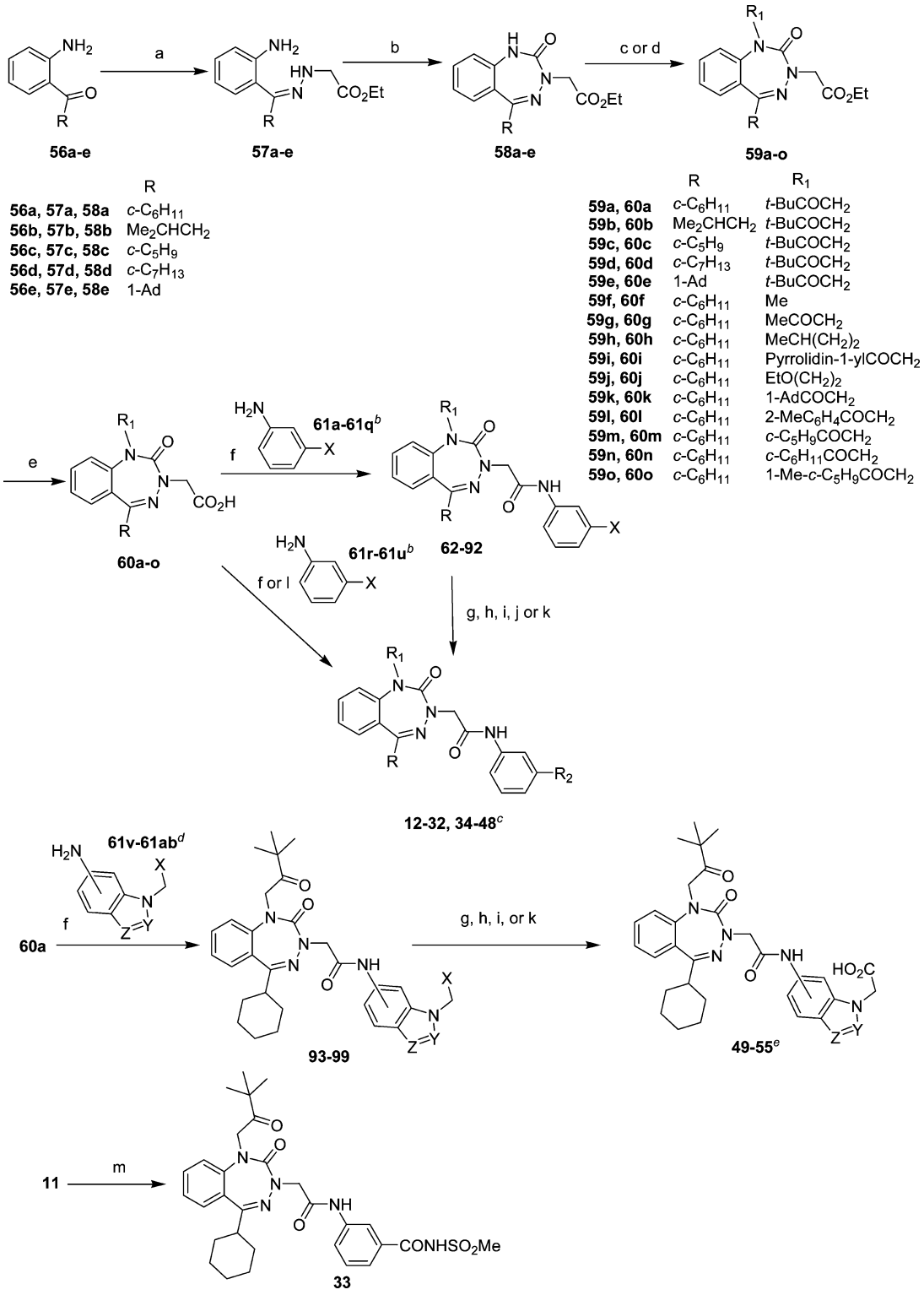
Results and Discussion

The compounds prepared for biological testing (**12**−**55**) were synthesized by the general route outlined in Scheme 1. The 2-aminophenyl ketones (**56a**−**56e**) were prepared either by reaction of 2-aminobenzonitrile with an appropriate alkyl Grignard reagent or by directed *ortho*-metalation of *N*-*tert*-butoxycarbonyl aniline followed by acylation with an appropriate alkyl ester. Their treatment with ethyl hydrazinoacetate afforded the ethoxycarbonylmethyl hydrazones (**57a**−**57e**), from which the corresponding 1,3,4-benzotriazepines (**58a**−**58e**) were obtained by reaction with triphosgene. The N-1 substituent was introduced by base-mediated alkylation using the appropriate alkyl halide to give **59a**−**59o** and subsequent hydrolysis of the ethyl ester group of the N-3 ethoxycarbonylmethyl substituent made available the corresponding carboxylic acid derivatives, **60a**−**60o**. Compounds **60a**−**60o** were reacted, using carbodiimide activation, with the appropriately substituted aniline, **61a**−**61q** (Table 1), affording the N-3 acetamide derivatives **62**−**92**, in which the functionality on the anilide moiety was in protected form (X). Compound **60a** was reacted similarly with amino-substituted bicyclic heteroaromatic systems, **61v**−**61ab** (Table 2) to afford **93**−**99**. Deprotection of compounds **62**−**99**, using the appropriate conditions, yielded **12**−**32**, **34**, **39**−**46**, and **48**−**55**. The unprotected substituted anilines **61r**−**61u** (Table 1) were also reacted with N-3 carboxymethyl-substituted 1,3,4-benzotriazepines **60a** and **60i** (either using carbodiimide activation or via the corresponding acid chloride) to obtain **35**−**38** and **47** directly. Compound **33** was obtained by treatment of **11** with methanesulfonamide and EDCI.

The biological activity of the compounds was examined in vitro (Tables 3 and 4) and in vivo using assays that have been described elsewhere. *N*-Methyl-D-glucamine salts of compounds **11**−**31**, **33**−**42**, **44**−**49**, and **51**−**54** were prepared for biological testing. Compounds **32**, **43**, and **50** were isolated as hydrochloride salts directly from their synthesis. Compound **55** was obtained as the trifluoroacetate salt in a similar manner. The affinity of the 1,3,4-benzotriazepines for CCK_2 receptors was determined primarily in a radioligand binding assay using recombinant, human CCK_2 receptors expressed in NIH3T3 cells.[27] Similarly, their selectivity with respect to CCK_1 receptors was established using recombinant, human CCK_1 receptors expressed in PC3 or CHO-K1 cells.[26] Most examples were subsequently tested for in vitro functional activity by their inhibition of pentagastrin-stimulated gastric acid secretion in an isolated, lumen-perfused, immature rat stomach bioassay.[28]

For progression to in vivo assays, greatest emphasis was placed on those compounds that displayed <10 nM affinity at human CCK_2 receptors ($pK_I \geq 8$) and where their potency in

Scheme 1. Synthesis of 1,3,4-Benzotriazepines[a]



[a] Reagents and conditions: (a) $NH_2NHCH_2CO_2Et$·HCl, pyridine/EtOH; (b) $(Cl_3CO)_2CO$, NEt_3/CH_2Cl_2; (c) R_1Br, NaH/DMF (**59a**−**59f**, **59h**−**59o**); (d) $MeCOCH_2Br$, K_2CO_3, KI/MeCN (**59g**); (e) NaOH/EtOH−H_2O; (f) EDCI, HOBt, DMAP/DMF (**35**−**38**, **54**−**60**, **62**−**99**); (g) NaOH/EtOH (**12**, **13**, **26**, **28**, **30**, **39**, **40**, **48**, **49**, **52**, **54**); (h) LiOH/THF−H_2O (**14**−**25**, **29**, **31**, **41**, **42**, **44**, **45**, **51**, **53**); (i) CF_3CO_2H/DCM (**27**, **46**, **55**); (j) NH_3−MeOH (**34**); (k) HCl-dioxan (**32**, **43**, **50**); (l) **60m**, $(COCl)_2$, DMF/DCM, then **61r**, NEt_3/DCM (**47**); (m) $MeSO_2NH_2$, EDCI, HOBt, DMAP/DMF (**33**). [b] See Table 1. [c] See Table 3. [d] See Table 2. [e] See Table 4.

the functional assay (pA_2) was within 30-fold of this parameter. In vivo potency was assessed initially by intravenous bolus administration in a Ghosh and Schild rat model of pentagastrin-stimulated gastric acid secretion.[12] The inhibitory effect was normalized with respect to a standard dose of **4** (see Experimental Section). The data obtained are displayed graphically in Figure 2. When the same reference was used, it was also possible to gain an indication of the enteral potency of each compound by a method of intragastric delivery (Figure 3).[29] For comparative purposes, the ratio of their potencies by the respective routes was used to gauge their bioavailability in this species (Figure 4). Following determination of their affinity for

Table 1. 3-Substituted Anilines **61a**−**61u** Used in Scheme 1

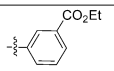
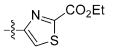
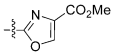
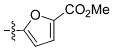
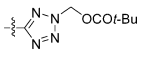
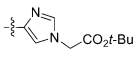
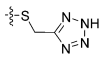
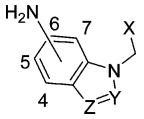
cmpd.	X	cmpd.	X	cmpd.	X	cmpd.	X
61a	CO_2Me	**61g**	$N(Me)CH_2CO_2Me$	**61l**		**61q**	
61b	CO_2Bn	**61h**	$SO_2CH_2CO_2Et$	**61m**		**61r**	
61c	CH_2CO_2Bn	**61i**	OCH_2CO_2Me	**61n**		**61s**	
61d	CH_2CO_2Me	**61j**	$N(Boc)CH_2CO_2Me$	**61o**		**61t**	
61e	$(CH_2)_2CO_2t$-Bu	**61k**		**61p**		**61u**	
61f	SCH_2CO_2Et						

Table 2. Amino-Substituted Bicyclic Heteroaromatic Systems **61v**−**61ab** Used in Scheme 1



cmpd	X	Y	Z	position of attachment	cmpd	X	Y	Z	position of attachment
61v	CO_2Et	CH	CH	6	**61z**	CO_2Me	N	CH	5
61w	CO_2t-Bu	CH	N	6	**61aa**	CO_2Et	CH	CH	4
61x	CO_2Me	N	CH	6	**61ab**	CO_2t-Bu	N	CH	4
61y	CO_2Et	CH	CH	5					

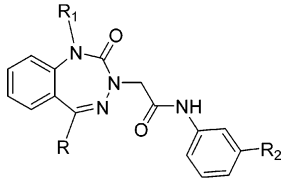
canine CCK_2 receptors, by displacement of [^{125}I]-BH-CCK-8S from CCK_2 receptors in canine gastric mucosa,[26] the effects of the same subset of compounds on pentagastrin-stimulated gastric acid output in conscious, chronic gastric fistula dogs, by intravenous bolus and intragastric routes of delivery were examined.[12] The results of these experiments are shown graphically in Figures 5 and 6.

We have previously reported on the in vitro biological activity of **11** at CCK_2 receptors (Table 3).[26] In contrast to closely related 1,3,4-benzotriazepine-based derivatives containing a basic substituent, the presence of the carboxylic acid group on the anilide moiety endowed **11** with sufficient aqueous solubility to enable its assessment in the rat in vivo assay. Compound **11** ($pA_2 = 9.01 \pm 0.16$) was as potent as **4** ($pA_2 = 9.06 \pm 0.32$) in the in vitro rat bioassay and it was as effective in the in vivo assay by intravenous bolus administration (Figure 2). When these same compounds were assessed by the intragastric route in this assay, **11** was less active than **4** (Figure 3). The affinity of **4** ($pK_I = 7.71 \pm 0.12$) and **11** ($pK_I = 7.91 \pm 0.20$) for canine CCK_2 receptors was also similar, and by intravenous bolus delivery in the in vivo setting, judging from the effect of only a single dose of each compound, their potency was within approximately 3-fold of one another (Figure 5). Although **11** was far short of the potency observed for **10** by a considerable margin in the rat in vivo assay by both routes of administration, the behavior of **11** indicated that a compound based on a 1,3,4-benzotriazepine ring system was orally active and provided the impetus to attempt to obtain superior compounds through the preparation of analogues of **11**.

In our earlier studies, we had found that the presence of a C-5 cyclohexyl group conferred higher affinity than either a 2-pyridyl or a phenyl substituent in this position. On making further changes of this type (**12**−**15**), only the cycloheptyl derivative **14** showed comparable affinity to **11**, with less potent compounds generally being obtained (Table 3). The significantly lower affinity observed for the N-1 methyl (**16**), acetylmethyl (**17**), and isoamyl (**18**) derivatives suggested that both the ketone carbonyl group and the bulky hydrophobic *tert*-butyl group of the pinacolyl group present in **11** were important elements in achieving high receptor affinity. This view was borne out with the lower affinity that resulted when amide- (**19**) and ether-based (**20**) substituents were used in its place. On the other hand, affinity was maintained at human CCK_2 receptors with respect to **11**, with N-1 1-adamantyl- or *o*-tolyl-carbonylmethyl-bearing derivatives, **21** and **22**, respectively. As might be expected given the lower potency of **22** ($pA_2 = 8.12 \pm 0.12$) compared to **11** ($pA_2 = 9.01 \pm 0.16$) in the rat in vitro assay, it was considerably less effective in vivo as judged by its behavior in the rat in vivo assays (Figures 2 and 3).

Introduction of alicyclic keto-methylene N-1 substituents in place of pinacolylmethyl, in certain 1,4-BDZ-based CCK_2 receptor antagonists, had afforded more potent derivatives.[30] In line with the earlier parallels that we had drawn between this class and 1,3,4-benzotriazepine-based CCK_2 receptor antagonists, compounds containing substituents of this type (**23**−**25**) displayed higher affinity at human CCK_2 receptors than the corresponding pinacolyl derivative **11**. Compound **23** stood out among the examples of this type due to its effectiveness in the

Table 3. In Vitro Biological Data for 1,3,4-Benzotriazepine-Based CCK_2 Receptor Antagonists [a]



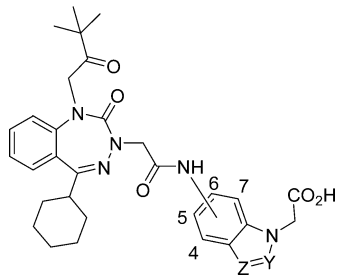
cmpd	R	R_1	R_2	CCK_2[b]	CCK_1[c]	CCK_2[d]	CCK_2[e]
11	*c*-C_6H_{11}	*t*-$BuCOCH_2$	CO_2H	8.29 ± 0.05	<5[f]	9.01 ± 0.16	7.91 ± 0.20
12	Me_2CHCH_2	*t*-$BuCOCH_2$	CO_2H	7.05 ± 0.18	5.15 ± 0.09[f]		
13	*c*-C_5H_9	*t*-$BuCOCH_2$	CO_2H	7.62 ± 0.09	<5[f]		
14	*c*-C_7H_{13}	*t*-$BuCOCH_2$	CO_2H	8.32 ± 0.22	5.24 ± 0.10[f]		
15	1-Ad	*t*-$BuCOCH_2$	CO_2H	7.62 ± 0.16	6.43 ± 0.07[f]		
16	*c*-C_6H_{11}	CH_3	CO_2H	5.92 ± 0.16	<5[f]		
17	*c*-C_6H_{11}	$MeCOCH_2$	CO_2H	6.48 ± 0.10	<5[f]		
18	*c*-C_6H_{11}	$Me_2CH(CH_2)_2$	CO_2H	7.69 ± 0.12	<5[f]		
19	*c*-C_6H_{11}	pyrrolidin-1-yl-$COCH_2$	CO_2H	7.79 ± 0.12	<5[f]		
20	*c*-C_6H_{11}	$EtO(CH_2)_2$	CO_2H	6.31 ± 0.17	NT[g]		
21	*c*-C_6H_{11}	1-$AdCOCH_2$	CO_2H	8.25 ± 0.10	5.72 ± 0.07[f]		
22	*c*-C_6H_{11}	2-$MeC_6H_4COCH_2$	CO_2H	8.12 ± 0.12	<5[f]	8.12 ± 0.12	7.58 ± 0.05
23	*c*-C_6H_{11}	*c*-$C_5H_9COCH_2$	CO_2H	9.00 ± 0.18	<5[f]	8.71 ± 0.20	8.15 ± 0.32
24	*c*-C_6H_{11}	*c*-$C_6H_{11}COCH_2$	CO_2H	9.10 ± 0.12	5.10 ± 0.07[h]		
25	*c*-C_6H_{11}	1-Me-*c*-$C_5H_9COCH_2$	CO_2H	8.92 ± 0.03	5.40 ± 0.04[h]		
26	*c*-C_6H_{11}	*t*-$BuCOCH_2$	CH_2CO_2H	8.67 ± 0.14	<5[f]	8.01 ± 0.20	8.28 ± 0.10
27	*c*-C_6H_{11}	*t*-$BuCOCH_2$	$(CH_2)_2CO_2H$	8.73 ± 0.14	<5[h]	8.35 ± 0.22	
28	*c*-C_6H_{11}	*t*-$BuCOCH_2$	SCH_2CO_2H	9.19 ± 0.07	6.19 ± 0.03[f]	8.56 ± 0.15	8.24 ± 0.36
29	*c*-C_6H_{11}	*t*-$BuCOCH_2$	$N(Me)CH_2CO_2H$	8.97 ± 0.07	5.19 ± 0.04[h]		
30	*c*-C_6H_{11}	*t*-$BuCOCH_2$	$SO_2CH_2CO_2H$	8.37 ± 0.21	<5[f]		
31	*c*-C_6H_{11}	*t*-$BuCOCH_2$	OCH_2CO_2H	8.26 ± 0.28	5.39 ± 0.11[f]		
32	*c*-C_6H_{11}	*t*-$BuCOCH_2$	$NHCH_2CO_2H$	8.21 ± 0.17	5.07 ± 0.08[f]		
33	*c*-C_6H_{11}	*t*-$BuCOCH_2$	$CONHSO_2Me$	8.41 ± 0.12	5.53 ± 0.14[f]		
34	*c*-C_6H_{11}	*t*-$BuCOCH_2$	1(2)*H*-tetrazol-5-yl	9.00 ± 0.14	5.76 ± 0.09[h]	8.11 ± 0.18	8.50 ± 0.12
35	*c*-C_6H_{11}	*t*-$BuCOCH_2$	1,2,4-oxadiazol-3-yl-5(2*H*)-one	9.70 ± 0.13	6.23 ± 0.01[h]	8.02 ± 0.37	8.35 ± 0.16
36	*c*-C_6H_{11}	*t*-$BuCOCH_2$	N(Me)-1(2)*H*-tetrazol-5-yl	8.71 ± 0.13	5.19 ± 0.02[f]	7.62 ± 0.21	8.33 ± 0.08
37	*c*-C_6H_{11}	*t*-$BuCOCH_2$	CH_2-1(2)*H*-tetrazol-5-yl	8.33 ± 0.13	<5[h]		
38	*c*-C_6H_{11}	*t*-$BuCOCH_2$	SCH_2-1(2)*H*-tetrazol-5-yl	9.15 ± 0.06	6.41 ± 0.08[h]		
39	*c*-C_6H_{11}	*t*-$BuCOCH_2$	3-$C_6H_4CO_2H$	8.80	6.26 ± 0.07[h]		
40	*c*-C_6H_{11}	*t*-$BuCOCH_2$	2-thiazol-4-yl-CO_2H	9.18 ± 0.03	<5[h]		
41	*c*-C_6H_{11}	*t*-$BuCOCH_2$	4-oxazol-2-yl-CO_2H	9.44	6.18 ± 0.04[h]		
42	*c*-C_6H_{11}	*t*-$BuCOCH_2$	5-furan-2-yl-CO_2H	9.61	6.34 ± 0.01[h]		
43	*c*-C_6H_{11}	*t*-$BuCOCH_2$	1-imidazol-4-yl-(1*H*)-CH_2CO_2H	8.39 ± 0.10	5.77 ± 0.05[h]		
44	*c*-C_6H_{11}	*t*-$BuCOCH_2$	1-pyrrol-2-yl-CH_2CO_2H	9.04 ± 0.02	NT[g]		
45	*c*-C_6H_{11}	*c*-$C_5H_9COCH_2$	CH_2CO_2H	9.55 ± 0.18	<5[h]	9.13 ± 0.22	8.20
46	*c*-C_6H_{11}	*c*-$C_5H_9COCH_2$	$(CH_2)_2CO_2H$	9.47 ± 0.05	5.60 ± 0.07[h]	8.91 ± 0.20	8.37 ± 0.39
47	*c*-C_6H_{11}	*c*-$C_5H_9COCH_2$	1,2,4-oxadiazol-3-yl-5(2*H*)-one	9.97 ± 0.02	6.33 ± 0.04[h]	8.74 ± 0.34	8.35 ± 0.06
48	*c*-C_6H_{11}	*c*-$C_5H_9COCH_2$	SCH_2CO_2H	9.48 ± 0.08	5.68 ± 0.06[h]	8.83 ± 0.18	8.32 ± 0.21
4				7.71 ± 0.05	<5[f]	9.06 ± 0.32	7.94 ± 0.18
10				9.86 ± 0.13	7.54 ± 0.02[h]	10.10 ± 0.09	8.98 ± 0.09[i]

[a] Data were generally obtained from at least three separate experiments. Where no SEM is recorded, the data were obtained from two experiments. [b] pK_I ± SEM values obtained from competition with 20 pM [^{125}I]-BH-CCK-8S for recombinant, human CCK_2 receptors expressed in NIH3T3 cells. [c] pK_I ± SEM values obtained from competition with 20 pM [^{3}H] L-364,718 for recombinant, human CCK_1 receptors expressed in either PC3 or CHO-K1 cells. [d] pA_2 ± SEM values, estimated from single shifts of pentagastrin concentration-effect curves in isolated, lumen-perfused immature rat stomachs. [e] Except for compound **10**, pK_I ± SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S for CCK_2 binding sites in canine gastric mucosa. [f] PC3 cells. [g] Not tested. [h] CHO-K1 cells. [i] Reported pK_I ± SEM value obtained from competition with [^{125}I]-BH-CCK-8S for recombinant, canine CCK_2 receptors expressed in CHO-K cells.[33]

in vivo assays. Although the similar potency of **23** and **11** in the rat in vitro bioassay was maintained in the in vivo assay when the compounds were administered by intravenous bolus delivery (Figure 2), the inhibitory effect achieved by **23** when given by the intragastric route was far greater than that produced by the same dose of **11** (Figure 3). This difference in potency was also evident in the dog in vivo assay, where **23** was significantly more effective than **11** by the intravenous route (Figure 5), yet the compounds had shown similar affinity in the canine CCK_2 receptor radioligand binding assay. Just as had been observed for **23** in the rat in vivo assay, potent inhibition of the pentagastrin-stimulated gastric acid output following enteral administration of this compound was also achieved in dogs (Figure 5). Moreover, the dose-dependent behavior of **23** in this species confirmed that it was considerably more potent than **4** and **11**. Thus, from the profile of **23**, the cyclopentylcarbonylmethyl group appeared to be the preferred N-1 substituent, particularly with respect to its impact on in vivo potency.

Previously we had considered that the carboxylic acid group on the anilide ring of **11** had little direct role in receptor interaction, because its presence was not essential in achieving high receptor affinity, at least in the human CCK_2 receptor radioligand binding assay.[26] However, as its presence appeared to be an important factor in the effectiveness of **11** in both the in vitro functional assay and the in vivo assays, we prepared compounds in which an acid group was retained, but in which it was attached to the anilide moiety by a range of linkers (**26**−**32**). In some instances this led to significantly higher affinity than **11** for human CCK_2 receptors (Table 3). This was most marked for lipophilic linkers such as methylene (**26**), ethylene (**27**), thiomethylene (**28**), and *N*-methyl amino methylene (**29**),

Table 4. In Vitro Biological Data for 1,3,4-Benzotriazepine-Based CCK_2 Receptor Antagonists[a]



cmpd	position of attachment	Y	Z	CCK_2[b]	CCK_1[c]	CCK_2[d]	CCK_2[e]
49	6	CH	CH	9.53 ± 0.11	6.26 ± 0.03	9.07 ± 0.23	8.62 ± 0.18
50	6	CH	N	7.77 ± 0.13	<5		
51	6	N	CH	9.08 ± 0.10	5.67 ± 0.10		
52	5	CH	CH	9.11 ± 0.01	5.60 ± 0.10		
53	5	N	CH	8.03 ± 0.03	5.09 ± 0.06		
54	4	CH	CH	8.22 ± 0.02	<5		
55	4	N	CH	8.56 ± 0.05	5.16 ± 0.01		

[a] Data were generally obtained from at least three separate experiments. [b] $pK_I \pm$ SEM values obtained from competition with 20 pM [^{125}I]-BH-CCK-8S for recombinant, human CCK_2 receptors expressed in NIH3T3 cells. [c] $pK_I \pm$ SEM values obtained from competition with 20 pM [^{3}H]-L-364,718 for recombinant, human CCK_1 receptors expressed in CHO-K1 cells. [d] $pA_2 \pm$ SEM values, estimated from single shifts of pentagastrin concentration-effect curves in isolated, lumen-perfused immature rat stomachs. [e] $pK_I \pm$ SEM values obtained from competition with 20 pM [^{125}I]BH-CCK-8S for CCK_2 binding sites in canine gastric mucosa.

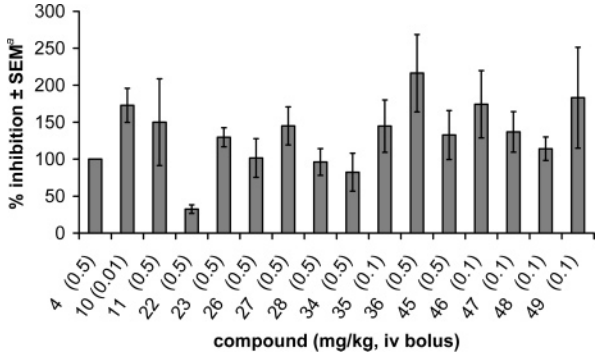


Figure 2. Inhibition achieved by compounds of pentagastrin-stimulated gastric acid secretion following intravenous bolus administration in the Ghosh and Schild rat assay. Data was obtained from at least three separate rats. [a]Relative to a 0.5 mg/kg (iv bolus) dose of **4**. Calculated using ΔpH at peak inhibition of stimulated gastric acid output produced by a submaximal continuous iv infusion of pentagastrin.

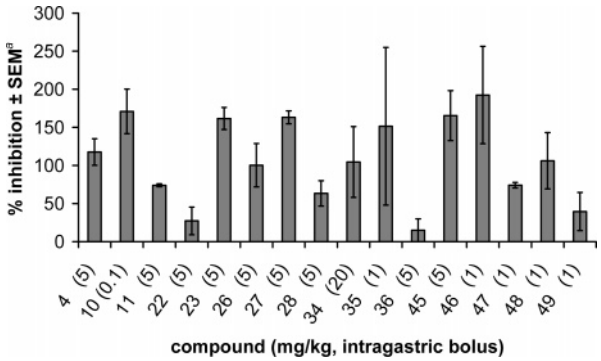


Figure 3. Inhibition achieved by compounds of pentagastrin-stimulated gastric acid secretion following intragastric bolus administration in the Ghosh and Schild rat assay. Data was obtained from at least three separate rats. [a]See legend to Figure 2.

although more polar linkers containing sulfonyl (**30**), ether (**31**), and amino (**32**) groups were also tolerated without altering affinity relative to that of **11**. Changes of this type generally resulted in lower potency than **11** in the rat in vitro assay, but among those compounds that were examined in the rat in vivo assays, **26**−**28** were at least as effective as **11** by both routes

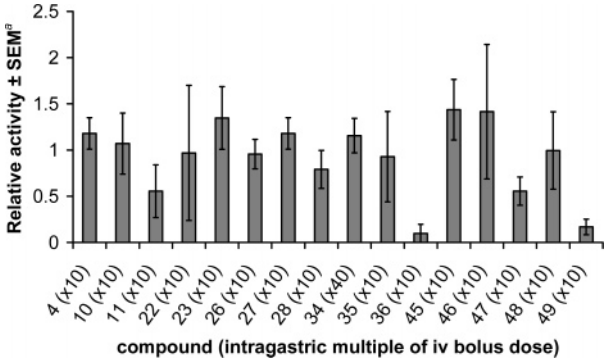


Figure 4. Relative activity of compounds following intragastric and intravenous bolus administration in the Ghosh and Schild rat assay. [a]Calculated from ratio of intragastric and intravenous potency.

of administration (Figures 2 and 3). In the dog in vivo assay, **26** showed dose-dependent inhibition when given intravenously and appeared to be more potent than **11** (Figure 5). Several compounds containing acid mimics (**33**−**35**) appeared to offer advantages over **11**, including those where this group was attached to the anilide ring by linkers (**36**−**38**). Not only was higher affinity at human CCK_2 receptors achieved in some cases, but more specific benefits were apparent from their in vivo potency. In particular, while the 1(2)*H*-tetrazol-5-yl-containing compound (**34**) showed broadly similar behavior to **11** in the rat in vivo assay by intravenous bolus administration (Figure 2), both the 1,2,4-oxadiazol-3-yl-5(2*H*)-one- (**35**) and *N*(Me)-1(2)*H*-tetrazol-5-yl-containing (**36**) derivatives were deemed to be significantly more potent by this route, as judged by the degree of inhibition produced at the doses used. Moreover, this was achieved even though **35** and **36** were around 10-fold less potent than **11** in the rat in vitro assay. At a 10-fold higher dose than that used in the intravenous experiment, **36** was only weakly effective when given intragastrically (Figure 3). The index of relative activity for **35** was not significantly different to that of **11** (Figure 4), but since a 10-fold lower dose of **35** by either route was capable of achieving a similar degree of inhibition to that produced by **11**, the 1,2,4-oxadiazol-3-yl-5(2*H*)-one substituent, present in **35**, was deemed to be superior to a carboxylic acid in terms of its influence on in vivo potency.

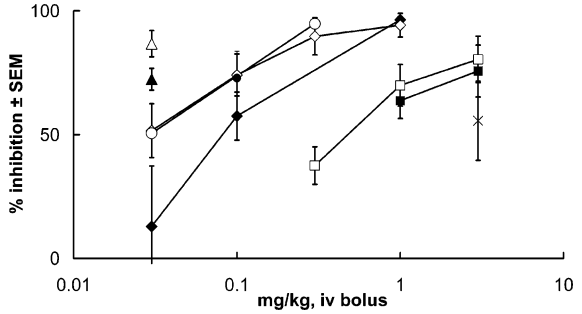


Figure 5. Inhibition achieved by selected compounds (**11** (×), **23** (◆), **26** (□), **34** (■), **35** (●), **45** (◇), **46** (▲), **47** (△), and **48** (○)) of the gastric acid secretion produced by a continuous intravenous infusion of pentagastrin, following intravenous bolus administration in conscious gastric fistula dogs. Each data point is the mean ± SEM determined from 3 to 6 dogs. The pentagastrin infusion rate was sufficient to produce submaximal acid output in each animal. The inhibition of gastric acid secretion is expressed as the percentage change in acid output between the mean acid output, measured during the two 15 min acid collection periods immediately preceding bolus dosing of the compound, and the peak inhibition produced by the compound during the four 15 min acid collection periods post-dosing. For comparison, **4** and **10** produced inhibitions of 66% (at 1 mg/kg) and 97% (at 0.05 mg/kg), respectively.

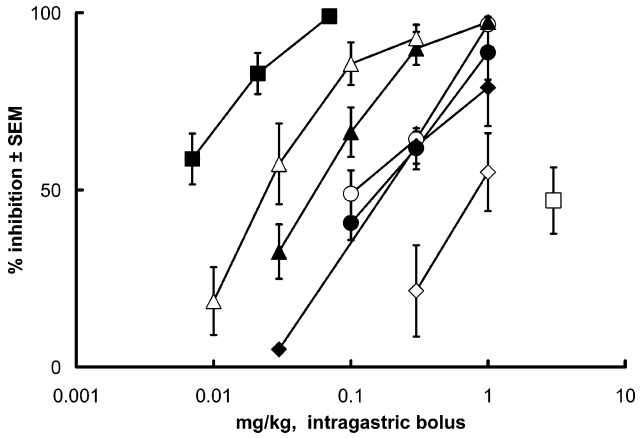


Figure 6. Inhibition achieved by selected compounds (**4** (□), **10** (■), **23** (◆), **35** (●), **45** (◇), **46** (▲), **47** (△), **48** (○)) of the gastric acid secretion produced by a subcutaneous bolus dose of pentagastrin, following intragastric bolus administration in conscious gastric fistula dogs. Each data point is the mean ± SEM determined from 3 to 6 dogs. The test compounds were given intragastrically, in a volume of 50 mL via the gastric fistula, followed 1 h later by a subcutaneous dose of pentagastrin, sufficient to produce submaximal acid output in each animal. Gastric contents were collected subsequently at 15 min intervals for a period of 90 min. The inhibition of gastric acid secretion is expressed as a percentage of the total acid secreted during this period following compound treatment of that produced when the same animal was treated with water (50 mL) prior to the pentagastrin challenge.

In the dog in vivo assay, the difference in behavior between **34** and **35** was more marked, with the latter compound being around 10-fold more potent by the intravenous route (Figure 5). The potency of **35** following enteral administration, evident in the rat in vivo assay, was maintained in the dog assay, where **35** showed dose-dependent inhibition (Figure 6).

Compounds containing acid-substituted aromatic and heterocyclic-substituted anilide groups (**39**−**44**) also maintained the high affinity at human CCK_2 receptors and selectivity over human CCK_1 receptors shown by the earlier derivatives (Table 3). However, their higher molecular weight and lengthier syntheses, which were not offset by significantly greater in vivo potency than that displayed by some of the examples discussed

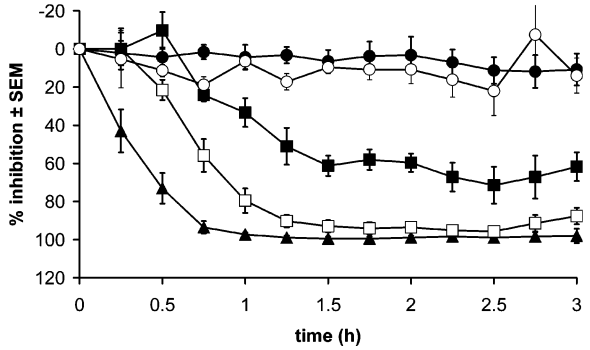


Figure 7. Time-course of the inhibition achieved by **47** (solvent (●), 0.01 mg/kg (○), 0.03 mg/kg (■), 0.1 mg/kg (□), 0.3 mg/kg (▲)) of the gastric acid secretion produced by a continuous intravenous infusion of pentagastrin, following intraduodenal bolus administration in conscious, dual gastric fistula dogs. Each data point is the mean ± SEM determined from 3 to 6 dogs. The pentagastrin dose used was sufficient to produce submaximal acid output in each animal. The inhibition of gastric acid secretion is expressed as the percentage change in acid output between the mean acid output measured during the two 15 min acid collection periods immediately preceding intraduodenal bolus dosing of the compound and the acid output during the collection periods post-dosing.

above, made further progression of compounds of this type unattractive. In addition, compounds containing acid-substituted bicyclic heteroaromatic groups in place of the 3-carboxyanilide moiety of **11**, also showed potent in vitro activity (Table 4). Indole- (**49**, **52**, **54**) and indazole-based (**51**, **53**, **55**) substituents were well tolerated, with the human CCK_2 receptor affinity showing only minimal sensitivity to changes in the position of attachment. The low relative activity index for **49** in the rat in vivo assay (Figure 4) stems from the potent antagonism produced by **49** by intravenous delivery (Figure 2), but only weak inhibition of pentagastrin-stimulated gastric acid secretion being achieved by the intragastric route (Figure 3).

From the foregoing discussion of the structure−activity in relation to the in vivo potency of this series of 1,3,4-benzotriazepine-based CCK_2 receptor antagonists, the presence of the cyclopentylcarbonylmethyl N-1 substituent, as in **23**, led to the most marked improvement over **11**, particularly in the dog in vivo assay. Consequently, compounds were prepared bearing this side chain in combination with what were judged to be the optimum acidic substituents (**45**−**48**) in anticipation that these derivatives would likely show the most potent inhibition of pentagastrin-stimulated gastric acid secretion in vivo. As with **23**, all these examples displayed ≤1 nM affinity at human CCK_2 receptors and potency in the rat in vitro functional bioassay within 10-fold of this value (Table 3). Furthermore, comparison of their respective affinities for human CCK_1 receptors indicated that their selectivity remained at least 100-fold in favor of human CCK_2 receptors. Of this group, the acetic acid-containing derivative **45** was the least effective in the rat in vivo assay and, along with the 1,2,4-oxadiazol-3-yl-5(2*H*)-one-containing analogue **47**, did not significantly differ in potency relative to their respective 1-pinacolylmethyl-containing analogues, **26** and **35** (Figures 2 and 3). On the other hand, the degree of inhibition achieved following intravenous bolus or intragastric administration by a 5-fold lower dose of the carboxymethylthio (**48**) and carboxyethyl (**46**) compounds than that used to achieve a comparable inhibition by **28** and **27**, respectively, was consistent with the cyclopentylcarbonyl methyl N-1 substituent contributing to an improved in vivo profile. However, this pattern was altered when the same group of compounds was assessed in the dog in vivo model. In this

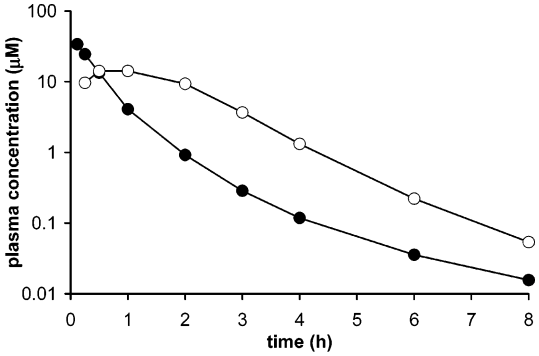


Figure 8. Plasma concentrations of **47** following intravenous bolus (2.5 mg/kg (●)) and enteral (10 mg/kg (○)) administration. Each data point is the mean concentration from two dogs. The following pharmacokinetic parameters were calculated: Vd_{ss} (iv) = 0.13 L/kg; Cl (iv) = 0.2 L/h/kg; C_{max} (po) = 15.0 μM; $t_{1/2\beta}$ (po) = 4.1 h; F_{abs} = 41%.

case, **47** and **46** were the most effective compounds. Compound **47** showed dose-dependent and potent inhibition of pentagastrin-stimulated gastric acid output by intravenous bolus (ID_{50} < 0.03 mg/kg) and intragastric (ID_{50} = 0.016 mg/kg) administration.

The benzotriazepine-based compounds described above and in the preceding paper[26] initially stemmed from consideration of 1,4-BDZ-based CCK_2 receptor antagonists. Initial examples of this series were considerably less potent than the most highly optimized 1,4-BDZ derivatives, such as **10**, but through efficient use of a combination of in vitro and in vivo assays, and placing particular emphasis on data generated from these latter assays, it has been possible to largely bridge this deficit. An obvious chemical advantage offered by examples of the current series over compounds such as **10** and the majority of the other 1,4-BDZ-based CCK_2 receptor antagonists, is the absence of a chiral center, thereby allowing their synthesis in a relatively straightforward manner. In addition, the biological profile of compounds such as **47**, where the high CCK_2 receptor affinity, evident in in vitro radioligand binding and functional bioassays, was also manifest in potent inhibition of pentagastrin-stimulated gastric acid secretion, following enteral dosing in both rats and dogs. In particular, the potency of **47** was within 3-fold of that of **10** by intragastric dosing in dogs and the dose-dependent and sustained gastric acid suppression achieved by this compound following intraduodenal bolus dosing in dual fistula dogs suggested that the inhibitory effects were long lasting (Figure 7). The effect of **47** on pentagastrin-stimulated gastric acid secretion in dogs was also consistent with the observed pharmacokinetic profile (Figure 8). Compound **47** benefits from a higher margin of receptor selectivity over the CCK_1 receptor than **10** and was also found to be highly selective over a broad range of other targets. (Compound **47** was at least 500-fold selective for CCK_2 receptors over 137 other membrane receptor and enzyme targets, based on its activity in these assays at 10 μM.) In a calcium fluorimetry assay in NIH3T3 cells expressing recombinant, human CCK_2 receptors, **47** did not stimulate Ca^{2+} mobilization on its own, but produced a rightward shift of the concentration-effect curves of CCK-8S, with potency consistent with its receptor affinity determined in the radioligand binding assay (data not shown). The collective properties of **47** justified its subsequent progression to clinical studies with a view to exploring its potential role ultimately in gastric acid related disorders, such as gastro esophageal reflux disease, and proton pump inhibitor-evoked rebound gastric acid hypersecretion as well as in the inhibition of the growth of some gastrointestinal tumors.

Experimental Section

All the compounds in Tables 3 and 4, except for **32**, **43**, **50**, and **55**, were tested as *N*-methyl-D-glucamine salts. These salts were prepared by stirring an aqueous mixture of the compound with one equivalent of *N*-methyl-D-glucamine until a solution was obtained (a minimum amount of 1,4-dioxan was added if necessary to complete dissolution) and the solutions were freeze-dried. Compounds **32**, **43**, and **50** were obtained as hydrochloride salts directly from the reaction medium. Compound **55** was obtained similarly as the trifluoroacetate salt. The hydrochloride and trifluoroacetate salts were freeze-dried as above for biological testing.

Flash column chromatography was performed on Merck silica gel 60 (40−63 μm) using the reported solvent systems. ^{1}H NMR spectra were recorded on a Bruker DRX-300 instrument at 300 MHz and the chemical shifts (δ_H) were recorded relative to an internal standard.

(*N*′-((2-Amino-phenyl)-cyclohexyl-methylene)-hydrazino)-acetic Acid Ethyl Ester (57a). A mixture of (2-aminophenyl)-cyclohexylmethanone (**56a**;[31] 20.3 g, 0.1 mol), ethyl hydrazinoacetate HCl (23.25 g, 0.15 mol), and pyridine (12.1 mL, 0.15 mol) was heated at reflux in EtOH (400 mL) for 72 h. On cooling, the solid precipitate was removed by filtration. The filtrate was evaporated and the residue was suspended in saturated $NaHCO_3$−EtOAc (1:1/500 mL). The organic layer was separated, washed with brine (250 mL), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography (EtOAc−hexane (1:4)) to afford **57a** as a pale yellow foam (21.2 g, 71%). ^{1}H NMR ($CDCl_3$) 7.17 (1H, dd, J = 7.8, 7.2 Hz, *H*-4), 6.98 (1H, d, J = 7.8 Hz, *H*-6), 6.80 (1H, dd, J = 7.8, 7.2 Hz, *H*-5), 6.73 (1H, d, J = 7.8 Hz, *H*-3), 5.32 (1H, t, J = 6.0 Hz, =NN*H*), 4.16 (2H, q, J = 7.2 Hz, COCH_2), 3.95 (2H, br s, NH_2), 3.89 (2H, 2 × d, J = 3.9, 3.6 Hz, NCH_2CO), 2.37 (1H, m, C*H*C=N), 1.80 (1H, m, C*H*), 1.75−1.61 (4H, m, CH_2), 1.33−1.19 (8H, m, C*H*, CH_2, and $COCH_2CH_3$).

Compounds **57b**−**57e** were obtained by the same method used to prepare **57a**.

(5-Cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (58a). A solution of bis(trichloromethyl) carbonate (11.4 g, 39 mmol) in DCM (100 mL) was added dropwise over 1 h to a solution of **57a** (23.39 g, 77.0 mmol), and NEt_3 (26.8 mL, 0.19 mol) in DCM (300 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, washed successively with H_2O (300 mL), saturated $NaHCO_3$ (300 mL), brine (300 mL), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by recrystallization (Et_2O−hexane (1:3)) to afford **58a** as a yellow solid (15.8 g, 62%). ^{1}H NMR ($CDCl_3$) 7.35 (2H, m, *H*-8 and *H*-9), 7.14 (1H, br s, N*H*), 7.10 (1H, d, J = 8.4 Hz, *H*-7), 6.85 (1H, d, J = 7.8 Hz, *H*-6), 4.32 (2H, s, NCH_2-CO), 4.18 (2H, q, J = 6.9 Hz, COCH_2), 2.68 (1H, m, C*H*C=N), 1.81−1.68 (5H, m, C*H* and CH_2), 1.49−1.22 (8H, m, C*H*, CH_2, and $COCH_2CH_3$); ^{13}C NMR ($CDCl_3$) 169.5, 169.2, 164.1 (*C*O_2Et/*C*-2/ *C*-5), 142.2 (Ar-*C*), 131.7 (Ar-*C*H), 127.4 (Ar-*C*H), 126.9 (Ar-*C*), 124.0 (Ar-*C*H),120.6 (Ar-*C*H), 61.1 (CO_2CH_2), 52.9 (NCH_2-CO_2), 44.6 (*C*HC=N), 31.8, 26.6, 26.5 (CH_2), 14.6 (CH_3).

Compounds **58b**−**58e** were obtained by the same method used to prepare **58a**.

(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (59a). NaH (60% dispersion in mineral oil, 0.48 g, 12.0 mmol) was added in small portions to an ice-cooled solution of **58a** (3.29 g, 10.0 mmol) in DMF (30 mL). The mixture was stirred at ambient temperature for 30 min then 1-bromo-3,3-dimethyl-butan-2-one (1.60 mL, 12.0 mmol) was added. The reaction mixture was stirred at ambient temperature for 2 h, diluted with H_2O (200 mL), and extracted with EtOAc (40 mL × 3). The combined extracts were washed with brine (50 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography (EtOAc−DCM (1:9)) to afford **59a** as a yellow foam (3.59 g, 84%). ^{1}H NMR ($CDCl_3$) 7.37 (2H, m, *H*-8 and *H*-9), 7.17 (1H, dd, J = 7.5, 8.4 Hz, *H*-7), 6.93 (1H, d, J = 8.4 Hz, *H*-6),

4.66 (2H, s, NCH_2CO*t*-Bu), 4.35 (1H, m, NCH_2CO$_2$C), 4.13 (3H, q, J = 6.9 Hz, COCH_2 and NCH_2CO$_2$C), 2.74 (1H, m, C*H*C═N), 1.90−1.70 (6H, m, CH_2), 1.31−1.16 (16H, m, CH_2, COCH$_2$CH_3, and C(CH_3)$_3$).

Compounds **59b**−**59f** and **59h**−**59o** were obtained by the same method used to prepare **59a**.

(5-Cyclohexyl-1-(2-oxo-propyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid Ethyl Ester (59g). A mixture of **58a** (300 mg, 1.00 mmol), K_2CO_3 (166 mg, 1.20 mmol), KI (20 mg), and 1-chloro-propan-2-one (90 μL, 1.10 mmol) in MeCN (5 mL) was heated at reflux for 48 h. A further portion of 1-chloro-propan-2-one (180 μL, 2.20 mmol) was added and heating was continued for 16 h. On cooling, the reaction mixture was filtered and the filtrate was evaporated. The residue was suspended in saturated $NaHCO_3$−EtOAc (1:1/60 mL). The organic layer was separated and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography (EtOAc−DCM (1:19)) to afford **59g** as a colorless foam (297 mg, 77%). ^{1}H NMR ($CDCl_3$) was obtained.

(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid (60a). A solution of **59a** (3.57 g, 8.20 mmol) and 1.0 M NaOH (8.70 mL, 8.70 mmol) in EtOH (30 mL) was stirred at ambient temperature for 16 h. The mixture was concentrated under reduced pressure, diluted with H_2O (30 mL), and acidified to pH 3 with 1 N HCl. The mixture was extracted with DCM (30 mL × 2) and the combined extracts were dried over $MgSO_4$. Filtration and evaporation of the solvent afforded **60a** as a pale yellow foam (3.10 g, 95%). ^{1}H NMR ($CDCl_3$) 11.00 (1H, br s, CO$_2$*H*), 7.45 (2H, m, *H*-8 and *H*-9), 7.25 (1H, m, *H*-7), 6.97 (1H, d, J = 8.4 Hz, *H*-6), 4.68 (2H, 2 × d, J = 17.4 Hz, NCH_2CO*t*-Bu), 4.25 (1H, d, J = 16.7 Hz, NCH_2CO$_2$H), 3.90 (1H, d, J = 16.7 Hz, NCH_2CO$_2$H), 2.80 (1H, m, C*H*C═N), 2.08−1.61 (6H, m, CH_2), 1.44−1.18 (13H, m, CH_2 and C(CH_3)$_3$).

Compounds **60b**−**60o** were obtained by the same method used to prepare **60a**.

(5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetic Acid (60m). Yield = 95%. ^{1}H NMR ($CDCl_3$) 11.00 (1H, br s), 7.45 (2H, m), 7.25 (1H, m), 7.03 (1H, d, J = 8.4 Hz), 4.55 (2H, s), 4.24 (1H, d, J = 13.8 Hz), 3.90 (1H, d, J = 13 Hz), 2.91 (1H, m), 2.82 (1H, m), 1.82−1.57 (14H, m), 1.28 (4H, m); ^{13}C NMR ($CDCl_3$) 206.5 (*C*O$_2$H), 172.3, 171.6, 163.6 (*c*-C$_5$H$_9$*C*O/ *C*-2/ *C*-5), 144.4 (Ar-*C*), 132.1 (Ar-*C*H), 129.6 (Ar-*C*), 127.0 (Ar-*C*H), 125.4 (Ar-*C*H), 121.0 (Ar-*C*H), 57.0 (*c*-C$_5$H$_9$CO*C*H$_2$), 52.8 (N*C*H$_2$CO$_2$), 49.2, 44.2 (*C*HC═N/*C*HCOCH$_2$), 33.1, 30.2, 29.3, 26.9, 26.4, 26.3 (*C*H$_2$).

3-(2-(1-(3,3-Dimethyl-2-oxo-butyl)-5-isobutyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid Methyl Ester (62). Compound **60b** (0.39 g, 1.0 mmol) was added to a solution of **61a** (0.18 g, 1.2 mmol), HOBt (0.21 g, 1.6 mmol), DMAP (1 mg), and EDCI (0.30 g, 1.6 mmol) in DMF (5 mL). The solution was maintained at ambient temperature for 16 h, diluted with H_2O (30 mL), and extracted with EtOAc (20 mL × 2). The combined extracts were washed with 5% $KHSO_4$ (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product which was purified by chromatography (EtOAc−hexanes (1:1−4:1)) to afford **62** as a yellow oil (0.48 g, 80%). ^{1}H NMR ($CDCl_3$) 8.39 (1H, s, CON*H*), 7.94−7.88 (2H, m, Ar-*H*), 7.74 (1H, d, J = 7.8 Hz, Ar-*H*), 7.51−7.43 (2H, m, Ar-*H*), 7.39−7.31 (2H, m, Ar-*H*), 7.04 (1H, d, J = 8.3 Hz, Ar-*H*), 4.71 (1H, d, J = 17.3 Hz, NCH_2CO*t*-Bu), 4.59 (1H, d, J = 17.3 Hz, NCH_2CO*t*-Bu), 4.27 (2H, s, NCH_2-CONH), 3.90 (3H, s, CO$_2$CH_3), 2.84 (1H, m, Me$_2$CHCH_2), 2.55 (1H, m, Me$_2$CHCH_2), 1.91 (1H, m, Me$_2$C*H*CH$_2$), 1.26 (9H, s, C(CH_3)$_3$), 0.98−0.90 (6H, m, (CH_3)$_2$CH).

Compounds **63**−**99** were obtained by the same method used to prepare **62**.

3-(2-(1-(3,3-Dimethyl-2-oxo-butyl)-5-isobutyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (12). A solution of **62** (0.42 g, 0.8 mmol) and 2.0 M NaOH (0.46 mL, 0.9 mmol) in EtOH (5 mL) was stirred at room temperature for 21 h. The reaction mixture was concentrated in vacuo, diluted with H_2O (20 mL), and acidified to pH 2 with 2 N HCl. The mixture was extracted with $CHCl_3$ (20 mL × 3) and the combined extracts were dried over $MgSO_4$. Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography (EtOAc−hexanes (1:1)−neat EtOAc) to afford **12** as an off-white foam (0.18 g, 44%). ^{1}H NMR (DMSO-d_6) 13.0 (1H, br s (ex. D_2O), CO$_2$*H*), 10.01 (1H, s, CON*H*), 8.17 (1H, s, Ar-*H*), 7.70 (1H, d, J = 7.8 Hz, Ar-*H*), 7.60−7.49 (3H, m, Ar-*H*), 7.38 (1H, t, J = 7.8 Hz, Ar-*H*), 7.24 (1H, t, J = 8.4 Hz, Ar-*H*), 7.13 (1H, d, J = 7.8 Hz, Ar-*H*), 4.74 (2H, br s, NCH_2CO*t*-Bu), 4.35 (1H, br, NCH_2-CONH), 4.02 (1H, br, NCH_2CONH), 2.85 (1H, br, Me$_2$CHCH_2), 2.35 (1H, br, Me$_2$CHCH_2), 1.74 (1H, m, Me$_2$C*H*CH$_2$), 1.15 (9H, s, C(CH_3)$_3$), 0.85 (6H, br, (CH_3)$_2$CH). The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{27}H_{32}N_4O_5$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

Compounds **13, 26**, **28**, **30**, **39**, **40**, **48**, **49**, **52**, and **54** were obtained by the same method used to prepare **12**.

3-(2-(5-Cyclopentyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (13). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{28}H_{32}N_4O_5$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-acetic Acid (26). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{36}N_4O_5$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenylsulfanyl)-acetic Acid (28). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{36}N_4O_5S$·$C_7H_{17}NO_5$·3.0H_2O) C, H, N.

(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzenesulfonyl)-acetic Acid (30). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{36}N_4O_7S$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

3′-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-biphenyl-3-carboxylic Acid (39). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{38}N_4O_5$·$C_7H_{17}NO_5$·1.9H_2O) C, H, N.

4-(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-thiazole-2-carboxylic Acid (40). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{35}N_5O_5S$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

(3-(2-(5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenylsulfanyl)-acetic Acid (48). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{36}N_4O_5S$·$C_7H_{17}NO_5$·5.0H_2O) C, H, N.

(6-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-indol-1-yl)-acetic Acid (49). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{37}N_5O_5$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

(5-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-indol-1-yl)-acetic Acid (52). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{37}N_5O_5$·$C_7H_{17}NO_5$·1.9H_2O·0.6dioxan) C, H, N.

(4-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-indol-1-yl)-acetic Acid (54). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{37}N_5O_5$·$C_7H_{17}NO_5$·1.6H_2O·0.5dioxan) C, H, N.

3-(2-(5-Cycloheptyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (14). 1.0 M LiOH (0.9 mL, 0.9 mmol) was added to a solution of **64** (0.16 g, 0.29 mmol) in THF−H_2O (2:1/9 mL), and the mixture

was stirred at ambient temperature for 16 h. The reaction mixture was concentrated in vacuo, diluted with H_2O (50 mL), and acidified to pH 3 with 1 N HCl. The mixture was extracted with DCM (30 mL × 2) and the combined extracts were washed with brine (50 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent afforded **14** as an off-white solid (0.16 g, 100%). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{36}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 3.5H_2O$) C, H, N.

Compounds **15**−**25**, **29**, **31**, **41**, **42**, **44**, **45**, **51**, and **53** were obtained by the same method used to prepare **14**.

3-(2-(5-Adamantan-1-yl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (15). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{33}H_{38}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 2.0H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-methyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (16). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{24}H_{26}N_4O_4 \cdot C_7H_{17}NO_5 \cdot 1.4H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-(2-oxo-propyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (17). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{26}H_{28}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 2.9H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-(3-methyl-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (18). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{28}H_{34}N_4O_4 \cdot C_7H_{17}NO_5 \cdot 1.3H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-(2-oxo-2-pyrrolidin-1-yl-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (19). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{29}H_{33}N_5O_5 \cdot C_7H_{17}NO_5 \cdot 2.3H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-(2-ethoxy-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (20). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{27}H_{32}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 1.8H_2O$) C, H, N.

3-(2-(1-(2-Adamantan-1-yl-2-oxo-ethyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (21). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{35}H_{40}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 2.7H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-(2-oxo-2-*o*-tolyl-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (22). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{32}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 1.4H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (23). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{34}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 1.9H_2O$) C, H, N.

3-(2-(1-(2-Cyclohexyl-2-oxo-ethyl)-5-cyclohexyl-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (24). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{36}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 2.9H_2O$) C, H, N.

3-(2-(5-Cyclohexyl-1-(2-(1-methyl-cyclopentyl)-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzoic Acid (25). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{36}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 2.8H_2O$) C, H, N.

((3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-methyl-amino)-acetic Acid (29). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{39}N_6O_5 \cdot C_7H_{17}NO_5 \cdot H_2O$) C, H, N.

(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenoxy)-acetic Acid (31) ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{36}N_4O_6 \cdot C_7H_{17}NO_5 \cdot 1.5H_2O$) C, H, N.

2-(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-oxazole-4-carboxylic Acid (41). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Found: Anal. ($C_{32}H_{35}N_6O_5 \cdot C_7H_{17}NO_5 \cdot 1.6H_2O$) C, H, N.

5-(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-furan-2-carboxylic Acid (42). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{33}H_{36}N_4O_6 \cdot C_7H_{17}NO_5 \cdot 1.7H_2O$) C, H, N.

(2-(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-pyrrol-1-yl)-acetic Acid (44). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{34}H_{39}N_5O_5 \cdot C_7H_{17}NO_5 \cdot 2.2H_2O$) C, H. N: calcd, 10.09; found, 9.65.

(3-(2-(5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-acetic Acid (45). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{36}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 2.1H_2O$) C, H, N.

(6-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-indazol-1-yl)-acetic Acid (51). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{36}N_6O_5 \cdot C_7H_{17}NO_5 \cdot CH_2Cl_2$) C, H, N.

(5-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-indazol-1-yl)-acetic Acid (53). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{36}N_6O_5 \cdot C_7H_{17}NO_5 \cdot 2.3H_2O$) C, H, N.

3-(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-propionic Acid (27). A mixture of **77** (0.22 g, 0.36 mmol) in trifluoroacetic acid (2 mL) was stirred at ambient temperature for 2 h. After concentration, the resulting gum was re-evaporated from DCM (20 mL × 2). Trituration of the residue with Et_2O afforded **27** as a yellow solid (0.19 g, 97%). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{38}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 3.0H_2O$) C, H, N.

Compounds **46** and **55** were obtained by the same method used to prepare **27**.

3-(3-(2-(5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-propionic Acid (46). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{32}H_{38}N_4O_5 \cdot C_7H_{17}NO_5 \cdot 1.8H_2O$) C, H, N.

(4-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-indazol-1-yl)-acetic Acid Trifluoroacetate Salt (55). ^{1}H NMR ($CDCl_3$) was obtained. Anal. ($C_{31}H_{36}N_6O_5 \cdot CF_3CO_2H$) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-(2*H*-tetrazol-5-yl)-phenyl)-acetamide (**34**). A solution of **83** (141 mg, 0.22 mmol) in saturated methanolic ammonia (10 mL) was stirred overnight at ambient temperature. After concentration in vacuo, the residue was dissolved in H_2O−MeOH (10:1/22 mL) and acidified to pH 3 by the addition of 5% $KHSO_4$ solution. Compound **34** was isolated as a light pink solid by filtration of the reaction mixture and dried in vacuo (70 mg, 60%). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{29}H_{34}N_8O_3 \cdot C_7H_{17}NO_5 \cdot 2.5H_2O$) C, H, N.

(4-(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-imidazol-1-yl)-acetic Acid Hydrochloride Salt (43). Compound **88** (275 mg, 0.5 mmol) was dissolved in 4 M HCl−dioxan (5 mL),

and the solution was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was dissolved in DCM (20 mL) and washed with H_2O (20 mL × 2). The organic phase was separated and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded **43** (215 mg, 81%). ^{1}H NMR (DMSO-d_6/D_2O) was obtained. Anal. ($C_{33}H_{38}N_6O_5$·1.6HCl·0.5dioxan) C, H, N.

(6-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-benzimidazol-1-yl)-acetic Acid Hydrochloride Salt (50). Compound **50** was obtained by the same method used to prepare **43**. ^{1}H NMR (DMSO-d_6) was obtained. Anal. ($C_{31}H_{36}N_6O_5$·HCl) C, H, N.

(3-(2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenylamino)-acetic Acid Hydrochloride Salt (32). Step A. (*tert*-Butoxycarbonyl-(3-(2-(5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-amino)-acetic acid was obtained by the same method used to prepare **12** except that **79** was used in place of **62** (76%). ^{1}H NMR (DMSO-d_6) 12.80 (1H, br s), 9.81 (1H, s), 7.52−7.47 (3H, m), 7.23−7.17 (4H, m), 6.88 (1H, d), 4.78 (2H, m), 4.25 (1H, d), 4.14 (2H, s), 3.94 (1H, d), 2.86 (1H, m), 1.90−1.45 (6H, m), 1.36−1.19 (13H, m), 1.12 (9H, s).

Step B. Compound **32** was obtained by the same method used to prepare **43**, except that (*tert*-butoxycarbonyl-(3-(2-(5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-acetylamino)-phenyl)-amino)-acetic acid was used in place of **88** (74%). ^{1}H NMR (DMSO-d_6) was obtained. Anal. ($C_{30}H_{37}N_5O_5$·HCl·0.5dioxan) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-N-(3-(5-oxo-2,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenyl)-acetamide (35). Compound **60a** (0.20 g, 0.5 mmol) was added to a solution of **61r**[32] (0.17 g, 0.6 mmol), HOBt (0.10 g, 0.7 mmol), DMAP (1 mg), and EDCI (0.14 g, 0.7 mmol) in DMF (10 mL). The solution was maintained at ambient temperature for 16 h, diluted with H_2O (30 mL), and extracted with EtOAc (20 mL × 2). The combined extracts were washed with 5% $KHSO_4$ (20 mL) and brine (20 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography (EtOAc−DCM (1:6)) to afford **35** as an orange solid (0.06 g, 22%). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{34}N_6O_5$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

Compounds **36**−**38** were obtained by the same method used to prepare **35**.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(4-(methyl-(2*H*-tetrazol-5-yl)-amino)-phenyl)-acetamide (36). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{37}N_9O_3$·$C_7H_{17}NO_5$) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-N-(3-(1*H*-tetrazol-5-ylmethyl)-phenyl)-acetamide (37). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{36}N_8O_3$·$C_7H_{17}NO_5$·1.9H_2O) C, H. N: calcd, 16.77; found, 16.08.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-N-(3-(1*H*-tetrazol-5-ylmethylsulfanyl)-phenyl)-acetamide (38). ^{1}H NMR ($CDCl_3$) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{36}N_8O_3$·$C_7H_{17}NO_5$·1.5H_2O·0.5dioxan) C, H, N.

2-(5-Cyclohexyl-1-(2-cyclopentyl-2-oxo-ethyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-(5-oxo-2,5-dihydro-[1,2,4]-oxadiazol-3-yl)-phenyl)-acetamide (47). Oxalyl chloride (1.9 mL, 22 mmol) was added dropwise to a solution of **60m** (6.0 g, 14.6 mmol) in DCM (100 mL) containing DMF (0.1 mL) at 0 °C under argon. The reaction mixture was allowed to warm to ambient temperature and stirred for 2.5 h. The solvent was evaporated in vacuo, and the residue was resuspended in DCM (30 mL × 2) and evaporated to dryness. The residue was dissolved in DCM (50 mL), cooled to 0 °C, to which a solution of **61r**[32] (3.36 g, 19 mmol) and triethylamine (6.1 mL, 44 mmol) in DCM (50 mL) was added dropwise. The reaction mixture was allowed to warm to ambient temperature, stirred for 16 h, washed with 1 N HCl (50 mL × 2) and brine (50 mL × 2), and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography (MeOH−DCM (1:19)) to afford **47** as a pale solid (2.5 g, 92%). ^{1}H NMR ($CDCl_3$) was obtained. ^{13}C NMR ($CDCl_3$) 207.0 (=N*C*O_2), 171.9, 169.4, 163.5, 160.8, 157.4 (*c*-C_5H_9*C*O/ *C*-2/ *C*-5/ CH_2CONH/ ArC(=N−)NH), 144.6 (Ar-*C*), 138.8 (Ar-*C*), 132.2 (Ar-*C*H), 130.3 (Ar-*C*H), 129.8 (Ar-*C*), 126.9 (Ar-*C*H), 125.7 (Ar-*C*H), 124.3 (Ar-*C*), 123.8 (Ar-*C*H), 122.2 (Ar-*C*H), 121.3 (Ar-*C*H), 118.2 (Ar-*C*H), 57.2 (*c*-C_5H_9CO*C*H_2), 55.4 (N*C*H_2CONH), 49.3, 44.3 (*C*HC=N/ *C*HCOCH_2), 33.1, 30.5, 29.3, 26.8, 26.4, 26.2 (*C*H_2). The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{31}H_{34}N_6O_5$·$C_7H_{17}NO_5$·1.7H_2O) C, H, N.

2-(5-Cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-1,2-dihydro-3*H*-1,3,4-benzotriazepin-3-yl)-*N*-(3-methanesulfonylaminocarbonyl-phenyl)-acetamide (33). Methanesulfonamide (96 mg, 1.00 mmol) was added to a solution of **11** (409 mg, 0.80 mmol), EDC (207 mg, 1.08 mmol), and DMAP (122 mg, 1.00 mmol) in DCM (20 mL) at ambient temperature. After stirring for 17 h, the mixture was washed with 5% $KHSO_4$ (50 mL) and brine (50 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude product, which was purified by chromatography (MeOH−DCM (1:10)) to afford **33** as a white crystalline solid (392 mg, 83%). ^{1}H NMR (DMSO-d_6) was obtained. The compound was further characterized as the *N*-methyl-D-glucamine salt. Anal. ($C_{30}H_{37}N_5O_6S$·$C_7H_{17}NO_5$·2.0H_2O) C, H, N.

In Vivo Method: Intravenous bolus administration of compounds in the anesthetized rat preparation was conducted as described previously.[12] A modification of this method that has been described in detail elsewhere,[29] also allowed intragastric delivery of compounds in this species. The inhibitory effect for each compound was determined from the maximum increase in pH achieved by the compound (ΔpH) of the stimulated gastric acid output (fall in basal pH) produced by a submaximal continuous intravenous infusion dose of pentagastrin. Because only a relatively low throughput was possible in this assay, the inhibition achieved by each compound was normalized with respect to that achieved by an intravenous bolus dose of **4** (0.5 mg/kg) sufficient to produce submaximal inhibition of the pentagastrin-stimulated acid output in the same animal. Consequently, compounds that are recorded as producing greater than 100% inhibition arise where the inhibition achieved by **4** was relatively low in any given rat. Following dose-ranging studies, a dose of test compound was selected, such that the extent of the inhibitory effect, as judged by the rise in pH, was not greater than the respective increase in gastric acid secretion (i.e., the fall in pH) evoked by the infusion of pentagastrin. This was considered to provide the most reliable method of comparing the potency of compounds that were not assayed in the same experiment.

Administration of the compounds by intravenous bolus and intragastric routes to conscious chronic gastric fistula dogs followed the previously published protocol.[12]

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Supporting Information Available: Experimental procedures for the preparation of compounds **61e**, **61g**, **61h**, **61j**−**61q**, **61v**, **61w**, and **61y**−**61ab**, ^{1}H NMR data for compounds **13**−**55**, **57a**−**57e**, **58b**−**58e**, **59b**−**59o**, **60b**−**60o**, and **63**−**99**, and elemental analysis of the novel compounds listed in Tables 3 and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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