Synthesis of Phenoxyacetic Acid Derivatives as Highly Potent Antagonists of Gastrin/Cholecystokinin-B Receptors. II

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A series of phenoxyacetanilide derivatives was synthesized and their antagonist activities for human gastrin/cholecystokinin (CCK)-B and CCK-A receptors were evaluated. Among the compounds synthesized, 2-[3-[3-[*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)carbamoylmethyl]-ureido]phenyl]acetic acid (20i, DA-3934) exhibited high affinity for gastrin/CCK-B receptors and high selectivity over CCK-A receptors. DA-3934 and its methyl ester derivative inhibited pentagastrin-induced gastric acid secretion in rats in a dose-dependent manner.

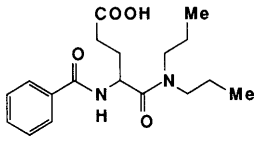
Key words phenoxyacetic acid; gastrin/cholecystokinin-B receptor antagonist; DA-3934; structure–activity relationship; gastric acid secretion; ureido-phenylacetic acid

Cholecystokinin (CCK) is a linear polypeptide hormone first isolated from the gastrointestinal tract and subsequently also identified in the central nervous system (CNS). Two CCK receptor subtypes which mediate the diverse biological functions of CCK have been identified, CCK-A and CCK-B. CCK-A receptors, primarily located in the gut, are thought to play a role in pancreatic enzyme secretion, gallbladder contraction, and intestinal motility.[1,2] CCK-B receptors are distributed throughout the CNS, and are involved in the modulation of anxiety,[3] panic attacks,[4] depression,[5] nociception,[6] and satiety.[7]

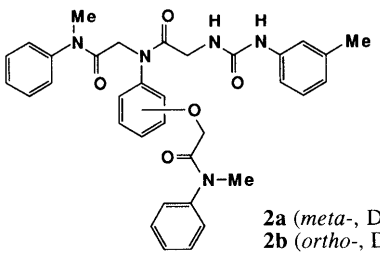
Peripheral gastrin receptors, which modulate acid secretion from parietal cells, have been shown to be closely related to or identical with CCK-B receptors in terms of binding properties.[8,9] Hence, gastrin and CCK-B receptors are described as gastrin/CCK-B receptors, and antagonists of these receptors have therapeutic potential for treating both peptic ulcers and CNS disorders. In fact, proglumide (**1**), which was the first gastrin antagonist to be available in the clinic, has been in use for some time for treating peptic ulcers, despite its weak gastrin antagonist activity.[10] Recent studies have shown that proglumide is also a weak CCK-A receptor antagonist.[11] Therefore, in order to avoid adverse effects derived from CCK-A receptor antagonist activity with gastrin/CCK-B receptor antagonists, it is necessary to find compounds which show high selectivity between gastrin/CCK-B receptors and CCK-A receptors.

In our previous paper, we reported a series of phenoxyacetic acid derivatives, exemplified by DZ-3514 (**2a**) and DA-3797 (**2b**), which show potent human gastrin/CCK-B receptor antagonist activity.[12] These two compounds, which differ principally in the substitution pattern of the phenyl ring, showed similar profiles of biological activity. The affinity for human gastrin receptors of these compounds is some two-fold less than that of YM022 (**3**), which is reported to be a potent and selective gastrin/CCK-B antagonist.[13] However, YM022 shows less selectivity for gastrin receptors over CCK-A receptors compared with DZ-3514 and DA-3797.[12]

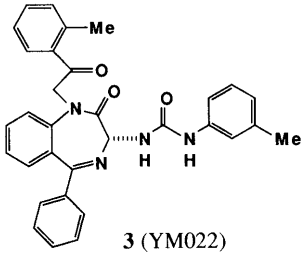
The discovery of these compounds encouraged us to investigate further modifications of their structures with the objective of increasing their potency and selectivity as gastrin antagonists. As a starting point for these structural modifications, we considered that the oxyacetamide moiety might correspond to the *C*5-phenyl moiety of benzodiaze-



1 (Proglumide)



2a (*meta*-, DZ-3514)
2b (*ortho*-, DA-3797)



3 (YM022)

Fig. 1

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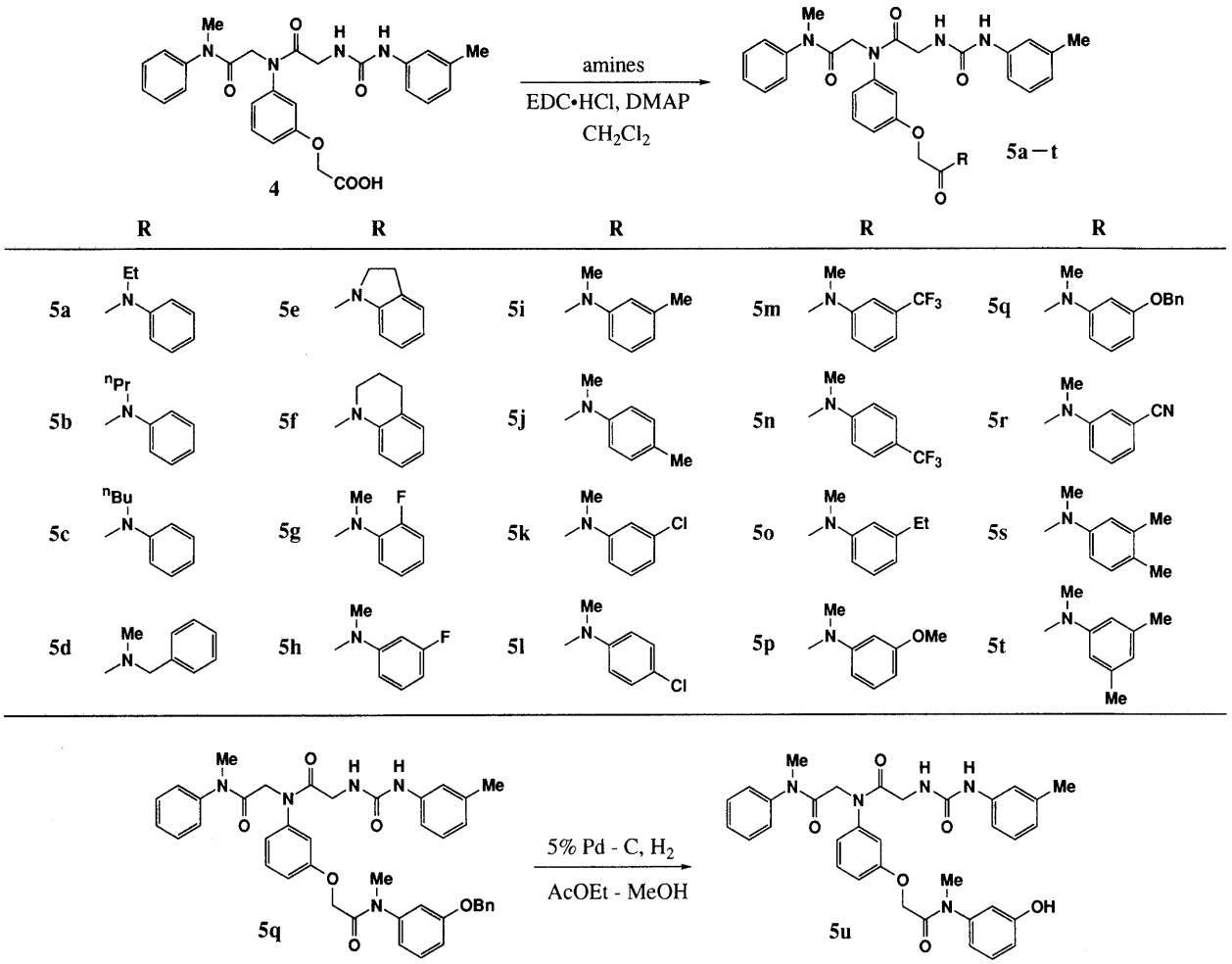


Chart 1

pine derivatives such as YM022. It has been documented that improvements in the potency of benzodiazepine gastrin/CCK-B receptor antagonists have been achieved by modification of the *C*5-phenyl moiety.[14] On the other hand, improvements in the activity of benzodiazepine gastrin/CCK-B antagonists by introduction of acidic functionalities into the ureido-phenyl moiety have also been reported.[15] The objective of making these modifications was mainly to improve water-solubility, but also resulted in the discovery of compounds with increased affinity for gastrin/CCK-B receptors.

Therefore, modification of the oxyacetamide and ureido-phenyl moieties of compounds in the phenoxyacetic acid series was considered likely to lead to more potent antagonists. Here we report the synthesis of a new series of phenoxyacetic acid derivatives related to DZ-3514 and DA-3797, with improved gastrin/CCK-B antagonist activity.

Synthesis

The syntheses of the *m*-phenoxyacetanilide derivatives **5a—u** are shown in Chart 1. The reaction of the *m*-phenoxyacetic acid[12] **4** with a variety of anilines afforded the target compounds **5a—t**. Cleavage of the benzyl moiety of compound **5q** by reduction provided the phenol derivative **5u**.

Amidation of **4** with *N*-methylanilines substituted in the 2-position of their phenyl rings by a methyl or methoxyl moiety did not proceed as expected. Hence, compounds **14a—c** were synthesized by an alternative route which is depicted in Chart 2. Acylation of the aniline **6** with *N*-*tert*-butoxycarbonyl (Boc)–Gly provided the amide **7**. Alkylation of **7** with bromoacetanilide[16] **8** and removal of the benzyl group by catalytic hydrogenation gave the phenol **10**. Condensation of **10** with bromoacetanilides **11a—c**, which were prepared by reaction of the corresponding *N*-methylanilines **16a—c** with 2-bromoacetyl bromide, and deprotection gave amines **13a—c** which were reacted with 3-tolyl isocyanate to give the desired compounds **14a—c**.

Compounds **20a—i** were synthesized from the intermediate aminoacetamide **19** by reaction with phenyl isocyanates, or from the corresponding anilines by utilizing *N*,*N*′-carbonyldiimidazole (CDI) or triphosgene-promoted coupling, followed by further modifications if necessary. The intermediate **19** was easily prepared from the phenol derivative[12] **17** in 2 steps (Chart 3).

Pharmacological Evaluation and Discussion

Receptor binding assays were used to determine the binding affinities of the synthesized compounds for human gastrin and CCK-A receptors. The activities are reported as IC_{50} values in Tables 1—3.

As shown in Table 1, the affinity for human gastrin

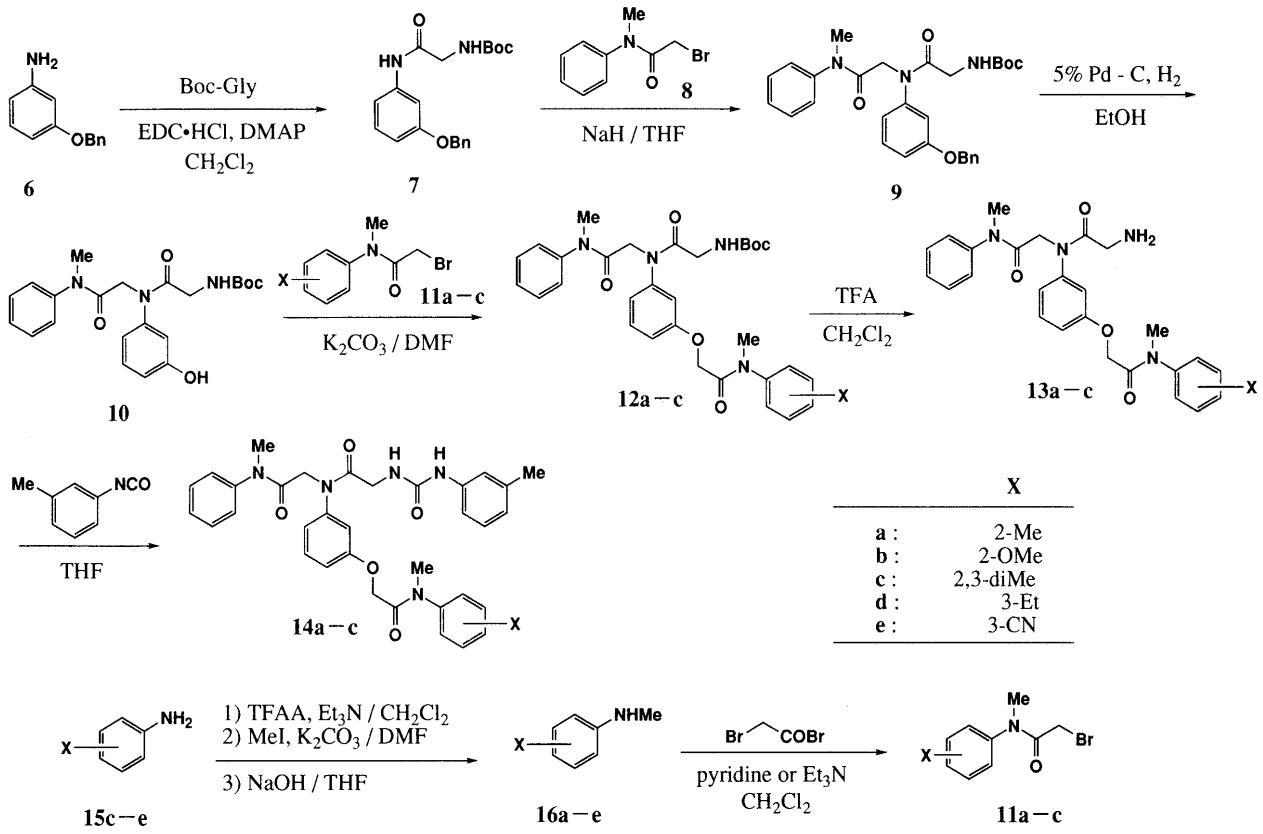


Chart 2

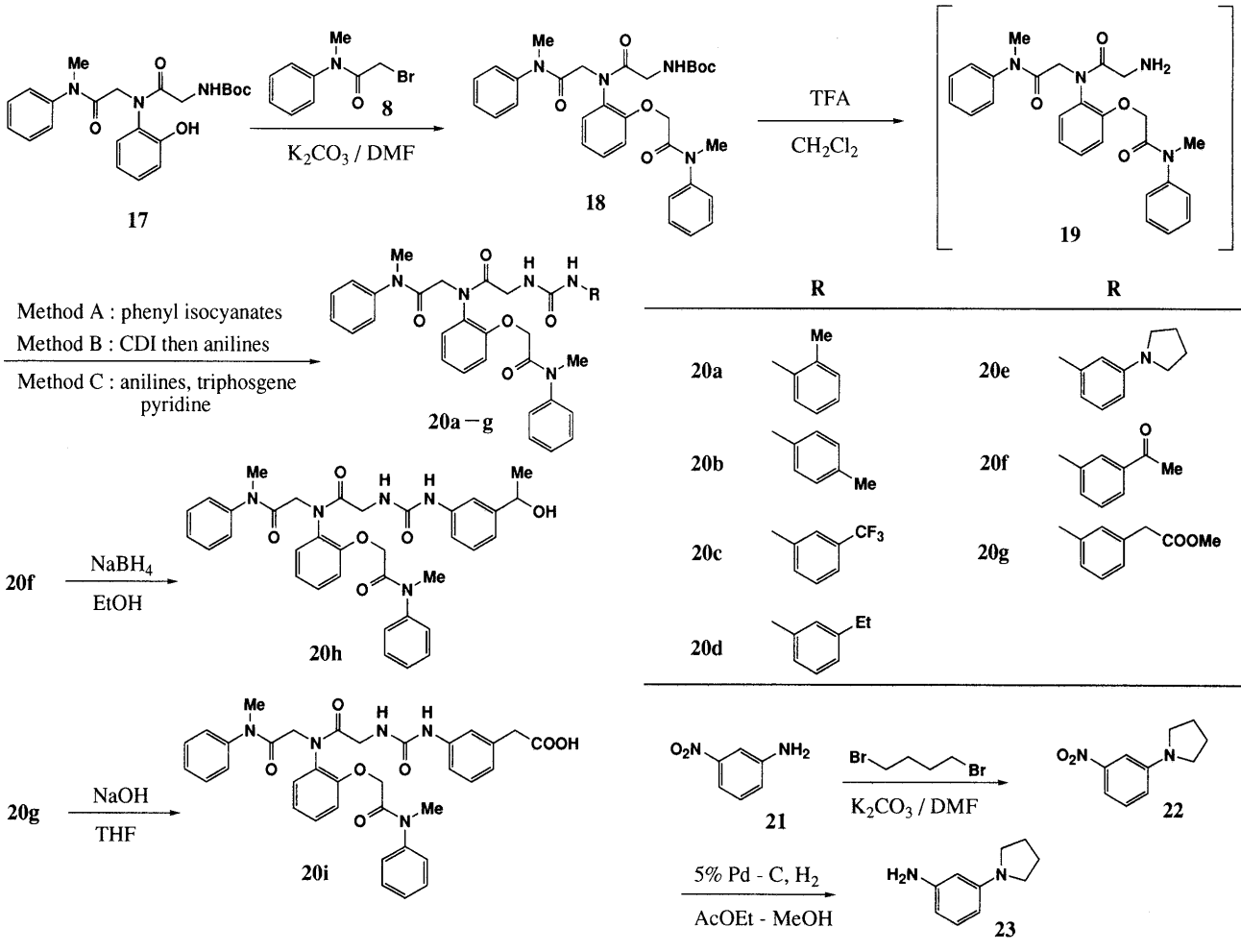
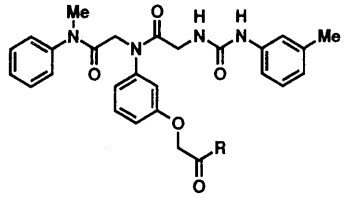
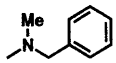


Chart 3

Table 1. Receptor Binding Affinities of *m*-Phenoxyacetanilide Derivatives **5a—f**



Compd.	R[a]	IC_{50} (nM)		Ratio (CCK-A/gastrin)
		Gastrin[b]	CCK-A[c]	
2a		0.8	178	223
5a		1.3	79	61
5b		7.3	N.T.	—
5c		9.8	N.T.	—
5d		7.7	210	27
5e		15.0	N.T.	—
5f		1.9	26	15
YM022		0.33	20	6

a) Abbreviations: Me, methyl; Et, ethyl; ^{n}Pr, *n*-propyl; ^{n}Bu, *n*-butyl. *b*) IC_{50} (nM) of [^{125}I]gastrin binding to human gastrin receptor. *c*) IC_{50} (nM) of [^{125}I]CCK-8 binding to human CCK-A receptor. N.T.; Not tested.

receptors decreased as the alkyl chain at the *N*-atom of the acetanilide moiety of this series of phenoxyacetic acid derivatives was lengthened, and compound **5c**, in which the methyl group of the parent compound **2a** was replaced by *n*-butyl, showed ten-fold less potent activity than **2a**. The benzyl type compound **5d**, in which a methylene group is inserted between the phenyl ring and the amide *N*-atom, and the fused bicyclic amine derivative, compound **5e**, also showed reduced potency. The cyclic compound **5f** showed similar potency to **2a**, but seven-fold more potent affinity for CCK-A receptors than **2a**, so the selectivity for gastrin/CCK-B over CCK-A receptors was decreased. These data suggest that the *N*-methylaniline group is near-optimal for high affinity for human gastrin receptors, so we next explored the effects of introduction of substituents into the phenyl ring.

In a series of phenyl ring-substituted acetanilide derivatives (Table 2), it was found that the introduction of smaller groups, such as methyl (**5i**, **5j**, **14a**), methoxyl (**5p**, **14b**) and fluoro (**5g**, **5h**), increased activity, whereas the introduction of trifluoromethyl (**5m**, **5n**) and benzyloxy (**5q**) substituents reduced potency. Furthermore, there were no significant differences in gastrin antagonist activity between compounds into which electron-withdrawing substituents, such as a chloro (**5k**, **5l**) or cyano (**5r**), had been introduced, and compounds with electron-donating substituents, such as methyl (**5i**, **5j**, **14a**) or methoxyl (**5p**, **14b**). Hence, it was concluded that the variation of gastrin antagonist activity is mainly influenced by steric, and not electronic, interactions.

Most of the compounds substituted in the 2- or 3-position of the phenyl ring of the oxyacetanilide moiety showed higher activity than the corresponding 4-substituted compounds. A similar trend was observed in a series of disubstituted compounds. The introduction of methyl groups into both the 3- and 4- positions of the phenyl ring (**5s**) led to somewhat decreased activity, while the 2,3- (**14c**) or 3,5-dimethyl-substituted compounds (**5t**) showed increased potency.

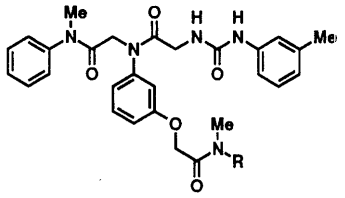
In summary, in this series of compounds the introduction of larger substituents or 4-position substituents into the phenyl ring decreased the affinity for human gastrin receptors. Among the compounds, shown in Table 2, the 2-methoxyl derivative (**14b**) had the most potent activity and its IC_{50} value was four-fold greater than that of compound **2a**.

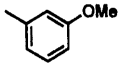
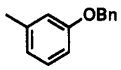
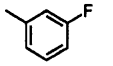
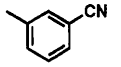
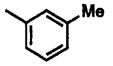
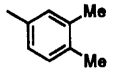
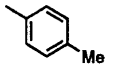
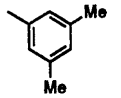
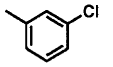
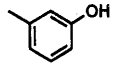
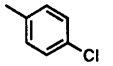
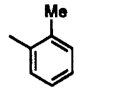
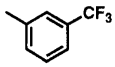
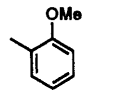
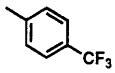
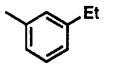
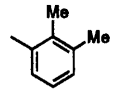
The affinities for CCK-A receptors of compounds, which showed similar or more potent affinity for human gastrin receptors compared with **2a**, are also reported in Table 2. In general, it was found that these compounds showed similar or somewhat greater affinity for CCK-A receptors than **2a**. It was concluded that the introduction of substituents into the phenyl ring of the oxyacetanilide moiety had little effect on receptor selectivity.

The effects of modification of the ureido-phenyl moiety on binding affinity are presented in Table 3. Relocating the methyl group of compound **2b** in the 2- (**20a**) or 4-position (**20b**) of the phenyl ring caused a significant drop in potency. Therefore, it appeared that location of a substituent in the 2- or 4-position is detrimental for biological activity, so further substitutions in the 3-position were also explored. Replacing the methyl group by trifluoromethyl (**20c**), ethyl (**20d**) and pyrrolidinyl (**20e**) somewhat decreased the potency. However, replacement by oxygenated substituents, such as acetyl (**20f**) and hydroxyethyl (**20h**), led to modestly increased potency and their IC_{50} values were some two-fold greater than that of compound **2b**. Furthermore, these compounds showed less affinity for human CCK-A receptors and thus the selectivity for gastrin receptors over CCK-A receptors was significantly increased. Compounds in which an acidic side chain was introduced into the 3-position (**20i**) also exhibited high affinity for human gastrin receptors, and the gastrin receptor selectivity of **20i** was ten-fold greater than that of compound **2b**. An additional binding interaction appears to be present for these compounds. The nature of this interaction has not yet been investigated.

To complete the biological profiling, compounds **20h** and **20i**, which are the most potent and selective gastrin/CCK-B receptor antagonists of this series, and also the methyl ester derivative **20g**, were evaluated *in vivo* for their acid secretion-inhibiting activity, with YM022 as a positive control. Inhibition of pentagastrin-induced gastric

Table 2. Receptor Binding Affinities of *m*-Phenoxyacetanilide Derivatives **5g—u** and **14a—c**



Compd.	R[a]	IC_{50} (nM)		Ratio (CCK-A/gastrin)	Compd.	R[a]	IC_{50} (nM)		Ratio (CCK-A/gastrin)
		Gastrin[b]	CCK-A[c]				Gastrin[b]	CCK-A[c]	
2a		0.8	178	223	**5p**		0.4	201	503
5g		0.9	N.T.	—	**5q**		81	576	7
5h		0.3	122	407	**5r**		0.4	83	208
5i		2.5	112	45	**5s**		1.4	291	208
5j		1.4	N.T.	—	**5t**		0.4	209	523
5k		0.7	83	119	**5u**		0.6	157	262
5l		0.7	241	344	**14a**		0.3	88	293
5m		2.5	263	105	**14b**		0.2	113	565
5n		5.8	210	36					
5o		0.6	340	567	**14c**		0.3	120	400

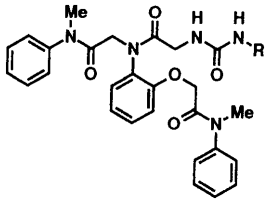
a) Abbreviations: Me, methyl; Et, ethyl; Bn, benzyl. *b*) IC_{50} (nM) of [^{125}I]gastrin binding to human gastrin receptor. *c*) IC_{50} (nM) of [^{125}I]CCK-8 binding to human CCK-A receptor. N.T.; Not tested.

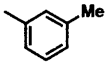
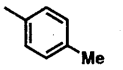
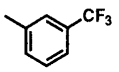
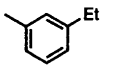
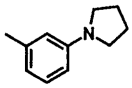
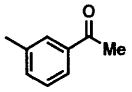
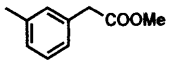
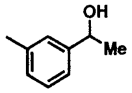
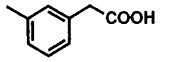
acid secretion in anesthetized rats was measured and the results are shown in Fig. 2 and Table 4. Compound **20i** inhibited gastric acid secretion induced by 16 μg/kg/h infusion of pentagastrin in a dose-dependent manner when administered either intraduodenally or intravenously; the ED_{50} values were 5.2 mg/kg and 12.5 μg/kg, respectively. Compound **20h** also inhibited pentagastrin-induced gastric acid secretion and its effect was very similar to that of compound **20i**. Compound **20g**, which showed weak *in vitro* activity compared with compound **20i**, also inhibited gastric acid secretion *in vivo*. It is possible that this is because of metabolism to the acid **20i** *in vivo*. In fact, the effect of compound **20g** *in vivo* was some 3-fold greater than that of compound **20i**. This may be because of improved absorption, with the ester **20g** functioning as a prodrug. Further experiments to confirm these hypotheses are in progress.

Conclusion

We have prepared a new series of phenoxyacetic acid derivatives starting from the known gastrin/CCK-B receptor antagonists **2a** and **2b** as lead compounds. High selectivity for gastrin/CCK-B receptors over CCK-A receptors was achieved by replacing the methyl moiety in the ureido-phenyl ring with oxygenated substituents. Compound **20i** (DA-3934) showed potent activity *in vitro* and also inhibited pentagastrin-induced gastric acid secretion in rats. Furthermore, its methyl ester derivative **20g** also inhibited gastric acid secretion *in vivo*, although it showed relatively weak affinity for the human gastrin/CCK-B receptor. The anti-secretory activity of **20g** was very similar to that of YM022 when administered intraduodenally. It is reasonable to expect that further improvements in activity can be achieved by introducing substituents into the phenyl ring of the oxyacetanilide moiety of **20i**. Additional research to explore this and other possibilities is in progress, and will be reported in due course.

Table 3. Receptor Binding Affinities of *o*-Phenoxyacetanilide Derivatives **20a—i**



Compd.	R[a]	IC_{50} (nM)		Ratio (CCK-A/gastrin)
		Gastrin[b]	CCK-A[c]	
2b		0.9	143	159
20a		37	1893	51
20b		5.1	1723	338
20c		3.0	301	100
20d		1.8	423	235
20e		1.2	561	468
20f		0.6	329	548
20g		1.1	660	600
20h		0.3	556	1853
20i		0.4	877	2193

a) Abbreivations: Me, methyl; Et, ethyl. *b*) IC_{50} (nM) of [^{125}I]gastrin binding to human gastrin receptor. *c*) IC_{50} (nM) of [^{125}I]CCK-8 binding to human CCK-A receptor.

Experimental

All chemicals and solvents used in the synthesis were reagent-grade products and were used without additional purification. Solvent and reagent names are abbreviated as follows: ethyl acetate (AcOEt), 4-dimethylaminopyridine (DMAP), *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), tetrahydrofuran (THF), and trifluoroacetic acid (TFA). Melting points were obtained on a Yanaco micro melting point apparatus and are uncorrected. NMR spectra were obtained on a JEOL EX-400 spectrometer, with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm, δ units). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained on a Hitachi 270-30 spectrometer using KBr disks. Elementary analyses were carried out by a Perkin-Elmer Model 240C elemental analyzer. Merck Kieselgel 60 (70—230 mesh) was used for column chromatography.

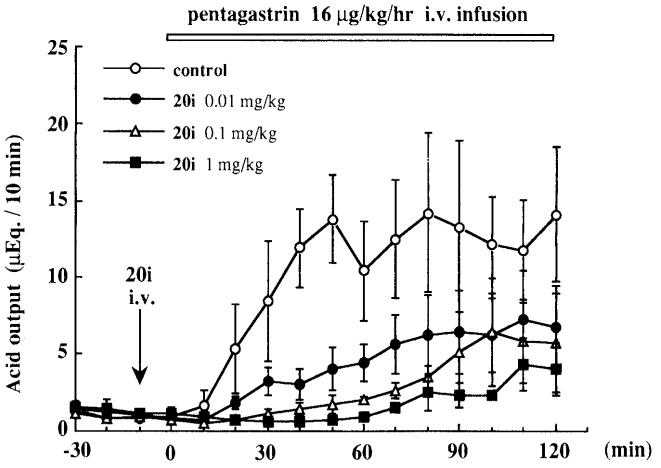


Fig. 2. Effect of Compound **20i** (Administered Intravenously) on Gastric Acid Secretion Stimulated by Pentagastrin in Anesthetized Rats (Mean±S.E., $n=3$)

Table 4. Anti-secretory Activity of Gastrin/CCK-B Antagonists

Compd.	IC_{50} (nM)	ED_{50} values and its 95% confidence limits	
	Gastrin	Pentagastrin-stimulated acid secretion (16 μg/kg/h)	
		i.d. route (mg/kg)	i.v. route (μg/kg)
20g	1.1	1.5 (0.9—2.7)	N.T.
20h	0.3	2.4 (1.8—3.3)	N.T.
20i	0.4	5.2 (3.2—8.0)	12.5 (8.0—19.8)
YM022	0.3	1.9 (1.1—3.6)	1.3 (0.6—2.3)

N.T.; Not tested.

***N*-Ethyl-*N*-phenyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (5a)** To a solution of **4** (0.5 g, 0.99 mmol) and *N*-ethylaniline (0.12 g, 0.99 mmol) in CH_2Cl_2 (20 ml) were added EDC·HCl (0.23 g, 1.2 mmol) and DMAP (0.15 g, 1.2 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between AcOEt and 1 N HCl. The layers were separated and the organic layer was washed with water, saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was recrystallized from CH_2Cl_2–diethyl ether. The product was collected by filtration to give **5a** (0.45 g, 75%) as a white powder, mp 135—137 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, $J=7.1$ Hz), 2.25 (3H, s), 3.22 (3H, s), 3.79 (2H, q, $J=7.1$ Hz), 3.86 (2H, d, $J=4.9$ Hz), 4.07 (2H, s), 4.36 (2H, s), 6.05 (1H, br s), 6.76—7.48 (18H, m), 7.72 (1H, s); IR: 3352, 1674, 1596, 1556, 1494, 1454 cm^{-1}; *Anal.* Calcd for $C_{35}H_{37}N_5O_5\cdot 0.5H_2O$: C, 68.17; H, 6.21; N, 11.36. Found: C, 68.39; H, 6.04; N, 11.37.

Compounds **5b—5t** were obtained by following an analogous procedure to that described for the preparation of **5a** from **4**; the yields, melting points and elemental analysis data are given in Table 5. The IR and ^{1}H-NMR data for these compounds are as follows:

N-Phenyl-*N*-(*n*-propyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5b**): **5b** was prepared by replacing *N*-ethylaniline with *N*-(*n*-propyl)aniline. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, $J=7.3$ Hz), 1.55 (2H, m), 2.25 (3H, s), 3.22 (3H, s), 3.69 (2H, t, $J=7.3$ Hz), 3.86 (2H, d, $J=4.7$ Hz), 4.07 (2H, s), 4.37 (2H, s), 6.08 (1H, br s), 6.75—7.47 (18H, m), 7.78 (1H, s); IR: 3352, 1674, 1596, 1554, 1494, 1454, 1428 cm^{-1}.

N-(*n*-Butyl)-*N*-phenyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5c**): **5c** was prepared by replacing *N*-ethylaniline with *N*-(*n*-butyl)-aniline. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, $J=7.3$ Hz), 1.30 (2H, m), 1.51 (2H, m), 2.25 (3H, s), 3.21 (3H, s), 3.73 (2H, t, $J=7.5$ Hz), 3.86 (2H, d, $J=4.9$ Hz), 4.07 (2H, s), 4.36 (2H, s), 6.10 (1H, br s), 6.74—7.47 (18H, m), 7.85 (1H, s); IR: 3356, 1672, 1596, 1556, 1494, 1454 cm^{-1}.

Table 5. Physicochemical Data for *m*-Phenoxyacetanilide Derivatives **5a**—**u** and **14a**—**c**

Compd.	Yield[a] (%)	mp[b] (°C)	Recryst.[c] solv.	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
5a	75	135—137	D–E	$C_{35}H_{37}N_5O_5 \cdot 0.5H_2O$	68.17	6.21	11.36	68.39	6.04	11.37
5b	65	149—150	D–E	$C_{36}H_{39}N_5O_5 \cdot 0.5H_2O$	68.55	6.39	11.10	68.57	5.96	11.11
5c	72	152—154	D–E	$C_{37}H_{41}N_5O_5 \cdot 0.5H_2O$	68.93	6.57	10.86	68.85	6.29	11.06
5d	75	Amorph.	—	$C_{35}H_{37}N_5O_5 \cdot 0.5H_2O$	68.17	6.21	11.36	68.30	6.40	10.93
5e	62	Amorph.	—	$C_{35}H_{35}N_5O_5 \cdot 0.5H_2O$	68.39	5.90	11.39	68.53	5.79	11.46
5f	44	Amorph.	—	$C_{36}H_{37}N_5O_5 \cdot 0.5H_2O$	68.77	6.09	11.14	68.60	6.10	11.14
5g	60	147—148	A–E	$C_{34}H_{34}FN_5O_5 \cdot 0.25H_2O$	66.28	5.64	11.37	66.10	5.61	11.12
5h	33	147—149	A–E	$C_{34}H_{34}FN_5O_5 \cdot 0.25H_2O$	66.28	5.64	11.37	66.34	5.61	11.38
5i	70	133—135	D–E	$C_{35}H_{37}N_5O_5$	69.18	6.14	11.52	68.96	6.27	11.41
5j	73	148—150	D–E	$C_{35}H_{37}N_5O_5$	69.18	6.14	11.52	68.89	6.30	11.50
5k	63	140—143	D–E	$C_{34}H_{34}ClN_5O_5 \cdot 0.25H_2O$	64.55	5.50	11.07	64.62	5.49	10.79
5l	82	108—110	H–A–E	$C_{34}H_{34}ClN_5O_5 \cdot 0.25H_2O$	64.55	5.50	11.07	64.55	5.78	10.76
5m	31	147—150	H–D–E	$C_{35}H_{34}F_3N_5O_5$	63.53	5.18	10.58	63.27	5.05	10.54
5n	54	128—131	D–E	$C_{35}H_{34}F_3N_5O_5$	63.53	5.18	10.58	63.50	5.33	10.59
5o	73	172—174	H–D–E	$C_{36}H_{39}N_5O_5$	69.55	6.32	11.26	69.85	6.35	11.33
5p	27	Amorph.	—	$C_{35}H_{37}N_5O_6 \cdot 0.5H_2O$	66.44	6.05	11.07	66.75	6.09	10.79
5q	50	133—134	H–D–E	$C_{41}H_{41}N_5O_6$	70.37	5.91	10.01	70.16	6.03	10.23
5r	37	Amorph.	—	$C_{35}H_{34}N_6O_5 \cdot H_2O$	66.02	5.70	13.20	66.30	5.55	12.97
5s	62	193—195	D–E	$C_{36}H_{39}N_5O_5 \cdot 0.25H_2O$	69.05	6.36	11.18	69.14	6.37	11.16
5t	41	192—194	D–E	$C_{36}H_{39}N_5O_5 \cdot 0.75H_2O$	68.07	6.43	11.02	68.13	6.30	11.02
5u	82	182—183	H–D–E	$C_{34}H_{35}N_5O_6 \cdot 0.5H_2O$	66.01	5.86	11.32	66.10	5.93	11.31
14a	84	Amorph.	—	$C_{35}H_{37}N_5O_5 \cdot 0.25H_2O$	68.67	6.17	11.44	68.63	6.35	11.14
14b	77	Amorph.	—	$C_{35}H_{37}N_5O_6 \cdot 0.5H_2O$	66.44	6.05	11.07	66.44	6.04	10.79
14c	72	188—190	D–E	$C_{36}H_{39}N_5O_5$	69.55	6.32	11.26	69.40	6.10	11.11

a) Yield from **4**, **5q** or **13a**—**c**. *b*) Abbreviation: Amorph., an amorphous powder. *c*) Abbreviations: A, ethyl acetate; D, dichloromethane; E, diethyl ether; H, *n*-hexane.

Table 6. Physicochemical Data for *o*-Phenoxyacetanilide Derivatives **20a**—**i**

Compd.	Yield[a] (%)	mp[b] (°C)	Recryst.[c] solv.	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
20a	56	211—212	H–D–E	$C_{34}H_{35}N_5O_5 \cdot 0.25H_2O$	68.27	5.98	11.71	68.46	6.06	11.68
20b	61	176—177	H–D–E	$C_{34}H_5N_5O_5 \cdot 0.25H_2O$	68.27	5.98	11.71	68.38	6.04	11.73
20c	45	148—150	D–E	$C_{34}H_{32}F_3N_5O_5$	63.05	4.98	10.71	62.77	4.93	10.68
20d	49	186—188	D–E	$C_{35}H_{37}N_5O_5 \cdot 0.25H_2O$	68.67	6.17	11.44	68.63	6.11	11.36
20e	66	227—228	A–E	$C_{37}H_{40}N_6O_5 \cdot 0.25H_2O$	68.03	6.25	12.86	67.86	6.18	12.58
20f	45	Amorph.	—	$C_{35}H_{35}N_5O_6 \cdot 0.75H_2O$	66.18	5.79	11.03	66.05	5.90	10.94
20g	38	147—149	D–E	$C_{36}H_{37}N_5O_7$	66.35	5.72	10.75	66.41	5.67	10.71
20h	91	Amorph.	—	$C_{35}H_{37}N_5O_6 \cdot 0.75H_2O$	65.97	6.09	10.99	66.12	6.09	10.83
20i	89	189—190	C–E	$C_{35}H_{35}N_5O_7$	65.92	5.53	10.98	66.23	5.57	10.84

a) Yield from **18**, **20f** or **20g**. *b*) Abbreviation : Amorph., an amorphous powder. *c*) Abbreviations: A, ethyl acetate; C, chloroform; D, dichloromethane; E, diethyl ether; H, *n*-hexane.

N-Benzyl-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5d**): **5d** was prepared by replacing *N*-ethylaniline with *N*-methylbenzylamine. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.93 (3H, s), 3.21 (3H, s), 3.90 (2H, d, J=5.4 Hz), 4.10 (2H, s), 4.59 (2H, s), 4.76 (2H, s), 6.08 (1H, br s), 6.98—7.23 (18H, m), 7.79 (1H, s); IR: 3352, 1662, 1596, 1556, 1494, 1454 cm^{-1}.

1-[2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetyl]indoline (**5e**): **5e** was prepared by replacing *N*-ethylaniline with indoline. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 3.14 (5H, m), 3.91 (2H, d, J=4.9 Hz), 4.09 (4H, m), 4.77 (2H, s), 6.04 (1H, m), 6.76 (1H, d, J=6.8 Hz), 7.01—7.34 (15H, m), 7.59 (1H, s), 8.21 (1H, d, J=8.3 Hz); IR: 3372, 2944, 1598, 1488, 1424, 1292 cm^{-1}.

1-[2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetyl]-1,2,3,4-tetrahydroquinoline (**5f**): **5f** was prepared by replacing *N*-ethylaniline with 1,2,3,4-tetrahydroquinoline. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (2H, m), 2.26 (3H, s), 2.69 (2H, m), 3.21 (3H, s), 3.80 (2H, m), 3.88 (2H, d, J=4.9 Hz), 4.07 (2H, s), 4.82 (2H, s), 5.96 (1H, m), 6.77—7.44 (18H, m); IR: 3368, 2948, 1598, 1494, 1428 cm^{-1}.

N-(2-Fluorophenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]-acetamide (**5g**): **5g** was prepared by replacing *N*-ethylaniline with *N*-methyl-2-fluoroaniline.[17] ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.22 (3H, s), 3.29 (3H, s), 3.84 (2H, s), 4.09 (2H, s), 4.44 (2H, m), 6.05 (1H, m), 6.72—6.84 (3H, m), 6.85—7.39 (14H, m), 7.51 (1H, br s); IR: 3344, 1680, 1594, 1554, 1494, 1426, 1394 cm^{-1}.

N-(3-Fluorophenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5h**): **5h** was prepared by replacing *N*-ethylaniline with *N*-methyl-3-fluoroaniline.[17] ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.23 (3H, s), 3.31 (3H, s), 3.85 (2H, s), 4.08 (2H, s), 4.47 (2H, br s), 5.99 (1H, br s), 6.78—7.08 (4H, m), 7.09—7.24 (7H, m), 7.25—7.32 (2H, m), 7.33—7.43 (4H, m), 7.55 (1H, br s); IR: 3344, 1676, 1594, 1554, 1488, 1430, 1394 cm^{-1}.

N-Methyl-*N*-(3-methylphenyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acet-

amide (**5i**): **5i** was prepared by replacing *N*-ethylaniline with *N*-methyl-3-toluidine. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.38 (3H, s), 3.21 (3H, s), 3.31 (3H, s), 3.86 (2H, d, J=4.9 Hz), 4.08 (2H, s), 4.42 (2H, s), 6.09 (1H, br s), 6.74—7.35 (17H, m), 7.79 (1H, s); IR: 3352, 1672, 1596, 1556, 1492, 1454 cm^{-1}.

N-Methyl-*N*-(4-methylphenyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5j**): **5j** was prepared by replacing *N*-ethylaniline with *N*-methyl-4-toluidine.[18] ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.37 (3H, s), 3.22 (3H, s), 3.29 (3H, s), 3.86 (2H, d, J=4.9 Hz), 4.08 (2H, s), 4.41 (2H, s), 6.09 (1H, br s), 6.75—7.35 (17H, m), 7.77 (1H, s); IR: 3356, 1670, 1596, 1554, 1514, 1490 cm^{-1}.

N-(3-Chlorophenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5k**): **5k** was prepared by replacing *N*-ethylaniline with *N*-methyl-3-chloroaniline. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.23 (3H, s), 3.31 (3H, s), 3.86 (2H, d, J=4.4 Hz), 4.08 (2H, s), 4.45 (2H, s), 5.97 (1H, br s), 6.77—7.36 (17H, m), 7.51 (1H, s); IR: 3380, 1676, 1594, 1554, 1490 cm^{-1}.

N-(4-Chlorophenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5l**): **5l** was prepared by replacing *N*-ethylaniline with *N*-methyl-4-chloroaniline. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 3.22 (3H, s), 3.28 (3H, s), 3.86 (2H, d, J=4.4 Hz), 4.09 (2H, s), 4.43 (2H, s), 6.14 (1H, br s), 6.74—7.42 (17H, m), 7.94 (1H, s); IR: 3360, 1668, 1596, 1554, 1492 cm^{-1}.

N-(3-Trifluoromethylphenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5m**): **5m** was prepared by replacing *N*-ethylaniline with *N*-methyl-3-trifluoromethylaniline.[19] ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 3.23 (3H, s), 3.34 (3H, s), 3.84 (2H, s), 4.07 (2H, s), 4.44 (2H, br s), 5.98 (1H, br s), 6.79 (2H, d, J=6.8 Hz), 6.89 (1H, br s), 7.00—7.61 (15H, m); IR: 3368, 1670, 1598, 1554, 1494, 1432 cm^{-1}.

N-(4-Trifluoromethylphenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5n**): **5n** was prepared by replacing *N*-ethylaniline with *N*-methyl-4-trifluoromethylaniline.[20] ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 3.23 (3H, s), 3.34 (3H, s), 3.84 (2H, d, J=4.0 Hz), 4.08 (2H, s), 4.45 (2H, s), 6.00 (1H, br s), 6.73—7.36 (17H, m), 7.61 (1H, s); IR: 3368, 1670, 1596, 1554, 1494 cm^{-1}.

N-(3-Ethylphenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5o**): **5o** was prepared by replacing *N*-ethylaniline with **16d**. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.8 Hz), 2.25 (3H, s), 2.67 (2H, q, J=7.8 Hz), 3.21 (3H, s), 3.32 (3H, s), 3.86 (2H, d, J=4.9 Hz), 4.07 (2H, s), 4.42 (2H, s), 6.08 (1H, br s), 6.74—6.80 (2H, m), 6.92 (1H, s), 7.00—7.38 (14H, m), 7.76 (1H, s); IR: 3360, 1674, 1598, 1556, 1492, 1454, 1428 cm^{-1}.

N-(3-Methoxyphenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5p**): **5p** was prepared by replacing *N*-ethylaniline with *N*-methyl-3-anisidine.[21] ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.25 (3H, s), 3.32 (3H, s), 3.81 (3H, s), 3.85 (2H, d, J=4.4 Hz), 4.07 (2H, br s), 4.46 (2H, br s), 5.76 (1H, br s), 6.81—7.40 (18H, m); IR: 3368, 1670, 1598, 1554, 1492, 1454, 1430, 1396 cm^{-1}.

N-(3-Benzyloxyphenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5q**): **5q** was prepared by replacing *N*-ethylaniline with *N*-methyl-3-benzyloxyaniline.[22] ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.24 (3H, s), 3.31 (3H, s), 3.83 (2H, d, J=4.4 Hz), 4.07 (2H, s), 4.41 (2H, s), 5.08 (2H, s), 5.65 (1H, br s), 6.80—7.44 (23H, m); IR: 3368, 1670, 1598, 1554, 1490, 1454, 1428 cm^{-1}.

N-(3-Cyanophenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5r**): **5r** was prepared by replacing *N*-ethylaniline with **16e**. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 3.24 (3H, s), 3.32 (3H, s), 3.84 (2H, s), 4.08 (2H, s), 4.47 (2H, s), 6.05 (1H, br s), 6.72—7.36 (14H, m), 7.55—7.64 (3H, m), 7.72 (1H, br s); IR: 3804, 3072, 2236, 1598, 1490, 1396, 1228 cm^{-1}.

N-Methyl-*N*-(3,4-dimethylphenyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5s**): **5s** was prepared by replacing *N*-ethylaniline with *N*-methyl-3,4-xylidine.[23] ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.26 (6H, s), 3.22 (3H, s), 3.29 (3H, s), 3.86 (2H, d, J=4.4 Hz), 4.08 (2H, s), 4.42 (2H, s), 6.03 (1H, br s), 6.76 (1H, d, J=7.3 Hz), 6.80 (1H, d, J=8.3 Hz), 6.99 (1H, s), 7.01—7.35 (13H, m), 7.62 (1H, br s); IR: 3376, 1668, 1598, 1556, 1492, 1454 cm^{-1}.

N-Methyl-*N*-(3,5-dimethylphenyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**5t**): **5t** was prepared by replacing *N*-ethylaniline with *N*-methyl-3,5-xylidine.[24] ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 2.33 (6H, s), 3.22 (3H, s), 3.29 (3H, s), 3.86 (2H, d, J=3.4 Hz), 4.07 (2H, s), 4.42 (2H, s), 5.91 (1H, br s), 6.78—7.36 (17H, m); IR: 3360, 1680, 1598, 1556, 1490, 1454, 1430 cm^{-1}.

***N*-(3-Hydroxyphenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (5u)** **5q** (0.45 g, 0.99 mmol) was hydrogenated in a mixture of MeOH (20 ml) and AcOEt (20 ml) over 5% Pd–C (0.1 g) at atmospheric pressure for 1 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was recrystallized from *n*-hexane–CH_2Cl_2–diethyl ether. The product was collected by filtration to give **5u** (0.32 g, 82%) as a white powder, mp 182—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 3.24 (3H, s), 3.28 (3H, s), 3.88 (2H, d, J=4.4 Hz), 4.10 (2H, s), 4.49 (2H, s), 6.21 (1H, br s), 6.68—7.35 (17H, m), 7.95 (1H, s), 9.14 (1H, s); IR: 3384, 1662, 1598, 1556, 1490, 1454, 1434 cm^{-1}; *Anal.* Calcd for $C_{34}H_{35}N_5O_6 \cdot 0.5H_2O$: C, 66.01; H, 5.86; N, 11.32. Found: C, 66.10; H, 5.93; N, 11.31.

***N*-(3-Benzyloxyphenyl)-2-(*N*-*tert*-butoxycarbonylamino)acetamide (7)** To a solution of **6** (32 g, 160 mmol), Boc–Gly (35 g, 200 mmol) and DMAP (24 g, 196 mmol) in CH_2Cl_2 (500 ml) was added EDC·HCl (38 g, 198 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between AcOEt and 1 N HCl. The layers were separated and the organic layer was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **7** (39 g, 68%) as a white powder, mp 165—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 3.91 (2H, d, J=5.9 Hz), 5.06 (2H, s), 5.20 (1H, br s), 6.74 (1H, m), 6.98 (1H, m), 7.19—7.23 (1H, m), 7.32—7.44 (6H, m), 8.10 (1H, br s).

***N*-Methyl-*N*-phenyl-2-[*N*-(3-benzyloxyphenyl)-*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]amino]acetamide (9)** To a solution of **7** (7.2 g, 20 mmol) in THF (100 ml) was added NaH (60% in oil, 0.96 g, 24 mmol), and the mixture was stirred at 55 °C for 20 min. After addition of a solution of **8** (5.5 g, 24 mmol) in THF (20 ml) to the reaction mixture with ice cooling, the resulting mixture was stirred at room temperature for 1.5 h. Ice-water was then added and the mixture was extracted with AcOEt. The extract was washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (1 : 1). The eluate was concentrated under reduced pressure to give **9** (7.5 g, 74%) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s), 3.29 (3H, s), 3.74 (2H, d, J=4.4 Hz), 4.07 (2H, s), 5.04 (2H, s), 5.34 (1H, br s), 6.94—6.97 (2H, m), 7.06 (1H, s), 7.25—7.46 (11H, m).

***N*-Methyl-*N*-phenyl-2-[*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]-*N*-(3-hydroxyphenyl)amino]acetamide (10)** **9** (25 g, 50 mmol) was hydrogenated in EtOH (500 ml) over 5% Pd–C (2.5 g) at atmospheric pressure for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was crystallized from *n*-hexane–diethyl ether. The product was collected by filtration to give **10** (17 g, 82%) as a white powder, mp 164—166 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s), 3.28 (3H, s), 3.76 (2H, d, J=4.9 Hz), 4.08 (2H, s), 5.42 (1H, br s), 6.80—6.83 (3H, m), 6.95 (1H, s), 7.17—7.24 (2H, m), 7.35—7.44 (4H, m).

***N*-Methyl-*N*-(2-methylphenyl)-2-[3-[*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (12a)** A mixture of **10** (6.2 g, 15 mmol), **11a** (6.0 g, 24.8 mmol) and K_2CO_3 (3.5 g, 25.0 mmol) in DMF (100 ml) was stirred overnight at 70 °C. The reaction mixture was poured into ice-water and the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **12a** (8.5 g, 99%) as a pale yellow amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 2.29 (3H, s), 3.25 (3H, s), 3.28 (3H, s), 3.68 (2H, d, J=3.9 Hz), 4.04 (2H, ABq, J=15.6 Hz), 4.18 (1H, d, J=15.2 Hz), 4.36 (1H, d, J=15.2 Hz), 5.32 (1H, br s), 6.77 (1H, d, J=8.3 Hz), 6.85 (1H, s), 6.95 (1H, d, J=7.8 Hz), 7.19—7.44

(10H, m).

Compounds **12b** and **12c** were obtained by following an analogous procedure to that described for the preparation of **12a** from **10**. Spectroscopic data for these compounds are as follows:

N-(2-Methoxyphenyl)-*N*-methyl-2-[3-[*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (**12b**): **12b** was prepared by replacing **11a** with **11b**. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 3.22 (3H, s), 3.28 (3H, s), 3.68 (2H, d, J=3.9 Hz), 3.87 (3H, s), 4.01 (1H, d, J=16.0 Hz), 4.11 (1H, d, J=16.0 Hz), 4.29 (1H, d, J=15.0 Hz), 4.39 (1H, d, J=15.0 Hz), 5.33 (1H, br s), 6.79—7.44 (13H, m).

N-Methyl-*N*-(2,3-dimethylphenyl)-2-[3-[*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (**12c**): **12c** was prepared by replacing **11a** with **11c**. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 2.19 (3H, s), 2.34 (3H, s), 3.23 (3H, s), 3.28 (3H, s), 3.68 (2H, d, J=4.4 Hz), 4.05 (2H, ABq, J=14.6 Hz), 4.16 (1H, d, J=14.7 Hz), 4.37 (1H, d, J=14.7 Hz), 5.33 (1H, br s), 6.77 (1H, d, J=8.3 Hz), 6.85 (1H, s), 6.95 (1H, d, J=7.3 Hz), 7.12—7.44 (9H, m).

***N*-Methyl-*N*-(2-methylphenyl)-2-[3-[*N*-(2-aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (13a)** To a solution of **12a** (2.2 g, 3.8 mmol) in CH_2Cl_2 (50 ml) was added TFA (20 ml) with ice cooling, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic solution was washed with saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **13a** (1.8 g, quant.) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (2H, br s), 2.29 (3H, s), 3.17 (2H, s), 3.25 (3H, s), 3.29 (3H, s), 4.05 (2H, ABq, J=14.6 Hz), 4.18 (1H, d, J=15.1 Hz), 4.37 (1H, d, J=15.1 Hz), 6.76 (1H, dd, J=2.0, 8.3 Hz), 6.83 (1H, s), 6.93 (1H, d, J=7.8 Hz), 7.20—7.44 (10H, m).

Compounds **13b** and **13c** were obtained by following an analogous procedure to that described for the preparation of **13a**. Spectroscopic data for these compounds are as follows:

N-(2-Methoxyphenyl)-*N*-methyl-2-[3-[*N*-(2-aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (**13b**): ^{1}H-NMR ($CDCl_3$) δ: 1.61 (2H, br s), 3.18 (2H, s), 3.22 (3H, s), 3.28 (3H, s), 3.87 (3H, s), 4.02 (1H, d, J=16.0 Hz), 4.10 (1H, d, J=16.0 Hz), 4.30 (1H, d, J=15.0 Hz), 4.39 (1H, d, J=15.0 Hz), 6.75—7.44 (13H, m).

N-Methyl-*N*-(2,3-dimethylphenyl)-2-[3-[*N*-(2-aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (**13c**): ^{1}H-NMR ($CDCl_3$) δ: 2.17 (2H, br s), 2.18 (3H, s), 2.33 (3H, s), 3.23 (3H, s), 3.25 (2H, s), 3.28 (3H, s), 4.05 (2H, ABq, J=14.7 Hz), 4.17 (1H, d, J=15.2 Hz), 4.38 (1H, d, J=15.2 Hz), 6.76 (1H, dd, J=2.4, 8.3 Hz), 6.84 (1H, s), 6.93 (1H, d, J=7.3 Hz), 7.11—7.44 (9H, m).

***N*-Methyl-*N*-(2-methylphenyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (14a)** To a solution of **13a** (0.5 g, 1.1 mmol) in THF (20 ml) was added a solution of 3-tolyl isocyanate (0.14 g, 1.1 mmol) in THF (20 ml), and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to give **14a** (0.56 g, 84%) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.29 (3H, s), 3.21 (3H, s), 3.24 (3H, s), 3.85 (2H, d, J=4.4 Hz), 4.06 (2H, ABq, J=15.4 Hz), 4.19 (1H, d, J=14.6 Hz), 4.39 (1H, d, J=14.6 Hz), 6.05 (1H, br s), 6.75—7.35 (17H, m), 7.68 (1H, s); IR: 3368, 1672, 1598, 1554, 1494, 1430 cm^{-1}; *Anal.* Calcd for $C_{35}H_{37}N_5O_5 \cdot 0.25H_2O$: C, 68.67; H, 6.17; N, 11.44. Found: C, 68.63; H, 6.35; N, 11.14.

Compounds **14b** and **14c** were obtained by following an analogous procedure to that described for the preparation of **14a**; the yields, melting points and elemental analysis data are given in Table 5. The IR and ^{1}H-NMR data for these compounds are as follows:

N-(2-Methoxyphenyl)-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**14b**): ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s), 3.22 (3H, s), 3.26 (3H, s), 3.85 (2H, d, J=3.9 Hz), 3.88 (3H, s), 4.08 (2H, ABq, J=17.0 Hz), 4.32 (1H, d, J=15.0 Hz), 4.42 (1H, d, J=15.0 Hz), 5.62 (1H, br s), 6.70—7.42 (18H, m); IR: 3368, 1668, 1598, 1554, 1496, 1454, 1430, 1394 cm^{-1}.

N-Methyl-*N*-(2,3-dimethylphenyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**14c**): ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, s), 2.25 (3H, s), 2.32 (3H, s), 3.21 (3H, s), 3.22 (3H, s), 3.85 (2H, d, J=4.9 Hz), 4.07 (2H, ABq, J=14.7 Hz), 4.19 (1H, d, J=15.1 Hz), 4.39 (1H, d, J=15.1 Hz), 6.01 (1H, s), 6.77—6.78 (2H, br s), 6.90 (1H, s), 7.00—7.35 (13H, m), 7.57 (1H, s); IR: 3368, 1674, 1596, 1556, 1490, 1454, 1434 cm^{-1}.

***N*-Methyl-2,3-xylidine (16c)** To a solution of 2,3-xylidine **15c** (10 g, 82.5 mmol) and triethylamine (12.5 ml, 90 mmol) in CH_2Cl_2 (100 ml) was added a solution of trifluoroacetic anhydride (12.7 ml, 90 mmol) in CH_2Cl_2 (50 ml) with ice cooling, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give *N*-(2,3-dimethylphenyl)trifluoroacetamide (15.5 g, 87%) as colorless needles, mp 90—92 °C. To a mixture of *N*-(2,3-dimethylphenyl)trifluoroacetamide (8.2 g, 37.8 mmol) and K_2CO_3 (6.0 g, 44.0 mmol) in DMF (50 ml) was added MeI (2.8 ml, 44.0 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with AcOEt. The extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in THF (50 ml). After addition of 2 N NaOH (50 ml) to the organic solution, the mixture was stirred overnight at room temperature. The reaction mixture was extracted with AcOEt and the extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **16c** (4.6 g, 90%) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s), 2.28 (3H, s), 2.88 (3H, s), 3.55 (1H, br s), 6.51 (1H, d, J=8.3 Hz), 6.60 (1H, d, J=8.3 Hz), 7.05 (1H, t, J=8.3 Hz).

Compounds **16d** and **16e** were obtained by following an analogous procedure to that described for the preparation of **16c**. Spectroscopic data for these compounds are as follows:

N-Methyl-3-ethylaniline (**16d**): **16d** was prepared by replacing 2,3-xylidine with 3-ethylaniline. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.8 Hz), 2.58 (2H, q, J=7.8 Hz), 2.83 (3H, s), 3.61 (1H, br s), 6.45 (1H, d, J=8.3 Hz), 6.46 (1H, s), 6.57 (1H, d, J=8.3 Hz), 7.11 (1H, t, J=8.3 Hz).

N-Methyl-3-cyanoaniline (**16e**): **16e** was prepared by replacing 2,3-xylidine with 3-aminobenzonitrile. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (3H, s), 4.02 (1H, br s), 6.76—6.79 (2H, m), 6.95 (1H, m), 7.19—7.24 (1H, m).

***N*-Methyl-*N*-(2-methylphenyl)-2-bromoacetamide (11a)** To a solution of *N*-methyl-2-toluidine (3.0 g, 24.8 mmol) and pyridine (2.0 ml, 24.8 mmol) in CH_2Cl_2 (100 ml) was added a solution of 2-bromoacetyl bromide (2.2 ml, 24.8 mmol) in CH_2Cl_2 (50 ml) with ice cooling, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with 1 N HCl, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **11a** (6.0 g, quant.) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.23 (3H, s), 3.55 (1H, d, J=11.2 Hz), 3.62 (1H, d, J=11.2 Hz), 7.19—7.33 (4H, m).

Compounds **11b** and **11c** were obtained by following a procedure similar to that described for the preparation of **11a**. Spectroscopic data for these compounds are as follows:

N-(2-Methoxyphenyl)-*N*-methyl-2-bromoacetamide (**11b**): **11b** was prepared by replacing *N*-methyl-2-toluidine with *N*-methyl-2-anisidine.[25] ^{1}H-NMR ($CDCl_3$) δ: 3.22 (3H, s), 3.64 (2H, ABq, J=11.0 Hz), 3.85 (3H, s), 6.98—7.03 (2H, m), 7.24—7.27 (1H, m), 7.34—7.39 (1H, m).

N-Methyl-*N*-(2,3-dimethylphenyl)-2-bromoacetamide (**11c**): **11c** was prepared by replacing *N*-methyl-2-toluidine with **16c**. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.33 (3H, s), 3.22 (3H, s), 3.59 (2H, ABq, J=10.8 Hz), 7.05 (1H, d, J=7.9 Hz), 7.15 (1H, d, J=7.9 Hz), 7.20 (1H, t, J=7.9 Hz).

***N*-Methyl-*N*-phenyl-2-[2-[*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (18)** A mixture of **17** (50 g, 121 mmol), **8** (33 g, 145 mmol) and K_2CO_3 (21 g, 150 mmol) in DMF (500 ml) was stirred at 70 °C for 2 d. The reaction mixture was cooled and poured into ice-water, then the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was washed with a mixture of AcOEt and diethyl ether to give **18** (56 g, 83%) as a white powder, mp 196—197 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (9H, s), 3.24 (3H, s), 3.27 (3H, s), 3.49—3.57 (2H, m), 3.76 (1H, dd, J=4.3, 17.5 Hz), 4.35 (2H, s), 4.73 (1H, d, J=16.6 Hz), 5.38 (1H, s), 6.64 (1H, d, J=7.8 Hz), 6.96 (1H, t, J=7.8 Hz), 7.18—7.42 (11H, m), 7.70 (1H, d, J=7.8 Hz).

***N*-Methyl-*N*-phenyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(2-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (20a)** To a solution of **18** (1.0 g, 1.8 mmol) in CH_2Cl_2 (20 ml) was added TFA (20 ml) with ice cooling, and the mixture was stirred at the same temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic

solution was washed with saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in THF (20 ml). To this solution was added a solution of 2-tolyl isocyanate (0.24 g, 1.8 mmol) in THF (10 ml) and the mixture was stirred at room temperature for 15 min. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1). The eluate was concentrated under reduced pressure and the product was recrystallized from *n*-hexane–AcOEt–diethyl ether. The product was collected by filtration to give **20a** (0.6 g, 56%) as a white powder, mp 211—212 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s), 3.22 (3H, s), 3.23 (3H, s), 3.54 (1H, d, J=16.6 Hz), 3.78 (1H, dd, J=4.4, 17.1 Hz), 3.92 (1H, dd, J=4.4, 17.1 Hz), 4.36 (2H, s), 4.67 (1H, d, J=16.6 Hz), 5.99 (1H, br s), 6.59 (1H, s), 6.63 (1H, d, J=8.3 Hz), 6.96—7.03, 7.12—7.43 (15H, m), 7.54 (1H, d, J=7.8 Hz) 7.68 (1H, d, J=7.8 Hz); IR: 3364, 1672, 1596, 1540, 1498, 1450 cm^{-1}; *Anal.* Calcd for $C_{34}H_{35}N_5O_5 \cdot 0.25H_2O$: C, 68.27; H, 5.98; N, 11.71. Found: C, 68.46; H, 6.06; N, 11.68.

Compounds **20b** and **20c** were obtained by following an analogous procedure to that described for the preparation of **20a** from **18**; the yields, melting points and elemental analysis data are given in Table 6. The IR and ^{1}H-NMR data for these compounds are as follows:

N-Methyl-*N*-phenyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(4-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**20b**): **20b** was prepared by replacing 2-tolyl isocyanate with 4-tolyl isocyanate. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.22 (3H, s), 3.25 (3H, s), 3.54 (1H, d, J=16.6 Hz), 3.90 (2H, m), 4.38 (2H, s), 4.68 (1H, d, J=16.6 Hz), 6.00 (1H, br s), 6.62 (1H, d, J=8.3 Hz), 6.96—7.03, 7.17—7.44 (17H, m), 7.69 (1H, d, J=7.3 Hz); IR: 3364, 1676, 1598, 1546, 1498, 1456, 1434 cm^{-1}.

N-Methyl-*N*-phenyl-2-[2-[*N*-[2-[3-(3-trifluoromethylphenyl)ureido]-acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (**20c**): **20c** was prepared by replacing 2-tolyl isocyanate with 3-trifluoromethylphenyl isocyanate. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (3H, s), 3.26 (3H, s), 3.60 (1H, d, J=16.6 Hz), 3.95 (2H, s), 4.43 (2H, s), 4.66 (1H, d, J=16.6 Hz), 6.65 (1H, d, J=7.8 Hz), 6.99 (1H, t, J=7.3 Hz), 7.12—7.70 (17H, m), 8.14 (1H, br s); IR: 3368, 1672, 1598, 1562, 1498, 1450 cm^{-1}.

***N*-Methyl-*N*-phenyl-2-[2-[*N*-[2-[3-(3-ethylphenyl)ureido]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (20d)** To a solution of **18** (1.5 g, 2.7 mmol) in CH_2Cl_2 (20 ml) was added TFA (20 ml) with ice cooling, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic solution was washed with saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in THF (20 ml). To this solution was added CDI (0.49 g, 3.0 mmol) and the mixture was stirred at room temperature for 15 min. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic solution was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in toluene (50 ml). After addition of 3-ethylaniline (0.65 g, 5.4 mmol) to this solution, the mixture was stirred under reflux for 1 h. It was then concentrated under reduced pressure and the residue was partitioned between $CHCl_3$ and 1 N HCl. The layers were separated and the organic layer was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with $CHCl_3$—MeOH (50 : 1). The eluate was concentrated under reduced pressure and the product was recrystallized from CH_2Cl_2–diethyl ether. The product was collected by filtration to give **20d** (0.8 g, 49%) as an off-white powder, mp 186—188 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.3 Hz), 2.56 (2H, q, J=7.3 Hz), 3.20 (3H, s), 3.25 (3H, s), 3.56 (1H, d, J=16.2 Hz), 3.90 (2H, ABq, J=16.6 Hz), 4.39 (2H, s), 4.69 (1H, d, J=16.2 Hz), 6.63 (1H, d, J=8.3 Hz), 6.79 (1H, d, J=7.3 Hz), 6.96—7.43 (17H, m), 7.69 (1H, d, J=7.8 Hz); IR: 3372, 1678, 1614, 1596, 1554, 1498, 1454 cm^{-1}; *Anal.* Calcd for $C_{35}H_{37}N_5O_5 \cdot 0.25H_2O$: C, 68.67; H, 6.17; N, 11.44. Found: C, 68.63; H, 6.11; N, 11.36.

Compounds **20f** and **20g** were obtained by following an analogous procedure to that described for the preparation of **20d** from **18**; the yields, melting points and elemental analysis data are given in Table 6. The IR and ^{1}H-NMR data for these compounds are as follows:

N-Methyl-*N*-phenyl-2-[2-[*N*-[2-[3-(3-acetylphenyl)ureido]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetamide (**20f**): **20f** was prepared by replacing 3-ethylaniline with 3-aminoacetophenone. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 3.20 (3H, s), 3.28 (3H, s), 3.58 (1H, d, J=16.6 Hz), 3.98 (2H, d, J=4.9 Hz), 4.43 (2H, s), 4.68 (1H, d, J=16.6 Hz), 6.32 (1H, br s), 6.64 (1H, d, J=7.9 Hz), 6.99 (1H, t, J=7.8 Hz), 7.15—7.57 (14H, m), 7.70 (1H, d, J=7.8 Hz), 7.89 (1H, s), 8.12 (1H, br s); IR: 3368, 1678, 1596, 1554, 1498, 1432 cm^{-1}.

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)carbamoylmethyl]ureido]-phenyl]acetate (**20g**): **20g** was prepared by replacing 3-ethylaniline with methyl 2-(3-aminophenyl)acetate.[26] ^{1}H-NMR ($CDCl_3$) δ: 3.22 (3H, s), 3.27 (3H, s), 3.54 (2H, s), 3.55 (1H, d, J=16.1 Hz), 3.64 (3H, s), 3.92 (2H, d, J=4.9 Hz), 4.40 (2H, s), 4.68 (1H, d, J=16.1 Hz), 6.06 (1H, br s), 6.62 (1H, d, J=8.3 Hz), 6.86 (1H, d, J=7.9 Hz), 6.98 (1H, t, J=7.8 Hz), 7.12—7.52 (15H, m), 7.68 (1H, d, J=8.3 Hz); IR: 3352, 1736, 1670, 1596, 1554, 1498, 1432, 1396 cm^{-1}.

***N*-Methyl-*N*-phenyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-[3-(1-pyrrolidinyl)phenyl]ureido]acetyl]amino]phenoxy]acetamide (20e)** To a solution of **18** (1.1 g, 2.0 mmol) in CH_2Cl_2 (20 ml) was added TFA (10 ml) with ice cooling, and the mixture was stirred at the same temperature for 20 min. It was then concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic solution was washed with saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 ml). To a solution of **23** (0.32 g, 2.0 mmol) and pyridine (0.16 m, 2.0 mmol) in CH_2Cl_2 (20 ml) was added triphosgene (0.22 g, 0.74 mmol) under an N_2 atmosphere at −20 °C, and the mixture was stirred at the same temperature for 30 min. To the reaction mixture were added successively pyridine (0.16 ml, 2.0 mmol) and the solution of **19** in CH_2Cl_2 obtained above, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1). The eluate was concentrated under reduced pressure and the product was recrystallized from AcOEt–diethyl ether. The product was collected by filtration to give **20e** (0.85 g, 66%) as a white powder, mp 227—228 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.94—1.98 (4H, m), 3.23—3.26 (10H, m), 3.51 (1H, d, J=17.9 Hz), 3.82 (1H, dd, J=4.4, 17.1 Hz), 3.93 (1H, dd, J=4.4, 17.1 Hz), 4.37 (2H, s), 4.71 (1H, d, J=17.9 Hz), 5.98 (1H, br s), 6.22 (1H, d, J=6.3 Hz), 6.42 (1H, d, J=7.8 Hz), 6.62 (1H, d, J=8.3 Hz), 6.71 (1H, s), 6.87 (1H, s), 6.98 (1H, t, J=7.8 Hz), 7.06 (1H, t, J=8.3 Hz), 7.20—7.44 (11H, m), 7.69 (1H, d, J=7.8 Hz); IR: 3336, 1668, 1614, 1554, 1502, 1454, 1424, 1392, 1354 cm^{-1}; *Anal.* Calcd for $C_{37}H_{40}N_6O_5 \cdot 0.25H_2O$: C, 68.03; H, 6.25; N, 12.86. Found: C, 67.86; H, 6.18; N, 12.58.

(±)-*N*-Methyl-*N*-phenyl-2-[2-[*N*-[2-[3-[3-(1-hydroxyethyl)phenyl]-ureido]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]-acetamide (20h) To a solution of **20f** (0.6 g, 0.97 mmol) in EtOH (30 ml) was added $NaBH_4$ (0.045 g, 1.2 mmol) with ice cooling, and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into ice-water and the resulting mixture was concentrated under reduced pressure. The residue was extracted with AcOEt and the extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (25 : 1). The eluate was concentrated under reduced pressure to give **20h** (0.55 g, 91%) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6.8 Hz), 2.15 (1H, br s), 3.17 (3H, s), 3.25 (3H, s), 3.57 (1H, d, J=16.6 Hz), 3.89 (2H, br s), 4.39 (2H, s), 4.67—4.71 (2H, m), 6.26 (1H, br s), 6.63 (1H, d, J=8.3 Hz), 6.85 (1H, d, J=7.8 Hz), 6.97—7.44 (15H, m), 7.71 (1H, d, J=7.3 Hz), 7.87 (1H, br s); IR: 3368, 1670, 1614, 1598, 1554, 1498 cm^{-1}; *Anal.* Calcd for $C_{35}H_{37}N_5O_6 \cdot 0.75H_2O$: C, 65.97; H, 6.09; N, 10.99. Found: C, 66.12; H, 6.09; N, 10.83.

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)carbamoylmethyl]ureido]phenyl]acetic Acid (20i) To a solution of **20g** (1.0 g, 1.5 mmol) in THF (20 ml) was added 0.2 N NaOH (10 ml) and the mixture was stirred at room temperature for 3.5 h. It was then acidified with 1 N HCl and the resulting mixture was extracted with $CHCl_3$. The extract was washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was recrystallized from $CHCl_3$–diethyl ether. The product was collected by filtration to give **20i** (0.85 g, 89%) as a white powder, mp 189—190 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.24 (6H, s), 3.53 (2H, s), 3.56 (1H, d, J=16.6 Hz), 3.84 (2H, ABq, J=13.6 Hz), 4.38 (2H, s), 4.70 (1H, d, J=16.6 Hz), 6.34 (1H, br s), 6.62 (1H, d, J=8.3 Hz), 6.84 (1H, d, J=7.8 Hz), 6.93 (1H, s), 6.97 (1H, t, J=7.8 Hz), 7.15 (1H, t,

$J=7.8$ Hz), 7.19—7.42 (11H, m), 7.50 (1H, d, $J=7.8$ Hz), 7.67—7.70 (2H, m); IR: 3382, 1734, 1640, 1594, 1552, 1494, 1448, 1430, 1396 cm^{-1}; *Anal.* Calcd for $C_{35}H_{35}N_5O_7$: C, 65.92; H, 5.53; N, 10.98. Found: C, 66.23; H, 5.57; N, 10.84.

1-(3-Nitrophenyl)pyrrolidine (22) A mixture of **21** (3.5 g, 25 mmol) and 1,4-dibromobutane (6.5 g, 30 mmol) in DMF (50 ml) containing K_2CO_3 (13.8 g, 100 mmol) was stirred at 70 °C for 3 h. After addition of a further portion of 1,4-dibromobutane (6.5 g, 30 mmol), the reaction mixture was stirred at 70 °C for 6 h, then allowed to cool. Water was added, and the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with *n*-hexane–AcOEt (3 : 1). The eluate was concentrated under reduced pressure to give **22** (1.9 g, 40 %) as small orange needles, mp 81—82 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (4H, m), 3.34 (4H, t, $J=6.4$ Hz), 6.79 (1H, d, $J=7.8$ Hz), 7.30 (1H, t, $J=7.8$ Hz), 7.32 (1H, s), 7.46 (1H, d, $J=7.8$ Hz).

1-(3-Aminophenyl)pyrrolidine (23) **22** (1.5 g, 7.8 mmol) was hydrogenated in a mixture of MeOH (50 ml) and AcOEt (50 ml) over 5% Pd–C (0.3 g) at atmospheric pressure for 2.5 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was dried over $MgSO_4$. The solvent was removed under reduced pressure to give **23** (1.3 g, quant.) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.95—1.96 (4H, m), 3.22—3.24 (4H, m), 3.56 (2H, br s), 5.91 (1H, s), 6.03 (2H, d, $J=8.3$ Hz), 7.00 (1H, t, $J=8.3$ Hz).

Binding Assay to Human Gastrin/CCK-B and CCK-A Receptors A stable transformed Chinese hamster ovary (CHO) cell line was established as follows. The coding region of human gastrin/CCK-B receptor or human CCK-A receptor was subcloned to give an expression vector carrying a neomycin resistance gene. The expression plasmid DNA (2 μg) and Lipofectamine (15 μl) were incubated in 200 ml of Opti-MEM® (Gibco BRL) for 30 min at 37 °C, then 800 ml of Opti-MEM® was added. The mixture was transformed into CHO cells (4×10^4 cells) cultured on a 35-mm dish. After 6 h, the medium was replaced with Dulbecco's modified Eagle's medium containing 10% fetal bovine serum (DMEM). CHO cell clones were established by selection with 400 μg/ml geneticin (Gibco BRL). The CHO cells permanently expressing human gastrin/CCK-B receptors or human CCK-A receptors were grown to 90—100% confluence in 2-cm^2 dishes in the DMEM. The culture medium was removed and the cells were pre-incubated in the Earle's balanced salts (EBSS) binding buffer containing 10 mM HEPES (pH 7.4), 0.1% bovine serum albumin (BSA), 2 mM glutamine, and 0.22% $NaHCO_3$. Test compounds were dissolved in DMSO (final concentration 0.1%) and 25 pM [^{125}I]Tyr-gastrin or [^{125}I]BH-CCK-8 was added to the binding buffer, followed by incubation for 60 min. The incubation was terminated by removing the binding buffer and washing the cells with phosphate-buffered saline (PBS) 3 times. The cells were lysed in 1% Triton-X 100 and the lysate was transferred into a tube for radioactivity counting. Specific binding was defined as the difference between total binding and non-specific binding in the presence of 1 μM human gastrin-17 or CCK-8, respectively.

Determination of Gastric Acid Secretion of Anesthetized Rats Male Sprague-Dawley rats weighing 180—200 g were used in all experiments. Rats were fasted for 18 h, but allowed free access to tap water. Under urethane anesthesia (1.25 g/kg, i.p.), tracheotomy was performed and the esophagus was ligated. The abdomen was incised, and the stomach and duodenum were exposed. The pylorus was ligated and a 1 cm diameter double lumen plastic gastric cannula was inserted into the forestomach and secured. The gastric lumen was washed once with 10 ml of isotonic saline under gravity drainage and then once every 10 min with 5 ml of the saline under a slight positive pressure of air. Each effluent was titrated to pH 7.0 with 0.02 N NaOH. After a 30 min basal period, acid secretion was stimulated by intravenous infusion of pentagastrin at 16 μg/kg/h for 120 min. Compounds were administered intravenously or intraduodenally 10 or 30 min prior to the onset of secretagogue administration, respectively. Control animals received the vehicle alone.

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