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

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In order to improve the biological characteristics of DA-3934 (5), a novel gastrin/cholecystokinin (CCK)-B receptor antagonist, phenoxyacetic acid derivatives replacing the *N*-methyl-*N*-phenylcarbamoylmethyl moiety of 5 with various alkyl chains have been synthesized and their biological activity evaluated. The relationship between the structure of these compounds and their human gastrin receptor binding affinity showed that there should be the optimal size among the various *N*-alkyl chains. Also a significant increase in the receptor binding affinity was achieved by several compounds. Among those compounds, 2-[3-[3-[*N*-cyclohexylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic acid (22c) and (±)-2-[3-[3-[*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylpentyl)carbamoylmethyl]ureido]phenyl]acetic acid (22h) exhibited high affinity for human gastrin receptors and were also more potent inhibitors in a pentagastrin-induced gastric acid secretion model than the parent compound, 5. The ED_{50} values of these compounds when administered intraduodenally to rats were 0.12 and 0.63 mg/kg, respectively.

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

Cholecystokinin (CCK) was first isolated from the gastrointestinal tract as an intestinal 33-amino acid peptide hormone that stimulates the secretion of pancreatic amylase and other enzymes. CCK was subsequently also identified in the central nervous system (CNS), where it probably acts as a neurotransmitter or neuromodulator. CCK receptors have been divided into CCK-A (alimentary) and CCK-B (brain) which mediate the diverse biological functions of CCK. CCK-A receptors are primarily located in the gut where they mediate pancreatic enzyme secretion, gallbladder contraction, gastric emptying, and intestinal motility,[1] but they are also found in discrete regions of brain[2] where they are believed to play a significant role in neuropsychiatric disorders.[3] CCK-B receptors are widely distributed in the CNS and studies in animals and humans using CCK-B receptor antagonists have suggested that anxiety, panic attacks, analgesia, and satiety may be modulated through CCK-B receptors.[4]

Gastrin is the first gastrointestinal hormone[5] to be identified and it plays a key role in the regulation of gastric acid secretion. The binding characteristics of high affinity ligands for brain CCK-B and stomach gastrin receptors have been demonstrated to be very similar.[6] Therefore, gastrin and CCK-B receptors are described as gastrin/CCK-B receptors, and studies in various animal models have suggested the potential usefulness of these receptor antagonists for treating ulcerogenic diseases, CNS disorders, and certain tumors.[7] It has been reported that the long-term treatment of gastric ulcers with histamine H_2-receptor antagonists or proton pump inhibitors causes hypergastrinemia and hyperplasia of the oxyntic mucosa, resulting in the gastric acid rebound phenomenon.[8] It is hoped that gastrin receptor antagonists will have a reduced propensity to produce these side-effects because of their completely different mode of action. Hence, they are expected to have clear clinical advantages over currently used drugs.

In recent years, a sustained research effort has been made to discover potent and selective antagonists of gastrin/CCK-B receptors. The benzodiazepine series of antagonists, exemplified by L-365,260 (**1**), has been particularly well documented.[9] Various modifications of the structure of L-365,260 have been carried out, and it has been reported that replacing the *N*1-methyl group of L-365,260 with an alkyl chain, such as isobutyl, cyclopropylmethyl and *n*-propyl, generally leads to improved affinity for CCK-B receptors.[10]

Another type of analogue at the *N*1-position of L-365,260 is replaced by a novel series of *N*1-aroylmethyl compounds. YM022 (**2**) is the leading compound of this series and one of the most potent gastrin/CCK-B receptor antagonists.[11] YM022 also suppresses gastric acid secretion in pylorus-ligated rats in a dose-dependent manner when administered orally, and its potency in this animal model is comparable with that of famotidine, an H_2-receptor antagonist.[12]

In a previous paper, we reported a series of phenoxyacetic acid derivatives which have potent gastrin receptor antagonistic activity.[13] In particular, DA-3934 (**5**), possessing an acid function in the ureido-phenyl ring, showed high affinity for human gastrin receptors, similar to that of YM022, and good selectivity for gastrin/CCK-B receptors over CCK-A receptors.[13b] However, the anti-gastric acid secretory activity of DA-3934 in rats was weaker than that of YM022.

With the objective of discovering new antagonists which retain the receptor binding affinity of DA-3934 and also inhibit acid secretion more potently than DA-3934, we reconsidered our molecular modeling studies which had shown that the *N*-methyl-*N*-phenylcarbamoylmethyl moiety of DA-3934 probably corresponds to the *N*1-aroylmethyl moiety of YM022.[13a] As described above, improvements in potency as gastrin/CCK-B receptor antagonists could be achieved by introducing a hydrophobic group at the *N*1-position of the benzodiazepine gastrin receptor antagonists. Hence, we tried to increase the receptor antagonist potency of phenoxyacetic

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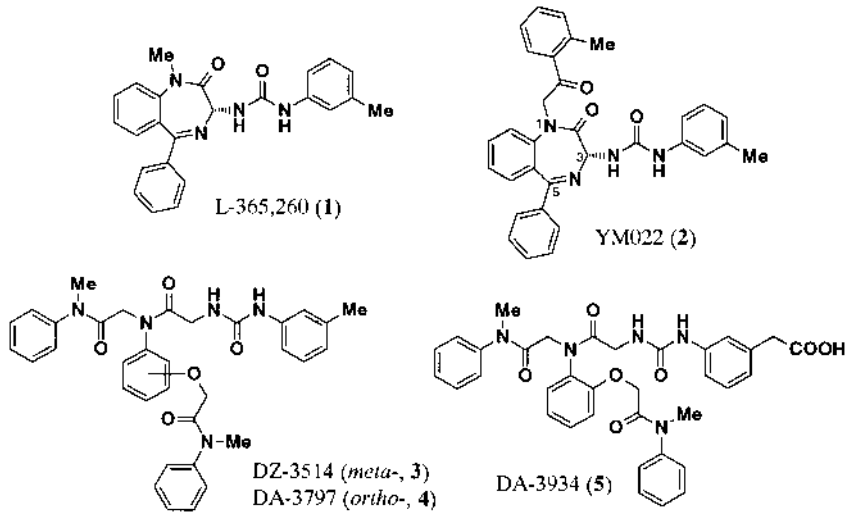


Fig. 1

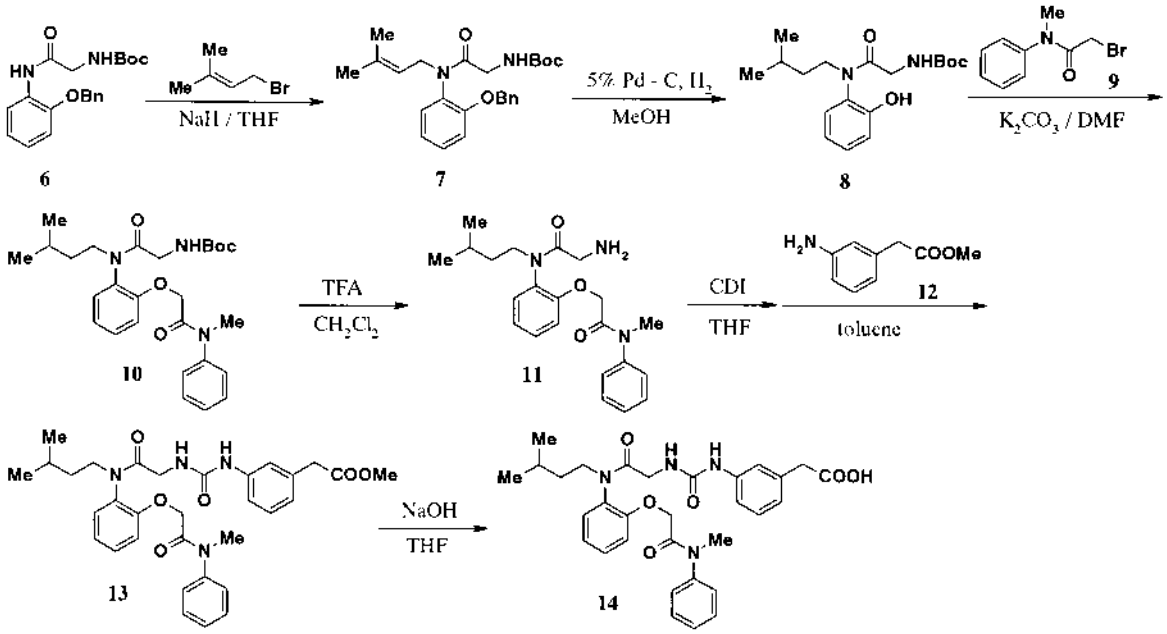


Chart 1

acid derivatives by replacing their *N*-methyl-*N*-phenylcarbamoylmethyl group with various hydrophobic groups. We report here the synthesis of a new series of phenoxyacetic acid amide derivatives related to DA-3934 with improved activity, especially *in vivo*.

Synthesis

Initially we used a similar procedure to that used in the preparation of DA-3934 for the introduction of the *N*-alkyl substituent,[13b] *e.g.* alkylation of the amide[13a] **6** with prenyl bromide. Hydrogenation of the olefin moiety of **7** with concomitant cleavage of the benzyl group afforded the phenol **8**. After condensation of **8** with bromoacetanilide[14] **9** and removal of the protecting group, the resulting amine **11** was condensed with methyl aminophenylacetate[15] **12** using *N*,*N*′-carbonyldiimidazole (CDI)-promoted coupling to give the ester **13**. Finally, hydrolysis of **13** afforded the target compound **14** (Chart 1).

Compound **14** was found to retain the *in vitro* potency of DA-3934 (Table 2). In fact, compound **14** showed greater affinity for gastrin receptors than DA-3934, and also had increased affinity for CCK-A receptors compared with DA-3934. This result encouraged us to proceed with further modifications of the *N*-alkyl substituent.

The synthetic approach used for the preparation of compound **14** turned out not to be generally applicable and so two alternative routes were devised which are shown in Charts 2 and 3.

The first alternative method involves alkylation of the aniline derivative **17** with alkyl bromides. The compounds which were synthesized by this method, **22a**—**m**, are shown in Chart 2. Amidation of 2-nitrophenoxyacetic acid (**15**) with *N*-methylaniline easily provided the nitro-amide **16** which was reduced to give the aniline **17**. Alkylation of **17** with a variety of alkyl bromides in the presence of K_2CO_3 afforded *N*-alkylanilines **18a**—**l**. Acylation of **18a**—**l** with *N*-ph-

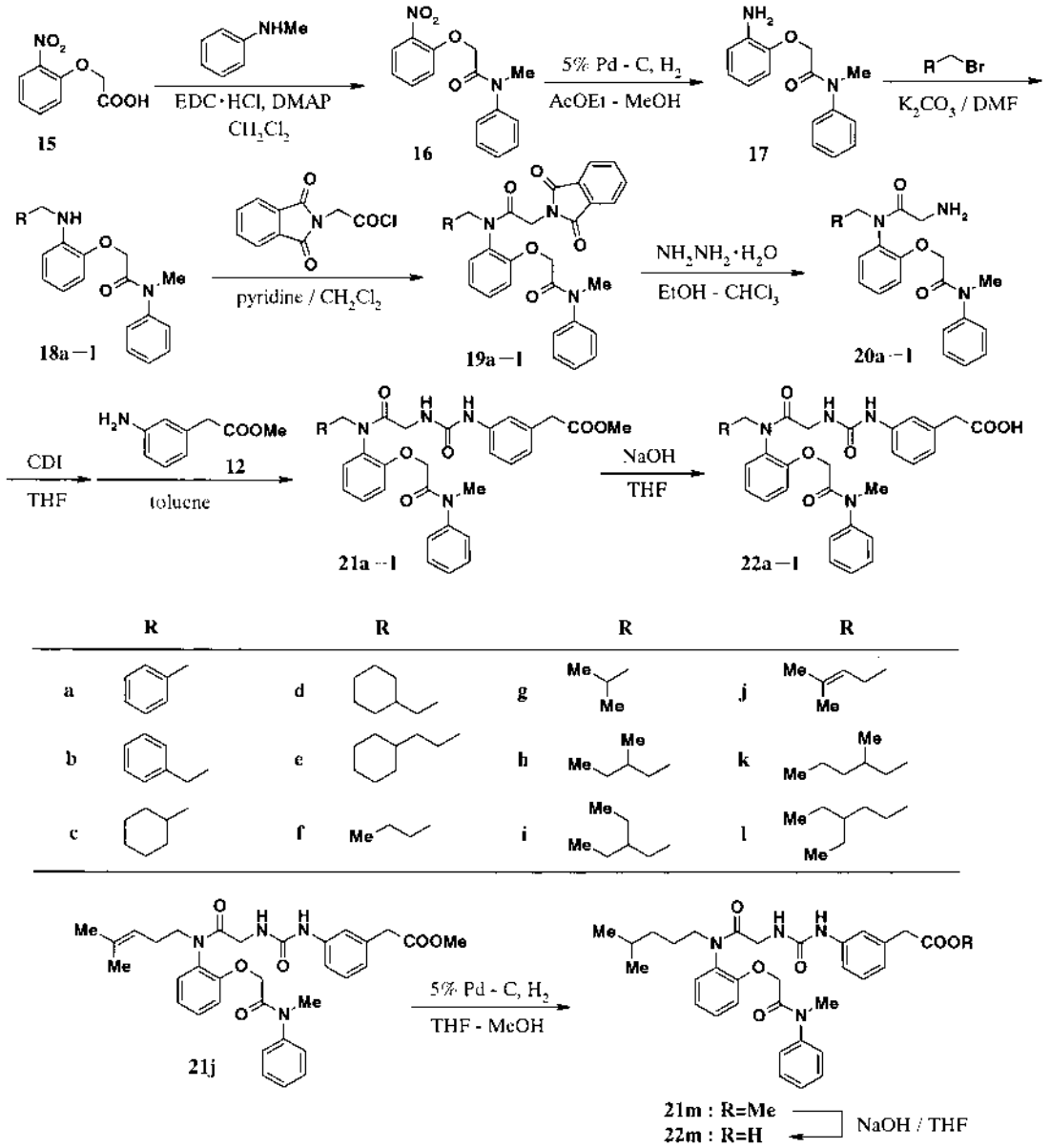


Chart 2

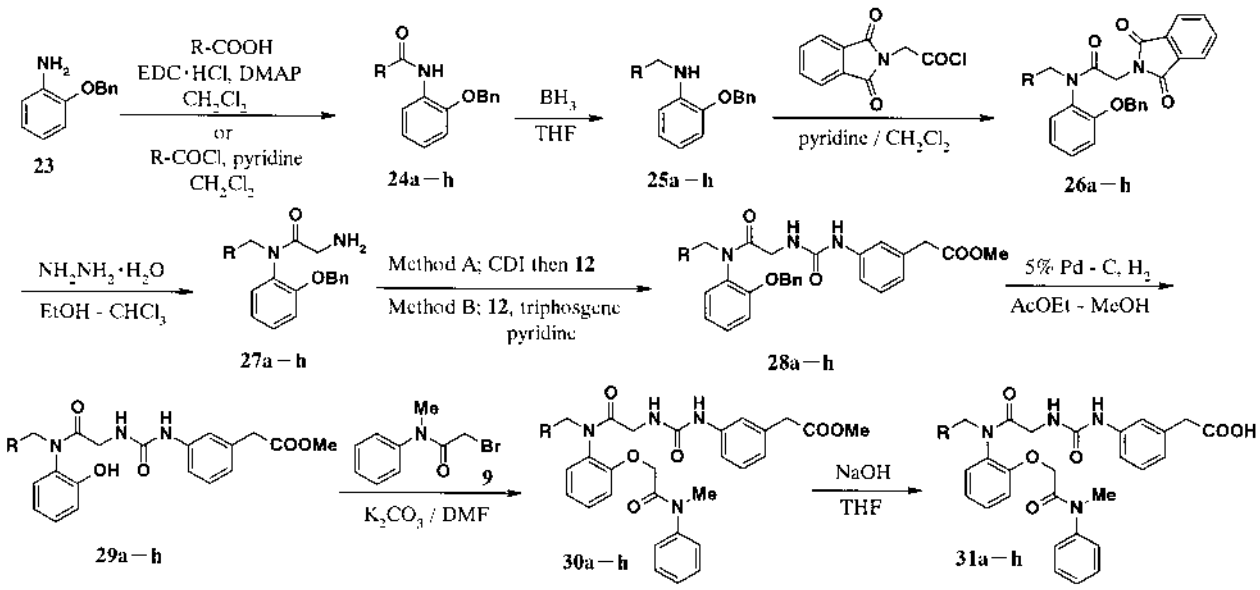
thaloylglycyl chloride, followed by deprotection to remove the phthaloyl moiety, gave the amines **20a**—**l**. Transformation of **20a**—**l** to **22a**—**m** was carried out using essentially the same procedure as for **11** to **14** (Chart 1). Compound **21m** was prepared from **21j** by catalytic hydrogenation.

The second method starts from acylation of benzyloxyaniline (**23**) (Chart 3). Coupling of the aniline[16] **23** with a variety of carboxylic acids or acid chlorides afforded the amides **24a**—**h**, which were reduced by BH_3–tetrahydrofuran (THF) complex to give *N*-alkylanilines **25a**—**h**. Conversion of **25a**—**h** to amines **27a**—**h** is essentially the same as the procedure described for the preparation of **20a**—**l** (Chart 2). Condensation of **27a**—**h** with **12** using CDI or triphosgene-promoted coupling provided the esters **28a**—**h**. Cleavage of the benzyl moiety of **28a**—**h** by catalytic hydrogenation gave the phenol derivatives **29a**—**h**. Condensation of **29a**—**h** with **9** afforded the ester derivatives **30a**—**h**, which were hydrolyzed to furnish the target compounds **31a**—**h**.

The previously reported compounds, DZ-3514 (**3**) and DA-3797 (**4**), which differ principally in the substitution pattern of the phenyl ring, showed similar profiles of biological activity.[13a] Therefore, we tried to synthesize new *meta*-substituted phenoxyacetic acid derivatives **39a**—**c** which were analogues of DZ-3514 (Chart 4). Synthesis of **39a**—**c** was carried out by using the same route as described for the preparation of **22a**—**m**, but starting from the appropriate *meta*-substituted precursor. Thus, the intermediate **33** was prepared from *m*-nitrophenol **32** by condensation with bromide **9**.

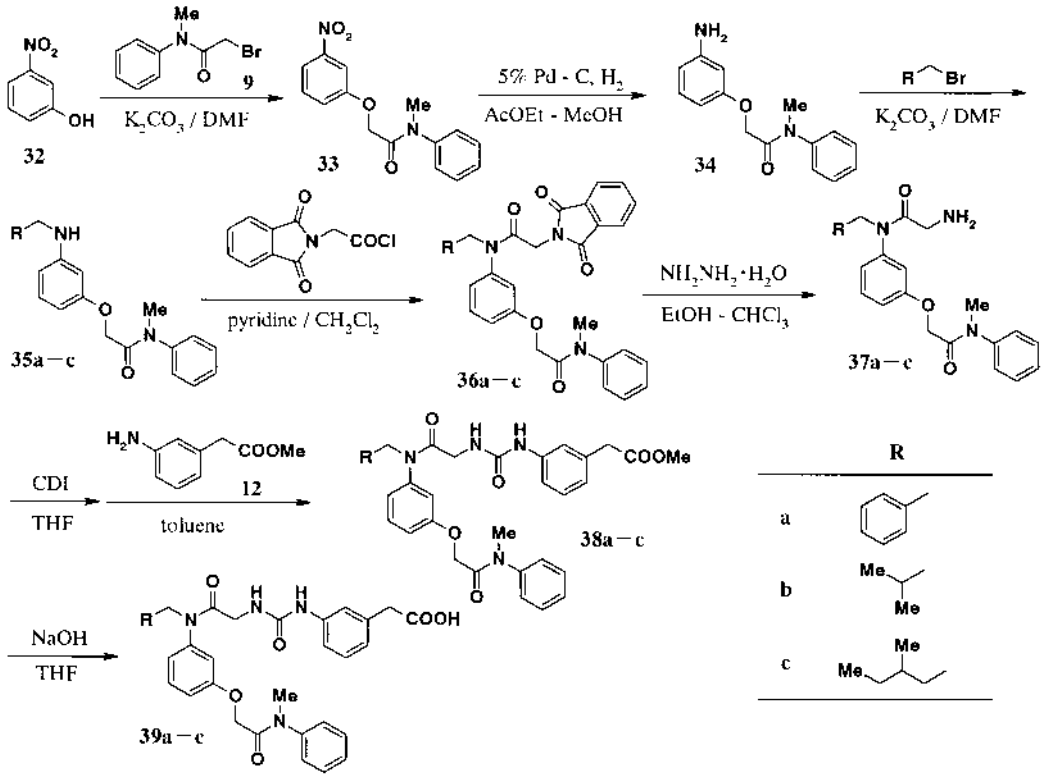
Pharmacological Evaluation and Discussion

Receptor binding assays of the newly synthesized compounds were used to investigate their affinities for gastrin and CCK-A receptors.[17] The results are summarized in Tables 1—3. For the primary *in vivo* study of compounds which showed high affinity for human gastrin receptors, the inhibition of pentagastrin-induced gastric acid secretion in anesthetized rats was measured. Test compounds were adminis-



	R		R		R
a		d		g	
b		e		h	
c		f			

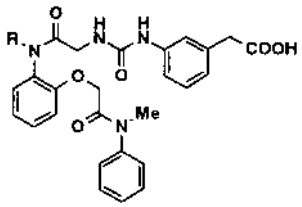
Chart 3

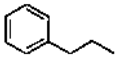
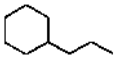
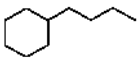
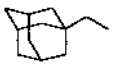


R	
a	
b	
c	

Chart 4

Table 1. Receptor Binding Affinity and Inhibitory Effect of Gastric Acid Secretion of *o*-Phenoxyacetanilide Derivatives **22a**—**e** and **31a**—**e**



Compd.	R	IC_{50} (nM)		Ratio (CCK-A/gastrin)	*In vivo* screening (% inhibition of H^+ secretion in rats at 1 mg/kg i.d.)
		Gastrin[a)]	CCK-A[b)]		
22a		0.10	264	2640	
22b		0.72	N.T.	—	
22c		0.06	61	1017	73
22d		0.42	307	731	
22e		0.29	60	207	
31a		0.25	1203	4812	
31b		0.05	358	7160	−59
31c		0.06	119	1983	53
31d		0.09	78	667	
31e		0.52	652	1254	
L-356,260 (**1**)		5.3	>2000	>577	
YM022 (**2**)		0.33	20	61	36
DZ-3514 (**3**)		0.8	178	223	
DA-3797 (**4**)		0.9	210	233	
DA-3934 (**5**)		0.42	877	2088	24

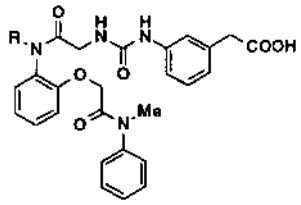
a) IC_{50} (nM) of [^{125}I]gastrin binding to human gastrin receptors. *b*) IC_{50} (nM) of [^{125}I]CCK-8 binding to human CCK-S receptors. N.T.: Not tested.

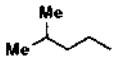
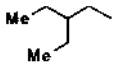
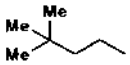
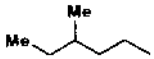
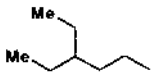
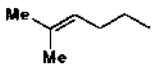
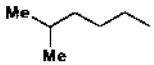
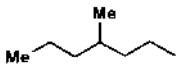
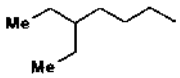
tered intraduodenally at 1 mg/kg, and the results are shown in Tables 1 and 2. ED_{50} values were also determined for compounds which significantly inhibited gastric acid secretion at a dose of 1 mg/kg (Table 4).

The biological activities of the compounds containing various rings in the *N*-alkyl substituents are shown in Table 1. Introduction of a phenyl or cyclic alkyl group into the *N*-alkyl substituent was found to increase the affinity for gastrin receptors. The benzyl-type compound (**22a**) showed greater affinity for both gastrin and CCK-A receptors than DA-3934 (**5**). In the phenethyl derivative **22b**, the distance between the ring and the *N*-atom is increased, which apparently reduces the affinity for human gastrin receptors, because the IC_{50} value was some 2-fold less than that of compound **5**. Replacement of the phenyl ring with a cyclohexyl ring (**22c**) increased the binding affinity for both human gastrin and CCK-A receptors, with IC_{50} values of 0.06 and 61 nM, respectively. The activity was found to depend on the length of the alkyl chain between the ring and the *N*-atom, and the order of potency was methylene (**22c**)>propylene (**22e**)≧ethylene (**22d**). These results suggest that a methylene is the optimal size for affinity for human gastrin receptors. It is assumed that these alkyl moieties interact with the receptor by occupying a lipophilic pocket of finite size.

The optimal distance between the ring and the *N*-atom having been fixed, the effects of changing the ring size were explored. The IC_{50} value of compound **31a**, which has a cyclopropyl ring, was similar to that of compound **5**. Com-

Table 2. Receptor Binding Affinity and Inhibitory Effect on Fastric Acid Secretion of *o*-Phenoxyacetanilide Derivatives **14**, **22f**—**m** and **31f**—**h**



Compd.	R	IC_{50} (nM)		Ratio (CCK-A/gastrin)	*In vivo* screening (% inhibition of H^+ secretion in rats at 1 mg/kg i.d.)
		Gastrin[a)]	CCK-A[b)]		
22g		0.12	337	2808	
31g		0.33	908	2752	
14		0.11	466	4236	13
22f		0.12	732	6100	
31f		0.10	64	640	63
31h		0.13	158	1215	
22h		0.06	172	2867	62
22i		0.18	276	1533	
22j		0.07	113	1614	24
22m		0.05	118	2360	25
22k		0.12	396	3300	
22l		0.35	101	289	

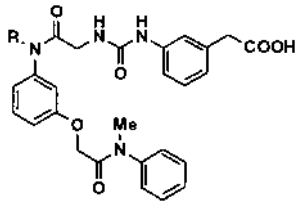
a) IC_{50} (nM) of [^{125}I]gastrin binding to human gastrin receptors. *b*) IC_{50} (nM) of [^{125}I]CCK-8 binding to human CCK-A receptors.

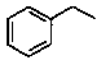
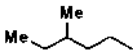
pounds with larger rings, cyclobutyl (**31b**), cyclopentyl (**31c**), and cycloheptyl (**31d**), exhibited significantly greater affinity for human gastrin receptors than compound **31a**, and their IC_{50} values were very similar to that of compound **22c**, which has a cyclohexyl ring (Table 1). The potency of compound **31e**, possessing a much bulkier adamantyl group, was significantly reduced. Therefore, it appears that the ring size for high affinity for human gastrin receptors should be in the range cyclobutyl to cycloheptyl.

A comparison of compounds having straight and branched chains is shown in Table 2. Compounds having a chain length in the range of three to six carbon atoms were synthesized. As noted above, it is proposed that the lipophilic pocket for the alkyl chain is of limited size. Hence, it was expected that compounds possessing either truncated or elongated side-chains would show reduced affinity for gastrin receptors.

Among the compounds substituted with alkyl groups having a chain length of three carbon atoms, introduction of the 2-methylpropyl (**22g**) and 2,2-dimethylpropyl (**31g**) groups resulted in compounds with activities which were higher than that of compound **5**. Compound **22g** showed 3-fold greater affinity for both human gastrin and CCK-A receptors than compound **31g**. This difference in potency may be due to a

Table 3. Receptor Binding Affinity of *m*-Phenoxyacetanilide Derivatives **39a**—**c**



Compd.	R	IC_{50} (nM)		Ratio (CCK-A/gastrin)
		Gastrin[a)]	CCK-A[b)]	
39a		0.33	337	1021
39b		9.9	615	62
39c		1.0	N.T.	—

a) IC_{50} (nM) of [^{125}I]gastrin binding to human gastrin receptors. *b*) IC_{50} (nM) of [^{125}I]CCK-8 binding to human CCK-A receptors. N.T.: Not tested.

positive steric interaction.

Among the compounds with a four carbon atom alkyl chain, *i.e.*, having 3-methylbutyl (**14**), *n*-butyl (**22f**), 2-ethylbutyl (**31f**), and 3,3-dimethylbutyl (**31h**) groups, there was little difference in affinity for gastrin receptors. The IC_{50} values ranged from 0.10 to 0.13 nM, and therefore, it was concluded that the affinity for human gastrin receptors is little affected by alkyl chain branching.

In general, compounds substituted with five carbon atom alkyl chains exhibited high affinity for human gastrin receptors (Table 2). The IC_{50} values of compounds possessing 3-methylpentyl (**22h**), 3-ethylpentyl (**22i**), 4-methyl-3-pentenyl (**22j**), and 4-methylpentyl (**22m**) groups were 0.06, 0.18, 0.07, and 0.05 nM, respectively. Comparing **22j** and **22m** indicates that introduction of a double bond into the side-chain does not improve the affinity for human gastrin receptors. It can also be deduced that the affinity for human gastrin receptors is largely independent of branch position by comparing compounds **22h** and **22m**. The activity of compound **22i** was somewhat reduced compared with the other three compounds; it also has a more sterically demanding alkyl group.

The activities of the compounds having six carbon atom side-chains (**22k**, **22l**) were reduced compared with compounds substituted with a five carbon atom alkyl chain (Table 2). It was, therefore, concluded that the optimal length of the alkyl chain is five atoms.

In Table 3, the receptor binding affinities of the *m*-phenoxyacetic acid derivatives (**39a**—**c**) are reported. These compounds showed 3- to 80-fold less potent activity compared with the corresponding *o*-phenoxyacetic acid derivatives, in contrast to DZ-3514 (**3**) and DA-3797 (**4**), which showed similar binding affinities for both gastrin and CCK-A receptors.[13a)] It seems likely that the conformation required for high affinity for human gastrin receptors is changed by replacing the *N*-methyl-*N*-phenylcarbamoylmethyl group with an alkyl group in the *m*-phenoxyacetic acid series.

With regard to CCK-A receptors, compounds **22c** and **22e** exhibited significantly greater affinity for these receptors than most of the other compounds shown in Table 1. Compound **22e** showed relatively weak affinity for gastrin receptors, similar to that of compound **5**, and thus the selectivity of **22e** for gastrin receptors over CCK-A receptors was reduced. In a previous paper,[13b)] we reported that high selectivity for gastrin receptors over CCK-A receptors could be achieved by introducing oxygenated substituents into the ureido-phenyl ring. However, it was found that compounds with hydrophobic side-chains replacing the *N*-methyl-*N*-phenylcarbamoylmethyl group showed somewhat greater affinity for CCK-A receptors. Therefore, it is apparent that selectivity is affected not only by introducing oxygenated function into the ureido-phenyl ring but also by modifying the hydrophobic *N*-alkyl substituents. The relationship between ring size and affinity for CCK-A receptors was similar to that for gastrin receptors; compounds possessing either a small ring, like cyclopropyl (**31a**), or a sterically bulky ring, like adamantyl (**31e**), exhibited reduced affinity (Table 1).

Among the compounds having straight and branched chains, compound **31f** (2-ethylbutyl) showed relatively greater affinity for CCK-A receptors than the other compounds in Table 2. It is noteworthy that compound **31f** exhibited similar binding affinity to compound **22c** (cyclohexylmethyl) at both receptors. It is possible that these two compounds adopt similar conformations at the receptor and, therefore, exhibit similar potency. On the other hand, compound **22f**, with a straight chain *n*-butyl group, exhibited significantly weaker affinity for CCK-A receptors.

The acid secretion-inhibiting activity of compounds **22c**, **31b** and **31c**, which exhibited high affinity for gastrin receptors among the compounds containing various rings in the *N*-alkyl substituents, was evaluated *in vivo* at a dose of 1 mg/kg. Contrary to our expectations, compound **31b** did not inhibit gastric acid secretion when administered intraduodenally but rather stimulated it. Although it was not clear whether the stimulating activity of compound **31b** might be due to its agonist activity or to other factors, we concluded that compound **31b** would not serve our purpose. On the other hand, compounds **22c** and **31c** potently inhibited acid secretion and both were superior to DA-3934 (**5**) while compound **22c** exhibited more potent activity than **31c** *in vivo*. Among the compounds in this new series of phenoxyacetic acid derivatives, compound **22c** is a promising candidate for further development, although lower gastrin/CCK-A selectivity was observed than for compound **5**.

The anti-secretory activity of the five compounds which showed highest affinity for human gastrin receptors among the compounds having straight and branched chains, *i.e.*, compounds **14**, **22h**, **22j**, **22m**, and **31f**, was evaluated. It was found that compounds **31f** (2-ethylbutyl) and **22h** (3-methylpentyl) inhibited acid secretion more potently than compound **5** (Table 2). The acid secretion-inhibiting activity of the other three compounds was similar to, or less than, that of compound **5**. The affinity for human gastrin receptors and the acid secretion-inhibiting activity of **31f** and **22h** are similar, but compound **22h** shows higher selectivity for human gastrin receptors over CCK-A receptors than compound **31f**. Therefore, compound **22h** is the most promising candidate for further development in this series.

The ED_{50} values for the *in vivo* gastric acid secretion in-

Table 4. Anti-secretory Activity of Gastrin/CCK-B Antagonists. Inhibition of Pentagastrin Induced Gastric Acid Secretion in Rats

Compd.	IC_{50} (nM)	ED_{50} values and their 95% confidence limits	
	Gastrin	Pentagastrin-stimulated acid secretion (16 μg/kg/h)	
		i.d. route (mg/kg)	i.v. route (mg/kg)
Da-3934	0.42	5.2 (3.2—8.0)	12.5 (8.0—19.8)
YM022	0.33	1.9 (1.1—3.6)	1.3 (0.6—2.3)
22c	0.06	0.12 (0.04—0.24)	6.0 (3.0—8.0)
22h	0.06	0.63 (0.36—1.03)	N.T.

N.T.; Not tested.

hibitory activity of compounds **22c** and **22h** are reported in Table 4. Compound **22c** inhibited gastric acid secretion induced by infusion of 16 μg/kg/h pentagastrin in a dose-dependent manner when administered either intraduodenally or intravenously; the ED_{50} values were 0.12 mg/kg (i.d.) and 6.0 mg/kg (i.v.), respectively. It is noted that the *in vivo* activity of compound **22c** was also significantly greater than that of parent compound **5**. Compound **22c** exhibited *ca*. 5-fold less potency than YM022 when administered intravenously but *ca*. 15-fold greater potency when administered intraduodenally. Compound **22c** may have shown reduced activity compared with YM022 when administered intravenously because of differences in the rates of metabolism and/or excretion.

Compound **22h** also inhibited pentagastrin-induced gastric acid secretion more potently than compound **5**, but was *ca*. 5-fold less potent than compound **22c**, despite showing similar activity *in vitro*, probably due to a difference in absorption rate. Compound **22h** is a racemic compound and, therefore, it will be necessary to synthesize both enantiomers in order to clarify their relative contributions to the pharmacological activity.

Compounds **22c** and **22h** may show greater *in vivo* activity than parent compound **5** because of their increased affinity for human gastrin receptors. Furthermore, replacement of the *N*-methyl-*N*-phenylcarbamoylmethyl group by an alkyl group reduces the hydrophobicity of the amide moiety, which may also improve absorption. Further work to modify the synthetic route so that both enantiomers of compound **22h** can be prepared and to investigate the pharmacokinetics of compound **22c** is in progress.

Conclusions

We have prepared a new series of phenoxyacetic acid derivatives which show enhanced *in vivo* acid secretion inhibiting activity compared to parent compound DA-3934 (**5**). Replacing the *N*-methyl-*N*-phenylcarbamoylmethyl group of compound **5** with various alkyl groups led to the discovery of compounds with increased affinity for human gastrin receptors and, with a few notable exceptions, also for CCK-A receptors. Compounds **22c** and **22h** exhibited potent activities *in vitro* and also inhibited pentagastrin-induced gastric acid secretion in rats. The anti-secretory activity of both compounds was greater than that of parent compound **5** and compared favorably with that of YM022.

Experimental

All chemicals and solvents used for synthesis were reagent-grade products and were used without additional purification. The following solvent and reagent names are abbreviated as follows: ethyl acetate (AcOEt), 4-dimethylaminopyridine (DMAP), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), trifluroacetic acid (TFA). Melting points were measured 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. Elemental analyses were performed using a Perkin-Elmer Model 240C elemental analyzer. Merck Kieselgel 60 (70—230 mesh) was used for column chromatography.

***N*-(2-Benzyloxyphenyl)-*N*-(3-methyl-2-butenyl)-2-(*N*-*tert*-butoxycarbonylamino)acetamide (7)** To a solution of **6** (17.8 g, 50 mmol) in THF (100 ml) was added NaH (60% in oil, 2.4 g, 60 mmol), and the mixture was stirred at 55 °C for 1.5 h. After adding a solution of 3-methyl-2-butenyl bromide (8.9 g, 60 mmol) in THF (20 ml) to the reaction mixture with ice cooling, the resulting mixture was stirred overnight at room temperature. To the reaction mixture was added ice-water, and the 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 **7** (18.4 g, 87%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s), 1.42 (3H, s), 1.61 (3H, s), 3.50 (1H, dd, J=3.9, 17.1 Hz), 3.70 (1H, dd, J=4.4, 17.1 Hz), 4.01 (1H, dd, J=7.8, 14.6 Hz), 4.53 (1H, dd, J=6.9, 14.6 Hz), 5.09 (2H, ABq, J=12.2 Hz), 5.20 (1H, t, J=7.8 Hz), 5.45 (1H, br s), 6.95 (1H, t, J=7.8 Hz), 7.00 (1H, d, J=8.3 Hz), 7.10 (1H, dd, J=2.0, 7.3 Hz), 7.27—7.37 (6H, m).

***N*-(2-Hydroxyphenyl)-*N*-(3-methylbutyl)-2-(*N*-*tert*-butoxycarbonylamino)acetamide (8)** **7** (18.3 g, 43.4 mmol) was hydrogenated in MeOH (400 ml) over 5% Pd–C (4 g) at atmospheric pressure for 3 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 AcOEt. The resulting powder was collected by filtration to give **8** (13.1 g 90%) as a white powder, mp 105—107 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.70—0.90 (6H, m), 1.39—1.42 (2H, m), 1.42 (9H, s), 1.55—1.59 (1H, m), 3.46 (1H, dd, J=5.3, 17.1 Hz), 3.58—3.76 (3H, m), 5.41 (1H, br s), 6.93 (1H, t, J=7.3 Hz), 7.00 (1H, d, J=7.3 Hz), 7.04 (1H, d, J=7.3 Hz), 7.23 (1H, t, J=7.3 Hz).

***N*-Methyl-*N*-phenyl-2-[2-[*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]-*N*-(3-methylbutyl)amino]phenoxy]acetamide (10)** A mixture of **8** (1.0 g, 3.0 mmol), **9** (0.9 g, 4.0 mmol) and K_2CO_3 (0.7 g, 5.0 mmol) in DMF (30 ml) was stirred at 70 °C for 3.5 h. To the reaction mixture was added 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 and the residue was chromatographed on silica-gel with *n*-hexane–AcOEt (1 : 1). The eluate was concentrated under reduced pressure to give **10** (1.1 g, 76%) as a colorless syrup. ^{1}H-NMR ($CDCl_3$) δ: 0.86—0.89 (6H, m), 1.38 (11H, br s), 1.54—1.61 (1H, m), 3.30 (3H, s), 3.32—3.37 (1H, m), 3.40 (1H, d, J=17.6 Hz), 3.66 (1H, dd, J=5.4, 17.6 Hz), 3.99—4.03 (1H, m), 4.43 (2H, s), 5.42 (1H, br s), 6.69 (1H, d, J=7.3 Hz), 6.95 (1H, t, J=7.3 Hz), 7.09 (1H, d, J=7.4 Hz), 7.26—7.28, 7.41—7.50 (6H, m).

***N*-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(3-methylbutyl)-amino]phenoxy]acetamide (11)** To a solution of **10** (1.0 g, 2.1 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 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 **11** (0.8 g, 99%) as a yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.89 (6H, m), 1.33—1.40 (2H, m), 1.53—1.60 (1H, m), 1.89 (2H, br s), 3.04 (1H, d, J=17.1 Hz), 3.17 (1H, d, J=17.1 Hz), 3.30 (3H, s), 3.33—3.40 (1H, m), 3.92—3.99 (1H, m), 4.44 (2H, s), 6.70 (1H, d, J=8.3 Hz), 6.96 (1H, t, J=7.8 Hz), 7.08 (1H, dd, J=1.5, 7.8 Hz), 7.25—7.30, 7.40—7.51 (6H, m).

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylbutyl)carbamoylmethyl]ureido]phenyl]acetate (13) To a solution of **11** (0.7 g, 1.8 mmol) in THF (20 ml) was added CDI (0.37 g, 2.2 mmol) and the mixture was stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in toluene (50 ml). After adding **12** (0.7 g, 3.6 mmol) to this solution, the resulting mixture was stirred under reflux for 1 h. The reaction

Table 5. Physicochemical Data for Phenoxyacetanilide Derivatives **14**, and **22a**—**m**

Compd.	Yield[a] (%)	mp (°C)	Recryst.[b] solv.	Formula	Analysis (%)					
					Calcd			Found		
					C	H	N	C	H	N
14	89	147—149	C–A–E	$C_{31}H_{36}N_4O_6$	66.41	6.47	9.99	66.18	6.30	9.79
22a	86	127—128	A–E	$C_{33}H_{32}N_4O_6 \cdot 0.75H_2O$	66.71	5.68	9.43	66.56	5.58	9.61
22b	86	152—154	C–A–E	$C_{34}H_{34}N_4O_6 \cdot 0.25H_2O$	68.16	5.80	9.35	68.05	5.66	9.53
22c	86	109—110	H–A–E	$C_{33}H_{38}N_4O_6 \cdot 0.25H_2O$	67.05	6.56	9.48	67.04	6.52	9.19
22d	88	185—186	C–E	$C_{34}H_{40}N_4O_6 \cdot 0.25H_2O$	67.48	6.74	9.26	67.68	6.69	9.01
22e	89	195—196	A–E	$C_{35}H_{42}N_4O_6 \cdot 0.25H_2O$	67.89	6.92	9.05	67.78	6.74	9.01
22f	81	139—141	H–A	$C_{30}H_{34}N_4O_6 \cdot 0.25H_2O$	65.38	6.31	10.17	65.57	6.24	10.17
22g	93	140—141	A–E	$C_{30}H_{34}N_4O_6 \cdot 0.25H_2O$	65.38	6.31	10.17	65.40	6.30	10.28
22h	77	140—142	A–E	$C_{32}H_{38}N_4O_6$	66.88	6.66	9.75	66.68	6.58	9.44
22i	79	182—183	A–E	$C_{33}H_{40}N_4O_6$	67.33	6.85	9.52	67.36	6.69	9.47
22j	83	168—169	A–E	$C_{32}H_{36}N_4O_6 \cdot 0.25H_2O$	66.59	6.37	9.71	66.85	6.21	9.61
22k	64	169—171	A–E	$C_{33}H_{40}N_4O_6$	67.33	6.85	9.52	67.14	6.83	9.47
22l	62	203—204	A–E	$C_{34}H_{42}N_4O_6 \cdot 0.25H_2O$	67.25	7.05	9.23	67.40	6.93	9.30
22m	92	177—179	A–E	$C_{32}H_{38}N_4O_6$	66.88	6.66	9.75	66.70	6.52	9.72

a) Yield from **13**, or **21a**—**m**. *b*) Abbreviations: A, ethyl acetate; C, dichloromethane; E, diethyl ether; H, *n*-hexane.

Table 6. Physicochemical Data for Phenoxyacetanilide Derivatives **31a**—**h** and **39a**—**c**

Compd.	Yield[a] (%)	mp (°C)	Recryst.[b] solv.	Formula	Analysis (%)					
					Calcd			Found		
					C	H	N	C	H	N
31a	77	184—185	A–E	$C_{30}H_{32}N_4O_6 \cdot 0.25H_2O$	65.62	5.97	10.20	65.50	6.01	10.02
31b	82	158—159	A–E	$C_{31}H_{34}N_4O_6 \cdot 0.25H_2O$	66.12	6.17	9.95	66.03	6.16	9.71
31c	51	141—143	C–H	$C_{32}H_{36}N_4O_6 \cdot 0.25H_2O$	66.59	6.37	9.71	66.78	6.30	9.68
31d	89	179—181	H–A	$C_{34}H_{40}N_4O_6$	67.98	6.71	9.33	67.73	6.76	9.12
31e	94	188—189	A–E	$C_{37}H_{42}N_4O_6 \cdot 0.25H_2O$	69.09	6.66	8.71	69.27	6.67	8.70
31f	89	140—142	A–E	$C_{32}H_{38}N_4O_6$	66.88	6.66	9.75	66.59	6.61	9.63
31g	80	172—173	A–E	$C_{31}H_{36}N_4O_6 \cdot 0.25H_2O$	65.88	6.51	9.91	65.92	6.51	9.64
31h	83	193—194	A–E	$C_{32}H_{38}N_4O_6 \cdot 0.25H_2O$	66.36	6.70	9.67	66.27	6.76	9.53
39a	78	112—114	C–A–E	$C_{33}H_{32}N_4O_6 \cdot 0.25H_2O$	67.22	5.64	9.50	67.23	5.50	9.40
39b	81	116—117	C–A–E	$C_{30}H_{34}N_4O_6 \cdot 0.25H_2O$	64.85	6.35	10.08	64.93	6.24	10.11
39c	81	140—142	C–E	$C_{32}H_{38}N_4O_6 \cdot 0.25H_2O$	65.85	6.73	9.60	65.98	6.63	9.61

a) Yield from **30a**—**h** or **38a**—**c**. *b*) Abbreviations: A, ethyl acetate; C, dichloromethane; E, diethyl ether; H, *n*-hexane.

mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic solution was washed with 1 N HCl, 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 (100 : 1). The eluate was concentrated under reduced pressure and the product was recrystallized from *n*-hexane–AcOEt–diethyl ether. The powder was collected by filtration to give **13** (0.5 g, 48%) as a white powder, mp 121—122 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.82—0.85 (6H, m), 1.31—1.40 (2H, m), 1.52—1.55 (1H, m), 3.33 (3H, s), 3.33—3.39 (1H, m), 3.56 (2H, s), 3.66 (3H, s), 3.84—3.96 (3H, m), 4.48 (2H, s), 6.09 (1H, br s), 6.66 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.8 Hz), 6.98 (1H, t, J=7.3 Hz), 7.15—7.52 (11H, m).

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylbutyl)carbamoylmethyl]ureido]phenyl]acetic Acid (14) To a solution of **13** (0.3 g, 0.52 mmol) in THF (6 ml) was added 0.1 N NaOH (6 ml) and the mixture was stirred at room temperature for 5 h. The reaction mixture was 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 CH_2Cl_2–AcOEt–diethyl ether. The powder was collected by filtration to give **14** (0.26 g, 89%) as a white powder, mp 147—149 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83—0.86 (6H, m), 1.32—1.41 (2H, m), 1.50—1.55 (1H, m), 3.29 (3H, s), 3.32—3.39 (1H, m), 3.59 (2H, s), 3.62 (1H, d, J=17.1 Hz), 3.84 (1H, dd, J=5.4, 17.1 Hz), 3.96—4.03 (1H, m), 4.45 (2H, d, J=4.4 Hz), 6.50 (1H, br s), 6.67 (1H, d, J=8.3 Hz), 6.86 (1H, d, J=7.3 Hz), 6.95—6.99 (2H, m), 7.12 (1H, d, J=7.8 Hz), 7.17 (1H, t, J=7.8 Hz), 7.25—7.29, 7.38—7.49 (6H, m), 7.58 (1H, d, J=8.3 Hz), 7.63 (1H, s); IR: 3352, 1738, 1666, 1646, 1618, 1598, 1564, 1498 1454, 1436, 1414, 1370 cm^{-1}; *Anal*. Calcd for $C_{31}H_{36}N_4O_6$: C, 66.41; H, 6.47; N, 9.99. Found: C, 66.18; H, 6.30; N, 9.79.

***N*-Methyl-*N*-phenyl-2-(2-nitrophenoxy)acetamide (16)** To a solution of **15** (39.4 g, 200 mmol) and *N*-methylaniline (21.4 g, 200 mmol) in CH_2Cl_2 (500 ml) were added EDC·HCl (46.0 g, 240 mmol) and DMAP (29.3 g, 240 mmol), and the mixture was stirred at room temperature for 3 d. The reaction mixture was washed with 2 N HCl, water, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was washed with *n*-hexane to give **16** (54 g, 94%) as small colorless needles, mp 120—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (3H, s), 4.59 (2H, s), 6.97 (1H, d, J=8.3 Hz), 7.03 (1H, t, J=7.8 Hz), 7.24 (2H, d, J=7.8 Hz), 7.37—7.49 (4H, m), 7.81 (1H, d, J=7.8 Hz).

***N*-Methyl-*N*-phenyl-2-(2-aminophenoxy)acetamide (17)** **16** (20 g, 69.9 mmol) was hydrogenated in a mixture of MeOH (250 ml) and AcOEt (250 ml) over 5% Pd–C (4 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 and the product was recrystallized from diethyl ether. The powder was collected by filtration to give **17** (16.3 g, 91%) as a white powder, mp 75—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (3H, s), 3.91 (2H, br s), 4.43 (2H, s), 6.59—6.63 (2H, m), 6.68 (1H, d, J=7.8 Hz), 6.79 (1H, t, J=7.8 Hz), 7.21 (2H, dd, J=1.4, 8.3 Hz), 7.36—7.46 (3H, m).

***N*-Methyl-*N*-phenyl-2-[2-(*N*-benzylamino)phenoxy]acetamide (18a)** A mixture of **17** (2.6 g, 10 mmol), benzyl bromide (1.7 g, 10 mmol) and K_2CO_3 (2.1 g, 15 mmol) in DMF (50 ml) was stirred at 70 °C for 2 d. To the reaction mixture was added 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 and the residue was chromatographed on silica-gel with *n*-hexane–AcOEt (2 : 1). The eluate was concentrated under reduced pressure to give **18a** (2.0 g, 58%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (3H, s), 4.33 (2H, s), 4.45 (2H, s), 4.96 (1H, br s), 6.50—6.58 (3H, m), 6.76—6.80 (2H, m), 7.17—7.45 (9H, m).

Compounds **18b**—**l** were obtained by following an analogous procedure to that described for the preparation of **18a**. Spectroscopic data for these compounds are as follows:

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-phenylethyl)amino]phenoxy]acetamide (**18b**): 67%. **18b** was prepared by replacing benzyl bromide with 2-phenylethyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 2.93 (2H, t, J=7.4 Hz), 3.31 (3H, s), 3.35 (2H, t, J=6.4 Hz), 4.38 (2H, s), 4.66 (1H, br s), 6.53—6.55 (3H, m), 6.61 (1H, d, J=8.3 Hz), 6.87 (1H, t, J=7.8 Hz), 7.17—7.43 (9H, m).

N-Methyl-*N*-phenyl-2-[2-(*N*-cyclohexylmethylamino)phenoxy]acetamide (**18c**): 48%. **18c** was prepared by replacing benzyl bromide with cyclohexylmethyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.96—1.02, 1.16—1.28, 1.66—1.85 (11H, m), 2.93 (2H, d, J=6.4 Hz), 3.32 (3H, s), 4.40 (2H, s), 4.59 (1H, br s), 6.49—6.56 (3H, m), 6.85 (1H, t, J=8.3 Hz), 7.21 (2H, d, J=7.3 Hz), 7.38—7.45 (3H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-cyclohexylethyl)amino]phenoxy]acetamide (**18d**): 57%. **18d** was prepared by replacing benzyl bromide with 2-cyclohexylethyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.92—1.77 (13H, m), 3.07—3.11 (2H, m), 3.32 (3H, s), 4.41 (3H, br s), 6.49—6.67 (3H, m), 6.84—6.88 (1H, m), 7.20—7.45 (5H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(3-cyclohexylpropyl)amino]phenoxy]acetamide (**18e**): 52%. **18e** was prepared by replacing benzyl bromide with 3-cyclohexylpropyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.88—0.94, 1.08—1.31, 1.60—1.74 (15H, m), 3.04 (2H, t, J=7.3 Hz), 3.31 (3H, s), 4.41 (2H, s), 4.46 (1H, br s), 6.49—6.57 (3H, m), 6.86 (1H, t, J=8.3 Hz), 7.21 (2H, d, J=7.3 Hz), 7.39—7.45 (3H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(*n*-butyl)amino]phenoxy]acetamide (**18f**): 80%. **18f** was prepared by replacing benzyl bromide with *n*-butyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.4 Hz), 1.41—1.48 (2H, m), 1.59—1.65 (2H, m), 3.08 (2H, t, J=6.8 Hz), 3.31 (3H, s), 4.41 (2H, s), 4.48 (1H, br s), 6.49—6.58 (3H, m), 6.86 (1H, t, J=8.3 Hz), 7.21 (2H, d, J=7.3 Hz), 7.36—7.45 (3H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-methylpropyl)amino]phenoxy]acetamide (**18g**): 48%. **18g** was prepared by replacing benzyl bromide with isobutyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (6H, d, J=6.4 Hz), 1.92 (1H, m), 2.91 (2H, d, J=6.4 Hz), 3.32 (3H, s), 4.40 (2H, s), 4.64 (1H, br s), 6.48—6.56 (3H, m), 6.85 (1H, t, J=7.8 Hz), 7.21 (2H, d, J=7.3 Hz), 7.38—7.45 (3H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[2-[*N*-(3-methylpentyl)amino]phenoxy]acetamide (**18h**): 50%. **18h** was prepared by replacing benzyl bromide with (±)-3-methylpentyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.88—0.93 (6H, m), 1.18—1.75 (5H, m), 3.05—3.12 (2H, m), 3.31 (3H, s), 4.41 (2H, s), 4.46 (1H, br s), 6.51—6.58 (3H, m), 6.86 (1H, t, J=8.3 Hz), 7.20 (2H, d, J=8.8 Hz), 7.38—7.45 (3H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(3-ethylpentyl)amino]phenoxy]acetamide (**18i**): 88%. **18i** was prepared by replacing benzyl bromide with 3-ethylpentyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, t, J=7.3 Hz), 1.32—1.37 (4H, m), 1.57—1.61 (3H, m), 3.06 (2H, t, J=7.8 Hz), 3.31 (3H, s), 441 (3H, br s), 6.51—6.58 (3H, m), 6.86 (1H, t, J=7.8 Hz), 7.21 (2H, d, J=7.3 Hz), 7.38—7.45 (3H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(4-methyl-3-pentenyl)amino]phenoxy]acetamide (**18j**): 56%. **18j** was prepared by replacing benzyl bromide with 4-methyl-3-pentenyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s), 1.73 (3H, s), 2.32 (2H, m), 3.08 (2H, t, J=7.4 Hz), 3.31 (3H, s), 4.40 (2H, s), 4.51 (1H, br s), 5.19 (1H, m), 6.52—6.53 (3H, m), 6.86 (1H, t, J=8.3 Hz), 7.21 (2H, d, J=7.3 Hz), 7.35—7.45 (3H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[2-[*N*-(3-methylhexyl)amino]phenoxy]acetamide (**18k**): 54%. **18k** was prepared by replacing benzyl bromide with (±)-3-methylhexyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.88—0.94 (6H, m), 1.14—1.61 (7H, m), 3.05—3.09 (2H, m), 3.31 (3H, s), 4.41 (2H, s), 4.46 (1H, br s), 6.51—6.58 (3H, m), 6.87 (1H, t, J=8.3 Hz), 7.21 (2H, d, J=7.4 Hz), 7.38—7.45 (3H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(4-ethylhexyl)amino]phenoxy]acetamide (**18l**): 41%. **18l** was prepared by replacing benzyl bromide with 4-ethylhexyl bromide. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (6H, t, J=7.3 Hz), 1.20—1.37 (7H, m), 1.57—1.65 (2H, m), 3.05 (2H, t, J=7.3 Hz), 3.31 (3H, s), 4.41 (2H, s), 4.49 (1H, br s), 6.51—6.58 (3H, m), 6.86 (1H, t, J=7.8 Hz), 7.21 (2H, d, J=7.3 Hz), 7.38—7.45 (3H, m).

***N*-Methyl-*N*-phenyl-2-[2-[*N*-benzyl-*N*-[2-(*N*-phthaloylamino)acetyl]-amino]phenoxy]acetamide (19a)** Thionyl chloride (0.73 ml, 10 mmol) was added to 2-(*N*-phthaloylamino)acetic acid (1.6 g, 8.0 mmol) containing a catalytic amount of DMF with ice cooling, and the mixture was stirred under reflux for 0.5 h. The excess thionyl chloride was distilled off and the residue was dissolved in CH_2Cl_2 (30 ml). This solution was added to a solution of **18a** (1.9 g, 5.5 mmol) and pyridine (0.64 ml, 8.0 mmol) in CH_2Cl_2 (50 ml) with ice cooling, and the resulting 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 and the product was washed with *n*-hexane–AcOEt to give **19a** (2.1 g, 72%) as an off-white solid, mp 162—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (3H, s), 4.17 (1H, d, J=16.6 Hz), 4.34 (1H, d, J=14.2 Hz), 4.43 (1H, d, J=16.6 Hz), 4.47 (2H, s), 5.34 (1H, d, J=14.2 Hz), 6.78 (1H, d, J=8.3 Hz), 6.86 (1H, t, J=7.8 Hz), 6.94 (1H, d, J=7.4 Hz), 7.20—7.54 (11H, m), 7.68—7.70 (2H, m), 7.83—7.85 (2H, m).

Compounds **19b**—**l** were obtained by following an analogous procedure to that described for the preparation of **19a**. Spectroscopic data for these compounds, except for **19d** and **19e**, are as follows. Compounds **19d** and **19e** were used for the subsequent reaction without purification.

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-phenylethyl)-*N*-[2-(*N*-phthaloylamino)-acetyl]amino]phenoxy]acetamide (**19b**): 77%. ^{1}H-NMR ($CDCl_3$) δ: 2.85—2.94 (2H, m), 3.31 (3H, s), 3.67—3.74 (1H, m), 3.94—3.98 (1H, m), 4.13 (1H, d, J=17.1 Hz), 4.45 (1H, d, J=17.1 Hz), 4.56 (2H, s), 6.78 (1H, d, J=7.8 Hz), 6.99 (1H, t, J=7.8 Hz), 7.13—7.52 (12H, m), 7.68—7.70 (2H, m), 7.83—7.85 (2H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-cylcohexylmethyl-*N*-[2-(*N*-phthaloylamino)-acetyl]amino]phenoxy]acetamide (**19c**): 82%. ^{1}H-NMR ($CDCl_3$) δ: 0.90—0.96 (2H, m), 1.10 (2H, br s), 1.49—1.74 (7H, m), 3.26 (1H, dd, J=6.3, 15.7 Hz), 3.32 (3H, s), 3.76 (1H, dd, J=8.3, 15.7 Hz), 4.12 (1H, d, J=16.6 Hz), 4.40 (1H, d, J=16.6 Hz), 4.57 (2H, s), 6.79 (1H, d, J=8.3 Hz), 7.03 (1H, t, J=7.4 Hz), 7.30—7.53 (7H, m), 7.66—7.68 (2H, m), 7.79—7.83 (2H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(*n*-butyl)-*N*-[2-(*N*-phthaloylamino)-acetyl]amino]phenoxy]acetamide (**19f**): 75%. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=6.4 Hz), 1.24—1.31 (2H, m), 1.44—1.49 (2H, m), 3.31 (3H, s), 3.42—3.49 (1H, m), 3.82—3.86 (1H, m), 4.12 (1H, d, J=16.6 Hz), 4.42 (1H, d, J=16.6 Hz), 4.57 (2H, s), 6.78 (1H, d, J=8.3 Hz), 7.03 (1H, t, J=7.8 Hz), 7.30—7.54 (7H, m), 7.66—7.68 (2H, m), 7.80—7.83 (2H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-methylpropyl)-*N*-[2-(*N*-phthaloylamino)-acetyl]amino]phenoxy]acetamide (**19g**): 94%. ^{1}H-NMR ($CDCl_3$) δ: 0.87—0.91 (6H, m), 1.78—1.81 (1H, m), 3.29 (1H, dd, J=6.4, 13.7 Hz), 3.32 (3H, s), 3.71 (1H, dd, J=8.3, 13.7 Hz), 4.13 (1H, d, J=16.1 Hz), 4.43 (1H, d, J=16.1 Hz), 4.57 (2H, s), 6.78 (1H, d, J=8.3 Hz), 7.03 (1H, t, J=7.8 Hz), 7.30—7.54 (7H, m), 7.66—7.70 (2H, m), 7.81—7.83 (2H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[2-[*N*-(3-methylpentyl)-*N*-[2-(*N*-phthaloylamino)acetyl]amino]phenoxy]acetamide (**19h**): 69%. ^{1}H-NMR ($CDCl_3$) δ: 0.75—0.82 (6H, m), 1.07—1.54 (5H, m), 3.31 (3H, s), 3.45 (1H, m), 3.88 (1H, m), 4.12 (1H, d, J=16.6 Hz), 4.40 (1H, d, J=16.6 Hz), 4.57 (2H, s), 6.78 (1H, d, J=7.8 Hz), 7.03 (1H, t, J=7.3 Hz), 7.29—7.51 (7H, m), 7.66—7.69 (2H, m), 7.80—7.83 (2H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(3-ethylpentyl)-*N*-[2-(*N*-phthaloylamino)-acetyl]amino]phenoxy]acetamide (**19i**): 66%. ^{1}H-NMR ($CDCl_3$) δ: 0.73—0.79 (6H, m), 1.24—1.28 (5H, m), 1.43—1.49 (2H, m), 3.31 (3H, s), 3.37—3.46 (1H, m), 3.83—3.91 (1H, m), 4.13 (1H, d, J=16.6 Hz), 4.43 (1H, d, J=16.6 Hz), 4.57 (2H, s), 6.79 (1H, d, J=8.3 Hz), 7.03 (1H, t, J=7.8 Hz), 7.30—7.53 (7H, m), 7.66—7.69 (2H, m), 7.81—7.83 (2H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(4-methyl-3-pentenyl)-*N*-[2-(*N*-phthaloylamino)acetyl]amino]phenoxy]acetamide (**19j**): 79%. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s), 1.60 (3H, s), 2.22 (2H, m), 3.31 (3H, s), 3.36—3.44 (1H, m), 3.77—3.84 (1H, m), 4.13 (1H, d, J=16.6 Hz), 4.40 (1H, d, J=16.6 Hz), 4.57 (2H, s), 5.01 (1H, t, J=6.8 Hz), 6.78 (1H, d, J=8.3 Hz), 7.02 (1H, t, J=7.8 Hz), 7.30—7.53 (7H, m), 7.67—7.69 (2H, m), 7.80—7.83 (2H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[2-[*N*-(3-methylhexyl)-*N*-[2-(*N*-phthaloylamino)acetyl]amino]phenoxy]acetamide (**19k**): 80%. ^{1}H-NMR ($CDCl_3$) δ: 0.80—0.83 (6H, m), 1.04—1.64 (7H, m), 3.32 (3H, s), 3.45—3.46 (1H, m), 3.89 (1H, m), 4.11—4.15 (1H, m), 4.43 (1H, dd, J=10.3, 16.6 Hz), 4.57 (2H, s), 6.79 (1H, d, J=7.8 Hz), 7.03 (1H, t, J=7.3 Hz), 7.26—7.52 (7H, m), 7.66—7.68 (2H, m), 7.81—7.83 (2H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(4-ethylhexyl)-*N*-[2-(*N*-phthaloylamino)-acetyl]amino]phenoxy]acetamide (**19l**): 85%. ^{1}H-NMR ($CDCl_3$) δ: 0.77

(6H, t, J=6.8 Hz), 1.08—1.26 (7H, m), 1.47—1.48 (2H, m), 3.31 (3H, s), 3.35—3.42 (1H, m), 3.80—3.85 (1H, m), 4.13 (1H, d, J=16.6 Hz), 4.41 (1H, d, J=16.6 Hz), 4.57 (2H, s), 6.79 (1H, d, J=8.3 Hz), 7.03 (1H, t, J=7.3 Hz), 7.30—7.53 (7H, m), 7.66—7.68 (2H, m), 7.81—7.83 (2H, m).

***N*-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-benzylamino]phenoxy]-acetamide (20a)** To a solution of **19a** (2.0 g, 3.8 mmol) in a mixture of $CHCl_3$ (20 ml) and EtOH (80 ml) was added hydrazine monohydrate (0.55 ml, 11.4 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was suspended in $CHCl_3$. The suspension was filtered and the filtrate was concentrated under reduced pressure. The residue was resuspended in $CHCl_3$ and the suspension was filtered. The filtrate was concentrated under reduced pressure to give crude **20a** (1.8 g) as a white amorphous powder. Compound **20a** was used for the subsequent reaction without purification. ^{1}H-NMR ($CDCl_3$) δ: 1.72 (2H, br s), 3.09 (1H, d, J=17.1 Hz), 3.21 (1H, d, J=17.1 Hz), 3.31 (3H, s), 4.31—4.37 (3H, m), 5.34 (1H, d, J=14.7 Hz), 6.67 (1H, t, J=8.3 Hz), 6.73 (1H, d, J=7.8 Hz), 6.81 (1H, t, J=7.8 Hz), 7.18—7.28, 7.44—7.52 (11H, m).

Compounds **20b**—**l** were obtained by following an analogous procedure to that described for the preparation of **20a** and used for the subsequent reaction without purification. Spectroscopic data for these compounds are as follows:

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(2-phenylethyl)amino]-phenoxy]acetamide (**20b**): ^{1}H-NMR ($CDCl_3$) δ: 1.76 (2H, br s), 2.83—2.90 (2H, m), 3.04 (1H, d, J=17.1 Hz), 3.17 (1H, d, J=17.1 Hz), 3.30 (3H, s), 3.59—3.67 (1H, m), 4.06—4.12 (1H, m), 4.42 (2H, s), 6.70 (1H, d, J=8.3 Hz), 6.93 (2H, m), 7.16—7.49 (11H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-cycohexylmethylamino]-phenoxy]acetamide (**20c**): ^{1}H-NMR ($CDCl_3$) δ: 0.97—1.15, 1.45—1.74 (13H, m), 3.05 (1H, d, J=17.1 Hz), 3.14 (1H, d, J=17.1 Hz), 3.16 (1H, dd, J=6.3, 13.2 Hz), 3.30 (3H, s), 3.85 (1H, dd, J=8.3, 13.2 Hz), 4.43 (2H, s), 6.71 (1H, d, J=8.3 Hz), 6.96 (1H, t, J=7.8 Hz), 7.09 (1H, d, J=7.8 Hz), 7.25—7.51 (6H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(2-cyclohexylethyl)-amino]phenoxy]acetamide (**20d**): ^{1}H-NMR ($CDCl_3$) δ: 0.82—0.94, 1.08—1.40, 1.62—1.84 (15H, m), 3.03 (1H, d, J=17.0 Hz), 3.15 (1H, d, J=17.0 Hz), 3.30 (3H, s), 3.34—3.39 (1H, m), 3.93—4.00 (1H, m), 4.43 (2H, s), 6.69 (1H, d, J=8.3 Hz), 6.96 (1H, t, J=7.8 Hz), 7.08 (1H, d, J=7.8 Hz), 7.25—7.29, 7.42—7.51 (6H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(3-cyclohexylpropyl)-amino]phenoxy]acetamide (**20e**): ^{1}H-NMR ($CDCl_3$) δ: 0.80—0.86, 1.05—1.31, 1.46—1.49, 1.63—1.88 (17H, m), 3.04 (1H, d, J=17.1 Hz), 3.61 (1H, d, J=17.1 Hz), 3.30 (3H, s), 3.30—3.36 (1H, m), 3.87—3.94 (1H, m), 4.43 (2H, s), 6.70 (1H, d, J=7.8 Hz), 6.96 (1H, t, J=7.8 Hz), 7.08 (1H, dd, J=1.5, 7.8 Hz), 7.16—7.29, 7.41—7.51 (6H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(*n*-butyl)amino]phenoxy]acetamide (**20f**): ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.3 Hz), 1.24—1.34 (2H, m), 1.42—1.47 (2H, m), 1.66 (2H, br s), 3.03 (1H, d, J=17.0 Hz), 3.14 (1H, d, J=17.0 Hz), 3.30 (3H, s), 3.32—3.39 (1H, m), 3.89—3.96 (1H, m), 4.43 (2H, s), 6.70 (1H, d, J=8.3 Hz), 6.96 (1H, t, J=7.8 Hz), 7.08 (1H, dd, J=1.4, 7.8 Hz), 7.25—7.29, 7.42—7.51 (6H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(2-methylpropyl)amino]-phenoxy]acetamide (**20g**): ^{1}H-NMR ($CDCl_3$) δ: 0.88—0.94 (6H, m), 1.75—1.76 (3H, br s), 3.06 (1H, d, J=17.1 Hz), 3.16 (1H, d, J=17.1 Hz), 3.19 (1H, dd, J=5.1, 13.2 Hz), 3.30 (3H, s), 3.80 (1H, dd, J=8.3, 13.2 Hz), 4.44 (2H, s), 6.69 (1H, d, J=7.3 Hz), 6.96 (1H, t, J=7.8 Hz), 7.10 (1H, d, J=7.8 Hz), 7.24—7.51 (6H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(3-methylpentyl)-amino]phenoxy]acetamide (**20h**): ^{1}H-NMR ($CDCl_3$) δ: 0.78—0.90 (6H, m), 1.10—1.51 (5H, m), 1.86 (2H, br s), 3.03 (1H, dd, J=2.0, 17.1 Hz), 3.15 (1H, dd, J=6.9, 17.1 Hz), 3.30 (3H, s), 3.33—3.39 (1H, m), 3.95—4.04 (1H, m), 4.43 (2H, s), 6.70 (1H, d, J=8.3 Hz), 6.96 (1H, t, J=7.8 Hz), 7.07 (1H, m), 7.25—7.51 (6H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(3-ethylpentyl)amino]-phenoxy]acetamide (**20i**): ^{1}H-NMR ($CDCl_3$) δ: 0.76—0.81 (6H, m), 1.17—1.29 (5H, m), 1.40—1.47 (2H, m), 1.99 (2H, br s), 3.03 (1H, d, J=17.0 Hz), 3.16 (1H, d, J=17.0 Hz), 3.30 (3H, s), 3.30—3.34 (1H, m), 3.94—3.97 (1H, m), 4.44 (2H, s), 6.70 (1H, d, J=7.8 Hz), 6.96 (1H, t, J=7.3 Hz), 7.08 (1H, d, J=7.8 Hz), 7.25—7.51 (6H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(4-methyl-3-pentenyl)-amino]phenoxy]acetamide (**20j**): ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, s), 1.65 (3H, s), 1.84 (2H, br s), 2.20 (2H, m), 3.04 (1H, d, J=17.1 Hz), 3.15 (1H, d, J=17.1 Hz), 3.30 (3H, s), 3.31—3.35 (1H, m), 3.89—3.92 (1H, m), 4.43 (2H, s), 5.05 (1H, t, J=6.8 Hz), 6.70 (1H, d, J=8.3 Hz), 6.95 (1H, t, J=7.8 Hz), 6.99 (1H, d, J=8.8 Hz), 7.07—7.16, 7.25—7.51 (6H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(3-methylhexyl)-amino]phenoxy]acetamide (**20k**): ^{1}H-NMR ($CDCl_3$) δ: 0.83—0.86 (6H, m), 1.07—1.50 (7H, m), 1.89 (2H, br s), 3.02 (1H, dd, J=2.4, 17.0 Hz), 3.16 (1H, dd, J=7.8, 17.0 Hz), 3.30 (3H, s), 3.30—3.39 (1H, m), 3.93—4.04 (1H, m), 4.43 (2H, s), 6.70 (1H, d, J=8.3 Hz), 6.96 (1H, t, J=7.8 Hz), 7.06 (1H, m), 7.25—7.51 (6H, m).

N-Methyl-*N*-phenyl-2-[2-[*N*-(2-aminoacetyl)-*N*-(4-ethylhexyl)amino]phenoxy]acetamide (**20l**): ^{1}H-NMR ($CDCl_3$) δ: 0.79 (6H, t, J=7.3 Hz), 1.10—1.24 (7H, m), 1.44—1.46 (2H, m), 1.91 (2H, br s), 3.04 (1H, d, J=17.1 Hz), 3.16 (1H, d, J=17.1 Hz), 3.26—3.33 (1H, m), 3.30 (3H, s), 3.89—3.94 (1H, m), 4.44 (2H, s), 6.70 (1H, d, J=8.3 Hz), 6.96 (1H, t, J=7.3 Hz), 7.09 (1H, d, J=7.8 Hz), 7.26—7.29, 7.42—7.51 (6H, m).

Compounds **21a**—**l** were obtained by following an analogous procedure to that described for the preparation of **13**. Spectroscopic data for these compounds are as follows:

Methyl 2-[3-[3-[*N*-Benzyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)-phenyl]carbamoylmethyl]ureido]phenyl]acetate (**21a**): 29% from **19a**. mp 138—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.35 (3H, s), 3.55 (2H, s), 3.66 (3H, s), 3.85 (1H, d, J=15.7 Hz), 3.98 (1H,dd, J=5.4, 15.7 Hz), 4.28 (1H, d, J=16.6 Hz), 4.36—4.42 (2H, m), 5.24 (1H, d, J=14.2 Hz), 6.12 (1H, s), 6.61 (1H, d, J=8.3 Hz), 6.83—6.90 (3H, m), 7.16—7.30, 7.46—7.54 (15H, m).

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2-phenylethyl)carbamoylmethyl]ureido]phenyl]acetate (**21b**): 52% from **19b**. mp 147—148 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.83—2.88 (2H, m), 3.34 (3H, s), 3.56 (2H, s), 3.59—3.64 (1H, m), 3.67 (3H, s), 3.89 (2H, d, J=4.9 Hz), 4.08—4.11 (1H, m), 4.46 (2H, s), 6.01 (1H, br s), 6.64 (1H, d, J=8.3 Hz), 6.89 (1H, d, J=7.8 Hz), 6.94 (1H, t, J=8.3 Hz), 7.03 (1H, dd, J=1.9, 7.8 Hz), 7.12—7.31, 7.42—7.52 (15H, m).

Methyl 2-[3-[3-[*N*-Cyclohexylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoyl-methoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**21c**): 29% from **19c**. mp 159—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.91—1.12, 1.43—1.73 (11H, m), 3.18 (1H, dd, J=6.4, 13.1 Hz), 3.33 (3H, s), 3.55 (2H, s), 3.66 (3H, s), 3.79—3.99 (3H, m), 4.48 (2H, s), 6.06 (1H, br s), 6.66 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.3 Hz), 6.98 (1H, t, J=7.8 Hz), 7.16—7.52 (11H, m)

Methyl 2-[3-[3-[*N*-(2-Cyclohexylethyl)-*N*-[2-(*N*-methyl-*N*-phenylcar-bamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**21d**): 31% from **18d**. ^{1}H-NMR ($CDCl_3$) δ: 0.79—0.88, 1.02—1.41, 1.60—1.78 (13H, m), 3.34 (3H, s), 3.34—3.36 (1H, m), 3.56 (2H, s), 3.67 (3H, s), 3.86 (2H, d, J=4.4 Hz), 3.91—3.98 (1H, m), 4.48 (2H, s), 6.05 (1H, br s), 6.65 (1H, d, J=7.8 Hz), 6.89 (1H, d, J=7.8 Hz), 6.97 (1H, t, J=7.3 Hz), 7.13—7.32, 7.42—7.68 (11H, m).

Methyl 2-[3-[3-[*N*-(3-Cyclohexylpropyl)-*N*-[2-(*N*-methyl-*N*-phenylcar-bamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**21e**): 34% from **18e**. mp 138—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.78—0.88, 1.04—1.78 (15H, m), 3.28—3.30 (1H, m), 3.34 (3H, s), 3.57 (2H, s), 3.67 (3H, s), 3.86—3.87 (3H, m), 4.48 (2H, s), 6.02 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.90 (1H, d, J=7.4 Hz), 6.98 (1H, t, J=7.8 Hz), 7.14—7.35, 7.43—7.53 (11H, m).

Methyl 2-[3-[3-[*N*-(*n*-Butyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)-phenyl]carbamoylmethyl]ureido]phenyl]acetate (**21f**): 45% from **19f**. mp 136—137 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7.3 Hz), 1.23—1.29 (2H, m), 1.41—1.45 (2H, m), 3.33 (3H, s), 3.36—3.39 (1H, m), 3.55 (2H, s), 3.66 (3H, s), 3.85 (1H, d, J=17.6 Hz), 3.89—3.94 (2H, m), 4.48 (2H, s), 6.15 (1H, br s), 6.66 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.8 Hz), 6.98 (1H, t, J=7.3 Hz), 7.14—7.31, 7.41—7.52 (11H, m).

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2-methylpropyl)carbamoylmethyl]ureido]phenyl]acetate (**21g**): 38% from **19g**. mp 110—111 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz), 1.75 (1H, m), 3.21 (1H, dd, J=5.9, 13.2 Hz), 3.33 (3H, s), 3.55 (2H, s), 3.66 (3H, s), 3.77—3.93 (3H, m), 4.48 (2H, s), 6.07 (1H, br s), 6.65 (1H, d, J=7.8 Hz), 6.88 (1H, d, J=7.3 Hz), 6.98 (1H, t, J=7.8 Hz), 7.17—7.52 (11H, m).

Methyl (±)-2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylpentyl)carbamoylmethyl]ureido]phenyl]acetate (**21h**): 23% from **19h**. mp 98—100 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.75—0.82 (6H, m), 1.04—1.50 (5H, m), 3.33 (4H, br s), 3.55 (2H, s), 3.66 (3H, s), 3.81—3.97 (3H, m), 4.48 (2H, s), 6.08 (1H, br s), 6.66 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=8.3 Hz), 6.98 (1H, t, J=7.8 Hz), 7.15—7.52 (11H, m).

Methyl 2-[3-[3-[*N*-(3-Ethylpentyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoyl-methoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**21i**): 36% from **19i**. mp 94—96 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.72—0.77 (6H, m), 1.15—1.23 (5H, m), 1.40—1.46 (2H, m), 3.30—3.33 (1H, m), 3.33 (3H, s), 3.55 (2H, s), 3.66 (3H, s), 3.84—3.95 (3H, m), 4.48 (2H, s), 6.12 (1H, br s), 6.66 (1H,

d, J=8.3 Hz), 6.87 (1H, d, J=7.8 Hz), 6.98 (1H, t, J=7.8 Hz), 7.16—7.50 (11H, m).

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(4-methyl-3-pentenyl)carbamoylmethyl]ureido]phenyl]acetate (**21j**): 34% from **19j**. mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, s), 1.69 (3H, s), 2.18 (2H, m), 3.29—3.33 (1H, m), 3.33 (3H, s), 3.56 (2H, s), 3.66 (3H, s), 3.87—3.93 (3H, m), 4.48 (2H, s), 5.00 (1H, br s), 6.08 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.3 Hz), 6.97 (1H, t, J=7.8 Hz), 7.15—7.52 (11H, m).

Methyl (±)-2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylhexyl)carbamoylmethyl]ureido]phenyl]acetate (**21k**): 55% from **19k**. ^{1}H-NMR ($CDCl_3$) δ: 0.78—0.83 (6H, m), 1.03—1.48 (7H, m), 3.32 (3H, s), 3.33—3.37 (1H, m), 3.55 (2H, s), 3.66 (3H, s), 3.87 (2H, d, J=4.4 Hz), 3.88—3.92 (1H, m), 4.47 (2H, s), 6.06 (1H, br s), 6.64 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.8 Hz), 6.94—6.99 (2H, m), 7.13—7.53 (10H, m).

Methyl 2-[3-[3-[*N*-(4-Ethylhexyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**21l**): 31% from **19l**. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (6H, t, J=7.3 Hz), 1.06—1.26 (7H, m), 1.43—1.46 (2H, m), 3.28—3.33 (1H, m), 3.33 (3H, s), 3.55 (2H, s), 3.66 (3H, s), 3.87—3.91 (3H, m), 4.48 (2H, s), 6.06 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.3 Hz), 6.97 (1H, t, J=7.3 Hz), 7.15—7.36, 7.42—7.53 (11H, m).

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(4-methylpentyl)carbamoylmethyl]ureido]phenyl]acetate (21m) 21j (0.4 g, 0.66 mmol) was hydrogenated in a mixture of THF (20 ml) and MeOH (20 ml) over 5% Pd–C (0.1 g) at atmospheric pressure for 3 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–AcOEt–diethyl ether. The powder was collected by filtration to give **21m** (0.32 g, 82%) as a white powder, mp 104—106 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (6H, d, J=6.4 Hz), 1.11—1.13 (2H, m), 1.45—1.46 (3H, m), 3.28—3.33 (1H, m), 3.34 (3H, s), 3.56 (2H, s), 3.67 (3H, s), 3.86 (3H, m), 4.48 (2H, s), 6.01 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.89 (1H, d, J=7.4 Hz), 6.98 (1H, t, J=7.3 Hz), 7.15—7.32, 7.44—7.51 (11H, m).

Compounds **22a**—**m** were obtained by following an analogous procedure to that described for the preparation of **14**; 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:.

2-[3-[3-[*N*-Benzyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]-carbamoylmethyl]ureido]phenyl]acetic Acid (**22a**): ^{1}H-NMR ($CDCl_3$) δ: 3.30 (3H, s), 3.58 (2H, s), 3.68 (1H, dd, J=3.4, 16.6 Hz), 3.92 (1H, dd, J=5.4, 16.6 Hz), 4.30—4.41 (3H, m), 5.35 (1H, d, J=14.2 Hz), 6.51 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.76—6.79 (2H, m), 6.86 (1H, d, J=7.4 Hz), 7.01 (1H, s), 7.14—7.26, 7.41—7.52 (13H, m), 7.58 (1H, s); IR: 3364, 1722, 1652, 1596, 1556, 1496, 1444, 1346 cm^{-1}.

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2-phenylethyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**22b**): ^{1}H-NMR ($CDCl_3$) δ: 2.85—2.89 (2H, m), 3.28 (3H, s), 3.60 (2H, s), 3.64—3.68 (2H, m), 3.86 (1H, dd, J=4.9, 17.6 Hz), 4.12 (1H, m), 4.44 (2H, s), 6.47 (1H, s), 6.67 (1H, d, J=8.3 Hz), 6.91—6.99 (4H, m), 7.13—7.26, 7.39—7.48 (13H, m), 7.58 (1H, s); IR: 3352, 1736, 1668, 1646, 1616, 1598, 1564, 1498, 1454, 1436, 1412, 1352 cm^{-1}.

2-[3-[3-[*N*-Cyclohexylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**22c**): ^{1}H-NMR ($CDCl_3$) δ: 0.90—0.97, 1.11—1.13, 1.43—1.71 (11H, m), 3.19 (1H, dd, J=5.9, 13.6 Hz), 3.29 (3H, s), 3.60 (2H, s), 3.61 (1H, d, J=14.7 Hz), 3.84—3.90 (2H, m), 4.44 (2H, d, J=3.5 Hz), 6.50 (1H, s), 6.68 (1H, d, J=8.3 Hz), 6.87 (1H, d, J=7.8 Hz), 6.96—6.99 (2H, m), 7.12—8.20 (2H, m), 7.25—7.62 (8H, m); IR: 3372, 1660, 1596, 1554, 1496, 1452, 1424, 1346 cm^{-1}.

2-[3-[3-[*N*-(2-Cyclohexylethyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**22d**): ^{1}H-NMR (DMSO-d_6) δ: 0.78—0.86, 1.06—1.30, 1.58—1.64 (13H, m), 3.19 (3H, s), 3.20—3.23 (1H, m), 3.46 (2H, s), 3.47 (1H, d, J=17.1 Hz), 3.65 (1H, dd, J=5.4, 17.1 Hz), 3.83—3.85 (1H, m), 4.55 (2H, s), 6.28 (1H, br s), 6.78 (1H, d, J=7.8 Hz), 6.88 (1H, br s), 7.03 (1H, t, J=7.3 Hz), 7.12 (1H, t, J=7.8 Hz), 7.23—7.50 (9H, m), 8.80 (1H, s); IR: 3376, 1730, 1632, 1596, 1552, 1496, 1448, 1430, 1344 cm^{-1}.

2-[3-[3-[*N*-(3-Cyclohexylpropyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**22e**): ^{1}H-NMR ($CDCl_3$) δ: 0.78—0.80, 1.12—1.21, 1.46—1.62 (15H, m), 3.29 (3H, s), 3.30—3.33 (1H, m), 3.59 (2H, s), 3.61 (1H, d, J=17.6 Hz), 3.85 (1H, dd, J=3.9, 17.6 Hz), 3.91—3.98 (1H, m), 4.45 (2H, s), 6.52 (1H, s), 6.68 (1H, d, J=8.3 Hz), 6.86 (1H, d, J=7.3 Hz), 6.96—6.97 (2H, m), 7.12 (1H, d, J=7.4 Hz), 7.17 (1H, t, J=7.8 Hz), 7.25—7.27 (3H, m), 7.40 (1H, d, J=7.3 Hz), 7.45—7.48 (2H, m), 7.59 (1H, d, J=7.8 Hz), 7.64 (1H, s); IR: 3368, 1650, 1596, 1554, 1496, 1448, 1428, 1346 cm^{-1}.

2-[3-[3-[*N*-(*n*-Butyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)-phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**22f**): ^{1}H-NMR (DMSO-d_6) δ: 0.83 (3H, t, J=7.3 Hz), 1.22—1.30 (2H, m), 1.33—1.39 (2H, m), 3.19 (3H, s), 3.30—3.35 (1H, m), 3.46 (2H, s), 3.47 (1H, d, J=17.1 Hz), 3.66 (1H, dd, J=5.4, 17.1 Hz), 3.81—3.86 (1H, m), 4.56 (2H, s), 6.28 (1H, br s), 6.77 (1H, d, J=7.3 Hz), 6.88 (1H, br s), 7.04 (1H, t, J=7.8 Hz), 7.13 (1H, t, J=7.8 Hz), 7.22—7.51 (9H, m), 8.82 (1H, s); IR: 3344, 1736, 1644, 1596, 1560, 1496, 1454, 1412, 1346 cm^{-1}.

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2-methylpropyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**22g**): ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.90 (6H, m), 1.72—1.77 (1H, m), 3.19—3.25 (1H, m), 3.28 (3H, s), 3.57 (2H, s), 3.63 (1H, d, J=17.5 Hz), 3.78—3.90 (2H, m), 4.45 (2H, s), 6.48 (1H, s), 6.67 (1H, d, J=7.8 Hz), 6.85 (1H, d, J=7.3 Hz), 6.95—6.98 (2H, m), 7.14—7.55 (9H, m), 7.66 (1H, s); IR: 3376, 1728, 1660, 1596, 1554, 1496, 1446, 1424, 1368 cm^{-1}.

(±)-2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylpentyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**22h**): ^{1}H-NMR ($CDCl_3$) δ: 0.77—0.83 (6H, m), 1.06—1.48 (5H, m), 3.29 (3H, s), 3.29—3.33 (1H, m), 3.60 (2H, s), 3.64 (1H, d, J=17.6 Hz), 3.85 (1H, dd, J=4.4, 17.6 Hz), 3.99—4.01 (1H, m), 4.45 (2H, ABq, J=15.7 Hz), 6.49 (1H, br s), 6.67 (1H, d, J=8.3 Hz), 6.87 (1H, d, J=7.3 Hz), 6.95—6.99 (2H, m), 7.12—7.27, 7.41—7.49 (8H, m), 7.58—7.61 (2H, m); IR: 3376, 1734, 1694, 1636, 1596, 1554, 1522, 1495, 1458, 1430, 1404 cm^{-1}.

2-[3-[3-[*N*-(3-Ethylpentyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)-phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**22i**): ^{1}H-NMR ($CDCl_3$) δ: 0.74—0.79 (6H, m), 1.14—1.29 (5H, m), 1.41—1.48 (2H, m), 3.29 (3H, s), 3.30—3.33 (1H, m), 3.60 (2H, s), 3.64 (1H, d, J=17.1 Hz), 3.85 (1H, dd, J=4.9, 17.1 Hz), 3.96—4.00 (1H, m), 4.45 (2H, d, J=4.9 Hz), 6.51 (1H, br s), 6.68 (1H, d, J=8.3 Hz), 6.87 (1H, d, J=7.9 Hz), 6.96—6.99 (2H, m), 7.13 (1H, d, J=7.4 Hz), 7.18 (1H, t, J=7.8 Hz), 7.25—7.27, 7.40—7.49 (6H, m), 7.59—7.62 (2H, m); IR: 3372, 1730, 1640, 1596, 1554, 1496, 1456, 1428, 1348 cm^{-1}.

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(4-methyl-3-pentenyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**22j**): ^{1}H-NMR (DMSO-d_6) δ: 1.51 (3H, s), 1.62 (3H, s), 2.12 (2H, m), 3.19 (3H, s), 3.25—3.30 (1H, m), 3.33 (2H, s), 3.46—3.47 (1H, m), 3.63—3.76 (2H, m), 4.55 (2H, s), 5.03 (1H, t, J=6.3 Hz), 6.28 (1H, br s), 6.76 (1H, d, J=7.3 Hz), 6.87 (1H, br s), 7.04 (1H, t, J=7.8 Hz), 7.12 (1H, t, J=7.8 Hz), 7.22—7.50 (9H, m), 8.80 (1H, s), 12.27 (1H, br s); IR: 3344, 1738, 1666, 1646, 1616, 1598, 1564, 1500, 1454, 1436, 1412 cm^{-1}.

(±)-2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylhexyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**22k**): ^{1}H-NMR ($CDCl_3$) δ: 0.81—0.85 (6H, m), 1.01—1.49 (7H, m), 3.29 (3H, s), 3.30—3.33 (1H, m), 3.59 (2H, s), 3.64 (1H, d, J=16.6 Hz), 3.85 (1H, dd, J=4.4, 16.6 Hz), 3.98—4.02 (1H, m), 4.45 (2H, s), 6.48 (1H, br s), 6.67 (1H, d, J=8.3 Hz), 6.86 (1H, d, J=7.3 Hz), 6.95—6.99 (2H, m), 7.11—7.51 (8H, m), 7.57 (1H, d, J=8.3 Hz), 7.61 (1H, s); IR: 3348, 1738, 1666, 1646, 1598, 1564, 1498, 1454, 1436, 1414, 1348 cm^{-1}.

2-[3-[3-[*N*-(4-Ethylhexyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)-phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**22l**): ^{1}H-NMR ($CDCl_3$) δ: 0.78 (6H, t, J=7.3 Hz), 1.09—1.23 (7H, m), 1.46 (2H, m), 3.26—3.30 (1H, m), 3.29 (3H, s), 3.60 (2H, s), 3.62 (1H, d, J=17.6 Hz), 3.86 (1H, dd, J=4.9, 17.6 Hz), 3.92—3.98 (1H, m), 4.45 (2H, s), 6.50 (1H, s), 6.68 (1H, d, J=7.9 Hz), 6.87 (1H, d, J=7.8 Hz), 6.97—6.99 (2H, m), 7.13 (1H, d, J=7.8 Hz), 7.18 (1H, t, J=7.8 Hz), 7.20—7.27, 7.40—7.49 (6H, m), 7.60 (2H, br s); IR: 3340, 1738, 1668, 1646, 1616, 1596, 1564, 1498, 1454, 1436, 1416 cm^{-1}.

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(4-methylpentyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**22m**): ^{1}H-NMR ($CDCl_3$) δ: 0.81 (6H, d, J=6.8 Hz), 1.09—1.15 (2H, m), 1.44—1.51 (3H, m), 3.27—3.34 (1H, m), 3.29 (3H, s), 3.60 (2H, s), 3.62 (1H, dd, J=3.4, 17.6 Hz), 3.85 (1H, dd, J=4.8, 17.6 Hz), 3.93—3.96 (1H, m), 4.45 (2H, d, J=3.4 Hz), 6.49 (1H, br s), 6.68 (1H, d, J=7.8 Hz), 6.87 (1H, d, J=7.8 Hz), 6.95—6.99 (2H, m), 7.12 (1H, dd, J=1.4, 7.8 Hz), 7.18 (1H, t, J=7.8 Hz), 7.25—7.29, 7.40—7.49 (6H, m), 7.57—7.61 (2H, m); IR: 3348, 1738, 1668, 1646, 1616, 1598, 1564, 1498, 1454, 1436, 1414 cm^{-1}.

***N*-(2-Benzyloxyphenyl)cyclopropylcarboxamide (24a)** To a solution of **23** (4.0 g, 20 mmol) and cyclopropylcarboxylic acid (1.7 g, 20 mmol) in CH_2Cl_2 (50 ml) were added EDC·HCl (4.6 g, 24 mmol) and DMAP (2.9 g,

24 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 $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was washed with *n*-hexane to give **24a** (4.7 g, 88%) as a white solid, mp 77—79 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.78—0.83 (2H, m), 1.04—1.08 (2H, m), 1.45—1.48 (1H, m), 5.12 (2H, s), 6.93—7.00 (3H, m), 7.36—7.43 (5H, m), 8.00 (1H, br s), 8.37 (1H, br s).

Compounds **24b**—**f** were obtained by following an analogous procedure to that described for the preparation of **24a**. Spectroscopic data for these compounds are as follows:

N-(2-Benzyloxyphenyl)cyclobutylcarboxamide (**24b**): 68%. **24b** was prepared by replacing cyclopropylcarboxylic acid with cyclobutylcarboxylic acid. ^{1}H-NMR ($CDCl_3$) δ: 1.88—2.04 (2H, m), 2.15—2.24 (2H, m), 2.30—2.40 (2H, m), 3.11—3.19 (1H, m), 5.11 (2H, s), 6.93—7.01 (3H, m), 7.34—7.44 (5H, m), 7.75 (1H, br s), 8.42 (1H, dd, J=1.9, 8.8 Hz).

N-(2-Benzyloxyphenyl)cyclopentylcarboxamide (**24c**): 81%. **24c** was prepared by replacing cyclopropylcarboxylic acid with cyclopentylcarboxylic acid. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.89 (8H, m), 2.64—2.72 (1H, m), 5.12 (2H, s), 6.93—6.99 (3H, m), 7.30—7.45 (5H, m), 7.84 (1H, br s), 8.41 (1H, d, J=7.4 Hz).

N-(2-Benzyloxyphenyl)cycloheptylcarboxamide (**24d**): 96%. **24d** was prepared by replacing cyclopropylcarboxylic acid with cycloheptylcarboxylic acid. ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.80, 1.93—2.00 (12H, m), 2.34—2.41 (1H, m), 5.13 (2H, s), 6.93—7.01 (3H, m), 7.37—7.42 (5H, m), 7.80 (1H, br s), 8.38 (1H, dd, J=1.9, 7.3 Hz).

N-(2-Benzyloxyphenyl)-1-adamantylcarboxamide (**24e**): 73%. **24e** was prepared by replacing cyclopropylcarboxylic acid with 1-adamantylcarboxylic acid. mp 117—119 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.66—1.76, 1.90—1.91 (12H, m), 2.04 (3H, br s), 5.13 (2H, s), 6.94—7.03 (3H, m), 7.34—7.44 (5H, m), 8.19 (1H, br s), 8.43 (1H, dd, J=1.9, 7.3 Hz).

N-(2-Benzyloxyphenyl)-2-ethylbutanamide (**24f**): 70%. **24f** was prepared by replacing cyclopropylcarboxylic acid with 2-ethylbutanoic acid. mp 48—49 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, t, J=7.3 Hz), 1.50—1.56 (2H, m), 1.65—1.72 (2H, m), 2.00—2.03 (1H, m), 5.12 (2H, s), 6.94—7.02 (3H, m), 7.36—7.42 (5H, m), 7.80 (1H, br s), 8.42 (1H, d, J=7.3 Hz).

***N*-(2-Benzyloxyphenyl)-2,2-dimethylpropanamide (24g)** To a solution of **23** (4.0 g, 20 mmol) and pyridine (1.8 ml, 22 mmol) in CH_2Cl_2 (100 ml) was added a solution of 2,2-dimethylpropanoyl chloride (2.7 ml, 22 mmol) in CH_2Cl_2 (30 ml) with ice cooling, and the mixture was stirred at room temperature for 1.5 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 **24g** (5.4 g, 95%) as a dark brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (9H, s), 5.12 (2H, s), 6.95—7.03 (3H, m), 7.34—7.42 (5H, m), 8.22 (1H, br s), 8.42 (1H, d, J=7.3 Hz).

Compounds **24h** was obtained by following an analogous procedure to that described for the preparation of **24g**. Spectroscopic data for this compound are as follows:

N-(2-Benzyloxyphenyl)-3,3-dimethylbutanamide (**24h**): 94%. **24h** was prepared by replacing 2,2-dimethylpropanoyl chloride with 3,3-dimethylbutanoyl chloride. mp 87—89 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (9H, s), 2.20 (2H, s), 5.11 (2H, s), 6.94—7.02 (3H, m), 7.36—7.41 (5H, m), 7.71 (1H, br s), 8.39 (1H, d, J=7.8 Hz).

***N*-Cyclopropylmethyl-2-benzyloxyaniline (25a)** To a solution of **24a** (4.0 g, 15 mmol) in THF (50 ml) was added BH_3–THF complex (1.0 M in THF, 45 ml, 45 mmol) with ice cooling under N_2, and the mixture was stirred at room temperature for 3 d. After adding ice-water and K_2CO_3 to the reaction mixture, the resulting 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 (5 : 1). The eluate was concentrated under reduced pressure to give **25a** (2.9 g, 76%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.21—0.25 (2H, m), 0.51—0.55 (2H, m), 1.10—1.13 (1H, m), 2.98 (2H, d, J=6.8 Hz), 4.38 (1H, br s), 5.09 (2H, s), 6.60—6.64 (2H, m), 6.82—6.89 (2H, m), 7.31—7.45 (5H, m).

Compounds **25b**—**h** were obtained by following an analogous procedure to that described for the preparation of **25a**. Spectroscopic data for these compounds are as follows:

N-Cyclobutylmethyl-2-benzyloxyaniline (**25b**): Quant. ^{1}H-NMR ($CDCl_3$) δ: 1.71—1.78 (2H, m), 1.87—1.98 (2H, m), 2.08—2.14 (2H, m), 2.56—2.67 (1H, m), 3.14 (2H, d, J=7.3 Hz), 4.24 (1H, br s), 5.07 (2H, s), 6.62 (2H, d, J=7.8 Hz), 6.82 (1H, dd, J=1.0, 7.8 Hz), 6.88 (1H, t, J=7.8 Hz), 7.33—7.43 (5H, m).

N-Cyclopentylmethyl-2-benzyloxyaniline (**25c**): 84%. ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.31, 1.55—1.65, 1.77—1.84 (8H, m), 2.15—2.28 (1H, m), 3.05 (2H, d, J=7.3 Hz), 4.31 (1H, br s), 5.08 (2H, s), 6.59—6.64 (2H, m), 6.82—6.90 (2H, m), 7.33—7.43 (5H, m).

N-Cycloheptylmethyl-2-benzyloxyaniline (**25d**): 60%. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.83 (13H, m), 2.96 (2H, d, J=6.9 Hz), 4.50 (1H, br s), 5.08 (2H, s), 6.61 (2H, d, J=7.8 Hz), 6.82 (1H, dd, J=1.4, 7.8 Hz), 6.88 (1H, t, J=7.8 Hz), 7.33—7.43 (5H, m).

N-(1-Adamantylmethyl)-2-benzyloxyaniline (**25e**): 55%. ^{1}H-NMR ($CDCl_3$) δ: 1.59—1.75 (12H, m), 1.99 (3H, br s), 2.82 (2H, d, J=5.8 Hz), 4.38 (1H, br s), 5.10 (2H, s), 6.58—6.66 (2H, m), 6.81—6.90 (2H, m), 7.32—7.46 (5H, m).

N-(2-Ethylbutyl)-2-benzyloxyaniline (**25f**): 71%. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (6H, t, J=7.3 Hz), 1.26—1.43 (4H, m), 1.51—1.56 (1H, m), 3.03 (2H, d, J=6.4 Hz), 4.29 (1H, br s), 5.08 (2H, s), 6.61—6.64 (2H, m), 6.83 (1H, d, J=7.8 Hz), 6.88 (1H, t, J=7.3 Hz), 7.31—7.43 (5H, m).

N-(2,2-Dimethylpropyl)-2-benzyloxyaniline (**25g**): 72%. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s), 2.91 (2H, s), 4.34 (1H, br s), 5.09 (2H, s), 6.60 (1H, t, J=7.8 Hz), 6.64 (1H, d, J=7.8 Hz), 6.83 (1H, d, J=7.8 Hz), 6.87 (1H, t, J=7.8 Hz), 7.31—7.44 (5H, m).

N-(3,3-Dimethylbutyl)-2-benzyloxyaniline (**25h**): 80%. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (9H, s), 1.55 (2H, t, J=7.3 Hz), 3.13 (2H, t, J=7.3 Hz), 4.13 (1H, br s), 5.07 (2H, s), 6.60—6.64 (2H, m), 6.83 (1H, d, J=7.8 Hz), 6.89 (1H, t, J=7.8 Hz), 7.33—7.43 (5H, m).

Compounds **26a**—**h** were obtained by following an analogous procedure to that described for the preparation of **19a**. Spectroscopic data for these compounds, except for **26b**—**d**, are as follows. Compounds **26b**—**d** were used for the subsequent reaction without purification.

N-(2-Benzyloxyphenyl)-*N*-cyclopropylmethyl-2-(*N*-phthaloylamino)acetamide (**26a**): 92%. ^{1}H-NMR ($CDCl_3$) δ: 0.04—0.07 (2H, m), 0.33—0.35 (2H, m), 0.90—0.94 (1H, m), 3.31 (1H, dd, J=7.3, 14.1 Hz), 3.78 (1H, dd, J=7.3, 14.1 Hz), 4.19 (2H, s), 5.14 (1H, d, J=12.2 Hz), 5.25 (1H, d, J=12.2 Hz), 7.02—7.09 (2H, m), 7.32—7.51 (7H, m), 7.68—7.70 (2H, m), 7.83—7.85 (2H, m).

N-(1-Adamantylmethyl)-*N*-(2-benzyloxyphenyl)-2-(*N*-phthaloylamino)acetamide (**26e**): 74%. mp 207—209 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.61 (12H, m), 1.82 (3H, br s), 3.47 (2H, s), 4.16 (1H, d, J=16.6 Hz), 4.28 (1H, d, J=16.6 Hz), 5.18 (1H, d, J=11.8 Hz), 5.31 (1H, d, J=11.8 Hz), 7.03—7.10 (2H, m), 7.30—7.46 (5H, m), 7.57 (2H, d, J=7.3 Hz), 7.67—7.71 (2H, m), 7.83—7.85 (2H, m).

N-(2-Benzyloxyphenyl)-*N*-(2-ethylbutyl)-2-(*N*-phthaloylamino)acetamide (**26f**): 89%. mp 130—132 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.68 (3H, t, J=7.3 Hz), 0.80 (3H, t, J=7.3 Hz), 1.24—1.42 (5H, m), 3.41 (1H, dd, J=4.3, 14.1 Hz), 3.81 (1H, dd, J=7.8, 14.1 Hz), 4.17 (2H, ABq, J=16.6 Hz), 5.16 (1H, d, J=12.2 Hz), 5.27 (1H, d, J=12.2 Hz), 7.03—7.10 (2H, m), 7.32—7.35 (3H, m), 7.42 (2H, t, J=7.3 Hz), 7.52 (2H, d, J=7.3 Hz), 7.68—7.70 (2H, m), 7.83—7.85 (2H, m).

N-(2-Benzyloxyphenyl)-*N*-(2,2-dimethylpropyl)-2-(*N*-phthaloylamino)acetamide (**26g**): 95%. mp 145—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (9H, s), 3.56 (1H, d, J=14.2 Hz), 3.64 (1H, d, J=14.2 Hz), 4.16 (1H, d, J=16.6 Hz), 4.25 (1H, d, J=16.6 Hz), 5.17 (1H, d, J=12.2 Hz), 5.29 (1H, d, J=12.2 Hz), 7.04 (1H, t, J=7.8 Hz), 7.09 (1H, d, J=7.8 Hz), 7.30—7.36 (2H, m), 7.41—7.45 (3H, m), 7.55 (2H, d, J=7.3 Hz), 7.67—7.70 (2H, m), 7.83—7.85 (2H, m).

N-(2-Benzyloxyphenyl)-*N*-(3,3-dimethylbutyl)-2-(*N*-phthaloylamino)acetamide (**26h**): 92%. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (9H, s), 1.40—1.49 (2H, m), 3.45—3.53 (1H, m), 3.81—3.88 (1H, m), 4.15 (2H, ABq, J=16.6 Hz), 5.17 (1H, d, J=12.2 Hz), 5.28 (1H, d, J=12.2 Hz), 7.04 (1H, t, J=7.8 Hz), 7.08 (1H, d, J=7.8 Hz), 7.31—7.51 (7H, m), 7.68—7.70 (2H, m), 7.83—7.85 (2H, m).

Compounds **27a**—**h** were obtained by following an analogous procedure to that described for the preparation of **20a** and used for the subsequent reaction without purification. Spectroscopic data for these compounds are as follows:

N-(2-Benzyloxyphenyl)-*N*-cyclopropylmethyl-2-aminoacetamide (**27a**): ^{1}H-NMR ($CDCl_3$) δ: 0.07—0.10 (2H, m), 0.35—0.38 (2H, m), 0.92—0.96 (1H, m), 1.65 (2H, br s), 2.99 (1H, d, J=17.1 Hz), 3.12 (1H, d, J=17.1 Hz), 3.30 (1H, dd, J=7.3, 14.1 Hz), 3.81 (1H, dd, J=7.3, 14.1 Hz), 5.10 (2H, s), 6.97—7.05 (3H, m), 7.21 (1H, dd, J=2.0, 7.8 Hz), 7.30—7.40 (5H, m).

N-(2-Benzyloxyphenyl)-*N*-cyclobutylmethyl-2-aminoacetamide (**27b**): ^{1}H-NMR ($CDCl_3$) δ: 1.59—1.97 (8H, m), 2.42—2.49 (1H, m), 2.95 (1H, d, J=17.1 Hz), 3.08 (1H, d, J=17.1 Hz), 3.51 (1H, dd, J=7.3, 13.2 Hz), 3.99 (1H, dd, J=7.8, 13.2 Hz), 5.09 (2H, s), 6.97 (1H, t, J=7.8 Hz), 7.03 (1H, d, J=7.4 Hz), 7.08 (1H, d, J=7.8 Hz), 7.28—7.39 (6H, m).

N-(2-Benzyloxyphenyl)-*N*-cyclopentylmethyl-2-aminoacetamide (**27c**): ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.32, 1.44—1.71 (10H, m), 1.96—2.08 (1H, m), 2.96 (1H, d, J=17.1 Hz), 3.10 (1H, d, J=17.1 Hz), 3.39 (1H, dd, J=6.8, 13.2 Hz), 3.92 (1H, dd, J=8.3, 13.2 Hz), 5.10 (2H, s), 6.98 (1H, t, J=7.8 Hz), 7.04 (1H, d, J=8.3 Hz), 7.14 (1H, d, J=7.8 Hz), 7.29—7.38 (6H, m).

N-(2-Benzyloxyphenyl)-*N*-cycloheptylmethyl-2-aminoacetamide (**27d**): ^{1}H-NMR ($CDCl_3$) δ: 1.13—1.70 (15H, m), 2.97 (1H, d, J=17.1 Hz), 3.10 (1H, d, J=17.1 Hz), 3.26 (1H, dd, J=6.9, 13.1 Hz), 3.85 (1H, dd, J=8.3, 13.1 Hz), 5.10 (2H, s), 6.99 (1H, dt, J=1.5, 7.8 Hz), 7.04 (1H, d, J=7.8 Hz), 7.11 (1H, dd, J=1.5, 7.8 Hz), 7.30—7.39 (6H, m).

N-(1-Adamantylmethyl)-*N*-(2-benzyloxyphenyl)-2-aminoacetamide (**27e**): ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.64 (12H, m), 1.78 (3H, br s), 1.87 (2H, br s), 3.03 (1H, d, J=17.1 Hz), 3.12 (1H, d, J=17.1 Hz), 3.42 (1H, d, J=13.7 Hz), 3.53 (1H, d, J=13.7 Hz), 5.12 (2H, s), 6.99 (1H, t, J=7.8 Hz), 7.03 (1H, d, J=7.8 Hz), 7.23—7.39 (7H, m).

N-(2-Benzyloxyphenyl)-*N*-(2-ethylbutyl)-2-aminoacetamide (**27f**): ^{1}H-NMR ($CDCl_3$) δ: 0.74 (3H, t, J=7.3 Hz), 0.83 (3H, t, J=7.3 Hz), 1.27—1.42 (5H, m), 1.70 (2H, br s), 2.98 (1H, d, J=17.1 Hz), 3.10 (1H, d, J=17.1 Hz), 3.38 (1H, dd, J=5.4, 13.7 Hz), 3.86 (1H, dd, J=6.8, 13.7 Hz), 5.10 (2H, s), 6.99 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=8.3 Hz), 7.11 (1H, dd, J=1.5, 7.8 Hz), 7.29—7.40 (6H, m).

N-(2-Benzyloxyphenyl)-*N*-(2,2-dimethylpropyl)-2-aminoacetamide (**27g**): ^{1}H-NMR ($CDCl_3$) δ: 0.86 (9H, s), 1.69 (2H, br s), 3.02 (1H, d, J=17.1 Hz), 3.11 (1H, d, J=17.1 Hz), 3.58 (1H, d, J=13.7 Hz), 3.65 (1H, d, J=13.7 Hz), 5.10 (2H, s), 6.98 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=8.3 Hz), 7.20—7.38 (7H, m).

N-(2-Benzyloxyphenyl)-*N*-(3,3-dimethylbutyl)-2-aminoacetamide (**27h**): ^{1}H-NMR ($CDCl_3$) δ: 0.87 (9H, s), 1.40—1.48 (2H, m), 1.67 (2H, br s), 2.95 (1H, d, J=17.1 Hz), 3.06 (1H, d, J=17.1 Hz), 3.45—3.52 (1H, m), 3.83—3.90 (1H, m), 5.11 (2H, s), 6.99 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=8.3 Hz), 7.11 (1H, d, J=7.8 Hz), 7.30—7.38 (6H, m).

Compounds **28a** and **28e**—**h** were obtained by following an analogous procedure to that described for the preparation of **13**. Spectroscopic data for these compounds are as follows:

Methyl 2-[3-[3-[*N*-(2-Benzyloxyphenyl)-*N*-cyclopropylmethylcarbamoylmethyl]ureido]phenyl]acetate (**28a**): 44% from **26a**. mp 132—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.01—0.06 (2H, m), 0.33—0.37 (2H, m), 0.90—0.94 (1H, m), 3.26 (1H, dd, J=7.3, 13.6 Hz), 3.54 (2H, s), 3.65 (1H, dd, J=3.9, 17.6 Hz), 3.65 (3H, s), 3.85 (1H, dd, J=6.9, 13.6 Hz), 3.93 (1H, dd, J=4.9, 17.6 Hz), 5.09 (2H, ABq, J=11.7 Hz), 6.15 (1H, br s), 6.90 (1H, d, J=6.8 Hz), 7.00 (1H, d, J=7.4 Hz), 7.04 (1H, dd, J=1.0, 8.3 Hz), 7.13—7.19, 7.26—7.36 (11H, m).

Methyl 2-[3-[3-[*N*-(1-Adamantylmethyl)-*N*-(2-benzyloxyphenyl)carbamoylmethyl]ureido]phenyl]acetate (**28e**): 71% from **26e**. ^{1}H-NMR ($CDCl_3$) δ: 1.41—1.61 (12H, m), 1.83 (3H, br s), 3.35 (1H, d, J=13.7 Hz), 3.54 (2H, s), 3.57 (1H, d, J=13.7 Hz), 3.65 (3H, s), 3.67 (1H, dd, J=3.9, 17.6 Hz), 3.90 (1H, dd, J=4.9, 17.6 Hz), 5.11 (2H, ABq, J=11.7 Hz), 6.03 (1H, br s), 6.90—7.04, 7.11—7.19, 7.22—7.38 (14H, m).

Methyl 2-[3-[3-[*N*-(2-Benzyloxyphenyl)-*N*-(2-ethylbutyl)carbamoylmethyl]-ureido]phenyl]acetate (**28f**): 20% from **26f**. mp 120—122 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, t, J=7.3 Hz), 0.81 (3H, t, J=7.3 Hz), 1.21—1.40 (5H, m), 3.35 (1H, dd, J=5.9, 13.2 Hz), 3.56 (2H, s), 3.61 (1H, dd, J=3.9, 17.6 Hz), 3.67 (3H, s), 3.85—3.92 (2H, m), 5.11 (2H, ABq, J=12.2 Hz), 5.90 (1H, br s), 6.83 (1H, br s), 6.93 (1H, d, J=7.4 Hz), 7.01 (1H, t, J=7.3 Hz), 7.05 (1H, d, J=8.3 Hz), 7.14—7.22, 7.26—7.35 (10H, m).

Methyl 2-[3-[3-[*N*-(2-Benzyloxyphenyl)-*N*-(2,2-dimethylpropyl)carbamoylmethyl]ureido]phenyl]acetate (**28g**): 19% from **26g**. mp 123—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (9H, s), 3.51 (1H, d, J=16.5 Hz), 3.53 (2H, s), 3.63—3.71 (2H, m), 3.65 (3H, s), 3.91 (1H, dd, J=4.4, 17.6 Hz), 5.10 (2H, ABq, J=12.2 Hz), 6.06 (1H, br s), 6.90 (1H, d, J=7.4 Hz), 6.99 (1H, t, J=7.8 Hz), 7.02 (1H, d, J=7.8 Hz), 7.10 (1H, d, J=7.8 Hz), 7.16 (1H, t, J=8.3 Hz), 7.27—7.38 (9H, m).

Methyl 2-[3-[3-[*N*-(2-Benzyloxyphenyl)-*N*-(3,3-dimethylbutyl)carbamoylmethyl]ureido]phenyl]acetate (**28h**): 46% from **26h**. mp 133—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (9H, s), 1.39—1.46 (2H, m), 3.46—3.49 (1H, m), 3.53 (2H, s), 3.61 (1H, dd, J=4.9, 17.1 Hz), 3.65 (3H, s), 3.84—3.90 (2H, m), 5.10 (2H, ABq, J=12.2 Hz), 6.17 (1H, br s), 6.90 (1H, d, J=7.3 Hz), 7.00 (1H, t, J=7.8 Hz), 7.04 (1H, d, J=7.3 Hz), 7.09 (1H, d, J=8.3 Hz), 7.13—7.18 (2H, m), 7.26—7.38 (8H, m).

Methyl 2-[3-[3-[*N*-(2-Benzyloxyphenyl)-*N*-cyclobutylmethylcarbamoylmethyl]ureido]phenyl]acetate (28b) To a solution of **12** (1.3 g, 7.7 mmol) and pyridine (0.61 g, 7.7 mmol) in CH_2Cl_2 (100 ml) was added triphosgene (0.76 g, 2.6 mmol) at −30 °C and the mixture was stirred at the same temperature for 0.5 h. Then, after adding pyridine (0.61 g, 7.7 mmol) and a solution of crude **27b** (2.5 g) in CH_2Cl_2 (20 ml) to the reaction mixture, the resulting mixture was stirred overnight at room temperature. The reaction mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica-gel eluting with $CHCl_3$–MeOH (50 : 1). The eluate was concentrated under reduced pressure to give **28b** (3.4 g, 85% from **25b**) as a pale yellow amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.93 (6H, m), 2.41—2.49 (1H, m), 3.48 (1H, dd, J=7.3, 13.2 Hz), 3.57 (2H, s), 3.67 (3H, s), 3.68 (1H, d, J=17.6 Hz), 3.85 (1H, dd, J=4.9, 17.6 Hz), 4.01 (1H, dd, J=7.8, 13.2 Hz), 5.10 (2H, ABq, J=11.8 Hz), 5.93 (1H, br s), 6.91—6.95 (2H, m), 6.99 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=8.3 Hz), 7.12—7.36 (10H, m).

Compounds **28c**, **d** were obtained by following an analogous procedure to that described for the preparation of **28b**. Spectroscopic data for these compounds are as follows:

Methyl 2-[3-[3-[*N*-(2-Benzyloxyphenyl)-*N*-cyclopentylmethylcarbamoylmethyl]ureido]phenyl]acetate (**28c**): 45% from **25c**. ^{1}H-NMR ($CDCl_3$) δ: 1.13—1.78 (8H, m), 1.97—2.05 (1H, m), 3.36 (1H, dd, J=7.3, 13.7 Hz), 3.57 (2H, s), 3.59 (1H, d, J=17.6 Hz), 3.67 (3H, s), 3.85 (1H, dd, J=4.4, 17.6 Hz), 3.93 (1H, dd, J=8.3, 13.7 Hz), 5.10 (2H, ABq, J=11.5 Hz), 5.86 (1H, br s), 6.72 (1H, s), 6.94 (1H, d, J=7.4 Hz), 7.01 (1H, t, J=7.8 Hz), 7.06 (1H, d, J=8.8 Hz), 7.12—7.35 (10H, m).

Methyl 2-[3-[3-[*N*-(2-Benzyloxyphenyl)-*N*-cycloheptylmethylcarbamoylmethyl]ureido]phenyl]acetate (**28d**): 79% from **25d**. ^{1}H-NMR ($CDCl_3$) δ: 1.09—1.66 (13H, m), 3.23 (1H, dd, J=5.8, 13.2 Hz), 3.55 (2H, s), 3.64 (1H, dd, J=4.0, 17.6 Hz), 3.66 (3H, s), 3.84—3.92 (2H, m), 5.11 (2H, ABq, J=12.2 Hz), 6.03 (1H, br s), 6.92 (1H, d, J=7.8 Hz), 7.00—7.21, 7.26—7.36 (13H, m).

Methyl 2-[3-[3-[*N*-Cyclopropylmethyl-*N*-(2-hydroxyphenyl)carbamoylmethyl]ureido]phenyl]acetate (29a) **28a** (2.1 g, 4.2 mmol) was hydrogenated in a mixture of MeOH (50 ml) and AcOEt (50 ml) over 5% Pd–C (0.4 g) at atmospheric pressure for 3 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **29a** (1.7 g, 96%) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.11—0.12 (2H, m), 0.42—0.44 (2H, m), 0.99—1.01 (1H, m), 3.45—3.53 (2H, m), 3.48 (2H, s), 3.65 (3H, s), 3.67—3.73 (1H, m), 3.94 (1H, dd, J=5.9, 17.1 Hz), 6.42 (1H, br s), 6.83 (1H, d, J=7.3 Hz), 6.89 (1H, t, J=7.8 Hz), 7.04—7.22 (6H, m), 7.65 (1H, s), 8.61 (1H, br s).

Compounds **29b**—**h** were obtained by following an analogous procedure to that described for the preparation of **29a**. Spectroscopic data for these compounds are as follows:

Methyl 2-[3-[3-[*N*-Cyclobutylmethyl-*N*-(2-hydroxyphenyl)carbamoylmethyl]ureido]phenyl]acetate (**29b**): 66%. ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.72 (4H, m), 1.78—1.86 (1H, m), 1.94—2.01 (1H, m), 2.47—2.55 (1H, m), 3.45 (1H, dd, J=5.4, 17.1 Hz), 3.50 (2H, s), 3.67 (3H, s), 3.74-3.86 (2H, m), 3.93 (1H, dd, J=5.8, 17.1 Hz), 6.45 (1H, br s), 6.84—6.90 (2H, m), 7.00—7.24 (6H, m), 7.63 (1H, br s), 8.67 (1H, br s).

Methyl 2-[3-[3-[*N*-Cyclopentylmethyl-*N*-(2-hydroxyphenyl)carbamoylmethyl]ureido]phenyl]acetate (**29c**): 96%. ^{1}H-NMR ($CDCl_3$) δ: 1.21—1.31, 1.47—1.78 (8H, m), 2.05—2.10 (1H, m), 3.46 (1H, dd, J=4.9, 17.1 Hz), 3.49 (2H, s), 3.65 (1H, dd, J=5.8, 13.7 Hz), 3.66 (3H, s), 3.76 (1H, dd, J=5.4, 13.7 Hz), 3.94 (1H, dd, J=5.4, 17.1 Hz), 6.49 (1H, br s), 6.84 (1H, d, J=7.3 Hz), 6.89 (1H, t, J=7.3 Hz), 7.05—7.24 (6H, m), 7.64 (1H, br s), 8.80 (1H, br s).

Methyl 2-[3-[3-[*N*-Cycloheptylmethyl-*N*-(2-hydroxyphenyl)carbamoylmethyl]ureido]phenyl]acetate (**29d**): Quant. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.87 (13H, m), 3.43—3.51 (1H, m), 3.46 (2H, s), 3.64 (3H, s), 3.67—3.76 (2H, m), 3.99 (1H, dd, J=5.9, 17.1 Hz), 6.57 (1H, br s), 6.81—6.88 (2H, m), 7.01—7.20 (6H, m), 7.91 (1H, s), 9.08 (1H, br s).

Methyl 2-[3-[3-[*N*-(1-Adamantylmethyl)-*N*-(2-hydroxyphenyl)carbamoylmethyl]ureido]phenyl]acetate (**29e**): 99%. ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.64 (12H, m), 1.86 (3H, br s), 3.39 (1H, d, J=13.7 Hz), 3.47 (2H, s), 3.50 (1H, d, J=13.7 Hz), 3.64 (3H, s), 3.66 (1H, dd, J=2.9, 17.1 Hz), 4.03 (1H, dd, J=5.4, 17.1 Hz), 6.56 (1H, br s), 6.74—6.85, 7.00—7.21 (8H, m), 7.95 (1H, s), 9.18 (1H, br s).

Methyl 2-[3-[3-[*N*-(2-Ethylbutyl)-*N*-(2-hydroxyphenyl)carbamoylmethyl]-ureido]phenyl]acetate (**29f**): Quant. ^{1}H-NMR ($CDCl_3$) δ: 0.77—0.83 (6H, m), 1.26—1.43 (5H, m), 3.45 (1H, dd, J=4.9, 16.6 Hz), 3.48 (2H, s), 3.58 (1H, dd, J=5.9, 13.7 Hz), 3.65 (3H, s), 3.75 (1H, dd, J=7.3, 13.7 Hz), 3.98 (1H, dd, J=6.4, 16.6 Hz), 6.54 (1H, br s), 6.83 (1H, d, J=7.3 Hz), 6.88 (1H, t, J=7.3 Hz), 7.03—7.22 (6H, m), 7.75 (1H, br s), 8.93 (1H, br s).

Methyl 2-[3-[3-[*N*-(2-Hydroxyphenyl)-*N*-(2,2-dimethylpropyl)carbamoyl-

methyl]ureido]phenyl]acetate (**29g**): Quant. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (9H, s), 3.42—3.46 (2H, m), 3.46 (2H, s), 3.65 (3H, s), 3.92 (1H, d, J=13.7 Hz), 4.07 (1H, dd, J=5.9, 17.1 Hz), 6.58 (1H, br s), 6.82 (1H, d, J=7.8 Hz), 6.86 (1H, t, J=7.3 Hz), 7.02—7.17 (6H, m), 7.71 (1H, s), 9.14 (1H, br s).

Methyl 2-[3-[3-[*N*-(2-Hydroxyphenyl)-*N*-(3,3-dimethylbutyl)carbamoylmethyl]ureido]phenyl]acetate (**29h**): 98%. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (9H, s), 1.45—1.53 (2H, m), 3.46 (2H, s), 3.46—3.50 (1H, m), 3.55—3.59 (1H, m), 3.63 (3H, s), 3.79—3.87 (1H, m), 3.97 (1H, dd, J=5.8, 17.1 Hz), 6.56 (1H, br s), 6.81 (1H, d, J=7.3 Hz), 6.86 (1H, t, J=7.8 Hz), 7.03—7.21 (6H, m), 7.99 (1H, br s), 9.09 (1H, br s).

Methyl 2-[3-[3-[*N*-Cyclopropylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (30a) A mixture of **29a** (0.5 g, 1.2 mmol), **9** (0.34 g, 1.5 mmol), and K_2CO_3 (0.41 g, 3.0 mmol) in DMF (30 ml) was stirred at 70 °C for 3.5 h. Ice-water was added to the reaction mixture 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 eluting with $CHCl_3$–MeOH (50 : 1). The eluate was concentrated under reduced pressure to give **30a** (0.7 g, quant.) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.01—0.07 (2H, m), 0.32—0.36 (2H, m), 0.90—0.93 (1H, m), 3.18 (1H, dd, J=7.3, 13.6 Hz), 3.33 (3H, s), 3.56 (2H, s), 3.66 (3H, s), 3.81—3.96 (3H, m), 4.47 (2H, s), 6.12 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.4 Hz), 6.98 (1H, t, J=7.3 Hz), 7.15—7.31, 7.44—7.52 (11H, m).

Compounds **30b**—**h** were obtained by following an analogous procedure to that described for the preparation of **30a**. Spectroscopic data for these compounds are as follows:

Methyl 2-[3-[3-[*N*-Cyclobutylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**30b**): 85%. mp 112—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.90 (6H, m), 2.39—2.46 (1H, m), 3.34 (3H, s), 3.42 (1H, dd, J=7.3, 13.2 Hz), 3.56 (2H, s), 3.67 (3H, s), 3.79—3.91 (2H, m), 3.99 (1H, dd, J=7.8, 13.2 Hz), 4.48 (2H, s), 6.01 (1H, s), 6.63 (1H, d, J=8.3 Hz), 6.89 (1H, d, J=7.8 Hz), 6.96 (1H, t, J=7.8 Hz), 7.11 (1H, d, J=7.8 Hz), 7.16—7.32, 7.42—7.53 (10H, m).

Methyl 2-[3-[3-[*N*-Cyclopentylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**30c**): 61%. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.31, 1.46—1.59 (8H, m), 1.94—2.00 (1H, m), 3.30—3.34 (1H, m), 3.34 (3H, s), 3.57 (2H, s), 3.67 (3H, s), 3.86—3.92 (3H, m), 4.48 (2H, s), 5.95 (1H, br s), 6.64 (1H, d, J=7.8 Hz), 6.90 (1H, d, J=7.4 Hz), 6.98 (1H, t, J=7.8 Hz), 7.17—7.32, 7.43—7.53 (11H, m).

Methyl 2-[3-[3-[*N*-Cycloheptylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**30d**): 85%. mp 123—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.68 (13H, m), 3.20 (1H, dd, J=5.9, 13.2 Hz), 3.33 (3H, s), 3.56 (2H, s), 3.66 (3H, s), 3.85—3.93 (3H, m), 4.48 (2H, s), 6.04 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.89 (1H, d, J=7.4 Hz), 6.98 (1H, t, J=7.3 Hz), 7.14—7.31, 7.44—7.53 (11H, m).

Methyl 2-[3-[3-[*N*-(1-Adamantylmethyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**30e**): 60%. mp 166—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41—1.63 (12H, m), 1.88 (3H, br s), 3.29 (1H, d, J=13.0 Hz), 3.32 (3H, s), 3.54 (2H, s), 3.61 (1H, d, J=16.6 Hz), 3.65 (3H, s), 3.81 (1H, d, J=13.0 Hz), 3.92 (1H, dd, J=4.8, 16.6 Hz), 4.50 (2H, s), 6.09 (1H, br s), 6.64 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.3 Hz), 6.97 (1H, t, J=7.8 Hz), 7.13—7.31, 7.40—7.50 (11H, m).

Methyl 2-[3-[3-[*N*-(2-Ethylbutyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetate (**30f**): 85%. mp 103—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, t, J=7.3 Hz), 0.80 (3H, t, J=6.8 Hz), 1.25—1.36 (5H, m), 3.29—3.32 (1H, m), 3.32 (3H, s), 3.55 (2H, s), 3.66 (3H, s), 3.80 (1H, d, J=16.6 Hz), 3.83—3.94 (2H, m), 4.48 (2H, s), 6.14 (1H, br s), 6.66 (1H, d, J=8.3 Hz), 6.87 (1H, d, J=7.8 Hz), 6.98 (1H, t, J=7.3 Hz), 7.13—7.31, 7.41—7.52 (11H, m).

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2,2-dimethylpropyl)carbamoylmethyl]ureido]phenyl]acetate (**30g**): 99%. mp 132—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (9H, s), 3.32 (3H, s), 3.53—3.55 (1H, m), 3.55 (2H, s), 3.66 (3H, s), 3.67 (1H, m), 3.90 (2H, s), 4.50 (2H, s), 5.98 (1H, br s), 6.62 (1H, d, J=8.3 Hz), 6.88 (1H, d, J=7.3 Hz), 6.97 (1H, t, J=7.3 Hz), 7.17—7.28, 7.31—7.51 (11H, m).

Methyl 2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3,3-dimethylbutyl)carbamoylmethyl]ureido]phenyl]acetate (**30h**): 87%. mp 135—136 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (9H, s), 1.36—1.47 (2H, m), 3.31 (3H, s), 3.35—3.38 (1H, m), 3.54 (2H, s), 3.65 (3H, s), 3.85 (1H, d, J=17.1 Hz), 3.93 (1H, dd, J=4.9, 17.1 Hz), 3.97—4.01 (1H, m), 4.48 (2H, s), 6.26 (1H, br s), 6.68 (1H, d, J=7.8 Hz), 6.86 (1H, d, J=7.4 Hz), 6.98 (1H, t, J=7.3 Hz), 7.11—7.51 (10H, m), 7.72 (1H, s).

Compounds **31a**—**h** were obtained by following an analogous procedure to that described for the preparation of **14**; 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:

2-[3-[3-[*N*-Cyclopropylmethyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**31a**): ^{1}H-NMR ($CDCl_3$) δ: 0.05—0.09 (2H, m), 0.35—0.37 (2H, m), 0.92 (1H, m), 3.18 (1H, dd, J=7.3, 13.6 Hz), 3.28 (3H, s), 3.58 (2H, s), 3.63 (1H, d, J=17.6 Hz), 3.86—3.93 (2H, m), 4.44 (2H, ABq, J=12.2 Hz), 6.50 (1H, br s), 6.66 (1H, d, J=8.3 Hz), 6.86 (1H, d, J=7.8 Hz), 6.95—6.99 (2H, m), 7.16 (1H, t, J=7.8 Hz), 7.22—7.29, 7.39—7.48 (7H, m), 7.56 (1H, d, J=7.8 Hz), 7.66 (1H, s); IR: 3312, 1732, 1672, 1632, 1596, 1498, 1482, 1452, 1426, 1394 cm^{-1}.

2-[3-[3-[*N*-Cyclobutyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**31b**): ^{1}H-NMR ($CDCl_3$) δ: 1.56—1.93 (6H, m), 2.41—2.47 (1H, m), 3.30 (3H, s), 3.42 (1H, dd, J=7.3, 13.7 Hz), 3.58 (1H, d, J=17.6 Hz), 3.61 (2H, s), 3.85 (1H, dd, J=4.9, 17.6 Hz), 4.04 (1H, dd, J=7.8, 13.7 Hz), 4.44 (2H, ABq, J=15.1 Hz), 6.52 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.87 (1H, d, J=7.3 Hz), 6.93—6.97 (2H, m), 7.07 (1H, dd, J=1.4, 7.8 Hz), 7.19 (1H, t, J=7.8 Hz), 7.24—7.28, 7.38—7.49, 7.62—7.64 (8H, m); IR: 3364, 1734, 1700, 1634, 1550, 1496, 1434, 1402, 1378 cm^{-1}.

2-[3-[3-[*N*-Cyclopentyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**31c**): ^{1}H-NMR (DMSO-d_6) δ: 1.11—1.24, 1.44—1.61 (8H, m), 1.91—1.94 (1H, m), 3.19 (3H, s), 3.24—3.42 (2H, m), 3.45 (2H, s), 3.68 (1H, dd, J=4.9, 17.6 Hz), 3.82 (1H, dd, J=8.8, 13.2 Hz), 4.55 (2H, s), 6.28 (1H, br s), 6.76 (1H, d, J=7.3 Hz), 6.87 (1H, br s), 7.03 (1H, t, J=7.3 Hz), 7.12 (1H, t, J=8.3 Hz), 7.22—7.51 (9H, m), 8.81 (1H, s); IR: 3348, 1736, 1646, 1598, 1558, 1496, 1454, 1412, 1348 cm^{-1}.

2-[3-[3-[*N*-Cycloheptyl-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**31d**): ^{1}H-NMR (DMSO-d_6) δ: 1.09—1.69 (13H, m), 3.19 (3H, s), 3.36—3.49 (2H, m), 3.46 (2H, s), 3.67—3.78 (2H, m), 4.56 (2H, s), 6.28 (1H, br s), 6.77 (1H, d, J=7.3 Hz), 6.89 (1H, br s), 7.05 (1H, t, J=7.3 Hz), 7.13 (1H, t, J=7.4 Hz), 7.23—7.30, 7.34—7.50 (9H, m), 8.81 (1H, s); IR: 3384, 1722, 1640, 1596, 1554, 1496, 1454, 1422, 1346 cm^{-1}.

2-[3-[3-[*N*-(1-Adamantylmethyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**31e**): ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.62 (12H, m), 1.87 (3H, br s), 3.23 (1H, d, J=14.1 Hz), 3.29 (3H, s), 3.58 (2H, s), 3.59 (1H, d, J=17.6 Hz), 3.66 (1H, d, J=14.1 Hz), 3.91 (1H, dd, J=5.4, 17.6 Hz), 4.46 (2H, ABq, J=15.2 Hz), 6.44 (1H, br s), 6.65 (1H, d, J=8.3 Hz), 6.86 (1H, d, J=7.8 Hz), 6.94—6.98 (2H, m), 7.14—7.28, 7.37—7.48 (8H, m), 7.54 (1H, d, J=7.8 Hz), 7.64 (1H, s); IR: 3392, 1728, 1644, 1596, 1552, 1496, 1450, 1410, 1372 cm^{-1}.

2-[3-[3-[*N*-(2-Ethylbutyl)-*N*-[2-(*N*-methyl-*N*-phenylcarbamoylmethoxy)phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**31f**): ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, t, J=7.3 Hz), 0.81 (3H, t, J=7.3 Hz), 1.25—1.39 (5H, m), 3.29 (3H, s), 3.29—3.32 (1H, m), 3.59 (2H, s), 3.63 (1H, d, J=17.6 Hz), 3.85—3.95 (2H, m), 4.44 (2H, d, J=3.9 Hz), 6.51 (1H, br s), 6.68 (1H, d, J=8.3 Hz), 6.87 (1H, d, J=7.4 Hz), 6.96—6.99 (2H, m), 7.13 (1H, d, J=7.8 Hz), 7.17 (1H, t, J=7.8 Hz), 7.25—7.29, 7.38—7.49 (6H, m), 7.59—7.60 (2H, m); IR: 3348, 1736, 1664, 1646, 1618, 1598, 1564, 1496, 1454, 1436, 1410, 1384 cm^{-1}.

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2,2-dimethylpropyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**31g**): ^{1}H-NMR (DMSO-d_6) δ: 0.82 (9H, s), 3.20 (3H, s), 3.33 (2H, s), 3.43 (1H, d, J=17.6 Hz), 3.49 (1H, d, J=16.6 Hz), 3.67—3.76 (2H, m), 4.56 (2H, s), 6.28 (1H, br s), 6.76 (1H, d, J=7.3 Hz), 6.83 (1H, br s), 7.02 (1H, t, J=7.3 Hz), 7.12 (1H, t, J=7.8 Hz), 7.22—7.51 (9H, m), 8.79 (1H, s), 12.26 (1H, br s); IR: 3380, 1728, 1696, 1640, 1594, 1556, 1526, 1496, 1460, 1430, 1398 cm^{-1}.

2-[3-[3-[*N*-[2-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3,3-dimethylbutyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**31h**): ^{1}H-NMR ($CDCl_3$) δ: 0.84 (9H, s), 1.38—1.47 (2H, m), 3.29 (3H, s), 3.30—3.33 (1H, m), 3.59 (2H, s), 3.62 (1H, d, J=17.1 Hz), 3.85 (1H, dd, J=4.9, 17.1 Hz), 3.99—4.02 (1H, m), 4.46 (2H, d, J=6.4 Hz), 6.49 (1H, br s), 6.68 (1H, d, J=8.3 Hz), 6.87 (1H, d, J=7.3 Hz), 6.95—6.99 (2H, m), 7.13 (1H, d, J=7.4 Hz), 7.18 (1H, t, J=7.8 Hz), 7.26—7.28 (3H, m), 7.40—7.49 (3H, m), 7.58 (1H, d, J=8.3 Hz), 7.64 (1H, s); IR: 3372, 1728, 1630, 1596, 1556, 1496, 1464, 1434, 1368 cm^{-1}.

***N*-Methyl-*N*-phenyl-2-(3-nitrophenoxy)acetamide (33)** A mixture of 3-nitrophenol **32** (7.0 g, 50 mmol), **9** (13.7 g, 60 mmol) and K_2CO_3 (13.8 g, 100 mmol) in DMF (100 ml) was stirred overnight at 70 °C. Ice-water was added to the reaction mixture 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 product was washed with *n*-hexane to give **33** (12.7 g, 89%) as colorless needles, mp 95—96 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.34 (3H, s), 4.49 (2H, s), 7.20 (1H, d, J=7.3 Hz), 7.30 (2H, d, J=7.3 Hz), 7.31—7.55 (5H, m), 7.82 (1H, d, J=8.3 Hz).

Compound **34** was obtained by following an analogous procedure to that described for the preparation of **17**. Spectroscopic data for this compound are as follows:

N-Methyl-*N*-phenyl-2-(3-aminophenoxy)acetamide (**34**): 90%. mp 78—79 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.32 (3H, s), 3.63 (2H, br s), 4.36 (2H, s), 6.13—6.15 (2H, m), 6.27 (1H, d, J=8.3 Hz), 6.98 (1H, t, J=7.8 Hz), 7.23—7.26, 7.36—7.46 (5H, m).

Compounds from **35a**—**c** to **39a**—**c** were obtained by following an analogous procedure to that described for the preparation of **22a** from **18a**. Compounds **37a**—**c** were used for the subsequent reaction without purification; the yields, melting points and elemental analysis data of compounds **39a**—**c** are given in Table 6. Spectroscopic data for these compounds are as follows:

N-Methyl-*N*-phenyl-2-[3-(*N*-benzylamino)phenoxy]acetamide (**35a**): 64%. mp 115—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (3H, s), 4.01 (1H, br s), 4.27 (2H, s), 4.34 (2H, s), 6.08 (1H, d, J=8.3 Hz), 6.11 (1H, s), 6.23 (1H, dd, J=1.5, 7.8 Hz), 6.99 (1H, t, J=8.3 Hz), 7.19—7.44 (10H, m).

N-Methyl-*N*-phenyl-2-[3-[*N*-(2-methylpropyl)amino]phenoxy]acetamide (**35b**): 32%. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, J=6.3 Hz), 1.82—1.89 (1H, m), 2.87 (2H, d, J=6.8 Hz), 3.32 (3H, s), 3.85 (1H, br s), 4.37 (2H, s), 6.02 (1H, d, J=7.8 Hz), 6.10 (1H, s), 6.20 (1H, d, J=7.8 Hz), 6.98 (1H, t, J=7.8 Hz), 7.23—7.26, 7.36—7.46 (5H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[3-[*N*-(3-methylpentyl)amino]phenoxy]acetamide (**35c**): 41%. ^{1}H-NMR ($CDCl_3$) δ: 0.87—0.92 (6H, m), 1.16—1.24, 1.28—1.75 (5H, m), 3.02—3.09 (1H, m), 3.32 (3H, s), 3.54 (1H, br s), 4.09—4.15 (1H, m), 4.36 (2H, s), 6.02 (1H, d, J=7.3 Hz), 6.09 (1H, s), 6.19 (1H, d, J=7.8 Hz), 6.98 (1H, t, J=7.8 Hz), 7.22—7.46 (5H, m).

N-Methyl-*N*-phenyl-2-[3-[*N*-benzyl-*N*-[2-(*N*-phthaloylamino)-acetyl]amino]phenoxy]acetamide (**36a**): 80%. ^{1}H-NMR ($CDCl_3$) δ: 3.32 (3H, s), 4.17 (2H, s), 4.35 (2H, s), 4.84 (2H, s), 6.51 (1H, s), 6.75 (1H, d, J=7.8 Hz), 6.83 (1H, d, J=7.8 Hz), 7.16—7.50 (11H, m), 7.71—7.73 (2H, m), 7.85—7.87 (2H, m).

N-Methyl-*N*-phenyl-2-[3-[*N*-(2-methylpentyl)-*N*-[2-(*N*-phthaloylamino)acetyl]amino]phenoxy]acetamide (**36b**): Quant. mp 171—173 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=6.9 Hz), 1.75—1.81 (1H, m), 3.34 (3H, s), 3.51 (2H, d, J=7.8 Hz), 4.14 (2H, s), 4.47 (2H, s), 6.74 (1H, s), 6.85 (1H, d, J=6.3 Hz), 6.95 (1H, d, J=7.4 Hz), 7.32—7.52 (6H, m), 7.68—7.72 (2H, m), 7.82—7.85 (2H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[3-[*N*-(3-methylpentyl)-*N*-[2-(*N*-phthaloylamino)acetyl]amino]phenoxy]acetamide (**36c**): 70%. ^{1}H-NMR ($CDCl_3$) δ: 0.79—0.84 (6H, m), 1.11 (1H, m), 1.26—1.58 (4H, m), 3.34 (3H, s), 3.67 (2H, t, J=6.8 Hz), 4.12 (2H, s), 4.47 (2H, s), 6.72 (1H, s), 6.86 (1H, d, J=7.3 Hz), 6.93 (1H, d, J=7.9 Hz), 7.31—7.50 (6H, m), 7.69—7.71 (2H, m), 7.83—7.85 (2H, m).

N-Methyl-*N*-phenyl-2-[3-[*N*-(2-aminoacetyl)-*N*-benzylamino]phenoxy]acetamide (**37a**): ^{1}H-NMR ($CDCl_3$) δ: 1.76 (2H, br s), 3.12 (2H, s), 3.30 (3H, s), 4.30 (2H, s), 4.84 (2H, s), 6.37 (1H, s), 6.54 (1H, d, J=7.3 Hz), 6.73 (1H, d, J=8.8 Hz), 7.16—7.48 (11H, m).

N-Methyl-*N*-phenyl-2-[3-[*N*-(2-aminoacetyl)-*N*-(2-methylpropyl)-amino]phenoxy]acetamide (**37b**): ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=6.8 Hz), 1.72—1.75 (3H, m), 3.10 (2H, s), 3.33 (3H, s), 3.53 (2H, d, J=7.3 Hz), 4.41 (2H, s), 6.60 (1H, s), 6.73 (2H, d, J=6.3 Hz), 7.24—7.26, 7.41—7.50 (6H, m).

(±)-*N*-Methyl-*N*-phenyl-2-[3-[*N*-(2-aminoacetyl)-*N*-(3-methylpentyl)-amino]phenoxy]acetamide (**37c**): ^{1}H-NMR ($CDCl_3$) δ: 0.81—0.87 (6H, m), 1.12—1.53 (5H, m), 1.91 (2H, br s), 3.07 (2H, s), 3.33 (3H, s), 3.64—3.72 (2H, m), 4.42 (2H, s), 6.58 (1H, s), 6.71—6.76 (2H, m), 7.24—7.26, 7.41—7.49 (6H, m).

Methyl 2-[3-[3-[*N*-Benzyl-*N*-[3-(*N*-methyl-*N*-phenylcarbamoylmethoxy)-phenyl]carbamoylmethyl]ureido]phenyl]acetate (**38a**): 29% from **36a**. mp 117—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (3H, s), 3.53 (2H, s), 3.65 (3H, s), 3.79 (2H, d, J=3.9 Hz), 4.35 (2H, s), 4.84 (2H, s), 5.97 (1H, br s), 6.49 (1H, s), 6.61 (1H, d, J=7.3 Hz), 6.73 (1H, d, J=7.8 Hz), 6.90 (1H, s), 7.16—7.45 (15H, m).

Methyl 2-[3-[3-[*N*-[3-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2-methylpropyl)carbamoylmethyl]ureido]phenyl]acetate (**38b**): 37% from **36b**. mp 132—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (6H, d, J=6.8 Hz), 1.73—1.76 (1H, m), 3.33 (3H, s), 3.52 (2H, d, J=7.3 Hz), 3.54 (2H, s), 3.66 (3H, s), 3.75 (2H, d, J=4.4 Hz), 4.48 (2H, s), 5.97 (1H, br s), 6.68 (1H, s), 6.75 (1H, d, J=7.8 Hz), 6.81 (1H, d, J=7.8 Hz), 6.91 (1H, s), 7.17—7.30, 7.39—7.49 (10H, m).

Methyl (±)-2-[3-[3-[*N*-[3-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylpentyl)carbamoylmethyl]ureido]phenyl]acetate (**38c**): 61% from **36c**. mp 163—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.77—0.82 (6H, m), 1.07—1.13, 1.24—1.29, 1.47—1.51 (5H, m), 3.33 (3H, s), 3.54 (2H, s), 3.62—3.70 (2H, m), 3.66 (3H, s), 3.72 (2H, d, J=3.9 Hz), 4.45 (2H, s), 6.06 (1H, br s), 6.67 (1H, s), 6.75—6.80 (2H, m), 6.89 (1H, d, J=7.9 Hz), 7.15—7.18 (2H, m), 7.26—7.28, 7.39—7.49 (8H, m).

2-[3-[3-[*N*-Benzyl-*N*-[3-(*N*-methyl-*N*-phenylcarbamoylmethoxy)-phenyl]carbamoylmethyl]ureido]phenyl]acetic Acid (**39a**): ^{1}H-NMR (DMSO-d_6) δ: 3.18 (3H, s), 3.47 (2H, s), 3.68 (2H, s), 4.42 (2H, s), 4.85 (2H, s), 6.38 (1H, s), 6.65—6.79, 7.14—7.44 (18H, m), 8.86 (1H, s), 12.28 (1H, s); IR: 3372, 1712, 1674, 1642, 1596, 1558, 1494, 1452, 1432, 1406, 1346 cm^{-1}.

2-[3-[3-[*N*-[3-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(2-methylpropyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**39b**): ^{1}H-NMR ($CDCl_3$) δ: 0.86 (6H, d, J=6.8 Hz), 1.73 (1H, m), 3.32 (3H, s), 3.50 (2H, d, J=7.3 Hz), 3.58 (2H, s), 3.72 (2H, d, J=3.9 Hz), 4.43 (2H, s), 6.50 (1H, br s), 6.64 (1H, s), 6.73 (1H, d, J=8.3 Hz), 6.77 (1H, d, J=7.4 Hz), 6.87 (1H, d, J=7.3 Hz), 6.95 (1H, s), 7.18 (1H, t, J=7.8 Hz), 7.20—7.48 (6H, m), 7.58 (1H, d, J=8.3 Hz), 7.66 (1H, s); IR: 3360, 1710, 1674, 1640, 1596, 1560, 1494, 1434, 1408, 1346 cm^{-1}.

(±)-2-[3-[3-[*N*-[3-(*N*-Methyl-*N*-phenylcarbamoylmethoxy)phenyl]-*N*-(3-methylpentyl)carbamoylmethyl]ureido]phenyl]acetic Acid (**39c**): ^{1}H-NMR (DMSO-d_6) δ: 0.79 (3H, t, J=7.3 Hz), 0.82 (3H, d, J=6.8 Hz), 1.21—1.40 (5H, m), 3.21 (3H, s), 3.34 (2H, d, J=6.3 Hz), 3.46 (2H, s), 3.68 (2H, m), 4.52 (2H, s), 6.30 (1H, br s), 6.76—6.78 (3H, m), 6.90 (1H, d, J=7.4 Hz), 7.13 (1H, t, J=7.8 Hz), 7.24—7.45 (8H, m), 8.83 (1H, s), 12.28 (1H, br s); IR: 3352, 1674, 1642, 1596, 1558, 1494, 1454, 1432, 1414, 1380 cm^{-1}.

Assay of Binding 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 Opti-MEM® (Gibco BRL) for 30 min at 37 °C, then 800 ml Opti-MEM® was added. The mixture was transferred to 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 DMEM. The culture medium was removed and the cells were pre-incubated in 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 to a tube to determine the radioactivity. Specific binding was defined as the difference between total and non-specific binding in the presence of 1 μM human gastrin-17 or CCK-8.

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 isotonic saline under gravity drainage and then once every 10 min with 5 ml saline under slight positive air pressure. 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 dissolved in polyethyleneglycol 300 or suspended in 1% methylcellulose when administered intravenously or intraduodenally, respectively. Compounds were administered intravenously or intraduodenally 10 or 30 min, respectively, prior to the onset of secretagogue administration. Control animals received vehicle alone.

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