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

Yasuyuki TAKEDA,* Keiichi KAWAGOE, Aki YOKOMIZO, Yoshihiro YOKOMIZO, Toru HOSOKAMI, Yoshiyasu OGIHARA, Yuko HONDA, and Shuichi YOKOHAMA

New Product Research Laboratories III, Daiichi Pharmaceutical Co., Ltd., 16–13, Kitakasai 1-chome, Edogawa-ku, Tokyo 134, Japan. Received July 8, 1997; accepted November 5, 1997

A novel series of phenoxyacetic acid derivatives was synthesized based on considerations of the three-dimensional structural similarity of YM022 and RP72540. The gastrin/cholecystokinin (CCK)-B and CCK-A receptor antagonist activities of these compounds were evaluated by investigation of their affinities for human gastrin/CCK-B receptors and human CCK-A receptors, respectively. It was found that *N*-methyl-*N*-phenyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (20k, DZ-3514) exhibited high affinity for gastrin/CCK-B receptors and high selectivity over CCK-A receptors.

Key words phenoxyacetic acid derivative; gastrin/cholecystokinin-B receptor antagonist; DZ-3514; structure–activity relationship; human gastrin/cholecystokinin-B receptor; human cholecystokinin-A receptor

The peptide cholecystokinin (CCK) displays hormonal and neurotransmitter activities in the gastrointestinal tract and the central nervous system (CNS), respectively,[1] and manifests its biological effects *via* at least two receptor types, termed CCK-A and CCK-B.[2] CCK-A receptors, previously known as peripheral CCK receptors, are located mainly in tissues of the gut,[3] and the receptor antagonist MK-329[4] (**1**) exhibits high affinity for these receptors. CCK-B receptors are located in the CNS. They are indistinguishable from peripheral gastrin receptors on the basis of both their binding properties[5] and comparison of the amino acid sequences deduced from cloned receptor cDNAs of brain and gastric mucosa.[6] Gastrin and CCK-B receptors are therefore described as gastrin/CCK-B receptors, and gastrin/CCK-B receptor antagonists have potential as therapeutic agents for treating both peptic ulcers and CNS disorders.

Recently, CCK-A and gastrin/CCK-B non-peptide antagonists have been developed. The benzodiazepine series exemplified by L-365,260 (**2**),[7] which was derived by chemical modifications from the natural product asperlicin,[8] as well as MK-329, has been well documented. Recent studies have shown that replacing the *C*5-phenyl moiety of the core benzodiazepine structure in L-365,260 with bulkier groups [*e.g.* homopiperidinyl in L-737,415 (**3**) and azabicylo[3.2.2]nonanyl in L-740,093 (**4**)][9] and the *N*1-methyl moiety with an aroyl group [*e.g.* 2-methylphenacyl in YM022 (**5**)][10] leads to higher affinity for gastrin/CCK-B receptors. It was therefore considered that a substituent at the *N*1-position and a bulky substituent at the *C*5-position of the benzodiazepine structure were indispensable for high affinity of benzodiazepine derivatives for gastrin/CCK-B receptors.

Recently, a new non-benzodiazepine family of potent and selective gastrin/CCK-B receptor antagonists, the ureidoacetamide derivatives exemplified by RP72540 (**6**), has been reported.[11] We estimated the stable conformations of two highly potent antagonists, YM022 and RP72540, by molecular mechanics calculation using CHARMm/QUANTA (version Quanta96, Molecular Simulations Inc.) and found that they have some common structural features (Fig. 2).

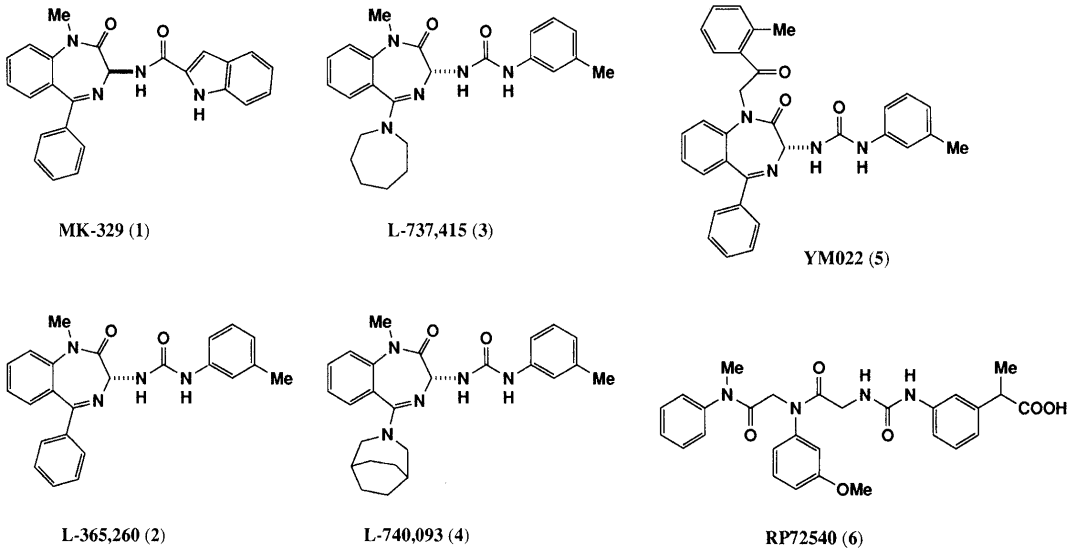


Fig. 1

* To whom correspondence should be addressed.

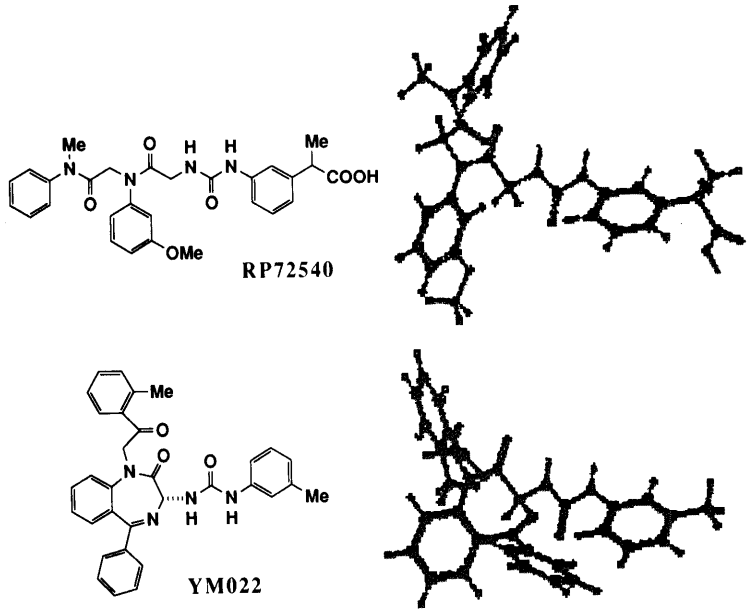


Fig. 2. Stable Conformations of RP72540 and YM022

The stable conformations of all compounds were estimated using CHARMm/QUANTA (version Quanta96, Molecular Simulations Inc.). Initial conformations were selected by conformational search around single bonds rotated 360° in 30° increments. The stable conformations were determined by energy minimization of the initial conformations.

The arrangement of the carbonylmethyl group at the *N*1-position, the benzene ring of the core benzodiazepine structure and the ureido-phenyl moiety of YM022 is similar to that of the carbonylmethyl group of the *N*-methyl-*N*-phenylcarbamoylmethyl moiety, the methoxyphenyl ring and the ureido-phenyl moiety, respectively, of RP72540. In spite of these similar features, which suggest that these two gastrin/CCK-B receptor antagonists might bind to a common site in the receptor, YM022 exhibited 100-fold[10] while RP72540 showed only 5-fold[11] more potent affinity for gastrin/CCK-B receptors than L-365,260. A comparison of the molecular structures of two compounds indicated that the *C*5-phenyl moiety of YM022 mimics the methoxyl moiety at the methoxyphenyl ring of RP72540. As stated above, replacing the *C*5-phenyl moiety in L-365,260 with bulkier groups leads to higher affinity for gastrin/CCK-B receptors. Therefore, we speculated that the replacement of the methoxyl moiety in RP72540 by more bulkier groups might lead to an increase in affinity for gastrin/CCK-B receptors. As regards the selectivity for gastrin/CCK-B receptors over CCK-A receptors, it is well known that the *C*3-position stereochemistry of the benzodiazepine structure is important for the selectivity; the active enantiomer with the (*R*)-configuration at the *C*3-position shows the greater affinity for gastrin/CCK-B receptors.[7,9] As can be seen in Fig. 2, the arrangement from the methoxyphenyl ring to the ureido-phenyl ring of RP72540 is very similar to that of YM022, the (*R*)-enantiomer, and in fact RP72540 shows high selectivity for gastrin/CCK-B receptors over CCK-A receptors. Hence, it was expected to be possible to retain high selectivity when the methoxyl moiety in RP72540 was replaced with bulkier groups. In the process of carrying out such modifications we have found several new, potent and selective gastrin/CCK-B antagonists.

Synthesis

The series of alkyl *m*-phenoxyacetates **17a—f** could be readily synthesized by using the methods depicted in Chart 1. Condensation of nitrophenol **7** with alkyl 2-bromoacetates **8a—c** or nitrophenoxyacetic acid **9** with alcohols **10d—f** provided nitrophenoxyacetates **11a—f**. Reduction of **11a—f** with Pd–C provided aminophenoxyacetates **12a—f**, which were subsequently condensed with *N*-*tert*-butoxycarbonyl(Boc)-Gly in CH_2Cl_2 to give amides **13a—f**. Following alkylation of **13a—f** with bromoacetamide[12] **14**, and removal of the Boc-protection, the resulting amines **16a—f** were reacted with 3-tolyl isocyanate to give the desired compounds **17a—f**.

The *m*-phenoxyacetamide derivatives (**18a—c**, **20a—k**) were synthesized as shown in Chart 2. Amidation of **17a** by reaction with aqueous amines gave the desired compounds **18a—c**. Alkaline hydrolysis of **17a** gave the acid **19**, which was condensed with various amines to afford the target compounds **20a—k**.

A series of alkyl *o*-nitrophenoxyacetates **27a—c** was prepared by condensation of the intermediate phenol derivative **26** with various alkyl bromoacetates **8a—c** (Chart 3). Acylation of aniline[13] **21** with Boc–Gly in CH_2Cl_2 provided the amide **22** in 39% yield. Following alkylation of **22** with bromoacetamide **14** and removal of the Boc-protection, the amine **24** was reacted with 3-tolyl isocyanate to give the phenylurea **25**. Cleavage of the benzyl moiety of **25** by reduction provided the desired intermediate **26**. The isopropyl ester derivative **27d** was prepared from **27a** by transesterification using $Ti(O^iPr)_4$.[14] The *o*-phenoxyacetamide derivatives **29a—e** were prepared from **27a** in 2 steps, using the same methods as for **20a—k** from **17a** (Chart 4).

Pharmacological Evaluation and Discussion

Receptor binding assays of the synthetic compounds

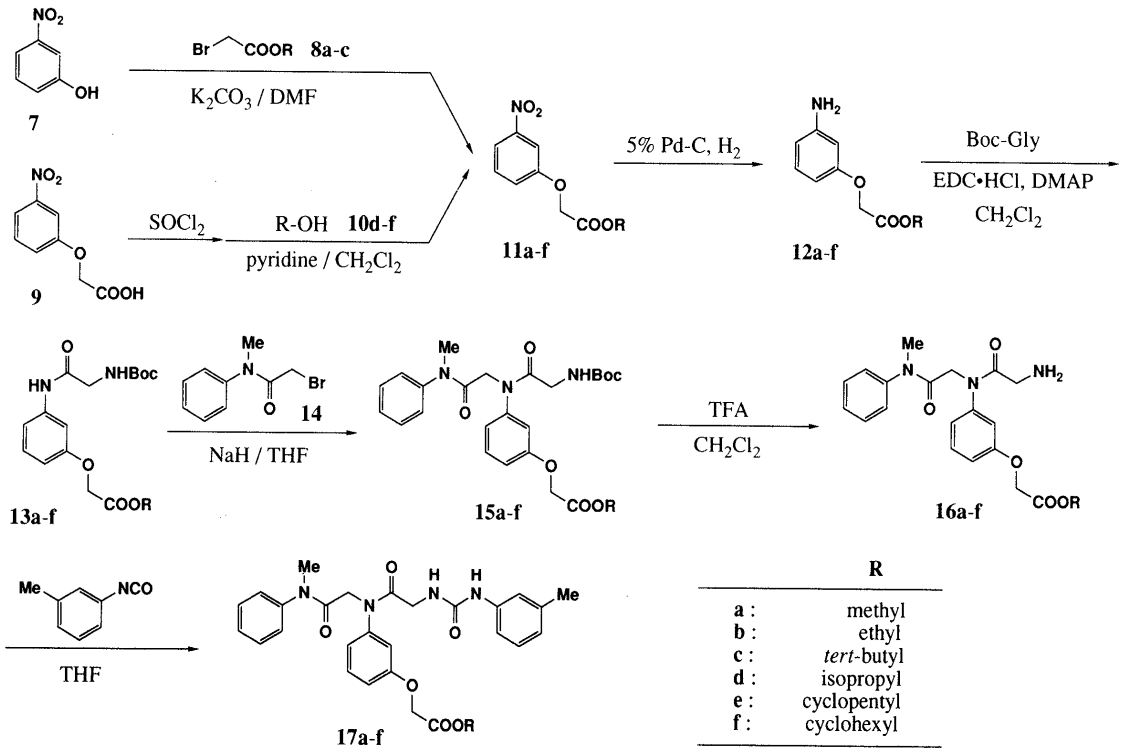
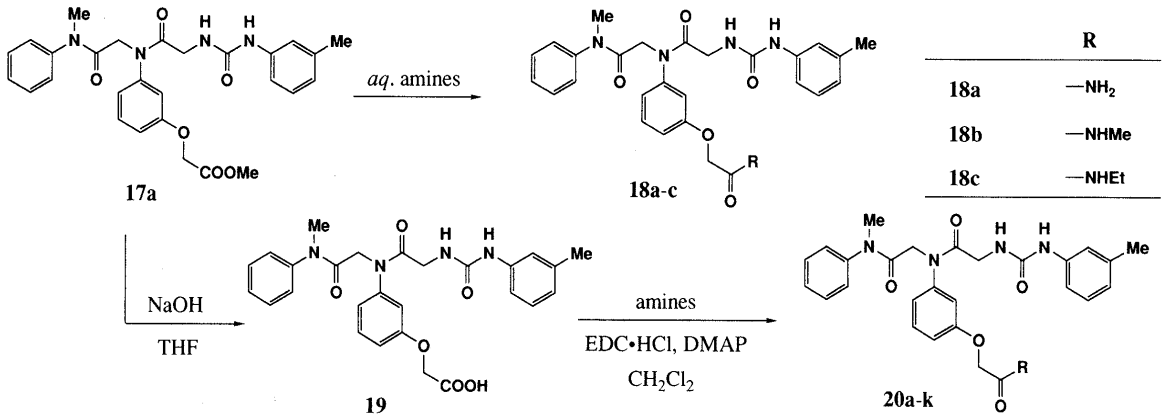


Chart 1



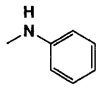
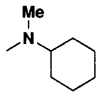
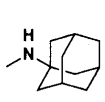
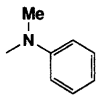
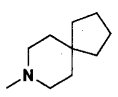
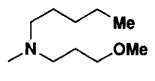
R		R		R		R	
20a		20d		20g		20j	
20b		20e		20h		20k	
20c		20f		20i			

Chart 2

were used to determine binding affinities for the human gastrin and CCK-A receptors.[6c] The activities are reported as IC_{50} values in Tables 1—3.

Initially, we synthesized a series of alkyl *m*-phenoxyacetate derivatives in order to investigate the effect on biological activity of the oxyacetic acid moiety, which we regarded as analogous to the *C*5-phenyl moiety of the benzodiazepine structure (Table 1). Compound **17a** exhibited affinity for human gastrin receptors. A comparison of the stable conformation of **17a** with that of YM022 indicated that the methyl oxyacetate group of **17a** was located in a similar position to the *C*5-phenyl

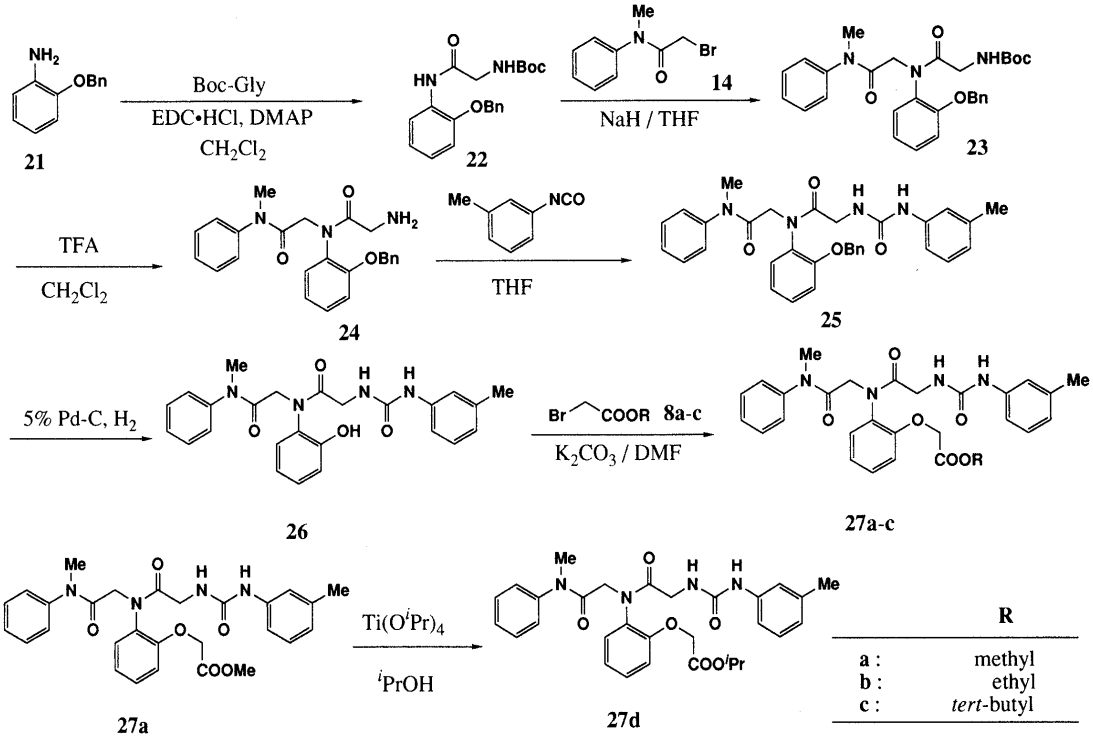


Chart 3

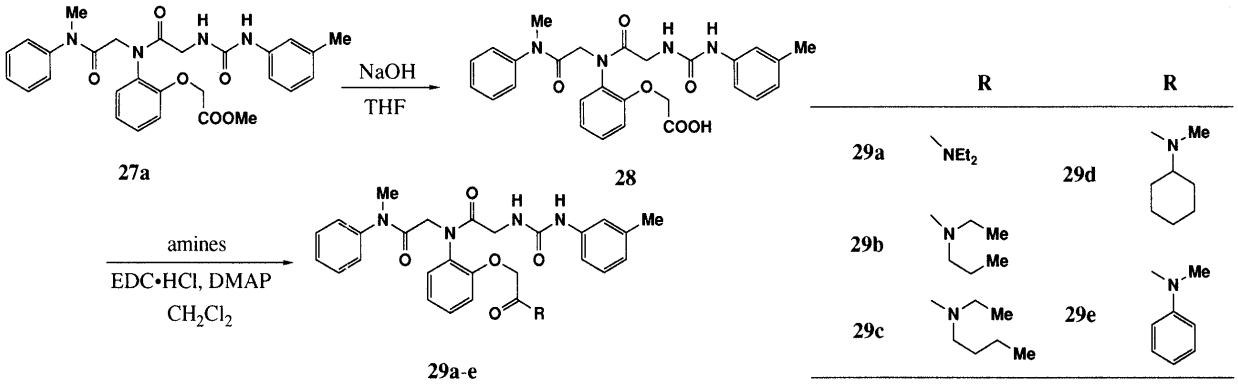


Chart 4

ring of YM022 (Fig. 3). However, the activity of **17a** was weak, being about 10-fold less potent than that of RP72540. Therefore, we next turned our attention to the replacement of the methyl ester moiety of **17a** with other alkyl groups.

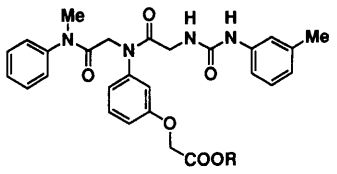
Replacement of the methyl moiety of **17a** with larger alkyl groups, such as ethyl **17b**, *tert*-butyl **17c**, isopropyl **17d** and cyclopentyl **17e**, led to increased affinities for gastrin receptors; compound **17c** showed the most potent activity among the six ester derivatives **17a—e**. These results indicate that a bulky substituent such as a *tert*-butyl moiety is necessary for potent activity, but the relationship between the size of the ester moiety and the activity appears not to be linear. Clearly other factors are also involved.

In the series of *m*-phenoxyacetamide derivatives (Table 2), *N*,*N*-disubstituted amide derivatives **20c—k** showed more potent activity than the *N*-unsubstituted or *N*-monosubstituted amide derivatives **18a—c** and **20a, b**. In general, the *N*-un- or monosubstituted amide derivatives had little affinity for human gastrin receptors; the activity of **18c**, which was the most potent compound in this series, was weak compared with that of the *tert*-butyl ester derivative **17c**. It was therefore assumed that two substituents at the *N*-atom of the amide moiety are essential in order to obtain high binding affinity for human gastrin receptors.

In the series of cyclic amine derivatives **20c—f**, the affinity for human gastrin receptors tended to increase as the ring size became larger. The affinity of the largest ring amine derivative **20e** for human gastrin receptors was similar to that of **17c**. However, the substituted ring derivative **20f** was devoid of activity, presumably due to the bulkiness at the amide moiety. Hence, it was considered that the size of the amide moiety might be an important determinant of the affinity for human gastrin receptors. Whereas the cyclic amine derivatives showed weak affinity, the acyclic amine derivatives **20g—k** showed high affinity for human gastrin receptors. However, the amine derivatives possessing a long alkyl chain, such as **20i**, showed weak activity, so it was supposed that bulkiness at the

amide moiety again decreased the potency. In this series, the aniline derivative **20k** showed the most potent activity and its affinity for human gastrin receptors was similar to or greater than that of RP72540. The aniline derivative **20k** exhibited more potent activity than the cyclohexylamine derivative **20j** and a similar tendency was observed in the *o*-phenoxyacetamide derivatives **29d** and **29e**. These differences of potency might be due to the difference in non-covalent binding interactions of the aliphatic and aromatic rings at the receptor.

Table 1. Receptor Binding Affinities of Alkyl *m*-Phenoxyacetate Derivatives **17a—f**



Compd.	R[a]	IC_{50} (nM)	
		Gastrin[b]	CCK-A[c]
17a	Me	11.0	N.T.
17b	Et	7.4	N.T.
17c	^{t}Bu	2.5	186
17d	^{i}Pr	3.0	130
17e		5.7	300
17f		10.0	750
1		120	0.40
2		5.3	>1000
5		0.33	20
6		1.6	>1000

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

Although the *m*-phenoxyacetic acid derivatives had high affinities for human gastrin receptors, *o*-phenoxyacetic acid derivatives showed weak activities. With the exception of the aniline derivative **29e**, the series of *o*-phenoxyacetic acid derivatives showed 3 to 10-fold less potent activity compared with the corresponding *m*-phenoxyacetic acid derivatives. Though it is not clear why *o*-phenoxyacetic acid derivatives in general show such a drop in efficacy, it is noteworthy that **29e** showed similar potency to the *meta*-substituted derivative **20k** (Table 3).

Finally, the stable conformations of two potent compounds **20k** and **29e** were estimated and compared with that of YM022 (Fig. 4). Similar arrangements from the phenol ring to the ureido-phenyl ring were seen in the conformations of **20k** and **29e**, and the positions of the oxyacetamide moiety in both compounds were similar to that of the *C*5-phenyl group of YM022. This may be the reason why **20k** and **29e** showed similar affinity for the human gastrin receptors.

Conclusion

A novel series of phenoxyacetic acid derivatives has been synthesized based on considerations of the three-dimensional structural similarity of YM022 and RP72540. Our evaluation of the human gastrin/CCK-B and CCK-A receptor antagonist activities of these compounds showed that analogues such as **20k** (DZ-3514) and **29e** (DA-3797) have high affinities for human gastrin/CCK-B receptors and good selectivity for these receptors over human CCK-A receptors. In the human gastrin receptor binding assay, YM022, one of the most potent and selective gastrin/CCK-B antagonists, is some 2-fold more potent

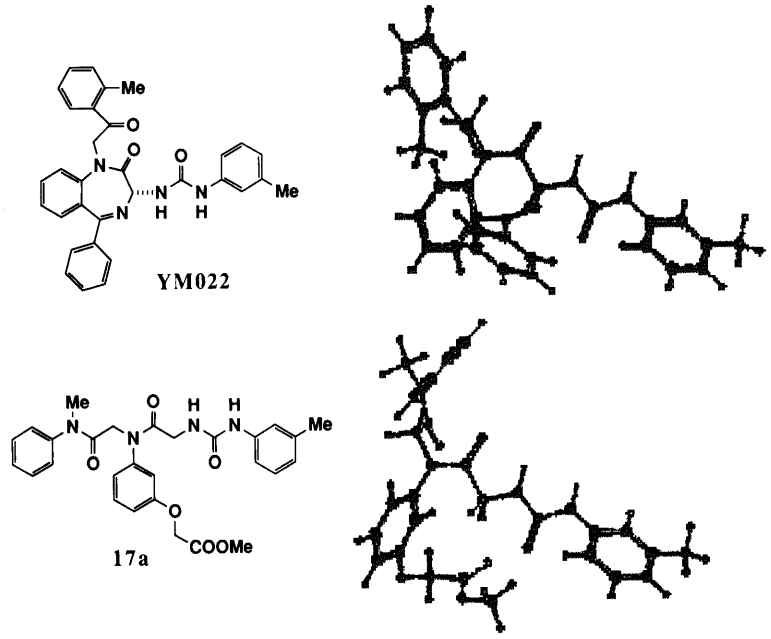
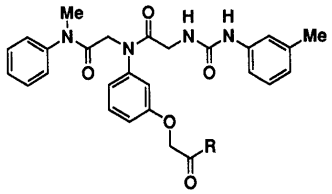
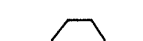
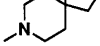


Fig. 3. Stable Conformations of YM022 and **17a**

Table 2. Receptor Binding Affinities of *m*-Phenoxyacetamide Derivatives **18a—c** and **20a—k**

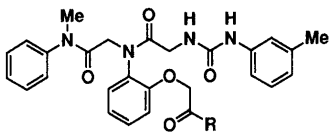


Compd.	R[a]	IC_{50} (nM)	
		Gastrin[b]	CCK-A[c]
18a		22	N.T.
18b		21	N.T.
18c		9.6	N.T.
20a		50	N.T.
20b		63	N.T.
20c		8.9	N.T.
20d		8.3	200
20e		4.8	N.T.
20f		59	N.T.
20g		1.9	130
20h		3.4	N.T.
20i		9.0	N.T.
20j		2.5	N.T.
20k		0.8	178

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

than our compounds. However, YM022 is much less selective for gastrin/CCK-B receptors than for CCK-A receptors. Efforts are continuing to improve this novel lead structure, and the results of further modification of these compounds will be reported in due course.

Table 3. Receptor Binding Affinities of *o*-Phenoxyacetic Acid Derivatives **27a—d** and **29a—e**



Compd.	R[a]	IC_{50} (nM)	
		Gastrin[b]	CCK-A[c]
27a		58	N.T.
27b		54	N.T.
27c		30	N.T.
27d		63	N.T.
29a		5.4	137
29b		7.8	N.T.
29c		11	N.T.
29d		6.0	249
29e		0.9	210

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

Experimental

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

Methyl 2-(3-Nitrophenoxy)acetate (11a) A mixture of 3-nitrophenol **7** (11.1 g, 80 mmol), methyl 2-bromoacetate **8a** (8.3 ml, 90 mmol) and K_2CO_3 (13.8 g, 100 mmol) in DMF (100 ml) was stirred at 70 °C for 3 h. The reaction mixture was poured into ice-water, and the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting solid was washed with *n*-hexane to give **11a** (13.9 g, 82%) as a yellow solid, mp 52—54 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s), 4.73 (2H, s), 7.26 (1H, dd, J=2.0, 8.3 Hz), 7.47 (1H, t, J=8.3 Hz),

7.73 (1H, dd, J=1.5, 2.0 Hz), 7.88 (1H, dd, J=1.5, 8.3 Hz).

Compounds **11b** and **11c** were obtained from the corresponding bromoacetates **8b** and **8c** by following a procedure similar to that described for the preparation of **11a**. **11b** was used in subsequent reactions without purification. NMR spectroscopic data for these compounds are as follows:

Ethyl 2-(3-Nitrophenoxy)acetate (**11b**): ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.3 Hz), 4.30 (2H, q, J=7.3 Hz), 4.72 (2H, s), 7.27 (1H, dd, J=2.4, 8.3 Hz), 7.47 (1H, t, J=8.3 Hz), 7.73 (1H, dd, J=2.3, 2.4 Hz), 7.88 (1H, dd, J=2.3, 8.3 Hz).

tert-Butyl 2-(3-Nitrophenoxy)acetate (**11c**): 82%. mp 45—46 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 4.61 (2H, s), 7.26 (1H, dd, J=2.4, 8.3 Hz), 7.46 (1H, t, J=8.3 Hz), 7.70 (1H, dd, J=1.5, 2.4 Hz), 7.87 (1H, dd, J=1.5, 8.3 Hz).

Isopropyl 2-(3-Nitrophenoxy)acetate (11d) Thionyl chloride ($SOCl_2$, 2.8 ml, 38.1 mmol) was added to a mixture of 2-(3-nitrophenoxy)acetic acid **9** (5.0 g, 25.4 mmol) and a catalytic amount of DMF (a few drops), and the mixture was stirred under reflux for 0.5 h. The excess $SOCl_2$ was distilled off and the residue was dissolved in CH_2Cl_2 (50 ml). This solution was added to a solution of isopropanol **10d** (3.8 ml, 50 mmol) and pyridine (4.0 ml, 50 mmol) in CH_2Cl_2 (200 ml) with ice cooling, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **11d** (6.1 g) as a yellow oil, which was used in subsequent reactions without purification. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (6H, d, J=6.3 Hz), 4.68 (2H, s), 5.16 (1H, m), 7.27 (1H, d, J=8.3 Hz), 7.46 (1H, t, J=8.3 Hz), 7.72 (1H, s), 7.88 (1H, d, J=8.3 Hz).

Compounds **11e** and **11f** were obtained from the corresponding alcohols **10e** and **10f** by following a procedure similar to that described for the preparation of **11d**. **11e** and **11f** were used in subsequent reactions without purification. Spectroscopic data for these compounds are as follows:

Cyclopentyl 2-(3-Nitrophenoxy)acetate (**11e**): ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.90 (8H, m), 4.68 (2H, s), 5.31 (1H, m), 7.26 (1H, dd, J=2.4, 8.3 Hz), 7.46 (1H, t, J=8.3 Hz), 7.71 (1H, dd, J=1.9, 2.4 Hz), 7.88 (1H, dd, J=1.9, 8.3 Hz).

Cyclohexyl 2-(3-Nitrophenoxy)acetate (**11f**): ^{1}H-NMR ($CDCl_3$) δ: 1.28—1.88 (10H, m), 4.69 (2H, s), 4.92 (1H, m), 7.26 (1H, dd, J=1.0, 8.3 Hz), 7.46 (1H, t, J=8.3 Hz), 7.72 (1H, s), 7.87 (1H, d, J=8.3 Hz).

Methyl 2-(3-Aminophenoxy)acetate (12a) **11a** (12.0 g, 56.9 mmol) was hydrogenated in a mixture of MeOH (200 ml) and AcOEt (200 ml) over 5% Pd–C (50% wet, 2.4 g) at atmospheric pressure for 45 min. 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 **12a** (9.7 g, 94%) as a white amorphous powder. ^{1}H-NMR (DMSO-d_6) δ: 3.22 (2H, s), 3.76 (3H, s), 4.90 (2H, s), 7.02—7.09 (3H, m), 7.47 (1H, t, J=7.8 Hz).

Compounds **12b—f** were obtained by following a procedure similar to that described for the preparation of **12a**. **12b—f** were used in

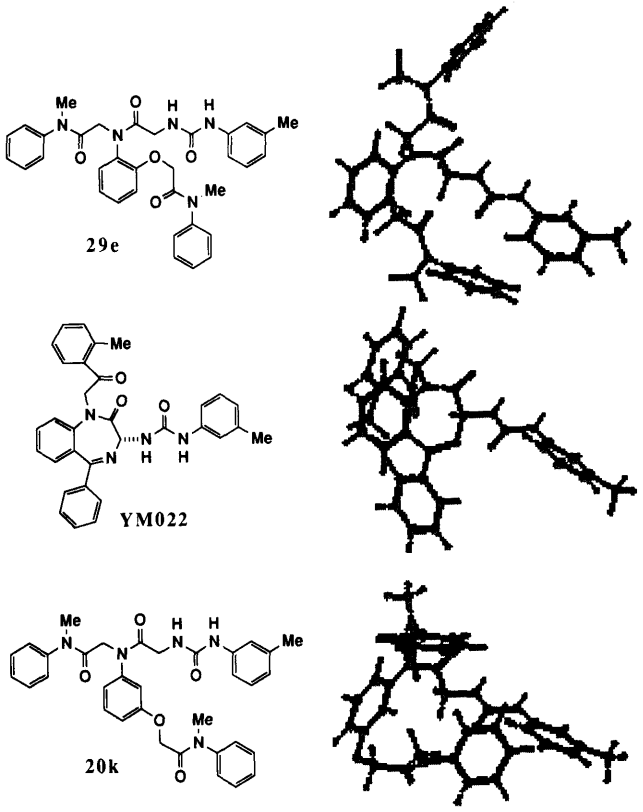


Fig. 4. Stable Conformations of **20k**, **29e** and YM022

Table 4. Physicochemical Data for *m*-Phenoxyacetic Acid Derivatives **17a—f**, **18a—c** and **20a—k**

Compd.	Yield[a] (%)	mp[b] (°C)	Recryst.[c] solv.	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
17a	97	127—128	A–E	$C_{28}H_{30}N_4O_6$	69.19	6.83	10.90	64.69	5.86	10.77
17b	83	97—99	A–E	$C_{29}H_{32}N_4O_6 \cdot 0.5H_2O$	64.31	6.14	10.34	64.57	6.14	10.27
17c	92	123—125	A–E	$C_{31}H_{36}N_4O_6 \cdot 0.25H_2O$	65.88	6.51	9.91	65.82	6.56	10.07
17d	86	108—110	H–A	$C_{30}H_{34}N_4O_6$	65.92	6.27	10.25	65.96	6.25	10.13
17e	86	100—101	A–E	$C_{32}H_{36}N_4O_6 \cdot 0.5H_2O$	66.08	6.41	9.63	66.26	6.56	9.16
17f	82	Amorph.	—	$C_{33}H_{38}N_4O_6 \cdot 0.25H_2O$	67.05	6.56	9.48	66.87	6.73	9.18
18a	82	115—117	H–E	$C_{27}H_{29}N_5O_5 \cdot 0.25H_2O$	63.83	5.85	13.78	63.72	5.98	13.52
18b	90	177—179	H–E	$C_{28}H_{31}N_5O_5$	64.98	6.04	13.53	64.86	6.05	13.38
18c	87	150—152	H–E	$C_{29}H_{33}N_5O_5 \cdot 0.25H_2O$	64.97	6.30	13.06	65.08	6.30	12.85
20a	86	215—217	H–A–E	$C_{33}H_{33}N_5O_5$	68.38	5.74	12.08	68.15	5.89	11.78
20b	73	130—132	A–E	$C_{37}H_{43}N_5O_5 \cdot 0.25H_2O$	69.19	6.83	10.90	69.18	6.79	10.87
20c	48	100—102	C–E	$C_{31}H_{35}N_5O_5 \cdot 0.75H_2O$	65.19	6.44	12.26	65.01	6.49	12.17
20d	65	106—108	C–E	$C_{32}H_{37}N_5O_5 \cdot 0.5H_2O$	66.19	6.60	12.06	66.23	6.79	11.89
20e	69	147—148	C–E	$C_{33}H_{39}N_5O_5 \cdot 0.75H_2O$	67.16	6.75	11.87	67.10	6.77	11.79
20f	53	187—188	C–E	$C_{36}H_{43}N_5O_5 \cdot 0.5H_2O$	68.12	6.99	11.03	68.14	7.07	10.92
20g	74	138—140	H–A–E	$C_{31}H_{37}N_5O_5 \cdot 0.25H_2O$	66.00	6.70	12.41	66.13	6.98	12.16
20h	48	Amorph.	—	$C_{29}H_{33}N_5O_6 \cdot 0.5H_2O$	62.58	6.16	12.58	62.83	6.22	12.63
20i	58	Amorph.	—	$C_{36}H_{47}N_5O_6 \cdot 0.5H_2O$	66.03	7.39	10.70	66.17	7.24	10.74
20j	63	Amorph.	—	$C_{34}H_{41}N_5O_5 \cdot 0.5H_2O$	67.09	6.95	11.50	66.93	6.89	11.54
20k	96	145—146	C–E	$C_{34}H_{35}N_5O_5 \cdot 0.25H_2O$	68.27	5.98	11.71	68.27	6.04	11.69

a) Yield from **16a—f**, **17a** or **19**. *b*) Abbreviation: Amorph., an amorphous powder. *c*) Abbreviations: A, ethyl acetate; C, dichloromethane; E, diethyl ether; H, *n*-hexane.

Table 5. Physicochemical Data for *o*-Phenoxyacetic Acid Derivatives **27a—d** and **29a—e**

Compd.	Yield[a] (%)	mp[b] (°C)	Recryst.[c] solv.	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
27a	81	165—166	A–E	$C_{28}H_{30}N_4O_6$	64.85	5.83	10.80	64.65	5.98	10.51
27b	89	146—147	A–E	$C_{29}H_{32}N_4O_6$	65.40	6.06	10.52	65.42	6.11	10.33
27c	85	89—90	A–E	$C_{31}H_{36}N_4O_6$	66.41	6.47	9.99	66.11	6.54	9.72
27d	67	173—174	A–E	$C_{30}H_{34}N_4O_6$	65.92	6.27	10.25	65.68	6.25	10.00
29a	31	Amorph.	—	$C_{31}H_{37}N_5O_5 \cdot 0.5H_2O$	65.48	6.74	12.32	65.66	6.82	12.08
29b	56	123—124	A–E	$C_{32}H_{39}N_5O_5 \cdot 0.25H_2O$	66.47	6.89	12.11	66.33	6.71	12.22
29c	60	121—122	A–E	$C_{33}H_{41}N_5O_5$	67.44	7.03	11.92	67.33	7.00	11.90
29d	51	172—173	A–E	$C_{34}H_{41}N_5O_5 \cdot 0.5H_2O$	67.09	6.95	11.51	67.29	6.82	11.86
29e	89	183—184	H–C–E	$C_{34}H_{35}N_5O_5 \cdot 0.25H_2O$	68.27	5.98	11.71	68.12	5.90	11.74

a) Yield from **26**, **27a** or **28**. *b*) Abbreviation: Amorph., an amorphous powder. *c*) Abbreviations: A, ethyl acetate; C, dichloromethane; E, diethyl ether; H, *n*-hexane.

subsequent reactions without purification. Spectroscopic data for these compounds are as follows:

Ethyl 2-(3-Aminophenoxy)acetate (**12b**): ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.3 Hz), 3.30 (2H, br s), 4.27 (2H, q, J=7.3 Hz), 4.57 (2H, s), 6.29—6.36 (3H, m), 7.06 (1H, t, J=7.8 Hz).

tert-Butyl 2-(3-Aminophenoxy)acetate (**12c**): ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 3.76 (2H, br s), 4.46 (2H, s), 6.30—6.36 (3H, m), 7.05 (1H, d, J=7.8 Hz).

Isopropyl 2-(3-Aminophenoxy)acetate (**12d**): ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, d, J=6.4 Hz), 3.54 (2H, br s), 4.54 (2H, s), 5.14 (1H, m), 6.28—6.35 (3H, m), 7.05 (1H, t, J=8.3 Hz).

Cyclopentyl 2-(3-Aminophenoxy)acetate (**12e**): ^{1}H-NMR ($CDCl_3$) δ: 1.57—1.91 (8H, m), 3.33 (2H, br s), 4.53 (2H, s), 5.29 (1H, m), 6.28—6.35 (3H, m), 7.05 (1H, t, J=7.8 Hz).

Cyclohexyl 2-(3-Aminophenoxy)acetate (**12f**): ^{1}H-NMR ($CDCl_3$) δ: 1.18—1.88 (10H, m), 3.21 (2H, br s), 4.55 (2H, s), 4.89 (1H, m), 6.28—6.34 (3H, m), 7.05 (1H, t, J=7.8 Hz).

Methyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]amino]phenoxy]acetate (13a) EDC·HCl (4.6 g, 24 mmol) and DMAP (2.9 g, 24 mmol) were added to a solution of **12a** (3.6 g, 20 mmol) and Boc–Gly (3.5 g, 20 mmol) in CH_2Cl_2 (100 ml) and the mixture was stirred overnight at room temperature. It was then concentrated under reduced pressure and the residue was partitioned between AcOEt and 1 N HCl. The organic layer was separated from the aqueous layer, washed with water, saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **13a** (5.1 g, 75%) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 3.80 (3H, s), 3.91 (2H, d, J=5.9 Hz), 4.63 (2H, s), 5.30 (1H, br s), 6.66 (1H, dd, J=2.0, 8.3 Hz), 7.02 (1H, d, J=8.3 Hz), 7.2 (1H, t, J=8.3 Hz), 7.29 (1H, s), 8.33 (1H, br s).

Compounds **13b—f** were obtained by following a procedure similar to that described for the preparation of **13a**. Spectroscopic data for these compounds are as follows:

Ethyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]amino]phenoxy]acetate (**13b**): 97% from **7**. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.3 Hz), 1.47 (9H, s), 3.91 (2H, d, J=5.8 Hz), 4.26 (2H, q, J=7.3 Hz), 4.60 (2H, s), 5.40 (1H, br s), 6.65 (1H, d, J=7.8 Hz), 7.03 (1H, d, J=7.8 Hz), 7.20 (1H, t, J=7.8 Hz), 7.29 (1H, s), 8.38 (1H, br s).

tert-Butyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]amino]phenoxy]acetate (**13c**): 99% from **11c**. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.49 (9H, s), 3.90 (2H, d, J=5.9 Hz), 4.51 (2H, s), 5.30 (1H, br s), 6.66 (1H, d, J=7.8 Hz), 7.01 (1H, d, J=7.8 Hz), 7.21 (1H, t, J=7.8 Hz), 7.29 (1H, s), 8.24 (1H, br s).

Isopropyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]amino]phenoxy]acetate (**13d**): 92% from **9**. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, d, J=5.8 Hz), 1.47 (9H, s), 3.91 (2H, d, J=5.8 Hz), 4.58 (2H, s), 5.14 (1H, m), 5.37 (1H, br s), 6.66 (1H, d, J=8.1 Hz), 7.03 (1H, d, J=8.1 Hz), 7.20 (1H, t, J=8.1 Hz), 7.30 (1H, s), 8.33 (1H, br s).

Cyclopentyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]amino]phenoxy]acetate (**13e**): 91% from **9**. ^{1}H-NMR ($CDCl_3$) δ: 1.44—1.88 (8H, m), 1.48 (9H, s), 3.91 (2H, d, J=5.8 Hz), 4.58 (2H, s), 5.28—5.29 (2H, br s), 6.67 (1H, d, J=7.8 Hz), 7.02 (1H, d, J=7.8 Hz), 7.21 (1H, t, J=7.8 Hz), 7.30 (1H, s), 8.17 (1H, br s).

Cyclohexyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]amino]phenoxy]acetate (**13f**): 56% from **9**. ^{1}H-NMR ($CDCl_3$) δ: 1.23—1.86 (10H, m), 1.47 (9H, s), 3.91 (2H, d, J=5.8 Hz), 4.60 (2H, s), 4.87—4.91 (1H, m), 5.41 (1H, br s), 6.66 (1H, d, J=8.1 Hz), 7.03 (1H, d, J=8.1 Hz), 7.20 (1H, t, J=8.1 Hz), 7.29 (1H, s), 8.38 (1H, br s).

Methyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (15a) A solution of **13a** (5.0 g, 14.8 mmol) in THF (50 ml) was treated with NaH (60% in oil, 0.72 g, 18.0 mmol), and the mixture was stirred at 60 °C for 15 min. A solution of *N*-methyl-*N*-phenyl-2-bromoacetamide **14** (3.7 g, 16.0 mmol) in THF (30 ml) was added to the reaction mixture with ice cooling, and the resulting mixture was stirred at room temperature for 1.5 h. Then ice-water was added, and the whole 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 **15a** (3.2 g, 45%) as a colorless syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 3.28 (3H, s), 3.73 (2H, d, J=4.4 Hz), 3.82 (3H, s), 4.07 (2H, s), 4.63 (2H, s), 5.34 (1H, br s), 6.88 (1H, d, J=8.0 Hz), 7.00—7.03 (2H, m), 7.24—7.45 (6H, m).

Compounds **15b—f** were obtained by following a procedure similar to that described for the preparation of **15a**. Spectroscopic data for these compounds are as follows:

Ethyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**15b**): 50%. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=6.8 Hz), 1.39 (9H, s), 3.28 (3H, s), 3.73 (2H, d, J=3.4 Hz), 4.07 (2H, s), 4.28 (2H, q, J=6.8 Hz), 4.61 (2H, s), 5.33 (1H, br s), 6.89 (1H, d, J=8.3 Hz), 7.00—7.02, 7.24—7.44 (8H, m).

tert-Butyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**15c**): 64%. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 1.50 (9H, s), 3.28 (3H, s), 3.73 (2H, d, J=4.4 Hz), 4.06 (2H, s), 4.50 (2H, s), 5.33 (1H, br s), 6.88 (1H, d, J=8.3 Hz), 6.97—7.00, 7.24—7.44 (8H, m).

Isopropyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**15d**): 51%. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=6.3 Hz), 1.39 (9H, s), 3.28 (3H, s), 3.72 (2H, d, J=3.9 Hz), 4.06 (2H, s), 4.57 (2H, s), 5.14 (1H, m), 5.33 (1H, br s), 6.88 (1H, d, J=8.3 Hz), 7.00—7.01, 7.24—7.44 (8H, m).

Cyclopentyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**15e**): 80%. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 1.59—1.89 (8H, m), 3.28 (3H, s), 3.72 (2H, d, J=4.4 Hz), 4.06 (2H, s), 4.57 (2H, s), 5.32—5.38 (2H, m), 6.88—7.01, 7.24—7.44 (9H, m).

Cyclohexyl 2-[3-[*N*-[2-[*N*-*tert*-Butoxycarbonylamino]acetyl]-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**15f**): 61%. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.85 (10H, m), 1.39 (9H, s), 3.28 (3H, s), 3.72 (2H, d, J=4.4 Hz), 4.06 (2H, s), 4.59 (2H, s), 4.90 (1H, m), 5.32 (1H, br s), 6.88—7.02, 7.24—7.44 (9H, m).

Methyl 2-[3-[*N*-(2-Aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (16a) TFA (30 ml) was added to a solution of **15a** (3.0 g, 6.2 mmol) in CH_2Cl_2 (30 ml) with ice cooling, and the mixture was stirred at the same temperature for 0.5 h. It was then concentrated under reduced pressure and the residue was dissolved in

$CHCl_3$. The organic solution was washed with saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **16a** (2.4 g, *quant.*) as a yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (2H, br s), 3.22 (2H, br s), 3.29 (3H, s), 3.82 (3H, s), 4.07 (2H, s), 4.64 (2H, s), 6.88 (1H, d, J=7.8 Hz), 7.28—7.45 (8H, m).

Compounds **16b—f** were obtained by following a procedure similar to that described for the preparation of **16a**. Spectroscopic data for these compounds are as follows:

Ethyl 2-[3-[*N*-(2-Aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**16b**): 69%. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.1 Hz), 1.61 (2H, br s), 3.21 (2H, s), 3.29 (3H, s), 4.07 (2H, s), 4.28 (2H, q, J=7.1 Hz), 4.62 (2H, s), 6.88—7.02, 7.25—7.45 (9H, m).

tert-Butyl 2-[3-[*N*-(2-Aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**16c**): 70%. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.51 (2H, br s), 3.21 (2H, s), 3.29 (3H, s), 4.06 (2H, s), 4.51 (2H, s), 6.87—6.98 (3H, m), 7.26—7.30 (3H, m), 7.36—7.45 (3H, m).

Isopropyl 2-[3-[*N*-(2-Aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**16d**): 68%. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J=6.4 Hz), 1.62 (2H, br s), 3.21 (2H, s), 3.29 (3H, s), 4.07 (2H, s), 4.58 (2H, s), 5.14 (1H, m), 6.88—7.00, 7.27—7.45 (9H, m).

Cyclopentyl 2-[3-[*N*-(2-Aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**16e**): 94%. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.89 (10H, m), 3.23 (2H, s), 3.29 (3H, s), 4.07 (2H, s), 4.58 (2H, s), 5.29 (1H, m), 6.87—6.99, 7.26—7.44 (9H, m).

Cyclohexyl 2-[3-[*N*-(2-Aminoacetyl)-*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)amino]phenoxy]acetate (**16f**): 98%. ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.84 (12H, m), 3.22 (2H, s), 3.26 (3H, s), 4.06 (2H, s), 4.59 (2H, s), 4.89 (1H, m), 6.88—6.99, 7.27—7.44 (9H, m).

Methyl 2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (17a) A solution of 3-tolyl isocyanate (0.83 g, 6.2 mmol) in THF (20 ml) was added to a solution of **16a** (2.4 g, 6.2 mmol) in THF (30 ml) and the mixture was stirred at room temperature for 0.5 h. It was then concentrated under reduced pressure and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1). The eluate was concentrated under reduced pressure and the product was recrystallized from AcOEt–diethyl ether. The product was collected by filtration to give **17a** (3.1 g, 97%) as a white powder, mp 127—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.22 (3H, s), 3.81 (3H, s), 3.89 (2H, d, J=4.4 Hz), 4.09 (2H, s), 4.63 (2H, s), 6.06 (1H, br s), 6.77—7.43 (13H, m), 7.69 (1H, br s); IR: 3376, 1756, 1672, 1646, 1598, 1552, 1494, 1428, 1394 cm^{-1}; *Anal.* Calcd for $C_{28}H_{30}N_4O_6$: C, 64.85; H, 5.83; N, 10.80. Found: C, 64.69; H, 5.86; N, 10.77.

Compounds **17b—f** were obtained by following a procedure similar to that described for the preparation of **17a**; the yields, melting points and elemental analysis data are shown in Table 4. The IR and ^{1}H-NMR data for these compounds are as follows:

Ethyl 2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (**17b**): ^{1}H-NMR (DMSO-d_6) δ: 1.21 (3H, t, J=7.3 Hz), 2.22 (3H, s), 3.18 (3H, s), 3.64 (2H, s), 4.04 (2H, s), 4.18 (2H, q, J=7.3 Hz), 4.80 (2H, s), 6.28 (1H, br s), 6.70 (1H, d, J=7.8 Hz), 6.95—7.17, 7.34—7.48 (12H, m), 8.70 (1H, s); IR: 3336, 1754, 1662, 1614, 1596, 1558, 1494, 1430 cm^{-1}.

tert-Butyl 2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (**17c**): ^{1}H-NMR (DMSO-d_6) δ: 1.43 (9H, s), 2.22 (3H, s), 3.18 (3H, s), 3.64 (2H, s), 4.04 (2H, s), 4.68 (2H, s), 6.28 (1H, br s), 6.69 (1H, d, J=7.8 Hz), 6.95 (1H, d, J=8.3 Hz), 7.05—7.17, 7.34—7.46 (11H, m), 8.71 (1H, s); IR: 3364, 1752, 1670, 1596, 1556, 1492, 1430, 1396 cm^{-1}.

Isopropyl 2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (**17d**): ^{1}H-NMR (DMSO-d_6) δ: 1.21 (6H, d, J=6.4 Hz), 2.22 (3H, s), 3.18 (3H, s), 3.64 (2H, s), 4.04 (2H, s), 4.77 (2H, s), 4.99 (1H, m), 6.28 (1H, br s), 6.70 (1H, d, J=7.3 Hz), 6.96—7.17, 7.33—7.46 (12H, m), 8.70 (1H, s); IR: 3356, 1754, 1666, 1596, 1556, 1492, 1430, 1392 cm^{-1}.

Cyclopentyl 2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (**17e**): ^{1}H-NMR ($CDCl_3$) δ: 1.57—1.88 (8H, m), 2.25 (3H, s), 3.21 (3H, s), 3.90 (2H, d, J=5.4 Hz), 4.09 (2H, s), 4.58 (2H, s), 5.29 (1H, m), 6.17 (1H, br s), 6.75 (1H, d, J=7.8 Hz), 6.89—7.14, 7.28—7.34 (12H, m), 7.93 (1H, s); IR: 3328, 1750, 1696, 1658, 1642, 1614, 1592, 1556, 1490, 1456, 1434, 1422 cm^{-1}.

Cyclohexyl 2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (**17f**): ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.86 (10H, m), 2.25 (3H, s), 3.21 (3H, s), 3.90 (2H, d, J=5.4 Hz), 4.09 (2H, s), 4.60 (2H, s), 4.90 (1H, m), 6.13 (1H, br s), 6.76 (1H, d, J=7.8 Hz), 6.90—7.15, 7.26—7.34 (12H, m), 7.85 (1H, s); IR: 3360, 1756, 1732, 1668, 1596, 1554, 1492, 1454, 1430 cm^{-1}.

2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (18a) A suspension of **17a** (0.5 g, 0.97 mmol) in 28% ammonium hydroxide (30 ml) was stirred at room temperature for 2 d. The reaction mixture was concentrated under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was recrystallized from *n*-hexane–diethyl ether. The product was collected by filtration to give **18a** (0.4 g, 82%) as a white powder, mp 115—117 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 3.18 (3H, s), 3.65 (2H, s), 4.06 (2H, s), 4.45 (2H, s), 6.30 (1H, br s), 6.70 (1H, d, J=7.3 Hz), 6.99—7.17 (6H, m), 7.35—7.47 (7H, m), 7.60 (1H, s), 8.72 (1H, s); IR: 3356, 1668, 1596, 1556, 1492, 1428 cm^{-1}; *Anal.* Calcd for $C_{27}H_{29}N_5O_5 \cdot 0.25H_2O$: C, 63.83; H, 5.85; N, 13.78. Found: C, 63.72; H, 5.98; N, 13.52.

Compounds **18b** and **18c** were obtained by following a procedure similar to that described for the preparation of **18a**; the yields, melting points and elemental analysis data are shown in Table 4. The IR and ^{1}H-NMR data for these compounds are as follows:

N-Methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**18b**): ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 2.66 (3H, d, J=4.8 Hz), 3.19 (3H, s), 3.66 (2H, s), 4.06 (2H, s), 4.49 (2H, s), 6.29 (1H, br s), 6.70 (1H, d, J=7.3 Hz), 7.00—7.17, 7.34—7.46 (12H, m), 8.08 (1H, d, J=4.8 Hz), 8.71 (1H, s); IR: 3352, 1664, 1596, 1556, 1490, 1434 cm^{-1}.

N-Ethyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**18c**): ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=7.1 Hz), 2.22 (3H, s), 3.15 (2H, m), 3.18 (3H, s), 3.65 (2H, d, J=2.5 Hz), 4.06 (2H, s), 4.48 (2H, s), 6.29 (1H, br s), 6.70 (1H, d, J=7.8 Hz), 7.00—7.17, 7.34—7.48 (12H, m), 8.14 (1H, br s), 8.71 (1H, s); IR: 3348, 1666, 1598, 1556, 1490, 1434 cm^{-1}.

2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetic Acid (19) A 0.5 N NaOH (20 ml) solution was added to a solution of **17a** (3.0 g, 5.8 mmol) in THF (20 ml), and the mixture was stirred at room temperature for 1 h. Then AcOEt was added and the layers were separated. The aqueous layer was acidified with 1 N HCl and extracted with $CHCl_3$. The extract was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **19** (2.5 g, 86%) as a white amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 3.24 (3H, s), 3.84 (2H, d, J=4.4 Hz), 4.11 (2H, br s), 4.70 (2H, s), 6.22 (1H, br s), 6.71—6.73, 6.92—7.35 (13H, m), 7.91 (1H, s).

***N*-Phenyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (20a)** EDC·HCl (0.14 g, 0.7 mmol) and DMAP (0.09 g, 0.7 mmol) were added to a solution of **19** (0.3 g, 0.6 mmol) and aniline (0.05 ml, 0.6 mmol) in CH_2Cl_2 (30 ml), and the mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between AcOEt and 1 N HCl. The organic layer was separated from the aqueous layer and washed with water, saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was crystallized from *n*-hexane–AcOEt–diethyl ether. The product was collected by filtration to give **20a** (0.3 g, 86%) as an off-white powder, mp 215—217 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 3.16 (3H, s), 3.67 (2H, s), 4.06 (2H, s), 4.74 (2H, s), 6.30 (1H, br s), 6.70 (1H, d, J=7.3 Hz), 7.04—7.65 (17H, m), 8.72 (1H, s), 10.14 (1H, s); IR: 3336, 1662, 1598, 1554, 1492, 1446, 1398, 1316 cm^{-1}; *Anal.* Calcd for $C_{33}H_{33}N_5O_5$: C, 68.38; H, 5.74; N, 12.08. Found: C, 68.15; H, 5.89; N, 11.78.

Compounds **20b—k** were obtained by following a procedure similar to that described for the preparation of **20a**; the yields, melting points and elemental analysis data are shown in Table 4. The IR and ^{1}H-NMR data for these compounds are as follows:

N-(1-Adamantyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**20b**): ^{1}H-NMR (DMSO-d_6) δ: 1.61 (6H, br s), 1.95 (6H, br s), 1.99 (3H, br s), 2.22 (3H, s), 3.19 (3H, s), 3.65 (2H, s), 4.05 (2H, s), 4.43 (2H, s), 6.29 (1H, br s), 6.69 (1H, d, J=7.8 Hz), 6.96—7.18, 7.35—7.46 (13H, m), 8.70 (1H, s); IR: 3352, 1668, 1598, 1556, 1492, 1454 cm^{-1}.

1-[2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-meth-

ylphenyl)ureido]acetyl]amino]phenoxy]acetyl]pyrrolidine (**20c**): ^{1}H-NMR (DMSO-d_6) δ: 1.75—1.90 (4H, m), 2.22 (3H, s), 3.18 (3H, s), 3.30—3.34 (4H, m), 3.64 (2H, br s), 4.05 (2H, br s), 4.74 (2H, br s), 6.29 (1H, br s), 6.69 (1H, d, J=7.3 Hz), 6.94—7.17, 7.36—7.46 (12H, m), 8.72 (1H, s); IR: 3352, 1668, 1596, 1556, 1492, 1454, 1430 cm^{-1}.

1-[2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetyl]piperidine (**20d**): ^{1}H-NMR ($CDCl_3$) δ: 1.56—1.65 (6H, m), 2.26 (3H, s), 3.22 (3H, s), 3.44 (2H, br s), 3.56 (2H, br s), 3.90 (2H, d, J=5.4 Hz), 4.10 (2H, s), 4.68 (2H, s), 6.06 (1H, br s), 6.77 (1H, d, J=7.8 Hz), 6.95—7.36 (12H, m), 7.71 (1H, s); IR: 3368, 1668, 1596, 1556, 1492, 1446 cm^{-1}.

1-[2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetyl]homopiperidine (**20e**): ^{1}H-NMR ($CDCl_3$) δ: 1.56, 1.72—1.80 (8H, m), 2.27 (3H, s), 3.23 (3H, s), 3.46 (2H, m), 3.54 (2H, m), 3.90 (2H, d, J=4.4 Hz), 4.10 (2H, s), 4.70 (2H, s), 6.00 (1H, br s), 6.78 (1H, d, J=7.9 Hz), 6.96—7.36 (12H, m), 7.58 (1H, s); IR: 3364, 1765, 1666, 1596, 1556, 1492 cm^{-1}.

8-[2-[3-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetyl]-8-azaspiro[4,5]decane (**20f**): ^{1}H-NMR ($CDCl_3$) δ: 1.45 (8H, br s), 1.63 (4H, br s), 2.27 (3H, s), 3.23 (3H, s), 3.41 (2H, br s), 3.57 (2H, br s), 3.91 (2H, d, J=4.9 Hz), 4.10 (2H, s), 4.68 (2H, s), 6.01 (1H, br s), 6.78 (1H, d, J=7.8 Hz), 6.95—7.36 (12H, m), 7.57 (1H, s); IR: 3356, 1760, 1666, 1596, 1556, 1492 cm^{-1}.

N,*N*-Diethyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**20g**): ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.1 Hz), 1.22 (3H, t, J=6.8 Hz), 2.27 (3H, s), 3.22 (3H, s), 3.35 (2H, q, J=6.8 Hz), 3.40 (2H, q, J=7.1 Hz), 3.90 (2H, d, J=5.4 Hz), 4.09 (2H, s), 4.68 (2H, s), 6.01 (1H, br s), 6.79 (1H, d, J=7.8 Hz), 6.97—7.37 (12H, m), 7.58 (1H, s); IR: 3360, 1668, 1596, 1556, 1492, 1434 cm^{-1}.

N-Methoxy-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**20h**): ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 3.21 (3H, s), 3.22 (3H, s), 3.75 (3H, s), 3.90 (2H, d, J=5.4 Hz), 4.09 (2H, s), 4.84 (2H, s), 6.10 (1H, m), 6.75 (1H, d, J=7.3 Hz), 6.94 (1H, d, J=7.3 Hz), 7.05—7.35 (11H, m), 7.84 (1H, s); IR: 3372, 1668, 1598, 1554, 1492, 1430, 1394 cm^{-1}.

N-(3-Methoxypropyl)-*N*-(*n*-pentyl)-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**20i**): ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, m), 1.23—1.86 (8H, m), 2.26 (3H, s), 3.21 (3H, s), 3.25—3.44 (6H, m), 3.30 (3H, s), 3.90 (2H, d, J=5.4 Hz), 4.09 (2H, s), 4.69 (2H, s), 6.06 (1H, br s), 6.76 (1H, d, J=7.9 Hz), 6.92—7.35 (12H, m), 7.72 (1H, s); IR: 3352, 1762, 1668, 1596, 1556, 1492 cm^{-1}.

N-Cyclohexyl-*N*-methyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**20j**): ^{1}H-NMR ($CDCl_3$) δ: 1.26—1.86 (10H, m), 2.27 (3H, s), 2.85 (3/2H, s), 2.87 (3/2H, s), 3.22 (3H, s), 3.57 (1/2H, m), 3.90 (2H, d, J=5.4 Hz), 4.09 (2H, s), 4.37 (1/2H, m), 4.67 (1H, s), 4.72 (1H, s), 6.01 (1H, m), 6.78 (1H, m), 6.93—7.57 (13H, m); IR: 3368, 1668, 1598, 1554, 1492, 1452, 1428 cm^{-1}.

N-Methyl-*N*-phenyl-2-[3-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**20k**): ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 3.22 (3H, s), 3.32 (3H, s), 3.85 (2H, d, J=4.9 Hz), 4.08 (2H, s), 4.42 (2H, s), 6.03 (1H, br s), 6.76—7.47 (18H, m), 7.66 (1H, br s); IR 3360, 1670, 1596, 1556, 1496, 1454, 1428 cm^{-1}.

***N*-(2-Benzyloxyphenyl)-2-(*N*-*tert*-butoxycarbonylamino)acetamide (22)** A solution of **21** (16.4 g, 82.4 mmol), Boc–Gly (14.4 g, 82.4 mmol) and DMAP (11.0 g, 90.0 mmol) in CH_2Cl_2 (200 ml) was treated with EDC·HCl (16.3 g, 85.0 mmol), and the mixture was stirred at room temperature for 12 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 **22** (11.5 g, 39%) as a white powder, mp 80—82 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s), 3.91 (2H, d, J=5.4 Hz), 5.12 (2H, s), 5.18 (1H, br s), 6.93—7.03 (3H, m), 7.35—7.41 (5H, m), 8.37—8.38 (2H, m).

***N*-Methyl-*N*-phenyl-2-[*N*-(2-benzyloxyphenyl)-*N*-[2-(*N*-*tert*-butoxycarbonylamino)acetyl]amino]acetamide (23)** A solution of **22** (12.5 g, 35.1 mmol) in THF (200 ml) was treated with NaH (60% in oil, 1.68 g, 42.0 mmol), and the mixture was stirred at 55 °C for 1 h. Then **14** (9.6 g, 42.0 mmol) was added to the reaction mixture with ice cooling, and the resulting mixture was stirred at room temperature for 2 h. Ice-water was added, and the whole 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 washed with ether to give **23** (12.0 g, 68%) as a white powder, mp 168—170 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (9H, s), 3.27 (3H, s), 3.37 (1H, d, J=17.0 Hz), 3.56 (1H, dd, J=4.9, 18.0 Hz), 3.80 (1H, dd, J=3.6, 18.0 Hz), 4.78 (1H, d, J=17.0 Hz), 4.95 (1H, d, J=12.0 Hz), 5.00 (1H, d, J=12.0 Hz), 5.38 (1H, br s), 6.94—7.00 (2H, m), 7.12 (2H, m), 7.21—7.35 (6H, m), 7.37—7.43 (3H, m), 7.66—7.68 (1H, m).

***N*-Methyl-*N*-phenyl-2-[*N*-(2-aminoacetyl)-*N*-(2-benzyloxyphenyl)amino]acetamide (24)** TFA (50 ml) was added to a solution of **23** (8.0 g, 15.9 mmol) in CH_2Cl_2 (100 ml) with ice cooling, and the mixture was stirred at the same temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The organic solution was washed with saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **24** (6.3 g, 98%) as a pale yellow syrup. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (2H, br s), 2.97 (1H, d, J=17.6 Hz), 3.27 (1H, d, J=17.6 Hz), 3.28 (3H, s), 3.35 (1H, d, J=16.6 Hz), 4.79 (1H, d, J=16.6 Hz), 4.98 (2H, ABq, J=12.2 Hz), 6.95—7.01 (2H, m), 7.12 (1H, s), 7.24—7.44 (10H, m), 7.66 (1H, d, J=7.8 Hz).

***N*-Methyl-*N*-phenyl-2-[*N*-(2-benzyloxyphenyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]acetamide (25)** A solution of 3-tolyl isocyanate (2.05 g, 15.4 mmol) in THF (10 ml) was added to a solution of **24** (6.2 g, 15.4 mmol) in THF (50 ml) and the mixture was stirred at room temperature for 15 min. It was then concentrated under reduced pressure and the residue was washed with AcOEt–diethyl ether to give **25** (6.9 g, 84%) as a white powder, mp 191—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.22 (3H, s), 3.41 (1H, d, J=16.6 Hz), 3.76 (1H, dd, J=4.8, 17.6 Hz), 3.95 (1H, dd, J=3.9, 17.6 Hz), 4.77 (1H, d, J=16.6 Hz), 4.99 (2H, ABq, J=12.2 Hz), 5.87 (1H, br s), 6.80—6.84 (2H, m), 6.97 (1H, d, J=7.8 Hz), 7.01 (1H, d, J=7.3 Hz), 7.04 (1H, d, J=8.3 Hz), 7.11—7.38 (13H, m), 7.66 (1H, dd, J=2.0, 7.8 Hz).

***N*-Methyl-*N*-phenyl-2-[*N*-(2-hydroxyphenyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]acetamide (26)** **25** (6.6 g, 12.3 mmol) was hydrogenated in a mixture of MeOH (200 ml) and AcOEt (200 ml) over 5% Pd–C (1.3 g) at atmospheric pressure for 2.5 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and the solution was dried over $MgSO_4$. The solvent was removed under reduced pressure to give **26** (5.3 g, 97%) as a pale yellow amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 3.27 (3H, s), 3.34 (1H, d, J=16.6 Hz), 3.65 (1H, d, J=17.6 Hz), 4.04 (1H, d, J=17.6 Hz), 4.72 (1H, d, J=16.6 Hz), 5.77 (1H, br s), 6.81—6.87 (2H, m), 7.00—7.38 (12H, m), 10.57 (1H, s).

Methyl 2-[2-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (27a) A mixture of **26** (1.9 g, 4.3 mmol), methyl 2-bromoacetate **8a** (0.98 g, 6.4 mmol) and K_2CO_3 (1.4 g, 10.0 mmol) in DMF (50 ml) was stirred at 70 °C for 2 h. Water was added to it 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 $CHCl_3$–MeOH (50 : 1). The eluate was concentrated under reduced pressure and the product was recrystallized from AcOEt–diethyl ether. The product was collected by filtration to give **27a** (1.8 g, 81%) as a white powder, mp 165—166 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.23 (3H, s), 3.53 (1H, d, J=16.6 Hz), 3.68 (3H, s), 3.89 (2H, m), 4.61 (2H, s), 4.76 (1H, d, J=16.6 Hz), 5.92 (1H, br s), 6.76 (1H, d, J=7.8 Hz), 6.82 (1H, d, J=7.8 Hz), 7.00—7.18, 7.28—7.35 (11H, m), 7.72 (1H, dd, J=1.0, 7.8 Hz); IR: 3332, 1760, 1672, 1646, 1612, 1596, 1554, 1496, 1432 cm^{-1}; *Anal.* Calcd for $C_{28}H_{30}N_4O_6$: C, 64.85; H, 5.83; N, 10.80. Found: C, 64.65; H, 5.98; N, 10.51.

Compounds **27b** and **27c** were obtained by following a procedure similar to that described for the preparation of **27a**; the yields, melting points and elemental analysis data are given in Table 5. The IR and ^{1}H-NMR data of these compounds are as follows:

Ethyl 2-[2-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (**27b**): ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=6.8 Hz), 2.26 (3H, s), 3.20 (3H, s), 3.58 (1H, d, J=16.6 Hz), 3.86 (1H, dd, J=4.9, 17.6 Hz), 3.95 (1H, dd, J=4.4, 17.6 Hz), 4.15 (2H, q, J=6.8 Hz), 4.59 (2H, s), 4.76 (1H, d, J=16.6 Hz), 6.13 (1H, br s), 6.75—6.78 (2H, m), 7.01—7.14, 7.20—7.31 (10H, m), 7.44 (1H, s), 7.73 (1H, d, J=7.8 Hz); IR: 3336, 1760, 1672, 1614, 1598, 1560, 1496, 1452, 1428 cm^{-1}.

tert-Butyl 2-[2-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (**27c**): ^{1}H-NMR

($CDCl_3$) δ: 1.40 (9H, s), 2.27 (3H, s), 3.21 (3H, s), 3.59 (1H, d, J=16.6 Hz), 3.83 (1H, dd, J=4.9, 17.6 Hz), 3.97 (1H, dd, J=4.4, 17.6 Hz), 4.47 (2H, ABq, J=12.2 Hz), 4.76 (1H, d, J=16.6 Hz), 6.04 (1H, br s), 6.74 (1H, d, J=8.3 Hz), 6.79 (1H, d, J=7.8 Hz), 7.02 (1H, t, J=7.8 Hz), 7.06—7.19, 7.27—7.33 (10H, m), 7.73 (1H, d, J=7.8 Hz); IR 3352, 1748, 1656, 1614, 1596, 1554, 1498, 1430, 1394 cm^{-1}.

Isopropyl 2-[2-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetate (27d) Titanium (IV) isopropoxide (0.55 g, 1.9 mmol) was added to a solution of **27a** (1.0 g, 1.9 mmol) in isopropanol (50 ml) and the mixture was stirred under reflux for 2 d. Then 1 N HCl was added, and 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 $CHCl_3$–MeOH (50 : 1). The eluate was concentrated under reduced pressure and the product was recrystallized from AcOEt–diethyl ether. The product was collected by filtration to give **27d** (0.7 g, 67%) as a white powder, mp 173—174 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.21 (6H, m), 2.27 (3H, s), 3.22 (3H, s), 3.56 (1H, d, J=16.6 Hz), 3.85 (1H, dd, J=4.9, 17.6 Hz), 3.95 (1H, dd, J=4.4, 17.6 Hz), 4.56 (2H, s), 4.76 (1H, d, J=16.6 Hz), 5.01 (1H, m), 6.00 (1H, br s), 6.74 (1H, d, J=8.3 Hz), 6.79 (1H, d, J=7.4 Hz), 7.01—7.33 (11H, m), 7.73 (1H, d, J=7.4 Hz); IR 3340, 1756, 1664, 1612, 1598, 1556, 1496, 1452, 1430 cm^{-1}; *Anal.* Calcd for $C_{30}H_{34}N_4O_6$: C, 65.92; H, 6.27; N, 10.25. Found: C, 65.68; H, 6.25; N, 10.00.

Compounds **28** and **29a—e** were obtained by following a procedure similar to that described for the preparation of **19** and **20a—k**, respectively; the yields, melting points and elemental analysis data are given in Table 5. The IR and ^{1}H-NMR data of these compounds are as follows:

2-[2-[*N*-(*N*-Methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetic Acid (**28**): ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s), 3.16 (3H, s), 3.58—3.63 (2H, m), 3.79 (1H, dd, J=5.3, 15.6 Hz), 4.49 (2H, s), 4.56—4.63 (1H, m), 6.47 (1H, s), 6.68 (1H, d, J=7.4 Hz), 6.96—7.45 (11H, m), 7.59 (1H, d, J=7.3 Hz), 8.82 (1H, s).

N,*N*-Diethyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**29a**): ^{1}H-NMR ($CDCl_3$) δ: 1.08—1.34 (6H, m), 2.27 (3H, s), 3.22—3.98 (11H, m), 4.71 (2H, s), 5.92 (1H, br s), 6.80—7.70 (14H, m); IR: 3368, 1614, 1554, 1434, 1222 cm^{-1}.

N-Ethyl-*N*-(*n*-propyl)-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**29b**): ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.8 Hz), 1.08 (3H, t, J=7.3 Hz), 1.47—1.58 (2H, m), 2.24 (3H, s), 3.21 (3H, s), 3.10—3.61 (5H, m), 3.92 (2H, d, J=5.3 Hz), 4.70—4.73 (3H, br s), 6.20 (1H, br s), 6.75—7.70 (14H, m); IR: 3368, 1664, 1614, 1598, 1556, 1498, 1458, 1434 cm^{-1}.

N-(*n*-Butyl)-*N*-ethyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**29c**): ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.11 (3H, t, J=6.8 Hz), 1.24—1.31 (2H, m), 1.45—1.54 (2H, m), 2.25 (3H, s), 3.22 (3H, s), 3.13—3.59 (5H, m), 3.92 (2H, d, J=5.9 Hz), 4.71 (3H, br s), 6.17 (1H, br s), 6.75—7.70 (14H, m); IR: 3352, 1668, 1614, 1598, 1554, 1498, 1456, 1432 cm^{-1}.

N-Cyclohexyl-*N*-methyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**29d**): ^{1}H-NMR ($CDCl_3$) δ: 1.06—1.78 (10H, m), 2.25 (3H, s), 2.75 (3/2H, s), 2.80 (3/2H, s), 3.21 (3H, s), 3.57 (1H, d, J=16.6 Hz), 3.92—3.98 (2H, m), 4.14 (1H, br s), 4.67—4.77 (3H, m), 6.17 (1H, br s), 6.74—7.73 (14H, m); IR: 3400, 1664, 1596, 1556, 1498, 1434 cm^{-1}.

N-Methyl-*N*-phenyl-2-[2-[*N*-(*N*-methyl-*N*-phenylcarbamoylmethyl)-*N*-[2-[3-(3-methylphenyl)ureido]acetyl]amino]phenoxy]acetamide (**29e**): ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 3.22 (3H, s), 3.26 (3H, s), 3.55 (1H, d, J=16.6 Hz), 3.90 (2H, m), 4.39 (2H, s), 4.68 (1H, d, J=16.6 Hz), 6.04 (1H, br s), 6.62 (1H, d, J=8.3 Hz), 6.76 (1H, d, J=7.4 Hz), 6.99—7.44 (16H, m), 7.69 (1H, d, J=7.4 Hz); IR: 3360, 1668, 1614, 1596, 1554, 1496, 1454 cm^{-1}.

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

References and Notes

1) Rehfeld J. F., *Am. J. Physiol.*, **240**, G255—266 (1981).
2) Innis R. B., Snyder S. H., *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 6917—6921 (1980).
3) Hill D. R., Campbell N. J., Shaw T. M., Woodruff G. N., *J. Neurosci.*, 7, 2967—2976 (1987); Hill D. R., Shaw T. M., Woodruff G. N., *Neurosci. Lett.*, **79**, 286—298 (1987).
4) Evans B. E., Bock M. G., Rittle K. E., DiPardo R. M., Whitter W. L., Veber D. F., Anderson P. S., Freidenger R. M., *Proc. Natl. Acad. Sci. U.S.A.*, **83**, 4918—4922 (1986).
5) Beinfeld M. C., *Neuropeptides*, **3**, 411—427 (1983).
6) *a*) Kopin A. S., Lee Y. M., McBride E. M., Miller L. J., Lu M., Lin H. Y., Kolakowski L. F., Jr., Beinborn M., *Proc. Natl. Acad. Sci. U.S.A.*, **89**, 3605—3609 (1992); *b*) Pisegna J. R., Weerth A. D., Huppi K., Wank S. A., *Biochem. Biophys. Res. Commun.*, **189**, 296—303 (1992); *c*) Lee Y. M., Beinborn M., McBride E. M., Lu M., Kolakowski L. F., Jr., Kopin A. S., *J. Biol. Chem.*, **268**, 8164—8169 (1993).
7) Bock M. G., Dipardo R. M., Evans B. E., Rittle K. E., Whitter W. L., Veber D. F., Anderson P. S., Freidenger R. M., *J. Med. Chem.*, **32**, 13—16 (1989).
8) Chang R. S., Lotti V. J., Monaghan J., Birnbaum J., Stapley E. O., Goetz M. A., Schonberg G. A., Patchett A. A., Liesch J. M., Hensens O. D., Springer J. P., *Science*, **230**, 177—179 (1985).
9) Showell G. A., Bourrain S., Neduvelil J. G., Fletcher S. R., Baker R., Watt A. P., Fletcher A. E., Freedman S. B., Kemp J. A., Marshall G. R., Patel S., Smith A. J., Matassa V. G., *J. Med. Chem.*, **37**, 719—721 (1994).
10) Satoh M., Kondoh Y., Okamoto Y., Nishida A., Miyata K., Ohta M., Mase T., Murase K., *Chem. Pharm. Bull.*, **43**, 2159—2167 (1995).
11) Bertrand P., Bohme G. A., Durieux C., Guyon C., Capet M., Jeantaud B., Boudeau P., Ducos B., Pendley C. E., Martin G. E., Floch A., Doble A., *Eur. J. Pharmacol.*, **262**, 233—245 (1994).
12) Ek A., Wiktop B., *J. Am. Chem. Soc.*, **76**, 5579—5588 (1954).
13) Bischoff C. A., *Chem. Ber.*, **34**, 2125 (1901); Drake N. L., Eaker C. M., Shenk W., *J. Am. Chem. Soc.*, **70**, 677—680 (1948).
14) Seebach D. Hungerbuhler E., Naef R., Schnurrenberger P., Weidmann B., Zuger M., *Synthesis*, **1982**, 138—141.