Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 8, pp 1695–1714, 1997

PII: S0968-0896(97)00104-1
0968-0896/97 $17.00 + 0.00

Synthesis and Pharmacological Properties of Ureidomethylcarbamoylphenylketone Derivatives. A New Potent and Subtype-selective Nonpeptide CCK-B/gastrin Receptor Antagonist, S-0509

Sanji Hagishita,* Yasushi Murakami, Kaoru Seno, Susumu Kamata,* Nobuhiro Haga, Toshiro Konoike, Yasuhiko Kanda, Ryuichi Kiyama, Takeshi Shiota, Yasunobu Ishihara,* Michio Ishikawa, Mayumi Shimamura, Koji Abe and Koji Yoshimura

Shionogi Research Laboratories, Shionogi & Co., Ltd, Fukushima-ku, Osaka 553, Japan

Abstract—A novel series of CCK-B/gastrin receptor antagonists—ureidomethylcarbamoylphenylketone derivatives—were designed, synthesized, and evaluated for activity. Structure–activity relationship studies revealed the importance of a carboxylic acid at substituent R_2 and a *tert*-butoxycarbonyl group at R_1 in structure **A**. Compound **7a** (**S-0509**) showed remarkable affinity for the CCK-B/gastrin receptor and a subtype selectivity profile in vitro. Administration (id) of **7a** led to excellent inhibition of gastric acid secretion induced by pentagastrin in anesthetized rats with an ED_{50} value of 0.014 mg/kg. Furthermore, **7a** proved to have poor blood–brain permeability by its small effect on enhancement of morphine analgesia. Thus, **S-0509** has an increase in selectivity for the peripheral effects of gastrin antagonism from the central effects of CCK-B antagonism. © 1997 Elsevier Science Ltd.

Introduction

Gastrin and cholecystokinin (CCK) belong to the polypeptide hormone family and are found in both the central nervous system (CNS) and gastrointestinal tissue. Gastrin is a stimulant of gastric acid secretion and a growth factor for mucosal cells including gastrin-dependent histamine secretory enterochromaphin-like cells (ECL cells).[1] The receptors for gastrin and CCK have been classified into two subtypes: CCK-A and CCK-B/gastrin. The CCK-A receptor subtype predominates in peripheral target organs and mediates control of gallbladder function and digestive enzyme secretion. The CCK-B/gastrin receptor shows widespread distribution in the CNS and mucosal cells and is responsible for neurotransmission or neuromodulation and for gastrin-stimulated acid secretion in the stomach during feeding.[2] Long-term treatment with histamine H_2-receptor antagonists, as well as proton-pump inhibitors, has been reported to cause hypergastrinemia[3] which can result in hyperplasia of ECL cells. After cessation of therapy there is a rebound of gastric acid secretion which results in a very high risk of recurrence of ulceration. Therefore, there may be a need for an alternative pharmacological approach such as development of gastrin antagonists.

Efforts to find potent and selective CCK-B/gastrin antagonists have been reported (Figure 1). The initial efforts of Merck chemists led to the discovery of the first nonpeptide CCK receptor antagonist, Asperlicin,[4] from a natural products screening program. Chemical modification using a benzodiazepine pharmacophore produced a potent selective CCK-A receptor antagonist MK-329[5] and a CCK-B/gastrin receptor antagonist L-365,260.[6] Since then compounds of various structures have been designed and prepared to improve the potency and subtype selectivity and to eliminate deficiencies, such as low oral bioavailability.[7] RP 73870[8] and CI-988,[9] which are nonbenzodiazepines, potently antagonize acid secretion induced by pentagastrin. YM022 inhibits gastric acid secretion without inducing gastrin-mediated side-effects such as hypergastrinemia and hyperplasia of oxyntic mucosa.[10] Recently, hydrophilic substituents have been introduced into the C-5 position or on the ureidobenzene ring of the C-3 position of benzodiazepine and benzazepine skeletons in order to increase water solubility.[7,11]

The benzodiazepine structure has been shown to satisfy many requirements of a useful *beta* structure, by closely maintaining the overall geometric requirements. Although many analogues have been synthesized we became interested in the biological activities of this novel class of acyclic compounds. This paper describes the synthesis and pharmacological properties of CCK-B/gastrin antagonists of nonbenzodiazepine derivatives—ureidomethylcarbamoylphenylketone—**A** (Figure 2 which are ring-cleaved derivatives at the C3–N4 bond of the 1,4-benzodiazepine compound. 2-(Aminoacetamindo)benzophenones are known to undergo spontaneous cyclization to corresponding benzodiazepines.[12] This suggests that acyclic compounds such as **A** have a stable conformation similar to the benzodiazepine ring system, which may be an active species. Active conformation of nonsulfonated CCK-8

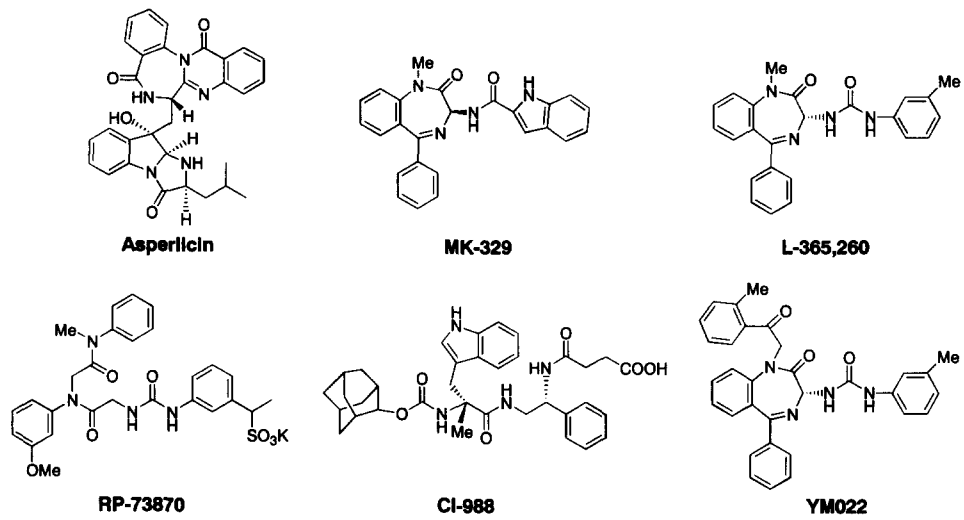


Figure 1.

for binding with the CCK-B/gastrin receptor was deduced to be of the same folded conformation of *N*-acetyl-CCK-7 as the one proposed by Pincus et al.[13] We then superimposed the stable conformation of L-365,260 on the folded conformation of *N*-acetyl-CCK-7 and found that the benzo, phenyl, and tolyl groups of L-365,260 correspond to the phenyl ring of Phe-1, the phenyl ring of Tyr-7, and the indole group of Try-4, respectively.[14] The *C*-terminal tetrapeptide Trp-Met-Asp-Phe-NH_2 appeared to be the minimum sequence required for activity on the gastrin receptor. The group R_3 in structure **A** corresponds to Tyr-7 and can be modified chemically as can be R_1 and R_2, to search for therapeutic drugs, especially for ulceration. Structure–activity relationships resulted in the discovery of the potent and selective CCK-B/gastrin antagonist S-0509. This compound very efficiently inhibited pentagastrin-induced gastric acid secretion in anesthetized rats.

Chemistry

The compounds described in this paper were prepared according to Schemes 1–4. Coupling reactions of *o*-acylaniline, (2-aminobenzophenone **1a,** 2-(cyclohexylcarbonyl)aniline **1b**[15], 2-(2-thienylcarbonyl)aniline **1c**[16] and 2-amino-4′-methoxybenzophenone **1d**[17]) and Cbz-Gly or Cbz-(*D*) or (*L*)-Ala were carried out with $SOCl_2$ in HMPA[18] or $POCl_3$ and imidazole to give amide compounds **2a–f**. After deprotection of the Cbz group with HBr/AcOH, the HBr salts, **3a–f** were treated with phenylisocyanate of various substituents to obtain the ureas **4a-z** (Table 1). The *N*-alkylation of **4a–z** with bromoacylpyrrolidine, bromomethylcyclopropylketone, *m*-(*N*-Boc-amino)benzyl bromide, *tert*-butylbromoacylamide or *tert*-butyl bromoacetate in the presence of K_2CO_3, KI and n-BuN^+Br^- furnished *N*-alkylated compounds **5a–c, e, f** or **6a–z**. Selective hydrolysis of allyl ester of diesters **6e–h, v, x, z** was achieved with $Pd(PPh_3)_4$, PPh_3 and pyrrolidine to obtain the desired half esters **7a–d, h–j**.

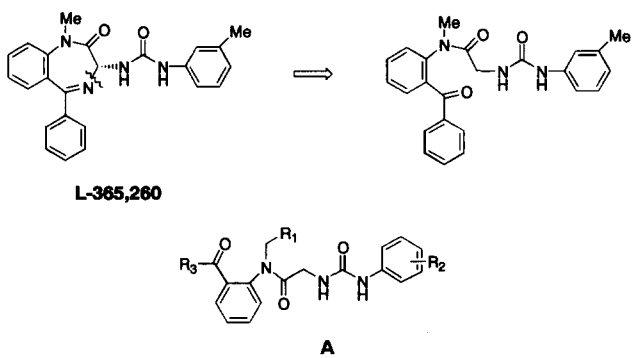
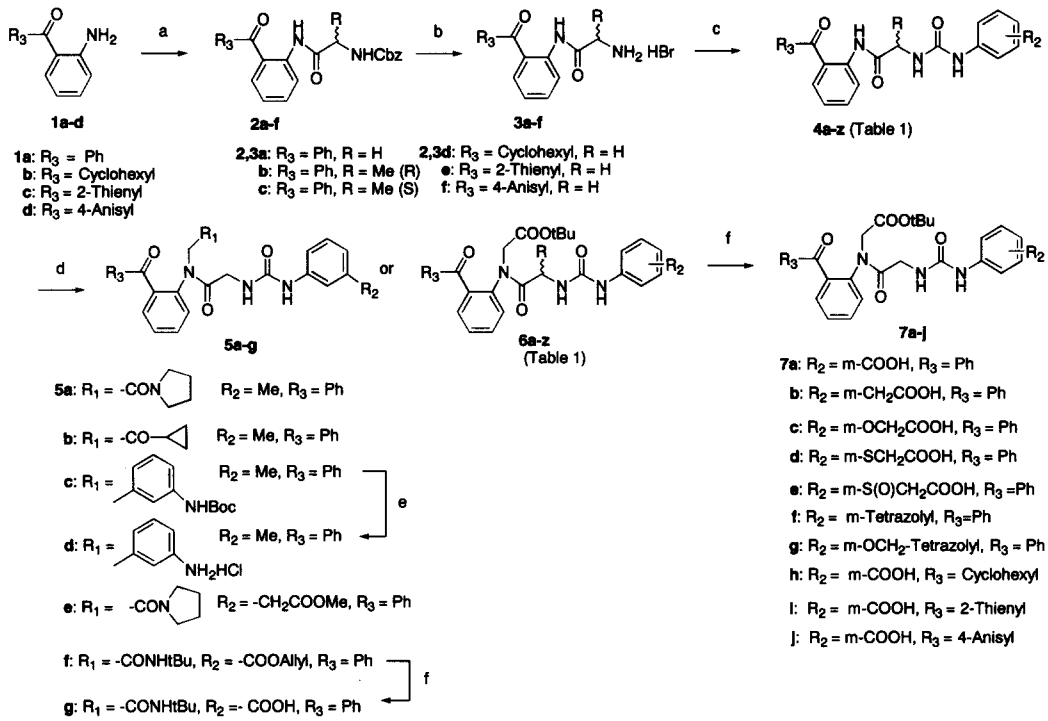


Figure 2. Ring cleavage of L-365,260 at C3–N4 bond and synthesized compound **A**.

The above procedure was done to modify mainly the substituents R_1 and R_2 in structure **A**. Effective modification of R_3 is described in Scheme 2, in which R_1 and R_2 were fixed with *tert*-butoxycarbonylmethyl and methyl groups, respectively. *o*-Iodoaniline **8** was treated by the same sequential procedures as the preparation of **6** from **1** cited in Scheme 1 to obtain **12**, the iodo group of which was then converted to the trimethyltin group to obtain compound **13**. Various acyl chloride compounds were allowed to react with **13** in the presence of a Pd-complex to obtain the desired benzoyl compounds **7k–s**.[19]

These sequential procedures could not be applied to the preparation of compounds having a carboxylic acid group at R_2 because of the incompatibility with the coupling reaction between acyl chloride and tin derivatives by the allyl ester. Scheme 3 shows a chemical modification at R_3 of compounds having a carboxylic acid group as the substituent R_2. The coupling reaction of tin compound **14** with acyl chloride was first achieved and then allyl isocyanatobenzoate was treated with deprotected amino compounds **3g–k** to obtain **15g–k**. *N*-Alkylation of **15g–k** followed by deprotection of the allyl group gave the carboxylic acid compounds **17g–k**

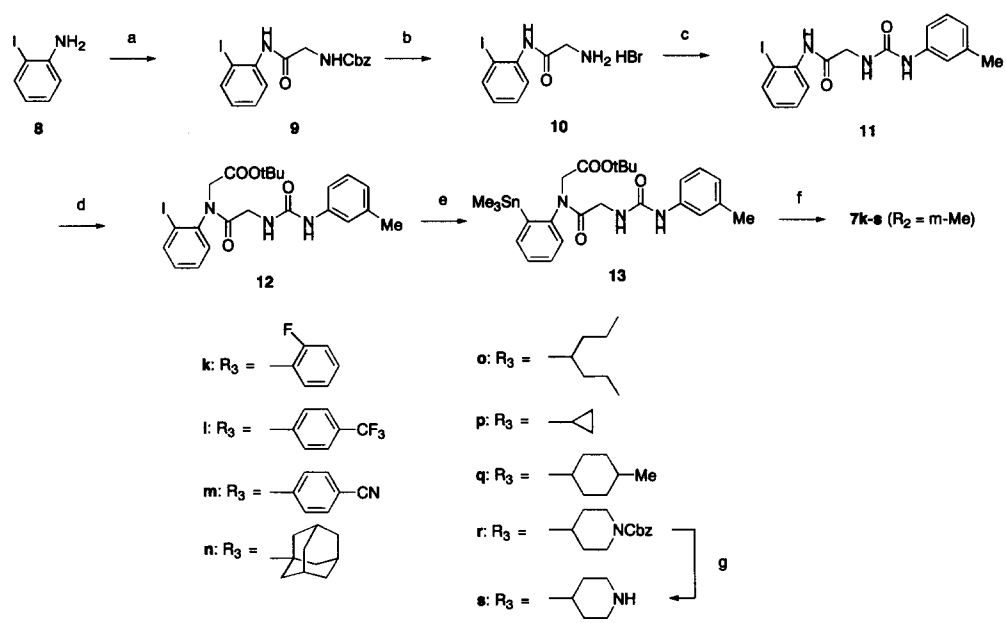


[a] Reagents: (a) Cbz-Gly or Cbz-(D), (L)-Ala, $SOCl_2$, HMPA or $POCl_3$, imidazole; (b) HBr-AcOH; (c) $R_2C_6H_4NCO$; (d) $BrCH_2R_1$, K_2CO_3, KI, $nBu_4N^+Br^-$; (e) HCl; (f) $Pd(PPh_3)_4$, PPh_3, pyrrolidine or HCl.

Scheme 1.[a]

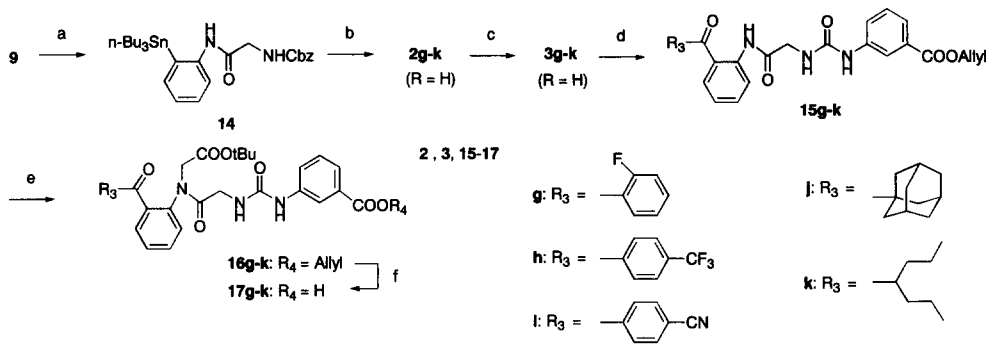
by the same procedure used for the preparation of **7** from **4** cited above.

In the preparation of piperidino-compound **17m** (Scheme 4), *N*-Boc-*o*-iodoaniline was converted to **20** by the same procedure used for the preparation of **7** via **13** from **12** described above. The Boc group of **20** was deprotected selectively with CF_3COOH and anisole to obtain **1e**. On the other hand, methyl isocyanatoacetate and allyl *m*-aminobenzoate gave diester **22**, which was then selectively hydrolyzed with 2 N HCl to obtain **23**. Coupling of compounds **1e** and **23** gave **15l**, which was then converted to **17l** by the procedure used to prepare **7** from **4** cited above.



[a] Reagents: (a) Cbz-Gly, $POCl_3$, imidazole; (b) HBr-AcOH; (c) m-MeC_6H_4NCO; (d) $BrCH_2COOtBu$, K_2CO_3, KI, $nBu_4N^+Br^-$; (e) $(Me_3Sn)_2$, $PhCH_2Pd(PPh_3)_2Cl$; (f) R_3COCl, $Pd(CH_3CN)_2Cl_2$; (g) H_2, 10% Pd/C.

Scheme 2.[a]



[a] Reagents: (a) $(n\text{-}Bu_3Sn)_2$, $PhCH_2Pd(PPh_3)_2Cl$; (b) R_3COCl, $Pd(CH_3CN)_2Cl_2$; (c) HBr-AcOH; (d) $3\text{-}NH_2C_6H_4COOAllyl$, $(CCl_3O)_2CO$; (e) $BrCH_2COOtBu$, K_2CO_3, KI, $nBu_4N^+Br^-$; (f) $Pd(PPh_3)_4$, PPh_3, pyrrolidine.

Scheme 3.[a]

Biology

In vitro receptor binding assays were used to measure the affinity of compounds for CCK-B receptor of mouse cortical membranes and CCK-A receptor of mouse pancreas, respectively. The affinity at the gastrin receptor was measured using guinea pig gastrin glands. IC_{50} values were obtained for the half-maximal inhibition of binding of [propionyl-^{3}H]CCK-8 (sulfonated) to CCK receptors and of binding human [^{125}I]gastrin I to gastrin receptor.[20] In vivo gastric acid secretion was measured in anesthetized rats following administration of pentagastrin by adding a test compound intraduodenally or intravenously.[21] Basal gastric acid secretion was determined in pylorus-ligated rats and a test compound or vehicle was given orally 30 min before ligation.

Following Dourish et al.'s[22] method CCK-B antagonist was injected intraperitoneally 10 min before subcutaneous injection with 2 mg/kg morphine, which showed approximately 40% analgesia. The potency of CCK-B antagonists for enhancing morphine analgesia was evaluated by the percentage of the maximum possible effect (%MPE = [(TL − BL)/(20.0 − BL)] × 100; where TL are the test latencies and BL are the baseline latencies). The %MPE are those at 40 min after subcutaneous injection of morphine.

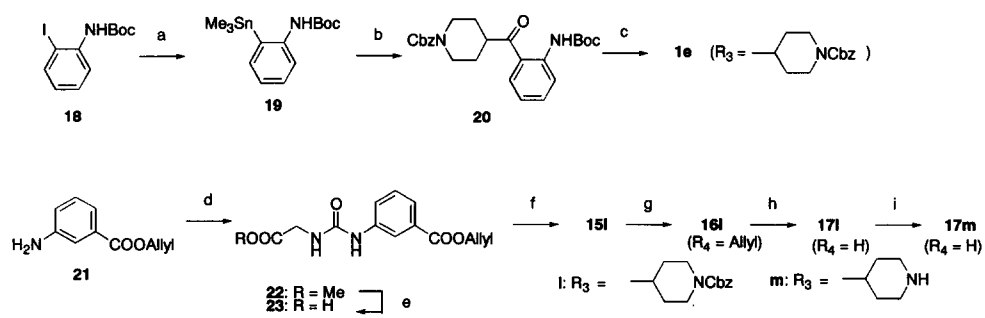
Structure–Activity Relationships and Discussion

Substituents R_2 and R_3 of compound **A** were fixed with phenyl and methyl groups, respectively, and the variation of R_1 was examined first. From the results of binding assays for gastrin of amide, ketone, aromatic amine, and ester compounds, **5a**, **b**, **d** and **6a**, the *tert*-butoxycarbonyl derivative showed the best affinity and the substituent was chosen for R_1, although the selectivity for the CCK-A receptor (CCK-A/CCK-B = 10) was not sufficient (Table 2).

Introduction of a methyl group to the methylene chain adjacent to the urea group of compound **A**, **6b** and **6c**, decreased the affinity for three receptors and the (*R*)-isomer showed greater reduction of affinity than the (*S*)-isomer.

The effect induced by the *meta*- or *para*-position of the substituent on the ureido benzene ring was examined next. Comparison of the *meta*-substituted derivatives, **6a** and **6m**, with *para*-substituted ones, **6r** and **6q**, showed the *meta*-position to offer better potency. Thus the *meta*-position was chosen for further modification.

The electronic effects of a substituent such as electron-donating and electron-withdrawing effects had little influence on the receptor affinities according to the results of compounds **6p**, **6l**, and **6o**.



[a] Reagents: (a) $(Me_3Sn)_2$, $PhCH_2Pd(PPh_3)_2Cl$; (b) N-Cbz-isonipecotonoyl chloride; (c) CF_3COOH, anisole; (d) $MeOOCCH_2NCO$; (e) 2N-HCl; (f) **1e**; (g) $BrCH_2COOtBu$, K_2CO_3, KI, $nBu_4N^+Br^-$; (h) $Pd(PPh_3)_4$, PPh_3, pyrrolidine; (i) 10% Pd/C, cyclohexene.

Scheme 4.[a]

Table 1. Substituents of compounds **4** and **6**

Compounds	R_2	R_3	R
4, 6a	*m*-Me	Ph	H
b	Me	Ph	Me(*R*)
c	*m*-Me	Ph	Me(*S*)
d	*m*-COOBn	Ph	H
e	*m*-COOAllyl	Ph	H
f	*m*-CH_2COOAllyl	Ph	H
g	*m*-OCH_2COOAllyl	Ph	H
h	*m*-SCH_2COOAllyl	Ph	H
i	*m*-3-Tr-Tetrazolyl	Ph	H
j	*m*-OCH_2-3-Tr-Tetrazolyl	Ph	H
k	*m*-CH_2COOMe	Ph	H
l	*m*-CF_3	Ph	H
m	*m*-Cl	Ph	H
n	*m*-Br	Ph	H
o	*m*-CN	Ph	H
p	*m*-OMe	Ph	H
q	p-Cl	Ph	H
r	p-Me	Ph	H
s	H	Ph	H
t	*m*-Me	Cyclohexyl	H
u	*m*-CF_3	Cyclohexyl	H
v	*m*-COOAllyl	Cyclohexyl	H
w	*m*-Me	2-Tienyl	H
x	*m*-COOAllyl	2-Tienyl	H
y	*m*-Me	4-Anisyl	H
z	p-COOAllyl	4-Anisyl	H

Substituents of R_1 and R_2 were fixed with *tert*-butoxycarbonyl and methyl groups, respectively, and modification of R_3 was carried out. Substitution at the *para*-position of the benzene ring had an unfavorable effect on the receptor affinity, regardless of the electron-donating or electron-withdrawing nature, as seen with **6y**, **7l**, and **m**. The *ortho*-fluoro group, **7k**, did not influence the receptor affinity and was equipotent to **6a**. The 2-thienyl derivative, **6w**, was also equipotent to the phenyl derivative, **6a**. Variation of R_3 with alkyl and alicyclic groups, **6t**, **7n–q**, indicated that R_3 of the small steric size, **7p**, decreased the gastrin receptor affinity and that the bulky substituent, **7n**, retained potency for receptor affinity. Introduction of the piperidine group, **7s**, was expected to increase the aqueous solubility but decreased the receptor affinity and subtype selectivity.

Introduction of a carboxylic acid group at R_2, **7a–e**, increased the selectivity of the receptor affinity for gastrin to CCK-A by one order of magnitude, except in the case of **7d**, in comparison with the receptor affinities of compounds **6a**, **l–p**, **s**. Compound **7f** with a tetrazole group showed remarkable affinity for the gastrin receptor and selectivity but the compound with a tetrazolylmethoxy group, **7g**, did not have the selectivity.

Substituents R_2 and R_3 were fixed with a carboxylic acid group and a phenyl ring, respectively, and R_1 was changed to the amide groups of pyrrolidinocarbonyl and *tert*-butylamide, **5e** and **5g**. However, these compounds did not exceed **7a** in potency and subtype selectivity.

Finally, the effects of R_3 were examined by fixing R_1 and R_2 with *tert*-butoxycarbonyl and carboxylic acid groups, respectively. The *para*-substitution, **17h** and **i**, decreased the gastrin receptor affinity by one order of magnitude, and analogues of *meta*-fluorophenyl, adamantyl and 4-heptyl substituents, **17g**, **i**, and **k**, retained high affinity and subtype selectivity. The piperidine derivative, **17m**, decreased the activity, although the water-solubility is expected to improve.

Intraduodenal administration of these active compounds inhibited gastric acid secretion induced by pentagastrin in anesthetized rats. The degrees of inhibition (ED_{50}) are shown in Table 2. Some compounds, **6a**, **o**, **t**, **7a**, **d**, **h–j** and **17g**, showed more active ED_{50} values than L-365,260 or YM022. Compounds having carboxylic acid at R_2 had high potency and excellent subtype selectivity in the in vitro assay, as mentioned above, and compound **7a** showed ED_{50} = 0.014 mg/kg with that of the Na-salt being 0.003 mg/kg. The latter was about 30 times more efficacious than L-365,260 and YM022.

Intravenous administration of the Na-salt inhibited pentagastrin-stimulated acid secretion, ED_{50} = 0.001 mg/kg. The salt was found to be 200 times more active than L-365,260, ED_{50} = 0.2 mg/kg. Maximal inhibition was observed 30 min after administration in the pylorus-ligated rat.

L-365,260 was reported to have no significant effect on basal acid secretion in the rat.[23] However, compound **7a** inhibited basal gastric acid secretion, ED_{50} = 3 mg/kg,

Table 2. Receptor antagonistic effects and inhibitory effects on gastric acid secretion

Compounds	Receptors (IC_{50}, nM)			Gastric acid inhibition ED_{50} id (mg/kg)
	Gastrin[a,b]	CCK-B[a,b]	CCK-A[a]	
5a	30	170	250	
5b	>1000[c]	>1000[c]	3200	
5d	180	>1000[c]	680	
5e	64	580	640	
5f	25	215	4400	
5g	6.1	210	>10,000[c]	
6a	5	19	200	0.03
6b	420	>1000[c]	4000	
6c	32	280	2400	
6d	64	420	2400	
6k	4	34	640	0.11
6l	62	125	500	
6m	4	26	210	
6n	7	22	100	
6o	4	36	460	0.08
6p	2	22	135	
6q	42	190	1800	>0.10[d]
6r	6	66	1900	
6s	5	32	640	>0.10[d]
6t	5	4	140	0.013
6u	5	6	1150	>0.03[d]
6w	5	30	340	
6y	120	>1000[c]	>10,000[c]	
7a	1.52	23.5	2813	0.014
Me ester	7	56	1350	0.04
Na salt	2	42	3400	0.003
7b	2	3	1700	0.17
Me ester	4	34	640	0.11
7c	3	8	2200	>0.30[d]
Me ester	2	11	1350	0.19
7d	2	1	200	0.07
Me ester	3	2	215	>0.10[d]
7e	3	21	2200	>0.30[d]
Me ester	23	33	1400	
7f	1	8	1650	>0.30[d]
7g	5	6	440	>0.10[d]
7h	3	6	2000	0.026
7i	5	130	6800	0.05
7j	7	180	5800	0.05
7k	4	22	440	
7l	210	420	1050	
7m	32	360	500	
7n	9	4	600	
7o	8	24	440	
7p	100	270	96	
7q	3	29	300	
7r	19	78	250	
7s	135	>1000[c]	4800	
17g	6	130	8200	0.03
17h	38	1600	8800	
17i	29	940	5000	
17j	2	6	4600	>0.1[d]
17k	9	170	>10,000[c]	
17m	520	>1000[c]	>10,000[c]	
L-365,260	2.1	15.5	14,100	0.104
YM022	0.88	0.89	75	0.107

[a]Binding results are the means of two to four independent determinations.
[b]The discrepancy of binding affinities for CCK-B and for gastrin may come from species difference (mouse for CCK-B and guinea pig for gastrin).
[c]Full IC_{50} not obtained.
[d]Full ED_{50} not obtained.

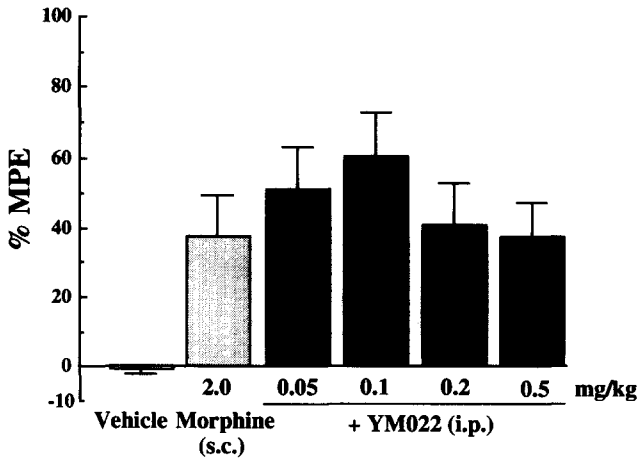


Figure 3. Enhancing effect of YM022 on morphine analgesia.

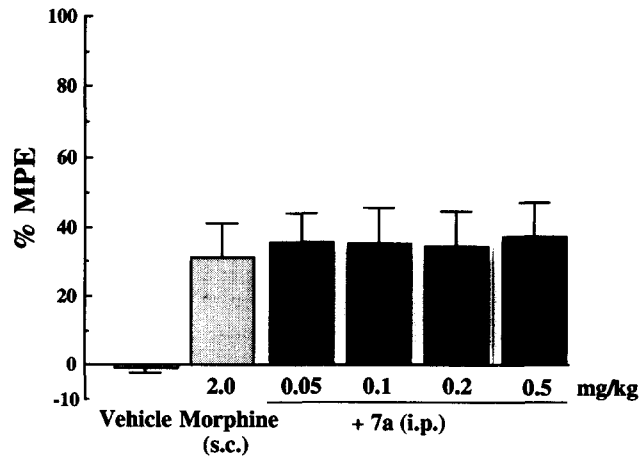


Figure 4. Effect of **7a** on morphine analgesia.

when given orally 30 min before pylorus ligation. Since the reference compounds had comparable or greater potencies in the in vitro assay, the marked increase in in vivo efficacy of ureidomethylcarbamoylphenylketone derivatives may come from the chain structure of the skeleton. Recent cloning of the CCK-B receptor and the gastrin receptor from rats, dogs, and humans has suggested that these receptors are highly homologous, if not identical.[24,25] The behavioral effects of CCK-B/gastrin receptor antagonists may be related to their capability to penetrate the brain. Suppression of the crossing of the blood–brain barrier is one of the ways of separating the activities of the receptor antagonist of gastrin from CCK-B.

It has been reported that morphine analgesia was enhanced by the selective CCK-B antagonist, L-365,260 in the rat tail flick test.[22] According to the method of Dourish et al.,[22] the potency of CCK-B antagonists for enhancing morphine analgesia was evaluated by the percentage of the maximum possible effect. The %MPE are shown in Figures 3 and 4. The dose–response curve of YM022 for morphine enhancement is bell shaped (Figure 3) and that of L-365,260 was reexamined and reaffirmed also to be bell shaped.[22] Compound **7a** had no effect on the tail flick test (Figure 4). Substitution of a carboxylic acid at R_2 adds one further hydrogen bonding group and is anticipated to have poorer membrane and blood–brain barrier permeability. Three hydrogen bonding groups would bring about an increase in the selectivity of gastrin from CCK-B receptor antagonist. Thus, compound **7a** was selected for further evaluation as gastrin receptor antagonist, **S-0509**. The tetrazole derivative, **7f**, was the best in the in vitro assay, but its ED_{50} value indicated unsatisfactory potency.

Conclusion

We have discovered the skeleton ureidomethylcarbamoylphenylketone to be a potent and subtype-selective CCK-B/gastrin receptor antagonist. Introduction of a *tert*-butoxycarbonyl group at R_1 and a *meta*-carboxylic acid group at R_2 in structure **A** afforded the best balance of potent affinity and subtype selectivity for the CCK-B/gastrin receptor. Also, compound **7a** potently inhibited pentagastrin-induced gastric acid secretion in anesthetized rats with an ED_{50} value of 0.014 mg/kg (id) and proved to have poor blood–brain permeability by its low effect on enhancement of morphine analgesia. Thus, **7a** has an increase in selectivity for the peripheral effects of gastrin antagonism from the central effects of CCK-B antagonism.

Compound **7a** was chosen for further evaluation as the compound **S-0509**.

Experimental

General methods

Melting points were not corrected. IR spectra were recorded on a Nicolet 20SXB FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian VXR-200 and VXR-300 FT-^1H NMR spectrometer with tetramethylsilane as an internal reference. Column chromatography was performed on Merck Kiesel gel 60 in a medium pressure unless otherwise noted. After the extraction of the reaction mixture, the solution was washed with water, dried over Na_2SO_4 and concentrated at reduced pressure. These procedures are indicated by the phrase 'the extracts were treated as usual' unless otherwise noted. Elemental analyses are given in Table 3.

2-(*N*-Cbz-Glycylamino)benzophenone (2a). Triethylamine (26 mL) was added to a mixture of 2-aminobenzophenone (12 g, 60.8 mmol), *N*-Cbz-glycine (12.73 g, 60.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (12.25 g, 63.9 mmol) and 1-hydroxybenzotriazole (1.07 g, 7.9 mmol) in THF (250 mL) under ice cooling. The mixture was stirred overnight at room temperature and poured. The resultant mixture was extracted with ethyl acetate. The extract was treated as usual. The residue was recrystallized from 2-propanol: yield

Table 3. Elemental analyses

Compd	Formula	Calculated				Found			
		C	H	N		C	H	N	
2a	$(C_{23}H_{20}N_2O_4)$	71.12	5.19	7.21		71.35	5.36	7.28	
2b	$(C_{24}H_{22}N_2O_4)$	71.63	5.51	6.96		71.64	5.49	6.99	
2d	$(C_{23}H_{26}N_2O_4 \cdot 0.2H_2O)$	69.40	6.68	7.04		69.42	6.58	7.06	
2e	$(C_{21}H_{18}N_2O_4S)$	63.95	4.60	7.10	S, 8.13	63.97	4.70	7.17	S, 8.03
2f	$(C_{24}H_{22}N_2O_5)$	68.88	5.30	6.69		68.91	5.34	6.72	
3d	$(C_{15}H_{21}BrN_2O_2 \cdot 0.4H_2O)$	51.70	6.31	8.04	Br, 22.93	51.86	6.05	8.04	Br, 22.86
4a	$(C_{23}H_{21}N_3O_3)$	71.30	5.46	10.85		71.45	5.54	10.90	
4b	$(C_{24}H_{23}N_3O_3)$	71.80	5.77	10.49		71.63	5.88	10.55	
4d	$(C_{30}H_{25}N_3O_5)$	71.00	4.97	8.28		71.15	5.06	8.30	
4e	$(C_{26}H_{23}N_3O_5)$	68.26	5.07	9.19		68.30	5.19	9.16	
4f	$(C_{27}H_{25}N_3O_5)$	68.78	5.34	8.91		68.89	5.46	8.88	
4g	$(C_{27}H_{25}N_3O_6)$	66.52	5.17	8.62		66.54	5.25	8.66	
4h	$(C_{27}H_{25}N_3O_5S)$	63.94	5.05	8.28	S, 6.32	63.96	5.18	8.24	S, 6.29
4i	$(C_{42}H_{33}N_7O_3 \cdot 0.5H_2O)$	72.82	4.95	14.15		72.92	5.17	13.16	
4j	$(C_{43}H_{35}N_7O_4 \cdot 0.5CH_3C_6H_5)$	73.50	5.17	12.90		73.30	5.37	12.90	
4t	$(C_{23}H_{27}N_2O_3 \cdot 0.2H_2O)$	69.57	6.95	10.58		69.37	6.85	10.53	
4u	$(C_{23}H_{24}F_3N_3O_3)$	61.74	5.41	9.39		61.70	5.45	9.40	
4v	$(C_{26}H_{29}N_3O_5)$	67.37	6.31	9.07		67.53	6.36	9.12	
4w	$(C_{21}H_{19}N_3O_3S)$	64.11	4.87	10.68	S, 8.15	64.09	4.92	10.74	S, 8.05
4x	$(C_{24}H_{21}N_2O_5S)$	62.19	4.57	9.07	S, 6.92	62.13	4.74	9.00	S, 6.81
4z	$(C_{27}H_{25}N_3O_6)$	66.52	5.17	8.62		66.37	5.29	8.58	
5a	$(C_{29}H_{30}N_4O_4)$	69.86	6.06	11.24		69.72	6.17	11.04	
5d	$(C_{30}H_{28}N_4O_3 \cdot 0.2H_2O)$	72.62	5.77	11.29		72.49	5.88	11.49	
5e	$(C_{31}H_{32}N_4O_6)$	66.89	5.79	10.07		66.66	5.83	10.05	
5f	$(C_{32}H_{34}N_4O_6 \cdot 0.2C_6H_{14} \cdot 0.1H_2O)$	67.44	6.31	9.47		67.19	6.55	9.59	
5f	$(C_{29}H_{30}N_4O_6 \cdot 0.1C_6H_{14} \cdot 0.25C_4H_{10} \cdot 0.4H_2O)$	65.06	6.19	9.92		64.92	6.48	10.22	
6a	$(C_{29}H_{31}N_3O_5)$	69.44	6.23	8.38		69.14	6.28	8.33	
6b	$(C_{30}H_{33}N_3O_5 \cdot 0.5H_2O)$	68.68	6.53	8.01		68.67	6.52	8.22	
6d	$(C_{36}H_{35}N_3O_7)$	69.55	5.67	6.76		69.41	5.74	6.79	
6e	$(C_{32}H_{33}N_3O_7)$	67.24	5.82	7.35		66.98	5.80	7.31	
6f	$(C_{33}H_{35}N_3O_7)$	67.68	6.02	7.18		67.68	6.09	7.19	
6g	$(C_{33}H_{35}N_3O_8)$	65.88	5.86	6.98		65.76	5.89	6.92	
6h	$(C_{33}H_{35}N_3O_7S)$	64.17	5.71	6.80	S, 5.19	64.22	5.80	6.79	S, 5.08
6i	$(C_{48}H_{43}N_7O_5 \cdot 0.5CH_3C_6H_5)$	73.29	5.61	11.62		72.95	5.76	11.31	
6j	$(C_{49}H_{45}N_7O_6 \cdot 0.3CH_3C_6H_5)$	71.74	5.58	11.46		71.58	5.65	11.38	
6k	$(C_{30}H_{31}N_3O_7 \cdot 1.3H_2O)$	63.33	5.95	7.38		62.12	5.51	7.30	
6m	$(C_{28}H_{28}N_3O_5Cl)$	64.43	5.41	8.05	Cl, 6.79	64.19	5.54	7.93	Cl, 6.65
6n	$(C_{28}H_{28}N_3O_5Br)$	59.37	4.98	7.42	Br, 14.11	59.25	4.98	7.33	Br, 13.85
6o	$(C_{29}H_{28}N_4O_5 \cdot 0.4H_2O)$	67.01	5.58	10.78		66.98	5.56	10.71	
6p	$(C_{29}H_{31}N_3O_6)$	67.30	6.04	8.12		67.30	6.10	8.16	
6q	$(C_{28}H_{28}N_3O_5Cl)$	64.43	5.41	8.05	Cl, 6.79	64.41	5.49	8.04	Cl, 6.90
6r	$(C_{29}H_{31}N_3O_5)$	69.44	6.23	8.38		69.68	6.33	8.34	
6s	$(C_{28}H_{29}N_3O_5)$	68.98	6.00	8.62		68.94	6.03	8.62	
6t	$(C_{29}H_{37}N_3O_5)$	68.62	7.35	8.28		68.42	7.34	8.32	
6u	$(C_{29}H_{34}F_3N_3O_5)$	62.02	6.10	7.48	F, 10.15	61.79	6.08	7.39	F, 9.89
6v	$(C_{32}H_{39}N_3O_7 \cdot 0.2H_2O)$	66.12	6.68	7.23		66.18	6.79	7.17	
6w	$(C_{27}H_{29}N_3O_5S)$	63.89	5.76	8.28	S, 6.32	64.01	5.88	8.25	S, 6.51
6x	$(C_{30}H_{31}N_3O_7S)$	62.38	5.41	7.27	S, 5.55	62.19	5.43	7.26	S, 5.53
6y	$(C_{30}H_{33}N_3O_6)$	67.78	6.25	7.90		67.75	6.35	7.98	
6z	$(C_{33}H_{35}N_3O_8)$	65.88	5.86	6.98		65.70	5.91	6.97	
7a	$(C_{29}H_{29}N_3O_7)$	65.53	5.50	7.91		65.27	5.60	8.07	
7a (Me ester)	$(C_{30}H_{37}N_3O_7\ 0.2H_2O)$	64.90	6.79	7.51		64.95	6.52	7.48	
7b	$(C_{30}H_{31}N_3O_7 \cdot 0.4H_2O)$	65.18	5.80	7.6		65.15	5.77	7.46	
7b (Me ester)	$(C_{31}H_{33}N_3O_7)$	66.53	5.94	7.56		66.41	6.02	7.61	
7c	$(C_{30}H_{31}N_3O_8 \cdot 0.4H_2O)$	63.35	5.64	7.39		63.34	5.70	7.29	
7c (Me ester)	$(C_{31}H_{33}N_3O_8)$	64.69	5.78	7.30		64.54	5.85	7.21	
7d	$(C_{30}H_{31}N_3O_7S \cdot 0.5H_2O)$	61.42	5.50	7.16	S, 5.47	61.51	5.51	7.04	
7d (Me ester)	$(C_{31}H_{33}N_3O_7S)$	62.93	5.62	7.10	S, 5.42	62.84	5.68	7.07	S, 5.26
7f	$(C_{29}H_{29}N_7O_5 \cdot H_2O)$	60.72	5.45	17.09		60.86	5.40	16.72	
7g	$(C_{30}H_{31}N_7O_6 \cdot 0.4H_2O)$	60.78	5.41	16.54		60.87	5.43	16.46	
7h	$(C_{29}H_{35}N_3O_7 \cdot 1.2H_2O)$	62.29	6.74	7.51		62.11	6.35	7.37	
7i	$(C_{27}H_{27}N_3O_5S \cdot 0.2H_2O)$	59.92	5.10	7.76	S, 5.92	59.87	5.17	7.66	S, 5.87
7j	$(C_{30}H_{31}N_3O_8)$	64.16	5.56	7.48		63.76	5.63	7.35	

65%, mp 115–117 °C. IR ν_{max} (KBr) 3306, 1693, 1637, 1538, 1534, 1521 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.07 (2H, d, J = 5.8 Hz), 5.17 (2H, s), 5.52 (1H, br s), 7.1–7.69 (9H, m), 8.63 (1H, d, J = 8.6 Hz), 11.36 (1H, br s). Anal. ($C_{23}H_{20}N_2O_4$) C, H, N.

$SOCl_2$ (4 mL, 55 mmol) was added dropwise to a solution of *N*-Cbz-glycine (12.6 g, 60 mmol) in HMPA (70 mL) and acetonitrile (20 mL) under stirring at −4 to −5 °C and stirring was continued at −5 °C for another 10 min. 2-Aminobenzophenone (9.86 g, 50 mmol) was added to the reaction mixture in five portions and the mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized with an aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The extracts were treated as usual. The residue was recrystallized from hexane, 18.89 g, 97.3%.

(−)- And (+)-2-(*N*-Cbz-alanylamino)benzophenone (2b, 2c). **2b**: yield 74.0%, mp 95 °C. $[\alpha]_D^{24}$ −16.7 (c 1.046, $CHCl_3$). IR ν_{max} (KBr) 3290, 1728, 1697, 1585, 1512 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.52 (3H, d, J = 7.0 Hz), 4.45 (1H, m), 5.14 (2H, s), 5.45 (1H, d, J = 5.0 Hz), 7.12 (1H, dt, J = 1.8, 8.0 Hz), 7.2–7.7 (13H, m), 8.65 (1H, d, J = 10.0 Hz). Anal. ($C_{24}H_{22}N_2O_4$) C, H, N. **2c**: $[\alpha]_D^{23}$ +13.6 (c 1.01, $CHCl_3$).

Cyclohexyl-(2-(*N*-Cbz-aminomethylcarbamoyl)phenyl)ketone (2d). Following the method described for the preparation of **2a**, the compound was synthesized by using cyclohexyl-(2-aminophenyl)ketone.[12] Mp 152–155 °C. IR ν_{max} (KBr) 3324, 1669, 1694, 1641, 1602, 1582, 1517 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.13–1.61 (5H, m), 1.69–1.94 (5H, m), 3.31 (1H, m), 4.09 (1H, d, J = 5.6 Hz), 5.20 (2H, s), 5.49 (1H, m), 7.14 (1H, t, J = 8.2 Hz), 7.20–7.48 (5H, m), 7.55 (1H, t, J = 8.2 Hz), 7.93 (1H, d, J = 8.0 Hz), 8.72 (1H, d, J = 8.6 Hz). Anal. ($C_{23}H_{26}N_2O_4 \cdot 0.2H_2O$) C, H, N.

(2-(*N*-Cbz-Glycylamino)phenyl)thienyl-2-ylketone (2e). Mp 115–116.5 °C. IR ν_{max} (KBr) 3274, 1716, 1671, 1619, 1601, 1579, 1514 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.04 (2H, d, J = 6.0 Hz), 5.18 (2H, s), 5.44–5.60 (1H, m), 7.15–7.50 (7H, m), 7.56–7.62 (2H, m), 7.75 (1H, dd, J = 4.8 Hz, 0.9 Hz), 7.84 (1H, dd, J = 7.8 Hz, 1.2 Hz), 8.55 (1H, d, J = 8.1 Hz), 10.80 (1H, s). Anal. ($C_{21}H_{18}N_2O_4S$) C, H, N, S.

4-Anisyl-(2-(*N*-Cbz-glycylamino)phenyl)ketone (2f). Mp 97–98 °C. IR ν_{max} (KBr) 3342, 1687, 1624, 1583, 1513 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.89 (3H, s), 4.05 (2H, d, J = 6.0 Hz), 5.16 (2H, s), 5.55–5.58 (1H, m), 6.93–6.98 (2H, m), 7.09–7.14 (1H, m), 7.30–7.42 (5H, m), 7.52–7.57 (2H, m), 7.69–7.72 (2H, m), 8.55 (1H, d, J = 7.5 Hz), 11.06 (1H, s). Anal. ($C_{24}H_{22}N_2O_5$) C, H, N.

2-(Glycylamino)benzophenone hydrobromide (3a). A mixture of *N*-Cbz derivative **2a** (3.13 g, 8.06 mmol) and a solution of 30% HBr in acetic acid was stirred for 1 h. Excess ether was added and the resultant precipitate was collected by filtration, washed with ether and dried, 2.50 g (92%). ^1H NMR ($CDCl_3$) δ 3.42 (2H, br s), 4.11 (2H, br s), 6.95 (1H, t, J = 7.8 Hz), 7.3–8.22 (9H, m), 10.80 (1H, br s).

(−)- And (+)-2-(alanylamino)benzophenone hydrobromide (3b and 3c). The compounds **2b** and **2c** were treated as above to give the desired compounds **3b** and **3c**.

Cyclohexyl-(2-(glycylamino)phenyl)ketone hydrobromide (3d). Mp 193–196 °C. IR ν_{max} (KBr) 3432, 1702, 1645, 1605, 1588, 1533 cm^{-1}. Anal. ($C_{15}H_{21}BrN_2O_2 \cdot 0.4H_2O$) C, H, Br, N.

(2-(Glycylamino)phenylthienyl-2-ylketone hydrobromide (3e). ^1H NMR ($CDCl_3$ + CD_3OD) δ 5.31 (2H, s), 7.08–7.24 (2H, m), 7.44–7.54 (2H, m), 7.66 (1H, d, J = 7.8 Hz), 7.74 (1H, dd, J = 5.0, 1.2 Hz), 8.09 (1H, dd, J = 8.2, 1.8 Hz), 10.35 (1H, s).

4-Anisyl-(2-(glycylamino)phenyl)ketone hydrobromide (3f). ^1H NMR (D_2O) δ 3.67 (2H, s), 3.92 (3H, s), 7.05–7.10 (2H, m), 7.40–7.78 (6H, m).

2-(*N'*-(*m*-Tolyl)ureidomethylcarbamoyl)benzophenone (4a). A solution of *m*-tolylisocyanate (0.846 g, 6.35 mmol) in DMF (3 mL) was added to a solution of the salt **3a** (1.937 g, 5.78 mmol) in DMF (8 mL). Triethylamine (32 mL) was added at 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature overnight. Water and then 10% HCl were added. The mixture was extracted with ethyl acetate. The extract was treated as usual. The residue was recrystallized from acetonitrile (1.39 g; yield 62%). IR ν_{max} (KBr) 3310, 1684, 1639, 1590, 1523 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.21 (3H, s). 4.07 (2H, d, J = 5.4 Hz), 5.93 (1H, t, J = 5.7 Hz), 6.83 (1H, m), 7.07–7.65 (13H, m), 8.56 (1H, d, J = 8.8 Hz), 11.20 (1H, s). Anal. ($C_{23}H_{21}N_3O_3$) C, H, N.

(+)- And (−)-2-(1-(*N'*-(*m*-tolyl)ureido)ethylcarbamoyl)-benzophenone (4b, 4c). Yield 75.0%, mp 160 °C. $[\alpha]_D^{23}$ +18.8 (c 1.075, $CHCl_3$). IR ν_{max} (Nujol) 3298, 1683, 1651, 1636, 1582, 1552 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.45 (3H, d, J = 7.0 Hz), 2.19 (3H, s), 4.61 (1H, qui, J = 7.0 Hz), 5.95 (1H, br s), 6.79 (1H, br s), 7.0–7.7 (12H, m), 8.55 (1H, d, J = 8.6 Hz), 11.32 (1H, s). Anal. ($C_{24}H_{23}N_3O_3$) C, H, N. **4c**: $[\alpha]_D^{23}$ −21.6 (c 1.012, $CHCl_3$)

2-(*N'*-(*m*-(Benzyloxycarbonyl)phenyl)ureidomethylcarbamoyl)benzophenone (4d). Mp 157–159 °C. IR ν_{max} (KBr) 3360, 1720, 1680, 1635, 1584, 1560, 1520 cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.74 (2H, d, J = 5.2 Hz), 5.33 (2H, s), 6.51 (1H, br s), 7.20–7.70 (16H, m), 7.88 (1H, d, J = 8.8 Hz), 8.06 (1H, br s), 9.13 (1H, s), 10.53 (1H, s). Anal. ($C_{30}H_{25}N_3O_5$)C, H, N.

2-(*N'*-(*m*-(2-Propenyloxycarbonyl)phenyl)ureidomethylcarbamoyl)benzophenone (4e). Mp 68–71 °C. IR ν_{max} (KBr) 3350, 1718, 1692, 1659, 1595, 1580, 1557, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.12 (2H, d, J = 5.6 Hz), 4.77 (2H, d, J = 5.6 Hz), 5.20–5.43 (2H, m),

5.88–6.10 (2H, m), 7.04–7.18 (3H, m), 7.36–7.70 (10H, m), 7.90 (1H, br s), 8.54 (1H, d, J = 8.6 Hz). Anal. ($C_{26}H_{23}N_3O_5$) C, H, N.

2-(*N'*-(*m*-(2-Propenyloxycarbonylmethyl)phenyl)-ureidomethylcarbamoyl)benzophenone (4f). Mp 125–127 °C. IR ν_{max} (KBr) 3330, 1740, 1682, 1639, 1600, 1560, 1520 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.55 (2H, s), 4.08 (2H, d, J = 5.8 Hz), 4.56 (2H, d, J = 5.8 Hz), 5.13–5.32 (2H, m), 6.91–5.98 (2H, m), 6.91–6.99 (1H, m), 7.05–7.32 (6H, m), 7.38–7.70 (7H, m), 8.57 (1H, d, J = 8.6 Hz). Anal. ($C_{27}H_{25}N_3O_5$)C, H, N.

2-(*N'*-(*m*-(2-Propenyloxycarbonylmethyloxy)phenyl)-ureidomethylcarbamoyl)benzophenone (4g). Mp 147–149 °C. IR ν_{max} (KBr) 3330, 1748, 1680, 1653, 1638, 1605, 1563, 1530, 1500 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.11 (2H, d, J = 5.8 Hz), 4.58 (2H, s), 5.18–5.37 (2H, m), 5.70–5.99 (2H, m), 6.60 (1H, dd, J = 7.6, 2.6 Hz), 6.90 (1H, d, J = 9.0 Hz), 7.05–7.18 (4H, m), 7.40–7.71 (7H, m), 8.59 (1H, d, J = 10.0 Hz), 11.28 (1H, s). Anal. ($C_{27}H_{25}N_3O_6$) C, H, N.

2-(*N'*-(*m*-(2-Propenyloxycarbonylmethylthio)phenyl)-ureidomethylcarbamoyl)benzophenone (4h). IR ν_{max} ($CHCl_3$) 3350, 1733, 1682, 1640, 1584, 1521 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.60 (2H, s), 4.09 (2H, d, J = 5.6 Hz), 4.47–4.62 (2H, m), 5.10–5.31 (2H, m), 5.70–5.93 (1H, m), 6.00–6.15 (1H, br s), 6.92–7.20 (4H, m), 7.32–7.71 (9H, m), 8.56 (1H, d, J = 8.6 Hz). Anal. ($C_{27}H_{25}N_3O_5S$) C, H, N.

2-(*N'*-(*m*-(2-(Triphenylmethyl)tetrazol-5-yl)phenyl)-ureidomethylcarbamoyl)benzophenone (4i). The isocyanate was synthesized *in situ* from 3-amino-(1*H*-(triphenylmethyl)-tetrazol-5-yl)benzene (567 mg, 3.52 mmol) which was synthesized from 3-aminobenzonitrile. Powder. IR ν_{max} (KBr) 3375, 1695, 1660, 1640, 1595, 1580, 1560, 1513 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.06 (2H, d, J = 5.8 Hz), 5.91 (1H, br s), 6.95–7.80 (28H, m), 7.91 (1H, s), 8.50 (1H, d, 10.0 Hz). Anal. ($C_{42}H_{33}N_7O_3 \cdot 0.5H_2O$) C, H, N.

2-(*N'*-(*m*-(2-Triphenylmethyl)tetrazol-5-ylmethyloxy)-phenyl)ureidomethylcarbonylamino)benzophenone (4j). The isocyanate was prepared *in situ* from 3-amino-(1*H*-(triphenylmethyl)tetrazolylmethoxybenzene and triphosgene. IR ν_{max} (KBr) 3380, 1690, 1660, 1639, 1600, 1580, 1553, 1520 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.04 (2H, d, J = 5.8 Hz), 5.24 (2H, s), 5.93 (1H, t, J = 5.8 Hz), 6.61–6.69 (1H, m), 6.88–7.65 (24H, m), 8.59 (1H, d, J = 8.8 Hz), 11.28 (1H, s). Anal. ($C_{43}H_{35}N_7O_4 \cdot 0.5CH_3C_6H_5$) C, H, N.

2-(*N'*-(*m*-(Trifluoromethylphenyl)ureidomethylcarbonyl-amino)benzophenone (4l). Yield 74%, mp 177–178 °C. ^{1}H NMR ($CDCl_3$) δ 4.15 (2H, s), 5.97–6.32 (1H, br s), 7.30–7.73 (13H, m), 8.53 (1H, d, J = 8.6 Hz), 11.27 (1H, s).

2-(*N'*-(*m*-Chlorophenyl)ureidomethylcarbonylamino)-benzophenone (4m). Yield 73%. IR ν_{max} (KBr) 1691, 1639, 1593, 1556, 1523 cm^{-1}. ^{1}H NMR($CDCl_3$) δ 4.08 (2H, s), 6.90–7.33 (5H, m), 7.40–7.73 (8H, m), 8.54 (1H, d, J = 8.2 Hz), 11.21 (1H, s).

2-(*N'*-(*m*-Bromophenyl)ureidomethylcarbonylamino)-benzophenone (4n). Yield 68%. IR ν_{max} (KBr) 1682, 1638, 1590, 1554, 1523 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 4.10 (2H, d, J = 5.7 Hz), 6.11 (1H, br s), 6.99–7.30 (5H, m), 7.41–7.70 (8H, m), 8.54 (1H, d, J = 8.4 Hz), 11.23 (1H, s).

2-(*N'*-(*m*-Cyanophenyl)ureidomethylcarbonylamino)-benzophenone (4o). Yield 88%. IR ν_{max} (KBr) 2230, 1686, 1638, 1603, 1589, 1558, 1522 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 4.09 (2H, d, J = 5.7 Hz, 7.09–7.72 (13H, m), 8.53 (1H, d, J = 8.7 Hz), 11.22 (1H, s).

2-(*N'*-(*m*-Methoxyphenyl)ureidomethylcarbonylamino)benzophenone (4p). Yield 80%. IR ν_{max} (KBr) 1693, 1640, 1619, 1606, 1591, 1560, 1515 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.68 (3H, s), 4.08 (2H, d, J = 2.9 Hz), 5.99 (1H, d, J = 5.8 Hz), 6.56 (1H, dd, J = 8.0, 1.8 Hz), 6.79 (1H, dd, J = 7.4, 1.0 Hz), 7.00–7.16 (3H, m), 7.37–7.69 (8H, m), 8.55 (1H, d, J = 7.8 Hz), 11.27 (1H, s).

2-(*N'*-(*p*-Chlorophenyl)ureidomethylcarbonylamino)benzophenone (4q). Yield 76%. IR ν_{max} (KBr) 1686, 1636, 1591, 1558, 1522 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 4.06 (2H, d, J = 5.7 Hz), 6.31 (1H, t, J = 6.0 Hz), 7.11–7.70 (13H, m), 8.52 (1H, d, J = 7.5 Hz).

2-(*N'*-(*p*-Tolyl)ureidomethylcarbonylamino)benzophenone (4r). Yield 85%. IR ν_{max} (KBr) 1685, 1639, 1604, 1593, 1555, 1519 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.27 (3H, s), 4.07 (2H, d, J = 6.0 Hz), 5.93 (1H, br s), 7.0–7.29 (6H, m), 7.43–7.68 (7H, m), 8.65 (1H, d, J = 8.4 Hz), 11.22 (1H, s).

2-(*N'*-(Phenyl)ureidomethylcarbonylamino)benzophenone (4s). Yield 67%. IR ν_{max} (KBr) 1685, 1638, 1595, 1583, 1556, 1523 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 4.07 (2H, s), 6.93–7.70 (14H, m), 8.54 (1H, d, J = 8.4 Hz), 11.22 (1H, s).

Cyclohexyl-(2-(*N'*-(*m*-tolyl)ureidomethylcarbamoyl)-phenyl)ketone (4t). Mp 192–193 °C. IR ν_{max} (KBr) 3328, 1669, 1644, 1594, 1583, 1559, 1518 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.05–1.52 (5H, m), 1.62–1.89 (5H, m), 2.32 (3H, s), 4.02 (2H, s), 6.85 (1H, d, J = 6.0 Hz), 7.09–7.31 (4H, m), 7.55 (1H, m), 7.95 (1H, d, J = 9.6 Hz), 8.65 (1H, d, J = 8.6 Hz). Anal. ($C_{23}H_{27}N_2O_3$ $0.2H_2O$) C, H, N.

Cyclohexyl-(2-(*N'*-(*m*-trifluoromethylphenyl)ureido-methylcarbamoyl)phenyl)ketone (4u). Mp 207–209 °C. IR ν_{max} (KBr) 3343, 1661, 1605, 1581, 1565, 1524 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.13 (1H, m), 1.23–1.48 (4H, m), 1.65–1.89 (5H, m), 3.28 (1H, m), 4.11 (2H, s), 7.10–7.41 (3H, m), 7.48–7.68 (2H, m),7.71 (1H, s), 7.90 (1H, d, J = 8.2 Hz), 8.68 (1H, d, J = 8.6 Hz). Anal. ($C_{23}H_{24}F_3N_3O_3$) C, H, N.

Cyclohexyl-(2-(*N'*-(*m*-(2-Propenyloxycarbonyl)phenyl)-ureidomethylcarbamoyl)phenyl)ketone (4v). Mp 188–190 °C. IR ν_{max} (KBr) 3335, 1720, 1660, 1582, 1557, 1524 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.03–1.52 (5H, m), 1.53–1.91 (5H, m), 3.23 (1H, m), 4.17 (2H, d, J = 6.0 Hz), 4.79 (2H, d, J = 5.8 Hz), 5.15-5.48 (2H, m), 5.82–6.13 (2H, m), 7.12 (1H, m), 7.31 (1H, t, J = 13.5 Hz), 7.49 (1H, m), 7.70 (1H, m), 7.96 (1H, m), 8.69 (1H, d, J = 9.4 Hz), 12.18 (1H, s). Anal. ($C_{26}H_{29}N_3O_5$) C, H, N.

Thienyl-2-yl-(2-(*N'*-(*m*-tolyl)ureidomethylcarbamoyl)-phenyl)ketone (4w). Mp 208–210 °C. IR ν_{max} (KBr) 3337, 1687, 1638, 1609, 1580, 1563, 1518 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.22 (3H, s), 3.79 (2H, d, J = 5.2 Hz), 6.50 (2H, t, J = 10.8 Hz), 6.72 (1H, dd, J = 2.6, 0.8 Hz), 7.04–7.32 (5H, m), 7.52–7.70 (3H, m), 7.94 (1H, d, J = 8.2 Hz), 8.04–8.10 (1H, m), 8.76 (1H, s), 10.33 (1H, s). Anal. ($C_{21}H_{19}N_3O_3S$) C, H, N, S.

(2-(*N'*-(*m*-(2-Propenyloxycarbonyl)phenyl)ureidomethyl-carbamoyl)phenyl)thienyl-2-ylketone (4x). Mp 140–141 °C. IR ν_{max} (KBr) 3284, 1714, 1689, 1648, 1618, 1584, 1560, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.09 (2H, d, J = 5.6 Hz), 4.77 (2H, dt, J = 5.4, 1.4 Hz), 5.25 (1H, dd, J = 10.2, 1.2 Hz), 5.37 (1H, dd, J = 17.2, 1.4 Hz), 5.85–6.10 (2H, m), 7.05–7.30 (3H, m), 7.50–7.80 (7H, m), 7.91 (1H, m), 8.45 (1H, dd, J = 8.2, 0.8 Hz), 10.71 (1H, s). Anal. ($C_{24}H_{21}N_2O_5S$) C, H, N, S.

4-Anisyl-(2-(*N'*-(*m*-tolyl)ureidomethylcarbamoyl)phenyl)-ketone (4y) . Amorphous powder. IR ν_{max} (KBr) 3313, 2925, 2855, 1654, 1597, 1581, 1559 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.18 (3H, s), 3.84 (3H, s), 4.02 (2H, d, J = 6.0 Hz), 6.10 (1H, t, J = 6.0 Hz), 6.75–6.90 (3H, m), 7.03–7.10 (4H, m), 7.45–7.68 (5H, m), 8.44 (1H, d, J = 7.2 Hz), 10.94 (1H, s).

4-Anisyl-(2-(*N'*-(*m*-(2-propenyloxycarbonyl)phenyl)-ureidomethylcarbamoyl)phenyl)ketone (4z). Mp 167–169 °C. IR ν_{max} (KBr) 3371, 3275, 1715, 1690, 1641, 1591, 1566, 1525 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.86 (3H, s), 4.07 (2H, d, J = 6.0 Hz), 4.78 (2H, dt, J = 5.7, 1.2 Hz), 5.24–5.28 (1H, m), 5.35–5.41 (1H, m), 5.94–6.07 (1H, m), 6.43 (1H, t, J = 5.4 Hz), 6.87–6.95 (2H, m), 7.07–7.12 (1H, m), 7.23–7.29 (1H, m), 7.49–7.55 (2H, m), 7.62–7.67 (3H, m), 7.75–7.78 (1H, m), 7.90–7.91 (1H, m), 8.35 (1H, s), 8.51 (1H, d, J = 7.5 Hz), 10.95 (1H, s). Anal. ($C_{27}H_{25}N_3O_6$) C, H, N.

2-(*N*-(Pyrrolidinocarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureido-methylcarbonyl)amino)benzophenone (5a). A solution of the amide (**4a**, 300 mg), *N*-(bromoacetyl)pyrrolidine (17.35 mg), K_2CO_3 (120 mg) and KI (10 mg) in DMF (5 mL) was stirred overnight. After pouring into water, the mixture was extracted with ethyl acetate. The extract was treated as usual. The residue was recrystallized from acetonitrile. Yield 53%, mp 204–205 °C. IR ν_{max} (KBr) 3310, 1655, 1637, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.81 (4H, m), 2.28 (3H, s), 3.34 (4H, m), 3.78 (1H, d, J = 18.0 Hz), 3.81 (1H, d, J = 16.4 Hz), 3.99 (1H, d, J = 17.2 Hz), 4.82 (1H, d, J = 16.4 Hz), 5.78 (1H, br s), 6.80–7.79 (13H, m). Anal. ($C_{29}H_{30}N_4O_4$) C, H, N.

2-(*N*-(Cyclopropylcarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureido-methylcarbonyl)amino)benzophenone (5c). Yield 3.3%, mp 114–118 °C. IR ν_{max} (KBr) 3391, 1650, 1611, 1596, 1556 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.16 (4H, m), 1.94 (1H, br s), 3.23 (3H, s), 3.43–4.67 (4H, m), 6.07 (1H, br s), 6.79 (2H, d, J = 6.4 Hz), 7.04–7.40 (13H, m), 8.27 (1H, s).

2-(*N*-(*m*-Aminobenzyl)-*N*-(*N'*-(*m*-tolyl)ureidomethyl-carbonyl)amino)benzophenone (5d). *N*-Alkylation was carried out using *m*-(*N*-BOC-amino)benzyl bromide. To the resultant BOC-compound, a solution of 4 N HCl in ethyl acetate was added. The mixture was stirred overnight, basified with an aqueous Na_2CO_3 and extracted with ethyl acetate. The extract was treated as usual. yield 12%, mp 96–100 °C. IR ν_{max} (KBr) 3359, 1662, 1594, 1555 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.22 (3H, s), 3.48 (2H, br s), 3.98 (2H, m), 4.27 (2H, d, J = 14.4 Hz), 5.07 (1H, d, J = 14.4 Hz), 6.32–7.69 (17H, m). Anal. ($C_{30}H_{28}N_4O_3 \cdot 0.2H_2O$) C, H, N.

2-(*N*-(*N'*-(*m*-(Carbomethoxymethyl)phenyl)ureidomethyl-carbonyl)-*N*-(pyrrolidinocarbonylmethyl)amino)benzo-phenone (5e) . Yield 30.4%, mp 189–194 °C. IR ν_{max} (KBr) 3378, 3332, 1740, 1653, 1595, 1561 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.84 (4H, m), 3.34 (4H, m), 3.56 (2H, s), 3.66 (3H, s), 3.82 (1H, d, J = 16.8 Hz), 3.86 (2H, q, J = 17.2 Hz), 4.82 (1H, d, J = 16.8 Hz), 5.84 (1H, br s), 6.90–6.98 (1H, m), 7.17–7.95 (13H, m). Anal. ($C_{31}H_{32}N_4O_6$) C, H, N.

2-(*N*-(*tert*-Butylcarbamoylmethyl)-*N*-(*N'*-(*m*-(2-propenyl-oxycarboyl)phenyl)ureidomethylcarbonyl)amino)-benzophenone (5f). Powder. IR ν_{max} (KBr) 3372, 3068, 2969, 2931, 1719, 1662 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.20 (7H, s), 1.36 (2H, s), 3.76 (1H, d, J = 15.6 Hz), 3.84 (1H, dd, J = 4.8, 17.4 Hz), 3.97 (1H, dd, J = 4.8, 17.1 Hz), 4.32 (1H, d, J = 15.6 Hz), 4.78 (1H, d, J = 3.8 Hz), 7.42–7.80 (12H, m), 7.95 (1H, t, J = 1.8 Hz). Anal. ($C_{32}H_{34}N_4O_6$ $0.2C_6H_{14} \cdot 0.1H_2O$) C, H, N.

2-(*N*-(*tert*-Butylcarbamoylmethyl)-*N*-(*N'*-(*m*-carboxy-phenyl)-ureidomethylcarbonyl)amino)benzophenone (5f). Powder. IR ν_{max} (KBr) 3376, 3067, 2969, 1661 cm^{-1}. ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.24 (9H, s), 3.76 (1H, d, J = 15.6 Hz), 3.80 (1H, d, J = 17.4 Hz), 3.99 (1H, d, J = 17.4 Hz), 4.40 (1H, d, J = 15.6 Hz), 7.30–7.89 (13H, m). Anal. ($C_{29}H_{30}N_4O_6 0.25C_4H_{10}$ $0.4H_2O$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureido-methylcarbonyl)amino)benzophenone (6a). Yield 50%, mp 183-184 °C. IR ν_{max} (KBr) 3344, 1746, 1658, 1618, 1561 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (9H, s), 2.28 (3H, s), 3.65 (1H, d, J = 17.8 Hz), 3.77 (1H, d, J = 17.8 Hz), 4.01 (1H, d, J = 17.4 Hz), 4.64 (1H, d, J = 17.4 Hz), 5.90 (1H, br s), 6.81–6.84 (1H, d, J = 6.0 Hz), 6.95–7.81 (13H, m). Anal. ($C_{29}H_{31}N_3O_5$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(2-(*N'*-(*m*-tolyl)-ureido)ethylcarbonyl)amino)benzophenone (6b, 6c). **6b**: yield 31.2%. $[\alpha]_D^{24}$ +14.4 (c 1.151, $CHCl_3$). IR ν_{max} (Nujol) 3368, 1741, 1665, 1642, 1553 cm^{-1}. ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.0–1.5 (9H, m), 2.31 and 2.28 (total 3H, s), 3.65–3.80 (1H, m), 4.35–4.75 (2H, m), 6.75–7.90 (13H, m). Anal. ($C_{30}H_{33}N_3O_5 \cdot 0.5H_2O$) C, H, N. **6c**: $[\alpha]_D^{23}$ −18.3 (c 0.717, $CHCl_3$).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*-(*N'*-(*m*-(benzyloxycarbonyl)phenyl)ureidomethylcarbonyl)amino)-benzophenone (6d). Mp 85–88 °C. IR ν_{max} (KBr) 3380, 1720, 1661, 1597, 1555 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.36 (9H, s), 3.53–3.85 (2H, m), 3.73 (1H, d, J = 16.8 Hz), 4.14 (1H, d, J = 16.8 Hz), 5.33 (2H, s), 6.38 (1H, br s), 7.30–7.85 (17H, m), 8.05 (1H, br s), 9.09 (1H, s). Anal. ($C_{36}H_{35}N_3O_7$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonyl)phenyl)ureidomethylcarbonyl)amino)-benzophenone (6e). Mp 105–107 °C. IR ν_{max} (KBr) 3385, 1743, 1722, 1662, 1597, 1558 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (9H, s), 3.65 (1H, d, J = 17.2 Hz), 3.80 (1H, dd, J = 17.2, 4.6 Hz), 4.63 (1H, d, J = 17.2 Hz), 4.79 (2H, d, J = 5.8 Hz), 5.20–5.46 (2H, m), 5.82–6.14 (2H, m), 7.01 (1H, s), 7.22–7.86 (12H, m), 7.96 (1H, br s). Anal. ($C_{32}H_{33}N_3O_7$) C, H.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonylmethyl)phenyl)ureidomethylcarbonyl)-amino)benzophenone (6f). Mp 122–124 °C. IR ν_{max} (KBr) 3360, 1740, 1662, 1645, 1610, 1595, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 3.59 (2H, s), 3.64 (1H, d, J = 17.2 Hz), 3.77 (1H, dd, J = 17.0, 5.0 Hz), 4.00 (1H, dd, J = 17.0, 5.0 Hz), 4.53-4.61 (2H, m), 4.64 (1H, d, J = 17.2 Hz), 5.13-5.32 (2H, m), 5.72–5.99 (2H, m), 6.75 (1H, s), 6.89–6.97 (1H, m), 7.11–7.30 (4H, m), 7.4–7.67 (6H, m), 7.72–7.84 (3H, m). Anal. ($C_{33}H_{35}N_3O_7$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonylmethyloxy)phenyl)ureidomethylcarbonyl)-amino)benzophenone (6g). Mp 134–136 °C. IR ν_{max} (KBr) 3390, 1760, 1739, 1660, 1650, 1610, 1560, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 3.63 (1H, d, J = 17.4 Hz), 3.76 (1H, dd, J = 17.4, 3.6 Hz), 4.00 (1H, dd, J = 17.4, 3.6 Hz), 4.62 (2H, s), 4.64 (1H, d, J = 17.4 Hz), 4.69 (1H, d, J = 5.6 Hz), 5.19–5.38 (2H, m), 5.77–6.01 (2H, m),6.57 (1H, dd, J = 7.6, 2.6 Hz), 6.73–6.87 (2H, m), 7.00–7.18 (2H, m), 7.37–7.68 (6H, m), 7.72–7.84 (3H, m). Anal. ($C_{33}H_{35}N_3O_8$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonylmethylthio)phenyl)ureidomethylcarbonyl)-amino)benzophenone (6h). Mp 155–157 °C. IR ν_{max} (KBr) 3380, 1740, 1650, 1595, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 3.63 (1H, d, J = 17.4 Hz), 3.67 (2H, s), 3.78 (1H, dd, J = 17.2, 5.6 Hz), 4.01 (1H, dd, J = 17.2, 5.6 Hz), 4.55–4.62 (2H, m), 4.73 (1H, d, J = 17.4 Hz), 5.16–5.32 (2H, m), 5.73–6.00 (2H, m), 6.86 (1H, s), 6.96–7.07 (1H, m), 7.08–7.16 (2H, m), 7.33 (10H, m). Anal. ($C_{33}H_{35}O_7S$) C, H, N, S.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-(triphenylmethyl)tetrazol-5-yl)phenyl)ureidomethylcarbonyl)-amino)benzophenone (6i). Powder. IR ν_{max} (KBr) 3380, 1740, 1662, 1595, 1560, 1515 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 3.63 (1H, d, J = 17.2 Hz), 3.80 (1H, d, J = 17.2 Hz), 3.99 (1H, dd, J = 17.2, 4.6 Hz), 4.63 (1H, d, J = 17.2 Hz), 5.71 (1H, br s), 6.70 (1H, s), 7.00–7.90 (28H, m). Anal. ($C_{48}H_{43}N_7O_5 \cdot 0.5CH_3C_6H_5$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-(triphenylmethyl)tetrazol-5-ylmethyloxy)phenyl)ureidomethylcarbonyl)amino)benzophenone (6j). IR ν_{max} (KBr) 3380, 1740, 1662, 1600, 1548 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (9H, s), 3.64 (1H, d, J = 17.4 Hz), 3.76 (1H, dd, J = 17.8, 4.6 Hz), 3.98 (1H, dd, J = 17.8, 4.6 Hz), 4.64 (1H, d, J = 17.4 Hz), 5.28 (2H, s), 5.81 (1H, br s), 6.58–6.73 (2H, m), 6.83–6.91 (1H, m), 6.99–7.66 (23H, m), 7.71–7.83 (3H, m). Anal. ($C_{49}H_{45}N_7O_6 \cdot 0.3CH_3C_6H_5$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(carbomethoxy)phenyl)ureidomethylcarbonyl)amino)benzophenone (6k). IR ν_{max} (KBr) 3390, 1740, 1725, 1660, 1595, 1556 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (9H, s), 3.66 (1H, d, J = 17.0 Hz), 3.80 (1H, dd, J = 17.6, 5.6 Hz), 4.04 (1H, dd, J = 17.6, 5.6 Hz), 4.63 (1H, d, J = 17.0 Hz), 5.96 (1H, br s), 7.11 (1H, s), 7.22–7.32 (1H, m), 7.42–7.69 (8H, m), 7.75–7.86 (3H, m), 7.96 (1H, br s). Anal. ($C_{30}H_{31}N_3O_7 \cdot 1.3H_2O$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-trifluoromethylphenyl)ureidomethylcarbonyl)amino)benzophenone (6l). Powder. ^1H NMR ($CDCl_3$) δ 1.36 (9H, s), 3.68 (1H, d, J = 17.2 Hz), 3.79 (1H, d, J = 17.4 Hz), 4.10 (1H, d, J = 17.4 Hz), 4.61 (1H, d, J = 17.2 Hz), 7.07–7.88 (13H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-chlorophenyl)ureidomethylcarbonyl)amino)benzophenone (6m). Yield 58%, mp 160–161 °C. IR ν_{max} (KBr) 1742, 1662, 1644, 1595, 1546 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.37 (9H, s), 3.67 (1H, d, J = 17.2 Hz), 3.77 (1H, dd, J = 17.4, 5.6 Hz), 4.05 (1H, dd, J = 17.4, 5.6 Hz), 4.05 (1H, dd, J = 17.2, 5.6 Hz), 4.60 (1H, d, J = 17.2 Hz), 6.12 (1H, br s), 6.89 (1H, br s), 7.06 (1H, m), 7.25 (2H, s), 7.41–7.69 (7H, m), 7.80 (2H, m). Anal. ($C_{28}H_{28}N_3O_5Cl$) C, H, Cl, N.

2-(*N*-(*N'*-(*m*-Bromophenyl)ureidomethylcarbonyl)-*N*-(*tert*-butoxycarbonylmethyl)amino)benzophenone (6n). IR ν_{max} (KBr) 1741, 1663, 1593, 1539 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (9H, s), 3.67 (1H, d, J = 17.2 Hz), 3.78 (1H, dd, J = 17.2, 4.4 Hz), 4,04 (1H, dd, J = 17.4, 4.4 Hz), 4.61 (1H, d, J = 17.2 Hz), 6.09 (1H, br s), 6.95–7.27 (5H, m), 7.42–7.70 (6H, m), 7.76–7.85 (3H, m). Anal. ($C_{28}H_{28}N_3O_5Br$) C, H, Br, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-cyanophenyl)ureidomethylcarbonyl)amino)benzophenone (6o). IR ν_{max} (KBr) 2228, 1741, 1664, 1594, 1553 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.36 (9H, s), 3.69 (1H, d, J = 17.2

Hz), 3.73 (1H, dd, J = 17.2, 6.0 Hz), 4.12 (1H, dd, J = 17.2, 6.0 Hz), 4.60 (1H, d, J = 17.2 Hz), 6.41 (1H, br s), 7.08–7.33 (4H, m), 7.43–7.91 (10H, m). Anal. ($C_{29}H_{28}N_4O_5 \cdot 0.4H_2O$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-methoxyphenyl)ureidomethylcarbonyl)amino)benzophenone (6p). Mp 153–155 °C. IR ν_{max} (KBr) 1743, 1663, 1646, 1608, 1556, 1575 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (9H, s), 3.64 (1H, d, J = 17.2 Hz), 3.75 (3H, s), 3.78 (1H, dd, J = 17.2, 4.0 Hz), 4.03 (1H, dd, J = 17.2, 4.0 Hz), 4.63 (1H, d, J = 17.2 Hz), 6.00 (1H, br s), 6.51–6.58 (1H, m), 6.68–6.77 (1H, m), 6.98–7.16 (3H, m), 7.40–7.67 (6H, m), 7.40–7.67 (6H, m). Anal. ($C_{29}H_{31}N_3O_6$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*p*-chlorophenyl)ureidomethylcarbonyl)amino)benzophenone (6q). Mp 196–197 °C. IR ν_{max} (KBr) 1742, 1660, 1578, 1548 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.37 (9H, s), 3.66 (1H, d, J = 17.2 Hz), 3.77 (1H, dd, J = 17.4, 4.4 Hz), 4.07 (1H, dd, J = 17.4, 4.4 Hz), 4.61 (1H, d, J = 17.2 Hz), 6.10 (1H, br s), 7.06–7.28 (6H, m), 7.43–7.83 (8H, m). Anal. ($C_{28}H_{28}N_3O_5Cl$) C, H, Cl, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*p*-tolyl)ureidomethylcarbonyl)amino)benzophenone (6r). Mp 182–183 °C. IR ν_{max} (KBr) 1742, 1661, 1598, 1577, 1548 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.43 (9H, s), 2.28 (3H, s), 3.64 (1H, d, J = 17.2 Hz), 3.74 (1H, dd, J = 17.4, 4.0 Hz), 4.01 (1H, dd, J = 17.4, 4.0 Hz), 4.63 (1H, d, J = 17.2 Hz), 5.77 (1H, br s), 7.00–7.22 (4H, m), 7.42–7.83 (10H, m). Anal. ($C_{29}H_{31}N_3O_5$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-phenylureidomethylcarbonyl)amino)benzophenone (6s). Mp 166–167 °C. IR ν_{max} (KBr) 1743, 1662, 1598, 1553, 1498 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (9H, s), 3.65 (1H, d, J = 17.4 Hz), 3.79 (1H, dd, J = 17.6, 4.2 Hz), 4.04 (1H, dd, J = 17.6, 4.2 Hz), 4.64 (1H, d, J = 17.4 Hz), 5.97 (1H, br s), 7.01 (2H, br s), 7.16–7.30 (5H, m), 7.40–7.85 (7H, m). Anal. ($C_{28}H_{29}N_3O_5$) C, H, N.

(2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureidomethylcarbonyl)amino)phenyl)cyclohexylketone (6t). Mp 128–130 °C. IR ν_{max} (KBr) 3383, 1741, 1673, 1647, 1612, 1595, 1557, 1522 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10–1.53 (5H, m), 1.47 (9H, s), 1.62–1.97 (5H, m), 2.27 (3H, s), 3.60 (1H, d, J = 17.2 Hz), 3.64 (1H, d, J = 17.2 Hz), 3.81 (1H, d, J = 17.2 Hz), 4.61 (1H, d, J = 17.2 Hz), 6.78 (1H, m), 7.06–7.20 (4H, m), 7.54–7.73 (4H, m), 7.91 (1H, m). Anal. ($C_{29}H_{37}N_3O_5$) C, H, N.

(2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-trifluoromethylphenyl)ureidomethylcarbonyl)amino)phenyl)cyclohexylketone (6u). Amorphous solid. IR ν_{max} (KBr) 3374, 1741, 1741, 1685, 1651, 1597, 1560, 1511 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.11–1.60 (5H, m), 1.47 (9H, s), 1.63–1.96 (5H, m), 3.20 (1H, m), 3.60 (1H, d, J = 17.0 Hz), 3.66 (1H, d, J = 18.4 Hz), 3.82 (1H, d, J = 18.4 Hz), 4.61 (1H, d, J = 17.0 Hz), 7.06–7.28 (2H, m), 7.33–7.52 (2H, m), 7.56–7.76 (2H, m), 7.81 (1H, br s), 7.88 (1H, m). Anal. ($C_{29}H_{34}F_3N_3O_5$) C, H, F, N.

(2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonyl)phenyl)ureidomethylcarbonyl)amino)phenyl)cyclohexylketone (6v). Amorphous solid. IR ν_{max} (KBr) 3374, 1722, 1685, 1650, 1594, 1555 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.12–1.95 (10H, m), 1.40 (9H, s), 3.07 (1H, m), 3.53 (1H, d, J = 17.2 Hz), 3.73 (1H, d, J = 17.4 Hz), 3.93 (1H, d, J = 17.4 Hz), 4.77–4.82 (2H, m), 4.80 (1H, d, J = 17.2 Hz), 5.19–5.47 (2H, m), 5.89–6.22 (2H, m), 7.13–7.35 (3H, m), 7.48–7.78 (4H, m), 7.80 (1H, br s). Anal. ($C_{32}H_{39}N_3O_7 \cdot 0.2H_2O$) C, H, N.

(2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureidomethylcarbonyl)amino)phenyl)thienyl-2-ylketone (6w). Mp 116 °C. IR ν_{max} (KBr) 3347, 1745, 1645, 1614, 1563 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.43 (9H, s), 2.31 (3H, s), 3.70 (1H, d, J = 17.1 Hz), 4.74 (1H, d, J = 17.1 Hz), 3.75 (1H, d, J = 17.4 Hz), 4.00 (1H, d, J = 17.4 Hz), 5.80 (1H, br s), 6.67 (1H, m), 6.87 (1H, m), 7.01 (1H, m), 7.10–7.22 (3H, m), 7.50–7.70 (4H, m), 7.75–7.80 (2H, m). Anal. ($C_{27}H_{29}N_3O_5S$) C, H, N, S.

(2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonyl)ureidomethylcarbonyl)amino)-phenyl)thienyl-2-ylketone (6x). Mp 142 °C. IR ν_{max} (KBr) 3343, 1742, 1722, 1645, 1595, 1561 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 3.69 (1H, d, J = 17.5 Hz), 4.71 (1H, d, J = 17.5 Hz), 3.78 (1H, d, J = 17.5 Hz), 4.00 (1H, d, J = 17.5 Hz), 4.80 (2H, dt, J = 6.0, 0.8 Hz), 5.26 (1H, dd, J = 9.0, 1.5 Hz), 5.39 (1H, dd, J = 17.4, 1.8 Hz), 5.80–6.08 (2H, m), 7.02 (1H, s), 7.15 (1H, m), 7.31 (1H, m), 7.50–7.70 (6H, m), 7.78 (2H, m), 7.93 (1H, m). Anal. ($C_{30}H_{31}N_3O_7S$) C, H, N, S.

4-Anisyl-2-(*N*-(*tert*-butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureidomethylcarbonyl)amino)phenyl)ketone (6y). Mp 228–230 °C. IR ν_{max} (KBr) 3330, 1744, 1670, 1640, 1600 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.36 (9H, s), 2.22 (3H, s), 3.62 (1H, dd, J = 18, 5.1 Hz), 3.68 (1H, d, J = 16.8 Hz), 3.77 (1H, dd, J = 18.0, 5.1 Hz), 3.83 (3H, s), 4.20 (1H, d, J = 16.8 Hz), 6.36 (1H, t, J = 5.1 Hz), 6.70 (1H, d, J = 7.5 Hz), 7.05–7.18 (5H, m), 7.52–7.76 (5H, m), 8.79 (1H, s). Anal. ($C_{30}H_{33}N_3O_6$) C, H, N.

4-Anisyl-2-(*N*-(*tert*-butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(2-propenyloxyphenyl)ureidomethylcarbonyl)amino)phenyl)ketone (6z). Mp 190–191 °C. IR ν_{max} (KBr) 1741, 1721, 1645, 1599, 1566 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.38 (9H, s), 3.60–3.85 (3H, m), 3.84 (3H, s), 4.20 (1H, d, J = 16.8 Hz), 4.79 (2H, d, J = 5.4 Hz), 5.27 (1H, d, J = 7.5 Hz), 5.39 (1H, d, J = 17.1 Hz), 5.98–6.11 (1H, m), 6.38 (1H, t, J = 4.5 Hz), 7.08 (2H, d, J = 9.0 Hz), 7.37 (1H, t, J = 8.0 Hz), 7.49–7.76 (8H, m), 8.10 (1H, s), 9.07 (1H, s). Anal. ($C_{33}H_{35}N_3O_8$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-carboxyphenyl)ureidomethylcarbonyl)amino)benzophenone (7a) . To a solution of the allyl ester **6e** (820 mg, 1.43 mmol), palladiumtetrakistriphenylphosphine (41.4 mg, 0.036 mmol) and triphenylphosphine (19 mg, 0.072 mmol) in dichloromethane (0.5 mL), a solution of pyrrolidine (127 μL, 1.51 mmol) in CH_2Cl_2 (0.5 mL) was added with stirring at 0 °C. After 15 min, the reaction solution was diluted with ethyl acetate and extracted with an aqueous 15% $NaHCO_3$. The alkaline layer was adjusted to pH 2 with 5% HCl and extracted with ethyl acetate. The extracts were treated as usual. Powder (256 mg, 34%), mp 187 °C (dec) (polymorphism). IR ν_{max} (KBr) 3380, 1665, 1595, 1555 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.69 (1H, d, J = 17.2 Hz), 3.83 (1H, dd, J = 17.2, 4.6 Hz), 4.05 (1H, dd, J = 17.2, 4.6 Hz), 4.70 (1H, d, J = 17.2 Hz), 7.17–7.27 (1H, br s), 7.30–7.85 (12H, m), 8.17 (1H, s), 8.30-8.41 (1H, m). Anal. ($C_{29}H_{29}N_3O_7$) C, H, N.

Methyl ester. Amorphous solid. IR ν_{max} (KBr) 3380, 1724, 1664, 1594, 1555 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.13–1.93 (10H, m), 1.43 (9H, s), 3.07 (1H, m), 3.49 (1H, d, J = 17.1 Hz), 3.75 (1H, dd, J = 17.1, 5.1 Hz), 3.88 (3H, s), 3.90 (1H, dd, J = 17.1, 5.1 Hz), 4.80 (1H, d, J = 17.1 Hz), 5.87 (1H, br s), 6.93 (1H, s), 7.43–7.84 (8H, s), 7.94 (1H,s). Anal. ($C_{30}H_{37}N_3O_7 \cdot 0.2H_2O$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(carboxymethyl)phenyl)ureidomethylcarbonyl)amino)benzophenone (7b). Mp 96–98 °C. IR ν_{max} (KBr) 3380, 1739, 1661, 1594, 1555 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.41 (9H, s), 3.57 (2H, s), 3.63 (1H, d, J = 17.2 Hz), 3.75 (1H, dd, J = 17.0, 5.0 Hz), 4.02 (1H, dd, J = 17.0, 5.0 Hz), 4.61 (1H, d, J = 17.2 Hz), 6.42 (1H, br s), 6.81–6.97 (2H, m), 7.12–7.24 (1H, m), 7.40–7.70 (7H, m), 7.71–7.82 (3H, m). Anal. ($C_{30}H_{31}N_3O_7 \cdot 0.4H_2O$) C, H, N.

Methyl ester. Yield 42%, mp 127–129 °C. IR ν_{max} (KBr) 3359, 1740, 1658, 1562, 1494 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (3H, s), 3.55 (2H, s), 3.65 (1H, d, J = 17.6 Hz), 3.67 (3H, s), 3.77 (1H, d, J = 18.2 Hz), 4.01 (1H, d, J = 17.6 Hz), 4.64 (1H, d, J = 17.6 Hz), 5.88 (1H, br s), 6.91 (1H, m), 7.15–7.81 (13H, m). Anal. ($C_{31}H_{33}N_3O_7$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(carboxymethyloxy)phenyl)ureidomethylcarbonyl)amino)benzophenone (7c). Powder IR ν_{max} (KBr) 3380, 1740, 1662, 1599, 1551 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.41 (9H, s), 3.67 (1H, d, J = 17.0 Hz), 3.76 (1H, dd, J = 17.4, 3.6 Hz), 4.06 (1H, dd, J = 17.4, 3.6 Hz), 4.59 (2H, s), 4.62 (1H, d, J = 17.0 Hz), 6.38–6.53 (2H, m), 6.71 (1H, br s), 7.04–7.26 (2H, m), 7.40–7.70 (6H, m), 7.73–7.82 (3H, m). Anal. ($C_{30}H_{31}N_3O_8 \cdot 0.4H_2O$) C, H, N.

Methyl ester. Mp 74–77 °C. IR ν_{max} (KBr) 3380, 1741, 1662, 1599, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 3.63 (1H, d, J = 17.4 Hz), 3.75 (1H, dd, J = 17.4, 8.6 Hz), 3.63 (1H, d, J = 17.4 Hz), 4.01 (1H, dd, J = 17.4, 8.6 Hz), 4.60 (2H, s), 4.63 (1H, d, J = 17.4 Hz), 5.82 (1H, br s), 6.57 (1H, dd, J = 7.6, 2.6 Hz), 6.72–6.88 (2H, m), 7.00–7.18 (2H, m), 7.37–7.68 (6H, m),7.72–7.85 (3H, m). Anal. ($C_{31}H_{33}N_3O_8$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(carboxymethylthio)phenyl)ureidomethylcarbonyl)amino)benzophenone (7d). IR ν_{max} (KBr) 3380, 1738, 1661, 1595, 1547 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (9H, s), 3.60 (2H, s), 3.68 (1H, d, J = 17.4 Hz), 3.80 (1H, dd, J = 17.2, 5.6 Hz), 4.03 (1H, dd, J = 17.2, 5.6 Hz), 4.60 (1H, d, J = 17.4 Hz), 6.28 (1H, br s), 6.97–7.24 (4H, m), 7.38–7.70 (7H, m), 7.76–7.88 (3H, m). Anal. ($C_{30}H_{31}N_3O_7S \cdot 0.5H_2O$) C, H, N.

Methyl ester. Mp 131–133 °C. IR ν_{max} (KBr) 3375, 1741, 1665, 1653, 1598, 1550 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 3.66 (1H, d, J = 17.4 Hz), 3.67 (2H, s), 3.72 (3H, s), 3.82 (1H, dd, J = 17.2, 5.6 Hz), 4.05 (1H, dd, J = 17.2, 5.6 Hz), 4.64 (1H, d, J = 17.4 Hz), 5.99 (1H, br s), 6.91–7.20 (4H, m), 7.32–7.73 (7H, m), 7.75–7.87 (3H, m). Anal. ($C_{31}H_{33}N_3O_7S$) C, H, H, S.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(carboxymethylsulfinyl)phenyl)ureidomethylcarbonyl)amino)benzophenone (7e). Powder ^1H NMR ($CDCl_3$) δ 1.43 (9H, s), 3.74 (1H, d, J = 17.2 Hz), 3.75–3.98 (4H, m), 4.37(1H, d, J = 17.2 Hz), 7.27–7.86 (13H, m).

Methyl ester. Powder. ^1H NMR ($CDCl_3$) δ 1.41 (9H, s), 3.70 (3H, s), 3.73 (1H, d, J = 17.2 Hz), 3.74–4.00 (4H, m), 4.37 (1H, d, J = 17.2 Hz), 7.09–7.87 (13H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(tetrazol-5-yl)phenyl)ureidomethylcarbonyl)amino)benzophenone (7f). To a solution of of **4i** (570 mg, 0.71 mmol) in THF (3 mL) and ethanol (10 mL) was added 1 N HCl (2.9 mL) and the mixture was stirred at room temperature for 3 h. Water was added. The mixture was extracted with ethyl acetate. The extracts were treated as usual (187 mg; 33.7%). Mp 163–175 °C. IR ν_{max} (KBr) 3380, 1740, 1661, 1595, 1570 cm^{-1}. ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.34 (9H, s), 3.67 (1H, d, J = 17.4 Hz), 3.85 (1H, d, J = 17.4 Hz), 4.01 (1H, d, J = 17.4 Hz), 7.07–7.92 (13H, m). Anal. ($C_{29}H_{29}N_7O_5 \cdot H_2O$) C, H, N.

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-(tetrazol-5-ylmethyloxy)phenyl)ureidomethylcarbonyl)amino)benzophenone (7g). IR ν_{max} (KBr) 3400, 1741, 1662, 1600, 1555 cm^{-1}. ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.39 (9H, s), 3.64 (1H, d, J = 17.4 Hz), 3.81 (1H, d, J = 17.4 Hz), 4.58 (1H, d, J = 17.4 Hz), 5.28 (2H, dd, J = 20.1, 14.0 Hz), 6.36–6.47 (1H, m), 6.77–7.03 (3H, m), 7.44-8.00 (11H, m). Anal. ($C_{30}H_{31}N_7O_6 \cdot 0.4H_2O$) C, H, N.

(2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-carboxyphenyl)ureidomethylcarbonyl)amino)phenyl)cyclohexylketone (7h). Mp 175–181 °C. IR ν_{max} (KBr) 3379, 1735, 1685, 1610, 1595, 1554 cm^{-1}. ^1H NMR ($CDCl_3$)

δ 1.08–1.55 (5H, m), 1.46 (9H, s), 1.61–1.98 (5H, m), 3.19 (1H, m), 3.60 (1H, d, J = 17.2 Hz), 3.66 (1H, d, J = 17.0 Hz), 3.83 (1H, d, J = 17.0 Hz), 4.62 (1H, d, J = 17.2 Hz), 7.27 (1H, t, J = 6.0 Hz), 7.51–7.75 (5H, m), 7.86–7.93 (2H, m). Anal. ($C_{29}H_{35}N_3O_7 \cdot 1.2H_2O$) C, H, N.

(2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-carboxyphenyl)ureidomethylcarbonyl)amino)phenyl)thienyl-2-ylketone (7i). Mp 184–186 °C. IR ν_{max} (KBr) 3385, 1735, 1698, 1648, 1560 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.38 (9H, s), 3.58 (1H, dd, J = 16.8, 4.2 Hz), 3.78 (1H, dd, J = 16.8, 4.2 Hz), 3.72 (1H, d, J = 17.2 Hz), 4.29 (1H, d, J = 17.2 Hz), 6.37 (1H, t, J = 4.4 Hz), 7.20–7.35 (2H, m), 7.40–7.80 (7H, m), 7.99 (1H, m), 8.18 (1H, dd, J = 5.0 Hz, 1.2 Hz), 8.99 (1H, s). Anal. ($C_{27}H_{27}N_3O_7S \cdot 0.2H_2O$) C, H, N, S.

4-Anisyl-(2-(*N*-(*tert*-butoxycarbonylmethyl)-*N*-(*N'*-(*m*-carboxyphenyl)ureidomethylcarbonyl)amino)-phenyl)ketone (7j). Mp 198–200 °C. IR ν_{max} (KBr) 1743, 1694, 1647, 1599, 1557 cm^{-1}. ^1H NMR (CD_3OD) δ 1.43 (9H, s), 3.69 (1H, d, J = 17.2 Hz), 3.79 (1H, d, J = 17.4 Hz), 3.85 (3H, s), 3.94 (1H, d, J = 17.2 Hz), 4.39 (1H, d, J = 17.2 Hz), 7.02–7.05 (2H, m), 7.28–7.36 (1H, m), 7.49–7.83 (8H, m), 7.97–7.99 (1H, m). Anal. ($C_{30}H_{31}N_3O_8$) C, H, N.

***N*-(*o*-Iodophenyl)-2-(*N*-Cbz-amino)acetamide (9)**. $POCl_3$ (2.2 mL, 24 mmol) was added to a solution of imidazole (2.7 g, 40 mmol) and *N*-Cbz-glycine (5.0 g, 24 mmol) in dimethylacetamide (32 mL) under cooling in ice. After stirring for 5 min, a solution of *o*-iodoaniline (4.4 g, 20 mmol) in DMA (10 mL) was added dropwise. The reaction mixture was stirred at 50 °C for 3 h. Water was added. Aqueous $NaHCO_3$ was added to make pH 9 and the mixture was extracted with ethyl acetate. The extracts were treated as usual. To the residue was added isopropylether (40 mL) and the precipitated solid was collected (7.10 g, yield 86%). ^1H NMR ($CDCl_3$) δ 4.06 (2H, d, J = 5.8 Hz), 5.19 (2H, s), 5.44 (1H, br s), 6.80–6.91 (1H, m), 7.20–7.45 (6H, m), 7.76 (1H, d, J = 8.0 Hz), 8.12 (1H, br s), 8.21 (1H, d, J = 8.0 Hz).

***N*-Glycyl-*o*-iodoaniline hydrochloride (10)**. Yield 96%. ^1H NMR ($CDCl_3$) δ 3.94 (2H, s), 6.99–7.07 (1H, m), 7.37–7.45 (1H, m), 7.55 (1H, d, J = 8.2 Hz), 7.92 (1H, d, J = 8.0 Hz).

***o*-Iodo-*N*-(*N'*-(*m*-tolyl)ureidoacetyl)aniline (11)**. Quantitative yield. ^1H NMR (DMSO-d_6) δ 2.25 (3H, s), 3.95 (2H, d, J = 5.4 Hz), 6.48–6.55 (1H, m), 6.73 (1H, d, J = 6.8 Hz), 6.93–7.45 (5H, m), 7.61 (1H, dd, J = 1.4, 8.1 Hz), 7.88 (1H, dd, J = 1.4, 8.0 Hz), 8.79 (1H, s), 9.45 (1H, s).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureidoacetyl)-*o*-iodoaniline (12)** . To a solution of **11** (1.02 g, 2.5 mmol) in DMSO (5mL) were added KI (83 mg, 0.2 mmol), tetra-*n*-butylammonium bromide (81 mg, 0.1 mmol), *tert*-butylbromoacetate (0.55 mL, 3.75 mmol) and K_2CO_3 (1.04 g, 7.5 mmol) at room temperature. The mixture was stirred for 2.25 h. Water was added and the pH was adjusted to 2 with 2 N HCl. The aqueous layer was extracted with ethyl acetate. The extracts were treated as usual. To the residue was added isopropylether and the precipitated solid was collected by filtration (1.20 g yield 92%). ^1H NMR ($CDCl_3$) δ 1.45 (9H, s), 2.35 (3H, s), 3.49 (1H, d, J = 17.6 Hz), 3.65 (1H, dd, J = 4.4, 17.6 Hz), 3.88 (1H, dd, J = 4.4, 17.7 Hz), 4.92 (1H, d, J = 17.6 Hz), 5.78–5.82 (1H, m), 6.59 (1H, br s), 6.87 (1H, d, J = 7.4 Hz), 7.14–7.48 (5H, m), 7.69 (1H, d, J =7.8 Hz), 7.95 (1H, d, J = 8.2 Hz).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidoacetyl)-2-(trimethylstannyl)aniline (13)**. To a solution of **12** (52 mg, 0.1 mmol) in toluene (2 mL) were added at room temperature *trans*-benzylchlorobistriphenylphosphinepalladium (3.8 mg, 5 μmol), tetraethylammonium chloride (3 mg, 20 μmol) and hexamethylditin (50 mg, 0.15 mmol). The mixture was stirred at 85 °C for 1 h and at 100 °C for 30 min. Ice-water was added. The aqeous layer was extracted with ethyl acetate. The extracts were treated as usual. The residue was purified by chromatography (35 mg, yield 64%). ^1H NMR ($CDCl_3$) δ 0.29 (9H, s), 1.43 (9H, s), 2.29 (3H, s), 3.56 (1H, d, J = 16.8 Hz), 3.80 (2H, s), 4.79 (1H, d, J = 16.8 Hz), 6.00 (1H, br s), 6.80–7.61 (9H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidomethylcarbonyl)amino)-2'-fluorobenzophenone (7l). To a solution of 4-trifluoromethylbenzoyl chloride (53 μl, 0.36 mmol) in toluene (4 mL) was added dichlorobisacetonitrile palladium (12.5 mg, 0.036 mmol) at room temperature. Compound **13** (200 mg, 0.36 mmol) was added and the mixture was stirred at 50 °C for 20 min. After addition of dichlorobisacetonitrile palladium (6.2 mg, 0.018 mmol), stirring was continued for a further 10 min. Ice-water was added. The mixture was extracted with ethyl acetate. The extracts were treated as usual. The residue was purified by column chromatography, 93 mg, yield 46%. ^1H NMR ($CDCl_3$) δ 1.40 (9H, s), 2.28 (3H, s), 3.70 (1H, d, J = 17.2 Hz), 3.80 (1H, dd, J = 4.4 Hz, 17.7 Hz), 3.97 (1H, dd, J = 4.6 Hz, 17.7 Hz), 4.63 (1H, d, J = 17.2 Hz), 5.77–5.87 (1H, m), 6.67 (1H, br s), 6.80–7.18 (4H, m), 7.41–7.94 (8H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidomethylcarbonyl)amino)-4'-(trifluoromethyl)-benzophenone (7k). Yield 30%. ^1H NMR ($CDCl_3$) δ 1.41 (9H, s), 2.28 (3H, s), 3.68 (1H, d, J = 17.6 Hz), 3.81 (1H, dd, J = 4.2, 17.5 Hz), 4.01 (1H, dd, J = 4.6, 17.5 Hz), 4.67 (1H, d, J = 17.6 Hz), 5.82–5.95 (1H, m), 5.98–7.75 (13H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidomethylcarbonyl)amino)-4'-cyanobenzophenone (7m). Yield 47%. 1H ^1H NMR ($CDCl_3$) δ 1.39 (9H, s), 2.29 (3H, s), 3.74 (1H, d, J = 17.2 Hz), 3.80 (1H, dd, J = 4.6, 17.6 Hz), 3.93 (1H, dd, J = 4.2, 17.6 Hz), 4.60

(1H, d, J = 17.2 Hz), 5.82–5.89 (1H, m), 6.73–7.20 (5H, m), 7.42–7.94 (8H, m).

2-(Adamantylcarbonyl)-*N*-(*tert*-butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)ureidoacetyl)aniline (7n). Yield 16%. 1H ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 1.71 (6H, s), 1.90 (6H, s), 2.05 (3H, s), 2.30 (3H, s), 3.69 (1H, d, J = 17.2 Hz), 3.90 (1H, d, J = 17.4 Hz), 4.01 (1H, d, J = 17.4 Hz), 4.63 (1H, d, J = 17.2 Hz), 5.83 (1H, br s), 6.74–7.46 (9H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidoacetyl)-2-(hept-4-ylcarbonyl)aniline (7o).** Yield 18%. ^{1}H NMR ($CDCl_3$) δ 0.85–0.91 (6H, m), 1.42 (9H, s), 2.30 (3H, s), 3.49 (1H, d, J = 17.4 Hz), 3.65 (1H, d, J = 17.4 Hz), 3.92 (1H, d, J = 17.4 Hz), 4.84 (1H, d, J = 17.4 Hz), 5.97 (1H, br s), 6.80–7.18 (5H, m), 7.38–7.78 (4H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidoacetyl)-2-(cyclopropylcarbonyl)aniline (7p).** Yield 48%. ^{1}H NMR ($CDCl_3$) δ 1.02—1.14 (2H, m), 1.19–1.31 (2H, m), 1.41 (9H, s), 2.28 (3H, s), 2.38–2.47 (1H, m), 3.56 (1H, d, J = 17.4 Hz), 3.76 (1H, dd, J = 5.0, 17.5 Hz), 3.90 (1H, dd, J = 4.6, 17.5 Hz), 4.82 (1H, d, J = 17.4 Hz), 5.98–6.07 (1H, m), 6.82 (1H, d, J = 7.0 Hz), 6.99–7.21 (4H, m), 7.39–7.70 (3H, m), 7.81–7.88 (1H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidoacetyl)-2-(4-methylcyclohexylcarbonyl)aniline (7q).** Yield 34%. ^{1}H NMR ($CDCl_3$) δ 0.84–1.93 (9H, m), 0.90 (3H, d, J = 6.4 Hz), 1.43 (9H, s), 2.30 (3H, s), 2.90–3.07 (1H, m), 3.48 (1H, d, J = 17.2 Hz), 3.68 (1H, dd, J = 4.6, 17.7 Hz), 3.89 (1H, dd, J = 4.6, 17.7 Hz), 4.80 (1H, d, J = 17.2 Hz), 5.85–5.99 (1H, m), 6.74 (1H, s), 6.85 (1H, d, J = 6.8 Hz), 7.02–7.32 (3H, m), 7.47–7.76 (4H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidoacetyl)-2-(*N*-Cbz-piperidinocarbonyl)aniline (7r).** The acid chloride was synthesized from thionyl chloride (220 μL) and *N*-Cbz-piperidine-4-carboxylic acid (198 mg) and treated as above. Yield 48%. ^{1}H NMR ($CDCl_3$) δ 1.41 (9H, s), 1.50–1.92 (4H, m), 2.28 (3H, s), 2.77–3.02 (2H, m), 3.16–3.36 (1H, m), 3.50 (1H, d, J = 17.2 Hz), 3.72 (1H, dd, J = 4.6 Hz, 17.6 Hz), 3.85 (1H, dd, J = 4.2, 17.6 Hz), 4.04–4.34 (2H, m), 4.75 (1H, d, J = 17.2 Hz), 5.86–5.97 (1H, m), 6.77–7.20 (5H, m), 7.48–7.73 (4H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-tolyl)-ureidoacetyl)-2-(piperidinocarbonyl)aniline (7s).** 10%-Pd(OH)$_2$–C (2 mg) was added to a solution of **7r** (9.7 mg, 0.015 m mol) in EtOH (0.5 mL) under H_2. The mixture was stirred overnight and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography, 6.0 mg yield 79%. ^{1}H NMR ($CDCl_3$) δ 1.42 (9H, s), 1.53–1.76 (2H, m), 1.76–1.92 (2H, m), 2.29 (3H, s), 2.60–2.82 (2H, m), 3.08–3.28 (3H, m), 3.52 (1H, d, J = 17.2 Hz), 3.63–3.76 (1H, m), 3.79–3.94 (1H, m), 4.77 (1H, d, J = 17.2 Hz), 5.99 (1H, br s), 6.83 (1H, d, J = 6.6 Hz), 7.02–7.19 (4H, m), 7.46–7.77 (4H, m).

***N*-(*N'*-Cbz-Glycyl)-2-(tri-*n*-butylstannyl)aniline (14).** To a solution of **9** (4.1 g, 0.01 mol) in CH_2Cl_2 (80 mL) were added dichlorobisacetonitrile palladium (190 mg, 0.25 mmol) and hexabutylditin (6.0 mL, 0.012 mol) at room temperature and the mixture was stirred at room temperature overnight. 50% Aqueous KF was added. The mixture was stirred for 30 min and the precipitate was removed by filteration. After this procedure was repeated again, the organic layer was treated as usual. The residue was purified by column chromatography, 4.4 g yield 77%. ^{1}H NMR ($CDCl_3$) δ 0.83–1.65 (27H, m), 4.03 (2H, d, J = 5.6 Hz), 5.16 (2H, s), 5.40 (1H, br s), 7.10–7.48 (1H, m), 7.71 (1H, d, J = 8.0 Hz).

2-(*N*-(*N'*-Cbz-Glycyl)amino)-2'-fluorobenzophenone (2g). Yield 80%. ^{1}H NMR ($CDCl_3$) δ 4.12 (2H, d, J = 6.0 Hz), 5.19 (2H, s), 5.50 (1H, br s), 7.05–7.66 (7H, m), 8.74 (1H, d, J = 8.2 Hz).

2-(*N*-(*N'*-Cbz-Glycyl)amino)-4'-(trifluoromethyl)-benzophenone (2h). Yield 74%. ^{1}H NMR ($CDCl_3$) δ 4.10 (2H, d, J = 6.0 Hz), 5.18 (2H, s), 5.50 (1H, br s), 7.08–7.67 (8H, m), 7.76 (4H, s), 8.68 (1H, d, J = 8.2 Hz).

2-(*N*-(*N'*-Cbz-Glycyl)amino)-4'-cyanobenzophenone (2i). Yield 76%. ^{1}H NMR ($CDCl_3$) δ 4.09 (2H, d, J = 6.0 Hz), 5.18 (2H, s), 5.50 (1H, br s), 7.08–7.69 (8H, m), 7.74 (2H, d, J = 8.6 Hz), 7.80 (2H, d, J = 8.6 Hz), 8.68 (1H, d, J = 8.2 Hz).

2-(Adamantylcarbonyl)-*N*-(*N'*-Cbz-glycyl)aniline (2j). Yield 6%. ^{1}H NMR ($CDCl_3$) δ 1.72 (6H, s), 2.00 (6H, s), 2.06 (3H, s), 4.00 (2H, d, J = 5.8 Hz), 5.20 (2H, s), 5.44 (1H, br s), 7.09–7.68 (8H, m), 8.28 (2H, d, J = 8.7 Hz), 9.57 (1H, br s).

***N*-(*N'*-Cbz-Glycyl)-2-(hept-4-ylcarbonyl)aniline (2k).** Yield 55%. ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, t, J = 7.0 Hz), 1.16–1.84 (8H, m), 3.43–3.58 (1H, m), 4.10 (2H, d, J = 5.4 Hz), 5.19 (2H, s), 5.44 (1H, br s), 7.10–7.62 (7H, m), 7.94 (1H, d, J = 8.2 Hz), 8.73 (1H, d, J = 8.2 Hz).

2'-Fluoro-2-(glycylamino)benzophenone hydrobromide (3g). Yield 94%. ^{1}H NMR (CD_3OD) δ 3.88 (2H, s), 6.99–7.07 (1H, m), 7.18–7.70 (7H, m), 8.20 (1H, d, J = 8.0 Hz).

2-(Glycylamino)-4'-(trifluoromethyl)benzophenone hydrobromide (3h). Yield 93%. ^{1}H NMR (CD_3OD) δ 3.90 (2H, s), 7.19–7.67 (3H, m), 7.76 (2H, d, J = 8.0 Hz), 7.86 (2H, d, J = 8.0 Hz), 8.19 (1H, d, J = 8.2 Hz).

4'-Cyano-2-(glycylamino)benzophenone hydrobromide (3i). Quantitative yield. ^{1}H NMR (CD_3OD) δ 3.76 (2H, s), 7.29–7.88 (3H, m), 7.89 (4H, s).

2-(Adamantylcarbonyl)-*N*-(glycyl)aniline hydrobromide (3j). Yield 69%. ^{1}H NMR (CD_3OD) δ 1.75 (6H, s), 1.97 (6H, s), 2.02 (3H, s), 3.83 (2H, s), 7.22–7.58 (4H, m).

***N*-(Glycyl)-2-(hept-4-ylcarbonyl)aniline hydrobromide (3k)**. Yield 78%. ^{1}H NMR (CD_3OD) δ 0.88 (6H, t, J = 7.2 Hz), 1.19–1.83 (8H, m), 3.58–3.73 (1H, m), 4.00 (2H, s), 7.26–7.69 (2H, m), 8.14 (1H, dd, J = 1.6, 8.2 Hz), 8.56 (1H, d, J = 8.2 Hz).

2′-Fluoro-2-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)uridomethylcarbamoyl)benzophenone (15g). Yield 67%. ^{1}H NMR ($CDCl_3$) δ 4.19 (2H, d, J = 5.4 Hz), 4.78 (2H, d, J = 5.4 Hz), 5.21–5.44 (2H, m), 5.79–6.10 (2H, m), 7.03–7.94 (12H, m), 8.69 (1H, d, J = 8.2 Hz).

2-(*N*′-(*m*-(2-Propenyloxycarbonyl)phenyl)uridomethylcarbamoyl)-4′-trifluorobenzophenone (15h). Yield 65%. ^{1}H NMR ($CDCl_3$) δ 4.14 (2H, d, J = 5.7 Hz), 4.76 (2H, d, J = 5.4 Hz), 5.22–5.41 (2H, m), 5.92–6.05 (2H, m), 7.06–7.76 (11H, m), 7.90 (1H, s), 8.57 (1H, d, J = 8.4 Hz), 11.31 (1H, s).

4′-Cyano-2-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)uridomethylcarbamoyl)benzophenone (15i). Yield 69%. ^{1}H NMR ($CDCl_3$) δ 4.13 (2H, d, J = 5.7 Hz), 4.79 (2H, d, J = 5.4 Hz), 5.22–5.44 (2H, m), 5.79–6.12 (2H, m), 7.06–7.80 (11H, m), 7.89 (1H, s), 8.58 (1H, d, J = 8.4 Hz).

2-(Adamantylcarbonyl)-*N*-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)uridomethylcarbonyl)aniline (15j). Yield 55%. ^{1}H NMR ($CDCl_3$) δ 1.63 (9H, s), 1.90 (6H, s), 4.05 (2H, d, J = 5.8 Hz), 4.81 (2H, d, J = 6.0 Hz), 5.23–5.45 (2H, m), 5.81–6.12 (2H, m), 7.07–7.98 (12H, m), 8.21 (1H, d, J = 8.0 Hz).

2-(Hept-4-ylcarbonyl)-*N*-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)uridomethylcarbonyl)aniline (15k). Yield 43%. ^{1}H NMR ($CDCl_3$) δ 0.83 (6H, t, J = 7.0 Hz), 1.12–1.78 (8H, m), 3.41–3.56 (1H, m), 5.22–5.45 (2H, m), 5.84–6.12 (2H, m), 7.10–7.98 (12H, m), 8.71 (1H, d, J = 8.4 Hz).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)ureidomethylcarbonyl)amino)-2′-fluorobenzophenone (16g). Yield 65%. ^{1}H NMR ($CDCl_3$) δ 1.38 (9H, s), 3.72 (1H, d, J = 17.6 Hz), 3.85 (1H, dd, J = 4.4, 17.4 Hz), 4.04 (1H, dd, J = 5.2, 17.4 Hz), 4.65 (1H, d, J = 17.6 Hz), 4.78 (2H, d, J = 5.4 Hz), 5.20–5.46 (2H, m), 5.91–6.12 (2H, m), 7.05–8.02 (13H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)ureidomethylcarbonyl)amino)-4′-(trifluoromethyl)benzophenone (16h). Yield 56%. ^{1}H NMR ($CDCl_3$) δ 1.36 (9H, s), 3.75 (1H, d, J = 17.2 Hz), 3.79 (1H, dd, J = 4.8, 17.6 Hz), 4.00 (1H, dd, J = 4.8, 17.6 Hz), 4.61 (1H, d, J = 17.2 Hz), 4.78 (2H, d, J = 5.4 Hz), 5.20–5.44 (2H, m), 5.90–6.12 (2H, m), 7.18–7.96 (13H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)ureidomethylcarbonyl)amino)-4′-cyanobenzophenone (16i). Yield 53%. ^{1}H NMR ($CDCl_3$) δ 1.36 (9H, s), 3.80 (1H, d, J = 17.2 Hz), 3.83 (1H, dd, J = 4.8, 17.6 Hz), 3.96 (1H, dd, J = 4.8, 17.6 Hz), 4.58 (1H, d, J = 17.2 Hz), 4.79 (2H, d, J = 5.6 Hz), 5.21–5.44 (2H, m), 5.91–6.12 (2H, m), 7.17–7.94 (13H, m).

2-(Adamantylcarbonyl)-*N*-(*tert*-butoxycarbonylmethyl)-*N*-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)ureidomethylcarbonyl)aniline (16j). Yield 56%. ^{1}H NMR ($CDCl_3$) δ 1.41 (9H, s), 1.70 (6H, s), 1.92 (6H, s), 2.05 (3H, s),3.73 (1H, d, J = 17.2 Hz), 3.93 (1H, dd, J = 4.4, 17.5 Hz), 4.07 (1H, dd, J = 4.8, 17.5 Hz), 4.63 (1H, d, J = 17.2 Hz), 4.79 (2H, d, J = 5.6 Hz) 5.22–5.46 (2H, m), 5.91–6.13 (2H, m), 7.22–8.02 (9H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*′-(*m*-(2-propenyloxycarbonyl)phenyl)ureidomethylcarbonyl)-2-(hept-4-ylcarbonyl)aniline (16k)**. Yield 6%. ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, t, J = 7.0 Hz), 1.20–1.78 (8H, m), 1.41 (9H, s), 3.18–3.31 (1H, m), 3.51 (1H, d, J = 17.2 Hz), 3.68 (1H, dd, J = 4.6, 17.6 Hz), 3.95 (1H, dd, J = 4.6, 17.6 Hz), 4.79 (1H, d, J = 5.6 Hz), 4.83 (2H, d, J = 17.2 Hz), 5.22–5.45 (2H, m), 5.91–6.13 (2H, m), 7.10–8.00 (9H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*′-(*m*-carboxylphenyl)ureidomethylcarbonyl)amino)-2′-fluorobenzophenone (17g). Yield 71%. ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 3.70 (1H, d, J = 17.0 Hz), 3.89 (1H, dd, J = 3.2, 18.1 Hz), 4.05 (1H, dd, J = 3.2, 18.1 Hz), 4.74 (1H, d, J = 17.0 Hz), 7.05–7.80 (13H, m), 8.20 (1H, s), 8.34–8.43 (1H, m).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*′-(*m*-carboxylphenyl)ureidomethylcarbonyl)amino)-4′-(trifluoromethyl)benzophenone (17h). Yield 20%. ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 3.73 (1H, d, J = 17.2 Hz), 3.84 (1H, dd, J = 3.8, 18.8 Hz), 3.94 (1H, dd, J = 3.8, 18.8 Hz), 4.70 (1H, d, J = 17.2 Hz), 7.17 (1H, br s), 7.29–7.98 (11H, m), 8.14 (1H, s), 8.28 (1H, d, J = 7.6 Hz).

2-(*N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N*′-(*m*-carboxylphenyl)ureidomethylcarbonyl)amino)-4′-cyanobenzophenone (17i). Yield 71%. ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 3.76 (1H, d, J = 17.2 Hz), 3.83 (1H, dd, J = 4.0, 17.6 Hz), 3.94 (1H, dd, J = 4.0, 17.6 Hz), 4.68 (1H, d, J = 17.2 Hz), 7.16 (1H, br s), 7.31–7.94 (11H, m), 8.15 (1H, s), 8.26–8.34 (1H, m).

2-(Adamantylcarbonyl)-*N*-(*tert*-butoxycarbonylmethyl)-*N*-(*N*′-(*m*-carboxylphenyl)ureidomethylcarbonyl)aniline (17j). Yield 61%. ^{1}H NMR ($CDCl_3$) δ 1.49 (9H, s), 1.68 (6H, s), 1.90 (6H, s), 2.05 (3H, s), 3.73 (1H, d, J = 17.2 Hz), 3.96 (1H, dd, J = 3.6, 18.4 Hz), 4.10 (1H, dd, J = 3.6, 18.4 Hz), 4.65 (1H, d, J = 17.2 Hz), 7.19 (1H, br s), 7.30–7.78 (8H, m), 8.15 (1H, s), 8.34–8.41 (1H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-*N*-(*N'*-(*m*-carboxylphenyl)ureidomethylcarbonyl)-2-(hept-4-ylcarbonyl)aniline (17k)**. Yield 54%. ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, t, J = 7.0 Hz), 1.18–1.76 (8H, m), 1.49 (9H, s), 3.18–3.34 (1H, m), 3.53 (1H, d, J = 17.2 Hz), 3.73 (1H, dd, J = 3.6, 18.2 Hz), 3.96 (1H, dd, J = 4.6, 17.6 Hz), 4.85 (1H, d, J = 17.2 Hz), 7.20–7.86 (7H, m), 8.23 (1H, s), 8.57 (1H, d, J = 7.8 Hz).

***N*-Boc-2-(Trimethylstannyl)aniline (19)**. Yield 69%. ^{1}H NMR ($CDCl_3$) δ 0.34 (9H, s), 1.51 (9H, s), 6.28 (1H, br s), 7.07–7.17(1H, m), 7.22–7.43 (2H, m), 7.52 (1H, d, J = 8.6 Hz).

2-(*N'*-Cbz-Piperidine-4-carbonyl)-*N*-Boc-aniline (20). Yield 81%. ^{1}H NMR ($CDCl_3$) δ 1.53 (9H, s), 1.63–1.95 (4H, m), 2.85–3.06 (2H, m), 3.37–3.58 (1H, m), 4.16–4.38 (2H, m), 5.15 (2H, s), 6.99–7.08 (1H, m), 7.36 (5H, s), 7.48–7.57 (1H, m), 7.86 (1H, dd, J = 1.2, 8.2 Hz), 8.51 (1H, dd, J = 1.0, 8.2 Hz).

2-(*N'*-Cbz-Piperidine-4-carbonyl)aniline (1e). CF_3COOH (13.0 mL) was added dropwise to a solution of **20** (1.30 g, 3.0 mmol) and anisole (2.0 mL) in CH_2Cl_2 (6.5 mL) under ice-cooling and the mixture was stirred at the same temperature for 1 h. The reaction solution was diluted with ethyl acetate and after adding ice–water, the solution was neutralized with an aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate. The extracts were treated as usual. The residue was purified by column chromatography, yield 99%. ^{1}H NMR ($CDCl_3$) δ 1.69–1.96 (4H, m), 2.83–3.08 (2H, m), 3.35–3.53 (1H, m), 4.17–4.39 (2H, m), 5.15 (2H, s), 6.30 (2H, br s), 6.61–6.70 (2H, m), 7.23–7.39 (1H, m), 7.36 (5H, s), 7.73 (1H, d, J = 8.2 Hz).

Methyl-*N'*-(*m*-(2-propenyloxycarbonyl)phenyl)-ureidoacetate (22). A suspension of triphosgene (2.5 g, 8.42 mmol) and allyl *m*-aminobenzoate HCl (4.0 g, 18.7 mmol) in CH_2Cl_2 (80 mL) was cooled to −20 °C and triethylamine (9.64 mL, 69.2 mmol) was added dropwise. The mixture was strirred for 30 min. Glycine methyl ester HCl (2.82 g, 22.44 mmol) was added. Triethylamine (3.75 mL, 18.7 mmol) was added dropwise, followed by stirring at −20 °C for 2.5 h. Ice–water was added. The mixture was extracted with ethyl acetate. The extracts were treated as usual, 5.27 g yield 96%. ^{1}H NMR ($CDCl_3$) δ 3.76 (3H, s), 4.08 (2H, s), 4.80 (2H, d, J = 5.5 Hz), 5.23–5.45 (2H, m), 5.92–6.12 (2H, m), 7.28–7.38 (1H, m), 7.67–7.90 (3H, m).

***N'*-(*m*-(2-Propenyloxycarbonyl)phenyl)ureidoacetic acid (23)**. To a solution of **22** (5.27 g, 18.7 mmol) in THF (27 mL) was added 2 N HCl (37.4 mL) and the mixture was refluxed for 2.5 h. Water and an aqueous $NaHCO_3$ were added to adjust the pH of the mixture to 8, which was then extracted with ethyl acetate. Concentrated HCl was added to adjust the pH to 1, followed by extraction with ethyl acetate. The extracts were treated as usual. The residue was crystallized from toluene, 3.66 g yield 70%. ^{1}H NMR (DMSO-d_6) δ 3.80 (2H, d, J = 5.9 Hz), 4.79 (2H, d, J = 5.4 Hz), 5.24–5.47 (2H, m), 5.95–6.16 (2H, m), 6.41 (1H, t, J = 5.9 Hz), 7.39 (1H, t, J = 7.8 Hz), 7.50–7.65 (2H, m), 8.14 (1H, s), 9.08 (1H, s).

2-(4-(*N*-Cbz-Piperidino)carbonyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonyl)phenyl)uridomethylcarbamoyl)-aniline (15l). Yield 65%. ^{1}H NMR (DMSO-d_6) δ 1.13–1.39 (2H, m), 1.54–1.79 (2H, m), 2.80–3.06 (2H, m), 3.52–3.69 (1H, m), 3.74–3.98 (2H, m), 3.88 (2H, d, J = 6.0 Hz), 3.76 (2H, d, J = 5.2 Hz), 5.06 (2H, s), 5.20–5.43 (2H, m), 5.90–6.13 (1H, m), 6.83 (1H, t, J = 6.0 Hz), 7.18–7.68 (10H, m), 8.05 (1H, d, J = 7.8 Hz), 8.15 (1H, s), 8.45 (1H, d, J = 7.8 Hz), 9.28 (1H, s), 11.60 (1H, s).

***N*-(*tert*-Butoxycarbonylmethyl)-2-(4-(*N*-Cbz-piperidino)carbonyl)-*N*-(*N'*-(*m*-(2-propenyloxycarbonyl)-phenyl)uridomethylcarbamoyl)aniline (16l)**. Yield 20%. ^{1}H NMR ($CDCl_3$) δ 1.47–1.74 (2H, m), 1.74–1.94 (2H, m), 1.39 (9H, s), 2.76–3.04 (2H, m), 3.17–3.37 (1H, m), 3.53 (1H, d, J = 17.6 Hz), 3.62 (1H, dd, J = 4.4, 17.5 Hz), 3.88 (1H, dd, J = 4.8, 17.5 Hz), 4.05–4.33 (2H, m), 4.74 (1H, d, J = 17.6 Hz), 4.77 (2H, d, J = 4.2 Hz), 5.12 (2H, s), 5.22–5.44 (2H, m), 5.90–6.17 (2H, m), 7.20–7.41 (7H, m), 7.47–7.76 (6H, m), 7.93 (1H, s).

***N*-(*tert*-Butoxycarbonylmethyl)-2-(4-(*N*-Cbz-piperidino)carbonyl)-*N*-(*N'*-(*m*-carboxylphenyl)uridomethylcarbamoyl)aniline (17l)**. Yield 78%. ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 1.51–1.95 (4H, m), 2.80–3.08 (2H, m), 3.20–3.44 (1H, m), 3.54 (1H, d, J = 17.2 Hz), 3.69–3.98 (2H, m), 4.18–4.38 (2H, m), 4.79 (1H, d, J = 17.2 Hz), 5.11 (2H, s), 7.16 (1H, br s), 7.40–7.87 (8H, m), 8.21–8.40 (2H, m).

***N*-(*tert*-Butoxycarbonylmethyl)-2-(4-(piperidino)-carbonyl)-*N*-(*N'*-(*m*-carboxylphenyl)uridomethyl-carbamoyl)aniline (17m)**. To a solution of **17l** (19 mg, 1.49 μmol) in ethanol (1.0 mL) were added cyclohexene (144 μL) and 10% Pd–C (15 mg), and the mixture was refluxed for 30 min. The mixture was filtered and the filtrate was concentrated under reduced pressure, 12 mg, yield 79%. ^{1}H NMR (CD_3OD) δ 1.44 (9H, s), 1.65–2.19 (4H, m), 3.17–3.91 (5H, m), 3.64 (1H, d, J = 17.2 Hz), 3.68 (1H, d, J = 17.2 Hz), 3.84 (1H, d, J = 17.2 Hz), 4.65 (1H, d, J = 17.2 Hz), 7.12–7.84 (7H, m), 8.17 (1H, m).

In vivo test for evaluation of inhibitory effect on gastric acid secretion by the schild method

Twenty-four-hour starved (water *ad libitum*) male Sprague–Dawley rats (8-week-old) were anesthetized with urethane (1.5 g/kg, sc). After tracheostomy, an esophagus cannula was inserted orally up to the proventriculus and ligated around the gastric cardiac. A perfusion cannula was inserted from the duodenum into the stomach and ligated around the pylorus.

Another cannula was placed into the duodenum and ligated for drug administration. The stomach was perfused via the esophagus cannula with physiological saline (37 °C) while collecting the perfusate for a 15-min period. The perfusate was subjected to titration with 0.01 N NaOH solution to determine the acidity. When the basal acid secretion became stable, pentagastrin (10 μg/kg/h) was administered in a sustained manner via the common carotid vein for about 90 min until the acid secretion reached approximately the highest level, when the test compound (0.5% MC suspension) was administered into the duodenum through the cannula. The perfusate was collected for a 15-min interval to monitor the acid secretion for 90 min. The percentage inhibition was calculated as follows:

$$\text{Percent inhibition } (\%) = 100 \times (C - A)/(C - B)$$

where A is the minimum value of total acidity observed after administration of the test compound; B is the total acidity immediately before pentagastrin administration; and C is the total acidity immediately before administration of the test compound.

In the case of intravenous administration, a test compound was administrated through tail vein.

Determination of gastric acid secretion in pylorus-ligated rats

Male Sprague–Dawley rats were allowed free access to tapwater before the experiment but were deprived of food for 24 h before the experiment. Under ether anesthesia, the abdomen was incised and the pylorus ligated. Two hours later, the animals were sacrificed with ether and the gastric contents were collected and analyzed for volume and acidity. Acidity was determined by automatic titration of the gastric juice against 0.01 N NaOH to pH 7.0. Compound **7a**, YM022 or vehicle alone was given orally 30 min before ligation.

In vitro test for evaluation of gastrin/CCK-B antagonism

The pharmacological effects of the compounds (**I**) prepared above were evaluated in vitro with respect to antagonistic activity against gastrin receptor, CCK-B receptor or CCK-A receptor, using fundic glands of guinea pig, crude membrane specimen from mouse cerebral cortex, or crude membrane specimen from mouse pancreas, respectively. Male Hartley guinea pigs (450–600 g) or male ddY mice (24–30 g) were used.[1]

Gastrin receptor antagonism

Male guinea pigs were killed by bleeding and the stomach was extracted from each animal immediately, from which gastric glands were prepared.

Preparation of test compounds and procedures of the displacing assay

A 1 mM solution of the compound to be tested in DMSO was prepared and diluted with 50% DMSO to obtain a 10-fold dilution series. The reaction was initiated by addition of gastric glands to solutions of different concentrations each containing [^{125}I]-labeled gastrin (final concentration, 0.2 nM). The mixture was incubated for 30 min at 25 °C and centrifuged at 2000 rpm for 5 min, then the supernatant was removed by aspiration. To the pellet was added ice-cooled incubation buffer, followed by gentle mixing, immediate centrifugation and removal of the supernatant by aspiration. The radioactivity was counted with a gamma counter. The same procedure was repeated using 50% DMSO solution or human gastrin I instead of a solution of test compound so as to obtain the control value regarding total binding or the value regarding non-specific binding, respectively.

CCK-A receptor antagonism and CCK-B receptor antagonism

Male mice were killed by decapitation and the cerebral cortex (CCK-B) and pancreas (CCK-A) were extracted immediately. Each was mixed with 50 mM Tris–HCl buffer (pH 7.4) and homogenized with a Teflon glass homogenizer and polytron homogenizer to obtain crude membrane specimens.

Preparation of test compounds and procedures of the displacing assay

A 1 M solution of a compound to be tested in DMSO was prepared and diluted with 50% DMSO to obtain a 10-fold dilution series. The reaction was initiated by the addition of crude membrane specimen to solutions of different concentrations each containing [^{3}H]CCK-8 (final concentration, 1 nM). The mixture was incubated for 90 min at 25 °C, filtered through a glass filter with aspiration and washed with a cooled 50 mM Tris buffer. After the addition of Aquazol-2 cocktail, the radioactivity was counted. The same procedure was repeated using 50% DMSO solution or Ceruletide instead of a solution of test compound to obtain the control value regarding total binding or the value regarding non-specific binding, respectively.

Calculation of IC_{50}

The IC_{50} was determined by plotting the ratio (%) of specific binding of a test compound to that of the control on a semilogarithmic graph and obtaining the concentration corresponding to 50%: specific binding of control = total binding (cpm) − nonspecific binding (cpm) and specific binding of test compound = total binding (cpm) − nonspecific binding (cpm).

Acknowledgements

We gratefully acknowledge the valuable discussions with Dr Tadahiko Tsushima. We also thank Dr Masayuki Narisada (forrmer Director of the Laboratories) and Dr Hiroshi Harada and Dr Takashi Matsubara for their generous support.

References

1. (a) Allen, J. M.; Bishop, A. E.; Daly, M. J. *Gastroenterology* **1986**, *90*, 970. (b) Larsson, H.; Carlsson, E.; Mattsson, H.; Lundell. L.; Sundler, F.; Sundell, G.; Wallmark, B.; Watanabe, T.; Hakanson, R. *Gastroenterology* **1986**, *90*, 391.

2. For general reviews: (a) Makovec, F. *Drugs Future* **1993**, *18*, 919. (b) Kerwin Jr., J. F. *Drugs Future* **1991**, *16*, 1111. (c) Bock, M. G. *Drugs Future* **1991**, *16*, 631.

3. Poyner, D.; Pick, C. R.; Harcourt, R. A.; Selway, S. A. M.; Ainge, G.; Harman, I. W.; Spurling, N. W.; Fluck, P. A.; Cook, J. L. *Gut* **1985**, *26*, 1284.

4. Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E, O.; Goetz, M. A.; Albers-Schönberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science* **1985**, *230*, 177.

5. Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918.

6. Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.* **1989**, *32*, 13.

7. Bock, M. G.; DiPardo, R. M.; Mellin, E. C.; Newton, R. C.; Veber, D. F.; Freedman, S. B.; Smith, A. J.; Patel, S.; Kemp, J. A.; Marshall, G. R.; Fletcher, A. E.; Chapman, K. L.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.* **1994**, *37*, 722.

8. (a) Bertrand, P.; Böhme, G. A.; Durieux, C.; Guyon, C.; Capet, M.; Jeantaud, B.; Boudeau, P.; Ducos, B.; Padley, C. E.; Martin, G. E.; Floch, A.; Doble, A. *Eur. J. Pharmacol.* **1994**, *262*, 233. (b) Pendley, C. E.; Fitzpatrick, L. R.; Capolino, A. J.; Davis, M. A.; Esterline, N. J.; Jakubowska, A.; Bertrand, P.; Guyon, C.; Dubroucq, M.-C.; Martin, G. E. *Am. Soc. Pharmaco. Exp. Therap.* **1995**, *273*, 1015.

9. (a) Hughes, J.; Boden, P.; Costall, B.; Domeney, A.; Kelly, E.; Horwell, D. C.; Hunter, J. C.; Pinnock, R. D.; Woodruff, G. N. *Proc. Natl. Acad. Sci. U. S. A.* **1990**, *87*, 6728. (b) Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N. *J. Med. Chem.* **1991**, *34*, 404. (c) Hayward, N. J.; Harding, M.; Lloyd, S. C. A.; McKnight, A. T.; Hughes, J.; Woodruff, G. N. *Br. J. Pharmacol.* **1991**, *104*, 973.

10. (a) Satoh, M.; Kondoh, Y.; Okamoto, Y.; Nishida, A.; Miyata, K.; Ohta, M.; Mase, T.; Murase, K. *Chem. Pharm. Bull.* **1995**, *43*, 2159. (b) Nishida, A.; Miyata, K; Tsutsumi, R.; Yuki, H.; Akuzawa, S,; Kobayashi, A.; Kamato, T.; Ito, H.; Yamano, M.; Katuyama, Y.; Satoh, M; Ohta, M.; Honda, K. *J. Pharmacol. Exp. Therap.* **1994**, *264*, 725. (c) Nishida, A.; Uchida, A. K.; Akuzawa, S.; Takinami, Y.; Shishido, T.; Kamato, T.; Ito, H.; Yamano, M.; Yuki, H.; Nagakura, Y.; Honda, K.; Miyata, K. *Am. J. Physiol.* **1995**, *269*, G699.

11. (a) 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.* **1994**, *37*, 719. (b) Patel, S.; Smith, A. J.; Chapman, K. L.; Fletcher, A. E.; Kemp, J. A.; Marshall, G. R.; Hargreaves, R. J.; Ryecroft, W.; Iversen, L. L.; Iversen, S. D.; Baker, R.; Showell, G. A.; Bourrain, S.; Neduvelil, J. G.; Matassa, V. G.; Freeman, S. B. *Mol. Pharmacol.* **1994**, *46*, 943. (c) Showell G. A.; Bourrain, S.; Fletcher S. R.; Neduvelil, J. G.; Fletcher A. E.; Freedman S. B.; Patel S.; Smith, A.J.; Marshall, G. R.; Graham, M. I.; Sohal, B.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **1995**, *24*, 3023. (d) van Niel, M. B.; Freedman, S. B.; Matassa, V. G.; Patel, S.; Pengilley, R. R.; Smith, A. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1421. (e) Lowe, III, J. A.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R. T.; Zorn, S.; Morrone, J.; Appleton, T. A.; Lombardo, F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1933.

12. Walser, A.; Szente, A.; Hellerbach, J. *J. Org. Chem.* **1973**, *38*, 449.

13. Pincus, M. R.; Carty, R. P.; Chen, J.; Lubowsky, J.; Avitable, M.; Shah, D.; Scheraga, H. A.; Murphy, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 4821.

14. Kawanishi, Y.; Ishihara, S.; Tsushima, T.; Seno, K.; Miyagoshi, M.; Hagishita, S.; Ishikawa, M.; Shima, N.; Shimamura, M.; Ishihara, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1421.

15. Chambers, M. S.; Hobbs, S. C.; Fletcher, S. R.; Matassa, V. G.; Mitchell, P. J.; Watt, A. P.; Baker, R.; Freedman, S. B.; Patel, S.; Smith, A. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1919.

16. Hunziker, F.; Fischer, R.; Kipfer, P.; Schmutz, J.; Burki, H. R.; Eichenberger, E.; White, T. G. *Eur. J. Med. Chem.* **1981**, *16*, 391.

17. Nunn, A. J.; Schofield, K. *J. Chem. Soc.* **1953**, 716.

18. Hirai, K.; Ishiba, T.; Sugimoto, H.; Fujishita, T.; Tsukinoki, Y.; Hirose, K. *J. Med. Chem.* **1981**, *24*, 20.

19. Salituro, F. G.; Tomlinson, R. C.; Baron, B. M.; Palfreyman, M. G.; McDonald, I. A. *J. Med. Chem.* **1994**, *37*, 334.

20. Chang, R. S. L.; Lotti, V. J. *Proc. Natl. Acad. Sci. U. S. A.* **1986**, *83*, 4923.

21. Ghosh, M. N.; Schild, H. O. *Br. J. Pharmacol. Chemother.* **1958**, *13*, 54.

22. Dourish, C. T.; O'Neil, M. F.; Coughlan, J.; Kitchener, S. J.; Hawley, D.; Iversen, S. D. *Eur. J. Pharmacol.* **1990**, *176*, 35.

23. Lotti, V. J.; Chang, R. S. L. *Eur. J. Pharmacol.* **1989**, *162*, 273.

24. Kopin, A. S.; Lee, Y.-M.; McBride, E. W.; Miller, L. J.; Lu, MLin, H. Y.; Kolokowski, L. F.; Beinborn, M. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 3605.

25. Wank, S. A.; Pisegna, J. R.; de Weerth, A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 8691.

(*Received in Japan* 12 *March* 1997; *accepted* 30 *April* 1997)