Synthesis and Structure–Activity Relationships of 4-Amino-5-chloro-2-ethoxybenzamides with Six- and Seven-Membered Heteroalicycles as Potential Gastroprokinetic Agents[1)]

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A new series of 4-amino-5-chloro-2-ethoxybenzamides 3b—f and 5—8 bearing six- and seven-membered heteroalicycles was prepared and evaluated for gastroprokinetic activity. Compounds 3b—e, derived by replacement of the morpholine oxygen of 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-ethoxybenzamide (3a) with other atoms (sulfur, nitrogen and carbon), generally exhibited a potent gastric emptying activity. *N*-(4-Benzyl-3-morpholinyl)methylbenzamide (5a) and its analogues 5b—e had weaker activity. However, *N*-(4-benzyl-3-morpholinyl)ethylbenzamide 8 was as potent as 3a. Benzamides 6a—e, having seven-membered heteroalicycles, showed fairly potent activity.

Molecular superimpositions of 5a, 6a and 8 upon 3a using computer graphics suggested that the direction of the *N*-benzyl group greatly influences the gastric emptying activity, whereas the location of the alicyclic nitrogen is less critical.

Key words 4-amino-5-chloro-2-ethoxybenzamide; gastroprokinetic activity; molecular superimposition; mosapride; gastric emptying; structure–activity relationship

Metoclopramide (**1**)[2)] and cisapride (**2**)[3)] are used clinically as gastroprokinetic agents. Their gastroprokinetic action is accepted to be due to agonistic activity at a new serotonin receptor subtype (5-HT_4).[4)] These agents, however, concurrently have dopamine D_2 receptor antagonistic activity, which is responsible for unfavorable side effects such as extrapyramidal symptoms and central nervous system depression.

A series of *N*-(2-morpholinylmethyl)benzamides typified by 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-ethoxybenzamide (**3a**) had previously been prepared with the aim of finding potent gastroprokinetic agents without dopamine D_2 receptor antagonistic activity.[5)] Modifications of the benzoyl[1)] and 4-benzyl groups[6,7)] of the morpholine ring of **3a** led to the discovery of mosapride (**4a**, 4-amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide) as a promising candidate for a selective and potent gastroprokinetic agent. Mosapride, which is currently under clinical evaluation, is superior to metoclopramide (**1**) and essentially equipotent to cisapride (**2**) in gastroprokinetic activity in rats. In addition, it is free from dopamine D_2 receptor an-

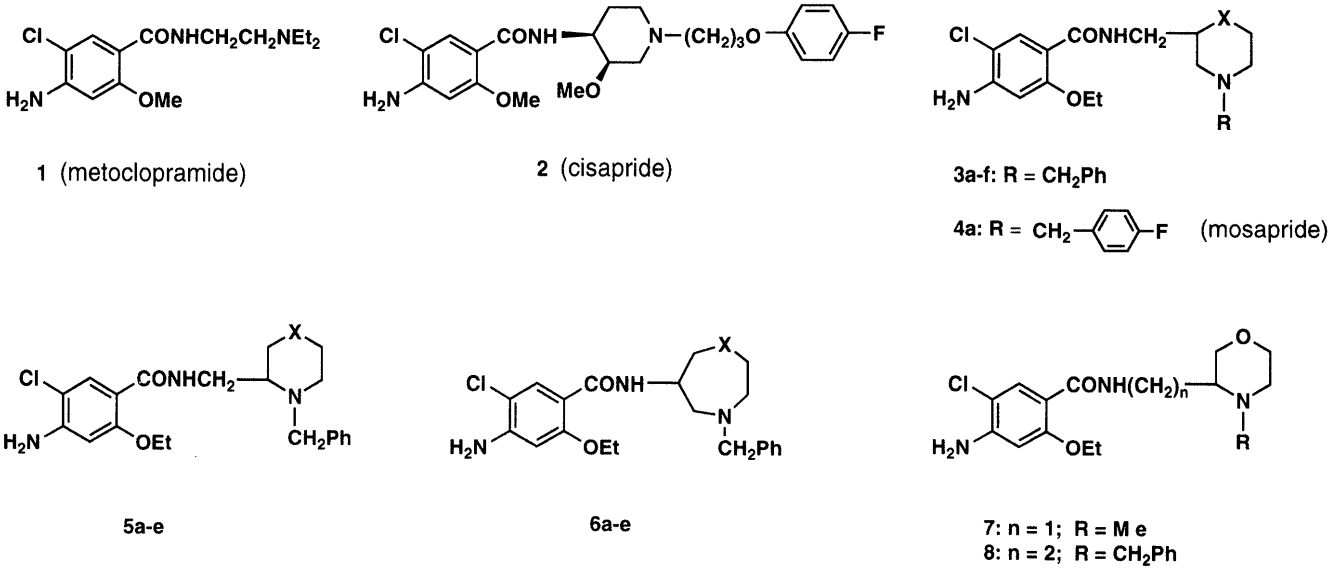

Chart 1

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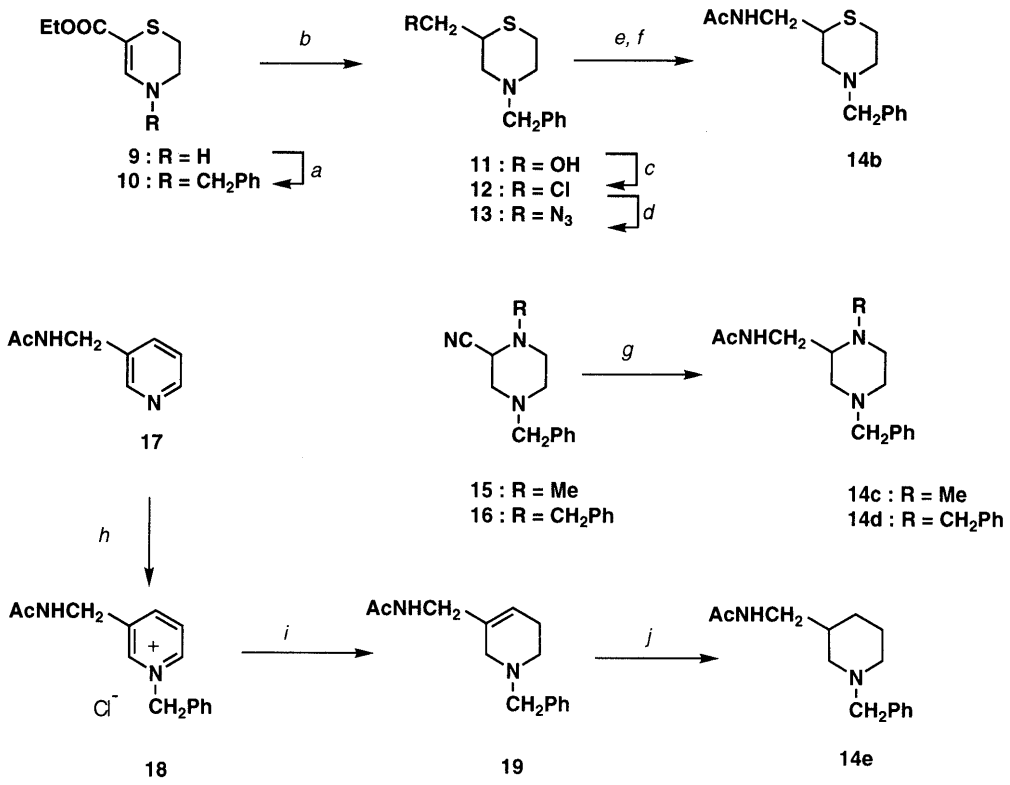
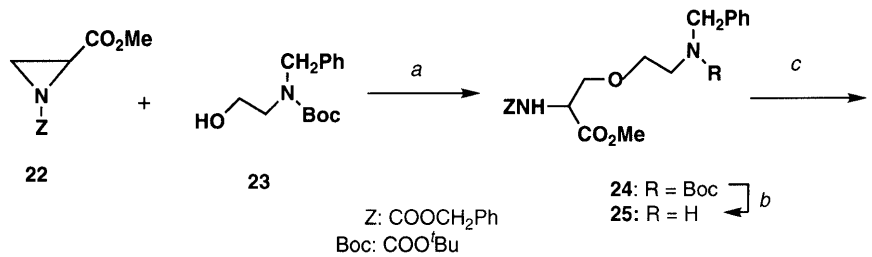
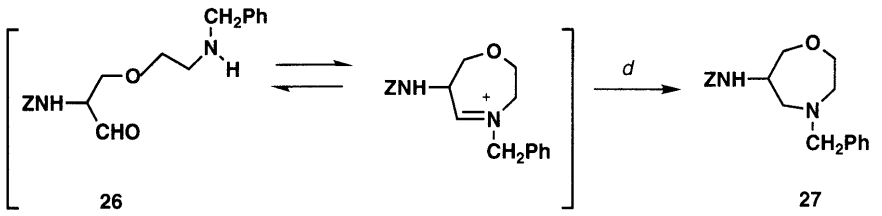


Reagents: *a* $PhCH_2Br$, NaH; *b* $LiAlH_4$; *c* $SOCl_2$; *d* NaN_3; *e* $Na[AlH_2(OCH_2CH_2OCH_3)_2]$; *f* Ac_2O; *g* H_2, Raney Ni, Ac_2O; *h* $PhCH_2Cl$; *i* $NaBH_4$; *j* H_2, Pd-C.

Chart 2

a: X = O; b: X = S; c: X = NMe; d: X = NCH_2Ph; e : X = CH_2





Reagents: *a* BF_3-Et_2O, $CHCl_3$; *b* HCl-MeOH; *c* DIBAH, toluene; *d* $NaBH_4$, MeOH.

Chart 3

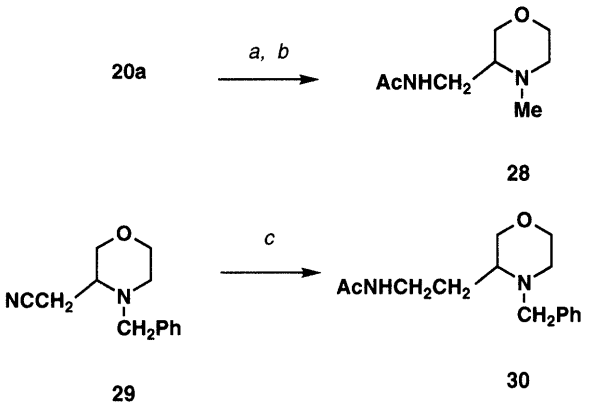
tagonistic activity.[8,9]

In order to study further the relationship between chemical structure and gastroprokinetic activity, we designed the new benzamide derivatives **3b—f** and **5—8** having various six- and seven-membered heteroalicycles containing at least one nitrogen atom. This paper describes the synthesis of **3b—f** and **5—8** and their structure–activity relationships (SARs) for gastroprokinetic activity.

Chemistry

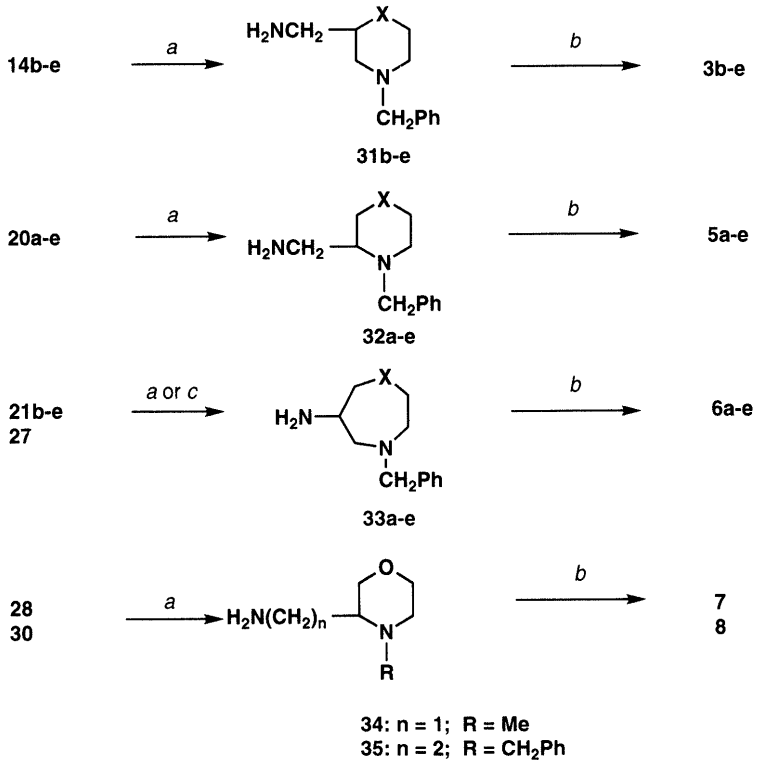
The requisite cyclic amines for the synthesis of the targeted benzamides were prepared by the methods depicted in Charts 2—4. The treatment of ethyl 5,6-dihydro-4*H*-1,4-thiazine-2-carboxylate (**9**)[10] with benzyl bromide in the presence of sodium hydride gave the *N*-benzyl derivative **10**. Reduction of **10** with lithium aluminum hydride, followed by chlorination of the resultant 2-hydroxymethyl derivative **11** with thionyl chloride, gave 4-benzyl-2-(chloromethyl)-3,4,5,6-tetrahydro-2*H*-1,4-thiazine (**12**). The reaction of **12** with sodium azide afforded the azide **13**, which was reduced with sodium bis-(2-methoxyethoxy)aluminum hydride, followed by acetylation with Ac_2O, thus affording *N*-(4-benzyl-3,4,5,6-tetrahydro-2*H*-1,4-thiazin-2-yl)methylacetamide (**14b**). 4-Benzyl-1-methyl-2-piperazinecarbonitrile (**15**)[11] and 1,4-dibenzyl-2-piperazinecarbonitrile (**16**)[11] were hydrogenated over Raney Ni in Ac_2O to yield *N*-(piperazin-2-yl)methylacetamide derivatives **14c** and **14d**, respectively. Treatment of **17**[12] with benzyl chloride, followed by reduction of the resultant 1-benzylpyridinium chloride **18** with sodium borohydride, produced *N*-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)methylacetamide (**19**). Hydrogenation of **19** over palladium-on-carbon gave the piperidine derivative **14e** (Chart 2).

The synthesis of *N*-(4-benzylmorpholin-3-yl)methylacetamide (**20a**), *N*-(4-benzyl-2,3,4,5,6,7-hexahydro-1,4-oxazepin-6-yl)acetamide (**21a**), and their analogs **20b—e** and **21b—e** was reported in our previous paper (Chart 3).[13] For **21a**, however, the yield by the reported method was low and the procedure was tedious. Therefore, we developed an alternative synthesis of **21a** from the



Reagents: *a* H_2, Pd-C; *b* HCHO, $NaBH_4$; *c* H_2, Raney Ni, Ac_2O.

Chart 4



a: X = O; b: X = S; c: X = NMe; d: X = NCH_2Ph; e: X = CH_2

Reagents: *a* 10% HCl; *b* 4-amino-5-chloro-2-ethoxybenzoic acid, Et-N=C=N-$(CH_2)_3NMe_2$· HCl; *c* $MeSO_3H$, anisole, $CHCl_3$.

Chart 5

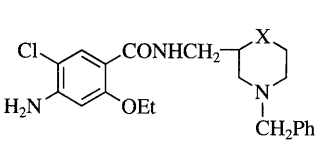
known methyl 1-benzyloxycarbonyl-2-aziridinecarboxylate (**22**)[14] (Chart 3). The treatment of **22** with 2-(*N*-benzyl-*N*-*tert*-butoxycarbonyl)aminoethanol (**23**) in the presence of BF_3–Et_2O gave methyl 2-(benzyloxycarbonyl)amino-3-[2-(*N*-benzyl-*N*-*tert*-butoxycarbonyl)aminoethyl]oxypropionate (**24**). Removal of the *tert*-butoxycarbonyl group of **24** with HCl–MeOH afforded the amino ester **25**. Partial reduction of **25** with diisobutylaluminum hydride at −70 °C, followed by reductive cyclization of the resulting aminoaldehyde **26** without isolation furnished the hexahydro-1,4-oxazepine **27** *via* the iminium salt of **26**.

The morpholine **20a** was subjected successively to hydrogenolysis and methylation, affording *N*-(4-methylmorpholin-3-yl)methylacetamide (**28**) (Chart 4). Hydrogenation of (4-benzylmorpholin-3-yl)acetonitrile (**29**)[15] gave *N*-[2-(4-benzylmorpholin-3-yl)ethyl]acetamide (**30**).

The acetamides **14**, **20**, **21**, **27**, **28** and **30** thus prepared were converted into the corresponding amines **31**—**35** by acidic hydrolysis (Chart 5). Finally, the reactions of **31**—**35** with 4-amino-5-chloro-2-ethoxybenzoic acid[6] in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride afforded the corresponding benzamides **3b**—**e** and **5**—**8** (Table 1). Oxidation of **3b** with equimolar *m*-chloroperbenzoic acid (*m*-CPBA) gave the sulfoxide **3f**.

X-Ray Crystallographic Study Mosapride (**4a**) was subjected to single-crystal X-ray analysis, to determine its solid-state conformation. The crystal structure was solved by standard methods.[16] The ORTEP drawing and stereo view of the structure of **4a** (as the monohydrate) are shown in Figs. 1 and 2, respectively. The characteristic structural features are as follows. a) Intramolecular hydrogen bonding was observed between O(1) and H(5) with a distance of 1.95(3) Å. The O(1)···H(5)–N(2) angle is 139(2)°. b) The morpholine ring is in a chair conformation. c) The torsion angles of N(2)–C(8)–C(9)–C(10), C(8)–C(9)–C(10)–N(3), C(9)–C(10)–N(3)–C(13) and C(10)–

Table 1. Physicochemical Data for 4-Amino-5-chloro-2-ethoxybenzamides **3** and **5**—**8**



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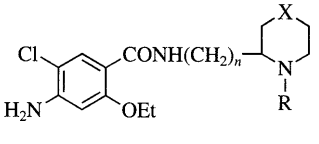
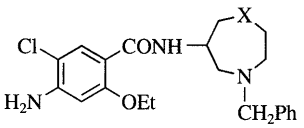


5, 7, 8



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Compd.	X	R	*n*	mp (°C) Recryst. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	Cl	N	S
3b	S	—	—	133—135 MeOH	67	$C_{21}H_{26}ClN_3O_2S \cdot 1/4H_2O$	59.42 (59.60	6.29 6.20	8.35 8.52	9.90 9.81	7.55 7.63)
3c	NMe	—	—	188—190 EtOH	78	$C_{22}H_{29}ClN_4O_2 \cdot C_4H_4O_4$[b]	58.59 (58.58	6.24 6.44	6.65 6.46	10.51 10.36)	
3d	NCH_2Ph	—	—	98—102 EtOH–Et_2O	47	$C_{28}H_{33}ClN_4O_2 \cdot C_2H_2O_4$[c] $\cdot H_2O$	59.95 (60.03	6.20 5.91	5.90 5.84	9.32 9.08)	
3e	CH_2	—	—	103—105 EtOH	64	$C_{22}H_{28}ClN_3O_2 \cdot C_2H_2O_4$[c]	65.74 (65.70	7.02 7.00	8.82 8.65	10.45 10.47)	
3f[d]	SO	—	—	193—195 iso-PrOH	29[e]	$C_{21}H_{26}ClN_3O_3S \cdot 1/4H_2O$	57.85 (57.65	6.01 6.06	8.13 8.23	9.64 9.41	7.35 7.05)
5a	O	CH_2Ph	1	90—92 EtOH–Et_2O	86	$C_{21}H_{26}ClN_3O_3 \cdot 1/2H_2O$	58.86 (58.93	6.06 6.15	7.90 7.59	9.36 9.32)	
5b	S	CH_2Ph	1	138—140 EtOH	74	$C_{21}H_{26}ClN_3O_2S$	60.06 (59.85	6.24 6.16	8.44 8.51	10.01 9.73	7.63 7.79)
5c	NMe	CH_2Ph	1	199—201 EtOH	81	$C_{22}H_{29}ClN_4O_2$	63.37 (63.30	7.01 7.10	8.50 8.58	13.44 13.44)	
5e	CH_2	CH_2Ph	1	164—166 EtOH	88	$C_{22}H_{28}ClN_3O_2$	65.74 (65.48	7.02 7.07	8.82 9.05	10.45 10.23)	
6a	O	—	—	137—138 EtOH	75	$C_{21}H_{26}ClN_3O_3 \cdot C_4H_4O_4$[b]	57.75 (57.56	5.82 5.89	6.82 6.79	8.08 8.03)	
6b	S	—	—	155—157 Acetone	77	$C_{21}H_{26}ClN_3O_2S \cdot C_4H_4O_4$[b]	56.02 (55.91	5.64 5.74	6.61 6.59	7.84 7.92	5.98 5.73)
6c	NMe	—	—	199—201 EtOH–Et_2O	78	$C_{22}H_{29}ClN_4O_2 \cdot 3/2C_4H_4O_4$[b]	56.90 (56.90	5.97 6.19	6.00 6.12	9.48 9.68)	
6d	NCH_2Ph	—	—	135—137 EtOH	79	$C_{28}H_{33}ClN_4O_2 \cdot 1/4H_2O$	67.59 (67.64	6.79 6.71	7.13 7.11	11.26 11.30)	
6e	CH_2	—	—	174—176 EtOH	83	$C_{22}H_{28}ClN_3O_2 \cdot C_4H_4O_4$[b]	60.29 (60.14	6.23 6.39	6.84 6.63	8.11 7.88)	
7	O	Me	1	157—160 EtOH–Et_2O	56	$C_{15}H_{22}ClN_3O_3$	54.96 (54.78	6.76 6.55	12.82 12.52	10.82 11.06)	
8	O	CH_2Ph	2	165—167 EtOH	75	$C_{22}H_{28}ClN_3O_3$	63.23 (62.98	6.75 6.75	8.48 8.55	10.05 9.94)	

a) Yields are based on the corresponding acetylamino derivatives unless otherwise specified. *b*) Fumaric acid. *c*) Oxalic acid. *d*) A mixture of diastereomers. *e*) Yield is based on **3b**.

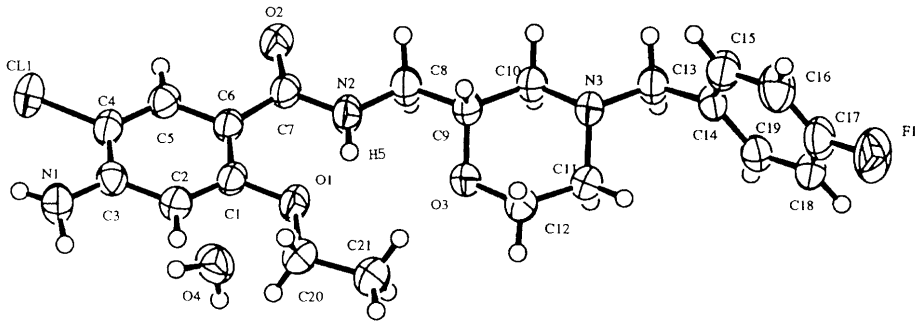

Fig. 1. An ORTEP Drawing of Mosapride **4a** (as the Monohydrate)

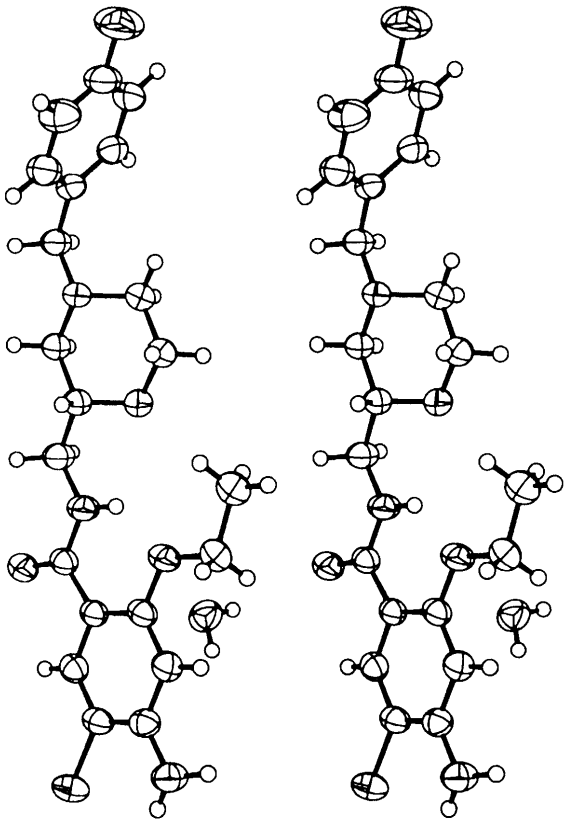

Fig. 2. Stereoscopic Drawing of Mosapride **4a** (as the Monohydrate)

N(3)–C(13)–C(14) are nearly equal to 180°.

Molecular Modeling Study Four compounds, **3a**, **5a**, **6a** and **8** (Chart 6), were selected for the molecular modeling study. We hoped that their geometric features would provide useful information for understanding the SARs of this class of compounds.

The geometry of compound **3a** was depicted on the basis of the X-ray crystal structure of mosapride (**4a**). Geometry optimization for **3a** was conducted by the AM1[17] method of MOPAC[18] to seek stable conformations. Molecular models for **5a**, **6a** and **8** were built up using three-dimensional fragments (*i.e.*, the 4-amino-5-chloro-2-ethoxybenzamide moiety and/or the *N*-benzyl morpholine group) of the X-ray crystal structure of **4a**. The conformational analysis was initially carried out with the Tripos force field[19] to find the conformations with local energy minima which have a similar shape to those of the template molecule **3a**. Further refinement was performed using the MOPAC/AM1 method for selected low-energy conformers with full geometry optimization. Details of the model building are given in Experimental.

Biological Results and Discussion

Compounds **3b**—**f**, **5a**—**e**, **6a**—**e**, **7** and **8** were evaluated for gastroprokinetic activity by determining their effects on the gastric emptying rate of a phenol red semisolid meal at an oral dose of 2.0 mg/kg in rats. The results are shown in Table 2, which includes, for comparison, the activities of metoclopramide (**1**), cisapride (**2**), 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-ethoxybenzamide (**3a**) and mosapride (**4a**).

First we examined the effect of replacement of the morpholine oxygen of **3a** by other atoms (X = S, N and C). The 1,4-thiazine derivative **3b** with a bioisosteric sulfur atom was less potent than the parent compound **3a** in terms of the % change. Oxidation of the sulfur atom of **3b** (yielding the sulfoxide **3f**) resulted in a considerable decrease in gastric emptying activity. The activity of **3f**, however, was almost equal to that of metoclopramide **1**. The *N*-methyl analogue **3c** exhibited the most potent activity among the series and was essentially equipotent to mosapride **4a**, whereas the *N*-benzyl analogue **3d** bearing rather a bulky group at position 4 was less potent than **3a**. Replacement of the morpholine oxygen atom of **3a** by a methylene group, yielding the piperidine derivative **3e**, retained the same level of activity as that of **3a**. Variation of X, as a whole, caused a decrease in activity in the order **4a** (mosapride) $\geq$ **3c** (N–Me) > **3e** (CH_2) $\geq$ **3a** (O) > **2** (cisapride) $\geq$ **3b** (S) > **3d** (N–CH_2Ph) $\gg$ **3f** (SO) $\geq$ **1** (metoclopramide). Even the least potent compound **3f** in this series is equipotent to **1** in terms of the % change. The SAR study of X on **3** revealed that the morpholine ring oxygen is not essential for the activity, and that a bulky group on the heteroalicycles has a detrimental influence on activity.

Compounds **5a**—**e**, in which the six-membered heteroalicycles are linked to the benzamide moiety at a different site from that in **3a**—**e**, were much less potent than compounds **3a**—**e**, except for the piperazine derivative **5c**, which showed a comparable activity to that of **1**. Variation of X influences the activity in the decreasing order **1** = **5c** (N–Me) > **5b** (S) > **5a** (O) > **5e** (CH_2).

The benzamides **6a**—**e**, substituted by novel seven-membered heteroalicycles were, in general, much more potent than **1**, but somewhat less potent than **2**. Replacement of the oxygen atom of **6a** by other atoms or groups had less influence on the gastric emptying activity.

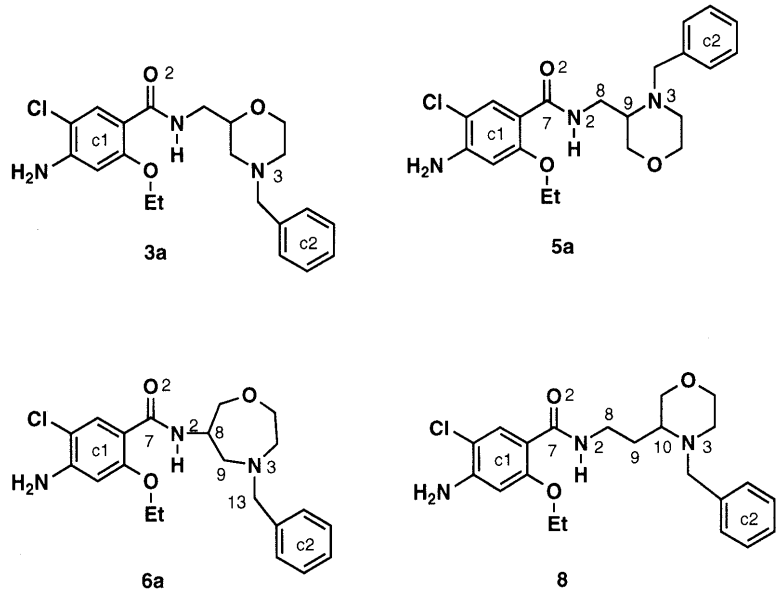

Chart 6. Structures of Compounds Selected for Molecular Modeling Studies

The atom numbering adopted for the conformational search is arbitrary. The abbreviations c1 and c2 denote the center of the phenyl rings.

Table 2. Effect of 4-Amino-5-chloro-2-ethoxybenzamides **3** and **5**—**8** on Gastric Emptying of Phenol Red Semisolid Meal in Rats

Compound	Gastric emptying rate (%)		
	Control Mean±S.E.M. (N^{b})	2.0 mg/kg, *p.o.* Mean±S.E.M. (N^{b})	% change[a]
3a	51.5±3.1 (5)	79.5±3.7 (4)	54**
3b	50.3±2.7 (5)	73.4±1.2 (4)	46**
3c	49.9±6.3 (5)	79.1±7.2 (4)	59**
3d	52.4±1.8 (5)	71.1±2.7 (4)	36**
3e	50.2±3.4 (5)	77.6±2.1 (4)	55**
3f	55.3±4.7 (5)	67.2±3.8 (4)	22
5a	54.1±3.4 (5)	59.6±5.8 (4)	10
5b	54.1±3.4 (5)	62.8±2.0 (4)	16
5c	62.6±2.0 (5)	75.6±2.7 (4)	21*
5e	52.8±7.0 (5)	56.3±5.2 (4)	7
6a	54.8±6.1 (4)	77.0±1.9 (4)	41**
6b	50.8±2.9 (5)	69.2±1.7 (4)	36**
6c	54.2±2.8 (5)	76.1±1.5 (4)	40**
6d	54.8±6.1 (4)	78.3±1.6 (4)	43**
6e	52.8±7.0 (5)	76.7±5.5 (4)	45**
7	51.9±5.7 (4)	70.9±8.7 (4)	37*
8	54.8±2.5 (7)	81.9±5.4 (4)	50**
Metoclopramide (**1**)	58.9±2.1 (5)	71.3±3.8 (5)	21*
Cisapride (**2**)	55.2±1.9 (5)	81.3±1.2 (5)	47**
Mosapride (**4a**)	51.8±2.1 (5)	83.6±2.4 (4)	61**

a) The asterisks indicate a statistically significant difference from the control group; *, $p<0.05$; **, $p<0.01$ (Duncan's multiple range test). *b*) Number of rats used.

Introduction of a bulky *N*-benzyl group (**6d**) caused no change in activity. The decreasing order of activity, in summary, is **2**≥**6e** (CH_2)≥**6d** (N–CH_2Ph)≥**6a** (O)≥**6c** (N–Me)≥**6b** (S)≫**1**.

In general, among the three types of isomers (**3**, **5** and **6**), the decreasing order of activity is **3**>cisapride≥**6**≫metoclopramide>**5**.

We have previously reported that replacement of the *N*-benzyl group of **3a** by an *N*-methyl group resulted in a decrease in activity.[7] An interest in such modification of the 3-morpholinyl benzamide **5a** led us to prepare the (4-methyl-3-morpholinyl)methylbenzamide **7**. Compound **7** was found to be much more potent than **5a**, in contrast to the 2-morpholinyl series **3a**.

Insertion of an additional carbon chain at position 3 of the morpholine ring of **5a** (thus forming a three-carbon chain between the amide nitrogen and the alicyclic nitrogen, giving **8**) caused a remarkable increase in the activity: the activity of **8** is close to that of **3a**. It is of interest to note that, in the series of 2-morpholinyl congeners **3a**, lengthening the carbon chain led to reduced activity, as reported previously.[5] In connection with this, there have been reports on SAR studies on the carbon chain length of a similar series of benzamides substituted by piperidine, quinolizidine and pyrrolizidine.[20] It was stated that, in a comparison between the three-carbon chain and the two-carbon chain to link the amide nitrogen and the alicyclic nitrogen, the former was preferable to the latter for enhancing the activity. Our findings with the morpholinyl benzamides **3a**, **5a** and **8** are in line with this precedent. Thus, **3a** and **8** having the three-carbon chain were far more active than **5a** having the two-carbon chain. Interestingly, the benzamide **6a** substituted with the seven-membered ring was much more potent than **5a**, although both compounds included the two-carbon chain between the benzamide nitrogen and the alicyclic nitrogen.

In order to get further insight into SARs of compounds **3a**, **5a**, **6a** and **8** their three-dimensional structures were examined by computer-assisted superimposition. Figures 3 to 5 show the structural features of compounds **5a**, **6a** and **8**, respectively, superposed upon **3a**.

The distances between the points O2–N3, c1–N3, O2–c2 and c1–c2 as values specifying the geometric features of **3a**, **5a**, **6a** and **8** were measured and are listed in Table 3. The four points, O2, N3, c1 and c2 (Chart 6), were selected on the assumption that these points are involved in the molecular interaction with the receptor. The lowest root mean square (RMS) values and the corresponding intersection volume values for the least-square fit of compounds **5a**, **6a** and **8** upon **3a** are given in Table 4. The

Table 3. Distances between O2–N3,[a] c1–N3, O2–c2 and c1–c2 for Minimized-Energy Conformations of **3a**, **5a**, **6a** and **8**

Compd.	Distances (Å)			
	O2–N3	c1–N3	O2–c2	c1–c2
3a	6.13	8.39	9.77	11.96
5a	5.05	7.56	7.13	10.33
6a	4.93	6.78	8.35	9.98
8	6.56	8.15	9.79	11.47

a) See Chart 6 for atom labeling.

Table 4. RMS and Intersection Volume Values for the Superimposition of **5a**, **6a** and **8** upon **3a**

Compound	RMS[a] (Å)	Intersection volume[b] (Å^3)
5a	1.012	201.3
6a	0.763	235.9
8	0.432	252.6

a) RMS means the root-mean-square distance. *b*) Van der Waals volume of compound **3a** is 388.8 Å^3.

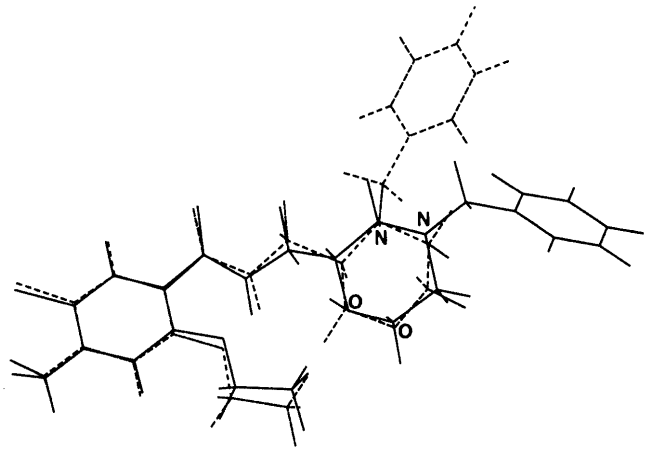

Fig. 3. Superimposition of **3a** (Solid Line) and **5a** (Dotted Line)

RMS and intersection volume values, indicating the degree of overlap, have a close relation to the overall molecular similarity.

In the case of **3a** and **5a** (Fig. 3), their respective morpholine ring nitrogens as well as their *N*-benzyl groups can never overlap each other. In particular, the *N*-benzyl groups extend in quite different directions. In accordance with these observations, every distance, O2–N3, c1–N3, O2–c2 and c1–c2, of **5a** (Table 3) is significantly different from that of **3a**. The RMS and intersection volume values for **5a** *versus* **3a** also show a poor fit between the compounds. The alicyclic nitrogen and the *N*-benzyl group of **6a** do not overlap the counterparts in **3a** (Fig. 4). This situation reflects the difference in distances between the points of **3a** and **6a** (Table 3). The *N*-benzyl group of **6a**, however, extends in the same direction as that of **3a**; this is different from the case of **5a**. The RMS and intersection volume values of **6a** indicate a better fit of **6a** than **5a** to **3a**.

Judging from these observations and the fact that the methyl analogue **7** of **5a** shows relatively potent activity

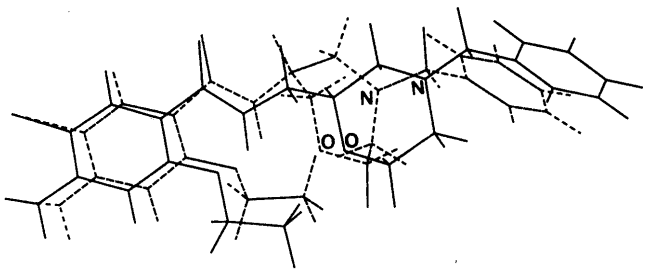

Fig. 4. Superimposition of **3a** (Solid Line) and **6a** (Dotted Line)

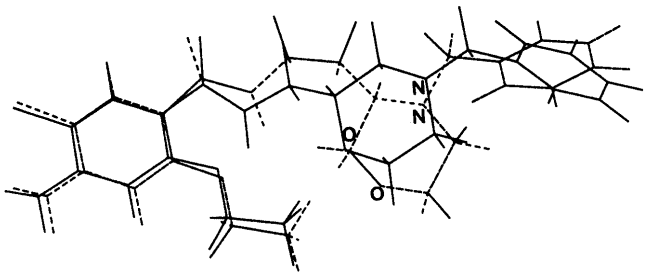

Fig. 5. Superimposition of **3a** (Solid Line) and **8** (Dotted Line)

(37% change), the reason why **5a** is far less active (10% change) may be an unfavorable location of its bulky *N*-benzyl group, which would hinder **5a** from binding to the receptor. In the case of **6a**, the *N*-benzyl group may occupy a position that is still favorable to the binding, so that **6a** shows a rather potent activity (41% change), despite being less active than **3a** (54% change).

The overall spatial structures of **3a** and **8** rather resemble each other (Fig. 5); their respective alicyclic nitrogens are near in space, and the *N*-benzyl groups are located in the same region. This situation is consistent with the fact that all distances between the points of **8** are very similar to those of the structure **3a**. The RMS and intersection volume values of **8** also show a good superimposition of **8** upon **3a**. This may account for the finding that **3a** and **8** displayed almost the same activity (54 and 50% change, respectively).

Thus, the superimposition study suggests that the spatial requirement of the binding site relevant to the alicyclic nitrogen is not so strict, whereas similarity of the direction of the benzyl group and/or the whole molecular shape is crucial for the activity.

In vitro dopamine D_2 receptor antagonism was determined with the [^{3}H]spiperone binding test. Compounds **3** and **5**—**8** showed no affinity at the concentration of 10^{-6} M for the dopamine D_2 binding site in rat brain synaptic membranes.

In summary, some compounds related to mosapride (**4a**), represented generically by **3** and **6**, showed more potent gastric emptying activity than metoclopramide (**1**). The 3-morpholinylmethylbenzamide **5a** and its analogues **5b**—**e** were less potent than the corresponding 2-morpholinyl regioisomers. On the other hand, the 3-morpholinylethylbenzamide **8**, which had one more methylene as compared with **5a**, displayed the same level of activity as that of **3a**. Superimposition of the minimized-energy structures of **5a**, **6a** and **8** upon that of **3a** suggests that the direction of the *N*-benzyl group and/or the whole molecular shape greatly influences the activity,

whereas the position of the alicyclic nitrogen is less important. Further biological evaluation of compounds **3**, **6**, and **8** is in progress.

Experimental

Chemistry All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer and electron-impact mass (EIMS) spectra on a JEOL JMS D-300 spectrometer. ^{1}H-NMR spectra were taken at 80 MHz with a Varian FT-80A spectrometer and at 200 MHz with a Varian Gemini-200 spectrometer in $CDCl_3$. Chemical shifts are expressed as δ (ppm) values with tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz (Hz). The extract was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Merck Kieselgel 60 was used for column chromatography.

***N*-(4-Benzyl-3,4,5,6-tetrahydro-2*H*-1,4-thiazin-2-yl)methylacetamide (14b)** Compound **9**[10] (32.1 g, 0.185 mol) was added at room temperature to a stirred suspension of 60% NaH (8.1 g, 0.2 mol) in tetrahydrofuran (THF, 330 ml). The mixture was stirred at the same temperature for 30 min, then benzyl bromide (31.7 g, 0.185 mol) was added. The reaction mixture was stirred at room temperature for an additional 3 h and then concentrated to dryness. The residue was diluted with water and extracted with ethyl acetate (AcOEt). The extract was dried and concentrated to dryness to give an oil, which was chromatographed on silica gel to afford 46.0 g (94%) of ethyl 4-benzyl-5,6-dihydro-4*H*-1,4-thiazine-2-carboxylate (**10**) as an oil. IR (neat): 1670 (COOEt) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.30 (3H, t, J=7, $CO_2CH_2CH_3$), 2.78—2.88 (2H, m, 5-H), 3.37—3.45 (2H, m, 6-H), 4.21 (2H, q, J=7, $CO_2CH_2CH_3$), 4.35 (2H, s, CH_2Ph), 7.20—7.42 (5H, s, CH_2Ph), 7.72 (1H, s, 3-H).

A solution of **10** (25 g, 0.095 mol) in anhydrous THF (50 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (7.2 g, 0.19 mol) in anhydrous THF (200 ml) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The excess of lithium aluminum hydride was decomposed by successive addition of AcOEt and water. The insoluble materials were removed by filtration. The filtrate was concentrated to dryness to give an oil, which was chromatographed on silica gel to give 5.8 g (27%) of 4-benzyl-3,4,5,6-tetrahydro-2*H*-1,4-thiazin-2-ylmethanol (**11**) as an oil. ^{1}H-NMR (200 MHz) δ: 2.45—3.10 (8H, m), 3.46 (1H, d, J=13, CH_2Ph), 3.54 (1H, d, J=13, CH_2Ph), 3.82 (1H, m, CH_2OH), 3.95 (1H, m, CH_2OH), 7.20—7.40 (5H, m, CH_2Ph). EIMS m/z: 223 (M^+).

A mixture of **11** (10.6 g, 48 mmol) and thionyl chloride (11.0 g, 92 mmol) in $CHCl_3$ (100 ml) was heated to reflux for 20 min. The reaction mixture was concentrated to dryness and the residue was extracted with $CHCl_3$. The extract was washed with saturated aqueous $NaHCO_3$, dried and concentrated to give **12** as an oil. ^{1}H-NMR (200 MHz) δ: 2.48—3.04 (7H, m), 3.53 (2H, s, CH_2Ph), 3.72 (1H, dd, J=10, 5, CH_2Cl), 3.93 (1H, dd, J=10, 7, CH_2Cl), 7.20—7.38 (5H, m, CHPh).

A mixture of **12**, NaN_3 (3.7 g, 57 mmol) and MeCN (100 ml) was heated to reflux for 2 h. The reaction mixture was filtered, and the filtrate was concentrated to dryness to give 7.0 g (59%) of 2-(azidomethyl)-4-benzyl-3,4,5,6-tetrahydro-2*H*-1,4-thiazine (**13**) as an oil. IR (neat): 2100 (N_3) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 2.55—3.01 (7H, m), 3.52 (2H, s, CH_2Ph), 3.46—3.66 (2H, m, CH_2N_3), 7.20—7.39 (5H, m, CH_2Ph). EIMS m/z: 248 (M^+).

Sodium bis(2-methoxyethoxy)aluminum hydride (16.0 g of 70% solution in toluene) was added to a mixture of **13** (7.0 g, 28 mmol) and toluene (70 ml) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The excess reagent was decomposed with water at 0 °C, then 48% NaOH was added, and the organic layer was separated, dried, and concentrated to dryness. The residue was dissolved in 100 ml of $CHCl_3$, and Ac_2O (5.7 g, 56 mmol) was added. The reaction mixture was stirred for 1 h and then washed successively with 48% NaOH and water. The organic layer was dried and concentrated to dryness to leave a crude product, which was chromatographed on silica gel to give 5.8 g (78%) of **14b** as an oil. IR (neat): 1645 (CONH) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.88 (3H, s, $COCH_3$), 2.48—2.96 (7H, m), 3.41 (1H, d, J=13, CH_2Ph), 3.55 (1H, d, J=13, CH_2Ph), 3.88—3.60 (2H, m, CH_2NHAc), 5.66 (1H, br s, CONH), 7.22—7.38 (5H, s, CH_2Ph). EIMS m/z: 264 (M^+). *Anal.* Calcd for $C_{14}H_{20}N_2OS \cdot H_2O$: C, 59.54; H, 7.85; N, 9.92; S, 11.35. Found: C, 59.32; H, 7.65; N, 9.71; S, 11.33.

***N*-(4-Benzyl-1-methylpiperazin-2-yl)methylacetamide (14c)** A solution of 4-benzyl-1-methyl-2-piperazinecarbonitrile (**15**[11]; 16.9 g, 78.6 mmol) in Ac_2O (150 ml) was hydrogenated over Raney Ni (3 g) at room temperature. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration. The filtrate was concentrated to dryness to give an oil, which was chromatographed on silica gel to afford 10.0 g (49%) of **14c**, mp 102—105 °C (Et_2O). ^{1}H-NMR (200 MHz) δ: 1.98 (3H, s, $COCH_3$), 2.05—2.25 (2H, m), 2.30 (3H, s, NCH_3), 2.30—2.50 (2H, m), 2.64—2.85 (3H, m), 3.30—3.40 (2H, m, CH_2NHAc), 3.47 (2H, s, CH_2Ph), 6.17 (1H, br s, CONH), 7.18—7.42 (5H, m, CH_2Ph). EIMS m/z: 261 (M^+). *Anal.* Calcd for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 68.93; H, 9.03; N, 16.35.

***N*-(1,4-Dibenzylpiperazin-2-yl)methylacetamide (14d)** According to the same procedure as described above, 1,4-dibenzyl-2-piperazinecarbonitrile (**16**[11]; 8.0 g, 24 mmol) was converted to 3.7 g (53%) of **14d** as an oil. IR (neat): 1640 (CONH) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.94 (3H, s, $COCH_3$), 2.25—2.90 (7H, m), 3.30—3.60 (2H, m), 3.40 (1H, d, J=14, CH_2Ph), 3.95 (1H, d, J=14, CH_2Ph), 3.50 (2H, s, CH_2Ph), 6.32 (1H, br s, NHAc), 7.22—7.41 (10H, m, CH_2Ph). EIMS m/z: 337 (M^+). *Anal.* Calcd for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.06; N, 12.45. Found: C, 74.50; H, 7.85; N, 12.30.

***N*-(1-Benzylpiperidin-3-yl)methylacetamide (14e)** A mixture of **17**[12] (6.8 g, 45 mmol), benzyl chloride (5.7 g, 45 mmol) and toluene (30 ml) was heated to reflux for 6 h. The resultant precipitate was collected by filtration to give 10.0 g (80%) of **18**, mp 196—198 °C (toluene). ^{1}H-NMR (80 MHz) δ: 1.92 (3H, s, $COCH_3$), 4.34 (2H, d, J=5, CH_2NHAc), 5.90 (2H, s, CH_2Ph), 7.38—7.63 (5H, m, CH_2Ph), 8.13 (1H, dd, J=8, 6, 5-H), 8.49 (1H, d, J=8, 4-H), 8.87 (1H, m, NHAc), 9.11—9.31 (2H, m, 2-H and 6-H).

A solution of **18** (10.0 g, 36 mmol) in a mixture of MeOH (30 ml) and H_2O (80 ml) was treated portionwise with $NaBH_4$ (6.3 g, 160 mmol) at 10 °C. The mixture was stirred at room temperature for 18 h and extracted with $CHCl_3$. The extract was washed successively with water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel to give 5.0 g (57%) of **19** as an oil. ^{1}H-NMR (200 MHz) δ: 1.95 (3H, s, $COCH_3$), 2.12—2.30 (2H, m, 5-H), 2.52 (2H, t, J=7, 6-H), 2.95 (2H, s, 2-H), 3.63 (2H, s, CH_2Ph), 3.75 (2H, d, J=8, CH_2NHAc), 5.50 (1H, m, NHCO), 5.65 (1H, m, 4-H), 7.25—7.41 (5H, m, CH_2Ph). EIMS m/z: 244 (M^+).

A solution of **19** (4.8 g, 20 mmol) in EtOH (200 ml) was hydrogenated over 5% palladium-on-carbon at room temperature. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration. The filtrate was concentrated to dryness to give 4.0 g (83%) of **14e** as an oil. ^{1}H-NMR (200 MHz) δ: 1.0—2.4 (7H, m), 1.95 (3H, s, $COCH_3$), 2.85—3.10 (2H, m), 3.05—3.35 (2H, m, CH_2NHAc), 3.70 (1H, d, J=14, CH_2Ph), 3.85 (1H, d, J=14, CH_2Ph), 6.10 (1H, m, NHCO), 7.27—7.44 (5H, m, CH_2Ph). EIMS m/z: 246 (M^+). *Anal.* Calcd for $C_{15}H_{22}N_2O \cdot H_2O$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.36; H, 8.93; N, 10.48.

2-(*N*-Benzyl-*N*-*tert*-butoxycarbonyl)aminoethanol (23) A solution of di-*tert*-butyl dicarbonate (15.9 g, 73 mmol) in $CHCl_3$ (70 ml) was added dropwise to a solution of *N*-benzylethanolamine (10.9 g, 73 mmol) in $CHCl_3$ (100 ml) at 10 °C. The reaction mixture was stirred at room temperature for 6 h and then washed with water, dried and concentrated to dryness. The residue was chromatographed on silica gel to give 16.5 g (90%) of **23** as an oil. ^{1}H-NMR (200 MHz) δ: 1.46 (9H, s, COO^{t}Bu), 3.38 (2H, t, J=6, NCH_2CH_2O), 3.70 (2H, t, J=6, NCH_2CH_2O), 4.49 (2H, s, CH_2Ph), 7.19—7.38 (5H, m, CH_2Ph).

Methyl 2-(Benzyloxycarbonyl)amino-3-[2-(*N*-benzyl-*N*-*tert*-butoxycarbonyl)aminoethyl]oxypropionate (24) After dropwise addition of BF_3–Et_2O (1.8 g, 6.6 mmol) to a mixture of **22**[14] (15.4 g, 66 mmol), **23** (16.5 g, 66 mmol) and $CHCl_3$ (200 ml) at 0 °C, the reaction mixture was stirred at room temperature for 16 h and then washed with saturated $NaHCO_3$, dried and concentrated to dryness. The residue was chromatographed on silica gel to give 15.4 g (57%) of **24** as an oil. IR (neat): 1740 (COOMe), 1710 ($NHCOOCH_2Ph$), 1680 (NCOO^{t}Bu) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.30—1.65 (9H, m, COO^{t}Bu), 3.20—3.95 (6H, m), 3.75 (3H, s, COOMe), 4.42 (2H, s, CH_2Ph), 4.48 (1H, m), 5.12 (2H, s, $COOCH_2Ph$), 5.65 (1H, m, $NHCOOCH_2Ph$), 7.15—7.45 (10H, m, $COOCH_2Ph$ and CH_2Ph).

Methyl 2-(Benzyloxycarbonyl)amino-3-[(2-benzylamino)ethyl]oxypropionate (25) A mixture of **24** (5.0 g, 11 mmol) and 10% HCl–MeOH (50 ml) was stirred at room temperature for 6 h and then concentrated to dryness. The residue was basified with saturated $NaHCO_3$ and

extracted with $CHCl_3$. The extract was washed with brine, dried and concentrated to give 4.0 g (94%) of **25** as an oil. IR (neat): 1740 (COOMe), 1710 ($NHCOOCH_2Ph$) cm^{-1}. ^1H-NMR (200 MHz) δ: 2.76 (2H, t, $J=5$, OCH_2CH_2N), 3.57 (2H, t, $J=5$, OCH_2CH_2N), 3.68 (1H, dd, $J=10$, 3, CH_2O), 3.91 (1H, dd, $J=10$, 3, CH_2O), 4.48 (1H, m), 5.11 (2H, s, $COOCH_2Ph$), 5.95 (1H, d, $J=8$, $NHCOOCH_2Ph$), 7.20—7.42 (5H, m, CH_2Ph). EIMS *m/z*: 386 (M^+).

6-(Benzyloxycarbonyl)amino-4-benzyl-2,3,4,5,6,7-hexahydro-1,4-oxazepine (27) A 1 M solution of diisobutylaluminum hydride in toluene (30.5 ml, 30 mmol) was added to a stirred solution of **25** (2.6 g, 7.6 mmol) in THF (26 ml) at −70 °C. The mixture was stirred at the same temperature for 1 h and the excess reagent was decomposed with MeOH (26 ml) at −70 °C. Then $NaBH_4$ (580 mg, 15 mmol) was added at −20 °C. The mixture was stirred at room temperature for 16 h and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$ to give **27** (1.8 g, 70%) as a pale brown oil. IR (neat): 1710 ($NHCOOCH_2Ph$) cm^{-1}. ^1H-NMR (200 MHz) δ: 2.49—2.91 (4H, m, CH_2NCH_2), 3.57—3.98 (7H, m), 5.16 (2H, s, $COOCH_2Ph$), 5.68 (1H, d, $J=8$, $NHCOOCH_2Ph$), 7.18—7.43 (5H, m, CH_2Ph and $COOCH_2Ph$). EIMS *m/z*: 340 (M^+).

***N*-(4-Methylmorpholin-3-yl)methylacetamide (28)** A solution of **20a**[13] (2.5 g, 10 mmol) in MeOH (50 ml) was hydrogenated over 10% palladium-on-carbon at room temperature. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration. The filtrate was treated with formaldehyde (1.4 g, 30 mmol). The mixture was stirred for 0.5 h, and $NaBH_4$ (2.4 g, 60 mmol) was added portionwise at 10 °C. The reaction mixture was stirred for 3 h and then concentrated to dryness. The residue was chromatographed on silica gel to give 1.2 g (72%) of **28** as an oil. IR (neat): 1640 (CONH) cm^{-1}. ^1H-NMR (200 MHz) δ: 1.84 (3H, s, $COCH_3$), 2.00 (3H, s, Me), 2.91—3.06 (3H, m), 3.19—3.31 (3H, m), 3.50 (1H, m), 3.75—3.86 (2H, m), 5.96 (1H, m, NHAc). *Anal.* Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.59; H, 9.09; N, 16.20.

***N*-[2-(4-Benzylmorpholin-3-yl)ethyl]acetamide (30)** According to the same procedure as employed in the synthesis of **14c**, compound **29**[15] (2.7 g, 12.5 mmol) was converted to 1.87 g (57%) of **3** as an oil. IR (neat): 1640 (CONH) cm^{-1}. ^1H-NMR (200 MHz) δ: 1.76—1.88 (2H, m, CH_2CH_2NHAc), 1.88 (3H, s, $COCH_3$), 2.26 (1H, ddd, $J=12$, 8, 3, 5-H), 2.50 (1H, m, 3-H), 2.74 (1H, ddd, $J=12$, 5, 3, 5-H), 3.29 (1H, d, $J=13$, CH_2Ph), 3.23—3.42 (2H, m, CH_2NHAc), 4.04 (1H, d, $J=13$, CH_2Ph), 3.46—3.82 (4H, m, 2-H and 6-H), 5.73 (1H, br s, NHAc), 7.25—7.40 (5H, m, CH_2Ph). *Anal.* Calcd for $C_{15}H_{22}N_2O_2 \cdot H_2O$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.05; H, 8.43; N, 9.78.

4-Amino-*N*-[(4-benzyl-3,4,5,6-tetrahydro-2*H*-1,4-thiazin-2-yl)methyl]-5-chloro-2-ethoxybenzamide (3b) A mixture of **14b** (3.2 g, 12 mmol) and 10% HCl (32 ml) was heated to reflux for 6 h and then cooled to 0 °C. The reaction mixture was basified with 10% NaOH and extracted with $CHCl_3$. The extract was dried and concentrated to dryness to give 2.2 g (82%) of **31b** as an oil. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.2 g, 11 mmol) was added to a stirred suspension of **31b** (2.2 g, 9.9 mmol) and 4-amino-5-chloro-2-ethoxybenzoic acid[6] (2.4 g, 11 mmol) in CH_2Cl_2 (30 ml), and this mixture was stirred at room temperature for 4 h. It was then washed successively with water and aqueous NaOH, dried, and concentrated to dryness to give a solid, which was recrystallized from MeOH to afford 2.8 g (67%) of **3b**. IR (KBr): 1630 (CONH) cm^{-1}. ^1H-NMR (200 MHz) δ: 1.50 (3H, t, $J=7$, OCH_2CH_3), 2.35—3.29 (7H, m), 3.60 (2H, s, CH_2Ph), 3.40—3.90 (2H, m, $CONHCH_2$), 4.10 (2H, q, $J=7$, OCH_2CH_3), 4.35 (2H, s, NH_2), 6.27 (1H, s, arom 3-H), 7.20—7.41 (5H, m, CH_2Ph), 8.09 (1H, s, arom 6-H), 8.08 (1H, br s, CONH).

Compounds **3c—e**, **5a—e**, **6b—e**, **7** and **8** were prepared by the same procedure as employed for the preparation of **3b**.

4-Amino-*N*-(4-benzyl-2,3,4,5,6,7-hexahydro-1,4-oxazepin-6-yl)-5-chloro-2-ethoxybenzamide (6a) A mixture of **27** (5.0 g, 15 mmol), $MeSO_3H$ (14.2 g, 150 mmol), anisole (50 ml) and $CHCl_3$ (50 ml) was heated to reflux for 1 h and then poured into ice water. The aqueous layer was separated, basified with 10% NaOH and extracted with $CHCl_3$. The extract was dried and concentrated to dryness to give 2.9 g (97%) of **33a** as an oil. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.7 g, 14 mmol) was added to a stirred suspension of **33a** (2.9 g, 14 mmol) and 4-amino-5-chloro-2-ethoxybenzoic acid[6] (3.1 g, 14 mmol) in CH_2Cl_2 (30 ml). The mixture was stirred at room temperature for 4 h, washed successively with water and aqueous NaOH, dried, and concentrated to dryness. The residue was chromatographed on silica gel to give 4.3 g (75%) of **6a** as an oil, which was converted to the fumarate in the usual manner. ^1H-NMR (200 MHz) δ: 1.42 (3H, t, $J=7$, OCH_2CH_3), 2.51—2.85 (4H, m, CH_2NCH_2), 3.50—4.00 (4H, m, CH_2OCH_2), 3.67 (2H, s, CH_2Ph), 4.12 (2H, q, $J=7$, OCH_2CH_3), 4.16 (1H, m, $CONHCH$), 5.95 (2H, s, NH_2), 6.51 (1H, s, arom 3-H), 6.63 (2H, s, fumaric acid), 7.10—7.41 (5H, m, CH_2Ph), 7.69 (1H, s, arom 6-H), 8.50 (1H, d, $J=9$, CONH), 13.12 (2H, br, fumaric acid).

4-Amino-*N*-[(4-benzyl-1-oxo-3,4,5,6-tetrahydro-2*H*-1,4-thiazin-2-yl)-methyl]-5-chloro-2-ethoxybenzamide (3f) A stirred solution of **3b** (1.1 g, 2.6 mmol) in CH_2Cl_2 (20 ml) was treated with *m*-CPBA (0.62 g, 3.6 mmol) at −15 °C. The reaction mixture was stirred at the same temperature

Table 5. Positional Parameters and B_{eq} for **4a**

Atom	*x*	*y*	*z*	B_{eq}
Cl(1)	0.78179 (5)	0.22894 (7)	0.34124 (3)	4.82 (3)
F(1)	−0.0773 (2)	0.2436 (2)	−0.48424 (8)	7.7 (1)
O(1)	0.4486 (1)	0.0618 (2)	0.09229 (8)	4.37 (7)
O(2)	0.5157 (1)	0.4828 (2)	0.13436 (9)	4.68 (8)
O(3)	0.2290 (1)	0.2588 (2)	−0.03201 (8)	4.31 (8)
O(4)	0.3537 (2)	0.1627 (2)	0.2656 (1)	5.3 (1)
N(1)	0.7273 (2)	−0.0644 (3)	0.2930 (1)	4.7 (1)
N(2)	0.4101 (2)	0.3314 (3)	0.0636 (1)	4.3 (1)
N(3)	0.1665 (1)	0.4015 (2)	−0.1673 (1)	3.51 (8)
C(1)	0.5275 (2)	0.0989 (3)	0.1501 (1)	3.6 (1)
C(2)	0.5873 (2)	0.0002 (3)	0.1932 (1)	3.9 (1)
C(3)	0.6677 (2)	0.0372 (3)	0.2528 (1)	3.6 (1)
C(4)	0.6837 (2)	0.1788 (3)	0.2666 (1)	3.7 (1)
C(5)	0.6252 (2)	0.2776 (3)	0.2232 (1)	3.6 (1)
C(6)	0.5459 (2)	0.2424 (3)	0.1631 (1)	3.3 (1)
C(7)	0.4892 (2)	0.3609 (3)	0.1198 (1)	3.5 (1)
C(8)	0.3482 (2)	0.4371 (3)	0.0188 (1)	4.2 (1)
C(9)	0.2922 (2)	0.3718 (3)	−0.0518 (1)	3.5 (1)
C(10)	0.2202 (2)	0.4729 (3)	−0.1009 (1)	3.6 (1)
C(11)	0.1019 (2)	0.2855 (3)	−0.1458 (2)	4.4 (1)
C(12)	0.1745 (3)	0.1876 (3)	−0.0958 (2)	4.7 (1)
C(13)	0.0978 (2)	0.4978 (3)	−0.2169 (1)	3.9 (1)
C(14)	0.0508 (2)	0.4315 (3)	−0.2893 (1)	3.7 (1)
C(15)	0.1166 (2)	0.3990 (3)	−0.3401 (1)	4.8 (1)
C(16)	0.0736 (3)	0.3356 (4)	−0.4056 (2)	5.6 (1)
C(17)	−0.0352 (2)	0.3063 (3)	−0.4196 (1)	5.0 (1)
C(18)	−0.1024 (2)	0.3361 (3)	−0.3712 (1)	4.7 (1)
C(19)	−0.0585 (2)	0.3992 (3)	−0.3060 (1)	4.1 (1)
C(20)	0.4293 (3)	−0.0838 (3)	0.0772 (2)	4.8 (1)
C(21)	0.3356 (3)	−0.0943 (4)	0.0148 (2)	5.6 (2)
H(1)	0.406 (3)	0.114 (4)	0.292 (2)	9 (1)
H(2)	0.294 (2)	0.147 (3)	0.285 (2)	6.9 (8)
H(3)	0.700 (2)	−0.158 (3)	0.285 (2)	6.8 (8)
H(4)	0.768 (2)	−0.037 (3)	0.332 (2)	7.6 (9)
H(5)	0.391 (2)	0.244 (3)	0.060 (1)	4.8 (7)
H(6)	0.575 (2)	−0.094 (3)	0.186 (1)	4.3 (6)
H(7)	0.637 (2)	0.371 (2)	0.234 (1)	2.8 (5)
H(8)	0.291 (2)	0.478 (2)	0.045 (1)	4.1 (6)
H(9)	0.398 (2)	0.513 (3)	0.008 (1)	4.5 (6)
H(10)	0.350 (2)	0.334 (2)	−0.079 (1)	4.0 (5)
H(11)	0.167 (2)	0.515 (2)	−0.074 (1)	3.6 (5)
H(12)	0.265 (2)	0.550 (2)	−0.117 (1)	4.2 (5)
H(13)	0.043 (2)	0.326 (2)	−0.118 (1)	4.4 (6)
H(14)	0.068 (2)	0.236 (3)	−0.191 (1)	5.1 (6)
H(15)	0.230 (2)	0.140 (3)	−0.123 (1)	4.8 (6)
H(16)	0.131 (2)	0.177 (3)	−0.078 (1)	4.9 (6)
H(17)	0.144 (2)	0.575 (2)	−0.225 (1)	4.1 (5)
H(18)	0.039 (2)	0.533 (2)	−0.192 (1)	4.1 (5)
H(19)	0.192 (2)	0.426 (3)	−0.329 (1)	5.5 (6)
H(20)	0.118 (2)	0.313 (3)	−0.440 (1)	6.2 (7)
H(21)	−0.178 (2)	0.315 (3)	−0.383 (1)	5.5 (7)
H(22)	−0.105 (2)	0.424 (2)	−0.273 (1)	4.2 (6)
H(23)	0.498 (2)	−0.123 (3)	0.061 (1)	6.8 (8)
H(24)	0.411 (2)	−0.126 (3)	0.120 (1)	5.5 (7)
H(25)	0.269 (3)	−0.048 (3)	0.028 (2)	8 (1)
H(26)	0.353 (2)	−0.046 (3)	−0.029 (1)	5.8 (7)
H(27)	0.325 (2)	−0.192 (3)	0.002 (2)	7.9 (9)

for 1 h, washed successively with 5% NaOH and brine, and then dried. The solvent was evaporated to leave a solid, which was recrystallized from iso-PrOH to afford 0.3 g (29%) of **3f**. IR (KBr): 1630 (CONH) cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.49 (3H, t, $J=7$, $OCH_2\underline{CH_3}$), 2.65—3.82 (7H, m), 3.62 (2H, s, $\underline{CH_2}Ph$), 3.50 (1H, m, $CONHC\underline{H_2}$), 3.75 (1H, m, $CONHC\underline{H_2}$), 4.10 (2H, q, $J=7$, $OC\underline{H_2}CH_3$), 4.33 (2H, s, NH_2), 6.27 (1H, s, arom 3-H), 7.25—7.43 (5H, m, $CH_2\underline{Ph}$), 8.07 (1H, s, arom 6-H), 8.23 (1H, t, $J=7$, CONH).

X-Ray Crystallographic Analysis of Mosapride (4a) A colorless, irregularly shaped crystal was formed from acetone: $C_{21}H_{27}ClFN_3O_4$; F.W. 439.91; monoclinic, space group $P2_1/c$; $a=12.444(2)$ Å, $b=9.593(2)$ Å, $c=18.511(2)$ Å, $\beta=99.901(9)°$; $V=2176.9(5)$ Å^3; $Z=4$; $D_{calcd}=1.342$ g/cm^3; μ (CuK_α radiation, $\lambda=1.54178$ Å) $=19.08$ cm^{-1}; sample dimensions, $0.30\times0.20\times0.20$ mm.

All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated CuK_α radiation and a 12KW rotating anode generator. Of the 3640 reflections which were collected using the ω–2θ scan technique to a $2\theta_{max}$ value of 120.3°, 3462 were unique ($R_{int}=0.026$) and were corrected for Lorentz and polarization effects. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement with the setting angles of 25 reflections in the range of $97.70°<2\theta<99.44°$ were used.

The crystal structure was solved by direct methods using SHELXS-86.[16] The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement was based on 2355 observed reflections with $I>3.00\sigma(I)$ and 380 variable parameters, and converged at $R=0.032$ and $R_w=0.038$. Neutral atom scattering factors, corrected for the real and anomalous scattering, were used for all atoms and were taken from ref. 16. In the least-squares iterations, $\sum\omega(|F_o|-|F_c|)^2$ $[\omega=4F_o^2/\sigma^2(F_o^2)]$ was minimized. Positional parameters, bond lengths and bond angles are given in Tables 5—8.

Molecular Modeling All molecular modeling was performed with SYBYL ver.5.5[21] on a Silicon Graphics IRIS 4D/35TG workstation. Computational procedures were as follows. Initial atomic coordinates of structure **3a** for molecular orbital calculation were obtained by

Table 6. Intramolecular Distances Involving the Nonhydrogen Atoms

Atom	Atom	Distance	Atom	Atom	Distance
Cl (1)	C(4)	1.746 (2)	C(3)	C(4)	1.390 (3)
F(1)	C(17)	1.361 (3)	C(4)	C(5)	1.369 (3)
O(1)	C(1)	1.370 (2)	C(5)	C(6)	1.396 (3)
O(1)	C(20)	1.436 (3)	C(6)	C(7)	1.496 (3)
O(2)	C(7)	1.232 (3)	C(8)	C(9)	1.509 (3)
O(3)	C(9)	1.424 (3)	C(9)	C(10)	1.513 (3)
O(3)	C(12)	1.430 (3)	C(11)	C(12)	1.506 (4)
N(1)	C(3)	1.366 (3)	C(13)	C(14)	1.509 (3)
N(2)	C(7)	1.335 (3)	C(14)	C(15)	1.385 (3)
N(2)	C(8)	1.445 (3)	C(14)	C(19)	1.377 (3)
N(3)	C(10)	1.465 (3)	C(15)	C(16)	1.378 (4)
N(3)	C(11)	1.467 (3)	C(16)	C(17)	1.364 (4)
N(3)	C(13)	1.469 (3)	C(17)	C(18)	1.357 (4)
C(1)	C(2)	1.372 (3)	C(18)	C(19)	1.377 (4)
C(1)	C(6)	1.409 (3)	C(20)	C(21)	1.498 (4)
C(2)	C(3)	1.401 (3)			

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Table 7. Intramolecular Distances Involving the Nonhydrogen Atoms

Atom	Atom	Distance	Atom	Atom	Distance
O(4)	H(1)	0.88 (3)	C(12)	H(15)	1.02 (2)
O(4)	H(2)	0.90 (3)	C(12)	H(16)	0.96 (2)
N(1)	H(3)	0.96 (3)	C(13)	H(17)	0.97 (2)
N(1)	H(4)	0.84 (3)	C(13)	H(18)	0.99 (2)
N(2)	H(5)	0.87 (3)	C(15)	H(19)	0.96 (2)
C(2)	H(6)	0.92 (2)	C(16)	H(20)	0.94 (3)
C(5)	H(7)	0.92 (2)	C(18)	H(21)	0.95 (2)
C(8)	H(8)	1.00 (2)	C(19)	H(22)	0.94 (2)
C(8)	H(9)	1.00 (2)	C(20)	H(23)	1.02 (3)
C(9)	H(10)	1.01 (2)	C(20)	H(24)	0.94 (2)
C(10)	H(11)	0.99 (2)	C(21)	H(25)	1.01 (3)
C(10)	H(12)	1.00 (2)	C(21)	H(26)	0.98 (3)
C(11)	H(13)	1.04 (2)	C(21)	H(27)	0.97 (3)
C(11)	H(14)	0.99 (2)			

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Table 8. Torsion or Conformation Angles

(1)	(2)	(3)	(4)	Angle	(1)	(2)	(3)	(4)	Angle
Cl(1)	C(4)	C(3)	N(1)	−2.3 (3)	C(2)	C(1)	C(6)	C(7)	−2.0 (3)
Cl(1)	C(4)	C(3)	C(2)	179.1 (2)	C(2)	C(1)	C(6)	C(7)	178.3 (2)
Cl(1)	C(4)	C(5)	C(6)	−179.8 (2)	C(2)	C(3)	C(4)	C(5)	−1.2 (4)
F(1)	C(17)	C(16)	C(15)	180.0 (3)	C(3)	C(2)	C(1)	C(6)	1.4 (4)
F(1)	C(17)	C(18)	C(19)	179.9 (2)	C(3)	C(4)	C(5)	C(6)	0.5 (4)
O(1)	C(1)	C(2)	C(3)	−179.5 (2)	C(4)	C(5)	C(6)	C(7)	−179.2 (2)
O(1)	C(1)	C(6)	C(5)	178.8 (2)	C(6)	C(1)	O(1)	C(20)	179.1 (2)
O(1)	C(1)	C(6)	C(7)	−0.8 (4)	C(6)	C(7)	N(2)	C(8)	178.7 (2)
O(2)	C(7)	N(2)	C(8)	−2.7 (4)	C(7)	N(2)	C(8)	C(9)	162.6 (2)
O(2)	C(7)	C(6)	C(1)	−176.6 (2)	C(8)	C(9)	O(3)	C(12)	178.6 (2)
O(2)	C(7)	C(6)	C(5)	3.8 (3)	C(9)	O(3)	C(12)	C(11)	−58.1 (3)
O(3)	C(9)	C(8)	N(2)	55.6 (3)	C(9)	C(10)	N(3)	C(11)	58.7 (3)
O(3)	C(9)	C(10)	N(3)	−59.2 (3)	C(9)	C(10)	N(3)	C(13)	178.8 (2)
O(3)	C(12)	C(11)	N(3)	58.1 (3)	C(10)	N(3)	C(11)	C(12)	−58.0 (3)
N(1)	C(3)	C(2)	C(1)	−178.3 (2)	C(10)	N(3)	C(13)	C(14)	173.8 (2)
N(1)	C(3)	C(4)	C(5)	177.3 (2)	C(10)	C(9)	O(3)	C(12)	58.3 (3)
N(2)	C(7)	C(6)	C(1)	2.0 (4)	C(11)	N(3)	C(13)	C(14)	−65.0 (3)
N(2)	C(7)	C(6)	C(5)	−177.6 (2)	C(12)	C(11)	N(3)	C(13)	179.3 (2)
N(2)	C(8)	C(9)	C(10)	177.0 (2)	C(13)	C(14)	C(15)	C(16)	178.6 (3)
N(3)	C(10)	C(9)	C(8)	−178.5 (2)	C(13)	C(14)	C(19)	C(18)	−178.7 (2)
N(3)	C(13)	C(14)	C(15)	−70.6 (3)	C(14)	C(15)	C(16)	C(17)	0.5 (5)
N(3)	C(13)	C(14)	C(19)	108.2 (3)	C(14)	C(19)	C(18)	C(17)	−0.3 (4)
C(1)	O(1)	C(20)	C(21)	176.7 (2)	C(15)	C(14)	C(19)	C(18)	0.2 (4)
C(1)	C(2)	C(3)	C(4)	0.3 (4)	C(15)	C(16)	C(17)	C(18)	−0.7 (5)
C(1)	C(6)	C(5)	C(4)	1.1 (3)	C(16)	C(15)	C(14)	C(19)	−0.3 (4)
C(2)	C(1)	O(1)	C(20)	−0.1 (3)	C(16)	C(17)	C(18)	C(19)	0.6 (5)

The sign is positive if, when looking from atom 2 to atom 3, a clockwise motion of atom 1 would superimpose it on atom 4.

replacement of the fluorine atom in the X-ray crystal structure of **4a** by hydrogen. The AM1 calculation with geometry optimization by MOPAC ver. 5.0 for all geometric variables was carried out with the keyword "MMOK". The optimized structure was used as a template for the molecular superimposition with structures **5a**, **6a** and **8**.

Molecular models for **5a**, **6a** and **8** were built up on the basis of three-dimensional fragments, *i.e.*, the 4-amino-5-chloro-2-ethoxybenzamide moiety and the *N*-benzylmorpholine group, of the X-ray crystal structure of **4a**. Seven-membered heteroalicycles and the other remaining substructures were constructed with standard bond lengths and bond angles.

Conformational searches of the structures **5a** and **8** were carried out by GRIDSEARCH implemented in SYBYL. GRIDSEARCH is a systematic search program with energy minimizations. Torsional angles were scanned for 7(C)–2(N)–8(C)–9(C) and 2(N)–8(C)–9(C)–3(N) of the structure **5a** with increments of 30°, for 7(C)–2(N)–8(C)–9(C), 2(N)–8(C)–9(C)–10(C) and 8(C)–9(C)–10(C)–3(N) of the structure **8** and increments 30°, 30° and 60°, respectively, in the range of 0—360° for all torsional angles. In the case of **6a**, RANDOMSEARCH was applied for the heteroalicyclic rings, and then systematic search was carried out for two bonds (2(N)–8(C) and 3(N)–13(C)) of **6a** with increments of 30°. One hundred and forty-four energy-minimized conformers were generated in the case of **5a**. Similarly, 864 and 81 conformers were generated from **8** and **6a**, respectively. We selected the conformers most resembling the structure **3a** with the intersection volumes as a measure of structure similarity under the RMS fitting conditions described in Figs. **3** to 5. Energy minimizations were conducted using SYBYL/MAXIMIN2 with neglect of the electrostatic term of the Tripos force field by setting default values for the operation, except that the number of iterations was fixed at 500. During energy minimizations, the geometry of the 4-amino-5-chloro-2-ethoxybenzamide moiety was fixed in space (not optimized) by AGGREGATES of SYBYL.

Finally, semiempirical molecular orbital calculations using MOPAC/AM1 with full geometry optimization were done to refine our molecular models.

Molecular superimpositions and intersection volume calculations were performed with the FIT and MVOLUME subroutines of SYBYL, respectively.

Pharmacology Male rats of the Wistar strain (Japan SLC Inc.) weighing 130—150 g were used, and were starved for 18 h before the experiments.

Gastric Emptying of Semisolid Meal A test meal (0.05% phenol red in 1.5% aqueous methylcellulose) of 1.5 ml per rat was given through a gastric tube. Fifteen minutes later, the animals were killed. The stomach was removed, and the amount of phenol red remaining in the stomach was measured according to the method of Scarpignato *et al.*[22] The test compounds, suspended in a 0.5% tragacanth solution, were orally administered 60 min before administration of the test meal. Statistically significant differences from the control group were analyzed using the MUSCOT statistical analysis program (Yukms Corp.) with Duncan's multiple range test.

Inhibition of [^{3}H]Spiperone Binding The test compounds at the concentration of 1 μM were tested in binding assays using rat brain synaptic membranes for competition with [^{3}H]spiperone in the striatum.[23] The assay was started by the addition of tissue preparations (10 mg wet tissue) and terminated by rapid filtration through Whatman GF/B glass-fiber filters under reduced pressure. The filters were washed two or three times with 5 ml of ice-cold buffer and transferred to scintillation vials that contained 1 ml of Soluene-350. After 1 h of incubation at 25 °C, the solubilized filters were shaken vigorously with 10 ml of toluene scintillator, and the radioactivity in the filters was counted with a Packard Tri-Carb scintillation counter (B-2450).

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References and Notes

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