Novel Benzamides as Selective and Potent Gastrokinetic Agents. IV.[1] Synthesis and Structure–Activity Relationships of 2-Substituted 4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chlorobenzamides

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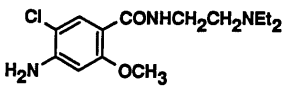
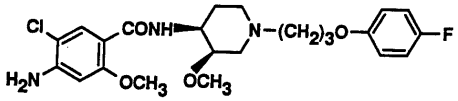
A new series of 2-substituted 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chlorobenzamides (4—39) including a few 4-fluorobenzyl analogues were prepared and evaluated for their gastrokinetic activity by determining their effects on the gastric emptying activity of phenol red semisolid meal in rats. The C-2 substituent comprises alkoxy and variously substituted alkoxy groups. Among the derivatives, 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-2-(*n*-butoxy)-5-chlorobenzamide (5), its 4-fluorobenzyl (6), and 3-methyl-2-butenyloxy analogues (22) were superior to cisapride and essentially equipotent to the 2-ethoxy analogue (1b, AS-4370 as its citrate) in gastrokinetic activity. These compounds, like AS-4370, had no dopamine D_2 receptor antagonistic activity.

Keywords 2-morpholinylbenzamide; gastrokinetic agent; gastric emptying; dopamine D_2 antagonism; [^{3}H]spiperone binding; structure–activity relationship

Metoclopramide is a dopamine D_2 receptor antagonist as well as a gastrointestinal motility stimulant.[2] Dopamine D_2 receptor antagonism of metoclopramide is responsible for its undesirable side effects such as akathisia and hyperprolactinemia.[3] The gastrokinetic action of metoclopramide is due to its antidopaminergic property and/or an increase of acetylcholine release in the myenteric plexus of the gut.[4] Cisapride, like metoclopramide, enhances acetylcholine release without affecting dopamine receptor.[5] The increase of acetylcholine release has been shown to be mediated by an activation of serotonin-4 receptor.[6]

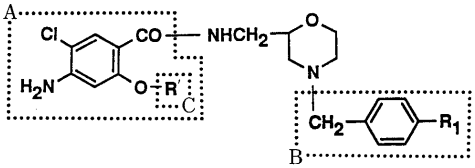


metoclopramide



cisapride

Chart 1



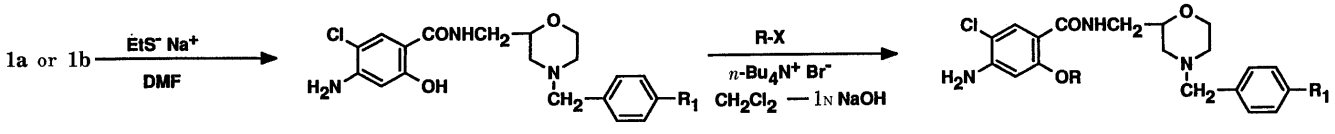
1a : R′=CH_3, R_1=H
1b : R′=C_2H_5, R_1=F
1c : R′=C_2H_5, R_1=H

Chart 2

To obtain gastrokinetic agents more potent and selective than metoclopramide, a series of *N*-(2-morpholinylmethyl)-benzamides **1** was designed and prepared.[7] 4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxybenzamide (**1a**) was found to have more potent gastric emptying activity and much less dopamine D_2 receptor antagonistic activity than metoclopramide. Subsequent modifications of the benzoyl moiety (A),[7] and the benzyl group (B),[1,8] of **1a** led to the finding of 4-amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]-benzamide (**1b**) which has more potent gastrokinetic activity than **1a**. As a continuation of this work, our effort was focused on further modifications of the C-2 substituent, *i.e.*, the alkoxy group (C), since variation of the substituent had been very limited in the previous study.[7] The present paper deals with synthesis and structure–activity relationships (SARs) of a series of 2-substituted 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chlorobenzamides (**4—39**) including a few 4-fluorobenzyl analogues.

Chemistry 4-Amino-5-chloro-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]-2-hydroxybenzamide (**3**) was prepared from the corresponding 4-fluorobenzyl benzamide (**1b**) using the method described in our previous paper[7]; thus dealkylation of **1b** with sodium ethanethiolate in *N*,*N*-dimethylformamide (DMF) gave the 2-hydroxybenzamide **3**. The conventional reaction of the 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-hydroxybenzamide (**2**)[7] and its 4-fluorobenzyl analogue (**3**) with various alkyl halides in the presence of tetrabutylammonium bromide gave the desired 2-substituted benzamides **4—39** except **29**, **31**, and **37** (Chart 3).

Treatment of the 2-(2-oxopropoxy)benzamide **28** with



2 : R_1=H
3 : R_1=F

4—28,30,32—36,38,39

Chart 3

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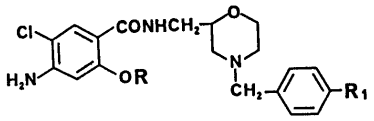
TABLE I. Physical Data for 2-Substituted 4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chlorobenzamides (**4**—**39**)



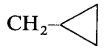
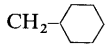
Compound	R[a]	R_1	Yield[b] (%)	mp (°C) (Recryst. solvent[c])	Formula	Analysis (%) Calcd (Found)			
						C	H	Cl	N
4	$(CH_2)_2CH_3$	H	97	192—195 (E)	$C_{22}H_{28}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/4H_2O$	57.99 (57.84)	6.08 6.04	6.58 6.58	7.80 7.57)
5	$(CH_2)_3CH_3$	H	95	188—190 (E)	$C_{23}H_{30}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/2H_2O$	58.22 (58.38)	6.33 6.12	6.36 6.47	7.54 7.50)
6	$(CH_2)_3CH_3$	F	98	178—184 (E)	$C_{23}H_{29}ClFN_3O_3 \cdot HCl \cdot 7/4H_2O$[e]	53.34 (53.45)	6.52 6.70	13.69 13.50	8.11 8.03)
7	$(CH_2)_4CH_3$	H	96	172—174 (E)	$C_{24}H_{32}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/4H_2O$	58.89 (58.82)	6.53 6.30	6.21 6.26	7.36 7.15)
8	$(CH_2)_5CH_3$	H	86	188—190 (E)	$C_{25}H_{34}ClN_3O_3 \cdot 3/2C_4H_4O_4$[d]	58.72 (58.62)	6.36 6.62	5.59 5.62	6.63 6.56)
9	$(CH_2)_6CH_3$	H	96	190—193 (E)	$C_{26}H_{36}ClN_3O_3 \cdot 3/2C_4H_4O_4$[d] $\cdot 1/2H_2O$	58.49 (58.49)	6.60 6.54	5.39 5.52	6.39 6.46)
10	$(CH_2)_7CH_3$	H	95	189—192 (E)	$C_{27}H_{38}ClN_3O_3 \cdot 3/2C_4H_4O_4$[d] $\cdot 1/2H_2O$	59.05 (59.29)	6.76 6.71	5.28 5.43	6.26 6.26)
11	$(CH_2)_8CH_3$	H	98	170—172 (E)	$C_{28}H_{40}ClN_3O_3 \cdot 7/4C_4H_4O_4$[d]	59.61 (59.47)	6.72 6.94	5.03 5.32	5.96 6.01)
12	$(CH_2)_9CH_3$	H	95	166—168 (E)	$C_{29}H_{42}ClN_3O_3 \cdot 7/4C_4H_4O_4$[d]	60.12 (59.88)	6.87 6.97	4.93 5.24	5.84 5.97)
13	$CH(CH_3)_2$	H	98	184—186 (E)	$C_{22}H_{28}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/2H_2O$	57.51 (57.64)	6.13 6.16	6.53 6.47	7.74 7.47)
14	$CH_2CH(CH_3)_2$	H	70	172—174 (E)	$C_{23}H_{30}ClN_3O_3 \cdot C_4H_4O_4$[d]	59.17 (58.92)	6.25 6.26	6.47 6.31	7.67 7.60)
15	$(CH_2)_2CH(CH_3)_2$	H	93	175—177 (E)	$C_{24}H_{32}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/2H_2O$	58.89 (59.16)	6.53 6.43	6.21 6.50	7.36 7.25)
16	$(CH_2)_2CH(CH_3)_2$	F	75	189—195 (E)	$C_{24}H_{31}ClFN_3O_3 \cdot HCl \cdot 3/2H_2O \cdot 2/5C_2H_5OH$[f,g]	54.57 (54.33)	6.91 7.22	12.99 13.26	7.70 7.86)
17	CH_2— 	H	96	201—204 (E)	$C_{23}H_{28}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/4H_2O$	58.91 (59.01)	5.95 6.25	6.44 6.51	7.63 7.58)
18	CH_2— 	H	64	144—146 (E)	$C_{26}H_{34}ClN_3O_3 \cdot 3C_4H_4O_4$[d]	55.64 (55.70)	5.65 5.92	4.32 4.62	5.12 5.07)
19		H	72	194—197 (E)	$C_{24}H_{30}ClN_3O_3 \cdot C_4H_4O_4$[d]	60.05 (59.76)	6.12 6.13	6.33 6.30	7.50 7.36)
20	$CH_2CH=CH_2$	H	85	177—180 (I)	$C_{22}H_{26}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/4H_2O$	58.21 (58.02)	5.73 5.66	6.61 6.57	7.89 7.80)
21	$(CH_2)_2CH=CH_2$	H	97	189—192 (E)	$C_{23}H_{28}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot 1/4H_2O$	58.91 (59.03)	5.95 6.04	6.44 6.42	7.63 7.59)
22	$CH_2CH=C(CH_3)_2$	H	94	155—159 (E–I)	$C_{24}H_{30}ClN_3O_3 \cdot 3/2C_4H_4O_4$[d] $\cdot 1/4H_2O$	57.88 (57.70)	5.91 5.84	5.69 5.66	6.75 6.75)
23	$CH_2CH=C(CH_3)_2$	F	95	170—172 (E)	$C_{24}H_{29}ClFN_3O_3 \cdot 2C_4H_4O_4$[d,h]	55.37 (55.58)	5.37 5.30	5.11 5.40	6.05 5.89)
24	$CH_2C\equiv CH$	H	91	143—147 (E)	$C_{22}H_{24}ClN_3O_3 \cdot 2C_4H_4O_4$[d] $\cdot 1/2H_2O$	55.01 (55.15)	5.08 5.01	5.41 5.65	6.41 6.47)
25	$CH_2C_6H_5$	H	75	103—108 (E)	$C_{26}H_{28}ClN_3O_3 \cdot C_2H_2O_2$[i] $\cdot H_2O$	58.59 (58.97)	5.62 5.22	6.18 6.22	7.32 6.97)
26	$(CH_2)_3C_6H_5$	H	67	85—88 (E)	$C_{28}H_{32}ClN_3O_3 \cdot C_4H_4O_4$[d] $\cdot H_2O$	61.19 (61.17)	6.10 6.15	5.64 5.72	6.69 6.60)
27	$CH_2COC_6H_5$	H	41	207—210 (E)	$C_{27}H_{28}ClN_3O_4 \cdot C_4H_4O_4$[d] $\cdot 1/2H_2O$	60.15 (60.17)	5.37 5.46	5.73 5.76	6.79 6.61)
28	CH_2COCH_3	H	77	133—135 (E)	$C_{22}H_{26}ClN_3O_4 \cdot C_4H_4O_4$[d] $\cdot H_2O$	55.17 (55.03)	5.70 5.38	6.26 6.34	7.42 7.42)
29	$CH_2CH(OH)CH_3$	H	81[j]	94—97 (E)	$C_{22}H_{28}ClN_3O_4 \cdot C_4H_4O_4$[d] $\cdot H_2O$	57.03 (56.89)	6.28 6.17	7.01 7.21	8.31 8.26)
30	$CH_2CO_2C_2H_5$	H	70	189—192 (E)	$C_{23}H_{28}ClN_3O_5$	59.80 (59.64)	6.11 6.17	7.67 7.56	9.10 8.95)
31	CH_2CO_2H	H	46[j]	252—255 (E–W)	$C_{21}H_{24}ClN_3O_5 \cdot 1/4H_2O$	57.54 (57.77)	5.63 5.41	8.09 8.04	9.59 9.37)
32	$CH_2O(CH_2)_2OCH_3$	H	81	153—156 (I)	$C_{23}H_{30}ClN_3O_5 \cdot 2C_4H_4O_4$[d]	53.49 (53.41)	5.50 5.51	5.09 5.30	6.04 6.16)
33	$(CH_2)_3OH$	H	96	154—156 (EA)	$C_{22}H_{28}ClN_3O_4 \cdot 1/4H_2O$	60.27 (60.44)	6.55 6.64	8.09 8.25	9.58 9.32)
34	$(CH_2)_2Cl$	H	85	131—133 (E)	$C_{21}H_{25}Cl_2N_3O_3 \cdot 1/4H_2O \cdot 1/10C_2H_5OH$[f]	56.91 (57.15)	5.88 5.89	15.85 16.12	9.39 8.99)

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TABLE I. (continued)

Compound	R[a]	R_1	Yield[b] (%)	mp (°C) (Recryst. solvent[c])	Formula	Analysis (%) Calcd (Found) C	H	Cl	N
35	CH_2CN	H	73	198—201 (E)	$C_{21}H_{23}ClN_4O_3 \cdot C_4H_4O_4$[d] $\cdot 1/4H_2O$	56.08 (56.18)	5.18 5.27	6.62 6.68	10.46 10.32)
36	$(CH_2)_3N(CO)_2C_6H_4$	H	71	139—143 (M)	$C_{30}H_{31}ClN_4O_5 \cdot C_4H_4O_4$[d] $\cdot 1/2H_2O$	59.35 (59.36	5.27 5.42	5.15 5.09	8.14 7.92)
37	$(CH_2)_3NH_2$	H	97[j]	77—79 (EA)	$C_{22}H_{29}ClN_4O_3 \cdot H_2O$	58.59 (58.47	6.93 6.64	7.86 7.82	12.42 12.13)
38	$(CH_2)_5OC_6H_4$(4-F)	H	81	145—147 (E)	$C_{30}H_{35}ClFN_3O_4 \cdot C_4H_4O_4$[d] $\cdot 3/2H_2O$[k]	58.41 (58.41	6.06 5.80	5.07 5.43	6.01 5.74)
39	$(CH_2)_3COC_6H_4$(4-F)	H	21	202—205 (E)	$C_{29}H_{31}ClFN_3O_4 \cdot 3/2C_4H_4O_4$[d] $\cdot 3/4H_2O$[l]	57.77 (57.95	5.33 5.63	4.87 4.93	5.77 5.65)

a) Alkylating agents RX except 5-(4-fluorophenoxy)pentyl bromide (**38**) were obtained from commercial suppliers. 5-(4-Fluorophenoxy)pentyl bromide was synthesized according to the literature.[15] *b*) Yield of the free base of 2-morpholinylbenzamides is based on **2** or **3**, except for **29**, **31**, and **37**. *c*) Abbreviations for the solvents used are as follows: E=ethanol, I=isopropanol, W=water, EA=ethyl acetate, M=methanol. *d*) Fumaric acid. *e*) Calcd for F: 3.67, Found: 3.38. *f*) The presence of a crystallization solvent (ethanol) was shown by ^{1}H-NMR. *g*) Calcd for F: 3.48, Found: 3.24. *h*) Calcd for F: 2.74, Found: 2.89. *i*) Oxalic acid. *j*) Yields of **29**, **31**, and **37** are based on **28**, **30**, and **36**, respectively. *k*) Calcd for F: 2.72, Found: 2.39. *l*) Calcd for F: 2.61, Found: 2.37.

TABLE II. Effect of 2-Morpholinylbenzamides (**4**—**39**) on Gastric Emptying of Phenol Red Semisolid Meal in Rats

Compound	Gastric emptying rate: Control (mean±S.E.M.) (n[a])	2.0 mg/kg, *p.o.* (mean±S.E.M.) (n)	% change
4	51.8±1.4 (5)	80.3±2.5 (4)	55[c]
5	51.8±1.4 (5)	79.6±1.7 (4)	54[c]
6	53.3±2.7 (5)	79.9±2.3 (4)	50[c]
7	51.7±3.4 (5)	72.9±1.0 (4)	41[c]
8	52.8±2.8 (5)	67.6±2.2 (4)	28[c]
9	51.2±1.7 (5)	73.6±2.7 (4)	44[c]
10	51.2±1.7 (5)	59.8±3.7 (4)	17
11	52.8±2.8 (5)	62.5±3.7 (4)	18
12	52.8±2.8 (5)	67.3±2.2 (4)	27[b]
13	51.8±1.4 (5)	71.6±4.3 (4)	38[c]
14	50.0±1.6 (5)	75.6±4.7 (4)	51[c]
15	50.0±1.6 (5)	72.1±2.1 (4)	44[c]
16	51.3±2.2 (5)	78.0±2.2 (4)	52[c]
17	52.8±2.8 (5)	78.5±2.3 (4)	49[c]
18	52.4±1.8 (5)	59.5±3.1 (4)	14
19	50.7±2.0 (5)	74.2±0.9 (4)	46[c]
20	52.6±1.7 (5)	76.6±2.1 (4)	46[c]
21	49.8±3.5 (5)	73.9±2.1 (4)	48[c]
22	51.7±3.4 (5)	78.8±3.1 (4)	52[c]
23	53.3±2.7 (5)	70.8±3.4 (4)	33[c]
24	49.8±3.5 (5)	70.0±4.6 (4)	41[b]
25	51.8±1.4 (5)	67.1±3.3 (4)	30[c]
26	52.4±1.8 (5)	67.4±3.0 (4)	29[c]
27	49.8±3.5 (5)	59.3±3.9 (4)	19
28	50.7±2.0 (5)	72.9±5.1 (4)	44[c]
29	50.0±1.6 (5)	76.0±3.1 (4)	52[c]
30	50.7±2.0 (5)	67.3±4.0 (4)	33[c]
31	52.4±1.8 (5)	60.4±3.3 (4)	15
32	53.0±2.4 (5)	63.2±3.9 (4)	19
33	50.2±3.4 (5)	68.6±3.2 (4)	37[c]
34	50.2±3.4 (5)	73.7±1.1 (4)	47[c]
35	52.9±1.0 (5)	68.9±3.9 (4)	30[c]
36	50.7±2.0 (5)	69.0±2.4 (4)	36[c]
37	51.8±2.1 (5)	56.3±5.4 (4)	9
38	52.5±2.6 (5)	66.0±3.2 (4)	26[b]
39	52.5±2.6 (5)	71.2±2.3 (4)	36[c]
Cisapride	55.2±1.9 (5)	81.3±1.2 (5)	47[c]
Metoclopramide	58.9±2.1 (5)	72.3±3.8 (5)	21[b]
1a	54.5±3.8 (5)	75.9±3.6 (4)	39[c]
1b	51.8±2.1 (5)	83.6±2.4 (4)	61[c]
1c	51.5±3.1 (5)	79.5±3.7 (4)	54[c]

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

sodium borohydride yielded the 2-(2-hydroxypropoxy)-benzamide **29** as a diastereomeric mixture. Alkaline hydrolysis of the ethyl phenoxyacetate **30** gave the phenoxyacetic acid **31**. The phthalimido group of **36** was converted to an amino group by treatment with hydrazine, thus giving **37**. The physical data for compounds thus prepared are listed in Table I. The structure of all compounds (as racemates) was also confirmed by their proton nuclear magnetic resonance (^{1}H-NMR) spectra.

Biological Results and Discussion Compounds **4**—**39** were evaluated for their gastrokinetic activity by determining their effects on the gastric emptying rates of phenol red semisolid meal through the stomach. The biological data for these compounds at an oral dose of 2.0 mg/kg in rats are shown in Table II, which includes, for comparison, data for **1a**, **1b**, 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-ethoxybenzamide (**1c**),[7] metoclopramide, and cisapride.

We previously reported that replacement of the methoxy group of **1a** by an ethoxy group, giving **1c**, enhanced the activity.[7] To learn the effect of variation of the C-2 substituent (OR) on activity, alkoxy groups with three to ten carbon atoms were introduced. Replacement of the methoxy group by an *n*-propoxy (**4**) or *n*-butoxy (**5**) group caused a remarkable increase in activity; compounds **4** and **5** were the most active in this series, with activities more potent than cisapride and equipotent to the 2-ethoxybenzamide **1c**. Further extension of the alkyl chain tended to reduce the activity. Replacement by the *n*-pentyloxy (**7**) and *n*-heptyloxy (**9**) groups gave slightly more active compounds than the methoxy derivative **1a** in the gastric emptying activity. Of much interest are compounds **10**—**12**, which have an *n*-alkyl group with eight to ten carbon atoms; they are practically comparable or somewhat superior to metoclopramide. An interest in the influence of a branched alkoxy group on activity led us to prepare compounds **13**—**15**. Conversion of the *n*-alkoxy group of compounds **4**, **5**, and **7** to isopropoxy, isobutoxy, and isopentyloxy groups (yielding **13**—**15**, respectively) had no favorable influence on activity. Overall, variation of an alkoxy group caused a decrease in activity in the order *n*-propoxy (**4**) = *n*-butoxy (**5**) ≥ ethoxy (**1c**) > isobutoxy

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TABLE III. Effect of the Selected 2-Morpholinylbenzamides on Gastric Emptying of Phenol Red Semisolid Meal in Rats

Compound	Gastric emptying rate[a]					
	Control (n^{b})/ 0.2 mg/kg, *p.o.* (*n*)	% change	Control (*n*)/ 0.5 mg/kg, *p.o.* (*n*)	% change	Control (*n*)/ 2.0 mg/kg, *p.o.* (*n*)	% change
5	52.2±4.6 (5)/69.3±3.3 (4)	33[c]	51.0±2.6 (5)/72.9±4.2 (4)	43[d]	51.8±1.4 (5)/79.6±1.7 (4)	54[d]
6	52.2±4.6 (5)/66.8±6.3 (4)	28	52.2±4.6 (5)/70.5±2.1 (4)	35[c]	53.3±2.7 (5)/79.9±2.3 (4)	50[d]
22	51.7±3.0 (6)/66.6±2.8 (4)	29[d]	49.3±3.6 (5)/69.7±3.9 (4)	41[d]	51.7±3.4 (5)/78.8±3.1 (4)	52[d]
1b[e]	52.5±2.6 (5)/75.4±2.1 (4)	44[d]	49.3±3.6 (5)/72.0±3.4 (4)	46[d]	51.8±2.1 (5)/83.6±2.4 (4)	61[d]

a) Each value represents the mean±S.E.M. *b*) Number of rats used. A statistically significant difference from the control group; *c*) $p<0.05$, *d*) $p<0.01$ (Duncan's multiple range test). *e*) The figures shown are the data for the **1b**·hydrochloride.

TABLE IV. Effect of the Selected 2-Morpholinylbenzamides on Gastric Emptying of Phenol Red Semisolid Meal in Mice

Compound	Gastric emptying rate[a]					
	Control (n^{b})/ 0.5 mg/kg, *p.o.* (*n*)	% change	Control (*n*)/ 1.0 mg/kg, *p.o.* (*n*)	% change	Control (*n*)/ 2.0 mg/kg, *p.o.* (*n*)	% change
5	NT		54.3±2.8 (7)/63.1±2.5 (5)	16	53.1±1.4 (7)/83.1±5.0 (5)	56[c]
6	52.8±3.7 (7)/65.6±4.9 (5)	24	53.7±4.6 (7)/70.5±3.4 (5)	31[c]	52.8±3.7 (7)/73.4±2.0 (5)	39[d]
22	NT		54.3±2.8 (7)/59.8±4.3 (5)	10	53.1±4.1 (7)/75.9±6.5 (5)	43[d]
1b[e]	53.1±4.1 (7)/76.7±4.1 (5)	44[d]	52.7±2.1 (7)/72.0±1.9 (5)	37[d]	54.3±2.8 (7)/69.5±3.3 (5)	28[d]

a) Each value represents the mean±S.E.M. *b*) Number of rats used. A statistically significant difference from the control group; *c*) $p<0.05$, *d*) $p<0.01$ (Duncan's multiple range test). *e*) The figures shown are the data for the **1b**·hydrochloride. NT, not tested.

(**14**)>cisapride>isopentyloxy (**15**)=*n*-heptyloxy (**9**)=*n*-pentyloxy (**7**)≥methoxy (**1a**)≥isopropoxy (**13**)≫*n*-hexyloxy (**8**)=*n*-decyloxy (**12**)>metoclopramide≥*n*-nonyloxy (**11**)≥*n*-octyloxy (**10**).

Replacement of the methoxy group of **1a** by cycloalkyloxy (**17**—**19**) and unsaturated alkyloxy (**20**—**22**, **24**) groups, in general, resulted in an increase in activity; the exception was the cyclohexylmethyl derivative (**18**), which showed the least activity of this series. Compounds **17** and **19**—**22** are practically comparable or somewhat superior to cisapride; compound **22** with a 3-methyl-2-butenyloxy group is essentially equipotent to **1c**.

In a previous paper,[8] we reported that introduction of a fluorine atom at the para-position of the benzyl group of **1c** (giving **1b**) caused an increase in activity. This finding led us to introduce a fluorine atom into the benzyl group of compounds **5**, **15**, and **22** (giving **6**, **16**, **23**, respectively). As a result, **16** was found to be significantly more active than the parent compound **15**, whereas **6** and **23** exhibited lower activity than **5** and **22**.

To know the influence of diversely functionalized C-2 alkoxy groups on activity, compounds **25**—**39** were prepared. Introduction of phenyl (**25**, **26**), benzoyl (**27**, **39**), acetyl (**28**), hydroxy (**29**, **33**), ethoxycarbonyl (**30**), carboxyl (**31**), (2-methoxy)ethoxy (**32**), chloro (**34**), cyano (**35**), phthalimido (**36**), amino (**37**), and 4-fluorophenoxy (**38**) groups into the C-2 position generally had no favorable influence on activity. Acetyl (**28**), secondary hydroxy (**29**), and chloro (**34**) groups exceptionally gave the derivatives with an activity greater than that of **1a**. Compound **29** with a secondary hydroxy group, in particular, had comparable activity to that of **1c**. Although there was, on the whole, no clear SAR for the C-2 substituent, seven compounds (**4**—**6**, **14**, **16**, **22**, **29**) were found to be more active than cisapride.

The activity for dopamine D_2 receptor antagonism *in vitro* was also determined by the [^{3}H]spiperone binding test as described previously.[8] None of the 2-morpholinylbenzamides prepared ever showed a dopamine D_2 binding affinity at the concentration of 10^{-6} M, nor did the analogues **1a**—**c**.

TABLE V. Effect of the Selected 2-Morpholinylbenzamides on Gastric Emptying of Resin Pellet Solid Meal in Rats

Compound	Control (mean±S.E.M.) (n^{a})	2.0 mg/kg, *p.o.* (mean±S.E.M.) (*n*)	% change
5	27.0±2.7 (5)	8.0±2.5 (4)	70[b]
6	27.0±2.7 (5)	4.3±0.9 (4)	84[b]
22	27.0±2.7 (5)	12.8±1.7 (4)	53[b]
1b	27.0±2.7 (5)	5.8±2.1 (4)	79[b]

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

In the light of the potent gastric emptying activity and the weak acute toxicity in mice,[9] three compounds (**5**, **6**, **22**) were selected for further biological assays including the gastric emptying activity of phenol red semisolid meal in rats and mice at different doses. Gastric emptying activity in rats using resin pellet solid meal was also tested, because assays with semisolid meal and solid meal have shown a difference in mechanism.[10,11] The results are presented in Tables III—V, where the activity of **1b** is included for comparison. In the gastric emptying activity of semisolid meal at oral doses of 0.2, 0.5, and 2.0 mg/kg in rats and of 1.0 mg/kg in mice, the three compounds were somewhat less potent than **1b**. In contrast, the gastric emptying activity of solid meal at an oral dose of 2.0 mg/kg of compound **6** was slightly more potent than that of **1b**. These compounds, on the whole, are essentially equipotent to **1b**.

In conclusion, the modification of the C-2 substituents

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on the benzoyl moieties of **1a** and **1b** led to many compounds (7 of 36 compounds examined in the present study) with a better activity than cisapride. Of these, 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-2-(*n*-butoxy)-5-chlorobenzamide (**5**), its 4-fluorobenzyl (**6**), and 3-methyl-2-butenyloxy analogues (**22**) were found to possess a potent gastrokinetic activity and to have no dopamine D_2 receptor antagonistic activity. Comparison of detailed biological properties of these compounds and **1b** showed, however, that none of **5**, **6**, or **22** has the overall advantage of **1b** previously reported.[8] Therefore **1b** (AS-4370 as its citrate) was selected as the most promising candidate as a selective and potent gastrokinetic agent. AS-4370,[12] now under clinical study, has the same mechanism of gastrokinetic action as does cisapride.

Experimental

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

The preparation of 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-hydroxybenzamide (**2**) was previously reported.[7]

4-Amino-5-chloro-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]-2-hydroxybenzamide (3) A solution of ethanethiol (1.9 g, 31 mmol) in DMF (10 ml) was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.2 g, 0.030 mol) in DMF (50 ml) under ice-cooling. After the reaction mixture was stirred at room temperature for 0.5 h, 4-amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]-methyl]benzamide[7] (**1b**, 8.4 g, 20 mmol) was added. The mixture was heated to reflux for 4 h, then cooled, and concentrated to dryness. The residue was taken up in water and washed with $CHCl_3$. The aqueous layer was neutralized with 10% HCl and extracted with AcOEt. The extract was washed successively with water and brine and evaporated. The crude product was chromatographed on silica gel with AcOEt to afford **3** as an oil, which was crystallized from toluene to give 6.4 g (82%) of **3**, mp 117—119 °C; its ^{1}H-NMR spectrum revealed that the crystal includes toluene as a crystallization solvent. *Anal.* Calcd for $C_{19}H_{21}ClFN_3O_3 \cdot 1/5C_6H_5CH_3$: C, 59.43; H, 5.53; Cl, 8.60; F, 4.61; N, 10.19. Found: C, 59.11; H, 5.51; Cl, 8.53; F, 4.28; N, 10.11. ^{1}H-NMR ($CDCl_3$): 1.95 (1H, t, J=10, 3-$H_{ax.}$), 2.18 (1H, td, J=10, 4, 5-$H_{ax.}$), 2.35 (0.6H, s, $C_6H_5C\underline{H}_3$), 2.56—2.84 (2H, m, 5-$H_{eq.}$ and 3-$H_{eq.}$), 3.17—3.38 (1H, m, NCH), 3.47 (2H, s, $FC_6H_4C\underline{H}_2$), 3.52—3.83 (3H, m, NCH, 2-H, 6-$H_{ax.}$), 3.83—3.95 (1H, m, 6-$H_{eq.}$), 4.39 (2H, s, NH_2), 6.29 (1H, s, arom 3-H), 6.37 (1H, br t, NHCO), 6.93—7.70, 7.14—7.37 (6H, m, arom H), 12.44 (1H, s, OH). EIMS m/z: 393 (M^+). IR ν cm^{-1}: 3430, 3340, 3220, 1645, 1580, 1280.

2-Substituted 4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chlorobenzamides and Its 4-Fluorobenzyl Analogues (4—28, 30, 32—36, 38, 39). A Typical Procedure. 4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-2-(*n*-butoxy)-5-chlorobenzamide (5) To a stirred solution of **2** (4.0 g, 11 mmol) in 1 N NaOH (32 ml) were added tetrabutylammonium bromide (3.4 g, 11 mmol) and a solution of *n*-butyl bromide (4.3 g, 31 mmol) in CH_2Cl_2 (32 ml). The reaction mixture was vigorously stirred at room temperature for 15 h and concentrated to dryness. The residue was dissolved in AcOEt. The organic layer was washed successively with water and brine and evaporated. The crude product was chromatographed on silica gel with $CHCl_3$–MeOH (95:5) to give 4.4 g (95%) of **5** as an oil. This oil was converted to the fumarate in the usual manner. EIMS m/z: 431 (M^+). ^{1}H-NMR (DMSO-d_6): 0.95 (3H, t, J=7, $OCH_2CH_2CH_2C\underline{H}_3$), 1.1—2.3, 2.4—2.9 (8H, m), 3.50 (2H, s, $C\underline{H}_2C_6H_5$), 3.1—3.8 (5H, m), 4.00 (2H, t, J=7, $OC\underline{H}_2CH_2CH_2CH_3$), 5.87 (2H, br s, NH_2), 6.64 (1H, s, arom 3-H), 7.30 (5H, s, $CH_2C_6\underline{H}_5$), 7.72 (1H, s, arom 6-H), 7.8—8.1 (1H, m, CONH). IR ν cm^{-1}: 3450, 3345, 3310, 3200, 2950, 2860, 1680, 1630, 1520.

4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-(2-hydroxypropoxy)benzamide (29) To a solution of the free base of **28** (1.6 g, 3.7 mmol) in MeOH (15 ml) was added portionwise $NaBH_4$ (0.14 g, 3.7 mmol) at 5 °C. The mixture was stirred at room temperature for 2 h and concentrated to dryness. The residue was dissolved in $CHCl_3$, and the organic layer was washed successively with water and brine and evaporated to leave 1.3 g (81%) of **29** as an oil. This oil was converted to the fumarate in the usual manner. EIMS m/z: 433 (M^+). ^{1}H-NMR (DMSO-d_6): 1.20 (3H, d, J=6, $OCH_2CH(OH)C\underline{H}_3$), 1.6—2.3, 2.4—2.9 (4H, m), 3.47 (2H, s, $C\underline{H}_2C_6H_5$), 3.1—4.2 (8H, m), 5.87 (2H, br s, NH_2), 6.47 (1H, s, arom 3-H), 7.30 (5H, s, $CH_2C_6\underline{H}_5$), 7.70 (1H, s, arom 6-H), 8.0—8.3 (1H, m, CONH). IR ν cm^{-1}: 3330, 3200, 1685, 1620, 1535.

4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-2-[(carboxymethyl)oxy]-5-chlorobenzamide (31) A solution of **30** (0.7 g, 1.5 mmol) in a mixture of EtOH (20 ml) and 1 N NaOH (4.5 ml) was heated to reflux for 1 h and then cooled to 5 °C. The reaction mixture was acidified with 10% HCl and concentrated to dryness. The crude product was recrystallized from EtOH–H_2O (1:1) to give 0.3 g (46%) of **31**. EIMS m/z: 433 (M^+). ^{1}H-NMR (DMSO-d_6): 1.7—2.4, 2.4—2.8 (4H, m), 3.50 (2H, s, $C\underline{H}_2C_6H_5$), 3.1—3.9 (6H, m), 4.66 (2H, s, $OC\underline{H}_2COOH$), 5.90 (2H, br s, NH_2), 6.38 (1H, s, arom 3-H), 7.30 (5H, s, $CH_2C_6\underline{H}_5$), 7.70 (1H, s, arom 6-H), 8.3—8.6 (1H, m, CONH). IR ν cm^{-1}: 3440, 3305, 3200, 2945, 1625, 1500.

4-Amino-2-(3-aminopropoxy)-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chlorobenzamide (37) A mixture of the free base of **36** (1.2 g, 2.1 mmol), 85% hydrazine monohydrate (0.22 g, 3.7 mmol), and EtOH (30 ml) was heated to reflux for 2 h and then cooled to room temperature. The reaction mixture was diluted with $CHCl_3$ (200 ml), and the insoluble materials were removed by filtration. The filtrate was washed successively with a small amount of water and then brine. The solvent was evaporated to leave a solid, which was recrystallized from AcOEt to give 0.9 g (97%) of **37**. EIMS m/z: 432 (M^+). ^{1}H-NMR (DMSO-d_6): 1.65 (2H, br s, $OCH_2CH_2CH_2N\underline{H}_2$), 1.8—2.4, 2.4—3.1, 3.1—3.9 (13H, m), 3.48 (2H, s, $C\underline{H}_2C_6H_5$), 4.10 (2H, t, J=6, $OC\underline{H}_2CH_2CH_2NH_2$), 4.35 (2H, br s, NH_2), 6.30 (1H, s, arom 3-H), 7.29 (5H, s, $CH_2C_6\underline{H}_5$), 8.09 (1H, s, arom 6-H), 8.0—8.3 (1H, m, CONH). IR ν cm^{-1}: 3395, 3325, 3200, 2940, 2850, 1620, 1530.

Pharmacology The male mouse of Std-ddY strain (Japan SLC Inc.) weighing 30—40 g and the male rat of Wistar strain (Japan SLC Inc.) weighing 130—150 g were used. The mice and rats were fasted for 18 h before the experiments.

Gastric Emptying of Semisolid Meal A test meal (0.05% phenol red in 1.5% aqueous methylcellulose solution) of 0.2 ml per mouse and 1.5 ml per rat was given through a gastric tube. Fifteen minutes later, the animals were sacrificed. The stomach was removed, and the amount of phenol red remaining in the stomach was measured according to the method of Scarpignato *et al.*[13] The test compounds, suspended in a 0.5% tragacanth solution, were orally administered 60 min before administration of the test meal.

Gastric Emptying of Solid Meal Gastric emptying of solid meal (resin pellets) was measured according to the method of Jacoby and Brodie.[14] Small resin pellets (Amberlite IRA-93, 1-mm diameter, 40 pellets per rat) were administered through a polyethylene tube (PE-200) into the stomach. One hour later, the animals were sacrificed and the number of pellets remaining in the stomach was counted. The test compounds were orally administered 30 min before administration of the resin pellets.

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