Novel Benzamides as Selective and Potent Gastrokinetic Agents. III.[1] Synthesis and Structure–Activity Relationships of 4-Amino-5-chloro-2-methoxy- and 2-Ethoxy-*N*-[(4-substituted 2-morpholinyl)methyl]-benzamides

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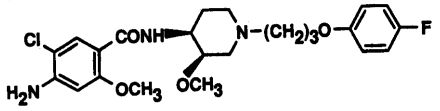
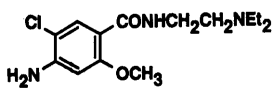
A series of 4-amino-5-chloro-2-methoxy- and 2-ethoxy-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides (11—64) were prepared and evaluated for gastrokinetic activity by determining their effects on the gastric emptying of phenol red semisolid meal in rats. The N-4 substituent includes alkyl, phenoxyalkyl, (4-fluorobenzoyl)alkyl, and heteroarylmethyl groups. The benzamide derivatives, having an isopropyl, isoamyl, neopentyl, 3-(4-chlorophenoxy)-propyl, or pyridylmethyl group at N-4, showed potent *in vivo* gastric emptying activity. In particular, 4-amino-5-chloro-2-ethoxy-*N*-[[4-(3-pyridylmethyl)-2-morpholinyl]methyl]benzamide (57b) was equipotent to the 4-fluorobenzyl analogue 1b (AS-4370 as its citrate) in the gastrokinetic activity on phenol red semisolid meal in rats and mice, and on resin pellet solid meal in rats. Moreover, compound 57b was free from dopamine D_2 receptor antagonistic activity in both *in vitro* ([^{3}H]spiperone binding) and *in vivo* (apomorphine-induced emesis in dogs) tests. Structure–activity relationships of compounds with various substituents at N-4 are also discussed.

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

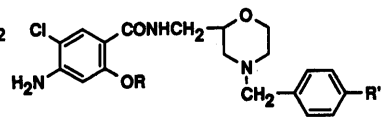
Our previous papers[1,2] reported that several benzamide derivatives represented generically by **1**, which appended a new amine moiety, 2-(aminomethyl)-4-benzylmorpholine, showed potent gastrokinetic activity without dopamine D_2 receptor antagonistic activity; this morpholinyl moiety had been newly designed after consideration of the side-chain structure of cisapride which is used clinically as a gastrokinetic agent. This finding had led us to modify the benzoyl moiety and to introduce various substituents into the N-4 benzyl group, resulting in the discovery of 4-amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide[1] (**1b**, AS-4370 as its citrate) which is substantially equipotent to cisapride and much higher than metoclopramide in gastrokinetic activity. AS-4370 is presently under clinical study.



cisapride



metoclopramide



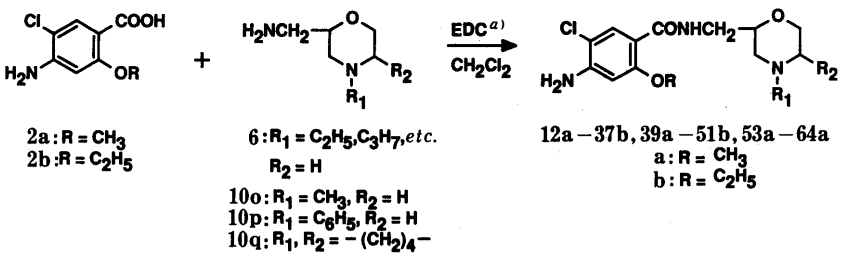
1a: R = CH_3, R' = H

1b: R = C_2H_5, R' = F

Chart 1

As an extention of that work, we have directed our effort to a search of N-4 substituents (R_1) that might cause a greater enhancement in gastrokinetic activity than the 4-fluorobenzyl group of **1b**. The present paper deals with a synthesis and structure–activity relationship (SAR) of a new series of morpholinyl benzamides appending alkyl, phenoxyalkyl, (4-fluorobenzoyl)alkyl, and heteroarylmethyl groups at N-4 of the morpholine ring as shown in Table I.

Chemistry 4-Amino-5-chloro-2methoxy- and 2-ethoxy-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides (**12a**—**64a**), except the previously reported derivative **38a**[1] and the aminophenoxy derivative **52a**, were synthesized by the reaction of 4-amino-5-chloro-2-methoxy- and 2-ethoxybenzoic acids (**2a** and **2b**)[1] with an appropriate 4-substituted 2-(aminomethyl)morpholine (**6** or **10o, p**) and 3-(aminomethyl)octahydropyrido[2,1-*c*][1,4]oxazine (**10q**) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride[3] as a coupling reagent (Chart 2). The aminophenoxy derivative **52a** was derived by



2a: R = CH_3
2b: R = C_2H_5

6: R_1 = C_2H_5, C_3H_7, *etc.*, R_2 = H
10o: R_1 = CH_3, R_2 = H
10p: R_1 = C_6H_5, R_2 = H
10q: R_1, R_2 = $-(CH_2)_4-$

12a–37b, 39a–51b, 53a–64a
a: R = CH_3
b: R = C_2H_5

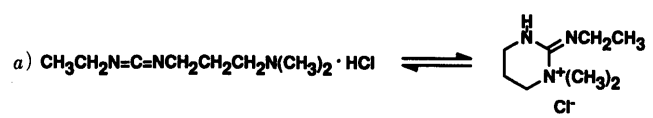
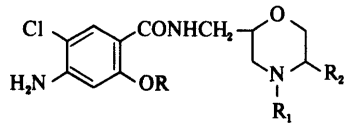


Chart 2

TABLE I. Physical Data for 2-Alkoxy-4-amino-5-chloro-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides (**12a—37b** and **39a—64a**)



Compd.	R	R_1[a]	R_2	Yield[b] (%) Method[c]	mp (°C) (Recryst. solvent[d])	Formula	Analysis (%) Calcd (Found) C	H	N	Cl	F
12a	CH_3	CH_3	H	10[e] C	237—239 (E)	$C_{14}H_{20}ClN_3O_3 \cdot HCl \cdot 1/4H_2O$	47.40 (47.33)	6.11 6.07	11.85 11.73	19.99 20.11)	
12b	C_2H_5	CH_3	H	16 C	183—185 (E)	$C_{15}H_{22}ClN_3O_3$	54.96 (54.90)	6.76 6.85	12.82 12.69	10.82 10.77)	
13a	CH_3	CH_3CH_2	H	23 A	235—237 (M)	$C_{15}H_{22}ClN_3O_3 \cdot HCl$	49.46 (49.32)	6.36 6.61	11.54 11.49	19.47 19.74)	
13b	C_2H_5	CH_3CH_2	H	25 A	150—151 (I)	$C_{16}H_{24}ClN_3O_3$	56.22 (56.32)	7.08 7.11	12.29 12.24	10.37 10.24)	
14a	CH_3	$CH_3(CH_2)_2$	H	48 A	224—228 (E)	$C_{16}H_{24}ClN_3O_3 \cdot HCl$	50.80 (50.70)	6.66 6.76	11.11 10.82	18.74 18.44)	
14b	C_2H_5	$CH_3(CH_2)_2$	H	60 A	141—142 (I)	$C_{17}H_{26}ClN_3O_3$	57.38 (57.37)	7.36 7.51	11.81 11.84	9.96 9.83)	
15b	C_2H_5	$(CH_3)_2CH$	H	41 A	134—139 (E)	$C_{17}H_{26}ClN_3O_3 \cdot 5/4HCl \cdot 7/4H_2O$	47.16 (46.91)	7.16 7.53	9.71 9.61	18.44 18.79)	
16a	CH_3	$CH_3(CH_2)_3$	H	68 A	231—235 (E)	$C_{17}H_{26}ClN_3O_3 \cdot HCl$	52.05 (52.00)	6.94 7.07	10.71 10.59	18.07 17.79)	
16b	C_2H_5	$CH_3(CH_2)_3$	H	59 A	209—210 (AC-W)	$C_{18}H_{28}ClN_3O_3 \cdot HCl \cdot 1/2H_2O$	52.05 (51.93)	7.28 7.09	10.12 9.92	17.07 17.01)	
17b	C_2H_5	$CH_3(CH_2)_4$	H	82 A	205—207 (M)	$C_{19}H_{30}ClN_3O_3 \cdot HCl \cdot 3/2H_2O$	51.01 (51.19)	7.66 7.83	9.39 9.41	15.85 15.68)	
18b	C_2H_5	$(CH_3)_2CH(CH_2)_2$	H	10 A	212—216 (E)	$C_{19}H_{30}ClN_3O_3 \cdot HCl \cdot 3H_2O$	48.10 (48.10)	7.86 7.86	8.86 8.86	14.94 15.18)	
19b	C_2H_5	$(CH_3)_3CCH_2$	H	2 A	210—214 (E)	$C_{19}H_{30}ClN_3O_3 \cdot 5/4HCl \cdot 3/4H_2O$	51.51 (51.84	7.45 7.75	9.49 9.11	18.01 17.92)	
20b	C_2H_5	$CH_3(CH_2)_5$	H	71 A	190—195 (I)	$C_{20}H_{32}ClN_3O_3 \cdot HCl \cdot 3H_2O$	49.18 (49.34	8.05 8.09	8.60 8.70	14.52 14.80)	
21b	C_2H_5	$CH_3(CH_2)_6$	H	61 A	207—210 (E)	$C_{21}H_{34}ClN_3O_3 \cdot 3/2HCl \cdot 1/2C_2H_5OH$[f]	53.96 (54.08	7.92 7.83	8.58 8.87	18.10 17.92)	
22b	C_2H_5	$CH_3(CH_2)_7$	H	74 A	203—206 (E)	$C_{22}H_{36}ClN_3O_3 \cdot 5/4HCl \cdot 1/2H_2O$	54.98 (55.30	8.02 8.03	8.74 8.74	16.60 16.70)	
23b	C_2H_5	$-(CH_2)_4-$		27[g] C	192—205 (M)	$C_{18}H_{26}ClN_3O_3$	58.77 (58.70	7.12 6.94	11.42 11.25	9.64 10.00)	
24a	CH_3		H	11 A	189—190 (I)	$C_{19}H_{28}ClN_3O_3$	59.76 (59.53	7.39 7.49	11.00 10.91	9.28 9.18)	
25a	CH_3		H	37 A	105—108 (I)	$C_{17}H_{24}ClN_3O_3 \cdot 1/4H_2O$	56.98 (56.69	6.89 6.98	11.73 11.65	9.89 9.86)	
26a	CH_3		H	84 B	159—163 (E)	$C_{20}H_{28}ClN_3O_3 \cdot C_4H_4O_4$[h] $\cdot 1/4H_2O$	56.03 (55.83	6.37 6.34	8.17 8.04	6.89 6.75)	
27a	CH_3	$CH_2=CHCH_2$	H	44 B	122—124 (I-DE)	$C_{16}H_{22}ClN_3O_3$	56.55 (56.25	6.53 6.59	12.37 12.13	10.43 10.71)	
28a	CH_3	$C_6H_5CH=CHCH_2$	H	58 B	124—127 (E-DE)	$C_{22}H_{26}ClN_3O_3 \cdot 3/2C_4H_4O_4$[h] $\cdot 3/4H_2O$	55.72 (55.69	5.59 5.82	6.96 6.83	5.87 5.82)	
29b	C_2H_5	$CH\equiv CCH_2$	H	23 A	148—151 (I)	$C_{17}H_{22}ClN_3O_3 \cdot 1/4H_2O$	57.30 (57.64	6.36 6.35	11.94 11.79	9.95 10.20)	
30b	C_2H_5	$C_6H_4(CO)_2N(CH_2)_4$	H	78 B	139—141 (E)	$C_{26}H_{31}ClN_4O_5$	60.64 (60.66	6.07 6.12	10.88 10.60	6.88 6.71)	
31a	CH_3	$C_6H_5NH(CH_2)_2$	H	13 A	117—125 (E)	$C_{21}H_{27}ClN_4O_3 \cdot C_2H_2O_4$[i] $\cdot 5/4H_2O$	51.94 (51.98	5.99 5.97	10.54 10.15	6.67 6.90)	
32b	C_2H_5	$(CH_3)_2N(CH_2)_3$	H	11 A	223—225 (M)	$C_{19}H_{31}ClN_4O_3 \cdot 5/2C_2H_2O_4$[i] $\cdot H_2O$	45.08 (44.90	6.03 5.97	8.37 8.73	5.69 5.52)	
33b	C_2H_5	$CH_3OCO(CH_2)_2$	H	7 A	125—127 (I)	$C_{18}H_{26}ClN_3O_5 \cdot 1/4H_2O$	53.46 (53.59	6.61 6.45	10.39 10.45	8.77 9.04)	
34b	C_2H_5	$HO(CH_2)_3$	H	43 A	162—164 (E)	$C_{17}H_{26}ClN_3O_4 \cdot 3/2C_4H_4O_4$[h]	50.60 (50.46	5.91 5.89	7.70 7.52	6.49 6.38)	
35b	C_2H_5	$NC(CH_2)_2$	H	14 B	182—183 (I)	$C_{17}H_{23}ClN_4O_3$	55.66 (55.36	6.32 6.27	15.27 14.97	9.66 9.69)	
36b	C_2H_5	$(C_2H_5O)_2CHCH_2$	H	77 B	168—170 (E)	$C_{20}H_{32}ClN_3O_5 \cdot 3/2C_4H_4O_4$[h]	51.70 (51.63	6.34 6.21	6.96 6.94	5.87 5.85)	
37b	C_2H_5	C_6H_5	H	24[j] C	163—165 (I)	$C_{20}H_{24}ClN_3O_3 \cdot 1/4H_2O$	60.91 (60.92	6.26 6.11	10.56 10.57	8.99 9.13)	
39a	CH_3	$C_6H_5O(CH_2)_3$	H	37 B	133—135 (E)	$C_{22}H_{28}ClN_3O_4$	60.89 (60.72	6.50 6.45	9.68 9.61	8.17 8.18)	

TABLE I. (continued)

Compd.	R	R_1[a]	R_2	Yield[b] (%) Method[c]	mp (°C) (Recryst. solvent[d])	Formula	Analysis (%) Calcd (Found) C	H	N	Cl	F
40a	CH_3	$C_6H_5OCH(CH_3)CH_2$	H	41 B	113—115 (E)	$C_{22}H_{28}ClN_3O_4 \cdot C_2H_2O_4$[i]	55.33 (55.02	5.85 5.77	8.14 8.02	6.79 6.77)	
41a	CH_3	4-$FC_6H_4O(CH_2)_2$	H	31 B	148—150 (I)	$C_{21}H_{25}ClFN_3O_4$	57.60 (57.64	5.75 6.12	9.60 9.45	8.10 8.03	4.34 4.38)
41b	C_2H_5	4-$FC_6H_4O(CH_2)_2$	H	44 B	182—184 (E)	$C_{22}H_{27}ClFN_3O_4 \cdot 2C_4H_4O_4$[h]	52.67 (52.66	5.16 5.14	6.14 6.07	5.18 5.31	2.78 2.78)
42a	CH_3	4-$FC_6H_4O(CH_2)_3$	H	14 B	127—129 (T–H)	$C_{22}H_{27}ClFN_3O_4$	58.47 (58.63	6.02 5.96	9.30 9.21	7.84 7.80	4.20 4.14)
42b	C_2H_5	4-$FC_6H_4O(CH_2)_3$	H	20 B	125—126 (I)	$C_{23}H_{29}ClFN_3O_4$	59.29 (58.93	6.27 6.48	9.02 9.06	7.61 7.84	4.08 3.81)
43a	CH_3	2-$FC_6H_4O(CH_2)_3$	H	25 B	69—72 (E)	$C_{22}H_{27}ClFN_3O_4$	58.47 (58.08	6.02 6.02	9.30 9.10	7.84 7.88	4.20 4.09)
44a	CH_3	3-$FC_6H_4O(CH_2)_3$	H	33 B	78—81 (E)	$C_{22}H_{27}ClFN_3O_4$	58.47 (58.11	6.02 5.97	9.30 9.12	7.84 7.92	4.20 4.09)
45a	CH_3	4-$FC_6H_4O(CH_2)_4$	H	64 B	158—161 (E–DE)	$C_{23}H_{29}ClFN_3O_4 \cdot 3/2C_4H_4O_4$[h]	54.42 (54.31	5.51 5.79	6.57 6.40	5.54 5.25	2.97 2.92)
46a	CH_3	4-$FC_6H_4O(CH_2)_5$	H	48 B	164—166 (E)	$C_{24}H_{31}ClFN_3O_4 \cdot C_2H_2O_4$[i] $\cdot 1/4H_2O$	54.26 (54.11	6.04 5.84	7.30 7.29	6.16 5.98	3.30 3.41)
47a	CH_3	4-$FC_6H_4O(CH_2)_6$	H	39 B	120—122 (E–DE)	$C_{25}H_{33}ClFN_3O_4 \cdot 3/2C_4H_4O_4$[h]	55.73 (55.49	5.88 5.91	6.29 6.27	5.31 5.16	2.84 2.85)
48a	CH_3	4-$ClC_6H_4O(CH_2)_3$	H	51 B	123—126 (I)	$C_{22}H_{27}Cl_2N_3O_4$	56.42 (56.27	5.81 5.73	8.97 8.98	15.14 15.33)	
48b	C_2H_5	4-$ClC_6H_4O(CH_2)_3$	H	59 B	149—151 (E)	$C_{23}H_{29}Cl_2N_3O_4$	57.27 (57.01	6.06 6.13	8.71 8.42	14.70 14.56)	
49a	CH_3	4-$ClC_6H_4O(CH_2)_2$	H	28 B	158—162 (E–DE)	$C_{21}H_{25}Cl_2N_3O_4 \cdot 5/2C_4H_4O_4$[h]	50.01 (50.05	4.74 4.84	5.64 5.48	9.52 9.17)	
49b	C_2H_5	4-$ClC_6H_4O(CH_2)_2$	H	31 B	190—192 (E)	$C_{22}H_{27}Cl_2N_3O_4 \cdot C_2H_2O_4$[i]	51.62 (51.76	5.23 5.33	7.53 7.46	12.70 12.46)	
50a	CH_3	4-$CNC_6H_4O(CH_2)_3$	H	46 B	170—172 (I)	$C_{23}H_{27}ClN_4O_4 \cdot 1/4H_2O$	59.61 (59.49	5.98 5.90	12.09 11.88	7.65 7.76)	
50b	C_2H_5	4-$CNC_6H_4O(CH_2)_3$	H	50 B	157—158 (E)	$C_{24}H_{29}ClN_4O_4$	60.95 (60.89	6.18 6.22	11.85 11.84	7.50 7.47)	
51a	CH_3	4-$NO_2C_6H_4O(CH_2)_3$	H	68 B	149—153 (E)	$C_{22}H_{27}ClN_4O_6 \cdot 1/5H_2O$	54.76 (54.98	5.72 5.64	11.61 11.28	7.35 7.52)	
51b	C_2H_5	4-$NO_2C_6H_4O(CH_2)_3$	H	65 B	137—139 (E)	$C_{23}H_{29}ClN_4O_6 \cdot 1/4H_2O$	55.53 (55.77	5.98 6.13	11.26 10.97	7.13 6.98)	
52a	CH_3	4-$NH_2C_6H_4O(CH_2)_3$	H	51 K	212—216 (I)	$C_{22}H_{29}ClN_4O_4 \cdot 3/2C_2H_2O_4$[i] $\cdot 4/5(CH_3)_2CHOH$[f]	52.07 (52.28	6.12 6.30	8.86 8.73	5.61 5.69)	
53a	CH_3	4-$FC_6H_4S(CH_2)_3$	H	60 B	127—130 (I)	$C_{22}H_{27}ClFN_3O_3S$[l]	56.46 (56.45	5.82 5.71	8.98 8.90	7.58 7.63	4.06 4.04)
53b	C_2H_5	4-$FC_6H_4S(CH_2)_3$	H	66 B	158—160 (E)	$C_{23}H_{29}ClFN_3O_3S \cdot C_4H_4O_4$[m,h]	54.22 (54.48	5.56 5.53	7.03 7.18	5.93 6.10	3.18 3.39)
54a	CH_3	4-$FC_6H_4CO(CH_2)_3$	H	15 A	148—152 (E)	$C_{23}H_{27}ClFN_3O_4 \cdot C_4H_4O_4$[h] $\cdot 1/4H_2O$	55.48 (55.20	5.43 5.62	7.19 7.11	6.07 6.26	3.25 3.14)
54b	C_2H_5	4-$FC_6H_4CO(CH_2)_3$	H	13 A	135—138 (M)	$C_{24}H_{29}ClFN_3O_4 \cdot 3/4C_2H_2O_4$[i] $\cdot 2H_2O$	52.67 (52.39	5.98 5.69	7.23 7.12	6.10 6.46	3.27 3.01)
55a	CH_3	4-$FC_6H_4COCH_2$	H	70 A	180—183 (E)	$C_{21}H_{23}ClFN_3O_4$	57.87 (57.78	5.32 5.31	9.64 9.60	8.13 8.21	4.36 4.22)
55b	C_2H_5	4-$FC_6H_4COCH_2$	H	77 A	187—189 (E)	$C_{22}H_{25}ClFN_3O_4 \cdot 3/4C_4H_4O_4$[h] $\cdot 1/2H_2O$	55.00 (54.69	5.35 5.47	7.70 7.48	6.49 6.77	3.48 3.20)
56a	CH_3	2-Pyridylmethyl	H	64 A	88—91 (E–DE)	$C_{19}H_{23}ClN_4O_3 \cdot 3/2C_4H_4O_4$[h] $\cdot H_2O$	51.51 (51.23	5.36 5.28	9.61 9.35	6.08 6.12)	
56b	C_2H_5	2-Pyridylmethyl	H	51 A	182—185 (I)	$C_{20}H_{25}ClN_4O_3 \cdot C_4H_4O_4$[h]	55.33 (55.11	5.61 5.90	10.75 10.45	6.81 6.70)	
57a	CH_3	3-Pyridylmethyl	H	26 A	126—128 (E–W)	$C_{19}H_{23}ClN_4O_3 \cdot C_2H_2O_4$[i] $\cdot 2/5C_2H_5OH$[f]	52.44 (52.27	5.53 5.65	11.22 10.95	7.10 7.20)	
57b	C_2H_5	3-Pyridylmethyl	H	34 A	150—152 (I)	$C_{20}H_{25}ClN_4O_3 \cdot C_4H_4O_4$[h] $\cdot 1/4(CH_3)_2CHOH$[f]	55.46 (55.33	5.83 5.90	10.45 10.15	6.61 6.69)	
58a	CH_3	4-Pyridylmethyl	H	50 A	167—170 (I)	$C_{19}H_{23}ClN_4O_3$	58.38 (58.12	5.93 5.93	14.33 14.19	9.07 9.35)	
58b	C_2H_5	4-Pyridylmethyl	H	51 A	175—176 (I)	$C_{20}H_{25}ClN_4O_3$	59.33 (59.13	6.22 6.45	13.84 13.58	8.76 8.70)	
59a	CH_3	2-Furylmethyl	H	60 B	131—134 (T–H)	$C_{18}H_{22}ClN_3O_4$	56.92 (57.23	5.84 5.82	11.06 10.88	9.33 9.43)	

TABLE I. (continued)

Compd.	R	R_1[a]	R_2	Yield[b] (%) Method[c]	mp (°C) (Recryst. solvent[d])	Formula	Analysis (%) Calcd (Found) C	H	N	Cl	F
60a	CH_3	3-Furylmethyl	H	50 B	166—168 (E–DE)	$C_{18}H_{22}ClN_3O_4 \cdot 1/2C_4H_4O_4$[h] $\cdot 1/4H_2O$	54.30 (54.35	5.58 5.58	9.50 9.33	8.01 7.88)	
61a	CH_3	2-Thienylmethyl	H	76 B	158—160 (E–DE)	$C_{18}H_{22}ClN_3O_3S \cdot 1/2C_4H_4O_4$[h] $\cdot 3/10H_2O$[m]	52.30 (52.58	5.40 5.26	9.15 9.04	7.72 7.40)	
62a	CH_3	3-Thienylmethyl	H	38 B	146—147 (I–DI)	$C_{18}H_{22}ClN_3O_3S \cdot 1/5H_2O$[o]	54.12 (54.23	5.65 5.40	10.52 10.50	8.87 9.07)	
63a	CH_3	3-Benzisoxazolylmethyl	H	86 A	128—129 (E)	$C_{21}H_{23}ClN_4O_4 \cdot 1/2C_4H_4O_4$[h] $\cdot 1/2H_2O$	55.48 (55.62	5.26 5.14	11.25 10.95	7.12 6.97)	
64a	CH_3	2-Naphthylmethyl	H	62 B	155—158 (E–DE)	$C_{24}H_{26}ClN_3O_3 \cdot C_4H_4O_4$[h] $\cdot 3/5H_2O$	59.33 (59.62	5.55 5.83	7.41 7.15	6.25 5.95)	

a) Alkylating agents R_1X are obtained from commercial suppliers or synthesized according to the literatures. *b*) Total yields of the free bases are based on 2-[(acetylamino)methyl]-4-benzylmorpholine (methods A and B) or 2-substituted aminoethanol (C). *c*) Capital letters refer to the procedures described in the experimental section. *d*) Abbreviations for the solvents used are as follows: E=ethanol, M=methanol, I=isopropanol, AC=acetone, W=water, DE=diethyl ether, T=toluene, H=*n*-hexane, DI=diisopropyl ether. *e*) 2-(Methylamino)ethanol is used as the starting material. *f*) The presence of crystallization solvent is shown by ^{1}H-NMR. *g*) 2-Piperidinemethanol is used as the starting material. *h*) Fumaric acid. *i*) Oxalic acid. *j*) 2-Anilinoethanol is used as the starting material. *k*) See the experimental section. *l*) Calcd for S: 6.85, Found: 7.12. *m*) Calcd for S: 5.36, Found: 5.63. *n*) Calcd for S: 6.98, Found: 6.67. *o*) Calcd for S: 8.03, Found: 7.76.

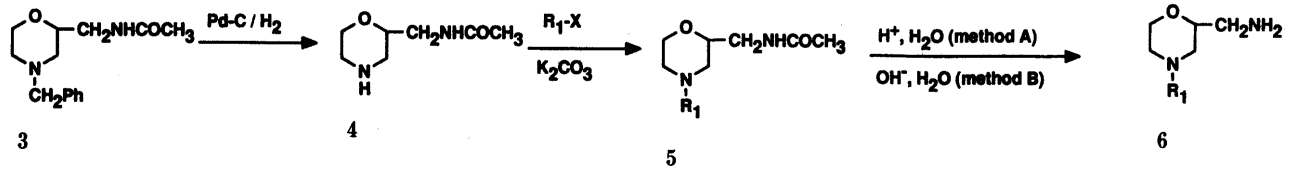


Chart 3

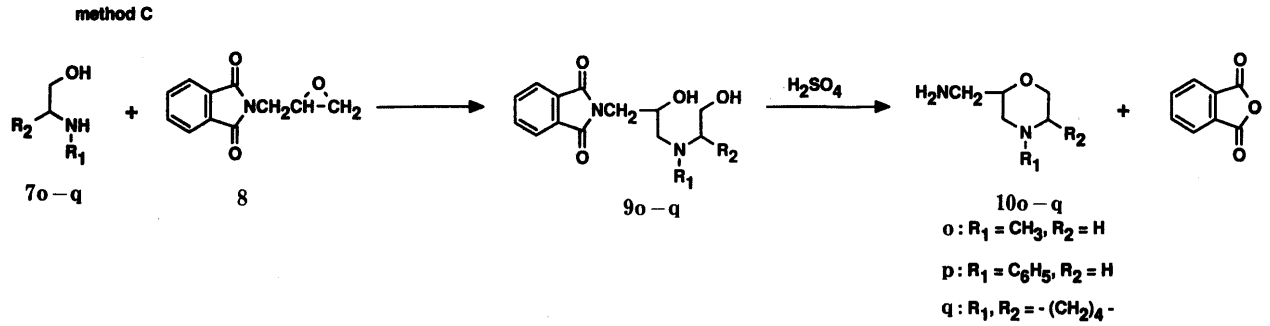


Chart 4

hydrogenation of the corresponding nitro compound **51a** in the presence of Raney nickel.

Most of the morpholine derivatives were derived as shown in Chart 3. Thus, hydrogenolysis of 2-[(acetylamino)methyl]-4-benzylmorpholine (**3**) over palladium on carbon gave 2-[(acetylamino)methyl]morpholine (**4**), which was subsequently treated with appropriate alkyl and aralkyl halides to give 4-substituted 2-[(acetylamino)methyl]morpholines (**5**). Acid or base catalized hydrolysis of the acetylamino group of **5** produced the desired 4-substituted 2-(aminomethyl)morpholines (**6**). 2-(Aminomethyl)-4-methylmorpholine (**10o**), 2-(aminomethyl)-4-phenylmorpholine (**10p**), and 3-(aminomethyl)octahydropyrido[2,1-*c*][1,4]oxazine (**10q**) were prepared according to the method described in the previous paper[2] (Chart 4). The reactions of 2-(methylamino)ethanol (**7o**), 2-anilinoethanol (**7p**), and 2-(hydroxymethyl)piperidine (**7q**) with *N*-(2,3-epoxypropyl)phthalimide (**8**) at 80 °C, followed by the treatment of the corresponding intermediate diols **9o—q** with concentrated sulfuric acid, gave (aminomethyl)-

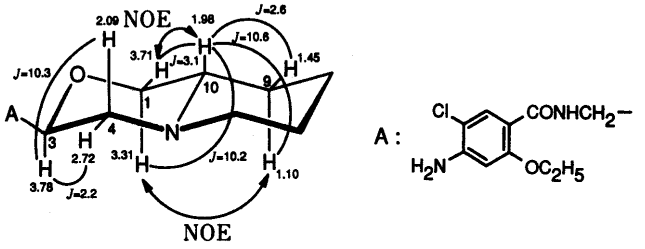


Fig. 1. ^{1}H-NMR Chemical Shifts (ppm), Coupling Constants (Hz), and NOE Correlation of the Octahydropyrido[2,1-*c*][1,4]oxazine Ring Protons of **23b** (^{1}H-NMR in $CDCl_3$)

morpholines **10o—q**, respectively, accompanied by the formation of phthalic anhydride. Acid treatment of the diols caused not only the cyclization to the morpholine ring but the concurrent hydrolysis of the phthalimide moiety to an amino group, thereby conveniently yielding the desired (aminomethyl)morpholines. The structures of all compounds thus prepared were confirmed by their proton nuclear magnetic resonance (^{1}H-NMR) spectra

TABLE II. Effect of 2-Alkoxy-4-amino-5-chloro-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides (**11a—64a**) on Gastric Emptying of Phenol Red Semisolid Meal in Rats

Compd.	Gastric emptying rate: Control (Mean±S.E.M.) ($N^{a)}$)	Gastric emptying rate: 2.0 mg/kg, *p.o.* (Mean±S.E.M.) (*N*)	% change	Acute toxicity[d] (1.0 g/kg, *p.o.*)
11a[e]	55.6±5.2 (5)	71.6±5.4 (4)	29	ND
12a	52.7±2.1 (5)	61.1±4.6 (4)	16	ND
12b	55.1±4.6 (4)	71.7±3.7 (3)	30[b)]	ND
13a	55.8±3.4 (5)	70.5±4.6 (4)	26[b)]	ND
13b	55.1±4.6 (4)	76.6±7.3 (3)	39[c)]	ND
14a	55.8±3.4 (5)	75.2±2.0 (4)	35[c)]	ND
14b	55.1±4.6 (4)	81.2±3.8 (3)	47[c)]	ND
15b	50.8±3.1 (5)	78.3±1.9 (4)	54[c)]	7/10
16a	57.2±4.2 (5)	73.0±3.2 (4)	28[b)]	ND
16b	50.8±3.1 (5)	75.2±3.8 (4)	48[c)]	10/10
17b	50.8±3.1 (5)	75.9±4.6 (4)	49[c)]	10/10
18b	50.2±3.4 (5)	79.5±2.5 (4)	58[c)]	10/10
19b	55.1±4.6 (4)	82.7±7.0 (3)	50[c)]	ND
20b	50.0±1.6 (5)	73.3±3.4 (4)	47[c)]	8/10
21b	54.2±2.6 (4)	67.5±3.6 (3)	25	ND
22b	54.2±2.6 (4)	58.7±7.9 (3)	8	ND
23b	51.3±4.9 (5)	54.4±4.9 (4)	6	ND
24a	52.8±3.4 (5)	63.2±4.9 (4)	20	ND
25a	52.8±3.4 (5)	65.6±4.5 (4)	24	ND
26a	54.5±3.9 (5)	61.6±3.4 (4)	13	ND
27a	53.2±1.9 (5)	60.3±5.1 (4)	13	ND
28a	56.6±2.1 (5)	67.2±1.8 (4)	19[b)]	ND
29b	51.2±1.7 (5)	67.6±1.8 (4)	32[c)]	ND
30b	45.0±5.2 (6)	60.8±5.6 (4)	35[c)]	ND
31a	53.1±3.1 (5)	57.2±3.0 (4)	8	ND
32b	52.4±1.8 (5)	67.1±2.9 (4)	28[c)]	ND
33b	55.1±4.6 (4)	70.6±4.3 (3)	28[b)]	ND
34b	55.1±4.6 (4)	67.8±4.2 (3)	23	ND
35b	55.1±4.6 (4)	67.6±3.4 (3)	23	ND
36b	54.2±1.6 (4)	70.1±5.5 (3)	29[b)]	ND
37b	54.5±1.0 (5)	66.0±4.9 (4)	21	ND
38a[e]	56.6±2.1 (5)	67.1±4.4 (4)	19	ND
39a	55.1±4.6 (4)	68.3±1.6 (3)	24[b)]	ND
40a	52.6±3.9 (5)	62.8±2.6 (4)	19	ND
41a	55.6±5.2 (5)	72.6±1.2 (4)	31[b)]	ND
41b	55.1±4.6 (4)	75.5±5.4 (3)	37[c)]	ND
42a	55.4±1.4 (15)	68.1±2.0 (4)	23[c)]	ND
42b	55.1±4.6 (4)	75.5±5.1 (3)	37[c)]	ND
43a	54.2±2.6 (4)	66.7±3.9 (3)	23[b)]	ND
44a	54.2±2.6 (4)	64.6±3.6 (3)	19	ND
45a	56.6±2.1 (5)	67.9±3.4 (4)	20[b)]	ND
46a	50.7±2.3 (5)	57.5±3.0 (4)	13	ND
47a	55.6±5.2 (5)	60.6±4.2 (4)	9	ND
48a	55.8±3.4 (5)	85.1±1.2 (4)	53[c)]	0/10
48b	51.2±1.7 (5)	68.5±4.9 (4)	34[b)]	ND
49a	54.2±2.6 (4)	71.5±1.1 (3)	32[b)]	ND
49b	51.8±2.1 (5)	70.0±1.6 (4)	35[c)]	ND
50a	52.6±1.7 (5)	67.9±2.8 (4)	29[c)]	ND
50b	54.2±2.6 (4)	80.3±4.2 (3)	48[c)]	ND
51a	50.0±1.8 (5)	63.8±3.0 (4)	28[c)]	ND
51b	54.2±2.6 (4)	69.0±6.7 (3)	27[b)]	ND
52a	51.7±3.4 (5)	58.0±2.8 (4)	12	ND
53a	50.0±1.8 (5)	68.1±1.9 (4)	36[c)]	ND
53b	55.1±4.6 (4)	77.1±0.7 (3)	40[c)]	ND
54a	56.6±2.1 (5)	70.0±1.9 (4)	24[c)]	ND
54b	51.1±1.2 (5)	69.9±3.5 (4)	37[c)]	ND
55a	55.8±3.4 (5)	74.3±4.1 (4)	33[b)]	ND
55b	54.2±2.6 (4)	80.0±2.3 (3)	48[c)]	ND
56a	52.8±3.4 (5)	68.4±2.6 (4)	30[b)]	ND
56b	54.1±1.5 (5)	81.7±1.2 (4)	51[c)]	ND
57a	53.1±3.1 (5)	71.7±2.5 (4)	35[c)]	ND
57b	50.8±2.9 (5)	84.1±3.7 (4)	66[c)]	4/10
58a	53.1±3.1 (5)	70.0±6.4 (4)	32[b)]	ND
58b	54.1±1.5 (5)	82.7±3.0 (4)	53[c)]	0/10
59a	52.6±1.7 (5)	59.0±3.1 (4)	12	ND
60a	50.5±1.3 (5)	57.1±5.8 (4)	13	ND
61a	51.1±2.7 (5)	63.2±4.8 (4)	24[b)]	ND
62a	51.1±2.7 (5)	62.5±3.6 (4)	22[b)]	ND
63a	50.5±1.3 (5)	62.6±2.6 (4)	24[c)]	ND
64a	52.6±1.7 (5)	69.3±1.8 (4)	32[c)]	ND
Cisapride	55.2±1.9 (5)	81.3±1.2 (5)	47[c)]	0/10
Metoclopramide	58.9±2.1 (5)	71.3±3.8 (5)	21[b)]	10/10
1a	54.5±3.8 (5)	75.9±3.6 (4)	39[c)]	6/10
1b	51.8±2.1 (5)	83.6±2.4 (4)	61[c)]	4/10

a) Number of rat used. A statistically significant difference from the control group; *b*) $p<0.05$; *c*) $p<0.01$ (Duncan's multiple range test). *d*) Number of dead mouse/number of mouse used. *e*) See ref. 1. ND, not done.

and elemental analyses.

The relative stereochemistry of the bicyclic octahydropyrido[2,1-*c*][1,4]oxazine ring of **23b** was confirmed on the basis of coupling constants and the nuclear Overhauser effect (NOE) in their ^{1}H-NMR experiments. The chemical shifts, coupling constants, and NOE correlation were shown in Fig. 1. The signal for the H-10 appeared as two pairs of a double doublet centered at δ 1.98 with coupling constants of 10.2/3.1 and 10.6/2.6 Hz owing to its spin–spin couplings to axial/equatorial protons at C-1 and C-9, respectively. NOEs were observed between the axial H-9 (δ 1.10) and the axial H-1 (δ 3.31), and the H-10 (δ 1.98) and the equatorial H-1 (δ 3.71) on irradiation at each former proton. The NOE experiment between the H-10 and the axial H-4 (δ 2.09), however, provided no information because their signals appeared quite closely. In infrared (IR) spectrum of **23b**, Bohlmann bands[4] (2700—2800 cm^{-1}) were observed. The signals for the axial and equatorial H-4's appeared as a double doublet centered at δ 2.09 and 2.72 with coupling constants of 10.3 and 2.2 Hz ($J_{gem\,H\text{-}4}=11.4$ Hz), respectively, owing to H-3; the configuration of H-3 therefore is axial. These data collectively indicate that the octahydropyrido[2,1-*c*][1,4]oxazine ring is of the *trans* configuration with the axial H-10.

Biological Results and Discussion

Compounds **12a—64a** were evaluated for gastrokinetic activity by determining their effects on the gastric emptying rates of phenol red semisolid meal through the stomach. The activity data at an oral dose of 2.0 mg/kg in rats are given in Table II, which includes, for comparison, data for 4-amino-5-chloro-2-methoxy-*N*-[(2-morpholinyl)methyl]-benzamide[1] (**11a**), cisapride, metoclopramide, 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxybenzamide[2] (**1a**) and 4-amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide[1] (**1b**, AS-4370 as its citrate). The series of benzamide derivatives, which have commonly a 2-alkoxy-4-amino-5-chlorobenzoyl group, are classified into the following two series for convenience: series **a**, 2-methoxybenzamides (analogues of **1a**) and series **b**, 2-ethoxybenzamides (analogues of **1b**).

The SARs associated with modification of the N-4 substituent (R_1) is first discussed. In series **a**, either removal of the benzyl group from **1a** (giving **11a**[1]) or replacement with an alkyl group at N-4 (giving **12a**—**14a** and **16a**) resulted in reducing activity; thus the decreasing order is *n*-C_3H_7 (**14a**) > H (**11a**) = *n*-C_4H_9 (**16a**) ≥ C_2H_5 (**13a**) > metoclopramide > CH_3 (**12a**). In series **b**, replacement of the 4-fluorobenzyl group of **1b** with an alkyl group (yielding **12b**—**22b**) caused a decrease in activity. However, compounds **14b**—**20b** bearing an alkyl group with three to six carbon atoms are practically comparable or somewhat superior to cisapride, and, in particular, the isoamyl substitution (**18b**) conferred the highest activity. Compounds bearing an *n*-alkyl group exhibit activity in the decreasing order pentyl (**17b**) ≥ butyl (**16b**) ≥ hexyl (**20b**) = propyl (**14b**) > ethyl (**13b**) > methyl (**12b**) > heptyl (**21b**) > metoclopramide ≫ octyl (**22b**). Overall, the 2-ethoxy compounds (**12b**—**14b**, **16b**) are clearly more active than the 2-methoxy counterparts (**12a**—**14a**, **16a**). Formation of a bicyclic octahydropyrido[2,1-*c*][1,4]oxazine ring as in **23b** (an *n*-butylene bridge between N-4 and C-5 of the morpholine ring) caused a profound decrease in activity as compared to the N-4 butyl derivative **16b**. Introduction of a cycloalkyl group as in **24a**—**26a** deteriorated the activity. Introduction of a double bond such as allyl (**27a**) and cinnamyl (**28a**) groups and a triple bond such as a propargyl (**29b**) group into the N-4 side chain reduced the activity. The N-4 alkyl group bearing substituted amino (**30b**, **31a**, **32b**), methoxycarbonyl (**33b**), hydroxy (**34b**), cyano (**35b**), and acetal (**36b**) groups also was deleterious. Replacement of the N-4 alkyl group by phenyl (**37b**) and ethoxycarbonyl (**38a**) groups caused a decrease in activity.

The next discussion concerns the SAR of a series of N-4 phenoxyalkyl derivatives (**39**—**52**). The 3-phenoxypropyl derivative (**39a**) is more potent than the 2-phenoxypropyl analogue (**40a**). Introduction of a fluoro group into the phenyl group of **39a** provided no favorable influence on activity, thus retaining (as in **42a**, **43a**) or slightly decreasing the activity (as in **44a**). As for the position of the fluoro group on the phenyl ring, the decreasing order of activity is *para* (**42a**) = *ortho* (**43a**) > *meta* (**44a**) positions. There has previously been observed a similar SAR concerning the position of the fluoro group on the phenyl ring of **1a** and **1b**.[1] With an increase in size of the alkyl moiety of the (4-fluorophenoxy)alkyl group in series **a**, the activity decreases in the order $(CH_2)_2$ (**41a**) > $(CH_2)_3$ (**42a**) > $(CH_2)_4$ (**45a**) > $(CH_2)_5$ (**46a**) > $(CH_2)_6$ (**47a**). In series **b**, on the other hand, the *n*-propylene group (**42b**) contributes to activity as same as the ethyl group (**41b**). It is noteworthy that compounds **41a** and **41b** with the shortest methylene chain are even more potent than metoclopramide, while compound **47a** with the longest methylene chain (–$(CH_2)_6$–) is the least active and practically inactive at this screening dose.

In general, replacement of the fluoro group of the 3-(4-fluorophenoxy)propyl derivative **42a** by an electron-withdrawing group such as chloro (**48a**), cyano (**50a**), and nitro (**51a**) groups tended to increase activity, whereas replacement by an electron-donating amino group (**52a**) led to a decrease in activity. Thus, variation of the *para* substituent causes a decrease in activity in the order chloro (**48a**) ≫ cyano (**50a**) ≥ nitro (**51a**) > hydrogen (**39a**) ≥ fluoro (**42a**) ≫ amino (**52a**) groups. In series **b**, the *para* substitution reduced activity in the order cyano (**50b**) > fluoro (**42b**) > chloro (**48b**) > nitro (**51b**) groups. Although the 3-(4-chlorophenoxy)propyl group gave compound **48a** with a greater activity compared with cisapride as well as **42a**, the substitution by this group in series **b** (giving **48b**) gave little effect on activity (*cf.* **48a** *vs.* **48b**). Similarly, replacement of the propylene moiety of the 3-(4-chlorophenoxy)propyl derivatives **48a** and **48b** by an ethylene moiety (giving **49a** and **49b**, respectively) provided no favorable influence on activity.

Replacement of the oxygen atom of the 3-(4-fluorophenoxy)propyl derivatives **42a** and **42b** by a sulfur atom (yielding **53a**, **53b**, respectively) resulted in an increase in activity. Replacement by a carbonyl group (yielding **54a**, **54b**) substantially retained the activity. Conversion of the propylene moiety of the 3-(4-fluorobenzoyl)propyl derivatives **54a** and **54b** into a methylene moiety gave compounds **55a** and **55b**, respectively, with a considerably increased activity.

In order to know the influence of a heteroaryl ring, instead of the phenyl ring of the *N*-benzyl groups of **1a** and **1b**, on the gastric emptying activity, compounds **56**—**64** were prepared. In series **a**, substitution by pyridyl

TABLE III. Effect of Selective 2-Alkoxy-4-amino-5-chloro-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides on Gastric Emptying of Phenol Red Semisolid Meal in Rats

Compd.	Gastric emptying rate[a]					
	Control (N^{b})	% change	Control (N)	% change	Control (N)	% change
	0.2 mg/kg, *p.o.* (N)		0.5 mg/kg, *p.o.* (N)		2.0 mg/kg, *p.o.* (N)	
48a	53.2±1.9 (5)		53.2±1.9 (5)		55.8±3.4 (5)	
	72.4±2.1 (4)	36[d]	66.3±3.2 (4)	25[c]	85.1±1.2 (4)	53[d]
57b	50.8±2.9 (5)		50.8±2.9 (5)		50.8±2.9 (5)	
	77.1±0.3 (4)	52[d]	81.3±2.1 (4)	60[d]	84.1±3.7 (4)	66[d]
1b[e]	52.5±2.6 (5)		49.3±3.6 (5)		51.8±2.1 (5)	
	75.4±2.1 (4)	44[d]	72.0±3.4 (4)	46[d]	83.6±2.4 (4)	61[d]

a) Each value represents the mean±S.E.M. *b*) Number of rat 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 Selective 2-Alkoxy-4-amino-5-chloro-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides on Gastric Emptying of Phenol Red Semisolid Meal in Mice and Resin Pellet Solid Meal in Rats

Compd.	Gastric emptying rate of phenol red semisolid meal in mice[a]				Gastric emptying rate of resin pellet solid meal in rats[a]	
	Control (N[b])	% change	Control (N)	% change	Control (N)	% change
	0.5 mg/kg, *p.o.* (N)		1.0 mg/kg, *p.o.* (N)		2.0 mg/kg, *p.o.* (N)	
48a	50.3±3.0 (14)		50.3±3.0 (14)		32.6±2.6 (5)	
	62.8±4.9 (5)	25	80.9±3.8 (5)	61[d]	22.5±3.5 (4)	31[c]
57b	52.5±2.1 (7)		52.5±2.1 (7)		32.6±2.6 (5)	
	87.8±3.1 (5)	67[d]	94.2±3.8 (5)	79[d]	13.0±2.2 (4)	60[d]
1b	53.1±4.1 (7)[e]		52.7±2.1 (7)[e]		27.0±2.7 (5)	
	76.7±4.1 (5)	44[d]	72.0±1.9 (5)	37[d]	5.8±2.1 (4)	79[d]

a) Each value represents the mean±S.E.M. *b*) Number of rat 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 V. Dopamine D_2 Receptor Antagonistic Activity of Selective 2-Alkoxy-4-amino-5-chloro-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides

Compound	[^{3}H]Spiperone binding (μM)	Apomorphine-induced emesis % inhibitory activity (3.0 mg/kg, *p.o.*)
48a	>1	7
57b	>1	0
1b	>1	0
Metoclopramide	0.63[a]	100[b]

a) The figure shown indicates the IC_{50} value, which is obtained by log-logit regression analysis. *b*) The ED_{50} value is 0.45 mg/kg, *p.o.*

(**56a—58a**) and naphthyl (**64a**) rings caused a slight decrease in activity. Furyl (**59a, 60a**), thienyl (**61a, 62a**), and benzisoxazolyl (**63a**) rings generally are deleterious to activity, although such heteroaryl rings except the furyl ring conferred slightly more active derivatives than metoclopramide in the gastric emptying activity. Overall, the decreasing order of contribution to activity is thus phenyl > pyridyl ≥ naphthyl > benzisoxazolyl ≥ thienyl > furyl and, hence, 6-membered > bicyclic > 5-membered heteroaryl rings. In series **b**, on the other hand, compounds **56b—58b** with a pyridyl ring are more potent than metoclopramide and even cisapride. In particular, compound **57b**, appending a 3-pyridylmethyl group, has a comparable activity to that of **1b** (AS-4370) which is the most potent compound in our previous study.[1] In a comparison between the regioisomeric pyridyl derivatives **56—58**, the 3-pyridyl analogues (**57a, 57b**) are very slightly more potent than the 2- and 4-pyridyl (**56a, 56b, 58a, 58b**) isomers.

In light of the gastric emptying activity, eight compounds (**15b—18b, 20b, 48a, 57b, 58b**) were selected and subjected to the acute toxicity test in mice (Table II). The N-4 alkyl (**15b—18b, 20b**) derivatives show a potent acute toxicity. The 3-(4-chlorophenoxy)propyl (**48a**), 3- and 4-pyridylmethyl (**57b, 58b**) derivatives, however, are weak in acute toxicity.

Compounds **48a** and **57b**, which showed potent gastric emptying activity as well as weak acute toxicity, were therefore selected for further biological assays including the gastric emptying rates of the phenol red semisolid meal in mice and rats and of resin pellet solid meal in rats at different doses (Tables III and IV). Overall, compound **57b** compares very favorably with **1b**, whereas compound **48a** is somewhat less potent than **1b**.

The activity for dopamine D_2 receptor antagonism was also determined by the [^{3}H]spiperone binding test and the suppression of apomorphine-induced emesis in dogs (Table V). All the selected compounds show no dopamine D_2 receptor antagonistic activity (the [^{3}H]spiperone binding test at the concentration of 10^{-6} M and antagonism of the apomorphine-induced emesis at an oral dose of 3.0 mg/kg). On the contrary, metoclopramide shows potent dopamine D_2 receptor antagonistic activity. As for compound **48a**, unfortunately, some unfavorable actions on the central nervous system, such as catalepsy and ptosis, were observed at an oral dose of 100 mg/kg in mice[5]; a similar side effect has been observed for metoclopramide and cisapride at an oral dose of 10—100 mg/kg.[6]

In summary, most compounds (52 of 70 compounds examined in the present study) displayed a gastric emptying activity superior to that of metoclopramide, and eleven compounds having alkyl, 4-substituted phenoxyalkyl, or pyridylmethyl group at N-4 were more potent than cisapride. The SAR study, including acute toxicity correlation, of the N-4 substituent of **1b** revealed that the 3-pyridylmethyl group was optimal. 4-Amino-5-chloro-2-ethoxy-*N*-[[4-(3-pyridylmethyl)-2-morpholinyl]methyl]-benzamide (**57b**), on the whole, was found to possess the most favorable activity profile of gastric emptying enhancement without the dopamine D_2 receptor antagonistic activity and is worthy of further biological evaluation as a potent and selective gastrokinetic agent.

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 with KBr disks and electron-impact mass (EIMS) spectra were recorded on a JEOL JMS D-300. ^{1}H-NMR spectra were taken at 200 MHz with a Varian GEMINI-200 spectrometer and at 300 MHz with a Varian XL-300 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 following known alkyl and aralkyl halides were prepared according to the cited literature: 3-cyclohexenylmethyl bromide,[7] 2-(4-fluorophenoxy)ethyl chloride,[8] 3-(4-fluorophenoxy)propyl chloride,[8,9] 3-(3-fluorophenoxy)propyl chloride,[8] 3-(2-fluorophenoxy)propyl chloride,[8] 4-(4-fluorophenoxy)butyl bromide,[8] 5-(4-fluorophenoxy)pentyl bromide,[8] 6-(4-fluorophenoxy)hexyl bromide,[8] 2-(4-chlorophenoxy)ethyl chloride,[8] 3-(4-chlorophenoxy)propyl bromide,[8] 3-(4-cyanophenoxy)propyl bromide,[8] 3-(4-nitrophenoxy)propyl bromide,[8,9] 3-(4-fluorophenylthio)propyl bromide,[8] furfuryl chloride,[10] 3-chloromethylfuran,[10] 2-chloromethylthiophen,[11] 3-bromomethylthiophen,[12] and 3-benzisoxazolylmethyl bromide.[13]

The preparation of compounds **11a** and **38a** was reported in the previous paper.[1]

2-Alkoxy-4-amino-5-chloro-*N*-[(4-substituted 2-morpholinyl)methyl]benzamides (12—37, 39—51, and 53—65); Method A. 4-Amino-5-chloro-2-ethoxy-*N*-[[(4-pyridylmethyl)-2-morpholinyl]methyl]benzamide (58b) A solution of 2-[(acetylamino)methyl]-4-benzylmorpholine[2] (**3**, 10.0 g, 40 mmol) in an EtOH (70 ml)–AcOH (5 ml) mixture was hydrogenated over 10% palladium on carbon (0.5 g) at 60 °C. After the theoretical amount of hydrogen was absorbed, the catalyst was removed by filtration. The filtrate was concentrated to dryness, giving *ca.* 7 g of [2-(acetylamino)methyl]morpholine acetate (**4**).

A mixture of crude **4** (7 g), 4-picolyl chloride hydrochloride (7.9 g, 48 mmol), K_2CO_3 (55.6 g, 397 mmol), KI (1 g), and methyl ethyl ketone (100 ml) was heated to reflux for 17 h and cooled to room temperature. The insoluble materials were removed by filtration, and the filtrate was concentrated to dryness. The residue was diluted with water and extracted with $CHCl_3$. The extract was washed with brine. The solvent was evaporated to give a solid, which was recrystallized from toluene to afford 9.4 g of 2-[(acetylamino)methyl]-4-(4-pyridylmethyl)morpholine [**5** (R_1 = 4-pyridylmethyl)].

A solution of **5** (2.9 g, 12 mmol) in 10% HCl (60 ml) was heated to reflux for 4 h and cooled to room temperature. The reaction mixture was basified with 10% NaOH and then extracted with $CHCl_3$. The extract was washed successively with water and brine. The solvent was evaporated to give 2.0 g of **6** (R_1 = 4-pyridylmethyl) as an oil. EIMS m/z: 195 (M^+). To a stirred solution of **6** (2.0 g, 10 mmol) in CH_2Cl_2 (50 ml) were added 4-amino-5-chloro-2-ethoxybenzoic acid[1] (**2b**, 2.1 g, 10 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.9 g, 10 mmol). The mixture was stirred at room temperature for 4 h and then washed successively with water, 10% NaOH, water, and brine. The organic phase was dried and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (9 : 1) to give a solid, which was recrystallized from iso-PrOH to afford 2.5 g (53%) of **58b**. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.48 (3H, t, J = 6, $OCH_2C\underline{H}_3$), 2.06 (1H, t, J = 10.5, 3-$H_{ax.}$), 2.21 (1H, td, J = 11, 3.5, 5-$H_{ax.}$), 2.65 (1H, dd, J = 11, 1, 5-$H_{eq.}$), 2.78 (1H, d, J = 11, 3-$H_{eq.}$), 3.38 (1H, ddd, J = 14, 8, 3, CONHC$\underline{H}$), 3.51 (2H, d, J = 3, $C\underline{H}_2C_5H_4N$), 3.6—3.8 (3H, m, CONHC$\underline{H}$, 2-H, and 6-$H_{ax.}$), 3.85 (1H, ddd, J = 11.5, 3.5, 2, 6-$H_{eq.}$), 4.07 (2H, q, J = 6, 15, $OC\underline{H}_2CH_3$), 4.39 (2H, br s, NH_2), 6.28 (1H, s, arom 3-H), 8.10 (1H, s, arom 6-H), 7.28 (2H, d, J = 5, $C_5\underline{H}_4N$), 8.55 (2H, dd, J = 4, 1.5, $C_5\underline{H}_4N$), 8.22 (1H, t, J = 6, CONH). EIMS m/z: 404 (M^+), 312 ($M^+ - 92$). IR ν cm^{-1}: 3355, 3300, 3190, 1620, 1510.

Method B. General Procedure In a manner similar to that described for the preparation of 2-[(acetylamino)methyl]-4-(4-pyridylmethyl)morpholine [**5** (R_1 = 4-pyridylmethyl)], **3** (10.0 g, 40 mmol) was converted into 4-substituted 2-[(acetylamino)methyl]morpholines **5**. A solution of **5** (10 mmol) in 10% NaOH (60 ml) was heated to reflux for 20 h and cooled to room temperature. The reaction mixture was extracted with $CHCl_3$, and the combined organic layers were washed successively twice with water and brine. The organic phase was dried and evaporated to give 4-substituted 2-(aminomethyl)morpholines **6** as an oil. The reaction of 4-substituted 2-(aminomethyl)morpholines with 4-amino-5-chloro-2-methoxy- or 2-ethoxybenzoic acid (**2a** or **2b**) was performed according to method A.

Method C. 4-Amino-5-chloro-2-methoxy-*N*-[(4-methyl-2-morpholinyl)methyl]benzamide (12a) A mixture of 2-(methylamino)ethanol (**7o**, R_1 = CH_3, R_2 = H, 5.0 g, 67 mmol), *N*-(2,3-epoxypropyl)phthalimide (**8**, 16.2 g, 80 mmol) was stirred at 80 °C for 1 h. To the reaction mixture consisting of the resultant diol **9o** (R_1 = CH_3, R_2 = H) was gradually added concentrated H_2SO_4 (39.2 g, 40 mmol), and the mixture was rapidly heated to 150 °C and kept at the same temperature for 2 h. The resulting brown solution was cooled, poured into ice-water, and washed with $CHCl_3$. The aqueous layer was basified with 25% NaOH, and then extracted with $CHCl_3$. The extract was washed successively with water and brine. The solvent was evaporated to give 1.3 g of **10o** as an oil, which was used in the next step without further purification. The reaction of **10o** with 4-amino-5-chloro-2-methoxybenzoic acid (**2a**) was performed according to method A to give **12a**. ^{1}H-NMR (200 MHz, dimethylsulfoxide (DMSO)-d_6): 2.77 (3H, d, J = 4, NCH_3), 2.9—3.2 (1H, m), 3.2—3.6 (4H, m), 3.7—4.1 (4H, m), 3.85 (3H, s, OCH_3), 6.00 (2H, br s, NH_2), 6.49 (1H, s, arom 3-H), 7.70 (1H, s, arom 6-H), 8.09 (1H, t, J = 6 CONH). EIMS m/z: 313 (M^+). IR ν cm^{-1}: 3340, 3290, 3190, 1620, 1530.

4-Amino-5-chloro-2-ethoxy-*N*-[3-(octahydropyrido[2,1-*c*][1,4]oxazinyl)methyl]benzamide (23b) 3-(Aminomethyl)octahydropyrido[2,1-*c*][1,4]-oxazine **10q** was prepared from 2-(hydroxymethyl)piperidine (**7q**, R_1, R_2 = $-(CH_2)_4-$) and *N*-(2,3-epoxypropyl)phthalimide **8** according to the same method. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.10 (1H, dddd, J = 12.8, 12.4, 10.6, 3.8, 9-$H_{ax.}$), 1.30 (1H, m, 8-$H_{ax.}$), 1.45 (1H, dd, J = 12.8, 2.6, 9-$H_{eq.}$), 1.50 (3H, t, J = 6.9, $OCH_2C\underline{H}_3$), 1.53—1.68 (2H, m, 7-H), 1.79 (1H, m, 8-$H_{eq.}$), 1.98 (1H, dddd, J = 10.6, 10.2, 3.1, 2.6, 10-H), 2.04 (1H, dd, J = 11.4, 11.2, 6-$H_{ax.}$), 2.09 (1H, dd, J = 11.4, 10.3, 4-$H_{ax.}$), 2.72 (1H, dd, J = 11.4, 2.2, 4-$H_{eq.}$), 2.79 (1H, dddd, J = 11.4, 3.8, 3.6, 1.4, 6-$H_{eq.}$), 3.31 (1H, dd, J = 11.2, 10.2, 1-$H_{ax.}$), 3.34 (2H, s, NH_2), 3.36 (1H, ddd, J = 13.8, 6.1, 3.6, CH_2), 3.69 (1H, ddd, J = 13.8, 7.3, 4.3, CH_2), 3.71 (1H, dd, J = 11.2, 3.1, 1-$H_{eq.}$), 3.78 (1H, m, 3-H), 4.08 (2H, q, J = 6.9, $OC\underline{H}_2CH_3$), 6.27 (1H, s, arom 3-H), 8.11 (1H, s, arom 6-H), 8.23 (1H, dd, J = 6.1, 4.3, CONH). EIMS m/z: 367 (M^+). IR ν cm^{-1}: 3450, 3360, 3280, 3150, 1620, 1525.

4-Amino-*N*-[[4-[3-(4-aminophenoxy)propyl]-2-morpholinyl]methyl]-5-chloro-2-methoxybenzamide (52a) A solution of compound **51a** (1.7 g, 3.5 mmol) in MeOH (50 ml) was hydrogenated over 5% palladium on carbon (0.3 g) at room temperature. The catalyst was removed by filtration and the filtrate was evaporated to give 0.8 g (51%) of **52a** as an oil. This oil was converted to the oxalate in the usual manner. ^{1}H-NMR (200 MHz, DMSO-d_6): 3.83 (3H, s, OCH_3), 5.99 (2H, br s, 4-NH_2), 6.49 (1H, s, arom 3-H), 7.70 (1H, s, arom 6-H), 6.54 and 6.73 (each 2H, d, J = 9, $OC_6\underline{H}_4NH_2$), 8.05 (1H, t, J = 6, CONH). EIMS m/z: 448 (M^+). IR ν cm^{-1}: 3380, 3310, 1750, 1605, 1515.

Pharmacology Male mice of Std-ddY strain (Japan SLC Inc.) weighing 30—40 g and male rats of Wister 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 (PR) in 1.5% aqueous methylcellulose solution) of 0.2 ml per mouse and 1.5 ml per rat was given with a gastric tube. Fifteen minutes later, the animals were sacrificed. The stomachs were removed, and the amount of PR remaining in them was measured according to the method of Scarpignato *et al.*[14]; the isolated stomachs were homogenated by 0.1 N NaOH solution (100 ml) and centrifuged. The resultant supernatant (5 ml) was deproteinized by 20% trichloroacetic acid solution (0.5 ml) and centrifuged. Thereafter, the supernatant (3 ml) obtained was added to 0.5 N NaOH solution (4 ml). The PR contents were determined by measuring the absorbance at 560 nm wave length. The gastric emptying rate was calculated according to the following equation. The test compounds, suspended in a 0.5% tragacanth solution, were orally administered 60 min before administration of the test meal.

$$\text{the rate (\%)} = \left(1 - \frac{\text{stomach PR contents 15 min after PR solution}}{\text{stomach PR contents immediately after PR solution}}\right) \times 100$$

Gastric Emptying of Solid Meal Gastric emptying of solid meal (resin pellets) was measured according to the method of Jacoby.[15] 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.

Inhibition on Apomorphine-Induced Emesis in Dogs The antiapomorphine test in dogs was carried out according to the method of Janssen[16] with modification. Male beagle dogs, weighing 10—16 kg, were used. Groups of three to six dogs received a subcutaneous injection of apomorphine hydrochloride (0.3 mg/kg) 2 h after pretreatment with test compounds. The frequency of emesis was then counted for 1 h.

Acute Toxicity Male ddY mice, weighing 18—25 g, were used in groups of 10 animals each. The test compounds, dissolved or suspended in a 0.5% tragacanth solution, were administered at an oral dose of 1.0 g/kg to the animals. The mortality was observed for 7 d after the administration.

Inhibition of [^{3}H]Spiperone Binding The test compounds at concentrations of 0.01—1000 μM were tested in binding assays using rat brain synaptic membranes for competition with [^{3}H]spiperone in the striatum.[17] 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 Tris-carb scintillation counter (B-2450).

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