Synthesis and Gastroprokinetic Activity of 2-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamide Derivatives

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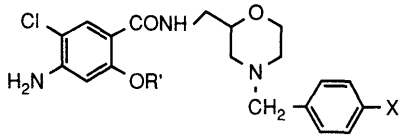
2-Alkoxy-4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chlorobenzamides had been identified as the interesting members of a series of selective and potent gastroprokinetic agents. A new series of 2-amino- and 2-(substituted amino)-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamides (13—35) has been synthesized and these compounds were examined to determine whether they have advantages over the 2-morpholinyl benzamides 1 with a 2-alkoxy group. The gastroprokinetic activity was generally reduced, but several compounds showed relatively potent activity, comparable to that of the standard agent, metoclopramide. *N*-[(4-Benzyl-2-morpholinyl)methyl]-4-chloro-2-[(4-chlorobenzoyl)amino]benzamide (32) showed the most potent activity in this series.

Key words mosapride; 2-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamide; gastroprokinetic agent; 2-morpholinyl benzamide; gastric emptying; structure–activity relationship

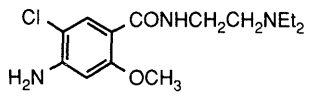
With the aim of obtaining more potent gastroprokinetic activity and much weaker dopamine D_2 antagonistic activity than those of the standard agent metoclopramide, a new benzamide **1a** with a morpholine ring in place of the 3-methoxypiperidine side chain of the new gastroprokinetic agent cisapride has been designed and prepared.[1] Subsequent modification of **1a** led to the finding of 4-amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)-2-morpholinyl]methyl}benzamide (**1b**, mosapride). Mosapride is substantially equipotent to cisapride and has much higher gastroprokinetic activity than metoclopramide. Furthermore, in contrast to cisapride and metoclopramide, mosapride had no dopamine D_2 receptor antagonistic activity.[2]

Earlier work by a Beecham group on benzamide derivatives demonstrated that replacement of the 2-alkoxy group of the benzoyl moiety by a substituted amino group, *e.g.*, compound **2**, increased the gastric motility-stimulanting activity.[3] Therefore, it was expected that replacement of the 2-alkoxy group of 2-morpholinyl benzamides **1** by an amino or a substituted amino group would cause enhancement of the gastroprokinetic activity. The present paper deals with the synthesis and structure–activity relationships (SARs) of a new series of 2-amino- and 2-(substituted amino)-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamides (**13**—**35**), as shown in Table 1.

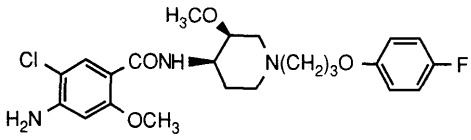


1a: R' = CH_3, X = H

1b: R' = C_2H_5, X = F (mosapride)



metoclopramide



cisapride

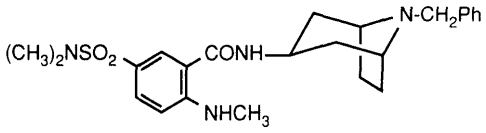


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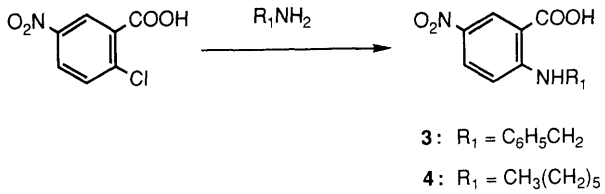
Chart 1

Chemistry

The requisite 2-amino and 2-(substituted amino)benzoic acid derivatives were obtained commercially or prepared according to the literature, except for compounds **3**, **4**, **7**, and **8**, which were prepared by the methods shown in Charts 2 and 3. Thus, the reaction of 2-chloro-5-nitrobenzoic acid with benzylamine and *n*-hexylamine in EtOH gave 2-(benzylamino)- and 2-(*n*-hexylamino)-5-nitrobenzoic acids (**3** and **4**, respectively) (Chart 2).

Nitration of 2-(acetylamino)-4-chlorobenzoic acid[4] with a mixed acid (fuming nitric acid and concentrated sulfuric acid) gave 2-(acetylamino)-4-chloro-5-nitroben-



3: R_1 = $C_6H_5CH_2$

4: R_1 = $CH_3(CH_2)_5$

Chart 2

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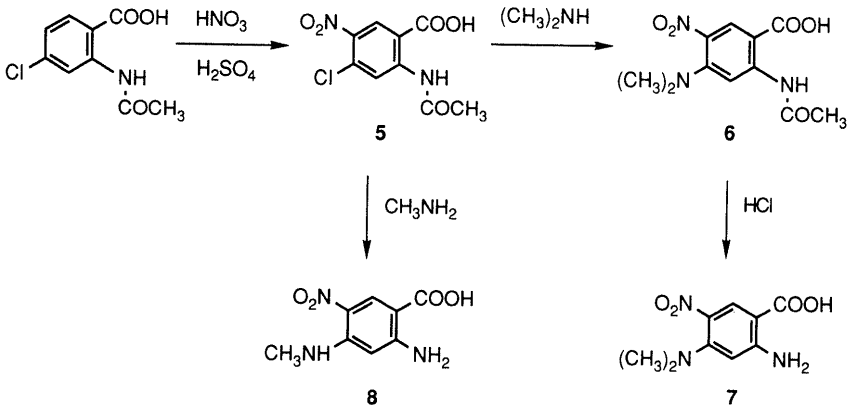
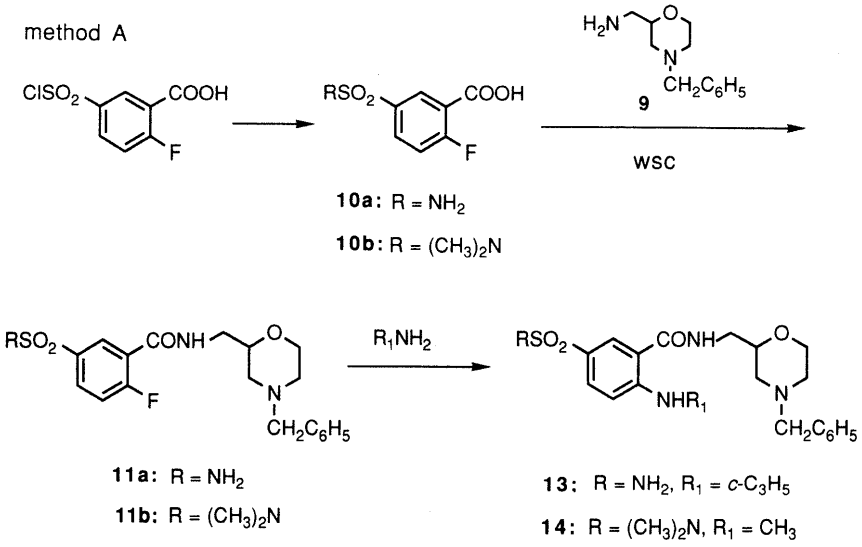


Chart 3



WSC: 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride

Chart 4

zoic acid (**5**), which was transformed to the 4-(dimethylamino) derivative **6** by treatment with dimethylamine. Compound **6** was hydrolyzed with HCl to afford 4-(dimethylamino)-5-nitroanthranilic acid (**7**). On the other hand, the displacement reaction of **5** with methylamine gave the desired 4-(methylamino)-5-nitroanthranilic acid (**8**), without isolation of the corresponding 2-acetylamino compound (Chart 3).

2-Amino- and 2-(substituted amino)-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamides (**13**—**35**) were prepared by the methods shown in Charts 4—7. 5-(Chlorosulfonyl)-2-fluorobenzoic acid[5] was converted to the 5-sulfamoyl analogue **10a** with ammonia water. The reaction of 5-sulfamoyl- and 5-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzoic acids (**10a** and **10b**[3]) with 2-(aminomethyl)-4-benzylmorpholine[1] (**9**) in the presence of water-soluble carbodiimide, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC), produced the 2-fluorobenzamide derivatives **11a** and **11b**, respectively, and then amination of **11a** with cyclopropylamine and of **11b** with methylamine gave the corresponding 2-(cyclopropylamino)- and 2-(methylamino)benzamides **13** and **14**, respectively (Chart 4, method A).

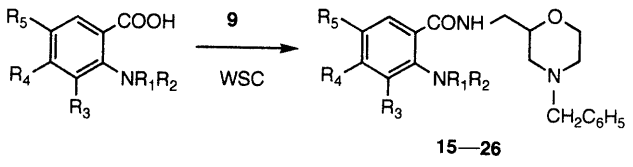


Chart 5

Compounds **15**—**26** were generally prepared from the anthranilic acid or 2-(substituted amino)benzoic acid derivatives and the amine **9** in the presence of WSC (Chart 5, method B). On the other hand, the reaction of the 2-(benzoylamino)benzoic acid derivatives with the amine **9** using WSC did not give the desired 2-(benzoylamino)-benzamides in good yield; the corresponding 2-phenyl-4*H*-3,1-benzoxazin-4-ones[6] (**12**) were obtained as the main product. These compounds **12**, however, could be transformed by treatment with the amine **9** in tetrahydrofuran (THF) to the 2-morpholinyl benzamides **27**, **28**, and **31**—**35**. 2-Phenyl- and 2-(substituted phenyl)-4*H*-3,1-benzoxazin-4-ones (**12a**—**g**) were alternatively prepared by the reaction of the anthranilic acid derivatives

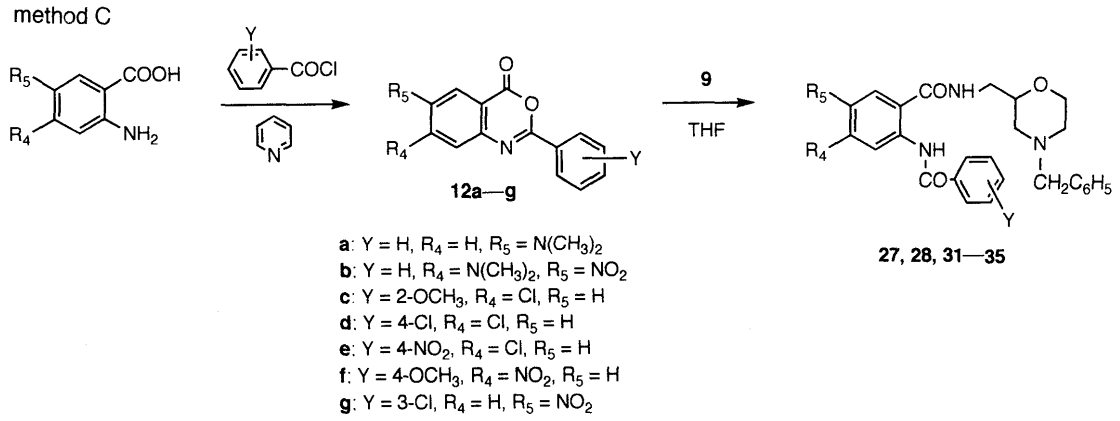


Chart 6

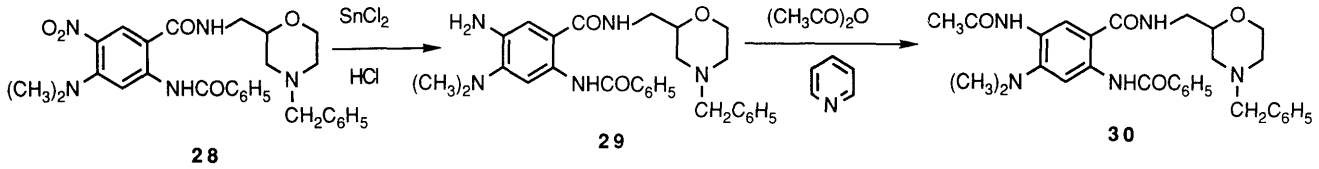


Chart 7

with the benzoyl and (substituted benzoyl) chlorides in pyridine in good yield (Chart 6, method C).

5-Nitrobenzamide **28** served as the starting compound for the preparation of the corresponding 5-aminobenzamide **29** and 5-(acetylamino)benzamide **30**; reduction of **28** with stannous chloride in concentrated HCl gave **29** and the subsequent acetylation of **29** with acetic anhydride afforded **30** (Chart 7).

The structures of all compounds thus prepared were supported by their ^{1}H-NMR spectra and elemental analyses.

Biological Results and Discussion

Compounds **13**—**35** were evaluated for gastroprokinetic activity by determining their effects on the gastric emptying rate of a phenol red semisolid meal through the stomach in rats. The activity data at an oral dose of 2.0 mg/kg are given in Table 2 , which includes, for comparison, data for metoclopramide and 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxybenzamide (**1a**).[1] We first prepared 5-(*N*,*N*-dimethylsulfamoyl)-2-(methylamino)benzamide (**13**) and its derivative, 5-sulfamoyl-2-(cyclopropylamino)benzamide (**14**), as analogues of compound **2**. These compounds possessed modest activity but were less potent than **1a**. Nonetheless we felt that this initial result justified further exploration; compound **13** showed higher gastroprokinetic activity than metoclopramide. The influence of nitro and halogeno groups at the 4- or 5-position of the 2-aminobenzamides on the gastric emptying activity was next considered. Although the 4- and 5-nitro compounds **16** and **17**, respectively, showed greater activity than metoclopramide, the 3-nitro analogue **15** was unfavorable. Replacement of the nitro group of **16** and **17** by a halogeno group (**18** and **19**, respectively) caused a decrease in activity. Introduction of chloro (**20**) and dimethylamino (**21**) groups at the 4-position of **17** also led to a decrease in activity. On the other hand, introduction of a methylamino group (giving **22**) retained the activity.

With respect to the effect of substituents on the 2-amino group of **17**, introduction of an alkyl group, *e.g.* monomethyl (**23**), dimethyl (**26**), and *n*-hexyl (**25**) groups, provided weakly active compounds. The benzylamino derivative (**24**) showed activity comparable to that of metoclopramide.

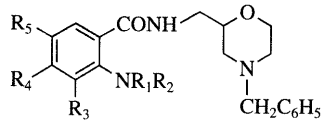
We will now discuss the SARs of the series of 2-(benzoylamino)benzamides and their derivatives (**27**—**35**). Compounds **27**—**30** with a benzoylamino group at the 2-position had poor activity or were practically inactive. On the other hand, introduction of a 2-(substituted benzoyl)amino group into **18** (yielding **31**—**33**) resulted in an increased activity. In particular, the 2-(4-chlorobenzoyl)amino derivative **32** had the highest activity in this series, being essentially equipotent to **1a**. Compounds **34** and **35** bearing 2-(4-methoxybenzoyl)- and 2-(3-chlorobenzoyl)amino groups, respectively, showed moderate activity.

In summary, we examined the gastroprokinetic activity of a series of 2-amino- and 2-(substituted amino)-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamides. Although we could not find compounds more potent than mosapride, seven compounds (**13**, **16**, **17**, **22**, **32**, **33**, and **35**) displayed a gastric emptying activity superior to that of metoclopramide. In particular, a new type of benzamide, *N*-[(4-benzyl-2-morpholinyl)methyl]-4-chloro-2-[(4-chlorobenzoyl)amino]benzamide (**32**), was essentially equipotent to the 2-methoxybenzamide **1a**.

Experimental

Chemistry All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Hitachi 260-10 spectrometer with KBr disks. Electron ionization (EI) and secondary ion (SI) mass spectra (abbreviated as EIMS and SIMS, respectively) were obtained on a JEOL JMS D-300 or Hitachi M-80B spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a

Table 1. Physical Data for 2-Amino- and 2-(Substituted Amino)-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamide Derivatives (**13**—**35**)



Compd.	R_1	R_2	R_3	R_4	R_5	mp (°C) (Recryst. solvent[a])	Yield[b] (%) Method[c]	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
13	CH_3	H	H	H	SO_2NMe	145—146 (E)	59 A	$C_{22}H_{30}N_4O_4S$[d]	59.17 (59.31	6.77 6.78	12.55 12.54)	
14	Cyclo-C_3H_5	H	H	H	SO_2NH_2	104—107 (M)	45 A	$C_{22}H_{28}N_4O_4S$[e]·H_2O	57.12 (57.06	6.54 6.37	12.11 12.08)	
15	H	H	NO_2	H	H	118—119 (E)	79 B	$C_{19}H_{22}N_4O_4$	61.61 (61.63	5.99 6.07	15.13 14.87)	
16	H	H	H	NO_2	H	146—151 (AC)	57 B	$C_{19}H_{22}N_4O_4 \cdot C_4H_4O_4$[f] ·1/2$(CH_3)_2CO$[g]	57.08 (57.06	5.67 5.93	10.87 10.59)	
17	H	H	H	H	NO_2	134 (E–D)	70 B	$C_{19}H_{22}N_4O_4$	61.61 (61.79	5.99 6.10	15.13 15.14)	
18	H	H	H	Cl	H	124—125 (E)	82 B	$C_{19}H_{22}ClN_3O_2$	63.42 (63.49	6.16 6.12	11.68 11.59	9.85 9.83)
19	H	H	H	H	Br	164—167 (E)	92 B	$C_{19}H_{22}BrN_3O_2$[h]	56.44 (56.25	5.48 5.69	10.39 10.44)	
20	H	H	H	Cl	NO_2	122—127 (AC)	63 B	$C_{19}H_{21}ClN_4O_4 \cdot C_4H_4O_4$[f] ·1/2$(CH_3)_2CO$[g]	53.51 (53.26	5.13 5.21	10.19 10.11	6.45 6.34)
21	H	H	H	NMe_2	NO_2	250—265 (I)	64 B	$C_{21}H_{27}N_5O_4 \cdot HCl$ ·3/10$(CH_3)_2CHOH$[g]	56.21 (56.11	6.55 6.53	14.97 14.78	7.58 7.76)
22	H	H	H	NHMe	NO_2	94—105 (C–H)	82 B	$C_{20}H_{25}N_5O_4 \cdot 1/4H_2O$	59.47 (59.26	6.36 6.29	17.34 17.27)	
23	Me	H	H	H	NO_2	151—154 (E)	46 B	$C_{20}H_{24}N_4O_4$	62.49 (62.32	6.29 6.18	14.57 14.47)	
24	$CH_2C_6H_5$	H	H	H	NO_2	189—195 (I)	47 B	$C_{26}H_{28}N_4O_4 \cdot C_4H_4O_4$[f]	62.49 (62.54	5.59 5.85	9.72 9.54)	
25	$(CH_2)_5CH_3$	H	H	H	NO_2	70—81 (D)	22 B	$C_{25}H_{34}N_4O_4 \cdot 4/3C_4H_4O_4$[f]	59.79 (59.85	6.51 6.63	9.19 9.22)	
26	Me	Me	H	H	NO_2	123—126 (E)	21 B	$C_{21}H_{26}N_4O_4$	63.30 (63.38	6.58 6.62	14.06 14.02)	
27	COC_6H_5	H	H	H	NMe_2	196—200 (dec.) (I–D)	30 C	$C_{28}H_{32}N_4O_3 \cdot C_2H_2O_4$[i]	64.04 (64.03	6.09 6.10	9.96 9.91)	
28	COC_6H_5	H	H	NMe_2	NO_2	161—164 (E)	61 C	$C_{28}H_{31}N_5O_5$	64.89 (64.87	6.04 6.01	13.53 13.49)	
29	COC_6H_5	H	H	NMe_2	NH_2	70—81 (Trit)	84 j)	$C_{28}H_{33}N_5O_3 \cdot 1/4H_2O$	68.34 (68.35	6.86 6.79	14.23 14.18)	
30	COC_6H_5	H	H	NMe_2	$NHCOCH_3$	82—95 (Trit)	61 j)	$C_{30}H_{35}N_5O_4 \cdot 1/2H_2O$	66.90 (66.69	6.74 6.62	13.00 12.89)	
31	2-MeO-C_6H_4CO	H	H	Cl	H	99—100 (I)	53 C	$C_{27}H_{28}ClN_3O_4$	65.65 (65.36	5.71 5.63	8.51 8.45	7.18 7.10)
32	4-Cl-C_6H_4CO	H	H	Cl	H	184—187 (C–M)	35 C	$C_{26}H_{25}Cl_2N_3O_3$	62.66 (62.68	5.06 4.97	8.43 8.41	14.23 14.22)
33	4-NO_2-C_6H_4CO	H	H	Cl	H	149—151 (C–M)	39 C	$C_{26}H_{25}ClN_4O_5$	61.36 (61.22	4.95 4.85	11.01 10.87	6.97 7.27)
34	4-MeO-C_6H_4CO	H	H	NO_2	H	206—209 (C–M)	35 C	$C_{27}H_{28}N_4O_6 \cdot 1/2H_2O$	63.15 (63.10	5.69 5.42	10.91 10.78)	
35	3-Cl-C_6H_4CO	H	H	H	NO_2	213—216 (C–M)	39 C	$C_{26}H_{25}ClN_4O_5$	61.36 (61.22	4.95 4.76	11.01 10.94	6.97 7.04)

a) Abbreviations for the solvents are as follows: E=ethanol, M=methanol, AC=acetone, D=diisopropyl ether, I=isopropanol, C=chloroform, H=*n*-hexane. Trit (trituration) refers to grinding of the solids to produce a fine powder. *b*) Yields were not optimized. Yields of compounds **13**—**28** and **31**—**35** are based on the corresponding 2-amino or 2-(substituted amino)benzoic acid derivatives. *c*) Capital letters refer to the methods described in Experimental. *d*) Calcd for S: 7.18, Found: 7.10. *e*) Calcd for S: 6.93, Found: 7.19. *f*) Fumaric acid. *g*) The presence of solvent of crystallization was shown by ^{1}H-NMR. *h*) Calcd for Br: 19.76, Found: 19.76. *i*) Oxalic acid. *j*) See Experimental.

Varian EM-360A spectrometer or 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 value) are given in hertz (Hz). Organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Merck silica gel 60 (70—270 mesh) was used for column chromatography.

The known anthranilic and benzoic acid derivatives were obtained from commercial suppliers or prepared according to the literature: 2-(acetylamino)-4-chlorobenzoic acid,[4] 5-(chlorosulfonyl)-2-fluorobenzoic acid,[5] 5-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzoic acid,[3] 3-nitroanthranilic acid,[7] 5-nitroanthranilic acid,[8] 4-chloro-5-nitroanthranilic acid,[9] 2-(methylamino)-5-nitrobenzoic acid,[10] 2-(dimethylamino)-5-nitrobenzoic acid,[11] 5-(dimethylamino)anthranilic acid.[12]

2-(Benzylamino)-5-nitrobenzoic Acid (3) A solution of 2-chloro-5-nitrobenzoic acid (5.0 g, 24 mmol) and benzylamine (15.0 g, 140 mmol) in EtOH (40 ml) was heated to reflux for 10 h, then concentrated to

Table 2. Effect of 2-Amino- and 2-(Substituted Amino)-*N*-[(4-benzyl-2-morpholinyl)methyl]benzamides (**13**—**35**) on Gastric Emptying of a Phenol Red Semisolid Meal in Rats

Compd	Gastric emptying rate (%)		
	Control (mean±S.E.M.) (*N*[a])	2.0 mg/kg, *p.o.* (mean±S.E.M.) (*N*)	% change
13	52.3±3.9 (5)	67.6±1.5 (4)	29[b]
14	52.6±3.9 (5)	63.3±2.2 (4)	20[c]
15	53.5±1.6 (5)	61.1±6.2 (4)	14
16	50.5±1.3 (5)	66.7±1.6 (4)	32[c]
17	53.5±1.6 (5)	69.5±4.9 (4)	30[c]
18	53.5±1.6 (5)	63.3±2.8 (4)	18[b]
19	51.8±2.6 (5)	56.3±4.6 (4)	9
20	50.5±1.3 (5)	60.9±3.6 (4)	21[b]
21	50.7±2.3 (5)	50.9±3.1 (4)	0
22	50.9±2.0 (5)	65.9±3.2 (4)	29[c]
23	52.6±3.9 (5)	53.7±4.1 (4)	2
24	52.6±3.9 (5)	63.6±4.7 (4)	21
25	49.3±3.6 (5)	54.2±2.1 (4)	10
26	51.1±2.7 (5)	52.1±4.2 (4)	2
27	51.8±2.6 (5)	51.9±2.6 (4)	0
28	53.0±2.4 (5)	57.5±3.7 (4)	8
29	51.8±2.6 (5)	51.7±2.6 (4)	0
30	51.8±2.6 (5)	53.8±1.8 (4)	4
31	56.1±2.5 (5)	67.1±2.1 (4)	20[c]
32	51.7±3.4 (5)	72.9±3.1 (4)	41[c]
33	51.7±3.4 (5)	70.4±3.4 (4)	36[c]
34	51.7±3.4 (5)	63.2±4.6 (4)	22[b]
35	51.7±3.4 (5)	64.5±3.3 (4)	25[b]
1a	54.5±3.8 (5)	75.9±3.6 (4)	39[c]
Metoclopramide	58.9±2.1 (5)	71.3±3.8 (4)	21[b]

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

dryness. Water (100 ml) was added to the residue, and the solution was adjusted to a pH of about 4 with CH_3COOH (AcOH) and stirred for 1 h. The resulting precipitates were collected by filtration, washed with water, and recrystallized from EtOH to give 4.8 g (71%) of **3**, mp 238—248 °C. ^{1}H-NMR (60 MHz, dimethyl sulfoxide (DMSO)-d_6) δ: 4.57 (1H, d, J=13, C$\underline{H}_2$Ph), 4.67(1H, d, J=13, C$\underline{H}_2$Ph), 6.80 (1H, d, J=9, arom. H), 7.35 (5H, s, arom. H), 8.10 (1H, dd, J=3, 9, arom. H), 8.65(1H, d, J=3, arom. H), 9.20 (1H, t, J=6, NH), 13.5 (1H, br s, COOH). IR νcm^{-1}: 3350, 1655, 1570, 1490, 1430, 1325, 1240. *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.36; H, 5.57; N, 11.13.

2-(*n*-Hexylamino)-5-nitrobenzoic Acid (4) In a similar manner to that described above, compound **4** was prepared from 2-chloro-5-nitrobenzoic acid and *n*-hexylamine in 38% yield, mp 161—163 °C (diisopropyl ether–*n*-hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.8—2.1 (11H, m), 3.0—3.6 (2H, m), 6.68 (1H, d, J=10, arom. H), 8.22 (1H, dd, J=4, 10, arom. H), 8.91 (1H, d, J=4, arom. H), 9.72 (1H, br s). IR νcm^{-1}: 3340, 1660, 1575, 1490, 1435, 1325, 1240. *Anal.* Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.50; H, 6.77; N, 10.54.

2-Amino-4-(dimethylamino)-5-nitrobenzoic Acid (7) Fuming HNO_3 (d=1.50, 15 ml) was added dropwise to concentrated H_2SO_4 (90 ml) at 20 °C. Then 2-(acetylamino)-4-chlorobenzoic acid (33.0 g, 155 mmol) was added portionwise while the temperature was maintained at 8 to 10 °C. The reaction mixture was stirred at room temperature for 3 h and poured into ice-water. The resulting precipitates were collected by filtration, washed with water, and recrystallized from EtOH–H_2O to give 30.0 g (75%) of 2-(acetylamino)-4-chloro-5-nitrobenzoic acid (**5**), mp 240—241 °C. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.21 (3H, s, $COCH_3$), 8.29 (1H, s, arom. H), 8.82 (1H, s, arom. H), 11.4 (1H, s, N$\underline{H}$COCH$_3$), 13.7 (1H, br s, COOH). IR νcm^{-1}: 3300, 1698, 1665, 1550, 1325, 1230, 1215. *Anal.* Calcd for $C_9H_7ClN_2O_5$: C, 41.80; H, 2.73; Cl, 13.71; N, 10.83. Found: C, 41.82; H, 2.68; Cl, 13.66; N, 10.77.

A solution of **5** (11.3 g, 53 mmol) and 40% dimethylamine aqueous solution (40 ml) in EtOH (100 ml) was heated to reflux for 5 h, then concentrated to dryness. Water (100 ml) was added to the residue, and the solution was adjusted to a pH of about 4 with AcOH. The resulting precipitates were collected by filtration, washed with water, and recrystallized from EtOH to give 8.6 g (74%) of 2-(acetylamino)-4-(dimethylamino)-5-nitrobenzoic acid (**6**), mp 230—255 °C (dec.). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.18 (3H, s, $COCH_3$), 2.90 (6H, s, $(CH_3)_2N$), 8.30 (1H, s, arom. H), 8.38 (1H, s, arom. H), 11.45 (1H, s, COOH). IR νcm^{-1}: 3130, 1695, 1660, 1620, 1540, 1280, 1225. *Anal.* Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.90; N, 15.72. Found: C, 49.16; H, 4.89; N, 15.73.

A mixture of **6** (6.5 g, 24 mmol), concentrated HCl (20 ml), and water (80 ml) was heated at 100 °C for 30 min and then cooled to room temperature. A 10% NaOH solution was added until a clear solution was obtained. The solution was adjusted to a pH of about 4 with AcOH. The resulting precipitates were collected by filtration, washed with water, and recrystallized from MeOH to give 4.8 g (86%) of **7**, mp 240—250 °C (dec.). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.80 (6H, s, $(CH_3)_2N$), 6.25 (1H, s, arom. 3-H), 8.48 (1H, s, arom. 6-H). IR νcm^{-1}: 3455, 3345, 1665, 1610, 1510, 1300, 1230. *Anal.* Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.15; H, 4.87; N, 18.64.

2-Amino-4-(methylamino)-5-nitrobenzoic Acid (8) A mixture of **5** (10.0 g, 47 mmol) and 40% methylamine aqueous solution (60 ml) was heated at 80 °C for 10 h. The mixture was concentrated to dryness, then 40% methylamine aqueous solution (100 ml) was added to the residue. The resulting solution was heated at 80 °C for an additional 20 h and then cooled to 5 °C. It was diluted with water (50 ml) and adjusted to a pH of about 4 with AcOH. The resulting precipitates were collected by filtration, washed with water, and recrystallized from CH_3CN to give 7.5 g (77%) of **8**, mp 260—272 °C (dec.). ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 2.88 (3H, d, J=5, CH_3N), 5.92 (1H, s, arom. 3-H), 7.55 (2H, br s, NH_2), 8.21 (1H, d, J=5, $CH_3N\underline{H}$), 8.70 (1H, s, arom. 6H), 10.7 (1H, br s, COOH). IR νcm^{-1}: 3455, 3360, 3350, 1670, 1620, 1600, 1300, 1210. *Anal.* Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.72; H, 4.25; N, 20.05.

2-Fluoro-5-sulfamoylbenzoic Acid (10a) A solution of 5-(chlorosulfonyl)-2-fluorobenzoic acid (7.0 g, 29 mmol) and 28% ammonia water (20 ml) in THF (70 ml) was stirred at 0 °C for 1.5 h. The reaction mixture was poured into water (200 ml), acidified with concentrated HCl, and extracted with $CHCl_3$. The extract was washed with water and evaporated. The residue was washed with a small quantity of MeOH to give 5.0 g (78%) of **10a**, mp 191—193 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.0—7.8 (2H, br s, SO_2NH_2), 7.49 (1H, dd, J_{3-4}=8.5, J_{3-F}=10.5, arom. 3-H), 7.99 (1H, ddd, J_{4-6}=2.5, J_{4-F}=4.5, J_{4-3}=8.5, arom. 4-H), 8.30 (1H, dd, J_{6-4}=2.5, J_{6-F}=6.5, arom. 6-H). IR νcm^{-1}: 3320, 3310, 3200, 3095, 1725, 1320, 1212, 1145. *Anal.* Calcd for $C_7H_6FNO_4S$: C, 38.36; H, 2.76; F, 8.67; N, 6.39; S, 14.63. Found: C, 38.24; H, 2.75; F, 8.58; N, 6.35; S, 14.89.

***N*-[(4-Benzyl-2-morpholinyl)methyl]-2-fluoro-5-sulfamoylbenzamide (11a)** A mixture of **10a** (3.0 g, 14 mmol), 2-(aminomethyl)-4-benzylmorpholine[1] (**9**, 2.9 g, 14 mmol), WSC (2.9 g, 15 mmol), and CH_2Cl_2 (100 ml) was stirred at room temperature for 4 h. The reaction mixture was washed successively with water, 10% NaOH and brine, and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (49 : 1) and then recrystallized from EtOH to give 4.0 g (72%) of **11a**, mp 186—187 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 1.86 (1H, t-like, J=11.0, 3-H$_{ax}$), 2.07 (1H, td, J=11.0, 3.5, 5-H$_{ax}$), 2.59 (1H, br d, J=11.0, 5-H$_{eq}$), 2.77 (1H, br d, J=11.0, 3-H$_{eq}$), 3.15—3.7 (4H, m), 3.47 (2H, s, C$\underline{H}_2$C$_6$H$_5$), 3.80 (1H, br d, J=11.0, 6-H$_{eq}$), 7.15—7.4 (7H, m, CH$_2$C$_6\underline{H}_5$, SO_2NH_2), 7.49 (1H, dd, J_{3-4}=8.5, J_{3-F}=10.5, arom. 3-H), 7.93 (1H, ddd, J_{4-6}=2.5, J_{4-F}=4.5, J_{4-3}=8.5, arom. 4-H), 8.02 (1H, dd, J_{6-4}=2.5, J_{6-F}=6.5, arom. 6-H), 8.57 (1H, br t, J=6.0, CONH). SIMS m/z: 408 (MH^+), 316 ($M^+-CH_2C_6H_5$), 91. IR νcm^{-1}: 3425, 3170, 1640, 1525, 1338. *Anal.* Calcd for $C_{19}H_{22}FN_3O_4S$: C, 56.01; H, 5.44; F, 4.66; N, 10.31; S, 7.87. Found: C, 56.14; H, 5.42; F, 4.70; N, 10.22; S, 8.16.

***N*-[(4-Benzyl-2-morpholinyl)methyl]-5-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzamide (11b)** In a similar manner to that described above, **11b** was prepared from 5-(*N*,*N*-dimethylsulfamoyl-2-fluorobenzoic acid (**10b**) and **9** in 70% yield, mp 153—154° C (trituration with Et_2O[13]). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.03 (1H, t-like, J=10.5, 3-H$_{ax}$), 2.23 (1H, td, J=11.5, 3.5, 5-H$_{ax}$), 2.6—2.95 (2H, m), 2.74 (6H, s, $(CH_3)_2N$), 3.4 (1H, m), 3.56 (2H, s, C$\underline{H}_2$C$_6$H$_5$), 3.65—3.95 (3H, m), 3.85 (1H, ddd, J=2.0, 3.5, 11.5, 6-H$_{eq}$), 7.0 (1H, m), 7.2—7.45 (6H, m, CH$_2$C$_6\underline{H}_5$, arom. 3-H), 7.91 (1H, ddd, J_{4-6}=2.5, J_{4-F}=4.5, J_{4-3}=9.5, arom. 4-H), 8.47 (1H,

dd, $J_{6-4}=2.5$, $J_{6-F}=7.0$, arom. 6-H). SIMS *m/z*: 436 (MH^+), 230, 188, 91. IR νcm^{-1}: 3295, 3080, 1630, 1545, 1338, 1165, 1110. *Anal.* Calcd for $C_{21}H_{26}FN_3O_4S$: C, 57.91; H, 6.02; F, 4.36; N, 9.65; S, 7.36. Found: C, 57.89; H, 6.08; F, 4.14; N, 9.73; S, 7.23.

2-Amino- and 2-(Substituted Amino)-*N*-[(4-benzyl-2-morpholinyl)-methyl]benzamide Derivatives (13—15). Method A. *N*-[(4-Benzyl-2-morpholinyl)methyl]-5-(*N*,*N*-dimethylsulfamoyl)-2-(methylamino)benzamide (14) A mixture of **11b** (1.0 g, 2.3 mmol), 30% methylamine in EtOH (1 ml), and EtOH (15 ml) was heated to reflux for 12 h. The reaction mixture was concentrated to dryness to leave a residue, which was then dissolved in $CHCl_3$. The organic layer was washed with water and evaporated to give a solid, which was recrystallized from EtOH to give 0.6 g of **14**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.96 (1H, t-like, $J=11.0$, 3-H_{ax}), 2.19 (1H, td, $J=11.0$, 3.5, 5-H_{ax}), 2.67 (6H, s, $(CH_3)_2N$), 2.6—2.85 (2H, m), 2.91 (3H, d, $J=5.0$, NCH_3), 3.29, 3.61 (each 1H, ddd, $J=4.5$, 6.5, 14.0, $NC\underline{H}_2$), 3.52 (2H, s, $C\underline{H}_2C_6H_5$), 3.6—3.8 (2H, m), 3.84 (1H, ddd, $J=1.8$, 3.5, 11.0, 6-H_{eq}), 6.77 (1H, br t, $J=4.5$, CONH), 6.69 (1H, d, $J=9.0$, arom. 3-H), 7.2—7.4 (5H, m), 7.67 (1H, dd, $J=2.0$, 9.0, arom. 4-H), 7.75 (1H, d, $J=2.0$, arom. 6-H), 8.09 (1H, br q, $J=5.0$, $CH_3N\underline{H}$). SIMS *m/z*: 447 (MH^+), 355 ($M^+-CH_2C_6H_5$), 241, 188. IR ν cm^{-1}: 3460, 3310, 1617, 1550, 1505, 1320, 1150, 1130.

Method B. General Procedure A mixture of an appropriate anthranilic acid or benzoic acid derivative (11 mmol), **9** (9.5 mmol), WSC (11 mmol), and CH_2Cl_2 (50 ml) was stirred at room temperature for 4 h. The reaction mixture was washed successively with water, 10% NaOH and brine, and concentrated to dryness. The residue was chromatographed on silica gel to give the crude product, which was purified by recrystallization from the solvent given in Table 1 or converted to the fumarate in the usual manner, followed by recrystallization.

Method C. 2-(Benzoylamino)-*N*-[(4-benzyl-2-morpholinyl)methyl]-4-(dimethylamino)-5-nitrobenzamide (28) Benzoyl chloride (5.1 g, 36 mmol) was added to a solution of 2-amino-4-(dimethylamino)-5-nitrobenzoic acid (3.6 g, 16 mmol) in pyridine (30 ml) at room temperature. The mixture was heated at about 90 °C for 2 h and poured into ice-water. The solution was acidified with AcOH. The resulting precipitates were collected by filtration, washed with ether, and recrystallized from CH_3CN to give 3.7 g (74%) of 7-(dimethylamino)-6-nitro-2-phenyl-4*H*-3,1-benzoxazin-4-one (**12b**: Y=H, $R_4=(CH_3)_2N$, $R_5=NO_2$), mp 178—179 °C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.02 (6H, s, $(CH_3)_2N$), 7.00 (1H, s, arom. H), 7.2—7.7, 8.1—8.4 (5H, m, arom. H), 8.50 (1H, s, arom. H). IR νcm^{-1}: 1745, 1615, 1600, 1520, 1220. *Anal.* Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.75; H, 4.24; N, 13.38. **12a**: (Y=H, $R_4=H$, $R_5=(CH_3)_2N$), mp 168—169 °C (CH_3CN). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.00 (6H, s, $(CH_3)_2N$), 7.0—7.7 (5H, m, arom. H), 8.1—8.4 (3H, m, arom. H). EIMS *m/z*: 236 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.13; H, 5.23; N, 10.54.

Compounds **12c—g** were used in the next step without purification or characterization.

A solution of **12b** (3.3 g, 11 mmol) and **9** (2.2 g, 11 mmol) in THF (60 ml) was heated to reflux for 4 h, then concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (49 : 1) and then recrystallized from EtOH to give 4.5 g (82%) of **28**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.98 (1H, t-like, $J=11.0$, 3-H_{ax}), 2.22 (1H, td, $J=11.0$, 3.5, 5-H_{ax}), 2.70 (1H, br d, $J=11.0$, 5-H_{eq}), 2.81 (1H, d, $J=11.0$, 3-H_{eq}), 3.02 (6H, s, $N(CH_3)_2$), 3.3 (1H, m), 3.52 (2H, s, $C\underline{H}_2C_6H_5$), 3.6—4.0 (4H, m), 6.65 (1H, br t, $J=5.0$, CONH), 7.15—7.4 (5H, m), 7.45—7.65 (3H, m), 8.0—8.1 (2H, m), 8.19 (1H, s, arom. H), 8.73 (1H, s, arom. H), 12.85 (1H, s, $N\underline{H}COC_6H_5$). SIMS *m/z*: 518 (MH^+), 426 ($M^+-CH_2C_6H_5$), 312, 207. IR νcm^{-1}: 3300, 1640, 1628, 1530, 1330.

5-Amino-2-(benzoylamino)-*N*-[(4-benzyl-2-morpholinyl)methyl]-4-(dimethylamino)benzamide (29) Stannous chloride dihydrate (5.0 g, 22 mmol) was added to a stirred solution of **28** (2.4 g, 4.6 mmol) in a mixture of concentrated HCl (15 ml) and MeOH (150 ml). The reaction mixture was stirred at room temperature for 1 h, poured into ice-water, basified with 10% NaOH, and extracted with $CHCl_3$. The extract was washed with brine and evaporated. The residue was subjected to column chromatography on silica gel with $CHCl_3$–MeOH (50:1) to give 1.9 g (84%) of **29**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.01 (1H, t-like, $J=11.0$, 3-H_{ax}), 2.24 (1H, td, $J=11.0$, 3.5, 5-H_{ax}), 2.65—2.9 (2H, m), 2.78 (6H, s, $N(CH_3)_2$), 3.35 (1H, m), 3.53 (2H, s, $C\underline{H}_2C_6H_5$), 3.6—4.0 (6H, m), 6.42 (1H, br t, $J=5.0$, CONH), 6.83 (1H, s, arom. H), 7.25—7.4 (5H, m), 7.40—7.60 (3H, m), 7.95—8.10 (2H, m), 8.54 (1H, s, arom. H), 12.04 (1H, s, $N\underline{H}COC_6H_5$). SIMS *m/z*: 488 (MH^+), 396 ($M^+-CH_2C_6H_5$), 282, 190. IR νcm^{-1}: 3305, 1640, 1625, 1510, 1240.

5-(Acetylamino)-2-(benzoylamino)-*N*-[(4-benzyl-2-morpholinyl)methyl]-4-(dimethylamino)benzamide (30) A mixture of **29** (0.6 g, 1.2 mmol), acetic anhydride (2 ml), and pyridine (5 ml) was stirred at room temperature for 15 h. The reaction mixture was diluted with water (100 ml) and then adjusted to a pH of about 8 with AcOH. The solution was extracted with $CHCl_3$, and the extract was washed with water and evaporated. The residue was subjected to column chromatography on silica gel with $CHCl_3$–MeOH (50 : 1) to give 0.4 g (61%) of **30**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.00 (1H, t-like, $J=11.0$, 3-H_{ax}), 2.2 (1H, m), 2.25 (3H, s, CH_3 CO), 3.6—3.9 (2H, m), 2.74 (6H, s, $N(CH_3)_2$), 3.4 (1H, m), 3.51 (2H, s, $C\underline{H}_2C_6H_5$), 3.5—3.95 (4H, m), 7.08 (1H, br t, $J=5.0$, CONH), 7.20—7.40 (5H, m), 7.41—7.60 (3H, m), 7.98—8.10 (2H, m), 8.12 (1H, s, $CH_3CON\underline{H}$), 8.59 (1H, s, arom. H), 8.80 (1H, s, arom. H), 12.46 (1H, s, $N\underline{H}COC_6H_5$). SIMS *m/z*: 530 (MH^+), 438 ($M^+-CH_2C_6H_5$), 324, 207. IR νcm^{-1}: 3260, 1655, 1630, 1525, 1518, 1395, 1278.

Reference Compound Metoclopramide (4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxybenzamide hydrochloride) was purchased from Sigma Chemical Co.

Pharmacology Male rats of the Wistar strain (Japan SLC Inc.) weighing 130—150 g were used. The rats were starved for 18 h before the experiments. A test meal (0.05% phenol red in 1.5% aqueous methylcellulose solution) 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 it was measured according to the method of Scarpignato *et al.*[14] The test compounds, suspended in a 0.5% tragacanth solution, were orally administered 60 min before administration of the test meal. The control value for the test compound was individually measured before each experiment. Differences from the control value that were statistically significant were identified by using Duncan's multiple range test.

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