^{31}P NMR δ −1.211; FAB mass spectrum, m/z 749, 751, 753 $(M + H)^+$ (1:2:1). Anal. ($C_{22}H_{24}Br_2N_4O_{12}PNa \cdot 2H_2O$) C, H.

Bis[2-(guanin-9-ylmethoxy)ethyl] 4-(Methylthio)phenyl Phosphate (7a). 4-(Methylthio)phenyl phosphorodichloridate (0.6 mL, 3.5 mmol) and 1-methylimidazole (1.5 L, 17 mmol) in pyridine (10 mL) were stirred for 5 min at room temperature and then added to a suspension of 9-[(2-hydroxyethoxy)methyl]-guanine (1.12 g, 5 mmol) in pyridine (20 mL) and the mixture was stirred for 20 h at room temperature. The resulting clear solution containing a viscous oil was poured into ice–water (100 mL) and the oil was isolated as a brown solid after trituration. The product was purified by dissolving this solid in a small volume of dimethyl sulfoxide followed by the addition of methanol until crystallization occurred (300 mg, 19% yield): UV λ_{max} 254 nm (ϵ 38 600); ^1H NMR δ 2.45 (3 H, s, SCH_3), 3.70 (4 H, m, $POCH_2CH_2O$), 4.15 (4 H, m, $POCH_2CH_2O$), 5.35 (4 H, s, OCH_2N), 6.52 (4 H, s, 2-NH_2), 7.17 (4 H, m, phenyl), 7.82 (2 H, s, H-8), 10.67 (2 H, s, NH); ^{31}P NMR δ −6.326; FAB mass spectrum, m/z 635 $(M + H)^+$. Anal. ($C_{23}H_{27}N_{10}O_8PS \cdot 2H_2O$) C, H, N.

Bis[2-(guanin-9-ylmethoxy)ethyl] 4-(Methylsulfonyl)-phenyl Phosphate (7b). 4-(Methylsulfonyl)phenyl phosphorochloridate (87 mg, 0.3 mmol), 1-methylimidazole (0.15 L, 1.7 mmol), and pyridine (5 mL) were stirred for 5 min and then added to a suspension of 9-[(2-hydroxyethoxy)methyl]guanine (112 mg, 0.5 mmol) in pyridine (10 mL). The resulting suspension was subjected to sonication in a Ultrasound bath for 2 h and then stirred overnight at room temperature. The resulting gum and solution were added to ice–water (100 mL), and after trituration, filtration, and repeated washing with methanol, the product was obtained as a pale yellow solid (10 mg, 6% yield): UV λ_{max} 253 nm (ϵ 41 000); ^1H NMR δ 3.24 (3 H, s, SO_2CH_3), 3.69 (4 H, m, $POCH_2CH_2O$), 4.19 (4 H, m, $POCH_2CH_2O$), 5.35 (4 H, s, OCH_2N), 6.52 (4 H, s, 2-NH_2), 7.42 (2 H, d, phenyl), 7.82 (2 H, s, H-8), 7.95 (2 H, d, phenyl), 10.65 (2 H, s, NH); ^{31}P NMR δ −6.596; FAB mass spectrum, m/z 667 $(M + H)^+$. Anal. ($C_{23}H_{27}N_{10}O_{10}PS \cdot 2H_2O$) C, H.

In Vitro Antiviral Assays. The in vitro antiviral assays were based on an inhibition of virus-induced cytopathogenicity in primary rabbit kidney (PRK) cell cultures.[21] Briefly, confluent PRK cell cultures in 96-well microtiter trays were inoculated with 100 $CCID_{50}$ of virus, 1 $CCID_{50}$ being the cell culture infective dose for 50% of the cell cultures. After 1 h of virus adsorption, residual virus was removed and the cell cultures were incubated in the presence of varying concentrations of the compounds. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures.

The following virus strains were used in our studies: HSV-1 (KOS, F, and McIntyre), HSV-2 (G, 196, and Lyons), thymidine kinase-deficient (TK^-) HSV-1 (B2006 and VMW 1837), vaccinia virus, and vesicular stomatitis virus.

In Vivo Antiviral Assays. Twenty-five to 30 day old athymic, nude (nu/nu) mice, weighing 15–20 g, were inoculated intracutaneously in the lumbosacral area with TK^- HSV-1 at 10^5 $CCID_{50}$/0.05 mL per mouse or wild-type HSV-1 (KOS) at $10^{4.7}$ PFU/0.05 mL per mouse, and treated topically with the indicated formulation four times a day for 5 days, starting immediately after virus infection. The appearance of skin lesions and paralysis of the hind legs and death of the mice were recorded daily.

Enzyme Studies. The examination of the hydrolysis of the test compounds by snake venom phosphodiesterase and human serum was performed as previously described.[22,23]

Acknowledgment. This work is supported by grants from the Wellcome Trust, the British Technology Group, the Belgian F.G.W.O. (Fonds voor Geneeskundig Wetenschappelijk Onderzoek, Projects No. 3.0097.87 and 3.0040.83) and the Belgian G.O.A. (Geconcerteerde Onderzoeksacties, Project No. 85/90-79). We are grateful to the British Science and Engineering Research Council for a research studentship (to S.N.F.). We also thank Anita Van Lierde, Frieda De Meyer, and Willy Zeegers for technical assistance and Christiane Callebaut and Dominique Brabants for fine editorial help.

Registry No. **3** 3′-*o*-acetyl derivative, 84218-88-2; **5a**, 125440-22-4; **5a** deacetyl derivative, 125440-37-1; **5b**, 125440-25-7; **5c**, 125440-28-0; **5d**, 125440-30-4; **5e**, 125440-32-6; **5f**, 125440-34-8; **6a**, 125440-23-5; **6b**, 125440-26-8; **6c**, 125440-29-1; **6d**, 125440-31-5; **6e**, 125440-33-7; **6e**·Na, 125515-24-4; **6f**, 125440-35-9; **7a**, 125440-24-6; **7b**, 125440-27-9; 4-(methylthio)phenyl phosphorodichloridate, 53676-21-4; 4-(methylsulfonyl)phenol, 14763-60-1; 4-(methylsulfonyl)phenyl phosphorodichloridate, 125440-36-0; *P*-(methylsulfonyl)phenol, phosphate, 28636-79-5; 3′-*O*-acetylthymidine, 21090-30-2; 9-[(2-hydroxyethoxy)methyl]guanine, 59277-89-3.

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Novel Benzamides as Selective and Potent Gastric Prokinetic Agents. 1. Synthesis and Structure–Activity Relationships of *N*-[(2-Morpholinyl)alkyl]benzamides

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With the purpose of obtaining more potent and selective gastric prokinetic agents than metoclopramide (1), a new series of *N*-[(2-morpholinyl)alkyl]benzamides (**17–52**) were synthesized and their gastric prokinetic activity was evaluated by determining effects on the gastric emptying of phenol red semisolid meal and of resin pellets solid meal in rats and mice. The morpholinyl moiety was newly designed after consideration of the side-chain structure of cisapride (**2**) and produced the desired activity when coupled with the 4-amino-5-chloro-2-methoxybenzoyl group of both metoclopramide and cisapride. Modification of the substituents of the benzoyl group markedly influenced the activity. In particular, 4-amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxybenzamide (**17**) and the 4-(dimethylamino) and 2-ethoxy analogues (**25** and **29**) of **17** showed potent and selective gastric prokinetic activity along with a weak dopamine D_2 receptor antagonistic activity.

Metoclopramide (**1**) is used clinically as a stimulant of upper gastrointestinal motility and as an antiemetic.[1] The gastric prokinetic action of metoclopramide is ascribed to stimulation of the gut motility by increase in acetylcholine

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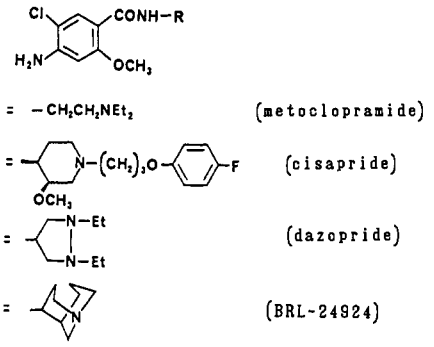
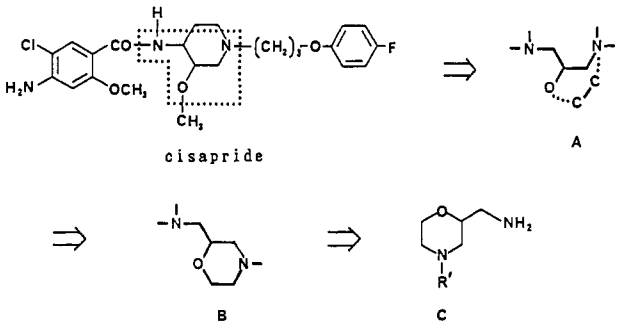
Chart I



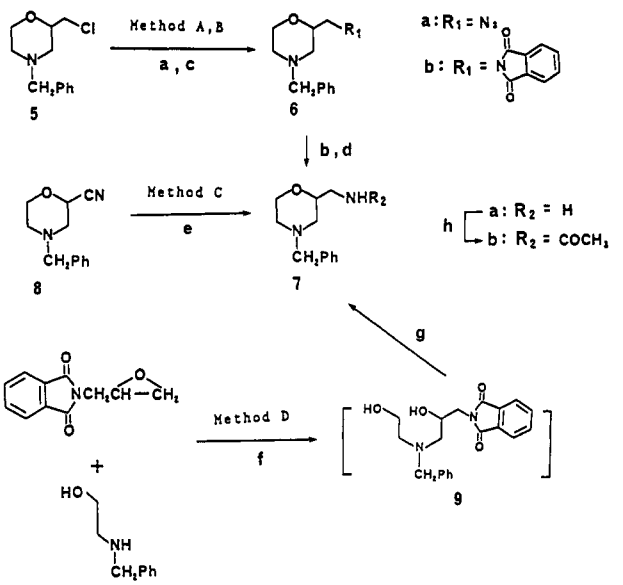
Scheme I



release from the cholinergic nerves of the gut.[2] Acetylcholine release is due to either blockade of the serotonin (5-HT_3)[3] receptors[4-6] or activation of particular 5-HT-like receptors which have not yet been characterized in the enteric nervous system.[7] This mechanism of action, however, remains to be determined. On the other hand, metoclopramide has a dopamine D_2 receptor antagonistic property, which is not related to its gastric prokinetic activity.[8,9] Blockade of dopamine D_2 receptors in metoclopramide is reported to reduce several unfavorable effects such as central nervous system depression and extrapyramidal syndrome in man,[10,11] which limits its clinical use.

Recently, several benzamide compounds such as cisapride (**2**),[12,13] dazopride (**3**),[14] and BRL-24924 (**4**)[15-17] (Chart I), showing potent gastric prokinetic action and reduced dopamine D_2 receptor antagonistic activity, were derived from modification of the side chain of metoclopramide. These compounds have clear therapeutic advantages of reducing central nervous system depression and extrapyramidal symptoms which are observed with metoclopramide and the other dopamine D_2 receptor antagonists.

Scheme II[a]



[a] Reagents and conditions: (a) NaN_3, DMF; (b) $Na[AlH_2(OCH_2CH_2OCH_3)_2]$, toluene; (c) $C_6H_4(CO)_2NK$, DMF; (D) $NH_2NH_2 \cdot H_2O$, EtOH; (e) Raney nickel/H_2, aqueous EtOH–AcOH; (f) 80 °C; (g) H_2SO_4; (h) $(CH_3CO)_2O$.

The present study was undertaken to obtain a new class of benzamides with a potent enhancement of the gastric motility without the dopamine D_2 receptor antagonistic property. A fundamental structural feature which plays an important role in pharmacological effects of cisapride (**2**) is a sequence of NCC(O)CN in the amine moiety (i.e., *cis*-4-amino-3-methoxypiperidine). Therefore, we designed a new series of 2-(aminomethyl)morpholines (the ring C in Scheme I) instead of the amine moiety of cisapride. Removal of the ethylene group from the piperidine ring of cisapride, followed by linkage of this group with the methoxy oxygen and the piperidine nitrogen as in A (Scheme I), provides formally a morpholine ring (B), thus leading to a 4-substituted-2-(aminomethyl)morpholine ring (C).

In the present paper, we describe the synthesis of a new series of benzamides with the new amine 2-(aminomethyl)-4-benzylmorpholine (**7a**) and structure–activity relationships concerning their gastric prokinetic activity and dopamine D_2 receptor antagonistic activity.

Chemistry

2-(Aminomethyl)-4-benzylmorpholine (**7a**) was synthesized by methods A–D as depicted in Scheme II. The requisite intermediate 4-benzyl-2-(chloromethyl)-morpholine (**5**)[18] was prepared by modification of the Loftus method.[19] The reaction of **5** with sodium azide

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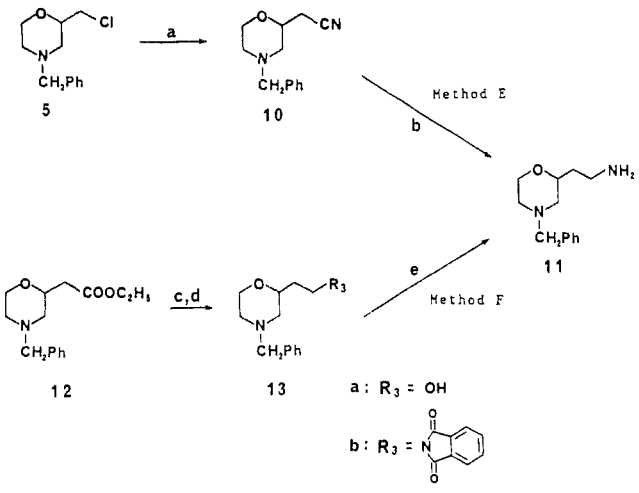
Scheme III[a]



[a] Reagents and conditions: (a) KCN, DMSO; (b) Raney nickel/H_2, EtOH-NH_4OH; (c) $LiAlH_4$, Et_2O; (d) Ph_3P, EtO_2CN=NCO_2Et, $C_6H_4(CO)_2NH$, THF; (e) $NH_2NH_2 \cdot H_2O$, EtOH.

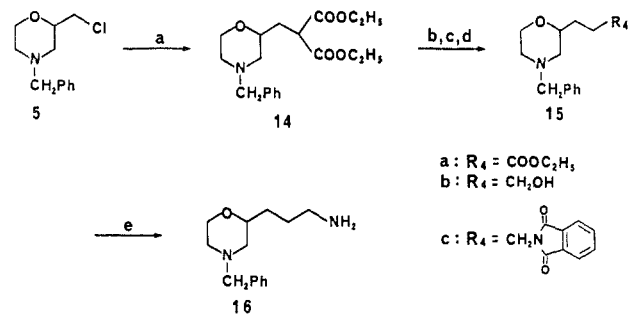
gave 2-(azidomethyl)-4-benzylmorpholine (**6a**), which on treatment with sodium bis(2-methoxyethoxy)aluminum hydride or lithium aluminum hydride gave the desired, novel 2-(aminomethyl)-4-benzylmorpholine (**7a**, method A). Morpholine **7a** was alternatively prepared by the reaction of **5** with potassium phthalimide and subsequent treatment with hydrazine monohydrate (method B), hydrogenation of 4-benzyl-2-cyanomorpholine (**8**)[20] with Raney nickel as catalyst (method C), and the reaction of *N*-benzylethanolamine with *N*-(2,3-epoxypropyl)phthalimide, followed by cyclization of intermediate diol **9** with sulfuric acid (method D). Oily product **7a** on acetylation with acetic anhydride was converted to 2-(acetylamino) derivative **7b**.

An analogue of **7a**, 2-(2-aminoethyl)-4-benzylmorpholine (**11**), was synthesized by the route shown in Scheme III. Thus the reaction of **5** with potassium cyanide gave 4-benzyl-2-(cyanomethyl)morpholine (**10**), which was then hydrogenated in the presence of Raney nickel to give aminoethyl compound **11** (method E). Ethyl 4-benzyl-2-morpholinylacetate (**12**)[19] was transformed by reduction with lithium aluminum hydride into 4-benzyl-2-(2-hydroxyethyl)morpholine (**13a**). *N*-[2-(4-Benzyl-2-morpholinyl)ethyl]phthalimide (**13b**), obtained from **13a** by using the Mitsunobu method,[21] was treated with hydrazine monohydrate to give aminoethyl compound **11** (method F).

For the synthesis of 2-(3-aminopropyl)-4-benzylmorpholine (**16**, Scheme IV), treatment of **5** with diethyl malonate in the presence of sodium hydride gave diethyl [(4-benzyl-2-morpholinyl)methyl]malonate (**14**), which was decarbethoxylated on treating with NaCl and H_2O[22] to give ethyl 3-(4-benzyl-2-morpholinyl)propionate (**15a**). Reduction of **15a** with sodium bis(2-methoxyethoxy)aluminum hydride afforded 4-benzyl-2-(3-hydroxypropyl)-morpholine (**15b**). Treatment of **15b** by method F gave requisite aminopropyl derivative **16**.

Amines **7a**, **11**, and **16** thus prepared were allowed to react with an appropriate benzoic acid or benzoyl chloride (methods G–J), giving a series of the morpholinyl derivatives **17–52** (Tables I and II).

Scheme IV[a]



[a] Reagents and conditions: (a) $CH_2(CO_2Et)_2$, NaH, DMF; (b) NaCl, H_2O, DMF; (c) $Na[AlH_2(OCH_2CH_2OCH_3)_2]$, toluene; (d) Ph_3P, EtO_2CN=NCO_2Et, $C_6H_4(CO)_2NH$, THF; (e) $NH_2NH_2 \cdot H_2O$, EtOH.

Pharmacological Results and Discussion

Compounds **17–52** (Tables I and II), metoclopramide (**1**), and cisapride (**2**) were tested for the gastric prokinetic activity by determining their effects on the gastric emptying rates of phenol red semisolid meal and of resin pellets solid meal through the stomach in rats and mice. Potency of a compound seems to be based on the stimulation of gastric motility by a nondopaminergic mechanism, because a compound which shows the potent dopamine D_2 receptor antagonistic activity as likely as domperidone is inactive on these tests.[12] The dopamine D_2 receptor antagonistic activity was tested for suppression of apomorphine-induced emesis in dogs. All compounds were first examined on gastric emptying in rats (semisolid meal at 2.0 mg/kg po), and compounds that showed a potent activity were subjected to further evaluation.

Compound **17a**, having the same benzoyl group (4-amino-5-chloro-2-methoxybenzoyl group) as that in the known compounds **1–4**, is comparable to metoclopramide in gastric prokinetic activity. Compound **17b**, however, was more potent than metoclopramide. There is greater than 10% difference in potency between the free base **17a** and its hydrochloride **17b**. This may be due to difference in rates of dissolution between them.

Influence of the substituents of the benzoyl group of **17** on the gastric emptying activity in rats was first examined. When the chlorine atom at position 5 is changed to a bromine (**18**), hydrogen (**19**), or nitro group (**22**), these compounds are inactive at the screening dose. Replacement of the amino group of **19** by an acetylamino (**20**) or chlorine group (**21**) caused a slight increase in activity; their activities are comparable to that of metoclopramide. Replacement of the amino group at position 4 of **17** by a hydrogen (**23**), methylamino (**24**), or diethylamino group (**26**) led to a poor activity. In contrast, compound **25** bearing a dimethylamino group instead of the amino group (**17**) is more potent than **17**.

Among substituted benzamide compounds which show the potent dopamine D_2 receptor antagonistic activity, the methoxy group adjacent to the amide group on the benzene ring is important for activity, because the methoxy group may stabilize a particular coplanar six-membered pseudoring conformation of the molecule by intramolecular hydrogen bonding.[23,24] We changed the methoxy group of **17** into a hydrogen (**27**), hydroxy (**28**), or ethoxy group (**29**), in order to see the importance of the substituent R_5

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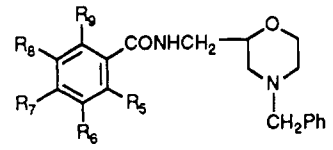
Table I. Physicochemical and Pharmacological Data for 2-Morpholinyl Benzamides



compd	R_5	R_6	R_7	R_8	R_9	mp, °C	recryst solvent[a]	formula[b]	method[c]	% GE[d] (2.0 mg/kg po)
17a	OCH_3	H	NH_2	Cl	H	148–150	AC-T	$C_{20}H_{24}ClN_3O_3$	G	26**
17b	OCH_3	H	NH_2	Cl	H	217–222	M-E	$C_{20}H_{24}ClN_3O_3 \cdot HCl$	G	39**
18	OCH_3	H	NH_2	Br	H	147–149	AC-T	$C_{20}H_{24}BrN_3O_3$	H	10
19	OCH_3	H	NH_2	H	H	119–122	P-H	$C_{20}H_{25}N_3O_3$	J	11
20	OCH_3	H	$NHCOCH_3$	H	H	108–113	P	$C_{22}H_{27}N_3O_4 \cdot H_2O$	H	24**
21	OCH_3	H	Cl	H	H	176–180	P-EA	$C_{20}H_{23}ClN_2O_3 \cdot HCl$	H	23
22	OCH_3	H	NH_2	NO_2	H	188–194	M	$C_{20}H_{24}N_4O_5 \cdot 0.25H_2O$	J	14
23	OCH_3	H	H	Cl	H	190–195	A-AC	$C_{20}H_{23}ClN_2O_3 \cdot HCl$	H	19
24	OCH_3	H	$NHCH_3$	Cl	H	158–162	A	$C_{21}H_{26}ClN_3O_3 \cdot C_4H_4O_4$[e] $\cdot 0.5H_2O$	H	14
25	OCH_3	H	$N(CH_3)_2$	Cl	H	132–134	P	$C_{22}H_{28}ClN_3O_3 \cdot 0.75C_4H_4O_4 \cdot 0.25H_2O$	H	52**
26	OCH_3	H	$N(C_2H_5)_2$	Cl	H	73–74	A-E	$C_{24}H_{32}ClN_3O_3 \cdot C_2H_2O_4$[f] $\cdot H_2O$	H	21*
27	H	H	NH_2	Cl	H	108–115	A-E	$C_{19}H_{22}ClN_3O_2 \cdot C_2H_2O_4$	H	30**
28	OH	H	NH_2	Cl	H	153–156	P	$C_{19}H_{22}ClN_3O_3 \cdot H_2O$	J	36*
29	OC_2H_5	H	NH_2	Cl	H	153–155	A	$C_{21}H_{26}ClN_3O_3 \cdot 0.25H_2O$	H	54**
30	OH	H	$N(CH_3)_2$	Cl	H	123–130	A-E	$C_{21}H_{26}ClN_3O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$	H	27*
31	OC_2H_5	H	$N(CH_3)_2$	Cl	H	188–191	AC-W	$C_{23}H_{30}ClN_3O_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$	H	51**
32	OH	H	$NHCOCH_3$	Cl	H	155–157	P	$C_{21}H_{24}ClN_3O_4$	H	11
33	OH	Cl	$N(CH_3)_2$	Cl	H	198–202	A	$C_{21}H_{25}Cl_2N_3O_3 \cdot C_2H_2O_4$	H	14
34	OCH_3	H	Cl	NH_2	H	116–117	T-H	$C_{20}H_{24}ClN_3O_3$	J	10
35	OCH_3	H	H	H	H	161–163	A	$C_{20}H_{24}N_2O_3 \cdot 2C_4H_4O_4$	H	17
36	F	F	F	F	F	208–210	A	$C_{19}H_{17}F_5N_2O_2 \cdot C_2H_2O_4$	I	9
37	OCH_3	H	H	SO_2NH_2	H	170–173	P	$C_{20}H_{25}N_3O_5S$	H	24*
38	OC_2H_5	H	H	SO_2NH_2	H	221–224	D-W	$C_{21}H_{27}N_3O_5S$	J	19*
39	SC_2H_5	H	H	SO_2NH_2	H	195–197	D-W	$C_{21}H_{27}N_3O_4S_2$	J	27*
40	Cl	H	H	SO_2NH_2	H	156–159	P	$C_{19}H_{22}ClN_3O_4S$	H	18
41	OCH_2O		H	H	H	144–146	A	$C_{20}H_{22}N_2O_4 \cdot C_4H_4O_4 \cdot 0.25H_2O$	I	30*
42	H		OCH_2O	H	H	161–163	P	$C_{20}H_{22}N_2O_4 \cdot 0.75C_4H_4O_4$	I	34**
43	H	OCH_3	OCH_3	OCH_3	H	198–200	A	$C_{22}H_{28}N_2O_5 \cdot C_2H_2O_4$	H	11
44	OCH_3	OCH_3	H	H	H	195–199	CH-T	$C_{21}H_{26}N_2O_4$	G	16[g]
45	OCH_3	Cl	H	Cl	OCH_3	116–120	T-H	$C_{21}H_{24}Cl_2N_2O_4$	I	4
46	OCH_3	H	NHN=N		H	145–147	AC-EA	$C_{20}H_{23}N_5O_3$	G	8[g]
1	metoclopramide									21*

[a] AC = acetone, T = toluene, M = MeOH, E = ether, P = *i*-PrOH, H = hexane, A = EtOH, W = water, D = dioxane, CH = $CHCl_3$, EA = AcOEt. [b] All compounds were analyzed for C, H, N, S and halogen; analytical results were within ±0.4% of the theoretical values. [c] See the Experimental Section. [d] GE = gastric emptying of phenol red semisolid meal in rats. Gastric emptying was expressed as the enhancing percentage which was based on comparison with the mean value for control groups (0.5% tragacanth). [e] Fumaric acid. [f] Oxalic acid. [g] Dose; 10.0 mg/kg po. The asterisk indicates a statistically significant difference from the control group; *, $p < 0.05$; **, $p < 0.01$ (Duncan's multiple range test).

for induction of the gastric prokinetic activity. Compounds **27** and **28** retained a comparable gastric prokinetic activity to that of **17**. Compound **29** showed the highest activity among this series. On the other hand, when the methoxy group of **25** was changed into a hydroxy (**30**) or ethoxy group (**31**), compound **30** showed a decrease in activity, whereas **31** showed a activity comparable to that of **25**. Although no clear SAR concerning the substituent R_5 of **17** and **25** was observed, several compounds were found to show potent activity.

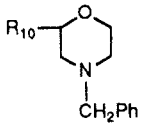
Replacement of the amino group of **28** by an acetylamino group (**32**) and introduction of a chlorine atom (**33**) at position 3 of **30** considerably reduced the activity. Compound **34** with the 4- and 5-substituents of **17** at the reverse site, compound **35** having only a methoxy group at position 2, and compound **36** having fluorine atoms at all positions have poor activity.

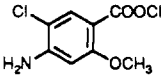
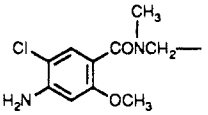
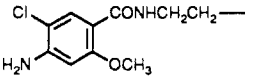
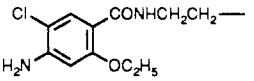
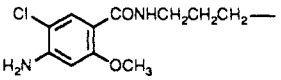
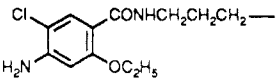
Compound **37**, bearing the same benzoyl group as that in sulpiride (one of effective antipsychotic agents), showed a comparable potency to that of metoclopramide. Variation of the substituent at position 2 of **37**, however, caused a decrease in the gastric emptying activity in the order of SC_2H_5 (**39**) > OCH_3 (**37**) > OC_2H_5 (**38**) > Cl (**40**). On the other hand, compounds **41** and **42** having the methylenedioxy group at positions 2 and 3 and at positions 3 and 4, respectively, of the benzene ring were more potent than metoclopramide. Other combinations of substituents (**43–45**) and introduction of a triazole ring (**46**) caused a loss of activity.

SARs associated with modification of the amide moiety of **17** are next discussed (Table II). In order to see importance of the –CONH– moiety of **17**, ester (**47**) and *N*-methyl amide (**48**) groups were introduced. Furthermore, the methylene group at position 2 of the morpholine ring of **17** was replaced by ethylene (**49** and **50**) and *n*-propylene (**51** and **52**) groups. Ester **47** and *N*-methyl amide **48** were less potent than **17**. Compounds **49** and **50** were approximately equipotent to or somewhat less active than **17** and **29**. However, they were more potent than metoclopramide. Compounds **51** and **52** are less active in comparison with **17** and **29**, respectively. As for the length of the alkylene chain at position 2 of the morpholine ring, the decreasing order of potency was the methylene ≥ ethylene > *n*-propylene group. Of much interest are compounds **49–51**, which have four or five carbon atoms between both nitrogen atoms of the amide group and the morpholine ring; they exhibit more potent activity than metoclopramide.

On the basis of the gastric emptying enhancement in rats, compounds **17a**, **25**, and **29** were selected for further

Table II. Physicochemical and Pharmacological Data for 2-Morpholinyl Derivatives



compd	R_{10}	mp, °C	recryst solvent[a]	formula[b]	method[c]	% GE[d] (2.0 mg/kg po)
47		93–96	P	$C_{20}H_{23}ClN_2O_4$	J	17
48		170–172	M	$C_{21}H_{26}ClN_3O_3 \cdot C_4H_4O_4$[e] $\cdot 0.25H_2O$	J	15
49		142–143	AC–W	$C_{21}H_{26}ClN_3O_3 \cdot 0.5C_4H_4O_4$	H	35**
50		149–151	M	$C_{22}H_{28}ClN_3O_3$	H	45**
51		118–121	A	$C_{22}H_{28}ClN_3O_3 \cdot C_2H_2O_4$[f] $\cdot 0.5H_2O$	H	23*
52		120–121	AN	$C_{23}H_{30}ClN_3O_3$	H	18
1	metoclopramide					21*

[a] See footnote *a* in Table I. AN = acetonitrile. [b–f] See footnotes *b–f* in Table I. The asterisks indicate a statistically significant difference from the control group; *, $p < 0.05$; **, $p < 0.01$ (Duncan's multiple range test).

Table III. Gastric Emptying of Phenol Red Semisolid Meal

compd		rat % GE[a] (mg/kg po)				mouse % GE[a] (mg/kg po)			
		0.5	2.0	5.0	10.0	0.5	1.0	2.0	5.0
17a		18	26**	35**	52**	50**	49**	46**	68**
25		27*	52**	47**	49**	7	33**	43**	43**
29		34**	54**	56**	49**	35*	23	52**	38**
1	metoclopramide	NT[b]	21*	26*	31*	NT	−10	20*	28**
2	cisapride	14*	47**	50**	43**	24*	29*	36**	38**

[a] See footnote *d* in Table I. [b] NT = not tested. The asterisks indicate a statistically significant difference from the control group; *, $p < 0.05$; **, $p < 0.01$ (Duncan's multiple range test).

evaluation including the dose–response on gastric prokinetic activities of phenol red semisolid meal in rats and mice and of resin pellets solid meal in rats and dopamine D_2 receptor antagonistic activity (antagonism of the apomorphine-induced emesis in dogs). The results are given in Tables III and IV. Regarding the gastric emptying rates of semisolid meal in rats, metoclopramide and compound **17a** were found to dose-relatedly enhance meal emptying at dose range of 2.0–10.0 mg/kg po. However, compounds **25**, **29**, and cisapride showed maximal enhancing effects at 2.0, 5.0, and 5.0 mg/kg po, respectively, without a dose–response relationship. In the gastric emptying of semisolid meal in mice, compounds **17a**, **25**, and **29** did not exhibit a dose-related increase and showed their maximal enhancing effects at a dose range of 2.0–5.0 mg/kg po. Overall, compounds **17a**, **25**, and **29** were 2–20 times as potent as metoclopramide and equipotent to or somewhat more potent than cisapride (Table III). On the other hand, compound **25** was inactive, whereas **17a** and **29** markedly ehanced the pellet emptying in the solid meal test. The maximal effect for **17a** and **29** was at a dose range of 5.0–10.0 mg/kg po, thus being approximately 5 times more potent than metoclopramide. Furthermore, the selected three compounds were found to be much less active than metoclopramide in the suppression of apomorphine-induced emesis in dogs (Table IV). In addition to potent gastric prokinetic activity, these compounds were free from dopamine D_2 receptor antagonistic activity in contrast with metoclopramide; hence these compounds may act via a nondopaminergic mechanism.

Table IV. Gastric Emptying of Resin Pellets Solid Meal in Rat and Apomorphine-Induced Emesis in Dog

compd		% GE[a] (mg/kg po)			apomorphine-induced emesis: (3.0 mg/kg po) % inhibitory activity
		2.0	5.0	10.0	
17a		49	70**	78**	4
25		15	5	NT[b]	0
29		58**	76**	NT	5
1	metoclopramide	NT	23	43*	100

[a] Gastric emptying was expressed as the enhancing percentage which was based on comparison with the mean value for control groups (0.5% tragacanth). [b] NT = not tested. The asterisks indicate a statistically significant difference from the control group; *, $p < 0.05$; **, $p < 0.01$ (Duncan's multiple range test).

Synthesis and biological activity of further series of morpholinyl benzamide derivatives are now in progress.

Experimental Section

Chemistry. All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer and electron-impact mass spectra (EIMS) were recorded on a JEOL

JMS D-300 or a Hitachi RMU-6L spectrometer. ^1H NMR spectra were taken at 80 MHz with a Varian FT-80A 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. Organic extracts were dried over anhydrous $MgSO_4$ unless otherwise specified. The solvent was evaporated under reduced pressure. Elemental analyses are given only by symbols of the elements and analytical results were within ±0.4% of theoretical values. Merck Kieselgel 60 was used for column chromatography.

4-Benzyl-2-(chloromethyl)morpholine (5). A mixture of *N*-benzylethanolamine (75.5 g, 0.50 mol) and epichlorohydrin (46.3 g, 0.50 mol) was stirred at room temperature for 3 h. To the resulting gummy oil was added dropwise concentrated H_2SO_4 (147 g, 1.5 mol), and the solution was rapidly heated to 150 °C and kept at the same temperature for 1 h. The resulting brown solution was cooled, added to ice, and basified with aqueous NaOH. The mixture was extracted with toluene. The extract was washed successively with water and brine and dried. The solvent was evaporated to give 87.6 g (78%) of **5** as a pale yellow oil, which was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 1.8–2.3, 2.4–2.9 (4 H, m), 3.3–4.0 (5 H, m), 3.50 (2 H, s, CH_2Ph), 7.30 (5 H, s, C_6H_5).

2-(Aminomethyl)-4-benzylmorpholine (7a). Method A. A mixture of **5** (15.0 g, 0.067 mol), sodium azide (8.6 g, 0.13 mol), and *N*,*N*-dimethylformamide (DMF, 150 mL) was stirred at 130 °C for 2 h. The reaction mixture was diluted with water and extracted with ether. The extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated to give 15.0 g (97%) of **6a** as an oil: IR (neat) 2100 (N_3) cm^{-1}. A solution of **6a** (15.0 g, 0.065 mol) in toluene (50 mL) was added dropwise to a stirred solution of 70% sodium bis(2-methoxyethoxy)aluminum hydride in toluene (60 mL) kept at −5 °C. The reaction mixture was stirred at room temperature for 1.5 h and cooled to 5 °C, and the excess of the reducing agent was decomposed by addition of aqueous NaOH. The organic layer was separated, washed successively with water and brine, dried, and evaporated to give 11.0 g (83%) of **7a** as an oil: IR (neat) 3460 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (2 H, br s, NH_2), 3.50 (2 H, s, CH_2Ph), 7.30 (5 H, s, C_6H_5). Fumarate of **7a**: mp 166–168 °C (C_2H_5OH–ether). Anal. ($C_{12}H_{18}N_2O \cdot 1.5C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

Method B. A mixture of **5** (86.4 g, 0.38 mol), potassium phthalimide (78.0 g, 0.42 mol), and DMF (700 mL) was heated to reflux for 5 h and then poured into ice–water. The resulting precipitates were collected and recrystallized from isopropyl alcohol (*i*-PrOH) to give 107.0 g (83%) of **6b**: mp 136–139 °C. Anal. ($C_{20}H_{20}N_2O_3$) C, H, N. A mixture of **6b** (62.2 g, 0.19 mol), 85% hydrazine monohydrate (20.0 g, 0.34 mol), and ethyl alcohol (EtOH, 180 mL) was heated to reflux for 0.5 h. After cooling to room temperature, the reaction mixture was diluted with $CHCl_3$ (600 mL). The precipitates were removed by filtration, and the filtrate was washed with a small amount of water and then with brine and dried. The solvent was evaporated to give 33.5 g (88%) of **7a**, which was identified with a sample obtained by method A.

Method C. Compound 8 (5.5 g, 0.027 mol) was dissolved in a mixture of 95% aqueous EtOH (200 mL) and acetic acid (20 mL). The resulting mixture was hydrogenated over Raney nickel (1 g, wet) at room temperature. The catalyst was removed by filtration, and the filtrate was evaporated. The resulting oil was dissolved in $CHCl_3$ (200 mL); acetic anhydride (5.6 g, 0.055 mol) was added to the solution. The mixture was stirred at room temperature for 2 h and then was poured into ice–water. The mixture was basified with aqueous NaOH. The organic layer was separated, washed successively with water and brine, and dried. The solvent was evaporated to give crude **7b**, which was chromatographed on silica gel. Elution with $CHCl_3$–CH_3OH (9:1) gave a solid, which was recrystallized from toluene to give 2.4 g (36%) of **7b** as fine needles: mp 110–111 °C; EIMS *m/z* 248 (M^+). Anal. ($C_{14}H_{20}N_2O_2$) C, H, N. A solution of **7b** (3.0 g, 0.012 mol) in 10% HCl (50 mL) was heated to reflux for 4 h. The reaction mixture was basified with aqueous NaOH and extracted with $CHCl_3$. The extract was washed successively with water and brine and dried. The solvent was evaporated to give 2.5 g (in quantitative yield) of **7a**, which was identified with a sample obtained by method A.

Method D. A mixture of *N*-benzylethanolamine (8.9 g, 0.059 mol) and *N*-(2,3-epoxypropyl)phthalimide (12.3 g, 0.061 mol) was stirred at 80 °C for 3 h. To the reaction mixture was gradually added concentrated H_2SO_4 (31.9 g, 0.33 mol), and the mixture was rapidly heated to 150 °C and kept at the same temperature for 1 h. The resulting mixture was cooled and added to ice, basified with aqueous NaOH, and extracted with $CHCl_3$. The extract was washed successively with water and brine, dried, and filtered. Acetic anhydride (6.0 g, 0.059 mol) was added to the filtrate. The mixture was stirred at room temperature for 2 h and then poured into ice–water. The mixture was basified with aqueous NaOH. The organic layer was separated, washed successively with water and brine, and dried. The solvent was evaporated to give a solid, which was recrystallized from toluene to afford 8.2 g (56%) of **7b**, which was identified with a sample by method C.

2-(2-Aminoethyl)-4-benzylmorpholine (11). Method E. A mixture of **5** (22.5 g, 0.10 mol), potassium cyanide (13.0 g, 0.20 mol), potassium iodide (1.0 g), and dimethyl sulfoxide (40 mL) was heated at 120 °C for 5 h. The reaction mixture was cooled, diluted with water, and extracted with ether. The extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated to give 20.0 g (93%) of **10** as an oil: IR (neat) 2240 (CN) cm^{-1}. Compound **10** (20.0 g, 0.093 mol) was dissolved in a mixture of EtOH (160 mL) and 28% ammonia water (10 mL) and was hydrogenated over Raney nickel (2 g, wet) at room temperature. The catalyst was removed by filtration, and the filtrate was evaporated to give 16.5 g (81%) of **11** as an oil. This oil was treated with a solution of maleic acid in EtOH to be converted into the maleate, which was recrystallized from EtOH: mp 144–147 °C. Anal. ($C_{13}H_{20}N_2O \cdot 2C_4H_4O_4$) C, H, N.

Method F. A solution of **12** (41.0 g, 0.16 mol) in anhydrous ether (100 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (59.2 g, 1.6 mol) in anhydrous ether (150 mL). The reaction mixture was stirred at room temperature for 1 h. The excess of lithium aluminum hydride was decomposed by successive addition of ethyl acetate (AcOEt) and water. The insoluble materials were removed by filtration, and the filtrate was evaporated to give 34.4 g of **13a** as an oil, which was used in the next step without further purification. A solution of diethyl azodicarboxylate (10.0 g, 0.057 mol) in anhydrous tetrahydrofuran (THF, 30 mL) was added dropwise to a stirred solution of **13a** (12.7 g, 0.057 mol), phthalimide (8.4 g, 0.057 mol), and triphenylphosphine (15.1 g, 0.058 mol) in anhydrous THF (80 mL). The mixture was stirred at room temperature for 20 h and concentrated to dryness. The residue was added to 10% HCl (200 mL), and the aqueous layer was washed with AcOEt, basified with aqueous NaOH, and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to give a solid, which was recrystallized from ether–hexane to afford 13.5 g (67%) of **13b**: mp 78–80 °C. Anal. ($C_{21}H_{22}N_2O_3$) C, H, N. To a stirred solution of **13b** (21.0 g, 0.060 mol) in EtOH (80 mL) was added dropwise 85% hydrazine monohydrate (6.3 g, 0.11 mol) in EtOH (20 mL). The mixture was heated to reflux for 1.5 h. After cooling to room temperature, the reaction mixture was diluted with $CHCl_3$ (200 mL). The resulting precipitates were removed by filtration, and the filtrate was washed with a small amount of water, dried, and concentrated to dryness to give 13.2 g of **11** as an oil. This oil was converted to the maleate in a usual manner.

Diethyl [(4-Benzyl-2-morpholinyl)methyl]malonate (14). To a cold (0 °C), stirred solution of diethyl malonate (19.2 g, 0.12 mol) in DMF (200 mL) was added portionwise 60% NaH (4.8 g, 0.12 mol). The mixture was stirred at 0 °C for 1 h. To this solution was added a solution of **5** (22.5 g, 0.10 mol) in DMF (50 mL) at room temperature. The mixture was heated at 140 °C for 15 h and poured into ice–water. The resulting solution was extracted with $CHCl_3$, and the extract was washed with water, dried, and evaporated to give 28.2 g (81%) of **14** as an oil, which was converted to the oxalate in a usual manner: mp 112–114 °C (acetone). Anal. ($C_{19}H_{27}NO_5 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N. The oxalate of **14** was added to aqueous K_2CO_3 and was extracted with $CHCl_3$. The extract was washed successively with water and brine, dried, and evaporated to give pure **14** as an oil.

Ethyl 3-(4-Benzyl-2-morpholinyl)propionate (15a). A mixture of **14** (10.0 g, 0.029 mol), NaCl (1.8 g, 0.031 mol), H_2O (1.0 g, 0.056 mol), and DMF (50 mL) was heated to reflux for 23

h and was poured into ice–water. The resulting solution was extracted with ether, and the extract was washed with water, dried over anhydrous Na_2SO_4, and evaporated to give 7.8 g (98%) of **15a** as an oil. This oil was converted to the oxalate in a usual manner: mp 143–145 °C (EtOH). Anal. ($C_{16}H_{23}NO_3 \cdot C_2H_2O_4$) C, H, N.

4-Benzyl-2-(3-hydroxypropyl)morpholine (15b). A solution of 70% sodium bis(2-methoxyethoxy)aluminum hydride in toluene (30 g, 0.10 mol) was added dropwise to a stirred solution of **15a** (26.6 g, 0.096 mol) in anhydrous toluene (150 mL) over 15 min. The mixture was stirred at room temperature for 5 h, and then the excess reducing agent was decomposed by addition of water. The organic layer was washed with water, dried, and evaporated to give an oil, which was chromatographed on silica gel to give 19.7 g (87%) of **15b** as an oil: EIMS m/z 235 (M^+).

***N*-[3-(4-Benzyl-2-morpholinyl)propyl]phthalimide (15c).** A solution of diethyl azodicarboxylate (10.0 g, 0.057 mol) in anhydrous THF (30 mL) was added dropwise to a stirred solution of **15b** (13.5 g, 0.057 mol), phthalimide (8.4 g, 0.057 mol), and triphenylphosphine (15.1 g, 0.058 mol) in anhydrous THF (80 mL). The mixture was stirred at room temperature for 20 h and concentrated to dryness. The residue was added to 10% HCl (200 mL), and the aquous layer was washed with AcOEt, basified with aqueous NaOH, and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to give 18.0 g (86%) of **15c**. This was recrystallized from *i*-PrOH to give **15c**: mp 103–106 °C. Anal. ($C_{22}H_{24}N_2O_3$) C, H, N.

2-(3-Aminopropyl)-4-benzylmorpholine (16). To a stirred solution of **15c** (17.3 g, 0.048 mol) in EtOH (80 mL) was added dropwise 100% hydrazine monohydrate (4.8 g, 0.096 mol) in EtOH (20 mL). The mixture was refluxed for 1.5 h, cooled to room temperature, and diluted with $CHCl_3$ (200 mL). The precipitates were removed by filtration. The filtrate was washed with a small amount of water, dried, and evaporated to give 6.0 g (54%) of **16** as an oil. This oil was converted to the maleate in a usual manner: mp 142–144 °C (EtOH). Anal. ($C_{14}H_{22}N_2O \cdot 2C_4H_4O_4$) C, H, N.

4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxybenzamide (17a). Method G. (General Procedure). To a stirred suspension of 4-amino-5-chloro-2-methoxybenzoic acid (2.9 g, 0.014 mol) in $CHCl_3$ (50 mL) was added triethylamine (1.6 g, 0.016 mol) at room temperature. Ethyl chloroformate (2.0 g, 0.018 mol) was added slowly to the resulting mixture at −10 °C. After the mixture was stirred at the same temperature for 1 h, a solution of **7a** (3.0 g, 0.015 mol) in $CHCl_3$ (10 mL) was added slowly. The reaction mixture was kept at −10 °C to −5 °C for 1 h and then at room temperature overnight. The mixture was washed successively with water, aqueous NaOH, and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (9:1) to afford 4.1 g (73%) of **17a** as a solid, which was recrystallized from acetone–toluene to give **17a**: EIMS m/z 389 (M^+); ^1H NMR ($CDCl_3$) δ 3.75 (2 H, s, CH_2Ph), 3.83 (3 H, s, OCH_3), 4.50 (2 H, br s, NH_2), 6.30 (1 H, s, arom 3-H), 7.30 (5 H, s, C_6H_5), 8.05 (1 H, s, arom 6-H); IR (KBr) 1620 (CONH) cm^{-1}.

***N*-[(4-Benzyl-2-morpholinyl)methyl]-5-chloro-4-(dimethylamino)-2-methoxybenzamide (25). Method H. (General Procedure).** 1-Ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (1.4 g, 0.0073 mol) was added to a stirred suspension of **7a** (1.5 g, 0.0073 mol) and 5-chloro-4-(dimethylamino)-2-methoxybenzoic acid (1.5 g, 0.0065 mol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was washed successively with water, aqueous NaOH, and brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel with $CHCl_3$–CH_3OH (9:1) to give 2.4 g (88%) of **25** as an oil. This oil was converted to the fumarate in a usual manner.

***N*-[(4-Benzyl-2-morpholinyl)methyl]-3,4-(methylenedioxy)benzamide (42). Method I. (General Procedure).** A mixture of 3,4-(methylenedioxy)benzoic acid (2.0 g, 0.012 mol), thionyl chloride (1.7 g, 0.014 mol), DMF (1 drop), and $CHCl_3$ (25 mL) was heated to reflux for 1 h. After removal of the solvent, the residue was dissolved in $CHCl_3$ (25 mL), and triethylamine (10 mL) was added. A solution of **7a** (2.5 g, 0.012 mol) in $CHCl_3$ (25 mL) was added dropwise to the mixture at 0 °C. The reaction mixture was stirred at room temperature overnight and then washed successively with water, aqueous NaOH, and brine and dried. The solvent was evaporated to give a crude product, which was chromatographed on silica gel with $CHCl_3$–CH_3OH (9:1) to afford 4.0 g (94%) of **42** as an oil. This oil was converted to the fumarate in a usual manner.

4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-2-methoxybenzamide (19). Method J. To a solution of NaOH (1.0 g, 0.025 mol) in H_2O (20 mL) was added a solution of **20** (4.0 g, 0.0096 mol) in EtOH (70 mL), and the mixture was heated to reflux for 8 h. After evaporation of the solvents, the residue was diluted with water and extracted with AcOEt. The extract was washed successively with water and brine, dried, and evaporated to give a solid, which was recrystallized from *i*-PrOH–hexane to afford 3.0 g (64%) of **19**.

4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-2-methoxy-5-nitrobenzamide (22). A mixture of **7a** (1.8 g, 0.0087 mol), 4-(acetylamino)-2-methoxy-5-nitrobenzoic acid (2.0 g, 0.0079 mol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (1.7 g, 0.0089 mol), and 50% aqueous DMF (80 mL) was stirred at room temperature for 20 h, poured into ice–water, and extracted with $CHCl_3$. The extract was washed successively with water and brine, dried, and evaporated to afford an oil, which was chromatographed on silica gel with $CHCl_3$–CH_3OH (30:1) to give a solid (**22**). The solid was recrystallized from CH_3OH to give 0.3 g (9%) of **22**.

4-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-hydroxybenzamide (28). (1) A mixture of **7a** (3.1 g, 0.015 mol), 2-acetoxy-4-(acetylamino)-5-chlorobenzoic acid (4.0 g, 0.015 mol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.9 g, 0.015 mol), and CH_2Cl_2 (40 mL) was stirred at room temperature for 4 h. The mixture was washed successively with water and brine and concentrated to dryness. The residue was dissolved in EtOH (80 mL), and 10% HCl (30 mL) was added. The mixture was heated to reflux for 2 h and concentrated. The residue was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed successively with water and brine, dried, and evaporated. The crude product was recrystallized from *i*-PrOH to give 3.9 g (67%) of **28**. (2) A solution of C_2H_5SH (0.81 g, 0.013 mol) in DMF (5 mL) was added to a stirred suspension of 60% NaH (0.52 g, 0.013 mol) in DMF (20 mL) under ice-cooling. After the reaction mixture was stirred at room temperature for 0.5 h, **17a** (3.4 g, 0.0087 mol) was added. The mixture was heated to 100 °C for 1 h and cooled. The reaction mixture was concentrated to dryness. The residue was taken up in water, washed with $CHCl_3$, and neutralized with 10% HCl. The resulting precipitates were collected, washed with water, and recrystallized from *i*-PrOH to give 2.3 g (67%) of **28**.

5-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-4-chloro-2-methoxybenzamide (34). A mixture of 4-chloro-2-methoxy-5-nitrobenzoic acid (10.0 g, 0.043 mol), **7a** (8.9 g, 0.043 mol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (8.2 g, 0.043 mol), and CH_2Cl_2 (100 mL) was stirred at room temperature for 5 h. The reaction mixture was washed successively with water, aqueous NaOH, water, and brine and then dried. The solvent was evaporated to give a solid, which was recrystallized from toluene to afford 9.0 g (50%) of *N*-[(4-benzyl-2-morpholinyl)methyl]-4-chloro-2-methoxy-5-nitrobenzamide (**34a**): mp 156–159 °C. Anal. ($C_{20}H_{22}ClN_3O_5$) C, H, N, Cl. Stannous chloride dihydrate (5.4 g, 0.024 mol) was added to a stirred mixture of **34a** (2.1 g, 0.0050 mol) in EtOH (30 mL) and AcOEt (30 mL). The mixture was stirred at 70 °C for 2 h. After evaporation of the solvent, the residue was basified with aqueous K_2CO_3 and extracted with AcOEt. The extract was washed successively with water and brine and dried. Concentration of the solvent gave the residue, which was recrystallized from toluene–hexane to give 1.0 g (51%) of **34**.

5-(Aminosulfonyl)-*N*-[(4-benzyl-2-morpholinyl)-methyl]-2-ethoxybenzamide (38). Compound **40** (5.0 g, 0.012 mol) was added to a stirred mixture of NaOEt (3.6 g, 0.053 mol) in dioxane (50 mL) and dimethyl sulfoxide (5 mL). The mixture was heated to reflux for 7 h. The reaction mixture was cooled, acidified with 10% HCl, and weakly basified with aqueous K_2CO_3. The resulting precipitates were collected, washed with water, and recrystallized from dioxane–water to give 3.0 g (59%) of **38**.

5-(Aminosulfonyl)-*N*-[(4-benzyl-2-morpholinyl)-methyl]-2-(ethylthio)benzamide (39). Sodium (1.1 g, 0.048 mol)

was added portionwise to a stirred anhydrous EtOH (50 mL). To the solution was added C_2H_5SH (2.9 g, 0.047 mol) and **40** (5.0 g, 0.012 mol). The mixture was heated to reflux for 6 h. The solvent was evaporated to give a residue, which was acidified with 10% HCl and weakly basified with aqueous K_2CO_3. The resulting precipitates were collected, washed with water, and recrystallized from dioxane–water to give 3.5 g (66%) of **39**.

(4-Benzyl-2-morpholinyl)methyl 4-Amino-5-chloro-2-methoxybenzoate (47). To a solution of 4-benzyl-2-(hydroxymethyl)morpholine[19] (2.3 g, 0.011 mol), 4-amino-5-chloro-2-methoxybenzoic acid (1.8 g, 0.0089 mol), and 4-(dimethylamino)pyridine (0.56 g, 0.0046 mol) in DMF (30 mL) was added 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.0 g, 0.010 mol) at 0 °C. The mixture was stirred at 0 °C for 2 h and then at room temperature for 15 h. After evaporation of the solvent, the residue was diluted with water and extracted with $CHCl_3$. The extract was washed successively with water and brine and dried. The solvent was evaporated to give an oil, which was chromatographed on silica gel with AcOEt–$CHCl_3$ (1:1) to give a solid. The solid was recrystallized from *i*-PrOH to give 2.0 g (57%) of **47**.

5-Amino-*N*-[(4-benzyl-2-morpholinyl)methyl]-5-chloro-2-methoxy-*N*-methylbenzamide (48). To a solution of **7b** (6.0 g, 0.024 mol) in THF (60 mL) was added portionwise 60% NaH (1.1 g, 0.028 mol). The mixture was stirred at room temperature for 1 h. Methyl iodide (3.8 g, 0.027 mol) was added to this solution. The resulting mixture was stirred at room temperature for 4 h. After evaporation of the solvent, the residue was diluted with water and extracted with AcOEt. The extract was washed successively with water and brine and dried. The solvent was evaporated to give 6.3 g of 2-[(*N*-acetyl-*N*-methylamino)methyl]-4-benzylmorpholine as an oil, which was dissolved in 10% HCl (120 mL). The solution was refluxed for 16 h. After cooling at 0 °C, the solution was basified with aqueous NaOH and extracted with $CHCl_3$. The extract was washed successively with water and brine and dried. The solvent was evaporated to give 4.7 g (89%) of 4-benzyl-2-[(methylamino)methyl]morpholine as an oil: ^1H NMR ($CDCl_3$) δ 2.42 (3 H, s, CH_3), 3.49 (2 H, s, CH_2Ph), 7.30 (5 H, s, C_6H_5). A mixture of 4-benzyl-2-[(methylamino)methyl]morpholine (2.2 g, 0.010 mol), 4-amino-5-chloro-2-methoxybenzoic acid (2.0 g, 0.0099 mol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (1.9 g, 0.0099 mol), and CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h. The mixture was washed successively with water and brine and dried. The solvent was evaporated to give an oil, which was chromatographed on silica gel with $CHCl_3$–CH_3OH (30:1) to give 3.2 g (80%) of **48** as an oil. This oil was converted to the fumarate in a usual manner.

Pharmacology. Five male mice of Std-ddY strain (Japan SLC Inc.) weighing 30–40 g and four male rats 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 with 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.[25] The test compounds, suspended in a 0.5% tragacanth solution, were orally administered 60 min before administration of test meal.

Gastric Emptying of Solid Meal. Gastric emptying of solid meal (resin pellets) was measured according to the method of Jacoby.[26] 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.

Effect on Apomorphine-Induced Emesis in Dogs. The antiapomorphine test in dogs was carried out according to the method of Janssen[27] 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 the pretreatment with test compounds. The frequency of emesis was then counted for 1 h.

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Synthesis, Pharmacological Effects, and Conformation of 4,4-Disubstituted 1,4-Dihydropyridines

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4,4-Disubstituted 1,4-dihydropyridines are synthesized by intramolecular addition of sulfinyl carbanions to pyridines. These disubstituted derivatives show a loss of Ca antagonistic potency of up to three powers of 10 both in vitro on aortic rings and in vivo on anaesthetized dogs as compared to examples that are monosubstituted at the 4-position of the DHP ring. As the X-ray structure shows, the 4-aryl substituent is present not in the accustomed axial conformation, but in an equatorial one. This dramatic change in conformation could be the reason for the major loss of activity and would indicate the need for axial conformation of the aryl residue in pharmacologically active 1,4-dihydropyridines. The change in conformation was also confirmed by quantum chemical calculations (AM1).

4-Aryl-substituted 1,4-dihydropyridines with structure **1a** (Scheme I) are easily accessible by using the classical method of Hantzsch synthesis.[1] Since the discovery of the coronary vasodilatory and antihypertensive properties of this class of substances,[2–4] a wide range of derivatives has been synthesized,[5–7] all of which, however, bear a hydrogen atom at the 4-position (**1a**), because the classical Hantzsch synthesis and its more recent modifications with aryl ketones instead of aldehydes do not yield the desired 4,4-disubstituted dihydropyridines **1b**.[8,9]

Another method for obtaining dihydropyridines is the addition of carbanions to pyridines. In this case, however,

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