hexane R_f 0.45; IR ($CDCl_3$) 1710, 1690 cm^{-1}; NMR ($CDCl_3$) δ 5.86 (s, 1 H, olefinic H), 2.17 (s, 3 H, $COCH_3$), 2.5–1.0 (m, 23 H); mass spectrum, m/z 300.2076 (M^+, calcd for $C_{20}H_{28}O_2$, 300.2082). Anal. ($C_{20}H_{28}O_2$) C, H.

13-(2-Oxopropyl)-3-methoxygona-1,3,5(10)-triene (19). To a solution of methylmagnesium iodide (made from Mg (48 mg, 2 mmol) and methyl iodide (580 mg, 2.2 mmol) in ether (25 mL) was added a solution of **17** (295 mg, 1 mmol) in anhydrous tetrahydrofuran (5 mL) and the mixture was stirred overnight. HCl (50%) was added and the mixture was stirred for 15 min. Isolation of the product by the standard procedure using ether extraction (2 × 50 mL) gave a viscous oil. This was purified by column chromatography on silica gel, using methylene chloride as the eluant, and led to a solid which on crystallization from ether–pentane afforded **19** as needles (118 mg, 37.8%): mp 122–123 °C; TLC CH_2Cl_2 R_f 0.45, 10% EtOAc/Hexane R_f 0.40; IR ($CDCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.12 (d, J = 7.9 Hz, 1 H, H-1), 6.70–6.60 (m, 2 H, H-2 and H-4), 3.70 (s, 3 H, Ar OCH_3), 2.15 (s, 3 H, $COCH_3$), 2.7–1.0 (m, 17 H); mass spectrum, m/z 312.2090 (M^+, calcd for $C_{21}H_{28}O_2$, 312.2082).

Acknowledgment. The work described in this paper was supported by a contract (No. NOIHD02817) provided by the National Institute for Child Health and Development, Grant AM 18171 from the National Institutes of Health, and by NIH Grant No. GM 07518, which provided predoctoral support for Mr. David Gordon. We thank Dr. C. R. Iden and P. Chang for mass spectral data and analyses.

Registry No. (±)-1, 90194-69-7; (±)-2, 90194-70-0; (±)-3, 90194-71-1; (±)-4a, 90194-72-2; (±)-4b, 90194-73-3; (±)-5, 90194-74-4; 6, 89321-99-3; (±)-7, 90194-75-5; 8, 3706-69-2; (±)-9, 90194-76-6; (±)-10, 90194-77-7; (±)-11a, 90194-78-8; (±)-11b, 90194-79-9; (±)-12, 90194-80-2; (±)-13, 90194-81-3; (±)-14, 64479-52-3; (±)-15, 90194-82-4; (±)-17, 90194-83-5; (±)-17 (acid), 90194-84-6; (±)-18, 90194-85-7; (±)-18-ol, 90194-86-8; (±)-19, 90194-87-9; (±)-20 (S alcohol), 90194-88-0; (±)-20 (R alcohol), 90194-96-0; (±)-21 (S alcohol), 90194-89-1; (±)-21 (R alcohol), 90194-97-1; (±)-22 (S alcohol), 90194-90-4; (±)-22 (R alcohol), 90194-98-2; (±)-23, 90194-91-5; (±)-24, 90194-92-6; (±)-25, 90194-93-7; (±)-18R-27a, 90194-94-8; (±)-18S-27b, 90194-95-9; 2-(methoxycarbonyl)cyclopentanone, 10472-24-9; butanethiol, 109-79-5; acetylenemagnesium bromide, 4301-14-8; methyl iodide, 74-88-4; ethylene glycol, 107-21-1.

Synthesis and Neuroleptic Activity of *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfonamidobenzamides

Masaru Ogata,* Hiroshi Matsumoto, Shiro Kida, Teruo Shiomi, Masami Eigyo, and Katsumi Hirose

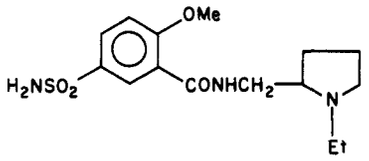
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan. *Received October 11, 1983*

A series of some novel *N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamides involving replacement of the sulfamoyl group in sulpiride with a sulfonamido group was synthesized and tested for dopamine receptor blockade. In comparison with sulpiride, several compounds were considerably more potent than sulpiride as dopamine receptor blockers. The structure–activity relationships are discussed.

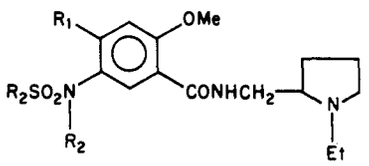
Sulpiride has been reported to be an effective antipsychotic agent and displays marked pharmacological differences from those of the "classical" neuroleptic drugs, e.g., haloperidol and chloropromazine.[1]

Sulpiride has a relatively low neuroleptic potency in both animals[1,2] and humans,[3] which could be due to a low degree of biological availability[4] including low penetration into the brain.[5] Thus, it should be of interest to synthesize and evaluate other types of neuroleptic benzamides[2,6] modified from sulpiride.

The present paper describes modifications involving replacement of the sulfamoyl residue in sulpiride with a sulfonamido residue, as shown in the general formula I.



sulpiride



I

Chemistry. A number of benzamides were synthesized by methods A–G from known 5-nitroanisic acids (**1a**,[7] **1b**,[8] **1c**[9]) as depicted in Scheme I.

2-Methoxy-4-substituted-5-nitrobenzoic acids (**1a–c**) were esterified with methanol via the acid chlorides and gave the methyl esters that on treatment with tin/hydrochloric acid or catalytic hydrogenation on platinum catalyst were reduced to the 2-methoxy-4-substituted-5-aminobenzoic acid methyl esters. Treatment of the above products with methanesulfonyl chloride gave the 5-methanesulfonamidobenzoic acid methyl esters (**2a–c**). Compounds **2a–c** were methylated with dimethyl sulfate in the presence of potassium carbonate in acetone and

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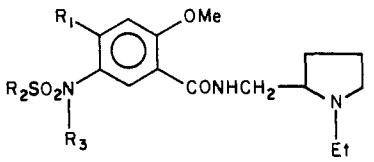
Table I. *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfonamidobenzamides



compd	R_1	R_2	R_3	method	mp, °C	recrystn solvent	yield,[a] %	formula	anal.
4a	H	Me	Me	A	94.5–96	AcOEt/(*i*-Pr)$_2$O	67	$C_{17}H_{27}N_3O_4S$	C, H, N. S
4b	Me	Me	Me	A	92–96	AcOEt/(*i*-Pr)$_2$O	52	$C_{18}H_{29}N_3O_4S$	C, H, N, S
4c	Cl	Me	Me	A	141–143	AcOEt/(*i*-Pr)$_2$O	80	$C_{17}H_{26}N_3O_4ClS$	C, H, N, Cl, S
6a	H	N(Me)Me	H	B	141–142	AcOEt/(*i*-Pr)$_2$O	39	$C_{17}H_{28}N_4O_4S$	C, H, N, S
6b	Me	N(Me)Me	H	B	129–129.5	AcOEt/(*i*-Pr)$_2$O	64	$C_{18}H_{30}N_4O_4S$	C, H, N, S
6c	Cl	N(Me)Me	H	B	118–120	AcOEt/(*i*-Pr)$_2$O	41	$C_{17}H_{27}N_4O_4ClS$	C, H, N, Cl, S
8a	H	N(Me)Me	Me	C	64.5–65.5	AcOEt/(*i*-Pr)$_2$O	36	$C_{18}H_{30}N_4O_4S$	C, H, N, S
8b	Me	N(Me)Me	Me	C	83–84	AcOEt/(*i*-Pr)$_2$O	61	$C_{19}H_{32}N_4O_4S$	C, H, N, S
8c	Cl	N(Me)Me	Me	C	93–94	(*i*-Pr)$_2$O	19	$C_{18}H_{29}N_4O_4ClS$	C, H, N, Cl, S
11a	H	Me	H	D	170–171	AcOEt	12	$C_{16}H_{25}N_3O_4S$	C, H, N, S
11b	Me	Me	H	D	131–132	AcOEt/(*i*-Pr)$_2$O	37	$C_{17}H_{27}N_3O_4S$	C, H, N, S
11c	Cl	Me	H	D	125.5–127	AcOEt/(*i*-Pr)$_2$O	25	$C_{16}H_{24}N_3O_4ClS$	C, H, N, Cl, S
12a	H	NHMe	H	E	159–160	AcOEt	57	$C_{16}H_{26}N_4O_4S$	C, H, N, S
12b	Me	NHMe	H	E	157–158	AcOEt/(*i*-Pr)$_2$O	50	$C_{17}H_{28}N_4O_4S$	C, H, N, S
12c	Cl	NHMe	H	E	134–136	AcOEt	67	$C_{16}H_{25}N_4O_4ClS$	C, H, N, Cl, S
14a	H	NH_2	H	F	140–141	MeOH/AcOEt	58	$C_{15}H_{24}N_4O_4S$	C, H, N, S
14b	Me	NH_2	H	F	140–141	AcOEt/Et$_2$O	67	$C_{16}H_{26}N_4O_4S$	C, H, N, S
14c	Cl	NH_2	H	F	158–159	MeOH/AcOEt	29	$C_{15}H_{23}N_4O_4ClS$	C, H, N, Cl, S
18a	H	NH_2	Me	G	129–130	AcOEt/Et$_2$O	50	$C_{16}H_{26}N_4O_4S$	C, H, N, S
18b	Me	NH_2	Me	G	149.5–150.5	AcOEt/(*i*-Pr)$_2$O	70	$C_{17}H_{28}N_4O_4S$	C, H, N, S
18c	Cl	NH_2	Me	G	137–138	AcOEt/(*i*-Pr)$_2$O	47	$C_{16}H_{25}N_4O_4ClS$	C, H, N, Cl, S

[a] Yield based on the last step.

subsequently hydrolyzed to the 5-(*N*-methylmethanesulfonamido)benzoic acids (**3a–c**) with aqueous sodium hydroxide. Compounds **3a–c** were then treated with thionyl chloride and 1-ethyl-2-(aminomethyl)pyrrolidine, giving the benzamides **4a–c** (method A).

The above 2-methoxy-4-substituted-5-aminobenzoic acid methyl esters gave on treatment with dimethylsulfamoyl chloride 5-[(dimethylsulfamoyl)amino]benzoic acid methyl esters (**5a–c**). Compounds **5a–c** were transformed into the desired benzamides (**6a–c**) through the corresponding acid chlorides by reaction with 1-ethyl-2-(aminoethyl)-pyrrolidine (method B).

Compounds **5a–c** were also methylated with dimethyl sulfate in the presence of potassium carbonate in acetone and subsequently hydrolyzed to the 5-[dimethylsulfamoyl)methylamino]benzoic acids (**7a–c**) with aqueous sodium hydroxide. Compounds **7a–c** were then treated with thionyl chloride and 1-ethyl-2-(aminomethyl)-pyrrolidine, giving the benzamides **8a–c** (method C).

The 5-nitrobenzamides **9a–c**, which were prepared from the corresponding benzoyl chlorides and 1-ethyl-2-(aminomethyl)pyrrolidine, were reduced with catalytic hydrogenation on platinum or tin/hydrochloric acid to the aniline compounds **10a–c**, which were used as starting material in methods D–G. Treatment of **10a–c** with methanesulfonyl chloride afforded the 5-methanesulfonamidobenzamides **11a–c** (method D). Methylsulfamoyl chloride also reacted with **10a–c** to yield the 5-[(methylsulfamoyl)amino]benzamides **12a–c** (method E).

The appropriate 5-(sulfamoylamino)benzamides **14a–c** were prepared by the reaction of **10a–c** with *tert*-butylsulfamoyl chloride in the presence of triethylamine followed by treatment of the resulting 5-[(*tert*-butylsulfamoyl)amino]benzamides **13a–c** with trifluoroacetic acid (method F).

The trifluoroacetates (**15a–c**), which were prepared by the reaction of trifluoroacetic anhydride with **10a–c**, were treated with sodium hydride and methyl iodide in dimethylformamide followed by hydrolysis with aqueous potassium carbonate and gave the *N*-methylaniline compounds **16a–c**. Treatment of **16a–c** with *tert*-butylsulfamoyl chloride in the presence of triethylamine gave the 5-[(*tert*-butylsulfamoyl)amino]benzamides **17a–c**. Compounds **17a–c** were treated with trifluoroacetic acid and yielded the desired 5-(sulfamoylmethylamino)benzamides **18a–c** (method G).

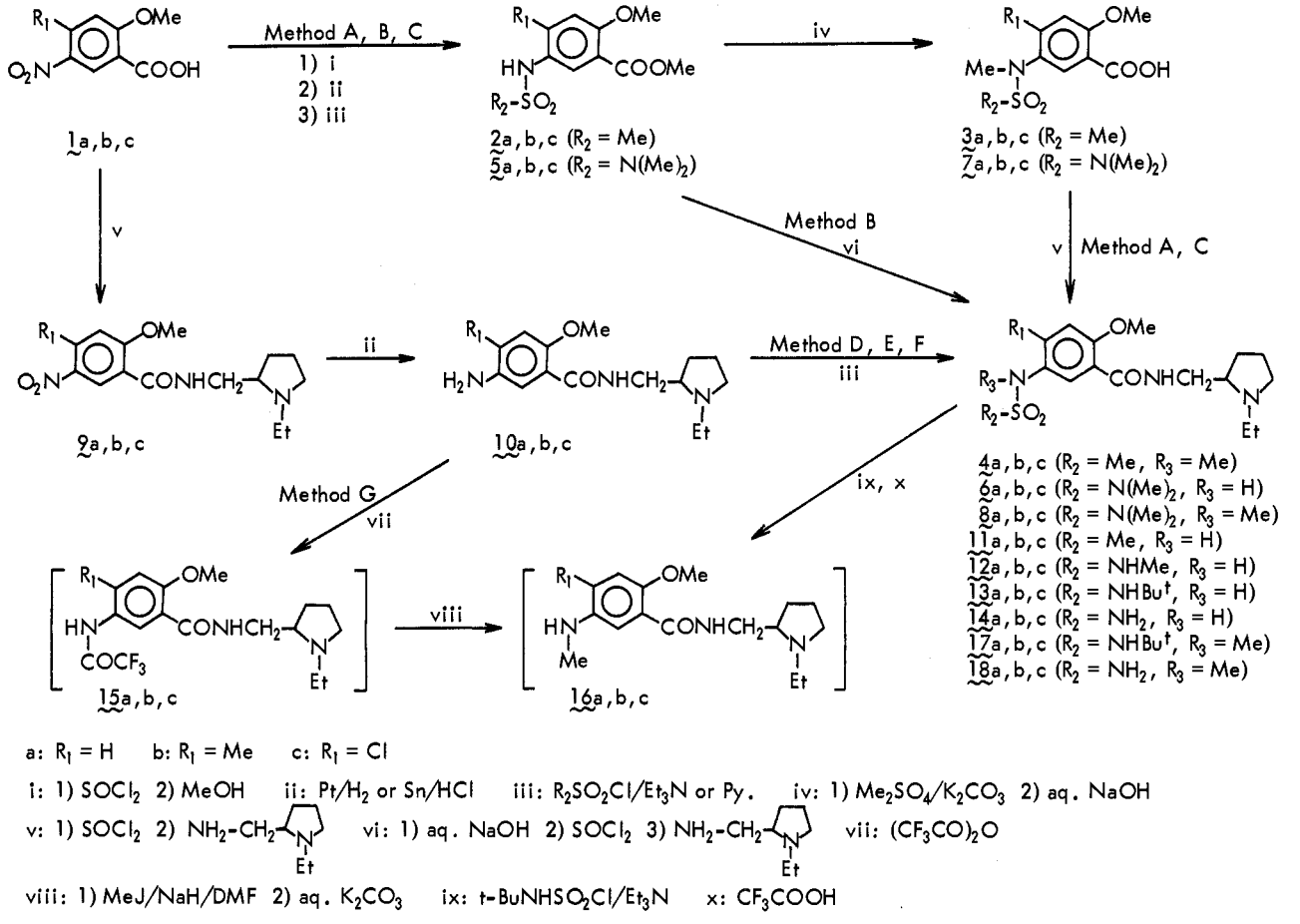
Table II. Pharmacological Evaluation of 5-Sulfonamidobenzamides (I)

compd	block of apomorphine: ED_{50}, mg/kg, oral		acute toxicity in mice: LD_{50},[c] mg/kg, oral
	antiemetic activity in dogs[a]	anticlimbing activity in mice[b]	
4a	0.17	22.9 (16.7–30.8)	>1000
4b	0.1–1.0	26.1 (20.9–33.4)	>1000
4c	0.05–0.1	7.7 (6.1–9.7)	>500
6a	0.1–1.0	>50	750
6b	0.01–0.05	13.3 (10.2–18.8)	>1000
6c	0.01–0.05	8.3 (5.9–12.1)	>1000
8a	0.5–1.0	36.2 (13.7–102.6)	750
8b	0.5–1.0	>50 (71.8–115.1)	750
8c	0.05–0.1	31.8 (21.2–46.8)	750
11a	1.0–2.0	>50	>500
11b	0.1–1.0	35.6 (25.2–66.1)	750
11c	0.05–0.1	9.1 (6.2–12.3)	>1000
12a	>1	>50	>1000
12b	>1	>50	>1000
12c	>1	>50	>1000
14a	5.0–10.0	>50	>1000
14b	>1	>50	>1000
14c	0.5–1.0	>50	>1000
18a	0.1–1.0	>50	>1000
18b	0.1–1.0	>50	>1000
18c	0.1–1.0	>50	>1000
sulpiride	0.09	174 (152–202)	>3000

[a] Up and down method of Brownlee et al.[10] [b] Regression analysis; 95% confidence limits are included parentheses. [c] Oral LD_{50} values were obtained by graphical interpolation.

Pharmacology. Structure–Activity. The pharmacological results obtained with the compound I series (Table I) are presented in Table II. The neuroleptic activities of I were determined by their inhibitory effects

Scheme I



a: R_1 = H b: R_1 = Me c: R_1 = Cl

i: 1) $SOCl_2$ 2) MeOH ii: Pt/H_2 or Sn/HCl iii: R_2SO_2Cl/Et_3N or Py. iv: 1) Me_2SO_4/K_2CO_3 2) aq. NaOH

v: 1) $SOCl_2$ 2) NH_2-CH_2-(N-Et) vi: 1) aq. NaOH 2) $SOCl_2$ 3) NH_2-CH_2-(N-Et) vii: $(CF_3CO)_2O$

viii: 1) MeJ/NaH/DMF 2) aq. K_2CO_3 ix: t-BuNHSO$_2$Cl/Et_3N x: CF_3COOH

on apomorphine-induced behavior (emesis in dogs and climbing in mice) and compared with those of sulpiride.

Introduction of $NH(Me)SO_2NH$, NH_2SO_2NH, and $NH_2SO_2N(Me)$ groups to the 5-position of the benzene nucleus resulted in poor activity, as shown by **12a–c**, **14a–c**, and **18a–c**. Several factors may contribute to the low potency of these sulfamoylamino compounds, such as metabolic degradation or low penetration into the brain. This finding demonstrated the importance of the sulfamoyl group (NH_2SO_2) in the sulpiride structure.

On the other hand, **4a–c**, **6a–c**, **8a–c**, and **11b,c** having the methanesulfonamido or (dimethylsulfamoyl)amino group, showed strong antidopaminergic potency compared to **12a–c**, **14a–c**, and **18a–c**. This finding suggests that introduction of the lipophilic group facilitates penetration of the compound through the blood–brain barrier.

In general, the 4-substituted (Cl or methyl group) methanesulfonamido- or [(dimethylsulfamoyl)amino]-benzamide series (**4c**, **6b,c**, **8c**, and **11b,c**) were more potent than the corresponding 4-unsubstituted sulfonamidobenzamides (**4a**, **6a**, **8a**, **11a**), with the exception of **4b** and **8b**. In compounds **4b** and **8b**, there were two methyl groups in both the 4-position in the benzene nucleus and the sulfonamido nitrogen. The different apomorphine blocking activity of **4b** and **8b** may be due to the conformation of the sulfonamido group moiety, which differs from that of the desmethyl compound. Introduction of a methyl group that is more bulky[10] than a chlorine atom would somewhat change the conformation of the sulfonamido group related to binding with the dopamine receptor.

(10) Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, NY 1960; p 260.

Experimental Section

Melting points were determined in a "Büchi" capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 spectrometer. Elemental analyses were performed by the analytical department of Shionogi Research Laboratories and are within ±0.4% of the calculated values.

Method A. Methyl 2-Methoxy-4-methyl-5-methanesulfonamidobenzoate (2b). A mixture of 2-methoxy-4-methyl-5-nitrobenzoic acid (**1b**; 84 g, 0.4 mol) and $SOCl_2$ (250 mL) was refluxed for 1 h, and the resultant mixture was evaporated to remove the $SOCl_2$. The residue was mixed with MeOH (200 mL) and evaporated to remove the MeOH. The residue was washed with $(i\text{-Pr})_2O$ to give methyl 2-methoxy-4-methyl-5-nitrobenzoate (84.9 g, mp 124.5–125.5 °C, 91%).

A mixture of the above ester (2.79 g, 0.012 mol), PtO_2 (280 mg), and MeOH (50 ml) was sujected to hydrogenation. The catalyst was filtered, and the filtrate was evaporated to give methyl 2-methoxy-4-methyl-5-aminobenzoate as a syrup (2.38 g, 0.012 mol). The ester was dissolved in pyridine (3 mL), and methanesulfonyl chloride (324 mg, 2.83 mmol) was added with stirring under ice cooling. After 30 min of stirring, the mixture was poured into ice water and acidified with dilute HCl and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was crystallized from AcOEt/$(i\text{-Pr})_2O$ to give **2b** (655 mg, mp 144–144.5 °C, 85%). Anal. ($C_{11}H_{15}NO_5S$) C, H, N.

Compounds **2a** (mp 84–86 °C, 53%) and **2c** (mp 183–185 °C, 48%) were obtained by the same method.

2-Methoxy-4-methyl-5-(*N*-methylmethanesulfonamido)-benzoic Acid (3b). A mixture of **2b** (1.0 g, 3.66 mmol), K_2CO_3 (1.01 g, 7.31 mmol), Me_2SO_4 (694 mg, 5.50 mmol), and acetone (20 mL) was refluxed for 1.5 h. After the solvent was evaporated, the residue was heated with aqueous NaOH (10% aqueous NaOH 10 mL, MeOH 5 mL) at 85 °C for 10 min. The organic solvent was removed, and the residue was acidified with dilute HCl. The resulting precipitate was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and filtered. The

filtrate was evaporatead, and the residue was washed with benzene to give **3b** (900 mg, mp 196–197 °C, 90%). Anal. ($C_{11}H_{15}NO_5S$) C, H, N, S.

Compounds **3a** (mp 147–148.5 °C, 72%) and **3c** (mp 175–177 °C, 64%) were obtained by the same method.

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-(*N*-methylmethanesulfonamido)benzamide (4b).** A mixture of **3b** (500 mg, 1.83 mmol) and $SOCl_2$ (5 mL) was refluxed for 30 min, and the resultant mixture was evaporated to remove $SOCl_2$. The residue was mixed with benzene and evaporated to remove excess $SOCl_2$. The residue was mixed with triethylamine (370 mg, 3.66 mmol) and dry CH_2Cl_2 (5 mL), and a solution of 1-ethyl-2-(aminomethyl)pyrrolidine (260 mg, 2.02 mmol) and CH_2Cl_2 (1 mL) was added dropwise with ice cooling and stirring. The resultant mixture was stirred at room temperature for 30 min. The reaction mixture was mixed with aqueous $NaHCO_3$ and shaken with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on alumina (activity II). The fractions eluted with 2% MeOH/CH_2Cl_2 were collected to obtain **4b** (362 mg, 52%).

Compounds **4a** and **4c** were obtained by the same method.

Method B. Methyl 2-Methoxy-4-methyl-5-[(dimethylsulfamoyl)amino]benzoate (5b). To a solution of methyl 2-methoxy-4-methyl-5-aminobenzoate (244.2 g, 1.25 mol, derived from **1b** in method A) in dry pyridine (488 mL) was added dropwise dimethylsulfamoyl chloride (233.5 g, 1.63 mol) with the temperature maintained at 50 °C. After the addition, the mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (1.2 L) and poured into ice–water (488 mL) and acidified with concentrated HCl (488 mL). The resultant precipitate was extracted with CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4 and evaporated to give **5b** (272.7 g, mp 119–120 °C, from AcOEt, 72%). Anal. ($C_{12}H_{18}N_2O_5S$) C, H, N, S.

Compounds **5a** (mp 101.5–102.5 °C, 43%) and **5c** (mp 171–172 °C, 51%) were obtained by the same method.

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-methyl-5-[(dimethylsulfamoyl)amino]benzamide (6b).** A mixture of **5b** (1.42 g, 4.70 mmol) and 10% NaOH (14.2 mL) was heated at 80 °C for 30 min. The reaction mixture was acidified with 6 N HCl and extracted with 5% MeOH/CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give 2-methoxy-4-methyl-5-[(dimethylsulfamoyl)amino]benzoic acid (1.24 g, mp 154–156 °C, 92%).

A mixture of 2-methoxy-4-methyl-5-[(dimethylsulfamoyl)-amino]benzoic acid (20.2 g, 70.1 mmol) and $SOCl_2$ (101 mL) was refluxed for 30 min, and the resultant mixture was evaporated to remove $SOCl_2$. The residue was mixed with triethylamine (14.15 g, 140 mmol) and dry CH_2Cl_2 (101 mL), and a solution of 1-ethyl-2-(aminomethyl)pyrrolidine (9.89 g, 77.14 mmol) and CH_2Cl_2 (20 mL) was added dropwise with ice cooling and stirring. The resultant mixture was stirred at room temperature for 15 min. The reaction mixture was mixed with aqueous $NaHCO_3$ and shaken with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporatead to remove the solvent. The residue was chromatographed on alumina (activity II). The fractions eluted with CH_2Cl_2–3% MeOH/CH_2Cl_2 were collected to obtain **6b** (17.8 g). Anal. ($C_{18}H_{30}N_4O_4S$) C, H, N, S.

Compounds **6a** and **6c** were obtained by the same method.

Method C. 2-Methoxy-4-methyl-5-[(dimethylsulfamoyl)-methylamino]benzoic Acid (7b). To a solution of methyl 2-methoxy-4-methyl-5-[(dimethylsulfamoyl)amino]benzoate (**5b**; 5 g, 16.53 mmol) in dry acetone (25 mL) were added K_2CO_3 (4.57 g, 33.1 mmol) and dimethyl sulfate (4.17 g, 33.1 mmol), and the resultant mixture was refluxed for 1 h. After evaporation of the acetone, the residue was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was heated with aqueous NaOH at 85 °C for 3 min. The reaction mixture was acidified with aqueous HCl and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried (Na_2SO_4). The organic solvent was removed to give **7b** (4.65 g, mp 157.5–159 °C, after washing with $(i\text{-Pr})_2O$, 93%). Anal. ($C_{12}H_{18}N_2O_5S$) C, H, N, S.

Compounds **7a** (mp 87–88 °C, 71%) and **7c** (mp 171–172 °C, 65%) were obtained by the same method.

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-methyl-5-[(dimethylsulfamoyl)methylamino]benzamide (8b).** A mixture of **7b** (23.3 g, 77.1 mmol) and $SOCl_2$ (116 mL) was refluxed for 30 min, and the resultant mixture was evaporated to remove $SOCl_2$. The residue was mixed with triethylamine (15.57 g, 0.15 mol) and dry CH_2Cl_2 (116 mL), and a solution of 1-ethyl-2-(aminomethyl)pyrrolidine (10.87 g, 0.85 mol) and CH_2Cl_2 (22 mL) was added dropwise with ice cooling and stirring. The resultant mixture was mixed with aqueous $NaHCO_3$ and shaken with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to remove the solvent. The residue was chromatographed on alumina (activity II). The fractions eluted with CH_2Cl_2 were collected to yield **8b** (19.35 g). Anal. ($C_{19}H_{32}N_4O_4S$) C, H, N, S.

Compounds **8a** and **8c**, were also obtained by the same method.

Method D. *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-chloro-5-nitrobenzamide (9c). A mixture of 2-methoxy-4-chloro-5-nitrobenzoic acid (900 mg, 3.89 mmol) and $SOCl_2$ (5 mL) was refluxed for 30 min, and the resultant mixture was evaporated to remove $SOCl_2$. Dry CH_2Cl_2 (9 mL) and triethylamine (790 mg, 7.82 mmol) were added, and a solution of 1-ethyl-2-(aminomethyl)pyrrolidine (750 mg, 5.85 mol) and CH_2Cl_2 (4 mL) was added dropwise with ice cooling and stirring. The resultant mixture was stirred at room temperature for 15 min. The reaction mixture was mixed with aqueous $NaHCO_3$ and shaken with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was mixed with Et_2O and shaken with dilute HCl. The aqueous layer was made alkaline with aqueous $NaHCO_3$ and shaken with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was recrystallized from AcOEt/$(i\text{-Pr})_2O$ to give **9c** (679 mg, mp 107–108 °C, 57%). Anal. ($C_{15}H_{20}N_3O_4Cl$) C, H, N, Cl.

Compounds **9a** (mp 106–106.5 °C, 69%) and **9b** (mp 113–113.5 °C, 45%) were obtained by the same method.

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-chloro-5-aminobenzamide (10c).** **9c** (7.33 g, 21.4 mmol) was mixed with a solution of concentrated HCl (36.7 mL) and H_2O (73.3 mL), and the resultant mixture was heated at 50 °C, mixed with tin chips (7.7 g, 64.9 mmol), and stirred at 50 °C for 4 h. After cooling, the reaction mixture was made alkaline with aqueous NaOH and shaken with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on a column of alumina, which was eluted with CH_2Cl_2. The elute was evaporated to remove the solvent. The residue was washed with $(i\text{-Pr})_2O$/petroleum ether to give **10c** (5.38 g, mp 85–86.5 °C, 81%). Anal. ($C_{15}H_{22}N_3O_2Cl$) C, H, N, Cl.

Compounds **10a** (HCl salt, mp 194–200 °C, 35%) and **10b** (mp 82.5–83 °C, 51%) were obtained by the same method.

***N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-chloro-5-methanesulfonamidobenzamide (11c).** To a solution of **10c** (1.58 g, 5.06 mmol) and dry pyridine (15.8 mL) was added dropwise methanesulfonyl chloride (880 mg, 7.6 mmol) with the temperature maintained at 0–5 °C. After addition, the mixture was stirred for 30 min at room temperature. The reaction mixture was poured into H_2O and made alkaline with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on a column of alumina (activity III), which was eluted with CH_2Cl_2 and 3% MeOH/CH_2Cl_2. The fractions were evaporated to remove the solvent. The residue was recrystallized from AcOEt/$(i\text{-Pr})_2O$ to give **11c** (498 mg, mp 125.5–127 °C, 25%). Anal. ($C_{16}H_{24}N_3O_4SCl$) C, H, N, S, Cl.

Compounds **11a** and **11b** were obtained by the same method.

Method E. *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-chloro-5-[(methylsulfamoyl)amino]benzamide (12c). To a solution of **10c** (1.0 g, 3.2 mmol), triethylamine (390 mg, 3.86 mmol), and dry CH_2Cl_2 (20 mL) was added a solution of methylsulfamoyl chloride (460 mg, 3.55 mmol) and CH_2Cl_2 (4 mL) with ice cooling and stirring. The resultant mixture was stirred for 15 min. The reaction mixture was mixed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to remove the

solvent. The residue was chromatographed on alumina (activity III). The fraction eluted with CH_2Cl_2 and 1% MeOH/CH_2Cl_2 was collected to obtain **12c** (863 mg). Anal. ($C_{16}H_{25}N_4O_4SCl$) C, H, N, S, Cl.

Compounds **12a** (mp 159–160 °C, 45%) and **12b** (mp 157–158 °C, 51%) were obtained by the same method.

Method F. *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-methyl-5-(sulfamoylamino)benzamide (14b). A mixture of **10b** (1.0 g, 3.43 mmol), dry CH_2Cl_2 (20 mL), and triethylamine (693 mg, 6.86 mmol) was added dropwise to a mixture of *tert*-butylsulfamoyl chloride (707 mg, 412 mmol) and CH_2Cl_2 (5 mL) with ice cooling and stirring. After stirring for 15 min, the reaction mixture was mixed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to remove the solvent. The residue was chromatographed on alumina (activity II) and eluted with CH_2Cl_2 and 2% MeOH/CH_2Cl_2 to give *N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-methyl-5-[(*tert*-butylsulfamoyl)amino]benzamide (**13b**; 1.0 g, mp 107–168 °C, 68.3% from AcOEt/(*i*-Pr)$_2$O). Anal. ($C_{20}H_{34}N_4O_4S$) C, H, N, S.

The above **13b** (700 mg, 1.64 mmol) was mixed with trifluoroacetic acid (7 mL), stirred at room temperature for 3 h, and evaporated to remove the trifluoroacetic acid. The residue was mixed with aqueous ammonia, NaCl was added, and the mixture was extracted with $CHCl_3$. The organic layer was washed with saturated brine, dried (Na_2SO_4), and recrystallized from AcOEt/Et_2O to give **14b** (408 mg). Anal. ($C_{16}H_{26}N_4O_4S$) C, H, N, S.

Compounds **14a** and **14c** were obtained by the same method.

Method G. *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-methyl-5-[(*tert*-butylsulfamoyl)methylamino]benzamide (17b). To a solution **10b** (423 g, 14.5 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise trifluoroacetic anhydride (4.57 g, 21.76 mmol) with ice cooling and stirring. The resultant mixture was stirred at room temperature for 15 min. The reaction mixture was mixed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to remove the solvent. The residue was washed with AcOEt/(*i*-Pr)$_2$O to give *N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-methyl-5-(trifluoroacetamido)benzamide (**15b**; 4.15 g, mp 125–127 °C, 74%).

The above **15b** (4.0 g, 10.32 mmol) was dissolved in DMF (20 mL), and NaH (50%, 520 mg, 10.83 mmol) was added with ice cooling and stirring. To the resultant mixture was added MeI (1.54 g, 10.85 mmol) with ice cooling and stirring. The reaction mixture was stirred for 30 min at room temperature, and diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to remove the solvent. The residue was mixed with 10% aqueous K_2CO_3 (40 mL) and MeOH (40 mL) and heated on water bath for 15 min. The organic solvent was removed, and the residue was diluted with H_2O and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and filtered, and the filtrate was evaporated to leave *N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-4-methyl-5-(methylamino)benzamide (**16b**) as an oil (2.6 g).

The above **16b** (2.6 g, 8.5 mmol) was mixed with dry CH_2Cl_2 (26 mL) and triethylamine (1.72 g, 17 mmol), and a solution of *tert*-butylsulfamoyl chloride (2.20 g, 12.8 mmol) in CH_2Cl_2 (6 mL) was added dropwise with ice cooling and stirring. The resultant mixture was stirred for 15 min at room temperature. The reaction mixture was mixed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to remove the solvent. The residue was chromatographed on alumina (activity II). The fractions eluted with 1–3% MeOH/CH_2Cl_2 were collected to obtain **17b** (975 mg, mp 142.5–143 °C, 21.4%, from AcOEt). Anal. ($C_{21}H_{36}N_4O_4S$) C, H, N, S. **17a** (mp 127–128 °C, 26%), **17c** (mp 135–140 °C, 13%).

The above **17b** (800 mg, 1.8 mmol) was refluxed with trifluoroacetic acid (8 mL), stirred at 50 °C for 30 min, and evaporated to remove the trifluoroacetic acid. The residue was mixed with aqueous ammonia, salted out with saturated brine, and extracted with $CHCl_3$. The organic layer was washed with saturated brine, dried (Na_2SO_4), and evaporated to remove the solvent. The residue was recrystallized from AcOEt/diisopropyl ether to give **18b** (485 mg). Anal. ($C_{17}H_{28}N_4O_4S$) C, H, N, S.

18a and **18c** were obtained by the same method.

Pharmacology. Antiemetic Activity. The method of Chen et al.[11] was used. One hour after administration of the compound, the number of vomitings within 30 min of subcutaneous injection of 0.1 mg/kg apomorphine in fasted dogs were observed. For each dose of the compound, the number of vomitings on the testing day was compared with that observed in the same dog 2 weeks before the test. ED_{50} values were calculated according to the up and down method of Brownlee et al.[12]

Anticlimbing Activity. The method of Protais et al.[13] was used. The test was carried out on two to three groups of animals, a group consisting of 10 mice. After subcutaneous injection of 1 mg/kg of apomorphine, the mouse was put in a stainless cage (10 × 10 × 20 cm) and showed wall-climbing behaviors by holding the wire mesh of the cage wall with their four paws. The test compound was given orally as an arabic gum suspension 60 min prior to the administration of apomorphine. Twenty minutes after the administration of apomorphine, the observation was made for 3 min. The criterion of climbing behaviors was determined in comparison with a control group of mice. Results were shown as the value of ED_{50} (milligrams/kilogram). ED_{50} values were calculated according to regression analysis.

Acute Toxicity. The acute toxicity of each drug was determined in groups of 10 mice on the seventh day after oral administration. The LD_{50} values were obtained by graphical interpolation.

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Registry No. **1a**, 40751-89-1; **1a** (acid chloride), 90763-46-5; **1a** (amine, acid chloride), 90763-48-7; **1b**, 90763-12-5; **1b** (acid chloride), 68256-33-7; **1b** (amine, acid chloride), 90763-49-8; **1c**, 68255-77-6; **1c** (acid chloride), 90763-47-6; **1c** (amine, acid chloride), 90763-50-1; **2a**, 68256-19-9; **2b**, 90763-13-6; **2c**, 90763-14-7; **3a**, 90763-15-8; **3b**, 90763-16-9; **3c**, 90763-17-0; **4a**, 90763-18-1; **4b**, 90763-19-2; **4c**, 68256-20-2; **5a**, 90763-20-5; **5b**, 90763-21-6; **5c**, 90763-22-7; **6a**, 68256-02-0; **6b**, 68256-12-2; **6c**, 90763-23-8; **7a**, 90763-24-9; **7b**, 90763-25-0; **7c**, 90763-26-1; **8a**, 90763-27-2; **8b**, 90763-28-3; **8c**, 90763-29-4; **9a**, 23694-03-3; **9b**, 90763-30-7; **9c**, 68255-78-7; **10a**, 68255-81-2; **10b**, 68255-94-7; **10c**, 68255-79-8; **11a**, 68255-83-4; **11b**, 68256-07-5; **11c**, 68256-41-7; **12a**, 90763-31-8; **12b**, 68256-24-6; **12c**, 90763-32-9; **13a**, 90763-33-0; **13b**, 68256-21-3; **13c**, 68256-23-5; **14a**, 68256-26-8; **14b**, 68256-22-4; **14c**, 68256-25-7; **15a**, 90763-34-1; **15b**, 90763-35-2; **15c**, 90763-36-3; **16a**, 90763-37-4; **16b**, 90763-38-5; **16c**, 90763-39-6; **17a**, 90763-40-9; **17b**, 90763-41-0; **17c**, 90763-42-1; **18a**, 90763-43-2; **18b**, 90763-44-3; **18c**, 90763-45-4.

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