The Interaction of Ammonium, Sulfonium, and Sulfide Analogues of Metoclopramide with the Dopamine D_2 Receptor

Marc W. Harrold,*,⊥ Anong Sriburi,⊥ Kazuhisa Matsumoto,‡ Duane D. Miller,‡ Tahira Farooqui,∥ and Norman Uretsky∥

Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, Pennsylvania 15282, and Divisions of Medicinal Chemistry & Pharmacognosy and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received May 21, 1993•

A series of permanently charged ammonium and sulfonium analogues of metoclopramide as well as a permanently uncharged sulfide analogue were synthesized and evaluated for their ability to inhibit apomorphine-induced responses on mouse striatal slices. Three of the four permanently charged analogues were found to inhibit apomorphine's effects, although at higher concentrations than either metoclopramide or its dimethyl analogue. In contrast, the sulfide analogue was inactive at concentrations up to 100 μM. These findings are consistent with earlier studies of chlorpromazine and sulpiride analogues and provide further evidence that dopamine antagonists bind in their charged molecular forms to anionic sites on the D_2 receptor. Further, the results of this study in conjunction with those of our earlier sulpiride study would seem to indicate that differences in the biological profiles of metoclopramide, a type 1 benzamide useful as a gastric prokinetic agent, and sulpiride, a type 2 benzamide useful for its antipsychotic effects, are not due to any appreciable differences in the binding of the basic nitrogen atom of these molecules.

Substituted o-methoxybenzamides (orthopramides) possess a wide variety of pharmacological actions based at least in part upon their ability to act as dopamine D_2 receptor antagonists. These agents display neuroleptic, antidyskinetic, antiemetic, antimanic, gut motility, and antiulcer effects.[1-4] Tremendous structural variability is seen within this class of agents; however the substituted o-methoxybenzamides can be represented by one of the two general structures (1A or 1B) shown in Chart I.[5] Benzene is the most common aromatic ring, and the basic side-chain nitrogen is separated from the benzamide nitrogen by either two or three carbon atoms. Hadley has classified the substituted benzamides into four structural types based on the structures of their side chains. Type 1 benzamides, exemplified by metoclopramide (2), have an acyclic side chain and a two-carbon spacing between the benzamide and tertiary nitrogen atoms; type 2 benzamides, exemplified by sulpiride (3) and raclopride (4), contain a 2-pyrrolidinylmethyl side chain; type 3 agents, exemplified by emonapride (5), contain a 3-pyrrolidinyl side chain; and type 4 agents, exemplified by cisapride (6), contain a 4-piperidyl side chain.[5]

Most of the current research involving the benzamides is centered around the development of either atypical neuroleptic agents[6-10] or gastric prokinetic agents.[11,12] Benzamides containing either a 2-pyrrolidinylmethyl or a 3-pyrrolidinyl side chain are potent dopamine D_2 receptor antagonists with a low tendency to produce extrapyramidal side effects. As a result, raclopride and several other type 2 and type 3 benzamides are currently undergoing clinical evaluation as atypical antipsychotic agents.[13,14] In contrast, metoclopramide and cisapride are used to stimulate gastrointestinal motility and are useful in the treatment of a number of GI disorders.[15] The mechanism of action of these latter drugs is not completely understood but is thought to involve serotonin-mediated release of acetylcholine in the gut.[11,15] Unlike raclopride and other related compounds, the therapeutic effects of metoclopramide are not related to its blockade of dopamine D_2 receptors.[11,16] In fact, metoclopramide's antagonism of D_2 receptors is responsible for extrapyramidal side effects and thus limits its clinical utility.[11]

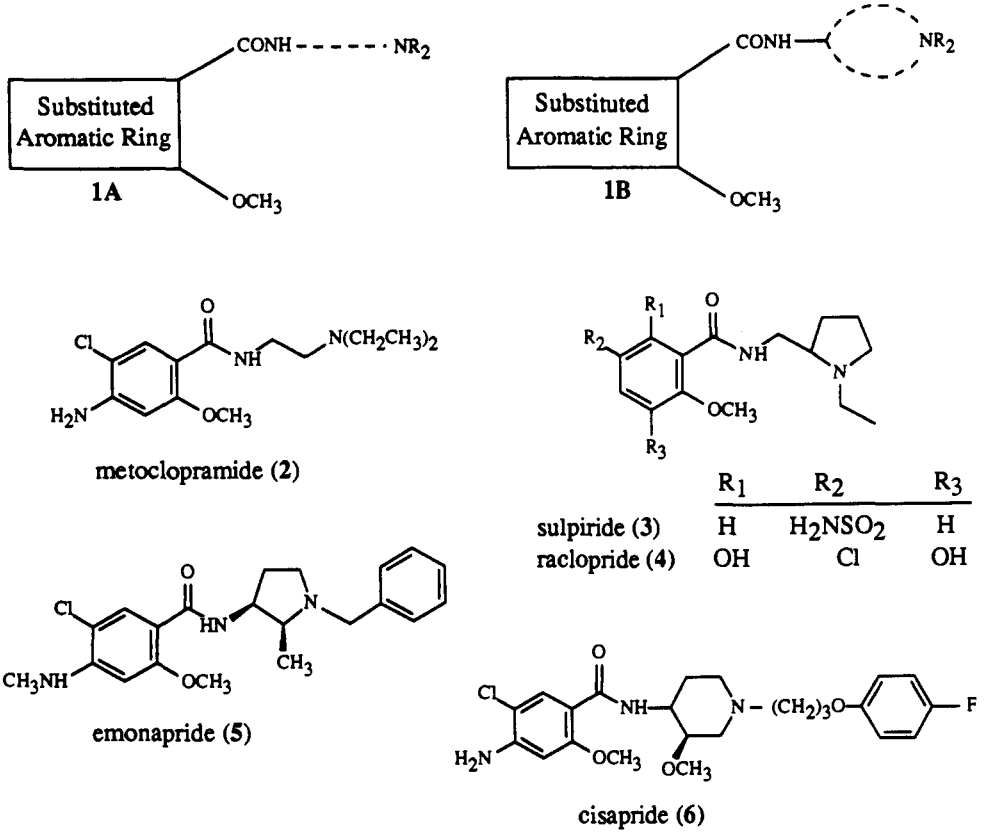
Recent studies have attempted to identify those structural features of the substituted benzamides which either improve,[7-10,17] in the case of pyrrolidine-containing antipsychotic agents, or abolish,[11,12] in the case of gastric prokinetic agents, binding to the dopamine D_2 receptor. A common structural feature of the benzamides as well as all dopamine antagonists is a basic nitrogen atom. At physiological pH, an equilibrium between a charged ammonium ion and an uncharged amine exists for these compounds. Over the past several years, our laboratory has been interested in determining which of these two molecular species is most important for binding to the dopamine receptor. In a recent study,[18] permanently charged pyrrolidinium (7, Chart II) and tetrahydrothiophenium (8) analogues of sulpiride were evaluated and were found to retain the ability to both bind and act as antagonists at the dopamine D_2 receptor. In contrast, a permanently uncharged tetrahydrothiophene (9) analogue was inactive at concentrations up to 100 μM. The results of this study were consistent with the results of an earlier study on permanently charged analogues of chlorpromazine[19] and provided further evidence that dopamine antagonists bind in their charged molecular forms to anionic sites on the dopamine D_2 receptor.

While the pharmacological differences between the various structural subtypes of benzamides may be due to differences in distribution, toxicity, or a variety of binding factors, we were interested in determining if type 1 and type 2 benzamides have similar or dissimilar requirements for the binding of the basic nitrogen atom. In the present study, we extended our previous work to the synthesis

* Author to whom all correspondence should be addressed.
⊥ Division of Medicinal Chemistry, Duquesne University.
‡ Division of Medicinal Chemistry & Pharmacognosy, The Ohio State University.
∥ Division of Pharmacology, The Ohio State University.
• Abstract published in *Advance ACS Abstracts*, September 15, 1993.

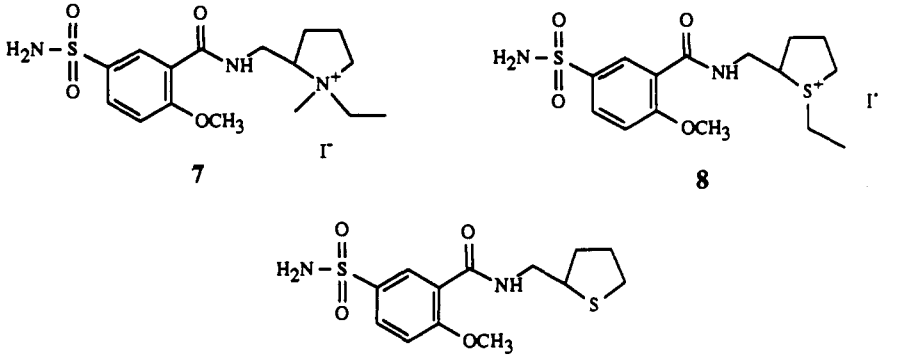
0022-2623/93/1836-3166$04.00/0

Chart I. Structural Subtypes of Benzamides



	R_1	R_2	R_3
sulpiride (3)	H	H_2NSO_2	H
raclopride (4)	OH	Cl	OH

Chart II. Permanently Charged and Uncharged Sulpiride Analogues

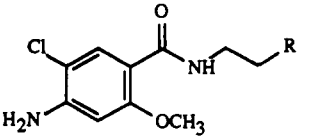


and *in vitro* evaluation of a series of ammonium (**10–12**), sulfide (**13**), and sulfonium (**14**) analogues of metoclopramide. The activities of these compounds were compared to those of the analogous sulpiride analogues to determine if type 1 benzamides, like type 2 benzamides, bind in their charged molecular forms to anionic sites on the dopamine D_2 receptor.

Chemistry

The syntheses of the target compounds were completed in a straightforward manner and are shown in Scheme I. Commercially available 4-amino-5-chloro-2-methoxybenzoic acid (**15**) was activated with ethyl chloroformate,[20] and the resulting adduct was reacted *in situ* with the appropriately substituted ethylamine. Metoclopramide (**2**) and its dimethyl analogue (**16**) were prepared using *N,N*-diethylethylenediamine and *N,N*-dimethylethylenediamine, respectively, while the methyl sulfide analogue was acquired using *S*-methyl-2-aminoethanethiol. This latter compound was synthesized according to the procedure of Burfield *et al.*[21] The quaternary ammonium compounds (**10–12**) were then obtained by reacting the appropriate amine (**2** or **16**) with $NaHCO_3$ and either

Chart III. Target Compounds



10 R = N^+Me_3 I^-

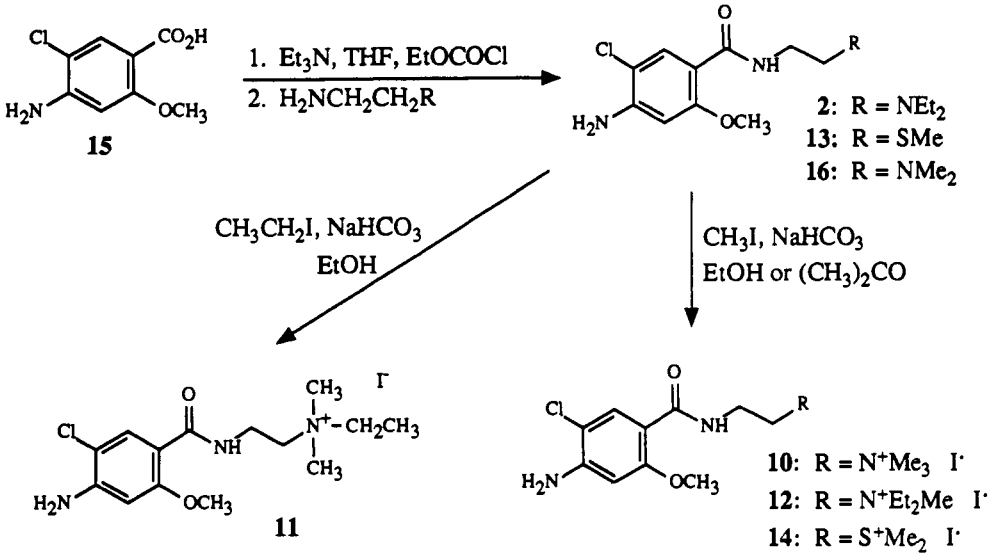
11 R = N^+Me_2Et I^-

12 R = N^+Et_2Me I^-

13 R = SCH_3

14 R = $S^+(CH_3)_2$ I^-

Scheme I



methyl or ethyl iodide. The reaction of metoclopramide with ethyl iodide consistently produced extremely poor yields of the desired compound, despite the use of a variety of reaction conditions. For this reason, the triethylammonium analogue is not included in this study. Finally, reaction of **13** with methyl iodide produced the sulfonium salt, **14**.

Biological Results and Discussion

Metoclopramide (**2**), its dimethyl analogue (**16**), and each of the five target compounds (**10**–**14**) were evaluated for their ability to antagonize apomorphine's effect on potassium-evoked [^{3}H]acetylcholine release. Apomorphine, a dopamine agonist, inhibits the potassium-induced release of acetylcholine from rat striatal slices by stimulating D_2 receptors. Our previous studies with chlorpromazine[18] and sulpiride[19] have demonstrated a good correlation between this functional assay and the ability of a compound to displace [^{3}H]spiperone from dopamine D_2 receptor binding sites. The ED_{50} values for apomorphine in the absence and presence of the various antagonists as well as the calculated antagonist equilibrium dissociation constants (K_B values) for all compounds are summarized in Table I. The ED_{50} values for apomorphine were relatively consistent within an experiment but varied among experiments. Consequently, for each experiment, the effects of apomorphine in the absence of antagonist was determined concurrently with the effects of apomorphine in the presence of antagonist. Thus, a separate apomorphine control group is presented for each apomorphine-antagonist group.

As expected, metoclopramide (**2**) and its dimethyl analogue (**16**) were found to antagonize the actions of apomorphine at the D_2 receptor. Metoclopramide, with a calculated K_B of 0.09 μM, was twice as potent as its dimethyl analogue. Three of the four permanently charged analogues—the trimethylammonium salt **10**, the dimethylethylammonium salt **11**, and the dimethylsulfonium salt **14**—were also found to inhibit apomorphine's effects, although at higher concentrations (from 12 to 57 times) than either metoclopramide or **16**. In contrast, the diethylmethylammonium salt **12** and the permanently uncharged sulfide analogue **13** were inactive at concentrations up to 100 μM. With the exception of compound **12**, these results are consistent with those of our earlier studies with chlorpromazine[18] and sulpiride.[19] In all of our studies, permanently charged ammonium and sulfonium salts retained the ability to act as dopamine antagonists, while permanently uncharged sulfide analogues were inactive. The lower potency of **10**, **11**, and **14** as compared to metoclopramide and **16** is also consistent with our earlier findings and may be due to the inability of these permanently charged compound to form a reinforced ionic bond with an anionic site on the dopamine D_2 receptor.[19]

Metoclopramide, a tertiary amine, exists in solution as an equilibrium mixture of charged ammonium and uncharged amine species. As a result, it is difficult to establish which of these two molecular species is actually responsible for its dopamine antagonist activity. There is not universal agreement as to which molecular species, charged or uncharged, is most important for the binding of dopamine antagonists to the dopamine receptor;[3,22-24] however, the results of this study provide further evidence that dopamine antagonists bind in their charged molecular forms to anionic sites on the D_2 receptor. In view of this, the inactivity of the diethylmethylammonium salt (**12**) was

Table I. The Effect of Various Metoclopramide Analogues on Agonist-Induced Inhibition of the K^+-Evoked Release of [^{3}H]Acetylcholine from Striatal Slices

compd		ED_{50} (μM) (95% C.I.)[a]	K_B (μM)
2	Apo[b]	0.047 (0.036–0.063)	
	Apo + **2** (1 μM)	0.576 (0.23–1.5)	0.09
10	Apo	0.045 (0.025–0.083)	
	Apo + **10** (30 μM)	0.310 (0.212–0.47)	5.1
11	Apo	0.069 (0.048–0.107)	
	Apo + **11** (100 μM)	1.85 (1.31–2.69)	3.9
12	Apo	0.092 (0.087–0.102)	
	Apo + **12** (100 μM)	0.090 (0.063–0.134)	NS[c]
13[d]	Apo	0.096 (0.036–0.269)	
	Apo + **13** (100 μM)	0.112 (0.052–0.248)	NS[c]
14	Apo	0.039 (0.026–0.056)	
	Apo + **14** (30 μM)	0.603 (0.322–1.129)	2.1
16	Apo	0.032 (0.008–2.04)	
	Apo + **16** (10 μM)	1.824 (0.69–4.98)	0.18

[a] 95% confidence intervals for the ED_{50} values for apomorphine in the absence and presence of antagonist. These values were used to determine statistically significant antagonism. [b] Apo = Apomorphine. [c] No statistically significant antagonism observed. [d] Compound **13** was dissolved in a special event (3 parts PEG 400, 1 part 95% ethanol, and 1 part DMSO). The final concentration of the solvent in the medium was 0.5%. The apomorphine control group for this experimenht also contained 0.5% of the solvent.

unexpected and is puzzling. At present, we do not have a good explanation for this discrepancy in our theory. It is possible that the inactivity of 12 is due to steric factors and that a critical volume surrounding the charged nitrogen has been exceeded. This supposition is however somewhat weakened by the facts that metoclopramide is twice as active as its dimethyl analogue and that the dimethylethylammonium salt (11) is slightly more potent than the trimethylammonium salt (10). We are currently investigating the inactivity of this compound.

Notwithstanding the inactivity of 12, the results of this study in conjunction with those of our earlier sulpiride study[19] would seem to indicate that metoclopramide, a type 1 benzamide useful as a gastric prokinetic agent, and sulpiride, a type 2 benzamide useful for its antipsychotic effects, both require a basic nitrogen atom in its charged molecular form for binding to D_2 receptor. Thus, differences in their biological profiles do not appear to be due to any appreciable differences in the binding of the basic nitrogen atom.

Experimental Section

Melting points were determined in capillary tubes on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on an IBM NR/250 FT NMR (250 MHz). Chemical shifts are expressed in ppm (δ) downfield from the internal standard tetramethylsilane (TMS). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN and were within ±0.4% of calculated values. IR spectra were recorded either on a Perkin-Elmer 1430 infrared spectrometer or Perkin-Elmer 1760X FT-IF spectrometer as KBr pellets. Mass spectra were obtained with a Kratos MS 25RFA double focusing mass spectrometer. All chemicals were obtained from Aldrich Chemical Co. and were used without purification.

General Procedure for the Synthesis of Compounds 2, 13, and 16. 4-Amino-5-chloro-2-methoxybenzoic acid (2.01 g, 10 mmol) was suspended in THF (35 mL), and triethylamine (1.42 mL, 10 mmol) was added. The mixture was cooled to 0 °C and ethyl chloroformate (0.96 mL, 10 mmol) was added slowly. The whole mixture was stirred at 0 °C for 1 h and then filtered. The filtrate was transferred to a 100-mL, round-bottomed flask, and the appropriate amine (10 mmol) was added. The resulting solution was stirred at room temperature for 3 h. The solvent was then removed, and the untreated residue was directly recrystallized from warm absolute ethanol.

4-Amino-5-chloro-*N*-[(diethylamino)ethyl]-2-methoxybenzamide (Metoclopramide, 2). *N,N*-Diethylethylenediamine was added to the filtrate. Recrystallization gave an off-white crystalline solid (2.17 g, 73%): mp 144–146 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.21 (br, 1H, NH), 8.12 (s, 1H, C_6-ArH), 6.29 (s, 1H, C_3-ArH), 4.38 (s, 2H, NH_2), 3.88 (s, 3H, OCH_3) 3.48 (m, 2H, $NHCH_2$) 2.61 (t, J = 6.2 Hz, 2H, $NHCH_2CH_2N$), 2.56 (q, J = 7.1 Hz, 4H, NCH_2CH_3) 1.04 (t, J = 7.1 Hz, 6H, NCH_2CH_3); IR (KBr, cm^{-1}) 3410, 3330, 3225 (NH and NH_2), 1635 (C=O); mass spectrum (FAB); 300 (M^+), 184, 99 (base), 87, 58. Anal. ($C_{14}H_{22}ClN_3O_2$) C, H, N.

***N*-[(2-Methylthio)ethyl]-4-amino-5-chloro-2-methoxybenzamide (13).** *S*-Methyl-2-aminoethanethiol[21] (0.91 mL, 10 mmol) was added to the filtrate. After removal of the solvent, 10 mL of $CHCl_3$ was added to the residue, and the solution was kept at 0 °C overnight. The solution was filtered, and the precipitate was dissolved in warm methanol. The suspended solid was filtered out and the methanol was removed. The residue was recrystallized from warm ethanol to provide off-white, needle-like crystals (1.31 g, 48%): mp 118–120 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.12 (s, 1H, C_6-ArH), 6.30 (s, 1H, C_3-ArH), 4.37 (s, 2H, NH_2), 3.92 (S, 3H, OCH_3) 3.65 (q, J = 6.4 Hz, 2H, $NHCH_2$), 2.73 (t, J = 6.4 Hz, 2H, SCH_2), 2.15 (s, 3H, SCH_3); IR (KBr, cm^{-1}) 3440, 3380, 3300, 3220 (NH and NH_2), 1640 (C=O); mass spectrum (FAB); 274, 201, 184 (base). Anal. ($C_{11}H_{15}ClN_2O_2S$) C, H, N.

4-Amino-5-chloro-*N*-[(dimethylamino)ethyl]-2-methoxybenzamide (6). *N,N*-Dimethylethylenediamine was added to the filtrate. Recrystallization gave off-white crystals (1.72 g, 63%): mp 164–166 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.09 (s, 2H, NH and C_6-ArH), 6.27 (s, 1H, C_3-ArH), 4.42 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 3.50 (m, 2H, $NHCH_2$), 2.49 (t, J = 6.2 Hz, 2H, $NHCH_2CH_2N$), 2.28 (s, 6H, NCH_3); IR (KBr, Cm^{-1}) 3480, 3360, 3318, 3220 (NH and NH_2), 1635 (C=O); mass spectrum (FAB); 272 (M^+), 201, 184, 71, 58 (base). Anal. ($C_{12}H_{18}ClN_3O_2$) C, H, N.

General Procedure for the Synthesis of Trialkylammonium Iodides (10–12). 4-Amino-5-chloro-*N*-[(dialkylamino)ethyl]-2-methoxybenzamide (10 mmol) was dissolved in absolute ethanol (50 mL) by gently heating the mixture. The solution was then allowed to cool to room temperature, and $NaHCO_3$ (1.83 g, 20 mmol) was added. The mixture was stirred for a few minutes, and iodoalkane (5 mL) was addes slowly. The whole mixture was stirred for 3 h at room temperature, during which time a white solid gradually fell out of the solution. The solvent and excess iodoalkane were removed, and the residue was dissolved in hot methanol and filtered to remove excess $NaHCO_3$. The methanol was removed, and the residue was dissolved in hot $CHCl_3$ and then filtered. The precipitate was recrystallized from warm absolute ethanol.

[2-(4-Amino-5-chloro-2-methoxybenzamido)ethyl]trimethylammonium Iodide (10). Iodomethane (5 mL) was added to a solution of 16 (2.71 g, 10 mmol). Recrystallization from absolute ethanol provided 3.32 g (80%) of off-white crystals: mp 230–231 °C; ^{1}H NMR (250 MHz, D_2O) δ 7.66 (s, 1H, C_6-ArH), 6.47 (s, 1H, C_3-ArH), 3.83 (S, 3H, OCH_3), 3.80–3.83 (t, partially obscured by OCH_3, 2H, $NHCH_2$), 3.52 (t, J = 6.6 Hz, 2H, NCH_2), 3.17 (s, 9H, NCH_3); IR (KBr, cm^{-1}) 3420, 3380, 3320, 3200 (NH and NH_2), 1640 (C=O); mass spectrum (FAB) 286, 227 (base), 180, 135, 85, 58. Anal. ($C_{13}H_{21}ClIN_3O_2$) C, H, N.

[2-(4-Amino-5-chloro-2-methoxybenzamido)ethyl]dimethylethylammonium Iodide (11). Iodoethane (5 mL) was added to a solution of 16 (2.71 g, 10 mmol). Recrystallization from absolute ethanol afforded 2.05 g (48%) of an off-white crystalline solid: mp 198–200 °C; ^{1}H NMR (250 MHz D_2O) δ 7.62 (s, 1H, C_6-ArH), 6.43 (s, 1H, C_3-ArH), 3.81 (s, 3H, OCH_3) 3.77 (t, J = 6.8 Hz, 2H, $NHCH_2$), 3.38–3.48 (m, 4H, 2 × NCH_2), 3.10 (s, 6H, NCH_3), 1.34 (t, J = 7.1 Hz, 3H, NCH_2CH_3); IR (KBr, cm^{01}) 3420, 3380, 3325 (NH and NH_2), 1635 (C=O); mass spectrum (FAB) 300, 227 (base), 180, 135, 85, 58. Anal. ($C_{14}H_{23}ClIN_3O_2$) C, H, N.

[2-(4-Amino-5-chloro-2-methoxybenzamido)ethyl]diethylmethylammonium Iodide (12). Iodomethane (5 mL) was added to a solution of 2 (3.00 g, 10 mmol). Recrystallization from absolute ethanol yielded 2.17 g (49%) of off-white crystals: mp 212–215 °C, ^{1}H NMR (250 MHz, D_2O) δ 7.60 (s, 1H, C_6-ArH), 6.41 (s, 1H, C_3-ArH), 3.81 (s, 3H, OCH_3) 3.73 (t, J = 7.1 Hz, 2H, $NHCH_2$), 3.38 (q, J = 7.1 Hz, 6H, NCH_2), 3.01 (s, 3H, NCH_3), 1.31 (t, J = 7.1 Hz, 6H, NCH_2CH_3); IR (KBr, cm^{-1}) 3415, 3380, 3330, 3220 (NH and NH_2), 1635 (C=O); mass spectrum (FAB) 314, 227 (base), 184, 135, 72. Anal. ($C_{15}H_{25}ClIN_3O_2$) C, H, N.

[2-(4-Amino-5-chloro-2-methoxybenzamido)ethyl]dimethylsulfonium Iodide (14). Compound 13 (1.00 g, 3.61 mmol) was dissolved in 50 mL of warm acetone. Iodomethane (2.5 mL) was added, and the solution was heated to reflux for 3.5 h. The solution was cooled to room temperature, and a solid gradually precipitated from the solution upon cooling. The suspension was filtered, and the precipitate was recrystallized from warm methanol to give pale yellow plates (0.62 g, 40%): mp 134–136 °C; ^{1}H NMR (250 MHz, D_2O) δ 7.62 (s, 1H, C_6-ArH), 6.45 (s, C_3-ArH), 3.81 (s, 3H, OCH_3), 3.81 (t, partially obscured by OCH_3, 2H, NHC_{H2}) 3.50 (t, J = 5.7 Hz, 2H, CH_2S) 2.90 (s, 6H, SCH_3); IR (KBr, cm^{-1}) 3450, 3370, 3330 (NH and NH_2) 1635 (C=O); mass spectrum (FAB) 289, 227 (base), 184, 119. Anal. ($C_{12}H_{18}ClIN_2O_2S$) C, H, N.

Measurement of the K^+-Induced Release of [^{3}H]Acetylcholine from Striatal Slices. This assay was run in an identical manner as described in our earlier publication.[19] Further experimental details can be found there. Striatal slices from reserpine and α-methyl-*p*-tyrosine-treated mice were incubated with [^{3}H]choline for 20 min at 37 °C. The slices were washed as previously described and where then incubated in a medium containing 250 μM α-methyl-*p*-tyrosine and various concentrations of apomorphine or apomorphine plus the test drug in the

presence of high K^+ (13.8 mM) for two (5-min) periods. The percentage of the tissue tritium released into the medium by the high K^+ was calculated by subtracting basal release.

Analysis of Data. The ED_{50} and the confidence interval (C.I.) values for apomorphine in the presence and absence of test drug were determined using a nonlinear regression procedure. Apomorphine concentration-response curves for inhibiting the potassium-evoked release of [^{3}H]acetylcholine were generated in the presence and absence of a given concentration of antagonist. The antagonist equilibrium dissociation constants (K_B values) were then calculated from the equation

$$K_B = [B]/(DR - 1)$$

were B is the concentration of antagonist used, and DR is the ratio of the concentrations of apomorphine required to produce a half-maximal inhibitory effect on [^{3}H]acetylcholine release in the presence and absence of antagonist.[25] Due to variability among the experiments, a group containing apomorphine plus the test drug was always run concurrently with a control group containing apomorphine alone for each set of determinations. The level of significance employed for all statistical tests was $P < 0.05$.

Acknowledgment. Support for this work was provided by a grant from the National Institute of Neurological Disorders and Stroke (RO1-NS17907). The authors also thank Marlene Muscik for her help in the preparation of this document.

References

(1) de Paulis, T. Antipsychotic Agents and Dopamine Agonists. *Ann. Rep. Med. Chem.* **1983**, *18*, 21–30.
(2) de Paulis, T.; Rämsby, S. Antipsychotic Agents. *Ann. Rep. Med. Chem.* **1984**, *19*, 21–30.
(3) van de Waterbeemd, H.; Carrupt, P. A. Molecular Electrostatic Potential of Orthopramides: Implications for Their Interaction with the D-2 Dopamine Receptor *J. Med. Chem.* **1986**, *29*, 600–606.
(4) Jenner, P.; Marsden, C. D. The Substituted Benzamides—A Novel Class of Dopamine Antagonists. *Life Sci.* **1979**, *25*, 479–486.
(5) Hadley, M. S. Substituted Benzamides as Dopamine Antagonists. In *The Chemical Regulation of Biological Mechanisms*; Creighton, A. M., Turner, S., Eds.; Royal Society of Chemistry: London, 1982; pp 140–153.
(6) de Paulis, T.; Kumar, Y.; Johansson, L.; Rämsby, S.; Florvall, L.; Hall, H.; Angeby-Möller, K.; Ogren, S. Potential Neuroleptic Agents. 3. Chemistry and Antidopaminergic Properties of Substituted 6-Methoxysalicylamides. *J. Med. Chem.* **1985**, *28*, 1263–1269.
(7) Högberg, T.; Bengtsson, S.; de Paulis, T.; Johansson, L.; Ström, P.; Hall, H.; Ogren, S. Potential Antipsychotic Agents. 5. Synthesis and Antidopaminergic Properties of Substituted 5,6-Dimethoxysalicylamides and Related Compounds. *J. Med. Chem.* **1990**, *33*, 1155–1163.
(8) Högberg, T.; de Paulis, T.; Johansson, L.; Kumar, Y.; Hall, H.; Ogren, S. Potential Antipsychotic Agents. 7. Synthesis and Antidopaminergic Properties of the Atypical Highly Potent (*S*)-5-bromo-2,3-dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide and Related Compounds. A Comparative Study. *J. Med. Chem.* **1990**, *33*, 2305–2309.
(9) Högberg, T.; Ström, P.; de Paulis, T.; Stensland, B.; Csöregh, I.; Lundin, K.; Hall, H.; Ogren, S. Potential Antipsychotic Agents. 9. Synthesis and Stereoselective Dopamine D-2 Receptor Blockade of a Potent Class of Substituted (*R*)-*N*-[(1-Benzyl-2-pyrrolidinyl)-methyl]benzamides. Relations to Other Side Chain Congeners. *J. Med. Chem.* **1991**, *34*, 948–955.
(10) Högberg, T.; Rämsby, S.; Ogren, S.; Norinder, U. New Selective Dopamine D-2 Antagonists as Antipsychotic Agents. Pharmacological, Chemical, Structural and Theoretical Considerations. *Acta Pharm. Suec.* **1987**, *24*, 289–328.
(11) Kato, S.; Morie, T.; Hino, K.; Kon, T.; Naruto, S.; Yoshida, N.; Karasawa, T.; Matsumoto, J. Novel Benzamides as Selective and Potent Gastric Prokinetic Agents. 1. Synthesis and Structure-Activity Relationships of *N*-[(2-Morpholinyl)alkyl]benzamides. *J. Med. Chem.* **1990**, *33*, 1406–1413.
(12) Kato, S.; Morie, T.; Kon, T.; Yoshida, N.; Karasawa, T.; Matsumoto, J. Novel Benzamides as Selective and Potent Gastrokinetic Agents. 2. Synthesis and Structure-Activity Relationships of 4-Amino-5-chloro-2-ethoxy-*N*-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]-benzamide Citrate (AS-4370) and Related Compounds. *J. Med. Chem.* **1991**, *34*, 616–624.
(13) Abou-Gharbia, M.; Moyer, J. A. Novel Antipsychotic Agents. *Ann. Rep. Med. Chem.* **1990**, *25*, 1–10.
(14) Wise, L. D.; Heffner, T. G. Antipsychotics. *Ann. Rep. Med. Chem.* **1991**, *26*, 53–62.
(15) Brunton, L. L. Agents Affecting Gastrointestinal Water Flux and Motility, Digestants, and Bile Acids. In *The Pharmacological Basis of Therapeutics*, 8th ed.; Gilman, A. G., Rall, T. W., Nies, A. S., Taylor, P., Eds.; Permagon Press: New York, 1990; pp 914–932.
(16) Buchheit, K. H.; Costall, B.; Engel, G.; Gunning, S. J.; Naylor, R. J.; Richardson, B. P. 5-Hydroxytryptamine Receptor Antagonism by Metoclopramide and ICS 205-930 in the Guinea-pig Leads to Enhancement of Contractions of Stomach Muscle Strips Induced by Electrical Field Stimulation and Facilitation of Gastric Emptying *in vivo*. *J. Pharm. Pharmacol.* **1985**, *37*, 664–667.
(17) Norinder, U.; Högberg, T. QSAR on Substituted Salicylamides. *In Quantitative Structure-Activity Relationships in Drug Design*; Fauchè, J. L.; Ed.; Alan R. Liss: New York, 1989; pp 369–372.
(18) Harrold, M. W.; Chang, Y.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller D. D. Charged Analogues of Chlorpromazine as Dopamine Antagonists. *J. Med. Chem.* **1987**, *30*, 1631–1635.
(19) Harrold, M. W.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller, D. D. Synthesis and D_2 Dopaminergic Activity of Pyrrolidinium, Tetrahydrothiophenium, and Tetrahydrothiophene Analogues of Sulpiride. *J. Med. Chem.* **1989**, *32*, 874–880.
(20) Taiyo Yakuhin Kogyo K. K., Jpn. Kokai Tokkyo Koho 80,113,761 (1980); Sempuku, K. *N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfamoylbenzamide. *Chem. Abstr.* **1981**, *94*, 103154y.
(21) Burfield, D. R.; Gan, S.; Smithers, R. H. Reactions of a Mono- and a Tri-substituted Epoxide with Some Simple and β-Substituted Primary Amines; Novel Examples of Electrophilic Anchimeric Assistance. *J. Chem. Soc., Perkin Trans. I* **1977**, 666–671.
(22) Philipp, A. H.; Humber, L. G.; Voith, K. Mapping the Dopamine Receptor. 2. Features Derived from Modifications in the Rings A/B Region of the Neuroleptic Butaclamol. *J. Med. Chem.* **1979**, *22*, 768–773.
(23) Olson, G. L; Cheung, H.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L; Davidson, A. B.; Boff, E. A Dopamine Receptor Model and its Application in the Design of a New Class of Rigid Pyrrolo-[2,3-*g*]isoquinoline Antipsychotics. *J. Med. Chem.* **1981**, *24*, 1026–1034.
(24) Chrzanowski, F. A.; McGrogan, B. A.; Maryanoff, B. E. The pK_a of Butaclamol and the Mode of Butaclamol Binding to Central Dopamine Receptors. *J. Med. Chem.* **1985**, *28*, 399–400.
(25) Furchgott, R. F. The Pharmacological Differentation of Adrenergic Receptors. *Ann. N.Y. Acad. Sci.* **1967**, *139*, 553–570.