Synthesis, Gastrointestinal Prokinetic Activity and Structure–Activity Relationships of Novel *N*-[[2-(Dialkylamino)ethoxy]benzyl]benzamide Derivatives

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Novel *N*-[[2-(dialkylamino)ethoxy]benzyl]benzamide derivatives (II-1—51), derived from the structural modification of metoclopramide (I), were synthesized and examined for their pharmacological activities. Among them, *N*-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide (II-34) which exhibited well balanced gastrointestinal prokinetic and antiemetic activities was selected as a new type of gastrointestinal prokinetic agent.

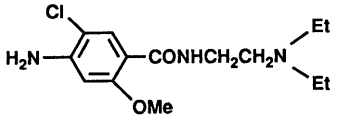
Keywords *N*-[[2-(dialkylamino)ethoxy]benzyl]benzamide; antiemetic activity; gastrointestinal prokinetic activity; acetylcholinesterase inhibition; structure–activity relationship

Metoclopramide (I)[1] is a gastrointestinal prokinetic agent and has been used as an antiemetic for a long time. The mechanisms of the gastrointestinal prokinetic activity of I are considered: i) stimulation of cholinergic neurons by release of acetylcholine, ii) blockage of dopamine D_2 receptor and/or iii) direct action on smooth muscle and antiemetic activity is the blockage of the dopamine D_2 receptor in the chemo-receptor trigger zone and at the peripheral site. Blockage of the dopamine D_2 receptor by the taking of I causes side effects on the central nervous system such as extrapyramidal syndrome and cryptorrhea such as sthenia of prolactin secretion. Therefore, the clinical use of I has been limited.

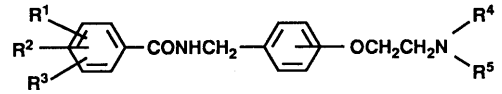
For the development of a new gastrointestinal prokinetic agent, a compound with fewer side effects and well balanced gastrointestinal prokinetic and antiemetic activities was synthesized. For this purpose a new series of *N*-[[2-(dialkylamino)ethoxy]benzyl]benzamides (II) with an oxybenzyl moiety in the side chain of I were produced (Chart 1). The synthesis and pharmacological activity of II and their structure–activity relationships are discussed in the following.

Chemistry A new series of *N*-[[2-(dialkylamino)ethoxy]-benzyl]benzamides (II) were synthesized by the methods as shown in Charts 2 and 3.

The reactions of mono-, di- and tri-substituted benzoic acids (III) with thionyl chloride afforded the corresponding acid chlorides, which on condensation with [4-(2-dimethylamino)ethoxy]benzylamine (IV)[2] gave the desired benzamides (II-1—8, 12—24, 26—29, 33—38, 40, 41[2]). Benzamides (II-9—11, 39, 42) each having a hydroxy group were prepared by the hydrolysis of the corresponding acetoxy-substituted benzamides (V) derived from the condensation of acid chloride with IV.



I : metoclopramide



II

Chart 1

Benzamides (II-31, 32) having an amino group at the *meta*- or *para*-position were synthesized by the catalytic reduction of the corresponding nitro-substituted benzamides (II-28, 29). The reaction of isatoic anhydride (VI) with the amine (IV) afforded benzamide (II-30) possessing an amino group at the *ortho*-position.

m-Sulfamoylbenzoic acid (VII) was treated with pivaloyl chloride to give a mixed acid anhydride, which on treatment with amine (IV) yielded the benzamide (II-25) having a sulfamoyl group at the *meta*-position. The mixed acid anhydride, derived from 4-amino-5-chloro-2-methoxybenzoic acid (VIII) and ethyl chloroformate was reacted with amine (IV) to give the desired product (II-43) having the same substituent groups as I.

Benzamides (II-44—51, XIII-1, 2) modified on the side chain of 3,4,5-trimethoxybenzamide (II-41), which had relatively potent activity, were synthesized. 3,4,5-Trimethoxybenzoic acid (III) was converted to acid chlorides with thionyl chloride, which on treatment with the corresponding amines (IX-1—7, X) afforded the desired benzamides (II-44—51).

Benzamides (XIII-1, 2) having an amide bond or an ester bond in the side chain were prepared as follows. Acid chloride of 3,4,5-trimethoxybenzoic acid (III) was reacted with methyl 4-aminomethylbenzoate (XI) and then hydrolyzed to give 4-(3,4,5-trimethoxybenzoylaminomethyl)benzoic acid (XII).[3] Compound (XII) was converted to the mixed acid anhydride with ethyl chloroformate or to the acid chloride with thionyl chloride and then reacted with 2-(dimethylamino)ethylamine or 2-(dimethylamino)ethanol, respectively, to give the desired products (XIII-1, 2).

Physicochemical data for II-1—51, XIII-1, 2 are shown in Tables I and II.

Results and Discussion

Pharmacological data for the compounds (II-1—51, XIII-1, 2,) synthesized here are summarized in Tables I and II. Gastrointestinal prokinetic and antiemetic activities were assessed by the constrictive activities on guinea pig ileum and by D_2 receptor affinity using [^{3}H]spiperone, respectively.

The effects of a substituent on the benzene ring were first examined after fixing the side chain site to the [2-(dimethylamino)ethoxy]benzyl group. Among monosubstituted benzamides (II-1—33), those having methoxy

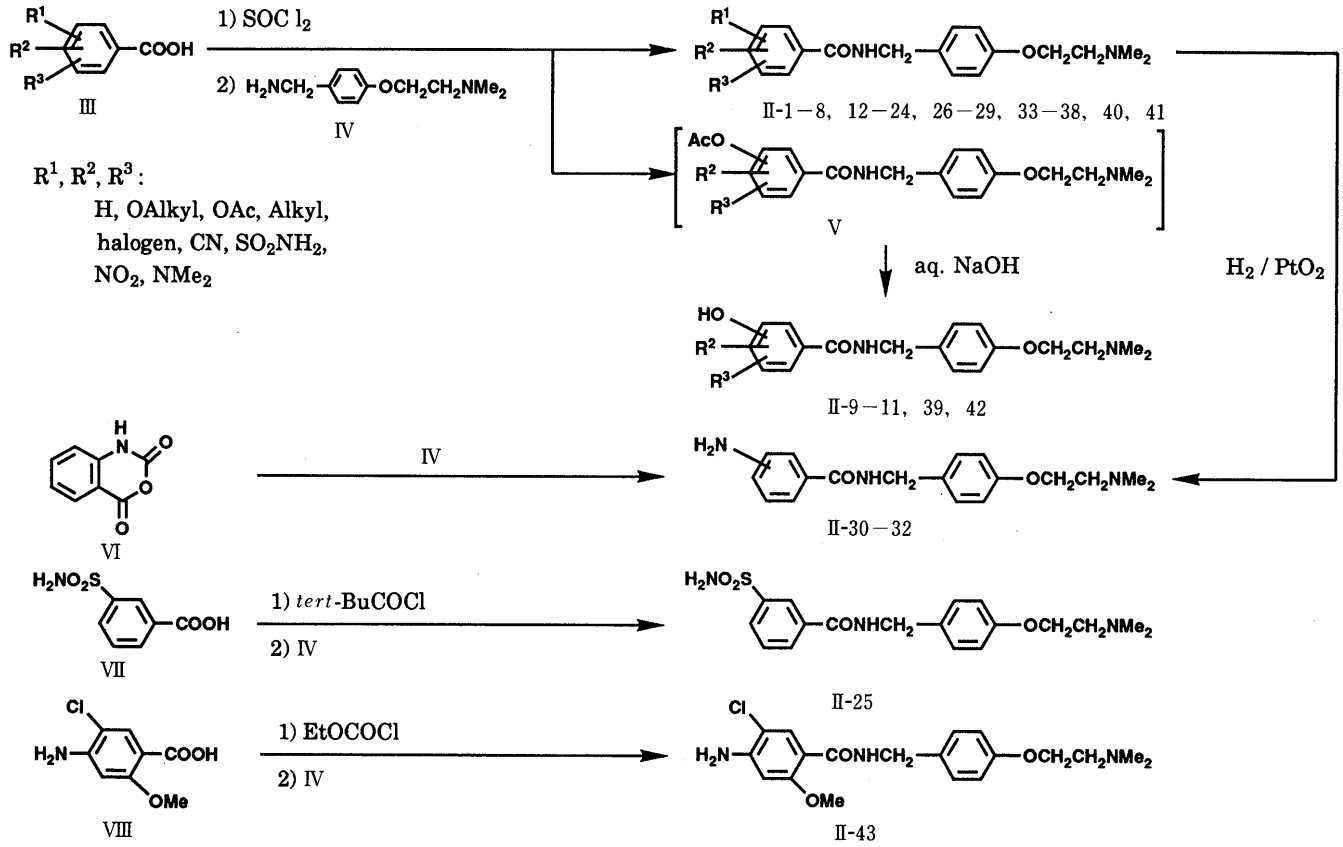


Chart 2

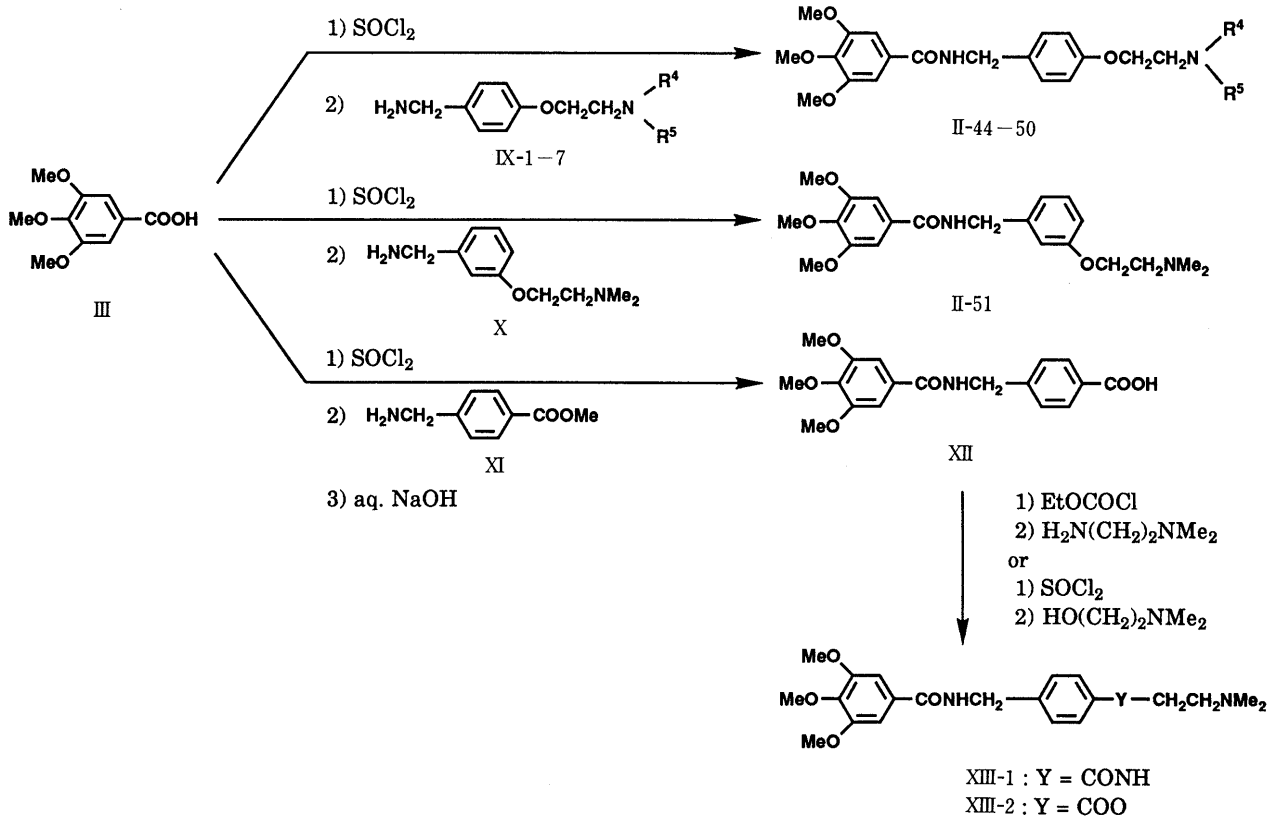
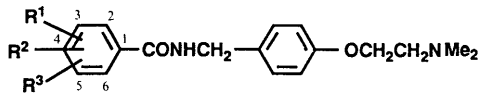


Chart 3

(II-2, 3), ethoxy (II-5, 6), hydroxy (II-11), methyl (II-13, 14), fluoro (II-18), chloro (II-21), cyano (II-23, 24), sulfamoyl (II-25, 26), nitro (II-28, 29) and dimethylamino groups (II-33) showed potent constrictive activity on the ileum. The substituents of these compounds were present at *meta*- and/or *para*-positions on the benzene ring.

TABLE I. Physicochemical and Pharmacological Data for Mono-substituted Benzamide Derivatives (II-1—43)



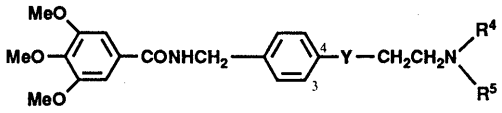
Compd. No.	R^1	R^2	R^3	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	% of constriction on ileum (10^{-5} M)	% of displacement on D_2 receptor (10^{-6} M)
II- 1	2-OMe	H	H	156.5—157.5 (EtOH)	$C_{19}H_{24}N_2O_3 \cdot HCl$	62.54 (62.53	6.91 6.99	7.68 7.38)	41	−4
II- 2	3-OMe	H	H	66—68 (iso-Pr_2O)	$C_{19}H_{24}N_2O_3$	69.49 (69.49	7.37 7.13	8.53 8.44)	75	15
II- 3	4-OMe	H	H	175—176 (EtOH)	$C_{19}H_{24}N_2O_3 \cdot HCl$	62.54 (62.46	6.91 6.97	7.68 7.52)	63	10
II- 4	2-OEt	H	H	127—130 (EtOH–hexane)	$C_{20}H_{26}N_2O_3 \cdot HCl$	63.40 (63.14	7.18 7.32	7.39 7.41)	5	1
II- 5	3-OEt	H	H	80—81 (iso-Pr_2O)	$C_{20}H_{26}N_2O_3$	70.15 (70.03	7.65 7.55	8.18 8.09)	75	14
II- 6	4-OEt	H	H	164—165 (EtOH–Et_2O)	$C_{20}H_{26}N_2O_3 \cdot HCl$	63.40 (63.15	7.18 7.32	7.39 7.23)	77	21
II- 7	4-OPr(*n*-)	H	H	117—119 (AcOEt)	$C_{21}H_{28}N_2O_3$	70.76 (70.58	7.92 7.93	7.86 7.81)	7	26
II- 8	4-OBu(*n*-)	H	H	131—132 (AcOEt)	$C_{22}H_{30}N_2O_3$	71.32 (71.17	8.16 8.26	7.56 7.53)	0	17
II- 9	2-OH	H	H	153—156 (EtOH)	$C_{18}H_{22}N_2O_3 \cdot HCl$	61.62 (61.63	6.61 6.66	7.98 7.95)	12	0
II-10	3-OH	H	H	151—153 (EtOH)	$C_{18}H_{22}N_2O_3$	68.77 (68.94	7.05 7.21	8.91 8.98)	10	2
II-11	4-OH	H	H	133—134 (EtOH)	$C_{18}H_{22}N_2O_3$	68.77 (69.04	7.05 7.15	8.91 8.95)	67	28
II-12	2-Me	H	H	186—187.5 (EtOH)	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41 (65.34	7.22 7.14	8.03 8.00)	17	15
II-13	3-Me	H	H	118—120 (EtOH–Me_2CO)	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41 (65.25	7.22 7.19	8.03 7.83)	73	7
II-14	4-Me	H	H	197—199 (EtOH–Et_2O)	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41 (65.20	7.22 7.32	8.03 7.70)	88	−9
II-15	4-Et	H	H	101—102 (iso-Pr_2O)	$C_{20}H_{26}N_2O_2$	73.59 (73.65	8.03 7.98	8.58 8.38)	12	14
II-16	4-Bu(*tert*-)	H	H	135—137 (AcOEt)	$C_{22}H_{30}N_2O_2$	74.54 (74.60	8.53 8.28	7.90 7.86)	5	11
II-17	2-F	H	H	139—142 (EtOH–Et_2O)	$C_{18}H_{21}FN_2O_2 \cdot HCl$	61.27 (61.15	6.28 6.30	7.94 7.97)	22	6
II-18	3-F	H	H	127—128 (EtOH)	$C_{18}H_{21}FN_2O_2 \cdot C_4H_4O_4$[b]	61.10 (60.94	5.83 5.88	6.48 6.55)	61	9
II-19	4-F	H	H	165—166 (EtOH)	$C_{18}H_{21}FN_2O_2 \cdot HCl$	61.27 (61.18	6.28 6.29	7.94 7.75)	30	20
II-20	2-Cl	H	H	207—209 (EtOH)	$C_{18}H_{21}ClN_2O_2 \cdot HCl$	58.54 (58.30	6.00 6.07	7.59 7.30)	0	4
II-21	3-Cl	H	H	166—167 (EtOH–Et_2O)	$C_{18}H_{21}ClN_2O_2 \cdot HCl$	58.54 (58.27	6.00 6.20	7.59 7.26)	70	21
II-22	4-Cl	H	H	186—188 (EtOH)	$C_{18}H_{21}ClN_2O_2 \cdot HCl$	58.54 (58.46	6.00 6.21	7.59 7.21)	28	−1
II-23	3-CN	H	H	155—157 (EtOH)	$C_{19}H_{21}N_3O_2 \cdot HCl$	63.42 (63.32	6.16 6.14	11.68 11.73)	67	1
II-24	4-CN	H	H	182—183 (EtOH)	$C_{19}H_{21}N_3O_2 \cdot HCl \cdot 1/4H_2O$	62.63 (62.94	6.22 6.13	11.53 11.25)	86	22
II-25	3-SO_2NH_2	H	H	169—172 (EtOH)	$C_{18}H_{23}N_3O_4S$	57.28 (57.30	6.14 6.07	11.13 11.12)	60	6
II-26	4-SO_2NH_2	H	H	173.5—174.5 (MeOH–AcOEt)	$C_{18}H_{23}N_3O_4S$	57.28 (57.58	6.14 6.40	11.13 10.95)	61	11
II-27	2-NO_2	H	H	190—191 (EtOH)	$C_{18}H_{21}N_3O_4 \cdot HCl$	56.92 (56.91	5.84 6.05	11.06 10.82)	41	27
II-28	3-NO_2	H	H	204—205 (EtOH)	$C_{18}H_{21}N_3O_4 \cdot HCl$	56.92 (56.95	5.84 6.04	11.06 10.79)	83	47[a]
II-29	4-NO_2	H	H	153—154 (AcOEt)	$C_{18}H_{21}N_3O_4$	62.96 (62.94	6.16 6.13	12.24 12.18)	65	17
II-30	2-NH_2	H	H	104—105 (AcOEt)	$C_{18}H_{23}N_3O_2$	68.98 (69.07	7.40 7.07	13.41 13.32)	25	19
II-31	3-NH_2	H	H	173—174 (MeOH–AcOEt)	$C_{18}H_{23}N_3O_2 \cdot 2HCl$	55.96 (56.13	6.52 6.49	10.88 10.89)	22	3

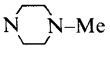
TABLE I. (continued)

Compd. No.	R^1	R^2	R^3	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	% of constriction on ileum (10^{-5} M)	% of displacement on D_2 receptor (10^{-6} M)
II-32	4-NH_2	H	H	171—173 (MeOH)	$C_{18}H_{23}N_3O_2 \cdot 2HCl$	55.96 (55.89	6.52 6.69	10.88 10.88)	39	−11
II-33	4-NMe_2	H	H	144—146 (AcOEt)	$C_{20}H_{27}N_3O_2$	70.35 (70.21	7.97 7.58	12.31 12.02)	81	13
II-34	3-MeO	4-MeO	H	190.5—191.5 (EtOH)	$C_{20}H_{26}N_2O_4 \cdot HCl$	60.83 (60.78	6.89 6.99	7.09 7.05)	90	53
II-35	3-MeO	5-MeO	H	71—72 (EtOH–iso-Pr_2O)	$C_{20}H_{26}N_2O_4$	67.02 (66.90	7.31 7.12	7.82 7.59)	53	57
II-36	2-MeO	4-MeO	H	75—76 (EtOH–iso-Pr_2O)	$C_{20}H_{26}N_2O_4$	67.02 (67.04	7.31 7.26	7.82 7.57)	97	−5
II-37	2-MeO	6-MeO	H	130—131 (AcOEt)	$C_{20}H_{26}N_2O_4$	67.02 (66.85	7.31 7.29	7.82 7.58)	0	15[a]
II-38	2-MeO	3-MeO	H	122—123 (EtOH)	$C_{20}H_{26}N_2O_4 \cdot C_4H_4O_4$[b]	60.75 (60.62	6.37 6.41	5.90 5.79)	28	44[a]
II-39	3-MeO	4-OH	H	129.5—130.5 (AcOEt)	$C_{19}H_{24}N_2O_4$	66.26 (66.34	7.02 7.05	8.13 7.97)	29	−8
II-40	3-EtO	4-EtO	H	127.5—129 (AcOEt)	$C_{22}H_{30}N_2O_4$	68.37 (68.39	7.82 7.54	7.25 7.11)	92	75
II-41	3-MeO	4-MeO	5-MeO	187—188 (EtOH)	$C_{21}H_{28}N_2O_5 \cdot HCl$	59.36 (59.28	6.88 6.81	6.59 6.51)	83	69
II-42	3-MeO	4-OH	5-MeO	145—146 (EtOH–Et_2O)	$C_{20}H_{26}N_2O_5S \cdot HCl \cdot H_2O$	56.01 (55.97	6.81 6.91	6.53 6.44)	57	−7
II-43	2-MeO	4-NH_2	5-Cl	206.5—208 (EtOH)	$C_{19}H_{24}ClN_3O_3 \cdot HCl$	55.08 (54.86	6.08 6.21	10.14 9.98)	96	−23
I									54	101

a) % of displacement on D_2 receptor (10^{-4} M). b) Fumarate.

TABLE II. Physicochemical and Pharmacological Data for Benzamide Derivatives (II-44—51, XIII-1, 2)



Compd. No.	NR^4R^5	Substituted position	Y	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	% of constriction on ileum (10^{-5} M)	% of displacement on D_2 receptor (10^{-6} M)
II-44	NPr_2	4	O	82—83 (iso-Pr_2O)	$C_{25}H_{36}N_2O_5$	67.54 (67.45	8.16 8.13	6.30 6.12)	22	47
II-45		4	O	102—102.5 (AcOEt)	$C_{26}H_{36}N_2O_5$	68.40 (68.29	7.95 8.00	6.14 6.04)	0	51
II-46		4	O	107—107.5 (AcOEt)	$C_{23}H_{30}N_2O_5$	66.65 (66.53	7.30 7.28	6.76 6.66)	51	58
II-47		4	O	122—123 (AcOEt)	$C_{24}H_{32}N_2O_5$	67.27 (67.28	7.53 7.58	6.54 6.45)	0	41
II-48		4	O	129—129.5 (AcOEt)	$C_{25}H_{34}N_2O_5$	67.85 (67.72	7.74 7.72	6.33 6.16)	13	39
II-49		4	O	178—179 (MeOH)	$C_{23}H_{30}N_2O_6 \cdot C_4H_4O_4$[a]	59.33 (59.03	6.27 6.30	5.13 4.92)	8	29
II-50		4	O	188—190 (MeOH)	$C_{24}H_{33}N_3O_5 \cdot 2HCl$	55.81 (55.47	6.83 6.78	8.14 7.93)	28	34
II-51	NMe_2	3	O	156.5—157 (EtOH)	$C_{21}H_{28}N_2O_5 \cdot HCl \cdot 1/2H_2O$	58.13 (57.87	6.97 6.84	6.46 6.17)	22	−4
XIII-1	NMe_2	4	CONH	130—131 (AcOEt)	$C_{22}H_{29}N_3O_5$	63.60 (63.56	7.04 7.02	10.11 9.98)	55	30
XIII-2	NMe_2	4	COO	163—163.5 (EtOH)	$C_{22}H_{28}N_2O_6 \cdot C_4H_4O_4$[a]	58.64 (58.62	6.06 6.13	5.26 5.09)	0	47

a) Fumarate.

However no clear structure–activity relationships on substituents on the benzene ring could be found. Compounds (II-1—33) showed little D_2 receptor affinity. It is thus evident that the mono-substituted benzamides show a selectivity toward constrictive activity on the ileum.

Attention was subsequently focused on alkoxy and

hydroxy groups possessing relatively potent constrictive activity on the ileum. The activity of these di- and tri-substituted analogs (II-34—42) was assessed. Among the analogs, II-34, 36, 40 and 41 having an alkoxy group at the *para*-position on the benzene ring showed potent constrictive activity. D_2 receptor affinity was noted anew on exchanging mono-substituted analogs for the di- and tri-substituted analogs. Among them, II-34, 35, 40 and 41 had potent affinity.

Introduction of the oxybenzyl moiety to I, compound II-43, increased constrictive activity on the ileum compared with I, accompanied by the disappearance of D_2 receptor affinity. It thus follows that the kind and number of substituents on the benzene ring are factors determining the expression activities concerning benzamide derivatives into which the oxybenzyl moiety has been introduced.

Examination was also made of the side chain amine site (R^4, R^5) after substituents on the benzene ring had been fixed to the 3,4,5-trimethoxy group which showed relatively potent activities. In the case of compounds II-44—50 in which structural modification was made of the dimethylamino group of II-41, the D_2 receptor affinity was essentially unchanged, but constrictive activity on the ileum almost disappeared except for that of the pyrrolidinyl group (II-46), which was relatively small. In the case of compound II-51 in which the substituted position of the dimethylaminoethoxy group was replaced from 4-position to 3-position, constrictive activity on the ileum and the D_2 receptor affinity both decreased compared with that of the 4-position analog (II-41). For compound XIII-1, 2 in which the ether moiety of II-41 was changed to the amide or ester moiety, constrictive activity on the ileum and the D_2 affinity of XIII-1 both decreased and constrictive activity on the ileum of XIII-2 disappeared. From these results, the dimethylamino group, 4-substituted position and ether bond of II played important roles in the appearance of both activities.

Based on the high potency of constrictive activity on the ileum and the D_2 receptor affinity, compounds II-34, 40, 41 were selected for further evaluation including the minimum effective dose of improving effects of small intestinal transit in mice and that of the inhibition effect of apomorphine-induced emesis in dogs (Table III). The antiemetic activity of II-40, 41 and I was 3 to 10 times more potent than gastroprokinetic activity. This hindered the objective of this study since it caused an unbalance in activity. Compound II-34 was suitable for the objective of this study since II-34 showed both activities at the same dose (10 mg/kg).

We examined the mechanism of constrictive activity on the ileum of compound II-34, and found this compound to express acetylcholinesterase inhibitory activity, this being a very new finding for gastrointestinal prokinetic agents.[4] The acetylcholinesterase inhibitory activity of compounds possessing alkoxy and hydroxy groups were measured (Table IV), and acetylcholinesterase inhibitory activity was found closely related to constrictive activity on the ileum (Fig. 1). The pK_I of acetylcholinesterase inhibitory activity and the D_2 receptor affinity of II-34 were 5.38 and 5.75, respectively, and these values showed II-34 to have essentially the same potency for gastroprokinetic and antiemetic activities.

TABLE III. Gastrointestinal Prokinetic and Antiemetic Activity of II-34, 40, 41 and I

Compd.	Improving effect of small intestinal transit in mice minimum effective dose (mg/kg)	Inhibition effect of apomorphine-induced emesis in dog minimum effective dose (mg/kg)
II-34	10	10
II-40	10	1
II-41	30	10
I	3	0.3

TABLE IV. Effect on Acetylcholinesterase for Benzamides

Compd. No.	% inhibitory of acetylcholinesterase (10^{-5} M)	Compd. No.	% inhibitory of acetylcholinesterase (10^{-5} M)
II- 1	58	II-38	15
II- 2	52	II-39	34
II- 3	41	II-40	69
II-34	73	II-41	82
II-35	60	II-42	66
II-36	91	II-43	94
II-37	9		

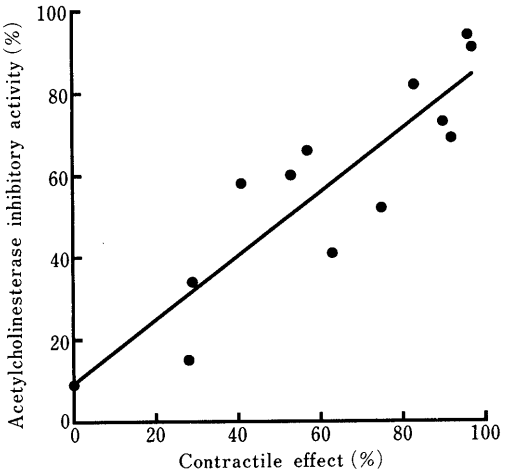


Fig. 1. Constrictive Activity–Acetylcholinesterase Inhibitory Activity Relationship

$y = 9.28 + 0.78x$, $R = 0.89$.

By structurally modifying I, a lead compound, significant data were obtained and the novel benzamide (II-34) having well balanced gastrointestinal prokinetic and antiemetic activities was found. The further detailed pharmacological data on II-34 were already reported.[5] This compound was given the code name; HSR-803, and is now undergoing a clinical study as a gastrointestinal prokinetic agent.

Experimental

All melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Spectral data were obtained using the following apparatus: proton nuclear magnetic resonance (^{1}H-NMR) spectra with JEOL FX-90Q (90 MHz) spectrometer with tetramethylsilane (TMS) as internal standard; mass spectra (MS) with JEOL JMS-DX 300 mass spectrometer; infrared (IR) spectra with Hitachi 270-30 spectrophotometer. Elemental analyses were performed using Yanagimoto MT-3 elemental analysis apparatus. All extracts were dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure.

TABLE V. Spectral Data for Substituted Benzamide Derivatives (II-1—51, XIII-1—2)

Compd. No.	Yield (%)	MS (m/z) (M^+)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR δ	^{1}H-NMR measured in
II- 1	64	328	1656 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, $J=5$ Hz, NCH_2), 3.87 (3H, s, OCH_3), 4.37 (2H, t, $J=5$ Hz, OCH_2), 4.44 (2H, d, $J=6$ Hz, $NHCH_2$), 6.90—7.50 (7H, m, Ar-H), 7.74 (1H, dd, $J=7.5$, 2 Hz, Ar-H), 8.45 (1H, br, CONH)	DMSO-d_6
II- 2	86	328	1640 (CO)	2.33 (6H, s, $NCH_3 \times 2$), 2.71 (2H, t, $J=5.5$ Hz, NCH_2), 3.83 (3H, s, OCH_3), 4.05 (2H, t, $J=5.5$ Hz, OCH_2), 4.56 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.30 (1H, br, CONH), 6.88, 7.26 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.93—7.40 (4H, m, Ar-H)	$CDCl_3$
II- 3	86	328	1640 (CO)	2.80 (6H, s, $NCH_3 \times 2$), 3.44 (2H, t, $J=5.5$ Hz, NCH_2), 3.80 (3H, s, OCH_3), 4.36 (2H, t, $J=5.5$ Hz, OCH_2), 4.39 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.96 7.28 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.94, 7.87 (each 2H, AB-q, $J=9$ Hz, Ar-H), 8.74 (1H, t, $J=5.5$ Hz, CONH)	DMSO-d_6
II- 4	58	342	1650 (CO)	1.31 (3H, t, $J=7$ Hz, OCH_2CH_3), 2.81 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, $J=5.5$ Hz, NCH_2), 4.14 (2H, q, $J=7$ Hz, OCH_2CH_3), 4.39 (2H, t, $J=5.5$ Hz, OCH_2), 4.25 (2H, d, $J=6$ Hz, $NHCH_2$), 6.97, 7.31 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.00—7.54 (3H, m, Ar-H), 7.75 (1H, dd, $J=7.5$, 2 Hz, Ar-H), 8.37 (1H, br, CONH)	DMSO-d_6
II- 5	78	342	1636 (CO)	1.41 (3H, t, $J=7$ Hz, OCH_2CH_3), 2.33 (6H, s, $NCH_3 \times 2$), 2.72 (2H, t, $J=5.5$ Hz, NCH_2), 4.05 (2H, t, $J=5.5$ Hz, OCH_2), 4.07 (2H, q, $J=7$ Hz, OCH_2CH_3), 4.56 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.30 (1H, br, CONH), 6.76—7.40 (8H, m, Ar-H)	$CDCl_3$
II- 6	44	342	1640 (CO)	1.39 (3H, t, $J=7$ Hz, OCH_2CH_3), 2.97 (6H, s, $NCH_3 \times 2$), 3.58 (2H, t, $J=5$ Hz, NCH_2), 4.08 (2H, q, $J=7$ Hz, OCH_2CH_3), 4.33 (2H, d, $J=5$ Hz, OCH_2), 4.49 (2H, s, $NHCH_2$), 6.95, 7.80 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.98, 7.33 (each 2H, AB-q, $J=9$ Hz, Ar-H)	CD_3OD
II- 7	56	356	1635 (CO)	1.03 (3H, t, $J=7$ Hz, CH_3), 1.81 (2H, sextet, $J=7$ Hz, CH_2), 2.32 (6H, s, $NCH_3 \times 2$), 2.71 (2H, t, $J=5.5$ Hz, NCH_2), 3.94 (2H, t, $J=7$ Hz, OCH_2CH_2), 4.05 (2H, t, $J=5.5$ Hz, OCH_2), 4.54 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.30 (1H, br, CONH), 6.88, 7.26 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.88, 7.73 (each 2H, AB-q, $J=9$ Hz, Ar-H)	$CDCl_3$
II- 8	70	370	1634 (CO)	0.84—1.08 (3H, m, CH_3), 1.24—1.96 (4H, m, $CH_2 \times 2$), 2.33 (6H, s, $NCH_3 \times 2$), 2.72 (2H, t, $J=5.5$ Hz, NCH_2), 3.99 (2H, t, $J=5.5$ Hz, OCH_2), 4.05 (2H, t, $J=5.5$ Hz, OCH_2), 4.55 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.20 (1H, br, CONH), 6.89, 7.27 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.89, 7.73 (each 2H, AB-q, $J=9$ Hz, Ar-H)	$CDCl_3$
II- 9	15 (2 steps)	314	1646 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 2.93 (1H, br, OH), 3.45 (2H, t, $J=5$ Hz, NCH_2), 4.36 (2H, t, $J=5$ Hz, OCH_2), 4.45 (2H, d, $J=6$ Hz, $NHCH_2$), 6.74—7.07 (2H, m, Ar-H), 6.96, 7.31 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.20—7.50 (1H, m, Ar-H), 7.83—8.00 (1H, m, Ar-H), 9.25 (1H, br, CONH)	DMSO-d_6
II-10	27 (2 steps)	314	1614 (CO)	2.21 (6H, s, $NCH_3 \times 2$), 2.61 (2H, t, $J=6$ Hz, NCH_2), 3.14 (1H, br, OH), 4.02 (2H, t, $J=6$ Hz, OCH_2), 4.37 (2H, d, $J=6$ Hz, $NHCH_2$), 6.74—6.95 (3H, m, Ar-H), 7.09—7.33 (5H, m, Ar-H), 8.65 (1H, br, CONH)	DMDO-d_6
II-11	86 (2 steps)	314	1626 (CO)	2.21 (6H, s, $NCH_3 \times 2$), 2.61 (2H, t, $J=6$ Hz, NCH_2), 4.02 (2H, t, $J=6$ Hz, OCH_2), 4.37 (2H, d, $J=6$ Hz, $NHCH_2$), 6.78, 7.74 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.86, 7.22 (each 2H, AB-q, $J=9$ Hz, Ar-H), 8.48 (1H, t, $J=6$ Hz, CONH), 9.75 (1H, br, OH)	DMSO-d_6
II-12	61	312	1642 (CO)	2.32 (3H, s, CH_3), 2.82 (6H, s, $NCH_3 \times 2$), 3.46 (2H, t, $J=5.5$ Hz, NCH_2), 4.37 (2H, t, $J=5$ Hz, OCH_2), 4.37 (2H, d, $J=6$ Hz, $NHCH_2$), 6.96, 7.30 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.17—7.47 (4H, m, Ar-H), 8.63 (1H, m, CONH)	DMSO-d_6
II-13	85	312	1662 (CO)	2.35 (3H, s, CH_3), 2.82 (6H, s, $NCH_3 \times 2$), 3.46 (2H, t, $J=5.5$ Hz, NCH_2), 4.35 (2H, t, $J=5.5$ Hz, OCH_2), 4.40 (2H, d, $J=6$ Hz, $NHCH_2$), 6.95, 7.29 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.15—7.36 (2H, m, Ar-H), 7.52—7.72 (2H, m, Ar-H), 8.75 (1H, t, $J=6$ Hz, CONH)	DMSO-d_6
II-14	69	312	1650 (CO)	2.38 (3H, s, CH_3), 2.97 (6H, s, $NCH_3 \times 2$), 3.58 (2H, t, $J=5$ Hz, NCH_2), 4.33 (2H, t, $J=5$ Hz, OCH_2), 4.50 (2H, s, $NHCH_2$), 6.98, 7.33 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.25, 7.73 (each 2H, AB-q, $J=8.5$ Hz, Ar-H)	CD_3OD
II-15	81	326	1640 (CO)	1.23 (3H, t, $J=7.5$ Hz, CH_3), 2.32 (6H, s, $NCH_3 \times 2$), 2.68 (2H, q, $J=7.5$ Hz, CH_2), 2.71 (2H, t, $J=5.5$ Hz, NCH_2), 4.05 (2H, t, $J=5.5$ Hz, OCH_2), 4.55 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.30 (1H, br, CONH), 6.88, 7.26 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.23, 7.70 (each 2H, AB-q, $J=8.5$ Hz, Ar-H)	$CDCl_3$
II-16	66	354	1640 (CO)	1.32 (9H, s, $CH_3 \times 3$), 2.32 (6H, s, $NCH_3 \times 2$), 2.71 (2H, t, $J=6$ Hz, NCH_2), 4.05 (2H, t, $J=6$ Hz, OCH_2), 4.55 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.40 (1H, br, CONH), 6.87, 7.25 (each 2H, AB-q, $J=8.5$ Hz, Ar-H), 7.41, 7.72 (each 2H, AB-q, $J=8.5$ Hz, Ar-H)	$CDCl_3$
II-17	46	316	1656 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, $J=5.5$ Hz, NCH_2), 4.38 (2H, t, $J=5.5$ Hz, OCH_2), 4.41 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.96, 7.30 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.07—7.77 (4H, m, Ar-H), 8.66 (1H, br, CONH)	DMSO-d_6
II-18	48	316	1662 (CO)	2.40 (6H, s, $NCH_3 \times 2$), 2.87 (2H, t, $J=5.5$ Hz, NCH_2), 4.12 (2H, t, $J=5.5$ Hz, OCH_2), 4.41 (2H, d, $J=6$ Hz, $NHCH_2$), 6.58 (2H, s, fumarate), 6.89, 7.25 (each 2H, AB-q, $J=8.5$ Hz, Ar-H), 7.20—7.80 (4H, m, Ar-H), 8.92 (1H, br, CONH)	DMSO-d_6
II-19	62	316	1648 (CO)	2.80 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, $J=5.5$ Hz, NCH_2), 4.37 (2H, t, $J=5.5$ Hz, OCH_2), 4.40 (2H, d, $J=6.5$ Hz, $NHCH_2$), 6.95, 7.29 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.26 (1H, t, $J=9$ Hz, Ar-H), 7.97 (2H, dd, $J=9$, 5.5 Hz, Ar-H)	DMSO-d_6
II-20	52	332 : 334 (3 : 1)	1652 (CO)	2.98 (6H, s, $NCH_3 \times 2$), 3.59 (2H, t, $J=5$ Hz, NCH_2), 4.35 (2H, t, $J=5$ Hz, OCH_2), 4.50 (2H, s, $NHCH_2$), 7.01 (2H, d, $J=9$ Hz, Ar-H), 7.24—7.50 (6H, m, Ar-H)	CD_3OD

TABLE V. (continued)

Compd. No.	Yield (%)	MS (m/z) (M^+)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR δ	^{1}H-NMR measured in
II-21	48	332 : 334 (3 : 1)	1668 (CO)	2.98 (6H, s, $NCH_3 \times 2$), 3.58 (2H, t, $J=5$ Hz, NCH_2), 4.34 (2H, t, $J=5$ Hz, OCH_2), 4.40—4.56 (2H, m, $NHCH_2$), 6.99 (2H, d, $J=9$ Hz, Ar-H), 7.15—7.87 (6H, m, Ar-H), 9.02 (1H, br, CONH)	CD_3OD
II-22	81	332 : 334 (3 : 1)	1668 (CO)	2.98 (6H, s, $NCH_3 \times 2$), 3.58 (2H, t, $J=5$ Hz, NCH_2), 4.34 (2H, t, $J=5$ Hz, OCH_2), 4.40—4.56 (2H, m, $NHCH_2$), 6.99, 7.34 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.45, 7.82 (each 2H, AB-q, $J=9$ Hz, Ar-H), 8.90 (1H, br, CONH)	CD_3OD
II-23	44	323	2232 (CN) 1668 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.46 (2H, t, $J=5$ Hz, NCH_2), 4.37 (2H, t, $J=5$ Hz, OCH_2), 4.43 (2H, d, $J=6$ Hz, $NHCH_2$), 6.96, 7.31 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.67 (1H, t, $J=8$ Hz, Ar-H), 7.97 (1H, dt, $J=8$, 1.5 Hz, Ar-H), 8.21 (1H, dt, $J=8$, 1.5 Hz, Ar-H), 8.31 (1H, t, $J=1.5$ Hz, Ar-H), 9.20 (1H, br, CONH)	DMSO-d_6
II-24	83	323	2232 (CN) 1650 (CO)	2.82 (6H, s, $NCH_3 \times 2$), 3.46 (2H, t, $J=5.5$ Hz, NCH_2), 4.34 (2H, t, $J=5.5$ Hz, OCH_2), 4.43 (2H, d, $J=6$ Hz, $NHCH_2$), 6.95, 7.29 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.90, 8.04 (each 2H, AB-q, $J=8.5$ Hz, Ar-H), 9.12 (1H, t, $J=6$ Hz, CONH)	DMSO-d_6
II-25	47	377	1642 (CO)	2.21 (6H, s, $NCH_3 \times 2$), 2.61 (2H, t, $J=6$ Hz, NCH_2), 3.18 (2H, br, NH_2), 4.02 (2H, t, $J=6$ Hz, OCH_2), 4.42 (2H, d, $J=6$ Hz, $NHCH_2$), 6.88, 7.24 (2H, AB-q, $J=9$ Hz, Ar-H), 7.63 (1H, t, $J=7.5$ Hz, Ar-H), 7.96 (1H, dt, $J=7.5$, 1.5 Hz, Ar-H), 8.06 (1H, dt, $J=7.5$, 1.5 Hz, Ar-H), 8.33 (1H, t, $J=1.5$ Hz, Ar-H), 9.03 (1H, br, CONH)	DMSO-d_6
II-26	23	377	1614 (CO)	2.22 (6H, s, $NCH_3 \times 2$), 2.62 (2H, t, $J=5.5$ Hz, NCH_2), 4.03 (2H, t, $J=5.5$ Hz, OCH_2), 4.42 (2H, d, $J=6$ Hz, $NHCH_2$), 6.88, 7.25 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.33 (2H, br, NH_2), 7.91, 8.02 (each 2H, AB-q, $J=9$ Hz, Ar-H), 11.90 (1H, br, CONH)	DMSO-d_6
II-27	87	343	1646 (CO)	2.83 (6H, s, $NCH_3 \times 2$), 3.47 (2H, t, $J=5.5$ Hz, NCH_2), 4.36 (2H, t, $J=5.5$ Hz, OCH_2), 4.39 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.97, 7.32 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.47—8.05 (4H, m, Ar-H), 9.00 (1H, t, $J=5.5$ Hz, CONH)	DMSO-d_6
II-28	72	343	1668 (CO)	2.82 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, $J=5.5$ Hz, NCH_2), 4.36 (2H, t, $J=5.5$ Hz, OCH_2), 4.45 (2H, d, $J=6$ Hz, $NHCH_2$), 6.96, 7.31 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.75 (1H, t, $J=7.5$ Hz, Ar-H), 8.20—8.40 (2H, m, Ar-H), 8.60—8.72 (1H, m, Ar-H), 9.20 (1H, t, $J=6$ Hz, CONH)	DMSO-d_6
II-29	36	343	1646 (CO)	2.32 (6H, s, $NCH_3 \times 2$), 2.71 (2H, t, $J=5.5$ Hz, NCH_2), 4.04 (2H, t, $J=5.5$ Hz, OCH_2), 4.57 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.54 (1H, br, CONH), 6.89, 7.26 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.92, 8.25 (each 2H, AB-q, $J=9$ Hz, Ar-H)	DMSO-d_6
II-30	56	313	1614 (CO)	2.31 (6H, s, $NCH_3 \times 2$), 2.70 (2H, t, $J=6$ Hz, NCH_2), 4.03 (2H, t, $J=6$ Hz, OCH_2), 4.49 (2H, d, $J=5.5$ Hz, $NHCH_2$), 5.53 (2H, br, NH_2), 6.40 (1H, br, CONH), 6.55—6.70 (2H, m, Ar-H), 6.89, 7.23 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.05—7.35 (2H, m, Ar-H)	$CDCl_3$
II-31	64	313	1642 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.46 (2H, t, $J=5.5$ Hz, NCH_2), 4.37 (2H, t, $J=5.5$ Hz, OCH_2), 4.41 (2H, d, $J=7$ Hz, $NHCH_2$), 5.90 (2H, br, NH_2), 6.95, 7.09 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.36—7.80 (4H, m, Ar-H), 8.97 (1H, br, CONH)	DMSO-d_6
II-32	60	313	1636 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, $J=5.5$ Hz, NCH_2), 4.37 (2H, t, $J=5.5$ Hz, OCH_2), 4.40 (2H, d, $J=5$ Hz, $NHCH_2$), 6.27 (3H, br, NH_2, CONH), 6.94, 7.81 (each 2H, AB-q, $J=8.5$ Hz, Ar-H), 7.06, 7.28 (each 2H, AB-q, $J=8.5$ Hz, Ar-H)	DMSO-d_6
II-33	24	341	1620 (CO)	2.33 (6H, s, $NCH_3 \times 2$), 2.72 (2H, t, $J=5.5$ Hz, NCH_2), 3.00 (6H, s, $NCH_3 \times 2$), 4.05 (1H, t, $J=5.5$ Hz, OCH_2), 4.61 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.20 (1H, br, CONH), 6.75, 7.37 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.98, 7.78 (each 2H, AB-q, $J=9$ Hz, Ar-H)	$CDCl_3$
II-34	72	358	1652 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, $J=5.5$ Hz, NCH_2), 3.80 (6H, s, $OCH_3 \times 2$), 4.37 (2H, t, $J=5.5$ Hz, OCH_2), 4.40 (2H, d, $J=6$ Hz, $NHCH_2$), 6.94, 7.28 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.99 (1H, d, $J=9$ Hz, Ar-H), 7.51 (1H, d, $J=2$ Hz, Ar-H), 7.52 (1H, dd, $J=9$, 2 Hz, Ar-H), 8.80 (1H, br, CONH)	DMSO-d_6
II-35	60	358	1642 (CO)	2.33 (6H, s, $NCH_3 \times 2$), 2.71 (2H, t, $J=5.5$ Hz, NCH_2), 3.80 (6H, s, $OCH_3 \times 2$), 4.05 (2H, t, $J=5.5$ Hz, OCH_2), 4.54 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.30 (1H, br, CONH), 6.56 (1H, t, $J=2$Hz, Ar-H), 6.89, 7.26 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.89 (2H, d, $J=2$ Hz, Ar-H)	$CDCl_3$
II-36	68	358	1640 (CO)	2.33 (6H, s, $NCH_3 \times 2$), 2.72 (2H, t, $J=5.5$ Hz, NCH_2), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.06 (2H, t, $J=5.5$ Hz, OCH_2), 4.59 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.46 (1H, d, $J=2.5$ Hz, Ar-H), 6.88, 7.27 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.97 (1H, br, NH), 8.22 (1H, d, $J=8.5$ Hz, Ar-H)	$CDCl_3$
II-37	34	358	1658 (CO)	2.31 (6H, s, $NCH_3 \times 2$), 2.69 (2H, t, $J=5.5$ Hz, NCH_2), 3.81 (6H, s, $OCH_3 \times 2$), 4.04 (2H, t, $J=5.5$ Hz, OCH_2), 4.59 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.00 (1H, br, NH), 6.54 (1H, d, $J=8$ Hz, Ar-H), 6.87, 7.31 (each 2H, AB-q, $J=9$ Hz, Ar-H), 7.26 (1H, t, $J=8$ Hz, Ar-H)	$CDCl_3$
II-38	82	358	1652 (CO)	2.35 (6H, s, $NCH_3 \times 2$), 2.81 (2H, t, $J=5.5$ Hz, NCH_2), 3.74 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.11 (2H, t, $J=5.5$ Hz, OCH_2), 4.40 (2H, d, $J=6$ Hz, $NHCH_2$), 6.59 (2H, s, fumarate), 6.90 (2H, d, $J=9$ Hz, Ar-H), 7.00—7.32 (5H, m, Ar-H), 8.40 (1H, br, CONH)	DMSO-d_6
II-39	85 (2 steps)	344	1628 (CO)	2.34 (6H, s, $NCH_3 \times 2$), 2.73 (2H, t, $J=5.5$ Hz, NCH_2), 3.86 (3H, s, OCH_3), 4.05 (2H, t, $J=5.5$ Hz, OCH_2), 4.52 (2H, d, $J=5.5$ Hz, $NHCH_2$), 6.50 (1H, d, $J=5.5$ Hz, CONH), 6.82, 7.22 (each 2H, AB-q, $J=9$ Hz, Ar-H), 6.83 (1H, d, $J=8.5$ Hz, Ar-H), 7.19 (1H, dd, $J=8.5$, 2 Hz, Ar-H), 7.44 (1H, d, $J=2$ Hz, Ar-H)	$CDCl_3$

TABLE V. (continued)

Compd. No.	Yield (%)	MS (m/z) (M^+)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR δ	^{1}H-NMR measured in
II-40	74	386	1636 (CO)	1.44 (3H, t, J=7 Hz, CH_3), 1.45 (3H, t, J=7 Hz, CH_3), 2.32 (6H, s, $NCH_3 \times 2$), 2.71 (2H, t, J=5.5 Hz, NCH_2), 4.05 (2H, t, J=5.5 Hz, OCH_2), 4.11 (2H, q, J=7 Hz, OCH_2), 4.12 (2H, q, J=7 Hz, OCH_2), 4.54 (2H, d, J=5.5 Hz, $NHCH_2$), 6.34 (1H, br, CONH), 6.82 (1H, d, J=8.5 Hz, Ar-H), 6.88, 7.26 (each 2H, AB-q, J=9 Hz, Ar-H), 7.25 (1H, dd, J=8.5, 2 Hz, Ar-H), 7.43 (1H, d, J=2 Hz, Ar-H)	$CDCl_3$
II-41	83	388	1630 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.24—3.63 (2H, m, NCH_2), 3.70 (3H, s, OCH_3), 3.82 (6H, s, $OCH_3 \times 2$), 4.24—4.53 (4H, m, OCH_2, $NHCH_2$), 6.95, 7.29 (each 2H, AB-q, J=8.5 Hz, Ar-H), 7.27 (2H, s, Ar-H), 9.07 (1H, br, CONH)	DMSO-d_6
II-42	62 (2 steps)	374	1628 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.45 (2H, t, J=5.5 Hz, NCH_2), 3.80 (6H, s, $OCH_3 \times 2$), 4.29 (2H, t, J=5.5 Hz, OCH_2), 4.38 (2H, d, J=5.5 Hz, $NHCH_2$), 6.94, 7.28 (each 2H, AB-q, J=9 Hz, Ar-H), 7.23 (2H, s, Ar-H), 8.73 (1H, t, J=5.5 Hz, NH)	DMSO-d_6
II-43	70	377 : 379 (3 : 1)	3304 (NH) 1642 (CO)	2.81 (6H, s, $NCH_3 \times 2$), 3.49 (2H, t, J=5.5 Hz, NCH_2), 3.82 (3H, s, OCH_3), 4.36 (2H, t, J=5.5 Hz, OCH_2), 4.41 (2H, d, J=7.5 Hz, NCH_2), 5.60 (1H, br, NH_2), 6.54 (1H, s, Ar-H), 6.94, 7.26 (each 2H, AB-q, J=8.8 Hz), 7.70 (1H, s, Ar-H), 8.23 (1H, br, NH), 10.96 (1H, br, HCl)	DMSO-d_6
II-44	80	444	1640 (CO)	0.88 (6H, t, J=7 Hz, $CH_3 \times 2$), 1.25—1.70 (4H, m, $CH_2CH_2CH_3 \times 2$), 2.35—2.60 (4H, m, $CH_2CH_2CH_3 \times 2$), 2.85 (2H, t, J=6 Hz, NCH_2), 3.87 (9H, s, $OCH_3 \times 3$), 4.01 (2H, t, J=6 Hz, OCH_2), 4.55 (2H, d, J=5.5 Hz, $NHCH_2$), 6.33 (1H, br, CONH), 6.87, 7.26 (each 2H, AB-q, J=9 Hz, Ar-H), 7.01 (2H, s, Ar-H)	$CDCl_3$
II-45	58	456	1624 (CO)	1.00—2.00 (11H, m, CH_2, CH), 2.37 (3H, s, NCH_3), 2.85 (2H, t, J=6 Hz, NCH_2), 3.87 (3H, s, OCH_3), 3.88 (6H, s, $OCH_3 \times 2$), 4.03 (2H, t, J=6 Hz, OCH_2), 4.56 (2H, d, J=5.5 Hz, $NHCH_2$), 6.31 (1H, br, CONH), 6.88, 7.27 (each 2H, AB-q, J=9 Hz, Ar-H), 7.01 (2H, s, Ar-H)	$CDCl_3$
II-46	41	414	1624 (CO)	1.70—1.90 (4H, m, $CH_2 \times 2$), 2.50—2.70 (4H, m, NCH_2), 2.89 (2H, t, J=6 Hz, NCH_2), 3.88 (9H, s, $OCH_3 \times 3$), 4.10 (2H, t, J=6 Hz, OCH_2), 4.55 (2H, d, J=5.5 Hz, $NHCH_2$), 6.33 (1H, br, CONH), 6.89, 7.27 (each 2H, AB-q, J=9 Hz, Ar-H), 7.01 (2H, s, Ar-H)	$CDCl_3$
II-47	64	428	1624 (CO)	1.40—1.80 (6H, m, CH_2), 2.40—2.60 (4H, m, NCH_2), 2.76 (2H, t, J=6 Hz, NCH_2), 3.87 (3H, s, OCH_3), 3.88 (6H, s, $OCH_3 \times 2$), 4.10 (2H, t, J=6 Hz, OCH_2), 4.56 (2H, d, J=5.5 Hz, $NHCH_2$), 6.27 (1H, br, CONH), 6.88, 7.27 (each 2H, AB-q, J=8.5 Hz, Ar-H), 7.00 (2H, s, Ar-H)	$CDCl_3$
II-48	74	442	1626 (CO)	0.80—1.00 (3H, m, CH_3), 1.10—1.75 (5H, m, CH_2, CH), 1.90—2.25 (2H, m, NCH_2), 2.77 (2H, t, J=6 Hz, NCH_2), 2.80—3.10 (2H, m, NCH_2), 3.87 (9H, s, $OCH_3 \times 3$), 4.09 (2H, t, J=6 Hz, OCH_2), 4.55 (2H, d, J=5.5 Hz, $NHCH_2$), 6.34 (1H, br, CONH), 6.88, 7.27 (each 2H, AB-q, J=9 Hz, Ar-H), 7.01 (2H, s, Ar-H)	$CDCl_3$
II-49	42	430	1636 (CO)	2.40—2.55 (4H, m, NCH_2), 2.70 (2H, t, J=5.5 Hz, NCH_2), 3.45—3.65 (4H, m, OCH_2), 3.72 (3H, s, OCH_3), 3.82 (6H, s, $OCH_3 \times 2$), 4.07 (2H, t, J=5.5 Hz, OCH_2), 4.41 (2H, d, J=6 Hz, $NHCH_2$), 6.63 (2H, s, fumarate), 6.88, 7.24 (each 2H, AB-q, J=9 Hz, Ar-H), 7.22 (2H, s, Ar-H), 11.58 (1H, br, CONH)	DMSO-d_6
II-50	31	443	1638 (CO)	2.80 (3H, s, NCH_3), 3.35—3.70 (10H, m, NCH_2), 3.71 (3H, s, OCH_3), 3.83 (6H, s, $OCH_3 \times 2$), 4.25—4.50 (4H, m, OCH_2, $NHCH_2$), 6.96, 7.29 (each 2H, AB-q, J=9 Hz, Ar-H), 7.25 (2H, s, Ar-H), 8.86 (1H, br, CONH)	DMSO-d_6
II-51	61	388	1628 (CO)	2.82 (6H, s, $NCH_3 \times 2$), 3.46 (2H, t, J=5.5 Hz, NCH_2), 3.72 (3H, s, OCH_3), 3.84 (6H, s, $OCH_3 \times 2$), 4.37 (2H, t, J=5.5 Hz, OCH_2), 4.46 (2H, d, J=6 Hz, $NHCH_2$), 6.80—7.00 (3H, m, Ar-H), 7.15—7.40 (3H, m, Ar-H), 8.97 (1H, br, CONH)	DMSO-d_6
XIII-1	28 (from XII)	415	1640 (CONH)	2.25 (6H, s, $NCH_3 \times 2$), 2.49 (2H, t, J=6 Hz, NCH_2), 3.47 (2H, q, J=6 Hz, $NHCH_2CH_2$), 3.87 (9H, s, $OCH_3 \times 3$), 4.62 (2H, d, J=6 Hz, $NHCH_2$), 6.80, 7.02 (each 1H, br, CONH), 7.10 (2H, s, Ar-H), 7.31, 7.68 (each 2H, AB-q, J=8.5 Hz, Ar-H)	$CDCl_3$
XIII-2	44 (from XII)	416	1722 (CO) 1658 (CONH)	2.92 (6H, s, $NCH_3 \times 2$), 3.40—3.60 (2H, m, NCH_2), 3.80 (3H, s, OCH_3), 3.87 (6H, s, $OCH_3 \times 2$), 4.50—4.73 (4H, m, OCH_2, $NHCH_2$), 6.60 (2H, s, fumarate), 7.22 (2H, s, Ar-H), 7.45, 8.03 (each 2H, AB-q, J=8.5 Hz, Ar-H)	CD_3OD

***N*-[4-[2-(Dimethylamino)ethoxy]benzyl]-2-methoxybenzamide Hydrochloride (II-1)** A suspension of 2-methoxybenzoic acid (1.72 g, 11.3 mmol) in $SOCl_2$ (10 ml) was refluxed for 30 min and evaporated. A solution of the residue in $CHCl_3$ (5 ml) was added dropwise to a solution of 4-[2-(dimethylamino)ethoxy]benzylamine (IV, 2.00 g, 10.3 mmol) and Et_3N (1.14 g, 11.3 mmol) in $CHCl_3$ (5 ml) with stirring. The reaction mixture was stirred for 2 h at room temperature and the solvent was evaporated. Aqueous HCl was added to the residue, then the aqueous layer was washed with AcOEt and made alkaline with K_2CO_3. The aqueous layer was extracted with AcOEt. The extract was washed with water, dried, and the solvent was evaporated. The residue was treated with a small amount of iso-Pr_2O to give pale brown crystals, which were converted into the hydrochloride in a usual manner. The resulting crystals were collected by filtration, washed with a mixed solution of EtOH and Et_2O and recrystallized from EtOH to give 2.41 g of colorless prisms (II-1).

***N*-[4-[2-(Dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide Hydrochloride (II-34)** A suspension of 3,4-dimethoxybenzoic acid (2.06 g, 11.3 mmol) in $SOCl_2$ (10 ml) was refluxed for 30 min and evaporated. A solution of the residue in $CHCl_3$ (5 ml) was added dropwise to a solution of IV (2.00 g, 10.3 mmol) and Et_3N (1.14 g, 11.3 mmol) in $CHCl_3$ (5 ml). The reaction mixture was stirred for 2 h at room temperature and then evaporated. Aqueous HCl was added to the residue, the aqueous layer was washed with AcOEt and made alkaline with K_2CO_3. The aqueous layer was extracted with AcOEt. The extract was washed with water, dried and the solvent was evaporated. The residue was treated with a small amount of iso-Pr_2O to give pale brown crystals, which were converted into the hydrochloride in a usual manner. The resulting crystals were collected by filtration, washed with a mixed solution of EtOH and Et_2O and recrystallized from EtOH to give 2.93 g of colorless prisms (II-34).

Compounds II-2—8, 12—24, 26—29, 33, 35—38, 40 and 41 were also prepared in the same manner as described above. The yields and physicochemical data for the product are listed in Tables I and V.

***N*-[4-[2-(Dimethylamino)ethoxy]benzyl]-4-hydroxybenzamide (II-11)** A suspension of 4-acethoxybenzoic acid (2.00 g, 11.1 mmol) in $SOCl_2$ (2.4 ml) was refluxed for 30 min and evaporated. A solution of the residue in $CHCl_3$ (4 ml) was added dropwise to a mixture of IV (2.00 g, 10.3 mmol) in $CHCl_3$ (6 ml). The reaction mixture was stirred for 10 min at room temperature and evaporated. Aqueous HCl was added to the residue, the aqueous layer was washed with AcOEt and made alkaline with K_2CO_3. The aqueous layer was extracted with AcOEt. The extract was washed with water, dried and evaporated to give corresponding crude V, which was used for the next step without further purification. To a solution of V in MeOH (10 ml) was added 10% aq. NaOH solution (4 ml), the reaction mixture was stirred for 10 min at room temperature and evaporated. To the residue was added water the resulting crystals were collected by filtration, washed with water, iso-Pr_2O and AcOEt, successively, and recrystallized from EtOH to give 2.80 g of colorless scales (II-11).

Compounds II-9, 10, 39 and 42 were also prepared in the same manner as described above. The yields and physicochemical data for the product are listed in Tables I and V.

4-Amino-*N*-[4-[2-(dimethylamino)ethoxy]benzyl]benzamides Hydrochloride (II-32) A solution of *N*-[4-[2-(dimethylamino)ethoxy]benzyl]-4-nitrobenzamide (II-29, 2.80 g, 8.2 mmol) was hydrogenated in MeOH (20 ml) over PtO_2 (100 mg) for 30 min under atmospheric pressure at room temperature. The catalyst was filtered off and the filtrate was evaporated. The residue was converted into the hydrochloride in a usual manner. The resulting crystals were collected by filtration, washed with a mixed solution of EtOH and Et_2O and recrystallized from MeOH to give 1.88 g of colorless needles (II-32).

Compound II-31 was also prepared in the same manner as described above. The yield and physicochemical data for the product are listed in Tables I and V.

2-Amino-*N*-[4-[2-(dimethylamino)ethoxy]benzyl]benzamides (II-30) A solution of isatoic anhydride (VI, 1.04 g, 10.8 mmol) and IV (2.00 g, 10.3 mmol) in AcOEt (20 ml) was stirred for 15 min at room temperature and evaporated. The residue was dissolved in aq. HCl and the solution was washed with AcOEt. The aqueous layer was made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with water, dried and evaporated. The residue was recrystallized from AcOEt to give 1.85 g of colorless columns (II-30).

The yield and physicochemical data for the product are listed in Tables I and V.

***N*-[4-[2-(Dimethylamino)ethoxy]benzyl]-3-sulfamoylbenzamide (II-25)** To a suspension of 3-sulfamoylbenzoic acid (VII, 3.72 g, 18.5 mmol) in tetrahydrofuran (THF) (30 ml) were added dropwise Et_3N (1.87 g, 18.5 mmol) and pivaloyl chloride (2.23 g, 18.5 mmol) under ice-cooling, successively. The reaction mixture was stirred for 2 h at room temperature and then to the reaction mixture was added dropwise a solution of IV (3.00 g, 15.4 mmol) in THF (5 ml). The reaction mixture was stirred further for 5 h at room temperature and then extracted with aq. HCl. The aqueous layer was washed with AcOEt, made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with water, dried and evaporated. The residue was washed with AcOEt and recrystallized from EtOH to give 2.71 g of colorless crystals (II-25).

The yield and physicochemical data for the product are listed in Tables I and V.

4-Amino-5-chloro-*N*-[4-[2-(dimethylamino)ethoxy]benzyl]-2-methoxybenzamide Hydrochloride (II-43) To a suspension of 4-amino-5-chloro-2-methoxybenzoic acid (VIII, 2.49 g, 18.5 mmol) in $CHCl_3$ (30 ml) were added dropwise Et_3N (1.26 g, 12.5 mmol) and ClCOOEt (1.35 g, 12.4 mmol) under ice-cooling, successively. The reaction mixture was stirred for 30 min at room temperature and then to the mixture was added dropwise a solution of IV (2.00 g, 10.3 mmol) in $CHCl_3$ (10 ml). The reaction mixture was stirred for 14 h at room temperature and then evaporated. The residue was dissolved in aq. HCl and the aqueous solution was washed with AcOEt, made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, dried and the solvent was evaporated. The residue was washed with Et_2O and converted into the hydrochloride in a usual manner. The resulting crystals were collected by filtration, washed with a mixed solution of EtOH and Et_2O and recrystallized from EtOH to give 3.00 g of colorless needles (II-43).

The yield and physicochemical data for the product are listed in Tables I and V.

***N*-[4-[2-(Di-*n*-propylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamides (II-44)** A suspension of 3,4,5-trimethoxybenzoic acid (III, 2.27 g, 10.7 mmol) in $SOCl_2$ (10 ml) was refluxed for 30 min and evaporated. A solution of the residue in $CHCl_3$ (5 ml) was added dropwise to a mixture of 4-[2-(di-*n*-propylamino)ethoxy]benzylamine (IX-1, 2.43 g, 9.7 mmol) and Et_3N (1.08 g, 10.7 mmol) in $CHCl_3$ (5 ml). The reaction mixture was stirred for 2 h at room temperature and evaporated. Aqueous HCl was added to the residue, the aqueous layer was washed with AcOEt and made alkaline with K_2CO_3. The aqueous layer was extracted with AcOEt. The extract was washed with water, dried and evaporated. The residue was treated with a small amount of iso-Pr_2O to give pale brown crystals, which were recrystallized from iso-Pr_2O to give 3.47 g of colorless needles (II-44).

Compounds II-45—50 were also prepared in the same manner as described above. The yields and physicochemical data for the product are listed in Tables I and V.

***N*-[3-[2-(Dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamides Hydrochloride (II-51)** A suspension of 3,4,5-trimethoxybenzoic acid (III, 2.27 g, 10.7 mmol) in $SOCl_2$ (10 ml) was refluxed for 30 min and evaporated. A solution of the residue in $CHCl_3$ (5 ml) was added dropwise to a mixture of 3-[2-(dimethylamino)ethoxy]benzylamine (X, 1.89 g, 9.7 mmol) and Et_3N (1.08 g, 10.7 mmol) in $CHCl_3$ (5 ml). The mixture was stirred for 2 h at room temperature and evaporated. Aqueous HCl was added to the residue, the aqueous layer was washed with AcOEt and made alkaline with K_2CO_3. The aqueous layer was extracted with AcOEt. The extract was washed with water, dried and evaporated. The residue was treated with a small amount of a mixed solution of iso-Pr_2O and *n*-hexane to give pale brown crystals, which were converted into the hydrochloride in a usual manner. The resulting crystals were collected by filtration, washed with a mixed solution of EtOH and Et_2O and recrystallized from EtOH to give 2.57 g of colorless needles (II-51).

The yield and physicochemical data for the product are listed in Tables II and V.

***N*-4-[2-(Di-*n*-propylamino)ethoxy]benzylamine (IX-1)** A suspension of 4-[2-(di-*n*-propylamino)ethoxy]benzaldehyde (2.27 g, 10.7 mmol) and $NH_2OH \cdot HCl$ (0.96 g, 13.9 mmol) in EtOH (20 ml) was refluxed for 10 min. After cooling, the resulting crystals were collected by filtration to give 3.26 g of 4-[2-(di-*n*-propylamino)ethoxy]benzaldoxime hydrochloride as colorless crystals, mp 183—184 °C, which was catalytic hydrogenated over Raney-Ni (W-2, 1 ml) in 20% NH_3–MeOH (100 ml) for 7 h under 50 atm at 30 °C. The catalyst was filtered off and the filtrate was evaporated to give 2.70 g of a pale yellowish viscous liquid (IX-1), which was used for the next step without further purification.

Compounds IX-2—7 were also prepared in the same manner as described above. The yields and physicochemical data for the product are listed in Table VI.

***N*-3-[2-(Dimethylamino)ethoxy]benzylamine (X)** A suspension of 3-[2-(dimethylamino)ethoxy]benzaldehyde (2.50 g, 13.0 mmol) and $NH_2OH \cdot HCl$ (1.35 g, 19.5 mmol) in EtOH (15 ml) was refluxed for 40 min and evaporated. The reaction mixture was diluted with water, made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The extract was evaporated to give a pale yellow viscous liquid. The liquid was treated with a small amount of iso-Pr_2O to give 2.21 g of 3-[2-(dimethylamino)ethoxy]-benzaldoxime as colorless crystals, mp 103—104 °C, which was catalytic hydrogenated over Raney-Ni (W-2, 1 ml) in 20% NH_3–MeOH (100 ml) for 7 h under 50 atm at 30 °C. The catalyst was filtered off and the filtrate was evaporated to give 2.12 g of a pale yellowish viscous liquid (X), which was used for the next step without further purification.

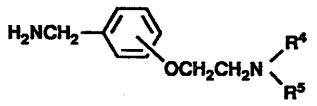
The yield and physicochemical data for the product are listed in Table VI.

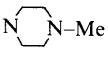
***N*-[4-[2-(Dimethylamino)ethylaminocarbonyl]benzyl]-3,4,5-trimethoxybenzamides (XIII-1)** By the reaction of 3,4,5-trimethoxybenzylchloride and methyl 4-aminomethylbenzoate (XI) was prepared XII, mp 253.5—255 °C (mp 254—256 °C[5]). To a suspension of XII (2.50 g, 7.2 mmol) in THF (30 ml) were added dropwise Et_3N (1.09 g, 10.8 mmol) and ClCOOEt (0.82 g, 7.6 mmol) under ice-cooling, successively. The reaction mixture was stirred for 30 min at room temperature and then to the mixture was added dropwise a solution of 2-(dimethylamino)ethylamine (0.70 g, 8.0 mmol) in THF (10 ml). The reaction mixture was stirred for 1 h at room temperature and evaporated. Aqueous HCl was added to the residue and the aqueous layer was washed with AcOEt, then made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with water, dried and evaporated. The residue was recrystallized from AcOEt to give 0.85 g of colorless needles (XIII-1).

The yield and physicochemical data for the product are listed in Table II and V.

***N*-[4-[2-(Dimethylamino)ethylaminocarbonyl]benzyl]-3,4,5-trimethoxybenzamides (XIII-2)** A suspension of XII (2.00 g, 5.8 mmol) in $SOCl_2$ (10 ml) was refluxed for 15 min and then evaporated. To a solution of the residue in $CHCl_3$ (30 ml) were added 2-(dimethylamino)ethanol (1.17 g, 11.6 mmol) and Et_3N (1.09g, 10.8 mmol) under ice-cooling, successively.

TABLE VI. Spectral Data for 4-[2-(Dialkylamino)ethoxy]benzylamine (IX-1—7, X)



Compd. No.	NR^4R^5	Substituted position	Yield[a] (%)	MS (m/z) (M^+)	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
IX-1	NPr_2	4	93	250	3375, 3300	0.88 (6H, t, J=7.5 Hz, $CH_3\times2$), 1.20—1.75 (4H, m, $CH_2CH_2CH_3\times2$), 2.40—2.60 (4H, m, $CH_2CH_2CH_3\times2$), 2.85 (2H, t, J=6.5 Hz, NCH_2), 3.85 (2H, br, NCH_2), 4.62 (2H, t, J=6.5 Hz, OCH_2), 6.86, 7.21 (each 2H, AB-q, J=9 Hz, Ar-H)
IX-2		4	85	262	3360, 3295	0.80—2.12 (12H, m, CH_2, NH_2), 2.37 (3H, s, NCH_3), 2.85 (2H, t, J=6.5 Hz, NCH_2), 3.87 (2H, br, NCH_2), 4.03 (2H, t, J=6.5 Hz, OCH_2), 6.86, 7.21 (each 2H, AB-q, J=8.5 Hz, Ar-H)
IX-3		4	81	220	3364, 3280	1.53 (2H, br, NH_2), 1.70—1.90 (4H, m, CH_2), 2.50—2.75 (4H, m, CH_2), 2.89 (2H, t, J=6 Hz, NCH_2), 3.79 (2H, s, NCH_2), 4.10 (2H, t, J=6 Hz, OCH_2), 6.88, 7.22 (each 2H, AB-q, J=9 Hz, Ar-H)
IX-4		4	91	234	3370, 3280	1.30—1.90 (8H, m, CH_2, NH_2), 2.40—2.60 (4H, m, CH_2), 2.76 (2H, t, J=6 Hz, NCH_2), 3.79 (2H, s, NCH_2), 4.09 (2H, t, J=6 Hz, OCH_2), 6.86, 7.21 (each 2H, AB-q, J=9 Hz, Ar-H)
IX-5		4	91	248	3370, 3300	0.80—1.00 (3H, m, CH_3), 1.10—1.80 (7H, m, CH_2, CH, NH_2), 1.90—2.30 (2H, m, CH_2), 2.80—3.10 (2H, m, CH_2), 2.77 (2H, t, J=6 Hz, NCH_2), 3.90 (2H, br, NCH_2), 4.09 (2H, t, J=6 Hz, OCH_2), 6.87, 7.21 (each 2H, AB-q, J=8.5 Hz, Ar-H)
IX-6		4	86	236	3375, 3300	1.48 (2H, br, NH_2), 2.57 (4H, t, J=4.5 Hz, NCH_2), 2.79 (2H, t, J=6 Hz, NCH_2), 3.73 (4H, t, J=4.5 Hz, OCH_2), 3.80 (2H, s, NCH_2), 4.10 (2H, t, J=6 Hz, OCH_2), 6.86, 7.22 (each 2H, AB-q, J=9 Hz, Ar-H)
IX-7		4	86	236	3375, 3300	1.48 (2H, br, NH_2), 2.57 (4H, t, J=4.5 Hz, NCH_2), 2.79 (2H, t, J=6 Hz, NCH_2), 3.73 (4H, t, J=4.5 Hz, OCH_2), 3.80 (2H, s, NCH_2), 4.10 (2H, t, J=6 Hz, OCH_2), 6.86, 7.22 (each 2H, AB-q, J=9 Hz, Ar-H)
X	NMe_2	3	82	194	3372, 3300	1.57 (2H, br, NH_2), 2.33 (6H, s, $NCH_3\times2$), 2.72 (2H, t, J=6 Hz, NCH_2), 3.90 (2H, br, NCH_2), 4.07 (2H, t, J=6 Hz, OCH_2), 6.68—7.00 (3H, m, Ar-H), 7.15—7.35 (1H, m, Ar-H)

a) These compounds were used for the next step without further purification.

The reaction mixture was stirred for 30 min at room temperature and evaporated. Aqueous HCl was added to the residue and the solution was washed with AcOEt. The aqueous layer was made alkaline with K_2CO_3 and extracted with AcOEt. The extract was washed with water, dried and evaporated. The residue was washed with Et_2O and converted into the fumarate in a usual manner. The resulting crystals were collected by filtration and recrystallized from EtOH to give 1.35 g of colorless needles (XIII-2).

The yield and physicochemical data for the product are listed in Tables II and V.

Constrictive Effect in Isolated Guinea Pig Ileum Male Hartley guinea pigs weighing about 450 g were used. The ileum was removed and cut into segments 1.5—2.0 cm in length. These preparations were suspended vertically in organ baths filled with Krebs-Henseleit's solution at 37 °C which was gassed with 95% O_2 and 5% CO_2. Rhythmic contractions of ileum were isotonically measured. Effects of the test compounds were expressed in percentage of 10^{-6} M acetylcholine-induced contractions.

D_2 Binding Affinity Dopamine D_2 receptor binding assays were performed according to the method of Coward *et al.*[6] Brain striata were isolated from male Wistar rats to obtain D_2 receptor preparations. [^{3}H]Spiperone was used as the ligand. Non-specific binding of [^{3}H]spiperone was determined in the presence of 10 μM sulpiride. Dissociation constants (K_i) of the test compounds were calculated with the equation of Cheng and Prusoff.

Improving Effect of Small Intestinal Transit in Mice Male ddY mice weighing about 22 g fasted for 24 h before the experiment were used. Test compounds (suspended in 0.5% carboxymethylcellulose) were administered orally. Thirty minutes later, charcoal meal (5% charcoal powder suspended in 10% gum arabic) was administered orally. Twenty minutes later the animals were sacrificed and the digestive tracts were isolated from the stomach to the cecum. The small intestinal transit was expressed as the ratio (%) of the length to which the charcoal meal traveled from the pylorus to the total length of small intestine. Statistical analysis was carried out by Student's t-test for unpaired observations.

Inhibition Effect on Apomorphine-Induced Emesis in Dogs Male beagle dogs weighing 7 to 11 kg and fasted overnight before the experiment were used. Test compounds or saline were orally administered to the dogs 30 min before feeding. Ten minutes after feeding, apomorphine (0.1 mg/kg, s.c.) was administered and then observation for vomiting was continued for 30 min. The time needed for apomorphine-induced emesis and the number of emesis were recorded.

Effect on Acetylcholinesterase Activity The potency of test compounds in inhibiting acetylcholinesterase activity was studied according to the method reported by Ellman *et al.* using pure acetylcholinesterase. The reaction was carried out at 30 °C in a cell of a spectrophotometer (Double beam spectrophotometer 200-20, Hitachi Ltd., Tokyo, Japan) and changes in absorbance with time at 412 nm, were recorded. Inhibitory activities of the test compounds were expressed by the percent decrease from the original enzyme activity obtained from the control experiment in which the test compounds were replaced with the Tris–HCl buffer.

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