Synthesis and Structure–Activity Relationships of 4-Amino-5-chloro-*N*-(1,4-dialkylhexahydro-1,4-diazepin-6-yl)-2-methoxybenzamide Derivatives, Novel and Potent Serotonin 5-HT$_3$ and Dopamine D$_2$ Receptors Dual Antagonist

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In search of a dopamine D$_2$ and serotonin 5-HT$_3$ receptors dual antagonist as a potential broad antiemetic agent, a number of benzamides were prepared from 4-amino-5-chloro-2-methoxybenzoic acid derivatives and 6-amino-1,4-dialkylhexahydro-1,4-diazepines and evaluated for their binding affinity for the dopamine D$_2$ and the serotonin 5-HT$_3$ receptors using rat brain synaptic and rat cortical membranes, respectively. From the results of both *in vitro* receptor binding and *in vivo* biological assays for the dopamine D$_2$ receptor, 1-ethyl-4-methylhexahydro-1,4-diazepine ring was selected as an optimum amine moiety. Introduction of one methyl group on the nitrogen atom at the 4-position and/or modification of the substituent at the 5-position of the 4-amino-5-chloro-2-methoxybenzoyl moiety caused a marked increase in the dopamine D$_2$ receptor binding affinity along with a potent 5-HT$_3$ receptor binding affinity. Among the compounds, 5-chloro-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-4-methylaminobenzamide (82), 5-bromo (110), and 5-iodo (112) analogues exhibited a much higher affinity for the dopamine D$_2$ receptor than that of metoclopramide (IC$_{50}$=17.5—61.0 nM *vs.* 483 nM). In particular, 82 showed a potent antagonistic activity for both receptors *in vivo* tests. Optical resolution of the racemate 82 brought about a dramatic change in the pharmacological profile with the (*R*)-enantiomer exhibiting a strong affinity for both the dopamine D$_2$ and the 5-HT$_3$ receptors, while the corresponding (*S*)-enantiomer had a potent and selective serotonin 5-HT$_3$ receptor binding affinity.

Key words serotonin 5-HT$_3$ receptor; dopamine D$_2$ receptor; hexahydro-1,4-diazepine; antiemetic; 4-amino-5-chloro-2-methoxybenzamide; optical resolution

A number of the 2-alkoxy-4-amino-5-chlorobenzamide family possessing a potent serotoninergic or dopaminergic activity has been reported.[1)] The potency and selectivity of the benzamides are dependent upon the structure of their basic moiety. The classic and parent benzamide of this family is metoclopramide, which is used clinically as a stimulant of upper gastrointestinal motility and an antiemetic agent.[2,3)] Effects of metoclopramide are believed to be due to a combination of a relatively weak serotonin (5-hydroxytryptamine) 5-HT$_3$ (5-HT$_3$) and dopamine D$_2$ receptors antagonism and a serotonin 5-HT$_4$ receptor agonism. The weak affinity and lack of selectivity of metoclopramide for these receptors can be explained by the large number of permissible conformers due to the flexibility of the 2-(diethylamino)ethyl chain. To date, several benzamide derivatives with potent and selective activity for the dopamine D$_2$, and the serotonin 5-HT$_4$, and 5-HT$_3$ receptors have been reported. Thus, zacopride,[4)] BRL 24682,[5)] renzapride,[6)] SC 53116,[7)] and mosapride[8,9)] with a rigid folded framework as the amine moiety showed good affinity for the 5-HT$_3$ and/or serotonin 5-HT$_4$ receptors. On the other hand, clebopride, a compound **1**, and BRL 25594 having a benzyl group on the nitrogen atom in the amine moiety had high affinity for the dopamine D$_2$ and D$_3$ receptors.[10)]

Several potent and selective 5-HT$_3$ receptor antagonists such as ondansetron and granisetron have been used clinically to prevent nausea and emesis induced by cancer chemotherapeutic agents such as cisplatin and radiation treatment.[11—14)] The nausea and emesis are common side effects that can cause patients to refuse subsequent chemotherapeutic sessions.[15)] On the other hand, dopamine D$_2$ receptor antagonists such as phenothiazines and butyrophenones are known to be effective in the treatment of emesis and vomiting induced by centrally acting emetic stimuli such as antiparkinsonian drugs, loperamide, apomorphine, and morphine.[16)] In addition, the traditional antiemetic agent domperidone, a peripheral dopamine D$_2$ receptor antagonist, has been shown to be effective for the treatment of chronic upper gastrointestinal distress and the prevention of nausea and vomiting resulting from variety of causes.[17,18)] However, dopamine D$_2$ receptor antagonists including domperidone are only minimally effective against chemotherapy- or radiation-induced nausea and vomiting.[19)] Previously, we reported that the structurally novel 4-amino-*N*-(1-benzyl-4-methylhexahydro-1,4-diazepin-6-yl)-5-chloro-2-methoxybenzamide (**2x**) and the corresponding 4-amino-5-chloro-2-ethoxybenzamide (**2y**) are potent and selective 5-HT$_3$ receptor antagonists.[20)] In the course of our studies on the structure–activity relationships (SARs) of **2x**, **y**, we found that replacement of the benzyl group in the hexahydro-1,4-diazepine ring by an alkyl group results in a significant increase in the dopamine D$_2$ receptor binding affinity along with a potent 5-HT$_3$ receptor antagonistic activity.[21)] Thus, the combination of a dopamine D$_2$ and a 5-HT$_3$ receptor antagonistic activity was seen as a good strategy for the development of effective therapeutic agents for the treatment of nausea and emesis induced by cancer chemotherapeutic agents, radiation treatment, antiparkinsonian drugs, morphine, and variety of causes. These observations led us to modify the alkyl group in the hexahydro-1,4-diazepine ring of **2x**, **y**, and prepare the optically active *N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamides, resulting in the discovery of (*R*)-5-chloro-*N*-(1-ethyl-

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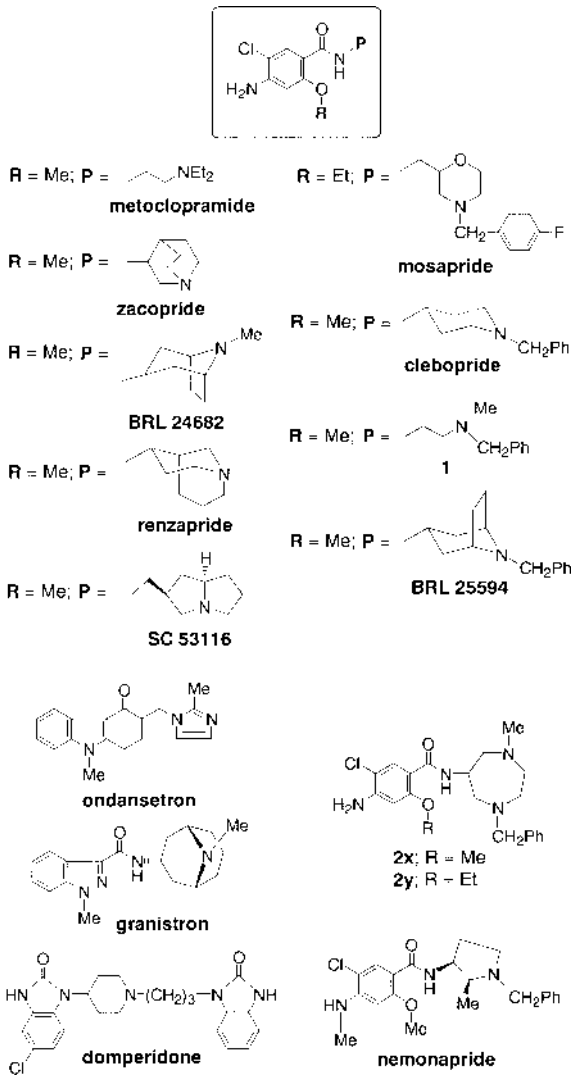


Fig. 1

4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-4-methylaminobenzamide [(*R*)-**82**], a potent dopamine D_2 and 5-HT_3 receptors antagonist. The present paper describes the synthesis of 4-amino-5-chloro-*N*-(1,4-dialkylhexahydro-1,4-diazepin-6-yl)-2-methoxybenzamides and other related compounds, and evaluates their SARs as regard to the binding affinity for the dopamine D_2 and the 5-HT_3 receptors.

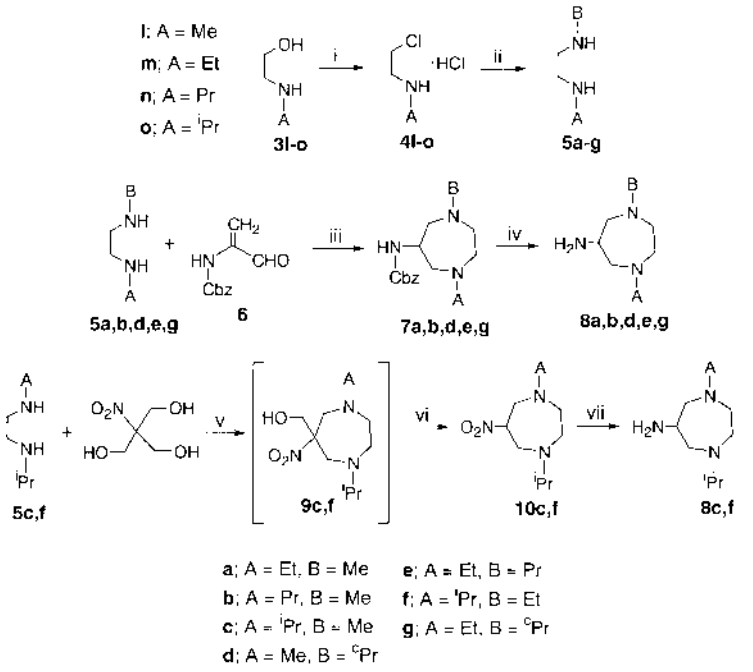
Chemistry

The requisite 6-aminohexahydro-1,4-diazepine derivatives **8a**—**l** were prepared by the methods shown in Charts 1 and 2. The *N*,*N*′-dialkylethylenediamines **5a**—**g** were obtained by reaction of the commercially available 2-alkylaminoethanols **3l**—**o** with thionyl chloride, followed by treatment of the resultant *N*-(*β*-chloroethyl)alkylamine hydrochlorides **4l**—**o** with an appropriate monoalkylamine. The 6-amino-1,4-dialkylhexahydro-1,4-diazepine derivatives **8a**, **b**, **d**, **e**, **g** were synthesized from the corresponding *N*,*N*′-dialkylethylenediamines **5a**, **b**, **d**, **e**, **g** and 2-benzyloxycarbonylaminopropenal[22] (**6**) *via* the 6-benzyloxycarbonylamino-1,4-dialkylhexahydro-1,4-diazepines **7a**, **b**, **d**, **e**, **g** in a similar manner to that described in our previous paper.[22] As the isopropylhexahydro-1,4-diazepines **8c**, **f** were not obtained by reaction of **5c**, **f** with **6**, a previously reported method[23] was used. Reaction of **5c** or **5f** with tris(hydroxymethyl)nitromethane gave the 6-hydroxymethyl-6-nitrohexahydro-1,4-diazepine **9c** or **9f**, which was treated with potassium *tert*-butoxide, followed by careful neutralization with an aqueous hydroxylamine hydrochloride, to produce the 6-nitorohexahydro-1,4-diazepine **10c** or **10f** as an unstable oil, respectively. Hydrogenation of **10c** or **10f** over Raney Ni gave the desired **8c** or **8f**, respectively (Chart 1).

Introduction of the butyl, 2,2,2-trifluoroethyl, 2,2-difluoroethyl, and 2-methoxyethyl groups at the nitrogen atom in the hexahydro-1,4-diazepine ring was performed by reductive alkylation according to the method of Marchini *et al.*[24] Treatment of 6-acetylamino-1-ethylhexahydro-1,4-diazepine (**12**) and 6-benzoylamino-1-methylhexahydro-1,4-diazepine (**15**) prepared by debenzylation of the 6-(protected amino)-hexahydro-1,4-diazepines **11**[20] and **14**[22] with the corresponding carboxylic acids and $NaBH_4$ directly gave the 6-(protected amino)hexahydro-1,4-diazepines **13** and **16i**—**k** in moderate to good yield. Deprotection of **13** and **16i**—**k** with aqueous HCl produced the desired amines **8h**—**k**. The 6-amino-1-(3-hydroxypropyl)-4-methylhexahydro-1,4-diazepine (**8l**) was prepared as follows. Addition of acrolein to **15**, followed by reduction of the formyl group with $NaBH_4$ gave the 1-(3-hydroxypropyl)-4-methylhexahydro-1,4-diazepine (**16l**). **16l** was attempted to hydrolyze with aqueous HCl, but the reaction was unsuccessful. Next, acetylation of the hydroxyl group of **16l**, followed by treatment of the resultant **17** with concentrated HCl afforded the amine **8l** in 39% overall yield (Chart 2).

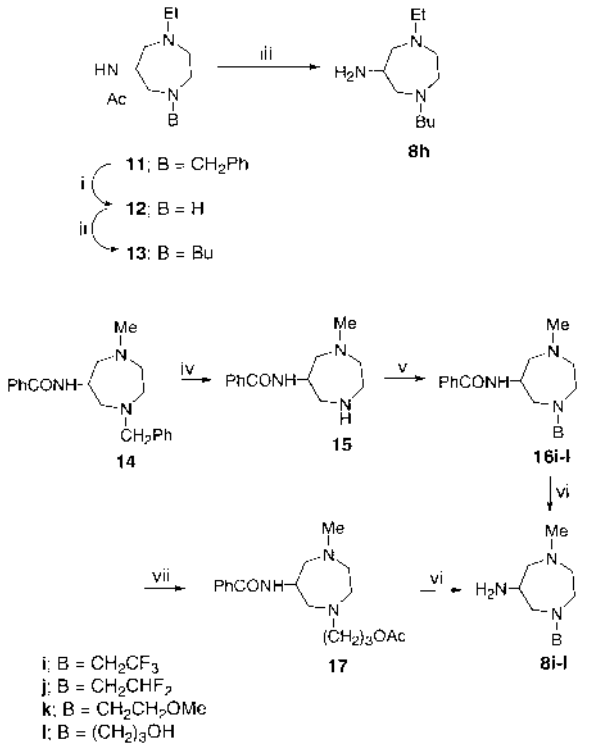
The optically active 6-amino-1-ethyl-4-methylhexahydro-1,4-diazepines [(*R*)- and (*S*)-**8a**] were prepared from the optically pure 1*H*-indazol-3-carboxamide (*R*)-**18** and its enantiomer (*S*)-**18**[25] as shown in Chart 3. Hydrogenation of (*R*)- and (*S*)-**18** over Pd/C, followed by reductive ethylation[26] of (*R*)- and (*S*)-**19** using acetaldehyde and $NaBH_4$ gave (*R*)- and (*S*)-**20**, which were treated with concentrated HCl to produce the optically pure (*R*)- and (*S*)-**8a** in excellent overall yield.

The preparation of various benzoic acid derivatives is exhibited in Charts 4—6. The 2-alkoxy-5-chlorobenzoic acids **23d**—**f**, **25**, **27**, **28**, **29a**, **b**, **30** were synthesized as follows. Reaction of methyl 4-acetylamino-5-chloro-2-hydroxybenzoate[27] (**21**) with ally bromide, benzyl bromide, and butyl iodide, followed by alkaline hydrolysis of the resultants **22d**—**f** gave 2-allyloxy-, 2-benzyloxy-, and 2-butoxy-4-amino-5-chlorobenzoic acids (**23d**—**f**), respectively. The 5-chloro-2-isopropoxy-4-methylaminobenzoic acid (**25**) was obtained by methylation of **22c**[20] with MeI in the presence of NaH, followed by alkaline hydrolysis of **24** in 72% overall yield. On the other hand, a similar reaction of **22a** with EtI produced the 4-(*N*-acetyl-*N*-ethyl)amino-5-chloro-2-methoxybenzoic acid **26** instead of the corresponding methyl ester. Alkaline hydrolysis of **26** furnished the corresponding 4-ethylaminobenzoic acid **27**. The 4-acetylaminobenzoic ester **22a** was treated with 1.2 molar equivalents of NaOH in aqueous MeOH at 60 °C for 1 h to give the corresponding 4-acetylaminobenzoic acid **28** in excellent yield. The 4-dimethylaminobenzoic acids **29a**, **b** were directly synthesized by reductive alkylation of **23a**, **b**[28,29] using HCHO and $NaBH_3CN$ in moderate yield. Treatment of **23a** with a mixture of HCO_2H and Ac_2O gave the corresponding 4-formylamino-



Reagents and conditions: i, $SOCl_2$, $CHCl_3$, reflux; ii, B-NH_2, EtOH–(H_2O), 50 °C; iii, 1) 5 °C, MeOH, 2) $NaBH_4$, room temperature; iv, HBr in AcOH, room temperature; v, $NaHCO_3$, H_2O, 40—50 °C; vi, 1) ^{t}BuOK, MeOH, <50 °C, 2) NH_2OH•HCl, H_2O; vii, Raney Ni, H_2, EtOH.

Chart 1

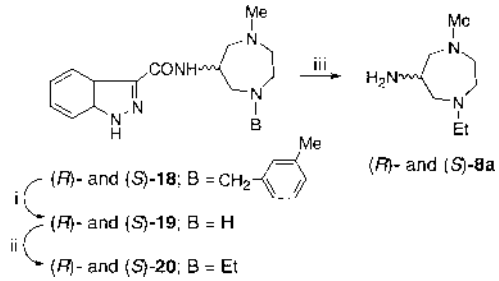


Reagents and conditions: i, 1) $ClCO_2(Cl)CHMe$, $ClCH_2CH_2Cl$, reflux, 2) MeOH, reflux; ii, $MeCH_2CH_2CO_2H$, $NaBH_4$, toluene, reflux; iii, 10% HCl, reflux; iv, Pd/C, H_2, EtOH–AcOH; v, CF_3CO_2H, (CHF_2CO_2H, $MeOCH_2CO_2H$, or CH_2=CHCHO), $NaBH_4$, toluene (MeOH); vi, 35% HCl, reflux; vii, Ac_2O, pyridine, $CHCl_3$, reflux.

Chart 2

benzoic acid **30** in 85% yield.

The preparation of the 5-substituted 4-amino-2-ethoxybenzoic acids **33a**, **b** is shown in Chart 5. Reaction of **31**[28,29] with *N*-bromosuccinimide (NBS) and iodine monochloride (ICl), followed by alkaline hydrolysis of the 5-halogenobenzoic esters **32a**, **b** gave the 5-bromo- and 5-iodo-4-amino-2-ethoxybenzoic acids (**33a**, **b**).



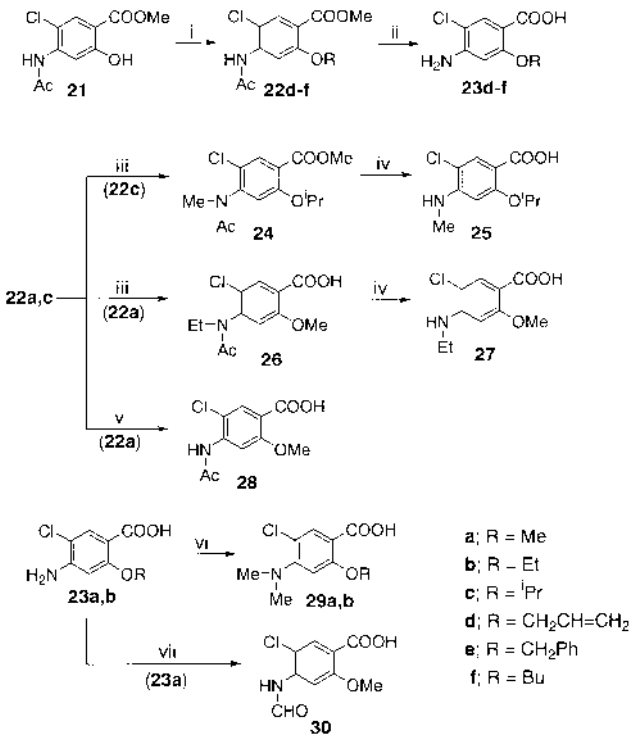
Reagents and conditions: i, Pd/C, H_2, EtOH; ii, 1) MeCHO, MeOH, 5 °C, 2) $NaBH_4$, room temperature; iii, 35% HCl, reflux.

Chart 3

The 5-substituted 2-methoxy-4-methylaminobenzoic acids **37a**—**d**, **43**, and **47** were prepared as shown in Chart 6. The 2-methoxy-4-[*N*-methyl-*N*-(*p*-toluenesulfonyl)]aminobenzoic acid (**35**) was synthesized by modification of the Iwanami *et al.* method.[30] The salicylic acid derivative **34**[30] was treated with *ca.* 3 molar equivalents of dimethylsulfate in the presence of KOH to produce **35** instead of the corresponding methyl ester in 67% yield. Reaction of **35** with NBS, *N*-chlorosuccinimide (NCS), ICl, and nitric acid-concentrated H_2SO_4 mixture afforded the 5-substituted 4-methylamino benzoic acids **36a**—**d**, respectively. Deprotection of **36a**—**d** with concentrated H_2SO_4 afforded the corresponding 4-methylaminobenzoic acids **37a**, **b**, **d**, except for the 5-iodobenzoic acid **37c**, in excellent yield. As the acidic hydrolysis of **36c** eliminates the iodine atom at the 5-position, another route for the preparation of **37c** was examined. Treat-

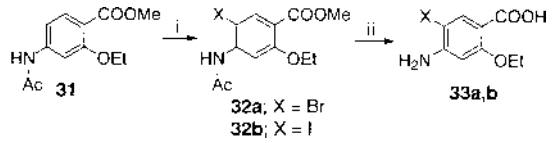
ment of the 4-methylamino-2-methoxybenzoic ester **38**[30] with Ac_2O provided the 4-(*N*-acetyl-*N*-methyl)aminobenzoic ester **39**, which was halogenated with ICl to give **40** in good yield. Instead of acid hydrolysis, alkaline hydrolysis of **40** smoothly proceeded to afford the desired 5-iodo-2-methoxy-4-methylaminobenzoic acid (**37c**) in 84% overall yield. In order to protect the 4-methylamino group of **38**, treatment of **38** with benzyl bromide in the presence of K_2CO_3 gave the 4-(*N*-benzyl-*N*-methyl)aminobenzoic ester **41**. Under Vilsmeier reaction conditions, **41** gave an inseparable mixture of the desired 5-formyl-4-methylaminobenzoic ester **42a** and the 5-formyl-4-(*N*-formyl-*N*-methyl)aminobenzoic ester **42b**. Vilsmeier reaction of the moderately reactive benzoic ester **41** caused not only formylation at the 5-position but also concurrent debenzylation at the 4-amino moiety, thereby producing **42a** and the further *N*-formylated product **42b**. Alkaline hydrolysis of the mixture of **42a**, **b** produced the single product **43** in 30% yield. On the other hand, reaction of **38** with Br_2 and ammonium thiocyanate, followed by treatment of the resulting 5-thiocyanobenzoic ester **44** with KOH and Et_2SO_4 gave the 5-ethylthiobenzoic ester **45**, although the yield was poor. Alkaline hydrolysis of **45** and successive oxidation of the resultant benzoic acid **46** with hydrogen peroxide afforded the 5-ethylsulfonylbenzoic acid derivative **47** in good yield.

The benzotriazole- and benzimidazole-5-carboxylic acids **51** and **53** were prepared as shown in Chart 7. Introduction of a nitro group at the 3-position of **22a**, followed by hydrogenation of the resultant methyl 4-acetylamino-5-chloro-2-methoxy-3-nitrobenzoate (**48**) over Raney Ni gave the 3-aminobenzoic ester **49**. Treatment of **49** with sodium nitrite in acidic solution, and successive acidic hydrolysis of the



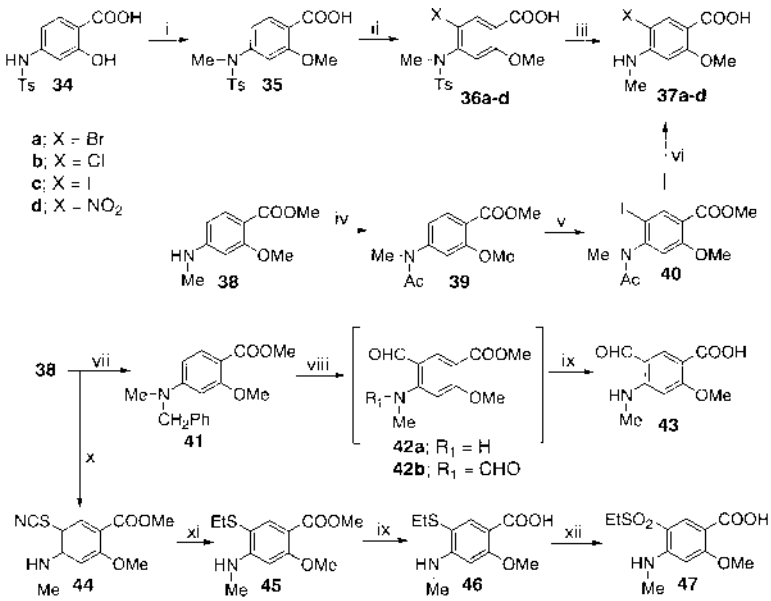
Reagents and conditions: i, CH_2=$CHCH_2Br$, ($PhCH_2Br$ or BuI), K_2CO_3, $Bu_4N^+Br^-$, MeCOEt, reflux; ii, NaOH, MeOH–H_2O, reflux; iii, MeI or EtI, NaH, THF, room temperature; iv, 20% NaOH, reflux; v, NaOH, MeOH–H_2O, 60 °C; vi, HCHO, $NaBH_3CN$, MeCN, room temperature; vii, Ac_2O, HCO_2H, 65 °C.

Chart 4



Reagents and conditions: i, NBS or ICl, DMF, 80 °C; ii, NaOH, MeOH–H_2O, reflux.

Chart 5



Reagents and conditions: i, Me_2SO_4, KOH, Me_2CO, reflux; ii, NBS (NCS, HNO_3–H_2SO_4), DMF, 80 °C; iii, H_2SO_4, 5 °C; iv, Ac_2O, Et_3N, room temperature; v, ICl, DMF, room temperature; vi, 20% NaOH, reflux; vii, $PhCH_2Br$, K_2CO_3, DMF, reflux; viii, $POCl_3$, DMF, 80 °C; ix, NaOH, MeOH–H_2O, reflux; x, Br_2, NH_4SCN, MeOH, 5 °C; xi, Et_2SO_4, KOH, MeOH, reflux; xii, H_2O_2, AcOH, room temperature.

Chart 6

benzotriazole **50** afforded 7-chloro-4-methoxy-1*H*-benzotriazole-5-carboxylic acid (**51**). Reflux of a solution of **49** in the presence of TsOH in toluene gave the benzimidazole-5-carboxylic ester **52**, and alkaline hydrolysis of **52** provided the benzimidazole-5-carboxylic acid **53**.

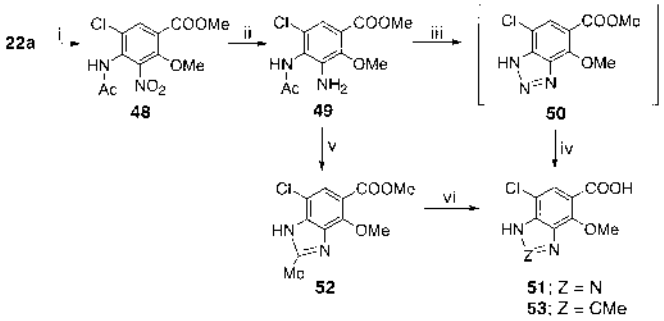
The benzamide and carboxamide derivatives **71**, **72**, **80**—**82**, **85**—**97**, **98**—**112**, **114**, **115**, **117**, **118**, **120**—**123**, **125**—**130**, (*R*)- and (*S*)-**81**, (*R*)- and (*S*)-**82**, (*R*)- and (*S*)-**110**, (*R*)- and (*S*)-**112** were synthesized by reaction of the appropriate benzoic acid or carboxylic acid with the amines **8a**—**o**, (*R*)- and (*S*)-**8a** in the presence of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (EDC) as a coupling reagent (Chart 8).

On the other hand, hydrogenation of **2x** over Pd/C gave the debenzylated benzamide **75**. The 1-(2-hydroxyethyl)benzamide derivative **96** was derived from the 1-(2-methoxyethyl)-4-methylhexahydro-1,4-diazepine analogue **95** using trimethylsilyl iodide. Treatment of the 6-(*tert*-butoxycarbonylamino)-2,3-dimethoxybenzoic acid[31] (**62**) with thionyl chloride followed by condensation of the resultant acid chloride with **8a** afforded directly the 6-amino-2,3-dimethoxybenzamide **124** in 49% yield (Chart 9).

The 5-fluoro-2-methoxy-4-methylaminbenzamide **113** was prepared from 2,4,5-trifluorobenzoic acid (**63**) as shown in Chart 10. Treatment of **63** with *N*-benzylmethylamine afforded the regioselective 4-(*N*-benzyl-*N*-methyl)amino-2,5-difluorobenzoic acid (**64**) in 49% yield. Condensation of **64** with **8a** produced the 4-(*N*-benzyl-*N*-methyl)aminobenzamide **65**, which was underwent a substitution reaction with NaOMe to provide the 2-methoxy-4-(*N*-benzyl-*N*-methyl)-aminobenzamide **66**. Hydrogenation of **66** over Pd/C afforded the desired 5-fluorobenzamide **113**. $NaBH_4$ reduction of **115** gave the corresponding 5-hydroxymethylbenzamide **116**. The 5-sulfamoylbenzamide **119** was prepared as follows. Introduction of a chlorosulfonyl group at the 5-position of the commercially available 4-chloro-2-methoxybezoic acid (**67**) was performed by reaction with chlorosulfuric acid. Reaction of the resultant 4-chloro-5-chlorosulfonyl-2-methoxybenzoic acid (**68**) with 28% aqueous ammonia gave the 5-sulfamoylbenzoic acid **69**, which was condensed with **8a** to provide the 4-chloro-5-sulfamoylbenzamide (**70**). Finally, treatment of **70** with $MeNH_2$ in a sealed tube afforded the desired **119** in 84% yield (Chart 10).

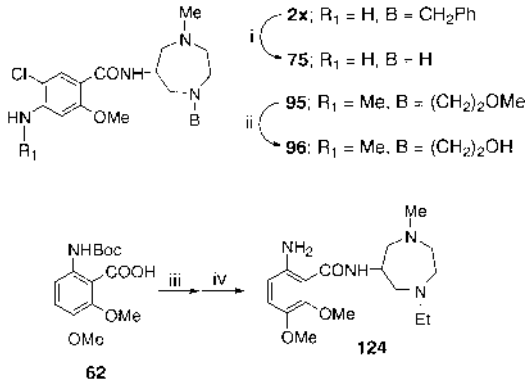
Results and Discussion

The affinity of the benzamide and carboxamide derivatives for the 5-HT_3 receptor in the central nervous system was determined by inhibition of the specific binding of [^{3}H]-GR65630 to rat cortical membrane according to the method previously reported for [^{3}H]quipazine binding.[20] The affinity for the dopamine D_2 receptor was evaluated in binding assays by competition for the binding of the radioligand [^{3}H]spiperone, a dopamine D_2 receptor agonist, to binding sites in rat



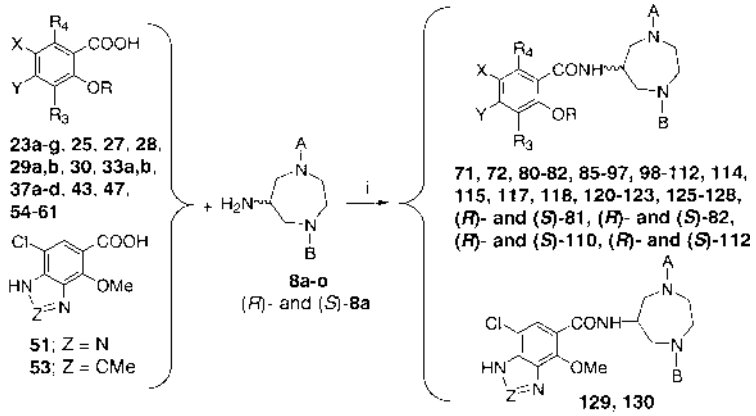
Reagents and conditions: i, HNO_3–H_2SO_4, <10 °C; ii, Raney Ni, H_2, EtOH–H_2O; iii, H_2SO_4, $NaNO_2$, H_2O, 5 °C; iv, reflux; v, *p*-TsOH, toluene, reflux; vi, NaOH, MeOH–H_2O, reflux.

Chart 7



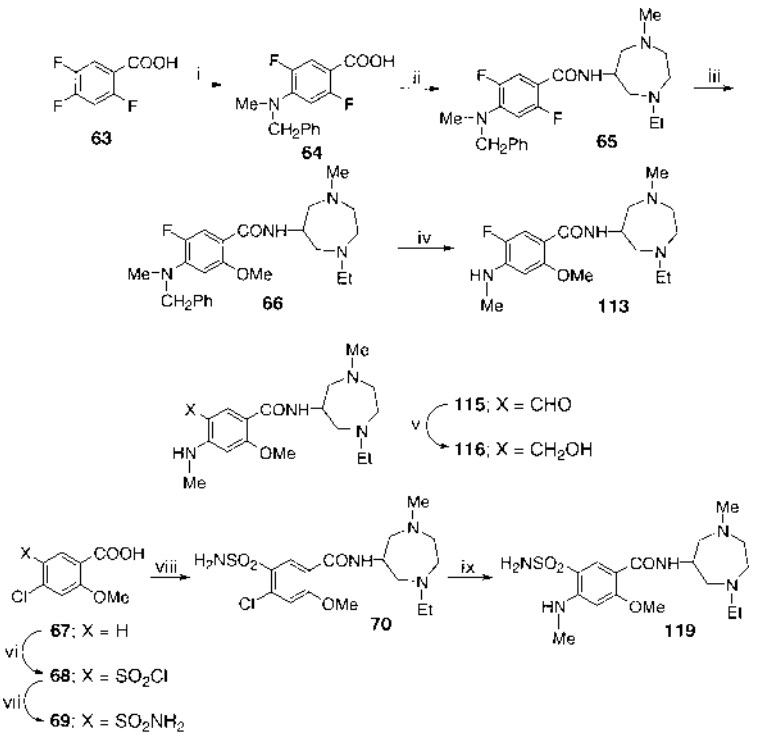
Reagents and conditions: i, Pd/C, H_2, EtOH, 50 °C; ii, TMSI, $CHCl_3$, room temperature; iii, $SOCl_2$, DMF, toluene, 60 °C; iv, **8a**, $CHCl_3$, room temperature.

Chart 9



Reagents and conditions: i, EDC, CH_2Cl_2, room temperature.

Chart 8



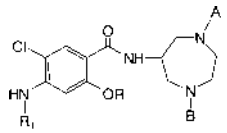
Reagents and conditions: i, $PhCH_2NHMe$, Et_3N, pyridine, reflux; ii, **8a**, EDC, CH_2Cl_2, room temperature; iii, NaOMe, DMF, 120 °C; iv, Pd/C, H_2, EtOH–AcOH, 50 °C; v, $NaBH_4$, MeOH, room temperature; vi, $ClSO_3H$, 60—70 °C; vii, aq. NH_3, 40—50 °C; viii, **8a**, EDC, CH_2Cl_2, room temperature; ix, NH_2Me, EtOH, 140 °C.

Chart 10

striatum.[32] Receptor binding data at the 5-HT_3 and the dopamine D_2 receptors for compounds **2x**, **y**, and **71**—**130** along with those for each enantiomer of **81**, **82**, **110**, and **112** are listed in Table 1. For comparison, data for metoclopramide, the potent and selective 5-HT_3 receptor antagonist, ondansetron, and the potent and selective dopamine D_2 receptor antagonist, domperidone are included in Table 6.

Metoclopramide was characterized by its weak affinity for the dopamine D_2 and the 5-HT_3 receptors, while domperidone (15.1 nM) showed a potent affinity for only dopamine D_2 receptor, and ondansetron (1.26 nM) was exhibited a potent affinity for only 5-HT_3 receptor. First, the effects on affinity of a substitution at the 1- and 4-positions in the hexahydro-1,4-diazepine ring of **2x**, **y** leading to **71**—**97** were examined and the newly prepared benzamides were compared to **2x**, **y**, two potent and selective 5-HT_3 receptor antagonists (serotonin 5-HT_4[33] and dopamine D_2 receptor binding affinities $>$1000 nM). Benzamides **71** and **72** having 1-benzyl-4-methylhexahydro-1,4-diazepine ring in the amine moiety, as well as **2x**, **y**, showed a much strong affinity for the 5-HT_3 receptor regardless of the substituent at the 2-alkoxy group in the benzoyl moiety. However, their affinity for the dopamine D_2 receptor was weak ($>$1000 nM). Replacement of the methyl group in **2x** by an ethyl group (giving **73**) resulted in an increase in affinity for the dopamine D_2 receptor (292 nM). On the other hand, the corresponding 2-ethoxybenzamide **74** did not show good affinity for the dopamine D_2 receptor, in spite of a potent 5-HT_3 receptor binding affinity. An interesting increase in the affinity of **73** for the dopamine D_2 receptor led us to prompt further modifications of the substituent in the hexahydro-1,4-diazepine ring. The debenzylated benzamide (**75**) of **2x** exhibited weak affinity for the dopamine D_2 receptor. Though **76**—**79**, having a 1,4-dimethylhexahydro-1,4-diazepine ring, did not display good binding affinity for the dopamine D_2 receptor, the 4-methylamino counterpart **80** showed an enhanced affinity for this receptor. Compound **80** exhibited a binding affinity for the dopamine D_2 receptor *ca.* 2.5-fold stronger than that of metoclopramide (198 nM *vs.* 483 nM) along with a potent 5-HT_3 receptor affinity (1.86 nM). Replacement of the benzyl group of **2x**, **73**, and **74** by an ethyl, propyl, isopropyl, or cyclopropyl group (yielding **81**, **83**, **84**, **86**—**91**) resulted in an increase in the binding affinity for the dopamine D_2 receptor except for **88** with a 1-isopropyl-4-methylhexahydro-1,4-diazepine ring. The affinity of the benzamides prepared for the dopamine D_2 receptor did not depend upon the size of the substituent and **91** with a 1-cyclopropyl-4-ethylhexahydro-1,4-diazepine ring had the most potent affinity (50.3 nM) for this receptor. The affinity of **91** for the dopamine D_2 receptor was *ca.* 10-fold more potent than that of metoclopramide and *ca.* 3-fold less potent than that of domperidone. The dopamine D_2 receptor binding site of the substituent in the hexahydro-1,4-diazepine ring is thought to have a spatial narrow pocket with an optimal volume for a methyl, ethyl, or cyclopropyl group. This results are in contrast with those previously reported regarding the recognition of the dopamine D_2 receptor[34]; *i.e.* the role of the *N*-benzyl substitution and the extended shape of the molecule were shown to be important for the recognition of the dopamine D_2 receptor by clebopride, BRL 25594, and other structurally-related dopaminergic antagonists, which displayed high affinity for this receptor. The *N*-methylamino analogous **82** and **85** increased the binding affinity for the

Table 1. Physical Data for 5-Chloro-2-alkoxy-*N*-(hexahydro-1,4-diazepin-6-yl)benzamides (**71**, **72**, **75**, **80**—**82**, **85**—**97**)

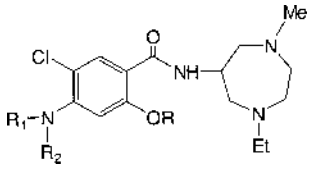


Compds.	R	R_1	A	B	mp, °C (Recryst solvent[a])	Formula[b]	Analysis (%) Calcd (Found)				
							C	H	N	Cl	F
2x[c]	Me	H	Me	CH_2Ph							
2y[c]	Et	H	Me	CH_2Ph							
71	Pr	H	Me	CH_2Ph	90—91 (E-DE)	$C_{23}H_{31}ClN_4O_2 \cdot 2C_2H_2O_4$[d] $\cdot 1/4H_2O$	52.56 (52.62)	5.81 (5.84)	9.10 (8.98)	5.76 (5.72)	
72	^{i}Pr	H	Me	CH_2Ph	100—103 (M-DE)	$C_{23}H_{31}ClN_4O_2 \cdot 2C_2H_2O_4$[d]	53.07 (52.81)	5.77 (5.95)	9.17 (9.19)	5.80 (5.90)	
73[c]	Me	H	Et	CH_2Ph							
74[c]	Et	H	Et	CH_2Ph							
75[e]	Me	H	Me	H	168—169 (E-DE)	$C_{14}H_{21}ClN_4O_2 \cdot 2C_4H_4O_4$[f]	48.49 (48.31)	5.36 (5.27)	10.28 (10.10)	6.51 (6.88)	
76[c]	Me	H	Me	Me							
77[c]	Et	H	Me	Me							
78[c]	Pr	H	Me	Me							
79[c]	^{i}Pr	H	Me	Me							
80	Me	Me	Me	Me	170—173 (IP-T)	$C_{16}H_{25}ClN_4O_2 \cdot 3/2C_4H_4O_4$[g] $\cdot 1/4H_2O$	50.87 (51.16)	6.11 (6.07)	10.79 (10.47)	6.82 (6.83)	
81	Me	H	Me	Et	123.5—124 (T)	$C_{16}H_{25}ClN_4O_2$	56.38 (56.26)	7.39 (7.46)	16.44 (16.18)	10.40 (10.49)	
82	Me	Me	Me	Et	173.5—175 (E)	$C_{17}H_{27}ClN_4O_2 \cdot 2C_2H_2O_4$[d] $\cdot H_2O$	45.61 (45.66)	6.02 (6.10)	10.13 (10.01)	6.41 (6.36)	
83[c]	Me	H	Et	Et							
84[c]	Et	H	Et	Et							
85	Me	Me	Et	Et	174—176 (E-IP)	$C_{18}H_{29}ClN_4O_2 \cdot 2C_2H_2O_4$[d] $\cdot 1/4H_2O$	47.74 (47.79)	6.10 (6.19)	10.12 (9.94)	6.41 (6.24)	
86	Me	H	Me	Pr	180—183 (E-IP)	$C_{17}H_{27}ClN_4O_2 \cdot 2C_2H_2O_4$[d] $\cdot 3/2H_2O \cdot 1/2$ ^{i}PrOH[h]	45.65 (45.93)	6.47 (6.08)	9.46 (9.07)	5.99 (6.13)	
87	Me	H	Et	Pr	114.5—116 (E-IP)	$C_{18}H_{29}ClN_4O_2 \cdot 2C_2H_2O_4$[d]	48.13 (47.85)	6.06 (6.10)	10.21 (10.00)	6.46 (6.46)	
88	Me	H	Me	^{i}Pr	Oil[i]						
89	Me	H	Et	^{i}Pr	Oil[i]						
90	Me	H	Me	^{c}Pr	119—120 (E-IP)	$C_{17}H_{25}ClN_4O_2$ $\cdot 3/2C_2H_2O_4$[d] $\cdot 1/10$ ^{i}PrOH[h]	49.36 (49.10)	5.88 (5.86)	11.34 (11.16)	7.18 (7.19)	
91	Me	H	Et	^{c}Pr	134—136 (E-IP)	$C_{18}H_{27}ClN_4O_2$ $\cdot 5/2C_2H_2O_4$[d] $\cdot 3/4$ ^{i}PrOH[h]	47.61 (47.95)	6.01 (6.08)	8.79 (8.96)	5.57 (5.84)	
92	Me	H	Et	Bu	119—120 (IP-T)	$C_{19}H_{31}ClN_4O_2 \cdot 2C_4H_4O_4$[g]	52.72 (52.74)	6.39 (6.33)	9.11 (8.95)	5.76 (5.94)	
93	Me	H	Me	CH_2CF_3	136.5—137 (T-E)	$C_{16}H_{22}ClF_3N_4O_2$	48.67 (48.67)	5.62 (5.58)	14.19 (14.01)	8.98 (9.22)	14.44 (14.20)
94	Me	H	Me	CH_2CHF_2	107—108 (T-E)	$C_{16}H_{23}ClF_2N_4O_2$	51.00 (51.15)	6.15 (6.15)	14.87 (14.69)	9.41 (9.67)	10.08 (9.69)
95	Me	Me	Me	$(CH_2)_2OMe$	72—73 (E-IP)	$C_{18}H_{29}ClN_4O_3$ $\cdot 9/4C_2H_2O_4$[d] $\cdot 1/4$ ^{i}PrOH[h]	46.35 (46.32)	5.94 (6.02)	9.30 (9.13)	5.88 (5.91)	
96[e]	Me	Me	Me	$(CH_2)_2OH$	90—92 (E-DE)	$C_{17}H_{27}ClN_4O_3 \cdot 2C_2H_2O_4$[d]	45.78 (45.73)	5.67 (5.75)	10.17 (10.18)	6.43 (6.46)	
97	Me	Me	Me	$(CH_2)_3OH$	172—174 (E-IP)	$C_{18}H_{29}ClN_4O_3 \cdot 9/4C_2H_2O_4$[d]	46.00 (45.76)	5.75 (5.88)	9.54 (9.31)	6.03 (6.00)	

a) Abbreviations for the solvents used are as follows: M=methanol, E=ethanol, T=toluene, IP=isopropanol, DE=diethyl ether. *b*) All compounds were analyzed for C, H, N, and halogen; analytical results were within±0.4% for the theoretical values. *c*) See ref. 20. *d*) Oxalic acid. *e*) See Experimental Section. *f*) Maleic acid. *g*) Fumaric acid. *h*) The presence of isopropanol was confirmed by ^{1}H-NMR spectra. *i*) The structure was confirmed by ^{1}H-NHR and MS spectra.

dopamine D_2 receptor compared with the parents **81** and **83**, respectively (61.0 nM and 48.4 nM *vs.* 127 nM and 216 nM, respectively). A similar result has been reported in the SARs study of the antipsychotic drug nemonapride (Fig. 1), which showed a very strong affinity for the dopamine D_2 receptor; *i.e.* the 5-chloro-2-methoxy-4-methylaminobenzamide showed a more potent affinity (1 order of magnitude) for the dopamine D_2 receptor than the corresponding 4-aminobenzamide.[30] Benzamides with a butyl group (**92**) and alkyl substituents having a fluoro (**93**, **94**), methoxy (**95**), and hydroxy (**96**, **97**) groups exhibited weak affinity for the dopamine D_2 receptor along with a potent 5-HT_3 receptor binding affinity. The presence of a large substituent with oxygen atom and fluorine had an unfavorable effect on the affinity for the

Table 2. Physical Data for 5-Chloro-2-alkoxy-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamides (**98**—**108**)



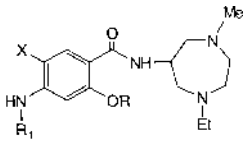
Compds.	R	R_1	R_2	mp, °C (Recryst solvent[a])	Formula[b]	Analysis (%) Calcd (Found)			
						C	H	N	C
98	Me	Et	H	180—182 (M-E)	$C_{18}H_{29}ClN_4O_2 \cdot 5/2C_2H_2O_4$[c]	46.51 (46.39)	5.77 (5.69)	9.43 (9.23)	5.97 (5.80)
99	Me	Me	Me	167.5—168.5 (E-IP)	$C_{18}H_{29}ClN_4O_2 \cdot 5/2C_2H_2O_4$[c]	46.51 (46.50)	5.77 (5.79)	9.43 (9.40)	5.97 (5.95)
100	Me	CHO	H	178—179 (M-IP)	$C_{17}H_{25}ClN_4O_3 \cdot 2C_2H_2O_4$[c] $\cdot 1/4H_2O$	45.58 (45.62)	5.37 (5.53)	10.12 (10.10)	6.41 (6.51)
101	Me	Ac	H	167—169 (E-IP)	$C_{18}H_{27}ClN_4O_3 \cdot 9/4C_2H_2O_4$[c] $\cdot 1/4$ EtOH[d]	46.27 (46.09)	5.57 (5.23)	9.39 (9.19)	5.94 (5.97)
102	Et	H	H	121—123 (T)	$C_{17}H_{27}ClN_4O_2 \cdot 1/4H_2O$	56.82 (57.06)	7.71 (7.60)	15.59 (15.61)	9.86 (9.86)
103	Et	Me	Me	149—151 (M-E)	$C_{19}H_{31}ClN_4O_2 \cdot 5/2C_2H_2O_4$[c] $\cdot 1/2H_2O$	46.72 (46.57)	6.04 (5.96)	9.08 (9.24)	5.75 (5.74)
104	^{i}Pr	H	H	111—114 (M-E)	$C_{18}H_{29}ClN_4O_2 \cdot 7/4C_2H_2O_4$[c] $\cdot 1/4H_2O$	48.63 (48.62)	6.26 (5.95)	10.55 (10.49)	6.68 (6.69)
105	^{i}Pr	Me	H	187—188 (E)	$C_{19}H_{31}ClN_4O_2 \cdot 2C_2H_2O_4$[c]	49.07 (48.95)	6.27 (6.25)	9.95 (9.68)	6.30 (6.02)
106	$CH_2CH{=}CH_2$	H	H	101—104 (M-E)	$C_{18}H_{27}ClN_4O_2 \cdot 5/2C_2H_2O_4$[c] $\cdot 1/2$EtOH[d]	46.87 (46.50)	5.74 (5.55)	9.11 (8.95)	5.76 (5.92)
107	CH_2Ph	H	H	161—164 (M-E)	$C_{22}H_{29}ClN_4O_2 \cdot 2C_2H_2O_4$[c]	52.31 (52.31)	5.57 (5.56)	9.38 (9.42)	5.94 (5.94)
108	Bu	H	H	95—97 (C-DE)	$C_{19}H_{31}ClN_4O_2$	59.59 (59.49)	8.16 (8.23)	14.63 (14.58)	9.26 (9.41)

a) Abbreviations for the solvents used are as follows: C=chloroform. See footnote *a* in Table 1. *b*, *c*) See footnote *b*, *c* in Table 1. *d*) The presence of ethanol was confirmed by ^{1}H-NMR spectra.

dopamine D_2 receptor. From the results above, benzamides **81**—**83**, **85**—**87**, **90**, and **91** with a moderate dopamine D_2 receptor binding affinity were selected and further *in vivo* biological assays involving inhibition of apomorphine-induced emesis in dogs at 1.0 mg/kg, *p.o.* were performed. The inhibition data for metoclopramide and domperidone was included for comparison. Benzamides **81** and **82** having 1-ethyl-4-methylhexahydro-1,4-diazepine ring showed a potent inhibition of apomorphine-induced emesis with ED_{50} values of 0.20 and 0.22 mg/kg, *p.o.*, respectively (Table 7). These ED_{50} values were *ca.* 2-fold stronger than the ED_{50} value of metoclopramide (0.45 mg/kg, *p.o.*). On the other hand, **83**, **85**—**87**, **90**, and **91** displayed weak inhibition of apomorphine-induced emesis compared with metoclopramide, although their affinity for the dopamine D_2 receptor was higher than that of metoclopramide. These compounds were, thus, considered to have low oral bioavailability. Therefore, the optimum substituents at the 1- and 4-positions in the hexahydro-1,4-diazepine ring were found to be ethyl and methyl groups, respectively.

Next, the influence of a substitution at the 4- and 2-positions in the benzoyl moiety of **81** was examined in detail, while keeping the 1-ethyl-4-methylhexahydro-1,4-diazepine ring constant (**98**—**108**). As mentioned above, the 4-methylaminobenzamide derivative **82** showed an increased affinity for the dopamine D_2 receptor with a maintained potent binding affinity for the 5-HT_3 receptor. Replacement of the methyl group of **82** by an ethyl group (yielding **98**) and further introduction of a methyl group into the 4-methylamino group of **82** (yielding **99** with 4-dimehylamino group) led to a decrease in the binding affinity for the dopamine D_2 receptor, although the affinity of **98** for the 5-HT_3 receptor was *ca.* 4-fold stronger than that of the parent **81**. The 4-dimethylaminobenzamide derivative **99**, on the other hand, showed a decrease in affinity for both the 5-HT_3 and the dopamine D_2 receptors. Introduction of a formyl group (giving **100**) weakened the affinity for the dopamine D_2 receptor, but maintained a strong 5-HT_3 receptor binding affinity. In contrast, the 4-acetylamino derivative **101** did not show any affinity for both receptors, although the reason for this was unclear. Replacement of the methoxy group at the 2-position of **81**, **82**, and **99** by an ethoxy (**102**, **103**), isopropoxy (**104**, **105**), allyloxy (**106**), benzyloxy (**107**), or butoxy (**108**) group tended to significantly decrease the affinity for the dopamine D_2 receptor. Thus, a small substituent, such as a methoxy group at this position, was found to be essential for recognition of the dopamine D_2 receptor. The 5-HT_3 receptor binding affinity of the compounds described above was potent, particularly that of the 2-isopropoxybenzamides **104** and **105** (0.46 nM and 0.75 nM, respectively) which had an affinity much stronger than that of ondansetron (1.26 nM). Thus, for both receptor binding assays, the optimum substituents at the 2- and 4-positions in the benzoyl moiety were found to be methoxy and methylamino groups, respectively.

Table 3. Physical Data for 2-Alkoxy-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamides (**109**—**119**)



Compds.	R	R_1	X	mp, °C (Recryst solvent[a)])	Formula[b)]	Analysis (%) Calcd (Found)					
						C	H	N	Cl (F)	Br (I)	S
109	Et	H	Br	127—129 (C-DE)	$C_{17}H_{27}BrN_4O_2$	51.13 (50.93)	6.82 (6.79)	14.03 (13.79)		20.01 (20.26)	
110	Me	Me	Br	144—144.5 (M-T)	$C_{17}H_{27}BrN_4O_2 \cdot 2C_4H_4O_4$[c)]	47.55 (47.56)	5.59 (5.60)	8.87 (8.88)		12.65 (12.53)	
111	Et	H	I	155—159 (M-E)	$C_{17}H_{27}IN_4O_2 \cdot 2C_2H_2O_4$[d)] $\cdot 1/4H_2O$	39.98 (39.95)	5.03 (4.94)	8.88 (8.85)		20.11 (20.08)	
112	Me	Me	I	162—162.5 (E-IP)	$C_{17}H_{27}IN_4O_2 \cdot 2C_2H_2O_4$[d)]	40.27 (40.54)	4.99 (5.03)	8.94 (8.86)		20.26 (19.87)	
113[e)]	Me	Me	F	165—166 (M-IP)	$C_{17}H_{27}FN_4O_2 \cdot 2C_4H_4O_4$[f)]	52.63 (52.41)	6.18 (6.10)	9.82 (9.95)	3.33 (3.52)		
114	Me	Me	NO_2	177—179 (E-IP)	$C_{17}H_{27}N_5O_4$	55.88 (55.77)	7.45 (7.58)	19.16 (19.20)			
115	Me	Me	CHO	140—141 (T-E)	$C_{18}H_{28}N_4O_3$	62.05 (62.08)	8.10 (8.03)	16.08 (16.01)			
116[e)]	Me	Me	CH_2OH	123—124 (T-E)	$C_{18}H_{30}N_4O_3 \cdot 1/4H_2O$	60.19 (60.93)	8.66 (8.61)	15.78 (15.70)			
117	Me	Me	SEt	175—176 (E-IP)	$C_{19}H_{32}N_4O_2S \cdot 5/2C_2H_2O_4$[d)]	47.60 (47.81)	6.16 (6.26)	9.25 (9.12)			5.29 (5.25)
118	Me	Me	SO_2Et	166—169 (E)	$C_{19}H_{32}N_4O_4S \cdot 5/2C_2H_2O_4$[d)]	45.21 (45.02)	5.85 (5.98)	9.79 (9.79)			5.03 (4.73)
119[e)]	Me	Me	SO_2NH_2	210—212 (E-DE)	$C_{17}H_{29}N_5O_4S$	51.11 (50.98)	7.32 (7.28)	17.53 (17.44)			8.03 (7.99)

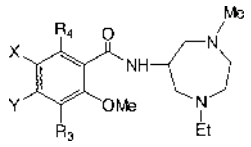
a) See footnote *a* in Table 1. *b*) All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% for the theoretical values. *c*) Fumaric acid. *d*) Oxalic acid. *e*) See Experimental Section. *f*) Maleic acid.

The influence of a substitution at the 5-position in the benzoyl moiety of **82** and **102** was next studied (**109**—**119**). Replacement of the chlorine atom of **102** and **82** by a bromine atom (giving **109** and **110**) caused a remarkable increase in affinity for both receptors. The 5-bromo-2-methoxy-4-methylaminobenzamide **110**, in particular, showed a potent affinity for the dopamine D_2 (35.5 nM) and the 5-HT_3 (2.54 nM) receptors. Replacement of the iodine atom in **102** and **82** (yielding **111** and **112**) resulted in an increase in the dopamine D_2 receptor binding affinity but no change in the 5-HT_3 receptor binding affinity. Introduction of fluoro, nitro, formyl, hydroxymethyl, ethylthio, ethylsulfonyl, and sulfamoyl groups at the 5-position (**113**—**119**) did not provide any improvements in affinity for both receptors, except for the 5-ethylthiobenzamide **117** (dopamine D_2 receptor binding affinity; 26.1 nM) and the 5-formylbenzamide **115** (5-HT_3 receptor binding affinity; 3.00 nM). From these results, the chlorine, bromine and iodine atoms were found to be optimal substituents at the 5-position in the benzoyl moiety.

The influence of several 2-methoxybenzamides and carboxamide derivatives (**120**—**130**) on the affinity for both the dopamine D_2 and the 5-HT_3 receptors was examined. The 5-iodo-2-methoxy (**120**), 3-bromo-2,6-dimethoxy (**121**), 3,5-dibromo-2,6-dimethoxy (**122**), 4-chloro-2-methoxy-5-nitro (**123**), 6-amino-2,3-dimethoxy (**124**), 5-bromo-3-chloro-6-hydroxy-2-methoxy (**125**), 5-ethylthio-2-methoxy (**126**), 5-ethylsulfonyl-2-methoxy (**127**), and 5-sulfamoyl-2-methoxy (**128**) benzamides, and the benzotriazole- (**129**) and the benzimidazole- (**130**) 5-carboxamides were examined. All the compounds showed weak affinity for both receptors except **128** which displayed a moderate affinity for the 5-HT_3 receptor (13.7 nM). From these results, the nitrogen atom at the 4-position, the halogeno atom at the 5-position, and the methoxy group at the 2-position in the benzoyl moiety were found to be essential for a potent affinity for both receptors. It is well-known that the pharmacophore for 5-HT_3 receptor antagonists consists of an aromatic ring, a carbonyl group, and a basic nitrogen, and that their location is crucial for the activity.[35)] Thus, it is convincing that a number of benzamides, regardless of the nature of the N^1,N^4-disubstituents on the hexahydro-1,4-diazepine ring and the benzoyl moiety, possess nanomolar affinity for the 5-HT_3 receptor and are essentially equipotent to previously described 5-HT_3 receptor antagonists such as ondansetron and granisetron. On the other hand, although no distinct SARs concerning the affinity of benzamides for the dopamine D_2 receptor were identified, 2-methoxy, 4-methylamino, and 5-bromo or iodo groups in the benzoyl moiety provided some improvement in the affinity for this receptor.

Finally, the binding affinity of the enantiomers of **81**, **82**, **110**, and **112** for both receptors was studied. The binding affinity for the dopamine D_2 receptor of the (*R*)-enantiomers of **81**, **82**, **110** [(*R*)-**81**, (*R*)-**82**, (*R*)-**110**] was *ca.* 2-fold higher than that of the corresponding racemates except the 5-

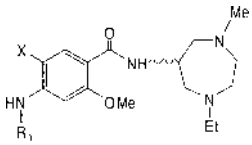
Table 4. Physical Data for *N*-(1-Ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamides (**120**—**130**)



Compds.	R_3	Y	X	R_4	mp, °C (Recryst solvent[a])	Formula[b]	Analysis (%) Calcd (Found)					
							C	H	N	Cl	Br (I)	S
120	H	H	I	H	83—84 (C-DE)	$C_{16}H_{24}IN_3O_2$	46.05 (46.06)	5.80 (5.66)	10.07 (9.87)		30.41 (30.34)	
121	Br	H	H	OMe	116—119 (M-E)	$C_{17}H_{26}BrN_3O_3 \cdot 5/2C_2H_2O_4$[c] $\cdot 1/2EtOH$[d]	42.60 (42.63)	5.29 (5.46)	6.48 (6.72)		12.32 (12.11)	
122	Br	H	Br	OMe	136—138 (T)	$C_{17}H_{25}Br_2N_3O_3$	42.61 (42.60)	5.26 (5.19)	8.77 (8.74)		33.35 (33.49)	
123	H	Cl	NO_2	H	91—92 (C-DE)	$C_{17}H_{25}ClN_4O_4$	51.82 (51.62)	6.25 (6.19)	15.11 (14.92)	9.56 (9.74)		
124[e]	OMe	H	H	NH_2	135—137 (M-E)	$C_{17}H_{28}N_4O_3 \cdot 7/4C_2H_2O_4$[c]	49.84 (49.59)	6.43 (6.43)	11.34 (11.52)			
125	Cl	H	Br	OH	127—129 (E)	$C_{16}H_{23}BrClN_4O_3$ $\cdot 3/2C_4H_4O_4$[f]	44.42 (44.33)	4.91 (4.97)	7.06 (7.10)	5.96 (6.08)	13.43 (13.43)	
126	H	H	SEt	H	114—116 (E-IP)	$C_{18}H_{29}N_3O_2S \cdot 2C_4H_4O_4$[g]	53.51 (53.78)	6.39 (6.45)	7.20 (7.37)			5.49 (5.61)
127	H	H	SO_2Et	H	150—151 (E-IP)	$C_{18}H_{29}N_3O_4S \cdot 5/2C_2H_2O_4$[c]	45.39 (45.55)	5.63 (5.89)	6.90 (6.73)			5.27 (5.29)
128	H	H	SO_2NH_2	H	168—169 (M-E)	$C_{16}H_{26}N_4O_4S \cdot 2C_4H_4O_4$[g]	51.13 (51.23)	7.13 (6.83)	14.91 (14.55)			8.53 (8.84)
129	–N=N–NH–		Cl	H	163—165 (AN)	$C_{16}H_{22}ClN_6O_2 \cdot 3/10H_2O$	51.62 (51.88)	6.39 (6.07)	22.58 (22.24)	9.52 (9.77)		
130	–N=C(Me)–NH–		Cl	H	181—182 (M-IP)	$C_{18}H_{26}ClN_5O_2$ $\cdot 2C_4H_4O_4$[g] $\cdot 1/10\ ^iPrOH$[h]	50.74 (50.82)	5.72 (5.56)	11.25 (10.96)	5.69 (5.53)		

a) Abbreviations for the solvents used are as follows: AN=acetonitrile. See footnote *a* in Table 1. *b*) See footnote *b* in Table 3. *c*) See footnote *c* in Table 1. *d*) The presence of ethanol was confirmed by the ^{1}H-NMR spectra. *e*) See Experimental Section. *f*) Fumaric acid. *g*) Maleic acid. *h*) The presence of isopropanol was confirmed by ^{1}H-NMR spectra.

Table 5. Physical Data for the Optically Active 2-Methoxy-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamides [(*R*)-**81**, **82**, **110**, **112** and (*S*)-**81**, **82**, **110**, **112**]



Compds.	R_1	X	mp, °C (Recryst solvent[a])	Formula[b]	$[\alpha]_D$ (MeOH) (°C, *c*)	Analysis (%) Calcd (Found)				
						C	H	N	Cl	Br (I)
(*R*)-**81**[c,d]	H	Cl	142—143 (T)	$C_{16}H_{25}ClN_4O_2$	−9.8° (27, 1.06)	56.38 (56.41)	7.39 (7.32)	16.44 (16.28)	10.40 (10.42)	
(*S*)-**81**[c,e]	H	Cl	142—143 (T)	$C_{16}H_{25}ClN_4O_2$	+9.5° (27, 1.00)	56.38 (56.42)	7.39 (7.51)	16.44 (16.18)	10.40 (10.55)	
(*R*)-**82**[d]	Me	Cl	161—161.5 (M-IP)	$C_{17}H_{27}ClN_4O_2 \cdot 2C_4H_4O_4$[f]	−3.6° (28, 1.04)	51.15 (51.20)	6.01 (6.02)	9.54 (9.47)	6.04 (6.02)	
(*S*)-**82**[e]	Me	Cl	178.5—179.5 (E-IP)	$C_{17}H_{27}ClN_4O_2 \cdot 5/2C_2H_2O_4$[g]	+4.3° (28, 1.04)	45.71 (45.98)	5.64 (5.81)	9.56 (9.77)	6.05 (6.27)	
(*R*)-**110**[d]	Me	Br	182—183 (E-IP)	$C_{17}H_{27}BrN_4O_2 \cdot 2C_2H_2O_4$[g] $\cdot 1/4\ ^iPrOH$[h]	−3.4° (25, 1.05)	43.95 (43.66)	5.60 (5.63)	9.43 (9.30)		13.44 (13.10)
(*S*)-**110**[e]	Me	Br	150—151 (M-E)	$C_{17}H_{27}BrN_4O_2 \cdot 2C_4H_4O_4$[f]	+3.2° (28, 1.61)	47.55 (47.59)	5.59 (5.64)	8.87 (8.76)		12.65 (12.64)
(*R*)-**112**[d]	Me	I	85—86 (E-DE)	$C_{17}H_{27}IN_4O_2 \cdot 2C_4H_4O_4$[f]	−2.5° (26, 1.06)	44.26 (44.28)	5.20 (5.29)	8.26 (8.16)		18.70 (18.70)
(*S*)-**112**[e]	Me	I	83—84 (M-IP)	$C_{17}H_{27}IN_4O_2 \cdot 2C_4H_4O_4$[f]	+2.5° (26, 1.13)	44.26 (44.54)	5.20 (5.40)	8.26 (8.26)		18.70 (18.45)

a, *b*) See footnote *a*, *b* in Table 1. *c*) The enantiomeric purity was confirmed to be >99% ee by HPLC analysis [column; CHIRALPAK AS (DAICEL Chemical Industries, Ltd.), 4.6×250 mm i.d., eluent; hexane/EtOH/Et_2NH=94/6/0.2, flow rate; 0.8 ml/min, column temperature; 25 °C, detection; 254 nm]. retention time: (*R*)-**81**; 24.4 min, (*S*)-**81**; 28.0 min. *d*) The absolute configuration of the amine moiety is *R*. *e*) The absolute configuration of the amine moiety is *S*. *f*) Maleic acid. *g*) Oxalic acid. *h*) The presence of isopropanol was confirmed by ^{1}H-NMR spectra.

Table 6. Dopamine D_2 and 5-HT_3 Receptors Binding Affinity for Benzamide and Carboxamide Derivatives

Compds.	Dopamine D_2 receptor binding affinity[a] IC_{50} (nM)	5-HT_3 receptor binding affinity[b] IC_{50} (nM)
2x	>1000	2.07
2y	>1000	0.30
71	>1000	2.35
72	>1000	>2.0
73	292	1.91
74	>1000	0.17
75	758	13.7
76	>1000	9.56
77	>1000	1.41
78	>1000	7.60
79	>1000	2.07
80	198	1.86
81	127	8.50
82	61.0	4.76
83	216	2.27
84	875	4.30
85	48.4	2.21
86	218	24.3
87	160	19.0
88	>1000	51.8
89	468	24.9
90	182	3.16
91	50.3	5.05
92	538	4.50
93	>1000	3.35
94	449	1.80
95	665	9.20
96	371	1.65
97	647	5.51
98	181	1.89
99	558	35.9
100	430	7.08
101	>1000	>100
102	747	5.66
103	>1000	14.6
104	>1000	0.46
105	>1000	0.75
106	>1000	4.75
107	>1000	2.38
108	>1000	4.53
109	492	1.63
110	35.5	2.54
111	539	5.33
112	17.5	5.14
113	186	11.4
114	88.4	11.0
115	245	3.00
116	>1000	>100
117	26.1	70.9
118	382	>100
119	725	>100
120	355	>100
121	>1000	>100
122	>1000	>100
123	>1000	>100
124	>1000	>100
125	>1000	>100
126	635	>100
127	>1000	>100
128	758	13.7
129	>1000	>100
130	>1000	66.3
(*R*)-**81**	86.9	11.8
(*S*)-**81**	517	7.00
(*R*)-**82**	34.6	2.86
(*S*)-**82**	320	1.49
(*R*)-**110**	18.8	3.40
(*S*)-**110**	133	16.7
(*R*)-**112**	30.9	8.70
(*S*)-**112**	71.9	2.80
Metoclopramide	483	308
Domperidone	15.1	>1000
Ondansetron	>1000	1.26

a) Determined in rat brain synaptic membrane using [^{3}H]spiperone. *b*) Determined in rat brain cortical membrane using [^{3}H]GR65630.

Table 7. Inhibition of Apomorphine-Induced Emesis in Dogs by **81**—**83**, **85**—**87**, **90**, **91**, **110**, (*R*)-**81**, (*R*)-**82**, (*R*)-**110**, and (*R*)-**112**

Compds.	Inhibition of apomorphine-induced emesis (1.0 mg/kg, *p.o.*) % [ED_{50}: mg/kg, *p.o.*]
81	100 [0.20]
(*R*)-**81**	87
82	100 [0.22]
(*R*)-**82**	100 [0.13]
83	52
85	49
86	25
87	14
90	40
91	52
110	56
(*R*)-**110**	79 [0.40]
(*R*)-**112**	90
Metoclopramide	100 [0.45]
Domperidone	100 [0.02]

iodobenzamide (*R*)-**112** which had an affinity for the dopamine D_2 receptor *ca.* 2-fold weaker than that of its racemate **112**. On the other hand, the affinity of all (*R*)-enantiomers for the 5-HT_3 receptor was approximately the same as that of each corresponding racemate. Although the (*S*)-enantiomers [(*S*)-**81**, (*S*)-**82**, (*S*)-**110**, (*S*)-**112**] exhibited weak affinity for the dopamine D_2 receptor, a strong 5-HT_3 receptor binding affinity was retained except (*S*)-**110**. Although there were marked differences in affinity for the dopamine D_2 receptor between the enantiomers examined, (*R*)-**110** showed the most potent affinity for both receptors (dopamine D_2 receptor; 18.8 nM, 5-HT_3 receptor; 3.40 nM). Moreover, each enantiomer's affinity for both receptors was slightly lower than the dopamine D_2 receptor affinity of domperidone and the 5-HT_3 receptor binding affinity of ondansetron, respectively, and was much stronger than the affinity of metoclopramide for both receptors (Table 6).

As for the inhibition of apomorphine-induced emesis in dogs, the results are presented in Table 7. (*R*)-**110** inhibited the emesis in dogs with an ED_{50} of 0.40 mg/kg, *p.o.* On the other hand, although (*R*)-**112**, at a dose of 1.0 mg/kg, *p.o.*, did not completely inhibit this emesis as compared with **82** (90% *vs.* 100% inhibition), it showed stronger inhibition than (*R*)-**110**. The inhibition percent caused by (*R*)-**81** and (*R*)-**82** at a dose of 1.0 mg/kg, *p.o.* was 87% and 100% (ED_{50}=0.13

mg/kg, *p.o.*), respectively. These results indicate that **82** and its (*R*)-enantiomer [(*R*)-**82**] have potent antagonistic activity for the dopamine D_2 receptor *in vivo* biological assay. Next, (*R*)-**82** was evaluated for its 5-HT_3 receptor antagonistic activity *in vivo* by measuring its ability to inhibit the von Bezold–Jarisch reflex induced 2-methyl-5-HT in rats[20]; the 5-HT_3 receptor antagonistic activity of (*R*)-**82**, **2x**, ondanstron, and metoclopramide was characterized by an IC_{50}=1.4, 0.86, 2.8, and 181 μg/kg, i.v., respectively. From the results above it was, thus, concluded that (*R*)-**82** exhibits a strong affinity for the dopamine D_2 and the 5-HT_3 receptors and a potent antagonistic activity *in vivo* biological assay for the both receptors. In addition, (*R*)-**82**, as well as **2x** and **2y**, showed a weak binding affinity for the serotonin 5-HT_4 receptor (>1000 nM)[33] and did not display any serotonin 5-HT_4 receptor agonistic activity even at 10^{-5} M in isolated guinea pig ileum preparations.

Benzamide derivatives with good affinity for the serotonin 5-HT_4 and 5-HT_3 or the serotonin 5-HT_4 and the dopamine D_2 receptors are well-known thus far.[36] However, there has been no report on benzamides having a potent affinity for both the dopamine D_2 and the 5-HT_3 receptors. In this study, we have shown that benzamide **82**, a novel dopamine D_2 and 5-HT_3 receptors dual antagonist, is structurally related to the 1-benzyl-4-methyl and 1,4-dimethylhexahydro-1,4-diazepinylbenzamides **2x** and **76**, which have been described as potent and selective 5-HT_3 receptor antagonists. Moreover, the fact that (*R*)-**82**, (*S*)-**82**, and **2x** had marked structural similarities but different pharmacological profiles, was intriguing. Although the hexahydro-1,4-diazepine ring of **82** is to some extent conformationally restricted compared with the (diethylamino)ethyl side chain of metoclopramide, it still has some degree of conformational freedom. It is speculated that the 1-ethyl-4-methylhexahydro-1,4-diazepine ring of **82** adopts a markedly favorable conformation in the binding site of the dopamine D_2 and the 5-HT_3 receptors where one or two basic nitrogen atoms and the ethyl and/or methyl groups occupy the correct orientation to block both receptors. The role of the substituents in the hexahydro-1,4-diazepine ring in the recognition of these compounds by the dopamine D_2 and the 5-HT_3 receptors and structural analysis of the differences in the pharmacological profile between each enantiomer are in progress.

In summary, replacement of the 1-benzyl group in the hexahydro-1,4-diazepine ring of **2x**, a potent and selective 5-HT_3 receptor antagonist, by an ethyl group resulted in a remarkable increase in affinity for the dopamine D_2 receptor, while keeping a potent 5-HT_3 receptor binding affinity. After modification of the 4-amino-5-chloro-2-methoxybenzoyl moiety of the 1-ethyl-4-methylhexahydro-1,4-diazepinylbenzamide **81**, the corresponding 4-methylaminobenzamide **82** was found to have strong antagonistic activity, both *in vitro* (binding affinity for the dopamine D_2 and the 5-HT_3 receptors) and *in vivo* (inhibition of apomorphine-induced emesis and the von Bezold–Jarisch reflex induced 2-methyl-5-HT) tests. Optical resolution of **82** brought about a drastic change in the binding affinity for the dopamine D_2 receptor, particularly, the (*R*)-enantiomer [(*R*)-**82**] exhibited an affinity for the dopamine D_2 receptor *ca.* 2-fold that of **82**, while (*S*)-**82** was found to have a weaker affinity for this receptor. On the other hand, the binding affinity for the 5-HT_3 receptor of each enantiomer [(*R*)-**82**, (*S*)-**82**] was *ca.* 2 times more potent than that of the racemate **82**. Although **82** and its enantiomers showed a significant difference in the binding affinity for the dopamine D_2 and the 5-HT_3 receptors, (*R*)-**82**, which constitute a novel amine moiety of the 4-amino-5-chloro-2-methoxybenzamide family, exhibited a potent dual antagonistic activity for the dopamine D_2 and the 5-HT_3 receptors and is expected to be a broad antiemetic agent.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Shimadzu FTIR-8200PC spectrometer with KBr disks unless otherwise stated. Electron ionization and atmospheric pressure chemical ionization mass spectra were obtained on a JEOL JMS D-300 and Hitachi M-1000 spectrometer, respectively. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) spectrometer using dilute solution in $CDCl_3$ unless otherwise stated. Chemical shifts were expressed as δ (ppm) value from tetramethylsilane as an internal standard and coupling constants (*J*) are given in Hz. Optical rotations were measured at 589 nm with a Jasco P-1020 digital polarimeter. Organic extracts were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure. Flash chromatography was carried out on 60 μm mesh silica gel (Fuji Silysia FL60D).

The following known 6-aminohexahydro-1,4-diazepines and benzoic acids were prepared according to the cited literature: 6-amino-1-benzyl-4-methylhexahydro-1,4-diazepine[23,37] (**8m**), 6-amino-1,4-dimethylhexahydro-1,4-diazepine[23] (**8n**), 6-amino-1,4-diethylhexahydro-1,4-diazepine[20] (**8o**), 4-amino-5-chloro-2-ethoxybenzoic acid[28,29] (**23b**), 4-amino-5-chloro-2-propoxybenzoic acid[20] (**23g**), 4-amino-5-chloro-2-(isopropoxy)benzoic acid[20] (**23c**), 5-iodo-2-methoxybenzoic acid[38] (**54**), 3-bromo-2,6-dimethoxybenzoic acid[39] (**55**), 3,5-dibromo-2,6-dimethoxybenzoic acid[39] (**56**), 4-chloro-2-methoxy-5-nitrobenzoic acid[40] (**57**), 3-bromo-5-chloro-2-hydroxy-6-methoxybenzoic acid[41] (**58**), 5-ethylthio-2-methoxybenzoic acid[42] (**59**), 5-ethylsulfonyl-2-methoxybenzoic acid[43] (**60**), and 2-methoxy-5-sulfamoylbenzoic acid[44] (**61**). Methyl 4-acetylamino-5-chloro-2-methoxybenzoate (**22a**), 4-amino-5-chloro-2-methoxybenzoic acid (**23a**), 2,4,5-trifluorobenzoic acid (**63**), and 4-chloro-2-methoxybenzoic acid (**67**) are commercially available.

***N*-Ethyl-*N'*-methylethylenediamine (5a)** $SOCl_2$ (267 g, 2.2 mol) was added dropwise to a solution of 2-(ethylamino)ethanol (**3m**, 100 g, 1.1 mol) in $CHCl_3$ (845 ml) kept at *ca.* 0 °C. The mixture was heated to reflux for 6 h and cooled to room temperature. The reaction mixture was poured into Et_2O (*ca.* 1000 ml), and the whole was stirred at room temperature for 15 h. In order to decompose the excess of $SOCl_2$, excess EtOH was added slowly to the solution at *ca.* 0 °C. The resulting powder was collected by filtration, washed with Et_2O, and dried to give 150 g (93%) of *N*-(2-chloroethyl)-*N*-ethylamine hydrochloride (**4m**), which was used in the next step without further purification. **4m** (100 g, 0.69 mol) was added portionwise to a mixture of 40% aqueous $MeNH_2$ (700 ml), EtOH (150 ml), and H_2O (600 ml) kept at 10 °C. The mixture was heated at 50 °C for 16 h and cooled to room temperature. After addition of a large amount of solid K_2CO_3, the upper layer was separated. EtOH was evaporated under atmospheric pressure, and the residue was dissolved in CH_2Cl_2. The organic solution was dried over anhydrous Na_2SO_4 and evaporated at *ca.* 35 °C to leave a pale brown oil, which was distilled to give 50.0 g (71%) of **5a** as a colorless oil, bp 30—31 °C/18 mmHg. ^{1}H-NMR δ: 1.12 (3H, t, *J*=7), 2.32 (2H, br s, NH×2), 2.43 (3H, s), 2.66 (2H, q, *J*=7), 2.69—2.76 (4H, m, NCH_2CH_2N). MS: *m/z*, 102 (M^+).

***N*-Ethyl-*N'*-propylethylenediamine (5e)** In a similar manner to that described above, crude **5e** was obtained by the reaction of **4m** (24.0 g, 0.17 mol) with $PrNH_2$ (150 ml, 1.8 mol) in EtOH (20 ml)–H_2O (100 ml) mixture in 35% yield as a pale yellow oil. Crude **5e** was used in the next step without distillation. ^{1}H-NMR δ: 0.92 (3H, t, *J*=7.5), 1.09 (3H, t, *J*=7.5), 1.48 (2H, sex, *J*=7.5), 1.63 (2H, br s), 2.55 (2H, q, *J*=7.5), 2.65 (2H, m), 2.98 (4H, m). MS: *m/z*, 130 (M^+).

***N*-Cyclopropyl-*N'*-ethylethylenediamine (5g)** In a similar manner to that described above, **5g** was obtained by the reaction of **4m** (50.0 g, 0.35 mol) with cyclopropylamine (240 ml, 3.5 mol) in EtOH (400 ml) in 43% yield as a colorless oil, bp 38—40 °C/*ca.* 20 mmHg. ^{1}H-NMR δ: 0.25—0.5 (4H, m), 1.11 (3H, t, *J*=7), 2.0 (2H, br s), 2.1 (1H, m), 2.65 (2H, q, *J*=7), 2.65—2.85 (4H, m). MS: *m/z*, 128 (M^+).

***N*-Methyl-*N'*-propylethylenediamine (5b)** $SOCl_2$ (60 ml, 0.82 mol)

was added dropwise to a solution of 2-(propylamino)ethanol (**3n**, 41.0 g, 0.40 mol) in $CHCl_3$ (300 ml) kept at *ca.* 0 °C. The mixture was heated to reflux for 6 h and cooled to room temperature. The reaction mixture was concentrated to dryness. A mixture of ^iPrOH and Et_2O was added carefully to the solid residue at *ca.* 0 °C. The resulting powder was collected by filtration, washed with Et_2O, and dried to give 20.3 g (32%) of *N*-(2-chloroethyl)-*N*-propylamine hydrochloride (**4n**) as a white powder, which was used in the next step without further purification. In a similar manner to that described above, crude **5b** was obtained from the reaction of **4n** (20.0 g, 0.13 mol) with 40% aqueous $MeNH_2$ (130 ml) in EtOH (120 ml) in 45% yield as a colorless oil and used in the next step without distillation. ^{1}H-NMR δ: 0.92 (3H, t, J=7), 1.48 (2H, sex, J=7), 1.80 (2H, br s), 2.44 (3H, s), 2.58 (2H, q, J=7), 2.71 (4H, m). MS: *m*/*z*, 116 (M^+).

***N*-Ethyl-*N′*-isopropylethylenediamine (5f)** $SOCl_2$ (182 g, 1.5 mol) was added dropwise to a solution of 2-(isopropylamino)ethanol (**3o**, 75.0 g, 0.73 mol) in $CHCl_3$ (550 ml) kept at *ca.* 0 °C. The mixture was heated to reflux for 6 h and cooled to room temperature. After addition of Et_2O, the mixture was stood overnight at room temperature. The resulting powder was collected by filtration, washed with Et_2O, and dried to give 114 g (99%) of *N*-(2-chloroethyl)-*N*-isopropylamine hydrochloride (**4o**) as a hygroscopic brown powder, which was used in the next step without further purification. In a similar manner to that described above, **5f** was obtained from the reaction of **4o** (57.0 g, 0.36 mol) with 70% aqueous $EtNH_2$ (340 ml) in EtOH (350 ml) in 26% yield as a colorless oil, bp 41—43 °C/5 mmHg. ^{1}H-NMR δ: 1.06 (6H, d, J=6.5), 1.11 (3H, t, J=7), 1.37 (2H, br s), 2.62 (2H, q, J=7), 2.72 (4H, m), 2.79 (1H, hep, J=6.5). MS: *m*/*z*, 130 (M^+).

***N*-Isopropyl-*N′*-methylethylenediamine (5c)** In a similar manner to that described above, **5c** was obtained by the reaction of **4o** (57.0 g, 0.37 mol) with 40% aqueous $MeNH_2$ (360 ml) in EtOH (350 ml) in 29% yield as a colorless oil. ^{1}H-NMR δ: 1.17 (6H, d, J=6.5), 2.34 (2H, br s), 2.43 (3H, s), 2.66—2.74 (4H, m), 2.79 (1H, hep, J=6.5). MS: *m*/*z*, 116 (M^+).

***N*-Cyclopropyl-*N′*-methylethylenediamine (5d)** $SOCl_2$ (332.5 g, 2.8 mol) was added dropwise to a solution of 2-(methylamino)ethanol (**3l**, 100 g, 1.3 mol) in $CHCl_3$ (1000 ml) kept at *ca.* 0 °C. The mixture was heated to reflux for 6 h and cooled to room temperature. The reaction mixture was poured into Et_2O (*ca.* 1500 ml) and stirred at room temperature for 15 h. In order to decompose the excess of $SOCl_2$, a large amount of EtOH was added carefully to the solution at *ca.* 0 °C. The resulting powder was collected by filtration, washed with Et_2O, and dried to give 165 g (95%) of *N*-(2-chloroethyl)-*N*-methylamine hydrochloride (**4l**), which was used in the next step without further purification. **4l** (53.0 g, 0.41 mol) was added portionwise to a mixture of cyclopropylamine (282 ml, 4.1 mol) and EtOH (470 ml) kept below 10 °C. The mixture was heated at 50 °C for 16 h and cooled to room temperature. After addition of a large amount of solid K_2CO_3, the upper layer was separated. EtOH was evaporated under atmospheric pressure, and the resultant residue was dissolved in CH_2Cl_2. The organic solution was dried over anhydrous Na_2SO_4 and evaporated at *ca.* 35 °C to leave a pale brown oil, which was distilled to give 25.4 g (55%) of **5d** as a colorless oil, bp 35—38 °C/*ca.* 20 mmHg. ^{1}H-NMR δ: 0.25—0.5 (4H, m), 2.0 (2H, br s), 2.1 (1H, m), 2.42 (3H, s), 2.64—2.85 (4H, m). MS: *m*/*z*, 114 (M^+).

6-Amino-1-ethyl-4-methylhexahydro-1,4-diazepine (8a) Our previously described procedure[22] was adopted. 1) To a solution of 2-benzyloxycarbonylaminopropenal[23] (**6**, 3.8 g, 19 mmol) in MeOH (50 ml) was added **5a** (3.8 g, 37 mmol) at *ca.* 5 °C. After being stirred for 3 h, $NaBH_4$ (2.8 g, 74 mmol) was added portionwise. The mixture was stirred at room temperature for 16 h and then concentrated to dryness. The residue was taken into $CHCl_3$ and H_2O. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 2.5 g (46% from **6**) of 6-benzyloxycarbonylamino-1-ethyl-4-methylhexahydro-1,4-diazepine (**7a**) as an oil. ^{1}H-NMR δ: 1.10 (3H, t, J=7), 2.23 (3H, s), 2.48—3.10 (10H, m), 3.97 (1H, m, 6-H), 5.10 (2H, s), 6.12 (1H, m, NH), 7.25—7.42 (5H, m). MS: *m*/*z*, 292 (MH^+), 113, 91. IR (neat) ν cm^{-1}: 3060, 3030, 1725, 1680, 1630. 2) A mixture of **7a** (2.1 g, 7.2 mmol) and 25% HBr in AcOH (15 ml) was stirred at room temperature for 1 h. The reaction mixture was concentrated, and the residue was dissolved in a small volume of H_2O. The aqueous solution was washed with Et_2O and basified with 48% aqueous NaOH. After addition of solid K_2CO_3, the mixture was extracted with $CHCl_3$. The extract was concentrated to dryness to give 1.0 g (88%) of **8a** as an oil. ^{1}H-NMR δ: 1.04 (3H, t, J=7), 1.46 (2H, br s), 2.37 (3H, s), 2.34—2.9 (10H, m), 3.05 (1H, m, 6-H). MS: *m*/*z*, 158 (MH^+).

6-Amino-1-methyl-4-propylhexahydro-1,4-diazepine (8b) In a similar manner to that described above, **8b** was prepared from **5b** and **6** *via* 6-benzyloxycarbonylamino-1-methyl-4-propylhexahydro-1,4-diazepine (**7b**) in 32% overall yield. **7b**; ^{1}H-NMR δ: 0.87 (3H, t, J=7), 1.49 (2H, sex, J=7), 2.24—3.06 (10H, m), 2.42 (3H, s), 3.93 (1H, m, 6-H), 5.10 (2H, s), 6.07 (1H, br, NH), 7.25—7.46 (5H, m). MS: *m*/*z*, 306 (MH^+), 91.

6-Amino-1-cyclopropyl-4-methylhexahydro-1,4-diazepine (8d) In a similar manner to that described above, **8d** was prepared from **5d** and **6** *via* 6-benzyloxycarbonylamino-1-cylcopropyl-4-methylhexahydro-1,4-diazepine (**7d**) in 5% overall yield. **7d**; ^{1}H-NMR δ: 0.2—0.5 (4H, m), 1.9 (1H, m), 2.43 (3H, s), 2.35—3.1 (8H, m), 3.82 (1H, m), 5.10 (2H, s), 5.73 (1H, br), 7.2—7.4 (5H, m). MS: *m*/*z*, 304 (MH^+), 91.

6-Amino-1-ethyl-4-propylhexahydro-1,4-diazepine (8e) In a similar manner to that described above, **8e** was prepared from **5e** and **6** *via* 6-benzyloxycarbonylamino-1-ethyl-4-propylhexahydro-1,4-diazepine (**7e**) in 30% overall yield. **7e**; ^{1}H-NMR δ: 0.86 (3H, t, J=7), 1.02 (3H, t, J=7), 1.30—1.56 (2H, m), 2.35—2.93 (12H, m), 3.85 (1H, m), 5.09 (2H, s), 5.90 (1H, br), 7.23—7.43 (5H, m). MS: *m*/*z*, 320 (MH^+), 91.

6-Amino-1-cyclopropyl-4-ethylhexahydro-1,4-diazepine (8g) In a similar manner to that described above, **8g** was prepared from **5g** and **6** *via* 6-benzyloxycarbonylamino-1-cyclopropyl-4-ethylhexahydro-1,4-diazepine (**7g**) in 5% overall yield. **7g**; ^{1}H-NMR δ: 0.2—0.6 (4H, m), 1.02 (3H, t, J=7), 1.92 (1H, m), 2.35—3.1 (10H, m), 4.05 (1H, m, 6-H), 5.10 (2H, s), 5.67 (1H, br), 7.25—7.4 (5H, m). MS: *m*/*z*, 318 (MH^+), 91.

6-Amino-1-ethyl-4-isopropylhexahydro-1,4-diazepine (8f) 1) **5f** (6.0 g, 46 mmol) was added to a solution of trishydroxymethylnitromethane (7.4 g, 49 mmol) and $NaHCO_3$ (2.5 g) in H_2O (50 ml) at room temperature. The mixture was stirred at 40—50 °C for 2 h and cooled to *ca.* 10 °C. The resulting oil was extracted with CH_2Cl_2. The extract was washed with brine and evaporated at *ca.* 25 °C. The oily residue containing 1-ethyl-6-hydroxymethyl-4-isopropyl-6-nitrohexahydro-1,4-diazepine (**9f**) was dissolved in MeOH, and potassium *tert*-butoxide (5.8 g, 52 mmol) was added portionwise below 50 °C. The mixture was stirred at the same temperature for 0.5 h and concentrated to dryness at 40—50 °C. After slow addition of a solution of $NH_2OH \cdot HCl$ (95%, 3.6 g, 49 mmol) in H_2O (24 ml), the mixture was extracted with CH_2Cl_2. The extract was washed with brine and evaporated. The oily residue was chromatographed on silica gel with AcOEt to give 4.3 g (43% from **5f**) of 1-ethyl-4-isopropyl-6-nitrohexahydro-1,4-diazepine (**10f**) as a pale yellow oil. ^{1}H-NMR δ: 0.97, 1.00 (each 3H, d, J=6.3), 1.04 (3H, t, J=7.0), 2.54—2.74 (6H, m), 2.91 (1H, hep, J=6.3), 3.14 (1H, dd, J=6.0, 10.4), 3.16 (1H, dd, J=5.8, 14.0), 3.27 (1H, dd, J=6.5, 14.0), 3.34 (1H, dd, J=6.0, 14.0), 4.54 (1H, quin, J=6.5, 6-H). MS: *m*/*z*, 216 (MH^+). 2) A solution of **10f** (4.3 g, 20 mmol) in EtOH (20 ml) was hydrogenated over Raney Ni (*ca.* 1 g) at room temperature for 3 h. The catalyst was removed by Celite filtration, and the filtrate was concentrated. The residue was dissolved in $CHCl_3$, and the solution was dried over anhydrous $MgSO_4$. The solvent was evaporated to give 3.2 g (86%) of **8f** as a pale yellow oil, which was used in the next step without further purification.

6-Amino-1-isopropyl-4-methylhexahydro-1,4-diazepine (8c) In a similar manner to that described above, **8c** was prepared from trishydroxymethylnitromethane and **5c** *via* **9c** and 1-isopropyl-4-methyl-6-nitrohexahydro-1,4-diazepine (**10c**) in 7% overall yield. **10c** (pale yellow oil); ^{1}H-NMR δ: 0.97, 1.02 (each 3H, d, J=6.3), 2.44 (3H, s), 2.5—2.75 (4H, m), 2.90 (1H, hep, J=6.3), 2.99 (1H, dd, J=6.0, 12.0), 3.12 (1H, dd, J=5.5, 8.5), 3.20 (1H, dd, J=6.0, 6.0), 3.30 (1H, dd, J=6.0, 13.5), 4.58 (1H, quin, J=6, 6-H). MS: *m*/*z*, 202 (MH^+).

6-Amino-1-butyl-4-ethylhexahydro-1,4-diazepine (8h) 1) The method of Olofson *et al.*[45,46] was applied. A solution of 6-acetylamino-1-benzyl-4-ethylhexahydro-1,4-diazepine[20] (**11**, 20.1 g, 73 mmol) and 1-chloroethyl chloroformate (12.6 g, 88 mmol) in 1,2-dichloroethane (200 ml) was heated to reflux for 1 h and cooled to room temperature. After evaporation of the solvent, the residue was dissolved in MeOH (200 ml). The solution was heated to reflux for 1 h and cooled to room temperature. The solvent was evaporated, and the residue was dissolved in a small volume of H_2O. The aqueous solution was basified with 48% aqueous NaOH. After addition of solid K_2CO_3, the mixture was extracted with $CHCl_3$. The extract was concentrated to dryness, and the oily residue was chromatographed on silica gel with $CHCl_3$/MeOH=15/1 to give 12.3 g (91%) of 6-acetylamino-1-ethylhexahydro-1,4-diazepine (**12**) as an oil. ^{1}H-NMR δ: 1.05 (3H, t, J=7.0), 2.00 (3H, s), 2.40 (1H, br s), 2.45—3.2 (10H, m), 4.09 (1H, m), 6.80 (1H, br). MS: *m*/*z*, 186 (MH^+). 2) **12** (2.0 g, 11 mmol) and $NaBH_4$ (2.1 g, 56 mmol) were added successively to a solution of butyric acid (15.7 g, 0.18 mol) in anhydrous toluene (27 ml) below 20 °C. The mixture was heated to reflux for 3 h and cooled to room temperature. The reaction mixture was washed with 2 N aqueous NaOH and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel with

$CHCl_3$/MeOH=10/1 to give 2.0 g (77%) of 6-acetylamino-1-butyl-4-ethylhexahydro-1,4-diazepine (**13**) as a pale yellow oil. ^{1}H-NMR δ: 0.96 (3H, t, J=7.0), 1.10 (3H, t, J=7.0), 1.18—1.55 (4H, m), 2.00 (3H, s), 2.5—3.1 (12H, m), 4.27 (1H, m), 7.82 (1H, br d, J=8.0). MS: m/z, 242 (MH^+). 3) A solution of **13** (2.0 g, 8.3 mmol) in 10% aqueous HCl (20 ml) was heated to reflux for 4 h and cooled to room temperature. The reaction mixture was washed with Et_2O and basified with 48% aqueous NaOH. After addition of solid K_2CO_3, the mixture was extracted with $CHCl_3$. The extract was evaporated to give 1.2 g (73%) of **8h** as a pale yellow oil. ^{1}H-NMR δ: 0.9 (3H, t, J=7.0), 1.05 (3H, t, J=7.0), 1.2—1.55 (4H, m), 1.75 (2H, s), 2.4—2.9 (12H, m), 3.03 (1H, m). MS: m/z, 200 (MH^+).

6-Amino-1-methyl-4-(2,2,2-trifluoroethyl)hexahydro-1,4-diazepine (8i) 1) A solution of **14**[22] (24.3 g, 75 mmol) in EtOH (400 ml)–AcOH (40 ml) mixture was hydrogenated over 10% Pd/C (3.5 g) at *ca.* 50 °C under atmospheric pressure. After no further change in the pressure of H_2 was observed, the solution was cooled to room temperature. The catalyst was filtered through Celite, the filtrate was concentrated, and the oily residue was dissolved in $CHCl_3$. The solution was washed successively with 10% aqueous $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated to give 16.3 g (93%) of *N*-(1-methylhexahydro-1,4-diazepin-6-yl)benzamide (**15**) as a colorless oil. ^{1}H-NMR δ: 2.47 (3H, s), 2.3—3.2 (9H, m), 4.34 (1H, m, 6-H), 7.2—7.6 (4H, m), 7.75—7.95 (2H, m). MS: m/z, 234 (MH^+). 2) $NaBH_4$ (2.1 g, 56 mmol) and **15** (2.2 g, 9.4 mmol) were added successively to a solution of CF_3CO_2H (21.1 g, 0.19 mol) in toluene (125 ml) below 20 °C. The mixture was heated to reflux for 3 h and cooled to room temperature. The reaction mixture was then washed with 2 N aqueous NaOH and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 2.0 g (67%) of *N*-[1-methyl-4-(2,2,2-trifluoroethyl)hexahydro-1,4-diazepin-6-yl]benzamide (**16i**) as a pale yellow oil. ^{1}H-NMR δ: 2.42 (3H, s), 2.4—3.5 (8H, m), 3.19 (2H, q, J=9.5, CH_2CF_3), 4.33 (1H, m, 6-H), 7.35—7.57 (4H, m), 7.77—7.87 (2H, m). MS: m/z, 316 (MH^+). 3) A solution of **16i** (1.5 g, 4.8 mmol) in 35% aqueous HCl (10 ml) was heated to reflux for 8 h and cooled to room temperature. The reaction mixture was washed with Et_2O and basified with 48% aqueous NaOH. After addition of solid K_2CO_3, the mixture was extracted with $CHCl_3$. The extract was evaporated to give 1.0 g (quantitative yield) of **8i** as a pale yellow oil.

6-Amino-1-(2,2-difluoroethyl)-4-methylhexahydro-1,4-diazepine (8j) In a similar manner to that described above, the reaction of **15** with CF_2HCO_2H and $NaBH_4$ gave *N*-[1-(2,2-difluoroethyl)-4-methylhexahydro-1,4-diazepin-6-yl]benzamide (**16j**) in 63% yield. ^{1}H-NMR δ: 2.44 (3H, s), 2.4—3.55 (10H, m), 4.35 (1H, m, 6-H), 5.81 (1H, tt, J=5.0, 56, CHF_2), 7.3—7.7 (4H, m), 7.75—7.9 (2H, m). MS: m/z, 298 (MH^+). In a similar manner to that described above, **16j** was converted into the corresponding amine **8j** in quantitative yield as an oil.

6-Amino-1-(2-methoxyethyl)-4-methylhexahydro-1,4-diazepine (8k) In a similar manner to that described above, the reaction of **15** with 2-methoxyacetic acid and $NaBH_4$ gave *N*-[1-(2-methoxyethyl)-4-methylhexahydro-1,4-diazepin-6-yl]benzamide (**16k**) in 60% yield. ^{1}H-NMR δ: 2.42 (3H, s), 2.5—3.1 (10H, m), 3.22 (3H, s), 3.36—3.52 (2H, m), 4.31 (1H, m, 6-H), 7.35—7.55 (3H, m), 7.7—8.0 (3H, m). MS: m/z, 292 (MH^+). In a similar manner to that described above, **16k** was converted into the corresponding amine **8k** in quantitative yield as an oil.

6-Amino-1-(3-hydroxypropyl)-4-methylhexahydro-1,4-diazepine (8l) 1) Acrolein (90%, 3.6 g, 58 mmol) was added to a solution of **15** (5.0 g, 21 mmol) and Et_3N (6.5 g, 64 mmol) in MeOH (50 ml) at *ca.* 0 °C. The mixture was stirred at this temperature for 2 h. Then, $NaBH_4$ (4.9 g, 0.13 mol) was added portionwise at *ca.* 0 °C, and the mixture was stirred at this temperature for 1 h and at room temperature overnight. After evaporation of the solvent, the residue was taken into H_2O and $CHCl_3$. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the oily residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 4.2 g (67%) of *N*-[1-(3-hydroxypropyl)-4-methylhexahydro-1,4-diazepin-6-yl]benzamide (**16l**) as a pale yellow oil. ^{1}H-NMR δ: 1.5—1.9 (2H, m), 2.40 (3H, s), 2.45—3.1 (10H, m), 3.85 (2H, t, J=7), 4.40 (1H, m), 5.48 (1H, br s), 7.35—7.55 (3H, m), 7.63 (1H, d, J=8), 7.85—7.95 (2H, m). MS: m/z, 292 (MH^+). 2) A mixture of **16l** (2.0 g, 6.9 mmol), Ac_2O (1.4 g, 14 mmol), pyridine (2 drops), and $CHCl_3$ (20 ml) was heated to reflux for 5 h and cooled to room temperature. The reaction mixture was washed successively with H_2O and brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the oily residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 1.4 g (61%) of *N*-[1-(3-acetoxypropyl)-4-methylhexahydro-1,4-diazepin-6-yl]benzamide (**17**) as a pale yellow oil. ^{1}H-NMR δ: 1.79 (2H, quin, J=7), 2.05 (3H, s), 2.55 (3H, s), 2.64 (2H, t, J=7), 2.5—3.02 (8H, m), 4.12 (2H, t, J=7), 4.50 (1H, m), 7.38—7.55 (3H, m), 7.85—8.1 (3H, m). MS: m/z, 334 (MH^+). 3) A solution of **17** (1.2 g, 3.6 mmol) in 35% aqueous HCl (10 ml) was heated to reflux for 8 h and cooled to room temperature. Following work-up similar to that described above, **8l** (0.65 g, 96% yield) was obtained as a pale yellow oil. ^{1}H-NMR δ: 1.68 (2H, quin, J=7), 2.37 (3H, s), 2.35—3.0 (12H, m), 3.15 (1H, m), 3.82 (2H, t, J=7). MS: m/z, 188 (MH^+).

(*R*)- and (*S*)-6-Amino-1-ethyl-4-methylhexahydro-1,4-diazepines [(*R*)- and (*S*)-8a] 1) A solution of (*R*)-*N*-[1-methyl-4-(3-methyl)benzylhexahydro-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide[25] [(*R*)-**18**, >99.5% ee, 28.8 g, 76 mmol] in EtOH (500 ml) was hydrogenated over 10% Pd/C (4.3 g) at room temperature under H_2 atmosphere. After no further change in the pressure of H_2 was observed, the catalyst was filtered through Celite. The filtrate was concentrated to dryness to give 20.9 g (quantitative yield) of (*R*)-*N*-(1-methylhexahydro-1,4-diazepin-6-yl)-1*H*-indazole-3-carboxamide [(*R*)-**19**] as a colorless oil. ^{1}H-NMR δ: 2.25 (1H, br s), 2.50 (3H, s), 2.6 (1H, m), 2.8—3.25 (6H, m), 3.45 (1H, d, J=7.5, 14.0), 4.62 (1H, m), 7.2—7.45 (4H, m), 8.42 (1H, d, J=9.0), 8.95 (1H, m). MS: m/z, 274 (MH^+). An analytical sample of (*R*)-**19** was obtained by crystallization of its hydrochloride from EtOH, mp 241—245 °C. *Anal.* Calcd for $C_{14}H_{19}N_5O\cdot 2HCl\cdot 1/4H_2O$: C, 47.94; H, 6.18; Cl, 20.22; N, 19.97. Found: C, 47.74; H, 6.22; Cl, 20.44; N, 19.88. $[\alpha]_D^{29}$ −3.0° (c=1.0, MeOH). 2) 80% Acetaldehyde (8.4 g, 0.15 mol) was added to a solution of (*R*)-**19** (20.9 g) and Et_3N (16.0 g, 0.16 mol) in MeOH (500 ml) under ice-cooling. The mixture was stirred at the same temperature for 2 h. Then, $NaBH_4$ (3.0 g, 79 mmol) was added portionwise to the reaction mixture at this temperature. The whole was warmed to room temperature, stirred for 16 h, and concentrated to dryness. The residue was taken into H_2O and $CHCl_3$, and the organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel with $CHCl_3$/MeOH=9/1 to give 22.9 g (quantitative yield) of (*R*)-*N*-[1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide [(*R*)-**20**] as a colorless oil. ^{1}H-NMR δ: 1.06 (3H, t, J=7.5), 2.52 (3H, s), 2.5—3.6 (10H, m), 4.61 (1H, m), 7.2—7.45 (3H, m), 8.44 (1H, d, J=8.0), 9.05 (1H, d, J=10), 13.20 (1H, s). MS: m/z, 302 (MH^+). 3) A solution of (*R*)-**20** (21.2 g, 70 mmol) in 35% aqueous HCl (70 ml) was heated to reflux for 8 h and cooled to *ca.* 5 °C. The resulting solid of 1*H*-indazole-3-carboxylic acid was filtered off and the filtrate was basified with 48% aqueous NaOH. After addition of solid K_2CO_3, the mixture was extracted with $CHCl_3$. The extract was evaporated to give *ca.* 11 g (quantitative yield) of (*R*)-**8a** as a pale yellow oil, which was used in the next step without further purification. This compound was identical to the sample obtained in an alternative preparation,[47] on the basis of ^{1}H-NMR, MS, and the retention time of chiral HPLC comparison.

In a similar manner to that described for the conversion of (*R*)-**18** to (*R*)-**8a**, (*S*)-**8a** was prepared from (*S*)-**18**,[25] the hydrochloride of (*S*)-**19**; mp 241—245 °C (EtOH). *Anal.* Calcd for $C_{14}H_{19}N_5O\cdot 2HCl\cdot 1/4H_2O$: C, 47.94; H, 6.18; Cl, 20.22; N, 19.97. Found: C, 48.14; H, 6.29; Cl, 19.95; N, 19.92. $[\alpha]_D^{29}$ +3.3° (c=1.0, MeOH).

2-Allyloxy-4-amino-5-chlorobenzoic Acid (23d) 1) A mixture of methyl 4-acetylamino-5-chloro-2-hydoxybenzoate[27] (**21**, 4.9 g, 20 mmol), K_2CO_3 (4.2 g, 30 mmol), KI (0.5 g), tetrabutylammonium bromide (0.3 g, 0.93 mmol), allyl bromide (2.4 g, 20 mmol), and methyl ethyl ketone (100 ml) was heated to reflux for 9 h and cooled to room temperature. The solvent was evaporated, and the residue was dissolved in H_2O and $CHCl_3$. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the oily residue was solidified on standing at room temperature. The solid was triturated with EtOH/Et_2O to give 1.9 g (33%) of methyl 4-acetylamino-2-allyloxy-5-chlorobenzoate (**22d**) as a colorless crystal, mp 110.5—112 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.16 (3H, s), 3.78 (3H, s), 4.58 (2H, d, J=3), 5.27 (1H, d, J=11), 5.52 (1H, d, J=16), 6.02 (1H, m), 7.76 (1H, s), 7.83 (1H, s), 9.57 (1H, s). *Anal.* Calcd for $C_{13}H_{14}ClNO_4$: C, 55.04; H, 4.97; Cl, 12.50; N, 4.94. Found: C, 54.78; H, 5.04; Cl, 12.43; N, 4.83. MS: m/z, 284 (MH^+). IR cm^{-1}: 3323, 1728, 1693, 1678, 1601, 1583, 1404, 1236. 2) A mixture of **22d** (1.8 g, 6.3 mmol), NaOH (2.0 g, 50 mmol), MeOH (10 ml), and H_2O (15 ml) was heated to reflux for 4 h and cooled to *ca.* 5 °C. After acidification with 35% aqueous HCl, the precipitates were collected by filtration and recrystallized from EtOH/hexane to give 1.0 g (69%) of **23d** as a colorless crystal, mp 142—143 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.50 (2H, s), 5.25 (1H, d, J=10.6), 5.51 (1H, d, J=17.2), 5.95—6.1 (3H, m), 6.42 (1H, s), 7.60 (1H, s), 11.90 (1H, s). *Anal.* Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; Cl, 15.57; N, 6.15. Found: C, 52.71; H, 4.47; Cl, 15.54; N, 6.07. MS: m/z, 228 (MH^+). IR cm^{-1}: 3474, 3327, 3254, 1705, 1622, 1443.

4-Amino-2-benzyloxy-5-chlorobenzoic Acid (23e) In a similar manner to that described above, 1) **22e** (colorless crystal) was prepared from **21** and

benzyl bromide in 31% yield, mp 125—126 °C (triturated with EtOH/Et_2O). ^{1}H-NMR (DMSO-d_6) δ: 2.15 (3H, s), 3.79 (3H, s), 5.15 (2H, s), 7.27—7.47, 7.47—7.60 (5H, m), 7.78 (1H, s), 7.92 (1H, s), 9.58 (1H, s). *Anal.* Calcd for $C_{17}H_{16}ClNO_4$: C, 61.18; H, 4.83; Cl, 10.62; N, 4.20. Found: C, 60.97; H, 4.88; Cl, 10.84; N, 4.12. MS: *m/z*, 334 (MH^+). IR cm^{-1}: 3352, 3333, 1707, 1684, 1605, 1580, 1411, 1238. 2) **23e** (colorless crystal) was obtained from **22e** in 80% yield, mp 190—191 °C. ^{1}H-NMR (DMSO-d_6) δ: 5.09 (2H, s), 6.08 (2H, s), 6.53 (1H, s), 7.25—7.45, 7.45—7.6 (5H, m), 7.62 (1H, s), 11.94 (1H, s). *Anal.* Calcd for $C_{14}H_{12}ClNO_3 \cdot 1/4H_2O$: C, 59.58; H, 4.46; Cl, 12.56; N, 4.96. Found: C, 59.78; H, 4.35; Cl, 12.48; N, 4.95. MS: *m/z*, 278 (MH^+). IR cm^{-1}: 3470, 3323, 3285, 1701, 1626, 1593, 1441, 1400, 1229.

4-Amino-2-butoxy-5-chlorobenzoic Acid (23f) In a similar manner to that described above, 1) **22f** (colorless fine needle) was prepared from **21** and BuI in 43% yield, mp 105.5—107 °C (EtOH/hexane). ^{1}H-NMR δ: 0.98 (3H, t, *J*=7), 1.42—1.63 (2H, m), 1.74—1.89 (2H, m), 2.27 (3H, s), 3.78 (3H, s), 4.07 (2H, t, *J*=6), 7.75 (1H, br s), 7.88 (1H, s), 8.27 (1H, s). *Anal.* Calcd for $C_{14}H_{18}ClNO_4$: C, 56.10; H, 6.05; Cl, 11.83; N, 4.67. Found: C, 55.85; H, 6.04; Cl, 11.70; N, 4.66. MS: *m/z*, 300 (MH^+). IR cm^{-1}: 3283, 1699, 1676, 1574, 1412, 1248. 2) **23f** (colorless fine needle) was obtained from **22f** in 94% yield, mp 124.5—125 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, *J*=7.4), 1.38—1.54 (2H, m), 1.62—1.74 (2H, m), 3.92 (2H, t, *J*=6.4), 6.03 (2H, s), 6.44 (1H, s), 7.57 (1H, s), 11.77 (1H, br s). *Anal.* Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; Cl, 14.55; N, 5.75. Found: C, 53.86; H, 5.72; Cl, 14.53; N, 5.70. MS: *m/z*, 244 (MH^+). IR cm^{-1}: 3497, 3381, 3267, 1724, 1620, 1591, 1441, 1410, 1230.

5-Chloro-2-isopropoxy-4-methylaminobenzoic Acid (25) 1) NaH (60% dispersion in mineral oil, 5.9 g, 0.15 mol) was added portionwise to a mixture of methyl 4-acetylamino-5-chloro-2-isopropoxybenzoate[20] (**22c**, 10.3 g, 36 mmol), MeI (30.6 g, 0.22 mol), and anhydrous THF (60 ml) at *ca.* 5 °C. The reaction mixture was stirred at room temperature for 16 h and concentrated to dryness. After careful addition of H_2O, the precipitates were collected by filtration, washed with H_2O, and dried to give 8.1 g (75%) of methyl 4-(*N*-acetyl-*N*-methyl)amino-5-chloro-2-isopropoxybenzoate (**24**) as a colorless crystal, mp 91—92.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (6H, d, *J*=6.1), 1.85 (3H, s), 3.19 (3H, s), 3.91 (3H, s), 4.55 (1H, hep, *J*=6.1), 6.88 (1H, s), 7.88 (1H, s). *Anal.* Calcd for $C_{14}H_{18}ClNO_4$: C, 56.10; H, 6.05; Cl, 11.83; N, 4.67. Found: C, 56.14; H, 6.11; Cl, 11.85; N, 4.55. MS: *m/z*, 300 (MH^+). IR cm^{-1}: 1715, 1666, 1599, 1244, 1105. 2) A mixture of **24** (4.5 g, 15 mmol) and 20% aqueous NaOH (60 ml) was heated to reflux for 15 h and cooled to *ca.* 5 °C. After acidification with 10% aqueous HCl, the precipitates were collected by filtration and recrystallized from MeOH to give 3.5 g (96%) of 25 as a colorless crystal, mp 154—155 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (6H, d, *J*=6.1), 2.82 (3H, d, *J*=4.8, NMe), 4.71 (1H, hep, *J*=6.1), 6.19 (1H, q, *J*=4.8, NH), 6.21 (1H, s), 7.52 (1H, s), 11.73 (1H, br s, CO_2H). *Anal.* Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; Cl, 14.55; N, 5.75. Found: C, 53.97; H, 5.84; Cl, 14.41; N, 5.72. MS: *m/z*, 243 (M^+). IR cm^{-1}: 3396, 1713, 1607, 1454, 1389.

5-Chloro-4-ethylamino-2-methoxybenzoic Acid (27) 1) Methyl 4-acetylamino-5-chloro-2-methoxybenzoate (**22a**, 10.0 g, 39 mmol) was added portionwise to a suspension of NaH (60% dispersion in mineral oil, 4.7 g, 0.12 mol) in anhydrous tetrahydrofuran (THF) (75 ml) under ice-cooling. The mixture was warmed to room temperature and stirred for 1 h. After the mixture was recooled to *ca.* 5 °C, EtI (31 ml, 0.39 mol) was added, and the whole was stirred at room temperature overnight. The reaction mixture was poured carefully into cold H_2O, and the volatiles were evaporated. The aqueous solution was washed with $CHCl_3$, acidified with 35% aqueous HCl, and extracted with $CHCl_3$. The extract was washed with brine and concentrated to dryness to give *ca.* 10 g of 4-(*N*-acetyl-*N*-ethyl)amino-5-chloro-2-methoxybenzoic acid (**26**) as a pale yellow amorphous solid, which was used in the next step without further purification. ^{1}H-NMR (DMSO-d_6) δ: 1.02 (3H, t, *J*=7.1), 3.11 (3H, s), 3.46 (1H, dq, *J*=7.1, 13.6), 3.77 (1H, dq, *J*=7.1, 13.6), 3.85 (3H, s), 7.26 (1H, s), 7.78 (1H, s), 13.09 (1H, br s). IR cm^{-1}: 1717, 1647, 1600, 1227. MS: *m/z*, 272 (MH^+). 2) In a similar manner to that described above, **27** was obtained from **26** in 63% yield from **22a**. An analytical sample of **27** was obtained by recrystallization from acetone/hexane, mp 128—130 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (3H, t, *J*=7.5), 3.28 (2H, q, *J*=7.5), 3.83 (3H, s), 6.00 (1H, br), 6.27 (1H, s), 7.64 (1H, s), 11.98 (1H, br s). *Anal.* Calcd for $C_{10}H_{12}ClNO_3$: C, 52.30; H, 5.27; Cl, 15.44; N, 6.10. Found: C, 52.11; H, 5.27; Cl, 15.21; N, 5.93. MS: *m/z*, 230 (MH^+). IR cm^{-1}: 3427, 3281, 1707, 1606, 1425, 1323.

4-Acetylamino-5-chloro-2-methoxybenzoic Acid (28) A suspension of **22a** (50.0 g, 0.19 mol) and NaOH (9.0 g, 0.23 mol) in a mixture of MeOH (80 ml) and H_2O (150 ml) was heated at 60 °C for 1 h and cooled to room temperature. After evaporation of MeOH, the resulting aqueous solution was acidified with 35% aqueous HCl. The precipitates were collected by filtration and dissolved in MeOH. The solution was concentrated, and the crystalline precipitates were collected by filtration and dried to give 39.6 g (84%) of **28** as a colorless crystal, mp 210—213 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.15 (3H, s), 3.77 (3H, s), 7.71 (1H, s), 7.76 (1H, s), 9.55 (1H, s). *Anal.* Calcd for $C_{10}H_{10}ClNO_4$: C, 49.30; H, 4.14; Cl, 14.55; N, 5.75. Found: C, 49.27; H, 4.22; Cl, 14.43; N, 5.66. MS: *m/z*, 244 (MH^+). IR cm^{-1}: 3369, 3260, 1720, 1693, 1604, 1582, 1522, 1450, 1408, 1337, 1240.

5-Chloro-4-dimethylamino-2-ethoxybenzoic Acid (29b) A mixture of 4-amino-5-chloro-2-ethoxybenzoic acid[28] (**23b**, 2.6 g, 12 mmol), HCHO (37% solution in H_2O, 8 ml, 0.11 mol), $NaBH_3CN$ (95%, 1.9 g, 27 mmol), and MeCN (40 ml) was stirred at room temperature for 6 h. After addition of HCHO (37% solution in H_2O, 4 ml, 54 mmol) and $NaBH_3CN$ (95%, 1.0 g, 14 mmol), the mixture was restirred at room temperature for 16 h. The solvent was evaporated, and the residue was acidified with 10% aqueous HCl. The precipitates were collected by filtration and recrystallized from EtOH to give 1.7 g (58%) of **29b** as a white crystal, mp 144—145 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, *J*=7.0), 2.83 (6H, s), 4.12 (2H, q, *J*=7.0), 6.66 (1H, s), 7.64 (1H, s), 12.29 (1H, br s). *Anal.* Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; Cl, 14.55; N, 5.75. Found: C, 54.00; H, 5.81; Cl, 14.62; N, 5.57. MS: *m/z*, 244 (MH^+). IR cm^{-1}: 3294, 1717, 1605, 1406, 1238.

5-Chloro-4-dimethylamino-2-methoxybenzoic Acid (29a) In a similar manner to that described above, **29a** (colorless crystal) was prepared from 4-amino-5-chloro-2-methoxybenzoic acid (**23a**) in 55% yield, mp 150—151.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.85 (6H, s), 3.83 (3H, s), 6.67 (1H, s), 7.65 (1H, s), 12.39 (1H, br s). *Anal.* Calcd for $C_{10}H_{12}ClNO_3$: C, 52.30; H, 5.27; Cl, 15.44; N, 6.10. Found: C, 52.36; H, 5.26; Cl, 15.36; N, 5.95. MS: *m/z*, 230 (MH^+). IR cm^{-1}: 1686, 1597, 1244.

5-Chloro-4-formylamino-2-methoxybenzoic Acid (30) A mixture of Ac_2O (55.7 g, 0.55 mol) and HCO_2H (99%, 100.6 g, 2.2 mol) was heated at 50 °C for 1 h. After addition of **23a** (11.0 g, 55 mmol), the whole was heated at 65 °C for 2 h and cooled to room temperature. The reaction mixture was poured into cold H_2O, and the precipitates were collected by filtration, washed with H_2O, and dried to give 10.6 g (85%) of **30** as a gray powder, mp 207—208 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.79 (3H, s), 7.75 (1H, s), 8.15 (1H, s), 8.44 (1H, s), 10.08 (1H, s), 12.76 (1H, s). *Anal.* Calcd for $C_9H_8ClNO_4$: C, 47.08; H, 3.51; Cl, 15.44; N, 6.10. Found: C, 46.99; H, 3.53; Cl, 15.41; N, 6.00. MS: *m/z*, 230 (MH^+). IR cm^{-1}: 3323, 3275, 1717, 1678, 1609, 1583, 1518, 1447, 1418, 1271.

4-Amino-5-bromo-2-ethoxybenzoic Acid (33a) 1) A solution of methyl 4-acetylamino-2-ethoxybenzoate[28,29] (**31**, 10.0 g, 42 mmol) and NBS (8.2 g, 46 mmol) in *N*,*N*-dimethylformamide (DMF) (60 ml) was heated at 80 °C for 3.5 h and cooled to room temperature. After addition of H_2O (100 ml), the precipitates were collected by filtration, washed with H_2O, and dried to give 12.5 g (94%) of methyl 4-acetylamino-5-bromo-2-ethoxybenzoate (**32a**) as a white fine needle, mp 172—173 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.31 (3H, t, *J*=7), 2.13 (3H, s), 3.76 (3H, s), 4.04 (2H, q, *J*=7), 7.64 (1H, s), 7.86 (1H, s), 9.44 (1H, s). *Anal.* Calcd for $C_{12}H_{14}BrNO_4$: C, 45.59; H, 4.46; Br, 25.27; N, 4.43. Found: C, 45.57; H, 4.48; Br, 25.38; N, 4.43. MS: *m/z*, 315 (M^+). IR cm^{-1}: 3231, 2988, 1690, 1665, 1572, 1408, 1389, 1252. 2) A mixture of **32a** (4.1 g, 13 mmol), NaOH (3.5 g, 88 mmol), MeOH (12 ml), and H_2O (16 ml) was heated to reflux for 4 h and cooled to *ca.* 5 °C. The reaction mixture was acidified with 25% aqueous H_2SO_4, and the precipitates were collected by filtration and recrystallized from MeOH to afford 3.3 g (98%) of **33a** as a colorless crystal, mp 179—181 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, *J*=7.0), 3.98 (2H, q, *J*=7.0), 5.99 (2H, br s, NH_2), 6.44 (1H, s), 7.73 (1H, s), 11.79 (1H, br s, CO_2H). *Anal.* Calcd for $C_9H_{10}BrNO_3$: C, 41.56; H, 3.88; Br, 30.72; N, 5.39. Found: C, 41.20; H, 3.87; Br, 30.50; N, 5.23. MS: *m/z*, 259 (M^+). IR cm^{-1}: 3489, 3327, 1699, 1628, 1585, 1447, 1402.

4-Amino-2-ethoxy-5-iodobenzoic Acid (33b) 1) A solution of **31** (5.0 g, 21 mmol) and ICl (3.8 g, 23 mmol) in DMF (25 ml) was stirred at room temperature for 0.5 h, heated at 80 °C for 2 h, and cooled to room temperature. After addition of H_2O (100 ml), the precipitates were collected by filtration and recrystallized from acetone to give 3.6 g (47%) of methyl 4-acetylamino-2-ethoxy-5-iodobenzoate (**32b**) as a colorless fine needle, mp 188—189 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.32 (3H, t, *J*=7), 2.10 (3H, s), 3.77 (3H, s), 4.04 (2H, q, *J*=7), 7.42 (1H, s), 8.06 (1H, s), 9.36 (1H, s). *Anal.* Calcd for $C_{12}H_{14}INO_4$: C, 39.69; H, 3.89; I, 34.95; N, 3.86. Found: C, 39.88; H, 3.93; I, 34.83; N, 3.67. MS: *m/z*, 363 (M^+). IR cm^{-1}: 3221, 2984, 1684, 1665, 1566, 1406, 1387, 1252. 2) In a similar manner to that described above, **32b** was hydrolyzed to give **33b** as a colorless crystal in 91% yield, mp 190—193 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.32 (3H, t, *J*=7.0), 3.98 (2H, q, *J*=7.0), 5.87 (2H, br s, NH_2), 6.42 (1H, s), 7.93 (1H, s), 11.75 (1H, br s).

Anal. Calcd for $C_9H_{10}INO_3$: C, 35.20; H, 3.28; I, 41.33; N, 4.56. Found: C, 35.18; H, 3.32; I, 41.20; N, 4.40. MS: *m/z*, 307 (M^+). IR cm^{-1}: 3468, 3314, 1703, 1622, 1583, 1435, 1400.

2-Methoxy-4-[*N*-methyl-*N*-(*p*-toluenesulfonyl)]aminobenzoic Acid (35) A mixture of 4-(*p*-toluenesulfonyl)aminosalicylic acid[30] (**34**, 250 g, 0.81 mol), acetone (1700 ml), and KOH (239 g, 4.3 mol) was stirred at room temperature for 20 min. Me_2SO_4 (339 g, 2.7 mol) was added dropwise to the mixture at a rate that maintained boiling. The whole was heated to reflux for 2 h and cooled to room temperature. After evaporation of the solvent, the residue was dissolved in H_2O and washed with AcOEt. The aqueous solution was acidified with 35% aqueous HCl, and the precipitates were collected by filtration, washed with H_2O, and dried to give 183 g (67%) of **35**. An analytic sample of **35** was obtained by recrystallization from acetone as a colorless prism, mp 136—137 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.48 (3H, s), 2.17 (3H, s), 3.72 (3H, s), 6.73 (1H, dd, J=2.0, 8.5), 6.86 (1H, d, J=2.0), 7.35—7.52 (4H, m), 7.59 (1H, d, J=8.5), 12.50 (1H, s, CO_2H). *Anal.* Calcd for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18; S, 9.56. Found: C, 57.04; H, 5.10; N, 4.16; S, 9.52. MS: *m/z*, 336 (MH^+). IR cm^{-1}: 3287, 1736, 1607, 1578, 1421, 1350.

5-Bromo-2-methoxy-4-methylaminobenzoic Acid (37a) 1) A mixture of **35** (2.8 g, 8.4 mmol), *N*-bromosuccinimide (NBS) (1.65 g, 9.3 mmol), and DMF (50 ml) was heated at 80 °C for 4 h and cooled to room temperature. After addition of H_2O, the precipitates were collected by filtration, washed successively with H_2O and Et_2O, and dried to give 3.4 g (98%) of 5-bromo-2-methoxy-4-[*N*-methyl-*N*-(*p*-toluenesulfonyl)]aminobenzoic acid (**36a**). An analytic sample of **36a** was obtained by recrystallization from acetone, mp 229—231 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.42 (3H, s), 3.10 (3H, s), 3.60 (3H, s), 6.54 (1H, s), 7.48 (2H, d, J=8.0), 7.67 (2H, d, J=8.0), 7.87 (1H, s), 13.10 (1H, s). *Anal.* Calcd for $C_{16}H_{16}BrNO_5S$: C, 46.39; H, 3.89; Br, 19.29; N, 3.38; S, 7.74. Found: C, 46.03; H, 3.85; Br, 19.62; N, 3.39; S, 7.68. MS: *m/z*, 414 (MH^+). IR cm^{-1}: 1688, 1342, 1153. 2) A mixture of **36a** (5.0 g, 12 mmol) and concentrated H_2SO_4 (30 ml) was stirred for 1.5 h under ice-cooling. The reaction mixture was poured into cold H_2O, and the resulting precipitates were collected by filtration, washed successively with H_2O and Et_2O, and dried to give 2.9 g (92%) of **37a**, mp 176—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.03 (3H, s), 3.93 (3H, s), 6.04 (1H, br), 6.17 (1H, s), 7.77 (1H, s), 11.60 (1H, s). *Anal.* Calcd for $C_9H_{10}BrNO_3$: C, 41.56; H, 3.88; Br, 30.72; N, 5.39. Found: C, 41.43; H, 3.88; Br, 30.36; N, 5.23. MS: *m/z*, 260 (MH^+). IR cm^{-1}: 3410, 1668, 1597, 1551, 1474, 1391, 1348, 1265, 1250, 1221.

5-Chloro-2-methoxy-4-methylaminobenzoic Acid (37b) In a similar manner to that described above, **37b** was obtained from 5-chloro-2-methoxy-4-[*N*-methyl-*N*-(*p*-toluenesulfonyl)]aminobenzoic acid (**36b**), which was prepared from **35** using *N*-chlorosuccinimide (NCS). **36b**; mp 210.5—212.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.42 (3H, s), 3.01 (3H, s), 3.62 (3H, s), 6.62 (1H, s), 7.47 (2H, d, J=8.0), 7.67 (2H, d, J=8.0), 7.72 (1H, s), 13.13 (1H, s). *Anal.* Calcd for $C_{16}H_{16}ClNO_5S$: C, 51.96; H, 4.43; Cl, 9.72; N, 3.62; S, 8.67. Found: C, 51.66; H, 4.43; Cl, 9.72; N, 3.62; S, 8.53. MS: *m/z*, 370 (MH^+). IR cm^{-1}: 1690, 1344, 1153. **37b**; mp 186—187 °C (EtOH, lit.[30] mp 188—189 °C). ^{1}H-NMR (DMSO-d_6) δ: 2.84 (3H, d, J=5.0, NMe), 3.83 (3H, s), 6.19 (1H, s), 6.23 (1H, br, J=5.0, NH), 7.61 (1H, s), 11.84 (1H, s). *Anal.* Calcd for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; Cl, 16.44; N, 6.50. Found: C, 50.04; H, 4.66; Cl, 16.38; N, 6.43. MS: *m/z*, 216 (MH^+). IR cm^{-1}: 3422, 1666, 1601, 1553, 1252, 1219.

2-Methoxy-4-methylamino-5-nitrobenzoic Acid (37d) In a similar manner to that described above, 2-methoxy-4-[*N*-methyl-*N*-(*p*-toluenesulfonyl)]amino-5-nitrobenzoic acid (**36d**) was prepared from **35** using fuming HNO_3 and concentrated H_2SO_4. **36d** was treated with concentrated H_2SO_4 to give **37d**. **36d**; mp 184—185 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.42 (3H, s), 3.03 (3H, s), 3.68 (3H, s), 6.60 (1H, s), 7.48 (2H, d, J=8.0), 7.53 (2H, d, J=8.0), 8.27 (1H, s), 13.39 (1H, s). *Anal.* Calcd for $C_{16}H_{16}N_2O_7S$: C, 50.52; H, 4.24; N, 7.36; S, 8.43. Found: C, 50.62; H, 4.26; N, 7.58; S, 8.40. MS: *m/z*, 381 (MH^+). IR cm^{-1}: 1690, 1611, 1531, 1441, 1352, 1271, 1171. **37d**; mp 280—283 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.03 (3H, d, J=5.0, NMe), 3.94 (3H, s), 6.28 (1H, s), 8.58 (1H, br, J=5.0, NH), 8.59 (1H, s), 12.50 (1H, br s). *Anal.* Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.64; H, 4.43; N, 12.34. MS: *m/z*, 227 (MH^+). IR cm^{-1}: 3371, 1682, 1620, 1572, 1514, 1248.

5-Iodo-2-methoxy-4-methylaminobenzoic Acid (37c) 1) A mixture of methyl 2-methoxy-4-methylaminobenzoate[30] (**38**, 4.0 g, 21 mmol), Ac_2O (10 ml, 0.11 mol), and Et_3N (1 ml) was stirred at room temperature for 15 h. The reaction mixture was diluted with H_2O, and then extracted with AcOEt. The extract was washed with brine and concentrated to dryness. The residue was chromatographed on silica gel with AcOEt to give 4.7 g (97%) of methyl 4-(*N*-acetyl-*N*-methyl)amino-2-methoxybenzoate (**39**) as a colorless oil, which was used in the next step without further purification. ^{1}H-NMR δ: 1.96 (3H, s), 3.28 (3H, s), 3.92 (6H, s), 6.81 (1H, d, J=2.0), 6.83 (1H, dd, J=2.0, 8.0), 7.84 (1H, d, J=8.0). IR cm^{-1}: 1728, 1661, 1603. MS: *m/z*, 238 (MH^+). 2) ICl (6.4 g, 39 mmol) was added to a solution of **39** (4.7 g, 20 mmol) in DMF (20 ml) under ice-cooling. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was poured into cold H_2O, and the precipitates were collected by filtration, washed with H_2O, and dried to give 6.8 g (94%) of methyl 4-(*N*-acetyl-*N*-methyl)amino-5-iodo-2-methoxybenzoate (**40**) as a pale yellow powder. An analytical sample of **40** was obtained by recrystallization from AcOEt, mp 162—163 °C. ^{1}H-NMR δ: 1.83 (3H, s), 3.28 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 6.89 (1H, s), 8.27 (1H, s). *Anal.* Calcd for $C_{12}H_{14}INO_4$: C, 39.69; H, 3.89; I, 34.95; N, 3.86. Found: C, 39.39; H, 3.79; I, 34.83; N, 3.78. MS; *m/z*, 236 ($M-I^+$). IR cm^{-1}: 1722, 1637, 1601. 3) A mixture of **40** (3.8 g, 10 mmol) and 20% aqueous NaOH (40 ml) was heated to reflux for 15 h and cooled to *ca.* 5 °C. After acidification with 35% aqueous HCl, the precipitates were collected by filtration, washed with H_2O, and dried to give 3.0 g (93%) of **37c**, mp 187—188 °C (dec., MeOH/EtOH). ^{1}H-NMR (DMSO-d_6) δ: 2.84 (3H, d, J=5.0, NMe), 3.83 (3H, s), 5.68 (1H, br, J=5.0, NH), 6.08 (1H, s), 8.00 (1H, s). *Anal.* Calcd for $C_9H_{10}INO_3$: C, 35.20; H, 3.28; I, 41.33; N, 4.56. Found: C, 35.36; H, 3.26; I, 41.15; N, 4.50. MS: *m/z*, 308 (MH^+). IR cm^{-1}: 3395, 1668, 1589, 1545, 1258, 1225.

5-Formyl-2-methoxy-4-methylaminobenzoic Acid (43) 1) A mixture of **38** (4.0 g, 21 mmol), benzyl bromide (5.3 g, 31 mmol), K_2CO_3 (5.7 g, 41 mmol), and DMF (40 ml) was heated to reflux for 4 h and cooled to room temperature. After evaporation of the solvent, the residue was dissolved in H_2O and $CHCl_3$. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was chromatographed on silica gel with AcOEt to afford 5.85 g of a white solid. The solid was recrystallized from AcOEt/hexane to give 3.8 g (65%) of methyl 4-(*N*-benzyl-*N*-methyl)amino-2-methoxybezoate (**41**), mp 71.5—72.5 °C. ^{1}H-NMR δ: 3.12 (3H, s), 3.82 (6H, s), 4.61 (2H, s), 6.21 (1H, d, J=2.5), 6.32 (1H, dd, J=2.5, 9.0), 7.14—7.4 (5H, m), 7.78 (1H, d, J=9.0). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.50; H, 6.75; N, 5.07. MS: *m/z*, 286 (MH^+). IR cm^{-1}: 2941, 1676, 1601, 1435, 1387, 1298, 1254. 2) $POCl_3$ (4.9 g, 32 mmol) was added dropwise to DMF (8.2 ml, 0.11 mol) under ice-cooling. The mixture was warmed to room temperature and stirred for 0.5 h. After addition of **41** (2.8 g, 9.8 mmol), the whole was heated at 80 °C for 4 h and cooled to room temperature. The reaction mixture was poured into ice H_2O (80 ml). Then, AcONa (25 g) and H_2O (62 ml) were added, and the mixture was extracted with AcOEt. The extract was washed with brine and concentrated. The resulting insoluble materials were filtered off, and the filtrate was chromatographed on silica gel with AcOEt to afford 0.75 g of an unseparatable mixture of methyl 5-formyl-2-methoxy-4-methylaminobenzoate (**42a**) and methyl 5-formyl-4-(*N*-formyl-*N*-methyl)-amino-2-methoxybenzoate (**42b**). ^{1}H-NMR δ: 3.37 (3H, s), 3.41 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 3.99 (3H, s), 4.01 (3H, s), 6.78 (1H, s), 6.83 (1H, s), 8.30 (1H, s), 8.37 (1H, s), 8.41 (1H, s), 8.42 (1H, s), 9.96 (1H, s), 9.88 (1H, s). MS: *m/z*, 224 (MH^+ of **42a**), 252 (MH^+ of **42b**). 3) A solution of the mixture of **42a** and **42b** (0.75 g) and NaOH (0.4 g, 10 mmol) in MeOH (2.5 ml)–H_2O (5 ml) mixture was heated to reflux for 1 h and cooled to room temperature. The reaction mixture was concentrated, and the aqueous solution was acidified with 35% aqueous HCl and extracted with $CHCl_3$. The extract was concentrated to dryness, and the residue was triturated with Et_2O to give 0.62 g (30% yield from **41**) of **43** as a white solid. An analytical sample of **43** was obtained by recrystallization from MeOH/Et_2O, mp 231—232 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.94 (3H, d, J=5.0, NMe), 3.90 (3H, s), 6.17 (1H, s), 8.09 (1H, s), 8.64 (1H, br, J=5.0, NH), 9.69 (1H, s, CHO), 12.08 (1H, s). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.34; H, 5.20; N, 6.79. MS: *m/z*, 209 (M^+). IR cm^{-1}: 3329, 1724, 1649, 1614, 1570, 1423, 1304, 1256.

5-Ethylthio-2-methoxy-4-methylaminobenzoic Acid (46) 1) A solution of Br_2 (2.8 ml, 55 mmol) in MeOH (7.8 ml) was added to a mixture of **38** (10.0 g, 51 mmol), NH_4SCN (6.2 g, 82 mmol), and MeOH (36 ml) under ice-cooling. The whole was stirred at this temperature for 5 h and poured into H_2O. The solid precipitate was collected by filtration, washed with H_2O, and dried to give 9.6 g (74%) of methyl 5-cyanothio-2-methoxy-4-methylaminobenzoate (**44**) as a white solid, mp 162—164 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.90 (3H, d, J=5.0, NMe), 3.72 (3H, s), 3.88 (3H, s), 6.21 (1H, s), 6.88 (1H, br, J=5.0, NH), 7.92 (1H, s). *Anal.* Calcd for $C_{11}H_{12}N_2O_3S \cdot 1/10H_2O$: C, 52.00; H, 4.84; N, 11.02; S, 12.62. Found: C, 51.87; H, 4.92; N, 10.81; S, 12.42. MS: *m/z*, 253 (MH^+). IR cm^{-1}: 3366, 2160, 1686, 1601, 1562, 1472, 1248. 2) A mixture of **44** (5.0 g, 20 mmol), KOH (1.3 g, 23

mmol), and MeOH (100 ml) was heated to reflux for 1 h and cooled to room temperature. After addition of Et_2SO_4 (2.3 g, 15 mmol), the whole was heated to reflux for 48 h and cooled to room temperature. The solvent was evaporated, and the residue was diluted with H_2O and acidified with 35% aqueous HCl. After addition of $CHCl_3$, the insoluble materials were filtered off. The organic layer of the filtrate was separated, washed with brine, and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/AcOEt=50/1 to give 1.7 g (34%) of methyl 5-ethylthio-2-methoxy-4-methylaminobenzoate (**45**) as an oil, which was used in the next step without further purification. ^{1}H-NMR δ: 1.18 (3H, t, J=7.5), 2.62 (2H, q, J=7.5), 2.85 (3H, d, J=5.0), 3.82 (3H, s), 3.93 (3H, s), 5.64 (1H, br, J=5.0), 6.05 (1H, s), 8.02 (1H, s). MS: m/z, 256 (MH^+). 3) In a similar manner to that described above, **45** was hydrolyzed with aqueous NaOH to give **46** as a pale yellow powder in 92% yield. **46**; mp 143—145 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.07 (3H, t, J=7.5), 2.59 (2H, q, J=7.5), 2.85 (3H, d, J=5.0), 3.84 (3H, s), 6.10 (1H, s), 6.28 (1H, br, J=5.0), 7.78 (1H, s), 11.68 (1H, s). *Anal.* Calcd for $C_{11}H_{15}NO_3S\cdot 1/4H_2O$: C, 53.75; H, 6.36; N, 5.70; S, 13.04. Found: C, 53.92; H, 6.07; N, 5.89; S, 12.93. MS: m/z, 242 (MH^+). IR cm^{-1}: 3364, 1678, 1595, 1549, 1252.

5-Ethylsulfonyl-2-methoxy-4-methylaminobenzoic Acid (47) A mixture of **46** (1.5 g, 6.2 mmol), 30% aqueous H_2O_2 (1.8 g, 16 mmol), and AcOH (15 ml) was stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in $CHCl_3$. The organic solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to dryness to give 1.2 g (71%) of **47** as a solid. An analytical sample of **47** was obtained by recrystallization from aqueous AcOH, mp 216—218 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.08 (3H, t, J=7.3), 2.91 (3H, d, J=5.0), 3.17 (2H, q, J=7.3), 3.31 (3H, s), 6.22 (1H, s), 6.68 (1H, br, J=5.0, NH), 8.04 (1H, s), 12.12 (1H, br s). *Anal.* Calcd for $C_{11}H_{15}NO_5S$: C, 48.34; H, 5.53; N, 5.12; S, 11.73. Found: C, 48.29; H, 5.67; N, 4.83; S, 11.65. MS: m/z, 274 (M^+). IR cm^{-1}: 3379, 1720, 1609, 1572.

Methyl 4-Acetylamino-5-chloro-2-methoxy-3-nitrobenzoate (48) Concentrated H_2SO_4 (18 ml) was added dropwise to fuming HNO_3 (d 1.52, 150 ml, 306 mol) under ice-cooling. **22a** (50.0 g, 0.19 mol) was added portionwise to the mixture below 10 °C. The whole was stirred at the same temperature for 5 min and poured into cold H_2O. The solid precipitate was collected by filtration, washed with H_2O, and dried to give 42.6 g (73%) of **48** as a pale yellow solid. An analytical sample of **48** was obtained by recrystallization from EtOH, mp 137—138 °C. ^{1}H-NMR δ: 2.21 (3H, s), 3.96 (3H, s), 4.00 (3H, s), 7.31 (1H, s), 8.10 (1H, s). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_6$: C, 43.65; H, 3.66; Cl, 11.71; N, 9.26. Found: C, 43.41; H, 3.68; Cl, 11.62; N, 9.17. MS: m/z, 303 (MH^+). IR cm^{-1}: 3321, 1711, 1541, 1491, 1363, 1240, 1146.

Methyl 4-Acetylamino-3-amino-5-chloro-2-methoxybenzoate (49) A mixture of **48** (18.0 g, 60 mmol), EtOH (180 ml), and H_2O (10 ml) was hydrogenated over Raney Ni (wet, *ca.* 2 g) at room temperature under an initial pressure of 4.4 kg/cm^2. After no further change in the pressure of H_2 (3.6 kg/cm^2, *ca.* 1 h) was observed, the catalyst was filtered through Celite. The filtrate was concentrated to dryness to give 15.6 g (96%) of **49** as a solid. An analytical sample of **49** was obtained by recrystallization from EtOH, mp 149—151 °C. ^{1}H-NMR δ: 2.29 (3H, s), 3.85 (3H, s), 3.90 (3H, s), 4.51 (2H, s), 7.23 (1H, s), 7.32 (1H, s). *Anal.* Calcd for $C_{11}H_{13}ClN_2O_4$: C, 48.45; H, 4.81; Cl, 13.00; N, 10.27. Found: C, 48.46; H, 4.85; Cl, 12.99; N, 10.06. MS: m/z, 273 (MH^+). IR cm^{-1}: 3319, 3242, 1736, 1655, 1609, 1522, 1475, 1290, 1205.

7-Chloro-4-methoxy-1*H*-benzotriazole-5-carboxylic Acid (51) A solution of **49** (8.8 g, 32 mmol) in concentrated H_2SO_4 (22 ml) was added to cold H_2O (88 ml). A solution of $NaNO_2$ (3.3 g, 48 mmol) in H_2O (10 ml) was added dropwise to the mixture under ice-cooling, and the whole was stirred at the same temperature for 1 h. The acidic solution containing methyl 7-chloro-4-methoxy-1*H*-benzotriazole-5-carboxylate (**50**) was heated to reflux for 18 h and cooled to *ca.* 5 °C. The precipitates were collected by filtration, washed with cold H_2O, and dried to give 4.7 g (64%) of **51**, mp 204—206 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.46 (3H, s), 7.78 (1H, s), 13.02 (1H, s). *Anal.* Calcd for $C_8H_6ClN_3O_3\cdot 7/4H_2O$: C, 37.08; H, 3.70; Cl, 13.68; N, 16.22. Found: C, 37.14; H, 3.59; Cl, 13.47; N, 16.29. MS: m/z, 228 (MH^+). IR cm^{-1}: 1701, 1612, 1609, 1501, 1364, 1246.

7-Chloro-4-methoxy-2-methyl-1*H*-benzimidazole-5-carboxylic Acid (53) 1) A mixture of **49** (3.0 g, 11 mmol), *p*-toluenesulfonic acid monohydrate (0.1 g), and toluene (50 ml) was heated to reflux with an attached Dean–Stark trap for 1 h and cooled to *ca.* 5 °C. The precipitates were collected by filtration, washed with toluene, and dried to give 2.8 g (quantitative yield) of methyl 7-chloro-4-methoxy-2-methyl-1*H*-benzimidazole-5-carboxylate (**52**). An analytic sample of **52** was obtained by recrystallization from EtOH/hexane, mp 195.5—197.5 °C. ^{1}H-NMR δ: 2.68 (3H, s), 3.93 (3H, s), 4.16 (3H, s), 6.78 (1H, s), 7.74 (1H, s). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_3$: C, 51.88; H, 4.35; Cl, 13.92; N, 11.00. Found: C, 51.89; H, 4.42; Cl, 13.75; N, 10.86. MS: m/z, 255 (MH^+). IR cm^{-1}: 1728, 1711, 1543, 1327, 1198. 2) A mixture of **52** (1.25 g, 4.9 mmol), MeOH (10 ml), H_2O (10 ml), and NaOH (1.0 g, 25 mmol) was heated to reflux for 1.5 h and cooled to room temperature. After evaporation of MeOH, the aqueous solution was acidified with 35% aqueous HCl. The solution was concentrated, and the residue was crystallized from aqueous EtOH to give 1.3 g (96%) of the hydrochloride of **53**, mp 213—215 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.82 (3H, d, J=2.5), 4.06 (3H, s), 7.69 (1H, J=2.5), 10.2 (br s). *Anal.* Calcd for $C_{10}H_9ClN_2O_3\cdot$HCl: C, 43.34; H, 3.64; Cl, 25.59; N, 10.11. Found: C, 43.29; H, 3.64; Cl, 25.77; N, 10.06. MS: m/z, 241 (MH^+ of free base). IR cm^{-1}: 2826, 1726, 1626, 1580, 1373, 1267, 1190.

4-Amino-5-chloro-2-methoxy-*N*-[1-methylhexahydro-1,4-diazepin-6-yl]benzamide Dimaleate (75) A solution of **2x** (1.4 g, 3.5 mmol) in EtOH (20 ml) was hydrogenated over 10% Pd/C (0.3 g) at 50 °C for 3 h under H_2 atmosphere. The catalyst was filtered through Celite. The filtrate was concentrated to dryness to give 1.1 g (quantitative yield) of **75** as a pale yellow oil, which was converted into the maleate in the usual manner. ^{1}H-NMR (DMSO-d_6) δ: 2.53 (3H, s), 2.7—3.45 (9H, m), 3.84 (3H, s), 4.30 (1H, m), 6.04 (2H, s), 6.14 (4H, s, maleic acid), 6.48 (1H, s), 7.80 (1H, s), 8.35 (1H, d, J=8.0). MS: m/z, 313 (MH^+). IR cm^{-1}: 3520, 3348, 1646, 1634, 1600, 1578, 1485, 1454, 1358.

5-Chloro-*N*-[1-(2-hydroxyethyl)-4-methylhexahydro-1,4-diazepin-6-yl]-2-methoxy-4-methylaminobenzamide Dioxalate (96) Trimethylsilyl iodide (TMSI, 0.4 ml, 2.8 mmol) was added to a solution of the free base of **95** (1.0 g, 2.6 mmol) in $CHCl_3$ (20 ml) at room temperature under N_2 atmosphere. After being stirred for 6 h, TMSI (0.4 ml, 2.8 mmol) was added. The mixture was stirred at this temperature overnight. MeOH was carefully added to the reaction mixture, and the volatiles were evaporated. The residue was dissolved in $CHCl_3$, and the solution was washed successively with saturated aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$, and brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 0.6 g (62%) of **96** as a pale yellow oil, which was converted into the oxalate in the usual manner. ^{1}H-NMR (DMSO-d_6) δ: 2.72 (3H, s), 2.79 (3H, t, J=6.0), 2.84 (3H, d, J=5.0, NMe), 2.87—3.4 (8H, m), 3.56 (2H, q, J=6.0), 3.95 (3H, s), 4.30 (1H, m), 6.17 (1H, br d, J=5.0, NH), 6.24 (1H, s), 7.74 (1H, s), 8.34 (1H, d, J=7.5). MS: m/z, 371 (MH^+). IR cm^{-1}: 3385, 1688, 1611, 1470.

***N*-(1-Ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-5-fluoro-2-methoxy-4-methylaminobenzamide Dimaleate (113)** 1) A mixture of 2,4,5-trifluorobenzoic acid (**63**, 10.0 g, 57 mmol), Et_3N (10 ml), pyridine (50 ml), and *N*-benzylmethylamine (20.7 g, 0.17 mol) was heated to reflux for 45 h and cooled to room temperature. After the volatiles were evaporated, the residue was dissolved in H_2O. The solution was then acidified with 35% aqueous HCl and extracted with $CHCl_3$. The extract was washed successively with H_2O and brine and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 7.7 g (49%) of 4-(*N*-benzyl-*N*-methyl)amino-2,5-difluorobenzoic acid (**64**) as a white solid. An analytic sample of **64** was obtained by recrystallization from acetone/hexane, mp 148—149 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.78 (3H, s), 4.49 (2H, s), 6.56 (1H, dd, J=7.5, 13.0), 7.2—7.4 (5H, m), 7.55 (1H, dd, J=7.0, 14.0), 7.82 (1H, br). *Anal.* Calcd for $C_{15}H_{13}F_2NO_2$: C, 64.98; H, 4.73; F, 13.70; N, 5.05. Found: C, 64.64; H, 4.66; F, 13.62; N, 5.08. MS: m/z, 278 (MH^+). IR cm^{-1}: 1686, 1626, 1537, 1406, 1277. 2) A mixture of **64** (5.0 g, 18 mmol), **8a** (2.8 g, 18 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) (3.8 g, 20 mmol), and CH_2Cl_2 (50 ml) was stirred at room temperature for 4 h. The reaction mixture was washed successively with H_2O, 10% aqueous NaOH, and brine and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 4.2 g (56%) of 4-(*N*-benzyl-*N*-methyl)amino-2,5-difluoro-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamide (**65**) as a pale yellow oil. ^{1}H-NMR δ: 1.05 (3H, t, J=7.5), 2.38 (3H, s), 2.45—3.00 (10H, m), 2.89 (3H, s), 4.30 (1H, m), 4.47 (2H, s), 6.45 (1H, dd, J=7.5, 14.0), 7.2—7.4 (5H, m), 7.72 (1H, dd, J=7.5, 14.0), 7.82 (1H, m). MS: m/z, 417 (MH^+). The oil was converted into the oxalate in the usual manner. An analytical sample of the oxalate was obtained by crystallization from EtOH/^{i}PrOH, mp 126—127 °C. *Anal.* Calcd for $C_{23}H_{30}F_2N_4O\cdot 5/2C_2H_2O_4\cdot 1/4H_2O$: C, 51.34; H, 5.62; F, 5.80; N, 8.55. Found: C, 51.23; H, 5.65; F, 5.94; N, 8.53. IR cm^{-1}: 3422, 1630, 1508. 3) A mixture of **65** (1.9 g, 4.6 mmol), NaOMe (powder, 0.8 g, 15 mmol), and anhydrous DMF (20 ml) was heated at 120 °C for 15 h and cooled to room temperature. After evaporation of the solvent, the residue was taken into H_2O and $CHCl_3$. The organic layer was separated, washed

with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 1.5 g (77%) of 4-(*N*-benzyl-*N*-methyl)amino-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-5-fluoro-2-methoxybenzamide (**66**) as a pale yellow oil. ^{1}H-NMR δ: 1.07 (3H, t, J=7.5), 2.42 (3H, s), 2.45—3.10 (10H, m), 2.90 (3H, s), 3.85 (3H, s), 4.34 (1H, m), 4.47 (2H, s), 6.29 (1H, d, J=7.0), 7.1—7.4 (5H, m), 7.85 (1H, d, J=15.0), 8.67 (1H, d, J=8.0). MS: m/z, 429 (MH^+). The oil was converted into the oxalate in the usual manner. An analytical sample of the oxalate was obtained by crystallization from EtOH/^{i}PrOH, mp 146—149 °C. *Anal.* Calcd for $C_{24}H_{33}FN_4O_2 \cdot 2C_2O_2H_4 \cdot H_2O$: C, 53.67; H, 6.27; F, 3.03; N, 8.94. Found: C, 53.41; H, 6.01; F, 3.16; N, 8.90. IR cm^{-1}: 3406, 1616, 1514. 4) A mixture of **66** (1.2 g, 2.8 mmol), EtOH (10 ml), and AcOH (10 ml) was hydrogenated over 10% Pd/C (0.12 g) at 50 °C for 2 h under atmospheric pressure. The catalyst was filtered through Celite, and the filtrate was concentrated to dryness. After addition of saturated aqueous $NaHCO_3$, the mixture was extracted with $CHCl_3$. The extract was washed with brine and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to give 0.7 g (74%) of **113** as a pale yellow oil, which was converted into the maleate in the usual manner. ^{1}H-NMR (DMSO-d_6) δ: 1.11 (3H, t, J=7.5), 2.68 (3H, s), 2.7-3.3 (13H, m), 3.94 (3H, s), 4.31 (1H, m), 6.16 (4H, s, maleic acid), 6.28 (1H, d, J=7.5), 6.31 (1H, br), 7.48 (1H, d, J=13.5), 8.43 (1H, d, J=7.5). MS: m/z, 339 (MH^+). IR cm^{-1}: 3364, 1624, 1576, 1528, 1487, 1364.

***N*-(1-Ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-5-hydroxymethyl-2-methoxy-4-methylaminobenzamide (116)** $NaBH_4$ (0.35 g, 9.3 mmol) was added to a solution of **115** (1.1 g, 3.2 mmol) in MeOH (20 ml) at room temperature. The reaction mixture was stirred at the same temperature for 4 h and concentrated to dryness. The residue was taken into H_2O and $CHCl_3$, and the organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to 7/1 to give 0.7 g (63%) of **116** as a pale yellow solid. ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, t, J=7.0), 2.0 (1H, br), 2.40 (3H, s), 2.5—3.05 (10H, m), 2.92 (3H, d, J=5.0), 3.96 (3H, s), 4.33 (1H, m), 4.63 (2H, s), 5.32 (1H, br, J=5.0), 6.10 (1H, s), 7.87 (1H, s), 8.56 (1H, d, J=8.0). MS: m/z, 351 (MH^+). IR cm^{-1}: 3312, 1632, 1601, 1522, 1456, 1352, 1286, 1215.

***N*-(1-Ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-4-methylamino-5-sulfamoylbenzamide (119)** 1) 4-Chloro-2-methoxybenzoic acid (**67**, 10.0 g, 54 mmol) was slowly added in small portions to cold (*ca.* 0 °C) $ClSO_3H$ (50 ml). The mixture was warmed to room temperature and stirred until **67** dissolved completely. The solution was then slowly warmed to 60—70 °C, stirred at this temperature for 2 h, and cooled to room temperature. The reaction mixture was carefully poured into crushed ice. (Caution: $ClSO_3H$ reacts violently with H_2O!) The solid precipitate was collected by filtration, washed with H_2O, and dried to give 13.4 g (88%) of 4-chloro-5-chlorosulfonyl-2-methoxybenzoic acid (**68**) as a white powder, mp 190—192 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.84 (3H, s), 7.12 (1H, s), 8.19 (1H, s), 13.87 (1H, s). *Anal.* Calcd for $C_8H_6Cl_2O_5S$: C, 33.70; H, 2.12; Cl, 24.87; S, 11.25. Found: C, 33.62; H, 2.25; Cl, 24.60; S, 11.21. MS: m/z, 284 (M^+). IR cm^{-1}: 1703, 1684, 1587, 1389, 1254. 2) To 28% aqueous NH_3 (50 ml) was added **68** (12.0 g, 42 mmol) in small portions under ice-cooling. The mixture was warmed to 40—50 °C and stirred for 2 h at this temperature. After being cooled to *ca.* 5 °C, the reaction mixture was acidified with 35% aqueous HCl. The solid was collected by filtration, washed with H_2O, and dried to give 10.0 g (89%) of 4-chloro-2-methoxy-5-sulfamoylbenzoic acid (**69**) as a white powder, mp 224—226 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.83 (3H, s), 7.41 (1H, s), 7.59 (2H, s), 8.26 (1H, s), 13.15 (1H, s). *Anal.* Calcd for $C_8H_8ClNO_5S$: C, 36.17; H, 3.04; Cl, 13.34; N, 5.27; S, 12.07. Found: C, 35.95; H, 3.11; Cl, 13.31; N, 5.21; S, 11.95. MS: m/z, 265 (M^+). IR cm^{-1}: 3398, 3290, 1694, 1595, 1556, 1352, 1244. 3) A mixture of **69** (1.7 g, 6.4 mmol), **8a** (1.2 g, 7.6 mmol), EDC (1.4 g, 7.3 mmol), and CH_2Cl_2 (20 ml) was stirred at room temperature for 4 h. The reaction mixture was concentrated to dryness, and the residue was dissolved in H_2O and washed with Et_2O. After addition of 2 N aqueous NaOH and solid K_2CO_3, the mixture was extracted with $CHCl_3$. The extract was concentrated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$/MeOH=9/1 to 7/1 to give 1.6 g (62% from **69**) of 4-chloro-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-5-sulfamoylbenzamide (**70**) as a pale yellow amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 0.96 (3H, t, J=7.5), 2.32 (3H, s), 2.4—2.9 (10H, m), 4.02 (3H, s), 4.11 (1H, m), 7.45 (1H, s), 7.58 (2H, s), 8.46 (1H, s), 8.74 (1H, d, J=7.5). MS: m/z, 405 (MH^+). IR cm^{-1}: 1697, 1647, 1593, 1529, 1339, 1242, 1169. The amorphous solid was converted into the dioxalate in the usual manner. An analytical sample of the dioxalate was obtained by crystallization from MeOH/EtOH, mp 192—194 °C. *Anal.* Calcd for $C_{16}H_{25}ClN_4O_4S \cdot 2C_2O_2H_4 \cdot 3/4H_2O$: C, 40.14; H, 5.14; Cl, 5.92; N, 9.36; S, 5.36. Found: C, 39.90; H, 5.26; Cl, 5.83; N, 9.27; S, 5.25. 4) A mixture of **70** (1.2 g, 3.0 mmol) and 30% NH_2Me in EtOH (60 ml) in a sealed tube was heated at 140 °C for 30 h and cooled to room temperature. The volatiles were evaporated, and 1 N aqueous NaOH was added to the residue. The mixture was extracted with AcOEt, and the extract was concentrated to dryness to give 1.0 g (84%) of **119** as a white solid. ^{1}H-NMR (DMSO-d_6) δ: 0.97 (3H, t, J=7.5), 2.30 (3H, s), 2.36—2.87 (10H, m), 2.92 (3H, d, J=5.0), 3.98 (3H, s), 4.07 (1H, m), 6.24 (1H, s), 6.30 (1H, br, J=5.0), 7.24 (2H, s), 8.30 (1H, s), 8.48 (1H, d, J=7.05). MS: m/z, 400 (MH^+). IR cm^{-1}: 3420, 3379, 1626, 1597, 1514, 1317.

6-Amino-2,3-dimethoxy-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)benzamide 7/4 Oxalate (124) $SOCl_2$ (0.36 ml, 4.9 mmol) was added to a suspension of 6-(*tert*-butoxycarbonyl)amino-2,3-dimethoxybenzoic acid (**62**, 0.9 g, 3.0 mmol), DMF (1 drop), and toluene (20 ml) at room temperature. The mixture was heated at 60 °C for 1.5 h and cooled to room temperature. The volatiles were evaporated, and the residue was dissolved in toluene. The solvent was then reevaporated and the oily residue was used in the next step without further purification. A solution of the oil obtained above in $CHCl_3$ (20 ml) was added dropwise to a solution of **8a** (0.48 g, 3.1 mmol) in $CHCl_3$ (10 ml) under ice-cooling. The mixture was stirred at room temperature for 3 h, washed successively with H_2O, saturated aqueous $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with $CHCl_3$/MeOH=10/1 to afford 0.5 g (49%) of **124** as a brown oil. The oil was converted into the oxalate in the usual manner. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, t, J=7), 2.62 (3H, s), 2.86 (2H, q, J=7), 3.04 (2H, s), 2.9—3.25 (8H, m), 3.69 (3H, s), 3.73 (3H, s), 4.48 (1H, m), 6.43 (1H, d, J=9), 6.92 (1H, d, J=9), 8.47 (1H, d, J=9). MS: m/z, 337 (MH^+). IR cm^{-1}: 3358, 1607, 1491, 1332.

General Procedure for the Preparation of the Benzamide and Carboxamide Derivatives [71, 72, 80—82, 85—97, 98—112, 114, 115, 117, 118, 120—123, 125—130, (*R*)- and (*S*)-81, (*R*)- and (*S*)-82, (*R*)- and (*S*)-110, (*R*)- and (*S*)-112] A mixture of the benzoic acid derivative or 1*H*-benzotriazole- and 1*H*-benzimidazole-5-carboxylic acids (10 mmol), amine (11 mmol), EDC (12 mmol), and CH_2Cl_2 (80 ml) was stirred at room temperature for 4—5 h. The reaction mixture was washed successively with H_2O, 10% aqueous NaOH, and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on silica gel. The free base thus obtained was recrystallized from the solvent shown in Tables 1—5 or converted into the fumarate, the maleate, or the oxalate in the usual manner, followed by recrystallization from the solvent shown in Tables 1—5. Physical data for the benzamide and the carboxamide derivatives are listed in Tables 1—5.

Binding Assays for Dopamine D_2 and 5-HT_3 Receptors The binding assays for the dopamine D_2 and the 5-HT_3 receptors were carried out according to the method described in previous papers.[20,32]

Effect on Apomorphine-Induced Emesis in Dogs[48] Male beagle dogs, weighing 10—16 kg, were used. Groups of three to six dogs received a subcutaneous injection of apomorphine hydrochloride (0.3 mg/kg) 2 h after pretreatment with test compounds (1.0 mg/kg, *p.o.*). Emesis inhibition was evaluated by the frequency of emetic episodes 1 h after treatment with apomorphine hydrochloride.

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