Dopamine D_3 and D_4 Receptor Antagonists: Synthesis and Structure−Activity Relationships of (*S*)-(+)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (YM-43611) and Related Compounds

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In this study, we synthesized a series of (*S*)-*N*-(3-pyrrolidinyl)benzamide derivatives, **1**, **2a**−**d**, **5a**−**l**, and **7**, and their enantiomers, (*R*)-**1** and (*R*)-**5c**−**e**, and evaluated their binding affinity for cloned dopamine D_2, D_3, and D_4 receptors and their inhibitory activity against apomorphine-induced climbing behavior in mice. The results indicate that D_2, D_3, and D_4 receptors have different bulk tolerance ($D_4 > D_3 > D_2$) for the substituent of the 4-amino group (R^1) on the benzamide nuclei and that cyclopropyl-, cyclobutyl-, and cyclopentylcarbonyl groups likely possess adequate bulkiness with respect to D_3 and D_4 affinity and selectivity over D_2 receptors in this series. The results also suggested that the *N*-substituent (R^2) on the pyrrolidin-3-yl group performs an important role in expressing affinity for D_2, D_3, and D_4 receptors and selectivity among the respective subtypes. One of the compounds, (*S*)-(+)-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (**5c**) (YM-43611), showed high affinity for D_3 and D_4 receptors (K_i values of 21 and 2.1 nM, respectively) with 110-fold D_4 selectivity and 10-fold D_3 preference over D_2 receptors and weak or negligible affinity for representative neurotransmitter receptors. Compound **5c** displayed potent antipsychotic activity in inhibiting apomorphine-induced climbing behavior in mice (ED_{50} value, 0.32 mg/kg sc).

Schizophrenia is one of the most severe psychiatric illnesses and is characterized by hallucinations, delusions, and disorganized thought and behavior which result in major impairment of the patient's social and occupational function. Current medications utilizing typical neuroleptic antipsychotics such as haloperidol (Figure 1) show some promised efficacy in controlling the positive symptoms of schizophrenia. However, their effects are only partial, and they induce a substantial incidence of extrapyramidal symptoms (EPS) as neurological side effects.[1,2]

Traditionally, two dopamine receptor subtypes have been classified on the basis of pharmacological evaluation, namely, the D_1 and D_2 receptors. Existing antipsychotics are considered to act via the blockade of the classical "D_2 receptor".[3−5] Recently, however, molecular biological approaches have led to the discovery of the novel dopamine D_3 and D_4 receptor isoforms,[6,7] which are classified as the D_2-like (D_2, D_3, and D_4) receptor subfamily, and the D_5 receptor,[8] which is classified as the D_1-like (D_1 and D_5) receptor subfamily. The D_2-like receptor subfamily isoforms correspond to the classical D_2 receptors. D_3 and D_4 receptors are particularly concentrated in the mesolimbic and mesolimbocortical regions of the central nervous system, respectively,[9,10] areas which are thought to control emotional and cognitive functions and to be implicated in the pathology of schizophrenia.[11−13] In contrast, few D_3 and D_4 receptors are found in the nigrostriatal region, which is rich in D_2 receptors and of which blockade of the dopamine system has been suggested to be associated with EPS.[10]

Clozapine (Figure 1), an atypical antipsychotic agent, exhibits good efficacy even in some patients with schizophrenia who fail to respond to typical antipsychotics and has a low incidence of EPS.[14,15] The atypical antipsychotic profile of clozapine is thought to result from its affinity for a multitude of receptors, including dopamine receptor subtypes, 5-HT_2 receptors, and α_1 adrenoceptors.[16] In particular, the favorable effects of clozapine are suggested to be derived from its relatively preferential blockade of D_4 over D_2 receptors (approximately 10-fold selectivity).[7,13] On the other hand, quinpirole, a selective D_3 receptor agonist, inhibits rather than stimulates rat locomotor activity. The negative symptoms of schizophrenia, which are generally resistant to antipsychotic treatment, may therefore result from overactivity in the D_3 receptor system.[17] Blockade of D_3 receptors may thus have a beneficial effect on these symptoms.

These observations indicate that selective D_3 and D_4 antagonism may represent a novel and potent psychotropic mechanism and may have application as an atypical antipsychotic drug which does not induce EPS.[18,19] Despite the upsurge of interest in the physiology and pharmacology of D_3 and D_4 receptors,[20−24] the limited number of selective antagonists has made it difficult to determine their functions.[25,26] This situation prompted us to search for selective D_3 and D_4 receptor antagonists and investigate their pharmacology.

Metoclopramide (Figure 1) and its derivatives are known as antagonists of the classical D_2 receptor. Among them, nemonapride, an antipsychotic of the

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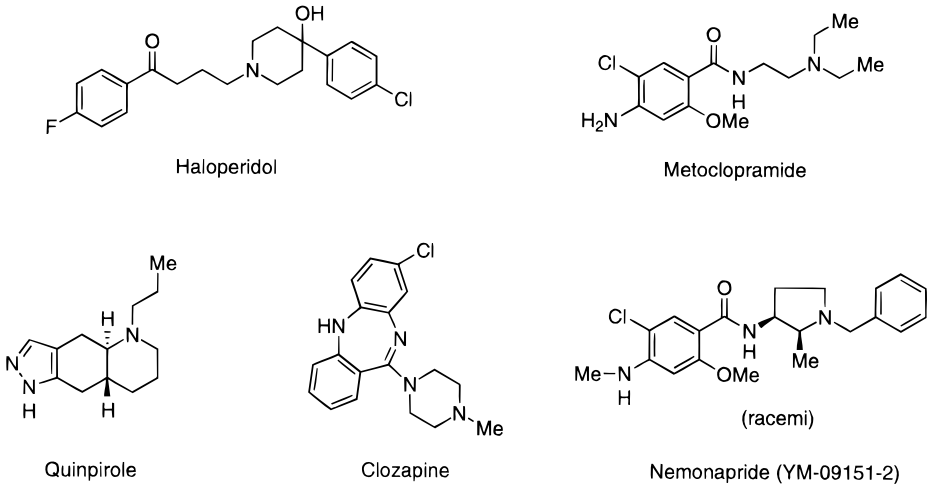


Figure 1.

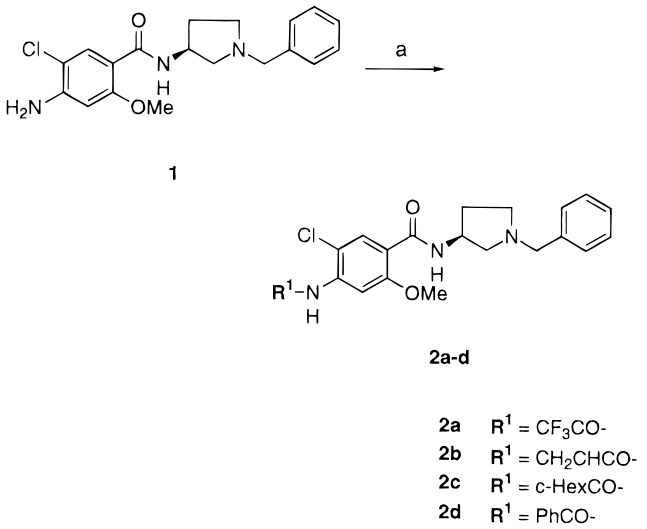
benzamide class developed in our laboratory, is recognized as one of the strongest and most selective antagonists of the classical D_2 receptor (Figure 1).[27] Nemonapride was recently shown to possess high affinity for D_2, D_3, and D_4 receptors with K_i values in the subnanomolar range.[12] To obtain selective D_3 and D_4 receptor antagonists, we carried out several modifications of *N*-(3-pyrrolidinyl)benzamide **1**, a nemonapride analogue, based on the results of screening for our in-house chemical file. In this paper we report the synthesis, structure−activity relationships (SAR) in affinity for D_3, D_4, and D_2 receptors, and behavioral test results in mice of the novel series of (*S*)- and (*R*)-4-[(cycloalkylcarbonyl)amino]-*N*-(3-pyrrolidinyl)benzamides **2c**,**d**, **5c**−**k**, (*R*)-**5c**−**e**, and **7** and related compounds **1**, (*R*)-**1**, **2a**,**b**, and **5a**,**b**,**l**.[28] Among these compounds, (*S*)-(+)-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (**5c**) showed high affinity and selectivity for D_3 and D_4 versus D_2 and other neurotransmitter receptors, as well as potent inhibitory activity on apomorphine-induced climbing behavior.[29,30]

Chemistry

Synthesis of the (*S*)-*N*-(3-pyrrolidinyl)benzamides **2a**−**d**, **5a**−**l**, and **7** is described in Schemes 1−3. (*S*)-4-Amino-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamide (**1**) was obtained from 4-amino-5-chloro-2-methoxybenzoic acid (**8**) and commercially available (*S*)-3-amino-1-benzylpyrrolidine (**9**) by a previously described procedure for (±)-**1**.[27] As shown in Scheme 1, acylation of **1** with the corresponding acyl chloride or anhydride led to the formation of trifluoroacetyl- (**2a**), acryloyl- (**2b**), cyclohexylcarbonyl- (**2c**), and benzoyl- (**2d**) aminobenzamide derivatives, respectively. The enantiomer (*R*)-**1** was prepared from (*R*)-3-amino-1-benzylpyrrolidine (**10**) by the same method.

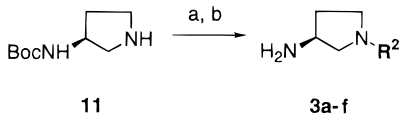
The other 4-(acylamino)benzamide derivatives **5a**−**l** were synthesized from suitable benzoic acids **4a**−**f** and aminopyrrolidines **3a**−**f** and **9** (Scheme 2). The pyrrolidine parts, 1-cyclohexyl- (**3a**), 1-cycloheptyl- (**3b**), 1-(bicyclo[3.3.1]non-9-yl)- (**3c**), 1-(2-adamantyl)- (**3d**), 1-cyclohexylmethyl- (**3e**), and 1-phenethyl- (**3f**) pyrrolidines, were obtained from commercially available (*S*)-3-[(*tert*-butoxycarbonyl)amino]pyrrolidine (**11**) by reductive alkylation with the corresponding cyclohexanone, cycloheptanone, bicyclo[3.3.1]nonan-9-one, 2-adamantanone, cyclohexanecarboxaldehyde, and phenylacetaldehyde and subsequent deprotection of their *tert*-butoxycarbonyl (BOC) group by treatment with 4 N HCl−ethyl acetate solution. The benzoic acid parts, 4-propionylamino- (**4a**) and 4-(2-methylpropionyl)amino- (**4b**) 5-chloro-2-methoxybenzoic acids, were directly prepared by acylation of benzoic acid **8** with propionyl chloride and 2-methylpropionyl chloride. Because this method resulted in the formation of substantial amounts of several byproducts, 4-[(cycloalkylcarbonyl)amino]-benzoic acids **4c**−**e** were prepared stepwise via ester derivatives as follows: Benzoic acid **8** was converted to the methyl ester **12**[31] by treatment with dimethyl sulfate in the presence of potassium carbonate,[32] treated with the respective cycloalkylcarbonyl chloride, and then hydrolyzed to give the corresponding 4-cyclopropyl- (**4c**), 4-cyclobutyl- (**4d**), and 4-cyclopentyl- (**4e**) carbonylaminobenzoic acids, respectively. The resulting **4a**−**e** were condensed with the appropriate 3-aminopyrrolidine derivatives **3a**−**f** and **9** by means of the mixed anhydride method[27] or diphenyl phosphorazidate method[33] to afford the desired benzamide derivatives **5a**−**k**. Compound **5l** was also synthesized from 5-chloro-2-methoxy-4-(methylamino)benzoic acid (**4f**)[27] and pyrrolidine **3c** by the mixed anhydride method. The (*R*)-enantiomers (*R*)-**5c**−**e** were synthesized from (*R*)-pyrrolidine **10** according to the method for the respective enantio isomers.

Scheme 1[a]



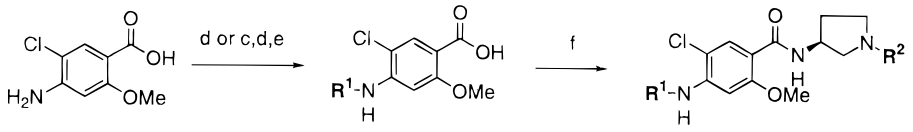
[a] (a) $(CF_3CO)_2O$ for **2a**, R^1Cl for **2b**−**d**, CH_2Cl_2.

Scheme 2[a]



11 3a-f

3a R^2 = c-Hex-
3b R^2 = c-Hep-
3c R^2 =
3d R^2 = 2-Adamantyl-
3e R^2 = c-Hexylmethyl-
3f R^2 = Phenethyl-



8 4a-f 5a-l

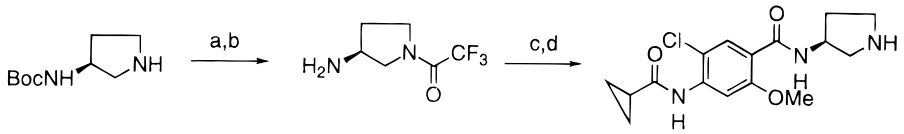
4a R^1 = EtCO-
4b R^1 = i-PrCO-
4c R^1 = c-PrCO-
4d R^1 = c-BuCO-
4e R^1 = c-PenCO-
4f R^1 = Me-

5a R^1 = EtCO- R^2 = Bn-
5b R^1 = i-PrCO- R^2 = Bn-
5c R^1 = c-PrCO- R^2 = Bn-
5d R^1 = c-BuCO- R^2 = Bn-
5e R^1 = c-PenCO- R^2 = Bn-
5f R^1 = c-PrCO- R^2 = c-Hex-

5g R^1 = c-PrCO- R^2 = c-Hep
5h R^1 = c-PrCO- R^2 =
5i R^1 = c-PrCO- R^2 = 2-Adamantyl-
5j R^1 = c-PrCO- R^2 = c-Hexylmethyl-
5k R^1 = c-PrCO- R^2 = Phenethyl-
5l R^1 = Me- R^2 =

[a] (a) R^2=O, H_2, Pd/C; (b) 4 N HCl−EtOAc; (c) Me_2SO_4, K_2CO_3; (d) R^1Cl, base; (e) 2 N NaOH, DMSO; (f) **3a**−**f** or (*S*)-3-amino-1-benzylpyrrolidine (**9**), EtOCOCl or $Ph_2P(O)N_3$, Et_3N, CH_2Cl_2 or DMF.

Scheme 3[a]



11 6 7

[a] (a) $(CF_3CO)_2O$; (b) 4 N HCl−EtOAc; (c) **4c**, EtOCOCl, Et_3N, CH_2Cl_2; (d) K_2CO_3.

Compound **7**, the debenzyl analogue of **5c**, was prepared by the following four steps (Scheme 3), namely, trifluoroacetylation of pyrrolidine **9**, deprotection of the BOC group by treatment with 4 N HCl−ethyl acetate solution, condensation with benzoic acid **4c**, and treatment with potassium carbonate to deprotect the trifluoroacetyl group to yield the desired product.

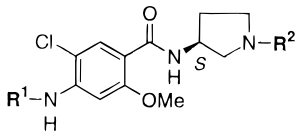
Results and Discussion

The structure of the benzamides and results of radiobinding assays for dopamine rat D_{2L} (D_2), rat D_3 (D_3), and human $D_{4.7}$ (D_4, containing seven polymorphic tandem repeats[36]) receptors are summarized in Table 1. The selected compounds were also assessed behaviorally by examining their inhibitory activity in apomorphine-induced climbing in mice (Table 1), a putative predictor of antipsychotic activity.[34] Binding affinity is presented as K_i (nM) and anticlimbing activity as ED_{50} (mg/kg sc) values.

The results of screening of our in-house chemical file, including nemonapride analogues, indicated that several series of benzamide analogues have affinity for D_2-like receptors. We also found that substituents on *N*-(3-pyrrolidinyl)benzamides somewhat affect their D_2, D_3, and D_4 selectivity. Among these compounds, (*S*)-4-amino-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamide (**1**) and its enantiomer [(*R*)-**1**] exhibited high affinity for D_2, D_3, and D_4 receptors (K_i values of **1** for D_2 = 0.98 nM, D_3 = 0.58 nM, and D_4 = 1.1 nM; those of (*R*)-**1** = 1.2, 1.9, and 0.55 nM, respectively) similar to or slightly less than haloperidol and nemonapride, with little or no selectivity for D_3 and D_4 versus D_2 receptors (K_{iD2}/K_{iD3} = 1.7 and 0.63; K_{iD2}/K_{iD4} = 0.89 and 2.2, respectively). Moreover, compound **1** and (*R*)-**1** possess only one asymmetric carbon, which is less than the number of nemonapride. These compounds were thus selected as lead compounds for further studies.

Initially, we investigated the effects of acyl substituents of the 4-amino group (R^1) on (*S*)-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamides. The linear-chained 4-acylamino analogues 4-trifluoroacetyl-, **2a**, 4-acryloyl-, **2b**, and 4-propionyl-, **5a**, aminobenzamides showed 12−33-fold weaker D_2 affinity (K_i values of 12−32 nM) and 8.1−10-fold weaker D_3 affinity (K_i = 4.7−5.9 nM) than **1**, in contrast to their D_4 affinity (K_i = 1.3−1.9 nM). The branched acylamino derivative **5b** exhibited a slightly greater decrease in D_3 affinity than **2a**,**b** and **5a**. Substitution of the amino group of **1** with cycloalkycarbonyl groups such as cyclopropylcarbonyl (**5c**) and cyclobutylcarbonyl (**5d**) resulted in equipotent D_4 (K_i = 2.1 and 5.2 nM) and D_3 (K_i = 21 and 36 nM) binding with those of **5b** and decreased D_2 binding (K_i = 220 and 170 nM). As a result, **5c** displayed about 100-fold weaker D_2 affinity than nonsubstituted **1** and 110-fold D_4 selectivity and 10-fold D_3 preference over D_2 receptors. The K_{iD2}/K_{iD4} ratio of **5c** is 15 times more than that of clozapine (K_{iD2}/K_{iD4} = 6.7). Even though the binding potency of cyclopentylcarbonyl derivative

Table 1. Biological Data of (*S*)- and (*R*)-*N*-(3-Pyrrolidinyl)benzamides



compd	R^1	R^2	receptor binding, K_i (nM)[a] D_2[b]	D_3[b]	D_4[c]	anticlimbing, in mice[d] ED_{50} (mg/kg sc)
1	H	Bn	0.98 (0.93−1.0)[e]	0.58 (0.56−0.60)	1.1 (1.0−1.2)	0.071 (0.038−0.13)
(*R*)-**1**	H	Bn	1.2 (1.1−1.3)	1.9 (1.8−2.0)	0.55 (0.54−0.57)	NT[f]
2a	CF_3CO	Bn	12 (12−12)	5.1 (4.8−5.4)	1.9 (1.8−2.1)	NT
2b	CH_2CHCO	Bn	27 (27−28)	4.7 (4.5−4.8)	1.3 (1.2−1.3)	NT
5a	EtCO	Bn	32 (31−33)	5.9 (5.5−6.2)	1.5 (1.4−1.6)	0.31 (0.21−0.45)
5b	*i*-PrCO	Bn	50 (48−52)	15 (14−16)	3.0 (2.9−3.2)	NT
5c	*c*-PrCO	Bn	220 (210−230)	21 (21−22)	2.1 (1.9−2.3)	0.32 (0.15−0.70)
(*R*)-**5c**	*c*-PrCO	Bn	190 (180−200)	60 (57−63)	5.6 (5.2−6.0)	0.45 (0.34−0.59)
5d	*c*-BuCO	Bn	170 (160−180)	36 (34−38)	5.2 (5.0−5.5)	0.14 (0.13−0.15)
(*R*)-**5d**	*c*-BuCO	Bn	240 (220−250)	100 (100−100)	7.0 (6.5−7.6)	NT
5e	*c*-PenCO	Bn	740 (670−820)	55 (43−69)	20 (18−21)	0.28 (0.16−0.49)
(*R*)-**5e**	*c*-PenCO	Bn	690 (310−1500)	150 (120−200)	18 (16−20)	NT
2c	*c*-HexCO	Bn	1200 (1100−1300)	200 (190−210)	110 (96−120)	NT
2d	PhCO	Bn	630 (610−640)	200 (190−210)	87 (82−93)	NT
7	*c*-PrCO	H	14 000 (14 000−15 000)	3000 (2900−3200)	2200 (2100−2400)	>30
5f	*c*-PrCO	*c*-Hex	84 (83−86)	4.4 (4.3−4.5)	2.1 (1.9−2.3)	1.4 (0.37−5.1)
5g	*c*-PrCO	*c*-Hep	20 (19−21)	1.5 (1.4−1.6)	2.7 (2.3−3.3)	NT
5h	*c*-PrCO	BCN[g]	140 (140−140)	2.2 (2.1−2.3)	3.8 (3.4−4.4)	>10
5i	*c*-PrCO	2-adamantyl	110 (110−120)	1.7 (1.6−1.8)	4.4 (4.2−4.6)	>10
5j	*c*-PrCO	*c*-hexylmethyl	32 (30−34)	3.7 (3.5−3.9)	3.3 (3.0−3.6)	NT
5k	*c*-PrCO	phenethyl	82 (79−85)	33 (30−35)	3.4 (3.0−3.9)	NT
5l	Me	BCN	0.81 (0.78−0.83)	0.24 (0.23−0.25)	0.67 (0.60−0.75)	NT
nemonapride			0.16 (0.13−0.19)	0.16 (0.15−0.17)	0.21 (0.16−0.27)[h]	0.012 (0.0082−0.019)
haloperidol			1.1 (1.0−1.2)	6.4 (6.1−6.8)	2.1 (1.7−2.5)	0.041 (0.033−0.050)
clozapine			260 (250−260)	230 (220−240)	39 (36−42)	6.8 (5.5−8.4)

[a] K_i values were determined by at least two experiments. Each inhibition curve consisted of four to eight points on each experiment. [b] K_i for [^{125}I]iodosulpride binding; rat D_{2L} and rat D_3 receptors expressed in CHO cells. [c] K_i for [^{3}H]nemonapride binding; human $D_{4.7}$ receptors expressed in CHO cells. [d] Test results for the free base. [e] Values in parentheses are 95% confidence intervals. [f] NT = not tested. [g] BCN = bicyclo[3.3.1]non-9-yl. [h] K_d value.

5e for D_2, D_3, and D_4 receptors was several to 10 times less than those of **5c**,**d**, its D_3 and D_4 selectivity was largely retained (K_{iD2}/K_{iD3} = 13 and K_{iD2}/K_{iD4} = 37). In the case of analogues with greater ring expansion, cyclohexylcarbonyl- (**2c**) and benzoyl- (**2d**) aminobenzamides, D_3 and D_4 affinity was even weaker and selectivity was lower than those of **5e**. On the other hand, (*R*)-**5c**−**e** exhibited closely similar or only slightly decreased affinity for D_2, D_3, and D_4 receptors and showed similar or somewhat reduced D_3 and D_4 selectivity over D_2 receptors in comparison with those of the corresponding (*S*)-enantiomers **5c**−**e**. It was therefore deduced that D_2, D_3, and D_4 receptors have different bulk tolerance ($D_4 > D_3 > D_2$) for the substituent of the 4-amino group (R^1) on the benzamide nuclei and that three- to five-membered cycloalkylcarbonyl groups such as cyclopropyl-, cyclobutyl-, and cyclopentylcarbonyl probably have suitable bulkiness for both D_3 and D_4 affinity and selectivity over D_2 receptors.

We next focused on the effects of *N*-substituents on the pyrrolidine ring of **5c** (R^2, Table 1). The lengthening of the *N*-benzyl of **5c** into *N*-phenethyl (**5k**) resulted in similar D_3 and D_4 affinity but severalfold stronger D_2 affinity. The saturated benzyl analogue of **5c**, (*S*)-*N*-[1-(cyclohexylmethyl)-3-pyrrolidinyl]benzamide (**5j**), displayed approximately 6-fold greater D_3 affinity (K_i = 3.7 nM) with maintained K_{iD2}/K_{iD3} ratio (8.6) as compared to **5c**, although it had increased D_2 affinity (K_i = 32 nM) and reduced K_{iD2}/K_{iD4} ratio (10). For compound **5f**, in which the cyclohexyl group is directly attached to the nitrogen atom of the pyrrolidine ring, high affinity for both D_3 and D_4 receptors (K_i for D_3 = 4.4 nM, D_4 = 2.1 nM) with improved selectivity over D_2 receptors (K_{iD2}/K_{iD3} = 19, K_{iD2}/K_{iD4} = 40), related to those of **5j**, was seen. Consequently, we converted the R^2 group of **5f** into the further bulky and sterically constrained bicyclic and tricyclic substituents *N*-bicyclo[3.3.1]non-9-yl (BCN) and adamantyl. The compounds **5h**,**i** also displayed high affinity for both D_3 and D_4 receptors (K_i for D_3 = 1.7−2.2 nM, D_4 = 3.8−4.4 nM) and 63−65-fold greater D_3 and 25−37-fold greater D_4 selectivity against D_2 receptors, respectively. The K_{iD2}/K_{iD3} ratio of **5h**,**i** is approximately 6 times better than that of **5c**. In contrast, the more expanded monocyclic analogue **5g** displayed increased D_2 affinity (K_i = 20 nM) and decreased K_{iD2}/K_{iD4} ratio (7.4) than **5f**. Moreover, *N*-unsubstituted **7** showed only weak affinity for all D_2-like receptor subtypes. Similar to **1** (R^1 = H, R^2 = benzyl), compound **5l** (R^1 = Me, R^2 = BCN) showed subnanomolar order K_i values for D_2, D_3, and D_4 receptors with a little or no D_3 and D_4 selectivity against D_2 receptors. These results indicated that the combination of appropriate R^1 and R^2 groups is important in improving D_3 and D_4 selectivity against D_2 receptors in these benzamides.

On this basis several interpretations of the SAR regarding the R^2 group can be suggested. With regard to the D_3 affinity, *N*-alicyclic derivatives such as **5f**−**j** may be more favorable in interacting with the receptors than *N*-aralkyl derivatives such as **5c**,**k**, a characteristic possibly mediated by the hydrophobicity and/or aromaticity of their R^2 groups. For D_2 affinity, despite their greater bulkiness, compounds **5g**,**k** exhibited a greater increase in affinity than the corresponding **5f**,**c**; hence, the bulkiness of the R^2 group is probably not the reason for the diminished affinity. On the other hand, less

Table 2. [29] Affinities of **5c**, Clozapine, and Haloperidol for Other Neurotransmitter Receptors[a,b]

receptors	binding (K_i, nM)		
	5c	clozapine	haloperidol
D_1	>10 000	180 (170−190)[c]	49 (46−52)
D_5	>10 000	780 (710−860)	260 (240−280)
α_1	5300 (4900−5700)	3.6 (3.5−3.8)	9.0 (8.0−10)
α_2	4300 (3400−5500)	230 (220−230)	9600 (8700−11 000)
β	>10 000	>10 000	>10 000
5-HT_{1A}	>10 000	130 (120−130)	1900 (1700−2000)
5-HT_{2A}	>10 000	17 (16−18)	87 (81−94)
5-HT_3	4000 (3800−4200)	32 (31−33)	>10 000
M_1	5400 (4900−6000)	2.1 (2.0−2.3)	1800 (1700−2000)
M_2	7300 (6900−7700)	46 (44−48)	2500 (2400−2600)
H_1	>10 000	5.0 (4.5−5.6)	2100 (1600−2700)

[a] See Table 1. [b] [^{3}H]SCH23390 binding to human cloned D_1 and D_5 receptors; [^{3}H]prazosin binding to rat cortical α_1 receptors; [^{3}H]Rx821002 binding to rat cortical α_2 receptors; [^{3}H]dihydroalprenolol binding to rat cortical β receptors; [^{3}H]-8-OH-DPAT binding to rat hippocampal 5-HT_{1A} receptors; [^{3}H]ketanserin binding to 5-HT_{2A} receptors in rat frontal cortex; [^{3}H]GR65630 binding to N1E-115 neuroblastoma 5-HT_3 receptors; [^{3}H]pirenzepine binding to rat cortical M_1 receptors; [^{3}H]quinucridinyl benzylate binding to rat heart M_2 receptors; and [^{3}H]pyrilamine binding to rat cortical H_1 receptors. [c] Values in parentheses are 95% confidence intervals.

flexible analogues displayed more enhanced D_3 and D_4 selectivity against D_2 receptors than more flexible analogues, e.g., **5c** versus **5k**, **5f** versus **5j**, and **5h**,**i** versus **5f**. On this basis, the negative interaction between the R^2 group and D_2 receptors may be caused by their rigidity, which is possibly caused by their inflexibility and/or through the effect on restriction of pyrrolidine ring conformations.[37] We therefore speculated that the *N*-substituent on the pyrrolidin-3-yl group (R^2) of the 4-[(cyclopropylcarbonyl)amino]benzamides plays an important role in expressing their binding affinity for each D_2-like receptor subtype and that their hydrophobicity, aromaticity, bulkiness, and rigidity are critical for their D_2, D_3, and D_4 affinity and selectivity.

In *in vivo* study, 4-[(cycloalkylcarbonyl)amino]benzamides (R^2 = benzyl) **5c**−**e** and (*R*)-**5c** displayed potent antidopaminergic activity in inhibiting apomorphine-induced climbing behavior, with ED_{50} values of 0.14−0.45 mg/kg on subcutaneous administration. These values are less than those of the traditional D_2 antagonists nemonapride and haloperidol but are about 20-fold more potent than that of the preferential D_4 antagonist clozapine (Table 1). Even though their D_2 affinity is 170−760-fold decreased, their ED_{50} values are only 2.0−6.3 times less than that of **1**. Possibly, D_3, D_4, or both receptors may be implicated in apomorphine-induced climbing behavior, at least in part. Anticlimbing activity of compound **5f** (R^2 = cyclohexyl) is also potent (ED_{50} value, 1.4 mg/kg) but at a level slightly less than those of **5c**−**e** and (*R*)-**5c**, despite its increased D_2 and D_3 affinity. Contrary to our expectations, compounds **5h**,**i**, which have high affinity and selectivity for both D_3 and D_4 receptors, showed very weak or no anticlimbing activity. We therefore speculated that the much greater hydrophobicity of the R^2 group of these compounds compared with that of cyclohexyl may produce a decrease in bioavailability in this behavioral test, because **5f**,**h**,**i** which have a more hydrophobic R^2 group showed weaker activity (π coefficients of benzyl, cyclohexyl, and adamantyl groups = 2.01, 2.51, and 3.30, respectively),[35] although unrelated to their binding affinity. For more reliable bioavailability discussions, the study for brain and blood level of the compounds should be required.

Among these benzamides, further *in vitro* characterization was done on the novel 4-[(cyclopropylcarbonyl)-amino]benzamide **5c**, which showed high affinity for D_3 and D_4 receptors, selectivity against D_2 receptors, and potent anticlimbing activity. Results showed that **5c** possesses weak or negligible affinity for other neurotransmitter receptors, namely, D_1, D_5, α_1, α_2, β, 5-HT_{1A}, 5-HT_{2A}, 5-HT_3, H_1, M_1, and M_2 receptors.[29] This profile is highly specific as compared to those of haloperidol and clozapine (Table 2). Moreover, compound **5c** exhibited full antagonist activity for D_2, D_3, and D_4 receptors in *in vitro* functional assays.[29]

Conclusion

We synthesized and evaluated a series of *N*-(3-pyrrolidinyl)benzamide derivatives, **1**, (*R*)-**1**, **2a**−**d**, **5a**−**l**, (*R*)-**5c**−**e**, and **7,** for their binding affinity for dopamine D_2-like receptor subtypes. The SAR studies indicate that the 4-substituent on the benzamide nuclei and the *N*-substituent on the pyrrolidine ring play a critical role in improving D_3 and D_4 selectivity over D_2 receptors. Some preferential D_3 and D_4 antagonists among them also exhibited potent inhibitory activity against apomorphine-induced climbing behavior in mice. The novel [(cyclopropylcarbonyl)amino]benzamide **5c** possesses high affinity for D_3 and D_4 receptors (K_i values of 21 and 2.1 nM, respectively) and selectivity for D_4 and D_3 receptors (K_{iD2}/K_{iD4} = 110, K_{iD2}/K_{iD3} = 10) with weak or negligible affinity for other neurotransmitter receptors. *In vivo*, **5c** exhibited inhibitory activity against apomorphine-induced climbing behavior with an ED_{50} value of 0.32 mg/kg (sc). To our knowledge, this biological profile is markedly different from those of known antipsychotics.[10] Thus compound **5c** may produce unique pharmacological effects, including atypical antipsychotic effects. Further, we believe that **5c** would contribute to our understanding of the physiological and pharmacological functions of D_2-like receptor isoforms.

Experimental Section

Chemistry. Melting points were measured on a Yanaco MP-3 melting point apparatus and are uncorrected. Unless stated otherwise, ^{1}H NMR spectra were measured in DMSO-d_6 or $CDCl_3$ with a JEOL FX90Q, FX100, EX400, or GX500 spectrometer; chemical shifts are expressed in δ units using tetramethylsilane as the standard (in NMR description: s = singlet, d = doublet, t = triplet, q = quartet, se = sextet, m = multiplet, and br = broad peak). Mass spectra were recorded with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. $[\alpha]^{20}_D$ was measured on a Horiba high-sensitive polarimeter (SEPA-200). The optically pure materials (*S*)- (**9**) and (*R*)- (**10**) 3-amino-1-benzylpyrrolidine and (*S*)-3-[(*tert*-butoxycarbonyl)-amino]pyrrolidine (**11**) were purchased from Tokyo Kasei Co., Ltd. The enantiomeric purity of **5c**−**e**, and (*R*)-**5c**−**e** was checked by HPLC analysis on a Hitachi HPLC system (L-4000H UV detector, L-6200 pump, D-2500 chromatointegrator)

utilizing a sugar−silica gel-based chiralcel OD-H column (4.6 i.d. × 250 mm) from Dicel Chemical Ind., Ltd., with the mobile phase consisting of 0.1% Et_2NH−EtOH and a flow rate on the column of 0.4 mL/min at room temperature. The results indicated that the compounds possess optical purity of at least 99.8% ee. Where elemental analyses (C, H, Cl, F, N) are indicated only by symbols of the elements, analytical results obtained for these elements were within 0.4% of theoretical values except where otherwise stated.

(*S*)-(+)-4-Amino-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamide (1). Benzamide **1** was prepared by the previously described method for (±)-**1**.[27] To an ice/salt-cold solution of 4-amino-5-chloro-2-methoxybenzoic acid (**8**; 8.06 g, 40.0 mmol) and triethylamine (6.07 g, 60.0 mmol) in CH_2Cl_2 (400 mL) was added dropwise ethoxycarbonyl chloride (4.68 g, 43.2 mmol), and the mixture was stirred for 20 min. To this solution was added dropwise a solution of (*S*)-3-amino-1-benzylpyrrolidine (**9**; 7.61 g, 43.2 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at the same temperature for 2 h. The mixture was then allowed to warm to room temperature, treated with saturated aqueous $NaHCO_3$ (400 mL), and extracted with CH_2Cl_2 (3 × 400 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo. The residue thus obtained was purified by chromatography on silica gel using $CHCl_3$−methanol as eluent and recrystallized from ethyl acetate−ether to give 10.7 g (74%) of benzamide **1** as a white solid: mp 139−140 °C (EtOAc−Et_2O); $[\alpha]^{20}_D = +28°$ (c = 2.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ 8.06 (s, 1H), 7.94 (brd, 1H), 7.29−7.48 (m, 4H), 7.23−7.26 (m, 1H), 6.25 (s, 1H), 4.56−4.62 (m, 1H), 4.45 (brs, 1H), 3.84 (s, 3H), 3.65 (d, 1H), 3.59 (d, 1H), 2.87−2.90 (m, 1H), 2.62−2.69 (m, 2H), 2.30−2.40 (m, 2H), 1.68−1.75 (m, 1H); MS (FAB) m/z 360 (M + 1). Anal. ($C_{19}H_{22}N_3O_3Cl$) C, H, N, Cl.

(*R*)-(−)-4-Amino-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamide [(*R*)-1]. The title compound was prepared by the method described above using (*R*)-3-amino-1-benzylpyrrolidine (**10**). The compound exhibited the same NMR and mass spectrum as its enantiomer **1**: 80% from **8**; mp 136−138 °C (EtOAc−Et_2O); $[\alpha]^{20}_D = -28°$ (c = 2.0 in MeOH). Anal. ($C_{19}H_{22}N_3O_3Cl$) C, H, N, Cl.

General Method for Preparation of Benzamides 2a−d. The compounds were prepared by acylation of **1** with acid anhydride (for **2a**) and acid chloride (for **2b−d**).

(*S*)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-2-methoxy-4-[(trifluoroacetyl)amino]benzamide Hydrochloride (2a·HCl). To an ice-cold solution of compound **1** (0.50 g, 1.4 mmol) in CH_2Cl_2 (50 mL) was added slowly a solution of trifluoroacetic anhydride (0.35 g, 1.7 mmol). After stirring for 1 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to yield an oily residue which was chromatographed on silica gel using $CHCl_3$−methanol as the eluent. The clear colorless syrup thus obtained was converted into the HCl salt by treatment with 1 equiv of 4 N HCl−ethyl acetate solution in ether to provide the title compound as a hygroscopic white solid (0.41 g, 60%): mp 119−124 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 13.17 (br, 1H), 8.58 (s, 1H), 8.15 (d, 2H), 7.61 (dd, 2H), 7.44 (t, 3H), 5.13 (br, 1H), 4.25 (dd, 2H), 4.11 (s, 3H), 3.72 (br, 1H), 3.54 (m, 1H), 3.30 (br, 1H), 2.93 (br, 1H), 2.58−2.63 (m, 1H), 2.37−2.47 (m, 1H); peaks caused by a small amount of ether observed at 3.38 (q) and 1.09 (t); MS (FAB) m/z 456 (M + 1). Anal. ($C_{21}H_{21}N_3O_3F_3Cl\cdot HCl\cdot 0.5H_2O\cdot 0.1Et_2O$) C, H, N, Cl, F.

(*S*)-(+)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclohexylcarbonyl)amino]-2-methoxybenzamide (2c). To an ice-cold solution of compound **1** (0.30 g, 0.83 mmol) in CH_2Cl_2 (15 mL), was added slowly a solution of cyclohexylcarbonyl chloride (0.15 g, 1.0 mmol). After stirring for 1 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo. The residue thus obtained was purified by chromatography on silica gel eluting with $CHCl_3$−methanol and recrystallized from ethyl acetate to give 0.22 g (56%) of benzamide **2d** as a white solid: mp 135−137 °C (EtOAc); $[\alpha]^{20}_D = +41°$ (c = 1.0 in THF); ^{1}H NMR (DMSO-d_6) δ 9.38 (s, 1H), 8.18 (d, 1H), 7.74 (s, 1H), 7.74 (s, 1H), 7.33 (d, 4H), 7.22−7.27 (m, 1H), 4.35 (m, 1H), 3.87 (s, 3H), 3.63 (d, 1H), 3.56 (d, 1H), 2.65−2.73 (m, 2H), 2.55−2.61 (m, 1H), 2.50 (t, 1H), 2.22−2.46 (m, 2H), 2.14−2.22 (m, 1H), 1.84 (d, 2H), 1.75 (d, 2H), 1.64−1.70 (m, 2H), 1.13−1.45 (m, 4H); MS (FAB) m/z 470 (M + 1). Anal. ($C_{26}H_{32}N_3O_3Cl$) C, H, N, Cl.

(*S*)-(+)-4-(Acryloylamino)-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamide (2b): 35% from **1**; mp 122−123 °C (EtOAc−Et_2O); $[\alpha]^{20}_D = +45°$ (c = 2.0 in MeOH); ^{1}H NMR (DMSO-d_6) δ 9.78 (s, 1H), 8.21 (d, 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.33 (d, 4H), 7.23−7.31 (m, 1H), 6.69−6.76 (m, 1H), 6.33 (dd, 1H), 5.83 (dd, 1H), 4.36 (m, 1H), 3.88 (s, 3H), 3.65 (d, 1H), 3.58 (d, 1H), 2.70 (m, 2H), 2.45 (m, 2H), 2.14−2.33 (m, 1H), 1.70 (m, 1H); MS (FAB) m/z 414 (M + 1). Anal. ($C_{22}H_{24}N_3O_3Cl\cdot 0.5H_2O$) C, H, N, Cl; Cl: calcd, 8.38; found, 9.28.

(*S*)-(+)-4-(Benzoylamino)-*N*-(1-benzyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamide (2d): 85% from **1**; mp 63−65 °C; $[\alpha]^{20}_D = +31°$ (c = 2.0 in MeOH); ^{1}H NMR (DMSO-d_6) δ 7.15−7.40 (m, 11H), 5.86 (s, 1H), 5.15 (qu, 1H), 3.70 (s, 2H), 3.62 (s, 3H), 3.11 (t, 1H), 2.91−2.95 (m, 1H), 2.80−2.88 (m, 2H), 2.28 (t, 2H); MS(FAB) m/z 464 (M + 1). Anal. ($C_{26}H_{26}N_3O_3Cl\cdot 0.25H_2O$) C, H, N, Cl.

(*S*)-3-Amino-1-cyclohexylpyrrolidine Dihydrochloride (3a·2HCl). A solution of (*S*)-3-[(*tert*-butoxycarbonyl)amino]-pyrrolidine (**11**; 10.0 g, 53.7 mmol) and cyclohexanone (5.55 g, 56.5 mmol) in methanol (250 mL) was hydrogenated under atmospheric pressure with 10% palladium on carbon (0.20 g) for 3 h at room temperature. The catalyst was filtered off, and the filtrate was concentrated to a solid residue and washed with a small amount of *n*-hexane to give 13.5 g (94%) of (*S*)-3-[(*tert*-butoxycarbonyl)amino]-1-cyclohexylpyrrolidine as the *N*-BOC intermediate: ^{1}H NMR ($CDCl_3$) δ 4.85 (br, 1H), 4.14 (m, 1H), 2.84 (m, 1H), 2.65 (m, 1H), 2.61 (m, 1H), 2.35 (m, 1H), 2.20−2.26 (m, 1H), 1.95−2.00 (m, 1H), 2.90 (m, 2H), 1.73 (m, 2H), 1.52−1.61 (m, 2H), 1.44 (s, 9H), 1.13−1.30 (m, 5H); MS (EI) m/z 268 (M).

The *N*-BOC intermediate, cyclohexylpyrrolidine (13.0 g, 48.4 mmol), was stirred with 4 N HCl−ethyl acetate solution until evolution of gas ceased at room temperature. The resulting precipitate was collected, washed with *n*-hexane, and dried under vacuum overnight to give 11.01 g (94%) of the title compound as a hygroscopic white solid. The product was used without further purification in the next step: MS (EI) m/z 168 (M).

The following examples (**3b−f**) were prepared by the method described above using the appropriate aldehydes or ketones.

(*S*)-3-Amino-1-cycloheptylpyrrolidine Dihydrochloride (3b·2HCl). *N*-BOC intermediate: 96% from **11**; ^{1}H NMR (DMSO-d_6) δ 6.87 (d, 1H), 3.83 (br, 1H), 3.31 (s, 1H), 2.75 (t, 1H), 2.22−2.29 (m, 2H), 1.91−1.99 (m, 1H), 1.54−1.71 (m, 6H), 1.44−1.52 (m, 8H), 1.21 (s, 9H); MS (FAB) m/z 283 (M + 1). The title compound **3b**, was obtained in 86% yield from the intermediate.

(*S*)-3-Amino-1-(bicyclo[3.3.1]non-9-yl)pyrrolidine dihydrochloride (3c·2HCl): 88% from **11** (two steps); ^{1}H NMR (DMSO-d_6) δ 10.73 (brs, 1H), 10.28 (brs, 1H), 8.80 (brs, 2H), 4.02−4.10 (m, 1H), 3.74−3.87 (m, 1H), 3.51−3.64 (m, 2H), 3.31 (m, 1H), 3.17−3.22 (m, 1H), 2.55 (m, 1H), 2.07−2.26 (m, 5H), 1.72−1.84 (m, 6H), 1.49−1.58 (m, 4H); MS (FAB) m/z 209 (M + 1).

(*S*)-3-Amino-1-(2-adamantyl)pyrrolidine dihydrochloride (3d·2HCl): 82% from **11** (two steps); ^{1}H NMR (DMSO-d_6) δ 10.0−10.90 (m, 2H), 9.02 (s, 2H), 4.12−4.20 (m, 1H), 3.89−4.11 (m, 1H), 3.47−3.89 (m, 2H), 3.22−3.45 (m, 1H), 2.70−3.00 (m, 1H), 2.30−2.58 (m, 4H), 2.12−2.30 (m, 2H), 1.80−2.00 (m, 4H), 1.75−1.87 (m, 4H), 1.60−1.75 (m, 2H); MS (EI) m/z 220 (M).

(*S*)-3-Amino-1-(cyclohexylmethyl)pyrrolidine dihydrochloride (3e·2HCl): 77% from **11** (two steps); ^{1}H NMR (DMSO-d_6) δ 11.07 (brs, 1H), 10.58 (brs, 1H), 8.78 (brd, 2H), 3.45−4.05 (m, 5H), 3.02−3.20 (m, 1H), 2.10−2.35 (m, 1H), 1.86 (m, 2H), 1.60−1.69 (m, 4H), 1.11−1.27 (m, 3H), 0.89−0.98 (q, 2H); MS (EI) m/z 182 (M).

(*S*)-3-Amino-1-phenethylpyrrolidine Dihydrochloride (3f·2HCl). *N*-BOC intermediate: 71% from **11**; ^{1}H NMR

($CDCl_3$) δ 7.19−7.30 (m, 5H), 5.00 (m, 1H), 4.20 (m, 1H), 2.58−3.10 (m, 7H), 2.20−2.40 (m, 2H), 1.56−1.71 (m, 1H), 1.49 (s, 9H); MS (FAB) *m*/*z* 291 (M + 1). The title compound **3f** was obtained in 60% yield from the intermediate: MS (EI) *m*/*z* 190 (M + 1).

5-Chloro-2-methoxy-4-(propionylamino)benzoic Acid (4a). To an ice-cold solution of **8** (0.76 g, 3.7 mmol) and pyridine (0.63 g, 7.9 mmol) in CH_2Cl_2 (20 mL) was added propionyl chloride (0.36 g, 3.9 mmol) dropwise. The mixture was stirred overnight at room temperature, poured onto aqueous 1 N HCl (20 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue thus obtained was purified by chromatography on silica gel eluting with $CHCl_3$−methanol to give 0.60 g (62%) of (propionylamino)benzoic acid **4a** as a white solid: 62%; ^{1}H NMR (DMSO-d_6) δ 12.70 (br, 1H), 9.41 (s, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 3.79 (s, 3H), 2.49 (q, 2H), 1.10 (t, 3H); MS (FAB) *m*/*z* 258 (M + 1).

5-Chloro-2-methoxy-4-[(2-methylpropionyl)amino]benzoic Acid (4b). The title compound was prepared by the method described for **4a** using 2-methylpropionyl chloride: 35% yield; mp 133−134 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ 9.41 (br, 1H), 7.72 (s, 2H), 3.79 (s, 3H), 2.89 (q, 1H), 1.13 (d, 6H); MS (FAB) *m*/*z* 272 (M + 1).

Methyl 4-Amino-5-chloro-2-methoxybenzoate (12).[31] A solution of benzoic acid **8** (20.0 g, 99.2 mmol), potassium carbonate (16.5 g, 119 mmol), and dimethyl sulfate (13.6 g, 109 mmol) in dimethyl sulfoxide (400 mL) was heated to reflux for 4 h.[32] After cooling to room temperature, the reaction mixture was poured onto ice−water (500 g), and the resulting precipitate was filtered, washed with H_2O, and recrystallized from methanol to give 16.0 g (75%) of methyl ester as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 6.29 (s, 1H), 4.46 (brs, 2H), 3.84 (s, 3H), 3.83 (s, 3H); MS (EI) *m*/*z* 215 (M).

5-Chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzoic Acid (4c). To an ice-cold solution of **12** (37.8 g, 175 mmol) and pyridine (30.5 g, 386 mmol) in CH_2Cl_2 (700 mL) was added dropwise cyclopropylcarbonyl chloride (20.2 g, 193 mmol) in CH_2Cl_2 (100 mL). The solution was allowed to warm to room temperature, stirred for 4 h, and then poured into H_2O (1 L). The organic layer was washed with saturated aqueous NaCl (200 mL) and then H_2O (200 mL), dried over Na_2SO_4, and evaporated in vacuo. The solid residue was washed with ether and dried under vacuum to give 43.1 g (87%) of acylated intermediate. The product (41.8 g) was dissolved in DMSO (120 mL) at 60 °C. The solution was cooled in a water bath and added dropwise to aqueous 2 N NaOH (200 mL), and the mixture was stirred for 30 min and then acidified with aqueous 6 N HCl to pH 1. The resulting precipitate was collected, washed with H_2O, and dried in vacuo to give 36.7 g (94%) of **4c** as a white solid: mp 167−169 °C; ^{1}H NMR (DMSO-d_6) δ 12.71 (br, 1H), 9.78 (s, 1H), 7.80 (s, 1H), 7.73 (s, 1H), 3.77 (s, 3H), 2.15 (m, 1H), 0.82−0.86 (m, 4H); MS (FAB) *m*/*z* 270 (M + 1).

The following examples (for **4d**,**e**) were prepared by the method described for **4c** using the appropriate acyl chloride.

5-Chloro-4-[(cyclobutylcarbonyl)amino]-2-methoxybenzoic acid (4d): 89% from **12** (two steps); mp 174−176 °C;^{1}H NMR (DMSO-d_6) δ 12.70 (br, 1H), 9.26 (br, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 3.80 (s, 3H), 3.42 (m, 1H), 1.68−2.41 (m, 6H); MS (FAB) *m*/*z* 284 (M + 1).

5-Chloro-4-[(cyclopentylcarbonyl)amino]-2-methoxybenzoic acid (4e): 77% from **12** (two steps); mp 160−162 °C; ^{1}H NMR (DMSO-d_6) δ 12.73 (brs, 1H), 9.41 (s, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 3.79 (s, 3H), 3.03 (m, 1H), 1.86−1.92 (m, 2H), 1.63−1.79 (m, 4H), 1.51−1.63 (m, 2H); MS (FAB) *m*/*z* 298 (M + 1).

General Method for Preparation of Benzamides 5a−k and (*R*)-5c−e. The compounds **5a**,**c**−**f**,**h**,**i** and (*R*)-**5c**−**e** were prepared by the method described for the preparation of **1** utilizing the appropriate (*S*)- or (*R*)-aminopyrrolidines **3a**−**f**, **9**, and **10** and benzoic acids **4a,c**−**e**. The compounds **5b,g,j,k** were prepared by the diphenyl phosphorazidate method[33] utilizing the aminopyrrolidines **3b,e,f** and **9** and benzoic acids **4b,c**.

(*S*)-(+)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-2-methoxy-4-(propionylamino)benzamide (5a): 72% from **4a**; mp 147−149 °C (Et_2O−EtOH); $[\alpha]^{20}_D$ = +43° (*c* = 1.0 in THF); ^{1}H NMR (DMSO-d_6) δ 9.45 (s, 1H), 8.18 (d, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 7.33 (d, 4H), 7.25 (m, 1H), 4.35 (m, 1H), 3.87 (s, 3H), 3.63 (d, 1H), 3.56 (d, 1H), 2.65−2.73 (m, 2H), 2.37−2.50 (m, 4H), 2.13−2.22 (m, 1H), 1.64−1.72 (m, 1H), 1.09 (t, 3H); MS (FAB) *m*/*z* 416 (M + 1). Anal. ($C_{22}H_{26}N_3O_3Cl$·0.25H_2O) C, H, N, Cl.

(*S*)-(+)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (5c): 86% from **4c**; mp 102−104 °C (Et_2O); $[\alpha]^{20}_D$ = +41° (*c* = 2.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 8.17 (d, 1H), 7.78 (s, 1H), 7.73 (s, 1H), 7.31−7.33 (m, 4H), 7.25 (m, 1H), 4.34 (m, 1H), 3.85 (s, 3H), 3.63 (d, 1H), 3.56 (d, 1H), 2.65−2.72 (m, 2H), 2.38−2.46 (m, 2H), 2.10−2.22 (m, 2H), 1.67 (m, 1H), 0.81−0.85 (m, 4H); MS (FAB) *m*/*z* 428 (M + 1). Anal. ($C_{23}H_{26}N_3O_3$-Cl) C, H, N, Cl.

(*R*)-(−)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide [(*R*)-5c]: 76% from **4c**; exhibited same NMR and mass spectrum as its enantiomer **5c**; mp 102−103 °C (Et_2O); $[\alpha]^{20}_D$ = −41° (*c* = 2.0 in MeOH). Anal. ($C_{23}H_{26}N_3O_3Cl$) C, H, N, Cl.

(*S*)-(+)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclobutylcarbonyl)amino]-2-methoxybenzamide (5d): 79% from **4d**; mp 109−110 °C (EtOAc−Et_2O); $[\alpha]^{20}_D$ = +36° (*c* = 2.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ 9.31 (s, 1H), 8.19 (d, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 7.33 (d, 4H), 7.25 (m, 1H), 4.35 (m, 1H), 3.88 (s, 3H), 3.63 (d, 1H), 3.56 (d, 1H), 3.44 (t, 1H), 2.68 (m, 2H), 2.38−2.46 (m, 2H), 2.12−2.29 (m, 5H), 1.94 (m, 1H), 1.83 (m, 1H), 1.69 (m, 1H); MS (FAB) *m*/*z* 442 (M + 1). Anal. ($C_{24}H_{28}N_3O_3Cl$) C, H, N, Cl.

(*R*)-(−)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclobutylcarbonyl)amino]-2-methoxybenzamide [(*R*)-5d]: 97% from **4d**; exhibited the same NMR and mass spectrum as its enantiomer **5d**; mp 110−112 °C (Et_2O); $[\alpha]^{20}_D$ = −37° (*c* = 2.0 in MeOH). Anal. ($C_{24}H_{28}N_3O_3Cl$) C, H, N, Cl.

(*S*)-(+)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopentylcarbonyl)amino]-2-methoxybenzamide (5e): 78% from **4e**; mp 120−121 °C (EtOAc−Et_2O); $[\alpha]^{20}_D$ = +35° (*c* = 2.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.19 (d, 1H), 8.09 (d, 1H), 7.86 (s, 1H), 7.30−7.35 (m, 4H), 7.23−7.27 (m, 1H), 4.60 (m, 1H), 3.97 (s, 3H), 3.69 (d, 1H), 3.60 (d, 1H), 2.87−2.92 (m, 1H), 2.77−2.84 (m, 1H), 2.64−2.70 (m, 2H), 2.31−2.40 (m, 2H), 1.98−2.03 (m, 2H), 1.88−1.94 (m, 2H), 1.77−1.84 (m, 2H), 1.66−1.74 (m, 3H); MS (FAB) *m*/*z* 456 (M + 1). Anal. ($C_{25}H_{30}N_3O_3Cl$·0.25H_2O) C, H, N, Cl.

(*R*)-(−)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-4-[(cyclopentylcarbonyl)amino]-2-methoxybenzamide [(*R*)-5e]: 68% from **4e**; exhibited the same NMR and mass spectrum as its enantiomer **5e**; mp 122−123 °C (EtOAc−Et_2O); $[\alpha]^{20}_D$ = −36° (*c* = 2.0 in MeOH). Anal. ($C_{25}H_{30}N_3O_3Cl$) C, H, N, Cl.

(*S*)-(+)-5-Chloro-*N*-(1-cyclohexyl-3-pyrrolidinyl)-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (5f): 74% from **4c**; mp 137−139 °C (*n*-hexane−EtOAc−Et_2O); $[\alpha]^{20}_D$ = +35° (*c* = 2.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ 8.33 (s, 1H), 8.20 (s, 1H), 8.03 (br, 2H), 4.58 (m, 1H), 3.95 (s, 3H), 2.94 (m, 1H), 2.79 (m, 1H), 2.73 (m, 1H), 2.43 (dd, 1H), 2.31 (m, 2H), 2.07 (m, 1H), 1.90 (m, 2H), 1.75 (m, 3H), 1.59−1.65 (m, 2H), 1.25 (m, 5H), 1.12−1.14 (m, 2H), 0.93−0.97 (m, 2H); MS (FAB) *m*/*z* 420 (M + 1). Anal. ($C_{22}H_{30}N_3O_3Cl$) C, H, N, Cl.

(*S*)-*N*-[1-(Bicyclo[3.3.1]non-9-yl)-3-pyrrolidinyl]-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (5h): 71% from **4c**; mp 159−163 C (MeOH); ^{1}H NMR ($CDCl_3$) δ 9.80 (s, 1H), 8.20−8.21 (d, 1H), 7.80−7.81 (m, 2H), 4.35−4.45 (m, 1H), 3.84 (s, 3H), 2.76−2.81 (m, 1H), 2.50−2.56 (m, 2H), 2.25−2.31 (m, 1H), 2.12−2.17 (m, 2H), 1.92−1.96 (m, 3H), 1.75−1.85 (m, 6H), 1.64−1.67 (m, 3H), 1.44−1.52 (m, 2H), 1.35−1.38 (m, 2H), 0.84−0.85 (m, 4H); MS (FAB) *m*/*z* 460 (M + 1). Anal. ($C_{25}H_{34}N_3O_3Cl$) C, H, N, Cl.

(*S*)-(+)-*N*-[1-(2-Adamantyl)-3-pyrrolidinyl]-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (5i): 71% from **4c**; mp 162−168 °C (EtOH); $[\alpha]^{20}_D$ = +20° (*c* = 1.0 in THF); ^{1}H NMR ($CDCl_3$) δ 9.81 (s, 1H), 8.21−8.23 (d, 1H), 7.80−7.81 (m, 2H), 4.35−4.45 (m, 1H), 3.84 (s, 3H), 2.80−2.85 (m, 1H), 2.56−2.61 (m, 1H), 2.47−2.51 (m, 1H), 2.22−2.26 (m, 1H), 2.02−2.19 (m, 5H), 1.85−1.95 (m, 2H), 1.79−1.81 (m, 4H), 1.65−1.69 (m, 5H), 1.41−1.44 (m, 2H), 0.84−0.85 (m, 4H); MS (FAB) *m*/*z* 472 (M + 1). Anal. ($C_{26}H_{34}N_3O_3Cl$·0.5H_2O) C, H, N, Cl; Cl: calcd, 7.37; found, 8.30.

(*S*)-(+)-*N*-(1-Benzyl-3-pyrrolidinyl)-5-chloro-2-methoxy-4-[(2-methylpropionyl)amino]benzamide (5b). To an ice-cold solution of benzoic acid **4b** (0.30 g, 1.10 mmol), pyrrolidine **8** (0.23 g, 1.30 mmol), and triethylamine (0.17 g, 1.66 mmol) in DMF (20 mL) was added dropwise diphenyl phosphorazidate (0.37 g, 1.35 mmol). The reaction mixture was stirred at the same temperature for 4 h and then allowed to warm up to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, the mixture was diluted with ethyl acetate (30 mL), and the organic layer was washed with saturated aqueous NaCl. The organic extract was dried over Na_2SO_4 and concentrated in vacuo to yielded an amorphous residue which was chromatographed on silica gel using $CHCl_3$−methanol as the eluent. The white solid thus obtained was recrystallized from ether to provide the title compound as a white solid (0.26 g, 55%): mp 95−97 °C (Et_2O); $[\alpha]^{20}_D = +35°$ (c = 2.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1H), 8.19 (d, 1H), 8.09 (d, 1H), 7.88 (s, 1H), 7.28−7.35 (m, 3H), 7.23−7.26 (m, 2H), 4.59−4.64 (m, 1H), 3.98 (s, 3H), 3.69 (d, 1H), 3.61 (d, 1H), 2.87−2.92 (m, 1H), 2.59−2.70 (m, 3H), 2.32−2.41 (m, 2H), 1.70−1.75 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H); MS (FAB) m/z 430 (M + 1). Anal. ($C_{23}H_{28}N_3O_3Cl$) C, H, N, Cl.

(*S*)-(+)-5-Chloro-*N*-(1-cycloheptyl-3-pyrrolidinyl)-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (5g): 52% from **4c**; mp 98−100 °C (Et_2O); $[\alpha]^{20}_D = +37°$ (c = 2.0 in MeOH);^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 8.14 (d, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 4.32 (m, 1H), 3.84 (s, 3H), 2.74 (m, 1H), 2.68 (m, 1H), 2.52 (m, 1H), 2.35−2.41 (m, 2H), 2.06−2.17 (m, 2H), 1.48−1.73 (m, 11H), 1.38−1.42 (m, 2H), 0.81−0.86 (m, 4H); MS (FAB) m/z 434 (M + 1). Anal. ($C_{23}H_{32}N_3O_3Cl$) C, H, N, Cl.

(*S*)-(+)-*N*-[1-(Cyclohexylmethyl)-3-pyrrolidinyl]-5-chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxybenzamide (5j): 38% from **4c**; mp 170−171 °C (EtOAc−Et_2O); $[\alpha]^{20}_D = +37°$ (c = 1.0 in THF); ^{1}H NMR (DMSO-d_6) δ 9.79 (s, 1H), 8.15 (d, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 4.34 (m, 1H), 3.84 (s, 3H), 2.65−2.70 (m, 1H), 2.56 (dd, 1H), 2.46 (dd, 1H), 2.09−2.34 (m, 5H), 1.77 (t, 2H), 1.64 (m, 4H), 1.42 (m, 1H), 1.12−1.25 (m, 3H), 0.83−0.86 (m, 6H); slight $CHCl_3$ peak observed at 8.32 (s), which was derived from the eluent of column chromatography; MS (FAB) m/z 434 (M + 1). Anal. ($C_{23}H_{32}N_3O_3Cl\cdot 0.02CHCl_3$) C, H, N, Cl.

(*S*)-(+)-5-Chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxy-*N*-(1-phenethyl-3-pyrrolidinyl)benzamide fumarate (5k·$C_4H_4O_4$): 43% from **4c**; amorphous (wash with EtOH); $[\alpha]^{20}_D = +29°$ (c = 2.0 in MeOH); ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 8.28 (d, 1H), 8.16 (s, 1H), 8.04 (s, 1H), 7.19−7.31 (m, 5H), 6.80 (s, 2H), 4.76 (m, 1H), 4.01 (s, 3H), 3.34 (m, 1H), 3.18 (m, 1H), 2.85−3.15 (m, 5H), 2.65 (m, 1H), 2.43 (m, 1H), 1.98 (m, 1H), 1.61 (m, 1H), 1.11−1.15 (m, 2H), 0.92−0.97 (m, 2H); MS (FAB) m/z 442 (M + 1). Anal. ($C_{24}H_{28}N_3O_3Cl\cdot C_4H_4O_4\cdot 1.5H_2O$) C, H, N, Cl.

(*S*)-(+)-*N*-[1-(Bicyclo[3.3.1]non-9-yl)-3-pyrrolidinyl]-5-chloro-2-methoxy-4-(methylamino)benzamide (5l). The title compound was prepared from 5-chloro-2-methoxy-4-(methylamino)benzoic acid (**4f**)[27] and pyrrolidine **3c** using the method described for **1**: 30% from benzoic acid; mp 183−184 °C (EtOAc); $[\alpha]^{20}_D = +45°$ (c = 1.0 in THF); ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 8.08 (br, 1H), 6.10 (s, 1H), 4.70 (brd, 1H), 4.63 (m, 1H), 3.94 (s, 3H), 2.95 (d, 3H), 2.74 (d, 1H), 2.45 (dd, 1H), 2.17−2.28 (m, 2H), 1.65−2.06 (m, 13H), 1.48−1.53 (m, 2H), 1.40−1.43 (m, 2H); MS (FAB) m/z 406 (M + 1). Anal. ($C_{22}H_{32}N_3O_2Cl$) C, H, N, Cl.

(*S*)-3-Amino-1-(trifluoroacetyl)pyrrolidine Hydrochloride (6·HCl). To a solution of **11** (1.00 g, 5.37 mmol) and pyridine (0.51 g, 6.44 mmol) in CH_2Cl_2 (25 mL) was added dropwise trifluoroacetic anhydride (1.24 g, 5.91 mmol). The reaction mixture was stirred overnight at room temperature and then evaporated in vacuo. The remaining oil was diluted with ethyl acetate (50 mL), washed with H_2O (50 mL) twice, dried over Na_2SO_4, and then concentrated under vacuum. The crude product was purified by chromatography on silica gel eluting with $CHCl_3$−MeOH to give the *N*-BOC intermediate as an oil (1.18 g, 90%): ^{1}H NMR ($CDCl_3$) δ 4.67−4.74 (m, 1H), 4.17−4.40 (m, 1H), 3.36−3.99 (m, 4H), 1.82−2.30 (m, 1H), 1.45 (s, 9H); MS (FAB) m/z 227 (M − H_2O + 1).

The product (1.07 g, 4.38 mmol) was stirred with 4 N HCl−ethyl acetate solution until evolution of gas ceased at room temperature. The solution was evaporated under vacuum, and the solid residue was washed with ether and dried in vacuo to yield the title compound (0.75 g, 78%) as a white solid: MS (FAB) m/z 183 (M + 1).

(*S*)-(+)-5-Chloro-4-[(cyclopropylcarbonyl)amino]-2-methoxy-*N*-(3-pyrrolidinyl)benzamide Hydrochloride (7·HCl). To an ice-cold solution of benzoic acid **4c** (0.88 g, 3.25 mmol), pyrrolidine **6·HCl** (0.71 g, 3.25 mmol), and triethylamine (0.82 g, 8.12 mmol) in DMF (50 mL) was added dropwise diphenyl phosphorazidate (1.07 g, 3.90 mmol). The reaction mixture was stirred at room temperature overnight and then evaporated in vacuo. The residue was diluted with ethyl acetate (30 mL) and washed with saturated aqueous $NaHCO_3$ and then saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to yielded an amorphous residue which was chromatographed on silica gel using $CHCl_3$−methanol as the eluent to provide the *N*-trifluoroacetyl intermediate as a white solid (1.23 g, 87%): ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1H), 8.19 (s, 1H), 8.06 (s, 1H), 7.92 (dd, 1H), 4.67−4.77 (m, 1H), 3.88−4.13 (m, 1H), 3.95 (s, 3H), 3.58−3.83 (m, 3H), 2.26−2.44 (m, 1H), 2.00−2.18 (m, 1H), 1.62−1.68 (m, 1H), 1.12−1.16 (m, 2H), 0.95−0.99 (m, 2H); MS (FAB) m/z 434 (M + 1).

The intermediate (1.01 g, 2.33 mmol) in a solution of MeOH (50 mL) and H_2O (10 mL) was treated with K_2CO_3 (0.64 g, 4.66 mmol) for 1 h at room temperature. The reaction mixture was evaporated under vacuum, and the amorphous residue was purified by chromatography on silica gel eluting with 1% $NH_4OH/CHCl_3$−MeOH (2:1), treated with 1 equiv of 4 N HCl−ethyl acetate solution in ethyl acetate, and dried under vacuum to give the title compound (0.23 g, 29%) as a white solid: mp 213−214 °C (EtOAc); $[\alpha]^{20}_D = +15°$ (c = 1.0 in MeOH); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 8.41 (s, 1H), 8.34 (d, 1H), 8.28 (s, 1H), 8.09 (s, 1H), 4.79−4.83 (m, 1H), 4.04 (s, 3H), 3.47−3.56 (m, 2H), 3.37−3.41 (m, 1H), 3.25−3.32 (m, 1H), 2.39 (se, 1H), 2.19 (se, 1H), 1.78−1.82 (m, 1H), 1.08−1.12 (m, 2H), 0.92−0.97 (m, 2H); MS (FAB) m/z 338 (M + 1). Anal. ($C_{16}H_{20}N_3O_3Cl\cdot HCl\cdot 0.5H_2O$) C, H, N, Cl; Cl: calcd, 18.50; found, 19.02.

Biology. Expression of Recombinant Receptors and Radiobinding Assays. The cloning of cDNAs, transfection into Chinese hamster ovary (CHO) cells, and membrane preparations for rat D_{2L} (D_2), rat D_3 (D_3), and human $D_{4.7}$ (D_4, containing seven polymorphic tandem repeats) receptors have been described in our previous reports.[29,36] Radioligand binding assays on D_2 and D_3 receptors were carried out in 30 mM HEPES-NaOH, 100 mM NaCl, and 10 mM $MgCl_2$ (pH 7.4), including either D_2 or D_3 receptor-expressed CHO cell membrane, 0.25 nM [^{125}I]iodosulpride, and vehicle, competing drug, or nonspecific ligand. In studies on D_4 receptors, the reaction buffer consisted of 50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$, 5 mM $MgCl_2$, and 5 mM EDTA (pH 7.4), including D_4 receptor-expressed CHO cell membrane, 0.26 nM [^{3}H]nemonapride, and vehicle, competing drug, or nonspecific ligand. The nonspecific ligands were used as follows: 10 μM sulpiride for D_2 receptors, 10 μM quinpirole for D_3 receptors, and 1 mM dopamine for D_4 receptors, respectively. After the reaction mixture was incubated at 25 °C for 60 min, the assay was terminated by a standard filtration method. The conditions of radioligand receptor binding assays for D_1, D_5, α_1, α_2, β, 5-HT_{1A}, 5-HT_{2A}, 5-HT_3, H_1, M_1, and M_2 receptors were described previously.[29,36] In all binding studies, the IC_{50} value was calculated by logit−log analysis with linear least-squares regression and converted to the K_i value as described previously.[38] [^{125}I]Iodosulpride and [^{3}H]nemonapride were purchased from Amersham and DuPont-New England Nuclear, respectively.

Behavioral Test on Apomorphine-Induced Climbing.[30,34] Male ICR mice (30−40 g) (N = 8−12) were individually habituated for 2 h in wire mesh cages. Apomorphine was subcutaneously injected 15 min after the administration of test compounds. Climbing behavior was scored every 1 min for 30 min beginning 10 min after treatment with apomorphine according to the intensity scale 0 = absent, 0.5 = occasional, and 1 = continuous.

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Supporting Information Available: Chiral HPLC chart for compounds **5c**−**e** and (*R*)-**5c**−**e** (6 pages). Ordering information is given on any current masthead page.

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