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Synthesis of 1-arylpiperazyl-2-phenylcyclopropanes designed as antidopaminergic agents: Cyclopropane-based conformationally restricted analogs of haloperidol

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ABSTRACT

A series of the cyclopropane-based conformationally restricted analogs of haloperidol were designed as potential antidopaminergic agents and were effectively synthesized using highly stereoselective Grignard reaction with *tert*-butanesulfinyl imines as the key step. Pharmacological evaluation of the compounds showed that the conformational restriction method can effectively work for improving the pharmacological selectivity of a parent compound and also for investigating the bioactive conformation.

1. Introduction

Conformational restriction of a biologically active compound with conformational flexibility often results in improving the potency, and, consequently, intensive effort has been made on designing and synthesizing the conformationally restricted analogs of biologically active compounds.[1] In conformationally restricted analogs, the spatial orientation of the functional groups, that are essential for the compound–target biomolecule interaction, should correspond to that in the bioactive conformation of the parent compound.[2] By such effective conformational restriction, binding affinity can be enhanced as a result of reducing the entropic loss upon binding to the target molecule.

In design of conformationally restricted analogs, it should be considered that the analogs are as similar as possible to the parent compound in size, shape, and molecular weight.[1a] Because of its characteristic small and rigid carbocyclic structural feature, a cyclopropane ring is effective in restricting the conformation of a molecule without significantly changing the chemical and physical properties of the parent compounds.[2,3] Thus, cyclopropanes have already been successfully used to restrict the bioactive conformations of a variety of pharmacologically active compounds.[4–6]

We devised a new method for restricting the conformation of cyclopropane derivatives based on the 'cyclopropylic strain'.[2,6c,6d] Adjacent *cis*-oriented substituents on a cyclopropane ring exert significant mutual steric repulsion, because they are fixed in the eclipsed orientation, which is 'cyclopropylic strain'.[2] Consequently, conformation of the substituents on a cyclopropane ring can be restricted to the conformation **B** by steric effect of the adjacent substituent, especially when it is bulky, as indicated in Figure 1a.

This method has been successfully applied to the design of the conformationally restriction analogs of milnacipran, which is a clinically effective antidepressant due to competitive inhibition of the re-uptake of serotonin (5-HT) and noradrenaline in the CNS, is also recognized as a weak noncompetitive NMDA receptor antagonist. As a result, a new class of NMDA receptor antagonist

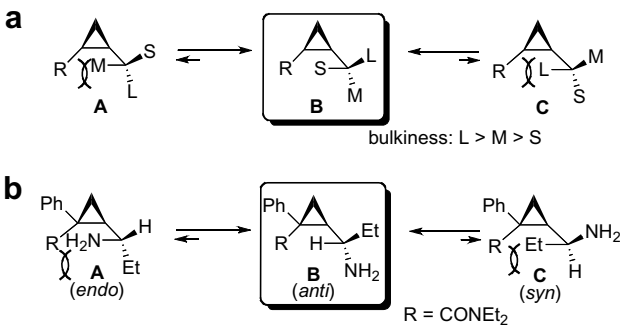

Figure 1. Conformational restriction due to the 'cyclopropylic strain'.

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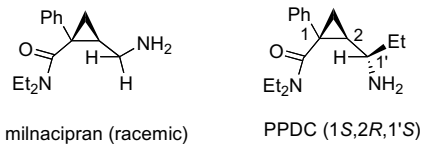


Figure 2. Milnacipran and its 'cyclopropylic strain'-based conformationally restricted analog PPDC.

PPDC (Fig. 2), which strongly antagonizes NMDA receptor without affecting the 5-HT and noradrenaline re-uptake.[6d] The conformation of PPDC was investigated in detail by X-ray crystallographic, ^{1}H NMR, and computational calculation analyses to show that the aminomethyl moiety, which is essential for the biological activity,[7] actually restricted to the conformation as **B** (*anti*) in Figure 1b due to the 'cyclopropylic strain'.[6a,6j]

With these encouraging results in mind, we applied the above descried method for designing conformationally restricted analogs of the well-known antipsychotic drug haloperidol (**1**, Fig. 3).

1.1. Design of the conformationally restricted analogs

Haloperidol (**1**) is a clinically effective antipsychotic drug, and its pharmacological effect is considered to be mainly due to the antagonism of dopaminergic receptors.[8] A drawback of haloperidol in clinical therapy is the side effects derived from its affinity for other receptors, such as adrenergic receptors.[8,9] Recently, Thurkauf and co-workers designed and synthesized arylpiperazine derivatives **2a** and **2b**, having a *trans*-cyclopropane structure, and identified them as dopamine receptor antagonists with reduced adrenergic α_1 receptor affinity.[9] These compounds can be considered conformationally restricted analogs of haloperidol, in which the three-dimensional positioning of the aromatic ring and the arylpiperazine moiety is restricted by the *trans*-cyclopropane structure. These results suggest that binding of haloperidol to the receptors other than the desired dopaminergic receptors may be attributed to its conformationally flexible structure, at least to some extent. The 2,4-disubstituent phenylpirerazine structure may also be important for the dopaminergic selective activity of the compounds. Thus, we planned to apply the 'cyclopropylic strain'-based conformational restriction method described above to the Thurkauf's compound **2b**.

We also were interested in the pharmacological effect of the *cis*-cyclopropane stereoisomer **3** of **2b** and its enantiomer ***ent*-3** (Fig. 3), in which the aromatic ring and the arylpiperazyl moiety

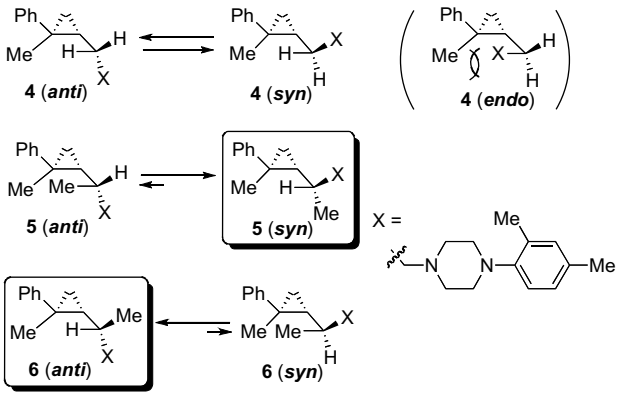


Figure 4. The 'cyclopropylic-strain'-based conformational restriction of **4**, **5**, and **6**.

are conformationally restricted differently from that in the corresponding *trans*-congener **2b**.

We designed conformationally restricted analogs **4**, **5**, and **6**, based on the 'cyclopropylic strain'. In analog **4**, a methyl group was introduced at the position *cis* to the piperazylmehyl moiety on the cyclopropane ring of **2b**. Accordingly, the positioning of the arylpiperazyl moiety would be restricted due to steric repulsion for the methyl group; as shown in Figure 4, the *syn* and *anti*-forms would be more stable than the *endo*-form in **4**. In analogs **5** and **6**, the methyl group additionally introduced at the interjacent carbon between the cyclopropane and piperazine rings would further restrict the three-dimensional positioning of aromatic and arylpiperazine rings differently depending on the configuration of the piperazylmethyl moiety, as shown in Figure 4. Thus, analogs **5** and **6** would prefer the *anti*-form and the *syn*-form, respectively.

We expected that some of these analogs might be selectively bind to the D_2 receptor or the D_4 receptor, and therefore, pharmacological evaluation of these analogs might clarify the bioactive conformation of haloperidol for these receptors. In addition, ligands highly selective to the D_2 or D_4 receptor may be useful as a drug lead and/or a pharmacological tool.

1.2. Synthesis

Considerable effort has been devoted to developing efficient methods for preparing cyclopropane derivatives.[3–6,10,11] In recent years, we have developed methods for synthesizing a variety of

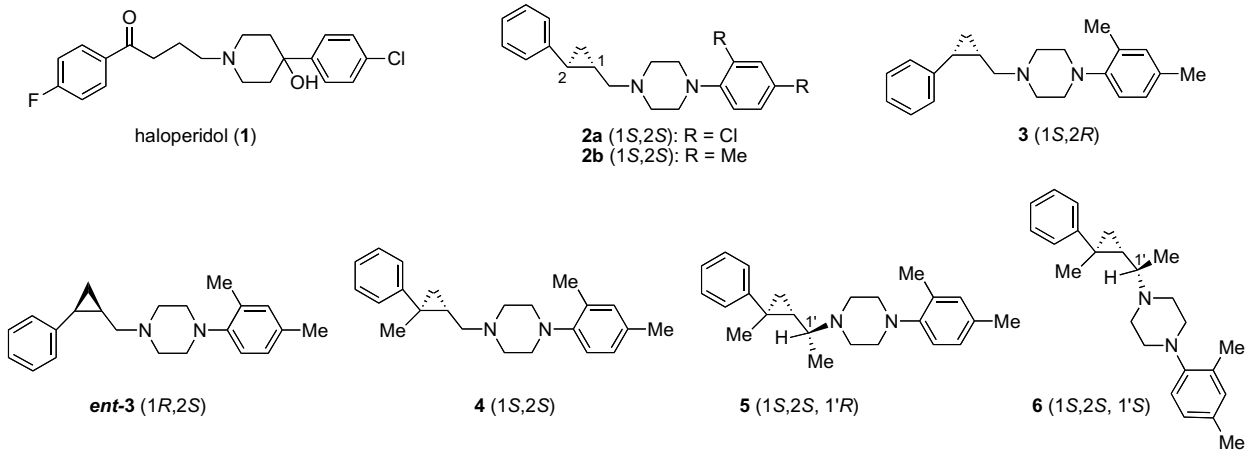


Figure 3. Haloperidol (**1**) and its conformationally restricted analogs.

chiral cyclopropane derivatives from easily available chiral (*R*)- and (*S*)-epichlorohydrins,[5,6,11,12] which were also applied to the synthesis of the target compounds in this study (Scheme 1).

The *cis*-cyclopropane compound **3** was synthesized from Weinreb amide **9**, which was prepared from (*S*)-epichlorohydrin [(*S*)-**7**] via lactone **8**, by the procedure reported previously.[12] The corresponding enantiomer ***ent*-3** was synthesized similarly starting from (*R*)-epichlorohydrin.

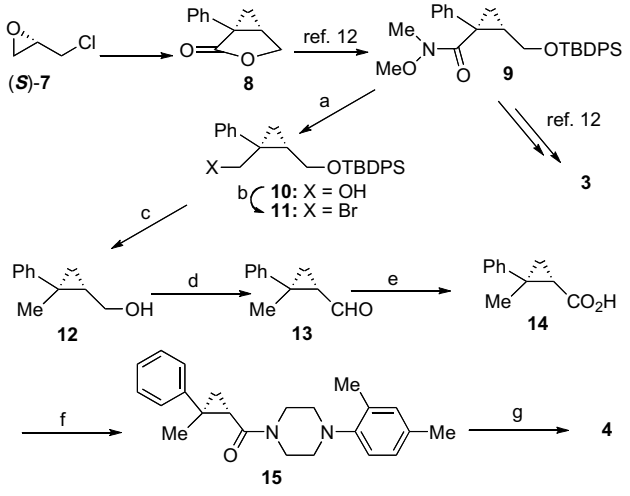
The methylcyclopropane-type target compound **4** was also synthesized from the Weinreb amide **9**. The amide **9** was treated with DIBAL-H in CH_2Cl_2 and then with $NaBH_4$ in THF/MeOH to give alcohol product **10**, which was converted into the corresponding bromide **11** with a $CBr_4/Ph_3P/CH_2Cl_2$ system. After reductive debromination of the **11** by treating it with $LiAlH_4$ in THF, the silyl-protecting group of the product was removed with TBAF/THF to afford the cyclopropanemethanol derivative **12**, of which two-steps oxidation gave the carboxylic acid **14**. Condensation between **14** and 2,4-dimethylphenylpiperazine effectively proceeded by treating them with EDC in CH_2Cl_2 to form the corresponding amide product **15**. Reduction of **15** was carried out with $LiAlH_4$ in THF to furnish the desired conformationally restricted analog **4**.

For the synthesis of the 1′*S*- and 1′*R*-methyl-substituted conformationally restricted analogs **5** and **6**, stereoselective construction of the 1′-carbon moieties was the key step. Ellman has reported that *tert*-butanesulfinyl imines are extremely effective substrates for the stereoselective 1,2-addition of Grignard reagents.[13] In this method, when *tert*-butanesulfinyl imines, prepared from chiral (*R*)- or (*S*)-*t*-$BuSONH_2$, are used as the substrates, the stereochemical outcome of the Grignard reaction can be dependent on the stereochemistry at the sulfinyl moiety. Recently, we have successfully developed a general synthetic procedure for systematically providing chiral 2,3- and 3,4-methanoamino acids with stereochemical diversity using the *tert*-butanesulfinyl imine method as the key step.[14] Thus, we expected that both of the targets **5** and **6** would be provided via the Grignard reaction of the (*R*)- and (*S*)-*tert*-butanesulfinyl imines derived from the cyclopropanecarbaldeyde **13**.

Treatment of **13** with (*R*)- or (*S*)-*t*-$BuSONH_2$ formed the corresponding (*E*)-sulfinyl imine **16** or **19**, respectively. When (*R*)-sulfinyl imine **16** was treated with MeMgBr in CH_2Cl_2 at room temperature, it stereoselectively gave the 1′*S*-product **17** (1′*R*:1′*S* = 1:12). The mixture was easily separated by silica gel column chromatography and the diastereomerically pure **17** was obtained in 93% yield. The 1′*R*-product **20** was exclusively obtained in quantitative yield, when the (*S*)-sulfinyl imine **19** was treated with MeMgBr in CH_2Cl_2 at room temperature. Thus, both of the 1′-diastereomers **17** and **20** were successfully obtained (Scheme 2).

The sulfinyl group of **17** or **20** was removed by acidic hydrolysis with HCl in aqueous dioxane to give amine **18** or **21**, respectively. The 1′-stereochemistry was confirmed based on the modified Mosher's method by the conversion of **21** into the corresponding MTPA amides, $\Delta\delta$ values of which are shown in Scheme 2.[15]

Reaction of **18** with *N*,*N*-di-(2-chloroethyl)aniline derivative **22**, which was prepared from 2,4-dimethylaniline (Scheme 3), produced the conformationally restricted analog **6** with 1′*S*-configuration. Similarly, the 1′*R*-analog **5** was prepared from **21**.

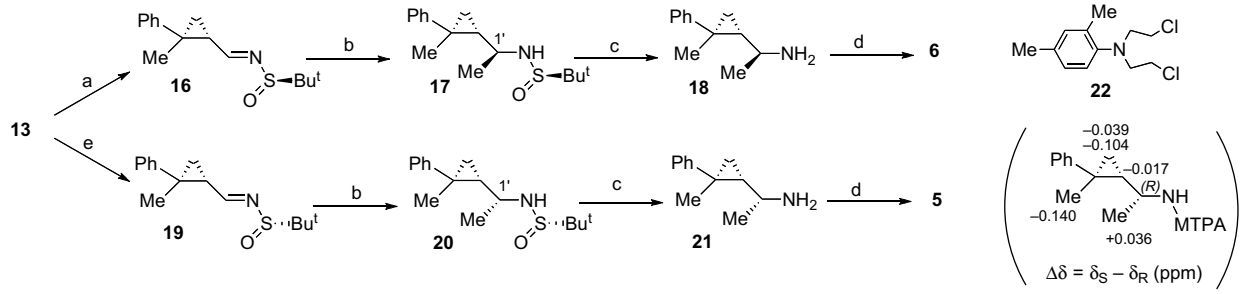


Scheme 1. Reagents and yields: (a) 1—DIBAL-H, CH_2Cl_2; 2—$NaBH_4$, THF/MeOH, 88%; (b) CBr_4, PPh_3, CH_2Cl_2, 93%; (c) 1—$LiAlH_4$, THF; 2—TBAF, THF, 96%; (d) Dess–Martin ox., 94%; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq acetone, 96%; (f) 2,4-dimethylphenylpiperazine, EDC, CH_2Cl_2, 96%; (g) $LiAlH_4$, THF, 77%.

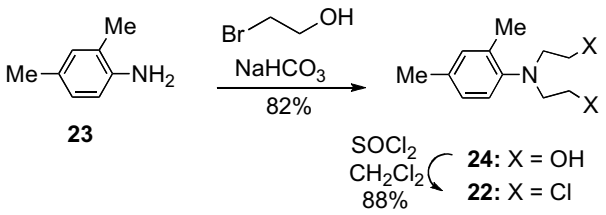
1.3. Biological activity

Thurkauf and co-workers identified compound **2** as a mixed dopamine D_2/D_4 receptor antagonist based on the working hypothesis that dopamine receptor antagonists with a ratio of D_2/D_4 receptor affinity of approximately 4–7 may be effective as antipsychotic drugs.[9] Therefore, we also evaluated binding affinities of the compounds for dopamine D_2 and D_4 receptors using membrane expressing human D_{2s} and $D_{4.2}$ receptors using [^{3}H]YM-09151-2 as a radioligand. Binding affinities for adrenaline α_1 receptor, which is related to cardiovascular side-effects,[9] were also evaluated. These results are summarized in Table 1.

In our evaluation systems, the binding affinities of Thurkauf's compound **2b**, synthesized by the procedure previously developed by us,[12] for dopamine receptors were moderate. The K_i values were 540 nM for D_2 and 130 nM for D_4, respectively, which were clearly weaker than haloperidol. The D_2/D_4 ratio of **2b** was about 4, which was similar to that reported by Thurkauf and co-workers.[9] The corresponding *cis*-cyclopropane congener **3** showed lower binding affinity than **2b** both for the D_2 and D_4 receptors and the D_2/D_4 ratio was about 1. Its enantiomer ***ent*-3** was active to D_2 receptor (K_i = 515 nM) similarly to the parent compound **2b** (K_i = 540 nM),



Scheme 2. Reagents and yields: (a) (*R*)-*t*-$BuSONH_2$, MS4A, benzene, 70%; (b) MeMgBr, CH_2Cl_2, 93% (**17**), quant. (**20**); (c) HCl, MeOH, quant. (**18**), 92% (**21**); (d) **22**, *i*-Pr_2NEt, MeCN, 55% (**6**), 41% (**5**); (e) (*S*)-*t*-$BuSONH_2$, $CuSO_4$, CH_2Cl_2, 72%.



Scheme 3.

while its affinity for D_4 receptor was significantly reduced (K_i = 2050 nM).

When a methyl substituent was introduced into the cyclopropane ring at the position *cis* to the arylpiperazine moiety of **2b**, that is, compound **4**, the affinity for the D_2 receptor was lost, while it preserved the affinity for the D_4 receptor. The conformationally restricted analogs **5** and **6** based on the 'cyclopropylic strain' showed only insignificant binding affinity.

All of these compounds synthesized showed similar moderate binding affinities for the α_1 receptor, irrespective of the structure (K_i = 250–906 nM).

As described above, the *cis*-methyl substituted analog **4** of **2b** was highly selectively active to the D_4 receptor ($D_2/D_4 > 42$). The selective affinity of **4** for the D_4 receptor suggested that the bioactive conformation of parent compound **2b** in its binding to the D_4 receptor seems not to be the *endo*-form, but to be the *syn*- or the *anti*-form, as indicated in Figure 4.

As described, we stereoselectively synthesized a series of the cyclopropane-based conformational restriction analogs of haloperidol, using highly stereoselective Grignard reaction with *tert*-butanesulfinyl imines as the key step. We showed that the conformational restriction method can effectively work for improving the selectivity of a parent compound to the receptors and for investigating the bioactive conformation, as indicated in the case of compound **4** selectively active to the D_4 receptor.

2. Experimental

2.1. General methods

NMR spectra were recorded at 400 MHz (^{1}H) and at 100 MHz (^{13}C), and are reported in ppm downfield from Me_4Si. The ^{1}H NMR assignments indicated were in agreement with COSY spectra. Thin-layer chromatography was performed on Merck coated plate 60 F_{254}. Silica gel chromatography was performed with Merck silica gel 5715 or 9385 (neutral). Reactions were carried out under an argon atmosphere.

Table 1
Binding affinities (K_i) of the compounds for dopaminergic and adrenergic receptors

Compound	D_{2s}[a]	$D_{4.2}$[a]	$D_{2s}/D_{4.2}$	α_1[b]
2b	540 ± 60	130 ± 33	4.2	432 ± 67
3	935 ± 109	897 ± 145	1.0	521 ± 105
***ent*-3**	515 ± 60	2050 ± 60	0.25	537 ± 102
4	>10,000	236 ± 53	>42	906 ± 204
5	>10,000	4660 ± 2060	>2.1	401 ± 64
6	>10,000	4190 ± 1320	>2.4	250 ± 15
Haloperidol	5.09 ± 0.36	9.32 ± 0.61	0.22	

[a] Assay was carried out with membrane expressing human D_{2s} or $D_{4.2}$ dopamine receptors, using [^{3}H]YM-09151 (n = 3).
[b] Assay was carried out with mouse brain homogenate, using [^{3}H]prazosin (n = 3).

2.1.1. (2*R*,1*S*)-1-(*tert*-Butyldiphenylsiloxy)methyl-2-hydroxymethyl-2-phenylcyclopropane (10)

A mixture of **9** (3.22 g,6.8 mmol) and DIBAL-H (1.0 M in hexane, 10.2 mL, 10.2 mmol) in CH_2Cl_2 (70 mL) was stirred at −78 °C for 4 h. After addition of MeOH, the solvent was evaporated, and the residue was partitioned between $CHCl_3$ and 1 M HCl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and $NaBH_4$ (270 mg, 6.8 mmol) in THF/MeOH (4:1, 70 mL) was stirred at room temperature for 4 h. After the solvent was evaporated, the residue was partitioned between AcOEt and 1 M HCl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 10:1) to give **10** (2.50 g, 88%) as an oil: $[\alpha]_D^{25}$ −52.6 (c 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (1H, dd, J = 5.3, 5.3 Hz), 1.03 (1H, dd, J = 5.3, 9.7 Hz), 1.10 (9H, s), 1.54 (1H, m), 3.50 (1H, t, J = 11.1 Hz), 3.54 (1H, t, J = 11.1 Hz), 3.71 (1H, d, J = 11.1 Hz), 4.15 (1H, t, J = 11.8 Hz), 4.19 (1H, dd, J = 5.5, 11.8 Hz), 7.23 (1H, m), 7.30–7.48 (10H, m), 7.72 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.75, 19.04, 25.79, 26.74, 32.76, 65.17, 67.62, 126.09, 127.51, 127.55, 127.94, 128.58, 129.59, 129.62, 132.44, 135.17, 135.24, 143.93; LR-MS (FAB) m/z 417 (MH^+). Anal. Calcd for $C_{27}H_{32}O_2Si$: C, 77.84; H, 7.74. Found: C, 77.81; H, 7.53.

2.1.2. (1*S*,2*R*)-1-(*tert*-Butylsiloxy)methyl-2-bromomethyl-2-phenylcyclopropane (11)

A mixture of **10** (414 mg, 1.0 mmol), CBr_4 (525 mg, 2.0 mmol) and PPh_3 (995 mg, 3.0 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 5 min. After addition of aqueous saturated $NaHCO_3$, the mixture was partitioned between $CHCl_3$ and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 15:1) to give **11** (448 mg, 93%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (1H, dd, J = 5.3, 5.9 Hz), 1.09 (9H, s), 1.28 (1H, dd, J = 5.2, 8.7 Hz), 1.71 (1H, m), 3.70 (1H, d, J = 10.5 Hz), 3.75 (1H, dd, J = 8.3, 11.5 Hz), 3.85 (1H, d, J = 10.5 Hz), 4.07 (1H, dd, J = 5.5, 10.5 Hz), 7.23–7.47 (11H, m), 7.68–7.72 (4H, m); HRMS (FAB) calcd for $C_{27}H_{31}BrOSi$: 479.1406 (MH^+), found 479.1413.

2.1.3 (1*S*,2*S*)-1-Hydroxymethyl-2-methyl-2-phenylcyclopropane (12)

A mixture of **11** (2.91 g, 6.1 mmol) and $LiAlH_4$ (920 mg, 24 mmol) in THF (60 mL) was heated under reflux for 1 h. After addition of MeOH, the resulting mixture was evaporated, and the residue was partitioned AcOEt and 1 M HCl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and TBAF (1.0 M in THF, 9.1 mL, 9.1 mmol) in THF (60 mL) was stirred at room temperature for 12 h and then evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 9:1) to give **12** (987 mg, 96%) as an oil: $[\alpha]_D^{23}$ +41.4 (c 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (1H, dd, J = 4.9, 5.6 Hz), 1.14 (1H, dd, J = 4.9, 8.8 Hz), 1.39 (1H, m), 1.46 (3H, s), 3.70 (1H, dd, J = 8.3, 11.9 Hz), 3.90 (1H, dd, J = 6.6, 11.9 Hz), 7.21–7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.83, 20.62, 24.96, 27.88, 63.56, 125.66, 127.06, 128.15, 147.34; LRMS (EI) m/z 162 (M^+). HRMS (EI) calcd for $C_{11}H_{14}O$: 162.1045 (M^+), found 162.1052.

2.1.4. (1*S*,2*S*)-2-Formyl-1-methyl-2-phenylcyclopropane (13)

A mixture of **12** (30 mg, 0.19 mmol) and Dess–Martin periodinate (119 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 30 min. After addition of aqueous saturated $Na_2S_2O_4$, the resulting mixture was partitioned between $CHCl_3$ and aqueous saturated $NaHCO_3$, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 4:1) to

give **13** (29 mg, 94%) as an oil: $[\alpha]_D^{22}$ +206.0 (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (3H, s), 1.65 (1H, dd, *J* = 4.9, 8.5 Hz), 1.70 (1H, dd, *J* = 4.9, 5.7 Hz), 2.17 (1H, m), 7.21–7.34 (5H, m), 9.59 (1H, d, *J* = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.01, 22.17, 34.12, 36.90, 126.69, 127.08, 128.45, 144.82, 200.35.

2.1.5. (1*S*,2*S*)-2-Carboxy-1-methyl-2-phenylcyclopropane (14)

A mixture of **13** (214 mg, 1.33 mmol), $NaClO_2$ (422 mg, 4.66 mmol), $NaH_2PO_4{\cdot}2H_2O$ (208 mg. 1.33 mmol) and 2-methyl-2-butene (503 μL, 5.99 mmol) in acetone/H_2O (4:1, 10 mL) was stirred at room temperature for 12 h and then evaporated. The residue was partitioned between AcOEt and 1 M HCl, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 15:1) to give **14** (225 mg, 96%) as an oil: $[\alpha]_D^{22}$ +199.3 (*c* 0.86, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (2H, m), 1.59 (3H, s), 1.99 (1H, dd, *J* = 6.0, 8.1 Hz), 7.28 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.28, 21.60, 27.59, 32.25, 126.52, 127.27, 128.38, 145.38, 178.33; HRMS (EI) calcd for $C_{11}H_{12}O_2$: 176.0837 (M^+), found 176.0835.

2.1.6. (1*S*,2*S*)-1-[4-(2,4-Dimethylphenyl)piperazyl]carbonyl-2-methyl-2-phenylcyclopropane (15)

A mixture of **14** (192 mg, 1.11 mmol), 2,4-dimethylphenylpiperazine (463 mmol, 2.44 mmol), and EDC (468 mg, 2.44 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 30 min and then at room temperature for 12 h. The resulting mixture was partitioned between $CHCl_3$ and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 30:1–15:1) to give **15** (225 mg, 96%) as an oil: $[\alpha]_D^{22}$ +111.0 (*c* 0.93, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (1H, m), 1.45 (3H, s), 1.63 (1H, t, *J* = 5.4 Hz), 1.99 (1H, dd, *J* = 5.9, 8.5 Hz), 2.23 (3H, s), 2.29 (3H, s), 2.82 (2H, m), 2.91 (2H, m), 3.71 (3H, m), 3.96 (1H, m), 6.88–7.02 (3H, m), 7.12–7.35 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.80, 19.25, 19.43, 20.84, 27.42, 30.00, 42.78, 46.34, 52.15, 52.75, 118.92, 125.78, 126.05, 126.96, 128.46, 131.75, 132.44, 133.07, 145.27, 148.25, 168.51; HRMS (EI) calcd for $C_{23}H_{28}N_2O$: 348.2202 (M^+), found 348.2201.

2.1.7. (1*S*,2*S*)-1-[4-(2,4-Dimethylphenyl)piperazyl]methyl-2-methyl-2-phenylcyclopropane (4)

A mixture of **15** (236 mg, 0.68 mmol) and $LiAlH_4$ (1.0 M in THF, 1.4 mL, 1.4 mmol) in THF (6 mL) was stirred at 0 °C for 30 min and then at room temperature for 3 h. The resulting mixture was partitioned between AcOEt and aqueous NaOH (10%), and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 5:1) to give **4** (176 mg, 77%) as an oil: $[\alpha]_D^{21}$ +49.9 (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (1H, dd, *J* = 4.6, 6.0 Hz), 1.18 (1H, dd, *J* = 4.6, 9.0 Hz), 1.28 (1H, m), 1.43 (3H, s), 2.27 (3H, s), 2.28 (3H, s), 2.54 (1H, dd, *J* = 6.6, 12.6 Hz), 2.72 (4H, br s), 2.76 (1H, dd, *J* = 6.0, 12.6 Hz), 2.94 (4H, t, *J* = 4.9 Hz), 6.94–7.00 (3H, m), 7.13–7.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.66, 20.36, 20.45, 20.63, 13.57, 23.65, 51.82, 53.62, 58.55, 118.62, 125.22, 126.44, 126.67, 127.89, 131.41, 132.12, 132.15, 147.58, 148.73. To a solution of **4** (free amine, 17 mg, 48 μmol) in *i*-PrOH (0.5 mL) was added aqueous HBr (48%, 17 μL) where the pH was ca. 3. To the resulting mixture was added *i*-Pr_2O to give white precipitates of **4** (24 mg, 96%) as a dihydrobromide: mp 215–217 °C (*i*-PrOH–*i*-Pr_2O); $[\alpha]_D^{22}$ +30.5 (*c* 0.87, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) d 0.79 (1H, m), 1.32 (2H, m, H-1), 1.39 (3H, s), 2.15 (3H, s), 2.20 (3H, s), 3.21 (7H, m), 3.62 (3H, m), 6.96 (3H, d, *J* = 15.7 Hz), 7.07–7.11 (1H, m), 7.18–7.25 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 17.82, 17.85, 20.54, 20.89, 20.92, 21.06, 21.16, 50.46, 53.77, 58.64, 120.04, 127.22, 127.90, 128.11, 129.39, 132.68, 133.68, 135.06, 147.18, 148.18; LRMS (FAB) *m/z* 335 (MH^+). Anal. Calcd for $C_{23}H_{31}N_2Br$: C, 66.50; H, 7.52; N, 6.74; Br 19.23. Found: C, 66.24; H, 7.52; N, 6.74; Br, 19.40.

2.1.8. (*R*)-*tert*-Butanesulfinyl imine (16)

A mixture of **13** (425 mg, 2.65 mmol), (*R*)-(+)-2-methyl-2-propanesulfinamide (353 mg, 2.91 mmol), and MS4A (powder, 70 mg) in benzene (30 mL) was heated under reflux for 6 h. The resulting mixture was filtered thorough Celite, and the filtrated was evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 19:1) to give **16** (490 mg, 70%) as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (9H, s), 1.50 (1H, dd, *J* = 5.1, 5.6 Hz), 1.56 (3H, s), 1.71 (1H, dd, *J* = 5.1, 8.5 Hz), 2.29 (1H, m), 7.21–7.40 (5H, m), 7.88 (1H, d, *J* = 8.1 Hz); HRMS calcd for $C_{15}H_{22}NOS$: 264.1422 (MH^+), found 264.1436.

2.1.9. Grignard reaction product (17)

A mixture of **16** (28 mg, 0.11 mmol) and MeMgBr (1.4 M in toluene/THF, 3:1, 91 μL, 0.13 mmol) in CH_2Cl_2 (1.1 mL) was stirred at room temperature for 6 h, and then aqueous saturated NH_4Cl was added. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue, the 1′*R*/1′*S* ratio of which was 1:12 based on the ^1H NMR spectrum, was purified by column chromatography (silica gel, hexane/AcOEt, 4:1–1:1) to give **17** (32 mg, 93%) as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (1H, m), 1.04 (1H, m), 1.18–1.29 (10H, m), 1.42 (3H, s), 3.03–3.22 (2H, m), 7.15–7.39 (5H, m); HRMS calcd for $C_{16}H_{26}NOS$: 280.1735 (MH^+), found 280.1712.

2.1.10. (1*S*,2*S*)-1-[(*S*)-1-Aminoethyl]-2-methyl-2-phenylcyclopropane hydrochloride (18)

A solution of **17** (22 mg, 80 μmol) and HCl (4 M in dioxane, 80 μL, 240 μmol) in MeOH (1 mL) was stirred at room temperature for 20 min. The resulting solution was evaporated to give **18** (17 mg, quant.) as a white solid: $[\alpha]_D^{22}$ +18.1 (*c* 0.92, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (1H, dd, *J* = 5.6, 5.6 Hz), 1.22 (1H, dd, *J* = 5.3, 8.5 Hz), 1.36 (1H, m), 1.39 (3H, s), 1.63 (3H, d, *J* = 6.6 Hz), 3.13 (1H, m), 7.16–7.28 (5H, m), 8.56 (3H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.38, 20.40, 21.22, 26.41, 28.84, 50.45, 126.16, 127.35, 128.29, 146.03; HRMS (FAB) calcd for $C_{12}H_{18}N$: 176.1436 (MH^+−HCl), found 176.1443 (MH^+−HCl).

2.1.11. (1*S*,2*S*)-1-[(*S*)-2-[4-(2,4-Dimethylphenyl)piperazyl]-ethyl]-2-methyl-2-phenylcyclopropane hydrobromide (6)

A mixture of **18** (free amine, 14 mg, 82 μmol), prepared by the treatment of hydrochloride of **18** with Diaion PA312 (HCO_3^- form), diisopropylethylamine (72 μL, 0.41 mmol), and **22** (41 mg, 0.16 mmol) in MeCN (2 mL) was heated under reflux for 2 days. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 15:1) to give **6** (16 mg, 55%) as an oil: $[\alpha]_D^{20}$ −14.0 (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (1H, dd, *J* = 5.9, 6.0 Hz), 1.10 (1H, m), 1.26 (2H, m), 1.35 (3H, d, *J* = 6.4 Hz), 1.41 (3H, s), 2.27–2.28 (7H, m) 2.76–3.00 (8 H), 6.93–6.99 (3H, m), 7.15 (1H, m), 7.25–7.28 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.68, 18.83, 20.63, 20.87, 21.67, 22.71, 28.42, 50.39, 52.16, 60.69, 118.60, 125.31, 126.67, 126.89, 127.94, 131.40, 132.07, 132.15, 147.93, 148.80. The hydrobromide of **6** was prepared as described above for **4**: mp (*i*-PrOH–*i*-Pr_2O) 192–194 °C; $[\alpha]_D^{21}$ −7.27 (*c* 0.63, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 0.99 (1H, dd, *J* = 5.4, 5.8 Hz), 1.21 (1H, m), 1.38–1.41 (4H, m), 1.60 (3H, d, *J* = 6.8 Hz), 2.16 (3H, s), 2.21 (3H, s), 3.05–3.38 (7H, m), 3.66 (1H, m), 3.77 (1H, m), 6.89–6.93 (3H, m), 7.08–7.12 (1H, m), 7.19–7.24 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 17.42,

17.85, 20.88, 21.31, 21.60, 26.22, 27.14, 50.64, 50.68, 51.23, 51.48, 65.58, 120.00, 127.30, 128.16, 128.19, 129.42, 132.74, 133.63, 135.28, 147.32, 147.13; HRMS (FAB) calcd for $C_{24}H_{33}N_2$: 349.2644, found 349.2649. Anal. Calcd for $C_{23}H_{31}N_2$: C, 55.50; H, 6.79; N, 5.39. Found: C, 55.26; H, 6.88; N, 5.30.

2.1.12. (*S*)-*tert*-Butanesulfinyl imine (19)

A mixture of **13** (29 mg, 0.18 mmol), (*S*)-(−)-2-methyl-2-propanesulfinamide (24 mg, 2.0 mmol), and $CuSO_4$ (70 mg, 0.44 mmol) in CH_2Cl_2 (1.8 mL) was heated under reflux for 6 h. The resulting mixture was filtered through Celite, and the filtrated was evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 19:1) to give **19** (34 mg, 72%) as an oil: $[\alpha]_D^{21}$ +417.09 (*c* 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (9H, s), 1.45 (1H, dd, *J* = 5.3, 5.3 Hz), 1.59 (3H, s), 1.76 (1H, dd, *J* = 5.1, 8.7 Hz), 2.29 (1H, m), 7.20–7.33 (5H, m), 7.88 (1H, d, *J* = 8.3 Hz); HRMS calcd for $C_{15}H_{22}NOS$: 264.1422. (MH^+), found 264.1414.

2.1.13. Grignard reaction product (20)

Compound **20** (110 mg, quant.) was obtained from **19** (100 mg, 0.38 mmol) as an oil, as described for the synthesis of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45 (1H, dd, *J* = 5.6, 5.7 Hz), 1.06 (1H, m, H-1), 1.14 (1H, dd, *J* = 4.5, 9.2 Hz,), 1.24 (s, 9H), 1.42 (3H, d, *J* = 6.5 Hz), 1.48 (3H, s), 3.17 (2H, m) 7.14–7.28 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.49, 2.72, 22.66, 22.80, 23.60, 25.99, 53.35, 55.49, 125.61, 127.10, 128.09, 147.38; HR-MS calcd for $C_{15}H_{22}NOS$: 280.1735. (MH^+), found 280.1740.

2.1.14. (1*S*,2*S*)-1-[(*R*)-1-Aminoethyl]-2-methyl-2-phenylcyclopropane hydrochloride (21)

Compound **21** (10 mg, quant.) was obtained from **20** (13 mg, 0.046 mmol) as an oil, as described for the synthesis of **18**: $[\alpha]_D^{22}$ +37.5 (*c* 0.92, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.49 (1H, dd, *J* = 5.2, 5.3 Hz), 1.26 (1H, dd, *J* = 5.1, 9.4 Hz), 1.38 (1H, m), 1.54 (3H, d, *J* = 6.6 Hz), 1.61 (3H, s), 3.07 (1H, m), 7.07–7.42 (5H, m), 8.72 (3H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.41, 19.27, 20.93, 26.23, 29.22, 49.52, 125.69, 127.29, 127.86, 145.42; HRMS (FAB) calcd for $C_{12}H_{18}N$: 176.1436 (MH^+−HCl), found 176.1441.

2.1.15. (1*S*,2*S*)-1-[(*R*)-2-[4-(2,4-Dimethylphenyl)piperazyl]-ethyl]-2-methyl-2-phenylcyclopropane dihydrobromide (5)

Compound **5** (free amine, 24 mg, 41%) was obtained from **21** (51 mg, 0.21 mmol) as an oil, as described for the synthesis of **6**: $[\alpha]_D^{21}$ +87.6 (*c* 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (1H, dd, *J* = 4.5, 5.5 Hz), 1.12–1.22 (2H, m), 1.25 (3H, d, *J* = 6.6 Hz), 1.47 (3H, s), 2.26 (3H, s), 2.28 (3H, s), 2.33 (1H, m), 2.79–2.93 (8 H), 6.92–6.99 (3H, m), 7.13–7.18 (1H, m), 7.24–7.28 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.63, 17.89, 19.12, 20.81, 21.44, 25.86, 31.06, 50.28, 52.48, 59.87, 118.75, 125.35, 126.33, 126.83, 128.10, 131.58, 132.18, 132.27, 147.58, 148.98. The hydrobromide of **5** was prepared as described above for **4**: mp 191–193 °C; $[\alpha]_D^{23}$ +68.0 (*c* 0.85, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.59 (1H, m), 1.32–1.39 (2H, m), 1.48 (3H, s), 1.54 (6H, d, *J* = 6.5 Hz), 2.15 (3H, s), 2.20 (3H, s), 3.06–3.38 (7H, m), 3.63–3.69 (2H, m), 6.88–6.93 (3H, m), 7.08–7.13 (1H, m), 7.20–7.25 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 17.51, 17.83, 19.31, 20.87, 21.31, 27.97, 29.67, 50.43, 50.71, 50.81, 52.60, 120.10, 126.84, 127.22, 128.17, 129.56, 132.73, 133.65, 135.36, 146.10, 147.68; Anal. Calcd for $C_{23}H_{31}N_2$: C, 67.12; H, 7.75; N, 6.52; Found: C, 66.94; H, 7.83; N, 6.46.

2.1.16. *N*,*N*-Bis-(2-hydroxyethyl)-2,4-dimethylaniline (24)

A mixture of 2,4-dimethylaniline (**23**, 1.24 mL, 10 mmol), 2-bromoethanol (3.52 mL, 50 mmol) and $NaHCO_3$ (1.68 g, 20 mmol) was stirred at 57 °C for 2 days. The resulting reaction mixture was partitioned between $CHCl_3$ and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 4:1–1:1) to give **24** (1.71 g, 82%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 2.32 (3H, s), 3.16 (4H, m), 3.60 (4H, m), 7.00–7.26 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.28, 20.93, 57.06, 60.05, 123.87, 127.37, 131.89, 134.61, 135.20, 146.14; HR-MS (EI) calcd for $C_{12}H_{19}NO_2$: 209.1416 (M^+), found 209.1420.

2.1.17. *N*,*N*-Bis-(2-chloroethyl)-2,4-dimethylaniline (22)

A mixture of **24** (37 mg, 0.18 mmol) and $SOCl_2$ (29 μL, 0.40 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 1 h. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 40:1) to give **22** (39 mg, 88%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (6H, s), 3.37 (4 H), 3.44 (4 H) 6.96–7.05 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.05, 20.95, 41.77, 56.79, 123.82, 127.13, 131.90, 134.50, 135.73, 144.32; LRMS (EI) *m/z* 245 (M^+). Anal. Calcd for $C_{12}H_{17}Cl_2N$: C, 58.55; H, 6.96; N, 5.69. Found: C, 58.87; H, 6.92; N, 5.54.

2.2. Binding assay of human D_{2s} and $D_{4.2}$ dopamine receptors

Membrane suspensions expressing human D_{2s} or $D_{4.2}$ dopamine receptors were purchased from PerkinElmer Life Sciences (Boston, MA), and radioreceptor binding assay was performed using [^{3}H]YM-09151-2 (3.15 TBq/mmol, DuPont-NEN, Boston, MA) as previously described.[9] Briefly, the membrane suspensions (3.3 and 43 μg protein for D_2 and D_4 receptor assays, respectively) were incubated with [^{3}H]YM-09151-2 (0.05–2.0 nM) for 2 h at 20 °C in 50 mM Tris–HCl buffer (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, and 1 mM EDTA. The reaction was terminated by rapid filtration (Cell Harvester, Brandel Co., Gaithersburg, MD, USA) through Whatman GF/B glass fiber filters, and the filters were rinsed three times with 2 mL of ice-cold buffer. Tissue-bound radioactivity was extracted from filters overnight in scintillation fluid (2 L of toluene, 1 L of Triton X-100, 15 g of 2,5-diphenyloxazole, and 0.3 g of 1,4-bis[2-(5-phenyloxazolyl)]benzene), and it was determined in a liquid scintillation counter. Specific binding of [^{3}H]YM-09151-2 was determined experimentally from the difference between counts in the absence and presence of 2.0 μM haloperidol.

2.3. Binding assay of mouse brain α_1-adrenoceptor

Male ICR strain mice at 6–8 weeks of age (Japan SLC Inc., Shizuoka, Japan) were exsanguinated by taking the blood from descending aorta under light anesthesia with Et_2O, and the whole brain tissue was removed. The brain tissue was homogenized in 19 vol. of 50 mM Tris–HCl buffer (pH 7.5) with a Polytron homogenizer, and the homogenate was centrifuged at 40,000*g* for 15 min. The pellet was resuspended in the buffer and centrifuged again. The resulting pellet was suspended in 24 vol. of the buffer and utilized for binding assay. The binding assay for α_1-adrenoceptor was performed according to the previous method[16] using [^{3}H]prazosin (2.98 TBq/mmol, DuPont-NEN, Boston, MA). Briefly, the brain homogenate (approximately 400 μg protein) was incubated with [^{3}H]prazosin (0.05–1 nM) for 1 h at 20 °C. The reaction was terminated as described above. Specific binding of [^{3}H]prazosin was determined experimentally from the difference between counts in the absence and presence of 10 μM phentolamine.

2.4. Data analysis

Analysis of binding data was performed as described previously.[17,18]

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