New Fluorinated Dopamine D2 Ligands with Benzofuran Skeleton. The Synthesis and *in Vitro* Evaluation

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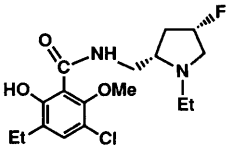
New fluorinated ligands with *N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dihydrobenzofuran-7-carboxamide skeleton, which are useful as a prototype to develop ^{18}F labelled *in vivo* radiotracer for positron emission tomography (PET), were synthesized, and their binding affinities for the dopamine D2 receptors were investigated. Fluorine atom was introduced at C-4 of the pyrrolidine ring (10) or at ethyl substituent at C-5 of the dihydrobenzofuran moiety (20). The *in vitro* IC_{50} values of these ligands for the dopamine D2 receptors which were determined by their ability to inhibit the binding of [^{3}H]spiperone binding in rat striatal membrane were 17 and 36 nM, respectively. Thus, the fluorinated compounds 10 and 20 may be possible candidates for further *in vivo* investigation.

Keywords fluoroethylbenzofuran; dopamine D2 ligand; *in vitro* binding affinity; fluorinated ligand; fluoroeticlopride

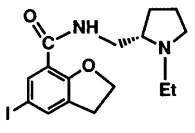
Dopaminergic neurons in the central nervous system (CNS) play an important role in brain functions, and development of dopaminergic drugs have been the major subject of search for suitable therapeutic approach. Dopamine receptors were classified into two subtypes, the D1 and the D2 receptors, the latter have long been regarded as the primary target of antipsychotics.[1] Recently, new dopamine receptor subtypes have been found by molecular biological approaches, and have led to the enlargement of the dopamine receptor family.[2] For instance, a new dopamine D3 receptor as a member of "D2-like" subtype has been suggested to be blocked by antipsychotics during the treatment of schizophrenia and related disorders.[2f] These discoveries have stimulated the development of new selective dopaminergic drugs for each receptor subtype.

Our investigation has been directed to develop new selective D2 ligands with fluorine atom, since the corresponding positron-emitting ($t_{1/2}$ = 110 min) ^{18}F-labelled ligands are expected to be useful as an *in vivo* radiotracer for positron emission tomography (PET) study of dopamine D2 receptors.[3] By modifying neuroleptics of a benzamide class such as raclopride, eticlopride, *etc.*, which are specific and high affinity ligands toward D2 receptors, a number of ^{18}F-labelled analogues have been synthesized and evaluated as *in vivo* tracers.[4–6] We reported in a previous paper that the ligand **1** with a fluorine atom at the C-4 of the pyrrolidine showed the high *in vitro* affinity toward D2 receptor.[5b] However, the corresponding ^{18}F-labelled **1** exhibited only moderate *in vivo* selectivity toward CNS D2 receptors as illustrated by the striatal to cerebellar radioactivity ratio of 5.2 at 90 min in rats.[6] This fact led us to design new fluorinated D2 ligands in order to develop more potent *in vivo* radiotracer. IBF (**2**) ((*S*)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodo-2,3-dihydrobenzofuran-7-carboxamide), a new benzamide class ligand with a tetrahydrobenzofuran moiety, has been reported to show specific and high affinity binding with D2 receptors in both *in vitro* and *in vivo* investigation.[7] Based on this IBF structure, new fluorinated ligands (type **3**) with a fluorine atom either at the pyrrolidine ring or at the aromatic ring were designed. We expected that fluoride introduction at C-4 of the pyrrolidine ring would be achieved without decreasing the ligand's *in vitro* affinity to CNS D2 receptors,[5b] and that fluoroalkyl substitution at C-5 of the benzofuran moiety would be synthetically more feasible, and would have similar lipophilic contribution with iodine atom.[8] This paper describes the syntheses and the *in vitro* D2 receptor binding affinities of new benzofuran analogues.

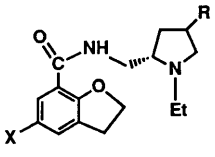
New substituted benzofuran derivatives were synthesized starting from 5-bromo-7-carboxy-2,3-dihydrobenzofuran (**4**)[7] (Chart 1). Amide bond formation between **4** and (2*S*,4*R*)-(−)-2-aminomethyl-4-*tert*-butyldimethylsilyloxy-1-ethylpyrrolidine (**5**)[5b] was performed using diethyl phosphorocyanidate (DEPC)[9] as a coupling agent to give **6** (90% yield). The brominated benzofuran derivatives **6** was converted to iodinated compound **7** by the reaction with hexabutylditin and successive iodination with iodine (39% yield). The *tert*-butyldimethylsilyloxy protecting group of **6** was removed with n-Bu_4NF to give the alcohol **8** (74% yield), which was methanesulfonylated with MsCl to afford **9** (79% yield). Displacement of the mesyloxy group by fluoride anion could not be achieved by several approaches. Eventually, the fluorinated compound **10** could be obtained by the reaction of the alcohol **8** with morpholinosulfur trifluoride (morph-DAST)[10] in a 59%



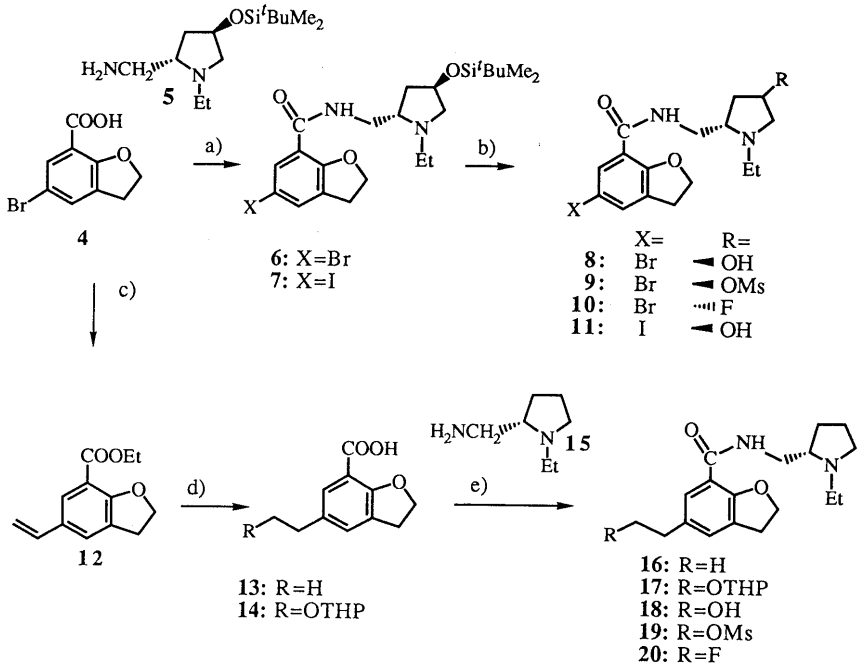
fluoroeticlopride (**1**)



IBF (**2**)



3 : X=Br, or X=I; R=F
X=CH_2CH_2F; R=H



a) **6**: DEPC, TEA, DMF; **7**: i) $Pd(PPh_3)_4$, $Pd(OAc)_2$, $(Bu_3Sn)_2$, TEA, ii) I_2, $CHCl_3$; b) **8**: *n*-Bu_4NF, THF; **9**: MsCl, TEA, ether; **10**: **8**, morph-DAST, CH_2Cl_2; **11**: **7**, *n*-Bu_4NF, THF; c) i) EtOH–toluene, H_2SO_4, ii) *n*-$Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, toluene; d) **13**: i) H_2, Pd/C, EtOH, ii) 1 N NaOH, MeOH; **14**: i) BH_3–THF, ii) H_2O_2, 2 N NaOH, iii) DHP, CSA, iv) 1 N NaOH, MeOH; e) **16** from **13**: DEPC, TEA, DMF; **20** from **14**: i) **17**: **14**, DEPC, TEA, DMF; ii) **18**: CSA, MeOH; iii) **19**: MsCl, TEA, ether; iv) **20**: *n*-Bu_4NF, THF

Abbreviations are as follows: DEPC: diethylphosphorocyanidate; TEA: triethylamine; THF: tetrahydrofuran; Ms: methanesulfonyl; morph-DAST: morpholinosulfur trifluoride; DHP: dihydropyran; CSA: 10-camphorsulfonic acid; DMF: dimethylformamide

Chart 1. Synthesis of Substituted Benzofuran Analogues

yield. The *S* configuration at the C-4 of the pyrrolidine ring was reasonably assumed based on our previous result.[5b] On the other hand, in spite of several approaches including the reaction of **11** with morph-DAST, the desired fluorinated compound with the iodobenzofuran unit (type **3**: X = I, R = F) could not be obtained.

5-Fluoroethyl tetrahydrobenzofuran derivative was prepared by a straightforward synthesis as shown in Chart 1. Esterification of **4** (74% yield) and successive vinylation with vinyltri-*n*-butyltin in the presence of $Pd(PPh_3)_4$ as a catalyst[11] afforded **12** (97% yield). Hydrogenation of **12** gave **13** (63% yield). **14** was obtained from **12** by the sequence of reactions, hydroboration with BH_3–tetrahydrofuran (THF) complex, and H_2O_2 treatment, then tetrahydropyranylation of the alcohol formed, in a 78% yield. The carboxamide derivatives (**16**, **17**) were prepared by amide formation between (*S*)-(−)-2-aminomethyl-1-ethylpyrrolidine (**15**)[12] and **13** or **14**, respectively, using DEPC as a coupling reagent. Tetrahydropyranyl (THP) protecting group of **17** was removed in methanol in the presence of 1.4 eq of 10-camphorsulfonic acid to give **18** (89% yield), which was mesylated with methanesulfonyl chloride and triethylamine in ether to afford **19** (75% yield). Nucleophilic substitution of **19** with *n*-Bu_4NF in THF at room temperature (17 h) afforded the desired fluorinated compound **20** in a 51% yield, which could also be obtained from **18** with morph-DAST in a 75% yield.

The *in vitro* binding affinity of the synthesized compounds toward CNS D2 receptors was investigated by measuring IC_{50} values against [^{3}H]spiperone binding in rat striatal tissue preparation. Nonspecific binding was determined by measuring binding in the presence of 10^{-4} M sulpiride. The results are summarized in Table I.

Table I. Inhibition of [^{3}H]Spiperone Binding in Striatal Homogenates of Rat Brain[a]

Compound	[^{3}H]Spiperone binding IC_{50} (nM)
1	1.9
8	6.3
9	8.9
10	17
11	2.2
16	21
17	>10000
18	29
19	37
20	36

a) Homogenates of the rat striatal tissue were incubated with 0.2 nM [^{3}H]spiperone and various concentrations of the compounds. Nonspecific binding was determined in the presence of 10^{-4} M sulpiride. IC_{50} represents the concentration of the compound required to inhibit 50% of specifically bound [^{3}H]spiperone. Values represent means of three determinations.

In the pyrrolidine-substituted series, the substitution variation slightly influenced the affinity for D2 dopamine receptors, similar to the finding in the previous study on **1**. 5-Iodo derivative **11** showed higher affinity (IC_{50} = 2.2 nM) than the 5-bromo counterpart **8** (IC_{50} = 6.3 nM). But, unfortunately, we could not get the fluorinated compound from **11**. The 5-ethylated benzofuran series (**16**—**20**) displays somewhat lower affinity. The ligands with the different functional group (R–CH_2CH_2–) have a similar

potency (IC_{50} values (nM): R=H, 21; R=OH, 29; R=OMs, 37; or R=F, 36). But the synthetic intermediate **17** with THP-protecting group did not maintain the receptor affinity ($IC_{50}>10\,\mu M$). These facts suggest that only a small substituent on the ethyl group at the C-5 of the dihydrobenzofuran is sterically allowed in the receptor binding site. In conclusion, the fluorinated ligands **10** and **20** were found to have lower affinities to the [^{3}H]spiperone binding site than **1** or **2**, although they still retain a high affinity with IC_{50} values in the nanomolar range. In preliminary *in vivo* binding studies in rats, ^{18}F-labelled **20** exhibited high *in vivo* selectivity toward CNS D2 receptors as illustrated by a high striatal/cerebellar radioactivity ratio of 10.5 at 60 min. These *in vivo* investigations will soon be reported in detail.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are not corrected. Optical rotations were determined by a JASCO DIP-360 digital polarimeter. ^{1}H-NMR spectra were taken at 270 MHz (JEOL GX-270), and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken on a JASCO IRA-1 spectrometer. Low resolution electron impact (EI), field desorption (FD), and fast atom bombardment (FAB) mass spectra (MS) (respective abbreviations are as follows: EIMS, FDMS, and FABMS) as well as high resolution EIMS (HRMS) were obtained on a JEOL TMS-D300 spectrometer. High resolution FABMS (HRFABMS) were taken on a JEOL NMS-SX 102 spectrometer. Low resolution secondary ion (SI) and high resolution SIMS (SIMS and HRSIMS) were obtained on a Hitachi M-2000 spectrometer. Kieselgel 60 (70—230 mesh, Merck) was used for column chromatography. Elemental analyses were performed by the staff of the microanalytical section of Kyushu University. [^{3}H]Spiperone (1.48 TBq/mmol) was purchased from New England Nuclear.

(2′*S*,4′*R*)-(−)-5-Bromo-*N*-[(4-*tert*-butyldimethylsilyloxy-1-ethyl-2-pyrrolidinyl)methyl]-2,3-dihydrobenzofuran-7-carboxamide (6) DEPC (0.11 g, 0.67 mmol) was added to a solution of 5-bromo-7-carboxy-2,3-dihydrobenzofuran (**4**)[7] (0.14 g, 0.57 mmol) and (2*S*,4*R*)-(−)-2-aminomethyl-4-*tert*-butyldimethylsilyloxy-1-ethylpyrrolidine (**5**)[12] (0.15 g, 0.58 mmol) in *N*,*N*-dimethylformamide (DMF) (2.5 ml) at 0 °C, followed by the addition of triethylamine (88 mg, 0.87 mmol). The mixture was stirred at 0 °C for 4 h and diluted with benzene–AcOEt (4 : 1) solution, then washed successively with 5% aqueous citric acid, brine, saturated aqueous $NaHCO_3$. The extract was dried over Na_2SO_4, and evaporated to dryness. The crude product was chromatographed on a silica gel column ($CHCl_3$: MeOH = 20 : 1) to give a yellow solid (0.25 g, 90%). mp 59—62 °C. $[\alpha]_D^{23}$ −27.0° (c=1.2, $CHCl_3$). IR (neat): 3350, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.04 (1H, d, J=2.0 Hz), 7.88 (1H, br), 7.39 (1H, m), 4.72 (2H, t, J=8.7 Hz), 4.28 (1H, qui, J=5.9 Hz), 3.67 (1H, ddd, J=13.5, 7.3, 3.0 Hz), 3.27 (2H, t, J=8.7 Hz), 3.37—3.24 (2H, m), 2.95 (1H, br), 2.87 (1H, dq, J=12.0, 7.1 Hz), 2.37 (1H, m), 2.24 (1H, dd, J=6.2, 5.9 Hz), 1.81 (2H, dd, J=7.4, 5.9 Hz), 1.09 (3H, t, J=7.1 Hz), 0.86 (9H, s), 0.03 (3H, s), 0.02 (3H, s). FABMS m/z: 483 (MH)$^+$, 485 (MH+2)$^+$. *Anal.* Calcd for $C_{22}H_{35}BrN_2O_3Si$: C, 54.65; H, 7.30; N, 5.79. Found: C, 54.90; H, 7.39; N, 5.47.

(2′*S*,4′*R*)-(+)-*N*-[(4-*tert*-Butyldimethylsilyloxy-1-ethyl-2-pyrrolidinyl)-methyl]-5-iodo-2,3-dihydrobenzofuran-7-carboxamide (7) A solution of **6** (0.10 g, 0.21 mmol), (n-Bu_3Sn)$_2$ (0.14 g, 0.25 mmol), $Pd(OAc)_2$ (5.0 mg, 0.022 mmol), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) in triethylamine (3 ml) was heated at 100 °C for 2.5 h under an argon atmosphere. Triethylamine was evaporated, and the residue was dissolved in CH_2Cl_2, then passed through a celite pad. The solution was evaporated to give a crude product, which was chromatographed on a silica gel column (AcOEt : hexane = 1 : 1) to afford (2′*S*,4′*R*)-(−)-*N*-[(4-*tert*-butyldimethylsilyloxy-1-ethyl-2-pyrrolidinyl)methyl]-5-tri-*n*-butylstannyl-2,3-dihydrobenzofuran-7-carboxamide as a colorless oil (62 mg, 43%). $[\alpha]_D^{23}$ −15.1° (c=1.1, $CHCl_3$). IR (neat): 3400, 1635, 1375, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.99 (1H, d, J=0.66 Hz), 7.92 (1H, br), 7.38 (1H, d, J=0.98 Hz), 4.68 (2H, t, J=8.7 Hz), 4.32 (1H, qui, J=5.8 Hz), 3.72 (1H, ddd, J=15.2, 6.8, 3.7 Hz), 3.26 (2H, t, J=8.6 Hz), 3.39—3.32 (2H, m), 2.97 (1H, br), 2.89 (1H, br), 2.40 (1H, br), 2.25 (1H, br), 1.84 (2H, t, J=7.1 Hz), 1.43—1.70 (6H, m), 1.23—1.40 (12H, m), 1.07 (3H, t, J=8.6 Hz), 0.88 (9H, t, J=7.1 Hz), 0.86 (9H, s), 0.026 (3H, s), 0.023 (3H, s). FABMS m/z: 695 (MH)$^+$. HRSIMS m/z: 695.3634 Calcd for $C_{34}H_{63}N_2O_3SiSn$. Found: 695.3627.

Iodine (0.21 g, 1.67 mmol) was added to a solution of the above oil (0.29 g, 0.42 mmol) in anhydrous $CHCl_3$ (1.5 ml). The mixture was stirred at room temperature for 2 d, and quenched by the addition of 10% aqueous $Na_2S_2O_3$, washed with water, then dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on a silica gel column ($CHCl_3$: MeOH = 100 : 1) to give **7** as an oil (0.20 g, 90%). $[\alpha]_D^{24}$ +4.3° (c=0.75, $CHCl_3$). IR (neat): 3350, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.21 (1H, d, J=2.0 Hz), 7.88 (1H, br), 7.58 (1H, m), 4.71 (2H, t, J=8.7 Hz), 4.30 (1H, qui, J=5.9 Hz), 3.67 (1H, ddd, J=13.9, 7.3, 3.3 Hz), 3.26 (2H, t, J=8.8 Hz), 3.30—3.37 (2H, m), 2.96 (1H, br), 2.85 (1H, dq, J=12.0, 7.6 Hz), 2.35 (1H, dq, J=16.2, 6.6 Hz), 2.25 (1H, dd, J=9.1, 6.3 Hz), 1.81 (2H, dd, J=7.9, 5.9 Hz), 1.09 (3H, t, J=7.3 Hz), 0.86 (9H, s), 0.026 (3H, s), 0.023 (3H, s). FDMS m/z: 530 (M$^+$), 531 (M+H)$^+$. HRSIMS m/z: 531.1540 Calcd for $C_{22}H_{36}IN_2O_3Si$. Found: 531.1552.

(2′*S*,4′*R*)-(−)-5-Bromo-*N*-[(1-ethyl-4-hydroxy-2-pyrrolidinyl)methyl]-2,3-dihydrobenzofuran-7-carboxamide (8) A solution of **6** (0.30 g, 0.62 mmol) and n-Bu_4NF (1 M THF solution, 1 ml, 1.0 mmol) in anhydrous THF (1 ml) was stirred at room temperature for 70 min and diluted with water–AcOEt. The organic layer was separated and dried over Na_2SO_4, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$: MeOH = 20 : 1) to give an oil (0.17 g, 74%). $[\alpha]_D^{25}$ −24.7° (c=0.84, $CHCl_3$). IR (neat): 3400, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.02 (1H, d, J=2.0 Hz), 7.94 (1H, br), 7.40 (1H, m), 4.73 (2H, dq, J=8.9, 0.99 Hz), 4.40 (1H, qui, J=5.0 Hz), 3.74 (1H, ddd, J=14.2, 7.3, 3.3 Hz), 3.50 (1H, dd, J=10.2, 5.6 Hz), 3.38—3.35 (1H, m), 3.27 (2H, t, J=8.7 Hz), 3.07 (1H, br), 2.91 (1H, dq, J=12.0, 7.3 Hz), 2.44 (2H, dq, J=11.7, 6.9 Hz), 2.34 (1H, dd, J=10.1, 4.6 Hz), 1.94—1.87 (2H, m), 1.13 (3H, t, J=7.3 Hz). FABMS m/z: 369 (MH)$^+$, 371 (MH+2)$^+$. HRSIMS m/z: 369.0787 Calcd for $C_{16}H_{22}BrN_2O_3$. Found: 369.0812.

(2′*S*,4′*R*)-(−)-5-Bromo-*N*-[(1-ethyl-4-methanesulfonyloxy-2-pyrrolidinyl)-methyl]-2,3-dihydrobenzofuran-7-carboxamide (9) Triethylamine was added to a solution of **8** (80 mg, 0.22 mmol) and methanesulfonyl chloride (30 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (1 ml) at 0 °C, and the mixture was stirred for 2 h. After water was added to the mixture, the organic layer was separated and dried over Na_2SO_4, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$: MeOH = 10 : 1) to give an oil (71 mg, 72%). $[\alpha]_D^{25}$ −33.0° (c=1.0, $CHCl_3$). IR (neat): 3400, 1650, 1375, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.21 (1H, d, J=2.0 Hz), 7.96 (1H, d, J=2.3 Hz), 7.43 (1H, m), 5.30 (1H, br), 4.79 (2H, dt, J=8.8, 0.65 Hz), 3.3—4.1 (7H, m), 3.28 (2H, t, J=8.7 Hz), 3.07 (1H, s), 2.43 (1H, m), 2.26 (1H, m), 1.94—1.87 (2H, m), 1.33 (3H, br). FABMS m/z: 447 (MH)$^+$, 449 (MH+2)$^+$. HRSIMS m/z: 447.0589 Calcd for $C_{17}H_{24}BrN_2O_5S$. Found: 447.0593.

(2′*S*,4′*S*)-(−)-5-Bromo-*N*-[(1-ethyl-4-fluoro-2-pyrrolidinyl)methyl]-2,3-dihydrobenzofuran-7-carboxamide (10) A solution **9** (21 mg, 0.056 mmol) in anhydrous CH_2Cl_2 (1 ml) was added dropwise to a solution of morph-DAST (20 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (0.2 ml) at −78 °C under an argon atmosphere. The mixture was stirred for 2 h while the temperature was raised to room temperature. The reaction mixture was poured into aqueous saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was separated, washed with water, and dried over Na_2SO_4, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$: MeOH = 100 : 1) to give an oil (12 mg, 58%). $[\alpha]_D^{25}$ −30.5° (c=1.0, $CHCl_3$). IR (neat): 3400, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.19 (1H, d, J=1.0 Hz), 8.07 (1H, br), 7.58 (1H, t, J=1.0 Hz), 5.12 (1H, dm, J=49.5 Hz), 4.71 (2H, t, J=8.8 Hz), 3.25 (2H, t, J=8.8 Hz), 1.8—3.8 (9H, m), 1.15 (3H, t, J=6.9 Hz). FDMS m/z: 371 (MH)$^+$, 373 (MH+2)$^+$. HRSIMS m/z: 371.0771 Calcd for $C_{16}H_{21}BrFN_2O_2$. Found: 371.0789.

(2′*S*,4′*R*)-(−)-*N*-[(1-Ethyl-4-hydroxy-2-pyrrolidinyl)methyl]-5-iodo-2,3-dihydrobenzofuran-7-carboxamide (11) A solution of **7** (62 mg, 0.117 mmol) and n-Bu_4NF (1 M THF solution, 0.18 ml, 0.18 mmol) in anhydrous THF (1 ml) was stirred at room temperature for 3 h and diluted with water–AcOEt. The organic layer was separated and dried over Na_2SO_4, then evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$: MeOH = 20 : 1) to give an oil (26 mg, 47%). $[\alpha]_D^{26}$ −23.4° (c=1.2, $CHCl_3$). IR (neat): 3400, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.18 (1H, d, J=1.0 Hz), 8.01 (1H, br), 7.59 (1H, dt, J=1.3, 1 Hz), 4.74 (2H, t, J=8.9 Hz), 4.45 (1H, br), 3.26 (2H, t, J=8.9 Hz), 1.6—3.85 (9H, m), 1.19 (3H, t, J=7.4 Hz). FDMS m/z: 471 (MH)$^+$. HRSIMS m/z:

417.0675 Calcd for $C_{16}H_{22}IN_2O_3$. Found: 417.0701.

7-Ethoxycarbonyl-5-vinyl-2,3-dihydrobenzofuran (12) A solution of **4**[7] (340 mg, 1.41 mmol) in ethanol (16 ml) was heated in the presence of 0.05 ml of concentrated H_2SO_4 for 34 h and neutralized with $NaHCO_3$. The mixture was filtered, and the filtrate was evaporated to give a crude oil which was chromatographed on a silica gel column (AcOEt : hexane = 1 : 7) to give 5-bromo-7-ethoxycarbonyl-2,3-dihydrobenzofuran as colorless needles (280 mg, 74%). mp 58—59 °C. IR (Nujol): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.82 (1H, m), 7.42 (1H, m), 4.72 (2H, t, J = 8.9 Hz), 4.37 (2H, q, J = 7.2 Hz), 3.20 (2H, t, J = 8.9 Hz), 1.38 (3H, t, J = 7.2 Hz). EIMS m/z: 272 $(M+2)^+$, 270 (M^+).

A solution of the above bromide (0.23 g, 0.84 mmol), $Pd(PPh_3)_4$ (31.5 mg, 0.027 mmol), vinyltri-*n*-butyltin (393 mg, 1.24 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (1 mg, 0.005 mmol) in toluene (4.5 ml) was heated under reflux for 3 h under an argon atmosphere. The mixture was cooled to room temperature, and 0.5 ml of pyridine was added followed by the addition of 1 ml of 1.2 N pyridinium poly (hydrogen fluoride) solution.[11] The resulting mixture was stirred for 16 h at room temperature, diluted with ether. The mixture was successively washed with water, 10% aqueous HCl, saturated aqueous $NaHCO_3$. The organic phase was separated, dried over $MgSO_4$, and evaporated to give a crude oil, which was chromatographed on a silica gel column (AcOEt : hexane = 1 : 4) to afford **12** as a colorless oil (180.5 mg, 97%). IR (neat): 1710, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.72 (1H, m), 7.46 (1H, m), 6.63 (1H, dd, J = 17.5, 10.9 Hz), 5.62 (1H, dd, J = 17.5, 1.0 Hz), 5.15 (1H, dd, J = 1.0, 10.9 Hz), 4.73 (2H, t, J = 8.3 Hz), 4.38 (2H, q, J = 6.9 Hz), 3.22 (2H, t, J = 8.3 Hz), 1.40 (3H, t, J = 7.3 Hz). EIMS m/z: 218 $(M-1)^+$. *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 71.45; H, 6.47. Found: C, 71.45; H, 6.40.

7-Carboxy-5-ethyl-2,3-dihydrobenzofuran (13) A mixture of **12** (567 mg, 2.6 mmol) and 5% palladium on carbon (30 mg) in 15 ml of ethanol was vigorously stirred for 2 h under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was evaporated to give a crude oil, which was chromatographed on a silica gel column (hexane : ether = 1 : 1) to give 7-ethoxycarbonyl-5-ethyl-2,3-dihydrobenzofuran as a pure oil (363 mg, 63%). The above oil was dissolved in a solution of 3 ml methanol and 4 ml 1 N NaOH, and the resulting mixture was stirred for 5.5 h at room temperature, then acidified with 1 N aqueous HCl. The mixture was extracted with ether, and the extract was washed with brine, dried over $MgSO_4$, then evaporated to give **13** as white powder (272 mg, 90%). This powder was used for the next reaction without further purification. mp 155—157 °C. IR (Nujol): 3200, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.67—7.61 (1H, m), 7.31—7.25 (1H, m), 4.80 (2H, t, J = 8.5 Hz), 3.27 (2H, t, J = 8.2 Hz), 2.63 (2H, q, J = 7.4 Hz), 1.21 (3H, t, J = 7.3 Hz). FABMS m/z: 193 $(MH)^+$, 192 (M^+). HRFABMS m/z: 193.0865 Calcd for $C_{11}H_{13}O_3$. Found: 193.0862.

7-Carboxy-5-(2-tetrahydropyranyloxyethyl)-2,3-dihydrobenzofuran (14) 1 M BH_3–THF complex solution (12.3 ml, 12.3 mmol) was added to a solution of **12** (1.79 g, 8.1 mmol) in THF (50 ml) at 0 °C under an argon atmosphere, and the mixture was stirred for 30 min. Water (6.7 ml), 3 N aqueous NaOH (23 ml), and 30% H_2O_2 (16 ml) were added, and the resulting mixture was stirred for 1.5 h at room temperature. The mixture was saturated with NaCl, and extracted with AcOEt. The extract was successively washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$, then evaporated. The crude oil was chromatographed on a silica gel column (AcOEt : hexane = 2 : 1) to give 7-ethoxycarbonyl-5-(2-hydroxyethyl)-2,3-dihydrobenzofuran (1.54 g, 80%) as colorless needles. mp 64—67 °C. IR (Nujol): 3400, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.56 (1H, d, J = 2.0 Hz), 7.23 (1H, d, J = 2.0 Hz), 4.71 (2H, t, J = 8.9 Hz), 4.37 (2H, q, J = 6.9 Hz), 3.85 (2H, dt, J = 6.5, 12.2 Hz), 3.21 (2H, t, J = 8.9 Hz), 2.82 (2H, t, J = 6.5 Hz), 1.38 (3H, t, J = 6.9 Hz). EIMS m/z: 236 (M^+), 205 $(M-CH_2OH)$. *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 66.03; H, 6.70. Found: C, 66.00; H, 6.73.

Dihydropyran (0.55 g, 6.54 mmol) was added to a solution of the above alcohol (1.54 g, 6.52 mmol) and 10-camphorsulfonic acid (163 mg, 0.7 mmol) in anhydrous CH_2Cl_2 at 0 °C, and the mixture was stirred for 2 h, then neutralized with $NaHCO_3$. The mixture was successively washed with water and brine, dried over Na_2SO_4, and then evaporated. The crude oil was chromatographed on a silica gel column (AcOEt : hexane = 1 : 4) to give 7-ethoxycarbonyl-5-(2-tetrahydropyranyloxyethyl)-2,3-dihydrobenzofuran (2.05 g, 98%) as a colorless oil. IR (neat): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.60 (1H, s), 7.23 (1H, s), 4.71 (2H, t, J = 8.9 Hz), 4.72 (2H, t, J = 8.8 Hz), 4.60 (1H, t, J = 2.6 Hz), 4.34 (2H, q, J = 7.1 Hz), 3.91 (2H, dt, J = 6.9, 9.9 Hz), 3.75 (1H, ddd, J = 3.3, 8.2, 11.5 Hz), 3.58 (1H, dt, J = 9.9, 6.9 Hz), 3.47 (1H, m), 3.22 (2H, t, J = 8.8 Hz), 2.87 (2H, t, J = 6.9 Hz), 1.9—1.47 (6H, m), 1.37 (3H, t, J = 7.1 Hz). EIMS m/z: 320 $(MH)^+$.

A solution of the above oil (2.0 g, 6.2 mmol) in methanol (13 ml) containing 1 N NaOH (12 ml, 12 mmol) was stirred for 2.5 h at room temperature, and acidified with saturated aqueous citric acid solution (1.3 ml). The mixture was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4, then evaporated. The crude product was chromatographed on a silica gel column ($CHCl_3$: MeOH = 30 : 1) to give **14** as a colorless oil (1.72 g, 95%). IR (neat): 3300, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.71 (1H, s), 7.31 (1H, s), 4.80 (2H, t, J = 8.9 Hz), 4.58 (1H, t, J = 3.3 Hz), 3.92 (1H, dt, J = 6.9, 9.8 Hz), 3.75 (1H, m), 3.58 (1H, dt, J = 9.8, 6.9 Hz), 3.47 (1H, m), 3.28 (2H, t, J = 8.9 Hz), 2.87 (2H, t, J = 6.9 Hz). EIMS m/z: 292 $(MH)^+$.

(*S*)-(−)-5-Ethyl-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,3-dihydrobenzofuran-7-carboxamide (16) DEPC (283 mg, 1.74 mmol) was added to a solution of **13** (167 mg, 0.87 mmol) and (*S*)-(−)-2-aminomethyl-1-ethylpyrrolidine (**15**)[12] (112 mg, 0.87 mmol) in DMF (5 ml) at 0 °C, followed by the addition of triethylamine (176 mg, 1.74 mmol). The mixture was stirred for 14 h at room temperature, and diluted with AcOEt, then washed successively with 5% aqueous citric acid, brine, and saturated aqueous $NaHCO_3$. The extract was dried over Na_2SO_4, and evaporated to dryness. The crude product was chromatographed on a silica gel column ($CHCl_3$: MeOH = 50 : 1) to give **16** (261 mg, 99%) as an oil. $[\alpha]_D^{23}$ −45.5° (c = 0.8, $CHCl_3$). IR (neat): 3400, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.98 (1H, br), 7.75 (1H, m), 7.14 (1H, m), 4.68 (2H, t, J = 8.9 Hz), 3.68 (1H, ddd, J = 13.5, 6.6, 3.6 Hz), 3.31 (1H, ddd, J = 13.5, 5.6, 4.0 Hz), 3.23 (2H, t, J = 8.9 Hz), 3.21—3.15 (1H, m), 2.88 (1H, dq, J = 11.9, 7.3 Hz), 2.71—2.64 (1H, m), 2.61 (2H, q, J = 7.6 Hz), 2.29 (2H, dq, J = 11.9, 6.9 Hz), 2.19 (1H, dt, J = 8.9, 7.6 Hz), 2.02—1.55 (4H, m), 1.21 (3H, t, J = 7.6 Hz), 1.13 (3H, dd, J = 7.3, 6.9 Hz). FABMS m/z: 303 $(MH)^+$, 302 $(M-H)^+$. HRFABMS m/z: 303.2072 Calcd for $C_{18}H_{27}N_2O_2$. Found: 303.2076.

(*S*)-(−)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-5-(2-tetrahydropyranyloxyethyl)-2,3-dihydrobenzofuran-7-carboxamide (17) DEPC (200 mg, 1.23 mmol) was added to a solution of **14** (200 mg, 0.69 mmol) and **15**[12] (150 mg, 1.17 mmol) in DMF (5 ml) at 0 °C, followed by the addition of triethylamine (120 mg, 1.19 mmol). The mixture was stirred for 13 h at room temperature, diluted with AcOEt, then washed successively with 5% aqueous citric acid, brine, and saturated aqueous $NaHCO_3$. The extract was dried over Na_2SO_4 and evaporated to dryness. The crude product was chromatographed on a silica gel column ($CHCl_3$: MeOH = 50 : 1) to give **17** (275 mg, 99%) as a pale yellow oil. $[\alpha]_D^{24}$ −18.7° (c = 1.04, $CHCl_3$). IR (neat): 3100, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.98 (1H, br), 7.77 (1H, s), 7.19 (1H, s), 4.68 (2H, t, J = 9.9 Hz), 4.58 (1H, t, J = 9.9 Hz), 3.90 (1H, dt, J = 9.9, 7.3 Hz), 3.79 (1H, ddd, J = 10.5, 7.3, 3.0 Hz), 3.68 (1H, ddd, J = 13.5, 6.6, 4.0 Hz), 3.58 (1H, dt, J = 9.9, 7.6 Hz), 3.46 (1H, ddd, J = 5.0, 5.0, 10.5 Hz), 3.32 (1H, ddd, J = 13.5, 5.0, 5.0 Hz), 3.23 (2H, t, J = 9.9 Hz), 3.23 (1H, m), 2.88 (1H, m), 2.72—2.64 (1H, m), 2.30 (2H, dq, J = 12.2, 7.0 Hz), 2.20 (1H, dd, J = 14.2, 6.3 Hz), 2.00—1.45 (10H, m), 1.13 (3H, t, J = 7.0 Hz). FABMS m/z: 403 $(MH)^+$, 402 (M^+). HRFABMS m/z: 403.2597 Calcd for $C_{23}H_{35}N_2O_4$. Found: 403.2596.

(*S*)-(−)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-5-(2-hydroxyethyl)-2,3-dihydrobenzofuran-7-carboxamide (18) A solution of **17** (500 mg, 1.24 mmol) and 10-camphorsulfonic acid (404 mg, 1.74 mmol) in methanol (10 ml) was stirred for 1.5 h at room temperature, then neutralized with $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the extract was washed with brine, then dried over Na_2SO_4. The crude product was chromatographed on a silica gel column ($CHCl_3$: MeOH = 4 : 1) to give **18** as a colorless oil (352 mg, 89%). $[\alpha]_D^{24}$ −20.1° (c = 1.8, $CHCl_3$). IR (neat): 3300, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.07 (1H, br), 7.74 (1H, s), 7.19 (1H, s), 4.70 (2H, t, J = 8.9 Hz), 3.83 (2H, t, J = 6.5 Hz), 3.70 (1H, ddd, J = 4.2, 6.6, 13.8 Hz), 3.37 (1H, ddd, J = 4.6, 8.2, 13.5 Hz), 3.23 (2H, t, J = 8.5 Hz), 2.95 (1H, dq, J = 4.6, 7.1 Hz), 2.83 (2H, t, J = 7.1 Hz), 2.81—2.51 (1H, br), 2.42 (1H, dq, J = 5.2, 6.9 Hz), 2.30 (1H, dd, J = 7.5, 16.8 Hz), 2.02—1.62 (6H, m), 1.16 (3H, t, J = 6.9 Hz). FABMS m/z: 319 $(MH)^+$, 318 (M^+). HRFABMS m/z: 319.2020 Calcd for $C_{18}H_{27}N_2O_3$. Found: 319.1982.

(*S*)-(−)-*N*-[(1-Ethyl-2-pyrrolidinyl)-methyl]-5-(2-methanesulfonyloxyethyl)-2,3-dihydrobenzofuran-7-carboxamide (19) Methanesulfonyl chloride (88.8 mg, 0.78 mmol) was added to a solution of **18** (50 mg, 0.16 mmol) and triethylamine (43.6 mg, 0.44 mmol) in ether (2 ml) at −20 °C, and the mixture was stirred for 2 h. The reaction mixture was extracted with AcOEt and the extract was washed with water, dried over $MgSO_4$, then evaporated. The crude product was chromatographed on a silica gel column ($CHCl_3$: MeOH = 10 : 1) to give **19** as a colorless

oil (46.5 mg, 75%). $[\alpha]_D^{24}$ −17.5° (c=0.96, $CHCl_3$). IR (neat): 3300, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.10 (1H, s), 7.79 (1H, s), 7.20 (1H, s), 4.75 (2H, t, J=8.6 Hz), 4.39 (2H, t, J=6.9 Hz), 3.75 (1H, ddd, J=4.9, 11.2, 13.5 Hz), 3.47 (1H, m), 3.27 (2H, t, J=8.5 Hz), 3.02 (2H, t, J=6.9 Hz), 2.91 (3H, s), 2.41 (2H, m), 2.05—1.65 (4H, m), 1.19 (3H, t, J=6.9 Hz). FABMS m/z: 397 $(MH)^+$, 399 $(MH+2)^+$. HRFABMS m/z: 397.1797 Calcd for $C_{19}H_{29}N_2O_5S$. Found: 397.1775.

(*S*)-(−)-*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-5-(2-fluoroethyl)-2,3-dihydrobenzofuran-7-carboxamide (20) A Method with n-Bu_4NF: A mixture of **19** (17 mg, 0.042 mmol) and n-Bu_4NF (1 M THF solution, 0.06 ml, 0.06 mmol) in 0.5 ml THF was stirred for 17 h at room temperature. The mixture was extracted with ether and the extract was washed with saturated aqueous $NaHCO_3$, then dried over Na_2SO_4. The crude product was purified by HPLC (Whatman Partisil 5PAC, n-hexane : AcOEt : EtOH = 400 : 100 : 45, flow rate: 3 ml/min) to give **20** as a colorless oil (7 mg, 51%). $[\alpha]_D^{24}$ −25.3° (c=0.53, $CHCl_3$). IR (neat): 3300, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.54 (1H, s), 7.66 (1H, s), 7.22 (1H, s), 4.79 (2H, t, J=8.9 Hz), 4.60 (2H, dt, J=47.2, 6.5 Hz), 3.99—3.81 (1H, br s), 3.24 (2H, t, J=8.9 Hz), 3.12 (2H, q, J=7.3 Hz), 2.97 (2H, dq, J=21.7, 6.6 Hz), 2.28—2.18 (2H, br s), 2.04—1.93 (2H, br s), 1.77—1.50 (3H, br s), 1.41 (3H, t, J=7.6 Hz). FABMS m/z: 321 $(MH)^+$, 323 $(MH+2)^+$. HRFABMS m/z: 321.2000 Calcd for $C_{18}H_{26}FN_2O_2$. Found: 321.1989.

A Method with Morph-DAST: A solution of **19** (27 mg, 0.067 mmol) in anhydrous CH_2Cl_2 (1.5 ml) was added dropwise into a solution of morph-DAST (30 mg, 0.085 mmol) in anhydrous CH_2Cl_2 (0.3 ml) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 1.5 h while the temperature was raised to room temperature. The mixture was extracted with CH_2Cl_2 and the extract was washed successively with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. The crude product was chromatographed on a silica gel column ($CHCl_3$: MeOH = 11 : 1) to give **20** as a colorless oil (26 mg, 75%). The spectral and HPLC data of this product were identical with those obtained above.

In Vitro* Receptor Binding Assay** The assays were performed in the rat striatal membranes using a previously described method.[13] Briefly, rat striata were homogenized in 100 volumes of ice-cold Tris–HCl buffer (50 mM, pH 7.7) and centrifuged (500g***, 10 min, 0 °C). The supernatant was centrifuged at 50000***g*** for 15 min. The pellet was suspended in 100 volumes of ice-cold Tris–HCl buffer (50 mM, pH 7.7) and recentrifuged (50000***g***, 15 min, 0 °C). The final pellet was resuspended in 150 volumes of ice-cold Tris–HCl buffer (50 mM, pH 7.1) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 1.1 mM ascorbic acid, and 10 mM pargyline and incubated at 37 °C for 10 min. A portion of this membrane suspension (900 μl) was placed in a tube and 50 μl of either test compound or vehicle solution was added, followed by 50 μl of [^{3}H]spiperone (1.48 TBq/mmol) at a final concentration of 0.2 nM, under which condition 70% of the D2 receptors are estimated to be bound by the ligand. The tubes were incubated at 37 °C for 20 min and filtered through Whatman GF/B glass filters, which were then washed three times with 3 ml of the Tris–HCl buffer (50 mM, pH 7.7). The nonspecific binding was determined in the presence of 10^{-4} M of (±)-sulpiride. The radioactivity trapped on the filters was measured by liquid-scintillation spectrometry. The IC_{50} values to displace specific [^{3}H]spiperone binding were determined from concentration–inhibition curves.

Acknowledgements This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan. We are also grateful to Mitsubishi Kasei Corporation for SIMS measurements.

References and Notes

1) D_1 and D_2: *a*) P. F. Spano, S. Govoni, and M. Trabucchi, *Adv. Biochem. Psychopharmacol.*, **19**, 155 (1978); *b*) J. W. Kebabian and D. B. Calne, *Nature* (London), **277**, 93 (1979).
2) D_{2A} and D_{2B}: *a*) B. P. Giros, P. Sokoloff, J.-F. Riou, L. J. Emorine, and J. C. Schwartz, *Nature* (London), **342**, 923 (1989); *b*) F. J. Monsma, Jr., L. D. McVittie, C. R. Gerfen, L. C. Mahan, and D. R. Sibley, *ibid.*, **342**, 926 (1989); *c*) L. A. Selbie, G. Hayes, and J. Shine, *DNA*, **8**, 683 (1989); *d*) D4 subtype: H. H. M. Vantol, J. R. Bunzow, H.-C. Guan, R. K. Sunahara, P. Seeman, H. B. Niznik, and O. Civelli, *Nature* (London), **350**, 610 (1991); *e*) D5 subtype: R. K. Sunahara, H. B. Niznik, D. M. Weiner, T. M. Stormann, M. R. Brann, J. L. Kennedy, J. E. Gelernter, R. Rozmahel, Y. Yang, Y. Isreal, and P. Seeman, *ibid.*, **347**, 80 (1990), *f*) P. Sokoloff, M.-P. Martres, B. Giros, M.-L. Bounthenet, and J. C. Schwartz, *Biochem. Pharmacol.*, **43**, 659 (1992), and references cited therein.
3) For example, S.-M. Aquilonius, *Acta Neurol. Scand.*, **84**, Suppl. 136, 37 (1991).
4) Recent examples of ^{18}F-labelled radioligands: *a*) Raclopride analog: D. O. Kieselwetter, R. Kawai, M. Chelliah, E. Owens, C. Mclellan, and R. G. Blasberg, *Nucl. Med. Biol.*, **17**, 347 (1990); *b*) Sulpiride analog: J. Mukherjee, K. E. Luh, N. Yasillo, B. D. Perry, D. Levy, C.-T. Chen, C. Ortega, R. N. Beck, and M. Cooper, *Eur. J. Pharmacol.*, **175**, 363 (1990), and references cited therein. Radioligands labelled with other nuclides have also been investigated; *c*) [^{125}I]Epidepride analog: R. M. Kessler, M. S. Ansari, D. E. Schmidt, T. Depaulis, J. A. Clanton, R. Innis, M. Altikriti, R. G. Manning, and D. Gillespie, *Life Sci.*, **49**, 617 (1991); *d*) [^{125}I]Spiperone analog: H. Saji, T. Tokui, I. Nakatsuka, A. Saiga, Y. Magata, K. Shiba, A. Yoshitake, and A. Yokoyama, *Chem. Pharm. Bull.*, **40**, 165 (1992).
5) [^{18}F]Eticlopride analog: *a*) T. Fukumura, H. Dohmoto, M. Maeda, E. Fukuzawa, and M. Kojima, *Chem. Pharm. Bull.*, **38**, 1740 (1990); *b*) K. Watanabe, T. Fukumura, S. Sasaki, M. Maeda, and S. Takehara, *ibid.*, **39**, 3211 (1991).
6) M. Maeda, S. Sasaki, T. Fukumura, E. Fukuzawa, K. Watanabe, M. Kojima, T. Tahara, K. Masuda, and Y. Ichiya, *Chem. Pharm. Bull.*, **40**, 1793 (1992).
7) R. A. Murphy, H. F. Kung, M.-L. Kung, and J. Billings, *J. Med. Chem.*, **33**, 171 (1990).
8) P. N. Craig, "The Basis of Medicinal Chemistry," 4th ed., Part 1, ed. by M. E. Wolff, Wiley-Interscience, New York, 1980, pp. 331—348.
9) S. Yamada, K. Kasai, and T. Shioiri, *Tetrahedron Lett.*, **1973**, 1595.
10) K. C. Mange and W. J. Middleton, *J. Fluorine Chem.*, **43**, 337 (1989).
11) D. R. McKean, G. Parrinello, A. F. Renaldo, and J. K. Stille, *J. Org. Chem.*, **52**, 422 (1987).
12) T. D. Paulis, A. Janowsky, R. M. Kessler, J. A. Clanton, and H. E. Smith, *J. Med. Chem.*, **31**, 2027 (1988).
13) I. Greese, R. Schneider, and S. H. Snyder, *Eur. J. Pharmacol.*, **46**, 377 (1977).