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SYNTHESIS OF RADIOIODINATED 2'-IODOBUTYROPHENONE DERIVATIVES

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SUMMARY

To develop new radioligands labelled with radioiodine (^{125}I, ^{131}I and ^{123}I) for in vitro and in vivo dopamine receptor studies, three iodinated butyrophenones (2'-iodospiperone, 2'-iodotrifluperidol and 2'-iodohaloperidol) were designed, synthesized and labelled with ^{125}I.

Key Words: 2'-Iodobutyrophenones, Dopamine Recepter, Radioiodine, Iodine-123

INTRODUCTION

In our previous papers [1-5], neuroleptic butyrophenones iodinated at the 2'-position have been demonstrated to have considerably high affinities to the dopamine receptors. Among them, 2'-iodospiperone (2'-ISP) has the most prominent property as a radioligand for the dopamine receptors and recently it has been proved that ^{123}I labelled 2'-ISP can clearly image the dopamine receptors in the living human brains after intravenous injection by means of SPECT method [6-8].

In this paper, we describe the synthetic methods for the radioactive and non-radioactive 2'-iodobutyrophenone derivatives.

RESULTS AND DISCUSSION

Drug Designing

A variety of neuroleptic butyrophenones such as spiperone (SP), trifluperidol (TP) and haloperidol (HP) is widely used as a major tranquilizer for various psychiatric diseases in the clinical

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fields. From the results of the *in vitro* receptor binding studies on the neuroleptic butyrophenones, it has been found that these drugs specifically bind to the dopamine receptors with high affinities [9-11]. To develop a new ligand for *in vitro* and *in vivo* dopamine receptor studies, we planned to synthesize radioiodinated neuroleptic butyrophenones, since iodine has some radioactive nuclides suitable for each purpose (^{123}I: $T_{1/2}$ = 13 hr, 159 KeV for *in vivo*; ^{125}I: $T_{1/2}$ = 60.2 day, 35.5 KeV for *in vitro*).

In the course of design for a new radioiodinated ligand, it was the most critical question to decide the position for labelling. A general structure of the neuroleptic butyrophenones is illustrated in Fig. 1.

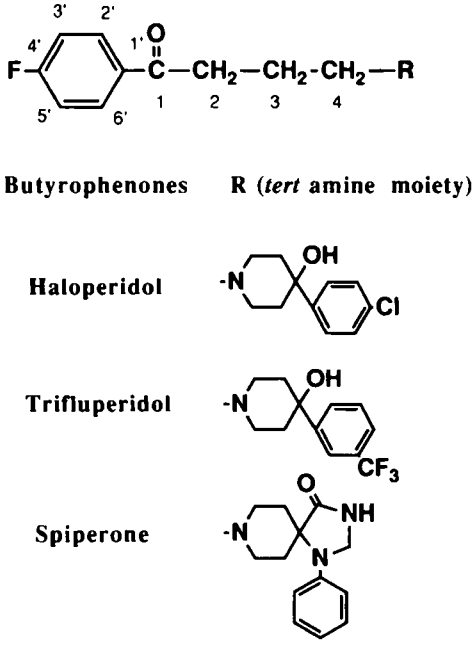


Fig.1 Chemical Structure of Neuroleptic Butyrophenones

The drugs commonly consist of the butyrophenone moiety and the *tert* amine moiety. First, we had to decide which moiety is better for labelling.

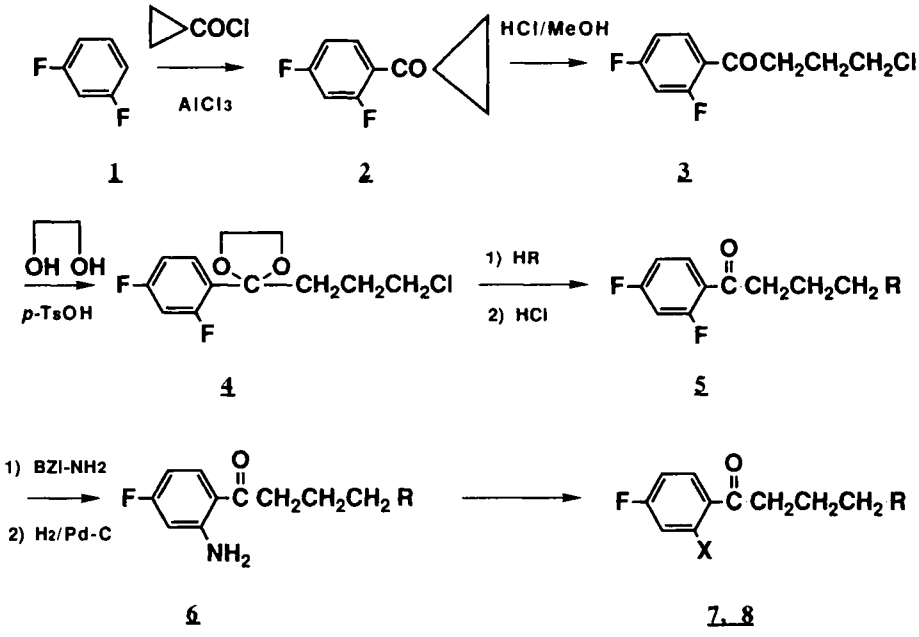
On the basis of the following thoughts, we chose the butyrophenone moiety as a labelling part. 1) Both the pharmacological activity and the binding affinity of the drugs to the dopamine receptors are drastically affected by modifying the structure of the *tert* amine moiety, so the incorporation of iodine into the *tert* amine moiety should be avoided. 2) Once the labelling methodology for the butyrophenone moiety is established, by which a series of radioiodinated neuroleptic butyrophenones can be synthesized.

Among several possible positions, on which a radio-iodine can be incorporated, we then selected the *ortho*- (2'-) position of the *p*-fluorophenyl ring of the butyrophenone moiety because of the following reasons: 1) with respect to the stability of the iodine-carbon bond, the iodine bound to the phenyl ring is more stable than that to the alkyl chain, and 2) iodine substitution at the *ortho* position leads to less disturbance of the electron distribution on the *p*-fluorophenyl ring system than that at the *meta* position.

Non-radioactive iodinated butyrophenones

Non-radioactive iodinated butyrophenones, 2'-iodospiperone (2'-ISP), 2'-iodotrifluperidol (2'-ITP) and 2'-iodohaloperidol (2'-IHP) were synthesized as candidates for radioligand and screened by *in vitro* receptor binding assay. Syntheses have been achieved by modifying our previous methods[13] as shown in Fig. 2.

Cyclopropyl-2,4-difluorophenyl ketone (**2**) was prepared by Friedel-Crafts reaction of cyclopropylcarbonyl chloride with an excess amount of *m*-difluorobenzene in the presence of anhydrous aluminum chloride at 5-10°C for 40 hr in an yield of 81% (purity 90%). Cyclopropyl-2,4-difluorophenyl ketone (**2**) was converted into 4-chloro-2',4'-difluorophenyl ketone (**3**) by treatment with HCl in methanol at room temperature in a quantitative yield. After ketalization of the ketone (**3**) by heating with ethyleneglycol and *p*-toluenesulfonic acid, the ketal (**4**) was condensed with a spiroamine and subsequently hydrolized with hydrochloric acid to give 2'-fluorospiperone (2'-FSP) (**5a**) in an yield of 28%, which was identified by ^{1}H-NMR, MS and IR spectra. Since the direct iodination of **5a** was unsuccessful despite of various attempts, we chose the route *via* the amine derivates. Selective monobenzylamination at the *ortho* position of 2'-FSP was achieved by heating of 2'-FSP with an excess of benzylamine in *n*-hexane for 16 hr according to the modified Sasajima's method [14] to give 2'-benzylaminospiperone in an yield of 69%. Debenzylation of the obtained 2'-benzylaminospiperone by catalytic hydrogenolysis with 10% Pd-C, followed by



1 2 3 4 5 6 7, 8

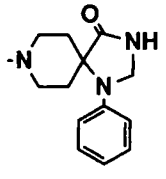
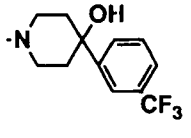
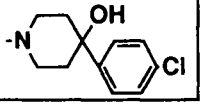
Compds.	X	R
2'-ISP (7a)	I	
2'-BrSP (8a)	Br	
2'-ITP (7b)	I	
2'-BrTP (8b)	Br	
2'-IHP (7c)	I	
2'-BrHP (8c)	Br	

Fig. 2 Synthesis of 2'-Halogenobutyrophenones

purification on silica gel chromatography gave 2'-aminospiperone (2'-ASP) (6a) in an yield of 61%, which was identified by ^{1}H-NMR, HR-MS, and IR. 2'-ASP was converted into 2'-iodospiperone (2'-ISP) (7a) *via* the diazonium salt by applying the modified Sandmeyer method as mentioned in the following section in detail. After column chromatography on silica gel, purified 2'-ISP was obtained in an yield of 36%, which was identified by ^{1}H-NMR, HR-MS and IR.

Table 1 Butyrophenone Derivatives

Compds.	mp.(°C)	^{13}C-,^{1}H-NMR(δ,ppm)	EI-MS	IR(cm^{-1})	Yield (%)[a]
2'-FSP (5a)	211-216	1.44-3.10 (m,14H), 4.73 (s,2H) 6.42(br.s,1H),6.74-7.98(m,8H)	413(M^+)	1700	27.9
2'-FTP (5b)	238-239	----[b]	----	1675,1615 1335,1130	75.0
2'-FHP (5c)	245-246	----	----	1670,1613 3460	74.0
2'-ASP (6a)	174-179	1.52-3.21(m,14H),4.57(s,2H) 6.20-7.92(m,8H)	410.2044[c] 410.2080[d]	1700,3480 3350	60.5
2'-ATP (6b)	205-206	----	424(M^+)	1655,1625 3440,3330	56.7
2'-AHP (6c)	236-237	18.4, 30.9, 34.9, 48.3, 55.6, 68.1, 101.3, 101.7, 102.3 102.6, 113.9, 126.7, 128.1, 131.5, 134.5, 134.7, 147.1 153.5, 153.7, 163.8, 167.5, 199.4	390(M^+)	1645	58.3
2'-ISP (7a)	171-172	1.40-3.18(m,14H),4.72(s,2H) 6.08(br.s,1H),6.87-7.70(m,8H)	521.0949[c] 521.0962[d]	1710	36.2
2'-ITP (7b)	----	1.50-3.00(m,15H) 7.00-7.90(m,7H)	535(M^+)	1690	10.7
2'-IHP (7c)	----	1.50-3.00(m,15H) 6.90-7.80(m,7H)	503(M^+)	1690	9.5

a) Yield of one step (Yieds of two steps in case of amino substituents)
b) Not measured.
c) Calcd. for high resolution-MS
d) Observed for high resolution-MS

Other iodinated butyrophenones, 2'-ITP and 2'-IHP were synthesized by applying the essentially the same reaction scheme as the above shown in Fig. 2. Thus, the key intermediate, the ketal (4) was condensed with the corresponding *secondary* amines and hydrolyzed. The obtained 5b and 5c were reacted with benzylamine, followed by debenzylation and iodination to afford the corresponding 2'-ITP (7b) and 2'-IHP (7c), respectively. Sepectral data on the intermediates and iodides and the yields of each step are summarized in Table 1.

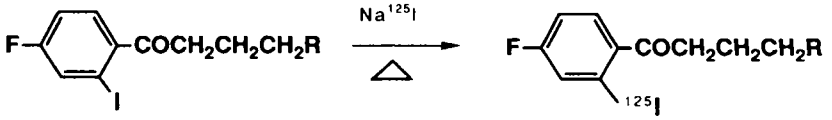


Fig.3 Iodine-Iodine Exchange Reaction

Labelling method for radioiodinated butyrophenones

For labelling, we tried the following three methods.

1. Iodine-Iodine exchange reaction

The reaction is illustrated in Fig. 3. Since the 2'-position of 2'-iodinated butyrophenones is activated for nucleophilic attacking due to the neighboring effect of the *ortho* carbonyl group, we supposed that radioactive iodine could be incorporated into the 2'-position of 2'-iodinated butyrophenones by the direct iodine-iodine exchange reaction.

On the basis of the above thoughts, we attempted this reaction using 2'-ISP as a representative iodide precursor under various conditions as summarized in Table 2.

As a result, it was found that [^{125}I]iodine can be incorporated into the 2'-position of 2'-ISP by this exchange reaction under the proper conditions, and that the radiochemical yield of [^{125}I]2'-ISP

Table 2 Yields of [^{125}I]2'-ISP under various reactive conditions

No.	2'-ISP (μg)	Na^{125}I (μCi)	Solvent (μl)	pH[a)]	Temp.(°C)	Time (hr)	Yield(%)
1	5	50	acetone (100)	B	60	6	-[b)]
2	5	50	dioxane (50) DMF (50)	N	90	6	-
3	5	50	dioxane (10) DMF (10)	N	90	6	36
4	5	50	dioxane (10) DMF (10)	B	90	6	27[c)]
5	5	50	dioxane (10) DMF (10)	N	120-130	3	5[c)]
6	5	50	DMF (20)	N	100	4	42
7	5	50	DMF (20)	A	100	4	37
8	5	50[d)]	DMF (20)	A	100	4	-

a)B:Basified (0.1 N NaOH), N: Neutralized (with 0.1 N HCl),
A:Acidified (addition of slight excess of 0.1 N HCl)
b) Not reactioned.
c) Containing lysis product
d) Na^{125}I was treated with 0.1% H_2O_2/0.1 N HCl. $^{125}I_2$ was reactant.

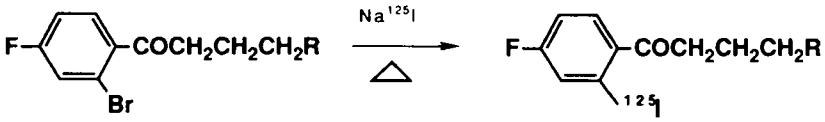


Fig.4 Bromine-Iodine Exchange Reaction

was markedly dependent on sorts of solvent, volume of the solvent, pH, and reaction temperature. Based on these data, entry No. 6 was chosen for the synthesis of carrier-added [^{125}I]2'-ISP, in which 2'-ISP was heated with sodium [^{125}I]iodide in DMF at 100°C for 4 hr. After preparative HPLC, [^{125}I]2'-ISP was obtained in an yield of 42%. The radiochemical purity was more than 98%.

[^{125}I]2'-ITP and [^{125}I]2'-IHP were also prepared by applying this method for 2'-ISP and 2'-IHP in the yields of 43% and 32%, respectively.

2. Bromine-Iodine exchange reaction

For preparation of carrier-free [^{125}I]2'-ISP, we attempted the bromine-iodine exchange reaction as illustrated in Fig. 4. Since we expected that this approach give us carrier-free [^{125}I]2'-ISP if formed [^{125}I]2'-ISP will be able to separate from an excess of the precursor, 2'-BrSP. Brominated butyrophenones, 2'-bromospiperone (2'-BrSP), 2'-bromohaloperidol (2'-BrHP) and 2'-bromotrifluperidol (2'-BrTP) were synthesized from the corresponding 2'-aminobutyrophenones (**6a**, **6b** and **6c**) by the modified Sandmeyer reaction as described in the experimentals.

To find out the best condition, the bromine-iodine exchange reaction of 2'-BrSP were examined under various reaction conditions. The results are summarized in Table 3.

Table 3 Yields of [^{125}I]2'-ISP under various reactive conditions.

No.	2'-BrSP(μmol)	Na^{125}I(μmol)	$CuSO_4$(μmol)	1-NS(μmol)	H_2SO_4(μmol)	Yield(%)
1	1.1	1.1	---	---	2.2	0.0
2	1.1	1.1	1.1	---	---	6.3
3	1.1	1.1	1.1	---	2.2	7.4
4	1.1	1.1	1.1	2.2	---	26.2
5	1.1	1.1	1.1	2.2	---	25.9
6	1.1	1.1	1.1	5.5	---	42.0
7	1.1	1.1	1.1	6.6	---	35.2

The reaction mixture was heated at 90-95°C in 100 μl of aqueous 50% DMF solution for 1 hr.

The yields are markedly influenced by the amount of 1-naphthalenesulfonic acid (1-NS) added and Copper(II) sulfate added and both seem likely to work as a catalysts. On the basis of these data, entry No. 6 was chosen for hot run. Thus, carrier-free sodium [^{125}I]iodide was allowed to heat with an excess of 2'-BrSP in the presence of 1-NS and Copper(II) sulfate at 90-95°C for 1hr to give crude products, from which carrier-free [^{125}I]2'-ISP was isolated effectively by the preparative HPLC. The radiochemical yield was 42% and the radiochemical purity was more than 98% on radio HPLC and radio TLC. [^{125}I]2'-ISP was also prepared by the similar exchange reaction but no detailed results were mentioned in the abstract[12].

Carrier-free [^{125}I]2'-ITP and [^{125}I]2'-IHP were also prepared from the corresponding bromides by applying the similar method in the yields of 37% and 30%, respectively.

3. Radioiodination through the diazonium intermediate

As an alternative method for carrier-free preparation of [^{125}I]2'-ISP, methods *via* a diazonium salt were tried. The diazonium salt, which was prepared from 2'-ASP by the treatment with sodium nitrite and 2N-hydrochloric acid, was coupled with radioactive iodine *in situ*. This approach led to carrier-free [^{125}I]2'-ISP but the yields never better than 20% in spite of various trials because of contamination with by-products, which was very difficult to separate from [^{125}I]2'-ISP. From these results, [^{123}I]-labelling of 2'-ISP has, therefore, been achieved by modifying the iodine-iodine and the bromine-iodine exchange method for SPECT studies [8].

EXPERIMENTAL

Melting points were determined on a Yanagimoto apparatus (Yanagimoto Co., Ltd., Japan) and are uncorrected. ^{1}H-NMR and ^{13}C-NMR were recorded on a Hitachi model R-90H spectrometer at 90 MHz (Hitachi, Japan) or on a JEOL model FX-100 spectrometer at 100 MHz (JEOL, Japan). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Mass spectra were performed on a Hitachi model M-80b spectrometer (Hitachi, Japan).

Gaschromatography was conducted on a Shimazdu GC-9A gaschromatograph equipped with a FID detector (Shimazdu, Japan). Glass column used were as follows: 10% DC-550 on Chromosorb (1.5 m x 3 mm I.D.) for the analyses of cyclopropyl-2,4-difluorophenyl ketone (**2**) and 4-chloro-1,1-ethylenedioxy-1-(2', 4'-difluorophenyl)butane (**4**). Operating conditions: column temperature 220°C, carrier gas He (26 ml/min), detector FID (H_2 50 ml/min). Retention times: cyclopropyl-2,4-difluoropheny ketone (**2**) 5.60 min, 4-chloro-1,1-ethylenedioxy-1-(2',4'-difluorophenyl)butane (**4**) 7.32 min.

High performance liquid chromatography (HPLC) was performed on a Hitachi model 635-50 liquid chromatograph equipped with a Hitachi model 635 LC fixed UV-detector (254 nm) (Hitachi, Japan) and an Aloka model 550 radioanalyzer (Aloka, Japan).

A column packed with 10 μm Lichrosorb RP-18 (0.30 m x 4 mm I.D.) was used for the analyses of 2'-ISP (**7a**), 2'-ITP (**7b**) and 2'-IHP (**7c**). The operating condition: mobile phase water/methanol/acetonitrile/triethylamine = 164/336/68/0.2 (v/v/v/v)[a] or 410/810/170/0.5 (v/v/v/v)[b],flow rate 0.7 ml/min, the retention time **7a** 14.0 min[a], **7b** 13.9 min[b] and **7c** 12.7 min[b]. A column packed with 10 μm Develosil ODS-10 (0.25 m x 10 mm I.D.) was used for the purification

of [^{125}I]2'-ISP. The operating condition: mobile phase water/methanol/acetonitrile/triethylamine = 164/336/68/0.2 (v/v/v/v), flow rate 3 ml/min, the retention times [^{125}I]2'-ISP 23.6 min, 2'-BrSP 18.9 min (resolution between [^{125}I]2'-ISP and 2'-BrSP: 1.5).

Cyclopropyl-2,4-difluorophenyl ketone (2).--To a solution of *m*-difluorobenzene (1.16 g, 10.2 mmol) were added cyclopropylcarbonyl chloride (0.533 g, 10.2 mmol) and $AlCl_3$ (1.36 g, 10.2 mmol), and the mixture stirred at 0-5°C for 40 hr. The mixture was poured into ice/water mixture and extracted with ether. The extract was washed with 5% aqueous Na_2CO_3 solution, water and brine, and dried over sodium sulfate. Evaporation under reduced pressure gave cyclopropyl-2,4-difluorophenyl ketone **2** (0.760 g, 81%). This was used in the synthesis of **3** without any purification:the chemical purity 90% on GC;^{1}H-NMR ($CDCl_3$) δ 0.90-1.50 (m,4H), 2.40-2.80 (m,1H), 6.66-7.20 (m,2H), 7.60-8.01 (m,1H); M/Z 184 (M^+), 143, 115, 69, 41; IR (film) 1673, 1610 cm^{-1}.

4-Chloro-2',4'-difluorophenyl ketone (3).--To methanol saturated with HCl gas (2.5 mL) were added a solution of cyclopropyl-2',4'-difluorophenyl ketone **2** (0.754 g, 4.10 mmol) in methanol (2.5 mL). The reaction mixture was stirred for 3 hr at room temperature and diluted with benzene. The organic solution was washed with water, 5% aqueous Na_2CO_3 solution and brine, and dried over sodium sulfate. Evaporation under reduced pressure gave 4-chloro-2',4'-difluorophenyl ketone **3** (0.886 g, 98%): ^{1}H-NMR ($CDCl_3$) δ 2.20 (m,2H), 3.16 (m,2H), 3.68 (t, J=6Hz, 2H), 6.65-7.30 (m,2H), 7.70-8.20 (m,1H);IR (liquid film) 1685, 1610 cm^{-1}.

4-Chloro-1,1-ethylenedioxy-1-(2',4'-difluorophenyl)butane (4).--To a solution of 4-chloro-2',4'-difluorophenyl ketone **3** (0.838 g, 3.80 mmol) in benzene (20 mL) were added ethyleneglycol (0.46 g) and *p*-toluene sulfonic acid (0.7 g). Being equipped with Cope apparatus (H tube), the reaction mixture was heated at reflux for 3 hr and then extracted with benzene. The benzene layer was washed with water, 5% aqueous Na_2CO_2 solution and brine, and dried over sodium sulfate. Evaporation under reduced pressure gave 4-chloro-1,1-ethylenedioxy-1-(2',4'-difluorophenyl)butane **4** (0.943 g, 93%). This was used in the following synthesis without any purification: the chemical purity 95% on GC.

8-[4-(2',4'-difluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decane-4-one (2'-FSP) (5a).-- 4-Chloro-1,1-ethylenedioxy-1-(2',4'-difluorophenyl)butane **4** (2.50 g, 9.53 mmol) and spiroamine (2.21 g, 9.53 mmol) were suspended in DMF (100 mL). To the

suspension were added K_2CO_3 (1.41 g, 9.53 mmol) and KI (0.8 g), and the mixture was stirred for 4 hr at 95°C. After cooling, the reaction mixture was poured into the ice/water mixture and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure. To the residue were added a mixture of methanol (50 mL), water (17 mL) and concentrated hydrochloric acid (8.7 mL), and the mixture was refluxed for 2 hr to hydrolyze.

After cooling to the room temperature, the reaction mixture was neutralized with aqueous NH_3 solution and extracted with $CHCl_3$. The organic layer was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (Kiesel gel 60, E.Merck) eluting with methanol/$CHCl_3$ (1/1 v/v). The main fractions were evaporated to gave **5a** (1.10 g, 27.9%): mp 211-216°C;^{1}H-NMR ($CDCl_3$) δ 1.44-3.10 (m,14H), 4.73 (s,2H), 6.42 br.s.,1H), 6.74-7.98 (m,8H); M/Z 413 (M^+); IR(nujol) 1700 cm^{-1}.

2'-Fluorotrifluperidol (2'-FTP) (5b).--By the method similar to that used for 2'-FSP, 2'-FTP was synthesized from **4** and corresponding amine in 75.0% yield:mp.238-239°C;IR(nujol) 1675, 1615, 1335, 1130 cm^{-1}

2'-Fluorohaloperidol (2'-FHP) (5c).--By the method similar to that used for 2'-FSP, 2'-FHP was synthesized from **4** and the corresponding amine in 74.0% yield:mp. 245-246°C;IR(nujol) 3460, 1670, 1613 cm^{-1}

8-[4-(2'-benzylamino-4'-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.-- 8-[4-(2',4'-difluorophenyl)-4,4-ethylenedioxybutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decane-4-one **5a** (600 mg, 1.45 mmol) was suspended in a mixture *n*-hexane (22 mL) and benzylamine (22 mL), and heated to reflux for 16 hr under nitrogen. After evaporation under reduced pressure, $CHCl_3$ was added to the residue, and the organic solution was washed with 5% hydrochloric acid, 5% aqueous Na_2CO_3 solution and brine, and dried over sodium sulfate. Evaporation of the solvent gave crystalline product, which was washed with acetone and dried *in vacuo* to give 8-[4-(2'-benzylamino-4'-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (500 mg, 69%): mp 219-221°C;^{1}H-NMR ($CDCl_3$) δ 1.63-3.07 (m,14H), 4.73 (s,2H),4.40 (d,J=5.6Hz,1H), 6.86- 7.46 (m,13H);IR (nujol) 3310, 1700 cm^{-1}.

2'-Aminospiperone (2'-ASP) (6a).-- A solution of 8-[4-(2'-benzylamino-4'-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-tri-azaspiro[4.5]decan-4-one (1.10 g, 2.19 mmol) in a mixture of

methanol (10 mL) and acetic acid (10 mL) was hydrogenated with 10% Pd-C (900 mg) under atmospheric pressure overnight.

The catalyst was removed by filtration through Celite. The combined filtrates and washings were neutralized with aqueous NH_3 solution and then extracted with $CHCl_3$. The organic layer was washed with water and dried over magnesium sulfate. After evaporation under reduced pressure, the residue was purified by a silica gel column chromatography (solvent system: methanol/$CHCl_3$ = 5/95 - 30/70, v/v) to give pure product (462 mg, 60.5%): mp 174-179°C;^{1}H-NMR (DMSO-d_6) δ 1.52-3.21 (m,14H), 4.57 (s,2H),6.20-7.92 (m,8H); HR-MS observed for (M^+) 410.2080, calcd. for (M^+) 410.2044; IR(nujol) 3480, 3350,1700 cm^{-1}.

2'-Aminotrifluperidol (2'-ATP) (6b). -- By the method similar to that used for 2'-ASP, 2'-ATP was synthesized from **5b** (427 mg, 1.0 mmol) in 56.7% yield (240 mg): mp. 205-206°C, M/Z 424 (M^+) 424; IR (nujol) 1625, 1655, 3440, 3330 cm^{-1}.

2'-Aminohaloperidol (2'-AHP) (6c).-- By the method similar to that used for 2'-ASP, 2'-AHP was synthesized from **5c** (393 mg, 1.0 mmol) in 58.3% yield (227 mg): mp. 236-237°C, ^{13}C-NMR (DMSO-d_6) δ 18.4 , 30.9, 34.9, 48.3, 55.6, 68.1, 101.3, 101.7, 102.3, 102.6, 113.9, 126.7, 128.1, 131.5, 134.5, 134.7, 147.1, 153.5, 153.7, 163.8, 167.5, 199.4 ; M/Z 390 (M^+); IR (nujol) 1645 cm^{-1}.

2'-Iodospiperone (2'-ISP) (7a). -- To an ice-cold suspension of 2'-ASP (205 mg, 0.50 mmol) in a mixture of 2N HCl (0.8 mL), water (0.25 mL) and acetonitrile (2.0 mL) in an ice bath, was added dropwise a solution of $NaNO_2$ (44 mg) in water (0.4 mL) and the reaction mixture was stirred for 30 min in an ice bath. The solution of the formed diazonium salts was added dropwise to a solution of KI (400 mg, 0.25 mmol) in water (0.42 mL) at 5°C and the reaction mixture was stirred for 2 hr at the same temperature. The mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with 5% aqueous $NaHCO_3$ solution and water, and dried over sodium sulfate.

Evaporation of the solvents gave yellow oil, which was purified by the silica gel column chromatography (solvent system:methanol/$CHCl_3$, 5/95) to give **7c** (94 mg, 36.2%): the chemical purity over 98% on HPLC;mp 171-172°C; ^{1}H-NMR ($CDCl_3$) δ 1.40-3.18 (m,14H), 4.72 (s,2H), 6.08 (br.s.,1H), 6.83-7.70 (m,8H); M/Z 521 (M^+); IR (nujol) 1710 cm^{-1}.

Anal. Calcd. for $C_{23}H_{25}FIN_3O_2$:C 52.99; H 4.83; N 8.06%, Found:C 52.87; H 4.81; N 8.01%

2'-Iodotrifluperidol (2'-ITP) (7b).--By the method similar to that used for 2'-ISP, 2'-ITP was synthesized from the hydrochloric acid salt of **6b** (1.5 g, 3.26 mmol) in the yield of 9.5% (166

mg):the chemical purity over 98% on HPLC; ^{1}H-NMR ($CDCl_3$) δ 1.50-3.00 (m,15H), 7.00-7.90 (m,7H); M/Z, 535(M^+); IR (nujol) 1690 cm^{-1}.

Anal. Calcd. for $C_{22}H_{22}F_4INO_2$:C 49.36; H 4.14; N 2.62%, Found:C 49.24; H 4.10; N 2.66%.

2'-Iodohaloperidol (2'-IHP) (**7c**).--By the method similar to that used for 2'-ISP, 2'-IHP was synthesized from the hydrochloric acid salt of **6c** (1.5 g, 3.52 mmol) in the yield of 10.7% (190 mg):the chemical purity over 99% on HPLC; ^{1}H-NMR ($CDCl_3$) δ 1.50-3.00 (m,15H), 6.90-7.80 (m,7H); M/Z 503 (M^+); IR (nujol) 1690 cm^{-1}.

Anal. Calcd. for $C_{21}H_{22}ClFINO_2$:C 50.27; H 4.42; N 2.79%, Found:C 50.34; H 4.37; N 2.82%

2'-Bromospiperone (2'-BrSP) (**8a**). -- To a mixture of **6a** (3 g,7.32 mmol), 1-naphthalene sulfonic acid (9 g), water (22 mL) and acetonirile (22 mL) was added dropwise a solution of $NaNO_2$ (0.61 g) in water (5.4 mL) within 5 min at 5°C, and the reaction mixture was stirred for 50 min at 5°C. After adding an aqueous solution of sulphamine (0.1 g), the formed precipitates were filtered and washed with ice-cold water (20 mL). The collected precipitates were dissolved in a mixture of acetonitrile (35 mL) and 47% HBr (27 mL) with stirring at 0°C, and stirred. To the mixture was added dropwise a solution of CuBr (1g) in 47% HBr (7 mL) and the reaction mixture was stirred for 1.5 hr at 0°C. The reaction mixture was poured into a mixture of NaOH (14 g), water (60 mL), ice (100 g) and $CHCl_3$ (150 mL). The mixture was stirred for 1 hr at the room temperature and filtered through Celite. The filtrate was extracted with $CHCl_3$ (50 mL) and the extract was washed with water, dried over magnesium sulfate and evapolated to give the residue. Purification by the silica gel column chromatography eluting with $CHCl_3$ and methanol (40/1, v/v) afforded 2'-BrSP (1.90 g, 55%):the chemical purity over 98% on HPLC; mp 167-168°C; ^{1}H-NMR($CDCl_3$) δ 1.40-3.18 (m,14H), 4.72 (s,2H), 6.08 (br.s.,1H), 6.83- 7.70 (m,8H) ; M/Z, 473 (M^+) ; IR (nujol) 1710 cm^{-1}.

Anal. Calcd. for $C_{23}H_{25}BrFN_3O_2$:C 58.24; H 5.31; N 8.86%, Found:C 58.33; H 5.27; N 8.91%.

2'-Bromotrifluperidol (2'-BrTP) (**8b**).-- By the method similar to that used for 2'-BrSP, 2'-BrTP was synthesized from **6b** (424mg, 1.0 mmol) in the yield of 51% (250 mg).: ^{1}H-NMR($CDCl_3$) δ 1.60-3.10 (m,15H), 6.90-7.80 (m,7H); M/Z, 489 (M^+)

Anal. Calcd. for $C_{22}H_{22}F_4BrNO_2$:C 54.11; H 4.54; N 2.87%, Found:C 54.21; H 4.57; N 2.90%.

2'-Bromohaloperidol (2'-BrHP) (**8c**).-- By the method similar to that used for 2'-BrSP, 2'-BrHP was synthesized from **6c** (390 mg, 1.0 mmol) in the yield of 44.9% (205 mg).: mp. 93.5-95.5°C, ^{1}H-NMR ($CDCl_3$) δ 1.60-3.10 (m,15H), 6.90-7.60 (m,7H); M/Z, 457 (M^+), 455, 453, 224, 226 (base).;IR (nujol) 1690 cm^{-1}.

Anal. Calcd. for $C_{21}H_{22}ClFBrNO_2$:C 55.46; H 4.88; N 3.08%, Found:C 55.31; H 4.84; N 3.12%.

[^{125}I]2'-ISP (iodine-iodine exchange reaction). --2'-ISP (**7a**) (5 μg) was heated with Na^{125}I (1.85 MBq) in DMF (20 μl) at 100°C for 4 hr. The reaction mixture was extracted with $CHCl_3$. The extract was washed twice with water and purified by HPLC. Evaporation of solvents gave [^{125}I]2'-ISP (0.78 MBq, 42%): the radiochemical purity over 98%.; specific activity 1.10TBq/mmol.

[^{125}I]2'-ITP (iodine-iodine exchange reaction).--By the method similar to that used for [^{125}I]2'-ISP (iodine-iodine exchnge reaction), [^{125}I]2'-ITP was synthesized from 2'-ITP (**7b**) in the yield of 43% (0.79 MBq): radiochemical purity over 98% on HPLC; specific activity 1.10 TBq/mmol.

[^{125}I]2'-IHP (iodine-iodine exchange reaction).--By the method similar to that used for [^{125}I]2'-ISP (iodine-iodine exchnge reaction), [^{125}I]2'-IHP was synthesized from 2'-ITP (**7c**) in the yield of 32% (0.59 MBq): radiochemical purity over 98% on HPLC; specific activity 1.10 TBq/mmol.

[^{125}I]2'-ISP (bromine-iodine exchane reaction).-- 2'-BrSP (431 μg) was allowed to heat with Na[^{125}I]iodide (74 MBq) in aqueous 50% DMF solution at 90-95°C for 1 hr in the presence of 1-NS (1 mg) and $CuSO_4$ (145 μg) to give a crude product, which was purified by HPLC to afford [^{125}I]2'-ISP (31 MBq, radiochemical purity: 98%, radiochemical yield: 42%, specific activity 81.4 TBq/mmol).

[^{125}I]2'-ITP (bromine-iodine exchange reaction). --By the method similar to that used for [^{125}I]2'-ISP (bromine-iodine exchange reaction), [^{125}I]2'-ITP was synthesized from 2'-BrTP (**8b**) in the yield of 37% (13.7MBq).:radiochemical purity over 98% on HPLC; specific activity 81.4 TBq/mmol.

[^{125}I]2'-IHP (bromine-iodine exchange reaction). --By the method similar to that used for [^{125}I]2'-ISP (bromine-iodine exchange reaction), [^{125}I]2'-IHP was synthesized from 2'-BrHP (**8c**) in the yield of 30% (11.1 MBq).:radiochemical purity over 98% on HPLC; specific activity 81.4 TBq/mmol.

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