Rapid and Efficient Synthesis of High-Purity Fluorine-18 Labeled Haloperidol and Spiperone via the Nitro Precursor in Combination with a New HPLC Separation Method

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We have completed a convenient synthesis of fluorine-18 labeled butyrophenone neuroleptics from their nitro precursors. Thus, we have developed an efficient single-column HPLC system using a C_{18}-bonded vinyl alcohol copolymer gel (octadecyl polymer, ODP) column and strongly alkaline solvent systems for purifying of the ^{18}F-labeled butyrophenone neuroleptics obtained by a single-step ^{18}F-for-nitro exchange reaction. The method has been applied to the synthesis of two typical butyrophenone neuroleptics ([^{18}F]haloperidol and [^{18}F]spiperone) with high purity in high yield. With information concerning the optimized conditions for the ^{18}F-for-nitro exchange reaction, the synthetic method would be useful for synthesizing various ^{18}F-labeled compounds.

Positron emitters are attractive as research tools in chemistry, biochemistry, and nuclear medicine. Fluorine-18 has the longest half-life (110 min) among unstable isotopes of fluorine (^{17}F, 1 min; ^{20}F, 12 s; ^{21}F, 4 s; ^{23}F, 4 s) and positron emitters (carbon-11, 20 min; nitrogen-13, 10 min; oxygen-15, 2 min) obtainable by a compact cyclotron, which allows us to handle it by chemical means.

Its low β^+-ray energy (maximum 0.61 MeV) and short range (maximum 2.1 mm) in living tissues together with the high specific activity attainable in the case of [^{18}F]fluoride generated by a nuclear reaction ^{18}O(p, n) ^{18}F also make it preferred for use in positron-emission tomography (PET) measurements.[1] However, the reactions applicable to ^{18}F-labeling with $^{18}F^-$ are limited, because the amount of available $^{18}F^-$ as the starting material is ultraminute (<1 nmol), and its chemical reactivity is low. Moreover, an automated synthesis apparatus must be used to carry out the synthetic processes in order to avoid radiation exposure. In spite of these difficulties, ^{18}F-labeled compounds are expected to be potentially effective tools to investigate new a reap of life science; in synthesizing those compounds is eagerly anticipated.[2,3]

It is well known that fluorinated compounds often show biological action similar or preferable to the corresponding nonfluorinated molecules, fluorinated butyrophenone neuroleptics being famous as successful examples.

A series of fluorine-containing butyrophenone derivatives is a potent ligand of the brain dopamine D_2 receptor; also the corresponding ^{18}F-labeled compounds are expected to be preferentially useful for evaluating the brain function.[4] Therefore, various synthetic methods for those ^{18}F-labeled compounds have been extensively investigated.

In 1975 Kook et al. synthesized [^{18}F]haloperidol by a thermal decomposition of the corresponding diazonium tetrafluoroborate, which had been described by Clark et al. in 1973.[5] However, the radiochemical yield was low (1%). In 1980s, Kilbourn et al. and Attina et al. found that a nitro group behaves as an effective leaving group in the nucleophilic replacement with [^{18}F]fluoride ion.[6,7] Also, Shiue et al. synthesized several butyrophenone derivatives starting from nitro- or (trimethylammonio)benzaldehyde. They finally raised the radiochemical yield up to 10—15% by the nitro precursor method.[8] However, we failed in following the method, because it had four or five steps of reaction and required skilled hands for constructing and operating the automated apparatus. A more convenient synthetic method is desired. Also, since the most effective leaving group would be the nitro group, a goal would be to combine a single-step fluoro-for-nitro exchange reaction and a single-step purification.[9]

However, it was not so easy to synthesize a ^{18}F-labeled butyrophenone neuroleptics in a single-step from its nitro precursor.[10] In the 1990s, Gysemann et al.[11] studied the single-step synthesis of [^{18}F]spiperone, and concluded that it is very difficult, due to an enolization of the starting alkyl phenyl ketones. Katsifis et al.[12] studied the reaction conditions for the single-step synthesis of [^{18}F]butyrophenone neuroleptics from the NO_2 or Cl precursor in detail, and proved that the ^{18}F-labeled compound was certainly produced. However, they reported that the preparative HPLC employed was not suitable as a purification method of a single-step reaction product, even in the case of a chloro precursor, where the purification was easier than in the case of a nitro precursor.[13,14] The fluoro group has a chemical constants akin to those of the nitro group (Table 1).[13] In the case of a molecule as large as butyrophenone neuroleptics, the difference in the chemical property between the fluoro and nitro compound is small

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Table 1.

Functional group (R)	Enspace (E_s)	Hydrophorbicity (π)
H	0.00	0.00
F	−0.46	0.14
Cl	−0.97	0.71
NO_2	−1.01	−0.28

Substituent constants for aromatic compounds.[13]

compared with that in smaller molecules, e.g., fluorobenzonitrile and nitrobenzonitrile. Furthermore, the quantity of a ^{18}F-labeled compound is minute (1 pmol—1 nmol) compared with that of the nitro precursor (1 μmol—100 μmol) present; therefore, when a ^{18}F-labeled compound was eluted after the nitro precursor on preparative HPLC, it was difficult to avoid contamination of the former by the latter due to the tailing phenomenon.

Thus, the single-step synthesis of butyrophenone neuroleptics was not completed before publication of our previous communications.[15]

Since a nitro precursor often has biological activity similar to that of the fluoro compound, it is desired that the ^{18}F-labeled compound should be eluted ahead of the precursor. Taking into consideration the importance to develop a novel HPLC system for separating a single-step synthesis product, we carried out search for the HPLC conditions which rather retain the nitro compound relative to the fluoro compound. We found that a HPLC system comprising an ODP column and an alkaline eluent gives a clear separation of the fluorinated product from the nitro precursor, and completed a convenient rapid synthesis of fluorine-18 labeled butyrophenone neuroleptics from their nitro precursors. This paper describes single-step syntheses of no-carrier-added [^{18}F]haloperidol and [^{18}F]spiperone as representatives of the labeled butyrophenone neuroleptics.

Results and Discussion

1. Syntheses of Haloperidol and Spiperone with [^{18}F]-Fluoride. Syntheses of Nitro Precursors: The synthetic routes to the nitro precursors are summarized in Fig. 1.

A Friedel–Crafts reaction of *N*-acetylaniline with 4-chlorobutyryl chloride gave 4′-acetylamino-4-chlorobutyrophenone (**1**). This reaction required especially the use of non-ground aluminum chloride. Deacylation of **1** gave 4-aminophenyl cyclopropyl ketone (**2**) by cyclization of the side chain (the chlorobutyryl group). The amino group of **2** was converted into a nitro group with sodium nitrite, giving cyclopropyl 4-nitrophenyl ketone (**3**).[8] Compound **3** was then treated with conc. hydrochloric acid to give 4-chloro-4′-nitrobutyrophenone (**4**), being accompanied by an the opening of the cyclopropane ring.

The coupling of **4** with the amine component, 4-(4-chlorophenyl)-4-piperidinol (**5**) or 1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one (**6**), was performed using potassium carbonate and potassium iodide as a catalyst to give 4-(4-chlorophenyl)-1-[4-(4-nitrophenyl)-4-oxobutyl]-4-piperidinol (ni-

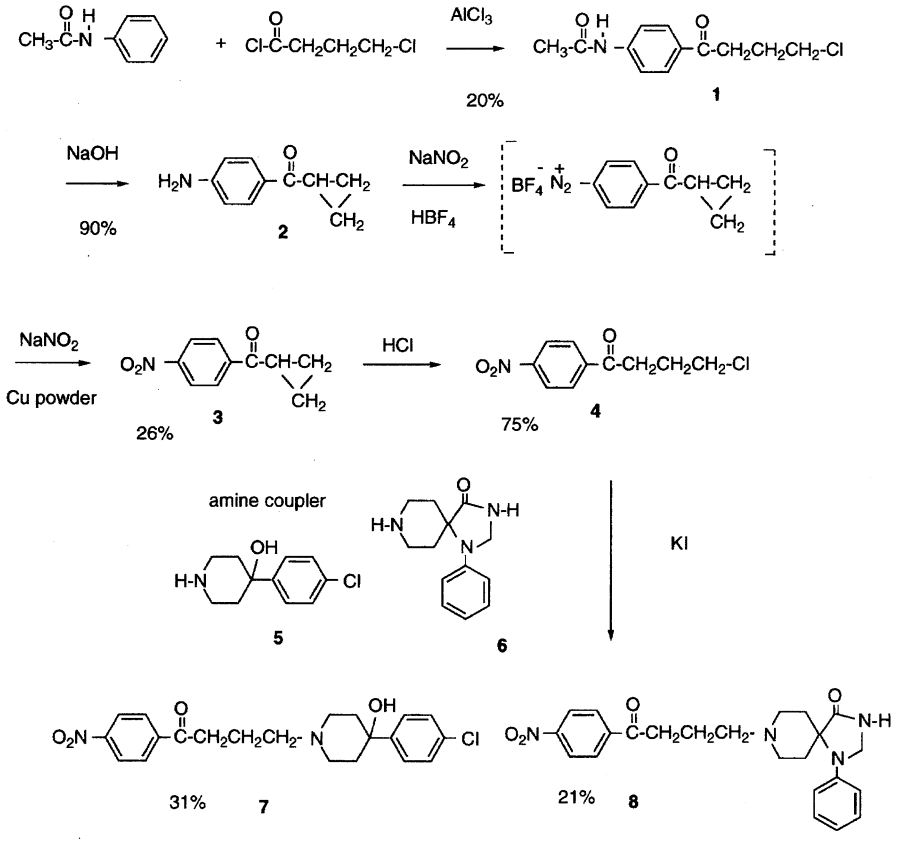

Fig. 1. Synthesis of nitro precursors.

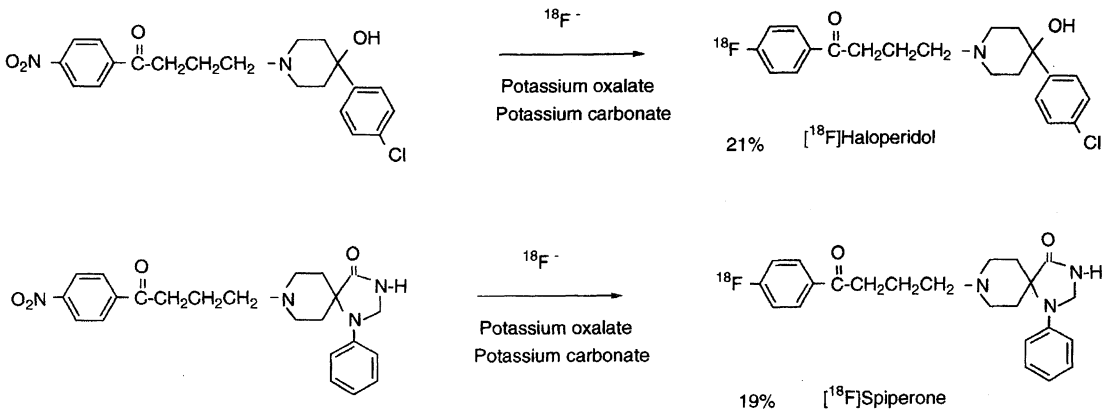

Fig. 2. Single-step syntheses of [^{18}F]haloperidol and [^{18}F]spiperone using nitro precursors.

trohaloperidol, **7**)[16] in 31% yield or 8-[4-(4-nitrophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (nitrospiperone, **8**) in 21% yield.[8]

Syntheses of haloperidol and Spiperone with [^{19}F]Fluoride: First, simulation experiments were carried out with dilute aqueous hydrofluoric acid (HF) instead of a H[^{18}F]F solution. A dilute aqueous HF solution, an aqueous solution (20 nmol, 20 μl) of potassium carbonate and potassium oxalate, kryptofix 222, and acetonitrile were mixed and evaporated under low pressure at 85 °C in a Pyrex® flask. After nitrohaloperidol (8 mg, 20 μmol) dissolved in DMSO was added to the residue, the mixture was stirred for 20 min at 160 °C in a low-humidity grove box in which the air was filled with argon. Haloperidol in the reaction mixture was detected by analytical HPLC. Thirteen nanomole (60%) of haloperidol was obtained. Similarly, 9 nmol (45%) of spiperone was obtained from 20 nmol HF.

^{18}F Radiochemistry:Production of [^{18}F]Fluoride: [^{18}F]Fluoride was produced by a nuclear reaction ^{18}O(p, n) ^{18}F with a cyclotron (Cypris HM-18). In optimization experiments, 370-740 MBq of [^{18}F]fluoride was used to avoid any unnecessary exposure to radiation, although over 30 GBq of [^{18}F]fluoride could be produced by irradiation of 120 min at 15 μA. The highest specific activity of the [^{18}F]fluoride obtainable was estimated to be over 1 TBq/μmol.

Recovery Volume from Target Water: It was interesting to see whether the radiochemical yield depends on the volume of the recovered irradiated water containing ^{18}F-fluoride, because it was suspected that, if the volume of the irradiated water recovered was too much, the anhydrous conditions needed for the preparation of [^{18}F]fluoride[12] might not be attained. In the reported single-step syntheses[12] of [^{18}F]butyrophenone neuroleptics, no more than 10—100 μl of the irradiated water was recovered and used. The recovery volume of irradiated water could be controlled by a valve on its delivery line from the target to the reactor. When haloperidol synthesis from the nitro precursor was repeated using different volumes (0.1, 0.3, 0.5, and 1 ml) of the irradiated water, the radiochemical yield did not change (<1 %) at a reaction temperature of 140 °C. This result meant that it is necessary to maximize the recovery volume of the irradiated water (2.4 g) to get as high a radiochemical yield as possible.

Preparation of the Fluorinating Reagent: The starting [^{18}F]fluoride was obtained as an aqueous solution, and dried up under fairly low pressure prior to use in [^{18}F]fluorination. When the [^{18}F]fluoride dried at 105 °C under a pressure of 3

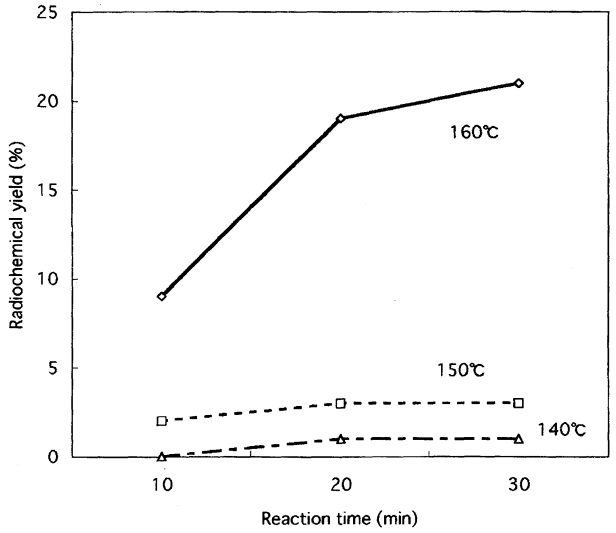

Fig. 3. Radiochemical yield (EOB) of [^{18}F]haloperidol.

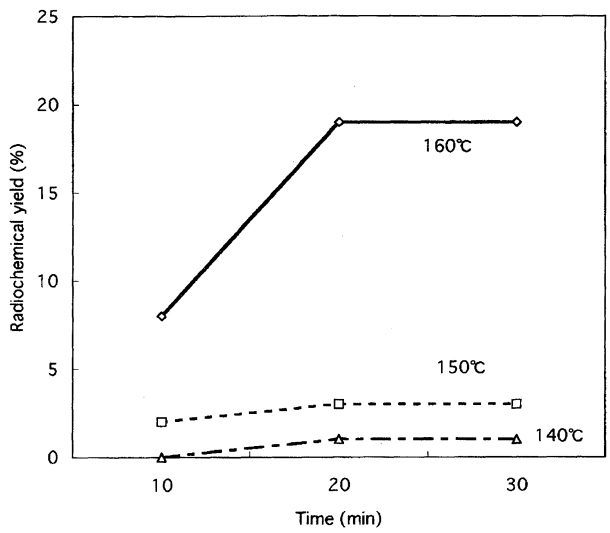

Fig. 4. Radiochemical yield (EOB) of [^{18}F]spiperone.

kPa was used, no [^{18}F] haloperidol or [^{18}F]spiperone was obtained. 4′-[^{18}F]Fluoroacetophenone was obtained, however, from 4′-nitroacetophenone in a radiochemical yield of 40%. On the other hand, when the [^{18}F]fluoride was dried at 2 kPa for 12 min, [^{18}F]haloperidol was obtained. Thus, sufficient drying of the fluorination reagent would be indispensable in the fluorination of a complex substrate, which was not very stable at the temperature required for the reaction (Fig. 2).

Reaction Temperature: Indeed, the fluorination reaction was found to be temperature dependent. In the haloperidol synthesis from its nitro precursor, the radiochemical yield was 21% at a reaction temperature of 160 °C, but was disappointingly low at 140—150 °C. At 170 °C, decomposition of the precursor occurred. This sharp temperature dependence may explain the discrepancy among the reported results. For example, Katsifis et al.[12] reported that they obtained the highest radiochemical yield at 140—150 °C in the synthesis of [^{18}F]haloperidol from its nitro precursor.

Reaction Time: The reaction time was also an important factor. The highest radiochemical yield was obtained when the reaction mixture was heated at 160 °C for 20—30 min. A shorter reaction time of 5—10 min gave the labeled product in lower yields. This was, on one hand, due to the fact that it took ca. 15 min until the temperature in the reactor reached to 160 °C from the low heat conductivity of the glassy carbon reactor.[17]

^{18}F-Labeling of Spiperone and Haloperidol: Nitrospiperone is less soluble in organic solvents, such as DMF, THF, and 1,4-dioxane, than nitrohaloperidol. Only DMSO could be used for labeling spiperone. The radiochemical yield of [^{18}F]spiperone was slightly low compared to that of [^{18}F]haloperidol (Fig. 3). This may have been due to the low solubility of the precursor of the presence of an amide NH group in its triazaspiro[4.5]decan-4-one, moiety which may trap the [^{18}F]fluoride anion through hydrogen-bond formation. This time, contrary to the negative results which have been reported,[12] we succeeded in obtaining ^{18}F-labeled spiperone of excellent purity (radiochemical purity >99%, chemical purity >99%) in good yield (Fig. 4).

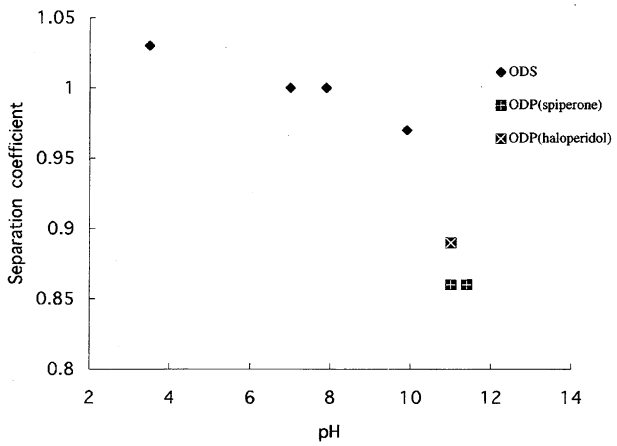

Fig. 5. Relation between of separation coefficient and the pH of the eluent. Column: Asahipak ODP-5, ϕ4.6 mm×150 mm+guard column ϕ4.6 mm×10 mm, flow rate 0.8 ml min^{-1}, UV 241 nm, Eluent: MeCN : 10 mM NaOH = 55 : 45 (v/v).

2. Separation of a Fluoro Compound from Its Nitro Precursor. An octadecyl polymer resin column (Asahipak ODP-50, Shoko Co., Ltd., Tokyo) with an alkaline mobile phase (10 mM NaOH/acetonitrile = 1—1.22) was used to

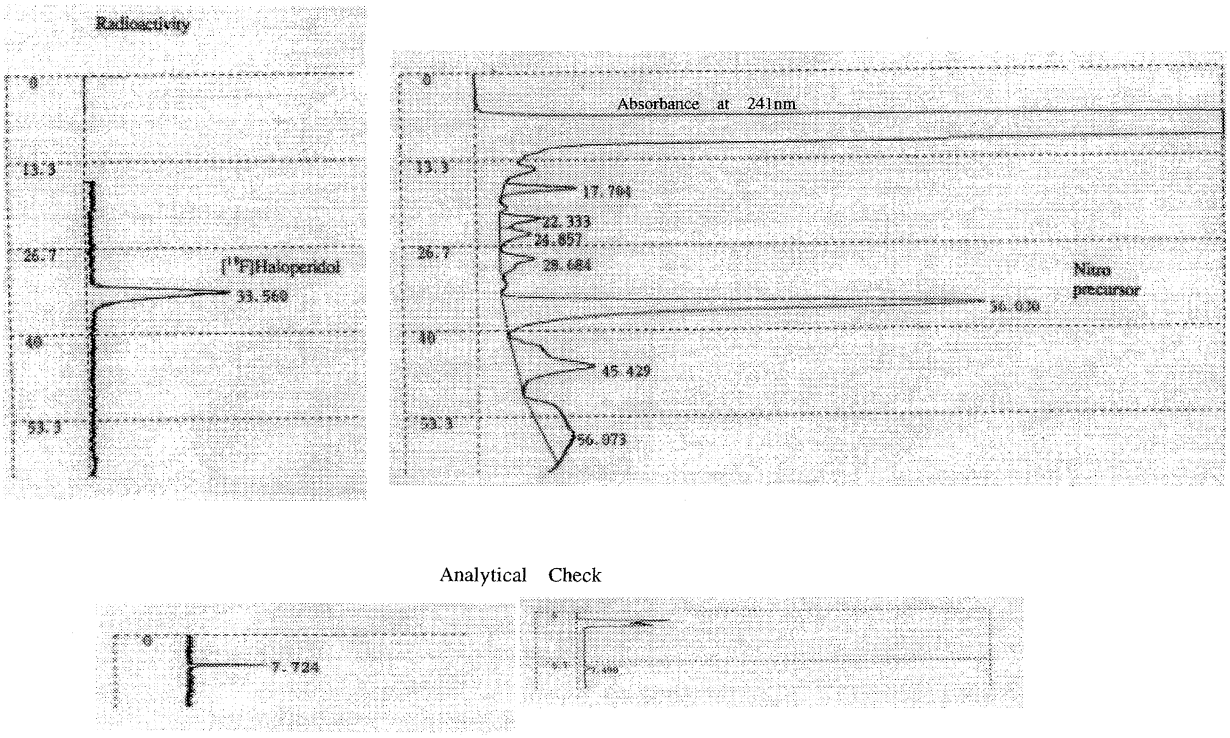

Fig. 6. High performance liquid chromatograms of [^{18}F]haloperidol from its nitro precursor.

separate a fluoro compound from its nitro precursor (nitrohaloperidol or nitrospiperone). The separation coefficient values [haloperidol {retention time (r.t.) = 16.72 min}/nitrohaloperidol (r.t. = 19.3 min), $\alpha = 0.86$; spiperone (r.t. = 22.26 min)/nitrospiperone (r.t. = 25 min); $\alpha = 0.89$] realized this time were superior to all those reported in HPLC using octadecyl silica gel. These values depended on the pH of the mobile phase, the best results having been obtained with pH > 11 (Fig. 5). With a neutral solvent, no better separation coefficient value was obtained than that with an alkaline solvent. One of the reasons for this might be that the interaction of the nitro group with the hydroxy groups of the resin increases when the nitro group exists in its aci-form (nitronic acid form), although, it may be suggested that, for a good separation, the piperidine moiety ($pK_b = 11.2$) sould be in its free-base form.

The separation coefficient (α) values with a preparative ODP column (Asahipak ODP-50) were <0.9. The values obtained with ODS (octadecyl silica gel) columns, which can not be used with a strongly basic mobile phase, were in the range of 0.92—1.2.

Analytical Check: Analytical HPLC was performed in order to check the radiochemical and chemical purities of the purified labeled compound, using both UV (241 nm) and a radio analyzer as detectors. No precursor was detected, and the radiochemical purity was over 99% (Fig. 6).

We believe that the present HPLC system is the most effective one ever used for separating fluoro-compounds from the corresponding nitro compounds.

3. Conclusion: A single-step synthesis of [^{18}F]haloperidol and [^{18}F]spiperone has been reported without referring to the purity data of the product.[12] We completed, as stated, syntheses of these compounds using a new separation method. Quite recently, a synthesis of *N*-methyl[^{18}F]-spiperone[18] was reported using an ODS separation column. It seems that α values of 0.92—0.93 were realized in the system. The results should be improved by using our separation method ($\alpha < 0.89$).

These successful examples strongly suggest the long-expected completion of the synthesis method of ^{18}F-labeled butyrophenone neuroleptics.

Experimental

Materials and Methods. An azimuthally-varying-field (AVF) cyclotron (Cypris HM-18, Sumitomo Heavy Industries, Ltd., Tokyo) was used to produce ^{18}F by the nuclear reaction ^{18}O(p, n) ^{18}F. [^{18}O]Water (isotopic enrichment: 10—99%) was purchased from Isotec Inc. (Ohio, USA) and Commissariat a L'Energie Atomique (Saint-Aubin Cedex, France). The target could produce 1—10 GBq of [^{18}F]fluoride in an irradiating time of 5—20 min (18 MeV proton beams) at a current of 5—15 μA. Anhydrous acetonitrile was purchased from Kokusan Chemical Works, Ltd. Anhydrous dimethyl sufoxide (DMSO), 4-chlorobutyryl chloride and tetrafluoroboric acid solution were purchased from Aldrich (Milwaukee, USA). DMSO was purified by distillation at 110 °C under reduced pressure, was used within a few months. 4-(4-Chlorophenyl)-4-piperidinol and 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one were purchased from Janssen Chimica (Geel, Belgium). Potassium carbonate, potassium oxalate and kryptofix 222 were purchased from Merck (Merck-Schuchardt, Munich, Germany). Aluminum chloride was purchased from Ishizu Seiyaku Ltd. (Osaka, Japan). *N*-Acetylaniline and sodium nitrite were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Spiperone was extracted from tablets made by Eisai Co., Ltd. (Tokyo, Japan). Haloperidol was purchased from Research Biochemicals International (RBI, Massachusetts, USA). The melting points were determined by a digital melting-point apparatus (IA 9100, Electrothermal Engineering LTD, Essex, England). ^{1}H NMR was measured by a Gemini 300 spectrometer (Varian). The chemical-shifts values were reported in parts per million (δ/ppm) relative to tetramethylsilane as an internal standard in ^{1}H NMR. The IR spectra and mass spectra were measured by an infrared spectrometer FT-300 (Horiba Ltd., Tokyo, Japan) and a mass spectrometer MS-100 (JOEL), respectively.

The radioactivity was measured using a positron monitor (TCS-R81; Aloka Co., Ltd., Tokyo) in preparative HPLC and with a RLC-700 radio analyzer (Aloka) in analytical HPLC.

4′-Acetylamino-4-chlorobutyrophenone (1): *N*-Acetylaniline (100 g, 0.74 mol) dissolved in carbon disulfide (400 ml) and the mixture aluminum chloride rods (400 g, 3 mol) was added to the solution. The mixture was cooled to 5 °C in an ice bath. After 4-chlorobutyryl chloride (300 g, 2.1 mmol) was added to it the mixture was stirred at room temperature for 30 min and 60 °C for 2 h. Then, the resulting solution was poured into ice water (1 L), and the precipitate formed was collected by filtration and recrystallized from 95% ethanol to give **1** (35 g, 20%) as colorless crystals, mp 167 °C, TLC: $R_f = 0.4$ (AcOEt : hexane = 1 : 1). ^{1}H NMR ($CDCl_3$) $\delta = 7.95$ (2H, d, $J = 7.8$ Hz, ArH), 7.61 (2H, d, $J = 7.2$ Hz, ArH), 3.67 (2H, t, $J = 5.7$ Hz, CH_2), 3.14 (2H, t, $J = 6.2$ Hz, CH_2), 2.11 (2H, m, CH_2).

4-Aminophenyl Cyclopropyl Ketone (2): Compound **1** (24 g, 105 mmol) was dissolved in ethanol (500 ml). To the solution 4 M NaOH (230 ml, 1 M = 1 mol dm^{-3}) was added; and the mixture was then heated under reflux for 2 h. After removing ethanol under reduced pressure, the residue was extracted with chloroform and the extract was washed with saturated brine, dried and concentrated to give **2** as pale-yellow crystals (13 g, 90%), mp 123 °C. TLC: $R_f = 0.3$ (AcOEt : hexane = 1 : 1). ^{1}H NMR ($CDCl_3$) $\delta = 7.79$ (2H, d, $J = 7.7$ Hz, ArH), 6.92 (2H, d, $J = 7.2$ Hz, ArH), 2.45 (1H, m, CH), 0.94 (4H, m, CH_2CH_2).

Cyclopropyl 4-Nitrophenyl Ketone (3): Compound **2** (17 g, 0.1 mol) was added in to a cold tetrafluoroboric acid solution (42%, 120 ml); the mixture was kept at 10 °C in an ice-bath. To this, a cold solution of $NaNO_2$ (7.2 g) in deionized water (20 ml) was added, and the mixture was stirred vigorously for 30 min. 4-(Cyclopropylcarbonyl)benzenediazonium tetrafluoroborate was separated as a participate, which was collected by filtration, and then washed with cold tetrafluoroboric acid (42%), ethanol and ether. The thus-obtained diazonium salts were suspended in water (100 ml); this suspension was slowly added to a mixture of $NaNO_2$ (8.4 g, 0.12 mmol) and copper powder (17.9 g) in water (100 ml), followed by stirring for 1 h. The solution became foamy. Ether (500 ml) was added to decompose the foams. The ether layer was separated, washed with saturated brine, dried with $MgSO_4$ and purified by silica-gel column chromatography with $CHCl_3$ to give **3**, as pale-yellow crystals (5 g, 26%), mp 102 °C. TLC: $R_f = 0.6$ (AcOEt : hexane = 1 : 1). EA: (Found: C, 62.64; H, 4.58; N, 7.32%. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33%).

4-Chloro-4′-nitrobutyrophenone (4): A solution of **3** (1 g, 5.23 mmol) in methanol (80 ml) and concd hydrochloric acid (20 ml) was heated to 120 °C for 30 min. The resulting mixture was

cooled and extracted with hexane. The separated organic layer was washed with water and dried up to give **4** (900 mg, 3.95 mmol, 75%). MS 228 (M^+); ^{1}H NMR (DMSO) δ = 8.31 (4H, d×d, J = 48, 8.1 Hz, ArH), 8.15 (2H, d, ArH), 3.70 (2H, t, J = 5.4 Hz, CH_2Cl), 3.24 (2H, t, J = 6.2 Hz, $COCH_2$), 2.25 (2H, m, CH_2).

4- (4- Chlorophenyl)- 1- [4- (4- nitrophenyl)- 4- oxobutyl]- 4- piperidinol (7) (*nitrohaloperidol*): A mixture of the **4** (113 mg, 0.5 mmol), 4-(4-chlorophenyl)-4-piperidinol **5** (211 mg, 1 mmol) and potassium iodide (0.05 g, 0.23 mmol) in toluene (50 ml) was heated at 100—110 °C under argon. After the reaction mixture was filtrated, the organic layer was washed with water, dried over $NaSO_4$ and purified by silica-gel column chromatography (charged with chloroform and eluted with a mixture of 10% methanol/chloroform). The yellow eluent was evaporated, and the residue was recrystallized from chloroform and hexane to give **7** as pale-yellow crystals (63 mg 31%), mp 153 °C. EA: (Found: C, 62.21; H, 5.47; N, 7.34%. Calcd for $C_{21}H_{23}N_2O_4$: C, 62.6; H, 5.75; N, 6.95%). IR (KBr) 3108, 1946, 2925, 2854, 1693, 1527, 1457 cm^{-1}; MS 402 (M^+). ^{1}H NMR ($CDCl_3$) δ = 8.21 (4H, d×d, J = 0.17, 47 Hz, ArH), 7.34 (4H, m, ArH), 1.68—3.11 (15H, m).

8-[4-(4-Nitrophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro-[4.5]decan-4-one (8) (*nitrospiperone*): A mixture of the ketone **4** (1 g, 4.3 mmol), 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one **6** (1.8 g, 7.7 mmol) and potassium iodide (0.1 g, 0.46 mmol) in toluene 80 ml and DMSO 10 ml was heated at 100—110 °C under argon. After the reaction mixture was filtrated, the organic layer was washed with water, dried over Na_2SO_4 and purified by silica-gel column chromatography (charged with chloroform, eluted with a mixture of 10% methanol/chloroform). The yellow eluent was evaporated and the residue was recrystallized from chloroform and methanol to give **8** as pale-yellow crystals (380 mg, 21%), mp 232 °C. (lit, 232—236 °C), MS 423 (MH^+). ^{1}H NMR (DMSO) δ = 8.27 (4H, m, d×d, J = 7.8, 41 Hz, ArH), 6.75—7.18 (5H, m, ArH), 4.57 (2H, s), 1.2—3.3 (15H).

Irradiation and Recovery of [^{18}F]Fluoride: [^{18}O]Water (2.0—2.4 g) was loaded to a target chamber (target volume 1.2 ml) made of titanium alloy. The chamber was then cooled with helium gas and water throughout the time of irradiation. The irradiated [^{18}O]water (10—99%) was directly transferred to a reactor and recovered in it.

To obtain as high a radiochemical yield of the labeled compound as possible, it was necessary to maximize the recovery volume of the irradiated water. We were able to recover much more irradiated water (2.4 g max, 50 GBq max) than that previously reported (100—1300 μl, <55.5 GBq).[13]

[^{18}F]Fluorination: The recovered aqueous solution containing ^{18}F-fluoride was dried up at a high temperature (105 °C) and under reduced pressure (2 kPa, 15 mmHg, 1 mmHg = 133.322 Pa); the time for dehydration was kept to within 15—25 min (under argon gas flow for 8—12 min and without gas flow below 2 kPa for 3—13 min).

After a dimethyl sulfoxide (0.5 ml) solution containing the nitro precursor was added to the residue, the mixture was heated to 150—170 °C. No carrier [^{19}F]fluoride ion was added.

4-(4-Chlorophenyl)-1-[4-(4-[^{18}F]fluorophenyl)-4-oxobutyl]-4-piperidinol ([^{18}F]haloperidol): 0.37—0.74 GBq [^{18}F]fluoride produced by the nuclear reaction (current 10—15 μA, 5—60 min) was poured into a glassy-carbon reactor containing 10 μl of a 1 mM potassium oxalate and 20 μl of a 10 μM potassium carbonate. Kryptofix 222 (15 mg) dissolved in anhydrous acetonitrile (1 ml) was then added to the solution. Volatiles were evaporated at 85 °C while introducing an argon-gas stream, and 1 ml anhydrous acetonitrile was added to the residue. The solution was dried at 85 °C under an argon-gas flow. Then, the argon-gas flow was stopped and the residue was completely dried below 2 kPa at 105 °C for 3 min. The reactor was cooled by liquid nitrogen to room temperature during 1.5 min and 500 μl of a DMSO solution containing **7** was injected into it. The mixture was heated to 160 °C for 30 min with stirring. The reaction solution was transferred to an injection vial, and then subjected to preparative HPLC [Column: Asahipak ODP-50 (Shoko Co., Ltd., Tokyo), ϕ21.5 mm×250 mm+guard column ϕ21.5 mm×100 mm, Eluent: MeCN : 10 mM NaOH=50 : 50 (v/v), flow rate 10—12 ml min^{-1}].

The objective radioactive fraction was collected and the organic solvent was evaporated to give an aqueous solution of the product.

The radiochemical yield was 21% [at the end of bombardment (EOB)]. The radiochemical purity and chemical purity were both over 99% (Fig. 6). The solvent front peak detected by UV absorption was excluded from a calculation of the chemical purity. No peak of haloperidol was detected on preparative HPLC, and only a very small (<1 nM) peak of it was observed on the analytical HPLC (1 M hydrochloric acid was used for the neutralization of HPLC eluent).

The total synthesis time (including evaporation, fluoriation and purification) was 90 min. The maximum specific activity of the obtained product was estimated to be over 259 GBq/μmol (at the end of synthesis, EOS), realized in its large-scale production (current 15 μA, 60 min, [^{18}O]water 50%).

8-[4-(4-[^{18}F]Fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one ([^{18}F]spiperone): The reaction procedure was similar to that of [^{18}F]haloperidol synthesis, except for that during the purification step the preparative HPLC was carried out with MeCN : 10 mM NaOH = 57.5 42.5 (v/v) as the eluent. The synthesis time was 90 min. The maximum radiochemical yield was 19% (EOB corrected).

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