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NOTE

Syntheses of ^{18}F-Labeled Reduced Haloperidol and ^{11}C-Labeled Reduced 3-N-Methylspiperone

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SUMMARY

^{18}F-Labeled reduced haloperidol and ^{11}C-labeled reduced 3-N-methylspiperone were synthesized in a convenient and quantitative one step reduction from ^{18}F-labeled haloperidol and ^{11}C-labeled N-methylspiperone, respectively. Both products were purified by semipreparative HPLC and were obtained at high specific activity and radiochemical purity.

Key Words: Reduced haloperidol, reduced methyl-spiperone, carbon-11, fluorine-18, positron emission tomography

INTRODUCTION

Since 1978 the butyrophenone neuroleptic haloperidol has been known to undergo metabolic reduction of its ketone to form the corresponding chiral secondary alcohol, reduced haloperidol (1). *In vitro* studies with rat and guinea pig liver microsomes have shown an interconversion of haloperidol and reduced haloperidol (2). This interconversion has also been observed in normal volunteers (3). Reduced haloperidol is known to cross the blood-brain barrier. Although reduced haloperidol has some uptake in the striatum, it is relatively ineffective as an antagonist of central dopamine receptors in the rat (4). A study of schizophrenics who did not respond to haloperidol therapy indicated high reduced haloperidol levels (5,6). Recently, a reduced metabolite of another butyrophenone, 3-N-methyl-spiperone, has been observed in guinea pigs (7).

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Positron emitting butyrophenone neuroleptic radiotracers for studying dopamine D-2 receptors would be expected to exhibit the same metabolic reduction as their stable counterparts. The radiosynthesis of the reduced form of the neuroleptic may help to understand the metabolic fate of the neuroleptic radiotracer and aid in mathematical modeling of receptor concentrations. This paper reports the facile reduction of ^{18}F-haloperidol to reduced ^{18}F-haloperidol and 3-N-[^{11}C-methyl]spiperone to reduced 3-N-[^{11}C-methyl]spiperone.

RESULTS

^{18}F-Haloperidol was synthesized according to the method of Shiue *et al* (8,9) with minor modifications that are described in the experimental section. Crude ^{18}F-haloperidol was reduced by excess $NaBH_4$ in methanol. Heating at 80° C for one minute resulted in quantitative conversion to reduced ^{18}F-haloperidol. Semipreparative HPLC using a silica stationary phase and a reverse mobile phase provided an suitable separation of ^{18}F-haloperidol (k' = 5.8) and reduced ^{18}F-haloperidol (k' = 7.1). A minor mass peak (k' = 6.4), possibly due to reduced nitrohaloperidol, lowered the apparent specific activity (10) to between 100 - 1500 mCi/μmole. The synthesis was completed in 88 minutes with an average yield of 10% (decay corrected from starting fluoride).

^{11}C-Labeled reduced 3-N-methylspiperone was synthesized by two slightly different methods. In method 1, 3-N-[^{11}C-methyl]spiperone (k' = 6.8) was purified by semipreparative reverse phase HPLC. The radiolabeled product was well separated from the unreacted spiperone (k' = 3.5) providing specific activities above 2000 mCi/μmole. The 3-N-[^{11}C-methyl]spiperone was dissolved in saline and $NaBH_4$ added. After heating at 80° C for two minutes, a quantitative conversion to reduced 3-N-[^{11}C-methyl]spiperone was obtained. The conversion to the reduced species was slower than observed with the reduction of ^{18}F-haloperidol; this is possibly due to the larger volume of solvent used in the radiocarbon synthesis. After dilution and filtration, the solution was determined to be chemically and radiochemically pure by analytical HPLC with specific activities still above 2000 mCi/μmole. The synthesis was completed in 20 minutes with a yield of 33% (decay corrected from $^{11}CH_3I$).

Method 2 involved the reduction of crude 3-N-[^{11}C-methyl]spiperone in its original DMF solution using excess $NaBH_4$ and methanol. After heating at 80° C for one minute, the reduction was complete. The same semipreparative HPLC conditions as used in method 1 rendered a poor separation of reduced 3-N-[^{11}C-methyl]spiperone (k' = 2.7) and another mass peak presumably reduced spiperone (k' = 1.8). The apparent specific activity for method 2 was an order of magnitude lower compared with the product specific activity from method 1. The synthesis was completed in 19 minutes with a yield of 11% (decay corrected from $^{11}CH_3I$).

EXPERIMENTAL

Spiperone and N-methylspiperone were synthesized according to the references cited and were analytically pure (11,12). Reduced haloperidol was obtained from Research Biochemicals Inc., Natick, MA. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. NMR and IR spectra were obtained on an IBM NR80 and a Perkin Elmer 399B instrument respectively. High performance liquid chromatographic analysis and purification were performed with two Waters 590EF HPLC pump, an in-line fixed wavelength (254 nm) uv detector, and a single two inch NaI crystal radioactive detector. HPLC chromatograms were recorded using two Hewlett-Packard 3390A integrators. HPLC semipreparative purifications were performed on either: column A - Alltech Econosil 10 μ C-18 column (1.0 x 25 cm) or Column B - Beckmann 10 μ silica column (1.0 x 25 cm). A dose calibrator (Capintec 12R) was used for all radioactivity measurements.

Reduced ^{18}F-Haloperidol. The first portion of the preparation is a modification of the reported synthesis of ^{18}F-haloperidol (8,9). The modifications include the use of K_2CO_3/Kryptofix instead of Cs_2CO_3 and changes in the solvents used in the alkylation step. No carrier added ^{18}F-fluoride, prepared by proton bombardment of ^{18}O-H_2O (95 - 99%) using a Scanditronix MC-16F biomedical cyclotron, was concentrated on a short column of anion exchange resin (Dowex 1-X8, 200-400 mesh, hydroxide form). ^{18}F-Fluoride was eluted from the column using K_2CO_3 (2.3 mg, 17 μmoles) dissolved in 300 μL water into a conical glass vial containing Kryptofix 2.2.2 (13 mg, 34 μmoles). The fluoride was dried by repeated

azeotropic distillation with CH_3CN at 120° C under argon gas flow.

After heating for an additional 3 minutes, cyclopropyl p-nitrophenyl ketone (2 mg, 10 μmoles) dissolved in 200 μL of dry freshly distilled DMSO was added and the vial was heated at 120° C for 10 minutes. After cooling to room temperature, 2 mL of concentrated HCl:methanol (1:1) was added to the vial. The vial was heated at 120° C for 3 minutes, then it was cooled and 3 mL of H_2O added. The resulting solution was applied to a C-18 SEP-PAK and the SEP-PAK was washed with 4 mL of H_2O and 0.5 mL of pentane.

The intermediate product was eluted from the SEP-PAK with an additional 5 mL of pentane through a K_2CO_3 column into a conical vial containing 4-(4-chlorophenyl)-4-hydroxypiperidine (3 mg, 14 μmoles) and KI (8 mg, 48 μmoles) dissolved in 200 μL of DMF. Volatile solvents were removed under an argon flow and the resulting DMF solution was heated at 120° C for 10 minutes. After cooling, 500 μL of methanol and 5 mL of H_2O were added. The mixture was passed through a C-18 SEP-PAK which was rinsed with 4 mL H_2O. The crude product was eluted from the SEP-PAK with 5 mL methylene chloride and passed through a K_2CO_3 column into a conical vial,and evaporated to dryness under a stream of argon.

Solid $NaBH_4$ (1 mg, 26 μmoles) and 200 μL of methanol were added. The vial was sealed and heated to 80° C for 2 minutes. HPLC buffer solution (400 μL) was added and the mixture was injected onto semi-preparative column B (70% CH_3CN / 30% 0.004 M $NH_4H_2PO_4$, flow rate of 11 mL/min). The reduced ^{18}F-haloperidol (retention time = 7.7 minutes, k' = 7.1) was collected, evaporated to dryness under reduced pressure, redissolved in 7 mL of sterile saline, and passed through a sterile 0.2 μ filter into a sterile evacuated vial. Sterile 8.4% sodium bicarbonate (3 mL) was added to the vial. The determination of chemical and radiochemical purity was performed using a Waters Novapak 4 μ C-18 column (0.39 x 15 cm) and mobile phase of 30% CH_3CN / 70% 0.1 M NH_4HCO_2 at flow rate of 2 mL/min. Under these conditions, reduced ^{18}F-reduced haloperidol and haloperidol have k's of 2.5 and 5.2, respectively.

Reduced 3-N-[^{11}C-methyl]spiperone. Method 1. The synthesis of this tracer involved the production of 3-N-[^{11}C-methyl]spiperone according to the published procedure (13). Briefly, $^{11}CH_3I$ produced from $^{11}CO_2$ was bubbled

through a DMF (200 μL) solution of spiperone (1 mg, 25 μmole). Tetrabutylammonium hydroxide (5 μL, 0.4 M in H_2O) was added to the vial and the vial was heated at 80° C for 1 minute. The intermediate product, 3-N-[^{11}C-methyl]spiperone (retention time = 7.0 minutes, k' = 6.8), was purified by semipreparative HPLC (column B, 50% CH_3CN / 50% 0.1 M NH_4HCO_2, flow rate of 11 mL/min) and reconstituted in 1 mL of sterile saline.

Solid $NaBH_4$ (2 mg, 52 μmole) was added and the flask was heated to 80° C for 2 minutes. The solution was diluted with 6 mL of sterile saline and passed through a sterile 0.2 μ filter into a sterile evacuated vial. Sterile 8.4% sodium bicarbonate (3 mL) was added to the vial. An Alltech Econosil 10 μ C-18 analytical (0.46 x 25 cm) column (50% CH_3CN/50% 0.1 M NH_4HCO_2) at a flow rate of 4 mL/min) was used for radiochemical and chemical purity determinations. Under these conditions, ^{11}C-reduced N-methylspiperone and N-methylspiperone have k's of 0.8 and 1.5, respectively.

Reduced 3-N-[^{11}C-methyl]spiperone. Method 2. 3-N-[^{11}C-Methyl]spiperone was synthesized in DMF as described in method 1. To the crude mixture was added $NaBH_4$ (1 mg, 26 μmole) and methanol (200μL). After heating the solution at 80° C for 1 minute, the mixture was diluted with HPLC mobile phase (200 μL) and applied to column B (50% CH_3CN / 50% 0.1 M NH_4HCO_2, flow rate: 11 mL/min). The product (k' = 2.7) was collected, evaporated to dryness under reduced pressure, and reconstituted in 7 mL of sterile saline. Following Millipore filtration into a sterile evacuated vial, sterile 8.4% sodium bicarbonate (3 mL) was added. The analytical HPLC conditions were the same as in method 1 above.

Reduced N-methylspiperone - (R,S)-8-[4-(4-fluorophenyl)-4-hydroxybutyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one. Sodium borohydride (20 mg, 530 μmole) was added to 3-N-methyl-spiperone (100 mg, 240 μmole) dissolved in 4 mL of methanol. After 5 minutes stirring, water (5 mL) was added and a white precipitate formed. The mixture was extracted with methylene chloride (3 x 5 mL). The organic layer was washed with water (5 mL), dried over Na_2SO_4, and filtered. After evaporation under vacuum, a colorless oil formed which was triturated with cyclohexane to form a white solid which was recrystallized from cyclohexane (yield: 83%); m.p. 148-150° C (uncorrected).

NMR (in $CDCl_3$) δ 7.74-6.82 (multiplet, 9H, ArH); 4.68 (singlet, 2H, CH_2 in imidazolone ring); 3.61 (singlet, 1H, OH exchangeable with D_2O); 2.99-1.53 (multiplet, 18H). IR (KBr) 1680 cm^{-1}. Elemental analysis for $C_{24}H_{28}N_3O_2F$ - Theoretical: C: 70.05, H: 7.35, N: 10.21. Found: C: 69.92, H: 7.39, N: 10.16.

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