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Production of Fluorine-18 Labeled (3-*N*-Methyl)benperidol for PET Investigation of Cerebral Dopaminergic Receptor Binding

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The multi-millicurie synthesis of the D-2 receptor ligand [^{18}F](3-*N*-methyl)benperidol (NMB; 1-[3-(4′-[^{18}F]fluorobenzoyl)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl)piperidine) is described. [^{18}F]NMB was produced via a 3-step reaction sequence with an overall radiochemical yield of 5–10% and a specific activity >3000 Ci/mmol within 100 min. *In vitro* binding assays indicated that NMB has high affinity for D-2 receptors in primate brain (K_i = 3.6 nM), with a receptor specificity exceeding that of spiperone. The technique described here permits the routine production of 10–20 mCi of this promising radiopharmaceutical for PET study of D-2 receptor binding *in vivo*.

Introduction

[^{18}F]Spiperone (Perlmutter *et al.*, 1987) and spiperone analogues labeled with carbon-11 (Wagner *et al.*, 1983; Hägglund *et al.*, 1987), fluorine-18 (Arnett *et al.*, 1986; Wienhard *et al.*, 1990) and bromine-76 (Martinot *et al.*, 1990) have been employed in several PET centers for the noninvasive study of human dopaminergic D-2 receptor binding *in vivo*. These radiolabeled derivatives of spiperone have high binding affinity for central D-2 receptors, but they are relatively nonspecific ligands with high affinity for binding to serotonergic S-2 receptors *in vivo* as well (Perlmutter *et al.*, 1991; Coenen *et al.*, 1988; Frost *et al.*, 1987).

In contrast, the benzamide raclopride is a very selective ligand for D-2 receptors, and [^{11}C]raclopride has been used successfully with PET for noninvasive study of dopamine receptor binding (Farde *et al.*, 1985). A limitation of this tracer, however, is its relatively low receptor-binding affinity, which leads to competition by endogenous dopamine for central D-2 receptors and complicates the derivation of receptor-binding information from PET data (Seeman *et al.*, 1989).

Thus, the search for a more ideal D-2 receptor-binding PET radiopharmaceutical continues. Like spiperone, benperidol (**1**) is also a potent D-2 ligand, and analogues of this butyrophenone have been labeled with ^{11}C (Suehiro *et al.*, 1990), ^{18}F (Arnett *et al.*, 1985) and ^{75}Br (Moerlein *et al.*, 1986) for use with positron emission tomography. *N*-Methyl benperidol (NMB; 1-[3-(4′-fluorobenzoyl)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl)piperidine; **2**) shows particular promise as a PET radiopharmaceutical due to its specific, reversible binding to dopamine receptors *in vivo* (Suehiro *et al.*, 1990).

The relatively short half-life of carbon-11 ($t_{1/2}$ = 20 min) limits the length of time that statistically-reasonable data can be acquired during PET scanning, as well as makes the laboratory analysis of plasma metabolites inconvenient. Because the longer-lived fluorine-18 ($t_{1/2}$ = 110 min) allows these problems to be surmounted, we report here the radiosynthesis of high specific-activity [^{18}F]NMB (**3**) suitable for investigation of D-2 receptor binding with PET.

Experimental

Authentic spiperone and ketanserin were purchased from Research Biochemicals, Inc. (Natick, MA), and benperidol was obtained from Janssen Pharmaceutica (Beerse, Belgium). Cyclopropyl-*p*-nitrophenyl ketone (**4**) was synthesized as previously reported (Shiue *et al.*, 1984). All other reagents were

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procured from Aldrich Chemical Co. (Milwaukee, WI) and used as received, with the exception of tetrahydrofuran (THF), which was predistilled from lithium aluminum hydride and finally distilled from sodium/benzophenone ketyl.

Melting points were determined using an Electrothermal melting point apparatus (Gillete, NJ) and were uncorrected. ^{1}H-NMR spectra were recorded on an EM-360 spectrometer (Varian Associates, Walnut Creek, CA) using tetramethylsilane as an internal reference. Low-resolution mass spectra were obtained on a Finnegan 3200 VG-AZB-3F GC-mass spectrometer and processed with a VG-11-250 data system. Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN), and were within $\pm 0.4\%$ of theoretical values.

1-[3-(4'-Fluorobenzoyl)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl) piperidine (NMB; 2)

The free base of benperidol **1** (0.1 g, 0.26 mmol) was dissolved in THF (5 mL) and NaH (0.019 g, 0.40 mmol) as a 50% dispersion in mineral oil was added in a single portion. The resulting mixture was refluxed for 10 min. After cooling to ambient temperature, iodomethane (0.056 g, 0.40 mmol) was added to the reaction mixture, which was then stirred for 2 h. The vessel contents were diluted with CH_2Cl_2 (15 mL), washed with H_2O (2 × 10 mL), dried (Na_2SO_4), decanted and concentrated *in vacuo*. Preparative TLC (Si: $CHCl_3$/MeOH/NH_4OH = 90/9/0.1) permitted isolation of **1** as a colorless foam (62.3 mg, 60.6%) which was dissolved in 5 mL CH_2Cl_2/Et_2O (1/1) and treated with anhydrous hydrochloric acid to yield the HCl salt as a colorless powder, m.p. 252–254°C. ^{1}H-NMR (acetone-d_6, 360 MHz): δ 1.3–3.2 (15H, m), 3.35 (3H, s), 7.1–7.5 (6H, m), 8.1–8.4 (2H, appt). MS (FABMS, *p*-nitrophenol): *m/z* (relative intensity) 396 (M + 1, 11), 381 (M + 1–15, 9), 231 (43), 216 (26), 188 (5). Anal ($C_{23}H_{27}N_3O_2FCl$): C, H, N.

4-(2-Keto-1-benzimidazolinyl)-1-triphenylmethylpiperidine (5)

Triphenylmethyl chloride (1.7 g, 5.9 mmol) and *N,N*-diisopropylethylamine (Hunig's base) (0.77 g, 5.9 mmol) were added to a solution of 4-(2-keto-1-benzimidazolinyl)piperidine (**6**) (1.3 g, 5.9 mmol) in dry $CHCl_3$ (5 mL). The mixture was allowed to stir overnight at room temperature. On the next day, the reaction was diluted with $CHCl_3$ (40 mL), washed with H_2O (2 × 20 mL), brine (20 mL), and once again with H_2O (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield **5** (2.6 g, 96%) as a colorless amorphous powder, m.p. 240°C (dec). ^{1}H-NMR (DMSO-d_6, 60 MHz): δ 1.3–3.3 (9H, m), 3.8–4.2 (1H, brs, CONH), 7.0–7.7 (19H, m, Ar). MS (FABMS, *p*-nitrophenol): *m/z* (relative intensity) 460 (M + 1, 10), 383 (5), 243 (100), 218 (35).

4-(2-Keto-3-methyl-1-benzimidazolinyl)-1-triphenylmethylpiperidine (7)

To a solution of **5** (0.2 g, 0.44 mmol) dissolved in THF (10 mL) was added, in a single portion, NaH (0.034 g, 0.65 mmol) as a 50% dispersion in mineral oil. The reaction mixture was refluxed for 30 min, and allowed to cool to room temperature. Iodomethane (0.16 g, 1.13 mmol) was added, and the mixture was refluxed for 2 h. The vessel contents were permitted to cool to ambient temperature, diluted with CH_2Cl_2 (25 mL), and washed with H_2O (2 × 20 mL). The organic layer was separated, dried (Na_2SO_4) and the volatiles removed under reduced pressure to give **7** as a tan solid (0.175 g, 87.2%). M.p. browning at 266°C, dec. at 298°C. ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 1.3–3.2 (9H, m), 3.35 (3H, s), 6.9–7.6 (19H, m). MS (FABMS, *p*-nitrophenol): *m/z* (relatively intensity) 474 (M + 1, 5), 459 (M + 1–15, 5), 341 (6), 243 (40), 230 (10), 215 (7), 148 (11), 120 (17), 107 (25).

4-(2-Keto-3-methyl-1-benzimidazolinyl)piperidine (8)

Ten percent HCl (20 mL) was added to a solution of **7** (0.175 g, 0.37 mmol) in THF (10 mL). The mixture was stirred at room temperature for 3 h, after which the volatiles were removed *in vacuo*. Additional 10% HCl (20 mL) was added, and the turbid mixture was washed with CH_2Cl_2 (2 × 25 mL). The aqueous layer was neutralized with concentrated NH_4OH until slightly basic, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **8** as an oil (0.071 g, 83%). ^{1}H-NMR ($CDCl_3$, 60 MHz): δ 1.4–3.1 (10H, m), 3.35 (3H, s), 4.1–4.6 (1H, vbrs), 6.9–7.5 (4H, m). MS (FABMS, *p*-nitrophenol): *m/z* (relative intensity) 232 (M + 1, 100), 217 (M + 1–15, 7), 188 (5), 156 (15).

1-[3-(4'-[^{18}F]Fluorobenzoyl)propyl]-4-(2-keto-3-methyl-1-benzimidazolinyl)piperidine ([^{18}F]NMB; 3)

[^{18}F]Fluoride was produced with use of an isotopically-enriched [^{18}O]water target and the ^{18}O(p, n)^{18}F nuclear reaction induced by the 16 MeV proton beam of the Washington University JSW BC-16/8 cyclotron. [^{18}F]Fluoride (300–400 mCi) in 0.3–0.5 mL of aqueous solution and tetra(n-butyl)ammonium hydroxide (5 μmol) in a 5-mL Reacti-vial® (Alltech Associates, Deerfield, IL) were brought to dryness by azeotropic evaporation with acetonitrile and resolubilized into methyl sulfoxide (DMSO, 0.3 mL). Cyclopropyl *p*-nitrophenyl ketone **4** (2.0 mg, 10.5 μmol) was added to the resolubilized [^{18}F]fluoride, and the vessel was sealed and subjected to microwave treatment (500 W, 8 min). A reflux condenser was attached to the Reacti-vial®, 2 mL of HCl/MeOH (1/1) was added, and the solution was refluxed for 5 min. The reaction mixture was diluted with H_2O (10 mL) and passed through a Sep-Pak® C_{18} Cartridge (Millipore Corp., Milford MA). The cartridge was washed with H_2O (12 mL), and the product γ-chloro-*p*-[^{18}F]fluorobutyrophenone **10** was

eluted from the Sep-Pak® with pentane (5 mL). The pentane solution was passed through a 15 × 45 mm column of Na_2SO_4 into a 5 mL Reacti-vial®, and the solution was dried by gentle heating (70°C).

To the dry **10** was added the amine **8** (5.0 mg, 21.6 mmol) dissolved in 1-methyl-2-pyrrolidinone (300 μL). Anhydrous potassium iodide (9 mg) was added, and the Reacti-vial® was sealed and heated at 135°C for 20 min. The vessel contents were then diluted with 10 mL H_2O and the solution was passed through a Sep-Pak® C_{18} Cartridge. The cartridge was washed with H_2O (10 mL) followed by pentane (1 mL), and the reaction products were eluted off the cartridge and through a 15 × 45 mm column of Na_2SO_4 into an HPLC syringe using 5 mL of CH_2Cl_2/MeOH/NH_4OH (9800/200/1).

The organic reaction products were loaded onto a preparative normal-phase HPLC column (Partisil M9 10/50, Whatman) eluted with CH_2Cl_2/MeOH/NH_4OH (9800/200/1) at a flow rate of 3 mL/min. The eluted [^{18}F]NMB fractions ($k' = 6.8$) were brought to dryness on a rotary evaporator, reconstituted in lactate-buffered isotonic saline solution (pH 4.5), and sterile-filtered through a 0.22 μm Millex filter (Millipore Corp., Bedford, MA) to yield 8.5–22 mCi of final product.

In vitro *binding assays*

Brains from adult *Macaca nemestrina* (both sexes) were obtained from the Tissue Distribution Program of the Regional Primate Center at the University of Washington, Seattle, WA. Tissue samples were prepared as described previously (Lannoye *et al.*, 1990); membranes were isolated from the caudate nuclei for assay of D-2 receptor binding, whereas membranes from the frontal cortex were employed for measurement of S-2 receptor binding.

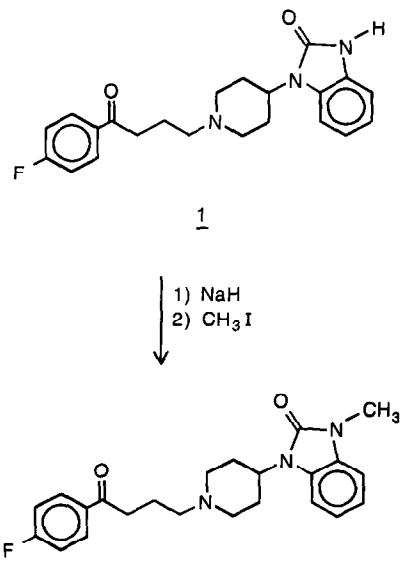
[^{3}H]Spiperone and [^{3}H]ketanserin were each purchased with a specific activity of 77 Ci/mmol from NEN Research Products (Boston, MA) and were used without further examination of radiochemical purity or specific activity. Details of the technique used for the determination of the inhibition constant (K_i) by displacement of [^{3}H]spiperone from D-2 binding sites on caudate membranes have been reported (Lannoye *et al.*, 1990). Methodology for measurement of the K_i for S-2 sites was the same, except that [^{3}H]ketanserin was displaced from its binding sites on cortical membranes. The effective specific activity of the final [^{18}F]NMB product was determined using *in vitro* receptor-binding techniques similar to those detailed elsewhere (Moerlein *et al.*, 1990). All competition experiments were analyzed by computer-assisted least-squares nonlinear regression analysis with the equations given elsewhere (Molinoff *et al.*, 1981).

Results and Discussion

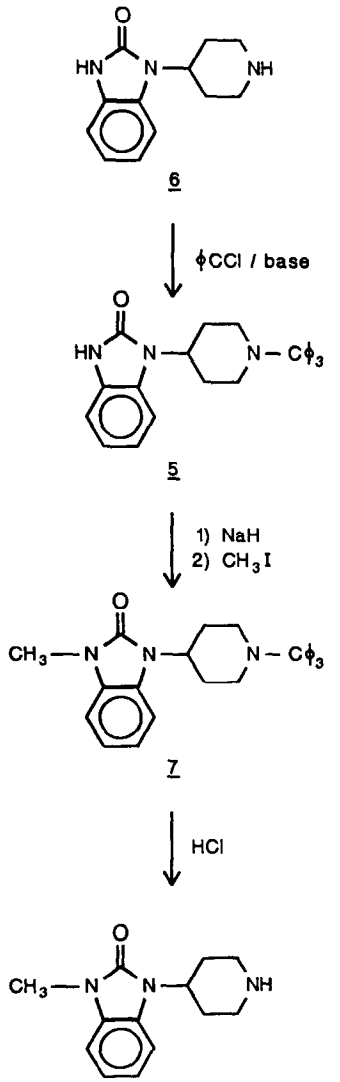
The synthesis of NMB standard was straightforward, and production of the *N*-methylated ligand proceeded efficiently. As shown in Scheme 1, benperidol was treated with sodium hydride to generate the amido anion, which was subsequently reacted with iodomethane to yield the *N*-methyl product NMB. Following chromatographic purification, the methylated butyrophenone was isolated as the hydrochloride salt with an overall yield exceeding 60%.

Receptor-binding assays performed using NMB prepared in this manner indicated that the ligand has both high affinity and high specificity for binding to D-2 receptors in primate brain tissue *in vitro*. NMB was characterized by an inhibition constant $K_i = 3.6$ nM for D-2 receptors, whereas $K_i = 89$ nM for S-2 receptor binding. Thus, the specificity of this potent dopaminergic ligand was high; the binding affinity of the butyrophenone for S-2 receptors relative to D-2 receptors was only 3.6/89 = 0.04. In contrast, spiperone had high *in vitro* binding affinity for primate D-2 ($K_i = 0.68$ nM) as well as S-2 ($K_i = 0.59$ nM) receptors. The low receptor-binding specificity of spiperone leads to analytical difficulties when this ligand is used as a radiotracer with PET to investigate D-2 receptor binding in the striatum, which also has large numbers of S-2 receptors (Perlmutter *et al.*, 1991). The high affinity and specificity of NMB have also been noted in receptor studies of rodent brain (Suehiro *et al.*, 1990), which underscores the potential advantages of this ligand over spiperone derivatives as a D-2 receptor-based radiopharmaceutical for PET.

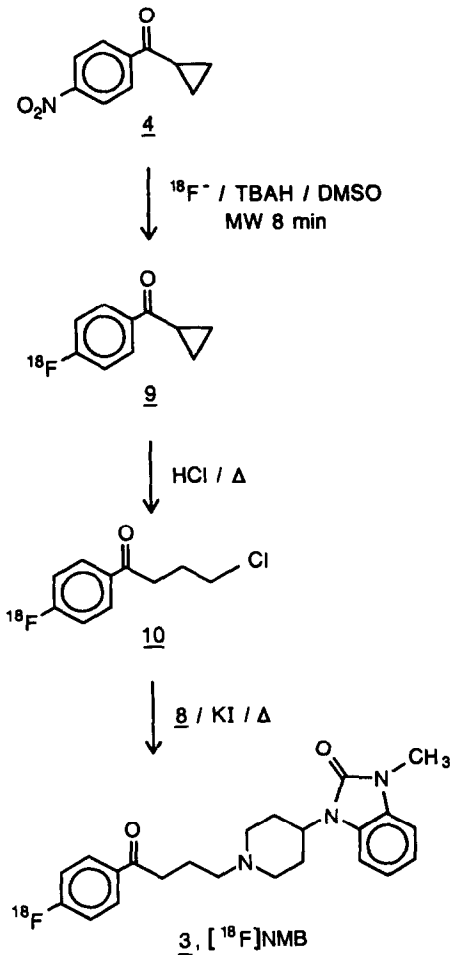
The radiosynthesis of [^{18}F]NMB was based on reported procedures for the production of high specific-activity [^{18}F]spiperone (Hwang *et al.*, 1989) or [^{18}F]*N*-methyl spiperone (Shiue *et al.*, 1986). A key intermediate in this multistep radiosynthetic procedure is 4-(2-keto-3-methyl-1-benzimidazolinyl)-piperidine (**8**), which was prepared as outlined in



Scheme 1



Scheme 2



Scheme 3

Scheme 2. The piperidine nitrogen of the commercially-available nonmethylated precursor **6** was protected by tritylation, which permitted selective methylation of the amide nitrogen via generation of the corresponding amido anion using sodium hydride, followed by treatment with iodomethane. The amine protecting group was finally removed by acid hydrolysis: labeling precursor **8** was recovered with an overall chemical yield of *ca* 70%.

The radiosynthetic pathway that was employed for the large-scale production of [^{18}F]NMB is illustrated in Scheme 3. The initiating step to this reaction sequence was the no-carrier-added nucleophilic aromatic fluorodenitration of cyclopropyl-*p*-nitrophenyl ketone (**4**) by [^{18}F]fluoride resolubilized into DMSO from aqueous solution with use of the base tetra(*n*-butyl)ammonium hydroxide (TBAH). Microwave heating was used to promote this labeling reaction, since this technology has been shown to shorten reaction times and hence give higher radiochemical yields (Hwang *et al.*, 1987), and has also been successfully employed for the routine, large-scale production of [^{18}F]spiperone (Hwang *et al.*, 1989).

Following a microwave-facilitated reaction interval of 8 min (and an exchange yield of 87 ± 4%), the [^{18}F]fluoroarene **9** was hydrolyzed to the ω-chlorobutyrophenone **10** by treatment with refluxing hydrochloric acid. Labeling intermediate **8** was then alkylated with this ^{18}F-labeled alkyl halide by heating in 1-methyl-2-pyrrolidinone in the presence of potassium iodide to give the title compound **3**. [^{18}F]NMB was purified using preparative HPLC; the radiopharmaceutical was produced with an overall radiochemical yield of 5–10% and a specific activity exceeding 3000 Ci/mmol, as determined using *in vitro* ligand binding assays. The overall radiopharmaceutical preparation time was 100 min, of which 70 min was dedicated to radiosynthetic manipulation and 30 min was required for chromatographic purification and final product work-up. The radiochemical yield, specific activity, and production

interval for large-scale synthesis of [^{18}F]NMB are very similar to those of [^{18}F]spiperone (Hwang *et al.*, 1989) prepared for imaging applications with PET.

In conclusion, in this work we have shown that [^{18}F]NMB can be synthesized in reasonable radiochemical yield and with a specific activity sufficiently high to permit application in receptor studies. *In vitro* binding assays using primate brain tissues have shown that NMB has high affinity for D-2 receptors and a binding specificity that exceeds that of spiperone. Using the methodology described here, [^{18}F]NMB can be routinely produced in 10–20 mCi batches for further evaluation as a tracer for PET investigation of D-2 receptor binding *in vivo*.

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