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Synthesis of [^{123}I]-8-[4-[2-(5-iodothienyl)]-4-oxobutyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one: A Potential Dopamine D_2 Receptor Radioligand for SPECT

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Summary

[^{123}I]-8-[4-[2-(5-Iodothienyl)]-4-oxobutyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one (**1**) has been synthesized as a potential ligand for dopamine D_2 receptors. This new compound proved to be moderate in lipophilicity (log P = 3.14) and exhibited high affinity (Ki = 1.9 nM) for the dopamine D_2 receptor as well as good selectivity for D_2 versus serotonin $5HT_2$ receptors (Ki $5HT_2/D_2$ = 16.7) *in vitro*. The corresponding radioligand, ^{123}I-**1**, was synthesized from a thienyl tributylstannane precursor using oxidative iododestannylation methods. The radiochemical yield was 64-80% EOS (n = 5) and the purified product was >99% radiochemically purity with a specific activity >3,500 mCi/μmol (>129,500 MBq/μmol).

Introduction

Perturbations of the dopaminergic system are thought to be central to the etiology of several neurological diseases and syndromes of considerable importance. These include schizophrenia, Parkinson's disease, Huntington's Chorea, tardive diskinesia and cocaine addiction. Several papers have been published concerning the pharmacology of the dopaminergic system (1, 2, 3). To date, it is known that at least five dopamine subtypes exist; These are referred to as dopamine D_1, D_2, D_3, D_4

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and D_5 receptors. In recent years much research has been focused on the *in vivo* tomographic imaging of the dopaminergic system in the mammalian brain. Most of the effort has centered on the D_2 receptor, largely because many of the clinically effective neuroleptics and anti-parkinson agents have high binding affinities for this subtype.

In vivo positron emission tomography (PET) investigations of dopamine D_2 receptor distribution have been conducted using a variety radioligands labelled with carbon-11, fluorine-18 or bromine-76. A few examples include [^{11}C]-N-methylspiperone (4, 5), [^{76}Br]bromolisuride (6), [^{18}F]fluoroethylspiperone (7), [^{18}F]benperidols (8) and [^{11}C]raclopride (9, 10). However, the greater clinical accessibility of single photon emission computed tomography (SPECT) imaging capabilities would allow more widespread study of dopaminergic function if highly selective ^{123}I-labelled D_2 receptor ligands were available. Several radioiodinated agents have been reported for the SPECT evaluation of D_2 receptors. Of these, ^{123}I-IBZM has emerged as one of the most widely used clinically, especially in the evaluation of Parkinson's disease (11, 12). However, the target to background contrast ratios obtained clinically using ^{123}I-IBZM are relatively low (< 2:1), perhaps due to a high degree of non-specific binding of the tracer (11).

Radioiodinated analogs of iodolisuride (12) and iodobenzofurans (13) have also been prepared and may prove useful for the SPECT evaluation of D_2 receptor densities. Other work has focused on the synthesis of radioiodinated spiperone analogs, including [^{125}I]-2'-iodospiperone (14, 15), [^{125}I]-4'-iodospiperone (16) and (*E*)- and (*Z*)-N-(iodoallyl)spiperone (17). However, the iodinated derivatives of spiperone were shown to exhibit a relatively large degree of non-specific binding which may be due to the increased lipophilicity resulting from the inclusion of an iodine atom into these molecules. Recent work in our groups has focused on the development of halogenated butyrothiophenone derivatives of spiperone as novel ligands for the dopamine D_2 receptor (18, 19). We have synthesized and characterized a series butyrothienones possessing a variety of alkyl and substituted benzyl groups off of the amide nitrogen. We have previously reported that these butyrothienones possess good selectivity for dopamine D_2 versus serotonin $5HT_2$ receptors and also lower lipophilicity as compared with the corresponding butyrophenone derivatives (18, 19). Therefore, we hypothesized that this new class of compounds might provide useful dopamine D_2 ligands for use in SPECT imaging studies. The first ligand of the series to be radiolabeled for *in vivo* evaluation is 8-[4-[2-(5-iodothienyl)]-4-oxobutyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one, **1**. We report here the synthesis and *in vitro* characterisation of **1**, and the radiolabeling and initial *in vivo* evaluation of the corresponding SPECT ligand, ^{123}I-**1**.

Materials and Methods

Proton and carbon NMR spectra were recorded using a Brucker AC-250 FT-NMR spectrometer. Chemical shifts were recorded in ppm (δ) in reference to an internal tetramethylsilane standard in deuterochloroform. Coupling constants (J) are reported in hertz. Mass spectral analysis (HRMS) was accomplished using a ZAB-EQ mass spectrometer at the Department of Chemistry, University of Tennessee (Knoxville, TN). Melting points were recorded on a GallenKamp melting point apparatus and are uncorrected. Elemental analysis was performed by Atlantic Microlabs Inc. (Norcross Georgia). Gravity chromatography was performed using silica gel (Fluka, 70-230 mesh, ASTM) using the solvent systems indicated in the text. For mixed solvent systems, the ratios are given with respect to volumes.

All reagents were purchased from commercial sources and were used without further purification. ^{123}I-iodide was obtained from the National Medical Cyclotron (Sydney, Australia) as a solution in 0.1 M sodium hydroxide. HPLC purification and analysis of the radioligand was performed using a Waters 510 HPLC pump, a Waters 440 UV detector, and a Berthold LB506 radiation detector. The column used was a reverse-phase base-deactivated column (Activon, Goldpak Exsil, ODS B, 4.6 x 250 mm or 10 x 250 mm, 10 μm particle size) and the mobile phases used are indicated in the text below.

1-Phenyl-8-(tert-butoxycarbonyl)-1,3,8-triazaspiro[4.5]decan-4-one, **3**

1-Phenyl-1,3,8-triazospiro[4.5]decan-4-one (3.00 g, 12.9 mmol), dichloromethane (210 ml), di-tert-butyl dicarbonate (3.70 g, 14.2 mmol) and freshly distilled triethylamine (2.17 ml, 0.155 mmol) were added to a 500 ml round-bottomed flask equipped with a magnetic stirring bar. The resulting clear yellow mixture was stirred at room temperature for 24 hours and the volatile components were removed under reduced pressure, leaving behind a yellow solid. The product was purified by recrystallization [dichloromethane/ethyl acetate (1:1)] to provide 3.93 g (11.8 mmol, 91%) of the desired product as a white solid having chemical and spectroscopic properties identical to those reported in literature: mp 208-210°C (lit. mp = 209-212°C); ^{1}H-NMR ($CDCl_3$) δ 1.51 (s, 9H), 1.95-2.91 (m, 4H), 3.12-4.26 (m, 4H), 4.77 (s, 2H), 6.70-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 28.56, 28.83, 40.75, 59.94, 79.75, 114.96, 119.14, 129.43, 142.97, 155.27, 178.08.

3-Methyl-1-phenyl-8-(tert-butoxycarbonyl)-1,3,8-triazaspiro[4.5]decan-4-one, 4

1-Phenyl-8-(tert-butoxycarbonyl)-1,3,8-triazaspiro[4.5]decan-4-one (732 mg, 2.21 mmol) was dissolved to anhydrous tetrahydrofuran (30 ml) in an argon-flushed, 100 ml round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and a gas outlet. To this solution was added solid sodium hydride (98 mg, 2.4 mmol, 60% in mineral oil) and the evolution of gas was immediately observed. The mixture was stirred at room temperature for 10 minutes and then methyl iodide (145 µL, 2.21 mmol) was added via an Eppendorf pipet. Stirring was continued for another 2 hours, after which time the reaction was quenched with water (5.0 ml). The product was extracted into dichloromethane (3 x 20 ml). The organic layers were combined, dried over anhydrous sodium sulfate and the solvent removed by vacuum to provide a clear, colorless oil. Purification was accomplished using column chromatography [silica gel; dichloromethane / ethyl acetate (1:1)] to yield 680 mg (1.97 mmol, 89%) of the desired compound as a white solid: mp 164-165°C; ^{1}H-NMR ($CDCl_3$) δ 1.51 (s, 9H), 2.35-2.80 (m, 4H), 3.01 (s, 3H), 3.26-3.59 (m, 4H), 4.69 (s, 2H), 6.69-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 28.56, 29.05, 40.65, 60.39, 65.18, 79.67, 114.64, 118.92, 129.43, 142.68, 155.25, 174.26. Anal. Calcd for $C_{19}H_{27}N_3O_3$: C, 66.06; H, 7.88; N, 12.16. Found: C, 66.00; H, 7.91; N, 12.17.

4-Chloro-1,1-(ethylenedioxy)-1-(2-thienyl)butane, 7

A 200 ml two-necked, round-bottomed flask was equipped with a Dean-Stark trap, a water-cooled condenser and a gas outlet (oil bubbler). Anhydrous benzene (200 ml) was added to the flask, followed by 4-chloro-1-(2-thienyl)-1-butanone (1.68 g, 8.90 mmol) , anhydrous ethylene glycol (3.0 ml, 53.4 mmol) and *p*-toluenesulfonic acid (100 mg, 0.55 mmol). The mixture was refluxed for 20 hours under a blanket of argon. The resulting dark brown reaction mixture was cooled to room temperature and neutralized with an aqueous, saturated sodium bicarbonate solution (55 ml). The product was then extracted into dichloromethane (2 x 70 ml) and the organic layers were combined, dried over anhydrous sodium sulfate, and the solvent evaporated under reduced pressure to provide a brown oil. The product was loaded onto a silica gel column and eluted with a mixture of dichloromethane and hexane (1:1) to give 1.36 g (5.86 mmol, 65.8%) of the desired ketal as a clear, colorless oil: ^{1}H-NMR ($CDCl_3$) δ1.68-2.26 (m, 4H), 3.54 (t, 2H, J = 6.35), 3.85-4.10 (m, 4H), 6.81-7.0 (m, 2H), 7.23 (dd, J = 4.5, 1.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 27.08, 37.86, 44.66, 64.80, 108.74, 124.61, 125.23, 126.94, 146.36. Anal. Calcd for $C_{10}H_{13}O_2SCl$: C, 51.61; H, 5.63; S, 13.78; Cl, 15.23. Found: C, 51.50; H, 5.65; S, 13.68; Cl, 15.26.

4-Chloro-1,1-(ethylenedioxy)-1-[2-(5-iodothienyl)]butane, **8**

4-Chloro-1,1-(ethylenedioxy)-1-(2-thienyl)butane (1.20 g, 5.16 mmol) and diethyl ether (50 ml, anhydrous) were added to a 250 ml oven-dried, round-bottomed flask equipped with a magnetic stirring bar and a gas outlet. This mixture was cooled to 0°C and n-butyllithum (4.84 ml, 7.74 mmol, 1.6 M in hexanes) was added via syringe. After 30 minutes, trimethyltinchloride (1.50 g, 7.74 mmol) was added in one portion. The reaction mixture quickly became clear and then cloudy again as copious amounts of a white precipitate formed. After stirring for 1.0 hour, 10 drops of water were added to destroy excess n-butyllithium. Next, iodine (1.57 g, 6.18 mmol) in diethyl ether (30 ml, anhydrous) was added to the reaction mixture and stirring continued for another 30 minutes. The resulting clear red solution was washed with an 10% aqueous sodium hydrogen sulfite (75 ml) solution to destroy the excess iodine. The product was extracted into ethyl acetate (3 x 50 ml) and the organic layers were combined, dried over anhydrous sodium sulfate, filtered by gravity filtration, and the solvent removed to provide an orange oil. The product was purified by column chromatography [silical gel; dichloromethane/hexane (1:1)] to afford 1.45 g (4.10 mmol, 80%) of the desired compound as a clear, colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.80-2.25 (m, 4H), 3.55 (t, 2H, J = 6.37), 3.90-4.11 (m, 4H), 6.69 (d, 1H, J = 3.74 Hz), 7.14 (d, 1H, J = 3.74 Hz); ^{13}C-NMR ($CDCl_3$) δ 27.04, 37.77, 44.92, 65.10, 73.35, 108.30, 126.94, 136.91, 152.43. Anal. Calcd for $C_{10}H_{12}O_2SICl$: C, 33.49; H, 3.37. Found: C, 33.57; H, 3.47.

8-[4,4-Ethylenedioxy-4-[2-(5-iodothienyl)]butyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, **2** 3-Methyl-1-phenyl-8-(tert-butoxycarbonyl)-1,3,8-triazaspiro[4.5]decan-4-one (494 mg, 1.43 mmol) was placed into a 100 ml round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and a gas outlet. The flask was flushed with argon and 10 ml anhydrous HCl in dioxane (4.0M, 40 mmol) was added via syringe. The resulting solution solution was stirred for 1.5 hours and all volatile components were removed by vacuum. The remaining yellow solid was mixed with saturated sodium carbonate solution (20 ml, aqueous) and the product extracted into dichloromethane (3 x 20 ml). The organic layers were combined, dried over anhydrous sodium sulfate and the solvent removed under vacuum to give 320 mg (1.31 mmol, 91%) of a yellow crystalline solid. This solid was not characterized but was used directly in the next synthetic step.

A 100 ml round-bottomed, two-necked flask was equipped with a magnetic stirring bar, a water-cooled condenser, a thermometer and a gas outlet (oil bubbler). To this flask was added

3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (220 mg, 0.89 mmol), 4-chloro-1,1-(ethylenedioxy)-1-[2-(5-iodothienyl)]butane (336 mg, 0.89 mmol), sodium carbonate (333 mg, 3.14 mmol), potassium iodide (35 mg, 0.21 mmol) and N,N-dimethyl formamide (25 ml, anhydrous). This mixture stirred at 60°C under an argon atmosphere for 24 hours, resulting in a yellow solution containing a white precipitate. The reaction mixture was cooled to room temperature, diluted with 30 ml of distilled water and the product was extracted into dichloromethane (3 x 25 ml). The organic layers were combined, dried over anhydrous sodium sulfate, decanted, and the solvent removed under vacuum to give a yellow oil. The product was purified by column chromatography [silica; dichloromethane / ethanol (50:2)] to provide 493 mg (0.89 mmol, 84%) of a white solid: mp 133.7-135.0 C; ^{1}H-NMR($CDCl_3$) δ 1.55-1.75 (m, 2H), 1.97-2.14 (m, 2H), 2.41 (t, 2H, J = 6.94 Hz), 2.55-2.99 (m, 11H), 3.90-4.10 (m, 4H), 4.72 (s, 2H), 6.70 (d, 1H, J = 3.59 Hz), 6.80-6.92 (m, 3H), 7.10 (d, 1H, J = 3.59 Hz), 7.20- 7.32 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 21.35, 27.53, 29.37, 38.49, 49.55, 58.17, 60.44, 65.07, 73.01, 108.74, 115.16, 118.79, 126.03, 129.32, 136.80, 142.89, 152.89, 174.53. Anal. Calcd for $C_{24}H_{30}O_3N_3SI$: C, 50.80; H, 5.33; N, 7.40; S, 5.65; I, 22.36. Found: C, 50.72; H, 5.40; N, 7.32; S, 5.72; I, 22.44.

8-[4-[2-(5-Iodothienyl)]-4-oxo-butyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, **1**

8-[4,4-Ethylenedioxy-4-[2-(5-iodothienyl)]butyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one (219 mg, 0.390 mmol) was dissolved in a mixture of HCl and methanol (14 ml, 1:40) and the resulting solution was heated at 40°C for 60 minutes. The reaction mixture was cooled to room temperature and neutralized slowly with aqueous saturated sodium bicarbonate. The product was extracted into dichloromethane (3 x 15 ml) and the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered by gravity filtration, and the solvent evaporated to give a clear, colorless oil. The product was purified by column chromatography [alumina; dichloromethane/ethanol (50:1)] to provide 180 mg (0.35 mmol, 91%) of the product as a white solid; mp 106-107°C; ^{1}H-NMR ($CDCl_3$) δ 1.90-2.08 (m, 2H), 2.45-3.10 (m, 15H), 4.65 (s, 2H), 6.65-7.40 (m, 7H); ^{13}C-NMR ($CDCl_3$) δ 22.22, 27.56, 29.40, 37.03, 49.58, 57.49, 60.44, 65.18, 84.87, 115.21, 118.84, 129.30, 132.47, 138.05, 142.98, 150.40, 174.51, 191.76. Anal. Calcd for $C_{22}H_{26}O_2N_3SI$: C, 50.48; H, 5.01; N, 8.03; S, 6.12; I, 24.24. Found: C, 50.74; H, 5.25; N, 7.82; S, 6.26; I, 24.04.

8-[4-[2-(5-(Tributyltin)thienyl)]-4-oxo-butyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, **10**

8-[4-[2-(5-iodothienyl)]-4-oxo-butyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (50 mg, 0.10 mmol) was dissolved in toluene (5 ml) and to this was added bis-(*tri*-n-butyltin) (119 µl, 0.29 mmol) and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.18 mmol). The resulting solution was stirred at reflux under a nitrogen atmosphere for 48 hours and then cooled to room temperature. The black precipitate that formed as the reaction progressed was removed by passing the reaction mixture through filter aid (1 gram). The eluant was loaded directly onto a silica gel column and the product (rf = 0.62) was eluted with ethyl acetate / ethanol (9:2) to provide a clear colorless oil (45 mg, 68%). This compound slowly degraded at room temperature and, therefore, it was stored at -40 °C prior to use: ^{1}H-NMR ($CDCl_3$) δ 1.90-2.15 (m, 11H), 2.45-3.50 (m, 33H), 4.60 (s, 2H), 6.85-7.74 (m, 9H). MS: m/z 687.

Radiolabeling

[^{123}I]-8-[4-[2-(5-Iodothienyl)]-4-oxobutyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, ^{123}I-**1**

To a solution of sodium [^{123}I]iodide (11.3 mCi) in aqueous sodium hydroxide (0.1 N, 70 µl) in a 3.0 ml Wheaton vial was added acetic acid (50 µl), chloramine-T (0.3 mg) dissolved in a solution of methanol and water (100 µl, 80:20), followed immediately by a solution of **5** in ethanol (1.0 mg, 200 µl). After standing for one minute, the reaction mixture was quenched with aqueous sodium metabisulfite (50 µl, 1.0 M) and then made basic by the addition of sodium carbonate (80 mg). The mixture was diluted with ethanol (400 µl) and decanted from the solid salts. The product purified by HPLC (mobile phase: methanol / water, 70:30, flow rate: 4 ml/min) to provide 8.0 mCi (73% EOS) of the desired radiotracer. The retention time of the radioligand was 18.5 minutes using these HPLC conditions.

The specific activity of the product was determined by HPLC analysis using a base-deactivated reverse-phase column (Goldpak ODS-B, 4.6 x 250 mm, 10 µm) and a mobile phase consisting of methanol and water (70:30), with a flow rate of 1.0 ml/min. The detection limit was determined to be the response of the detector providing a peak height 2.5 times the noise level (at 235 nm UV wavelength). Upon analysis of a 30 µCi aliquot of ^{123}I-**1**, the specific activity was determined to be >3,500 mCi/µmol (129,500 MBq/µmol). The radiochemical purity of the product was >99%.

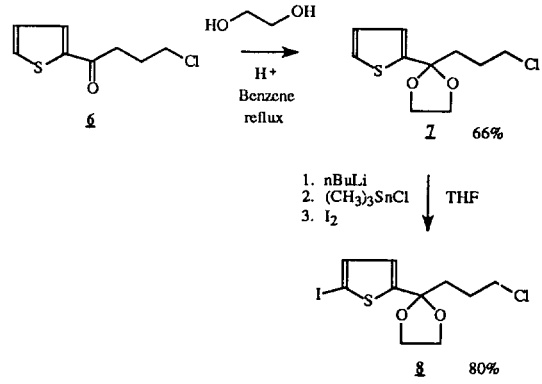
To obtain suitable preparations of ^{123}I-**1** for use *in vivo*, the mobile phase was removed *in vacuo* and the product was redissolved in saline (0.9 % NaCl, sterile). The saline solution was passed through a sterile filter into an evacuated sterile vial and diluted with saline to provide approximately 10 μCi of ^{123}I-**1** per 100 μl solution.

Ligand Binding Assays

Compound **1** was tested through the NIMH/NovaScreen Drug Discovery & Development Program (Contract No. NIMH-2003). Briefly, competitive binding assays were performed in either 250 or 500 μl volumes containing, by volume, 80% receptor preparations, 10% radiolabeled competing ligand and 10% of **1** (non-specific binding determinant / 4% DMSO (total binding determinant)). All compounds were solubilized in neat DMSO and diluted with water to a final concentration of 0.4% DMSO for use in the assay. Assays were terminated by rapid vacuum filtration over glass fiber filters (Whatman) followed by rapid washing with cold buffer. Radioactivity was determined by either liquid scintillation or gamma spectrometry. Data was reduced by a software program proprietary to NOVASCREEN. Details of methods used in the *in vitro* receptor binding assays are provided in the references indicated in Table I.

Results and Discussion

The goal of this study was to synthesize a novel radioiodinated agent suitable for *in vivo* SPECT analysis of dopamine D_2 receptors. In particular, a radioiodinated analog of spiperone having high affinity and selectivity for dopamine D_2 receptors and good *in vitro* pharmacological characteristics was to be prepared. The preparation of the target compound **1** was accomplished using established methodologies with slight modifications (20). The 5'-iodothiophenone ketal **8** was synthesized in 52% yield in two steps from 4-chloro-1-(2-thienyl)-1-oxo-butane, **6** (Scheme I). Treatment of **6** with ethylene glycol and p-toluenesulfonic acid in benzene afforded 4-chloro-1,1-(ethylenedioxy)-1-(2-thienyl)butane **2** in 66% yield. Compound **8** was obtained in 80% yield using a one-pot procedure developed to allow for the formation of the trimethyltin derivative *in situ* followed by the addition of iodine. The synthesis of the 5'-iodothiophenone **8** was confirmed by the presence of an AB pattern in the aromatic region of the ^{1}H-NMR spectrum. The resonances were centered at 6.69 ppm and 7.14 ppm and substitution at the 5 position of the thiophene ring was confirmed by



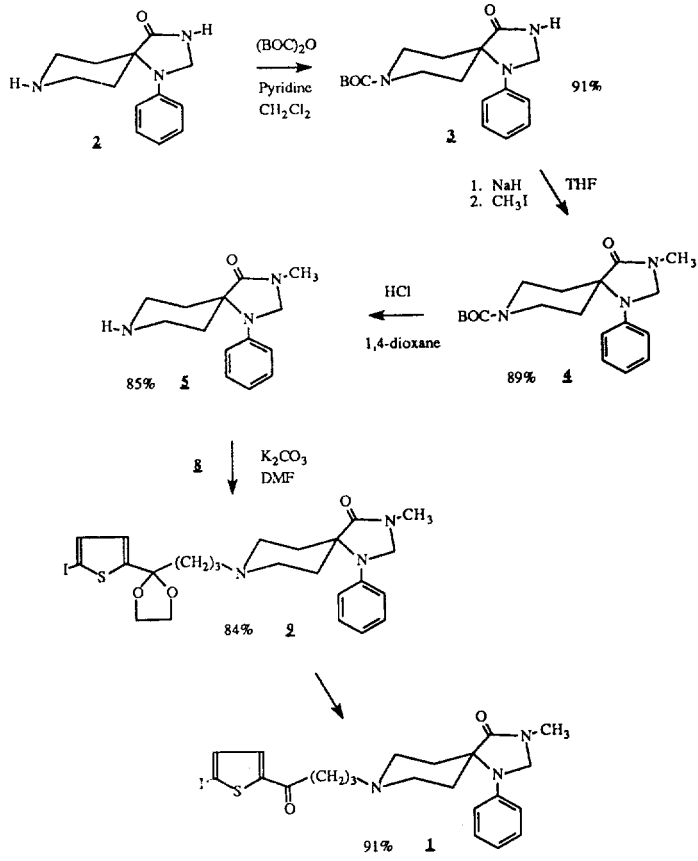
Scheme I: Synthesis of 4-Chloro-1,1-(ethylenedioxy)-1-[2-(5-iodothienyl)]butane, **8**

determination of the coupling constant between the aromatic protons (J = 3.74 Hz) which were values representative of coupling between protons at the 3 and 4 positions of thiophene (21).

The N-methyliodobutyrothienone **1** was synthesized from **2** in five steps with an overall yield of 52% (Scheme II). 1-Phenyl-8-(tert-butyloxycarbonyl)-1,3,8-triazaspiro[4.5]decan-4-one **3** was prepared by the reaction of **2** with di-*tert*-butyl dicarbonate in dichloromethane. Alkylation of **3** with methyl iodide followed by the removal of the BOC group with HCl in dioxane afforded the N-methyl derivative **5** in good yield. Alkylation of **5** with **8** in dimethyformamide using potassium iodide as a catalyst provided **9** in 84% yield. The final step involved the hydrolysis of the ethylenedioxy protecting group of **9** using methanolic HCl to provide the target compound **1** in 91% yield.

In Vitro Pharmacological Characterization and Lipophilicity Estimation

To evaluate the *in vitro* binding affinity and specificity of **1** for dopamine D_2 receptors, the ligand was screened in a variety of receptor binding assays conducted by the NIMH/NovaScreen Drug Discovery and Development Program (Table I). It was determined that **1** had high affinity (Ki = 1.9 nM) for dopamine D_2 receptors and negligible affinity (Ki >10,000 nM) for dopamine D_1 receptors. High affinity of **1** for serotonin $5HT_2$ receptors was also found, however, the selectivity of the ligand for the D_2 receptor is good (Ki $5HT_2/D_2$ = 16.7). Moderate affinity for serotonin $5HT_{1a}$ receptors was also noted. It should be noted that the assay used for D_1 receptors also included some measure of binding to D_3 and D_4 receptors, however, the affinity of **1** for the D_5 Receptor was not specifically examined. These results indicate that ^{123}I-**1** may interact selectively with dopamine D_2 receptors *in vivo* when administered at tracer levels.

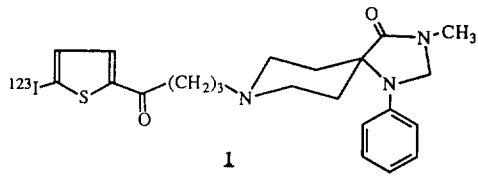


Scheme II. Synthesis of N-Methyliodothienylspiroperidol, **1**.

The lipophilicity of **1** was examined by determination of its log $P_{7.5}$ value using HPLC methods previously described (19). The log $P_{7.5}$ value of **2** was found to be 3.14, indicating that the ligand should readily cross the blood brain barrier and should not exhibit a prohibitive degree of non-specific binding as is sometimes found with imaging agents having high lipophilicities (log P values > 4.0) (22).

Radiosynthesis

In view of the promising *in vitro* results obtained in the characterization of **1**, the organostannane precursor **10** was prepared by refluxing together hexabutylditin and **1** in toluene in the presence of a palladium catalyst (23). It was observed that **10** slowly degraded at room temperature and the compound was therefore stored at -40 °C or prepared just prior to use. The SPECT ligand, ^{123}I-**1**, was synthesized from **10** by electrophilic radioiododestannylation at acidic pH using N-chloramine-T dihydrate as the oxidant (24, 25) (Scheme III). After quenching the reaction with



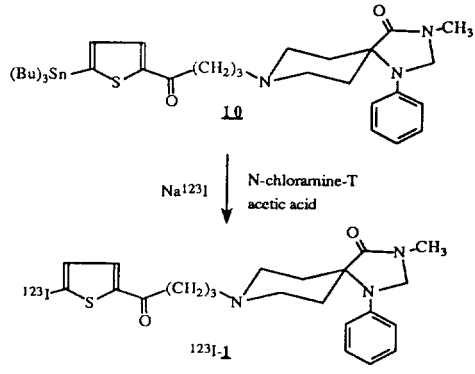
1

Assay	Ki (nM)	Reference
D_2	1.9	26
D_1	>10,000	27
$5HT_2$	29.3	28
5HT1a	295	29
$Alpha_1$	293	30

Table I. *In Vitro* Pharmacological Characterization of 1.

aqueous sodium metabisulfite, HPLC purification provided ^{123}I-1 in yields of 64-80% EOS (n = 5). For these experiments, the starting activity varied between 2.61-11.30 mCi and the average radiochemical yield was 71 ± 7% EOS. The radiochemical purity was >99% and the specific activity was >3,500 mCi/μmol (>129,500 MBq/μmol) as determined by HPLC analysis. To prepare formulations of ^{123}I-1 suitable for pre-clinical evaluations, the radiotracer was dissolved in an appropriate amount sterile saline to provide activities of 10 μl per 100 μl solution. By HLC analysis, such solutions proved stable for at least 6 hours when stored at room temperature.

In conclusion, [^{123}I]-8-[4-[2-(5-Iodothienyl)]-4-oxobutyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (1) has been synthesized as a potential probe for dopamine D_2 receptors. This new compound exhibited high affinity (Ki = 1.9 nM) for the dopamine D_2 receptor and good



10

^{123}I-1

Scheme III. Synthesis of ^{123}I-1.

selectivity for D_2 versus serotonin $5HT_2$ receptors (Ki $5HT_2/D_2$ = 16.7) *in vitro*. The lipophilicity of **1** was moderate (log $P_{7.5}$ = 3.14), indicating that it should readily cross the blood/brain barrier but not exhibit a large degree of non-specific binding. The corresponding SPECT radioligand, ^{123}I-**1**, was synthesized from the corresponding aryl tributylstannane precursor under acidic conditions using oxidative iododestannylation methods. After HPLC purification, the radioligand was obtained in yields of 64-80% EOS (n = 5) in >99% radiochemical purity and a specific activity >3,500 mCi/μmol (>129,500 MBq/μmol). Studies to evaluate this new radioligand for the *in vivo* assessment of D_2 receptor densities are underway.

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