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6-[^{123}I]Iodo-2-[[4-(2-methoxyphenyl) piperazin-1-yl]methyl]imidazo[1,2-*a*]pyridine as potential SPECT agent for imaging dopamine D_4 receptor: synthesis and *in vivo* evaluation in a nonhuman primate

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The dopamine D_4 receptor subtype has drawn considerable attention due to its potential implication in schizophrenia and erectile dysfunction. 6-[^{123}I]Iodo-2-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]imidazo[1,2-*a*]pyridine [^{123}I]-1, a potent and selective new dopamine D_4 agonist, was synthesized by classical iododestannylation using sodium [^{123}I]iodide and chloramine-T. Radiolabeling yield varied from 34 to 38% with a radiochemical purity exceeding 99%. Despite a good *in vitro* profile, *in vivo* evaluation of this radioligand in baboon showed no brain uptake after i.v. injection.

Keywords: dopamine; D4; SPECT; schizophrenia; erectile dysfunction

Introduction

Dopamine, a predominant catecholamine neurotransmitter in the mammalian brain binds to two families of G-protein-coupled receptors. Activation of receptors of the excitatory D_1-like family (D_1 and D_5 subtypes) is coupled to the G-protein $G_{\alpha s}$, which activates adenylyl cyclase, whereas activation of members of the inhibitory D_2-like family (D_2, D_3, and D_4 subtypes) is coupled to the G-protein $G_{\alpha i}$, which increases phosphodiesterase activity.[1–3]

The dopamine D_4 receptor subtype has drawn considerable attention due to its potential implication in schizophrenia and erectile dysfunction (ED). The classical dopamine hypothesis of schizophrenia is based on the correlation between clinical doses of antipsychotic drugs and their potency to antagonize the dopamine D_2 receptor.[4] Antipsychotic drugs, however, manifest a high level of side effects including extrapyramidal symptoms (dystonia, parkinsonism, and tardive dyskinesia) and hyperprolactinemia, which are presumably mediated by D_2 receptors.[5] The atypical antipsychotic clozapine, shown to be effective in schizophrenic patients who are refractory to other neuroleptics, displays a reduced risk of extrapyramidal symptoms.[6] The atypical pharmacological profile of clozapine was attributed to its 10-fold greater affinity for the dopamine D_4 receptor vs the D_2 subtype.[7] The potential clinical importance of the D_4 subtype in schizophrenia has stimulated numerous attempts to evaluate the density of these receptors in post-mortem schizophrenic brain. The results of those studies are contradictory, whereas some suggest a six-fold increase in the D_4 receptor density in schizophrenic patients compared with age-matched control;[8,9] others were unable to detect any D_4 density variation in the two populations.[10,11] This discrepancy might be explained by the indirect methodology used to determine the D_4 density derived by subtracting the number of binding sites identified with the selective D_2/D_3 antagonist [^{3}H]raclopride from the total number binding sites associated with nonselective $D_2/D_3/D_4$ antagonists [^{3}H]spiperone or [^{3}H]nemonapride.

Another potentially important application of selective D_4 agonists is the treatment of ED. Apomorphine, a nonselective dopamine receptor antagonist, was clinically proven to be effective medication for patients with ED.[12,13] The erectogenic effect of apomorphine may be attributable to its interaction with the dopamine D_4 receptor, whereas the dose-limiting side effects (nausea and vomiting) are mediated via the D_2 subtype.[14–16]

The lack of specific SPECT/PET imaging agents for *in vivo* imaging of D_4 receptor makes it difficult to fully understand its

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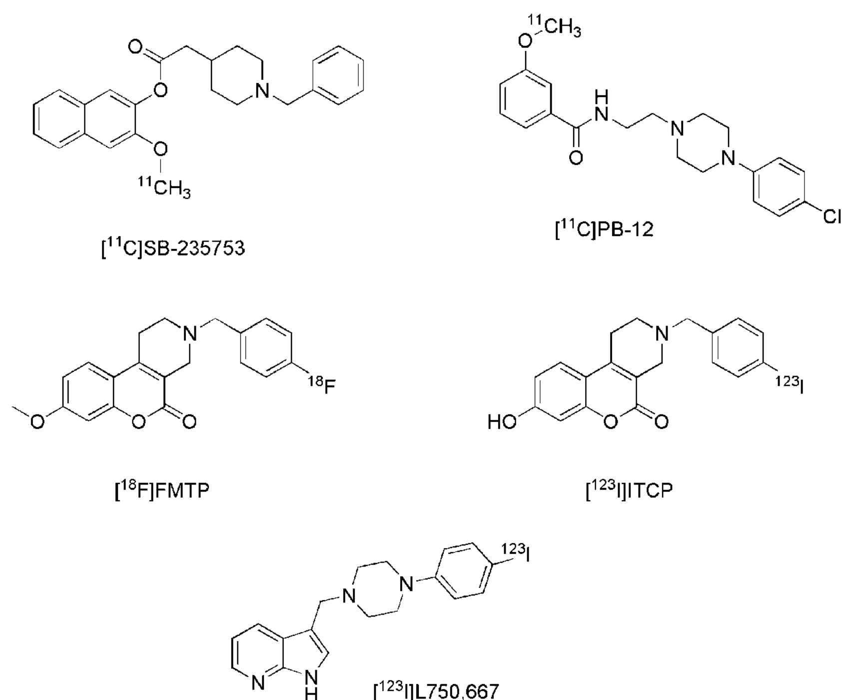

Figure 1. Examples of previously reported putative D_4 radiotracers.

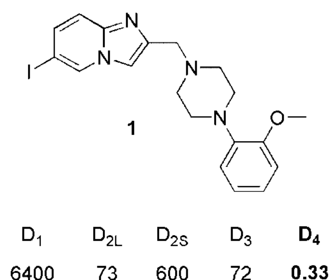

Figure 2. Structure and binding profile (K_i, nM)[23] of the target compound.

involvement in both schizophrenia and ED. Over the past decade, significant effort has been applied toward the development of PET and SPECT radiotracer enabling *in vivo* imaging of D_4 receptors. A large structural variety of ligands with high affinity for dopamine D_4 receptors have been labeled and studied without success in rodent, rabbit, and non-human primate (Figure 1). In the 2-naphthoate series, [^{11}C]SB-235753 shows low brain uptake, fast wash-out, and fast metabolic rate with a uniform distribution within the brain.[17] In the benzamide series, although [^{11}C]PB-12 shows promising results in rat brain (specific cortical uptake), no specific binding in the monkey brain was observed.[18,19] In the chromen series, two tracers were evaluated; [^{18}F]FMTP shows specific uptake in rat frontal cortex and medulla,[20] but this study used cold FMTP as a self-blocking agent and those results should be confirmed by use of known displacing agents. [^{123}I]ITCP shows brain uptake in rabbit, which did not correlate the D_4 distribution, and was not displaceable by known D_4 ligand.[21] The azaindole [^{123}I]L750,667 shows uniform distribution within the monkey brain and is not displaced by known D_4 receptor antagonists at saturation doses.[22]

Recently, Enguehard-Gueiffier and coworkers[23] described the synthesis and structure–activity relationship of novel potent and selective D_4 partial agonists featuring a 2-[[4-(2-methoxyphenyl)-piperazin-1-yl]methyl]H-imidazo[1,2-*a*]pyridine core. Of particular interest in this series was the 6-iodo analogue **1** (Figure 2), which was reported to have high affinity for the D_4 receptor ($K_i = 0.33$ nM) and good selectivity over the $D_1/D_2/D_3$ subtypes. Because D_4 receptors are present in small densities in the brain (6.5–25.5 fmol/mg),[24] *in vivo* imaging of this receptor requires a radiotracer with high affinity to obtain a reasonable binding potential ($BP = B_{max}/K_D$). It is normally expected that to obtain sufficient signal *in vivo*, the BP should exceed 0.5,[25] which implies in the case of D_4 imaging, ligands require a $K_D < 3$–12 nM. In the case of compound **1**, K_D is unknown (K_D is often in the same value range as K_i) but even with the approximation of a K_D 10 time superior to K_i for compound **1** the resulting BP should be sufficient for imaging D_4 receptors. We therefore describe the synthesis of a trimethyltin precursor for **1**, the radiosynthesis of [^{123}I]-**1**, and its *in vivo* evaluation in baboon as potential D_4 imaging agent.

Results and discussion

Chemistry

The synthesis of compound **3** was performed according to the procedure developed by Enguehard-Gueiffier and coworkers[23] (Scheme 1). The latter was converted into the stannylated derivative **4** by the tetrakis(triphenylphosphine)palladium-catalyzed reaction with excess of hexamethylditin. Finally, the iodo compound **1** (used as a reference standard for the ^{123}I-radiolabeled product) was obtained by simple iodo-destannylation of **4** (Scheme 1).

Radiochemistry

[^{123}I]–**1** was prepared by reaction of trimethylstannyl precursor **4** with electrophilic [^{123}I]iodine species generated *in situ* from sodium [^{123}I]iodide (Scheme 2). The reaction was carried out at

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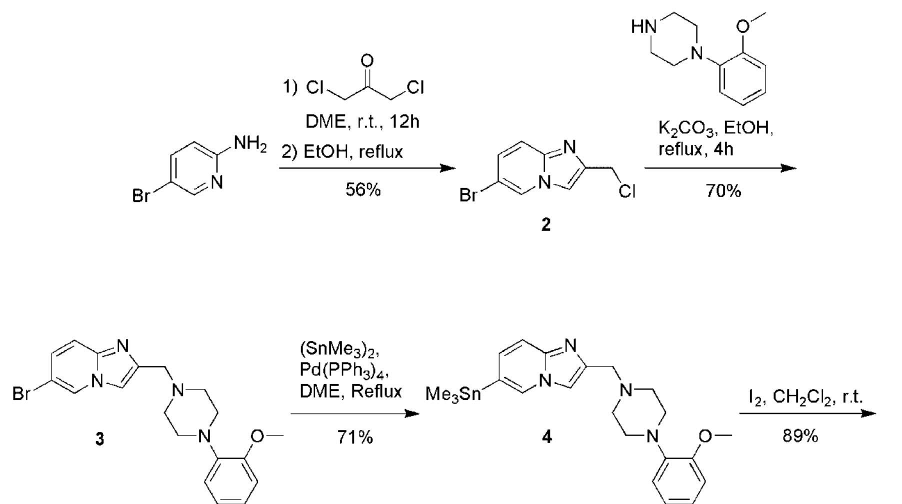
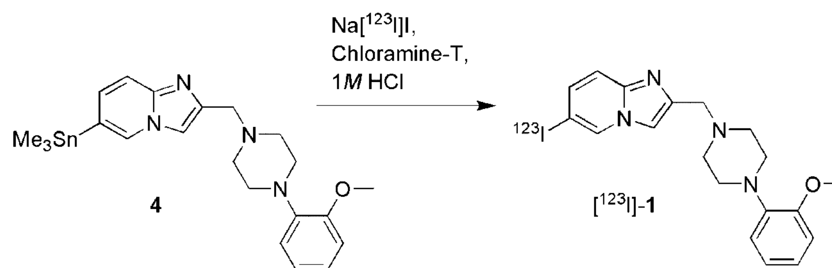


Scheme 1



Scheme 2

room temperature using Chloramine-T as the oxidizing agent in the presence of HCl. Purification by reverse-phase high-performance liquid chromatography (HPLC) with concomitant UV and radioactivity detection allowed identity confirmation of [^{123}I]-**1** by comparison to its corresponding unlabeled analog. [^{123}I]-**1** was obtained with a radiolabeling yield varying from 34 to 38% and was not optimized; the overall production yield averaged 27%. Radiochemical purity exceeded 99% with a specific activity above 185 GBq/μmol, based on the limits of detection of the HPLC UV detector. Partition coefficient of [^{123}I]-**1** was determined using the 'shake-flask' method[26] at pH = 7.4. The log $D_{7.4}$ of 2.31 was in the range of values that is considered acceptable for sufficient blood–brain barrier penetration.[26,27]

In vivo studies

The injection of 7.6 mCi of [^{123}I]-**1** through an intravenous perfusion 0.9% saline line resulted in no detectable activity in the brain during the 120-min scan acquisition. The overall low availability of [^{123}I]-**1** to the central nervous system may be attributable to the observed high degree of plasma protein binding (97.5%) and/or to Pgp efflux. As the stability of [^{123}I]-**1** was not assessed, a fast metabolic rate could also explain the absence of tracer in the brain.

Experimental

General

All chemicals and solvents were purchased from Sigma-Aldrich and were used without further purification. Organic reactions were monitored by thin layer chromatography with UV detection at 254 nm. Purification of non-radioactive products was achieved with flash column chromatography on silica gel (240–400 mesh) or neutral aluminum oxide (150 mesh). Solvent systems are indicated in the text. Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Bruker DPX 400 instrument with tetramethylsilane as internal standard. Yields refer to purified product and are not optimized. No-carrier-added Na[^{123}I]I was purchased from MDS-Nordion (BC, Canada).

Chemistry

6-Bromo-2-(chloromethyl)imidazo[1,2-a]pyridine (**2**)[23]

2-Amino-5-bromopyridine (1 g, 1 eq) and 1,3-dichloroacetone (734 mg, 1 eq) were dissolved in 3 mL of 1,2-dimethoxy ethane (DME), and the resulting solution was stirred for 12 h at room temperature. The formed white precipitate was filtered off, washed with 1 mL of DME, redissolved in 10 mL of EtOH, and refluxed for 2 h. The ethanol was evaporated, and the residue was dissolved in 10 mL of water followed by adjusting pH to 11 with NaOH. The resulting precipitate was extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated in vacuum, and purified by column chromatography on neutral aluminum oxide using CH_2Cl_2 as an eluent. The intended product was obtained in 56% (794 mg) yield as a white solid (m.p. = 125–127°C). NMR ^{1}H ($CDCl_3$), δ = 4.70 (s, 2H, CH_2); 7.18 (dd, 1H, J = 9.6; 2.0 Hz, CHAr); 7.40 (d, 1H, J = 9.6 Hz, CHAr); 7.54 (s, 1H, CHAr); 8.17 (d, 1H, J = 2.0 Hz, CHAr). NMR ^{13}C ($CDCl_3$), δ = 39.7 (1C, CH_2); 107.6 (1C, Cq), 111.4 (1C, CHAr); 118.5 (1C, CHAr); 126.1 (1C, CHAr); 129.0 (1C, CHAr); 144.0 (1C, Cq); 144.2 (1C, Cq).

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*6-Bromo-2-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]imidazo[1,2-a]pyridine (**3**)*[23]

To a solution of **2** (300 mg, 1 eq) in 2 mL of EtOH 1-(2-methoxyphenyl)piperazine (243 mg, 1 eq) and K_2CO_3 (163 mg, 1 eq) were successively added. The resulting mixture was stirred at reflux for 4 h before evaporation of the solvent. The residue was purified by chromatography on silica gel using a mixture of CH_2Cl_2 and Et_3N (99:1) as eluent. The title compound was obtained as a colorless oil in 70% (343 mg) yield. NMR ^1H ($CDCl_3$), $\delta = 2.63$ (bs, 4H, $2CH_2$); 2.98 (bs, 4H, $2CH_2$); 3.64 (s, 2H, CH_2); 3.68 (s, 3H, OCH_3); 6.69 (d, 1H, $J = 7.6$ Hz, CHAr); 6.75–6.85 (m, 3H, CHAr); 7.02 (dd, 1H, $J = 9.2$; 1.6 Hz, CHAr); 7.29 (d, 1H, $J = 9.2$ Hz, CHAr); 7.35 (s, 1H, CHAr); 8.04 (d, 1H, $J = 1.6$ Hz, CHAr). NMR ^{13}C ($CDCl_3$), $\delta = 50.8$ (2C, $2CH_2$); 53.7 (2C, $2CH_2$); 55.7 (1C, OCH_3); 56.8 (1C, CH2); 107.0 (1C, Cq); 111.5 (1C, CHAr); 111.8 (1C, CHAr); 118.3 (1C, CHAr); 118.5 (1C, CHAr); 121.3 (1C, CHAr); 123.2 (1C, CHAr); 125.9 (1C, CHAr); 127.9 (1C, CHAr); 141.6 (1C, Cq); 143.8 (1C, Cq); 144.8 (1C, Cq); 152.5 (1C, Cq).

*2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-6-trimethylstannylimidazo[1,2-a]pyridine (**4**)*

In 2 mL of degassed DME, **3** (260 mg, 1 eq), hexamethylditin (1.1 g, 5 eq), and $Pd(PPh_3)_4$ (74 mg, 0.1 eq) were dissolved successively. The resulting mixture was refluxed for 5 h before evaporation of the solvent under vacuum. The residue was purified by chromatography on silica gel using a mixture of CH_2Cl_2 and Et_3N (99:1) as eluent. The title compound was obtained as a colorless oil at 71% (223 mg) yield. NMR ^1H ($CDCl_3$), $\delta = 0.05$ (s, 9H, $3CH_3$); 2.49 (bs, 4H, $2CH_2$); 2.83 (4H, $2CH_2$); 3.50 (s, 2H, CH_2); 3.52 (s, 3H, OCH_3); 6.53 (d, 1H, $J = 8.0$ Hz, CHAr); 6.59–6.68 (m, 3H, CHAr); 7.15 (dd, 1H, $J = 8.0$; 1.5 Hz, CHAr); 7.25 (d, 1H, $J = 8.0$ Hz, CHAr); 7.37 (s, 1H, CHAr); 7.69 (d, 1H, $J = 1.5$ Hz, CHAr). NMR ^{13}C ($CDCl_3$), $\delta = -8.9$ (s, 3C, $3CH_3$); 50.9 (2C, $2CH_2$); 53.8 (2C, $2CH_2$); 55.6 (1C, OCH_3); 57.0 (1C, CH_2); 110.5 (1C, CHAr); 111.5 (1C, CHAr); 117.4 (1C, CHAr); 118.5 (1C, CHAr); 121.3 (1C, CHAr); 123.1 (1C, CHAr); 128.9 (1C, CHAr); 130.4 (1C, Cq); 132.4 (1C, CHAr); 141.8 (1C, Cq); 143.4 (1C, Cq); 145.3 (1C, Cq); 152.6 (1C, Cq).

*6-Iodo-2-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]imidazo[1,2-a]pyridine (**1**)*

To a solution of **4** (100 mg, 1 eq) in 5 mL of CH_2Cl_2 I_2 (58 mg, 1.1 eq) was added, and the resulting mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residue purified by chromatography on silica gel using a mixture of CH_2Cl_2 and Et_3N (99:1) as eluent. The target compound was obtained as a colorless oil in 89% (82 mg) yield . NMR ^1H ($CDCl_3$), $\delta = 2.71$ ((bs, 4H, $2CH_2$); 3.06 (bs, 4H, $2CH_2$); 3.71 (s, 2H, CH_2); 3.77 (s, 3H, OCH_3); 6.77 (d, 1H, $J = 8.0$ Hz, CHAr); 6.83–6.91 (m, 3H, CHAr); 7.20 (dd, 1H, $J = 9.0$; 2.0 Hz, CHAr); 7.28 (dd, 1H, $J = 9.0$; 2.0 Hz, CHAr); 7.42 (d, 1H, $J = 2.0$ Hz, CHAr); 8.24 (s, 1H, CHAr).

Radiochemistry

*6-[^{123}I]Iodo-2-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]imidazo[1,2-a]pyridine ([^{123}I]-**1**)*

To a 1 mL serum-stoppered cone V vial as provided by the vendor containing Na[^{123}I]I and NaOH, 1.0 M HCl (20 μL over the amount just enough to neutralize the NaOH), 50 μg of the trialkylstannyl precursor **4** in 50 μL of methanol, and 50 μL of chloramine-T trihydrate solution (1 mg/mL in water) were added. After standing for 15 min at room temperature, the reaction mixture was quenched with 100 μL of $Na_2S_2O_5/NaHCO_3$ solution (100 mg $Na_2S_2O_5$/mL $NaHCO_3$ sat.) and injected onto a reverse-phase HPLC column (Waters Nova-Pak C18, 4.6 × 250 mm) eluted with a mixture of acetonitrile–water–-triethylamine (40:60:0.2 v/v/v) at a flow rate of 1 mL/min. The fraction containing the target radiolabeled compound (15.5–17 min) was diluted to a volume of 10 mL with water, and the resulting solution was passed through a preconditioned solid-phase extraction cartridge (Waters Sep-Pak C18 Light). The cartridge was then rinsed with 4 mL of 25% ethanol. The product retained on the cartridge was eluted with 0.9 mL of 100% ethanol into a sterile vial through a 0.2 μm sterilizing filter (Pall, ♯4454). The formulation was finalized by the addition of 9 mL of sterile 0.9% NaCl for injection through the same filter. The radiolabeling yield varied from 34 to 38%, and the overall production yield averaged 27%. Radiochemical purity and chemical purity were assessed by HPLC in the same system, with sequential gamma and UV detection, compared with a standard of non-radioactive authentic **1**. The radiochemical purity exceeded 99% with a specific activity above 185 GBq/μmol. Quality control of the formulated product also included visual inspection, determination of specific concentration, pH, pyrogen content, and sterility. Sterility was confirmed by lack of growth in two media, fluid thioglycollate at 35°C and soybean-casein digest at 25°C for 2 weeks. Partition coefficient was determined using published methods.[26] Briefly, from stock solutions of 1-octanol and 0.02 M phosphate buffer (pH = 7.4) pre-saturated with each other, 2 mL of each was pipetted into a 12 mL test tube containing 10 μL of radiotracer. The test tube was stoppered, vigorously vortexed for 10 min, and centrifuged for 5 min at 4000 rpm. Aliquots (0.5 mL) of both organic and buffer layers were transferred into a pre-weighed test tube for counting. The amount of radioactivity in each tube was measured by γ counter and corrected for decay. Accurate volumes of each counted phase were determined by weight differences and known densities. The partition coefficient was calculated, and the reported value log $D_{7.4} = 2.31$ represents the mean of three measurements.

In vivo SPECT imaging

Baboon SPECT imaging was carried out as previously described[22] under institutional animal-care protocols complying with Federal regulations. A single female baboon (ovariectomized *Papio anubis*, 20 kg) was fasted for 18–24 h before the study. At 2 h before injection, the animal was anesthetized with intramuscular ketamine (10 mg/kg) and glycopyrrolate (0.01 mg/kg), transferred to the SPECT camera, and immediately intubated with an endotracheal tube for continued anesthesia with 2.5% isoflurane. The baboon's head was immobilized within the gantry with a 'bean bag' that hardens upon evacuation (Olympic Medical, Seattle, WA, USA). Body temperature was kept at 36.4 ± 0.3°C using a heated water blanket. Vital signs, including heart rate, respiration rate, oxygen saturation, and body temperature, were monitored every 15 min during the study. An intravenous perfusion line with 0.9% saline was placed and used for a single bolus injection of the radiolabeled compound [^{123}I]-**1**.

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SPECT data acquisition

SPECT data were acquired with a brain-dedicated multislice CERASPECT camera (Digital Scintigraphics, Waltham, MA, USA) with a resolution in all three axes of approximately 12 mm full-width half-maximum measured using an ^{123}I line source and a 20-cm water-filled cylindrical phantom. The distribution of radioactivity was assessed after administration of a single injected bolus of 7.6 mCi. Brain images ($128 \times 128 \times 64$ matrix, pixel size = 1.67×1.67 mm, slice thickness = 1.67 mm, voxel volume = 4.66 mm^3) were acquired at 159 keV in step-and-shoot mode at 15 min each, for a total of 120 min and eight acquisitions.

Conclusion

6-[^{123}I]Iodo-2-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]imidazo[1,2-*a*]pyridine **1** can be readily prepared from the corresponding trimethylstannyl precursor and commercially available sodium [^{123}I]iodide. The compound displays high binding affinity and selectivity for the D_4 dopamine receptor, adequate lipophilicity, and moderately elevated free parent fraction in blood plasma. However, *in vivo* evaluation of this radioligand showed no brain uptake in baboon (*P. anubis*) after i.v. injection. This outcome indicates that the studied compound is not suitable for imaging D_4 dopamine receptor *in vivo*.

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