Bioorganic & Medicinal Chemistry Letters 20 (2010) 2529–2532

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

[^{11}C]Dimebon, radiosynthesis and lipophilicity of a new potential PET agent for imaging of Alzheimer's disease and Huntington's disease

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ARTICLE INFO

Article history:
Received 11 February 2010
Revised 23 February 2010
Accepted 25 February 2010
Available online 3 March 2010

Keywords:
[^{11}C]Dimebon
Radiosynthesis
Lipophilicity
Positron emission tomography (PET)
Alzheimer's disease
Huntington's disease

ABSTRACT

[^{11}C]Dimebon (2-[^{11}C]methyl-8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole), a new potential PET agent for imaging of Alzheimer's disease and Huntington's disease, was prepared by N-[^{11}C]methylation of desmethyl-Domebon precursor with [^{11}C]CH_3OTf and purified with a semi-preparative HPLC method in 30–40% decay corrected radiochemical yield and 222–296 GBq/μmol specific activity at EOB. The measured lipophilicity coefficient (Log *P*) value of [^{11}C]Dimebon was 2.53.

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Dimebon (2,8-dimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole), as indicated in Figure 1, is an orally-available, small molecule antihistamine drug that has been developed and used in Russia since 1983.[1–7] This old drug has been recently proposed to be useful for treating different types of schizophrenia and various neurodegenerative disorders such as Alzheimer's disease (AD) and Huntington's disease (HD),[6–9] since Dimebon was discovered to inhibit enzymes butyrylcholinesterase (BChE) and acetylcholinesterase (AChE),[10] and mitochondrial permeability transition pore opening, to block the *N*-methyl-D-aspartate (NMDA) receptor signaling pathway, and to display neuroprotective effects in models for AD and HD.[8] Carbon-11-labeled Dimebon may serve as a new radioligand for the biomedical imaging technique positron emission tomography (PET), and enable non-invasive monitoring of enzyme such as BChE and AChE and receptor such as NMDA expression in AD and HD, and AD and HD response to Dimebon treatment using PET. To facilitate imaging AD and HD and monitoring the therapeutic efficacy of the drug Dimebon as a novel treatment for AD and HD, we have designed and synthesized [^{11}C]Dimebon (2-[^{11}C]methyl-8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole) (Fig. 1) as a new potential PET agent, for the first time.

The Dimebon standard compound (**7b**) and its desmethylated precursor desmathyl-Dimebon (8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole, **7a**) were prepared as outlined in Scheme 1 according to the published procedures with modifications.[2–5] 4-Methyl-*N*-(2-(6-methylpyridin-

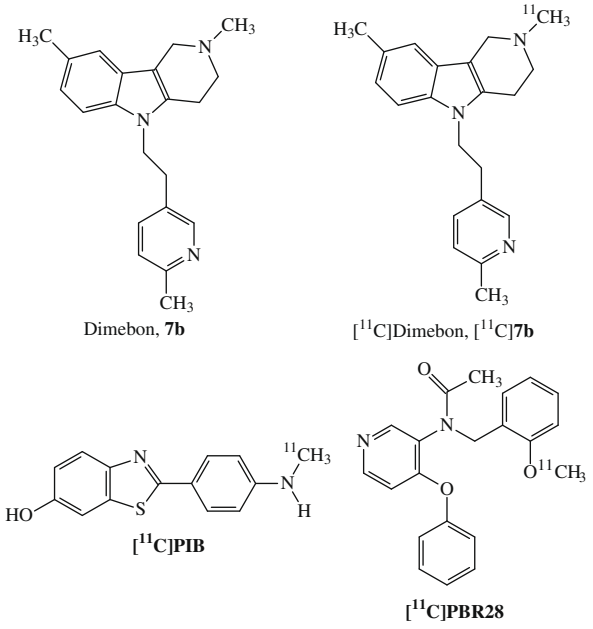

Figure 1. Chemical structures of Dimebon and [^{11}C]Dimebon, [^{11}C]PIB and [^{11}C]PBR28.

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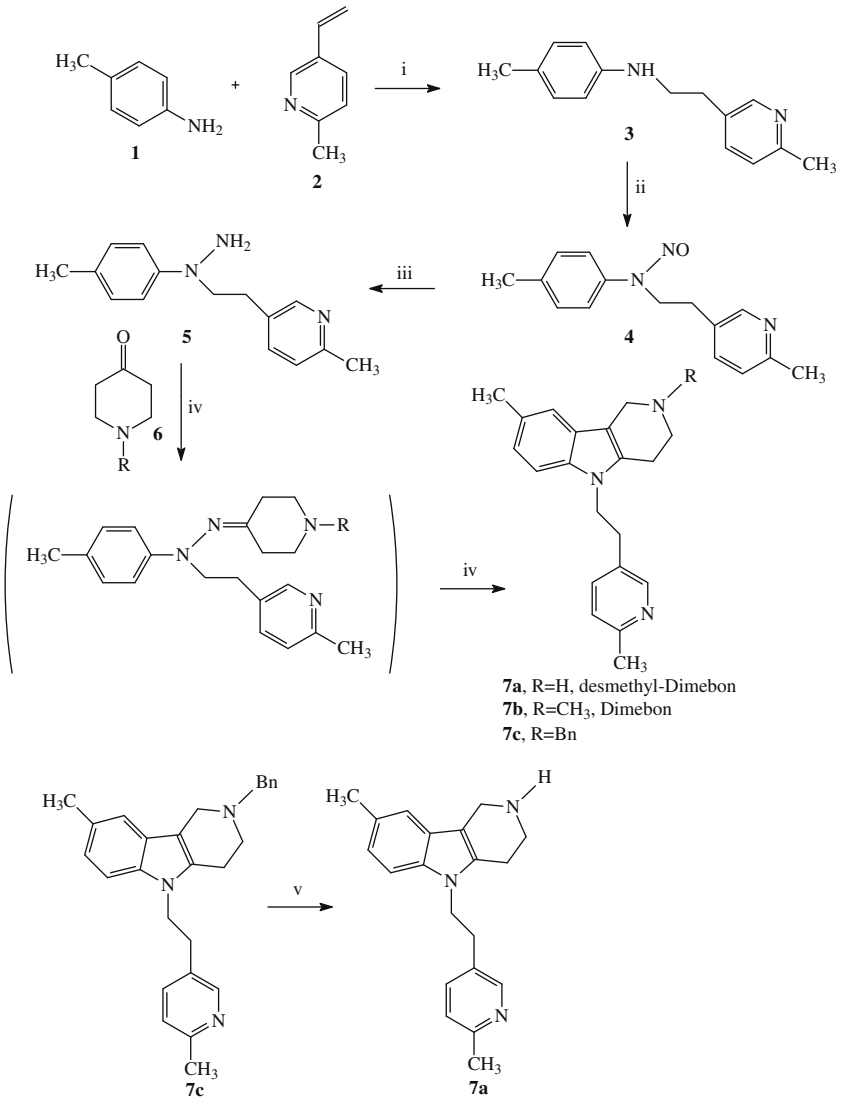
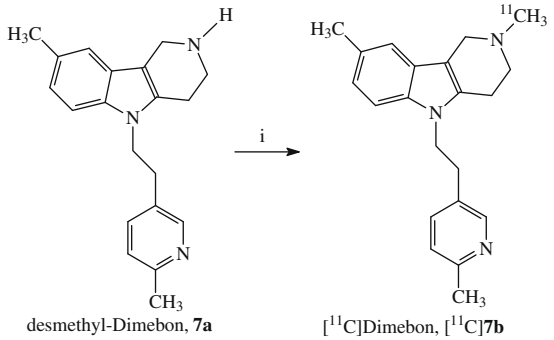
doi:10.1016/j.bmcl.2010.02.094



Scheme 1. Synthesis of desmethyl-Dimebon and Dimebon. Reagents, conditions, and yields: (i) Na, 100 °C, 78%; (ii) HCl, $NaNO_2$, 5 °C, 85%; (iii) $LiAlH_4$, THF, reflux, 73%; (iv) HAc, reflux, 61–70%; (v) Pd/C, HCO_2NH_4, MeOH, reflux, 80%.

3-yl)ethyl)aniline (**3**) was prepared by the condensation of two commercially available starting materials *p*-toluidine (**1**) and 2-methyl-5-vinylpyridine (**2**) under sodium catalysis in 78% yield. This reaction failed either under acidic catalyst or without catalyst. Nitration of compound **3** with hydrochloric acid and sodium nitrite under 5 °C easily provided *N*-(2-(6-methylpyridin-3-yl)ethyl)-*N*-(*p*-tolyl)nitrous amide (**4**) in 85% yield. Reduction of compound **4** with $LiAlH_4$ gave 2-methyl-5-(2-(1-(*p*-tolyl)hydrazinyl)ethyl)pyridine (**5**) in 73% yield. Several other reduction reagents were tested in this reaction, including Zn/HAc,[4] $NaBH_4$ and Pd/C–H_2. $NaBH_4$ and Pd/C–H_2 failed to produce compound **5**, and Zn/HAc[2] just produced compound **3** instead of compound **5**. Condensation and cyclization of compound **5** with various 1-substituted piperidin-4-one (**6**) was carried out at reflux temperature in 80% HAc to afford desmethyl-Dimebon precursor (**7a**), Dimebon (**7b**) and 2-benzyl-8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**7c**) in 61–70% yield. This was a one-pot two-step reaction. We used 80% HAc instead of benzene and HCl/EtOH in the literature procedure.[2] This modification significantly improved the work-up procedures. In order to obtain significant amount of precursor for radiolabeling, an alternate synthetic approach for desmethyl-Dimebon was developed as shown in Scheme 1. Debenzylation of compound **7c** with Pd/C and ammonium formate afforded **7a** in 80% yield.



Scheme 2. Synthesis of [^{11}C]Dimebon. Reagents, conditions, and yields: (i) NaH, [^{11}C]CH_3OTf, CH_3CN, 80 °C, 3 min, 30–40%.

Synthesis of the target tracer [^{11}C]Dimebon ([^{11}C]**7b**) is indicated in Scheme 2. Desmethyl-Dimebon (**7a**) was labeled using [^{11}C]methyl triflate ([^{11}C]CH_3OTf)[11,12] through N-[^{11}C]methyla-

tion[13] under basic conditions (NaH) and isolated by a semi-preparative HPLC method[14] to produce the corresponding pure radiolabeled compound [^{11}C]**7b** in 30–40% radiochemical yield, decay corrected to end of bombardment (EOB), based on [^{11}C]CO_2. The radiosynthesis was performed in an in-house automated multi-purpose ^{11}C-radiosynthesis module, allowing measurement of specific radioactivity during synthesis.[15,16] The overall synthesis, purification and formulation time was 25–30 min from EOB. The specific radioactivity was in a range of 222–296 GBq/μmol at EOB. Chemical purity and radiochemical purity were determined by analytical HPLC.[17] The chemical purity of the precursor and reference standard was >97%. The radiochemical purity of the target tracer was >99% determined by radio-HPLC through γ-ray (PIN diode) flow detector, and the chemical purity of the target tracer was >95% determined by reverse-phase HPLC through UV flow detector.

The measured HPLC lipophilicity coefficient (octanol–water partition coefficient, Log *P*) is an important parameter in selecting PET brain ligand candidates (small organic molecules) for further evaluations. The ability of a brain radioligand to penetrate the blood brain barrier (BBB) could be due, at least in part, to its lipophilicity, and thus we were interested in identifying an analogue that was significantly lipophilic brain tracer. We calculated Log *P* values of [^{11}C]Dimebon in comparison with two other brain imaging agents [^{11}C]PIB and [^{11}C]PBR28 (detecting AD amyloid plaques and translocator protein formerly known as the peripheral benzodiazepine receptor, respectively, in the living human brain, Fig. 1)[18–21] based on their retention times that were measured by C-18 HPLC method.[22–24] Briefly, the chromatographic capacity factors (k') were measured by reversed-phase HPLC. $k' = (t_R - t_{R0})/t_{R0}$, where t_R is the compound's retention time, and t_{R0} is retention of an unretained substance determined by injection of an aqueous solution of potassium nitrite (t_{R0} = 1.84 min). Log *P* measurement is based on the linear relationship, which has been established between the Log k' values of most compounds and their Log *P* values. Four compounds, benzyl alcohol (Log *P* 1.16), acetophenone (Log *P* 1.66), toluene (Log *P* 2.74) and naphthalene (Log *P* 3.37), were chosen as a 'standard' calibration mixture for the evaluation of the Log *P*'s of unknowns. Log *P*exp = partition coefficient calculated from k' value and calibration curve established by these four compounds. Calibration equation: Log *P* = 2.222 Log k' + 1.915. Retention times in the analytical HPLC system for [^{11}C]Dimebon, [^{11}C]PIB, and [^{11}C]PBR28 were 5.32, 4.97, and 4.35 min, respectively. The calculation results showed the Log *P* values for [^{11}C]Dimebon, [^{11}C]PIB, and [^{11}C]PBR28 were 2.53, 2.43, and 2.21, respectively. The Log *P* value of [^{11}C]Dimebon is higher than that of either [^{11}C]PIB or [^{11}C]PBR28. The results indicate [^{11}C]Dimebon is more lipophilic than both [^{11}C]PIB and [^{11}C]PBR28. The calculated Log *P* values from ChemDraw Ultra 9.0 (ChemOffice 2005) for Dimebon, PIB, and PBR28 are 3.48, 3.41, and 2.98, respectively. Obviously, the measured Log *P* data sequence of [^{11}C]Dimebon, [^{11}C]PIB, and [^{11}C]PBR28 is consistent with the calculated Log *P* data sequence of Dimebon, PIB, and PBR28. The data suggest [^{11}C]Dimebon has similar lipophilicity to [^{11}C]PIB. Therefore, we assume the tracer [^{11}C]Dimebon has suitable ability to pass the BBB, and is a promising candidate as potential brain imaging agent.

The evaluation of Dimebon in AD and HD represents new applications of a known drug. However, the synthetic information of Dimebon was limited in the literature. Thus, the experimental details and characterization data for compounds **3–5** and **7a–c** and for the tracer [^{11}C]**7b** are given.[25]

In conclusion, improved and efficient syntheses of Dimebon and its precursor desmethyl-Dimebon (new compound for carbon-11 labeling) have been developed. An automated multi-purpose ^{11}C-radiosynthesis module of our own design for fully automated synthesis of [^{11}C]Dimebon has been built, featuring the measurement of specific activity by the on-the-fly technique. Desmethyl-Dimebon was labeled with a reactive [^{11}C]methylating agent [^{11}C]CH_3OTf, and isolated by a semi-preparative HPLC purification procedure to provide [^{11}C]Dimebon in high radiochemical yields, short overall synthesis time, and good specific radioactivity. The Log *P* value of [^{11}C]Dimebon was calculated, and the data indicated [^{11}C]Dimebon has suitable lipophilicity as a candidate brain radioligand. These results facilitate the potential preclinical and clinical PET studies of [^{11}C]Dimebon in animals and humans.

Acknowledgments

This work was partially supported by the Indiana Genomics Initiative (INGEN) of Indiana University, which is supported in part by Lilly Endowment Inc. The authors would like to thank Dr. Bruce H. Mock and Barbara E. Glick-Wilson for their assistance in production of [^{11}C]CH_3OTf. ^{1}H NMR spectra were recorded on a Bruker Avance II 500 MHz NMR spectrometer in the Department of Chemistry and Chemical Biology at Indiana University Purdue University Indianapolis (IUPUI), which is supported by a NSF-MRI grant CHE-0619254. The referees' criticisms and editor's comments for the revision of the manuscript are greatly appreciated.

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25. (a) *General*: All commercial reagents and solvents from Sigma–Aldrich, Fisher Scientific and ChemPacific Corporation were used without further purification. [^{11}C]CH_3OTf was prepared according to a literature procedure.[12] Melting points were determined on a MEL-TEMP II capillary tube apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Varian Gemini 2000 200 MHz FT-NMR and Bruker Avance II 500 MHz NMR spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shift data for the proton resonances were reported in parts per million (ppm, δ scale) relative to internal standard TMS (δ 0.0), and coupling constants (*J*) were reported in hertz (Hz). Low resolution mass spectra (LRMS) were obtained using a Bruker Biflex III MALDI-Tof mass spectrometer, and high resolution mass spectra (HRMS) were obtained using a Thermo MAT 95XP-Trap spectrometer. Chromatographic solvent proportions are indicated as volume: volume ratio. Thin-layer chromatography (TLC) was run using Analtech silica gel GF uniplates (5 × 10 cm^2). Plates were visualized under UV light. Normal phase flash column

chromatography was carried out on EM Science Silica Gel 60 (230–400 mesh) with a forced flow of the indicated solvent system in the proportions described below. All moisture- and/or air-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Analytical HPLC was performed using a Prodigy (Phenomenex) 5 μm C-18 column, 4.6 × 250 mm; 3:1:4 CH_3CN:MeOH:20 mM, pH 6.7 phosphate (buffer solution) mobile phase; flow rate 1.5 mL/min; and UV (254 nm) and γ-ray (PIN diode) flow detectors. Semi-preparative HPLC was performed using a Prodigy (Phenomenex) 5 μm C-18 column, 10 × 250 mm; 3:1:4 CH_3CN:MeOH:20 mM, pH 6.7 phosphate (buffer solution) mobile phase; flow rate 5.0 mL/min; and UV (254 nm) and γ-ray (PIN diode) flow detectors. Sterile Millex-GS 0.22 μm vented filter unit was obtained from Millipore Corporation, Bedford, MA; (b) 4-Methyl-*N*-(2-(6-methylpyridin-3-yl)ethyl)aniline (**3**). To a stirred mixture of new distilled 2-methyl-5-vinylpyridine **2** (31.2 g, 262 mmol) and *p*-toluidine **1** (33.6 g, 314 mmol), small pieces of Na (0.90 g, 39.2 mmol) was added. Then the reaction mixture was heated to 100 °C for 7 h. After the reaction was cooled to room temperature, absolute EtOH (30 mL) was added followed by ice-water (60 mL). The mixture was extracted with ether (3 × 150 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed by distillation. The residue was purified by distillation in vacuum to obtain a white solid product **3** (55.0 g, 78%). R_f = 0.30 (MeOH/CH_2Cl_2 1:19); bp: 179–181 °C/3 Torr; mp: 64–65 °C; ^{1}H NMR ($CDCl_3$) δ: 2.17 (s, 1H, NH), 2.24 (s, 3H, CH_3), 2.53 (s, 1H, 3H, CH_3), 2.86 (t, J = 7.0 Hz, 2H, CH_2), 3.36 (t, J = 7.0 Hz, 2H, CH_2), 6.55 (d, J = 8.0 Hz, 2H, Ph–H), 6.98 (d, J = 8.0 Hz, 2H, Ph–H), 7.08 (d, J = 8.0 Hz, 1H, Py–H), 7.41 (dd, J = 2.0, 8.0 Hz, 1H, Py–H), 8.35 (d, J = 2.0 Hz, 1H, Py–H). MS (ESI): 227 ([M+H]$^+$, 100%); (c) *N*-(2-(6-Methylpyridin-3-yl)ethyl)-*N*-(*p*-tolyl)nitrous amide (**4**). To a solution of 1 N HCl (87 mL) and EtOH (96 mL) was added compound **3** (16.95 g, 75 mmol). The mixture was stirred at room temperature until complete solution was obtained, and cooled to 0 °C by ice bath. A solution of $NaNO_2$ (6.21 g, 90 mmol) in water (36 mL) was added dropwise with stirring while the temperature was kept under 5 °C. The reaction mixture was stirred under 5 °C for 2 h, and allowed to stir for another 3 h at room temperature. Then the mixture was again cooled to 0 °C for 1 h. The mixture was filtered. The filter solid was washed with cold water and allowed to dry on air for 36 h to give a yellow solid product **4** (16.3 g, 85%). R_f = 0.40 (MeOH/CH_2Cl_2 1:19); mp: 73–75 °C; ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, CH_3), 2.51 (s, 1H, 3H, CH_3), 2.80 (t, J = 8.0 Hz, 2H, CH_2), 4.20 (t, J = 8.0 Hz, 2H, CH_2), 7.07 (d, J = 7.5 Hz, 1H, Py–H), 7.25–7.43 (m, 4H, Ph–H), 7.41 (dd, J = 2.5, 7.5 Hz, 1H, Py–H), 8.28 (d, J = 2.5 Hz, 1H, Py–H). MS (ESI): 256 ([M+H]$^+$, 100%); (d) 2-Methyl-5-(2-(1-(*p*-tolyl)hydrazinyl)ethyl)pyridine (**5**). A solution of compound **4** (5.11 g, 20 mmol) in anhydrous THF (50 mL) was added to $LiAlH_4$ (1.52 g, 40 mmol) in anhydrous THF (100 mL), and the reaction mixture was refluxed for 3 h. The solvent was partially removed by distillation and excess $LiAlH_4$ was destroyed by the careful addition of ice-water. The mixture was filtered through Celite and washed with ether. The filtered solution was extracted with ether (3 × 100 mL), washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using eluent (MeOH/CH_2Cl_2 3%) to afford a brown liquid product **5** (3.51 g, 73%). R_f = 0.76 (MeOH/CH_2Cl_2 1:9); ^{1}H NMR ($CDCl_3$) δ: 2.11 (s, 3H, CH_3), 2.25 (s, 2H, NH_2), 2.52 (s, 1H, 3H, CH_3), 2.83 (t, J = 7.5 Hz, 2H, CH_2), 3.58 (t, J = 7.5 Hz, 2H, CH_2), 6.69 (d, J = 8.0 Hz, 2H, Ph–H), 7.02 (d, J = 8.0 Hz, 2H, Ph–H), 7.06 (d, J = 8.0 Hz, 1H, Py–H), 7.42 (dd, J = 2.0, 8.0 Hz, 1H, Py–H), 8.33 (d, J = 2.0 Hz, 1H, Py–H). MS (ESI): 242 ([M+H]$^+$, 100%); (e) General procedure for preparation of compounds **7a**–**c**. The mixture of 1-substituted piperidin-4-one **6** (2.0 mmol) and 30 mL of 80% HOAc (24 mL of HOAc and 6 mL of H_2O) was stirred at room temperature under N_2 for 2 h and heated to reflux for 2 h. Then the mixture was concentrated under reduced pressure, added 1 N NaOH to adjust pH to 9, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography using eluent (MeOH/CH_2Cl_2 3–20%) to give product **7a**–**c** (61–70%). 8-Methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**7a**, desmethyl-Dimebon). Yellow solid, mp: 93–95 °C; R_f = 0.18 (MeOH/CH_2Cl_2 1:4); ^{1}H NMR ($CDCl_3$) δ: 1.98 (s, 1H, NH), 2.31 (t, J = 6.0 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.96 (t, J = 7.0 Hz, 2H, CH_2), 3.08 (t, J = 6.0 Hz, 2H, CH_2), 4.01 (s, 2H, CH_2), 4.17 (t, J = 7.0 Hz, 2H, CH_2), 6.99–7.00 (m, 2H, Ar–H), 7.02 (dd, J = 2.0, 8.0 Hz, 1H, Ar–H), 7.17 (d, J = 8.0 Hz, 1H, Ar–H), 7.22 (s, 1H, Ar–H), 8.19 (s, 1H, Ar–H). MS (ESI): 306 ([M+H]$^+$, 100%). HRMS (CI), calcd for $C_{20}H_{23}N_3$ (M^+), 305.1886, found 305.1894; calcd for $C_{20}H_{24}N_3$ ([M+H]$^+$), 306.1965, found 306.1964. 2,8-Dimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**7b**, Dimebon). Yellow solid, mp: 115–116 °C; R_f = 0.34 (MeOH/CH_2Cl_2 1:4); ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, CH_3), 2.49 (m, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.71 (t, J = 5.5 Hz, 2H, CH_2), 2.95 (t, J = 7.0 Hz, 2H, CH_2), 3.64 (s, 2H, CH_2), 4.17 (t, J = 7.0 Hz, 2H, CH_2), 6.97–6.99 (m, 2H, Ar–H), 7.05 (dd, J = 2.0, 8.0 Hz, 1H, Ar–H), 7.13 (d, J = 8.0 Hz, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 8.23 (s, 1H, Ar–H). MS (ESI): 320 ([M+H]$^+$, 100%). HRMS (ESI), calcd for $C_{21}H_{26}N_3$ ([M+H]$^+$), 320.2127, found 320.2111. 2-Benzyl-8-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**7c**). Brown liquid, R_f = 0.69 (MeOH/CH_2Cl_2 1:4); ^{1}H NMR ($CDCl_3$) δ: 2.41 (t, J = 5.5 Hz, 2H, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.74 (t, J = 5.5 Hz, 2H, CH_2), 2.95 (t, J = 7.0 Hz, 2H, CH_2), 3.68 (s, 2H, CH_2), 3.73 (s, 2H, CH_2), 4.15 (t, J = 7.0 Hz, 2H, CH_2), 6.97–6.99 (m, 2H, Ar–H), 7.02 (dd, J = 2.0, 8.0 Hz, 1H, Ar–H), 7.14–7.16 (m, 2H, Ar–H), 7.25–7.28 (m, 1H, Ar–H), 7.31–7.34 (m, 2H, Ar–H), 7.37 (d, J = 7.0 Hz, 2H, Ph–H), 8.23 (d, J = 2.0 Hz, 1H, Py–H). MS (ESI): 396 ([M+H]$^+$, 100%); (f) Alternate synthetic procedure for compound **7a**. Compound **7c** (0.395 g, 1.0 mmol) was dissolved in MeOH (25 mL), Pd/C (10%, 90 mg) and dried HCO_2NH_4 (0.315 g, 5.0 mmol) were added. The resulting mixture was stirred and heated to reflux for 3 h. After additional amount of HCO_2NH_4 (0.189 g, 3.0 mmol) was added, the mixture was refluxed for another 2 h. Then the mixture was cooled down to room temperature, it was filtered through Celite. The solvent was removed, and the residue was purified by column chromatography using eluent (MeOH/CH_2Cl_2 5% to 20%) to afford product **7a** (0.245 g, 80%). The analytical data were obtained as same as above; (g) Production of the tracer [^{11}C]Dimebon ([^{11}C]**7b**). [^{11}C]CO_2 was produced by the ^{14}N(p,α)^{11}C nuclear reaction in small volume (9.5 cm^3) aluminum gas target (CTI) from 11 MeV proton cyclotron on research purity nitrogen (+1% O_2) in a Siemens radionuclide delivery system (Eclipse RDS-111). In a small reaction vial (5 mL), the precursor **7a** (0.3–0.5 mg) was dissolved in CH_3CN (300 μL). To this solution was added NaH (1 mg). No carrier-added (high specific activity) [^{11}C]CH_3OTf that was produced by the gas-phase production method[12] from [^{11}C]CO_2 through [^{11}C]CH_4 and [^{11}C]CH_3Br with silver triflate (AgOTf) column was passed into the reaction vial at room temperature, until radioactivity reached a maximum (~2 min), and then the reaction vial was isolated and reacted at 80 °C for 3 min. The contents of the reaction vial were diluted with $NaHCO_3$ (1 mL, 0.1 M), and injected onto the semi-preparative HPLC column with 2 mL injection loop for purification. The product fraction was collected, the solvent was removed by rotatory evaporation under vacuum, and the final product, [^{11}C]Dimebon ([^{11}C]**7b**), was formulated in saline, sterile-filtered through a sterile vented Millex-GS 0.22 μm cellulose acetate membrane, and collected into a sterile vial. Total radioactivity was assayed and total volume was noted for dose dispensing. The overall synthesis, purification and formulation time was 25–30 min from EOB. Retention times in the analytical HPLC were: t_R **7a** = 2.78 min, t_R **7b** = 5.32 min, t_R [^{11}C]**7b** = 5.32 min. Retention times in the semi-preparative HPLC were: t_R **7a** = 6.35 min, t_R **7b** = 8.67 min, t_R [^{11}C]**7b** = 8.67 min. The radiochemical yields were 30–40% decay corrected to EOB, based on [^{11}C]CO_2.