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Synthesis and in vivo evaluation of [*O*-methyl-^{11}C] *N*-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide as an imaging probe for 5-HT$_6$ receptors

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ABSTRACT

The serotonin receptor 6 (5-HT$_6$) is implicated in the pathophysiology of cognitive diseases, schizophrenia, anxiety and obesity and in vivo studies of this receptor would be of value for studying the pathophysiology of these disorders. Therefore, *N*-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide (SB399885), a selective and high affinity (pK_i = 9.11) 5-HT$_6$ antagonist, has been radiolabeled with carbon-11 by O-methylation of the corresponding desmethyl analogue with [^{11}C]MeOTf in order to determine the suitability of [^{11}C]SB399885 to quantify 5-HT$_6$R in living brain using PET. Desmethyl-SB399885 was prepared, starting from 1-(2-methoxyphenyl) piperazine hydrochloride, in excellent yield. The yield obtained for radiolabeling of [^{11}C]SB399885 was 30 ± 5% (EOS) and the total synthesis time was 30 min at EOB. PET studies with [^{11}C]SB399885 in baboon showed fast uptake followed by rapid clearance in the brain. Highest uptake of radioactivity of [^{11}C]SB399885 in baboon brain were found in temporal cortex, parahippocampal gyrus, pareital cortex, amygdala, and hippocampus. Poor brain entry and inconsistent brain uptake of [^{11}C]SB399885 compared to known 5-HT$_6$R distribution limits its usefulness for the in vivo quantification of 5-HT$_6$R with PET.

1. Introduction

The 5-hydroxytryptamine 6 receptor (5-HT$_6$R) is the most recently identified mammalian 5-hydroxytryptamine (5-HT) receptor.[1–3] In the central nervous system (CNS), an important role of the 5-HT$_6$R has been confirmed in cognitive functions, seizures, feeding behavior, anxiety, epilepsy, dementia psychosis, addiction and affective disorder.[4–11] In vitro studies using 5-HT$_6$R antagonists revealed that 5-HT$_6$R are localized almost exclusively in the CNS.[12] Several human postmortem studies demonstrated that the distribution of 5-HT$_6$R appear to be similar to that in rats, with the highest 5-HT$_6$R densities found in the striatum, nucleus accumbens and olfactory tubercle, moderate densities in the amygdala, hypothalamus, thalamus, hippocampus and cerebral cortex, but none have been detected in the periphery.[13–15]

In vivo imaging of 5-HT$_6$R with positron emission tomography (PET) may facilitate the understanding of the pathophysiology of diseases associated with the changes in this receptor and allow occupancy studies to assist new drug development. However, the utility of the currently developed radiotracers for in vivo imaging of 5-HT$_6$R are limited in scope. The [^{18}F]-labeled 5-HT$_6$ ligand [^{18}F]12ST05 did not reveal any specific binding to the 5-HT$_6$R in the rats and cat, although the radioligand showed excellent brain penetration.[16] [^{11}C]GSK224558, an undisclosed Glaxo Smithkline's compound rapidly enters the porcine brain, but undergoes rapid metabolism with peak regional tissue concentrations reached at approximately 20 min post-injection. The research group at Glaxo Smithkline also reported the synthesis and evaluation of a new

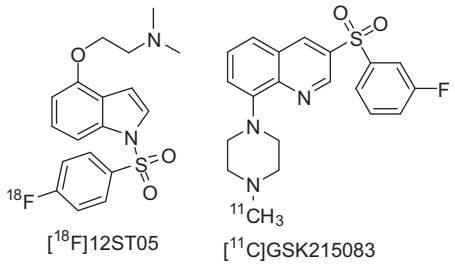

Figure 1. 5-HT$_6$ PET tracers available in literature.

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generation of 5-HT_6R antagonists based on the 3-benzenesulfonyl-8-piperazine-1-yl-quinoline scaffold namely [^{11}C]GSK215083.[17,18] [^{11}C]GSK215083 (Fig. 1), is currently evaluated in human and demonstrated uptake and retention in the human brain, and the highest BP was observed in caudate and putamen followed by the frontal cortex. However, treatment with selective 5-HT_{2A} antagonist ketanserin decreased 90% of specific binding of [^{11}C]GSK215083 in cortical regions thereby demonstrating non-specific binding.[19,20]

SB399885, (*N*-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide), is a brain-penetrating, potent and selective 5-HT_6R antagonist (pK_i = 9.11). SB399885 also possesses excellent selectivity (>200-fold) over 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_4, 5-HT_7, α_{1B}, D_2, D_3 and D_4 receptors as well as ion channels and enzymes.[21–23] In addition the lipophilicity of SB399885 was adequate for BBB penetration. The attractive affinity, selectivity and moderate lipophilicity (Clog*P* value 3.5 ± 0.68 measured with *ACD* log $_P$DB program) and the presence of C-11 labeling site prompted us to develop [^{11}C]SB399885 as a PET tracer for 5-HT_6R. Herein, we describe preparation of the desmethyl precursor, radiosynthesis of [^{11}C]SB399885 and its in vivo evaluation in non-human primate with PET.

2. Results

2.1. Chemistry and radiochemistry

The precursor phenolic alcohol **5** was synthesized from commercially available 1-(2-methoxyphenyl)piperazine hydrochloride in four steps (Scheme 1).

Protection of piperazine moiety by trichloroacetyl chloride in the presence of diisopropylethylamine provided 1-(2-methoxyphenyl)-4-trichloroacetylpiperazin **2** in 87% yields. The crude product was treated with excess of chlorosulfonic acid to give the key intermediate 3-(4-trichloroacetylpiperazin-1-yl)-4-methoxybenzenesulfonyl chloride (**3**) in 77% overall yield. Coupling of compound **3** with 2-amino-4,6-dichlorophenol in the presence of pyridine afforded the corresponding trichloroacetylsulfonamide **4**. Removal of the protecting group under basic condition gave the final compound, desmethyl SB399885 precursor **5**, *N*-(3,5-dichloro-2-hydroxyphenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide. The synthesis of [^{11}C]SB399885 was achieved by *O*-alkylation of the normethyl moiety of the precursor using [^{11}C]MeOTf in acetone at room temperature for 5 min (Scheme 2). The radiolabeled product was separated from the reaction mixture by reverse phase high performance liquid chromatography (RP-HPLC) giving an average radiochemical yield of 30 ± 5% (EOS, n = 4). The chemical identity of [^{11}C]SB399885 was confirmed by co-injection with a sample of standard SB399885 on analytical RP-HPLC. Chemical and radiochemical purities of [^{11}C]SB399885 were found to be >95% with a specific activity 2500 ± 500 Ci/mmol (EOS, n = 4). Average time required for the [^{11}C]-labeling was 30 min.

2.2. Determination of unchanged radioligand in plasma

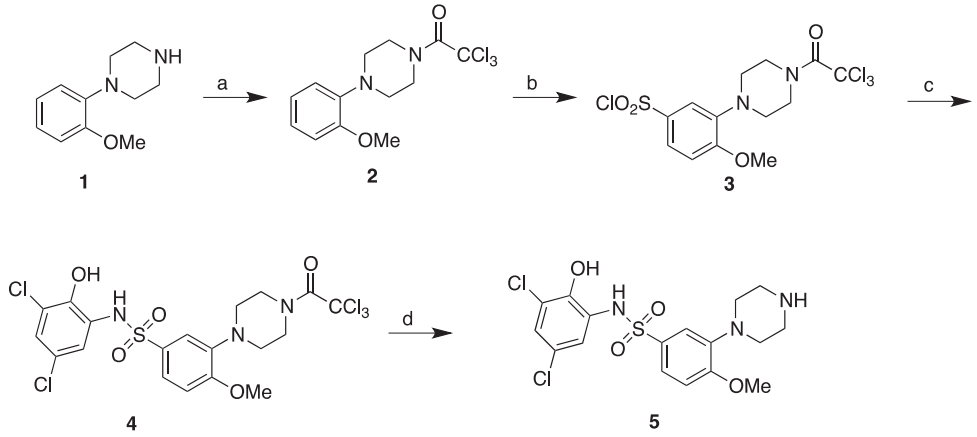
Figure 2 shows the time course of the unmetabolized fraction of [^{11}C]SB399885 in baboon plasma. Only polar metabolites were observed and the fraction of unmetabolized [^{11}C]SB399885 was 99% at 2 min, 94% at 4 min, 71% at 12 min, 45% at 30 min, 32% at 60 min and 27% at 90 min. The [^{11}C]SB399885 exhibits 1% and 5% free fraction (fp or unbound radiotracer) in human and baboon plasma respectively.

2.3. PET imaging studies with [^{11}C]SB399885 in baboon

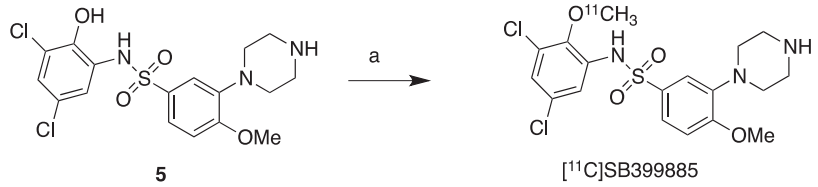
PET images in baboon show that [^{11}C]SB399885 enter the BBB and the radioactivity is not retained in brain. The time activity curves (TACs) demonstrate the higher uptake of radioactivity is found in temporal cortex, parahippocampal gyrus, pareital cortex, amygdala, and hippocampus, whereas, prefrontal cortex, anterior cingulate, striatum and cerebellum shows lower uptake of radioactivity (Fig .3).

3. Discussion

The affinity (pK_i = 9.11) and selectivity of SB399885 for 5HT_6R makes [^{11}C]SB399885 promising candidate as a PET tracer. The presence of an aromatic methoxy function gives easy access to [^{11}C]-methylation of the corresponding desmethyl compound with [^{11}C]CH_3I or [^{11}C]CH_3OTf. The optimum reaction condition for [^{11}C]-labeling was found to be [^{11}C]MeOTf in acetone containing precursor and aqueous NaOH, providing [^{11}C]SB399885 in high yield and specific activity suitable for imaging studies. The lipophilicity value of 3.5 ± 0.5, measured in terms of log $P_{o/w}$, is favourable for BBB penetration of [^{11}C]SB399885. Radiolabeled metabolites found in baboon during the time of PET scanning elutes before the parent compound on a reverse phase HPLC column, indicating higher polarity than [^{11}C]SB399885. These metabolites are unlikely to cross the BBB because of their high polarity and hence the image obtained could be attributed to the parent



Scheme 1. Synthesis of **5.** Reagents and conditions: (a) CCl_3COCl, CH_2Cl_2, rt, 4 h: 87%; (b) $ClSO_2OH$, CH_2Cl_2, rt, 1 h: 77.5%; (c) 2-amino-4,6-dichlorophenol, CH_2Cl_2, pyridine, 0 °C, overnight: 96%; (d) KOH, THF, reflux, 20 h, 74%.



5 [11C]SB399885

Scheme 2. Radiosynthesis of [11C]SB399885. Reagents and conditions: (a) [11C]CH_3OTf, NaOH, acetone, rt, 5 min.

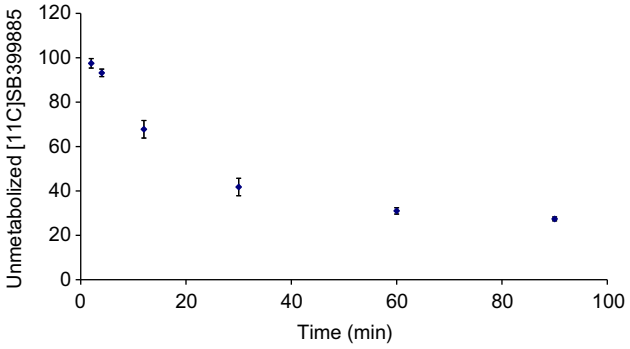


Figure 2. Unmetabolized parent fraction of [11C]SB399885 in baboon plasma.

[11C]SB399885. The distribution of [11C]SB399885 binding in the baboon did not correspond to distribution of 5-HT_6R reported for rats and human in which striatum, shows higher binding whereas cortical regions, amygdala, thalamus and hippocampus shows moderate binding.[28,29] Highest uptake of radioactivity of [11C]SB399885 in baboon were found in temporal cortex, parahippocampal gyrus, pareital cortex, amygdala, and hippocampus. The reason for the discrepancies of [11C]SB399885 binding regions in baboon is not clear and may be attributed to a species difference or the ligand can be a P-glycoprotein substrate which prevent the brain uptake of the radioligand. The poor brain accumulation of [11C]SB399885 and the lack of selectivity to ROI in brain limits the potential of [11C]SB399885 as an in vivo imaging agent to quantify 5-HT_6R. However, a structure–activity relationship study of SB399885 may provide a better PET ligand with in vivo kinetics that permit valid and reliable measurement of 5-HT_6R binding.

4. Materials and methods

4.1. General

The commercial chemicals and solvents used in the synthesis were purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO), Fisher Scientific Inc. (Springfield, NJ), or Lancaster (Windham, NH) and were used without further purification. Analytical grade reagents were purchased from standard commercial sources. ^{1}H NMR spectra were recorded on a Bruker PPX 300 and 400 MHz spectrometer. Spectra were recorded in $CDCl_3$ or CD_3OD and chemical shifts and reported in ppm relative to TMS as internal standard. The mass spectra were recorded on JKS-HX 11UHF/HX110 HF Tandem Mass Spectrometer in the FAB+ mode. Thin layer chromatography (TLC) was performed using Silica gel 60 F254 plates from E Merck. HPLC analyses were performed using a Waters 1525 binary HPLC system (analytical: Phenomenex, Prodigy ODS 4.6 × 250 mm, 5 μm column; semipreparative: Phenomenex, Prodigy ODS(3) 10 × 250 mm, 10 μm column). Flash column chromatography was performed on Silica gel (Fisher 200–400 mesh) using the solvent system indicated. [11C]carbon dioxide was produced from an RDS112 cyclotron (Siemens, Knoxville, TN) and [11C]Methyl iodide was synthesized using the reaction of [11C]CO_2 with lithium aluminum hydride, followed by hydroiodic acid and was then converted to [11C]methyl triflate at 200 °C by passing through a glass column impregnated with silver triflate.[24] For detection of radiolabeled [11C]SB399885, gamma ray detector (Bioscan Flow-Count fitted with a NaI detector) was used in series with the UV detector (Waters Model 996 set at 254 nm). Data acquisition for both the analytical and preparative systems was accomplished using a Waters Empower Chromatography System.

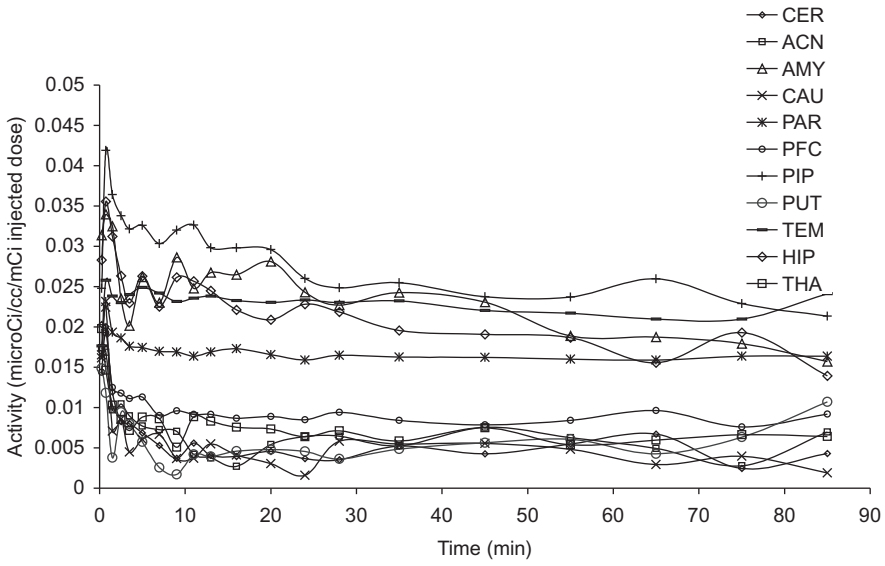


Figure 3. Time activity curves of [11C]SB399885 in baboon. AMY = Amygdala; ACN = Anterior cingulate, CAU = Caudate; CER = Cerebellum; HIP = Hippocampus; PAR = Parietal cortex; PFC = Prefrontal cortex, PIP = Parahippocampal gyrus; PUT = Puteman; TEM = Temporal cortex; THA = Thalamus.

PET studies were performed in baboon with an ECAT EXACT HR+ scanner (Siemens, Knoxville, TN). All animal experiments were carried out with the approval of the Institutional Animal Care and Use Committee of Columbia University Medical Center and New York State Psychiatric Institute. Metabolite analyses were performed using Phenomenex Prodigy column (ODS3, 4.6 × 250 mm, 10 μm. The free fractions and metabolites were measured using Packard Instruments Gamma Counter (Model E5005, Downers Grove, IL).

4.2. Synthesis

Synthesis of desmethyl-SB399885 (**5**) was based on a published procedure with few modifications.[25]

4.2.1. 1-(2-Methoxyphenyl)-4-trichloroacetylpiperazin (2)

A solution of trichloroacetyl chloride (0.5 ml, 4.46 mmol) in anhydrous dichloromethane (5 ml) was added over 10 min to a stirred solution of 1-(2-methoxyphenyl) piperazine hydrochloride (**1**) (1.00 g, 4.37 mmol) in anhydrous dichloromethane (5 ml) in the presence of diisopropylethylamine (1.6 ml, 8.92 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 4 h at room temperature under N_2. Then the reaction was quenched with water (5 ml) and extracted with CH_2Cl_2. The combined organic layers were washed with water (3 × 15 ml) and brine (10 ml), and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (**2**) as light brown oil (1.28 g, 87%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.09–7.06 (1H, m), 6.96–6.90 (m, 3H) 4.13 (3H, m), 3.89 (s, 3H), 3.19–3.18 (4H, m), 1.32–1.26 (1H m). HRMS calculated (FAB+): $C_{13}H_{15}Cl_3N_2O_2$, 336.0199: Observed, 336.0188.

4.2.2. 3-(4-Trichloroacetylpiperazin-1-yl)-4-methoxybenzenesulfonyl chloride (3)

A solution of 1-(2-methoxyphenyl)-4-trichloroacetylpiperazine (2) (1.00 g, 2.96 mmol) in anhydrous dichloromethane (7 ml) was added over 30 min to ice-cooled chlorosufonic acid (6 ml, mmol). After stirring for 0.5 h at 0 °C, the reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. Then the reaction mixture was poured into a mixture of ice-water (20 ml) and dichloromethane (20 ml) with rapid stirring. The layers were separated and the organic phase was washed with water (4 × 15 ml) and brine (10 ml), and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (**3**) as viscous oil (1.03 g, 77.5%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.80–7.76 (1H, m), 7.50–7.49 (m, 1H), 7.06–7.02 (m, 1H), 4.04 (4H, m), 4.02 (s, 3H), 3.25–3.22 (4H, m). HRMS calculated (FAB+): $C_{13}H_{14}Cl_4N_2O_4S$, 433.9428, Observed, 433.9431.

4.2.3. *N*-(3,5-Dichloro-2-hydroxyphenyl)-4-methoxy-3-[4-(2,2,2-trichloro-ethanoyl)-piperain-1-yl]-benzenesulfonmide (4)

A solution of 3-(4-trichloroacetylpiperazin-1-yl)-4-methoxybenzenesulfonyl chloride (**3**) (512 mg, 1.17 mmol) in dry dichloromethane (15 ml) was added dropwise to a mixture of 2-amino-4,6-dichlorophenol (276 mg, 1.55 mmol) in dry dichloromethane (5 ml) and dry pyridine (0.1 ml) at 0 °C under nitrogen atmosphere. After stirring overnight at room temperature, the reaction mixture was washed with 1 M hydrochloric acid (2 ml), water (2 × 15 ml) and brine 10 (ml), and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the product was purified by silica gel column chromatography using 1% methanol in methylene chloride as eluent to afford the compound (**4**) as a brown solid (655 mg, 96%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.82–7.78 (1H, m), 7.59–7.55 (1H, d, *J* = 5.6), 7.43 (2H, m), 7.06 (1H, m), 6.94–6.90 (1H, d, J=), 5.32 (1H, s), 4.04–4.02 (4H, m), 3.94 (s, 3H), 3.11 (4H, m). HRMS calculated (FAB+): $C_{19}H_{18}Cl_5N_3O_5S$, 574.9410, Observed, 574.9400

4.2.4. N-(3,5-Dichloro-2-hydroxyphenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide (5)

A 1 M solution of potassium hydroxide (0.6 ml) was added over 5 min to a rapidly stirred solution of N-(3,5-Dichloro-2-hydroxyphenyl)-4-methoxy-3-[4-(2,2,2-trichloro-ethanoyl)-piperain-1-yl]-benzenesulfonmide (**4**) (100 mg) in tetrahydrofuran (15 mL) at room temperature. After stirring for 20 h, the stirred, ice-cooled mixture was adjusted to pH 7.0 by the addition of concentrated hydrochloric acid to afford the title compound (**5**) as a light brown solid which was extracted with dichloromethane (2 X 10 ml) and washed with water (10 ml), brine (10 ml) and dried (62 mg, 74%).

^{1}HNMR ($CDCl_3$, 400 MHz): 7.48–7.38 (2H, m), 7.25–7.23 (m, 1H), 7.18 (m,1H), 6.97–6.95 (m, 1H), 6.85–6.77 (1H, d, *J* =), 5.27 (m,1H), 3.97–3.86 (m, 4H), 3.83 (3H, s), 3.12–3.02 (m,4H), 1.80 (1H,s). HRMS calculated (FAB+): $C_{17}H_{20}O_4N_3Cl_2S$, 432.0552, Observed, 432.0556.

4.3. Radiosynthesis of [*O*-methyl-^{11}C]-*N*-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl) benzenesulfonamide([^{11}C]SB399885)

The precursor desmethyl-SB399885 (**5**) (0.5–1.0 mg) was dissolved in 400 μl of acetone in a capped 1-ml V-vial. NaOH (8 μl, 5 N) was added and the resultant solution was allowed to stand for 1 min. [^{11}C]CH_3OTf was transported by a stream of argon (20–30 ml/min) into the vial over approximately 5 min at room temperature. At the end of the trapping, the product mixture was diluted with 0.5 ml of deionized water and directly injected onto a semipreparative RP-HPLC (Phenomenex, prodigy C18, 10 × 250 mm, 10 μm), and eluted under isocratic conditions with a mobile phase composed of acetonitrile/0.1 M AMF ammonium formate buffer 30:70 (v/v) at a flow rate of 10 mL/min. The product fraction with a retention time of 6–7 min based on a gamma detector was collected, diluted with 100 ml of deionized water, and passed through a classic C-18 Sep-Pak ® cartridge, and washed with 10 ml water. The yield of formation of [^{11}C]SB399885 is typically in the range of 100–200 mCi (30% yield, based on [^{11}C]CH_3OTf at end of synthesis (EOS)). The product fraction was reconstituted with 1 ml of absolute ethanol and 9 ml of sterile saline. The saline solution of [^{11}C]SB399885 was passed through a sterile 0.22 μm membrane filter into a vented sterile, pyrogen-free bottle. Aliquots of the formulated solution was analyzed by analytical HPLC column using UV and gamma detectors (Phenomenex C18, Prodigy ODS3, 4.6 × 250 mm, 5 μm; mobile phase: acetonitrile/0.1 M AMF, 35/65 (v/v), flow rate: 2 ml/min, retention time: 8.1 min) to determine the specific activity and chemical and radiochemical purity.

4.4. Partition coefficient measurement

Partition coefficient (log $P_{o/w}$) of [^{11}C]SB399885 was measured by mixing 0.1 mL of the radioligand formulation with 5 gram each of 1-octanol and freshly prepared PBS buffer (pH 7.4) in a culture tube.[26] The culture tube was shaken mechanically for 5 min followed by centrifugation for 5 min. Radioactivity per 0.5 g each of 1-octanol and aqueous layer was measured using a well counter. The partition coefficient was determined by calculating the ratio of counts/g of 1-octanol to that of buffer. 1-Octanol fractions were repeatedly portioned with fresh buffer to get consistent values for partition coefficient. All the experimental measurements were performed in triplicate.

4.5. PET studies in baboons

PET studies were performed according to a protocol approved by the Institutional Animal Care and Use Committee of Columbia University Medical Center and New York State Psychiatric Institute.

4.5.1. General imaging procedure

PET scans were performed in two male baboons with an ECAT EXACT HR+ scanner (CPS/Knoxville, TN). The fasted animal was immobilized with ketamine (10 mg/kg, im) and anesthetized with 1.5–2.0% isoflurane via an endotracheal tube. Core temperature was kept constant at 37 °C with a heated water blanket. An intravenous infusion line with 0.9% NaCl was maintained during the experiment and used for hydration and radiotracer injection. An arterial line was placed for obtaining arterial samples for the input function. The head was positioned at centre of the field of view, and a 10 min transmission scan was performed before the tracer injection. For each scan, 5 ± 1 mCi (S.A. of 2300 ± 250 Ci/mmol) of [^{11}C]SB399885 was injected as an iv bolus and emission data were collected for 90 min in 3-D mode. Plasma samples were taken every 10 s for the first 2 min, using an automatic system, and thereafter manually for a total of 30 samples over 90 min.

4.5.2. Protein binding and metabolite analyses

The protein binding of [^{11}C]SB399885 in baboon blood samples were determined as described elsewhere.[27] The percentage of radioactivity in plasma as unchanged [^{11}C]SB399885 was determined by HPLC. The HPLC system consisted of a pump (Renin), and an injector equipped with a sensitive γ-detector. The injection volume loaded on the HPLC column was 10–1000 μl. Blood samples were taken at 2, 6, 12, 30, 60, and 90 min after radioactivity injection for metabolite analysis. The supernatant liquid obtained after centrifugation of the blood sample at 2,000 rpm for 1 min was transferred (0.5 ml) into a tube and mixed with acetonitrile (0.7 ml). The resulting mixture was vortexed for 10 s, and centrifuged at 14,000 rpm for 4 min. The supernatant liquid (1 ml) was removed and the radioactivity was measured in a well-counter and the majority (0.8 ml) was subsequently injected onto the HPLC column [column: Phenomenex, Prodigy ODS (3) 4.6 × 250 mm, 10 μm; mobile phase: acetonitrile/0.1 M AMF, 35:65 (v/v), flow rate: 2 ml/min, retention time: 6 min] connected to a Waters guard column (Resolve™ 10 μm, 90 Å) equipped with a radioactivity detector. The metabolite and free fractions were collected using a Bioscan gamma detector. All the acquired data were then subjected to correction for background radioactivity and physical decay to calculate the percentage of the parent compound in the plasma at different time points. In order to reaffirm that the retention time of the parent had not shifted during the course of the metabolite analysis, a quality control sample of [^{11}C]SB399885 was injected at the beginning and the end of the study. The percentage of radioactive parent obtained was used for the measurement of metabolite-corrected arterial input functions.

5. Conclusion

The radiosynthesis of [^{11}C]SB399885, a 5-HT$_6$R antagonist has been achieved. Total time required for the synthesis of [^{11}C]SB399885 is 30 min from EOB using [^{11}C]MeOTf in acetone, with a 30% yield at EOS with excellent chemical and radiochemical purities and high specific activity. PET studies of [^{11}C]SB399885 in anesthetized baboon showed that the tracer penetrates the BBB and the influx into brain was high for the first few minutes, but radioactivity then declined rapidly. The distribution of [^{11}C]SB399885 was also found to be not identical to 5-HT$_6$R distribution reported for rat and human. This suggests that [^{11}C]SB399885 is not a useful PET tracer for imaging 5-HT$_6$R in baboon. However, structure activity relationship study of [^{11}C]SB399885 may provide ligands for identifying the optimal PET tracer for imaging 5HT$_6$R.

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