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Synthesis and Evaluation of Pyridyloxypyridyl Indole Carboxamides as Potential PET Imaging Agents for 5-HT_{2C} Receptors

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Keywords: 5-HT_{2C} receptor, carbon-11 radiolabelling, PET ligands, non-human primate imaging

ABSTRACT: Nine pyridyloxypyridyl indole carboxamides were synthesized and displayed high affinities for 5-HT_{2C} receptors and high selectivity over 5-HT_{2A} and 5-HT_{2B}. Among them, 6-methyl-*N*-[6-[(2-methyl-3-pyridinyl)oxy]-3-pyridinyl]1*H*-indole-3-carboxamide (**8**) exhibits the highest 5-HT_{2C} binding affinity (Ki=1.3 nM) and high selectivity over 5-HT_{2A} (~1000 times) and 5-HT_{2B} (~140 times). [^{11}C]**8** was synthesized by palladium-catalyzed coupling reaction between pinacolboranate **16** and [^{11}C]CH_3I with an average radiochemical yield of 27 ± 4% (n = 8, decay-corrected from end of [^{11}C]CH_3I synthesis). MicroPET imaging studies in rhesus monkeys showed regional uptake of [^{11}C]**8** in the choroid plexus, whereas the bindings in all other brain regions were low. The specific binding in the choroid plexus was confirmed by administration of a blocking dose of 0.1mg/kg of the 5-HT_{2C} antagonist SB-242084.

The 5-HT_{2C} receptor (5-HT_{2C}R), a G protein-coupled receptor expressed by GABAergic, glutamatergic, and dopaminergic neurons, is one of the three closely related serotonin receptor subtypes (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}) in the 5-HT_2 receptor family and expressed in high abundance throughout the mammalian CNS. The choroid plexus, which is named as the recognition site for 5-HT_{2C}R, has the highest density of 5-HT_{2C}R. Other brain regions that moderately express 5-HT_{2C}R include frontal cortex, basal ganglia, hippocampus, amygdala, and hypothalamus, whereas lower density of 5-HT_{2C}R is identified in the cerebellum.[1-5] With the availability of selective agonists and antagonists, 5-HT_{2C}R has been indicated as a novel pharmacotherapeutic target for the treatment of depression, schizophrenia, anxiety, drug abuse, obesity, and Parkinson's disease.[6-10] For example, 5-HT_{2C}R-selective antagonists have demonstrated to produce antipsychotic-like effects and enhance the antidepressant-like behavioral efficacy of selective serotonin reuptake inhibitors in rodent studies. Moreover, a recent study demonstrated that pretreatment with a 5-HT_{2C}R-selective agonist reduced the abuse-related effects of cocaine in nonhuman primates.[11] Indeed, lorcaserin, a selective 5-HT_{2C}R agonist, was approved by the FDA in June 2012 for use in the treatment of obesity.

Although the involvement of the 5-HT_{2C}R in the pathophysiology of neuropsychiatric disorders has long been recognized, many results were obtained from animal models, postmortem tissues and molecular neuroscience studies. A direct relationship between 5-HT_{2C}R physiology and brain diseases has proven difficult to establish due to an inability to accurately quantify 5-HT_{2C}R density and functional status in vivo. Therefore, development of a selective radioligand that will enable in vivo imaging and quantification of 5-HT_{2C}R densities represents a significant technological advancement in understanding both the normal function and pathophysiology of the 5-HT_{2C}R. Furthermore, by enabling functional imaging studies to determine dose-receptor occupancy, its application will provide an excellent tool to facilitate the discovery of therapeutic agents targeting 5-HT_{2C}R.

Over the past decade, significant progress has been made in the quantitative mapping serotonin receptors using noninvasive imaging.[12] Research on the serotonin subtype receptors, 5-HT_{1A} and 5-HT_{2A}, has benefited from the availability of suitable PET radioligands.[13-17] In contrast, 5-HT_{2C}R is less well studied and the radioligands developed so far are not ideal for in vivo brain imaging. Three agonists [^{11}C]WAY-163909[18] (**1**), [^{11}C]Vabicaserin[18] (**2**), and [^{11}C]10-(azetidin-1-yl)-7-methyl-6,7,8,9-tetrahydro-5*H*-pyrazolo[1',5':1,2]pyrimido[4,5-d]azepine[19] (**3**) were reported with Ki of ~10, 3, and 75 nM for 5-HT_{2C}, respectively. In vivo imaging in baboons has shown that these radiotracers penetrated the blood-brain barrier (BBB), however, they did not display specific binding to brain regions rich in 5HT_{2C}R. An agonist [^{11}C]Cimbi-36[20] (**4**) was shown to penetrate the BBB and had specific binding to 5HT_{2C} receptors in the choroid plexus of the primate brain, however, [^{11}C]Cimbi-36 is not selective and has a higher binding affinity, over 2-to-1, for 5HT_{2A} (Ki=0.5 nM) vs 5HT_{2C} (Ki=1.7 nM). This major shortcoming necessitated blocking 5HT_{2a} prior to administration of [^{11}C]Cimbi-36 to determine 5HT_{2C} concentration. Recently, [^{18}F]4-(3-fluorophenethoxy)pyrimidine (**5**) was reported to exhibit

specific binding to 5-HT_{2C} receptors in rat brain but with a fast washout from choroid plexus.[21]

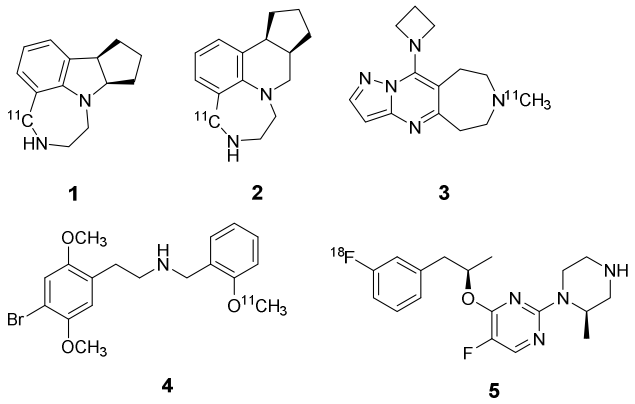
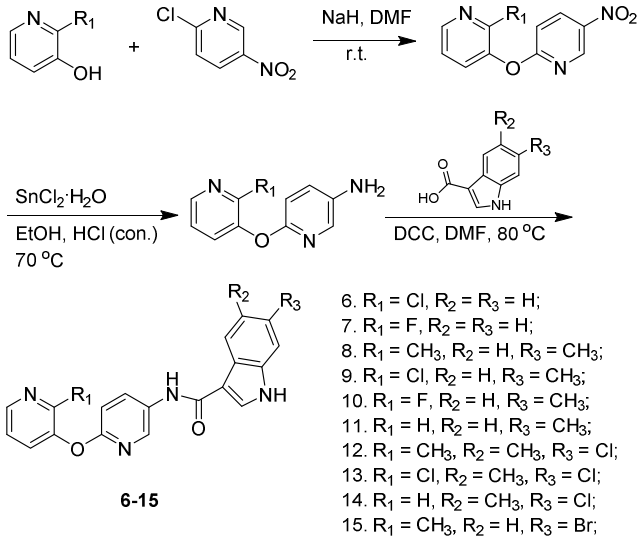


Figure 1. Chemical structures of reported PET imaging agents for 5-HT_{2C}R

In an attempt to develop potent 5-HT_{2C}R-specific PET imaging agents, we have chosen to investigate pyridyloxypyridyl indole carboxamides represented by **6**. Seong et al. recently reported a series of pyridyloxypyridyl indole carboxamides as 5-HT_{2C}R antagonists. Among them, *N*-[6-[(2-chloro-3-pyridinyl)oxy]3-pyridinyl]1*H*-indole-3-carboxamide (**6**) exhibits the highest 5-HT_{2C}R affinity (IC_{50}=0.5 nM) and high selectivity (>100 times) over other serotonin (5-HT_{1A}-5-HT_7) and dopamine receptor (D_2-D_4) subtypes.[22] In addition, **6** exhibits a favorable lipophilicity profile with ClogP = 2.86 and its structure enables convenient approaches for radiochemical modifications. **6** does not have positions available for radiolabeling, however, fluorine-18 or carbon-11 could be easily incorporated into the structure by fluorine-18 fluoride or carbon-11 methyl substitution on the ortho-position of the pyridine ring or on the indole ring without significant structural modification. Therefore, we synthesized the fluorine derivative (**7**) and a methyl derivative (**8**) which also has a methyl group on the 6-position of the indole ring, as well as seven other related derivatives to further explore the structure-activity relationship. After comparing their binding affinity and selectivity at 5-HT_{2C}R, we chose to radiolabel compound **8** with carbon-11 and conducted microPET imaging studies in nonhuman primates for evaluation as a candidate PET 5-HT_{2C}R radioligand.

Nine new pyridyloxypyridyl indole carboxamides (**7-15**) and **6** were synthesized in three steps according to a previously described procedure, which includes treating substituted 3-pyridinols with 2-chloro-5-nitropyridine using NaH in DMF, reduction of the resulting nitropyridines with $SnCl_2$ in a mixture of EtOH and concentrated HCl, and coupling the resulting pyridin-3-yl amines with the corresponding 1*H*-indole-3-carboxylic acid (Scheme 1).[22]

Scheme 1. Schematic synthesis approach to pyridyloxypyridyl indole carboxamides



6. R_1 = Cl, R_2 = R_3 = H;
7. R_1 = F, R_2 = R_3 = H;
8. R_1 = CH_3, R_2 = H, R_3 = CH_3;
9. R_1 = Cl, R_2 = H, R_3 = CH_3;
10. R_1 = F, R_2 = H, R_3 = CH_3;
11. R_1 = H, R_2 = H, R_3 = CH_3;
12. R_1 = CH_3, R_2 = CH_3, R_3 = Cl;
13. R_1 = Cl, R_2 = CH_3, R_3 = Cl;
14. R_1 = H, R_2 = CH_3, R_3 = Cl;
15. R_1 = CH_3, R_2 = H, R_3 = Br;

In vitro competition assays were conducted by NIMH Psychoactive Drug Screening Program (PDSP). Data in Table 1 indicate that all pyridyloxypyridyl indole carboxamides tested displayed high affinities for 5-HT_{2C} and high selectivity over 5-HT_{2A} and 5-HT_{2B}. Replacing a chloro by a fluoro group at the pyridine ortho-position retained the 5-HT_{2C} potency and selectivity as seen in compounds **6** and **7**. Introduction of a methyl group at 6-position of the indole ring increased the affinity for 5-HT_{2C} 3 to 5-fold and retained the lower affinity for 5-HT_{2A} and 5-HT_{2B} as seen in compound **6** vs **9**, and compound **7** vs **10**. Compared to compound **8**, **9**, **11**, which has 6-methyl substitution on the indole ring, compound **12**, **13**, **14** with 5-methyl, 6-chloro substitution exhibited the similar affinity for 5-HT_{2C}, while their selectivity over 5-HT_{2A} and 5-HT_{2B} decreased, respectively. Replacing the 6-methyl group on the indole ring of **8** with a bromo group afforded **15**, whose affinity for 5-HT_{2C} decreased 2-fold, while the affinity for 5-HT_{2A} and 5-HT_{2B} remained low. Among all the compounds tested, compound **8** is a very attractive candidate with 5-HT_{2C} binding, Ki=1.3 nM, equivalent to Cimbi-36, Ki = 1.7 nM, and high selectivity over 5-HT_{2A} (~1000 times) and 5-HT_{2B} (~140 times).

Table 1. **Binding affinities of pyridyloxypyridyl indole carboxamides at 5-HT_2 receptors (*Ki*, nM)[a]**

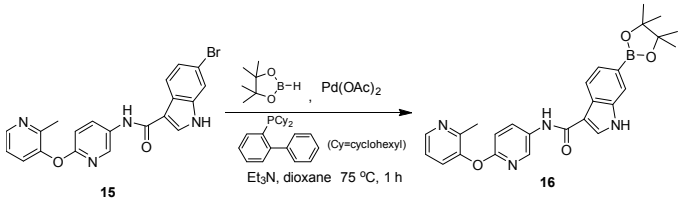
Compound	5-HT_{2C}	5-HT_{2A}	5-HT_{2B}
6	23.3±7.5	791±178	579±160
7	25.3±12.6	344±123	472±167
8	1.3±0.6	1398±230	183±61
9	5.2±3.3	240±80	432±120
10	7.9±2.6	1637±182	209±68
11	5.0±2.9	370±184	66±9

12	3.4±1.6	316±163	184±108
13	7.9±3.7	369±123	166±38
14	2.0±1.1	28±15	26±12
15	2.6±1.2	1487±459	338±48

[a]Data are reported as means of three separate competitive experiments ± standard deviation.

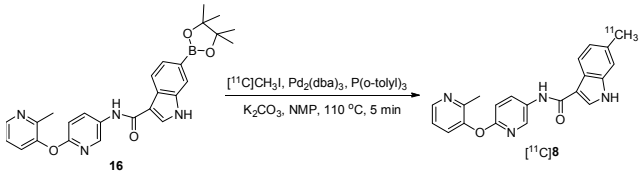
Preparation of [^{11}C]**8** was successfully achieved by palladium-catalyzed methylation of the organoboronic ester precursor with [^{11}C]CH_3I based on Suzuki-Miyaura couping.[23] As shown in Scheme 2, the pinacolboranate precursor **16** was synthesized in a moderate yield of 49% by borylation of the bromo compound **15** with pinacolborane in the presence of the catalytic system of $Pd(OAc)_2$ and a sterically hindered phosphine ligand and Et_3N as base under relatively mild condition.[24,25] [^{11}C]**8** was prepared by the coupling reaction between **16** and [^{11}C]CH_3I using a modified procedure developed by Suzuki *et al.*[26] Reacting **16** (2 mg) with [^{11}C]CH_3I at 110 °C for 5 min using palladium complex generated *in situ* from $Pd_2(dba)_3$ and (*o*-$CH_3C_6H_4)_3P$ (1:12) together with K_2CO_3 as the co-catalyst in NMP gave us a high coupling yield. (Scheme 3)

Scheme 2. Synthesis of the pinacolboranate precursor for radiolabeling of [^{11}C]8.



Starting with 380-420 mCi of cyclotron produced [^{11}C]CH_3I, typical syntheses provided 34-45 mCi (uncorrected) of [^{11}C]**8** in an average radiochemical yield of 27 ± 4% (n = 8, decay corrected) in a total synthesis time of 45 ± 5 min end of bombardment. Analytical HPLC demonstrated that the radiochemical and chemical purities of [^{11}C]**8** were consistently greater than 98%, and the specific activity was in the range of 0.4-0.9 Ci/μmol at time of injection. The lipophilicity of **8** was measured according to a previously reported procedure.[27] The log $P_{7.4}$ value of **8** is 2.79 which is in the optimal range (1.0-3.0) for compounds expected to readily enter the brain.[28]

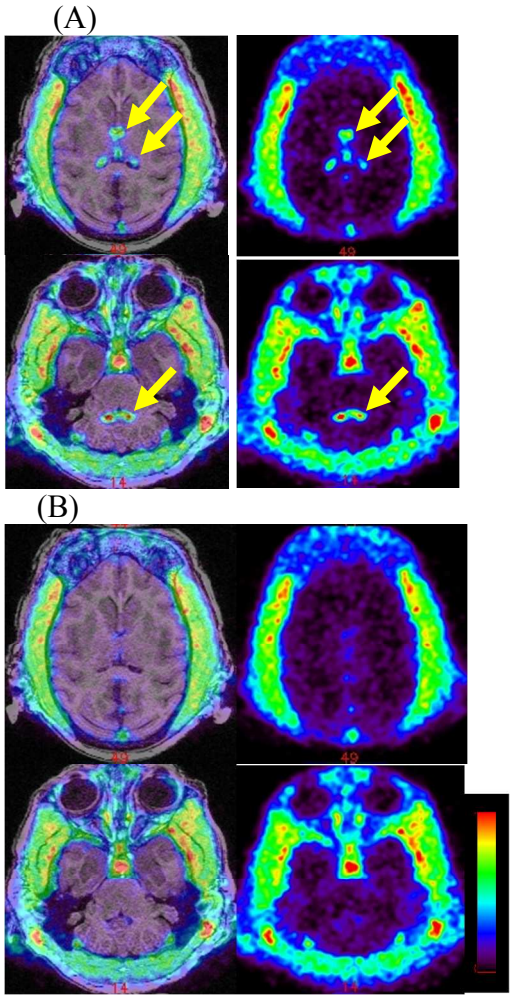
Scheme 3. Radiosynthesis of [^{11}C]8.



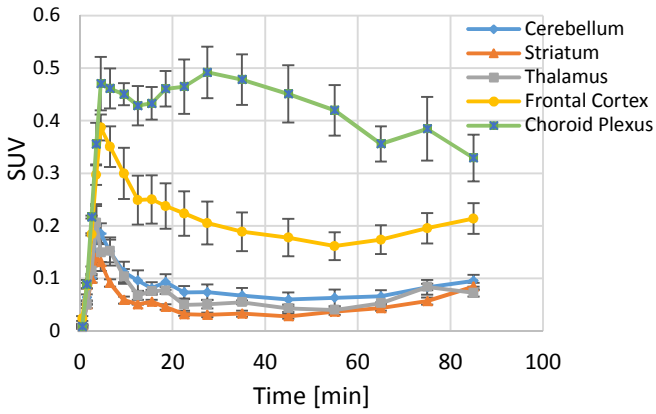
[^{11}C]**8** was intravenously administered to rhesus monkeys (n=3) for dynamic microPET imaging to assess in vivo regional brain uptake. Baseline studies were initially performed to determine the extent of brain uptake (Figure 2A and 2C). The regional uptake of [^{11}C]**8** was observed in the choroid plexus, the region with the highest density of 5-HT_{2C}R, whereas retention in all other brain regions was low. Overall, [^{11}C]**8** did not enter the brain in high amounts during the time course of PET studies, but the contrast of binding to the choroid plexus was excellent at greater than 10:1 compared to the cerebellum.

The low brain uptake of [^{11}C]**8** does not seem to be explained by its log P7.4 value, suggesting a factor other than lipophilicity prevents [^{11}C]**8** from penetrating the BBB. High plasma protein binding or involvement in active action of efflux transporters (e.g. P-gp) at BBB may contribute to the low brain penetration, but further studies would be needed for validation.[29]

To test specific binding of [^{11}C]**8** to the choroid plexus, an *in vivo* microPET blocking study (n=1) was performed with SB-242084, a 5-HT_{2C}R antagonist (Ki at 5-HT_{2C}R = 3.6 nM). Pretreating the monkey with a dose of 0.1 mg/kg 30 min prior to injection resulted in a marked reduction of radioactivity at the choroid plexus, suggesting that the uptake of [^{11}C]**8** in choroid plexus reflected specific binding. (Figure 2B and 2D)



(C)



(D)

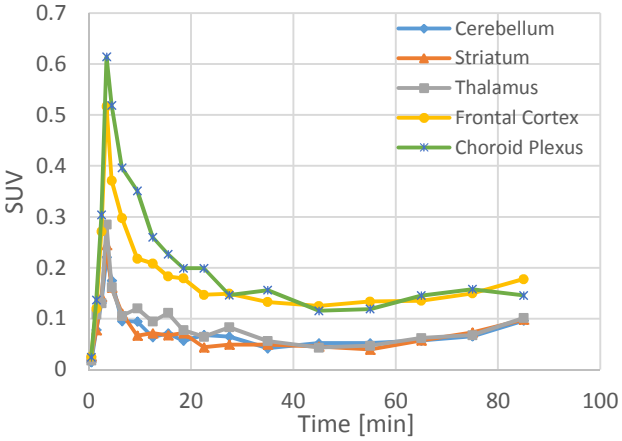


Figure 2. PET-MRI analysis of [^{11}C]**8** in rhesus monkey. (A) MicroPET images (right) and corresponding fused PET/MRI images at baseline. Arrows depict choroid plexus. (B) MicroPET images (right) and corresponding fused PET/MRI images after pretreatment with 0.1 mg/kg of SB-242084. All images (panels A & B) are scaled to a maximum SUV of 2.6 and performed on the same monkey. (C) Mean (n=3) time-activity curves for brain regions of interest at baseline with standard error. (D) Representative time-activity curves of one monkey for brain regions after pretreatment with 0.1 mg/kg of SB-242084.

In summary, as an effort to develop potential PET imaging agents for 5-HT$_{2C}$R, nine pyridyloxypyridyl indole carboxamides with methyl substitution on the ortho-position of the pyridine ring or on the indole ring were synthesized. Among them, compound **8** was identified to possess the highest 5-HT$_{2C}$ binding affinity and high selectivity over 5-HT$_{2A}$ and 5-HT$_{2B}$. [^{11}C]**8** was successfully synthesized by palladium-catalyzed Suzuki coupling reaction between pinacolboranate precursor and [^{11}C]CH_3I. In vivo microPET imaging studies demonstrated that [^{11}C]**8** displays a specific binding to 5-HT$_{2C}$R in the choroid plexus, albeit there was low overall uptake and retention of the tracer in the monkey brain. Structural modification is underway in order to increase BBB penetration.

ASSOCIATED CONTENT

Supporting Information

Procedure for the preparation of new ligands, radiolabelling, and microPET studies. This material is available free of charge via the internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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