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Radiosynthesis of novel carbon-11-labeled triaryl ligands for cannabinoid-type 2 receptor

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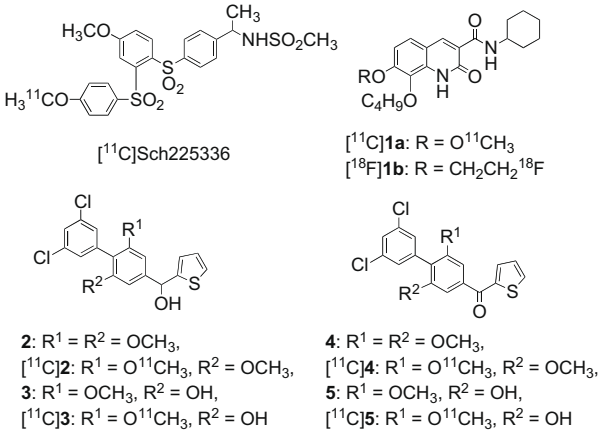
ABSTRACT

Two novel triaryl ligands **2** and **5** with potent in vitro binding affinities for the cannabinoid subtype-2 (CB2) receptor were labeled with a positron-emitting radioactive nuclide ^{11}C. Radioligands [^{11}C]**2**, [^{11}C]**5**, and their analogs [^{11}C]**3** and [^{11}C]**4** were synthesized by *O*-[^{11}C]methylation of their corresponding phenol precursors with [^{11}C]CH_3I. [^{11}C]**2**–**5** had relatively high uptakes (>1.2% injected dose/g tissue) in mouse brains.

Two seven-transmembrane G protein-coupled cannabinoid receptors have been identified and divided into the cannabinoid-type 1 (CB1) and -type 2 (CB2) receptors.[1,2] The CB1 receptor is one of the most abundant neuromodulatory receptors in the brain; both CB1 and CB2 receptors are widely distributed in peripheral tissues.[3] The CB2 receptor is particularly enriched in immune tissues, but is also present in the brain at a low concentration.[4] The protective effect of the CB2 receptor in activated microglial cells due to inflammation-induced damage to the central nervous system (CNS) has been demonstrated in mouse models of multiple sclerosis.[5] The CB2 receptor is therefore considered to be a powerful neuroprotective target for treating neurodegenerative disorders.[6] Administration of CB2-selective agonists to wild-type mice subjected to excytotoxicity reduced neuroinflammation, brain edema, striatal neuronal loss, and motor symptoms.[6,7] The precise distribution and physiological significance of events mediated by the CB2 receptor are still controversial.[8] The therapeutic potential of CB2 ligands in the pathology and/or etiology of CNS disorders needs to be elucidated more clearly.

Positron emission tomography (PET) is an in vivo imaging modality that uses short-lived, positron-emitting radioligands to probe biochemical processes in living humans and animals. PET studies with ^{11}C- or ^{18}F-labeled ligands have been performed for imaging of cannabinoid receptors in the human brain.[9–12] These PET ligands belonged mostly to probes specific for the CB1 receptor. However, to our knowledge, PET ligands that can be used for imaging of the CB2 receptor in animals and humans have not been developed.

Thus far, only three PET ligands for the CB2 receptor have been reported. [^{11}C]Sch225336 and ^{11}C- and ^{18}F-labeled 2-oxoquinoline analogs ([^{11}C]**1a** and [^{18}F]**1b**) were synthesized and evaluated in normal rodents by a same research group (Scheme 1).[13,14]



Scheme 1. Chemical structures of PET ligands for the cannabinoid-type 2 receptor.

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Sch225336, **1a** and **1b** had potent in vitro binding affinities for human CB2 receptor (K_i = 4.5, 9.6, and 35.8 nM) and low affinities for CB1 receptor. However, [^{11}C]Sch225336 did not pass through the blood–brain barrier (BBB) to enter the mouse brain.[13] [^{11}C]**1a** and [^{18}F]**1b** had much higher uptakes of radioactivity in the mouse brain when compared to [^{11}C]Sch225336, and were characterized to have some specific binding in the brain and peripheral systems. Based on these results, it is indicated that [^{11}C]**1a** and [^{18}F]**1b** are promising PET ligands for the CB2 receptor.[14]

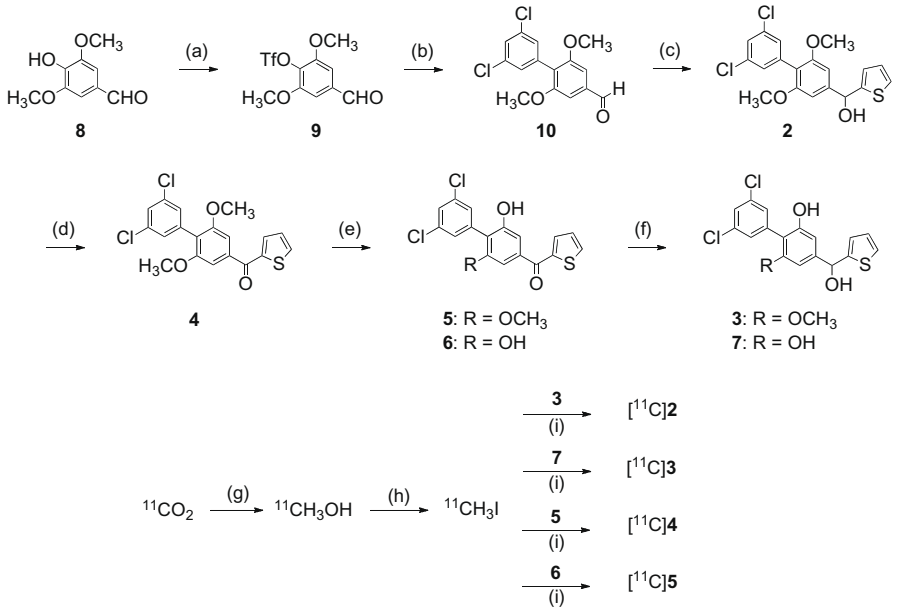
The aim of the present study was to label two novel triaryl ligands **2** and **5** for the CB2 receptor with ^{11}C. The two ligands exhibited high in vitro binding affinities (**2**, K_i = 0.27 nM; **5**, 2.32 nM) for CB2 in the homogenate fractions of rat brains.[15] Moreover, they had low affinity (**2**, >1000 nM; **5**, 503 nM) for CB1. For the first time, we labeled them with ^{11}C to obtain [^{11}C]**2** and [^{11}C]**5**. We also synthesized two novel analogs **3** and **4** and labeled them with ^{11}C. Analog **3** or **4** was derived by removing or adding one methyl group in **2** or **5**. Compound **3** is a bioister of **2** and is less lipophilic than **2**, which may decrease non-specific binding in vivo. By searching this triaryl compound's library,[15] we assumed that **3** and **4** maintain binding affinities with the CB2 receptor similar to those for **2** and **5**. In this study, we report: (1) chemical synthesis of non-radioactive ligands **2**–**5** and their corresponding desmethyl precursors, (2) radiosynthesis of [^{11}C]**2**–**5**, and (3) radioactivity concentrations of these radioligands in whole brain and blood of mice.

The triaryl ligands **2**–**5** and their desmethyl precursors for radiosynthesis were prepared according to reaction sequences delineated in Scheme 2.[16] Coupling of triflate **9** with dichlorophenylboronic acid was a challenging step. We attempted this coupling according to a conventional procedure[15] in which $Pd(PPh_3)_4$ was used as a catalyst, but we obtained the biaryl **10** only at a low yield. LiCl addition to the reaction mixture caused the coupling to proceed efficiently to produce **10**. The desired triaryl **2** was prepared by treatment of **10** with 2-thienylmagnesium bromide. Oxidation of **2** readily afforded **4** with a yield of 96%. Cleavage of one or two methoxy groups in **4** at the same time was carried out with 2 equiv of BBr_3, which produced a mixture of mono- (**5**) and bis- (**6**) desmethylated compounds. This mixture was purified using column chromatography to give **5** (57%) and **6** (33%). Reduction of the carbonyl group in **5** and **6** with $NaBH_4$ afforded alcohols **3** and **7** at high yields of 91% and 90%, respectively.

Labeling of **2**–**5** with ^{11}C was performed using a home-made automated synthesis system[17] (Scheme 2). The labeling reagent [^{11}C]methyl iodide ([^{11}C]CH_3I) for radiosynthesis was produced by reduction of the cyclotron-produced [^{11}C]CO_2 with $LiAlH_4$, followed by iodination with 47% hydroiodic acid. [^{11}C]CH_3I was purified by distillation and trapped in a solution of DMF (300 mL) containing desmethyl phenol precursor **3**, **7**, **5**, or **6** (1 mg, 3–4 mmol) and aqueous NaOH (7 μL, 0.5 N) at −15 °C. After [^{11}C]CH_3I trapping ceased, the radioactive mixture was warmed to 50 °C and kept for 5 min. The *O*-[^{11}C]methylation reaction was terminated by adding CH_3CN/H_2O, and the radioactive mixture was applied onto a reversed phase semi-preparative HPLC system.

Purification of the reaction mixtures using this system (CAPCELL PAK C_{18} column: 10 mm ID × 250 mm, CH_3CN/H_2O: 7/3 or 8/2) provided [^{11}C]**2**–**5** in 34 ± 15%, 33 ± 9%, 28 ± 5%, and 19 ± 3% radiochemical yields (n = 3 for each ligand based on [^{11}C]CO_2, corrected for decay), respectively. Starting from 13–21 GBq of [^{11}C]CO_2, [^{11}C]**2**–**5** was reliably obtained as an injectable solution with 1.0–3.6 GBq. This amount of radioactivity is generally sufficient for animal experiments. The identity of these radioactive products was confirmed by co-injection of non-radioactive **2**–**5** on analytic HPLC (CAPCELL PAK C_{18} column: 4.6 mm ID × 250 mm, CH_3CN/H_2O: 7/3 or 8/2). In the final product solution, no significant peak of the corresponding desmethyl precursor was observed in their HPLC charts. The radiochemical purity of [^{11}C]**2**–**5** was higher than 98% and the specific activity was 48–103 GBq/μmol. The radiochemical purity of [^{11}C]**2**–**5** remained >95% after being maintained at 25 °C for 180 min, indicating these radioligands were stable for the time of a PET scan.

We determined radioactivity concentrations of [^{11}C]**2**–**5** in the brain and blood of mice. A solution of each [^{11}C]ligand (mean of 8 MBq/200 mL) was injected into the tail vein of male Wister mice (~30 g, 7 weeks). Three mice were sacrificed by cervical dislocation at 1, 5, 15, 30, and 60 min after injection with each ligand. Whole brain and blood samples were quickly removed. The radioactivity present in these tissues was measured and expressed as a



Scheme 2. Chemical synthesis and radiosynthesis: Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt, 2 h, 80%; (b) 3,5-dichlorophenylboronic acid, LiCl, $Pd(PPh_3)_4$, 2 M Na_2CO_3, Toluene, 90 °C, 24 h, 69%; (c) 2-thienylmagnesium bromide, THF, −20 °C, 5 h, 66%; (d) pyridinium chlorochromate, CH_2Cl_2, rt, 4 h, 96%; (e) BBr_3, CH_2Cl_2, −40 °C to rt, 19 h, 57% (**5**), 33% (**6**); (f) $NaBH_4$, EtOH, 0 °C to rt, 5 h; 91% (**3**), 90% (**7**); (g) $LiAlH_4$, THF, −15 °C, 2 min; (h) HI, 180 °C, 2 min; (i) NaOH, DMF, 50 °C, 5 min; 34% ([^{11}C]**2**, corrected for decay from [^{11}C]CO_2), 33% ([^{11}C]**3**), 28% ([^{11}C]**4**), 17% ([^{11}C]**5**).

Table 1
Radioactivity (% of injected dose/g tissue: mean ± SD, $n = 3$) in the brain and blood of mice at 1, 5, 15, 30, and 60 min after injection

Tissue	Time (min)	[^{11}C]**2**	[^{11}C]**3**	[^{11}C]**4**	[^{11}C]**5**
Brain	1	1.93 ± 0.15	1.94 ± 0.29	1.20 ± 0.13	1.54 ± 0.04
	5	1.87 ± 0.24	2.07 ± 0.13	1.29 ± 0.10	1.63 ± 0.26
	15	1.50 ± 0.14	1.77 ± 0.12	1.10 ± 0.09	1.01 ± 0.10
	30	1.09 ± 0.05	0.96 ± 0.08	0.85 ± 0.15	0.56 ± 0.04
	60	0.65 ± 0.05	0.45 ± 0.05	0.62 ± 0.12	0.18 ± 0.02
Blood	1	3.90 ± 0.14	2.20 ± 0.33	2.71 ± 0.32	1.56 ± 0.12
	5	2.12 ± 0.10	1.18 ± 0.24	2.93 ± 0.17	1.00 ± 0.03
	15	2.25 ± 0.51	0.70 ± 0.03	3.45 ± 0.24	0.63 ± 0.15
	30	2.38 ± 0.13	0.35 ± 0.03	3.42 ± 0.35	0.36 ± 0.04
	60	2.27 ± 0.13	0.37 ± 0.28	3.38 ± 0.04	0.21 ± 0.05

percentage of the injected dose per gram of wet tissue (% ID/g). Radioactivity measurements were corrected for decay.

Table 1 shows uptakes of [^{11}C]**2**–**5** in the brain and blood of mice after injection at different time points. These radioligands entered the brain rapidly and their maximum radioactivity levels reached >1.2% ID/g, indicating that they could pass through the BBB. This is a prerequisite for a good PET ligand used in brain imaging, and was probably due to their high lipophilicity (*c*log *D* >4; Pallas 3.4 Software). Although the maximum brain uptakes of [^{11}C]**2**–**5** were half-fold lower than those of [^{11}C]**1a** and [^{18}F]**1b**, their radioactivity levels in the brain were higher than those of some useful PET probes[17–19] developed by us for clinical brain imaging. Uptakes of alcohols [^{11}C]**2** and [^{11}C]**3** in the brain were higher than those of ketones [^{11}C]**4** and [^{11}C]**5**. After initial uptakes, the radioactivity levels of [^{11}C]**2**–**5** in the brain decreased over time, and their brain washout expressed as 1 min/60 min ratio ID was 2.9, 4.3, 1.9, and 8.6, respectively.

In the blood, [^{11}C]**2**–**5** displayed a different pattern of uptake over time and dimethoxy [^{11}C]**2** displayed a slow decrease of radioactivity in the blood. Uptake of another dimethoxy [^{11}C]**4** did not reduce and its uptake at 60 min even increased by 1.2-fold in comparison with that at 1 min after injection. This result may be related to the high lipophilicity (*c*log *D* = 5.7) of [^{11}C]**4**. A high lipophilic ligand could bind to plasma proteins, which would significantly obstruct its penetration into the brain. Indeed, among the radioligands in the present study, the maximum uptake of [^{11}C]**4** in the brain was the lowest.

[^{11}C]**3** and [^{11}C]**5** displayed rapid decrease of radioactivity in the blood in contrast to [^{11}C]**2** and [^{11}C]**4**. Uptakes of [^{11}C]**3** and [^{11}C]**5** at 60 min reduced to 17% and 13% of their values at 1 min, respectively. Their ID ratios of brain/blood increased over time after injection. The maximum value was 2.7 for [^{11}C]**3** at 30 min, 1.7 for [^{11}C]**5** at 15 min, whereas that was 0.9 for [^{11}C]**2** at 5 min and 0.4 for [^{11}C]**4** at 5 min. These results suggest that [^{11}C]**3** and [^{11}C]**5** have more suitable in vivo properties in the brain than do [^{11}C]**2** and [^{11}C]**4**.

We did not measure the radioactivity concentrations of [^{11}C]**2**–**5** in the mouse brain regions because of the possible low density and unclear distribution of the CB2 receptor in the brain.[4] It has been reported that the CB2 receptor was increased in microglia activated by brain injury and neuroinflammation.[5,6] Based on the brain kinetics of [^{11}C]**5**, it is worth characterizing whether [^{11}C]**5** has in vivo specific binding with the CB2 receptor in the brain. Due to its similar structure and brain kinetics with [^{11}C]**5**, [^{11}C]**3** derived from the reduction of [^{11}C]**5** may also be a promising radioligand for brain imaging, although the affinity of **3** for the CB2 receptor still needs to be measured. We are currently using inflammatory animal models to evaluate the potential of [^{11}C]**3** and [^{11}C]**5** for the CB2 receptor in the brain.

In conclusion, four novel radioligands [^{11}C]**2**–**5** were synthesized and they exhibited relatively high uptakes into mouse brains. [^{11}C]**3** and [^{11}C]**5** may become promising PET ligands for in vivo imaging of the CB2 receptor in the brain.

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16. *Compound* **2** *(3′,5′-dichloro-2,6-dimethoxybiphenyl-4-yl)(thiophen-2-yl)methanol):* White powder; mp: 158–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.68 (s, 6H), 5.96 (d, J = 4.4 Hz, 1H), 6.31 (d, J = 4.8 Hz, 1H), 6.85 (s, 2H), 6.93–6.97 (m, 2H), 7.23 (d, J = 1.8 Hz, 2H), 7.41 (dd, J = 1.5, 3.3 Hz, 1H), 7.50 (t, J = 2.0 Hz, 1H); GC–MS (EI), *m/z*: 394.
Compound **3** *(3′,5′-dichloro-2-hydroxy-6-methoxybiphenyl-4-yl)(thiophen-2-yl)-methanol):* White powder; mp: 124–126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.67 (s, 3H), 5.86 (d, J = 4.0 Hz, 1H), 6.22 (d, J = 4.3 Hz, 1H), 6.67 (s, 2H), 6.93–6.96 (m, 2H), 7.26 (d, J = 2.1 Hz, 2H), 7.39–7.41 (m, 1H), 7.47 (t, J = 2.0 Hz, 1H), 9.58 (s,1H); GC–MS (EI), *m/z*: 380.
Compound **4** *(3′,5′-dichloro-2,6-dimethoxybiphenyl-4-yl)(thiophen-2-yl)methanone):* White powder; mp: 203–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80 (s, 6H), 7.12 (s, 2H), 7.21 (t, J = 4.4 Hz, 1H), 7.25 (d, J = 1.8 Hz, 2H), 7.34 (t, J = 1.8 Hz, 1H), 7.76–7.77 (m, 2H); High-resolution MS (FAB), *m/z*: 393.0084 (calculated for $C_{19}H_{15}O_3Cl_2S$, 393.0119).
Compound **5** *(3′,5′-dichloro-2-hydroxy-6-methoxybiphenyl-4-yl)(thiophen-2-yl)-methanone):* Yellow powder; mp: 199–201 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.76 (s, 3H), 6.98 (s, 1H), 7.10 (s, 1H), 7.32 (t, J = 4.2 Hz, 1H), 7.36 (d, J = 0.9 Hz,

2H), 7.56 (t, J = 1.3 Hz, 1H), 7.85 (d, J = 3.7 Hz, 1H), 8.14 (d, J = 5.1 Hz, 1H), 10.09 (s, 1H); High-resolution MS (FAB), m/z: 378.9929 (calculated for $C_{18}H_{13}O_3Cl_2S$, 378.9962).

Compound **6** *(3′,5′-dichloro-2,6-dihydroxybiphenyl-4-yl)(thiophen-2-yl)methanone):* White powder; mp: 187–189 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.94 (s, 2H), 7.32 (t, J = 4.0 Hz, 1H), 7.40 (d, J = 1.8 Hz, 2H), 7.54 (t, J = 1.6 Hz, 1H), 7.80 (d, J = 3.3 Hz, 1H), 8.12 (d, J = 4.8 Hz, 1H), 9.96 (s, 2H); High-resolution MS (FAB), m/z: 364.9848 (calculated for $C_{17}H_{11}O_3Cl_2S$, 364.9806).

Compound **7** *(3′,5′-dichloro-2,6-dihydroxybiphenyl-4-yl)(thiophen-2-yl)methanol):* White powder; mp: 58–61 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.76 (d, J = 3.7 Hz, 1H), 6.12 (d, J = 4.0 Hz, 1H), 6.50 (s, 2H), 6.93–6.96 (m, 2H), 7.31 (d, J = 1.5 Hz, 2H), 7.40 (d, J = 4.9 Hz, 1H), 7.44 (t, J = 2.0 Hz, 1H), 9.45 (s, 2H); GC–MS (EI), m/z: 350.

Compound **9** *(trifluoromethanesulfonic acid 4-formyl-2,6-dimethoxyphenyl ester):* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.98 (s, 6H), 7.17 (s, 2H), 9.94 (s, 1H); GC–MS (EI), m/z: 314.

Compound **10** *(3′,5′-dichloro-2,6-dimethoxybiphenyl-4-carbaldehyde):* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.83 (s, 6H), 7.15 (s, 2H), 7.21 (d, J = 1.8 Hz, 2H), 7.35 (t, J = 1.8 Hz, 1H), 9.98 (s, 1H); GC–MS (EI), m/z: 310.

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