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Synthesis of carbon-11-labeled aminoalkylindole derivatives as new candidates of cannabinoid receptor radioligands for PET imaging of alcohol abuse

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ABSTRACT

Carbon-11-labeled aminoalkylindole derivatives (1-butyl-7-[^{11}C]methoxy-1*H*-indol-3-yl)(naphthalene-1-yl)methanone ([^{11}C]**3**), 1-butyl-7-[^{11}C]methoxy-3-(naphthalene-1-ylmethyl)-1*H*-indole ([^{11}C]**5**), and 1-butyl-7-[^{11}C]methoxy-3-(naphthalene-2-yl)-1*H*-indole ([^{11}C]**8**) were prepared by O-[^{11}C]methylation of their corresponding precursors with [^{11}C]CH_3OTf under basic condition (2 N NaOH) and isolated by a simplified solid-phase extraction (SPE) method in 50–60% radiochemical yields based on [^{11}C]CO_2 and decay corrected to end of bombardment (EOB). The overall synthesis time from EOB was 23 min, the radiochemical purity was >99%, and the specific activity at end of synthesis (EOS) was 185–555 GBq/μmol.

Alcohol abuse is a major substance abuse, approximately 2.5 million people die from alcohol use every year, and its annual health- and crime-related costs are estimated around $235 billion.[1] There are several therapeutic options available for the treatment of alcohol abuse, but all existing therapies have only modest efficacy.[2] The cause of alcohol abuse is still unknown. However, alcohol abuse results in chemical and biological changes in the brain, and it is often associated with substantial psychiatric comorbidity, brain damage and disease.[3] Brain imaging techniques such as positron emission tomography (PET) enable scientists to better understand alcohol abuse and alcohol-related diseases, for example, with PET, researchers can compare groups of alcohol-abusing and non-abusing individuals by quantifying differences in their levels of a particular neurotransmitter molecule like dopamine or neurotransmission component such as a receptor or a transporter.[4] We are interested in PET imaging of alcohol abuse, and we have extensively used [^{11}C]raclopride-PET and [^{18}F]fallypride-PET to study D_2 receptor in alcohol abuse, since alcohol abuse significantly affects the neurotransmitter dopamine and alters its neurotransmission in the central nervous system (CNS).[5–10]

More and more evidences suggest that endocannabinoid (eCB) system is another neurotransmitter involved in alcohol abuse, and cannabinoid (CB) receptor (CBR) antagonist/agonist might offer a new therapeutic direction for treatment of alcohol abuse.[11,12] Recently a new class of aminoalkylindole derivatives has been developed as CBR ligands with dual CB1R antagonist/CB2R agonist activity with potential for treatment of alcohol abuse.[1] CBR has become an interesting target for PET imaging of alcohol abuse.[13] In our previous works, we have developed a series of selective CB1R radioligands and CB2R radioligands, as indicated in Figure 1.[14–16] In this ongoing study, we report the design and synthesis of carbon-11-labeled aminoalkylindole derivatives as new candidate dual CB1R/CB2R radioligands for PET imaging of alcohol abuse.

Aminoalkylindole derivatives (1-butyl-7-methoxy-1*H*-indol-3-yl)(naphthalene-1-yl)methanone (**3**), 1-butyl-7-methoxy-3-(naphthalene-1-ylmethyl)-1*H*-indole (**5**), and 1-butyl-7-methoxy-3-(naphthalene-2-yl)-1*H*-indole (**8**) are dual CB1R/CB2R ligands with high affinity, and the low nanomolar K_i values for CB1R and CB2R are 1.7 and 0.81 nM, 15.4 and 10.9 nM, and 37.3 and 26.5 nM, respectively.[1] According to their in vitro K_i values, compound **3** is the most potent ligand for CB1R and CB2R in comparison with compounds **5** and **8**. However, the overall biological evaluation including both in vitro and in vivo studies suggested compounds **5** and **8** appeared to have the most promise to be CBR ligands for use as treatment of alcohol abuse.[1] These three representative compounds are selected as the reference standards for radiolabeling.

As outlined in Scheme 1, commercially available starting material 7-methoxyindole (**1**) was subjected to mild alkylating

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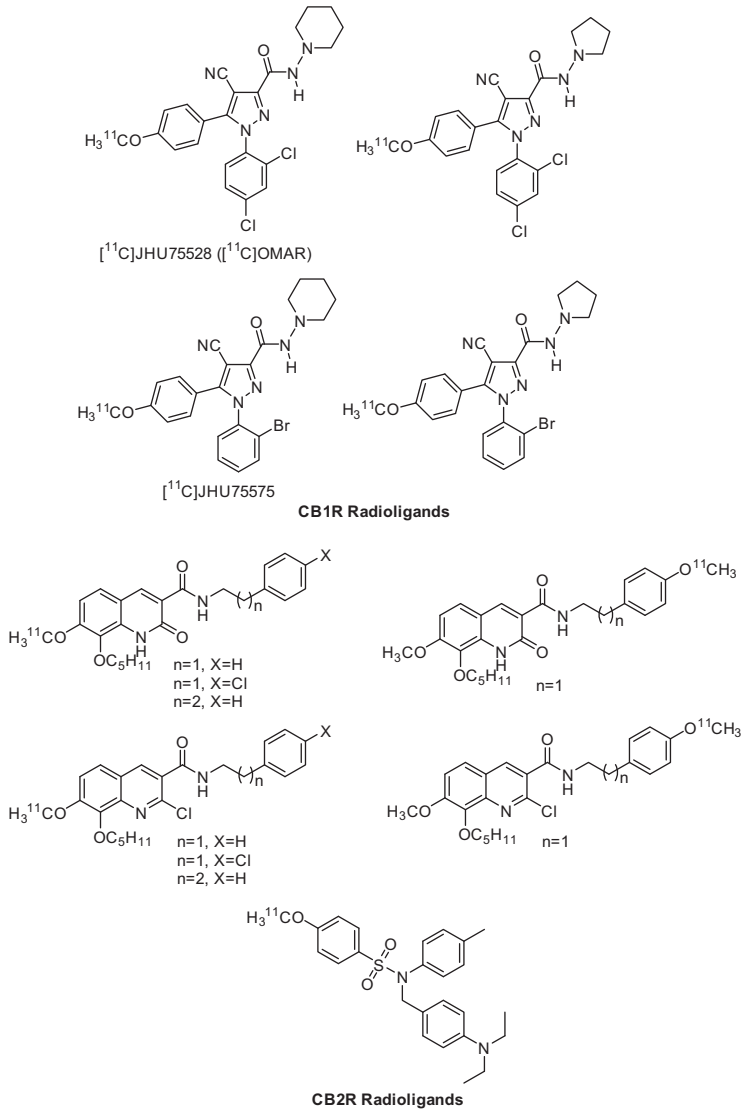
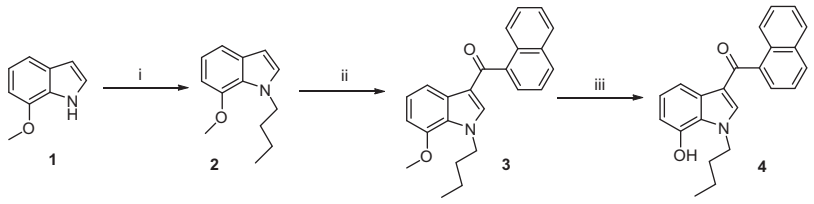


Figure 1. CB1R and CB2R radioligands.[14–16]



Scheme 1. Synthesis of aminoalkylindole derivative reference standard **3** and its precursor **4**. Reagents, conditions and yields: (i) KOH, 1-bromobutane, DMF, 50 °C, 88%; (ii) Me_2AlCl, 1-naphthoyl chloride, CH_2Cl_2, 0 °C, 52%; (iii) 48% HBr, HOAc, reflux, 70%.

conditions to give 1-butyl-7-methoxy-1*H*-indole (**2**) in 88% yield. Intermediate **2** was then subjected to Friedel–Crafts like acylation conditions, using dimethylaluminum chloride and acid chloride at 0 °C to afford the standard **3** in 52% yield. The desmethylation of compound **3** with 48% HBr in the solution of HOAc provided its desmethylated precursor (1-butyl-7-hydroxy-1*H*-indol-3-yl)(naphthalene-1-yl)methanone (**4**) in 70% yield. Using protic acid (HBr) instead of the literature method Lewis acid (BBr_3)[1] as the desmethylating reagent, it significantly improved the yield of desmethylation reaction, because protic acid promoted the desmethylation reaction of phenolic methoxy aminoalkylindole derivatives to easily form phenolic hydroxyl precursor and CH_3Br.[17,18]

As shown in Scheme 2, the reduction of compound **3** with $LiAlH_4$ gave the standard **5** in 49% yield. Careful workup by adjusting appropriate pH to 5 improved the yield of the reduction from 18% to 49%. Likewise, using 48% HBr in HOAc as the desmethylating reagent, compound **5** was desmethylated to produce its desmethylated precursor 1-butyl-7-hydroxy-3-(naphthalene-1-ylmethyl)-1*H*-indole (**6**) in 43% yield. Using Lewis acid (BBr_3)[1] as the desmethylating reagent, compound **5** failed to give **6** in desmethylation reaction.