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Synthesis of carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as new potential PET AMPA receptor ligands

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Abstract—New carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives were designed and synthesized as potential positron emission tomography AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid) receptor ligands to image brain diseases. The single crystal structure of the most potent compound *N*-acetyl-1-(4′-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5a**) is first reported.

The AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid) receptor antagonists may be useful as potential neuroprotective agents in the treatment of neurological diseases such as epilepsy, ischemia, Parkinson's disease, and multiple sclerosis, since AMPA receptors are involved in learning, memory, neuronal degeneration, and even cell death. *N*-Acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives are novel and highly potent noncompetitive AMPA receptor antagonists recently developed by Gitto et al.[1] In vivo biomedical imaging technique positron emission tomography (PET) coupled with appropriate receptor radioligands has become a clinically valuable and accepted diagnostic tool to image brain diseases.[2] To further develop potential therapeutic drugs as diagnostic agents, we designed and synthesized carbon-11 and fluorine-18 labeled *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives.

The synthesis of reference standard and desmethylated precursors *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**5a**–**g**), *N*-acetyl-1-aryl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines (**6a**–**c**), and *N*-acetyl-1-aryl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinolines (**7a**–**b**) was performed using a modification of the literature procedure.[1] The synthetic approach is outlined in Scheme 1. Commercially available starting materials, suitable aromatic aldehydes (**2a**–**g**), were reacted with 2-(3′,4′-dimethoxyphenyl)ethylamine (**1**) to afford the desired imine benziliden[2-(3′,4′-dimethoxyphenyl)ethyl]amines (**3a**–**g**). The crude products were used for the next step reaction without further purification. The intramolecular cyclization reaction of the intermediate imines (**3a**–**g**) catalyzed by trifluoroacetic acid (TFA) formed the corresponding 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (**4a**–**g**). The acetylation of the isoquinoline derivatives (**4a**–**g**) with acetyl chloride provided *N*-acetyl compounds (**5a**–**g**). The demethylation of the *N*-acetyl compounds (**5a**–**c**) with aluminium trichloride and ethanethiol[3] yielded monodesmethylated products 6-desmethylated isoquinoline derivatives (**6a**–**c**) and 7-desmethylated isoquinoline derivatives (**7a**–**b**).

The synthesis of target radioligands *N*-acetyl-1-aryl-6-[^{11}C]methoxy-7-methoxy-1,2,3,4-tetrahydroisoquinolines (6-[^{11}C]**5a**–**c**), *N*-acetyl-1-aryl-6-methoxy-7-[^{11}C]methoxy-1,2,3,4-tetrahydroisoquinolines (7-[^{11}C]**5a**–**b**), *N*-acetyl-1-(4′-[^{11}C]methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ([^{11}C]**5e**), and *N*-acetyl-1-(4′-[^{18}F]fluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ([^{18}F]**5g**) is shown in Scheme 2. 6-Desmethylated isoquinoline derivatives (**6a**–**c**), 7-desmethylated

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Keywords: *N*-Acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives; Carbon-11; Fluorine-18; Positron emission tomography; 2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid receptor; Brain diseases.

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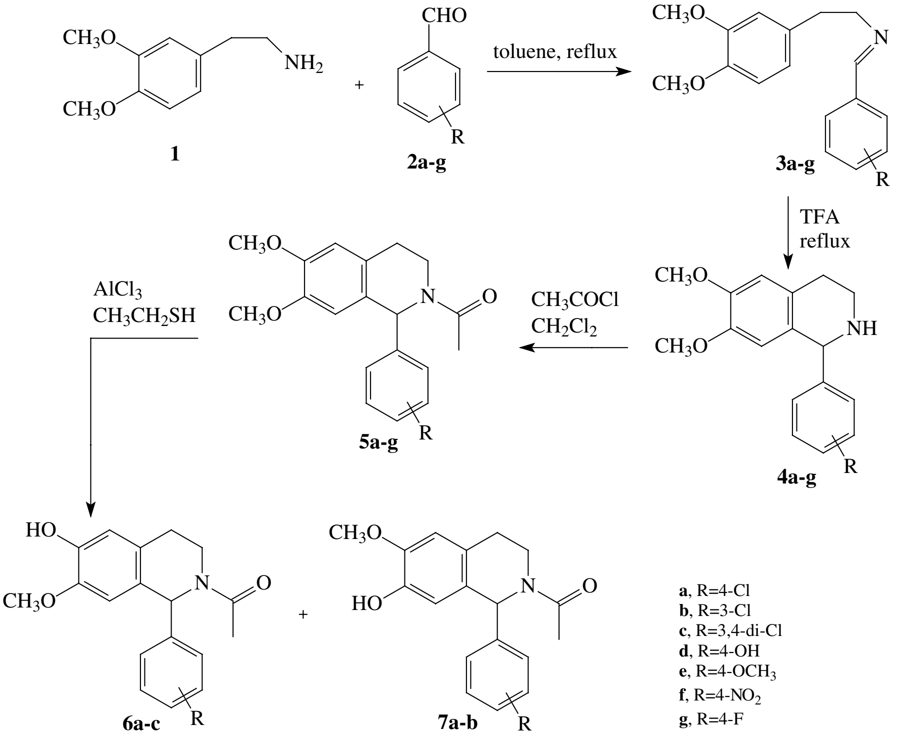
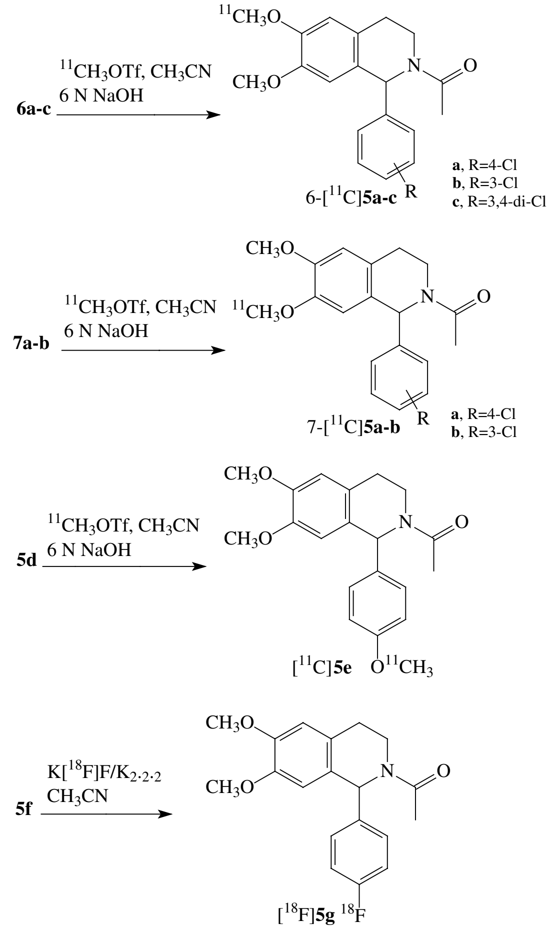


Scheme 1. Synthesis of isoquinoline derivatives.

isoquinoline derivatives (**7a–b**), and *N*-acetyl-1-(4′-hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5e**) were reacted with [^{11}C]methyl triflate ($^{11}CH_3OTf$)[4] under basic conditions through *O*-[^{11}C]methylation and isolated by solid-phase extraction (SPE) purification procedure using a C18 Sep-Pak cartridge[5] to give carbon-11 labeled isoquinoline derivative radiotracers 6-[^{11}C]**5a–c**, 7-[^{11}C]**5a–b**, and [^{11}C]**5e** in 30–45% radiochemical yields based on [^{11}C]CO_2, 15–20 min overall synthesis time from end of bombardment (EOB), >95% radiochemical purity, and >1.0 Ci/μmol specific activity at the end of synthesis (EOS) measured by analytical HPLC method.[6] *N*-Acetyl-1-(4′-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5f**) was labeled by a conventional nucleophilic substitution with K^{18}F/Kryptofix 2.2.2 in acetonitrile at 120 °C for 15–20 min and purified by HPLC method[7] to afford fluorine-18 labeled isoquinoline derivative radiotracer [^{18}F]**5g** in 15-25% radiochemical yield at EOB. The specific activity was 1.0–1.2 Ci/μmol at EOS.

Compounds **5b–e** are new noncompetitive AMPA receptor antagonists first synthesized in this laboratory. Compound **5a** has been reported to be more potent than talampanel, a noncompetitive AMPA receptor antagonist currently being investigated in phase III trials as an antiepileptic agent, and a highly effective noncompetitive-type modulator of the AMPA receptor indicated by electrophysiological studies.[1] To better understand the structure of the new PET radioligands, the structure of the ligand **5a** was determined by X-ray crystallography. Compound **5a** was obtained in the form of air-stable, colorless crystals by slow evaporation from a solution of **5a** in ethyl acetate.



Scheme 2. Synthesis of carbon-11 and fluorine-18 labeled isoquinoline derivatives.