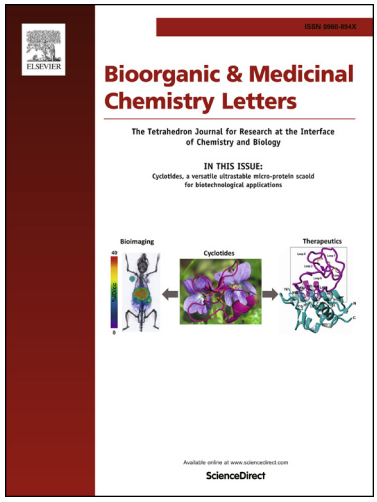

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Synthesis of carbon-11-labeled 5-HT$_6$R antagonists as new candidate PET radioligands for imaging of Alzheimer's disease

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Abstract—Carbon-11-labeled serotonin (5-hydroxytryptamine) 6 receptor (5-HT$_6$R) antagonists, 1-[(2-bromophenyl)sulfonyl]-5-[^{11}C]methoxy-3-[(4-methyl-1-piperazinyl)methyl]-1*H*-indole (*O*-[^{11}C]**2a**) and 1-[(2-bromophenyl)sulfonyl]-5-methoxy-3-[(4-[^{11}C]methyl-1-piperazinyl)methyl]-1*H*-indole (*N*-[^{11}C]**2a**), 5-[^{11}C]methoxy-3-((4-methylpiperazin-1-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole (*O*-[^{11}C]**2b**) and 5-methoxy-3-((4-[^{11}C]methylpiperazin-1-yl)methyl)-1-(phenylsulfonyl)-1*H*-indole (*N*-[^{11}C]**2b**), 1-((4-isopropylphenyl)sulfonyl)-5-[^{11}C]methoxy-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole (*O*-[^{11}C]**2c**) and 1-((4-isopropylphenyl)sulfonyl)-5-methoxy-3-((4-[^{11}C]methylpiperazin-1-yl)methyl)-1*H*-indole (*N*-[^{11}C]**2c**), 1-((4-fluorophenyl)sulfonyl)-5-[^{11}C]methoxy-3-((4-methylpiperazin-1-yl)methyl)-1*H*-indole (*O*-[^{11}C]**2d**) and 1-((4-fluorophenyl)sulfonyl)-5-methoxy-3-((4-[^{11}C]methylpiperazin-1-yl)methyl)-1*H*-indole (*N*-[^{11}C]**2d**), were prepared from their *O*- or *N*-desmethylated precursors with [^{11}C]CH_3OTf through *O*- or *N*-[^{11}C]methylation and isolated by HPLC combined with SPE in 40-50% radiochemical yield, based on [^{11}C]CO_2 and decay corrected to end of bombardment (EOB). The radiochemical purity was >99%, and the molar activity (MA) at EOB was 370-740 GBq/μmol with a total synthesis time of ~40-minutes from EOB.

Keywords: Serotonin (5-hydroxytryptamine) 6 receptor (5-HT$_6$R); Carbon-11-labeled 5-HT$_6$R antagonists; Radiosynthesis; Positron emission tomography (PET); Alzheimer's disease (AD).

Alzheimer's disease (AD) is the most common form of dementia and affects close to 50 million people worldwide in 2017.[1] The disease is divided into four stages, including predementia, early dementia, moderate AD and advanced AD.[2] The cause for most AD cases is still unknown, and there are several competing hypotheses like genetic, cholinergic hypothesis, amyloid hypothesis, and tau hypothesis, trying to explain it.[3] AD might be treated by symptomatic treatments and disease-modifying therapies such as neuroprotective and neurorestorative therapies, however, none effective strategy is approved for preventing, curing and slowing the progress of AD.[4] The current available medications can only be used to treat the cognitive problems of AD, focused on acetylcholinesterase inhibitors (AChEIs) including tacrine, rivastigmine, galantamine, and donepezil, as well as a *N*-methyl-$_D$-aspartate (NMDA) receptor antagonist memantine.[5] The benefit from these approved cognitive enhancing drugs for AD is small, and novel alternate therapy for treating cognitive disorders is eagerly needed.[6] Since the clinical trial of the disease-modifying therapies in AD is an extremely complex process with very high failure rate, the researchers have turned their focus to symptomatic