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Synthesis of carbon-11-labeled isonicotinamides as new potential PET agents for imaging of GSK-3 enzyme in Alzheimer's disease

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Abstract—The authentic standards 2-(cyclopropanecarboxamido)-*N*-(4-methoxypyridin-3-yl)isonicotinamide (**4a**) and 2-(cyclopropanecarboxamido)-*N*-(4-(4-methoxyphenyl)pyridin-3-yl)isonicotinamide (**7a**), and their corresponding precursors 2-(cyclopropanecarboxamido)-*N*-(4-hydroxypyridin-3-yl)isonicotinamide (**4b**) and 2-(cyclopropanecarboxamido)-*N*-(4-(4-hydroxyphenyl)pyridin-3-yl)isonicotinamide (**7b**) were synthesized from methyl 2-aminoisonicotinate and cyclopropanecarbonyl chloride with overall chemical yield 47% in three steps, 22% in four steps, 40% in three steps, and 17% in four steps, respectively. The target tracers 2-(cyclopropanecarboxamido)-*N*-(4-[^{11}C]methoxypyridin-3-yl)isonicotinamide ([^{11}C]**4a**) and 2-(cyclopropanecarboxamido)-*N*-(4-(4-[^{11}C]methoxyphenyl)pyridin-3-yl)isonicotinamide ([^{11}C]**7a**) were prepared from the precursors (**4b** and **7b**) with [^{11}C]CH_3OTf through *O*-[^{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 specific activity (SA) at EOB was 370-1110 GBq/μmol with a total synthesis time of ~40-minutes from EOB.

Keywords: Carbon-11-labeled isonicotinamides; Glycogen synthase kinase-3 (GSK-3); Radiosynthesis; Positron emission tomography (PET); Alzheimer's disease (AD).

Alzheimer's disease (AD) is the most common form of dementia and affects over 30 million people worldwide, and there are no reliable disease-modifying therapies at present.[1-4] Currently, the cause of AD remains unclear and no any effective strategy is approved for preventing, curing and slowing the progress of AD.[5-7] To discover more effective treatments, a reliable diagnostic tool is really needed.[8] Neuroimaging of AD is one of the most active as well as most challenging areas in neuroscience.[9] Advanced biomedical imaging technique positron emission tomography (PET) is a promising modality for AD, and significant advances have accomplished in this field of molecular imaging.[10] The development of PET imaging probes for *in vivo* detection of Alzheimer's brains is critical for early and accurate diagnosis and for the successful discovery of disease-modifying therapies.[11-13] Currently, aggregated β-amyloid plaques (Aβ) and tau protein are two major biomarkers for AD.[14,15] The representative Aβ PET tracers are [^{11}C]PIB[16] and [^{18}F]Amyvid (formerly known as [^{18}F]AV-45),[17] as displayed in Figure 1, the representative PET tau tracers include [^{11}C]PBB[18] and [^{18}F]T807 ([^{18}F]AV-1451)[19] (Figure 1), and promising clinical PET imaging results with these tracers have been reported.

The success and limitations of Aβ imaging and tau imaging have spurred efforts worldwide to develop new selective PET tracers for different imaging targets, and glycogen synthase kinase-3 (GSK-3) has become a novel and attractive molecular target for treatment and PET imaging of AD.[20] The enzyme GSK-3 is a serine/threonine protein kinase, which exists as two isoforms GSK-3α and GSK-3β. GSK-3 plays an important role in a number of diverse cellular processes including metabolism, differentiation, proliferation, and