11C-Labeling of a Potent Hydroxyethylamine BACE-1 Inhibitor and Evaluation in vitro and in vivo

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Introduction

Background: Alzheimer’s disease (AD) is the most frequent form of dementia, representing a majority of all severe dementia cases. The disorder is characterized by neurodegeneration leading to progressive decline in cognitive functions [1]. Although the AD pathology is not fully understood, the current hypothesis is accumulation of aggregated extracellular amyloid-\(\beta\) peptides. These aggregates consists of two fragments (A/\(\beta\)40 and A/\(\beta\)42), of the membrane bound protein amyloid-\(\beta\) precursor protein (APP) obtained by cleavage by the enzymes \(\beta\)-secretase (BACE-1) and subsequently by \(\gamma\)-secretase in the C-terminal. BACE-1 is required for the formation of A/\(\beta\) in the brain and BACE-1 inhibitors are thus attractive as potential anti-amyloid agents preventing or slowing down the neurodegenerative process in AD [2]. We herein describe the synthesis, 11C-radiolabeling, in vitro and in vivo evaluation of a BACE-1 inhibitor as a potential biomarker for AD.

Experimental and Results

Chemistry: Three different precursors were synthesized starting from methyl-3-nitrobenzoate (1). After halogenation with NBS or NIS, reduction, mesylation, methylation and hydrolysis the two intermediates 2a and 2b were further peptide coupled with a chiral amine to produce the three different precursors 3a, 3b and 3c. Several different palladium/ligand systems were tested resulting in 29±12% radiochemical yield using 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos). Other ligands such as Triphenyphosphine, tri(o-tolyl)phosphine and 1,1’-bis(diphenylphosphino)ferrocene yielded desired product in lower yields (3-15% RCY).

Biology and Conclusion: Autoradiography showed low affinity for BACE-1 enzyme. Ex vivo organ distribution studies in rats showed fast clearance into small intestines and low brain uptake at all time points investigated. Small animal PET in three animals confirmed ex vivo findings. The preclinical studies in rats showed fast blood clearance probably through biliary excretion into the small intestines. The brain uptake and the brain to blood ratio was very low suggesting that this radioligand is not useful as a tracer for the BACE-1 enzyme.