DEVELOPMENT OF SELECTIVE GAMMA-SECRETASE MODULATORS FOR THE POTENTIAL TREATMENT OF AD

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Alzheimer’s disease (AD) is the most common dementia in elderly. It is characterized by progressive memory loss together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes. In the brain of AD patients extracellular senile plaques composed of β-amyloid (Aβ) peptides, intracellular neurofibrillary tangles consisting mainly of hyperphosphorylated tau proteins and neuronal loss is observed. Gene mutations of patients with familial AD and in-vivo results from transgenic animal models suggest that AD is caused by elevated levels of Aβ in the brain. Aβ is formed through a consecutive cleavage of the two aspartic proteases β- and γ-secretase from the amyloid precursor protein (APP). Therefore γ-secretase is an attractive target for developing AD drugs. However, inhibition of γ-secretase also leads to notch related toxicity in the thymus, gut and spleen. To circumvent this liability we screened for compounds which do not inhibit but modulate γ-secretase activity by shifting the formation of the toxic Aβ42 peptide mainly to the formation of the shorter non-toxic Aβ fragments. Compound 1 was identified as potent (IC₅₀(Aβ42) = 800 nM) selective γ-secretase modulator belonging to the structural class of Aminothiazoles. SAR could be established rapidly leading to compound 2 with increased potency (IC₅₀ = 200 nM) and more favorable properties showing activity in a transgenic in vivo model for AD. We will show detailed SAR and compound properties which lead to highly potent compounds in vitro and in vivo.