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Development of Dual-acting Modulators for Proteolytic Cleavage of Amyloid Precursor Proteins

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One of the pathological hallmarks of Alzheimer's disease (AD) is the cerebral accumulation of amyloid plaques, and the major constituents of these plaques are the 40–42 residue amyloid-β peptides (Aβs), to which the amount of generation was dependent on the proteolytic processing of amyloid precursor proteins (APPs) sequentially by the β- and γ-secretases. An alternative processing of APP by α-secretase could be regulated via activation of mitogen-activated protein kinase (MAPK) pathway and considered to be beneficial, because this process generates neuroprotective secretory amyloid precursor protein (sAPP) and thus precludes the production of amyloidogenic Aβs and reduces the risk of AD. On the basis of these investigations, strategies to the development of single chemical entities to modulate multiple targets were suitably applied to the therapeutic approaches for AD.

Here, efforts to identify dual-acting molecules and the screening for selectivity against γ-secretase and simultaneously modulation of MAPK pathway of these compounds are presented.