Medicinal Chemistry & Drug Discovery

Current Progress in Quinazoline Derivatives as Acetylcholinesterase and Monoamine Oxidase Inhibitors

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Among the *N*-containing heterocyclic compounds, quinazoline-4-(3H)-one derivatives have been the center of attraction of medicinal and synthetic chemists due to their excellent versatility in biological activities that are witnessed by many approved drugs available in the market which contains quinazoline as main pharmacophore unit. This review mainly focuses the recent and current progresses in quinazoline derivatives as an acetylcholinesterase (AChE) and monoamine oxidase (MAO)-B inhibitors. The review has leanings towards the molecular determinants and structure-activity relationships (SAR) of quinazoline derivatives on AChE and MAO inhibitory potencies.

Introduction

Alzheimer's disease (AD) is one of the major common causes of dementia in the elderly people. AD is characterized by the gradual decline in both cognitive and non-cognitive functions, which leads to the impairment of the short term or the long term memory like language skills, attention and concentration. The major impact of the AD is to affect the non-cognitive functions like depression, personality changes, behaviors etc. Atrophy of cerebral cortex, hippocampus and narrowing of gyri are commonly found in the brains of the AD patient.[1] Formation of intracellular neurofibrillary tangles and extracellular senile plaques formation are the major reasons for the changes in the AD patients' brain.

The cholinergic hypothesis states that reduction in the acetylcholine synthesis is one of the major reasons for AD, and thus the therapeutic strategies aimed at the inhibition of acetylcholinesterase (AChE) activity to avoid the lowering of the acetylcholine level. Therefore, AChE inhibitors are used to improve the function of neuronal cells and to limit the degradation of acetylcholine. For the normal growth and repair, amyloid precursor protein (APP) is essential. The two major pathways, viz. amyloidogenic and non- amyloidogenic, are responsible for the AAP breakdown.[2–5] These pathways help to cleanse the APP into fragments in AD patients. Accumulation of plaques (tau proteins, neurofibrillary tangles) in the brain results in the blocking of neurotransmitters from neural communications.[6–9] In the Tau hypothesis, the pathology of AD is related to the tau protein hyperphosphorylation, which leads to the formation of intracellular neurofibrillary tangles. Based on these pieces of evidence, AD is considered to be a multifactorial disease, and hence multi-targeted drug approach should be taken into consideration for treating them, which would be able to reduce AChE activity, oxidative stress, amyloid-beta (Aβ) aggregation, tau aggregation and metal dyshomeostasis.[10–14]

AChE is the enzyme responsible for the degradation of the acetylcholine neurotransmitter, and serves as the function of ending synaptic transmission. AChE plays a major role in a cholinergic neuron, including central and peripheral nerves system.[15] FDA-approved drugs currently available in the market for treating AD are memantine, galantamine, donepezil

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