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Design, synthesis and biological evaluation of novel 2-phenyl-1-benzopyran-4-one derivatives as potential poly-functional anti-Alzheimer's agents†

Manjinder Singh and Om Silakari*

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The development of Multi-Target Directed Ligands (MTDLs) has emerged as a promising approach for targeting the complex etiology of Alzheimer's disease (AD). Following this approach, a new series of 2-phenyl-1-benzopyran-4-one derivatives was designed, synthesized and biologically evaluated as inhibitors of acetylcholinesterases (AChEs), advanced glycation end product (AGEs) formation and also for their radical scavenging activity. The *in vitro* studies showed that the majority of the synthesized derivatives inhibited acetylcholinesterase (AChE) with IC_{50} values in the low-micromolar range. Among them, inhibitors **7a**, **7h** and **7k**, strongly inhibited AChE, with IC_{50} values of 6.33, 7.56 and 11.0 nM, respectively, and were more potent than the reference compound donepezil. Moreover, the molecular docking study showed that most potent compounds simultaneously bind to the catalytic active site and the peripheral anionic site of AChE. Additionally, these compounds exhibited a greater ability to inhibit advanced glycation end product formation with additional radical scavenging properties. Thus, 2-phenyl-1-benzopyran-4-one derivatives might be promising lead compounds for potential poly-functional anti-Alzheimer's agents.

1. Introduction

Alzheimer's disease (AD) is the most common form of irreversible dementia in ageing patients. It is a neurodegenerative disorder associated with a selective loss of cholinergic neurons and a subsequent reduction of acetylcholine (ACh) in the brain leading to progressive decline in cognitive, executive and memory functions and eventually to incapacitating dementia before death.[1,2] The prevalence of AD dramatically increases with age and it doubles for every five-year interval after the age of 65.[3] Besides several diverse hallmarks such as β-amyloid (Aβ) deposits, τ-protein aggregation and low levels of acetylcholine (ACh), AD brains display constant evidence of oxidative damage.[4–7] The cholinergic hypothesis represents one of the conventional hypotheses proposing that the extensive decrease of ACh leads to cognitive and memory deficits in AD patients. Acetylcholinesterase (AChE) is the key enzyme, which hydrolyse acetylcholine (ACh) at the cholinergic synapses. Acetylcholinesterase inhibitors (AChEIs) could increase the level of ACh in AD patients through the inhibition AChE and, therefore, relieve some symptoms experienced by patients.[8,9] Till now, AChEIs are the only drugs used clinically for the treatment of AD (Fig. 1).[10,11]

Pathogenesis of AD is significantly impacted by oxidative stress which may further promotes the formation of amyloid plaques and neurofibrillary (NFT) tangles in AD.[12,13] Oxidative stress particularly induces injury in the most cellular macromolecules of AD brain including nucleic acids, proteins, and lipids. These findings support the 'oxidative stress' hypotheses of AD, of which reactive oxygen species (ROS) play a key role in AD onset and progression.[14] Therefore, drugs aimed at clearing or preventing the formation of the free radicals may be useful for the management of AD.

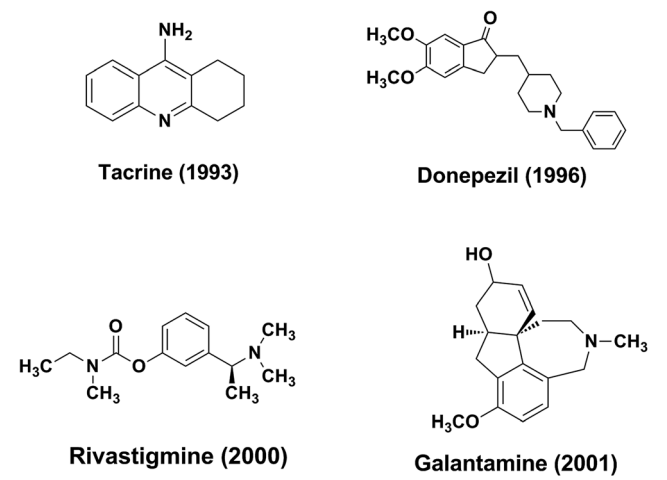

Fig. 1 FDA approved drugs for the treatment of Alzheimer's disease.

Molecular Modeling Lab, Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Punjab, India, 147002. E-mail: omsilakari@gmail.com; Tel: +91 9501542696

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