



Imidazopyridine–coumarin derivatives as novel multi-target directed ligands (MTDLs): Balancing acetylcholinesterase inhibition and antioxidant activity for neuroprotection

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ABSTRACT

Quick, green and efficient chemical synthesis of imidazo[1,2-a]pyridine (IMPY) derivatives has been developed, affording good to excellent yields within short reaction times (20–60 min) fulfilling Green Chemistry principle 2 (atom economy), 3 (less hazardous synthesis), 4 (Design Benign Chemicals), and 8 (Reduce Derivatives). The synthesized compounds were characterized by standard spectroscopic techniques like ¹HNMR, ¹³CNMR and Mass spectroscopy which validate the formation of required heterocyclic compounds without any purification which reduce the unnecessary usage and wastage of organic solvents. Compounds were tested further for their antioxidant properties using 2,2-diphenyl-1-picrylhydrazyl (DPPH assay) and Ferric Reducing Antioxidant Power Assay (FRAP assay) spectrophotometrically which revealed significant antioxidant behavior, with IMPY 1 (87.7%, 40 mins), IMPY 6 (82.7%, 60 mins) and IMPY 3 (75.1%, 40 mins) showing promising radical scavenging potential comparable to ascorbic acid (98%). Further Molecular docking studies validate the results IMPY4 and IMPY6 also had an excellent docking score of -8.452 and -8.188 respectively, indicating a strong AChE binding affinity for the target protein (1EVE). IMPY1 displayed significant AChE inhibitory activity, with inhibition values exceeding 80% at concentrations between 1 and 100 μM, and an estimated IC₅₀ around 0.5 μM. This dual biological evaluation ensures that a single therapeutic agent can tackle both the cholinergic deficit and oxidative stress simultaneously.

1. Introduction

Neurodegenerative disorders or neurological conditions are characterized by change in composition and operation of central nervous system (CNS), gradual loss of neuronal structure and function and are commonly known as neurodegenerative diseases (NDDs) [1]. Among these, Parkinson's disease (PD) and Alzheimer's disease (AD) are well-known common (NDDs) that affect millions of people worldwide. For (AD) the main root cause of neuronal damage are the accumulation of beta-amyloid (Aβ) plaques and tau protein that forms tangles in the brain, leading to irreversible cognitive decline, memory impairment, and behavioral disturbances [2] For Parkinson's disease (PD) affecting major the movement of aged population and is caused by loss of dopaminergic neurons in the Substantia Nigra(SN) of pars compacta (SNpc)

and decrease in amount of neurotransmitter dopamine (DA) [3]. These behavioral disturbance and memory impairment in (NDDs) are directly linked to the progressive reduction of cholinergic neurotransmission in the brain. The neurotransmitter acetylcholine (Ache) is an essential factor for cognitive functions as learning and memory building. Cognitive decline in AD has been associated with a progressive loss of basal forebrain cholinergic neurons and a disruption of cholinergic signaling. Thus, acetylcholinesterase (AChE), the enzyme responsible for ACh hydrolysis, is an important therapeutic target for improving cholinergic neurotransmission and alleviating cognitive and behavioral symptoms of AD [4]. However, as AD progresses these levels of AChE decreases up to 67% of normal levels. Overexpression of Ache in AD brains has been shown to accelerate A-beta aggregation and to promote tau phosphorylation contributing to the formation of neurofibrillary tangles [5].

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