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Aldoxime- and hydroxy-functionalized chalcones as highly potent and selective monoamine oxidase-B inhibitors

Jong Min Oh[a,1], T.M. Rangarajan[b,1,*], Reeta Chaudhary[c], Nicola Gambacorta[d], Orazio Nicolotti[d], Sunil Kumar[e], Bijo Mathew[e,*], Hoon Kim[a,*]

[a] Department of Pharmacy, and Research Institute of Life Pharmaceutical Sciences, Sunchon National University, Suncheon 57922, Republic of Korea
[b] Department of Chemistry, Sri Venketeswara College, University of Delhi, New Delhi 110 021, India
[c] Department of ENT, All India Institute of Medical Sciences (AIIMS), New Delhi 110 029, India
[d] Dipartimento di Farmacia Scienze del Farmaco, Università degli Studi di Bari "Aldo Moro", Via E. Orabona, 4, I-70125 Bari, Italy
[e] Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, AIMS Health Sciences Campus, Kochi 682 041, India

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ABSTRACT

A panel of 30 chalcone derivatives, including 19 aldoxime-chalcone ethers (ACE), and 11 hydroxyl–chalcones (HC), previously synthesized using a Pd-catalyzed C–O cross-coupling method were evaluated for their inhibitory activities against monoamine oxidases (MAOs), cholinesterases (ChEs), and β-secretase (BACE-1). **HC6** was the most potent inhibitor of MAO-B with an IC_{50} value of 0.0046 μM and a selectivity index (SI) of 1,113. **HC3** also potently inhibited MAO-B (IC_{50} = 0.0067 μM) and had the highest SI (1,455). **ACE7** and **ACE15** were also potent MAO-B inhibitors (IC_{50} = 0.012 and 0.018 μM, respectively), with SIs of 260 and 1,161, respectively. **HC3** and **HC6** were reversible competitive inhibitors of MAO-B, with K_i values of 0.0036 and 0.0013 μM, respectively. A structure–activity relationship revealed that methyl and fluorine substituents contributed to increasing both inhibition and selectivity. **ACE7** was the most effective inhibitor of MAO-A (IC_{50} = 1.49 μM), followed by **ACE3** (IC_{50} = 3.75 μM). No compounds effectively inhibited AChE, BChE, or BACE-1. A docking simulation showed that the ligand efficiency and docking scores of **HC3** and **HC6** toward MAO-B were consistent with the experimental IC_{50} values. These results suggest that **HC3** and **HC6** can be considered promising candidates for the treatment of neurological disorders.

1. Introduction

Monoamine oxidases (MAOs) are a family of mitochondria-bound flavin-dependent enzymes that play a crucial role in the catalytic degradation of biogenic amines [1]. MAOs have two isoforms, namely MAO-A and MAO-B, which have almost 70% similarity in their amino acid chain sequences but differ in inhibitor specificities, substrate preferences, tissue distributions, and immunological properties [2,3]. Both isoforms are composed of hydrophobic cavities and extend from the flavin region of the enzyme to the opposite side of the adenosine ring of flavin adenine dinucleotide (FAD) on another protein surface [4]. The elucidation of the crystal structures of MAO-A and MAO-B provided a new understanding of the structural requirements for the rational design and development of a new class of selective MAO inhibitors [5]. Hydrazines, amphetamine derivatives, benzoxazin acetamides, nitrofurans, oxazolidinones, curuminoids, and flavonoids are the first generation of non-selective MAO inhibitors, whereas propargylamines, morpholinobenzamides, coumarins, chalcones, and pyridinecarboxamides are a selective class of reversible or irreversible MAO-A/MAO-B inhibitors [6].

Considering their therapeutic potential in the management of anxiety disorders and depression, selective MAO-A or MAO-B inhibitors can be used as adjuvant therapies for various neurodegenerative diseases [7]. Parkinson's disease (PD) is a second-line major neurological disorder, in which MAO-B is mainly involved in the catalysis of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) oxidation into MPP^+ in the astrocyte triggering parkinsonian indicators [8]. The formed metabolite $MPP^+$is due to increased MAO-B activity that can lead to neurological insults in the nerve terminals and cause parkinsonian symptoms [9]. To date, selegiline and rasagiline are the two FDA-approved selective and irreversible MAO-B inhibitors, which are effectively used in the management of early-stage PD [10]. The irreversible nature of the existing MAO-B inhibitors has certain major drawbacks, such as target disruption, immunogenicity, and poor pharmacokinetic profiles [11]. Therefore, the development of highly selective and reversible MAO-B in-

* Corresponding authors.
E-mail addresses: rangarajan93150@gmail.com (T.M. Rangarajan), bijomathew@aims.amrita.edu (B. Mathew), hoon@sunchon.ac.kr (H. Kim).
[1] Both the authors contributed equally to this work.

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