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Two dimensional-QSAR and molecular dynamics studies of a selected class of aldoxime- and hydroxy-functionalized chalcones as monoamine oxidase-B inhibitors

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ABSTRACT

Candidates generated from unsaturated ketone (chalcone) demonstrated as strong, reversible and specific monoamine oxidase-B (MAO-B) inhibitory activity. For the research on MAO-B inhibition, our team has synthesized and evaluated a panel of aldoxime-chalcone ethers (ACE) and hydroxylchalcones (HC). The MAO-B inhibitory activity of several candidates is in the micro- to nanomolar range in these series. The purpose of this research was to develop predictive QSAR models and look into the relation between MAO-B inhibition by aldoxime and hydroxyl-functionalized chalcones. It was shown that the molecular descriptors ETA Shape P, MDEO-12, ETA dBetaP, SpMax1 Bhi and ETA EtaP B are significant in the inhibitory action of the MAO-B target. Using the current 2D QSAR models, potential chalcone-based MAO-B inhibitors might be created. The lead molecules were further analyzed by the detailed molecular dynamics study to establish the stability of the ligand–enzyme complex.

Abbreviations: MAO-B: Monoamine oxidase-B; FAD: Flavin adenine dinucleotide; QSAR: Quantitative structure-activity relation; ACE: Aldoxime-chalcone ethers; HC: Hydroxychalcones

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Introduction

Chemicals called neurotransmitters are mostly located in the brain and are responsible for all body activities. Diffusion, reuptake and enzyme-mediated breakdown are the three mechanisms that control the concentration of neurotransmitters in a synaptic cleft after they have served their purpose. Based on their uses and chemical compositions, more than 40 neurotransmitters have been identified and categorized. Biogenic amines, also known as monoamine neurochemicals, are key neurotransmitters that play a variety of roles in the brain, including neuroexcitatory, neuroinhibitory and neuromodulatory transmissions. Examples of these neurochemicals include epinephrine and others (Harilal et al., 2020).

Excessive degradation and quick reuptake of the neurotransmitters from the synapse cause neurotransmitter imbalance, leading to several neurodegenerative disorders (Szatmari et al., 2019). Human monoamine oxidase (MAO) is a membrane-bound flavoenzyme expressed in peripheral and neural tissues and is crucial for the oxidative degradation of dietary amines and amine neurotransmitters (Guglielmi et al., 2019; Tripathi & Ayyannan, 2019). There are two types of MAO: MAO-A and MAO-B, both of which include the cofactor flavin adenine dinucleotide (FAD) (Hong & Li, 2018). The substrate specificity, amino acid sequences and inhibitor selectivity of these variants are used to describe them (Ramsay, 2016). While MAO-B preferentially deaminates phenylethylamine and benzylamine, MAO-A has a greater affinity for serotonin and noradrenaline (Riederer & Müller, 2017). MAO-B inhibitors are used to treat Alzheimer's and Parkinson's disorders, whereas MAO-A inhibitors work as antidepressants and anti-anxiety medications (Carradori et al., 2018; Guglielmi et al., 2022; Mathew & Kim, 2020).

In recent years, MAO inhibitors have been extensively studied using ligand-based computer-aided drug design techniques, such as 2D and 3D-quantitative structure–activity relationship (QSAR), in order to understand better the binding process and the structural requirements for achieving high activity. (Ambure et al., 2019; Is et al., 2020; Mathew et al., 2017; Mellado et al., 2021; Ramesh & Muthuraman,

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