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RESEARCH ARTICLE

Development of 2D, 3D-QSAR and Pharmacophore Modeling of Chalcones for the Inhibition of Monoamine Oxidase B

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ARTICLE HISTORY

Received: February 09, 2021
Revised: June 04, 2021
Accepted: June 21, 2021

DOI:
10.2174/1386207324666210816125738

Abstract: ***Background*:** Selective and reversible types of MAO-B inhibitors have emerged as promising candidates for the management of neurodegenerative diseases. Several functionalized chalcone derivatives were shown to have potential reversible MAO-B inhibitory activity, which have recently been reported from our laboratory.

***Methods*:** With the experimental results of about 70 chalcone derivatives, we further developed a pharmacophore modelling, and 2D and 3D- QSAR analyses of these reported chalcones for MAO-B inhibition.

***Results*:** The 2D-QSAR model presented four variables (MATS7v, GATS 1i and 3i, and C-006) from 143 Dragon 7 molecular descriptors, with a r^2 value of 0.76 and a Q^2_{cv} for cross-validation equal to 0.72. An external validation also was performed using 11 chalcones, obtaining a Q^2_{ext} value of 0.74. The second 3D-QSAR model using MLR (multiple linear regression) was built starting from 128 Volsurf+ molecular descriptors, being identified as 4 variables (Molecular descriptors): D3, CW1 and LgS11, and L2LGS. Adetermination coefficient (r^2) value of 0.76 and a Q^2_{cv} for cross-validation equal to 0.72 were obtained for this model. An external validation also was performed using 11 chalcones and a Q^2_{ext} value of 0.74 was found.

***Conclusion*:** This report exhibited a good correlation and satisfactory agreement between experiment and theory.

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Keywords: Chalcones, MAO-B, 2D-QSAR, 3D-QSAR, pharmacophore modeling, Q^2_{ext}.

1. INTRODUCTION

Designing a new class of inhibitors against Monoamine oxidases (MAOs) is a promising drug design strategy for various neurodegenerative disorders [1]. The enzyme is found in two isoforms, *viz*., MAO-A, and MAO-B, which metabolize amines in the brain and peripheral tissues [2]. During the oxidative deamination process of biogenic amines catalysed by MAOs, the hydrogen peroxide by-product is formed which can further initiate the Reactive Oxygen Species (ROS) formation. The generation of these reactive free radicals promotes oxidative damage in the neuronal tissues [3]. Many of the clinical studies evidenced that elevated expression of MAO-B can manipulate neurotoxicity, which leads to Parkinson's Diseases (PD), Alzheimer's Disease (AD) *etc*., which are commonly known as neurodegenerative diseases [4]. The first line class of MAO-B inhibitors like deprenyl and rasagiline are irreversible in nature, making covalent bond interaction with flavin unit of MAO-B and propargyl group of drugs [5]. These suicidal inhibitors show poor pharmacokinetic profile, target disruption, and immunogenicity of enzyme-inhibitor adducts [6].

Some works have been performed using QSAR models and MAO-B. A description of ligand-based models to

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