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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

An expeditious one-pot microwave facilitated versus conventional syntheses: in vivo biological screening and molecular docking studies of some 3,5-disubstituted-4,5-dihydro-(1*H*)-pyrazole derivatives

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Abstract A series of 3,5-disubstituted-2-pyrazoline derivatives (**2a**–**2t**) were synthesized by reacting different aromatic/heteroaromatic aldehydes and ketones, in a two-step reaction through Claisen Schmidt condensation, followed by cyclization of the resulted chalcones with hydrazine hydrate in the presence of a base using conventional and microwave approaches. The synthesized derivatives were characterized by various physicochemical methods, and their chemical structures were established by IR, Mass, ^{1}H-NMR, ^{13}C-NMR spectroscopic data and elemental analysis. The antidepressant with tail suspension test and forced swim test and anti-anxiety with Elevated Plus Maze Test activities were evaluated using suitable animal models. Compounds **2i**, and **2j** showed noticeable antidepressant activity, by reducing the duration of immobility in both the tests, while compounds **2a** and **2b** were found to possess good anxiolytic activity, by increasing the number of arm entries and open arm exploratory time at the tested doses (50 and 100 mg/kg b.w.), when compared to the standard drugs imipramine and diazepam, respectively. In order to ascertain the binding interactions of the synthesized derivatives to the MAO-A target protein, molecular docking was employed which demonstrated the key interactions with the amino acid residues Asn181, Phe208, Tyr69, Tyr197, Tyr444 and Met445 at the binding site. In addition, the most active derivatives **2i** and **2b** showed some imperative conserved interactions of the PDB co-crystal ligand 2Z5X with the amino acid residues at the binding site of MAO-A protein. The results of the study also demonstrated that the Glide gscores of the synthesized derivatives were in close correlation with the in vivo biological activity data, in particular with the forced swim test of the antidepressant activity with a very good correlation coefficient of 0.754103. Furthermore, the ADME properties of the synthesized derivatives were predicted and found to be within the affirmed limits.

Keywords 2-Pyrazolines · Antidepressant · Anti-anxiety · MAO inhibitors · Neurotoxicity · Microwave synthesis · Molecular docking · In silico ADME prediction

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Introduction

Monoamine oxidase (MAO) [E.C. 1.4.3.4] is a flavin-containing key enzyme located on the outer membrane of the mitochondria, bound via a C-terminal transmembrane polypeptide segment (Mitoma and Ito, 1992) and inserted in the membrane by means of ubiquitin, with energy provided by ATP (Zhuang *et al.*, 1992), in neuronal, glial, and other cells, regulating monoaminergic homeostasis and possibly neurotransmission. Low level of certain

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