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FACILE ONE-POT SYNTHESIS METHODOLOGY FOR NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVES OF 3,5-DISUBSTITUTED 4,5-DIHYDRO-1H-PYRAZOLE, THEIR BIOLOGICAL EVALUATION AND MOLECULAR DOCKING STUDIES

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A series of 2-pyrazoline derivatives (**PS-1** to **PS-16**) were synthesized by reacting different aromatic/heteroaromatic aldehydes and ketones, in a two-step reaction through Claisen – Schmidt condensation, followed by cyclization of the resulting chalcones with hydrazine hydrate in the presence of a base using conventional and microwave approaches. The synthesized derivatives were characterized by various physicochemical methods including IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopic data and elemental analysis. The antidepressant and anti-anxiety activities were evaluated using suitable animal models. Compounds **PS-3,** and **PS-14** showed noticeable antidepressant activity, by reducing the duration of immobility in both tests, while compounds **PS-9** and **PS-12** 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.) in comparison to standard drugs imipramine and diazepam, respectively. In order to elucidate binding interactions of the synthesized derivatives to the MAO-A target protein, molecular docking was employed which demonstrated the key interactions with amino acid residues Phe208, Asn181, and Tyr407 at the binding site. Further, the ADME properties of the synthesized derivatives were predicted and found to fall within the stated limits.

Keywords: 3, 5-Disubstituted-4,5-dihydro-(1H)-pyrazoles; antidepressant; anti-anxiety: MAO inhibitors; microwave synthesis; molecular docking.

1. INTRODUCTION

Amine oxidases (AOs) are a heterogeneous superfamily of enzymes that catalyze the oxidative deamination of mono-, di- and polyamines [4, 20]. Monoamine oxidases (MAOs) are present in the outer mitochondrial membranes of neuronal glial and other mammalian tissues, anchored by C-terminal domain. The oxidative deamination of biogenic amines in the brain and the peripheral tissues are catalyzed by MAOs. The proper functioning of synaptic neurotransmission is due to rapid degradation of these molecules and is critically important for the regulation of emotional behaviors and other brain functions [2]. MAOs exist in two isoforms, MAO-A and MAO-B, which differ in substrate specificity and sensitivity to acetylenic inhibitors clorgyline and *l*-deprenyl (selegiline) [36]. Due to their key role, both MAO isoforms provide a better understanding of the pharmacophoric requirements needed for the rational design of potent and selective enzyme inhibitors [1, 8]. MAO inhibitors are best known for their powerful antidepressant effects and are efficient in treating certain anxiety disorders including panic disorder and social phobia [31, 37]. In particular, reversible and selective MAO-A inhibitors are used as anti-depressant and anti-anxiety drugs [21], while MAO-B inhibitors have proved to be useful in the treatment of Parkinson's disease (PD) and Alzheimer's disease (AD). Under some other conditions including affective disorders, neurodegenerative diseases, stroke, and ageing, MAO inhibitors have proved to be of great therapeutic value [24, 36].

Pyrazolines are well known nitrogen-containing 5-membered heterocyclic scaffolds with diverse chemical reactivity. 2-Pyrazolines seem to be the most frequently studied pyrazoline type compounds arising from structural modification of the prototype drug molecule. They have several pro-

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