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2-PYRAZOLINE DERIVATIVES IN NEUROPHARMACOLOGY: SYNTHESIS, ADME PREDICTION, MOLECULAR DOCKING AND *IN VIVO* BIOLOGICAL EVALUATION

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ABSTRACT

A novel series of 1,3,5-trisubstituted-2-pyrazoline derivatives **(PFC-1 to PFC-16**) were synthesized in a three step reaction using conventional and microwave assisted green chemistry approach. The synthesized derivatives were characterized and their chemical structures were established by various physicochemical methods such as IR, Mass, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. The synthesized compounds were tested for their neuropharmacological potential. The compounds exhibited significant antidepressant and anti-anxiety activities against various behavioral *in vivo* models. Compounds **PFC-3** and **PFC-12** were found to be the most active derivatives in the series. The 2-pyrazoline analogs, having 2-hydroxyphenyl and anthracen-9-yl substitution at 3rd position while 4-benzyloxyphenyl and 4-methylphenyl substitution at 5th position, were decisive in eliciting good antidepressant and anxiolytic properties, respectively. The docking experiments revealed that the synthesized derivatives were potential inhibitors of MAO-A protein, which plays a central role in managing depression and anxiety disorders. The most potent derivatives were found to be involved in some key interactions with Tyr407, Tyr444, Phe352 and Ala68 amino acid residues at the binding site of MAO-A protein. All the synthesized derivatives successfully passed the pharmacokinetic barriers of absorption, distribution, metabolism and elimination as predicted using *in silico* techniques without showing any substantial indication of acute and neurotoxicity. This was further confirmed in the laboratory by performing acute toxicity studies as per OECD guidelines.

Keywords: 4,5-Dihydro-(1*H*)-pyrazoles, antidepressant, anxiolytic, MAO inhibitors, neurotoxicity, microwave synthesis, molecular docking

INTRODUCTION

The monoamine oxidase (EC 1.4.3.2; amine oxygen oxidoreductase) is a FAD-dependent major neurotransmitter degrading enzyme present in the outer mitochondria of neuronal, glial and other cells, that catalyse the aerobic oxidation of structurally diverse xenobiotic arylalkylamine substrates including neurotransmitters and exogenous amines to the corresponding aldehyde and imines with the generation of hydrogen peroxide (Rose et al., 1989). In mammals MAO exists