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N1-BENZENESULFONYL-2-PYRAZOLINE HYBRIDS IN NEUROLOGICAL DISORDERS: SYNTHESES, BIOLOGICAL SCREENING AND COMPUTATIONAL STUDIES

Avinash C. Tripathi[1], Savita Upadhyay[1], Sarvesh Paliwal[2], Shailendra K. Saraf[1*]

[1] Division of Pharmaceutical Chemistry, Faculty of Pharmacy, Babu Banarasi Das Northern India Institute of Technology, Lucknow-226028, U.P., India
[2] Professor and Head, Department of Pharmacy, Banasthali Vidyapith, Banasthali, Tonk-304022, Rajasthan, India

E-mails: aviniec31@gmail.com; savvypharma@gmail.com; y paliwalsarvesh@yahoo.com; dirpharmniec@gmail.com

[*] Corresponding author:Prof. (Dr.) Shailendra K. Saraf, Director (Pharmacy), Division of Pharmaceutical Chemistry, Faculty of Pharmacy, Babu Banarasi Das Northern India Institute of Technology, BBD City, Faizabad Road, Chinhat, Lucknow-226028, U.P., India.
Voice Contact: +91-522-3911052 (office), +919839228022(mobile),
Fax: +91-522-3911152,E-mail: dirpharmniec@gmail.com

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ABSTRACT

A novel series of 1,3,5-trisubstituted-2-pyrazolines **(5a-5t)** was prepared via Claisen Schmidt condensation, followed by heterocyclization with hydrazine hydrate, substitution of N1 hydrogen of 2-pyrazoline nucleus with 4-chlorobenzenesulfonylchloride, applying conventional and green chemistry approaches. Among the two, microwave assisted organic synthesis (MAOS) emerged as a better synthetic tool in terms of faster reaction rate and high yield. Various physicochemical and spectral studies were conducted to characterize the synthesized derivatives including- IR, Mass, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. During pharmacological evaluation, compound **5b** showed excellent anti-anxiety activity and compound **5k** exhibited the best antidepressant effect at the tested doses, 50 and 100 mg/kg b.w., being comparable to diazepam and imipramine, respectively. The docking experiments confirmed the probable mechanism of neuropharmacological action, showing excellent affinity towards MAO-A target protein, which was also evidenced from some of the key interactions with binding site residues Ala68, Tyr69 and Phe352. Furthermore, complimentary *in silico* pharmacokinetic recital without any potential risk of neurotoxicity (as evaluated by rotarod and actophotometer tests), or carcinogenicity, mutagenicity, reproductive toxicity, acute toxicity and irritancy (as predicted by LAZAR and OSIRIS programs) signified their probable use in depression and anxiety disorders.

Keywords: 2-Pyrazolines, antidepressant and anti-anxiety, neurotoxicity, microwave synthesis, molecular docking, *in silico* ADME prediction

INTRODUCTION

Monoamine oxidase (MAO) regulates monoaminergic homeostasis and neurotransmission in the nervous system. Low level of certain neurotransmitters (NTs) in the brain, like dopamine (DA), norepinephrine (NE), serotonin (5-HT), and gamma amino butyric acid (GABA), is the main cause of depressive mental disorders. These NTs are released during neurotransmission and are degraded by the MAOs enzymes.