Medicinal Chemistry Research
https://doi.org/10.1007/s00044-018-2167-z

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Derivatives of 4,5-dihydro (*1H*) pyrazoles as possible MAO-A inhibitors in depression and anxiety disorders: synthesis, biological evaluation and molecular modeling studies

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

Received: 20 January 2018 / Accepted: 9 March 2018

Abstract
A series of 1,3,5-trisubstituted-2-pyrazoline derivatives **(3a–3t)** were synthesized in appreciable yields by substituting N1 position of 2-pyrazoline nucleus with 4-nitrobenzenesulfonylchloride using conventional and microwave assisted synthetic approaches. The physicochemical and spectral characterization such as IR, Mass, ^{1}H-NMR and ^{13}C-NMR, and elemental analysis, assured the formation of proposed derivatives. Pharmacological studies revealed that compound **3d** exhibited highest antidepressant activity however, compound **3l** was found to be most effective anxiolytic agent at the tested doses (50 and 100 mg/kg b.w.), when compared to the control group. Molecular docking simulations established the possible mechanism of their neuropharmacological effects, with admirable affinity towards MAO-A protein. This was also evidenced from some of the key interactions of these compounds with the amino acid residues Ala68, Tyr69, Phe208, Tyr407 and Tyr444. Moreover, synthesized derivatives showed encouraging pharmacokinetic (ADME) and toxicological (neurotoxicity, carcinogenicity, mutagenicity, reproductive toxicity, irritancy and acute toxicity) parameters as predicted by computational programs. Some of these toxicity studies were further examined in wet laboratory by accomplishing behavioral neurotoxicity studies and acute toxicity studies as per OECD guidelines.

Key words 2-Pyrazoline · Anxiolytic · Antidepressant · Locomotor and neuromuscular coordination studies · Glide docking · FST and TST

Introduction

In the nervous system, the monoaminergic homeostasis and neurotransmission is regulated by monoamine oxidases (MAOs). Low level of certain neurotransmitters (NTs) in the brain, like-dopamine (DA), norepinephrine, serotonin (5-HT), and gamma amino butyric acid, is the main cause of depressive mental disorders. The concentration of NTs in the brain is increased by blocking the action of MOAs through monoamine oxidase inhibitors (MAOIs) (Meyer et al. 2006; Mitoma and Ito 1992). MAOIs belong to the first generation antidepressants used for decades to treat the patients suffering from high level of anxiety, atypical depression (Pletscher 1991), anergic bipolar depression and treatment resistant depression (Thase 2012), specific phobias, post-traumatic stress disorder and migraine headaches resistant to other therapies (Gareri et al. 2000). The MAO-A inhibitors are employed in the treatment of certain mental disorders such as depression and anxiety (Amrein et al. 1999). However, MAO-B inhibitors have proven their corrective value in neurodegenerative diseases (Foley et al. 2000; Youdim et al. 2006) such as Parkinson's (Cesura and Pletscher 1992) and Alzheimer's (Volz and Gleiter 1998). The initial hydrazine class of MAO inhibitors was associated with some severe adverse effects, such as liver toxicity and cheese reaction (Brown et al. 1989). These side-effects were correlated to nonselective and irreversible MAO inhibition. Pyrazoline derivatives have attracted substantial attention for years, chiefly 1,3,5-trisubstituted-2-pyrazoline pharmacophore has been associated with encouraging neurological activities such as tranquilizer, anticonvulsant, and antidepressant (Kaplancikli et al. 2010;

✉ Shailendra K. Saraf
dirpharmniec@gmail.com

[1] Division of Pharmaceutical Chemistry, Faculty of Pharmacy, Babu Banarasi Das Northern India Institute of Technology, Lucknow, U.P. 226028, India

[2] Professor and Head, Department of Pharmacy, Banasthali Vidyapith, Banasthali, Tonk, Rajasthan 304022, India

Published online: 23 March 2018