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A Review on the CNS Activity of Pyrazolines

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Abstract
The five membered heterocyclic compound pyrazoline is a significant group in heterocyclic chemistry. Many pyrazoline compounds are found possess broad spectrum of biological activities. They are found to possess anti convulsant, neuroprotective, antidepressant, anti inflammatory, anticancer, antimicrobial activities etc. Various pyrazoline derivatives were synthesized and their CNS activities were studied In this review various CNS activities of pyrazolines were discussed. The results shows that pyrazolines and it's derivatives found to possess CNS activity.
Keywords: *Pyrazolines, CNS activity, molecular docking, antidepressant.*

Introduction

Pyrazolines are an important class of heterocyclic compounds containing two nitrogen in the five membered ring. Pyrazoline derivatives are the electron rich nitrogen heterocycles which play an important role in diverse biological activities. The heterocyclic compounds widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Pyrazolines are reported to possess anti-inflammatory, analgesic, antimicrobial, anticancer, anti depressant and various other activities. As the ring is stable structural changes can be made in the ring which has inspired scientists and chemists.

Heterocyclic chemistry has grown very rapidly particularly in the development of synthetic methods and investigation of bioactive properties of the synthesized materials. The compounds having pyrazoline structure are a significant group in the heterocyclic chemistry. These compounds are scaffold target compounds in the field of medicinal and synthetic chemistry. These compounds were used in the development of drug research and agricultural products. Many pyrazoline compounds are reported to possess a broad spectrum of biological activities such as antimicrobial, antidepressant, neuroprotective, anticonvulsant, anti- inflammatory, analgesic, antitubercular, local anesthetic, hypoglycemic, hypotensive, insecticide, herbicide, and molluscicidal. The structure of pyrazoline is given in figure 1.

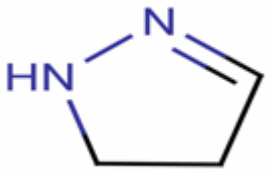

Fig 1: structure of pyrazoline

Substituted pyrazolines and their derivatives with different functional groups are important biological agents and many of research activities

are directed towards this class. Pyrazoline derivatives are the electron rich nitrogen heterocycles which play an important role in the diverse biological activities. These heterocyclic compounds widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Huge interest has been focused on the pyrazolines and substituted pyrazolines due to their diverse biological activities.

Considerable interest has been focused on the pyrazole structure, which has been known to possess a broad spectrum of biological activities such as tranquillising, muscle relaxant, psychoanaleptic, anticonvulsant and antihypotensive activities. The reported central nervous system (CNS) pharmacological actions of pyrazoline derivatives include antiepileptic and antidepressant effects; in addition to neurodegenerative disorders.

CNS Activity of Pyrazolines

Depression is one of the central nervous system disorder. Pyrazolines have been found to possess antidepressant potential. Some New 1,3,5-trisubstituted-2-pyrazolines were synthesized by Atla Srinivasa Rao et al and evaluated for their antidepressant profile and the compound showed antidepressant activity similar to standard, tranylcypromine. The presence of electron releasing group on phenyl ring attached at C-5 position of 2-pyrazoline is important for activity.

A series of 1,3,5-trisubstituted-2-pyrazolines[1] were synthesized by claisen Schmidt condensation, with hydrazine hydrate by heterocyclization, by conventional and green chemistry approaches. This gives high yield and as a better synthetic tool in terms of faster reaction rate. Spectral studies and physicochemical characterizations were done. After the pharmacological evaluation, the compound showed best anti depressant effect. Docking studies shows that it has good affinity towards the target protein, which is probable for mechanism of neuropharmacological action. *In silico* pharmacokinetic studies shows that they have reduced the risk of neurotoxicity, mutagenicity, reproductive toxicity, carcinogenicity in which they are signified their probable use in depression.

A classical synthesis of these compounds involves the base-catalyzed aldol condensation reaction[2] of aromatic ketones and aldehydes to give, α, β - unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazines affording 2- pyrazolines. Here, hydrazones are formed as intermediates, which can be cyclized to 2- pyrazolines in the presence of acetic acid, a cyclizing agent. The compounds showed significant anti depressant activity.

Derivatives of pyrazolines like 1, 3, 5-triphenyl-2-pyrazolines [3]were synthesized and evaluated them for antidepressant activity with a majority of the synthesized compounds possessing significant antidepressant activity in mice ($P < 0.05$) in the Porsolt behavioral despair test. Similarly, some 1-phenyl-, 1-thio carbamoyl- and 1-N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives were synthesized and investigated for antidepressant activitiy by the Porsolt test (forced swimming) test on albino mice.

Ten new 3,5-diphenyl-2-pyrazoline[4] derivatives were synthesised by reacting 1,3-diphenyl-2-propen-1-one with hydrazine hydrate. The chemical structures of the compounds were proved by means of their IR, 1 H-NMR spectroscopic data and microanalyses. The anti depressant activity was evaluated by porsolt behavioral test on swiss Webster mice. 3-(4-Methoxyphenyl)-5-(3,4-dimethoxyphenyl)-2-pyrazoline, 3-(4-methoxyphenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline and 3-(4-chlorophenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline reduced 41.94–48.62% immobility times at 100 mg kg−1 dose level. It was found that 4-chloro and 4-methoxy substituents on the phenyl ring at position of the pyrazoline ring increased the antidepressant activity. The replacement of chloro groups by bromo group and

methoxy by methyl group decreased activity in mice.

Based on the neuroprotective properties of 2-pyrazoline derivatives[5], were synthesized via the cyclization of the chalcones with suitable phenyl hydrazine hydrochloride derivatives. The compounds were investigated for neuroprotective effect in rat pheochromocytoma (PC-12) Adh cell line. *In silico* pharmacokinetic study predicted by the QikProp module of Schrodinger's Maestro molecular modelling package. 4-Methylsulfonylphenyl substituted compounds 3h (20%) and 4h (23%) were determined as the most promising neuroprotective agents related to their inductive roles in cell viability when compared with the 6-OHDA-positive control group (43% and 42%, respectively). *In silico* pharmacokinetic results shows that all compounds were within the acceptable range intended for human use. The compound has drawn attention as potential orally bioavailable therapeutic drug candidates against neurodegeneration in Parkinson's disease.

A novel series of 1,3,5-trisubstituted-2-pyrazoline[6] derivatives were synthesized in a three step reaction using conventional and microwave assisted green chemistry approach. The synthesized compounds were characterized by physicochemical parameters and by spectral studies. The neuropharmacological effect of the synthesized compounds were tested. By *in vivo* models their anti depressant activity was established. Compounds were found to be the most active derivatives in the series. The 2-pyrazoline analogs, were decisive in eliciting good antidepressant properties. The docking experiments revealed that the synthesized derivatives play a central role in managing depression. 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.

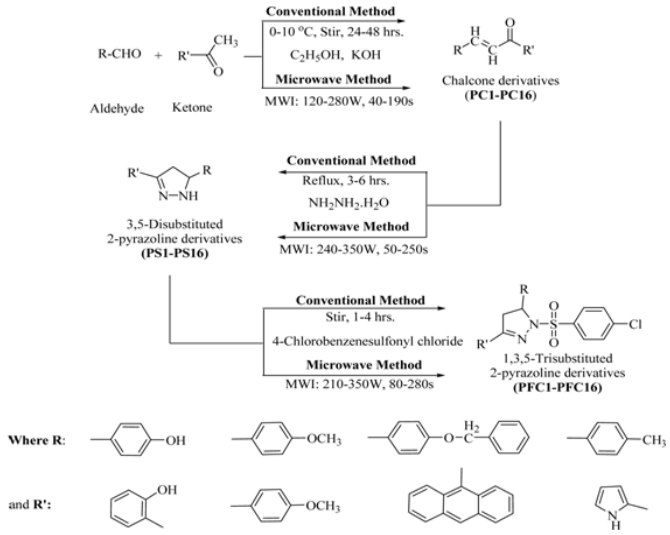

Figure 2 : Synthesis of 1,3,5-trisubstituted-2-pyrazoline

Novel 1,3,5-trisubstituted-2-pyrazoline[7] derivatives and investigated for their anticonvulsant activity. Among the screened compounds, was found to be protective against scMet and MES-induced seizures. The results shows pyrazoline nucleus significantly enhanced anticonvulsant efficacy. Three new structures in the form of 3- substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3 Hindeno [1,2-c] pyrazol carboxamide analogs were prepared. The neuroprotective and anti convulsant activities were examined on ADD protocol. Currently, Beyhan et al. promoted 3,5-disubstituted-4,5-dihydro-1Hpyrazole-1-carbothioamides as potential anticonvulsant agent.

4,5-Dihydro-1H-pyrazole or a 2-pyrazoline[8] ring is a cyclic hydrazine moiety and a nitrogen-containing five-membered heterocyclic compound with important biological activities.12 Modifications of the pyrazoline ring on carbon (C3, C4, and C5) or nitrogen (N1 and N2) expanded the spectrum of pharmacological activity, leading to anticancer, anti-inflammatory, antimicrobial, anti-amoebic, and antiprotozoal activities.13–18 A number of pyrazoline analogues have been identified or developed to

target neurological disorders such as AD, depression, and Parkinson's disease. In addition, some 3,5- diarylpyrazolines with ChE inhibitory activity in the nanomolar range have been claimed as good candidates for treatment of AD in the literature. The complexity of AD and the lack of effective treatment for this disease prompted us to search for a multi-target directed ligand combining crucial features, such as ChE inhibitory, Aβ anti-aggregating, and neuroprotective activities. For this purpose, a series of 2-pyrazolines were synthesized and their inhibitory activity towards ChE was investigated. The active derivatives were also evaluated for their Aβ anti aggregating activity and neuro protective properties. Molecular docking studies were performed to investigate binding interactions inside the active sites. Compounds have multifunctional potential for use against Alzheimer's disease.

Pyrazoline derivative 1,3,5-trisubstituted-2-pyrazoline[9] were examined for depression, anxiety, and spontaneous locomotor activity parameters of mice.. Pyrazolines decreased the immobility and increased the swimming times of mice without any change in climbing durations suggesting the antidepressant effect compared to test compounds. Pyrazoline benzimidazole derivative exhibits significant antidepressant effect.

A series of *N*-substituted-3-(napthalen-2-yl)-5-substituted phenyl-4,5-dihydropyrazole-1-carbothioamide[10] derivatives were synthesized with the view of structural requirements of pharmacophore for potential anticonvulsant agents. Neurologic deficit was evaluated by rotarod method. Molecular docking studies of the compounds were also done with 3D crystal structure of human cytosolic branched chain amino transferase (hBCATc) enzyme. The molecular docking studies were performed to establish the binding ability of the synthesized compounds to the human cytosolic branched chain amino transferase (hBCATc). The docking scores and binding free energy of all the compounds and co-crystal ligand (gabapentin) with the active site of human cytosolic branched chain amino transferase (hBCATc). The results of docking studies showed that compounds exhibited higher docking score. The ligand interaction diagram is shown in figure 3.

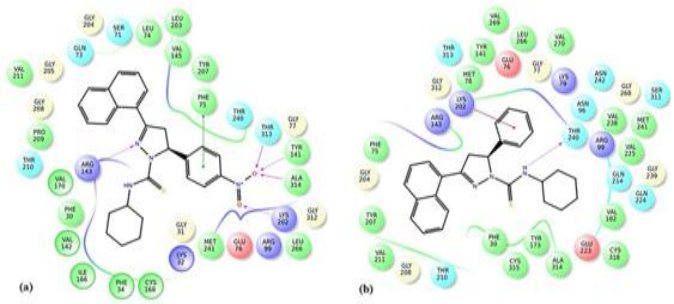

Fig 3: The ligand interaction diagram

Alzheimer's disease (AD) is a complicated neurodegenerative disorder with a multifaceted pathogenesis. Alzheimer's disease is characterized by gradual memory loss, falling in language ability and other cognitive deterioration. In this way, a new thiophene-2-pyrazoline derivatives[11] have been synthesized to give beneficial compounds to controlling and battling against (AD). The synthesis of new thiophene-2-pyrazoline and benzothiazole derivatives targeting AChE/(MAO-A)/(MAO-B) enzymes was described. Molecular docking and toxicity test establishes the therapeutic potential for the active derivatives. Therefore, these compounds may be accepted as promising leads for future research efforts in fighting against AD.

New series of substituted bicyclic pyrazolines[12] exhibited a modest CNS depressant profile when given to rats by the ip route. We prepared a series of analogues which were expected to show enhanced CNS depressant activity. Some of these products were also screened for antiinflammatory activity. Compound was obtained by the interaction of 3,5-dibenzylidene-1-methyl-4-piperidone with methylhydrazine. The structural assignment was based on the IR (absence of CO and NH bands) and NMR spectral data.

A series of five new 1,3,5-triphenyl-2-pyrazolines[13]were synthesised by reacting 1,3-

diphenyl-2-propene-1-one with phenyl hydrazine hydrochloride. The structures of the compounds were proved by means of their IR, ^{1}H NMR spectroscopic data, and microanalyses. Their antidepressant activity was evaluated by 'Porsolt behavioral despair test' on Swiss-Webster mice. 1-Phenyl-3- (2″-hydroxyphenyl)-5-(4′-dimethylaminophenyl)-2-pyrazoline, 5-(4′-dimethylaminophenyl)-1,3-diphenyl-2-pyrazoline, 1-phenyl-3-(2″-hydroxynaphthalen-1″-yl)-5-(3′,4′,5′-trimethoxyphenyl)-2-pyrazoline, 1-phenyl-3-(4″-methylphenyl)-5-(4′-dimethylaminophenyl)-2-pyrazoline and 1-phenyl-3-(4″-bromophenyl)-5-(4′-dimethyl amino phenyl)-2-pyrazoline reduced immobility times 25.63–59.25% at 100 mg/kg dose level. It was found that the compounds possessing electron-releasing groups such as dimethyl amino, methoxy and hydroxyl substituents enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the phenyl rings.

Twelve derivatives of pyrazolines were synthesized and antiepileptic activity of 1-thiocarbamoyl- 1-phenyl, and 1-N-substituted thiocarbamoyl-3-(2- furyl)-5-phenyl/ (2-furyl)-2-pyrazoline[14] and other derivatives were synthesized and studied their antiepileptic action by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet.) tests, neurotoxicities by rotarod toxicity test on albino mice. 1-Thiocarbamoyl-3, 5-di(2-furyl)-2- pyrazoline, 1-N-methylthiocarbamoyl-3, 5-di(2-furyl)-2- pyrazoline and 1-N-ethylthiocarbamoyl-3, 5-di(2-furyl)- 2-pyrazoline were found protective against MES and scMet at 30-300 mg.kg-1 dose levels. Kucukguzel et al[13] synthesized a new series of 4- Arylhydrazono-2-pyrazoline-5-ones derivatives and evaluated for their anticonvulsant activity. Compounds showed 40% protection against pentylenetetrazole (PTZ)-induced seizures in albino Swiss mice. Singh et al synthesized several 3-(3-Acetoamino) phenyl- 1, 5-substituted phenyl-2-pyrazolines and evaluated for their anticonvulsant activity. All the substituted pyrazolines exhibited anticonvulsant activity. Kornet et al synthesized 1-Phenyl-2-(phenylcarbamoyl) pyrazolidines as potential anticonvulsant agents. These adduct showed little anticonvulsant activity in the MES and PTZ seizure assays.

A new series of pyrazoline [15]derivatives was evaluated for antidepressant, anxiogenic and MAO-A and -B inhibitory activities by in vivo and in vitro tests respectively. The synthesized compounds showed good activity against MAO-A and MAO-B isoforms. However, none of the novel compounds showed antidepressant activity. Biological properties was investigated by computational methods using crystallographic models. These were due to the differences in the intermolecular hydrophobic and H-bonding of ligands to the active site of each MAO isoforms.

Synthesis of 2-pyrazoline[16] derivatives has been an active field of research due to their established pharmacological effects. Here, a series of chalcones were prepared through claisen schmidth condensation with methyl aryl ketones and substituted aldehydes in the presence of sodium hydroxide and methanol .By refluxing chalcones and thiosemicarbazide 3,5-Disubstituted-4,5-dihydro-1*H*-pyrazole-1-carbothioamides were synthesized in alkaline medium. By refluxing selected chalcones N-3,5-trisubstituted-4,5-dihydro-1 *H*-pyrazole-1-carboxamides were also synthesized with N-(4-chlorophenyl) semicarbazide in alkaline medium. Structures of the synthesized compounds were confirmed by spectral datas and were within the anticipated values. All compounds were tested for their anticonvulsant activity in mice.

The antidepressant activity of a series of 2-pyrazoline derivatives[17] and two compounds showed promising antidepressant activity. 3,5-Diaryl pyrazolines analogs were developed as selective and reversible MAO-A inhibitors by M. Karuppasamy et al. For understanding the active site docking studies were performed.. Kaplancikli et al studied the antidepressant activity of synthesized triazolopyrazoline.

Conclusion

Pyrazoline, five membered heterocyclic ring has diverse biological activities and can be denoted as pharmaceutically important molecule. The synthesis of certain derivatives and exploration of various pharmacological activities of pyrazolines have become an interesting topic in the field of heterocycic chemistry. Various studies have highlighted that there were several pyrazoline derivatives which display significant pharmacological activity and have higher activities compared to standard commercial drugs. In the view of this study, further research can be carried out on the development of new effective CNS agents by the modification of compound.

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