Pharmacological Potential Of A Resourceful Heterocycle: Pyrazoline – A Review

Cinsila Vincent*, K.Krishnakumar, Geetha Elias
Department of Pharmaceutical Chemistry, St James College of Pharmaceutical Sciences, Chalakudy. St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized).

ABSTRACT

Pyrazolines, the eminent five-membered nitrogen-containing heterocyclic compounds, have received significant interest in the fields of therapeutic and agricultural chemistry because of their broad spectrum of biological activities. The Pyrazoline ring is relatively stable and has inspired chemists to carry out various research activities. Pyrazolines, a class of electron-rich nitrogen heterocyclic compounds, possess a broad range of pharmacological functions such as anticancer, antitubercular, antimalarial, antibacterial, antifungal, anti-inflammatory, analgesic, anticonvulsant, and antioxidant activities. This review provides an outline on the recent grade of pyrazoline derivatives in terms of synthesis and various applications to realize their full potential as drugs.

Keywords: Pyrazoline, Synthesis, Biological activities

INTRODUCTION

Heterocyclic chemistry constitutes an essential branch of organic chemistry and heterocycles are widely known to display an array of biological properties. Heterocyclic compounds are those which possess a cyclic structure with at least two different kinds of atoms in the ring, one of which is nitrogen and can be aliphatic or aromatic. Heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyse or depolymerise. Pyrazolines symbolize key structural motifs in heterocyclic chemistry and are present in a large number of biologically active molecules relevant to the pharmaceutical and agrochemical industries. Pyrazolines are five membered heterocyclic having two adjacent nitrogen atoms within the ring, only one endocyclic double bond and is basic in nature.

![Pyrazoline](image1.png)

**Figure 1: Pyrazoline**

The structural elucidation of pyrazoles and derivatives has been greatly aided by NMR spectroscopy, particularly for distinguishing between isomeric structures. Depending on the position of the double bond, can exist in three separate forms.

![Types of Pyrazolines](image2.png)

**Figure 2: Types of Pyrazolines**

Previous research have shown pyrazolines to be an interesting pharmacophore for drug discovery. These heterocyclic compounds occur widely in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Significant number of activities have been directed towards diversely substituted pyrazolines such as antimicrobial, anti-
inflammatory, antidepressant, antitubercular, anticonvulsant, anticancer, antioxidant, antimalarial, and many more. A typical method for the synthesis of these compounds involves the base catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give unsaturated ketones (chalcones), which undergo subsequent cyclization reaction with hydrazines affording 2-pyrazolines. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2 pyrazolines in the presence of a suitable cyclizing reagent like acetic acid. Chalcones are generally synthesized by Claisen–Schmidt condensation, which involves cross aldol condensation of appropriate aldehydes and ketones by base catalysed or acid catalysed reactions followed by dehydration. The presence of reactive α,β-unsaturated keto group in chalcones is found to be responsible for producing their biological activity. Chalcone derivatives are considered as key intermediates for the synthesis of different classes of heterocyclic compounds such as pyrazolines, oxazoles, isoxazoles, thiophenes and pyrimidines.

Commercially available drug with pyrazole moiety such as Celecoxib is a potent COX-2 inhibitor. Some other examples of pyrazole derivatives as NSAID’s are Phenylbutazone, Ramifenazone, Lonazolac and Rimonabant. Pyrazofurin has exhibited potential for antiviral activity.

**Synthesis of Pyrazoline Derivatives**

The name pyrazole was given by Ludwig Knorr in 1883 and refers to the class of simple aromatic ring organic compounds of the heterocyclic series, characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions.

![Scheme for the synthesis of Pyrazoline](image-url)

**Figure 3: Scheme for the synthesis of Pyrazoline**
In the 19th century, Fischer and Knoevenagel synthesized and characterized 2-pyrazolines, by simple reflux reaction of α, β-unsaturated aldehydes and ketones with phenyl hydrazine in acetic acid. A variety of methods exist for the synthesis of Pyrazoline derivatives. Tan Nhut Doan *et al.*, have synthesized various pyrazoline (Figure 3) by the reaction of respective chalcones and hydrazine hydrate in presence of 99% ethanol at 70°C for 7 hours. They evaluated the anti-microbial and antioxidant activities.

Nagihan Beyhan, have synthesized various 3,5-disubstituted-4,5-dihydro-1H-pyrazole-1-carbothioamides by refluxing selected chalcones and thiosemicarbazide in alkaline medium. Similarly N-3,5-trisubstituted-4,5-dihydro-1H-pyrazole-1-carboxamides were synthesized by refluxing selected chalcones with N-(4-chlorophenyl)semicarbazide in alkaline medium. They evaluated the anticonvulsant activity of the synthesized compounds using pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES) tests.

Mohammad. Shaharyar *et al* have reported an efficient method for the synthesis of pyrazoline derivatives by condensing chalcones with isoniazid giving a series of N1-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines and were tested for their in-vitro antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB) and INH-resistant *M. tuberculosis* (INHR-MTB) using the agar dilution method.

**Figure 4: synthesis of N1-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines**

**BIOLOGICAL ACTIVITIES OF PYRAZOLINE**

**Pyrazoline as Antimicrobial agent**

www.aijptr.com
Dilesh Indorkar et al have synthesized 1-acetyl-3-(4-nitrophenyl)-5-(substituted phenyl)-2-pyrazoline (Figure 5) derivatives and evaluated their antimicrobial activity. In this study a series of structurally related 1,3,5-trisubstituted-2-pyrazoline derivatives have been synthesized by introducing furan rings regarded as bioactive substructure into the scaffold of pyrazolines and tested for their activities against six plant pathogenic fungi in vitro. The preliminary bioassays indicated that almost all synthesized compounds had displayed variable growth inhibitory effects on the tested pathogenic fungi.

Figure 5: 1-acetyl-3-(4-nitrophenyl)-5-(3,4,5-trimethyl phenyl)-2-pyrazoline

Ramalingam Sasikala et al have developed an efficient catalytic method for synthesis of 1-phenyl-3(5-bromothiophen-2-yl)-5-(substituted phenyl)-2-pyrazolines by solid phase cyclization using a solvent-free environmentally greener catalyst fly ash: H₂SO₄ under microwave irradiation between aryl chalcones and hydrazine hydrate. All synthesized pyrazoline derivatives showed moderate antimicrobial activities against bacterial and fungal strains.

Ponnurengam Malliappan Sivakumar et al have synthesized 1,3,5-triphenyl-2-pyrazolines (Figure 6) and evaluated for their antibacterial activity against six microorganisms, namely Bacillus subtilis NCIM 2718, Staphylococcus aureus NCIM 5021, Salmonella typhi NCIM 2501, Enterobacter aerogenes NCIM 5139, Pseudomonas aeruginosa NCIM 5029, and Proteus vulgaris NCIM 2813 by twofold dilution method using resazurin as the indicator dye.
Figure 6: 5-(4-chlorophenyl)-3-(2,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1-pyrazole.

Pyrazoline as Anti tubercular agent

Mohammad. Shaharyar et al have synthesized and reported the in-vitro anti mycobacterial activity of \(N^1\)-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines. Among the synthesized compounds, compound \(N^1\)-nicotinyl-3-(4′-hydroxy-3′-methylphenyl)-5-(2-chlorophenyl)-2-pyrazoline (Figure.7) was found to be the most active agent against MTB and INHR-MTB, with minimum inhibitory concentration of 0.26 \(\mu m\).17

Figure 7: \(N^1\)-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(4-fluorophenyl)-2-pyrazoline

Mohamed Ashraf Ali et al have synthesized a series of 5-[(4-(substituted) phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-toluidino methane thione and 5-(substituted)phenyl-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-methoxyanilino methane thione were synthesized by the reaction between hydrazine hydrate and chalcones followed by condensation with appropriate aryl isothiocyanate which yielded N-substituted pyrazoline derivatives. Among the synthesized compounds, compound anilino-3-(4-hydroxy-3-methylphenyl)-5-(2,6-dichlorophenyl)-4,5-dihydro-1H-1-pyrazolylmethanethione was found to be more active agent against M. tuberculosis H37Rv.22

Pyrazoline as Anti-malarial agent

Shilpy Aggarwal et al have synthesized a series of 1,3,5-trisubstituted pyrazoline(Figure.8) and were screened for in-vitro schizont maturation assay against chloroquine (CQ) sensitive 3D7 strain of \(Plasmodium falciparum\). Most of the compounds showed promising in-vitro antimalarial activity against CQ sensitive strain. SAR study showed that quinoline substitution at position N-1 showed maximal activity and compounds having electron withdrawing group at \(p\)-position on phenyl ring displayed better antimalarial activity than electron releasing group23.
Badri Narayan Acharya et al reported synthesis of 1,3,5-trisubstituted pyrazolines derivative and were evaluated for in-vitro anti-malarial efficacy against Chloroquine sensitive and Chloroquine resistant strains of *Plasmodium falciparum*. β-hematin formation inhibition activity (BHIA50) of the pyrazolines were determined and correlated with antimalarial activity24.

**Pyrazoline as Anti-inflammatory agent**

R. Surendra Kumar et al have reported some novel pyrazole analogues from condensation technique utilizing ultrasound irradiation. Synthesized compounds were screened for anti-inflammatory activity and the compound 2-((5-hydroxy-3-methyl-1H-pyrazol-4-yl) (4-nitrophenyl) methyl) hydrazine carboxamide showed better anti-inflammatory activity, when compared with standard drugs (Diclofenac sodium)25.

Harathi et al have synthesized various 3, 5-diphenyl-4, 5-dihydro-pyrazole-1-carbothoic acid amide(Figure.9) derivatives using respective chalcones and thiosemicarbazide. They evaluated the anti-inflammatory activity of synthesized compounds by egg-albumin induced rat paw edema method and compared with standard anti-inflammatory agent Diclofenac Sodium. Compounds with electron withdrawing groups Cl, NO2 exhibited better anti-inflammatory activity26.
Pyrazoline as Anti-cancer agent

Fadi M. Awadallah et al synthesized two series of 2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitriles and 4-(4-chlorophenyl)-2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitriles. The target compounds were screened for their antiproliferative activity against A 549 (lung), HT 29 (colon), MCF 7 and MDA-MB 231 (breast) cell lines. Mohammad Abdel-Halim et al reported that derivatives with scaffolds of 1,3,5-tri-substituted pyrazoline and 1,3,4,5-tetra-substituted pyrazoline were synthesized and tested for their inhibitory effects versus the p53+/+ HCT116 and p53−/− H1299 human tumor cell lines.

Bhat et al synthesized a series of substituted pyrazoles and also evaluated for in-vitro cytotoxic activity against a panel of human cancer cell lines. They concluded that pyrazoles such as 3,5-diphenyl, 1H-pyrazoles(Figure.10) are potent cytotoxic agents.

Figure 9: \(N\)-[(E)-(4-chlorophenyl) methylidene]-3, 5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide

Figure 10: 5-(4-fluorophenyl)-3-(2,3,4,5-tetramethoxyphenyl)-1H-pyrazole
Pyrazoline as Anticonvulsant agent

Nagihan Beyhan et al. were reported some 2-Pyrazolines derived from Chalcones having anticonvulsant activity. Various 3,5-disubstituted-4,5-dihydro-1H-pyrazole-1-carbothioamides and N-3,5-trisubstituted-4,5-dihydro-1H-pyrazole-1-carboxamides were evaluated the anticonvulsant activity of using pentylentetrazole induced seizure (PTZ) and maximal electroshock seizure (MES). The anticonvulsant screening indicated that among the tested compounds, 2-pyrazoline-1-carboxamide derivatives carrying 5-bromothiophen, 5-chlorothiophen and 2,6-dichlorophenyl groups exhibited noteworthy activity in PTZ test.\textsuperscript{16}

Mohamed Jawed Ahsan had synthesized 3-substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3H-indenopyrazole-2-carboxamide(Figure.11). These compounds showed significant anticonvulsant and neuroprotective activities\textsuperscript{29}.

![Figure 11: 3-(Pyridin-4-yl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indenopyrazole-2-carboxamide](image.jpg)

STRUCTURAL ACTIVITY RELATIONSHIP (SAR) OF PYRAZOLINES

SAR of 1,3,5-triphenyl-2-pyrazoline derivatives as antibacterial agent.

It has been reported that lipophilic/ hydrophilic balance is required for antibacterial activities of 1,3,5-triphenyl-2-pyrazolines(Figure.12). The substitution patterns of the aryl ring in all derivatives are observed to affect biological activities. The most active 1,3,5-triphenyl-2-pyrazolines have chloro substitution in their A-ring at R1 position. The least active compounds have benzyloxy substitution in their A-ring at R1 position. The B-ring requires slightly hydrophilic substitution like dimethoxy and methylene dioxy groups compared to hydroxyl substitution for good antibacterial activity.
SAR of 1,3,5-Trisubstituted Pyrazoline Derivatives as antimalarial agent.

Studies reported that quinoline substituted analog at position N-1 showed maximum activity followed by benzothiazole substitution, while phenyl substitution decreases the antimalarial activity. When position 5 of aromatic ring B is substituted with chlorine atom at para position it showed significant increases in activity (Figure.13). Presence of electron releasing group like methyl & methoxy substituted compounds reduced the antimalarial activity when compared to electron withdrawing groups. Replacement of phenyl groups with 2-thienyl reduces the antimalarial activity. It has been reported that large hydrophobic group (at position 1) is the basic vital structural requirement for exhibiting the antimalarial activity and para substitution with electron withdrawing group at phenyl ring increases the antimalarial activity.

Figure 12: SAR of 1,3,5-triphenyl-2-pyrazoline derivatives as antibacterial agent

Figure 13: SAR of 1, 3, 5-trisubstituted pyrazoline as antimalarial agent
CONCLUSION

Pyrazoline is an amazing heterocyclic compound that has been designed and synthesized for a variety of biological activities. In this review, biological profiles of various pyrazoline derivatives have been analyzed. They have exhibited numerous effects, such as antimicrobial, antimycobacterial, anti-malarial, anti-inflammatory, anticonvulsant and anticancer activities. Among various pyrazoline derivatives, 2-pyrazolines exhibited more biological activities. The discovery of new drugs for malaria is challenging due to the unavailability of vaccine and lack of newer drugs. The emergence of drug resistance in the parasite (Plasmodium strains) against nearly all existing antimalarial drugs has inspired the researchers to identify new pharmacophores. The 2-pyrazolines have shown various biological activities but the most exciting finding in this review is the antimalarial activity of N-1 Quinoline substituted 2-pyrazolines, which is a promising pharmacophore for further research against the malarial parasite.

ACKNOWLEDGEMENT

The authors wish to thank the Principal and Management of St.James College of Pharmaceutical Sciences, Chalakudy, Kerala for providing the facilities to carry out this review.

REFERENCES


