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Recent Developments in the Biological Activities of 2-Pyrazoline Derivatives

Attreyee Mukherjee

Department of Chemistry, Ananda Mohan College, Kolkata, West Bengal, India

Corresponding Author's Email: attreyee.m@gmail.com

Abstract

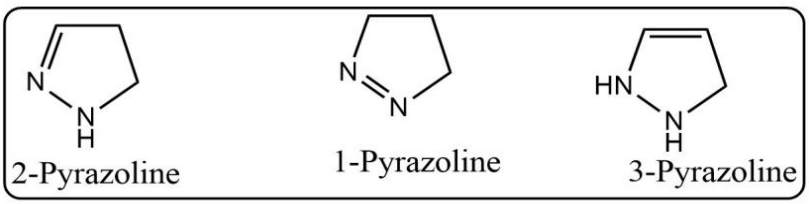
Pyrazolines, a significant class of heterocyclic compounds, have gathered attention in medicinal chemistry for their diverse biological activities. In recent years, scientists have explored structural modifications, leading to pharmacologically active derivatives incorporated into therapeutic agents. 2-pyrazoline scaffold is found to be present in various important drug molecules e.g antipyrine, phenylbutazone, oxyphenbutazone, ibipinabant, ramiphenazone etc. 2- Pyrazoline derivatives have been reported to possess broad-spectrum biological activities such as antimalarial, antidepressant, antiinflammatory, antitumor, antibacterial, anticancer and also MAO (monoamine oxidase), acetylcholine esterase (AChE), cannabinoid (CB_1) etc. inhibitory activities. Pyrazoline based drugs are also used to treat neurodegenerative diseases such as Alzheimer's disease, Perkinson's disease, psychiatric disorders etc. The variation of substituents in the pyrazoline scaffold has had a tremendous impact on biological activity. It has been shown from different research studies that the electronegativity and steric factor of the substituents present in N-1, C-3 and C-5 positions have a great influence on the biological properties of the compounds. This article will cover numerous biological significances of 2-pyrazoline based compounds in medicinal chemistry and SAR (structure-activity relationship) for the improvement of therapeutic implications.

Keywords: *Biological Activity; Pharmacologically Active; 2-Pyrazoline; Structure-Activity Relationship*

Introduction

Pyrazolines, five-membered heterocycles with two adjacent nitrogens, have emerged with huge attention from organic and medicinal chemists due to their potent biological activities and the numerous possibilities for structural diversification. Among three isomers of pyrazolines, 2-pyrazoline is most common in the literature and it has huge applications in the field of medicine. 2-pyrazoline scaffold is present in a number of drug molecules, such as antipyrine, ibipinabant, ramiphenazone, oxyphenbutazone, phenylbutazone etc. A wide spectrum of biological activities has been found in the pyrazoline based heterocyclic compounds (Nehra *et al.*, 2020). Pyrazoline derivatives are reported to possess biological activities such as anti-inflammatory (Mantzanidou, Pontiki & Hadjipavlou-Litina, 2021), antimalarial (Ravindar *et al.,* 2023), anticancer

(Haider *et al.,* 2022), antitubercular (Joshi *et al.,* 2016), antifungal (Elewa *et al*., 2020), antidepressant (Kaplancıklı *et al.,* 2010), antitumor (Matiadis & Sagnou, 2020) and cholinesterase (Mishra & Sasmal, 2013), EGFR tyrosine kinase (Sahoo *et al.,* 2010), cannabinoid CB1 (Lange *et al.,* 2010) inhibitory activities. Modern research on pyrazoline scaffold reveals that the biological property of this heterocycle is largely influenced by the substituents present N1, C3, C5 position. This review covers the various biological activities of pyrazoline derivatives.



Scheme 1

Biological Activities of 2-Pyrazoline Derivatives

Antiinflammatory activity

Eid and George (2018) synthesised new pyrazoline derivatives attached to the furan and thiophene ring at C-3 and acetyl and amide group at N1and examined *in vivo* anti-inflammatory activity. The compounds are reported to exhibit potent anti-inflammatory activity. It was also shown by the researcher that furan appended N-acetyl pyrazolines possess better activity than the thiophene pyrazoline derivatives.

New phenyl-pyrazoline-coumarin hybrids were synthesised by Chen *et al.* (2017) and the results of *in vivo* anti-inflammatory activity showed significant inhibition in edema.

Abdel-Sayed *et al.* (2016) synthesised 1,3,5-trisubstituted pyrazoline derivatives and evaluated for *in vivo* anti-inflammatory activity. Some of the compounds showed no inhibition of COX-1 up to 100 μM, but 3-phenyl 5-(4-nitrophenyl)N-acetylphenylpyrazoline and 3-(4-fluorophenyl) 5-(4-nitrophenyl)N-acetylphenylpyrazoline exhibited *in vitro* COX-2 inhibitory activity with IC_{50} values of 10 and 12.1, respectively. Barsoum, Hosni and Girgis (2006) synthesized novel bis(1-acyl-2-pyrazolines) derivatives and reported remarkable anti-inflammatory properties with a lower ulcerogenic liability than standard drug used. The synthesis and *in vivo* screening of a new series of fluoro substituted pyrazoline derivatives were reported by Jadhav *et al.* (2013) and the results showed that the compounds exhibited antiinflammatory and analgesic activity.

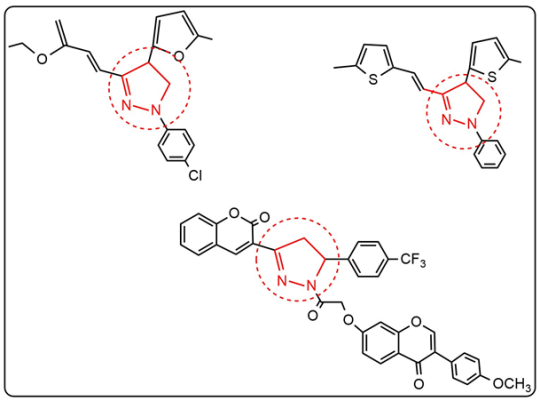


Figure 1: Pyrazoline as anti-inflammatory agents

Antimalarial activity

A series of novel pyrazolepyrazoline derivatives bearing benzenesulfonamide were synthesized (Kumar *et al.*, 2018) and evaluated for *in vitro*, and *in vivo* antimalarial activity. The test results revealed that some of the compounds exhibited significant activity against CQS and CQR strains of *P. falciparum*. It was observed by the researchers that the substituents on the pyrazole and pyrazoline rings control the activity. R_1= -Me, -OMe enhances the activity, while monohalo and dihalo substitutions lower the activity.

The antimalarial activity of a series of newly synthesised oxazoline pyrazoline derivatives was evaluated (Pandey *et al.*, 2016); among them, compounds with 4-methoxyphenyl substitution showed significant potential against *P. falciparum.* Both *in vivo* and *in vitro* studies against *P. falciparum* and *P. berghei* showed satisfactory result with 79.33% and 63.89% suppression of parasitemia at a dose of 50 mg/kg and 25 mg/kg, respectively, on day 4.

Marella *et al.* (2015) synthesised and examined new pyrimidine cubbed nitrile-pyrazoline hybrid derivatives for *in vitro* gametocytocidal activity, and the results indicated that most of the compounds exhibited promising antimalarial activity against the chloroquine-sensitive (CQS, 3D7) strain of *P. falciparum.* SAR studies showed that (a) -OMe substitution in ring A enhances the potency; (b) dimethoxy and trimethoxy substitution in ring C was reported to be most effective.

Akhter *et al.* (2015) reported a series of coumarin based pyrazoline derivatives and examined antimalarial and antimicrobial activity. The compound with 3,4,5-trimethoxybenzene showed the highest inhibitory activities against CQs strain of *P. falciparum* with IC_{50} 11.63 µg/mL. The activity was enhanced by (a) the number of methoxy group present in the phenyl group. (b) Bulky group substituted N1and acyl, phenyl substituted N1. Some synthesized derivatives were also evaluated for antimicrobial activity against *E. coli* and *S. aureus* and fungal strains *R. oryza* and

P.citrum with MIC values 10, 12.5 and 12.5 µg/mL against *S.aureus, E.coli* and *R.oryza* respectively.

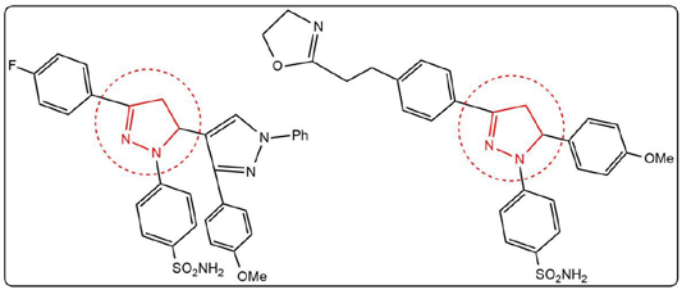


Figure 2: Pyrazoline as anti-malarial agents

Anticancer activity

In recent years, a number of chemotherapeutic drugs have been used that contain nitrogen heterocycles and pyrazoline moiety, such as axitinib (Wu, Nielsen & Clausen, 2015) (renal cell carcinoma treatment) and ibrutinib (Byrd *et al.*, 2013) (chronic lymphocytic leukemia treatment).

Some of the compounds were reported as therapeutic agents to treat drug-resistant breast cancer. The compounds were synthesised and evaluated by Luan *et al.* (2017) and it has been shown that these have high sensitivity against MCF-7/Adr cell lines.

The coumarin based pyrazolines showed antiproliferative activity and some of the compounds were also treated as cytotoxic agents.

Wu and coworkers (2014) showed inhibitory activity against tolemerase with IC_{50} 0.92 µM, supposed to cause the inhibition of cancer cells growth. Wei and coworkers (2018) synthesised pyrazolines and examined for anticancer activity and concluded that this compound exhibited inhibitiry activity with IC_{50} 4.7 for A549 lung cancer cell.

Mehmood *et al.* (2022) synthesised a series of 1,3,5-triaryl 2-pyrazoline and examined for anticancer activity. The compound showed inhibitory activities against urease and some of the synthesised compounds were found to inhibit strongly against α-glucosidase. SAR studies revealed that size and ewg and edg group affected the activity. The compounds were also found to have cytotoxic activity against MCF-7 and HeLa cell lines.

The author synthesised series of pyrazoloyl pyrazoline and one of the compounds (5-ethoxy pyrazoline derivative) coupled with doxorubicine (PYZ-DOX) was applied for bioimaging in the living HepG2 cells (Rana, Dhar & Bhattacharya, 2014; Mukherjee & Mahalanabis, 2009). The Compound showed fluorescent blue image while incubated to living HepG2 cells but when coupled with DOX, it showed strong fluorescent red image.

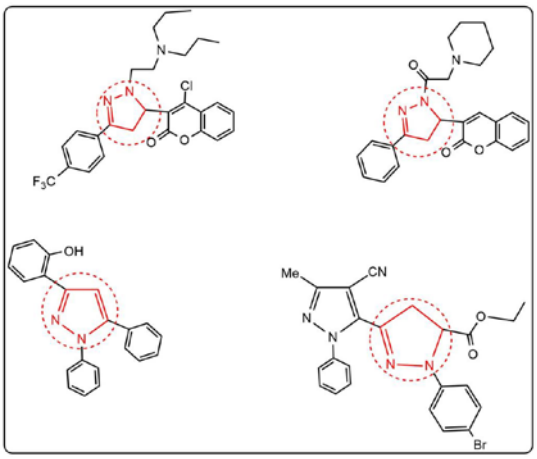


Figure 3: Pyrazoline as anticancer agents

Antibacterial and antifungal activity

The design and synthesis of a series of new 1,3,5-trisubstitutedpyrazolines were reported by Mishra *et al*. (2017) and compounds with fluoro/chlorophenyl substitution at 3-position of pyrazoline derivatives showed strong antibacterial activity against bacterial strains *S. aureus* and *B. subtilis* (gram positive) and *E. coli* (gram negative) having MIC values3.25-25µg/Ml. *In vitro* antifungal study of one of the pyrazoline derivative in the series showed very satisfactory result.

The new series of thiophene based pyrazolines was reported by Edrees *et al.* (2018) and their antifungal evaluation showed potent activity against the fungal strains *A. fumigatus* and *C. albicans*.

Montoya *et al.* (2016) synthesised novel substituted 2-pyrazoline derivatives containing 7-chloro 4-aminoquinoline moiety and evaluation of antifungal test showed satisfactory results. The strong antofungal effects were shown against *C. albicans and C. neoformans* compared to the drug Amphotericin B.

Some pyrazoline derivatives with a sulfonamide moiety (Sadashiva *et al.,* 2017) found to exhibit antituberculosis activities with MIC values 0.8 to 100 µg/mL compared to pyrazinamide (3.125µg/mL). All the compounds were reported to possess antibacterial and antifungal activity against *S. aureus* and *B. subtilis* (gram positive) and *E. coli*, *P. aeruginosa* (gram negative) bacteria and *A. niger, C. albicans, A. fumigatus* and *A. flavus* fungal strains. In vitro antimicrobial studies showed that most of the compounds in this series exhibited strong antibacterial and antifungal activities.

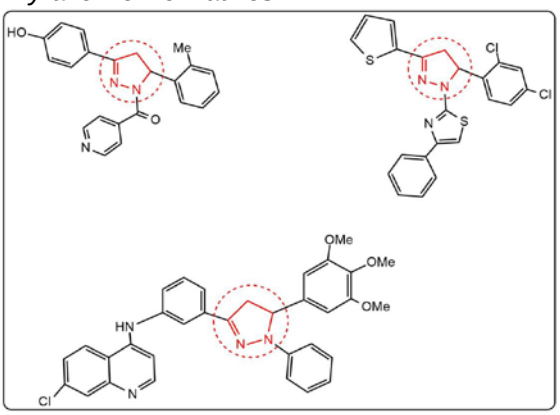


Figure 4: Pyrazoline as antibacterial and antifungal agents

MAO inhibitory activities

Salgin-Goksen *et al*. (2021) synthesised new 2-pyrazoline and acetohydrazide derivatives and tested for MAO inhibitory activity. The results showed the selective MAO-A inhibitor activity. The in vitro studies of hydrazone derivatives revealed the compounds exhibit strong inhibition toward hMAO-A.

All of the compounds exhibited antidepressant activity (Salgin-Goksen *et al*., 2021). It has been reported by Nair *et al.* (2021) that the halogenated phenyl ring at the 5-position of the pyrazoline ring increases the potency against MAO-B and the activity increases in the order F>Cl>Br> I. Tripathi and his coworkers (2016) designed some novel 3,5-disubstituted 2-pyrazoline derivatives and the *in vivo* antidepressant study showed a good to moderate response.

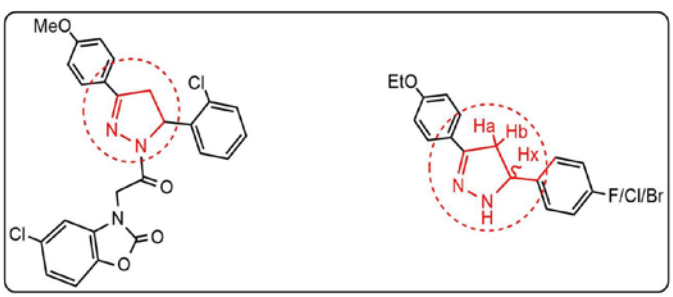


Figure 5: Pyrazoline having MAO Inhibitory Activities

Carbonic anhydrase inhibitory activities

Carbonic anhydrase is an enzyme that helps in the interconversion of CO_2 and H_2O and dissociates ions of carbonic acid. Several diseases epilepsy, glaucoma, obesity, cancer, tumor cell growth are associated with CA. CA inhibition controls these diseases. Alaa and co-workers (2019) reported the synthesis of some novel 1,3,5-trisubstituted 2-pyrazoline derivatives with benzene sulfonamide fragments, and in vitro assay results

revealed the inhibitory effect against hCA1. Moi *et al*. (2019) synthesised and evaluated pyrazoline based aromatic sulfamate derivatives and in vitro studies of most of the compounds showed strong inhibition against hCAII.

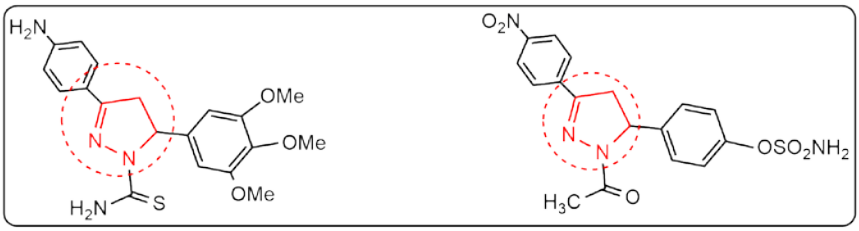
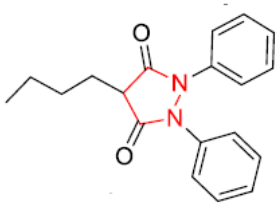
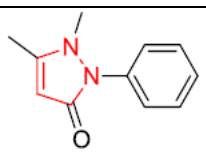
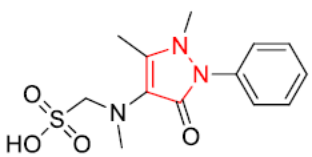
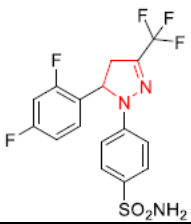
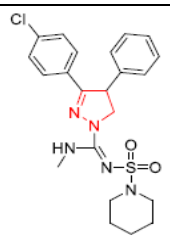
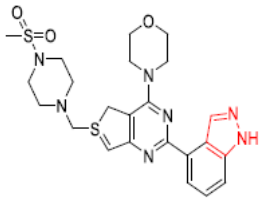
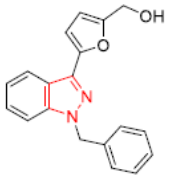
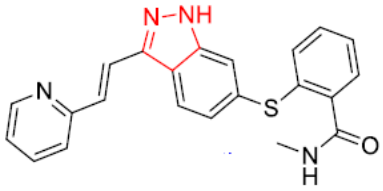


Figure 6: Pyrazoline having Carbonic anhydrase Inhibitory Activities

Table 1: *Clinically used Drugs containing pyrazoline ring*

Sl. no.	**Name of the drug**	**Structure of the compound**	**Clinical Use**
1.	Phenylbutazone		Anti-inflammatory drug (NSID), analgesic, antipyretic.
2.	Antipyrine		Anti-inflammatory drug (NSID), analgesic, antipyretic
3.	Metamizole		analgesic, antipyretic
4.	Enficoxib (E-6087)		NSID for treatment of osteoarthritis pain, inhibits selectively the enzyme COX-2.

5.	(SLV-330)		CB_1 receptor antagonist for the treatment of CNS disorder
6.	GDC-0941		Anticancer agent, P13 kinase inhibitor
7.	YC-1		Anticancer agent, inhibits abnormal cell growth
8.	Axinib		Anticancer drug for the treatment of metastatic renal cell carcinoma.

Conclusion

In this review, the biological activities such as anti-inflammatory, antimalarial, anticancer, antibacterial, MAO inhibitory activities, and CA inhibitory activities of various pyrazoline derivatives have been discussed. The SAR study reveals that the activity of pyrazoline derivatives depends on the substituents present in pyrazoline. The biological activities are evaluated by in vitro and in vivo studies of the compounds discussed in this literature. In conclusion, pyrazoline is now an important pharmacophore for new drug design.

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