

PYRAZOLINE DERIVATIVES AS EMERGING SCAFFOLDS AGAINST TUBERCULOSIS: CHEMISTRY, BIOLOGICAL INSIGHTS, AND BROADER THERAPEUTIC POTENTIAL

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Abstract — Tuberculosis (TB) remains a major global infectious-disease challenge, particularly because treatment is complicated by drug resistance and limitations of existing regimens. Pyrazoline derivatives have attracted attention as versatile heterocyclic scaffolds with reported antimycobacterial activity and interactions with targets such as shikimate kinase and enoyl-acyl carrier protein reductase (InhA). Studies summarized in this review indicate that changes in substitution pattern, including halogen, nitro, and methoxy groups, and fusion or hybridization with benzothiazole, oxadiazole, pyrimidine, and quinazolinone systems can substantially influence activity. Several reported analogues show low MIC values in experimental mycobacterial models. In addition to antitubercular effects, pyrazoline-containing compounds have been investigated for antimicrobial, antifungal, antiviral, antiparasitic, anti-inflammatory, antioxidant, analgesic, and other pharmacological activities. The biological response is frequently dependent on both the nature and position of substituents. Taken together, the available literature supports continued investigation of pyrazoline-based structures as multifunctional medicinal-chemistry leads, while further optimization and appropriate biological and safety evaluation remain necessary.

Keywords: Pyrazoline, Antitubercular, Antioxidant, Anti-inflammatory, Biological activity.

INTRODUCTION

Tuberculosis

Tuberculosis (TB) is a chronic infectious disease caused primarily by *Mycobacterium tuberculosis*. The *M. tuberculosis* complex includes *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, and *M. canettii*. Among these organisms, *M. tuberculosis* is the principal human pathogen.¹

Transmission of disease

M. tuberculosis is transmitted mainly through airborne droplet nuclei generated when a person with pulmonary or laryngeal TB coughs, sneezes, or speaks. These small particles may remain airborne for prolonged periods, and the probability of transmission is influenced by factors such as bacillary burden, organismal virulence, ventilation, ultraviolet exposure, and the extent of aerosol generation.²

After inhalation, bacilli may disseminate through lymphatic and hematogenous routes and reach sites outside the lungs, including the kidneys, liver, spleen, bones, and central nervous system, resulting in extrapulmonary disease.^{2,3}

Epidemiology

Tuberculosis continues to represent a substantial public-health burden worldwide. Its distribution is influenced by social and clinical determinants, including population movement, homelessness, substance use, and HIV/AIDS.^{1,3,4} Although TB is preventable and treatable, it remains an important cause of morbidity and mortality, particularly in resource-limited settings.⁵

Pyrazoline nucleus in Tubercular treatment

Pyrazolines are five-membered nitrogen-containing heterocycles consisting of three carbon atoms and two adjacent nitrogen atoms.⁶ The pyrazoline ring is a weakly basic system, with reported pK_b and conjugate-acid pK_a

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values of 11.5 and 2.49, respectively, at 25 °C.⁷ Pyrazoline derivatives are of considerable pharmacological interest and have been associated with antibacterial, antifungal, antiviral, antiparasitic, antimicrobial, analgesic, anti-inflammatory, antitumour, and antidepressant activities.⁸⁻¹² Their chemical versatility has therefore made the nucleus a useful starting point for medicinal-chemistry optimization.

Shikimate kinase (SK) is an essential enzyme in the shikimate pathway of *M. tuberculosis* and is considered an attractive antimicrobial target because this metabolic pathway is absent in mammals. Structure- and ligand-based screening approaches have identified pyrazole and pyrazolone-containing structures among compounds capable

of interacting with this target.¹³ [Figure: 2] The structural flexibility of pyrazole-containing systems permits the preparation of diverse derivatives through several synthetic strategies, providing considerable scope for medicinal-chemistry optimization.^{14,15} Such structural analogues have consequently been investigated for antitubercular activity¹² [Figure: 1]

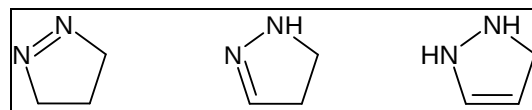


Figure: 1. 1-Pyrazoline, 2-Pyrazoline and 3-Pyrazoline

MECHANISM OF ANTITUBERCULAR ACTIVITY

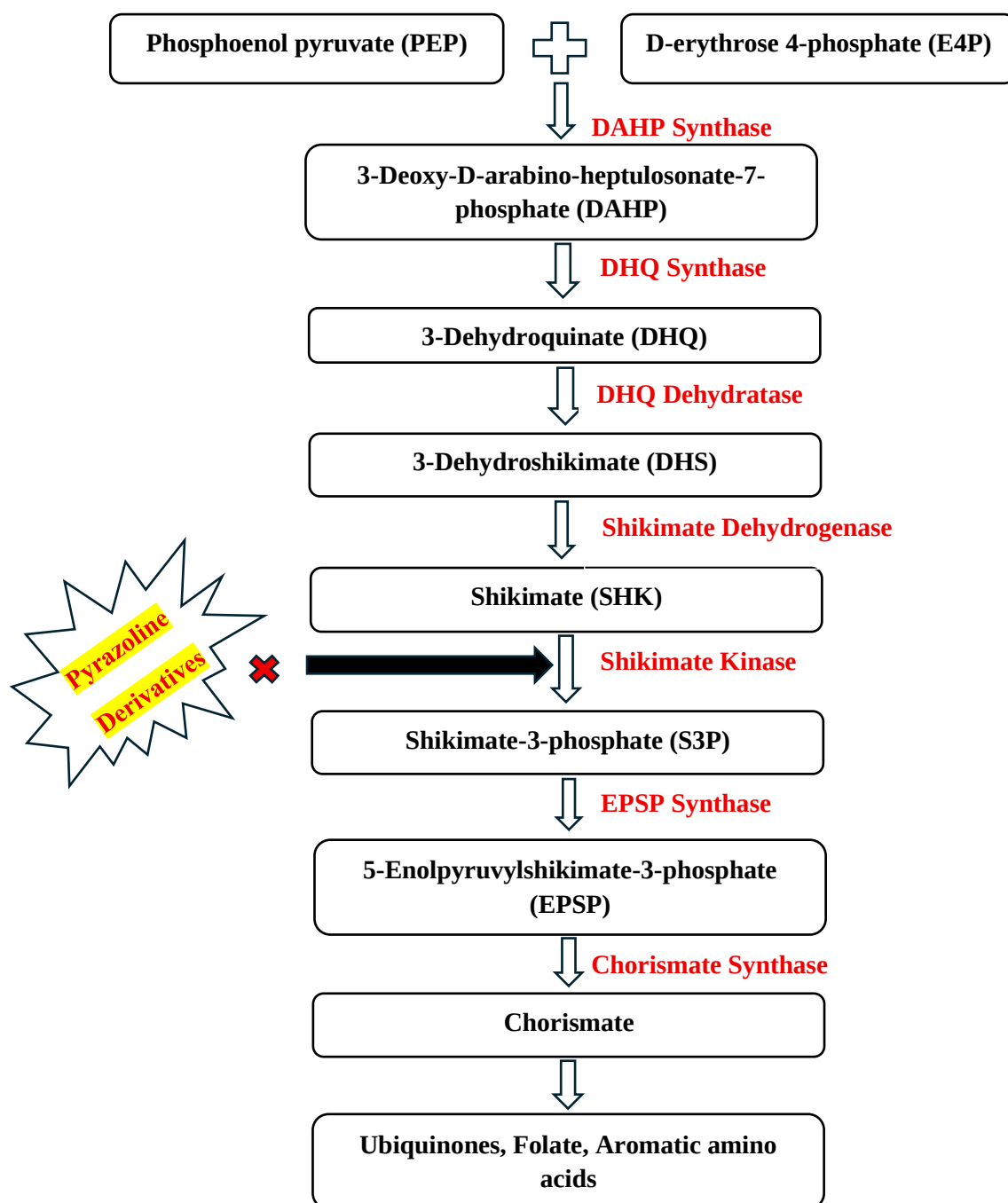


Figure: 2. Mechanism by which pyrazoline derivatives shows antitubercular activity

ANTITUBERCULAR ACTIVITY OF PYRAZOLINE-BASED COMPOUNDS

Shikimate kinase catalyses an essential phosphorylation step in the mycobacterial shikimate pathway. Pyrazoline-related compounds may interfere with this enzyme by occupying regions associated with substrate or ATP recognition, thereby preventing productive catalytic interactions.¹⁶

Ahmad et al. reported two series of pyrazoline derivatives obtained from chalcones derived from p-acetamidophenol and cyclized with either phenylhydrazine or isonicotinic acid hydrazide. IR, ¹H-NMR, mass spectrometry, and elemental analysis were used for structural characterization. The isoniazid-derived series generally showed greater antimycobacterial activity than the phenylhydrazine analogues. Several chlorinated and nitro-substituted compounds exhibited MIC values lower than streptomycin against *M. tuberculosis* H37Rv. These findings indicate that modification of the aromatic substituents and incorporation of an isoniazid-derived pharmacophore can influence activity.¹⁷

A series of pyrazoline derivatives was synthesized through Claisen–Schmidt formation of chalcones, cyclization with hydrazine hydrate, and subsequent reaction with aryl isothiocyanates. The products were characterized by IR, ¹H-NMR, and elemental analysis and evaluated against *M. tuberculosis* H37Rv using the BACTEC 460 system. The 2,6-dichlorophenyl derivative produced more than 90% inhibition at 0.0034 mM. In this series, dichloro substitution was associated with greater activity, whereas methoxy substitution generally reduced it.¹⁸

Pyrazole–benzothiazole hybrids have also been investigated against drug-sensitive, multidrug-resistant, and extensively drug-resistant *M. tuberculosis*. Two derivatives, containing 2,5-dimethylphenoxy and pyrrolidine substituents, respectively, showed MIC values of 0.24 µg/mL. Docking studies suggested interactions within the InhA active site, including contacts with NAD and residues such as Met103, Ala198, and Phe97.¹⁹

Thienyl-pyrazole and fused thienyl-pyrazolopyrimidine derivatives were prepared using ZnO nanoparticles as catalysts and tested against *M. tuberculosis* ATCC 27294. Two nitrophenyl-containing compounds showed the strongest activity in the reported series, with MIC values of 0.70 and 1.29 µM/mL, respectively, compared with 0.60 µM/mL for rifampicin. Docking and enzyme-inhibition studies supported interaction with InhA; the corresponding IC₅₀ values were 2.69 and 3.91 µg/mL.²⁰

Poce et al. investigated pyrazole-containing five-membered heterocycles as potential MmpL3 inhibitors. Forty-nine compounds were prepared, with structural changes intended in part to improve polarity and solubility. Several 1,3,5-trisubstituted pyrazoles displayed potent antimycobacterial

activity. SAR analysis identified cyclic amines at position 3 as important contributors, while some silicon-containing analogues combined high potency with less favourable safety characteristics. Piperidine- and pyridinepiperazine-containing analogues provided a more balanced activity profile. Resistance mapping by whole-genome sequencing supported MmpL3 as the principal target.²¹

Cyclization of chalcone precursors to pyrazolines was reported to increase antimycobacterial activity relative to the corresponding uncyclized compounds. Within the investigated series, an N-acetylated pyrazoline showed the highest activity.²²

Pyrazolines generated by cyclization of chalcones with hydrazine derivatives were characterized by spectroscopic methods and evaluated for antimicrobial activity. Halogen- and nitro-substituted members of the series generally showed stronger effects, and selected compounds were active against *M. tuberculosis* H37Rv at MIC values comparable with standard antimycobacterial agents.²³

Pyrazole–1,3,4-oxadiazole hybrids have been explored as antimycobacterial candidates. The synthesised compounds were characterised by NMR, FT-IR, and HRMS and tested against *M. tuberculosis* H37Rv. Para-hydroxy and para-amino derivatives showed activity comparable with ethambutol in the reported assay, whereas a nitro substituent was associated with lower activity.²⁴

Nitrogen-rich piperazine–pyrimidine–pyrazole hybrids were prepared through a multistep sequence involving hydrazinolysis, cyclization, and coupling reactions. In the H37Rv assay, a methoxyphenyl-substituted analogue showed the strongest activity in the series. Docking using PDB entry 4TRO indicated hydrogen-bond interactions involving Ile122, Val65, and Leu197. The SAR analysis further indicated that anisole, phenyl, and naphthyl groups at the piperazine N-4 position favoured activity, whereas ethyl and pyridyl groups were detrimental.²⁵

Pyrazole–thiazole hybrids were evaluated against both *Trypanosoma cruzi* and *M. tuberculosis*. A 4-bromo derivative showed an MIC of 32.28 µM against *M. tuberculosis* H37Rv. The reported SAR indicated that halogen substitution, particularly meta-fluoro and para-bromo groups, influenced antimycobacterial activity, whereas some electron-donating or disubstituted analogues were less active.²⁶

1,3-Substituted pyrazole carboxamides were synthesized through multistep preparation of pyrazole intermediates followed by coupling with carboxylic acids. Several compounds inhibited *M. tuberculosis* selectively, with a 3,5-dinitrophenyl carboxamide among the more active structures. Subsequent heteroaromatic modifications further improved activity in the reported series, including against drug-resistant strains. Nitro substitution on the carboxamide

and heteroaromatic groups on the pyrazole ring were identified as favourable structural features.²⁷

A one-pot Biginelli approach was used to prepare pyrazole–tetrahydropyrimidinethione hybrids from a 1,3-dicarbonyl compound, thiourea, and aromatic aldehydes under acidic conditions. Against *M. tuberculosis* H37Rv, halogenated derivatives were the most active, with the 4-trifluoromethylphenyl compound followed by the 4-fluorophenyl analogue. Electron-donating substituents produced comparatively little change in activity.²⁸

Pyrazole-4-carboxamide derivatives were synthesized in three steps from phenylhydrazine and evaluated against *M. tuberculosis* H37Rv. Several hydroxy-substituted carboxamides showed significant activity, although they were less potent than isoniazid and pyrazinamide. Nitro and chloro substituents were associated with improved antimycobacterial activity in the reported series.²⁹

Pyrazoline derivatives have been investigated as inhibitors of mycobacterial cell-wall biosynthesis, particularly through interference with InhA and consequent disruption of mycolic-acid formation. Reported optimization strategies include 1,3,4-trisubstitution, incorporation of thienyl or fused pyrazolo-pyrimidine systems, and addition of hydrogen-bond-donor groups.³⁰

A two-step synthesis was used to obtain 1,3,5-trisubstituted pyrazolines. Chalcones were first prepared by Claisen–Schmidt condensation of 1-acetylnaphthalene with p-nitrobenzaldehyde and were then cyclized with different hydrazine derivatives under acidic conditions. The products were screened against nine microorganisms using cup-plate and tube-dilution methods; antibacterial effects were generally stronger than antifungal effects.³¹

Coumarinyl–pyrazole derivatives incorporating the isoniazid pharmacophore were synthesized and characterized by IR, NMR, and elemental analysis. Eleven compounds were assessed against *M. tuberculosis* H37Rv using a resazurin MIC assay. The 4-fluorophenyl derivative gave the highest reported growth inhibition, while chloro- and nitro-substituted analogues showed moderate activity. Electron-withdrawing groups at the C-3 phenyl ring of the pyrazole were associated with increased antimycobacterial potency.³²

Pyrazole–quinazolinone hybrids were synthesized and evaluated against *M. tuberculosis* H37Rv after structural confirmation by IR, NMR, and mass spectrometry. The reported SAR suggested that ortho methyl or methoxy groups and chloro substituents at selected ortho or para positions could improve activity, while some bulky or differently positioned substituents were less favourable. Several hybrids showed activity approaching that of isoniazid in the reported experiments.³³

Thiazolyl-pyrazole derivatives, together with related chalcones, bis-pyrazoles, and chromen-4-one derivatives,

were evaluated against dormant *M. tuberculosis* H37Ra and *M. bovis* BCG. Several compounds showed MIC values in the low- $\mu\text{g/mL}$ range. Methyl and halogen substitution affected activity, and cyclization of chalcones into bis-pyrazole or chromanone systems was associated with improved antimycobacterial effects. Selected active derivatives also showed low cytotoxicity in human cell lines.³⁴

RELATIONSHIP BETWEEN TUBERCULOSIS AND INFLAMMATION

Chemokines and cytokines coordinate the recruitment and activation of immune cells during pulmonary *M. tuberculosis* infection.³⁵ Cytokines are soluble mediators that regulate neighbouring or distant cells and include tumour necrosis factors, interleukins, and chemokines.³⁶

Following infection, phagocytic cells recognize *M. tuberculosis* and initiate the release of pro-inflammatory mediators. TNF- α is produced predominantly by macrophages, although lymphocytes, mast cells, endothelial cells, and fibroblasts can also contribute. It is initially synthesized as a transmembrane protein and can be released after proteolytic processing. Binding of TNF- α to its receptors activates signalling pathways including NF- κB , JNK, and p38 and can also promote apoptosis.^{37–41}

During progression of TB, TNF- α contributes to chemokine regulation and granuloma development. It is also produced by CD4+ and CD8+ T cells and contributes to macrophage activation.^{42,43}

TNF- α contributes to communication between innate and adaptive immunity by promoting chemokines such as CCL5, CXCL9, and CXCL10. These mediators help recruit CXCR3+ T cells, macrophages, and neutrophils to infected lung tissue.^{44,45}

TNF- α is important for the organization and maintenance of granulomas, which contain macrophages, T and B lymphocytes, giant cells, and neutrophils. Granuloma formation helps restrict mycobacterial dissemination. Experimental and clinical observations indicate that interruption of TNF- α signalling can permit *M. tuberculosis* reactivation or dissemination, including involvement of the central nervous system.^{46–48}

TNF- α supports macrophage activation and can contribute to apoptosis of infected host cells. Thus, an appropriately regulated TNF- α response is important for host defence, whereas excessive signalling may contribute to inflammatory tissue injury.⁴⁹

Hydroxybenzofuranyl-pyrazolyl and hydroxyphenyl-pyrazolyl chalcones have been reported to possess anti-inflammatory activity through preferential inhibition of cyclooxygenase-2 (COX-2). This activity was associated with reduced production of inflammatory mediators,

including prostaglandins and TNF- α , while showing greater selectivity for COX-2 than COX-1 in the reported studies.⁵⁰

A series of 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines and related 1-benzoyl derivatives was obtained from chalcones prepared by condensation of 4-acetylphenyl with aromatic aldehydes, followed by hydrazine-mediated cyclization. One 4'-methylphenyl derivative showed strong anti-inflammatory activity in the reported pharmacological evaluation.⁵¹

Fourteen pyrazoline-benzothiazole derivatives were synthesized through chalcone intermediates followed by cyclization with a hydrazinobenzothiazole sulfonamide component. The active hybrids were reported to reduce inflammatory responses through inhibition of COX-2 and suppression of TNF- α production.⁵²

Pyrazolylpyrazoline derivatives containing a benzenesulfonamide group were synthesized and evaluated for anti-inflammatory activity. Two derivatives bearing fluoro- or bromo-substituted aryl groups showed significant in vivo effects. Their activity was interpreted in relation to the spatial arrangement of the sulfonamide group and its ability to occupy the secondary hydrophobic pocket characteristic of COX-2.⁵³

ANTIOXIDANT ACTIVITY

Mycobacterial infection can stimulate reactive oxygen species (ROS) production through activation of phagocytic cells.⁵⁴ Although ROS contribute to antimicrobial defence,

excessive oxidative activity can increase tissue injury and intensify inflammation.⁵⁵⁻⁵⁸

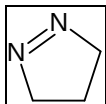
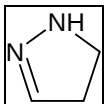
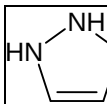
Lipid peroxidation is an important consequence of free-radical-mediated oxidative damage. During pulmonary inflammation, the respiratory burst increases the formation of ROS and reactive nitrogen intermediates, contributing to oxidative stress within the lung.^{59,60}

Patients with active pulmonary TB may exhibit an imbalance between oxidant generation and antioxidant defence, together with increased lipid peroxidation and greater susceptibility of lipoproteins to oxidative modification.^{61,62}

3,5-Disubstituted-2-pyrazolines have been investigated as synthetic radical scavengers. The compounds were prepared from substituted benzaldehydes and 3-methoxy-4-hydroxyacetophenone through chalcone intermediates, followed by cyclization with hydrazine hydrate. DPPH, nitric oxide, superoxide, and hydrogen-peroxide scavenging assays indicated antioxidant activity across the series, with some compounds showing activity comparable with ascorbic acid.⁶³

1-Thiazolyl-2-pyrazolines have been explored as dual antioxidant and anti-inflammatory candidates. Their proposed antioxidant behaviour involves direct interaction with reactive oxygen and nitrogen species through proton- or electron-transfer processes, with structural substitutions influencing the efficiency of radical trapping.⁶⁴

Table 1: Activities of different pyrazolines

		
1-Pyrazoline	2-Pyrazoline	3-Pyrazoline
Anti-inflammatory Antidepressant CNS Activity Analgesic Antimicrobial Antitubercular	Antioxidant Antitumor Antidepressant CNS Activity Antiviral Antidiabetic Antimicrobial	Anti-hypertensive Antidiabetic Antimicrobial Antitubercular

OTHER ACTIVITIES OF PYRAZOLINE-BASED COMPOUNDS

The pharmacological behaviour of pyrazoline derivatives is strongly affected by both the identity and position of substituents attached to the aromatic ring.

Ortho-hydroxy and ortho-nitro derivatives showed antibacterial activity against *E. coli*, *P. aeruginosa*, and *S. aureus*, while a para-methoxy analogue was particularly active against *S. aureus*. A meta-nitro derivative also showed activity against *P. aeruginosa* and *S. aureus*.⁶⁵[Table 1]

Substituent-dependent differences in antibacterial activity were observed among pyrazoline derivatives. Cyano- and dimethylamino-containing compounds showed comparatively strong inhibition of *S. aureus*, *E. coli*, *P. aeruginosa*, and *E. faecalis*, with low MIC values reported for selected analogues.⁶⁶

Across another series, hydroxyl and methoxy groups at selected ortho or para positions were associated with increased antibacterial activity, whereas nitro substitution at ortho or meta positions also produced notable inhibition. Chlorinated derivatives and replacement of phenyl with furan generally reduced activity, and the compounds showed little or no activity against *Candida albicans*.⁶⁷

Nitro- and halogen-substituted pyrazolines showed appreciable antiamoebic activity against *Entamoeba histolytica*, whereas hydroxyl- and methoxy-containing analogues were generally less active. Unsubstituted compounds showed intermediate activity, and some heteroaryl substitutions were unfavourable.⁶⁸

For 1-N-substituted thiocarbamoyl-3-phenyl-2-pyrazolines, activity against *E. histolytica* varied with both the aryl substituent and the N-1 group. A 3-bromo substituent was associated with enhanced activity, while 3-chloro analogues were also active when combined with bulky cyclic or aromatic amines.⁶⁹

The collected antimicrobial and antiamoebic data indicate that electron-withdrawing groups such as nitro and halogens can favour activity in several pyrazoline series, whereas hydroxyl and methoxy groups often produce weaker effects in these assays. Heteroaryl replacement of the phenyl ring was also frequently associated with reduced potency.⁷⁰

Similar trends were reported for additional pyrazoline series: nitro- and halogen-substituted derivatives generally showed stronger antimicrobial or antiamoebic effects, whereas electron-donating groups and unsubstituted analogues were less active. Some derivatives exceeded the activity of metronidazole in the reported *E. histolytica* assays.⁷¹

Substituent effects also differed according to the pharmacological endpoint. Hydroxyl- and methoxy-containing derivatives were associated more often with analgesic and anti-inflammatory activity, whereas nitro- and halogen-substituted structures tended to show stronger antimicrobial and antiamoebic effects.⁷²

Overall, the reviewed studies indicate that electronic and positional changes on the pyrazoline aryl group can redirect biological activity. Electron-withdrawing substituents were frequently associated with antimicrobial effects, while electron-donating groups were reported in some analgesic and anti-inflammatory series.⁷³

Selected chloro- and methoxy-substituted pyrazolines showed moderate cytotoxicity toward MCF7, T47D, and HeLa cell lines, with the strongest effect in the reported

T47D assay. Hydroxyl-containing analogues were inactive or less active against the tested cancer cells but showed selectivity relative to normal cells. Docking studies suggested interactions with EGFR through hydrogen-bonding and π -cation contacts.⁷⁴

In several anticancer studies, halogenated pyrazoline derivatives, particularly chloro- and bromo-substituted compounds, showed notable cytotoxic effects against breast and cervical cancer cell lines. Hydroxyl- or methoxy-substituted analogues generally displayed weaker or moderate activity.⁷⁵

Isatin-pyrazoline conjugates have also been investigated as anticancer agents. A 5-bromo isatin derivative bearing 4-chlorophenyl and 4-methoxyphenyl substituents on the pyrazoline system showed activity across several tumour-cell models, including leukemia, colon, lung, ovarian, renal, and breast cancer lines.⁷⁶

Halogenated pyrazolines have been reported to interact favourably with cancer-associated targets, including EGFR, in molecular-docking studies. Their cytotoxic activity has been observed in breast and cervical cancer models and, in some studies, in leukemia models.⁷⁷

N1-Benzenesulfonyl-2-pyrazoline derivatives have shown neuropharmacological activity. A 4-chlorophenyl-substituted analogue was associated with the strongest anxiolytic effect in the reported series, whereas a derivative containing naphthalen-1-yl and furan-2-yl groups showed the greatest antidepressant activity.⁷⁸

The 1,3,5-trisubstituted-2-pyrazoline framework has been examined for antidepressant and anxiolytic effects. A 2-hydroxyphenyl/4-benzyloxyphenyl substitution pattern was associated with stronger antidepressant activity, while an anthracen-9-yl/4-methylphenyl combination produced a prominent anxiolytic response in the reported experiments.⁷⁹

Triazolo-pyrazoline derivatives produced antidepressant-like responses in experimental behavioural models, including reduced immobility and increased swimming, without the reported impairment of motor coordination in the Rota-Rod test.⁸⁰

Some 2-pyrazoline derivatives have been reported as selective acetylcholinesterase inhibitors. The absence of appreciable butyrylcholinesterase inhibition in the reported compounds suggests a degree of target selectivity and supports further investigation in neurodegenerative-disease models.⁸¹

Antiviral activity has been reported for several pyrazoline derivatives, with the response influenced by aromatic substitution. Chloro- and bromo-substituted compounds showed inhibition of viral replication in experimental influenza and herpesvirus models.⁸²

Additional halogenated pyrazolines, particularly chloro- and bromo-containing analogues, displayed antiviral activity in influenza and herpesvirus models.⁸³

Some studies indicate that heteroaryl substitution can alter antiviral selectivity, while halogenated derivatives retain activity against influenza and herpesvirus models.⁸⁴

Camphor- and adamantanone-derived pyrazolinium systems have also been evaluated as antiviral compounds. Among the reported structures, 1-bornylidene-3-phenylpyrazolinium tetrafluoroborate showed an IC₅₀ of 6.2 μ M and a selectivity index of 107 in the cited assay.⁸⁵

Quinoline-containing 2-pyrazolines (ACP1–ACP10) were investigated for effects on ATP-sensitive potassium channels in pancreatic β -cells. The oxo-linked analogues produced stronger antidiabetic responses than the corresponding amino-linked compounds and were associated with reduced carbohydrate metabolism and postprandial glucose elevation in the reported models.⁸⁶

N-Carbamoyl pyrazolines were assessed for antidiabetic activity, including inhibition of α -amylase relative to acarbose. Several compounds showed moderate-to-strong inhibition, and docking studies indicated favourable interactions with residues in PPAR- γ , a regulator of glucose homeostasis.⁸⁷

Pyrazoline derivatives have also shown α -amylase inhibitory activity. In the reported series, oxo-linked structures were more active than amino-linked analogues, suggesting that this linkage can influence the antidiabetic response.⁸⁸

2-Pyrazolines have been evaluated against both α -amylase and α -glucosidase. Chlorine-, fluorine-, and nitro-substituted derivatives showed particularly strong α -glucosidase inhibition, demonstrating that substituent electronics can influence carbohydrate-hydrolysing enzyme inhibition.⁸⁹

The reported antidiabetic activity of pyrazoline derivatives is partly related to inhibition of carbohydrate-digesting enzymes. Compounds containing chloro, fluoro, or nitro substituents showed enhanced inhibitory effects in some α -amylase or α -glucosidase assays.⁹⁰

Sulfonamide-bearing 1,2-pyrazolines have been designed as structural analogues of angiotensin II receptor antagonists. Chloro-substituted members showed the strongest inhibition of angiotensin-II-related activity within the reported series.⁹¹

1,3,5-Trisubstituted pyrazolines bearing a benzenesulfonamide moiety have been synthesized and examined as inhibitors of carbonic anhydrase isoenzymes.⁹²

3-(2-Furyl)pyrazoline derivatives have demonstrated both antidepressant and anticonvulsant activity in experimental models. Compounds carrying a 2-furyl group at the 5-position of the pyrazoline ring showed notable anticonvulsant effects in the reported series.⁹³

Unsaturated carbonyl compounds and their corresponding pyrazoline derivatives have been investigated for antifungal activity against *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis*.⁹⁴

The antifungal activity of 2-pyrazolines has been discussed in relation to structural features shared with azole-type antifungal agents. Reported modifications include N-1 acetyl, thiocarbamoyl, or carboxamide groups together with electron-withdrawing halogens on the aromatic rings, which may influence interaction with fungal sterol 14 α -demethylase (CYP51).⁹⁵

Chalcone-derived pyrazolines containing N-acetyl groups showed notable antifungal effects against pathogenic fungi. Introduction of a halogen, particularly ortho-fluorine, was associated with increased activity in the reported series.⁹⁶

Conversion of chalcone structures into pyrazoline-containing analogues was reported to improve antifungal activity. N-acetylated compounds and halogenated derivatives, especially ortho-fluoro analogues, showed stronger inhibition against *Candida albicans*, *C. tropicalis*, and *C. parapsilosis*.⁹⁷

1,3,5-Trisubstituted-2-pyrazolines containing furan moieties have shown antifungal activity against several plant-pathogenic fungi.⁹⁸ Related chalcone-derived, N-acetylated pyrazolines were also active against *Candida* species, including *C. albicans*, *C. tropicalis*, and *C. parapsilosis*.⁹⁹ Thiazolyl-substituted pyrazolines and fluorinated 4,5-dihydro-1H-pyrazoles have likewise been investigated as antifungal or fungicidal candidates.^{100,101}

CONCLUSION

Pyrazoline is a versatile heterocyclic scaffold with reported activity across several pharmacological areas, including tuberculosis, inflammation, oxidative stress, microbial infection, and selected neurological, metabolic, antiviral, and anticancer models. Within TB research, pyrazole- and pyrazoline-containing compounds have been investigated against targets such as shikimate kinase, InhA, and MmpL3, with activity influenced by substitution pattern and incorporation of additional pharmacophores. The reviewed studies also demonstrate that structural changes can alter activity across different biological targets, emphasizing the importance of systematic structure–activity relationship studies. Although several derivatives show encouraging in vitro or experimental activity, these findings should be interpreted as early-stage medicinal-chemistry evidence rather than proof of clinical efficacy. Further work should address selectivity, cytotoxicity, resistance, pharmacokinetics, mechanism of action, and in vivo efficacy before pyrazoline-based compounds can be considered for therapeutic development.

AI DISCLOSURE

Artificial intelligence tools (Microsoft Copilot) were used only for supportive purposes, specifically language editing and formatting. No AI tool was involved in data analysis, interpretation, or authorship. The authors remain fully responsible for the accuracy, originality, and integrity of the manuscript.

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