

Pyrazoline Scaffold: A Comprehensive Review of Synthetic Strategies, Structure Activity Relationship and Antimicrobial Activities

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ABSTRACT

Pyrazoline, a crucial five-membered heterocyclic compound, having versatile biological activities. It is a dihydro derivative of pyrazole moiety widely recognized in pharmaceutical chemistry for its significant therapeutic approaches. The versatility of the pyrazoline ring system allows for extensive structural modifications often by attaching aromatic and heteroaromatic. This article reviews various synthetic methodologies employed for the preparation of pyrazoline derivatives and effect of this modification on biological activity. This article also summarizes their antimicrobial activity. Common synthetic routes involve the cyclization reaction of chalcones with hydrazine or substituted hydrazine's. Techniques discussed include conventional heating, ultrasonic irradiation, and efficient microwave-assisted methods, often utilizing catalysts like Amberlyst-15 or simple acids/bases. The antimicrobial screening results consistently demonstrate that many pyrazoline derivatives exhibit activity against wide range of microbial strains, including both Gram-positive and Gram-negative bacteria, and even drug-resistant strains like *H. pylori*. The pharmacological potency is often influenced by specific substituent groups and the overall structure, highlighting the pyrazoline scaffold as a promising core for the development of new antibacterial agents.

Key words: Pyrazoline, conventional synthesis, green synthesis antimicrobial activities.

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1. INTRODUCTION

Pharmaceutical chemistry is mainly involved in the discovery and development of new drugs for treating the disease which are not cured by the conventional medicaments. Inorganic compounds are used as antacids, mineral supplements, and radiopharmaceuticals, but organic compounds are leading because of their potent therapeutic action. The five members nitrogen containing hetero cyclic rings like pyrazole, pyrazolidine etc. are most important for discover and development of new drugs [1]. Pyrazoline, as a kind of five-membered nitrogen heterocyclic framework and its derivatives exhibits many biological activities such as anti-bacterial, anti-fungal, anti-inflammatory, anticonvulsant, diuretics, and anti-histaminic etc[2]. Pyrazoline is a dihydro derivative of pyrazole, containing two adjacent nitrogen atoms and one endocyclic double bond in the ring. 1-pyrazoline, 2-pyrazoline and 3-pyrazoline are the isomer of pyrazoline scaffold. Fig. 1, in which 2-pyrazoline is most studied due to its stability compare to the other two forms, represented [2,3].

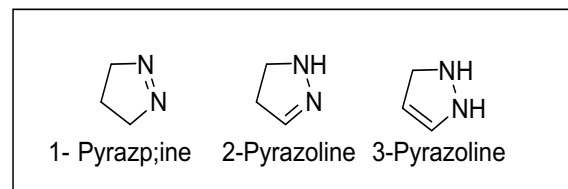


Fig. 1: Different structures of pyrazoline

This heterocyclic ring system is quite stable, and from various study, researchers have been found that attaching different electron withdrawing groups, aromatic and heteroaromatic units at the 1st, 3rd, and 5th positions of the ring, alter the potency and biological activity [4].

Naturally pyrazolines are present in plants belongs to family *Piperaceae* which has *Pigeongram* (black pepper) [5]. Sponges, corals, and other marine organisms showed cytotoxic and anti-inflammatory due to presence of pyrazoline alkaloids. Natural pyrazolines interact with living organisms by forming an N–N bond, making pyrazoline derivatives widely recognized heterocyclic compounds with significant biological activities [6]. In our article we are

2. DIFFERENT METHODS OF SYNTHESIZED PYRAZOLINE DERIVATIVES

The ultrasonic technique was used for synthesizing chalcones and pyrazolines Fig. 2. By Claisen-Schmidt condensation of aryl methyl ketones with 4-chlorobenzaldehyde in the presence of sodium hydroxide condense to give 1,3-diarylprop-2-en-1-ones. Then under ultrasonic irradiation at temperatures ranging from 25 to 45 °C for 25 to 150 minutes, 2-pyrazolines were synthesized by treating the chalcones with glacial acetic acid [7].

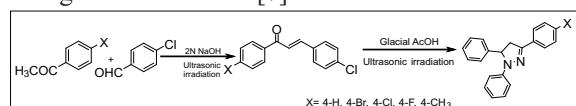


Fig. 2. Ultrasonic irradiation synthesis of 2-Pyrazolines derivatives

By using the amberlyst-15 as a catalyst, 3-aryl-5-(substituted phenyl/phenyl furanyl/thienyl)-2-pyrazolines was synthesized. By the condensation of various aromatic ketones with aromatic aldehydes under Fig. 3, 1-aryl-3-(substituted phenyl/phenyl furanyl/thienyl)-2-propan-1-ones were prepared. These intermediates then underwent a clean and efficient cyclization with hydrazine or substituted hydrazine, leading to the formation of the target pyrazoline derivatives [8].

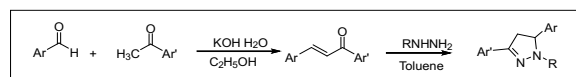


Fig. 3. Synthesis of Pyrazoline derivatives by using Amberlyst-15 as catalyst

Under heat using methanolic acid as a catalyst, 1,3,5-trisubstituted-2-pyrazoline derivatives were prepared by cyclizing phenyl hydrazine with α , β -unsaturated ketones Fig. 4. They explored how different solvents and varying amounts of catalyst influenced the reaction time and product yield [9].

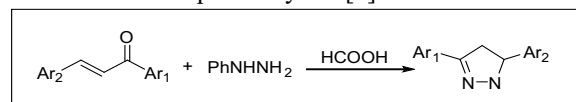


Fig. 4. Synthesis of Trisubstituted Pyrazolines derives
In the presence of hot acetic acid or hot propionic acid 3-arylidenechromanones and 3-arylidene-1-thiochromanones were reacted with hydrazine hydrate to yield the tricyclic pyrazolines Fig. 5 [10].

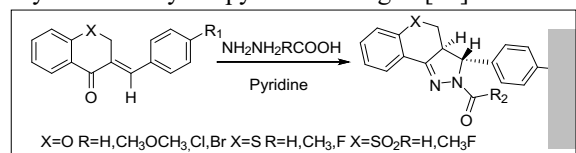


Fig. 5. Synthesis of tricyclic fused pyrazolines derivatives

Development of a novel series of pyrazoline derivatives through 1,3-dipolar cycloaddition reactions Fig. 6. Initially, in the presence of K_2CO_3 in DMF, 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde was alkylated with 4'-bromomethyl-biphenyl-2-carbonitrile. The resulting compound treated with phenyl hydrazine. These formed intermediates underwent oxidative dehydrogenation using chloramine-T (CAT), generating a nitrile imine, which was subsequently reacted with various olefins under reflux in ethanol. 4,5-dihydro-3-(substituted imidazole)-5-substituted-1-phenyl-1H-pyrazolines, were obtained finally in good yields and purity [11]

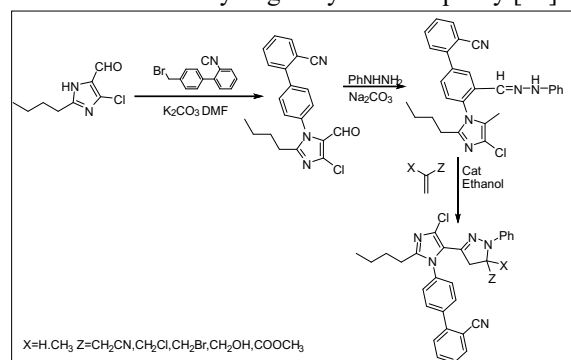


Fig. 6. Synthesis of pyrazoline derivatives through 1,3-dipolar cycloaddition)

In a phase transfer catalysis (PTC) process, using tetrabutyl ammonium iodide (TBAI) as a catalyst, new 1,3,5-triaryl pyrazoline compounds were synthesized by using Claisen-Schmidt condensation Fig. 7 [12].

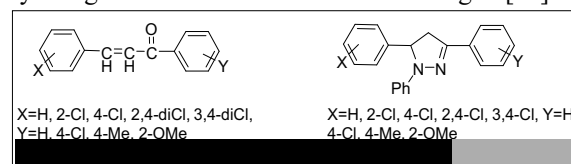


Fig. 7. 1,3,5-triaryl pyrazoline derivatives synthesized
Four specific compounds Fig. 8 were synthesized by using two pyrazole-carbaldehydes and two ethenones/propanone these were reacted with chalcones with hydrazine hydrate. They used formic acid, acetic acid, and propionic acid as catalysts for this reaction [13].

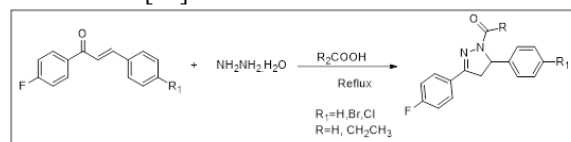


Fig. 8. Four pyrazoline derivatives

New 2-pyrazoline compounds were synthesized by treating 3-acetyl-2,5-dimethylfuran with different aldehydes in a solution of ethanol and aqueous KOH. The intermediate compounds produced reacted with phenyl hydrazine to create the final product, 1-phenyl-3-(2',5'-dimethyl-3'-foryl)-3-(aryl)-2-pyrazoline Fig. 9 [14].

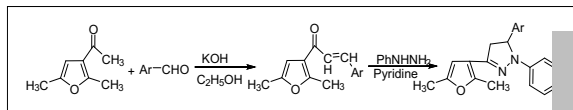


Fig. 9. 1-phenyl-3-(2',5'-dimethyl-3'-foryl)-3-(aryl)-2-pyrazoline

By using Claisen-Schmidt condensation several 1-acetyl-3,5-diaryl-2-pyrazolines Fig.10 of various halogen-substituted benzaldehydes and 20 acetyl indoles in an ethanol solution containing 10% NaOH to produce chalcone intermediates. These intermediates were then reacted with hydrazine hydrate in hot glacial acetic acid [15].

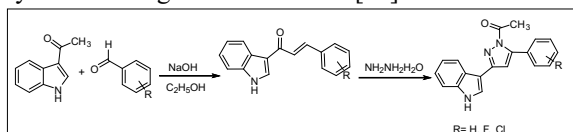


Fig. 10. 1-acetyl-3,5-diaryl-2-pyrazolines (2011). 1-(2-Carboxyphenyl)-2-pyrazolines and 1-(4-Carboxyphenyl)-2-pyrazolines Fig. 11 were created by Levai and Jeko in 2009. The compounds by reacting specific 3-aryl-1-(3-coumarinyl) propen-1-ones with either (2-carboxyphenyl) hydrazine or (4-carboxyphenyl) hydrazine in a heated acetic acid solution [16].

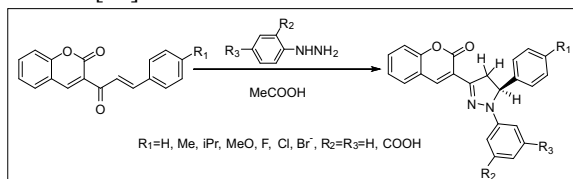


Fig. 11- 2-pyrazoline derives synthesized by Levai and Jeko (2009).

New Pyrazoline derivatives Fig.12 was synthesized from several new chalcone derivatives. The reaction involved the starting material 3-(4-chlorobenzyloxy) paraldehyde reacting with various substituted acetophenones. Finally, they treated the resulting chalcones with hydrazine hydrate in a Michael addition reaction to produce the new pyrazoline derivatives [17,18].

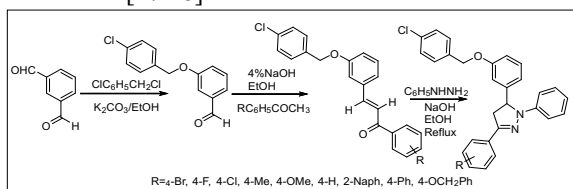


Fig. 12- Pyrazoline derives synthesized by Hawaiz (2011).

Chalcones ere created by reacting substituted aldehydes and ketones in an alkaline solution of NaOH and alcohol. These chalcones were then converted into 1,3,5-trisubstituted pyrazoline derivatives Fig 13 by reacting them with isoniazid in glacial acetic acid [19].

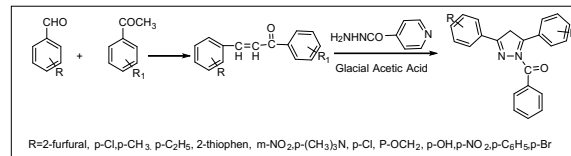


Fig. 13. 1,3,5-trisubstituted pyrazoline derivatives
A new series of pyrazolines by heating Piperazine chalcones and hydrazine hydrate in an alkaline solution Fig. 14[20] gives a new series of pyrazolines.

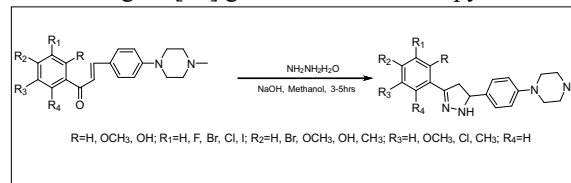


Fig. 14. Pyrazoline derivative having piperazine.
Several new pyrazoline derivatives starting with 2-hydroxy-aceto-naphthanone and a substituted vanillin derivative. This pyrazoline was then further modified through alkylation to produce the new pyrazoline derivatives Fig. 15 [21]

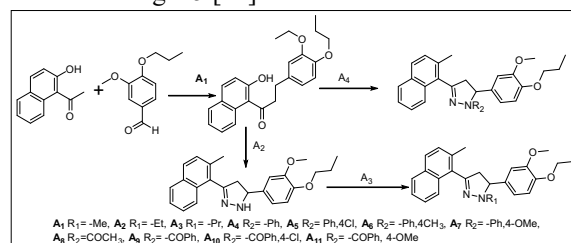


Fig. 15. Pyrazoline derivatives synthesized by 2-hydroxy-aceto-naphthanone

Joshi and his colleagues synthesized various pyrazoline derivatives starting from chalcones. They first created the chalcones by using Claisen-Schmidt condensation to react furan-2-carbaldehyde with different acetophenones Fig. 16. The resulting chalcones were then reacted with either phenyl hydrazine or hydrazine hydrate in an ethanol solution under reflux to form the new pyrazolines [22].

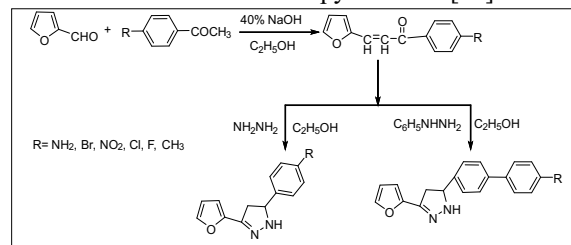


Fig. 16. Pyrazoline derivatives synthesized from furan-2-carbaldehyde

3,5-dinaphthyl substituted 2-pyrazolines Fig. 17 were synthesized by reacting 1-acetylnaphthalenes with 1-naphthaldehydes in an ethanolic NaOH solution and with hydrazine reagents, which had specific groups attached to the naphthalene and pyrazoline rings [23].

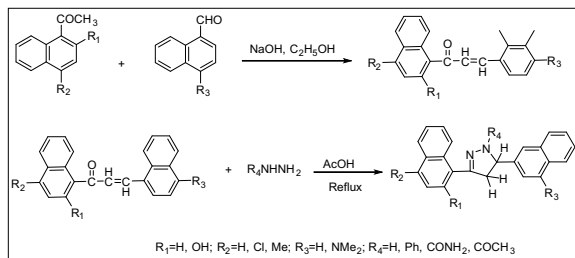


Fig. 17. 3,5-dinaphthyl substituted 2-pyrazolines

A 2-acetyl thiophene pyrazoline derivative is a heterocyclic organic compound synthesized by reacting a chalcone of 2-acetyl thiophene with a hydrazine derivative (such as phenylhydrazine or hydrazinobenzothiazole) Fig. 18 [24].

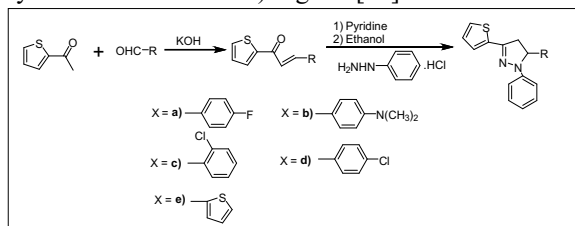


Fig.18. 2-acetyl thiophene pyrazolines

New pyrazolines were synthesized by a reaction between 3-acetylpyridine and specific aldehydes in an alcohol solution with 40% aqueous KOH to produce chalcones. These chalcones were reacted with phenylhydrazine hydrochloride to yield. 1-phenyl-3-(3'-pyridyl)-5-(substituted phenyl)-2-pyrazoline derivatives Fig. 19 [25].

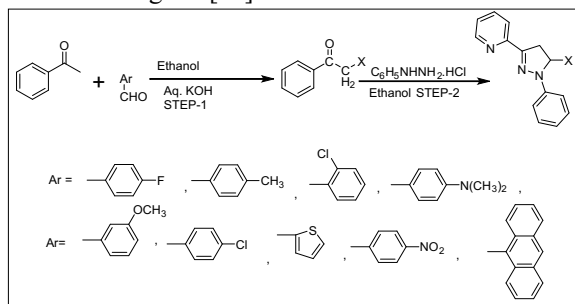


Fig. 19. 1-phenyl-3-(3'-pyridyl)-5-(substituted phenyl)-2-pyrazoline derivatives.

A new and simpler one-pot method for creating substituted 2-pyrazolines. They claimed this method was better than traditional heating techniques [26]. The 4'-(4"-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-carboxaldehydes Fig. 20 was prepared by irradiated a methanol solution containing 4-(4'-nitrophenoxy) acetophenone and a substituted aryl aldehyde in a microwave at 300 watts for 3–4 minutes and then produced 4'-(4"-nitrophenoxy) chalcones was treated with hydrazine hydrate in hot formic acid and microwaved it at 600 watts for 2–4 minutes.

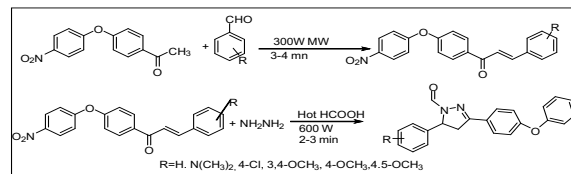


Fig. 20. [4'-(4"-nitrophenoxy)-phenyl]-5-(substituted aryl)-2-pyrazoline-1-carboxaldehydes

Several new 3,5-diphenyl and 1,3,5-triphenyl-2-pyrazoline derivatives were synthesized by condensing various acetophenones with benzaldehydes in a diluted ethanolic solution of sodium hydroxide at room temperature Fig. 21 [27].

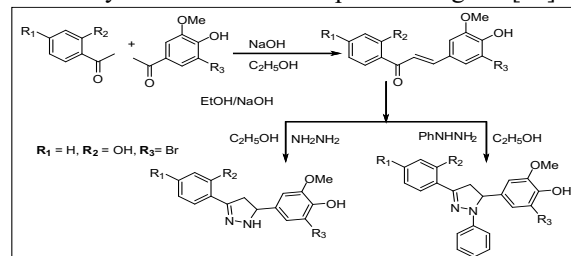


Fig. 21. 3,5-diphenyl-2-pyrazolines and 1,3,5-triphenyl-2-pyrazolines

A new set of pyrazolines and isoxazoles were synthesized .by using the Claisen-Schmidt condensation reaction to treat 4-acetylthioanisole with substituted aryl/heteroaryl aldehydes in the presence of NaOH. These intermediates were then used as a base for synthesizing the target compounds. To produce 3-[4-(methylthio) phenyl]-5-aryl/heteroaryl-pyrazolines, they reacted the intermediates with hydrazine hydrate in ethanol. To produce the 3-[4-(methylthio) phenyl]-5-aryl/heteroaryl-isoxazoles Fig. 22 they reacted the intermediates with hydroxylamine hydrochloride in a solution of dimethylformamide and sodium acetate [28].

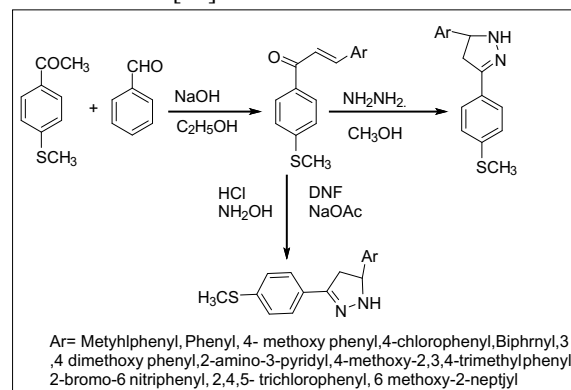


Fig. 22. 3-[4-(methylthio) phenyl]-5-aryl/heteroaryl-isoxazoles

Synthesis and analysis of 4,5-dihydropyrazolines containing a pyrimidine group, as well as their medicinal properties were reported²⁹. They reacted 1,1,3,3-tetramethoxy propane with urea and concentrated hydrochloric acid in methanol to produce

2-hydroxypyrimidine. This compound was then brominated with bromine, yielding 5-bromo-2-hydroxypyrimidine. Using phosphorus oxychloride (POCl_3) at a temperature of 105-110 °C, they converted the brominated compound into 5-bromo-2-chloropyrimidine. This new compound was reacted with hydrazine, which resulted in 5-bromo-2-pyrimidinylhydrazine. Finally, this hydrazine derivative was reacted with 1,3-diaryl-2-propen-1-one. This final step, using both traditional heating and microwave irradiation, yielded the target compound, 5-bromo-2-(3,5-dihydro-1H-pyrazol-1-yl) pyrimidine Fig. 23 [29,30].

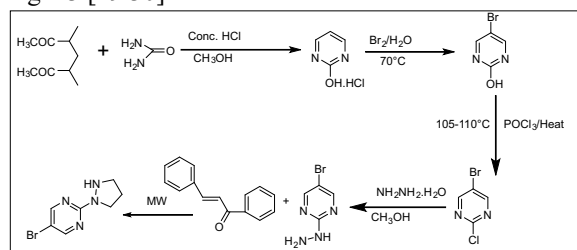


Fig. 24. 5-bromo-2-(3,5-dihydro-1H-pyrazol-1-yl) pyrimidine

3. STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF PYRAZOLINE DERIVATIVES

By analyzing the literature review of synthesis, structural modifications and bioactivities a well-defined Structure-Activity Relationship (SAR) among the 2-pyrazoline derivatives has been established for its potent use as anti-bacterial, antibacterial, antifungal, and antitubercular agents [31]. The biological activities of core 2-pyrazoline scaffold depends upon nature, position and electronic properties of substituents present on the 2-pyrazoline.

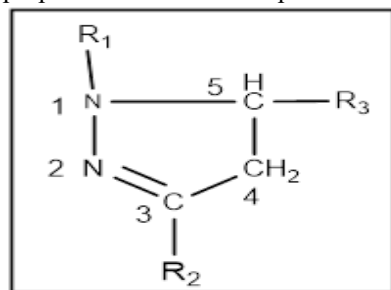


Fig. 25. Basic Structure of Pyrazoline

1. Modifications at the N-1 Position (R-1)

- The pyrazoline literature, the N-1 position is a major diversification site, with substitutions including H, acyl, benzoyl, carboxamide, carbothioamide, acetyl, alkyl, and acid hydrazide groups, and these changes alter stability, lipophilicity and target engagement [32].
- Replacing the N-1 hydrogen with acetyl, thiocarbonyl, or carboxamide moieties on pyrazoline scaffolds consistently yields potent MAO inhibitors with predicted blood-brain

barrier permeability [33]. N-1 acylation converts these unstable NH pyrazolines into more stable derivatives and enhances antibacterial potency, particularly against Gram-positive strains (*S. aureus*, *B. subtilis*) and *Helicobacter pylori* [34]. Carboxamide/carbothioamide at N1 position supports the antiproliferative or antiparasitic activity [35].

- N-1 benzylation lowered antibacterial spectrum and potency relative to N1-H [36].
- Alkylation of N1 position enabled potent AChE and hCA inhibition in a fused analog series [37].
- Formyl derivatives (–CHO) demonstrate improved cell membrane permeability and favorable broad-spectrum inhibition [38].
- Introducing a para-amino sulfonamide (SO_2NH_2) or para-methyl sulfonyl (SO_2CH_3) group on the N-1 phenyl ring of pyrazoline derivatives consistently produces high COX-2 selectivity over COX-1, with potent anti-inflammatory and analgesic effects [39].
- Heteroaryl substitution at the N-1 position of pyrazoline derivatives is associated with enhanced antimalarial and antimicrobial activity, though the evidence for a direct DNA-intercalation mechanism remains largely indirect and scaffold-dependent [40,41]
- Isoniazid (INH) derivatives incorporating pyrazoline, pyrazole, and related heterocyclic scaffolds represent a major strategy to overcome KatG-mediated resistance, with multiple compound classes achieving low-micromolar or sub-micromolar potency against H37Rv and resistant clinical isolate [42].

2. Modifications at the C-3 Position (R-2)

An aromatic or heteroaromatic ring present on the C-3 position participates in hydrophobic and pi-pi bond interactions with amino acid residues in the target active site. The substituent at C-3 dictates electron distribution across the endocyclic double bond N2 and C-3.

- Electron-Withdrawing Groups Substitution with halogenated aryl groups (e.g., p-chlorophenyl, p-fluorophenyl, or nitrophenyl) at C-3 markedly increases anti-cancer, antidepressant and antibacterial efficacy against Gram-negative species. Halogens also improve metabolic stability against Cytochrome P450 enzymes [43,44,45].
- Heteroaryl Substitutions: Replacing standard phenyl rings with heteroaromatic systems such as thiophene, furan, quinoline, or chromone drastically improves antimicrobial broadness [46,47,48,49]. Thiophen-2-yl and furan-2-yl substituents specifically bolster antifungal action

against *Candida albicans* and *Aspergillus niger* [50,51,52,53].

- Biphenyl or bicyclic aryl groups (e.g., 2-naphthyl, quinoliny) at C-3 enhance binding within hydrophobic pockets of microbial targets [54,55].

3. Modifications at the C-5 Position (R-3)

The C-5 carbon atom is a chiral center in 2-pyrazoline derivatives. Substituents at C-5 control the spatial orientation of the molecule inside hydrophobic binding pockets

- Poly-methoxy Phenyl Rings: Phenyl rings at C-5 substituted with multiple methoxy groups (e.g., 3,4,5-trimethoxyphenyl or 2,4-dimethoxyphenyl) significantly boost cytotoxicity against tumor cell lines (e.g., breast, cervical, and lung cancers) and enhance tubulin polymerization inhibition [56,57,58,59].
- Steric Considerations: Unsubstituted or small alkyl groups at C-5 decrease biological activity, whereas bulky aromatic/heteroaromatic rings are generally required to anchor the compound within target hydrophobic grooves [60].
- The C-5 region forms a critical hydrophobic region that balances the lipophilic-hydrophilic profile of the molecule. Electron-withdrawing groups on the C-5 of phenyl ring are key positive contributors to antimicrobial activity. Chlorine substitution in particular acts as a primary activity driver [61,62].
- Methoxy (–OCH₃), hydroxy (–OH), or isopropyl groups attached to the aromatic ring at C-5 enhance efficacy against specific strains, such as *H. pylori* and *S. aureus*. Methoxy/hydroxy combinations (vanillin-derived frameworks) provide dual anti-inflammatory and antibacterial activity [63,64].
- Large fused rings (naphthyl, indolyl, ferrocenyl, or steroidal frameworks) at C-5 alter stereochemistry and target selectivity, often translating into potent antifungal properties [65,66,67,68,69]. Targets for Neurodegenerative Disorders

4. C-4 Position Substitution

- Unsubstituted (C-4 Hydrogen): In most bioactive pyrazoline series, C-4 is kept unsubstituted (–CH₂–) to minimize steric hindrance around the central ring [70]
- Ring Fusion / Carbonyl Groups: Functionalizing C-4 with keto groups or fusing it to form polycyclic structures (e.g., pyrazolo-pyridines or steroid-pyrazoline hybrids) shifts target specificity toward topoisomerase II inhibition or kinase inhibition [71,72].

4. ANTI-BACTERIAL ACTIVITY OF PYRAZOLINE DERIVATIVES

Antibacterial and antifungal properties of compounds with N-substituted 3,5-diphenyl pyrazoline were

evaluated. The compounds having a N-acetyl group and a methoxy group at position 4 on the phenyl ring exhibited the greatest potential against metronidazole-resistant *H. pylori* strains at concentrations of 1–4 µg/ml [73]

Ozdemir *et al.* (2007) synthesized a series of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives Fig. 26. All synthesized compounds were subsequently evaluated for antimicrobial activity against *E. coli*, *S. typhimurium*, *S. aureus*, *S. faecalis*, *B. cereus*, *A. hydrophila*, *C. albicans*, and *C. glabrata*. A significant level of activity was observed [74]

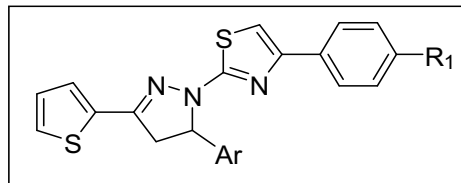


Fig.26. (4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives

A synthetic route for aryl furyl propenones via the reflux condensation of aryl furfurals with various acetophenones. Subsequent cyclo-condensation of these aryl furyl propenones with hydrazine hydrate and phenylhydrazine afforded 1H-pyrazoline and N-phenylpyrazolines derivatives Fig. 27. The authors reported significant antibacterial activity for these novel pyrazoline compounds [75].

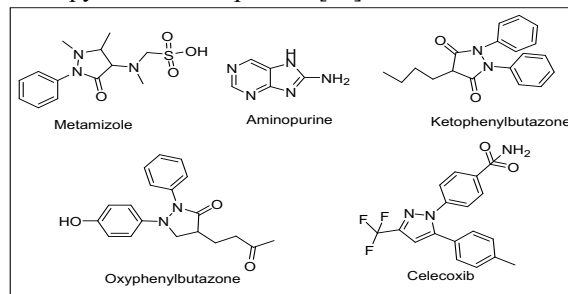


Fig. 27. 1H-pyrazoline and N-phenylpyrazoline derivatives.

By reacting phenacyl bromides with different 3-(2-thienyl)-5-aryl-1-thiocarbamoyl-2-pyrazolines the 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives were prepared. Antimicrobial activity against *S. typhimurium*, *E. coli*, *B. cereus*, *A. hydrophila*, *L. monocytogenes*, *S. aureus*, *C. albicans*, and *C. glabrata* [76] were tested for all the synthesized compounds.

Pyrazoline derivatives were synthesized by condensed 4-hydroxy-3-methylacetophenone with various aromatic aldehydes, then reacted with hydrazine hydrate to yielding the desired pyrazoline derivatives Fig. 28. All synthesized derivatives were subsequently evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv. Notably, the novel heterocyclic compounds demonstrated

favorable anti-tubercular activity against both drug-sensitive and drug-resistant strains of *Mycobacterium tuberculosis* [77].

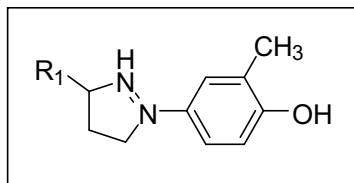


Fig. 28. 4-hydroxy phenyl pyrazoline derivatives

By reacting quinolinyl chalcones with phenyl hydrazine, a series of new compounds were synthesized Fig. 29 and those were evaluated for antimicrobial activity against *S. aureus*, *S. typhi*, *E. coli*, and *Shigella dysentery*. The study found that all derivatives displayed antimicrobial activity [78].

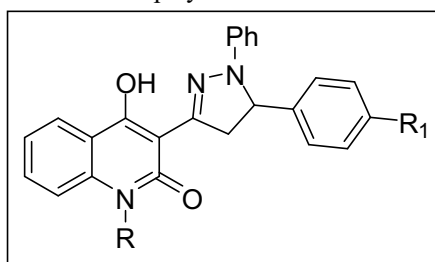


Fig. 29. Quinolinyl 2-pyrazoline derivatives

By reacting isoniazid with various diaryl chalcones in N, N-dimethylformamide (DMF), 1,3,5-trisubstituted-2-pyrazoline derivatives were synthesized Fig. 30. All the synthesized derivatives were then screened for their *in vitro* antimicrobial activity against *E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus*, and *A. niger*. The study found that these compounds exhibited significant antimicrobial activity [79].

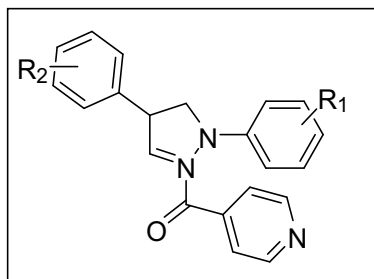


Fig.30. 1, 3, 5-trisubstituted-2-pyrazoline derivatives
Novel pyrazoline derivatives were synthesized by refluxing 2-acetyl thiophene chalcones with phenylhydrazine hydrochloride in an alkaline alcohol solution Fig. 31. The researchers found that some of these derivatives possessed antimicrobial properties [80].

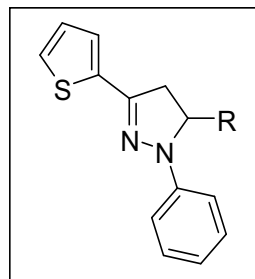


Fig. 31. Thiophene pyrazoline derivatives

By microwave-assisted method, a series of 2-[1-(5,8-Dihydroquinoxalino[2,3-b] indoloacetyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5-yl] phenyl derivatives Fig. 32 were synthesized. Some compounds were showed decent antibacterial activity against *S. aureus*, *P. aeruginosa* and *E. coli* [81].

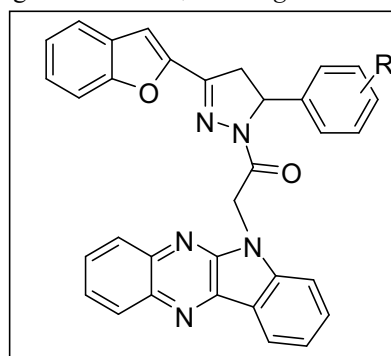


Fig. 32. 2-[1-(5, 8-Dihydroquinoxalino [2, 3-b] indoloacetyl)-3-(1-benzofuran-2-yl)-4,5 dihydro-1H-pyrazol-5-yl] phenyl derivatives

By microwave techniques, substituted [3-(4-phenyl)-5-phenyl-4, 5-dihydropyrazol-1-yl] (pyridine-4-yl) methadone and 3-substituted phenyl-5-substituted phenyl-4,5-dihydro-pyrazole-1-carbothioamides were synthesized Fig. 33 were evaluated for antibacterial activity against *B. subtilis*, *E. coli*, *P. aeruginosa* and *S. aureus* and antifungal activity beside *C. albicans*, *A. niger*. The derivatives showed adequate antibacterial and respectable antifungal actions [82].

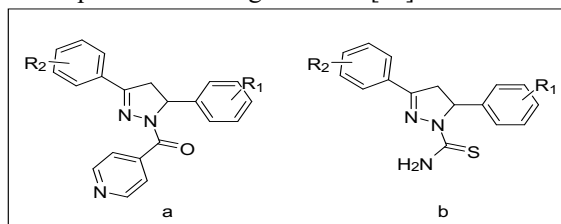


Fig. 33. Substituted [3-(4-phenyl)-5-phenyl-4,5-dihydropyrazol-1-yl](pyridine-4 yl)methanones
In order to screen for antibacterial activity against *S. aureus*, *S. typhi*, *B. subtilis*, *E. aerogenes*, *P. aeruginosa*, and *Proteus vulgaris*, a novel 1, 3, 5-triphenyl-2-pyrazoline derivatives Fig. 34 [83].

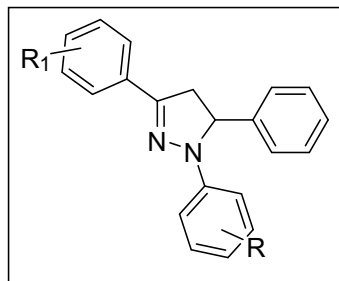


Fig. 34. Novel 1, 3, 5-triphenyl-2-pyrazoline derivatives

New pyrazoline derivatives synthesized by different acetophenones react with different benzaldehydes and condensed with hydrazine hydrate, Figure 35. were tested for *in vitro* antibacterial and anti-inflammatory activities. All synthesized derivatives were confirmed activity against *S. aureus*, *B. subtilis*, *E. coli*, *P. aureginosa*. Some of the new derivatives exhibited promising anti-inflammatory activities [84].

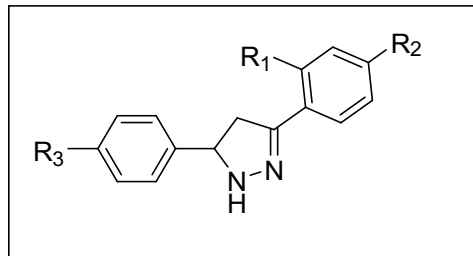


Fig. 35. 3, 5 diphenyl pyrazoline

2-naphthyl pyrazoline derivatives Fig. 36 were synthesized by reacting 2-naphthyl chalcones with phenylhydrazine hydrochloride and sodium. 2-naphthyl pyrazoline derivatives subjected for antimicrobial activity [85].

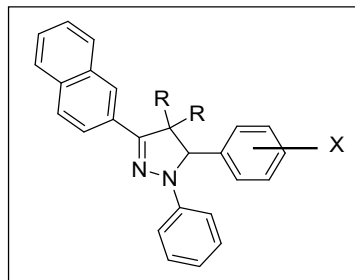


Fig. 36. 2-naphthyl pyrazoline derivatives
4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(substitutedphenyl)-1-phenyl-4,5-dihydro-pyrazol-3-yl] phenyl} azetidin-2-one Fig. 37 synthesized All the synthesized derivatives were screened for antimicrobial activity through broth dilution method. The compound containing chloro substitution in the phenyl ring has shown respectable antibacterial activity [86].

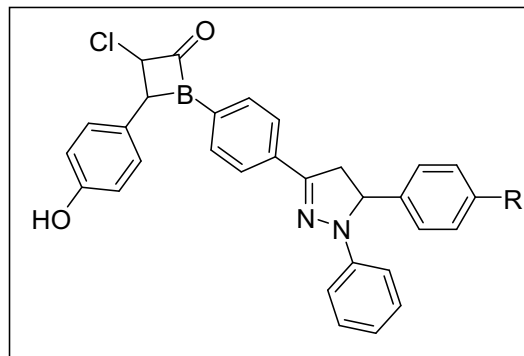


Fig. 37. 4-(4-hydroxyphenyl)-3-chloro-1-{4-[5-(substituted phenyl)-1-phenyl-4,5-dihydro pyrazol-3-yl] phenyl} azetidin-2-one

A number of N-propionyl 2-pyrazolines by reacting propionic acid with hydrazine hydrate Fig. 38. Gram-positive bacterial strains (*B. Subtilis*, *S. Aureus*) and gram-negative bacterial strains (*E. Coli*, *P. Peli*) were used to test the antibacterial activity of each novel chemical. Significant activity against bacteria is shown by all novel drugs [87].

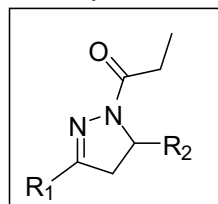


Fig.38. N-propionyl 2-pyrazolines

Synthesized compounds by combining pyrazoline, 1,2,3-triazole, and benzene sulfonamide molecules were test ed for their anti-bacterial activity [88]. Ferrocenyl ketones were converted into novel pyrazoline derivatives through a reaction with hydrazine in an acidic environment. The researchers then tested the synthesized compounds' antimicrobial activities against twelve microbial strains (both bacteria and fungi), comparing their effectiveness to a standard agent [89].

Chalcones were prepared by reacting acetophenone with various benzaldehydes. These chalcones were subsequently converted into novel pyrazoline derivatives using hydrazine hydrate in an alkaline ethanol solution Fig. 39 All synthesized compounds were then tested for antibacterial activity against both Gram-positive (*S. Aureus*, *B. Subtilis*) and Gram-negative (*E. coli*, *K. Pneuminoae*) bacteria at a suitable concentration, compared against the standard drug ciprofloxacin. Encouragingly, all the new pyrazolines demonstrated moderate to potent antibacterial activity[90].

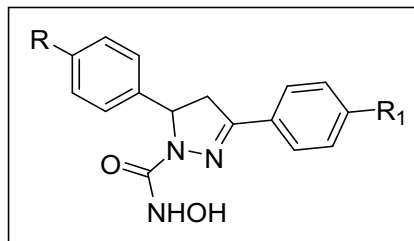


Fig.39. New pyrazoline derivatives

Bis(chalcones) were synthesized by condensation of *p*-hydroxyacetophenone with 2-furfuraldehyde. They then synthesized a series of bispyrazolines, by cyclizing these bis(chalcones) with phenylhydrazine under acidic reflux conditions (Fig. 40). Finally, the new compounds were screened for antimicrobial activity against seven bacterial and five fungal strains using the serial tube dilution method, with efficacy compared to the standard drugs amoxicillin and fluconazole [91].

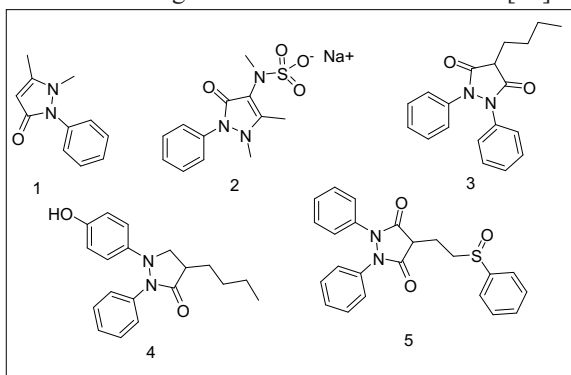


Fig.39. Bispyrazolines derivatives

A new pyrazole derivative was synthesized by first preparing chalcones from 2-acetyl-5-bromothiophene and aromatic aldehydes, followed by condensation with phenylhydrazine hydrochloride catalyzed by pyridine (Fig. 41). The synthesized compounds were then comprehensively evaluated for antibacterial activity against four bacterial strains (including Gram-positive and Gram-negative types) and antifungal activity against two fungal strains (*A. niger* and *P. crysogenium*) [92].

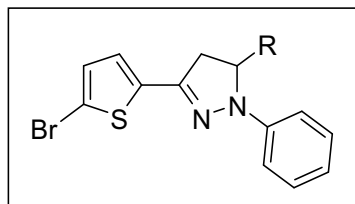


Fig. 41. 3-(5-bromo thiophene-2-yl)-1-phenyl-1-pyrazole derivatives

In 2017, Sadashiva and colleagues published research detailing the design and synthesis of a series of molecules containing a pyrazoline moiety linked to a 2,4-disubstituted 1,3-thiazole structure (Fig. 42). The researchers then tested these compounds in vitro

antimicrobial activity against various pathogenic microbial strains [93,94].

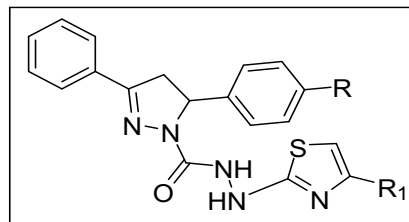


Fig. 42. 2, 4 disubstituted 1,3-thiazoles linked pyrazolines

Novel series of four 1-thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives (Fig. 43). They were tested for antibacterial activity using the well diffusion method against four strains: the Gram-positive *Staphylococcus aureus* MRSA and *Pseudomonas* spp., and the Gram-negative *Escherichia coli* and *Bacillus cereus*. Two synthesized compounds—1-thiocarbamoyl-3,5-diphenyl-2-pyrazoline and 1-thiocarbamoyl-3-(4'-chlorophenyl)-5-(4-chlorophenyl)-2-pyrazoline demonstrated potent activity against both of the Gram-positive strain [95].

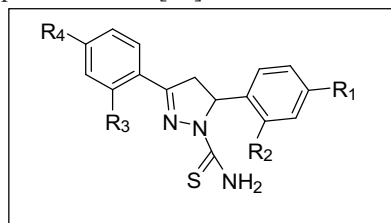


Fig.42. 1-thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives

A novel series of 1,3,5-trisubstituted pyrazoline derivatives were synthesized (Fig. 44), and were screened for antibacterial activity against four bacterial strains (*S. aureus*, *B. Subtilis*, *E. coli*, and *P. aeruginosa*) compared to the standard drug ciprofloxacin. They also demonstrated antifungal activity against *A. niger* [96].

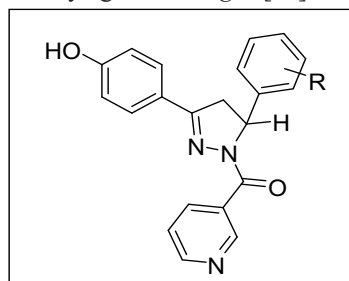


Fig.44. Novel series of 1, 3, 5-trisubstituted pyrazolines

Several novel derivatives featuring (5-(2-chloroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl) methanone as a core structure and screened these derivatives for antimicrobial activity against four bacterial strains (*S.*

aureus, *S. pyogenes*, *E. coli*, *P. aeruginosa*) and three fungal strains (*C. albicans*, *A. niger*, *A. clavatus*) [97]. The synthesis of 2-pyrazolines was reported from chalcones using both conventional heating and microwave-assisted techniques. These compounds were subsequently evaluated for antibacterial potency against two Gram-positive strains (*S. Aureus*, *S. Pyrogens*) and two Gram-negative strains (*P. Aeruginosa*, *E. coli*) at 500 and results compared to ampicillin. Additionally, antifungal potency was tested against *A. niger*, *C. Albicans*, and *A. Clavatus* using griseofulvin and nystatin as standards [98]. A series of novel morpholino quinoline conjugates incorporating a pyrazoline moiety were synthesized achieving this using a microwave irradiation technique Fig. 45. The resulting new compounds were subsequently evaluated for in vitro antibacterial and antifungal activity against various pathogenic strains, with their efficacy compared to the standard drugs ampicillin, chloramphenicol, ciprofloxacin, and griseofulvin [99].

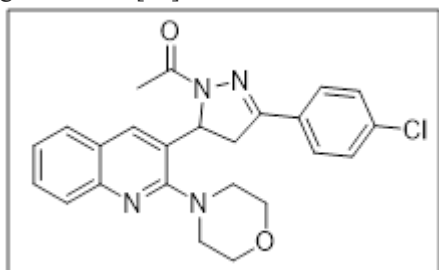


Fig.45. Morpholino quinoline conjugates incorporating a pyrazoline

The synthesis of a novel series of steroidal pyrazoline derivatives was reported Fig. 46. These compounds were subsequently evaluated for antibacterial activity against *Corynebacterium xerosis*, *S. epidermidis*, and *E. coli* (using the disc diffusion method and gentamicin as a standard), and for antifungal activity against *M. azygospous*, *A. niger*, and *C. purpurea* [100].

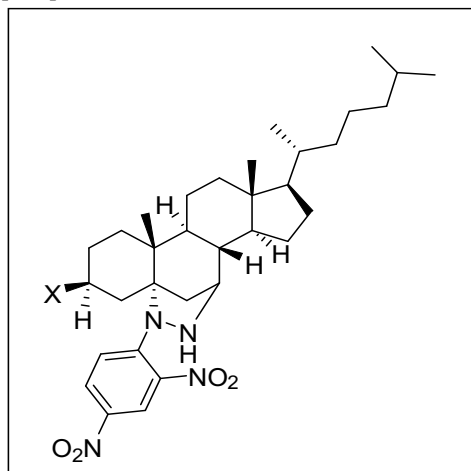


Fig. 46. New steroidal pyrazoline derivatives 1-formyl-3-phenyl-5-(4-isopropylphenyl)-2-pyrazoline was synthesized Fig. 47, obtaining the pure product as a crystal. The researchers evaluated this compound for antimicrobial activity, which was found to be favorable [101,102].

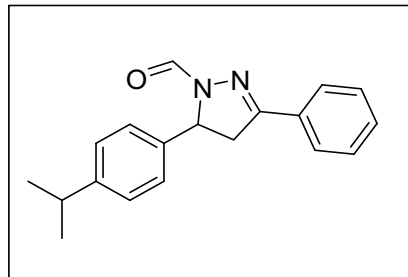


Fig. 47. 1-formyl-3-phenyl-5-(4-isopropylphenyl)-2-pyrazoline

Biologically active pyrazoline derivatives were synthesized via a Claisen–Schmidt condensation reaction between imidazole-2-carboxaldehyde and 1-acetyl-2-hydroxynaphthalene. The synthesized derivatives were subsequently screened for antibacterial activity against five strains (*E. coli*, *S. aureus*, *K. pneumoniae*, *Proteus mirabilis*, and *S. typhi*) compared to streptomycin, and for in vitro antimycobacterial activity against *Mycobacterium tuberculosis* [103].

It was reported that two series of pyrazoline derivatives starting from p-acetamidophenol (paracetamol). The synthetic route involved two steps: first, forming chalcones by reacting 3-acetyl-4-hydroxyphenyl acetamide with various aromatic aldehydes; second, condensing these chalcones with phenylhydrazine and isoniazid to yield phenylpyrazolines and isoniazid-pyrazolines Fig.48, respectively. When screened for antibacterial potency against *E. coli*, *S. aureus*, and *P. aeruginosa* (compared to the standard antibiotic ciprofloxacin), some of the new derivatives, particularly, showed powerful antibacterial activity against *S. aureus* and *P. aeruginosa* at a low concentration of 3.12 mg/mg [104].

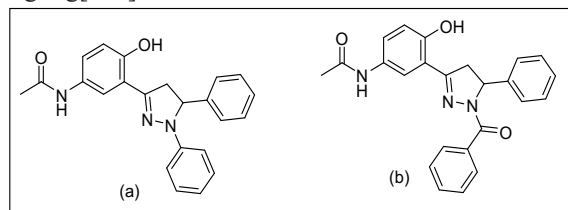


Fig. 48. (a) phenyl-pyrazolines and (b) isoniazid-pyrazolines 3-(Aryl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydro pyrazolines and their corresponding 4,5-dihydroacetyl pyrazoline derivatives were synthesized Fig. 49. The final

synthesized compounds were evaluated for their antimicrobial activity [105,106,107].

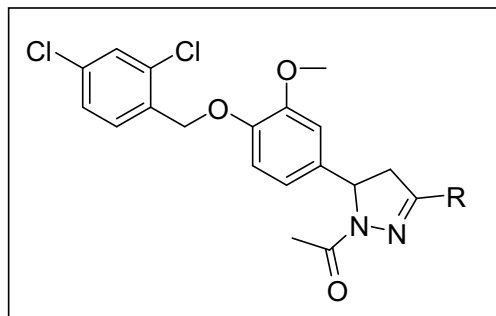


Fig.49. 3-(Aryl)-5-[4-(2,4-Dichlorophenylmethoxy)-3-methoxyphenyl]-4,5-dihydro pyrazoline

A series of 1-acetyl/acetophenyl-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazoline derivatives were synthesized and evaluated for antimicrobial potency against pathogenic microbes, (*B. subtilis*, *E. coli*, *K. pneumonia*, *S. aureus*) and four fungal strains (*A. niger*, *A. flavus*, *T. viride*, *C. albicans*). All the synthesized pyrazoline derivatives Fig. 50 demonstrated variable growth inhibitory effects against these pathogens [108].

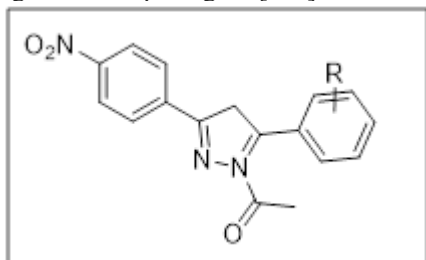


Fig. 50. 1-acetyl/acetophenyl-3-(4-nitrophenyl)-5-(substituted phenyl) pyrazoline derivative

Thiazolyl-pyrazoline derivatives Fig. 51 were synthesized and evaluated their antifungal activity.. Their efficacy was compared to the standard drug ketoconazole at a Minimum Inhibitory Concentration MIC of 250 µg/ml [109,110,111].

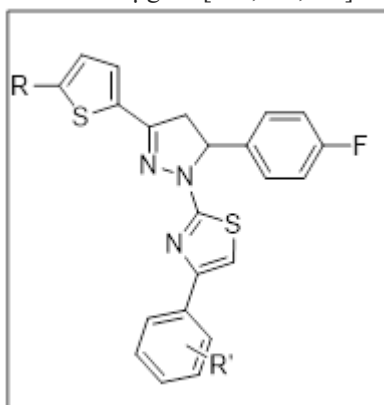


Fig. 51. Thiazolyl-pyrazoline derivatives

A novel pyrazolone derivative (3-phenyl-5-(4-dimethylaminophenyl)-1-phenyl-pyrazolone) Fig. 52

was synthesized and screened for antibacterial activity against three strains and *S. faecalis*, *S. aureus*, and *E. coli*. The evaluation determined that the new pyrazolone derivatives possessed sufficient antibacterial efficacy against *S. aureus* [112].

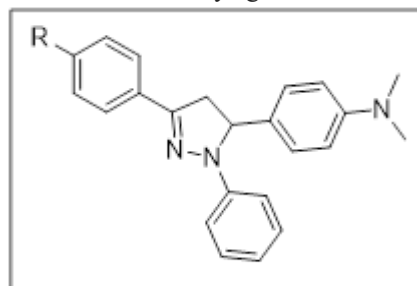


Fig. 52. 3-phenyl-5-(4-dimethylaminophenyl)-1-phenyl-pyrazolone

A series of pyrazoline were synthesized and these new compounds Fig. 53 were then evaluated for antimicrobial activity against four fungal strains (*C. Albicans*, *A. Flavus*, *A. Fumigatus*, *A. versicola*) at 12.5 µg/ml compared to fluconazole. The study concluded that all compounds possess moderate to potent antifungal properties [113,114].

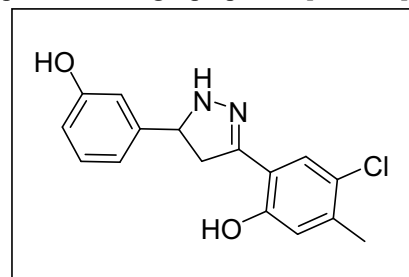


Fig. 53. Disubstituted pyrazoline derivatives

A novel pyrazoline derivatives linked to a substituted pyrazole framework through a multi-step synthesis was synthesized and were evaluated for their antibacterial, analgesic [115] and anti-inflammatory activities. Compounds with a halogen atom at the phenyl ring (on the 3rd position of the pyrazoline ring) showed potent antibacterial activity. Compounds containing the N-propionyl pyrazolyl-pyrazoline group were found to possess beneficial dual anti-inflammatory and antibacterial properties [116].

1,3,5-substituted pyrazoline derivatives Fig. 54. were screened and showed significant antibacterial activity when compared to the standard drug ampicillin, moderate to significant antifungal activity relative to griseofulvin, and good antitubercular activity when evaluated against the standard isoniazid [117].

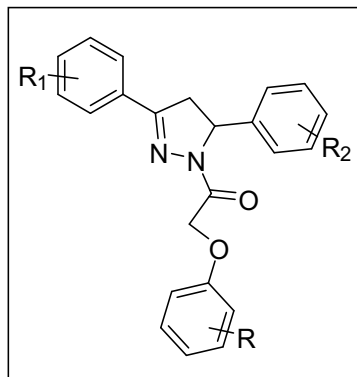


Fig. 54: 1, 3, 5 Substituted pyrazoline derivatives
Quinazolinyl-2-pyrazoline derivatives Fig. 55, were synthesized and assessed against two Gram-positive and two Gram-negative bacterial strains (*S. Aureus*, *B. Subtilis*, *E. coli*, *P. aeruginosa*) in comparison to ampicillin, amoxycillin, and penicillin. Additionally, the antifungal potency against *C. Albicans* and *C. Krusei* was measured relative to the standard drug fluconazole [118].

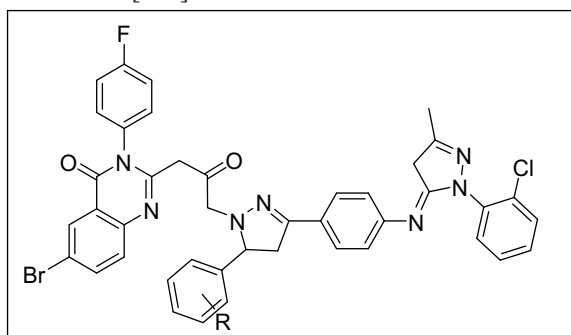


Fig. 55: Quinazolinyl-2-pyrazoline
Chalcones were reacted with hydrazine hydrate, isoniazid, or toluenesulfonyl hydrazide to produce novel 2-pyrazoline derivatives Fig. 56. And subsequently evaluated for antimicrobial activity against several microbes and were found to possess a high degree of activity [119,120].

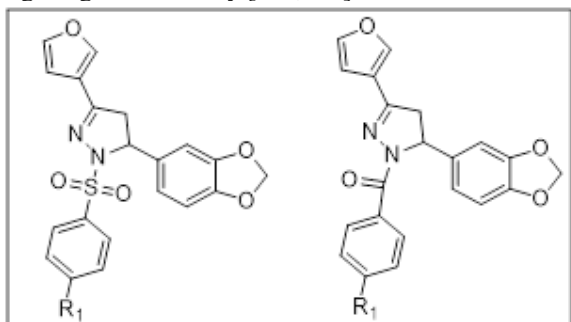


Fig. 56: Novel 2-pyrazolines
New pyrazoline derivatives (Tricyclic pyrazoline derivatives) Fig. 57 were synthesized and screened for antimicrobial activity against specific pathogens, including *Y. enterocolitica*, *A. hydrophila*, *S. aureus*, and *L. monocytogene*. The synthesized compounds

The study demonstrated comparable or superior activity when compared to the standard drugs tetracycline (30µg) and gentamicin (10µg)[121].

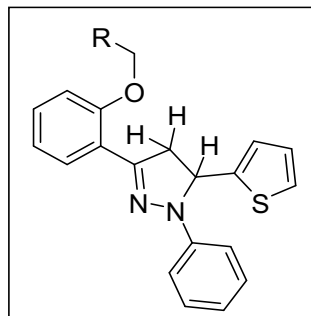


Fig. 57. Tricyclic pyrazoline derivative
A new derivative of 2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-phenylthiazoles Fig. 58 was synthesized and subjected to antibacterial activity screening [122].

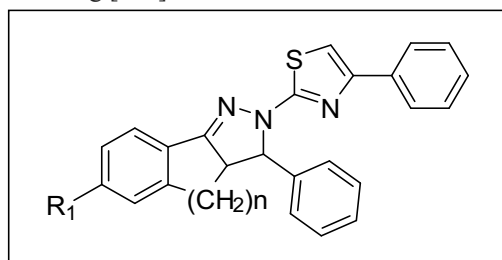


Fig. 58. Substituted 2-(3, 5-diphenyl-4, 5-dihydro-1H-pyrazol-1-yl)-4-phenylthiazoles
A series of novel 2-pyrazoline derivatives Fig. containing benzene sulfonamide moieties and their antimicrobial activity was assessed against the bacteria *S. aureus*, *P. aeruginosa*, *E. coli* and the fungus *C. albicans* using diffusion method [123].

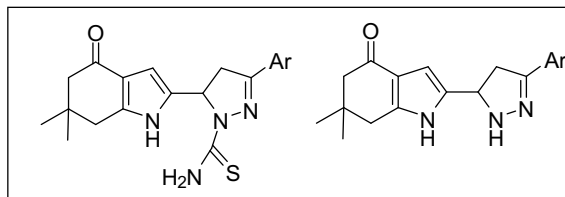


Fig. 59. Pyrazoline derivative carrying benzene sulfonamide

Twelve novel 2-pyrazoline derivatives were synthesized via a multi-step process and evaluated for antimicrobial activity against *A. niger* and *S. aureus*, showed good activity at concentrations ranging from 20-70 µg/ml [124].

A series of novel N-substituted pyrazoline derivatives called 5-(furan-2-yl)-3-[2-(alkoxy) phenyl]-4,5-dihydro-1H-pyrazole-1-carbothioamide Fig. 60 were synthesized and were tested for *in vitro* antibacterial activity against *A. hydrophila*, *Y. enterocolitica*, *L. monocytogenes*, and *S. aureus* 5-(furan-2-yl)-2-(benzyloxy) phenyl]-4,5-dihydro-1H-pyrazole-1-carbothioamide and 5-(furan-2-yl)-1-[2-(naphthalen-

2-yl -methoxy) phenyl]-4,5-dihydro-1H-pyrazole-1-carbothioamide displayed the most potent antibacterial activity compared to the standard drugs gentamycin and tetracycline [125].

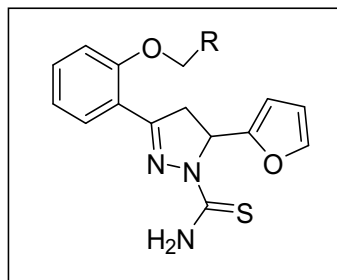


Fig. 60. N-substituted cyclized pyrazoline

5. CONCLUSION

The pyrazoline core, a versatile N-heterocyclic scaffold, remains highly significant in pharmaceutical chemistry due to its diverse biological activities, particularly its potent antimicrobial properties. This review highlighted the effectiveness of various synthetic strategies including conventional heating, ultrasonic, and microwave-assisted cyclization of chalcones with hydrazine in generating a broad range of pyrazoline derivatives. The previous observations and literature confirm pyrazoline derivatives potential against both Gram-positive and Gram-negative bacteria, and even drug-resistant strains. The ease of structural modification allows for tuning the pharmacological profile through different substituent groups. Therefore, the pyrazoline moiety is an excellent template for ongoing research aimed at developing novel and effective antibacterial agents to combat emerging resistance.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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