International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 22s, 2025
https://www.theaspd.com/ijes.php

Pyrazoline-Based Molecules In Antimicrobial Research: A Systematic Review

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Abstract
Pyrazoline derivatives have become important compounds in medicinal chemistry because of their extensive array of biological activities, especially their antibacterial properties. The escalating problem of antimicrobial resistance (AMR) and the rising incidence of fungal infections underscore the urgent demand for new therapeutic agents. Pyrazoline derivatives, characterized by their unique five-membered heterocyclic framework, exhibit strong antibacterial and antifungal effects through mechanisms that involve interactions with microbial enzymes, DNA, and cellular membranes. Developments in synthetic methods, including environmentally friendly techniques and computational drug design, have facilitated the synthesis of derivatives with enhanced efficacy and reduced resistance. This review encapsulates recent progress in the synthesis, structural diversity, and biological efficacy of pyrazoline derivatives, emphasizing their significance in addressing global infectious disease challenges. It also reviews commercially available antimicrobial agents and the specific modifications that enhance pharmacokinetic and pharmacodynamic properties. The potential future applications of pyrazoline derivatives in combating AMR and invasive fungal infections are thoroughly examined, offering a comprehensive reference for advancing research and therapeutic innovations in this field.

INTRODUCTION

Pyrazoline derivatives have surfaced as a significant group of heterocyclic compounds in medicinal chemistry because of their extensive range of biological properties [1]. Among these effects, their antibacterial and antifungal properties have garnered considerable interest, particularly considering the pressing demand for novel therapeutic agents to address the escalating challenge of microbial resistance and fungal infections. The identification and creation of antimicrobial medications has historically depended on the structural and functional diversity of organic compounds, and pyrazoline derivatives, with their unique chemical structure, have proven to be a promising area for such research [2, 38-43].

The pyrazoline core consists of a five-membered heterocyclic ring containing two adjacent nitrogen atoms. This structural feature is not only versatile in synthetic applications but also significant in biological contexts, facilitating the development of compounds with enhanced pharmacological properties [3]. Pyrazoline derivatives are typically produced by cyclizing α,β-unsaturated carbonyl substances with hydrazines, enabling structural modifications. These modifications permit researchers to optimize the physicochemical and biological properties of the resulting molecules [4].

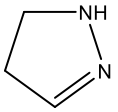


Figure-1: Structure of Pyrazoline

The concerning rise of antimicrobial resistance (AMR) has been recognized as one of the most urgent global health challenges of the twenty-first century. Pathogens such as multidrug-resistant *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* are becoming increasingly challenging to treat with existing therapies, leading to higher death rates, prolonged hospital stays, and rising healthcare costs [5]. Simultaneously, the incidence of invasive fungal infections caused by species like *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* has increased, which is often worsened by patients with weakened immune systems [6]. These developments emphasize the vital necessity for new antibacterial and antifungal therapies with innovative mechanisms of action. Pyrazoline derivatives have shown significant effectiveness against a variety of microbial and fungal infections, rendering them attractive options for drug development. The antimicrobial efficacy of these compounds is often associated with their ability to bind with bacterial and fungal cellular targets, including enzymes, DNA, and

components of the cell membrane, thereby disrupting essential physiological functions [7]. Additionally, their structural variability facilitates the exploration of different mechanisms of action, which lowers the risk of resistance emergence.

In addition to their natural biological roles, pyrazoline derivatives possess beneficial pharmacokinetic and pharmacodynamic properties, which include significant bioavailability, metabolic stability, and minimal toxicity [8]. These traits enhance their prospects as therapeutic agents. Moreover, progress in synthetic methods, including green chemistry and computational drug design, has facilitated the effective and sustainable development of pyrazoline-derived compounds featuring improved activity profiles.

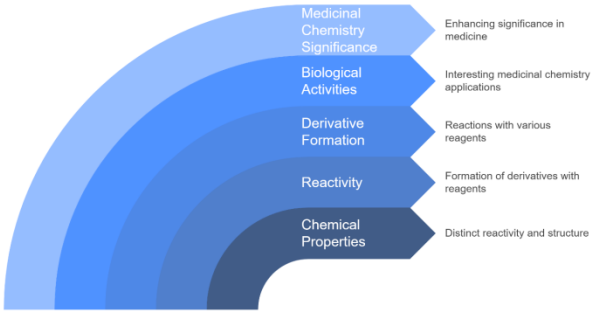
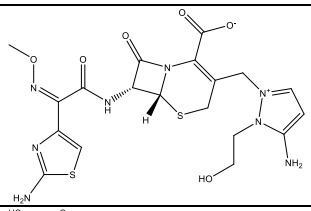
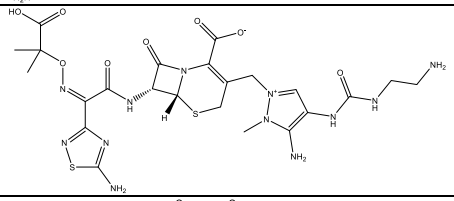
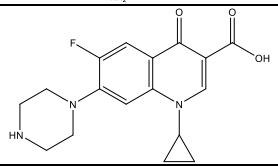
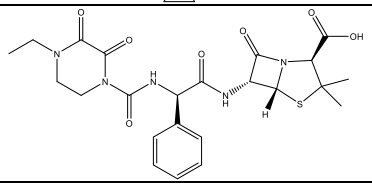
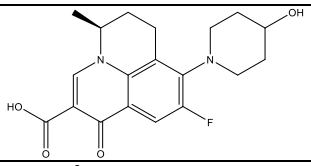
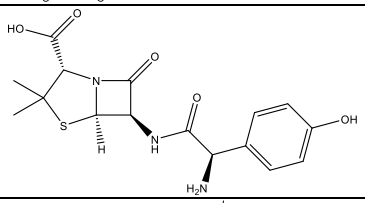
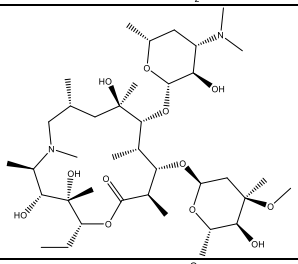
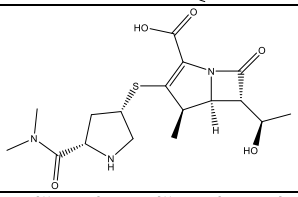
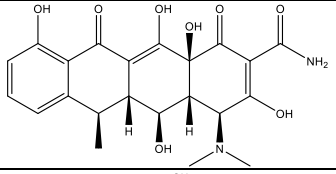
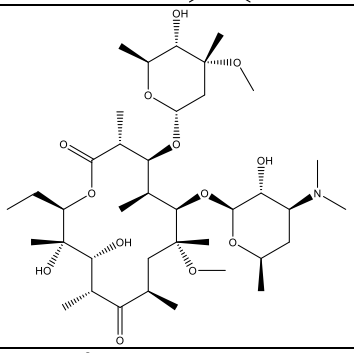
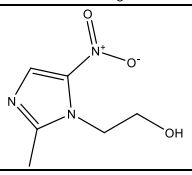
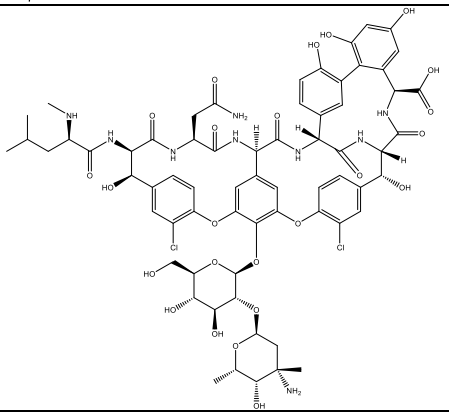


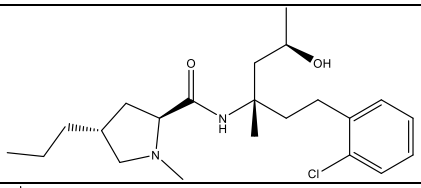
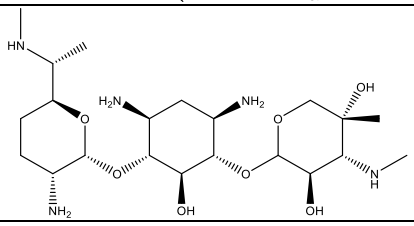
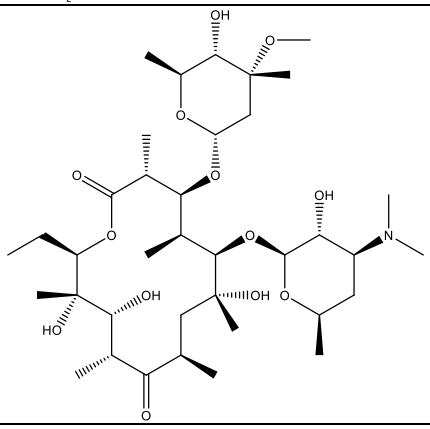
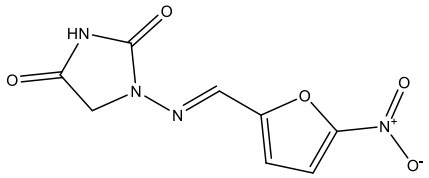
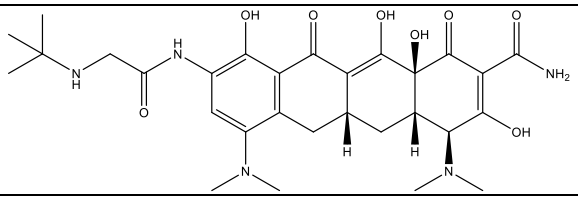
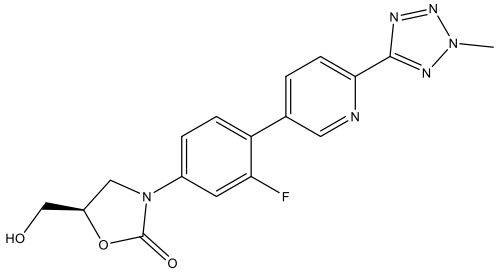
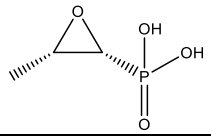
Figure-2: Varied significance of Pyrazoline and its derivatives [44-46]

This review will offer a thorough overview of existing studies concerning pyrazoline derivatives used as antibacterial and antifungal agents. It will examine the synthesis and structural differences of these compounds, their mechanisms of action, and the spectrum of their biological activities. Furthermore, the review will investigate recent progress, challenges, and future perspectives in this field, emphasizing the role of pyrazoline derivatives in alleviating the global impact of infectious diseases. By merging current knowledge and pointing out research deficiencies, this review seeks to encourage upcoming research and advancements in the creation of pyrazoline-based treatments.

Table-1: Some Marketed Drugs for Anti-Bacterial Activity

S. No.	Marketed Drug	Structure	Reference
1.	Cefoselis		[47]
2.	Ceftolozane		[48]
3.	Ciprofloxacin		[49]
4.	Piperacillin		[50]

5.	Levonadifloxacin		[51]
6.	Amoxicillin		[52]
7.	Azithromycin		[53]
8.	Meropenem		[54]
9.	Doxycycline		[55]
10.	Clarithromycin		[56]
11.	Metronidazole		[57]
12.	Vancomycin		[58]

13.	Clindamycin		[59]
14.	Gentamicin		[60]
15.	Erythromycin		[61]
16.	Nitrofurantoin		[62]
17.	Tigecycline		[63]
18.	Tedizolid		[64]
19.	Fosfomycin		[65]

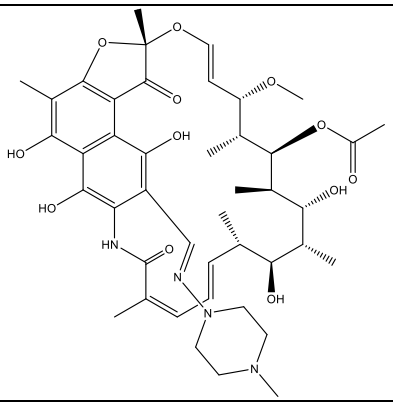
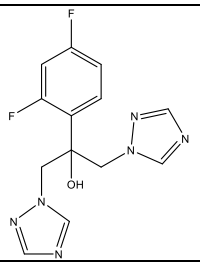
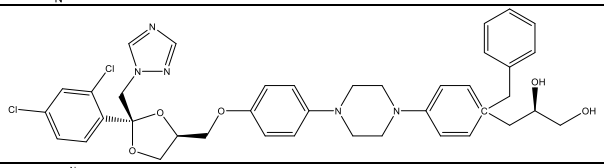
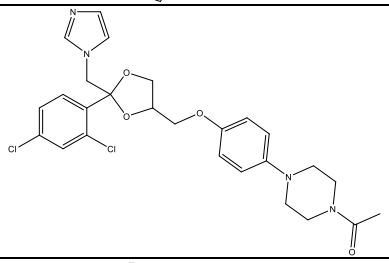
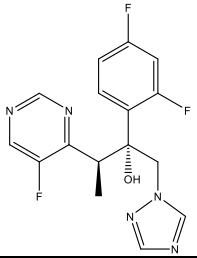
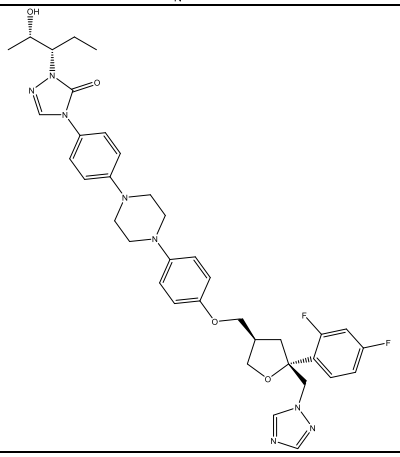
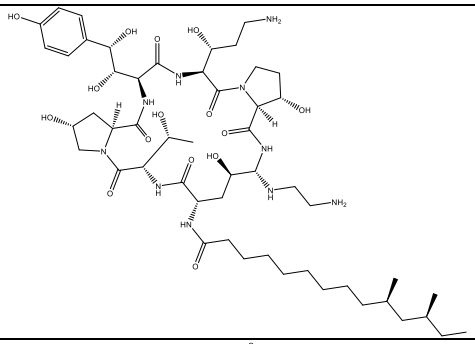
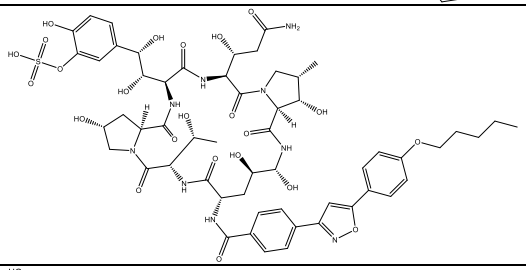
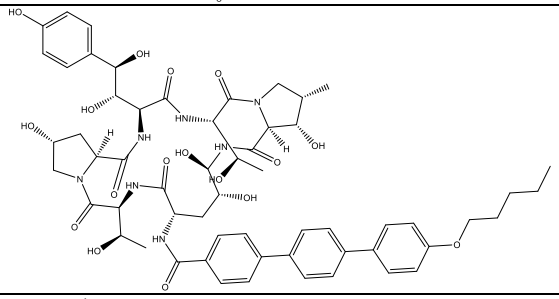
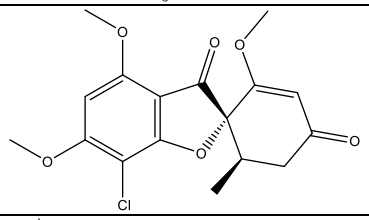
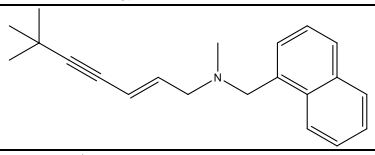
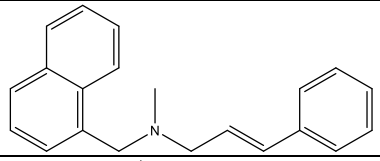
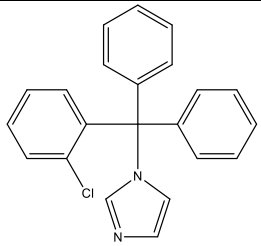
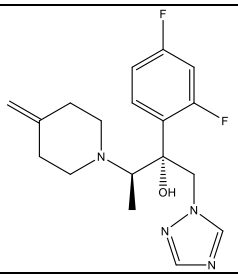
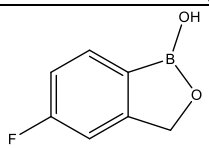
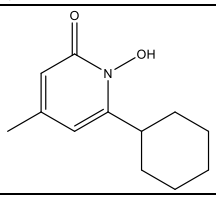
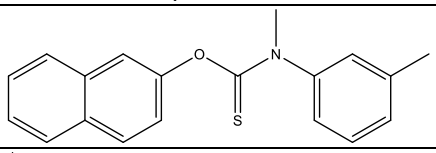
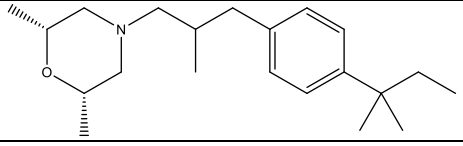
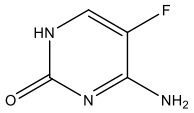
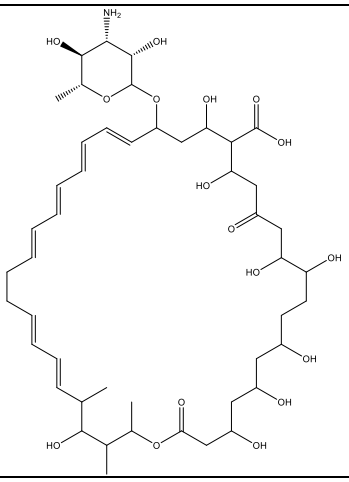
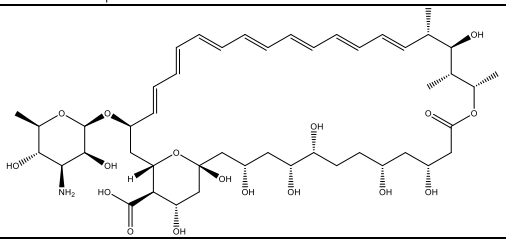
20.	Rifampicin		[66]

Table-2: Some Marketed Drugs for Anti-Fungal Activity

S. No.	Marketed Drug	Structure	Reference
1.	Fluconazole		[67]
2.	Itraconazole		[68]
3.	Ketoconazole		[69]
4.	Voriconazole		[70]
5.	Posaconazole		[71]

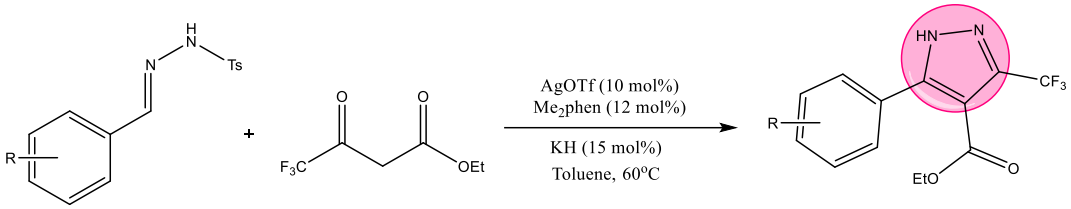
6.	Caspofungin		[72]
7.	Micafungin		[73]
8.	Anidulafungin		[74]
9.	Griseofulvin		[75]
10.	Terbinafine		[76]
11.	Naftifine		[77]
12.	Clotrimazole		[78]

13.	Efinaconazole		[79]
14.	Tavaborole		[80]
15.	Ciclopirox		[81]
16.	Tolnaftate		[82]
17.	Amorolfine		[83]
18.	Flucytosine		[84]
19.	Nystatin		[85]
20.	Amphotericin B		[86]

Routes of Synthesis Pyrazoline Derivatives

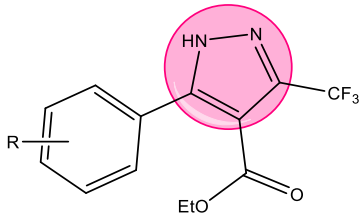
In 2020, Xu et al. [9] reported a silver-catalyzed protocol for synthesizing 5-aryl-3-trifluoromethylpyrazoles via the coupling of N′-benzylidene tolylsulfonohydrazides with ethyl 4,4,4-trifluoro-3-oxobutanoate. The reaction sequence proceeds through nucleophilic attack, intramolecular cyclization, dehydrobenzenesulfonyl elimination,

and a final [1,5]-hydrogen shift, affording the desired trifluoromethylpyrazoles in moderate to good yields.Optimization studies revealed that raising the temperature to 60°C improved yields, whereas higher temperatures led to decreased product formation. Among catalysts, Cu $(OTf)_2$ afforded a 60% yield, while $Fe(OTf)_3$ was ineffective. Toluene proved superior to THF and dioxane as the solvent. For bases, K_2CO_3 outperformed NaH, t-BuOK, and t-BuONa. Notably, the combination of neocuproine as a ligand with a silver catalyst provided the best result, delivering yields exceeding 99%, whereas 2,2′-bipyridine and 1,10-phenanthroline gave 57% and 92% yields, respectively.

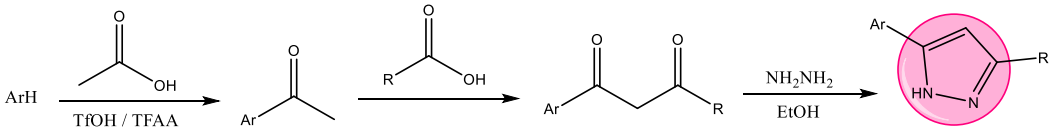


Scheme-1: Synthesis of 5–aryl–3–trifluoromethyl pyrazoles utilizing a silver catalyst

Table-3: Structural Modification to synthesized pyrazole derivative by Xu et al.

Structure	Modification (R)
	H
	4-Me
	4-tBu
	4-O-CH_2-Ph
	4-OMe
	4-N(Me)$_2$
	3-CF_3
	4-CN
	4-F
	2,4-diF
	(2-F, 5-Br)
	4-Cl
	4-Br
	2-Br

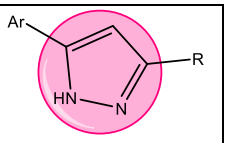
In 2020, Kim et al. [10] developed a rapid and efficient "one-pot" strategy for synthesizing pyrazoles from (hetero) arenes and carboxylic acids**.** The method involves the in situ formation of ketones and β-diketones, followed by heterocyclization with hydrazine. The underlying concept was that three simple steps could yield 3,5-disubstituted pyrazoles. Initially, a TfOH/TFAA-mediated "one-pot" synthesis of 1,3-diketones was accomplished from methylarylketones**,** utilizing arenes and carboxylic acids. The resulting dicarbonyl intermediates were subsequently converted into 3,5-disubstituted pyrazoles under Knorr reaction conditions**.**



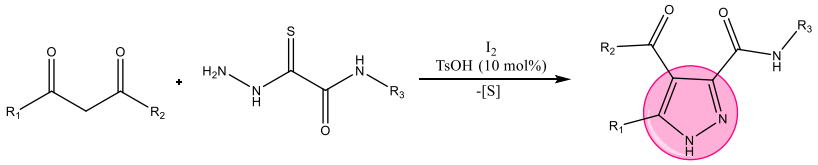
Scheme-2: The synthetic method for producing pyrazoles from arenes and carboxylic acids through a one-pot synthesis

Table-4: Structural Modification to synthesized pyrazole derivative by Kim et al.

Modifications		Structure
R	Ar	

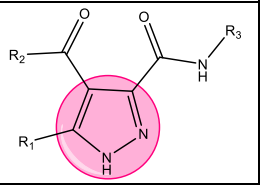
Me t-BuCH$_2$ 1-AdCH$_2$ 3-HO-1-AdCH$_2$	Ph 3,4-diMePh 2,4-diClPh 4-OMePh Thiophenyl 5-Br-Thiophenyl 5-(dibenzo[b,d]furan-2-yl)	

In 2020, Komendantova et al. [11] reported a novel approach for the synthesis of 3,4-dicarbonyl-substituted pyrazoles. The reaction employs 1,3-dicarbonyl compounds and oxamic acid thiohydrazides in the presence of catalytic TsOH, followed by sulfur elimination. The process proceeds via an iodine-accelerated imination/halogenation/cyclization/ring-contraction sequence. Using readily available substrates and mild conditions, this method provides a straightforward and highly efficient strategy for the synthesis of functionalized pyrazoles.

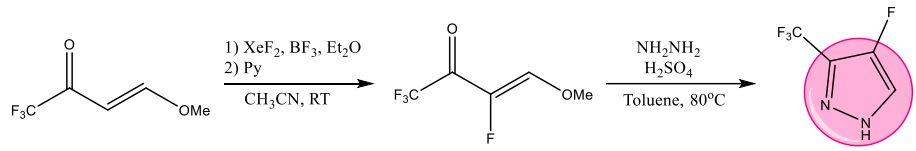


Scheme-3: Production of substituted pyrazoles from 1,3–diketones and hydrazine derivatives

Table-5: Structural Modification to synthesized pyrazole derivative by Komendantova et al.

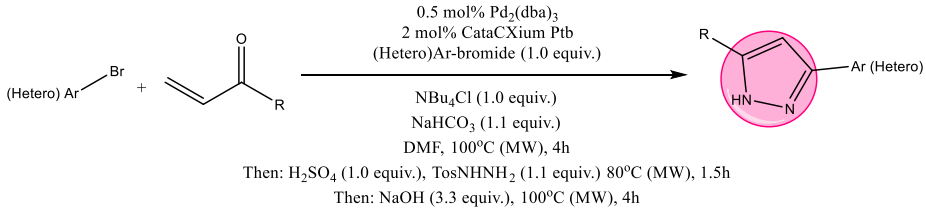
Modifications			**Structure**
R$_1$	**R$_2$**	**R$_3$**	
Alk Ar Bn	Alk OAlk	Alk Ar Het Bn	

In 2020, Gerus et al. [12] investigated the fluorination of enones using XeF_2 in the presence of $BF_3 \cdot Et_2O$. The inclusion of pyridine in the reaction mixture afforded fluoroenones in a 68% yield. Subsequent treatment of fluoroenones with hydrazine sulfate produced fluoropyrazoles in an excellent 87% yield.



Scheme-4: Synthesis of fluoropyrazole by Gerus etal., [12]

In 2020, Stephan et al. [13] developed a versatile strategy for synthesizing pyrazole derivatives. Initially, a Heck reaction between (hetero) aryl bromides and acrolein or vinyl ketones generated 3-(hetero)aryl propenals and propenones. The reaction was performed under Jeffery's and Fu's conditions with Beller's CataCXium Ptb ligand. The resulting 3-substituted α,β-unsaturated carbonyl compounds served as key intermediates for the preparation of 3,5-diarylpyrazoles and 3-(hetero)aryl pyrazoles via consecutive three- and pseudo-four-component reactions, providing low to good yields. This flexible approach is suitable for constructing diverse pyrazole libraries.

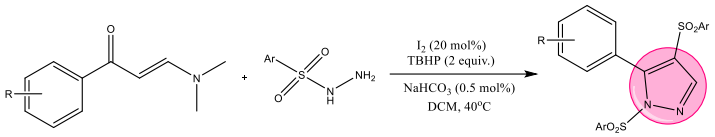


Scheme-5: Synthesis of pyrazole derivative by Stephan et al., [13]

Table-6: Structural Modification to synthesized pyrazole derivative by Stephan et al.

Modifications		Structure
R	Ar	
H	Ph	
Me	4-FPh	
Ph	4-CNPh	
4-OMePh	4-NMe_2Ph	
4-NMe_2Ph	4-CF_3Ph	
Penthyl	4-OMePh	
	3-F,4-OMePh	
	2-OMePh	
	2-thiophenyl	

In 2020, Tian et al. [14] reported a transition-metal-free synthesis of 4-sulfonyl pyrazoles through a tandem C(sp^2)-H sulfonylation/pyrazole annulation process. The reaction involves N,N-dimethyl enaminones and sulfonyl hydrazines, catalyzed by molecular iodine at room temperature in the presence of TBHP and $NaHCO_3$. This method provides an efficient and straightforward route to sulfonyl-substituted pyrazoles.

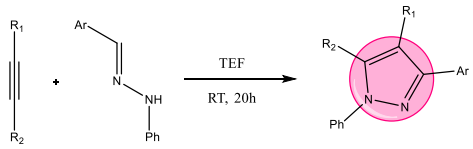


Scheme-6: Synthetic pathways for pyrazole derivatives utilizing I_2/TBHP, $NaHCO_3$ as a catalyst.

Table-7: Structural Modification to synthesized pyrazole derivative by Tian et al.

Modifications		Structure
R	Ar	
4-OMe	4-ClPh	
4-NMe_2	3,5-diClPh	
3-Cl	4-OMePh	
	4-FPh	
	4-ClPh	
	4-BrPh	
	2-ClPh	

In 2020, Bhaskaran et al. [15] developed a metal-free protocol for synthesizing pyrazoles and chromeno-pyrazoles from aldehydic hydrazones and acetylenic esters. The method accommodates both symmetrical and unsymmetrical hydrazones and alkynes, affording a wide range of products in moderate to very high yields.

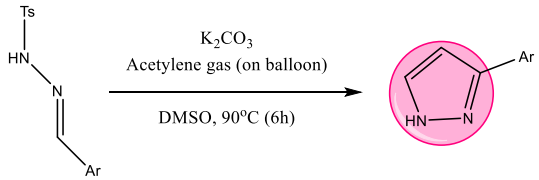


Scheme-7: Synthesis of pyrazole derivatives by Bhaskaran et al., [15]

Table-8: Structural Modification to synthesized pyrazole derivative by Bhaskaran et al.

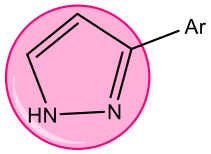
Modifications			Structure
R_1	R_2	Ar	
CO_2Et	H	Ph	
CO_2Me	CO_2Et	4-OMePh	
	CO_2Me	4-BrPh	
	Ph	4-FPh	
		2-BrPh	

In 2020, Li et al. [16] explored the 1,3-dipolar cycloaddition of N-tosylhydrazones with acetylene gas using a simple balloon setup. Screening of bases and solvents identified K_2CO_3 as the most effective base. The reaction provided pyrazoles in reasonable to good yields, with DMSO performing better than NMP for reactions involving ketone-derived N-tosylhydrazones. This straightforward method holds promise for commercial applications.

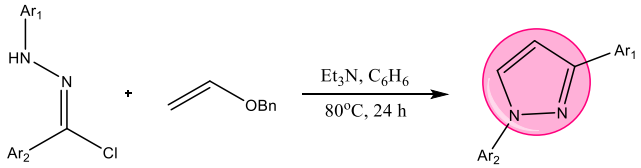


Scheme-8: Synthesis of pyrazole derivatives by Li et al., [16]

Table-9: Structural Modification to synthesized pyrazole derivative by Li et al.

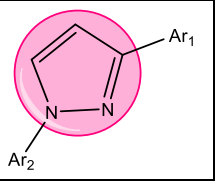
Modifications (Ar)	Structure
Ph 4-MePh 3-MePh 2-MePh 4-NMe_2Ph 2-OMePh 4-OMePh 4-CF_3Ph 4-BrPh 3-BrPh	

In 2020, Ledovskaya et al. [17] achieved a regioselective synthesis of 1,3-disubstituted pyrazoles via 1,3-dipolar cycloaddition of vinyl ethers with hydrazonoyl chlorides, promoted by triethylamine (TEA) as a mild base.

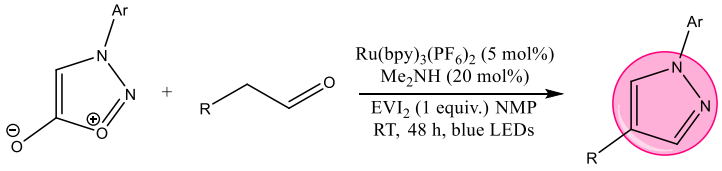


Scheme-9: Synthesis of pyrazole derivatives by Ledovskaya et al., [17]

Table-10: Structural Modification to synthesized pyrazole derivative by Ledovskaya et al.

Modifications		Structure
Ar_1	Ar_2	
Ph	Ph	
4-MePh	4-MePh	
4-OMePh	4-BrPh	
	4-FPh	

In 2020, Lakeland et al. [18] reported a visible-light photoredox-catalyzed approach for synthesizing 1,4-disubstituted pyrazoles using $Ru(bpy)_3(PF_6)_2$ as the catalyst. The method exhibited excellent yields and broad substrate scope.



International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 22s, 2025
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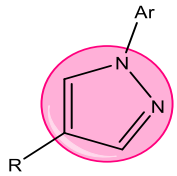
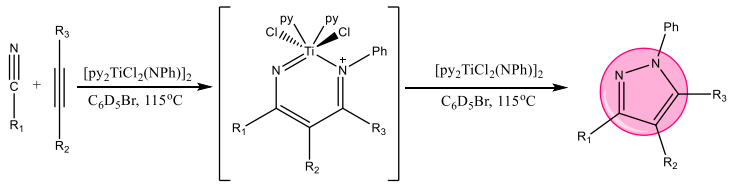
Scheme-10: Synthesis of pyrazole derivatives by Lakeland et al., [18]

Table-11: Structural Modification to synthesized pyrazole derivative by Lakeland et al.

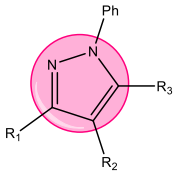
Modifications		**Structure**
R	**Ar**	
Buthyl	H	
iPr	4-OMePh	
Cyclohexyl	4-CNPh	
Me	4-FPh	
Ph	4-ClPh	
Benzyl	4-BrPh	
TBSO-Butyl	4-CF_3Ph	
$(CH_2)_2CO_2Me$	3-MePh	
$(CH_2)_2CO_2N(OMe)Me$		

In 2020, Pearce et al. [19] developed a multicomponent oxidative coupling strategy to access multi-substituted pyrazoles. The reaction involves the combination of alkynes, nitriles, and titanium imido complexes, proceeding through diazatitana-cyclohexadiene intermediates and a 2-electron oxidation pathway mediated by TEMPO.

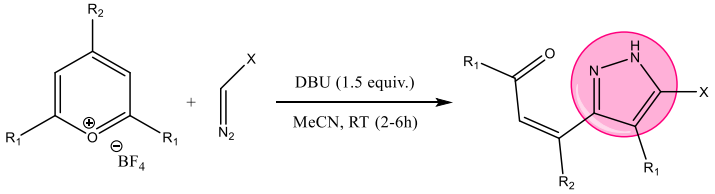


Scheme-11: Synthesis of pyrazole derivatives by Pearce et al., [19]

Table-12: Structural Modification to synthesized pyrazole derivative by Pearce et al.

Modifications			**Structure**
R_1	**R_2**	**R_3**	
Ph	Me	Me	
4-Me-Ph	Et	Et	
4-MeOPh	Ph	4-^{t}BuPh	
4-CF3-Ph	4-^{t}BuPh		
IPr			
Me			

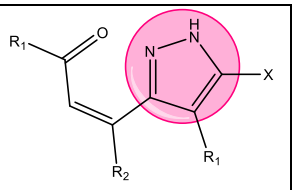
In 2021, Devi et al. [20] designed an elegant method for synthesizing functionalized pyrazole chalcones and indenyl-pyrazoles through a 1,3-dipolar cycloaddition of α-diazo phosphonates, sulfones, and trifluoromethanes with 2,4,6-trisubstituted pyrylium tetrafluoroborate salts. The reaction proceeds via nucleophilic addition to pyrylium salts, base-catalyzed ring opening, and intramolecular 1,5-cyclization, yielding 1,3-dipolar cycloaddition products. Subsequent hydride reduction and Nazarov-type cyclization, followed by acidic workup, afforded the target molecules in high yields. This strategy offers an efficient route to bioactive pyrazole derivatives.



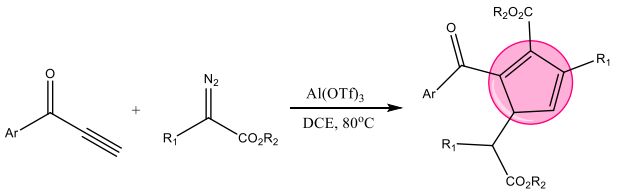
Scheme-12: Synthesis of pyrazole derivatives by Devi et al., [20]

Table-13: Structural Modification to synthesized pyrazole derivative by Devi et al.

Modifications			**Structure**
R_1	**R_2**	**X**	

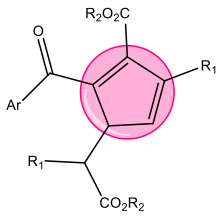
Ph 4-OMePh 4-MePh 4-ClPh	Ph 4-OMePh 4-MePh 3-OMePh 3-ClPh	SO_2Ph Tsyl CF_3	

In 2021, Zhao et al. [21] investigated cascade reactions of alkyl α-diazoesters with ynones catalyzed by Al(OTf)₃, enabling the efficient synthesis of a series of 4-substituted pyrazoles. The transformation proceeds via a [3 + 2] cycloaddition, followed by 1,5-ester shift, 1,3-hydrogen shift, and N–H insertion steps. Mechanistic insights were obtained through deuterium labeling, kinetic studies, and control experiments, providing valuable data for understanding the underlying reaction pathways.

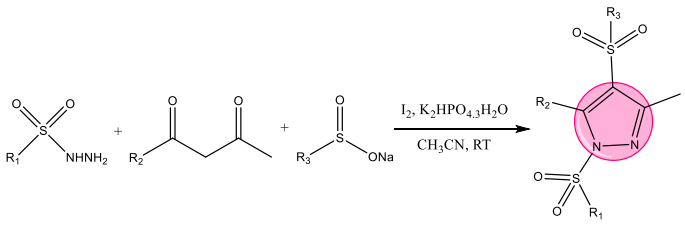


Scheme-13: Synthesis of pyrazole derivatives by Zhao et al., [21]

Table-14: Structural Modification to synthesized pyrazole derivative by Zhao et al.

Modifications			Structure
R_1	R_2	Ar	
Me Ph	Me Et	Ph 4-FPh 4-MePh 4-ClPh 4-BrPh 4-CF_3Ph CO_2MePh	

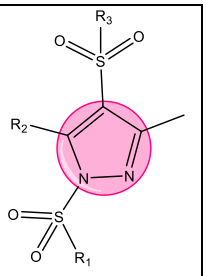
In 2021, Chen et al. [22] developed a transition-metal-free protocol under mild conditions for synthesizing disulfonated pyrazoles from sulfonyl hydrazides, 1,3-diketones, and sodium sulfinates using molecular iodine as the catalyst. The reaction proceeds via the in situ generation of sulfonyl iodide from sodium sulfinate and iodine, followed by imine formation (from sulfonyl hydrazides and 1,3-diketones), tautomerization to an enol form, and nucleophilic attack of the sulfonyl iodide, culminating in intramolecular condensation to afford the desired pyrazoles in a single step.



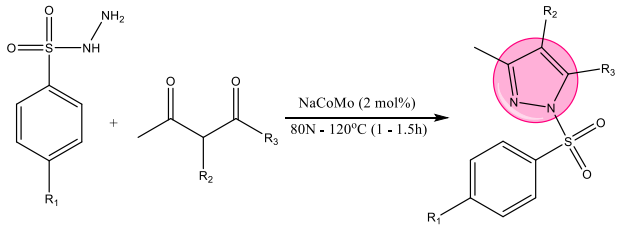
Scheme-14: Synthesis of pyrazole derivatives by Chen et al., [22]

Table-15: Structural Modification to synthesized pyrazole derivative by Chen et al.

Modifications			Structure
R_1	R_2	R_3	

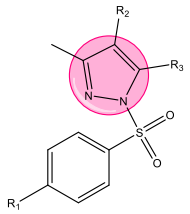
Ph 4-MePh 4-PhPh Naphthyl 4-^{t}BuPh 3-MePh 4-OMePh 4-FPh 4-BrPh 4-ClPh 4-IPh	Me ^{t}Bu n-C_5H_{11} Ph 4-MePh 4-OMePh Naphthyl 4-FPh 4-BrPh 4-ClPh 3-ClPh 3-Thiophenyl 2-Furanyl 2-Pyridinyl	Ts PhO_2S	

In 2022, Yang et al. [23] introduced a novel metal-oxo-cluster-based inorganic framework, described as a 3D platelike ternary-oxo-cluster (NaCoMo), which serves as a highly efficient catalyst for the condensation and cyclization of 1,3-diketones with sulfanylhydrazides to yield pyrazoles. This method achieved excellent yields (up to 99%) under mild conditions. The development of NaCoMo opens avenues for utilizing non-classical polyoxometalates in pyrazole synthesis.

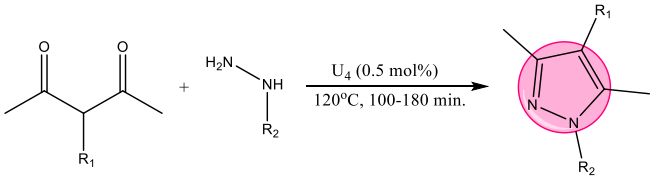


Scheme-15: Synthesis of pyrazole derivatives by Yan et al., [23]

Table-16: Structural Modification to synthesized pyrazole derivative by Yan et al.

Modifications			**Structure**
R_1	**R_2**	**R_3**	
H Me OMe Cl Br NO_2	H Cl Me	Me Cyclopropyl	

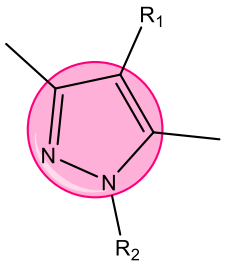
In 2022, Liu et al. [24] reported the catalytic application of a Keggin-based U(VI)-containing polytungstate (U-POW) tetramer (U4), which exhibits bifunctional Lewis acid-base properties. Under mild conditions, U4 efficiently catalyzed the reaction of various hydrazines with 1,3-diketones to produce pyrazoles in high yields. This work not only highlights the potential of actinide-containing polyoxometalates (POMs) in catalytic synthesis but also represents the first example of a U-POW tetramer applied to pyrazole synthesis.



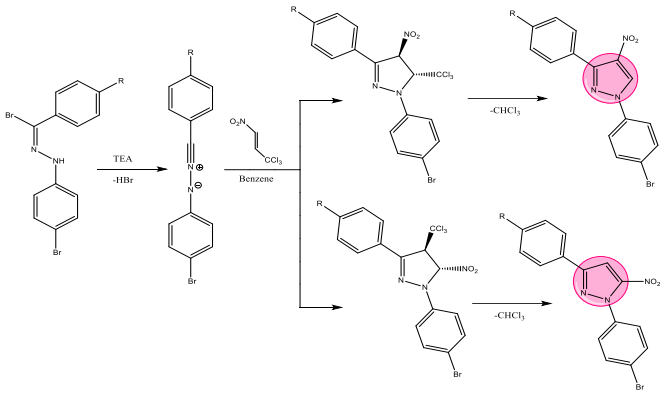
Scheme-16: Synthesis of pyrazole derivatives by Liu et al., [24]

Table-17: Structural Modification to synthesized pyrazole derivative by Liu et al.

Modifications		**Structure**
R_1	**R_2**	

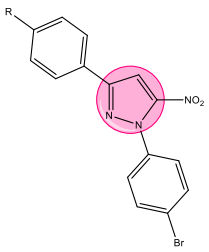
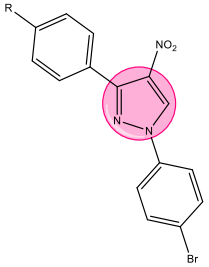
H Me Cl	Ph Penthyl PhCO 4-MePhCO 4-OMePhCO 4-FPhCO 4-ClPhCO 4-BrPhCO	

In 2022, Kula et al. [25] investigated the reaction mechanisms involving (E)-3,3,3-trichloro-1-nitroprop-1-ene and N-(4-bromophenyl)-C-arylnitrylimine, providing insights into the structural and electronic factors governing the formation of substituted pyrazoles.



Scheme-17: Synthesis of pyrazole derivatives by Kula et al., [25]

Table-18: Structural Modification to synthesized pyrazole derivative by Kula et al.

Modifications (R)	Structure	
H Cl OMe		

Anti-Microbial Activity

In 2017, Afaq et al. [26] reported that glacial acetic acid (GAA) promoted the thermal cyclization of hydrazine hydrate with 1,6-diphenylhexa-1,5-diene-3,4-dione, affording five pyrazoline derivatives (1a–e) in high yields (70–87%). Antibacterial evaluation showed inhibition zones (mm) against Escherichia coli (11.5, 12.0, 12.0, 7.5, and 16.0 mm) and Staphylococcus aureus (13.0, 13.5, 14.0, 8.0, and 18.0 mm). Compound 1e, bearing OCH_3 and OH groups, exhibited the strongest antibacterial activity.

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 22s, 2025
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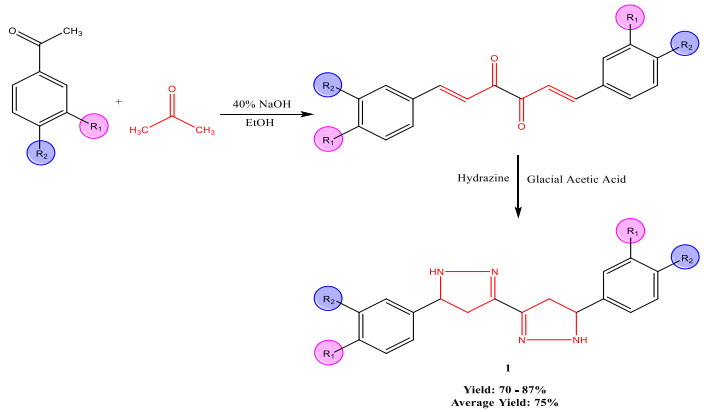
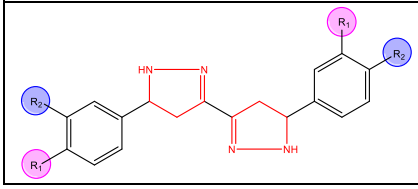
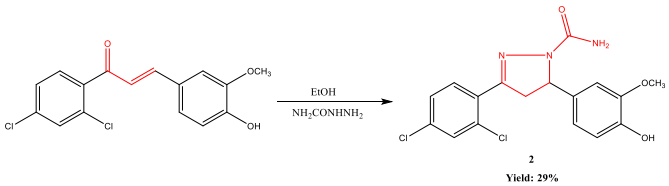


Scheme-18: Synthesis of derivatives of bi-pyrazoline (1a – 1e)

Table-19: Structural Modifications of Synthesized Compound 1

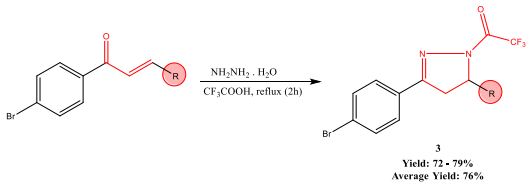
Synthesized Compound	Compound Name	R_1	R_2
	1a	H	H
	1b	H	CH_3
	1c	H	OCH_3
	1d	H	Cl
	1e	OCH_3	OH

In 2019, Fariana Nur Santi et al. [27] synthesized a new pyrazoline derivative (2) and evaluated its toxicity and antibacterial properties. The brine shrimp lethality test (BSLT) yielded an LC_{50} of 96.96 ppm, indicating potential anticancer activity. The compound demonstrated moderate to significant antibacterial effects against S. aureus ATCC 25923 and E. coli ATCC 25922 by the agar diffusion method.



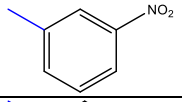
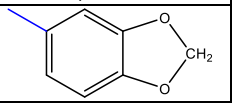
Scheme-19: Synthesis of pyrazoline derivative exhibiting potential Anti-Bacterial activity against *S. aureus* and *E. coli*

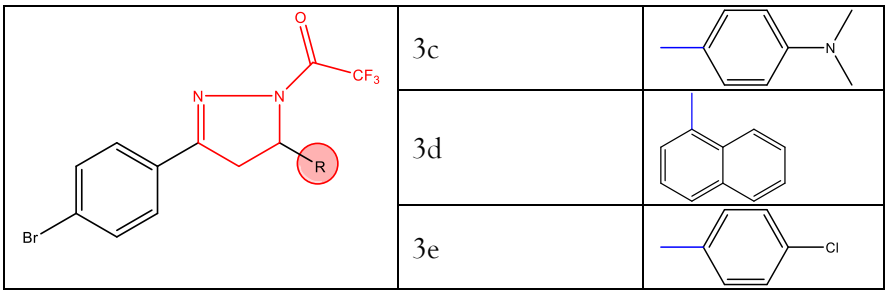
In 2020, Mohammad Asad et al. [28] synthesized five N-trifluoroacetyl-2-pyrazolines (3a–e) via the cyclization of chalcones with hydrazine and trifluoroacetic acid, achieving yields of 72–79%. Among them, 3a (bearing a NO_2 group) exhibited strong antibacterial activity, with MICs of 79 μM for Pseudomonas aeruginosa and 90 μM for E. coli. SEM analysis revealed complete bacterial membrane rupture upon treatment.



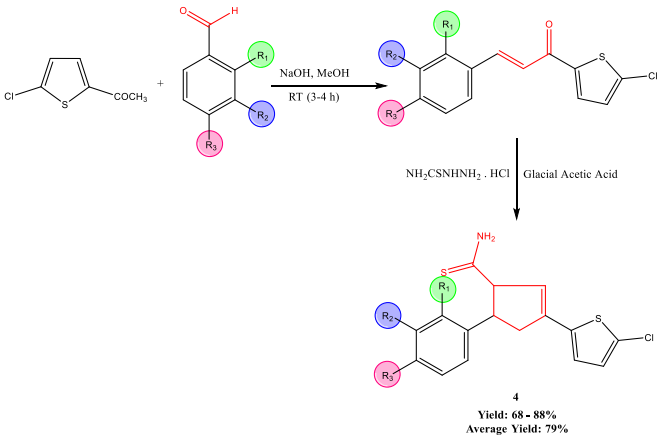
Scheme-20: Synthesis of f N-trifluoroacetyl-2-pyrazoline derivatives (3a – 3e)

Table-20: Structural Modifications of Synthesized Compound 3

Synthesized Compound	Compound Name	R
	3a	
	3b	

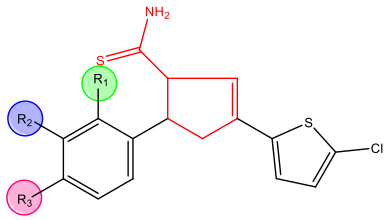


In 2020, Dileep Kumar Achutha et al. [29] synthesized thiophene-tethered pyrazoline carbothioamide derivatives (4a–k) via an eco-friendly 3 + 2 annulation of chalcones and thiosemicarbazide hydrochloride in aqueous citrus extract. Antioxidant studies revealed DPPH and hydroxyl radical scavenging activity, while 4c and 4k showed notable antibacterial activity against S. aureus (20 and 15 µg/mL), E. coli (15 and 15 µg/mL), B. subtilis (25 and 20 µg/mL), and antifungal activity against A. niger, A. flavus, and C. albicans.

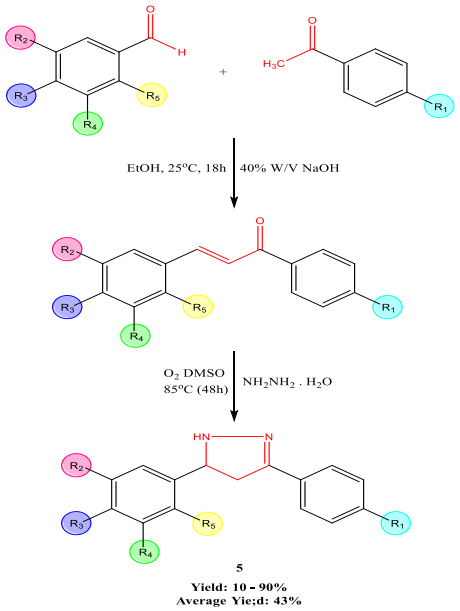


Scheme-21: Synthesis of pyrazoline derivatives (4a – 4k) via thiophene-tethered pyrazoline carbothioamide

Table-21: Structural Modifications of Synthesized Compound 4

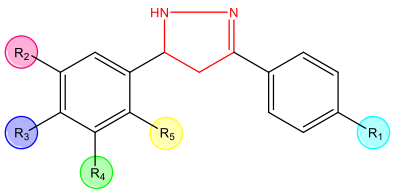
Synthesized Compound	**Compound Name**	**R_1**	**R_2**	**R_3**
	4a	H	H	H
	4b	H	H	F
	4c	H	H	Cl
	4d	H	H	CH_3
	4e	H	H	OCH_3
	4f	H	H	NO_2
	4g	H	H	$N(CH_3)_2$
	4h	H	H	Br
	4i	CH_3	H	CH_3
	4j	H	OCH_3	OCH_3
	4k	Cl	H	Cl

In 2021, Matthew Payne et al. [30] developed a one-pot oxidative cyclization of chalcones with hydrazine monohydrate, producing fifteen 3,5-diaryl-1H-pyrazoles (5a–q) with yields ranging from 10–90%. 5p, possessing OCH_3 and OH groups, exhibited significant antibacterial activity against S. aureus (MIC = 8 µg/mL) and altered B. subtilis morphogenesis before cell lysis, without cytotoxic effects on 3T3-L1 mammalian cells.

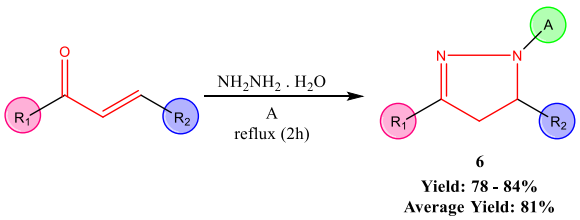


Scheme-22: Synthesis of potential anti-bacterial agents of 3,5-diaryl-1H-pyrazole derivatives (5a – 5q)

Table-22: Structural Modifications of Synthesized Compound 5

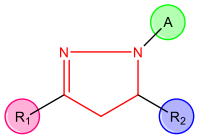
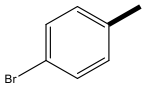
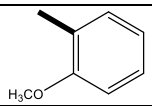
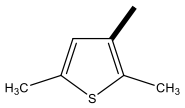
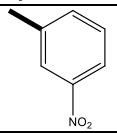
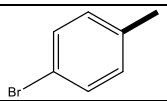
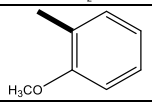
Synthesized Compound	Compound Name	R_1	R_2	R_3	R_4	R_5
	5a	p-ClPh	H	OCH_3	OCH_3	H
	5b	p-ClPh	H	OCH_3	H	OCH_3
	5c	p-ClPh	OCH_3	H	H	OCH_3
	5d	p-ClPh	H	OCH_3	H	H
	5e	p-ClPh	H	OBn	H	H
	5f	p-ClPh	H	H	OBn	H
	5g	p-ClPh	H	OBn	OCH_3	H
	5h	p-$C(CH_3)_3$Ph	H	OCH_3	H	H
	5i	p-$C(CH_3)_3$Ph	OCH_3	H	H	OCH_3
	5j	p-$C(CH_3)_3$Ph	H	OCH_3	OCH_3	H
	5k	p-$C(CH_3)_3$Ph	H	OBn	H	H
	5l	Ph	H	OCH_3	H	H
	5m	Ph	OCH_3	H	H	OCH_3
	5n	Ph	H	OCH_3	OCH_3	H
	5o	tert-Bu	H	OH	OCH_3	H
	5p	Ph	H	OH	OCH_3	H
	5q	Ph	H	H	OH	H

Also in 2021, Mohammad Asad et al. [31] synthesized three N-acyl-2-pyrazolines (6a–c) by cyclizing chalcones with hydrazine hydrate in the presence of aliphatic acids, yielding 78–84%. Compound 6b showed the best antibacterial activity (MIC: S. aureus & E. coli = 32 µg/mL; S. pyogenes & S. typhimurium = 64 µg/mL).

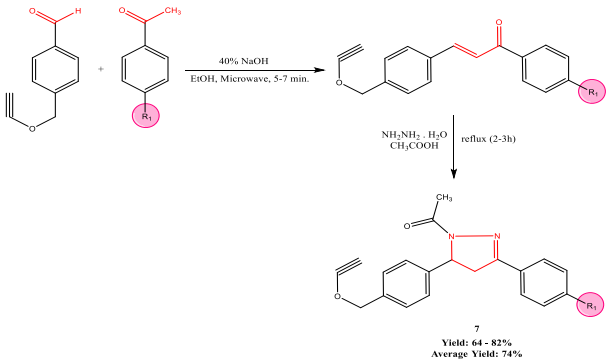


Scheme-23: Synthesis of pyrazoline derivatives (6a – 6c) as N-acyl-2-pyrazolines

Table-23: Structural Modifications of Synthesized Compound 6

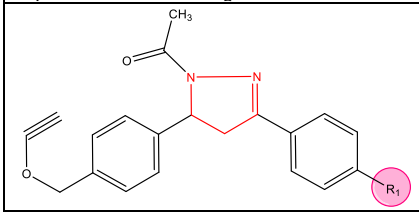
Synthesized Compound	Compound Name	R_1	R_2	A
	6a			CH_3COOH
	6b			CH_3CH_2COOH
	6c			$CH_3CH_2CH_2COOH$

In 2021, Lokesh Kumar et al. [32] employed 1,3-dipolar cycloaddition between pyrazoline-linked alkynes and 2-bromo-N-arylacetamide to synthesize pyrazoline–amide–1,2,3-triazole hybrids (7a–d) in 64–82% yields. 7a–c exhibited potent antibacterial and antifungal activity (MIC = 0.062–0.078 µmol/mL), with molecular dynamics simulations confirming 7a as the most promising antibacterial candidate.

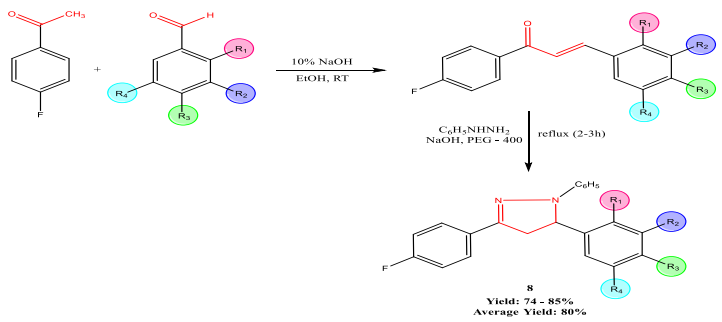


Scheme-24: Synthesis of pyrazoline derivatives (7a – 7d)

Table-24: Structural Modifications of Synthesized Compound 7

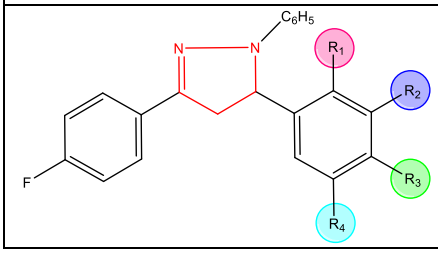
Synthesized Compound	Compound Name	R_1
	7a	H
	7b	CH_3
	7c	OCH_3
	7d	Br

In 2021, Pathade et al. [33] described an eco-friendly PEG-400-mediated synthesis of pyrazoline derivatives (8a–d), which demonstrated antibacterial activity against S. aureus, B. subtilis, E. coli, and P. vulgaris (zones ≥15–20 mm, comparable to chloramphenicol) and antifungal activity against A. niger and C. albicans (zones ≥15–20 mm, comparable to amphotericin-B).

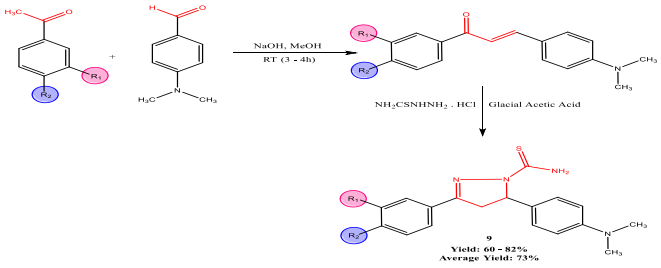


Scheme-25: Synthesis of pyrazoline derivatives (8a – 8d)

Table-25: Structural Modifications of Synthesized Compound 8

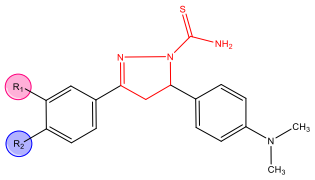
Synthesized Compound	Compound Name	R_1	R_2	R_3	R_4
	8a	H	OCH_3	OCH_3	H
	8b	Cl	H	Cl	H
	8c	H	OCH_3	OCH_3	OCH_3
	8d	H	H	F	H

In 2021, Deepashree Nagaraj et al. [34] synthesized N-dimethylaminophenyl-substituted pyrazoline carbothioamide derivatives (9a–g) via a 3 + 2 cycloaddition of chalcones and hydrazinecarbothioamide hydrochloride with amberlyst-15. Compounds 9a, 9b, and 9g showed strong antibacterial activity against S. aureus, E. coli, and B. subtilis at low MICs, surpassing ciprofloxacin in some cases. However, 9e and 9g, bearing methoxy substituents, showed no significant activity even at 100 µg/mL.

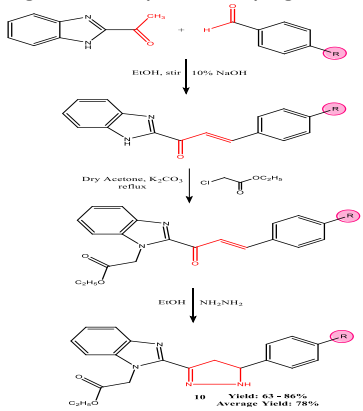


Scheme-26: Synthesis of pyrazoline derivatives (9a – 9g)

Table-26: Structural Modifications of Synthesized Compound 9

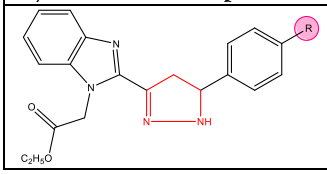
Synthesized Compound	Compound Name	R_1	R_2
	9a	H	H
	9b	H	F
	9c	H	Cl
	9d	H	CH_3
	9e	OCH_3	H
	9f	H	OCH_3
	9g	OCH_3	OCH_3

In 2023, Padhy et al. [35] synthesized pyrazolone derivatives (10a–d) by fusing benzimidazole chalcones with hydrazine hydrate, producing hybrids with antibacterial and anticancer activities. Compounds 10a (GI_{50} = 26.13 µM) and 10c (GI_{50} = 12.27 µM) showed significant cytotoxicity against the MDA-MB-231 breast cancer cell line.

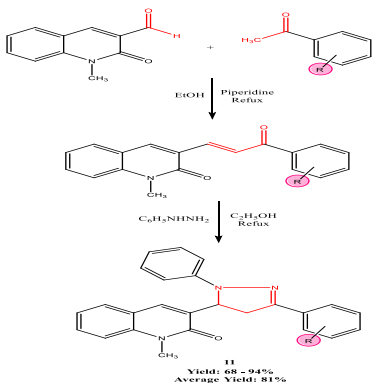


Scheme-27: Synthesis of pyrazoline derivatives (10a – 10d)

Table-27: Structural Modifications of Synthesized Compound 10

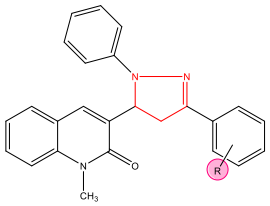
Synthesized Compound	Compound Name	R
	10a	H
	10b	CH_3
	10c	Cl
	10d	Br

In 2023, Kumar et al. [36] prepared pyrazoline derivatives (11a–i) from chalcones and phenyl hydrazine. Compounds 11b, 11f, and 11h displayed notable antibacterial activity against Shigella sp., B. subtilis, S. typhi, and S. aureus. Additionally, 11h exhibited significant antifungal activity against C. albicans and A. fusarium.

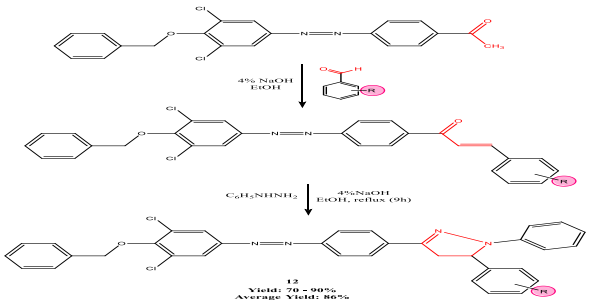


Scheme-28: Synthesis of pyrazoline derivatives (11a – 11i)

Table-28: Structural Modifications of Synthesized Compound 11

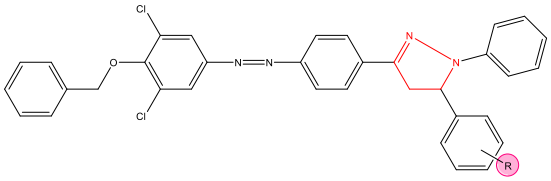
Synthesized Compound	Compound Name	R
	11a	H
	11b	3-NO_2
	11c	4-NO_2
	11d	4-NH_3
	11e	4-OCH_3
	11f	4-CH_3
	11g	4-Cl
	11h	4-OH
	11i	4-CH_2CH_3

In 2023, Finally, Daryan O. Ali et al. [37] synthesized azo-benzyloxy-pyrazoline hybrids (12a–j) via the Michael addition of azo-benzyloxy chalcones with phenylhydrazine. The compounds exhibited moderate antibacterial activity against S. aureus and E. coli at 200–1000 ppm, compared to azithromycin as a standard.



Scheme-29: Synthesis of pyrazoline derivatives (12a – 12j)

Table-29: Structural Modifications of Synthesized Compound 12

Synthesized Compound	Compound Name	R
	12a	H
	12b	2-Cl
	12c	2-F
	12d	4-Cl
	12e	4-F
	12f	OCH_3
	12g	CH_3
	12h	4-NO_2
	12i	4-$PhOCH_2$
	12j	4-$ClPhOCH_2$

CONCLUSION

Pyrazoline derivatives represent a highly promising category of molecules within the realm of medicinal chemistry, especially due to their antibacterial characteristics. Their structural versatility, combined with the simplicity of synthetic alterations, has facilitated the creation of derivatives exhibiting enhanced antibacterial and antifungal effects. These compounds demonstrate significant efficacy against a diverse array of pathogens, including multidrug-resistant bacterial strains and invasive fungal species, through mechanisms that target vital cellular components and functions. Innovations in synthetic methods, such as green chemistry and catalytic systems, have expanded the potential for producing compounds with improved pharmacological profiles and reduced toxicity. Regardless of these advancements, customizing these molecules for clinical use continues to pose a challenge, particularly concerning selectivity, bioavailability, and resistance to microbial defences This review underscores the importance of ongoing investigation into pyrazoline derivatives as possible solutions to the urgent global challenge of infectious diseases. Pyrazoline derivatives hold substantial promise for the advancement of next-generation antimicrobial agents as they tackle existing limitations and pursue innovative strategies.

Declaration: This manuscript has Integral University Manuscript Communication Number: IU/R&D/2025-MCN0003864.

Author Contributions:
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Iqbal Azad: Resources, Supervision, Writing-Review & Editing
Naseem Ahmad: Supervision, Writing-original draft, Supervision, Formal Analysis

Conflict of Interest: The authors declare no competing interests.
Ethical Approval: Not applicable.
Consent to Participate: All authors have agreed to participate.
Consent to Publish: All authors agree upon publication of the present paper.

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