*Quest Journals*
*Journal of Research in Pharmaceutical Science*
*Volume 9 ~ Issue 4 (2023) pp: 12-19*
*ISSN(Online) : 2347-2995*
www.questjournals.org

**Research Paper**

# Review on Synthesis & Characterization of Pyrazoline Containing Benzene Derivatives as Anti-infective

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***ABSTRACT:*** *Chalcone and its derivatives have a wide range of antiproliferative, antifungal, antibacterial, antiviral, antimalarial, and antisteroidal pharmacological effects because they contain a reactive alpha, beta - unsaturated carbonyl group. Due to the presence of the CO-CH=CH- ketoethylenic moiety, chalcone derivatives are sought-after species. Chalcone derivatives were created as a result of recent advances in heterocyclic chemistry and were biologically tested against specific targets. According to a survey of the literature, numerous chalcone - heterocycle hybrids show promise as potential new medication candidates because of their comparable or superior activities to those of the industry norms. So, based on previously established methods, this review may prove useful for the creation of fresh, strong therapeutic medications. This review's main focus is on the most recent synthesis of chalcones with benzene rings incorporating pyrazolines, which reveals their biological potential over the previous 10 years.*
***KEYWORDS:*** *Chalcone, Pyrazoline, Anti-infective.*

***R****eceived 01 Apr., 2023;* ***R****evised 09 Apr., 2023;* ***A****ccepted 11 Apr., 2023 © The author(s) 2023.*
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## I. INTRODUCTION

The development of various antimicrobial agent resistance in pathogenic bacteria over the past few decades has become a severe problem. The overuse of antimicrobial medications to treat illnesses has resulted in the development of resistance in a number of microorganism strains, including malignant cells and bacteria, fungi, enveloped viruses, and parasites. Animal and human infectious diseases have been significant throughout history [1]. In fact, bacteria and viruses frequently wiped out entire regions, caused migration, or started wars. For instance, between one-third and fifty percent of Europe's population perished during the Black Death epidemic in the fourteenth century [2].

As a result, the one of the primary issues of the 21st century is the long-term development of new treatments to fight existing infectious diseases and novel infections as well as to overcome resistance barriers [3,4]. The quest for secondary metabolites, or active chemicals produced by bacteria, appears to hold the most promise.

Given that chalcones are a significant class of natural goods, there is increased interest in the pharmacological potential of natural products [9].

Many plant species have specific active compounds and substances, which makes nature a useful source of medicine. Many plant extracts have been discovered to be effective treatments for a variety of medical problems. Chalcones are one of the phytochemicals that have undergone extensive research [5,6].In plants, the production of flavonoids and isoflavonoids is thought to begin with chalcones as the main precursor. Several plant species, particularly those that produce fruits and vegetables, include them. Moreover, large quantities of these therapeutic compounds can be produced in a lab. The synthesis of these substances has been described using a variety of approaches and techniques [14,15]. These processes include the Aldol condensation, Claisen-Schmidt condensation, Friedel-Crafts acylation, Witting reaction, Suzuki reaction and the photo-Fries rearrangement of phenyl cinnamate, to name a few [8].

These are open chain flavanoids made up of three carbon alpha and beta unsaturated carbonyl systems that connect two aromatic rings. The antibacterial action of chalcones is discovered to be caused by the presence of a reactive alpha, beta unsaturated keto function [6,9].

Recent research has examined the impact of numerous different chalcones on cytotoxicity, cancer prevention through chemotherapy, mutagenicity, as well as insecticidal, antiviral, and enzyme inhibitory activities. Numerous chalcones with hydroxy and alkoxy groups in different positions have been reported to have antimalarial, antiulcer antibacterial, antifungal, antileshmanial, vasodilatory, antimitotic, antioxidant, antimalarial, antileshmanial, and inhibition of chemical mediator release, inhibition of leukotriene, inhibition of tyrosinase, and inhibition of aldose reductase activities. [11,12,14]. We created Chalcones as a possible model for antimicrobial medications because we were inspired by these results. It should be highlighted that this scaffold offers a pattern of substitution on the nucleus of benzylidenacetophenones [16].

Several studies have shown that particular chalcone types can have an impact on key targets in virally-induced diseases. Due to their beneficial range of antiviral bioactivities, the most recent viral pandemic, COVID-19, has a strong broad-spectrum candidate in chalcone derivative as well as any other conceivably forthcoming viral diseases. As potential pharmacological agents capable of focusing on a variety of human viruses, including hepatitis B virus (HBV), severe acute respiratory syndrome-related coronavirus (SARS-CoV), MERS-CoV, herpes simplex virus (HSV), dengue virus (DEN), human rhinovirus, human cytomegalovirus (HCMV), hepatitis B virus (HBV), Rift Valley fever (RVF), hepatitis C virus (HCV)[16,17,18].

Chalcone scaffolds have recently been demonstrated to serve as a foundation for MAO inhibition. A relatively recent review underlined the importance of the chalcone scaffold as a favoured structure in medicinal chemistry [19]. Many potential candidates from this family have been thoroughly studied and patented up to this point, despite the drawbacks of chalcone scaffold's ability to create irreversible connections with other molecules, leading to harmful effects, such as allergic responses, mutagenicity, and carcinogenicity [21].

Over the past few decades, pathogenic bacterial resistance to various antimicrobial agents has grown to be a serious issue. Resistance has been developed in a variety of microorganism strains, including malignant cells and bacteria, fungi, enveloped viruses, and parasites, as a result of the misuse of antimicrobial drugs to treat ailments. Infectious diseases in both animals and people have had a huge historical impact [23,24]. In actuality, bacteria and viruses frequently destroyed entire regions, sparked migration, or ignited wars. For instance, during the Black Death outbreak in the fourteenth century, between one-third and fifty percent of Europe's population died [26].

In order to combat emerging pathogens, infectious diseases, and resistance barriers, it is crucial to continuously generate new drugs.

**PYRAZOLINES: -** The mixture Pyrazoline is a 5-membered heterocyclic compound with 2 nearby nitrogen atoms. It is basic in nature and only has 1 endocyclic double bond. The 2-pyrazolines appear to be the pyrazoline type of chemicals that are examined the most frequently among its many derivatives. Consider 2-pyrazolines to be a cyclic hydrazine moiety. According to the results of the X-ray investigation, it possesses envelope conformation and a five-membered dihydropyrazole ring structure [25,26,27]. The C-5 atom of the heterocyclic ring deviates from almost planar structure of the other four atoms.It is widely employed as helpful synthons in organic synthesis and plays an important part in the development of heterocyclic chemistry theory. Due to its lipophilic nature, 2-pyrazoline is soluble in propylene glycol but insoluble in water [28,29].

It has been demonstrated that at high temperatures (200°C), the compounds of the 2-pyrazoline group without a heteroring's one-position substitute reacts with benzaldehyde to form 4-benzylidine derivatives. Because of their potent blue fluorescence in solution, pyrazolone derivatives, which are frequently found in ICT (Intramolecular Charge Transfer) chemicals [8], are referred to as a class of fluorescent brightening agents. They tend to move things about generally. It has been hypothesised that in excited state, it displays an intramolecular conjugated charge transfer process [29,30,31]. In the conjugated part of the ring, the nitrogen atom at position one and the carbon atom at position three respectively, withdrawing moieties (-N1-N2-C3-) and electron-donating.

The 4- and 5-position carbon atoms do not conjugate with the previously conjugated portion. As the solvents' polarity gets higher, there is a noticeable a reddened fluorescence shift spectrum of this substance. Because of the cyclization-induced double bond hindrance, these compounds exhibit greater fluorescence. Diverse restoration pyrazolines and their derivatives imbedded with various functional groups are significant biological agents, and this class has been the subject of a lot of research [32,33].They are specifically employed as antiparasitic, anticancer, antifungal, insecticidal antiviral, antibacterial agents. Some of these substances also have substantial selective activity, such as cannabinoid CB1 receptor antagonists, nitric oxide synthase (NOS) inhibitor as well as anti-diabetic, analgesic, anaesthetic, anti-inflammatory and anaesthetic properties. In a traditional method of making these chemicals, aromatic ketones and aldehydes undergo a base-catalyzed aldol condensation process to produce α and β unsaturated ketones (chalcones), which are then cyclized with hydrazines to produce 2-pyrazolines [34,35].


Figure 1: St. of Pyrazoline

**Chemistry of Chalcones**

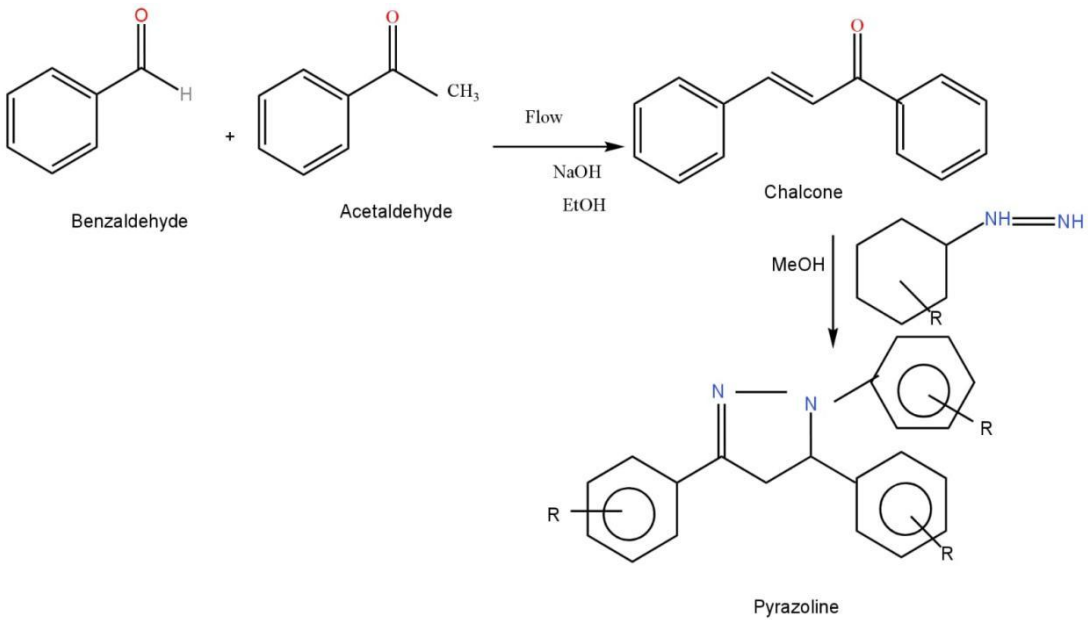
Around the world, there have been extensive scientific investigations on the chemistry of chalcones. The synthesis of chalcones and their biodynamic activities have drawn a lot of attention. Kostanecki and Tambor1 are the authors of the name "Chalcones". These substances also referred to as benzylidene acetophenone or benzalacetophenone [17,18]. In chalcones, an aliphatic 3-carbon chain connects 2 aromatic rings. Chalcone has a very good synthon, making it possible to construct a wide range of new heterocycles with favourable pharmacological properties. Chalcones are unsaturated ketones with the reactive CO-CH=CH- ketoethylenic group.The presence of other auxochromes is necessary for the chromophore -CO-CH=CH- to function, gives these compounds their colour. Chalcones can be prepared using a variety of techniques [35,36]. The simplest method involves arylmethylketone and aryl aldehyde being combined via Claisen-Schmidt condensation in the presence of an alcoholic alkali. Chalcones are utilized to create a variety of derivatives with various heterocyclic ring systems, including cyanopyridines, pyrazolines, isoxazoles, and pyrimidines [37].

**Mechanism of Reaction**

In the Claisen-Schmidt condensation reaction, an aromatic carbonyl molecule that lacks any -hydrogens combines with a ketone or aldehyde that has a -hydrogen. The chemists J.G. Schmidt and Rainer Ludwig Claisen are honored by the name of this reaction [38].

The acidic -hydrogen of the ketone molecule is first abstracted by a base in the Claisen-Schmidt condensation reaction mechanism, and the resultant species subsequently undergoes a keto-enol tautomerism. The nucleophilic addition of the enolate, the anion of acetophenone, to the carbonyl carbon of the benzaldehyde results in the intermediate -hydroxyl ketone, which is then dehydrated to produce chalcone as rate-determining step of the overall process. Seldom is the solvent in which a chemical reaction occurs a non-inert media. The intricate interactions it has with the solute molecules and potential intermediates may change the chemical pathway [7,8,9].

In this second step of the preparation, chalcones 4a-f react with various aryl aldehydes under alkaline conditions with methanol acting as a solvent to create pyrazoline derivatives.




Scheme 1

**Pyrazoline's Biological Effects**

**Microbiological Activity**

In a study on anti-microbe strategies, Zampieri et al. created 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives and assessed the effectiveness of those compounds against two different bacterial strains, Candida albicans and Mycobacterium tuberculosis H37Rv [25, 26].

The imidazole derivatives exhibited promising antifungal and antimycobacterial properties when tested against these strains. These findings suggest the potential derivatives of 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole as effective antimicrobial agents.

A group of researchers led by Shaharyar synthesized and evaluated Mycobacterium tuberculosis (MTB) and INHR-MTB were tested in vitro using a variety of N1-nicotinoyl-3-(4-hydroxy-3-methylphenyl)-5-(substituted phenyl)-2-pyrazolines [35,36].The most potent compound was found to be 2-pyrazoline with 0.26 µM is the minimal inhibitory concentration.

In a separate study, Muhammad et al. synthesized 5-(4-aryl)-3-(benzofuran-2-yl) -(4-aryl)-4,5-dihydropyrazole-1-carbothioamides by cyclizing chalcones with thiosemicarbazide under basic refluxing conditions and using nitromethane under Michael addition conditions [38,39,40]. Thiazole-substituted pyrazolines were obtained by reacting these pyrazolines with phenacyl bromides. Several of compounds exhibited significant antibacterial activity against Escherichia coli and Aspergillus niger.

Furthermore, by reacting chalcone dibromides with aryloxy acid hydrazides in the presence of triethylamine, a series of chlorofluorine-containing hydroxy pyrazolines were produced [35,36]. These compounds showed excellent antifungal and antibacterial activities against several microbes.

Overall, pyrazolines and their derivatives have shown promising antimicrobial activity against various bacterial and fungal strains.

**Antiamoebic Activity**

By cyclizing Mannich bases with thiosemicarbazide, Abid et al. created a new class of 1-N-substituted cyclized pyrazoline analogues of thiosemicarbazones. The antiamoebic efficacy of these compounds was evaluated using the HM1:1MSS Entamoeba histolytica parasitic worm strain. The compound with the highest antiamoebic activity had an IC50 of 0.6 µM, which was higher than metronidazole's (IC50 = 1.8 µM) [41]. Additionally, when compared to other ligands, 1-N-substituted thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives demonstrated stronger antiamoebic activity against Aspergillus niger and Escherichia coli complexes [42,43,44].

Bhat et al. reported the synthesis of bis-pyrazolines under standard conditions by cyclizing chalcones with N-4 substituted thiosemicarbazides. Antiamoebic activity tests revealed that compounds with aromatic substituents at the thiocarbamoyl group outperformed those with cyclic groups [45,46]. Furthermore, refluxing the reaction of 1-N-thiocarbamoyl 3,5-diphenyl-2-pyrazoline with 2,3-dichloro quinoxaline produced a number of novel pyrazolines containing thiazolo [4,5-b] quinoxaline 9. The effectiveness of these compounds as antiamoebics against Entamoeba histolytica was evaluated [47].

By cyclizing Mannich bases and substituting thiosemicarbazides with different cyclic and aromatic amines, a group of thirty novel pyrazoline derivatives were synthesized. The most potent compound against Entamoeba histolytica was found to be compound 10 after assessing the compounds' in vitro antiamoebic activity [48,49].

**Anti-inflammatory Activity**

The anti-inflammatory properties of new 1,3,5-trisubstituted pyrazolines were investigated by Rathish et al. containing benzene sulfonamides 11, with some compounds demonstrating promising results. The inhibitory effects of various lipoxygenase and 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines on COX-2 were also examined. Additionally, the analgesic and anti-inflammatory effects of 1-benzoyl-3-phenyl-2-pyrazolines and 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines were investigated [50,51].

Barsoum et al. developed novel bis(1-acyl-2-pyrazolines) compounds and studied their ulcerogenic and anti-inflammatory properties. Some of the substances exhibited surprising anti-inflammatory effects and were less likely to cause ulcers compared to traditional drugs. [52].

**Anticancer Activity**

Havrylyuk and colleagues investigated a novel series compounds based on thiazolone and comprising the 5-aryl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl motif for their potential anticancer activity [53]. Anticancer activity in vitro assays conducted by the National Cancer Institute (NCI) revealed that the majority of the compounds were effective against various cancer cell lines such as melanoma, colon, leukemia, ovarian, lung renal, prostate, brain and breast cancer. The most effective anticancer agent was found to be selectively active against colon cancer cell lines, particularly HT 29.

Johnson and colleagues developed and tested a series of novel pyrazoline compounds for their anticancer activity and found that they were comparable to combretastatin-A4 [54,55,56].

Several cyclolignan 20-fused pyrazole derivatives were identified and tested for cytotoxicity in P-388 murine leukaemia, A-549 lung carcinoma, and HT-29 colon carcinoma cultured cells. Additionally, despite the absence of a lactone moiety in their structures, 1,4-diaryl-4,5-dihydropyrazoles 19 were synthesised and found to be potent, selective inhibitors of the mitotic kinesin spindle protein (KSP), with KSP IC50 values in the micromolar range. [57,58].

Manna and colleagues tested a series of substituted pyrazolines 21 because of their ability to decrease multidrug resistance mediated by P-glycoprotein directly interacting with a purified protein domain featuring an ATP-binding domain and a signal generator interconnected region. Some of the mixtures were discovered to be more capable of binding to the P-glycoprotein than others [59,60].

The National Cancer Institute recommends the use of indene fused sulfonylthiourea pharmacophores, N1- N3-disubstituted sulfonylurea and 3-(4-chlorophenyl)-1,2-c] pyrazolines as well as certain derived thiazolidinone and thiazoles for evaluating anticancer efficacy. In their tests, eight drugs demonstrated promising a broad range anticancer efficacy against the majority of the subpanel tumour cellular lines [61,62].

**Antidepressant Activity**

According to a study on the novel compound 1, 3, 5-triphenyl-2-pyrazolines 23, the majority of the produced compounds significantly reduced depression in mice the Porsolt behavioural despair test. The Porsolt test, also known as forced swimming, was used to evaluate the antidepressant effect of certain 1-thiocarbamoyl-, and (2-furyl)-2-pyrazoline derivatives/1-N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl,1-phenyl [63].

Two specific compounds, namely 1-N-allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline,1-N-Ethylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline were discovered to reduce the duration of immobility periods by 33.80-31.42% at the 10 mg kg1 dosing level [64].

Chimenti et al. classified several derivatives of N1-propanoyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole were reported and tested in 25 as MAO-A and MAO-B isoform inhibitors [65]. The majority of the investigated drugs showed micromolar inhibitory action and MAO-A selectivity.

The majority of the examined drugs demonstrated inhibition in the micromolar range and were selective towards MAO-A. The goal was to create 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-(1H)-pyrazole derivatives that inhibit monoamine oxidase (MAO). The majority of the compounds were active against both the MAO-A and MAO-B isoforms [66].

**Steroidal Activity**

Through in vivo screening, Zhang and their team developed a novel pyrazoline series known as 27, which were assessed as in tissue -specific androgen receptor modulators. The study analyzed thestructure activity relationships (SAR) at positions R1 to R6,the anilide linker and the central pyrazoline ring. Generally, AR agonist activity is optimal withR1 and R2 contain strong electron-drawing groups, as well as a moderate grouping at R5 and R6. While mifepristone serves as an anti-endometriosis and abortifacient, it is alsoa non-

selective 3-oxosteroid receptor antagonist. Important progesterone receptor modulators consist of mifepristone and non-steroidal progesterone mimics (PR) [45, 50, 61].

Jones and their team discovered 28 derivatives of 4-substituted pyrazolines through docking substancesinto a model of PR homology. Upon synthesis and evaluation, these compounds exhibited functional antagonism of PR. Additionally, a series of androstano pyrazolines and their oxidized derivatives were produced, a starting material, 3-hydroxyandrostan-17-one is used. The anti-androgenic activities of these compounds were compared to cyproterone, a positive check, and some of the compounds showed superior anti-androgenic characteristics to reference medication [55].

**Antiviral Action**

Globally the prevalence of viral infections has steadily increased fluctuating, and the advancement of effective antiviral medications have been developed slower compared to other forms of anti-infective treatment. One of the main obstacles to antiviral drug development has been accelerated the absence of distinct viral "targets," as viral replication primarily utilizes host cell pathways [57,58].

Recent research by El-Sabbagh et al. suggests that pyrazoline derivatives have fascinating antiviral qualities. To develop novel unsaturated ketones 4,5-dihydropyrazole N-acetyl and N-thiocarbamoyl derivatives were utilized.

These unique compounds were discovered in terms of their antiviral activity against a wide rangeof viruses in numerous cell cultures. Several of the substances were discovered to be the most effective variants, suggesting that derivatives of pyrazoline could be a possible future development target effective antiviral drug.

Shaharyar et al., acetyl 4,5-dihydropyrazole was reported as the only pyrazoline derivative of phenoxyacetic acid and was tested for antiviral activity cytotoxicity and cytotoxicity in vitro. Among the group, acetic acid had the least cytotoxicity with a minimum cytotoxic [59,60,61].

Compound library high-throughput screening with a West Nile (WN) virus infection assay using luciferase identified several triaryl pyrazolines ([5-(4-chloro-phenyl)-3-thiophen-2-yl4,5-dihydro-pyrazol-1-yl]-phenyl-methanone), as inhibitors of infection with a flavivirus in cell culture [62]. This compound inhibited an epidemic WN virus strain without producing any observable cytotoxicity (IC50 of 28 M).

Moreover, the compound inhibited not only the WN virus other flaviviruses such as yellow fever, dengue, alphavirus (Western equine encephalitis virus), St. Louis encephalitis viruses, as well as coronavirus (mouse hepatitis virus), and a rhabdovirus, are also present (vesicular stomatitis virus) [63,64]. These findings suggest that pyrazoline derivatives such as compound 34 could be promising candidatesin order to develop antiviral drugs.

Studies on mode of operation of WN virus revealed that compound 34, a triaryl pyrazoline derivative, reduced viral RNA synthesis rather than viral entry or assembly. Further investigations by the research group resulted in early structure-activity relationship(SAR) data show that aryl rings are required for WNV action.

Additionally, the inhibition of RNA synthesis by pyrazolines suggests the potential targeting of viral replication enzymes such as RNA polymerase or RNA helicase [67]. These findings support the potential of pyrazoline derivatives as antiviral drugs, particularly for flaviviruses such as the WN virus.

## II. Conclusion

Researchers have concluded that this is because pyrazolines have been demonstrated to have antibacterial, antiviral, antiinflammatory, anticancer belongings family of substances has considerable potential. The chemical and biological characteristics of numerous substituted pyrazoline derivatives are outlined in this article. We talk about these traits in connection to one another. Medical professionals employ a huge number of compounds made from pyrazoline to treat a wide range of disorders.Many substances that have the potential to operate as anti-inflammatories, anti-depressants, anti-viral, and other similar things have been the subject of in-depth and concentrated research, but none of these molecules have yet reached the market or the clinic. This could be as a result of the lack of a centralized repository for all the research that has been done on any certain activity that could provide insight into the SAR of the substances. This review of numerous sources gives medicinal chemists and drug designers the chance to find the complete and target-oriented knowledge they're looking for in order to create therapeutically effective molecules.

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