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A Review on Synthesis of Novel Pyrazoline Derivatives as Antimicrobial Agents

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HUMAN

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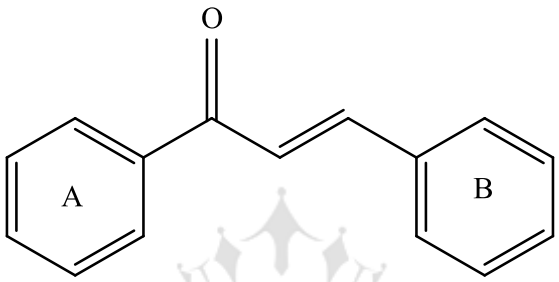
ABSTRACT

At present, there is a lot of research about the pyrazoline heterocyclic compound, its ring structure is being changed and new derivatives are being made, many of which have antimicrobial activity over the derivatives. The synthesis of novel pyrazoline derivatives and the investigation of their chemical and biological behavior have gained more importance in recent decades. The pyrazoline derivatives are found to be chemotherapeutically active and they are found to possess anti-inflammatory, anti-bacterial, antifungal, antiviral, and analgesic activities. This review provides an outline of the recent grade of pyrazoline derivatives in terms of synthesis and various applications to realize their potential as drugs. This review also provides a small survey relating to the advantages of pyrazoline and its derivatives in the pharmaceutical field, especially as anticancer, anticonvulsant, anti-inflammatory, antimalarial agents.

INTRODUCTION

Heterocyclic Chemistry constitutes an essential branch of organic chemistry and heterocycles are widely known to display an array of biological properties. Heterocyclic compounds are those which possess a cyclic structure with at least two different kinds of atoms in the ring, one of which is nitrogen and can be aliphatic or aromatic (1). Heterocyclic compounds are well known for their wide range of biological applications out of which pyrazoline occupies a unique position due to dominant applications. One of the important applications of pyrazoline is the use of pyrazolines as a fluorescent brightening agent (2).

Chalcones are 1, 3-diphenyl-2-propane-1-one in which two aromatic rings are linked by a three-carbon α, β- unsaturated carbonyl system.



Structure of Chalcone

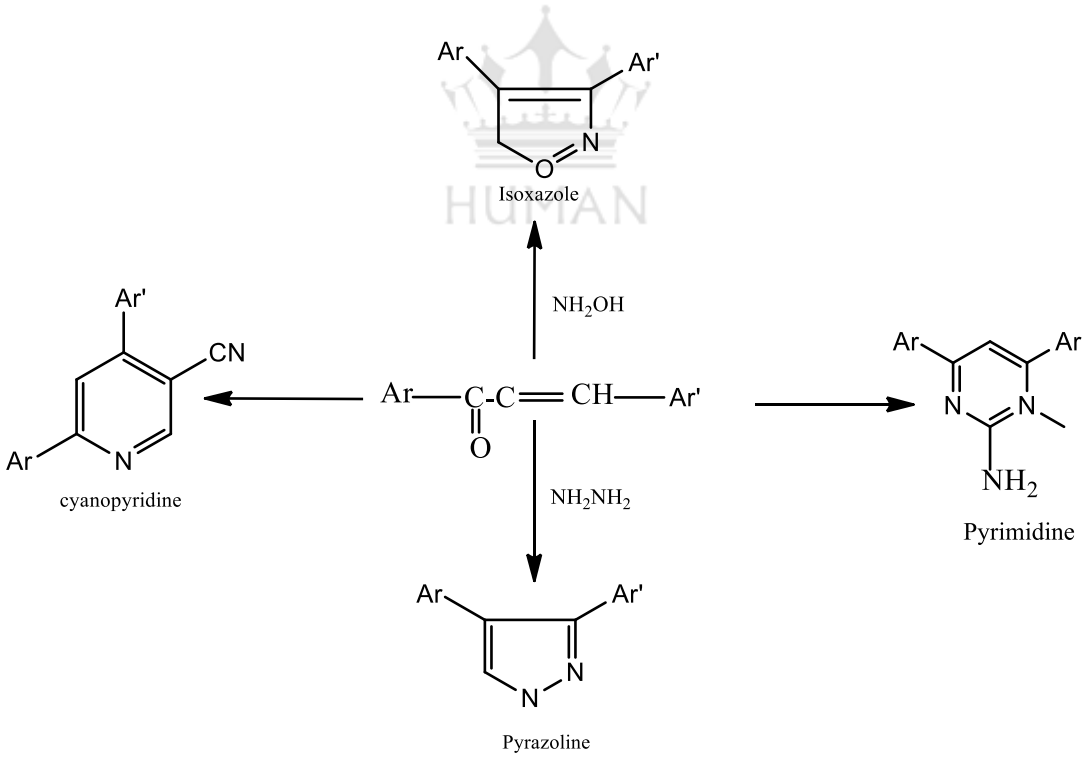
These are abundant in edible plants and are considered to be precursors of flavonoids and isoflavonoids. Chalcones possess conjugated double bonds and a completely delocalized π-electron system on both benzene rings has less intermolecular force hence low melting point. Molecules possessing such a system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions (3).

Chalcones are prepared by Claisen-Schmidt Condensation of aromatic aldehyde and ketone by base-catalyzed or acid-catalyzed followed by dehydration. The presence of α, β-unsaturated functional group is responsible for antimicrobial activity, which can be altered depending upon the type of substituent present on the aromatic rings. They also serve as a backbone for the synthesis of various heterocyclic compounds, as they undergo a variety of reactions. Hence Chalcones play an important role in the synthesis of medicinal compounds (4, 5).

Chemistry of chalcones

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. The name “Chalcones” was given by benzalactophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three-carbon chain. Chalcones bears a very good synthon so a variety of novel heterocycles with a good pharmaceutical profile can be designed.

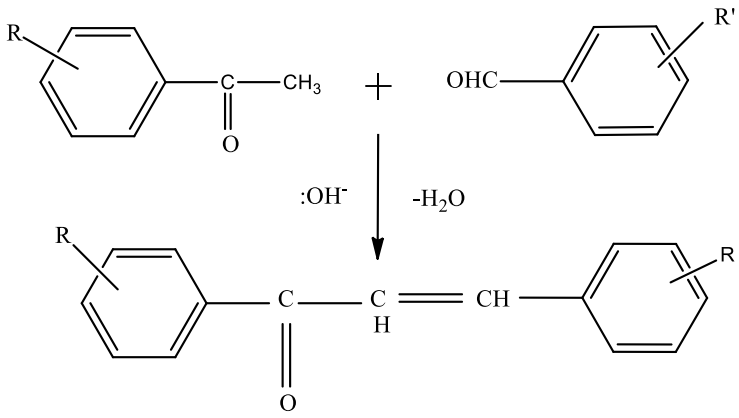
Chalcones are -unsaturated ketone containing the reactive keto ethylenic group -CO-CH=CH- . These are colored compounds because of the presence of the chromophore -CO-CH=CH-, which depends on the presence of other auxochromes, Different methods are available for the preparation of chalcones. The most convenient method is the Claisen-Schmidt condensation of equimolar quantities of aryl methyl ketone with aryl aldehyde in the presence of alcoholic alkali. Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines isoxazoles, and pyrimidines having different heterocyclic ring systems.



SYNTHETIC METHODS FOR PREPARING CHALCONES

Claisen-Schmidt reaction: A variety of methods are available for the synthesis of chalcones, the most convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of substituted acetophenone with substituted aldehydes in the presence

of aqueous-alcoholic alkali. In the Claisen-Schmidt reaction, the concentration of alkali used usually ranges between 10 and 60%. The reaction is carried out at about 50°C for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizzaro reaction also takes place and thereby decreases the yield of the desired product. To avoid the disproportionation of aldehyde in the above reaction, the use of benzylidene-diacetate in place of aldehyde has been recommended.



Importance of Chalcone:

1. They have a close relationship with flavones, aurones, tetralones, and aziridines.

2. Chalcones and their derivatives find application as artificial sweeteners, scintillator polymerization catalyst, and fluorescent whitening agent, and organic brightening agent, stabilizer against heat, visible light, ultraviolet light, and aging.

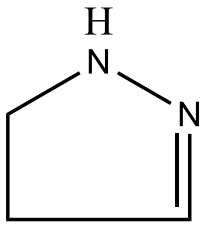
3. 3, 2', 4', 6'-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside has been used as a synthetic sweetener and is 2200 times sweeter than glucose.

4. They contain a keto-ethylenic group and are therefore reactive towards several reagents e.g. (a) phenyl hydrazine, (b) 2-amino thiophenol, etc.

5. The Chalcones have been found useful in elucidating the structure of natural products like hemlock tannin cyanomaclurin, ploretin.

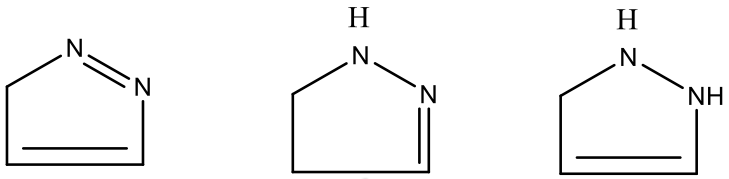
Pyrazoline is considered an important compound in organic chemistry because of its application in heterocyclic synthesis and medicinal applications. Pyrazolines are compounds with noteworthy applications and have been reported to show a wide spectrum of biological activity, including antibacterial, antifungal, anti-inflammatory, anti-amoebic, antidepressant, analgesic, and anticonvulsant activities (6-16).

Pyrazolines are five-membered heterocyclic having two adjacent nitrogen atoms within the ring, only one endocyclic double bond and are basic.



Pyrazoline

The structural elucidation of pyrazoles and derivatives has been greatly aided by NMR spectroscopy, particularly for distinguishing between isomeric structures. Depending on the position of the double bond, can exist in three different forms (17).



1-pyrazoline 2-pyrazoline 3-pyrazoline

Types of pyrazoline

Previous research has shown Pyrazolines to be an interesting pharmacophore for drug discovery. These heterocyclic compounds occur widely in nature in the form of alkaloids, vitamins, pigments, and constituents of plant and animal cells (18).

Pyrazoline and its derivatives is a member of nitrogen-containing heterocycles (19). In their structure, two nitrogen atoms are present in five-membered rings (Figure 1). This nucleus contains a C=N double bond (20). Pyrazoline derivatives have been found in natural products in form of vitamins, alkaloids, and pigments (21). In the last decade, great attention has been paid to the Pyrazoline derivatives due to their unique molecular structure with the simplicity of preparation and wide application in the pharmaceutical field. They have shown interesting pharmacological activities such as anticancer (22), anti-inflammatory (23), antimicrobial (24), antioxidant (25), and antidepressant (26).

Antimicrobial agents:

The modern era of antimicrobial chemotherapy began following Fleming's discovery in 1929 of the powerful bactericidal substance penicillin and Domagk's discovery in 1935 of synthetic chemicals (sulphonamides) with broad antimicrobial activity. In 1939, Gerhard

Domagk, a German Bacteriologist and pathologist, awarded the Nobel Prize for the discovery of the first synthetic antibacterial compound “prontosil”.

Antimicrobial agents may be either bactericidal, killing the target bacterium or fungus, or bacteriostatic, inhibiting its growth. Bactericidal agents are more effective, but bacteriostatic agents can be extremely beneficial since they permit the normal defences of the host to destroy microorganisms. Antimicrobial agents may be classified according to the type of organism against which they are active i.e. antibacterial, antiviral, antifungal, antiprotozoal, and anthelmintic drugs. It can also be useful to combine various antimicrobial agents for broadening the activity spectrums and to minimize the possibility of the development of bacterial resistance. Some antibiotic combinations are more effective together than the combined effect of the single agent. This is termed synergism. Combinations therapy has proved its value as the latest therapy for antimicrobials. Some bacteriostatic agents on novel combinations give bactericidal activity. Sulphathiazole is bacteriostatic and Trimethoprim is also bacteriostatic but the combination of both drugs is now widely used as a bactericidal combination. Two such bactericidal drugs are also used in combination therapy. In the medical and pharmaceutical worlds, all these antimicrobial agents used in the treatment of disease are referred to as antibiotics, chemicals that are produced by living organisms that, even in minute amounts, inhibit the growth of or kill another organism.

CHARACTERISTICS OF ANTIMICROBIAL AGENTS-

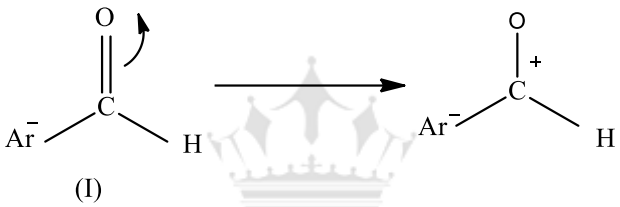
- It should have a wide spectrum of activity with the ability to destroy or inhibit many different species of pathogenic organisms.
- It should be nonallergenic and nontoxic to the host and without undesirable side effects.
- It should not eliminate the normal flora of the host.
- It should be able to reach the part of the human body where the infection is occurring.
- It should be inexpensive and easy to produce.
- It should be chemically stable.
- It should have a wide spectrum of activity with the ability to destroy or inhibit many different species of a pathogenic organism.
- It should be non-allergic and non-toxic to the host and without undesirable side effects.
- It should not eliminate.
- Microbial resistance is uncommon and unlikely to develop.
- It must have solubility in body fluids to be active and can rapidly penetrate body tissues.

Chemistry: pyrazoline is a derivative of chalcone has also been represented to display a broad spectrum of potential pharmacological activities (27). For the synthesis of five, six, and seven-member heterocycles, chalcones are the convenient intermediates, often have exhibited diverse biological activity.

The chalcones were synthesized from an aldol condensation between benzaldehyde and acetophenone by an Aldol condensation reaction. These condensation reactions are important inorganic chemistry in which an enol or an enolate ion reacts with a carbonyl compound to form a β-hydroxy aldehyde or β-hydroxy ketone, followed by dehydration to give a conjugated enone (28).

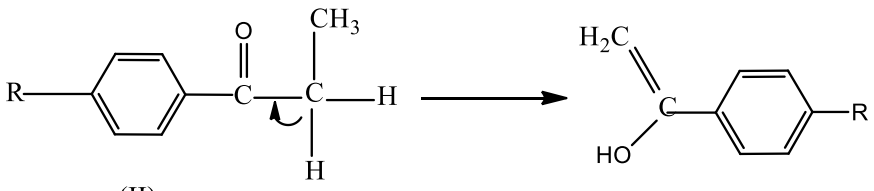
Mechanism:

The mechanism involves the aromatic aldehyde rearranged into carbonium ion (I) intermediate with the negative charge on the oxygen atom.



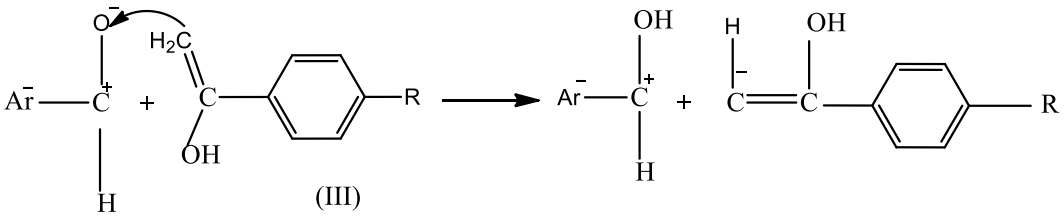
(I)

Acetophenone derivatives are readjusted into their enolic form (II) by using strong alkali.



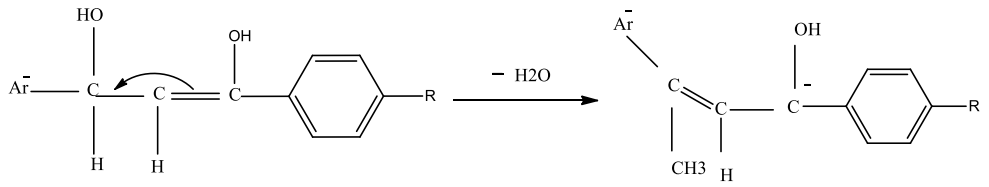
(II)

This enolic form donates a proton from the carbon to condense with the oxygen atom of aldehyde.



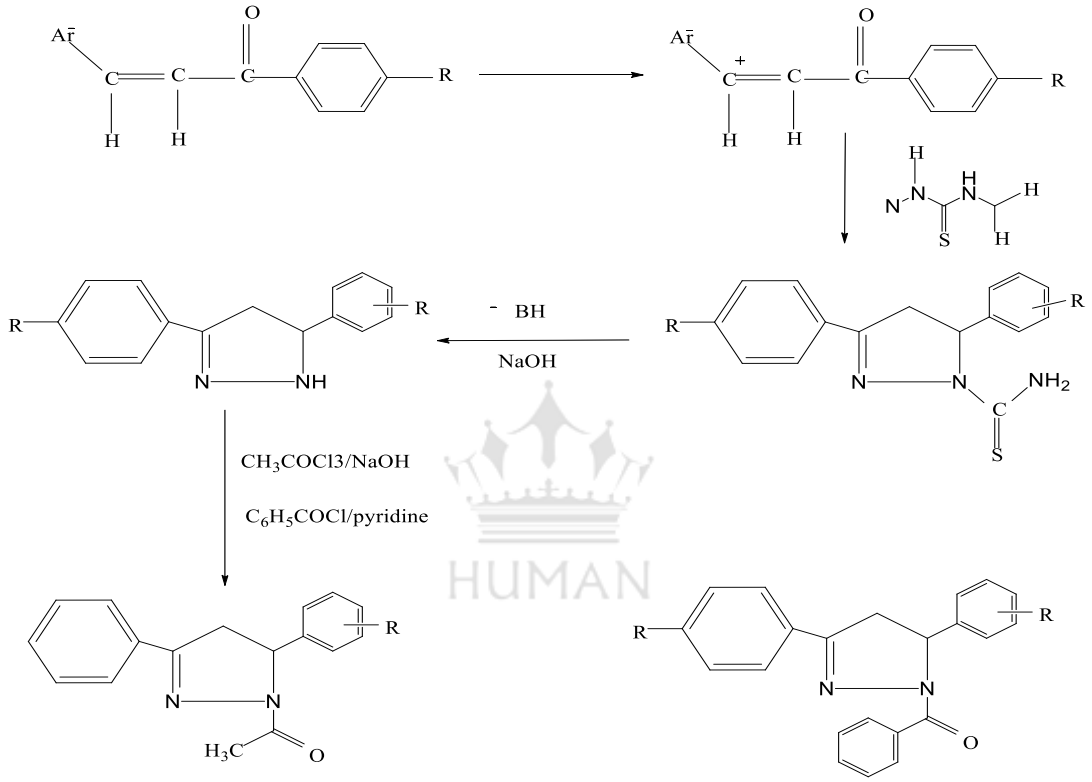
(III)

The carbanion iron (III) which condenses with the aromatic carbonium ion gives a diol (IV) which is again readjusted by removing water molecules to form (V) (29).



(IV) (V)

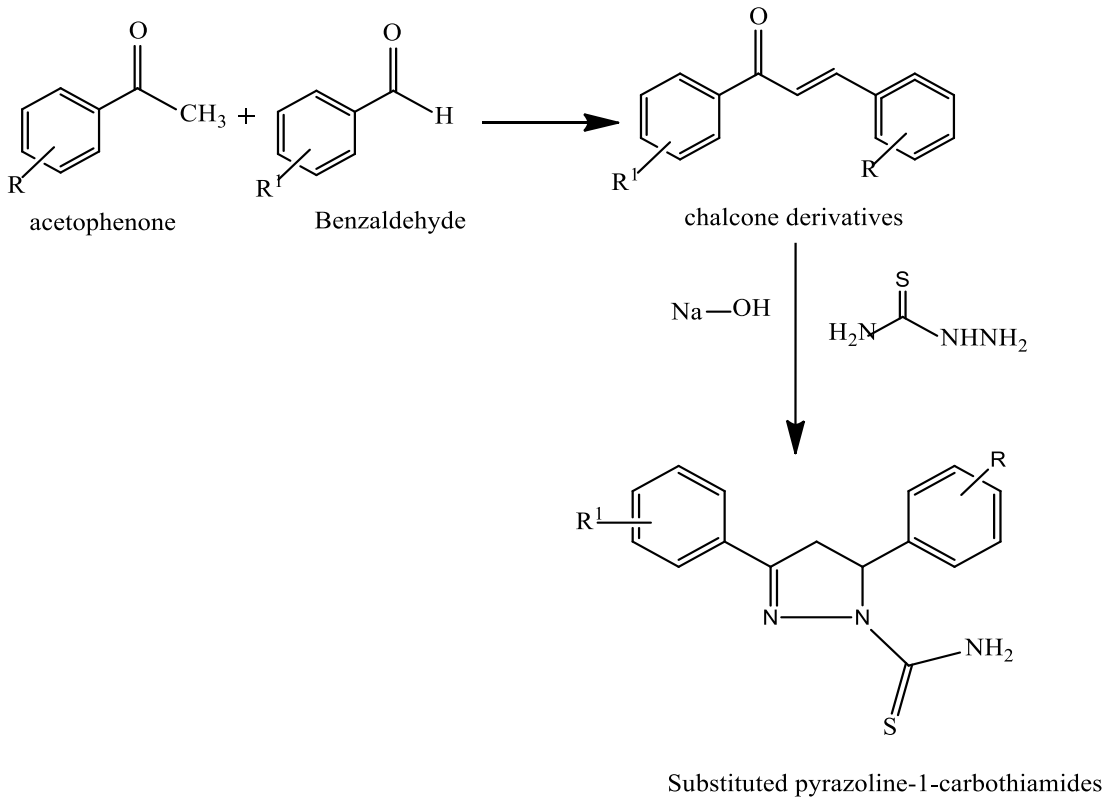
These chalcone derivatives (V) cyclized on reaction with thiosemicarbazone to give substituted pyrazoline (IV).



Methods of preparation:

Scheme 1: Pyrazoline linked with thiosemicarbazide

Abu Baker M. Osman *et al.* Substituted pyrazoline-1-carbothiamides have been synthesized using cyclization reaction of chalcones and thiosemicarbazide. These chalcones were treated with thiosemicarbazide and the new substituted 3, 5-diphenyl-4, 5-1-H-pyrazole -1-carbothioamides which are named as 2- pyrazoline derivatives were obtained which have a variety of significant and a present synthetic method is a low-cost approach (30).

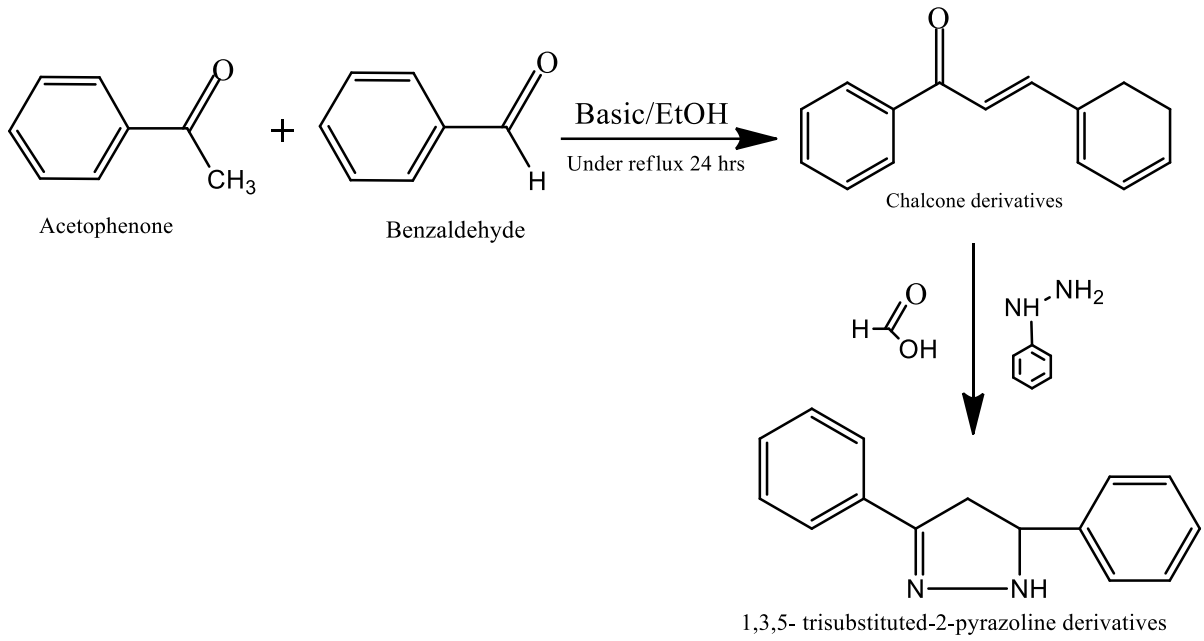


Where R and R' groups are:

R= H, 3-NO2, 4-OCH3, 4-N, N (CH3)2 and R'= H, 4-NH2, 4-NO2 and 4-Br

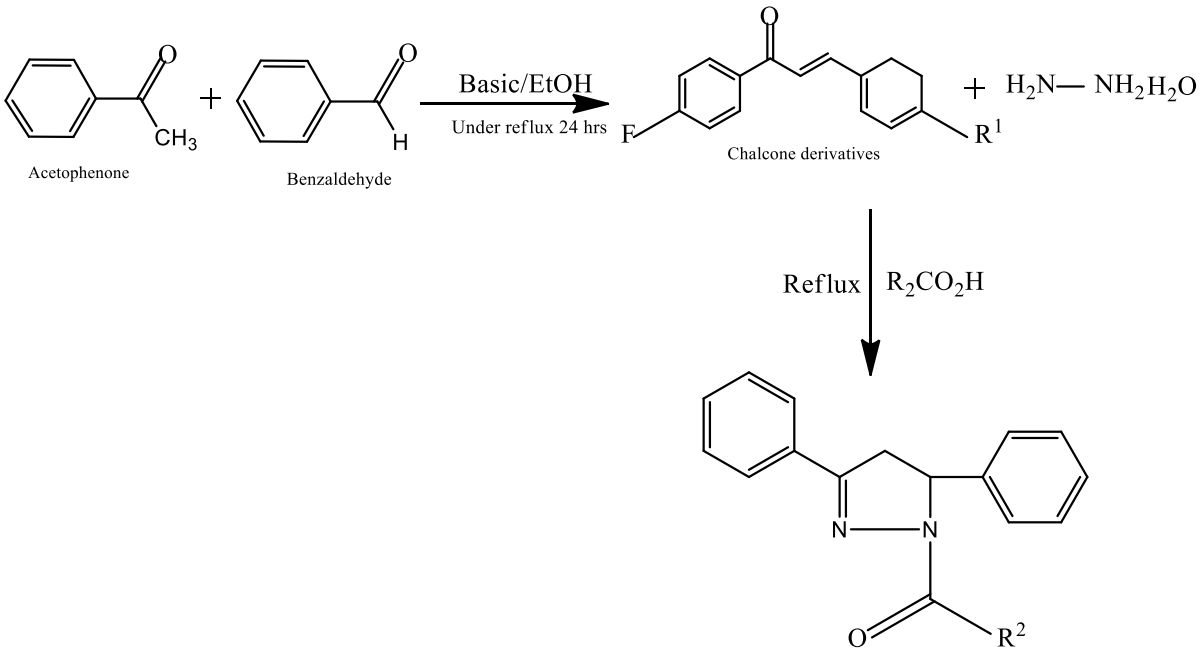
Scheme 2: Pyrazoline linked with phenyl hydrazine

Maleki *et al.*, (2009) were synthesized a series of 1, 3, 5-trisubstituted-2-pyrazoline derivatives by cyclization of phenyl hydrazine with α, β-unsaturated ketones by using methanoic acid as catalyst under normal conditions. The yield and time of the same reaction affected by different solvents and the amount of catalyst were investigated. It was found that ethanol was the best solvent and 2.5ml of the catalyst was sufficient to resolve the reaction towards the formation of 1, 3, 5-trisubstituted-2-pyrazoline derivatives in terms of time and yield (31).



Scheme 3: Pyrazoline linked with hydrazine hydrate

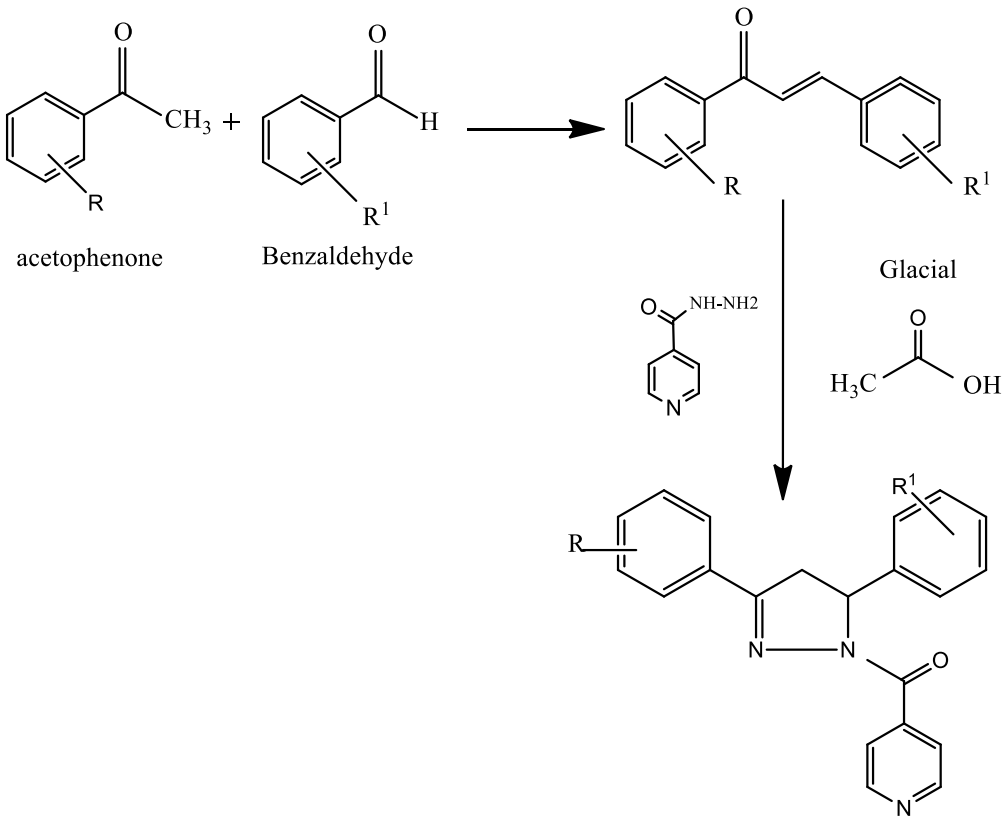
Loch *et al.*, (2013) have been synthesized a series of four pyrazole compounds namely 3-(4flurophenyl)-5-phenyl-4,5-dihydro-1Hpyrazole-carbaldehyde, 5-(4-bromophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazolecarbaldehyde,1-[5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl]ethenone and 1-[3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]propan-1-one by condensing chalcones with hydrazine hydrate by using aliphatic acids, acetic acid, and propionic acid. The structures were characterized by X-ray single-crystal structure determination (32).



Where, R^1=H, Br, Cl and R^2=H, CH_3, CH_2CH_3

Scheme 4: Pyrazoline linked with isoniazid

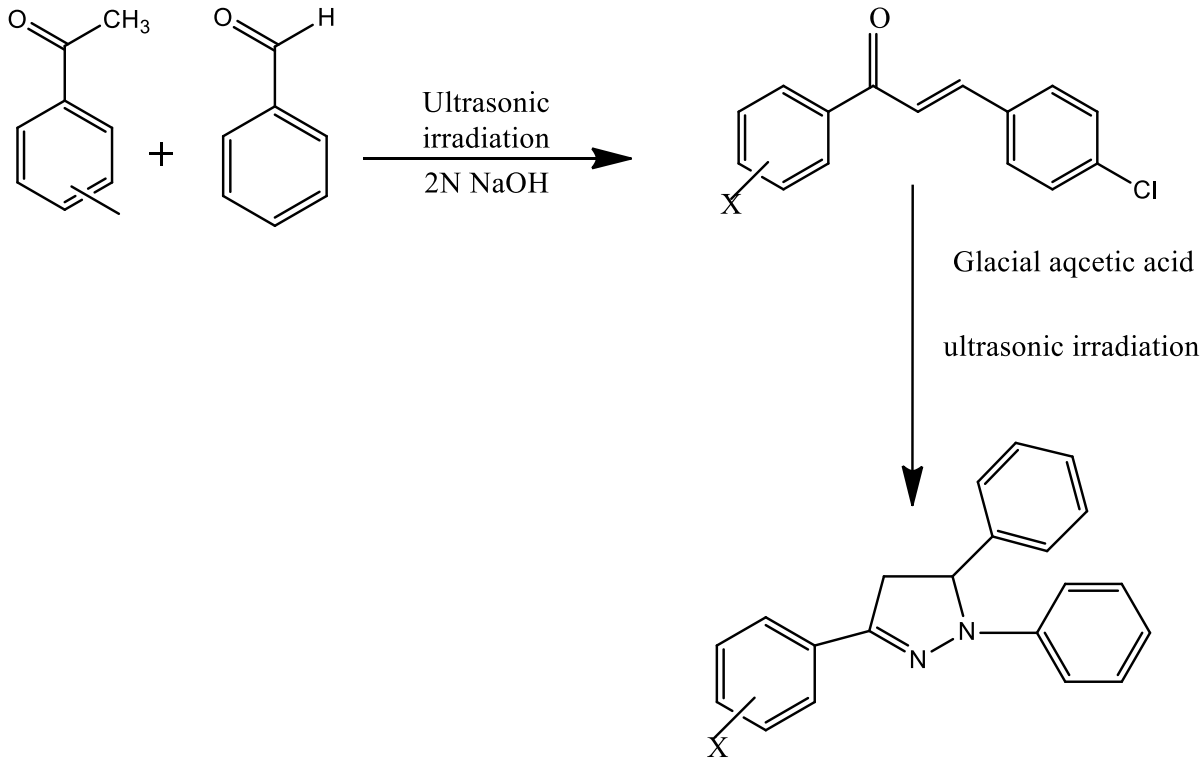
Revanasiddappa *et al.*, (2010) reported the synthesis and biological evaluation of some novel pyrazoline derivatives. First, the chalcones were prepared from substituted aldehydes and ketones in the presence of alkali NaOH and alcohol as a solvent medium. Then the chalcones were converted into 1, 3, 5-trisubstituted pyrazoline derivatives by treating with isoniazid (INH) in a glacial acetic acid medium. The structures of newly synthesized compounds were determined by spectroscopy. All the synthesized compounds were evaluated for their antibacterial and antifungal activities and it was found that most of the compounds were moderately active against both bacteria and fungi (33).



Where, R=2-furfuryl, p-CH_3, p-Cl, C_6H_5, p-OCH_3, 2-Thiophene, m-NO_2, p-(CH_3)2-N, p-OCH_3, p-Cl, p-OH, p- NO_2, C_6H_5, p-Br.

Scheme 5: Pyrazoline linked with phenyl hydrazine under ultrasonic irradiation

Gupta *et al.*, (2010) represented a new, synthesis of chalcones and pyrazolines by the ultrasonic method. This is a two-step process. In the first step, 1, 3-diary prop-2-en-1-ones were prepared by Claisen-Schmidt condensation of aryl methyl ketones and 4-chlorobenzaldehyde in the presence of sodium hydroxide under ultrasonic irradiation. In the second step, synthesis of 2-pyrazolines was performed by glacial acetic acid under ultrasonic irradiation at a 25-45°C temperature within 25-150 minutes. It had been noticed that in the conventional method, the mixture of chalcone, phenyl hydrazine, and glacial acetic acid was refluxed at 30-40°C for 3-4 hours to produce 2-pyrazolines in 70% yield. Though when this reaction was carried out under sonication, the reaction completed rapidly within 30 minutes and the yield was 80%. The synthesized compounds were screened for their antimicrobial activity against bacteria and fungi and they showed good activity (34).



Where, X=4-H, 4-Br, 4-Cl, 4-F, 4-CH_3

Chemical used for synthesis:

1. Benzaldehyde

2. Acetophenone

3. Ethanol

4. Glacial acetic acid

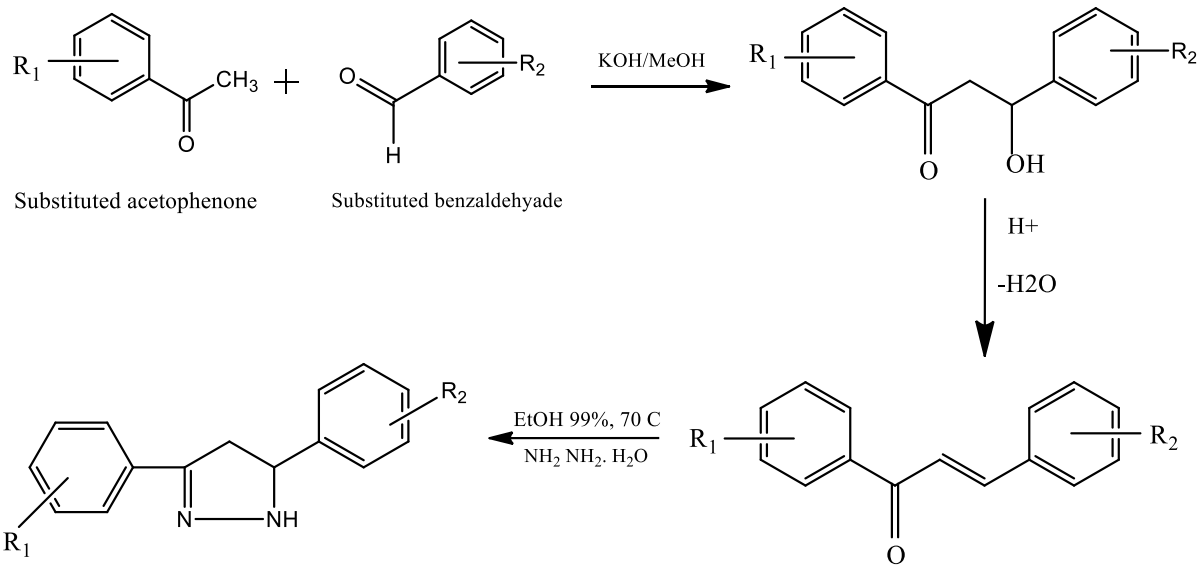
5. Hydrazine hydrate

6. Methanol

7. Hydrochloric acid

SYNTHESIS OF PYRAZOLINE DERIVATIVES-

The name Pyrazole was given by Ludwig Knorr in 1883 and refers to the class of simple aromatic ring organic compounds of the heterocyclic series, characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions (35).



Pyrazoline

Chalcone

a: R_1= 2'-OH, 4'-OCH_3 ; R_2= 3-OCH_3, 4-OCH_3

b:R_1= 4'-NO_2 ; R_2= 4-$N(CH_3)_2$

c: R_1= 2'-OH ; R_2= 2-OCH_3, 4-OCH_3

Scheme for the synthesis of pyrazoline

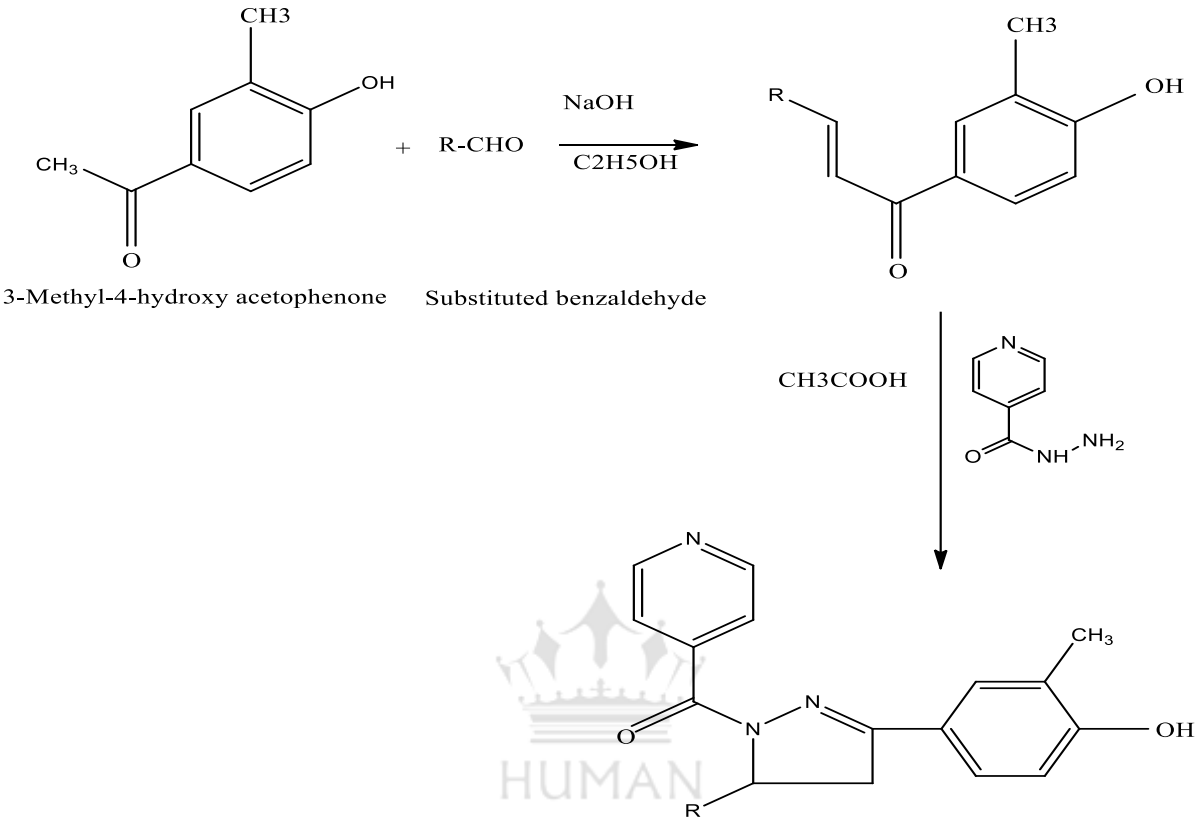
In the 19th century, Fischer and Knoevenagel synthesized and characterized 2-pyrazolines, by simple reflex reaction of α, β-unsaturated aldehydes, and ketones with phenyl hydrazine in acetic acid. A variety of methods exist for the synthesis of pyrazoline derivatives (36).

Tan Nhut Doan *et al*, have synthesized various pyrazoline (figure.1) by the reaction of respective chalcones and hydrazine hydrate in presence of 99% ethanol at 70℃ for 7 hours. They evaluated the anti-microbial and antioxidant activities (37).

Nagihan Beyhan has synthesized various 3,5-disubstituted-4,5-dihydro-1H-pyrazole-1-carbothioamides by refluxing selected chalcones and thiosemicarbazone in an alkaline medium. Similarly, N-3,5-trisubstituted -4,5-dihydro-1H-pyrazole-1-carboxamides were synthesized by refluxing selected chalcones with N-(4-chlorophenyl) semicarbazide in an alkaline medium. They evaluated the anticonvulsant activity of the synthesized compounds using pentylenetetrazol-induced seizure (PTZ) and maximal electroshock seizure (MES) tests (38).

Mohammad. Shaharyar *et al*, have reported an efficient method for the synthesis of pyrazoline derivatives by condensing chalcones with Isoniazid giving a series of N1-

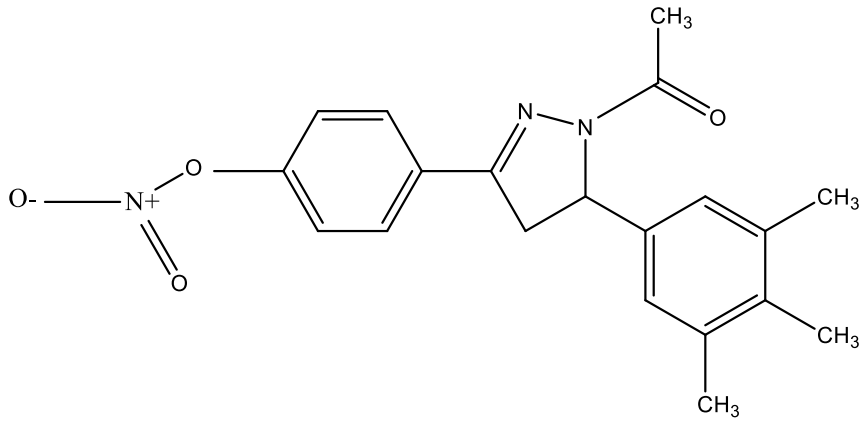
isonicotinoyl-3-(4'-hydroxy-3'-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines and were tested for their in-vitro antimycobacterial activity against Mycobacterium tuberculosis H37Rv (Mtb) and INH-resistant M. tuberculosis (INHR-MTB) using the agar dilution method (39).



Synthesis of N1-isonicotinoyl-3-(4'-hydroxy-3'-methyl phenyl)-5-(substituted phenyl)-2-pyrazoline

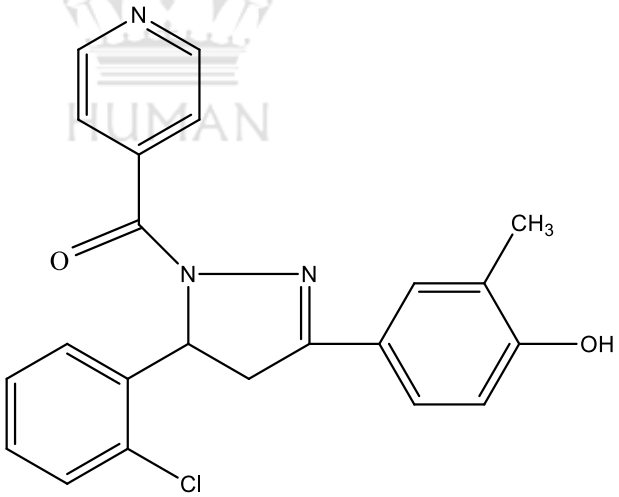
Biological activities of Pyrazoline-

1. Pyrazoline as an antimicrobial agent- Dilish Indarkar *et al* have synthesized 1-acetyl-3-(4-nitro phenyl)-5-(substituted phenyl)-2-Pyrazoline (Figure 6) derivatives and evaluated their antimicrobial activity. In this study a series of structurally related 1,3,5- trisubstituted-2-Pyrazoline have been synthesized by introducing furan rings regarded as bioactive substructure into the Scaffold of pyrazoline and tested for their activities against six plant pathogenic fungi in vitro. The preliminary bioassays indicated that almost all synthesized compounds had displayed variable growth inhibitory effects on the tested pathogenic fungi (40).



1-acetyl-3-(4-nitrophenyl)-5-(3,4,5-trimethyl phenyl)-2-pyrazoline

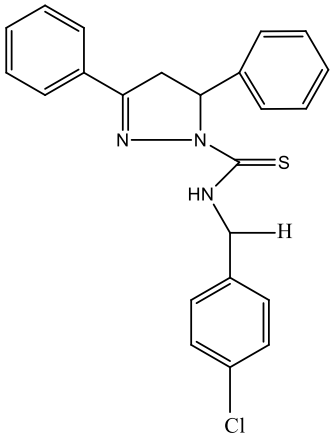
2. Pyrazoline as antitubercular agent-: Mohammad. Shaharyar *et al* have synthesized and reported the in-vitro anti-mycobacterial activity of N^1- isonicotinoyl-3-(4^1- hydroxy-3^1-methyl phenyl) -5-(substituted phenyl)-2-Pyrazolines. Among the synthesized compounds, compound N^1nicotinyl-3 (4^1-hydroxy-3^1-methyl phenyl)-5-(2- chlorophenyl)-2-pyrazoline (Figure 7) was found to be the most active agent against MTB and INHR-MTB, with the minimum inhibitory concentration of 0.26µm (41).



N^1 isonicotinoyl-3-(4^1-hydroxy-3^1-methyl phenyl)-5-(4-fluorophenyl)-2-Pyrazoline

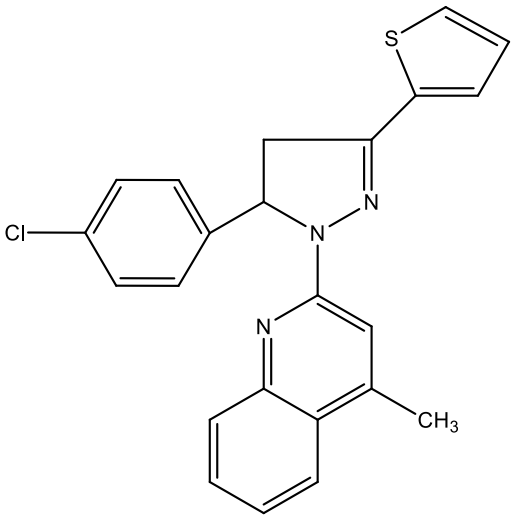
3. Pyrazoline as Anti-inflammatory agent- R. Surendra Kumar *et al* has reported some novel pyrazole analogs from condensation technique utilizing ultrasound irradiation. Synthesized compounds were screened for anti-inflammatory activity and the compound 2-[(5-hydroxy -3-methyl-1H-pyrazole-4-yl) (4- nitrophenyl) methyl] hydrazine carboxamide showed better anti-inflammatory activity when compared with standard drug (Diclofenac sodium) (42).

Harathi *et al* have synthesized various 3,5-diphenyl -4,5-dihydro-pyrazole-1-carbothoic acid amide (Figure 8) using respective chalcones and thiosemicarbazide. Compounds with electron-withdrawing groups cl, No_2 exhibited better anti-inflammatory activity (43).



N-[(E)-(4-Chlorophenyl) mrthylidine]-3,5-diphenyl-4,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbithioamide

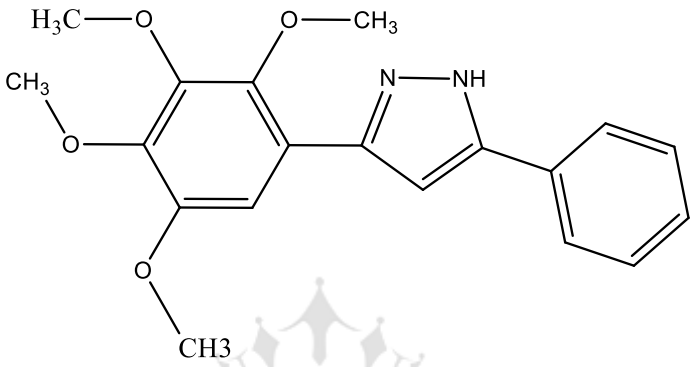
4. Pyrazoline as Anti-malarial agent- Shilpy Aggarwal *et al* synthesized a series of 1,3,5-trisubstituted pyrazoline (Figure 9) and were screened for in-vitro schizont maturation assay against chloroquine (CQ) sensitive 3D7 strain of plasmodium falciparum. Most of the compounds showed Promising in-vitro antimalarial activity against CQ sensitive strain. SAR study showed that quinoline substitution at position N-1 showed maximal activity and compounds having an electron-withdrawing group at p- position on phenyl ring displayed better antimalarial activity than electron releasing group (44).



2-[5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl]-4-methylquinoline

5. Pyrazoline as anticancer agent- Fadi M. Awadallah *et al* synthesized two series of 2-(3,5- diaryl-4,5-dihydropyrazol-1-yl)-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitriles and 4-(4- chlorophenyl)-2-(3,5-diaryl -4,5-dihydropyrazol-1-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitriles.The target compounds were screened for their antiproliferative activity against A 549 (lung), HT 29 (colon), MCF 7 and MDA-MB 231 (breast) cell lines (45).

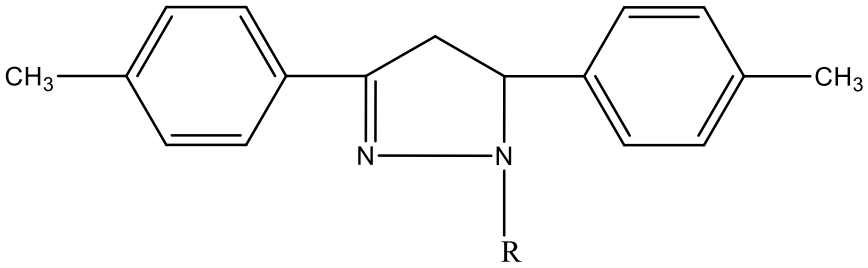
Bhat *et al* were synthesized a series of substituted pyrazoles and also evaluated for in-vitro cytotoxic activity against a panel of human cancer cell lines. They concluded that pyrazoles such as 3,5- diphenyl,1H-pyrazole (Figure10) are potent cytotoxic agents (46).



5-(4-fluorophenyl)-3-(2,3,4,5- tetramethoxyphenyl)-1H-pyrazole

6. Antidiabetic activity:

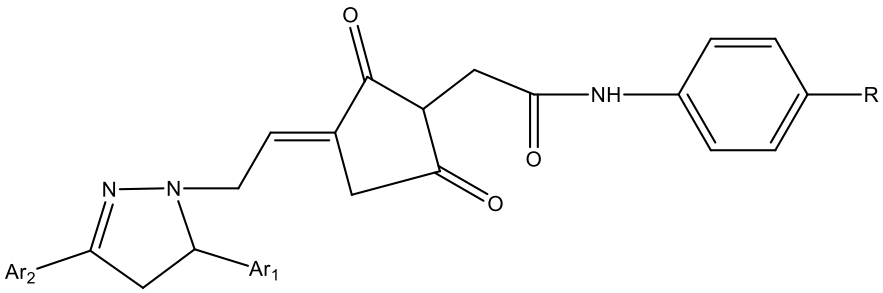
N. Santhi *et al* prepared 1,3,5- triaryl-2-pyrazolines and studied their antidiabetic activity and were found to be a better hypoglycaemic agent compared with standard drug insulin in reducing the blood glucose level.



Where, R=$CONH_2$, $CSNH_2$, C_6H_5, SO_2, COC_6H_5

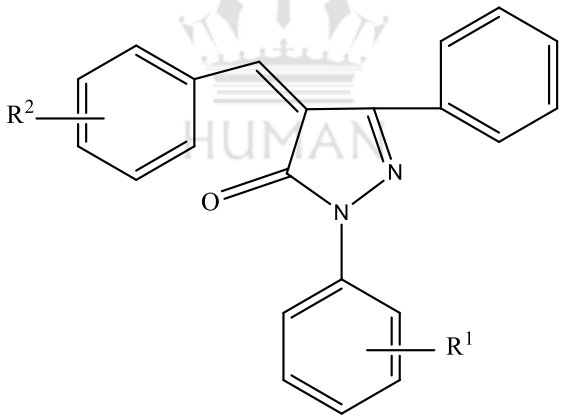
7. Antiviral activity:

Pyrazolines were analyzed by antiviral activity. Thiazolidinonepyrazoline hybrids (2a) were synthesized by **D Havrylyuk *et al*** and the antiviral activity of synthesized compounds was determined (47).



Where, Ar_1=4-Cl-C6H5, 4-OMe-C6H5 Ar_2=Ph, naphthalene-2-yl R=Me, OMe, Cl

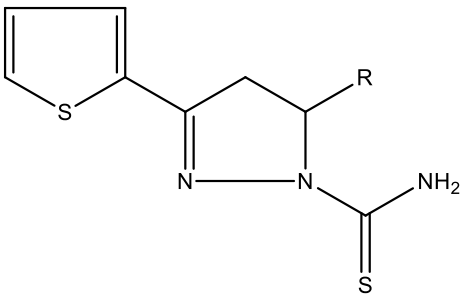
The compounds presented insignificant activities against the four strains of the influenza virus. **Ramajayam *et al*** demonstrated the potency of synthesized pyrazolines (2b) as protease inhibitors of the SARS virus (48).



Where, R^1= H, 4-Cl, 4-OCH_3, 4-$CH(CH_3)_2$, 4-$C(CH_3)_3$, 4-CN, 4-OCF_3, 4-CN, 4-OCH_3, 4-Cl, 3,4-Cl_2, 4-F, 3-NO_2, and R^2= H, 3-OCH_3, 3-NO_2, H, 4-Cl, 4-OCH_3, 4-OH, 4-COOH

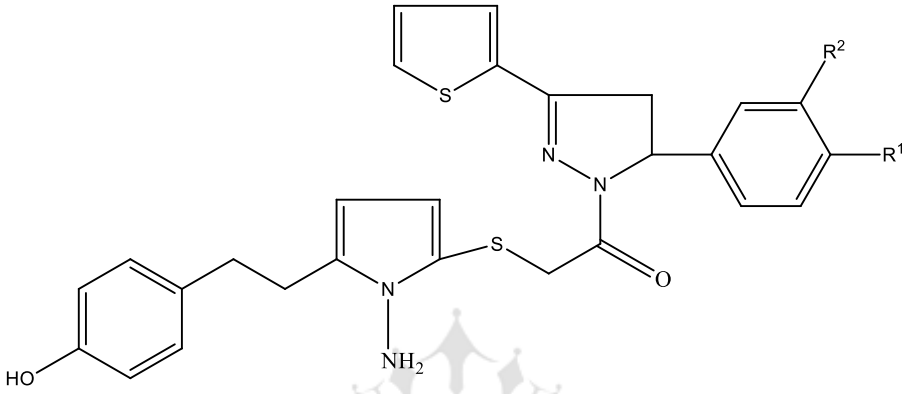
8. Antidepressant activity: Depression is a central nervous system disorder. Pyrazolines have been found to develop antidepressant potential.

Bijo Mathew *et al* synthesized thiophene containing pyrazoline carbothioamides (3a) with promising antidepressant action. It was revealed that they exhibit a typical reduction in immobility in the forced swim test by increasing the swimming behavior (49).



Where, R=Phenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-nitrophenyl, 2-hydroxyphenyl, 4-hydroxyphenyl, 4-N,N-dimethylphenyl

Kaplancikli *et al* studied the antidepressant activity of synthesized triazolo pyrazolines 3(b) (50).

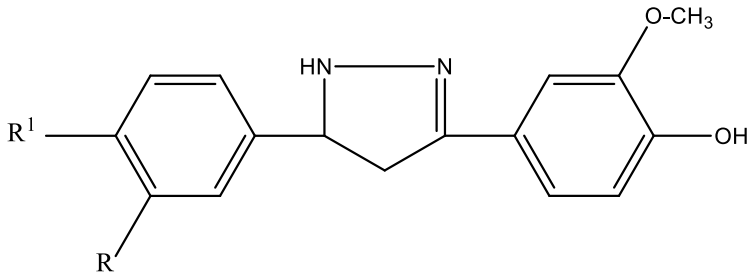


Where, R_1= H, F, Cl, CH_3, $N(CH_3)_2$, O-CH_2-O R_2=H

9. Antioxidant activity:

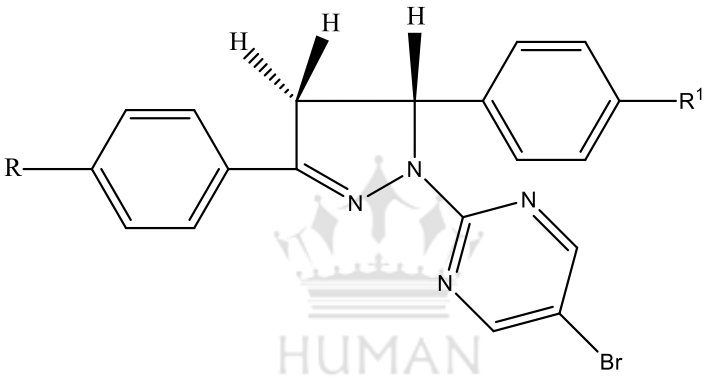
Antioxidants are substances that may protect cells from damage due to unstable molecules named free radicals.

A Kumar *et al* synthesized 3,5-disubstituted -2-pyrazolines 4(a) and were screened for antioxidant activity using DPPH radical scavenging method, No scavenging assay, superoxide radical scavenging assay, and hydrogen peroxide radical scavenging assay. All the compounds showed good free radical scavenging activity which is comparable to that of the standard ascorbic acid (51).



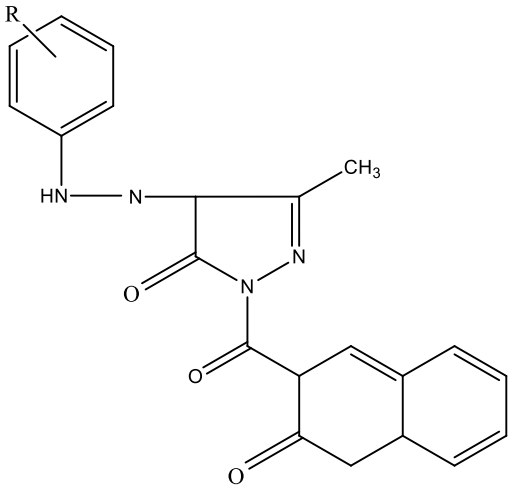
Where R= H, CH_3, Br, Cl, OH, OCH_3 and R^1= H, CH_3, Br, Cl, OCH_3, NO_2

4,5-dihydropyrazolines carrying pyrimidine moiety 4 (b) were prepared by **A. Adhikari *et al*** under conventional heating as well as microwave reaction condition. Newly synthesized pyrazolines were screened for their free radical scavenging activity by the DPPH method (52).



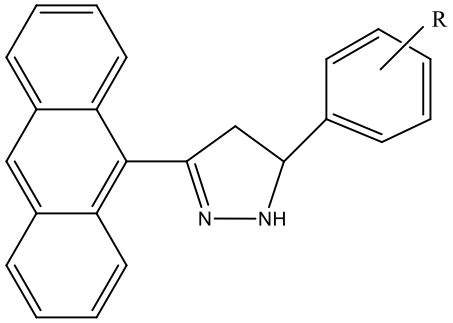
Where R= H, Br, Cl and R^1= CH_3, Br, Cl, OCH_3, NO_2

A new series of coumarin fused pyrazoline-5-one derivatives 4 (c) were developed by P. Venkatesh *et al* and examined for antioxidant activity by DPPH and Nitric oxide methods. Compound 2 acquires antioxidant activity in both methods.



10. Acetylcholinesterase Inhibitory activity:

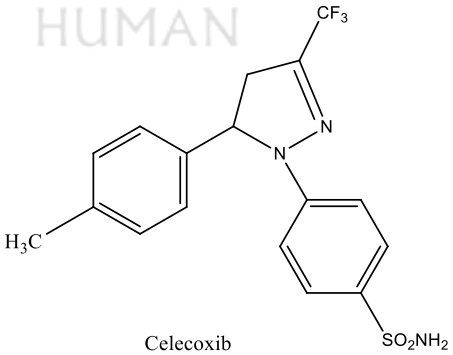
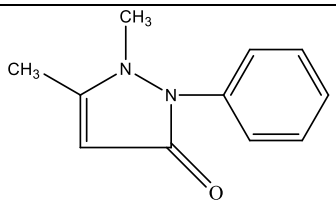
The acetylcholinesterase inhibitory property of diaryl pyrazoline derivatives 5 (a) studied by **Nibha Mishra *et al*** (53).

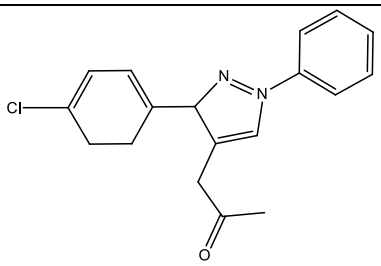
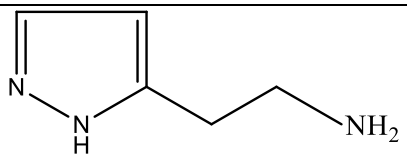
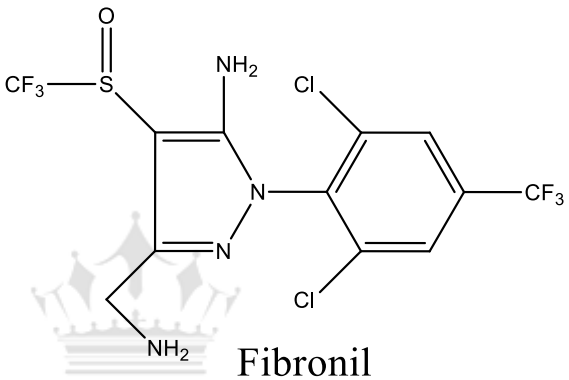
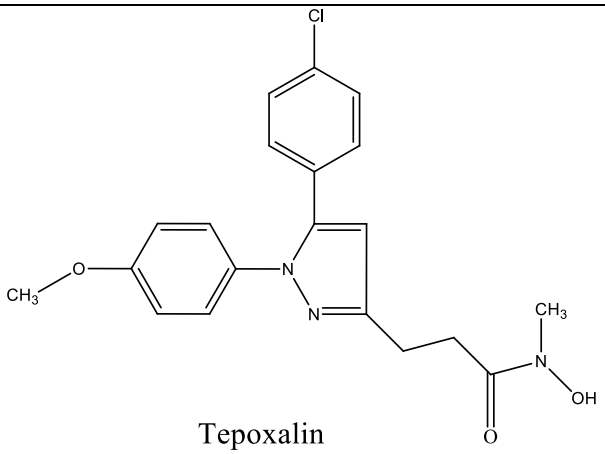


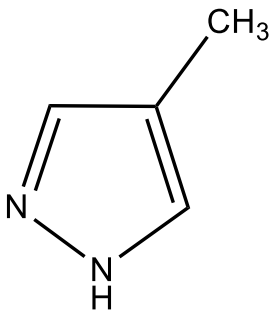
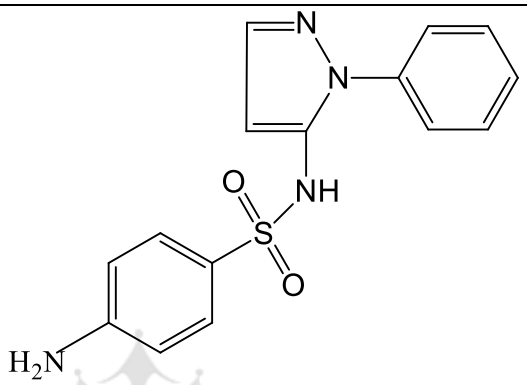
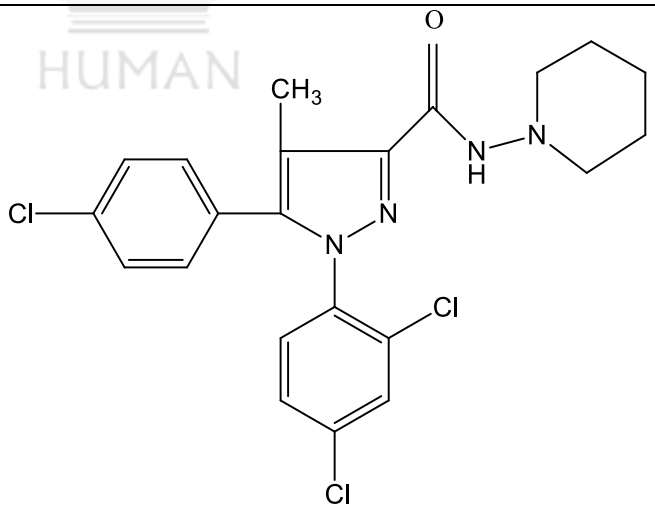
Where, R= 4-NO_2, 4-OH, 4-Cl, 4-CH_3, -H, 2-OH, 2,4-Di-OH, 3-NO_2, 4-OCH_3

Due to its wide range of biological activity, the pyrazole ring constitutes a relevant synthetic route in the pharmaceutical industry. Such a heterocyclic moiety represents the core structure for several drugs. Some of the marketed products of the pyrazole nucleus are listed below.

Table no 1: Marketed products containing Pyrazole moiety.

MARKETED DRUG	STRUCTURE
Celecoxib is a Non-Steroidal Anti-inflammatory Drug (NSAIDs) used in the treatment of rheumatoid arthritis, osteoarthritis, acute pain, menstruation.	 Celecoxib
Phenazone, (phenazone or antipyrine) is used as an analgesic and antipyretic.	 Phenazone

Lonazolacis used as a Non-Steroidal Anti-inflammatory Drug.	 Lonazolac
Betazole is a H_2 receptor agonist. It is used clinically to test gastric secretory function.	 Betazole
Fipronil is a broad-spectrum insecticide that disrupts the insect central nervous system by blocking the passage of chloride ions through the GABA receptor and glutamate-gated chloride channels, components of the central system.	 Fibronil
Tepoxalin is a NSAIDS approved for veterinary use.	 Tepoxalin

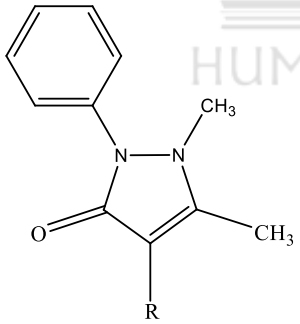
Fomipazole or 4- methyl pyrazole is indicated for use as an antidote in confirmed or suspended methanol or ethylene glycol poisoning. Apart from medicinal uses, the role of 4-methyl pyrazole in coordination chemistry has been studied.	 Fomipazole
Sulfaphenazole contains a sulphonamide group which is used as antibacterial.	 Sulfaphenazole
Rimonabant is an anorectic anti-obesity drug. Its main avenue of effect is the reduction in appetite.	

A systemic investigation of this class of heterocyclic compounds revealed that pyrazole agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic leads.

APPLICATION OF PYRAZOLINE DERIVATIVES: Various pyrazoline derivatives are widely used as an intermediate in the synthesis of pharmaceuticals, medicines, and other organic compounds.

- Pyrazoline is used as an antimicrobial, antitumor, antibacterial agent.
- One of the important applications of pyrazoline is the use of pyrazolines as a fluorescent brightening agent.
- Pyrazoline is widely used as a useful substrate in organic synthesis.
- Pyrazoline derivatives play an important role in the field of synthetic and medicinal chemistry.

Pyrazoles and their derivatives have attracted much attention due to their diverse biological properties (54). Pyrazoles itself several N-substituted pyrazoles are inhibitors and deactivators of liver alcohol dehydrogenase (55-57). The oldest pyrazole derivatives, which have been widely used in medicine as analgesic and antipyretic, are antipyrine (1; 2,3-dimethyl -1-phenyl-3-pyrazolin-5-one) (58). However, aminopyrine (2; 4-dimethylamino derivative of antipyrine) (59) and novalgin 3; (60) have been found to possess better analgesic properties than antipyrines.

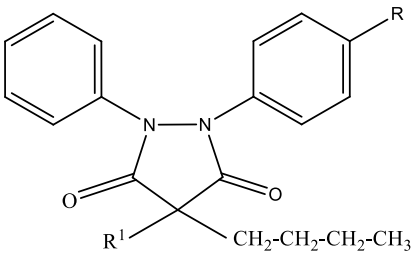


1 R=H
2 R=$N(CH_3)_2$
3 R=$N(CH_3)CH_2SO_3Na^+$

Phenylbutazone (4; 4-n-butyl-1,2-diphenyl-3,5-pyrazolidinedione) (61) is one of the most widely used anti-inflammatory agents. However, prolonged therapy with 4 creatives some medical complications such as headache, vertigo and often causes gastrointestinal disorders (62).

Oxyphenbutazone 5; a metabolite of 4, though less toxic than 4 possesses anti-inflammatory properties comparable to 4 (63). Similarly, hydroperoxide 6; (64) obtained by oxidation of phenylbutazone 4 with di-t-butyl peroxalate was found to possess stronger cardiac depressant and coronary constricting activity than 4 and 5 and was also devoid of side effects. Kebuzone 7; (65) which is widely used in Europe, is another anti-inflammatory agent in which 4-n-butyl

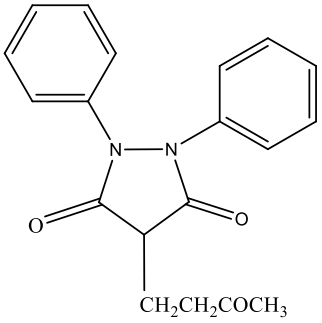
group phenylbutazone has been replaced by a 3-ketobutyl substituent. Pyrazole 8; 1-(4-fluorophenyl)-4-(4-chlorophenyl)-3-pyrazolylacetic acid (66) has been reported to possess an impressive level of anti-inflammatory activity.



4 R= H, R'= H

5 R= OH, R'= H

6 R=H, R'= OH



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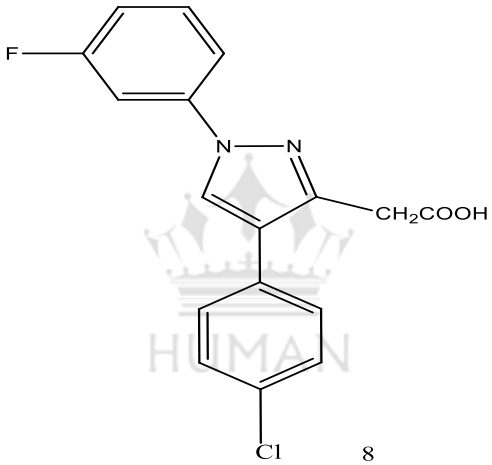
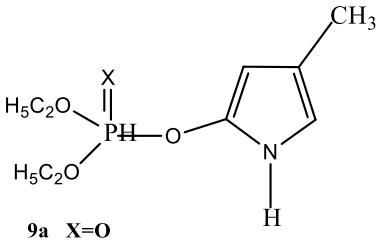
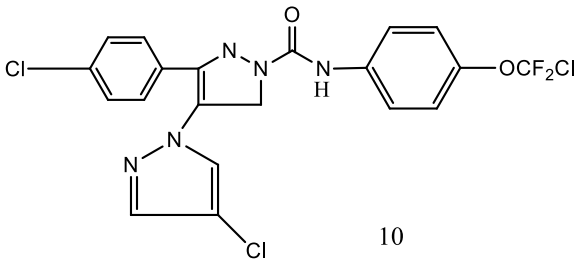


8

Besides, these pyrazole derivatives have found applications in the agrochemical field as insecticides(9a-9b) (67) both having a pyrazole ring, constitute a good example of compound safer and use insecticides. 9 used as pesticides (68-69) and 10 and 11 as herbicides (70-71).



9a X=O
9b X=S



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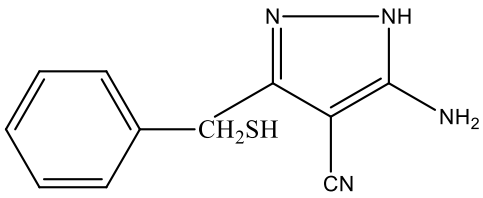
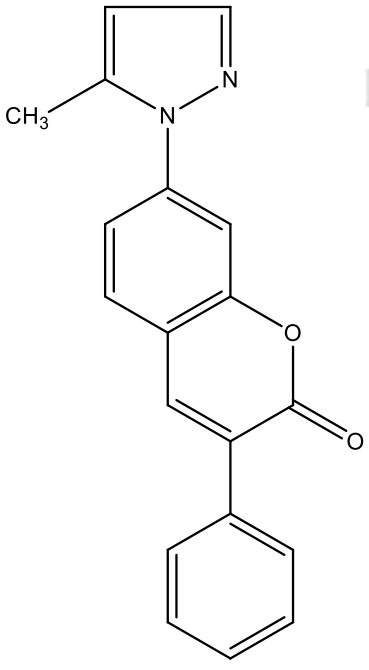


11

Some pyrazole derivatives 12 and 13 (72) have been used as optical brighteners which are colourless fluorescent dyestuffs that absorb in the near UV region 350-390 nm and fluorescence in the violet to blue region 425-445 nm of the visible portion of the electromagnetic spectrum, 5-pyrazolone derivatives such as Oxanthrene orange 13 and pyrazole orange 14 (73) have found application as cotton azo dyes.



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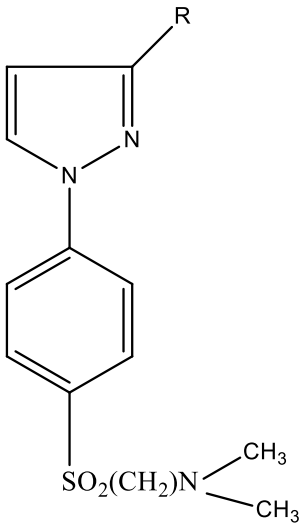

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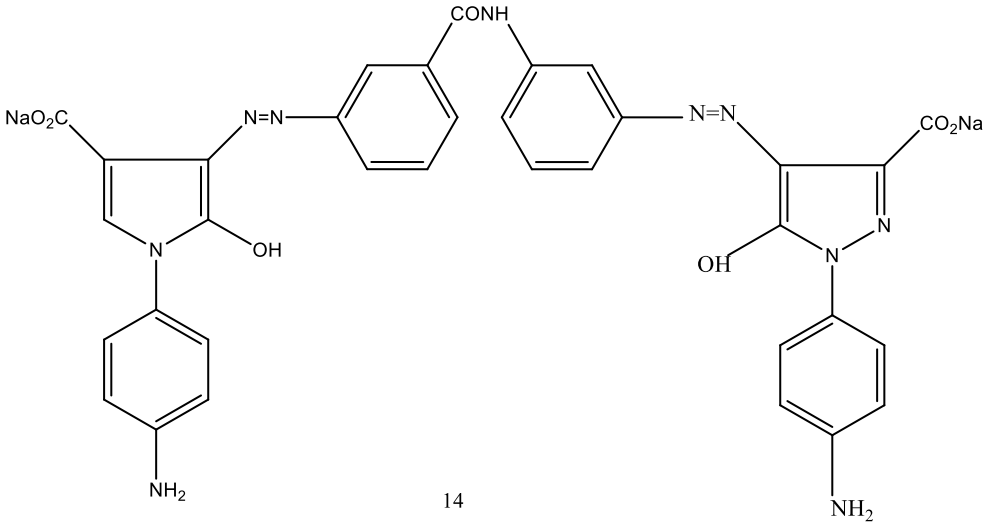

14

SUMMARY:

Pyrazoline is well known and popular nitrogen consist of 5-membered heterocyclic compounds and several methods have been developed for their synthesis. Various pyrazoline derivatives have been found to report considerable biological activities, which accelerated the research activity in this field. It is a brief review of different methods for the synthesis of biologically active pyrazoline derivatives. The literature review shows that pyrazoline derivatives are pharmacologically very potent and therefore their design and synthesis is the potential area of research. Previous studies have shown that the structural modification on the different positions of the basic molecule allows for improving its pharmacological profile, giving it antimicrobial, anticonvulsant, analgesic, anti-inflammatory, anti-viral, anti-malarial, and anti-cancer properties. Pyrazolines are well-known and popular nitrogen consists of the 5-membered heterocyclic compound and several methods have been developed for their synthesis. Various pyrazoline derivatives have been found to report considerable biological activities, which accelerated the research activity in this field. It is a brief review of different methods for the synthesis of biologically active pyrazoline derivatives.

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