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REVIEW ON SYNTHESIS OF PYRAZOLINE DERIVATIVES AND ITS BIOLOGICAL ACTIVITIES

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Abstract:

Pyrazolines are prominent nitrogen-containing heterocyclic compounds and hence, various procedures have been accomplished for their synthesis. Fischer and Knoevenagel i.e. the reaction of α, β-unsaturated ketones treat with phenylhydrazine in acetic acid under refluxing condition. it is one of the most popular methods instead of other various methods for the synthesis of pyrazolines. Though, They had synthesized the pyrazolines under various solvent media and acidic or basic conditions based on the reactivity of molecules and the need of the chemist.

The synthesis of novel pyrazoline derivatives and the investigation of their chemical and biological behavior has gained more importance in recent decades. Earlier, modifications of the pyrazoline ring have proven highly effective along the improved potency and lesser toxicity. The analyzed review provides an accelerated view of work done so far on pyrazoline and its biological activities covering anticancer, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory, and antitubercular activities.

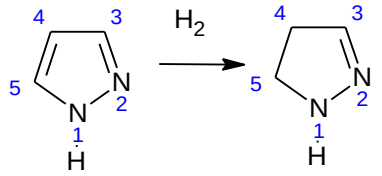
Keywords: Pyrazoline, Claisen-Schmidth Condensation, Mechanism, Scheme, Pharmacological Activity.

Introduction:

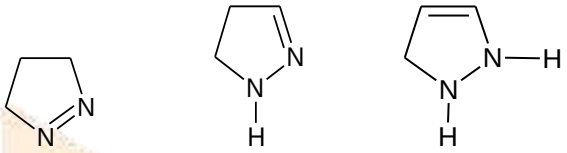
Pyrazole is an extended heterocyclic compound which is a five-membered ring consists of two nitrogen atoms in adjacent position and also contains two endocyclic double bonds as represented by the molecular formula $C_3H_6N_2$. It is a weak base, with pKb 11.5 (pKa of the conjugated acid 2.49 at 25°C)[1]. Pyrazoline is dihydro pyrazole bearing only one endocyclic double bond. Depending on the position of the double bonds, there are three forms of pyrazoline are possible such as 1- pyrazoline, 2-pyrazoline, and 1, 3- pyrazoline.

Between all the pyrazolines, 2-pyrazoline has gained attraction and is frequently studied one[2].

Nomenclature: The application of present heterocyclic nomenclature to pyrazolines reports that nitrogen atoms be numbered one and two in each structure. Substituted 1-pyrazolines are categorized to yield the lower of two possible numbers for substituent group locants, or in the case of complicated structures to produce the simplest name persistent with clarity of meaning. The numbering of the 2-pyrazolines begins with the amino nitrogen and 3-pyrazolines are numbered to obtain for the double bond the lower of the two possible numbers[3].



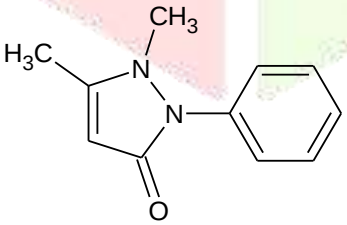
pyrazole **pyrazoline**



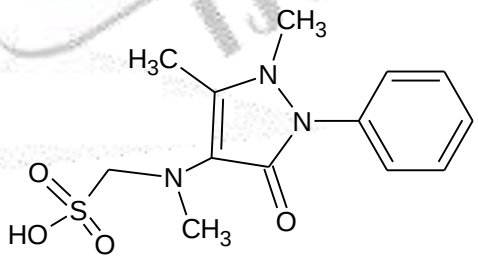
1-pyrazoline **2-pyrazoline** **1,3-pyrazoline**

The above three structure represents the tautomeric forms of pyrazoline structures.

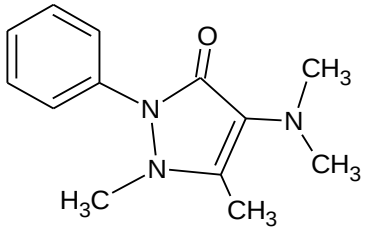
Pyrazole and 2-pyrazoline are recorded to acquire a wide range of biological activities. Several functions of pyrazole derivatives have already found as NSAIDs clinically like Antipyrine or phenazone (analgesic and antipyretic), Metamizole or dipyrone (analgesic and antipyretic), Aminopyrine or aminophenazone (anti-inflammatory, analgesic and antipyretic), Phenylbutazone or bute (anti-inflammatory, antipyretic mainly used in Osteoarthritis, Rheumatoid arthritis, Spondylitis, Reiter's disease), Sulfinpyrazone (Chronic gout), Oxyphenbutazone (antipyretic, analgesic, anti-inflammatory, mild uricosuric).



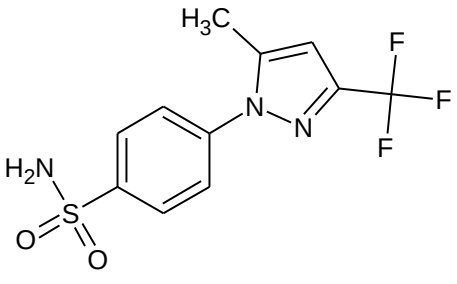
Phenazone(Antipyrine)



Metamizole(Dipyrone)

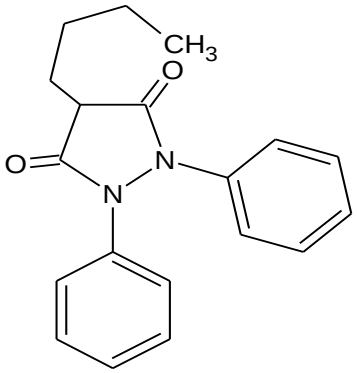


Aminophenazone

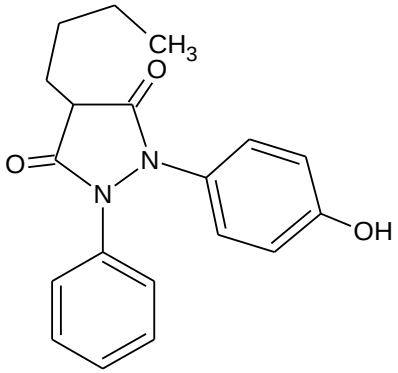


Celecoxib

some of the pyrazole and 2-pyrazoline derivatives are represented which are reported to possess analgesic and anti-inflammatory activity by many researchers[4].



Phenylbutazone



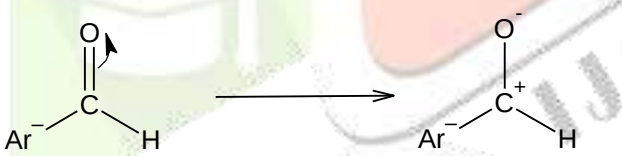
Oxyphenbutazone

Chemistry: Pyrazoline is a derivative of chalcone has also been represented to display a broad spectrum of potential pharmacological activities[5]. 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 Aldol condensation reaction. These condensation reactions are important in organic 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[6].

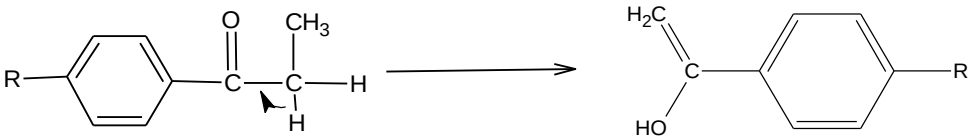
Mechanism:

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



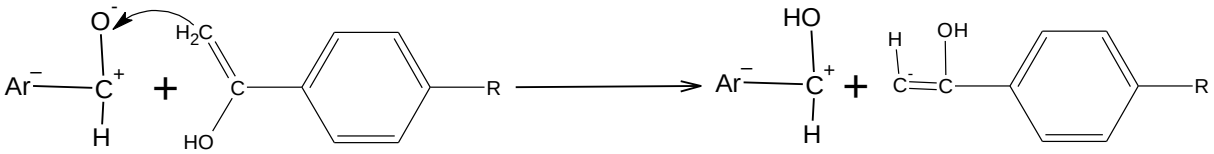
(I)

Acetophenone derivative is readjusted into its enolic form(II) by using strong alkali.



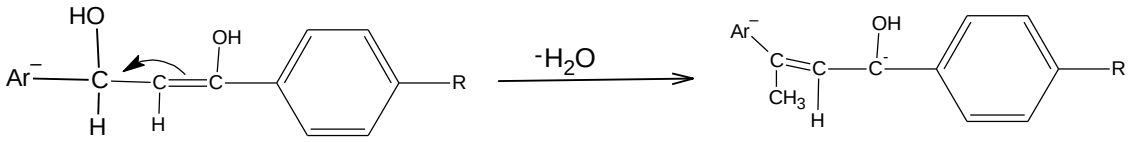
(II)

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



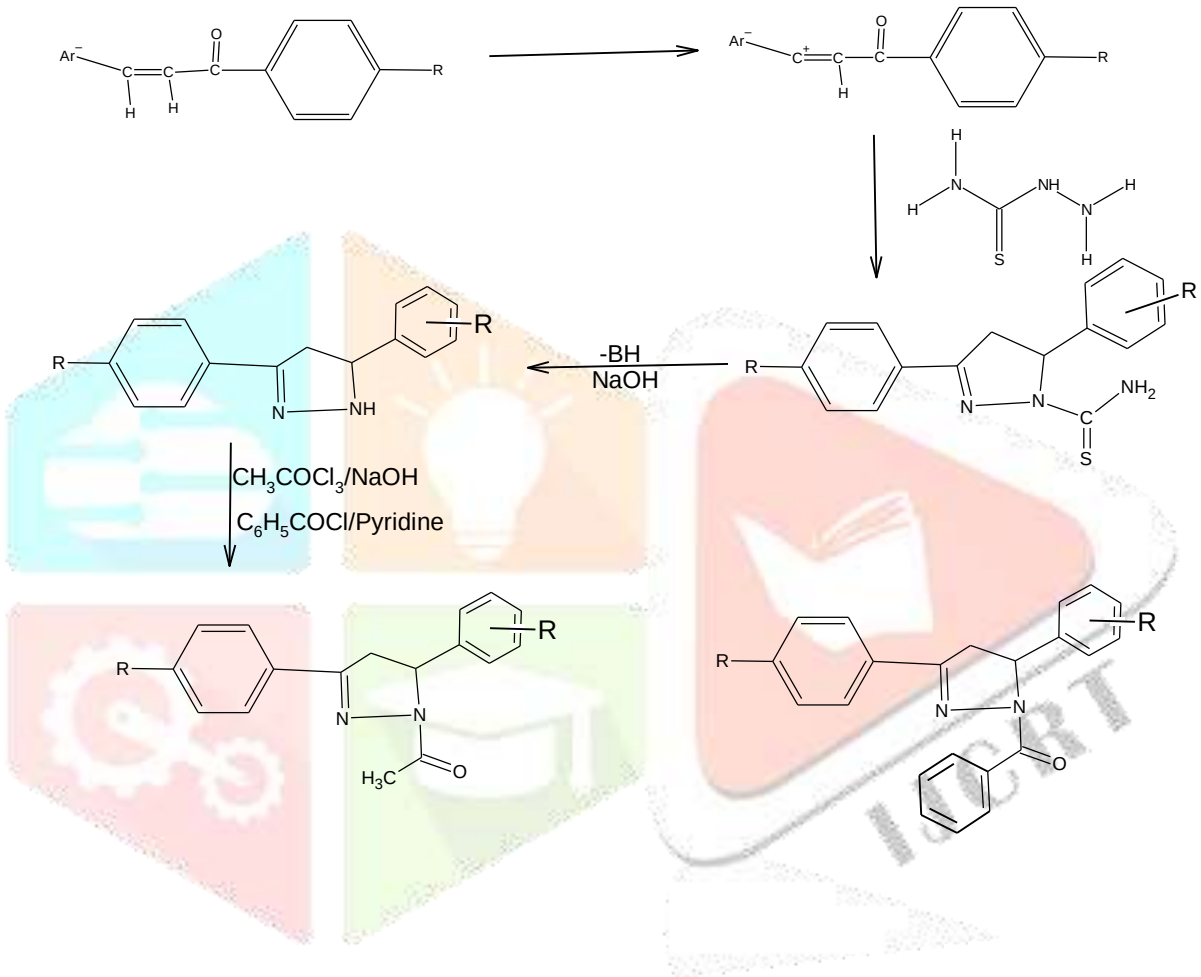
(III)

The carbanion ion(III) which condenses with the aromatic carbonium ion gives a diol(IV) which again readjusted by removing water molecules to form chalcones(V)[7].



(IV) (V)

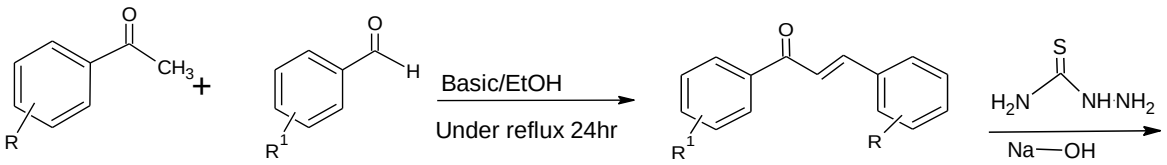
These chalcone derivatives(V) cyclised on reaction with thiosemicarbazide to give substituted pyrazoline(IV).



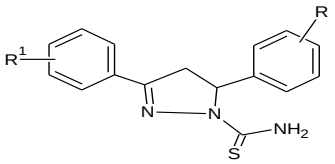
Methods Of Preparation:

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-dihydro-1-H-pyrazole-1-carbothioamides which are named as 2-pyrazoline derivatives were obtained which have a variety of significant and the present synthetic method is a low cost approach[8].



Acetophenone Benzaldehyde Chalcone derivatives



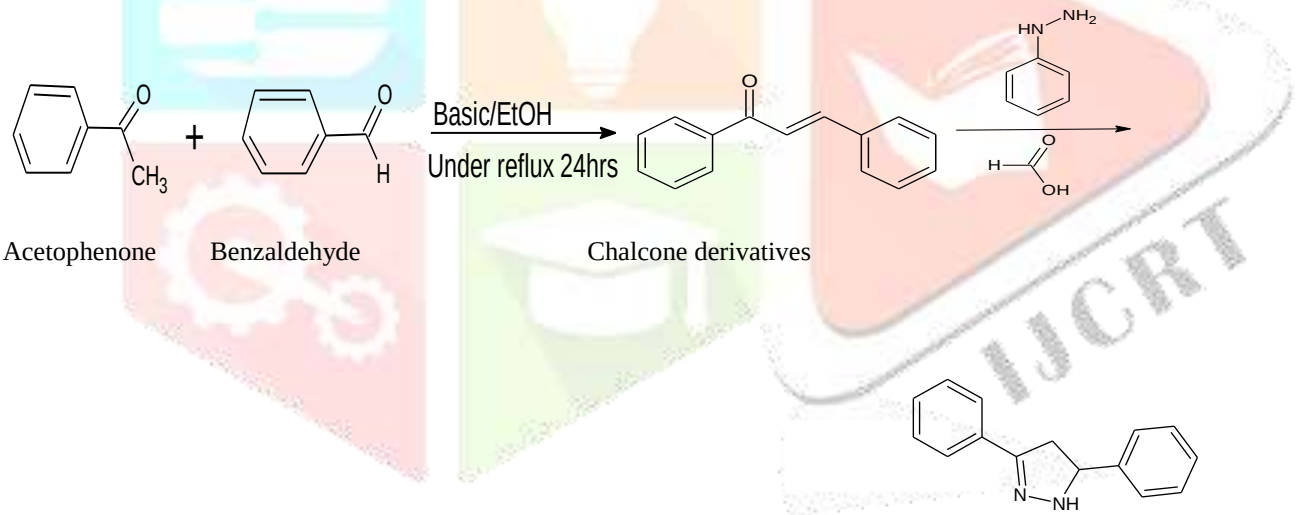
substituted pyrazoline -1-carbothiamides

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 phenylhydrazine

Maleki et al., (2009) were synthesized a series of 1, 3, 5-trisubstituted-2-pyrazoline derivatives by cyclization of phenylhydrazine with α, β-unsaturated ketones by using methanoic acid as catalyst under thermal 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 2.5 mL 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[9].

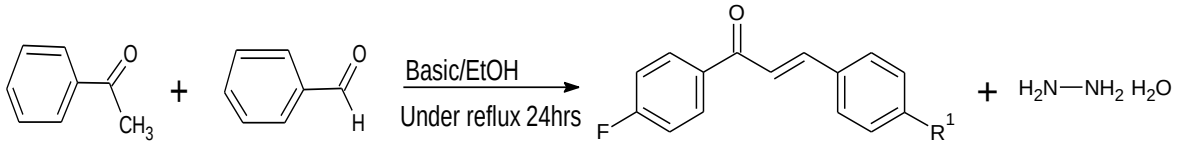


Acetophenone Benzaldehyde Chalcone derivatives

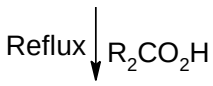
1, 3, 5- trisubstituted-2-pyrazoline derivatives

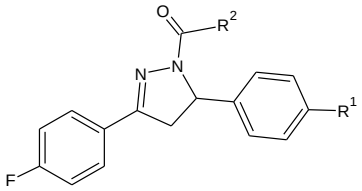
Scheme 3: Pyrazoline linked with hydrazine hydrate

Loh et al.,(2013) have been synthesized a series of four pyrazole compounds namely 3(4flourophenyl)-5-phenyl-4,5-dihydro-1*H*pyrazole-carbaldehyde, 5-(4-bromophenyl)-3(4flourophenyl)-4,5-dihydro-1*H*-pyrazolecarbaldehyde,1-[5-(4-chlorophenyl)-3(4fluorophenyl) -4,5-dihydro-1*H*-pyrazol-1-yl] ethanone and 1-[3-(4-fluorophenyl)-5phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]propan-1-one by condensing chalcones with hydrazine hydrate by using aliphatic acids specially formic acid, acetic acid, and propionic acid. The structures were characterized by x-ray single crystal structure determination.[10].



Acetophenone Benzaldehyde

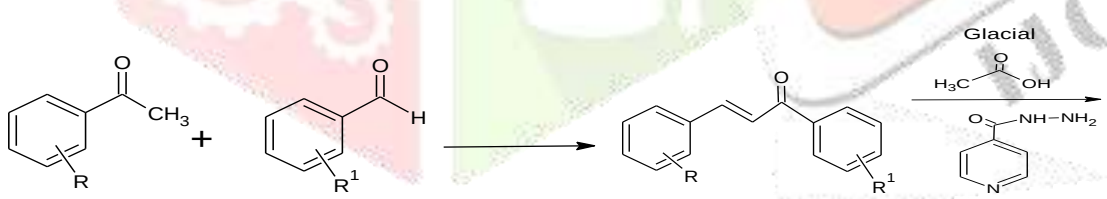




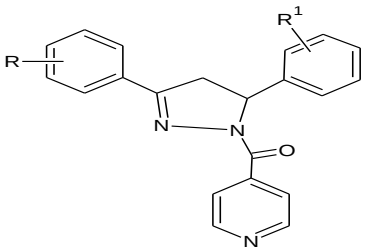
Where, R1=H, Br, Cl R2=H, CH3, CH2CH3

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 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[11].



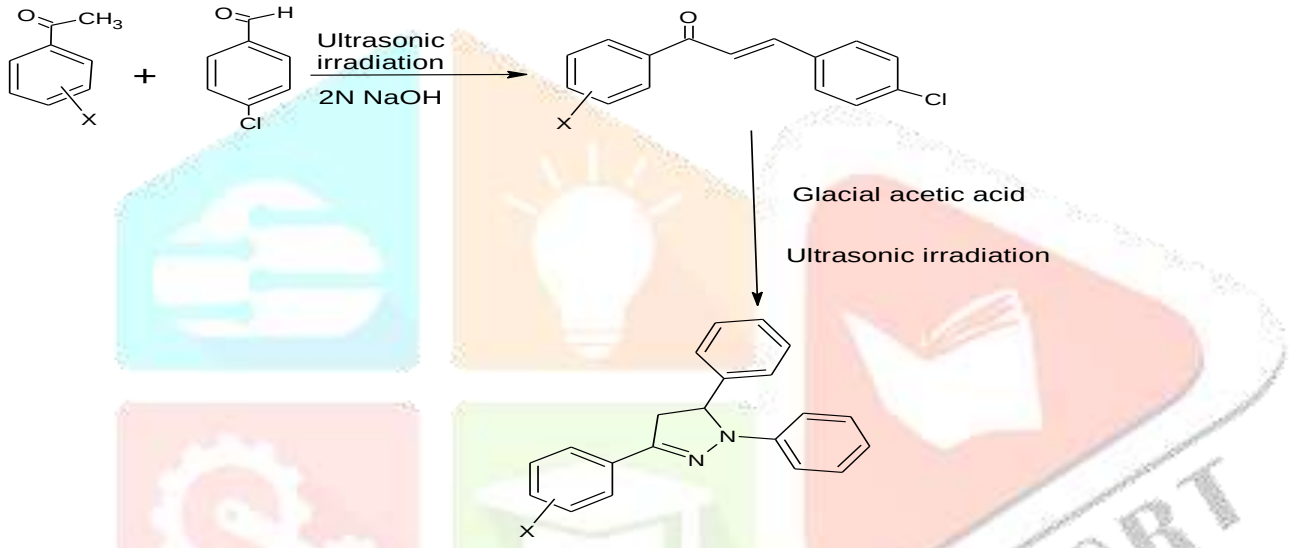
Acetophenone Benzaldehyde



Where, R=2-furfural, p-CH3, p-Cl, C6H5, p-OCH3, 2-Thiophene, m-NO2, p-(CH3)2-N, p-OCH3, p-Cl, p-OH, p-NO2, C6H5, p-Br.

Scheme 5: Pyrazoline linked with phenylhydrazine 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-diarylprop-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^{o}C temperature within 25-150 minutes. It had been noticed that in the conventional method, the mixture of chalcone, phenylhydrazine and glacial acetic acid was refluxed at 30- 40^{o}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 yield was 80%. The synthesized compounds were screened for their antimicrobial activity against bacteria and fungi and they showed good activity[12].

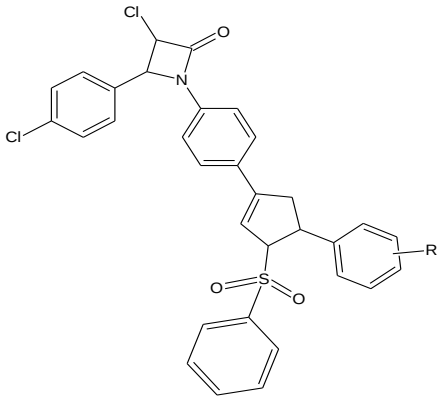


Where, X= 4-H, 4-Br, 4-Cl, 4-F, 4-CH3

Pharmacological Activity:

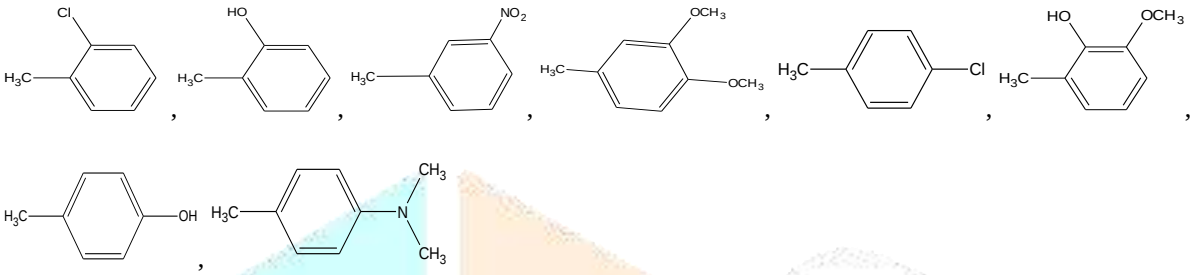
Antimicrobial Activity: Comprehensive work has been done describing the antimicrobial profile of pyrazoline. The Development of resistance to antimicrobial agents throughout important bacterial pathogens occurs rapidly, so there is much need to analyze new antimicrobial agents.

Shailesh H. Shah et al prepared Azetidin-2-One based Phenyl Sulfonyl Pyrazoline derivatives (1a) and explored them for antimicrobial activity concluding that compound having methoxy- hydroxide type linkage has shown good activity against the bacterial strains[13].

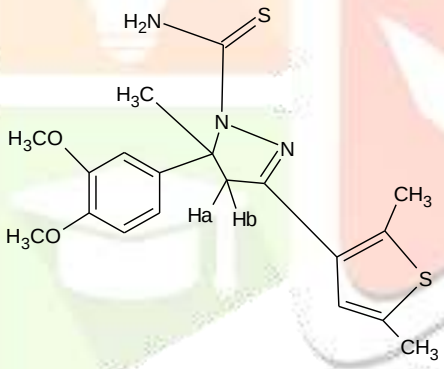


1(a)

Where,

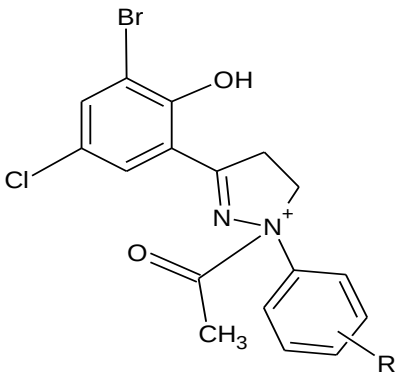


Many pyrazoline derivatives (1b) were synthesized by **Salman Ahmad Khan et al** under microwave irradiation and evaluated them against various bacterial strains[14].



1(b)

P. R. Desai et al synthesized acetyl pyrazoline derivatives (1c) and were evaluated for antimicrobial activity. They inferred that electronic effect seems to play an important role in increasing antimicrobial activity[15].

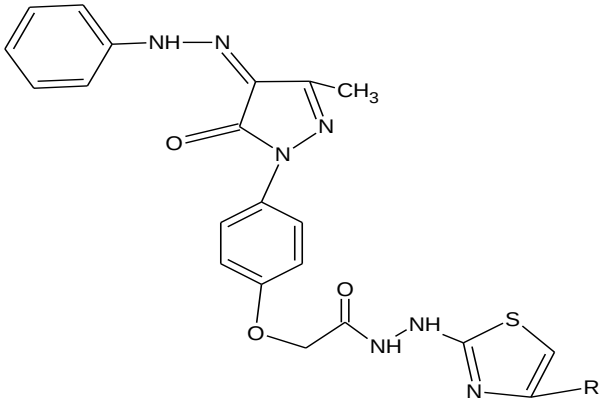


1(c)

Where, R= H, 3-Br, 4-OCH3, 3-Cl, 4-CH3, 2-Cl, 4-Cl, 3,4-di-OCH3, 2,4-di-OCH3

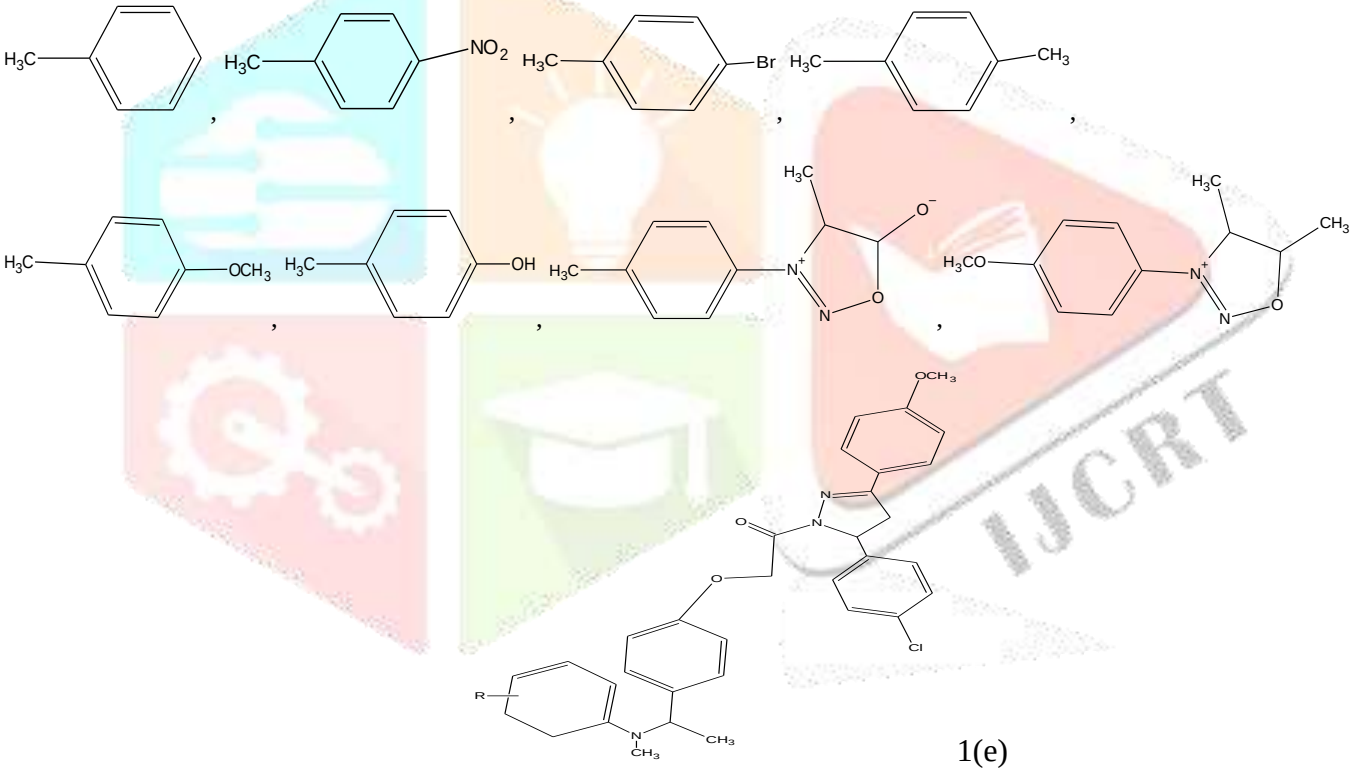
Pyrazolines (1d) developed by **Krishna et al** showed promising antimicrobial activity against all the tested microbes[16]. **Pinka Patel et al** synthesized a new series of pyrazolines based thiazolidin-4-one derivatives (1e) and

published that amongst newly synthesized, compound having 4-chlorophenyl type linkage has shown good activity against the bacterial strains[17].



1(d)

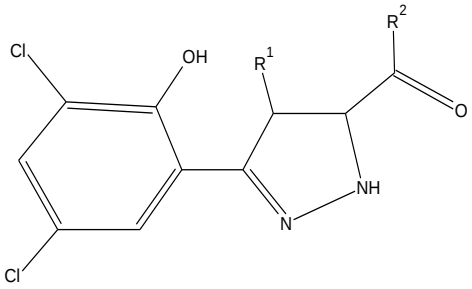
Where, R=



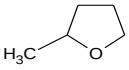
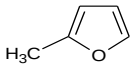
1(e)

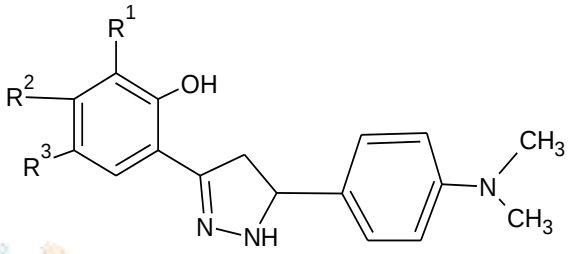
Where, R= 4 -CH3, 3-CH3, 2-NO2, 3-NO2, 4-NO2, 2-Cl, 3-Cl, 4-Cl N

Some new chlorosubstituted 4-Aroylpyrazolines (1f) were synthesised by **Shreya M. Rathore et al** and were assayed for their antimicrobial activity on E.coli, S. aureus, P. aeruginosa, P. vulgaris[18]. Antimicrobial active Pyrazoline derivatives (1g) were efficiently synthesized by **M.M. Kendre et al** reflecting moderate to good activity against different strains of bacteria and fungi[19].



1(f)

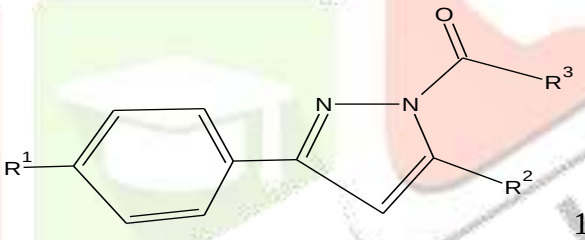
Where, R^1= C6H5,  R^2=  , C6H5



1(g)

Where, R1= Cl, I, Br, H R2= H, CH3 R3= Cl, Br, CH3, Br

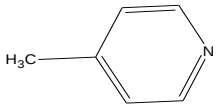
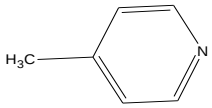
2-pyrazoline derivatives (1h) synthesized by **Dipankar et al** were found to have good antimicrobial activity in the range of 20-70 µg/ml[4]. Green synthesis of 1-phenyl-3(5-bromothiophen-2- yl)-5-(substituted phenyl)-2-pyrazolines (1i) was done by **Sasikala et al** and all synthesized pyrazoline derivatives showed moderate antimicrobial activities against bacterial and fungal strains[20].

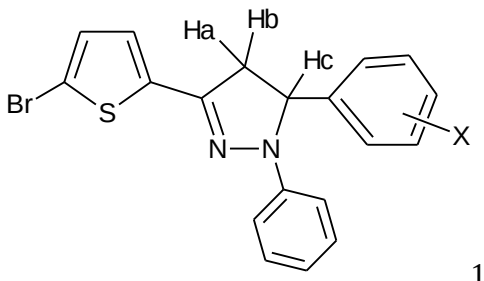


1(h)

Where, R1= Cl, OH R2= 4-NO2C6H5, 2-furyl, 2-thienyl

R3=

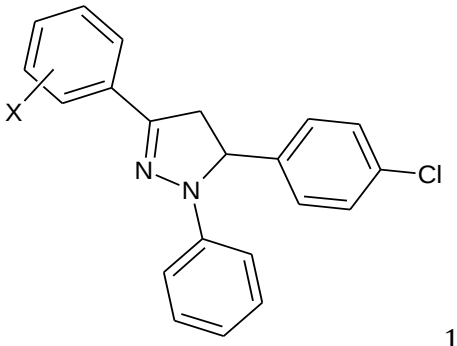
 , 



1(i)

X= H,4-Br, 2-Cl, 4-Cl, 3,4 -(OCH3)2, 4-I, 4-OCH3, 4-CH3

Ragini Gupta (1j) et al synthesized pyrazolines under ultrasonic irradiation and synthesized compounds were screened for their antimicrobial activity. Some of the compounds showed significant antimicrobial activity[12].

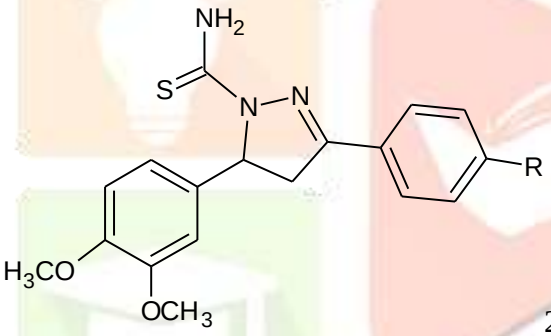


1(j)

Where, X= 4-H, 4-Br, 4-Cl, 4-F, 4CH3

Anti-inflammatory and Analgesic agents:

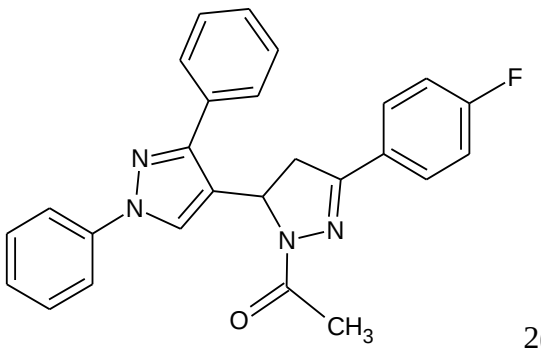
An extensive work has been done to study the anti-inflammatory and analgesic effect of pyrazolines. **Neethu et al** demonstrated the anti-inflammatory activity of the synthesized Pyrazoline analogues of Vanillin by cyclooxygenase assay. The synthesized compounds (2a) showed significant anti-inflammatory effect.



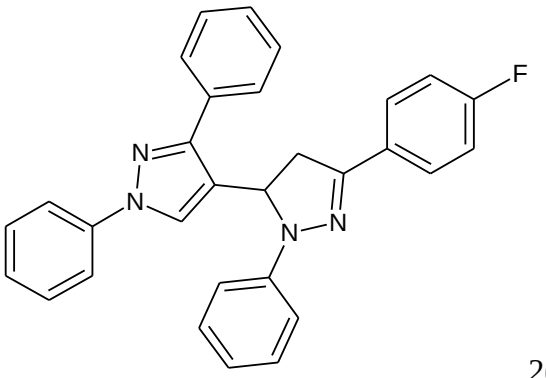
2(a)

Where, R= CH3, NH2, H, OCH3, NO2

A new series of fluoro substituted pyrazoline derivatives were prepared by **S. Y. Jadhav et al** and screened for their in vivo anti-inflammatory and analgesic activity and showed that two compounds (2b) and (2c) exhibit excellent activity[21].

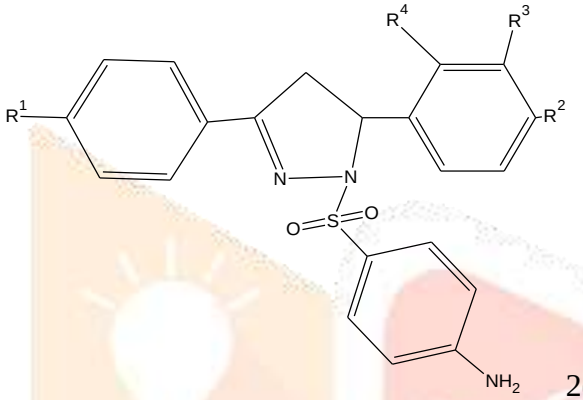


2(b)



2(c)

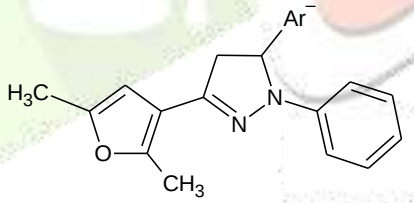
Suhas S. Awati et al concluded that the modified pyrazoline derivatives (2d) showed remarkable anti-inflammatory action.



2(d)

Where, R1=Cl, OCH3 R2= OCH3, CH3, Cl, OH R3= H, Cl R4= H,OCH3

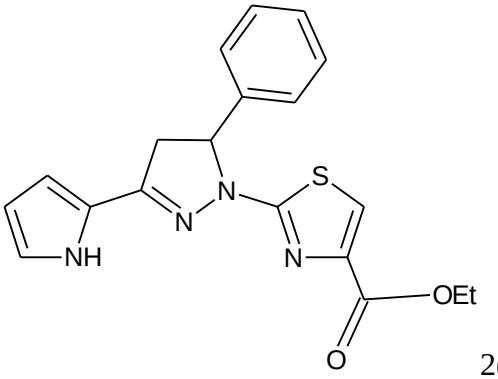
Pyrazoline derivatives (2e) by **S. Sridhar et al** have been found to possess an interesting profile of analgesic activity[22].



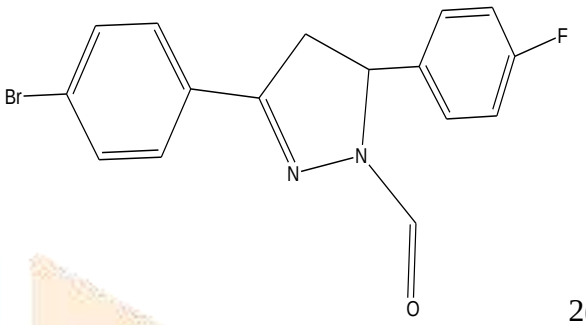
2(e)

Where, Ar = 4''-methoxyphenyl, 3''4'-dimethoxyphenyl, 4''-fluorophenyl, 4''-nitrophenyl, 2''-thienyl, 3'',4'',5''-trimethoxyphenyl, 4''-chlorophenyl, 2','4''-dichlorophenyl, 4''-methylphenyl, 9''-anthryl

Jyothi M V et al synthesized pyrazolines (2f) and studied for their anti-inflammatory activity[23]. Compounds possess some degree of anti- inflammatory activity and were free from toxicity **Khalil et al** inferred the compound (2g) of 3, 5- Diaryl-2-Pyrazoline Derivatives as most potent, which has shown higher percentage of inhibition of edema than the standard drug indomethacin[24].

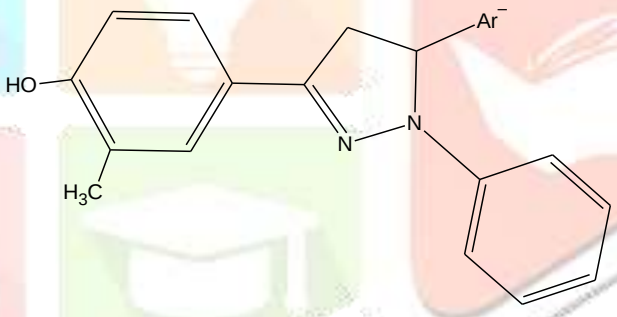


2(f)



2(g)

Srinath N et al screened the 1, 3, 5-Trisubstituted-2-Pyrazolines (2h) and screened them for their analgesic profile indicating the favourable effect of electron releasing substituents on the analgesic activity of the 2-pyrazolines[25].

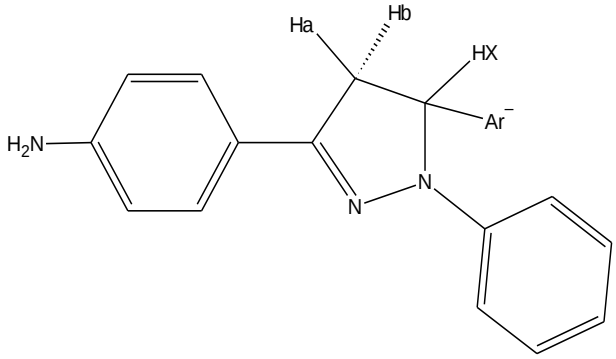


2(h)

Anti-depressant activity:

Depression is the central nervous system disorder. Pyrazolines have been found to develop antidepressant potential.

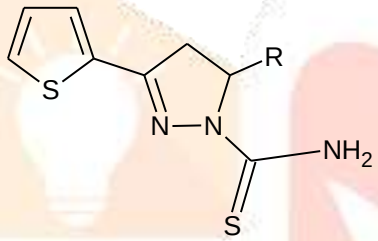
Some New 1,3,5-trisubstituted-2-pyrazolines (3a) were synthesized by **Atla Srinivasa Rao et al** and characterized for their antidepressant profile. Compound 3a represented antidepressant activity similar to standard, tranylcypromine. It was revealed that the presence of electron releasing group on phenyl ring system attached at C-5 position of 2-pyrazoline is important for their activity[26].



3(a)

Where, Ar= 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 4-bromiophenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 2,4-dimethoxyphenyl, 4-methylphenyl, 3,4,5-timethoxyphenyl, 9-anthracenyl, 3-pyridinyl, 4-pyridinyl.

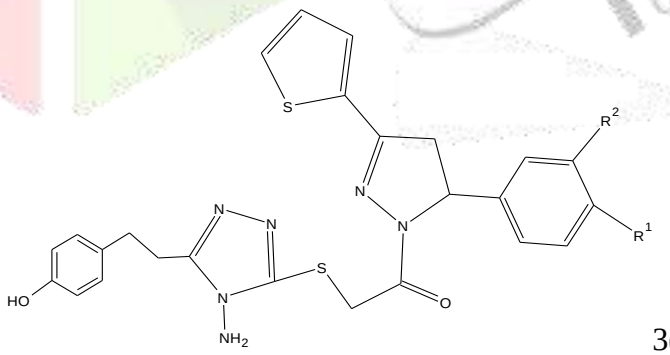
Bijo Mathew et al synthesized thiophene containing pyrazoline carbothioamides (3b) with promising antidepressant action. It was revealed that they exhibit a typical reduction in immobility in the forced swim test by increasing the swimming behaviour[27].



3(b)

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

Kaplancikli et al studied the antidepressant activity of synthesized triazolopyrazolines(3c)[28].

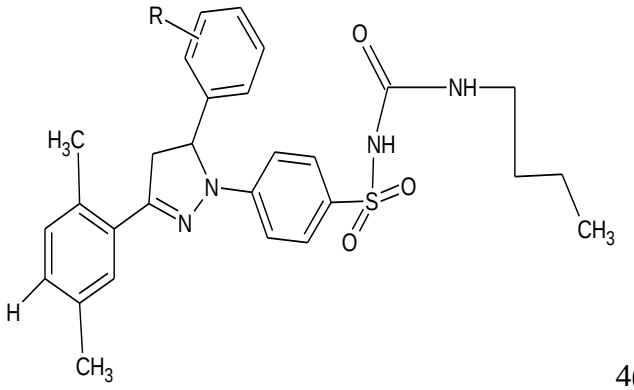


3(c)

Where, R1= H, F, Cl, CH3, N(CH3)2, O-CH2-O R2=H

Anti-cancer Activity:

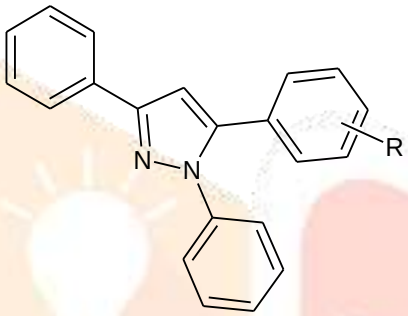
Many chemists have designed pyrazolines to examine their influence on cancer. **P. Rathore et al** synthesized pyrazoline substituted benzene sulfonylureas and screened them for potential antiproliferative agents. The compound (4a) displayed remarkable antiproliferative activity[29].



4(a)

Where, R= 3,4,5- trimethoxy

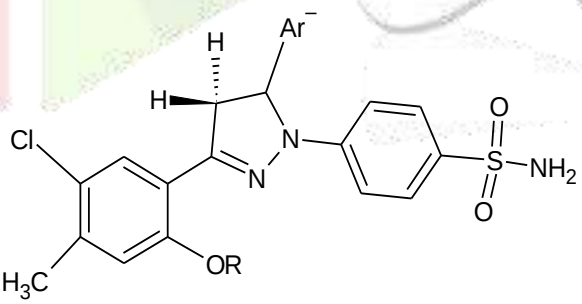
Neera Raghav et al prepared cyclized derivatives, pyrazolines (4b) and evaluated them for inhibitors of mammalian cathepsin B and cathepsin-H as cancer therapeutics[30].



4(b)

Where, R= H, p-Cl, p-Br, p-NO2, p-CH3,p-OCH3

1,3,5-trisubstituted pyrazolines bearing benzene sulphonamide (4c) were synthesized by **R. Bashir et al** and evaluated for antitumor activity. Compounds exhibited considerable antitumor activities against the entire tested tumour cell lines[31].

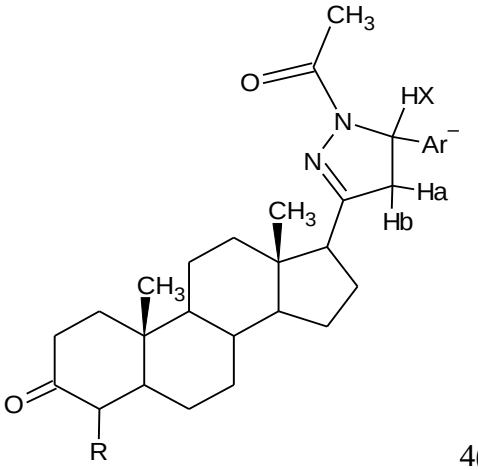


4(c)

Where R as follows,

R= H, CH3 Ar= phenyl, 2-chlorophenyl,ethylenephenyl, 3,4,5-trimethoxyphenyl 3-hydroxyphenyl, N,N-dimethylaminophenyl, 2-hydroxyphenyl, 4-Clphenyl, 3,4-dimethoxyphenyl

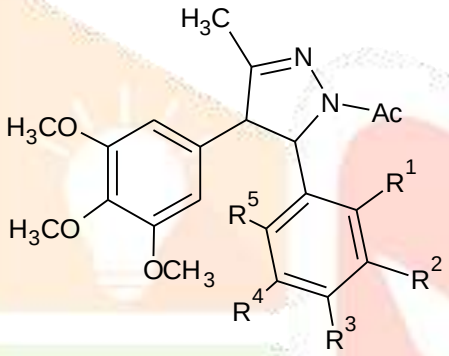
N.J. Fan et al prepared certain steroidal C-17 pyrazolinyl derivatives (4d) and proved for their cytotoxic activity across brine shrimp and three human cancer cell lines (NCI-H460, HeLa, and HepG2). Some of these synthetic compounds exhibited significant cytotoxic activity[32].



4(d)

Where, R=H, Cl

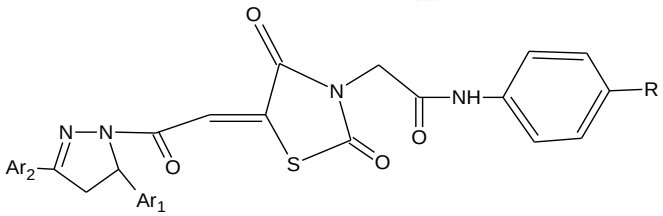
M. Lee et al synthesized methyl pyrazoline analogs (4e) of combretastatin A-4 were tested to determine their cytotoxicity against the growth of cancer cells in culture using an invitro 72 h continuous exposure-MTT assay[33].



4(e)

Where, R1= H, OCH3 R2= H, NO2, Cl, OCH3, OH, NO2 R3= H, CH3, Cl, Br, NO2, OCH3 R4= H, OCH3 R5= H

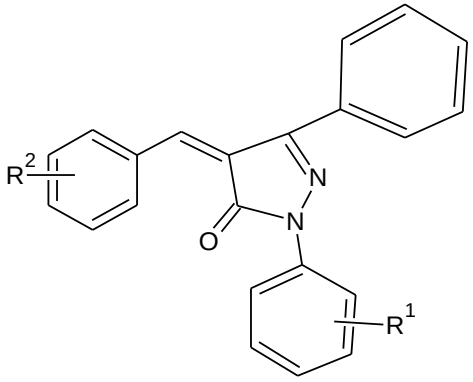
Antiviral activity: Pyrazolines was analyzed by chemists for antiviral activity. Thiazolidinonepyrazoline hybrids (5a) were synthesized by **D Havrylyuk et al** and antiviral activity of synthesized compounds was determined[34].



5(a)

Where, Ar1= 4-Cl-C6H5, 4-OMe-C6H5 Ar2= Ph, naphthalen-2-yl R= Me, OMe, Cl

The compounds presented insignificant activities against the four strains of influenza virus. **Ramajayam et al** demonstrated the potency of synthesized pyrazolines (5b) as protease inhibitor of SARS virus[35].



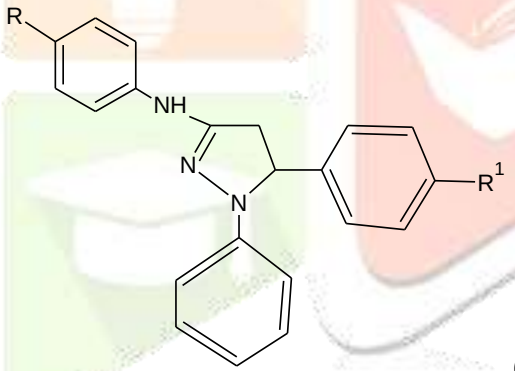
5(b)

Where, R1= H, 4-Cl, 4-OCH3, 4-CH(CH3)2, 4-C(CH3)3, 4-CN, 4-OCF3, 4-Cl, 3,4-Cl2, 4-F, 3-NO2 R2= H, 3-OCH3, 3-NO2, H, 4-Cl, 4-COOH, 4-OCH3, 4-OH, 4-COOH

Anti-tubercular activity:

Tuberculosis arise from infection with Mycobacterium Tuberculosis. Pyrazolines was investigated for its antitubercular activity many of times.

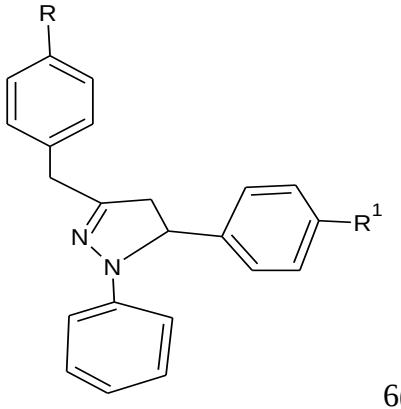
A series of 2-pyrazoline compounds (6a) were synthesized by **Hipparagi and Bhanushali et al** and were screened for anti-tubercular activity against isoniazid resistance mycobacterium tuberculosis, using Microplate Alamar Blue assay method. None of the compound was found to be equipotent with standard isoniazid[36].



6(a)

Where, R=H, F, Cl, Br R1= Cl, OH, NO2

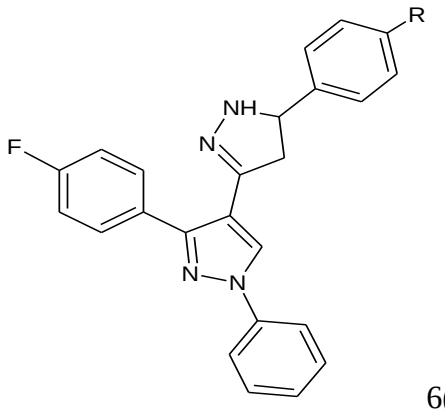
The anti-tubercular screening of all synthesized pyrazoline derivatives (6b) was carried out by **Bhanushali & Shivkumar** against Mycobacterium tuberculosis of H37Rv strain[37].



6(b)

Where, R=H, F, Cl, Br R1= Cl, OH, NO2

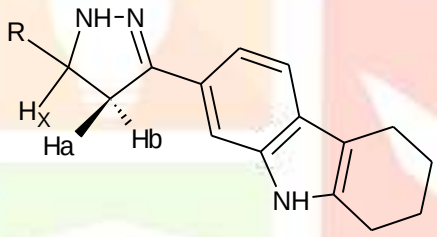
A new series of fluorinated pyrazoles (6c) were synthesized from the corresponding chalcones, by ultrasonic irradiation by **S. N. Shelke et al**. The newly synthesized compounds were investigated for their anti-tubercular activities against Mycobacterium tuberculosis H37Rv[38].



6(c)

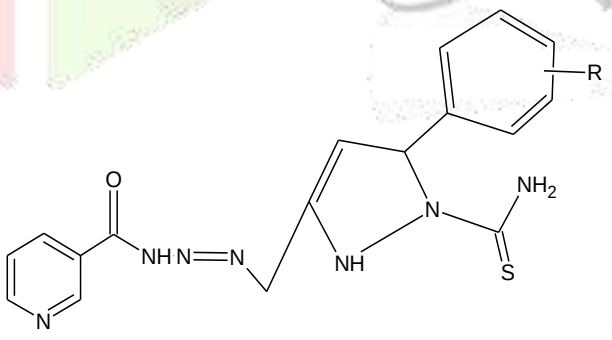
Where, R= H, CH3, F, Cl, Br

Taj et al synthesized new pyrazoline derivatised carbazoles (6d) and screened for their antitubercular activity against the standard atreptomycin and pyrazinamide[39]. **Kasabes et al** observed good antitubercular activity of synthesized pyrazolines(6e)[40].



6(d)

Where, R= phenyl, o-chlorophenyl, m-chlorophenyl, p-chlorophenyl, p-nitrophenyl, o-hydroxyphenyl, p-hydroxyphenyl, styryl, methyl, p-anisyl, p-tolyl

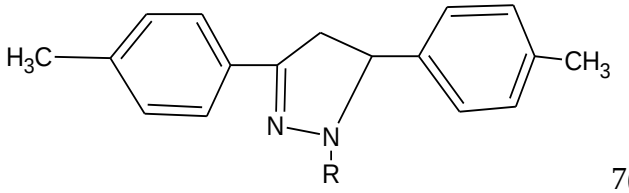


6(e)

Where, R= 2-NO2, 4-OCH3, 4-NO2, 4-Cl, 3-OCH3

Anti-diabetic activity:

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

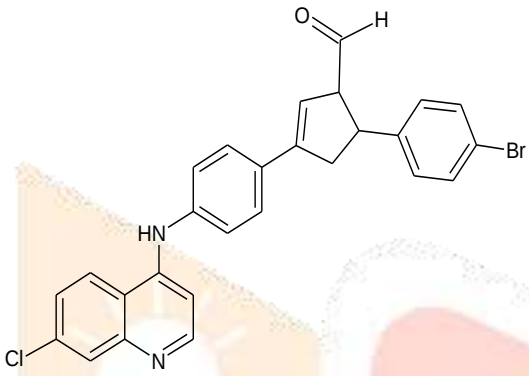


7(a)

Where, R= CONH2, CSNH2, C6H4, SO2, COC6H5

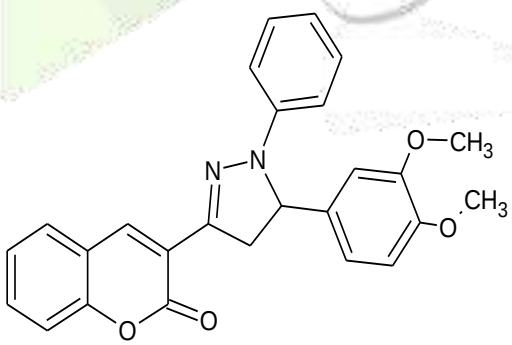
Antimalarial activity:

A new series of N- acetyl and N-formyl-pyrazoline derivatives synthesized by **B. Insuasty et al** and determined their antimalarial activity. Compound (8a) showed remarkable antimalarial activity[41].

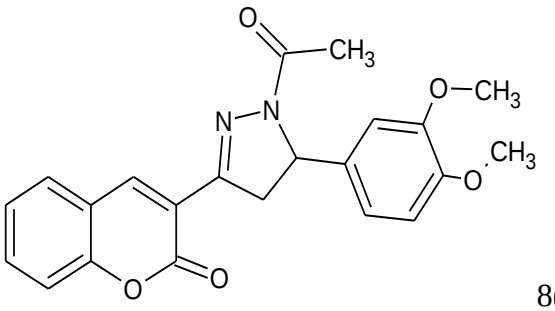


8(a)

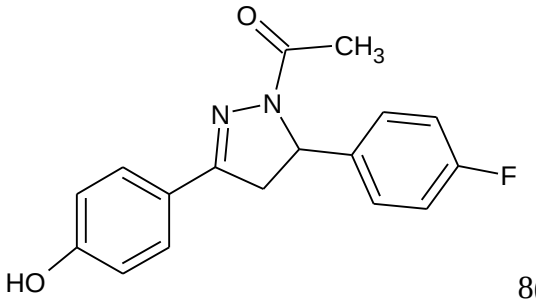
G. Wanare et al prepared pyrazoline analogs (8b-b2) and investigated for antimalarial activity across both chloroquine sensitive strain (3D7) and chloroquine resistant field isolate (RKL9) of P. Falciparum. All the tested compounds showed promising antimalarial activity[42]. A series of 1,3,5- trisubstituted pyrazolines (8c) were synthesized by **B.N. Acharya et al** and evaluated for in vitro antimalarial efficacy against chloroquine sensitive (MRC-02) as well as chloroquine resistant (RKL9) strains of Plasmodium falciparum and obtained promising results[43].



8(b)



8(b1)

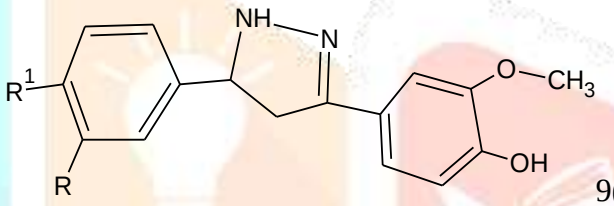


8(b2)

Antioxidant activity:

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

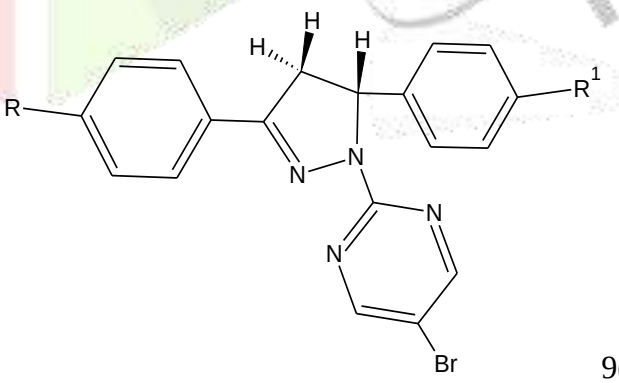
A **Kumar et al** synthesized 3,5-disubstituted-2- pyrazolines (9a)and were screened for antioxidant activity using DPPH radical scavenging method, NO scavenging assay, superoxide radical scavenging assay and hydrogen peroxide radical scavenging assay. All the compounds showed good free radical scavenging activity which is comparable to that of the standard ascorbic acid[44].



9(a)

R= H, CH3, Br, Cl, OH, OCH3 R1= H, CH3, Br, Cl, OCH3, NO2

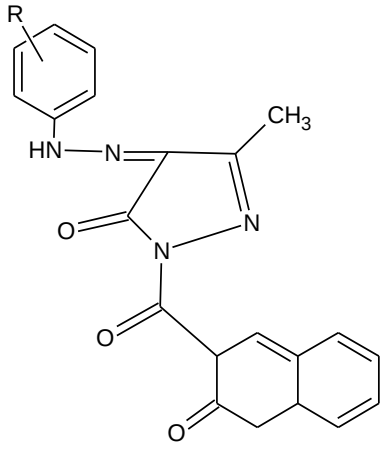
4,5-dihydropyrazolines carrying pyrimidine moiety (9b) were prepared by **A. Adhikari et al** under conventional heating as well as microwave reaction condition. Newly synthesized pyrazolines were screened for their free radical scavenging activity by DPPH method[45].



9(b)

Where, R= H, Br, Cl R1= NO2, CH3, Cl, Br, OCH3

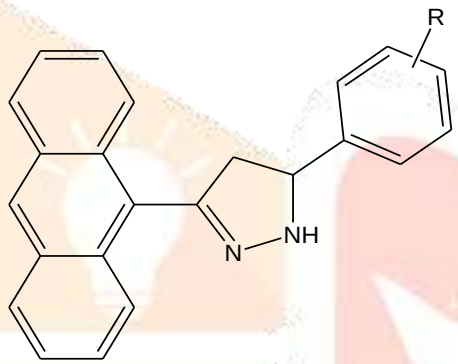
A new series of Coumarin fused pyrazoline-5-one derivatives (9c) were developed **P. Venkatesh et al** and examined for antioxidant activity by DPPH and Nitric oxide methods. Compound 2 acquire good antioxidant activity in both methods.



9(c)

Acetylcholinesterase Inhibitory activity:

The acetyl cholinesterase inhibitory property of diaryl pyrazoline derivatives (10a) studied by **Nibha Mishra et al**[46]**.**



10(a)

Where, R= 4-NO2, 4-OH, 4-Cl, 4-CH3, -H, 2-OH, 2,4-Di-OH, 3-NO2, 4-OCH3

Conclusion:

Pyrazolines are well known and popular nitrogen consists 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 about different methods for the synthesis of biologically active pyrazoline derivatives.

References:

1. Muralidharan V, C AD, Raja S. a Review on Pyrazoline Derivatives of Potent Antimicrobial Activity. *Int J Res Anal Rev*. 2019;6(1):1264-1299.

2. Li JT, Zhang XH, Lin ZP. An improved synthesis of 1,3,5-triaryl-2-pyrazolines in acetic acid aqueous solution under ultrasound irradiation. *Beilstein J Org Chem*. 2007;3:2005-2008. doi:10.1186/1860-5397-3-13

3. Jadhav SA, Kulkarni KM, Patil PB, Dhole VR, Patil SS. Design, synthesis and biological evaluation of some novel pyrazoline derivatives. *Der Pharma Chem*. 2016.

4. Bardalai D, Panneerselvam P. Int . Res J Pharm . App Sci ., 2012 ; 2 (3): 1-8 Review Article Pyrazole and

2-Pyrazoline Derivatives : Potential Anti-Inflammatory and Analgesic Agents. 2012;2(Iii):1-8.

5. Kharatmol MG, Jagdale D. Eco-Friendly Synthesis of Pyrazoline Derivatives. *Int J Pharm Clin Res*. 2017;9(04):302-308. doi:10.25258/ijpcr.v9i04.8538

6. Patel MR, Dodiya BL, Ghetiya RM, et al. Synthesis and antimicrobial evaluation of pyrazoline derivatives. *Int J ChemTech Res*. 2011;3(2):967-974. doi:10.15373/2249555x/aug2013/23

7. Attarde M, Vora A, Varghese A, Kachwala Y. Synthesis and evaluation of chalcone derivatives for its alpha amylase inhibitory activity. *Org Chem an Indian J*. 2014;10(5):192-204.

8. Osman ABM, Nour AH, Ali DMH, Osman HA. Design and synthesis of 2-pyrazoline derivatives Design and synthesis of 2-pyrazoline derivatives. 2016;(March).

9. Maleki B, Azarifar D, Moghaddam MK, Hojati SF, Gholizadeh M, Salehabadi H. Synthesis and characterization of a series of 1,3,5-trisubstituted-2-pyrazolines derivatives using methanoic acid under thermal condition. *J Serbian Chem Soc*. 2009;74(12):1371-1376. doi:10.2298/JSC0912371M

10. Loh WS, Quah CK, Chia TS, et al. Synthesis and crystal structures of N-substituted pyrazolines. *Molecules*. 2013. doi:10.3390/molecules18022386

11. Revanasiddappa BC, Rao RN, Subrahmanyam EVS, Satyanarayana D. Synthesis and biological evaluation of some novel 1, 3, 5-trisubstituted pyrazolines. *E-Journal Chem*. 2010. doi:10.1155/2010/415723

12. Gupta R, Gupta N, Jain A. Improved synthesis of chalcones and pyrazolines under ultrasonic irradiation. *Indian J Chem - Sect B Org Med Chem*. 2010;49(3):351-355. doi:10.1002/chin.201030126

13. Shah SH, Patel PS, Prajapati M, Vaghari B. Synthesis , Characterization and Antimicrobial Activity of Azetidin-2-One based Phenyl Sulfonyl Pyrazoline Derivatives Synthesis , Characterization and Antimicrobial Activity ofAzetidin-2-OnebasedPhenylSulfonylPyrazoline Derivatives. 2015;(January 2014).

14. Arabia S, Arabia S, Africa S. European Journal of Chemistry. 2014;5(1):85-90. doi:10.5155/eurjchem.5.1.85

15. Chemistry OF, Nmr H. STUDIES ON SYNTHESIS OF BIOLOGICALLY ACTIVE. 2013;2845:81-88.

16. Naik K, Raghavendra A, Prasad G, Spoorthy YN. DESIGN , SYNTHESIS , CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF NEW PYRAZOLINE-5-ONES. 2013;04(01):720-730.

17. Patel PS. Design , Synthesis and Pharmacological Evaluation of New Series of Pyrazolines Based Thiazolidin-4-one Derivatives. 2013;2(4):1089-1093. doi:10.7598/cst2013.301

18. Rathore MM, Parhate V V, Rajput PR. Synthesis and antimicrobial study of some new chloro substituted 4-aroyl pyrazolines. 2012;4(1):28-32.

19. Kendre MM, Baseer MA. Synthesis and Evaluation of Some New Pyrazoline Derivatives as Antimicrobial Agents. 2013:3-6.

20. Sasikala R, Thirumurthy K, Mayavel P, Thirunarayanan G. Eco-friendly synthesis and antimicrobial activities (substituted phenyl) -2-pyrazolines. 2012:1-13.

21. Jadhav SY, Shirame SP, Kulkarni SD, Patil SB, Pasale SK, Bhosale RB. Bioorganic & Medicinal Chemistry Letters PEG mediated synthesis and pharmacological evaluation of some fluoro substituted pyrazoline derivatives as antiinflammatory and analgesic agents. *Bioorg Med Chem Lett*. 2013;23(9):2575-2578. doi:10.1016/j.bmcl.2013.02.105

22. Sridhar S, Rajendraprasad Y. Synthesis and analgesic studies of some new 2-pyrazolines. *E-Journal Chem*. 2012;9(4):1810-1815. doi:10.1155/2012/476989

23. Jyothi M, Merugu R. A review on synthesis and biological significance of pyrazoles. *Int J PharmTech Res*. 2015. doi:10.1002/chin.201610259

24. Khalil OM, Refaat HM. Synthesis and Anti-inflammatory Activity of Some 3 , 5-Diaryl-2-Pyrazoline Derivatives. 2011.

25. Srinath N, Prasad YR, Mukkanti K. Synthesis and analgesic activity of some 1, 3, 5-trisubstituted-2-pyrazolines. 2011;3(1).

26. Rao AS, Saalim M, Bhupesu KV, Prasad K. Anticonvulsant and Antidepressant Activity Studies of Synthesized Some New 1 , 3 , 5-trisubstituted-2-pyrazolines. 2014;6(3):1113-1123.

27. Mathew B, Suresh J, Anbazhagan S. Original article : SYNTHESIS , PRECLINICAL EVALUATION AND ANTIDEPRESSANT ACTIVITY OF 5-SUBSTITUTED PHENYL-3- (THIOPHEN-2-YL) -4 , 5-. 2014:437-445.

28. Kaplanckl ZA, Özdemir A, Turan-Zitouni G, Altntop MD, Can ÖD. New pyrazoline derivatives and their antidepressant activity. *Eur J Med Chem*. 2010. doi:10.1016/j.ejmech.2010.06.011

29. Rathore P, Yaseen S, Ovais S, et al. Bioorganic & Medicinal Chemistry Letters Synthesis and evaluation of some new pyrazoline substituted benzenesulfonylureas as potential antiproliferative agents. *Bioorg Med Chem Lett*. 2014;24(7):1685-1691. doi:10.1016/j.bmcl.2014.02.059

30. Raghav N, Singh M. Bioorganic & Medicinal Chemistry SAR studies of differently functionalized chalcones based hydrazones and their cyclized derivatives as inhibitors of mammalian cathepsin B and cathepsin H. *Bioorg Med Chem*. 2014. doi:10.1016/j.bmc.2014.05.037

31. Bashir R, Ovais S, Yaseen S, et al. Bioorganic & Medicinal Chemistry Letters Synthesis of some new 1 , 3 , 5-trisubstituted pyrazolines bearing benzene sulfonamide as anticancer and anti-inflammatory agents. *Bioorg Med Chem Lett*. 2011;21(14):4301-4305. doi:10.1016/j.bmcl.2011.05.061

32. Fan N, Tang J, Li H, Li X, Luo B, Gao J. European Journal of Medicinal Chemistry Synthesis and cytotoxic activity of some novel steroidal C-17 pyrazolinyl derivatives. 2013;69:182-190. doi:10.1016/j.ejmech.2013.08.016

33. Lee M, Brockway O, Dandavati A, et al. A novel class of trans-methylpyrazoline analogs of combretastatins: Synthesis and in-vitro biological testing. *Eur J Med Chem*. 2011;46(7):3099-3104. doi:10.1016/j.ejmech.2011.03.064

34. Havrylyuk D, Zimenkovsky B, Vasylenko O, et al. Synthesis and biological activity evaluation of 5-pyrazoline substituted 4-thiazolidinones. *Eur J Med Chem*. 2013;66:228-237. doi:10.1016/j.ejmech.2013.05.044

35. Ramajayam R, Tan K, Liu H, Liang P. Bioorganic & Medicinal Chemistry Synthesis and evaluation of pyrazolone compounds as SARS-coronavirus 3C-like protease inhibitors. *Bioorg Med Chem*. 2010;18(22):7849-7854. doi:10.1016/j.bmc.2010.09.050

36. Hipparagi SM. Synthesis and evaluation of anti - tubercular activity of some novel 2 - pyrazoline derivatives. 2013;40(2):80-83. doi:10.4103/0974-5009.115475

37. Bhanushali MD, Shivakumar M. Synthesis and Evaluation of New Substituted Pyrazoline Derivatives as Biological Agents. 2013.

38. Shelke SN, Mhaske GR, Bonifácio VDB, Gawande MB. Green synthesis and anti-infective activities of fluorinated pyrazoline derivatives. *Bioorganic Med Chem Lett*. 2012;22(17):5727-5730. doi:10.1016/j.bmcl.2012.06.072

39. Taj T, Kamble RR, Gireesh TM, Hunnur RK, Margankop SB. One-pot synthesis of pyrazoline derivatised carbazoles as antitubercular, anticancer agents, their DNA cleavage and antioxidant activities. *Eur J Med Chem*. 2011;46(9):4366-4373. doi:10.1016/j.ejmech.2011.07.007

40. Kasabe AJ, Kasabe PJ. Synthesis, anti tubercular and analgesic activity evaluation of new 3-pyrazoline derivatives. *Int J Pharm Pharm Sci*. 2010.

41. Insuasty B, Montoya A, Becerra D, et al. Synthesis of novel analogs of 2-pyrazoline obtained from [(7-chloroquinolin-4-yl)amino]chalcones and hydrazine as potential antitumor and antimalarial agents. *Eur J Med Chem*. 2013;67:252-262. doi:10.1016/j.ejmech.2013.06.049

42. Wanare G, Aher R, Kawathekar N, Ranjan R, Kaushik NK, Sahal D. Synthesis of novel α-pyranochalcones and pyrazoline derivatives as Plasmodium falciparum growth inhibitors. *Bioorganic Med Chem Lett*. 2010;20(15):4675-4678. doi:10.1016/j.bmcl.2010.05.069

43. Acharya BN, Saraswat D, Tiwari M, et al. Synthesis and antimalarial evaluation of 1, 3, 5-trisubstituted pyrazolines. *Eur J Med Chem*. 2010;45(2):430-438. doi:10.1016/j.ejmech.2009.10.023

44. Kumar MNVR, Muzzarelli RAA, Muzzarelli C, Sashiwa H, Domb AJ. Chitosan chemistry and pharmaceutical perspectives. *Chem Rev*. 2004;104(12):6017-6084. doi:10.1021/cr030441b

45. Adhikari A, Kalluraya B, Sujith KV, et al. Synthesis, characterization and pharmacological study of 4,5-dihydropyrazolines carrying pyrimidine moiety. *Eur J Med Chem*. 2012;55:467-474.

doi:10.1016/j.ejmech.2012.07.002

46. Mishra N, Sasmal D. Additional acetyl cholinesterase inhibitory property of diaryl pyrazoline derivatives. *Bioorganic Med Chem Lett*. 2013;23(3):702-705. doi:10.1016/j.bmcl.2012.11.100