



INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

PYRAZOLE DERIVATIVES: A WORTHY INSIGHT INTO POTENT BIOLOGICAL ACTIVITIES: A REVIEW

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Accepted Date: 21/08/2013; Published Date: 27/08/2013

Abstract: Pyrazole derivatives display a broad spectrum of potential pharmacological activities and are active constituent of pharmaceutical drug molecules. Their structural modification offered a high degree of diversity that has proven useful for the development of new therapeutic agents with improved potency and reduction in toxicity. In the present article we have studied these pharmacological activities with their active compound have been highlighted.

Keywords: Pyrazole Derivatives, Antimicrobial, Antitubercular , Anticancer



PAPER-QR CODE

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How to Cite This Article:

Neelam Malik, IJPRBS, 2013; Volume 2(4): 415-427

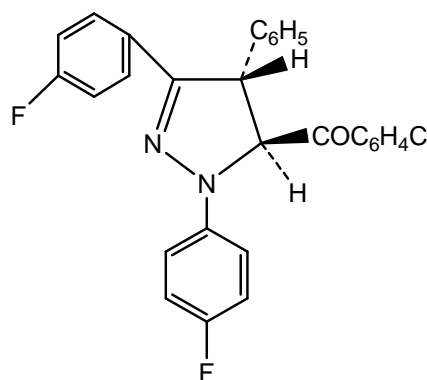
INTRODUCTION

Pyrazole is a five-membered heterocyclic moiety having two adjacent nitrogen atoms within the ring. It has only one endocyclic double bond and is basic in nature. [1] Pyrazole moiety and its reduced form pyrazoline are well known nitrogen containing compounds and various procedures have been deployed for their synthesis. Among its various derivatives, 2-pyrazolines have been found to be the most frequently studied pyrazoline type compounds. [2] 2-Pyrazolines can be considered as a cyclic hydrazine moiety. [3] The interest towards the synthesis of these compounds was encouraged by various promising pharmacological properties [4]. Pyrazole derivatives have attained great interest for these compounds because they are widely used as drugs, dyes, anesthetics, and agricultural chemicals [5]. Pyrazole moiety have been found to be associated with a variety of biological and pharmacological activity such as anticancer [6], anti-inflammatory [7], antinociceptive [8], antidepressant [9], antibacterial [10], antifungal [11] and many more. Thus pyrazole have been found to be involved in many pharmacological activities and many drugs that contains pyrazole moiety as their active ingredients, such as phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), azolid/tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric).

BIOLOGICAL ACTIVITIES OF PYRAZOLE DERIVATIVES

1. Antibacterial activity

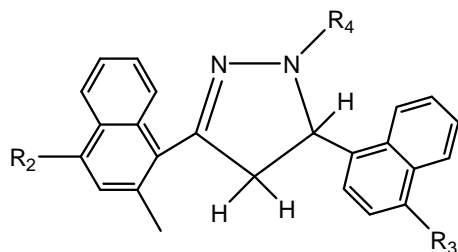
Abunada *et al*^[12] (2008) synthesized 1,3-diaryl-5-(cyano-, aminocarbonyl- and ethoxycarbonyl)-2-pyrazoline, pyrrolo[3,4-c]pyrazole-4,6-dione and 1,3,4,5-tetraaryl-2-pyrazoline derivatives by the reaction of nitrilimine with different dipolarophilic reagents. Compound **1** was found to active against *E. coli*, and *S. aureus*.



1

Azarifar *et al*^[13] (2002) synthesized new 3,5-dinaphthyl substituted 2-pyrazolines (2ag-2fk) by reacting chalcones (prepared by reaction of substituted 1-acetylnaphthalenes with 1-naphthaldehyde in ethanolic NaOH solutions) with hydrazine hydrochloride, phenyl hydrazine and semicarbazide hydrochloride in the presence of dry acetic acid. All the synthesized against a variety of test organisms: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Shigella dysentery* and *Salmonella*

typhii. Compounds 2cg, 2eh, 2ci, 2di and 2ei positively acted against all six organisms.

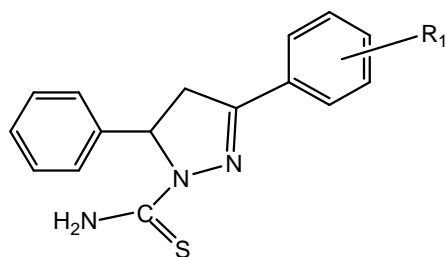


2ag-2fk

a R₁ = H, R₂ = H, R₃ = H, **b** R₁ = H, R₂ = H, R₃ = NMe₂ **c** R₁ = OH, R₂ = H, R₃ = NMe₂

d R₁ = OH, R₂ = Cl, R₃ = NMe₂, **e** R₁ = OH, R₂ = Me, R₃ = NMe₂, **f** R₁ = H, R₂ = Cl, R₃ = NMe₂, **g** R₄ = H, **h** R₄ = Ph, **i** R₄ = CONH₂, **k** R₄ = COCH₃

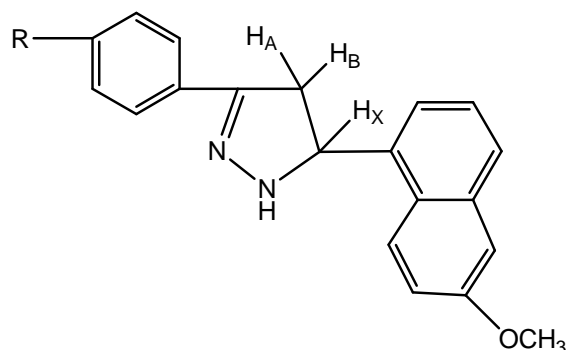
Chawla *et al*^[14] (2010) synthesized new [3-(4-phenyl)-5-phenyl-4,5-dihydropyrazol-1-yl](pyridine-4-yl)methanones **3(a-f)** by applying microwave techniques. All the synthesized compounds were evaluated for antimicrobial activity against two Gram-positive strains (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*) synthesized compounds exhibited moderate antibacterial activities and significant antifungal activities.



3(a-f)

R₁ = **a**= 4-OCH₃, **b**= 4-Cl, **c**= 3-NO₂ **d**= 4-OCH₃, **e**= 4-Cl, **f**= NO₂

Jadhav *et al*^[15] (2009) synthesized new series of 1H-3-(4'-substituted phenyl)-5-(6''-methoxy naphthalene)-2-pyrazolines (**4a-e**) by reacting-(4'-substituted phenyl)-3-(6''-methoxynaphthalene)-2-propene-1-one with hydrazine hydrate and hydroxylamine hydrochloride respectively. All the synthesized compounds were evaluated for their antimicrobial activity. All the compounds exhibited significant to moderate antimicrobial activity.

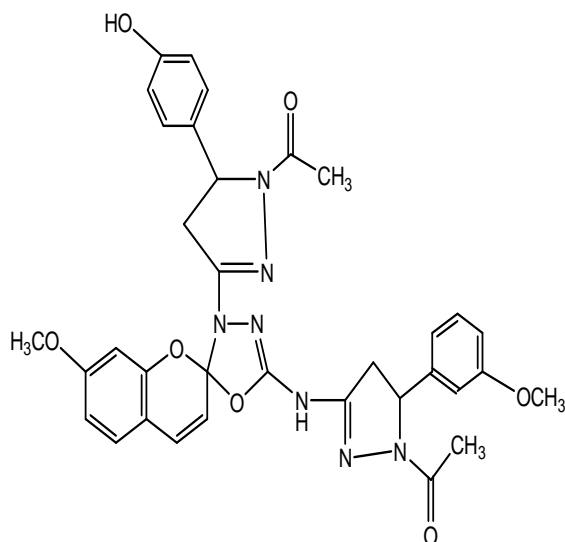


4(a-e)

R= **a**= H, **b**= Br, **c**= F, **d**= CH₃ **e**= OCH₃

Kaur *et al*^[16] (2010) synthesized a series of 7- substituted- 2- spiro- [5- ((1-acetyl-(substitutedphenyl) amino)-3-(1-acetyl-5-(substitutedphenyl)) pyazolin-3-yl)- 1, 3, 4-oxadiazol-2-yl] coumarins by the reaction of 7- un/substituted- 2- spiro- (3-substitutedarylidinyl chalconyl)- 5-(substituted- arylidinyl- amino- chalconyl)-oxadiazol-2-yl) coumarins with hydrazine hydrate and hydroxyl amine respectively. All the newly synthesized compounds were

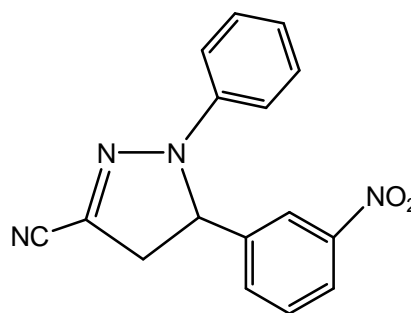
screened for their antibacterial activity against *K. pneumoniae*, *S. aureus*, *E. coli* and *B. subtilis* and were compared with the standard drug ciprofloxacin. The most



5g

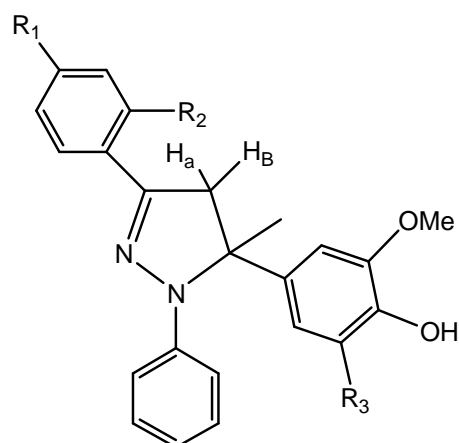
Fathalla *et al*^[17] (2005) synthesized new 2-thiouracil-5-sulphonamide derivatives by reacting 2-thiouracil-5-sulphonic acid N-(4-acetylphenyl) amide with a series of aromatic aldehydes giving chalcones (Claisen-Schmidt reaction). All the synthesized compounds were evaluated for their antimicrobial activity. Compound 6a was found to most potent among all the synthesized compounds.

potent antibacterial compound of this series was 5g. Structures of all the compounds were established by the elemental analysis.



6a

Shinde *et al*^[18] (2004) synthesized some new 3,5-diphenyl and 1,3,5-triphenyl-2-pyrazolines derivatives by reacting 1,3-diphenyl-2-propen-1-ones with hydrazine hydrates and phenyl hydrazine in ethanol. All the synthesized compounds were investigated for their antimicrobial activity and they exhibited moderate antimicrobial activity.



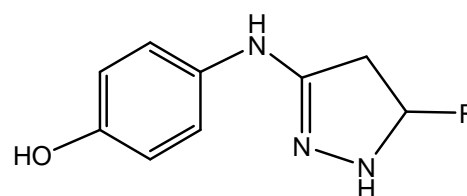
7

R= H, R_1 = OH

Tripathi *et al*^[19] (2009) synthesized arsenic(III) tripyrazolinates and bismuth(III) tripyrazolinates of the type $M(C_{15}H_{12}N_2OX)_3$ [where $C_{15}H_{12}N_2OX = 3(2'$ -hydroxyphenyl)-5-(4-substituted phenyl)pyrazoline] have been synthesized by the reaction of MCl_3 and sodium salt of pyrazolines in 1:3 molar ratio in anhydrous benzene at elevated temperature and tested for *in vitro* antibacterial and antifungal activity against *Bacillus subtilis* (+ve), *E. coli* (-ve), *albicans* (+ve) and *Aspergillus niger* (-ve). These compounds showed mild to good antibacterial activity and antifungal activity. The bismuth(III) tripyrazolinates exhibit greater antibacterial activity and comparable antifungal activity compared to free pyrazoline and some of the antibiotics, such as chloramphenicol, and the antifungal agent terbinafine, respectively. The arsenic (III) tripyrazolinates exhibit comparable antifungal activity compared to free pyrazoline.

2. Analgesic activity

Sahu *et al*^[20] (2008) synthesized a series of novel 4-(5-substituted aryl-4, 5-dihydropyrazole-3-yl-amino) phenols **8a-f** by treating substituted aryl-N-chalconyl amino phenols with hydrazine hydrate. All the synthesized compounds were evaluated for their antimicrobial activity. The observed increase in analgesic, anti-inflammatory and antimicrobial activities are attributed to the presence of 4- NO_2 , 2-OH and 4-Cl in phenyl ring at 5-position of pyrazoline ring of synthesized compounds. In some cases their activities are equal or more potent than the standard drugs.

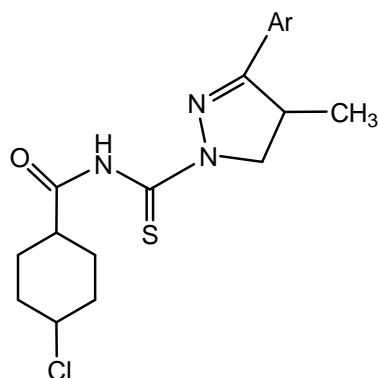


8(a-f)

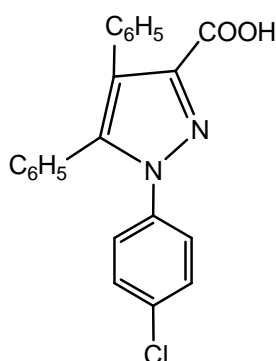
R= a C_6H_5 , b 2-furyl c 4- NO_2 - C_6H_5 d 4- OCH_3 - C_6H_4 e 2-OH- C_6H_5 f 4-Cl- C_6H_5

Gawad *et al*^[21] (2011) Designed and synthesized some pyrazole derivatives of expected anti-inflammatory and analgesic activities. Compound 9a and 10b exhibited significant analgesic activity with gastric ulcerogenic potential less than that of ibuprofen. Results of the analgesic activity showed that compounds possessing good anti-inflammatory activity showed also good analgesic. Substitution of pyrazole ring with at least one aryl moiety was found to be essential for analgesic activity. Free NH

(of pyrazole ring) and/or acidic group (COOH) will improve the analgesic activity.

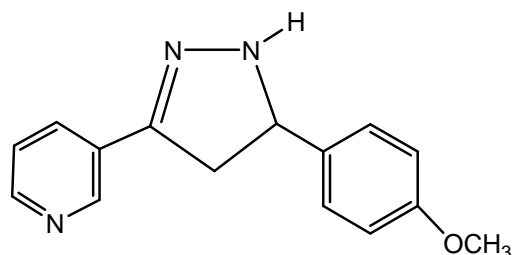


9a



10b

Abdel-Latif *et al*^[22] (2007) synthesized a series of substituted pyridine, pyrazoline, and thiopyrimidine derivatives from 3-acetylpyridine, which was prepared from nicotinic acid as a naturally starting material. All the synthesized compounds were evaluated for the analgesic activity. The pharmacological screening showed that many of these compounds have good analgesic and antiparkinsonian activities comparable to Voltarene as reference drug.

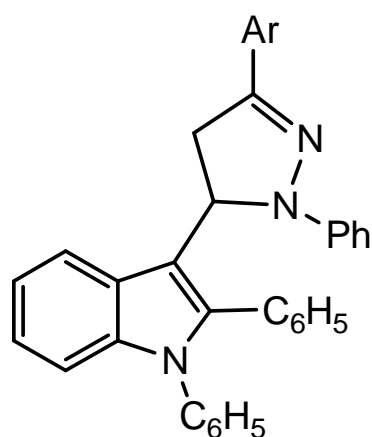


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3. Anticancer activity

Nassar^[23] (2010) synthesized new pyrazoline derivatives by aldol condensation reaction between 3-indolaldehyde 1 and 4-methoxyacetophenone 2 afforded chalcone compounds. Some of the synthesized new compounds were screened against antitumor activity and they have been found to have promising anticancer activity.

Zahran *et al*^[24] (2010) synthesized 2-Aryl-1H-indole-3-carbaldehyde derivatives by Claisen-Schmidt condensation with acetophenone derivatives under microwave irradiation condition compared with the conventional heating to afford excellent yields of trans substituted indolylchalcones which subjected to condensation reaction with phenylhydrazine to afford their indolylpyrazoline analogues. The antitumor activity of the synthesized compounds was examined and evaluated against human hepatocellular carcinoma cell line (Hep-G2) as well as the half maximal inhibitory concentration (IC₅₀). Most of them showed high potent antitumor activity.

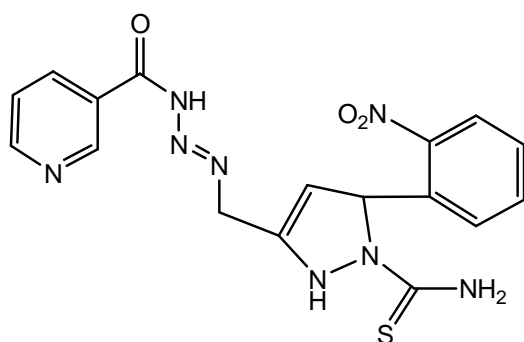


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4. Antitubercular activity

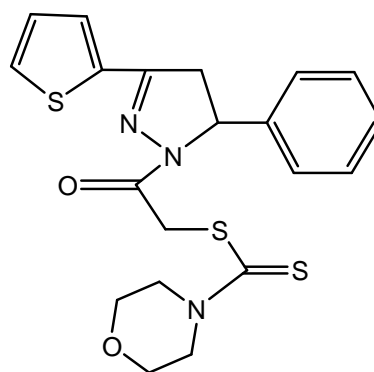
Ozdemir *et al*^[25] (2008) synthesized new 1-[(N,N-disubstitutedthiocarbamoylthio)acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives by reacting 1-(chloroacetyl)-3-(2-thienyl)-5-aryl-2-pyrazolines and appropriate sodium salts of N,N-disubstituted dithiocarbamic acids in acetone.

The compounds were evaluated for in vitro antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv using



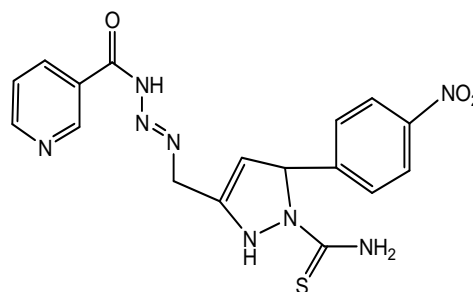
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the BACTEC 460 radiometric system and BACTEC 12B medium. The preliminary results showed that all of the tested compounds were inactive against the test organism.

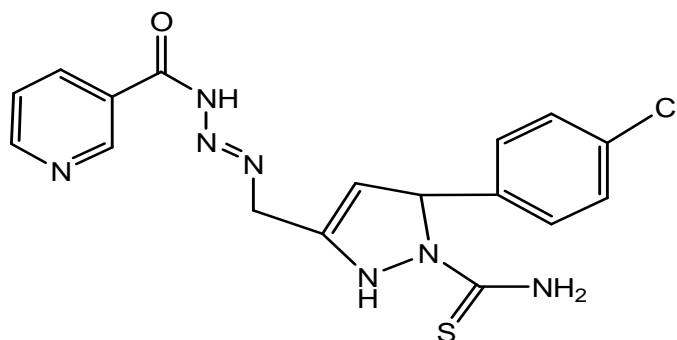


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Kasabe *et al*^[26] (2010) synthesized new 3-Pyrazoline derivatives prepared from 3-β-picolinoyl amino azo methyl-5-aromatics substituted-1-thioamide-3-pyrazoline (prepared by refluxing with thiosemicarbazide in presence of sodium hydroxide and ethanol). The synthesized compounds were evaluated for anti-tubercular activity. Compound 14, 15, and 16 shows good antitubercular activity.



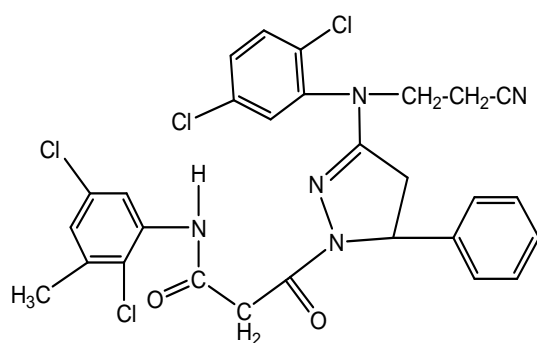
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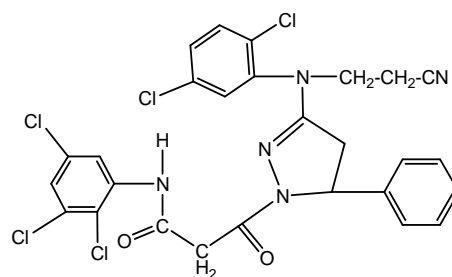
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Sharma *et al*^[27] (2010) synthesized a series of new 1-[(2, 5-dichloroanilinomalonyl)]-3-(N-2'-cyanoethyl-N-2, 5-dichloroanilino)-5-phenyl pyrazoline derivatives by the reaction of N-cinnamoyl-N-2'-cyanoethyl-2,5-dichloroaniline with Ethyl-2-(2, 5-dichloroanilido) acetohydrazide. Newly synthesized compounds have been tested for their antitubercular activity *in-vitro*

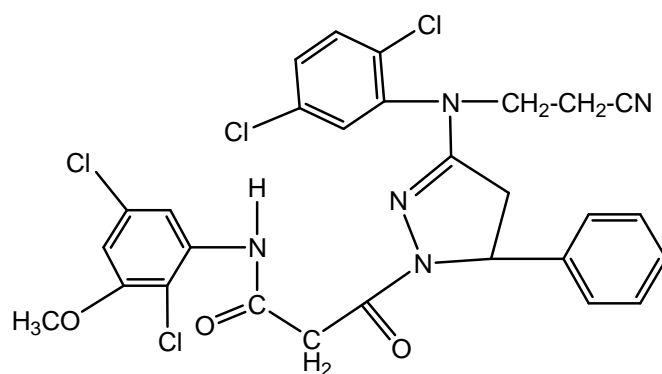
using *Mycobacterium tuberculosis*. The compounds were incorporated into Lowenstein Jensen egg medium having concentrations of 10 and 100 mg/mL and were inoculated with *Mycobacterium tuberculosis*, H27, Rv strains, incubated at 37°C and observed, the compound 17, 18, 19, and 20 inhibited the growth of *Mycobacterium tuberculosis* at 100mg/mL concentration.



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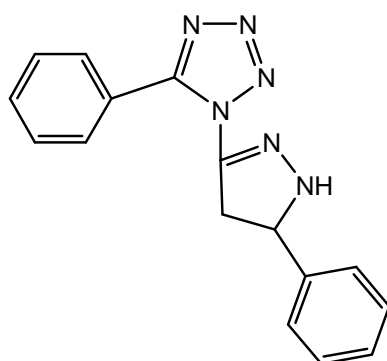
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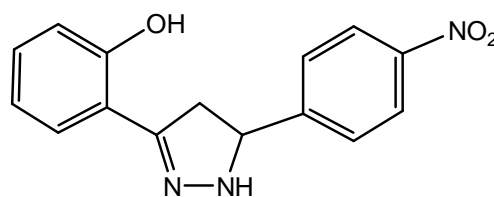
5. Anti-inflammatory activity

Bhaskar *et al*^[28] (2011) synthesized different derivatives of substituted 5-phenyl-1-(5-substituted phenyl)-4,5-dihydro-1H-pyrazol-3-yl)-1H-tetrazole were synthesized by reacting the chalcones with hydrazine hydrate in presence of glacial acetic. All the synthesized compounds were screened for anti-inflammatory activity. The observed increase in, anti-inflammatory activity was attributed to the presence of 4-NO₂, 4-OH and 4-Cl in phenyl ring at 5-position of pyrazoline ring of synthesized compounds. In some cases their activities are equal or more potent than the standard drugs.



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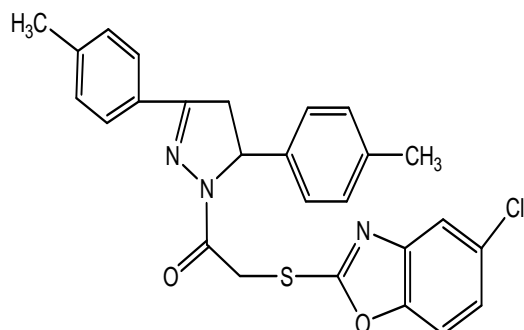
Venkataraman *et al*^[29] (2010) synthesized Pyrazoline derivatives from Chalcones (prepared from substituted acetophenones and substituted benzaldehydes and condensed with hydrazine hydrate in ethanol). All the synthesized compounds were screened for their anti-inflammatory activity. Some of tested compounds exhibited promising anti-inflammatory activity.



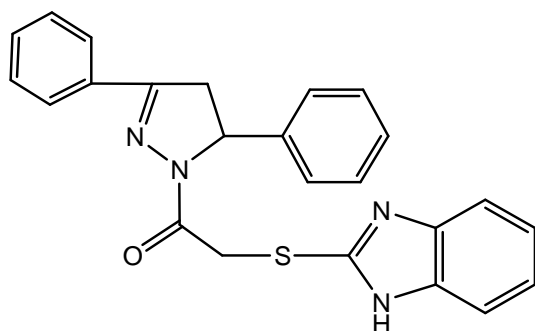
21

Can *et al*^[30] (2008) synthesized some 1,3,5-trisubstitued-2-pyrazoline derivatives. All the synthesized compounds were evaluated for their antidepressant activity. Pyrazoline-benzoxazole derivative test compound **22a** and pyrazoline-benzimidazole derivative test compound **23d** in the series were

exhibited significant antidepressant effects in modified forced swimming tests.



22a

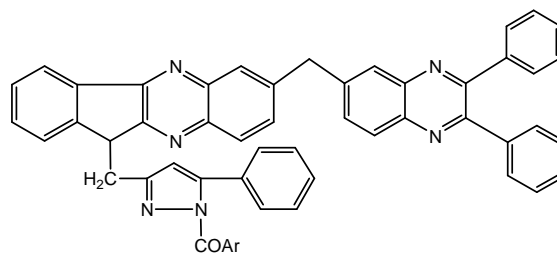


23d

6. Antioxidant activity

Sridevi *et al*^[31] (2010) synthesized phenyl pyrazolo indoquinoxaline derivatives from Indoloquinoxalin fused with 2,3 diphenyl quinoxaline by a methylene bridge which was then allowed for acetylation. All the synthesized compounds were screened for their antioxidant activity. The acetylated product was made to react with different aromatic aldehydes to give

chalcones. Chalcones refluxed with substituted acid hydrazides to afford different indoloquinoxaline pyrazolines.



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CONCLUSION

In the present article various pharmacological activities of pyrazole derivatives have been reviewed. By studying all these activities it can be concluded that pyrazole and its reduced form pyrazoline had been involved in many pharmaceutical and pharmacological activities with small modification in the structure. Further, it can be evolved for other pharmacological activities in the future.

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