IJPSR (2022), Volume 13, Issue 12 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 January 2022; received in revised form, 22 October 2022; accepted 05 November 2022; published 01 December 2022

PHARMACEUTICAL POTENTIAL OF A RESOURCEFUL NITROGEN-CONTAINING HETEROCYCLE: PYRAZOLINE-A REVIEW

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Keywords:

Pyrazoline, Therapeutic activity, Heterocycle

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ABSTRACT: Heterocyclic chemistry has grown very rapidly, particularly in evaluating synthetic methods and investigating synthesized materials' bioactive properties. Heterocycle compounds are important in many facets of life's pharmacological activities. In their structure, many biologically active compounds such as amino acids, vitamins, hormones, nucleic acids, alkaloids, dyes, and drugs (natural and synthetic) possess heterocyclic ring molecules. Various pyrazole derivatives and their numerous physiological and pharmacological effects have been the subject of numerous investigations during the last decade. Part of the goal of these investigations was to uncover the vast spectrum of drug-like properties of pyrazole derivatives and their structure-activity connections to unlock the full potential of these molecules. This article focuses on the chemistry and pharmaceutic activity of the heterocycle pyrazoline, *i.e.*, nitrogen-containing five-membered ring. An account of a different mode of synthesis from different starting materials is shown, along with the highlights of the therapeutic activity of pyrazoline.

INTRODUCTION: Pyrazolines, which are one of the most studied classes of the azole family, are comprised of a five-membered aromatic system [1]. Pyrazolines are fused heterocyclic deferential tested with anti-inflammatory action from an important family of compounds for the invention of novel drugs. When connected to various substituents such as alkyl, aromatic, heterocyclic rings, and several other groups at a different positions, the pyrazoline nucleus demonstrates significant anti-inflammatory activity to be more effectual [2]. The broad variety of bioactivities of pyrazolines leads many researchers to like to synthesize new pyrazoline derivatives [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(12).4848-56

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(12).4848-56

Pyrazoline substituents are important target molecules for chemists because of their many potential applications, such as pharmaceuticals. Some pyrazoline derivatives have been shown to exhibit pharmacological effects such as antidepressant [4] antibacterial [5] antitumor [6] and anti-inflammatory [7] activities. Pyrazolines have only one double bond within the nucleus and, depending on the position of the double bond, can exist in three separate forms: 1-pyrazoline, 2-pyrazoline, and 3-pyrazoline.

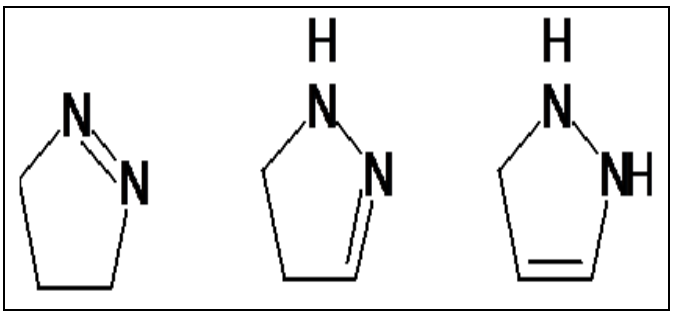
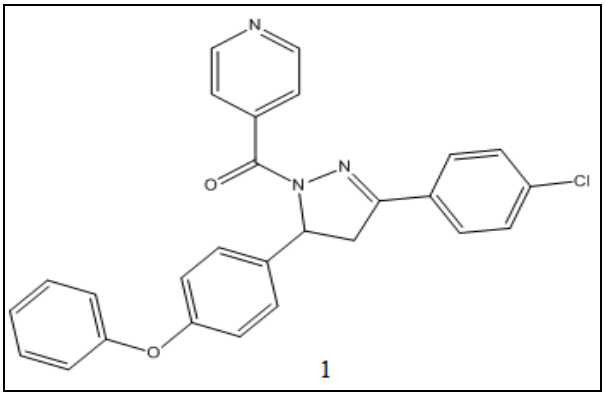


FIG. 1: THREE DIFFERENT FORMS OF PYRAZOLINE

Literature Survey:

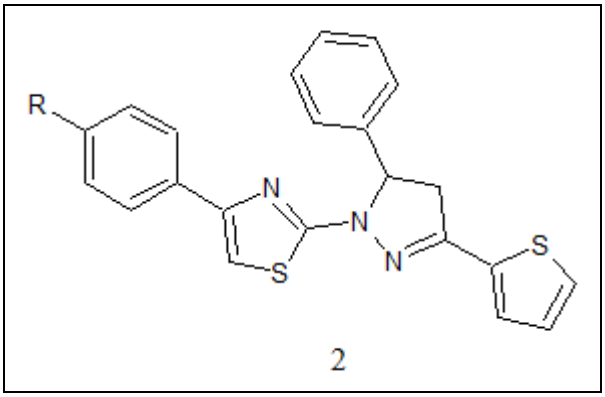
Antimicrobial Activity: A central scaffold of antimicrobials, including antibacterial, antifungals, antivirals, and antiemetics, is the pyrazoline ring. However, antitubercular, could be considered a sub-class from antibacterial, we opted here to separate it under a specific subtitle because of its clinical importance.

Antibacterial and Antifungal Activity: Narsinh. K. Desai *et al*. [8] have reported antimicrobial activity inhibition of bacterial growth procedure by test compounds for a broad range of antimicrobial activity inhibiting growth of Gram-positive bacterial strains *B. subtillis* and *S. aureus* and Gram-negative bacterial strains *E. coli* and *P. aeruginosa*.



1

Several derivatives of 1-(4-aryl-2-thiazolyl)-3-(2 thienyl)-5-aryl-2-pyrazoline 2 were synthesized by Ozdemir *et al.* [9] and evaluated against *Escherichia coli, Bacillus cereus, Salmonella typhimurium, Streptococcus faecalis, Staphylococcus aureus, Aeromonas hydrophila, Candida glabrata* and *Candida albicans* for their antimicrobial activities. A substantial activity level was observed.



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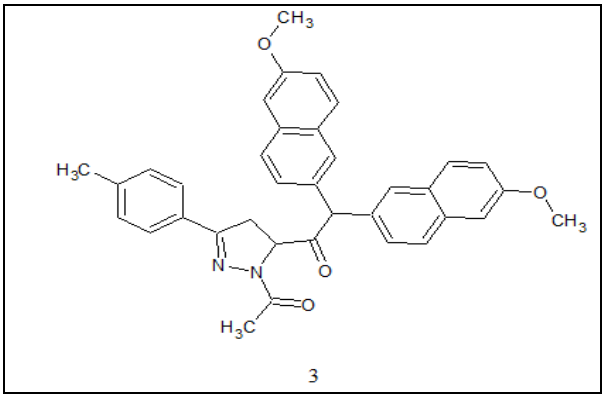
Udupi *et al* [10] have achieved the synthesis of naproxen pyrazoline derivatives, as represented by compound 3 (1-(1-acetyl-3-(4-aminophenyl)-4, 5-dihydro - 1H – pyrazol – 5 - yl)-2, 2-bis (6-methoxynaphthalen – 2 - yl) ethan-1-one). The biological assessment indicated that some of the series compounds had important dual antimicrobial and anti-inflammatory activities.



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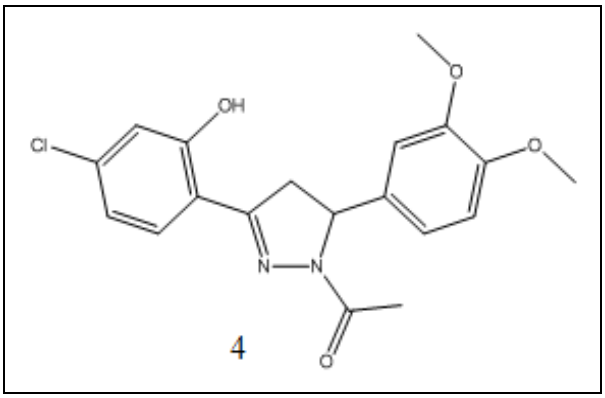
Anticancer Activity: Tutik Dwi Wahyuningsih *et al.* [11] have reported the synthesized pyrazolines were evaluated as anticancer agents using MTT against breast cancer lines (MCF7 and T47D), the cervical cancer line (HeLa), and the normal cell line (Vero). The novel N-acetyl pyrazoline derivatives (5-chloro-2-(5-(3,4-dimethoxyphenyl)-1-(prop-1-en-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenol) containing methoxy groups obtained from veratraldehyde were successfully synthesized in excellent yield and purity by the cyclocondensation of chalcones and hydrazine hydrate in glacial acetic acid. Cytotoxicity evaluation revealed the presence of a halogen substituent such as Chloro on a pyrazoline derivative.



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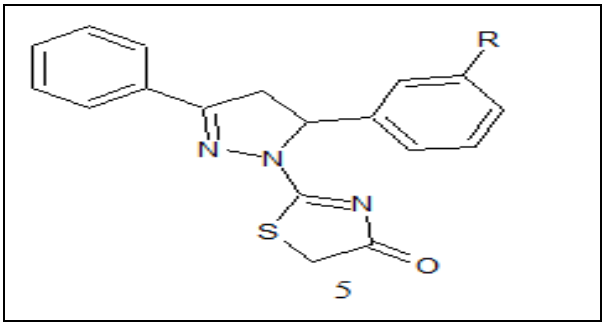
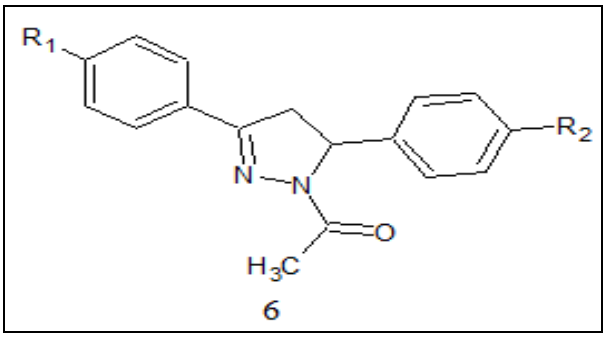
Havrylyuk *et al.* [12] have been identified many novel thiazolone-based compounds containing 5-aryl-3-phenyl-4,5 dihydro-1H pyrazol-1-yl framework 5. The compound synthesized were tested for their

cytotoxic activity *in-vitro*. Most of the compounds examined demonstrated promising anticancer activity compared to several forms of cancer, including leukaemia, melanoma, thyroid, colon, ovarian, renal, prosthetic, lung and breast cancer cell lines.



5

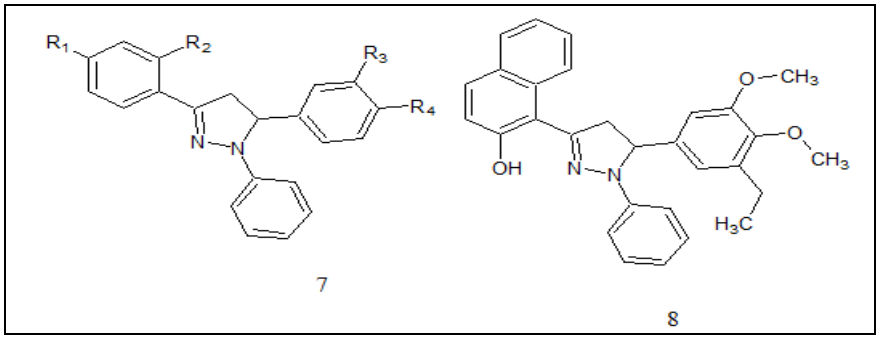
A series of replacements were prepared by Manna *et al.* [13] Pyrazolines structure 6 (1-(3-phenyl-5-(p-tolyl)-4, 5-dihydro-1H-pyrazol-1-yl) ethan-1-one) and tested for their anticancer role. Action and for their ability to inhibit multidrug resistance mediated through p-glycoprotein by direct binding to a purified an ATP- binding site and a protein domain-containing interacting region modulator compound discovery to bind to higher-affinity P-glycoprotein.



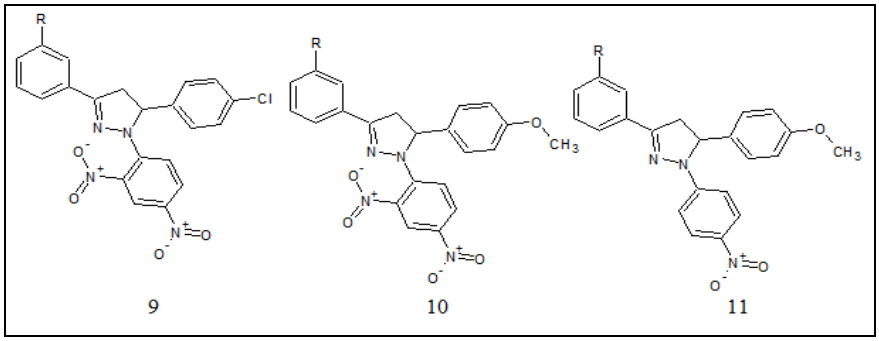
6

CNS Effects: The reported central nervous system (CNS) pharmacological role of pyrazoline derivatives includes antiepileptic and antidepressant effects and neurodegenerative disorders.

Antidepressant Activity: Some 1,3,5-triphenyl-2-pyrazolines having the general formula 7 and 3-(2-hydroxynapthalen-1-yl)-1,5-diphenyl-2 pyrazolines 8were synthesized by Prasad *et al.* [14] and their antidepressant activity was evaluated.

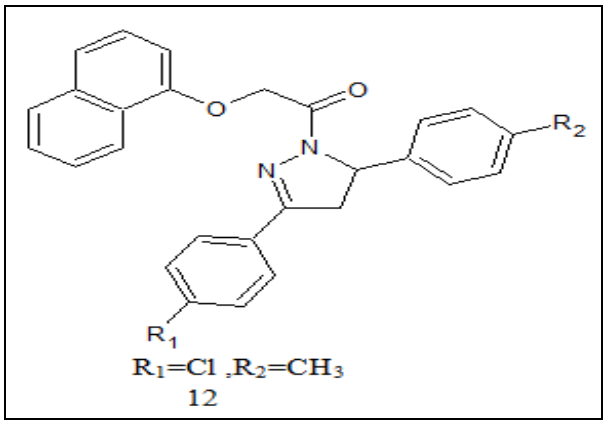


Antiepileptic Activity: Several 3-(3-acetoamino) phenyl-1,5-substituted phenyl-2 pyrazolines 9-11 have been synthesized and tested for their anticonvulsant activity by Singh *et al.* [15] The synthesized pyrazolines 9-11 displayed anticonvulsant activity, which was reflected by the safety observed by 60-80 percent versus seizures by PTZ. By inhibiting the oxidation of some nicotinamide-adenine-dinucleotide substrates, these compounds demonstrate their anticonvulsant ability.



Antiamoebic Activity: Compound 12 (1-(3-(4-aminophenyl)-5-(4-hydroxyphenyl)-4, 5-dihydro-1H-pyrazol-1-yl)-2-(naphthalen-1-yloxy) ethan-1-one) were synthesized by Hayat *et al* [16] and tested *in-vitro* for their anti-amoebic activity against *Entamoeba histolytica* strain HM1: IMSS.

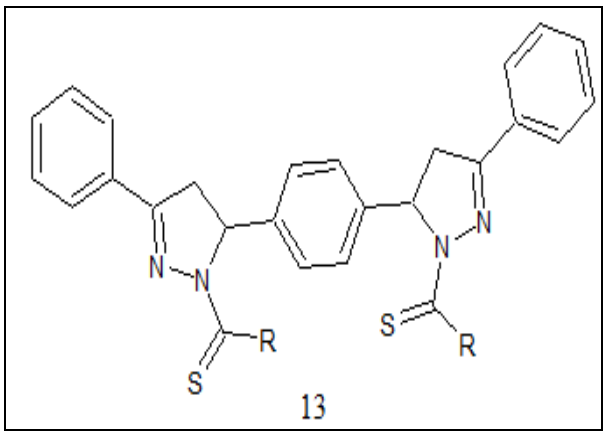
The findings showed that the antiamoebic activity of these compounds was promising (IC_{50} = 0.05, 0.31, 0.06 and 0.29 μM, respectively)



12

Some interesting bis-pyrazolines 13 prepared by cyclizing chalcones with N-4- substituted thiosemicarbazides under basic conditions by Bhat *et al.* [17].

Anti-amoebic activity research found that compounds with aromatic substituents were more active in the thiocorbamoyl group than in the cyclic groups.



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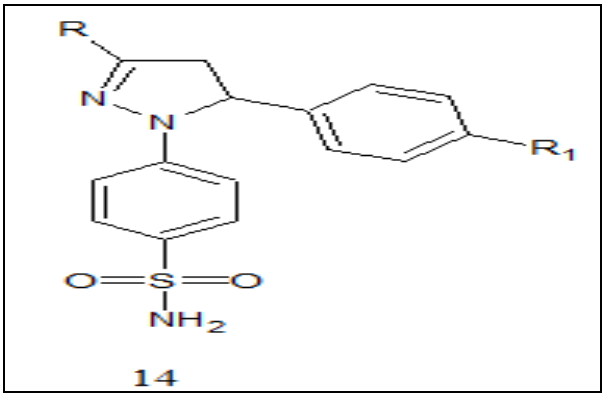
Anti-inflammatory, Antipyretic and Analgesic Activities: Rathish *et al.* [18] Synthesized the new 1, 3, 5-trisubstituted pyrazolines bearing sulphonamides 14 of benzene and evaluated multiple compounds, their anti-inflammatory activity promising activity demonstrated.



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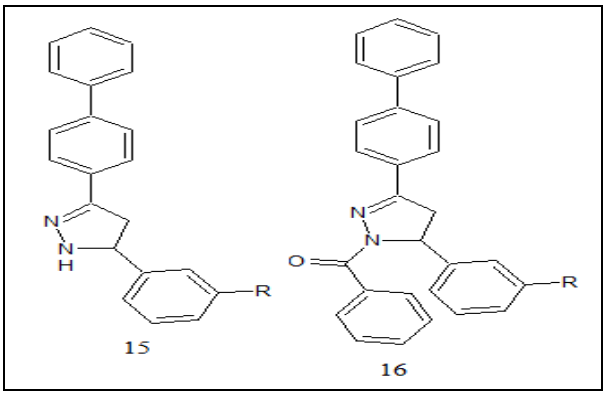
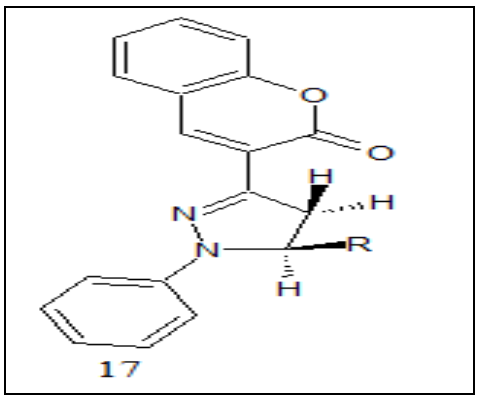
Amir *et al.* [19] have published a series of 3-(4-biphenyl)-5-replacement phenyl-2-pyrazolines 15 and 1-benzoyl – 3 - (4-biphenyl) – 5 - replacement phenyl-2-pyrazolines 16 and have been screened for their anti-inflammatory and analgesic activity.



15 16

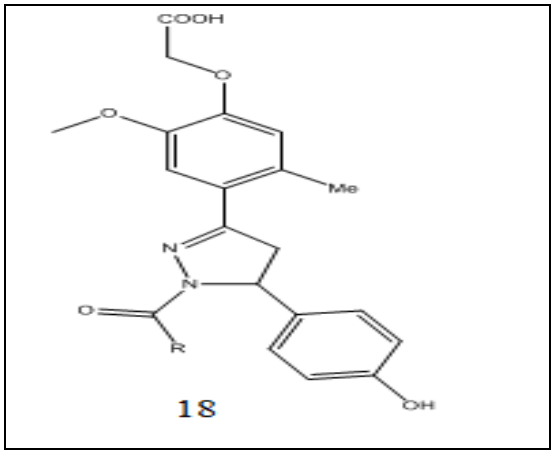
Khode *et al.* [20] synthesized screened as sequence of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl 2 pyrazolines 17 for in vivo anti-inflammatory analgesic activity.



17

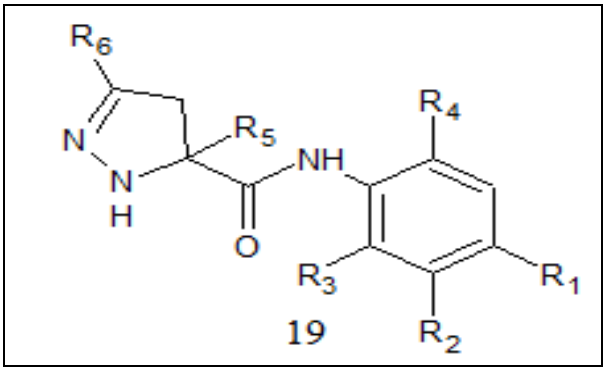
Antiviral Activity: The frequency of viral infections has been gradually growing. Emerging on a global scale and re-emerging. Effectual there has been a much slower production of antiviral drugs than other forms of chemotherapy with anti-infective agents.

Some new 4,5-dihydropyrazoles derivatives of N-acetyl and N-thiocorbamoyl 18 have been synthesized by EI-Sabbagh *et al* [21] and tested against a wide variety of viruses in different cell cultures N-Acetyl 4,5-dihydropyrazole was the only active compound in HEL cell cultures with an EC_{50} value of 7 µg/ml at subtoxic concentrations against vaccinia virus (Lederle strain).



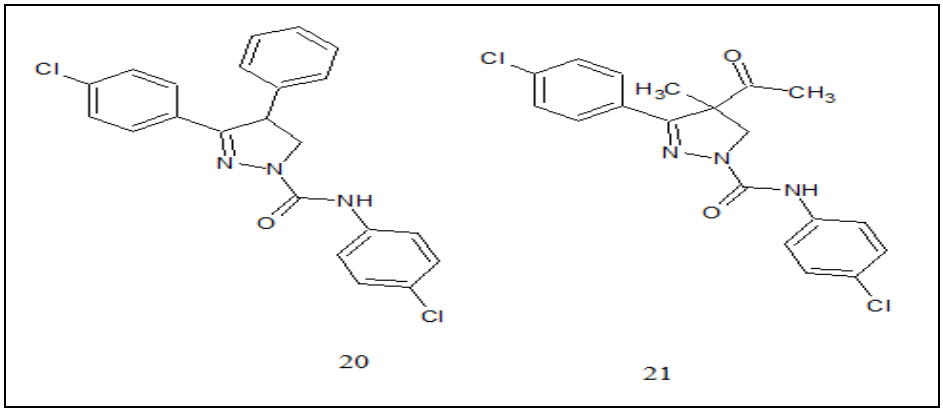
18

Antisteroidal Activity: Zhang *et al.* [22] engineered several general formulas 19 pyrazolines and tested them as tissue-selective androgen receptor modulators by *in-vivo* screening (SARMs). As well as the core pyrazoline ring and the anilide linker, SARs were investigated at the R1 to R6 positions. Large electron-withdrawing groups at the positions of R1 and R2 and small groups at the positions of R5 and R6 were found to be optimal for androgen receptor agonist action.



19

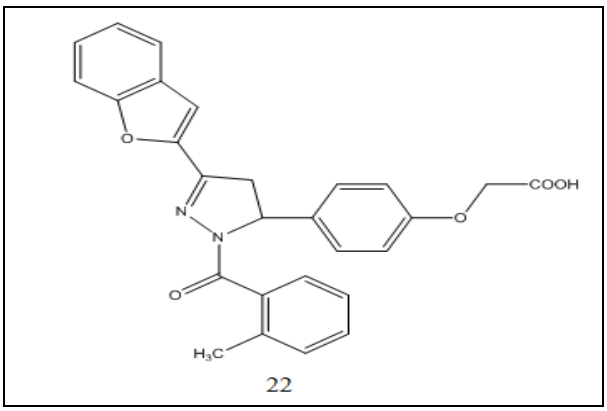
Insecticidal Activity: Some insecticides related to pyrazolines (methyl 3-(4-chlorophenyl)-1-((4-chlorophenyl) carbamoyl)-4-methyl-4,5-dihydro-1H-pyrazole-4-carboxylate) 20 and 21 were synthesized by Silver and Soderlund *et al.* [23] and their mode of action based on electrophysiological, pharmacological and toxicological information was examined. Eventually, these compounds were found to exert their insecticidal activity through neuronal targets.



20 21

Antioxidant Activity: A novel series of pyrazolines derivatives have been synthesized by Babu *et al.* [24] and evaluated their antioxidant activity at various concentrations against standard ascorbic acid.

The pyrazoline 22 (2-(4-(3-(benzofuran – 2 - yl) – 1 - (2 - methylbenzoyl) - 4, 5-dihydro-1H-pyrazol-5-yl) phenoxy)acetic acid) among the series of the synthesized compounds showed excellent antioxidant activity as compared with ascorbic acid.



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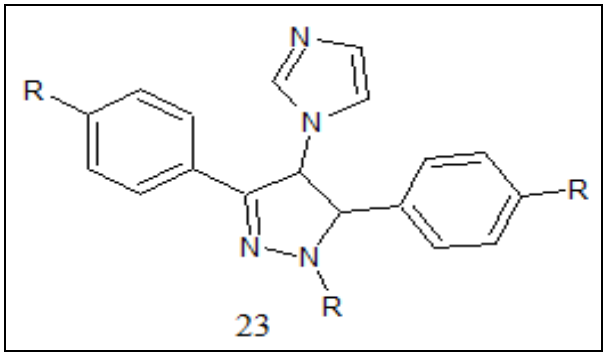
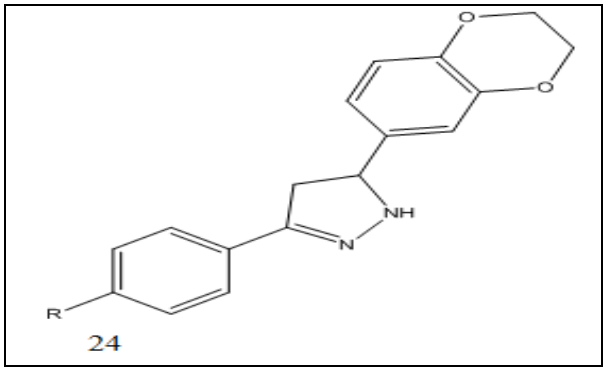
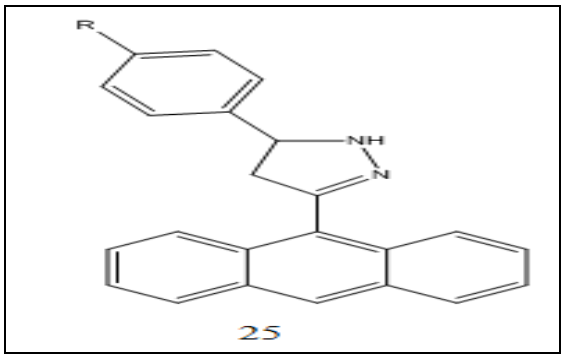
Antimycobacterial Activity: The synthesis of 1-(3, 5-diaryl-4, 5 – dihydro - 1H-pyrazole - 4 -yl)-1H-imidazole derivative 23 was reported by Zampieri *et al.* [25] and tested against strains of C. A strain of albicans and M. H37Rv tuberculosis.



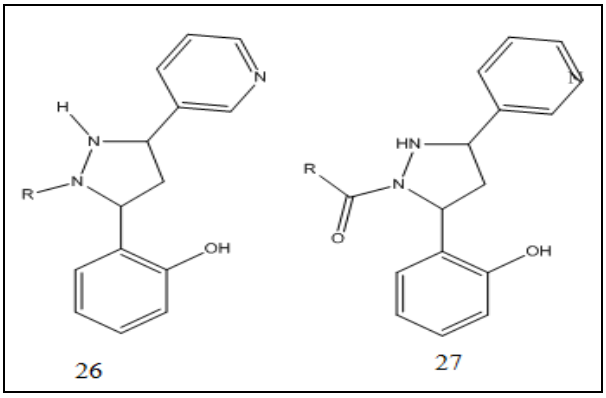
Antihepatotoxic Activity: Some novel 1,4-dioxane ring system pyrazoline derivatives were prepared by Habibullah Khalilullah *et al* [26]. Some of the synthesized compounds 24 (5-(2,3-dihydrobenzo[b] [1,4] dioxin-6-yl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazole) were tested against ccl_4-induced hepatotoxicity in rats for antihepatotoxicity activity. Important activity comparableto standard drug silymarin was demonstrated by compounds.



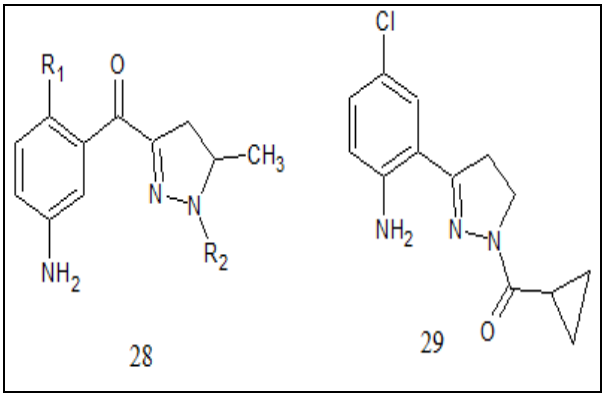
Acetyl Cholinesterase Inhibitory Activity: The acetylcholinesterase inhibitory property of diaryl pyrazoline derivatives was investigated by Nibha Mishra *et al* [27].



Raf Kinase Inhibition: The 3D QSAR analysis for amino-substituted N-acetyl and N-aroylpyrazolines 26 as B-Raf kinase inhibitors was performed by Omprakash Tanwar *et al* [28], using a common five-point pharmacophore modal. The B-Raf inhibitory activity of selected compounds was investigated by Blackburn *et al.* [29] from a large screening library of n an N-acetyl and N-aroylpyrazolines 27.

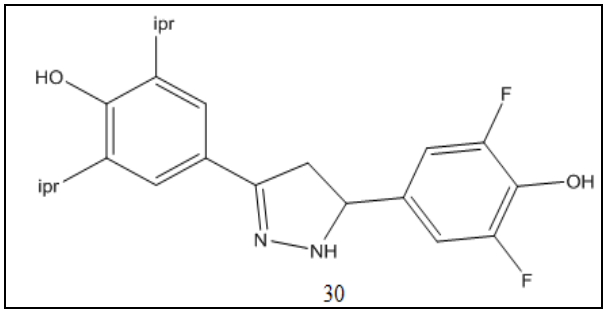


Nitric Oxide Synthaseinhibitors: In an attempt to find new compounds with neuroprotective activity, Camacho *et al.* [30] have synthesized a new series of neural nitric oxide synthase (nNOS) inhibitors with 4, 5- di hydro-1h-pyrazole structure 28 pyrazolines 29 showed the highest activity with70 percent inhibition percentages.



Cholesterol Metabolism Modulators: A sequence of 3-(3,5 dialkyl-4-hydroxyphenyl)5-(multi substituted- 4-hydroxyphenyl)-2-pyrazolines have been prepared and evaluated for their inhibitory activity on acetyl coenzyme A cholesterol acetyltransferase which is responsible for the formation of the mevalonate pathway cholesterol precursor acetoacetyl CoA [31].

As an example of this series, pyrazoline 30 displayed *in-vitro* inhibitory activity on hACAT-1 and-2 [32].



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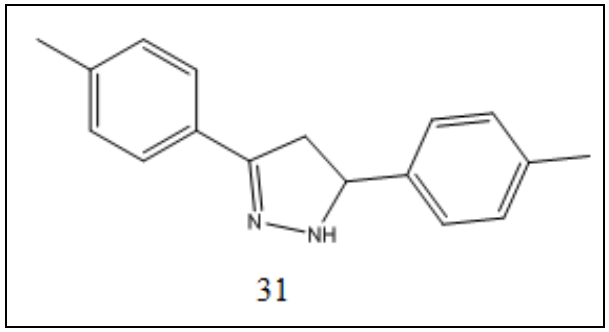


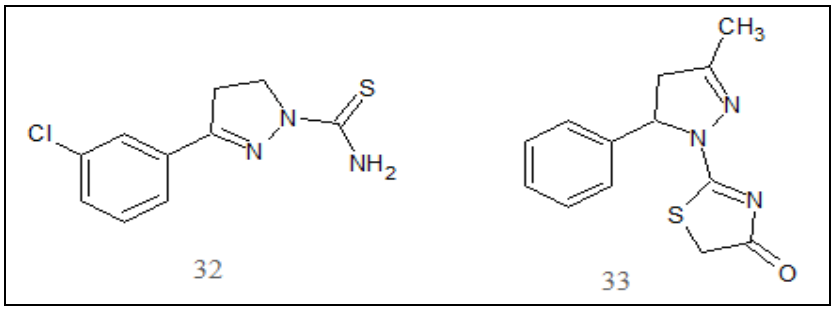
31

Antimalarial: A new series of N-formyl-pyrazoline derivatives were prepared by Insuasty *et al.* [35] and demonstrated their antimalarial activity. Compound 31 demonstrated excellent antimalarial activity. Wanare *et al* [36] synthesized pyrazoline analogues 33 and evaluated for both chloroquine-sensitive strain (3D7) and chloroquine-resistant field isolate (RKL9) antimalarial activity of P. with falciparum. All of the compounds tested demonstrated promising antimalarial activity. B.N. synthesized a sequence of 1, 3, 5- trisubstituted pyrazolines. Acharya *et al* [37] assessed *in-vitro* antimalarial efficacy against Plasmodium falciparum strains susceptible to chloroquine (MRC-02) and immune to chloroquine A (RKL9) and obtained encouraging results.

Antitrypanosomal Activity: Pyrazoline derivatives based on semi-carbazone described by compound 32 were designed as drug candidates for Chagas disease (American trypanosomiasis) [38]. As low as 80nm, compound 32 demonstrated inhibitory activity versus Trypanosoma cruzi.

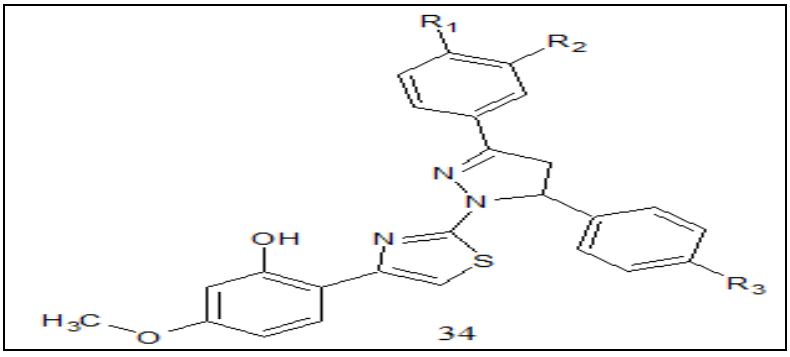
Interestingly, compound 32 and its analogues demonstrated their antitrypanosomal behaviour by targeting cysteine protease cruzain with low cellular toxicity.

Seebacher *et al.* [38] Along with a few others, I prepared compound 32 in 2003. Moderate activity against T cruzi [39] was shown by compound 33.



32 33

Hypotensive Activity: Several 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazolines 34 were synthesized by Turan-Zitouni *et al* [40] and their hypotensive behaviour was examined by the tail-cuff process.



34

All of the pyrazolines synthesized demonstrated sub substantial hypotensive behaviour comparable to clonidine as a reference drug.

CONCLUSION: Substituted Pyrazoline has been synthesized successfully using a variety of methods. The screening results indicated the nature

of substitution in newly synthesized compounds that affected biological activity. All of the synthesized compounds demonstrated improved biological activity against a variety of microorganisms. Pyrazoline is a biologically important compound that has attracted the attention of many medicinal chemists. This review looks at the pharmacological profiles of various pyrazoline derivatives. This article is a valuable resource for future research on bioactive pyrazoline rings and for better medicinal agent developments. This review aims to provide a forum to have all the scholars, academicians, chemists, and industrialists' details about pyrazolines' therapeutic activity.

ACKNOWLEDGEMENT: We sincerely thank the department of chemistry, Govt. Motilal Vigyan Mahavidyalaya, Bhopal, India, for providing necessary facilities.

CONFLICTS OF INTEREST: There is no conflict of interest.

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How to cite this article:
Pradhan A and Dwivedi P: Pharmaceutical potential of a resourceful nitrogen-containing heterocycle: pyrazoline-a review. Int J Pharm Sci & Res 2022; 13(12): 4848-56. doi: 10.13040/IJPSR.0975-8232.13(12).4848-56.