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PHARMACOLOGICAL ACTIVITIES OF PYRAZOLONE DERIVATIVES

Rishi Ram Parajuli, Priyanka Pokhrel, Amish Kumar Tiwari, Janmajoy Banerjee*
Department of Pharmacy, Sunsari Technical College, Dharan, Nepal

Pyrazoline is a five member heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. The review of the literature shows that the pyrazoline derivatives are quite stable and has inspired the chemists to synthesize the new pyrazoline derivatives. The past studies of pyrazoline derivative revealed that they are useful in pharmaceutical and agrochemical research. Pyrazoline derivatives display various pharmacological activities such as antitumor, antitubercular, antimicrobial, antibacterial, anti-inflammatory and antioxidant etc. and the pharmacological activities of different synthesized compound are reviewed in the present article.

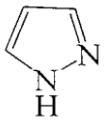
Key words: Pyrazoline, antimicrobial, anti-inflammatory, antitumor activity

INTRODUCTION

Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as Azoles [1]. It has only one endocyclic double bond and is basic in nature. The best described property of almost every group of pyrazoles is in the treatment of inflammation and inflammation associated disorders, such as arthritis [2]. Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as antimicrobial [3], antiviral [4], antitumor [5, 6], antihistaminic [7], antidepressant [8], anti-inflammatory [9], tranquillizing [10], anticancer [11, 12], anti-hypertensive [13], anti-arrhythmic [14], psychoanaleptic [15], anticonvulsant [16] & anti-diabetic activities [17]. Mostly pyarazolone are synthesized taking ethylacetoacetate and substituted hydrazine as starting chemicals. Pyrazolone was first prepared by Knorr in1883 when he was trying to synthesis quinoline derivatives, but he obtained pyrazolone derivative called antipyrin , and also called phenazone .Pyrazolone can be considered as intermediate compound for synthesis of various cyclic compounds of high biological activity.

Pyrazoline is basic in nature. An intra molecular conjugated charge transfer process has been reported to exist in it in the excited state.

The conjugated part (–N1–N2–C3–) of the ring, the nitrogen atom at the 1-position and the carbon atom at the 3-position are, respectively, electron donating and withdrawing moieties. The carbon atoms at 4- and 5-positions do not conjugate with the remaining part of the ring. In general pyrazolones are yellow solids with high melting points and moderate solubility in water, alkaline and acidic solutions. They react with aldehydes in alcoholic basic medium and with the bromine to give high biologically active compounds. It is reported that pyrazolones undergo tautomerism to certain extent which are affected by substituent and solvents.

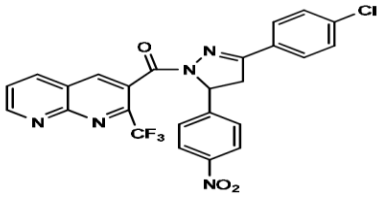


For Correspondence
jj.banderjee983@gmail.com

Pharmacological Activities

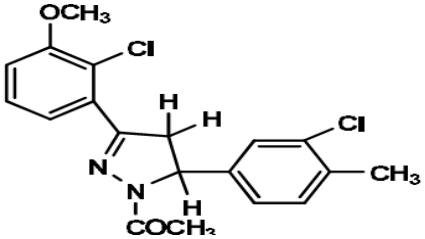
[A] Antibacterial activity

Mogilaiah et al [18] synthesized & found antibacterial activities of 1, 3, 4-Oxadiazole and pyrazoline derivatives containing 1, 8-Naphthyridine moiety. All the compounds were far less active than the standard drug (gentamycin) taken.

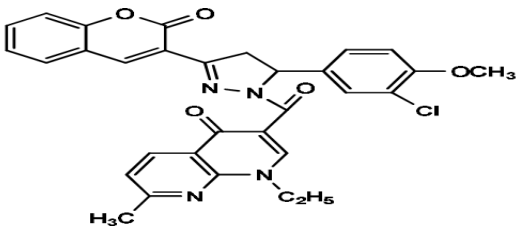


Vergiya et al [19] synthesized some new 3, 5-Diaryl-1-phenyl/isonicotinoyl-2-pyrazolines and evaluated its

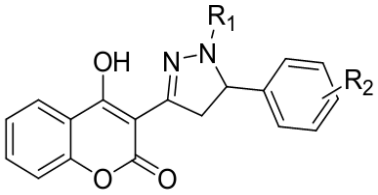
biological activity. All the synthesized compounds showed antibacterial activity against Gram +ve bacteria *S. Aureus*, *S.albus*, *S. pyogenes*, *S. Viridians* and Gram -ve bacteria *E. coli*, *S. Typhosa*



Waheed et al [20] synthesized certain substituted 1, 2-Pyrazolines from nalidixic acid as antibacterial and analgesic agents. They were found to have significant antibacterial activity against Gram –ve bacteria and possessed appreciable analgesic activity.

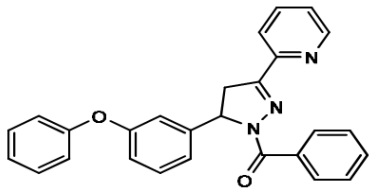


Abdullah et al [21] Synthesized of new 3-(5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-2H- chromene-2-one derivatives and evaluation of their antibacterial activity.

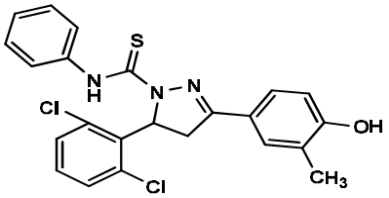


[B] Antitubercular activity

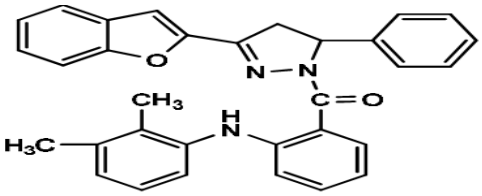
Kini et al [22] synthesized a novel series of heterocyclic o/m/psubstituteddiphenyl ether derivatives and determined their activity against H37Rv strain of Mycobacterium. All 10 compounds inhibited the growth at concentrations as low as 1 μg.ml-1. This level of activity was found comparable to the reference drugs rifampicin and isoniazid at the same concentration.



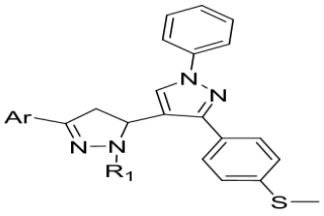
Ali et al [23] synthesized a series of 5-(-4-(Substituted) phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-toluidino methanethione and 5-(Substituted)phenyl-3- (4-hydroxy-3-methylphenyl)- 4, 5 – dihydro – 1H – 1 – pyrazolyl – 2 – methoxyanilino methanethione and tested for their *in vitro* antitubercular activity against *M. tuberculosis* H37Rv. Among the synthesized compounds, compound Anilino – 3 - (4 – hydroxyl – 3 – methylphenyl) – 5 - (2, 6-dichloro phenyl)-4, 5-dihydro- 1H- 1-pyrazolyl methanethione was found to be more active agent against *M. tuberculosis* H37Rv with minimum inhibitory concentration of 0.0034μM.



Babu et al [24] synthesized and evaluated biological activity of 1, 3, 5 – Trisubstituted pyrazolines bearing benzofuran. They were found to be antitubercular, antimicrobial and anti-inflammatory in nature.

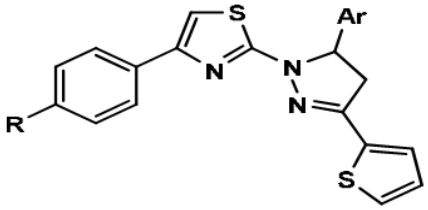


Joshi et al [25] Synthesized a series of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives and evaluation of their antitubercular activity.

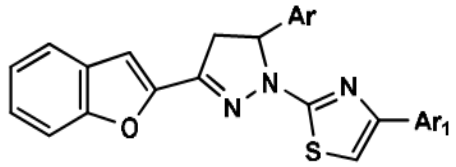


[C] Antimicrobial activity

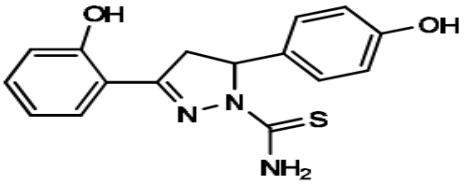
Ozdemir et al [26] synthesized several 1-(4-Aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives and investigated their antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Bacillus cereus*, *Streptococcus faecalis*, *Aeromonas hydrophila*, *Candida albicans* and *Candida glabrata*. A significant level of activity was observed.



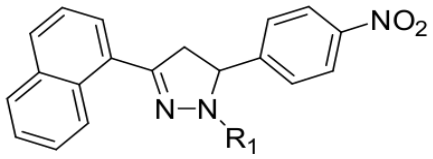
Abdelwahab et al [27] synthesized 1-(Benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3(Benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazolesand evaluated their antibacterial and antifungal activities at 100 µg concentration. Some of the compounds showed excellent antimicrobial activities than control drugs.



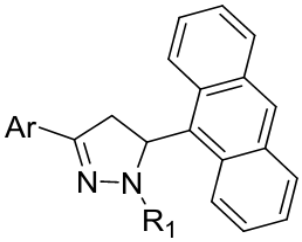
Stirrett et al [28] synthesized small molecules with structural similarities to siderophores and evaluated as novel antimicrobials against *Mycobacterium tuberculosis* and *Yersinia pestis*.



Agrawal et al [29] Synthesized of 1,3,5-trisubstituted pyrazoline derivatives and screening for their antimicrobial activity.

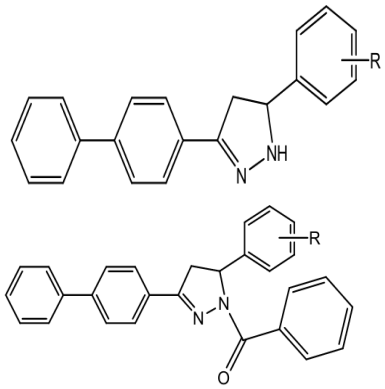


Hassan [30] synthesized new pyrazoline derivatives and evaluated their anti microbial activity.



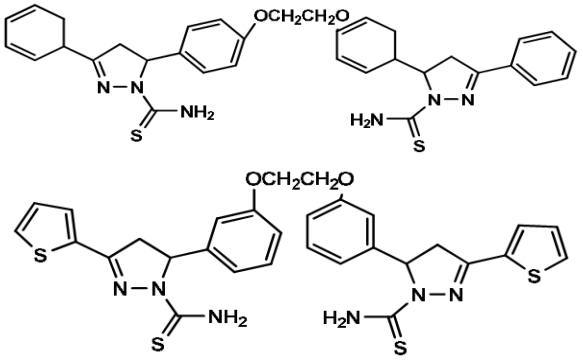
[D]Anti-inflammatory activity

Amir et al [31] synthesized a series of 3-(4-Biphenyl)-5-substituted phenyl-2-pyrazolines and 1-Benzoyl-3-(4-biphenyl)-5-substituted phenyl-2- pyrazolines and screened for their anti-inflammatory and analgesic activity. Among the compounds studied, compound-17 showed more potent anti-inflammatory and analgesic activity than the standard drug, along with minimum ulcerogenic index.

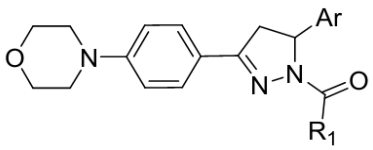


Barsoum et al [32] synthesized a variety of Bis(3 – aryl – 4, 5 – dihydro – 1H – pyrazole – 1 – carboxamides) and screened for their anti-inflammatory properties and PGE2 inhibitory properties (at a dose level of 50 $mg.kg^{-1}$) utilizing *in vivo* acute carrageenan – induced paw oedema standard method in rats. They exhibited that many of the tested compounds reveal considerable anti-inflammatory properties, especially which reveal remarkable activities related to indomethacin (which was used as a reference standard at a dose of 10 mg.kg-1 of body weight). They exhibited lower ulcer index

values than the used reference standard (indomethacin).



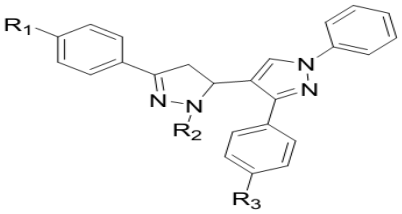
Khalil [33] synthesized 1 – acetyl/propanoyl – 5 – aryl – 3 – (4 – morpholinophenyl) – 4, 5 – dihydro – 1H – pyrazole derivatives and evaluated their anti-inflammatory activity.



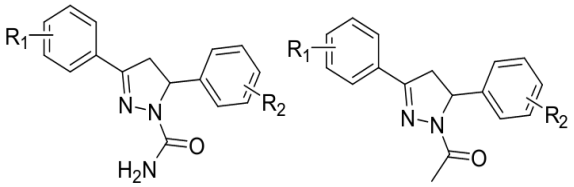
Mahesh et al [34] synthesized a new series of 3, 5-diaryl-1-phenyl-2-pyrazoline by cyclocondensation of chalcones with phenyl hydrazine. The compounds were screened *in vivo* for their anti – inflammatory activity by using carrageenan induced rat paw edema method. Compounds P4, P7, P8 , P10 have shown maximum anti-inflammatory activity.

[E] ANTITUMOR ACTIVITY

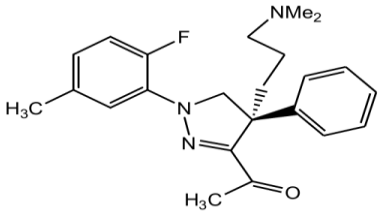
Braulio et al [35] synthesized a series of novel 3- aryl-4-(3- aryl -4, 5-dihydro-1H-pyrazol-5-yl)-1-phenyl -1H-pyrazoles and 1-substituted 3-aryl-5-aryl (hetaryl)-2-pyrazolines and screened their antitumor activity.



Zhu et al [36] Synthesized a series of 3-(substituted phenyl) - 5-(substituted phenyl) - 4, 5-dihydro-1H-pyrazole- 1-carbothioamide and 1-(5-(substituted phenyl)-3-(substituted phenyl)-4, 5-dihydro-1H-pyrazol-1-yl) ethanone as anticancer agents.

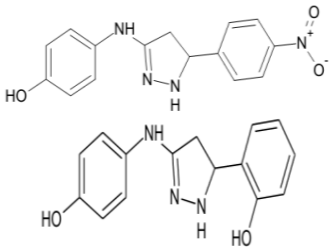


Havrylyuk et al [37] synthesized several novel thiazolone based compounds containing 5-Aryl-3-phenyl-4, 5-dihydro-1Hpyrazol-1-yl framework and tested for in vitro anticancer activity. Most of them displayed anticancer activity on leukemia, melanoma, lung, colon, CNS, ovarian, renal, and prostate and breast cancer cell lines. The most efficient anticancer compound-39 was found to be active with selective influence on colon cancer cell lines, especially on HT 29 (log GI50 = -6.37).



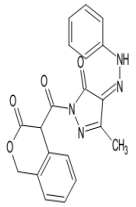
[F] ANALGESIC ACTIVITY:

Shau et al [38] synthesized a series of novel 4-(5-substituted aryl-4, 5-dihydropyrazole-3-yl-amino) phenols 2a-f where introduction of p-nitro and phydroxy group in aryl moiety of the pyrazoleanalogs 2c and 2e produce compounds with potent analgesic, anti-inflamatory and, in a few cases, antimicrobial properties.



Sivakumar et al [39], synthesized a series of (4Z)-3-methyl-1-[(2-oxo-2H-chromen-4-yl) carbonyl]-1H-pyrazole- 4, 5- dione 4- [(4- substituted phenyl) hydrazone] (5a-i). The titled compounds were screened for their anti-inflammatory and analgesic activity. Among the synthesized compounds, compound 5a, 5c, 5g and 5h exhibited significant anti-microbial activity

and compound 5a, 5b, 5d, 5h and 5i exhibited significant analgesic activity compared with the standard drug (indomethacin5mg/kg) at the dose level of 50mg/kg on oral administration.



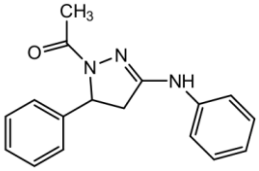
[G] ANTIFUNGAL ACTIVITY:

Baseer et al [40] synthesized fourteen new N-acetylated and non-acetylated pyrazoline derivatives by reacting chalcones with hydrazine in the presence of absolute ethanol however reaction was carried out in the presence of glacial acetic acid to afford N-acetylated pyrazolines. The pyrazolines (1-14) were screened for antifungal activity against *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus pterus*. Pyrazolines (1-14) found to exhibit well to excellent anti fungal properties

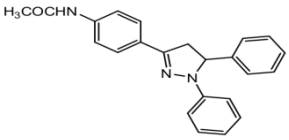
Ramiz et al [41] synthesized a series of new pyrazolone and pyrazole derivatives with expected anti fungicidal activity through the reactions 3-phenyl-1-H-pyrazol-5(4H)- one (3) and 4-(dimethyl amino methylene)-3-phenyl-1H-pyrazol-5(4H)-one (5) with a variety of electrophilic reagents and nucleophilic reagents.

[H] ANTICONVULSANT ACTIVITY:

Singh et al [42] synthesized a series of 1-[(4,5-dihydro-5-phenyl-3-(phenyl amino) pyrazol-1yl)] ethanone derivatives I-VI were synthesized and evaluated for their anticonvulsant activity against electric shock induced convulsion method. Compounds III and V are found to be the most potent compounds of all synthesized compounds.

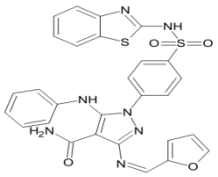


Singh et al [43] synthesized several 3-(3-Acetoamino) phenyl-1, 5-substituted phenyl-2-pyrazolines [21] which were evaluated for their anticonvulsant activity. All the substituted pyrazolines exhibited anticonvulsant activity, which was reflected by 30-80% protection observed against PTZ-induced seizures.



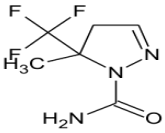
[I] ANTIHELMINTIC ACTIVITY:

Sreenivasa et al [44] synthesized a series of pyrazole derivatives and evaluated for their anthelmentic activity. Synthesized compounds of pyrazole derivatives were tested for anthelmintic activity against earthworms, Peritumaposthuma compared to standard Albendazole. VII P8, VIII P6,VIII P7, VIII P8, VIII P9, VIII P10, VIII P11, VIII P12 showed significant activity compared to standard Albendazole.

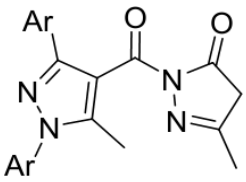


[J] ANTIOXIDANT ACTIVITY

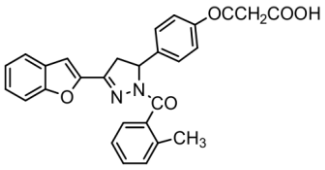
Pasin et al [45] synthesized a series of pyrazole derivatives and screened for their antioxidant activity. All compound showing good activity.



Umesha et al [46] Synthesized of 5-methyl-2- (5-methyl- 1,3-diphenyl-1H-pyrazole-4- carbonyl)-2, 4-dihydro- pyrazol-3-one and evaluation of their antioxidant activity.

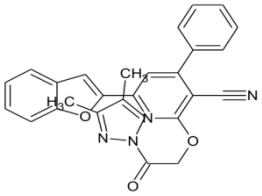


Babu et al [47] synthesized a series of pyrazoline derivatives and evaluated antioxidant activity at 1000, 500, 250, 100, 50, 25 and 10 mg.ml-1 concentrations against standard drug ascorbic acid. Six of the synthesized compounds showed interesting antioxidant activity as compared with ascorbic acid.



[K] CYTOTOXIC ACTIVITY

Zahar et al [48] synthesized a series of pyrazole derivatives which show good activity



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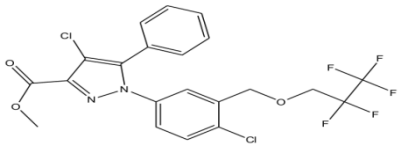
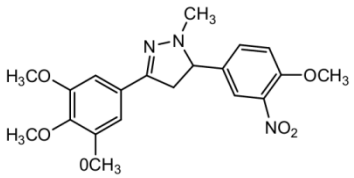
[L] HERBICIDAL

Noriaki et al [49] synthesized a series of 1,5-Diarylpyrazole Derivatives Some of these compounds showed noticeable pre-emergent herbicidal activities against various kinds of weeds. Among the synthesized compounds, methyl 4-chloro-1-(2,5-difluorophenyl)-5-(4-flurophenyl)-pyrazole-3-carboxylate 19t exhibited good activity. Diarylimidazole carboxylates and carboxamides were also synthesized, but they did not show any herbicidal activities.



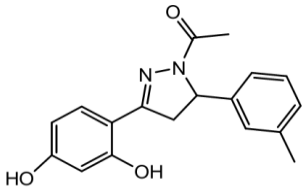
[M] ACE INHIBITORY ACTIVITY

Bonesi et al [50] synthesized a series of pyrazole derivatives and investigated their angiotensin I converting enzyme inhibitory activity by performing assay. The following pyrazole derivative-25 showed effective ACE-inhibitory activity with0.123m MIC value.



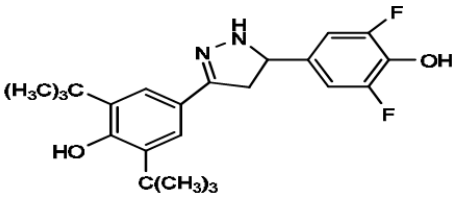
[N] ANTIHYPERTENSIVE ACTIVITY

Zitouni et al [51] synthesized some 1-(4-Arylthiazol-2-yl)-3, 5-diaryl-2- pyrazoline derivatives and investigated their hypotensive activity by the tail-cut method using clonidine as reference compound. All examined compounds showed appreciable hypotensive activities. One of the active compounds is given below



[O] CHOLESTEROL INHIBITORY ACTIVITY:

Jeong et al [52] synthesized a series of 3-(3, 5-Di-tert-butyl-4-hydroxyphenyl)-5-(multi-substituted 4-hydroxy phenyl)-2-pyrazolines and carried out their inhibitory activity on acyl-CoA: cholesterol acyltransferase.They showed invitroinhibitory activity on hACAT-1 and -2. One of the active compounds is shown below



CONCLUSION:

Pyrazolone moiety and its various derivatives was studied frequently in the past time and found potent in various pharmacological and pathological conditions, which are discussed in brief in this article.In conclusion,we have described thebiological activities of pyrazoline derivatives such as antitumor, antitubercular, antimicrobial, antibacterial, anti-inflammatory and antioxidant etc.Various other activities are also been studied like anticonvulsant,

anticancer, antihelmintic etc. Thus by studying all the derivatives showing variety of activities we can say that pyrazole ring have been explored in past years and is still be used for future development of new drugs against many more pathological conditions.

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