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Review Article

2 - PYRAZOLINE: A PHARMACOLOGICALLY ACTIVE MOIETY

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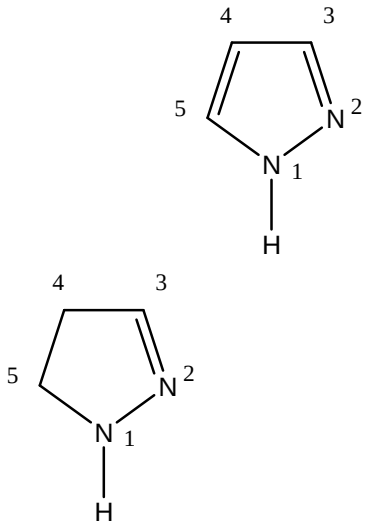
ABSTRACT
The aim of this review was to collate literature work reported by many researchers on 2-pyrazoline derivatives for their varoius pharmacological activities and also to report the recent efforts made on this moiety. This interesting group of compound has diverse biological activities such as antimicrobial, antimyobacterial, antiamoebic, antiviral, antihelminthic, antiparasitic, insecticidal, anti-inflammatory, analgesic, anticonvulsant, antidepressant, anticancer, anaesthetic, antidiabetic, antioxidant, ACE inhibitory, hypotensive, cholesterol inhibitory and selective activity such as Nitric oxide synthase (NOS) inhibitor and Cannabinoid CB1 receptor antagonists activity. The purpose of this review is to provide an overview of diverse pharmacological activities of 2-pyrazoline moiety. Various derivatives of 2-pyrazoline have been analysed in this review for varying pharmacological activities.

KEY WORDS: 2-Pyrazoline derivatives, analgesic, anti-inflammatory, anticancer, anticonvulsant, antimicrobial, antimycobacterial.

INTRODUCTION

Heterocyclic compounds are cyclic compounds in which the ring atoms are of carbon and some other element called as hetero atoms (for example N,S,O).Among five membered heterocyclic compounds containing two hetero atoms pyrazole is one of the most important in medicinal chemistry with regard to its widespreaded biological importance.

Pyrazoline is dihydropyrazole which is a five membered heterocyclic compound containing two nitrogen atoms in adjacent position having only one endocyclic double bond. Among all the pyrazoline dervatives 2-pyrazoline has gained the most importance because of its diverse biological activities.



Pyrazole
Pyrazoline/ 4,5-dihydropyrazole

Pyrazoline is basic in nature. An intramolecular 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 the synthesis of pyrazolines involves the base-catalyzed aldol condensation of aromatic ketones to give alpha,beta- unsaturated ketones (also named as chalcones), which undergo a subsequent cyclization reaction with hydrazine and hydrazine derivatives affording 2-pyrazoline and 2-pyrazoline derivatives. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2-pyrazolines in the presence of suitable cyclizing reagent like acetic acid.

2- pyrazoline may be regarded as one of the versatile lead compound for designing potent bioactive agents. This interesting moiety has been found to be associated with diverse biological activities such as antimicrobial, antimyobacterial, antiviral, antiamoebic, antihelminthic, antiparasitic, insecticidal, anti-inflammatory, analgesic, anticonvulsant, anti depressant, anticancer, anaesthetic, antidiabetic, antioxidant, ACE inhibitory , cholesterol inhibitory and selective activity such as Nitric oxide synthase (NOS) inhibitor and Cannabinoid CB1 receptor antagonists activity.

CLINICALLY AVAILABLE DRUGS CONTAINING PYRAZOLINE MOIETY

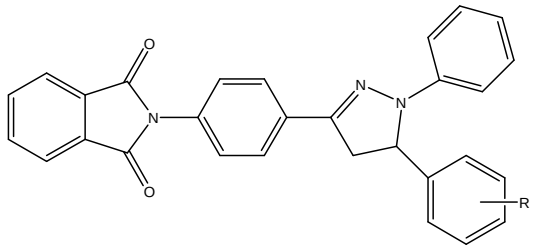
Numerous studies have been reported on the synthesis of a variety of pyrazoline derivatives covering a wide range of bioactivities. As a result, a large number of pyrazoline containing compounds have been developed, and some products have gained application on the clinical level such as azolid/ tandearil (anti-inflammatory), phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), indoxacarb (insecticidal), anturane (uricosuric) etc.

PHARMACOLOGICAL ACTIVITIES BASED ON LITERATURE REVIEW

Some of the 2-pyrazoline derivatives synthesized and evaluated for diverse biological activities by various researchers have been represented below.

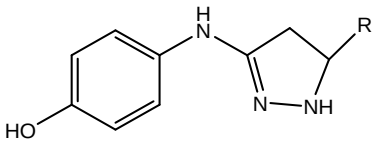
Anti-inflammatory and analgesic activity:

Meenakshi N. Deodhar *et al.*[1] reported synthesis and evaluation of anti-inflammatory activity of 2-(4-(1-Phenyl-5-(substituted phenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)isoindoline-1,3-dione [**1**]. A series of pyrazoline were prepared by treatment 1-(4-aminophenyl)-3-(substitutedphenyl) prop-2-en-1-one (chalcone) with phenyl hydrazine . Pyrazolines when treated with phthalic anhydride in presence of glacial acetic acid furnished phthalimide derivatives. Maximum of the synthesized compounds had shown interesting anti-inflammatory activity in carrageenin induced rat paw edema model [2] while three compounds exhibited good analgesic activity when screened against acetic acid induced writhings in mice [3].



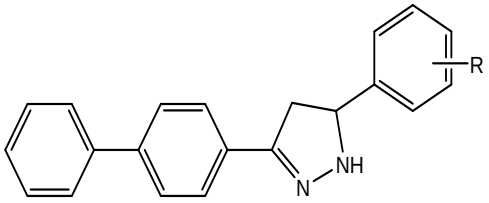
[**1**]

SK Sahu *et al.*[4] synthesized a series of novel 4-(5-substituted aryl-4, 5-dihydropyrazole-3-yl-amino) phenols [**2**] by treating substituted aryl-N-chalconyl amino phenols with hydrazine hydrate and investigated their analgesic and anti-inflammatory activities. The introduction of p-nitro and p-hydroxy group in aryl moiety of the pyrazole analogs resulted in potent analgesic, anti-inflamatory activity which were carried out by tail flick[5] and Carrageenan induced paw edema[2] method respectively.

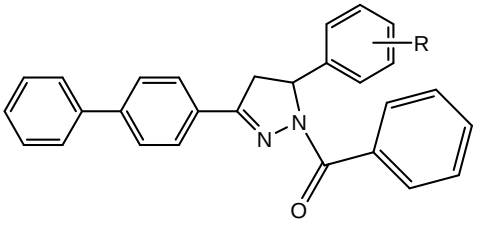


[**2**]

Amir *et al.*[6] reported a series of 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines [3] and 1-benzoyl-3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines [4] and screened them for their anti-inflammatory and analgesic activity.

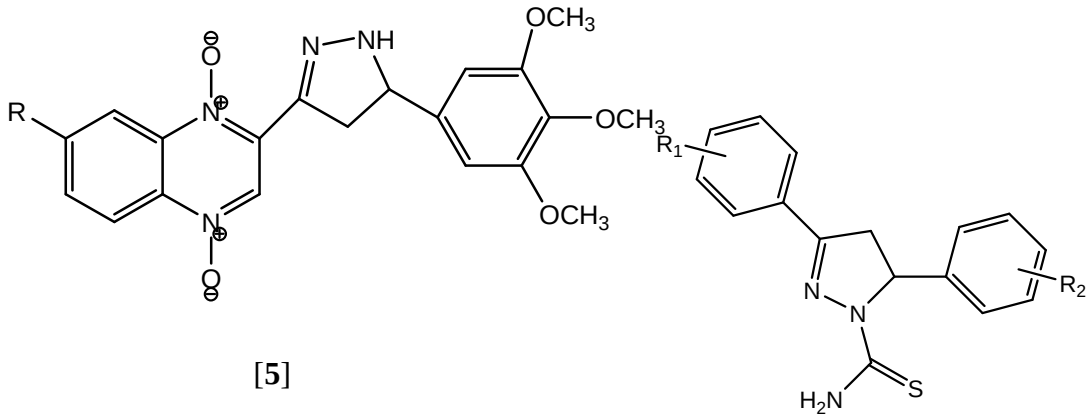


[**3**]



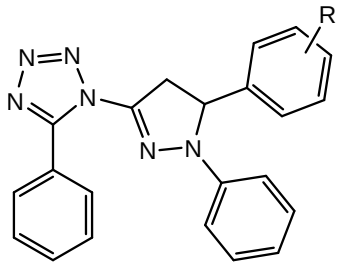
[**4**]

Asuncio´n Burguete *et al.*[7] synthesized pyrazoline derivatives [**5**] and evaluated them for their anti-inflammatory activities. Three compounds showed good anti-inflammatory activity against carrageenan induced rat paw edema method.



[**5**]

In attempt to find new pharmacologically active molecules, P.B. Mohite *et al.*[8] reported the synthesis and in vitro anti-inflammatory activity of various 1-[5-(substituted phenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]-5-phenyl-1H-tetrazole [**6**] .The anti-inflammatory activity of title compounds were examined by denaturation of proteins method. All the compounds exhibited weak to potent anti-inflammatory activity. Some derivatives bearing a methoxy group exhibited very good anti-inflammatory activity.



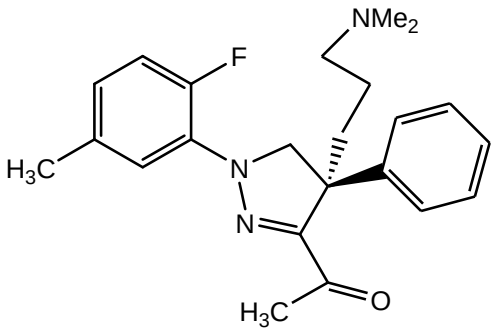
[6]

Antitumor activity

Peng-cheng Lv *et al* [9]synthesized a series of pyrazoline derivatives [**7**] which had been evaluated for antiproliferative activity.The compound carrying substitution R1= 3, 4- 2CH3 and R2=4-OCH3 resulted in high antiproliferative activity against MCF-7 with IC50 0.08 μM.

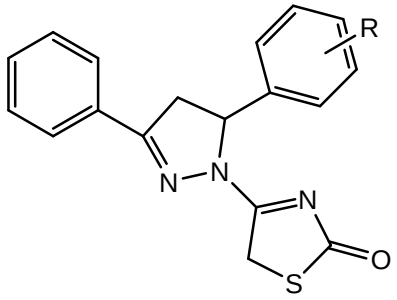
[**7**]

Roecker AJ *et al* [10] synthesized 1,4-Diaryl-4,5-dihydropyrazoles [**8**] which were evaluated their selective inhibitory effect against mitotic kinesin Spindle Protein (KSP) with IC50 of 0.2 nM and Cell EC50 values of 3.2nM.

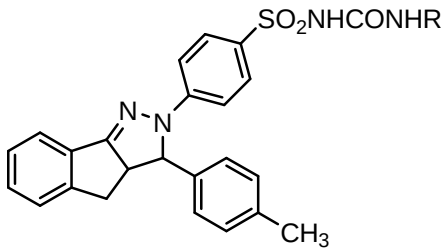


[**8**]

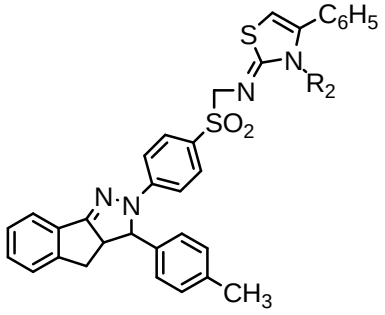
Havrylyuk *et al.*[10] synthesized novel pyrazoline derivatives containing thiazolone moiety [**8**] which were screened for anticancer activity in vitro. The compounds exhibited interesting anticancer activity on anticancer melanoma, lung, colon, CNS, ovarian, activity on leukemia, renal, prostate and breast cancer cell lines.



This research work by Mohammed S. M. Al-Saadi[11] describes the synthesis of some pyrazole and pyrazoline fused ring systems substituted with variable biologically-active chemical species. All of the newly synthesized target compounds were selected by the NCI for *in-vitro* antitumor screening. The following compounds [**9** and **10**] have passed successfully through the primary 3-cell line assay and were promoted for the full panel 60-cell line assay. These active compounds exhibited broad spectrum of antitumor activity against most of the tested tumor cell lines. Thesecompounds showed variable degrees of appreciable antitumor activity (GI50 and TGI MG-MID values range 14.1-19.5 and 38.0-53.7 μM, respectively).



[**9**]



R=cyclohexyl,phenyl
R2= phenyl,benzyl

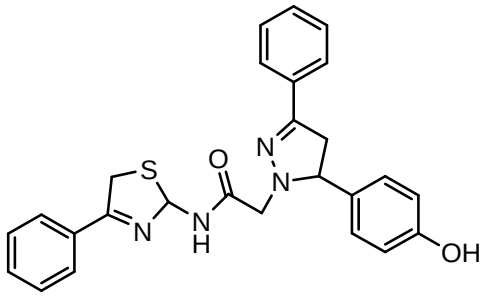
[**10**]

Antimicrobial activity

S. K. Sahu *et al* [3]synthesized novel novel 4-(5-substituted aryl-4, 5-dihydropyrazole-3-yl-amino) phenols [**2**] derivatives. The derivatives containing 4-NO2, 4-Cl, 2-OH substitutions showed potent Antimicrobial activity: Antibacterial activity was carried on muller hinton agar (Hi-media) plates by agar diffusion cup-plate method against Staphylococcus aureus, Salmonella typhi & E. coli. Antifungal activity was carried out on sabouraud dextrose agar plates by cup-plate method against Candida albicans & Aspergillus niger). Ciprofloxacin and cotrimazole were used as standard drugs for antibacterial and antifungal activity respectively.

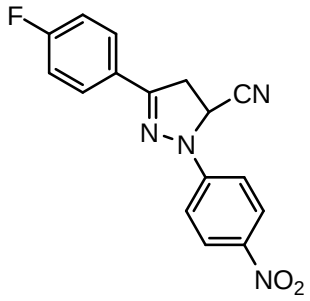
G. Saravanan *et. Al*[12], synthesized a series pyrazoline derivatives which were screened for anti-bacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, *Klebsiella pneumoniae* ATCC 11298)) and anti-fungal activities (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) by paper disc diffusion technique. Most of

the compounds exhibited significant anti-bacterial and anti-fungal activities. Among them 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4phenylthiazol- 2-yl) acetamide [**11**] was found to exhibit the highest anti-bacterial activity and 2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)- N-(4-phenylthiazol-2-yl)acetamide [exhibited highest anti-fungal activity.

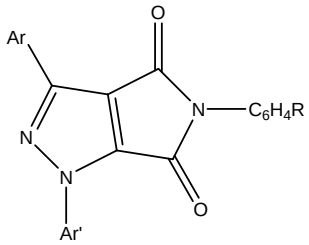


[**11**]

Nada M. Abunada *et al.*[13] reported the synthesis of a series of 2-pyrazolines and four of the newly synthesized compounds [**12** and **13**] were screened for their antibacterial activity against the Gram –ve bacteria *Escherchia coli* and the Gram +ve bacteria *Staphylococcus aureus*, in addition to their antifungal activity against *Asperagillus flavus* and *Candida albicans* using the agar diffusion method at a concentration 20 mg/mL using DMSO as a solvent. The compounds exhibited appreciable antimicrobial activity.



[**12**]

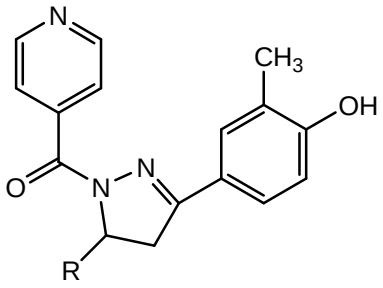


Ar = a,4-C_6H_4 ; b,2,4 $Cl_2C_6H_3$

Ar' = 4-$NO_2C_6H_4$; R= 4-Br,4-C_2H_5

[**13**]

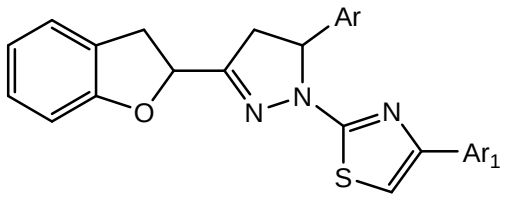
Shaharyar *et al.*[14] prepared a series of *N*1-nicotinoyl-3-(4'-hydroxy-3'-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines [**14**]and tested *in vitro* for their antimycobacterial activity. Compounds *N*1-nicotinyl-3-(4'-hydroxy-3'-methylphenyl)-5-(1'-chlorophenyl)-2-pyrazoline was the most active agent against MTB and INHR-MTB, with minimum inhibitory concentration of 0.26 μm .



[**14**]

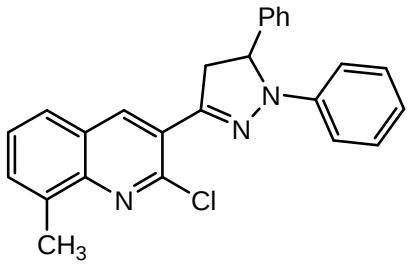
Abdelwahab *et al.*[15] synthesized 1-(Benzofuran-2-yl)-4-nitro-3-arylbutan-1-

ones and 3-(Benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1*H*-pyrazoles [**15**] [and evaluated their antibacterial and antifungal activities at 100 µg concentration. Some of the compounds showed excellent antimicrobial activities than control drugs.



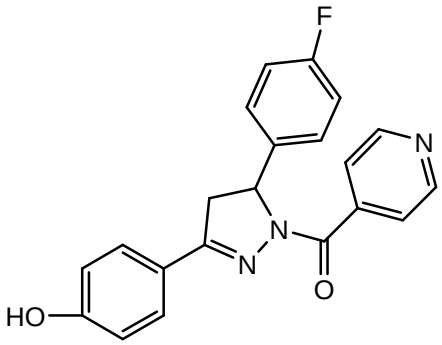
[**15**]

Bharmal *et al.*[16] synthesized some pyrazoline derivatives as biologically active agents. All the compounds exhibited interesting antimicrobial activity against *S. typhosa* and *A. niger*. One of the active compound [**16**] is represented below.



[**16**]

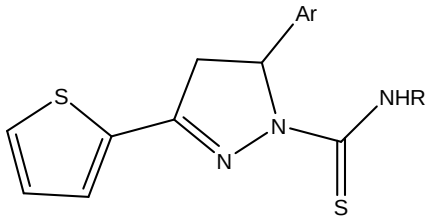
Shenoy *et al.*[17]synthesized 1, 3, 5-Trisubstituted-2-pyrazolines [**17**] and evaluated their antimicrobial activity. Some of the compounds exhibited good antitubercular activity.



[**17**]

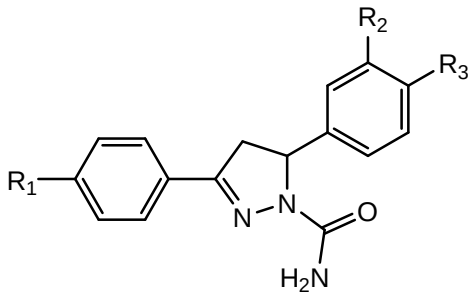
Anticonvulsant and Antidepressant activity

Zuhal Ozdemir et al.[18] synthesised twelve 3-(2-thienyl)pyrazoline derivatives 3-(2-Thienyl)pyrazoline derivatives. In the pharmacological studies, antidepressant and anticonvulsant activities of these compounds have been screened. The antidepressant activities of the compounds were investigated by Porsolt's behavioral despair test (forced swimming)[19] on albino mice and compared with tranylcypromine.Among the compounds examined, the compounds 1-N-Methylthiocarbamoyl-3,5-di-(2-thienyl)-2-pyrazoline and 1-N-Phenylthiocarbamoyl-3,5-di-(2-thienyl)-2-pyrazoline showed significant antidepressant activity. Anticonvulsant activities of the compounds were determined by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet.) tests, neurotoxicities were determined by rotarod toxicity test on albino mice. Compound 1-N-Phenylthiocarbamoyl-3-(2-thienyl)-5-phenyl-2-pyrazoline was found to be protective against MES in the range of 30–300 mg/kg dose levels at four hours. None of the synthesized compounds showed neurotoxicity at 30–300 mg/kg dose levels.



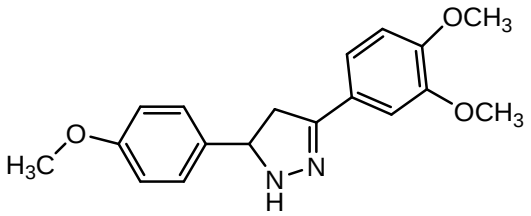
[**18**]

Some substituted 3,5-diphenyl-2-pyrazoline-1-carboxamide derivatives [**20**]were synthesized by Ravinesh Mishra *et al.*[20] from appropriate substituted 1,3-diphenylprop-2-en-1-one (chalcone) on reaction with semicarbazide hydrochloride . The final compounds were evaluated for anticonvulsant activity by the maximal electroshock seizure (MES) method. The neurotoxicity was determined by rotorod toxicity test on male albino mice. The preliminary results showed that all of the tested compounds were protective against MES at 100-300 mg/kg dose levels. The compounds numbered 4d-4e, 4j-4k, and 4m-4t were most protective against MES even at 30 mg/kg dose levels.



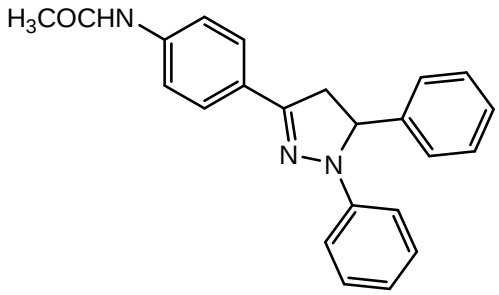
[**19**]

Palaska et al [21] synthesized ten new 3, 5-Diphenyl-2-pyrazoline derivatives and evaluated antidepressant activities of the synthesized compounds by the 'Porsolt Behavioural Despair Test' on Swiss-Wister mice. 3-(4-Methoxyphenyl)-5-(3, 4-dimethoxyphenyl)-2-pyrazoline [**20**] , 3-(4-methoxyphenyl)-5-(2-chloro-3, 4-dimethoxyphenyl)-2-pyrazoline and 3-(4-chlorophenyl)-5-(2-chloro-3, 4-dimethoxyphenyl)-2-pyrazoline reduced 41.94-48.62% immobility times at 100 mg.kg-1 dose level. In addition, it was found that 4-methoxy and 4-chloro substituents on the phenyl ring at position 3 of the pyrazoline ring increased the antidepressant activity; the replacement of these groups by bromo and methyl substituents decreased activity.



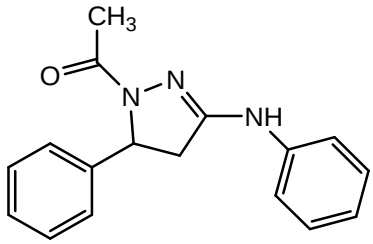
[**20**]

Singh S.P. *et al.*[22] 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. Most of these substituted pyrazolines inhibited selectively the *invitro* oxidation of substrates requiring nicotinamide adenine dinucleotide (NAD dependent) by rat brain homogenates.



[**21**]

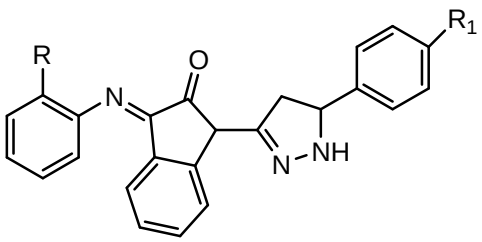
Anoop Singh, *et al*.[23] synthesized a series of 1-[(4, 5- dihydro-5-phenyl-3-(phenylamino) pyrazol-1yl)] ethanone derivatives **[22**] were synthesized and evaluated for their anticonvulsant activity against electric shock induced convulsion method. Compounds III and V are found to be the most potent compounds of all synthesized compounds.



[**22**]

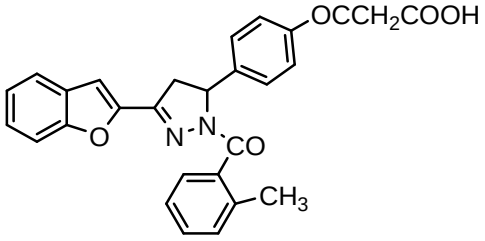
Antioxidant activity

P. Mondal *et al*.[24] synthesized a series of "novel 3[(substituted phenyl)imino] 1-3(substituted phenyl)4,4dihydro pyrazol-3-yl] 1- 3 di hydro 2H indole-2-one" [**23**] which were evaluated for anti-oxidant activity. The antioxidant activity the reducing power of the synthetic drug was determined by the method of Oyaizu. Substances which have reduction potential reacts withpotassium ferricyanide (Fe+3) to form potassium ferrocyanide (Fe+2) which then reacts with ferric chloride to form ferric ferrous complex that has an absorption maximum at 700nm. Accurately weighed 10mg of the synthetic drug in1ml of distilled water was mixed into the mixture of 2.5ml of 0.2m phosphate buffer (pH 6.6) and 2.5ml of 1% potassium ferricyanide. The mixture was then incubated at 500C for 20 minutes. Following incubation 2.5ml of 10% trichloro acetic acid was added to the mixture which was then centrifuged at 3000rpm for 10minutes. The upper layer of the solution (2.5ml) was mixed with distilled water (2.5ml) and FeCl3 (0.5ml, 0.1%). Increase absorbance of the reaction mixture was indicated the increased reducing power. It shows pmethoxy substitution makes more potent antioxidant.



[**23**]

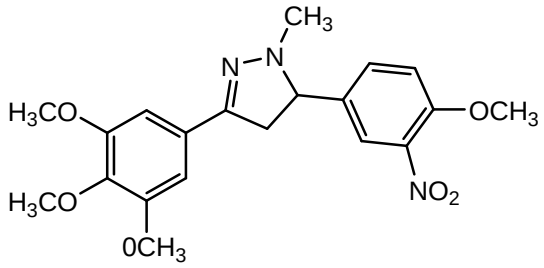
Babu *et al*.[25]synthesized a series of pyrazoline derivatives [**24**] and evaluated for antioxidant activity at 1000, 500, 250, 100, 50, 25 and 10 mg.ml-1 concentrations against standard drug ascorbic acid. Six of the synthesized compounds compounds showed interesting antioxidant activity as compared with ascorbic acid.



[**24**]

ACE inhibitory activity

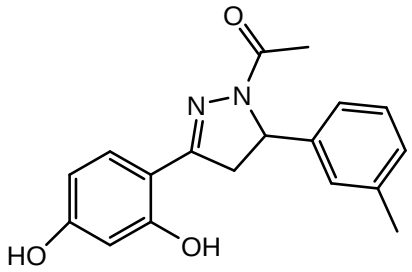
Macro Bonesi *et al.*[26], synthesized a series of pyrazole derivatives investigated their ngiotensin-I-converting enzyme inhibitory activity by performing assay.The following pyrazole derivative [25] showed effective ACE-inhibitory activity with 0.123 mM IC50 value.



[**25**]

Antihypertensive activity

Turan-Zitouni *et al.*[27] synthesized some 1-(4-Arylthiazol-2-yl)-3, 5-diaryl-2-pyrazoline derivatives and investigated their hypotensive activity by the tail-cutt method using clonidine as reference compound. All examined compounds showed appreciable hypotensive activities. One of the active compound is given [**27**] .

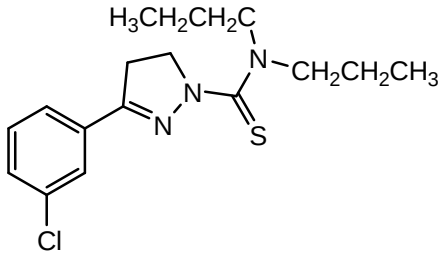


[**27**]

Antiamoebic activity

Abid *et al.*[28] synthesized a series of new 1-*N*-substituted cyclised pyrazoline analogues of thiosemicarbazones by cyclisation of Mannich bases with thiosemicarbazide and were subsequently evaluated for their antiamoebic activity by microdilution method against *HM1*:*1MSS* strain of *Entamoeba histolytica*.Following

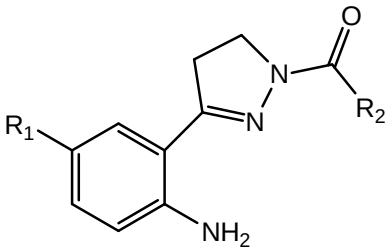
Compound [**28**] showed the most promising antiamoebic activity with an IC50 = 0.6 μM vs IC50 = 1.8 μM of metronidazole .



[**28**]

Nitric oxide inhibitory activity

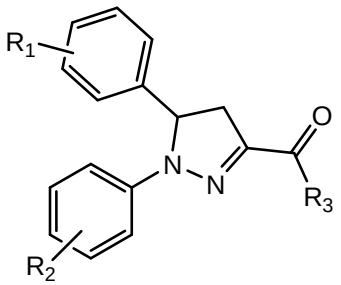
Camacho *et al.*[29] designed and synthesized some nNOS inhibitors with a 4,5-dihydro-*1H*-pyrazole derivatives [**29**] in an attempt to find new compounds with neuroprotective activity. Compounds 1-cyclopropanecarbonyl-3-(2-amino-5-chlorophenyl)-4,5-dihydro-*1H*-pyrazole and 1-cyclopropane carbonyl-3-(2-amino-5-methoxyphenyl)- 4,5-dihydro*1H*-pyrazole showed the highest activities with inhibition percentages of 70% and 62%, respectively .



[**29**]

Cannabinoid CB1 receptor antagonism activity

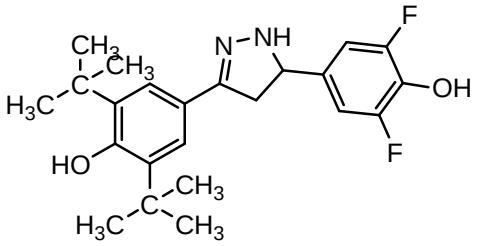
Srivastava *et al.*[30] synthesized a number of analogues of diaryl dihydropyrazole-3-carboxamides [**30**] and evaluated appetite suppression and body weight reduction in animal models. The lead compounds bisulfate salt of (±)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1Hpyrazole-3-carboxylic acid morpholin-4-ylamide and thebisulfate salt of (-)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide exhibited significant body weight reduction *invivo*, which is attributed to their CB1 antagonistic activity and showed a favorable pharmacokinetic profile .



[**30**]

Cholesterol inhibitory activity

Jeong *et al.*[31]synthesized a series of 3-(3, 5-Di-*tert*-butyl-4-hydroxyphenyl)-5-(multi-substituted 4-hydroxyphenyl)-2-pyrazolines and carried out their inhibitory activity on acyl-*CoA*: cholesterol acyltransferase. They showed *invitro* inhibitory activity on hACAT-1 and -2. One of the active compounds [**31**] is represented below.



[**31**]

CONCLUSION

Medicinal chemistry concerned with the invention, discovery, design, identification of biologically active compounds, the study of their metabolism, interpretation of their mode of action at the molecular level and the construction of structure activity relationship (SAR), the relationship between chemical structure and pharmacological activity for a series of compounds. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and biological activity.

2-Pyrazoline is a unique moiety that is associated with diverse biological activities. This article highlightened research work of many researchers reported in literature for number pharmacological activities on pyrazoline derivatives synthesized. 2-Pyrazoline derivatives have gained much attraction as anti-inflammatory, analgesic , antimicrobial ,anticanacer compounds. Much work must be carried out in order to have more clinically important compounds containing moiety.

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