



Pyrazoline Derivatives: A Worthy Insight into the Recent Advances and Potential Pharmacological Activities

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ABSTRACT

2-Pyrazolines display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), azolid/ tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric). Changes in their structure have offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity. In this context, the recently synthesized 2-pyrazoline derivatives possessing important pharmacological activities have been highlighted.

Keywords: 2-Pyrazoline derivatives, Potential pharmacological activities.

INTRODUCTION

The title compound (Pyrazoline) [1] is five-membered heterocyclic having two adjacent nitrogen atoms within the ring. It has only one endocyclic double bond and is basic in nature. [1] Among its various derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. [2] 2-Pyrazolines can be considered as a cyclic hydrazine moiety. [3] As follows from the X-ray analysis, it has the structure of the five-membered dihydropyrazole ring, has an envelope conformation [2]. [4] C₅ atom is deviated from the almost planar system of the other four atoms of the heterocyclic ring. [5] It plays a crucial role in the development of theory in heterocyclic chemistry and is also extensively used as useful synthons in organic synthesis. [6]

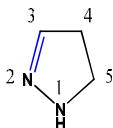


Fig.1. 4,5-Dihydro-1H-pyrazole/ Pyrazoline



Fig. 2: Single crystal X-ray structure of 1-Carboxamido-2-pyrazoline (ORTEP representation) [4]

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2-pyrazoline is insoluble in water but soluble in propylene glycol because of its lipophilic character. [7] It is known that the compounds of the 2-pyrazoline group that do not contain a substituent at the 1-position of the heteroring can react with benzaldehyde at high temperature (200°C) and in an inert atmosphere to give 4-benzylidine derivatives.

Pyrazoline derivatives, typical ICT (Intramolecular Charge Transfer) compounds [8], are known as a kind of fluorescent brightening agents because they have strong blue [9] fluorescence in solution. They have a hole transport tendency. [10] An intramolecular conjugated charge transfer process has been reported to exist in it in the excited state. In 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 above conjugated part. Its fluorescence spectrum exhibits a large red shift with an increase in the polarity of solvents. [8] These compounds show stronger fluorescence because of the double bond hindering which occurred due to cyclization.

Bulky groups in both the 4- and 5-positions improved both the fluorescence efficiency and the stability to light of the molecule. It has significance for the design of pyrazoline whitening agents. [11] Aryl group at position-5 is also responsible for spiroconjugated charge transfer quenching of pyrazoline fluorescence.

PHARMACOLOGICAL ACTIVITIES

2-Pyrazolines display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone/amidopyrene/ methampyrone (analgesic and antipyretic), azolid/ tandearil (anti-inflammatory), indoxacarb (insecticidal), anturane (uricosuric), etc. Considerable interest has been focused on the pyrazoline structure. The discovery of this class of drugs provides an outstanding case history of modern drug development and also points out the unpredictability of pharmacological activity from structural modification of a prototype drug molecule. It is having a variety of medicinal applications. Pyrazoline derivatives were found to have potential antipyretic-analgesic, tranquillizing, muscle relaxant, psycho analeptic, antiepileptic, antidepressant, anti-inflammatory, insecticidal and antimicrobial and antihypotensive activities. Their derivatives were also found to exhibit cytotoxic activity, inhibitory activity of platelet aggregation, herbicidal activity and cannabinoid CB₁-receptor modulators. Pyrazoline interest extended to dyes and dye couplers too.

Antiepileptic activity

Ozdemir *et al.* [12] synthesized twelve 1-phenyl-, 1-thiocarbamoyl- and 1-N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/ (2-furyl)-2-pyrazoline derivatives and studied their antiepileptic action by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet.) tests, neurotoxicities by rotarod toxicity test on albino mice. 1-Thiocarbamoyl-3, 5-di(2-furyl)-2-pyrazoline [3], 1-N-methylthiocarbamoyl-3, 5-di(2-furyl)-2-pyrazoline [4] and 1-N-ethylthiocarbamoyl-3, 5-di(2-furyl)-2-pyrazoline [5] were found protective against MES and scMet at 30-300 mg.kg⁻¹ dose levels.

Kucukguzel *et al.* [13] synthesized a new series of 4-Arylhydrazono-2-pyrazoline-5-ones derivatives and evaluated for their anticonvulsant activity. Compound [6] showed 40% protection against pentylenetetrazole (PTZ)-induced seizures in albino Swiss mice.

Singh *et al.* [14] synthesized several 3-(3-Acetoamino) phenyl-1, 5-substituted phenyl-2-pyrazolines [7] and 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 *in vitro* oxidation of substrates requiring nicotinamide adenine dinucleotide (NAD dependent) by rat brain homogenates.

Kornet *et al.* [15] synthesized 1-Phenyl-2-(phenylcarbamoyl) pyrazolidines [8] as potential anticonvulsant agents. These adduct showed little anticonvulsant activity in the MES and PTZ seizure assays.

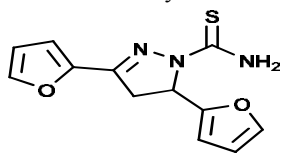


Fig.3. 3,5-di(furan-2-yl)-2-pyrazoline-1-carbothioamide

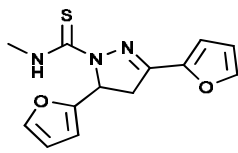


Fig.4. 3,5-di(furan-2-yl)-N-methyl-2-pyrazolin-1-carbothioamide

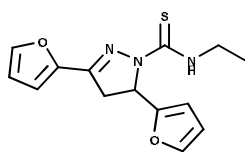


Fig.5. N-ethyl-3,5-di(furan-2-yl)-4,5-dihydro-N-ethyl-1,3,5-di(furan-2-yl)-2-pyrazolin-1-carbothioamide

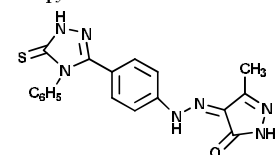


Fig.6. (Z)-3-methyl-4-(2-(4-(4-phenyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl)hydrazono)-1H-pyrazol-5(4H)-one

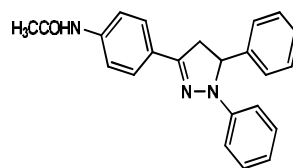


Fig.7. 3-(3-(3-acetamino)phenyl)-1,5-phenyl-2-pyrazoline

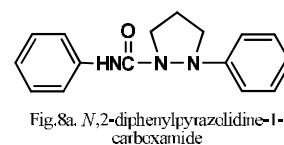


Fig.8a. N-(2-diphenylpyrazolidine-1-carboxamide)

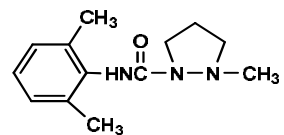


Fig.8b. N-(2,6-dimethylphenyl)-2-methylpyrazolidine-1-carboxamide

Antidepressant activity

Palaska *et al.* [16] synthesized ten new 3, 5-Diphenyl-2-pyrazoline derivatives and evaluated their antidepressant activities by the 'Porsolt Behavioural Despair Test' on Swiss-Webster mice. 3-(4-Methoxyphenyl)-5-(3, 4-dimethoxyphenyl)-2-pyrazoline [9], 3-(4-methoxyphenyl)-5-(2-chloro-3, 4-dimethoxyphenyl)-2-pyrazoline [10] and 3-(4-chlorophenyl)-5-(2-chloro-3, 4-dimethoxyphenyl)-2-pyrazoline [11] 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.

Prasad *et al.* [17] synthesized five new 1, 3, 5-Triphenyl-2-pyrazolines and another five new 3-(2'' Hydroxynaphthalen-1''-yl)-1, 5-diphenyl-2-pyrazolines and evaluated their antidepressant activity by the Porsolt behavioural despair test on Swiss-Webster mice. 1-Phenyl-3-(2''-hydroxyphenyl)-5-(4'-dimethylaminophenyl)-2-pyrazoline [12], 5-(4'-Dimethylaminophenyl)-1,3-diphenyl-2-pyrazoline, 1-Phenyl-3-(2''-hydroxynaphthalen-1''-yl)-5-(3',4',5'-trimethoxyphenyl)-2-pyrazoline, 1-Phenyl-3-(4''-methylphenyl)-5-(4'-dimethylaminophenyl)-2-pyrazoline [13] and 1-Phenyl-3-(4''-bromophenyl)-5-(4'-dimethyl amino phenyl)-2-pyrazoline reduced immobility times 25.63-59.25% at 100 mg.kg⁻¹ dose level. In addition, it was found that the compounds possessing electron-releasing groups such as dimethyl amino, methoxy and hydroxyl substituents, on both the aromatic rings at positions 3 and 5 of pyrazolines, considerably enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the phenyl rings.

Kelekci *et al.* [3] synthesized a new series of pyrazoline derivatives and evaluated for antidepressant, anxiogenic and MAO-A and -B inhibitory activities by *in vivo* and *in vitro* tests respectively. Most of the synthesized compounds showed high activity against both the MAO-A and MAO-B isoforms. However, none of the novel compounds showed antidepressant activity except for [14]. The reason for such biological properties was investigated by computational methods using recently published crystallographic models of MAO-A and MAO-B. These were due to the differences in the intermolecular hydrophobic and *H*-bonding of ligands to the active site of each MAO isoforms.

Jayaprakash *et al.* [18] synthesized several 3, 5-Diaryl carbothioamide pyrazolines designed as mycobactin analogs (mycobacterial siderophore) and evaluated their antidepressant and MAO inhibitory activity; because, they were in the search of designing antitubercular molecules with reduced MAO-inhibitory activity (since pyrazoline has

antidepressant and MAO inhibitory activity). They found that antitubercular compound [15] was also selective inhibitor of rat liver MAO-B.

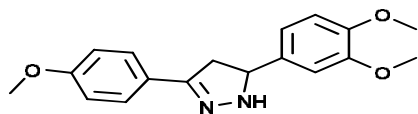


Fig.9. 5-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-pyrazoline

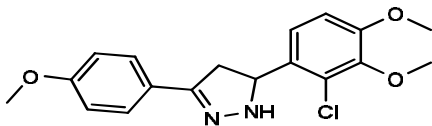


Fig.10. 5-(2-chloro-3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-pyrazoline

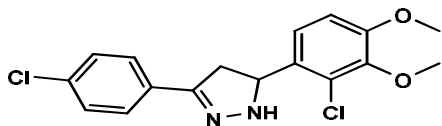


Fig.11. 5-(2-chloro-3,4-dimethoxyphenyl)-3-(4-chlorophenyl)-2-pyrazoline

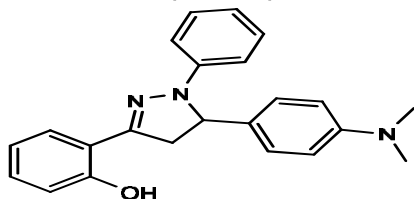


Fig.12. 2-(5-(4-(dimethylamino)phenyl)-3-phenyl-2-pyrazolin-3-yl)phenol

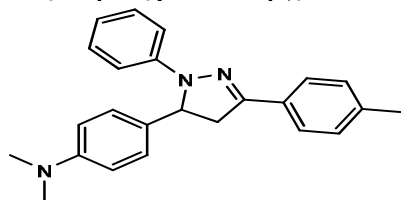


Fig.13. *N,N*-dimethyl-4-(1-phenyl-3-*p*-tolyl-2-pyrazolin-5-yl)aniline

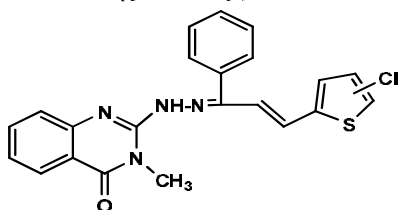


Fig.14. 3-methyl-2-(2-(1-phenyl-3-(chlorosubstituted thiophen-2-yl)allylidene)hydrazinyl)quinazolin-4-one

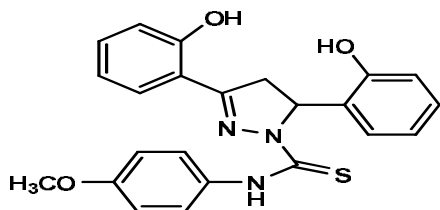


Fig.15. 3,5-bis(2-hydroxyphenyl)-*N*-(4-methoxyphenyl)-2-pyrazolin-1-carbothioamide

Anti-inflammatory activity

Barsoum *et al.* [19] synthesized a variety of Bis(3-aryl-4,5-dihydro-1*H*-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 [16.a and 16.b] which reveal remarkable activities relative 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).

Amir *et al.* [20] 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.

Rathish *et al.* [21] synthesized new 2-pyrazoline bearing benzenesulfonamide derivatives and screened for their anti-inflammatory activity at dose of 20 mg.kg⁻¹ (in carrageenan induced rat paw edema model) and volume of paw edema was measured at 0, 3 and 5 h. Two compounds [18.a] and [18.b] were found to be more active than celecoxib throughout the study (at 3 and 5 h). They were devoid of ulcerogenic potential when administered orally at a dose of 60 mg.kg⁻¹ of body weight.

Rani *et al.* [22] synthesized pyrazoline derivatives and evaluated for their anti-inflammatory activity against carrageenan induced oedema in albino rats at a dose of 50 mg.kg⁻¹ oral. All the compounds of this series showed promising anti-inflammatory activity. The most active compound of the series, 3-[1-Acetyl-5-(*p*-hydroxyphenyl)-2-pyrazolin-3-yl]indole [19] was found to be most potent, which had shown higher percent of inhibition of oedema, lower ulcerogenic liability and acute toxicity than the standard drug phenylbutazone.

Kelekc *et al.* [23] synthesized a novel series of 1-Thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-1*H*-pyrazole derivatives and tested for their *in vivo* anti-inflammatory activity by two different bio-assays namely, carrageenan-induced oedema and acetic acid-induced increase in capillary permeability in mice. In addition, analgesic and ulcerogenic activities were also determined. The combined anti-inflammatory data from *in vivo* animal models showed that compound [20] exhibited anti-inflammatory activity comparable to that of indomethacin with no ulcerogenic effects.

Khode *et al.* [24] synthesized a novel series of 5-(Substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines and screened for *in vivo* anti-inflammatory and analgesic activities at a dose of 200 mg.kg⁻¹ of body weight. Among the 12 prepared compounds, Compounds [21.a, 21.b, 21.c and 21.d] exhibited significant anti-inflammatory activity in model of acute inflammation such as carrageenan-induced rat edema paw.

Shoman *et al.* [25] synthesized a group of NO-donating 2-pyrazoline derivatives [22] and evaluated for their anti-inflammatory activity using carrageenan induced rat paw edema and compared to a well-known NSAID, indomethacin as a reference drug. The ability of the prepared compounds to induce gastric toxicity was also evaluated. Most of the prepared compounds showed significant anti-inflammatory activity at the injected dose of 100 mg.kg⁻¹ of body weight, but they were safer than indomethacin in regard to gastric toxicity. The incorporation of the NO-donating group into the

parent pyrazoline derivatives caused a non-significant reduction in the anti-inflammatory activity while a marked decrease in gastric ulcerations induced by their parent pyrazolines was observed.

Kaplancikli *et al.* [26] synthesized 1-[(Benzoxazole/Benzimidazole-2-yl) thioacetyl] pyrazoline derivatives [23] and evaluated for antinociceptive activities. All of the compounds (100 mg.kg⁻¹ of body weight) exhibited significant antinociceptive activities in both hot plate and acetic acid-induced writhing tests. Naloxone (5 mg.kg⁻¹ of body weight) pre-treatment reversed the antinociceptive activities suggesting the involvement of opioid system in the analgesic actions. None of the compounds impaired motor coordination of animals when assessed in the Rotarod model.

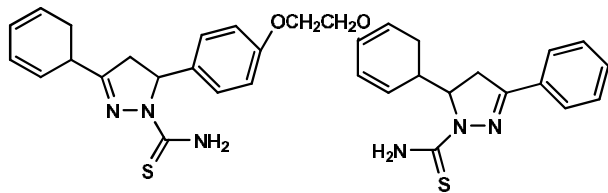


Fig.16a. 5,5'-(1,2-Ethanedylbis(oxy-4,1-phenylene)) bis(3-phenyl-2-pyrazolin-1-thiocarboxamide)

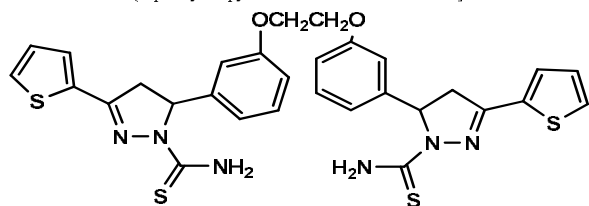


Fig.16b. 5,5'-(3,3'-(ethane-1,2-diylbis(oxy))bis(3,1-phenylene)) bis(3-(thiophen-2-yl)-2-pyrazolin-1-carbothioamide)

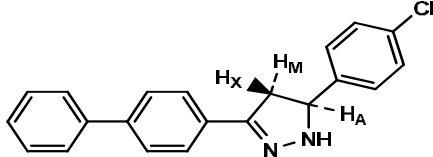


Fig.17. 3-(biphenyl-4-yl)-5-(4-chlorophenyl)-2-pyrazoline

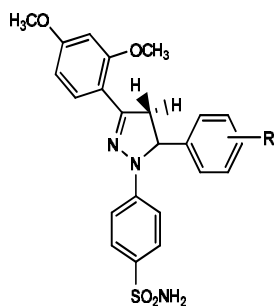


Fig.18. 4-(3-(2,4-dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2-pyrazolin-1-yl)benzenesulfonamide, where, R=3,4,5-(OCH₃)₂; 4-(3-(2,4-dimethoxyphenyl)-5-(4-(dimethylamino)phenyl)-2-pyrazolin-1-yl)benzenesulfonamide, where, R=4-N,N(CH₃)₂

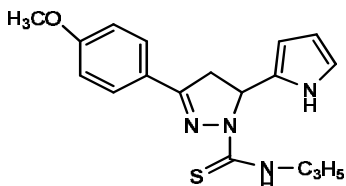


Fig.20. 1-N-Allylthiocarbonyl-3-(4-methoxyphenyl)-5-(2-pyrrolyl)-2-pyrazoline

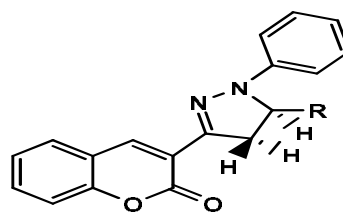


Fig.21. 3-(5-(4-chlorophenyl)-1-phenyl-2-pyrazolin-3-yl)-2H-chromen-2-one, where, R= 4-Cl-C₆H₄; 3-(5-(2,4-dichlorophenyl)-1-phenyl-2-pyrazolin-3-yl)-2H-chromen-2-one, where, R= 2,4-(Cl)₂-C₆H₃; 3-(5-(3-methoxyphenyl)-1-phenyl-2-pyrazolin-3-yl)-2H-chromen-2-one, where, R= 3-OMe-C₆H₄; 3-(5-(4-fluorophenyl)-1-phenyl-2-pyrazolin-3-yl)-2H-chromen-2-one, where, R= 4-F-C₆H₄;

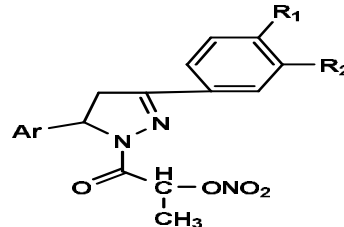


Fig.22. 5-(2-Furyl)-3-(3,4-dimethoxyphenyl)-1-(2-nitrooxypropionyl)-2-pyrazoline, where, R₁=R₂= OCH₃, Ar= Furyl; 5-(2,4-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-1-(2-nitrooxypropionyl)-2-pyrazoline, where, R₁=R₂= OCH₃, Ar= 2,4-Di-OCH₃ phenyl; 5-(2,6-Dichlorophenyl)-3-(3,4-dimethoxyphenyl)-1-(2-nitrooxypropionyl)-2-pyrazoline, where, R₁=R₂= OCH₃, Ar= 2,6-Di-Cl phenyl.

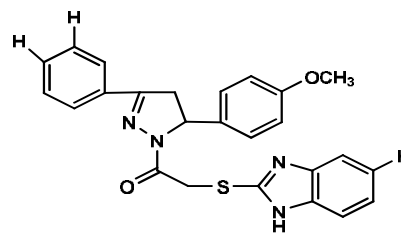


Fig.23. 2-(5-chlorobenzo[d]oxazol-2-ylthio)-1-(3,5-diphenyl-2-pyrazolin-1-yl)ethanone, where, R₁=R₂=R₃=H, R₄=Cl, X=O; 2-(5-chlorobenzo[d]oxazol-2-ylthio)-1-(3-(3,4-dimethylphenyl)-5-phenyl-2-pyrazolin-1-yl)ethanone, where, R₁=H, R₂=R₃=CH₃, R₄=Cl, X=O; 2-(5-chlorobenzo[d]oxazol-2-ylthio)-1-(5-(4-methoxyphenyl)-3-phenyl-2-pyrazolin-1-yl)ethanone, where, R₁=OCH₃, R₂=R₃=CH₃, R₄=Cl, X=O; 2-(1H-benzo[d]imidazol-2-ylthio)-1-(3,5-diphenyl-2-pyrazolin-1-yl)ethanone, where, R₁=R₂=R₃=R₄=H, X=NH

Antimicrobial activity

Ozdemir *et al.* [27] synthesized several 1-(4-Aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives [24] 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.* [28] 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-pyrazoles [25] and evaluated their antibacterial and antifungal activities at 100 µg concentration. Some of the compounds showed excellent antimicrobial activities than control drugs.

Stirrett *et al.* [29] synthesized small molecules [26] with structural similarities to siderophores and evaluated as novel antimicrobials against *Mycobacterium tuberculosis* and *Yersinia pestis*.

Abunada *et al.* [30] synthesized several 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 [27] and screened their antimicrobial activities against *E. coli*, *S. aureus*, *Aspergillus flavus* and *C. albicans*.

Bhatt *et al.* [31] synthesized different types of pyrazolines and cyanopyridines [28] as potential antimicrobial agents. They found that these have remarkable activity against *B. mega*, *B. subtilis*, *E. coli* and *M. tuberculosis* H37 Rv.

Udupi *et al.* [32] synthesized certain pyrazoline derivatives of naproxen [29]. Biological evaluation showed that some members of the series had significant antimicrobial and anti-inflammatory activities.

Bharmal *et al.* [33] synthesized some pyrazoline derivatives as biologically active agents. All the compounds [30] showed antimicrobial activity against *S. typhosa* and *A. niger*.

Basawaraj *et al.* [34] synthesized some 1*H*-pyrazolines bearing benzofuran [31] as biologically active agents. They exhibited high antimicrobial activity against *S. aureus* and moderate activity against *E. coli*.

Desai *et al.* [35] synthesized some new pyrazolines, phenyl pyrazolines, flavanones, and related compounds [32] and evaluated their antimicrobial activities. The products exhibited activity against Gram +ve bacteria.

Jamode *et al.* [36] synthesized some 1-Isonicotinoyl/Carboxamido-2-pyrazolines [33] and evaluated their antimicrobial properties against *S. aureus*, *E. coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Most of the compounds were found to be moderately active.

Shenoy *et al.* [37] synthesized 1, 3, 5-Trisubstituted-2-pyrazolines [34] and evaluated their antimicrobial activity. Some of the compounds exhibited antitubercular activity.

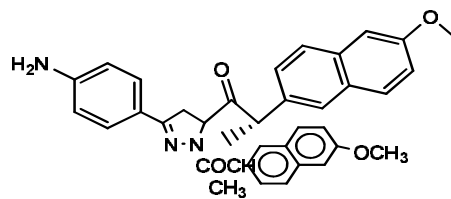


Fig.29. 1-(3-(4-aminophenyl)-1-(2-(6-methoxynaphthalen-2-yl)propanoyl)-2-(6-methoxynaphthalen-2-yl)propan-1-one

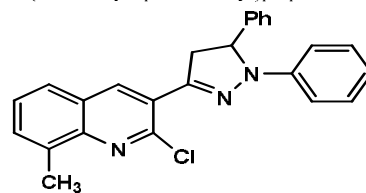


Fig.30. 2-chloro-3-(1,5-diphenyl-2-pyrazolin-3-yl)-8-methylquinoline

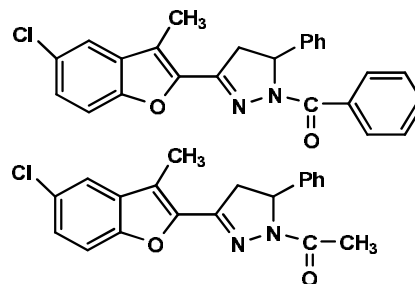


Fig.31. 3-(5-chloro-3-methylbenzofuran-2-yl)-5-phenyl-2-pyrazolin-1-yl(phenyl)methanone; 1-(3-(5-chloro-3-methylbenzofuran-2-yl)-5-phenyl-2-pyrazolin-1-yl)ethanone

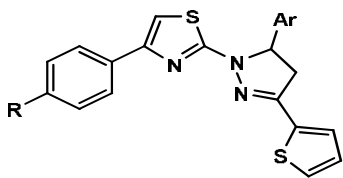


Fig.24. 4-phenyl-2-(5-(pyridin-4-yl)-3-(thiophen-2-yl)-2-pyrazolin-1-yl)thiazole, where, R=H, Ar= Pyridyl; 4-(4-chlorophenyl)-2-(5-(pyridin-4-yl)-3-(thiophen-2-yl)-2-pyrazolin-1-yl)thiazole, where, R=Cl, Ar= Pyridyl

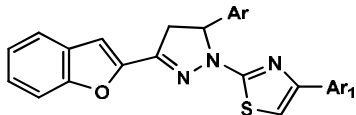


Fig.25. 2-(3-(benzofuran-2-yl)-5-(4-chlorophenyl)-2-pyrazolin-1-yl)-4-phenylthiazole, where, Ar= 4-Cl-C₆H₄, Ar₁= Ph; 2-(3-(benzofuran-2-yl)-5-(4-chlorophenyl)-2-pyrazolin-1-yl)-4-(4-bromophenyl)thiazole, where Ar= 4Cl-C₆H₄, Ar₁= 4Br-C₆H₄.

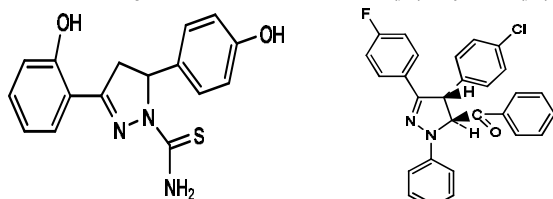


Fig.26. 3-(2-hydroxyphenyl)-5-(4-hydroxyphenyl)-2-pyrazolin-1-carbothioamide

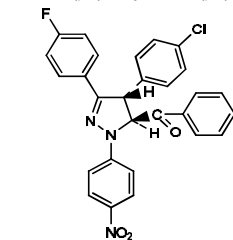


Fig.27. 4-(4-chlorophenyl)-3-(4-fluorophenyl)-1-(4-nitrophenyl)-2-pyrazolin-5-yl(phenyl)methanone

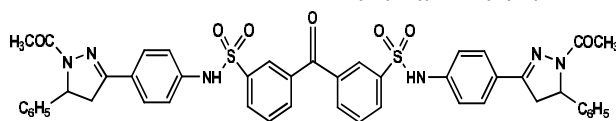


Fig.28. 3,3'-carbonylbis(N-(4-(1-acetyl-5-phenyl-2-pyrazolin-3-yl)phenyl)benzenesulfonamide

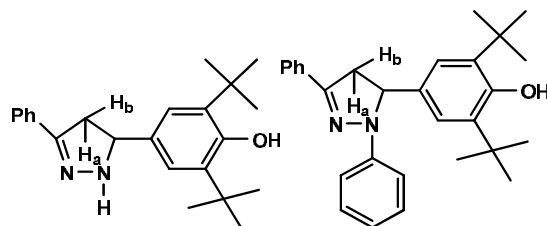


Fig.32. 2,6-di-tert-butyl-4-(3-phenyl-2-pyrazolin-5-yl)phenol; 2,6-di-tert-butyl-4-(1,3-diphenyl-2-pyrazolin-5-yl)phenol

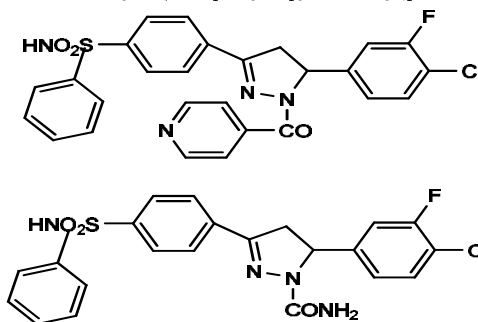


Fig.33. 5-(4-chloro-3-fluorophenyl)-3-*p*-benzenesulphonamido-2-pyrazolin-1-yl(pyridin-4-yl)methanone; 5-(4-chloro-3-fluorophenyl)-3-*p*-benzenesulphonamido-2-pyrazolin-1-carboxamide

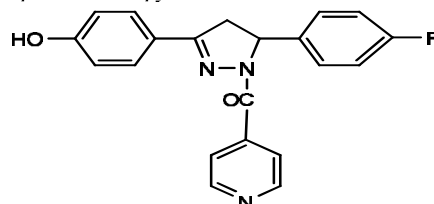


Fig.34. 5-(4-fluorophenyl)-3-(4-hydroxyphenyl)-2-pyrazolin-1-yl(pyridin-4-yl)methanone

Antimycobacterial activity

Mamolo et al.^[38] synthesized 5-Aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4, 5-dihydro-1*H*-pyrazole derivatives [35] and tested for their *in vitro* antimycobacterial activity. The compounds showed an interesting activity against a strain of *M. tuberculosis* and a human strain of *M. tuberculosis* H4.

Ozdemir et al.^[39] synthesized new 1-[(N, N-disubstituted thiocarbamoylthio) acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives [36] and evaluated for *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv.

Shaharyar et al.^[40] synthesized several phenoxy acetic acid derivatives [37] and evaluated for their antimycobacterial activities against *M. tuberculosis* H37Rv.

Zampieri et al.^[41] synthesized several 1-(3, 5-Diaryl-4, 5-dihydro-1*H*-pyrazol-4-yl)-1*H*-imidazole derivatives [38] and tested for their *in vitro* antifungal and antimycobacterial activities. These imidazole derivatives showed an excellent antifungal activity against a clinical strain of *C. albicans* and an interesting antitubercular activity against *M. tuberculosis* H37R.

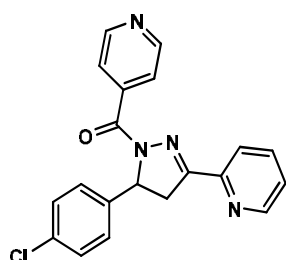


Fig.35. 5-(4-Chlorophenyl)-1-isonicotinoyl-3-(pyridin-2-yl)-2-pyrazoline

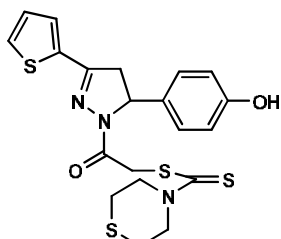


Fig.36. 2-(5-(4-hydroxyphenyl)-3-(thiophen-2-yl)-2-pyrazolin-1-yl)-2-oxoethyl thiomorpholine-4-carbodithioate

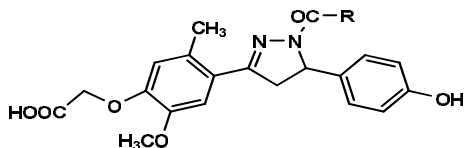


Fig.37. 2-(4-(5-(4-hydroxyphenyl)-1-(2-phenoxyacetyl)-2-pyrazolin-3-yl)-2-methoxy-5-methylphenoxy)acetic acid, where, R=CH₂OC₆H₅; 2-(4-(1-alkylacetoxy-5-(4-hydroxyphenyl)-2-pyrazolin-3-yl)-2-methoxy-5-methylphenoxy)acetic acid, where, R=CH₂OC₁₀H₇

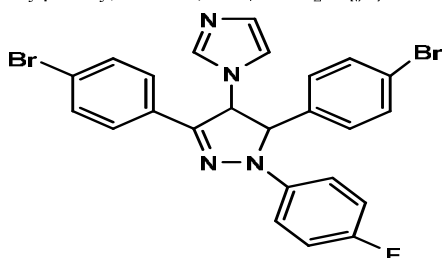


Fig.38. 3,5-bis(4-bromophenyl)-1-(4-fluorophenyl)-4-(1*H*-imidazol-1-yl)-2-pyrazoline

Anticancer activity

Havrylyuk et al.^[5] synthesized several novel thiazolone-based compounds containing 5-Aryl-3-phenyl-4, 5-dihydro-1*H*-pyrazol-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).

Bhat et al.^[42] synthesized a series of substituted pyrazoles [40] and evaluated for *in vitro* cytotoxic activity against a

panel of human cancer cell lines. Out of 93 compounds screened, 8 compounds showed marked activity.

Manna et al.^[43] synthesized a series of substituted pyrazolines (1-Acetyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole) and evaluated for their anticancer activity and for their ability to inhibit *P*-glycoprotein-mediated multidrug resistance by direct binding to a purified protein domain containing an ATP-binding site and a modulator interacting region. Compounds [41.a and 41.b] have been found to bind to *P*-glycoprotein with greater affinity.

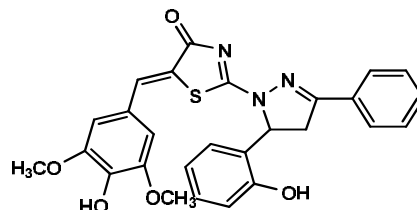


Fig.39. 5-(4-hydroxy-3,5-dimethoxybenzylidene)-2-(5-(2-hydroxyphenyl)-3-phenyl-2-pyrazolin-1-yl)thiazol-4(5*H*)-one

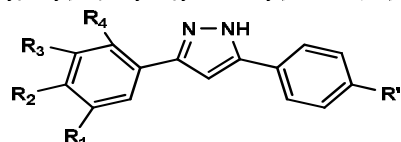


Fig.40. 5-phenyl-3-(2,3,4,5-tetramethoxyphenyl)-1*H*-pyrazole, where, R₁=R₂=R₃=R₄=OCH₃; 5-(4-fluorophenyl)-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole, where, R₁=R₂=R₃=OCH₃, R₄=F

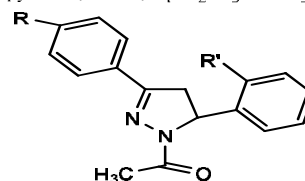


Fig.41. 1-(3,5-diphenyl-2-pyrazolin-1-yl)ethanone, where, R=R'=H; 1-(5-(2-methoxyphenyl)-3-phenyl-2-pyrazolin-1-yl)ethanone, where, R=H, R'=OCH₃

Antitubercular activity

Kini et al.^[44] synthesized a novel series of heterocyclic o/m/p-substituted diphenyl ether derivatives [42] 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.^[45] synthesized a series of 5-(4-(Substituted)phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-pyrazolyl-2-toluidino methanethione and 5-(Substituted)phenyl-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-pyrazolyl-2-methoxyanilino methanethione [43] and tested for their *in vitro* antitubercular activity against *M. tuberculosis* H37Rv. Among the synthesized compounds, compound Anilino-3-(4-hydroxy-3-methylphenyl)-5-(2, 6-dichlorophenyl)-4, 5-dihydro-1*H*-1-pyrazolylmethanethione was found to be more active agent against *M. tuberculosis* H37Rv with minimum inhibitory concentration of 0.0034 µM.

Babu et al.^[46] synthesized and evaluated biological activity of 1, 3, 5-Trisubstituted pyrazolines bearing benzofuran [44]. They were found to be antitubercular, antimicrobial and anti-inflammatory in nature.

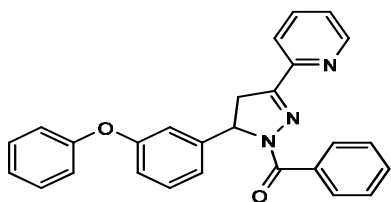


Fig.42. 5-(3-phenoxyphenyl)-3-(pyridin-2-yl)-2-pyrazolin-1-yl(phenyl)methanone

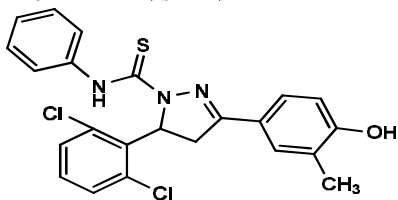


Fig.43. 5-(2,6-dichlorophenyl)-3-(4-hydroxy-3-methylphenyl)-N-phenyl-2-pyrazolin-1-carbothioamide

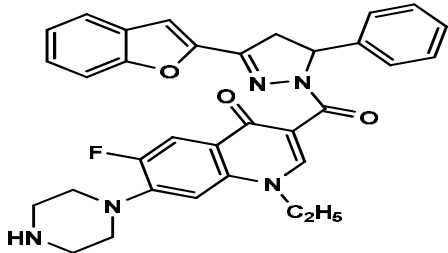


Fig.44a. 3-(3-(benzofuran-2-yl)-5-phenyl-2-pyrazolin-1-carbonyl)-1-ethyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one

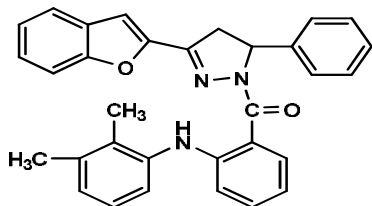


Fig.44b. 3-(benzofuran-2-yl)-5-phenyl-2-pyrazolin-1-yl(2-(2,3-dimethylphenylamino)phenyl)methanone

Antibacterial activity

Chimenti *et al* [47] synthesized a series of N1-substituted 3, 5-diphenyl pyrazolines [45] and evaluated for their *in vitro* antibacterial activity against *H. pylori*. Among the prepared compounds those with an N1-acetyl group and a 4-methoxy substituent in the 5-phenyl ring showed the best activity against *H. pylori* metronidazole resistant strains in the 1-4 $\mu\text{g.mL}^{-1}$ MIC range.

Mogilaiah *et al* [48] synthesized and found antibacterial activities of 1, 3, 4-Oxadiazole and pyrazoline derivatives containing 1,8-Naphthyridine moiety [46]. All the compounds were far less active than the standard drug (gentamycin) taken.

Vijayvergiya *et al* [49] synthesized some new 3, 5-Diaryl-1-phenyl/isonicotinoyl-2-pyrazolines [47] and evaluated its biological activity. All the synthesized compounds showed antibacterial activity against Gram +ve bacteria *S. aureus*, *S. albus*, *S. pyogenes*, *S. viridans* and Gram -ve bacteria *E. coli*, *S. typhosa*, etc.

Waheed *et al* [50] synthesized certain substituted 1, 2-Pyrazolines [48] 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.

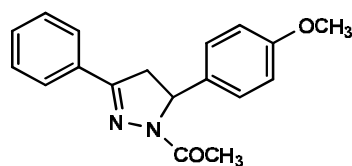


Fig.45. 1-(5-(4-methoxyphenyl)-3-phenyl-2-pyrazolin-1-yl)ethanone

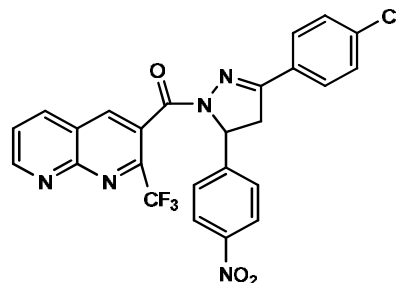


Fig.46. 3-(4-chlorophenyl)-5-(4-nitrophenyl)-2-pyrazolin-1-yl(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)methanone

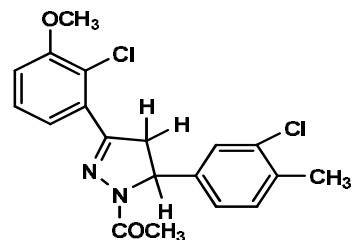


Fig.47. 1-(3-(2-chloro-3-methoxyphenyl)-5-(3-chloro-4-methylphenyl)-2-pyrazolin-1-yl)ethanone

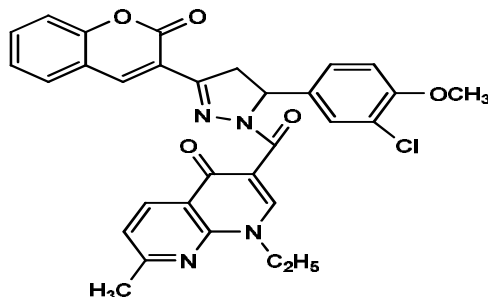


Fig.48. 3-(5-(3-chloro-4-methoxyphenyl)-3-(2-oxo-2H-chromen-3-yl)-2-pyrazolin-1-carbonyl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one

Photoluminescence (PL) activity

Wang *et al* [51] synthesized 5-(9-Anthryl)-3-(4-nitrophenyl)-1-phenyl-2-pyrazoline (ANPP) [49] and screened its photoluminescence property. The absorption of anthryl moiety at about 325-400 nm superimposed on the broader absorption of 3-(4-Nitrophenyl)-1-phenyl-2-pyrazoline moiety peaked at 420 nm. Photo-induced intramolecular energy transfer from the anthryl to pyrazoline moiety exists simultaneously with the charge transfer from N1 to C3 in the pyrazoline moiety in the excited state and both compete with each other.

Jin *et al* [52] synthesized Triphenyl pyrazoline derivatives (TPPs) bearing electron withdrawing and pushing substituents [50] and investigated their photoluminescent property in the solution and doped in poly (N-vinylcarbazole) (PVK) thin films. When TPPs were doped into PVK films the photoluminescence intensity was enhanced with increasing TPPs concentration. It indicated that the energy transfer from PVK to TPPs has happened. The pyrazoline derivative with both electron withdrawing and pushing

substituents was the optimistic candidate for electroluminescent emitter due to higher transfer efficiency from electric energy to light energy as well as larger luminance.

Lu *et al.* [10] synthesized a novel pyrazoline derivative 3-(4-Methoxyphenyl)-5-[4-(1, 1-dimethylethylphenyl)]-4, 5-dihydro-1-phenyl 1-*H*-Pyrazole (**P₃**) [51] and investigated for its light emitter property in blue organic electroluminescent devices. It had hole-transporting ability, good film-formation, and excellent PL property. The device with a structure of ITO/PVK/**P₃**/Al could emit blue light (451 nm) and the turn-on voltage was 25 V.

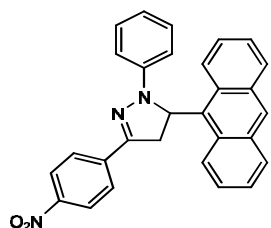


Fig.49. 5-(anthracen-9-yl)-3-(4-nitrophenyl)-1-phenyl-2-pyrazoline

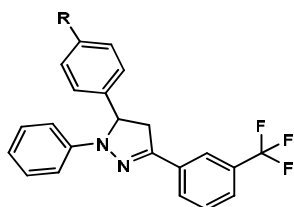


Fig.50. 1,5-Diphenyl-3-(3-trifluoromethylphenyl)-2-pyrazoline, where, R=H; 1-Phenyl-5-(4-hydroxyphenyl)-3-(3-trifluoromethylphenyl)-2-pyrazoline, where, R=OH

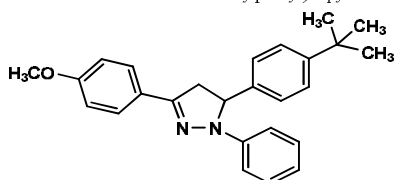


Fig.51. 5-(4-*tert*-butylphenyl)-3-(4-methoxyphenyl)-1-phenyl-2-pyrazoline

Polarity probes activity

Svechkarev *et al.* [53] synthesized two novel 1,3,5-Triphenyl-2-pyrazoline moiety containing derivatives of 3-hydroxychromone [**1a**, **1b**] and discussed the prospects of practical application of these compounds exhibiting high solvatofluorochromism into analytical chemistry and biophysics as effective ratiometric polarity probes proceeding from the data on their fluorescent properties.

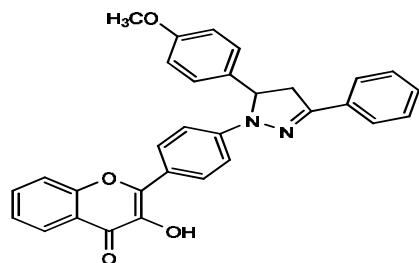


Fig.A. 3-hydroxy-2-(4-(5-(4-methoxyphenyl)-3-phenyl-2-pyrazolin-1-yl)phenyl)-4*H*-chromen-4-one

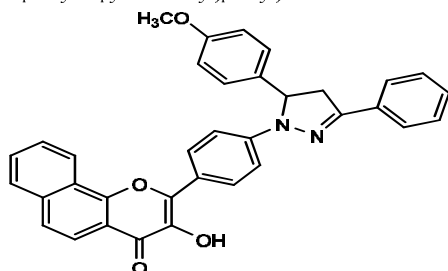


Fig.B. 3-hydroxy-2-(4-(5-(4-methoxyphenyl)-3-phenyl-2-pyrazolin-1-yl)phenyl)-4*H*-benzo[*h*]chromen-4-one

Antiamoebic activity

Budakoti *et al.* [54] synthesized a variety of 3-(3-Bromophenyl)-5-phenyl-1-(thiazolo[4,5-*b*] quinoxaline-2-yl)-2-pyrazoline derivatives [52] and screened for their antiamoebic activity against *HML:IMSS* strain of *E. histolytica* by microdilution method and compared the *IC*₅₀ values with the standard drug metronidazole. Some of the quinoxaline derivatives showed less *IC*₅₀ values than metronidazole. All the compounds were non-toxic.

Budakoti *et al.* [55] synthesized new Pd (II) complexes with 1-*N*-substituted thiocarbamoyl-3, 5-diphenyl-2-pyrazoline derivatives and evaluated their antiamoebic activity by microdilution method against *HML: IMSS* strain of *E. histolytica* and compared the results with the standard drug metronidazole. Generally palladium complexes showed better activity than their corresponding ligands. Compound [53] showed better *IC*₅₀ = 0.05 μ M as compared to metronidazole *IC*₅₀ = 1.82 μ M.

Abid *et al.* [56] synthesized new 1-*N*-substituted thiocarbamoyl-3-phenyl-2-pyrazoline derivatives [54] and evaluated their *in vitro* antiamoebic activities against *E. histolytica* in comparison with metronidazole used as reference substance. Out of the 30 compounds screened for antiamoebic activity, 10 were found to be better inhibitors of *E. histolytica* since they showed lesser *IC*₅₀ values than metronidazole. The preliminary results indicated that the presence of 3-chloro or 3-bromo substituent on the phenyl ring at position 3 of the pyrazoline ring enhanced the antiamoebic activity as compared to unsubstituted phenyl ring.

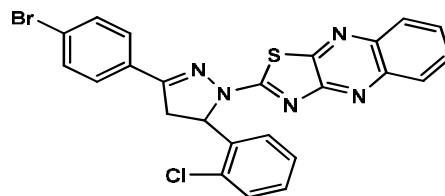


Fig.52. 2-(3-(4-bromophenyl)-5-(2-chlorophenyl)-2-pyrazolin-1-yl)thiazolo[4,5-*b*]quinoxaline

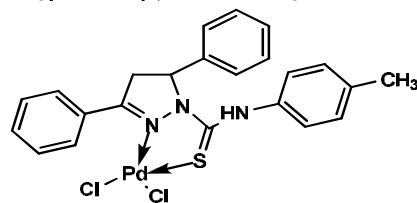


Fig.53. NS complex of 3,5-diphenyl-*N*-*p*-tolyl-2-pyrazolin-1-carbothioamide with palladium dichloride

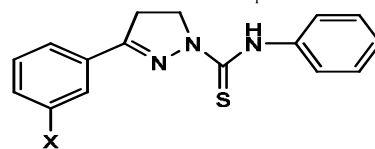


Fig.54. 3-(3-bromophenyl)-*N*-phenyl-2-pyrazolin-1-carbothioamide, where, X=Br; 3-(3-chlorophenyl)-*N*-phenyl-2-pyrazolin-1-carbothioamide, where, X=Cl

MAO-inhibitory activity

Chimenti *et al.* [57] synthesized a series of *N*1-propanoyl-3, 5-diphenyl-4, 5-dihydro-(1*H*)-pyrazole derivatives [55] and assayed as inhibitors of MAO-A and MAO-B isoforms. These showed inhibitory activity with micromolar values and MAO-A selectivity and found to be useful as co-adjuvants in

the treatment of **Parkinson's disease (PD)** and **Alzheimer's disease**.

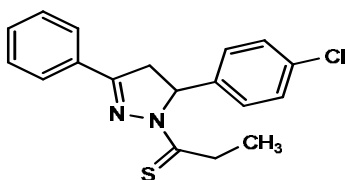


Fig.55. 1-(5-(4-chlorophenyl)-3-phenyl-2-pyrazolin-1-yl)propane-1-thione

Insecticidal activity

Silver *et al* ^[58] synthesized pyrazoline-type insecticides [56] and examined the mechanism of action of these compounds based on available electrophysiological, pharmacological and toxicological information and found to act at neuronal target sites.

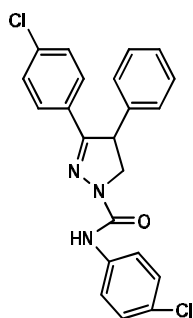


Fig.56a. N,3-bis(4-chlorophenyl)-4-phenyl-2-pyrazoline-1-carboxamide

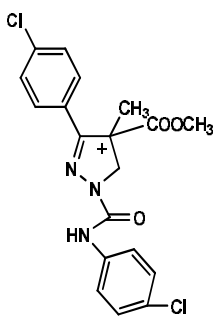


Fig.56b. methyl 3-(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-4-methyl-2-pyrazolin-4-carboxylate

Antinociceptive activity

Godoy *et al* ^[59] investigated whether spinal noradrenergic and serotonergic systems are involved in the antinociception induced by the novel pyrazolines MPCA and PPCA [57]. The results suggested that spinal 5-HT receptors and α_2 -adrenoceptors are involved in the antinociception induced by MPCA and PPCA, but not in that elicited by dipyrone.

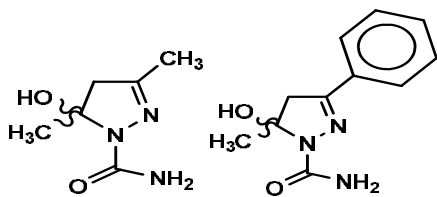


Fig. 57. MPCA

PPCA

Hypotensive activity

Turan-Zitouni *et al* ^[60] synthesized some 1-(4-Arylthiazol-2-yl)-3, 5-diaryl-2-pyrazoline derivatives [58] and investigated their hypotensive activity by the tail-cuff method using clonidine as reference standard. All examined compounds showed appreciable hypotensive activities.

Cholesterol inhibitory activity

Jeong *et al* ^[61] synthesized a series of 3-(3, 5-Di-*tert*-butyl-4-hydroxyphenyl)-5-(multi-substituted 4-hydroxyphenyl)-2-pyrazolines [59] and evaluated their inhibitory action on acyl-CoA: cholesterol acyltransferase. They showed *in vitro* inhibitory activity on hACAT-1 and -2.

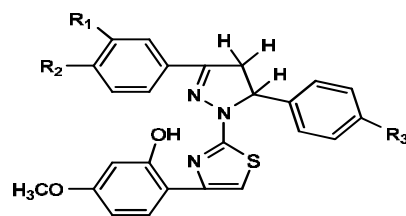


Fig.58. 2-(2-(3,5-diphenyl-2-pyrazolin-1-yl)thiazol-4-yl)-5-methoxyphenol, where, $R_1=R_2=R_3=H$, 2-(2-(3-(3,4-dimethylphenyl)-5-phenyl-2-pyrazolin-1-yl)thiazol-4-yl)-5-methoxyphenol, where, $R_1=R_2=CH_3$, $R_3=H$, and, 5-methoxy-2-(2-(5-(4-methoxyphenyl)-3-phenyl-2-pyrazolin-1-yl)thiazol-4-yl)phenol, where, $R_1=R_2=H$, $R_3=OCH_3$

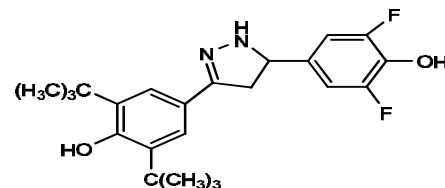


Fig.59. 2,6-di-*tert*-butyl-4-(5-(3,5-difluoro-4-hydroxyphenyl)-2-pyrazolin-3-yl)phenol

Amine Oxidase inhibitory activity

Manna *et al* ^[62] synthesized a novel series of 1-Acetyl-3, 5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives and investigated for the ability to inhibit selectively MAOs, swine kidney oxidase, and bovine serum amine oxidase. 1-Acetyl-3-(2,4-dihydroxyphenyl)-5-(3-methylphenyl)-4,5-dihydro-(1*H*)-pyrazole [60] showed to be a potent monoamine oxidase inhibitor with a K_i value of about 10^{-8} M.

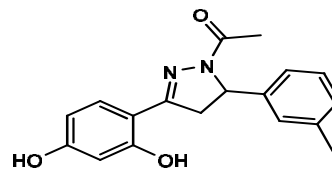


Fig.60. 1-(3-(2,4-dihydroxyphenyl)-5-*m*-tolyl-2-pyrazolin-1-yl)ethanone

Antioxidant activity

Babu *et al* ^[63] synthesized a series of pyrazoline derivatives and evaluated for antioxidant activity at 1000, 500, 250, 100, 50, 25 and 10 mg.ml⁻¹ concentrations against standard drug ascorbic acid. Six compounds [eg. 61] showed excellent antioxidant activity as compared with ascorbic acid.

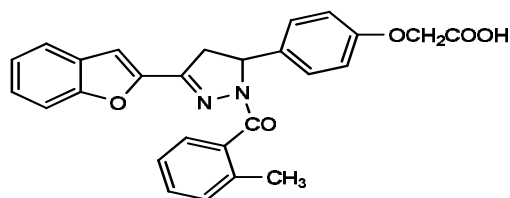


Fig.61. 2-(4-(3-(benzofuran-2-yl)-1-(2-methylbenzoyl)-2-pyrazolin-5-yl)phenoxy)acetic acid

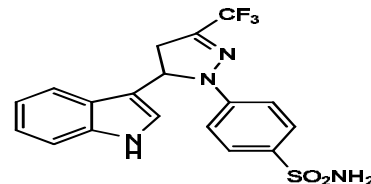


Fig.62. 4-(5-(1*H*-indol-3-yl)-3-(trifluoromethyl)-2-pyrazolin-1-yl)benzenesulfonamide

CURRENT ASPECT OF PYRAZOLINE DERIVATIVES

Reddy *et al.* [64] designed and synthesized a series of twenty novel 1-(4-Sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines and screened *in vitro* for anti-inflammatory activity. These compounds were designed for evaluation as dual inhibitors of cyclo-oxygenases (COX-1 and COX-2) and lipoxygenases (LOX-5, LOX-12 and LOX-15) that are responsible for inflammation and pain. All pyrazoline molecules prepared were optically active and compounds that were more potent in COX-2 inhibitory activity [62] were resolved by chiral column and each enantiomer was tested for cyclo-oxygenase inhibitory activity. Molecular modeling and comparison of molecular models of its enantiomers with that of celecoxib model showed that [62]'s (enantiomer-1) have more hydrogen bonding interactions in the catalytic domain of COX-2 enzyme than celecoxib. This compound showed moderate to good LOX-5 and LOX-15 inhibitory activity and this is comparable to that of celecoxib and more potent than rofecoxib.

REFERENCES

1. ElShora AI. Crystal and molecular structure of 3-hydrazino-1-hydrazinothio-carbonyl pyrazoline (TNT3). *Egypt J Sol.* 2000; 23:251-254
2. Li JT, Zhang XH, Lin ZP. An improved synthesis of 1, 3, 5-triaryl-2-pyrazolines in acetic acid aqueous solution under ultrasound irradiation. *BJ Org Chem.* 2007; 3:1860-5397.
3. Kelekci NG, Koyunoglu S, Yabanoglu S, Yelekci K, Ozgen O, Ucar G, Erol K, Kendi E, Yesilada A. New pyrazoline bearing 4-(3H)-quinazolinone inhibitors of monoamine oxidase: Synthesis, biological evaluation and structural determinants of MAO-A and MAO-B selectivity. *Bioorg Med Chem.* 2008; 22:23-25.
4. Powers DG, Casebier DS, Fokas D, Ryan WJ, Troth JR, Coffin DL. Automated parallel synthesis of chalcone-based screening libraries. *Tetrahed.* 1998; 54:4085-4096.
5. Havrylyuk D, Zimenkovsky B, Vasylenko O, Zaprutko L, Gzella A, Lesyk R. Synthesis of novel thiazolone-based compounds containing pyrazoline moiety and evaluation of their anticancer activity. *Eur J Med Chem.* 2008; 42:1-9.
6. Sobhia HR, Yaminib Y, Esrafil A, Adiba M. Extraction and determination of 2-pyrazoline derivatives using liquid phase microextraction based on solidification of floating organic drop. *J Pharm Biomed Anal.* 2008; 45:316-320.
7. Eisinger J, Boens N and Flores J. Fluorescence polarization study of human erythrocyte membranes with 1-phenyl-3-(2-naphthyl)-2-pyrazoline as orientational probe. *Biochim Biophys Act.* 1981; 646:334-343.
8. Li JF, Guan B, Li DX, Dong C. Study on the fluorescence properties of a new intramolecular charge transfer compound 1,5-diphenyl-3-(N-ethylcarbazole-3-yl)-2-pyrazoline. *Spectrochim Act.* 2007; 68:404-408.
9. Bai G, Li J, Li D, Dong C, Han X, Lin P. Synthesis and spectrum characteristic of four new organic fluorescent dyes of pyrazoline compounds. *Dy Pigmen.* 2007; 75:93-98.
10. Lu Z, Jiang Q, Zhu W, Xie M, Hou Y, Chen X, Wang Z. Novel pyrazoline derivative used as light emitter in blue organic electroluminescent devices. *Syn Met.* 2000; 111:465-468.
11. Evans NA, Rivett DE, Wilshire JFK. The chemical and photochemical properties of some 1, 3-diphenyl-2-pyrazolines. *Austr J Chem.* 2005; 27:2267-2274.
12. Ozdemir Z, Kandilci HBK, Gumusxl B, Unsalalix, Bilgin AA. Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives. *Eur J Med Chem.* 2007; 42:373-379.
13. Kucukguzel SG, Rollas S, Erdeniz H, Kiraz M, Ekinici AC, Vidin A. Synthesis, characterization and pharmacological properties of some 4-arylhydrazono-2-pyrazoline-5-one derivatives obtained from heterocyclic amines. *Eur J Med Chem.* 2000; 35:761-771.
14. Singh SP, Chaudhari A, Barthwal JP, Parmar SS. Anticonvulsant activity and selective inhibition of nicotinamide adenine dinucleotide-dependent oxidations by 1, 3, 5-trisubstituted pyrazolines. *Wiley interscience.* 1974
15. Kornet MJ, Carrett RJ. Synthesis of 1-phenyl-2-(phenylcarbamoyl) pyrazolidines as potential anticonvulsant agents. *J Pharm Sci.* 1979; 68:313-318.
16. Palaska E, Aytemira M, Uzbay IT, Erola D. Synthesis and antidepressant activities of some 3,5-diphenyl-2-pyrazolines. *Eur J Med Chem.* 2001; 36:539-543.
17. Prasad YR, Rao AL, Prasoon L, Murali K, Kumar PR. Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2-hydroxynaphthalen-1-yl)-1,5-diphenyl-2-pyrazolines. *Bioorg Med Chem Lett.* 2005; 15:5030-5034.
18. Jayaprakash V, Sinha BN, Ucar G, Ercan A. Pyrazoline-based mycobactin analogues as MAO inhibitors. *Bioorg Med Chem Lett.* 2008; 18:6362-6368.
19. Barsom FF, Girgis AS. Facile synthesis of bis (4,5-dihydro-1H-pyrazole-1-carboxamides) and their thio-analogues of potential PGE2 inhibitory properties. *Eur J Med Chem.* 2008; 15:1-6.
20. Amir M, Kumar H, Khan SA. Synthesis and pharmacological evaluation of pyrazoline derivatives as new anti-inflammatory and analgesic agents. *Bioorg Med Chem Lett.* 2008; 18:918-922.
21. Rathish IG, Javed K, Ahmad S, Bano S, Alam MS, Pillai KK, Singh S, Bagchi V. Synthesis and anti-inflammatory activity of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulfonamide. *Bioorg Med Chem Lett.* 2008; 21:212-213.
22. Rani P, Srivastava VK, Kumar A. Synthesis and anti-inflammatory activity of heterocyclic indole derivatives. *Eur J Med Chem.* 2004; 39:449-452.
23. Kelekci NG, Yabanoglu S, Kupeli E, Salgin U, Ozgen O, Ucar G, Erdem Yesilada, Kendi E, Yesiladaf A, Bilgin AA. A new therapeutic approach in Alzheimer disease: Some novel pyrazole derivatives as dual MAO-B inhibitors and antiinflammatory analgesics. *Bioorg Med Chem.* 2007; 15:5775-5786.
24. Khode S, Maddi V, Aragade P, Palkar M, Ronad PK, Mamledesai S, Thippeswamy AHM, Satyanarayana D. Synthesis and pharmacological evaluation of a novel series of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agents. *Eur J Med Chem.* 2008; 21:1-7.
25. Shoman ME, AbdelAziz M, Aly OM, Farag HH, Morsy MA. Synthesis and investigation of anti-inflammatory activity and gastric ulcerogenicity of novel nitric oxide-donating pyrazoline derivatives. *Eur J Med Chem.* 2008; 22:1-9.
26. Kaplancikli ZA, TuranZitouni G, Ozdemir A, DevrimCan O, Chevallet P. Synthesis and antinociceptive activities of some pyrazoline derivatives. *Eur J Med Chem.* 2008; 17:1-5.
27. Ozdemir A, TuranZitouni G, Kaplancikli ZA, Revial G, Guven K. Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives. *Eur J Med Chem.* 2007; 42:403-409.
28. AbdelWahab BA, AbdelAziz HA, Ahmed EM. Synthesis and antimicrobial evaluation of 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-pyrazoles. *Eur J Med Chem.* 2008; 43:1-4.
29. Stirrett KL, Ferreras JA, Jayaprakash V, Sinha BN, Renc T, Quadri LEN. Small molecules with structural similarities to siderophores as novel antimicrobials against *Mycobacterium tuberculosis* and *Yersinia pestis*. *Bioorg Med Chem Lett.* 2008; 18:2662-2668.
30. Abunada NM, Hassaneen HM, Kandile NG, Miqdad OA. Synthesis and biological activity of some new pyrazoline and pyrrolo [3, 4-c] pyrazole-4, 6-dione derivatives: Reaction of nitrilimines with some dipolarophiles. *Molecules* 2008; 13:1011-1024.
31. Bhatt AH, Parekh HH, Parikh KA, Parikh AR. Synthesis of pyrazolines and cyanopyridines as potential antimicrobial agents. *Ind J Chem.* 2001; 40:57-61.
32. Udupi RH, Kushnoor AS. Synthesis and biological evaluation of certain pyrazoline derivatives of naproxen. *Ind J Het Chem.* 1998; 8:63-66.
33. Bharmal FM, Kaneriya DJ, Parekh HH. Synthesis of some pyrazoline derivatives as biologically active agents. *Ind J Het Chem.* 2000; 10:189-192.
34. Basawaraj R, Yadav B, Sangapure SS. Synthesis of some 1H-pyrazolines bearing benzofuran as biologically active agents. *Ind J Het Chem.* 2001; 11:31-34.
35. Desai J, Nair KB, Misra AN. Synthesis and antimicrobial activities of some new pyrazolines, phenyl pyrazolines, flavanones, and related compounds. *Ind J Het Chem.* 2001; 10:261-266.