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Pharmacological Potential Of A Resourceful Heterocycle: Pyrazoline – A Review

Cinsila Vincent*, K.Krishnakumar, Geetha Elias

Department of Pharmaceutical Chemistry, St James College of Pharmaceutical Sciences, Chalakudy. St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized).

ABSTRACT

Pyrazolines, the eminent five-membered nitrogen-containing heterocyclic compounds, have received significant interest in the fields of therapeutic and agricultural chemistry because of their broad spectrum of biological activities. The Pyrazoline ring is relatively stable and has inspired chemists to carry out various research activities. Pyrazolines, a class of electron-rich nitrogen heterocyclic compounds, possess a broad range of pharmacological functions such as anticancer, antitubercular, antimalarial, antibacterial, antifungal, anti-inflammatory, analgesic, anticonvulsant, and antioxidant activities. This review provides an outline on the recent grade of pyrazoline derivatives in terms of synthesis and various applications to realize their full potential as drugs.

Keywords: Pyrazoline, Synthesis, Biological activities

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*Corresponding Author Email: geet26862@gmail.com
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INTRODUCTION

Heterocyclic chemistry constitutes an essential branch of organic chemistry and heterocycles are widely known to display an array of biological properties. Heterocyclic compounds are those which possess a cyclic structure with at least two different kinds of atoms in the ring, one of which is nitrogen and can be aliphatic or aromatic. Heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyse or depolymerise[1]. Pyrazolines symbolize key structural motifs in heterocyclic chemistry and are present in a large number of biologically active molecules relevant to the pharmaceutical and agrochemical industries. Pyrazolines are five membered heterocyclic having two adjacent nitrogen atoms within the ring, only one endocyclic double bond and is basic in nature.

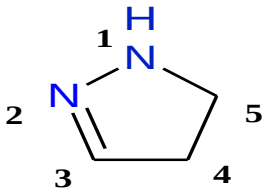


Figure 1: Pyrazoline

The structural elucidation of pyrazoles and derivatives has been greatly aided by NMR spectroscopy, particularly for distinguishing between isomeric structures. Depending on the position of the double bond, can exist in three separate forms[2].

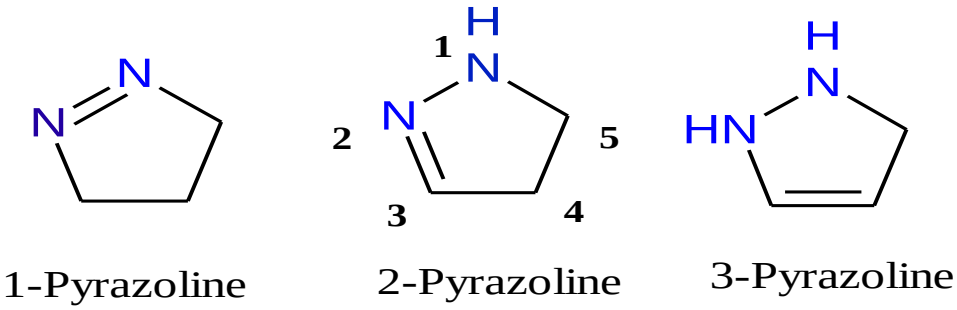


Figure 2: Types of Pyrazolines

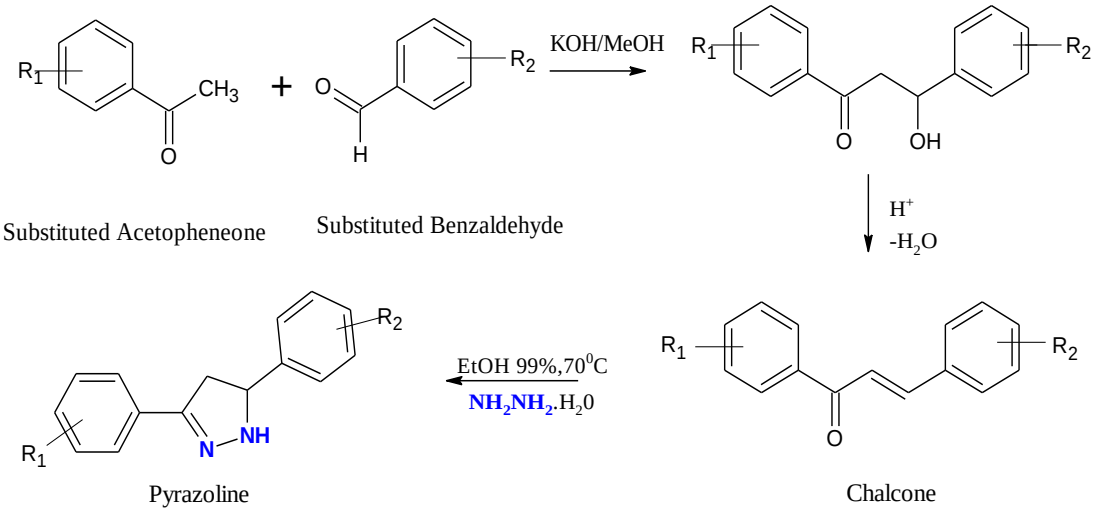
Previous research have shown pyrazolines to be an interesting pharmacophore for drug discovery. These heterocyclic compounds occur widely in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell[3].Significant number of activities have been directed towards diversely substituted pyrazolines such as antimicrobial[4], anti-

inflammatory[5],antidepressant[6], antitubercular[7], anticonvulsant[8], anticancer[9], antioxidant[10], antimalarial[11] , and many more. A typical method for the synthesis of these compounds involves the base catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give unsaturated ketones (chalcones), which undergo subsequent cyclization reaction with hydrazines affording 2-pyrazolines. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2 pyrazolines in the presence of a suitable cyclizing reagent like acetic acid. Chalcones are generally synthesized by Claisen–Schmidt condensation, which involves cross aldol condensation of appropriate aldehydes and ketones by base catalysed or acid catalysed reactions followed by dehydration. The presence of reactive α,β-unsaturated keto group in chalcones is found to be responsible for producing their biological activity. Chalcone derivatives are considered as key intermediatesfor the synthesis of different classes of heterocyclic compounds such as pyrazolines, oxazoles, isoxazoles, thiophenes and pyrimidines.

Commercially available drug with pyrazole moiety such as Celecoxib is a potent COX-2 inhibitor. Some other examples of pyrazole derivatives as NSAID's are Phenylbutazone, Ramifenazone, Lonazolac and Rimonabant. Pyrazofurin has exhibited potential for antiviral activity[12].

Synthesis of Pyrazoline Derivatives

The name pyrazole was given by Ludwig Knorr in 1883 and refers to the class of simple aromatic ring organic compounds of the heterocyclic series, characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions[13].



a: R_1 = 2'-OH, 4'-OCH_3 ; R_2 = 3-OCH_3, 4-OCH_3
b: R_1 = 4'-NO_2; R_2 = 4-$N(CH_3)_2$
c : R_1 = 2'-OH; R_2 = 2-OCH_3, 4-OCH_3

Figure 3: Scheme for the synthesis of Pyrazoline

In the 19th century, Fischer and Knoevenagel synthesized and characterized 2-pyrazolines, by simple reflux reaction of α, β-unsaturated aldehydes and ketones with phenyl hydrazine in acetic acid. A variety of methods exist for the synthesis of Pyrazoline derivatives[14].

Tan Nhut Doan *et al*, have synthesized various pyrazoline (Figure.3) by the reaction of respective chalcones and hydrazine hydrate in presence of 99% ethanol at 70^0C for 7 hours. They evaluated the anti-microbial and antioxidant activities[15].

Nagihan Beyhan, have synthesized various3,5-disubstituted-4,5-dihydro-1*H*-pyrazole-1-carbothioamides by refluxing selected chalcones and thiosemicarbazide in alkaline medium. Similiarly N-3,5-trisubstituted-4,5-dihydro-1*H*-pyrazole-1-carboxamides were synthesized by refluxing selected chalcones with N-(4-chlorophenyl)semicarbazide in alkaline medium. They evaluated the anticonvulsant activity of the synthesized compounds using pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES) tests [16].

Mohammad. Shaharyar *et al* have reported an efficient method for the synthesis of pyrazoline derivatives by condensing chalcones with isoniazid giving a series of N^1-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines and were tested for their *in- vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB) and INH-resistant *M. tuberculosis* (INHR-MTB) using the agar dilution method[17].

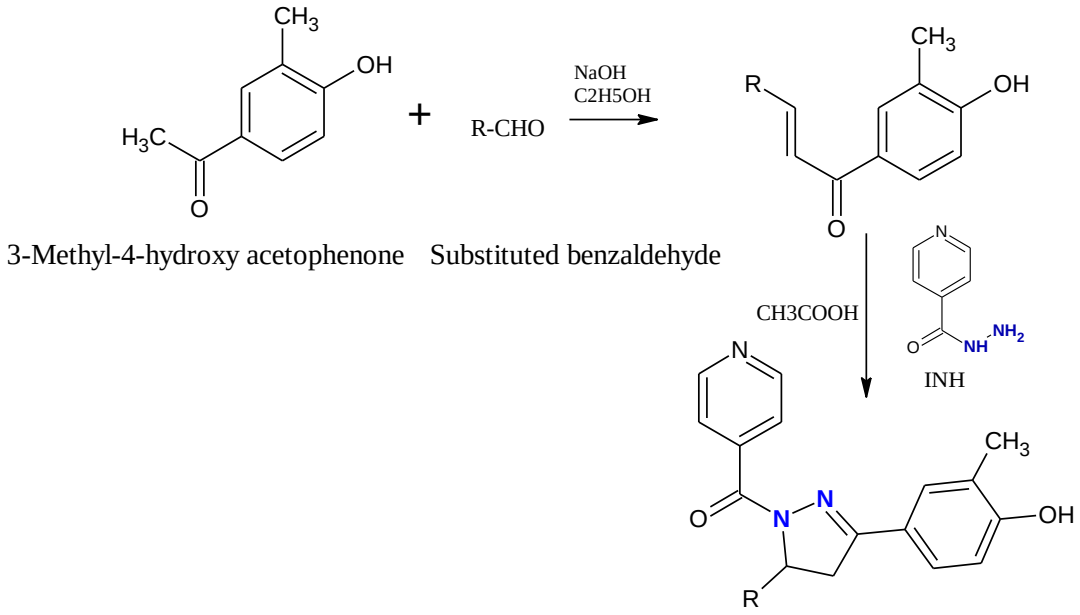


Figure 4: synthesis of N^1-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines

BIOLOGICAL ACTIVITIES OF PYRAZOLINE

Pyrazoline as Antimicrobial agent

Dilesh Indorkar *et al* have Synthesized 1-acetyl-3-(4-nitrophenyl)-5-(substituted phenyl)-2-pyrazoline(Figure.5) derivatives and evaluated their antimicrobial activity. In this study a series of structurally related 1,3,5-trisubstituted-2-pyrazoline derivatives have been synthesized by introducing furan rings regarded as bioactive substructure into the scaffold of pyrazolines and tested for their activities against six plant pathogenic fungi in vitro. The preliminary bioassays indicated that almost all synthesized compounds had displayed variable growth inhibitory effects on the tested pathogenic fungi[18].

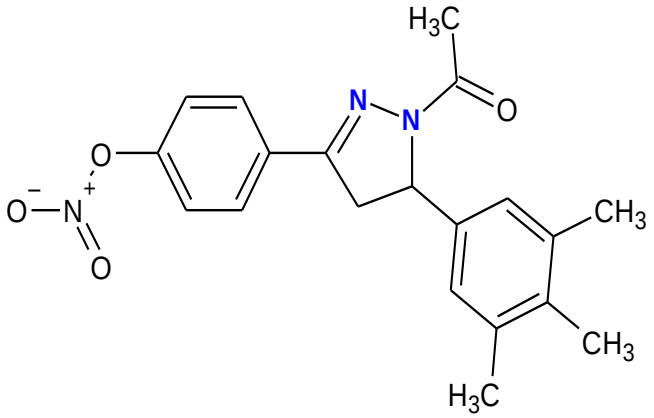


Figure 5: 1-acetyl-3-(4-nitrophenyl)-5-(3,4,5-trimethyl phenyl)-2- pyrazoline

Ramalingam Sasikala *et al* have developed an efficient catalytic method for synthesis of 1-phenyl-3(5-bromothiophen-2-yl)-5- (substituted phenyl)-2-pyrazolines by solid phase cyclization using a solvent-free environmentally greener catalyst fly ash: H_2SO_4 under microwave irradiation between aryl chalcones and hydrazine hydrate. All synthesized pyrazoline derivatives showed moderate antimicrobial activities against bacterial and fungal strains[19].

Ponnurengam Malliappan Sivakumar *et al* have synthesized 1,3,5-triphenyl-2-pyrazolines(Figure.6) and evaluated for their antibacterial activity against six micro-organisms, namely *Bacillus subtilis* NCIM 2718, *Staphylococcus aureus* NCIM 5021, *Salmonella typhi* NCIM 2501, *Enterobacter aerogenes* NCIM 5139, *Pseudomonas aeruginosa* NCIM 5029, and *Proteus vulgaris* NCIM 2813 by twofold dilution method using resazurin as the indicator dye[20].

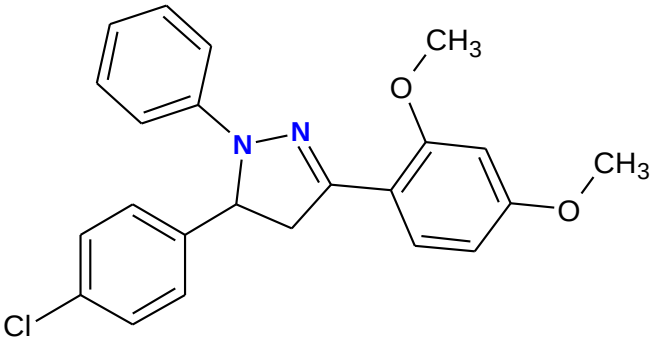


Figure 6: 5-(4-chlorophenyl)-3-(2,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1-pyrazole.

Pyrazoline as Anti tubercular agent

Mohammad. Shaharyar *et al* have synthesized and reported the *in-vitro* anti mycobacterial activity of N^1-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines. Among the synthesized compounds, compound N^1-nicotinyl-3-(4′-hydroxy-3′-methylphenyl)-5-(2-chlorophenyl)-2-pyrazoline (Figure.7) was found to be the most active agent against MTB and INHR-MTB, with minimum inhibitory concentration of 0.26 μm[17].

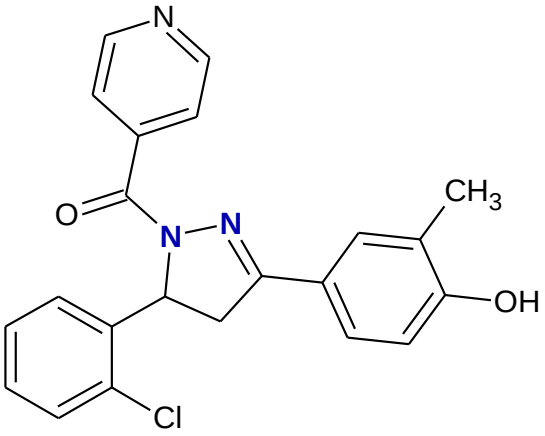


Figure 7: N^1-isonicotinoyl-3- (4′-hydroxy-3′-methyl phenyl)-5-(4-fluorophenyl)-2-pyrazoline

Mohamed Ashraf Ali *et al* have synthesized a series of 5-(-4-(substituted) phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-toluidino methane thione and 5-(substituted)phenyl-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-methoxyanilino methane thione were synthesized by the reaction between hydrazine hydrate and chalcones followed by condensation with appropriate aryl isothiocyanate which yielded N-substituted pyrazoline derivatives. Among the synthesized compounds, compound anilino-3-(4-hydroxy-3-methylphenyl)-5-(2,6-dichlorophenyl)-4,5-dihydro-1H-1-pyrazolylmethanethione was found to be more active agent against M. tuberculosis H37Rv[22].

Pyrazoline as Anti-malarial agent

Shilpy Aggarwal *et al* have synthesized a series of 1,3,5-trisubstitiuted pyrazoline(Figure.8) and were screened for *in-vitro* schizont maturation assay against chloroquine (CQ) sensitive 3D7 strain of *Plasmodium falciparum*. Most of the compounds showed promising *in-vitro* antimalarial activity against CQ sensitive strain. SAR study showed that quinoline substitution at position N-1 showed maximal activity and compounds having electron withdrawing group at *p*-position on phenyl ring displayed better antimalarial activity than electron releasing group[23].

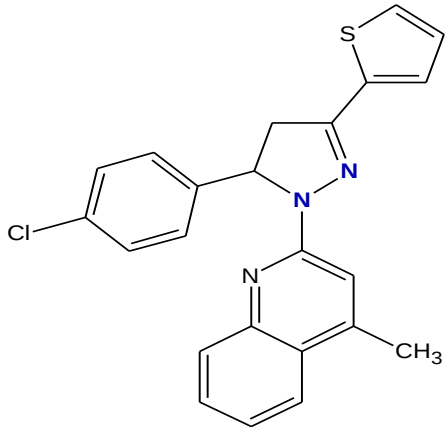


Figure 8: 2-[5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1*H*-pyrazol-1-yl]-4-methylquinoline

Badri Narayan Acharya *et al* reported synthesis of 1,3,5-trisubstituted pyrazolines derivative and were evaluated for *in-vitro* anti-malarial efficacy against Chloroquine sensitive and Chloroquine resistant strains of *Plasmodium falciparum*. *β*-hematin formation inhibition activity ($BHIA_{50}$) of the pyrazolines were determined and correlated with antimalarial activity[24].

Pyrazoline as Anti-inflammatory agent

R. Surendra Kumar *et al* have reported some novel pyrazole analogues from condensation technique utilizing ultrasound irradiation. Synthesized compounds were screened for anti inflammatory activity and the compound 2-((5-hydroxy-3-methyl-1H-pyrazol-4-yl) (4-nitrophenyl) methyl) hydrazine carboxamide showed better anti-inflammatory activity, when compared with standard drugs (Diclofenac sodium)[25].

Harathi *et al* have synthesized various 3, 5-diphenyl-4, 5-dihydro-pyrazole-1-carbothoic acid amide(Figure.9) derivatives using respective chalcones and thiosemicarbazide. They evaluated the anti-inflammatory activity of synthesized compounds by egg-albumin induced rat paw edema method and compared with standard anti-inflammatory agent Diclofenac Sodium. Compounds with electron withdrawing groups Cl, NO_2 exhibited better anti-inflammatory activity[26].

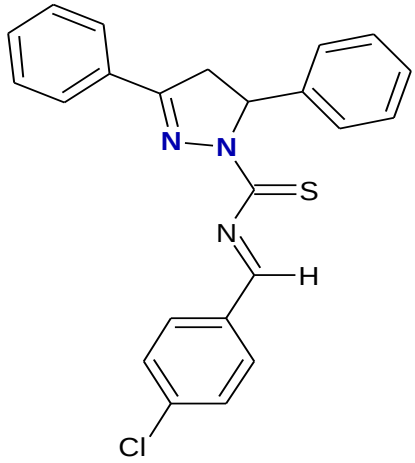


Figure 9: *N*-[(*E*)-(4-chlorophenyl) methylidene]-3, 5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide

Pyrazoline as Anti-cancer agent

Fadi M. Awadallah *et al* synthesized two series of 2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitriles and 4-(4-chlorophenyl)-2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitriles . The target compounds were screened for their antiproliferative activity against A 549 (lung), HT 29 (colon), MCF 7 and MDA-MB 231 (breast) cell lines[27].

Mohammad Abdel-Halim *et al* reported that derivatives with scaffolds of 1,3,5-tri-substituted pyrazoline and 1,3,4,5-tetra-substituted pyrazoline were synthesized and tested for their inhibitory effects versus the $p53^{+/+}$ HCT116 and $p53^{-/-}$ H1299 human tumor cell lines[28].

Bhat *et al* were synthesized a series of substituted pyrazoles and also evaluated for *in-vitro* cytotoxic activity against a panel of human cancer cell lines. They concluded that pyrazoles such as 3,5-diphenyl, 1*H*-pyrazoles(Figure.10) are potent cytotoxic agents[28].

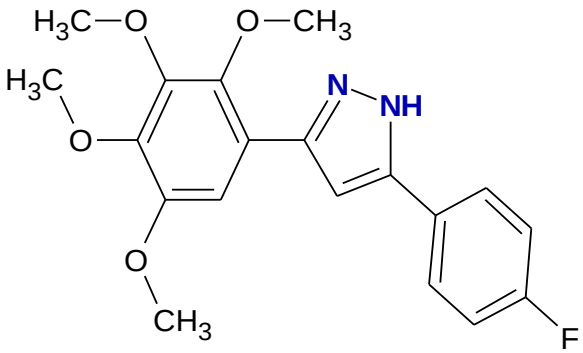


Figure 10: 5-(4-fluorophenyl)-3-(2,3,4,5-tetramethoxyphenyl)-1*H*-pyrazole

Pyrazoline as Anticonvulsant agent

Nagihan Beyhan *et al* were reported Some 2-Pyrazolines Derived From Chalcones having anticonvulsant activity. Various 3,5-disubstituted-4,5-dihydro-1*H*-pyrazole-1-carbothioamides and N-3,5-trisubstituted-4,5-dihydro-1*H*-pyrazole-1-carboxamideswere evaluated the anticonvulsant activity of using pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES). The anticonvulsant screening indicated that among the tested compounds, 2-pyrazoline-1-carboxamide derivatives carrying 5-bromothiophen, 5-chlorothiophen and 2,6-dichlorophenyl groups exhibited noteworthy activity in PTZ test.[16]

Mohamed Jawed Ahsan had synthesized 3-substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3H-indenopyrazole-2-carboxamide(Figure.11).These compounds showed significant anticonvulsant and neuroprotective activities[29].

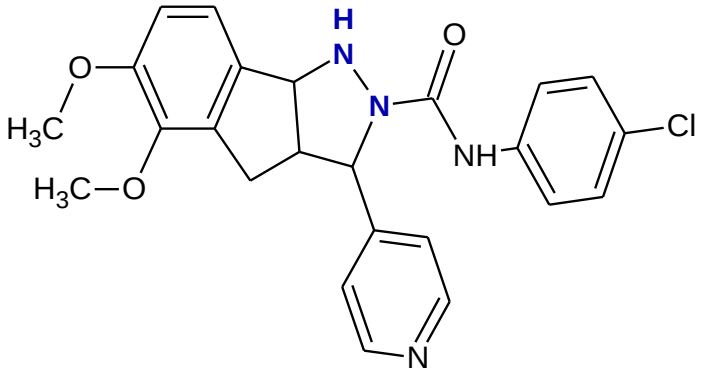


Figure 11: 3-(Pyridin-4-yl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indenopyrazole-2-carboxamide

STRUCTURAL ACTIVITY RELATIONSHIP (SAR) OF PYRAZOLINES

SAR of 1,3,5-triphenyl-2-pyrazoline derivatives as antibacterial agent.

It has been reported that lipophilic⁄ hydrophilic balance is required for antibacterial activities of 1,3,5-triphenyl-2-pyrazolines(Figure.12). The substitution patterns of the aryl ring in all derivatives are observed to affect biological activities. The most active 1,3,5-triphenyl-2-pyrazolines have chloro substitution in their A-ring at R1 position. The least active compounds have benzyloxy substitution in their A-ring at R1 position. The B-ring requires slightly hydrophilic substitution like dimethoxy and methylene dioxy groups compared to hydroxyl substitution for good antibacterial activity.

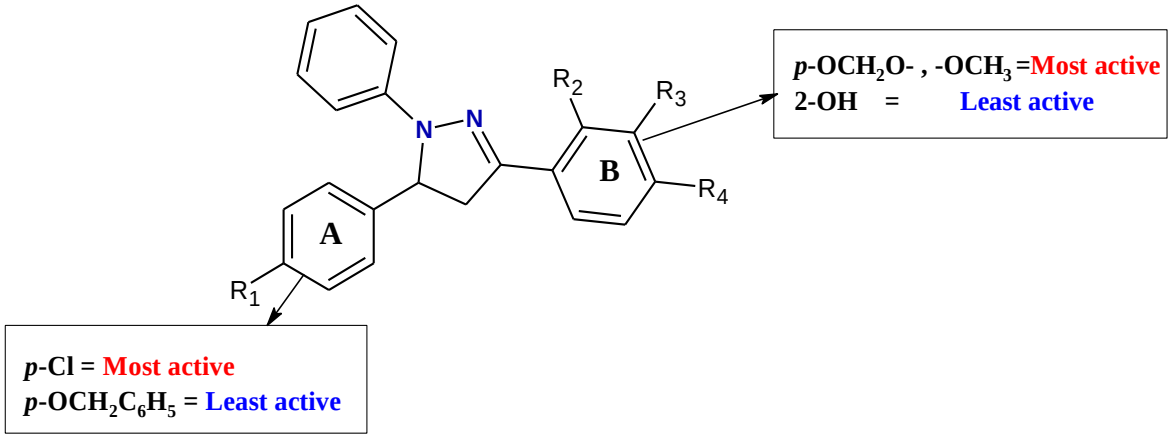


Figure 12: SAR of 1,3,5-triphenyl-2-pyrazoline derivatives as antibacterial agent

SAR of 1,3,5-Trisubstituted Pyrazoline Derivatives as antimalarial agent.

Studies reported that quinoline substituted analog at position N-1 showed maximum activity followed by benzothiazole substitution, while phenyl substitution decreases the antimalarial activity. When position 5 of aromatic ring B is substituted with chlorine atom at para position it showed significant increases in activity (Figure.13). Presence of electron releasing group like methyl & methoxy substituted compounds reduced the antimalarial activity when compared to electron withdrawing groups. Replacement of phenyl groups with 2-thienyl reduces the antimalarial activity. It has been reported that large hydrophobic group (at position 1) is the basic vital structural require for exhibiting the antimalarial activity and para substitution with electron withdrawing group at phenyl ring increases the antimalarial activity.

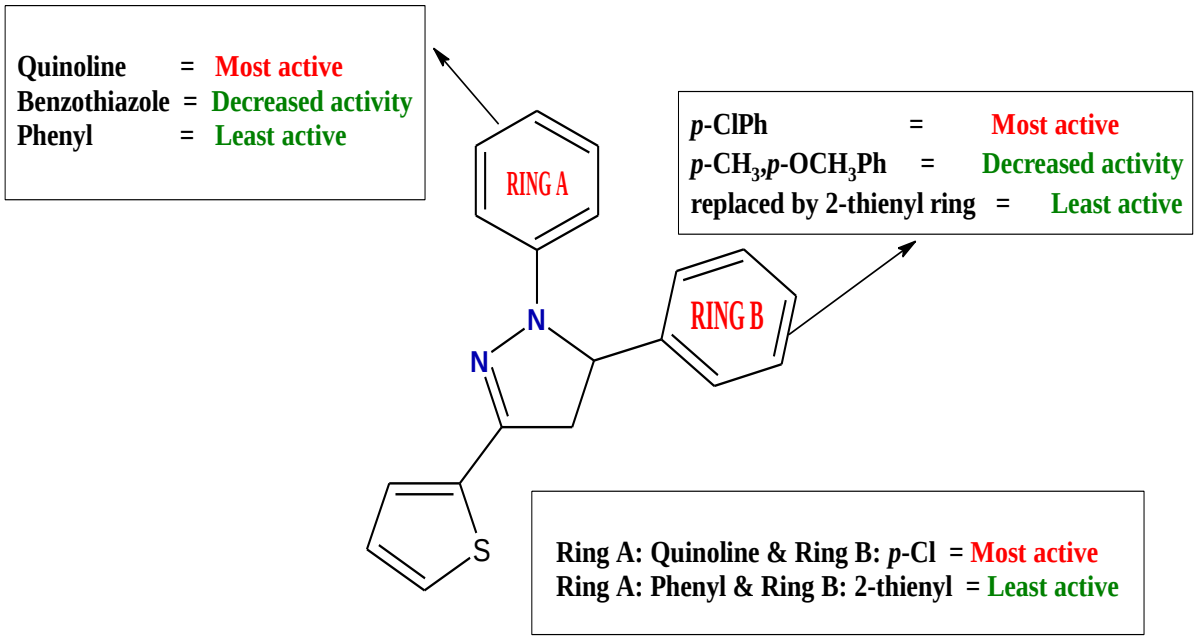


Figure 13: SAR of 1, 3, 5-trisubstituted pyrazoline as antimalarial agent

CONCLUSION

Pyrazoline is an amazing heterocyclic compound that has been designed and synthesized for a variety of biological activities. In this review, biological profiles of various pyrazoline derivatives have been analyzed. They have exhibited numerous effects, such as antimicrobial, antimycobacterial, anti-malarial, anti-inflammatory, anticonvulsant and anticancer activities. Among various pyrazoline derivatives, 2-pyrazolines exhibited more biological activities. The discovery of new drugs for malaria is challenging due to the unavailability of vaccine and lack of newer drugs. The emergence of drug resistance in the parasite (*Plasmodium* strains) against nearly all existing antimalarial drugs has inspired the researchers to identify new pharmacophores. The 2-pyrazolines have shown various biological activities but the most exciting finding in this review is the antimalarial activity of N-1 Quinoline substituted 2-pyrazolines, which is a promising pharmacophore for further research against the malarial parasite.

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REFERENCES

1. Donald J. Abraham, David P. Rotella. Burger's Medicinal Chemistry and Drug Discovery, 6th edition, John Wiley and Sons, New Jersey 2007, 539-543.
2. Kaur Rajwant, Kaur Parminder, Gupta Suman. International Journal of Universal Pharmacy and Bio Sciences.2018;7(4):6-23.
3. Mohamad Yusuf, Payal Jain. Synthetic and Biological Studies of Pyrazolines and Related Heterocyclic Compounds. Arabian Journal of Chemistry. 2014; 7: 553–596.
4. Ozdemir A, TuranZitouni G, Kaplancıklı ZA, Revial G, Guven K. Synthesis and Antimicrobial Activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives. European Journal of Medicinal Chemistry.2007;42:403-409.
5. Aggarwal R and Bansal Molecular Modeling Study of 5-Trifluoromethyl-D2-Pyrazoline and isomeric 5/3-trifluoromethylpyrazole derivatives as Anti-inflammatory agents. European Journal of Medicinal Chemistry.2013; 70: 350-357.
6. Prasad YR, Rao LA, Prasoona L, Murali K, Kumar PR. Synthesis and Antidepressant activity of some 1, 3, 5-Triphenyl-2-Pyrazolines and 3-(200-hydroxy naphthalen-100-*yl*)-1, 5-Diphenyl-2-Pyrazolines. Bioorganic& Medicinal Chemistry Letter.2005; 15: 5030–5034.

7. Ali MA, Shaharyar M, Siddiqui AA. Synthesis, Structural Activity Relationship and Anti-tubercular activity of Novel Pyrazoline Derivatives. European Journal of Medicinal Chemstry. 2007;42: 268-275.
8. Ozdemir, Kandilci, H.B, Gumus_el, B, C¸ Alıs, U, Bilgin, A. Synthesis and Studies on Antidepressant and Anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives. Eur. J. Medicinal Chemistry.2007;42:373–379.
9. Zhu SL,Wua Y, Liu CJ, Wei CY, Tao JC and Liu HM. Design and Stereo selective Synthesis of Novel Isosteviol-fused Pyrazolines and Pyrazoles as Potential Anticancer agents. Eur J Med Chem. 2013; 65: 70-82.
10. Akshay Kumar, Bhat G. Varadaraj, Rajeev K. Singla. Synthesis and Evaluation of Antioxidant activity of novel 3,5-Disubstituted-2-Pyrazolines.Bulletin of Faculty of Pharmacy, Cairo University.2013;51:167–173.
11. Braulio Insuasty , Alba Montoya , Diana Becerra, Jairo Quiroga, Rodrigo Abonia,Sara Robledo, Ivan Darío Vélez, Yulieth Upegui, Manuel Noguerasc, Justo Cobo. Synthesis of Novel analogs of 2-Pyrazoline obtained from[(7-chloroquinolin-4-yl)amino] chalcones and hydrazine as Potential Antitumor and Antimalarial agents. European Journal of Medicinal Chemistry.2013;67: 252-262.
12. R. Surendra Kumar , Ibrahim A. Arif , Anis Ahamed , Akbar Idhayadhulla. Anti-inflammatory and antimicrobial activities of novel pyrazole analogues. Saudi Journal of Biological Sciences.2016; 23: 614–620.
13. L. Knorr, Ber. Dtsch. Chem. Ges., 1883; 16: 2597.
14. Beena Varghese, Saleh N. Al-Busafi, FakhrEldin O. Suliman and Salma M. Z. Al-Kindy. Unveiling a Versatile Heterocyclic: Pyrazoline –a review. The Royal Society of Chemistry.2017; 7: 46999–47016.
15. Tan Nhut Doan and Dao Thanh Tran. Synthesis, Antioxidant and Antimicrobial Activities of a Novel Series of Chalcones, Pyrazolic Chalcones and Allylic Chalcones. Scientific Research, Pharmacology and Pharmacy.2011; 2: 282-288.
16. NagihanBeyhan, BediaKocyigit-Kaymakcioglu, Salih Gümrü, FeyzaAricioglu. Synthesis and Anticonvulsant Activity of Some 2-Pyrazolines Derived From Chalcones. Arabian Journal of Chemistry.2013;07:037.
17. Shaharyar M, Siddiqui AA, Ali MA, Sriram D, Yogeeswari P. Synthesis and *in-vitro* antimycobacterial activity of N1-nicotinoyl-3-(4'-hydroxy-3'-methyl phenyl)-5-[(sub)phenyl]-2-pyrazolines.Bioorganic & Medicinal Chemistry Letters 16 2006;3947-3949.

18. DileshIndorkar, O.P. Chourasia and S.N. Limaye. Synthesis and Characterization of some new Synthesis of 1-Acetyl-3-(4-nitrophenyl)-5-(substituted phenyl) Pyrazoline Derivative and Antimicrobial activity. International Journal of Current Microbiology and Applied Sciences 2015; 4(2): 670-678
19. Ramalingam Sasikala, Kannan Thirumurthy, Perumal Mayavel and Ganesamoorthy Thirunarayanan. Eco-friendly Synthesis and Antimicrobial activities of some 1-phenyl-3(5-bromothiophen-2-yl)-5-(substituted phenyl)-2-pyrazolines. Organic and Medicinal Chemistry Letters.2012; 2:20.
20. PonnurengamMalliappan Sivakumar, Suresh Ganesan, Prabhawathi Veluchamy and Mukesh Doble. Novel Chalcones and 1,3,5-Triphenyl-2-Pyrazoline derivatives as Antibacterial agents . Chem Biol Drug Des. 2010; 76: 407–411.
21. Mohamed Ashraf Ali, Mohammad Shaharyar, Anees Ahamed Siddiqui. Synthesis, Structural Activity Relationship and Anti-tubercular activity of Novel Pyrazoline derivatives. European Journal of Medicinal Chemistry.2007; 42:268-275.
22. Shilpy Aggarwal1, Deepika Paliwal2,3, Dhirender Kaushik3, Girish Kumar Gupta4 and Ajay Kumar. Synthesis, Antimalarial Evaluation and SAR Study of Some 1,3,5-Trisubstituted Pyrazoline Derivatives.Letters in Organic Chemistry.2019; 16: 807-817.
23. Acharya BN, Saraswat D, Tiwari M, Shrivastava AK, Ghorpade R, Bapna S, Kaushik PM. Synthesis and Antimalarial Evaluation of 1, 3, 5-Trisubstituted Pyrazolines. European Journal of Medicinal Chemistry.2010;45:430–438.
24. R. Surendra Kumar , Ibrahim A. Arif , Anis Ahamed , Akbar Idhayadhulla. Anti-inflammatory and Antimicrobial activities of Novel Pyrazole analogues. Saudi Journal of Biological Sciences.2016;23: 614–620
25. Harathi P, Rajendra Prasad, Satyavati D, Siva Subramanian. Synthesis, Characterization and Anti-Inflammatory activity of novel Pyrazole derivatives. Asian Journal Of Pharmaceutical and Clinical Research.2015;Vol 8: Issue 5,82-86.
26. Fadi M. Awadallaha, Gary A. Piazzab, Bernard D. Gary, Adam B. Keeton and Joshua C. Canzoneri. Synthesis of Some Dihydropyrimidine-based compounds bearing Pyrazoline moiety and Evaluation of their Antiproliferative activity. Eur J Med Chem. 2013 ; 70: 273–279.
27. Mohammad Abdel-Halim, Adam B Keeton, Evrim Gurpinar, Bernard D Gary, Simon M Vogel, Matthias Engel, Gary A Piazza, Frank M Boeckler, Rolf W Hartmann, Ashraf H Abadi. Trisubstituted and Tetra substituted pyrazolines as a Novel class of cell-growth

inhibitors in tumor cells with wild type p53.Bioorganic and Medicinal Chemistry.2013;21: 7343-7356.

28. Bhat BA, Dhar KL, Puri SC, Saxena AK, Shanmugavel M, Qazi GN. Synthesis and Biological Evaluation of Chalcones and their derived Pyrazoles as Potential Cytotoxic agents. Bioorg Med Chem Lett.2005;15: 3177-3180.
29. Mohamed Jawed Ahsan. Anticonvulsant activity and Neuroprotection Assay of 3-substituted-N-aryl-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide analogues. Arabian Journal of Chemistry.2017; 10: S2762–S2766.

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