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DEVELOPMENT OF PYRAZOLINE AS A PHARMACOLOGICALLY ACTIVE MOLECULE: A REVIEW

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ABSTRACT: This review aims to offer a top level view of the diverse pharmacological activities of pyrazoline moiety. Among the various 5-membered heterocyclic compound Pyrazoline, derivatives, has drawn interest in the direction of it due to its diverse pharmacologically activities associated with it. Pyrazolines are a five-membered heterocyclic compounds with two adjacent nitrogen atoms in the ring with one endocyclic double bond and is basic in nature. A lot of research work has been performed at the synthesis and organic activities of numerous pyrazoline derivatives through the years. Pyrazolines derivatives display excellent biological functions along with antimicrobial, anti-inflammatory, analgesic, antipyretic, antidepressant, antitubercular, antiamoebic, anthelmintic, anticonvulsant, antihypertensive, antidiabetic, antitumor, anti-HIV, local anesthetic, antioxidant, insecticidal, tranquilizing, and receptor-selective biological pastime. The record of pyrazoline indicates that it attracted many chemists to explore pyrazoline as a biologically active molecule. Have a look at of organic evaluation of pyrazoline derivatives has been an exciting discipline of pharmaceutical chemistry. This assessment article makes a speciality of the pharmacological profile of pyrazoline with various activities and examples.

Keywords: Pyrazolines, Anticancer, Pharmacologically Active, Antimicrobial.

INTRODUCTION

Many heterocyclic compounds due to their unique activity are hired within the remedy of many infectious diseases. Their use in the treatment is attributed to their natural toxicity to various pathogens. Among a diverse range of heterocyclic compounds that have been associated with the development of pharmacologically important molecules, Diversely substituted pyrazolines and their derivatives embedded with a variety of functional groups are important biological agents and a great amount of research activity has been incorporated in this class. In particular, they are used as antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular, and insecticidal agents. Some of these compounds also have anti-inflammatory, anti-diabetic, anesthetic, analgesic, and potent selective activity such as Nitric oxide synthase (NOS) inhibitor and Cannabinoid CB1 receptor antagonists activity.

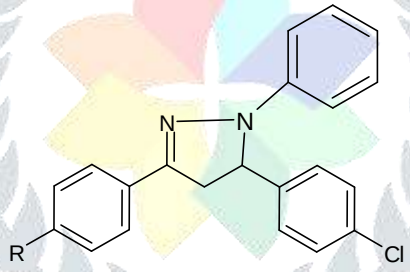
A classical synthesis of these compounds involves the base-catalyzed aldol condensation reaction of aromatic ketones and aldehydes to give α,β-unsaturated ketones (chalcones), which undergo a subsequent cyclization reaction with hydrazines affording 2-pyrazolines. In this approach, hydrazones are formed as intermediates, which can be finally cyclized to 2-pyrazolines within the presence of an appropriate cyclizing reagent like acetic acid. In recent years, a major portion of research in heterocyclic chemistry has been dedicated to 2-pyrazolines comprising different aryl groups as a substituent, as evident from the literature. The preceding section of the review is focusing on the recent development on pyrazolines along with their biological properties.

There are several heterocyclic ring compounds having nitrogen atom such as pyrazole, pyrrolones, pyridazinones, pyrazolines have been considered generally used for the improvement of essential

antimicrobial action. The powerful new drugs must be displayed to save lives when used to give some severe infections and to reduce the trouble of illness when used prophylactically in a certain clinical situation. A lot of effort has been made for synthesis of new antibiotics, researchers effort lots on chemical compounds and pyrazoline derivatives are valuable as antimicrobial agents. Pyrazolines are enormously valuable nitrogen-containing heterocyclic compounds that occur in a diversity of chemical and biological agents and improve their activities. N–N bond of the pyrazoline ring is considered to be the important cause in their biological activities. Pyrazoline also defined as dihydropyrazole containing only one endocyclic double bond. On the basis of position of double bond there are three pyrazolines are posiible: (i) 1-pyrazoline (ii) 2-pyrazoline and (iii) 1, 3-pyrazoline, 2-pyrazoline is maximum attractive and crucial among all types of pyrazolines for frequent studies. Pyrazolines are the reduced forms of pyrazoles, while pyrazolidine is a fully reduced form of pyrazole. Pyrazoline end products were stated to retain several evident pharmacological activities, antiamoebic, antimicrobial, antibacterial, antidepressant, antitubercular, antifungal, antiviral, anticancer, anticonvulsant. Some of the modern drugs of the pyrazoline nucleus include Phenazone, Metamizole, Aminopyrine, Phenylbutazone, Sulfinpyrazone, Oxyphenbutazone and Celecoxib.

SOME BIOLOGICAL ACTIVITIES OF PYRAZOLINES

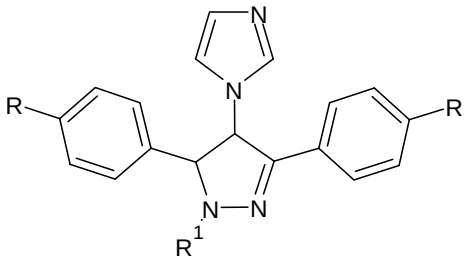
Extensive work has been executed showing the antimicrobial properties of pyrazolines. Gupta et al.[1] reported a novel, ultrasonic method for the synthesis of chalcones and pyrazolines **1**. This a two-step process. In the first step, 1, 3-diarylprop-2-en-1-ones were synthesized by Claisen-Schmidt condensation of aryl methyl ketones and 4-chlorobenzaldehyde in the presence of sodium hydroxide under ultrasonic irradiation. In the second step, synthesis of 2-pyrazolines was carried out by glacial acetic acid under ultrasonic irradiation at 25-45 ^{0}C temperature within 25-150 minutes. It has been observed that in the conventional method, the mixture of chalcone, phenyl hydrazine and glacial acetic acid was refluxed at 30-40 ^{0}C for 3-4 hours to produce 2- pyrazolines in 70% yield. However, when this reaction was carried out under sonication, the reaction was completed rapidly within 30 minutes and the yield was 80%. Newly synthesized compounds were screened for their anti-microbial activity against bacteria and fungi and they showed good activity.



R= H, Br, Cl, F, CH_3

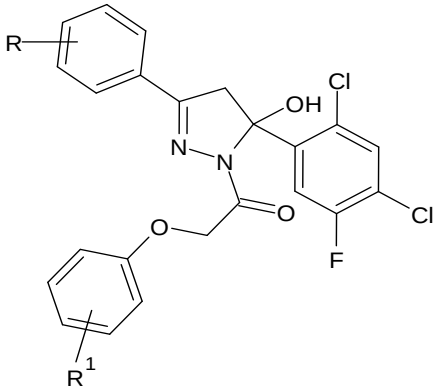
1

Zampieri et al.[2] reported the synthesis of 1-(3,5-diaryl-4,5dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives **2** tested towards a strain of Candida albicans and a strain of Mycobacterium tuberculosis H37Rv. Imidazole derivatives displayed remarkable antifungal and antimycobacterial action against the tested strains.



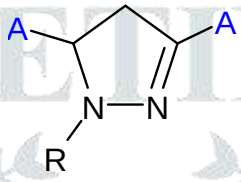
2

A novel series of chlorofluorine containing pyrazoline **3** were prepared by treatment of chalcone dibromides with aryloxy acid hydrazides in the presence of triethylamine gave chloro-fluorine containing hydroxy pyrazolines rather than the probable 1-aryloxy-3aryl-5-aryl pyrazoles. Some compounds showed very good antibacterial and antifungal activity[3].



3

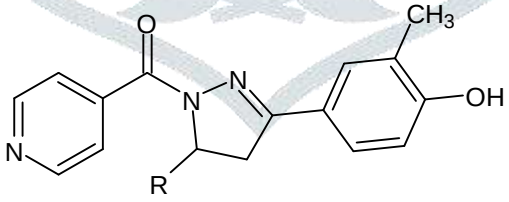
Holla et al[4]. Reported synthesis of 3-aryl-5-(substituted phenyl/phenylfuranyl/thienyl)-2pyrazolines using Amberlyst-15 catalyst. Synthesis of 1-Aryl-3-(substituted phenyl/phenyl furanyl/ thienyl)2-propan-1-ones carried out by the condensation of a series of aromatic ketones with aromatic aldehydes under the aldol conditions. The resulting compounds were exposed to a facile and clean cyclization reaction with hydrazine and substituted hydrazine derivatives to yield 3aryl-5--(substituted phenyl/phenylfuranyl/thienyl)-2-pyrazolines. This reaction was carried out within the presence of Amberlyst-15 catalyst to yield the pyrazolines in considerably good amount. The synthesized compounds were characterized and confirmed by spectral studies.



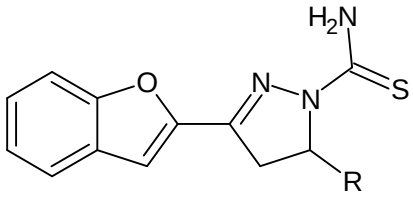
4

Shaharyar et al[5]. presented a series of N1-nicotinoyl-3-(4hydroxy-3-methyl phenyl)-5-(substituted phenyl)-2-pyrazolines **5** and tested in vitro for their antimycobacterial activity. Compounds N1-nicotinyl-3-(4-hydroxy-3-methyl phenyl)-5-(1chlorophenyl)-2-pyrazoline was found to be the most active against MTB and INHR-MTB, with the minimum inhibitory concentration of 0.26 μm.

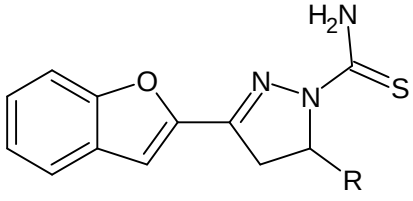
Ahmed et al[6]. reported the synthesis of pyrazolines by treatment of the chalcones with nitromethane under Michael-addition condition and their successive cyclization with thiosemicarbazide under basic and refluxing conditions yield 3-(benzofuran-2-yl)-5-(4aryl)-4,5-dihydropyrazole-1-carbothioamides **6**. These pyrazolines were further treated with phenacyl bromides to formed thiazole substituted pyrazolines **7**. Some of these compound exhibits significant antimicrobial behavior against Escherichia coli and Aspergillus niger.



5

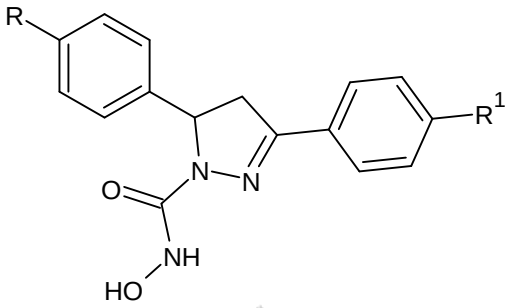


6



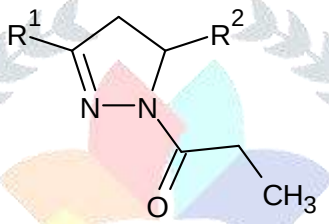
7

Kumarswami et al[7]. reported some new pyrazoline derivatives **8** from chalcones and the hydrazine hydrate in alkaline ethanol condition. The chalcones have been prepared by the reaction of acetophenone with several benzaldehyde. The newly synthesized compounds were characterized by NMR, IR and mass spectroscopy. All the compounds were evaluated for antibacterial activity against gram-positive strains (S. Aureus, B. Subtilis) and gram negative strains (E. coli, K. Pneuminoae) at suitable concentration as compared to standard drug ciprofloxacin. All these compounds showed moderate to potent antibacterial action.



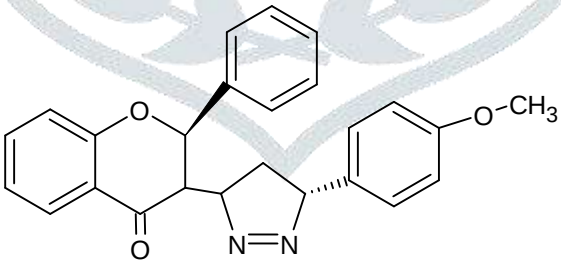
8

Asad et al[8]. presentesd a synthesis of a series of N-propionyl 2-pyrazolines **9** from the chalcones by reacting propionic acid with hydrazine hydrate. The atomic structure of new pyrazoline derivatives were confirmed by FT-IR, NMR spectroscopy, crystal structure, X-ray diffraction techniques. All new compounds were evaluated for antibacterial activity against gram-positive bacterial strain (B. Subtilis, S. Aureus) and gram-negative bacterial strain (E. Coli, P. Peli). All new compounds display significant activity against bacteria.



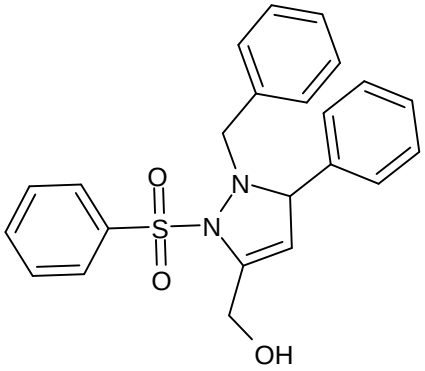
9

Budziz et al[9] reported the biological investigation of a series of chromanone-spiro-1-pyrazoline hybrids. Among them, **10** was found to be the most potent against HL-60, NALM-6, and WM-115 cell lines (IC50 = 3.0–6.8 μM). The presence of p-methoxyphenyl group found essential since the non-substituted compounds showed more than 330- fold lower cytotoxicity against HL-60. **10** induced 60% of HL-60 cells to be arrested in G2/M phase.



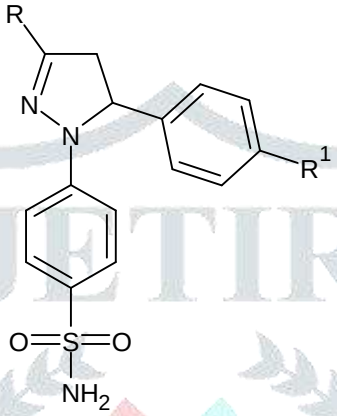
10

Mamedova et al[10]. studied the biological evaluation of pyrazine, pyridazine, and three-pyrazoline sulphonilimine compounds with restricted records on their anticancer activity. Compound **11** become determined energetic against MCF-7 however not against PC-3 cells IC50 values were now not pronounced. This report is noted herein parenthetically, due to the fact that it's far the second one of the anticancer 3-pyrazoline libraries, even though now not hybrid.



11

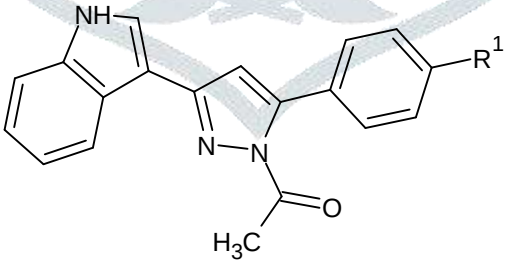
Rathish et al[11]. Reported a synthesis of a series of 1,3,5-trisubstituted pyrazolines-bearing benzene sulfonamides **12** and evaluated their anti-inflammatory activity. Among the examined compounds, several showed promising anti-inflammatory activity.



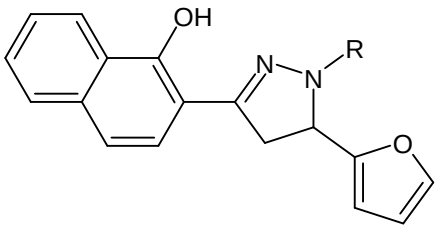
12

Suman et al[12] reported work by using Claisen-Schmidt condensation for the synthesis of chalcone intermediates from various halogen substituted benzaldehydes and 20 acetyl indole in ethanol in the presence of 10% NaOH solution. All the chalcones were treated with hydrazine hydrate in hot glacial acetic acid to give 1-acetyl-3,5-diaryl-2-pyrazolines in good yield. These synthesized acetylated pyrazoline derivatives **13** were tested for their anti-inflammatory activity by the membrane stabilization method. These compounds showed effective stabilization of RBC membrane.

S.E.Bhandarkar synthesized 3-(1-hydroxy naphthalene-2-yl)-5-(furan-2-yl)-1 substituted pyrazolines derivatives with core moiety **14**. After that, they investigate these compounds for various biological applications most of the derivatives were found to be potent against bacterial infection.



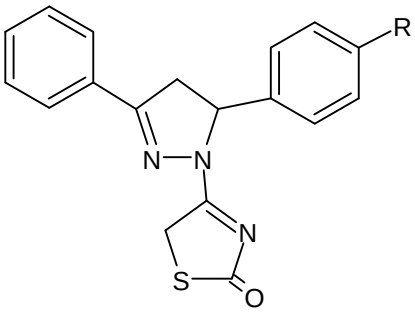
13



14

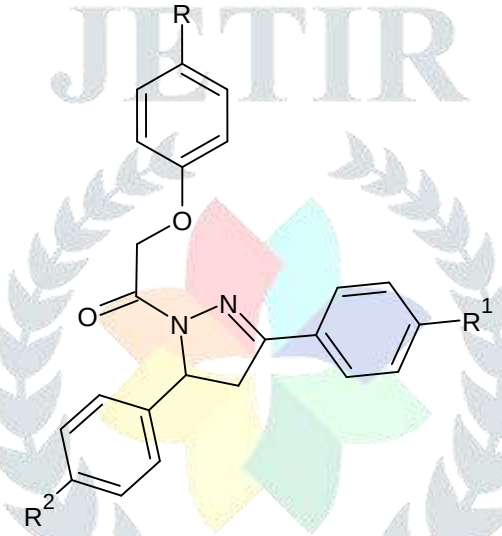
Havrylyuk et al[14]. Investigated the anticancer activity of several novel thiazolone-based compounds having the 5aryl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl framework **15**. The in- vitro anticancer activity had been tested by the National Cancer Institute and most of them displayed anticancer potency on leukemia,

melanoma, lung, colon, CNS, ovarian, renal, prostate and breast most cancers cellular traces and the maximum efficient anticancer compound became determined to be energetic with selective influence on colon cancers cell lines mobile strains, specifically on HT 29 (log GI50 = - 6.37).



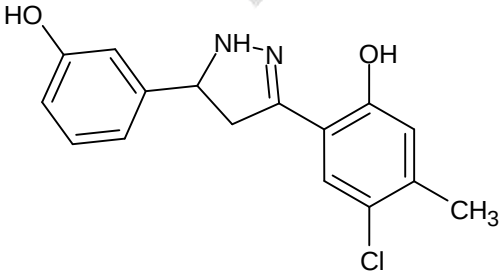
15

Ishwar Bhat et al[15]. were reported that the reactions of chalcones with aryloxy acetyl hydrazines yield (70-80%) 1, 3, 5 substituted pyrazoline derivatives **16** in the presence of hot glacial acetic acid. Synthesized compounds were tested for antibacterial, antifungal and antitubercular activity studies. Synthesized compounds showed significant activity against ampicillin and moderate to significant antifungal activity against griseofulvin. Antibacterial activity studies reveal those good antitubercular activities against isoniazid as a standard drug.



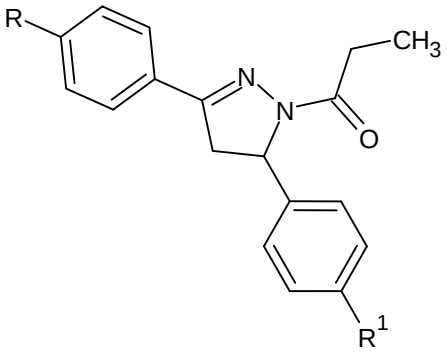
16

Alam et al[16].synthesized a series of pyrazoline derivatives **17** and structural identification done by 1H-NMR, [13]C-NMR, IR and Mass spectrum. All newly synthesized derivatives were evaluated against two bacterial and four fungal strain (C. Albicans, A. Flavus, A. Fumigatus, A. versicola) at the conc. of 12.5µg/ml compared with the standard drug fluconazole. All compounds display moderate to potent antifungal activity.



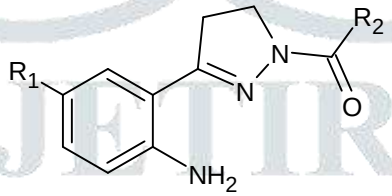
17

Chimenti et al[17]. reported a series of N^1-propanoyl-3,5diphenyl-4,5-dihydro-(1H)-pyrazole derivatives **18** and assayed as inhibitors of MAO-A and MAO-B isoforms. Most of the tested compound showed inhibitory activity with micromolar values and MAO-A selectivity.



18

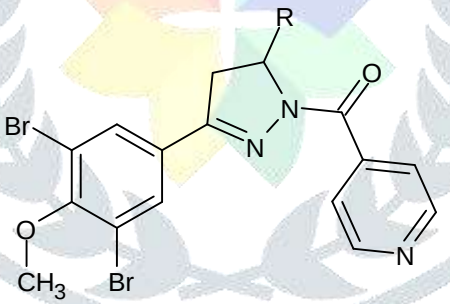
Camacho et al[18]. reported a synthesis of **19** new nNOS inhibitors with a 4,5-dihydro-1H-pyrazole structure **19** in an attempt to find new compounds with neuroprotective activity. Compounds 1-cyclopropanecarbonyl-3-(2-amino5chlorophenyl)-
4,5-dihydro-1H-pyrazoleand1cyclopropane caron-
yl-3-(2-amino-5 methoxyphenyl)- 4,5-dihydro 1H-pyrazole show the highest activities with inhibition percentages of 70% and 62%, respectively.



19

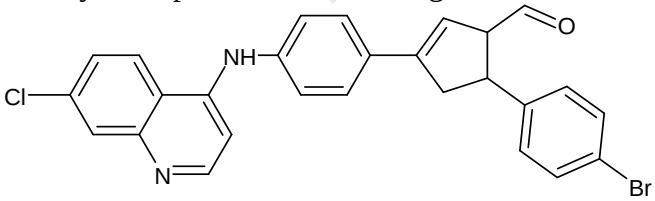
R_1 = H, Cl, OMe
R_2 = Me, Et, Bu, Bn

H.S.Joshi et al[19]. synthesized a series of pyrazoline derivatives **20**. Most of the synthesized compound shows promising antimicrobial activity against bacterial strains.



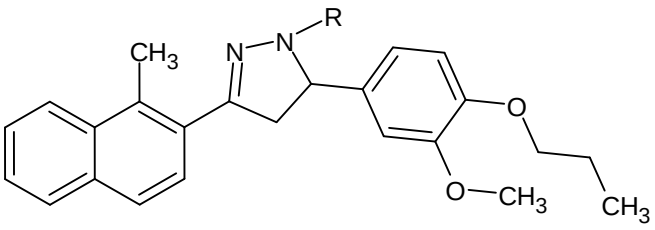
20

B. Insuasty et al[20]. synthesized a new series of N-acetyl and N-formyl-pyrazoline derivatives and confirmed their antimalarial activity. Compound **21** showed significant antimalarial activity.



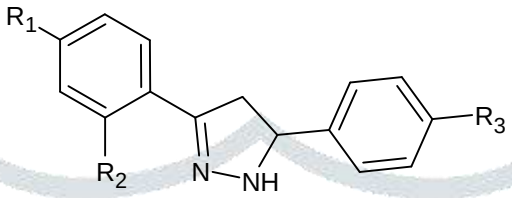
21

Hareesh et al[21]. synthesized some novel pyrazoline derivatives **22** from commercially available 2-hydroxy-aceto-naphthanone and substituted vanillin derivative. First the key intermediate chalcone was prepared by treating 2-hydroxy-aceto-naphthanone with aldehyde in the presence of NaOH in methanol. Chalcones were then treated with the hydrazine hydrate in the presence of sodium acetate in ethanol to give a pyrazoline that was further alkylated to some new pyrazoline derivatives. These derivatives were then tested for their antibacterial activity. All the compounds exhibited good activity. The compounds containing amide functionality exhibited significant activity against bacteria.



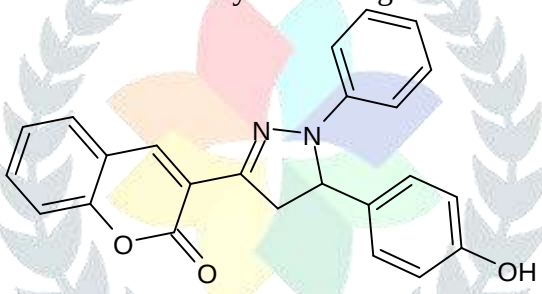
22

Venkataraman et al[22]. reported some new pyrazoline derivatives from chalcones **23**. Which may be synthesized by different acetophenones reacting with different benzaldehydes to give chalcone, which on condensed with hydrazine hydrate in ethanol to acquire pyrazoline derivatives. All derivatives were screened for in- vitro antibacterial and anti-inflammatory activities. All synthesized derivatives were tested for activity against S. aureus, B. subtilis, E. coli, P. aureginosa. Some of the new derivatives exhibited promising anti-inflammatory activities.



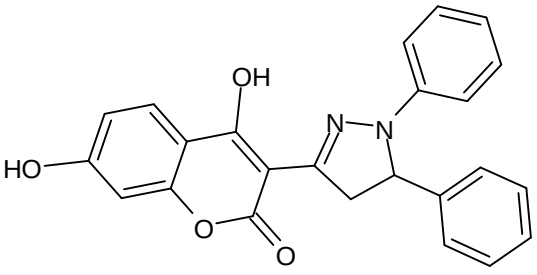
23

Kumar et al[23]. reported the synthesis of four N-phenyl pyrazoline-coumarin hybrids and their screening for anticancer activity against cancer cell lines by NCI. Compound **24** was found to be the most potent among the pyrazoline derivatives against non-small cell lung cancer NCI-H522. The data obtained showed that in this small series of four different substituents on C-5 phenyl ring, the simple non-hybrid coumarin compounds were more active than their hybrid analogs.



24

Recently Miao et al[24]. showed the discovery of simple N-phenyl pyrazoline-coumarin hybrids as novel heat shock protein (HSP90) inhibitors. Compound **25** the simplest unsubstituted N-phenyl and C-5 phenyl derivatives exhibited the best binding ability and inhibited the activity of HSP90 possessing at the same time an IC50 value of 4.7 µM for A549 lung cancer cell inhibition. This molecule proved to be most effective than their initially identified HSP90 inhibitor, a more complex coumarin-pyrazoline hybrid bearing a benzoic acid moiety. The authors stated that **25** not only induced apoptosis as their original inhibitor did but also blocked autophagic flux in A549 cells.



25

CONCLUSION

Pyrazolines are well-known and important nitrogen-containing 5-membered heterocyclic compounds and various methods have been worked out for their synthesis. Numerous pyrazoline derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field. This manuscript is a brief review of different methods for the synthesis of biologically active pyrazoline derivatives. The objective of this review is to provide a platform for researchers, academicians, chemists, and industrialists to have all the information regarding the antimicrobial activity of pyrazoline. As the

literature shows that there is always a demand for novel antimicrobial agents due to pathogen resistance. So, this literature would be fruitful to society as well. This would provide the researcher a lead that they may come with a new and potent pyrazoline-bearing derivative.

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