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Pharmaceutical Sciences **REVIEW ARTICLE ……!!!**

PHARMACOLOGICAL ACTIVITIES OF PYRAZOLINE DERIVATIVES: A REVIEW

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KEYWORDS:

Heterocyclic Chemistry, Pharmacological Activities, Potent Compounds, Pyrazoline.

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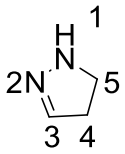
ABSTRACT

Pyrazoline is a highly privileged structure and well known heterocyclic, derivatives of which exhibit a wide range of biological activities including Anti-epileptic Activity, Anti-depressant Activity, Anti-Inflammatory Activity, Anti-Microbial Activity, Anti-Tubercular Activity, Anti-Cancer Activity, Anti-Bacterial Activity, Anti-Amoebic Activity, Insecticidal Activity, Anti-Oxidant Activity, Hypotensive Activity. The broad and potent activity of Pyrazoline and its derivatives has been established as pharmacologically significant scaffolds. In this paper, an attempt has been made with recent research findings on this nucleus, to review the structural modifications on different Pyrazoline derivatives for various pharmacological activities.

INTRODUCTION:

Heterocyclic compounds are those which possess a cyclic structure with at least two different kinds of atoms in the ring, one of which is carbon and can be Aliphatic or Aromatic. Heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyse or depolymerize [1]. Among different five membered heterocyclic system pyrazoline, pyrrole, oxadiazole, thiadiazole and their derivatives have gained importance as they constitute the structural features of many bioactive compounds. Pyrazolines are of significant interest in medicinal chemistry [2]. Literature reveals that pyrazolines is a highly privileged structure, the derivatives of which exhibit a wide range of biological activities including Anti-Epileptic Activity [3], Anti-Depressant Activity [4], Anti-Inflammatory Activity [5], Anti-Microbial Activity [6], Anti-Tubercular Activity [7], Anti-Cancer Activity [8], Anti-Bacterial Activity[9], Anti-Amoebic Activity[10], Insecticidal Activity [11], Anti-Oxidant Activity [12], Hypotensive Activity [13].

Pyrazoline is heterocyclic having two adjacent nitrogen atoms within the ring. It has only one endo-cyclic double bond and is basic in nature. Among its various derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type compounds [14]. It plays a crucial role in the development of theory in heterocyclic chemistry and is also extensively used as useful symptoms in organic synthesis [15].



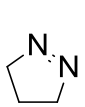
(1)

Numbering of the 2-pyrazolins begins with the amino nitrogen and pyrazolines are numbered to obtain for the double bond the lower of the two possible numbers. Being so composed and having pharmacological effects on humans, they are classified as Alkaloids, although they are rare in nature [16].

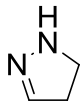
Types of Pyrazolines

Pyrazolines have only one double bond (endo-cyclic) within the nucleus. The structural elucidation of pyrazoles and derivatives has been greatly aided by NMR spectroscopy, especially

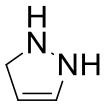
for distinguishing between isomeric structures [17]. Depending on the position of the double bond, can exist in three separate forms:



1-pyrazoline (2)



2-pyrazoline (3)



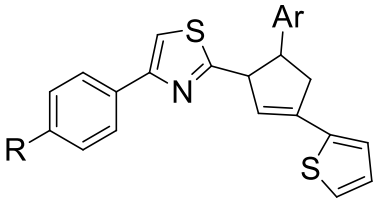
3-pyrazoline (4)

Among various pyrazolines derivatives, 2-pyrazolines seem to be the most frequently studied pyrazoline type of compounds. It has one double bond at 2nd position, one hydrogen atom linked to nitrogen atom. The pyrazoline ring protons were bonded with carbon atoms on a spatially different environment [18].

Pharmacological Activities of Pyrazolines

Pyrazoline as Anti-microbial Agents

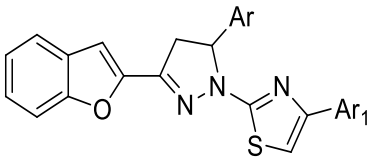
Ozdemir *et al* synthesized 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives (5) and investigated their antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Bacillus cereus*, *Streptococcus faecalis*, *Aeromonas hydrophila*, *Candida albicans* and *Candida glabrata*. A significant level of activity was observed and Following compound showed significant inhibition against all the strains tested, when compared to standard drugs [18].



(5)

Compound No.	R	Ar
2a	H	Pyridyl
2b	Cl	Pyridyl

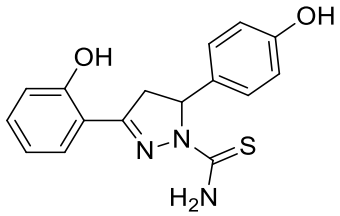
Abdelwahab *et al* synthesized 1-(benzofuran-2-*yl*)-4-nitro-3-arylbutan-1-ones and 3-(Benzofuran-2-*yl*)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-*yl*]-1*H*-pyrazoles (6) and also evaluated their Anti-Bacterial and Anti-fungal Activities at 100 µg concentration. Some of the compounds showed excellent antimicrobial activities than control drugs [19].



(6)

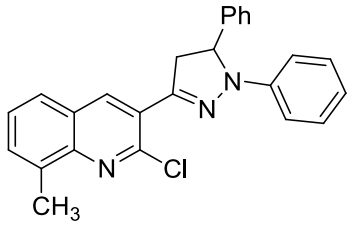
Compound No.	Ar	Ar_1
4a	4-Cl-C_6H_4	Ph
4b	4-Cl-C_6H_4	4Br-C_6H_4

Stirrett *et al* synthesized small molecules (7) having structural similarities to siderophores and evaluated as novel Anti-Microbials against *Mycobacterium tuberculosis* and *yersinia pesti* [20].



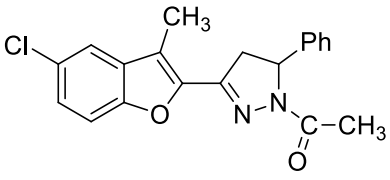
(7)

Bharmal *et al* synthesize pyrazoline derivatives as biologically active agents. All the compounds **(**8) showed Antimicrobial activity against *S. typhosa* and *A. niger* [21].

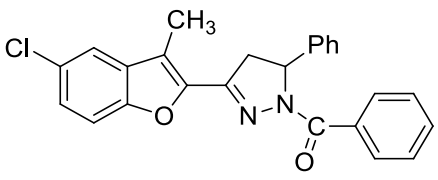


(8)

Basawaraj *et al* synthesized 1*H*-pyrazolines bearing benzofuran (9a and 9b) as biologically active agents. These Pyrazoline Derivatives exhibited high antimicrobial activity against *S. aureus* and moderate activity against *E. coli* [22].



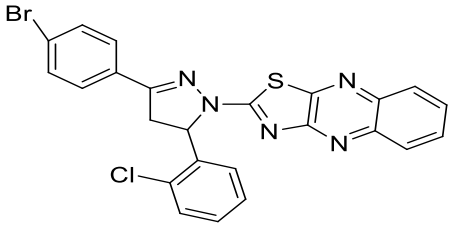
(9a)



(9b)

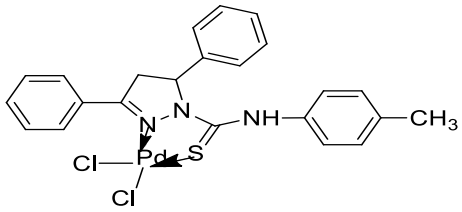
Pyrazoline as Anti-Amoebic

Budakoti *et al* synthesized a variety of 3-(3-bromophenyl)-5-phenyl-1-(thiazolo[4,5-b] quinoxaline-2-*yl*)-2-pyrazoline derivatives (10) and screened for their Anti-amoebic activity against *HMI:IMSS* strain of *E. Histolytica* by Microdilution method and compared the *IC50* values with the standard drug metronidazole. Some of the quinoxaline derivatives showed less *IC50* values than metronidazole. All the compounds were found non-toxic [23].



(10)

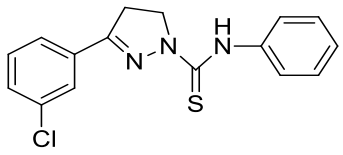
Budakoti *et al* synthesized Pd (II) complexes with 1-N-substituted thiocarbamoyl-3, 5-diphenyl-2-pyrazoline derivatives (11) and also evaluated its Anti-amoebic activity by Micro-dilution method against *HM1: IMSS* strain of *E. histolytica* and compared the results with the standard drug Metronidazole. Generally palladium complexes showed better activity than their corresponding ligands. Compound (Compound 8) reported better *IC50* = 0.05 μM as compared to Metronidazole *IC50* = 1.82 μM [24].



(11)

Abid *et al* synthesized 1-*N*-substituted thiocarbamoyl-3-phenyl-2-pyrazoline derivatives (12) and evaluated *in vitro* Anti-Amoebic activities against *E. histolytica* in comparison with Metronidazole used as reference substance. Out of the 30 compounds screened for anti-amoebic

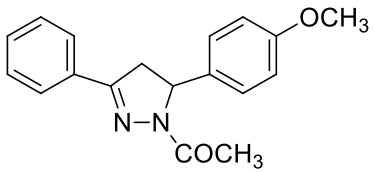
activity, 10 were found to be better inhibitors of *E. histolytica* since they showed lesser *IC50* values than Metronidazole. The preliminary results indicated that the presence of 3-Chloro or 3-Bromo substituent on the phenyl ring at position 3 of the pyrazoline ring enhanced the Anti-Amoebic activity as compared to an un-substituted phenyl ring [25].



(12)

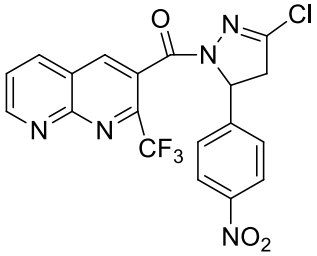
Pyrazolines as antibacterial agent

Chimenti *et al* synthesized a new series of N_1-substituted 3,5-diphenyl pyrazolines (13) and evaluated for their *in vitro* Antibacterial activity against *H. pylori.* Among the prepared compounds those with an N_1-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 $\mu g.ml^{-1}$ MIC range [26].



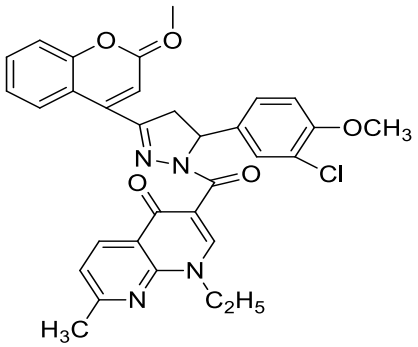
(13)

Mogilaiah *et al* synthesized and found anti-bacterial activities of 1,3,4-oxadiazole and pyrazoline derivatives containing 1, 8-Naphthyridine moiety (14). All the compounds were far less active than the standard drug (Gentamycin) taken [27].



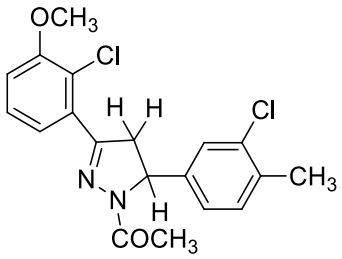
(14)

Waheed *et al* synthesized certain substituted 1, 2-Pyrazolines (15) from Nalidixic Acid as antibacterial and analgesic agents. They were found to have significant anti-bacterial activity against Gram -ve bacteria and showed appreciable analgesic activity [28].



(15)

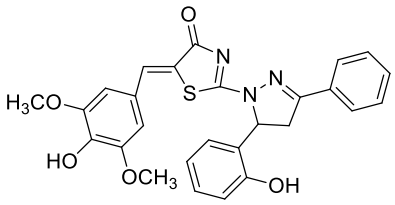
Vijayvergiya *et al* synthesized new 3, 5-diaryl-1-phenyl/isonicotinoyl-2-pyrazolines (16) and evaluated its Biological activity. The synthesized compounds showed Antibacterial activity against Gram +ve bacteria *S. aureus, S.albus, S. pyogenes, S. viridans* and Gram -ve bacteria *E. coli, S. typhosa*, etc [29].



(16)

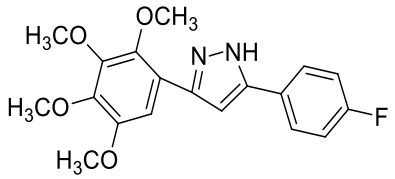
Pyrazolines as Anti-Cancer Agent

Havrylyuk *et al* synthesized novel thiazolone-based compounds containing 5-aryl-3-phenyl-4, 5-dihydro-*1H*-pyrazol- 1-*yl* (17) and tested for *in-vitro* Anti-Cancer activity. Most of them displayed anti-cancer activity on Leukemia, Melanoma, Lung, Colon, CNS, Ovarian, Renal, and Prostate and Breast Cancer cell lines. The most efficient Anti-Cancer compound (15) was found to be active with selective influence on Colon Cancer cell lines, especially on HT 29 (log GI50 = -6.37) [30].



(17)

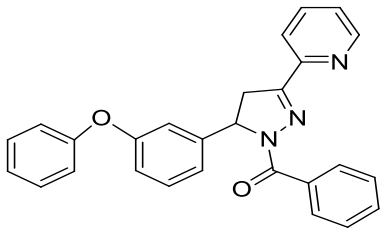
Bhat *et al* synthesized a series of substituted pyrazoles (18) and also evaluated for *in-vitro* cytotoxic activity against a panel of human cancer cell lines. Out of 93 synthesized compounds screened, 8 compounds showed marked cytotoxic activity [31].



(18)

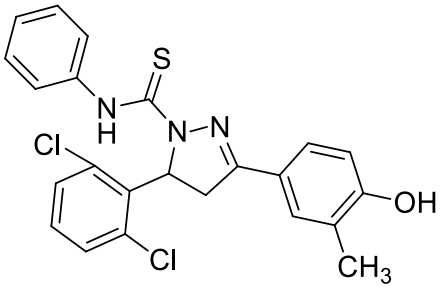
Pyrazolines as Anti-Tubercular Agent

Kini *et al* synthesized series of heterocyclic Ortho/Meta/Para substituted diphenyl ether derivatives (19) and evaluated their activity against H37Rv strain of *Mycobacterium*. All Compounds inhibited the growth at concentrations as low as 1μgml^{-1}. This level of activity was found comparable to the reference drugs Rifampicin and Isoniazid at the same concentration [32].



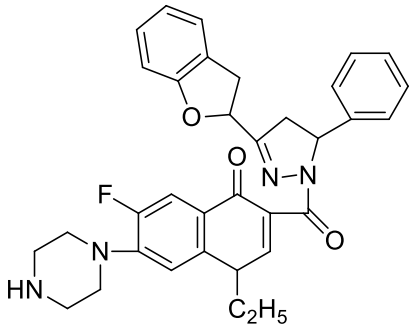
(19)

Ali *et al* synthesized a series of 5-(-4-(substituted) phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-*1H*-1-pyrazolyl-2-toluidino methanethione and 5-(Substituted) phenyl-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-*1H*-1-pyrazolyl-2-methoxyanilino methanethione (20) and tested for their *in-vitro* anti-tubercular activity against *M.tuberculosis* H37Rv [33].

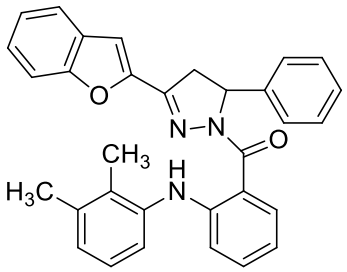


(20)

Babu *et al* synthesized and evaluated biological activity of 1,3,5-trisubstituted pyrazolines bearing benzofuran (19a and 19b). They were found to be anti-tubercular, anti-microbial and anti-inflammatory [34].



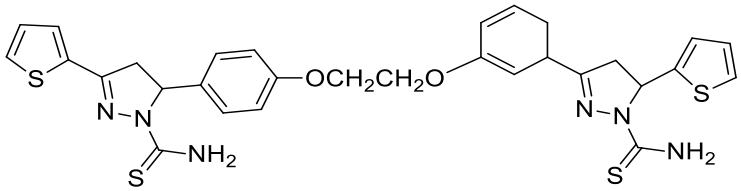
21a



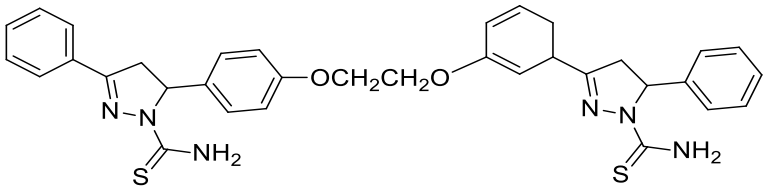
21b

Pyrazolines as anti-inflammatory agent

Barsoum *et al* synthesized derivative as bis(3-aryl- 4, 5-dihydro-1*H*-pyrazole-1-carboxamides) and screened for their Anti-Inflammatory properties and PGE2 inhibitory properties utilizing *in - vivo* Acute Carrageenan - induced paw oedema standard method in rats. It exhibited that many of the tested compounds showed considerable Anti-inflammatory properties (22a and 22b) [35].

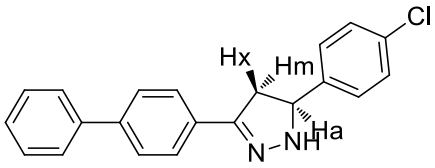


(22a)



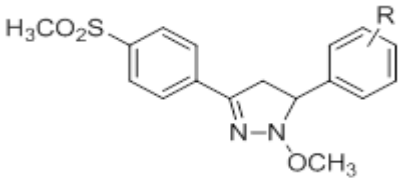
(22b)

Amir *et al* 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 studied compounds, (23) showed more potent anti-inflammatory and analgesic activity than the standard drug, along with minimum ulcerogenic index [36].



(23)

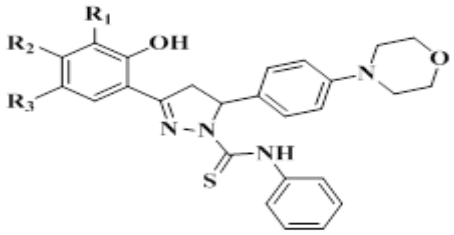
Fioravanti *et al* reported synthesis and biological evaluation of *N*-substituted-3, 5-diphenyl-2-pyrazoline derivatives as Cyclooxygenase (COX-2) inhibitors. New 1-*N*-substituted-3, 5-diphenyl-2-pyrazoline derivatives (24) have been synthesized and cyclooxygenase (COX-1 and COX-2) inhibitory activities have been evaluated. The results of these biological assays showed that all of new derivatives are not endowed with improved anti-inflammatory activity against Cyclooxygenase (COX-1) but some of them showed a good activity against (Cyclooxygenase) COX-2 [37].



(24)

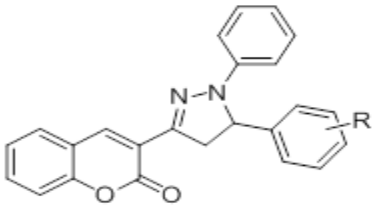
Gill *et al* reported analgesic, anti-inflammatory activities and synthesis of novel pyrazolines derivatives. In search for a new analgesic and anti-inflammatory agent with improved potency,

also designed and synthesized a series of 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl) phenols (25) [38].



(25)

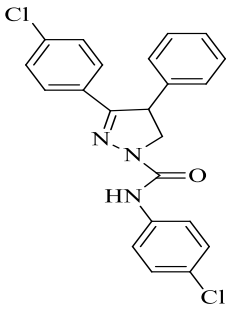
Maddi *et al* reported synthesis and evaluation of a series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines (26) as novel anti-inflammatory and analgesic agent. Synthesized compounds were also found to have significant Analgesic activity in the Acetic acid induced writhing model and antipyretic activity in yeast-induced pyrexia model along with minimum Ulcerogenic index [39].



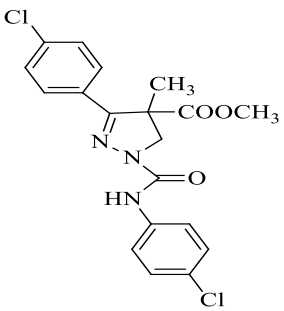
(26)

Pyrazolines as insecticidal agent

Silver *et al* synthesized pyrazoline-type insecticides (27a and 27b) and examined the mode of action synthesized compounds based on available electrophysiological, pharmacological and toxicological information and found to act at neuronal target sites [40].



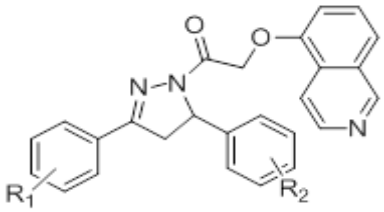
27a



27b

Pyrazolines as Anti-Amoebic Agent

Hayat *et al* reported synthesis, characterization, anti-amoebic activity and cytotoxic evaluation of novel series of Pyrazoline derivatives bearing Quinoline tail (28). The cyclization of chalcones with 2-(quinolin-8-yloxy) Acetohydrazide under basic conditions led to the formation of pyrazoline derivatives. *In-vitro* Anti-Amoebic activity was performed against HM1: IMSS strain of *Entamoeba histolytica*. The results showed that the compounds exhibited promising Anti-Amoebic activity respectively than standard drug Metronidazole [41].

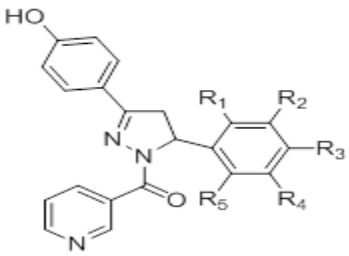


(28)

R_1- 4-Br, 4-Cl; R_2- 4-OCH_3, H, 4-CH_3

Pyrazolines as Anti-Malarial Agent

Acharya *et al* reported synthesis of 1,3,5-trisubstituted pyrazolines derivative (29) and was evaluated for *in-vitro* Anti-malarial efficacy against Chloroquine sensitive and Chloroquine resistant strains of *Plasmodium falciparum*. Formation of B-hematin and inhibition activity of the Pyrazolines were determined, correlated with Anti-malarial activity. The Anti-malarial mode of action was found similar to that of Chloroquine inhibit hemozoin formation. The derivatives were showing better anti-malarial activity than Chloroquine against resistant strain of *P. falciparum* [42].

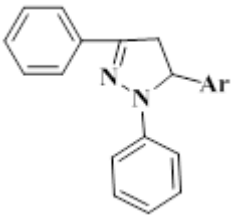


R_1: H, Me, Cl, Br; R_2: H, OMe, NO_2; R_3: H, Cl, OMe; R_4: H, Br, OMe; R_5: H

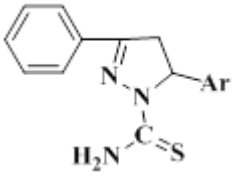
(29)

Pyrazolines as Anti-Depressant Agent

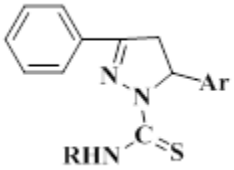
Ruhoglu *et al* synthesized and evaluated for anti-depressant and anti-convulsant activities of some 1, 3, 5-trisubstituted pyrazolines. Chalcones were obtained from acetophenone and aldehydes. The solution of appropriate chalcone and phenlyhydrazine in ethanolic sodium hydroxide or in glacial acetic acid was refluxed. 1-Thiocarbamoyl-3-phenyl-5-heteroaryl-2-pyrazolines were obtained by heating thiosemicarbazide with chalcones, sodium hydroxide in ethanol. Hydrazine hydrate, Iso- thiocyanate and triethylamine were finally added to form the Pyrazoline derivative [43].



(30)

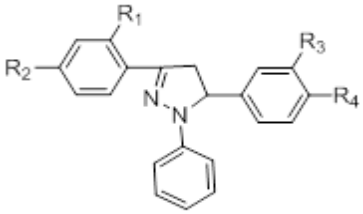


(31)



(32)

Prasad *et al* reported synthesis and anti-depressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2-hydroxynaphthalen-1-*yl*)-1,5-diphenyl-2-pyrazolines (33). The Synthesized compound was evaluated for Anti-depressant activity [44].



(33)

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