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Review Article

Pyrazole: A potent drug candidate with various Pharmacological activities

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ABSTRACT: Aromatic organic heterocycle containing pyrimidine scaffolds. Pyrazole possess, a five-membered hetero aromatic ring with two nitrogen atoms. Presence of this nucleus in these Pyrazole skeletons comprise various ranges of pharmacological activities viz. analgesic, antipyretic, anticancer, antiviral, anti-Inflammatory, antioxidants, antimicrobial, anti-diabetic, anticonvulsant & antiarrhythmic. Pyrazole is a multipurpose lead compound which is developed by chemical architecture for effective molecules which are mostly biologically active. Several synthetic routes are accorded for the development of pyrazole containing reactions to afford a novel molecule.

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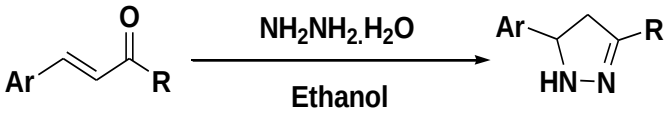
INTRODUCTION

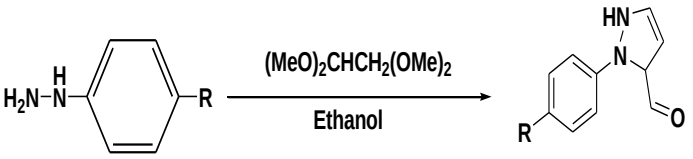
Pyrazoline is characterized by a 5-membered heterocyclic ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions [1]. Pyrazolines represent an important class of heterocycles due to their highly pronounced biological and pharmacological activities such as Antimicrobial, Anti-Inflammatory, Antihypertensive [2]. Pyrazolines derivative is also important core structures of many pharmaceutical and agrochemical substances [3]. A recent approach in treatment of many serious diseases such as cancer, AIDS, cardiovascular diseases and Alzheimer's disease is the development of drugs with multiple actions [2].

GENERAL METHOD OF PREPARATION

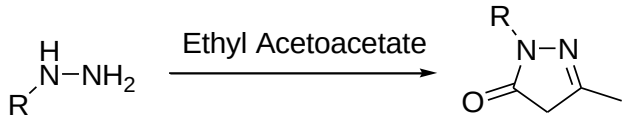
Pyrazolines is prepared by treating substituted chalcones with hydrazine monohydrate 95% in absolute ethanol [4].



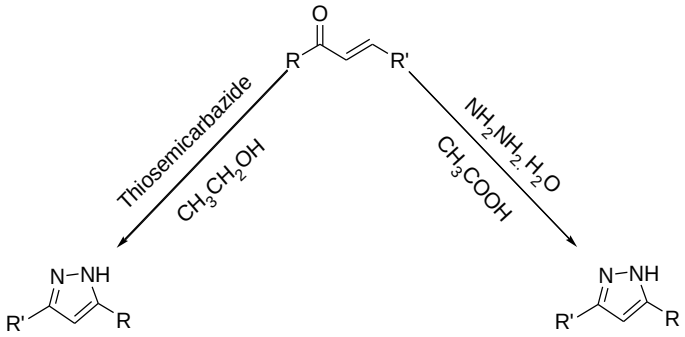
Substituted phenylhydrazine Condense with bis- dimethylacetate of maloaldehyde to give N-arylsubstituted pyrazole [5].



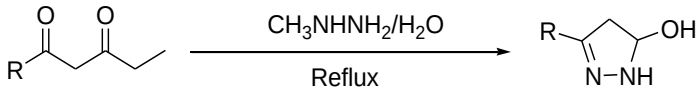
Refluxing substituted phenyl hydrazine and ethyl acetoacetate in methanol (25 mL), containing concentrated hydrochloric acid to form substituted pyrazoline [6].



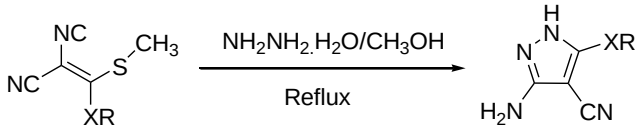
Pyrazoline is prepared by treating mixture of chalcone with thiosemicarbazide in ethanol or hydrazine hydrate in acetic acid [7].



Substituted acetoacetate react with solution of 40% methylhydrazine and then heated to 65 °C to form substituted pyrazoline [8].



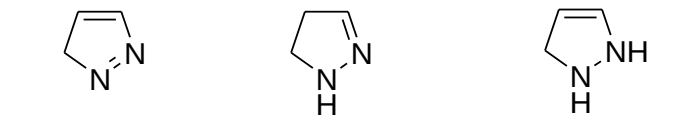
Commercially available substituted 3, 3-bis (methylthio) - 2-cyanoacrylonitrile treated with hydrazine hydrate in methanol to form substituted pyrazole [9].



Alkyl dihalides react with primary amines or alkyl hydrazines under microwave irradiation via a simple and efficient cyclo condensation in an alkaline aqueous medium to give pyrazoline [10].

Properties of Pyrazoline

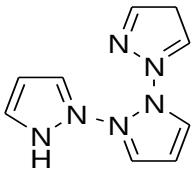
Physical: Pyrazole is a π-excessive heterocycle and contains two nitrogen atoms, pyrrole type and pyridine type, at positions 1 and 2. Pyrazole exists in three partially reduced forms.



1-Pyrazoline 2-Pyrazoline 3-Pyrazoline

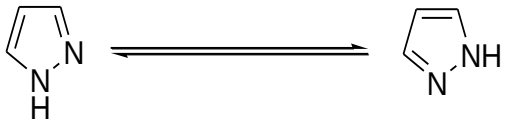
Hydrogen bonding

Pyrazole is a colourless solid with m.pt. 68-70°C**,** boiling point of Pyrazole (186-188°**C)** is due to intermolecular hydrogen bonding.



Tautomerism

Pyrazole exist in two identical and non-separable tautomers due to rapid interconversion of tautomers.



Chemical properties: Pyrazole contain two type of nitrogen atom pyrrole and pyridine at position 1 and 2 respectively.

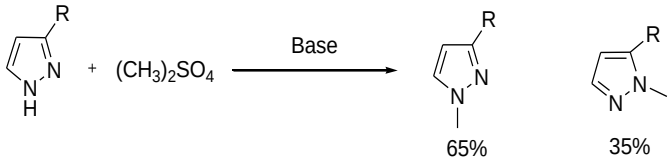
Pyridine type nitrogen is susceptible to electrophilic attack, and the hydrogen atom attached to the nitrogen at position 1 is more acidic then pyrrolic N-H so easily removed by nucleophiles.

Electrophilic attack at nitrogen

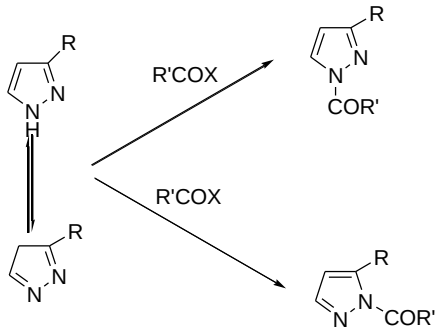
Basicity- Pyrazole is weaker base (pKa= 2.52), lower basicity is due to extra destabilization of π-bonding after protonation.

Acidity: Pyrazole is very weak acid (pKa=14.21), introduction of electron withdrawing group (-I & -M effect) increase the acidity.

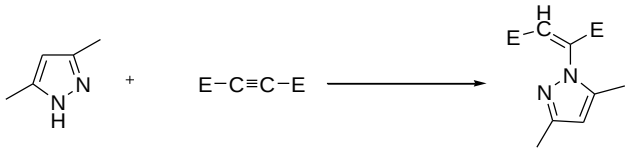
N-Alkylation: Pyrazoles with –NH group are readily alkylated by CH_3I or $(CH_3)_2SO4$. In unsymmetrical pyrazoles the position taken by entering alkyl group depend upon alkylating agent and experimental condition.



N-Acylation:

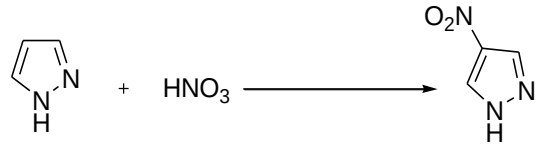


Michael Addition: N-Unsubstituted pyrazoles undergo Michael addition with activated alkenes and alkynes.

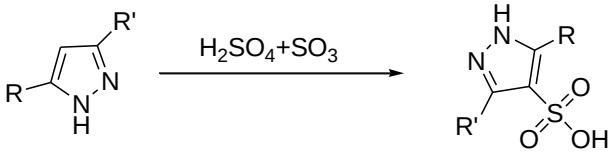


Electrophilic attack at carbon atom

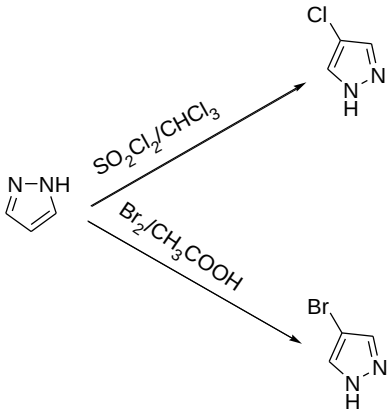
Nitration:



Sulfonation:

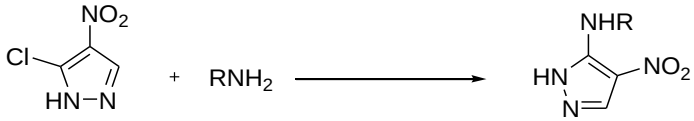


Halogenation:

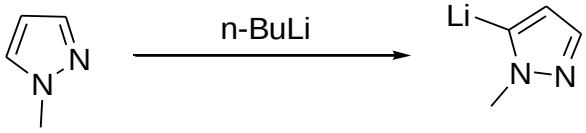


Reaction with Nucleophiles

Nucleophilic attack at carbon:



Nucleophilic attack at Hydrogen:



Spectral characterization

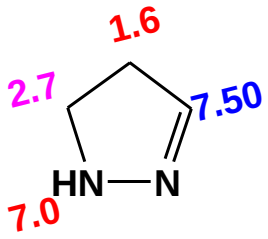
IR:

C=N 1615-1565cm^{-1}

N-H 3335cm^{-1}

=C-N 1360-1250

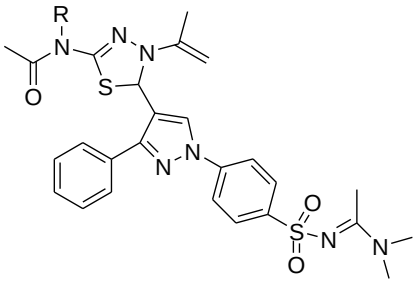
^{1}HNMR



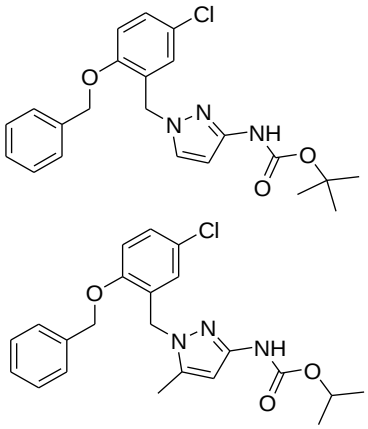
Recent Literature Review

Anti-Inflammatory Activity

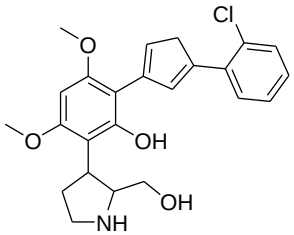
Bekhit *et al,* reported a series of thiazolyl and thiadiazolyl derivatives of 1H-pyrazole and showing anti-inflammatory activity [11].

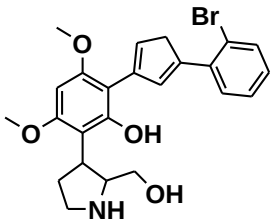


Hall *et al,* find compounds in a series of methylene linked pyrazole EP1 receptor antagonist and having anti-inflammatory activity [12].

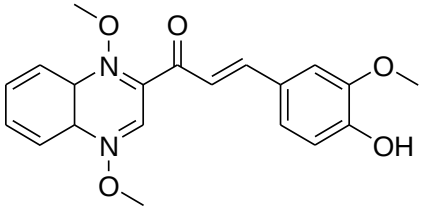


Bandgar *et al,* synthesized a combinatorial library of 3, 5-diaryl pyrazole derivatives showing anti-inflammatory activity against TNF-α and IL6.Out of 15 few compounds showed anticancer activity [13].

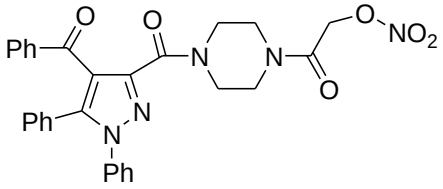




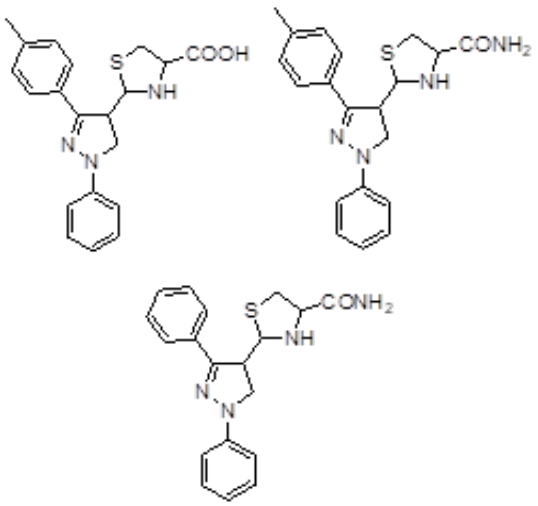
Burguete *et al,* synthesised substituted 3-phenyl-1-(1,4-di-N-oxidequinoxalin-2-yl)-2 propen1-one derivatives and their 4,5-dihydro-(1H)-pyrazole analogues. The compounds are reported to possess anti-inflammatory and antioxidant activities [14].



Abdel-Hafez *et al,* prepared novel pyrazole-NO hybrid molecules and evaluated them for nitric oxide release, antibacterial and anti- inflammatory activities [15].

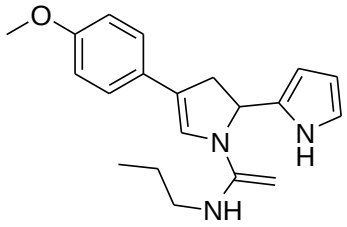


Bekhit *et al,* synthesised a series of 4-thiazolyl pyrazolyl cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2), compounds showing antimicrobial activity, anti-inflammatory activity with no or minimal ulcerogenic effect [16].

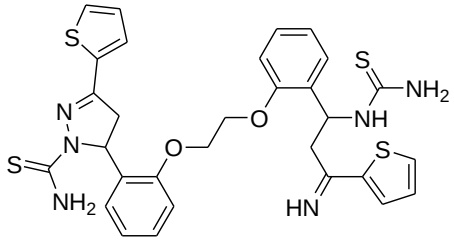


Milano *et al,* studied and evaluated the antinociceptive effect of the novel pyrazoline methyl est er: 4-methyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1H-pyrazole methyl ester (MPF4), effect of MPF4 in two models of arthritic pain caused by Complete Freund's Adjuvant (CFA) and postoperative pain caused by surgical incision in mice [17].

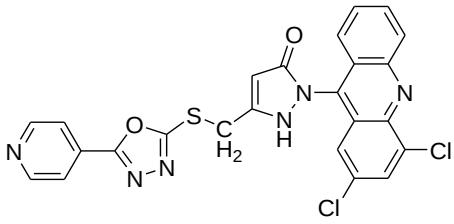
Kelekc *et al*, revealed that monoamine oxidase-B (MAO-B) inhibitors and anti-inflammatory agents might be effective in treating AD they synthesized a novel series of 1-thiocarbamoyl 3-substituted phenyl-5-(2-pyrrolyl)-4, 5-dihydro-(1H)-pyrazole derivatives as promising MAO inhibitor. Compound 20 exhibit both anti-inflammatory analgesic activity and MAO-B inhibitiory activity [18].



Barsoum *et al*, prepared a series bis (3-aryl-4, 5-dihydro-1H-pyrazole-1-thiocarboxamides) and bis (3-aryl-4, 5-dihydro-1H-pyrazole-1-carboxamides). Synthesized compounds were tested for anti-inflammatory activity on carrageenan-induced paw oedema method [19].

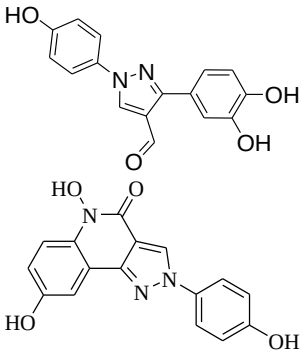


Chandra *et al*, reported a series of compounds with anti-inflammatory and analgesic activities. The compound 1-(2, 4-Chloroacridine-9-yl)-3-(5-pyridine-4-yl)-(1, 3, 4-oxadiazol-2-yl thiomethyl)-pyrazole-5-one 24 showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg p.o [20].

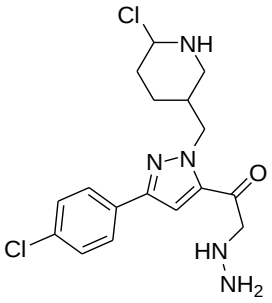


Anticancer activity

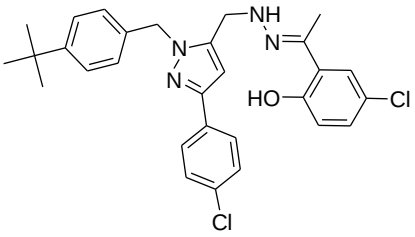
Christodoulou *et al,* synthesised a series of trisubstituted pyrazole derivatives and PIFA- mediated conversion to molecules bearing the fused pyrazolo [4, 3-c] quinoline ring system is reported, and anti-angiogenic activity [21].



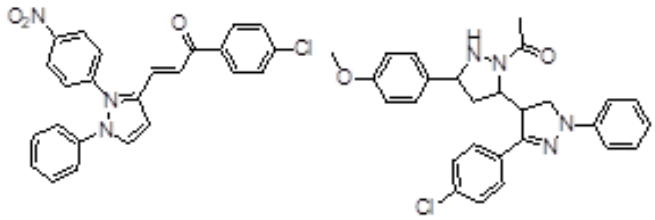
Xia *et al*, synthesised a series of novel 1-arylmethyl-3-aryl-1H-pyrazole-5-carbohydrazide derivatives, nine compounds of the series are reported to inhibit the growth of A549 cells and induced the cell apoptosis [22].



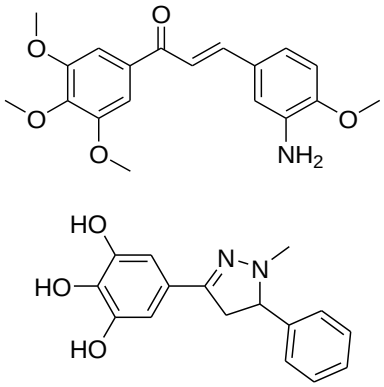
Liang-Wen Zheng *et al*, synthesised a series of novel 3-aryl-1-(4-tert-butylbenzyl)-1H-pyrazole-5-carbohydrazide hydrazone derivatives and investigated their effects on A549 cell growth, the compound (E)-1-(4-tert-butylbenzyl)-NO-(1-(5-chloro-2-hydroxyphenyl) ethylidene)-3-(4-chlorophenyl)-1H-pyrazole-5-carbohydrazide 26 possessed the highest growth inhibitory effect and induced apoptosis of A549 lung cancer cells [23].



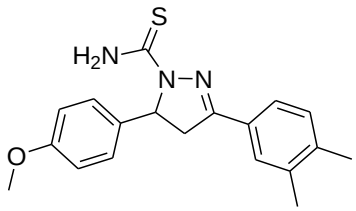
Braulio Insuasty *et al*, synthesized novel (E)-1-aryl-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-ones 5/6 (pyrazolic chalcones) some compound showed Potent activity against leukemia (K-562 and SR), renal cancer (UO-31) and non-small cell lung cancer (HOP-92) cell lines, with the most important GI_{50} values ranging from 0.04 to 11.4 lM, from the in vitro assays [24].



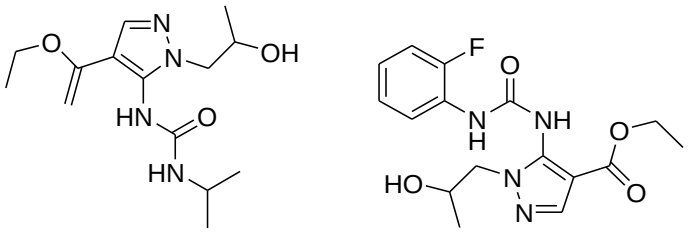
Bonesi *et al,* prepared a series of chalcones and their pyrazoles derivatives and investigated them for Angiotensin I-Converting Enzyme (ACE) inhibitory activity. They have reported the chalcone 2 exerted the highest activity with an IC_{50} value of 0.219 mM, while the most potent pyrazole was (IC_{50} value of 0.213 mM) [25].



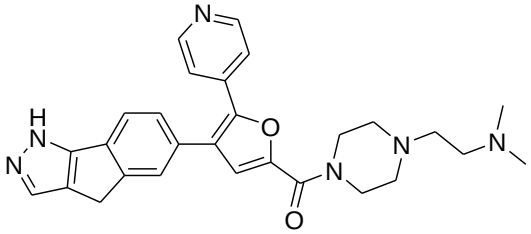
Peng-Cheng Lv *et al,* designed two series of pyrazole derivatives and evaluated for their potential EGFR kinase inhibitors activity, Compound 3-(3, 4-dimethylphenyl)-5-(4-methoxy phenyl)-4, 5-dihydro-1H-pyrazole-1-carbothioamide (C5) is most potent with IC_{50} of 0.07 lM, as compared to positive control erlotinib [26].



Olga Bruno *et al*, reported the synthesis and the chemo taxis inhibitory activity of number of 1H pyrazole-4-carboxylic acid ethyl esters, few compounds has been reported as potent inhibitors of IL8- and fMLPOMe- stimulated Olga neutrophil chemotaxis, most active compound in the fMLP-OMe induced chemotaxis test showed IC_{50} in the range 0.19 nM–2Lm [27].

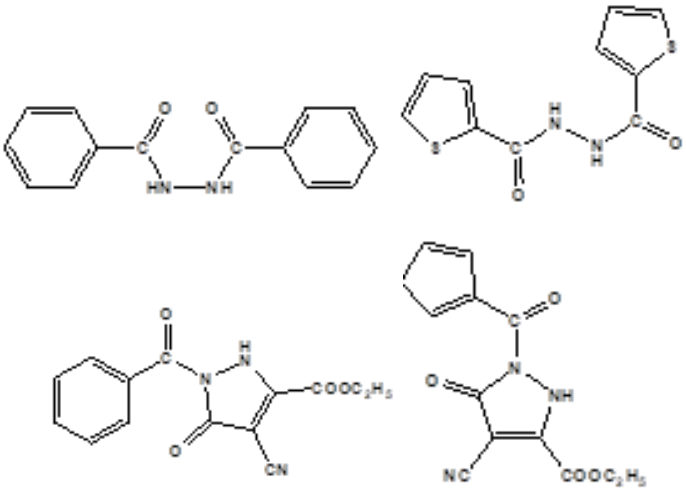


Dan Niculescu-Duvaz *et al,* studied the BRAF, they synthesized a series of analogues leading to the discovery of 6-{2-[4-(4 methylpiperazin-1-yl)-phenyl]-5-pyridin-4-yl-3H-imidazol-4-yl}-2,4-dihydro-indeno [1,2-c] pyrazole and carried out three bioassay inhibition of purified mutant BRAF activity *in vitro*; inhibition of oncogenic BRAF-driven extracellular regulated kinase (ERK) activation in BRAF mutant melanoma cell lines; and inhibition of proliferation in these cells [28].

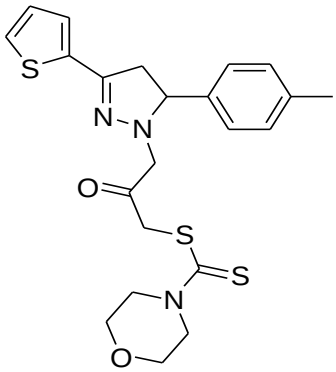


Antidepressant activity

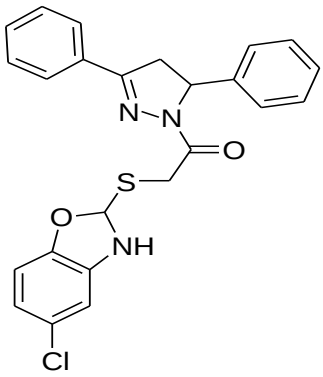
Abdel-Aziz *et al*, described two synthetic paths for the formation of diacylhydrazines, 5amino-1-substiuted pyrazole-3, 3, 4-tricarbonitriles and oxadiazole, pyrazolone derivatives, showing antidepressant activity [29].



Sule *et al,* studies pyrazoline derivatives have therapeutic potential as antidepressant drugs, they synthesised 1-[(N,N-disubstituted thiocarbamoylthio) acetyl]-3-(2-thienyl)-5-aryl-2-pyrazolines. Antidepressant-like activity was investigated in mouse forced swimming test (FST). Results suggest that the N,Ndisubstituted dithiocarbamate moiety of pyrazoline derivatives may have therapeutic antidepressant potential [30].



Özgür *et al,* examining the effects of some 1,3,5-trisubstituted-2-pyrazoline derivatives on depression anxiety and spontaneous locomotor activity parameters of mice. They synthesised a pyrazoline-benzimidazole derivative series and some compound in the series were exhibited significant antidepressant effects in modified forced swimming tests [31].



RESULTS

Pyrazolines are synthetically active substrates and important nitrogen containing 5-membered heterocyclic compounds and which can be used for the synthesis of new heterocyclic compounds and is also used as a raw material for the synthesis of biologically active drug. Many pyrazole derivatives have been made which possess considerable biological activities. This manuscript contains a brief review about different methods which were used for the synthesis of biologically active pyrazole derivatives.

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