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Synthesis and bioevaluation of novel pyrazole by different methods: A review

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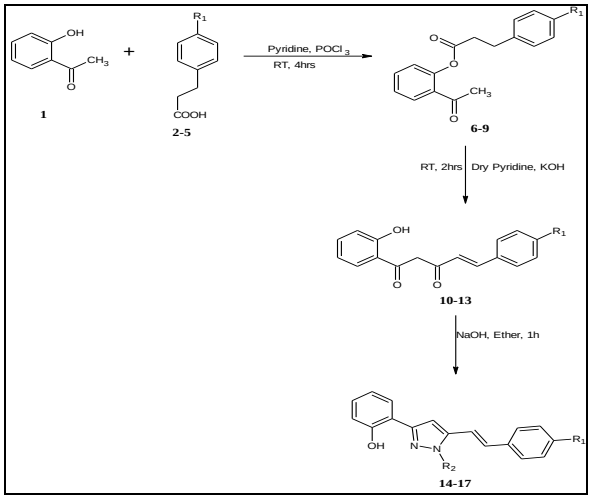
Abstract
Pyrazoles are an important class of heterocyclic compounds; are widely found as the core structure in a large variety of compounds that shown important agrochemical and pharmaceutical activities. The aim of this review is to given an important developments in the synthetic strategies, biological activities found in pyrazole derivatives. A new series of pyrazole derivatives have been synthesized under microwave conditions in ethanol or methanol/glacial acetic acid mixture by the reaction of hydrazines and several kinds of chalcone derivatives. The structures of these compounds were characterized by 1H NMR, IR, TLC and elemental analysis. These compounds shows potential physical and chemical properties like herbicidal, antimicrobial, antifungal, antiviral and antioxidant.

Keywords: Pyrazole, chalcone, 2,4-dinitrohydrazine, synthetic methods, bioactivity

1. Introduction
Heterocyclic compounds have attracted significant interest due to their useful biological and pharmaceutical properties. Many natural and synthetic drugs, dyes, pesticides are heterocyclic in nature (Remington 2005) [2]. Pyrazoles are synthesized by the reaction of 1,3-diketones with hydrazines and the reaction of α,β-unsaturated aldehydes and ketones with hydrazines (Kumar and Jayaroopa 2013) [4]. For example, Fenpyroximate, a potent acaricide with a significant pyrazole ring in the structure, was found to display excellent acaricidal properties against some phytophagous mites (Wang *et al*. 2015) [3].

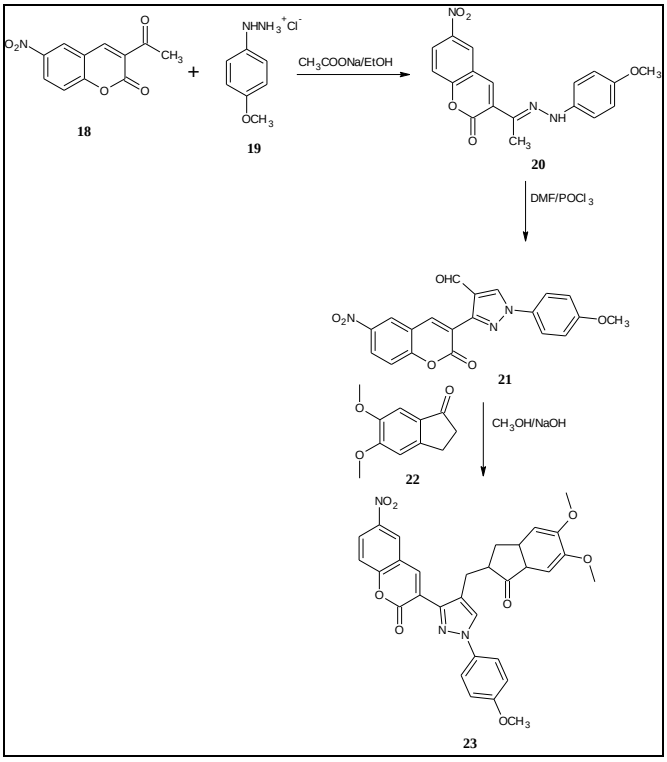
2. Various synthetic routes
2.1 Conventional method
Priyadarshini *et al.*, (2012) [20] revealed the first step of synthetic method involve preparation of the desired 2'-cinnamoyl- oxyacetophenones (6-9) from commercially available 2-hydroxyacetophenone (1) with various cinnnamic acids (2-5) in pyridine using $POCl_3$ as good reagent given better yields. The resulting esters were then converted into corresponding 1,3-diketones (10-13) by stirring the reaction solution in the presence of KOH in better yield. Pyrazole compounds (14-17) were formed in good yields from 1,3-diketones by using alkaline solution of hydrazine (Scheme-1).



Scheme-1

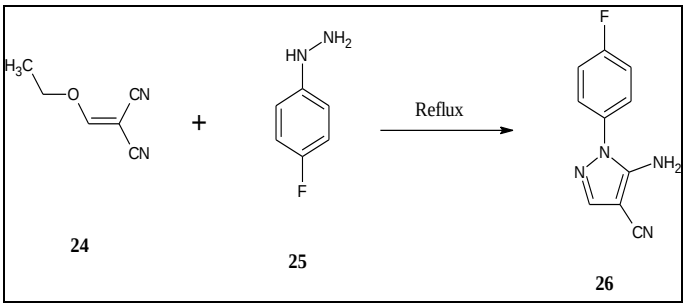
14; R_1= Cl R_2= Ph
15; R_1= OCH_3 R_2= Ph
16; R_1= Cl R_2= H
17; R_1= H R_2= Ph

Vijaya Laxmi *et al.*, (2013) [15] investigated the pyrazole compound (23) by first reaction of 3-acetyl-6-nitro-2H-chromene-2-one (18) and 4-methoxybenzenediazoniumchloride (19) in presence of sodium acetate and ethanol. The compound (20) formed and treated with DMF/$POCl_3$ for half an hour by maintaining the temperature. The compound (21) formed was further react with this solution, 3-[(1E)-1-(2-phenylhydrazinylidene) ethyl]-2H-chromen-2-one (22) was added and the reaction mixture was stirred. After complete addition, the stirring was continued for 30 min at lower temperature and then the temperature was raised for about 6 h. Completion of reaction was confirmed by TLC, reaction mixture was poured into ice water and neutralized by 10% NaOH solution. The solid precipitated out was filtered, dried and recrystallized from ethanol (Scheme-2).



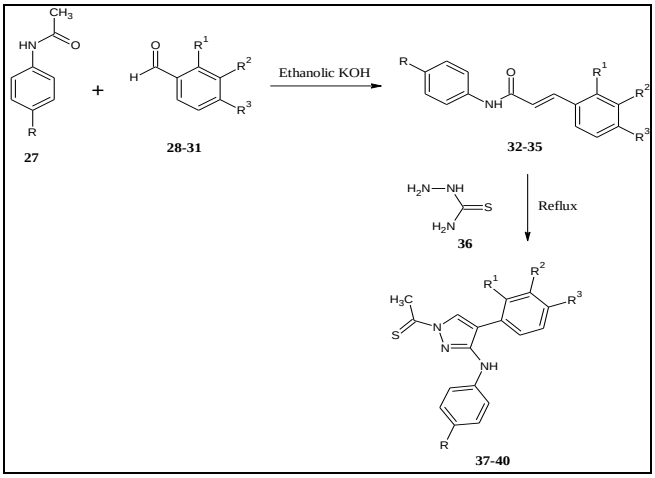
Scheme 2

Plem *et al*., (2015) [7] reported the pyrazole compound like 5-amino-1-aryl-1H-pyrazole-4-carbonitrile (26) by Michael addition reaction of malononitrile (24) and fluorinated and non-fluorinated aryl hydrazine (25) using ethanol and fluorinated ethanol as solvent at reflux. The completion of reaction was checked by TLC (Scheme-3).



Scheme 3

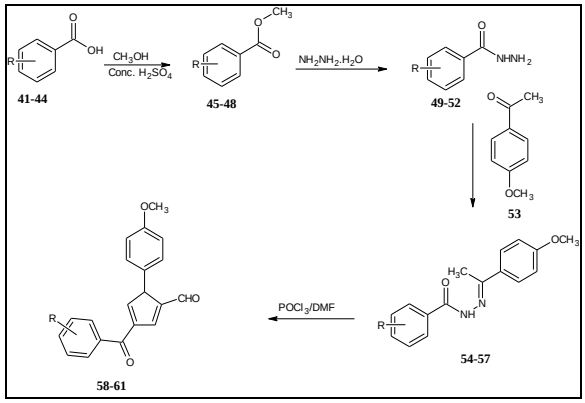
Beena K. P. *et al*., (2016) [6] synthesized pyrazole derivatives (37-40) by first formed chalcone by reaction of equimolar amount of p-chloro acetanilide (27) and substituted benzaldehydes (28-31) in presence of methanol and KOH and the reaction mixture was stirred for 3 hours using qqwmagnetic stirrer. Then the product formed were chalcones (32-35) and further react with these compounds with thiosemicarbazide (36) and reflux for 6 hours in the presence of NaOH and ethanol. The reaction mixture obtained was filtered, washed and dried. The product was recrystallized with a proper solvent (Scheme-4).



Scheme 4

Compound No.	R	R^1	R^2	R^3
37	Cl	H	H	OH
38	Cl	OH	OCH_3	H
39	Cl	H	Br	NO_2
40	Cl	H	H	Cl

Rao *et al.*, (2017) [14] synthesized the pyrazole derivatives (58-61) by Vilsmeier-Haack reaction by refluxing method. Ist reflux substituted aromatic acid (41-44) with methanol in presence of conc. H_2SO_4 as a catalyst. Substituted ester (45-48) was formed and react with hydrazine hydrate. The compound formed was benzene hydrate (49-52) and this further react with 4-methoxy acetophenone (53) in 30 ml methanol by using glacial acetic acid as a catalyst. Vilsmeier-Haack reagent prepared by using DMF and $POCl_3$. Substituted hydrazone (54-57) was refluxed with this reagent. This mixture was Neutralized with sodium acetate trihydrate. Reaction mixture was work-up with ice water. The formed compound was recrystallized by chloroform (Scheme-5).

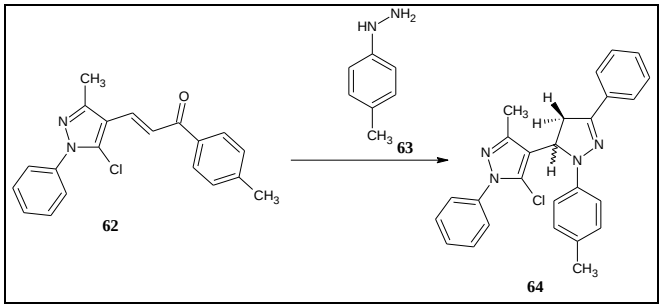


Scheme 5.

58; R= Br
59; R= OH
60; R= NO_2
61; R= OCH_3

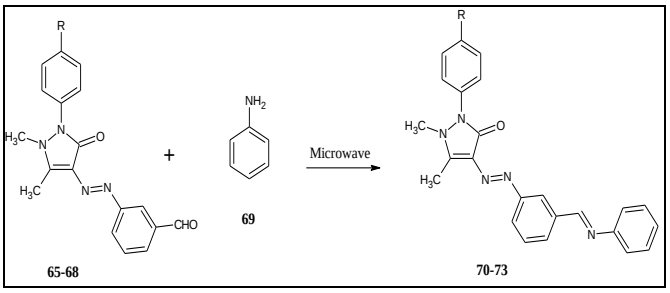
2.2 Microwave method

Trilleras *et al*., (2013) [1] synthesized pyrazole derivative (64) by cyclocondensation reaction of (E)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-yl)-1-arylprop-2-en-1-one (62) with phenyl hydrazines (63) in the presence of methanol and acetic acid under microwave condition. The compound was recrystallized by ethanol (Scheme-6).



Scheme 6

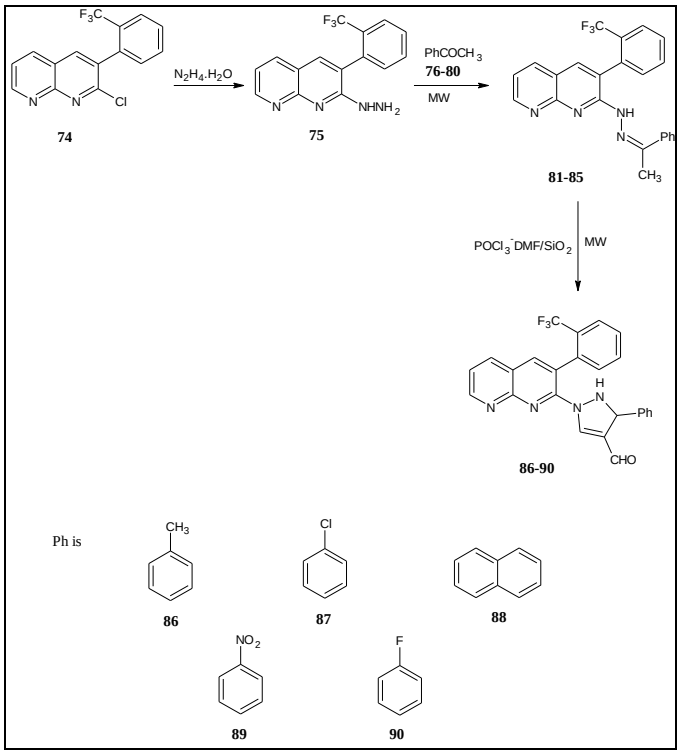
Sharma *et al*., (2014) [9] reported the pyrazole derivatives (70-73) by reaction of equimolar amount of azo compound (65-68) and amine (69) under microwave condition (360W). The completion of reaction checked by layer chromatography with in 1or 2 minutes. The compound formed was recrystallized by proper solvent (Scheme-7).



Scheme-7

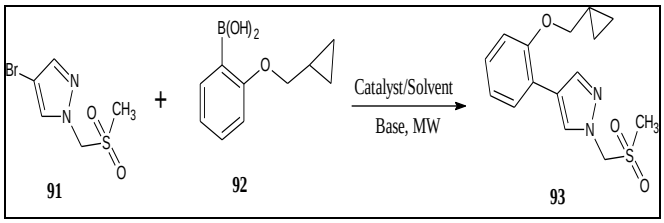
70; R= Cl
71; R= OH
72; R= COOH
73; R= NO_2

Mogilaiah *et al.,* (2015) [10] synthesized pyrazole compounds (86-90) by reaction of 3-(2-trifluoromethyl phenyl)-1,8-naphthyridine (74) with hydrazine then the compound formed was 3-(2-trifluoromethyl phenyl)-1,8-naphthyridine hydrazine (75). Then condensation of these compounds with substituted acetophenones (76-80) in the presence of catalytic amount of DMF under microwave irradiation resulted in the formation of 1-aryl-1-ethanone 1-{3-[2-(trifluoromethyl)phenyl][1,8]-naphthyridin-2-yl}hydrazones (81-85) in good yields. Reaction of hydrazones with Vilsmeier-Haack reagent over silica gel in the presence of microwave irradiation give the pyrazole compounds. These compounds were recrystallized by ethanol (Scheme-8).



Scheme 8

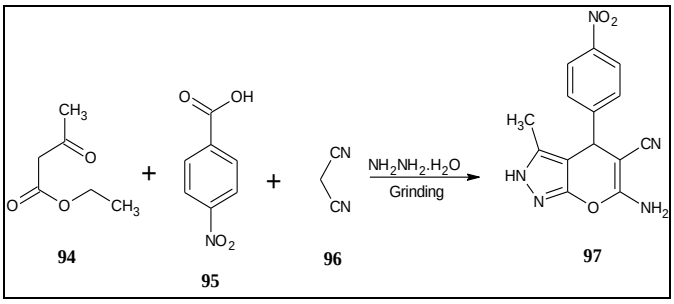
Reddy *et al.,* (2017) [23] depicted the 4-bromo-(2-(cyclopropylmethoxy)phenyl)-1-((methylsulfonyl) methyl)-1*H*-pyrazole (93) by reaction of 4-Bromo-1-[(methylsulfonyl)methyl]-1H-pyrazole (91) and (2-(cyclopropylmethoxy)phenyl)boronic acid (92) in presence of K_3PO_4 and Silica as a catalyst and 1,4-dioxane/water were added. The reaction mixture was placed in Microwave for 5 min. The complection of reaction was checked by TLC and the catalyst was filtered, rinsed with DCM, dried under vacuum. The reaction mixture was filtered and crude mass was obtained. The product formed was recrystallized by ethyl acetate (Scheme-9).



Scheme 9

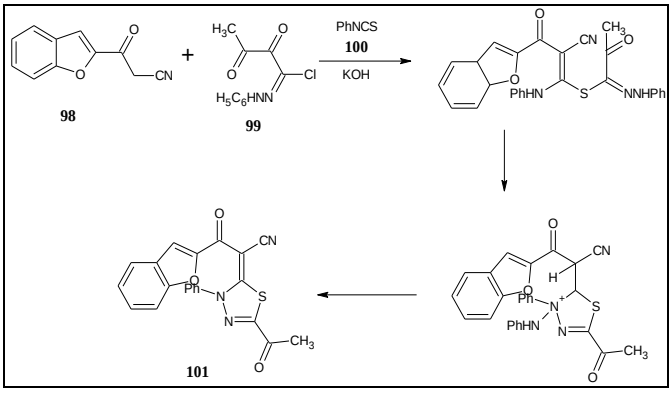
2.3 Grinding method

Bihani *et al.,* (2012) [22] synthesized the compound (97) by taking mixture of ethyl acetoacetate (94), 4-nitro benzaldehyde (95) and malononitrile (96) in presence of hydrazine hydrate. The solid mass was formed and completion of reaction checked TLC. Recrystallization of product takes place by ethanol (Scheme-10).



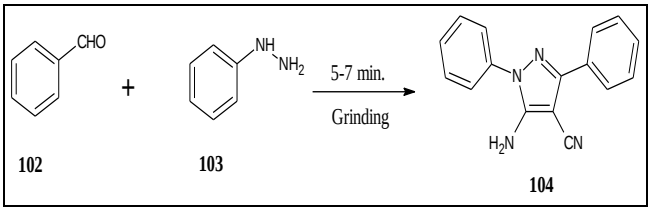
Scheme 10

Abdel-Aziem and Abdelhamid (2013) [21] studied the pyrazole derivative (101) by first reaction of 3-(benzofuran-2-yl)-3-oxopropanenitrile (98), hydrazonoyl halides (99), phenyl isothiocyanate (100) in presence of KOH was ground in pestle mortar at room temperature for 5-10 min. The reaction was checked by TLC in methanol:hexane. The solid product was washed with ethanol-water and recrystallization takes place by a proper solvent (Scheme-11).



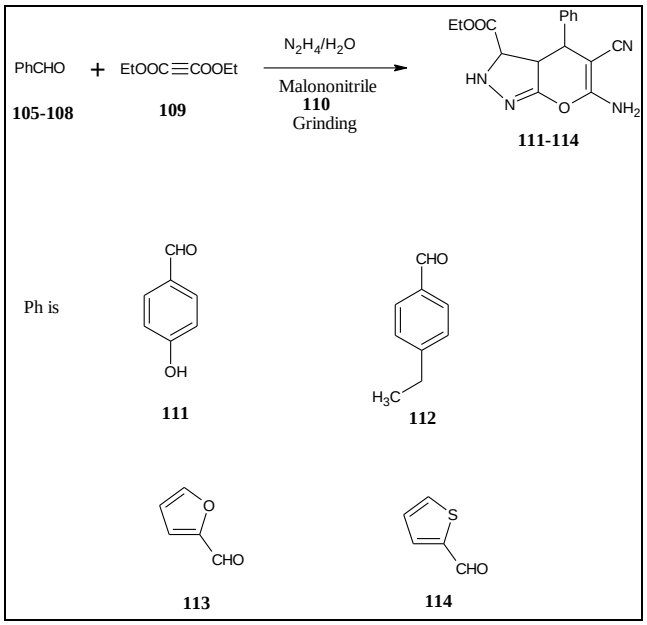
Scheme 11

Bhale *et al*, 2014 [13] given the amino pyrazole cmpounds (104) by grinding benzaldehyde (102) and phenyl hydrazine (103) in the presence of malononitrile in mortar. This is a one pot three component system, catalyst free method. Completion of reaction was monitored by TLC in ethyl acetate:hexane. The compound was recrystallized by methanol (Scheme -12).



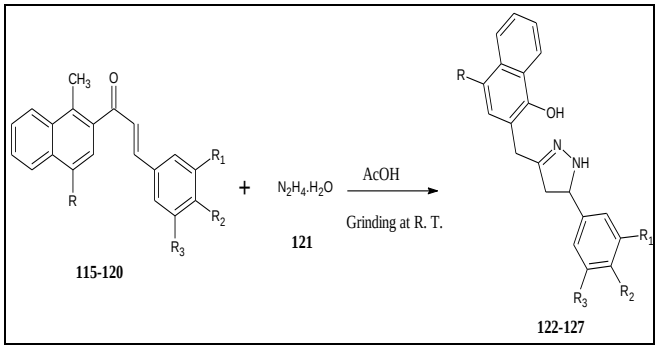
Scheme 12

Ambethkar *et al.*, (2015) [11] reported the pyrazole derivatives (111-114) by grinding of equimolar mixture of different aldehydes (105-108), acetylene ester (109), malono nitriles (110) in presence of hydrazine hydrate in a pestel mortar. The completion of reaction was checked by TLC. The product formed was recrystallized by methanol. This method is high efficient for the synthesis of pyrazoles and give good yields in solvent free condition (Scheme-13).



Scheme 13.

Kharatmal and Jagdale (2017) [20] synthesized the derivatives of pyrazole (122-127) in solvent free condition by grinding the mixture of chalcone derivatives (115-120) and hydrazine hydrate (121) in phenolic condition at room temperature. The reaction mixture was work up in ice-water. The product formed was recrystallized with a proper solvent (Scheme-14).



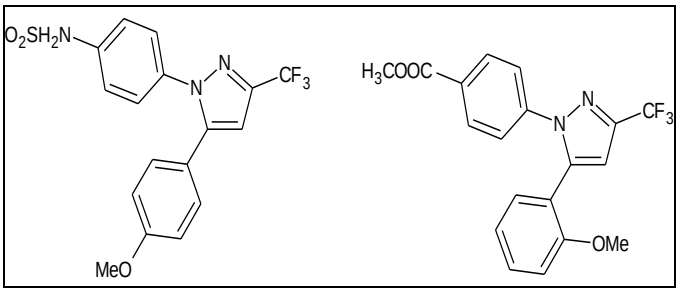
Scheme-14

Compound No.	R	R_1	R_2	R_3
122	Br	H	COOH	OH
123	OH	CH_3	OCH_3	H
124	COOH	F	Br	NO_2
125	Cl	H	CN	Cl
126	H	I	Br	NO_2
127	NO_2	OH	F	H

3. Agrochemical and Pharmacological activities of pyrazole

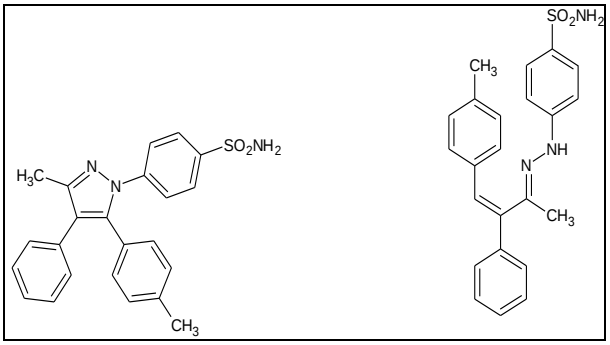
Pyrazole derivatives shows a broad spectrum of agrochemicals and demonstrate the characteristics of medication substances which explains the extensive variety of pharmacological activities which are given below:-

Gao *et al.*, (2011) [17] prepared compounds (I-II) were screened for their biological activity, indicated that the synthesized new compounds a and b display similar strong inhibitory effectiveness in the MDA-MB-435 human cancer cell line in cmparison with the parent compound celecoxib.



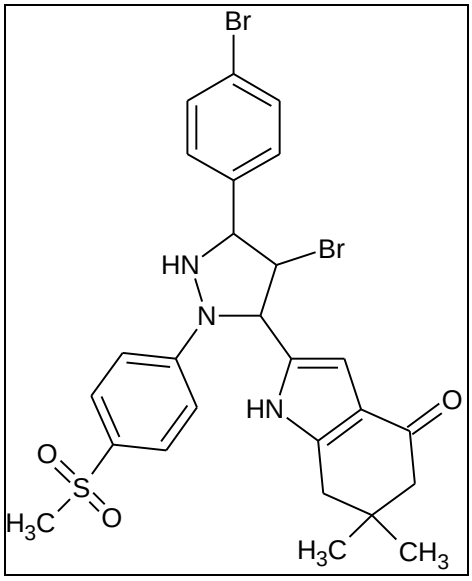
I **II**

Sharshira and Hamada (2012) [8] given the antimicrobial activity of pyrazole compounds (III-IV). These compounds were tested for antimicrobial activity against four test organisms: *Staphylococcus aureus ATCC6538P, Escherichia coli ATCC873, Pseudomonas aeruginosa ATCC9027 and Candida albicans ATCC2091*using rifampicin and ampicillin as standard drugs.



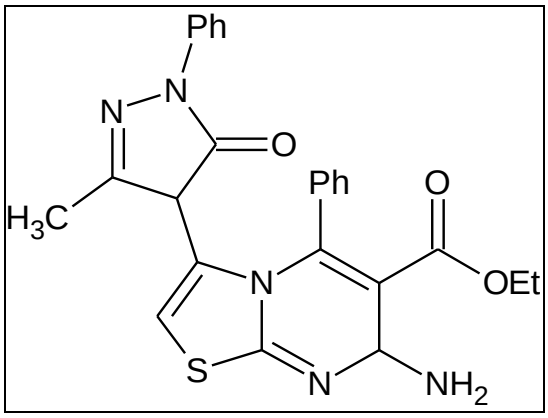
III **IV**

Hassen *et al.,* (2013) [19] found that 4-[4-Bromo-3-(4-bromophenyl)-5-(6, 6-dimethyl-4-oxo-4, 5, 6, 7-tetrahydro-1H-indol-2-yl)-1H-pyrazole-1-yl] benzenesulphonamide **(V)** exhibited good activity against *Candida albicans*.



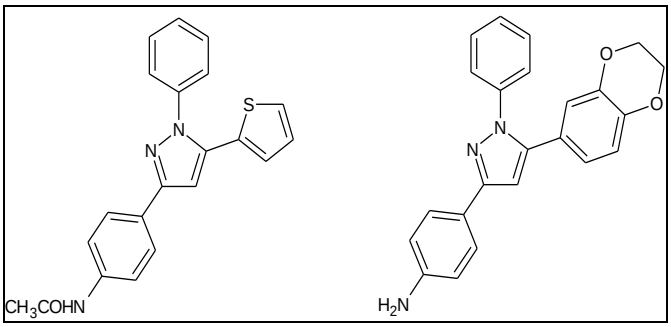
V

Mohamed *et al.,* (2015) [16] revealed Ethyl 7-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-aryl-5*H*thiazolo5*H*thiazolo[3,2-*a*]pyrimidine-6-carboxylate (VI) by the reaction of 4-(2-aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline with arylidene ethyl cyanoacetate. Pyrazole compound exhibited good ant-microbial activity.



VI

Given the *in vitro* study of the 1, 3, 5-trisubstituted pyrazole derivatives (VII-VIII) against several microbial species. *In Vitro* study achived using two concentrations of synthesized derivatives 10 and 100 mg/mL. These compounds shows good antimicrobial activity against *candida albicans* at 10 and 100 mg/ mL concentrations.



VII **VIII**

4. Conclusion

In conclusion, this review article presents a brief summary of a series of pyrazoles were synthesized in good yields. It was further proved by its pharmacological activity. These compounds possess good analgesic and antimicrobial activity.

5. Reference

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