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A REVIEW ON THE CURRENT STUDIES IN PYRAZOLE DERIVATIVES, THEIR BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

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ABSTRACT

The purpose of this present review is to highlight an overview of the versatile biological and pharmacological activities of pyrazole derivatives. The review deals with recent literature survey on the reported methods of synthesis and biological studies on pyrazole derivatives that are considered as most active heterocyclic compounds in nature; which possess a wide range of biological and various pharmacological activities such as: anti diabetic, hypnotic sedative, anti-inflammatory, antimicrobial, anticonvulsant, anthelmintic, antihypertensive, antiviral, anticancer, antioxidant, analgesic, antipyretic, antibacterial, anti-tuberculosis and so on.

KEYWORDS: Pyrazole derivatives; biological activity; pharmacological activity; chemical synthesis.

INTRODUCTION

The term pyrazole was coined by Knorr in 1883. Pyrazole refers to a group of simple aromatic heterocyclic compounds which impart pharmacological effects on human beings. They are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons.[1] The pyrazole ring is a predominant structural motif found in numerous pharmaceutically active compounds. This is mainly due to its ease of preparation and versatile pharmacological activity.[2]

Pyrazole, a five membered ring heterocycle constitute a group of pharmaceutically useful compounds which find application in medicinal chemistry and in organic synthesis. Substituted pyrazoles find various applications in different areas such as: medicine, agriculture and nanotechnology.[3,4]

Pyrazole moiety has attracted the attention of many organic chemists and pharmacologists in recent years because of its very interesting pharmacological activities.[5,12] The chemical structure and reactivity of pyrazole moiety can be interpreted by the effect of individual atoms present in the ring system. The N-atom at position 2 with two electrons is basic and therefore reacts with electrophiles, while as the N-atom at position 1 is acicic due to its imide nature, and pyrazole can lose this proton easily in the presence of a base. Pyrazoles are aromatic molecules due to their planar conjugated ring structure with six delocalized π-electrons. Therefore, many important properties of pyrazole molecules were analyzed by comparing with the properties of benzene derivatives.[13]

Very similar to the other nitrogen containing heterocycles, different tautomeric structures can be written for pyrazole. Unsubstituted pyrazole can be represented in three tautomeric forms.[14] They have been known to exhibit antimicrobial, analgesic, anticancer,[15,16] anti-tubercular,[17] anti-inflammatory,[18,19] antidepressant,[20,21] anticonvulsant, antihyperglycemic,[22] antipyretic, antileukemia,[23] antitubercular,[24] antihypertensive, antipyretic, sedatives, and antidiabetic activities,[25,26] antihelmintic, antioxidant,[27] and herbicidal properties. The pyrazole ring is present as the core in a variety of leading drugs such as Ionazlac, Rimonabant and Difenamizole etc. Further pyridine derivatives are found to exhibit fungicidal,[28] insecticidal activities[29] **Figure-1**. Fused pyrazole derivatives are composed of the pyrazole moiety attached to other heterocyclic moieties which enhanced them to exhibit more improved pharmacological and biological activities compared to the isolated pyrazoles. Currently these compounds are used in several marketed drugs like Cartazolate, Zaleplon, Sildenafil, Allopurinol, Indiplon and Etazolate.[30] Celecoxib demonstrates anti-inflammatory effects and inhibits COX-2; Rimonabant functions as a cannabinoid receptor and is utilized to treat obesity; Fomepizole inhibits alcohol dehydrogenase; and Sildenafil inhibits phosphodiesterase[31] **Figure- 2**.

In this review, we present brief and concise descriptions and discussions on the most relevant applications, synthesis methods, biological and pharmacological properties of pyrazole-derived heterocyclic systems.

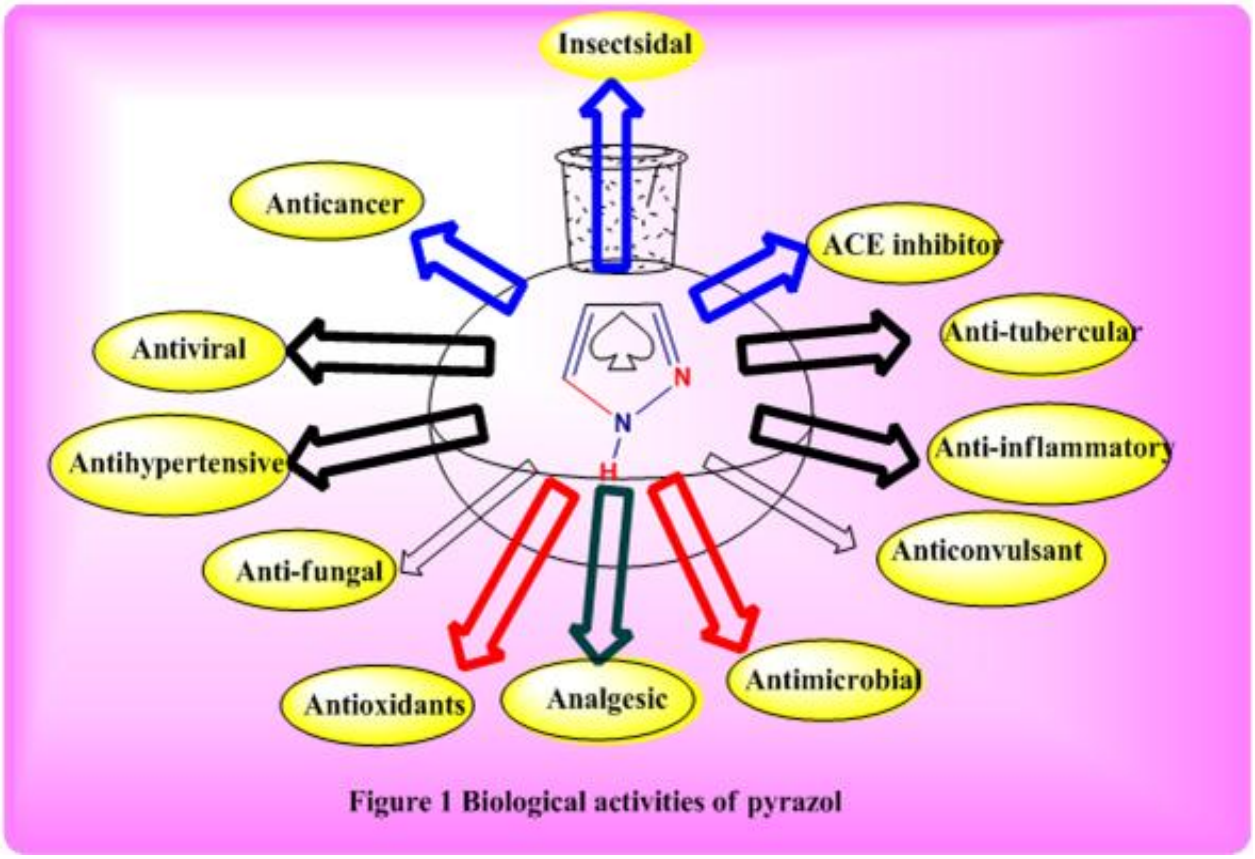
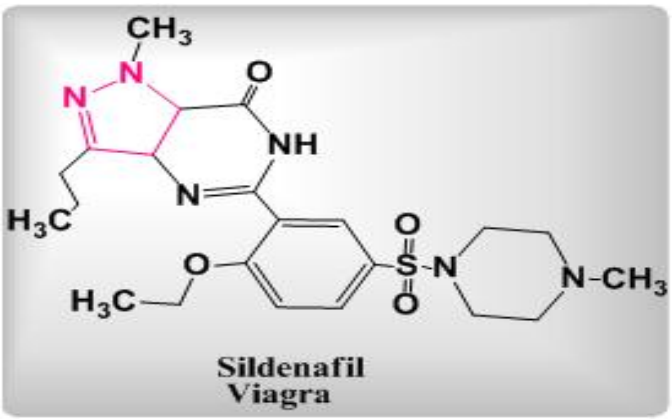
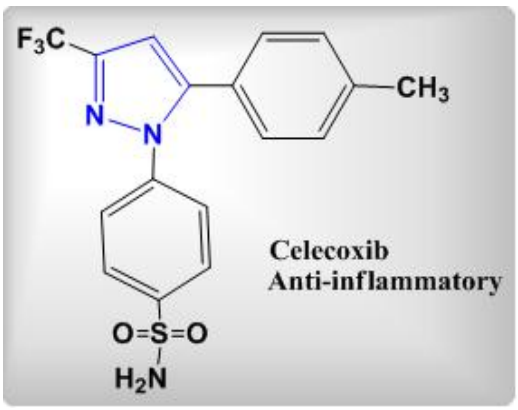
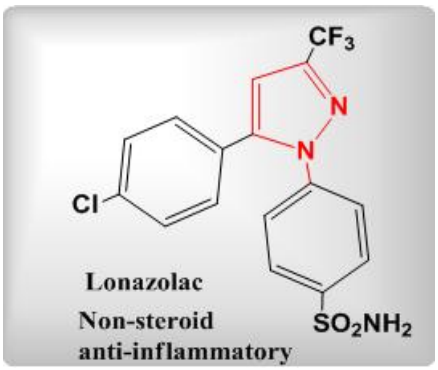
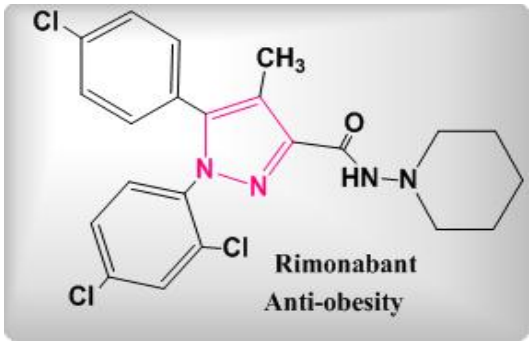


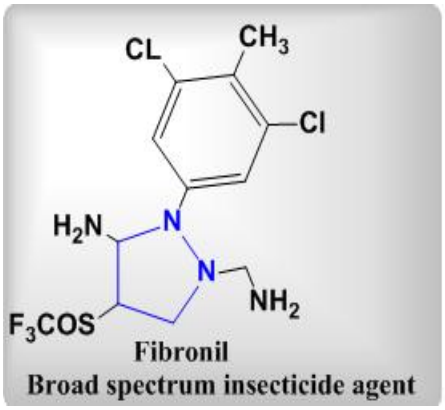
Figure 1 Biological activities of pyrazol





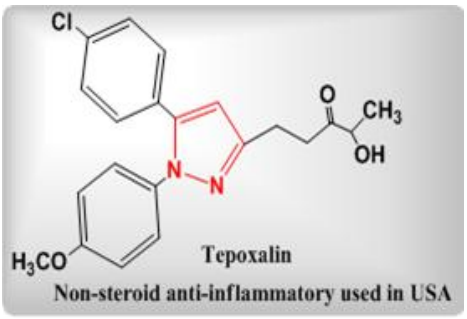






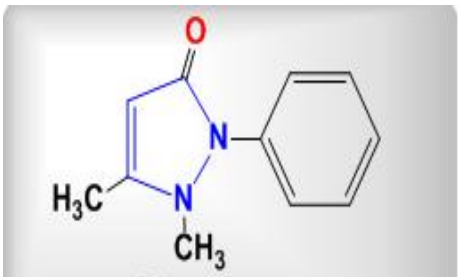
Fibronil

Broad spectrum insecticide agent



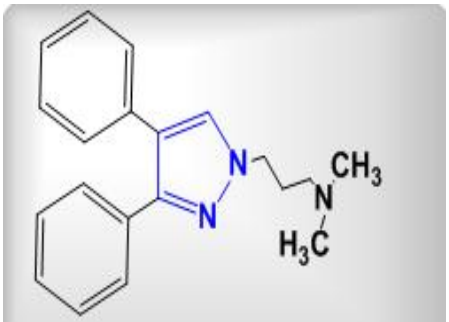
Tepoxalin

Non-steroid anti-inflammatory used in USA

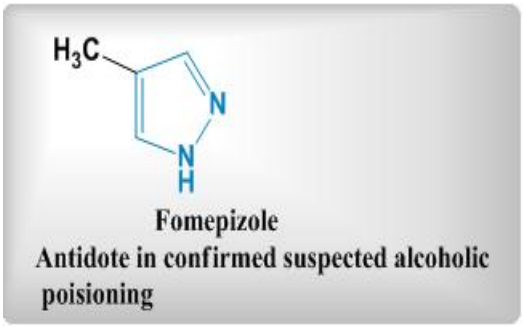


Phenazone

Analgesic and antipyretic drug

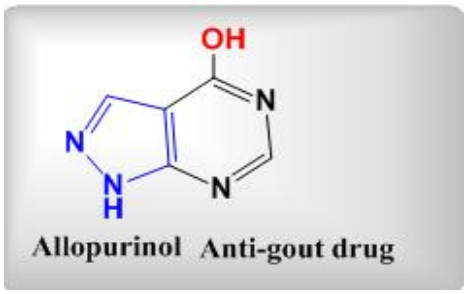


Fezolamine: Antidepressant

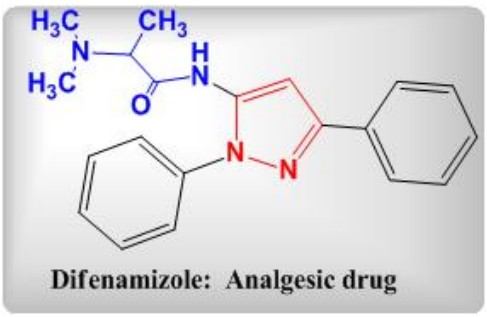


Fomepizole

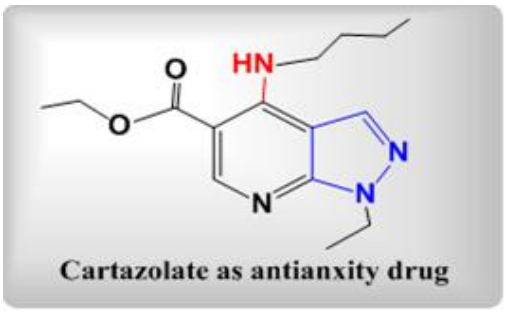
Antidote in confirmed suspected alcoholic poisioning



Allopurinol Anti-gout drug



Difenamizole: Analgesic drug



Cartazolate as antianxity drug

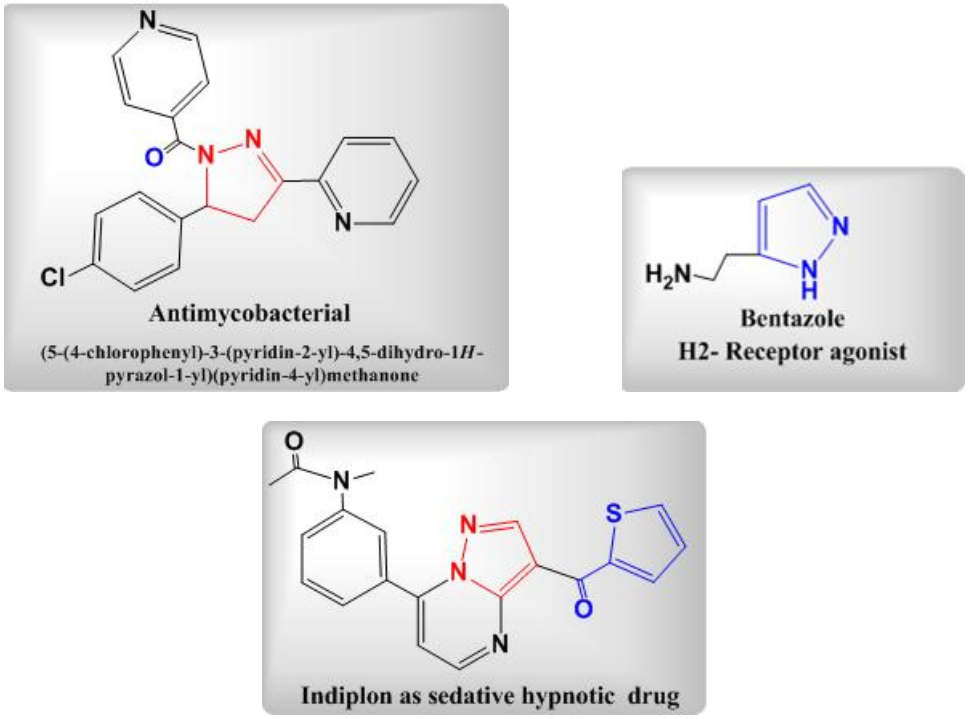
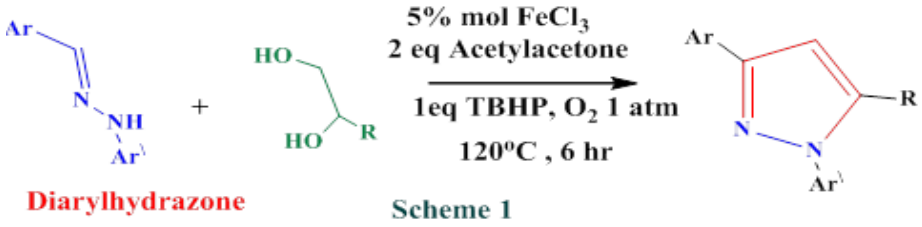


Figure 2: Some example marketing Drug molecules containing pyrazole scaffold.

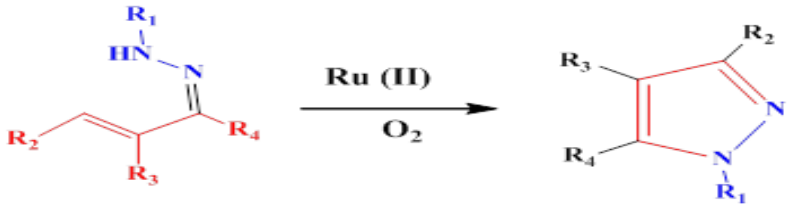
Some methods of the synthesis of pyrazoles

1. *Synthesis of 1, 3-di and 1, 3, 5-tri substituted pyrazoles*: An iron-catalyzed route to the regioselective synthesis of 1, 3- and 1, 3, 5-substituted pyrazoles by the reaction of diarylhydrazones with vicinal diols is reported [**Scheme-1**].[32]



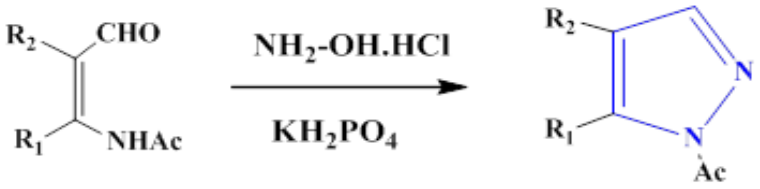
Scheme 1

2. *Synthesis of tri- and tetra-substituted pyrazoles*: A ruthenium (II)-catalyzed intramolecular oxidative CN coupling for the facile synthesis of tri- and tetra-substituted pyrazoles is found in the literature. Dioxygen gas is employed as the oxidant in this transformation and the reaction demonstrates excellent reactivity, functional group tolerance, and gives the products in high yield [**Scheme-2**].[33]



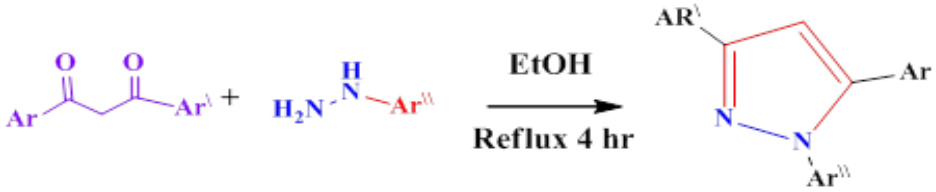
Scheme 2: Synthesis of tri- and tetra-substituted pyrazoles

3. *Synthesis of 1-(4, 5-disubstitutedpyrazol-1-yl)-ethanones:* A novel one-pot synthesis of pyrazoles has been accomplished by the reaction of β-formyl enamides with hydroxylamine hydrochloride and catalytic potassium dihydrogen phosphate in acidic medium [**Scheme-3**].[34]



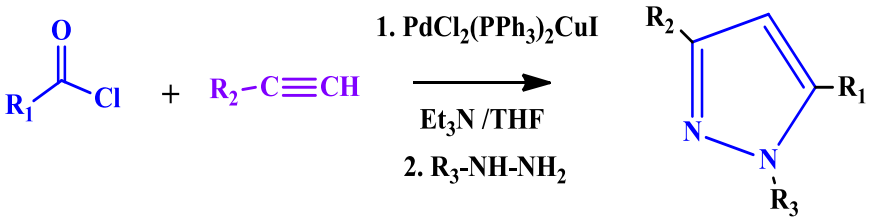
Scheme3: Synthesis of 1-(4,5-disubstitutedpyrazol-1-yl)-ethanone

4. *Synthesis of 1, 3, 5-trisubstituted-1H-pyrazole*: The reaction of the easily accessible 1,3-*bis*-aryl-monothio-1,3-diketone or 3-(methylthio)-1,3-*bis*-aryl-2-propenones with arylhydrazines gives 1-aryl-3,5-bisarylpyrazoles with complementary regioselectivity at position 3 and 5 [**Scheme-4**].[35]



Scheme 4: Synthesis of 1,3,5-trisubstituted-1H-pyrazole

5. An efficient and general one-pot three-component procedure for the construction of pyrazoles *via* a tandem coupling-cyclocondensation sequence catalyzed by $Pd(PPh_3)_2Cl_2$/CuI is reported [**Scheme-5**].[36]

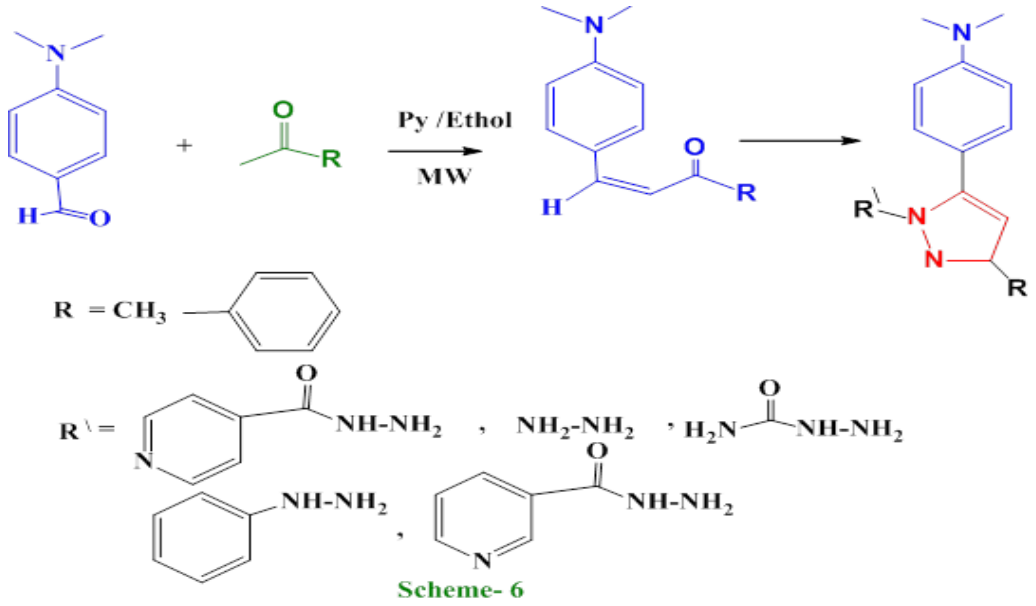


Scheme 5 : Three components synthesis of pyrazole

Review of literature on the biological and pharmacological activities of pyrazoles.

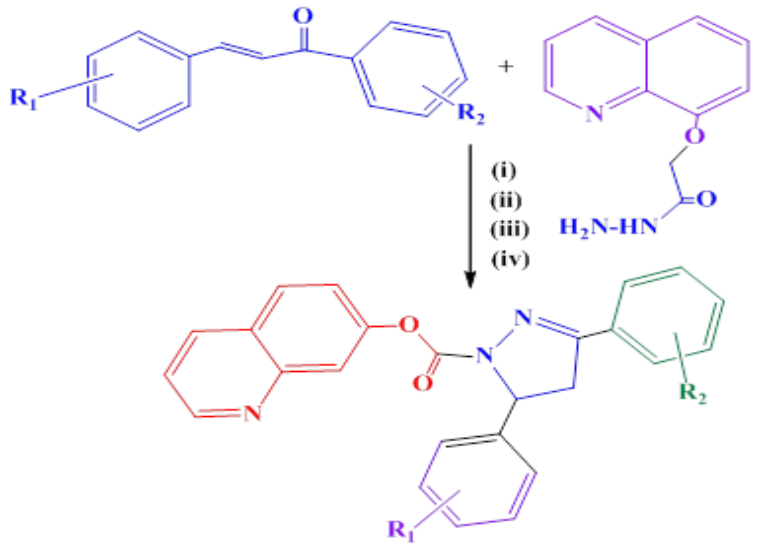
Synthesis of Antimicrobial Pyrazoles

1. Deepak Swarnkar, *et al* (2014),[37] have reported the microwave-assisted synthesis, characterization and antimicrobial activity of some pyrazole derivatives. All the synthesized compounds have been characterized by the IR, ^{1}H NMR,[13] C NMR, Mass and chemical analysis studies [**Scheme-6**].



Scheme- 6

2. G. Manjunath, *et. al* (2016),[38] have reported the synthesis of new Pyrazole derivatives containing quinoline moiety *via* Chalcones, having potential antibacterial and antifungal activity [**Scheme 7**]. The synthesized compounds are found to exhibit antibacterial activity against two kinds of strains i.e. gram-positive organism: Staphylococcus aureus and gram-negative organism: Escherichia coli and antifungal activity against Aspergillus niger at very low concentrations.



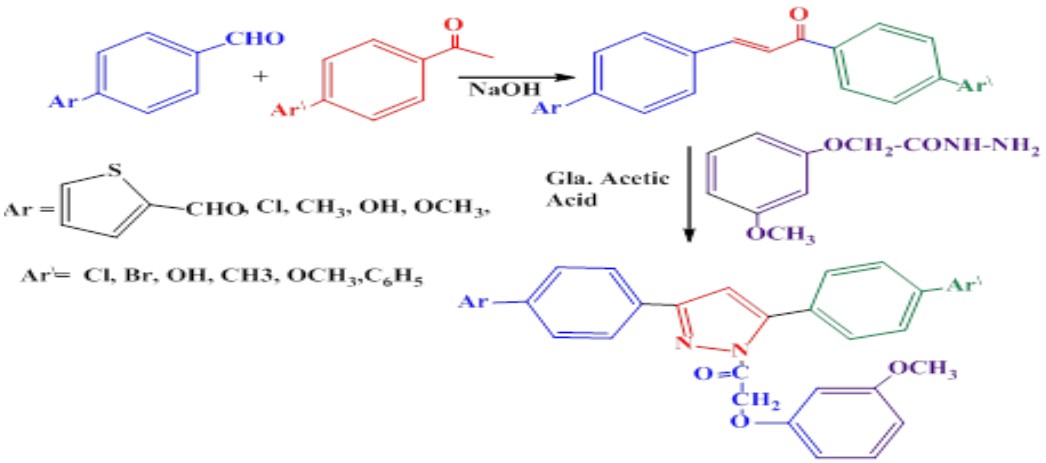
(i) $ClCH_2COOC_2H_5$, K_2CO_3, DMF (ii) N_2H_4,H_2O, ErOH (iii) NaOH, ErOH (iv) Giacial acetic acid
R_1=p-OCH_3, o-OH R_2=—H, p-OH, o-OH, p-Cl, p-NO_2

Scheme- 7

3. P. B. R. Kumar *et. al* (2011),[39] have reported the synthesis of some novel 1-*H* pyrazole derivatives and their antibacterial activity studies. The procedure involves reaction between hydrazides with different acetophenones in methanol followed by Vilsmeier-Haack reaction [**Scheme-8**]. All the compounds synthesized were tested for their antibacterial activity on nutrient medium against Bacillus pumilus, Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa.

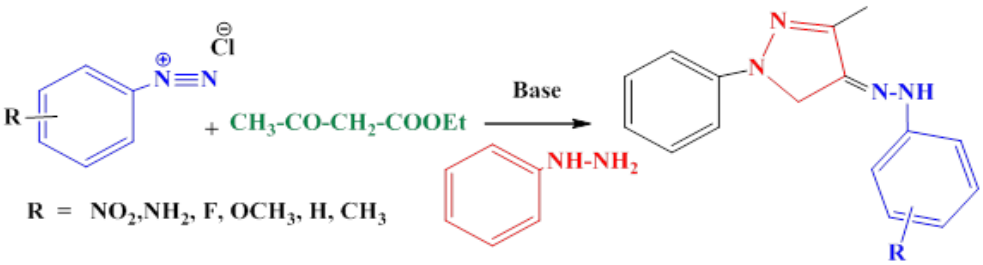
Scheme-8

4. B. C. Revanasiddappa *et. al* (2018),[40] have reported the synthesis, antibacterial and antifungal evaluation of novel pyrazole derivatives [**Scheme-9**]. The synthesized compounds were screened for their antibacterial activity against two gram positive bacterial strains: Bacillus subtilis and Staphylococcus aureus and two gram negative bacterial strains: Pseudomonas aeruginosa and Escherichia coli as well as antifungal activity against Aspergillus flavus and A. fumigatus by using modified Kirby-Bauer disc diffusion method.[41]



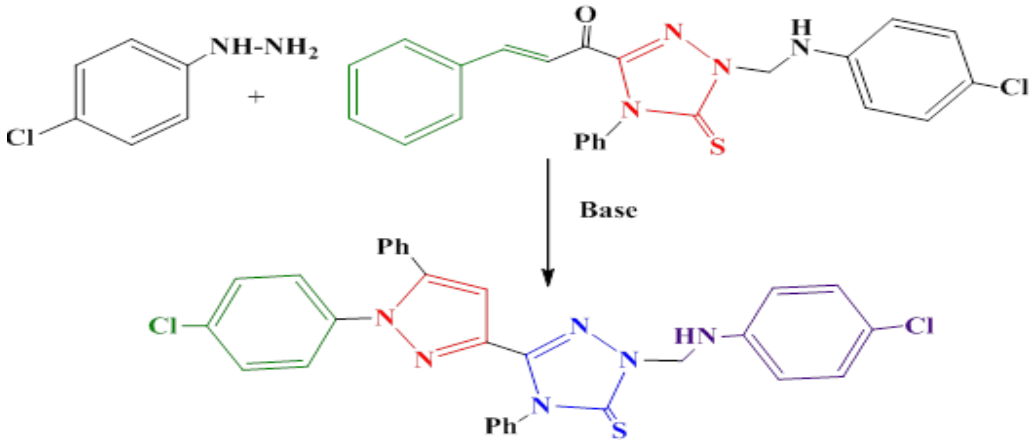
Scheme-9

5. Yuvaraj S. *et.al* (2009),[42] have reported the synthesis and biological evaluation of pyrazole derivatives. Pyrazole derivatives were prepared from aryldiazonium chloride and ethyl acetoacetate. The resulting intermediates were condensed with phenylhydrazine to afford the respective pyrazole derivatives. All the synthesized compounds were screened for antibacterial activity against gram-positive and gram. negative microorganisms by Cup and Plate method and were found to exhibit good activity against Staphylococcus aureus (gram-positive bacteria) [**Scheme-10**].



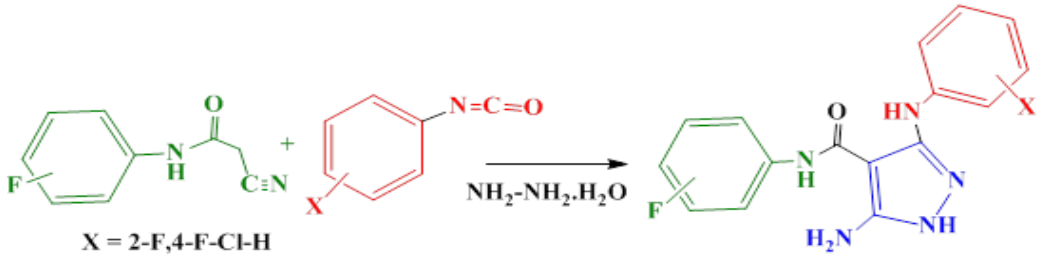
Scheme - 10

6. Eman M. Flefel *et. al* (2012),[43] have reported the base catalysed synthesis of some triazolopyrazole derivatives. All the synthesized compounds were tested for their antibacterial and antifungal activities and they showed high activity compared with the standard drugs like ciprofloxacin and fusidic acid [**Scheme-11**].



Scheme- 11

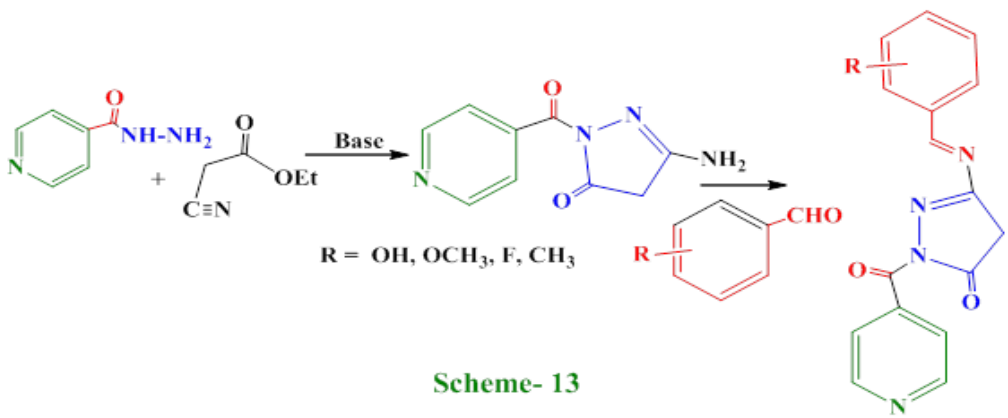
7. Kurz T. *et.al* (2006),[44] have reported the synthesis of fluoro substituted derivatives of pyrazoles. The synthesized compounds were screened for their anti microbial activity [**Scheme-12**].



X = 2-F,4-F-Cl-H

Scheme- 12

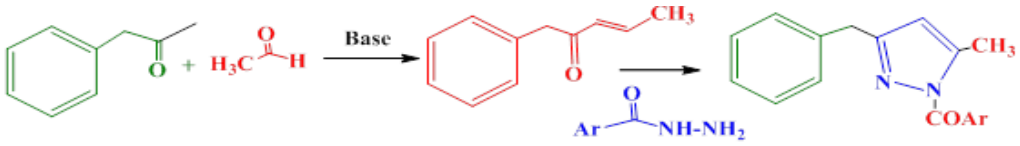
8. Bharat Parashar *et.al* (2010),[45] have reported the microwave assisted synthesis and antimicrobial activity of some novel *iso*-nicotinoyl-pyrazole derivatives. The derivatives (substituted 3-(benzylidene amino)-1-*iso*-nicotinoyl-1*H*-pyrazole-5(4*H*)-one were prepared by the condensation of *iso*-nicotinohydrazide with ethyl-2-cyanoacetate and benzaldehyde derivatives. All the newly compounds were screened for their anti microbial activity against E. coli, S. aureus, P. aeruginosa and fungi such as: C. albicans and they showed promising antifungal and antibacterial activities [**Scheme-13**].



R = OH, OCH_3, F, CH_3

Scheme- 13

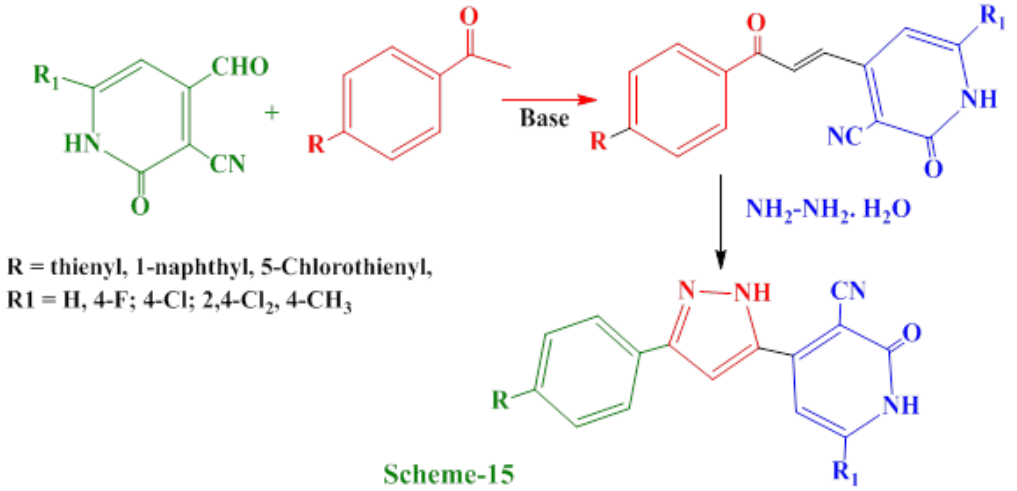
9. D.P. Gupta *et.al* (2010),[46] reported the synthesis and antimicrobial activity studies of *N*-substituted pyrazole derivatives. *N*-substituted-3-benzyl-5-methylpyrazole derivatives were prepared from substituted arylhydrazides. All the synthesized compounds were screened for their antimicrobial activity against different bacterial strains such as: Bacillus subtilis, Bacillus aureus, E. coli. Standard drugs like ampicilin, amoxicillin were used [**Scheme-14**].



Scheme-14

Synthesis of Anti fungal pyrazoles

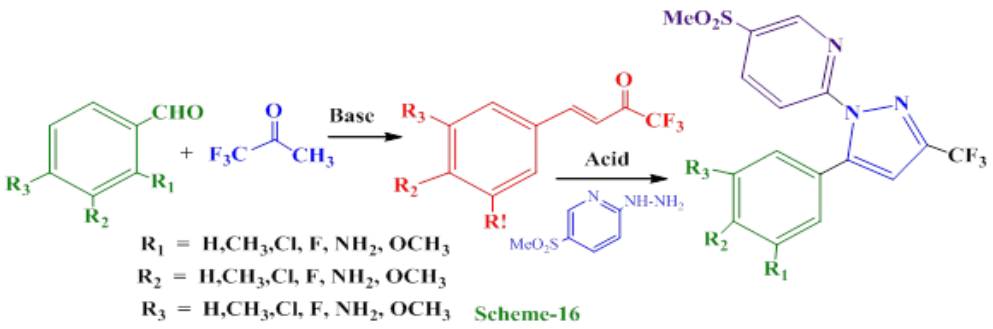
Arun M. Isloor *et. al* (2012),[47] have reported the synthesis of pyrazoles containing cyanopyridone moiety (*i.e.*, 4,6-disubstituted-3-cyano-2-pyridone) and these compounds were screened for antibacterial and antifungal activity and found to exhibit significant activity when compared with the standard drug: streptomycin. The synthesized compounds showed good antibacterial activity against the bacterial strain (E. coli, Staphylococcus aureus and Pseudomonas aeruginosa) and antifungal activity against Aspergillus flavus [**Scheme-15**].



Scheme-15

Synthesis of anti- inflammatory, analgesic and cox-2 inhibiting pyrazoles

1. Cheng H. *et.al* (2006), [48] have reported the synthesis and SAR of heteroaryl-phenyl-substituted pyrazole derivatives as highly selective and potent canine COX-2 inhibitors [**Scheme-16**].



Scheme-16

2. Alegaon *et.al* (2014),[49] have reported the synthesis of 1, 3, 4-trisubstituted pyrazole derivatives and the structure of newly synthesized compounds were characterized by infrared (IR), ^{1}H nuclear magnetic resonance (NMR),[13] CNMR, and mass spectral analysis. These compounds were screened for the anti-

inflammatory activity by carrageenan-induced paw oedema method. One compound showed excellent anti-inflammatory activity (≥84.2% inhibition) as compared to that of the standard drug diclofenac (86.72%) when measured 3 h after administering the carrageenan injection [**Figure-3**].

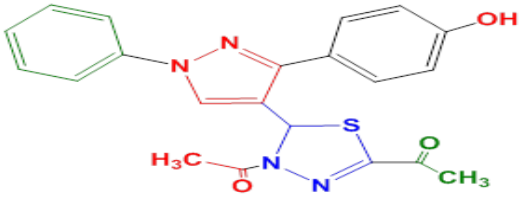
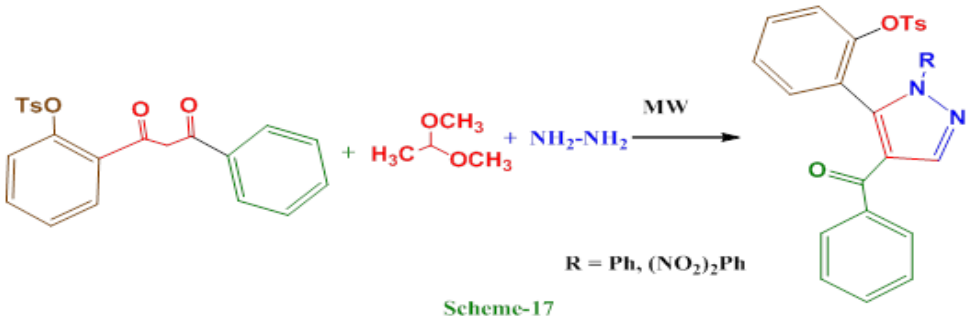


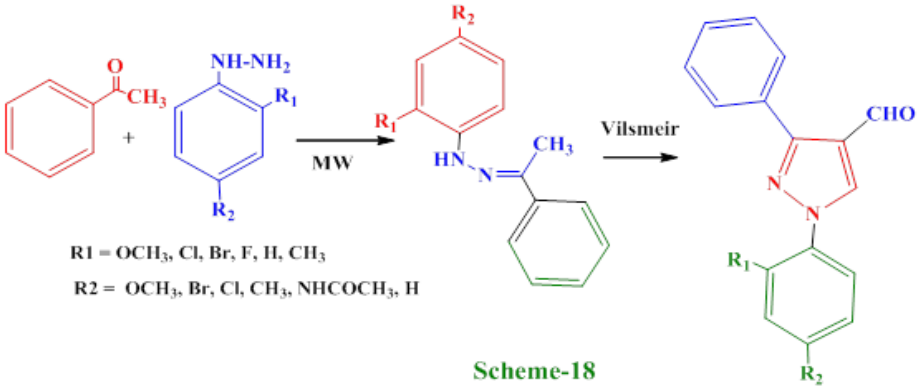
Figure-3

3. Kendre *et.al* (2019),[50] have synthesized a new series of pyrazole, isoxazole, benzoxazepine, benzothiazepine, and benzodiazepine derivatives by the one-pot multi-component cyclo-condensation reaction of 1-phenyl-3-[2-(tosyloxy)phenyl]propane-1, 3-dione, DMF dimethyl acetal, and hydrazine or hydroxylamine hydrochloride or 2-aminothiophenol or 2-aminophenol or benzene-1, 2-diamine by microwave induction technique in aqueous media. One of the synthesized compounds was screened for the anti-inflammatory activity using indomethacin as the standard drug, and was found to be potent [**Scheme-17**].



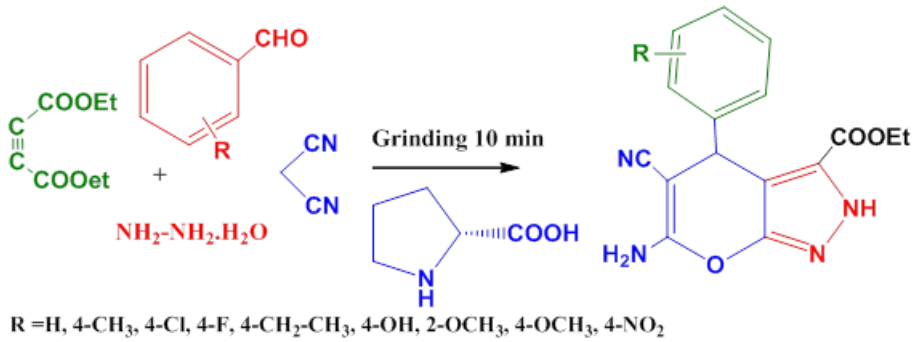
Scheme-17

4. Another microwave-assisted synthetic route to synthesize pyrazole-4-carbaldehyde with analgesic and anti-inflammatory activity was reported by Selvam *et. al* (2014),[51] [**Scheme-18**].



Scheme-18

5. An interesting synthesis of pyrazolylbenzyltriazole derivatives as cyclooxygenase inhibitors was developed by Chandna *et. al* (2014)[52] by using 1-[(4-hydrazinophen-1-yl) methyl]-1*H*-1, 2, 4-triazole hydrochloride **[Scheme-19]**. The triazole intermediate was obtained *via* the condensation of 4-nitrobenzyl bromide and 4-aminotriazole in ethyl acetate followed by diazotization and reduction.

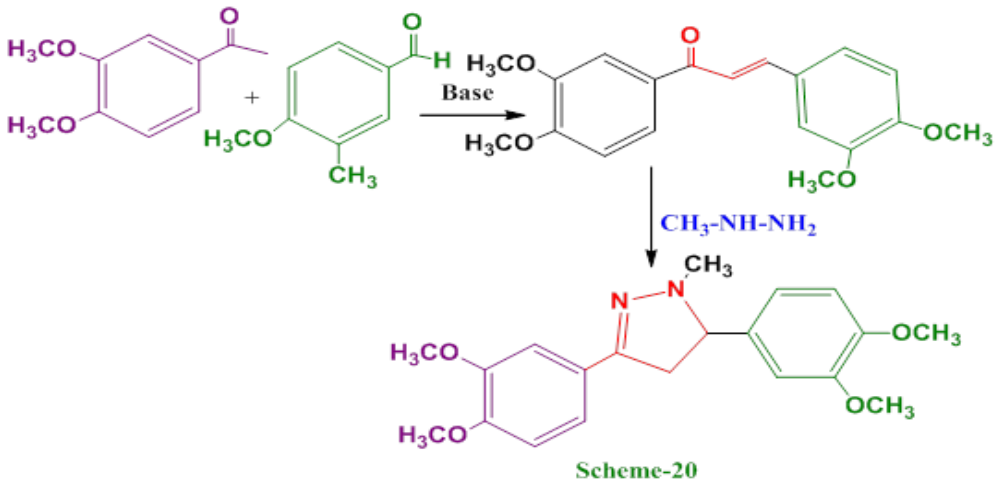


R =H, 4-CH_3, 4-Cl, 4-F, 4-CH_2-CH_3, 4-OH, 2-OCH_3, 4-OCH_3, 4-NO_2

Scheme-19

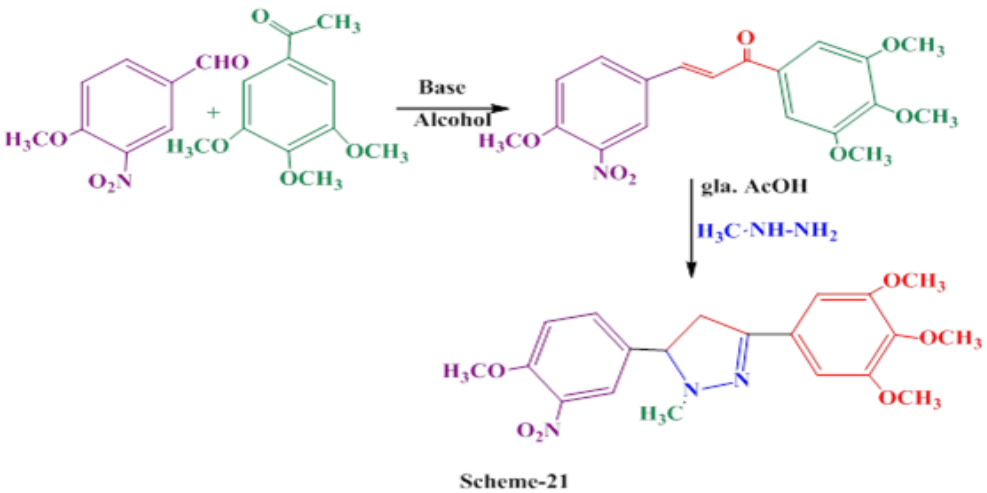
Synthesis of Anti hypertensive and ACE inhibiting pyrazoles

Bonsei, M., *et. al(*2010),[53] have reported the synthesis and have studied the Angiotensin Converting Enzyme inhibitory activity of Chalcones and their Pyrazole derivatives [**Scheme-20**].



Scheme-20

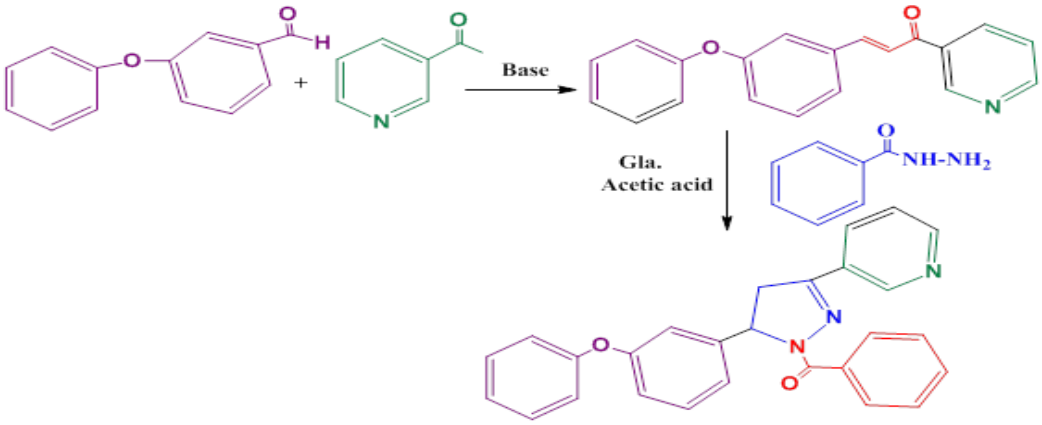
2. Bonesi *et. al* (2010),[53] have synthesized a series of pyrazole derivatives and investigated their potential ACE inhibitor activity by performing the assay. One of the prepared derivatives of pyrazole showed effective ACE-inhibitory activity with 0.123 mM IC50 value [**Scheme-21**].



Scheme-21

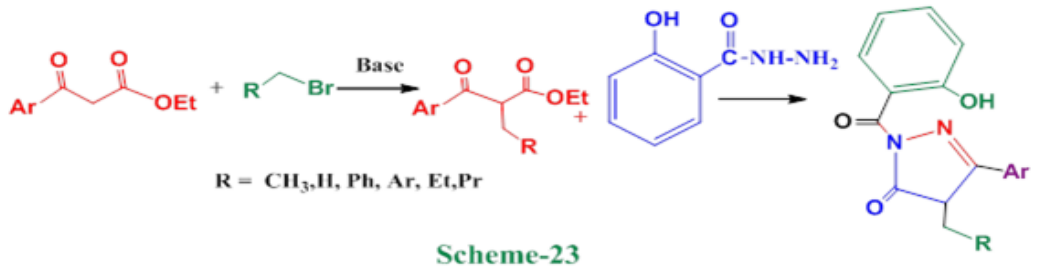
Synthesis of Anti-tubercular pyrazoles

1. Kini, S.G., *et. al* (2008),[54] have reported the synthesis, antitubercular activity and docking study of novel cyclic azole substituted diphenyl ether derivatives [**Scheme-22**].



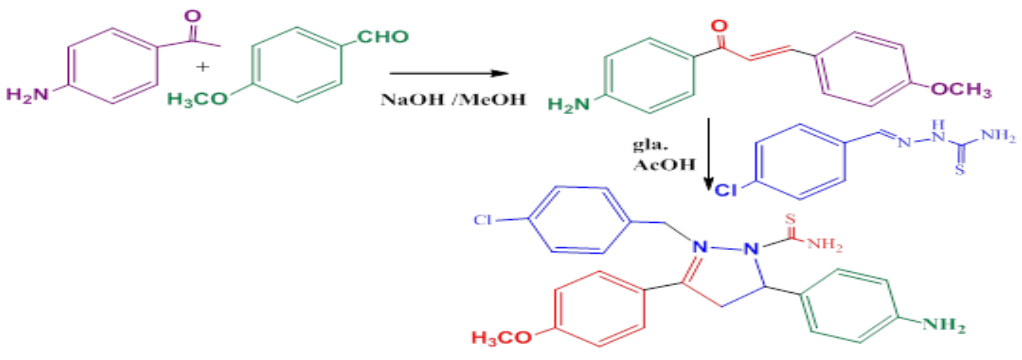
Scheme-22

2. Pattan, S. R *et. al* (2009),[55] have synthesized a series 3-methyl-pyrazol-5(4*H*)-one derivatives. The synthesized compounds are evaluated for antitubercular activity. All the structures of the newly synthesized compounds have been supported by IR, ^{1}H NMR, MS and CHN analysis [**Scheme-23**].



Scheme-23

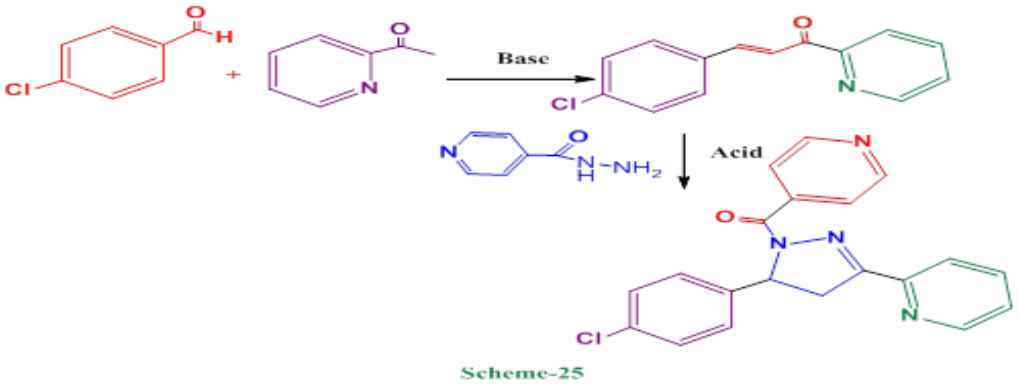
3. Ahsan and Saini, *et. al* (2015),[56] have designed and synthesized a series of thiocetazone based pyrazoline analogs by the condensation of 4-aminoacetophenone and p-anisidaldehyde in methanolic sodium hydroxide solution followed by the cyclization of intermediate chalcone with appropriate semicarbazide/thiosemicarbazide in glacial acetic acid. All the synthesized compounds were characterized by ^{1}H NMR, IR, and mass spectral data and the purity of the compounds was checked by elemental analysis. Some of the prepared compounds showed maximum activity against Mycobacterium tuberculosis (MTB H37Rv) with minimum inhibitory concentration (MIC) of 7.41 mM [**Scheme-24**].



Scheme-24

Synthesis of antimycobacterial pyrazoles

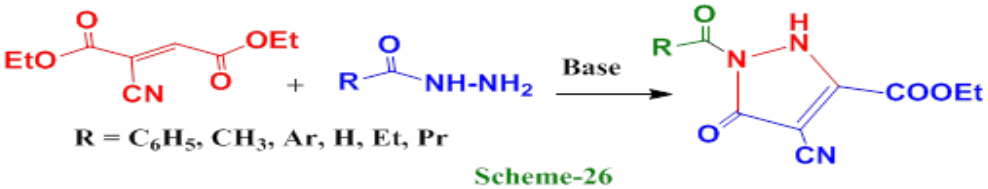
Ozdamir A., Zitouni, G. T., *et.al* (2008),[57] have reported synthesis of novel analogues of 2- pyrazoline, their characterization and antimycobacterial evaluation [**Scheme-25**].



Scheme-25

Synthesis of antidepressant and anti-convulsant pyrazoles

1. Aziz M. A., *et. al* (2009),[58] have reported the synthesis of novel pyrazole derivatives by the reaction of 2-cyano-diethylfumarate with hydrazide derivatives and evaluation of their antidepressant and anti convulsant activities [**Scheme-26**].



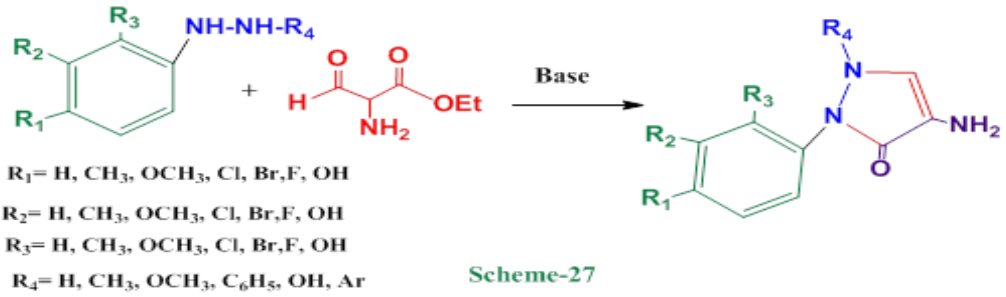
Scheme-26

2. Chimenti, *et. al* (2004),[59] have synthesized a novel series of 1-acetyl-3-(4-hydroxy- and 2,4-dihydroxyphenyl)-5-phenyl-4,5-dihydro-(1*H*)-pyrazole derivatives and investigated their ability to selectively inhibit the activity of the isoforms of MAO. The newly synthesized compounds have proved to be more reversible, potent, and selective inhibitors of MAO-A than of MAO-B [**Figure-4**].

Figure-4

Synthesis of anti-diabetic and hypoglycemic pyrazoles

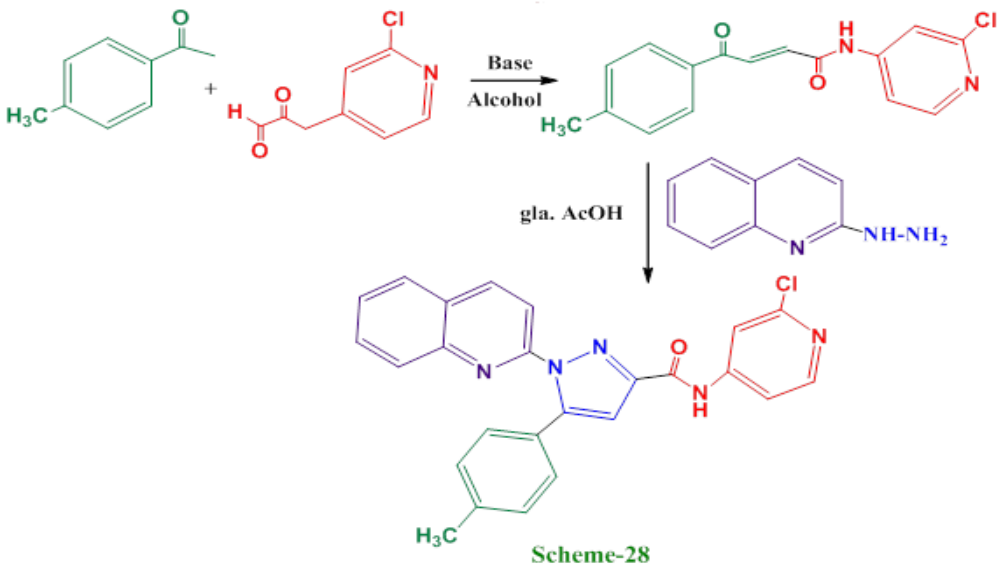
Das, N *et. al* (2008),[60] have reported the synthesis of some new aryl pyrazol-3-one derivatives. The biological evaluation is carried out for potential hypoglycemic activity. All the synthesized compounds were characterized by UV, IR and NMR spectroscopy [**Scheme-27**].



Scheme-27

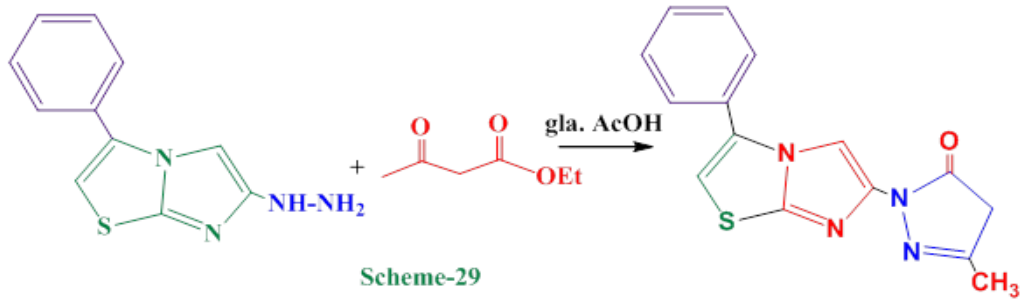
Synthesis of anticancer pyrazoles

1. Cankara Pirol *et. al* (2014),[61] have synthesized a series of novel amide derivatives of 5-(*p*-tolyl)-1-(quinolin-2-yl)pyrazole-3-carboxylic acid and tested their anti-proliferative activities against three human cancer cell lines: Huh 7, human liver; MCF 7, breast; and HCT 116, colon carcinoma cell lines. It was found that, the synthetic compound with 2-chloro-4-pyridinyl group in the amide part showed good cytotoxic activity against all cell lines with IC_{50} values of: 1.6 mM, 3.3 mM, and 1.1 mM for Huh7, MCF7 and HCT116 cells [**Scheme-28**].



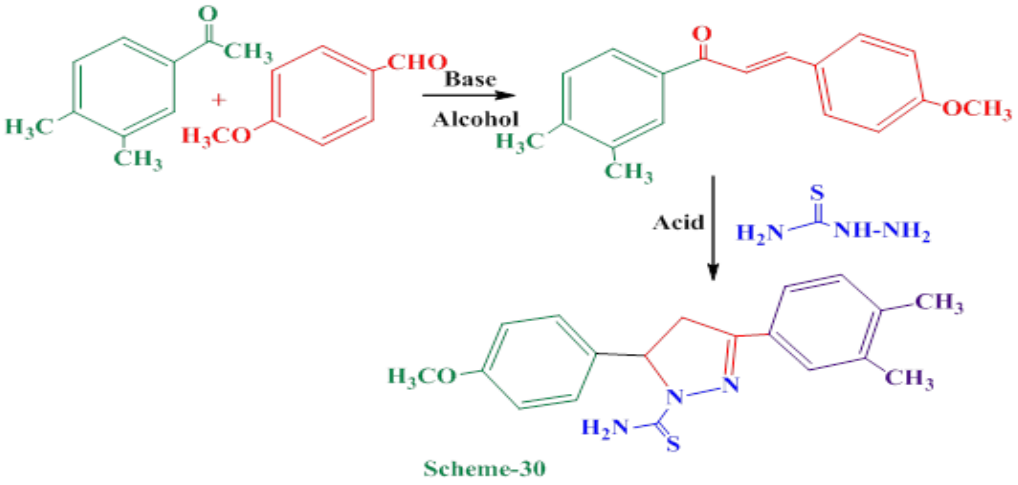
Scheme-28

2. Ali *et. al* (2014),[62] have synthesized a series of imidazo [2,1-*b*] thiazoles having pyrazole moiety through the reaction of 6-hydrazinylimidazo [2, 1-*b*]thiazoles with different dicarbonyl compounds. The compounds were screened for the anticancer activity and one of the synthesized compounds showed promising results [**Scheme-29**].



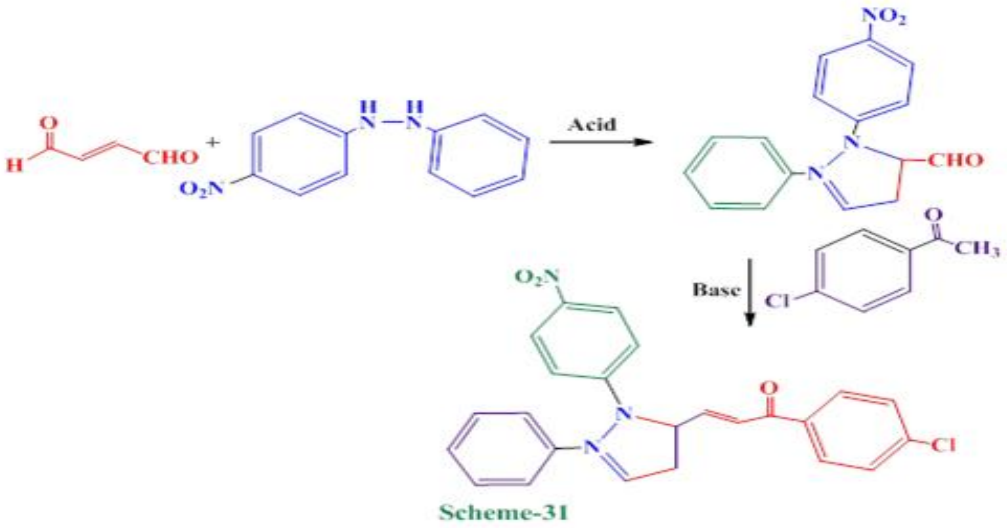
Scheme-29

3. Lv *et. al* (2010),[63] have designed two series of pyrazole derivatives and evaluated them for their potential epidermal growth factor receptor kinase inhibitors activity. One of the synthesized compounds: 3-(3,4-dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide was found to be most potent with IC_{50} of 0.07 µM as compared to positive control erlotini [**Scheme-30**].



Scheme-30

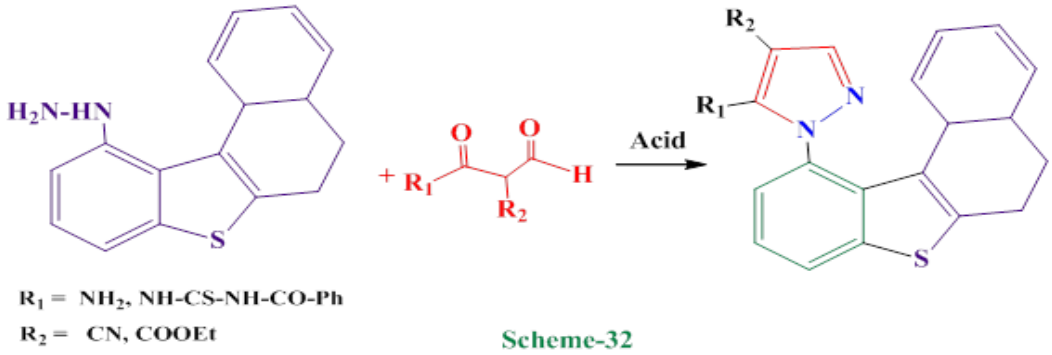
4. Insuasty *et. al* (2010),[64] have synthesized novel (E)-1-aryl-3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-ones (pyrazolic chalcones), among them some of the compounds showed potent activity against leukemia (K-562 and SR), renal cancer (UO-31), and non-small cell lung cancer (HOP-92) cell lines, with the most important GI50 values ranging from 0.04 μ to 11.4 lμ, from the *in vitro* assays[**Scheme-31**].



Scheme-31

Synthesis of Antiviral pyrazoles

1. Rashad *et. al* (2008),[65] have synthesized substituted pyrazole derivatives which showed promising antiviral activity against Hepatitis A virus and Herpes simplex virus type-1 by plaque infective assay method. Some of the prepared compounds showed good activity when compared to amantadine and acyclovir (used as controls) [**Scheme-32**].



Scheme-32

2. Rashad, A. E., *et. al* (2008),[65] have reported the synthesis of a new pyrazole derivative having a pyrimidine moiety in it; and it was found be a very effective and a potent antiviral agent [**Figure-5**].

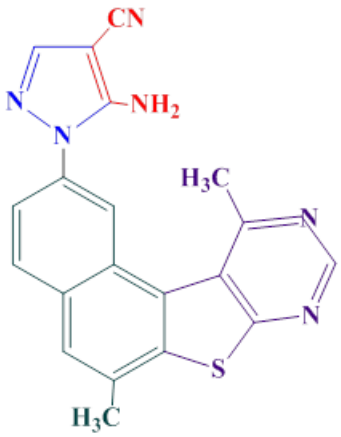


Figure-5

Synthesis of HMGCoA inhibiting pyrazole

Larsen, S. D., *et. al* (2007),[66] have reported the synthesis of a pyrazole inhibitor of HMG-CoA reductase [**Figure-6**].

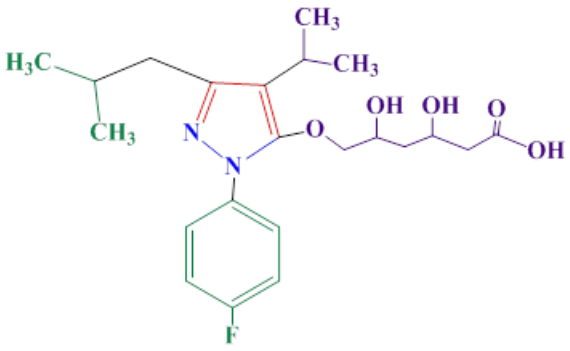
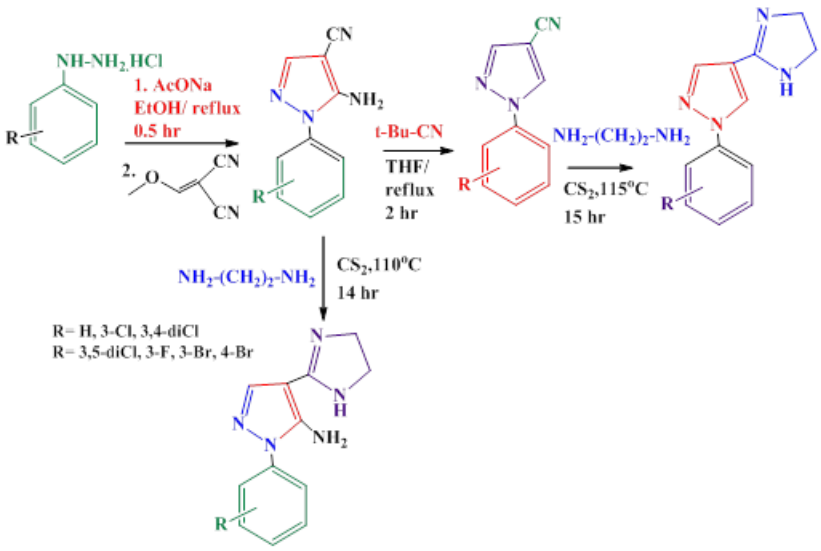


Figure- 6

Synthesis of Antileishmanial pyrazoles

Leishmaniasis is a tropical vector-borne disease caused by protozoan parasites of the genus Leishmania and spread by the bites of infected female Phlebotomine sand flies.[67,68] The 1-aryl-4-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-pyrazole derivatives reported by Santos *et. al* (2011)[69] (**Scheme-33**), were tested against the promastigote stages of L. amazonensis, L. infantum and L. braziliensis parasites.



Scheme33 Synthetic path of 1-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazoles and 5-amino-1- aryl-4- (4,5- dihydro-1H-imidazol-2-yl)-1H-pyrazoles).

Synthesis of antioxidant pyrazoles

Free radicals are highly reactive species that can potentially harm cells and are capable of attacking the healthy cells of the body, causing damage of biomolecules. The ability of antioxidants is affected by the age, diet and health status of an individual. However, the body relies on external (exogenous) sources, primarily the diet, to obtain the rest of the antioxidants it needs. Free radicals may also responsible for other diseases such as cardiovascular disease, neural disorders, Alzheimer's disease, alcohol-induced liver disease. Therefore, the search for new antioxidants has received much attention. Kenchappa *et. al* (2014),[70] have synthesized coumarin based pyrazoles as potent antioxidant agents [**Figure-7**].

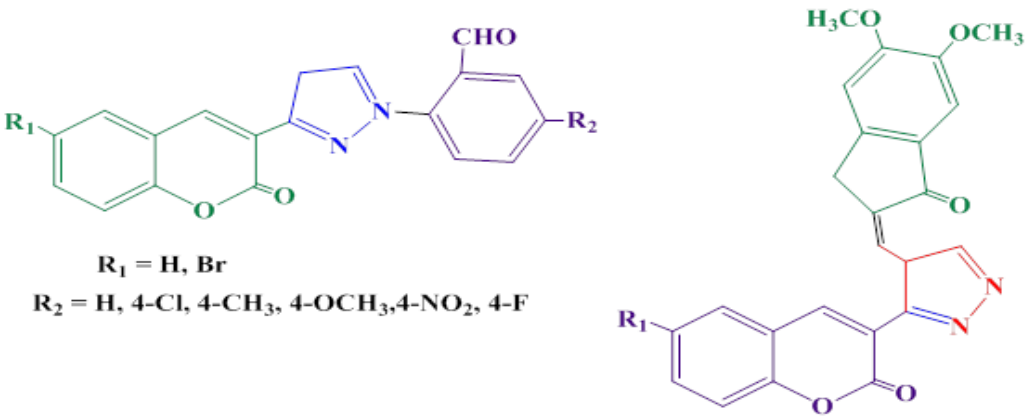
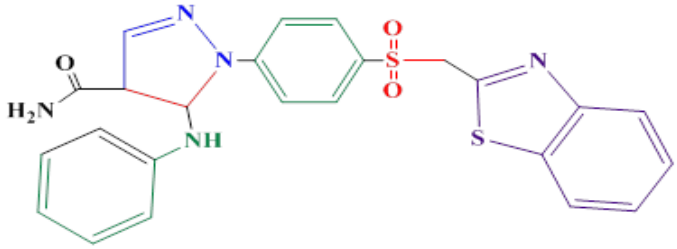


Figure -7 Pyrazole derivative Anioxidant

Synthesis of antihelmintic pyrazoles

Sreenivasa, G. M., *et. al* (2009),[71] have reported the synthesis of bioactive fluorobenzothiazole comprising of potent heterocyclic moieties towards anthelmintic activity [**Figure-8**].



1-(4-((benzo[*d*]thiazol-2-ylmethyl)sulfonyl)phenyl)-5-(phenylamino)-4,5-dihydro-1*H*-pyrazole-4-carboxamide

Figure -8 Pyrazole derivative as Anthelmintic bioactive

CONCLUSIONS

We conclude in this review that, pyrazole derivatives are found to be pharmacologically more potent and hence, their design and synthesis is a highly potential area of research. It is also found that, modification of pyrazole moiety displayed variable and valuable biological activities. It was interesting to observe that, these modifications can be utilized as potent therapeutic agents in future. The biological profiles of these new generations of pyrazole derivatives would represent a wonderful matrix for the further development and discovery of the best medicinal agents. Recent observations suggest that, substituted pyrazoles are the structural isosters and bioisosters of nucleotides owing to their fused heterocyclic nature in purine based bases, allow them to interact easily with the biopolymers, and exhibit potential activity with lower toxicities in the chemotherapeutic approach in humans. Right now, researchers have been attracted to design and discover more potent pyrazole derivatives which can produce a wide diversity of biological activity and pharmaceutical uses. The ability to predict drug-like and lead-like properties along with recent technological advances could be sufficient to revitalize the exploitation of the value of pyrazole derivatives in the quest for new drugs.

ACKNOWLEDGEMENTS

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