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Pyrazole and Its Derivatives: An Excellent N-Hetrocycle with Wide Range of Biological Applications (A Review)

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ABSTRACT

The pyrazole derivatives have been recognized as a unique heterocyclic molecule exerting broad range of biological activities such as analgesic, anti-viral, anti-histaminic, anti-microbial, anti-tumor, insecticides fungicides, anti-depressant, antipyretic, anti-inflammatory, angiotensin converting enzyme (ACE) inhibitory and estrogen receptor (ER) ligand activity etc. Pyrazoles also find applications in agrochemical and pharmaceutical industry. Pyrazoles have different chemical properties which may be attributed due to the effect of particular N-atoms present in pyrazole molecule. N-Atom present at position-2 having non Huckel lone pair is more reactive towards electrophiles while N-atom present at position-1 is unreactive. However, in the presence of strong base, the proton from N-atom at position-1 is abstracted thereby providing pyrazole anion after deprotonation, which in turn increases reactivity towards the electrophiles. There are wide range of drugs available in the market possessing pyrazole nuclei. The present manuscript is aimed to describe major developments achieved till date towards the synthesis and biological applications of pyrazole/pyrazole derivatives and is likely to be beneficial to the researchers working in the area.

Keyword: Pyrazole, N-hetrocycle, Anti-viral, Drugs, Biological applications.

INTRODUCTION

Pyrazole[1] a five-membered planar N-heterocyclic compound which is aromatic in nature having 4 π-electrons and one unshaired pair of electrons delocalized with π-electrons. Pyrazole ring structure contains three carbon atoms along with two nitrogen atoms present in adjacent positions. The lone pair of first N-atom participates in delocalization with π-electrons while the other lone pair present on the second N-atom is non-Huckel lone pair and due to that lone-pair pyrazole shows lewis basicity with PK_b11.5. The pyrazole is represented by the following structure.

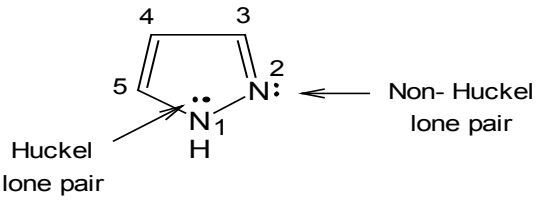
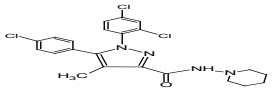
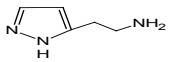
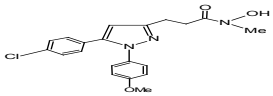
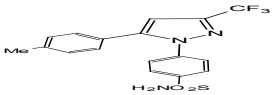
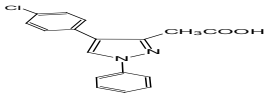
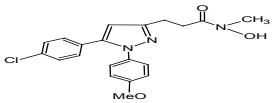
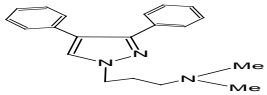
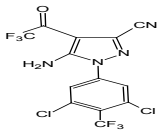
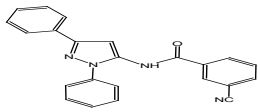
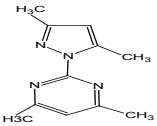
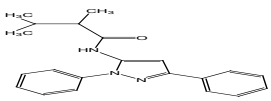


Fig. 1. Structure of pyrazole[1]

Back ground and medicinal importance

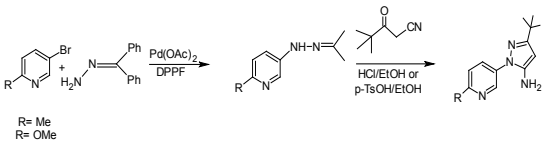
In 1883 Ludwig Knorr was first to abbreviate the term of pyrazole. The first natural pyrazole is 1-pyrazole-alanine which was isolated in 1959 from watermelon seeds[1,2]. Pyrazoles are also known as azoles[3] and pyrazoles act as ligands for different Lewis acids[3]. The pyrazole derivatives have shown a long range of biological activities including antioxident[4], anti-viral[5], anti-histaminic[6], anti-microbial[7], anti-tumor[8,9], fungicides[10], anti-depressant[11], antipyretic[12], analgesic[12], anti-inflammatory[12], angiotensin converting enzyme inhibitory[13], and estrogen receptor ligand activity[14] etc. Pyrazoles also find applications in agrochemical and pharmaceutical industry[15]. Pyrazoles have different chemical properties which can be described by the effect of particular atoms present in pyrazole molecule. N-Atom at position-2 having non Huckel lone pair is more reactive towards electrophiles while N-atom at position-1 is unreactive[16]. However in the presence of a strong base, the proton from N-atom at position-1 is abstracted thereby providing pyrazole anion after deprotonation, which in turn increases reactivity towards the electrophiles[17]. There are wide range of drugs available in the market possessing pyrazole nuclei and few of these are summarized below[18-29].

Table 1: Few important drugs possessing pyrazole nuclei[18-29]

S.No.	Drug Name	Drug Structure	Act as a
1	Rimonabant[18,20,25]		Anorectic anti-obesity drug
2	Betazole[26,28]		Used in testing gastric secretory function
3	Tepoxalin[19]		Anti-inflammatory drug & anti histamines
4	Celecoxib[22]		Anti-inflammatory drug
5	Lonazolac[21,24]		Anti-inflammatory drug
6	Tepoxalin[18]		Anti-inflammatory drug
7	Fezolamin[29]		Anti-depressant
8	Fibronil[18]		Broadly used as insecticide and also commonly used as pesticide
9	CDPPS[23]		Anti-psychotic
10	Mepirizole[29]		Anti-inflammatory
11	Diffenamizole[27,28]		Analgesic

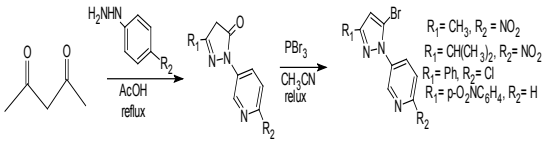
Synthesis of pyrazole and its derivatives

Taking into amount the wide range of biological activities associated with pyrazole and its derivatives, numerous synthetic strategies are reported for the preparation of pyrazoles/pyrazole derivatives and few of these selected ones are being described in the present communication. In one of the strategy N-Hetero aryl compound was converted to pyrazole derivative via transhydra zonation or cyclization in the presence of strongly acidic medium. Initial step for the amination of deactivated 5-bromo-2-Methyl pyridine to benzophenone hydrazone was carefully carried out using 1,1'-Bis-(diphenylphosphino)-ferrocene(DPPF) and Palladium(II) acetate ($Pd(OAc)_2$) (Scheme 1)[30].



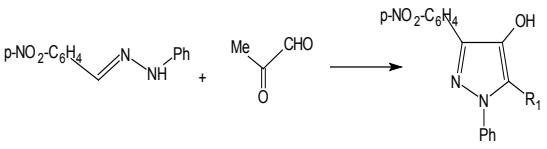
Scheme 1. Synthesis of pyrazole derivative via trans-hydrazonationor cyclization[30]

The synthetic strategy for 3,5-disubstituted pyrazoles have been achieved by the condensation of 1,3-dienophilic synthons such as propargylic ketones (Scheme 2)[31].



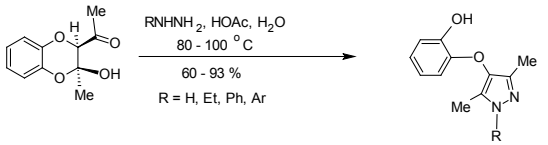
Scheme 2. Synthesis of 3,5-disubstituted pyrazolesthrough the condensation of 1,3-dienophilic synthons[31]

p-Nitrobenzaldehyde phenylhydrazone was condensed with methylglyoxal to furnish the 4-hydroxy-3-para-nitrophenyl-5-methyl-N-phenylpyrazol (Scheme 3)[32].



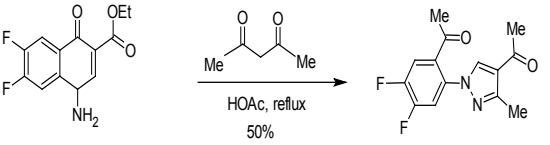
Scheme 3. Synthesis of 4-hydroxy-3-para-nitrophenyl-5-methyl-N-phenyl-pyrazole[32]

Dzvinchuk *et al.,* explored a strategy for the synthesis of Pyrazole derivatives from (Z)-3-Acetyl-2-methyl-2,3-dihydro-1,4-benzodioxin-2-ol (Scheme 4)[33].



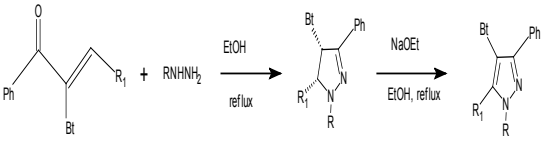
Scheme 4. Synthesis of Pyrazole derivative from (Z)-3-Acetyl-2-methyl-2,3-dihydro-1,4-benzodioxin-2-ol[33]

Y. A. Azev *et al.,* synthesized Pyrazole derivatives from the condensation of 1-amino-6,7-difluoro-4-oxoquinolyl-3-ethylcarboxylate with acetoacetone (Scheme 5)[34].



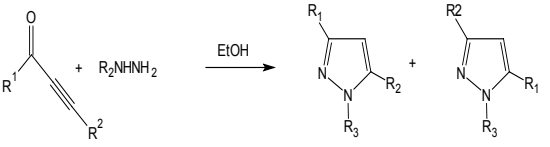
Scheme 5. Synthesis of Pyrazole derivative from 1-amino-6,7-difluoro-4-oxoquinolyl-3- ethylcarboxylate with acetoacetone[34]

Katritzky *et al.,* reported a regioselective condensation of α-benzotriazolylenones with phenyl or methyl-hyrdrazines and pyrazolines as the intermediate which gave 1-methyl(aryl)-3-phenyl-5-alkyl(aryl)pyrazoles in basic medium (Scheme 6)[35].



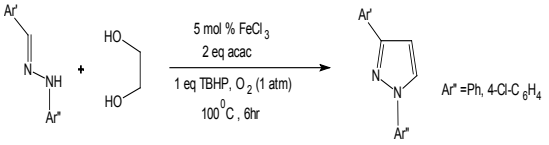
Scheme 6. Synthesis of 1-methyl(aryl)-3-phenyl-5-alkyl(aryl)pyrazoles by condensation of α-benzotriazolylenones[35]

Mourea and Delange *et al.,* reported the cyclo condensation of acetylenic ketones and hydrazine derivatives to form pyrazoles derivatives. The saidmethodology was investigated for almost more than a century back in 1901. However the two isomers were reported to be obtained (Scheme 7)[36].



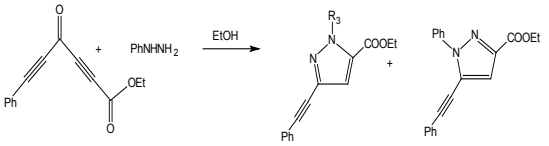
Scheme 7. Cyclo-condensation of acetylenic ketones and hydrazine derivatives leading to pyrazolesderivatives[36]

1,3-di substituted pyrazoles can also be obtained from the reaction of diaryl-hyrazones and 1,2-diols in presence of Ferric chloride($FeCl_3$) (Scheme 8)[37].



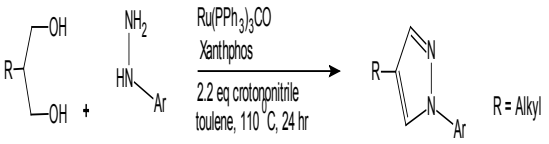
Scheme 8. Synthesis of 1,3-di substituted pyrazoles[37]

Baldwin *et al.,* reported the synthesis of two isomeric pyrazoles by the reaction of Phenyl hydrazine with diacetylene Ketones in ethyl alcohol (Scheme 9)[38].



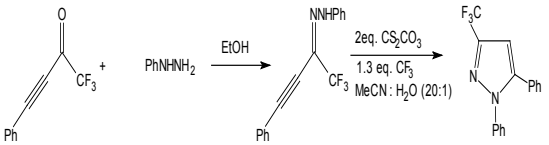
Scheme 9. Synthesis of two isomeric pyrazoles by the reaction of Phenyl hydrazine with diacetylene Ketones[38]

1,4-disubstitued pyrazoles have been synthesized from 1,3-diols and aryl hydrazine through Ruthenium catalyzed condensation (Scheme 10)[39].



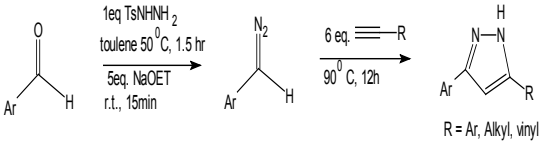
Scheme 10. Synthesis of 1,4-disubstituedpyrazolesby the reaction of 1,3-diols with aryl hydrazine through Ruthenium catalyzed condensation[39]

Guojing and wang *et al.,* synthesized 3-trifluoromethyl pyrazole via cyclization/ trifluoromethylation of phenyl hydrazine and acetylenic Ketones using hypervalent iodine under transition metal free conditions, which gave Togni reagent and subsequently furnished 3-trifluromethyl pyrazole in high yields (70%) (Scheme 11)[40].



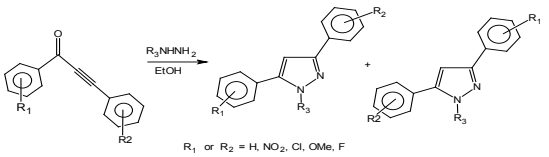
Scheme 11. Synthesis of 3-trifluoromethyl pyrazole via cyclization/trifluoromethylation of phenyl hydrazine and acetylenic ketones[40]

3,5-disubstituted 1H-pyrazoles were synthesized by the cyclo-addition reaction of tosylhydrazones of aromatic aldehydes with terminal alkynes (Scheme 12)[41].



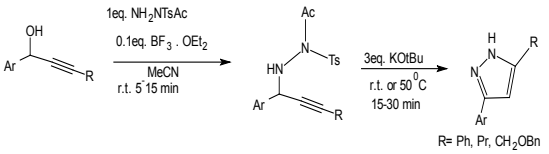
Scheme 12. Synthesis of 3,5-disubstituted 1H-pyrazoles[41]

Bishop *et al.,* explored the synthesis of 3,5-di aryl pyrazoles by the cyclo-condensation of acetylenic ketones and aryl hydrazines or methyl hydrazines in ethyl alcohol which afforded two isomeric pyrazole derivatives (Scheme 13)[42].



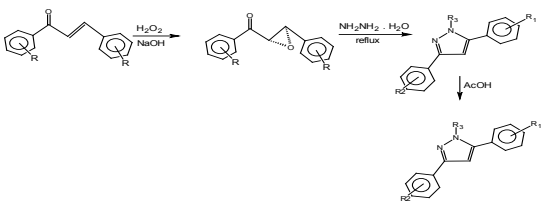
Scheme 13. Synthesis of 3,5-di aryl pyrazoles by the cyclocondensation of acetylenic ketones and aryl hydrazines[42]

Reddy *et al.,* reported an easy approach for the synthesis of 3,5-disubstituted 1H-pyrazole from propargylic alcohols via an acid-catalyzed propargylation followed by cyclization of N,N-disubstituted hydrazines under basic conditions (Scheme 14)[43].



Scheme 14. Synthesis of 3,5-disubstituted 1H-pyrazole from propargylic alcohols via acid-catalyzed propargylation followed by cyclization of N,N-disubstitutedhydrazines[43]

Bhat *et al.,* reported the synthesis of pyrazole derivatives by the reaction of β-aryl chalcones and H_2O_2 furnishing epoxides. The addition of hydrated hydrazine to it, followed by dehydration provided 3,5-diaryl-1H-pyrazole (Scheme 15)[44].

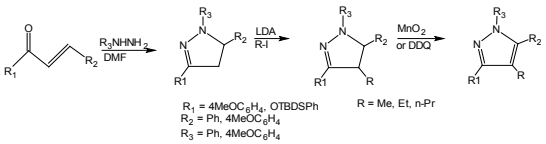


Scheme 15. Synthesis of pyrazole derivatives by the reaction of β-aryl chalcones and H_2O_2 followed by dehydration[44]

Ding *et al.,* reported the synthesis of 3,5-disubstituted pyrazoles from Michael acceptors and methyl hydrazine under mild conditions. The reaction proceeded through Visible Light Photoredox Catalysis (VLPC) (Scheme 16)[45].

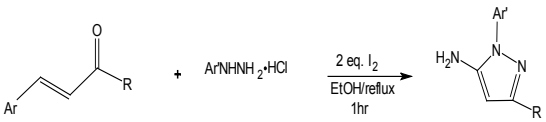
Scheme 16. Synthesis of 3,5-disubstituted pyrazoles from Michael acceptors and methyl hydrazine[45]

Huang and Katzenellenbogen *et al.,* described the synthesis of 4-alkyl-1,3,5-triaryl pyrazoles by the condensation of α,β-ethylenic ketons with hydrazines in N,N-dimethyl formamide providing pyrazoline as intermediate. The alkylation of pyrazoline in presence of lithium diisopropyl amide(LDA) furnished 4-alkyl-1,3,5-triarly pyrazole (Scheme 17)[46].



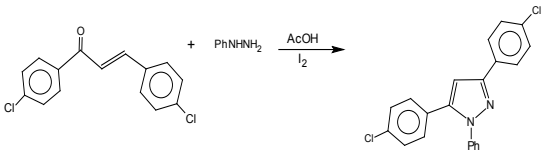
Scheme 17. Synthesis of 4-alkyl-1,3,5-triaryl pyrazoles by the condensation of α,β-ethylenic ketones with hydrazines[46]

Zhang *et al.,* reported the synthesis of polysubstituted pyrazoles from α,β-unsaturated carbonyls (aldehyde and ketone) and salts of hydrazine (Scheme 18)[47].



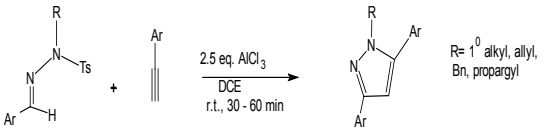
Scheme 18. Synthesis of polysubstituted pyrazoles from α,β-unsaturated carbonyls and salts of hydrazine[47]

Jiany *et al.,* described an efficient method for the synthesis of 3,5-disubstituted-N-phenyl pyrazole by the cyclocondensation of phenylhydrazine and α,β ethylenic ketone in presence of molecular Iodine(I_2) (Scheme 19)[48].



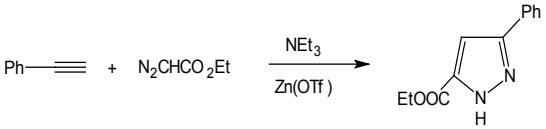
Scheme 19. Synthesis of 3,5-disubstituted-N-phenyl pyrazole by the cyclo-condensation of phenyl hydrazine and α,β-ethylenic ketone[48]

Tang *et al.,* reported the reaction of terminal alkynes and N-alkylated tosylhydrazones in the presence of $AlCl_3$, thereby affording 1,3,5-trisubstituted pyrazoles in good yields (Scheme 20)[49].



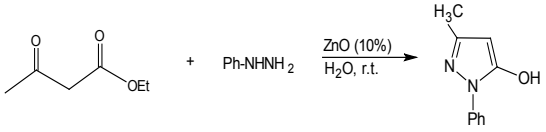
Scheme 20. Synthesis of 1,3,5-trisubstituted pyrazoles[49]

He and Chen *et al.,* reported the synthesis of pyrazole derivatives by the cycloaddition reaction of phenyl propargyl and ethyl α-diazoacetate in presence of triethylamine as base and triflate as a catalyst (Scheme 21)[50].



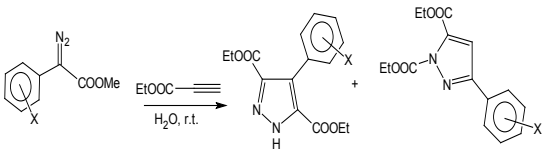
Scheme 21. Synthesis of pyrazole derivatives by the cycloaddition reaction of phenyl propargyl and ethyl α-diazoacetate[50]

Girish & Kumar *et al.,* synthesis 1,3,5,-tri substituted pyrazole by the condensation of ethyl acetoacetate with phenylhydrazine (Scheme 22).[51]



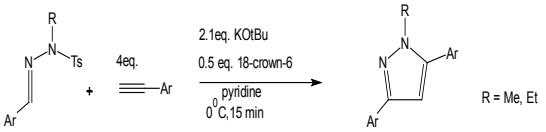
Scheme 22. synthesis 1,3,5,-tri substituted pyrazole by condensation

Jiang *et al.,* developed the synthesis of regioisomer of pyrazole derivatives from the cyclisation of α-diazoarylacetate and propionate followed by prototropic Rearrangement (Scheme 23)[52].



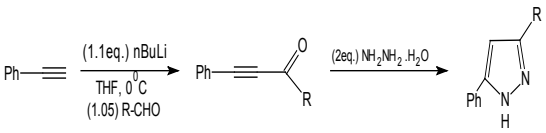
Scheme 23. Synthesis of regioisomer of pyrazole derivatives by the cyclisation of α-diazoarylacetate and propionate followed by prototropic Rearrangement[52]

Y. Kong *et al.,* synthesized 1,3,5-trisubstituted pyrazoles from terminal alkynes and N-alkylated tosylhydrazones. This methodology provided trisubstituted pyrazoles with high regioselectivity (Scheme 24)[53].



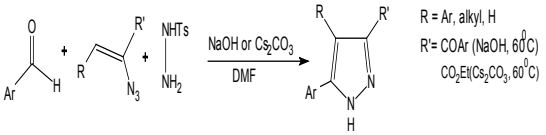
Scheme 24. Synthesis of 1,3,5-trisubstituted pyrazoles[53]

Harigae and Moriyam *et al.,* synthesized 3,5-substituted pyrazole in high yields by the reaction of terminal alkynes with hydrated hydrazine furnishing 3,5-substituted pyrazole (Scheme 25)[54].



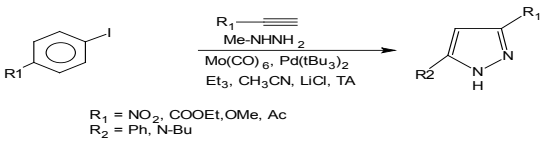
Scheme 25. Synthesis of 3,5-substituted pyrazoleby the reaction of terminal alkynes with hydrated hydrazine[54]

Zhang *et al.,* developed an easy approach for the synthesis of trisubstituted 1H-pyrazoles from vinyl azide, tosylhydrazine and aldehydes using of base (Scheme 26)[55].



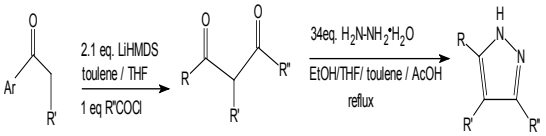
Scheme 26. Synthesis of trisubstituted 1H-pyrazoles from vinyl azide, tosylhydrazine and aldehydes[55]

Lizuka *et al.,* described the palladium catalyzed carbonylation reaction of acetylenic acids with aryl iodides using of Molybdenum hexacarbonyl($Mo(CO)_6$) toget 1,3,5-trisubstituted pyrazole in good yields (Scheme 27)[56].



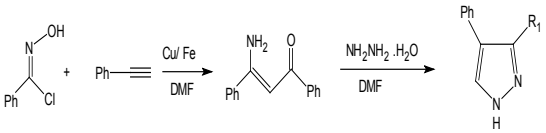
Scheme 27. Synthesis of 1,3,5-trisubstituted pyrazole[56]

Heller *et al.,* explored a synthetic methodology for trisubstituted pyrazoles from by 1,3-diketones which were obtained from acid chloride and ketone (Scheme 28)[57].



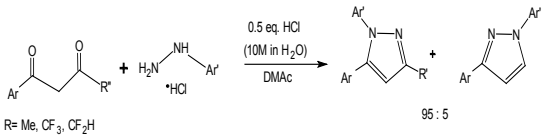
Scheme 28. Synthesis of tri substituted pyrazoles from 1,3-diketones[57]

Kovacs and Co- workers reported a new route for the synthesis of 3,5-disubstituted pyrazoles by the coupling reaction of an oxime with alkyne in the presence of Cu/Fe providing β-aminoenone which on addition with hydrazine in DMF provided 3,5-disubstitued pyrazoles in satisfactory yields(70%) (Scheme 29)[58].



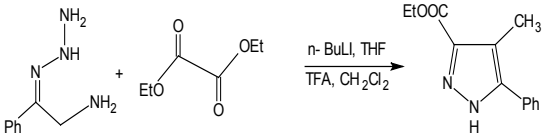
Scheme 29. Synthesis of 3,5-disubstituted pyrazoles by the coupling reaction[58]

Gosselin *et al.,* synthesized N-aryl-3,5-substituted pyrazoles by the condensation of 1,3-diketones and arylhydrazines at room temperature using N,N-dimethylacetamide as solvent (Scheme 30)[59].



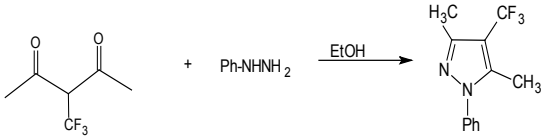
Scheme 30. Synthesis of N-aryl-3,5-substituted pyrazoles by the condensation of 1,3-diketones with arylhydrazines[59]

Dang and Fischer *et al.,* developed a method for the synthesis of pyrazole-3-carboxylate by cyclization of diethyl dioxalate and hydrazones furnishing pyrazole-3-carboxylate in 53% yield (Scheme 31)[60].



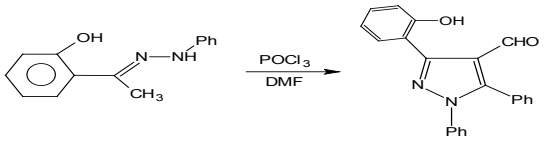
Scheme 31. Synthesis of pyrazole-3-carboxylate by cyclization of diethyl dioxalate and hydrazones[60]

Ohtsuka and Uraguchi *et al.,* Synthesis of 1,3,4,5-tetra substituted pyrazole derivative from condensation of phenyl hydrazine with 2-(trifluoromethyl)-1,3-diketone in solvent of ethanol. (Scheme 32)[61].



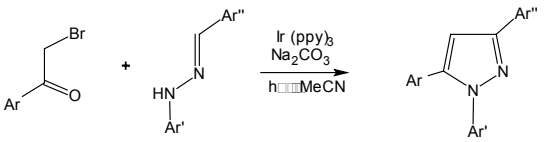
Scheme 32. Synthesis of 1,3,4,5-tetra substituted pyrazole derivative from condensation

Lokhande and Hasanzadeh *et al.,* synthesized 4-formyl pyrazole by the condensation of hydrazine in presence of Phosphorus oxychloride($POCl_3$) in DMF (Scheme 33)[62].



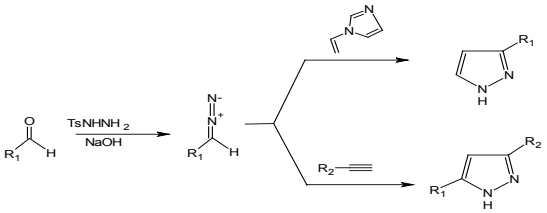
Scheme 33. Synthesis of 4-formyl pyrazole[62]

Fan and Lei *et al.,* explored an efficient method for the synthesis of tri-substituted pyrazoles from α-bromo ketones and hydrazones. The reaction involved radical addition reaction followed by intramolecular cyclisation (Scheme 34)[63].



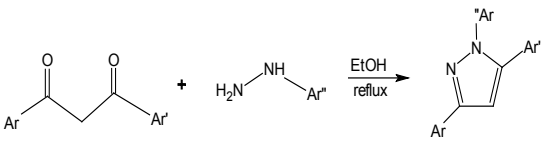
Scheme 34. Synthesis of tri-substitutedpyrazoles from α-bromo ketones and hydrazones[63]

Aggarwal and Vicente *et al.,* developed a process in which diazo derivatives formed in situ from aldehyde and tosylhydrazines by 1,3-dipolar cycloaddition reaction in between diazo compound & terminal alkynes and N-Vinylimidazole furnishing corresponding pyrazole derivatives (Scheme 35)[64].



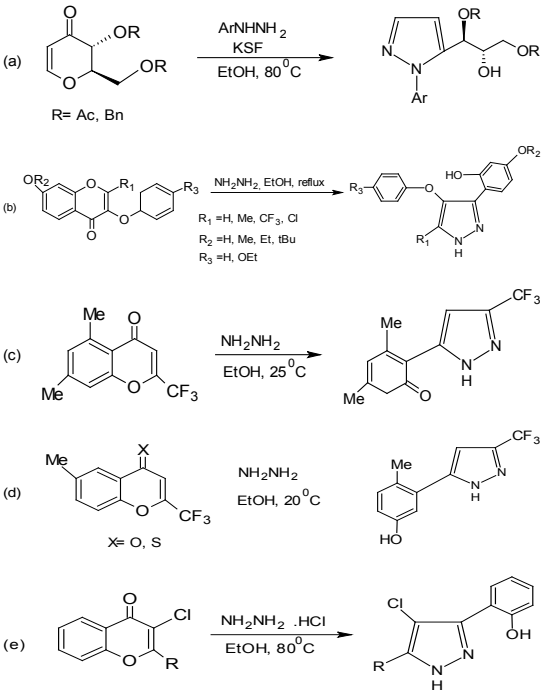
Scheme 35. 1,3-Dipolar cyclo-addition reaction in between diazo compound & terminal alkynes and N-Vinylimidazole leading to pyrazoles derivatives[64]

Kumar and Yadav *et al.,* reported the synthesis of substituted pyrazoles by the reaction of 1,3-bisaryl monothio-1,3-diketone and arylhydrazines in ethyl alcohol (Scheme 36)[65].



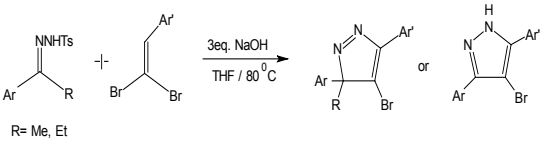
Scheme 36. Synthesis of substituted pyrazoles by the reaction of 1,3-bisaryl monothio-1,3-diketone and arylhydrazines[65]

Many methods for the synthesis of pyrazoles by the reaction of hydrazines with heterocycle compounds have been reported (Scheme 37)[66-70].



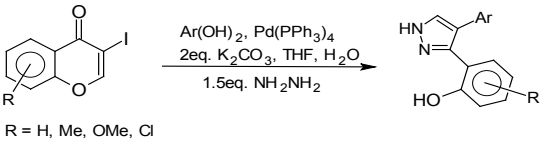
Scheme 37. Different strategies for the synthesis of pyrazoles by the reaction of hydrazines with heterocyclic compounds[66-70]

Sha *et al.,* synthesized 3,5-diaryl-4-bromo-1H-pyrazoles from alkenyl bromides and diazo compounds by 1,3-dipolar cyclo-addition, where other isomeric products were also obtained (Scheme 38)[71].



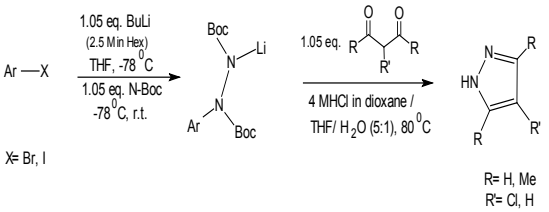
Scheme 38. Synthesis of 3,5-diaryl-4-bromo-1H-pyrazoles from alkenyl bromides and diazocompounds[71]

Xie and Chen *et al.,* reported the synthesis of pyrazoles by Suzuki coupling reactions(Scheme 39)[72].



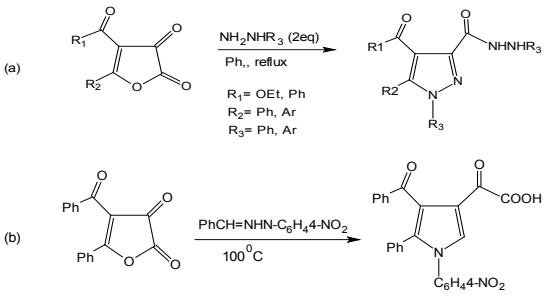
Scheme 39. Synthesis of pyrazoles by Suzuki coupling reactions[72]

Gerstenberger *et al.,* synthesized N-aryl 3,4,5-trisubstituted pyrazoles from aryl halide, di-tert-butylazodicarboxlate (Boc) and 1,3-dicarbonyl compounds (Scheme 40)[73].



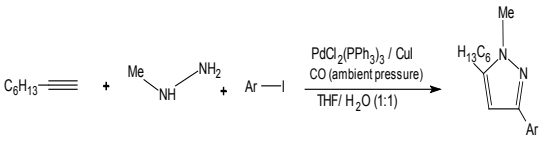
Scheme 40. Synthesis of N-aryl 3,4,5-trisubstituted pyrazoles[73]

Liham and Saripinar *et al.,* reported the condensation of furan 2,3-dione with aryl hydrazine providing pyrazole derivatives.Similarly Sener *et al.,* reported the condensation of furan-2,3-dione with N-benzylidene-N'- (4-nitrophenyl) hydrazine furnishing 4-benzoyl-1-(4-nitropphenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (Scheme 41)[74-75].



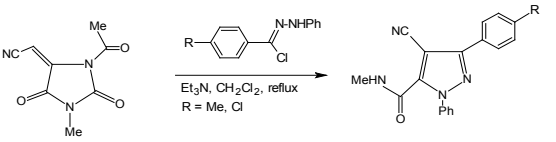
Scheme 41. Synthesis of pyrazoles by the condensation of furan 2,3-dione with aryl hydrazine[74-75].

Ahmed and Kobayashi *et al.,* reported an efficient method for the synthesis of N-methyl 3,5-disubstituted pyrazoles from terminal alkynes, methyl hydrazine and aryl halide (Scheme 42)[76].



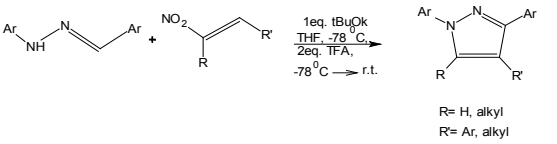
Scheme 42. Synthesis of N-methyl 3,5-disubstituted pyrazoles from terminal alkynes, methyl hydrazine and aryl halide[76]

Groseli *et al.,* developed a new method for the preparation of pyrazole derivatives by the following cyclo-addition reaction (Scheme 43)[77].



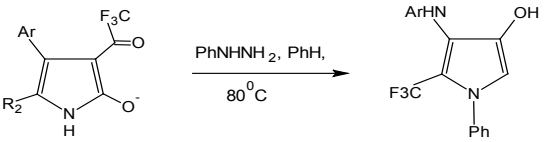
Scheme 43. Synthesisofpyrazole derivatives by cycloaddition reaction[77].

Deng *et al.,* reported a of highly regioselective synthesis of tetra-substituted pyrazoles from nitro-olefins and hydrazones in the presence of strong base (Scheme 44)[78].



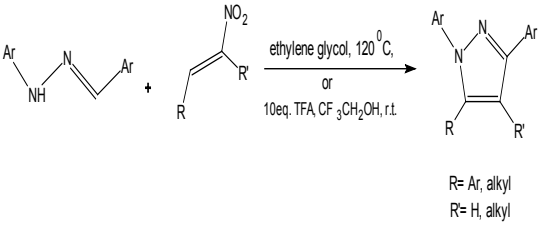
Scheme 44. Synthesis of tetra-substituted pyrazoles from nitro-olefins and hydrazones[78]

When 4-trifluoroacetyl-1,3-oxazolium-5-olates were heated with phenylhydrazine, it provided 5-trifluoromethyl pyrazole derivative a procedure developed by Kawase and Koiwai *et al.,* (Scheme 45)[79].



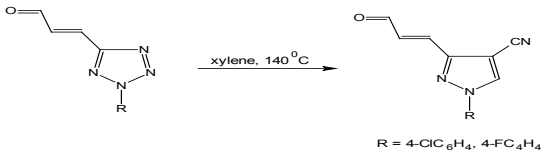
Scheme 45. Synthesis of 5-trifluoromethyl pyrazole derivatives by reaction of 4-trifluoroacetyl-1, 3-oxazolium-5-olate with phenylhydrazine[79]

Deng *et al.,* reported the synthesis of 1,3,4,5-tetra-substituted pyrazoles and 1,3,5-tri substituted pyrazoles with high regioselectivity from N-aryl hydrazones and nitro-olefins in the presence of ethyl glycol at 120°C (Scheme 46)[80].



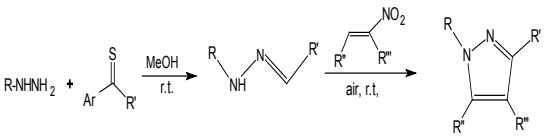
Scheme 46. RegioselectiveSynthesis of 1,3,4,5-tetra-substituted pyrazoles and 1,3,5-trisubstituted pyrazoles[80]

When tetrazolylacroleins were allowed to undergo reaction with fumaronitrile at 140°C in xylene it provided pyrazole as reported by Simoni *et al.,* (Scheme 47)[81].



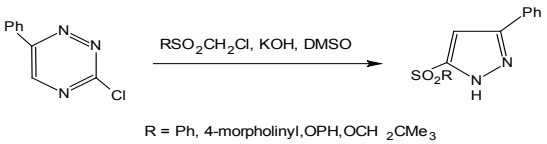
Scheme 47. Synthesis of pyrazoleby reaction of tetrazolylacroleins with fumaronitrile[81]

Deng *et al.,* reported the synthesis of tetra substituted pyrazoles by the reaction of N-substituted hydrazones with nitro-olefins in high yields (Scheme 48)[82].



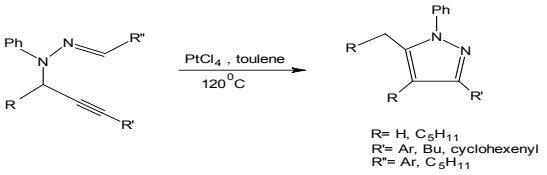
Scheme 48. Synthesis of tetra substituted pyrazoles by the reaction of N-substituted hydrazones with nitro-olefins[82]

Rykowski and Branowska *et al.,* explored an efficient method for the synthesis of pyrazoles by the condensation of 3-chloro-6-phenyl-1,2,4-triazines with α-chlorosulfonyls in DMSO using Potassium hydroxide as base (Scheme 49)[83].



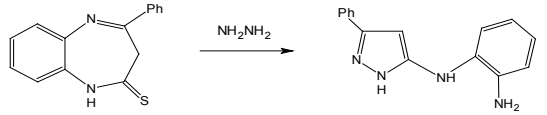
Scheme 49. Synthesis of pyrazoles by the condensation of 3-chloro-6-phenyl-1,2,4-triazines with α-chlorosulfonyls[83]

Wen and Tang *et al.,* synthesized various highly functionalized pyrazoles by Pt-catalyzed (3,3)-sigmatropic rearrangement of N-propargyl hydrazones (Scheme 50)[84].



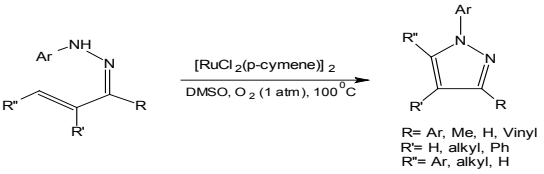
Scheme 50. Synthesispyrazoles by Pt-catalyzed (3,3)-sigmatropic rearrangement of N-propargylhydrazones[84]

Ferfra and Ahabchane *et al.,* described a method for the synthesis of pyrazoles by the reaction of benzodiazepine-2-thiones with hydrazine (Scheme 51)[85].



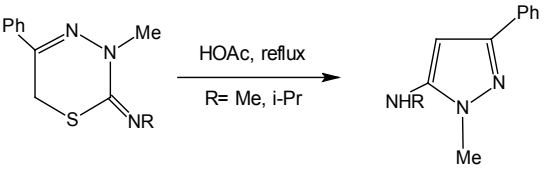
Scheme 51. Synthesis of pyrazoles by the reaction of benzodiazepine-2-thiones with hydrazine[85]

Hu and Chen *et al.,* synthesized various tetrasubstituted pyrazoles by the ruthenium-catalyzed oxidative coupling reaction in presence of O_2 as an oxidant (Scheme 52)[86].



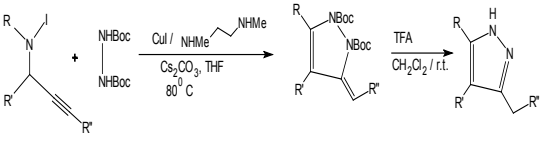
Scheme 52. Synthesis oftetra-substitutedpyrazoles by the ruthenium-catalyzed oxidative coupling reaction[86]

Pfeffer *et al.,* reported 5-amino-pyrazoles which were obtained by heating 3-methyl-6H-1,3,4-thiadiazine acetic acid (Scheme 53)[87].



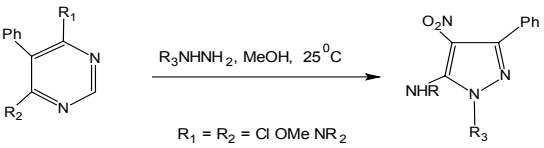
Scheme 53. Synthesis of5-amino-pyrazoles from 3-methyl-6H-1,3,4-thiadiazine acetic acid[87]

Martin *et al.,* prepared pyrazole derivatives by Cu-catalyzed C-N coupling reaction (Scheme 54)[88].



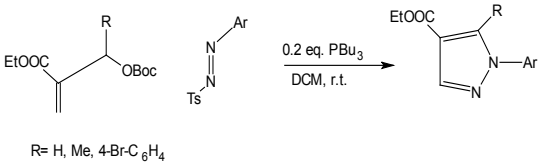
Scheme 54. Synthesis ofpyrazole derivatives by Cu-catalyzed C-N coupling reaction[88]

When nitropyrimidine was allowed to undergo reaction with aryl hydrazines in methyl alcohol at 25°C temperature, it furnished 4-nitro-3,5-diamino-pyrazole in good yields (Scheme 55)[89].



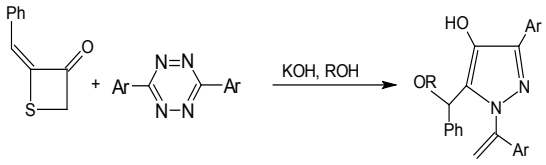
Scheme 55. Synthesis of4-nitro-3,5-diamino-pyrazole in good yields[89]

Q. Zhang *et al.,* synthesized pyrazole derivatives in good yields by cyclo-addition of allylic carbonate and arylazosulfones in presence of tri-butylphosphine(PBu_3) under mild reaction conditions (Scheme 56)[90].



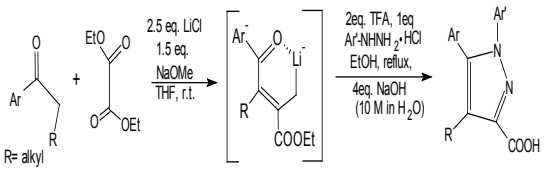
Scheme 56. Synthesis ofpyrazole derivatives in good yields by cyclo-addition of allylic carbonate and arylazosulfones[90]

Suen and Hope *et al.,* described a method to prepare a series of pyrazole derivatives by the condensation of thietanone & 1,2,4,5-tetrazine in alcohol in the presence of KOH (Scheme 57)[91].



Scheme 57. Synthesis ofpyrazole derivatives by the condensation of thietanone & 1,2,4,5-tetrazine in alcohol[91]

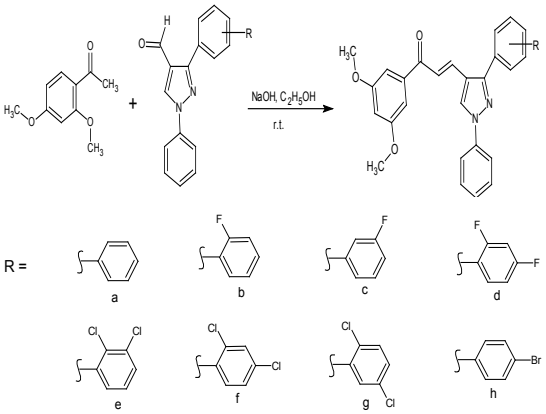
Jiang *et al.,* synthesized 4-substituted 1,5-diaryl pyrazole-3-carboxylic acids via claisen condensation-Knorr reaction which was carried out in the presence of Lithium chloride (LiCl) and Sodium methoxide (NaOMe) (Scheme 58)[92].



Scheme 58. Synthesis of4-substituted 1,5-diaryl pyrazole-3-carboxylic acids via claisen condensation-Knorr reaction[92]

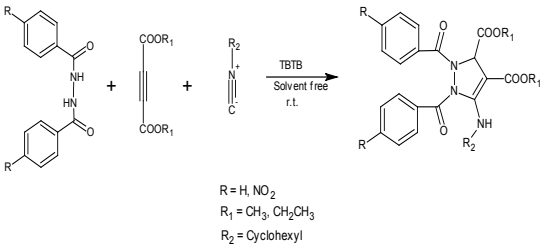
Synthesis of pyrazole derivatives through green synthesis

The pyrazole/substituted pyrazoles have also been frequently employed in green synthesis leading to formation of various pyrazole derivatives possessing diversified biological activities[93,94] The Claisen–Schmidt condensation of substituted 1,3-diphenyl-1H-pyrazole-4-carbaldehydes and 1-(2,4-dimethoxy-phenyl)-ethanone led to the development of novel chalcones, 1-(2,4-dimethoxy-phenyl)-3-(1,3-diphenyl1H-pyrazol-4-yl)-propenone. The reaction was carried out at room temperature in ethanol. Out of the several derivatives synthesized it was concluded that most of the compounds were nontoxic except compound g (Scheme 59)[95].



Scheme 59

The reaction of dialkyl acetylenedicarboxylates, isocyanides and the 1,2-dibenzoylhydrazines with tetrabutylammonium bromide was carried out, where tetrabutylammonium bromide was used as an environment friendly organic ionic salt as well as high polar reaction medium under solvent free conditions at room temperature. This green synthetic approach was explored to get highly functionalized pyrazole derivative (Scheme 60)[96].



Scheme 60

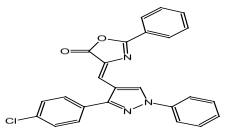
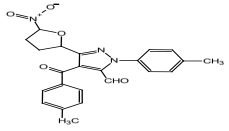
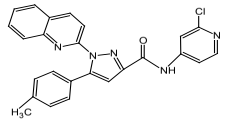
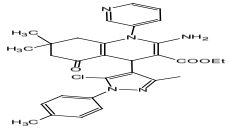
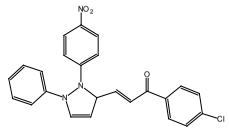
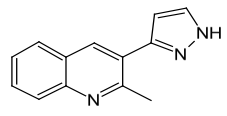
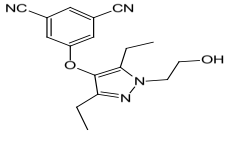
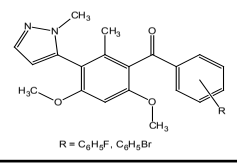
Pharmaceutical applications

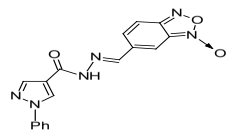
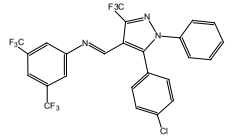
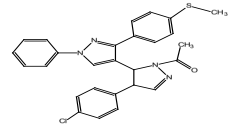
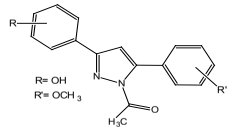
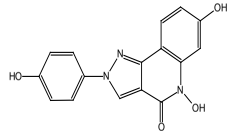
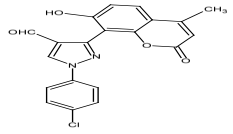
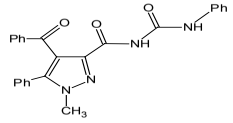
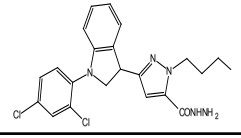
Derivatives of pyrazole are reported to be physiologically and pharmacologically active and these find use in various drugs for the treatment of several diseases. Hence pyrazole derivatives are biologically and pharmaceutically quite indispensable. The compounds having pyrazole nuclei have wide uses in agro-chemistry and pharmaceuticals. Various potential biological activities have been reported. The biological evaluation such as anti-bacterial activities of pyrazole derivatives has been done in an exhaustive manner, where a series of pyrazole derivatives were screened for the activities against the *Gram-negative* bacteria such as *Pseudomonas piosineus, E. coli* etc. applying agar plate diffusion

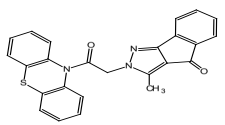
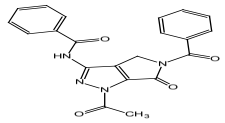
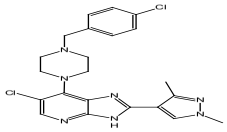
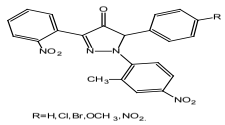
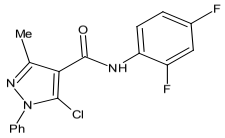
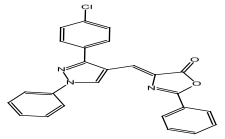
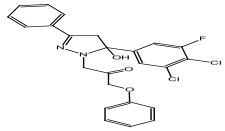
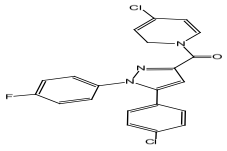
technique[97] and *Gram-positive* bacteria such as *S. aureus, S. albus* etc[98]. Pyrazole derivatives have also been found to have anti-HIV activity which involved the susceptible human host cells and have been tested for their anti-viral activity[99] particularly AIDS. Pyrazoles also act as herbicidal[100], insecticidal[101], anti-schistosomal[102] and anticancer[100-104] properties. 1-N-arylpyrazole derivatives show sedative, analgesic and hypnotic activities[105-107]. Different pyrazoles exhibit different biological activities as shown in the table given below.

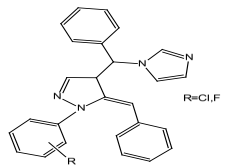
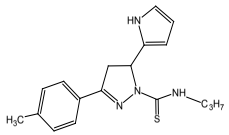
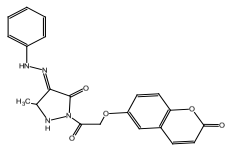
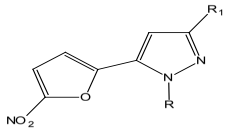
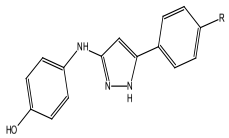
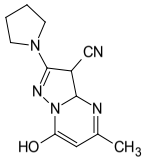
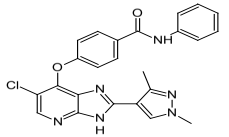
Table 2: Pyrazole derivatives with their biological activity

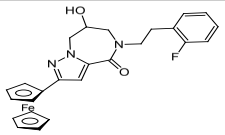
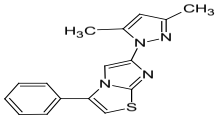
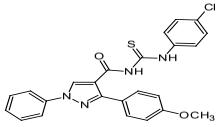
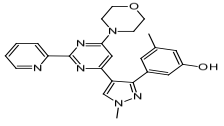
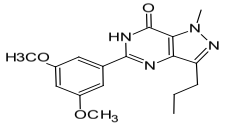
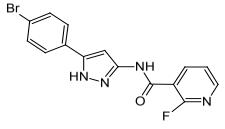
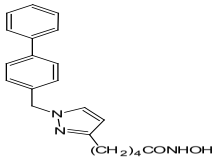
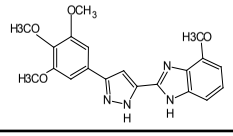
S.No.	Structure of pyrazole derivative	Bio activity	Activity against
1		4-thiazolyl pyrazolyl derivatives act as Anti-microbial agent[108]	Activity against *E. coli, staphylococcus* aureus and *Candida albicans*.
2		1-(2,4-dimethoxy-phenyl)-3-(1,3-diphenyl-1 H-pyrazol-4-yl)-propenone acts as anti-inflammatory agent[109]	Activity by TNF-α and IL-6 inhibition assays activity using dexamethasone as the standard drug.
3		Bis(3-aryl-4,5-dihydro-1H-pyrazole-thiocarboxamides) act as anti-inflammatory agent[110]	Activity in carrageenan-induced paw edema method in rats and these compounds were also found to be most vigorous using relative to indo-metacin.
4		3-(5-Bromo-2-thienyl)-4-[1-phenyl-thio-carbonyl-3-(4-methylphenyl)-2-pyrazolin-5-yl]-1-phenyl-1H-pyrazole act as anti-inflammatory agent[111]	Activity by sponge implantation model of inflammation and cotton pellet-induced granuloma in rats and this compound was found as most potent relative to indomethacin.
5		Pyrazoline analogs act as anti-tuberculosis agent[112]	Activity against mycobacterium tuberculosis with MIC of 7.41mM. (MIC=minimum inhibitory concentration)
6		Pyrazole derivative act as anti-tuberculosis agent[113]	Its activity against MTB H37Rv strain and it found to be most potent.
7		Fused pyrazole pyrimidine derivatives act as anti fungal[114]	Activity against *Fusarium oxysporum* and *Aspergillus funigatus*. (MIC of 6.25 μ/ml)

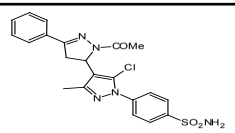
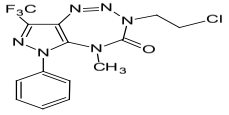
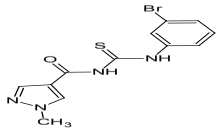
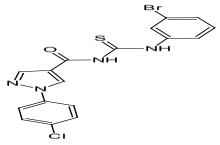
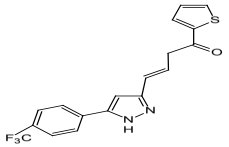
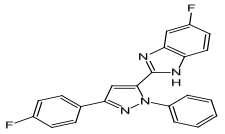
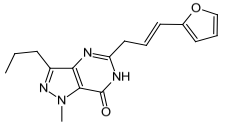
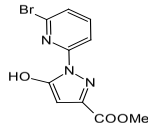
8		2,4-di substituted oxazol-5-one pyrazole derivative act as anti-microbial[115]	Its acts against ketoconazole and ampicillin anti-bacterial agent.
9		1,3,4,5-tetrasubstitued pyrazole derivatives act as anti- fungal and anti- bacterial agent[116]	Its activity against *C. albicans* as antifungal and activity against *S. aureus, B. subtilis* and *E. coli* as anti-bacterial agent.
10		5-(p-Tolyl)-1-(quinonlin-2-yl) pyrazole-3-carboxylicacid act as anti-proliferative agent[117]	Its activitiesagainst human cancer cell likeMCF7 human liver, breast and Huh7.(IC_{50} value= 3.3Mm and 1.6Mm)
11		Pyrazole quinolone-pyridine hybrids act as anti-cancer and anti- bacterial agent[118]	Its activities against human cancer cells and *B. subtilis* and *E. coli* and this compound show the promising results.
12		(E)-1-aryl-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl) prop-2-ene-1-one (pyrazolic-chalcones) act as anti-cancer agent[119]	Its activity against renal cancer (UO-31), leukemia (K-562 and SR) and non-small cell cancer (HOP-92).
13		Quinolinyl pyrazole hybrids act as anti-mycobacterial agent[120].	Activity against *M. smegmatis*. (MIC=14.66 μg/mL).
14		N-hydroxyethyl pyrazole derivatives act as anti-HIV agent[121].	It's activities against drug-resistant HIV consistent
15	 R = C_6H_5F, C_6H_5Br	1-methyl-5-(2,4,6-tri-methoxyphenyl)-1H-pyrazole as anti-inflammatory agent[122]	It showed activity against various inflammatorymediators and show the activity as most potent drug

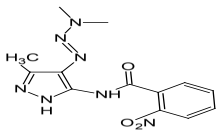
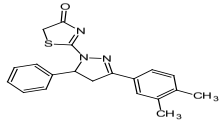
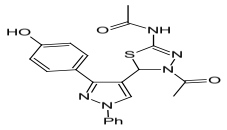
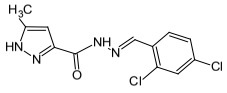
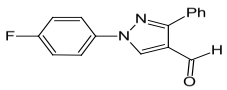
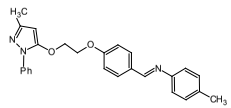
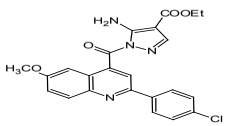
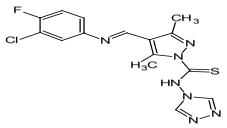
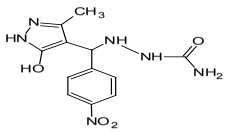
16		Pyrazole derivative act as anti-tuberculosis agent[123].	It's activity against *M. tuberculosis*. (MIC value = 17.9μM)
17		N-((5-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl) -1H-pyrazol-4-yl) methylene)-3,5-bis (tri-fluoro-methyl) aniline acts as anti-inflammatory agent[124]	Its activity against various inflammatorymediators and it exhibited optimal COX-1/COX-2 inhibitor potency IC_{50}=0.26μM comparable with reference standard drug Celcoxib, IC_{50}=0.28μM
18		1-Acetyl- 3,5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives act as anti-microbial and anti-tubercular agent[125]	Its activity against the fungi *Aspergillus niger* and *Bacillus subtiles*, *Bacillus coccus, Proteus vulgaris, E. coli* using amoxilane, benzyl penicillin and norfloxacin as standard drugs.
19		4,5-Disubstituted pyrazole derivatives act as anti-viral[126]	Its activity against the viruses (HEL cell culture) in different cell culture.
20		Tri-substituted pyrazole act as anti-angiogenic agent[127]	Its action by *In vitro* assays for migration and endothelial cell proliferation.
21		Pyrazole derivative act as antifungal as well as antibacterial agent[128].	It's activities against different organisms tested. (MIC value =15-60μg/mL)
22		1H-pyrazole-3-carboxylic acid derivatives act as anti-bacterial[129] and the result showed that this compound was the most potent in the series	It's activities against both *Gram-negative* and *Gram-positive*, *Staphylo-coccus aureus, Bacillus cereus*.
23		3-(1H-indole-3-yl)-1H-pyrazole-5-carbohydrazide act as anti-cancer agent[130]	It showed activity against NCI-60 cancer cell line panel.

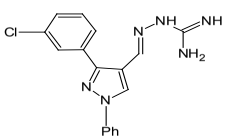
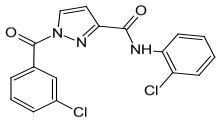
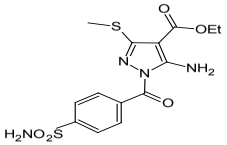
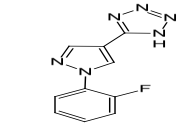
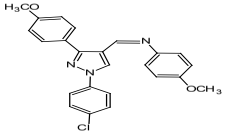
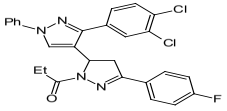
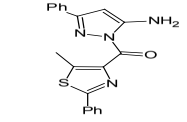
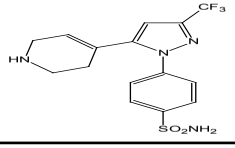
24		Pyrazole derivative acts as anti-cancer agent[131]	It showed activity against NCI-60, HCT-116, SK-MEL-5 cancer cell line panel.
25		Pyrazole derivative showed in vitro anti-cancer[132] activity	It showed activity against human colon carcinoma HCT-116 cancer cell line. (IC_{50} value=0.58μM)
26		Pyrazole derivative acts as anti-cancer[133] agent	It's action against human colon carcinoma HCT-116, human tumor cancer cell lines are remarkable. GI_{50} value=0.300 μM (Growth inhibitory power of the test agent)
27		1,3,5-Triaryl-2-pyrazoines acts as anti-microbial agent[134]	It's activities against micro-organism and tested strains.
28		1,3,4,5-Tetra substituted pyrazole derivative acts as antifungal agent[135]	It's showed activities against *P. ultimum* fungus (concentration =100μg/mL) with good control efficacy (77.78%)
29		2,4-Disubstituted oxazo-5-one pyrazole derivative acts as anti- fungal as well as anti-bacterial agent[136]	It's activities against fungus and *Gram-positive* as well as *Gram-negative* bacteria.
30		Chloro-fluorine containing hydroxyl pyrazolines derivative acts as anti- fungal as well as anti-bacterial agent[137]	It showed activities against *Gram-positive*, *Gram-negative* bacteria and fungi.
31		1,3,5-Tri substituted pyrazole derivative acts as anti- fungal as well as anti-bacterial agent[138]	It showed activities against *Gram-positive*, *Gram-negative* bacteria and fungus.

32		1,4,5-tri substituted pyrazole derivative acts as anti- fungal as well as anti-bacterial agent[139]	It showed activities against bacteria and fungus.
33		1-Thiocarbomyl-3-substituted phenyl-5-(2-pyrole)-4,5-dihydro-(1H)-derivatives act as analgesics and anti-inflammatory[140] agent	It's activities against MAO.
34		Pyrazole derivatives act as cyto-toxic agents and anti-oxidants[141]	It's activities against DLA (Dalton's lymphoma ascites tumour cells) and EAC (Ehrlich ascites carcinoma cells) and show promising antioxidant activity *In vitro*.
35		1,3,5-tri substituted pyrazole derivative act as anti-bacterial agent[142]	It showed activities against *P. aerugiosa* and *E. coli*.
36		4-(5-substituted aryl-4,5-dihydropyrazole-3-yl-amino) phenols acts as anti-microbial and anti-inflammatory agent[143]	It showed activities against micro-organisms.
37		Pyrazole derivative acts as Anticancer agent[144]	It showed activities against human tumor cells including Aurora-A Kinase inhibitory activity. (IC_{50}=12.71μM)
38		1,3-dimethyl pyrazole derivatives act asAnticancer agent[145]	It showed activities against human colon carcinoma cells (HCT116).p-T288, IC_{50}=0.065μM;p-HH3, IC_{50}=24.65μM.

39		Pyrazole derivatives act as Anticancer[146] agent	It's activities against as lung cancer cells (A549, H1299 & H 322)
40		Pyrazole derivative acts as Anticancer agent[147]	It showed activities against as renal cancer cells (UO-31) line and CNS SNB-75.
41		Pyrazole derivatives acts as Anticancer agent[148]	It showed activities act as CDks inhibitors or anti-proliferatives with IC_{50} value= 25nM
42		1H-Pyrazole [4,3-d] pyrimidin-7(6H)-ones acts as anticancer agent[149]	It showed activities against human cancer cells, Pc-3, A549 Mia Paca-2 with IC_{50} value=13.6nM
43		Pyrazole derivatives act as anticancer agent[150]	It showed activities against human cancer cells Pc-3 HeLa, CAKI-1, through apoptosis mechanism.
44		5-Phenyl-1H pyrazole derivatives act asAnticancer[151] agent	It acts as anti-proliferative agent against A375 & WM266.4 with IC_{50} value=0.33μM.
45		Pyrazole derivatives act as anticancer agent[152]	It showed activities against class-I & II b HDAC and several cancer cell lines with most potent inhibitory activity.
46		Pyrazole derivatives act as anticancer agent[153]	It showed activities against the cell lines ranging from 0.3 to 3 μM with promising.

47		Pyrazole-Pyrazolines act as anticancer agent[154]	It's activities against cytosolic human isozymes and it exhibited most potent inhibition profile against h CA II (Ki=0.17 nm)
48		Pyrazole derivatives act as Anticancer agent[155]	It showed activities as antiproliferative with GI50 value of 2.3 µM
49		Pyrazole thiourea derivatives act as anticancer agent[156]	It's activities against human cancer cells and showed high apoptosis inducing effect.
50		Pyrazole thiourea derivatives as anticancer agent[157]	It showed activities against human cancer cells and showed result as a promising anticancer drug.
51		Pyrazole derivative acts as anticancer agent[158]	It showed activities against HeLa and MCF-7 cell lines with IC_{50} value=18 and 47μM respectively.
52		Pyrazole derivative containing benzimidazole moiety acts as anticancer[159]	Its activities human tumour cells, , MCF-7, A 549, HaCa T & HeLa cell lines with IC_{50} value=0.95, 1.13 & 1.5 7 μM respectively.
53		Pyrazole derivatives act as anticancer agent[160]	It's activities against MGC-803 Cells and showed promising telomerase inhibitory activity.
54		1H-Pyrazole-3-3-carboxylate derivative act as anticancer agent[161]	It's activities against Hep G2, with IC_{50} value=129.75 μM.

55		4-(3,3-Dimethyltriazeno)-5-benz-amido-pyrazole derivatives act asAnti-cancer agent[162]	It showed activities against against K562 and it's growth inhibition values is 97.8%
56		Dihydro pyrazolyl-thiazaolin-one derivatives acts as anti- inflammatoryas well as analgesic agent[163]	It showed COX-2 inhibitory activities with IC_{50} of 0.5 µM
57		1,3,4-trisybstituted pyrazole acts as Anti-inflammatory agent[164]	It showed COX-1/ COX-2 inhibitory & its anti-inhibitory activities (≥84.2% inhibition) comparable to diclo-fenac class of drugs.
58		Pyrazole-hydrazone derivatives act as anti-inflammatory as well as Analgesic agent[165]	It showed activities against inflammation (92.59% inhibition) at the dose of 100 mg/kg.
59		1-(4-substituted-phenyl)-3-phenyl-1H-pyrazole-4-carbaldehydes act as anti-inflammatory as well as analgesic agent[166]	It exhibited best most potent analgesic & anti- inflammatory activities.
60		Pyrazole derivatives act as anti-inflammatoryas well as Analgesic *agent*[167]	It showed promising anti- inflammatory activities comparable to nimesulide.
61		Pyrazole derivatives acts as anti-inflammatory agent[168]	It has good anti-inflammatory activity and has good binding profiles with COX-2 binding site.
62		Pyrazole derivatives act as *Analgesic* agent[169]	It has moderate analgesic activity to compare with their standard drugs.
63		Pyrazole derivatives act as anti-inflammatory agent[170]	It showed anti-inflammatory activity camparable to diclofenac sodium a standard drug.

64		Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent[171]	It showed most potent anti-inflammatory activity (93.59% inhibition) as comparable to ibuprofen & standard drug indomethacin.
65		Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent[172]	It is the most potent inhibitors for human 15-Lipoxygenase.
66		Pyrazole derivatives act as anti-inflammatory as well Asanalgesic[173]	It exhibited significant anti-inflammatory & analgesic activities with a dose of 25 mg/kg.
67		Pyrazole- containing tetrazole moiety act as anti-inflammatory agent[174]	It is anti-inflammatory non-steroidal drug
68		Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent[175]	It is most active analgesic as well as anti-inflammatory drug.
69		Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent[176]	It is most active analgesic as well as anti-inflammatory drug.
70		Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent[177]	It is most active analgesic as well as anti-inflammatory drugs.
71		1, 3, 5-Trisubstituted Pyrazole derivatives act as anti-inflammatory agent[178]	It showed good activity as anti-inflammatory drug. (ED_{50} value=61.2 mg/kg)

72		1,3,5- Tri-substituted pyrazole derivatives act as anti-inflammatory drug[179]	It showed good activity as anti-inflammatory drug.
73		Pyrazole derivative containing sulfonamide group & ortho hydroxymethyl group acts as anti-inflammatory agent[180]	It has selectivity toward COX-2 enzyme. (IC_{50}=0.036 mM, SI=297).
74		Pyrazole derivatives act as anti-inflammatory agent[181]	It is most potent COX-2 inhibitor IC_{50}=0.067 Mm, SI=132).
75		Pyrazole derivatives act as anti-inflammatory agent[182]	It is most selective & potent COX-2 inhibitor(IC_{50}=0.012 mM).
76		Pyrazole derivatives act as anti-inflammatory agent[183]	It is most potent COX-2 inhibitor (IC_{50}=0.063 mM, SI=262).

CONCLUSION

Based on the literature reports Pyrazole and its derivatives are undoubtedly one of the most important class of organic heterocyclic possessing wide range of biological activities some of the representatives such as anti-histamine, anti-viral, anti-tumor, anti-microbial, anti-bacterial, anti-pyretic, anti-depressant, anti-inflammatory, anti-cancer, fungicides, insecticides, analgesic etc. have been summarized in the present communication. However there is still a used to explore a cheap and easy synthetic strategy for the synthesis of such an important molecule list wise the biological application and medicinal importance in wide spectrum is yet to be investigated to prove the pyrazole/pyrazole derivatives as one of the important tool for organic/Medicinal chemist and to exploit further the chemistry of pyrazole for the welfare of mankind over the globe.

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Conflict of interest

The author declare that we have no conflict of interest.

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