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

MUNISH KUMAR and SHARAD KUMAR PANDAY*

Department of Chemistry, Faculty of Engineering and Technology
M. J. P. Rohilkhand University, Bareilly, U.P., India.
*Corresponding author E-mail: skpanday@mjpru.ac.in

http://dx.doi.org/10.13005/ojc/380306

(Received: February 18, 2022; Accepted: June 05, 2022)

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-heterocycle, Anti-viral, Drugs, Biological applications.

INTRODUCTION

Pyrazole, a five-membered planar N-heterocyclic compound which is aromatic in nature having 4 π-electrons and one unshared 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 $\text{PK}_b 11.5$. The pyrazole is represented by the following structure.

![Fig. 1. Structure of pyrazole](image-url)
Background 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 antioxidant\(^4\), anti-viral\(^5\), anti-histaminic\(^6\), anti-microbial\(^7\), anti-tumor\(^8,9,10\), fungicides\(^10\), anti-depressant\(^11\), antipyretic\(^12\), analgesic\(^12,12\), 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>
<thead>
<tr>
<th>S.No.</th>
<th>Drug Name</th>
<th>Drug Structure</th>
<th>Act as a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rimonabant(^18,20,25)</td>
<td><img src="image" alt="Rimonabant.png" /></td>
<td>Anorectic anti-obesity drug</td>
</tr>
<tr>
<td>2</td>
<td>Betazole(^26,28)</td>
<td><img src="image" alt="Betazole.png" /></td>
<td>Used in testing gastric secretory function</td>
</tr>
<tr>
<td>3</td>
<td>Tepoxalin(^19)</td>
<td><img src="image" alt="Tepoxalin.png" /></td>
<td>Anti-inflammatory drug &amp; anti histamines</td>
</tr>
<tr>
<td>4</td>
<td>Celecoxib(^22)</td>
<td><img src="image" alt="Celecoxib.png" /></td>
<td>Anti-inflammatory drug</td>
</tr>
<tr>
<td>5</td>
<td>Lonazolac(^21,24)</td>
<td><img src="image" alt="Lonazolac.png" /></td>
<td>Anti-inflammatory drug</td>
</tr>
<tr>
<td>6</td>
<td>Tepoxalin(^18)</td>
<td><img src="image" alt="Tepoxalin.png" /></td>
<td>Anti-inflammatory drug</td>
</tr>
<tr>
<td>7</td>
<td>Fezolamin(^29)</td>
<td><img src="image" alt="Fezolamin.png" /></td>
<td>Anti-depressant</td>
</tr>
<tr>
<td>8</td>
<td>Fibronil(^18)</td>
<td><img src="image" alt="Fibronil.png" /></td>
<td>Broadly used as insecticide and also commonly used as pesticide</td>
</tr>
<tr>
<td>9</td>
<td>CDPPS(^23)</td>
<td><img src="image" alt="CDPPS.png" /></td>
<td>Anti-psychotic</td>
</tr>
<tr>
<td>10</td>
<td>Mepirizole(^29)</td>
<td><img src="image" alt="Mepirizole.png" /></td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>11</td>
<td>Diffenamizole(^27,28)</td>
<td><img src="image" alt="Diffenamizole.png" /></td>
<td>Analgesic</td>
</tr>
</tbody>
</table>
Synthesis of pyrazole and its derivatives

Taking into account 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 transhydrazonation 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).

Scheme 1. Synthesis of pyrazole derivative via trans-hydrazonation or cyclization

\[
\begin{align*}
\text{NR} & \quad \text{Br} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{R} & \quad \text{N} \\
\text{N} & \quad \text{2} \\
\text{R} & \quad \text{Me} \\
\text{N} & \quad \text{Ph} \\
\text{Ph} & \quad \text{NH}_2 \\
+ & \quad \text{Pd(OAc)}_2 \\
\text{DPPF} & \quad \text{HCl/EtOH} \quad \text{or} \quad \text{p-TsOH/EtOH} \\
\rightarrow & \quad \text{CN} \\
\text{O} & \quad \text{O} \\
\text{R} = & \quad \text{Me} \\
\text{R} = & \quad \text{OMe} \\
\end{align*}
\]

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).

Scheme 2. Synthesis of 3,5-disubstituted pyrazoles through the condensation of 1,3-dienophilic synthons

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\text{H} & \quad \text{Me} \\
\text{RNHNH}_2, \text{HOAc, H}_2 \text{O} & \quad 80 - 90^\circ \text{C} \\
\rightarrow & \quad 60 - 93\% \\
\text{R} = & \quad \text{H, Et, Ph, Ar} \\
\end{align*}
\]

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

Scheme 6. Synthesis of 1-methyl(aryl)-3-phenyl-5-alkyl(aryl)pyrazoles by condensation of α-benzotriazolylolenones

\[
\begin{align*}
\text{Ph} & \quad \text{R}_1 \\
\text{R}_2 & \quad \text{O} \\
\text{Bt} & \quad \text{R}_1 \\
+ & \quad \text{RNHNH}_2 \\
\text{EtOH} & \quad \text{reflux} \\
\text{NaOEt} & \quad \text{EtOH, reflux} \\
\rightarrow & \quad \text{N} \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{F} & \quad \text{F} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{50\%} \\
\end{align*}
\]

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

Scheme 7. Cyclo-condensation of acetylenic ketones and hydrazine derivatives leading to pyrazoles derivatives

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R}_2 \text{NHNNH}_2 \\
\text{BOD} & \quad \text{reflux} \\
\text{NaOEt} & \quad \text{BOD, reflux} \\
\rightarrow & \quad \text{N} \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_3 \\
\text{R}_4 & \quad \text{R}_4 \\
\text{R}_5 & \quad \text{R}_5 \\
\end{align*}
\]

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).

Scheme 8. Cyclo-condensation of acetylenic ketones and hydrazine derivatives leading to pyrazoles derivatives

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R}_2 \text{NHNNH}_2 \\
\text{BOD} & \quad \text{reflux} \\
\text{NaOEt} & \quad \text{BOD, reflux} \\
\rightarrow & \quad \text{N} \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_3 \\
\text{R}_4 & \quad \text{R}_4 \\
\text{R}_5 & \quad \text{R}_5 \\
\end{align*}
\]
Baldwin et al., reported the synthesis of two isomeric pyrazoles by the reaction of Phenyl hydrazine with diacetylene Ketones in ethyl alcohol (Scheme 9)\(^{38}\).

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-trifluoromethyl pyrazole in high yields (70%) (Scheme 11)\(^{40}\).

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

Bhat et al., reported the synthesis of pyrazole derivatives by the reaction of β-aryl chalcones and \(\text{H}_2\text{O}_2\) furnishing epoxides. The addition of hydrated hydrazine to it, followed by dehydration provided 3,5-diaryl-1H-pyrazole (Scheme 15)\(^{44}\).
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)\(^{45}\).

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)\(^{49}\).

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)\(^{50}\).

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

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)\(^{52}\).

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)\(^{53}\).
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-disubstituted pyrazoles in satisfactory yields (70%) (Scheme 29).

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

Harigae and Moriyama 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).

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

Lizuka et al., described the palladium catalyzed carbonylation reaction of acetylenic acids with aryl iodides using of Molybdenum hexacarbonyl (Mo(CO)₆) to get 1,3,5-trisubstituted pyrazole in good yields (Scheme 27).

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

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).

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).

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).
Lokhande and Hasanzadeh et al., synthesized 4-formyl pyrazole by the condensation of hydrazine in presence of Phosphorus oxychloride(POCl₃) in DMF (Scheme 33)⁶².

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

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.

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.

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.

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.

Sha et al., synthesized 3,5-diaryl-4-bromo-1H-pyrazoles from alkenyl bromides and diazocompounds⁷¹.

Xie and Chen et al., reported the synthesis of pyrazoles by Suzuki coupling reactions(Scheme 39)⁷².
Gerstenberger et al., synthesized N-aryl 3,4,5-trisubstituted pyrazoles from aryl halide, di-tert-butylazodicarboxylate (Boc) and 1,3-dicarbonyl compounds (Scheme 40).

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-nitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (Scheme 41).

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).

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

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).

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

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

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

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

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).

Q. Zhang et al., synthesized pyrazole derivatives in good yields by cyclo-addition of allylic carbonate and aryl azosulfones in presence of tri-butylphosphine(PBu₃) under mild reaction conditions (Scheme 56).

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).

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 $\alpha$-chlorosulfonyls in DMSO using Potassium hydroxide as base (Scheme 49).

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

Ferfra and Ahabchane et al., described a method for the synthesis of pyrazoles by the reaction of benzodiazepine-2-thiones with hydrazine (Scheme 51).
The pyrazole/ substituted pyrazoles have also been frequently employed in green synthesis leading to formation of various pyrazole derivatives possessing diversified biological activities. 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).

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).

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 and Gram-positive bacteria such as *S. aureus* and *S. albus* 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 particularly AIDS. Pyrazoles also act as antituberculosis agents and antitumor, anti-schistosomal and anticancer activities. Different pyrazoles exhibit different biological activities as shown in the table given below.

Table 2: Pyrazole derivatives with their biological activity

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Structure of pyrazole derivative</th>
<th>Bio activity</th>
<th>Activity against</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>4-thiazolyl pyrazolyl derivatives act as Anti-microbial agent</td>
<td>Activity against <em>E. coli</em>, <em>staphylococcus aureus</em> and <em>Candida albicans</em>.</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>1-(2,4-dimethoxy-phenyl)-3-(1,3-diphenyl-1 H-pyrazol-4-yl)-propenone acts as anti-inflammatory agent</td>
<td>Activity by TNF-α and IL-6 inhibition assays activity using dexamethasone as the standard drug.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>Bis(3-aryl-4,5-dihydro-1H-pyrazole-thiocarboxamides) act as anti-inflammatory agent</td>
<td>Activity in carrageenan-induced paw edema method in rats and these compounds were also found to be most vigorous using relative to indo-metacin.</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>Pyrazoline analogs act as anti-tuberculosis agent</td>
<td>Activity against <em>mycobacterium tuberculosis</em> with MIC of 7.41mM. (MIC=minimum inhibitory concentration)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>Pyrazole derivative act as anti-tuberculosis agent</td>
<td>Its activity against MTB H37Rv strain and it found to be most potent.</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>Fused pyrazole pyrimidine derivatives act as anti fungal</td>
<td>Activity against <em>Fusarium oxysporum</em> and <em>Aspergillus fungatus</em>. (MIC of 6.25 µ/ml)</td>
</tr>
<tr>
<td>8</td>
<td>2,4-di substituted oxazol-5-one pyrazole derivative act as anti-microbial. Its acts against ketoconazole and ampicillin anti-bacterial agent.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1,3,4,5-tetrasubstituted pyrazole derivatives act as anti-fungal and anti-bacterial agent. Its activity against C. albicans as antifungal and activity against S. aureus, B. subtilis and E. coli as anti-bacterial agent.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5-(p-Tolyl)-1-(quinolin-2-yl) pyrazole-3-carboxylic acid act as anti-proliferative agent. Its activities against human cancer cell like MCF7 human liver, breast and Huh7. (IC_{50} value= 3.3Mm and 1.6Mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Pyrazole quinolone-pyridine hybrids act as anti-cancer and anti-bacterial agent. Its activities against human cancer cells and B. subtilis and E. coli and this compound show the promising results.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(E)-1-aryl-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl) prop-2-ene-1-one (pyrazolic-chalcones) act as anti-cancer agent. Its activity against renal cancer (UO-31), leukemia (K-562 and SR) and non-small cell cancer (HOP-92).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Quinolinyl pyrazole hybrids act as anti-mycobacterial agent. Activity against M. smegmatis. (MIC=14.66 µg/mL).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>N-hydroxyethyl pyrazole derivatives act as anti-HIV agent. It's activities against drug-resistant HIV consistent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1-methyl-5-(2,4,6-tri-methoxyphenyl)-1H-pyrazole as anti-inflammatory agent. It showed activity against various inflammatory mediators and show the activity as most potent drug</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
16  Pyrazole derivative act as anti-tuberculosis agent\textsuperscript{16}. It's activity against \textit{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\textsuperscript{17}. Its activity against various inflammatory mediators and it exhibited optimal COX-1/COX-2 inhibitor potency IC\textsubscript{50} = 0.26µM comparable with reference standard drug Celcoxib, IC\textsubscript{50} = 0.28µM.

18  1-Acetyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives act as anti-microbial and anti-tubercular agent\textsuperscript{18}. Its activity against the fungi \textit{Aspergillus niger} and \textit{Bacillus subtiles}, \textit{Bacillus coccus}, \textit{Proteus vulgaris}, \textit{E. coli} using amoxilane, benzyl penicillin and norfloxaclin as standard drugs.

19  4,5-Disubstituted pyrazole derivatives act as anti-viral\textsuperscript{19}. Its activity against the viruses (HEL cell culture) in different cell culture.

20  Tri-substituted pyrazole act as anti-angiogenic agent\textsuperscript{20}. Its action by \textit{In vitro} assays for migration and endothelial cell proliferation.

21  Pyrazole derivative act as antifungal as well as antibacterial agent\textsuperscript{21}. It's activities against different organisms tested. (MIC value = 15-60µg/mL)

22  1H-pyrazole-3-carboxylic acid derivatives act as anti-bacterial\textsuperscript{22} and the result showed that this compound was the most potent in the series \textit{Staphylo-coccus aureus}, \textit{Bacillus cereus}.

23  3-(1H-indole-3-yl)-1H-pyrazole-5-carboxyhydrazide act as anti-cancer agent\textsuperscript{23}. It showed activity against NCI-60 cancer cell line panel.
Pyrazole derivative acts as anti-cancer agent\textsuperscript{131}

Pyrazole derivative showed in vitro anti-cancer\textsuperscript{132} activity

Pyrazole derivative acts as anti-cancer\textsuperscript{133} agent

1,3,5-Triaryl-2-pyrazoines acts as anti-microbial agent\textsuperscript{134}

1,3,4,5-Tetra substituted pyrazole derivative acts as antifungal agent\textsuperscript{135}

2,4-Disubstituted oxazo-5-one pyrazole derivative acts as anti-fungal as well as anti-bacterial agent\textsuperscript{136}

Chloro-fluorine containing hydroxyl pyrazolines derivative acts as anti-fungal as well as anti-bacterial agent\textsuperscript{137}

1,3,5-Tri substituted pyrazole derivative acts as anti-fungal as well as anti-bacterial agent\textsuperscript{138}

It showed activity against NCI-60, HCT-116, SK-MEL-5 cancer cell line panel.

It showed activity against human colon carcinoma HCT-116 cancer cell line. (IC\textsubscript{50} value=0.58µM)

It's action against human colon carcinoma HCT-116, human tumor cancer cell lines are remarkable. GI\textsubscript{50} value=0.300 µM (Growth inhibitory power of the test agent)

It's activities against micro-organism and tested strains.

It's showed activities against P. ultimum fungus (concentration =100µg/mL) with good control efficacy (77.78%)\textsuperscript{136}

It's activities against fungus and Gram-positive as well as Gram-negative bacteria.

It showed activities against Gram-positive, Gram-negative bacteria and fungi.

It showed activities against Gram-positive, Gram-negative bacteria and fungus.
1,4,5-tri substituted pyrazole derivative acts as anti-fungal as well as anti-bacterial agent. It showed activities against bacteria and fungus.

1-Thiocarbomyl-3-substituted phenyl-5-(2-pyrole)-4,5-dihydro-(1H)-derivatives act as analgesics and anti-inflammatory agent. It’s activities against MAO.

Pyrazole derivatives act as cytotoxic agents and anti-oxidants. It’s activities against DLA (Dalton’s lymphoma ascites tumour cells) and EAC (Ehrlich ascites carcinoma cells) and show promising antioxidant activity in vitro.

1,3,5-tri substituted pyrazole derivative acts as anti-bacterial agent. It showed activities against P. aerugiosa and E. coli.

4-(5-substituted aryl-4,5-dihydropyrazole-3-yl-amino) phenols acts as anti-microbial and anti-inflammatory agent. It showed activities against micro-organisms.

Pyrazole derivative acts as Anticancer agent. It showed activities against human tumor cells including Aurora-A Kinase inhibitory activity. (IC$_{50}$=12.71µM)

1,3-dimethyl pyrazole derivatives act as Anticancer agent. It showed activities against human colon carcinoma cells (HCT 116), p-T288, IC$_{50}$=0.065µM; p-HH3, IC$_{50}$=24.65µM.
Pyrazole derivatives act as Anticancer agent It’s activities against lung cancer cells (A549, H1299 & H 322)

Pyrazole derivative acts as Anticancer agent It showed activities against renal cancer cells (UO-31) line and CNS SNB-75.

Pyrazole derivatives act as Anticancer agent It showed activities act as CDks inhibitors or anti-proliferatives with IC<sub>50</sub> value = 25nM

1H-Pyrazole [4,3-d] pyrimidin-7(6H)-ones acts as anticancer agent It showed activities against human cancer cells, Pc-3, A549 Mia Paca-2 with IC<sub>50</sub> value=13.6nM

Pyrazole derivatives act as anticancer agent It showed activities against human cancer cells Pc-3 HeLa, CAKI-1, through apoptosis mechanism.

5-Phenyl-1H pyrazole derivatives act as Anticancer agent It acts as anti-proliferative agent against A375 & WM266.4 with IC<sub>50</sub> value =0.33µM.

Pyrazole derivatives act as anticancer agent It showed activities against class-I & II b HDAC and several cancer cell lines with most potent inhibitory activity.

Pyrazole derivatives act as anticancer agent It showed activities against the cell lines ranging from 0.3 to 3 µM with promising.
Pyrazole-Pyrazolines act as anticancer agent\textsuperscript{154} It's activities against cytosolic human isozymes and it exhibited most potent inhibition profile against h CA II (Ki=0.17 nm)

Pyrazole derivatives act as Anticancer agent\textsuperscript{155} It showed activities as antiproliferative with GI50 value of 2.3 μM

Pyrazole thiourea derivatives act as anticancer agent\textsuperscript{156} It's activities against human cancer cells and showed high apoptosis inducing effect.

Pyrazole thiourea derivatives act as anticancer agent\textsuperscript{157} It showed activities against human cancer cells and showed result as a promising anticancer drug.

Pyrazole derivative acts as anticancer agent\textsuperscript{158} It showed activities against HeLa and MCF-7 cell lines with IC\textsubscript{50} value=18 and 47μM respectively.

Pyrazole derivative containing benzimidazole moiety acts as anticancer\textsuperscript{159} Its activities human tumour cells, MCF-7, A549, HaCa T & HeLa cell lines with IC\textsubscript{50} value=0.95, 1.13 & 1.57 µM respectively.

Pyrazole derivatives act as anticancer agent\textsuperscript{160} It's activities against MGC-803 Cells and showed promising telomerase inhibitory activity.

1H-Pyrazole-3-3-carboxylate derivative act as anticancer agent\textsuperscript{161} It's activities against Hep G2, with IC\textsubscript{50} value=129.75 μM.
4-(3,3-Dimethyltriazeno)-5-benz-amido-pyrazole derivatives act as Anti-cancer agent. It showed activities against K562 and it's growth inhibition values is 97.8%.

Dihydro pyrazolyl-thiazaolin-one derivatives act as anti-inflammatory as well as analgesic agent. It showed COX-2 inhibitory activities with $IC_{50}$ of 0.5 μM.

1,3,4-trisubstitued pyrazole acts as Anti-inflammatory agent. It showed COX-1/COX-2 inhibitory & its anti-inhibitory activities (≥84.2% inhibition) comparable to diclofenac class of drugs.

Pyrazole-hydrazine derivatives act as anti-inflammatory as well as Analgesic agent. It showed activities against inflammation (92.59% inhibition) at the dose of 100 mg/kg.

1-(4-substituted-phenyl)-3-phenyl-1H-pyrazole-4-carbaldehydes act as anti-inflammatory as well as analgesic agent. It exhibited best most potent analgesic & anti-inflammatory activities.

Pyrazole derivatives act as anti-inflammatoryas well as Analgesic agent. It showed promising anti-inflammatory activities comparable to nimesulide.

Pyrazole derivatives acts as anti-inflammatory agent. It has good anti-inflammatory activity and has good binding profiles with COX-2 binding site.

Pyrazole derivatives act as Analgesic agent. It has moderate analgesic activity to compare with their standard drugs.

Pyrazole derivatives act as anti-inflammatory agent. It showed anti-inflammatory activity comparable to diclofenac sodium a standard drug.
Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent\textsuperscript{176} It is most active analgesic as well as anti-inflammatory drug.

Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent\textsuperscript{176} It is most active analgesic as well as anti-inflammatory drug.

Pyrazole derivatives act as anti-inflammatory as well as Analgesic agent\textsuperscript{177} It is most active analgesic as well as anti-inflammatory drugs.

1, 3, 5-Trisubstituted Pyrazole derivatives act as anti-inflammatory agent\textsuperscript{179} It showed good activity as anti-inflammatory drug. (ED\textsubscript{50} value=61.2 mg/kg)
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, analgesics 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.

ACKNOWLEDGEMENT

The Principal author is thankful to TEQIP-III (MHRD) for financial support in form of minor research project and first author Munish Kumar is thankful to Council of Scientific and Industrial Research, India for providing financial assistance in form of Junior Research Fellowship and Senior Research Fellowship.

Conflict of interest

The author declare that we have no conflict of interest.
REFERENCES
