Review Article

# Pyrazole Scaffold: A Remarkable Tool in Drug Development

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**ABSTRACT**

The main objective of this review is to overview the enormous pharmacological activities of pyrazole that has already secured an eccentric status in field of medicinal chemistry. The review highlighted recent developments of anticancer, antimicrobial, anti-inflammatory, antioxidant, anti-tubercular activities of some novel pyrazole derivatives. In this review we summarize the literature work reported by researchers on pyrazole for their innumerable pharmacological activities and to demonstrate that this class of compound can be targeted for the discovery of new drugs and can readily prepared owing to recent achievements in synthetic medicinal chemistry.

**Keywords:** Pyrazole, Anticancer activity, Antimicrobial activity, Anti-inflammatory activity, Antioxidant activity, Antitubercular activity.

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## INTRODUCTION

Pyrazole is a heterocyclic compound characterized by a ring structure composed by three carbon and two nitrogen atoms in adjacent positions[1, 2]. Pyrazoles are five membered ring containing heterocyclic compounds with two nitrogen atoms in adjacent position and are also called as azoles[3] and the structure represented in **figure 1**.

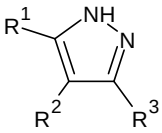
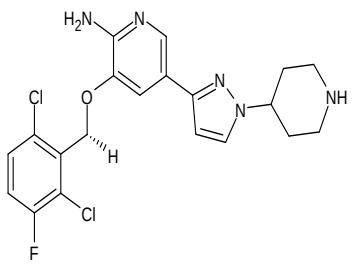


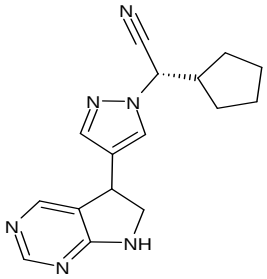

**Figure 1:** General structure of pyrazoles

Pyrazole contains an acidic pyrrole like nitrogen having two lone pair of electrons which is involved in aromaticity, a basic sp2- hybridized pyridine like nitrogen and three carbon atoms. They are aromatic in nature due to their planar conjugated ring structures with six delocalized Π electrons[4]. Pyrazoles are highly reactive due to their challenging structure, with the possibility of tautomerim and multifarious frame work, providing versatility for application in synthetic organic chemistry[5].

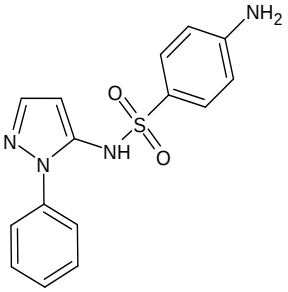
Pyrazole is an organic compound having the molecular formula C3H3N2H and molar mass 68.079g.mol$^{-1}$. Pyrazole is a class of weak base, with $pK_b$ 11.5 and $pK_a$ of the conjugated acid is 2.49 at 25°C. Melting point and boiling point are found to be 66-70°C and 186-188°C respectively[1]. They exhibit wide range of activity[6,7] such as antioxidant[8,9], anti inflammatory[10,11], antibacterial[12,13,14], antifungal[15,16], anticonvulsant[17], anti hyperglycemic[18], analgesic[19], anticancer[20,21,22] etc. pyrazole containing drugs play an important role in medicinal chemistry. Pyrazole in combination with carbonyl functional group known to have various pharmacological activities like anti inflammatory, antiviral, anti tumor, anti tubercular and antiparasitic activity. Notable drugs that containing a pyrazole ring are crizotinib, ruxolitinib, sulfaphenazole, sedaxane, celecoxib, lonazolac.



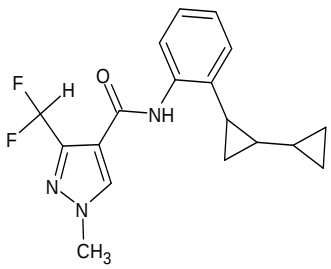

Crizotinib



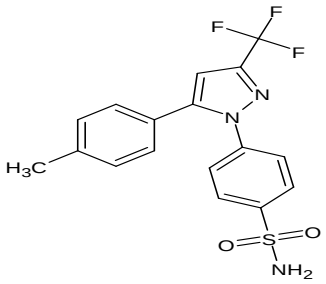

Ruxolitinib



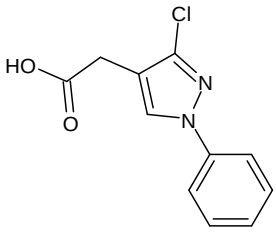

Sulfaphenazole




Sedaxane



Celecoxib



Lonazolac

**Synthetic strategies of pyrazole**

Pyrazoles can be generally prepared by the reaction between α, β-unsaturated aldehydes and hydrazine followed by dehydrogenation. Substituted pyrazoles are synthesized by various reactions such as Knorr-type reactions. **(Figure 2)**

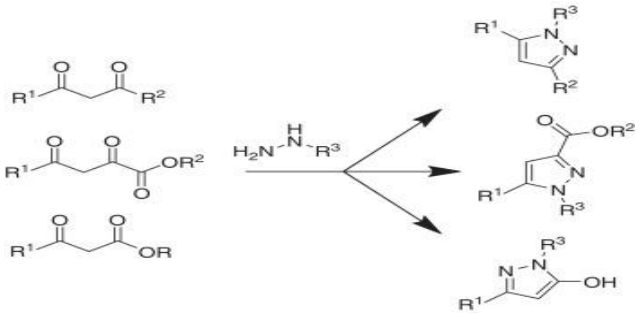
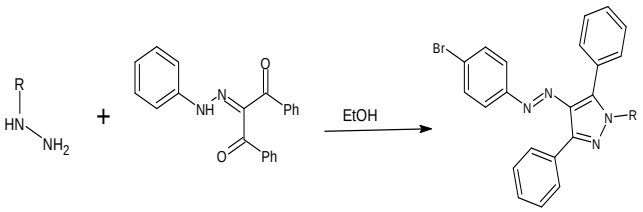


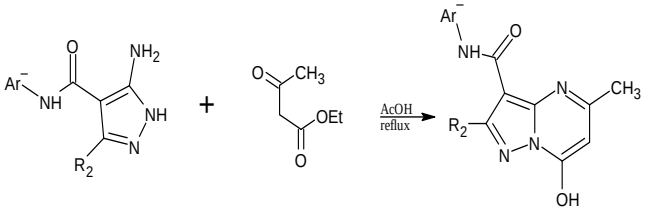
**Figure 2:** pyrazole synthesis in classical technique[23]

1. Cyclocondesation of hydrazines with 1,3-Dicarbonyl and related compounds: A series of potent carbonic anhydrase, α-glycosidase and cholinesterase inhibitors were synthesized by cyclocondesation of the 1, 3-diketone and corresponding hydrazine. (Scheme 1)[24]



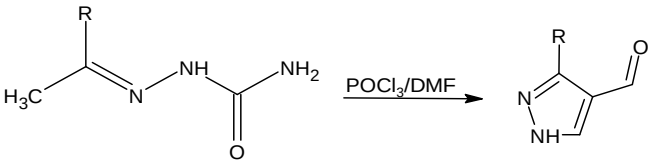
**Scheme 1**

2. Synthesis of 7-hydroxy-5-methyl-N-(aryl) pyrazolo [1,5a] pyrimidine by refluxing 5-amino-4-pyraolecarboxamide with acetate in presence of glacial acetic acid for 6 hr. (Scheme 2)[25]



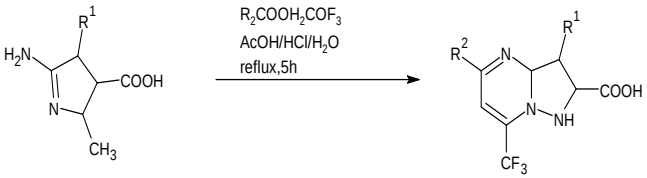
**Scheme 2**

3. 3-Substituted pyrazole-4-carbaldehyde was prepared by formylation of semicarbazones, derived from alkyl, phenyl, and cycloalkyl methyl ketones, with the complex of $POCl_3$ with dimethylformamide. (Scheme 3)[26]



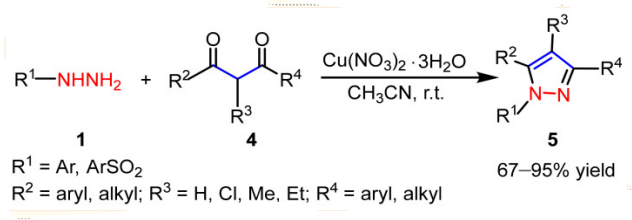
**Scheme 3**

4. Condensation reaction of derivative I with corresponding trifluro methyl a-deconate for 5hr. (Scheme 4)[27]



**Scheme 4**

5. Acid free condensation of 1, 3 diketones with substituted hydrazines to generate 1, 3, 5-trisubstituted and fully substituted pyrazoles by use of copper (II) nitrate as catalyst. (Scheme 5)[28]



**Scheme 5**

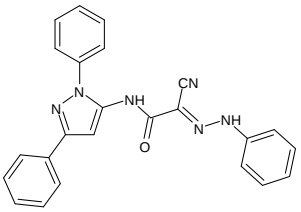
**BIOLOGICAL ACTIVITY PROFILE OF NEWER PYRAZOLE DERIVATIVES**

The main objective of present review is to search biologically active pyrazole containing derivatives with lesser adverse effects. Pyrazoles have a long history of application in pharmaceuticals, agrochemicals and are well established in literatures due to their versatile character. Literature review revealed that pyrazoles are well active heterocyclic nucleus with various pharmacological activities:

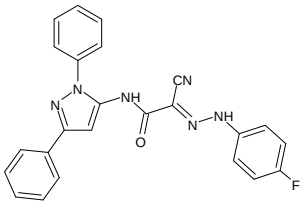
**Anticancer Activity**

Cancer is one of the most serious health issues that are currently facing, which is characterized by loss of control of growth leading to death[29]. Chemotherapy is still one of the primary paradigms for the treatment of cancer, even though its usage is limited due to toxicities and drug resistance. Pyrazole derivatives have displayed anticancer activity[30] by inhibiting various targets such as Topoisomerase II, EGFR, IGF-1R, CDKs, P13K and Tubulin, among others. Furthermore, pyrazole containing anticancer drugs are well known and are included in best selling pharmaceutical products. Crizotinib and ruxolitinib are important pyrazole based anticancer drugs.

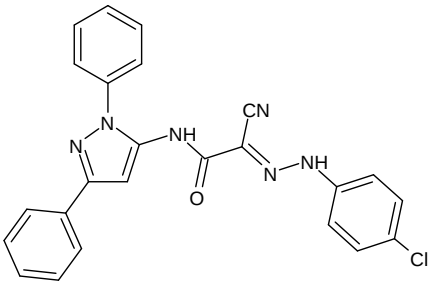
**Essraa. Z. Mohammed *et al.,*** (2021)[31], synthesized diphenyl-1H-pyrazole derivatives and evaluated for CDK2 inhibition. Among these some of them exhibited promising activity. Furthermore, some selected compounds are screened for preliminary anti proliferative activity on 60 cancer cell lines. Compounds showed favorable growth inhibitory activity and they were selected for five dose assay, exhibiting pronounced against almost full panel. The compounds were synthesized and showed inhibition of CDK isoforms. One of the compound exhibited inhibition equally for all CDK isoforms. Another compound inhibits CDK/D1 preferentially and a compound inhibits CDK1, CDK2, CDK4 and CDK7. These compounds were studied on Non small lung carcinoma (NSCC HOP-92) cell line for flow cytometry. This revealed that the compound arrests S phase and G1phase.Docking to CDK2 active binding site show similar interaction as that of ligand R- Roscovitire (PDB code; 3ddq). All these reports show that these compounds act as promising proliferative agents.



8a

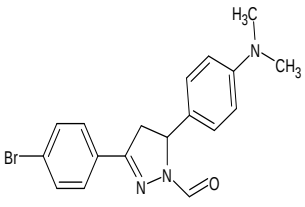


8b

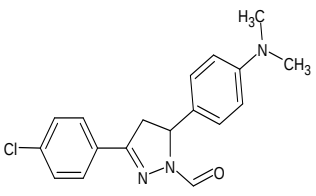


8c

**Manish Rana *et.al,*** (2021)[32] designed and synthesized N-formyl pyrazoline derivatives via Michael addition reaction through cyclization of chalcones with hydrazine hydrate in presence of formic acid. Various spectral techniques were carried out for the structural elucidation the derivatives. By the use of MTT assay anticancer activity of pyrazoline derivatives are evaluated against human lung cancer (A549), fibrosarcoma cell lines (HT 1080) and human primary normal lung cells (HFL-1). The results showed that potent analogs **3b** and **3d** exhibited promising activity against A549 (IC=12.47 ± 1.08 and 14.46 ± 2.76µM) and HT1080 (IC=11.40 ± 0.66 and 23.74 ± 13.30µM) but low toxic against HFL-1 (IC=116.47 ± 43.38 and 152.36 ± 22.18µM).

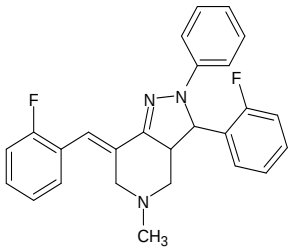


3d

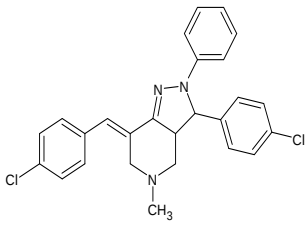


3b

**Ashraf M. Mohamed *et.al,*** (2011)[33], synthesized a series of novel pyrazolopyridine derivatives by the use of 3, 5-bisarylmethylene-1-methylpiperidone as the starting material. These newly synthesized compounds were evaluated for their anticancer activity using 59 different human tumor cell lines, representing cancers of ovary, CNS, renal, kidney as well as prostate. 3, 5-bisarylmethylene-1-methyl-4-piperidone was synthesized and used as the starting material, it was reacted with phenyl hydrazine in dioxane/ acetic acid to afford the corresponding pyrazolo[4,3-c]pyridine derivatives **2a-e**. Each compound was tested at five different concentration for the anti cancer activity. Out of these compounds five of them show highest activity, including **2b** and **2d.** Based on the studies and structural activity correlations it was clear that pyrazole and pyrimidine moieties when fused to nitrogen-methyl piperidone ring systems results in increased antitumor activities.

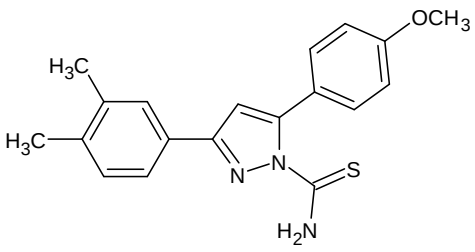


2b



2d

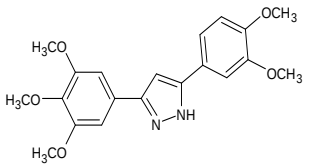
**Peng cheng Lv *et al.,*** (2010)[34], conducted synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents. Potential EGFR kinase inhibitors were discovered from two series of pyrazole derivatives (C1-C30 and D1-D16). Some of them exhibited EGFR inhibitory activity and compound **$C_5$** showed most potent EGFR inhibitory activity with $IC_{50}$ of 0.07µM. Inhibition constant for pyrazole derivatives with thiourea skeleton shows good inhibitory activity around 0.07-13.37µM. 1-acetyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives (compounds D1-D16) tested for their EGFR kinase inhibitory activity and showed moderate activity with $IC_{50}$ ranging from 15.24 to 28.69µM. These results showed that pyrazole derivatives with thiourea skeleton plays an important role in the inhibition of EGFR.



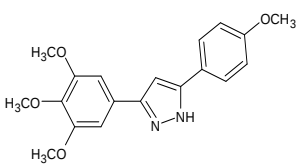
C5

**B.A. Bhat** *et al.,* (2005)[35], synthesized a series of chalcones and their corresponding pyrazole derivatives then evaluated for invitro cytotoxic activity against various human cancer cell lines. Out of various compounds were synthesized 8 compounds showed marked activity. Assay was conducted using sulforhodamine B for in vitro cytotoxicity against 12 human cancer cells, HT-29, HCT-15,

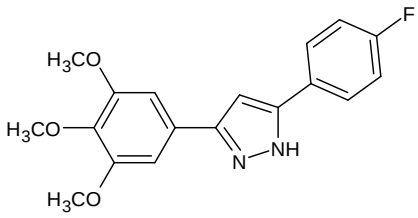
SW-620 (colon) A-549, HOP-62 (lung),Hep-2 (liver), SiHa (cervix), SKOV-3, OVCAR-5 (ovary), PC-3, DU-145 (prostate) and SNB-78 (CNS).Three compounds that showed most promising activity are **4j,4n,4s** based on $IC_{50}$ values. They reported that a novel class of chalcone derived pyrazole derivatives such as 3,5- diphenyl 1H-pyrazoles as potential cytotoxic agents. SAR studies and evaluation of more analogues are continuing.



4s



4j

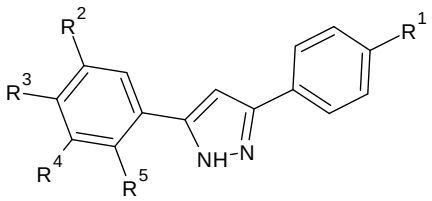


4n

**ANTI MICROBIAL ACTIVITY**

Both in developed and developing countries microbial infection becomes a major cause of illness in human[36]. It leads to huge amount of death every year. More over these pernicious microbes become resistant to drugs (Multi drug resistance) which worsen the condition[37,38]. Old antibiotics such as tetracycline, methicillin, aminoglycosides, macrolides and penicillin become ineffectual day by day. Sulfaphenazole[39] and sedaxane[40] are two clinically used pyrazole containing antibacterial and antifungal drugs.

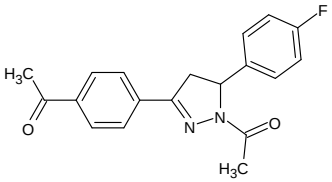
**Matthew Payne *et.al.,*** (2021)[41], synthesized some novel 3,5 substituted pyrazole derivatives and conducted their biological evaluation for anti-bacterial activity. These novel drugs help to overcome multidrug resistant bacteria which are considered as the greatest threat in modern medicine. Fifteen novel 3,5-diaryl -1H-pyrazoles are synthesized by one-pot cyclic oxidation of chalcone and hydrazine monohydrate. These synthesized pyrazole derivatives are screened against *Staphylococcus aureus* and *Escherichia coli* to determine their antibacterial potential. Based on the results compound shown below (**7p**) is bacteriostatic at MIC 8µg/mL. Furthermore, this compound is shown to be non toxic to healthy mammalian cells 3 T3-L1 at MIC and at higher concentration they are found to cause morphological changes in *B. subtilis*.



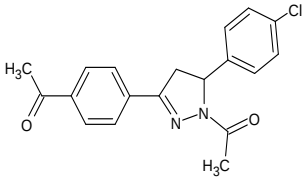
Where R1= Ph, R2= H, R3= OH, R4= OCH3, R5= H

7p

**Peng cheng Lv *et al.,***(2010)[42], conducted studies on the design, synthesis and structural activity relationships of pyrazole derivatives as potential FabH inhibitors. FabH, β-keto acyl-acyl carrier protein (ACP), synthase III is important for initiation of fatty acid biosynthesis which is essential for bacterial survival. These are highly conserved among gram positive and gram negative bacteria. In this study they synthesized fifty six 1-acetyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazole derivatives and developed as potent inhibitor of FabH. Compounds **12** and **13** on *Escherichia coli* FabH inhibitory assay and docking stimulation indicated that they were potent inhibitors of *E. coli* FabH. They not only displayed significant antibacterial activity against ACCT 35218 but also favorable activity against other five bacterial strains, indicating that they posses broad spectrum antibacterial activity.

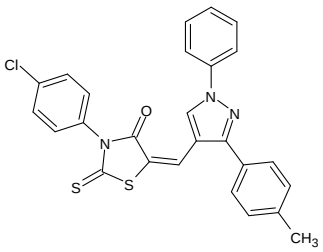


12

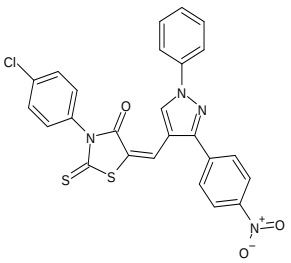


13

**H. B Bhatt *et.al.,*** (2013)[43], synthesized a series of novel pyrazole containing 2-thioxothiazolidin-4-one derivatives (**3a-h)** from 3-(4-chlorophenyl)-2-thioxothiazolidin-4-one and 1-phenyl-3-(p-substituted phenyl)-1H-pyrazole-4-carbaldehyde. Structures of synthesized compounds were confirmed by elemental analysis such as FT-IR, $^{1}H$ NMR, $^{13}C$ NMR and mass spectra. These newly synthesized compounds were screened for in vitro antibacterial activity using ampicillin as the standard drug. Compound **3c** was found active against *E. coli* (MTCC 443), compounds **3a, 3d** and **3g** against *S.aureus.* For in vitro anti fungal activity griseofulvin was used as the standard drug. Compounds **3b** and **3d** were found to have good activity against *C. albicans*.



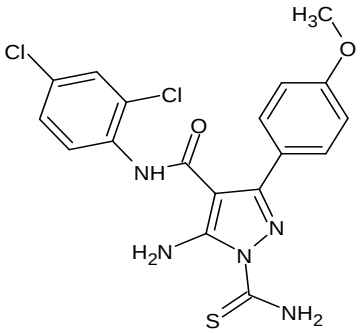
3b



3d

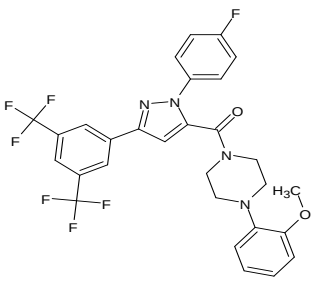
**Khadija E. Saadon. *et.al,*** (2021)[44] designed and synthesized some novel pyridine-2-one and pyrazole derivatives based on the cyanoacrylamide derivatives. Novel pyridinone derivatives were synthesized by the condensation of cyanoacrylamide derivatives in the presence of piperidine as basic catalyst. Furthermore, cyanoacrylamide derivatives reaction with hydrazine hydrate and thiosemicarbazide gives corresponding pyrazole derivatives. Structures of the compounds were confirmed by elemental analysis. Anti-bacterial activity was evaluated against four bacterial strains and results

indicated that most active five derivatives (**3a, 4a, 4b, 9** and **16**) might lead to antibacterial agent, mostly against *B. subtilis* and *P. vulgaris*. Electronic properties and geometric structure were estimated by DFT calculations. In addition, most active derivatives were further evaluated for In silico physicochemical, drug likeness and toxicity prediction. Molecular docking studies conducted with active site of Topoisomerase IV (PDB: 3FV5). It displayed good binding energy with hydrogen bonding and arene-cation interaction. Therefore, these derivatives were suggested as good antibacterial agents via Topoisomerase IV inhibitor.

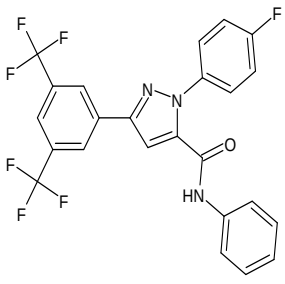


16

**Amar Patil *et.al,*** (2014)[45], prepared diaryl pyrazole carboxamide derivatives and evaluated their antifungal activities. By varying the active part of pyrazole (amide group), series of seven 5-phenyl-1H-pyrazole-3-carboxilic acid amide were synthesized. All the synthesized compounds were confirmed by $^{1}H$ NMR, $^{13}C$ NMR and mass spectroscopy and screened for antifungal activity. These newly synthesized compounds are tested against four pathogens such as Candida albicans, Aspergillus flavus, *Aspergillus fumigates* and *Aspergillus niger*. Active compounds were also tested for MIC (minimum inhibitory concentration) and MFC (minimum fungicidal concentration) which are reported in **Table 1**. Actidione was used as the reference drug, studies show that some lead molecules with appreciable antifungal activity. Compound 5a, 5c, 5d, 5e and 5g was inactive against all pathogens, but **5b** and **5f** exhibited excellent activity than standard drug. Based on the observation it can be concluded that these two compounds holds great promise and further studies are necessary to lead them as a drug molecule.



5b

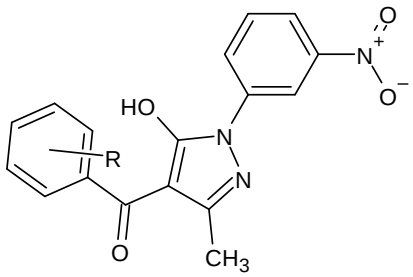


5f

| Compds | MIC and MFC µg/mL | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *C. albicans* | | *A.flavus* | | *A.fumigatus* | | *A.niger* | |
| | MIC | MFC | MIC | MFC | MIC | MFC | MIC | MFC |
| **Actidione** | **1000** | **1000** | **500** | **2000** | **1000** | **2000** | **500** | **500** |
| 4 | NA | NA | NA | NA | NA | NA | NA | NA |
| 5a | NA | NA | NA | NA | NA | NA | NA | NA |
| 5b | **250** | **500** | NA | NA | NA | NA | NA | NA |
| 5c | NA | NA | NA | NA | NA | NA | NA | NA |
| 5d | NA | NA | NA | NA | NA | NA | NA | NA |
| 5e | NA | NA | NA | NA | NA | NA | NA | NA |
| 5f | **500** | **500** | NA | NA | NA | NA | NA | NA |
| 5g | NA | NA | NA | NA | NA | NA | NA | NA |

**Table 1**[45]

**Mehta Hardik Ashokbhai *et.al,*** (2014)[46], synthesized various substituted pyrazole derivatives and evaluated for their antimicrobial activity. Pyrazolone derivatives are prepared by cyclization of phenyl hydrazine with EAA and further treated with benzoyl chlorides to get substituted pyrazole moiety. The structure of newly synthesized compounds are confirmed by spectral analysis and screened for antimicrobial activity against gram positive bacterial strain such as *B.cocous* and *B. subtilis* & gram negative bacterial strain such as *Proteus vulgaris* and *Escherichia coli*. The antifungal test was carried out against *Aspergillus niger.* Most of the synthesized compounds show significant activity against tested bacteria and fungi (Table 2).



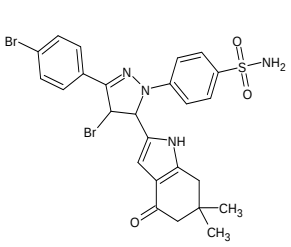
General structure of synthesized compounds

| Sr. No. | R | Antimicrobial activity Zone of inhibition (mm) | | | | Antifungal activity Zone of inhibition (mm) |
|---|---|---|---|---|---|---|
| | | *B. cocous* | *B.subtillus* | *P.vulgaris* | *E. coli* | *A. niger* |
| A | 4-F | 15 | 17 | 17 | 18 | 19 |
| B | 3,4-dimethoxy | 14 | 18 | 17 | 19 | 18 |
| C | -H | 16 | 16 | 17 | 18 | 15 |
| D | 4-$OCH_3$ | 17 | 16 | 18 | 18 | 14 |
| E | 2-OH | 17 | 16 | 19 | 17 | 12 |
| F | 2-Cl | 19 | 18 | 15 | 17 | 18 |
| G | 3-OH | 16 | 20 | 18 | 17 | 16 |
| H | 3-Cl | 17 | 22 | 14 | 16 | 14 |
| I | 2-Br | 19 | 19 | 16 | 19 | 14 |
| J | 3-$OCH_3$ | 18 | 17 | 16 | 18 | 14 |
| K | 3-$OCF_3$ | 16 | 15 | 18 | 17 | 15 |
| | Amoxycillin | 21 | 26 | 20 | 24 | - |
| | Benzoylpenicillin | 22 | 22 | 25 | 22 | - |
| | Ciprofloxacin | 19 | 21 | 23 | 22 | - |
| | Erythromycin | 21 | 16 | 18 | 21 | - |
| | Greseofulvin | - | - | - | - | 26 |

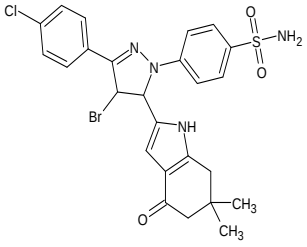
**Table 2**[46]

**Seham Y. Hassan *et.al,*** (2013)[47], conducted a study to synthesize and evaluate the newly series of pyrazolines and pyrazoles for its antimicrobial and antifungal activity. Compounds (2-44) were screened for its biological activity against *Escherichia coli, pseudomonas aeruginosa, Staphylococcus aurous* and *Candida albicans*. None of the compounds displayed activity against E. coli and P.

aeruginosa. It was noted that compound **16** showed good antimicrobial activity against Staphylococcus aureus comparable to that of ampicillin and ciprofloxacin, while compound **17** showed activity than that of ampicillin, ciprofloxacin and imipenam. Also compared to clotrimazole compound 17 has comparable IZ (inhibition zone measurement) against Candida albicans. MIC value of compounds 19, 20, 31 indicates good antifungal activity. Based on the results, we can say that compounds 16, 17, 19 and 20 which is having benzenesulfonamide as substituents displayed good antimicrobial and antifungal activity.



16

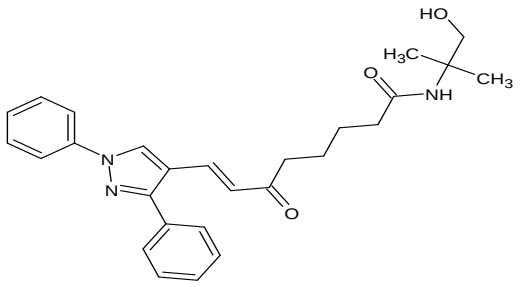


17

## ANTI INFLAMMATORY ACTIVITY

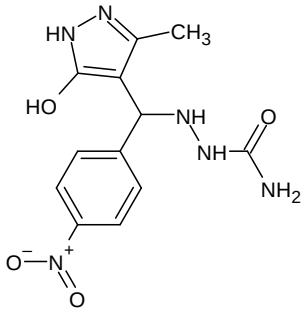
Non-steroidal anti-inflammatory drugs (NSAIDS) continue to be the cornerstone of managing pain and inflammation in chronic condition, even though prolonged use of NSAIDS was found to be associated with several adverse effects such as ulceration, gastrointestinal erosions, bleeding etc[48]. Pyrazole derivatives are well known for their anti-inflammatory action. Commercially available pyrazole moiety containing COX-2 inhibitors are Celecoxib[49], Ramifenazone[50], Lonazolac[51] and Rimonabant[52].

**Azza. T. Taher *et.al,*** (2019)[53] conducted synthesis and biological evaluation of novel pyrazole derivatives. Various amine moieties bearing pyrazole derivatives are studied by lengthening of the carbon chain. Pyrazole ring are combined with either pyrazole or quinoline rings (floctafenine derivatives) through the synthesis of chalcones and followed by cyclization into pyrazolines. Structures of targeted compound were confirmed by elemental analysis and spectral data. Newly synthesized compounds are compared to indomethacin as a reference drug for their anti inflammatory and analgesic activity. The results showed that both anti inflammatory and analgesic activity were affected by the length of carbon chain. Finally, a compound (**14b**) that had the highest binding affinity among the selected compounds and compatible with anti inflammatory results is shown below.

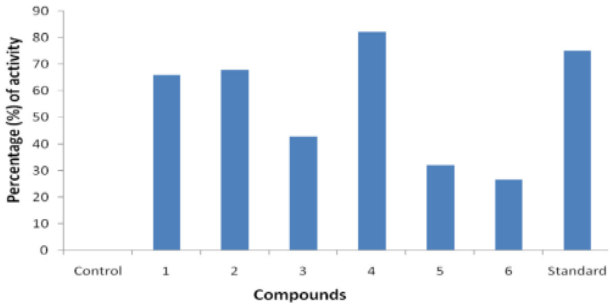


14b

**R. Surendra Kumar *et.al,*** (2015)[54] performed synthesis of new series pyrazole derivatives by the use of ultrasound radiation. Synthesized compounds identified by IR, 1H NMR, 13C NMR, mass and elemental analysis. Six compounds were synthesized by this technique and evaluated for anti-inflammatory (Graph 1), anti-bacterial and antifungal activity. Compound 4 showed better anti-inflammatory activity when compared to standard drug diclofenac sodium. Compound 3 showed MIC: 0.25µg/ML found to be exceedingly antibacterial against gram negative *Escherichia coli* and compound **4** highly active against gram positive streptococcus epidermidis compared to ciprofloxacin as standard. Compounds screened for antifungal activity against *Aspergillus niger* taking reference as propionate to clotrimazole and found compound 2 (MIC: 1µg/ML) to have high antifungal activity.



**Compound 4:** Anti-inflammatory activity



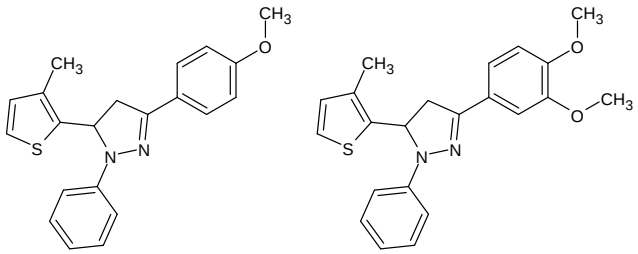

**Graph 1:** Anti-inflammatory activity of compounds (1-6)[54]

## ANTIOXIDANT ACTIVITY

Oxidative stress persuade by the free radical damage cell membrane, and nucleic acids, which results in aging, cancer, atherosclerosis and Alzheimer's disease. Pyrazole containing drug molecules remain as a choice in medicinal chemistry as practical antioxidant agents[55].

**Karthik kumara *et.al,*** (2021)[55] presented study by use of amberlyst-15 catalyst and efficient synthesis of 2-pyrazoline derivatives, 5(a-g) via (3+2) annulations of chalcones with phenylhydrazines. Structural proof of newly synthesized compounds was offered by spectral analysis and crystallographic studies are conducted. DPPH and radical scavenging activities are studied to evaluate the antioxidant properties (Table 3). Among the compounds, compound **5g** and **5h** showed excellent DPPH ($IC_{50}$ = 0.245 ± 0.01 and 0.284 ± 0.02µM) and hydroxy radical scavenging activities ($IC_{50}$ = 0.905 ± 0.01 and 0.892 ± 0.01µM) comparable with respective controls, ascorbic

acid and BHA (Table 1). Moreover, molecular docking and ADME/Tox studies indicated that these compounds have good antioxidant property and might lead antioxidant for further investigations.



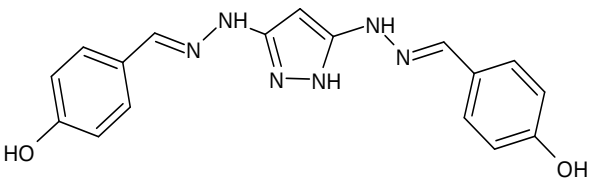
**5g** **5h**

DPPH and hydroxy radical scavenging assay of compound 5(a-i).

| Compounds | DPPH radical assay | Hydroxyl radical assay |
|---|---|---|
| | $IC_{50}$ (μM)[a] | $IC_{50}$ (μM)[b] |
| 5a | 0.807 ± 0.01 | 3.534 ± 0.01 |
| 5b | 0.488 ± 0.02 | 1.439 ± 0.01 |
| 5c | 0.529 ± 0.02 | 1.813 ± 0.01 |
| 5d | 0.673 ± 0.01 | 2.641 ± 0.02 |
| 5e | 0.616 ± 0.03 | 1.965 ± 0.04 |
| 5f | 0.694 ± 0.04 | 2.649 ± 0.02 |
| 5g | 0.245 ± 0.01 | 0.905 ± 0.01 |
| 5h | 0.284 ± 0.02 | 0.892 ± 0.01 |
| 5i | 0.491 ± 0.01 | 1.913 ± 0.04 |
| AA* | 0.483 ± 0.01 | – |
| BHA** | – | 1.739 ± 0.01 |

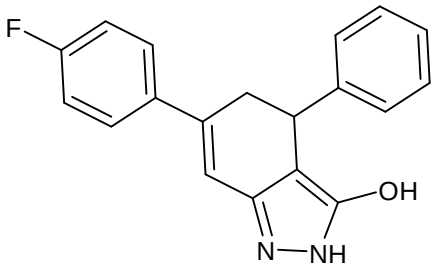
Table 3[55]

**Ebraheem Abdu Musad *et.al,*** (2011)[56] synthesized some novel bis( 1,3,4-oxadiazole),3,5-bis(substituted)pyrazoles and isoxazoles via oxidative cyclization of some diarylhydrazones using chloramines-T and cyclocondensation reaction with hydrazine hydrate and hydroxylamine hydrochloride respectively. These compounds are tested for antioxidant and antimicrobial activity. Compared to vitamin C as standard compounds 2e, 3b and 4a showed good antioxidant activity at 10μg/ML and compounds 2a, 3a, 3f and 4a showed good antimicrobial activity at 100μg/ML against ciprofloxacin. DPPH radical scavenging activity at 10μg/ml and anti lipid peroxidation at 40μg/ml. 2,2-diphenyl-1-picryl hydrazl(DPPH) radical scavenging activity evaluation is a standard assay to determine antioxidant activity. Compounds 3(a,b,d,i) series **3b** that has substitution on phenyl ring highly favored antioxidant activity.

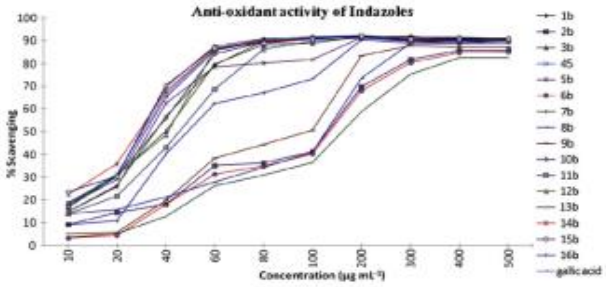


3b

**N.A. Shakil *et.al,*** (2021)[57] synthesized novel chalcone based 2H-indazol-3-ol and 6-carbethoxy-2-cyclohexen-1-one derivatives and are characterized by spectral techniques like IR, NMR, GC-MS, 13C NMR and 1H NMR. Newly synthesized compounds were screened for antifungal, antibacterial and antioxidant activity. Cyclohexane derivatives showed better antimicrobial activity than parent chalcones, whereas indazole derivatives showed good antioxidant activity. Among the studied compounds 15 was found to be good antifungal agent (against *Rhizoctonia solani*, $LC_{50}$ = 2.36μg/ml) and 15b as antibacterial agent (against *Klebsiella pneumonia*, MIC = 24.68μg/ml). Compound **14b** (indazole derivative) found to be most active antioxidant ($IC_{50}$=19.81μg/ml) when tested at different concentration (Graph 2)



14b



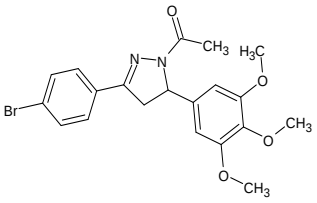

**Graph 2:** Antioxidant activity of indazole derivatives[57]

**ANTI TUBERCULAR ACTIVITY**

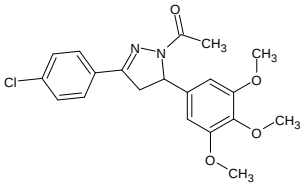
Tuberculosis (TB) is a rejuvenating global health threat that caused by infectious bacillus called Mycobacterium tuberculosis and it is the leading infectious killer disease in the world, claiming 1.5 million lives every year. Despite of the progress in anti-tubercular agents, multi-drug resistance tuberculosis (MDR-TB), extremely drug resistance tuberculosis (XDR-TB) and HIV co-infection are considered as stumbling block in controlling tubercular infection. Therefore, new chemical entities have to be discovered with novel mechanism of action that are safe and highly efficient[58].

**Vinay Pathak *et.al,*** (2014)[59] conducted studies on 3,5-diphenyl-4,5-dihydro-1H-pyrazoles and 4,6-diarylpyrimidines synthesized and evaluated for their activities as anti-tubercular agents. Various derivatives are synthesized for these compounds and screened for anti-tubercular activity against mycobacterium tuberculosis H37Rv strain. Out of all compounds synthesized four showed significant activity at MIC values 25, 25, 12.5, and 12.5μM concentration. Invitro cytotoxicity was evaluated using MTT assay in non cancerous hepatic monocytes (THP-1)cells and found that MIC values approximately double of $IC_{50}$ values therefore considering anti tubercular activity and cytotoxicity, two (**7b** and **7c**) from the four

most active compound were showed to be safe as their MIC values much lower than cytotoxic values. Compounds **7b** and **7c** are considered to be eight times selective toward anti-tubercular activity versus healthy cell.




7b




7c

## CONCLUSION

From the extensive review of pyrazole derivatives carried out it can be easily concluded that pyrazole derivatives display diverse pharmacological activities against dreaded disorders like cancer, inflammatory, bacterial, fungal and mycobacterial infections. This versatility of synthesized derivatives has obviously turned the attention of medicinal as well as synthetic chemist to strategize newer synthetic methods as well as to carry out their biological evaluation so that more and more active and comparatively safer pyrazole derivatives are delivered to the therapeutic world. In this endeavor, newer arsenals like combinatorial library synthesis, DNA hybridization, artificial intelligence and robotics and many more may be utilized by the scientific community so that ultimately effective and safe drug scaffolds are presented to the therapeutic world.

## REFERENCES

1. Singh G, Chandra P, Sachan N. Chemistry and pharmacological activities of pyrazole and pyrazole derivatives: A review. Inter. J. Pharm. Sci. Rev. Res. 2020;65:201-14.
2. Speicher A, Eicher T, Hauptmann S. The Chemistry of Heterocycles: Structures, Reactions, Synthesis and Applications.
3. Yerragunta V, Suman D, Anusha V, Patil P, Naresh M. Pyrazole and its biological activity. PharmaTutor. 2014 Jan 15;2(1):40-8.
4. Krygowski TM, Anulewicz R, Cyrański MK, Puchala A, Rasala D. Separation of the energetic and geometric contribution to the aromaticity. Part IX. Aromaticity of pyrazoles in dependence on the kind of substitution. Tetrahedron. 1998 Oct 1;54(40):12295-300.
5. Barry WJ. More Heterocyclic Chemistry. Nature. 1967 Dec;216(5121):1252-3.
6. Costa RF, Turones LC, Cavalcante KV, Rosa Júnior IA, Xavier CH, Rosseto LP, Napolitano HB, Castro PF, Neto ML, Galvão GM, Menegatti R. Heterocyclic compounds: pharmacology of pyrazole analogs from rational structural considerations. Frontiers in pharmacology. 2021 May 10;12:666725.
7. Chauhan A, Sharma PK, Kaushik N. Pyrazole: a versatile moiety. Int. J. ChemTech Res. 2011;3(1):11-7.
8. Kumara K, Prabhudeva MG, Vagish CB, Vivek HK, Rai KM, Lokanath NK, Kumar KA. Design, synthesis, characterization, and antioxidant activity studies of novel thienyl-pyrazoles. Heliyon. 2021 Jul 1;7(7):e07592.
9. Badgujar JR, More DH, Meshram JS. Synthesis, antimicrobial and antioxidant activity of pyrazole based sulfonamide derivatives. Indian journal of microbiology. 2018 Mar;58(1):93-9.
10. El-Moghazy SM, Barsoum FF, Abdel-Rahman HM, Marzouk AA. Synthesis and anti-inflammatory activity of some pyrazole derivatives. Medicinal Chemistry Research. 2012 Aug;21(8):1722-33.
11. Bansal G, Singh S, Monga V, Thanikachalam PV, Chawla P. Synthesis and biological evaluation of thiazolidine-2, 4-dione-pyrazole conjugates as antidiabetic, anti-inflammatory and antioxidant agents. Bioorganic chemistry. 2019 Nov 1;92:103271.
12. Saleh I, Kc HR, Roy S, Abugazleh MK, Ali H, Gilmore D, Alam MA. Design, synthesis, and antibacterial activity of N-(trifluoromethyl) phenyl substituted pyrazole derivatives. RSC Medicinal Chemistry. 2021;12(10):1690-7.
13. Hassan AS, Askar AA, Naglah AM, Almehizia AA, Ragab A. Discovery of new schiff bases tethered pyrazole moiety: design, synthesis, biological evaluation, and molecular docking study as dual targeting DHFR/DNA gyrase inhibitors with immunomodulatory activity. Molecules. 2020 Jan;25(11):2593.
14. Karthikeyan MS, Holla BS, Kumari NS. Synthesis and antimicrobial studies on novel chloro-fluorine containing hydroxy pyrazolines. European Journal of Medicinal Chemistry. 2007 Jan 1;42(1):30-6.
15. Abd El-Karim SS, Mohamed HS, Abdelhameed MF, Amr AE, Almehizia AA, Nossier ES. Design, synthesis and molecular docking of new pyrazole-thiazolidinones as potent anti-inflammatory and analgesic agents with TNF-α inhibitory activity. Bioorganic chemistry. 2021 Jun 1;111:104827.
16. Vicentini CB, Romagnoli C, Andreotti E, Mares D. Synthetic pyrazole derivatives as growth inhibitors of some phytopathogenic fungi. Journal of agricultural and food chemistry. 2007 Dec 12;55(25):10331-8.
17. Michon V, du Penhoat CH, Tombret F, Gillardin JM, Lepage F, Berthon L. Preparation, structural analysis and anticonvulsant activity of 3-and 5-aminopyrazole N-benzoyl derivatives. European journal of medicinal chemistry. 1995 Jan 1;30(2):147-55.
18. Kees KL, Fitzgerald JJ, Steiner KE, Mattes JF, Mihan B, Tosi T, Mondoro D, McCaleb ML. New potent antihyperglycemic agents in db/db mice: Synthesis and structure− activity relationship studies of (4-substituted benzyl)(trifluoromethyl) pyrazoles and-pyrazolones. Journal of medicinal chemistry. 1996 Sep 27;39(20):3920-8.
19. Domiati S, El-Mallah A, Ghoneim A, Bekhit A, El Razik HA. Evaluation of anti-inflammatory, analgesic activities, and side effects of some pyrazole derivatives. Inflammopharmacology. 2016 Aug;24(4):163-72.
20. Akhtar MJ, Khan AA, Ali Z, Dewangan RP, Rafi M, Hassan MQ, Akhtar MS, Siddiqui AA, Partap S, Pasha S, Yar MS. Synthesis of stable benzimidazole derivatives bearing pyrazole as anticancer and EGFR receptor inhibitors. Bioorganic Chemistry. 2018 Aug 1;78:158-69.

21. Sigroha S, Narasimhan B, Kumar P, Khatkar A, Ramasamy K, Mani V, Mishra RK, Majeed AB. Design, synthesis, antimicrobial, anticancer evaluation, and QSAR studies of 4-(substituted benzylidene-amino)-1, 5-dimethyl-2-phenyl-1, 2-dihydropyrazol-3-ones. Medicinal Chemistry Research. 2012 Nov;21(11):3863-75.

22. Balbi A, Anzaldi M, Macciò C, Aiello C, Mazzei M, Gangemi R, Castagnola P, Miele M, Rosano C, Viale M. Synthesis and biological evaluation of novel pyrazole derivatives with anticancer activity. European journal of medicinal chemistry. 2011 Nov 1;46(11):5293-309.

23. Grierson DS, Husson HP. Heteroatom manipulation. Comprehensive Organic Synthesis. 1991;6:909-47.

24. Turkan F, Cetin A, Taslimi P, Gulçin İ. Some pyrazoles derivatives: Potent carbonic anhydrase, α-glycosidase, and cholinesterase enzymes inhibitors. Archiv der pharmazie. 2018 Oct;351(10):1800200.

25. Hassan AS, Hafez TS, Osman SA, Ali MM. Synthesis and in vitro cytotoxic activity of novel pyrazolo [1, 5-$ a $] pyrimidines and related Schiff bases. Turkish Journal of Chemistry. 2015;39(5):1102-13.

26. Lebedev AV, Lebedeva AB, Sheludyakov VD, Kovaleva EA, Ustinova OL, Kozhevnikov IB. Vilsmeier formylation of hydrazones and semicarbazones derived from alkyl, benzyl, and cycloalkyl methyl ketones. Russian journal of general chemistry. 2005 Mar;75(3):412-6.

27. Dalinger IL, Vatsadse IA, Shevelev SA, Ivachtchenko AV. Liquid-phase synthesis of combinatorial libraries based on 7-trifluoromethyl-substituted pyrazolo [1, 5-a] pyrimidine scaffold. Journal of combinatorial chemistry. 2005 Mar 14;7(2):236-45.

28. Wang H, Sun X, Zhang S, Liu G, Wang C, Zhu L, Zhang H. Efficient copper-catalyzed synthesis of substituted pyrazoles at room temperature. Synlett. 2018 Dec;29(20):2689-92.

29. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015 Mar 1;136(5):E359-86.

30. Nitulescu GM, Draghici C, Missir AV. Synthesis of new pyrazole derivatives and their anticancer evaluation. European journal of medicinal chemistry. 2010 Nov 1;45(11):4914-9.

31. Mohammed EZ, Mahmoud WR, George RF, Hassan GS, Omar FA, Georgey HH. Synthesis, in vitro anticancer activity and in silico studies of certain pyrazole-based derivatives as potential inhibitors of cyclin dependent kinases (CDKs). Bioorganic Chemistry. 2021 Nov 1;116:105347.

32. Rana M, Arif R, Khan FI, Maurya V, Singh R, Faizan MI, Yasmeen S, Dar SH, Alam R, Sahu A, Ahmad T. Pyrazoline analogs as potential anticancer agents and their apoptosis, molecular docking, MD simulation, DNA binding and antioxidant studies. Bioorganic Chemistry. 2021 Mar 1;108:104665.

33. Mohamed AM, El-Sayed WA, Alsharari MA, Al-Qalawi HR, Germoush MO. Anticancer activities of some newly synthesized pyrazole and pyrimidine derivatives. Archives of pharmacal research. 2013 Sep;36(9):1055-65.

34. Lv PC, Li HQ, Sun J, Zhou Y, Zhu HL. Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents. Bioorganic & medicinal chemistry. 2010 Jul 1;18(13):4606-14.

35. Bhat BA, Dhar KL, Puri SC, Saxena AK, Shanmugavel M, Qazi GN. Synthesis and biological evaluation of chalcones and their derived pyrazoles as potential cytotoxic agents. Bioorganic & medicinal chemistry letters. 2005 Jun 15;15(12):3177-80.

36. Todar K. Textbook of bacteriology. 2019.

37. Shrivastava SR, Shrivastava PS, Ramasamy J. Responding to the challenge of antibiotic resistance: World Health Organization. Journal of Research in Medical Sciences. 2018 Jan 1;23(1):21.

38. La Fauci V, Alessi V. Antibiotic resistance: Where are we going. Ann Ig. 2018 Jul 1;30(4):52-7.

39. Surve N, Bagde U. Effect of sulphaphenazole on pathogenic microorganism Klebsiella aerogenes. International Journal of Biology. 2011 Apr 1;3(2):106.

40. Zeun R, Scalliet G, Oostendorp M. Biological activity of sedaxane–a novel broad-spectrum fungicide for seed treatment. Pest management science. 2013 Apr;69(4):527-34.

41. Payne M, Bottomley AL, Och A, Asmara AP, Harry EJ, Ung AT. Synthesis and biological evaluation of 3, 5-substituted pyrazoles as possible antibacterial agents. Bioorganic & medicinal chemistry. 2021 Oct 15;48:116401.

42. Lv PC, Sun J, Luo Y, Yang Y, Zhu HL. Design, synthesis, and structure–activity relationships of pyrazole derivatives as potential FabH inhibitors. Bioorganic & medicinal chemistry letters. 2010 Aug 1;20(15):4657-60.

43. B'Bhatt H, Sharma S. Synthesis and antimicrobial activity of pyrazole nucleus containing 2-thioxothiazolidin-4-one derivatives. Arabian Journal of Chemistry. 2017 May 1;10:S1590-6.

44. Saadon KE, Taha NM, Mahmoud NA, Elhagali GA, Ragab A. Synthesis, characterization, and in vitro antibacterial activity of some new pyridinone and pyrazole derivatives with some in silico ADME and molecular modeling study. Journal of the Iranian Chemical Society. 2022 May 12:1-9.

45. Patil A, Jadhav R, Raundal H, Sharma L, Badgujar R, Bobade V. Synthesis and antifungal activities of diaryl pyrazoles carboxamide derivatives. Journal of Chemical and Pharmaceutical Research. 2014;6(8):218-23.

46. Ashokbhai M, Merambhai P, Narbherambhai P, Kaushik K, Praful K. Synthesis of substituted pyrazole derivatives and evaluation of their antimicrobial activity. Arch. Appl. Sci. Res. 2014;6(3):74-7.

47. Hassan SY. Synthesis, antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives. Molecules. 2013 Feb 28;18(3):2683-711.

48. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal antiinflammatory drugs. New England Journal of Medicine. 1992 Sep 10;327(11):749-54.

49. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM,

Rogers RS. Synthesis and biological evaluation of the 1, 5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H-pyrazol-1-yl] benzenesulfonamide (SC-58635, celecoxib). Journal of medicinal chemistry. 1997 Apr 25;40(9):1347-65.

50. Fioravanti R, Bolasco A, Manna F, Rossi F, Orallo F, Ortuso F, Alcaro S, Cirilli R. Synthesis and biological evaluation of N-substituted-3, 5-diphenyl-2-pyrazoline derivatives as cyclooxygenase (COX-2) inhibitors. European journal of medicinal chemistry. 2010 Dec 1;45(12):6135-8.

51. Riedel R. Lonazolac-Calcium (3-(p-chlorophenyl)-1-phenylpyrazole-4)-acetate/pharmacological properties of a new antiinflammatory/antirheumatic drug [various animals]. Arzneimittelforschung-Drug Research (Germany, FR). 1981.

52. Isidro ML, Cordido F. Drug treatment of obesity: established and emerging therapies. Mini reviews in medicinal chemistry. 2009 Jun 1;9(6):664-73.

53. Taher AT, Sarg MT, Ali NR, Elnagdi NH. Design, synthesis, modeling studies and biological screening of novel pyrazole derivatives as potential analgesic and anti-inflammatory agents. Bioorganic chemistry. 2019 Aug 1;89:103023.

54. Kumar RS, Arif IA, Ahamed A, Idhayadhulla A. Anti-inflammatory and antimicrobial activities of novel pyrazole analogues. Saudi journal of biological sciences. 2016 Sep 1;23(5):614-20.

55. Kumara K, Prabhudeva MG, Vagish CB, Vivek HK, Rai KM, Lokanath NK, Kumar KA. Design, synthesis, characterization, and antioxidant activity studies of novel thienyl-pyrazoles. Heliyon. 2021 Jul 1;7(7):e07592.

56. Musad EA, Mohamed R, Saeed BA, Vishwanath BS, Rai KL. Synthesis and evaluation of antioxidant and antibacterial activities of new substituted bis (1, 3, 4-oxadiazoles), 3, 5-bis (substituted) pyrazoles and isoxazoles. Bioorganic & medicinal chemistry letters. 2011 Jun 15;21(12):3536-40.

57. Shakil NA, Singh MK, Sathiyendiran M, Kumar J, Padaria JC. Microwave synthesis, characterization and bio-efficacy evaluation of novel chalcone based 6-carbethoxy-2-cyclohexen-1-one and 2H-indazol-3-ol derivatives. European Journal of Medicinal Chemistry. 2013 Jan 1;59:120-31.

58. Shaikh SI, Zaheer ZA, Mokale SN, Lokwani DK. Development of new pyrazole hybrids as antitubercular agents: Synthesis, biological evaluation and molecular docking study. Inter. J. Pharm. Pharm. Sci. 2017;19:50-6.

59. Pathak V, Maurya HK, Sharma S, Srivastava KK, Gupta A. Synthesis and biological evaluation of substituted 4, 6-diarylpyrimidines and 3, 5-diphenyl-4, 5-dihydro-1H-pyrazoles as anti-tubercular agents. Bioorganic & Medicinal Chemistry Letters. 2014 Jul 1;24(13):2892-6.

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