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Synthesis and Biological Activities of Some Pyrazole Derivatives: A Comprehensive Review

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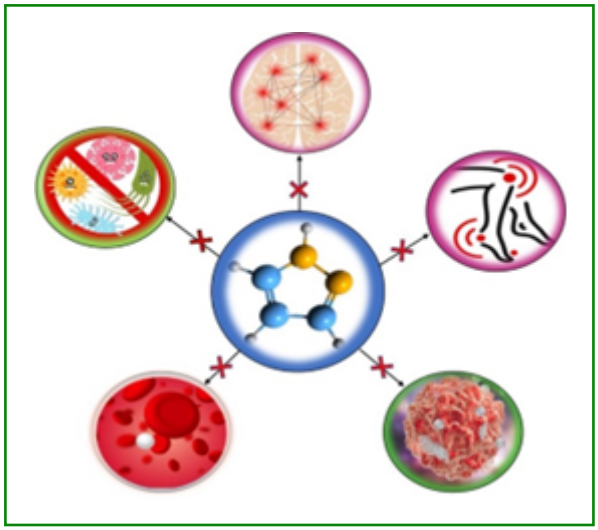
Graphical Abstract



Abstract

Nitrogen-containing heterocyclic compounds with five members are called pyrazoles. Derivatives of pyrazole have been used extensively in fluorescent compounds, agricultural chemicals, and colors. Nucleus can be found in pharmaceutical products across a range of therapeutic categories. Many researchers have been interested in studying the chemical and biological skeleton of this nucleus because of the diversity found in the biological field. The various synthesis techniques and pharmacological characteristics of pyrazole derivatives are highlighted in this review. Research on the biological activity and synthesis of pyrazole derivatives, conducted by numerous scientists worldwide is published. Because of its significant diversity in biological activity, pyrazole and its derivatives has become a prominent scaffold that has caught the interest of medicinal chemistry researchers. Almost all pharmacological activities are found in pyrazole and its derivatives, which are regarded as an important

pharmacological active scaffold. Meanwhile, target structures known as pyrazole derivatives have been created and have shown a wide range of biological functions, including anti-inflammatory, anti-tumor, anti-viral, anti-microbial, anti-hepatotoxic, anti-oxidant, hypoglycemic, anti-convulsant and anti-proliferative. The newly synthesized compound structures were validated using elemental analysis, mass spectrum investigations, 1H and 13C NMR, FT-IR, etc. The results of published studies on the synthesis and biological activity of pyrazole derivatives are compiled in this review.

Keywords: Pyrazole Derivatives; Synthesis; Anti-Tumor Activity; Anti- Microbial Activity; Hypoglycemic Activity; Anti-Convulsant Activity

Abbreviations: FDA: Food and Drug Administration; SRB: Sulforhodamine B; MIC: Minimum Inhibitory Concentration; ADME: Absorption Distribution Metabolism and Excretion; MBC: Minimum Bactericidal Concentration, MFC: Minimum Fungicidal Concentration; DM: Diabetes Mellitus.

Introduction

Pyrazole is an unsaturated five-membered heterocyclic ring consisting of two nitrogen heteroatoms and compounds. It is beneficial in organic synthesis. In auto-substitution, a five-membered ring that contains three carbon atoms. With pKb of 11.5 (pKa of the conjugate acid is 2.49 at 25°C). It is a weak base and Pyrazole is an organic compound with azole group. Pyrazole ring is widely used in medicinal chemistry and drug development strategies. Pyrazole is a compound that has a formula of C3H4N2. Other aromatic compounds with two double bonds, namely parasol, indazole, and iso-indazole, are nonaromatic isomers, including pyrazolenine, isopyrole, and 1H-pyrazole-2-ium salts. It has been reported that pyrazole derivatives possess anti-inflammatory, anticarcinogenic, antiviral, antiasthmatic, antimalarial, antimicrobial, antibacterial, diuretic, hyperlipidemia, antipyretic, antidepressant, anti-proliferative, antimycotics, and other properties [1]. There are several ways to make pyrazole, including the 1,3-dipolar cycloaddition of diazo compounds with alkenes or alkynes (as 1,3- dipoles). There is a significant group of molecules that possess a vast array of biological functions. Over the last ten years, investigations have documented a growing amount of information regarding diverse pyrazole derivatives and their numerous physiological and pharmacological effects. In 1883, German scientist Ludwig Knorr gave a name to this chemical class as pyrazole. In 1898, Hons Von Pechmann used acetylene and diazomethane in a traditional process to create Pyrazole. Watermelon seeds are where the first naturally occurring pyrazole was extracted in 1959. It was thought that pyrazoles could not be obtained naturally until 1954 when the first naturally occurring pyrazole derivatives were discovered. More than 40 medications containing pyrazoles have been approved by the Food and Drug Administration (FDA) for the treatment of various clinical conditions over the past few decades—the colorless crystalline solid known as Pyrazole has a pyridine-like smell [1,2].

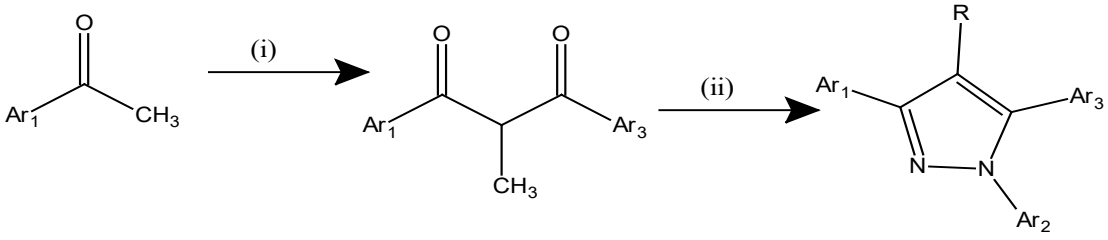
Preparation of Pyrazole Using Synthetic Methods

Several studies have reported that the synthetic methods of pyrazole are discussed below:

- Dhawan, et al. [3] Revealed how to synthesize indeno (1,2-c) pyrazol-4(1H)-ones through the production of intermediates in good yields during the condensation of 2-benzoylindane-1,3-diones with 2-hydrazinobenzothiazoles, as illustrated in Figure 1.
- Ming, et al. [4] produced N-substituted benzoyl pyrazoles in good yields (58–88%) by refluxing, for 6-10 hours, an equimolar mixture of acetylacetone and trifluoromethyl that contained substituted benzoyl hydrazine in ethanol with a few drops of HCl, as illustrated in Figure 2.
- Chougala, et al. [5] Reported a green, environmentally friendly method for synthesizing substituted 4-coumarinyl-pyranoido (2,3-c) pyrazoles in high yields (77-94%) using a multi-component reaction involving equimolar ethyl acetoacetate, hydrazine hydrate, suitably substituted 4-formylcoumarins, and suitably substituted malononitriles. This reaction was carried out using DMAP in a water-ethanol medium at ambient temperature. As illustrated in Figure 3.
- Huang, et al. [6] Oxidized pyrazolines refluxing at a high temperature for 48 hours, leading to the regioselective synthesis of 4-alkyl-1,3,5-triarylpyrazoles in high yields (86–88%). Figure 4 illustrates how the pyrazolines were previously made by regioselective cyclo condensation of diarylenones and amino hydrazine in DMF under an inert atmosphere, which was followed by alkylation of C-4 of the pyrazoline ring.
- Markovic, et al. [7] Using water as a solvent and created a straightforward, environmentally friendly, and extremely effective method for synthesizing 3,5-disubstituted pyrazoles by refluxing an equimolar mixture of suitable 4-aryl (hetaryl, alkyl)-2,4-diketoester or 1,3-diketone and semicarbazide hydrochloride. The result was excellent yields, ranging from 85 to 98% as shown in

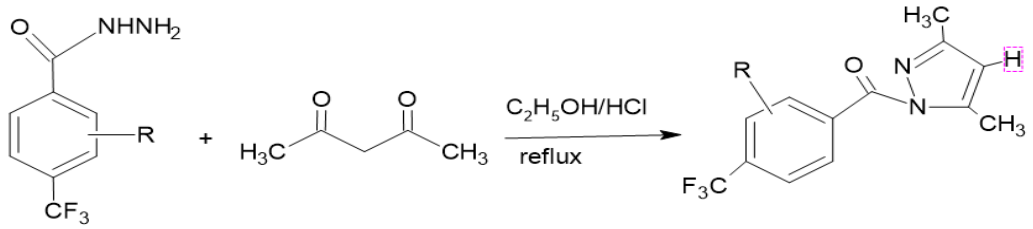
Figure 5.

- Fang, et al. [8] created a quick and effective method for synthesizing a range of 2H-indazoles using [3+2] dipolar cycloaddition of synthons (1equiv.) and arynes (1.2equiv.), with good to excellent yields (63-98%) as shown in Figure 6.
- Reddy, et al. [9] revealed, as illustrated in Figure 7, a fast, easy, and environmentally friendly way to synthesize pyrazolyl phenols from an equimolar combination of enamino ketones and hydrazine hydrate in high yields (71–77%) utilizing montmorillonite K10 as solid acid support under heterogeneous catalytic conditions.
- Raghunadh, et al. [10] conducted a successful one-pot multi-component synthesis of 1,3-disubstituted pyrazole using a regioselective copper catalyst in high yields of 72% to 84% by reacting an equimolar combination of 3-Hydrazine, (dimethyl amino)-1-phenylprop-2-en-1-one with aryl halide at high temperatures (80–90°C) for a period of a 14-hour window after the series of reactions, including Dehydration, hetero cyclization, the addition of Michael, and Figure 8 illustrates Ullmann cross-coupling.
- Lebedev, et al. [11] investigated a Drawing from alkyl, phenyl, and cycloalkyl methyl ketones, Vilsmeier formylation of semi-carbazones yielded poor to good yields (35-70%) when stirred at 80°C for two hours, as Figure 9 illustrates.
- Sathiyaseelan, et al. [12] using V. H. reagent (DMF-POCl3) and stirring in an ice bath, synthesized 3-phenyl-1-(3-phenylquinolin-2-yl)-1H-pyrazole-4-carbaldehyde Figure 10. The reaction mixture was then heated at room temperature for 15 minutes and then heated in a water bath for a total of seventeen hours. One important synthetic strategy for the synthesis of formyl pyrazoles is the use of inexpensive precursors in conjunction with streamlined work-up protocols.
- Nikpassand, et al. [13] Using 1,2-dichloroethane and Baylis Hillman adducts (1mmol) and substituted arylhydrazines (1mmol) over KSF catalyst (0.2g) created an effective and regioselective synthesis of 1,5-diaryl-3,4-dimethylpyrazoles in high yields (70-90%) as shown in Figure 11.
- Xie, et al. [14] reported an enantioselective asymmetric synthesis of pyrano [2,3-c] pyrazoles (up to>99:1drandupto98%ee) by using a cascade reaction of nitroalkene and pyrazolone Morita-Baylis-Hillman acetates in the presence of 5mol% KH2PO4 and 20mol% chiral squaramide as shown in Figure 12.



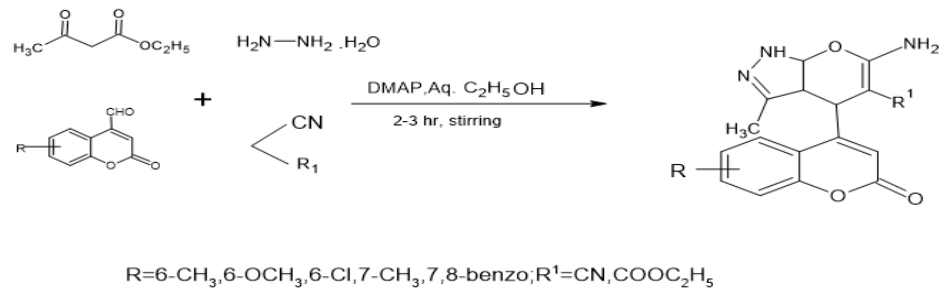
(i) 4-Nitrophenyl 4-methoxybenzoate,LHMDS/THF
(ii)1.Ar^2NHNH_2.HCl,THF/DMF(1:3),110-120C;2.BBr_3/CH_2Cl_2
Ar^1=4-OCH_3-C_6H_4,R=CH_3,C_2H_5,n-C_3H_7,i-C_4H_9;Ar^2=C_6H_5,4-OH-C_6H_5;Ar^3=4-HO-C_6H_4

Figure 1: Synthesis of tetrasubstituted pyrazoles a crossed-Claisen condensation.



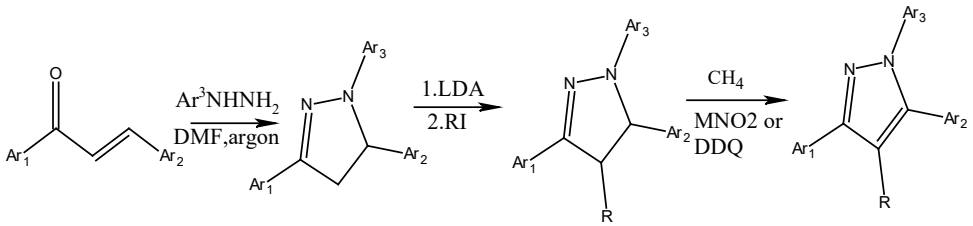
R=H, 2-NO_2

Figure 2: Synthesis of N-substituted benzoyl pyrazoles.



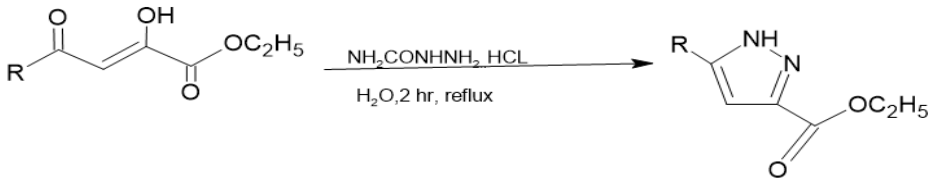
R=6-CH_3,6-OCH_3,6-Cl,7-CH_3,7,8-benzo;R^1=CN,$COOC_2H_5$

Figure 3: Synthesis of coumarin based pyrano (2,3) pyrazole.



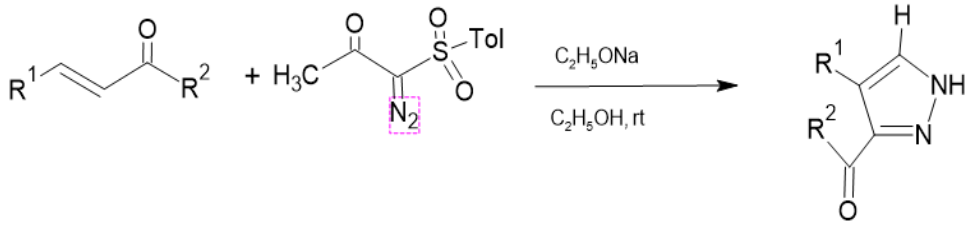
Ar^1=C_6H_5,4-OCH_3-C_6H_5;Ar^2=C_6H_5,4-OCH_3-C_6H_5,4-OTBDPS-C_6H_5
Ar^3=C_6H_5,4-OCH_3-C_6H_5,R=CH_3,C_2H_5,n-C_3H_7

Figure 4: Regioselective synthesis of 4- alkyl 1,2,3-diarylpyrazoles.



R = C_6H_5, 2-CH_3-C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4, 2-OCH_3-C_6H_4, 3-OCH_3-C_6H_4, 4-OCH_3-C_6H_4
2-F-C_6H_4, 4-F-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-NHCOCH_3-C_6H_4, indol-3-yl, CH_3, i-C_3H_7

Figure 5: Synthesis of 3,5-disubstituted pyrazole.



R^1 = C_6H_5, 4-CH_3-C_6H_4, 3-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-CN-C_6H_4, 3-NO_2-C_6H_4,4-NO_2-C_6H_4;
R^2 = C_6H_5 , 4-Cl-C_6H_4

Figure 6: Rapid and efficient synthesis of a series of 2H-indazoles.

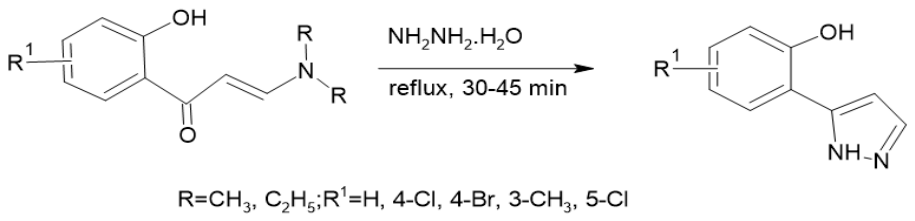


Figure 7: Ecofriendly, rapid and facile synthesis of pyrazolyl phenols.

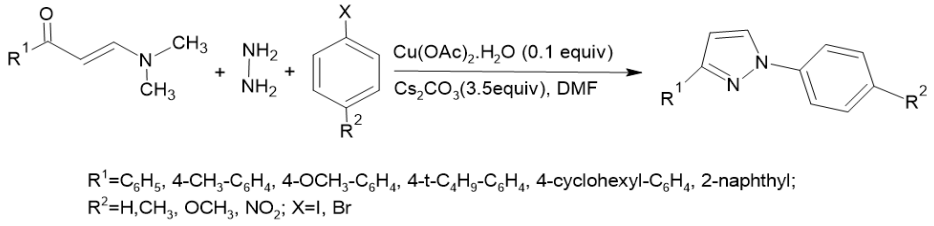


Figure 8: Synthesis of 1,3-disubstituted pyrazoles.

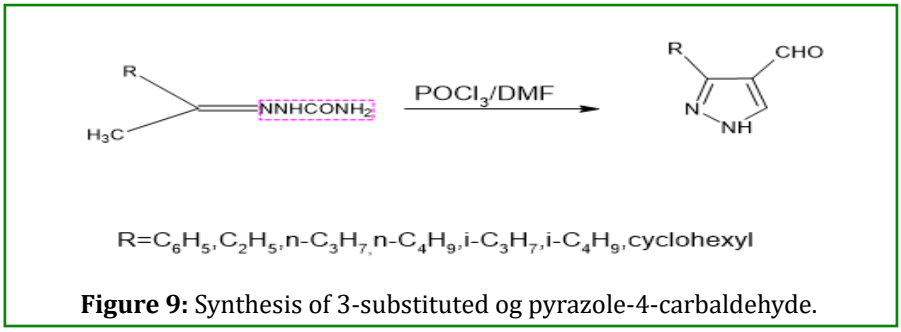


Figure 9: Synthesis of 3-substituted og pyrazole-4-carbaldehyde.

Figure 10: Synthesis of pyrazoles by treating hydrazones with DMF/ POCl3.

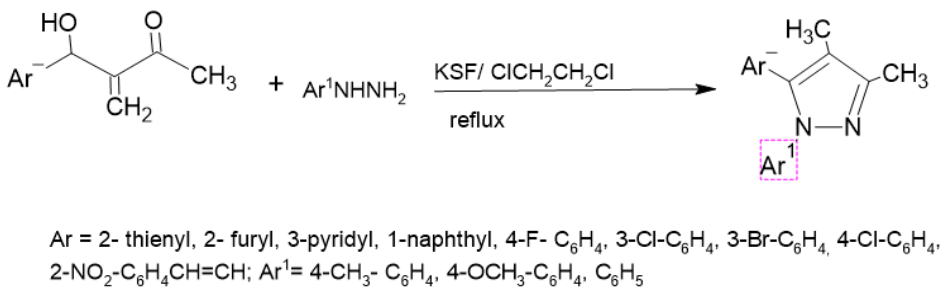
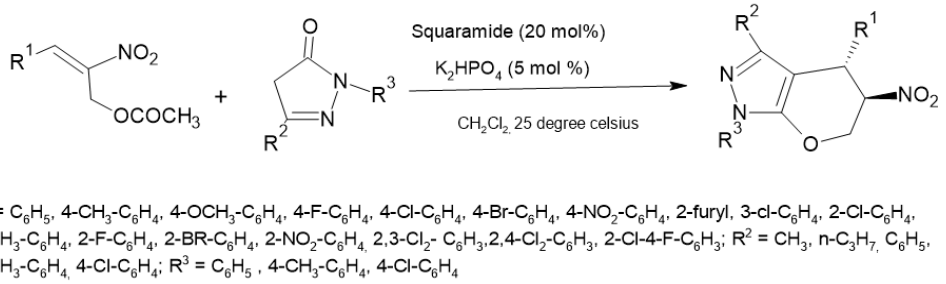


Figure 11: Regioselective synthesis of 1,5-diaryl-3,4-dimethyl-pyrazoles.



R^1 = C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 2-furyl, 3-cl-C_6H_4, 2-Cl-C_6H_4, 2-CH_3-C_6H_4, 2-F-C_6H_4, 2-BR-C_6H_4, 2-NO_2-C_6H_4, 2,3-Cl_2- C_6H_3,2,4-Cl_2-C_6H_3, 2-Cl-4-F-C_6H_3; R^2 = CH_3, n-C_3H_7, C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4; R^3 = C_6H_5 , 4-CH_3-C_6H_4, 4-Cl-C_6H_4

Figure 12: Enantioselective a symmetric synthesis of pyrano (2,3-C) pyrazole.

Biological Activities of Pyrazole Derivatives

Anti-inflammatory activity: The human body uses inflammation as a defense mechanism against stimuli or foreign particles that could harm or injure its cells. Many pyrazole compounds, including antipyrine or phenazone, lonazolac, epirizole, phenylbutazone, and oxyphenbutazone, have found therapeutic applications as nonsteroidal anti-inflammatory medications. The multi-stage process of inflammation is thought to be initiated in part by abruptly produced arachidonic acid and its prostaglandin-like metabolites [15]. Souraya AD, et al. [16] Published structure-guided approach on the role of substitution on amide-linked bipyrazoles and its effect on their anti-inflammatory activity. Yields of (2-cyano-N-(4cyano-3-(methylsulfanyl) -1-phenyl-1H-pyrazol-5yl) acetamide] and [5-amino-3-methysulfanyl-1H pyrazole-4-carbonitride) of (74% and (96%). The best *in vitro* anti-inflammatory activity was demonstrated by fluoro (5d) and methyl (5e) derivatives, with selectivity indices for cox-2 vs cox-1 (Figure 13) [16].

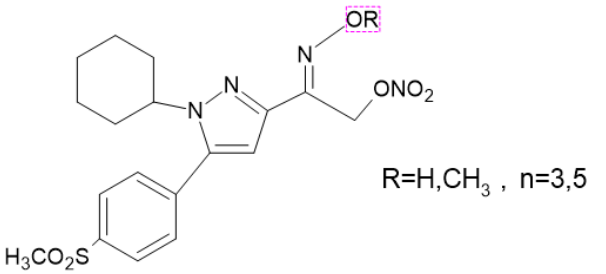


Figure 13: Novel pyrazole derivatives as COX-2 inhibitors.

Anup, et al. [17] Discovered novel pyrazole derivatives as a potent anti-inflammatory agent in RAW264.7 cells inhibition of NF-KB for potential benefit against SARS-CoV-2. Transcriptional activity of NF-KB: The culture media used for RAW264.7 macrophages (ATCC) was Dulbecco's modified Eagle's medium, which was enhanced with 10% FBS. Finally, luciferase tests were conducted using cell extract and luciferin substrate. Using the Dual-luciferase reporter assay technique, the luciferase activity was computed- alpha, interleukin-1beta, and interleukin -6 assay: RAW264. 7 cells are pretreated with compound 6c for one hour following a 16-hour incubation period. The assay for enzyme-linked immunosorbent was used to measure the number of cytokines. Preparation of nuclear extracts: RAW 264.7 cells were treated with lysis buffer and then allowed to sit on ice for ten minutes. After centrifuging, the nuclear extract was obtained. Lastly, "compound 6c" inhibits the release of different proinflammatory cytokines, maybe as a result of blocking NF-KB activity. It might serve as a promising therapeutic lead for managing the inflammatory response in SARS-CoV-2 infections [17]. Mishra P, et al. [18] synthesized the same novel pyrazole derivatives with Phenyl Hydrazine, a substituted acetophenone, with glacial acetic acid. Described mixture (1a-h). Synthesis of 4, carbaldehyde (2a–h) containing 1,3-diphenyl-1H-pyrazole, neutralized with saturated sodium bicarbonate. The substitution of benzanamine (3a-h) with (E) -N-[(substituted phenyl) -4,5 dihydro-1- phenyl-1H- pyrazole -3-yl) methylene] was synthesized and recrystallized from ethanol. Ultimately, compounds 3a and 3d had the strongest anti-inflammatory properties because presence of a chloro group [18].

Rios MC, et al. [19] Published recent advances in synthesis and properties of pyrazole. Aminopyrazole to 5-aminopyrazole conversion saw the creation of the Pyrazole-oxindole hybrid by using N-substituted isatin and the condensation reaction of 5-aminopyrazole. 5-alkyl-3 amino-1H-pyrazoles that are synthesized from carboxylic acid, etc., Formyl pyrazoles, Acylpyrazole, Pyrazoles formyl 3. aryl-1-(pyridin-2-yl) pyrazole with 1H Carbaldehydes, Additional Derivatives Acylated: substituted N-methyl pyrazoles (4, 5, 3, 4). Halopyrazole is one type of functional pyrazole (NH2, CHO, OH, CF3, SR, CN, CO2R, Cl, Br, etc.), (1,5-a) pyrazole pyramidal. Photophysically active pyrazoles have a methoxyphenyl group (like fluorine and chlorine) substituted with halogen atoms, which have significant

biological properties [19]. More VS, et al. [20] published a synthesis of analgesic, and Anti-inflammatory activity of some pyrazole (3, 4-c) pyrazole derivatives by condensation with a 1,3-dicarbonyl compound. Pyrazole derivatives were created from hydrazine, hydrazides, semi carbazides, thiosemicarbazides, and aminoguanidines. Compounds are measured for their LD50 Value using Karber's method. The rat paw edema was induced by carrageenan and investigates the anti-inflammatory properties of the synthesized compound. 1,3- methyl-4-phenyl - 1,3a, 4,5-tetrahydro pyrazole characterization (3, 4-c) Na1 pyrazole Four (2) Chlorophenyl 4,5 tetrahydro pyrazole, 3a, -3-methyl-1 (3, 4c) Nb1) pyrazole (3, 4-c) 2-(4-methyl-2, 3,3a, 6-tetrahydro pyrazole phenol, pyrazol-3-yl), etc. Last, the synthesis of a new series of compounds called "pyrazole - pyrazole". While all of the compounds exhibited anti-inflammatory properties, the most notable ones were IVd, IVd2, IVd3, IVb1, IVb2, and IVb3 [20].

Antitumor activity: After cardiovascular diseases, cancer is the second most deadly disease in terms of death and morbidity [21]. It is typified by the unchecked expansion of aberrant cells, 13% of global fatalities. Due to their detrimental effects on normal cells, chemotherapy and radiation therapy effective cancer treatments still have some limits [22]. Therefore, it is thought of as a vibrant area of medicinal chemistry to search for novel, potent, selective, and safer anticancer drugs [23]. The anticancer medication celecoxib is commercialized and contains pyrazoles. As a result, numerous researchers have created the following pyrazole-based anticancer medications. When Li and colleagues synthesized 4-pyrazolyl-1,8-naphthalimide derivatives and evaluated their biological efficacy as anticancer medications, they found that the MCF-7, HeLa, and A549 cells exhibited a pertinent toxicity profile. From the derived compounds, the two compounds exhibited greater inhibitory activity against MCF-7 cells with IC50 values of 0.51 μM and 0.79 μM [24].

Mohammed EZ, et al. [25] synthesized pyrazole-based derivatives as potential inhibitors of CDKs, and new diphenyl-1h-pyrazole was synthesis and screened for CDK2 inhibition where 8d, 9b, 9c, and 9e exhibited promising activity compared to R-Roscovitin [25] Shown in Figure 14. In light of the positive outcomes of 1-isonicotinoyl-3-methyl-4-[2-(4-nitrophenyl) hydrazono]-2-pyrazolin-5-one (IC50 0.2-3.4μM) as a putative lead molecule with anticancer properties, we concentrated on enhancing the anticancer potential of arylhydrazono-pyrazole derivatives with various phenyl ring replacements. Using the sulforhodamine B (SRB) assay, the newly synthesized compounds 1 and 2 were assessed for their antiproliferative activity against three human tumor cell lines: MCF-7 for breast cancer, HepG2 for hepatocellular carcinoma, and HCT-116 for colorectal cancer.

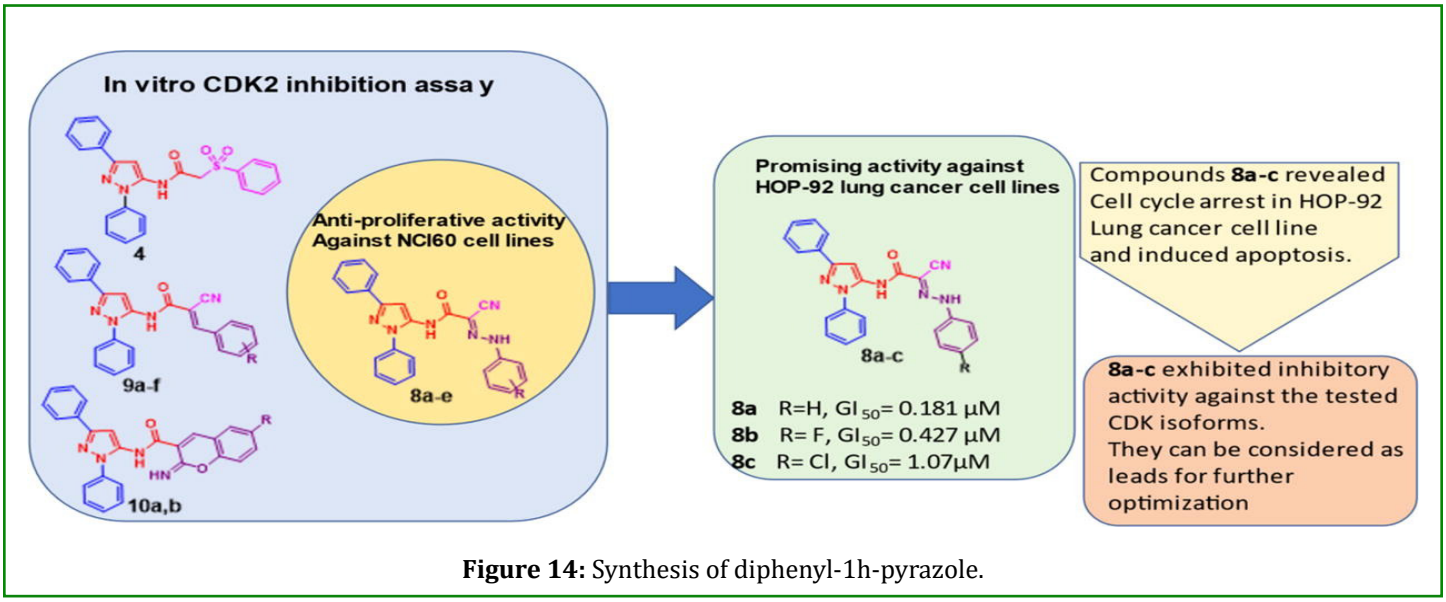


Figure 14: Synthesis of diphenyl-1h-pyrazole.

Perina M, et al. [26] presented a ring fused pyrazoles of dihydrotestosterone targeting prostate cancer cells via downregulation of androgen receptors. Herein, synthesis of steroidal pyrazoles derived from the natural sex hormone 5α dihydro testosterone and a ring fused 1,5 disubstituted pyrazole as the main product lead compound(3d) was found to be a potent AR antagonist by suppressing AR signaling (Figure 15). Confirm the antiproliferative activity of 3d compound in AR-positive cell line. Cellular and biochemical domain [26].

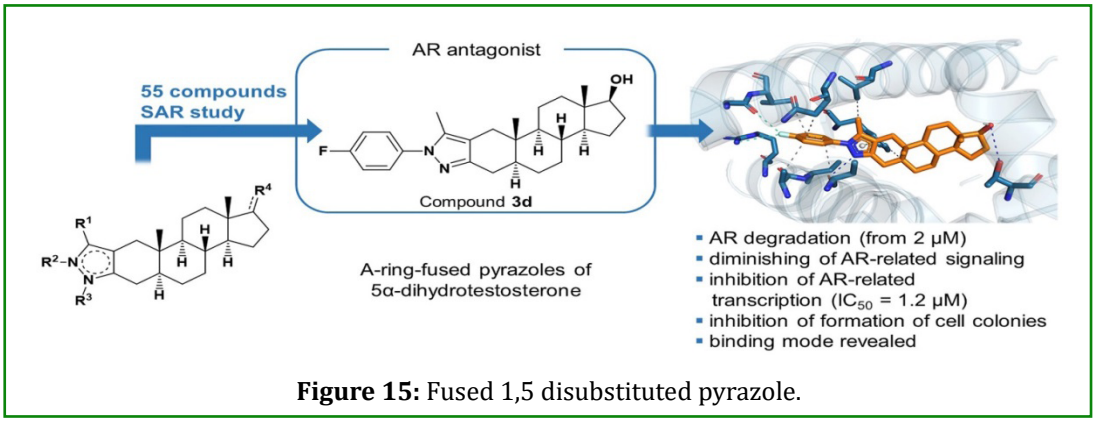


Figure 15: Fused 1,5 disubstituted pyrazole.

Anti-microbial activity: An increasing and significant hazard to public health is the emergence of infectious diseases brought on by pathogens. A number of pathogenic microorganisms including bacteria, fungi, yeast and viruses, or typically a source of serious diseases. Antibiotics primarily combat harmful germs by either eradicating the bacteria or preventing its growth. Antibiotics have advantages, but when overused, they can worsen the condition being examined [27]. A variety of physiologically active natural products, particularly alkaloids, require pyrazole as their essential building block. Many popular medications, including Difenamizole, Rimonabant, Celebrex, and Viagra, contain the pyrazole ring as their central component [28]. Several pyrazole compounds with antimicrobial activity have been identified by numerous researchers, these are covered here:

Chalkha M, et al. [27] published Design, synthesis, characterization, *in-vitro* Screening, Molecular Docking, 3D-QSAR, and ADME-Tox investigations of novel pyrazole derivatives as antimicrobial agents. Using the broth microdilution method, *in-vitro* antimicrobial tests were conducted to assess the antimicrobial activity of target compounds 4–9 against various pathogenic microbes. Standard drugs, such as fluconazole (F) and streptomycin (S), were used. The microdilution method was used to determine the minimum inhibitory concentration (MIC), which represents the concentration required to inhibit the growth of pathogenic microorganisms. The results obtained demonstrate a moderate level of antimicrobial activity against strains of bacteria and fungi. Among the compounds tested, compound 9b exhibits the most significant inhibitory activity against strains of Candida albicans, Staphylococcus aureus, Escherichia coli, and Listeria innocuous, with MIC values ranging from 0.52 to 2.11 mmol mL^{1}. The compounds with significant antimicrobial activity are then tested for minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC). Compound 9b shows bactericidal and fungicidal effects against all the tested microbe strains. In addition, compounds 5c and 9c exhibit good activity with MIC values of 0.46 mmol mL^{1} and 0.92 mmol mL^{1} against E. coli and L. innocuous strains, respectively. Compound 9c displays inhibition against E. coli with a MIC value of 1.04 mmol mL^{-1} [27].

Boutaina A, et al. [28] worked on the synthesis, *in-vitro* Antimicrobial Activity, and Docking Studies of some Pyrano [2,3-c] Pyrazole Derivatives. The pyrano [2,3-c] pyrazole product was prepared by mixing aldehyde (1mmol), ethyl acetoacetate (1mmol), malononitrile (1.2mmol), hydrazine hydrate (2mmol), and 1 ml of water in a flask equipped with a reflux condenser. Pyrano [2,3-c] 5(a-e) pyrazole was obtained by recrystallization with 96% ethanol [28]. The MIC was determined after incubation time, based on visual growth (turbidity). The outcomes were expressed as the mean of a minimum of three separate assays [28]. We found that the 5c derivative had exceptional potential for inhibition against the chosen bacteria. We measured the inhibition zone diameter, or IZD, at 25 mg/mL, which came out to be 13mm. The results of compound 5c's antimicrobial susceptibility tests about a panel of control antibiotics. The most effective antibiotic was chloramphenicol. No discernible inhibition was seen for vancomycin, ampicillin, penicillin G, novobiocin, or ampicillin in comparison to (5c). It was discovered that every synthesized compound, 5a–e, exhibited observable antimicrobial activity against the examined microbes. The strains under investigation were found to be sensitive to these derivatives. Notably, strain 5c exhibited the highest level of activity against both *K. pneumonia* and *E. coli*, with a MIC of 6.25 mg/mL. In addition, at concentrations of 12.5 mg/mL, this product exhibits activity against the strains of *S. aureus* and *L. monocytogenes*. Conversely, products 5a, 5b, 5d, and 5e have the highest activity against *K. pneumonia* and *E. coli* (MIC=12.5 mg/mL). Additionally, we observed that *S. aureus* is more susceptible to 5d and 5e than 5a and 5b (the MIC was 12.5 mg/mL) [28].

Pham EC, et al. [29] Design, synthesis, antimicrobial evaluations and in silico studies of novel pyrazol-5(4H)-one

and 1H-pyrazol-5-ol derivatives [29]. The phenylhydrazine derivatives with a 3-nitro or 4-nitro group are the starting material for the preparation of 3-methylpyrazol-5(4H)-one and 3-methyl-1H-pyrazol-5-ol derivatives. Antimicrobial activity of the synthesized compounds was shown against two strains of *Aspergillus niger* and *Candida albicans*, three strains of Gram-positive bacteria (*Streptococcus faecalis*, MSSA, and MRSA), and two strains of Gram-negative bacteria (EC and PA). The presence of the chloro/ fluoro group in the aromatic ring at position 4 of 1-(3-nitrophenyl)-1H-pyrazol-5-ol scaffold is more desirable for enhanced antibacterial activity in 4a, 4b, 4d, and 4g, and antifungal activity in 4a. Analogs of the well-known radical scavenger "edaravone," 1,3-disubstituted-1H-pyrazol-5-ol derivatives, demonstrated good radical scavenging capacity. Furthermore, azo clubbed 1H-pyrazol-5-ol derivatives demonstrated good affinity for DNA and moderate antibacterial potential against Gram-negative strains, with a MIC value of 312.5µg/mL. In comparison to ciprofloxacin, streptomycin, and fluconazole, some 4,4′-(aryl methylene)bis-(3-methyl-1-phenyl-1H-pyrazol-5-ol) derivatives with thiophene rings or bearing $N(CH_3)_2$, OCH_3, and Cl groups on the phenyl ring have demonstrated excellent DPPH radical scavenging activity (EC50 7.69–19.03 µg/mL), good anti-inflammatory activity (EC50 10.87–12.25 µg/mL), and potent *in-vitro* antimicrobial activity against various bacterial strains. A few of the compounds synthesized demonstrated greater potential for antimicrobial activity (Figure 16). This included additional aryl groups at position 4 of the 1H-pyrazol-5-ol nucleus and nitro substituent (NO_2) at positions 3 or 4 on the phenyl ring of the 1-phenyl-1H-pyrazol-5-ol scaffold [29].

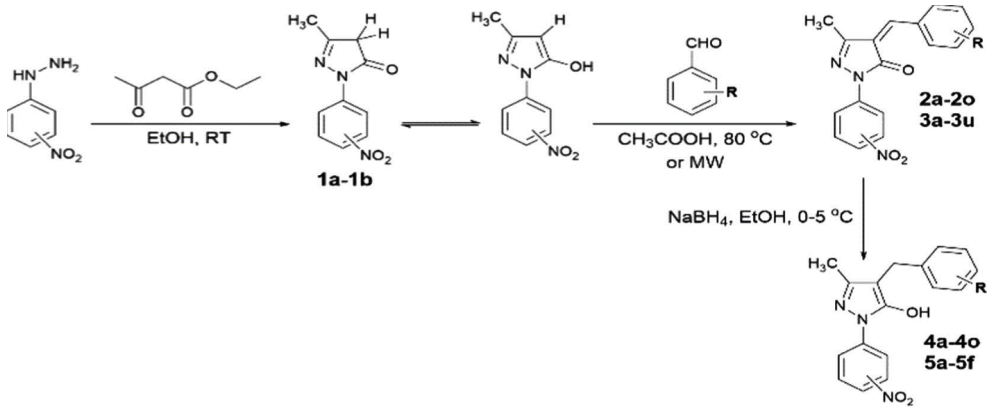


Figure 16: Synthesis pyrazol-5(4H)-one and 1H-pyrazol-5-ol derivatives.

In 2020, the antimicrobial assessment and molecular property prediction of pyrazolines containing benzofuran and pyrazole moieties were investigated by Elsherif MA, et al. [30]. With the use of an agar well-diffusion method, the synthesized compounds (Chalcones 3–5, 1H-pyrazolines 6–8, N-phenyl pyrazolines 9–11, and N-acetylpyrazolines 12–14) were assessed for their *in-vitro* antimicrobial properties against *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (NRRL-B-4219), *Aspergillus niger* (ATCC 16888), and *Candida albicans* (ATCC 10231) and compared with antibiotic drugs (Negram, Vancomycin, and Nystatin) as standards. Antimicrobial activity *in-vitro* testing the synthesized compounds 3–14 against a panel of pathogenic organisms, the results of their antibacterial and antifungal activities showed that certain synthesized derivatives demonstrated excellent to moderate inhibitory effects (Figure 17). Every synthetic compound underwent screening to determine its level of *in-vitro* antimicrobial activity. Compounds 4, 7, 10, 11, and 13 were the most effective against a panel of pathogenic tested organisms, according to the evaluations. Additionally, the two compounds 7 and 13 were found to have maximum DLS values of 0.75 and 0.83, respectively, based on the pharmacokinetic properties and drug-likeness calculation [30].

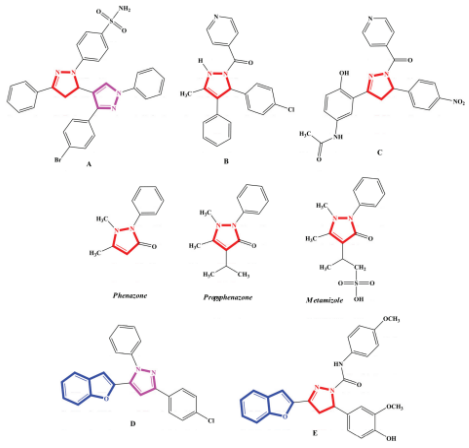


Figure 17: Synthesis of pyrazole moieties.

Hypoglycemic Activity: Lakshmana RA, et al. [31] Design, Synthesis, Hypoglycemic Activity and Molecular Docking Studies of 3-substituted-5-{(furan-2-yl)-methylene}-thiazolidine-3,4-dione derivatives. Diabetes mellitus (DM) is a chronic metabolic disease that is widely distributed, characterized by raised blood sugar levels over an extended period and symptoms such as increased thirst, hunger, and frequency of urination. Diabetes mellitus is associated with several severe degenerative consequences, including stroke, accelerated atherosclerosis, retinopathy, nephropathy, cataracts, and neuropathy, as well as an elevated risk of myocardial infarction. The onset of these diseases in people with type 1 and type 2 diabetes is a noteworthy event. Type 2 diabetes was once only observed in adults, but it is now frequently encountered in kids as well. Diabetes patients face extremely difficult therapeutic challenges for both prevention and control, as they are among the main causes of morbidity and mortality [31].

Cottineau, et al. [32] produced and tested some substituted pyrazole-4-carboxylic acids for hypoglycemic action in vivo. The compound was found to be the most effective hypoglycemic agent across the entire series [32]. Das, et al. [33] developed compounds of pyrazol-3-one and evaluated their hypoglycemic efficacy against metformin, a reference medication. The derivatives were found to be effective hypoglycemic agents among them [33]. Ovasis, et al. [34] created a number of unique pyrazolines with benzene sulfonamide moiety and tested the effect of these compounds on blood glucose reduction in rats that were fed glucose and were hyperglycemic. The substance was discovered to possess considerable blood glucose-lowering efficacy among all the produced compounds [34].

Anti-convulsant activity: A common neurological condition called epilepsy is linked to aberrant neuronal discharge in the central nervous system [35]. People with epilepsy frequently have common symptoms such as brief episodes of disorientation, loss of consciousness, recurrent thoughts, a fixation, emotional outbursts, unusual feelings, uncontrollable movements, and odd sensations [36]. Researchers from all over the world are searching for new, minimally toxic epileptic medications due to the significant side effects of the already existing drugs, such as anemia, hyperplasia, and ataxia [37].

Abdel A, et al. [38] created several unique pyrazole compounds and used PTZ-induced convulsions in mice to investigate their anticonvulsant and antidepressant properties. The compounds were shown to have considerable anticonvulsant action over the entire sequence [38]. Farghaly, et al. [39] created several novel pyrazole (3,4-b) pyrazines with heterocyclic substituents, and tested the anticonvulsant effect of these compounds at a dose of 10 mg/kg on mice that were convulsed by pentylene tetrazole. It was discovered that the substance had good anticonvulsant action among them [39]. Viveka, et al. [40] created and manufactured a variety of 3-(3,4-dihalophenyl)-1H-pyrazole-4-carbaldehyde compounds with a range of heterocyclic substituents, then used the maximal electroshock seizure test to assess their anticonvulsant efficacy. When compared to the common medication phenytoin [40], the molecule has the strongest anticonvulsant activity among all the produced derivatives without exhibiting any toxicity.

Analgesic activity: Analgesics are medications that, without altering consciousness, selectively reduce pain by influencing the central nervous system and peripheral pain mediators. Analogs can be either non-narcotic or narcotic. There are ethical, philosophical, and technical issues with studying animal pain. Rajasekaran, et al. [41] novel (1-(3-(5-aryl-4,5-dihydro pyrazol-1-yl)-5-chloro-2-hydroxy phenyl)) After being created, ethanone derivatives were examined for analgesic effect through inhibition of writhing brought on by acetic acid approach. Findings indicated that every synthesized substance demonstrated notable activity when contrasted compared to a standard drug [41].

Nesrin Gokhan-Kelekci, et al. have created phenyl-5 A-(2-pyrole)-4, 5-dihydro-(1H)-derivatives, substituting 1-thiocarbomyl-3, and examined their potential to inhibit MAO. The majority of the compounds exhibited strong anti-MAO activity. Furthermore, the anti-inflammatory and analgesic properties were identified. Compound (3k) demonstrated no ulcerogenic effect and anti-inflammatory and analgesic activity similar to indomethacin. Alam, et al. [42] for their analgesic properties, pyrazole derivatives with good anti-inflammatory activity were chosen. For abdominal constriction responses, acetic acid was administered intraperitoneally. This significantly produces peripherally acting analgesics that may raise PGE2 and PGF2α levels. Twelve different compounds were tested, and the analgesic activity inhibition ranged from 29.56% to 73.72%. The analgesic activity of compounds 5i, 5b, 5n, 5q, 5r, 5d, and 5t was noteworthy. Compounds 5s (73.56% inhibition) and 5u (73.72% inhibition) were found to have analgesic activity that was comparable to that of the benchmark medication ibuprofen (74.12% inhibition) [42].

Conclusion

The review showed that parasol is a versatile heterocyclic nucleus that can be used to create new compounds with great potential. In this article, numerous researchers' research on current developments in diverse synthesis techniques and various pharmacological actions related to pyrazoles were

emphasized. The pharmacological effects and applications of pyrazole-based derivatives have prompted a significant amount of research into their chemistry. Heterocyclic compounds in many fields, such as organic synthesis, medicine, film, catalysis, etc. That review may serve as inspiration for medicinal chemists to produce a wide range of distinctive, physiologically active compounds.

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