Substituted Pyrazoles and Their Heteroannulated Analogs—Recent Syntheses and Biological Activities

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Abstract: Pyrazoles are considered privileged scaffolds in medicinal chemistry. Previous reviews have discussed the importance of pyrazoles and their biological activities; however, few have dealt with the chemistry and the biology of heteroannulated derivatives. Therefore, we focused our attention on recent topics, up until 2020, for the synthesis of pyrazoles, their heteroannulated derivatives, and their applications as biologically active moieties. Moreover, we focused on traditional procedures used in the synthesis of pyrazoles.

Keywords: pyrazole; heteroannulated; synthesis; reactions; biological activity

1. Introduction

Pyrazoles consist of two nitrogen atoms adjacent to three carbon atoms in a five-membered aromatic ring structure (Figure 1). Due to the broad spectrum of biological activities, the pyrazole ring is considered an interesting class in drug discovery [1].

Unsubstituted pyrazole can be represented in three tautomeric forms [2] (Figure 2).

Interestingly, pyrazoles as a class of azoles, are found in naturally occurring compounds. Kikuchi et al. [3] reported on two compounds, 1-[2-(5-hydroxymethyl-1H-pyrrole-2-carbonyl)-1H-pyrazol-3-yl]ethyl]pyrazole (5) and 1-[2-(5-hydroxymethyl-1H-pyrrole-2-carbonyl)-1H-pyrazol-3-yl]ethyl]pyrazole (6) (Figure 3).
2-carbaldehyde-1-yl)ethyl]-1H-pyrazole (1) and 1-((5-(α-D-galactopyranosyloxy)methyl]-1H-pyrrole-2-carbaldehyde-1-yl)-ethyl]-1H-pyrazole (2), which were isolated from an extract of watermelon seeds (Figure 3). Pyrazoles also display innumerable chemical, biological, agrochemical, and pharmacological properties [4]. Moreover, a large number of structurally diverse natural compounds containing azole nucleus constitute an important class of biologically active heterocycles that are gaining more attention in the field of medicinal chemistry [5].

![Structure of isolated pyrazoles of watermelon seeds.](image)

Many pyrazoles have shown luminescent and fluorescent agents. Some of these compounds have important applications in material chemistry [6] and as brightening agents [7]. Others exhibit solvatochromic [8] and electroluminescence [9] properties. Moreover, some pyrazoles act as semiconductors [10], liquid crystals [11], and organic light-emitting diodes [12].

In biological aspects, pyrazoles are known to exhibit antibacterial [13], anticancer [14,15], anti-tubercular [16], anti-inflammatory [17,18], antidepressant [19,20], antifungal [21], anxiolytic [22], anti-AIDS [23], and anti-malarial activities [24]. Pyrazoles also exhibit promising antioxidant activities [25], analgesic properties [26], they bind to estrogen receptors [27], have neuroprotective properties [28], have the capability of binding to the monoamine oxidase enzyme [29], they have antituberculosis properties [30], antileishmanial properties [31], antiproliferative properties [32], are preferred for tissue non-specific alkaline phosphatase inhibitors [33], act as cyclin-dependent kinase inhibitors [34], have anti-hyperglycemic properties [35], anti-nitric oxide synthases (NOSs) [36], have immunosuppressant properties [37], and demonstrate insecticidal activities [38].

Pyrazoles are frequently observed as bioactive components in commercially available medicines. For example, rimonabant is a cannabinoid ligand and is used for treating obesity; fomepizole prevents alcohol dehydrogenase, celecoxib is a nonsteroidal anti-inflammatory drug (NSAID), specifically, a COX-2 inhibitor, which relieves pain and inflammation, and sildenafil is a PDE5 inhibitor used in the treatment of erectile dysfunction [39] (Figure 4). This review summarizes the updated methods (until the end of 2020) that are generally used to prepare substituted pyrazoles and their heteroannulated pyrazoles and sheds light on their biological activities. Different approaches can be considered for synthesizing pyrazoles, such as $2 + 2 + 1, 2 + 3, 4 + 1, 6 - 1$, etc. (Scheme 1).
In addition, these methods can be combined with metal-catalyzed, organo-catalyzed, flow chemistry, and other methods. In this context, many methods address atom economy (“green”) and multi-component reactions.

2. Synthesis of Pyrazoles

2.1. Cyclocondensation of Hydrazines

2.1.1. Cyclocondensation of Hydrazines with 1,3-Dicarbonyl Compounds

Cyclocondensation of 1,3-dicarbonyl compounds 3 with substituted hydrazines 4 gave the corresponding substituted pyrazoles regioisomers 5 and 5’ (Scheme 2) in different yield percentages depending on the electronic effects, such as the inductive (electron or withdrawing character) and the steric factors of both substituents R1 and R3 (R1 and R3 are unequal). For example, if R1 constitutes an aryl group and R3 constitutes an alkyl substituent, the reaction proceeds, under conventional conditions, to give the regioisomer 5 as the major product, whereas 5’ is formed in traces. The selectivity obtained is of the order of 98:2 (i.e., R1 = Ar and R3 = CH3) [40].
Iodine was used as a halogenated agent that enhances the cyclization process. Starting
with ethyl acetoacetate (6) and oxamic acid thiohydrazide (7) as model substrates (Scheme 3),
using an equimolar amount of I$_2$ in the presence of 10 mol% of TsOH as an additive,
afforded pyrazole derivative 8 in 83% yield within 48 h [41]. Different trials using other
halogenated agents, such as Br$_2$, NCS, or NBS, were also carried out. Iodine was proven as
the proper one that gave high yields.

Ohtsuka et al. [42] prepared 1,3,4,5-tetrasubstituted pyrazole 10 in 63% yield by the
condensation of phenyl hydrazine (4) with the 2-(trifluoromethyl)-1,3-diketone (9) in
refluxing ethanol (Scheme 4) [42].

Girish et al. [43] showed an efficient nano-ZnO procedure that catalyzed the prepara-
tion of 3-methyl-1-phenyl-1H-pyrazol-5-ol (11) in excellent yield (95%) during the conden-
sation reaction between ethyl acetoacetate and phenyl hydrazine (Scheme 5) [43]. Table 1
summarizes the experimental trials used and the optimal conditions of the chosen catalyst
and its concentrations.
Table 1. Synthesis of 11 under different reaction conditions.

| Entry | Catalyst      | Amount (mol%) | Time (min) | Yield (%) |
|-------|---------------|---------------|------------|-----------|
| 1     | ZnO (Bulk)    | 5             | 45         | 50        |
| 2     | TiO₂          | 5             | 40         | 30        |
| 3     | Al₂O₃         | 5             | 45         | 55        |
| 4     | ZnO (nano)    | 10            | 15         | 95        |
| 5     | ZnO (nano)    | 10            | 25         | 85        |
| 6     | ZnO (nano)    | 20            | 15         | 93        |

In 2006, Heller and Natarajan synthesized pyrazoles 5 from the reaction between hydrazine and 1,3-diketones (Scheme 6). The diketo compounds 3 were successfully prepared in good yields by lithiation, using lithium bis(trimethylsilyl)amide (LiHMDS), followed by subsequent addition of the acid chlorides (Scheme 6) [38].

![Scheme 6](image)

Scheme 6. Synthesis of trisubstituted pyrazoles 5. Reagents and conditions; (a) i—2.1 eq LiHMDS, Toluene/THF, 0 °C, 1 min, ii—1 eq R⁢3COCl, r.t, 1 min; (b) i—34 eq NH₂NH₂·2O, ii—EtOH/THF/Toluene/AcOH (10:7:5:5), reflux 5 min.

3-Methyl-5-oxo-4-(2-arylhazdrazono)-4,5-dihydro-1H-pyrazole-1-carbothioamides 15a,b obtained from the reaction of ethyl 3-oxo-2-(2-arylhazdrazono)butanoates 13a,b with thiosemicarbazide (14) (Scheme 7) [44]. Reaction proceeds via condensed products are shown in Scheme 7.

![Scheme 7](image)

Scheme 7. Synthesis of pyrazoles 15a,b.

2.1.2. With α,β-Unsaturated Ketones

The regioselectivity of the reaction of various β-aminoenones on different monoalkyl, acetyl-, methoxycarbonylhydrazine, and semicarbazide was studied by Alberola et al. [45]. They found that the smallest bulky group, when attached at the β-position of the enone, obtained high regioselectivity from the reaction of β-aminoenones 16a-c, which possessed the least bulky substituent (CH₃) in the β-position with alkyl hydrazines 4, in DMSO. Subsequently, pyrazoles 5a-c and 5′a-c were obtained with high regioselectivity (Scheme 8) [45]. When different β-aminoenones 16a-c with bulkier β-substituents were used, the reactivity towards product formation decreased, but more important than this decrease in reactivity was the drop in regioselectivity. This phenomenon was greater when R² and the alkyl hydrazine were bulkier [45]. Compounds 5a-c were formed in yield percentages from 78–97% compared with their regioisomers 5′a-c [45].
Sahu et al. [46] prepared a group of 4-(5-substituted aryl-4,5-dihydropyrazole-3-yl-amino)phenols 18 (Scheme 9) from the reaction of N-(4-hydroxyphenyl)-3-phenylacrylamides 17 with hydrazine hydrate [46].

Kovacs et al. [47] developed a technique for preparing 3,5-disubstituted pyrazole 5 via Cu/Fe catalyzed coupling between phenylacetylene (20) and an oxime 19 in DMF as a solvent provided the β-aminoenone 21. In the one-pot procedure, the valuable β-aminoenone was transformed into 5 with the addition of hydrazine hydrate (Scheme 10) [47].

Rao et al. [48] described a method to prepare pyrazole derivative 5 via condensation of a chalcone 22 with p-((t-butyl)phenyl)hydrazine 4 in the presence of copper triflate and 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM- PF₆] 23 as a catalyst. The reaction proceeded via the formation of compound 24 (Scheme 11) [48]. Further optimization of the reaction conditions was carried out by changing solvents, catalysts, and catalyst loading. The use of 20 mol% Cu(OTf)₂ in 23 gave the desired product 5 in excellent yield (82%). When Cu(OTf)₂ was replaced with other catalysts, such as p-TSA, Sc(OTf)₃, Ce(OTf)₃, Zn(OTf)₂, AgOTf, or Yb(OTf)₃, a mixture of 24 and 5 was observed. The use of Ce(OTf)₃ in 23 resulted in a 75% yield of 24 along with 10% of 5, whereas the use of p-TSA in 23 gave 69% of 24. The obtained data indicate that Cu(OTf)₂ was involved in the aerobic oxidation of 24 to 5. It is necessary to mention that 5 was not formed in the absence of
Cu(OTf)$_2$ in 23 ionic liquids, and only 24 was isolated in 20% yield along with the starting material, and the yield of 24 did not increase with increasing the time up to 2 h [48].

![Scheme 11](image)

**Scheme 11.** Synthesis of 1,3,5-trisubstituted pyrazole 5.

Bonacorso et al. [49] synthesized a series of 3-aryl(alkyl)-5-trifluoromethyl-1H-pyrazoles 27a–g from the reaction of 4-alkoxy-4-aryl(alkyl)-1,1,1-trifluoro-3-buten-2-ones 25 with thiosemicarbazide (14). The reaction gave the corresponding 5-hydroxy-5-trifluoromethyl-pyrazole thiocarboxamides 26. Subsequently, dehydration and removal of the thiocarboxyamide group with sulfuric acid 96% produced the desired products 27a–g in 57–75% yields (Scheme 12) [49]. It was concluded that the presence of the thiocarboxyamide group on position 1 of the pyrazolines 26 acts as a protective group with an electron-withdrawing effect, hindering the elimination of water and the subsequent aromatization of the five-membered ring. The presence of a trifluoromethyl group on the vinyl ketones 25 and the thiocarboxyamide group on the dinucleophile (thiosemicarbazide) was the determining factor of the regiochemistry of the reaction. Moreover, the presence of α-alkyl- and β-alkyl[aryl]-substituent on the vinyl ketones 25 did not show observable effects on the regiochemistry of the reaction.

![Scheme 12](image)

**Scheme 12.** Synthesis of 3-aryl(alkyl)-5-trifluoromethyl-1H-pyrazoles 27a–g. Reagents and conditions; (a) NH$_2$NHC(S)NH$_2$ (14), CH$_3$OH; (b) r.t. to 45 °C, 20–24 h; (c) H$_2$SO$_4$ 96%, reflux, 4 h.

Synthesis of pyrazoles substituted by thiophene moiety 29 could be carried during the reaction of chalcone-type compound 28 with phenyl hydrazine hydrochloride 4·HCl via 3 + 2 annulations (Scheme 13). The obtained thiophene-pyrazole hybrids 29 were screened as antimicrobial and antioxidant agents (Scheme 13) [50].
A series of dihydropyrazole-1-carboxamides 32a–o were obtained by the base-catalyzed condensation of isoxazolyl chalcones 30 with semicarbazide (31) (Scheme 14) [51]. The preliminary in vitro antitubercular activity of the synthesized pyrazoles 32a–o was performed by the microplate Alamar Blue assay (MABA) using isoniazid (0.25 μg/mL) as the positive control.

Similarly, pyrazole derivatives 36a–c were obtained via reaction of α,β-unsaturated ketones 35, together with hydrazine, as indicated in Scheme 15. The carboxylated multi-walled carbon nanotubes/dolomite (MWCNTs) successfully grafted the surface of the obtained compounds. Good antibacterial activity toward some pathogenic types of bacteria was found for the synthesized compounds [52].

Scheme 14. Synthesis of isoxazole appended 1-carboxamido-4,5-dihydro-1H-pyrazoles 32a–o.

Scheme 15. Synthesis of pyrazole derivatives 36a–c.
2.1.3. With Acetylenic Compounds

The cyclocondensation reaction of acetylenic ketones 37 with hydrazine derivatives 4 yielded nearly equal yields percentages of the two regioisomers 5 and 5' (Scheme 16) [53].

\[
\begin{align*}
R^1\text{C}≡\text{C}R^2 + R^3\text{NHNH}_2 \rightarrow \text{EtOH} & \rightarrow \text{N}_{R^1R^2}N_{R^3}R^2 + \text{N}_{R^1R^2}N_{R^3}R^3' \\
\text{Scheme 16. Cyclocondensation reaction of hydrazine derivatives on the acetylenic ketones 37.}
\end{align*}
\]

Harigae et al. [54] reported on the synthesis of 3,5-disubstituted pyrazole 5 with high regioselectivity in a one-pot procedure via the reaction of phenylacetylene (20) with aromatic aldehydes 34, molecular iodine, and hydrazines 4 (Scheme 17) [54]. The mechanism explains the formation of acyl phenylacetylene 38 due to the lithiation process that generates an acetylenic nucleophilic site and attacks the aldehydic carbonyl to form the intermediate 39 (Scheme 17). Subsequently, the formed nucleophilic center would attack to the iodine molecule to form the intermediate 40, which executes HI to form 38 (Scheme 17) [54]. The formed intermediate 38 with substituted hydrazines would give compounds 5 accompanied by the elimination of H$_2$O (Scheme 17).

\[
\begin{align*}
\text{Ph}≡\text{H} (20) & \xrightarrow{\text{a)} n\text{-BuLi (1.1 eq), THF, 0 °C, } \frac{1}{2}\text{ ArCHO (2.0 eq)}} \text{Ph}≡\text{C}≡\text{CPh} (\text{38}) \xrightarrow{\text{c)} RNHNH}_2 \rightarrow \text{Ph}≡\text{N} = \text{C} = \text{N} \text{Ph} (\text{5}) \\
\text{R = } & \text{C}_6\text{H}_5, 4\text{-OCH}_3\text{C}_6\text{H}_4, 4\text{-CH}_3\text{C}_6\text{H}_4, 2\text{-CH}_3\text{C}_6\text{H}_4, 3\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-CF}_3\text{C}_6\text{H}_4 \\
\text{Scheme 17. Synthesis of 3,5-disubstituted pyrazole 5. Reagents and conditions; } & \text{a) } n\text{-BuLi (1.1 eq), THF, 0 °C; } \text{b) } \text{ArCHO (2.0 eq); } \text{c) } RNHNH}_2 \text{ (2.0 eq).}
\end{align*}
\]

Ji et al. [55] reported on an efficient procedure for synthesizing 3-trifluoromethylpyrazole 5 in 60% yield via trifluoromethylation/cyclization of acetylenic ketones 38 with phenylhydrazine (4) using (1-trifluoromethyl-1,2-benziodoxol-3(1H)-one) (Togni reagent) (Scheme 18) [55].
Ma et al. [56] developed an efficient copper-catalyzed reaction to prepare polysubstituted pyrazoles 43 from phenylhydrazones 41 and dialkyl acetylenedicarboxylates 42 (Scheme 19). Table 2 summarizes the reaction conditions from the molar ratios of the catalyst and base. Moreover, the reaction yields the products in the absence of a catalyst and case of nitrogen atmosphere. The best condition was equal equivalents of the starting substances, base, catalyst, and N₂ atmosphere [56].

![Scheme 18. Synthesis of 3-trifluoromethylpyrazoles 5. Reagents and conditions; (a) Togni reagent, CH₂CN, H₂O (20:1), r.t., 24 h.]

![Scheme 19. Synthesis of polysubstituted pyrazoles 43 (41 (0.2 mmol), 42 (0.2 mmol), base (0.2 mmol), catalysts (0.02 mmol) in 2 mL of solvent for 2 h under air).]

| Entry | Catalyst | Base | Solvent | Yield (%) a |
|-------|----------|------|---------|-------------|
| 1     | CuI      | NaOAc | DME     | 73          |
| 2 b   | CuI      | NaOAc | DME     | 44          |
| 3     | CuI      | -     | DME     | trace       |
| 4 c   | CuI      | NaOAc | DME     | 75          |
| 5 d   | CuI      | NaOAc | DME     | 75          |
| 6     | -        | NaOAc | DME     | 0           |

a Isolated yield. b Reaction was carried out with 0.2 equiv. of base. c Reaction was carried out with 2 equiv. of base. d Reaction was carried out with 1.0 equiv. of base under nitrogen.

Martin et al. [57] reported a facile method in preparing pyrazoles 5 via Cu-catalyzed domino C-N coupling hydroamination reaction (Scheme 20). The procedure involving the reaction of acetylenes 44 and diamine 45 in the presence of copper (I) iodide and N⁴,N⁵-dimethylethan-1,2-diamine (46) under reflux of THF at 80 °C to give 47 and then pyrazoles 5 were formed in 66–93% yields (Scheme 20) [57].
Scheme 20. Synthesis of pyrazoles 5. Reagents and conditions; (a) 5 mol% CuI; (b) 1.5 eq Cs₂CO₃, THF, 80 °C, 6–16 h, (c) 10 eq TFA, CH₂Cl₂, r.t.-2h.

In 2011, Jackowski et al. showed heterocycles 50 could be obtained by a simple metatation cyclization process (Scheme 21).

Scheme 21. Synthesis of trisubstituted pyrazoles 50. Reagents and conditions; (a) Al(CH₃)₃, toluene, r.t. = 5 min; (b) 1 eq, 50 °C, 1 h; (c) E⁺ = (EX): D (CH₂OD, Cl (NCS), I (NIS), CONH₂ (Cl₃C-NCO)).

The carbon–aluminum bond can react further with several electrophiles without the need for transmetalation, providing direct access to trisubstituted pyrazoles 50 (Scheme 21) [58].

2.1.4. With π-Deficient Compounds

Aly et al. reported that N-arylbenzamidrazones 51 reacted with diaminomaleonitrile (52) in EtOH/Et₃N (Method I) to give substituted pyrazoles 53 (Scheme 22). When microwave irradiation assisted the former reaction for a few min, the corresponding compounds 53 were obtained in good yields (75–87%, Method II, Scheme 22) [59].

Scheme 22. MW assisted synthesis of pyrazoles 53. Reagents and conditions. Method (I) EtOH/Et₃N, reflux 10–16 h (10–25%). Method (II) MW (75–87%).

In addition, Aly et al. prepared 5-amino-1-(1-ethyl-2-oxo-1,2-dihydroquinolin-4-yl)-1H-pyrazole-3,4-dicarbonitrile (56) from the reaction 2-quinolonyl hydrazine 54 with 1,1,2,2-ethenetetracarbonitrile (55) (Scheme 23). Compound 56 was evaluated as good antiproliferative EGFR-TK inhibitors against many tumor cell lines (Scheme 23) [60].
Scheme 23. Synthesis of 4-pyrazolquinolin-2-one 56.

Gentle heating at 50 °C of equimolar solutions of N-phenylhydrazinecarbothioamide (57) and 2-bis(methylthio)methylene)malononitrile (58) in absolute ethanol containing 0.5 mL Et₃N for 3 h gave compound 59 in 65 % yield (Scheme 24) [61].

Scheme 24. Synthesis of pyrazole 59.

Aly and his co-workers also investigated the antioxidant activity, anti-apoptotic activity, and caspase-3 inhibition of pyrazoloquinolones 61a–f as described in Scheme 25. Formation of 61a–f was established via the reaction of 2-quinoloyl-4-hydrazines 54a–f with ethyl 2-cyano-3,3-bis(methylthio)acrylate (60) (Scheme 25). Compound 61c was the most potent against inflammation, whereas 61d showed the most active caspase-3 [61].

Scheme 25. Pyrazoloquinoliones 61a–f with antioxidant and anti-apoptotic activity, and caspase-3 inhibition.

In 2017, Aly et al. showed that amidrazone 51 reacted with ethyl 2-cyano-3-ethoxybut-2-enoate (62) in refluxing absolute EtOH containing triethylamine (Et₃N), compounds 63 (70–85%) were obtained, after chromatographic purification and recrystallization (Scheme 26) [62].
Scheme 25. Pyrazoloquinolinones 61a–f with antioxidant and anti-apoptotic activity, and caspase-3 inhibition.

In 2017, Aly et al. showed that amidrazones 51 reacted with ethyl 2-cyano-3-ethoxy-butyrate (62) in refluxing absolute EtOH containing triethylamine (Et₃N), compounds 63 (70–85%) were obtained, after chromatographic purification and recrystallization (Scheme 26) [62].

Scheme 26. Synthesis of pyrazoles 63.

1-Aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-3-methyl-1H-pyrazoles 67 were obtained in three steps as outlined in Scheme 27.

Scheme 27. Synthesis of pyrazoles 65–67.

Compounds 67, which were obtained in 50–85% yields (Scheme 27), showed good antithrombotic activity in a murine model of arterial thrombosis [63].

Synthesis of pyrazole derivatives 69a–c bearing imidazo[4,5-b]indole moiety was achieved by the reaction of ylidenes 68a–c with hydrazine hydrate (Scheme 28). The obtained products were successfully examined for their antibacterial activities against four bacterial strains (Bacillus subtilis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa) and antifungal activities against two fungi (Aspergillus flavus and Candida albicans) [64].

N-Tosyl hydrazones 70 with unactivated bromovinyl acetals 71 via 1,3-dipolar cycloaddition reaction to give 3,5-disubstituted 72 pyrazoles was obtained in yields of up to 92% (Scheme 29) [65].
Synthesis of pyrazole derivatives 69a–c bearing imidazole moiety was achieved by the condensation of hydrazones 68a–c with unactivated bromovinyl acetals 71 via Vilsmeier–Haack reaction. The condensation process of a hydrazone 70 with hydrazine hydrate (Scheme 28) [65] reported that when acetophenone, substituted phenyl hydrazine (4) in DMF were exposed to MW at 200 W intermittently at 10 s intervals, reaction provided 1-substituted phenyl-2-(1-phenyl-ethylidene)hydrazines 73. When compound 73 was added portion-wise with Vilsmeier–Haack reagent (POCl₃–DMF/SiO₂), and the powder is then irradiated in a microwave oven at 400 W intermittently at 30 s intervals, pyrazoles 74 were obtained in moderate to good yields (Scheme 30) [66].

Lokhande et al. prepared 3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (74) using the Vilsmeier–Haack reaction. The condensation process of a hydrazone 73 in POCl₃/DMF as a solvent gave the 4-formyl pyrazole derivative 74 (Scheme 31) [67].

2.1.5. Via Vilsmeier–Haack Reaction

In 2014, Selvam et al. [66] reported that when acetophenone, substituted phenyl hydrazine (4) in DMF were exposed to MW at 200 W intermittently at 10 s intervals, reaction provided 1-substituted phenyl-2-(1-phenyl-ethylidene)hydrazines 73. When compound 73 was added portion-wise with Vilsmeier–Haack reagent (POCl₃–DMF/SiO₂), and the powder is then irradiated in a microwave oven at 400 W intermittently at 30 s intervals, pyrazoles 74 were obtained in moderate to good yields (Scheme 30) [66].

Lokhande et al. prepared 3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (74) using the Vilsmeier–Haack reaction. The condensation process of a hydrazone 73 in POCl₃/DMF as a solvent gave the 4-formyl pyrazole derivative 74 (Scheme 31) [67].
Scheme 30. MW assisted the Vilsmeier–Haack reagent in the synthesis of pyrazoles 74.

A series of pyrazole derivatives 74a–j has been obtained from arylhydrazones 73a–j via a Vilsmeier–Haack reaction. Among them, a p-nitrophenyl moiety connected to a pyrazole scaffold exerted the highest anti-inflammatory activity, which is superior to the standard diclofenac sodium (Scheme 32) [68].

Scheme 31. Synthesis of pyrazole-4-carbaldehyde derivatives 74.

A series of pyrazole derived by thiophene derivatives 76 was achieved. As 1,3-disubstituted-1H-pyrazole-4-carbaldehydes 74 were synthesized by Vilsmeier–Haack reaction of hydrazones 73 (Scheme 33). Subsequently, a reaction of 74 with 2-amino-5-(2,4-dichlorophenyl)thiophene-3-carbonitrile (75) in the presence of a catalytic amount of glacial acetic acid in ethanol provided 76 in good yields (Scheme 33) [69]. The obtained products were then evaluated for their antibacterial, anti-inflammatory, and antitubercular studies.
Pyrazole-4-carbaldehyde sulfonate derivatives 74a–f were synthesized via Vilsmeier-Haack reaction hydrazone of sulfonic acids 73a–f with acetophenones. Treatment of compounds 74a–f with thiazolidine-2,4-dione gave the corresponding condensed products 77a–f (Scheme 34) [70].

Compounds 77a–f were evaluated for their COX inhibition, AI activity, ulcerogenic liability, and anti-diabetic activity. The target compounds were assessed in vitro against α-glucosidase and β-glucosidase, in vivo hypoglycemic activity in addition to PPARγ activation study. Two derivatives gave higher COX-2 S.I. (8.69–9.26) than the COX-2 selective drug celecoxib (COX-2 S.I. = 8.60) and showed the highest AI activities and the lowest ulcerogenic than other derivatives. Moreover, these derivatives showed higher inhibitory activities against α- and β-glucosidase (% inhibitory activity = 62.15 and 55.30 for α-glucosidase and 57.42 and 60.07 for β-glucosidase) than reference compounds (acarbose with % inhibitory activity = 49.50 for α-glucosidase and D-saccharic acid 1,4-lactone monohydrate with % inhibitory activity = 53.42 for β-glucosidase) and also showed good PPAR-γ activation and good hypoglycemic effect in comparison to pioglitazone and rosiglitazone.

Similarly, two sets of trisubstituted pyrazole derivatives 78a–e and 79a–e were synthesized by the steps shown in Scheme 35. The obtained products were evaluated for their anti-inflammatory effects, cyclooxygenase (COX) inhibitory activity, and ulcerogenic liability (Scheme 35) [71]. Some derivatives of compounds 78a–e and 79a–e showed considerable edema inhibition percentage range compared with celecoxib (13–93% and 58–93%, respectively) at different time intervals. Compound 79e showed the best screening results if compared with celecoxib (inhibition % = 93.62 and 93.51% at 5 h, COX-1/COX-2 selectivity index SI = 215.44 and 308.16, and ulcer index = 7.25 and 8, respectively).

2.2. Pyrazoles from Diazo Compounds

Diazoalkanes served as starting materials for the classical Pechmann reaction. Aggarwal et al. reported a one-pot approach proposed using diazo compounds 81 generated in situ from tosyl hydrazone salts 80 (Scheme 36). Direct 1,3-cycloaddition of diazo compounds 81 would afford the pyrazole 5 after an aromatization of the cycloadduct intermediate 82 (Scheme 36) [72].
Scheme 33. Pyrazole-clubbed thiophene derivatives 76. ... were assessed in vitro against α-glucosidase and β-glucosidase, in vivo hypoglycemic activity in addition to PPARγ ac-

Scheme 34. Synthesis of pyrazole sulfonate derivatives 77a–f.

1,3,4,5-Tetrasubstituted pyrazoles 85 were synthesized in moderate to good yields through the one-pot reaction of the Huisgen zwitterion from triphenylphosphine in dimethoxyethane (DME) and dialkyl azodicarboxylates 83 with 3-substituted allenates 84 (Scheme 37) [73].

In 2006, Hari et al. [74] synthesized di- and trisubstituted pyrazoles 89 by the reaction of (diazomethyl)trimethylsilane (86) with MgBr₂ and ketones to give 87, which subsequently reacted with ethyl propiolate (88) or dimethyl acetylenedicarboxylate (42) under reflux of THF to give pyrazoles 89 (Scheme 38) [74].

Cross-coupling/electrocyclization reaction of substituted acyclic and cyclic enol tri-flates 90 with diazoacetates 91 provided the corresponding 3,4,5-trisubstituted pyrazoles 93 [75]. The reaction of 90 with 91 in the presence of N-methylmorpholine (NMM, Scheme 39) was established via the formation of intermediate 92 (Scheme 39) [75].
Scheme 35. Synthesis of pyrazole derivatives 78a–e and 79a–e. Reagents and conditions; (a) glacial AcOH/EtOH, reflux; (b) POCI3/DMF; (c) R1-Ph-NH2, glacial AcOH/EtOH, Reflux; (d) R2-Ph-CO-CH3, glacial AcOH/EtOH, reflux.

Scheme 36. Formation of pyrazoles 5 via intramolecular cycloaddition of vinyldiazonium salt 81.

Scheme 37. One-pot synthesis of pyrazoles 85.
Scheme 36. Formation of pyrazoles 5 via intramolecular cycloaddition of vinyldiazonium salt 88 or 42. Reagents and conditions; (a) 5 mol% Pd(PPh3)4; (b) 2 eq. NMM. DMF, r.t., 3–6 h; (c) 60 °C, 12–18 h.

Scheme 38. Synthesis of pyrazole derivatives 89. Reagents and conditions; (a) 1.2 eq. n-BuLi/THF, −78 °C, 20 min; (b) 1–1.2 eq. MgBr2, 10 min, 2.1 eq. RCO′, 1.5 h; (c) THF, reflux, 1 d.

Scheme 39. Synthesis of pyrazole derivatives 93. Reagents and conditions; (a) 5 mol% Pd(PPh3)4; (b) 2 eq. NMM. DMF, r.t., 3–6 h; (c) 60 °C, 12–18 h.

Parham et al. [76] developed a facile reaction of (Z)-(2-nitroprop-1-en-1-yl)benzene 94 with diazomethane to give pyrazoline 95 that lose the nitro group as oxides of nitrogen on heating, or with acids or bases, to give 3-methyl-4-phenyl-1H-pyrazole 5 (Scheme 40) [76].

Scheme 40. Synthesis of 3-methyl-4-phenyl-1H-pyrazole 5.

The group mentioned above also reported that diphenyl diazomethane and secondary nitroolefin 96 gave 5,5-diphenyl-3-nitro pyrazoline 97, which rearrange as shown when treated with acids or bases to give 3-methyl-4,5-diphenyl-1H-pyrazole 5 (Scheme 41) [77].

Scheme 41. The reaction of diphenyl diazomethane and secondary nitro olefins 96; synthesis of pyrazole 5.

Auwers et al. [78] prepared the pyrazole 5 from the reaction of cinnamonic acid 98 with diazomethane, which gave an unstable pyrazoline 99 that losses hydrogen cyanide and gave 5 (Scheme 42) [78].
The reaction of diphenyl diazomethane and secondary nitro olefins (Scheme 43) gave diazomethane aryl nitroolefin 41) [77].

The group mentioned above also reported that diphenyl diazomethane and secondary nitroolefin 98 with diazomethane to give pyrazoline 99 or with acids or bases that lose the nitro group as oxides of nitrogen to give 3-nitro pyrazoline 5.

Julia et al. [79] reported on the synthesis of 1,3,4,5-tetrasubstituted pyrazoles 5 (Scheme 43) via the reaction 100 with various substituted nitriles 101 in the presence of cupper acetate at 110–120 °C (Scheme 43) [79].

**Scheme 43.** Facile synthesis of tetrasubstituted pyrazoles 5.

Rai et al. [80] reported on the synthesis of nitrofurans containing 1,3,4,5-tetrasubstituted pyrazole derivatives 104 (Scheme 44). Compounds 104 were obtained by refluxing 3-(5-nitrofuran-2-yl)-1-phenylprop-2-yn-1-ones 102 with 4-bromo-3-(aryl)-4,5-dihydro-1,2,3-oxadiazol-3-im-5-olates 103 in xylene. Compound 2-(5-bromo-3-(5-nitrofuran-2-yl)-1-(p-tolyl)-1H-pyrazol-4-yl)-1-(4-bromophenyl)-ethan-1-one (Scheme 44) showed highest antibacterial and antifungal activity than all other compounds [80].

Chen et al. conducted the synthesis of a trisubstituted pyrazole 105, in 41–48% yields, via 1,3-dipolar cycloaddition reaction between arylsydnones 103 and α,β-unsaturated ketones 22 in dry xylene (Scheme 45) [81].

Delaunay et al. [82] described the synthesis of the two regioisomeric 1,3,4,5-substituted pyrazoles 107 and 108 by a cycloaddition reaction of a 4-iodo-3-(4-methoxy phenyl)-1,2,3-oxadiazol-3-im-5-olate 103 with ethyl bromopropiolate (106). The separation of pyrazoles 107 and 108 was easily performed by silica gel chromatography (Scheme 46) [82].
2.3. Heterocyclic Ring Rearrangement

Rai et al. [80] reported on the synthesis of nitrofuran containing 1,3,4,5-tetrasubstituted pyrazole derivatives 104 (Scheme 44). Compounds 104 were obtained by refluxing 3-(5-nitrofuran-2-y1)-1-phenylprop-2-yn-1-one 102 with 4-bromo-3-(aryl)-4,5-dihydro-1,2,3-oxadiazol-5-olates 103 in xylene. Compound 2-(5-bromo-3-(5-nitrofuran-2-y1)-(p-tolyl)-1H-pyrazol-4-yl)-1-(4-bromophenyl)ethan-1-one (Scheme 44) showed highest antibacterial and antifungal activity than all other compounds [80].

Scheme 44. Synthesis of 1,3,4,5-tetrasubstituted pyrazole derivatives 104.

Chen et al. conducted the synthesis of a trisubstituted pyrazole 105, in 41–48% yields, via 1,3-dipolar cycloaddition reaction between arylsydnones 103 and α,β-unsaturated ketones 22 in dry xylene (Scheme 45) [81].

Scheme 45. Synthesis of trisubstituted pyrazoles 105.
5-Trifluoromethyl-3-hydroxypyrazoles 110 (Scheme 47) were readily prepared from 4-trifluoroacetyl-1,3-oxazolium-5-olates 109 and phenyl hydrazine (4) [83].

Xie et al. [84] have developed an efficient protocol to prepare 3,4-diarylpyrazoles 5 in 48–95% yields [84]. The strategy involves sequential Suzuki coupling between iodothiophenes 111 and phenylboronic acids 112 in the presence of Pd(PPh3)4 and K2CO3, followed by condensation with hydrazine hydrate (Scheme 48) [84].

Rykowski et al. [85] prepared pyrazoles from triazines by condensation of 3-chloro-6-phenyl-1,2,4-triazines 113 on α-chlorosulfonyls in the presence of KOH and DMSO as a solvent to give the corresponding pyrazoles 114 in 47–93% yields (Scheme 49) [85].

In 2000, Simoni et al. [86] reported that tetrazolyl acroleins 115 reacted with fumaronitrile (116) in xylene at 140 °C to give the corresponding pyrazoles 117 (Scheme 50) [86].
Liu et al. [87] reported on a one-pot, three-component approach consisting of acid chlorides, terminal alkynes, and hydrazine catalyzed by Pd(PPh₃)₂Cl₂/Cul to give 3,5-diaryl-1H-pyrazoles 5 in moderate to good yields (Scheme 51). However, the aliphatic alkyne 1-octyne led to its corresponding pyrazole derivative in only 15% yield [87]. A general procedure for the preparation of compounds 5 was described as a mixture of PdCl₂(PPh₃)₂ (0.01 mmol), Cul (0.03 mmol), Et₃N (2.0 mmol) acid chloride (1.5 mmol), and alkyne 20 (1.0 mmol) in THF (5 mL) was stirred at room temperature for 2 h under N₂. Then hydrazine (3.0 mmol) in CH₂CN (2 mL) was added, and the reaction mixture continued to stir for 16 h. The reaction mixture was diluted with water and extracted with dichloromethane. Column chromatography to obtain the pure products 5.

The four-component reaction of aromatic aldehydes 34, malononitrile, phenylhydrazine (4), and ethyl acetoacetate (6) in the presence of sodium benzoate in an aqueous solution (Scheme 52) was reported to give compounds 118 [88]. Sodium benzoate was used

![Scheme 49](image-url)  
**Scheme 49.** Preparation of pyrazoles 114 from triazines 113.

![Scheme 50](image-url)  
**Scheme 50.** Synthesis of cyanopyrazoles 117.

### 2.4. Multicomponent Synthesis

![Scheme 51](image-url)  
**Scheme 51.** Cyclocondensation of acid chlorides with acetylenes and hydrazine in the presence of PdCl₂(PPh₃)₂/Cul. Reagents and conditions; (a) PdCl₂(PPh₃)₂/Cul, Et₃N, THF/CH₂CN, rt 2 h, THF; (b) NH₂NH₂/CH₂CN.
as the mild basic catalyst. Table 3 summarizes the trials using different molar % of catalysts and the corresponding yields of products [88].

![Scheme 52](image)

**Scheme 52.** Synthesis 1,4-dihydropyrano[2,3-c]pyrazole derivatives 118.

| Entry | Solvent | Amounts of Catalyst (mol%) | Time (min) | Yield (%) |
|-------|---------|----------------------------|------------|-----------|
| 1     | H₂O     | 2.5                        | 35         | 45        |
| 2     | H₂O     | 5                          | 30         | 53        |
| 3     | H₂O     | 10                         | 30         | 84        |
| 4     | H₂O     | 15                         | 30         | 90        |
| 5     | H₂O     | 20                         | 35         | 81        |

It was reported that the pyrazoles 5 were obtained in 59–93% yields during the reaction of palladium-catalyzed four-component coupling of phenylacetylene (20), hydrazine derivatives 4, aryl iodide, carbon monoxide under ambient pressure, and room temperature for 24 to 36 h (Scheme 53) [89].

![Scheme 53](image)

**Scheme 53.** Four component reaction for preparation of pyrazoles 5. Reagents and conditions; (a) 1 mol, PdCl₂(PPh₃)₂, CO (ambient pressure); (b) THF/H₂O(1:1), r.t., 24–36 h.

Pyranopyrazoles 118 were efficiently synthesized in 88–95% yields via the one-pot four-component reactions of ethyl acetoacetate (6), hydrazine hydrate, aldehydes 34, and malononitrile in the presence of Co₃O₄-SiO₂-NH₂ nanocomposites as a catalyst (Scheme 54) [90].

![Scheme 54](image)

**Scheme 54.** Four component reaction for preparation of pyrazoles 118.
2.5. Eco-Friendly Methods for Pyrazole Synthesis

Beyzaei et al. [91] synthesized polysubstituted pyrazoles 65 in 84–91% yields through a two-step, one-pot procedure. In this technique, the reaction of 2,4-dinitrophenylhydrazine, malononitrile, and different aldehydes 34 in deep eutectic solvent (DES) were carried out (Scheme 55) [91].

![Scheme 55. Synthesis of polysubstituted pyrazoles 65 using a deep eutectic solvent. Reagents and conditions; (a) Gly/K₂CO₃/H₂O (4:1:14; W/W), 80 °C, 2 min; (b) 2,4-(NO₂)₂-C₆H₃NH₂, 80 °C, 18–28 min.](image)

Four-component one-pot preparation of 1,4-dihydropyran[2,3-c]pyrazoles 118 using phenylhydrazine 4 or hydrazine monohydrate, acetoacetic ester (6), malononitrile, and aldehydes 34 under thermal and solvent-less conditions with maltose as a catalyst was reported by Kangani et al. The reaction efficiently proceeded to produce the respective products 118 in 74–89% yields (Scheme 56) [92].

![Scheme 56. Synthesis of polysubstituted pyrazoles 118.](image)

Zolfigol et al. described an effective three-component condensation reaction of malononitrile, aryl aldehydes, and phenyl hydrazine (4) under solvent-free conditions using 1-methylimidazolium trinitromethanide [[HMIM][NO₂]₃] (119) as a catalyst in the formation of 5-aminopyrazole-4-carbonitriles 65 (Scheme 57) [93].

![Scheme 57. Synthesis of polysubstituted pyrazoles 65.](image)
Under microwave irradiation, the reaction of 1,3-diketones 3 with phenylhydrazine (4) in the presence of organic nanocatalyst in an aqueous medium produced pyrazoles 5 in 78–98% yields (Scheme 58) [94].

![Scheme 58. Synthesis of pyrazoles 5.](image)

Facile formation of functionalized pyrazole derivatives 120 under solvent-less conditions was achieved by treating 4 with aldehydes 34 and acetoacetic ester (6). This methodology showed the synthetic potential of microwave irradiation and scandium (III) triflate Sc(OTf)₃ as a catalyst (Scheme 59) [95].

![Scheme 59. Synthesis of polysubstituted pyrazoles 120.](image)

A grinding induced the formation of highly substituted pyrazoles 65 by applying malononitrile, functionalized aldehydes 34, and phenylhydrazine (4). Singh et al. reported this procedure utilizing IL 121 as a catalyst without the formation of any byproducts (Scheme 60). Most importantly, simple handling and attainment of high yield up to 97% are the advantages of this methodology [96].
3. Heteroannulated Pyrazoles

3.1. Heteroannulation with Six-Membered Heterocycles

Pyranopyrazoles consists of four possible isomeric forms naming as pyrano[2,3-c]pyrazole, pyrano[4,3-c]pyrazole, pyrano[3,2-c]pyrazole, pyrano[3,4-c]pyrazole and pyrano[2,3-c]pyrazole, are found as the most widely studied (Figure 5).

4-Benzylidene-pyrazol-5-one 122 with malononitrile in methanol in the presence of sodium acetate catalyst has been used to obtain pyrano[2,3-c]pyrazoles 118 (Scheme 61) [97].

Peng and co-workers reacted 5-alkoxycarbonyl-2-amino-4-aryl-3-cyano-6-methyl-4H-pyrans 123 with hydrazine hydrate in the presence of a catalytic quantity of piperazine, and the corresponding pyranopyrazoles 118 were obtained (Scheme 62). The strategy of the synthesis was carried out in three methods, namely (i) heating; (ii) exposure to microwave irradiation; (iii) exposure to a combination of microwave and ultrasound irradiation (CMUI). The procedure was later found to be excellent in yield within a short time (Scheme 62) [98].
Dyachenko and Rusanov allowed stirring benzylidene-pyrazolone 122 with cyanothioacetamide in morpholine containing an ethanolic solution to obtain various pyrano[2,3-c]pyrazoles 118 (Scheme 63) [99].

It was reported that the reaction of (2-cyano-3-furan/thiophen-2-yl)acrylonitriles 124 with 3-aminopyrazolin-5-one (125) in the presence of the base, which, via Michael addition, afforded 3-aminopyranopyrazoles 126 (Scheme 64) [100].

Hafez and co-workers reacted 2-oxo-3-substituted indole 127 with pyrazolone 128 in boiling ethanol and catalyzed by Et$_3$N to prepare spiroarylpynyldolones 129 (Scheme 65) [101].

Pyranopyrazoles 118 were obtained in good yields by a three-component reaction of aldehydes 34, malononitrile, and pyrazol-5-one 128, in refluxing ethanol with piperididine catalyst (Scheme 66) [102].
Scheme 65. Synthesis of spiropyranylindolones 129a–d.

Pyran[2,3-c]pyrazoles 118 were prepared by a four-component reaction of aldehydes 34, malononitrile, β-ketoester (6), and hydrazines 4 with/without catalyst. Several carbonyl compounds, β-keto ester, and un/substituted hydrazine were chosen together with various catalysts, solvents, temperatures, and green techniques, which were also applied (Scheme 66) [103].

Scheme 66. Synthesis of pyranopyrazoles 118.

Enders and co-workers prepared the enantioselective tetrahydropyrano-pyrazoles 131 from the reaction of pyrazolone 128, α,β-unsaturated aldehydes, and Wittig reagent 130 in the presence of secondary amines, such as catalysts (Scheme 68) [104].

Scheme 67. Synthesis of pyranopyrazoles 118.

Scheme 68. Synthesis of pyranopyrazoles 118. 
Scheme 68. Enantioselective formation of tetrahydropyrano-pyrazoles 131.

Lu and co-workers reported on a one-pot synthesis of pyranopyrazoles 118 via Suzuki coupling between 4-bromobenzaldehyde and aryl boronic acid 132 together with KF·2H2O as a dehalogenating agent in the presence of Pd/C at 80 °C. Firstly, 4-bromobenzaldehyde and aryl boronic acid was added to form substituted biphenyl aldehydes; subsequently, other reagents were added and allowed to react for 5–6 h (Scheme 69) [105].

Another five components, synthesis of pyranopyrazoles 118, involved a mixture of acid chlorides, Meldrum’s acid (133), aromatic aldehydes 34, hydrazine hydrate, and malononitrile in the presence of CuI nanoparticles (Scheme 70) [106].

3.1.2. Pyrazolopyrimidine

Pyrazolopyrimidines are considered the structural analogs of the biogenic purine class. Pyrazolopyrimidines are of interest as potential bioactive molecules. Pyrazolopyrimidines have four known structures, as illustrated in Figure 6.
\[
\text{R'}\text{COCl} + \text{CHO} + \text{NH}_2\text{NH}_2 + \text{O} = \text{H}_2\text{O, reflux} \rightarrow \text{Cul nanoparticles} \rightarrow \text{CN} \rightarrow \text{R'} \text{H}_2\text{N}_{2} \text{H}_2 \rightarrow \text{118 (84–95%)}
\]

\( R' = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_{15} \)

\( R^2 = \text{H, 4-Cl, 4-Br, 3-CH}_3, \text{4-CH}_3, \text{3-NO}_2, \text{4-NO}_2, \text{3-OCH}_3 \)

Scheme 70. Multicomponent synthesis of pyrano-pyrazoles 118.

![Pyrazolo[3,4-d]pyrimidines](image1)

Figure 6. Isomeric forms of pyrazolopyrimidines.

One of the essential pharmacological applications of pyrazolo[4,3-d]pyrimidine derivatives is Sildenafil (Viagra® 134) and its analogs 135 (Figure 7). Compounds 135 were used as a selective phosphodiesterase 5 (PDE5) to treat male erectile dysfunction as an oral agent. Recently, a series of Sildenafil analogs (R = Me, Et; R2 = Me, Et, -CH2CH2OH) was prepared, and the in vitro PDE5 inhibitory activities were evaluated; the results revealed improved activity and selectivity [107].

![Sildenafil structure](image2)

Figure 7. Chemical structure of Sildenafil 134 and Sildenafil analog 135.

The reaction of compound 136 with benzoyl isocyanate in the presence of ammonium hydroxide gave 5-amino-1-phenylpyrazolo[3,4-d]pyrimidinone derivative (137) (Scheme 71) [108]. Treatment of 136 with triethyl orthoformate in acetic anhydride afforded the methanimidate 138, which on treatment with ammonia gave pyrazolo[3,4-d]pyrimidin-4-ylaminederivative 139 (Scheme 71) [109].
Scheme 71. Synthesis of pyrazolopyrimidinone derivatives 137 and 139.

5-Amino-1H-pyrazolo[3,4-d]pyrimidine derivative 140 could be obtained directly by treatment of 5-aminopyrazole-4-carbonitrile (65) formamidine in acetic acid (Scheme 72) [110].

Scheme 72. Synthesis of 5-Amino-1H-pyrazolo[3,4-d]pyrimidine derivative 140.

The reaction of 5-amino-1-methyl-1H-pyrazole-3,4-dicarbonitrile 141 with N-methylformamide gave the imine intermediate 142. The latter intermediate underwent ring opening by a typical Dimroth rearrangement and recylized to furnish the pyrazolo[3,4-d]pyrimidine 143 carrying a methylamino group at 4-position (Scheme 73) [111].

Scheme 73. Synthesis of pyrazolo[3,4-d]pyrimidine 143.

Conversion of compound 65 into corresponding carboxylic acid amide derivative 144 was achieved by the hydrolysis of the nitrile group using sulfuric acid. On the fusion of 144 with thiourea, the reaction proceeded to give 4-hydroxy-6-mercaptopyrazolo[3,4-d]pyrimidine 145 (Scheme 74) [112].
5-Benzamido-1H-pyrazolo[3,4-d]pyrimidin-4-one (147) was prepared by reacting 5-amino-1H-pyrazole-4(N-benzoyl)carbohydrazide (146) with triethyl orthoformate (TEOF) (Scheme 75) [113].

Similarly, reaction of 5-amino-1-phenyl-1H-pyrazole-4-carboxylic acid hydrazide (148) with urea in decalin gave pyrazolo[3,4-d]pyrimidine-4,6-dione derivative 149 (Scheme 76) [114].

El-Enany et al. [115] reacted 5-amino-3-methylsulphanyl-1-phenyl-1H-pyrazole-4-carboxylic acid amide (150) with propionic anhydride, chloroacetyl chloride or 3-chloropropionyl chloride to produce the 6-substituted pyrazolo[3,4-d]pyrimidin-4(5H)-one derivatives 151a–c in 83–96% yield (Scheme 77) [115].

Kandeel et al. [116] synthesized pyrazolo[3,4-d]pyrimidin-4(5H)-one 152 via the reaction of 5-amino-3-methyl-1H-phenylpyrazole-4-carbonitrile 65 with formic acid (Scheme 78) [116].
El-Enany et al. [115] reacted 5-methylsulfanyl-1-(1,3,4-thiadiazolyl-2-yl)pyrazolo[3,4-d]pyrimidines 154 (Scheme 79) [117].

When pyrazolylcarbothiohydrazide 155 was treated with formic acid or triethyl orthoformate, it gave 3-methylsulfonyl-1-(1,3,4-thiadiazolyl-2-yl)pyrazolo[3,4-d]pyrimidin-4(5H)-one 156 (Scheme 80) [118].
Ghorab et al. [114] reacted ethyl 5-amino-1-phenyl-1H-pyrazole-4-carboxylate (157) with hydrazine hydrate or benzyl amine in the presence of triethyl orthoformate (TEOF) to obtain the 5-substituted derivatives 158a,b (Scheme 81) [114].

![Scheme 81. Synthesis of 5-substituted pyrazolo[3,4-d]pyrimidin-4(5f)-ones 158a,b.](image)

Fusion of 159 with formamide at 200 °C for 8 h afforded the corresponding pyrazolo[3,4-d]pyrimidin-4-one 160 (Scheme 82) [119].

![Scheme 82. Synthesis of pyrazolo[3,4-d]pyrimidin-4-one 160.](image)

5-Amino-1H-pyrazol-4-carbonitrile derivative 65 afforded with carbon disulfide in pyridine 4,6-dithioxopyrazolo[3,4-d]pyrimidine derivative 162 upon gentle refluxing. The reaction underwent a rearrangement process of the thiazine intermediate 161 during treatment with NaOH (Scheme 83) [120].

![Scheme 83. Synthesis of 4,6-dithioxopyrazolo[3,4-d]pyrimidine derivatives 162.](image)

### 3.1.3. Pyrazolopyridines

The pyrazolo[3,4-b]pyridine moiety is known as a privileged structural motif of drug-like molecules. Tracazolate 163, etazolate 164, and glicaramide 165 are considered as drug-analogous containing pyrazolo[3,4-b]pyridine (Figure 8) [121–123].
Figure 8. Drugs containing pyrazolo[3,4-b]pyridine scaffold 163–165.

Jiang and co-workers [124] reported on microwave irradiation of a multicomponent reaction of 5-amino-pyrazoles 166 with arylglyoxal monohydrates 167 and aromatic amines in the presence of p-TsOH/DMF produced substituted acyl pyrazolo[3,4-b]pyridines 168 in good yields (Scheme 84) [124].

Scheme 84. Synthesis of pyrazolo[3,4-b]pyridines 168.

One-pot synthesis of fully substituted 1H-pyrazolo[3,4-b]pyridines 169 was established based on a three-component approach between 5-aminopyrazoles 166, β-ketonitriles, and aromatic/aliphatic aldehydes 34 in the presence of triethylamine (Scheme 85) [125].
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Figure 8. Drugs containing pyrazolo[3,4-b]pyridine scaffold... derivatives 169. Reagents and conditions; (a) Et3N (2 eq), DMF, 90 °C; (b) NaNO2 (3 eq) AcOH, rt.

Lee and Park [126] reported on the synthesis of aryl pyrazolo[3,4-b]pyridines 171 from 5-aminopyrazoles 166 and indole-3-carboxaldehydes 170 catalyzed by AlCl3 by the indole ring-opening without using catalysis with transition metals (Scheme 86) [126].

In 2017, Portilla and co-workers [127] reported on the synthesis of substituted pyrazolo[3,4-b]pyridines 173 under microwave-assisted regioselective reaction to 5-aminopyrazoles 166 with 3-(3-oxo-2-benzofuran-1(3H)-ylidene)pentane-2,4-dione 172. The reaction was based on a domino aza-Michael-cyclization-dehydration sequence (Scheme 87) [127].

An efficient facile synthesis of substituted pyrazolo[3,4-b]pyridines 175 in 53–86% yield was reported by Miliutina and co-workers [128]. The protocol was achieved by the reaction of 5-aminopyrazoles 166 with 3-chlorochromones 174 in the presence of phosphoric acid (Scheme 88) [128].
Scheme 88. Synthesis of substituted pyrazolo[3,4-b]pyridines 175.

3.2. Heteroannulation with Five-Membered Heterocycles
3.2.1. Imidazo-Pyrazole

2-Phenyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazole-7-carboxamide 177 was prepared by cyclization of 5-amino-1-(2-hydroxy-2-phenylethyl)-1H-pyrazole-4-carboxamide 176 in the presence of concentrated sulfuric acid (Scheme 89) [129].

Scheme 89. Synthesis of imidazo[1,2-b]pyrazole-7-carboxamide 177.

Ethyl 5-amino-1-(2,2-diethoxyethyl)-1H-pyrazole-4-carboxylate 178 was reacted with hydrazine followed by a reaction with nitrous acid to afford 1H-imidazo[1,2-b]pyrazole-7-carbonyl azide 179 rearranged to produce carbamates 180 (Scheme 90) [130].

Scheme 90. Synthesis of 7-substituted 1H-imidazo[1,2-b]pyrazoles 180.

Amino-1-(2-hydroxyethyl)pyrazole 181 was formylated, treated with methanesulfonyl chloride and triethylamine, followed by cyclization with sodium hydride, to give 1-formyl-2,3-dihydro-1H-imidazo[1,2-b]pyrazole 182 (Scheme 91) [131].
Scheme 89. Synthesis of imidazo[1,2-b]pyrazole-7-carboxamide derivatives 187. In THF in the presence of triethylamine afforded 3H-imidazo[1,2-b]pyrazoles 187 in good yields (Scheme 93) [133].

The 3-amino-5-phenylpyrazoles 183 reacted with 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-oxo-N-phenylethanehydrazoneyl bromide 184 in boiling ethanol to give 3-phenylazo-2-(4-methyl-2-phenyl-thiazol-5-yl)-6-phenyl-5H-imidazo[1,2-b]pyrazoles 185 (Scheme 92) [132].

Scheme 92. Synthesis of imidazo[1,2-b]pyrazoles 185.

Regioselective cyclization reaction between compound 166 and oxaldiimidoyl dichlorides 186 in THF in the presence of triethylamine afforded 3H-imidazo[1,2-b]pyrazoles 187 in good yields (Scheme 93) [133].

Scheme 93. Synthesis of 3H-imidazo[1,2-b]pyrazoles 187.

5-Aminopyrazole 166 was reacted with either ethyl α-chloroacetoacetate or chloroacetyl chloride to yielded 1-(2-hydroxy-3H-imidazo[1,2-b]pyrazole-3-yl)ethanone 188 and 3H-imidazo[1,2-b]pyrazole-2-ol 189, respectively (Scheme 94) [134].
Figure 9. Regioisomers of thienopyrazoles. A series of N-alkyl-2-aryl-5H-imidazo[1,2-b]pyrazole-3-amines 191 in good to high yields were synthesized by the three-component condensation of aromatic aldehydes 34, amino-pyrazole 166, and isocyanide 190 in acetonitrile in the presence of 4-toluenesulfonic acid as a catalyst at room temperature (Scheme 95) [135].

There are three different regioisomers of thienopyrazoles, as shown in Figure 9.

4,5-Dihydro-3-methyl-1-phenyl-5-thioxo-1H-pyrazole-4-carboxaldehyde 192 reacted with nitromethane in the presence of dibenzoyl peroxide, Et$_3$N in ethanol to produce 5-nitro-3-methyl-1-phenylthieno[2,3-c]pyrazole 193 (Scheme 96) [136].
Scheme 96. Synthesis of 5-nitro-3-methyl-1-phenylthieno[2,3-c]pyrazole 193.

5-Chloro-3-methyl (or phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde 194a,b reacted with ethyl thioglycolate in ethanol and presence of sodium ethoxide to give ethyl thienopyrazole carboxylate 195. In a similar procedure, compounds 196a,b were prepared after saponification with methanolic sodium hydroxide (Scheme 97) [137].

Scheme 97. Synthesis of thieno[2,3-c]pyrazoles 195 and 196a,b. Reagents and conditions; (a) HS-CH2-COOEt; (b) NaOEt/EtOH; (c) HS-CH2-COOMe; (d) 1-MeONa, MeOH, 60 °C, 2-NaOH, MeOH, reflux.

4-Bromo-3-methyl-1-phenyl-2-pyrazolin-5-one (197) reacted with ethyl 3-mercaptocrotonate (198) in an equimolar ratio in ethanol to afford thieno[2,3-b]pyrazole 199 (Scheme 98) [138].

Scheme 98. Synthesis of thieno[2,3-b]pyrazole 199.

1-Phenyl-3-(pyridin-3-yl)-1H-thieno[2,3-c]pyrazole-5-carboxylic acid ethyl ester (200) was synthesized by the reaction of 5-chloro-1-phenyl-3-(pyridin-3-yl)-1H-pyrazole-4-carbaldehyde 194 with ethyl bromoacetate and sodium sulfide. First, reaction of 2-phenyl-5-pyridin-3-yl-2,4-dihydro-pyrazol-3-one (128) with Vilsmeier–Haack reagent gave 194 in 55% yield (Scheme 99) [139].
A practical and straightforward synthesis of 1-methyl-1H-thieno[2,3-c]pyrazoles from 3-amino-1H-pyrazole-4-carboxylic acid ethyl ester were reported by Toto et al. The 3-substituted ethyl pyrazole-5-sulfonylacetate derivatives 202a–c were synthesized by the reaction of 3-substituted ethyl 5-bromo-N-methyl-pyrazole-4-carboxylates 201a–c with ethyl bromoacetate and sodium sulfide in DMF. Base-catalyzed cyclization of the S-alkylated pyrazoles 202a,b was accomplished using sodium ethoxide in toluene to afford the expected ethyl 4-hydroxythieno[2,3-c]pyrazole-5-carboxylate derivatives 203a,b. Moreover, cyclization of the amine analog 202c under the same conditions yielded the imine derivative 204, which probably came from the self-condensation of the expected amino-thieno fused compound 202c (Scheme 100) [140].

Scheme 100. Synthesis of thieno[2,3-c]pyrazoles 203a,b and 204.

Using the Sonogashira coupling method and starting with pyrazole derivatives to synthesize thieno[2,3-c]pyrazole was reported by Eller et al. [141]. The strategy depends upon the treatment of the available 1,3-disubstituted-5-chloro-1H-pyrazoles 205a,b with I2–HIO3 to obtain the corresponding 5-chloro-4-iodopyrazoles 206a,b. The latter compounds were selectively connected to phenylacetylene (20) by a Sonogashira cross-coupling reaction, yielding only the 4-(phenylethynyl)pyrazoles 207a,b in good yields (87–92%). The final
reaction step, compounds 207a,b, was then subjected to sodium sulfide in DMF to produce compounds 208a,b (Scheme 101) [141].

\[
\begin{align*}
\text{R}^2 \quad & \quad \text{N} & \quad \text{Cl} \\
\text{R}^1 & \quad \text{I} \quad \text{N} \quad \text{Cl} \quad \text{Ph} \\
\text{PdCl}_2(\text{PPh}_3)_2 & \quad \text{DMF/} \text{Et}_3\text{N/Cul} \\
\text{Na}_2\text{S} & \quad \text{DMF} \\
\text{R}^2 & \quad \text{N} \quad \text{Cl} \quad \text{Ph} \\
\end{align*}
\]

\(205\text{a,b} \quad \text{(75–62\%)} \quad 206\text{a,b} \quad \text{(87–92\%)} \quad 207\text{a,b} \quad \text{(75–86\%)} \quad 208\text{a,b}

**Scheme 101.** Sonogashira coupling method to synthesize thieno[2,3-c]pyrazoles 208a,b.

Sabaa et al. and Rabie et al. [142,143] have synthesized thieno[2,3-c]pyrazole 209 using the Gewald reaction. The \(N\)-phenyl pyrazolone 128 underwent the Gewald reaction and reacted with sulfur and malononitrile in equimolar ratios under reflux for 3 h in the presence of triethyl amine (TEA) and absolute ethanol as a solvent to give the amino cyano derivative of thienopyrazole 209 (Scheme 102) [142,143].

\[
\text{N} \quad \text{O} + \text{S} + \text{CH}_2(\text{CN})_2 \quad \text{TEA/} \text{EtOH/heat} \quad \text{N} \quad \text{H} \\
\text{Ph} & \quad \text{Ph} \quad \text{209}
\]

**Scheme 102.** Synthesis of amino cyano thieno[2,3-c]pyrazole 209.

Elgemeie et al. [144] reported the synthesis of thieno[3,4-c]pyrazole ring system 212 (Scheme 103). Preparation of 212 started through the reaction of pyrazolin-5-one 128 reacted carbon disulfide in the presence of sodium ethoxide to afford the sodium dithiolate 210. Then, one equivalent of phenacyl bromide was added to 210 to give the corresponding sodium salt of monoaalkylated product 211. Finally, compound 211 was cyclized to afford the thienopyrazole-4-thiol 212 upon refluxing with sodium ethoxide, followed by acidification (Scheme 103) [144].

El-Saraf et al. [145] prepared a series of thieno[3,4-c]pyrazoles via reaction of the 3-aminopyrazolin-5-one 213 with \(\text{CS}_2\) and different molar ratios of various halo compounds having active methylene under phase transfer condition (PTC), which afforded compounds 214–217 (Scheme 104) [145].
Scheme 103. Synthesis of thienopyrazole-4-thiol 212.

El-Saraf et al. [145] prepared a series of thieno[3,4-c]pyrazoles via reaction of the 3-aminopyrazolin-5-one 213 with CS$_2$ and different molar ratios of various halo compounds having active methylene under phase transfer condition (PTC), which afforded compounds 214–217 (Scheme 104) [145].

3.2.3. Furopyrazole

Furopyrazoles are known to have antitumor, antiproliferative, and antimicrobial activities. Aziz et al. observed that equimolecular amounts of 3-methyl-4-bromo-2-pyrazolin-5-one (197) and malononitrile reacted in absolute ethanol in the presence of piperidine under reflux for 3 h to give furo[2,3-c]pyrazole 218 in 85% yield (Scheme 105) [146]. Then compound 197 reacted with ethyl cyanoacetate to give furo[2,3-c]pyrazole 219 in 80% yield. Whereas benzoylacetonitrile reacted with compound 197 to afford furo[2,3-c]pyrazole 220 in 83% yield (Scheme 105) [147].
Scheme 105. Synthesis of furo[2,3-c]pyrazoles 218–220.

Reaction of 3-methyl-1-phenyl-pyrazol-5-one (128) with bromomalononitrile under PTC conditions [K$_2$CO$_3$/benzene/tetrabutyl ammonium bromide (TBAB) catalyst] afforded 5-amino-4-cyano-3-methyl-N-phenyl-furo[2,3-c]pyrazole 218 in 38% yield (Scheme 106) [148]. The formation of compound 218 was assumed to involve HBr elimination followed by a nucleophilic attack of the OH group to electrophilic carbonitrile, followed by cyclization and aromatization (Scheme 106) [148].

Scheme 106. Synthesis of N-phenyl furo[2,3-c]pyrazole 218.

Rh$_2$(OAc)$_4$ was used as a catalyst of [3 + 2]cycloaddition reaction between 4-diazo-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one 221 and aromatic alkynes 20 (Scheme 107) [149].

In 2019, Milištinaitė et al. [150] reported that the synthesis of 2H-furo[2,3-c]pyrazoles 224 was achieved 5-endo-dig cyclization to afford 4-alkynyl-3-hydroxy-1-phenyl-1H-pyrazoles 223 as a key step and catalyzed by AgOTf/K$_2$CO$_3$. The reactions were complete in DMF at 120 °C after 14 h, and the products 224 were obtained in 64–85% yields (Scheme 108) [150].
Scheme 107. Synthesis of CF₃-substituted ring-fused furo[2,3-c]pyrazoles 222.

Scheme 108. Synthesis of 2H-furo[2,3-c]pyrazoles 224.

Synthesis of dihydrospirofuro[2,3-c]pyrazoles 225 was reported by Kale et al. [151] from the reaction of pyrazolones 128 with aldehydes (34) in boiling water for 30 min followed by addition of bis(acetoxy)-iodobenzene at room temperature for 5 min (Scheme 109) [151].

Scheme 109. Synthesis of dihydrospirofuro[2,3-c]pyrazoles 225.

4,5-Dihydro-1H-furo[2,3-c]pyrazole derivatives 226 were synthesized by a one-pot domino reaction involving pyrazolone 128, aromatic aldehydes 34, and a pyridinium salt catalyzed by DABCO with high diastereoselectivity in H₂O under microwave irradiation (Scheme 110) [152].
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Scheme 110. Synthesis of furo[2,3-c]pyrazole derivatives 226.

Reaction of 128 with p-chloranil (227) in the presence of pyridine in EtOH at reflux for 6–8 h afforded 4,9-dimethyl-2,7-diphenyl-benzo[2,3-b;2',3'-b]bis-furo[3,2-d]pyrazole-5,10-dione (228) in 94% yield (Scheme 111) [153].

Scheme 111. Synthesis of benzo[2,3-b;2',3'-b]bis-furo[3,2-d]pyrazole-5,10-dione 228.

4. Biological Activities

4.1. Anticancer Activity

It was previously mentioned by Aly et al. (see Scheme 23) [60] that 5-amino-1-(1-ethyl-2-oxo-1,2-dihydroquinolin-4-yl)-1H-pyrazole-3,4-dicarbonitrile 56 showed a good antiproliferative EGFR-TK inhibition activity against many tumor cell lines. Moreover, a series of pyrazole/quinolones 61a–f (Figure 10) showed remarkable anticancer activities [61]. Compounds 61a, 61c, and 61f showed a significant decrease in inflammatory mediators TNFα and CRB greater than NAC when compared to model group exhibited a significant decrease in comparison to NAC, especially compound 61c whose found CRB conc 1.90 (mg/dL) in comparison to NAC of conc 2.13 mg/dL.

In 2016, Wu, P.; reported that 5-((4-(2,3-dimethyl-2H-indazol-6-yl)(methyl)amino)pyrimidin-2-yl)amino)-2-methylbenzene-sulfonamide (Figure 10, 229) as molecule kinase inhibitor [154].

Galunisertib (Figure 10) is known as 6-quinoline carboxamide of pyrazole derivative 230 [155], and it is an oral drug that is described as an available, small molecule antagonist of the tyrosine kinase transforming growth factor-beta (TGF-β) receptor type 1 (TGFBR1), with potential antineoplastic activity.
Another pyrazolo-anticancer drug known as Lorlatinib 231 (Figure 10) [156] is an orally available drug known as ATP-competitive inhibitor of the receptor tyrosine kinases, anaplastic lymphoma kinase (ALK), and C-ros oncogene 1 (Ros1), with potential anti-neoplastic activity. Lorlatinib binds to and inhibits both ALK and ROS1 kinases. The kinase inhibition leads to disruption of ALK- and ROS1-mediated signaling and eventually inhibits tumor cell growth in ALK- and ROS1-overexpressing tumor cells.

Al-Saadi et al. [157] synthesized a series of pyrazole and pyrazoline 232 fused ring systems substituted with anticancer biologically active chemical species. Lv et al. [158] synthesized a series of pyrazole-1-carbothioamide derivatives that showed high antiproliferative activity against MCF-7 with IC$_{50}$ 0.08 µM. Among them, compound 3-(3,4-dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide 233 is most potent with IC$_{50}$ of 0.07 µM, as compared to positive control erlotinib (IC$_{50}$ of 0.03 µM) [158].

The anticancer activity of several thiazolone-based compounds containing the 5-aryl-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl 234 was examined by Havrylyuk et al. (Figure 10) [159]. Whereas Zheng et al. synthesized a series of 3-aryl-1-(4-tert-butylbenzyl)-1H-pyrazole-5-carboxyhydrazidehydrazone derivatives and investigated their effects on A549 cell growth, the compound (E)-2-(1-(2-((1-(4-(tert-butyl)benzyl)-3-(4-chlorophenyl)-1H-pyrazol-5-yl)
methyl)hydrazono)ethyl)-4-chlorophenol 235 (Figure 10) showed high growth inhibitory effect and induced apoptosis of A549 lung cancer cells [160]. On the other hand, Kamal et al. reported the synthesis of oxindole–pyrazole derivatives as potent microtubules binders/anticancer agents. Among all, compound 236 (Figure 10) showed anti-proliferative agents with average IC$_{50}$ = 3 µM against HeLa, A549, MCF7, and DU145 cancer cell lines compared to the reference drug nocodazole with average IC$_{50}$ = 1.72 µM [161].

Inhibitor 238 was synthesized by McElroy et al. [162]. The reaction of the pyrazole 166 with pyrazolo[1,5-$a$]pyrimidine-3-carbonyl chloride (237) in the presence of N, N-diisopropylethylamine, or Hünig’s base (DIPEA), produced a series of potent, selective, and orally pyrazole interleukin receptor-associated kinase4 (IRAK4), as shown in Scheme 112 [162].

Lim et al. reported on synthesizing a series of 5-amino-N-(1H-pyrazol-4-yl)-pyrazolo[1,5-$a$]pyrimidine-3-carboxamides 239 and 240 as IRAK4 inhibitors.

Different substituents of 239 and 240 led to identifying IRAK4 inhibitors with excellent potency, kinase selectivity, and pharmacokinetic properties suitable for oral dosing (Figure 11) [163].

Scheme 112. Synthesis of pyrazole IRAK4 inhibitor 238.
Figure 11. Structures of some IRAK4 inhibitors pyrazoles 239 and 240.

4.2. Monoamine Oxidase Inhibitors

Palaska et al. reported on synthesizing several $N^1$-thiocarbamoyl-3,5-diaryl-4,5-dihydro-(1H)-pyrazoles 241a–j. The obtained compounds were screened as monoamine oxidase (MAO) inhibitors against monoamine oxidases isolated and purified from the mitochondrial extracts of rat liver homogenates and human platelets (Figure 12) [164].

Figure 12. Structures of some IRAK4 inhibitors pyrazoles 241a–j.

4.3. Antimicrobial and Antifungal Activity

5-Aryl-isonicotinoyl-3-(pyridine-2-yl)-4,5-dihydro-1H-pyrazoles 242 (Figure 13) were synthesized and showed significant antimycobacterial activity [165].

Özdemir et al. prepared several series of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives 243 (Figure 13) and screened them for antimicrobial activities against, e.g., Escherichia coli, Staphylococcus aureus, Salmonella typhimurium, Bacillus cereus, Streptococcus faecalis, Aeromonas hydrophila, Candida albicans, and Candida glabrata [166].

Zampieri et al. synthesized several 1-(3,5-diaryl-4,5-dihydropyrazol-4-yl)-1H-imidazole derivatives 244 (Figure 13) and tested for their in vitro antifungal and antimycobacterial activities. These imidazole derivatives showed excellent antifungal activity against the clinical strain of C. albicans [167].
A series of 5-amido-1-(2,4-dinitrophenyl)-1H-pyrazole-4-carbonitriles was reported by Rahimizadeh et al., showing that compound 246 (Figure 14) indicated excellent antibacterial activity against methicillin-susceptible, Staphylococcus aureus (MSSA), and methicillin-resistant Staphylococcus aureus (MRSA), with MIC values of 25.1 μM [169].

A series of pyrazole derivatives were synthesized and screened as antibacterial agents against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa. Among the tested compounds, 247–250 (Figure 14) indicated excellent antibacterial activity against all the tested bacterial strains as compared with the standard drug ceftriaxone, which was active at 3.125, 1.6125, 1.6125, and 1.6125 μg/mL against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa strains, respectively (Figure 14) [170].

Compound 251 inhibits activity against both Gram-positive and Gram-negative bacteria [171]. In addition, pyrazole derivatives 252–253 (Figure 14) were prepared and screened for their antibacterial and antifungal activities using ampicillin and norcadine as standard drugs. All compounds were screened for their antimicrobial activities [172].

3-(4-Chlorophenyl)-5-((1-phenyl-3-aryl-1H-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-ones were prepared by B’Bhatt and Sharma. Compound 254 (Figure 14), as a derivative of the last series, was found to show potent activity against Escherichia coli, while compound 255 (Figure 14) was found to be potent against S. aureus, S. pyogenes, and was found to have very good activity against Candida albicans [173].

In 2020, Alnufaie et al. reported on the synthesis of series of naphthyl-substituted pyrazole-derived hydrazones 260 [174].
Figure 14. Structures of some antibacterial active pyrazoles 247–255.

Reaction of 4-hyrazinobenzoic acid (256) with 2-acetylpyrazole (257) afforded the corresponding condensed product 258, which on Vilsmeier–Haack reagent gave compound 259. Finally reaction of 259 with hydrazine derivatives produced the corresponding pyrazoles 260 (Scheme 113) [174]. Many of these pyrazoles showed potent growth inhibitory properties for planktonic Staphylococcus aureus and Acinetobacter baumannii, and its drug-resistant variants with MIC values as low as 0.78 and 1.56 µg/mL, respectively. These compounds also show potent activity against Staphylococcus aureus and Acinetobacter baumannii biofilm formation and eradication properties [174].

Similarly, the same group published on the synthesis and antimicrobial studies of 31 coumarin-substituted pyrazole derivatives 264 [175]. The reaction of 4-hyrazinobenzoic acid 256 with fluoro 261a and hydroxy 261b substituted 3-acetylpyrazole formed the corresponding hydrazones 262a,b, which were subjected to further reaction with POCl₃/DMF to give the formyl-substituted pyrazole derivatives 363a,b (Scheme 114). A series of hydrazine derivatives were then obtained via the reaction of 263a,b with various hydrazine derivatives (Scheme 114) [175]. Some of these compounds have shown potent activity against methicillin-resistant Staphylococcus aureus (MRSA) with MIC as low as 3.125 µg/mL. These results are very significant, as MRSA strains have emerged as one of the most menacing pathogens of humans, and this bacterium is bypassing HIV (in terms of fatality rate). Some pyrazole derivatives inhibited the growth of cell lines with an IC₅₀ around 15 µg/mL [175].
Scheme 113. Synthesis of 4-[4-formyl-3-(2-naphthyl)pyrazol-1-yl] benzoic acid derivatives 260 as potent growth inhibitors of drug-resistant *Staphylococcus aureus* and *Acinetobacter baumannii*.

Scheme 114. Synthesis of antibacterial pyrazole derivatives 264.

Sahu et al. also prepared 4-((5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)amino) phenol (18) (Figure 15), which showed antimicrobial activity and antibacterial activity. Antifungal activity was tested on Sabouraud Dextrose Agar plates by the cup–plate method against *Candida albicans* and *Aspergillus niger*. In both of these assays, ciprofloxacin and clotrimazole were used as standard drugs [46].
Figure 15. Structures of some inflammatory active pyrazoles 18 and 265.

Bondock et al. reported on the synthesis of groups of pyrazole-pyrimidine derivatives. One of them, N-(benzo[d]thiazol-2-yl)-7-methyl-2-(phenylamino)pyrazolo[1,5-a]pyrimidine-3-carboxamide 265, was found to exhibit the most potent in vitro antifungal activity with MICs (6.25 μ/mL) against A. fumigatus and F. Oxysporum, comparable with cycloheximide (3.125 μ/mL) [176].

4.4. Anti-Inflammatory Activity

Kendre et al. reported some 1H-pyrazole derivatives containing aryl sulfonate moieties 266 with anti-inflammatory effects (Figure 16) [177].

Figure 16. Structures of anti-inflammatory pyrazoles 266–269.

Tewari et al. prepared pyrazole derivatives 267–269, and their anti-inflammatory activities were screened using carrageenan rat paw edema bioassay. Among the reported compounds, 268b showed maximum COX-2 inhibitory potency (IC₅₀ = 0.44 μM), while compounds 269a and 269b showed intermediate effects. (Figure 16) [178].
3,6-Disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles bearing pyrazole moieties 270a–g (Figure 17) were screened as anti-inflammatory agents [179]. Among the reported compounds, compound 270g showed the most significant anti-inflammatory activity (64.7% inhibition) compared to the standard drug diclofenac sodium (80.4% inhibition), whereas compounds 270d and 270f showed 56.9% inhibition. The propyl and p-chlorophenyl substituents of 270b and 270f showed significant activity. Whereas compounds have ethyl and p-chlorophenyl moieties, 270a and 270c accounted for moderate activities [179].

El-Sayed et al. also synthesized pyrazole derivatives 271 and 272 (Figure 17), and their anti-inflammatory activities were screened. Compounds 271a and 271d were found as the most selective among the tested compounds with good inhibitory profiles against COX-2 (Figure 17) [180].

### 4.5. Antiviral Activity

It was reported that the derivative containing the R = Cl group of a series of 4,5-disubstituted pyrazole derivatives 273 (Figure 18) showed broad potent antiviral activity against a broad panel of viruses in different cells cultures (HEL Cell cultures) [181]. Moreover, substituted pyrazole derivatives 274 (Figure 18) showed good antiviral activity against hepatitis A [182].
4.6. Anti-Alzheimer’s Activity

A series of 3,5-diaryl pyrazoles 5 (Figure 19) was assayed for their ability to inhibit monoamine oxidase-A (MAO-A) and monoamine oxidase B (MAO-B) reversibly. Several compounds show inhibitory activity with concentration values in the nanomolar range [183]. Kuduk et al. identified compound 275 (Figure 19) as a potent and selective full agonist of the M1 positive allosteric modulators [184]. In the same manner, compound 275 showed good inhibitory activity against MAO-A and MAO-B but low selectivity (IC\textsubscript{50} MAO-A = 9.00 nM, IC\textsubscript{50} MAO-B = 8.00 nM, and SI = 1.00).

Figure 19. Structures of some pyrazoles 5 and 275–279 of anti-Alzheimer's activity.

A group of pyrazolyl and thienyl aminohydatoins was prepared by Malamas et al. and was tested as potent BACE1 inhibitors [185]. The \textit{n}-butyl analog 276 was the most potent analog, with an IC\textsubscript{50} value of 8 nM.

Zou et al. reported on the synthesis of a series of pyrazole-based compound 277 (Figure 19) and identified as C-terminus \beta-secretase 1 (BACE1) inhibitors [186]. Further, modification over the pyrazole scaffold leads to the identification of compound 278 as a potent inhibitor of BACE1 with an IC\textsubscript{50} value of 0.025 \textmu M.

Results reported by Han et al. indicated that the most active analogs 279 (Figure 19) exhibited higher inhibitory activities, with significant brain A \beta-lowering effects, as well as favorable aqueous solubility [187].
As acetylcholinesterase (AChE) inhibitors, pyrazolotarcines 280 (Figure 20) were reported by Silva et al. The results showed that compound 280 was the most potent inhibitor of AChE, which inhibited the enzyme above with an IC$_{50}$ value of 0.069 µM [188]. Whereas Khoobi et al. synthesized compound 281 bearing 3,4-dimethoxyphenyl group was the most potent compound against acetylcholinesterase (AChE) [189], being more active than the reference drug tacrine.

Interestingly, it was reported that treatment of Cognitive impairment associated with Alzheimer’s disease (AD) and schizophrenia was associated with α7 nicotinic acetylcholine receptor (α7nAChR) that represented promising therapeutic candidates [190]. As compound 282 (Figure 20) was found, a potent and selective full agonist of the α7 nAChR demonstrated improved plasma stability, brain levels, and efficacy in behavioral cognition models.

On the other side, it was demonstrated that pyrazole 283 proved to be a potent and selective fair pharmacokinetic profile accompanied by efficacy in rodent behavioral cognition models. Compound 284 (Figure 20) was investigated and found as the most potent inhibitor of α7 nAChR with an IC$_{50}$ value of 0.07 µM [191]. Astra Zeneca AB developed diverse series of pyrazole derivatives as positive allosteric modulators (PAMs).
Compound 285 (Figure 20) expressed good activity by inhibiting nicotinic acetylcholine receptors (nAChRs) [192]. The trisubstituted pyrazole 286 (Figure 20) showed unusual activity with a \( \text{PEC}_{50} \) value of 7.11 (62.68% efficacy) and a PAM type 4 profile [193].

4.7. Insecticides and Herbicides

Synthesized pyrazoline-type insecticides 287 (Figure 21) were achieved and examined the mechanism of action of these compounds based on available electrophysiological, pharmacological, and toxicological information, and they were found to act at neuronal target sites [194].

![Figure 21. Structures of some pyrazoles 287 and 288 of insecticidal and herbicidal activity.](image)

Compounds 1,5-diarylpyrazole derivative 288 (Figure 21) were prepared and showed noticeable pre-emergent herbicide activities against various kinds of weeds [195].

4.8. Anticonvulsant and Antidepressant Activity

A series of 1-(5-phenyl-3-(phenylamino)pyrazolidin-1-yl)ethanone (289) [196] was prepared (Figure 22) and evaluated for anticonvulsant activity against the electric shock-induced convulsion method.

![Figure 22. Structures of some pyrazoles 289–292 of anticonvulsant and antidepressant activity.](image)

Anti-depressant potency pyrazoles 290–292 (Figure 22) showed using tail suspension behavioral despair test and anti-convulsant potency against pentylenetetrazol (PTZ)-induced seizures in mice [197]

4.9. Pyrazole as Hypotensive Agents

The hypotensive activity of the synthesized 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazoline derivatives 293a,b (Figure 23) [198] and the compounds were investigated by a tail-cuff method using clonidine as a reference standard. The obtained compounds showed appreciable hypotensive activities.
ed compounds showed appreciable hypotensive activities. The hypotensive activity of the synthesized 1,5-diaryl pyrazole derivatives 295–297 (Figure 25) were synthesized, and the compounds were investigated the biological activity in metabolic disorders, and their hypoglycemic activity in an in vivo model were tested. Interestingly, a high degree of correlation was observed between the predicted pKᵢ and hypoglycemic effect after administration. Compounds 295–297 showed significant plasma glucose reduction with decreases of 60%, 64%, and 60%, respectively [200].

4.12. Anti-Oxidant Activity

In 2021, Vagish C. B. et al. [201] reported that the synthesized compounds 298 (Figure 26), which revealed modest to good antioxidant activities. The synthesized pyrazoles, 298, were screened for their antioxidant activity by in vitro DPPH and hydroxyl radical scavenging activity. Assessment result showed that compounds 3-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole 298a revealed % radical scavenging activity.
The synthesis of the pyrazolines and pyrroles was accomplished via the condensation of substituted suitable chalcones and hydrazine hydrate in absolute ethanol in the presence of drops of glacial acetic acid, as presented in Scheme 115 [202].

Mantzianidou et al. [202] evaluated the antioxidant activity of pyrazole derivatives. Compounds 5a and 299a were found as the most lipophilic compounds and showed antioxidant activity using the ABTS radical cation (ABTS+) generated through potassium persulfate by oxidation with no participation of an intermediary radical. The activities in both DPPH and hydroxyl radical scavenging assay comparable with ascorbic acid and BHA, even with the reported structurally related compounds.

In 2021, Vagish C. B. et al. [201] reported that the synthesized compounds showed significant plasma glucose reduction with decreases of 60%, 64%, and 60%, respectively. Moreover, compounds revealed modest to good antioxidant activities. The synthesized pyrazoles, even with the reported structurally related compounds.

Figure 25. Structures of some pyrazoles 295–297.

Figure 26. Structures of pyrazoles 298–c.

(% I) (20.76–45.14% and 19.46–43.56%), while, 1-(3-chlorophenyl)-3-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazole (298b) showed (23.91–46.16% and 20.46–45.07%). Moreover, 1-(3-chlorophenyl)-5-(2,4-dichlorophenyl)-3-(2-methoxyphenyl)-4,5-dihydro-1H-pyrazole (298c) showed (22.50–42.48% and 20.55–42.80%) show the excellent activities in both DPPH and hydroxyl radical scavenging assay comparable with ascorbic acid and BHA, even with the reported structurally related compounds.

Mantzianidou et al. [202] evaluated the antioxidant activity of pyrazole derivatives 5a and 299a. Compounds 5a and 299a were found as the most lipophilic compounds and showed antioxidant activity using the ABTS radical cation (ABTS+) generated through potassium persulfate by oxidation with no participation of an intermediary radical. The synthesis of the pyrazolines and pyrazole derivatives was accomplished via the condensation of substituted suitable chalcones and hydrazine hydrate in absolute ethanol in the presence of drops of glacial acetic acid, as presented in Scheme 115 [202].
5. Conclusions

There is a growing body of evidence that pyrazole and its heteroannulated derivatives provide a viable and valuable area for drug discovery. Here, we illustrated an overview of the many efficient, mild, operationally simple, and non-conventional synthetic methods to access a library of highly functionalized pyrazole together with their heteroannulated derivatives. We also shed more light on the broad range of biological activities displayed by these scaffolds that can optimally present a way to capture their intrinsic values. The ability to predict drug-like and lead-like properties along with recent technological advances could be sufficient to revitalize the exploitation of the value of pyrazoles and their heteroannulated derivatives in the quest for new drugs.

Previous studies have shown that the structural modification on the different positions of the basic molecule allows for improving its pharmacological profile, giving it antimicrobial, anticonvulsant, analgesic, anti-inflammatory, anti-viral, anti-malarial, and anti-cancer properties. Recently, researchers have established the design of more potent pyrazole derivatives having a great diversity of biological activity. Afterward, they synthesized the prospective biologically active classes and finally screened the synthesized compounds towards the aim and type of biological activity.

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