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A Comprehensive Review On Synthetic Routes and Pharmacological Activities of Pyrazoles and Quinolines

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ABSTRACT

In the modern world, a number of heterocycles have emerged and are showing important roles in a variety of human-beneficial pharmaceutical compounds. Pyrazoles are nitrogen-containing heterocyclic compounds with five members. They have garnered a lot of attention because they belong to a significant class of chemicals for therapeutic development and Quinolines, A typical example of bicyclic heterocyclic compounds. Meanwhile, derivatives of pyrazole and quinoline have been synthesized as target structures and have shown a wide range of biological actions, including antitubercular, anticancer, antifungal, anti-inflammatory, antibacterial, and anti-tuberculosis properties. The findings of published studies on the synthesis and biological activity of quinoline and pyrazole derivatives are compiled in this review. The Scopus database was consulted to gather and evaluate the published research papers on the biological activities and synthesis of pyrazole and quinoline derivatives that were published between January 2019 and December 2023.

Keywords: Heterocycles, pyrazoles, quinoline, anticancer, anti-inflammatory, research papers.

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INTRODUCTION

The chemistry of heterocycles represents a vital branch of chemical sciences, forming the basis for a substantial portion of modern research. Heterocyclic scaffolds are often utilized to arrange different pharmacophores, resulting in effective and selective drugs. Thus, heterocycles play a crucial role in the design of new bioactive compounds [1]. Continuous improvements in synthetic protocols for these scaffolds are always in demand [2].

Quinoline derivatives are crucial structures in bioactive molecules found in nature and in numerous pharmaceutically active compounds [8, 9]. Annulated 1, 3, 4-oxadiazoles are notably bioactive and have attracted significant attention due to their applications as antibacterial [10], antitubercular[11], antitumor[12], antifungal[13], anti-inflammatory[14], and antimalarial agents[15].

Pyrazole derivatives are significant due to their diverse biological activities, contributing extensively to pharmaceutical chemistry and pesticide development. They exhibit various bioactivities, including analgesic[16], anticancer[17], anticonvulsant[18], antibacterial, anti-inflammatory[20], hypoglycemic[21], antifungal, antituberculosis[22], antimycobacterial[19], antimalarial[23], and antioxidant properties. Pyrazolopyrimidine is a notable nitrogenous heterocyclic moiety present in many drugs [24]. Fluorine-containing heterocycles play a crucial role in enhancing the pharmacodynamic and pharmacokinetic properties of drug molecules [25, 26].

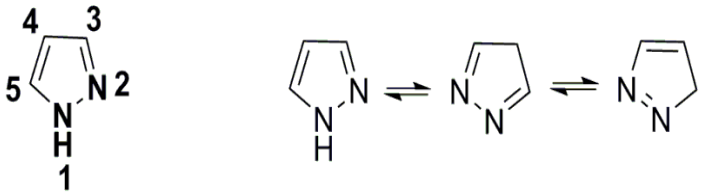


Figure 1.1 Structure of 1*H*-Pyrazole and its tautomeric structure

Pyrazole is an azole class of heterocycles having five member ring structure. Two nitrogen atoms are located at adjacent positions with the alternate double bond (Figure 1.1). During synthesis of antipyretic drug, its structure was invented by Knorr [27, 28].

Natural occurrence of Pyrazole

Pyrazole-containing alkaloid withasomnine was isolated from Withania somnifera by Akira and Morimoto et al.[29]. Numerous naturally occurring remedies exhibit a wide range of pharmacological properties, including antidiabetic [30], antiviral [31, 32], antitumor [33, 34], antimicrobial [35], antileishmanial[36], analgesic[37], and anti-inflammatory[38] activities. Figure 1.2 below showcases some significant natural products featuring a pyrazole core.

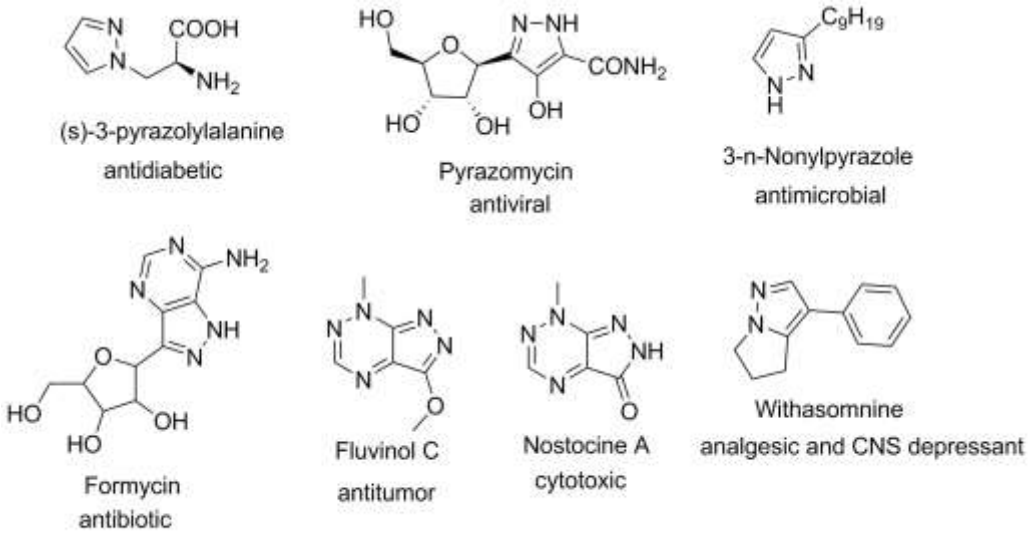
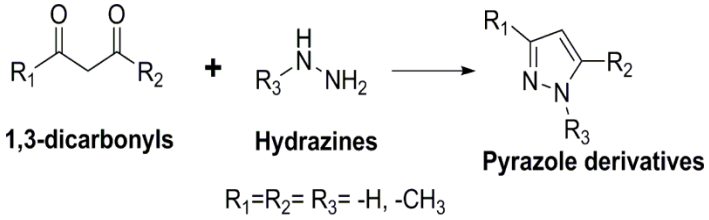


Figure 1.2 Pyrazole skeletal in naturally occuring drugs

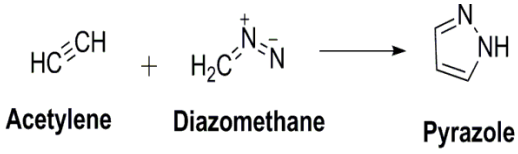
Pyrazole History and Synthetic Methods



Scheme 1.1 Synthesis of Pyrazole (Given by Knorr)

In 1833, Knorr[27] synthesized a pyrazole compound through the condensation of 1,3-dicarbonyl compounds and hydrazines. This classical method is straightforward and efficient for producing pyrazoles (Scheme 1.1). Pyrazole and its derivatives are particularly valuable in the synthesis of antipyretic drugs.

Another synthetic method for producing pyrazole involves the reaction between diazomethane and acetylenes (Scheme 1.2), which was developed by Pechmann in 1898[39].



Scheme 1.2 Synthesis of Pyrazole (Given by Pechmann)

L. Knorr[40] synthesized phenyl-3-methyl-5-pyrazolone by heating phenyl hydrazine with ethyl acetoacetate. The pyrazole nucleus containing a carbonyl group is known as pyrazolone (Figure 1.3). This compound, along with pyrazole and its substituted heterocycles, has attracted

considerable research attention due to its broad spectrum of biological activities.

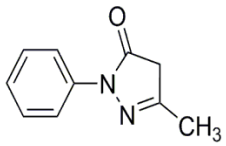


Figure 1.3 1-phenyl-3-methyl-5-pyrazolone

Pyrazole as Pharmacological Agents

The pyrazole moiety is present in many pesticides and drugs molecules [41-47]. Some examples are put on view in Figure 1.4:

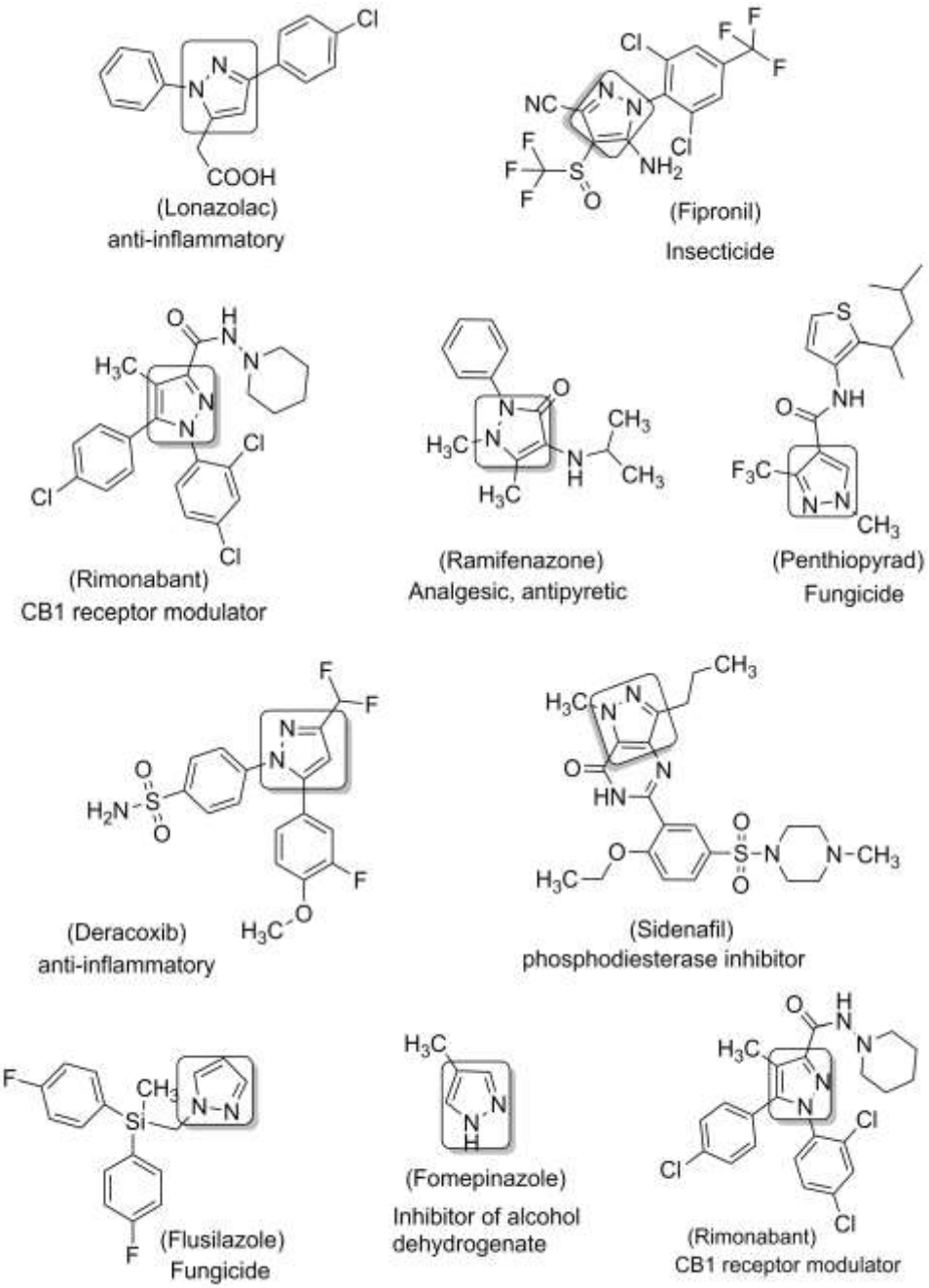
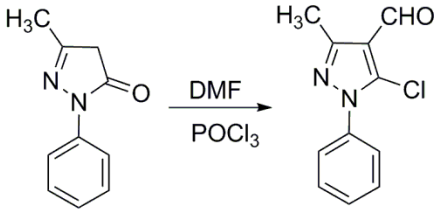


Figure 1.4 Drugs and pesticides having pyrazole nucleus

1*H*-Pyrazole-4-Carbaldehyde

Pyrazoles with an aldehydic functional group, such as 1H-pyrazole-4-carbaldehyde and its derivatives, are significant as drug intermediates. The pyrazole derivatives discussed in this thesis are synthesized from 1-aryl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde. The following sections will explore the biological and synthetic aspects of 1H-pyrazole-4-carbaldehydes.

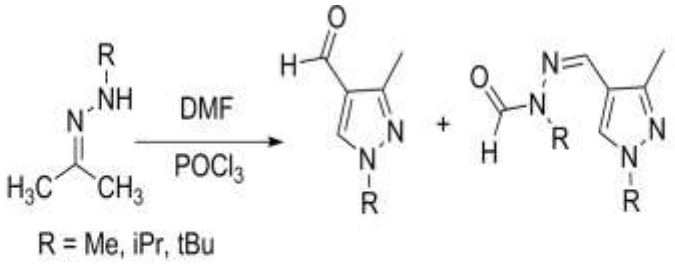
Synthesis of Pyrazole-4-Carbaldehyde derivatives



Scheme 1.3 Vilsmeier-Haack reaction of 3-methyl-1-phenyl-pyrazol-5(4*H*)-one

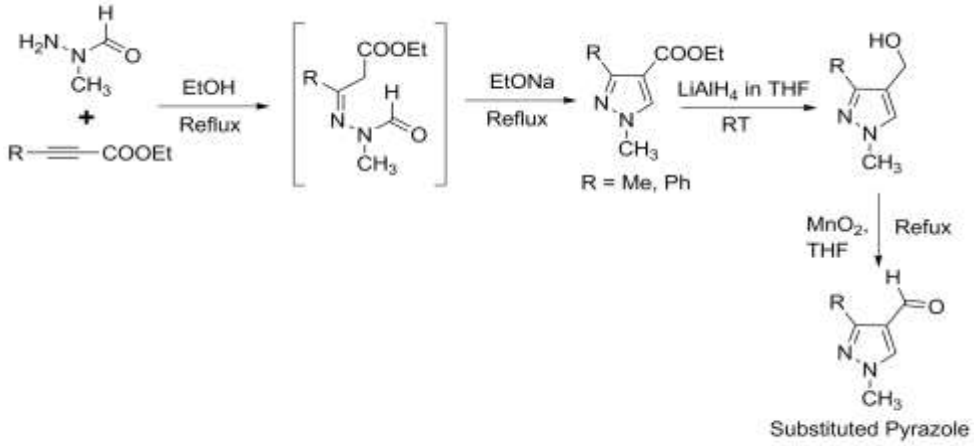
Synthesis of 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde *via* Vilsmeier-Haack synthesis of 3-methyl-1-phenyl-pyrazol-5(4*H*)-one (Scheme 1.3) was reported in 1966 [48].

E.B. Rusanov and his coworkers[49] reported non-symmetric 1,3,4- trisubstituted pyrazoles via Vilsmeier–Haack reaction of schiff base prepared from the corresponding ketone and substituted hydrazines (Scheme 1.4).



Scheme 1.4 Reaction of acetone N-alkylhydrazones with Vilsmeier-Haack reagent.

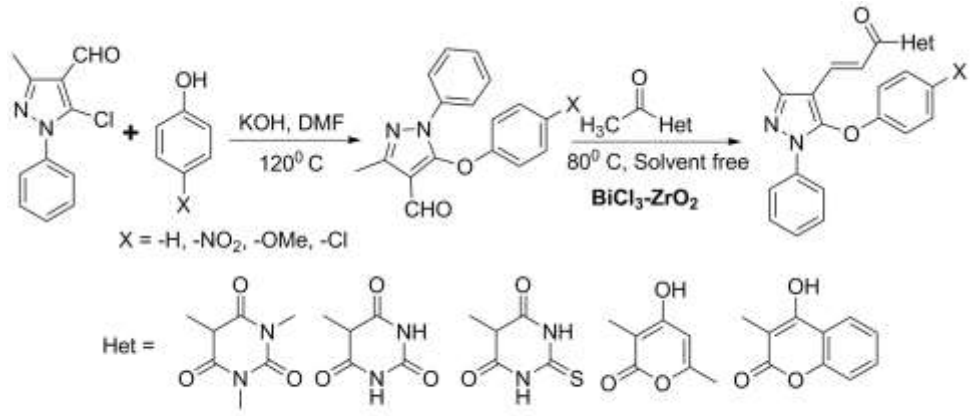
Andrew and his team[50] reported a one-pot regioselective synthesis of trisubstituted-1H-pyrazoles. This method involves a three-step tandem reaction, which has been extensively used in the synthesis of various pharmacologically active pyrazole-based drugs (Scheme 1.5).



Scheme 1.5 Regioselective one-pot synthesis of 1,3,4-trisubstituted-1*H*-pyrazoles

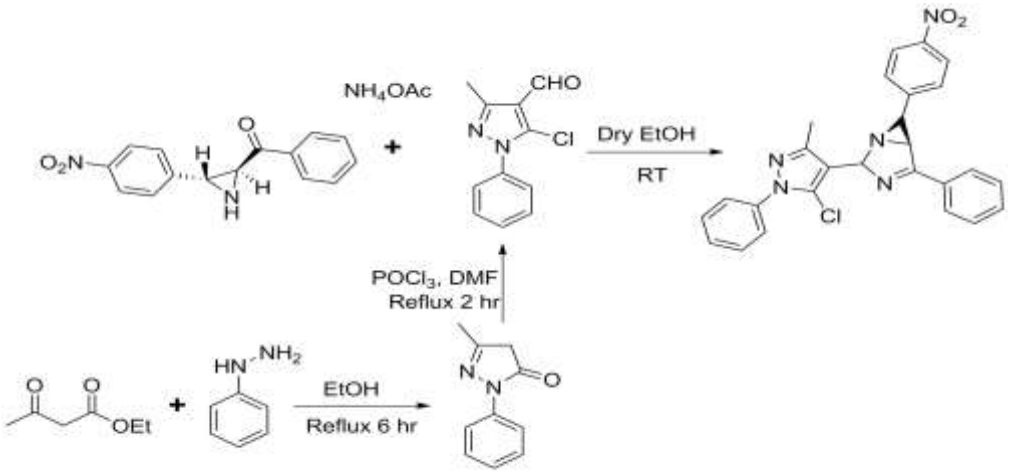
Reactions of Pyrazole-4-Carbaldehyde derivatives

Siddiqui and his team[51] developed a zirconia-based heterogeneous catalyst to evaluate its catalytic efficiency for substituted pyrazolic chalcones. The catalyst demonstrated significant activity and produced a good yield under standard reaction conditions (Scheme 1.6).



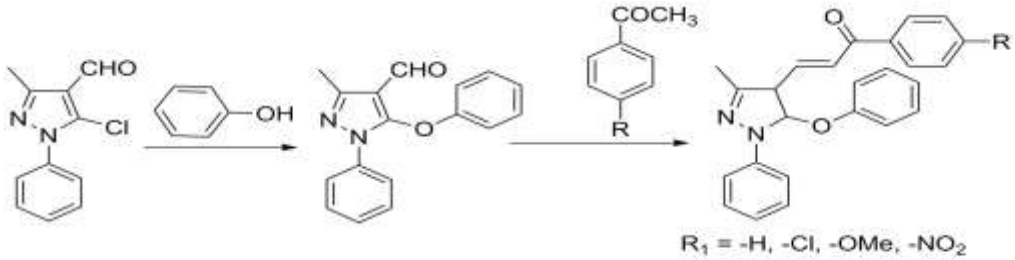
Scheme 1.6 Heterogeneous catalyst based synthesis of novel pyrazolic chalcones

H. Kiyani [52] synthesized pyrazolyl-1,3-diazabicyclo[3.1.0]hex-3-ene through a one-pot multicomponent synthesis involving ((2S,3R)-3-(4-nitrophenyl)aziridin-2-yl)(phenyl)methanone, 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde, and ammonium acetate. The synthesized pyrazole-based compounds exhibited photochromic properties (Scheme 1.7).



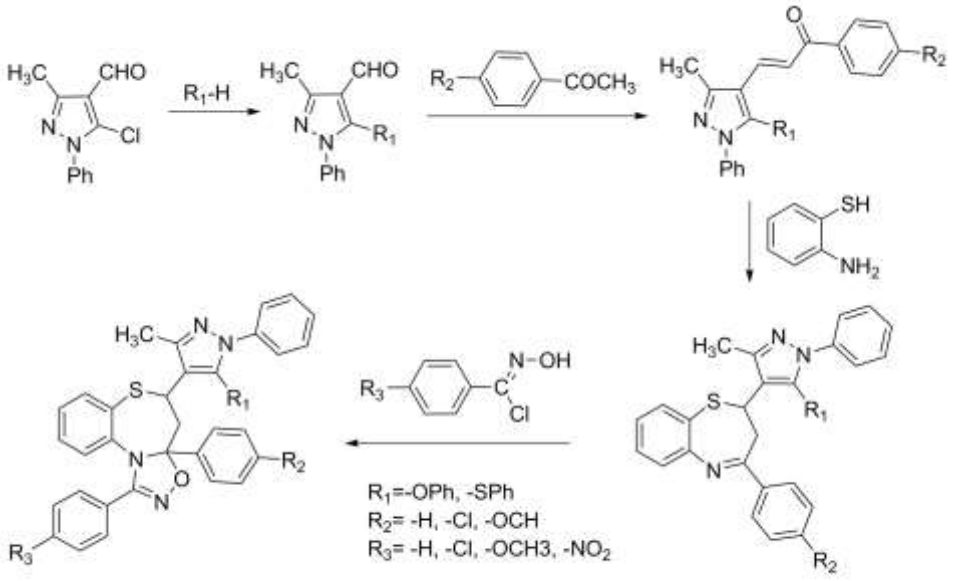
Scheme 1.7 Synthesis of photochromically active pyrazole compounds

Zhou Y. L. and colleagues [53] conducted the synthesis of (E)-3-(3-methyl-5-phenoxy-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-1-(p-substituted)prop-2-en-1-one and characterized the chalcone structure using both crystallography and spectroscopic techniques (Scheme 1.8).

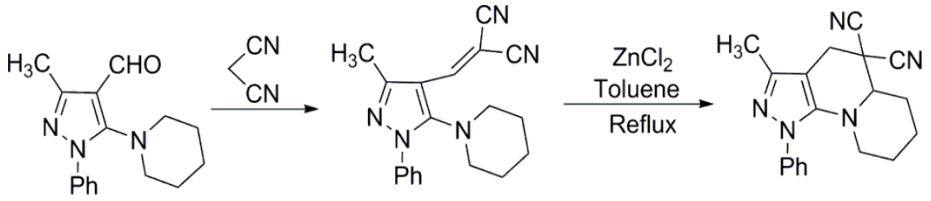


Scheme 1.8 Synthesis of 1,3-disubstituted-2-propyleno-1-one containing pyrazole compounds

F. M. Liu and colleagues[54] synthesized novel derivatives of pyrazole-substituted [1,2,4]-oxadiazolo-[5,4-d]-[1,5]-benzothiazepine through the cycloaddition of substituted-benzohydroximinoyl chlorides and substituted-pyrazolo[1,5]benzothiazepines using triethylamine (Et3N). The synthesized benzothiazepines were characterized using crystallographic and spectroscopic methods (Scheme 1.9).



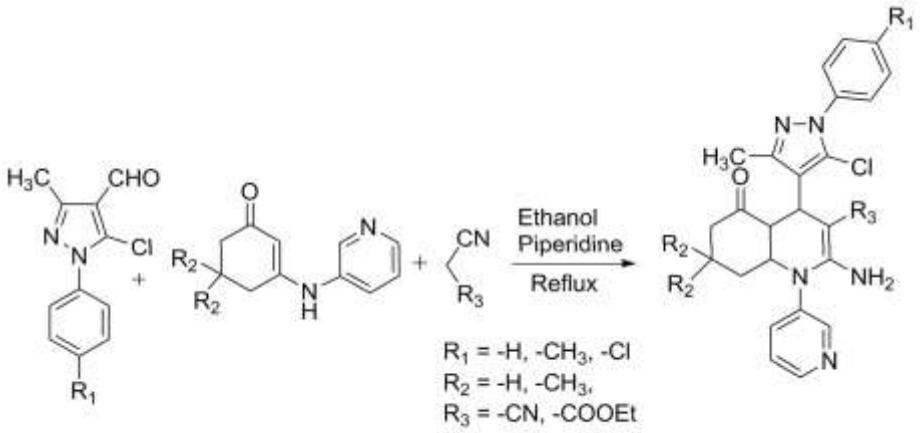
Scheme 1.9 Synthesis of pyrazole substituted-[1,2,4]-oxadiazolo-[5,4-*d*]-[1,5]-benzothiazepine derivatives



Scheme 1.10 Synthesis of substituted fused pyrazole derivatives

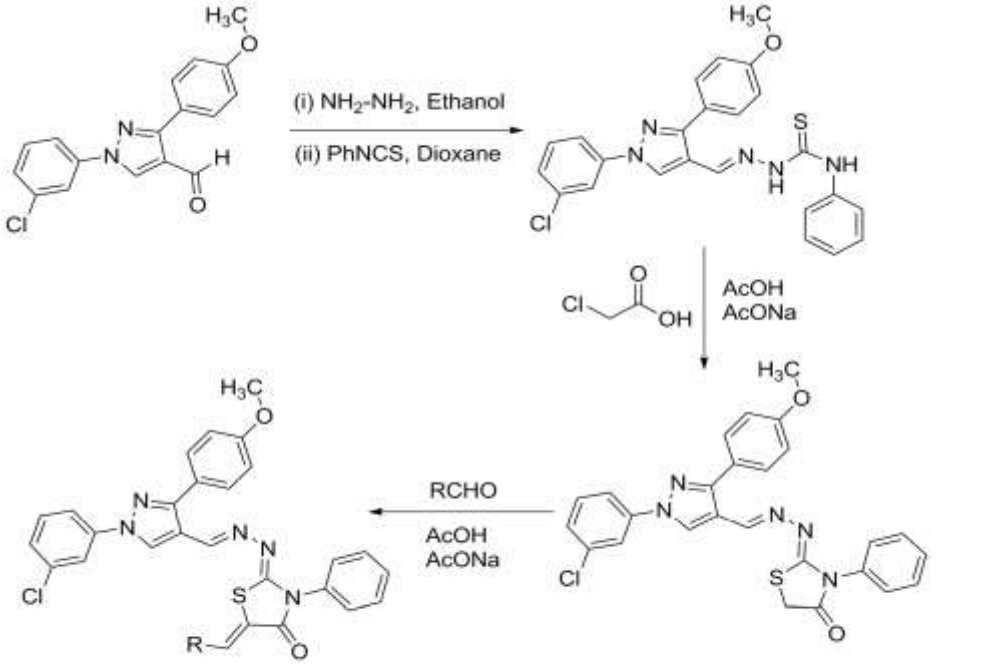
Prajapati et al. [55] synthesized substituted fused pyrazole derivatives by cyclizing the Knoevenagel product using anhydrous zinc chloride in toluene as the reaction medium. The product was obtained from pyrazole carbaldehyde and malononitrile (active methylene). Analysis of the product was conducted using spectroscopic techniques (Scheme 1.10).

C. Sangani et al. [56] developed a novel library of pyrazole-quinoline-pyridine hybrids using a multicomponent cyclocondensation approach starting from pyrazole carbaldehyde. The synthesized compounds were characterized using spectroscopic techniques. All compounds underwent screening to evaluate their antimicrobial and anticancer activities (Scheme 1.11).



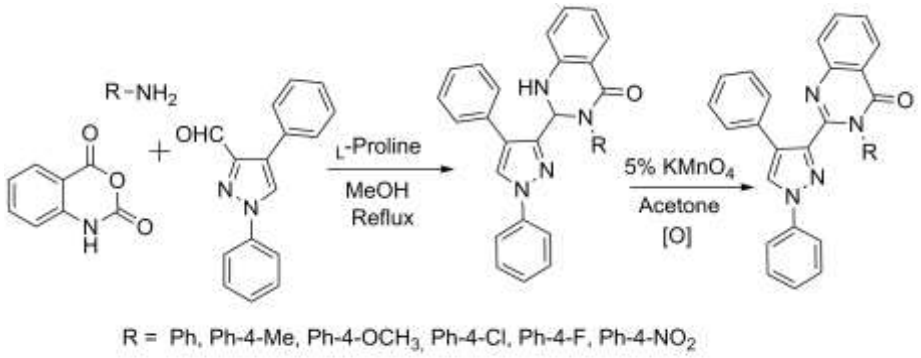
Scheme 1.11 Synthesis of biological active pyrazole-quinoline-pyridine hybrids

N. Khalifa and colleagues [57] synthesized novel substituted pyrazolyl thiazolidinone derivatives using a three-step reaction. The synthesized compounds were characterized using spectral techniques and exhibited significant antimicrobial activity (Scheme 1.12).



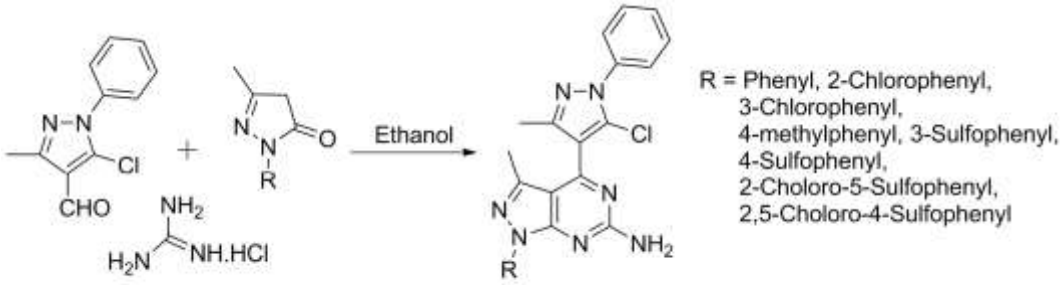
scheme 1.12 Synthesis of pyrazolylthiazolidinone derivatives

R. Dixit and her team[58] utilized L-Proline promotion for the preparation of pyrazole quinazoline analogues via a one-pot multicomponent reaction. This involved isatoic anhydride, various amino derivatives, and substituted diphenyl pyrazole-carbaldehyde. The synthesized compounds underwent screening for their antitubercular and antibacterial activities (Scheme 1.13).



Scheme 1.13 Biologically active pyrazole-quinazoline derivatives

S. Jarsania and colleagues [59] developed a straightforward method for synthesizing novel pyrazolo [3,4-d] pyrimidines and characterized the products using spectroscopic methods. The synthesized compounds were evaluated for their antitubercular and antibacterial activities (Scheme 1.14).



Scheme 1.14 Antibacterial active pyrazolo[3,4-*d*]pyrimidines derivatives

P. Kalaria et al. [60] synthesized a novel library of bipyrazolyl thiazolones using molecular hybridization. The synthesized derivatives were characterized using various spectroscopic techniques and elemental analysis. They were tested for their in vitro antibacterial activity against two Gram-negative and two Gram-positive bacteria, as well as E. coli FabH, with Penicillin G and Kanamycin B used as standards. Molecular docking studies were also conducted for the synthesized derivatives (Figure 1.5).

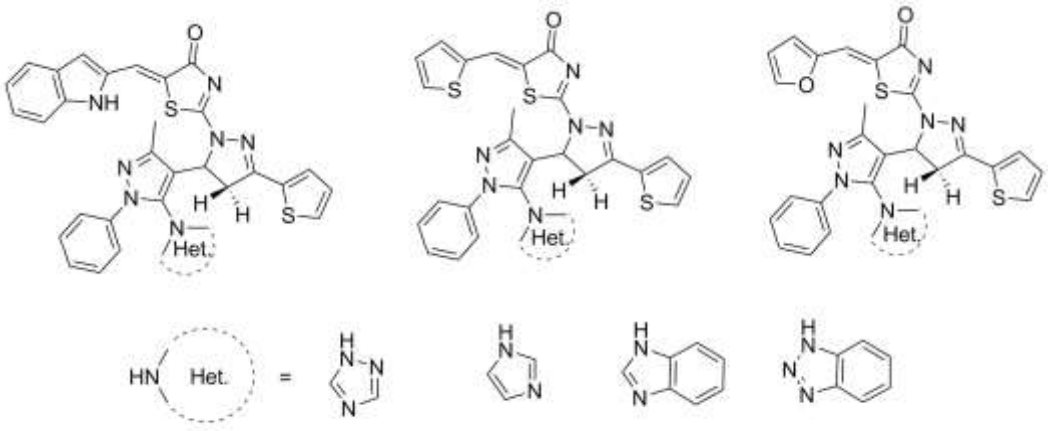


Figure 1.5 Synthesis and molecular docking study of novel bipyrazolyl thiazolone scaffold

V. M. Shah and colleagues [61] synthesized various substituted derivatives of pyrazole-4-carbaldehyde, including 5-imidazolinones (a), azomethines (b), sulfonamides (c), and formazans (d), through a multicomponent reaction. The synthesized compounds were evaluated for their antimicrobial activity (Figure 1.6).

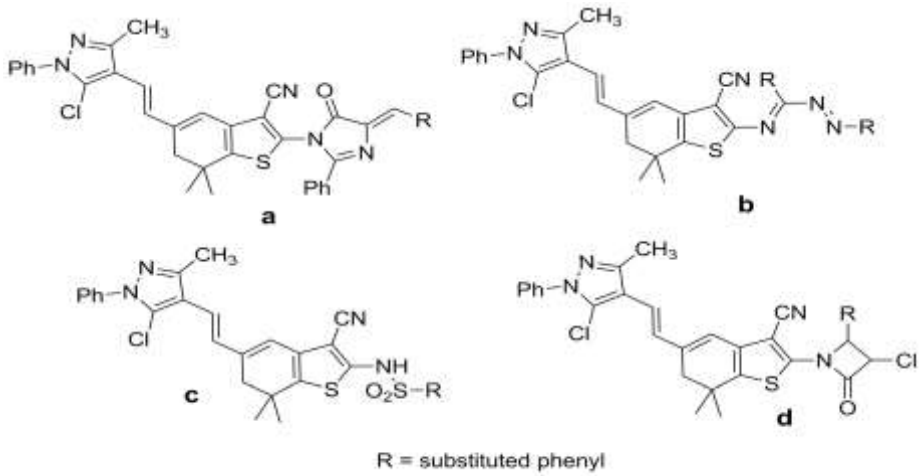
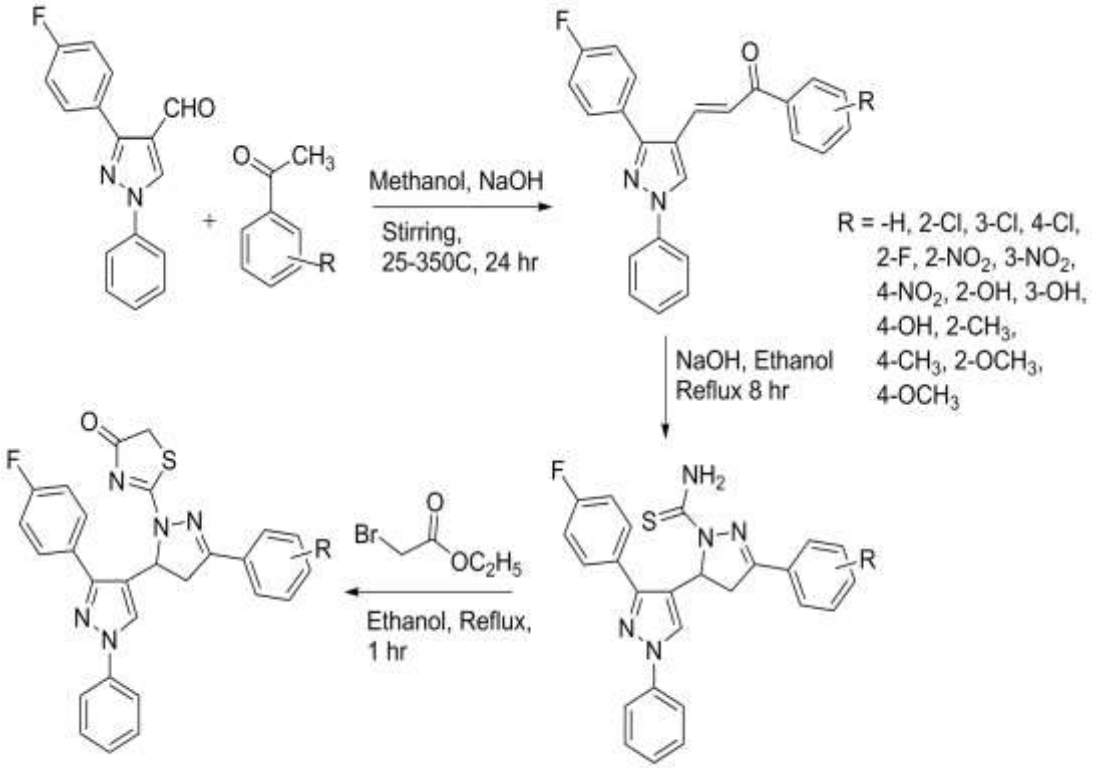


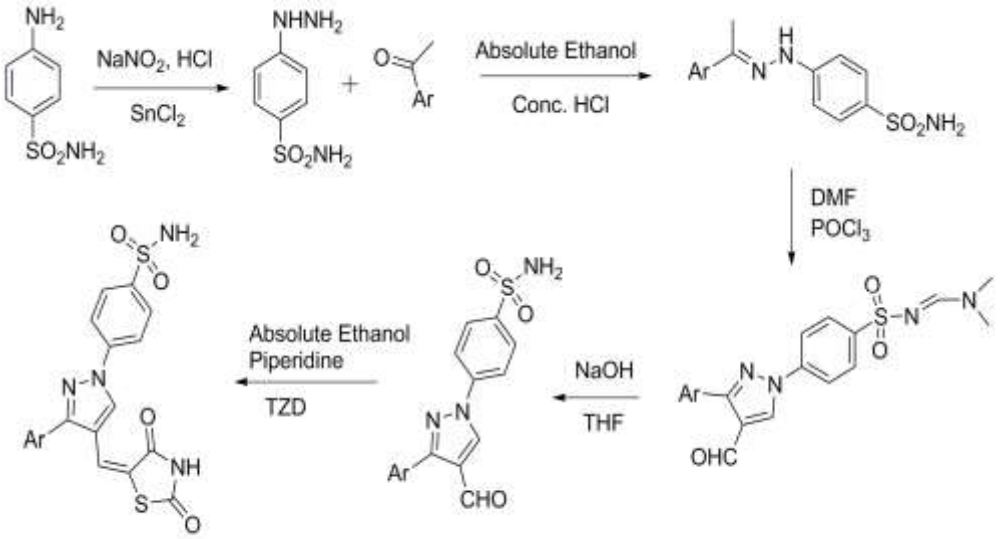
Figure 1.6 Antimicrobially active pyrazole derivatives

N. Desai and colleagues [62] described a straightforward method for synthesizing fluoro-substituted pyrazole-based thiazolidinone derivatives, which were characterized spectroscopically. The synthesized compounds were subsequently evaluated for their in vitro antimicrobial activity (Scheme 1.15).



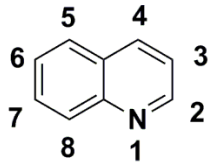
Scheme 1.15 Biologically active pyrazole based thiazolidinone

Ozair Alam et al. [63] investigated pyrazole-based benzene sulphonamide derivatives containing a thiazolidinedione core moiety. These compounds were evaluated for their potential as antidiabetic agents. A molecular docking study was conducted to assess the binding capacity of the prepared ligands with their corresponding receptors (Scheme 1.16).



Scheme 1.16 Synthesis of biologically active thaiazolidinedione based sulphonamide derivatives

Quinoline



Molecular formula: C_9H_7N
Molecular weight :129.16 gm/mol

Figure 1.7 Structure of Quinoline

Quinoline is an aromatic structure containing two fused rings, where a pyridine ring is fused with a benzene ring at adjacent carbon atoms (Figure 1.7). It was first obtained from coal tar in 1834[64]. Subsequently, quinoline was isolated from cinchonine by heating with strong alkali.

Quinoline is a weak tertiary base, typically appearing as a yellowish oil with hygroscopic properties. It exhibits low solubility in cold water but is highly soluble in most organic solvents and hot water. Quinoline and its derivatives form a crucial class of heterocycles found both naturally and synthetically. They play essential roles in biologically active compounds, both in natural products and synthetic molecules [8, 9, 66, 67].

Natural occurrence of Quinoline

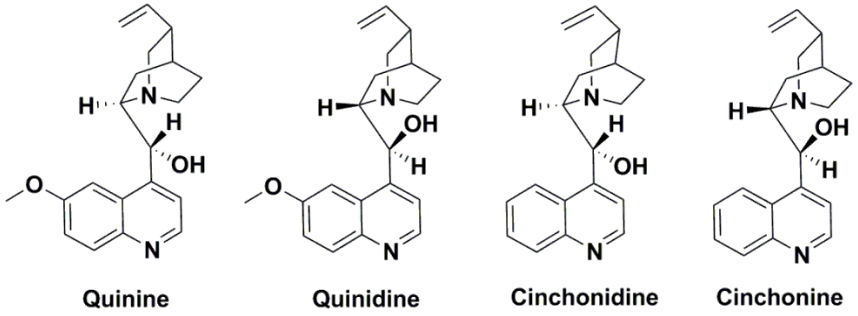


Figure 1.8 Structure of chinchona based alkaloids

The quinoline nucleus is primarily sourced from a series of alkaloids found in cinchona bark. Compounds such as quinine, cinchonidine, quinidine, and cinchonine are derived from cinchona bark and are stereoisomers of each other. Quinine [68] is a white crystalline solid with a bitter taste. Quinidine is a stereoisomer of quinine.

Cinchonidine is the stereoisomer of cinchonine and exhibits various pharmacological properties such as antimalarial, antipyretic, analgesic, and anti-inflammatory effects. Quinine was the first quinoline-based compound used effectively for treating Plasmodium falciparum infections. Figure 1.8 illustrates the different alkaloids derived from cinchona.

Figure 1.9 displays natural products featuring the quinoline core, which are known for their pharmacological activity [69-75].

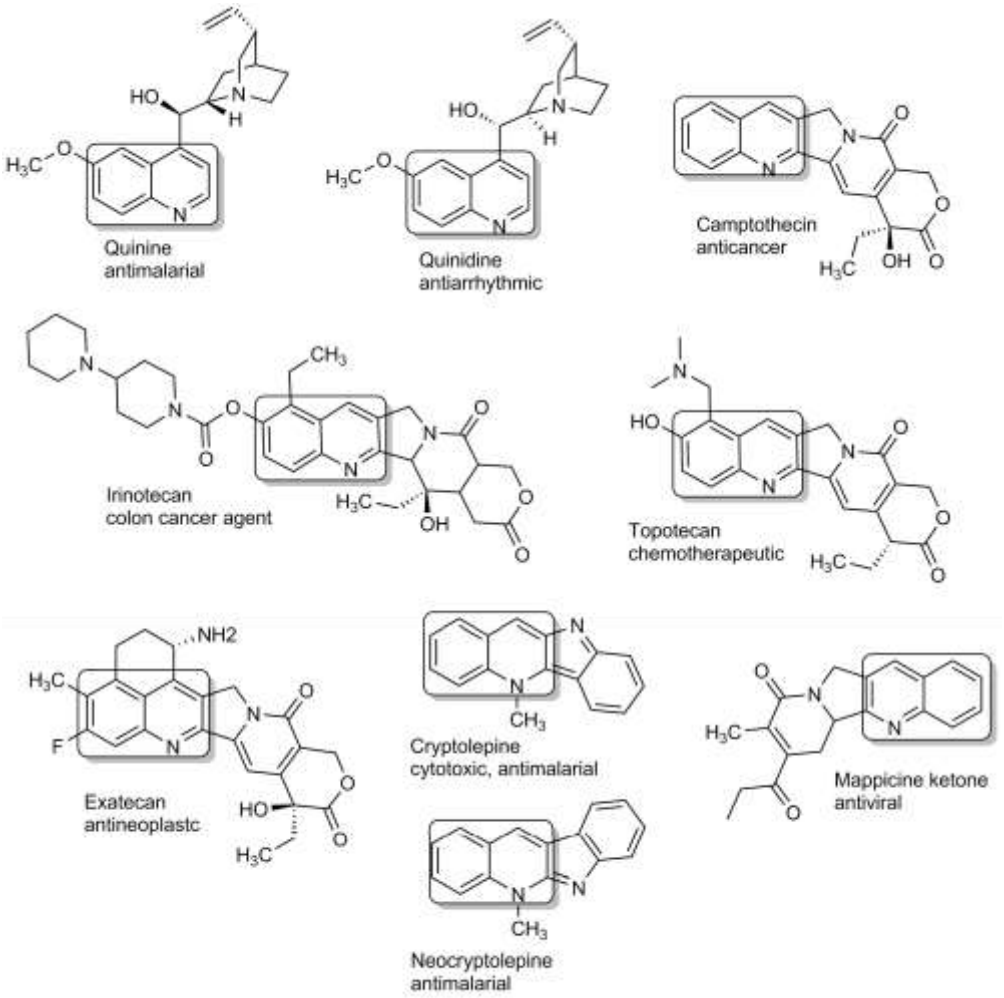
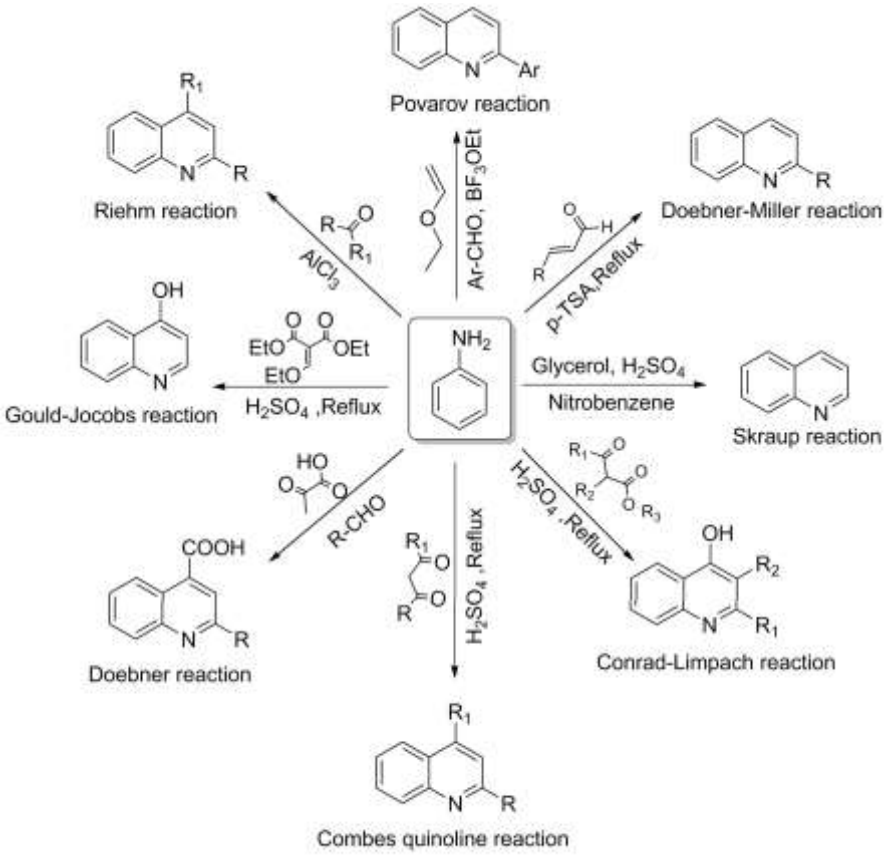


Figure 1.9 Some therapeutically active quinoline moieties

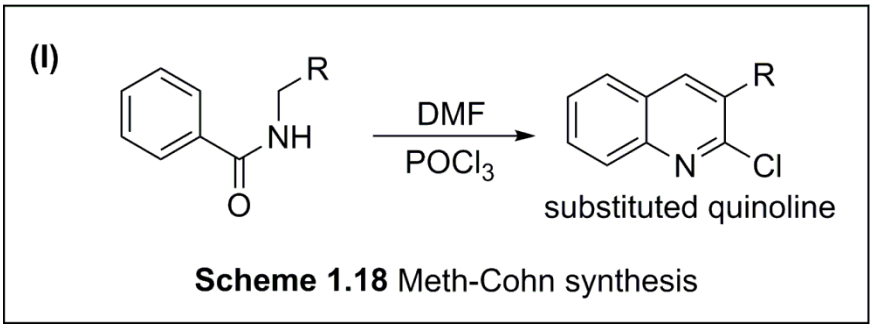
Quinoline synthesis

Quinoline is synthesized from aniline by various reactions given by different scientists are put on view in scheme 1.17.

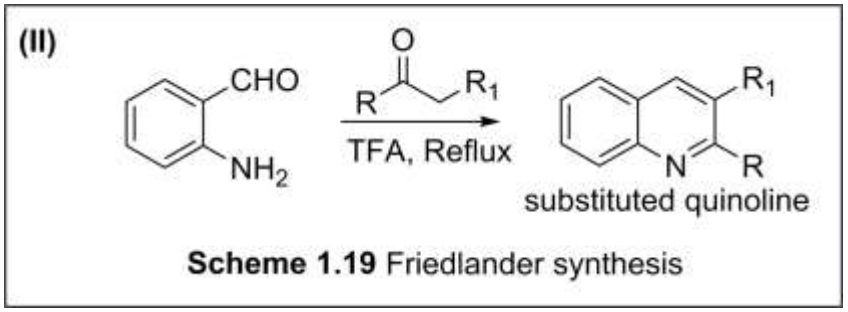


Scheme 1.17 Synthesis of quinoline starting from aniline

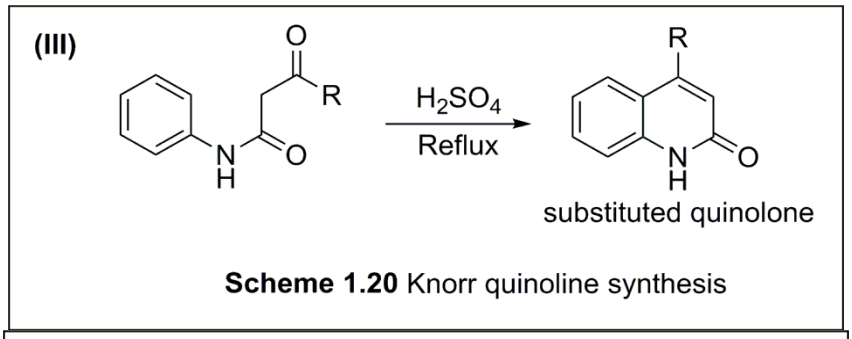
Apart from the reactions mentioned above, quinoline can also be synthesized from substituted anilines and other compounds listed in Schemes 1.18-1.23 as starting materials.



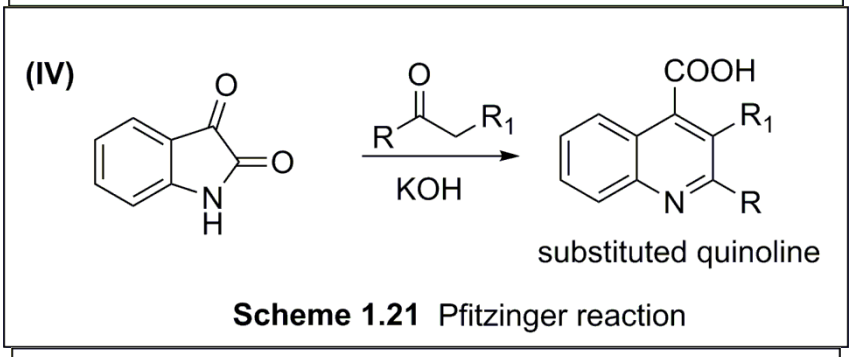
Scheme 1.18 Meth-Cohn synthesis



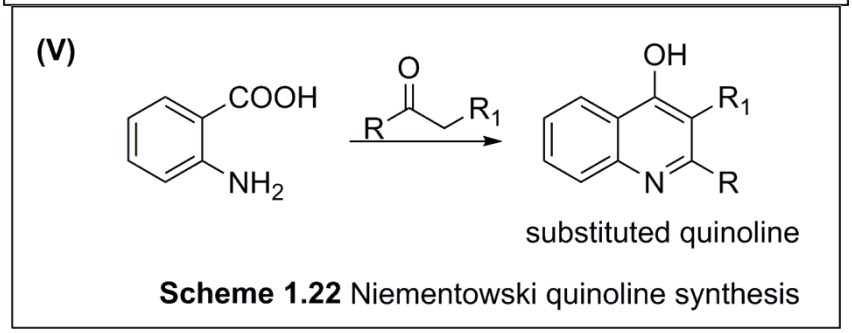
Scheme 1.19 Friedlander synthesis



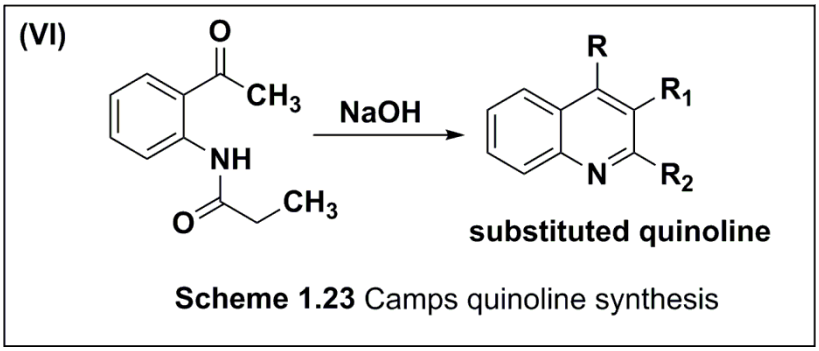
Scheme 1.20 Knorr quinoline synthesis



Scheme 1.21 Pfitzinger reaction



Scheme 1.22 Niementowski quinoline synthesis



Scheme 1.23 Camps quinoline synthesis

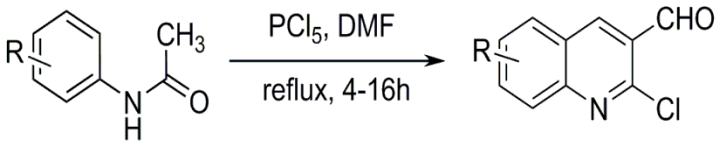
Quinoline derivatives as Pharmacological Agents

The quinoline scaffold is essential in a variety of pharmacologically active derivatives substituted with quinoline [76-83]. Examples of these derivatives are illustrated in Figure 1.7 below.

Synthesis of 2-chloroquinoline-3-carbaldehyde

Nitrogen-containing heterocycles have numerous medicinal applications [84-87]. 2-Chloroquinoline-3-carbaldehyde plays a crucial role as an intermediate in various heterocyclic and drug synthesis pathways. It is synthesized from acetanilide using the Vilsmeier-Haack reagent, a halomethyleneiminium salt (Scheme 1.24). This reagent is prepared from DMF and POCl3 [88,

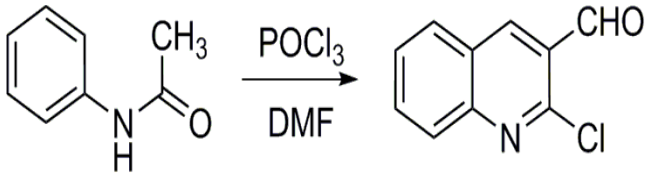
89], and is particularly valuable for introducing a carbaldehyde (-CHO) group into aromatic and heteroaromatic compounds [90].



R = -H, 6-CH_3, 7-CH_3, 8-CH_3, 6-OCH_3, 7-OCH_3, 6-Br, 7-Cl, 6-NO_2

Scheme 1.25 Synthesis of substituted-2-chloroquinoline-3-carbaldehyde derivative using PCl_5

(Quinoline) Meth-Cohn Synthesis

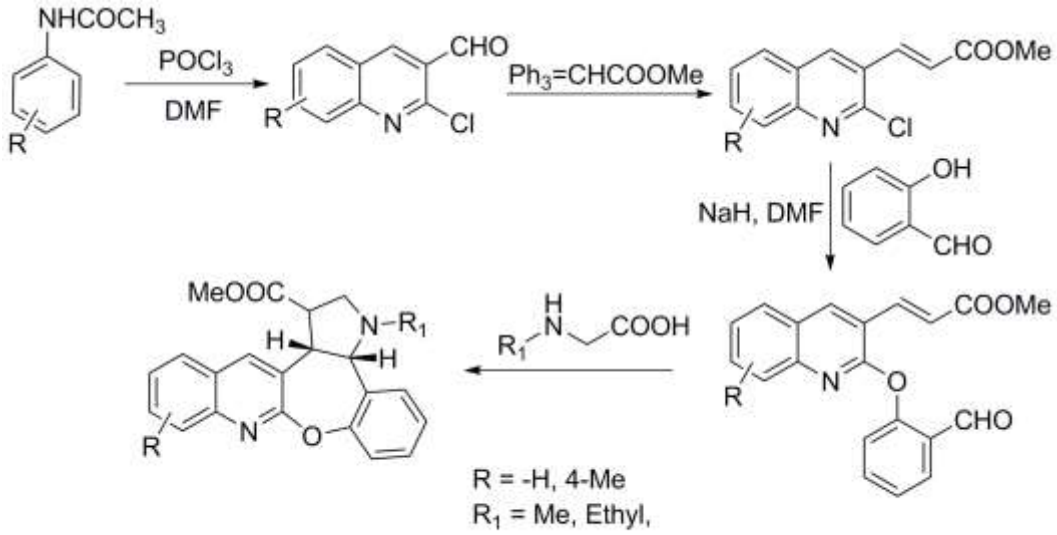


Scheme 1.24 Meth-cohn synthesis of quinoline.

A. Romero [91] synthesized 2-chloroquinoline-3-carbaldehyde using the Vilsmeier-Haack reaction of substituted acetanilides. Phosphorus pentachloride was used as the chlorinating agent instead of phosphorous oxychloride (Scheme 1.25).

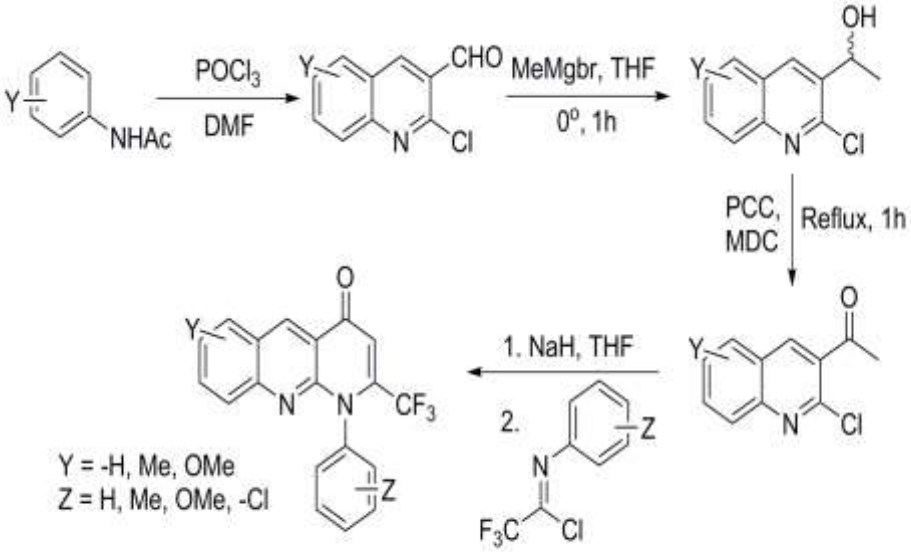
Reactions 2-chloroquinoline-3-carbaldehyde

N. Saravanan et al. [92] synthesized quinolo-oxepane derivatives through intramolecular dipolar cycloaddition between α,β-unsaturated ester and azomethine ylides. The synthesized oxepane derivatives exhibited stereo selectivity at their bridge carbons (Scheme 1.26).



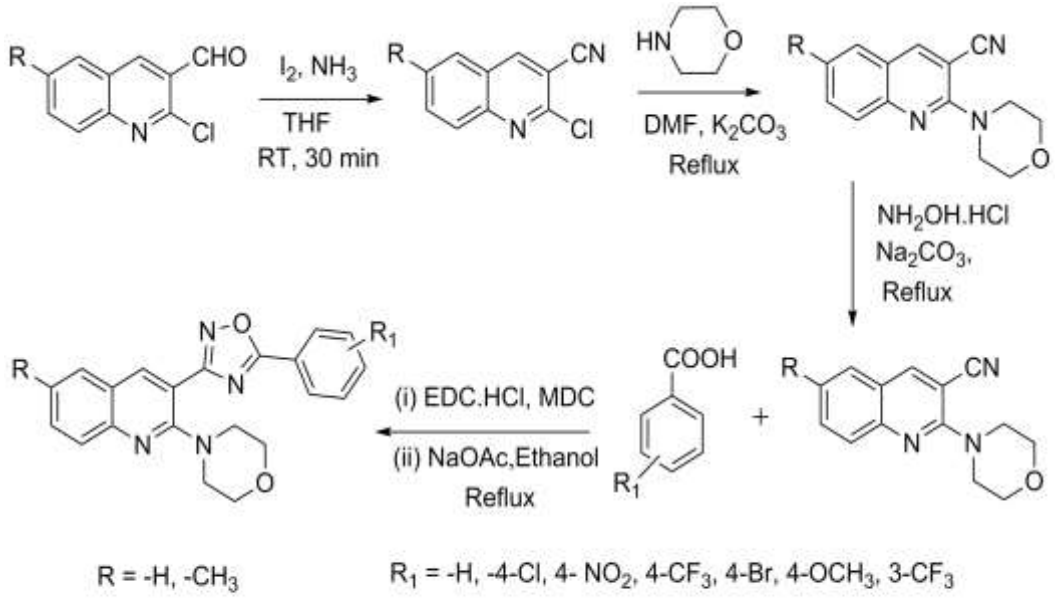
Scheme 1.26 Synthesis of quinolo-oxepane scaffolds

A. Romero and colleagues [93] synthesized a variety of 2-trifluoromethylsubstituted-benzo[b-1,8]naphthyridin-4(1H)-ones in similar yields starting from 3-acetyl derivatives of 2-chloroquinolines (Scheme 1.27).



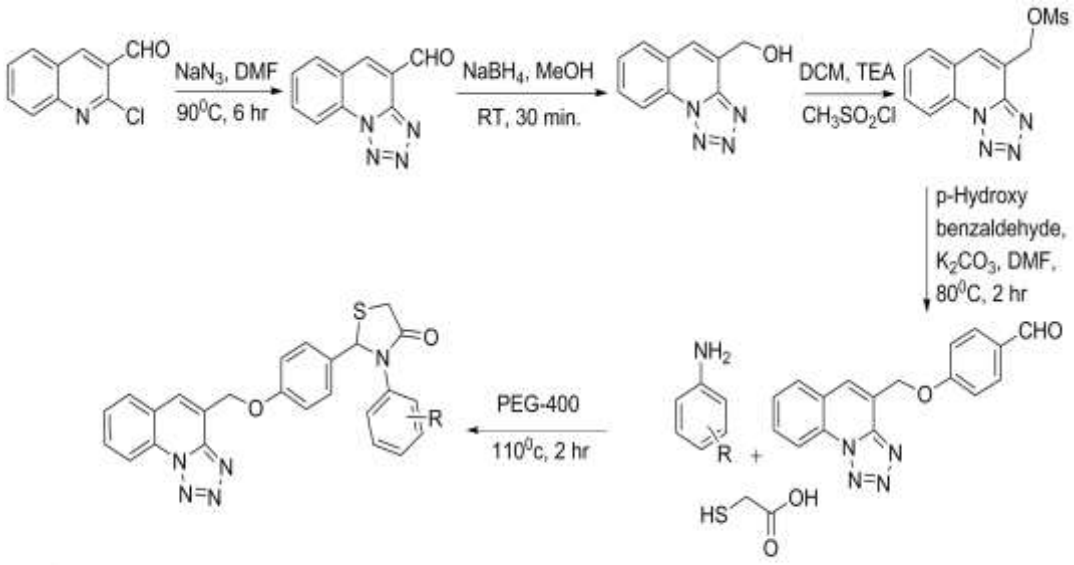
Scheme 1.27 Synthesis of 2-(trifluoromethyl)substitutedbenzo[*b*-1,8]naphthyridin-4(1*H*)-one derivatives

S. Karad and colleagues [94] synthesized a novel library of 2-morpholinoquinoline-based oxadiazoles to evaluate their diverse properties including antitubercular, cytotoxic, antimicrobial, and antimalarial activities. Additionally, they conducted molecular docking studies to assess the pharmacodynamic and pharmacokinetic properties of the synthesized compounds (Scheme 1.28).



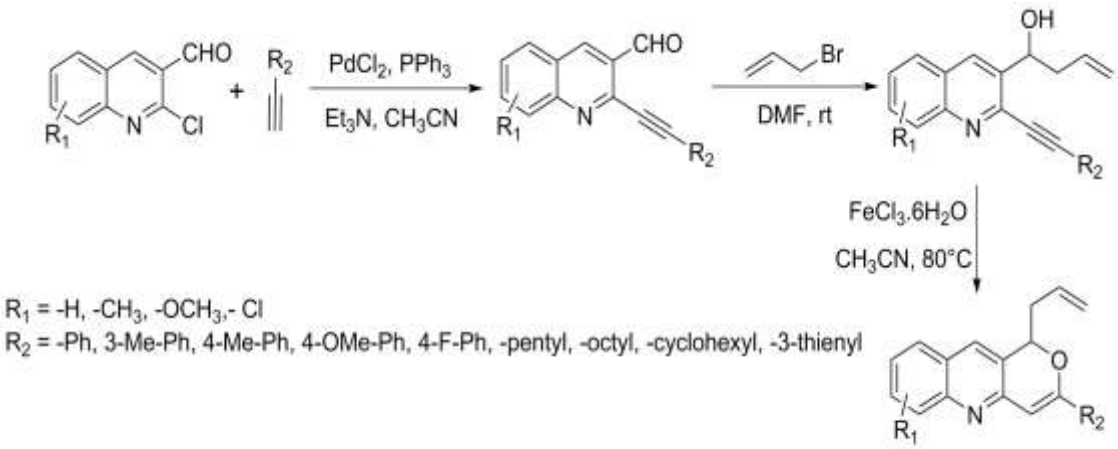
Scheme 1.28 Synthesis of biologically active 1,2,4-oxadiazole based morpholinoquinoline derivatives

A. Deshmukh and colleagues [95] reported the synthesis of substituted phenyl-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones via a one-pot condensation starting from 2-chloroquinoline-3-carbaldehyde (Scheme 1.29).



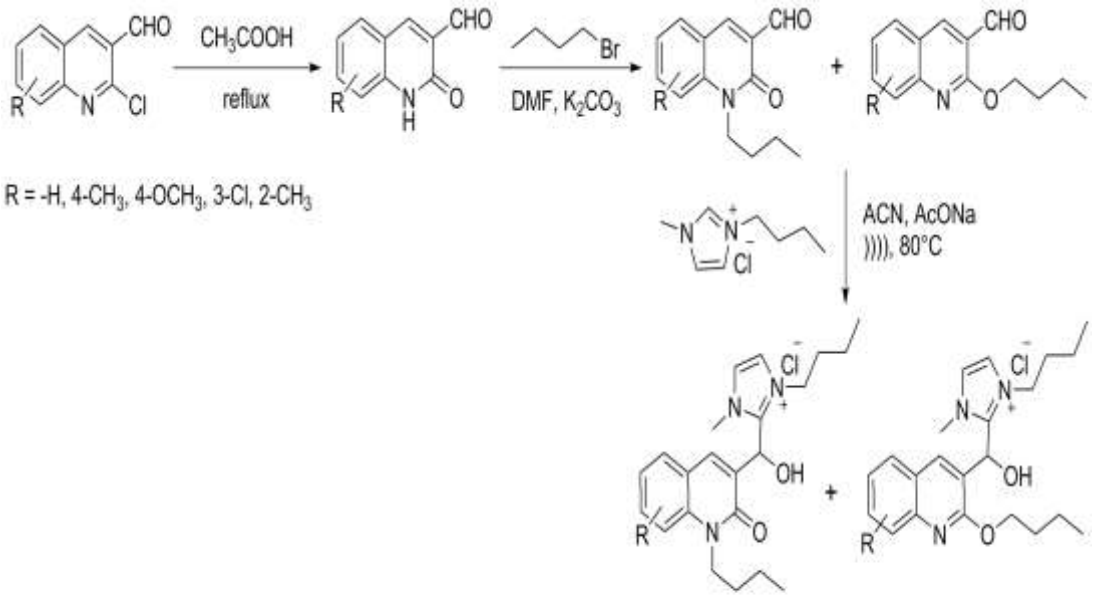
Scheme 1.29 Synthesis of new 3-substituted-phenyl-2-(4-(tetrazolo[1,5-*a*]quinoline-4-ylmethoxy)phenyl)thiazolidine-4-ones

Radhey Singh et al. [96] devised an economical reagent (FeCl3·6H2O) for the consecutive transformation of o-arylethynylquinonylmethanol into disubstituted-1H-pyrano[4,3-b]quinolines through a ring-closing reaction. This developed reagent exhibited notable efficiency in converting the initial substrate into the targeted product (Scheme 1.30).



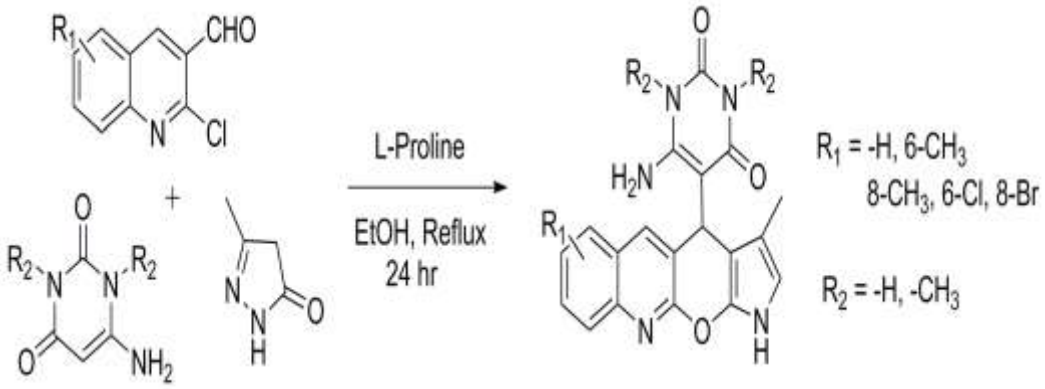
Scheme 1.30 Synthesis of $FeCl_3.6H_2O$ promoted pyrano[4,3-*b*]quinolines

S. D. Bunge and colleagues [97] reported an ultrasound-promoted reaction involving quinoline-3-carbaldehydes and 2-oxoquinoline-3-carbaldehyde to yield quinoline-imidazolium derivatives using 1-butyl-3-methylimidazolium chloride ([BMIM][Cl]) under mild conditions (Scheme 1.31).



Scheme 1.31 Synthesis of ultrasound promoted quinoline-imidazolium derivatives in presence of [Bmim]Cl

M. Shiri *et al.* [98] examined mild and organocatalysed based synthesis of dihydrobenzo[*b*][1,8]-naphthyridine and substituted-pyrano[2,3-*b*]quinoline derivatives.

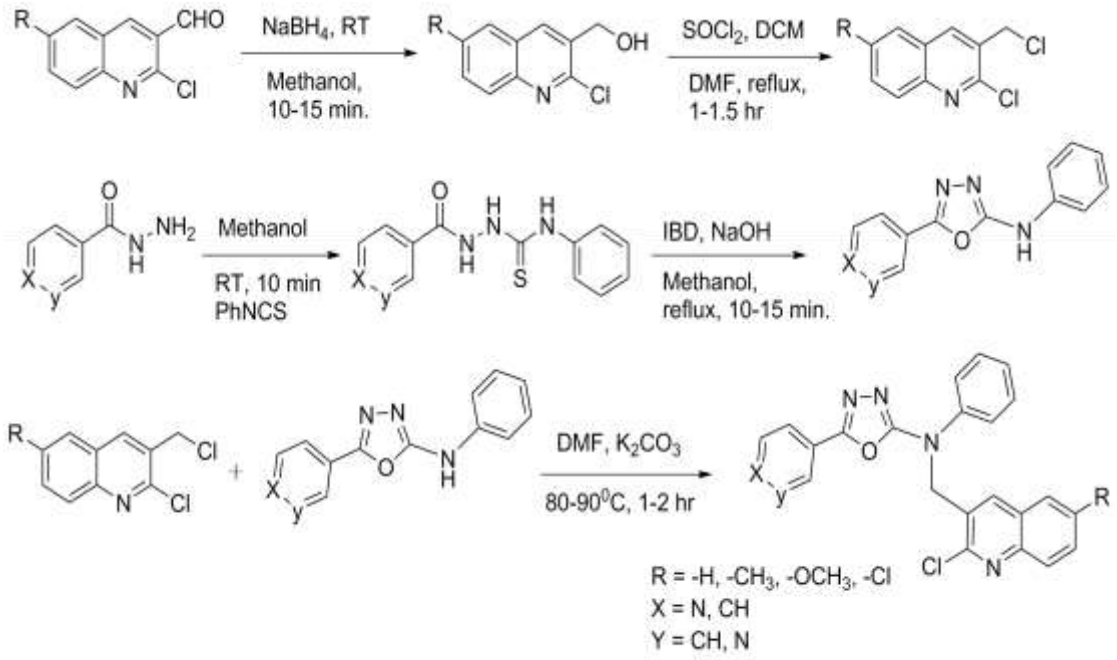


Scheme 1.32 Organocalaysed synthesis of pyrano[2,3-*b*]quinoline and substituted-dihydrobenzo[b][1,8]-naphthyridine derivatives

The compounds were synthesized from 6-substituted-aminouracils, chloroquinoline-3-carbaldehydes, and either 3-methyl-1H-pyrazol-5(4H)-one or dimedone using an organocatalyst (Scheme 1.32).

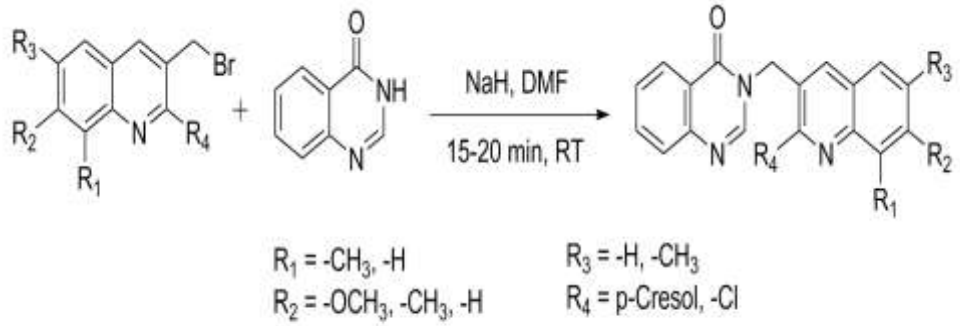
G. Ladani and colleagues [99] synthesized quinolino-oxadiazole derivatives in excellent yields via a halo-amine coupling reaction. The synthesized compounds were evaluated for their

antitubercular, antimicrobial, cytotoxic, and antimalarial activities (Scheme 1.33).



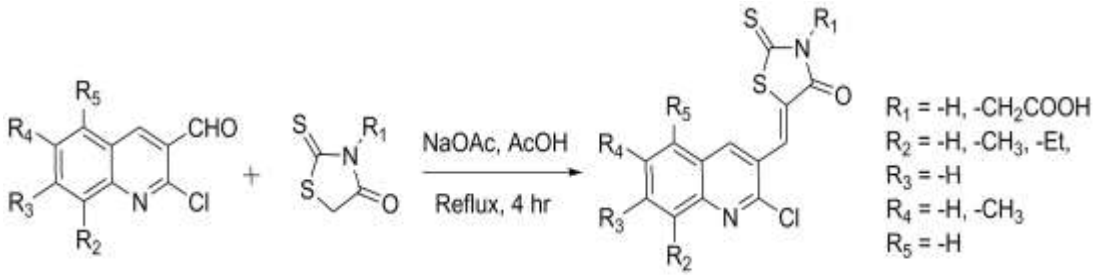
Scheme 1.33 Synthesis of biologically active quinoline-oxadiazole compounds

C. Gill [100] described the synthesis of quinazolinone derivatives via halo-amine cross-coupling reactions, showcasing their biological activity. The synthesized compounds underwent testing for their antibacterial and antifungal potency (Scheme 1.34).



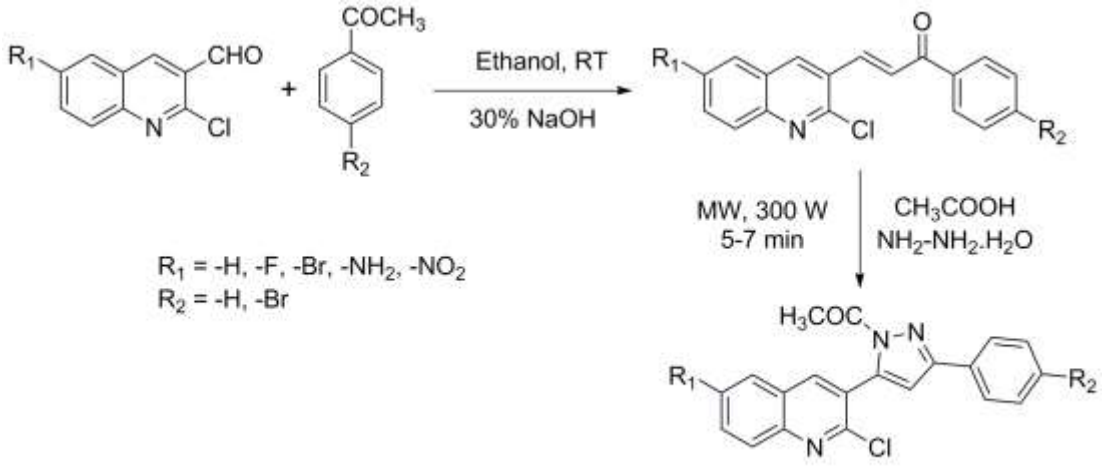
Scheme 1.34 Synthesis of biologically active 3-substituted((2-chloroquinolin-3-yl)methyl)quinazolin-4(3H)-ones

V. Ramesh and colleagues [101] synthesized rhodanine analogues incorporating benzo[h]quinoline and 2-chloroquinoline scaffolds, and evaluated their anticancer potency (Scheme 1.35).



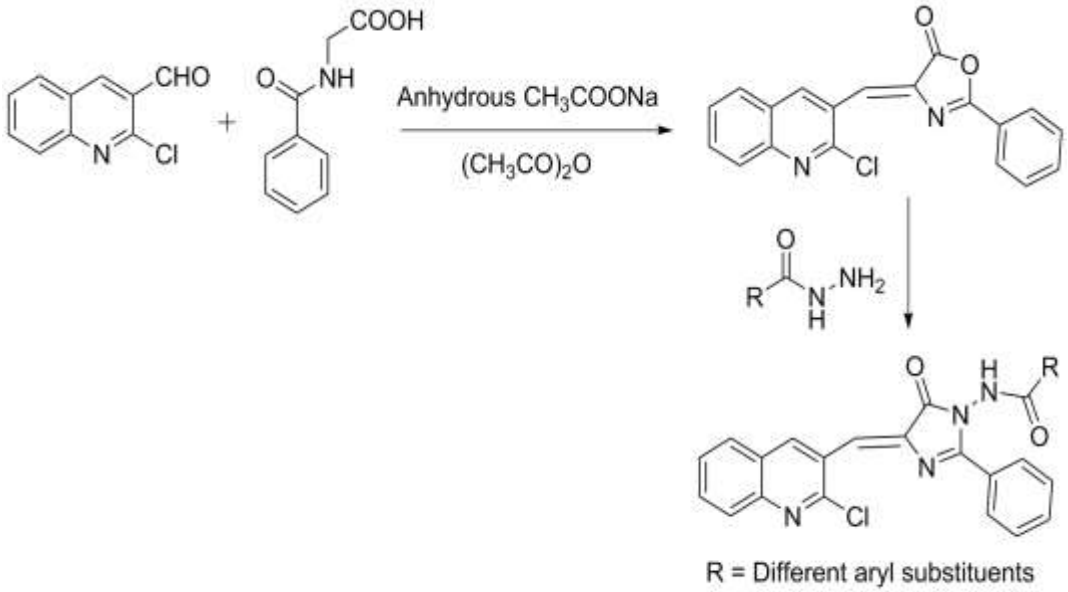
Scheme 1.35 Synthesis of anticancer active rhodanine derivatives

P. Miniyar *et al.*[102] synthesized chloroquinoline based pyrazoline derivatives and tested for antimicrobial potency (Scheme 1.36).



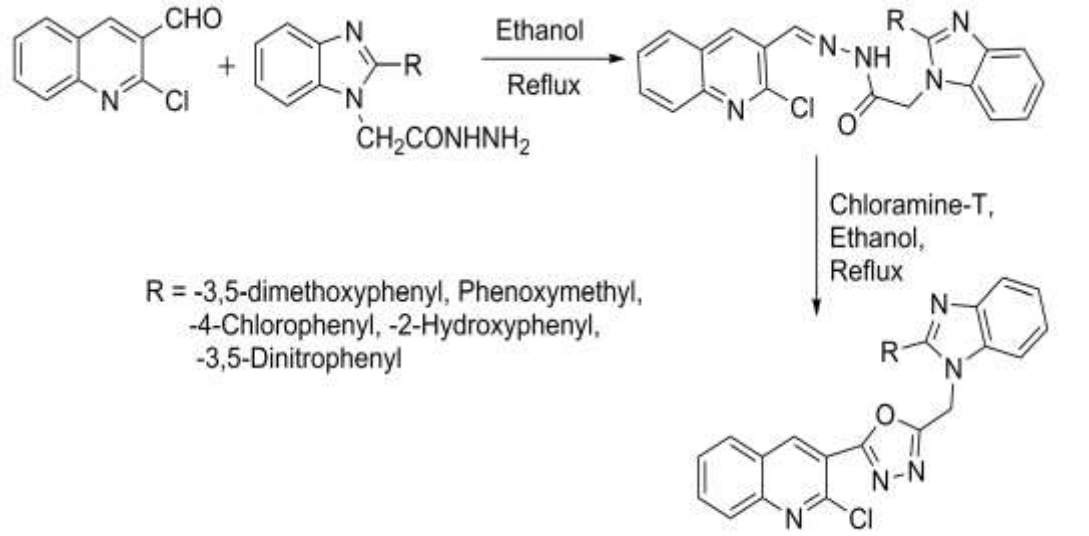
Scheme 1.36 Synthesis of biologically active quinoline based pyrazoline derivatives

N. Desai et al. [103] synthesized quinolinoimidazole derivatives using both microwave-assisted and conventional methods. They investigated the antimicrobial potency of the synthesized compounds (Scheme 1.37).



Scheme 1.37 Synthesis of biologically active quinolinoimidazole derivatives

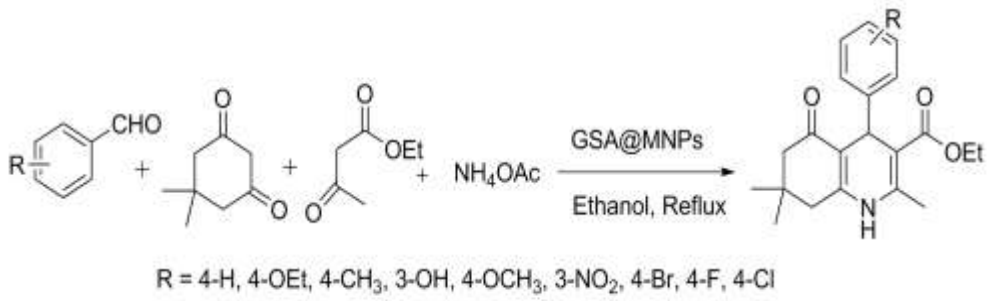
N. Desai et al. [103] synthesized quinolinoimidazole derivatives using both microwave-assisted and conventional methods. They conducted evaluations of the antimicrobial potency of these synthesized compounds (Scheme 1.37).



Scheme 1.38 Synthesis of Quinoline containing oxadiazole derivatives as an anticancer agents

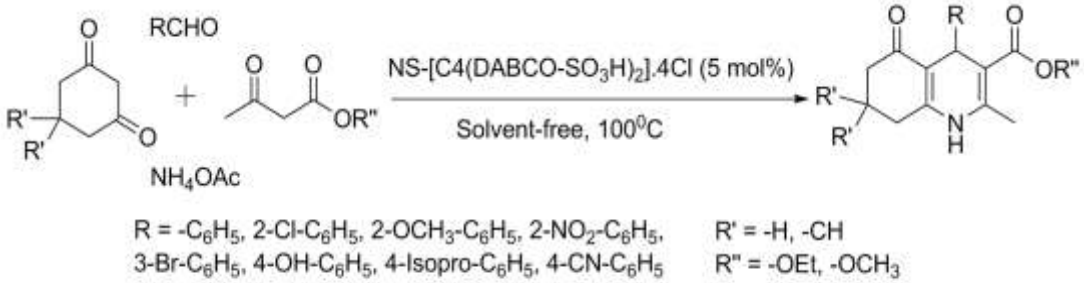
Literature survey on polyhydroquinoline derivatives

M. Hajjami and B. Tahmasbi [104] reported the use of Fe3O4 magnetic nanoparticles to promote the single-pot synthesis of 2,3-dihydroquinazolin-4(1H)-one and polyhydroquinoline derivatives in ethanol. The formation of these compounds was confirmed using spectrophotometric techniques for structural characterization (Scheme 2.1).



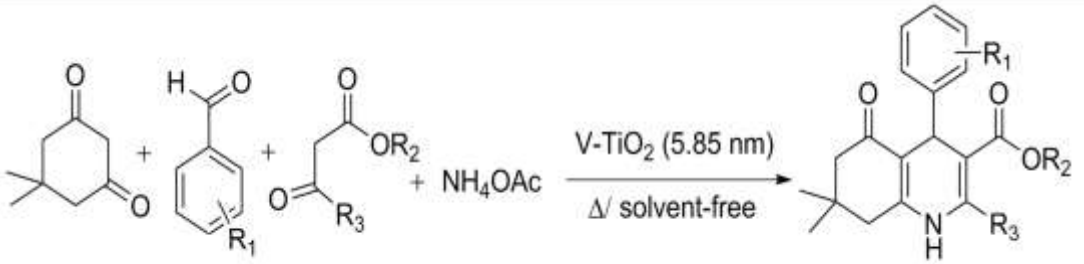
Scheme 2.1 Glucosulfonic acid immobilized MNPs catalyzed one-pot synthesis of polyhydroquinolines

F. Shirini and colleagues [105] successfully synthesized a novel nano-sized Bronsted acid catalyst and utilized it for the synthesis of hexahydroquinoline compounds via the Hantzsch condensation approach under solvent-free conditions (Scheme 2.2).



Scheme 2.2 Synthesis of hexahydroquinolines catalysed by NS-[C4(DABCO-$SO_3H)_2$].4Cl

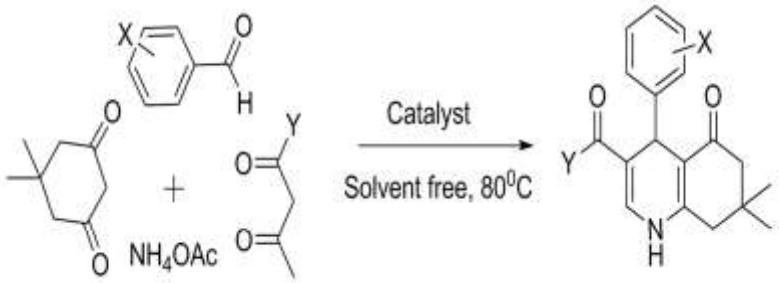
G. Dharma Rao et al. [106] utilized vanadium ion-doped mesoporous titania nanoparticles to prepare polyfunctionalized hydroquinoline compounds. They employed active methylene compounds, substituted aldehydes, and dimedone under solvent-free conditions. The nanoparticle-based catalyst could be easily recovered and recycled without a significant decrease in catalytic efficiency (Scheme 2.3).



R_1 = -H, 4-CH_3, 4-OCH_3, 4-F, 4-Br, 3-Br, 3-Pyridyl, 4-$N(CH_3)_2$, 2-Furyl, 3-NO_2, 2-NO_2 R_2 = -CH_3 R_3 = -OEt, -OCH_3

Scheme 2.3 Polyfunctionalized hydroquinoline derivatives *via* Hantzsch hetero annulations

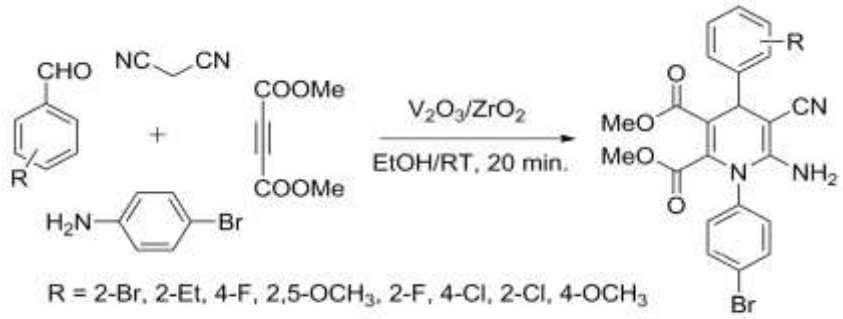
M. Yarie and colleagues [107] endeavored to prepare a magnetically recoverable nano-catalyst. The catalyst underwent characterization using various spectroscopic methods including XRD, FESEM, TGA, DTA, VSM, and SEM analyses. This heterogeneous catalyst was employed for the single-pot preparation of polyhydroquinolines under mild and solvent-free conditions (Scheme 2.4).



X = -H, 4-Cl, 2,4-Cl, 4-OCH_3, 3-Br, 2-Cl, 4-CH_3, 4-F, 4-NO_2, 3-OH Y = -OCH_3, -OEt

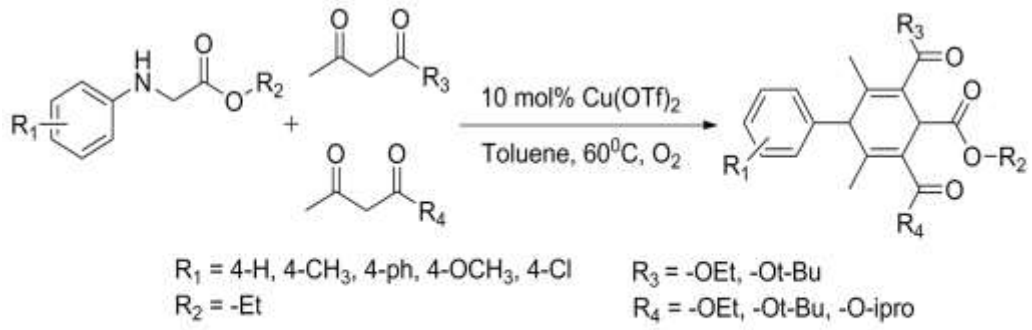
Scheme 2.4 Synthesis of the polyhydroquinolines in the presence of {Fe_3O_4@SiO_2@$(CH_2)_3$Im}$C(NO_2)_3$.

S. Jonnalagadda et al. [108] introduced a new route for synthesizing 1,4-dihydropyridine derivatives using a heterogeneous catalyst Y2O3/ZrO2. The protocol involved the reaction between malononitrile, substituted aldehyde dimethylacetylenedicarboxylate, and 4-bromoaniline with a catalyst loading of 2.5% in ethanol (Scheme 2.5).



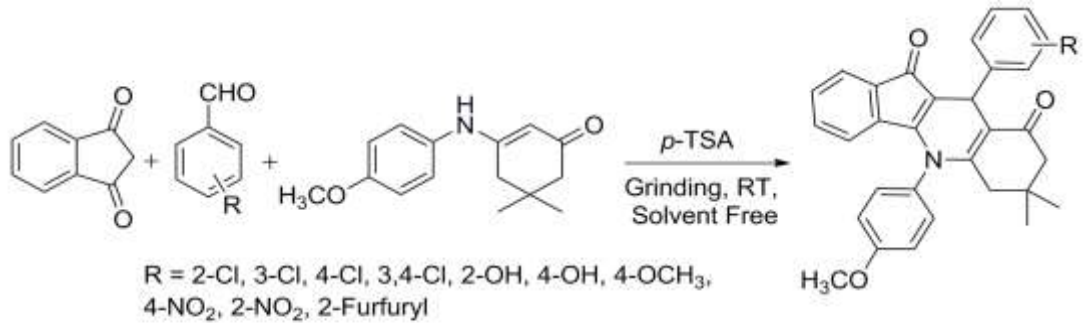
Scheme 2.5 Synthesis of novel 1,4-dihydropyridine derivatives

Z. Zhu et al. [109] synthesized 1,4-dihydropyridine scaffolds via copper-catalyzed aerobic oxidative coupling/cyclization. Various 1,3-dicarbonyl compounds and N-arylglycine esters underwent the tandem reaction smoothly, yielding the targeted products in high yields (Scheme 2.6).



Scheme 2.6 Copper-Catalyzed aerobic cascade oxidative coupling/cyclization for the construction of 1,4-Dihydropyridine derivatives

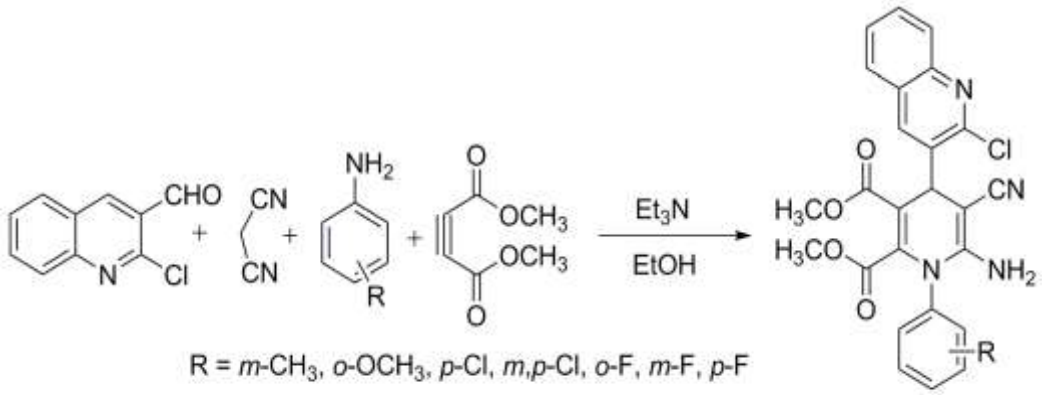
K. Ahmed et al. [110] reported the single-pot preparation of 5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione derivatives using p-toluene sulfonic acid. Molecular docking studies revealed good binding interactions of the active molecules with the serotonin 5-HT2A receptor (Scheme 2.7).



Scheme 2.7 p-TSA-catalyzed one-pot synthesis of 5*H*-indeno[1,2-*b*]quinoline-11(6*H*,10*H*) -dione derivatives as anticonvulsant agents

S'busiso Mfan'vele Nkosi et al. [111] synthesized quinoline-based dihydropyridines through a one-pot multicomponent reaction using 2-chloro-3-formyl quinoline, arylamines, dimethyl

acetylenedicarboxylate, and malononitrile with triethylamine as a catalyst. The antimicrobial and anticancer activities of the compounds were reported, along with molecular studies (Scheme 2.8).



Scheme 2.8 Novel quinoline bearing dihydropyridines

Many of them were reported to be very good anticancer and antifungal agents as displayed in the Figure 2.1.

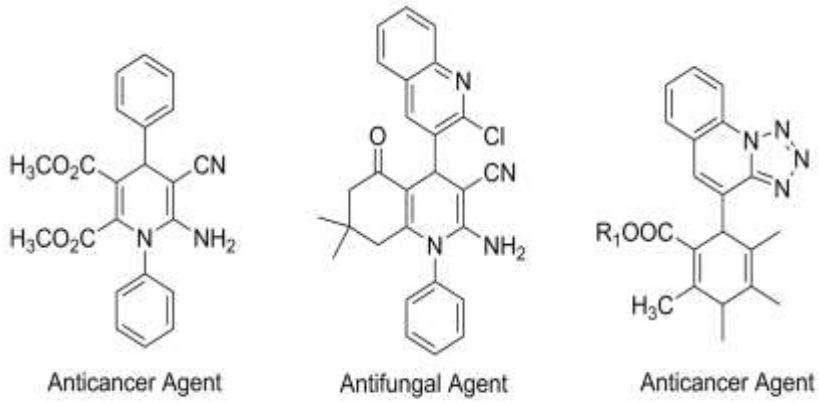


Figure 2.1 Dihydropyridine-based bioactive compounds

P. Kalaria et al. [112] developed a novel library of bipyrazolyl thiazolone scaffolds using a molecular hybridization method. The synthesized derivatives were characterized using various spectroscopic techniques and elemental analysis. These compounds were evaluated for their in vitro antibacterial activity against two Gram-negative and two Gram-positive bacteria, as well as E. coli FabH, with Penicillin G and Kanamycin B serving as reference drugs. Molecular docking studies were also performed on the synthesized derivatives (Figure 2.2).

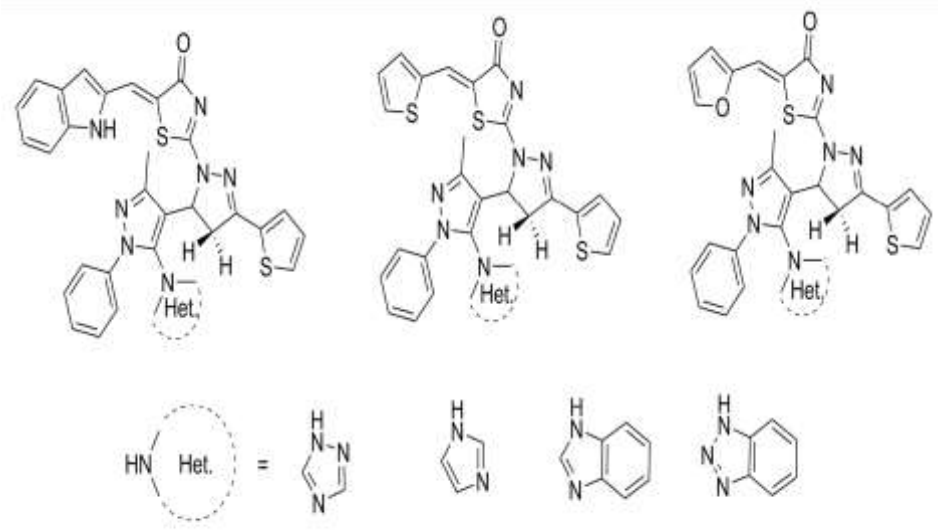
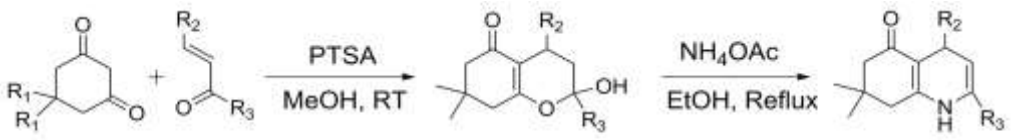


Figure 2.2 Synthesis and molecular docking study of novel bipyrazolyl thiazolone scaffold

A. Kumar and his team [113] synthesized 2,4-disubstituted polyhydroquinolines using p-toluenesulfonic acid in ethanol. The in vivo antihyperglycemic and antidyslipidemic potencies of the compounds were evaluated, with some synthesized compounds demonstrating good lipid-modulating activity (Scheme 2.9).

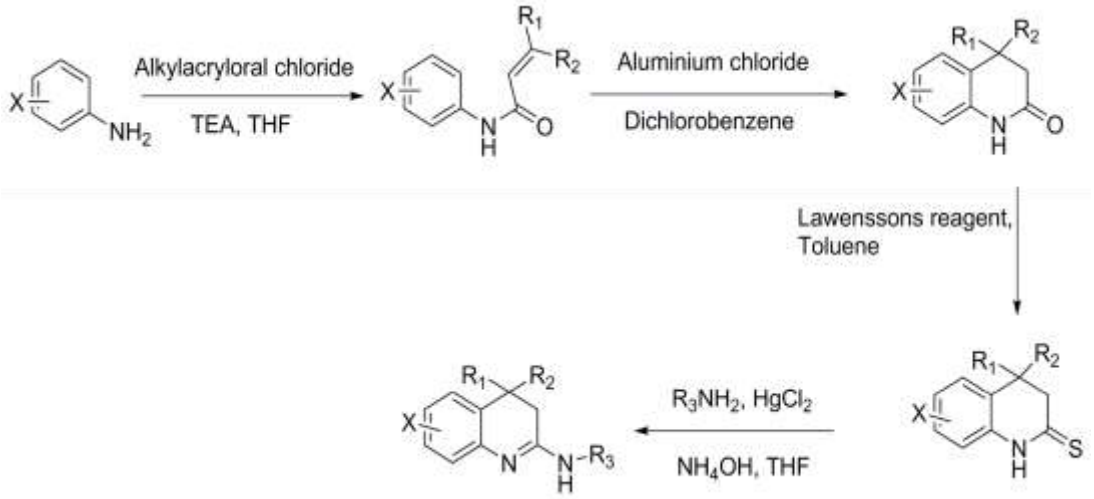


R_2 = -Ph, 4-NO_2 Ph, 4-Cl Ph, 4-F Ph, 4-OMe Ph, Indolyl, Furyl

R_1 = -H, -CH_3 R_3 = 4-OMe Ph, 4-CH_3 Ph

Scheme 2.9 Synthesis of substituted lactol and polyhydroquinoline derivatives

E. Lee and her team [114] synthesized a library of 2-aminodihydroquinoline derivatives intended for use as proapoptotic agents. The in vitro cytotoxicity and anticancer activity of these compounds were evaluated against the MDA-MB-231 adenocarcinoma metastatic breast cell line (Scheme 2.10).

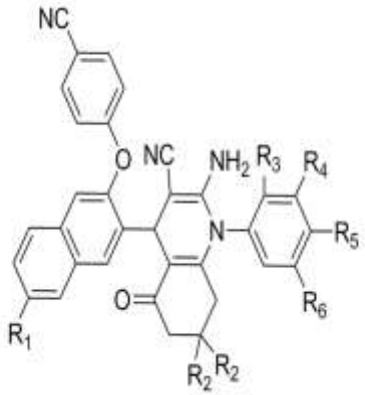


X = *p*-Cl, *m*-Cl, -H R_2 = $-CH_3$, -Ph

R_1 = -H, $-CH_3$ R_3 = -H, $-CH_3$, $-CH_2CH_3$, -Propyl, -Hydroxybutyl, -Dimethyl aminopropyl, -Diethyl aminopropyl, -Benzyl, -Morpholinyl

Scheme 2.10 Synthesis of 2-aminodihydroquinoline analogs

H. Kathrotiya and his team [115] synthesized fluoro-substituted N-aryl quinolone derivatives and evaluated their in vitro antituberculosis, antioxidant, and antimicrobial activities (Figure 2.3).



R_1 = -H, $-CH_3$, -Cl, $-OCH_3$ R_2 = -H, $-CH_3$

R_3 = R_5 = R_6 = -H, -F R4 = -H, -F, $-CF_3$

Figure 2.3 Synthesis of fluoro substituted β-aryloxyquinoline based polyhydroquinoline derivatives

CONCLUSION

A significant pharmacophore with a variety of biological characteristics is quinolines and pyrazoles, and certain derivatives containing these compounds have already been applied to medicine. This review of the literature demonstrates the pharmacological potency of pyrazole and quinolines derivatives, suggesting that their synthesis and design represent a promising field of

study. Due to their wide variety of biological actions, they have garnered the interest of scientists working on the synthesis of several quinoline AND pyrazole analogues in order to create new and more potent medications. This examination of the literature identified several synthetic routes leading to derivatives of pyrazoles and quinolines as well as the current biological promise of several pyrazole and quinolines derivatives. This review included a full analysis of their biological activity capabilities, which included antibacterial, analgesic, anti-inflammatory, anticancer, antibacterial, antidiabetic, antioxidant, and agrochemical effects. The data in this review will help future researchers look into the derivatives of quinolines and pyrazoles in more detail and will keep scientists informed about the promising biological activities of freshly produced derivatives. Furthermore, we will investigate in our upcoming work the molecular hybridization of pyrazole and quinolines with additional bioactive molecules.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Thanks to God and all the authors for contribution.

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