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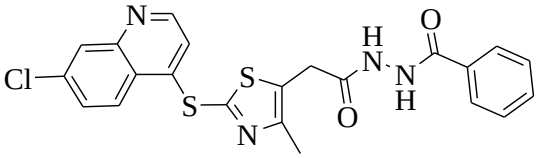
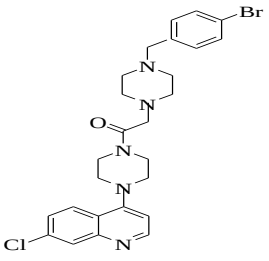


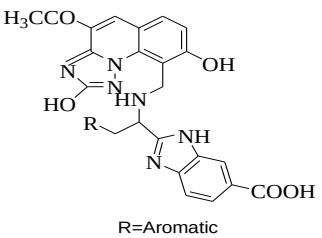
71

Scheme 71: It shown good activity against human breast cancer

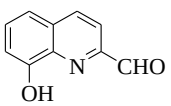


72

Scheme 72: It had the highest level of cytotoxicity for the PC3 and MCF-7 types of cell lines



73

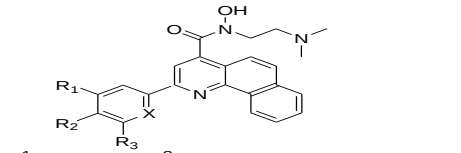


74

Scheme 73, 74: These have shown anticancer effects

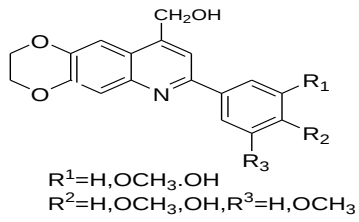
Conclusion

Since quinoline and its derivatives are known for their broad range of pharmacological activities, numerous synthetic methods have been created from time to time for their synthesis by common, homogeneous, and heterogeneous acid-catalyzed processes; rare-earth-catalyzed, transition metal-catalyzed, radical catalyzed; microwave-assisted; ultrasound-promoted; or solvent-free conditions; among others. For the future development of powerful quinoline derivatives with good or increased biological activity, the researchers working on this subject will find this review valuable.

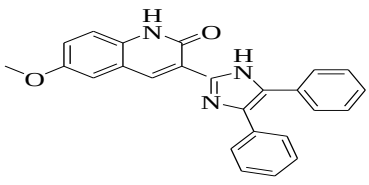


66

Scheme 66: It is effective in human cancer cell lines

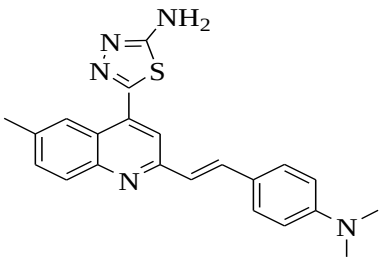


67

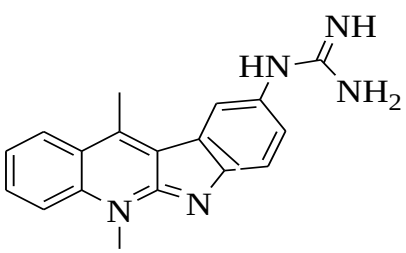


68

Scheme 67: It has lower carcinogenic activity. **Scheme 68.** It had the most potent cytotoxic effects on lung cancer

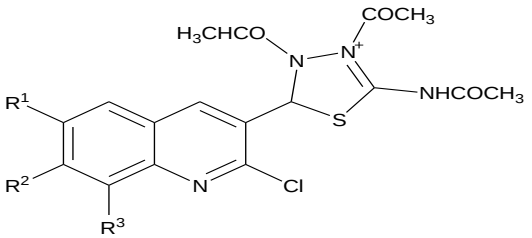


69



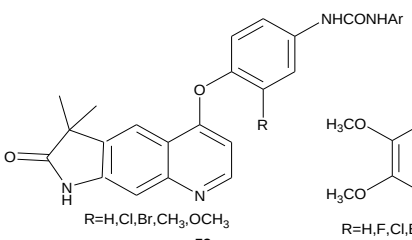
70

Scheme 69: It had the strongest anticancer effects. **Scheme 70.** It had cytotoxic and antifungal properties



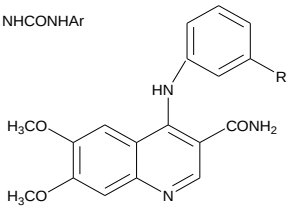
$R^1=R^2=R^3$=-H,-CH_3,-OCH_3

58

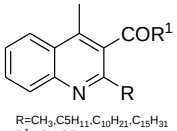


R=H,Cl,Br,CH_3,OCH_3

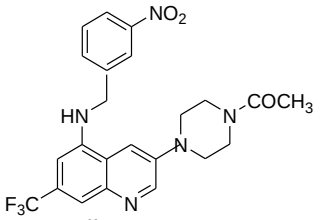
59



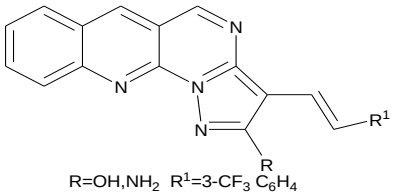
R=H,F,Cl,Br,CH_3 **60**



R=CH_3,C_5H_{11},$C_{10}H_{21}$,$C_{15}H_{31}$
R^1= OH,OEt **61**

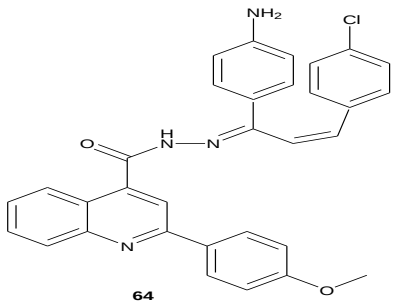


62



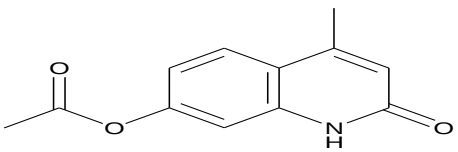
R=OH,NH_2 R^1=3-CF_3 C_6H_4

63



64

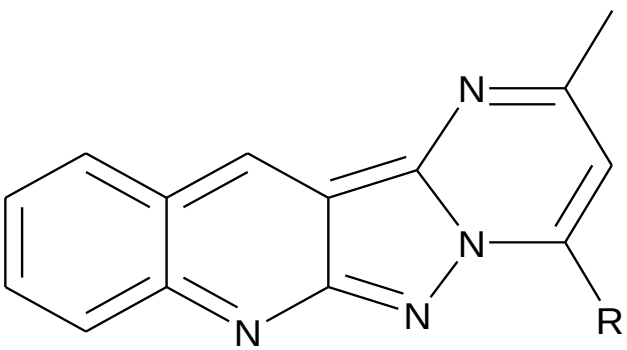
Scheme 58, 59, 60, 61, 62, 63, 64: These have anti-cancer properties



65

Scheme 65: It is effective in DNA intercalating agents

of 12.99 nm and proapoptotic and antiproliferative effects. They also showed that the lysosomes cause the suppression of autophagy and that the mechanism is linked to the obstruction of heme production (58). A new quinoline ring substituted moiety's in vitro anticancer efficacy against the PC3 (prostate cancer) and MCF-7 (human breast cancer) cell lines was described by Aboul-Enein et al. They discovered that compound (72), out of all the produced compounds, had the highest level of cytotoxicity for the PC3 and MCF-7 types of cell lines, with IC_{50} values of 11.751 and 6.502 M, respectively, in comparison to doxorubicin as the reference molecule (PC3: 7.7316 M, MCF-7: 6.774 M) (59). To assess biological activities like in vitro anticancer activity against human cancer cell lines' antibacterial and antifungal properties, Bassyouni et al. produced triazolo[1, 5-a] quinoline (73) derivatives (60). Novel 8-hydroxy quinoline (74) compounds were created by Tang et al. as anticancer medications (61).

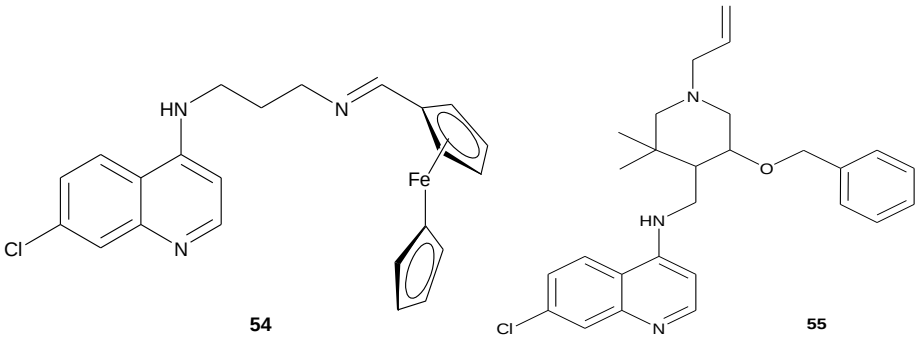


R= OH,Cl,Substituted amines **57**

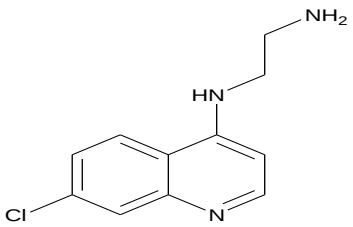
Scheme 57: It is effective in the cancerous colon

with an IC_{50} value of 3.91 M and 1.91 M, respectively. The SAR (structure-activity relationship) investigations showed that the chlorine atoms increase the cytotoxic activity of chalcone rings (51). In a report on synthesizing hybrid quinolinone derivatives, Moustafa and colleagues used the MTT assay to assess the antiproliferative effectiveness of the MCF-7 (human breast cancer) cell line. According to the findings, the cell cycle was interrupted at the S and G2/M phases. Of all the synthesized derivatives, the best active compound **(**65) had an IC50 value of 5.51 M (52). To better understand some known DNA intercalating agents, Ghodsi et al. explored the molecular structure and chemical synthesis of a series of new benzo-[h] quinolines (66) bearing a flexible (dimethylamino) ethylcarboxamide side chain at position-4 of the quinoline (53). By Ghodsi et al., three human cancer cell lines—MCF-7 (human breast cancer cells), DU145 (human prostate cancer cell lines), and A549 (adenocarcinomic human alveolar basal epithelial cells)—were used to test the cytotoxic effect of the produced quinoline (67) compounds (54). Heme Oxygenase-1 receptor inhibitors that are synthesized from imidazole-substituted quinolines were characterized by Mohan and colleagues as having lower carcinogenic activity. The most active substance (68**),** which had IC_{50} values of 39.35, 62.03, and 50.10 M, respectively, had the most potent cytotoxic effects on A549 (lung cancer) cell lines (55). Using the human hepatoma and colorectal cancer cell lines HepG2 and HCT116, El-Sayed et al. reported the synthesis of 2-styryl quinolines and assessed their in vitro anticancer efficacy. They noticed that out of all the compounds they had created, compound **(**69) had the most potent anticancer effects, with IC_{50} values of 7.70.15 and 8.80.26 g/ml against the HepG2 and HCT116 cell lines, respectively. The activity was also compared to that of the common medications 5-Flouro Uracil and Afatinib, with IC_{50} values of 7.90.17 and 5.30.32g/ml against HepG2 cell lines and 5.40.25, 11.41.26g/ml against HCT116 cell lines, respectively (56). According to Sidoryk et al., the synthesis of indolo[2, 3-b] quinoline derivatives (70) with guanidine, amino acid, or guanylamino acid substituents, as well as an assessment of their in vitro cytotoxic and antifungal properties (57).

The molecular hybridization approach was used by Ramrez et al. to create the new compounds, one of which, compound (71), showed good activity against the human breast cancer cell line (MCF-7 cells) with an IC_{50} value



Scheme 54, 55: Were the most effective against the NF54 and K1 strains

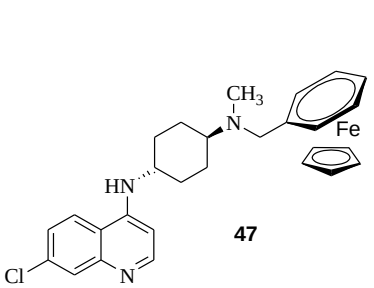


Scheme 56: Antimalarial activity against

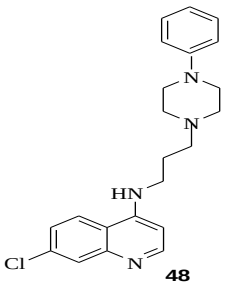
Anticancer activity

According to the World Health Organization, cancer is the deadliest disease in the world. It is the second leading cause of death after other diseases, and there are now 18.1 million deaths from cancer worldwide. Despite numerous improvements in the treatment, thus far, there has only been a small amount of success. Trials are still looking for improved preventive measures as cancer faces many obstacles (49). Polycyclic heterocycles with a pyrimido[1″,2″:1,5]pyrazolo[3,4-b]quinoline (57) framework were developed and created by Tiwari et al. The substances were tested for activity against cancerous Madin-Darby canine kidney (MDCK), mouse embryonic fibroblast (NIH/3T3), and human embryonic kidney (HEK293) cells as well as non-cancerous colon, prostate, breast, ovarian, hepatic, and ovarian cancer cells (HCT-116, S1-MI-80, PC3, DU-145, MCF-7, and A2780). The chemical structures of quinoline and its derivatives which have anticancer properties (58–63)(50).

Abbas and colleagues described the quinoline chalcone hybrid compounds as a nonselective PI3K inhibitor. The most effective anticancer activity was demonstrated by compound (64) against the A549 (adenocarcinomic human alveolar basal epithelial cells) and K-562 (lymphoblasts) cell lines,



47



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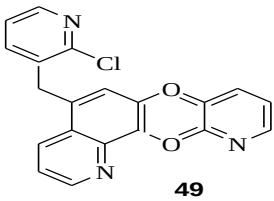
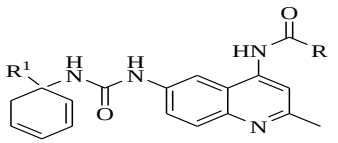


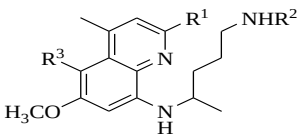
49

Scheme 47, 48, 49: These compounds had considerable antimalarial efficacy against



R= -CH_3 ,Ph,CH_2Cl,2- Furyl
R^1=F,Cl,Br,CF_3

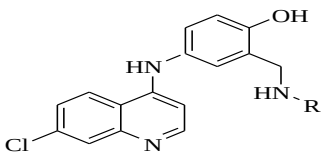
50



R^1= OCH_3,CF_3 R^2= H or $C(O)OC(CH_3)_3$
R^3= Ar

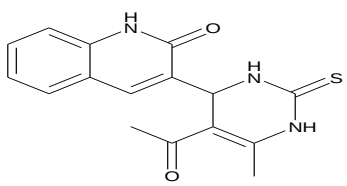
51

Scheme 50, 51: These compounds have antimalarial action.



R= H,Ph,iPr,n-Bu

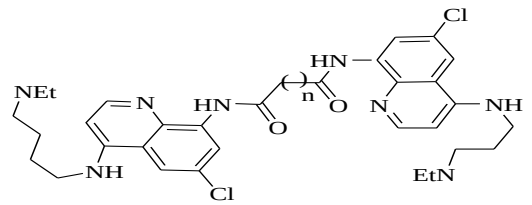
52



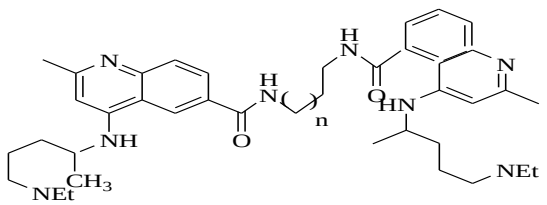
53

Scheme 52, 53: These compounds have antimalarial action

With IC_{50} values for the NF54 and K1 strains of 0.0120.0010 and 0.0260.0057M, respectively, compound (55**)** was the most active in the study (47). Compound (56), a novel 4,7-dichloroquinoline derivative produced by Murugan et al., had considerable in vitro antimalarial activity against P. falciparum strains that were CQ-resistant (INDO) and CQ-sensitive (3D7), with IC_{50} values of 6.7 and 8.5 nm, respectively (48).

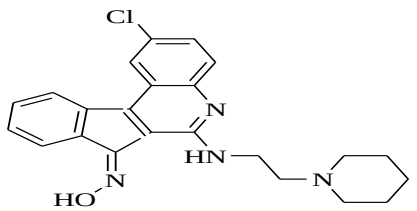


n=4,6,8 **43**



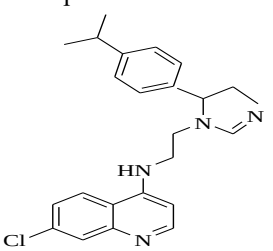
n=2,4,6,8 **44**

Scheme 43, 44: These compounds have a powerful antimalarial effect



45

Scheme 45: This compound has inhibited strains the best

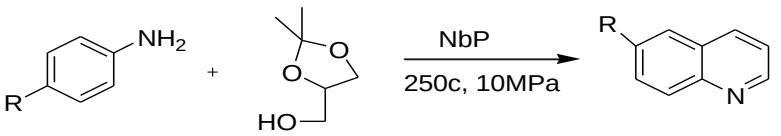


46

Scheme 46: This compound had anti-plasmodial action against K1 strains

chloroquinolin-4-amine significantly affected the anti-plasmodial action. Alkyl groups and phenyl rings with alkyl substituents were the most pharmacophore-friendly substituents (39). Using in-vitro anti-plasmodial activity against P. falciparum CQ-sensitive (F32/Tanzania) and CQ-resistant (K1/Thailand and FcB1/Colombia) strains, Maguene et al. disclosed the synthesis of ferrocenyl aminoquinoline derivatives. They found that compound (47) had considerable antimalarial efficacy against the P. falciparum strains, with an IC_{50} value for the F32, FcB1, and K1 strains of 33, 27, and 26 nM, respectively (40). New quinoline-acridine hybrid molecules were created, and Kumar et al assessed their in-vitro antimalarial efficacy against the P. falciparum NF-54 strain type. With a minimum inhibitory concentration (MIC) of 0.125 g/ml, they found that compound (48) displayed superior in-vitro action (41).

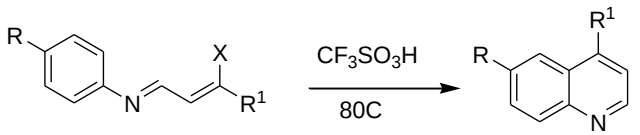
Singh et al. created several antimalarial 4-anilinoquinolines (49) that effectively combated P. falciparum strains sensitive to chloroquine (42). A couple of ureido-4-quinolinamides were created by Madapa et al. (50), and they demonstrated antimalarial activity against a chloroquine-sensitive P. falciparum strain at MICs of 0.25 mg/mL (43). Certain 5-aryl-8-aminoquinolines (51) with potential antimalarial action were created by Shiraki et al., but they had less hemolytic activity than Tafenoquine (44). Singh et al. synthesize 4-anilinoquinoline-ringed antimalarial drugs (52). The compounds effectively inhibited the rodent malaria parasite P. yoelii and chloroquine-sensitive P. falciparum strains (42). New quinoline compounds have been developed, synthesized, and tested for their biological activity in vitro as antimalarial medicines by Radini et al. Combination (53) was shown to be the most effective against P. falciparum, showing greater activity than the industry standard medication chloroquine (IC_{50} = 0.49 g/ml) (45). Stringer et al. tested NF54 (CQS) and K1 (CQR) strains of P. falciparum for in-vitro antiplasmodial action by Stringer et al., who also described quinoline-based polyamines with ferrocene added. Additionally, they noted that compound (54), a ferrocenyl derivative, was the most effective against the NF54 and K1 strains, with corresponding IC_{50} values of 0.083, 0.01, and 0.59, 0.03 M (46). Van de Walle et al. conducted in vitro tests of quinoline compounds with piperidine side chains for antiplasmodium action on CQ-sensitive (NF54) and CQ-resistant (K1) strains of P. falciparum.



R=4-OCH_3,4-$NH_2C_6H_4CH_2$-, **41**

Scheme 41: Synthesis of quinolines from anilines and solketal over a solid acid niobium phosphate

A novel technique for synthesizing quinolines (42**)** using vinylogous imines, which are, in turn, made from anilines and cinnamaldehydes, was reported by Vuong et al. Quinolines and similar compounds are produced by the reaction of these substrates in a very acidic media (37).



R=H,Br,Cl R^1=H,C_6H_5,NaPthyl **42**
X=OAc,Cl

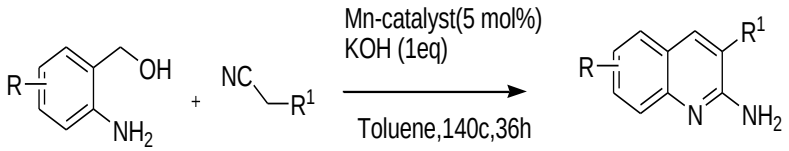
Scheme 42: Synthesis of quinolines that use vinylogous imines.

Biological activity

Antimalarial

Quinolines are renowned for having powerful antimalarial effects. Bisquinolines synthesized have antimalarial efficacy against both (43,44) chloroquine-sensitive and -resistant parasites (27) .In a study against the W-2 (CQ-R), D-10, and 3D7(CQ-S) strains of Plasmodium falciparum, Barteselli et al. characterized a novel indeno[2,1-c] quinoline derivative evaluated its in-vitro anti-plasmodial efficacy. They also noted that compound (45), with IC_{50} values of 0.2550.119, 0.8500.181, and 0.8430.096 M, respectively, inhibited W-2, D-10, and 3D7 strains the best. It has been further shown that the indeno[2,1-c] quinoline scaffolding was responsible for the synthesized derivatives' anti-plasmodial action (38). The anti-plasmodial activity of novel imidazole derivatives against chloroquine-resistant (K1) and chloroquine-sensitive (3D7) strains of P. falciparum was assessed by Kondaparla et al. Additionally, they discovered that compound (46) had anti-plasmodial action against K1 strains and had an IC_{50} of 0.29 0.018 M, equivalent to the established chloroquine medication (IC_{50} = 0.255 0.049 M). Their findings demonstrated that substituting the pharmacophore N-(2-[1H-imidazol-1-yl] ethyl)-7-

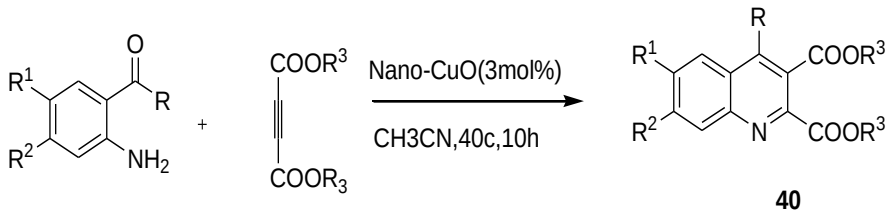
Using an earth-abundant, well-defined manganese complex **(39)** with NNS ligands, 2-aminobenzyl alcohol and substituted benzyl nitriles can be synthesized sustainably by acceptor-less dehydrogenative annulation (34).



R=H,4-Cl R1=4-ClC_6H_4-, 4-$OCH_3C_6H_4$-,2,4,6-$(Cl)_3C_6H_2$

Scheme 39: Synthesize of 2- amino 3- substitution quinoline from amino benzyl alcohol and substituted benzyl nitriles

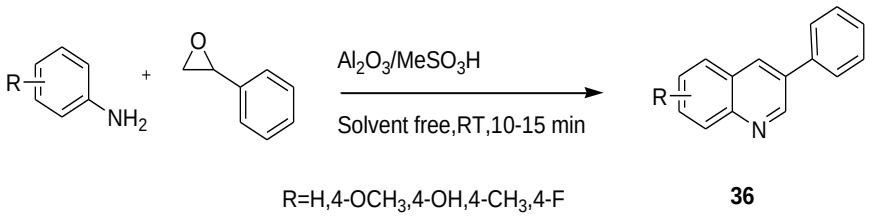
Venkanna et al. used CuO nanomaterial under acetonitrile at 40 C to produce a straightforward, smooth, air-defiant, inexpensive catalytic method to access quinolines (40) from substituted o-amino carbonyl compounds and diacetylene dicarboxylate in one pot. As catalytic candidates for the processes, many copper catalysts, including copper (I) acetate (CuOAc), copper bromide (CuBr), and copper iodide (CuI), were evaluated. The results show that Nano-CuO is more effective in yield than the other catalysts listed (35).



R=H,CH_3,C_6H_5. R^1=H,Cl,OCH_3. R^2=H,OCH_3,Br. R^3=CH_3,CH_2CH_3,(CH_2)

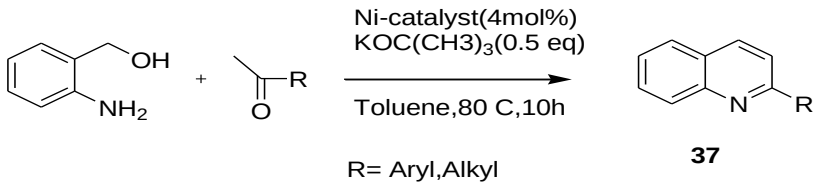
Scheme 40. Synthesis of quinolines from substituted o-amino carbonyl compounds and diacetylene dicarboxylate with catalyst of CuO.

Jin and a collaborator created a continuous Skraup synthesis (Skraup reaction) of quinolines (41) using anilines and solketal over a solid acid niobium phosphate (NbP) catalyst at 250 C and 10 MPa pressure. The chosen technique showed a 60% quinoline synthesis selectivity. The need for reactors and the demanding reaction conditions, such as high temperature and pressure, reduced its usefulness for scholarly research. However, this technique might be helpful for commercial applications (36).



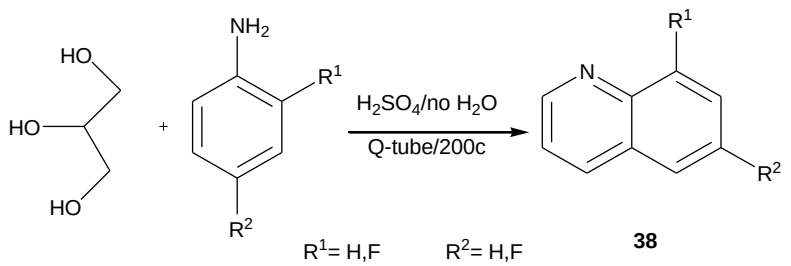
Scheme 36: synthesis of 3-aryl quinolines from anilines and styrene oxide.

By using biomimetic dehydrogenative condensation or coupling reactions, Chakraborty et al. reported a straightforward, affordable, and atom-efficient method for synthesizing quinolines from 2-amino benzyl alcohol and (37) carbonyl compounds. The responses were catalyzed by well-defined, reasonable, and simple-to-prepare singlet diradical (biradicals) Ni (II)-catalysts in a good yield(32).



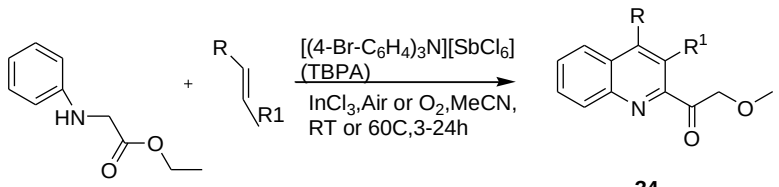
Scheme 37: synthesis of quinolines from 2-amino benzyl alcohol and carbonyl compounds with a catalyst of Ni

Glycerol's role as a green bio-based solvent (obtained from renewable sources), reactant, and/or catalyst in synthesizing novel heterocycles (**38)** under pressure has been studied by Al Marzouq et al. Using a new modified Skraup synthesis that uses glycerol and pressure Q-tubes, it was possible to synthesize novel quinolines and their derivatives in good yields successfully. Under pressure in an aqueous acidic media, substituted anilines and glycerol synthesize novel quinolines (33).



Scheme 38: synthesize novel quinolines and their derivatives from substituted anilines and glycerol

Under catalytic radical cation salt-induced conditions, Jia et al. reported achieving a domino C-H functionalization of glycine derivatives to produce a series (34) of quinolines. The hypothesized mechanism is that the reaction is carried out by a peroxyl radical cation produced by coupling O_2 and TBPA (29).

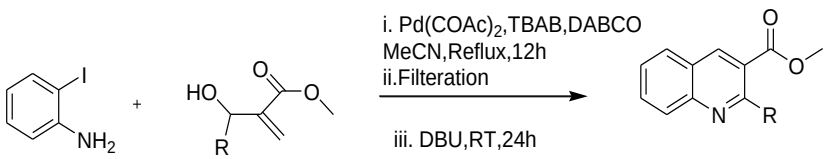


R= Aromatic R1=H ,CH3,Benzyl

34

Scheme 34: Synthesis of quinolines using glycine derivatives by the coupling of O_2 and TBPA

By cyclizing 2-iodo aniline and a-benzyl b-keto ester derivatives, Selvakumar et al. were able to efficiently obtain 2,3-disubstituted quinoline compounds (35) from het/aryl-substituted Morita-Baylis-Hillman adducts. This method converts the MBH adducts into a-benzyl b-keto ester derivatives, which can cyclize to produce quinolines in high yields (30).

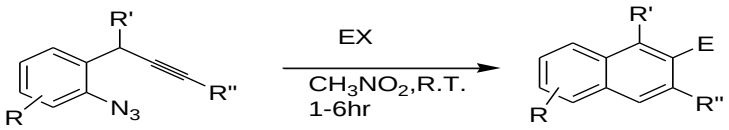


35

R= Aromatic

Scheme 35: Synthesis of 2,3-disubstituted quinoline compounds from 2-iodo aniline and a-benzyl b-keto ester derivatives

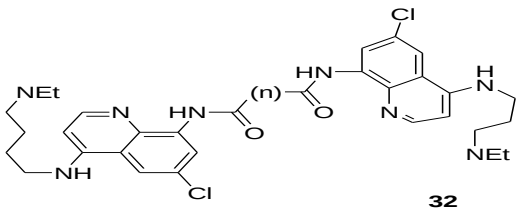
In the presence of $Al_2O_3/MeSO_3H$, Sharghi H et al. described the straightforward, extremely effective, and green synthesis of 3-aryl quinolines via a one-pot reaction between anilines and styrene oxide. This method allows for the quick and efficient synthesis of 3-aryl quinolines at room temperature (36) without needing solvent (31).



EX=NIS,Br_2 R'=H,OAC R''=Alkyl.Aryl **31**

Scheme 31: Synthesis of quinolines from 1-azido-2-(2-propynyl) benzene by catalyst

Researchers have discovered that the bisquinolines (32) synthesized by Raynes et al. had a good amount of antimalarial activity against chloroquine-resistant and chloroquine-sensitive parasites (27).

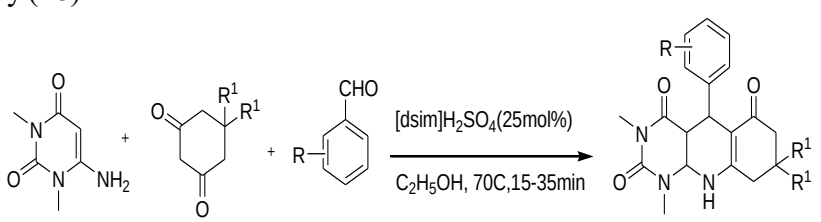


32

n=4,6,8

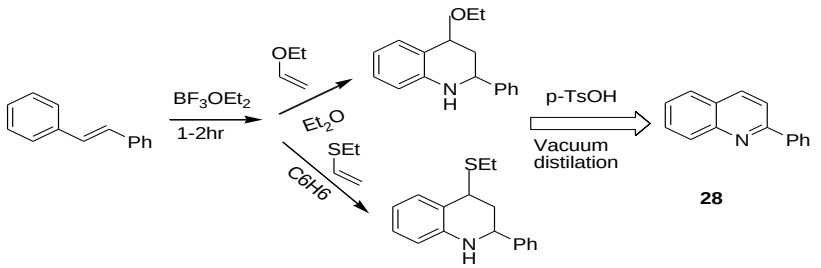
Scheme 32: This compound has a good antimalarial activity

The multi-component synthesis of pyrimido[4,5-b]-quinoline derivatives **(33**) was reported by Mohammadi et al. using 1,3-disulfonic acid imidazolium hydrogen sulfate as the ionic catalyst for condensation of 6-amino-1,3-dimethyluracil, cyclic 1,3-diketones, and aromatic aldehydes in ethanol at 70 C. The current methodology offers several benefits, including great yields, a straightforward process, quick reaction times, high product yields, and simple work-up procedures. The catalyst may also be easily retrieved and recycled multiple times without clearly losing any of its activity (28).



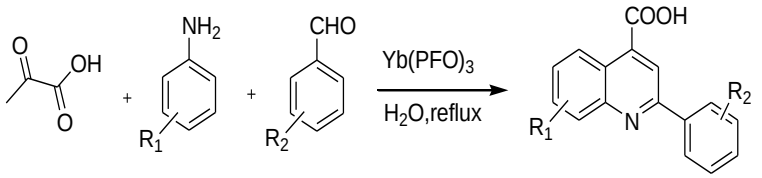
R=6-F,4-F,4Cl,4-Br,4-OCH_3,4-CH_3,3-Br,3-NO_2,2-Cl R^1=H,CH_3 **33**

Scheme 33: Synthesis of pyrimido[4,5-b]-quinoline derivatives using 1,3-disulfonic acid imidazolium hydrogen sulfate as the catalyst for condensation of 6-amino-1,3-dimethyluracil, cyclic 1,3-diketones, and aromatic aldehydes



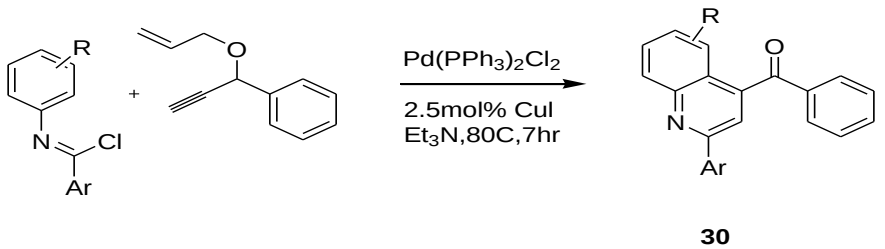
Scheme 28: Synthesis of 2-phenyl substituted quinolines from distillation with tosylic acid (p-TsOH)

Treating 2-oxo propionic acid with aniline and benzaldehyde while using rare earth metal catalysts and refluxing it in water makes it possible to synthesize **(29**) 2-phenylquinoline-4-carboxylic acid (24).



Scheme 29: Synthesis of 2-phenylquinoline-4-carboxylic acid from 2-oxo propionic acid with aniline and benzaldehyde

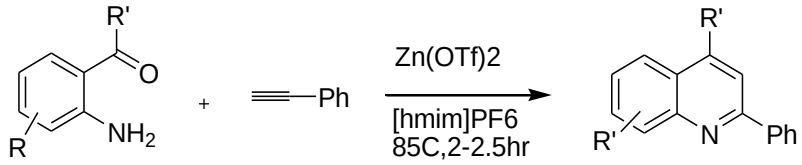
By means of palladium-catalyzed Sonogashira coupling and subsequent cyclization, 1-(1-(allyloxy) prop-2ynyl) benzene (1,6-enynes) **(30**) and benzimidoyl chlorides react to produce quinoline derivatives (25).



Scheme 30: Synthesis of quinoline derivatives from 1-(1-(allyloxy) prop-2ynyl) benzene (1,6-enynes) and benzimidoyl chlorides

When 1-azido-2-(2-propynyl) benzene is intramolecularly cyclized in nitromethane (CH_3NO2) at room temperature or in THF at 100C in the presence of catalytic (**31**) quantities of $AuCl_3/AgNTF_2$, the resulting quinolines are produced in good yields (26).

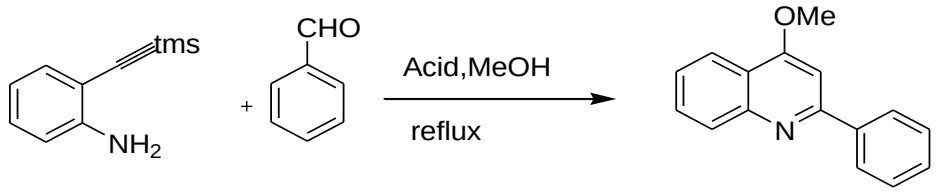
Meyer-Schuster rearrangement has been used to synthesize 2,4-disubstituted quinolines (19). This procedure produces 2,4-disubstituted quinolines by rearranging 2-amino aryl ketones (26) and phenylacetylenes in the presence of zinc trifluoromethanesulfonate in the ionic liquid 1-hexyl-3-methylilmidazolium hexafluorophosphate [hmim][PF_6]. The same product was produced via microwave irradiation without a solvent when indium (III) trifluoro methane sulfonate was present (20).



26

Scheme 26: synthesis of 2,4-disubstituted quinolines by rearranging 2-amino aryl ketones and phenylacetylenes in the presence of zinc trifluoromethanesulfonate

By condensation and cyclization of 2-(2-trimethylsilyl) ethynyl) aniline with aryl aldehydes, 2-Phenyl-4-alkoxy quinoline **(27**) has been synthesize. In the presence of methanol as a solvent, sulfuric acid accelerates the process (21).



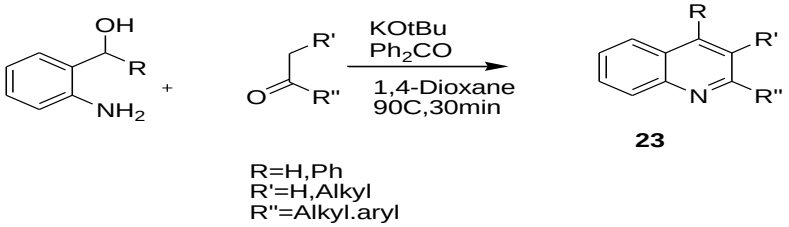
27

Scheme 27: Synthesis of 2-Phenyl-4-alkoxy quinoline from 2-(2-trimethylsilyl) ethynyl) aniline with aryl aldehydes

Reacting 2-iodoanilines and ethyl acrylate with azobisisobutyronitrile (AIBN) and tributyltin hydride, 3,4-dihydroquinolin-2-one has been synthesized (22).

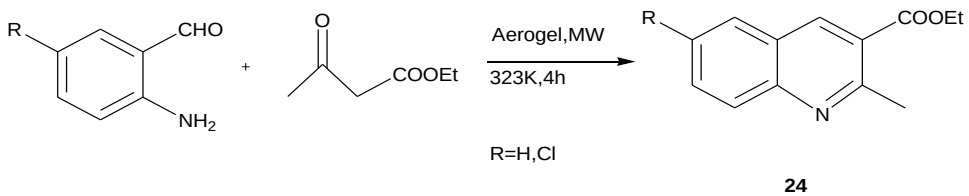
Kuznetsova created phenyl-substituted quinol using acidic catalysis in the presence of boron trifluoride etherate to produce 2,4-substituted tetrahydroquinolines. These quinolines were then converted to 2-phenyl-substituted quinolines (28) under vacuum distillation with tosylic acid (p-TsOH) (23).

By reacting 2-amino benzylic alcohol derivatives with ketones or alcohols in the presence of base and benzophenone as hydride scavengers, poly-substituted quinolines have (23) been synthesized (16).



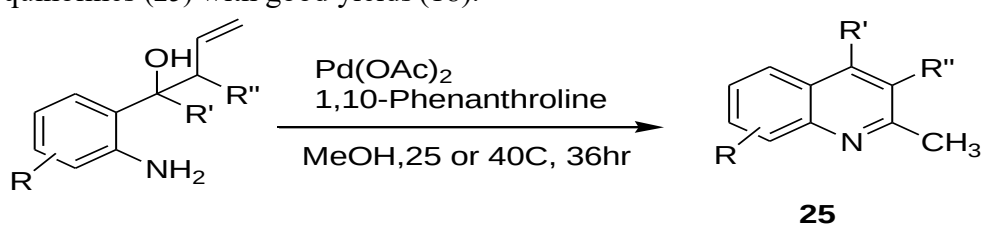
Scheme 23. Synthesis of poly-substituted quinolines from 2-amino benzylic alcohol derivatives with ketones or alcohols in the presence of base and benzophenone

Recently, under the impact of MW radiations, Ojer et al. described an exciting and significant metal-free Friedlander synthesis of 2,3,6-substituted quinolines using substituted 2-aminobenzaldehydes and ethyl acetoacetate catalyzed by nano-carbon aerogels. Their surface chemistry significantly influenced the catalytic performance of carbon aerogels, and the presence of oxygenated functional groups **(24),** particularly COOH, boosted the catalytic activity and, consequently, the yields of quinolines (17).



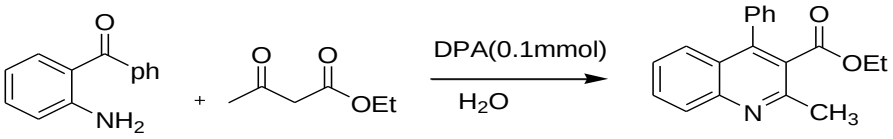
Scheme 24: synthesis of 2,3,6-substituted quinolines using substituted 2-aminobenzaldehydes and ethyl acetoacetate catalyzed by nano-carbon aerogels

Wacker-type oxidative cyclization with palladium as the catalyst has been presented as a method for the mild-condition synthesis of 2-methyl quinolines (25) with good yields (18).



Scheme 25: synthesis of 2-methyl quinolines uses palladium as the catalyst

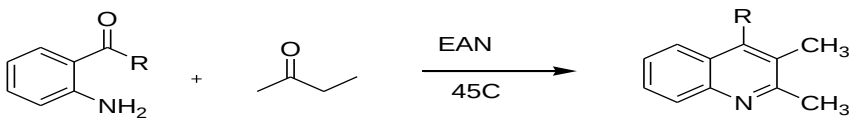
In the presence of dodecyl phosphonic acid (DPA) as a catalyst, poly-substituted quinolines (19) have been produced using 2-amino-substituted ketone and ketone as reactants in aqueous media and solvent-free conditions (14).



19

Scheme 19: To synthesize poly-substituted quinolines, use phosphonic acid as a catalyst and 2-amino-substituted ketone and ketone

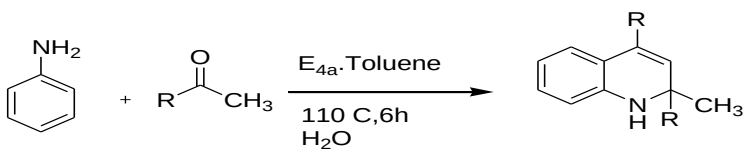
2,3,4-trisubstituted quinolines (20) have been synthesized by stirring 2-amino substituted aromatic ketones and carbonyl compounds with a reactive methylene group in ethyl ammonium nitrate (EAN) [12].



20

Scheme20: To synthesize 2,3,4-trisubstituted quinolines, 2-amino substituted aromatic ketones, carbonyl compounds, and ethyl ammonium nitrate

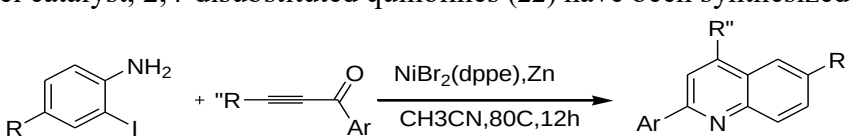
Aniline and acetophenone were used to synthesize 2,4-diphenyl-2-methyl-1,2 dihydroquinoline (21) in the presence of an E4a zeolite catalyst with tiny pores (15).



21

Scheme 21: For the synthesis of 2,4-diphenyl-2-methyl-1,2, dihydroquinoline used Aniline and acetophenone

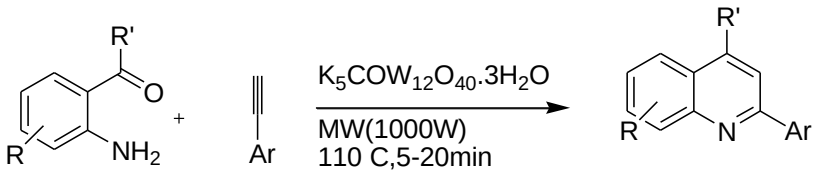
By cyclizing 2-iodoanilines with alkynyl aryl ketones in the presence of a nickel catalyst, 2,4-disubstituted quinolines (22) have been synthesized (3).



22

Scheme 22: Synthesis 2,4-disubstituted quinolines from cyclizing 2-iodoanilines with alkynyl aryl ketones in the presence of a nickel catalyst

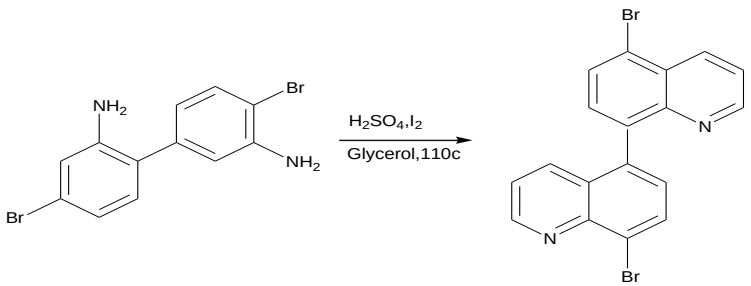
Iraj et al. have reported the use of potassium dodecatugstocobaltate trihydrate (K5CoW12O403H2O) as a reusable and environmentally friendly catalyst to create 2,4-disubstituted quinolines (16) in a single pot by reacting structurally different 2-amino aryl ketones with various aryl acetylenes under microwave irradiation and solvent-free conditions (11).



16

Scheme 16: To synthesize 2,4-disubstituted quinolines, a potassium dodecatugstocobaltate trihydrate (K5CoW12O403H2O) was used as a reusable and environmentally friendly catalyst

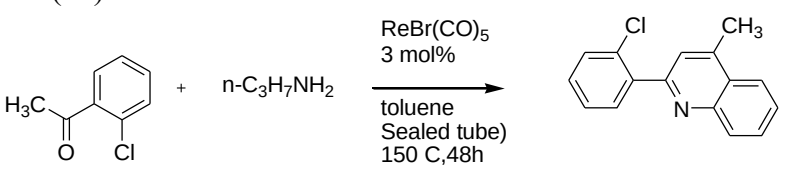
Tomar et al. reported on the Skraup synthesis of dibromo quinolines (17) from 4,4-dibromo-2,3-diamino biphenyl utilizing H_2SO_4 and I_2 as a more environmentally friendly catalyst. Based on these cores, a significant change in the design of conjugated materials was shown (12).



17

Scheme 17: synthesis of dibromo quinolines from 4,4-dibromo-2,3-diamino biphenyl utilizing H_2SO_4 and I_2

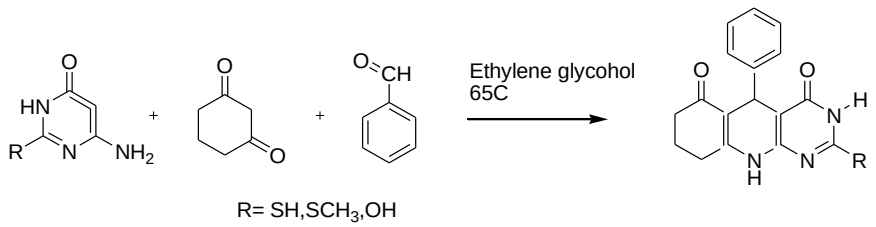
Two molecules of o-halo acetophenones were condensed and cycled with urea or primary amines to create specific halogen-substituted (18) quinolines (13).



18

Scheme 18: Synthesize halogen-substituted quinolines from Two molecules of o-halo acetophenones with urea

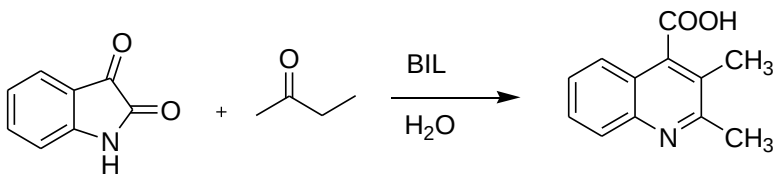
aldehyde under ultrasonic irradiation in ethylene glycol as solvent at temperature ٦٥°C to produce pyrimido[4,5-b] (13) quinoline derivatives. This process produced fused pyrimidine derivatives in short amounts (10–33 min), with high to exceptional yields (9).



13

Scheme13: 6-amino-2-(alkylthio)-pyrimidine -4(3H) one, 1,3-cyclohexadiene, and aryl aldehyde under ultrasonic irradiation in ethylene glycol as solvent to produce Pyrimido[4,5-b] quinoline

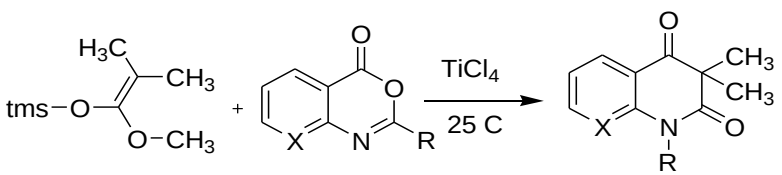
According to Kowari and Mallak Mohammadi (2011), basic ionic liquids (BIL) in aqueous media were used in the ultrasound-promoted synthesis of (14) quinolines. This process is easy to use and produces high yields—ultrasonic frequencies of 20–50 kHz cure conditions by producing aromatic methyl ketones (10).



14

Scheme 14: Basic ionic liquids (BIL) in aqueous media were used in the ultrasound-promoted synthesis of quinolines

The production of quinoline alkaloid (15) analogs now uses a one-step process. The Mukaiyamaaldol condensation is modified to form the basis of the process by utilizing the high reactivity of lactones or anhydrides.



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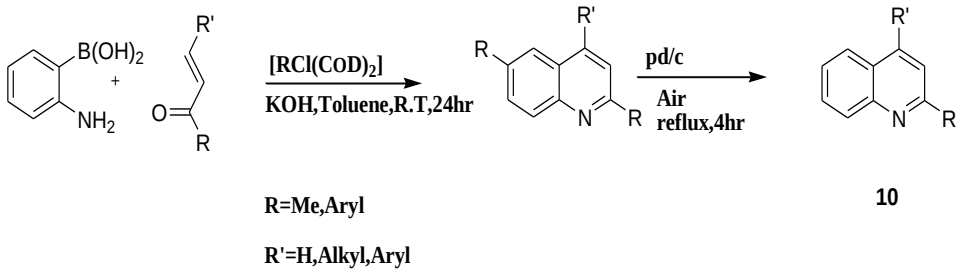
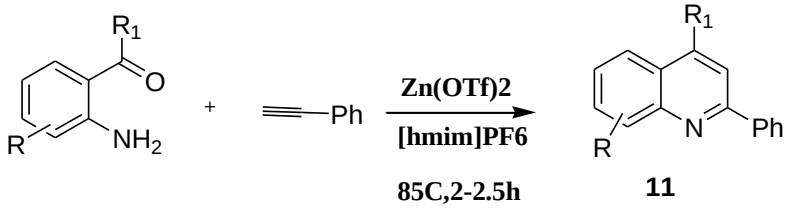
Scheme15: By utilizing the high reactivity of lactones or anhydrides, synthesize quinoline alkaloids



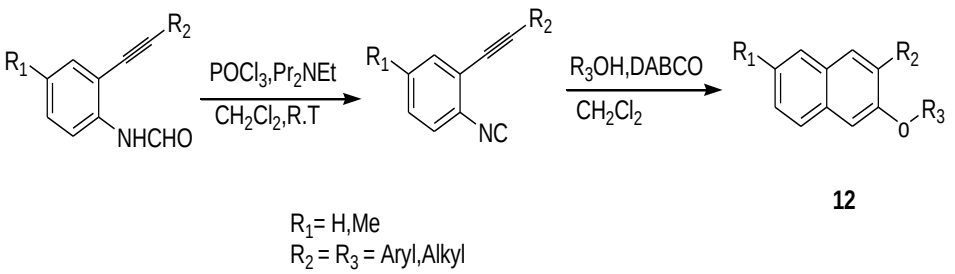
Scheme 10: synthesis of quinolines from derivatives of o-amino phenylboronic acid and a, b-unsaturated ketones

2-Aminoaryl ketones were cyclized with phenylacetylenes to produce 2,4-disubstituted quinolones. This reaction takes place with a zinc trifluoromethanesulfonate catalyst in an ionic liquid media ([hmim]PF_6) (6). Lekhok et al., under microwave and solvent-free conditions, the same product (**11**) was produced in the presence of a catalytic quantity of indium (III) trifluoromethane sulfonate (7).



Scheme 11: 2-Aminoaryl ketones were cyclized with phenylacetylenes to produce 2,4-disubstituted quinolones.

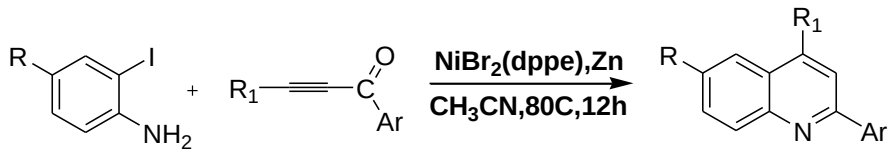
With the aid of 1,4-diazabicyclo[2.2.2]octane (DABCO), diverse 2-alkoxy- and 2-aroxy-3-substituted quinolines(**12**) have been created from o-alkynyl aryl isocyanides, alcohols, and phenols (8).



Scheme 12: 1,4-diazabicyclo [2.2.2] octane diverse 2-alkoxy- and 2-aroxy-3-substituted quinolines have been created from o-alkynyl aryl isocyanides, alcohols, and phenols.

Araghi et al. reported the one-pot three-component reaction involving 6-amino-2-(alkylthio)-pyrimidine -4(3H) one, 1,3-cyclohexadiene, and aryl

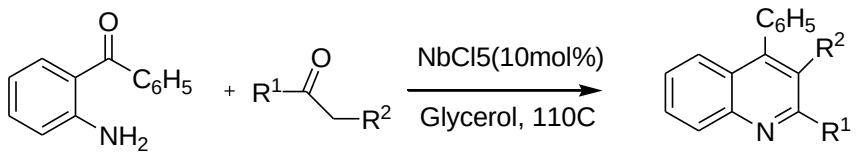
To synthesize quinoline and quinoline derivatives, (**8**) numerous synthetic pathways have been devised in addition to the traditional approaches. Chen et al.reported the condensation of 2-iodoanilines with alkynyl aryl ketones using nickel as a catalyst to produce 2,4-disubstituted quinolines (3).



8

Scheme 8: Condensation of 2-iodoanilines with alkynyl aryl ketones using nickel as a catalyst to produce 2,4-disubstituted quinolines

Nasseri and colleagues using a cheap catalyst called NbCl5 to condense o-amino aryl ketones and carbonyl compounds (Scheme9) have synthesized quinolines**.** The quinoline derivatives were produced in glycerol, which has a low environmental impact and high yields (76–98%) over a quick (20–90 minute) reaction time. Both ketones and diketones provided the desired compounds (**9)** in this investigation with good to outstanding yields (4).



9

Scheme 9: Using a catalyst of NbCl5 to condense o-amino aryl ketones and carbonyl compounds and produce 2,3 di alkyl 4- phenyl quinoline

Horn et al. reported the synthesis of quinolines from derivatives of o-amino phenylboronic acid and a, b-unsaturated ketones, which is a change from the standard (**10**) SkraupDoebner-von Miller synthesis. The approach has the benefit that it can operate in basic circumstances as opposed to highly acidic ones (5).

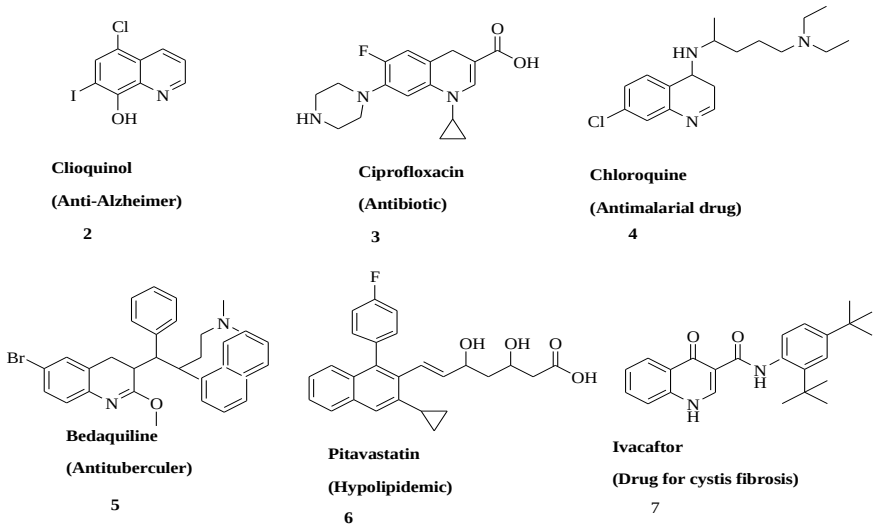


Fig1: A few promising compounds with the quinoline ring

Synthesis

Several established protocols are there for synthesizing quinoline rings, which can be well modified to prepare a number of differently substituted quinolines. These can be changed to yield a variety of different substituted quinolines. The Skraup, Doebner-Von Miller, Pfitzinger, Friedlander, Conrad-Limpach, and Combes synthesizes, among others, have been commonly used to create the quinoline ring (Figure 2).

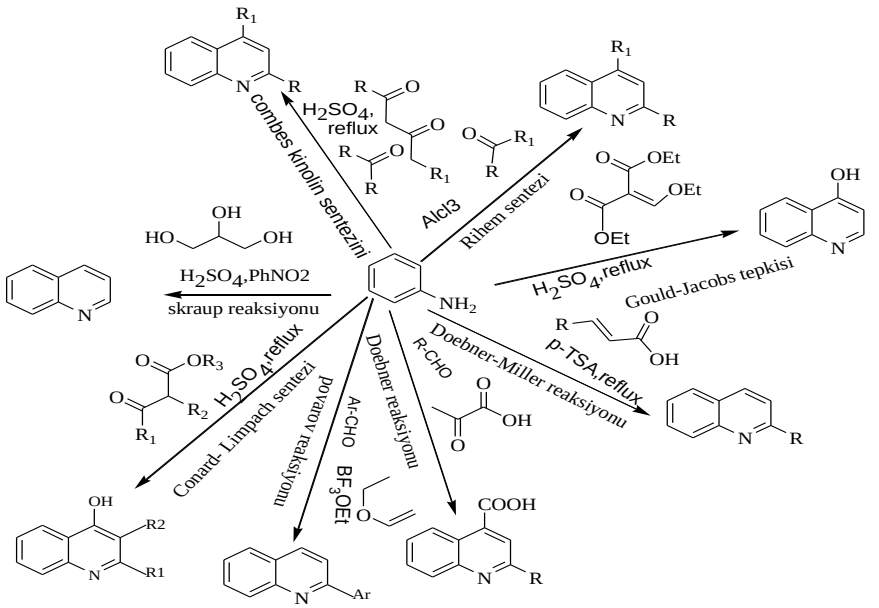
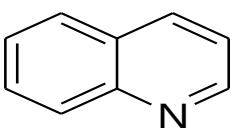


Fig 2: Traditional techniques for synthesizing different substituents of quinolines

Introduction

Quinoline (1) is a double-ringed organic molecule with the chemical formula C_9H_7N with a benzene ring fused to pyridine at two adjacent carbon atoms. Quinoline is a heterocyclic aromatic organic compound. Benzo pyridine, benzo[b]pyridine, 1-benzazine, and benzo are other names for quinoline. It is a hygroscopic, yellowish oily liquid that is soluble in many different organic solvents as well as alcohol, ether, and small amounts of water. The scientific community, particularly those interested in the chemistry of natural products, has taken a keen interest in quinoline and isoquinoline alkaloids derived from natural sources due to their amazing biological activity and comparatively simple structures (1). Synthetic organic chemists have expressed a growing interest in quinoline and its related compounds, driven by the increasing demand for larger quantities in advanced biological research. This heightened focus stems from the need to facilitate extensive studies and investigations in the field, underscoring the crucial role these compounds play in furthering our understanding of various biological processes. As a result, researchers are actively working to develop efficient synthetic methodologies to produce quinoline and its congeners on a larger scale, enabling more comprehensive and impactful biological studies.



1

Quinoline alkaloids, sourced from animals, plants, and microbes alike, exhibit diverse biological activities. Numerous quinoline derivatives have been created and reported for use in various applications. Quinoline derivatives are frequently employed as "parental" compounds to develop molecules with therapeutic properties, particularly those with anti-malarial and anti-microbial properties. Quinolines' antibacterial, anticancer, antifungal, hypotensive, anti-HIV, analgesic, and anti-inflammatory properties and their derivatives are well documented (2). A few promising compounds (2–7) with the quinoline ring system are given in Figure1.

A Comprehensive Review of the Quinoline Heterocyclic Ring and Its Antimalarial and Anticancer Biological Activities

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Abstract
Quinoline is a preferred scaffold that emerges as a significant assembly motif for creating novel pharmacological molecules among heterocyclic compounds. Due to the extensive spectrum of biological and pharmacological properties of quinoline and its derivatives, numerous synthetic pathways have been created for their synthesis. Quinoline and its derivatives tested with diverse biological activity constitute an essential class of compounds for new drug development. As a result, these compounds have been produced as intentional structures, and numerous scientific communities have assessed their biological activities. This review will investigate the quinoline heterocyclic ring and the antimalarial and anticancer biological effects of quinoline derivatives.

Keywords: Quinoline; Heterocyclic; Biological Activity; Antimalarial; Anticancer; Pharmacology

بررسی جامع حلقه هتروسیکلیک کینولین و فعالیت های بیولوژیکی ضد مالاریا و ضد سرطان آن

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چکیده
کینولین یک داربست ترجیحی است که به عنوان یک موتیف مونتاژ مهم برای ایجاد مولکول‌های دارویی جدید در میان ترکیبات هتروسیکلیک ظاهر می‌شود. با توجه به طیف گسترده ای از خواص بیولوژیکی و دارویی کینولین و مشتقات آن، مسیرهای مصنوعی متعددی برای سنتز آنها ایجاد شده است. کینولین و مشتقات آن که با فعالیت های بیولوژیکی متنوع آزمایش شده اند، یک کلاس مهم از ترکیبات برای توسعه داروی جدید را تشکیل می دهند، در نتیجه این ترکیبات به عنوان ساختارهای عمدی تولید شده‌اند و فعالیت‌های بیولوژیکی آن‌ها توسط جوامع علمی متعددی ارزیابی شده است. دراین بررسی حلقه هتروسیکلیک کینولین، همچنین اثرات بیولوژیکی ضد مالاریا و ضد سرطانی مشتقات کینولین پرداخته شده است.

اصطلاحات کلیدی: کینولین؛ هتروسیکلیک؛ فعالیت بیولوژیکی؛ ضد مالاریا؛ ضد سرطان؛ فارماکولوژی