



REVIEW

Quinoline: A versatile heterocyclic

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KEYWORDS

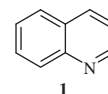
Quinoline;
Synthesis;
Biological activity

Abstract Quinoline or 1-aza-naphthalene is a weak tertiary base. Quinoline ring has been found to possess antimalarial, anti-bacterial, antifungal, anthelmintic, cardiotoxic, anticonvulsant, anti-inflammatory, and analgesic activity. Quinoline not only has a wide range of biological and pharmacological activities but there are several established protocols for the synthesis of this ring. The article aims at highlighting these very diversities of the ring.

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1. Introduction

Quinoline [1] or 1-aza-naphthalene or benzo[*b*]pyridine is nitrogen containing heterocyclic aromatic compound. It has a molecular formula of C_9H_7N and its molecular weight is 129.16. The $\log P$ value is 2.04 and has an acidic pK_b of 4.85 and a basic pK_a of 9.5. Quinoline is a weak tertiary base. It can form salt with acids and displays reactions similar to those of pyridine and benzene. It shows both electrophilic and nucleophilic substitution reactions. It is nontoxic to humans on oral absorption and inhalation.



Quinoline nucleus occurs in several natural compounds (Cinchona Alkaloids) and pharmacologically active substances displaying a broad range of biological activity. Quinoline has been found to possess antimalarial, anti-bacterial, antifungal, anthelmintic, cardiotoxic, anticonvulsant, anti-inflammatory, and analgesic activity. A few promising compounds [2–6] with quinoline ring system are given in Fig. 1.

2. Synthesis

A number of established protocols are there for the synthesis of quinoline ring, which can be well modified to prepare a number of differently substituted quinoline.

2-Phenylquinoline-4-carboxylic acid [7] has been synthesized by treatment of 2-oxopropionic acid with aniline and benzaldehyde in the presence of rare earth metal catalysts and refluxing in water (Wang et al., 2009a).

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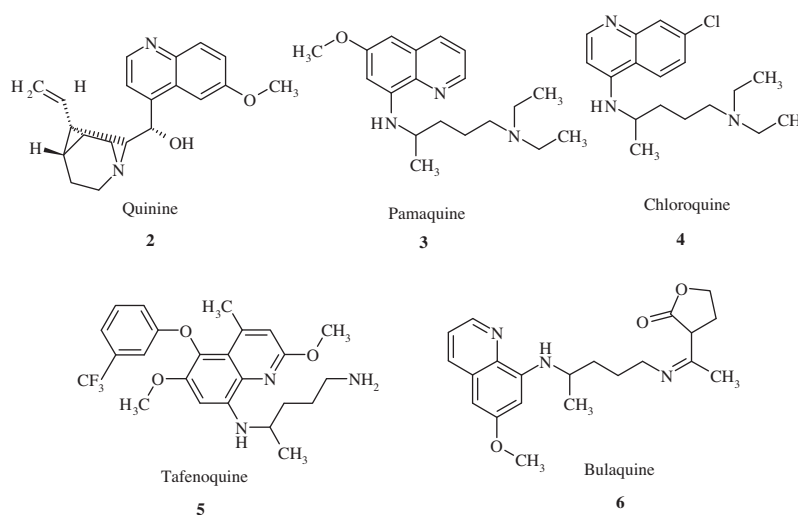
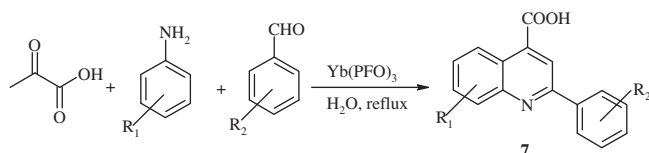
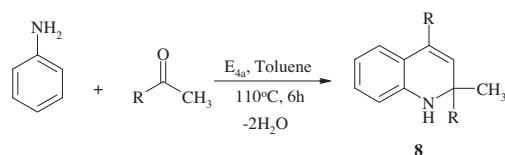


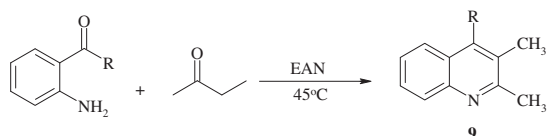
Figure 1 Few promising compounds with quinoline ring system.



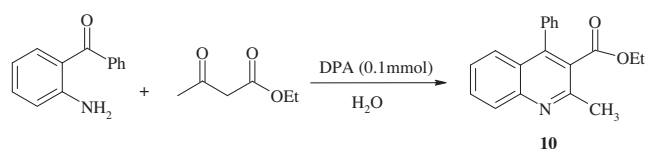
2,4-Diphenyl-2-methyl-1,2-dihydroquinoline (**8**) has been synthesized by using aniline and acetophenone in the presence of a small pore size E_{4a} zeolite catalyst (Hegedus et al., 2007).



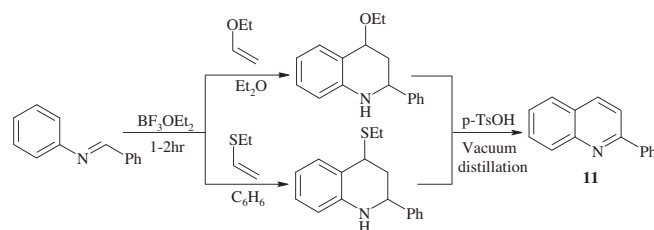
By stirring 2-amino substituted aromatic ketones and carbonyl compounds having a reactive α -methylene group in ethyl ammonium nitrate (EAN) 2,3,4-trisubstituted quinolines (**9**) have been developed (Zhou et al., 2008).



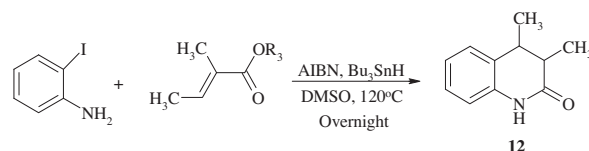
Using 2-aminosubstituted ketone and ketone as reactants poly-substituted quinolines (**10**) have been synthesized in aqueous media and solvent-free conditions in the presence of dodecylphosphonic acid (DPA) as catalyst (Ghassamipour and Sardarian, 2009).



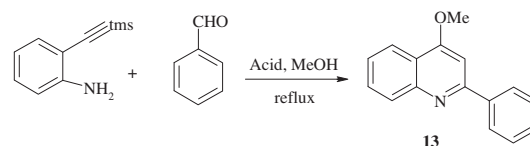
Kouznetsov (2009) synthesized phenyl substituted quinolines [**11**] by subjecting a mixture of ethyl vinyl ether or ethyl vinyl sulfide and *N*-aryaldimine to acidic catalysis in the presence of boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$) to yield 2,4-substituted tetrahydroquinolines, which were then converted to 2-phenyl substituted quinolines under vacuum distillation with tosylic acid (*p*-TsOH).



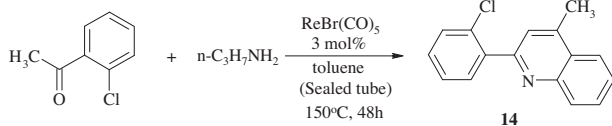
3,4-Dihydroquinolin-2-one [**12**] has been developed by treating 2-iodoanilines and ethyl acrylate with Azobisisobutyronitrile (AIBN) in presence of tributyltin hydride ($n\text{-Bu}_3\text{SnH}$) (Zhou et al., 2009).



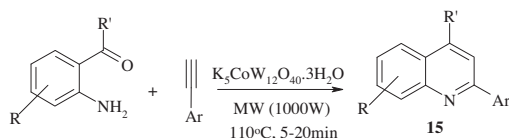
2-Phenyl-4-alkoxy quinoline [**13**] has been synthesized by condensation and cyclization of 2-(2-trimethylsilyl)ethynyl aniline with arylaldehydes. The reaction is promoted by sulfuric acid in the presence of methanol as solvent (Wang et al., 2009b).



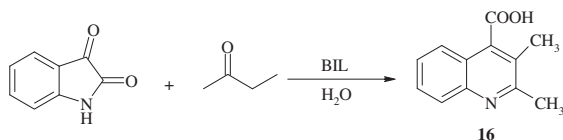
Certain halogen-substituted quinolines [14] have been synthesized by the condensation and cyclization of two molecules of *o*-haloacetophenones with urea or primary amines (Qi et al., 2009).



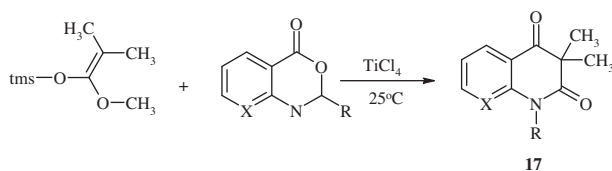
Iraj et al. (2010) synthesized 2,4-disubstituted quinolines [15] through a one-pot reaction of structurally diverse 2-aminoaryl ketones with various arylacetylenes in the presence of potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40} \cdot 3H_2O$) as a reusable and environmentally benign catalyst under microwave irradiation and solvent-free conditions.



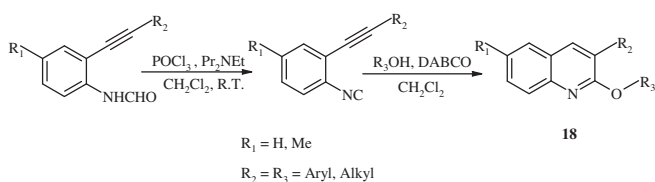
Ultrasound promoted synthesis of quinolines [16] using basic ionic liquids (BIL) in aqueous media has been reported by Kowari and Mallakmohammadi (2011). The advantage of such procedure being that it is simple in operation and high yields are obtained. The reaction involves treating isatin with aromatic methyl ketones at ultrasonic frequencies of 20–50 kHz.



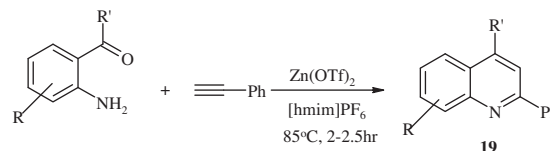
One-step methodology has been introduced for the synthesis of quinoline alkaloid analogues [17] (Zografos et al., 1999). The reaction is based on a modification of the *Mukaiyama aldol condensation*, making use of the high reactivity of lactones or anhydrides.



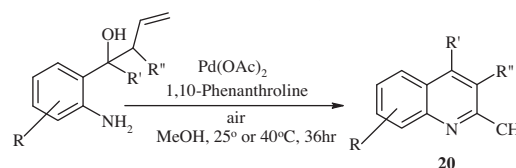
Diversified 2-alkoxy- and 2-aroxy-3-substituted quinolines [18] have been synthesized from *o*-alkynylaryl isocyanides and alcohols and phenols promoted by 1,4-diazabicyclo[2.2.2]octane (DABCO) (Zhao et al., 2010).



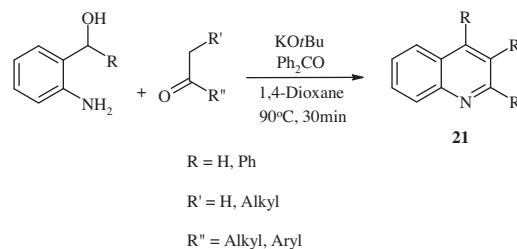
2,4-Disubstituted quinolines [19] have been synthesized according to *Meyer-Schuster rearrangement* (Sarma and Prajapati, 2008). In this method 2-aminoaryl ketones and phenylacetylenes rearrange in the presence of a catalytic amount of zinc trifluoromethanesulfonate in the ionic liquid 1-hexyl-3-methylimidazolium hexafluorophosphate [hmim][PF₆] resulting in 2,4-disubstituted quinolines. The same product has also been obtained in the presence of indium(III)trifluoromethanesulfonate ($In(CF_3SO_3)_3$) under microwave irradiation without any solvent (Lekhhok et al., 2008).



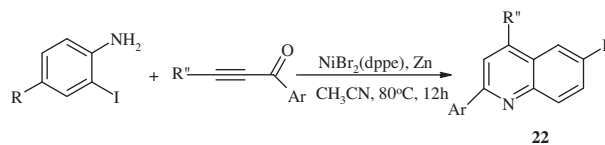
Palladium-catalysed Wacker-type oxidative cyclization has been proposed for the synthesis of 2-methylquinolines [20] with good yields under mild conditions (Wang et al., 2011).



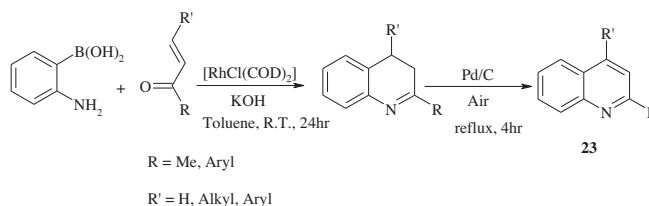
Poly-substituted quinolines [21] have been developed by the reaction of 2-aminobenzyl alcohol derivatives with ketones or alcohols in the presence of base and benzophenone as hydride scavenger (Martinez et al., 2008).



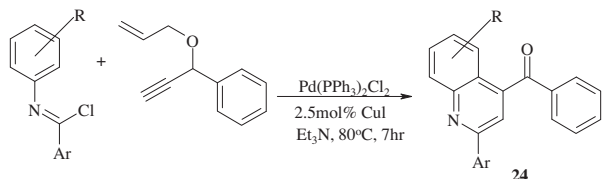
2,4-Disubstituted quinolines [22] have been synthesized by cyclization of 2-iodoanilines with alkynyl aryl ketones in the presence of nickel catalyst (Chen et al., 2006).



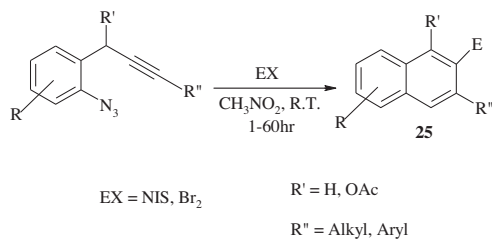
Horn et al. (2008) reported synthesis of quinolines [23] from α,β -unsaturated ketones and *o*-aminophenylboronic acid derivatives which is a modification of the traditional Skraup-Doebner-von Miller synthesis. The method has an advantage that it can proceed under basic conditions rather than strongly acidic conditions.



The reaction of benzimidoyl chlorides with 1-(1-(allyloxy)prop-2-ynyl)benzene (1,6-enynes) forms quinoline derivatives [24] via palladium-catalysed Sonogashira coupling and subsequent cyclization (Gao et al., 2010).



Intramolecular cyclization of 1-azido-2-(2-propynyl)benzene in the presence of electrophilic reagents in nitromethane (CH₃NO₂) at room temperature or in the presence of catalytic amounts of AuCl₃/AgNTf₂ in THF at 100 °C gives corresponding quinolines [25] in good yields (Huo et al., 2010).

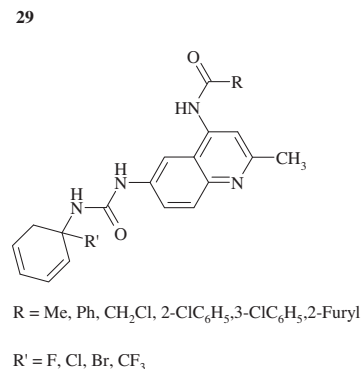
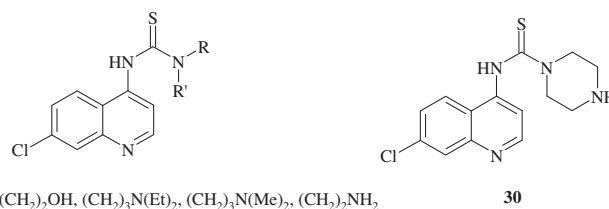
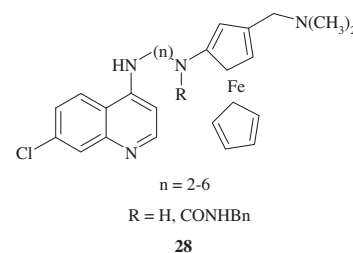
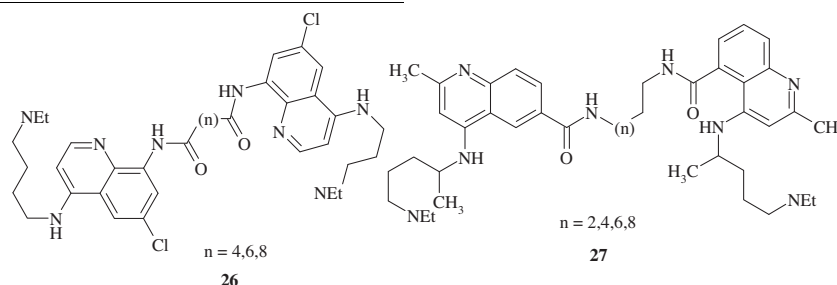


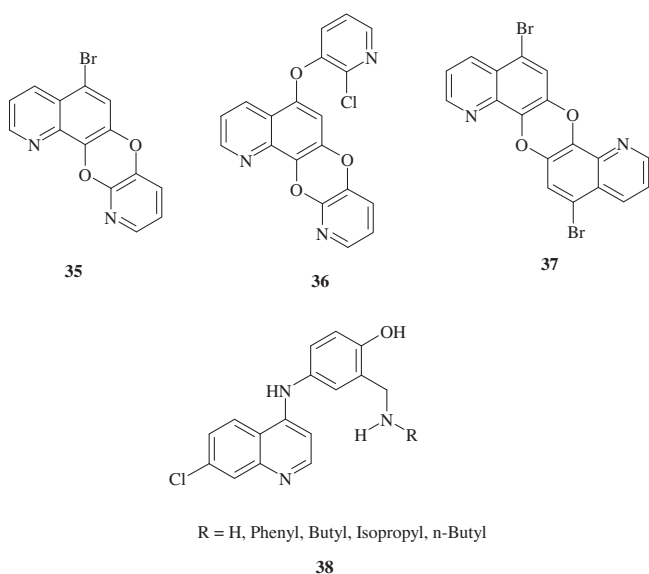
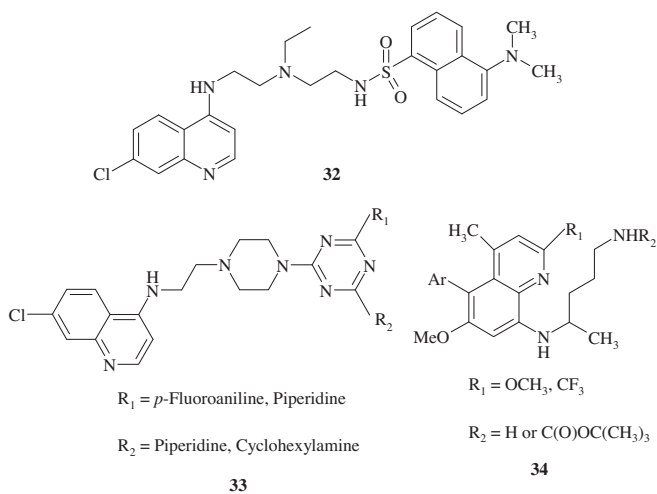
3. Biological activity

3.1. Antimalarial

Most important use of the quinoline ring is its antimalarial potential. Bisquinolines [26, 27] developed by Raynes et al. (1996) are found to possess a good degree of antimalarial activity against both chloroquine-resistant and chloroquine-sensitive parasites. Analogues of ferrochloroquine [28] were also found to have antimalarial activity by Chibale et al. (2000). In these analogues carbon chain of chloroquine is replaced by hydrophobic ferrocenyl group. Certain 7-chloroquinolinyl thioureas [29, 30] synthesized by Mahajan et al. (2007) are potential antimalarial agents. Modapa et al. (2009) synthesized few ureido-4-quinolinamides [31] which showed antimalarial effect at MIC of 0.25 mg/mL against chloroquine-sensitive *Plasmodium falciparum* strain. Chloroquinolyl derivative [32] developed by Kovi et al. (2009) also

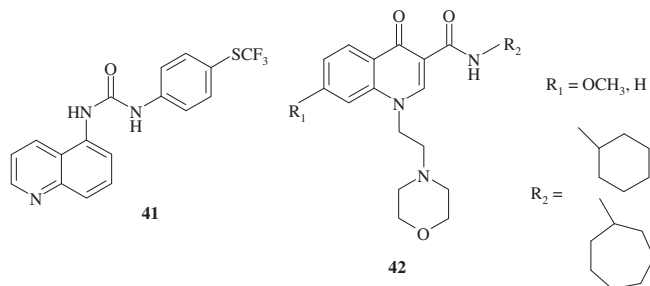
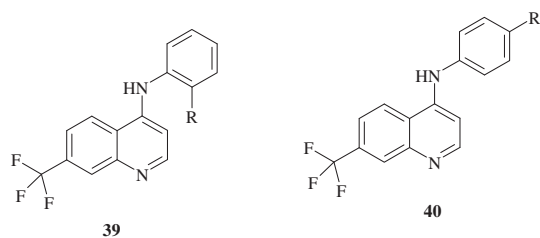
has a potent antimalarial activity at submicromolar levels. Certain 4-aminoquinoline triazines [33] synthesized by Kumar et al. (2008) also have antimalarial activity screened against chloroquine (CQ) sensitive strain 3D7 of *P. falciparum* in an *in vitro* model. Shiraki et al. (2011) developed certain 5-aryl-8-aminoquinolines [34] with promising antimalarial activity which had lesser haemolytic activity compared to tafenoquine. Acharya et al. (2008) synthesized and evaluated the antimalarial activity of some pyridine-quinoline hybrids [35–37] against chloroquine susceptible strain of *P. falciparum*. Singh et al. (2011) developed antimalarial agents with 4-aminquinoline ring [38]. The compounds showed good activity against chloroquine-sensitive *P. falciparum* strains as well as against rodent malaria parasite *P. yoelii*.





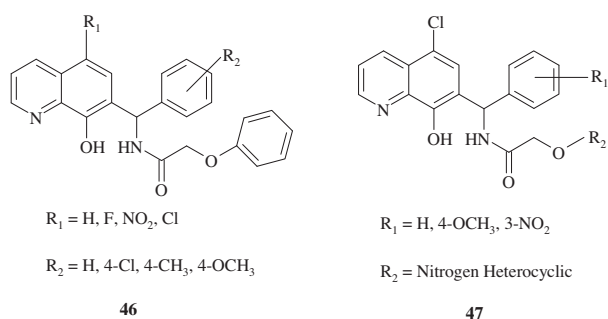
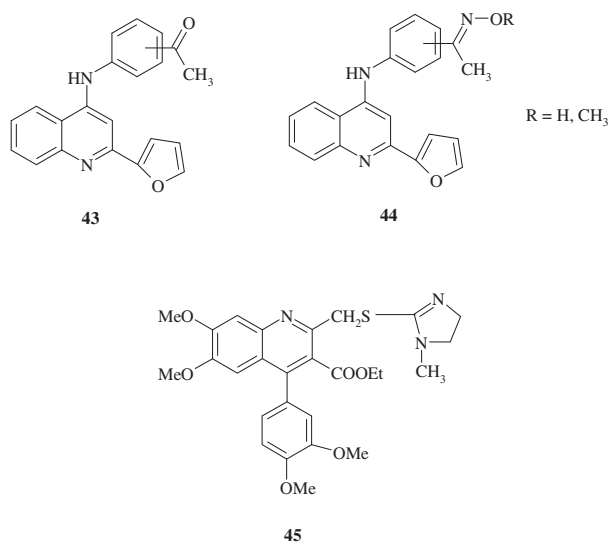
3.2. Analgesic activity

4-Substituted-7-trifluoromethylquinolines [39, 40] synthesized by Abadi et al. (2005) have been found to have a good analgesic activity. The activity is attributed to their nitric oxide releasing properties. Gomtsyan et al. (2005) developed a quinoline [41] based analgesic agent whose activity was attributed to its antagonism at Vanilloid receptors. A few quinoline derivatives [42] developed by Manera et al. (2007) by acting as selective agonists at Cannabinoid CB₂ receptors show their analgesic activity.



3.3. Anti-inflammatory activity

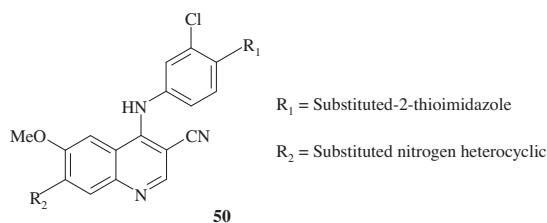
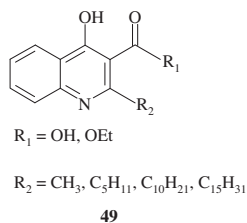
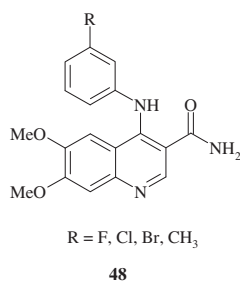
2-(Furan-2-yl)-4-phenoxy-quinoline [43, 44] derivatives developed by Chen et al. (2006) are found to be inhibitors of lysozyme and β -glucuronidase release. Baba et al. (1996) developed a quinoline derivative [45] with potent anti-inflammatory effect in adjuvant arthritis rat model. Certain quinoline derivatives [46, 47] have been developed for treating osteoarthritis by Gilbert et al. (2008). These are amino-acetamide inhibitors of Aggrecanase-2.



3.4. Antineoplastic

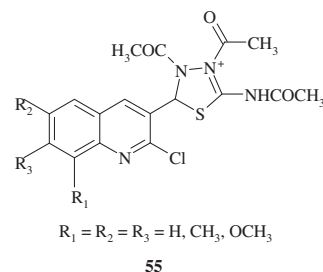
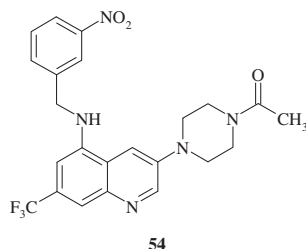
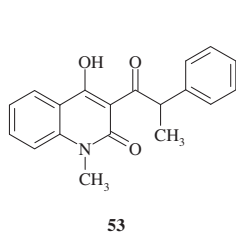
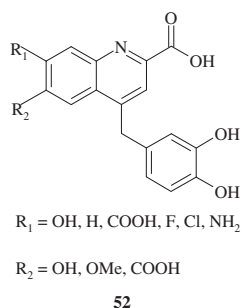
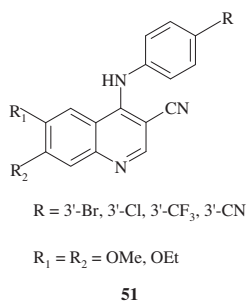
Some of the amido-anilinoquinolines [48] developed by Scott et al. (2009) act as anti-tumour agents by inhibiting CSF-1R kinase. Novel 4-hydroxyquinolines [49] synthesized by Mai et al. (2009) are histone acetyltransferase (HAT) inhibitors. Miller et al. (2009) developed a few 3-cyanoquinolines [50] as

inhibitors of insulin like growth factor receptors (IGF-1R) for the treatment of cancer.



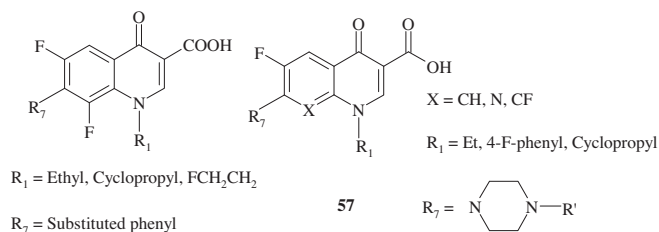
A few 4-anilinoquinolines [51] developed by Assefa et al. (2003) have been found to be tyrosine kinase inhibitors. Potent quinoline carboxylic acids [52] have been developed by Chen et al. (2009) which act by inhibiting insulin like growth factors. Linomide [53] has been found to have action against androgen responsive cancer and rat prostatic cancer by Vukanovic et al. (1993). c-Met kinase inhibitory quinolines [54] with IC₅₀ less than 1 nM have been developed by Wang et al. (2011). It produces the inhibition of c-Met phosphorylation in c-Met dependent cell lines.

Marganakop et al. (2012) developed certain 6,7,8-substituted thiosemicarbazones of 2-chloro-3-formyl-quinoline derivatives [55] which had anticancer activities. The compounds had a better drug score and *clog P* values.



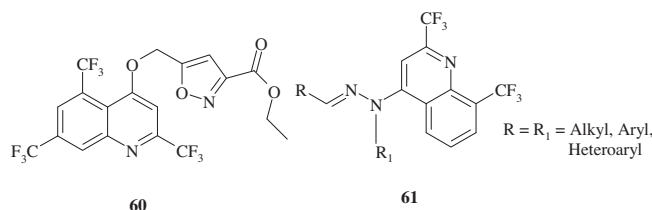
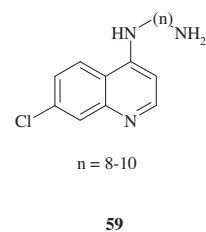
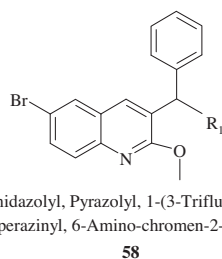
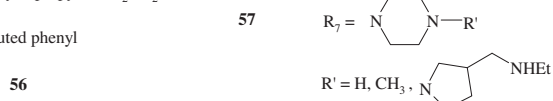
3.5. Antibacterial

Ma et al. (2009) synthesized phenoxy, phenylthio and benzyl-oxy substituted quinolones [56] with a fair amount of anti-bacterial activity. Sanchez et al. (1988) developed certain 8-substituted quinoline carboxylic acids [57] with anti-bacterial activity. Upadhayaya et al. (2009) developed quinoline derivatives [58] through molecular modelling techniques which were found to be active against *Mycobacterium tuberculosis* H37Rv strain. These were derivatives of 3-benzyl-6-bromo-2-methoxy quinolines. De Souza et al. (2009) developed 7-chloro quinoline derivatives [59] effective against multi-drug resistant tuberculosis. Lilienkampf et al. (2009) developed quinoline based compound bearing an isoxazole containing side chain [60] active against *Mycobacterium tuberculosis*. Some novel anti-tubercular quinolines [61] have been developed by Eswaran et al. (2010) using mefloquine as the lead, wherein active pharmacophores viz. hydrazones, ureas, thioureas and pyrazoles have been attached at the 4th position.



R₁ = Ethyl, Cyclopropyl, FCH₂CH₂

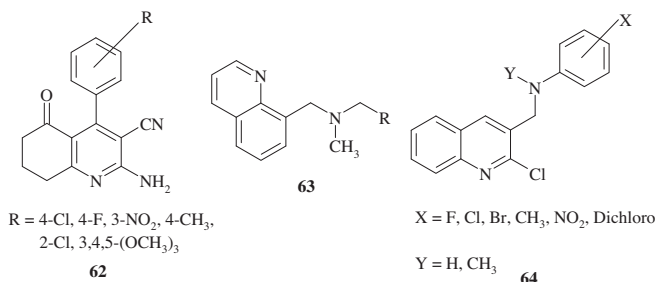
R₇ = Substituted phenyl



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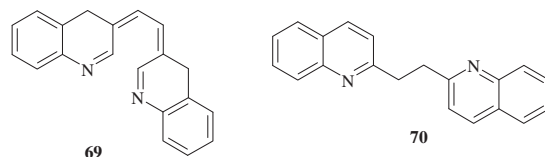
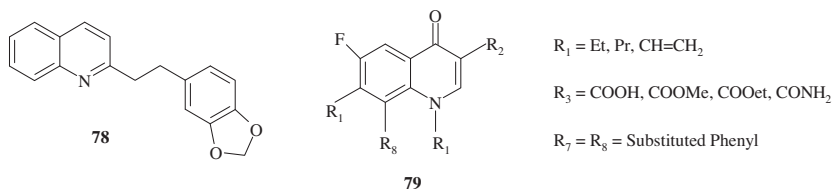
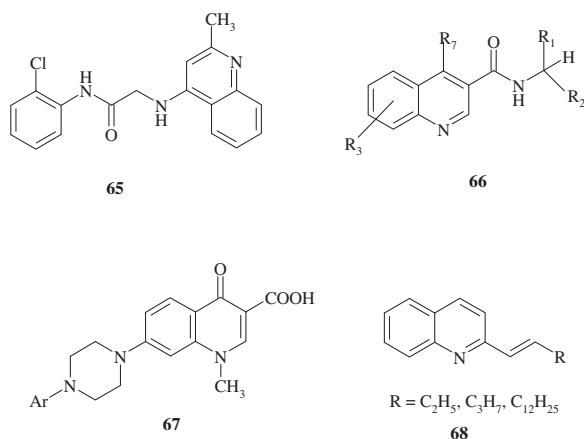
3.6. Antifungal

Gholap et al. (2007) developed certain tetrahydroquinolines [62] which are found to have a good degree of activity against fungi *Candida albicans*, *Fusarium oxysporum* and *Mucor* sp. Kharkar et al. (2009) developed a series of quinoline derivatives [63] using terbinafine as lead as antifungal agents. The developed compounds contained different bulky aromatic rings in the side chain. The compounds were designed using LeapFrog drug design program. Kumar et al. (2011) developed certain secondary amines [64] containing 2-chloroquinoline and evaluated them for their antimycotic activity against *Aspergillus niger*, *A. flavus*, *Monascus purpureus* and *Penicillium citrinum*. These are non-azole antimycotic agents.



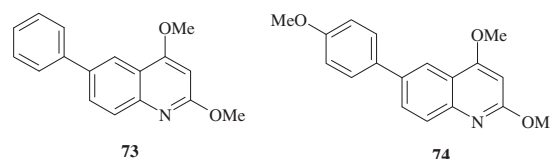
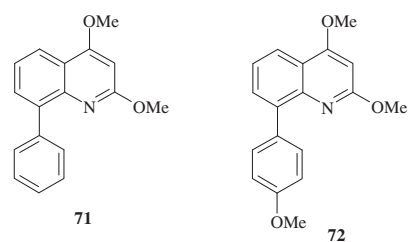
3.7. Antiviral

Anilidoquinoline [65] derivatives synthesized by Ghosh et al. (2008) are found to have a good degree of *in vitro* activity against Japanese encephalitis virus. Certain quinoline derivatives [66] synthesized by Chen et al. (2009) act by behaving as HIV-1 Tat-TAR interaction inhibitors. Massari et al. (2009) developed certain desfluoroquinolones [67] for the treatment of HIV infection. Certain mono and polysubstituted quinolines [68–70] synthesized by Fakhfakh et al. (2003) have activity against HIV-1.



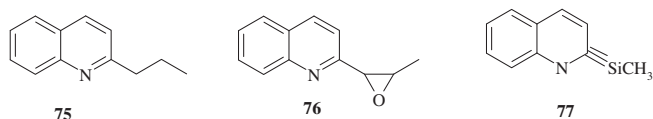
3.8. Anthelmintic

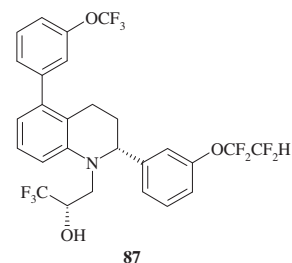
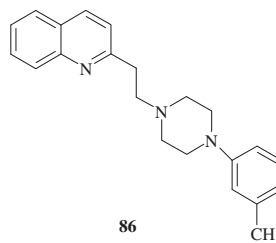
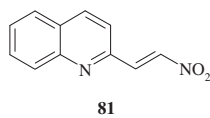
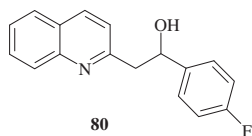
Rossiter et al. (2005) synthesized substituted 2,4-arylquinolines [71–74] which have a good degree of activity against the nematode *Haemonchus contortus*. These arylquinolines maintain their activity against levamisole, ivermectin and thiabendazole resistant strains of *H. contortus*.



3.9. Anti-protozoal

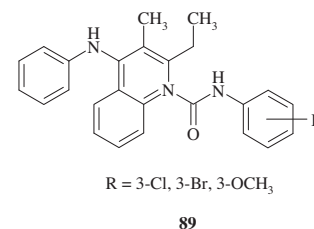
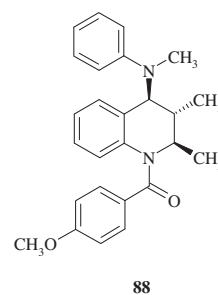
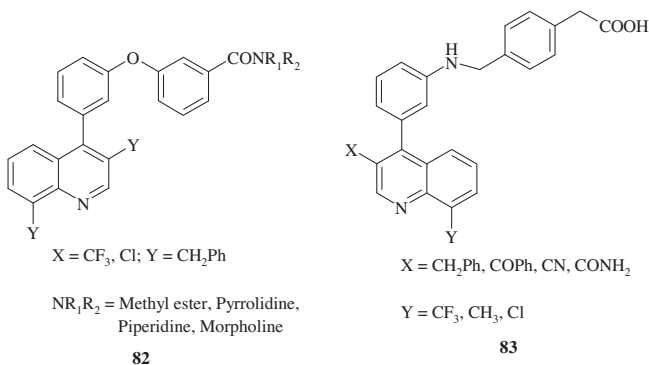
Fournet et al. (1993) found that 2-substituted quinoline alkaloids isolated from *G. longiflora* plant used for the treatment of new world cutaneous leishmaniasis have *in vitro* antileishmanial activity against the extracellular forms of *Leishmania* spp. These include 2-substituted 3-carbon chain quinoline alkaloids and 2-substituted aryl quinoline alkaloids [75, 76]. Alkenyl and alkynyl quinolines [77, 78] developed by Fakhfakh et al. (2003) show activity against the causal agents of cutaneous leishmaniasis, visceral leishmaniasis, African trypanosomiasis and Chagas' disease. Ma et al. (2009) developed certain quinolones [79] which had activity against *Trypanosoma cruzi*. Franck et al. (2004) developed quinoline derivatives [80, 81] which showed activity against *T. cruzi*.





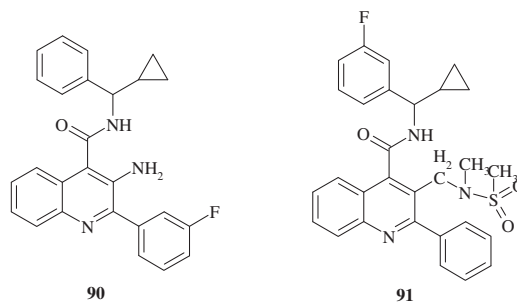
3.10. Cardiovascular activity

Certain biarylether amide quinolines [82] developed by Bernotas et al. (2009) act as liver X receptor agonists and are useful in conditions of dyslipidaemia. These agents also reverse the conditions of arteriosclerosis. A few phenyl acetic acid based quinolines [83] developed by Hu et al. (2007) also act as agonists at liver X receptors. These agents have good binding affinity for LXR β and LXR α receptors. 4-Thiophenyl quinolines [84] developed by Cai et al. (2007) are HMG-CoA reductase inhibitors and have utility as hypocholesterolaemic agents. Quinoline-4-carboxylic acids [85] synthesized by Lloyd et al. (1994) are angiotensin II receptor antagonists and hence act as hypotensive agents. Hypotensive activity of centhaquin [86] has been demonstrated by Srimal et al. (1990) and it has been shown to reduce the blood pressure in cat in a dose dependent manner. Tetrahydroquinolines [87] which inhibit cholesteryl ester transfer protein have been developed by Rano et al. (2009). Tetrahydroquinolinamines [88, 89] developed by Ramos et al. (2008) have been found to be inhibitors of platelet aggregation.



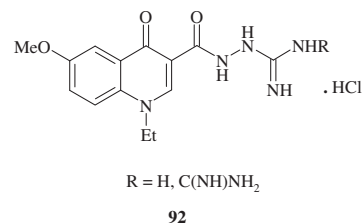
3.11. CNS effects

Quinoline based NK3 receptor antagonists [90, 91] with CNS activity have been developed by Smith et al. (2009).



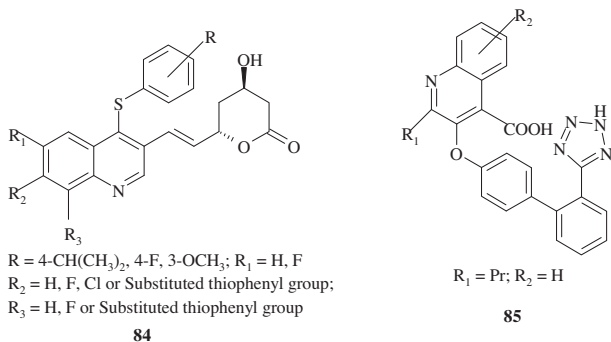
3.12. Hypoglycaemic activity

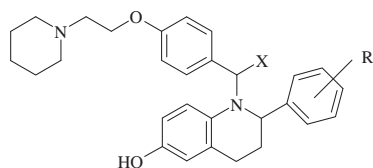
Quinoline carboxyguanides [92] prepared by Edmont et al. (2000) are hypoglycaemic agents.



3.13. Reproductive System

Certain tetrahydroquinolines [93] developed by Wallace et al. (2003) are selective oestrogen receptor modulators.

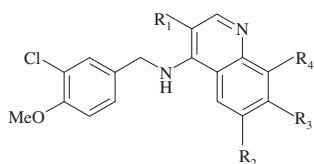




R = H, 3-OH, 4-OH; X = CH₂, O

93

Bi et al. (2004) developed certain quinolines [94] which act as potent PDE₅ inhibitors thus having utility in the treatment of erectile dysfunction.



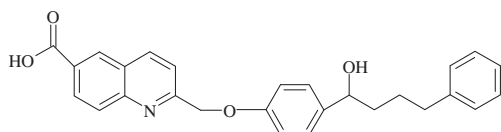
R₁ = COOEt; R₂ = H, CN; R₃ = H, CF₃; R₄ = H, Et

94

3.14. Miscellaneous

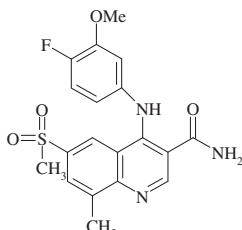
Quinolines have been found to possess a number of other activities as well.

Evans et al. (1991) developed certain quinoline based leukotriene synthesis inhibitors [95].

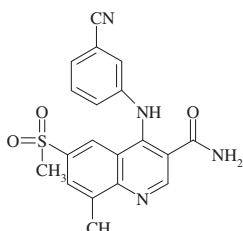


95

Selective PDE₄ inhibitor quinolines [96, 97] have been developed by Lunniss et al. (2009) with utility in chronic obstructive pulmonary disorder.

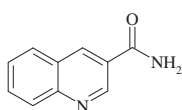


96



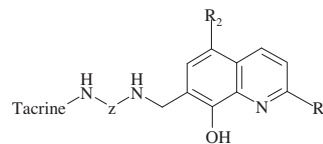
97

Quinoline 3-carboxamide [98] is used for the treatment of chronic relapsing autoimmune encephalitis. This activity was studied by Karussis et al. (1993).



98

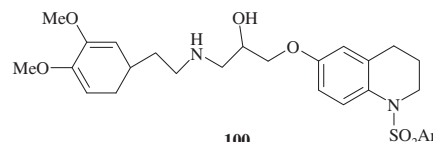
Bachiller et al. (2010a,b) have developed some novel tacrine-8-hydroxyquinoline hybrids [99] with activity against Alzheimer's. Tacrine has cholinesterase inhibition action while 8-hydroxyquinoline derivatives have metal-chelating, neuro-protective and anti-oxidant properties.



99

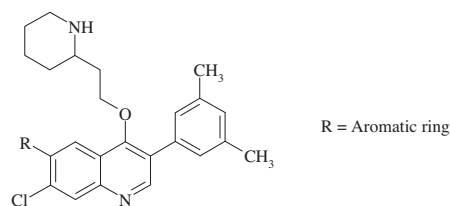
Z = Alkyl chain;
Str-I: R₁ = R₂ = H
Str-II: R₁ = CH₃; R₂ = H
Str-III: R₁ = H; R₂ = Cl

Tetrahydroquinolin-6-yloxy propanes [100] have been developed by Shakya et al. (2009) which are β-3 agonists.



100

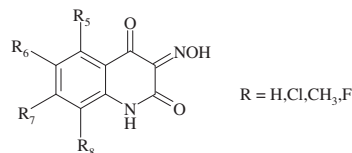
Certain aminoalkoxyquinolines [101] as somatostatin receptor subtype-2 agonists have been reported by Wolkenberg et al. (2011) which have utility in proliferative diabetic retinopathy and exudative age related macular degeneration.



101

R = Aromatic ring

The 1,2,3,4-tetrahydroquinoline-2,2,4-trione oximes developed by Cai et al. (1996) [102] act as antagonists of NDMA in glycine receptors. These compounds can be used as agents against neurodegenerative diseases (e.g., Alzheimer's disease).



102

R = H, Cl, CH₃, F

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