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An Extensive Review on Biological Interest of Quinoline and Its Analogues

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ABSTRACT

The medicinal potential of quinoline, a flexible bicyclic heterocyclic scaffold, is significant. Some compounds with quinoline nuclei are preferred therapeutic agents for various diseases. Several quinoline derivatives demonstrate a wide range of antibacterial, anti-inflammatory, anticancer, anthelmintic, antidiabetic, antifungal and antiprotozoal activities, many of which are being studied in clinical studies to treat potentially fatal diseases and disorders. Clinically effective drugs widely used to treat various human diseases/disorders include several compounds with quinoline skeletons. In the development of more recent drugs, medicinal chemists' attention was drawn to the clinical efficacy of some of these compounds and the adaptability of the quinoline nucleus. This pharmacophore is becoming more and more important, as seen by the disproportionately large number of patents filed in a short amount of time. The multi-target approach or hybridization is considered a promising strategy in drug design and discovery; hybridization may improve affinity and potency while simultaneously decreasing the resistance and side effects. The main part of this review focuses on and highlights the functionalization of quinoline for biological and pharmaceutical activities.

Keywords: [Quinoline, Antibacterial activity, Antimalarial activity, Antifungal activity]

INTRODUCTION

A large number of drugs have a heterocyclic ring structure, which can be of natural origin or synthetic. There are numerous types of heterocyclic systems, which can be monocyclic or have fusion or bridging with carbocyclic or similar or distinct heterocyclic systems; there may be varying degrees of unsaturation or complete saturation. A large number of well-known drugs contain a heterocyclic system with specific substitution and functionalization.[1] Quinoline is a heterocyclic aromatic compound that refers to parent compound C9H7N bearing N-atom at position one and it is also known as benzo(b)pyridine. Quinoline and relative compounds represent a significant category of nitrogen-containing heterocycles as they are functional intermediates in organic Synthesis. In the last few years, much attention has been drawn on their Synthesis as they own beneficial biological activities like antimalarial,[2] anti-inflammatory,[3] antiviral,[4] fungicidal,[5] anticancer[6] and antibacterial activity.[7]

Biological activities possessed by quinoline-hybrids

Antibacterial activity:

The antibacterial capabilities of annulated novel quinoline analogues fused with triazole, pyrazole, pyrimidine, imidazole and pyrrole systems (1) were tested in-vitro against B. cereus.[7] The Baylis- Hillman reaction was used to synthesize some novel multi-substituted quinolines (2), which were then tested against various bacterial strains, including B. sphaericus, B. subtilis, S. aureus, C. violaceum and P.aeruginosa.[8] Multi substituted novel quinolone carboxamides fused with imidazole were synthesized and tested for antibacterial activity, the majority of the compounds had modest activity.[9] Newly synthesized quinoline derivatives (3) were proven to have potency against the M. tuberculosis H37Rv strain.[10] Recently synthesized analogues of 7-chloro quinolines (4) were proven effective in multidrug-resistant tuberculosis.[11] The Synthesis of new multisubstituted quinoline-based compounds(5), including an isoxazole unit as well as a side chain that have been found to be active towards M. tuberculosis.[12] Substituted quinoline carboxy hydrazides were prepared and evaluated for antibacterial activity against E.coli and B.subtilis as well as antifungal activity against C. albicans and A. niger and antitubercular activity against M. Tuberculosis were investigated.[13] Some novel substituted hydroxyquinoline (6) were synthesized and evaluated for antimicrobial efficacy.[14] Recently synthesized thieno quinoline, pyrrolo quinoline and N-methylpyrrolo quinoline systems (7) were evaluated for biological activity towards a wide range of pathogenic bacterial and fungal strains.14 Novel 3-chloro-6-substituted quinoline carboxamides were designed and assessed for antimicrobial activity.[15] Substituted quinoline carboxamides were prepared and evaluated for antimicrobial activity.[16] Novel compounds comprising chloroquinoline methanone moieties with antibacterial and cytotoxic properties were synthesized.[17] Newly synthesized sequences of quinoline compounds with pyrazole components have been synthesized for the development of novel antibacterial drugs. The expected antifungal and antibacterial activities of the synthesized derivatives were investigated, and maximum of these compounds demonstrated significant antibacterial and antifungal activity towards the investigated strains of several bacteria and fungi.[18] Fig.I- Structures of quinoline derivatives (1-7) showing antibacterial activity.

Antifungal activity:

Sequences of antifungal quinoline compounds were prepared with terbinafine as the lead compound and side chain present in the compounds include various bulky aromatic rings (8).[19] The antimycotic activity of secondary amines, including 2-chloroquinolines (9) was examined against A. flavus, A. niger, P. citrinum and M. purpureus and proven to have potent action.[20] Novel quinoline derivatives (10) were prepared and investigated for microbiological activity towards E.coli and C. albicans using the filter paper disc method. The results demonstrated that azetidine-containing quinoline derivatives completely dominated both types of organisms in limiting growth.[21] Sequence of quinoline derivatives were synthesized and

examined for antifungal activity; many of the components have been demonstrated to be more efficient when compared to standard drugs.[22] Variety of new quinoline derivatives incorporating a perfluoropropanyl moiety (11) were synthesized. Bioassay findings revealed that many were effective at controlling P. oryae and the substituted position in the molecule influenced the fungicidal action. At various concentrations, it was observed that several compounds had the most significant effect against P. oryae; it is superior to the control Tebufloquin.[23] New classes of quinoline-based perflouropropane derivatives (12) were synthesized, and the assay findings demonstrated that newer compounds have significant fungicidal activity towards E. graminis. Several compounds had moderate action with EC50 values as low as 1.48 mg/l, which was more effective than the marketed fungicide tebufloquin.[24,25] Fig.II-Structures of quinoline derivatives (8-12) exhibiting antifungal activity.

Figure: I-Structures of quinoline derivatives (1-7) showing antibacterial activity.

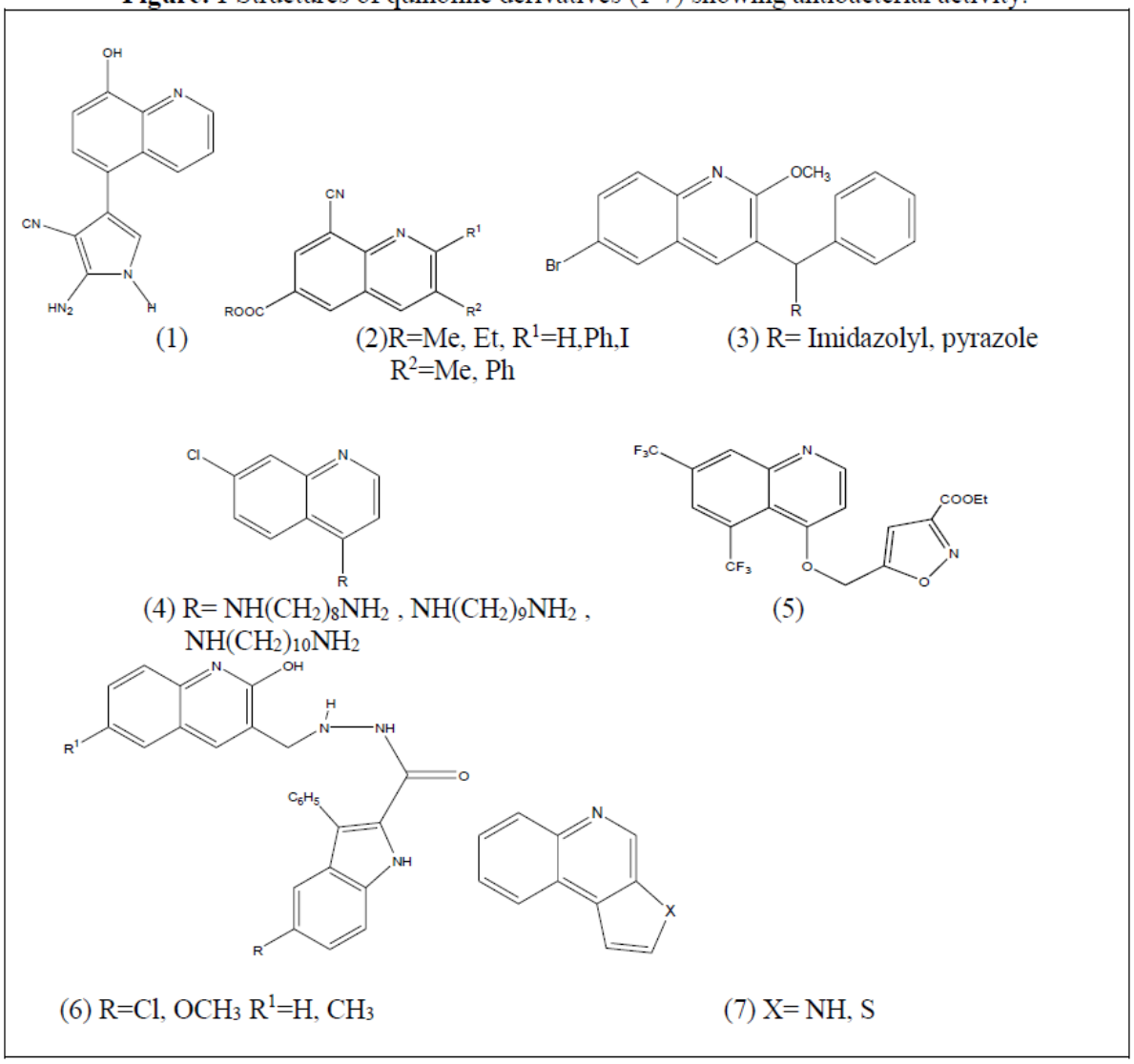
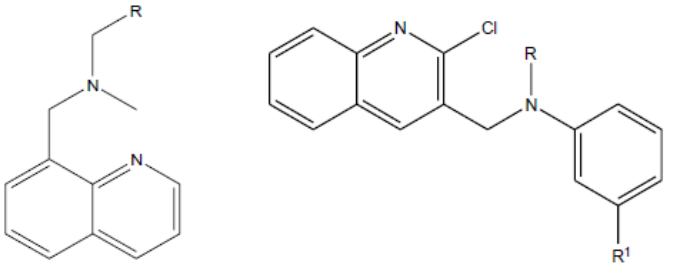
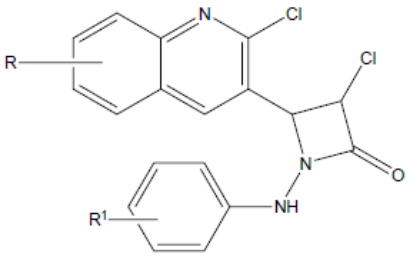


Fig.II- Structures of quinoline derivatives (8-12) exhibiting antifungal activity

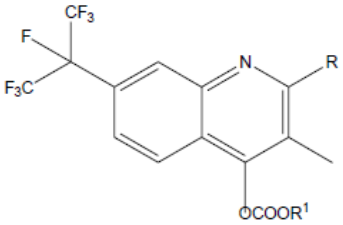


(8) R= quinoline, substituted benzimidazole, naphthalene

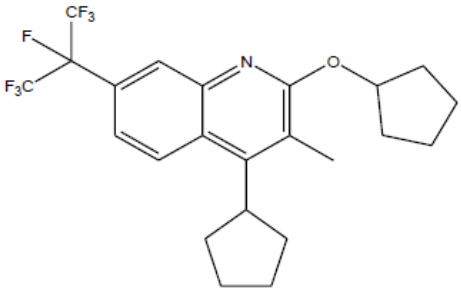
(9) R= H, CH_3, R^1= F, Cl



(10) R=6-Cl, 6-OCH_3, R^1= 4-NO_2, 2,4-di NO_2



(11)R=H, R^1= CH_3, $CH_2CH_2CH_3$



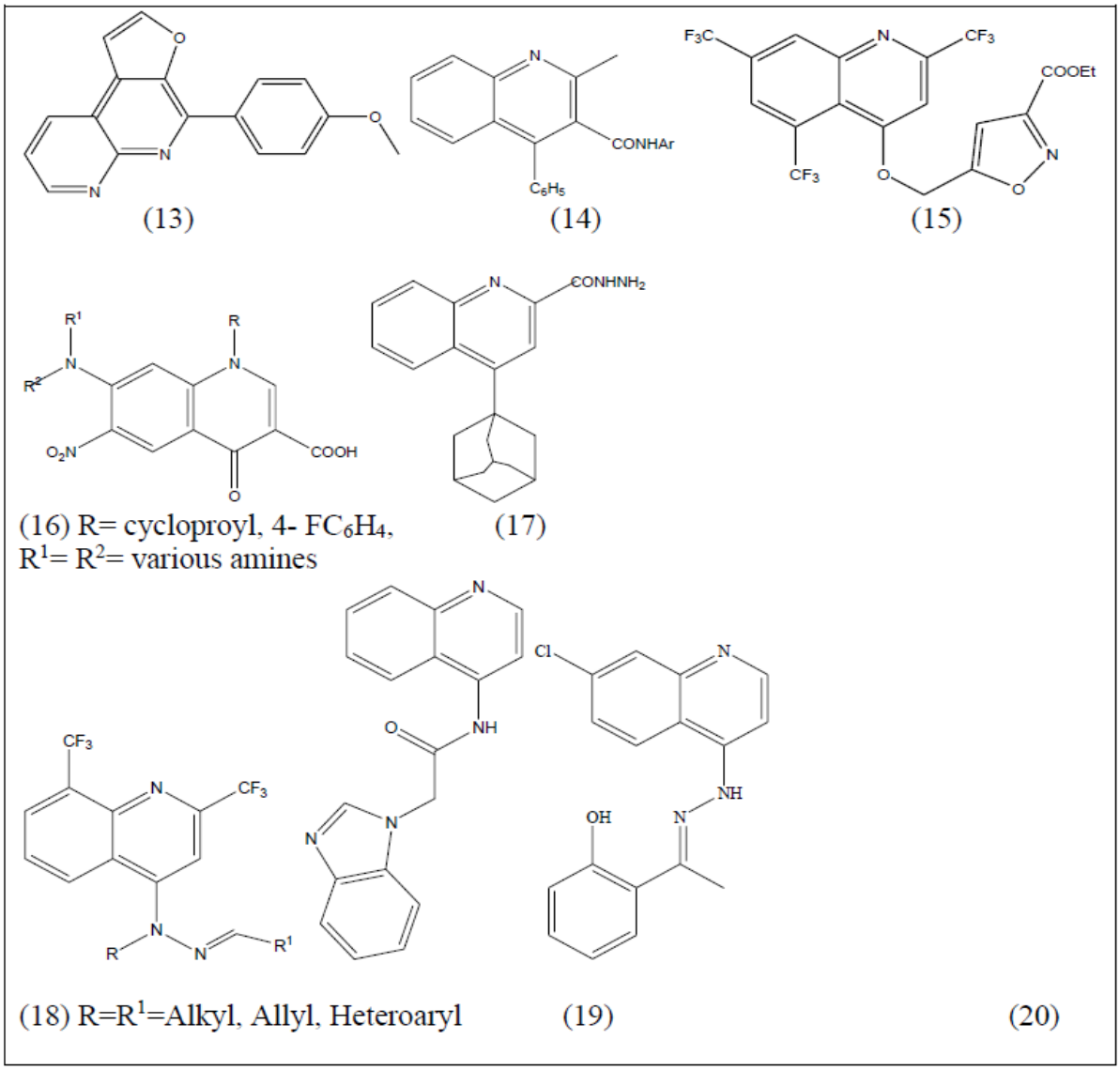
(12)

Antimycobacterial activity:

A novel synthetic procedure for the Synthesis of fused thieno/ furo-quinoline compounds (13) and antimycobacterial potency of the compounds were reported and assessed, displaying the maximum activity and the pre-eminent MIC value achieved was 5.6 µmol, which when compared to ethambutol (First line anti-tubercular drug) was found to be superior (7.6 µmol).[26] Two quinoline-related compounds (14) sequences were designed, synthesized and analyzed for antitubercular activity against H37Rv (mycobacterial strain).[27] Quinoline- related molecules (15) with side chain and isoxazole unit were produced and assessed for antimycobacterial activity.[28] Carboxylic acid derivatives of quinoline were produced and evaluated for antimycobacterial activity against multi-drug-resistant for strain (MDR-TB), M. tuberculosis for strain H37Rv (MTB) and M. smegmatis for strain (MC2) as well as mycobacterial supercoiling was inhibited of DNA gyrase.[29] Novel nitroquinolone derivatives were designed, and the molecule was found to have potent activity in vitro towards MDR-TB and MTB. Furthermore, quinolines containing carboxylic acid derivatives (16) were synthesized and

assessed in vitro for M. tuberculosis against several strains H37Rv (MTB), MDR-TB and M. smegmatis (MC2).[30] Two novel analogues of quinolines substituted with adamantine were produced, and 3D-QSAR analysis was used to understand the link between synthesized compound and anti-tubercular activity and the most effective analogue 17 in the series inhibited 99 per cent of drug-sensitive strains at 1.00 µg/ml.[31] Some novel antitubercular quinolines (18) were developed with reference drug mefloquine and active moieties such as hydrazones, thioureas, ureas and pyrazoles linked at position 4.[32] Production of novel quinoline substituted with pyridine/ imidazole (19) and assessed in vitro for antimycobacterial and anticancer activity.[33] Fe(II), Co(II), Cu(II), UO2(VI) and Mn(II) complexes containing a novel hydroxy acetophenone quinoline possessing hydrazine moieties (20) were designed, synthesized and evaluated for biological activity.[34] Fig. III - Structures of quinoline derivatives (13-20) having antimycobacterial activity.

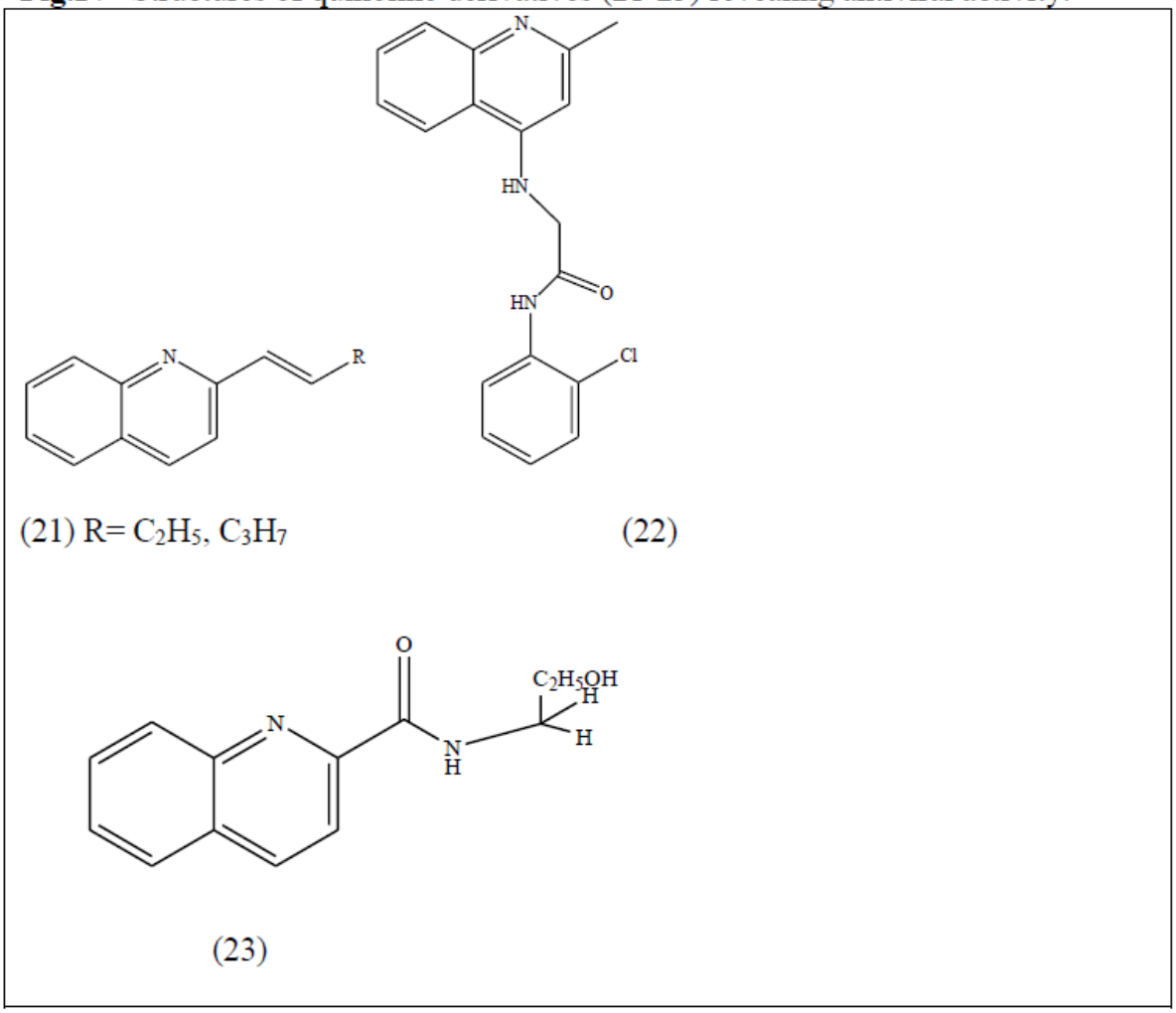
Fig.III- Structures of quinoline derivatives (13-20) possessing antimycobacterial activity



Antiviral activity:

Some mono and polysubstituted quinolines (21) were developed and reported to have anti-HIV-1 activity.[35] Anilido quinoline compounds (22) demonstrated good antiviral efficacy towards the Japanese strain of encephalitis virus.[36] A promising class of drugs synthesized by focusing on the N-1 and C-6 locations for treating HIV infections.[37] Novel quinoline compound 23 was designed and synthesized, which works as an inhibitor against HIV-1 Tat-Tar interaction.[38] Novel N-tricyclic compounds were synthesized that yields triazole[4,5-g] quinolines produced by condensation of quinolines and examined the assays for antiviral activity against Flaviviridae genera, namely YFV (Flavivirus), BVDV (Pestivirus) and HCV (Hepacivirus).[39] Fig.IV - Structures of quinoline derivatives (21-23) revealing antiviral activity.

Fig.IV- Structures of quinoline derivatives (21-23) revealing antiviral activity.

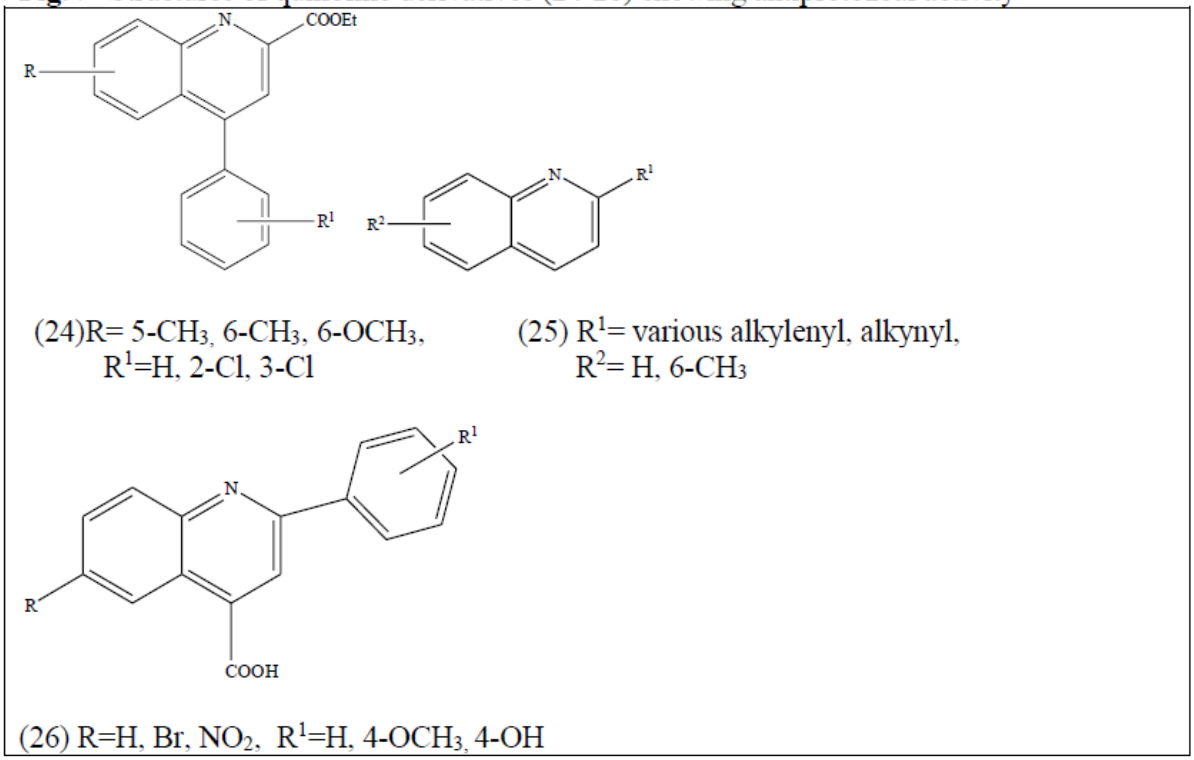


Antiprotozoal activity:

A single-step synthesis of arylquinoline constituting carboxylates (24) was reported and assessed for antiprotozoal action against T. gondii.[40] Nakayama et al. discovered that alkenyl and alkynyl quinolones (25) had antiprotozoal activity towards African trypanosomiasis, Cutaneous leishmaniasis, Visceral leishmaniasis and Chagas disease.[41] Using the Ugi- azide reaction to, new compounds with a tetrazole ring and 7-chloroquinoline were prepared, and their

antiplasmodial action was tested against multiresistant (K1) strain and Plasmodium falciparum sensitive strain (NF54).[42] Quinoline-4-carboxylic acids (26) were produced and tested the antileishmanial efficacy and evaluated for activity towards D. promastigote at various concentrations (1.56 µg/ml to 200 µg/ml) against sodium stibogluconate.[43] Fig.V- Structures of quinoline derivatives (24-26) showing antiprotozoal activity.

Fig.V- Structures of quinoline derivatives (24-26) showing antiprotozoal activity

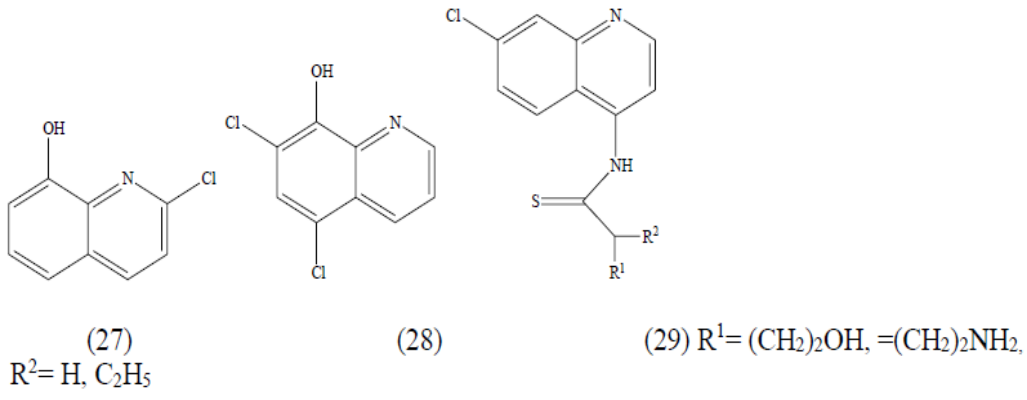


Antimalarial activity:

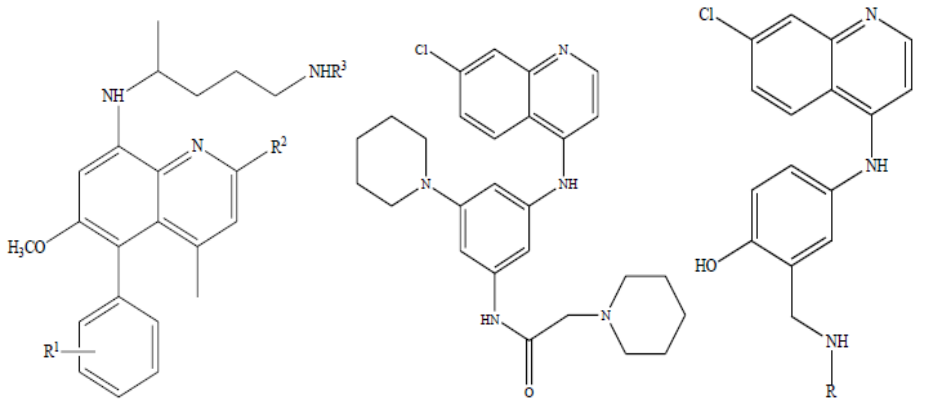
A series of Ferro-chloroquine amine and urea analogues with variable methylene spacer lengths were prepared and tested in vitro. Many of the analogues were found to have more powerful action than chloroquine. D10 Ureas were shown to have more active potency than amines, and potent action in various strains was well related to methylene spacer length and redox potentials.[44] Reactivity studies of two quinoline derivatives (27,28) were reported as potential lead compounds as antimalarials using Discrete Fourier Transform (DFT) and Molecular Dynamics (MD) simulations.[45] Various 7-chloroquinolinyl thioureas were synthesized (29).[46] New hybrid conjugates of 1, 3, 5- triazine with quinolines were produced, which on modifying the substitution pattern, the hybrid molecules showed significant antimalarial efficacy towards both mutant and wild parasites.[47] A variety of aminoquinoline derivatives (30) were synthesized and evaluated for antimalarial activity. The novel compounds were found to be as effective as or more effective than primaquine against P. falciparum cell proliferation.[48] Novel 4-anilinoquinoline compounds were synthesized, demonstrating potent antimalarial action against P. falciparum strains (chloroquine-

sensitive).[49] A new family of anilinoquinolines (31) were discovered, and the properties of side chains were shown to be strongly reliant on antimalarial efficacy and cytotoxicity activity.[50] Several quinolinamides were prepared that showed antimalarial activity against P. falciparum.[51,52] Novel antimalarials with a 4-anilinoquinoline ring (32) were synthesized, and the activity of new compounds was evaluated in Swiss mice, and BM-1 were demonstrated to have substantial suppressive action.[53] Fig.VI- Structures of quinoline derivatives (27-32) possessing antimalarial activity.

Fig.VI- Structures of quinoline derivatives (27-32) possessing antimalarial activity



(27) (28) (29) R^1= $(CH_2)_2OH$, $=(CH_2)_2NH_2$, R^2= H, C_2H_5



(31) (32) R= H, Ph

(30) R^1=H, 3-CF_3, R^2= OCH_3,CF_3, R^3=H, $COOC(CH3)_3$

Anticancer activity:

New chloro/ phenoxyquinoline compounds were prepared, and the newly formed molecular entities were assessed in vitro for cytotoxic efficacy against various cancer cell lines.[54] A series of new quinoline derivatives were synthesized by using the MTT method. The targeted new compounds were screened against 4 human cancer cores in vitro, namely U2OS, HCT 116, A549 and MCF 7.[55]. A sequence of new benzo-[h] quinolines were designed and synthesized with ethylcarboxamide side chain present at 4th position of quinoline, in the same way as in several DNA-intercalating agents.[56] Newly prepared quinoline compounds were

evaluated for the anticancer action towards various cancer cell lines of the human body namely, DU145 (human prostate cancer cell lines), MCF-7 and A549. On MCF-7 cells, some of the drugs had considerable cytotoxic activity, and the most effective anti-proliferative drugs were also evaluated against Hsp90, Her2 client protein.[57] Substantial series of tetracyclic quinoxalines were designed, synthesized and evaluated, which shows topoisomerase II inhibitory activity.[58] Newly synthesized indolo quinoline derivatives consisting of amino acid, guanylamino acid or guanidine substituents were evaluated for antifungal and cytotoxic activities in vitro.[59] New sequence of alkynyl- quinoline derivatives were synthesized and physiologically tested for their PI3K inhibitory activity and anti-proliferative activity on HCT-116 and PC-3.[60] New chain of trimethoxy quinoline analogues were prepared and assessed for anti- cancer potency considering standard to methoxylated flavones against various cancer cell lines namely, MCF-7/MX, A-2780/RCIS, A-2780 and MCF-7.[61] Triazolo quinoline derivatives were synthesized and examined for multiple activities such as antifungal activity, antibacterial activity and anticancer activity.[62] Novel 8-Hydroxy quinoline compound (33) was designed, synthesized and evaluated for antiproliferative activity.[63] Variety of newly synthesized quinoline derivatives consisting of dihydrocinnoline carboxamides were evaluated against several distinct cancer cell lines.[64] Sequence of disubstituted quinoline derivatives comprising a 1,2,3- triazole- 4-carboxamide moiety were synthesized and assessed towards c-Met kinase and cancer cell lines (H460, A549, MKN-45, HT-29 and U87MG).[65] New 4H-pyrano[3, 2-h]quinolines (34) were prepared and evaluated for anticancer activities.[66] The biological activity of substituted nitro quinoline analogue (35) was examined against cancer cell lines.[67] Imidazolone moiety in a series of newly developed fluorophenoxy quinoline derivatives were synthesized and assessed for biological activities on c- Met kinase and some standard cancer cell lines (MKN-45, H460, A549 and HT-29).[68] Novel quinoline compound (36) was synthesized and tested for anti- prostate activity.[69] New quinoline-2-one derivative (37) was synthesized and evaluated for anticancer activity.[70] Novel quinoline derivatives were prepared and assessed for anti-proliferative activity.[71]Quinolines were synthesized and found to possess antiproliferative activity by inhibiting c- Met kinase with IC50 values less than 1 nM. It inhibits c-Met phosphorylation in cell lines that are c-Met dependent.[72] Anticancer activity in substituted thiosemicarbazones of 2-chloro-3-formyl-quinoline derivatives was discovered, and the compounds performed better in terms of drug score and c LogP values.[73] Amido- anilinoquinolines were prepared that serve as anticancer agents by inhibiting CSF-1R kinase.[74] 4-Hydroxyquinoline derivatives (38) were synthesized with Histone Acetyltransferase (HAT) inhibitory action.[75] Schiff bases, pyrazolo chromenquinoline, fused pyrazolo pyrimidoquinolines and pyrazolo thiazolidinquinoline, variously substituted thiazolo [3,2-a] pyridine and thiazoloquinoline derivatives were produced and studied chemical structures using spectral and elemental analysis as well as assessed for cytotoxic activities on tubulin polymerization inhibition, caspase-3

activation, several cancer cell lines and cell cycle analysis.[76] Fluoroquinolones were synthesized and evaluated for anticancer activity.[77] Fig.VII- Structures of quinoline derivatives (33-38) exhibiting anticancer activity.

Fig.VII- Structures of quinoline derivatives (33-38) exhibiting anticancer activity.

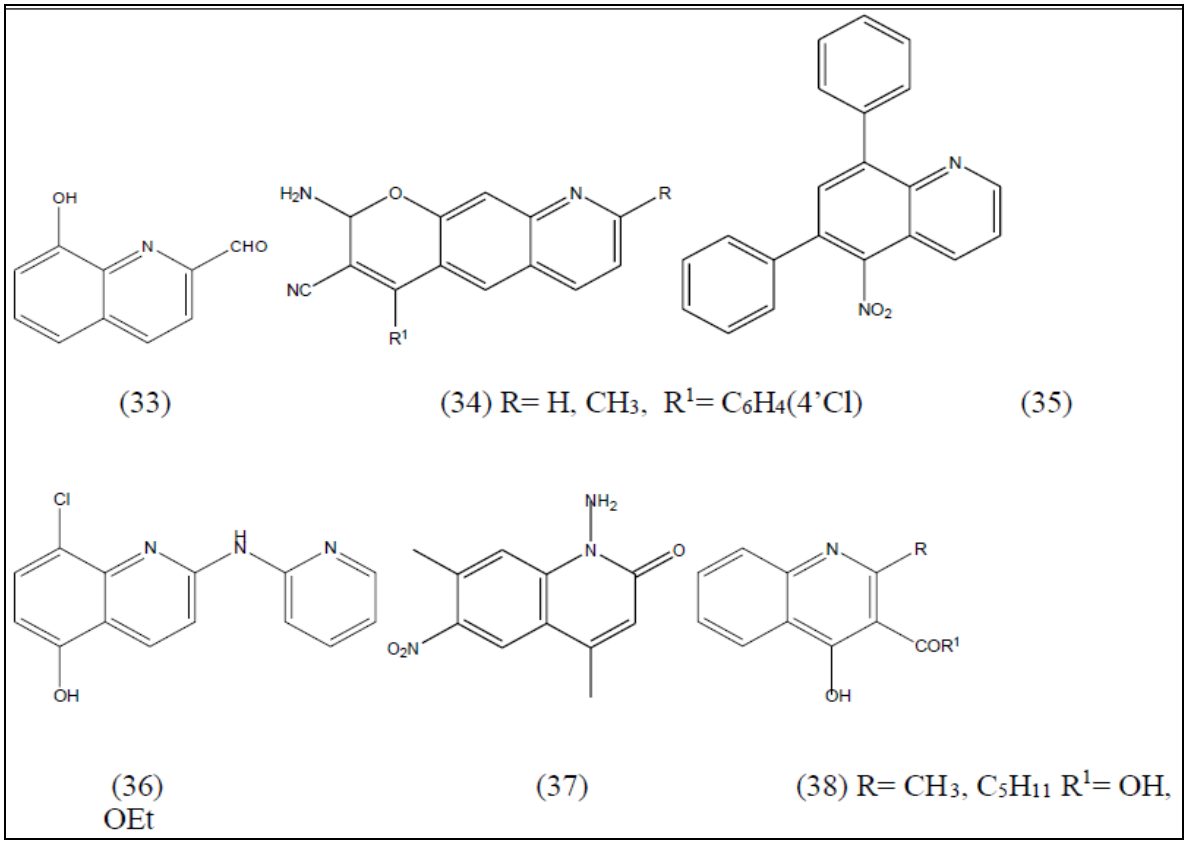
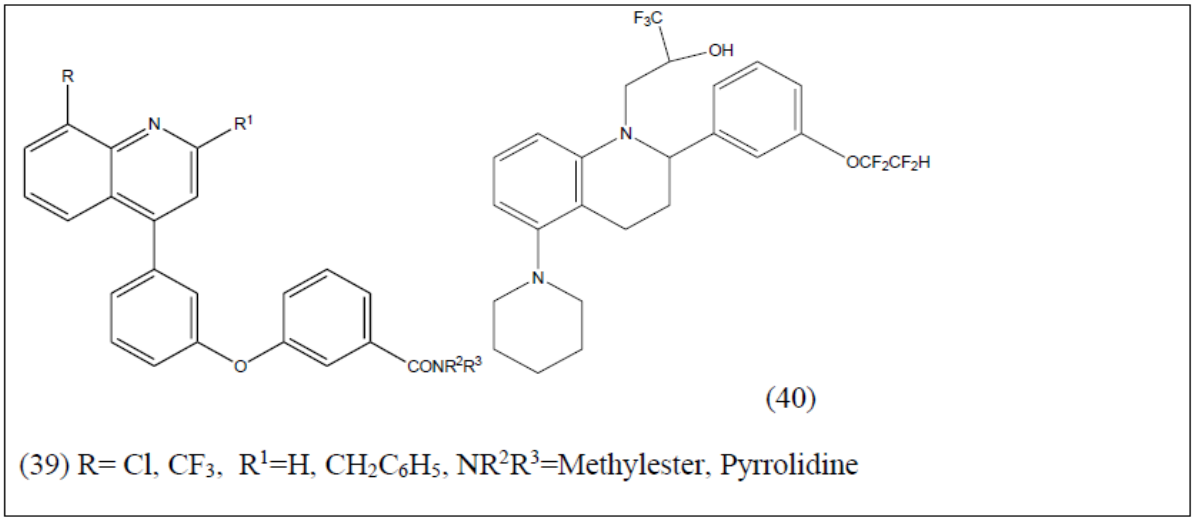


Fig.VIII- Structures of quinoline derivatives (39-40) revealing cardiovascular activity



Cardiovascular activity:

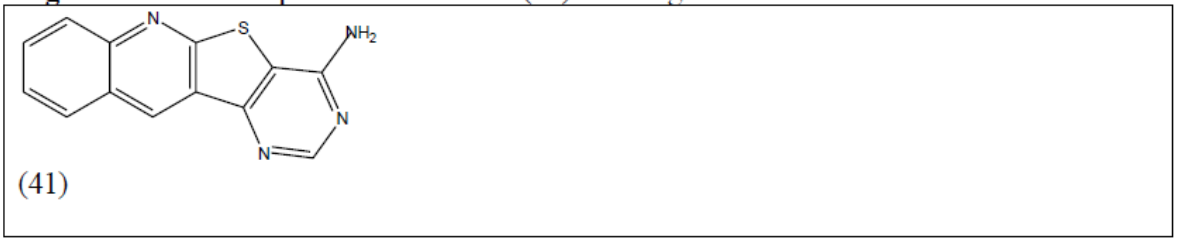
Several biarylether amide quinolines (39) were synthesized that were beneficial in the treatment of dyslipidemia that possesses an excellent binding property for LXRb and LXRa receptors.[78] Tetrahydroquinolines (40) were designed and prepared that block

the cholesteryl ester transfer protein.[79] Fig.VIII - Structures of quinoline derivatives (39-40) revealing cardiovascular activity.

CNS effects:

3-Aminoquinoline was discovered as an NK3 antagonist with good CNS penetration.[80] New procedures were found for producing pyrimidothienoquinoline compound (41) based on cyanohexahydro quinoline and assessed for CNS effects.[81] Fig.IX - Structure of quinoline derivative (41) showing CNS effects.

Fig.IX- Structure of quinoline derivative (41) showing CNS effects

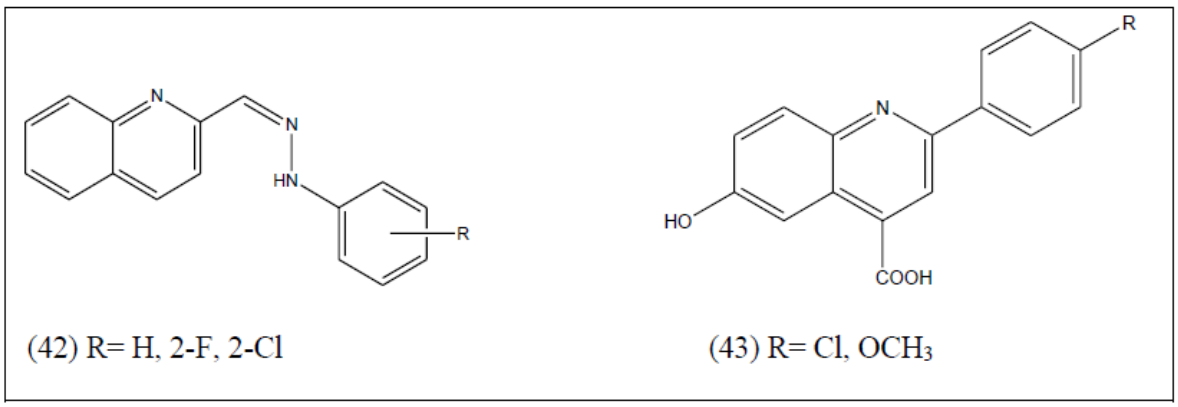


(41)

Antioxidant activity:

A series of quinoline carbaldehyde hydrazone derivatives (42) was discovered as the bioisosteric derivative of Melatonin, characterized and tested in vitro for antioxidant activity. MTT assay and Lactate dehydrogenase leakage assay was used to assess the cytotoxicity of all substances.[82,83] Bactericidal and antioxidant properties of quinoline derivatives of zingerone and tetrahydro curcumin were investigated.[84] Quinoline derivatives were synthesized by the interaction between aldehyde, and pyruvic acid yielded quinoline possessing carboxylic acid (43). In vitro and in silico antioxidant experiments were performed on newly synthesized molecules.[85] Fig.X- Structures of quinoline derivatives (42-43) possessing Antioxidant activity.

Fig.X- Structures of quinoline derivatives (42-43) possessing Antioxidant activity.



(42) R= H, 2-F, 2-Cl

(43) R= Cl, OCH_3

Anticonvulsant activity:

A triazolo quinoline derivative (44) was synthesized, which had neurotoxicities determined by the rotarod test and anticonvulsant activity as shown by the maximum electroshock test (MES).[86]Among several compounds synthesized, the most active anticonvulsant was found to be 45.

The neurotoxicity and anticonvulsant effect of the compounds were determined using the rota rod tests and maximal electroshock test in Kun Ming mice.[87] Fig.XI- Structures of quinoline derivatives (44-45) exhibiting Anticonvulsant activity.

Fig. XI- Structures of quinoline derivatives (44-45) exhibiting Anticonvulsant activity

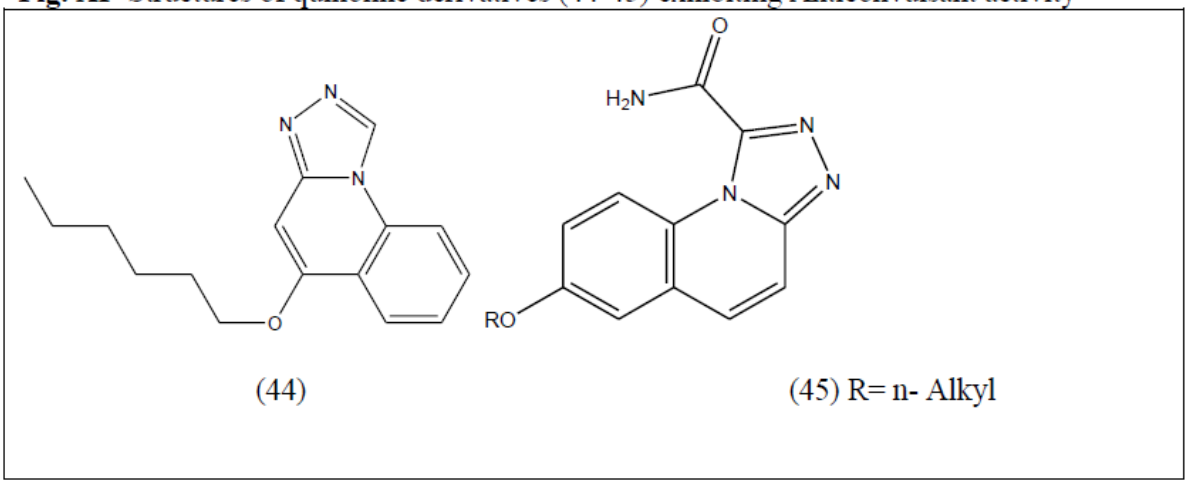
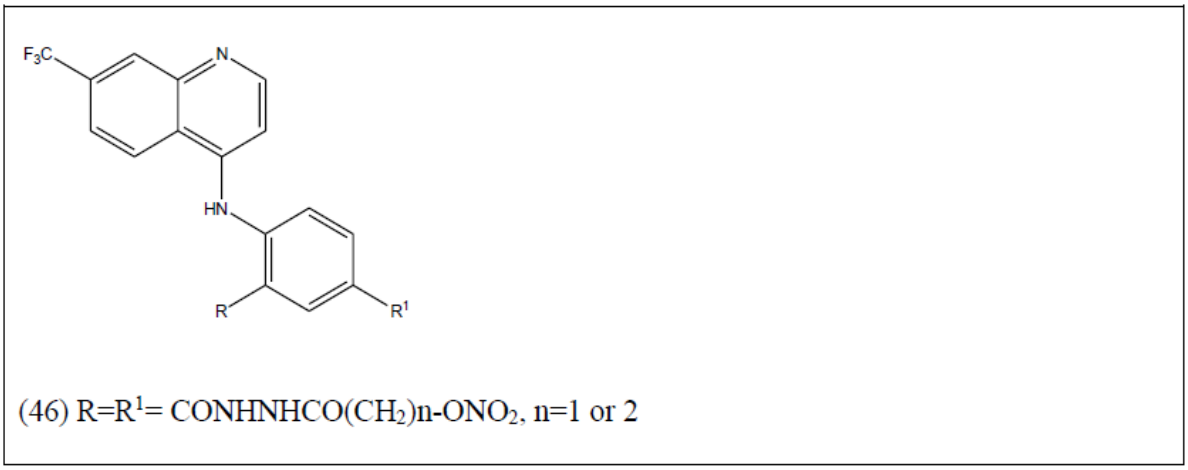


Fig.XII- Structure of quinoline derivative (46) showing Analgesic activity.



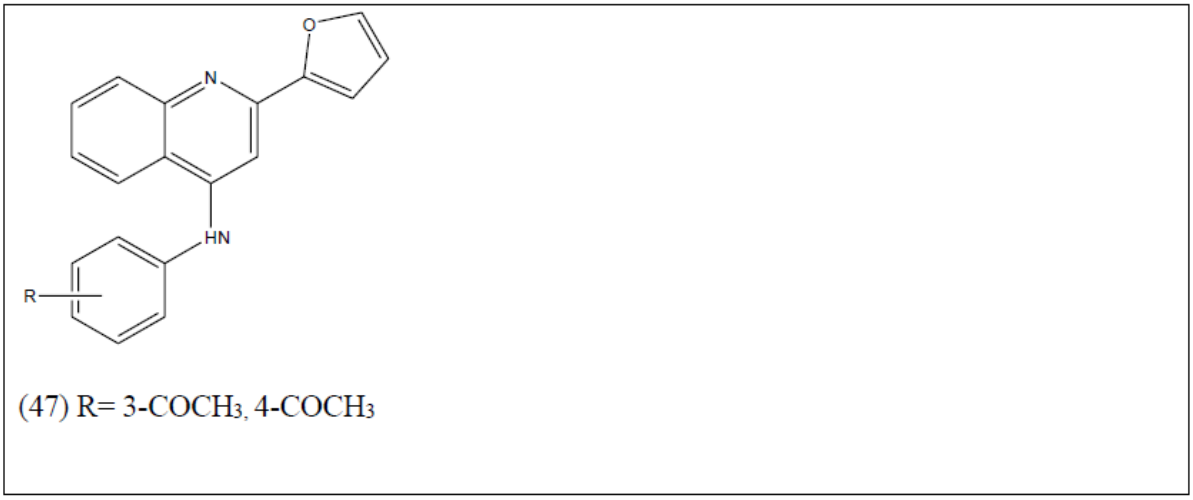
Analgesic activity:

Trifluoromethyl quinolines (46) were prepared and discovered to have decisive analgesic action and nitric oxide-releasing properties.[88] An effective analgesic derivative was produced, and its activity stems from its antagonistic effect on vanilloid receptors.[89] Quinoline compounds were created that have analgesic action and are specific agonists at CB2 Cannabinoid receptors.[90] Fig. XII- Structure of quinoline derivatives (46) showing Analgesic activity.

Anti-inflammatory activity:

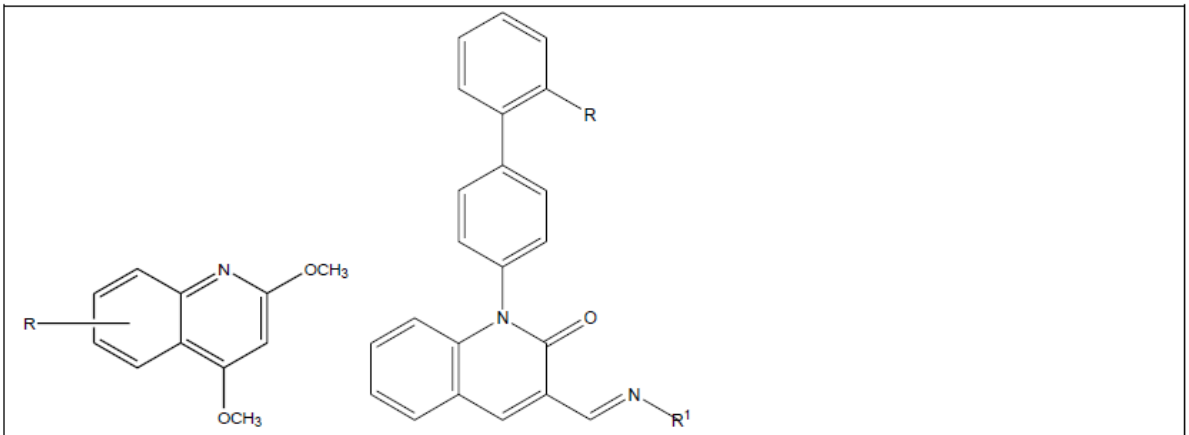
Several phenoxyquinoline compounds (47) were produced and tested for anti-inflammatory activity.[91] Novel quinoline derivatives were synthesized with a COX-2 methylsulfonyl pharmacophore as selective COX-2 inhibitors.[92] Fig.XIII- Structure of quinoline derivatives (47) possessing Anti-inflammatory activity.

Fig.XIII- Structure of quinoline derivative (47) possessing Anti-inflammatory activity.



(47) R= 3-$COCH_3$, 4-$COCH_3$

Fig.XIV- Structures of quinoline derivatives (48-49) exhibiting Anthelmintic activity.



(48) R= 6-C_6H_5, 6-C_6H_4(4'-OCH_3)

(49) R= COOH, tetrazole,
R^1= 1-triazole, 4-benzyl triazole

Anthelmintic activity:

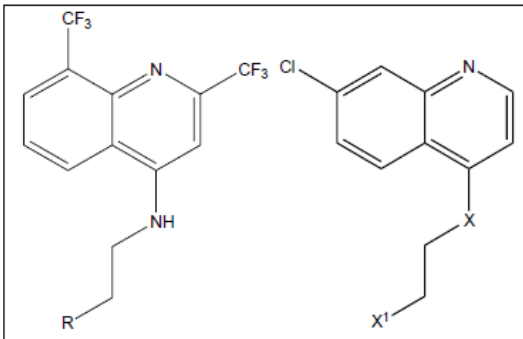
Substituted arylquinolines (48) were produced, which exhibit potent anthelmintic action than thiabendazole, ivermectin and levamisole.[93] New quinoline derivatives (49) were synthesized with a biphenyl ring and tested the compounds for antibacterial, anthelmintic and free radical scavenging activities against the DPPH radical.[94] Fig.XIV- Structures of quinoline derivatives (48-49) exhibiting Anthelmintic activity.

Miscellaneous activities:

To increase the potency of mefloquine, researchers used medicinal chemistry-driven techniques to synthesize and test a series of novel trifluoromethyl quinoline derivatives (50) in vitro.[95] Several quinoline compounds were produced and reported biological properties as well as evaluated as potential telomerase inhibitors.[96] Quinoline derivatives (51) were produced and investigated for leishmanicidal action.[97] The

efficacy of quinoline compounds for the control of Toxoplasmosis was examined.[98] Quinoline derivatives were produced and tested against Leishmania ama-zonensis promastigote and amastigote forms.[99] Click chemistry-inspired molecular hybridization techniques were used to produce a variety of phenylquinoline-3- carboxylate derivatives and tested against L. donovani.[100] A series of novel quinoline compounds were developed and studied their antiproliferative properties.[101] Fig.XV- Structures of quinoline derivatives (50-51) exhibiting miscellaneous activities.

Fig.XV- Structures of quinoline derivatives (50-51) exhibiting miscellaneous activities.



(50) R= OH, Cl

(51) X=S, NH ,
X^1= NH_2, OH

CONCLUSION

In the realm of medication research and discovery, quinoline and its analogues are extremely notable heterocyclic molecules. They represent an essential class of scaffolds that are potentially found in nature and have a considerable impact on medicinal chemistry. Using quinoline derivatives as therapeutic molecules to treat various diseases and pathogens has drawn increasing attention. The review of the bioactivity of quinolines presented here is expected to be helpful to future practitioners of the field and to stimulate innovative abilities for current and upcoming issues in synthetic and medicinal chemistry. Quinoline hybrid compounds with different biological activities are cost-effective with the minimal risk associated with drug-drug interaction. When designing a hybrid compound, the pharmacokinetic nature of the drug is influenced by the linker group as stated in "Lipinski's rule"; that is, hybrid compounds comprising large size can cause reduced oral bioavailability. However, hybrid compounds are potentially active and can be an effective therapy to overcome drug resistance; compounds might show poor bioavailability if hybrid compound comprises of more than five hydrogen-bond donors, if the molecular mass is more than 500 and if the sum of oxygen and nitrogen atoms are more than 10. The above-stated rule does not apply to substrates of biological transporter and Natural drugs as of protein and antibodies. "Lipinski rule of 5" is necessary to be followed for maintaining oral bioavailability of hybrid compounds.

Declaration by Authors

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