

QUINOLINE: ITS SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES

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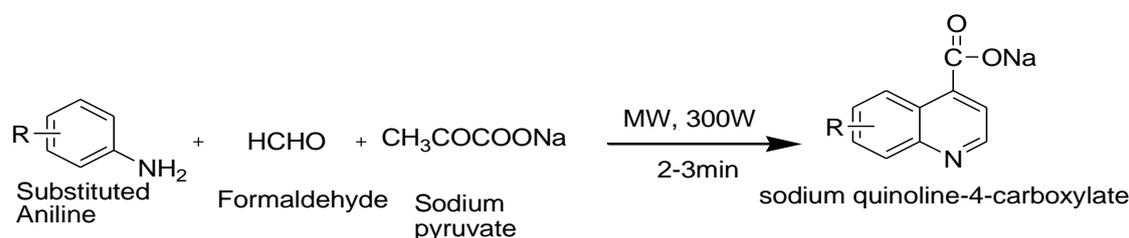
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ABSTRACT

Different heterocyclic analogues were evaluated for their different and variety of biological activities that have led to an intense study and research of these compounds. Out of them, the quinoline nucleus is a ubiquitous structural feature of many synthetic compounds with diversified therapeutic efficacy. It occurs in several natural compounds (Cinchona Alkaloids) and pharmacologically active substances displaying a broad range of biological activities such as anti-malarial, anti-microbial, anti-inflammatory, anti-convulsant, anti-cancer and anti-mycobacterial activity. Sodium quinolone-4-carboxylate derivatives were prepared with the help of microwave by taking different chemicals such as formaldehyde, sodium pyruvate, p-chloroanilines. Our aim is to produce the quinoline derivatives with the more therapeutic properties, lesser toxicity and by simpler method as the conventional methods of synthesis consumes longer hours. This project is based on microwave synthesis which relies on the principle of green chemistry, basically involve 'Go Green' concept. Purpose of green synthesis is to proceed with all the synthetic procedures which are ecofriendly and economic. Great deal of better yield in lesser time than conventional methods was observed. The characterization of the derived compounds was carried out by melting point, thin layer chromatography and infrared spectroscopy.

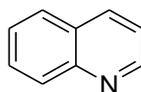


Keywords: Heterocyclic chemistry, Quinoline, Pharmacological activities, Spectroscopic analysis, SAR

INTRODUCTION

Quinoline (1) or 1-aza-naphtalene or benz[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 non-toxic 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 an anti-malarial, antimicrobial, ant-inflammatory, anticonvulsant, anticancer and anti-mycobacterial activity [1].

Quinolines and their derivatives are very important in medicinal chemistry because of their wide occurrence in natural products and drugs. In addition to the medicinal applications, quinolones have been employed in the study of bioorganic and bio organometallic processes. Quinolones are also known for their formation of conjugated molecules and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent mechanical properties [2].



(1)

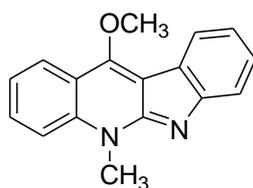
PHARMACOLOGICAL ACTIVITIES

Anti-cancer

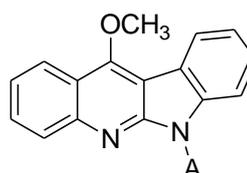
Cancer, rapid unregulated pathological proliferation of abnormal cells, is the second leading cause of death in humans after cardiovascular diseases. According to data from the World Health Organization, of the 58 million deaths occurred worldwide in 2008, 7.6 million (13%) were due to cancer. The pathologies that contribute most to mortality are lung (1.3 million annual deaths), stomach (740.000 deaths per year), liver (662.000 deaths annually), colon (655.000 deaths annually), and breast cancer (502.000 deaths per year). It is expected that the global number of cancer deaths will continue to rise around the world and will reach 9 million by the year 2015 and 11.4 million by 2030. The most common cancers in the world are, in order of mortality in men - lung, stomach, liver, colon and rectum, esophagus and prostate and in women - breast, lung, stomach; colon and rectum, and cervix. The search for new anticancer agents is an important and challenging task scientist [3].

Chen *et al* presented the report describing the synthesis of certain 11-substituted 6*H*-indolo [2,3-*b*] quinolones and their methylated derivatives. These 6*H*-indolo derivatives were prepared from the

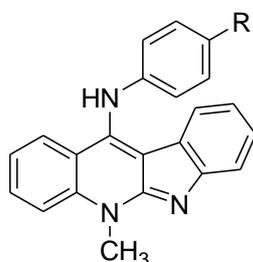
commercially available 1,4-dihydroxyquinoline through alkylation, chlorination, nucleophilic reaction, and ring cyclization. The in-vitro anti-cancer assay indicated 5-methylated derivatives 2a, 2b, 2c are more cyto-toxin than their respective 6-methylated counterparts 3a, 3b, 3c and 6*H*-Indolo[2,3,b] quinoline (2c) was the most cytotoxic with a mean GI50 value of 0.78 μ M and also exhibited selective cytotoxicities for HL-60 (TB),K-562,MOLT-4, RPMI-8226, and SR with GI50 values of 0.11, 0.42, 0.09, 0.14, and 0.19 μ M respectively [4].



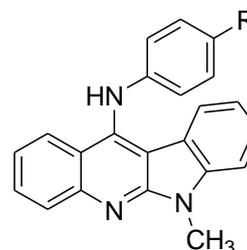
(2a)



(3a)

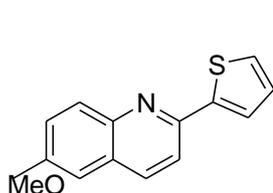


(2b) R = H (3b) R = H

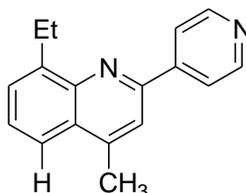


(2c) R = OCH3 (3c) R = OCH3

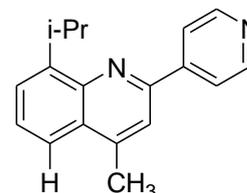
Kouznetsov *et al* tested sixteen C-2-substituted quinolines in both human cancer cell lines (MCF-7, H-460 and SF-268) and normal cell lines (Vero and THP-1). Preliminary results indicate that 2- α -furyl- and 2- β -pyridinylquinoline derivatives 4a, 4b and 4c are active against three human cancer cell lines and, at the same time, were devoid of cytotoxic effect on normal cells. Biological activity and SAR results were compared with different molecular descriptors determined in silico using online available software, in an attempt to show a relationship with the possible mode of action of this quinoline derivative [3].



(4a)



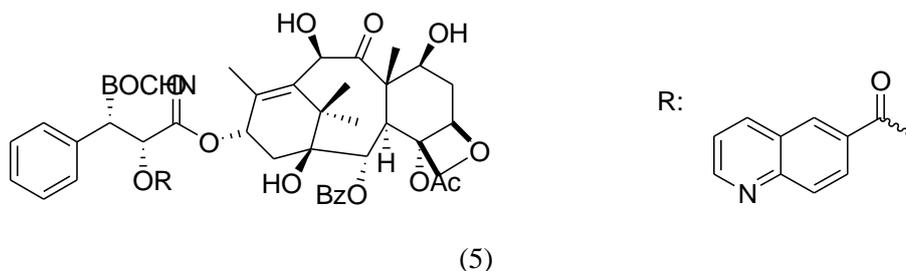
(4b)



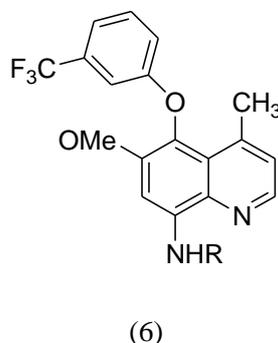
(4c)

Chen *et al* designed and synthesized a series of novel quinoline-docetaxel analogues by introducing bioactive quinoline scaffold to C2'-OH of docetaxel. The anticancer activities of these novel

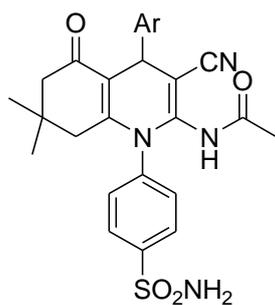
analogues were investigated against different human cancer cell lines including HeLa, A549, A2780, MCF-7 and two resistant strains A2780-MDR and MCF-7-MDR. The data showed these analogues possessed similar to better cytotoxicity than docetaxel. Compound 5 was found to be the most potent one, and its IC₅₀ value against MCF-7-MDR was 8.8 nM (IC₅₀ of A series of novel quinoline-docetaxel analogues). The work indicated that the introduction of quinolyl group in Docetaxel could enhance cytotoxicity and reduce drug-resistance [5].



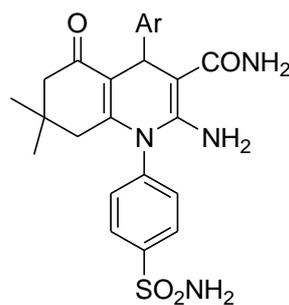
Shi et al derived promising anti-breast cancer agents from substituted quinolines. The quinolines were readily synthesized in a large scale from a sequence of reactions starting from 4-acetamidoanisole. Effects of the substituted quinolines on cell viability of T47D breast cancer cells using trypan blue exclusion assay were examined. The results showed that the IC₅₀ value of 6-methoxy-8-[(2-furanylmethyl)amino]-4-methyl-5-(3-trifluoromethylphenoxy)quinoline is 16 ± 3 nM, the lowest IC₅₀ out of all the quinolines tested [6].



Ghorab et al synthesized the twenty novel quinoline and pyrimido[4,5-b]quinoline derivatives bearing a sulfonamide moiety. All the newly synthesized compounds were evaluated for their in vitro anticancer activity against human breast cancer cell line (MCF7). Compounds 7b showed IC₅₀ values (72.9 μ M, 72.1 μ M and 71.9 μ M, respectively) comparable to that of the reference drug doxorubicin (IC₅₀ = 71.8 μ M). On the other hand, compound 7a exhibited better activity than doxorubicin with an IC₅₀ value of 64.5 μ M [7].

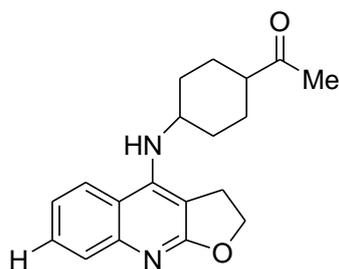


(7a)

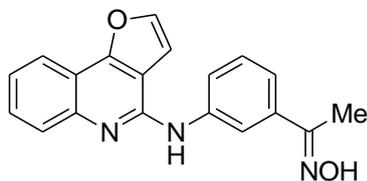


(7b)

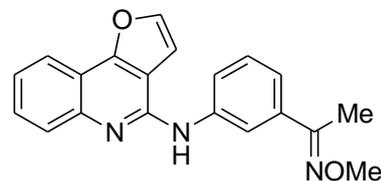
Chen *et al* synthesized certain linear 4-anilino-furo[2,3-b]quinoline and angular 4-anilino-furo[3,2-c]quinoline derivatives and evaluated *in vitro* against the full panel of NCI's 60 cancer cell lines. For the linear 4-anilino-furo[2,3-b]quinoline derivatives, 1-[4-(furo[2,3-b]quinolin-4-ylamino)phenyl]ethanone (8a) is the most cytotoxic with a mean GI50 value of 0.025 μM . For the angular 4-anilino-furo[3,2-c]quinoline derivatives, (*E*)-1-[3-(furo[3,2-c]quinolin-4-ylamino)phenyl]ethanone oxime (8b) exhibited potent inhibitory activities on UO-31, UACC-257, and UACC-62 respectively. These results deserve full attention especially because 8b and 8c are relatively non-cytotoxic with the mean GI50 value of 7.73 and 8.91 μM respectively [8].



(8a)

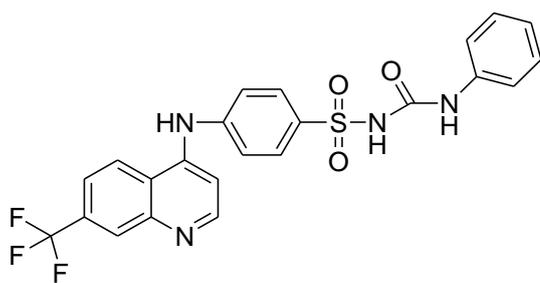


(8b)

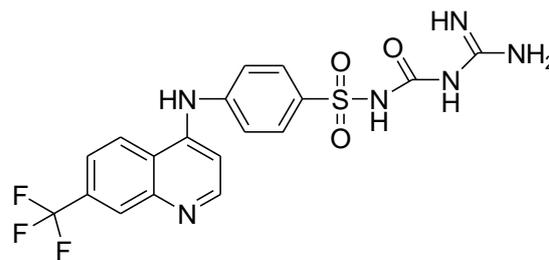


(8c)

Dosari *et al* synthesized several trifluoromethylquinoline derivatives containing a biologically active benzenesulfonamide moiety, urea derivatives, 4-isothiocyanate and the corresponding carbamimidothioic acid derivatives and were evaluated for their *in vitro* anticancer activity against various cancer cell lines. Most of the synthesized compounds showed good activity, especially compound 9a which exhibited higher activity than the reference drug doxorubicin. In order to suggest the mechanism of action for their cytotoxic activity, molecular docking for all synthesized compounds was done on the active site of PI3K and good results were obtained [9].

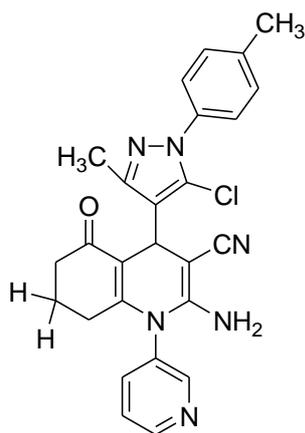


(9a)

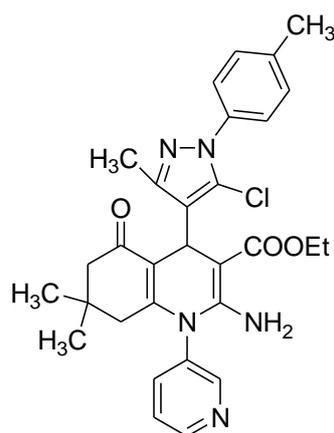


(9b)

Sangani *et al* designed a new series of pyrazol-quinoline-pyridine hybrid based on molecular hybridization technique and synthesized by a base-catalyzed cyclo-condensation reaction through one-pot multicomponent reaction and were tested for *in vitro* anti-cancer activities. Enzyme inhibitory activities of all compounds were carried out against FabH and EGFR. Majority of the compounds showed effective anticancer activity against cancer cell lines. Compound 10a ($IC_{50} = 0.51 \pm 0.05 \mu M$) against EGFR and 10b displayed the most potent inhibitory activity with IC_{50} of $3.1 \mu M$ against FabH as compared to other members [10].



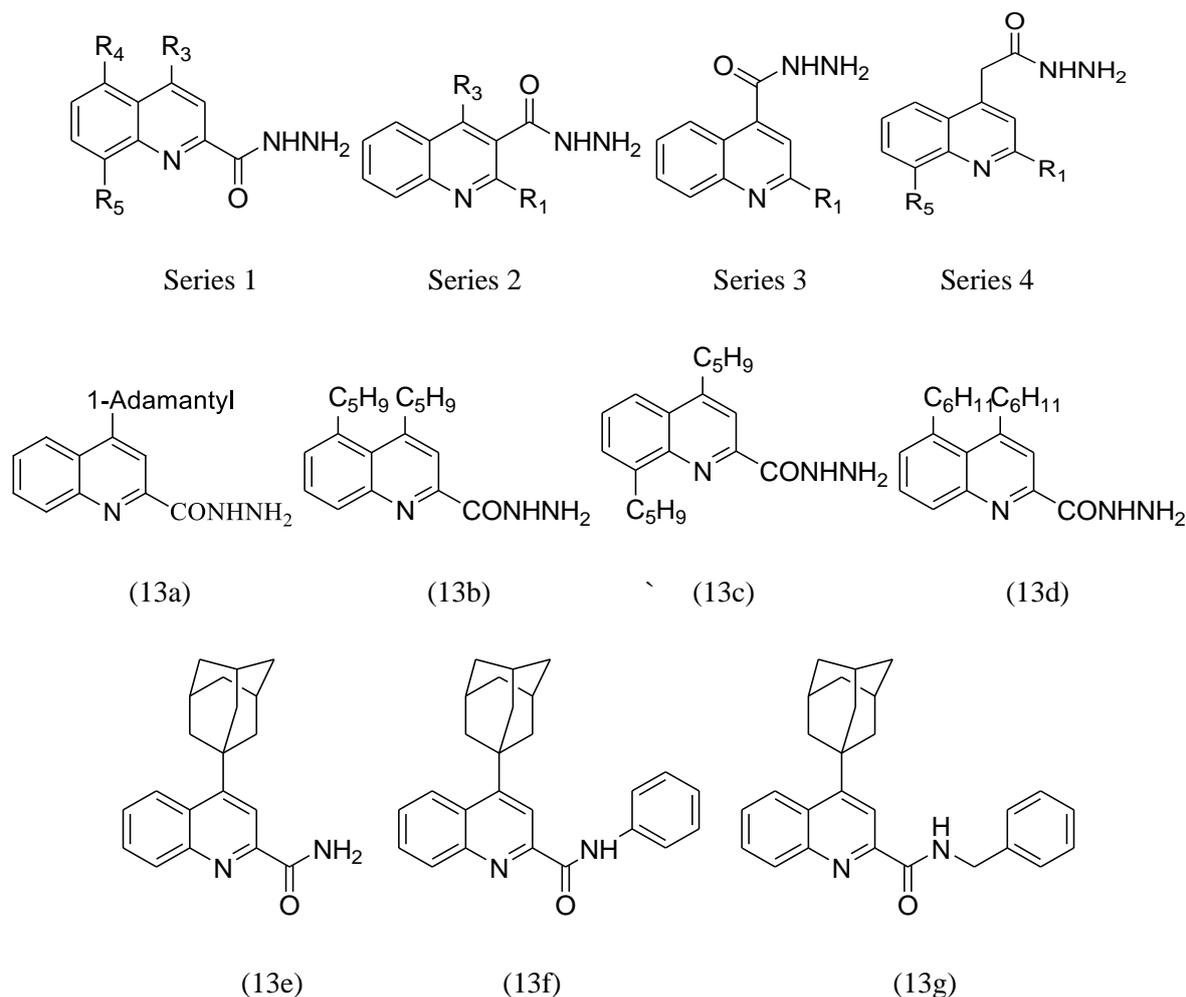
(10a)



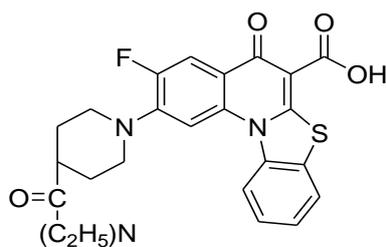
(10b)

Ghorab *et al* synthesized some novel 4-(quinolin-1-yl)-benzenesul-fonamide and 4-(pyrimido[4,5-b]quinolin-10-yl)-benzenesulfonamide derivatives. All the newly synthesized target compounds were subjected to *in vitro* cytotoxic screening to be evaluated for their anticancer activity against Ehrlich ascites carcinoma cells. Among these new compounds, compounds 11a, 11b, 11c showed promising *in vitro* cytotoxic activity compared with Doxorubicin (CAS 23214-92-8) as a reference drug [11].

and 13 reported herein have exhibited excellent anti-mycobacterial activities in the range of 6.25–3.1251g/mL against drug-sensitive and drug-resistant *M. tuberculosis* H37Rv strains [14].

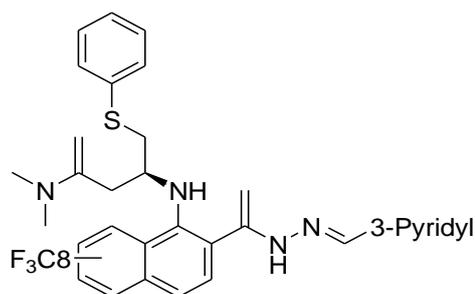


Dinakaran et al synthesized various 2-(sub)-3-fluoro/nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid derivatives from 2-aminothiophenol by a five-step reaction, evaluated for in-vitro and in-vivo anti-mycobacterial activities against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB), and *Mycobacterium smegmatis* (MC2), and also tested for the ability to inhibit the supercoiling activity of DNA gyrase from *M. smegmatis*. Among the 34 synthesized compounds, 2-(3-(diethylcarbamoyl)piperidin-1-yl)-3-fluoro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acid (14) was found to be the most active compound in vitro with MIC of 0.18 and 0.08 μ M against MTB and MDR-TB respectively [13].

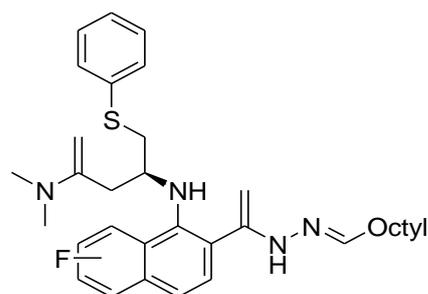


(14)

Eswaran *et al* synthesized a series of 26 new quinoline derivatives carrying active pharmacophores and evaluated for their *in vitro* anti-tuberculosis activity against *Mycobacterium tuberculosis* H37Rv (MTB), *Mycobacterium smegmatis* and *Mycobacterium fortuitum* following the broth micro dilution assay method. Compounds 15a and 15b exhibited significant minimum inhibition concentrations, when compared with first line drugs isoniazid (INH) and Rifampicin (RIF) and could be ideally suited for further modifications to obtain more efficacious compounds in the fight against multi-drug resistant tuberculosis [15].

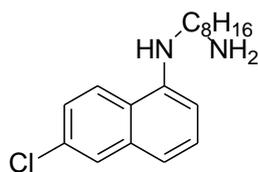


(15a)

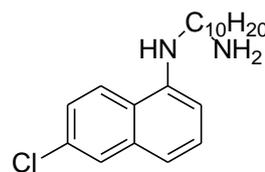


(15b)

Souza *et al* synthesized a series of 33 quinoline derivatives and evaluated for their *in vitro* antibacterial activity against *Mycobacterium tuberculosis* H37Rv using the Alamar Blue susceptibility test and the activity expressed as the minimum inhibitory concentration (MIC) in $\mu\text{g/mL}$. Compounds 16a and 16b exhibited a significant activity at 6.25 and 3.12 $\mu\text{g/mL}$, respectively, when compared with first line drugs such as Ethambutol and could be a good starting point to develop new lead compounds in the fight against multi-drug resistant tuberculosis [16].

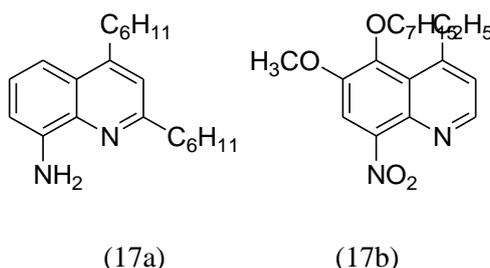


(16a)

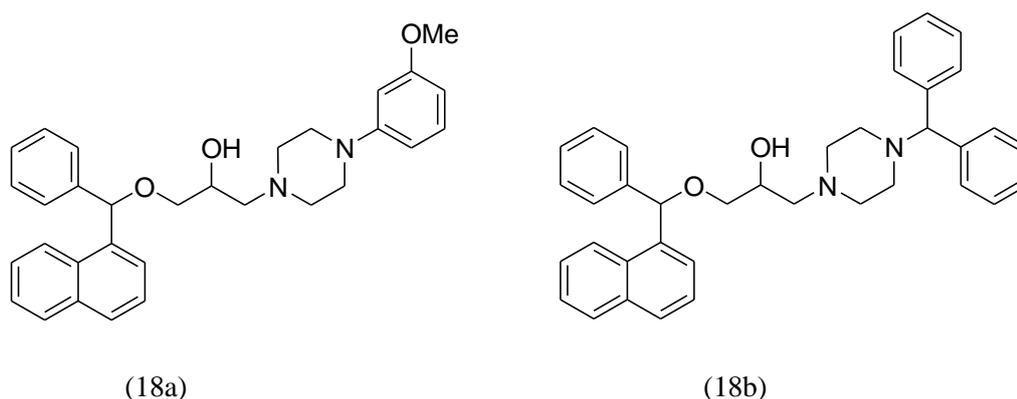


(16b)

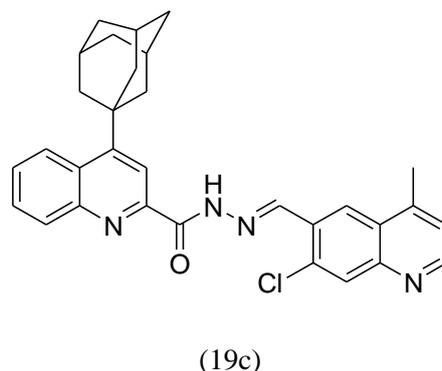
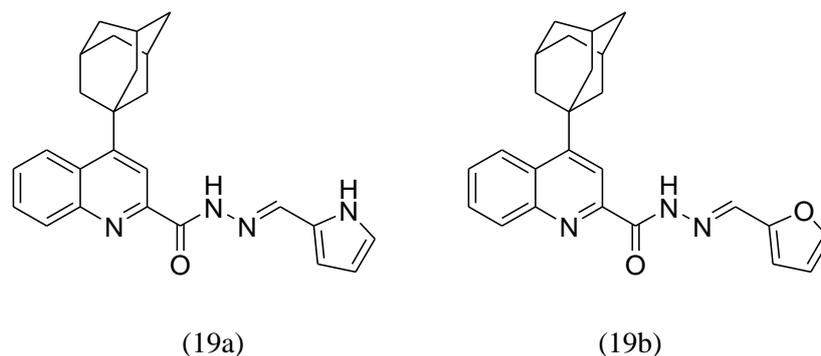
Vangapandu *et al* reported *in vitro* anti-mycobacterial properties of ring-substituted quinolines (series 1–4) constituting 56 analogues against drug-sensitive and drug-resistant *M. tuberculosis* H37Rv strains. The most effective compounds 2h (R1=R2= c-C6H11, R3=NO₂, series 1) and 13g (R1=OC₇H₁₅, R2=NO₂, series 4) have exhibited an MIC value of 1 µg/mL against drug-sensitive *M. tuberculosis* H37Rv strain that is comparable to first line anti-tuberculosis drug, isoniazid. Selected analogues (17a and 17b MIC: ≤6.25 µg/mL) upon further evaluation against single-drug-resistant (SDR) strains of *M. tuberculosis* H37Rv have produced potent efficacy in the range between 6.25 and 50 µg/mL [17].



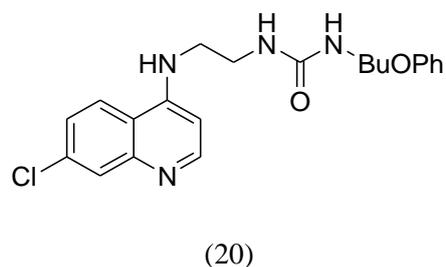
Upadhayaya *et al* designed and synthesized the quinoline based molecules influenced by the unique structural make-up of Mefloquine. These compounds were evaluated for their anti-mycobacterial activity against drug sensitive *Mycobacterium tuberculosis* H37Rv *in vitro* at single-dose concentration (6.25µg/mL). The compounds 18a and 18b inhibited the growth of *M. tuberculosis* H37Rv 99% and 98% respectively. Minimum inhibitory concentration of compounds 18a and 18b was found to be 6.25µg/mL. SAR analysis indicates importance of hydroxyl group and nature of substituents on piperazinyl-phenyl ring was critical in dictating the biological activity of newly synthesized compounds [18].



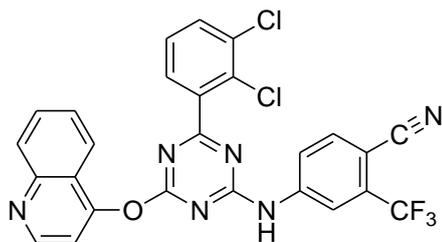
Nayar *et al* reported the synthesis of two series of 4-(adamantan-1-yl)-2-substituted quinolines. All new derivatives were evaluated *in vitro* for anti-mycobacterial activities against drug-sensitive *M. tuberculosis* H37Rv strain. Analogs 19a, 19b and 19c have produced promising anti-mycobacterial activities (99% inhibition) at 3.125µg/mL against drug-sensitive *M. tuberculosis* H37Rv strain [19].



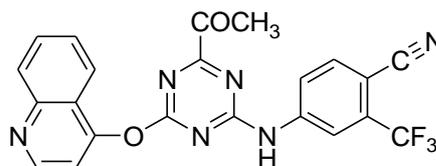
Nava-Zuazo *et al* has synthesized a new series of quinoline tripartite hybrids from chloroquine, ethambutol and isoxyl drugs, using a short synthetic route. Compounds were tested *in vitro* against five protozoa (*Giardia intestinalis*, *Trichomonas vaginalis*, *Entamoeba histolytica*, *Leishmania mexicana* and *Trypanosoma cruzi*) and *Mycobacterium tuberculosis*. *N*-(4-Butoxyphenyl)-*N'*-{2-[(7-chloroquinolin-4-yl)amino]ethyl}urea (20) was the most active compound against all parasites tested as compare to Metronidazole against *G. intestinalis* [20].



Patel *et al* synthesized a series of novel *s*-triazine analogs and characterized by IR, ¹H NMR, ¹³C NMR, ¹⁹F NMR spectroscopy and elemental analysis. Preliminary screening of target compounds against *Mycobacterium tuberculosis* H37Rv indicated that 21a and 21b were the most active compounds among twenty one studied.²¹

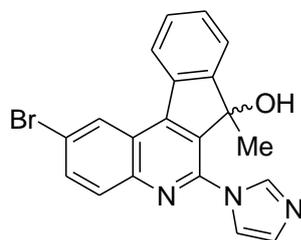


(21a)

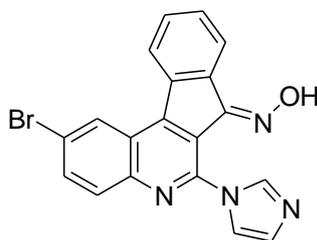


(21b)

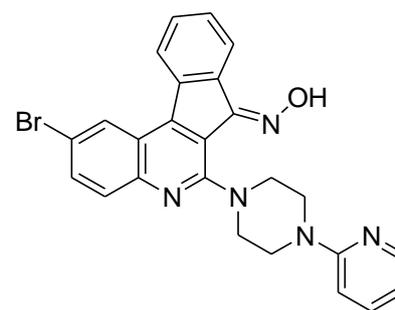
Upadhyaya *et al* recently reported anti-TB properties of a new class of conformationally-constrained indeno[2,1-c]quinolines, which are although considerably active (MIC 0.39–0.78 $\mu\text{g}/\text{mL}$) suffered from intense solubility problems. Accordingly esters of the “Lead” indeno[2,1-c]quinolines 22a, 22b and 22c derivatives were synthesized and their prodrug nature at the physiological pH were confirmed. Prodrugs were evaluated for their anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv by MABA assay to show that they have 2- to 4-fold improved anti-TB activities, increased aqueous solubility and superior selectivity index over their respective parent compounds. MIC of these prodrugs was in the range of <0.20–6.0 $\mu\text{g}/\text{mL}$, and in general, no cytotoxicity was observed in VERO cells.²²



(22a)



(22b)



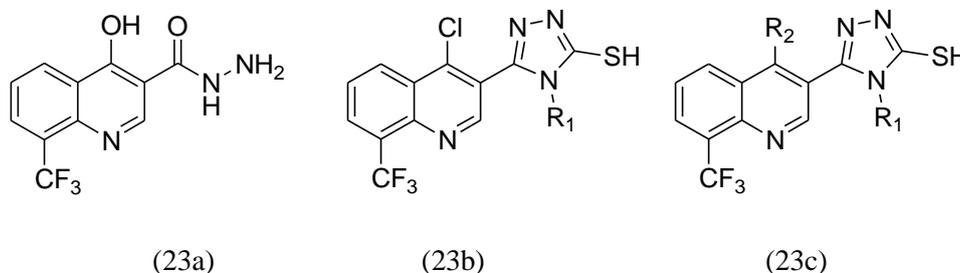
(22c)

Anti-microbial

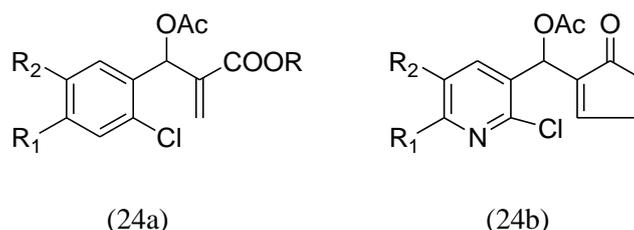
Currently resistance to first-line antibiotic agents is a severe problem. Infections caused by these resistant microbes fail to respond to treatment resulting in prolonged illness and greater risk of death. The alarming rates of emerging and reemerging microbial threats coupled with increasing antibacterial resistance, particularly in regard to multi drug-resistant Gram-positive bacteria, are major concerns to the public health as well scientific communities worldwide. These trends have emphasized the pressing need for new, more effective and safe antibacterial agents and which in turn has opened up a new area of research for the scientists.²³

Eswaran *et al* synthesized a new class of quinoline derivatives containing 1,2,4-triazole moiety from derivatives of 4-hydroxy-8-(trifluoromethyl) quinoline-3-carbohydrazide through multistep reaction.

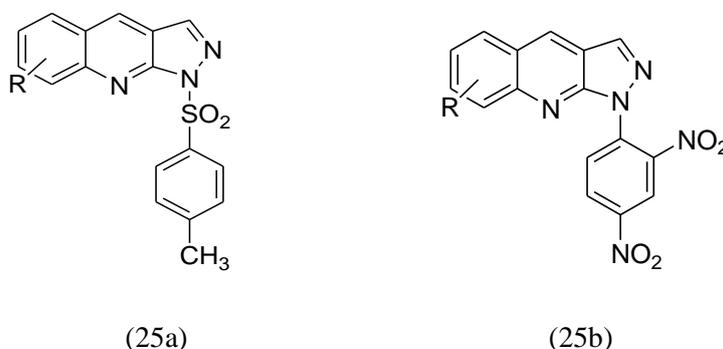
The newly synthesized compounds were evaluated for their *in vitro* antibacterial and antifungal activities against four strains each and the strains were photogenic strains. Preliminary result indicates that the most of the compounds demonstrate the very good antimicrobial activity such as 23a, 23b and 23c, comparable to the first line standard drugs. The most effective compound have exhibited activity at MIC of 6.25 μ g/mL.²⁴



Narender *et al* synthesized Baylis-Hillman acetates from substituted 2-chloronicotinaldehydes and were conveniently transformed into multi-substitutedquinolones and cyclopenta-quinolones via a successive S_N2' - S_NAr elimination strategy. Thus, synthesized quinolones were evaluated for antimicrobial activity and found having substantial antibacterial and antifungal activity.²⁵

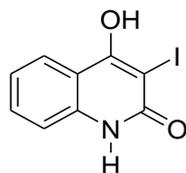


Selvi *et al* synthesized a series of 2-oxypyrimido[4,5-b]-, 2-thio[4,5-b]-, 1-(*p*-tosyl)pyrazolo[3,4-b] and 1-(2',4'-dinitrophenyl)pyrazolo[3,4-b]-quinolines by environmentally benign solvent free microwave-induced techniques. All the synthesized compounds were evaluated for their anti-bacterial and anti-fungal activities. Most of the compounds showed the best activity against *Escherichia coli* and *Pseudomonas aeruginosa*.²⁶



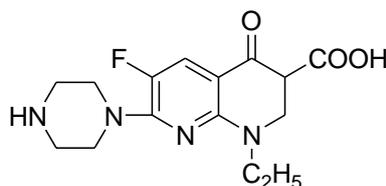
Donnell *et al* studied the antimicrobial activities of 60 naturally occurring and synthetic quinolines and were tested against a range of gram-positive and gram-negative bacteria, including a hospital

isolate of Meticillin-resistant *Staphylococcus aureus* (MRSA). In particular, 4-hydroxy-3-iodo-quinolin-2-one (26) showed MIC values of 0.097 $\mu\text{g/mL}$ against an Irish hospital MRSA-1 strain and 0.049 $\mu\text{g/mL}$ against a distinct MRSA strain as well as a non-typeable MRSA strain, the values are comparable with the antibiotic Vancomycin used in the treatment of MRSA infections.²⁷



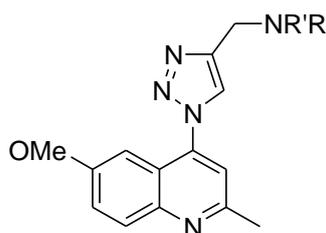
(26)

Wise *et al* compared the *in-vitro* activity of enoxacin (CI-919), a new synthetic quinolone derivative with that of three other quinolones Ofloxacin, Norfloxacin and Nalidixic acid. The MICs of enoxacin for 90% of *Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*, *Proteus spp.*, *Providencia stuartii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were less than 4 mg/L, for *Haemophilus influenzae* less than 0.25 mg/L and *Neisseria gonorrhoeae* less than 0.03 mg/L. *Bacteroides fragilis* and streptococci (including *Streptococcus pneumoniae*) were less susceptible, MIC90, 16 mg/L.²⁸



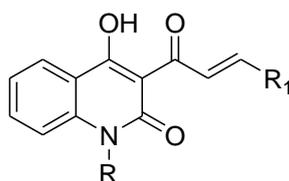
(27)

Thomas *et al* synthesized a new series of [1-(6-methoxy-2-methylquinolin-4-yl)-1H-1,2,3-triazol-4-yl]methanamine derivatives. All the new compounds were characterized by spectral and elemental analyses. The newly synthesized final compounds were evaluated for their *in vitro* antibacterial and antifungal activities against pathogenic strains. The preliminary screening results indicated that 28 compound demonstrated very good antibacterial and antifungal activities, comparable to the first-line drugs.²³



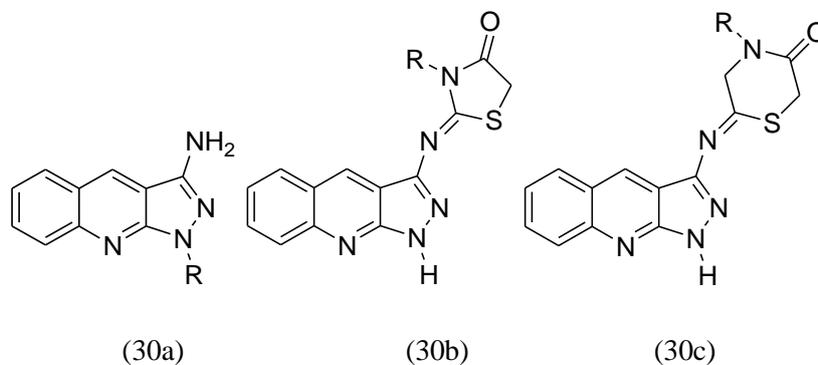
(28)

Azad *et al* prepared a series of quinoline-based chalcones by the condensation of quinoline-3-carbaldehyde with acetophenone and *N*-substituted-3-acetyl-4-hydroxy-2-quinolones with heterocyclic aldehydes. The prepared chalcones have been screened for anti-microbial activities against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Klebsiella aerogenes*, *Staphylococcus albus*, *Aspergillus flavus*, *Aspergillus niger*, *Rhodospirillum rubrum*, *Lipomyces loofae* and *Candida albicans*. All the prepared chalcones have shown significant antimicrobial activity.²⁹



(29)

El-Sayed *et al* prepared new pyrazolo[3,4-*b*]quinoline derivatives by cyclization of the intermediate 2-chloroquinoline-3-carbonitrile, namely 3-amino-1*H*-pyrazolo[3,4-*b*]quinoline, 3-amino-1-phenyl/(*p*-substituted)phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (30a). Furthermore, 3-[(3-aryl-4-oxothiazolidin-2-ylidene)amino]-1*H*-pyrazolo[3,4-*b*]quinolines (30b) and 3-[(3-aryl-4-oxothiazin-2-ylidene)amino]-1*H*-pyrazolo[3,4-*b*]quinolines (30c) were synthesized. The antimicrobial activity was evaluated for most of the prepared compounds.³⁰

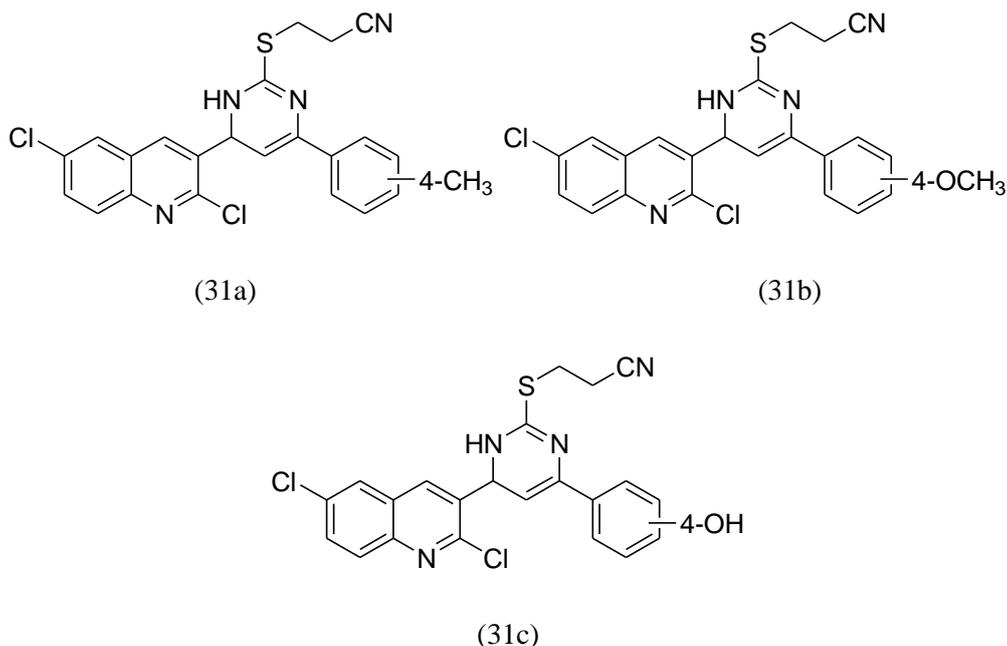


(30a)

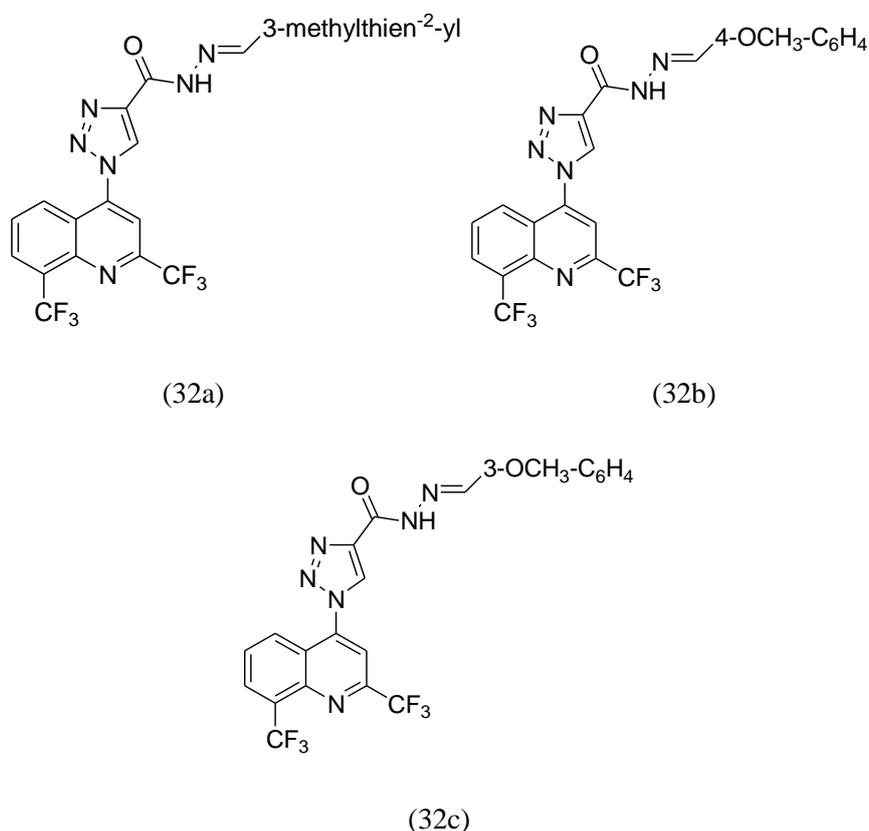
(30b)

(30c)

Desai *et al* synthesized a series of 3-((6-(2,6-dichloroquinolin-3-yl)-4-aryl-1,6-dihydro-pyrimidin-2-yl)thio)propanenitriles and subjected to molecular properties prediction and drug-likeness model score by Molinspiration property calculation toolkit and MolSoft software, respectively. Compounds 31a, 31b and 31c displayed broad spectrum antibacterial activity against all the bacterial strains. Moreover, compound 31b was found to be the most potent antifungal agent.³¹



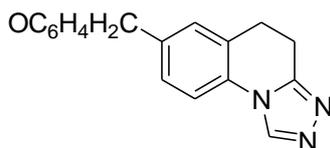
Sumangala et al synthesized a new series of substituted 1,2,3-triazoles from 4-azido-2,8-bistrifluoromethylquinoline and were evaluated *in vitro* for their antibacterial and antifungal activity. Among the newly synthesized compounds, the most active compound was 32a, which contained the 3-methylthien-2-yl moiety and showed a broad spectrum of antimicrobial activity against all the strains used for testing. Compounds 32b and 32c showed significant antimicrobial activity at the concentration of 6.25 $\mu\text{g/mL}$.³²



Anti-convulsant Activity

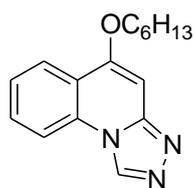
Epilepsy, a ubiquitous disease characterized by recurrent seizures, inflicts more than 60 million people worldwide according to epidemiological studies. For epilepsy treatment, nearly 95percent of clinically available drugs were approved before 1985 and they could provide satisfactory seizure control for 60-70percent of patients. These drugs, however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia, and even life threatening conditions. Research to find more effective and safer anticonvulsant drugs are therefore a challenging task.³³

Xie *et al* synthesized a series of 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline derivatives and were evaluated by the maximal electroshock test (MES test) and the subcutaneous (sc) pentylenetetrazol test (scMet test), and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES and scMet tests show that 7-(4-fluorobenzoyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline 33 was found to be the most potent with ED₅₀ value of 11.8 and 6.7 mg kg⁻¹ and protective index (PI=TD₅₀/ED₅₀) value of 4.6 and 8.1 respectively.³⁴

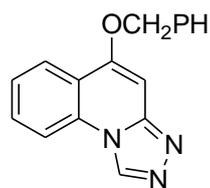


(33)

Guo *et al* synthesized a series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives were evaluated by the maximal electroshock test (MES) and their neurotoxicities were measured by the rotarod test. The results of these tests demonstrated that 5-hexyloxy-[1,2,4]triazolo[4,3-a]quinoline (34a) was the most potent anticonvulsant, with median effective dose (ED₅₀) of 19.0 mg/kg and protective index (PI=TD₅₀/ED₅₀) values of 5.8 in the MES test. Compound 5-benzyloxy-[1,2,4]triazolo[4,3-a]quinoline (34b) possessed lower neurotoxicity with PI value of 12.0, which was safer than marketed drug Carbamazepine. To explain the possible mechanism of anticonvulsant activity, compound 34b was tested in pentylenetetrazole test, isoniazoid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test.³³

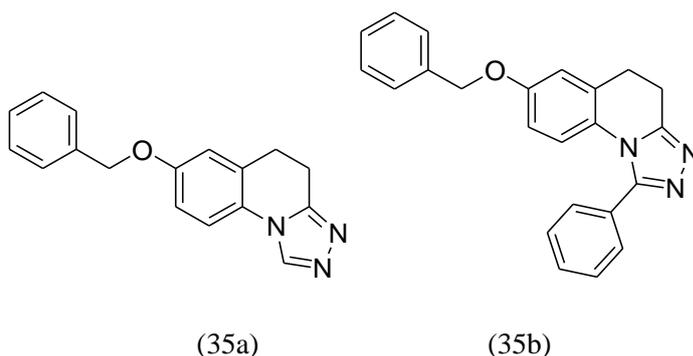


(34a)

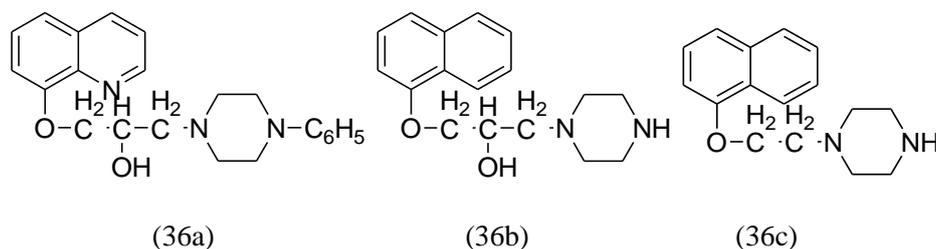


(34b)

Cui *et al* synthesized a series of 1-substituted-7-benzyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a] and was evaluated in the maximal electroshock (MES) test, subcutaneous pentylenetetrazol (scMet) test, and rotarod neurotoxicity test. The most active compound was 7-benzyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline 35a. Its ED₅₀ in the MES and scMet tests was 17.3 and 24 mg·kg⁻¹, respectively. The safest compound was 35b, 1-phenyl-7-benzyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline, with TD₅₀ and protective index (PI) (PI=TD₅₀/ED₅₀) values of greater than 300 mg·kg⁻¹ and 13, respectively. The PI value of compound 35b was better than that of most marketed drugs.³⁵

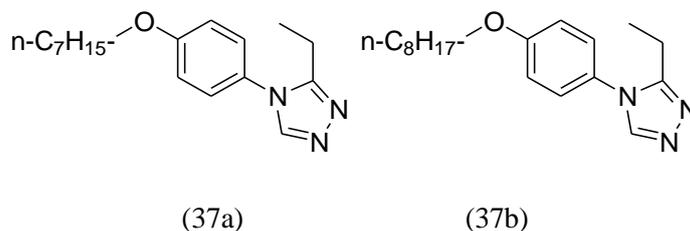


Muruganatham *et al* synthesized a series of 8-substituted quinolines and tested against seizures induced by maximal electro shock (MES), pentylenetetrazole (scMet) and neurologic deficit by the rotarod test. Compounds with a 2-hydroxypropyloxyquinoline moiety displayed excellent anticonvulsant activities. Compound 36a (8-(3'-(4''-phenylpiperazino)-2'-hydroxypropyloxy)quinoline) was potent in both series as an anticonvulsive agent. 36b (8-(3'-piperazino)-2'-hydroxypropyloxyquinoline) showed very good anticonvulsant activities in the propanol series of compound, whereas in the ethane series, 36c (8-(2'-piperazino-ethanoxy)quinoline) was the most active as anticonvulsive agents.³⁶

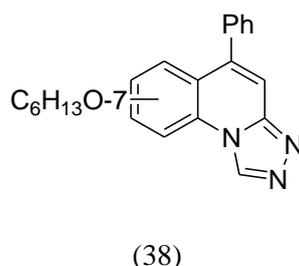


Chen *et al* synthesized a series of 4-(4-alkoxyphenyl)-3-ethyl-4*H*-1,2,4-triazole derivatives and were evaluated by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES test showed that 3-ethyl-4-(4-octyloxyphenyl)-4*H*-1,2,4-triazole 37a was found to be the most potent with ED₅₀ value of 8.3 mg/kg and protective index (PI = TD₅₀/ED₅₀) value of 5.5, but compound ,37b 3-ethyl-4-(4-octyloxyphenyl)-4*H*-1,2,4-triazole,

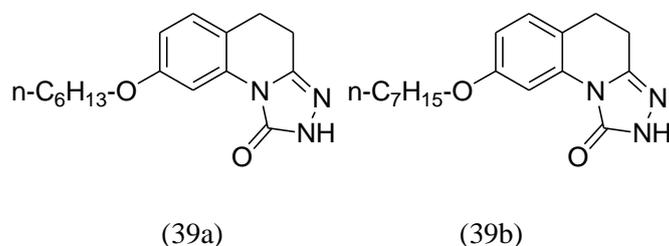
exhibited better PI value of 9.3, which was much greater than PI value of the prototype drug Phenytoin.³⁷



Guan *et al* synthesized a series of novel 5-phenyl-[1,2,4]-triazolo[4,3-a]quinoline derivatives by the cyclization, were evaluated by the maximal electroshock (MES) test and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). The maximal electroshock test showed that 7-hexyloxy-5-phenyl-[1,2,4]-triazolo[4,3-a]quinoline 38 was found to be the most potent compound with an ED50 value of 6.5 mg/kg and a protective index (PI = ED50 / TD50) value of 35.1, which was much higher than the PI of the reference drug phenytoin.³⁸

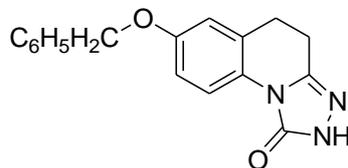


Sun *et al* synthesized a series of 8-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1-one derivatives, were evaluated by the maximal electroshock test (MES) and the subcutaneous pentylenetetrazole test (sc-PTZ), and their neurotoxicities were measured by the rotarod neurotoxicity test (Tox). The tests demonstrated that 8-hexyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1-one (39a) and 8-heptyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1-one (39b) were the most potent anticonvulsants, with 4e having ED50 values of 17.17 mg/kg and 24.55 mg/kg and protective index (PI=TD50/ED50) values of 41.9 and 29.3 in the MES and sc-PTZ tests, respectively.³⁹



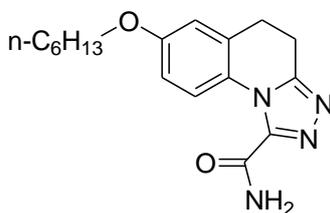
Jin *et al* synthesized a series of 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1(2H)-one derivatives. In initial (phase I) screening and quantitative (phase II) evaluation, compound 7-benzyloxy-4,5-dihydro-[1,2,4]thiazolo[4,3-a]quinoline-1(2H)-one (40) was among the most active

but also has the lowest toxicity. In the anti-MES potency test, it showed median effective dose (ED50) of 12.3 mg/kg, median toxicity dose (TD50) of 547.5 mg/kg, and the protective index (PI) of 44.5, which is much greater than PI of the prototype drugs Phenytoin, Phenobarbital, Carbamazepine, and Valproate.⁴⁰



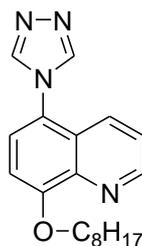
(40)

Wei et al synthesized a series of 1-formamide-triazolo[4,3-a]quinoline derivatives, the anticonvulsant effect and neurotoxicity of the compounds was calculated with maximal electroshock test and rotarod tests with intra-peritoneally injected in KunMing mice. Compound 7-(hexyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1-carboxamide (41) was the most active one and also had the lowest toxicity. In the anti-maximal electroshock potency test, it showed median effective dose (ED50) of 30.1 mg/kg, median toxicity dose (TD50) of 286 mg/kg, and the protective index of 9.5 which is greater than the reference drug Carbamazepine with the protective index value of 6.0.⁴¹



(41)

Wang et al synthesized the two series of 8-alkoxy-5-(4*H*-1,2,4-triazol-4-yl)quinolines and 8-alkoxy-5-(2*H*-1,2,4-triazol-3-one-4-yl)quinolines. The anticonvulsant activity of these compounds was evaluated with maximal electroshock seizure test and rotarod test. Among the synthesized compounds, 8-octoxy-5-(4*H*-1,2,4-triazol-4-yl)quinoline (42) was the most active compound with ED50 of 8.80 mg/kg, TD50 of 176.03 mg/kg and protective index of 20.0. Its neurotoxicity was lower than all other synthesized compounds and also markedly lower than that of the reference drug carbamazepine.⁴²

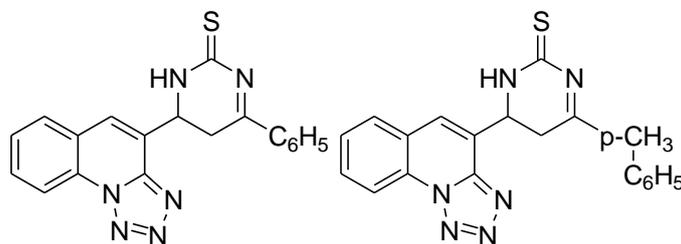


(42)

Anti-inflammatory Activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful tools in the treatment of acute and chronic inflammation, pain, and fever. However, long term clinical usage of NSAIDs is associated with significant side effects of gastro-intestinal lesions, bleeding, and nephrotoxicity. Therefore the discovery of new and safer anti-inflammatory drugs represents a challenging goal for such a research area.⁴³

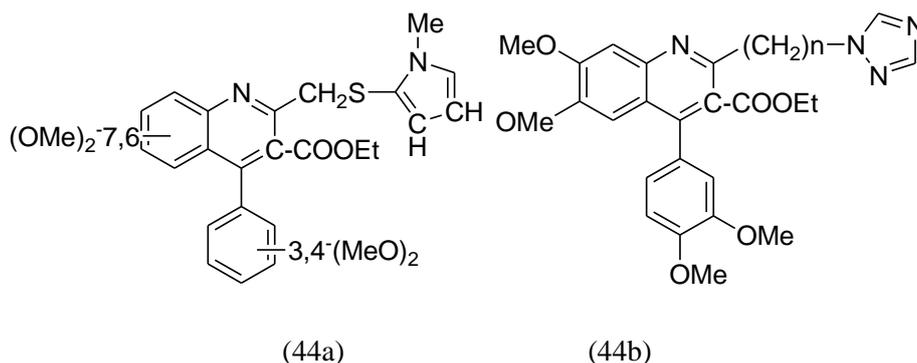
Bekhit *et al* synthesized three series of tetrazolo[1,5-a]quinolone derivatives by the condensation of various compounds. The newly synthesized compounds were evaluated for their anti-inflammatory and antimicrobial activities. Compounds 43a and 43b (ED₅₀ values range 8.50– 9.84 μmol) have anti-inflammatory activity comparable to that of indomethacin (ED₅₀ value 9.28 μmol).⁴⁴



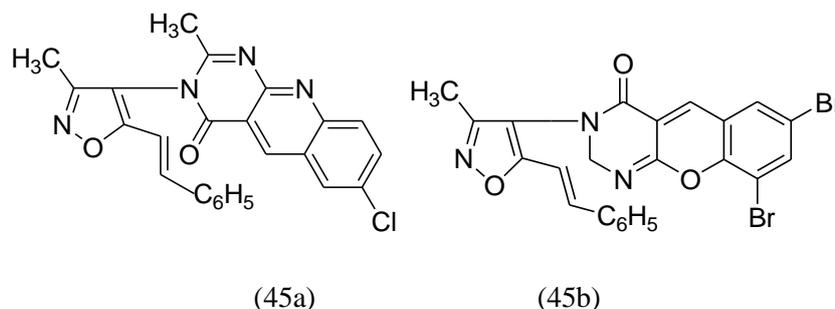
(43a)

(43b)

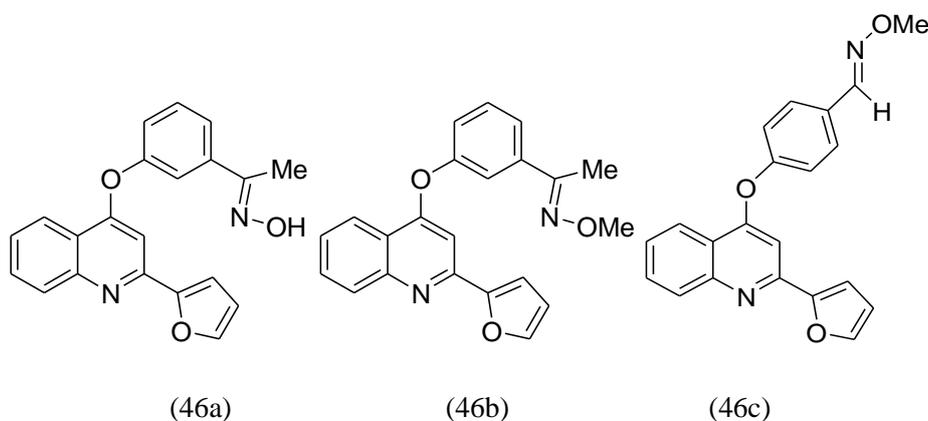
Baba *et al* found that quinoline derivative had a potent anti-inflammatory effect in an adjuvant arthritis (AA) rat model. These compounds were evaluated for anti-inflammatory effects using the AA rat model. Among the compounds synthesized, ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl)quinoline-3-carboxylate (44b), having an ED₅₀ value of 2.6 mg/kg/day, was selected as a candidate for further investigation.⁴⁵



Rajanarendar *et al* synthesized a novel series of 2-methyl-3-{3-methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-3,4-dihydropyrimido[4,5-b]quinolin-4-ones **5** and 3-{3-methyl-5-[(E)-2-phenyl-1-ethenyl]-4-isoxazolyl}-3,4-dihydro-2*H*-chromeno[2,3-d]pyrimidin-4-ones. The title compounds were evaluated for their anti-inflammatory activity. Compounds **45a** and **45b** exhibited significant potent anti-inflammatory activity as that of standard drugs.⁴⁶

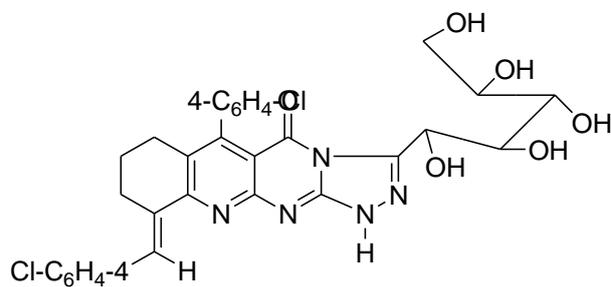


Chen *et al* synthesized a number of 2-(furan-2-yl)-4-phenoxyquinoline derivative and evaluated for anti-inflammatory evaluation. For the inhibitory activity of fMLP-induced superoxide anion generation, **46a** (2.7 μ M), **46b** (2.8 μ M), and **46c** (2.2 μ M) are three of the most active. They show the anti-inflammatory activity. None of above compounds exhibited significant cytotoxicity.⁴⁷

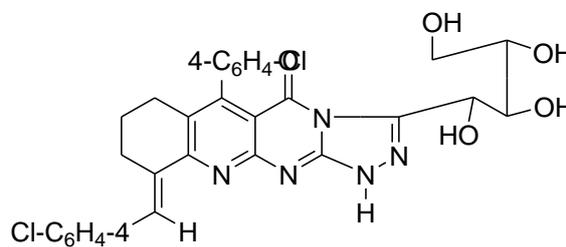


El-Gazzar *et al* synthesized of 2-thioxopyrimido[4,5-b]quinoline by microwave oven was used as a base to synthesis acyclic nucleosides analogue. The title compounds were investigated for anti-

inflammatory activity. Compounds 47a and 47b showed more potent anti-inflammatory than the acetylated glycoside derivatives.⁴⁸

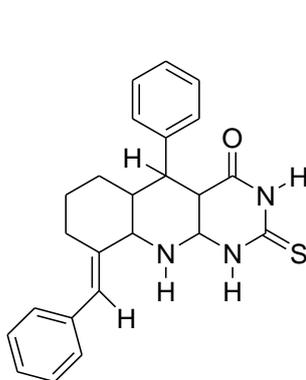


(47a)

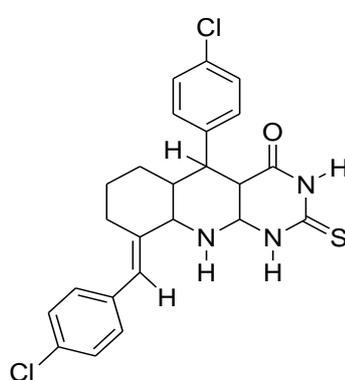


(47b)

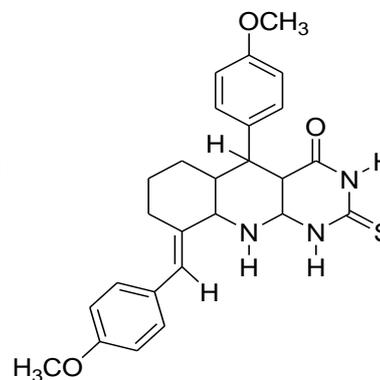
El-Gazzar *et al* synthesis the 5,10-dihydro-2-thioxo-pyrimido[4,5-b]quinolines and its oxidized form were prepared and used as key intermediates for the synthesis of thiazolo[3',2':1,2]pyrimido[4,5-b]quinolines, isoxazolo[5'',4'':4',5']thiazolo[3',2':1,2]pyrimido[4,5-b]quinolines, 4-chloro-2-methylthio-pyrimido[4,5-b]quinoline, its amino derivatives and 10,11,12,13-tetrahydro-5H-quinolo[2',3':4,5]pyrimido[6,1-b]quinazoline and evaluated for anti-inflammatory activity. Compounds 48a, 48b, and 48c exhibited a potent anti-inflammatory activity using carrageenan-induced paw edema test in rats.⁴⁹



(48a)

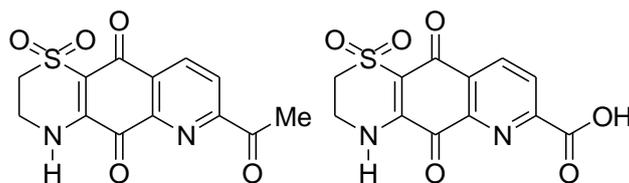


(48b)



(48c)

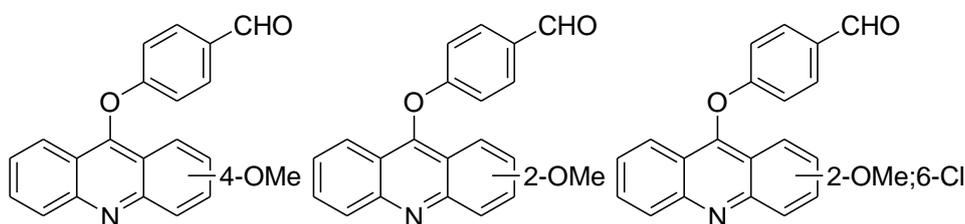
Chia *et al* synthesized sixteen new thiazine-quinoline-quinones, plus one bicyclic analogue. These compounds inhibited neutrophil superoxide production *in vitro* with IC₅₀s as low as 60 nM. Compounds with high *in vitro* anti-inflammatory activity were also tested in a mouse model of acute inflammation. The most active compounds 49a and 49b inhibited both neutrophil infiltration and superoxide production at doses 2.5 μmol/kg.⁵⁰



(49a)

(49b)

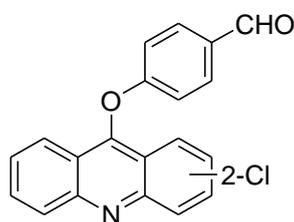
Chen *et al* synthesized certain 9-phenoxycridine and 4-phenoxylfuro[2,3-b]quinoline derivatives and evaluated their anti-inflammatory activities on inhibitory effects on the activation of mast cells, neutrophils and macrophages. Four 9-(4-formylphenoxy)acridine derivatives 50a–50d were proved to be more potent than the reference inhibitor, Mepacrine for the inhibition of rat peritoneal mast cell degranulation with IC₅₀ values of 6.1, 5.9, 13.5, and 4.7 μM, respectively.⁵¹



(50a)

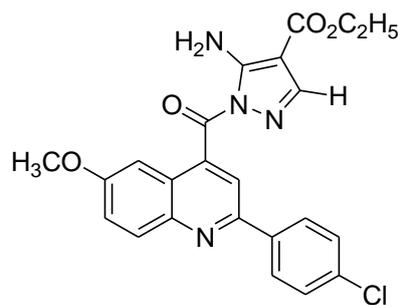
(50b)

(50c)



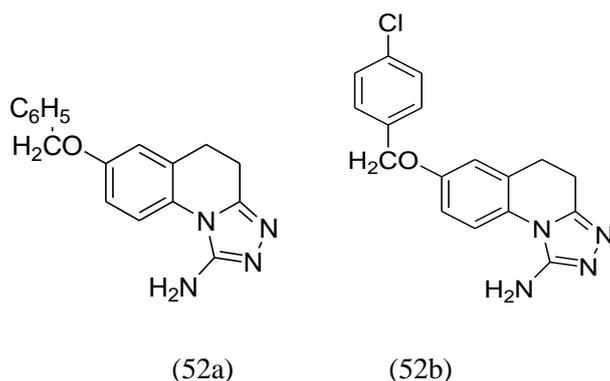
(50d)

El-Feky *et al* studied novel quinolines with anti-inflammatory activity and by using the Pfitzinger reaction, several new quinoline derivatives were synthesized and tested for their anti-inflammatory effect. A docking study on the COX-2 binding pocket was carried out for the target compounds to rationalize the possible selectivity of them against COX-2 enzyme. Compound 51 demonstrated the highest anti-inflammatory activity.⁵²



(51)

Sun et al synthesized a novel series of 7-alkoxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinolines and were evaluated for anti-inflammatory activity through monitoring their ability to inhibit xylene-induced ear edema in mice. Some of the tested compounds exhibited significant activity, and the compounds 52a (7-(benzyloxy)-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolin-1-amine) and 52b (7-(*p*-chlorobenzyloxy)-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolin-1-amine) showed the highest anti-inflammatory activity (52% and 58% inhibition, respectively, at 2 h pre-administration) which were comparable to or even slightly more potent than the Reference drug Ibuprofen (55%).⁴³



(52a)

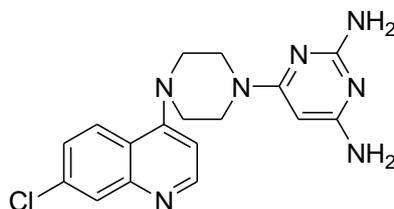
(52b)

Anti-Malarial activity

Malaria, in particular infection with *P.falciparum* (the most lethal of the human malaria parasite species, responsible for nearly one million deaths every year), is one of the most devastating and common infection diseases throughout the world. Malaria claimed the lives of 0.564 million children 5 years younger in 2010. The treatment of this widespread disease has become a growing therapeutic challenge due to rapid appearance of multidrug resistant *Plasmodium falciparum* parasites. *Plasmodium falciparum* species are known for causing the most severe cases and death in humans.⁵³

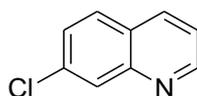
Pretorius et al synthesized a series of quinoline–pyrimidine hybrids and evaluated *in vitro* antimalarial activity. The hybrids were brought about in a two-step nucleophilic substitution process involving quinolone moieties. They were screened alongside Chloroquine (CQ), Pyrimethamine (PM) and fixed combinations thereof against the D10 and Dd2 strains of *Plasmodium falciparum*. The

cytotoxicity was determined against the mammalian Chinese Hamster Ovarian cell line. Compound (53) stood as the most active of all. It was found as potent as CQ and PM against the ^{D10} strain.⁵⁴



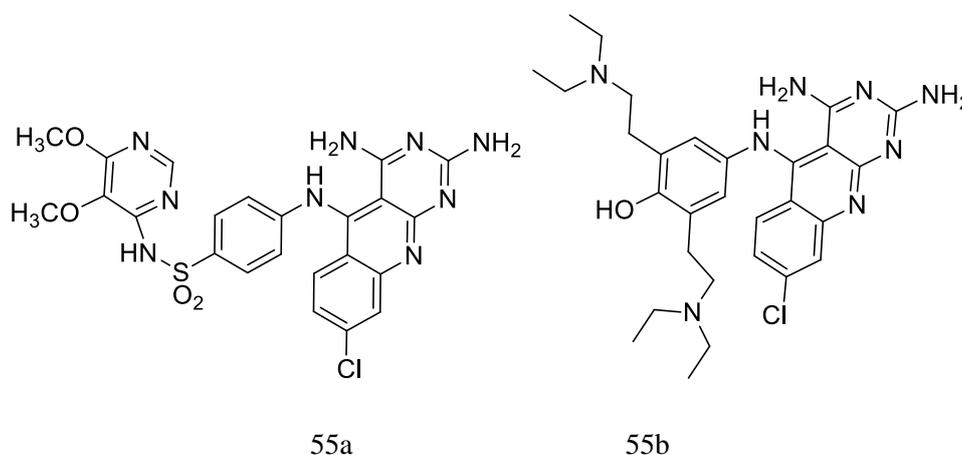
(53)

Madrid *et al* synthesized a B-ring-substituted 4-hydroxyquinolines by simple two step method, allowing analysis of the effect of ring substitutions on inhibition of growth of chloroquine sensitive and resistant strains of *Plasmodium falciparum*, the dominant cause of malaria morbidity. Substituted quinoline rings were found to have significant activity against the drug-resistant strain of *P. falciparum* W2.⁵⁵



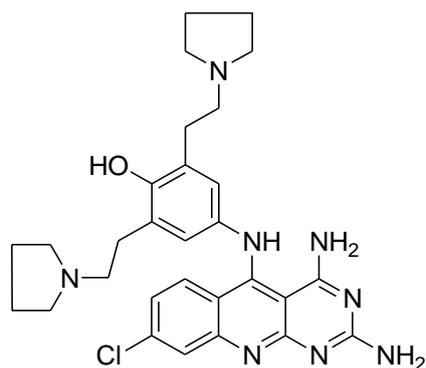
(54)

Joshi *et al* designed a novel 5-substituted amino-2,4-diamino-8-chloropyrimido-[4,5-b]quinolines based on a pharmacophore developed for potent antimalarial activity using Chem-X and MOE softwares. The designed molecules were synthesized by following a novel route and were evaluated by Rane's test for blood schizonticidal activity in mice infected by *Plasmodium berghei*. Based on the Mean Survival Time (MST) data, of the nine compounds evaluated, three had curative potential when compared with chloroquine.⁵⁶



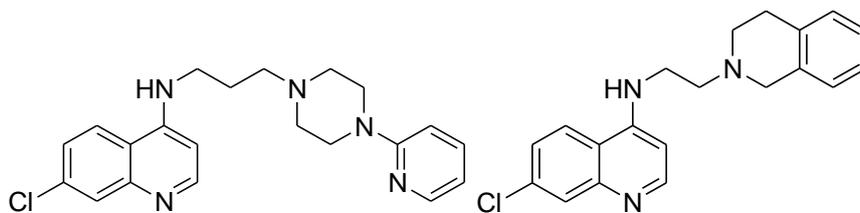
55a

55b



(55c)

Kumar *et al* synthesized a new side chain modified 4-aminoquinoline derivatives and quinoline–acridine hybrids and evaluated *in vitro* against NF 54 strain of *Plasmodium falciparum*. Among the evaluated compounds, compound 17 (MIC = 0.125 $\mu\text{g}/\text{mL}$) was equipotent to standard drug CQ (MIC = 0.125 $\mu\text{g}/\text{mL}$) and compound 21 (MIC = 0.031 $\mu\text{g}/\text{mL}$) was four times more potent than CQ.⁵⁷



(56a)

(56b)

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