Biological Activities of Quinoline Derivatives

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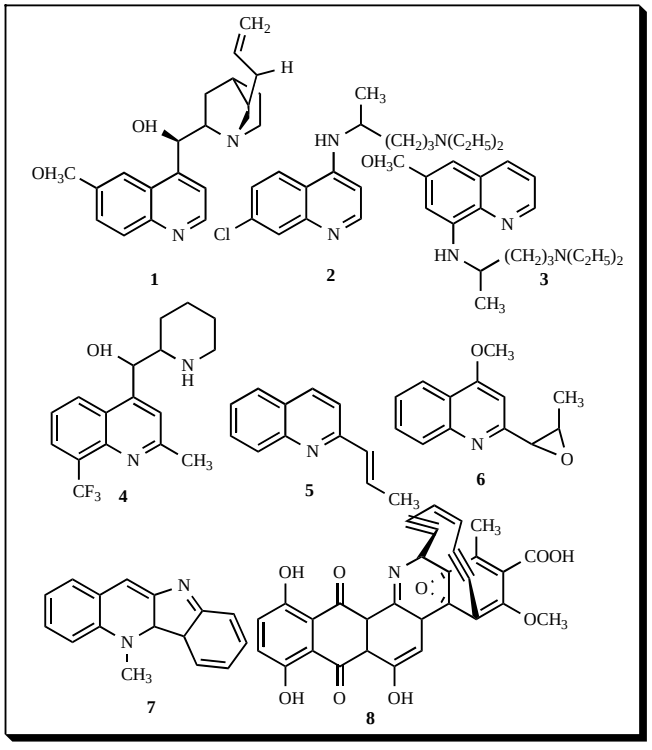
Abstract: Quinoline and its fused heterocyclic derivatives tested with diverse pharmacological activity constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. The present review provides an in depth view of work done so far on quinolines and its biological activities covering anticancer, antimycobacterial, antimicrobial, anticonvulsant, antiinflamatory and cardiovascular activities.

Keywords: Quinoline, anticancer, antimycobacterial, anticonvulsant, antibacterial activity, cardiovascular activities.

INTRODUCTION

Quinoline and its derivatives have always attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties. Apart from classical method for the synthesis of quinoline ring available like Skraup, Doebner-von Miller, Friedländer, Pfitzinger, Conrad-Limpach, Combes syntheses [1]. Various new methods have been developed which employed metallic or organometellic reagents such as CuCN, LiCl [2]. Ruthenium (III) chloride $RuCl_3.nH_2O/3PPh_3$ [3] Ytterbium (III) triflate $Yb(OTf)_3$ [4], Tungsten vinylidene complex $W(CO)_5(THF)$ [5], Boron trifluoride etherate $BF_3.OEt_2$ [6,7], Benzotriazoleiminium salts etc. [8] for the synthesis of quinoline derivatives. Moreover, the quinoline ring system occurs in various natural products, especially in alkaloids and is often used for the design of many synthetic compounds with diverse pharmacological properties. There are number of natural products of quinoline skeleton used as a medicine or employed as lead molecule for the development newer and potent molecules.

For example, quinine (Structure **1**) was isolated as the active ingredient from the bark of Cinchona trees and has been used for the treatment of malaria. Its structure determination and SAR studies resulted in discovery of newer antimalarial drugs like chloroquine (Structure **2**), primaquine (Structure **3**), mefloquine (Structure **4**) [9] etc. Chimanine alkaloids, simple quinolines (Structure **5**-**6**), isolated from the bark of *Galipea longiflora* trees of the Rutaceae family are effective against the parasites *Leishmania* sp., which are the agents of leishmaniasis [10], Cryptolepine (Structure **7**) is an indoloquinoline alkaloid found in the west African climbing shrub *Cryptolepis sanguinolenta* [11]. Dynemicin A (Structure **8**) and Streptonigrin (Structure **9**), naturally occurring members of the class of antitumor antibiotics [12,13]. The 8- (diethylaminohexylamino)-6-methoxy-4-methyl quinoline (Structure **10**) is highly effective against the protozoan parasite *Trypanosoma cruzy*, which is the agent of Chagas' disease [14] and the 2-(2-methylquinolin-4-ylamino)-*N*phenylacetamide (Structure **11**) is more active than the standard antileishmanial drug.



BIOLOGICAL ACTIVITIES

Anticancer

Quinoline derivatives fused with various heterocycles haves displayed potent anticancer activity targeting different sites like topoisomerase I, telomerase, farnasyl transferase,

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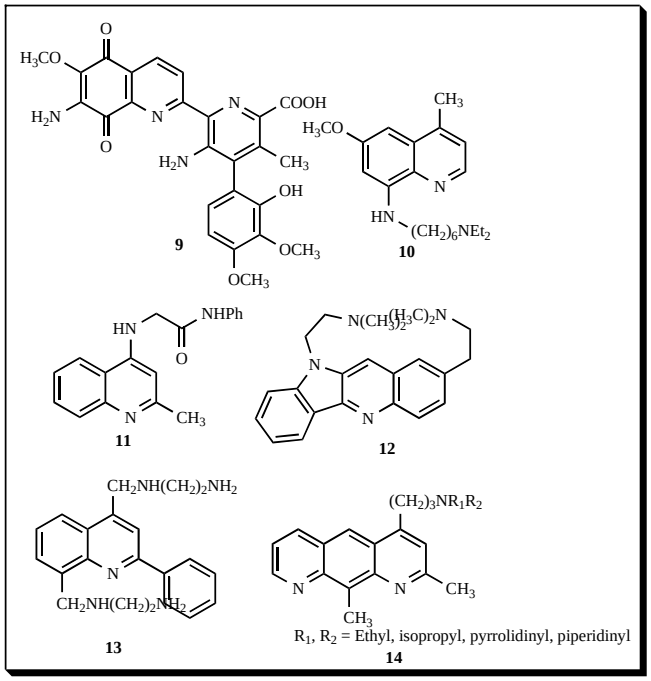
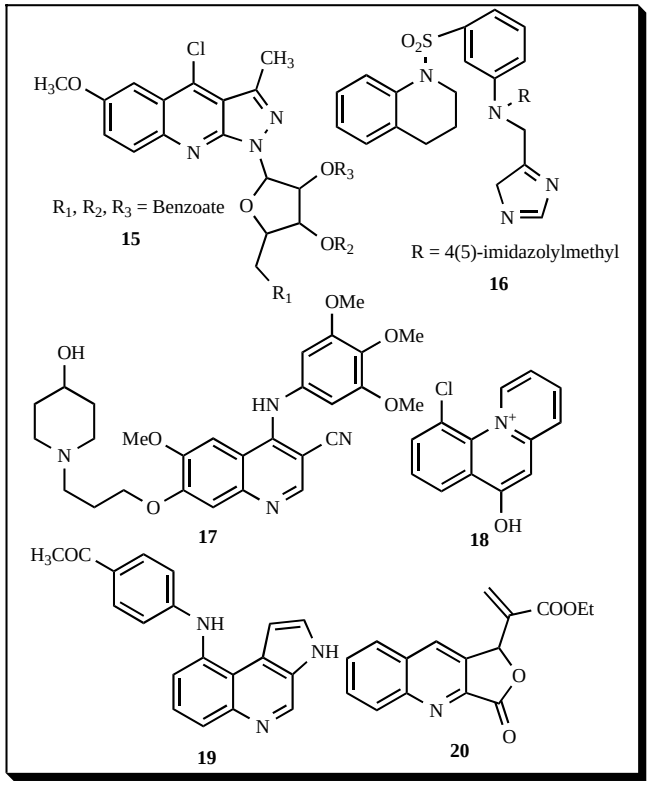
Src tyrosine kinase, protein kinase CK-II etc. Indole fused 10H-indolo[3,2-b]quinoline bearing bis-dimethylaminoethyl chain have been synthesized and evaluated for anticancer activity by Vittorio Caprio *et al.* [15] and compound (Structure **12**) was found to be act on telomerase with IC_{50} 16μM . Intercalation with double stranded DNA is important target for cytotoxicity Yuzi Mikata *et al.* [16] reported the synthesis of new derivatives of 2-phenyl quinoline having [(2-aminoethyl)aminomethyl] group and compound (Structure **13**) showed ability to intercalate into double stranded DNA. Similarly pyridine fused pyrido[3,2-g] quinoline derivative (Structure **14**) showed strong binding to DNA [17]. Various pyrazolo[3,4-b]quinoline ribofuranosides prepared and evaluated by Ronald Wolin *et al.* [18] for their ability to inhibit the nucleotide exchange process on oncogenic Ras gene and compounds (Structure **15**) was found to be most active *in-vitro* studies. A series of 3-imidazolymethylaminophenylsulphonyltetrahydroquinoline designed and synthesized by Charles Z. Ding *et al.* as FTI (farnesyl transferase inhibitors) and compound (Structure **16**) was found to be most active with $FTIC_{50}$ of 0.13 μM [19]. Similarly Src Tyrosine Kinase inhibitors having 4-anilino-3-cyanoquinolines (Structure **17**) moiety were developed with IC_{50} of 5.3 μM [20]. Inhibitors of protein kinase CK-II have been synthesized by Y. Mettey *et al.* [21] and compound (Structure **18**) 6-hydroxy-10-chlorobenzo[c]quinololizinum was found to be most potent inhibitor and exhibited good selectivity for CK-II with IC_{50} 0.005 μM.



Dalla Via *et al.* synthesized 1-[4-(3*H*-pyrrolo[3,2-*f*]quinolin-9-ylamino)-phenyl]-ethanone hydrochloride (Structure **19**) it showed high antiproliferative activity by forming an intercalative complex with DNA and inhibiting DNA topoisomerase II and by blocking the cell cycle in G_2/M phase [22]. *In-vitro* antiproliferative activity 8 Baylis–Hillman adducts and their derivatives against a panel of humor tumor cell lines was studied by Luciana K. Kohn *et al.* [23] and quinoline–phthalide (Structure **20**) derivative exhibited a potent effect on the proliferation of all cell lines. William Kemnitzer *et al.* identified novel apoptosis inducer through caspase and cell-based high-throughput screening assay and compound 1-(4-(1*H*-imidazol-1-yl)benzoyl)-3-cyanopyrrolo[1,2-*a*]quinoline (Structure **21**) was found to be highly active in human breast cancer cells T47D, human colon cancer cells HCT116, and hepatocellular carcinoma cancer cells SNU398 cell lines [24].

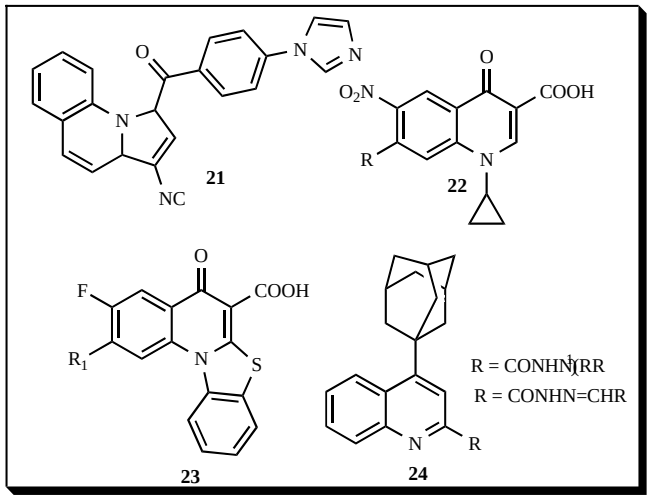


Antimycobacterial Activity

Tuberculosis (TB) has become a global health problem because of lack of proper therapeutic agents for its remedy. There is another serious and alarming problem due to the resurgence of TB especially for the synergy with global human immunodeficiency virus (HIV) and the emergence of multi-drug-resistant (MDR) strains. Thus, there is an urgent need for developing new anti-tubercular drugs which will effectively kill MDR strains, less toxic, shortened duration of therapy, rapid mycobactericidal mechanism of action in the intracellular environment.

In this direction various quinoline containing molecules have been synthesized tested for anti-TB activity all over the world. D. Sriram *et al.* [25] synthesized 48 novel 6-nitroquinolone-3-carboxylic acids derivatives and compound (Structure **22**) having R = (4-((benzo[*d*][1,3]dioxol-5-yl)methyll)piperazin-1-yl) was found to be the most active compound *in vitro* with MIC of 0.08 and 0.16 μM against MTB and MDR-TB, respectively. They also extend their work to synthesized various 2-(sub)-3-fluoro/nitro-5, 12-dihydro-5-oxobenzothiazolo[3,2-*a*]quinoline-6-carboxylic acid and evaluated for *in-vitro* against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB), and *Mycobacterium smegmatis* (MC2).

Compound (Structure **23**) bearing R^1=2-(3-(diethyl carbamoyl)piperidin-1-yl)-) was found to be the most active compound with MIC of 0.18 and 0.08 μM against MTB and MTR-TB [26]. 3D-QSAR analysis has been employed by Rahul Jain and co-worker to understand the relationship between structure and anti-TB activity. They developed new 4-(adamantan-1-yl)-2-substituted quinolines derivatives (Structure **24**) the most potent analog of the series produced 99% inhibition at 1.00 μg/mL against drug-sensitive strain, and MIC of 3.125 μg/mL against isoniazid-resistant TB strain [27].



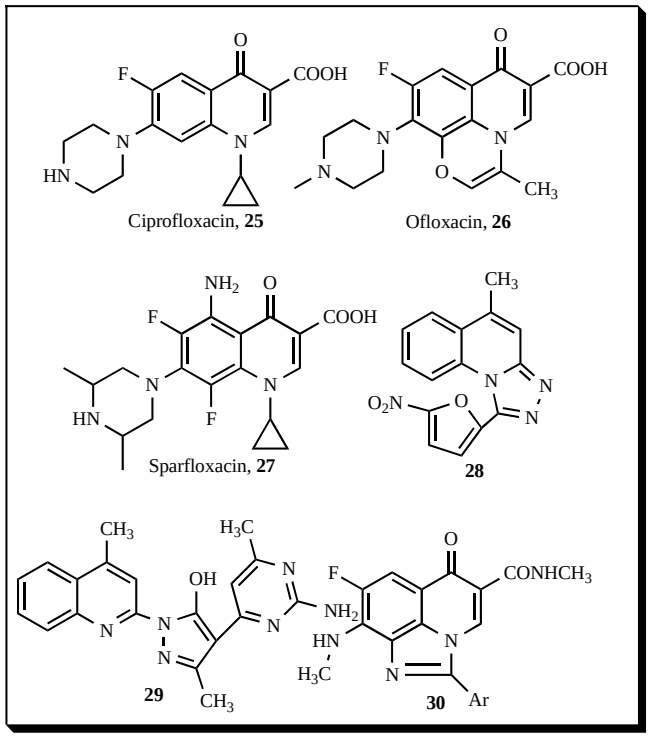
Antimicrobial Activity

The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists

Quinolones [28] is a special structural class of quinoline antimicrobial agents. It is characterized by 1,4-dihydro-4-oxo-3-pyridine carboxylic acid and a fused benzene ring moiety. Extensive SAR have been established on this nucleus and resulted in number of currently marketed synthetic antimicrobial agent like ciprofloxacin (Structure25), ofloxacin (Structure **26**) and sparfloxacin (Structure **27**) etc.

1-aryl / heteroaryl-5 methyl-1, 2, 4-triazolo[4,3-a]quinoline derivatives synthesized and tested *in vitro* for their antibacterial activity and compound (Structure **28**) exhibited MIC 10 μg/ml against salmonella typhae [29]. Shiv P. Singh *et al.* [30] reported 4-(4-pyrozolyl)-2-aminopyrimidines and compound (Structure **29**) showed moderate activity against *C. albicans, A. niger, Salmonella typhae.*

V. Jayathirtha Rao *et al.* [31] reported synthesis of some new multi substituted quinoline by Baylis–Hillman reaction and screened them against no. of Gram-positive organisms, viz., *Bacillus subtilis*, *Bacillus sphaericus*, and *S. aureus*, and three Gram-negative organisms, viz., *Chromobacterium violaceum*, *Klebsiella aerogenes*, and *Pseudomonas aeruginosa* most of compound exerted a wide range of broad spectrum of antibacterial activity. G. Venkat Reddy *et al.* reported a series of novel imidazo fused quinolone carboxamides (Structure **30**) and evaluated against antibacterial activity, derivatives exhibit moderate antibacterial activity [32].



A novel 2-amino-4-(8-quinolinol-5-yl)-1-(p-tolyl)-pyrrole-3-cabonitrile (Structure **31**) was annulated to various fused analogue such as triazole, pyrimidine, pyrazole and imidazole system by S. A. Abdel-Mohsen [33] and screened *in vitro* for their antimicrobial activities against two strains of bacteria and fungi, compound showed moderate to good activity. A. R. Parikh *et al.* [34] synthesized isoxazoline and cyanopyridines bearing 2-chloro-7-methoxyquinoline moiety and screened for antimicrobial activity against *E.coli, S. aureus, A. niger* etc. Compound (Structure **32**) was most active. Acetamides analogues of 2-chloro-8-methyl quinoline (Structure **33**) reported to have antimicrobial activity [35].

Anticonvulsant Activity

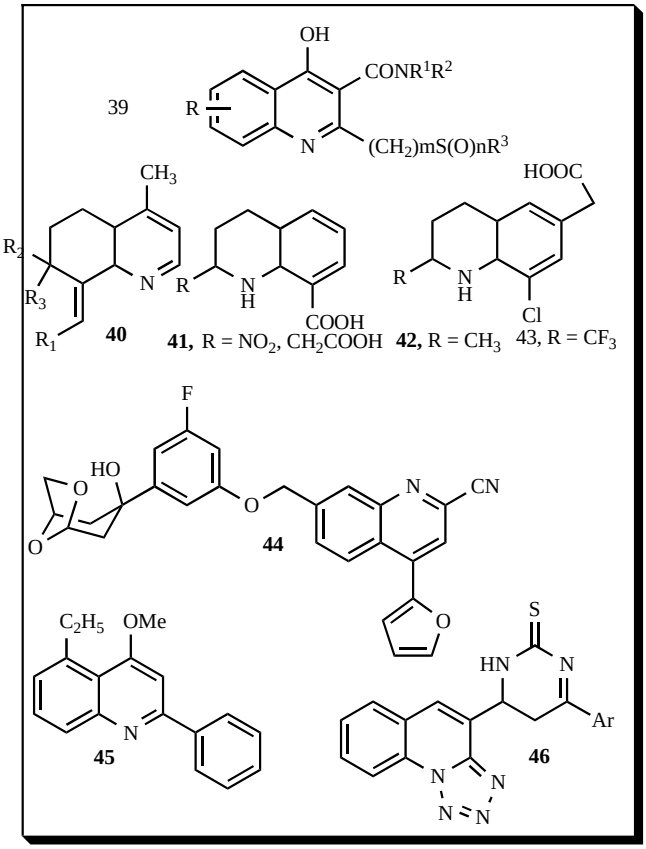
Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity of new compounds.

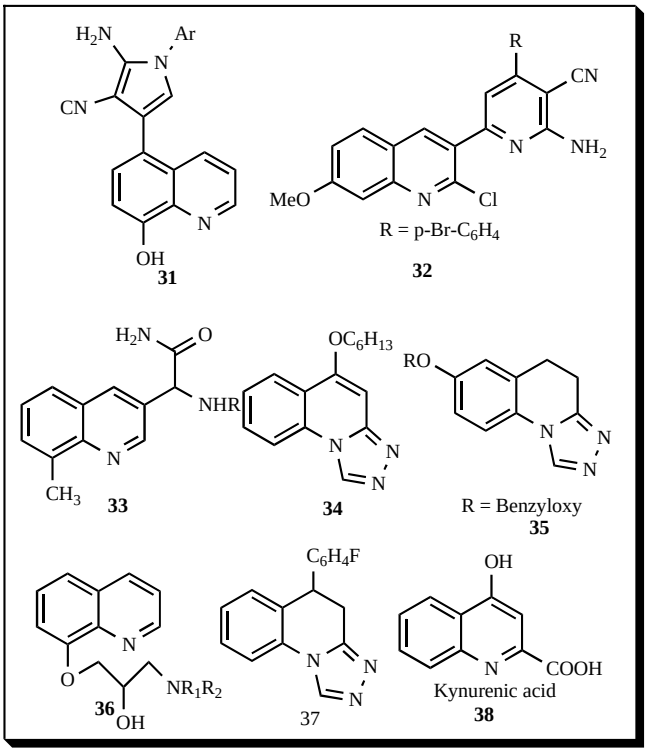
In recent years various molecular modifications of quinoline derivatives have been reported with promising anticonvulsant results. Zhe-Shan Quan *et al.* [36] reported a series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivative with anticonvulsant activity evaluated by the maximal electroshock test (MES) and their neurotoxicities were measured by the rotarod test. 5-hexyloxy-[1,2,4]triazolo[4,3-a] quinoline (Structure **34**) was found to be most potent anticonvulsant, with median effective dose (ED_{50}) of 19.0 mg/kg.

They extended their work to synthesized a series of 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1(2*H*)-

one [37] derivatives and compound 7-benzyloxyl-4,5-dihydro-[1,2,4]thiazolo [4,3-*a*]quinoline-1(2*H*)-one (Structure **35**) was among the most active with (ED_{50}) of 12.3 mg/kg. Derivatives of 8-substituted quinoline were synthesized and tested against seizures induced by maximal electro shock (MES), pentylenetetrazole (scMet) and compound (Structure **36**) 8-(3'-(4''-phenylpiperazino)-2'-hydroxypropyloxy)quinoline was potent in both model of seizure [38].

A fused triazole and triazolone derivatives of quinoline-2(1*H*)-one and their anticonvulsant activity were reported [39]. Results of the study revealed that triazole, but not the triazolone showed stronger anticonvulsant effects and compound (Structure **37**)**,** 5-(*p*-fluorophenyl)-4,5–dihydro-1,2,4-triazolo[4,3-*a*]quinoline, showed the strongest anticonvulsant effect with (ED_{50}) of 27.4mg/kg and 22.0mg/kg in the anti-MES and anti-PTZ test, respectively. Kynurenic acid (Structure **38**) derivatives analogue 4-urea-5,7-dichlorokynurenic acid were synthesized and subsequently screened in mice for anticonvulsant activity by Nichols, *et al.* [40] most of the compound showed excellent anticonvulsant activity.





Antiinflammatory Activity.

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthiritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. Generally aryl or heteroaryl acetic acid derivatives have been exploited for this activity like indomethacin, tolmetin etc. Later on selective legend for COX-2 were developed with low gastrointestinal injury, suppression of TXA2 formation and platelet aggregation.

Various 4–hydroxyquinoline derivatives bearing number of heterocyclic rings derivatives (Structure **39**) were synthesized and evaluated for their analgesic and anti-inflammatory activity by Clemence Francois *et al.* [41] interesting biological results were obtained in *in-vivo* study.

Similarly some new 8–(phenylmethylene)tetrahydroquinoline analogue were synthesized and evaluated for anti-inflammatory activity both *in vivo* and *in vitro*. Compound with general structure (Structure **40**) totally inhibit both 5–LOX and COX in rat polymorphonuclear leukocytes assay (PMN) at 50μM [42]. Quinoline with acidic function were reported by Yasushi Kohno *et al.* [43, 44] as novel substituted 1,2,3,4,-tetrahydroquinoline derivatives and evaluated for disease modifying anti-rheumatic drugs (DMARD). Of these synthesized compounds (Structure **41, 42, 43**), significantly suppressed the swelling of adjunct arthritic rat paw at doses less than 25 mg/kg (acute/chronic).

Ability to inhibit the formation of Leukotrienes via the 5–lipoxygenase enzyme has also been studied as a target for antiinflammatory drugs. Substituted 2–cyanoquinoline derivatives (Structure **44**) represent a distinct class of 5-LOX inhibitors and posses *in vitro* and *in vivo* potency comparable or superior to naphthalenic acid analogue [45]. Li-Jiau

Huang *et al.* [46] reported the synthesis of novel antiplatelet agents 4–alkoxy derivatives and compound (Structure **45**) 5–ethyl–4–methoxy–2–phenyl quinoline was the most potent with an IC_{50} 0.08μM and was about threefold more active than indomethacin. Various tetrazolo[1,5-*a*]quinoline derivatives (Structure **46**) containing pyrimidine ring were reported to possess dual antiinflammatory and antibacterial activity [47].

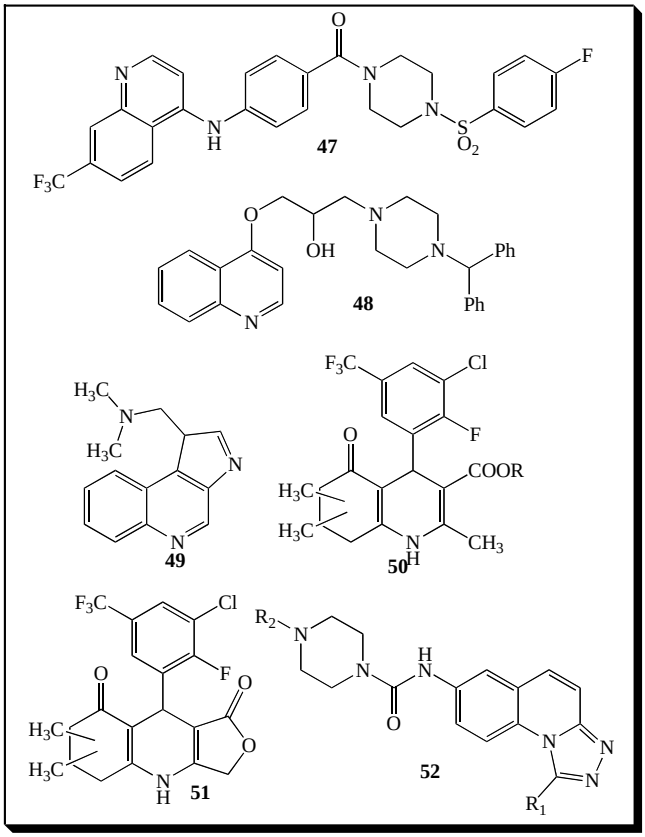
Cardiovascular Activity

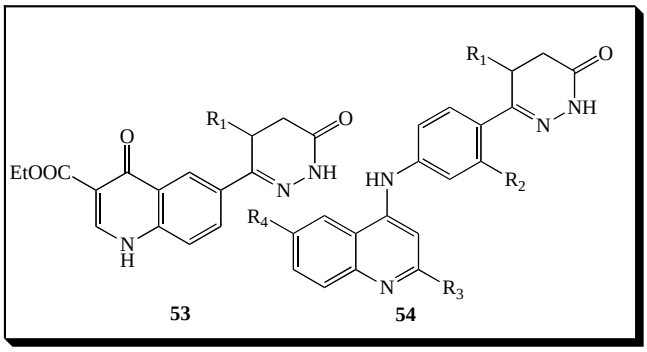
In an attempt to identify potential cardiovascular agent as Ca channel blocker, cAMP phosphodiesterase III etc various chemical modification of quinoline derivatives have attempted with positives results and have come up new lead compounds.

John M. MeCall *et al*. [48] reported synthesis and SAR study on a series of 7- (trifluoromethyl)-4-aminoquinoline and evaluated their hypotensive activity. Compound (Structure **47**) 1-[(4-fluorophenyl) sulphonyl)-4-[4-[(7-(fluoromethyl)-4-quinolinyl] amino] benzoyl] piperazine. i.e. losulazine selected for clinical development and shows hypotensive effect in rat, cat and dog. Some new 4-(diphenyl methyl)-α-[(4-quinolinyloxy]methyl]-1-piperazinethanol derivatives were also exhibit cardiovascular activity on isolated perfused rat and guinea pig heart and compound (Structure **48**) DPI 201-106 showed potent inotropic effect in rat heart [49].

Mannich bases [50] prepared by aminoalkylation of 3H-pyrrolo[3,2-f]quinoline (Structure **49**) showed vasorelexation in the presence of β-blocker propanolol. B. Bahadir *et al.* [51] designed new alkyl 4-(2-fluoro-3-chloro-5-trifluoromethyl-phenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxy-lates (Structure **50**) and 9-(3-chloro-2-fluoro-5-trifluoromethylphenyl)-6,7-dihydrofuro[3,4-*b*]quinoline-1,8-dione (Structure **51**) as a structurally analogue of 1,4-dihydro pyridines and investigated their calcium antagonistic activities on isolated rabbit sigmoid colon and compared with Nifedipine.

Various *N*-(4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolin-7-yl)-2-(piperazin-1-yl)acetamide (Structure **52**) have been synthesized and their positive inotropic activity was evaluated by measuring left atrium stroke volume on isolated rabbit heart preparations and the most potent derivative showed 13.2% increased stroke volume (milrinone 4.7%) at concentration of 3×10^{-5} M in *in vitro* study [52]. Quinoline having pyridazinone moiety (Structure **53, 54**) were designed and their vasodilator activity was examined on the isolated main pulmonary artery of the rabbit and compounds showed moderate vasorelaxant activity compared with standard drug Milrinone [53].





CONCLUSION

Many researchers have synthesized quinoline and its fused heterocyclic derivatives. These observations have been guiding for the development of new quinoline derivatives that possess varied biological activities i.e. anticancer, antimycobacterial, antimicrobial, anticonvulsant, antiinflamatory and cardiovascular activities. A lot of work have been done and more to go. Development of newer quinolines have immense possibilities and scope for drug development scientist. We have presented a concise compilation of this work to aid in present knowledge and to help researchers to explore an interesting quinoline class.

REFERENCES

[1] Elderfield, R.C. *Heterocyclic compounds.* John-Wiley & Sons: New York, **1960**, Vol. *4*. pp. 6-59.

[2] Swenson, R.E.; Sowin, T.J.; Zhang, H.Q. Synthesis of substituted quinolines using the dianion addition of *N*-Boc-anilines and α-tolylsulfonyl-α,β-unsaturated ketones. *J. Org. Chem.,* **2002**, *67*, 9182-9185.

[3] Cho, C.K; Hooh, B.; Shim, S.C. Synthesis of quinolines by ruthenium- catalyzed heteroannulation of anilines with 3- amino-1-propanol. *J. Heterocycl. Chem*., **1999**, *36*, 1175-1178.

[4] Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis*, **1995**, 801-806.

[5] Sangu, K.; Fuchibe, K.; Akiyama, T. A Novel approach to 2-arylated quinolines: electrocyclization of alkynyl imines via vinylidene complexes. *Org. Lett*., **2004**, *6*, 353-355.

[6] Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. Synthesis of tetrahydroquinoline derivatives from α-CF_3-N-arylaldimine and vinyl ethers. *Tetrahedron Lett.*, **1998**, *39*, 5765-5768.

[7] Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. Synthesis of 2-CF_3-tetrahydroquinoline and quinoline derivatives from CF_3-*N*-Arylaldimine. *J. Org. Chem.*, **2000**, *65*, 5009-5013.

[8] Katrizky, A.R.; Arend, M. A. Convenient and highly regioselective one-pot synthesis of quinolines by addition of a vilsmeier-type reagent to N-Arylimines, *J. Org. Chem.* **1998,** *63*, 9989-9991.

[9] Delgado, J.N.; Remers, W.A. *Wilson and Gisvold's Text Book of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed. Lippincott Williams & Wilkins **1998**, pp. 235-252.

[10] Fournet, A.; Barrios, A.A.; Muñoz, V.; Hocquemiller, R.; Cavé, A.; Richomme, P.; Bruneton. *J. Antimicrob. Agents Chemother*., **1993**, *37*, 859-863.

[11] Wright, C.W.; Addae-Kyereme, J.; Breen, A.-G.; Brown, J.E.; Cox, M.F.; Croft, S.L.; Gökçek, Y.; Kendrick, H.; Phillips, R.M.; Pollet, P.L. Synthesis and evaluation of cryptolepine analogues for their potential as new antimalarial agents. *J. Med. Chem*., **2001**, *44*, 3187-3194.

[12] Nicolaou, K.C.; Gross, J.L.; Kerr, M.A. Synthesis of novel heterocycles related to the dynemicin a ring skeleton. *J. Heterocycl. Chem*., **1996**, *33*, 735-746.

[13] Bringmann, G.; Reichert, Y.; Kane, V. The total synthesis of streptonigrin and related antitumor antibiotic natural products. *Tetrahedron*, **2004**, *60*, 3539-3574.

[14] Chiari, E.; Oliveira, A.B.; Prado, M.A.F.; Alves, R.J.; Galvão, L.M.C.; Araujo, F.G. *Antimicrob. Agents Chemother*., **1996**, *40*, 613-615.

[15] Vittorio, C.; Guyen, B.; Opoku-Boahen, Y.; Mann, J.; Gowan, S.M.; Lloyd, M.; Martin, A.R.; Stephen, N. A novel inhibitor of human telomerase derived from 10*H*-indolo[3,2-*b*]quinoline. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 2063-2066.

[16] Mikata, Y.; Mika, Y.; Shun-ichiro, O.; Ichiro, O.; Kawasaki, M.; Maeda, M.; Shigenobu, Y. Effect of side chain location in (2-aminoethyl)aminomethyl-2-phenylquinolines as antitumor agents. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1243-1248.

[17] Sharples, D, Spengler, C.; Molnar, J.; Zsuzsanna, A.; Molnar, A.; Kiss, J.T.; Szabo, J.A.; Hilgeroth, A.; Gallo, S.; Mohamoud, A.; Barbe, J. The interaction between resistance modifiers such as pyrido[3,2-g]quinoline, aza-oxafluorene and pregnane derivatives with DNA, plasmid DNA and tRNA. *Eur. J. Med. Chem*., **2005**, *40*,195-202.

[18] Ronald, W.; Wang, D.; Kelly, J.; Afonso, A.; Linda, J.; Paul, K.; McPhail, A.T. Synthesis and evaluation of pyrazolo[3,4-b]quinoline ribofuranosides and their derivatives as inhibitors of oncogenic *Ras*. *Bioorg. Med. Chem. Lett*., **1996**, *6*, 195-200.

[19] Charles, Z.D.; Hunt, J.T.; Ricca, C.; Manne, V. 3-Imidazolylmethyl amino phenyl sulfonyl tetra hydroquinolines, a novel series of farnesyltransferase inhibitors. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 273-275.

[20] Yanong D.W, Miller, K.; Boschelli, D.H.; Fei, Y.; Biqi, W.; Floyd, M.B.; Powell, D.W.; Wissner, A.; Weber, J.M.; Boschelli, F. Inhibitors of Src tyrosine kinase: the preparation and structure–activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 2477-2480.

[21] Mettey, Y.; Vierfond, J.M. Benzo[*c*]quinoliziniums: A new family of inhibitors for protein kinase CK II. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 961-964.

[22] Dalla, V.L.; Gia, O.; Gasparotto, V.; Ferlin, M.G. Discovery of a new anilino-3*H*-pyrrolo[3,2-*f*]quinoline derivative as potential anticancer agent. *Eur. J. Med. Chem*., **2008**, *43*, 429-434.

[23] Kohn, L.K.; Pavam, C.H.; Veronese, D.; Coelho, F.; De Carvalho, J.E.; Almeida, W.P. Antiproliferative effect of Baylis–Hillman adducts and a new phthalide derivative on human tumor cell lines. *Eur. J. Med. Chem*., **2006**, *41*, 738-744.

[24] Kemnitzer, W.; Kuemmerle , J.; Jiang, S.; Zhang, H-Z.; Sirisoma, N.; Kasibhatla, S.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, X.Z. Discovery of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinolines as a new series of apoptosis inducers using a cell- and caspase-based high-throughput screening assay. Part 1: Structure–activity relationships of the 1- and 3-positions. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 6259-6264.

[25] Senthilkumar, P.; Dinakaran, M.; Yogeeswari, P.; Sriram, D.; China, A.; Nagaraja, V. Synthesis and antimycobacterial activities of novel 6-nitroquinolone-3-carboxylic acids. *Eur. J. Med. Chem.*, **2009**, *44*, 345-358.

[26] Senthilkumar, P.; Dinakaran, M.; Yogeeswari, P.; Sriram, D.; China, A.; Nagaraja, V. Novel ofloxacin derivatives: Synthesis, antimycobacterial and toxicological evaluation. *Bioorg. Med. Chem. Lett*., **2008**, *18*, 1229-1236.

[27] Nayyar, A.; Monga, V.; Malde, A.K.; Coutinho, E.; Jain, R. Synthesis, anti-tuberculosis activity, and 3D-QSAR study of 4-(adamantan-1-yl)-2-substituted quinolines, *Bioorg. Med. Chem.*, **2007**, *15*, 626-640.

[28] Delgado, J.N.; Remers, W.A. *Wilson and Gisvold's Text Book of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed. Lippincott Williams & Wilkins, **1998**, pp.197-202.

[29] Sadana, A.K.; Mirza, Y.; Om, P. Hypervalent iodine mediated synthesis of 1-aryl/hetryl-1,2,4-triazolo[4,3-a] pyridines and 1-aryl/hetryl 5-methyl-1,2,4-triazolo[4,3-a]quinolines as antibacterial agents. *Eur. J. Med. Chem.*, **2003**, *38*, 533-536.

[30] Singh, S.P.; Batra, H.; Naithani, R.; Om, P. *Indian J. Heterocycl. Chem*., **1999**, *9*, 73-74.

[31] Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B.A.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U.S.N.; Rao, V.J. Synthesis of multisubstituted quinolines from Baylis–Hillman adducts obtained from substituted 2-chloronicotinaldehydes and their antimicrobial activity. *Bioorg. Med. Chem*., **2006**, *14*, 4600-4609.

[32] Reddy, V.G.; Kanth, R.S.; Maitraie, D.; Narsaiah, B.; Rao, S.P.; Kishore, K.H.; Murthy, U.S.; Ravi, B.; Ashok, K.B.; Parthasarathy, T. Design, synthesis, structure-activity relationship and antibacterial activity series of novel imidazo fused quinolone carboxamides. *Eur. J. Med. Chem.*, **2009**, *44*, 1570-1578.

[33] Abdel-Mohsen. S.A. Synthesis, Reactions and Antimicrobial Activity of 2-Amino-4-(8-quinolinol-5-yl)-1-(p-tolyl)-pyrrole-3-carbonitrile. *Bull. Korean Chem. Soc*. **2005**, *26*, 719-726.

[34] Khunt, R.C.; Datta, N.J.; Bharmal, F.M.; Mankad, G.P.; Parikh, A.R. *Indian J. Heterocycl. Chem*., **2000**, *10*, 97-100.

[35] Bharmal, F.M.; Kaneriya, D.J.; Parekh, H.H. *Indian J. Heterocycl. Chem*., **2003,** *12*, 279-280.

[36] Guo, L-J.; Wei, C-X.; Jia, J-H.; Zhao, L-M.; Quan, Z-S. Design and synthesis of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives with anticonvulsant activity. *Eur. J. Med. Chem*., **2009**, *44*, 954–958.

[37] Jin, H-G.; Sun, X-Y.; Chai, K-Y.; Piao, H-R.; Quan, Z-S. Anticonvulsant and toxicity evaluation of some 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline-1(2*H*)-ones. *Bioorg. Med. Chem*., **2006**, *14*, 6868-6873.

[38] Murugananthamn, N.; Sivakumar, R.; Anbalagan, N.; Gunasekaran, V.; Leonard, J.T. Synthesis, Anticonvulsant and Antihypertensive Activities of 8-Substituted Quinoline Derivatives. *Biol. Pharm. Bull.*, **2004**, *27*, 1683-1687.

[39] Guan, L-P.; Jin, Q-H.; Tian, G-R.; Chai, K-Y.; Quan, Z-S. Synthesis of some quinoline-2(1***H***)-one and 1, 2, 4 - triazolo [4 , 3 -***a***] quinoline derivatives as potent anticonvulsants, *J. Pharm. Pharmaceut. Sci*., **2007**, *10*, 254-262.

[40] U.S Patent Documents: 4788188; 5017576.

[41] Clemence, F.; Martret, O.L.; Delevallee, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. 4-Hydroxy-3-quinolinecarboxamides with antiarthritic and analgesic activities, *J. Med. Chem.*, **1988**, *31*, 1453–1462.

[42] Calhoun, W.; Carlson, R.P.; Crossley, R.; Datko, L.J.; Dietrich, S.; Healtheringtoj, K.; Marshall, L.A.; Meade, P.J.; Opalko, A.; Shephard, R.G. Synthesis and Antiinflammatory Activity of Certain 5,6,7,8-Tetrahydroquinolines and Related Compounds. *J. Med. Chem*., **1995**, *38*, 1473-1481.

[43] Kohno, Y.; Awano, K.; Miyashita, M.; Fujimori, S.; Kuriyama, K.; Sakoe, Y.; Kudoh, S.; Saito, K.; Kojima, E. Synthesis and antirheumatic activity of novel tetrahydroquinoline-8-carboxylic acid derivatives. *Bioorg. Med. Chem. Lett*., **1997**, *7*, 1515-1518.

[44] Kohno, Y.; Awano, K.; Miyashita, M.; Ishizaki, T.; Kuriyama, K.; Sakoe, Y.; Kudoh, S.; Saito, K.; Kojima, E. Synthesis and antirheumatic activity of novel tetrahydro-6-quinolineacetic acid derivatives. *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 1519-1524.

[45] Dube, D.; Blouin, M.; Brideau, C.; Chan, C-C.; Desmarais, Y.; Ethier, D.; Falgueyret, J-P.; Friesen, R.W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R.N. Quinolines as po-

tent 5-lipoxygenase inhibitors: Synthesis and biological profile of L-746,530. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1255-1260.

[46] Ko, T.C.; Hour, M.J.; Lien, J.C.; Teng, C.M.; Lee, K.H.; Kuo, S.C.; Huang, L.J. Synthesis of 4-alkoxy-2-phenylquinoline derivatives as potent antiplatelet agents. *Bioorg. Med. Chem. Lett*., **2001**, *11*, 279-282.

[47] Bekhit, A.A.; El-Sayed, O.A.; Aboulmagd, E.; Park, J.Y. Tetrazolo[1,5-*a*]quinoline as a potential promising new scaffold for the synthesis of novel anti-inflammatory and antibacterial agents. *Eur. J. Med. Chem.*, **2004**, *39*, 249-255.

[48] McCall, J.M.; Brink, R.E.; Kamdar, B.V.; Ska-Letzky, L.L.; Perricone, S.C.; Piper, R.C.; Delehonty, P.J. 7-(Trifluoromethyl)-4-aminoquinoline hypotensives: novel peripheral sympatholytics. *J. Med. Chem.*, **1986**, *29*, 133-137.

[49] Sircar, I.; Haleen, S.J.; Burke, S.E.; Barth, H.; Synthesis and biological activity of 4-(diphenylmethyl)-.alpha.-[(4-quinolinyloxy-)methyl]-1-piperazineethanol and related compounds. *J. Med. Chem*., **1992**, *35*, 4442–4449.

[50] Ferlin, M.G.; Chiarelotto, G.; Antonucci, F.; Caparrotta, L.; Froldi, G. Mannich bases of 3*H*-pyrrolo [3,2-*f*]quinoline having vasorelaxing activity. *Eur. J. Med. Chem.*, **2002**, *37*, 427-434.

[51] Bülbül, B.; Öztürk, G.S.; Vural, M.; Şimşek, R.; Sarioğlu, Y.; Linden, A.; Ülgen, M.; Şafak, C. Condensed 1,4-dihydropyridines with various esters and their calcium channel antagonist activities. *Eur. J. Med. Chem*., **2009**, *44, 2052-2058*.

[52] Zhang, C-B.; Xun, C.; Hong, L.; Quan, Z-S.; Piao, H-R. Synthesis and positive inotropic activity of *N*-(4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolin-7-yl)-2-(piperazin-1-yl) acetamide derivatives. *Bioorg. Med. Chem. Lett*., **2008**, *18*, 4606-4609.

[53] Abouzid, K.; Hakeem, M.A.; Khalil, O.; Maklad, Y. Pyridazinone derivatives: design, synthesis, and *in-vitro* vasorelaxant activity. *Bioorg. Med. Chem.*, **2008**, *16*, 382-389.

Received: July 01, 2009 Revised: October 05, 2009 Accepted: October 05, 2009