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QUINOLINE: A DIVERSE THERAPEUTIC AGENT

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Keywords:

Antimalarial, Anticancer, Antibacterial, Anthelmintic, Antiviral, Antifungal

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ABSTRACT: Quinoline and its derivatives are diverse pharmacological agents. They play a vital role in the development of new therapeutic agents. Many new therapeutic agents have been developed by using quinoline nucleus. Hence quinoline and its derivatives constitute an important class of heterocyclic compounds for the new drug development. Quinoline is also known as 1-azanapthalene and many researchers have synthesized large number of quinoline derivatives. Different synthetic routes have been developed by these researchers for the synthesis of quinoline derivatives. These derivatives have also been evaluated for the relevant biological activity by *in vitro* as well as *in vivo* methods. The present review focuses on detailed work done so far on the quinoline and its derivatives in the search of new therapeutic agents. The review covers the synthesis as well as biological activities of quinoline derivatives such as antimalarial, anticancer, antibacterial, anthelmintic, antiviral, antiprotozoal, antifungal, anti-inflammatory, analgesic, cardiovascular, reproductive, central nervous system activity, hypoglycemic and miscellaneous activity.

INTRODUCTION: Quinoline a nitrogen containing heterocyclic compound is known for its diverse therapeutic potential . The derivatives of quinoline have been synthesized by many routes in the search of potent therapeutic agents. Quinoline has a molecular formula C_9H_7N and molecular weight of 129.16 [1]. Quinoline was first extracted from coal tar in 1934 by Friedel Ferdinand Runge. Coal tar remains the principal source of commercial quinoline. Quinolones are synthesized from simple anilines using a number of named reactios for example combes synthesis, Conrad limpach synthesis, Doebner reaction, Doebner miller reaction, Gould Jacobs reaction and Skraup synthesis [2].

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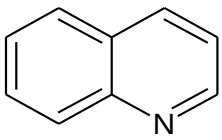
Various new methods have been developed which employed metallic or organometellic reagents such as CuCN, LiCl [3] Ruthenium(III) chloride RuCl3.nH2O/3PPh3 [4] Ytterbium (III) triflate Yb(OTf)3 [5], Tungsten vinylidene complex W(CO)5(THF) [6], Boron trifluoride etherate BF3.OEt2 [7, 8], Benzotriazoleiminiumsalts etc. [9] for the synthesis of quinoline derivatives.



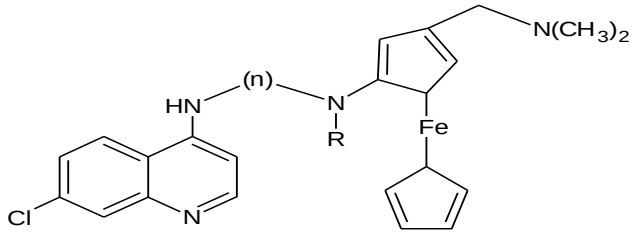
Moreover quinoline also occurs in plants in the form of alkaloids which is used for the design of many synthetic compounds with diverse pharmacological activities. Many natural compounds with quinoline skeleton are used as medicine or as lead compound for design and development of novel and potent molecules. For example quinine was isolated from the bark of cinchone trees and has been employed as an

antimalarial agent. Quinoline has also been found to possess antimalarial, anticancer, antibacterial, anticonvulsant, cardiotonic, antifungal, anthelmintic, anti-inflammatory and analgesic activity.

Biological activities:

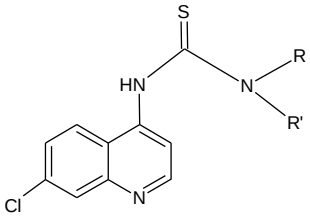
Antimalarial activity

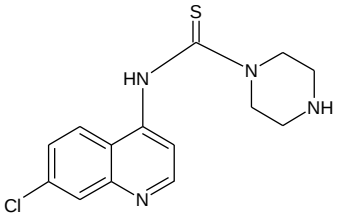
- Analogues of ferrochloroquine by *Chibale et al.* In 2000 also showed antimalarial activity. In these analogues carbon chain of chloroquine is replaced by ferrocenyl group [10].



n = 2-6
R = H, CONHBn

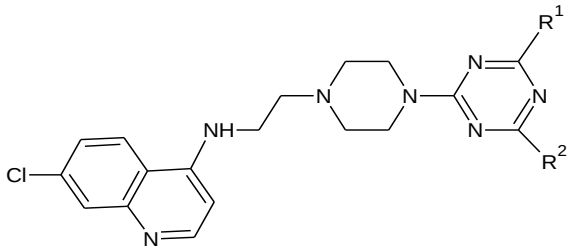
- A series of 7-chloroquinolinyl thioureas were synthesized by *Mahajan et al.* in 2007 as potential antimalarials [11, 12].





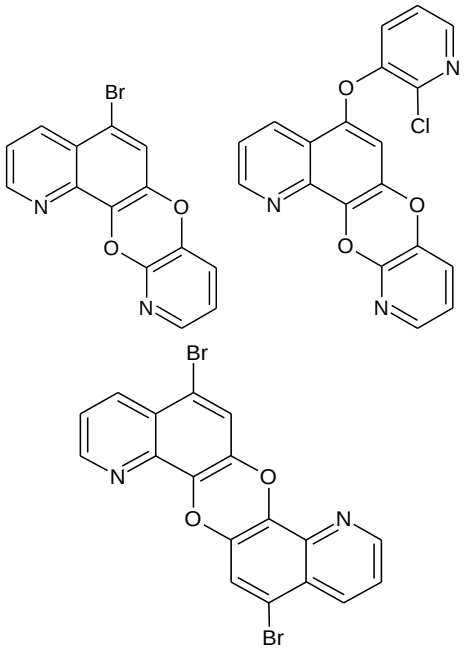
R = $(CH_2)_2OH$, $(CH_2)_3N(Et)_2$, $(CH_2)_3N(Me)_2$, $(CH2)_2NH_2$
R' = H, C_6H_5, $CH_2C_6H_5$, $COOC_2H_5$

- Few 4-aminoquinoline triazines synthesized by *Kumar et al.* in 2008 showed antimmalarial activity against chloroquine sensitive strain 3D7 of *P.falciparum* in an *in-vitro* model [13].

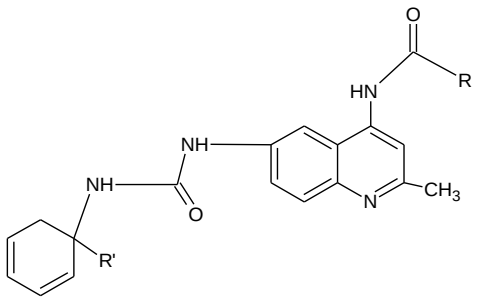


R1 = *p*-Fluoroaniline, Piperidine
R2 = Piperidine, Cyclohexylamine

- Few pyrimidine quinoline hybrids were synthesized by *Acharya et al.* in 2008 evaluated as antimalarial agent against chloroquine susceptible strain of *P. Falciparum* [14, 15].

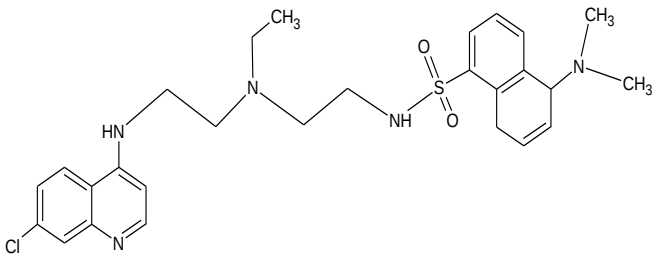


- A series of ureido-4-quinolinamides synthesized by *Modapa et al. in 2009*sowed antimalarial effect at MIC OF 0.25mg/ml against chloroquine sensitive *Plasmodium* falciparum strain[16].

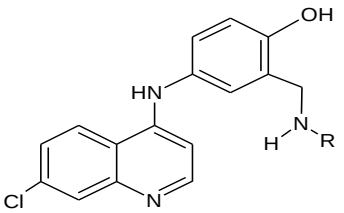


R = Me, Ph, CH_2Cl, 2-ClC_6H_5, 3-ClC_6H_5,2-Furyl ,
R' = F, Cl, Br, CF_3

- Few chloroquinolyl derivatives were synthesized by *Kovi et al. in* 2009 as potent antimalarials at submicromolar levels [17].

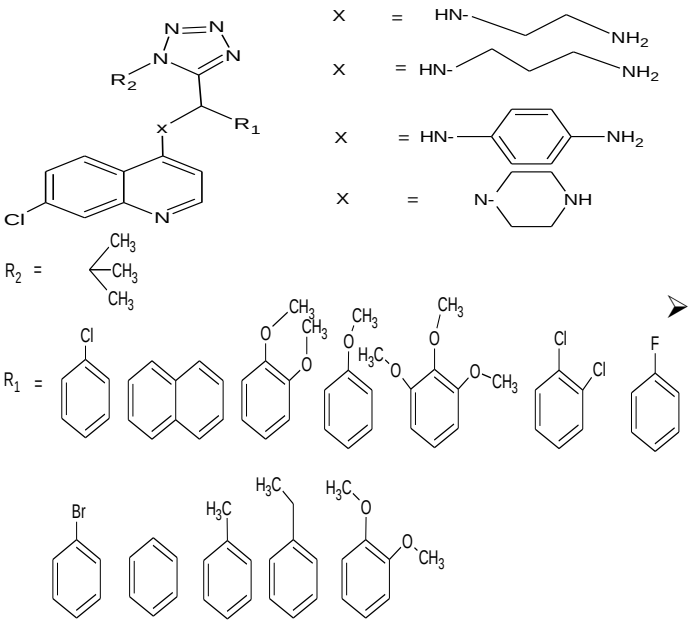


- Some derivatives with 4-anilinoquinoline ring developed by *Singh et al.* in 2011 showed good degree of activity against chloroquine sensitive *P.falciparum* stain as well as against rodent malaria parasite. *P.yoeii* [18].



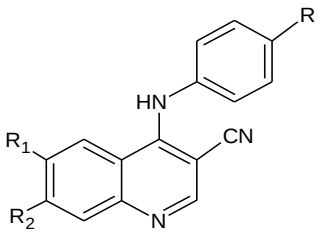
R = H, Phenyl, Butyl, Isopropyl, n-Butyl

- A series of tetrazole derivatives of 4-aminoquinoline were synthesized by *Pandey et al.* in 2013 and screened for their antimalarial activity against both chloroquine sensitive 3D7 and chloroquine resistant K1 strains of *P.falciparum* as well as for cytotoxicity against VERO cell lines [19].



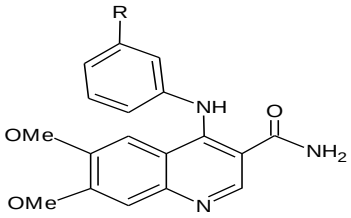
Anticancer activity:

- A series of 4-anilinoquinolines synthesized by *Assefa et al.* in 2003 have been found to be tyrosine kynase inhibitors [20].



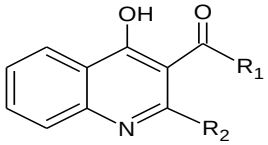
R = 3'-Br, 3'-Cl, 3'-CF3, 3'-CN, R1 = R2 = OMe, OEt

- Certain derivatives of amido-anilinoquinolines developed by *Scott et al*. in 2009 showed antitumor activity by inhibiting CSF-1R kinase [21].



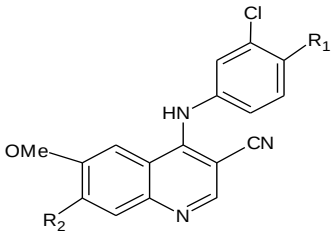
R = F, Cl, Br, CH_3

- Few 4-hydroxyquinolines synthesized by *Mai et al*. in 2009 as histone acetyltransferase (HAT) inhibitors [2]



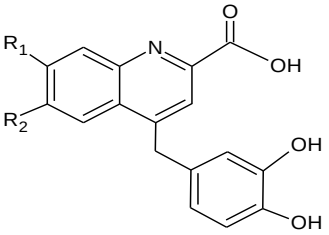
R1 = OH, OEt, R2 = CH_3, C_5H_{11}, $C_{10}H_{21}$, $C_{15}H_{31}$

Novel derivatives of 3-cyanoquinolines were developed by *Miller et al.* in 2009 and evaluated as inhibitors of insulin like growth factors receptors (IGH-1R) for treatment of cancer [23].



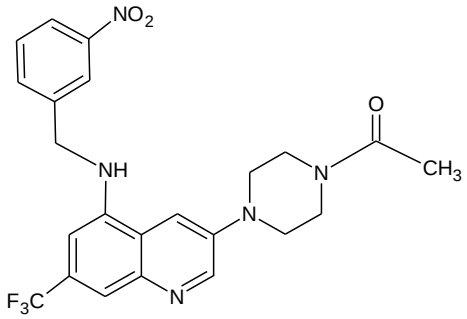
R1 = Substituted-2-thioimidazole,
R2 = Substituted nitrogen heterocyclic

- Potent quinoline carboxylic acids have been developed by *Chen et al*. in 2009 and found to be act by inhibiting insulin like growth factors [24].

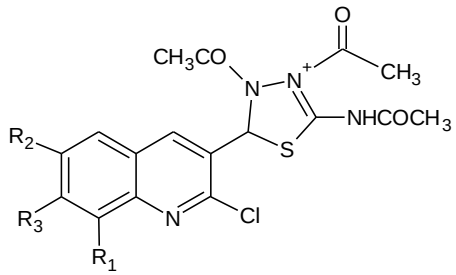


R1 = OH, H, COOH, F, Cl, NH_2,
R2 = OH, OMe, COOH

- Some quinoline derivatives synthesized by *Wang et al*. in 2011 as c- Met kinase inhibitors with IC_{50} less than 1nM. It produces the inhibition of c-Met phosphorylation in c-Met dependent cell lines [25].

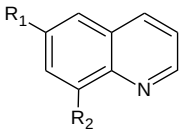


- A series of 6,7,8-substituted thiosemacarbazones of 2-chloro-3-formylquinoline derivatives developed by *Merganakop et al*. in 2012 with anticancer activity. The compounds had a better drug store and clog P values [26].



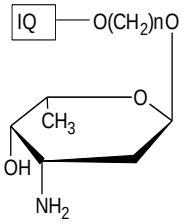
R1 = R2 = R3 = H, CH_3, OCH_3

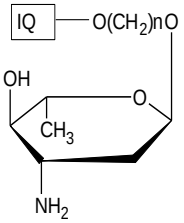
- A novel series of 6,8-disubstituted derivatives of quinoline and 1,2,3,4-tetrahydroquinoline synthesized by *Salih et al*. in 2013 found to be as potent anticancer agent.6,8-dibromo-1,2,3,4-tetrahydroquinoline and 6,8-dimetoxy quinoline showed significant anticancer activities against the tumors cell lines [27].



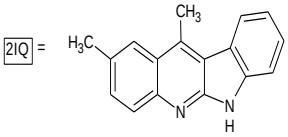
$R_1 = R_2$ = Br_2 , OCH_3

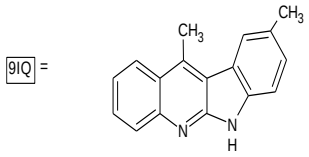
- Certain derivatives of 6H-indolo[2,3-b] quinoline substituted at C-2,C-9 or N-6with O-L-daunosamine or L-acosamine connected with the chromophore via an alkoxy alkyl linker were synthesized by *Katarzyna et al* in 2013 and found to be effective multidrug resistance in cancer treatment. All derivatives showed cytotoxicity against A549, MCF-7 and Hs294T. as well as multidrug resistance in colorectal adenocarcinolma LoVo/DX. Uterine sarcoma MES-SA/DX5 and promyelocytic leukemia. Compounds also induceG_2M or G0/G1 phasse cell cycle arrest in the JurkatT-cell leukemia cells [28].

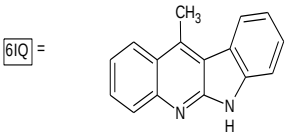




2IQ, n=2 2IQ, n=5
2IQ, n=5 6IQ, n=5
9IQ, n=2 9IQ, n=5
9IQ, =5
6IQ, n=2
6IQ, n=5

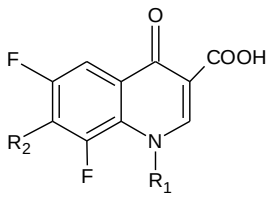






Antibacterial activity:

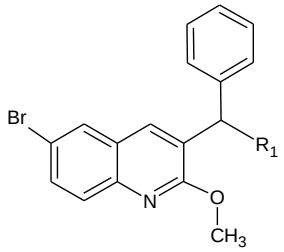
- A series of phenoxy, phenylthio and benzyloxy substituted quinolones were synthesized by *Ma et el*. in 2009 with a good degree of antibacterial activity [29].



R1 = Ethyl, Cyclopropyl, FCH_2CH_2, R_2 = Substituted phenyl

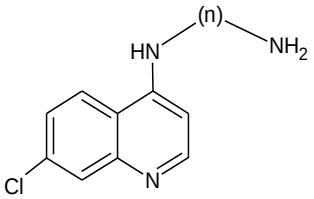
Few 3-benzyl-6-bromo-2-methoxy quinoline derivatives synthesized by *Upadhayaya et al*. in 2009 through molecular modeling techniques found

to be active against *Mycobacterium tuberculosis H37Rv strain* [30].



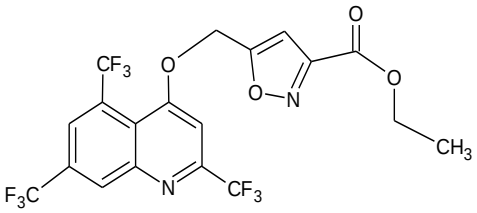
R1 = Imidazolyl, Pyrazolyl, 1-(3-Trifluoromethyl-phenyl)-piperazinyl, 6-Amino-chromen-2-one

- Certain 7-chloroquinoline derivatives developed by *De souza et al*. in 2009 were found to be effective against multi drug resistant tuberculosis [31].

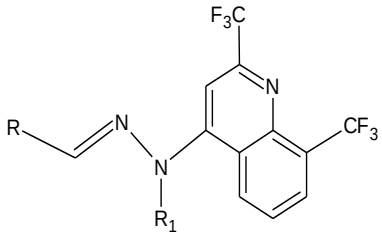


n = 8-10

- A series of quinoline based compounds bearing an isoxazole containing side chain were developed by *Lileinkampf et al*. in 2009 and found to be active against *Mycobacterium tuberculosis* [32].

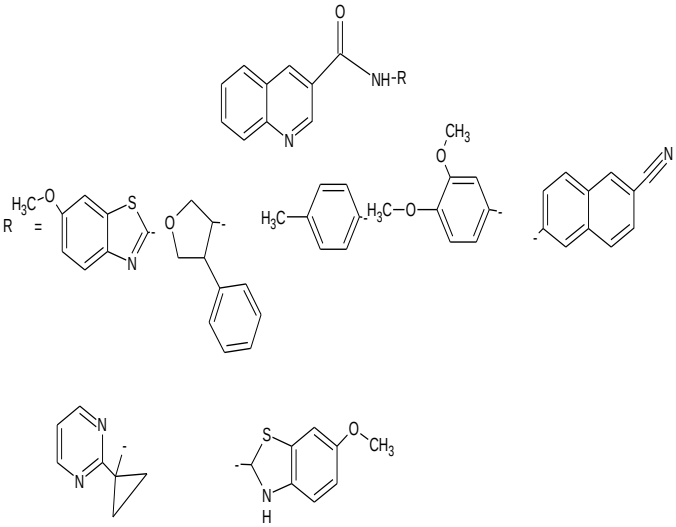


- Some novel quinoline have been designed by *Eswaran et al*. in 2010 as antibacterial agents using mefloquine as the lead, wherein active pharmacophores i.e. hydrazones, ureas, thoureas and pyrazoles have been attached at the fourth position [33].

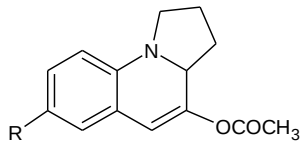


R = R1 = Alkyl, Aryl, Heteroaryl

A series of novel quinoline-6-carboxamides and 2-chloroquinoline-4-carboxamides derivatives of quinoline were synthesized by *Vijaykumar et al*. in 2012 by the reaction of their analogous carboxylic acids with various amine derivatives and evaluated for their antibacterial activity against *Escherchia coli* and *Staphyllococcus aureus* [34].

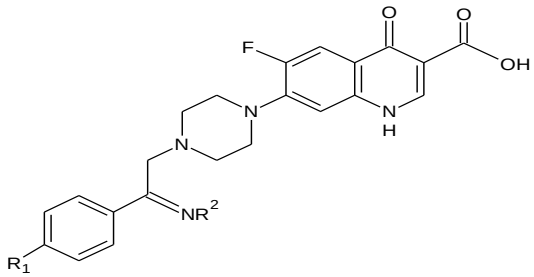


- Few substituted pyrroloquinoline derivatives developed by *Farah et al* in 2014 found to be potent antibacterial agents against strains of *E.coli* and *S.aureus* [35].



R=H, CH_3, Cl

- Novel flouroquinole derivatives were developed by *Patel et al.* in 2014 as active antibacterial agents by studying there *in vitro* activity as well as interaction with topoisomerase II DNA gyrase enzymes by using molecular docking protocol [36].

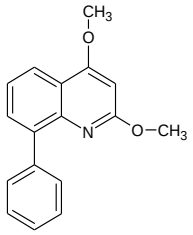


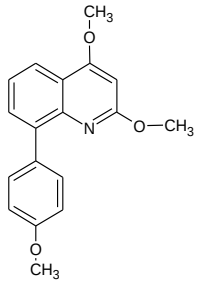
R_1 = -H ,OCH_3, $-CH_3$,NO_2

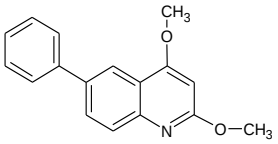
R_2 = $-NHC_6H_5$, $-NH_2$, -OH , $-NHC(=O)NH_2$, $-OCH_3$

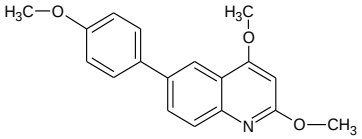
Anthelmintic activity:

A novel series of substituted 2,4-arylquinolines were developed by *Rossiter et al*. in 2005 and found to have a good degree of activity against the nematode *Haemoncus contortus*. These derivatives also showed activity against levamisole, ivermectin and thiabendazole resistant strains of *H. contortus* [37].



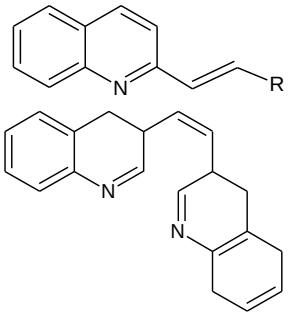




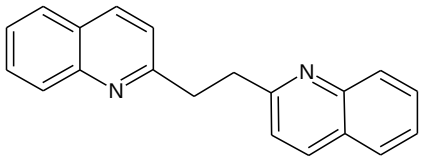


Antiviral activity:

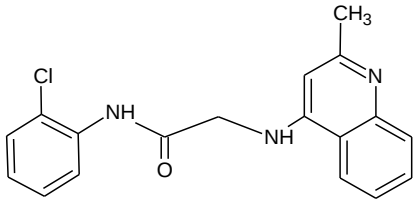
- Some derivatives of mono and polysubstituted quinoline were synthesized by *Fakhfakh et al*. in 2003 and found to be active against *HIV-1* [38, 39, 40].



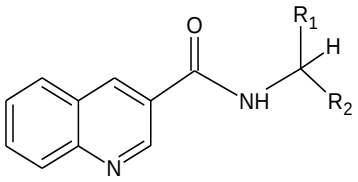
R = C_2H_5, C_3H_7, $C_{12}H_{25}$



- Novel anilidoquinoline derivatives developed by *Ghosh et al*. in 2008 showed good degree of in vitro antiviral activity against *Japanese encephalitis virus* [41].



- Certain quinoline derivatives synthesized by *Chen et al*. in 2009 showed activity by behaving as HIV-1 Tat-TAR interaction inhibitors [42].



- Few desflouroquinoline derivatives developed by *Massari et al*. in 2009 found to be effective antiviral agents in the treatment of HIV infection [43].

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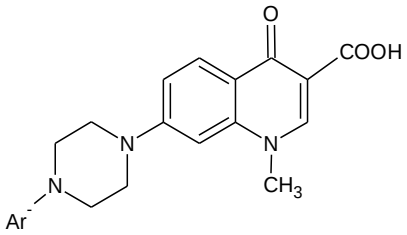
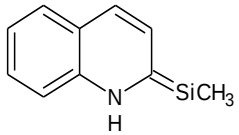
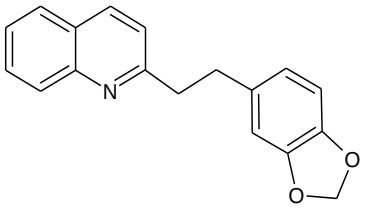


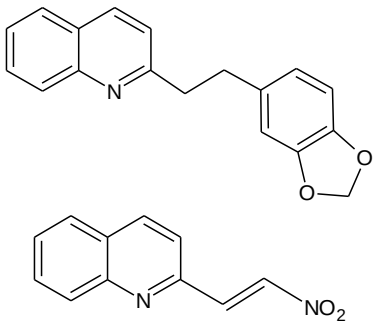
Antiprotozoal activity:

- A novel series of Alkenyl and alkynyl derivatives of quinoline were synthesized by *Fakhfakh et al*. in 2003 and found to be active against the casual agents of cutaneous leishmaniasis, visceral leishmaniasis, African trypanosomiasis and Chagas' disease [44, 45].

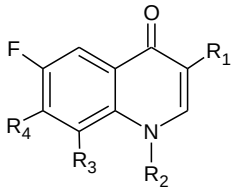




- Some derivatives of quinoline designed by *Franck et al*. showed activity against *Trypanosoma cruzi* [46].



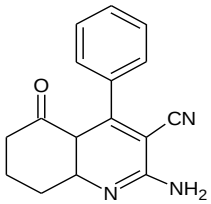
- A few quinolones developed by *Ma et al*. showed activity against *Trypanosoma cruzi* [47].



R_1 = Et, Pr, CH=CH_2
R_2 = COOH, COOMe, COOet, $CONH_2$
R_3 = R_4 = Substituted Phenyl

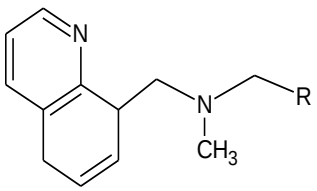
Antifungal activity:

- A series of tetrahydroquinoline derivatives were developed by *Gholap et al*. in 2007 and evaluated as a potent antifungal agent against fungi *Candida albicans , Fusarium oxysporum and Mucor sp* [48].



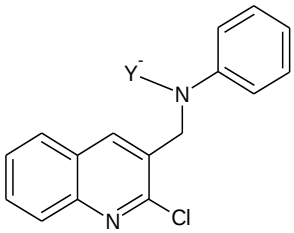
R = 4-Cl, 4-F, 3-NO_2, 4-CH_3, 2-Cl, 3,4,5-$(OCH_3)_3$

- Few derivatives of quinoline were designed by *Kharkar et al*. in 2009 using terbenafine as lead as antifungal agents. The developed compounds contained different bulky aromatic rings in the side chain. These compounds were designed using Leap Frog Drug Design programme [49].



R = 4-Cl, 4-F, 3-NO_2, 4-CH_3, 2-Cl, 3,4,5-$(OCH_3)_3$

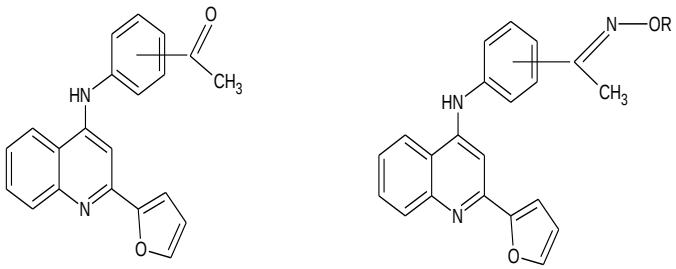
Some secondary amines containing 2-chloroquinoline synthesized by *Kumar et al*. in 2011 and evaluated to be active as antimycotic agent against *Aspergillus niger, As.flavus, Monascus purpureus* and *Penicillium citrinum*. These were non-azole antimycotic agent [50].



X = F, Cl, Br, CH_3, NO_2, Dichloro
Y = H, CH_3

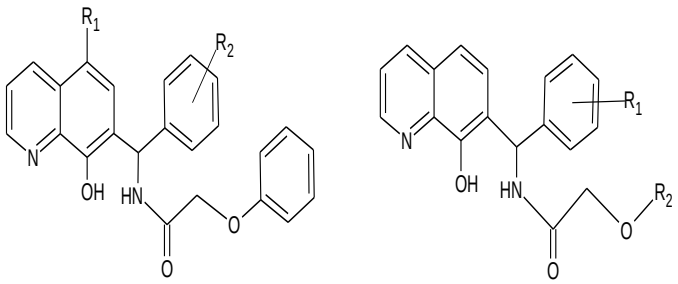
Antiinflammatory activity:

- A novel series of 2-(furan-2-yl)-4-phenoxyquinoline derivatives were synthesized by *Chen et al*. in 2006 and found to be as inhibitors of lysozyme and β-glucoronidase [51, 52].



R = H, CH3

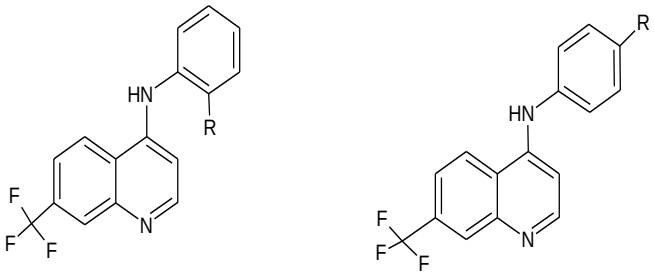
- Few quinoline derivatives developed by *Gilbert et al*. in 2008 found to be as amino acetamide inhibitors of Aggecanase-2 for the treatment of osteoarthritis [53, 54].



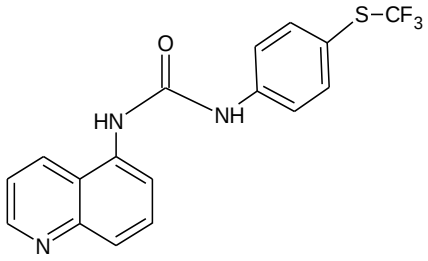
R1 = H, F, NO_2, Cl
R=H, 4-Cl, 4-CH, 4-OCH
R1 = H, 4-OCH_3, 3-NO_2
R2 = Nitrogen Heterocyclic

Analgesic activity:

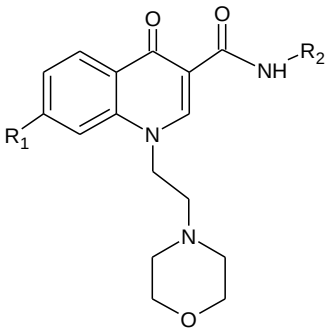
- Certain 4-substituted-7-trifluoromethyl quinoline derivatives have been synthesized by *Abadi et al*. in 2005 and showed a good degree of analgesic actrivity. The activity is attributed to their notric oxide releasing properties [55].

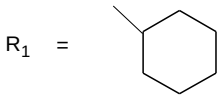


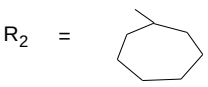
- Novel derivatives of quinoline were developed by *Gomtsyan et al*. as active analgesis agent and activity is attributed to antagonism at Vanilloid receptors [56].



- A series of quinoline derivatives designed by *Manera et al*. in 2007 found to active analgesic by acting as selective agonists at Cannaboid CB_2 receptors [57].

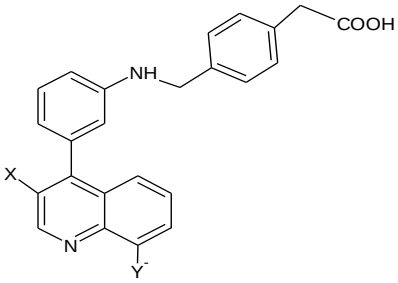






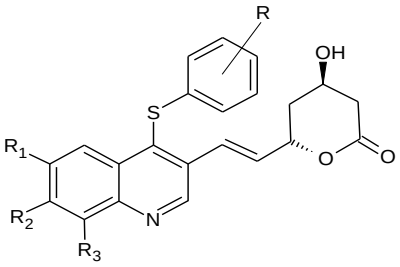
Cardiovascular activity:

- A series of phenyl acetic acid based derivatives of quinoline were synthesized by *Hu et al*. in 2007 as agonist at liver X receptors. These agents have good binding affinity for LXRb and LXRa receptors [58].



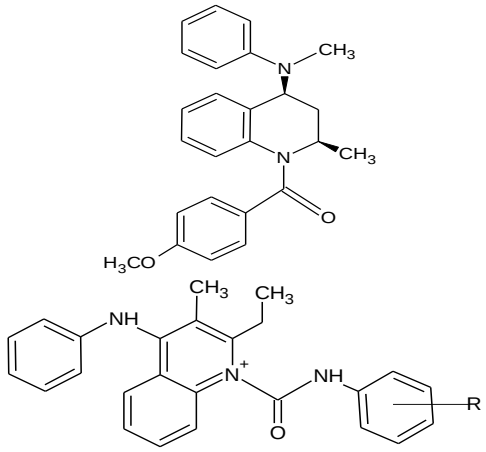
X = CH_2Ph, COPh, CN, $CONH_2$, Y = CF_3, CH_3, Cl

- Few 4-thiopheny derivatives of quinoline developed by *Cai et al*. in 2007 as HMGCoA reductase inhibitors and also as hypocholestrolaemic agents [59].



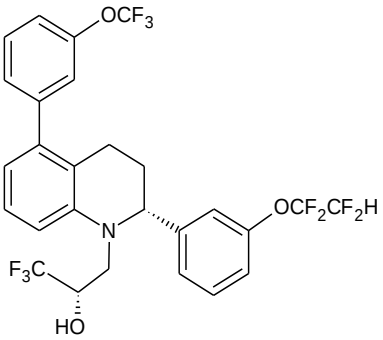
R = 4-CH(CH3)2, 4-F, 3-OCH3; R1 = H, F
R2 = H, F, Cl or Substituted thiophenyl group;
R3 = H, F or Substituted thiophenyl group

- Certain tetrahydroquinolinamides synthesized by *Ramos et al*. in 2008 found to be as inhibitors of platelet aggregation [60].

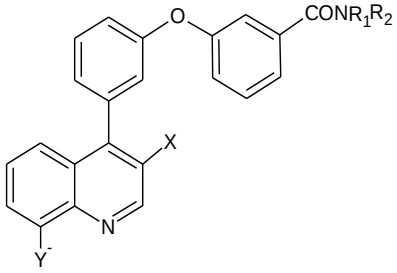


R = 3-Cl, 3-Br, 3-OCH_3

- Some tetrahydroquinoline derivatives have been designed by *Rano et al*. in 2009 as cholesteryl ester transfer protein inhibitors [61].



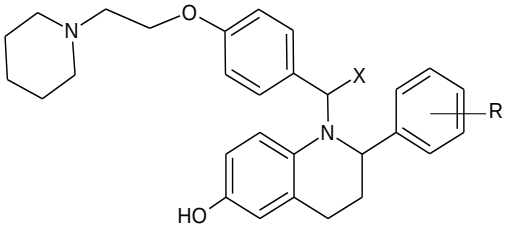
- A novel series of biaryletheramide derivatives of quinoline were developed by *Bernotas et al*. in 2009 and showed activity as agonist of liver X receptor and are useful in conditions of dyslipidaemia. These agents also reverse the conditions of arteriosclerosis [62].



X = CF_3, Cl; Y = CH_2 Ph, NR1R2 = Methyl ester, Pyrrolidine, Piperidine, Morpholine

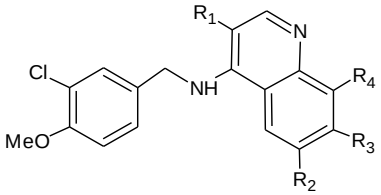
Reproductive system:

- A series of tetrahydroquinoline derivatives were synthesized by *Wallace et al*. in 2003 as selective estrogen receptor modulator [63].



R = H, 3-OH, 4-OH; X = CH_2, O

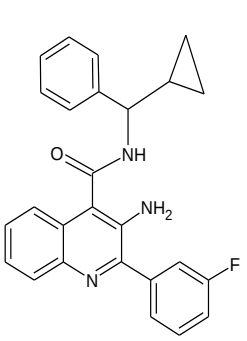
- Novel quinolines developed by *Bi et al*. in 2004 as potent PDE5 inhibitors having utility in the treatment of erectile dysfunction [64].

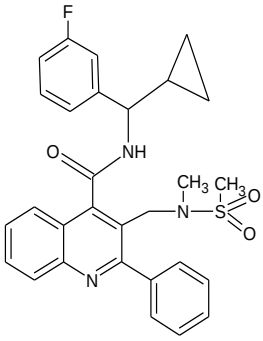


R1 = COOEt; R2 = H, CN; R3 = H, CF_3; R4 = H, Et

CNS activity:

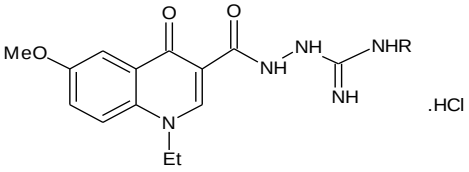
- A series of quinoline derivatives have been developed by *Smith et al*. in 2009 having CNS activity as NK3 receptor antagonist [65].





Hypoglycemic activity:

- A series of quinoline carboxyguanides were designed by *Edmont et al*. in 2000 as hypoglycemic agents [66].

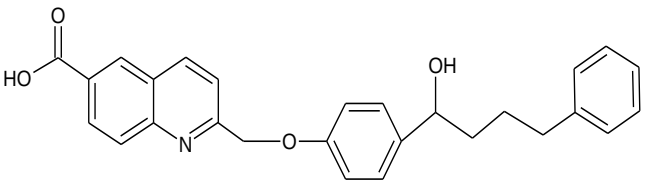


R = H, $C(NH)NH_2$

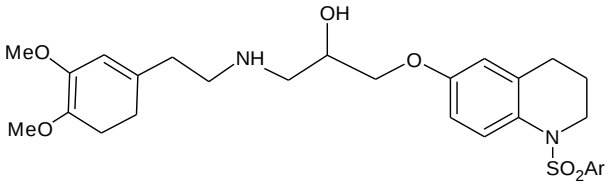
Miscellaneous activity:

Quinolines have been found to possess other activities as well.

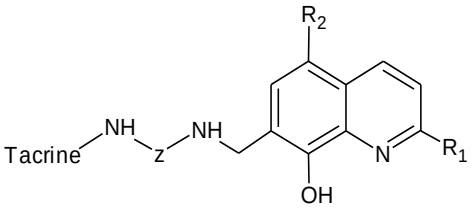
- Some quinolines have been synthesized by *Evans et al.* in 2009 and found to be as PDE4 inhibitors which can be utilized in treatment of chronic obstructive pulmonary disorder [67].



- Some novel tetrahydroquinoline-6-yloxy propanes were designed by *Shakya et al*. in 2009 as β-3 agonists [68].

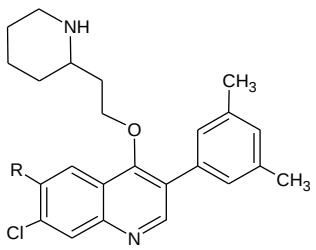


- Certain tacrine 8-hydroxyquinoline derivatives were developed by *Bachiller et al* in 2010 which showed activity against Alzeihmer'. Tacrine has cholinesterase inhibition action while8-hydroxyquinoline derivatives have metal-chelating, neuroprotective and anti-oxidant properties [69].



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

- Few aminoalkoxyquinolines were synthesized by *Wolkenberg et al*. in 2011 as somatostatin receptor subtype-2 agonist which have utility in proliferative diabetic retinopathy and oxidative age related macular degeneration [70].



R = Aromatic ring

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, anti-inflammatory and cardiovascular activities. A lot of work have been done and more to go. Developments 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.

ACKNOWLEDGEMENT: We are grateful to the director, Dr. D.P. Pathak for the valuable discussion and suggestions and to the college authorities of Delhi Pharmaceutical Sciences and Research University (DPSRU) for financial support.

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