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Review Article

A REVIEW ON CHEMOTHERAPEUTIC ACTIVITIES OF QUINOLINE

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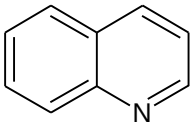
ABSTRACT

Quinoline has emerged as a valuable scaffold in medicinal chemistry possessing diverse range of pharmacological activities. Its value has further been increased by its natural occurrence as alkaloids in variety of plants. The first chemical compound which was a breakthrough for treating the malaria was quinine, an alkaloid isolated from bark of tree cinchona. The main moiety of quinine which exhibited the antimalarial activity was quinoline, on the basis of which later a large number of synthetic quinoline derivatives like chloroquin, amodiaquin, mefloquin were prepared and used as antimalarial agents. Our review is to address the various advances made on quinoline and its derivatives as potent chemotherapeutic agents, this will provide insights for the medicinal chemist for the designing and synthesis of novel quinoline derivatives with novel improved range of pharmacological implications.

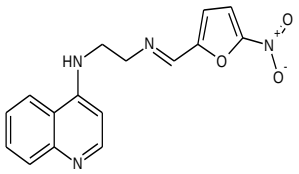
Keywords: Quinoline and its derivatives, antimalarial, antitumor and antimicrobial activities.

INTRODUCTION

Quinoline a well-known heterocyclic compound, which has been exploited immensely than any other heterocyclic moiety because of its wide diversity in pharmacological activities like antimalarial, antibacterial, antifungal, and anticancer, etc. Various chemical modifications of quinoline have been attempted to achieve analogs with potent antimalarial properties against sensitive as well as resistant strains of *Plasmodium species* with minimal potential of undesirable side effects.



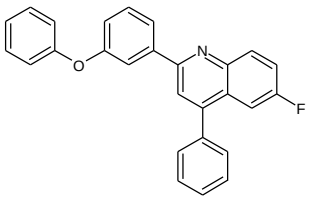
Giselle Barbosa L et al. [1], Synthesized novel quinoline derivatives, among the series the compound *N*-(2-((5-nitrofuran-2-yl)methylimino)ethyl)-7-chloroquinolin-4-amine, **(1),** exhibited EC_{50} value of 0.8 ± 0.07 µM, compared to that of chloroquine of 12 ± 3.2 µM by reducing ZIKV replication by 72% at 10 µM.



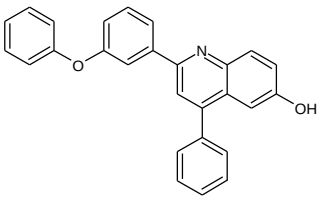
1

Manikandan A et al. [2], Synthesized and performed molecular validation of 6-substituted-2-(3-phenoxyphenyl)-4-phenylquinoline derivatives (4a-h) and evaluated for their antibacterial/DNA gyrase inhibition. The compounds 6-fluoro-2-(3-phenoxyphenyl)-4-phenylquinoline **(2a)**, 2-(3-phenoxyphenyl)-4-phenylquinolin-6-ol **(2b)**, and 5,7-dichloro-2-(3-phenoxyphenyl)-4-phenylquinolin-6-ol **(2c)**, exhibited

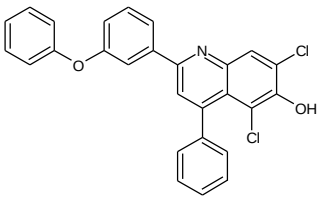
IC_{50} values of 0.389 µg/mL, IC_{50} 0.328 µg/mL and IC_{50} 0.214 µg/mL respectively, revealing that the 6-substituted-2-(3-phenoxyphenyl)-4-phenylquinoline derivatives are highly potent to cancer cells.



2a

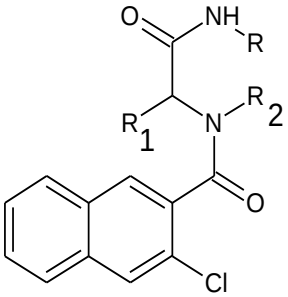


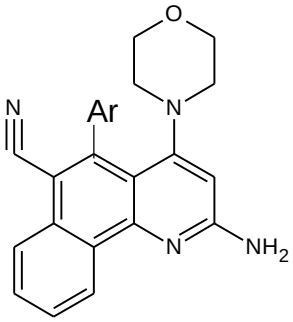
2b



2c

Dharmendra K. Yadav et al. [3], Synthesized a series of new arylated benzo[h]quinolines induced anti-cancer activity by oxidative stress-mediated DNA damage. The anti-cancer activity of the benzo[h]quinolines was evaluated on cultured human skin cancer (G361), lung cancer (H460), breast cancer (MCF7) and colon cancer (HCT116) cell lines. The compounds **3a, 3b, 3c** and **3d** showed potential cytotoxicity against these human cancer cell lines.





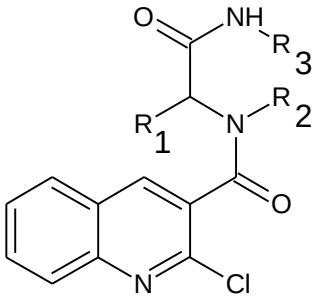
3a: Ar= 2-Furyl

3b: Ar= 2-Thienyl

3c: Ar=C_6H_4Cl-4

3d: Ar=C_6H_4 Br-4

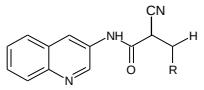
Morteza Shiri et al. [4], Synthesized a series of diamide derivatives containing 2-chloroquinoline and evaluated for their antibacterial and antifungal activities, most of the compounds **4a, 4b & 4c**displayed moderate to good antibacterial and antifungal activities.



4a : R_1= 2-indolyl, R_2-4-MeC_6H_4, R_3-Cyc Hex
4b :R_1= 4-MeC_6H_4, R_2-4-MeC_6H_4, R_3-Cyc Hex
4c : R_1= Ph CH=CH, R_2-4-MeC_6H_4, R_3-t-butyl

Mostafa M.Ghorab et al. [5], Synthesized some novel quinoline derivatives and evaluated for their cytotoxic activity against Breast cancer cell line MCF7. The compounds 2-cyano-3-(4-hydroxy-3-methoxy phenyl)-N-(quinolin-3-yl)acrylamide (5a), 3-oxo-N-(quinolin-3yl)-3H-benzol(f)chromene-2-carboxamide (5b), 2-cyano-3-(4-fluorophenyl)-N-(quinolin-3-yl)acrylamide (5c), 2-cyano-5-(4-(dimethyl-

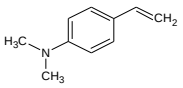
amino)phenyl)-N-quinolin-3-yl)penta-2,4-dienamide (5d) exhibited higher activity compared to Doxorubicin (IC50 value of 47.9 µmol/L) with IC50 values of 29.8,39.0,40.0,40.4 µmol/L respectively.

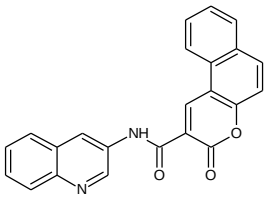


5a, R=

5c, R=

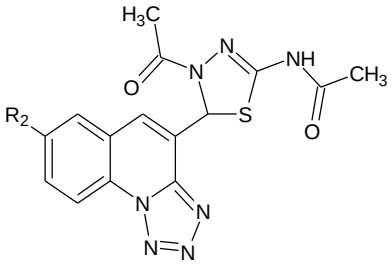
5d, R=





5b

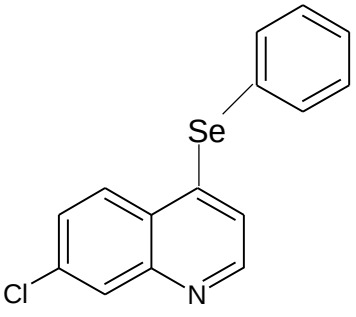
Sheetal Babu Marganakop et al. [6], Synthesized a series of novel N- (4-acetyl-4,5-dihydro-5-(7,8,9-substituted-tetrazolo[1,5-a]- quinolin-4-yl)-1,3,4-thiadiazol-2-yl)acetamides (6a-j) and evaluated for their in vitro anticancer activity against two cell lines viz.,among the series the compounds **6a** and **6b** with halogen substituent at 7th position of the target molecules have shown potent activity against human cervix cancer cell line HeLa.



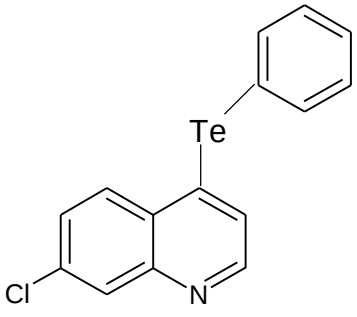
6a: R_2= Br

6b: R_2=Cl

Lucielli Savegnago et al. [7], Synthesized novel quinoline-chalcogenium compounds and evaluated for their invitro Anti-oxidant properties using Sodium nitroprussate (SNP) assay at a concentration equal or superior than 0.1 and 50µM. The compound Organo Tellurium (**7b)** was more effective than Organo Selenium (**7a**).



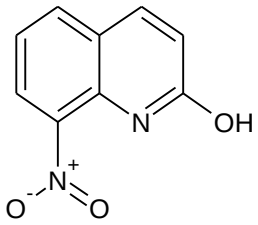
7a



7b

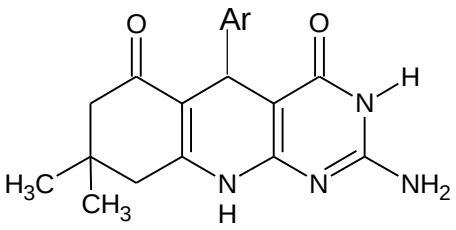
Lucie Paloque at al. [8], Synthesized a series of nitrated 8-substituted-quinolines and evaluated in vitro antileishmanial activity. The compound **8a** displayed a very promising selective activity with a IC50:

value of 6.6M and CC50 value of ≥100 M, conferring quite good selectivity index to this molecule, in comparison with three drug-compounds of reference (amphotericin B, miltefosine and pentamidine).

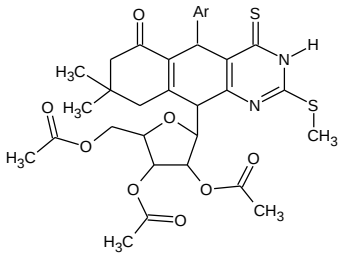


8a

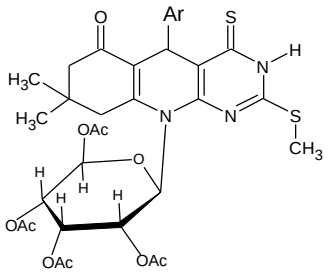
Hebat-Allah S et al. [9], Synthesized a series of seven pyrimidoquinoline derivatives and evaluated for their antibacterial, antifungal and anticancer activities. Some of the novel pyrimidoquinoline derivatives possess high activity toward the bacteria and fungi species and were also evaluated for their anticancer activity toward human cancer cell lines. Most of them had excellent growth inhibition activity, having LD_{50} values in the low micromolar to nanomolar concentration range.



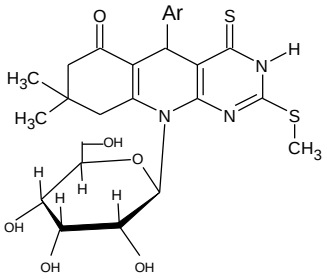
9a



9b

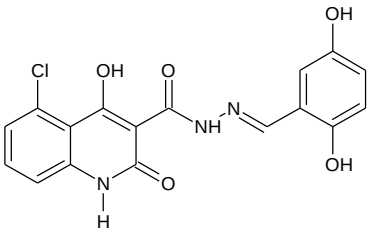


9c

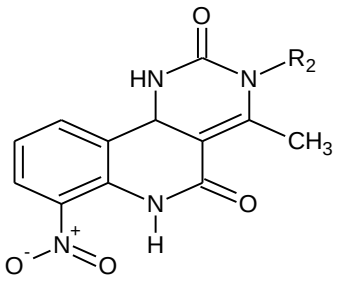


9d

Isabelle Tomassoli et al. [10], Synthesized novel quinoline derivatives and evaluated for their anticholinesterase activity. The compound 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides(**10a**) exhibited equipotent inhibition of cholinesterases, whereas 4-hydroxy-2-oxo-1,2-dihydro-N-methylquinoline-3-carboxamides(**10b**) proved selective for BuChE and the compounds 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbohydrazide (**10c**), and some hexahydropyrimido-N-methyl[5,4-c]quinoline-2,5-diones (**10d**), hexahydropyrimido-N-ethyl[5,4-c]quinoline-2,5-diones (**10e**) were selective for AChE.



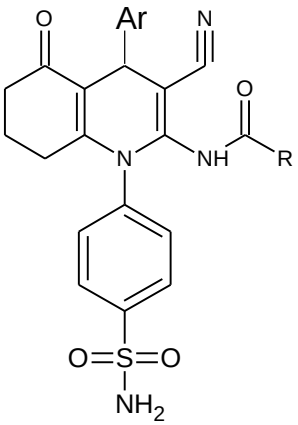
10c



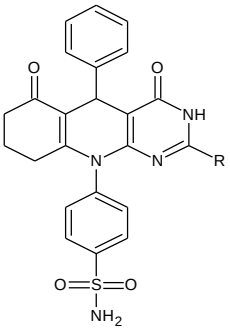
10d: $R_2=CH_3$

10e: $R_2=C_2H_5$

Mansour S Al-Said et al. [11], Synthesized a series of novel hexahydroquinoline derivatives having a benzenesulfonamide moiety and evaluated for their invitro anticancer activity, amongst the series of quinoline derivatives, the most potent is compound 11a having benzamide side chain and for pyrimidoquinoline derivatives, the most potent is 11b having 4-bromophenyl side chain.

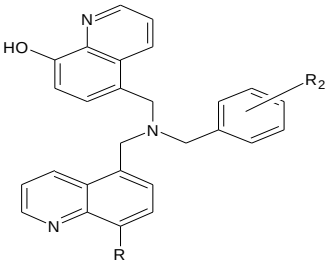


11a: R= $-C_6H_5$



11b: $R=C_6H_4Br\text{-}4$

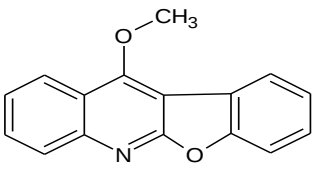
Madonna S et al. [12], Synthesized a series of twenty six 8-hydroxyquinoline substituted amines, and evaluated for their antitumor activity on a wide variety of cancer cell lines within glioma and carcinoma models. The analogues represent new promising anti-cancer activity targeting accessible thiols from specific proteins.



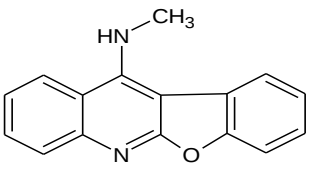
12a

Chiao-Li Yang et al. [13], Synthesized a series of 11-alkoxylated and 11-aminated benzofuro[2,3-b]quinoline derivatives and evaluated for their anti-TB and cytotoxic activities. Among the tested compounds, 11-methoxybenzofuro[2,3-b]quinoline (**13a**), 11-methylamino- benzofuro[2,3-b]quinoline (**13b**), and 11-dimethylaminobenzofuro[2,3-b]quinoline (**13c**) exhibited significant activities against the

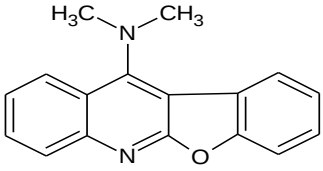
growth of M. tuberculosis with MIC values of <0.20 µg/mL and low Cytotoxic activity against VERO cell with IC_{50} values of 11.77 µg/mL, 5.55 µg/mL, and >30.00 µg/mL respectively.



13a

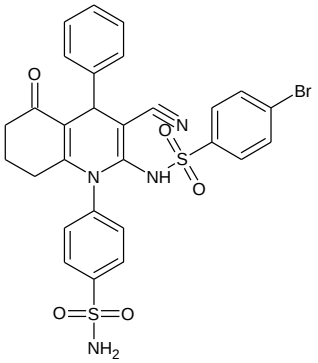


13b

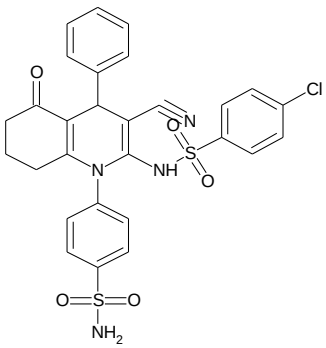


13c

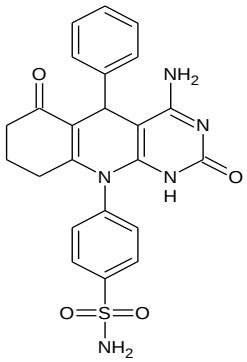
Saleh I.Alqasoumi et al. [14], Synthesized a series of novel quinolines and pyrimido[4,5-b]quinoline derivatives , and subjected to in-vitro antitumor activity against Ehrlich Ascites Carcinoma (EAC) cells. Amongst the quinoline derivatives compounds 4-bromobenzenesulfonamide quinoline (**14a**) showed IC_{50} value of 5.5µg/ml, 4-chlorobenzenesulfonamide quinoline moiety (**14b**) exhibited higher Anti-tumour activity & pyrimidoquinoline derivatives like cyclic urea pyrimidoquinoline (**14c**) showed IC_{50} value of 6.9µg/ml , N-butyl cyclic thio urea pyrimidoquinoline (**14d**) showed IC_{50} value of 7µg/ml , p-chloro phenyl cyclic thio urea pyrimidoquinoline (**14e**), and cyclic thio urea pyrimidoquinoline (**14f**) exhibited higher potency than the Doxorubicin with IC_{50} value of 38µg/ml.



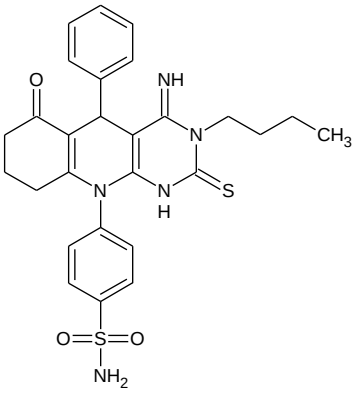
14a



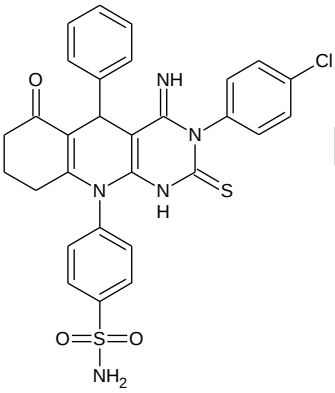
14b



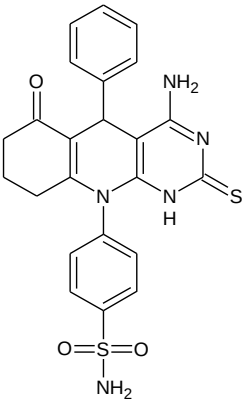
14c



14d

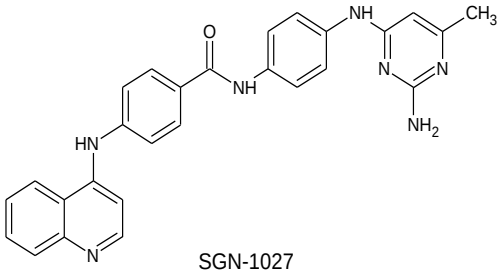


14e



14f

Jharna Datta at al. [15], Synthesized a new class of quinoline based DNA hypomethylating agents, among which the compound SGI-1027 inhibited DNMT1, DNMT3A and DNMT3B as well M. SssI with comparable IC_{50} value of 6-13 µmol/L, without exhibiting significant toxicity in a rat hepatoma (H4IIE) cell line revealing the potential use in epigenetic cancer therapy.

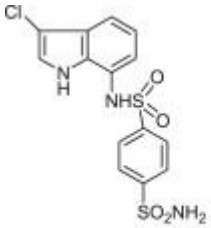


SGN-1027

15a

Mostafa M.Ghorab et al. [16], Synthesized a series of tetrahydroquinoline derivatives containing sulfonamide moiety and evaluated for their anticaner activity Most of the compounds showed

interesting cytotoxic activities compared to a reference drug.



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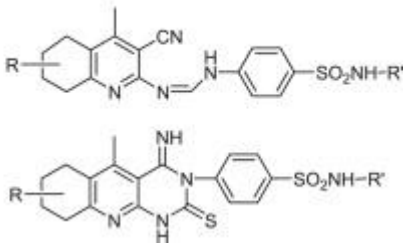
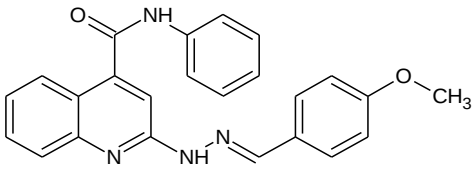


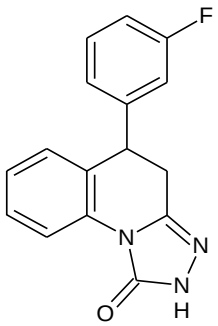
16a

Rahul Jain et al. [17], Synthesized a series of 2,4 di substituted quinolines and evaluated for their Anti-Tubercular activity. The synthesized **17a** analogues have been found to exhibit 99% inhibition at 6.25µg/ml against drug-sensitive M.tuberculosis H37Rv and >90% inhibition at 12.5 µg/ml against Isoniazid resistant M.tuberculosis H37Rv strain.



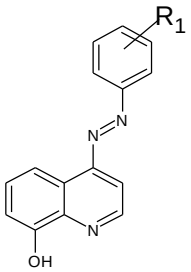
17a

Li-Ping Guan et al. [18], Synthesized a series of quinoline-2(1H)-one and 1,2,4 triazolo(4,3-a) quinoline derivatives and evaluated for their anticonvulsant activities. The compound 5-(p-fluoro phenyl)-4,5-dihydro-1,2,4-triazolo(4,3-a)quinoline (**18a)**, showed the strongest anticonvulsant activity with ED50 value of 27.4mg/kg & 22.0mg/kg in anti-MES and anti-PTZ test respectively.

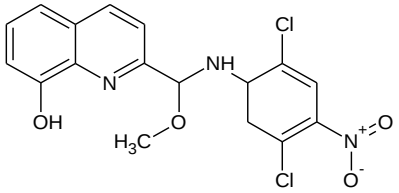


18a

Musiol R et al. [19], synthesized a series of quinoline derivatives and evaluated for their antifungal activity amongst which the compound 2-[(3-Hydroxyphenylimino)methyl]quinolin-8-ol (**19a**), 2-[(4-hydroxyphenylimino)methyl]quinolin-8-ol (**19b**) and 2-[(2,5-dichloro-4-nitrophenylamino)methoxymethyl]quinolin-8-ol (**19c**) showed in vitro antifungal activity comparable to or higher than that of the standard fluconazole.

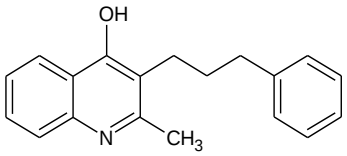


19a, R1=OH(3)
19b, R1=OH(4)



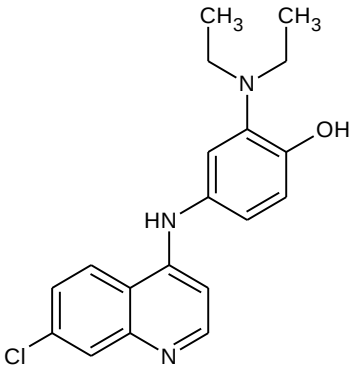
19c

Andre Gustavo T et al. [20], Synthesized a series of four novel quinoline derivatives and evaluated for their antileishmanial activity against chagasi, the compound **20a** exhibited the lowest IC_{50} value of 0.091 µg/mL and 22-fold greater activity than the standard pentavalent antimony or pentamidine.



20a

O'Neill PM et al. [21], Synthesized a series of 10 isomeric amodiaquine analogues and evaluated in vitro activity against chloroquine resistant K1 and sensitive HB3 strains of Plasmodium falciparum. The compound isoquine (**21a**) exhibited IC_{50} value of 6.01 nM +/- 8.0 versus K1 strain, with excellent oral in vivo ED_{50} value of 1.6 and 3.7 mg/kg against the P.yoelii NS strain compared to 7.9 and 7.4 mg/kg for amodiaquine.



21a

CONCLUSION

The fused bicyclic quinoline moiety with one nitrogen atom at first position has emerged as a valuable scaffold in the medicinal chemistry and drug design. Not only the pharmacophoric features of core moiety, but substitution of different groups especially at N-1, C-4 and C-2, positions of ring resulted in development of potent compounds with anticancer, antileishmanial, antimalarial, antifungal and bacterial activities. Further efficient optimization of quinoline derivatives with multiple biological activities can lead to a potential polyfunctinal agents for treatment of various diseases. In the future it is expected that research will reveal interesting aspects of quinoline as flexible moiety in order to develop a wide range of potent compounds.

Conflict of interest

No author declared conflict of interest

REFERENCES

1. Giselle Barbosa L. Synthesized a series of N-(2-(arylmethylimino)ethyl)-7-chloroquinolin-4-amine derivatives, synthesized by thermal and ultrasonic means and evaluated with anti-Zika virus activity. European J of Med Chem. 2017;127:434-441.
2. Manikandan A and Siva kumar A. Performed Molecular docking, discovery, synthesis, and pharmacological properties of new 6-substituted-2-(3-phenoxyphenyl)-4-phenyl quinoline derivatives; an approach to developing potent DNA gyrase inhibitors/antibacterial agents. Bioorg and Med Chem. 2017;25(4):1448-1455.
3. Dharmendra Yadav K. New arylated benzo[h]quinolines induce anti-cancer activity by oxidative stress-mediated DNA damage Sci Rep. 2016;6:38128.
4. Morteza Shiri. Synthesis and biological evaluation of novel quinoline derivatives as antibacterial and antifungal agents, Org Chem Res. 2016;2(2):113-119.
5. Mostafa Ghorab M. Anti breast activity of some novel quinoline derivatives. The Journal of Croatian Pharmaceutical Society. 2015;65(3):271-283.
6. Sheetal Babu M. Facile synthesis of novel quinoline derivatives as anticancer agents. Med Chem Res. 2014; 23:2727–2735.
7. Lucielli Savegnago and Diego Alves. Synthesis and Anti-Oxidant properties of novel quinoline-Chalcogenium compounds. Tetrahedron Letters. 2013;54(1):40-44.
8. Lucie P. Discovery of a new antileishmanial hit in 8-nitroquinoline series. European j of Med Chem. 2012;54:75-86.
9. Hebat Allah S. Synthesis, in vitro antimicrobial and in vivo antitumor evaluation of novel pyrimidoquinolines and its nucleoside derivatives. European J of Med Chem. 2011;46(1):21-30.
10. Isabelle T. Synthesis, biological assessment and molecular modeling of new dihydroquinoline-3-carboxamides and dihydroquinoline-3-carbohydrazide derivatives as cholinesterase inhibitors and Ca channel antagonists. European J of Med Chem. 2011;46(1):1–10.
11. Mansour Al-Said S. Synthesis and in vitro anticancer evaluation of some novel hexahydroquinoline derivatives having a benzene sulfonamide moiety. European J of Med Chem. 2011;46(1):201-207.
12. Madonna S. Structure–activity relationships and mechanism of action of antitumor bis 8-hydroxyquinoline substituted benzylamines. European J of Med Chem. 2010;45(2):623-638.
13. Chiao Li Y. Identification of benzofuro[2,3-b]quinoline derivatives as a new class of antituberculosis agents. European J of Med Chem. 2010;45(2):602-607.
14. Saleh Alqasoumi I. Novel quinolines and pyrimido[4,5-b]quinolines bearing biologically active sulfonamide moiety as a new class of antitumor agents. European J of Med Chem. 2010;45(2):738-744.
15. Jharna D. A New Class of Quinoline-Based DNA Hypomethylating Agents Reactivates Tumor Suppressor Genes by Blocking DNA Methyltransferase 1 Activity and Inducing Its Degradation. Experimental Therapeutics, Molecular Targets, and Chemical Biology, Cancer Res. 2009;69(10):4277–4285.
16. Mostafa Ghorab M. Design, synthesis and anticancer evaluation of novel tetrahydroquinoline derivatives containing sulfonamide moiety. European J of Med Chem. 2009;44(10):4211-4217.
17. Rahul Jain and Amit Nayyar. Synthesis and Anti-Tuberculosis activity of 2,4-disubstituted quinolines. Indian Journal of Chemistry. 2008;47:117-128.
18. Li Ping G. Synthesis of some quinoline-2(1H)-one and 1,2,4 triazolo(4,3-a) quinoline derivatives as potent Anticonvulsants. J Pharm Pharmaceut Sci. 2007;10 (3):254-262.
19. Musiol R. Antifungal properties of new series of quinoline derivatives. Bioorg Med Chem. 2006;14(10):3592-3598.
20. Andre Gustavo T. Synthesis and Antileishmanial Activities of Novel 3-Substituted Quinolines. Antimicrob Agents Chemother 2005;49(3):1076–1080.
21. O Neill PM. Isoquine and related amodiaquine analogues: a new generation of improved 4-aminoquinoline antimalarials. J Med Chem. 2003;46(23):4933-45.