Journal of PharmaSciTech
ISSN: 2231 3788 (Print)
2321 4376 (Online)
Review Article

Indispensability of Quinoline Moiety in the Field of Medicinal Chemistry Research-A Review

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Abstract

The significance of quinoline heterocyclic nucleus in the field of medicinal chemistry research is worth mentioning. The wide range of its application has drawn an immense attention to the researchers to generate various quinoline derivatives, which may possess novel therapeutic efficacy. In this review we tried to track down the immense potentiality of this ring system when accompanied with diversified substituents. This study may help the researchers to grasp the importance of various substituents in attenuating the pharmacological activity and incorporate these understanding in designing various drugs like compounds.

Keywords: Quinoline, Anti-microbial activity, Anti-cancer activity, Anti-inflammatory activity, Anti-tubercular activity, Anti-malarial activity

1.Introduction

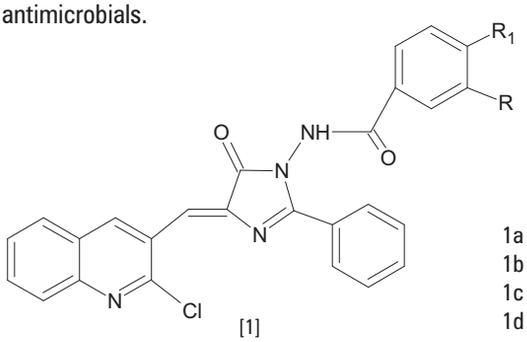
Quinoline is a heterocyclic aromatic organic compound featuring nitrogen atom as part of the ring system, with the chemical formula C_9H_7N. It can also be named as, benzopyridine, benzo[b]pyridine, 1-benzazine and benzazine. It is a colorless hygroscopic liquid with a strong odor. Aged samples, if exposed to light, become yellow and later brown.

Pharmaceutically a wide variety of substituted quinoline derivatives possess a broad range of bioactivities as anticancer, anti malarial, antibiotic, antihypertensive, platelet-derived growth factor - receptors tyrosine kinase (PDGF-RTK) inhibition, DNA-intercalating carrier, anti-inflammatory and analgesic, anti-HIV, antitumour, DNA binding capability, and many other functional material.[1-18] In the foregoing section, we preferentially wanted to shape our study in a manner to get an efficient knowledge about the target oriented development of quinoline.

2. Quinoline as antimicrobials

2.1. 2, 3-disubstituted quinolines

A series of quinoline based imidazole derivatives were synthesized by Desai *et al*[25] and subsequently evaluated their activity as antimicrobials.

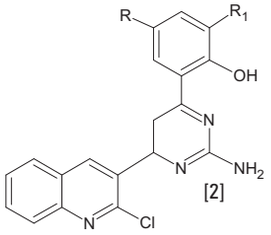


[1]

	R	R_1
1a	Cl	H
1b	H	Cl
1c	H	F
1d	OH	H

All the compounds in the above series showed good antimicrobial activity against different microbial strain like, *Escherichia coli* (MTCC443), *Pseudomonus aeruginosa* (MTCC 1688), *Staphyllococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282), *Aspergillus clavatus* (MTCC 1323).

A series of quinoline scaffold derived pyrimidine derivatives were synthesized by Dave *et al*[26] and subsequently evaluated their moderate activity against *Pseudomonas vulgaris*, *Staphylococcus aureus*, *Aspergillus niger* and *Pseudomonas chrysogenum*.

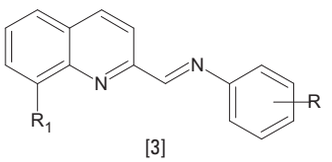


[2]

	R	R_1
2a	CH_3	Br
2b	CH_3	H
2c	Cl	No_2

2.2. 2, 8-disubstituted quinolines

Musiol *et al*[29] developed the synthesis of a series of 8-hydroxyquinoline derivatives and evaluated their antifungal potential against various pathogenic fungal strains.



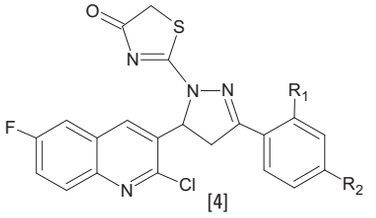
[3]

	R_1	R
3a	CH_3	*p*-OH
3b	OH	*p*-OH
3c	OH	2,5-di Cl, *p*-NO_2

Among all the synthesized compounds 3a, 3b and 3c showed very promising activity against different fungal strains like *Candida albicans* (ATCC 44859), *Candida glabrata* 20/I and *Aspergillus fumigatus* 231.

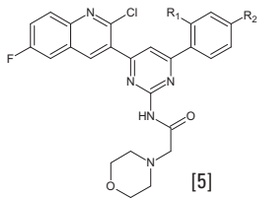
2.3. 2, 3, 6-trisubstituted quinolines

Desai *et al*[46] synthesized a series of new quinoline derivatives and evaluated their pharmacological activity as antimicrobial agents.



[4]

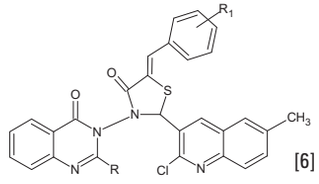
	R_1	R_2
4a	H	F
4b	NO_2	H



[5]

	R_1	R_2
5a	F	H
5b	H	NO_2

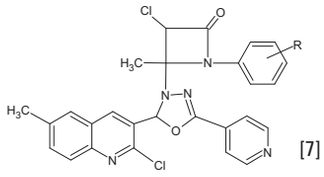
A series of quinoline based quinazolinone-4-thiazolidinone heterocycle derivatives was synthesized by Desai *et al*[47] and subsequently evaluated their activity as antimicrobial agents.



[6]

	R	R_1
6a	C_6H_4Cl	2-Cl
6b	C_6H_4Cl	3-OH
6c	C_6H_4Cl	4-Cl
6d	C_6H_4Cl	2-OH

Following their previous work, Desai *et al* [48] came up with the synthesis of quinoline containing 1, 3, 4-oxadiazole and 2-azetidinone derivatives and subsequently screened their activity as antimicrobial agents.

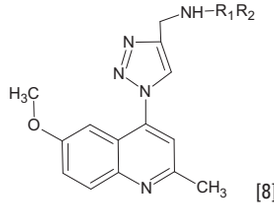


[7]

	R
7a	2-Cl
7b	3-NO_2
7c	4-Cl
7d	4-CH_3

2.4. 2, 4, 6-trisubstituted quinolines

Thomas *et al*[49] synthesized a series of quinoline derivatives containing 1, 2, 3-triazole moiety and evaluated their activity as antimicrobial agents.

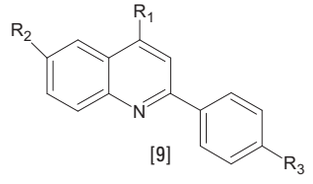


[8]

	R_1R_2
8a	cyclopropyl
8b	1-acetyl piperazine
8c	1-methyl piperizine
8d	morpholine

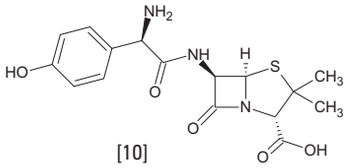
All the synthesized compounds showed good anti bacterial and anti fungal activity against different microbial strain like, *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (recultured), *Streptococcus pyogenes* and *Aspergillus flavus* (NCIM No. 524), *Aspergillus fumigatus* (NCIM No. 902), *Penicillium marneffei* (recultured), *Trichophyton mentagrophytes* (recultured), *Candida albicans.*

Praveen *et al*[50] synthesized quinoline and bis(indolyl)methane derivatives and subsequently screened their pharmacological activity as antimicrobial agents.

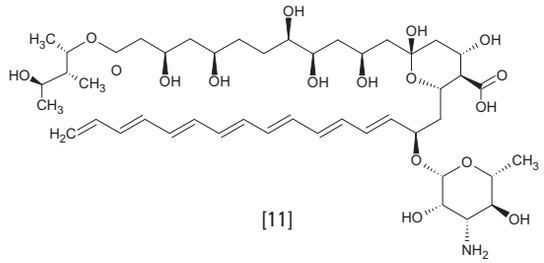


[9]

	R_1	R_2	R_3
9a	C_6H_5	CH_3	3-Br-phenyl
9b	C_6H_5	H	*p*-tolyl
9c	C_6H_5	Cl	*p*-tolyl
9d	C_6H_5	H	3-anisyl



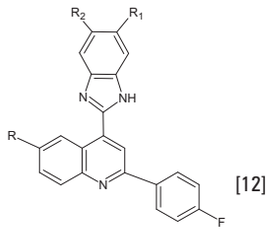
[10]



[11]

All the compounds showed moderate to good zone of inhibition (mm), with respect to two reference standards, Amoxicillin [10] and Amphotericin-B [11], against different fungal and bacterial strain like *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*.

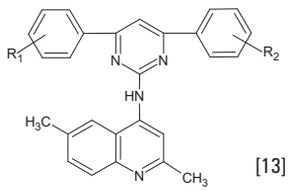
Garudachari *et al*[51] synthesized, characterized and evaluated the antimicrobial properties of some new quinoline linked benzimidazole derivatives.



[12]

	R	R_1	R_2
12a	Cl	H	H
12b	Cl	Cl	Cl
12c	H	Cl	Cl
12d	H	Cl	H

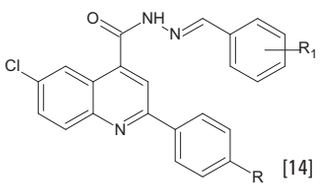
A series of pyrimidine-quinoline clubbed derivatives was synthesized by Patel *et al*[52] and subsequently evaluated their anti microbial activity.



[13]

	R_1	R_2
13a	2, 4-Cl	4-F
13b	4-Cl	3-Br
13c	4-OCH_3	3-Br
13d	4-OCH_3	4-F

Metwally *et al*[53] synthesized a series of hydrazones of 2-aryl-quinoline-4-carboxylic acid hydrazide derivatives and evaluated their activity as antimicrobial agents.

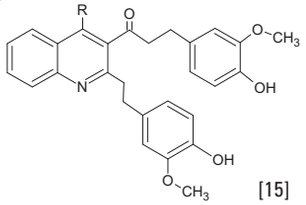


[14]

	R	R_1
14a	Br	4-NO_2
14b	OCH_3	3-NO_2
14c	OCH_3	4-NO_2

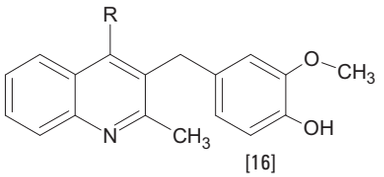
2.5. 2, 3, 4-trisubstituted quinolines

Manjunatha et al[61] synthesized a series of quinoline derivative of tetrahydro curcumine and zingerone and subsequently evaluated their pharmacological activity as novel antioxidant and antibacterial agents.



[15]

	R
15a	C_6H_5
15b	CH_3



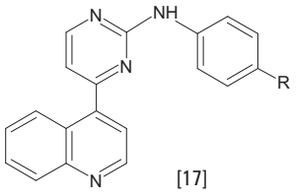
[16]

	R
16a	CH_3
16b	C_6H_5

3. Quinolines as anticancer

3.1. 4-substituted quinolines

A series of 2-methylimidazo[1,2-a]pyridine and quinoline substituted 2-aminopyrimidine derivatives were synthesized by Reyes et al[22] and evaluated their cytotoxic activity.



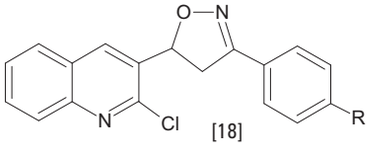
[17]

	R
17a	CH_3
17b	OCH_3

Most of the compounds showed good anticancer activity when subjected to different cancer cell lines like, U251 (Glioma), PC-3 (Prostate), K562 (Leukemia), HCT-15 (Colon), MCF7 (Breast), and SK-LU-1 (Lung)

3.2. 2, 3-disubstituted quinolines

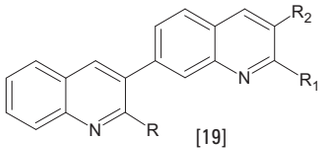
Bindu *et al*[27] synthesized 2-chloro-3-(5-aryl-4, 5-dihydroisoxazol-3-yl)quinolines derivatives and subsequently studied photo-induced DNA cleavage properties as a possible target for anticancer therapy.



[18]

	R
18a	CH_3
18b	No_2

Broch *et al*[28] designed and synthesized new quinoline derivaives and evaluated them for their in vitro antiproliferative activities.



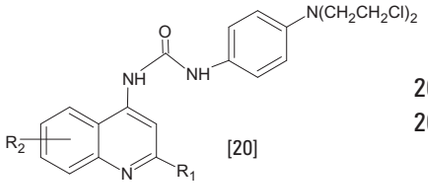
[19]

	R	R_1	R_2
19a	OCH_3	OCH_3	H
19b	OC_2H_5	OC_2H_5	H
19c	OC_2H_5	OC_2H_5	

Compounds 19a and 19b were slightly active toward PA1 and MCF-7 cell lines with IC_{50} values in the range of 36–54 μM, and showed better cytotoxicities toward two human solid cancer cell lines. Compound 19c was mildly active against the PA1 cell line with an IC_{50} value of 50 μM.

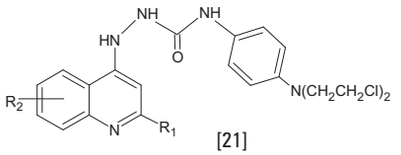
3.3. 2, 4, 6-trisubstituted quinolines

Kakadiya *et al*[54] synthesized a series of phenyl N-mustard quinoline conjugates as a potent DNA-directed alkylating agents.



[20]

	R_1	R_2
20a	Me	H
20b	3- CH_3O-C_6H_4	6-OCH_3



[21]

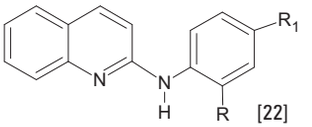
	R_1	R_2
21a	CH_3	6-$N(CH_3)_2$
21b	CH_3	6,7-(OCH_2O)

Compounds with the above substituents showed good anticancer activity against breast carcinoma MX-1 xenograft.

4. Quinoline as anti-inflammatory and analgesic agents

4.1. 2-substituted quinolines

Saari *et al*[20] designed microwave assisted synthesis of quinoline, isoquinole, quinoxaline and quinazoline derivatives as a potential cannabinoid (CB2) receptor agonists.

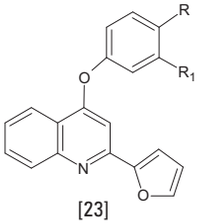


[22]

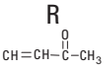
	R	R_1
22a	H	Cl
22b	OCH_3	H

4.2. 2, 4-disubstituted quinolines

Chen *et al*[34] synthesized a series of 2-(furan-2-yl)-4-(phenoxy)quinoline derivatives and evaluated their anti-inflammatory as well as cytotoxic activity.

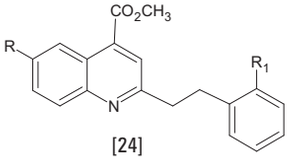


[23]

	R	R_1
23a		H
23b	CHO	H
23c	H	

4.3. 2, 4, 6-trisubstituted quinolines

A series of quinoline-4-methyl ester derivatives was synthesized by Wu et al[58] and evaluated their activity as human nonpancreatic secretory phospholipase A2 inhibitors.

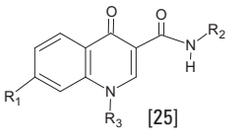


[24]

	R	R_1
24a	Cl	H
24b	OCH_3	H
24c	F	OCH_3

4.4. 1, 3, 7-trisubstituted quinolin-4(1H)-one

A new series of 1, 8-naphthyridine and quinoline derivatives was synthesized by Manera *et al*[60] and subsequently evaluated their activity as CB2 selective agonists.



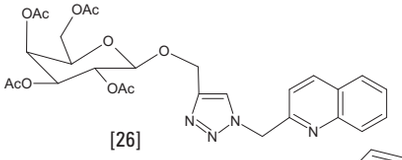
[25]

	R_1	R_2	R_3
25a	OCH_3	cyclohexyl	ethylmorpholine
25b	H	cycloheptyl	ethylmorpholine
25c	Cl	cyclohexyl	benzyl

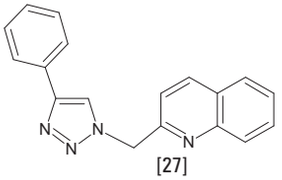
5. Quinoline as anti-tubercular agents

5.1. 2-substituted quinolines

Kumar *et al*[19] synthesized a series of quinoline coupled [1, 2, 3]-triazole derivatives and screened their activity as antitubercular agents.



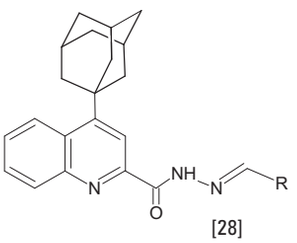
[26]



[27]

5.2. 2, 4-disubstituted quinolines

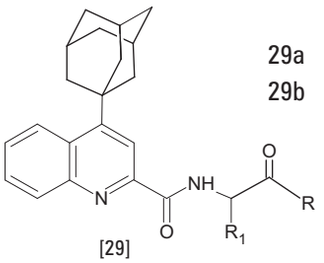
Nayyar *et al*[32] designed and synthesized a series of 4-(adamantan-1-yl)-2-substituted quinolines derivatives and evaluated their activity as potent anti-tubercular agents.



[28]

	R
28a	
28b	
28c	

The earlier work of Nayyar *et al*[33] was followed by the synthesis of a series of amino acid conjugates of 4-(adamantan-1-yl) group containing quinoline derivatives and subsequently evaluated their activity as anti-tubercular agent.

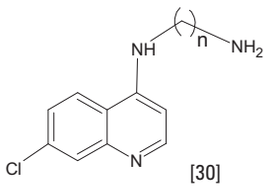


[29]

	R	R_1
29a	$NHNH_2$	$(CH_2)_3NHC(=NH)NH_2$
29b	OCH_3	$(CH_2)_3NHC(=NH)NH_2$

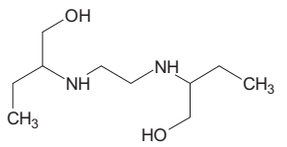
5.3. 4, 7-disubstituted quinolines

Souza *et al*[38] synthesized a series of quinolines evaluated their *in vitro* antitubercular activity.



[30]

	n
30a	8
30b	10

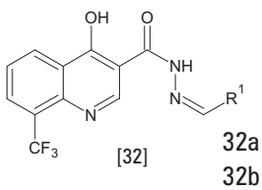


[31]

Compounds 30a and 30b exhibited a significant activity at 6.25 and 3.12 μg/ml respectively, when compared with first line drug such as ethambutol [31].

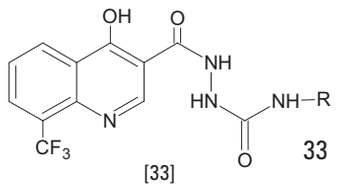
5.4. 3, 4, 8-trisubstituted quinolines

A series of new quinoline-3-carbohydrazide derivatives as antitubercular agents was synthesized by Thomas *et al*[40]. Compound 32a, 32b and 33 showed μg activity against *Klebsiella pneumoniae* and *Escherichia coli*.



[32]

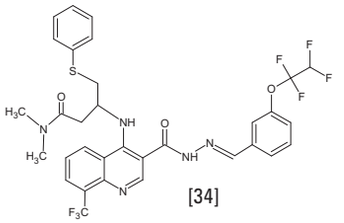
	R^1
32a	5-Methoxy-1H-imidazole-4-carbaldehyde
32b	5-Fluoro-2-hydroxy-benzaldehyde



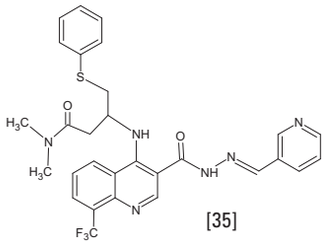
[33]

	R
33	1-isocyanato-4-methylbenzene

A series of new quinoline-3-carbohydrazone derivatives was synthesized by Eswaran *et al*[41] and evaluated their activity as antimycobacterial agents.



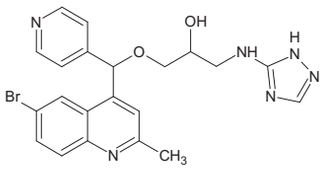
[34]



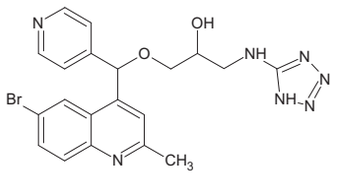
[35]

5.5. 2, 4, 6-trisubstituted quinolines

A series of naphthalene and quinoline derivatives were synthesized by Upadhayaya *et al*[55] and subsequently evaluated their potent inhibitory activity against *Mycobacterium tuberculosis* (37Rv).



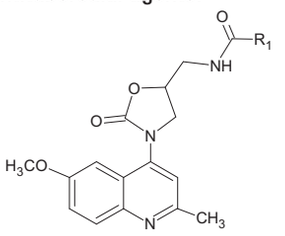
[36]



[37]

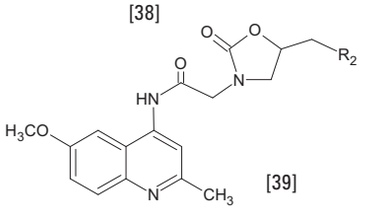
Compounds 36 and 37 inhibited the growth of *Mycobacterium tuberculosis* (H37Rv)

Thomas *et al*[56] synthesized and docked a new series of quinoline-oxazolidinone hybrid derivatives and evaluated their activity as potent antitubercular agents.



[38]

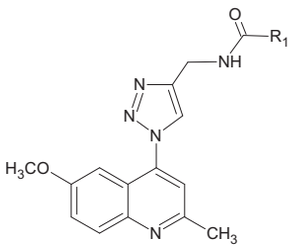
	R_1
38a	CH_3
38b	p-CF_3-C_6H_4



[39]

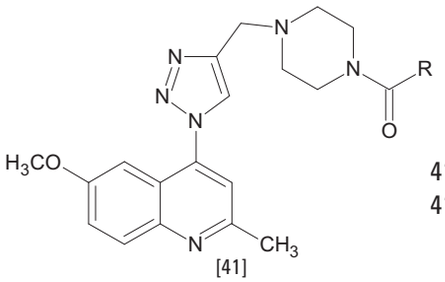
	R_2
39a	$-N(CH_3)_2$
39b	morpholinyl

In continuation of their previous work, Thomas *et al*[57] synthesised a new series of quinolin-4-yl-1, 2, 3-triazolylamides, sulphonamides and amidopiperazines as potential antitubercular agents.



[40]

	R_1
40a	CH_3
40b	4-methoxyphenyl

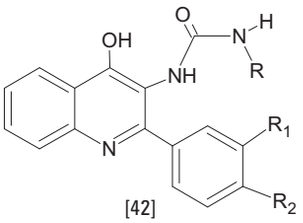


[41]

	R
41a	CH_3
41b	4-methoxybenzoyl

5.6. 2, 3, 4-trisubstituted quinolines

A series of new 1, 3-oxazolo[4,5-c]quinoline derivatives was synthesized by Eswaran *et al* [62] and subsequently screened their activity as potent antitubercular agents.



[42]

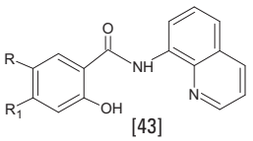
	R	R_1	R_2
42a	2-OCH_3-C_6H_4	F	H
42b	2-OCH_3-C_6H_4	H	F
42c	-$CH_2C_6H_5$	F	H

These synthesized entities showed good to moderate inhibitory activity against different bacterial strains, while compounds 42a and 42b emerged as the lead antitubercular agents with better therapeutic profile than INH (MIC: 1.5 μg/ml) with MIC 1 μg/ml.

6. Quinoline as antitumor agents

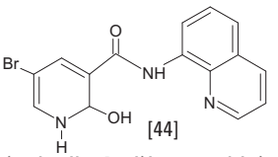
6.1. 8-substituted quinolines

A series of quinoline amide derivatives were synthesized by Yang *et al*[24] and biologically evaluated their activity as novel VEGFR-2 inhibitors.



[43]

	R	R_1
43a	Cl	H
43b	H	CH_3

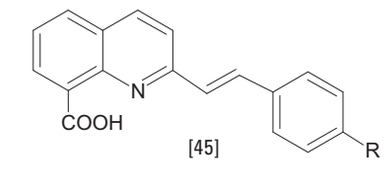


[44]

Compound 43a (5-chloro-2-hydroxy-N-(quinolin-8-yl)benzamide) exhibited the most potent inhibitory activity (IC50 = 3.8 and 5.5 μM for VEGFR-2 kinase and HUVEC, respectively).

6.2. 2, 8-disubstituted quinolines

Podeszwa *et al*[30] synthesized quinoline-5, 8-diones and styrylquinolinecarboxylic acid derivatives and investigating their moderate anticancer activity in different tumor cell lines.



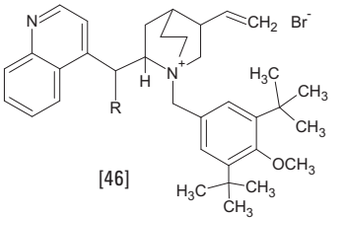
[45]

	R
45a	*p*-Cl
45b	*o*-OH

7. Quinoline as antimalarial agents

7.1. 4-substituted quinolines

Park *et al*[23] synthesized a series of new antimalarial analogues of quinoline, which showed good therapeutic profile.

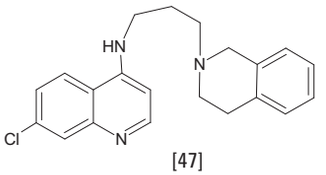


[46]

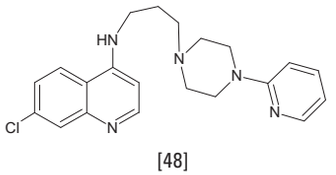
	R
46a	OH
46b	

7.2. 4, 7-disubstituted quinolines

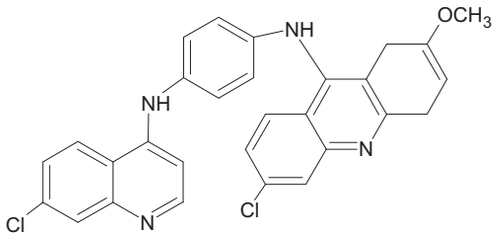
Kumar *et al*[39] synthesized a new series of 4-aminoquinolines and quinoline–acridine hybrids derivatives and screened their pharmacological activity as antimalarial.



[47]



[48]

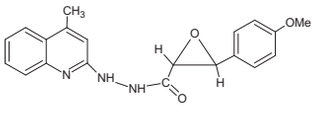


[49]

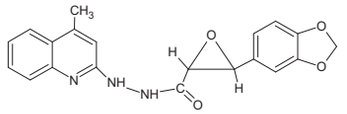
8. Quinoline as antiviral agents

8.1. 2, 4-disubstituted quinolines

Kidwai *et al*[35] synthesized oxiranes with quinoline substituted derivatives and evaluated their pharmacological activity as moderate antiviral agents.



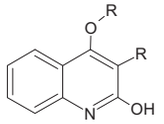
[50]



[51]

8.2. 2, 3, 4-trisubstituted quinolines

Ahmed *et al*[63] synthesized a series of alkylated quinoline 2, 4-diols and evaluated their potential anti-HIV activity in human CD4+ T cell line.



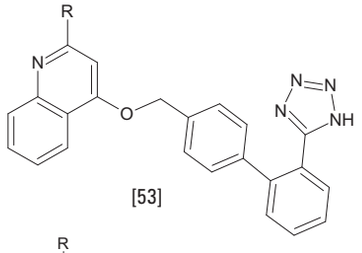
[52]

	R
52a	-$CH_2CH_2CH=C(CH_3)_2$
52b	-$CH_2CH=C(CH_3)_2$

9. Quinoline as antihypertensive agents

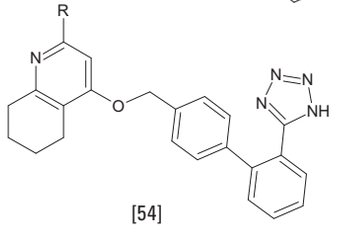
9.1. 2, 4-disubstituted quinolines

Allott *et al*[36] synthesized a series of Quinoline-1, 5-naphthyridine and pyridine derivatives as potent nonpeptidic angiotensin II receptor antagonists.



[53]

	R
53	CH_3

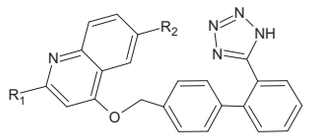


[54]

	R
54a	Et
54b	Me

9.2. 2, 4, 6-trisubstituted quinolines

Sharma *et al*[59] performed a 3D QSAR kNN-MFA approach on a series of substituted quinolines as potent angiotensin II receptor antagonists.

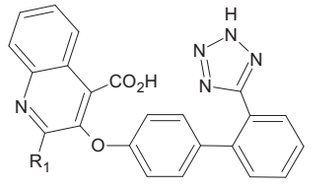


[55]

	R_1	R_2
55a	C_2H_5	$-CH_2CH_2F$
55b	C_2H_5	$-COOCH_3$
55c	C_2H_5	$-OCH_3$

9.3. 2, 3, 4-trisubstituted quinolines

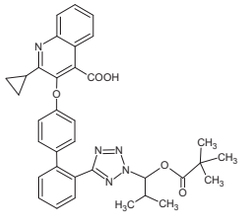
Lloyd *et al*[65] synthesized a series of quinoline-4-carboxylic acid derivatives as potent anti-hypertensives by inhibiting angiotensin II receptor.



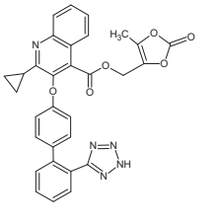
[56]

	R_1
56a	*c*-C_3H_7
56b	CH_3
56c	*n*-C_3H_7

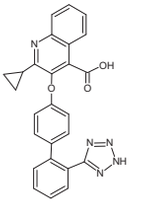
Ryono *et al*[66] synthesized a series of newly orally active prodrug of quinoline-4-carboxylic acid derivatives and evaluated their activity as angiotensin II receptor antagonists.



[57]



[58]

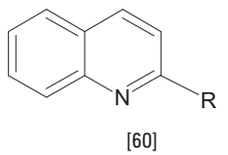


[59]

10. Quinoline as antileishmanial agents

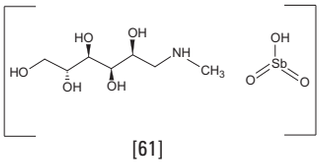
10.1. 2-substituted quinolines

A series of new quinoline derivatives were designed and synthesized by Fakhfakh *et al* [21] and screened their therapeutic potentiality as anti-protozoal and anti-retroviral.



[60]

	R
60a	-CH=CH-Br
60b	-C ≡CH
60c	$-CH=CH-CH_2-OH$
60d	$-CH(OH)-CH_2-CH_3$
60f	$-C \equiv C-Si(CH_3)_3$



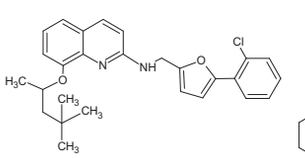
[61]

Among the synthesized compounds 60a, 60b and 60c showed good activity against *Leishmania amazonensis* amastigotes a lower IC_{50} (around 5 μM) than the reference drug, glucantime1[61] (20 μM). Compounds 60d and 60c have a significant inhibitory activity against *Trypanosoma brucei* and *Leishmania infantum* (both compounds have an IC_{50} of 3 μM and 2 μM, respectively). Compound 60f exhibited submicromolar antiviral activity against HIV-1 replication in CEM4fx cells (IC_{50} around 0.5 μM).

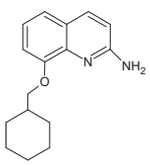
11. Quinoline as antiobesity agents

11.1. 2, 8-disubstituted quinolines

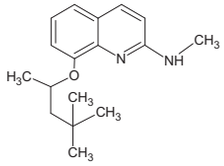
A series of 2-amino-8-alkoxy quinoline derivatives were synthesized by Souers *et al*[31] and subsequently evaluated their activity as MCHr1 antagonists.



[62]



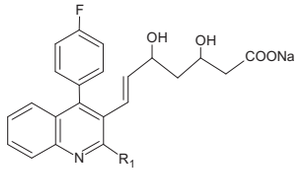
[63]



[64]

11.2. 2, 3, 4-trisubstituted quinolines

Suzuki *et al*[64] synthesized a series of quinolines and biologically evaluated their HMG-CoA reductase inhibitory activity.



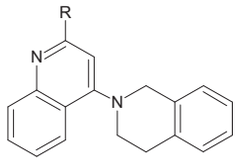
[65]

	R_1
65a	cyclopropyl
65b	C_6H_5
65c	CF_3

12. Quinoline as neurodegenerative agents

12.1. 2, 4-disubstituted quinolines

Buttelmann *et al*[37] synthesized a series of 4-(3, 4-dihydro-1H-isoquinolin-2-yl)-quinolines derivatives as potent NR1/2B subtype selective NMDA receptor antagonists.



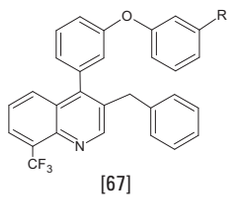
[66]

	R
66a	H
66b	NH_2
66c	$NH(CH_2)OH$

13. Quinoline as liver X-receptor agonist

13.1. 3, 4, 8-trisubstituted quinolines

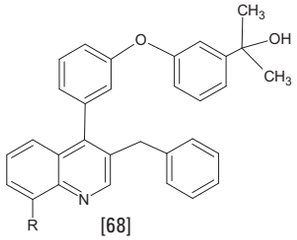
Bernotas *et al*[42] synthesized a series of biarylether amide quinoline derivatives and subsequently evaluated their pharmacological activity as liver X receptor agonists.



[67]

	R
67a	
67b	
67c	

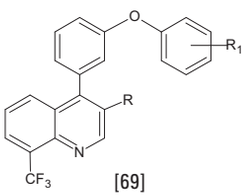
Following their previous work the same worker[43] synthesized a series of 4-(3-aryloxyaryl)quinoline derivatives and subsequent screening of their activity as a potent liver X receptor agents.



[68]

	R
68a	CF_3
68b	Cl

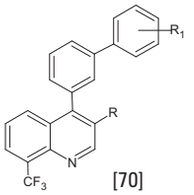
It was Bernotas *et al*[44] further, synthesized a series of 4-(3-aryloxyaryl)quinoline sulfone derivatives and screened their activity as potent liver X receptor agonist.



	R	R_1
69a	CH_3	$3\text{-}SO_2CH_3$
69b	$CH_2C_6H_5$	$3\text{-}SO_2CH_3$
69c	CH_3	$3\text{-}SO_2C_3H_7$

[69]

Ullrich *et al*[45] synthesized a series of 4-(3-biaryl)quinoline sulfone derivatives as potent liver X receptor agonists.



	R	R_1
70a	C_2H_5	$3\text{-}SO_2\ CH_3$
70b	H	$3\text{-}SO_2\ CH_3$
70c	CH_3	$3\text{-}SO_2\ CH_3$

[70]

14. Conclusion

Quinoline is a unique scaffold in the field of medicinal chemistry research. The above studies distinctly mention the potentiality of quinoline moiety, when linked with various functional groups in easing out diverse range of disease states. Thus, we can conclude that this review will clearly provide the researchers a vast array of information about the structure activity relationship study, which in turn help in designing a handful number of novel quinoline derivatives as well as analogs with a strong impact in curing many life threatening diseases.

Acknowledgements

Both the authors convey their heartiest thanks to their respective principals and management for the proper facilities provided to them in completion of the manuscript.

Conflicts of Interest

The authors report no conflict of interest.

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