Recent developments of quinoline based antimalarial agents

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Estudios recientes acerca de los agentes antipalúdicos o antimaláricos a base de quinolina

Recent estudis sobre els agents antipalúdics o antimalàrics basats en la quinolina

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SUMMARY

Malaria is a well known death causing disease worldwide. A number of quinoline based antimalarial compounds have been synthesized up till now after the discovery of antimalarial character of quinine. This review covered a diversified quinoline derivatives presented during the last five years, thus highlighting their importance as antimalarial agents.

Keywords: Quinoline derivatives; antimalarial activity; naturally occurring quinolines; quinine; synthetic quinolines.

RESUMEN

La malaria es una enfermedad conocida en todo el mundo que puede causar la muerte. Por el momento se han sintetizado una serie de compuestos antimaláricos a base de quinolina tras la síntesis de la quinina. Esta revisión ha abarcado una serie diversificada de derivados de quinolina que se han presentado en estos últimos cinco años, y destaca su importancia como agentes antimaláricos.

Palabras clave: Derivados de quinolina; actividad antipalúdica; quinolinas de origen natural; quinina; quinolinas sintéticas.

RESUM

La malària es una infermetat coneguda arreu del mon que pot causar la mort. Fins al moment s'han sintetitzat una sèrie de compostos antimalàrics a base de quinolina després de la síntesi de la quinina. Aquesta revisió ha tractat una sèrie amplia de derivats de quinolina que s'han presentat en aquests darrers cinc anys, i ressalta la seva importància com agents antimalàrics.

Paraules clau: Derivats de quinolina; activitat antipalúdica; quinolines d'origen natural; quinina; quinolines sintètique

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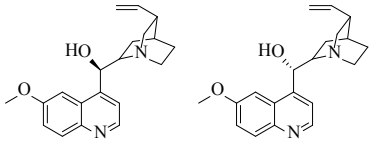
INTRODUCTION

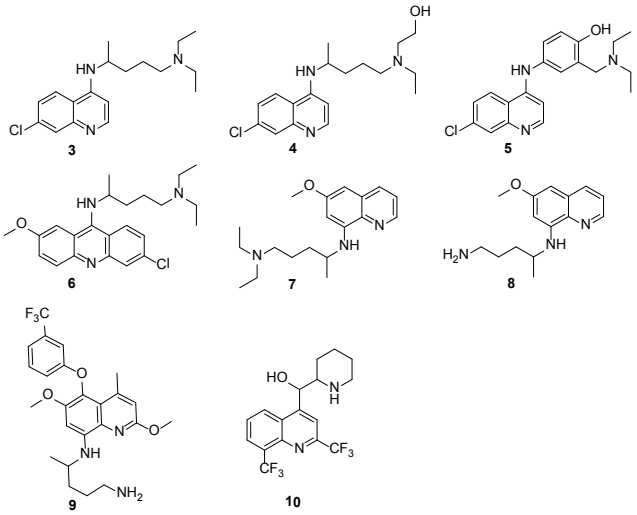
The history of quinoline based antimalarial drugs started from the alkaloid quinine **1** (Fig. 1). The natural source of quinine is Cinchona tree which was named after the Countess of Chinchon because the bark of Cinchona tree was used to cure her from malaria first time in 1630s and properties of Cinchona tree were discovered. After that, the use of Cinchona tree's bark started to treat malaria in different countries in different ways. This discovery developed the interest of scientists to explore new ways and drugs to cure malaria that led to the achievement of novel antimalarial drugs. For the first time, Woodward and von Doering provided the synthetic pathway for quinine **1**. Quinidine **2** (Fig. 1) is also an antimalarial drug which is a stereoisomer of quinine[1].



1 **2**

Literature elaborated a lot of important quinoline based antimalarial agents and among them 4-aminoquinoline antimalarial drugs (Fig. 2) are illustrated in the proceeding lines. Chloroquine **3**, sold under the trade name "aralen" is manufactured in the form of diphosphate (aralen phosphate, resochin) for oral administration. It is also available as intramuscular injection in the form of hydrochloride for the treatment of malaria induced coma[1]. Hydroxychloroquine **4**, also known as "Plaquenil" and "Axemal" in India, shows fast gastrointestinal absorption and quick elimination from the body[2]. Similarly, Amodiaquine **5**, sold under the trade name "Camoquin" or "Flavoquine", has been used in Africa for the treatment of malaria in combination therapy[3]. Another 4-aminoquinoline is quinacrine **6** (substituted acridine), also known as mepacrine. It was introduced as antimalarial drug in the mid-1930s[4]. Now days, it is sold under the trade name "Atabrine" for the treatment of other diseases. Similarly, there is also a variety of 8-aminoquinolines (Fig. 2), among them first antimalarial 8-amino quinoline, Pamaquine **7**, was synthesized in 1924 and used for the treatment of malaria in birds in 1926 and then in humans too[5]. Later on, Primaquine **8** was synthesized by Robert Elderfield in 1940[6] and is used for the treatment of malaria against *P. vivax or P. ovale*[7]. Similarly, Tafenoquine **9** is also an 8-aminoquinoline drug, used for the treatment and prevention of malaria against *Plasmodium falciparum*[8].

In addition, Mefloquine **10** (trade name "Lariam") possessing fluoro and hydroxy groups in its structure (Fig. 2) has been used for the treatment of Chloroquine-resistant as well as Chloroquine-sensitive *Plasmodium falciparum* malaria[9].

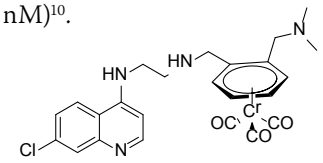


3 **4** **5** **6** **7** **8** **9** **10**

REVIEW OF LITERATURE

4-Aminoquinolines

As a result of interest in 4-aminoquinoline derivatives, two chromium arene-quinoline half sandwich complexes were prepared by Glans et al in their laboratory. Screening of compounds for their *in vitro* antimalarial activity against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* proved *N*[1]-(7-chloroquinolin-4-yl)-*N*[2]-(2-((dimethylamino)methyl)benzyl) ethane-1,2-diamine **11** (IC_{50} = 33.9nM), twice active against malarial parasite than organic ligand alone (IC_{50} = 63.1 nM)[10].



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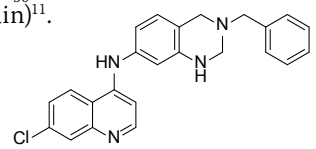
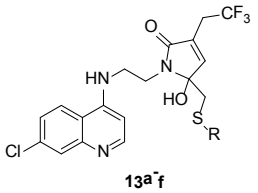
Quinoline based benzoxazines were synthesized and evaluated for *in vitro* and *in vivo* antimalarial activity against chloroquine sensitive (D10), chloroquine resistant (W2) strains of *P. falciparum* and mouse malaria respectively by Gemma and co-workers. Among the synthesized compounds, 3-benzyl-*N*-(7-chloroquinolin-4-yl)-1,2,3,4-tetrahydroquinazolin-7-amine **12** was mirrored as the most promising antimalarial agent with IC_{50} value 53nM (for D10 strain) and 67 nM (for W2 strain)[11].



12

In 2013, Kanishchev and colleagues reported a multi-step synthesis of new 4-aminoquinoline γ-lactams and evaluated their *in vitro* antimalarial activity against Chloroquine-sensitive (3D7) and Chloroquine-resistant (W2) strains of *P. falciparum*. Most of the synthesized lactams **13a-f** demonstrated excellent potential against W2 strain while against 3D7 strain only 1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-5-hy-

droxy-5-((pyridin-4-ylthio)methyl)-3-(2,2,2-trifluoroethyl) -1*H*-pyrrol-2(5*H*)-one **13d** exhibited activity (IC_{50} = 89nM) comparable to chloroquine (IC_{50} = 750nM (for W2) and 30nM (for 3D7)) (Table 1)[12].

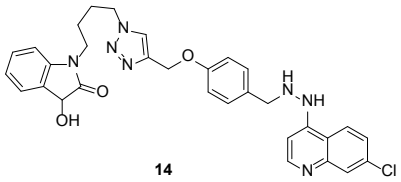


13a-f

Table 1: *Antimalarial potential of compounds* **13a-f** *against W2) strain of P. falciparum.*

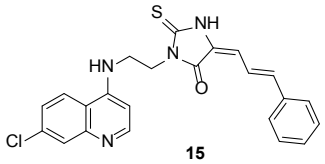
Compound	R	IC_{50} (nM)	Compound	R	IC_{50} (nM)
13a	Ph	167	**13d**	4-Pyridyl	666
13b	*p*-$MeOC_6H_4$	173	**13e**	2-Pyrimidyl	458
13c	2-Pyridyl	218	**13f**	2-Pyridyl-N-oxide	274

In the next year, a series of 1*H*-1,2,3-triazole-tethered isatin-7-chloroquinoline and 3-hydroxy-indole-7-chloroquinoline conjugates were synthesized by Raj et al. A screening of synthesized compounds for their antimalarial activity against chloroquine-resistant W2 strain of *Plasmodium falciparum* showed that the 1-(4-(4-((4-((2-(7-chloroquinolin-4-yl)hydrazinyl)methyl)phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)butyl)-3-hydroxyindolin-2-one **14** exhibited highest activity (IC_{50} = 69.0 nM) comparable to the reference drug, chloroquine (IC_{50} = 60.0 nM) but less than artemisinin (IC_{50} = 7.00 nM)[13].



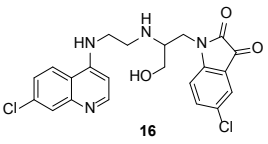
14

After that, Raj and co-workers synthesized C-3 thiourea functionalized β-lactams, β-lactam-7-chloroquinoline conjugates and 7-chloroquinoline-thiohydantoin derivatives. An assessment of their *in vitro* anitimalarial activity against Chloroquine-reistant(W2) strain of *Plasmodium falciparum* revealed that (E)-3-(2-((7-chloroquinolin-4-yl)amino) ethyl)-5-((E)-3-phenylallylidene)-2-thioxoimidazolidin-4-one **15** was found to be the most active with no cytotoxicity (IC_{50} values in nM: **15** = 39.84, Chloroquine = 99.0, Artemisinin = 14.0)[14].



15

Later on, a series of β-amino alcohol tethered 4-aminoquinoline-isatin conjugates was synthesized by Nisha et al. A test for their *in vitro* antimalarial activity against chloroquine resistant W2 strain of *Plasmodium falciparum* concluded that 5-chloro-1-(2-((2-((7-chloroquinolin-4-yl)amino)ethyl)amino)-3-hydroxypropyl)indoline-2,3-dione **16** (IC_{50} = 11.8 nM) and 5-chloro-1-(2-((3-((7-chloroquinolin-4-yl)amino) propyl)amino)-3-hydroxypropyl)indoline-2,3-dione **17** (IC_{50} = 13.5 nM) exhibited significant antimalarial efficacy (no toxicity) greater than chloroquine (IC_{50} = 36.37 nM) but less than Artemisinin (IC_{50} = 4.37 nM)[15].



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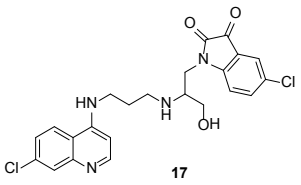
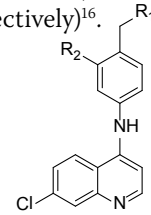


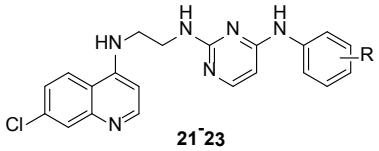
17

Further investigation of antimalarial activity of dehydroxy-isotebuquine derivatives against *Plasmodium berghei* by Romero and co-workers revealed that derivatives **18**, **19** and **20** remarkably inhibited the haemozoin formation (%IHF values: 97.080, 98.490 and 97.250 respectively)[16].



18 R_1 = piperidin-1-yl, R_2 = Ph
19 R_1 = pyrrolidin-1-yl, R_2 = Ph
20 R_1 = pyrrolidin-1-yl, R_2 = 4-Cl-C_6H_4

Similarly, a series of novel 4-aminoquinoline-pyrimidine hybrids was synthesized and evaluated by Kumar et al. for their *in vitro* antimalarial activity against a D6-chloroquine sensitive and a W2-chloroquine resistant clone of *P. falciparum.* In the synthesized series, three 4-aminoquinoline-pyrimidine hybrids **21-23** showed potent antimalarial activity with low cytotoxicity (Table 2)[17].

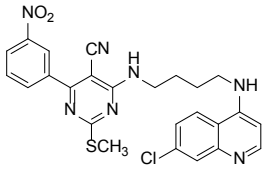


21-23

Table 2: *In vitro antimalarial activity of compounds* **21-23** *against D6 and W2 strains of P. falciparum.*

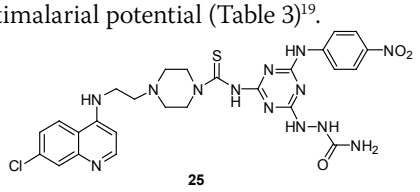
Compounds	21	22	23	Chloroquine	Pyrimethamine
R	3,5-OMe	H	4-F	-	-
IC_{50} (D6, μM)	0.033	0.019	0.028	0.035	0.01
IC_{50} (W2, μM)	0.058	0.144	0.094	0.367	Not tested

Due to excellent potency of 4-anino quinolines, Kaur and colleagues obtained hybrids of 5-cyanopyrimidine and quinoline. Screening of *in vitro* antimalarial activity against NF54-chloroquine sensitive and Dd2-chloroquine resistant strains of *Plasmodium falciparum* pointed out 4-((4-((7-chloroquinolin-4-yl) amino)butyl)amino)-2-(methylthio)-6-(3-nitrophenyl)pyrimidine-5-carbonitrile **24** the best antimalarial agent against Dd2 strain of *Plasmodium falciparum* with IC_{50}=55.8 nM which is four-fold greater than chloroquine having IC_{50}=257.6 nM[18].



24

In the same year, the synthesized series of novel 4-aminoquinoline-1,3,5-triazine derivatives was evaluated by Bhat et al. for their *in vitro* antimalarial activity against Chloroquine-sensitive (3D-7) and Chloroquine-resistant (RKL-2) strains of *Plasmodium falciparum* and *in vivo* antimalarial activity against *P. berghei*. Finally, authors concluded that 2-(4-(4-(2-((7-chloroquinolin-4-yl)amino)ethyl)piperazine-1-carbothioamido)-6-((4-nitrophenyl)amino)-1,3,5-triazin-2-yl) hydrazinecarboxamide **25** showed good *in vitro* and *in vivo* antimalarial potential (Table 3)[19].

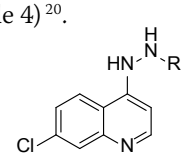


25

Table 3: *In vitro and in vivo antimalarial activity of compound* **25**.

Compound	% Dead asexual parasites (in vitro)			
	3D-7		RKL-2	
25	5 µg/ml	50 µg/ml	5 µg/ml	50 µg/ml
Chloroquine (0.7 µg/ml)	22.0	36.0	22.3	45.3
Chloroquine (1.2 µg/ml)	49.5		45.0	
Proguanil (>200µg/ml)	50.0		50.0	
Treatment	Mean % parasitaemia inhibition (in vivo)			
25	64.50			
Chloroquine	90.35			

Similarly, Soares and colleagues evaluated hydrazine/hydrazide derivatives for their *in vitro* antimalarial activity against *Plasmodium falciparum* (Chloroquine-sensitive 3D-7 and Chloroquine-resistant W2 strains). Among all tested compounds, hydrazine derivatives **26, 27** demonstrated antimalarial potential better than hydrazides **28**,**29** and comparable to chloroquine (Table 4) [20].

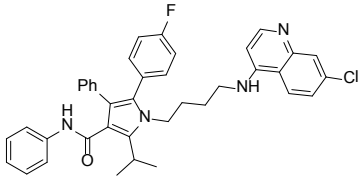


26-29

Table 4: *In vitro antimalarial activity of compounds* **26-29** *against 3D7 and W2 strains of Plasmodium falciparum.*

Compounds	R	IC_{50} (3D7, µg/mL)	IC_{50} (W2, µg/mL)
26	H	0.46	<0.39
27	Ph	<0.19	<0.39
28	CO-3-Pyridyl	1.76	1.57
29	COPh	0.89	0.58
Chloroquine	-	<0.19	<0.39

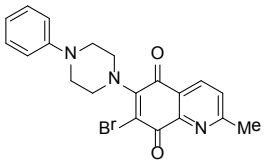
Recently, a new class of hybrids of Atorvastatin (AVA) and aminoquinolines (primaquine and chloroquine derivatives) was achieved by Carvalho and colleagues. An assessment of *in vitro* antimalarial activity against a W2-chloroquine resistant *P. falciparum* clone, revealed that the among the synthesized compounds, 1-(4-((7-chloroquinolin-4-yl)amino)butyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide **30** emerged as the most effective one in terms of activity and toxicity (IC_{50} values in **µM**, chloroquine = 0.59, Primaquine = 1.89, Atorvastatin = 10.3, **30** = 0.40)[21].



30

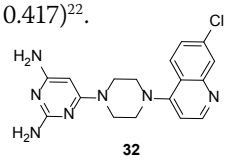
Piperazine based quinolines

In 2012, Hussain and co-workers reported the synthesis of new quinoline-5,8-dione and hydroxynaphthoquinone derivatives. An investigation of their *in vitro* antimalarial activity against chloroquine-sensitive strain NF54 of *Plasmodium falciparum* pointed out 7-bromo-2-methyl-6-(4-phenylpiperazin-1-yl) quinoline-5,8-dione **31**, the most active antimalarial agent (IC_{50} values in **µM, 31** = 2.21, chloroquine = 0.02)[22].



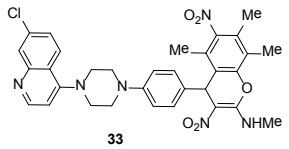
31

Quinoline–pyrimidine hybrids were synthesized by Pretorius and co-workers in 2013. An evaluation of the synthesized compounds for *in vitro* antimalarial activity against both chloroquine sensitive (D10) and chloroquine resistant strains (Dd2) of two clones of the human *Plasmodium* falciparum malaria, concluded that 6-(4-(7-chloroquinolin-4-yl)piperazin-1-yl) pyrimidine-2,4-diamine **32** (IC_{50} in µM: D10 = 0.070, Dd2 = 0.157) demonstrated significant antimalarial potential compared to chloroquine (IC_{50} in µM: D10 = 0.040, Dd2 = 0.417)[22].



32

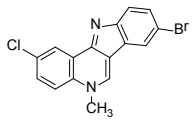
Later on, Parthiban and co-workers synthesized a series of chloroquinoline-4*H*-chromene conjugates incorporating piperizine or azipane tethers and evaluated their antimalarial activity against two *Plasmodium falciparum* strains namely 3D7 chloroquine sensitive (CQS) and K1 chloroquine resistant (CQR). Among all the synthetic conjugates, 4-(4-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)phenyl)-*N*,5,7,8-tetramethyl-3,6-dinitro-4*H*-chromen-2-amine **33** (IC_{50} in µM: 3D7 = 0.62, KI = 1.78) showed good antimalarial activity against two strains of *P. falciparum* (Chloroquinine IC_{50} in µM: 3D7 = 0.005, KI = 0.254)[24].



33

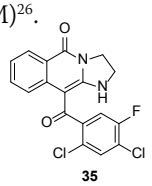
Quinolines fused with other ring systems

In 2011, Whittell et al. synthesized a series of mono- and di-substituted analogues of isocryptolepine and evaluated for *in vitro* antimalarial activity against chloroquine-sensitive (3D7) and chloroquine-resistant (W2mef) *Plasmodium falciparum* strains.Di-halogenated compounds were found the most potent derivatives and 8-bromo-2-chloroisocryptolepine **34** displayed good antimalarial activity against (3D7) and (W2mef) strains with IC_{50} values 57 ± 14nM and 85 ± 5.6nM respectively[25].



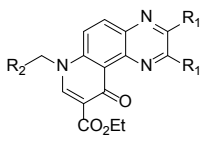
34

A series of novel imidazoisoquinolinone derivatives were synthesized and evaluated for *in vitro* antimalarial activity against chloroquine sensitive strain of *Plasmodium falciparum* by Bollini et al. 10-(2,4-dichloro-5-fluorobenzoyl)-2,3-dihydroimidazo[1,2-b] isoquinolin-5(1*H*)-one **35** (IC_{50} = 0.13μM) exhibited good antimalarial activity comparable to chloroquinine (IC_{50} = 0.09 μM)[26].



35

A series of novel N-alkyl dihydropyridoquinoxaline derivatives were successfully synthesized by Shekhar and colleagues. Ethyl 7-(4-fluorobenzyl)-10-oxo-2,3-diphenyl-7,10-dihydropyrido[3,2-f]quinoxaline-9-carboxylate **36** and ethyl 2,3-bis(4-fluorophenyl)-10-oxo-7-(2,2,2-trifluoroethyl)-7,10-dihydropyrido[3,2-f] quinoxaline-9-carboxylate **37** emerged as the most potent compounds as a result of their screening for in vitro antimalarial activity against chloroquine sensitive (3D7) and drug resistant (Dd2) strains of Plasmodium falciparum (Table 5)27.



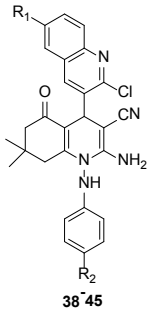
36-37

Table 5: *In vitro antimalarial activity of compound* **36** *and* **37** *against chloroquine sensitive (3D7) and drug resistant (Dd2) strains of Plasmodium falciparum.*

Compounds	R_1	R_2	IC_{50} (3D7, μM)	IC_{50} (Dd2, μM)
ciprofloxacin	-	-	23.1	33.9
36	Ph	4-F-C_6H_4	6.94	6.27
37	4-F-C_6H_4	CF_3	3.92	4.60

Oxoquinolines

Later on, *N*-aryaminobiquinoline derivatives were synthesized and evaluated for their antimalarial activity against chloroquine-sensitive (3D7) strain of *Plasmodium falciparum* by Shah and colleagues. They concluded that *N*-aryaminobiquinoline derivatives **38-45** have superior antimalarial activity compared to chloroquine (Table 6)[28].

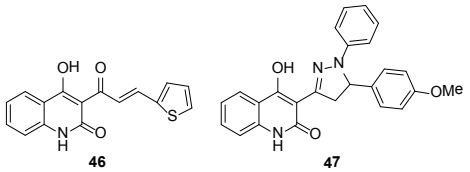


38-45

Table 6: *Antimalarial activity of compounds* **38-45** *against 3D7 strain of Plasmodium falciparum.*

Compound	R_1	R_2	IC_{50} (μg/mL)	**Compound**	R_1	R_2	IC_{50} (μg/mL)
38	H	H	0.015	**43**	OCH_3	OCH_3	0.019
39	CH_3	H	0.008	**44**	CH_3	Br	0.012
40	OCH_3	Cl	0.009	**45**	OCH_3	Br	0.014
41	H	CH_3	0.005	Chloro-quine			0.020
42	Cl	CH_3	0.014				

Microwave assisted green syntheses and protein–ligand docking calculations on *P. falciparum* UCHL3 protein, were carried out by Sarveswari and colleagues in 2015 for 4-hydroxy-3-(3-arylacryloyl)quinolin-2(1*H*)-ones and 3-(4,5-dihydro-5-aryl-1-phenyl-1*H*-pyrazol-3-yl)-4-hydroxyquinolin-2(1*H*)-ones. Experimental results revealed that (E)-4-hydroxy-3-(3-(thiophen-2-yl)acryloyl)quinolin-2(1*H*)-one **46** and 4-hydroxy-3-(5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)quinolin-2(1*H*)-one **47** exhibited greater potential for the inhibition of targeted protein as indicated by their lowest binding energy values, -6.59 and -8.05 Kcal/mol respectively[29].

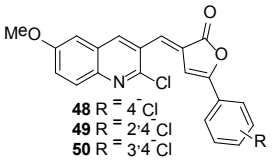


46 47

Substituted quinolines

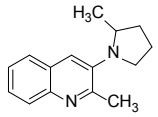
Akhter et al. synthesized a series of Quinoline-substituted furanone derivatives and checked their antimalarial activity for the inhibition of gametocyte-producing *P. falciparum* culture lines (FDL-HD). Among the synthesized compound, (*E*)-3-((2-chloro-6-methoxyquinolin-3-yl)methylene)-5-(4-chlorophenyl)furan-2(3*H*)-one **48** (IC_{50} = 0.61 μg/mL), (*E*)-3-((2-chloro-6-methoxyquinolin-3-yl)methylene)-5-(2,4-chlorophenyl)furan-2(3*H*)-one (IC_{50} = 0.50 μg/mL)**49** and (*E*)-3-((2-chloro-6-methoxyquinolin-

3-yl)methylene)-5-(3,4-chlorophenyl)furan-2(3*H*)-one (IC_{50} = 0.72 µg/mL) **50** showed good antimalarial activity (chloroquine IC_{50} = 0.002 µg/mL)[30].



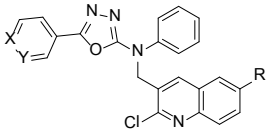
48 R = 4-Cl
49 R = 2,4-Cl
50 R = 3,4-Cl

In the same year, Vandekerckhove et al. synthesized a series of aminoquinolines and evaluated for their *in vitro* antimalarial activity. Antimalarial activity was tested against both chloroquine sensitive (NF54) and chloroquine resistant strains (Dd2) of *Plasmodium falciparum*. All the compounds showed moderate activity and among them 2-methyl-3-(2-methylpyrrolidin-1-yl)quinoline **51** (IC_{50} values in µM: NF54 = 13.3, Dd2 = 38.0) showed best results (chloroquine IC_{50} values in µM: NF54 = 0.021, Dd2 = 0.274)[31].



51

Later on, the synthesized quinoline based 1,3,4-oxadiazoles derivatives were screened for their antimalarial potential against chloroquine and quinine sensitive strain of *Plasmodium falciparum* strain and according to results 1,3,4-oxadiazoles derivatives **52-56** demonstrated excellent antimalarial activity (Table 7)[32].

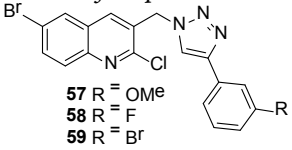


52-56

Table 7: *In vitro antimalarial activity of compounds* **52-56**.

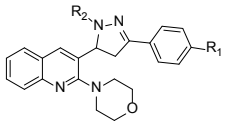
Compounds	52	53	54	55	56	Quinine	Chloroquine
X	CH	CH	CH	N	CH	-	-
Y	N	N	N	CH	N	-	-
R	H	CH_3	OCH_3	Cl	Cl	-	-
IC_{50} (µM)	0.386	0.467	0.202	0.089	0.156	0.826	0.062

In the same year, Parthasaradhi and colleagues synthesized a series of novel 6-bromo-2-chloro-3-(4-phenyl-[1,2,3] triazol-1-ylmethyl)-quinoline and its derivatives. Analysis of antimalarial activity inferred that 6-bromo-2-chloro-3-((4-(3-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)methyl)quinoline **57** (IC_{50} = 5.09µM), 6-bromo-2-chloro-3-((4-(3-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)quinoline **58** (IC_{50} = 3.25µM) and 6-bromo-2-chloro-3-((4-(3-bromophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)quinoline **59** (IC_{50} = 2.13µM) exhibited remarkable potential against W2 strain of *Plasmodium falciparum*[33].



57 R = OMe
58 R = F
59 R = Br

In recent reports, Karad et at. 2016 synthesized a series of novel morpholinoquinoline based conjugates with pyrazoline moiety was achieved and evaluated for their *in vitro* antimalarial activity against *P. falciparum* strain by Karad and colleagues. Seven conjugates **60-66** exhibited excellent *in vitro* antimalarial activity compared to reference drugs (Table 8)[34].



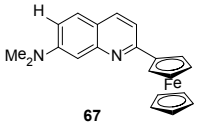
60-66

Table 8: *In vitro antimalarial activity of compounds* **60-66** *against P. falciparum strain.*

Compound	R_1	R_2	IC_{50} (µM)	Compound	R_1	R_2	IC_{50} (µM)
60	OMe	COMe	0.034	**65**	Br	CHO	0.040
61	Br	COMe	0.018	**66**	Cl	CHO	0.028
62	Br	$CSNH_2$	0.044	Chloroquine	-	-	0.062
63	OMe	4-F-C_6H_4	0.051	Quinine	-	-	0.826
64	Br	4-F-C_6H_4	0.015				

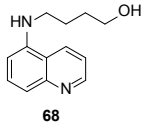
2.6 Miscellenous quinolines

In 2012, Patti et al. reported the synthesis and *in vitro* antimalarial activity of 2-ferrocenylquinoline derivatives against chloroquine-susceptible D10 and chloroquine-resistant W2 strains of *Plasmodium falciparum*. Among all the synthesized compounds, 2-ferrocenylquinoline derivative **67** showed good antimalarial activity against both chloroquine-susceptible D10 and chloroquine-resistant W2 strains of *Plasmodium falciparum* with IC_{50} values 14.8µM and 13.8µM respectively[35].



67

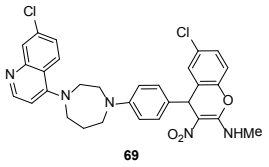
Vandekerckhove et al. synthesized a series of aminoquinolines and evaluated for their *in vitro* antimalarial activity. Antimalarial activity was tested against both chloroquine sensitive (NF54) and chloroquine resistant strains (Dd2) of *Plasmodium falciparum*. All the compounds showed moderate activity and among them 4-(quinolin-5-ylamino)butan-1-ol **68** (IC_{50} values: NF54 = 19.9 µM, Dd2 = 49.0) showed best results (Quinoline IC_{50} values: NF54 = 0.021 µM, Dd2 = 0.274)[31].



68

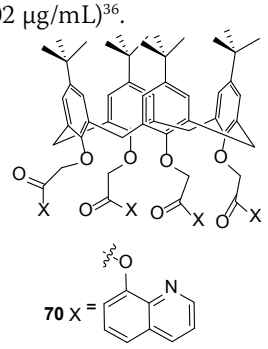
Later on, Parthiban and co-workers synthesized a series of chloroquinoline-4*H*-chromene conjugates incorporating piperizine or azipane tethers and evaluated their antimalarial activity against two *Plasmodium falciparum* strains namely 3D7 chloroquine sensitive (CQS) and K1 chloroquine resistant (CQR). Among all the synthetic conjugates, 6-chloro-4-(4-(4-(7-chloroquinolin-4-yl)-1,4-diazepan-1-yl)phenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine **69** (IC_{50} values:

3D7 = 0.29 μM, KI = 0.496) showed good antimalarial activity against two strains (3D7 and K1) of *P. falciparum* (Quinoline IC_{50} values: 3D7 = 0.005 μM, KI = 0.254)[21].



69

In the same year, Shah et al. reported the synthesis of a series of quinoline-pyrimidine linked calix[4] arene derivatives with different functional groups. Results of antimalarial activity assay showed that 8-hydroxy quinoline linked calix[4]arene derivative **70** have good antimalarial activity with IC_{50} values of 0.073 μg/ml comparable to the standard drug chloroquine (IC_{50} 0.02 μg/mL)[36].



CONCLUSION

Quinoline and its derivatives are important antimalarial agents. So, keeping their significance we have reviewed a variety of quinoline based compounds reported during the last five years as potent antimalarial agents. We hope so that this effort may prove stimulation for the future pharmaceutical chemists.

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