2. LITERATURE

Malaria continues to be a major global health challenge, with Plasmodium falciparum and Plasmodium vivax being the most virulent species affecting humans. The growing resistance to conventional antimalarial drugs, such as chloroquine and artemisinin-based combination therapies (ACTs), highlights the urgent need for new treatment strategies. One promising approach is the development of hybrid antimalarial drugs, which combine two distinct pharmacophores with different mechanisms of action into a single molecule. Unlike combination therapy, where drugs are administered separately, hybrid drugs ensure that both pharmacophores act simultaneously on the parasite, offering advantages such as enhanced efficacy, improved pharmacokinetic properties, and reduced resistance development[1]. Various hybrid compounds are under investigation, including quinoline-artemisinin hybrids, which target both heme detoxification and oxidative stress pathways; antifolate-based hybrids, which inhibit the folate synthesis pathway; and chloroquine-pyrimidine hybrids, which disrupt heme detoxification and pyrimidine biosynthesis. Metal-based hybrids, such as ferroquine, incorporate organometallic components to enhance drug stability and redox activity, while aminoquinoline hybrids merge aminoquinolines with other pharmacophores to extend therapeutic activity. The hybrid approach offers multiple benefits, including increased effectiveness, lower risk of resistance, cost-effectiveness, and simplified treatment regimens. However, challenges remain, such as the complexity of drug design, the need for extensive clinical validation, regulatory hurdles, and the scalability of production. Despite these obstacles, hybrid drugs represent a promising frontier in malaria treatment, with the potential to improve patient outcomes and combat drug-resistant strains effectively[2].

In this literature review various potent compounds synthesized via hybrid approach as anti-malarial agents are discussed.

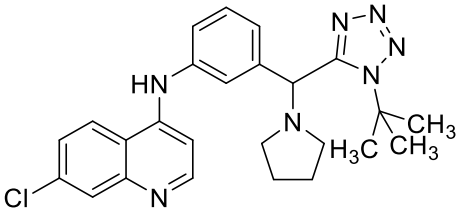
2.1 Azole-based antimalarial agents

2.1.1Tetrazole based antimalarial hybrids

Tetrazole is a crucial heterocyclic compound in medicinal chemistry, valued for its metabolic stability and diverse pharmacological properties. It serves as a bioisostere for carboxylic acid and amide functional groups, enhancing drug design and efficacy. Tetrazole derivatives have demonstrated significant therapeutic potential, particularly

in antimalarial drug development. Additionally, tetrazole-based compounds have been widely explored for their antibacterial activity, with agents such as ceftezole and cefamandole inhibiting bacterial cell wall synthesis. Beyond this, tetrazole hybrids have shown promise as anticancer, antifungal, and antihypertensive agents, further highlighting their versatility in pharmaceutical applications.[2].

The antimalarial properties of tetrazole derivatives were reported by Tukulula *et al*., who investigated deoxyamodiaquine-linked tetrazole hybrids. These synthesized compounds exhibited significant potency against *Plasmodium falciparum*, including the chloroquine-sensitive 3D7 strain and chloroquine-resistant K1 and W2 strains, with IC_{50} values of 0.010 μM, 0.0096 μM, and 0.077 μM, respectively. However, despite their strong inhibition of CYP450, these hybrids **(35)** faced challenges related to poor bioavailability and low pharmacokinetic properties, limiting their clinical potential[3].



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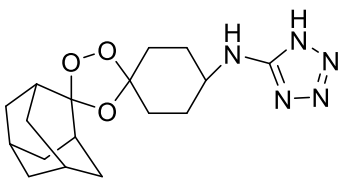
Further research led to the development of a different series of tetrazole-peroxide hybrids exhibiting potent antimalarial activity against both chloroquine-sensitive 3D7 and multidrug-resistant Dd2 *Plasmodium falciparum* strains. Among the synthesized compounds, derivatives (**36)** (IC_{50}: 2.5 and 2.8 nM) and **(37)** (IC_{50}: 2.1 and 2.9 nM) demonstrated efficacy comparable to or exceeding that of artemisinin (IC_{50}: 2.5 and 4.0 nM), artesunate (IC_{50}: 4.6 and 5.1 nM), and dihydroartemisinin (IC_{50}: 4.2 and 4.7 nM)[4].



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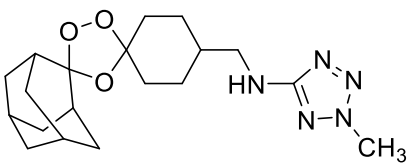

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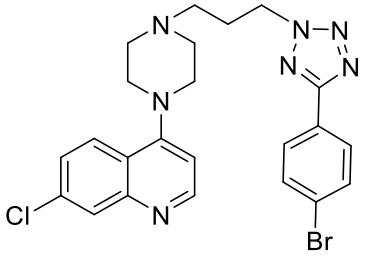
Additionally, Barmade *et al*. developed a hybrid series of quinolinepiperazinyl-aryltetrazoles that demonstrated potent antimalarial activity, specifically targeting the

asexual stage of the parasite. Several derivatives were synthesized, with most, including compounds (**38)** and (**39)**, exhibiting significant antimalarial efficacy, achieving IC_{50} values below 10 μM[5].



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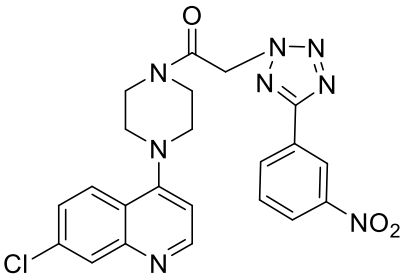

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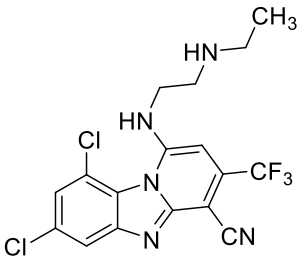
2.1.2 Benzimidazole based antimalarial agents

In 2022, Caroline C. Sousa *et al.* investigated pyrido[1,2-*a*]benzimidazoles as antimalarial agents. Among the synthesized compounds, compound **(40)** exhibited potent parasiticidal activity, with IC_{50} values of 60 ± 5.9 nM and 58.8 ± 9.3 nM against the asexual blood stage of chloroquine (CQ)-susceptible (3D7) and CQ-resistant (W2) strains of *P. falciparum*. Additionally, this compound demonstrated β-hematin inhibitory activity (BHIA) with a value of 2.53 ± 0.25 mM. It displayed superior efficacy in eliminating asexual blood-stage parasites compared to CQ, amodiaquine (AQ), and mefloquine (MFQ), while also showing in vivo parasite clearance and significant suppression of heme detoxification[6].



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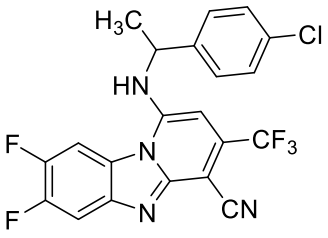

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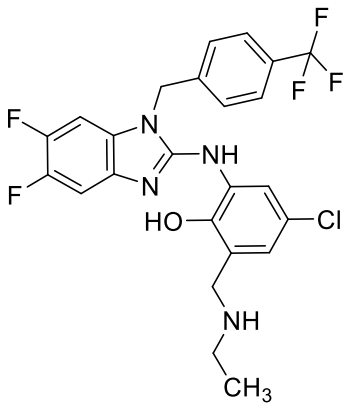
In 2021, Meta Leshabane *et al.* developed and synthesized benzimidazole derivatives as potential novel antimalarial agents. These compounds were evaluated for their activity against the intraerythrocytic asexual blood stages, which cause malaria symptoms, as well as the transmissible gametocyte stages of *Plasmodium falciparum*. Among the synthesized series, 54 compounds exhibited activity, demonstrating submicromolar potency against the asexual blood-stage parasite, while six compounds

showed high potency with IC_{50} values below 100 nM, without significant toxicity toward mammalian cells. Notably, compound (**41)** displayed the highest potency, with an IC_{50} of 94.2 nM against the asexual blood stage, below 5 μM in early-stage gametocytes, and 568.6 nM in late-stage gametocytes. Additionally, it exhibited strong inhibition of male gamete formation, showing 99.8% inhibition at 2 μM (IC_{50} = 697.1 nM)[7].

In 2021, Godwin Akpeko Dziwornu *et al.* explored a series of novel benzimidazole derivatives with phenolic Mannich base side chains at the C2 position, exhibiting potent activity against both the asexual blood and sexual stages of *Plasmodium falciparum*. The 1-benzylbenzimidazole analogues demonstrated submicromolar potency against both parasite stages, whereas the 1H-benzimidazole analogues were primarily effective against the asexual blood stage. Most of the synthesized compounds displayed strong antiplasmodial activity against the NF54 and K1 strains, with IC_{50} values below 1 μM, while maintaining favorable selectivity margins regarding cytotoxicity. Notably, the benzylated benzimidazole derivatives exhibited potent early-stage gametocytocidal activity, with IC_{50} values below 1 μM. Among the 52 synthesized analogues, compound **(42)** emerged as the most promising candidate, demonstrating an IC_{50} of 0.19 μM against *P. falciparum* NF54 and 0.08 μM against the K1 strain. Furthermore, in vivo studies in *P. berghei*-infected mice showed a 98% reduction in parasitemia, highlighting its potential as a strong antimalarial candidate.[8].



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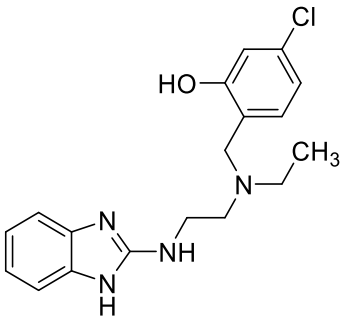
In 2021, Henrietta Dede Attra *et al.* investigated novel benzimidazole derivatives, focusing on structural modifications around the benzimidazole scaffold. This led to the classification of the synthesized analogues into two groups: 1*H*-

benzimidazoles and N-benzyl benzimidazoles, the latter based on astemizole. Among the compounds studied, compound (**43)** demonstrated notable potency against early-stage gametocytes, with an IC_{50} of 0.382 µM. Additionally, it exhibited low cytotoxicity and improved cardiotoxicity, making it a promising candidate for further antimalarial development[9].



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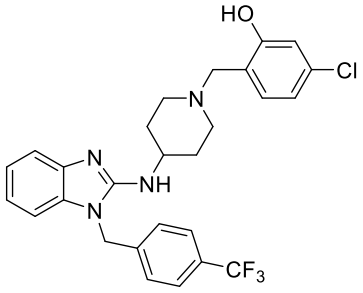

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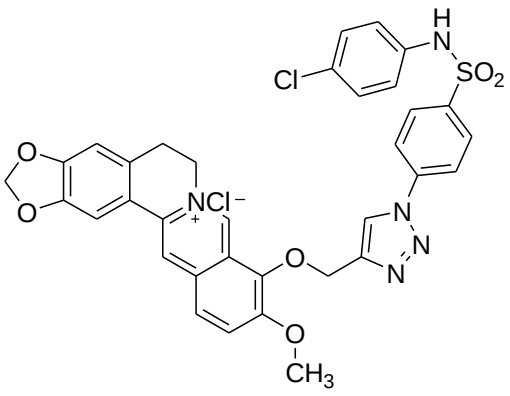
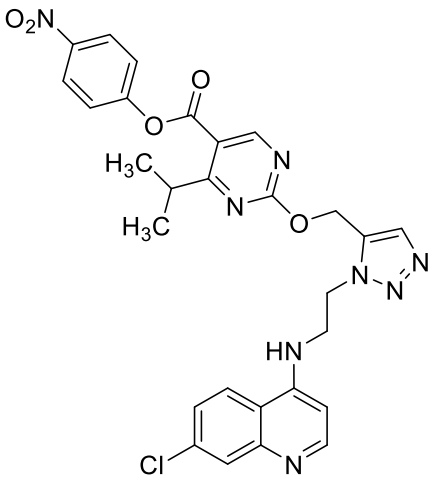
Similarly, in 2020, Baartzes *et al.* reported the synthesis of a series of aminoquinoline-benzimidazole complexes and assessed their *in vitro* antiplasmodial activity against both the CQ-sensitive NF54 strain and the multidrug-resistant (MDR) K1 strain of *P. falciparum*. Among the synthesized compounds, the most potent, compound (**44)**, exhibited significant antimalarial activity, with IC_{50} values of 0.488 µM against the NF54 strain and 0.688 µM against the K1 strain[10].

2.1.3 Triazole based antimalarial agents

Batra *et al.* synthesized a series of [1,2,3]-triazole-tethered sulfonamide–berberine hybrids using the Huisgen [3 + 2] cycloaddition reaction between azides and



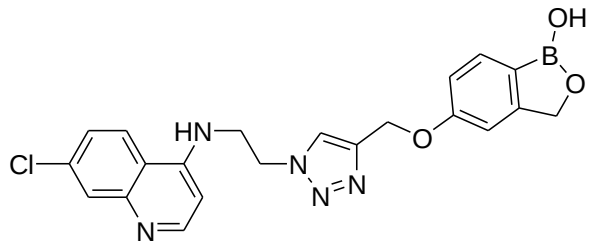
(**45**)



(**46**)

9-O-(propyne) berberine chloride under click chemistry conditions. These hybrids were evaluated for their antiplasmodial activity against *P. falciparum* (3D7). Among the synthesized compounds, compound (**45)**, which featured a *p*-chlorophenyl amino group, exhibited the highest potency, with an IC_{50} value of 0.1 μg/mL[11]. In 2018, Chopra *et al.* designed a series of 1,2,3-triazole-tethered pyrimidine-chloroquinoline hybrids and assessed their *in vitro* antiplasmodial efficacy against the CQ-sensitive NF54 strain of *P. falciparum*. Among the synthesized compounds, the most potent, compound (**46),** exhibited significant antimalarial activity with an IC_{50} value of 0.048 μM[12].

In 2021, Saini *et al*. synthesized a series of 1*H*-1,2,3-triazole-4-aminoquinoline-benzoxaborole hybrids and aryl-substituted benzoxaborole analogues. These compounds were evaluated for their antiplasmodial activity against both CQ-sensitive 3D7 and CQ-resistant W2 strains of *P. falciparum*. Among the synthesized hybrids, compound (**47),** featuring an ethyl linker, demonstrated the most potent activity, with IC_{50} values of 4.15 μM against the 3D7 strain and 3.78 μM against the W2 strain.[13].



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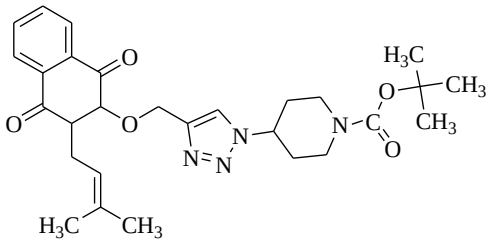

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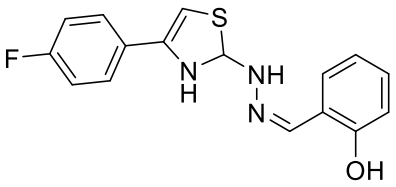
In 2018, Brandão *et al.* synthesized a series of naphthoquinonolyl-1,2,3-triazole hybrids using a copper-catalyzed cycloaddition reaction. These compounds were evaluated for their antiplasmodial activity against the CQ-resistant W2 strain of *P. falciparum* and assessed for cytotoxicity in HepG2 cells. Among the synthesized hybrids, compound (**48)** exhibited the potent activity, with an IC_{50} value of 4.0 μM[14].

2.1.4 Thiazole based antimalarial agents

Vishnu A. Gore *et al.* explored novel thiazole derivatives as potential antimalarial agents. These compounds were synthesized by refluxing thiosemicarbazones of salicylaldehyde and 5-chlorosalicylaldehyde in ethanol, using phenacyl bromide as a reagent. A total of 14 compounds were synthesized and screened

for their antimalarial activity against *Plasmodium falciparum*. Among them, compound (**49)** exhibited the highest potency, with an IC_{50} value of 0.60 μg/ml[15].



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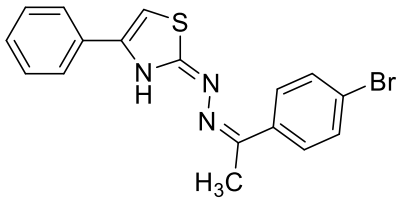

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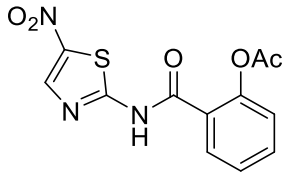
In 2021, Kamalpreet Kaur *et al.* designed and synthesized a series of thiosemicarbazone and thiazole derivatives as potential antimalarial agents. Among the synthesized compounds, compound (**50)** demonstrated significant antimalarial activity against *Plasmodium falciparum*, with an IC_{50} value of 0.29 μg/ml. Structure-activity relationship (SAR) studies revealed that introducing an electron-withdrawing group to the phenyl ring enhanced the antimalarial potency[16].

Camila Irabuena *et al.* synthesized nitro-thiazole and aminothiazole hybrids using two different methodologies and estimated their antimalarial activity against *Plasmodium falciparum* 3D7. Among the synthesized derivatives, compounds (**51)** and (**52)** exhibited the most potent activity, with EC_{50} values of 5.9 μM and 8 μM, respectively, while demonstrating minimal toxicity toward HepG2 cells[17].



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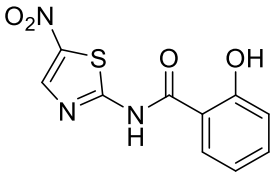

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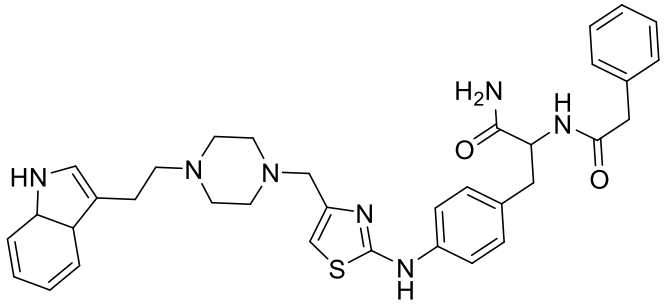
Ramanjaneyulu Rayala *et al.* investigated thiazole-linked piperazine derivatives, synthesizing a series of compounds for antimalarial evaluation. Among



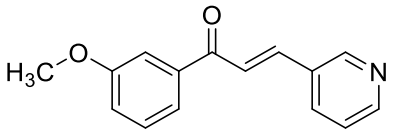
(53)

them, compound (**53)** exhibited the most potent activity against the *Plasmodium falciparum* CQ-resistant Dd2 strain, with an EC_{50} of 102 nM and a selectivity index of 140.[18].

2.2 Chalcone based hybrids as antimalarial agents

Chalcones have emerged as promising lead molecules in medicinal chemistry. Initially isolated as secondary metabolites from plants of the flavonoid family, they have been recognized for their diverse pharmacological properties. Notably, chalcones exhibit antimalarial activity by targeting *Plasmodium* aspartate proteases and cysteine proteases.

To develop potent antimalarial agents, Mulyana et al. synthesized a novel series of pyridine-based chalcone derivatives. These compounds were evaluated against *Plasmodium falciparum* 3D7 and FCR3 strains.



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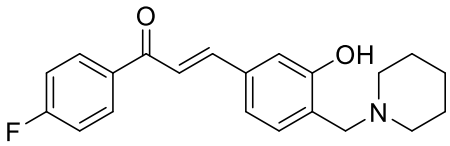
Among them, compound **(54)** exhibited significant activity, with IC_{50} values of 0.48 µg/ml and 0.31 µg/ml against the 3D7 and FCR3 strains, respectively. Computational studies suggested that the potent antimalarial activity was attributed to the presence of methoxy and pyridine substitutions. Additionally, docking studies revealed that the chalcone's carbonyl group interacted with the Asn108 amino acid at the active site of *Pf*DHFR-TS, further supporting its potential as an effective antimalarial agent[19].

To enhance the antimalarial activity of chalcones based on docking studies, Syahri *et al*. modified the substitutions on the amine group, leading to increased potency and reduced cross-resistance with chloroquine. The modified derivatives (**55–57)** exhibited significant antimalarial activity against *Plasmodium knowlesi* A1H1 and *Plasmodium falciparum* 3D7 strains, with EC_{50} values of 2.64, 2.98, and 0.10 µM for *P. knowlesi* and 0.08, 2.69, and 0.15 µM for *P. falciparum,* respectively.[20].



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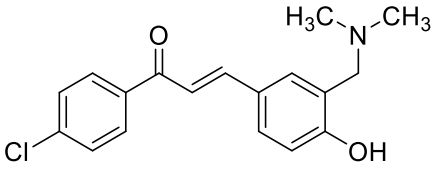

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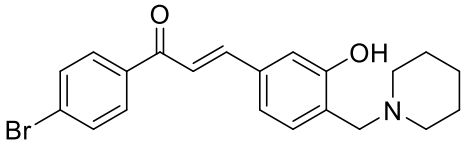
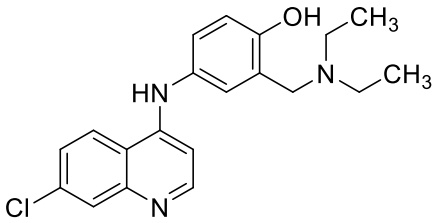


(57)

Continuing their research, Syahri *et al.* in 2020 synthesized a hybrid series of aminoalkylated chalcones as potential antimalarial agents. These hybrid molecules were developed using the Claisen-Schmidt condensation and Mannich base reaction, followed by in silico and in vitro evaluations. Among the synthesized compounds, compound (**58)** exhibited the highest binding affinity against PDB ID 1J3I.pdb and demonstrated the most potent activity against *P. falciparum*, with an IC_{50} value of 0.54 μM[21]. Additionally, the group designed another hybrid series of chalcones based on QSAR studies, which predicted antimalarial activity with 93.7% accuracy. *In vitro* studies further confirmed the potency of compound (**59)** against the *P. falciparum* 3D7 strain, with IC_{50} values ranging from 0.54 to 0.649 μM[22].



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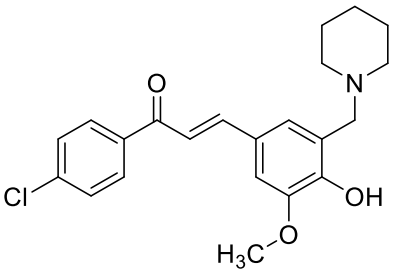

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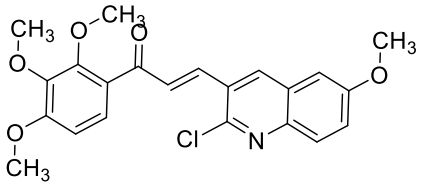
The emerging role of chalcone hybrids has encouraged researchers to explore a variety of scaffolds. One such researcher, Hamza *et al.* synthesized quinolinyl chalcones targeting *Plasmodium berghei*. Among the synthesized hybrid molecules, compound (**60)** demonstrated potent in vivo antimalarial activity, comparable to chloroquine, at a dose of 100 mg/kg, while chloroquine was effective at 25 mg/kg. Additionally, this compound exhibited the highest chemo-suppressive activity among the tested hybrids, which is believed to be due to the presence of the 6"-OCH_3 group[23].



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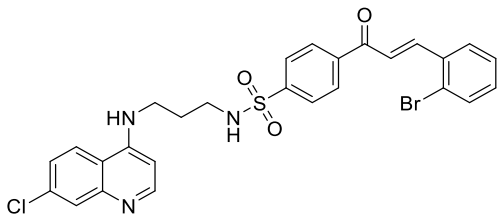
In 2021, Vinindwa *et al*. synthesized a series of chalcone-quinoline-based molecular hybrids as potential antimalarial agents. A total of 22 compounds were developed, exhibiting promising antiplasmodial activity with IC_{50} values ranging from 0.10 to 4.45 µM. Among these, three hybrid compounds (**61–63**) demonstrated the most potent activity, with IC_{50} values of 0.10, 0.10, and 0.11 µM, respectively. These findings suggest that the enhanced activity may be attributed to the electronic effects introduced by the presence of more electronegative atoms[24].



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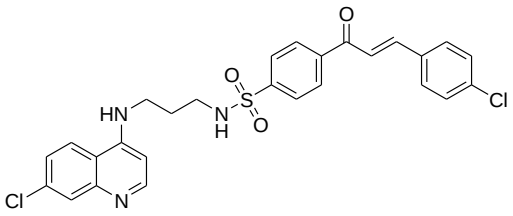

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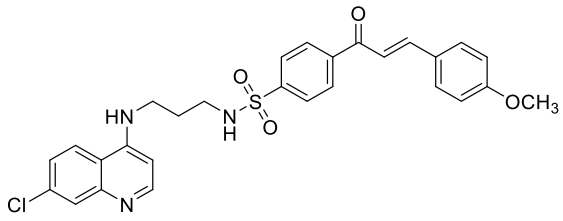

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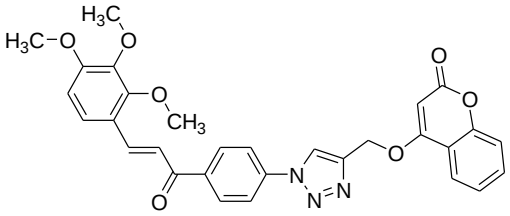
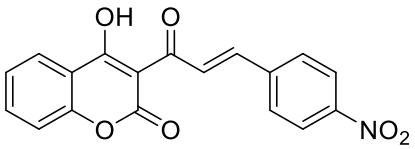


(64)

Mishra *et al*. synthesized triazole-linked chalcone analogues as potent antimalarial agents to target the asexual blood stages of the human malaria parasite *P. falciparum* (3D7). Among the synthesized compounds, compound (**64)**, which features a para-triazole substituent on one aryl ring and a para-chloro substituent on the other, exhibited the most potent antiplasmodial activity, with an IC_{50} value of 1.52 mg/mL[25].

Patel *et al.* synthesized a series of coumarinyl-chalcone hybrids via the Knoevenagel condensation reaction and evaluated their antimalarial activity. Among the synthesized compounds, compound (**65)** exhibited the most potent antimalarial activity, with an IC_{50} value of less than 5 mg/mL. SAR studies of the most active compound revealed that substituents at the meta and para positions of the chalcone

phenyl ring significantly influenced antiplasmodial activity. Notably, the presence of an electron-withdrawing group (EWG) at the para position was found to enhance antimalarial efficacy.[26].



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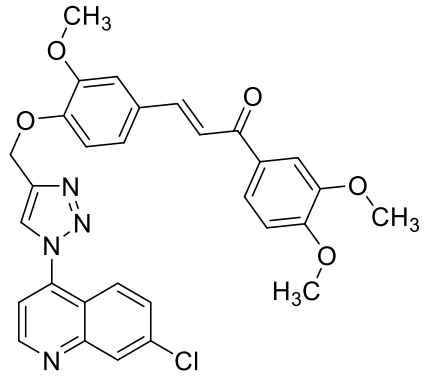
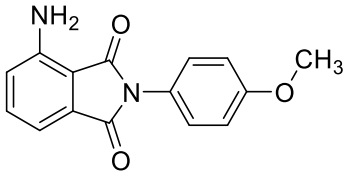


(66)

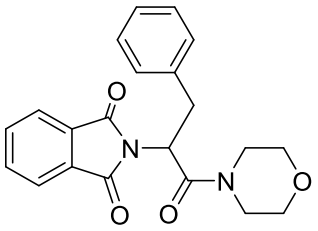
Guantai *et al*. synthesized a series of chalcones and dienone-containing aminoquinoline-based triazoles and evaluated their in vitro antimalarial efficacy. Among the synthesized compounds, compound (**66)** emerged as the most potent antimalarial agent against *P. falciparum* strains, exhibiting IC_{50} values of 0.09 mM for the W2 strain, 0.04 mM for the D10 strain, and 0.07 mM for the Dd2 strain.[27].

2.3 Phthalimide based antimalarial agents

In 2018, Okada-Junior *et al.* investigated phthalimide-based hybrid molecules as potential antimalarial agents targeting the *P. falciparum* bc1 cytochrome complex., Among the reported series compound **(67)** exhibited the most potent activity, with an IC_{50} value of less than 10 μM and a favorable selectivity index (SI > 30). Notably, the compound demonstrated no cytotoxicity against HepG2 cells[28].



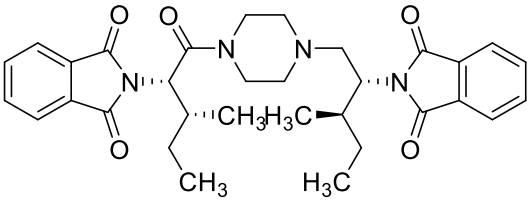
(**67**)



(**68**)

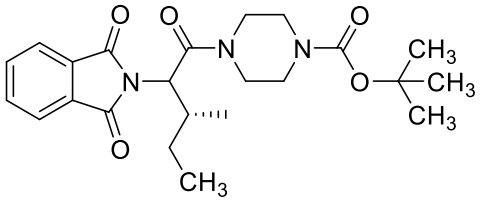
Singh *et al*. designed and synthesized phthalimide hybrids as potent antimalarial agents targeting falcipain-2. The synthesized compounds were evaluated for their antimalarial activity against the *P. falciparum* 3D7 strain, with compounds (**68)** and (**69)** demonstrating the highest potency. These compounds exhibited IC_{50} values of 18

± 0.77 µM, 5.0 ± 0.86 µM, and 3.8 ± 1.10 µM at 42, 60, and 90 hours, respectively. Notably, a decrease in IC_{50} values was observed with increased exposure time, indicating enhanced efficacy with prolonged interaction between the parasite and the drug molecule[29].



(**69**)

Bansal *et al.* explored phthalimide-based piperazine scaffolds as potential antimalarial agents. They synthesized a series of 12 analogues and evaluated their antiplasmodial activity against *P. falciparum* cultures. Among the synthesized compounds, compounds (**70)** and (**71)** exhibited significant inhibitory activity, with IC_{50} values of 1.20 µM and 1.66 µM, respectively[30].



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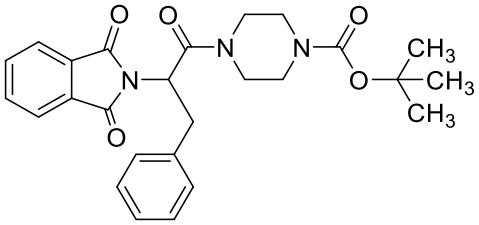
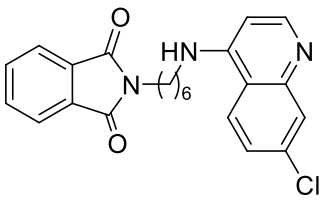
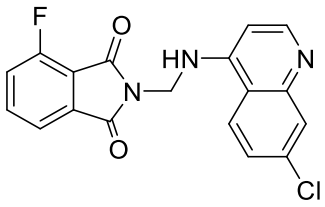


(71)

Kumar *et al*. investigated 4-aminoquinoline-based phthalimide derivatives as potent antimalarial agents targeting the chloroquine-resistant *P. falciparum* W2 strain. They synthesized a series of 25 phthalimide analogues, among which four compounds (**72–75**) exhibited antimalarial activity comparable to chloroquine, with IC_{50} values of 110, 120, 120, and 100 nM, respectively. Additionally, these analogues demonstrated low cytotoxicity and a favorable therapeutic index.[31].





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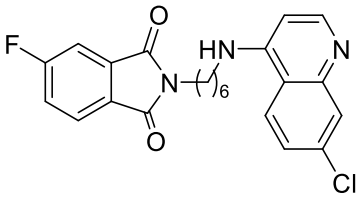

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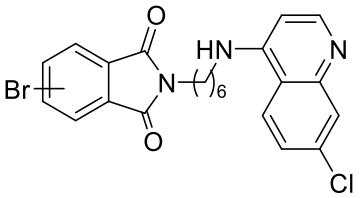
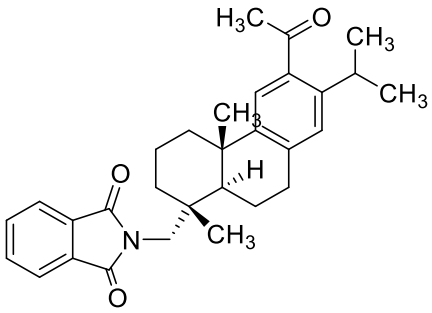


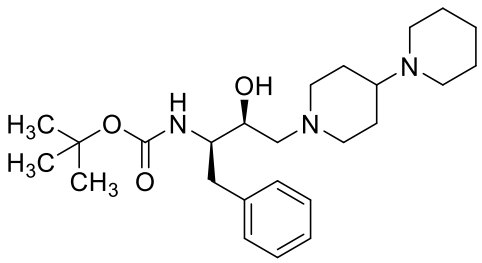
(74) **(75)**

Gonzalez *et al.* synthesized phthalimide-based hybrids incorporating a ferruginol moiety and evaluated their antimalarial activity against *P. falciparum* strains 3D7 and K1. A total of 11 derivatives were synthesized, among which compound (**76)** exhibited the highest potency, with EC_{50} values of 86 nM for the 3D7 strain and 201 nM for the K1 strain.[32].



(76)

Singh *et al.* designed a series of hydroxyethyl amine-phthalimide hybrid analogues as potential antimalarial agents. Synthesized 27 hybrid molecules and evaluated their activity against the *P. falciparum* 3D7 strain. Among these, compound (**77)** displayed the most effective activity, with an IC_{50} of 1160 nM. Additionally, three other compounds (**78–80**) demonstrated significant antimalarial activity, with IC_{50} values of 1330 nM, 1250 nM, and 1300 nM, respectively.[33].



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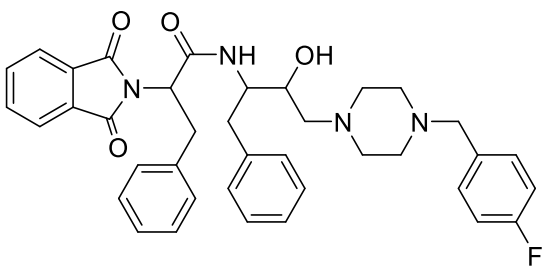

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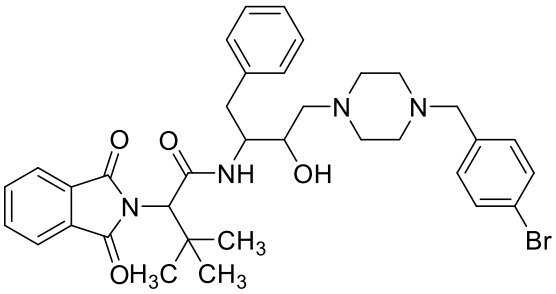

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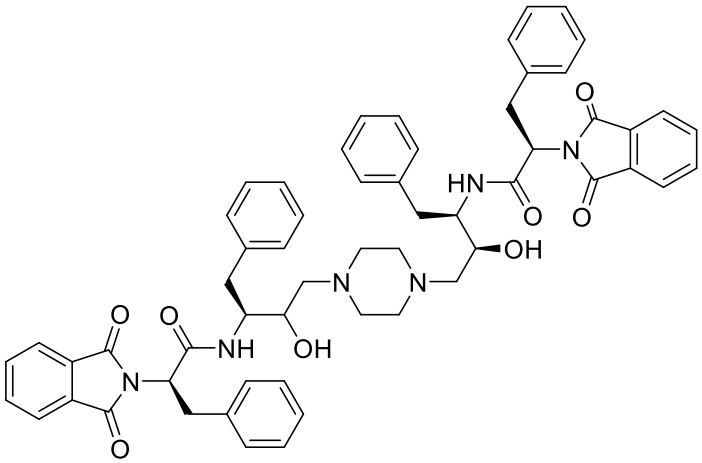
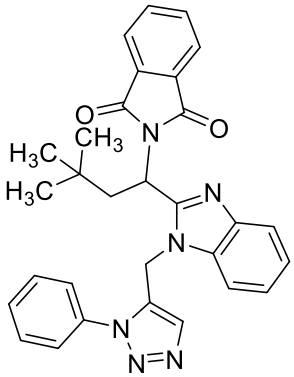


(**80**)

In 2017, Kumar *et al.* explored benzimidazole- and triazole-based phthalimide derivatives as potential antimalarial agents. Using click chemistry and non-conventional microwave irradiation, they synthesized a series of 31 derivatives. Among these, three compounds (**81–83**) exhibited the most potent activity against the *P. falciparum* 3D7 strain, with IC_{50} values of 900 nM, 900 nM, and 700 nM, respectively. Additionally, these potent molecules demonstrated significant inhibitory activity against the chloroquine-resistant W2 strain, with IC_{50} values of 700 nM, 1300 nM, and 900 nM[34].



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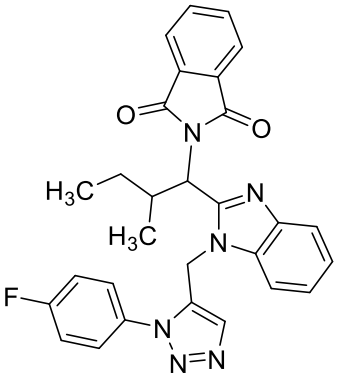

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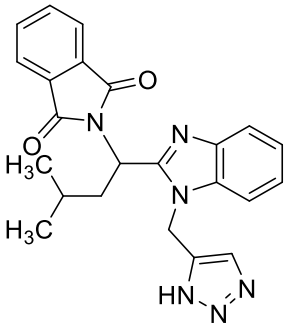
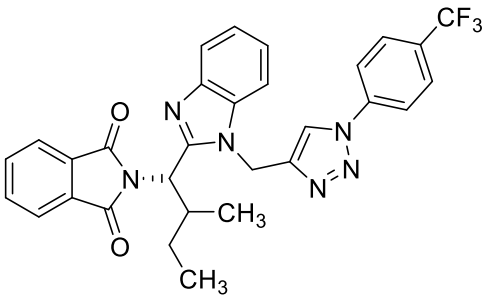


(83)

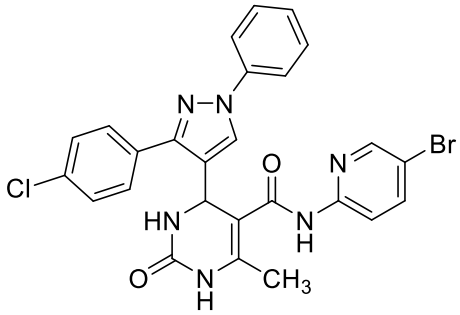
In 2021, Singh *et al*. synthesized a series of 18 phthalimide derivatives as potent anti-tubulin hybrid molecules for malaria treatment. Evaluated phthalimide (Pht) analogs incorporating bioactive scaffolds such as benzimidazole and 1,2,3-triazole for both *in vitro* and *in vivo* antiplasmodial activity, demonstrating efficacy without any apparent hemolysis or cytotoxicity. Among the synthesized compounds, compound **(84)** exhibited the highest activity, with an IC_{50} value of 0.64 μM. Structure-activity relationship (SAR) studies revealed that substituting fluorine on the triazole ring with other functional groups enhanced antiparasitic activity, while the introduction of a trifluoromethyl group improved target enzyme affinity and influenced neighboring groups due to its lipophilic nature.[11].



(**84**)

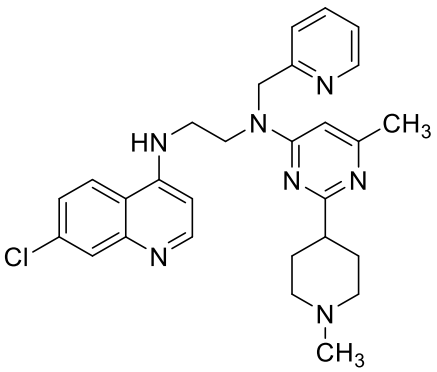
2.4 Pyrimidine-based hybrids as antimalarial agents

Bhatt *et al.* synthesized a series of diarylpyrazole-dihydropyrimidine derivatives using a one-pot multicomponent synthesis approach to develop potent antimalarial agents. A total of five derivatives were synthesized, among which compound (**85)** exhibited the highest potency, with an IC_{50} value of 0.03 μg/mL.[35].



(85)

In 2019, Maurya *et al*. investigated 4-aminoquinoline-pyrimidine-based molecular hybrids and synthesized a series of derivatives as potential antimalarial agents. Among the synthesized compounds, compound **(86)** exhibited the most potent antimalarial activity, with an IC_{50} value of 0.027 μM against the *P. falciparum* D6 strain[36].



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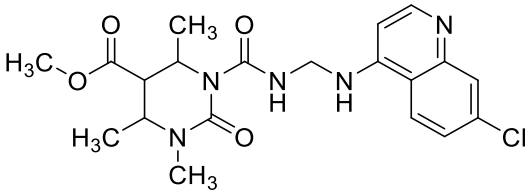


(87)

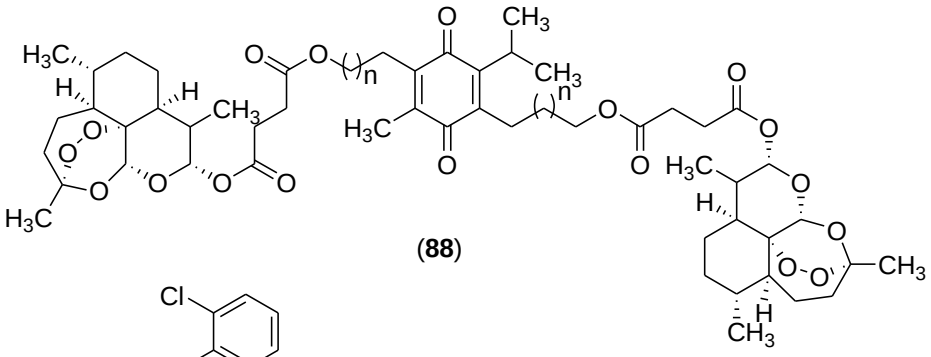
In 2022, Adigun *et al.* synthesized dihydropyrimidinone-quinoline hybrids as potent antimalarial agents, utilizing a triazole/amide linker. The synthesized compounds were evaluated for their in vitro antiplasmodial activity against the chloroquine-resistant *P. falciparum* K1 strain. Among all the synthesized derivatives, compound (**87)**, featuring a C-4 spacer, exhibited the highest potency, with an IC_{50} value of 5 μM[37].

2.5 Miscellaneous antimalarial hybrids

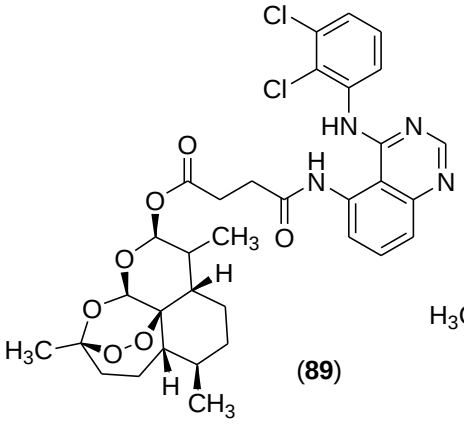
2.5.1 Compounds developed using artemisinin scaffold

Fröhlich *et al*. synthesized a series of thymoquinone-artemisinin, thymoquinone-artesunic acid, and thymoquinone-artesunic acid hybrid molecules featuring a dimethyl

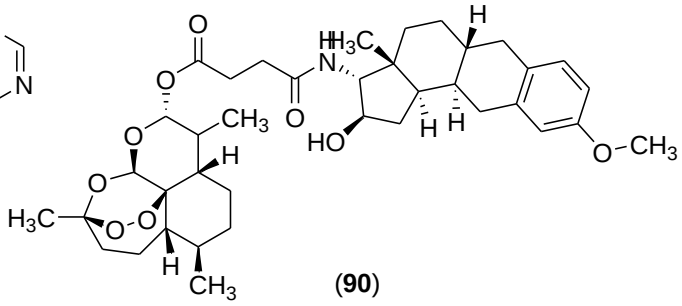
malonate linkage. Among these, compound (**88)** exhibited the highest activity, with an EC_{50} value of 4.3 nM[38]. Additionally, they developed quinazoline-artemisinin hybrids and evaluated their antimalarial activity against the *P. falciparum* 3D7 strain,



(**88**)



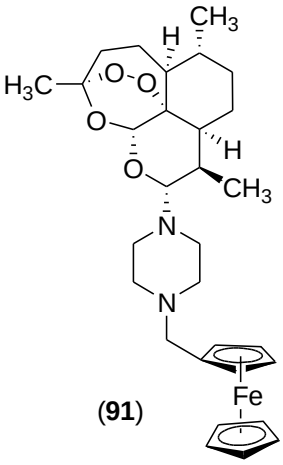
(**89**)



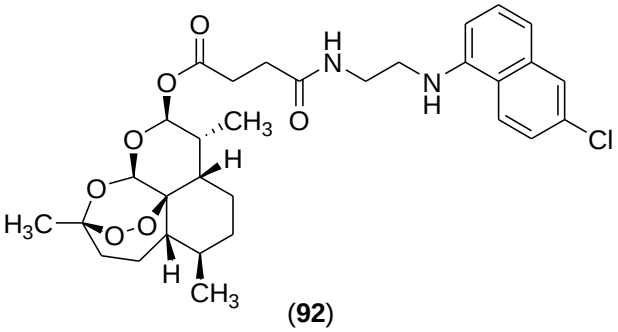
(**90**)

identifying compound (**89)** as the most potent, with an EC_{50} value of 1.4 nM[39]. This research group also explored artemisinin-estrogen hybrids, synthesizing a range of compounds, among which hybrid (**90)** demonstrated significant potency, with an EC_{50} value of 8.9 nM—twice as potent as artesunic acid[40].

Lange *et al.* synthesized amino-artemisinin–ferrocene hybrids as potential antimalarial agents. Among the synthesized compounds, hybrid (**91)**, featuring an



(**91**)



(**92**)

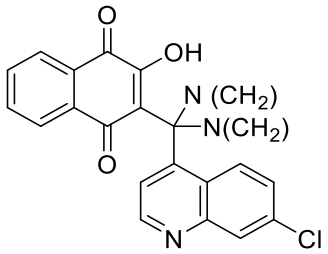
electron-donating aminomethylene group introduced via alkylation, exhibited the highest potency, with an IC_{50} value of 4.6 nM[41].

Capci *et al.* synthesized novel ART–isoquinoline and ART–quinoline hybrids using click chemistry and esterification reactions. A total of eight hybrids were developed, among which hybrid **(92)** exhibited the highest potency, with IC_{50} values of 2.7 nM, 1.0 nM, and 0.78 nM against the *P. falciparum* 3D7, Dd2, and K1 strains, respectively[42].

2.5.2 Quinoline-based hybrids

Quinolines are among the most active scaffolds in antimalarial research, exhibiting multiple targeted effects against malaria. Recognizing their therapeutic potential, numerous researchers have explored this moiety to develop a variety of hybrid compounds.

Kashyap *et al.* synthesized a novel series of quinoline–lawsone hybrids and evaluated their *in vitro* antimalarial activity against chloroquine-sensitive (CQS, RKL-2) and chloroquine-resistant (CQR, RKL-9) strains of *P. falciparum*. Among the synthesized hybrids, compound **(93)** demonstrated the highest potency, with IC_{50} values of 0.391 µM and 1.091 µM against the RKL-2 and RKL-9 strains, respectively[41].



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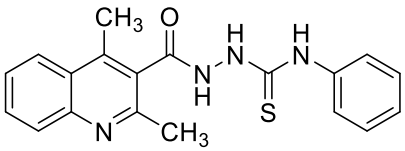
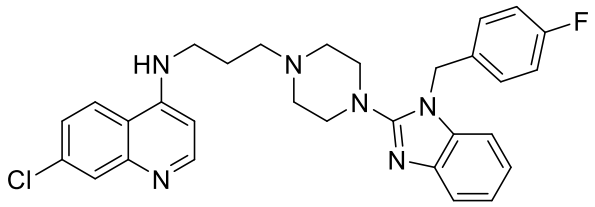


(94)

Similarly, in 2019, Patel *et al.* synthesized a novel series of fluorine-containing quinoline–thiosemicarbazide hybrids and evaluated their antimalarial activity against a chloroquine-resistant (*P. falciparum*) strain. A total of five compounds were synthesized, among which compound (**94)** exhibited the highest potency, with an IC_{50} value of 0.02 µg/mL. Structure-activity relationship (SAR) studies revealed that analogs containing electron-withdrawing groups, such as trifluoro and chloro, as well as those with electron-donating groups like methoxy and substituted methyl, demonstrated significant antimalarial efficacy[43].

Whitlock *et al.* designed and synthesized hybrid molecules by combining two highly active antimalarial moieties, chloroquine (CQ) and astemizole, linked through a core structure. These hybrids were evaluated for their antimalarial efficacy against the chloroquine-resistant (*P. falciparum*) K1 strain. Among the synthesized derivatives, compound (**95)** exhibited the highest potency, with an IC_{50} value of 23 nM [43]**.**



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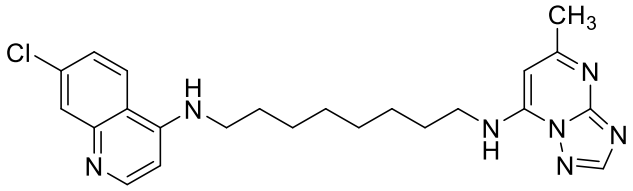
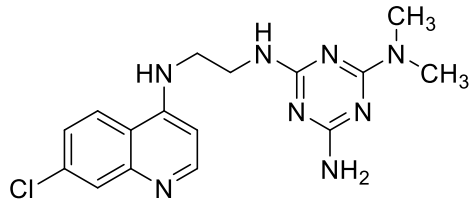


(96)

Chowdhary *et al.* synthesized bis-triazolopyrimidines and 4-aminoquinoline–triazolopyrimidine hybrids and evaluated their *in vitro* antiplasmodial activity against chloroquine-sensitive (3D7) and chloroquine-resistant (W2) *P. falciparum* strains. Among the synthesized compounds, compound **(96)** exhibited the highest potency, with an IC_{50} value of 0.20 μM, demonstrating threefold greater activity than the standard drug chloroquine. SAR studies revealed that increasing the spacer length enhanced antiplasmodial activity in 4-aminoquinoline–triazolopyrimidine hybrids, whereas bis-triazolopyrimidines exhibited relatively poor activity profiles[43].

Sahu *et al.* synthesized a series of 4-aminoquinoline–triazine hybrids and evaluated their antimalarial activity against the *P. falciparum* 3D7 strain. Among the synthesized compounds, compound (**97)** exhibited the highest potency, with an IC_{50} value of 46.33 μg/mL, demonstrating significant activity at both 5 μg/mL and 50 μg/mL doses. The enhanced activity of this compound was attributed to the presence of primary, secondary, and tertiary amines, which contributed to its superior antimalarial efficacy compared to other synthesized derivative[44].



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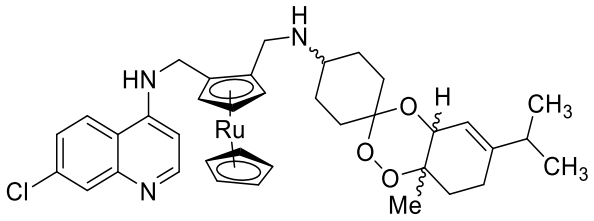
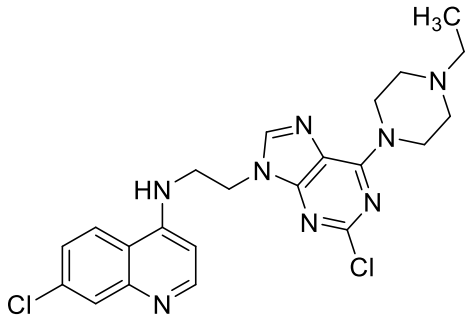


(98)

Martínez *et al*. designed an organo-ruthenium aminoquinoline–trioxane hybrid and evaluated its antiplasmodial activity against the chloroquine-resistant (*P. falciparum*) K1 and Dd2 strains. Among the synthesized compounds, hybrid (**98)** exhibited the highest potency, with IC_{50} values of 16.93 nM and 51.16 nM against the K1 and Dd2 strains, respectively[45].

Reddy *et al.* synthesized a series of 4-aminoquinoline–purine hybrids and evaluated their antimalarial activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) *P. falciparum* strains. Among the synthesized compounds, compound (**99)** exhibited the highest potency as an antimalarial agent[46].



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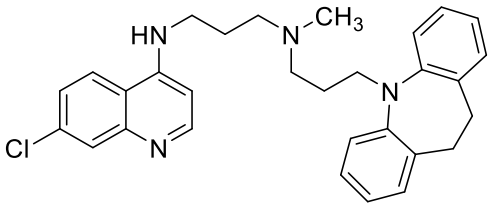
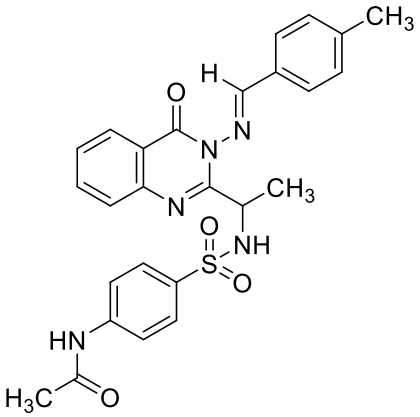


(100)

Peyton *et al.* designed a 4-aminoquinoline–imipramine hybrid, which exhibited potent antimalarial activity at low nanomolar concentrations. The resulting hybrid, compound (**100)**, demonstrated high efficacy against both chloroquine-sensitive (D6) and chloroquine-resistant (Dd2) *P. falciparum* strains, with IC_{50} values of 3 nM and 5 nM, respectively. Additionally, it showed oral efficacy in the *P. chabaudi* model without any signs of toxicity.[47].

In 2019, Patel *et al.* synthesized a series of quinazolinone–sulfonamide hybrids using green reaction conditions. A total of five compounds were developed, among which compound (**101)** exhibited the highest antimalarial activity, with an IC_{50} value of 0.062 μg/mL[35] .

Kholiya *et al.* synthesized a series of 4-aminoquinoline–piperonyl pyrimidine hybrids and evaluated their antimalarial activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) *P. falciparum* strains. Among the 20 compounds synthesized, compound (**102)** exhibited the highest potency, with IC_{50} values of 0.02 µM and 0.05 µM against the D6 and W2 strains, respectively[47].



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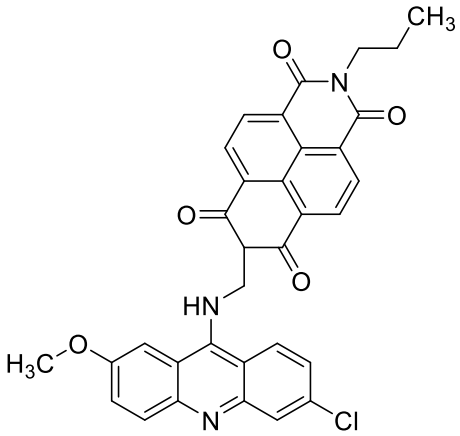
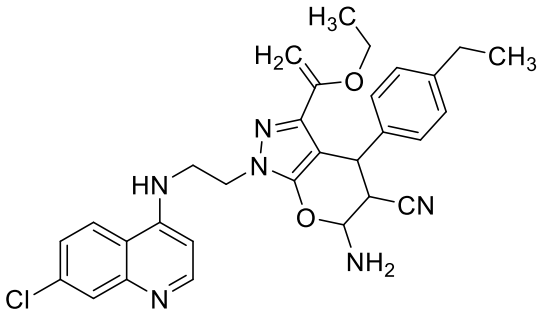
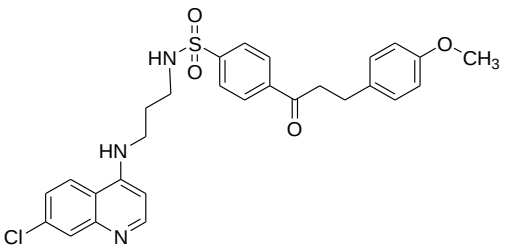


(102)

In 2021, Shamsuddin *et al.* synthesized a series of pyrano[2,3-*c*]pyrazole–aminoquinoline hybrid compounds and evaluated their antimalarial activity against chloroquine-sensitive (3D7) and chloroquine-resistant (K1) *P. falciparum* strains. Among the synthesized compounds, compound (**103)** exhibited the highest potency, with EC_{50} values of 0.0130 µM against the 3D7 strain and 0.02 µM against the K1 strain.[48].



(**103)**



(104)

Similarly, in 2021, Vinindwa *et al.* synthesized a series of quinoline-based sulfonamide hybrids using an amino alkyl sulfonamide linker. A total of 24 hybrids were developed and evaluated for their *in vitro* antiplasmodial activity against chloroquine-sensitive (NF54) and multidrug-resistant (K1) *P. falciparum* strains. Among them, compound (**104)** exhibited the highest potency, with an IC_{50} value of

2.9748 µM[49].

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