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Review Article

Quinoline conjugates for enhanced antimalarial activity: a review on synthesis by molecular hybridization and structure-activity relationship (SAR) investigation

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Abstract: Malaria, caused by the various *Plasmodium falciparum* strains, has been one of the deadliest diseases spread across the world. Over the years, several researchers have been employed to analyse molecular hybridization techniques for the synthesis of combination drugs to overcome the resistance gained by the parasite against the existing drugs. Hence, some of the significant contributions since 2019 till date have been summarised in the present review. Based on structure, the hybrids have been classified into bi-pharmacophores - having two pharmacologically active groups, tri-pharmacophores - having three pharmacologically active groups, metal-based and other miscellaneous hybrids. A thorough study of existing molecules could also reveal new leads for the development of anti-malarial agents with efficacy better than the preceding ones.

Keywords: Malaria, bi-pharmacophores, tri-pharmacophores, metal-based hybrids, plasmodium falciparum

Introduction

Malaria has been one of the most widespread diseases globally affecting millions of people. The maximum cases of infection were reported in sub-Saharan Africa and south/southeast Asian countries [1]. *P. falciparum* strains were observed to be the most commonly infecting parasites in these regions which were believed to be the deadliest ones causing life-threatening clinical conditions [2]. The first anti-malarial drug quinine 1 (**Figure 1**), which is an isomer of quinoline 2, was isolated from the bark of Cinchona tree by serendipity in the 17th century [3]. Prior to the identification of quinine, the dried powder of the bark was mixed with wine for consumption. Once identified, it was extensively used as a monotherapy against the parasite. Although it was effective, its mode of action was unknown and at times led to severe complications. This was then replaced by synthetic derivatives like chloroquine 3, amodiaquine 4, piperaquine 5, primaquine 6, and mefloquine 7, having quinoline nucleus 2 consisting of a benzene ring fused with pyridine ring [4], throughout the 20th century [5].

Chloroquine works against the blood and liver stages of the parasite by accumulation of the drug in the vacuole of the parasite due to its weak basic property. In the vacuole, the erythrocytes being degraded release toxic hematin, which is polymerized into non-toxic hemozoin by the parasite as a detoxification process. The accumulation of the drug results in the inhibition of the polymerization and the accumulation of free hematin thus killing the parasite [6]. However, the parasite developed resistance against chloroquine due to the presence of chloroquine resistance transporter (*Pf*CRT) along the membrane of the digestive vacuole. *Pf*CRT is involved in the efflux of the drug and the continuation of the polymerization of hematin, supporting the proliferation of the parasite [7]. To overcome this resistance, researchers came up with techniques to modify the structure of quinoline and its derivatives [8].

Quinoline and its various analogues play an important role as a starting material for the synthesis of various therapeutic agents [9]. Some of the other pharmacological activities exhibit-

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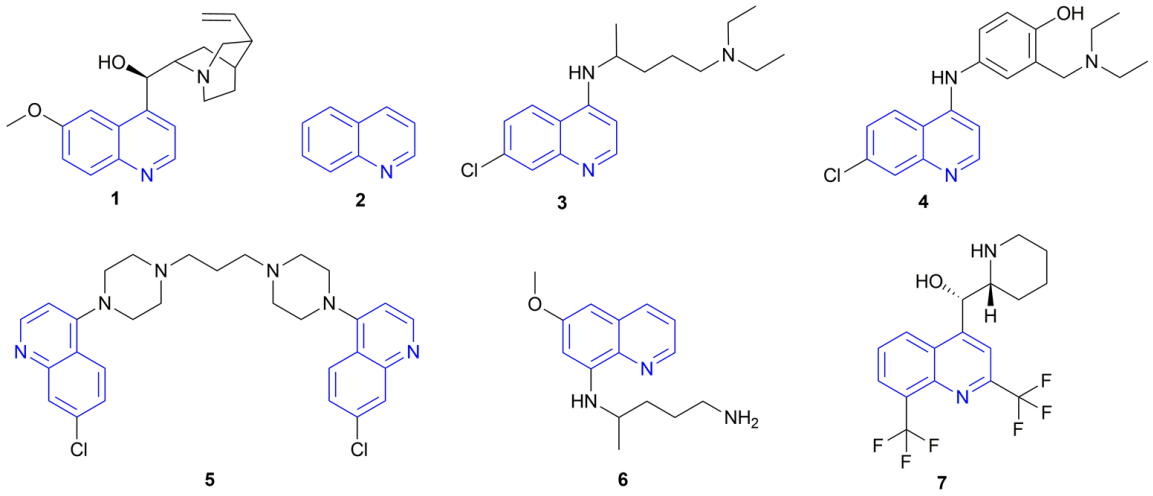


Figure 1. Quinoline-containing drugs as anti-malarial agents.

ed by quinoline include anti-cancer [10-13], anti-mycobacterial [14, 15], anti-inflammatory [16, 17], anti-microbial [18] and anti-fungal [19]. For anti-malarial enhancement, quinoline has been modified by the technique of molecular hybridization to synthesize conjugates with other pharmacophores. The molecular hybridization technique involves the synthesis of new prototypes of drugs by the conjugation of two or more sub-units based on the knowledge of the pharmacological effect of each scaffold introduced [20].

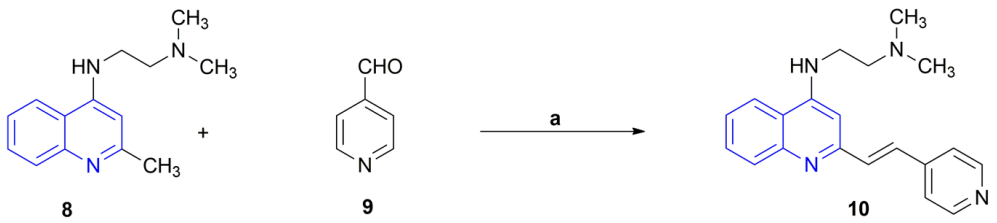
In the current review, the recent advancements in the synthesis of quinoline conjugates by molecular hybridization and their anti-malarial efficacy since 2019 have been discussed. The hybrids are classified into bi-pharmacophores, tri-pharmacophores, metal-based hybrids, and some as miscellaneous.

Bi-pharmacophores

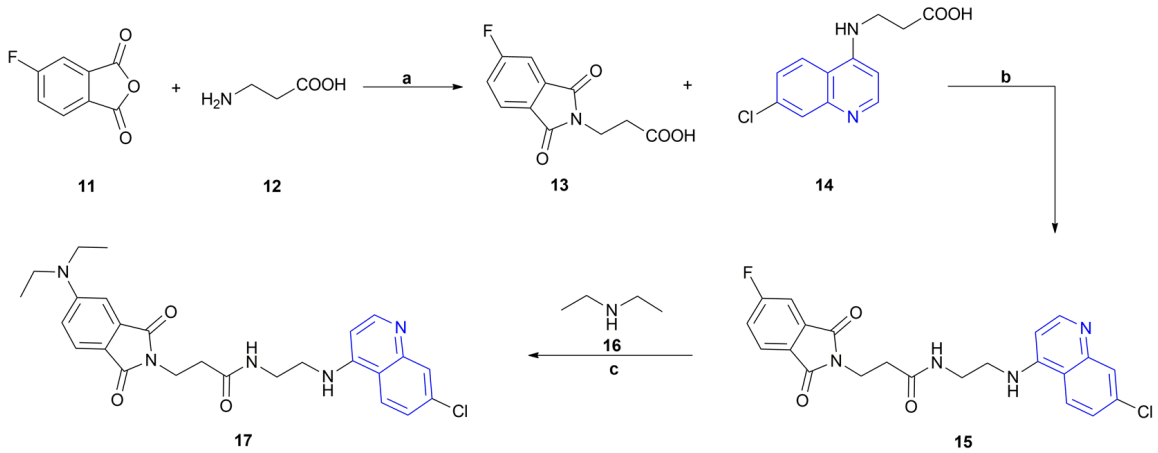
The synthesis and activity of some of the recently synthesized hybrids having two major pharmacophores conjugated through linkers have been discussed here.

In June 2019, Debopam *et al.* [21] designed a rapid olefination technique for the synthesis of 2-vinylquinoline derivatives by microwave irradiation method using trifluoromethanesulfonamide ($TfNH_2$) as the catalyst. 2-methylquinoline derivatives were made to react with suitable aldehydes for the formation of aldimines by aldol condensation and were evaluated for *in vitro* activity against chloroquine-resistant (CQR) *Pf*Dd2. Compound 10 exhibited an IC_{50} value of 0.033 ± 0.007 μM which is approximately 5 times as strong as the standard drug chloroquine which exhibited an IC_{50} value of 0.172 μM. Compound 10 was synthesized by the condensation of aldehyde 9 with C2-methyl of the quinoline derivative 8 (**Scheme 1**). The most suitable condition leading to a 93% yield of the hybrids was observed when DMF was used as the solvent with 1.5 equivalents of the aldehyde while the reaction was carried out for 20 minutes at 140°C. The anti-malarial potency is believed to be better than aminoquinolines due to the presence of the vinyl group at the C2 position of the quinoline [22].

The various pharmacological applications of isoindole nuclei against cancer, hyperglycemia, tuberculosis, inflammation, and hypertension are already well known [23-26]. Conjugation of dioxoisoindoline derivatives and quinoline under microwave irradiation was achieved by Vipan *et al.* in July 2019 by means of amide linkage between them. When evaluated for *in vitro* anti-malarial activity against CQR *Pf*W2, compound 17 showed an IC_{50} value of 0.097 ± 0.006 μM thus making it two-fold more active than standard drug chloroquine which exhibited an IC_{50} value of 0.23 ± 0.07 μM. Since compound 17 has diethyl amine substitution at the C5-fluoro position, there was an overall increase in the basicity of the compound which led to better accumulation of the drug in the vacuole of the parasite. C5-Fluoro dioxoisoindoline 11



Scheme 1. Synthesis of compound 10; a. $TfNH_2$, MWI, 140°C, 20 mins, DMF.

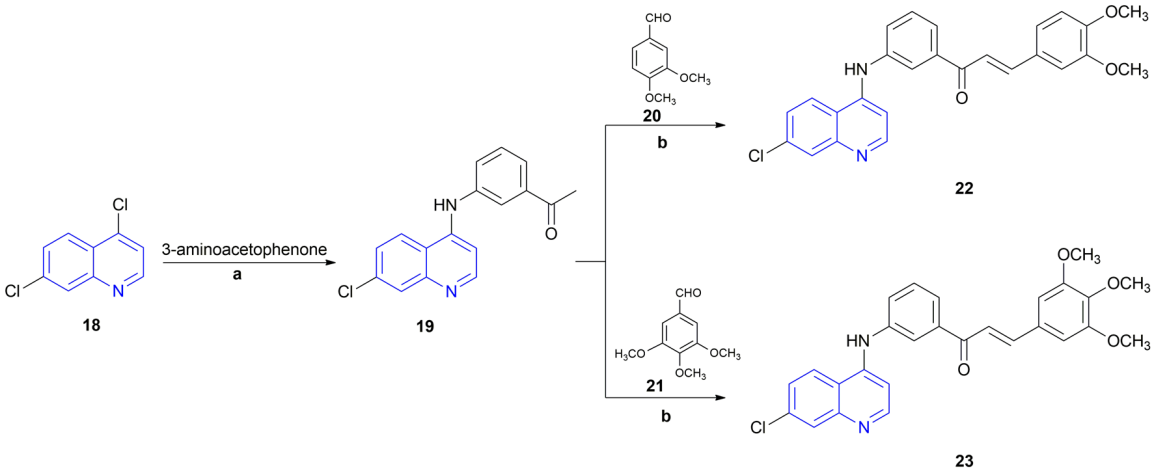


Scheme 2. Synthesis of compound 17; a. Toluene, TEA, reflux, 6 h; b. EDC, HOBt, DIEA, DMF, RT, 3 h; c. MWI, NMP, 160°C, 5 mins.

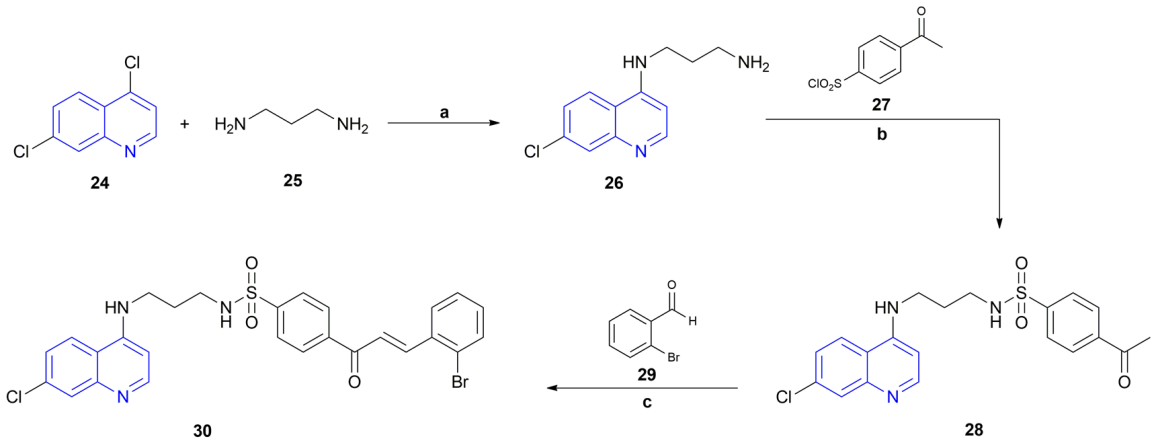
was first reacted with 3-amino propanoic acid 12 producing compound 13 which was further linked with the 4-aminoquinoline derivative 14. The C5 fluoro group of the synthesized hybrid 15 is then replaced with diethyl amine 16 finally yielding the required compound 17 (**Scheme 2**). It was observed that the containing C5-substitution was more affective when compared with the unsubstituted analogues. Additionally, the linker also played a role in reducing the cytotoxicity of the compound [27].

In September 2019, Jaime *et al.* synthesized a series of hybrids of quinoline and chalcone with an amino group as a linker to test its *in vitro* and *in vivo* activity against certain *P. falciparum* strains. When tested for *in vitro* β-haematin inhibition activity, compounds 22 and 23 showed 89.73 ± 0.25% and 87.75 ± 0.01% inhibition respectively, which were comparatively lesser than the other synthesized compounds. However, these were also selected as the most potent compounds due to the very low percentage of parasitemia exhibited post-treatment of mice infected with *P. berghi* strain ANKA. The presence of methoxy groups in both compounds might have resulted in better activity. However, the additional methoxy group in the meta position of compound 23 which is absent in compound 22 did not contribute to any significant enhancement in the activity but rather showed a decrease. 4, 7-dichloroquinoline 18 was reacted with 3-aminoacetophenone to give rise to compound 19. Compound 19 was then hybridized with 3,4-dimethoxy benzaldehyde 20 and 3,4,5-trimethoxybenzaldehyde 21 in the presence of KOH and methanol as solvent to produce compounds 22 and 23 respectively (**Scheme 3**) [28].

Yet another series of chalcone and quinoline hybrids linked by aminoalkyl sulphonamide was synthesized by Vinindwa *et al.* in July 2021 [29]. Out of the synthesized 22 molecules, compound 30 showed an IC_{50} value and selectivity index of 0.10 μM and 435 respectively against Chloroquine Sensitive (CQS) *Pf*NF54 when tested for *in vitro* anti-malarial activity. The possible reason for the better activity of compound 30 was due to the presence of a longer alkyl



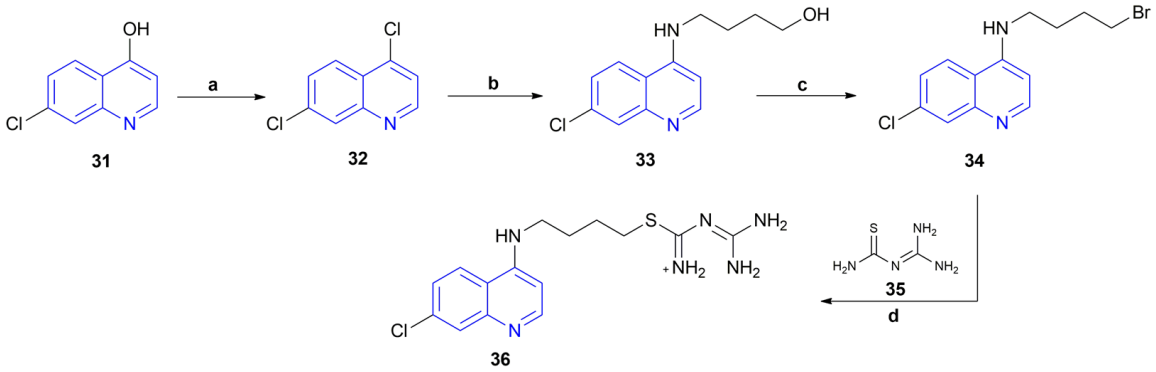
Scheme 3. Synthesis of compounds 22 and 23; a. EtOH, HCl, D, 4 h; b. KOH, CH_3OH, RT, 72-120 h.



Scheme 4. Synthesis of compound 30; a. reflux, 16 h; b. dioxane, NaOH, RT, 24 h; c. MeOH, NaOH, reflux overnight.

(n=3) linker as compared to the other compounds containing shorter alkyl (n=2) linker. 4, 7-Dichloroquinoline 24 and propane-1, 3-diamine 25 was combined to give N-(7-chloroquinol-4-yl) propane-1, 3-diamine 26. This was further condensed with 4-acetyl-benzene sulfonyl chloride 27 in the presence of NaOH to yield compound 28. Finally, base-catalyzed Claisen-Schmidt coupling between compound 28 and 2-bromobenzaldehyde 29 is carried out to yield the required product 30 (**Scheme 4**). Unfortunately, it did not show the same efficiency when tested against Multi-Drug Resistant (MDR) *Pf*K1.

Guanylthiourea derivatives have proven to be potent anti-malarial compounds [30]. Guanylthiourea was further conjugated with 4-aminoquinoline through a suitable alkyl linker to intensify its activity by Bhagat *et al*. in October 2019. Molecular docking was performed to evaluate the ability of the synthesized compounds to bind with PDB: 1J3I (wild-type *Pf*DHFR) and PDB: 1J3K (mutant *Pf*DHFR) [31]. *Pf*DHFR enzyme produces folate, an essential for the multiplication of the parasite; its inhibition will prove to be antagonistic to parasitemia [32]. Among all the synthesized compounds, compound 36 showed binding affinities with 1J3I and 1J3K which was comparable to that of the standard anti-folate molecule WR99210. The binding energy of 36 with Ile14 was comparable to that of the standard anti-folate molecule WR99210 but that with Asp54, it was 3 kcal/mol less than WR99210. Compound 36 formed a bidentate H-bond with Asp54 energy



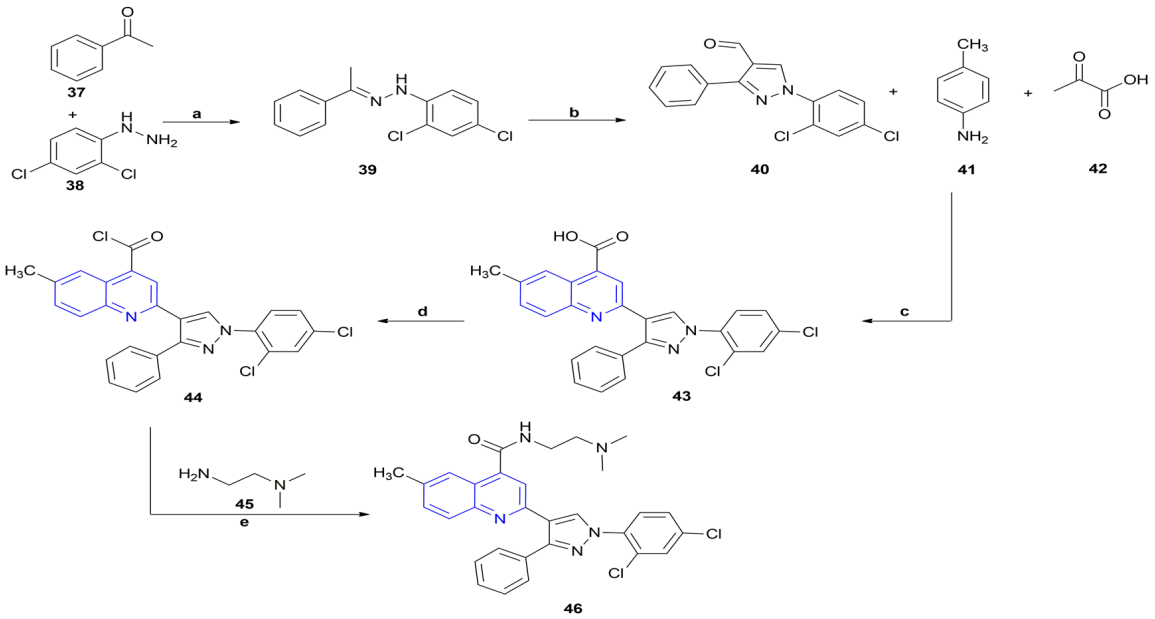
Scheme 5. Synthesis of compound 36; a. $POCl_3$, 150°C, 3 h; b. 4-aminobutan-1-ol, 130°C, 3 h; c. HBr, a few drops of H_2SO_4, 140°C, 6 h; d. CH_3CN, reflux, 12-24 h.

with occupancy of more than 100%. It also showed an IC_{50} value of 0.61 μM and 0.43 μM against CQS *Pf*D6 and CQR *Pf*W2 respectively. The synthesis of 36 begins with the conversion of 7-chloroquinolin-4-ol 31 into N-(4-bromobutyl)-7-chloroquinolin-4-amine 34 through a series of reactions (**Scheme 5**). Compound 34 is then conjugated with guanylthiourea 35 in the presence of CH_3CN by S-alkylation to give rise to the hybrid 36. Again, the presence of a butyl linker between the two scaffolds led to a better activity.

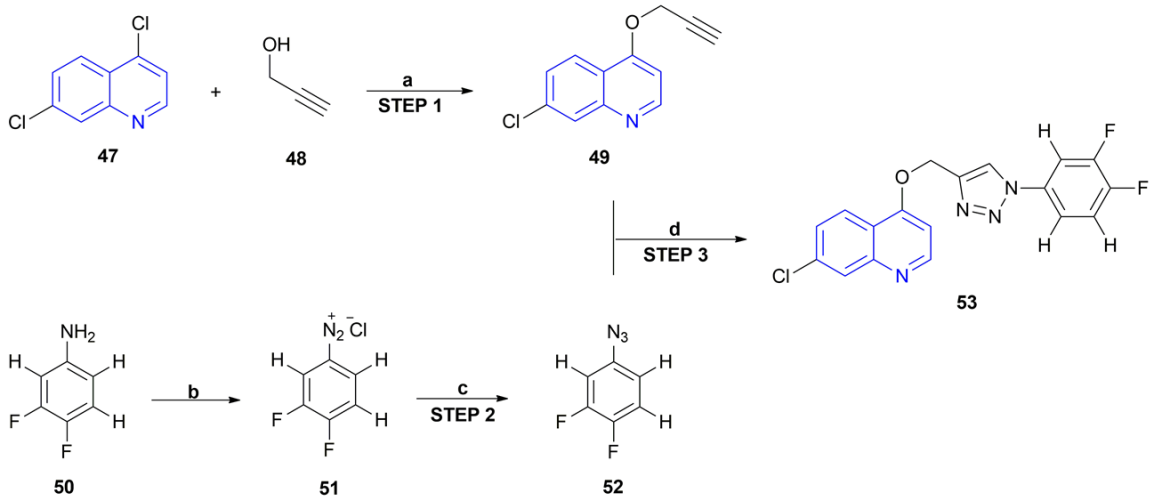
Anti-malarial activity of pyrazole-quinoline derivatives has been evaluated [33] and this has been further evaluated by Pandya *et al.* in October 2019 by synthesizing compounds containing quinoline clubbed with phenyl derivatives of pyrazole [34, 35]. The electronic characteristic of pyrazole has been ameliorated by suitable substitutions in the phenyl groups. Compound 46 exhibited the best *in vitro* activity against *P. falciparum* by exhibiting an IC_{50} value of 0.036 μg/mL, comparable to control chloroquine which showed an IC_{50} value of 0.020 μg/mL. Hydrazone 39 was synthesized by the condensation between acetophenone 37 and hydrazine 38. The hydrazone 39 undergoes cyclization via the Doebner reaction (**Scheme 6**) forming pyrazole derivative 40. Compound 40 was further refluxed with p-toluidine 41 and 2-oxo-propanoic acid 42 in the presence of ethanol to yield compound 43 which was then converted to 44 by reacting with thionyl chloride. Compound 46 was finally obtained by the substitution of N, N-dimethylaminoethyl amine 45 at the C4 position of the quinoline scaffold of compound 44 in the presence of THF. The substitution at the C6 position of quinoline and the two phenyl substitutions in the pyrazole ring could be the possible reason for the higher activity of compound 46 [35].

Anju Singh *et al.* synthesized a quinoline-triazoles hybrid in November 2019 [36]. Among the 10 synthesized compounds, 53 had proven to be effective for the inhibition of falciparum-2, hence preventing the growth of CQS *Pf*3D7 strain with an EC_{50} value of 21.89 ± 4.51 μM. The compound also exhibited an IC_{50} value of 25.64 ± 4.13 μM in FP-2 inhibition studies. The synthesis includes three steps (**Scheme 7**). 4,7-dichloro quinoline 47 was converted into 7-chloro-4-(prop-2-ynyloxy) quinoline 49 by combining with prop-2-yn-1-ol 48 in the presence of sodium hydride and dry dimethylformamide at room temperature. Simultaneously, the synthesis of phenyl azide derivative 52 from aniline 50 was carried out via the Sandmeyer reaction. Finally, the azide 52 is refluxed with compound 49 in the presence of $CuSO_4.5H_2O$, sodium ascorbate (THF: H_2O, 1:2) at 80°C for 8 hours to obtain 53.

In February 2020, Dhaval *et al.* came up with a microwave-assisted synthesis of a novel hybrid of ethyl-2,4-dimethylquinoline-3-carboxylate and N^4-benzyl thiosemicarbazides [37]. The synthesized molecules were evaluated for their *in vitro* anti-malarial activity. One of the compounds (compound 60), showed the potency for further development as it exhibited an IC_{50} value of 0.19 μg/mL against *P. falciparum* and this surpassed the activity of standard chloroquine which exhibited an IC_{50} value of 0.20 μg/mL. This could be due to the presence



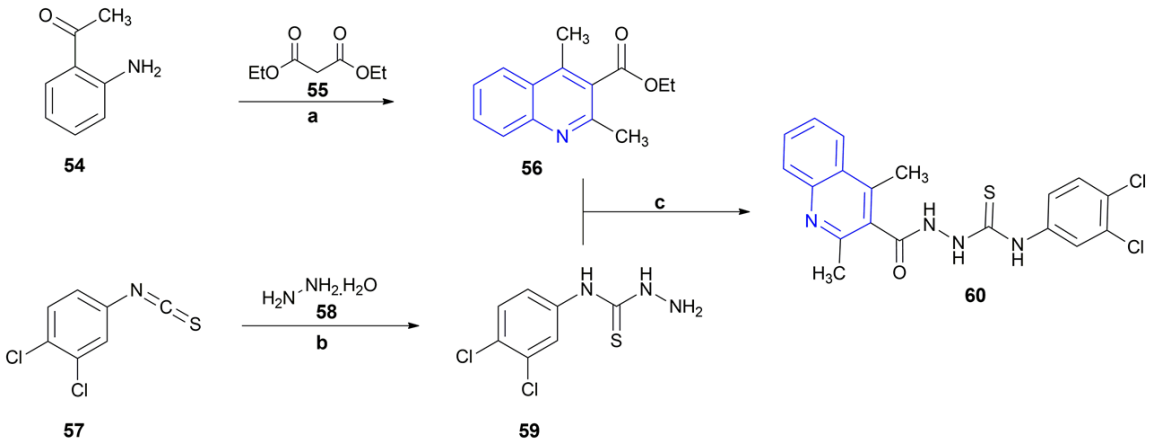
Scheme 6. Synthesis of compound 46; a. AcOH/EtOH, 0°C-RT, 2 h; b. DMF/$POCl_3$, 0°C to 60°C, 1 h; c. EtOH, reflux, 78-80°C, 5 days; d. $SOCl_2$, 6 h; e. THF or Ether/DIPEA, 0-15°C, 40 mins, RT, 24 h.



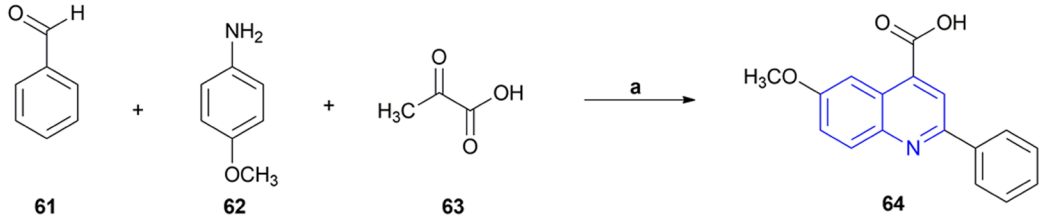
Scheme 7. Synthesis of compound 53; a. NaH, dry DMF, RT, 4 h; b. $NaNO_2$, HCl (3N), ice bath; c. NaN_3, H_2O, RT, 4 h; d. $CuSO_4.5H_2O$, sodium ascorbate, THF:H_2O=1:2, 80°C, 8 h.

of the cyclophenyl group (**Scheme 8**). Ethyl-2,4-dimethylquinoline-3-carboxylate 56 was synthesized by a reaction of ethyl acetoacetate 55 and alpha amino-acetophenone 54 with p-TSA as the catalyst. Simultaneously, benzyl-isothiocyanate derivative 57 was reacted with hydrazine hydrate 58 to give benzyl thiocarbazide derivative 59. Finally, compound 56 and compound 59 were hybridized in the presence of a few drops of glacial acetic acid and ethanol yielding compound 60. Compound 60 showed the best dock when checked for its stability and molecular interaction with PDB: 3JSU under molecular docking.

One pot synthesis of quinoline carboxylates has been done by Maryam *et al.* in the presence of NaH and MeCN as solvents [38]. A similar approach of one pot three components green synthetic route was employed by Hitesh



Scheme 8. Synthesis of compound 60; a. p-TSA, ethanol, MWI, 300 W, 4 mins; b. ethanol, MWI, 300 W, 2-4 mins; c. glacial acetic acid, ethanol, MWI, 300 W, 3-8 mins.

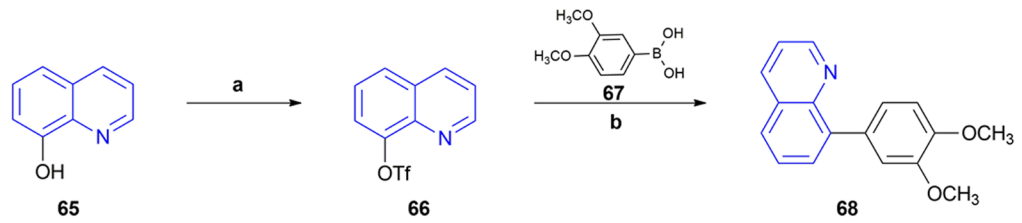


Scheme 9. Synthesis of compound 64; a. p-TSA (10%), ethanol, MWI, 300 W, 3-4 mins.

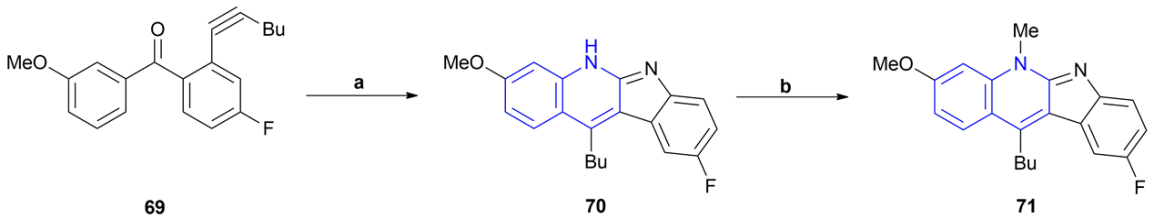
et al. in February 2020 using *p*-toluenesulfonic acid to synthesize quinoline-4-carboxylic derivatives. It involved the usage of microwave irradiation making it an environmentally friendly technique. Among the 16 synthesized compounds, 64 showed an IC_{50} value of 0.12 μM/mL against the tested *P. falciparum* strains. The reaction mixture consisted of benzaldehyde 61, 4-methoxy aniline 62, and pyruvic acid 63 which were microwave irradiated for 3-4 minutes in the presence of *p*-toluenesulfonic acid as a catalyst to yield compound 64 (**Scheme 9**). The potency of compound 64 was observed due to the presence of a strong electron-donating group like the methoxy group at the C6 position of the quinoline ring. Molecular docking revealed that compound 64 fitted exactly in the binding pocket and had a significant correlation with the biological activity and was further selected for ADME-Tox and MD studies [39].

Previously, biphenyl-substituted quinolines have been investigated for their anti-microbial, anti-helminthic, and antioxidant properties [39, 40]. Inspired by this, in March 2020, Wilson *et al.* synthesized quinoline-biphenyl hybrids which were further evaluated against *P. falciparum*. The synthesized compound 68, containing 3, 4-di-substituted methoxy groups showed better activity with an EC_{50} value of 42.70 μM as compared to the other di and mono-substituted hybrids [41]. The synthesis of the most active compound 68 was done by converting hydroxyquinoline 65 into triflate 66 in the presence of triflic anhydride. Suzuki cross-coupling reaction of triflate 66 with boronic acid 67 was carried out to yield the final compound 68 (**Scheme 10**). The drug-likeness of the compound was studied which proved it to have a good permeability across the cell membrane as a result of its LogP value being 4.152. Lipinski's rule of five [42] was followed and thus it was also found to be an acceptable oral drug [41].

A polycyclic quinoline, neocryptolepine was isolated from the *Cryptolepis sanguinolenta* plant which was extensively used for treating malarial. Analogues of this compound were synthesized by Akkachairin *et al.* in May 2020 to evaluate its anti-plasmodium activity [43]. Out of all the analogues, 71 showed good activity against



Scheme 10. Synthesis of compound 68; a. Triflic anhydride, Py, 0°C, 2 h, 80%; b. $Pd(AcO)_2/PPh_3/Na_2CO_3$, n-propanol/H_2O, 50°C, 2 h, Ar.



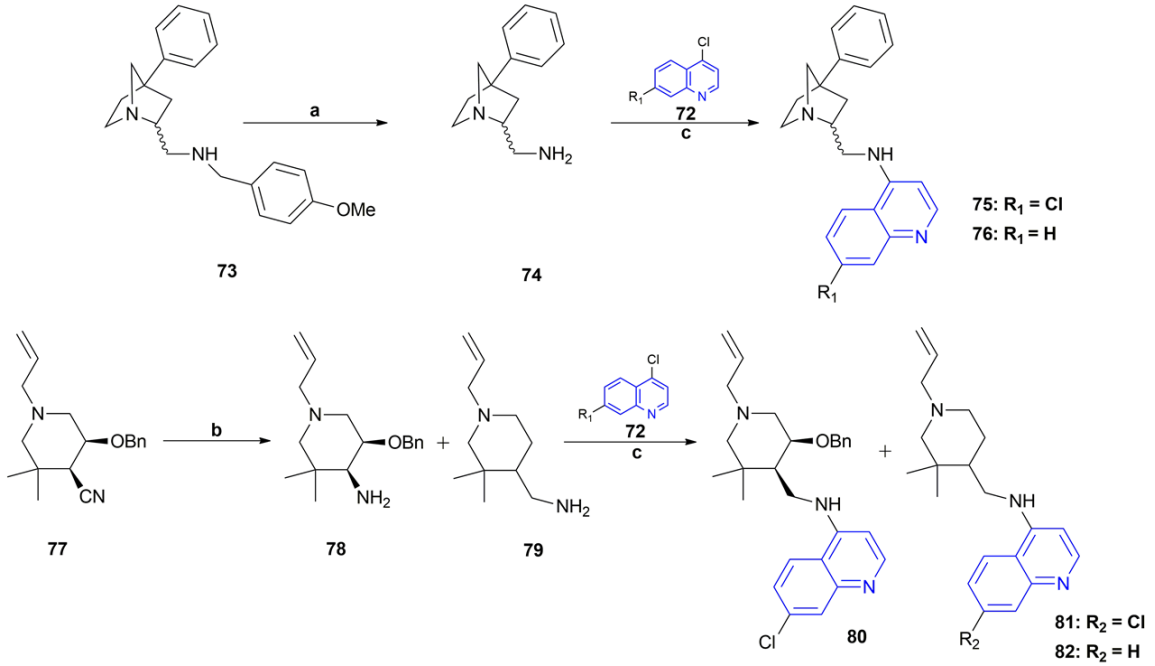
Scheme 11. Synthesis of compound 71; a. $TMSN_3$, TfOH, DCM; b. MeI, 85°C.

CQS *Pf*3D7 and MDR *Pf*K1 with an IC_{50} value of 1233.1 ± 176.5 nM and 1361.3 ± 6.4 nM respectively. Alkynylarylketone 69 undergoes double cyclization to produce 5*H*-indolo[2,3-*b*] quinoline derivative 70 using $TMSN_3$ and TfOH. Compound 70 was further methylated at the nitrogen atom of the quinoline nucleus to yield neocrytoplepine derivative 71 (**Scheme 11**).

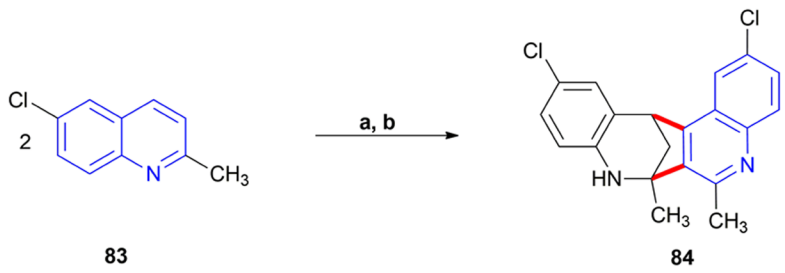
In July 2020, Van de Walle *et al*. synthesized a hybrid of quinoline and piperidine, thus validating the addition of a piperidine side chain as beneficial for the uptake and accumulation of anti-malarial drugs [44]. Out of 18 novel scaffolds synthesized, compounds 75, 76, 80, 81, and 82 have shown extraordinary IC_{50} value against MDR *Pf*K1 in a nano-molar range. Azabicyclo[2.2.1]heptane 73 is treated with cerium ammonium nitrate (CAN) giving rise to 2-aminomethyl-4-phenyl-1-azabicyclo[2.2.1] heptane 74. Compound 74 is further fused with chloroquinoline derivative 72 under microwave irradiation, in neat conditions to produce 4-aminoquinolines 75 and 76. The nitrile group of piperidine-4-carbonitrile 77 is reduced in the presence of $LiAlH_4$ to produce the major product 4-(aminomethyl)piperidine 78 and side product 5-unsubstituted piperidine 79. Compounds 78 and 79 were further hybridized with chloroquinoline derivatives under microwave irradiation, in neat conditions to produce piperidine-quinoline analogues 80, 81, and 82 (**Scheme 12**).

Benzomorphan is a derivative of morphine which has previously been studied for its analgesic properties [45]. The norbenzomorphan skeleton was derived from the conjugation of quinoline moieties by Kumar *et al*. [46]. A photocatalytic reaction was carried out using an iridium-based catalyst which led to unsymmetrical coupling between two molecules of 2-methylquinoline 83 derivatives to give rise to β-norbenzomorphan containing hybrids 84 (**Scheme 13**). The compounds were assessed for antiplasmodial activity by SYBR green I-based fluorescence assay [42] of which compound 84, containing the C6-chloro group, showed pronounced activity. It showed an IC_{50} value of 0.65 μM and 0.089 μM against *Pf*INDO and *Pf*3D7 respectively.

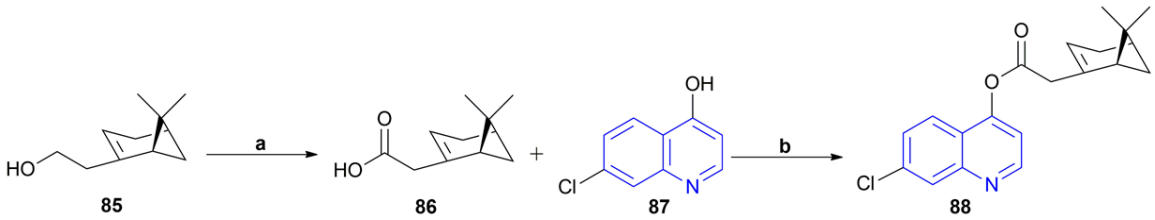
Several quinoline-based nopol amide and ester derivatives were synthesized by Nyamwihura *et al*. in February 2021 [47, 48]. It was observed that having a chloro group in the 7th position of the quinoline ring enhanced the anti-plasmodial activity as compared to all other compounds. As a result, compound 88 being 7-chloroquinolinyl nopoyl ester proved to be antagonistic to MDR *Pf*K1 with an EC_{50} value of 0.164 ± 0.06 μM. Nopol 85 was first converted to nopoic acid 86 using the Jones reagent. Nopoic acid 86 was then combined with 7-chloro-4-hydroxyquinoline 87 to yield the corresponding hybrid 88 (**Scheme 14**). The possible hypothesis for



Scheme 12. Synthesis of compounds 75, 76, 80, 81 and 82; a. CAN, CH_3CN/H_2O: 1/4, RT, 24 h; b. 5 equiv. $LiAlH_4$, THF, D, 15 h; c. 'neat', 130°C (MWI), 2-2.5 h.



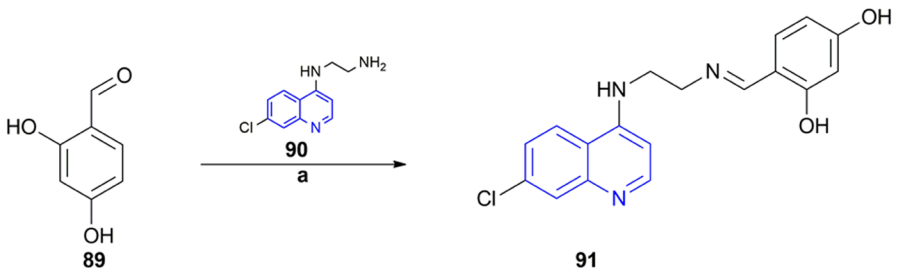
Scheme 13. Synthesis of compounds 84; a. $[Ir\{dF(CF_3)(ppy)\}_2(dtbpy)]PF_6$ (1.0 mol%), B_2pin_2 (1. equiv.); b. 1,4-dioxane, Blue LED 34 W, rt, Ar, 24 h.



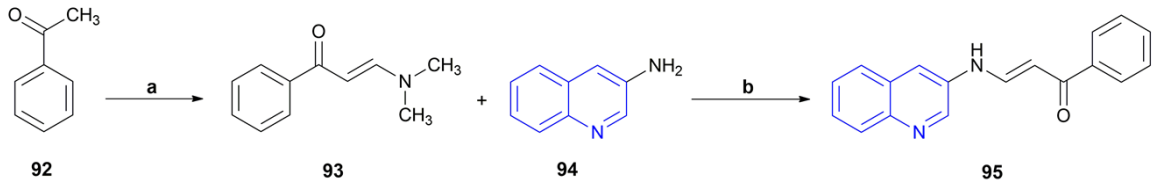
Scheme 14. Synthesis of compound 88; a. Jones reagent: Acetone, H_2O, 50°C, 12 h, 33-45%; b. THF, EDCI, DMAP, ROH, DIEA, 0°C to RT, 3 h, 25-45%.

the high susceptibility exhibited by the K1 strain towards compound "88" lies in the higher efficiency of transport of the drug by the *Pf*CRT transporter instead of hemoglobin degradation resulting in the anti-hemozoin activity.

Molecular hybridization was done by Marinho *et al*. in April 2021 to obtain imine linkage between N-(7-chloroquine in-4-yl)-ethylenediamine and benzaldehyde derivatives using alcohol as a solvent [49]. By inhibiting the CQR



Scheme 15. Synthesis of compound 91; a. ethanol.



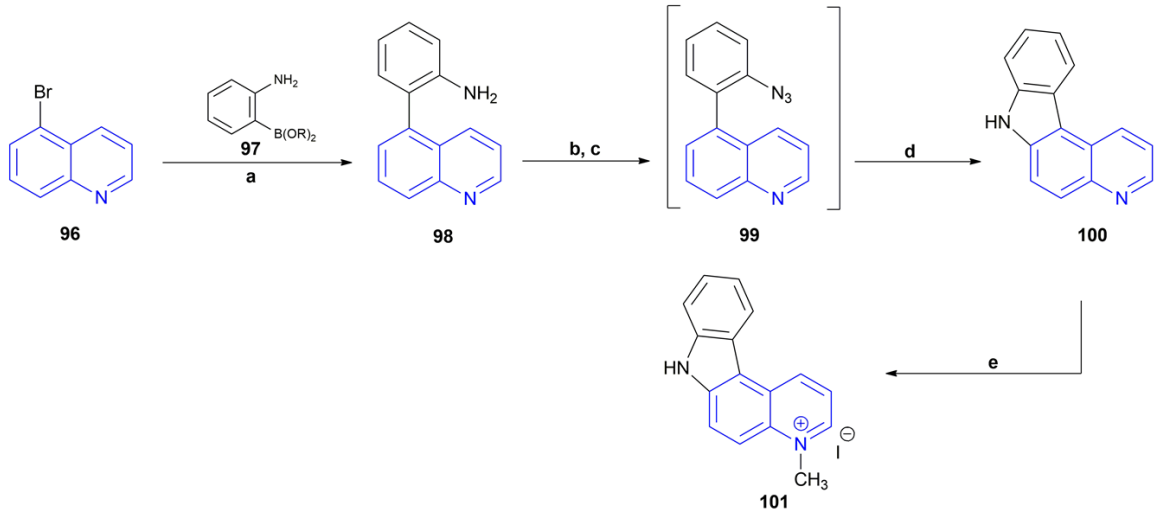
Scheme 16. Synthesis of compound 95; a. DMF-DMA, D; b. 2 eq.mol.$KHSO_4$ (aq), 10 mins, ultrasound irradiation at RT.

*Pf*W2 strain, compound 91 showed CQ-like interaction with ferriprotoporphyrin IX, thus proving to be a class of new antimalarial drugs by inhibiting the formation of hemozoin. Compound 91 showed the least IC_{50} value of 0.172 ± 0.003 μM with an SI value of 989.62. 2, 4-dihydroxy benzaldehyde 89 was reacted with 4-aminoquinoline 90 in the presence of ethanol to give rise to compound 91 (**Scheme 15**).

Enaminones are a group of compounds that have the conjugate system of N-C=C-C=O and these have been explored for their antibacterial, analgesic, anti-cancer, and anti-convulsant properties [50-53]. The field of application of enaminones was further expanded into antiparasitic activity by Khanikar *et al.* in May 2021 by synthesizing novel quinolinyl β-enaminone hybrids [54]. The compounds were tested against *P. falciparum* and it was observed that compound 95 exhibited an IC_{50} value of 3.89 μM and more than 5 μM against MDR *Pf*K1 and CQS *Pf*3D7 respectively. The synthesis route converts acetophenone 92 into 3-(dimethylamino)-1-phenylprop-2-en-1-one 93 by reacting with DMF and DMA. Further, compound 93 is hybridized with 3-aminoquinoline 94 to obtain the final compound 95 (**Scheme 16**).

Novel iodo salts of pyridocarbazole were synthesized by Håheim *et al.* in May 2021 to evaluate its antiplasmodial activity [55]. 4-Methyl-7*H*-pyrido[2,3-*c*]carbazolium iodide, compound 101, exhibited an IC_{50} value of 128 ± 2 nM with a selectivity index of 213.9 against CQS *Pf*3D7 which makes it more effective and selective than standard drug chloroquine which exhibited an IC_{50} value of 24 ± 1 nM. For the synthesis of 101, quinoline derivative 96 and boronic acid 97 underwent a Suzuki-Miyaura reaction to produce corresponding bi-aryl 98. Compound 98 is further oxidized into the aryl azide 99 via the installation of a diazonium salt. Aryl azide 99 when refluxed with 1,2-dichlorobenzene, undergoes thermal decomposition to produce the precursor 100 which is then regioselectively *N*-methylated using excess CH_3I in refluxing acetonitrile to finally produce 101 (**Scheme 17**). The precursor compound 7*H*-pyrido[2,3-*c*]carbazole 100 showed very negligible activity as compared to compound 101, hence emphasizing the importance of *N*-methyl functionalization. The increased availability of compound 101, which is a salt derivative, is due to its higher solubility in aqueous medium.

Derivatives of pyrimidine have exhibited anticancer and anti-folate activity [56]. To enhance the inhibition of the malarial parasite, Ademola *et al.* synthesized a conjugate of quinoline and pyrimidine derivatives using varying *n*-alkyl chain diamines as linkers [57]. The compounds were carefully designed such that the quinoline moiety and pyridine derivative are responsible

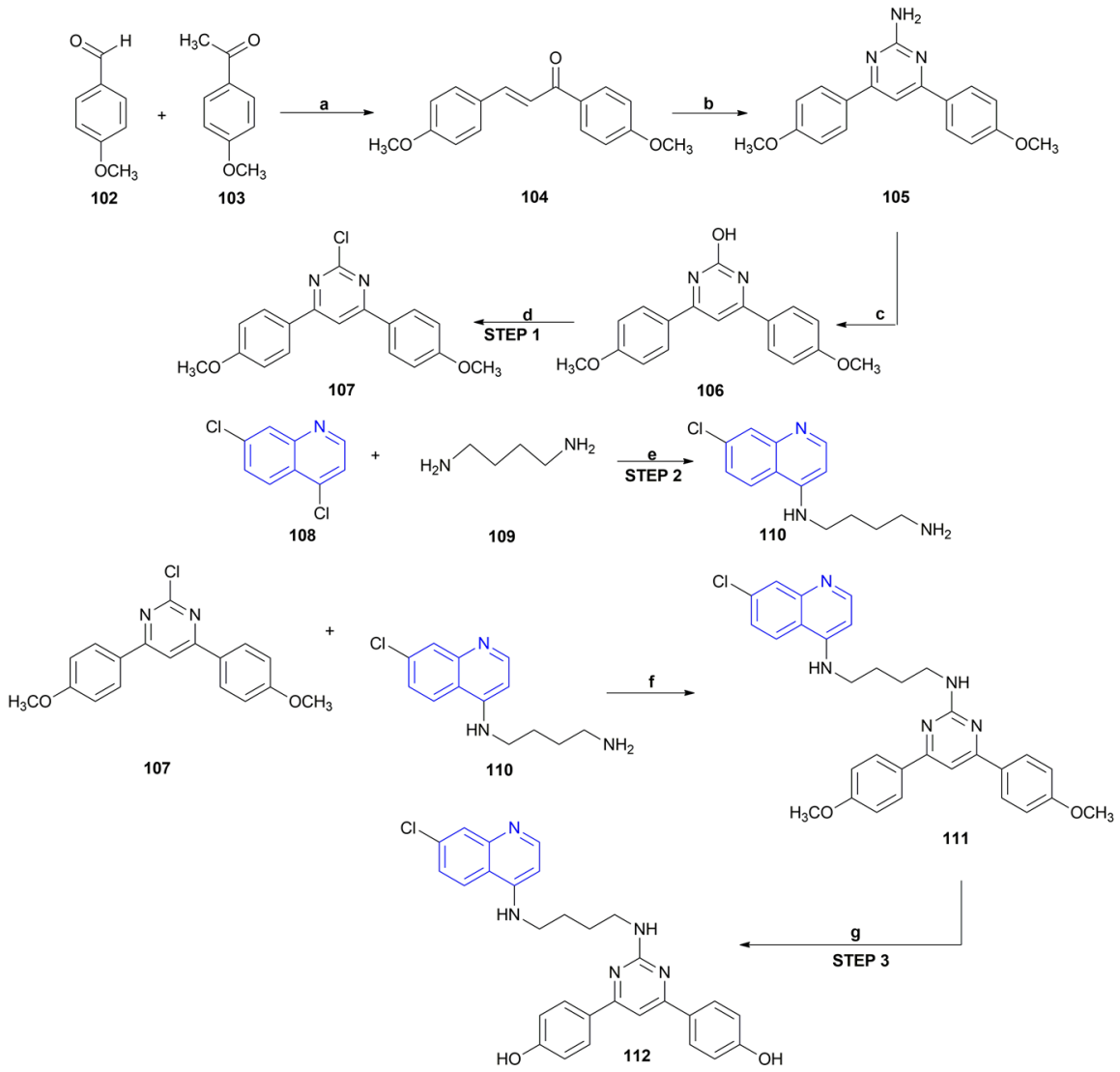


Scheme 17. Synthesis of compound 101; a. Cs_2CO_3, $Pd(PPh_3)_4$ (5 mol%), DME/H_2O, 80°C; b. HCl (37%), $NaNO_2$ (0.4 M), 0°C, 1.5 h; c. NaN_3/NaOAc, 0°C, 1 h; d. 1,2-dichlorobenzene, 180°C, 3 h; e. CH_3I, CH_3CN, reflux.

for heme inhibition and the inhibition of *Pf*DHRF respectively. *N-alkyl* diamine enhances the lipophilicity of the molecule. The conjugates were evaluated for *in vitro* anti-malarial activity against CQS *Pf*N5F4 which resulted in an IC_{50} value of 0.32 ± 0.06 μM expressed by compound 112. The synthesis includes three steps where the two parent compounds are synthesized separately and hybridized to form the final compound. Step one is the synthesis of 2-Chloro-4,6-diphenylpyrimidine 107. For this, aldol condensation between 102 and 103 was carried out to yield the chalcone 104 which on treatment with guanidine hydrochloride undergoes cyclisation to yield 4,6-diphenylpyrimidin-2-amine analogue 105. Through Sandmeyer's reaction, compound 105 is substituted to produce the hydroxyl derivative 106 which is finally converted to its chloro derivative 107. Step two includes the synthesis of quinoline diamine 110 by refluxing quinoline 108 and butane-1, 4-diamine 109 in isopropanol. Finally, in step three, compounds 107 and 110 are hybridized to yield compound 111 which is further demethylated to produce compound 112 (**Scheme 18**). In compound 112, the presence of a strong electron-withdrawing phenoxy group in the pyrimidine derivative along with synchronization of the other pharmacophores resulted in an aggravated anti-malarial activity.

When CQ resistance was observed in the parasite, analogues of 4-aminoquinolines were extensively studied for their anti-malarial activity [58]. Following this, Tiwari *et al.* synthesized *N*-substituted amino acid derivatives to overcome the resistance and evaluated them for *in vitro* antimalarial activity [59]. When tested for *in vitro* activity against CQS *Pf*3D7 and MDR *Pf*K1, it was observed that compound 116 exhibited an IC_{50} value of 0.04 ± 0.0 μM and 0.06 ± 0.04 μM respectively. The activity against CQR strain was approximately 13 times more effective than standard chloroquine which exhibited an IC_{50} value of 0.795 ± 0.15 μM. Tert-butoxy carbonyl (Boc)-protected amino acid 113 was coupled with piperidine to produce (Boc)-protected amino acid amide 114. The amide bond in 114 was reduced using mild reducing agent nitride to remove the (Boc) protection group to yield compound 115. Compound 115 was finally conjugated with 4,7-dichloro quinoline to produce compound 116 (**Scheme 19**). The presence of the piperidine group, which is an electron-donating group, could have been the grounds for the activity exhibited by compound 116.

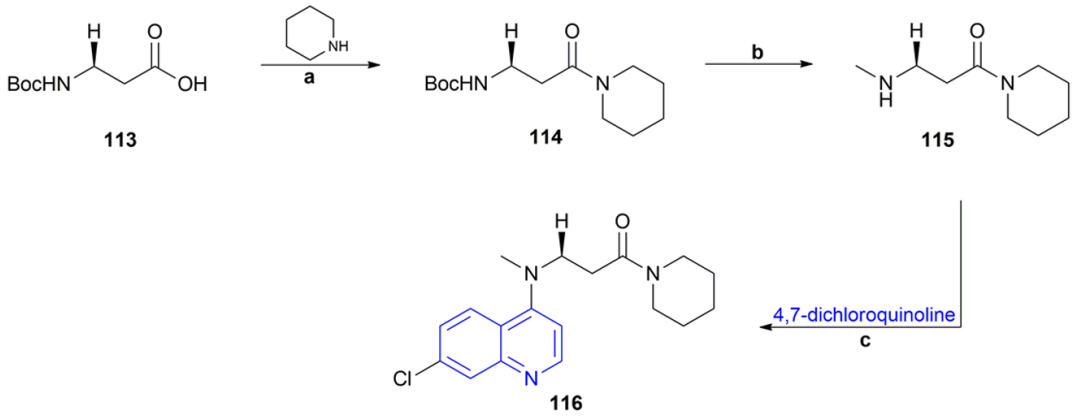
Anti-malarial activity of amino-alcohols has been previously studied using various conjugations with carbazoles, anthracene, 4-aminoquinoline-isatin, and triazoles [60-63]. Following these, a series of amino-alcohol quinolines and their derivatives were studied by Klimpt *et al.* in January 2022 [64]. Five different series with various modifications were done to the basic amino-quinoline core resulting in compounds with a broad range of *in vitro*



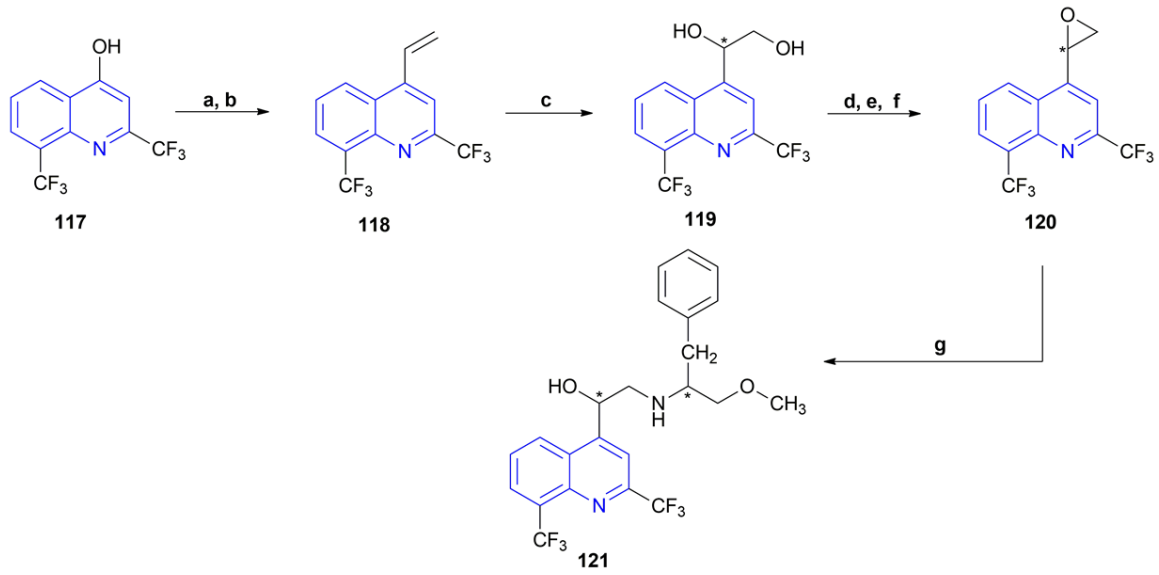
Scheme 18. Synthesis of compound 112; a. EtOH, NaOH, sonicate, 35°C, 1 h; b. Guanidine hydrochloride, NaOH, EtOH, reflux, 24 h; c. Acetic acid, $NaNO_2$, H_2O, RT, 3 h; d. $POCl_3$, DMF, 100°C, reflux, 6 h; e. Isopropanol, reflux, 100°C, 16 h; f. K_2CO_3, DMF, MWR, 120°C, 40 mins; g. HBr, MWI, 100°C, 20 mins.

activity against CQS *Pf*3D7 and CQR *Pf*W2. Among all the synthesized compounds, 121 showed better activity as compared to standard chloroquine. It is also notable that it proved to be 15 times more effective than chloroquine against the CQR strain. Enantiopure epoxide 120 was synthesized and was then conjugated with amine *via* microwave irradiation to yield compound 121 (**Scheme 20**). The activity of 121 is due to the methylation of the primary alcohol. Unfortunately, the *in vivo* assessment of the compound in the PbA infected mice model could not back the nano-molar range of IC_{50} value which was exhibited in vitro assay.

Cinnamic acid derivatives (CAD) have been previously studied for their ability to inhibit lactate transport which prevents plasmodial multiplication as lactic acid is utilized by the parasite for ATP production. Therefore, CADs were already considered as potential antimalarials [65]. Further property of hemazoin inhibition was explored by Bokosi *et al*. in March 2022 [66], by the synthesis of conjugates of 4-amino quinoline and cinnamic acid. All the synthesized molecules obeyed Lipinski's rule of five [42] and Veber's rule [67], thus possessing drug-likeness. Compound 126 exhibited an IC_{50} value of 1.81 ± 0.01 μM against CQS *Pf*3D7 and almost showed no cytotoxicity against



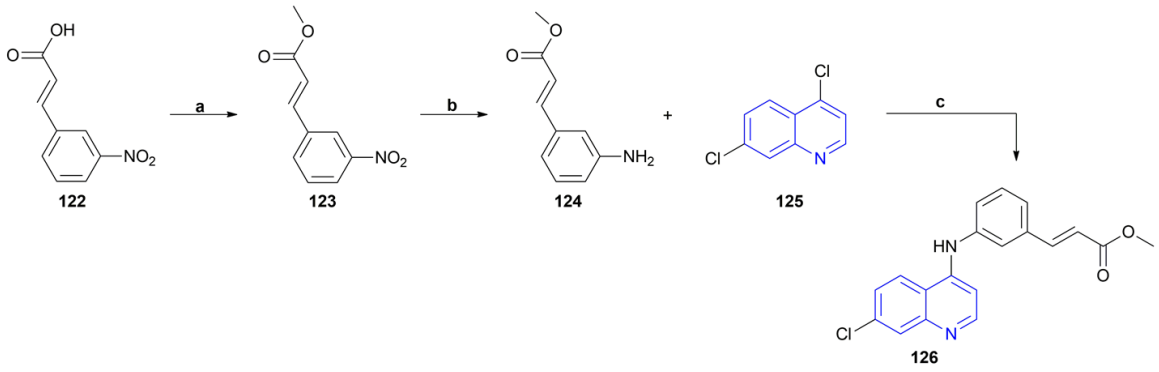
Scheme 19. Synthesis of compound 116; a. hydroxybenzotriole, DCM, DCC, DMF; b. vitrine, THF, 0°C to reflux; c. phenol, MWI (50 W), 145°C, 30 mins.



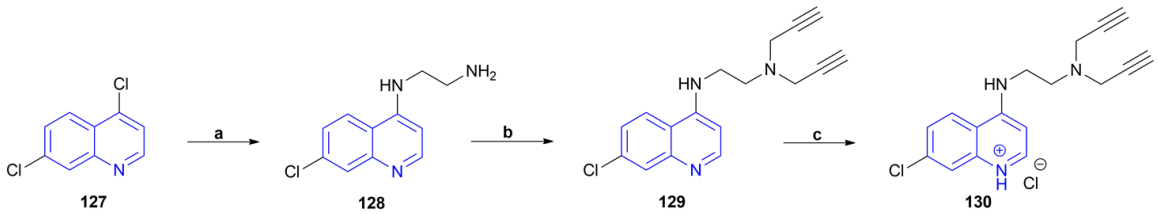
Scheme 20. Synthesis of compound 121; a. $POBr_3$, 150°C; b. CH_2=$CHBF_3K$, $PdCl_2(dppf).CH_2Cl_2$, $CsCO_3$, THF/H_2O; c. AD-mix a, $K_2OsO_2(OH)_4$, t-BuOH, H_2O, 20°C; d. trimethyl orthoacetate, APTS (cat.), CH_2Cl_2; e. CH_3SiCl, CH_2Cl_2; f. K_2CO_3, MeOH; g. Amine, EtOH, MWI, 150 W, 130°C, 30 mins.

HeLa cells. The synthesis of 126 involves the combination of synthesized methyl(*E*)-3-(3-aminophenyl)acrylate 124 with 4,7-dichloroquinoline 125 to yield compound 126 (**Scheme 21**) [66].

Surface-active ionic liquids derived from chloroquine were previously reported to have antiplasmodial activity higher than chloroquine and this was mainly due to its amphiphilic character [65]. Following this, Scopel *et al*. synthesized chloride salts of quinoline derivatives to test their efficiency against CQR *Pf*W2 through *in vitro* activity [68]. Compound 130 exhibited an IC_{50} value of 0.27 ± 0.09 μM and this was further found to obey Lipinski's rule of five [42]. Next, it was tested for *in vivo* activity in C57BL female mice infected with *P. berghei* as an oral drug and it was observed that the compound could inhibit 90% parasitemia when given orally within 4 days of infection. The synthesis begins with the reaction of 4,7-dichloroquinoline 127 with ethylene diamine resulting in compound 128 which was further converted into compound 129 by the addition of two propargyl groups at the terminal amine group. Finally, 129 was treated with HCl to produce its salt 130 (**Scheme 22**).



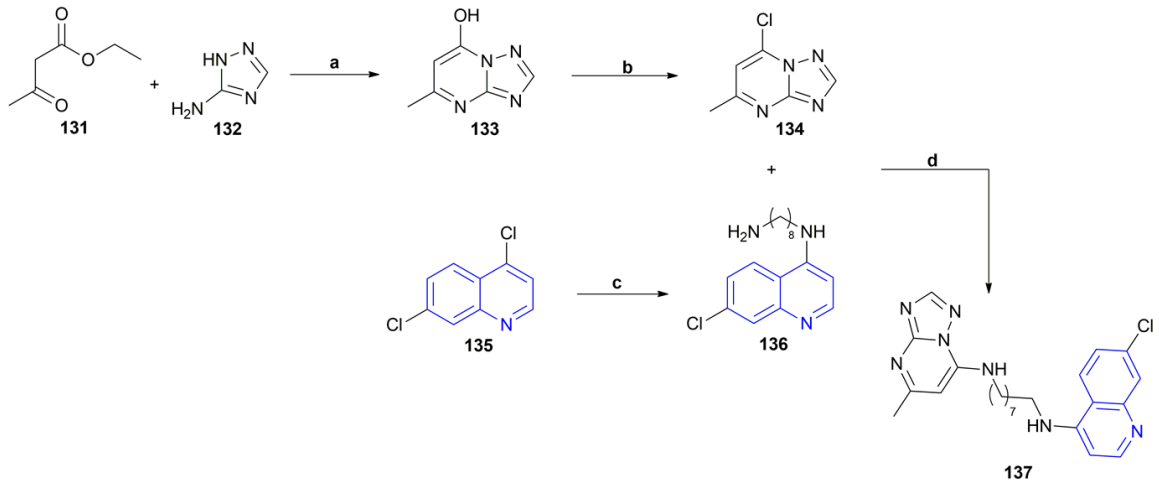
Scheme 21. Synthesis of compound 126; a. CH_3OH, conc. H_2SO_4 (cat), 65°C, 3 h; b. Zn, NH_4Cl, CH_3OH, RT, 3 h; c. dry EtOH, reflux, 9 h.



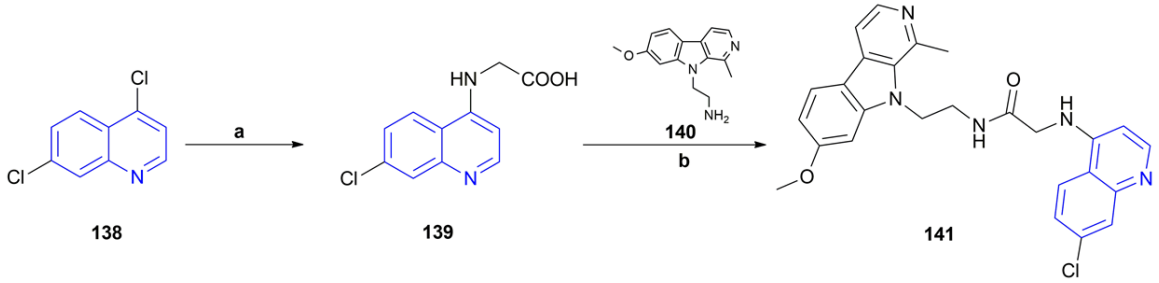
Scheme 22. Synthesis of compound 130; a. ethylenediamine, 80-110°C; b. propargyl bromide, K_2CO_3, ethanol, RT; c. HCl, acetone, RT.

In June 2022, Chowdhary *et al.* [69] have synthesized a hybrid of 4-aminoquinoline and triazolopyrimidine and evaluated its activity against *P. falciparum* strains and *P. falciparum* dihydroorotate dehydrogenase (*Pf*DHODH). *Pf*DHODH has been the most drug-targeted enzyme as this is essential for genetic material replication by playing a role in the *de novo* synthesis of pyrimidines. Since the parasite lacks the salvage pathway for utilization of preformed nucleosides, inhibition of *Pf*DHODH has always shown an inhibition in the growth of the parasite [70]. Among the synthesized compounds, the best activity was shown by compound 137 with an IC_{50} value of 0.17 ± 0.05 μM and 0.20 ± 0.06 μM against CQS *Pf*3D7 and CQR *Pf*W2 respectively making it approximately two-fold more active than standard drug chloroquine which exhibited an IC_{50} value of 0.023 ± 0.006 μM and 0.53 ± 0.13 μM against CQS *Pf*3D7 and CQR *Pf*W2 respectively. A docking study of 137 with drug targets *Pf*CRT and *Pf*DHODH revealed stable binding of the compound with the targets, making it a potential anti-malarial drug. The synthesis includes the preparation of the precursor triazolopyrimidine analogue 134 and 4-amino-quinoline derivative 136 which were then hybridized by nucleophilic substitution reaction to yield compound 137 (**Scheme 23**) [71].

It had been reported that harmines along with chloroquine have a synergistic effect against plasmodium species [72]. Following this, conjugates of harmine and chloroquine through triazole-type (TT) and amide-type (AT) links have been synthesized by Poje *et al.* in August 2022 [73]. The compounds were tested against several strains of *P. falciparum*. The maximum activity was shown by compound 141 which exhibited an IC_{50} value of 2 ± 0.3 nM, 16.2 ± 2.83 nM, 24.8 ± 1.3 nM, and 7.4 ± 1.3 nM respectively against CQS *Pf*3D, MDR *Pf*Dd2, low-CQR *Pf*K1 and high-CQR *Pf*7G8 with a selectivity index of 4450 against HepG2 cells. The compound 141 was synthesized by the reaction of 7-chloroquinoline-based carboxylic acid 139 with harmine-based amine 140 with the coupling reagent TEA/T3P in DMF (**Scheme 24**). Compound 141 exhibited a better binding with *Pf*Hsp90 when compared with either of the parent compounds. Hence, it was almost 5.5 times more effective than the standard drug chloroquine. It was also observed that AT hybrids were better than TT hybrids. The enhanced activity of compound 141 was due to



Scheme 23. Synthesis of compound 137; a. AcOH, 150°C, 30 mins, MWI; b. $POCl_3$, 45 mins; c. octane diamine, Et_3N, reflux, 10 h; d. DMF, K_2CO_3, RT, 24 h.



Scheme 24. Synthesis of compound 141; a. H_2NCH_2COOH, C_6H_5OH, 125°C, 18 h; b. T3P, TEA, DMF, RT, 18 h.

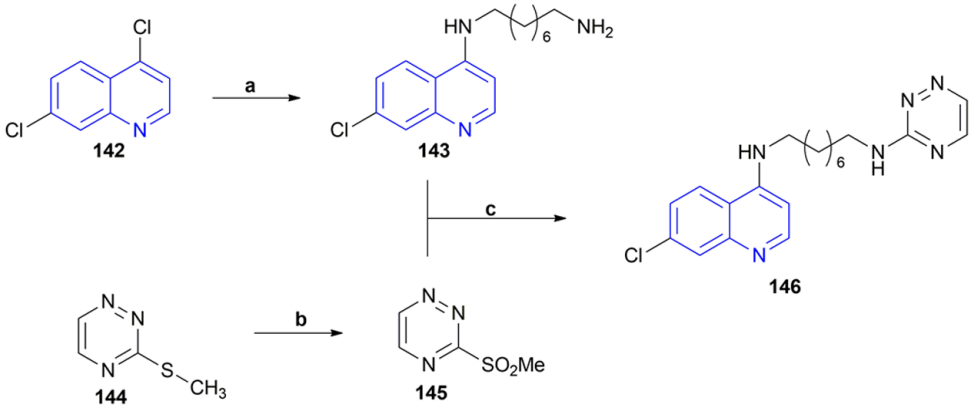
the *N*-9 substitution of the β-carboline ring [73].

Triazines have been previously studied for their anti-viral, anti-fungal, anti-convulsant, and hypotensive properties [74]. They have also proved to enhance anti-malarial activity when included as a linker in quinoline conjugates [75]. Conjugates of quinoline and triazine were synthesized by Feng *et al.* in January 2023 [76] using different linker groups and evaluated for *in vitro* β-hematin inhibition. It was observed that compound 146 was the most effective one among all the others due to its ability to bind with hemin and prevent β-hematin formation. 4-amino-7-chloro-quinoline derivative 143 and 3-(methylsulfonyl)-1,2,4-triazine 145 were hybridized in acetonitrile and then reacted in sodium carbonate for four hours to produce compound 146 (**Scheme 25**). The long linker chain enhanced the lipophilicity and the presence of multiple N atoms in the compound thus increasing the basicity which promotes the binding between the drug and hemin.

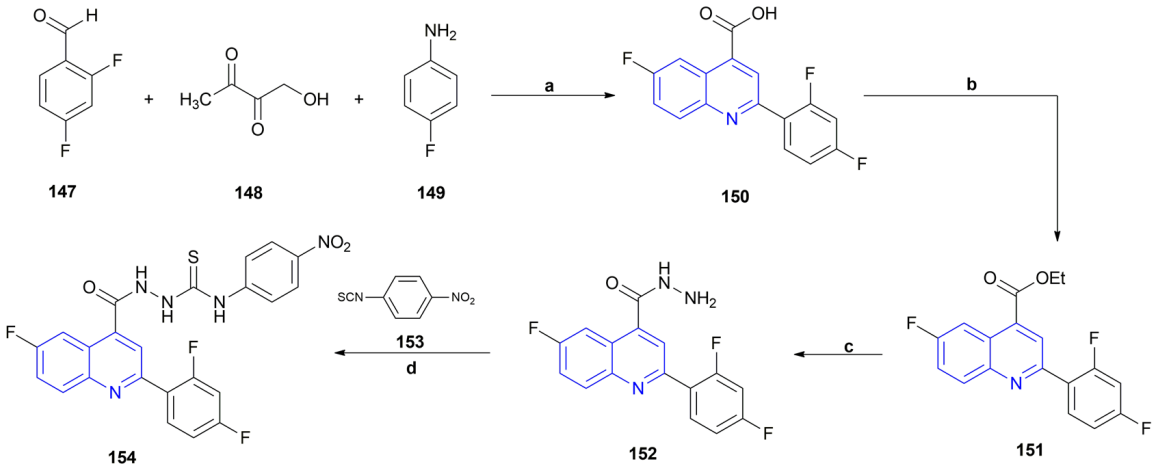
Tri pharmacophores

The synthesis and activity of some of the recently synthesized hybrids having three major pharmacophores conjugated through linkers have been discussed here.

One pot reaction between benzaldehyde derivative 147, pyruvic acid 148, and 4-fluoro aniline 149 was carried out to produce fluorine-containing quinoline-thiocarbazide compound by Patel *et al*. in July 2019 [77]. These compounds were then tested against the CQR *P. falciparum* strain. It was observed that compound 154 showed better results than all the other synthesized compounds as it exhibited an IC_{50} value of 0.10 μM/mL. The initial one-pot reaction under reflux conditions resulted in the formation of quinoline-like compound 150 by cyclization



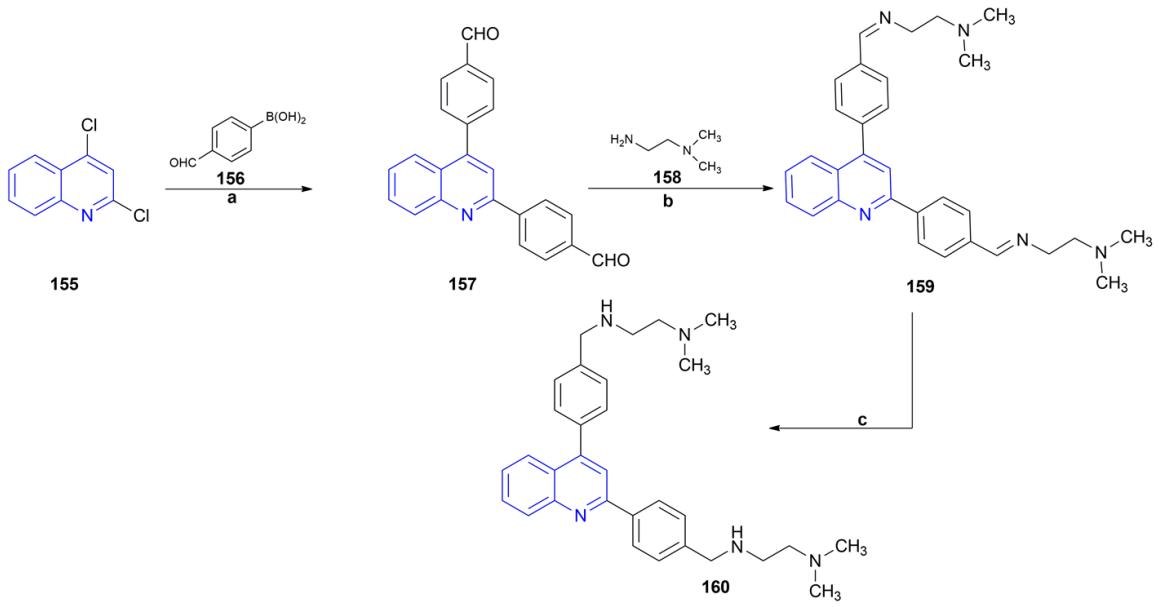
Scheme 25. Synthesis of compound 146; a. diamine, ethanol, reflux, 12 h; b. mCPBA, CH_2Cl_2, -10°C, RT, 3 h; c. acetonitrile, $NaCO_3$, RT, 4 h.



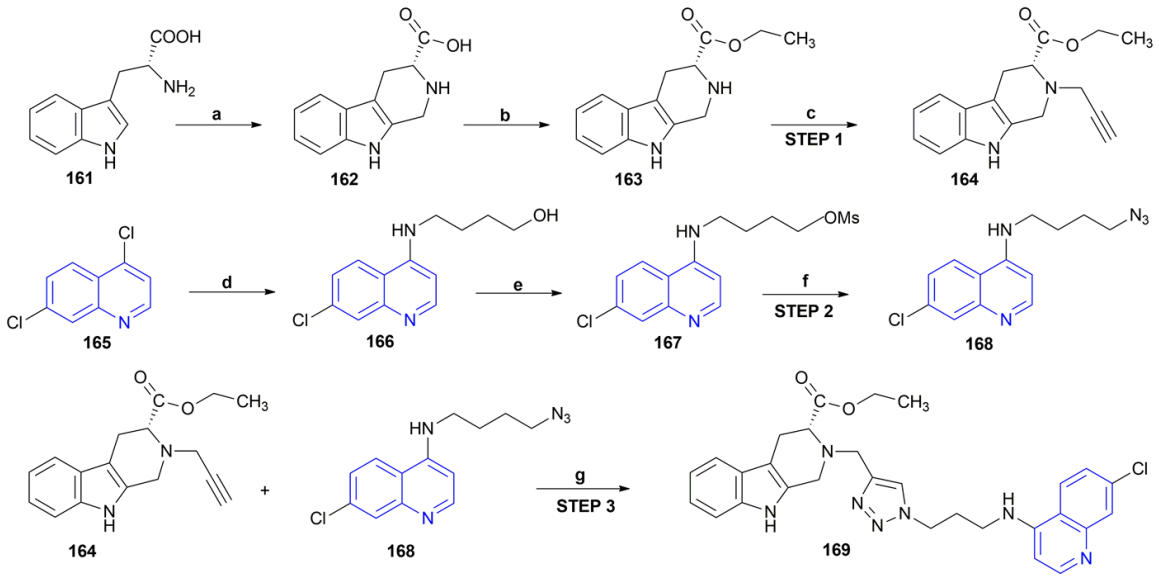
Scheme 26. Synthesis of compound 151; a. Trifluoroacetic acid (TFA), ethanol, reflux, 3 h; b. Conc. H_2SO_4, ethanol, reflux, 4 h; c. $NH_2NH_2.H_2O$, ethanol, reflux, 4 h; d. Ethanol, glacial AcOH, Reflux, 3-4 h.

(**Scheme 26**). Followed by esterification and ethanolic condensation, compound 152 was formed. Finally, compound 152 is refluxed with isocyanate 153 in ethanol to yield compound 154 which consists of a quinoine derivative with hydrazine-carbothiomide group and nitrophenyl group. This comparable potency of compound 154 with chloroquine is due to the presence of electron-withdrawing tri-fluoro groups. It was also observed that the fluoro group in the C6 position of the quinoline moiety led to an increase in anti-malarial activity when compared with the other synthesized analogues with the fluoro group at carbon positions other than C6 and this finding was backed by molecular docking studies [78].

A series of bis-substituted quinolines, quinazolines, and isoquinolines were synthesized by Guillon *et al*. in January 2020 [79], starting with 2,4-dichloroquinoline. The synthesized novel quinoline-like derivatives were tested for their *in vitro* activity anti-parasitic activity against CQS *Pf*3D7 and CQR *Pf*W2 strains. Among all the synthesised compounds, 2,4-bis{4-[(2-dimethylaminoethyl)aminomethyl] phenyl} quinolines, 160 showed high inhibition potential, exhibiting an IC_{50} value between the range of 0.032 to 0.34 μM against the tested strains. The synthesis route begins with the reaction of 2,4-dichloro quinoline 155 and 4-formylphenyl boronic acid 156 in the presence of tetrakis (triphenylphosphine) palladium to give rise to disubstituted quinoline 157 which was then reacted with diamine 158 in ethanol to yield compound 159. Compound 159 was further dehydrogenated by sodium borohydride to yield compound 160 (**Scheme 27**).

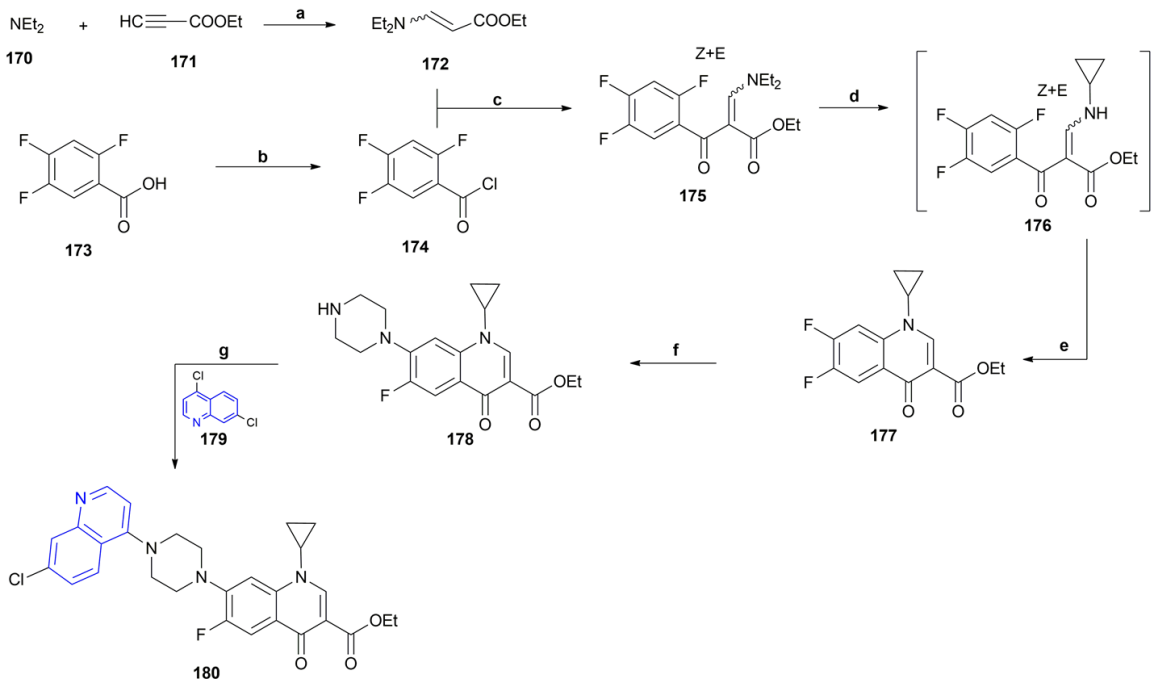


Scheme 27. Synthesis of compound 160; a. $Pd[P(C_6H_5)_3]_4$/D; b. EtOH/D; c. $NaBH_4$, MeOH/D.



Scheme 28. Synthesis of compound 169; a. 30% formaldehyde, NaOH, H_2O, reflux, 98%; b. $SOCl_2$, EtOH, 6 h, reflux, 92%; c. propargyl bromide, acetonitrile, RT, 6-8 h, 94%; d. ethanolamine, 130 °C, 8 h, 75%; e. $MeSO_2Cl$, THF, 0 °C, 2 h, 65%; f. NaN_3, DMF, 60 °C, 2 h, 98%; g. $CuSO_4.5H_2O$, sodium ascorbate, EtOH:H_2O (8:2), RT, 6 h.

Tetrahydro-β-carbolines have previously been investigated for their anti-cancer [80] and antifungal properties [81]. Further biological activity evaluations were conducted by Sharma *et al.* [82] by synthesizing a hybrid of tetrahydro-β-carboline with 4-aminoquinoline linked via an acyl-hydrazide or 1H-triazole core which was tested against CQR *Pf*W2. The synthesized compound 169 proved to be the most active with an IC_{50} value of 0.49 ± 0.02 μM. The synthesis includes three steps (**Scheme 28**). The first step involves the base promoted cyclisation of tryptophan 161 in the presence of formalin via Pictet-Spengler cyclization to produce compound 162 which was then esterified with ethanol to yield 163. Then it was treated

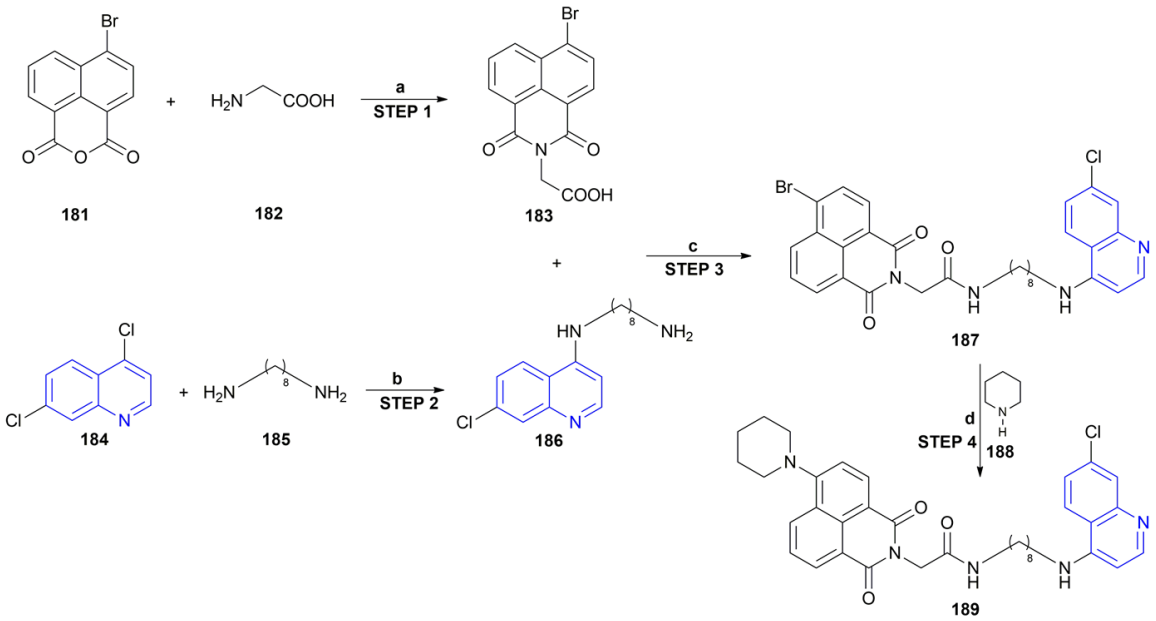


Scheme 29. Synthesis of compound 180; a. CH_3CN, N_2 atm, RT, 24 h; b. $(COCl)_2$, DMF, DCM, N_2 atm, RT, 24 h; c. Et_3N, Toluene, N_2 atm, 90°C, 5 h; d. cyclopropanamine, EtOH/Et_2O (1:2), RT, 3 h; e. K_2CO_3, DMF, 100°C, 5 h; f. piperazine, Et_3N, CH_3CN, reflux, 7 days; g. Et_3N, DMF, 110°C, 5 h or Et_3N, DCM, RT, 16 h.

with propargyl bromide to yield compound 164. The second step involves the modification of 4,7-dichloroquinoline 165 into its azido derivative 168. Finally in step three, compound 164 and 168 were hybridised to form compound 169 by Cu-promoted azide-alkyne cyclo addition. The activity of 169 is entitled to the non-cytotoxic triazole group present as the linker between the carboline and aminoquinoline moieties. The selective index of the compound is 495.76 making it a very potent derivative.

Ciprofloxacin-quinoline hybrid was synthesized by Dana *et al*. in June 2020 [83]. The piperazine ring present on the C7 position of the quinoline nucleus of ciprofloxacin was chosen for the substitution based on the previous potentiality expressed by it. The terminal nitrogen present in the piperizine in the fourth position was substituted with various heterocyclics. Among the synthesized compounds, the best activity was exhibited by compound 180, consisting of 7-chloro-quinoline substitution, as it showed an IC_{50} value of 13.52 ± 0.2 nM and 30.64 ± 1.07 nM against CQS *Pf*3D7 and CQR *Pf*W2 respectively in its second life cycle after 96 hours. The hybrid did not retain the mechanism of both ciprofloxacin and quinoline and thus it's mode of action is yet to be explored. *De nova* synthesis of ciprofloxacin 178 was carried out and then hybridised with 4,7-dichloroquinoline 179 to yield compound 180 (**Scheme 29**).

Some of the hybrids of naphthalimide have shown good anti-plasmodial activity [84]. This was further studied by Shakuni *et al*. in November 2020 [85] by synthesizing hybrids of naphthalimide with 4-aminoquinoline. Twenty-five of such hybrids were synthesized and analysed for *in vitro* activity against *P. falciparum* strains. Among all the tested compounds, 189 showed an enhanced IC_{50} value compared to parent drug 4,7-dichloroquinoline. It was observed to be 0.121 ± 0.033 μM and 0.070 ± 0.019 μM against CQS *Pf*3D7 and CQR *Pf*W2 strains respectively with a selectivity index of 1319.80 and 2281.37 respectively. The synthesis includes four steps. Step one is the synthesis of naphthalimide derivative 183 by the reaction of 181 and 182 by heating in anhydrous DMF with triethyl amine as a mild base. Step two is the synthesis of 4-aminoquinoline derivative 186 by the reflux of quinoline 184 and diamine 185. Step three consists of the

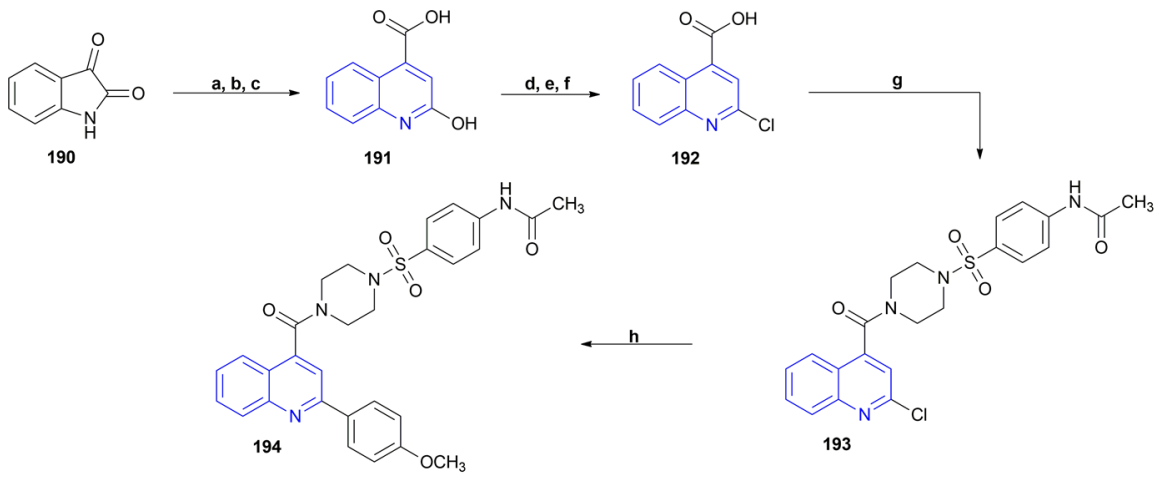


Scheme 30. Synthesis of compound 189; a. Et_3N, DMF, 100 °C, 5 h; b. Et_3N, reflux, 10 h; c. EDC, HOBt, DIPEA, DMF, RT, 1 h; d. NMP, 180 °C, 1 h.

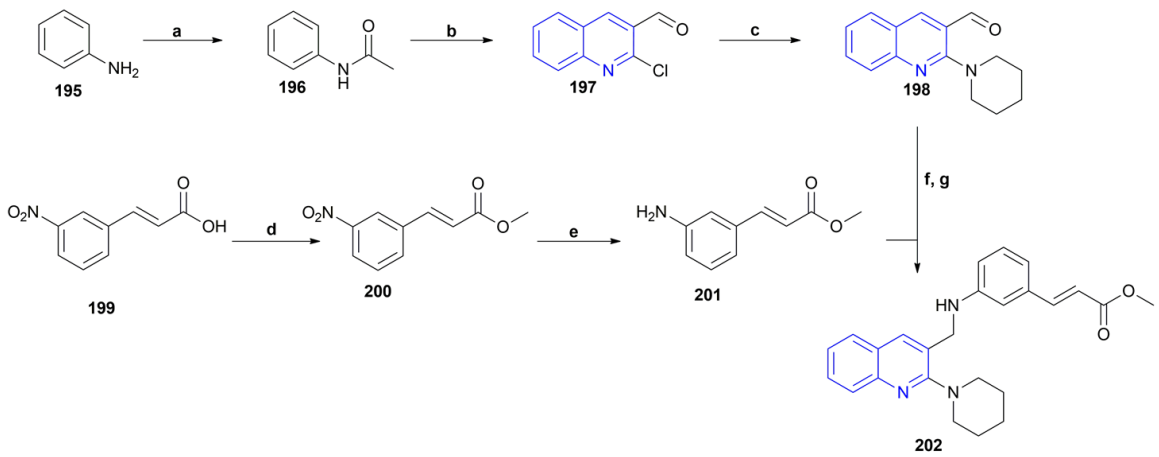
hybridisation of naphthalimide 183 and quinoline 186. Finally, in step four, amide tethered 4-aminoquinoline-naphthalimides 189 using *N*-methylpyrrolidin-2-one (NMP) as solvent by combining 187 with piperizine 188 (**Scheme 30**). This potency of the synthesized hybrid is suspected due to inhibition of hemozoin formation and *Pf*CRT.

In March 2021, Singh *et al.* [86] synthesized a group of quinoline-4-carboxamide compounds which served as the analogue of E64 inhibitor. The synthesized derivative worked by inhibiting the cysteine protease Falcipain-2 (FP2), which plays a role in the proliferation of the malarial parasite by inducing hemolysis. The synthesis of the derivatives has been described below and among the 25 synthesized compounds, 194 proved to be the most effective by exhibiting IC_{50} value of 2.14 ± 0.64 μM and 0.81 ± 0.31 μM for FP2 inhibition and CQS *Pf*3D7 parasite inhibition respectively. Isatin 190 was refluxed with malonic acid to yield 191 which was further refluxed for two hours and treated with ice water and filtered. The filtrate obtained was treated with KOH to obtained 2-chloroquinoline-4-carboxylic acid 192. Further reaction with TEA, HBTU and DMSO resulted in the formation of compound 193. Finally, the C2 chloro group of the quinoline in 193 was substituted with 4-methoxy-phenyl group to produce 194 (**Scheme 31**). The *in silico* study of compound 194 with FP2 enzyme revealed π-π stacking interactions with Trp206, Trp210, and Phe156. In addition, a strong H-bond was observed between oxygen of p-methoxy benzene of 194 and hydrogen of Gln171.

2-(*N*-cyclicamino)quinolines were conjugated with methyl (*E*)-3-(2,3,4-aminophenyl)acrylates to give rise to a new series of compounds by Bokosi *et al*. These compounds were then evaluated for *in vitro* activity against CQS *Pf*3D7. It was observed that compound 202 was the most effective one among all the others. It exhibited an IC_{50} value of 1.4 ± 0.05 μM when tested against CQS *Pf*3D7. It also obeyed the Lipinski's rule of five [42] with just one violation. The *in silico* study of protein-ligand interaction proved the *in vitro* activity result by showing a very good binding affinity which could be due to formation of two H-bonds. The synthesis of compound 202 began with the synthesis of *N*-phenylacetamide 196 by the reaction of aniline 195 with acetic anhydride in the presence of glacial acetic acid [87]. Further it undergoes cyclisation by Vilsmeier-Haack reaction to yield quinoline-carbaldehyde derivative 197 whose C2 position of the quinoline was substituted with piperadine in refluxing condition to produce compound 198. The synthesized aminophenylacrylate derivative 201 (**Scheme 32**)



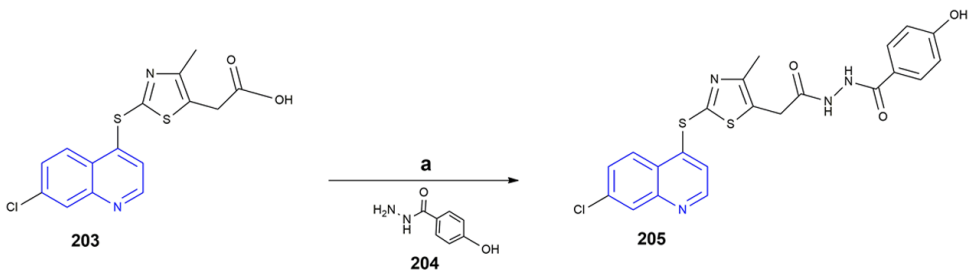
Scheme 31. Synthesis of compound 194; a. refluxed with malonic acid, 16 h; b. treated with aq. $NaHCO_3$; c. filtrate acidified with HCl (pH=1-2); d. refluxed for 2 h, e. treated with ice water; f. filtrate treated with KOH; g. TEA, HBTU, DMSO, 7 h; h. (4-methoxyphenyl)boronic acid, toluene, K_2CO_3.



Scheme 32. Synthesis of compound 202; a. Ac_2O, AcOH, reflux, 30 mins; b. DMF-$POCl_3$, 80°C, 5-18 h; c. DMF, K_2CO_3, piperidine, reflux, 2.5-10 h; d. CH_3OH, H_2SO_4 (cat), reflux, 3 h; e. Zn, NH_4Cl, CH_3OH, reflux, 3 h; f. CH_3OH, AcOH (cat), reflux, 12 h; g. $NaCNBH_3$, 0°C to RT, 12 h.

was reacted with compound 198 to produce compound 202. The meta position of acrylate in the aryl ring proved to be beneficial for the anti-plasmodial activity as compared to para and ortho position.

Novel 2-mercapto-4-methyl-5-thiazoleacetic acid derivatives of 4,7-dichloroquinoline have been synthesized by Ramírez *et al.* [88] and tested for its *in vitro* β-haematin inhibition activity and *in vivo* activity against *P. berghei* ANKA infected mice. Among the 12 synthesized compounds, 205 showed very good inhibition of β-haematin formation along with hemolysis which was observed to be lesser than that of chloroquine, but a similar trend was not observed in the *in vivo* testing. The compound showed a survival time of 15-20 days which is lesser than that of chloroquine without any major changes in development of the parasitemia over the days. Compound 203 was synthesized by the nuceophilic addition of 4,7-dichloroquinoline with 2-mercapto-4-methyl-5-thiazolacetic acid. Compound 203 was reacted with 4-hydroxyphenyl acetohydrazine 204 to yield the derivative 205 (**Scheme 33**). The substitution of the benzyl group in "R" at para position had resulted to be beneficiary for the anti-malarial activity.

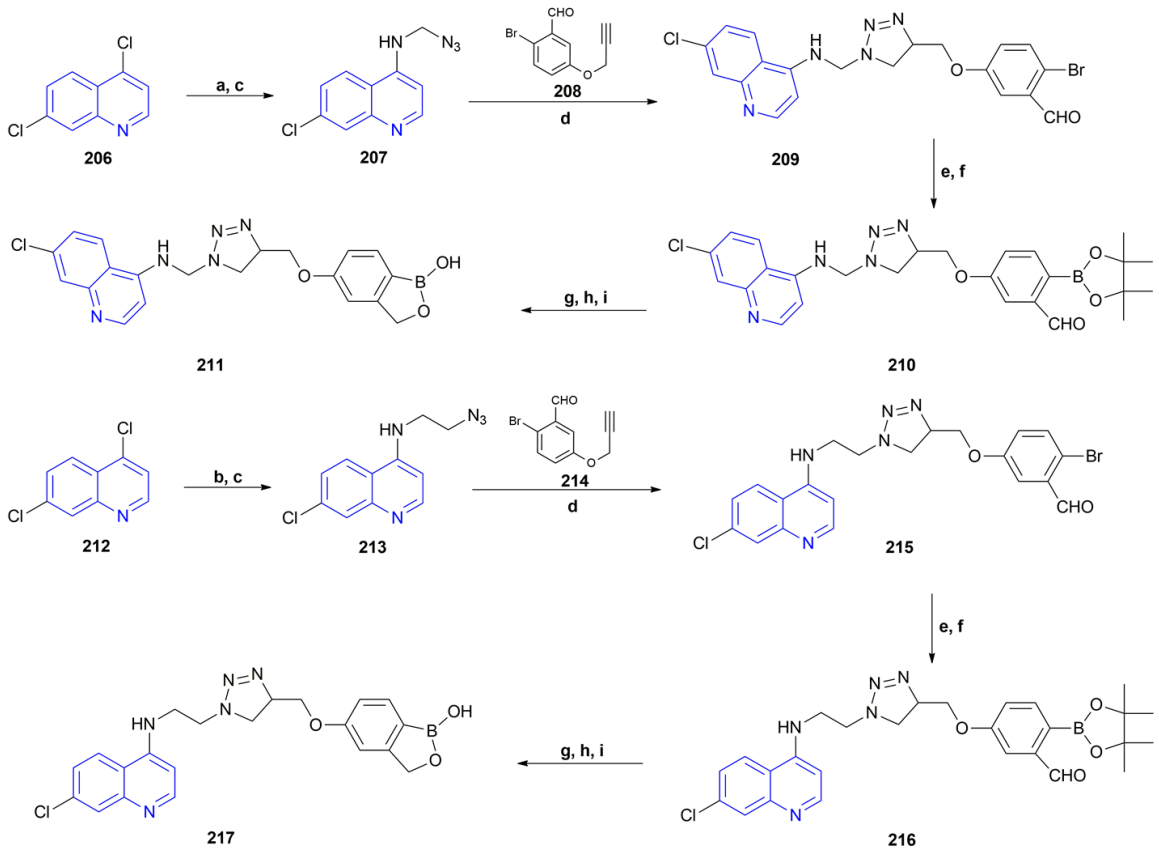


Scheme 33. Synthesis of compound 205; a. EDC, DMAP, 0 °C-RT.

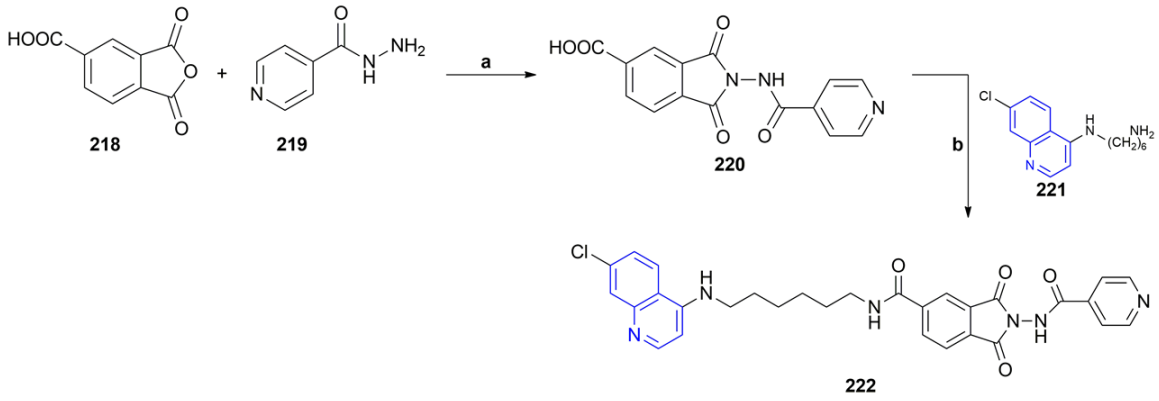
Benzoxaboroles and its various quinoline derivatives have been investigated for anti-malarial activity against *P. falciparum* [89] and *P. berghei* [90]. Further investigations for enhancing antimalarial activity were done by Saini *et al.* in April 2021 [91] by incorporating a triazole linker between quinoline and benzoxaboroles as a result of the ability of triazole to improve pharmacokinetic properties. The compounds were tested for *in vitro* activity against CQS *Pf*3D7 and CQR *Pf*W2 and the compounds were more active against the CQR strain. It was observed that the increase in chain length of 4-amino group of quinoline supplemented the activity and this was observed in compounds 211 and 217. Compound 211 exhibited an IC_{50} value of 4.15 μM and 3.78 μM against CQS *Pf*3D7 and CQR *Pf*W2 respectively whereas compound 217 exhibited an IC_{50} value of 4.13 μM and 3.91 μM respectively. The synthesis begins with the reaction of *O*-propargylated bromobenzaldehyde 208 and methyl-azido derivative of 4-amino-7-chloro-quinoline 207 in presence of $CuSO_4$ and sodium ascorbate resulting in the formation of compound 209. Boronic ester 210 was then synthesised by the reaction of 209 with Pin_2B_2 in presence of $Pd(dppf)Cl_2$ and KOAc as base. Finally, the ester 210 was subjected to reduction by $NaBH_4$ followed by acidification resulting in the formation of compound 211. Compound 217 was synthesized in a similar fashion with the ethyl-azido derivative 213 in the initial step of reaction with *O*-propargylated bromobenzaldehyde 214 (**Scheme 34**).

In June 2021, a triad of quinoline-isoniazid-phthalimide has been studied by Rani *et al.* [92] in comparison with chloroquine. The synthesised compound 222 had a very promising *in vitro* activity against CQR *Pf*W2 with an IC_{50} value of 11.5 ± 1.6 nM which makes it 12 times more potent than standard drug chloroquine which exhibited an IC_{50} value of 141.9 ± 0.7 nM. The synthesis of compound 222 is carried out via microwave by the coupling of substituted phthalic anhydride 218 with Iso Nicotino Hydrazide (INH/isoniazid) 219 which gives the product INH-phthalimide 220. Following this, compound 220 undergoes amide/ester coupling reaction with 4-aminoquinoline diamine 221 with EDC as the catalyst to produce the compound 222 (**Scheme 35**). The compound also showed good binding with heme which resulted in the inhibition of β-haematin formation along with 4.12 as LogP value.

Piperazine is a medically well-known moiety due to the immense number of activities exhibited in biological studies [89, 93]. Molecular hybridisation was done by Lagdhir *et al*. in July 2021 to produce piperazine-quinoline conjugate derivatives. All the compounds were tested for *in vitro* anti-malarial activity against CQS *Pf*3D7 and its structure activity relationship was elucidated. The least mean IC_{50} value of 0.85 μg/mL was exhibited by compound 229 which makes it's the most potent derivative. The synthesis began with the cyclisation of acetanilide 223 in the presence of $POCl_3$ and DMF to yield 2-chloroquinoline-3-carbaldehyde 224 which was further converted into tert-butyl 4-(3-formylquinolin-2-yl)piperazine-1-carboxylate 226 by the reaction of compound 224 with tert-butyl piperazine-1-carboxylate 225 in the presence of DMF and K_2CO_3. The compound 3-amino-toluene 227 was then added to compound 226 in the presence of $NaCNBH_3$ resulting in the formation of compound 228. Finally, compound 228 was reacted with 1,4-dioxane to yield final compound 299 (**Scheme 36**). The activity was due to the presence of electron donating methyl group on the phenyl ring. Although the compound has good activity, it is lesser than that of quinoline [90].

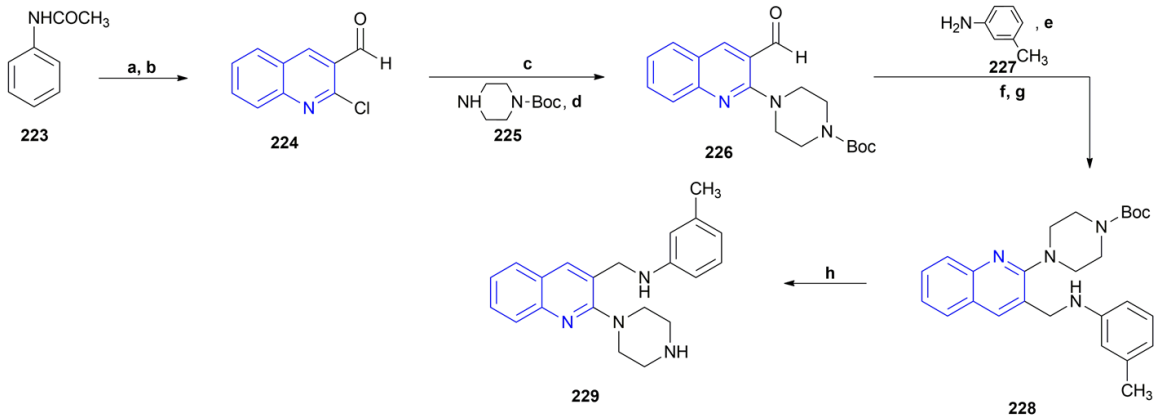


Scheme 34. Synthesis of compounds 211 and 217; a. ethanol amine, triethylamine; b. propanol amine, triethylamine; c. mesylation, NaN_3; d. EtOH:H_2O (90:10), $CuSO_4.5H_2O$, sodium ascorbate, RT, 7-8 h; e. N_2 bubbled through a solution in 1,4-dioxane, 15 mins; f. CH_3COOK, $Pd(dppf)Cl_2$, bis(pinacolato)diboron, 16-20 h, 100°C; g. methanol, $NaBH_4$, 0-10°C, 1 h, RT; h. HCl, pH=3; i. cold H_2O.

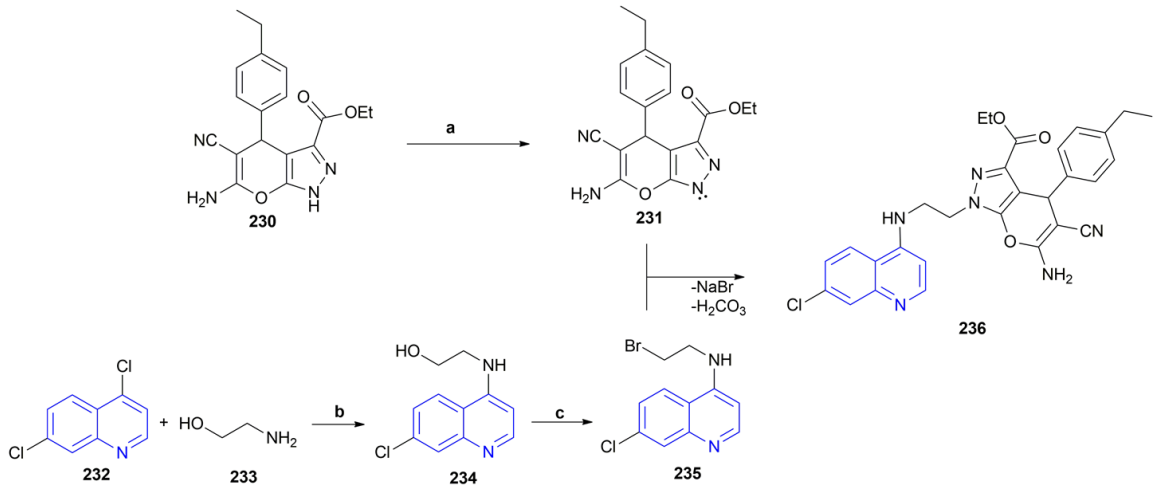


Scheme 35. Synthesis of compound 222; a. DMSO, MWI, 150°C, 10 mins; b. EDC, HOBu, DIEA, DMF, RT, 5 h.

Another set of pyrazole-quinoline conjugates have been synthesized by Shamsuddin *et al*. in November 2021 where pyranopyrazole derivatives have been linked with 4-aminoquinoline [94] based on the previously unveiled anti-malarial potential of pyranopyrazole moieties [95]. The compounds were evaluated for *in vitro* and *in silico* anti-malarial activity. *In vitro* evaluation revealed that compound 236 showed an optimal EC_{50} value of 0.0130 ± 0.0002



Scheme 36. Synthesis of compound 229; a. $POCl_3$, DMF, 0°C, 10 mins; b. acetanilide, D, 80°C, 6 h; c. DMF, K_2CO_3, 20 mins, RT; d. 110°C, 5 h; e. CH_3COOH, 1 h, RT; f. cool to 0°C, 10 mins; g. $NaCNBH_3$, RT, 1 h; h. 1,4-dioxane, 0°C, 4 M HCl.



Scheme 37. Synthesis of compound 236; a. sodium methoxide; b. reflux, 180°C; c. HBr, H_2SO_4, reflux, 60 mins.

μM and 0.02 ± 0.01 μM against CQS *Pf*3D7 and MDR *Pf*K1 respectively making it 16 times more effective than chloroquine, which exhibited EC_{50} value of 0.33 μM against the CQR strain. The activity was then confirmed through molecular docking studies of the ligand 236 with *Pf*LDH enzyme and it was observed that the ligand was successful in binding with the active site of the enzyme over the cofactor binding site. Inhibition of *Pf*LDH resulted in hampering with the recycling of NAD^+ which is required for the parasitic glycolytic pathways [96] and this has been exhibited by compound 236 as it showed the highest binding energy with the active site of the enzyme making it a potential lead. The synthesis of 236 was initiated with the deprotonation of the bi-pharmacophore containing hybrid scaffold 230 by the activity of sodium methoxide to produce compound 231. This further underwent nucleophilic attack by the quinoline derivative 235 to finally produce compound 236 (**Scheme 37**).

The synthesis of piperazinyl derivatives of quinolines by nucleophilic addition of piperazine to 4,7-dichloroquinoline was carried out by Mahajan *et al*. in December 2021, and these were further evaluated for the *in vitro* antimalarial activity against *P. falciparum* using Microassay Protocol devised by Rieckmann *et al.* [97]. Out of 18 synthesized compounds, 5 of them proved to be plausible leads for further development by structural optimization. The compound 242 showed MIC value of 0.18 μg/

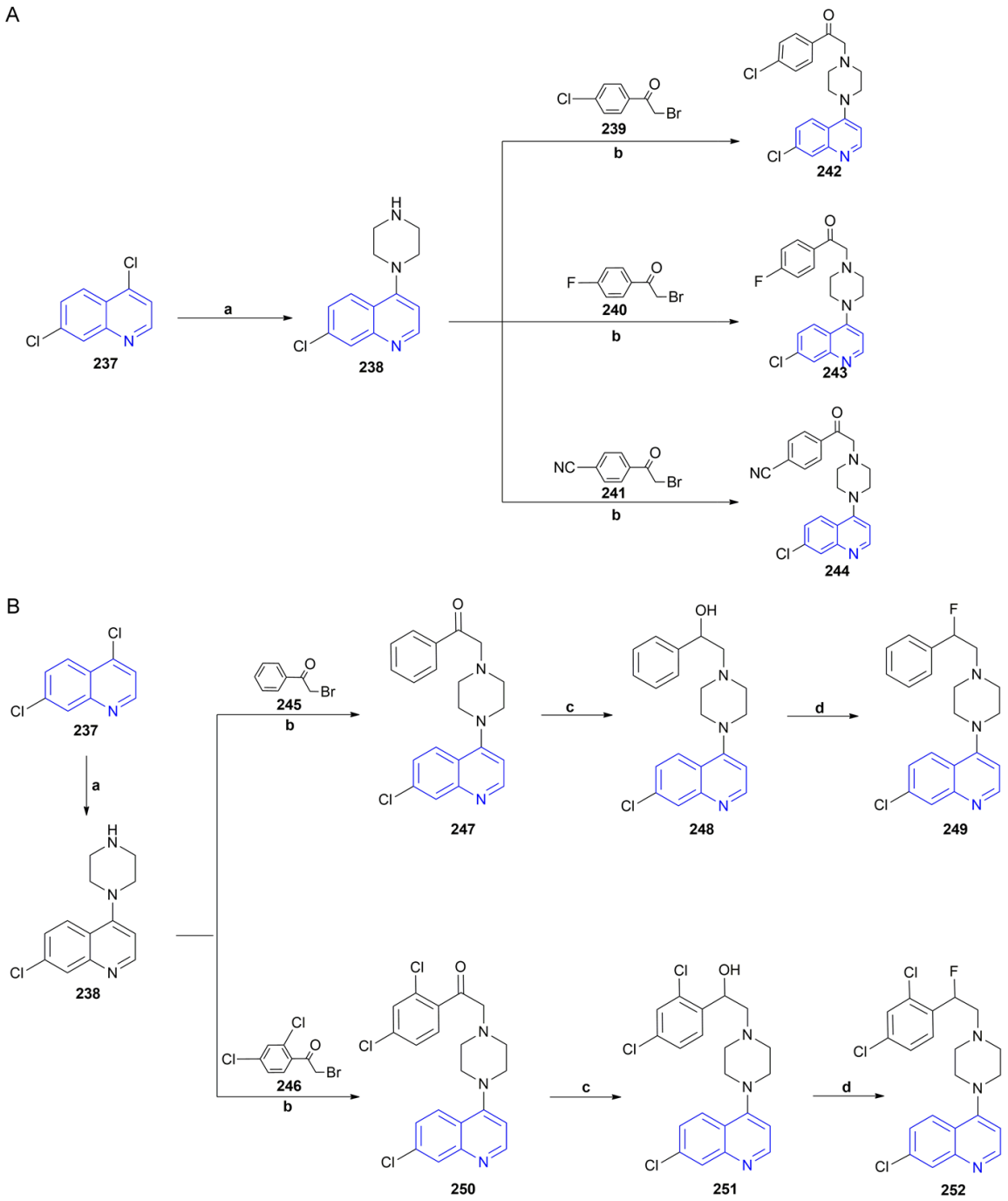
mL, being the most active compound. 243, 244, 249 and 252 showed MIC of 0.26 μg/mL which is equipotent with the standard drug chloroquine. The first step in the synthesis of all these compounds involves the formation of 4-piperazynyl derivative of quinoline 238 by the reaction of 4,7-dichloroquinoline 237 with piperazine in the presence of DIPEA. Subsequently, 238 was combined with chloro, fluoro and cyano phenacyl bromide derivatives to yield compounds 242, 243 and 244 respectively (**Scheme 38A**). Similarly, compound 238 was treated with phenacyl bromide 245 and 2,4-dichloro phenacyl bromide 246 to yield compounds 247 and 250 which were further modified to produce compounds 249 and 252 respectively (**Scheme 38B**) [98].

In November 2022, hybrid molecules of 4-aminoquinoline derivatives with triazole and *N*-containing heterocyclic hydrazide were synthesizes by Sharma *et al.* [99] using diamine alkyl or piperazine as linkers. Various modifications were done to the basic structure to analyse the structure activity relationship. Each component was strategically chosen to enhance the overall activity. The linkers were present to increase the lipophilicity, the triazole to enhance anti-plasmodial activity and the heterocyclic hydrazide component to increase the basicity resulting in drug accumulation. The position of these components also played a major role in enhancement of the activity. For example, when triazole is directly linked to the quinoline ring, the activity was compromised as compared to the activity shown by the compound where quinoline and triazole were combined by a linker. Among all the synthesised compounds, 258 showed the best anti-plasmodium activity with an IC_{50} value of 0.26 ± 0.03 μM against CQR *Pf*W2 while all the others exhibited values more than 0.7 μM. As observed in the synthesis (**Scheme 39**), the compound contains all the components mentioned above giving rise to a synergistic activity. The synthesis began with the reaction of 4-hydroxybenzaldehyde 253 with propargyl bromide in dry acetone resulting in the formation of alkyne 254. Cu-promoted click reaction was carried out between compound 254 and quinoline azide 255 to yield compound 256. Finally, compound 256 was combined with heterocyclic hydrazide 257 to yield compound 258.

1,2,3-Triazole-dihydropyrimidinone hybrids, which were precedently explored for its anti-cancer activity [100, 101], were used to synthesize novel hybrids with quinoline by Rasheed *et al*. in February 2023 [102]. Compound 262, when tested for *in vitro* anti-malarial activity against CQS *Pf*NF54 and MDR *Pf*K1, exhibited an IC_{50} value of 138.03 ± 1.82 nM and 498.47 ± 13.94 nM respectively. Dihydropyrimidone (DHPM) derivative 261, was reacted with propargyl derivative of quinoline 260 in the presence of $CuSO_4$, sodium ascorbate and DMF to give rise to compound 262 which is a 1,2,3-triazole-linked dihydropyrimidinone quinoline hybrid (**Scheme 40**). The intensified activity of the compound was observed due to the functionalization of the 4-amino group.

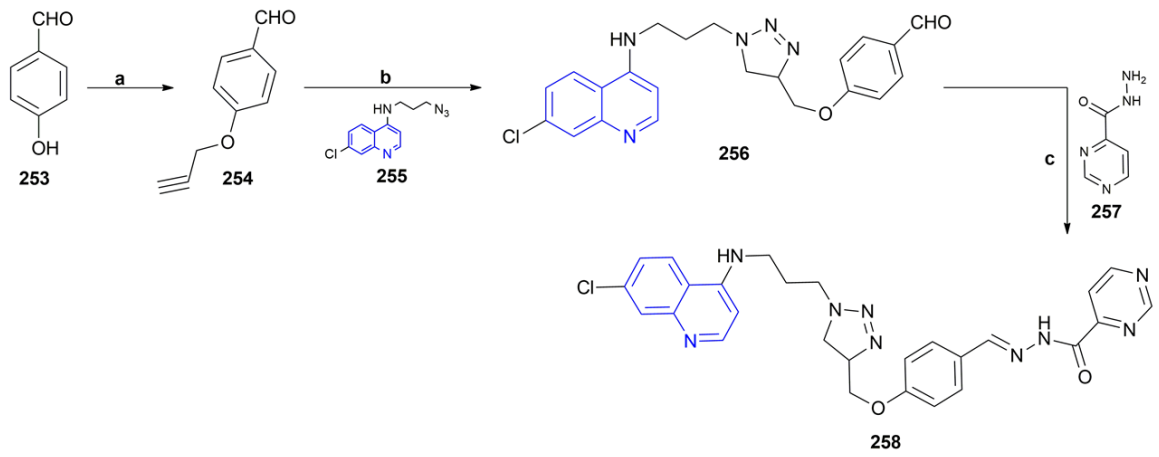
Benzofuran and benzothiophene have been extensively studied for their antimicrobial activity [103-105]. Conjugates of quinoline with benzofuran and benzothiophene derivatives were synthesized and evaluated for its anti-malarial activity to expand the scope of application of these diverse molecules [106]. The synthesis was carried out by conjugating these molecules via an amide or ester linkage. These compounds were evaluated against *P. falciparum* strains and it was observed that none of the synthesized compounds were comparable with chloroquine. Also, there was no observable correlation between the structure and the β-haematin inhibition shown by the compounds in case of the ester linked compounds. However, their amide-linked counterparts showed better consistency. Among all the synthesized compounds, 270, 271, 279 and 280 showed the best efficacy with and IC_{50} value in the range of 0.89-2.38 μM against CQS *Pf*NF54. Compounds 270 and 271 were synthesised by the conjugation of suitable benzofuran derivative 267 with 4-diamine derivative of quinoline 269 (**Scheme 41A**). Compounds 279 and 280 were synthesized by the conjugation of benzothiophene derivative 276 and 4-hydroxylamine derivative of quinoline 278 (**Scheme 41B**).

Anti-bacterial, anti-tumour, anti-fungal, anti-tuberculosis and anti-oxidant properties of pyridones have been previously investigated [17, 107-109]. In September 2023, Ibrahim *et al.* further assessed the anti-malarial activity of pyridone-dihydronaphthalene conjugates [110]. These tetrahydrobenzo[*h*]quinolines were evaluated for *in vitro* against *P. falciparum, in vivo* activity against *P. berghi* and *in silico* binding studies with *Pf*DHFR-TS. The com-

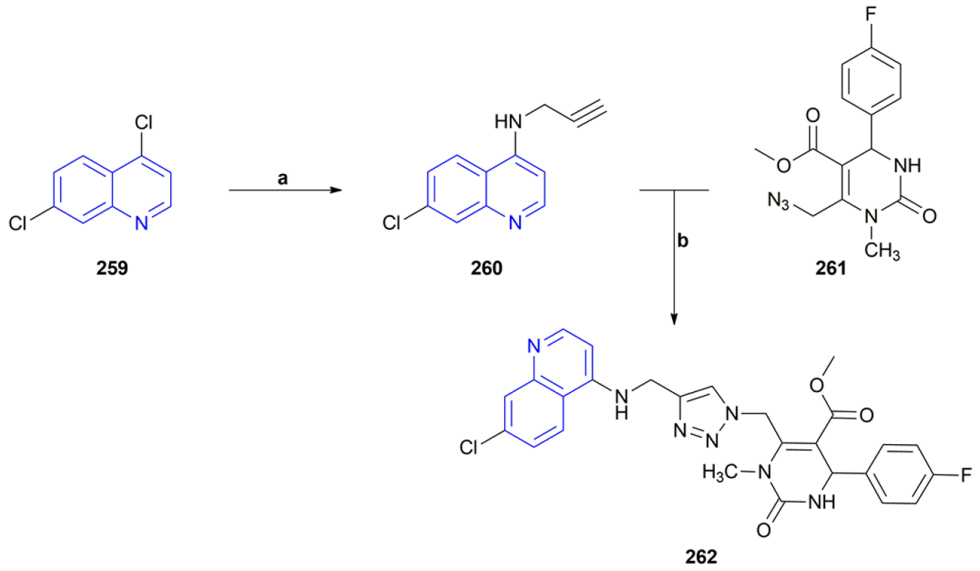


Scheme 38. A. Synthesis of compounds 242, 243 and 244; a. Piperazine (2.0 eq.), DIPEA (5 v), 140°C, 16 h; b. K_2CO_3 (2.5 eq.), DMF (10 v), 0°C-RT, 6-8 h. B. Synthesis of compounds 249 and 252; a. Piperazine (2.0 eq.), DIPEA (5 v), 140°C, 16 h; b. K_2CO_3 (2.5 eq.), DMF (10 v), 0°C-RT, 6-8 h; c. $NaBH_4$ (2.0 eq.), EtOH/THF (1:1), 0°C-RT, 2-4 h; d. DAST (2.0 eq.), DCM (10 v), 0°C-RT, 2-4 h.

pounds were administered in mice infected with *P. berghi* at the dose of 48 μM/kg/day. Among all the synthesized compounds, 284 and 288 exhibited a maximum suppression percentage of 97.78% with no reported death of the mice. Following this, IC_{50} value of these effective molecules was found to be 0.01980 ± 0.002 nM and 0.02072 ± 0.014 nM respectively against CQR *Pf*RKL9. The *in vitro* and *in vivo* anti-malarial activity was backed by molecular



Scheme 39. Synthesis of compound 258; a. K_2CO_3, propargyl bromide, acetone, RT to reflux, 12 h; b. $CuSO_4.5H_2O$, sodium ascorbate, EtOH:H_2O (8:2), RT, 6 h; c. EtOH, MWI, 110 °C, 10-20 mins.



Scheme 40. Synthesis of compound 262; a. propargylamine, 110 °C, N_2, 18 h; b. $CuSO_4$, sodium ascorbate, DMF, H_2O, 25 °C, 12 h.

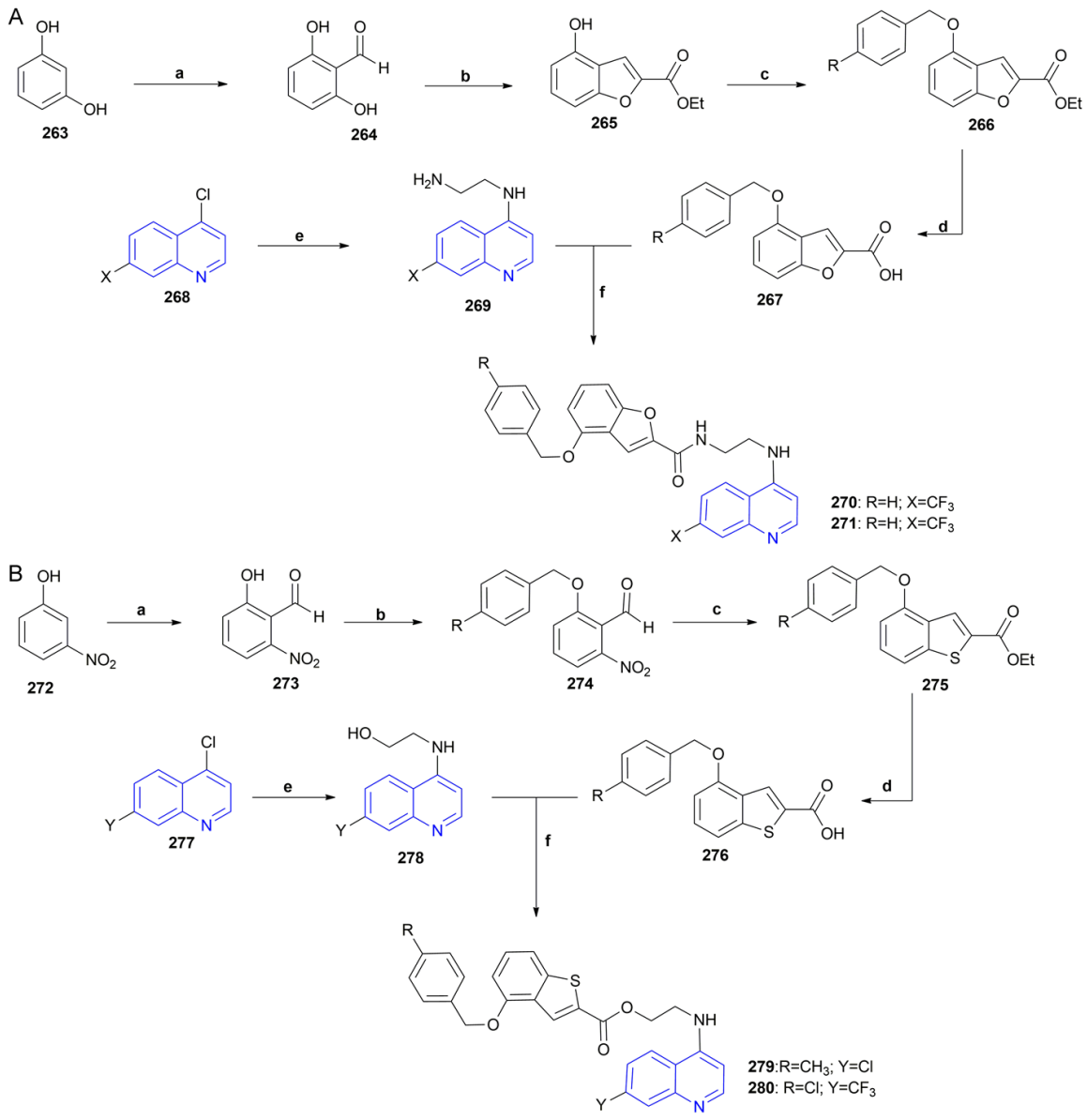
docking study of 284 which exhibited a docking score of -10.55 with mutant *Pf*DHFR-TS and -12.93 with wild *Pf*DHFR-TS as compared to pyrimethamine which exhibited docking score of -10.21 and -10.99 with mutant *Pf*DHFR-TS and wild *Pf*DHFR-TS respectively. This proved its ability as an anti-folate drug which plays a role in suppression of parasitemia. 4-hydroxy-3-methoxy benzaldehyde 281, ethyl 2-cyanoacetate 282 and 3,4-dihydronaphthalen-1(2*H*)-one 283 were combined in the presence of ammonium salt of ethanoic acid while being refluxed in ethanol to produce compound 284.

Similarly, compound 288 was synthesised using thiophene-2-carbaldehyde 285 instead of 281 (**Scheme 42**).

Metal-based hybrids

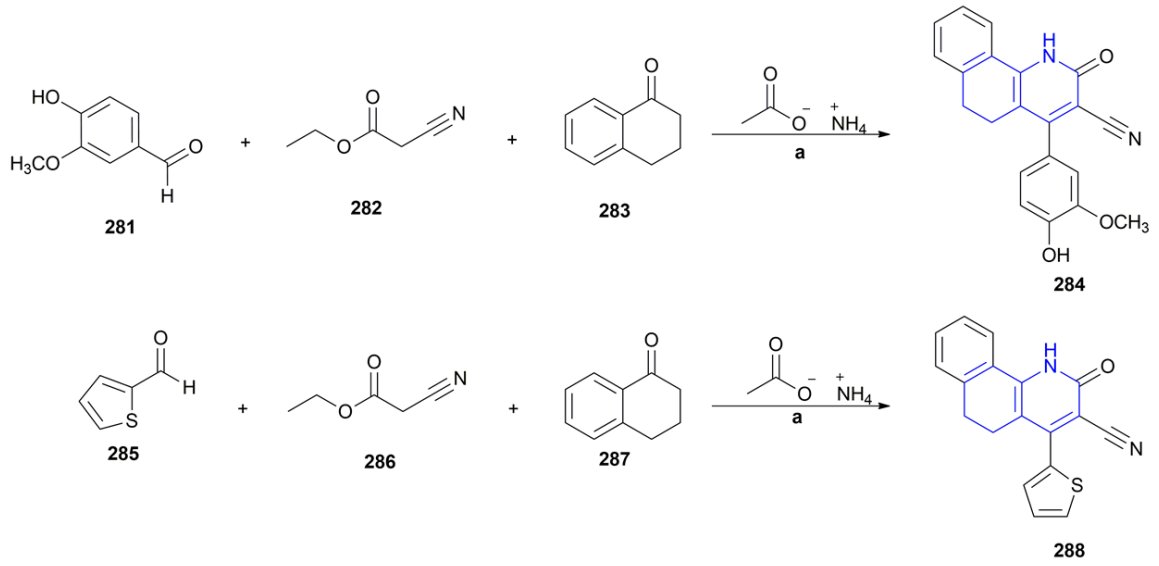
Due to the variable oxidation state exhibited by transition metals, they were widely explored for their pharmacological activity [111]. Here, we discuss the anti-malarial efficacy of some of the metal-containing hybrids.

Neutral ruthenium and iridium containing complexes which had been synthesized earlier

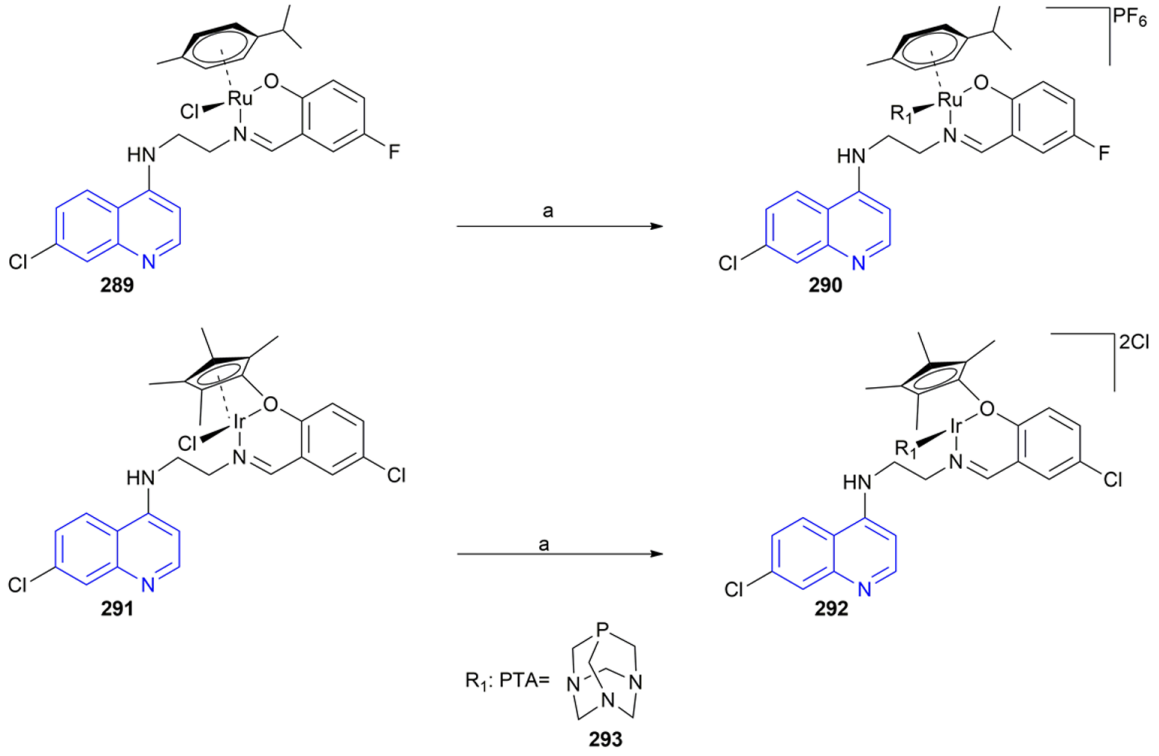


Scheme 41. A. Synthesis of compounds 270 and 271; a. i. NaH, DMF, MOM-Cl, RT, 5 h; ii. n-BuLi (1.2 eq.), THF, 0°C, 2 h/DMF (4 eq.), RT, 18 h; conc. HCl, MeOH, dioxane, 50°C, 4 h; b. ethyl bromoacetate, K_2CO_3, anhydrous acetone, 80°C, 48 h (product not isolated); c. benzyl bromide or p-methyl benzyl bromide, K_2CO_3, ethanol, reflux, 5 h; d. LiOH, EtOH/H_2O, reflux, 2.5 h; e. 5 eq. diaminoethane, 160°C, 24 h; f. synthesized acid (267) CDI, imidazole. HCl, anhydrous DMSO, 55°C, 1-4 h. B. Synthesis of compounds 279 and 280; a. HTMA, TFA, 90°C, 24 h; b. p-methyl benzyl bromide (for 279), p-chloro benzyl bromide (for 280) K_2CO_3, DMF, 70°C, 20 h; c. ethyl thiolglycolate, K_2CO_3, DMF, 0-70°C, 20 h; d. LiOH, EtOH, 60°C, 6 h; e. 2-aminoethanol, toluene, n-butanol, 160°C, 24 h; f. synthesized acid (276) DIC, DMAP, DCM, 60°C, 24-48 h.

[112, 113] were further modified by Smith *et al*. in February 2019 [114]. The cationic form of the complexes was synthesized and combined with hexafluorophosphorus anion along with 1,3,5-triaza-phosphaadamantane (PTA) 293 complexed with the metal. Ruthenium complex 290 showed an IC_{50} value of 0.1 ± 0.069 μM and 3.8 ± 0.68 μM against CQS *Pf*NF54 and CQR *Pf*K1 respectively. Iridium complex 292 showed an IC_{50} value of 0.11 ± 0.015 μM and 1.2 ± 0.19 μM against CQS *Pf*NF54 and MDR *Pf*K1 respectively. The synthesis of compound 290 containing Ruthenium was carried out by the reaction of Ru-containing



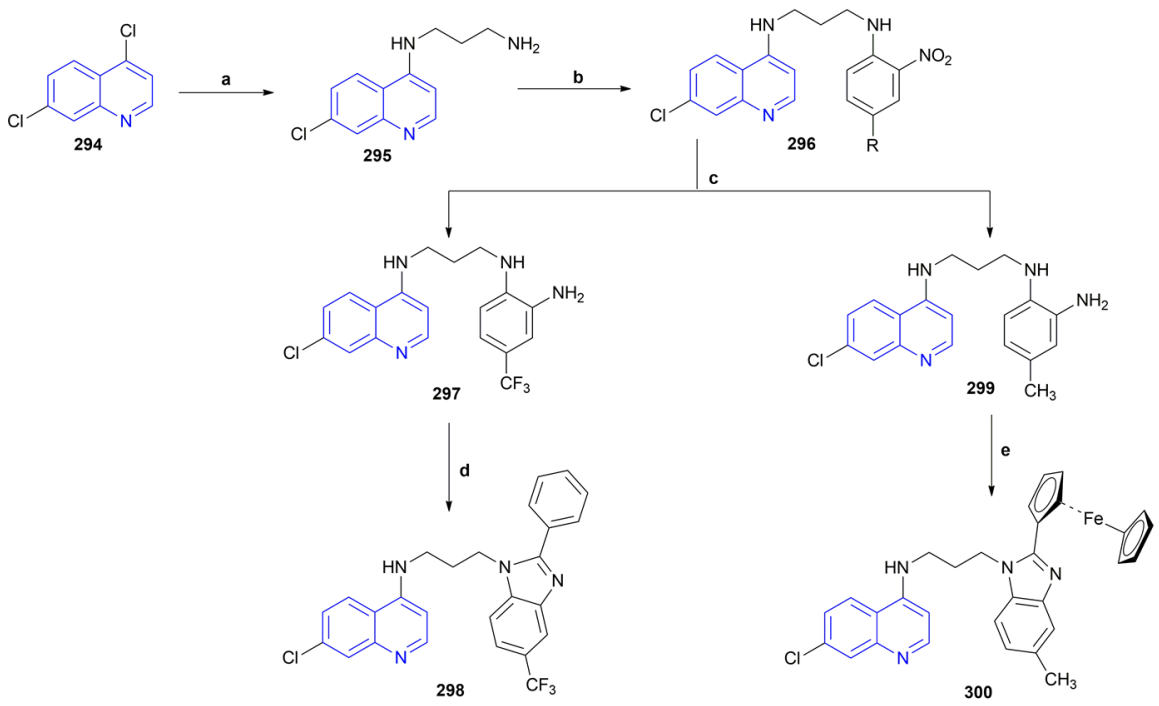
Scheme 42. Synthesis of compounds 284 and 288; a. Ethanol, reflux, 10 h.



Scheme 43. Synthesis of compounds 290 and 292; a. EtOH or CH_2Cl_2, RT, 1-8 h, NH_4PF_6, RT, additional 1 h.

fluoro-quinoline 289 with PTA 293 in the presence of ethanol or dichloromethane. Similarly, synthesis of compound 292 containing Iridium was carried out by the reaction of Iridium-containing chloro-quinoline 291 instead of 289 (**Scheme 43**).

It has been established that ferrocene derivatives have seemingly shown two major modes of actions against the malarial parasite: (i) accumulation of the drug in the digestive vacuole of the parasite which results in inhibition of haemozoin formation and (ii) production of free

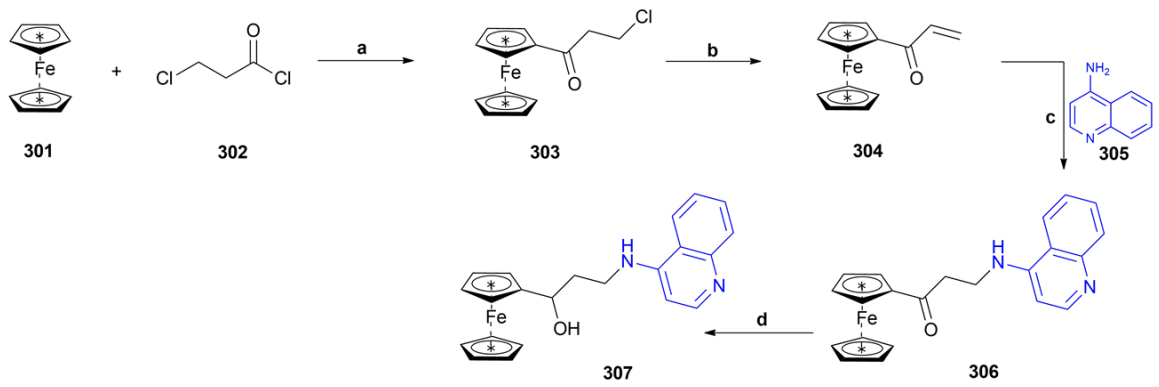


Scheme 44. Synthesis of compounds 298 and 300; a. 1,3-diaminopropane, 140°C, 17 h; b. nitrobenzene derivative, DMF, RT, 24 h; c. Zn, NH_4Cl, CH_3OH, RT, 24 h; d. benzaldehyde, TFA, $MgSO_4$, EtOH, 80°C, 24 h; e. ferrocenecarboxaldehyde, TFA, $MgSO_4$, EtOH, TFA, $MgSO_4$, EtOH.

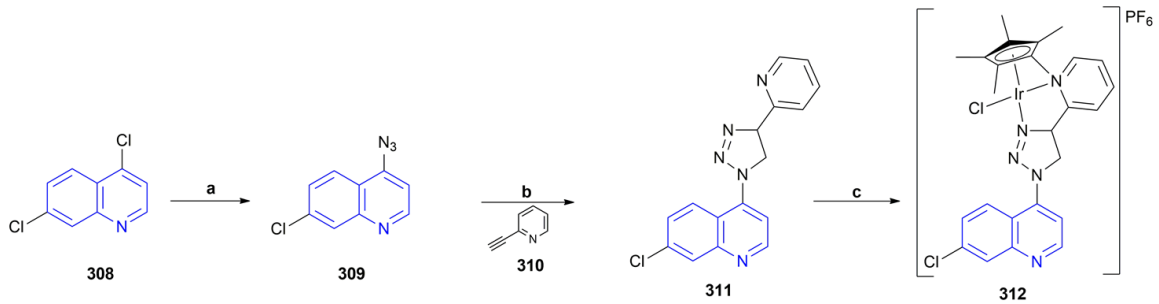
radical (•OH) in the infected red blood cells [115-117]. In October 2019, this property of ferrocene was amplified by Baartnez *et al.* [118] who studied the β-haematin inhibition and reactive oxygen species (ROS) formation ability of the synthesized phenyl- and ferrocenyl-derived aminoquinoline-benzimidazole hybrid. It was observed that compounds 298 and 300 showed potential β-haematin inhibition activity with an IC_{50} value of 16 μM. Meanwhile, both were tested for *in vitro* and *in vivo* antimalarial activity against CQS *Pf*NF54 and m=MDR *Pf*K1. They were found to be more active against the resistant strains as compared to the sensitive one [119]. Further, compound 300 was chosen for DNA cleavage study to check for the production of ROS which is essential for the anti-malarial activity but unfortunately it was observed that its activity was not as good as ferrocene. In general, the ferrocene containing derivatives were less potent than the phenyl derivatives and this could be due to the diminished production of ROS. The initial synthetic steps, being identical for both the compounds, include the modification of 4,7-dichloroquinoline 294 its 4-diamine derivative 295 followed by reaction with nitrobenzene derivative resulting in formation of compound 296. Following this, compound 296 was modified to yield compounds 298 and 300 (**Scheme 44**).

A group of ferrocene-quinoline conjugates have been synthesised by Minić *et al.* in February 2020 [120] and evaluated against CQS *Pf*NF54 and CQR *Pf*K1. 4-aminoquinoline 305 across 1-ferrocenylpropenone 304 were used to synthesize the bioactive compound 2-ferrocenoyl ethyl aryl amines 306 by Aza-Michael addition. The resultant Mannich's base, 2-ferrocenoyl ethyl aryl amines 306 were excellent starting material for synthesis of the conjugate derivative. Among the synthesized compounds, compound 307 showed exceptional activity against both the test strains with an IC_{50} value of 0.39 ± 0.01 μM and 0.77 ± 0.07 μM against CQS *Pf*NF54 and MDR *Pf*K1 respectively. Compound 307 was synthesized by the reduction of the oxo group in 2-ferrocenoyl ethyl aryl amine 306 in the presence of $NaBH_4$ as the reducing agent (**Scheme 45**).

In July 2020, Melis *et al.* [121] synthesized *N*,*N*-chelated half-sandwich iridium (III) conjugated



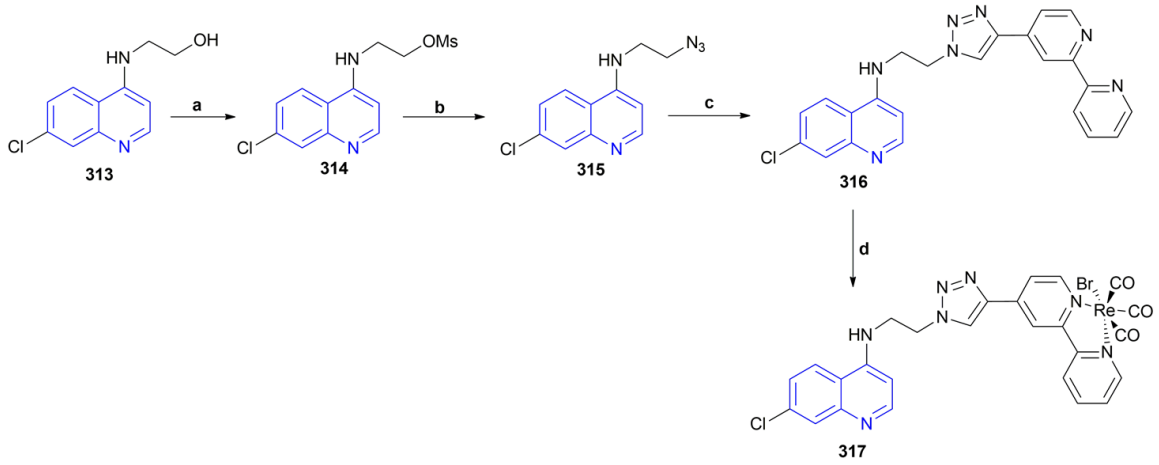
Scheme 45. Synthesis of compound 307; a. 33 mol% $AlCl_3$, DCM, RT; b. KOAc, EtOH/D; c. 0.5 eq. 0.1 M Na_2CO_3, 16 h, D; d. 5 equiv. $NaBH_4$, MeOH, 2 h, RT.



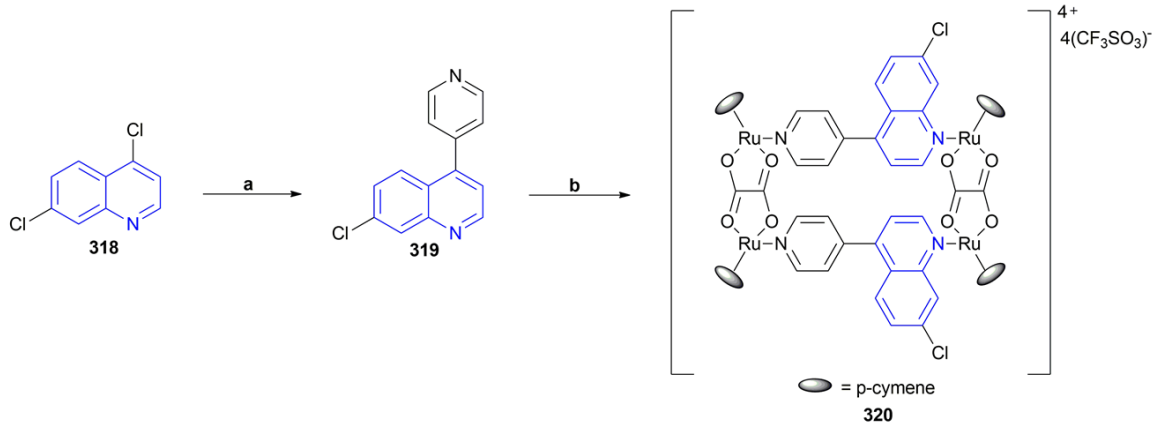
Scheme 46. Synthesis of compound 312; a. NaN_3, DMF, 65°C, 5 h; b. t-BuOH or CH_2Cl_2/H_2O (1:1), $CuSO_4{\cdot}5H_2O$, sodium ascorbate, 30°C, 2-72 h; c. $[IrCp^*(\mu\text{-}Cl)Cl]_2$ (0.5 eq.), NH_4PF_6 (4 eq.), CH_2Cl_2/EtOH, RT, 22 h.

with quinoline derivative through triazole linkage to produce a cationic complex which was neutralized with hexafluorophosphorus anion. Compound 312, containing pyridyl derivative of triazole, showed an IC_{50} value of 0.25 ± 0.11 μM and 0.65 ± 0.06 μM against CQS *Pf*NF54 and MDR *Pf*K1 respectively. The metal-nitrogen bond in the complex proved to be beneficial for the anti-malarial activity. Irrespective of this, the complex did not show the ability of reducing NAD^+. The synthesis involves the conversion of 4,7-dichloroquinoline 308 into its azide derivative 309 by reaction with sodium azide in the presence of DMF. Compound 309 and alkyne 310 undergoes Cu-mediated azide-alkyne click reaction yielding compound 311 which is then added with the iridium complex to produce the final compound 312 (**Scheme 46**).

Organo-rhenium tricarbonyl chloride complexes have been explored for their anti-cancer activity [122-124]. Further investigation into similar compounds has been done by Sovari *et al*. in September 2022 [125] by synthesizing novel aminoquinoline-ruthenium complexes. Initially, hybrid 316 of aminoquinoline 315 and bipyrimidine were synthesized with triazole as the linking heterocycle. Further, these compounds were complexed with rhenium (I) facial-tricarbonyl bromide giving rise to metal complex 317. These compounds were evaluated for *in vitro* β-haematin inhibition activity and it was observed that compound 316 and its metal complex 317 exhibited better inhibition than chloroquine along with very good activity against CQS *Pf*NF54 and MDR *Pf*K1. *In silico* hemozoin binding studies also revealed high docking scores for both the ligands with docking score of -16.50 and -14.33 exhibited by 316 and 317 respectively, which were higher than that of chloroquine which exhibited a docking score of -13.57. Thus, these complexes were suitable for future modifications. Amino-alcohol 313 was converted to its azide derivative 315 by a series of reactions (**Scheme 47**). Compound 315 undergoes azide-alkyne cycloaddition reaction with 4-ethynyl-2,2'-bipyridine to yield bidentate ligand 316. Finally, the ligand



Scheme 47. Synthesis of compound 317; a. MsCl, THF (dry), Et_3N, 0-4 °C, 3-4 h; b. NaN_3, DMF, RT, 8 h; c. CuI, Et_3N, CH_3CN, RT, 4-ethynyl-2,2'-bipyridine, overnight; d. $Re(CO)_5Br$, toluene, reflux, overnight.

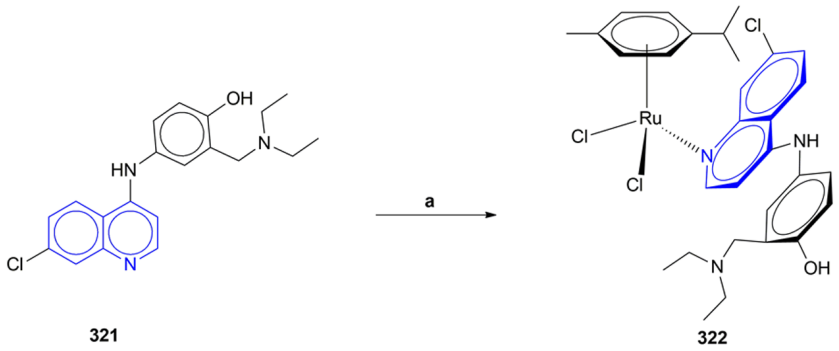


Scheme 48. Synthesis of compound 320; a. 4-pyridinylboronic acid (1.1 eq.), $Pd(OAc)_2$ (0.01 eq.), PCy_3 (0.024 eq.), K_3PO_4(aq) (1.7 eq.), 1,4-dioxane, reflux, 18 h; b. [{Ru(p-cymene)}$_2$(μ-η_2-η_2-C_2O_4)] (1 eq.), $AgCF_3SO_3$ (2.0 eq.) in CH_3CN, CH_3OH, RT, 24 h.

316 was treated with [$Re(CO)_5$ Br] to yield compound 317.

Quinoline based ligands half-sandwiched with ruthenium (II) and iridium (III) were synthesised by Golding *et al.* in October 2021 [126]. These were tested for in vitro anti-plasmodial activity against *P. falciparum* strains and β-haematin inhibition activity. It was observed that the complexes with ruthenium were way more effective than the ones with iridium. Particularly, compound 320, having ruthenium metal, was found to be the most effective one showing an IC_{50} value of 9.82 ± 0.89 μM and 7.65 ± 0.77 μM against CQS *Pf*NF54 and MDR *Pf*K1 respectively. It also exhibited β-haematin inhibition which was almost equivalent to that of standard chloroquine. Compound 320 contained oxalato bridging ligands which might have influenced the effective inhibition. Ditopic quinoline containing ligand 319 was synthesized by the reaction of 4,7-dichloroquinoline 318 with 4-pyridinyl boronic acid *via* Suzuki cross-coupling reaction. Ligand 319 was then subjected to coordination driven self-assembly with [{RuCl(*p*-cymene)}$_2$(μ-η^2-η^2-C_2O_4)] in the presence of silver trifluoromethane-sulfonate to give rise to metallarectangle containing compound 320 (**Scheme 48**).

Ruthenium complexes have majorly been explored for their anti-metastatic activity [127, 128] and its possible anti-malarial activity has been studied by Colina-Vegas *et al.* in July 2023



Scheme 49. Synthesis of compound 322; a. $(CH_3)_2CO$, 60°C, 2 h, $[Ru(Cl)_2(\eta_6\text{-p-cymene})]_2$.

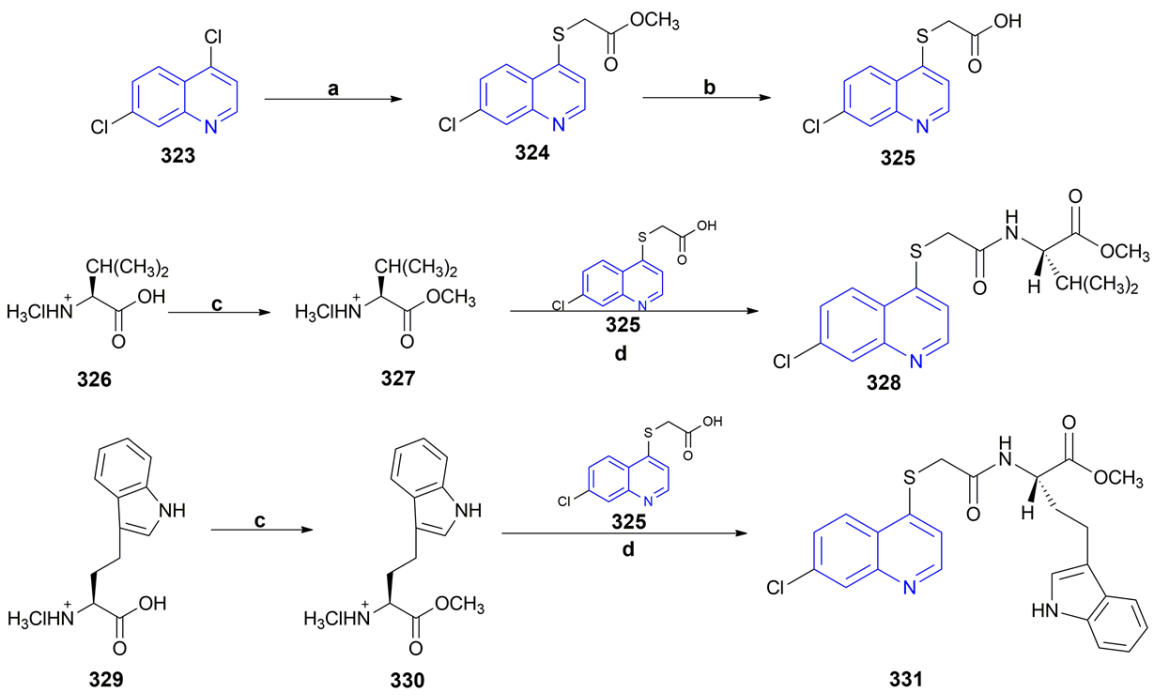
[129] by synthesizing conjugates of amodiaquine, a 4-amino-7-chloro-quinoline derivative, with ruthenium-cymene complex. The activity was tested for *in vitro* activity against the asexual blood stages of the parasite. Compound 322 was found to be the most affective with an IC_{50} value of 3.2 nM MDR *Pf*W2 with a selectivity index of 1156, making it almost 122 times more effective than standard drug chloroquine which exhibited an IC_{50} value of 114 nM and was two times more effective than amodiaquine which exhibited an IC_{50} value of 16.5 nM. It was also tested against murine *P. berghei* and exhibited up to 84.1% inhibition of parasitemia. The complexing with metals neither hampered with the anti-malarial activity of quinoline, nor did it affect the cytotoxicity. It is believed that the binding of the compound with hemin could have been increased due to interaction of non-quinolinic nitrogen atoms present in the compound. The substitution of one chloride ligand in the metal precursor $[RuCl_3(\eta_6\text{-}p\text{-cymene})]$ with amodiaquine derivative 321 led to the synthesis of the complex 322 by Schlenk technique in an argon atmosphere (**Scheme 49**).

Miscellaneous

Apart from the above discussed hybrids, below discussed are some of the hybrids which have also expressed exceptional anti-malarial activity.

Synthesis of novel (S)-methyl-(7-chloroquinolin-4-ylthio)acetamidoalquilate derivatives were carried out by Colmenarez *et al.* in December 2019 [130]. The reaction between different l-amino acid methyl esters and 2-(7-chloroquinolin-4-ylthio)acetic acid was carried under a modified version of the Steglich esterification reaction. Hemozoin is inhibited at its synthetic phase taking place in the digestive vacuole (DV) of the malaria parasite *P. falciparum*. The synthesised drugs were tested against *P. berghei* strain ANKA which was inoculated into mice. The compounds 328 and 331 showed pronounced survival rates of 26.04 and 24.60 respectively and exhibited approximately 70.7% and 61.08% of inhibition of β-hematin formation. The synthetic route involves the combination of the synthesized thiolacetic acid derivative of 4,7-dichloroquinoline 325 with amino acid derivatives 327 and 330 via modified Steglich esterification reaction to yield the required compounds 328 and 331 respectively (**Scheme 50**).

A conjugation of heteroaryl methanamine and quinoline derivatives was done by Bokosi *et al.* in April 2021 [131] resulting in the formation of mono- and bisquinoline methanamines. The quinolines were synthesized by cyclisation of aniline derivatives and novel compounds were evaluated against CQS *Pf*3D7 and were compared with standard chloroquine. Most of the bisquinoline heteroaryl methanamine showed better activity as compared to their preceding monoquinoline heteroaryl methanamines with an exception of 337 which showed an IC_{50} value of 0.23 ± 0.02 μM. The enhanced activity is observed due to the presence of an additional quinoline ring. Among the bisquinoline heteroaryl methanamines, compound 348 exceeded the other compounds by exhibiting an IC_{50} value of 0.93 ± 0.04 μM. Acetanilide 333 was subjected to Vilsemeier-Haack reaction forming intermediate 334. Compound 334 was further refluxed in a methanolic KOH solution leading



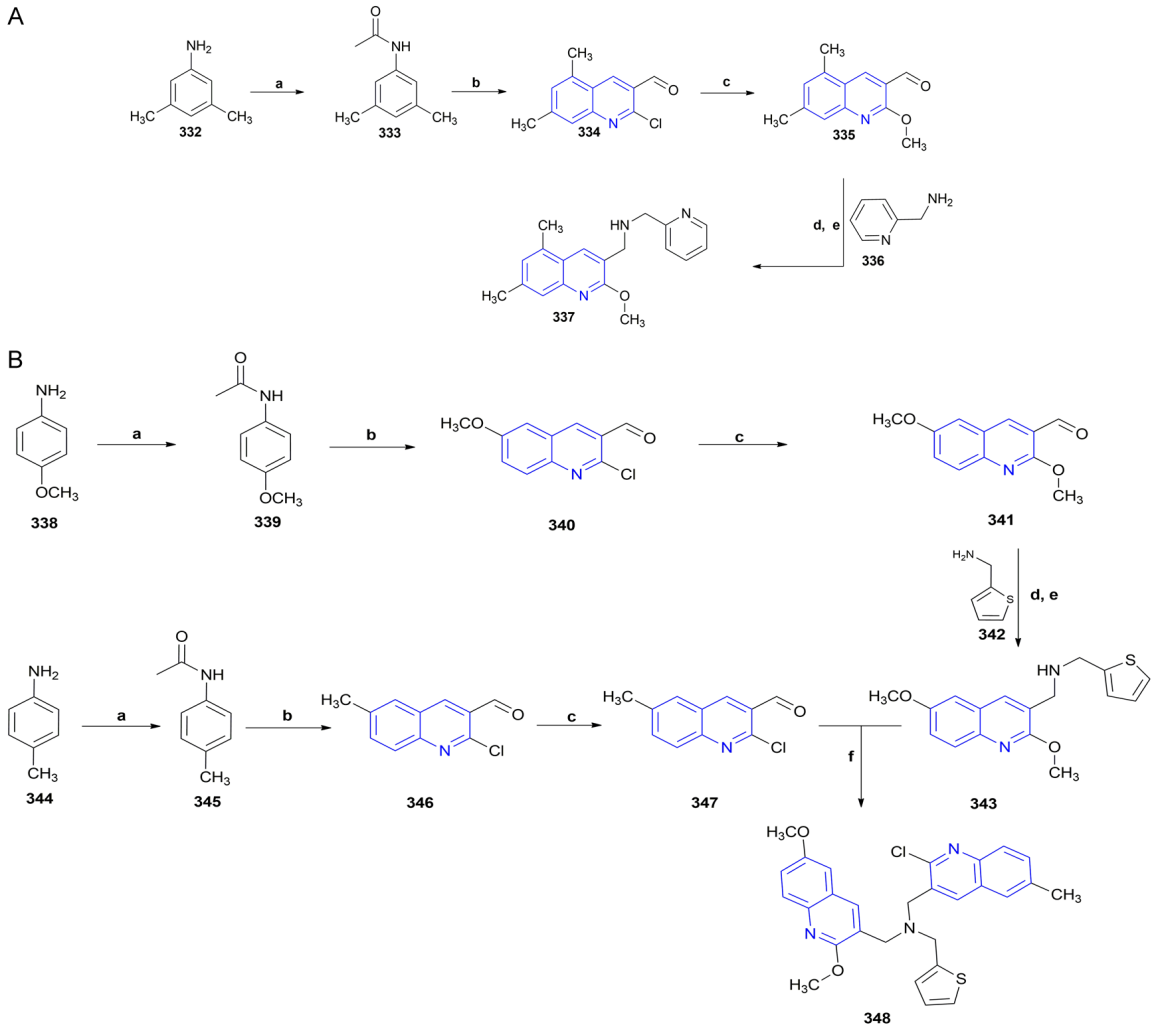
Scheme 50. Synthesis of compounds 328 and 331; a. Methyl thioglycolate, Et_3N; MeOH, 60 °C; b. 1 N NaOH, 60 °C, 1 h; c. $SOCl_2$, MeOH, 0 °C, 12 h; d. EDC, DMAP, DMF, -10 °C to RT, 12 h.

to methoxy substitution at C2 position *via* nucleophilic substitution to yield compound 335. Subsequently, compound 335 was subjected to reductive amination with heteroaryl 336 to finally yield monoquinoline compound 337 (**Scheme 51A**). For synthesis of bisquinoline compound 348, similarly synthesized carbaldehyde compound 347 without heteroaryl was combined with compound 343 with heteroaryl 342 (**Scheme 51B**).

4-Amino quinoline-chalcone conjugates with various linker components like *N*-acetylpyrazoline and piperazinyl rings have been previously explored for anti-malarial property [132]. Further, hybrids of quinoline with pyrzolylchalcones have been synthesised by Saini *et al.* and evaluated for *in vitro* inhibition of schizont and *in silico* binding with cysteine protease falcipain-2 (FP2) enzyme [133]. Compound 354 was the most affective one with an EC_{50} value of 0.313 ± 0.017 μM and 0.801 ± 0.019 μM against CQS *Pf*3D7 and CQR *Pf*RKL9 respectively. The Structure-activity relationship (SAR) studies revealed that the presence of two methyl groups on the aryl rings enhanced the activity. To back the *in vitro* results, 354 was also tested for its ability to bind with active site of FP2 enzyme, as its inhibition will prevent the growth of the parasite. It was concluded that compound 354 is potential lead compound for further molecular modifications for better activity as it also obeyed Lipinski's rule of five [42]. The only drawback was that the percentage yield of the product was less as it was only close to 50%. Further modifications in the procedure could result in higher yield of this potent lead. Ketone 349 was added to quinoline derivative 350 to yield compound 351 which was then converted to compound 352 by the Vilsemeier-Haack reaction. Compound 352 was added with ketone 353 to yield the final chalcone derivative 354 (**Scheme 52**).

Conclusion

Over the years, the synthesis of conjugates of quinoline with other biologically active compounds has been devised to enhance the antimalarial activity exhibited by the quinoline core. In this review, efforts were made to report the drug design and the synthetic routes employed for the past five years. It was observed that majority of the compounds were designed based on the pharmacokinetics and pharmacodynamics and were thus classified on the basis



Scheme 51. A. Synthesis of compound 337; a. Ac_2O, AcOH, reflux, 30 mins; b. DMF/$POCl_3$, 80°C, 5-18 h; c. MeOH/KOH, 60°C, 2.5-6 h; d. EtOH, AcOH (cat), 78°C, 12-48 h; e. EtOH, $NaBH_4$, RT, 6 h. B. Synthesis of compound 348; a. Ac_2O, AcOH, reflux, 30 mins; b. DMF/$POCl_3$, 80°C, 5-18 h; c. MeOH/KOH, 60°C, 2.5-6 h; d. EtOH, AcOH (cat), 78°C, 12-48 h; e. EtOH, $NaBH_4$, RT, 6 h; f. EtOH, TEA, 78°C, 12-18 h.

Scheme 52. Synthesis of compound 354; a. 1-2 drops glacial CH_3COOH, ethanol, stir, 60°C, 6 h; b. DMF, $POCl_3$, stir, 55-60°C, 5 h; c. CH_3COOH, CH_3COONa, reflux, 4 h.

of the number and type of major pharmacophores present in the final molecule. The synthesis of the molecule exhibiting the best antimalarial efficacy in each case has been elaborated which will serve the purpose of achieving activity-specific drug synthesis.

In general, there was no co-relation between the number of active groups present in a compound and the anti-malarial activity exhibited by it, but the enhancement was observed due to the presence of specific groups. A common trend of better activity was observed in compounds having chloro substitution at C6 and C7 position of the quinoline. 4-aminoquinoline derivatives continued to show enhanced activity. Compounds having strong electron donating groups at ortho and para position of the substituted benzyl groups also proved to be beneficial. Presence of long alkyl chain as linkers between the pharmacophores increased the lipophilicity of the compound as whole, thus increasing its drug-likeness and the use of metals resulted in higher accumulation of the drug. It was also observed that substituents like heterocyclic compounds, which have more number of nitrogen atoms, exhibited more interactions with the target proteins. Since the main focus of this review is the synthesis and the study of structure activity relationship, this will be useful for researchers to generate complexes effective against the continuously mutating malarial parasite.

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Disclosure of conflict of interest

None.

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