**Quinoline-based antimalarial hybrid compounds**

Stéphanie Vandekerckhove and Matthias D’hooghe[[1]](#footnote-1)

*SynBioC Research Group, Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

**ABSTRACT**

Quinoline-containing compounds, such as quinine and chloroquine, have a long-standing history as potent antimalarial agents. However, the increasing resistance of the *Plasmodium* parasite against these drugs and the lack of licensed malaria vaccines have forced chemists to develop synthetic strategies toward novel biologically active molecules. A strategy that has attracted considerable attention in current medicinal chemistry is based on the conjugation of two biologically active molecules into one hybrid compound. Since quinolines are considered to be priviliged antimalarial building blocks, the synthesis of quinoline-containing antimalarial hybrids has been elaborated extensively in recent years. This review provides a literature overview of antimalarial hybrid molecules containing a quinoline core, covering publications between 2009 and 2014.

*Keywords*: quinolines, hybrids, antimalarial agents

**Contents**

[1. Introduction 3](#_Toc405329950)

[2. Classes of quinoline-containing antimalarial hybrids 4](#_Toc405329951)

[2.1. Hybrids of quinoline and artemisinin (or derivatives) 4](#_Toc405329952)

[2.2. Hybrids of quinoline and a synthetic peroxide 8](#_Toc405329953)

[2.3. Hybrids of quinoline and a synthetic reversal agent 10](#_Toc405329954)

[2.4. Hybrids of quinoline and a new motif 18](#_Toc405329955)

[2.4.1. 7-Chloroquinoline-chalcone hybrids 18](#_Toc405329956)

[2.4.2. 7-Chloroquinoline-β/γ-lactam hybrids 22](#_Toc405329957)

[2.4.3. 7-Chloroquinoline-cinnamic acid hybrids 25](#_Toc405329958)

[2.4.4. Quinoline-HDAC inhibitor hybrids 27](#_Toc405329959)

[2.4.5. Quinoline-ferrocene hybrids 28](#_Toc405329960)

[2.4.6. Quinoline-Rhodanine hybrids 29](#_Toc405329962)

[2.4.7. Quinoline-iron chelator hybrids 30](#_Toc405329964)

[2.4.8. Quinoline-isatin hybrids 31](#_Toc405329967)

[2.4.9. Hybrids of quinolines and antimicrobial agents 31](#_Toc405329969)

[2.4.10. Hybrids of quinolines and antiparasitic agents 35](#_Toc405329973)

[2.4.11. Hybrids of quinolines and anticancer agents 39](#_Toc405329974)

[2.4.12. Hybrids of quinolines and anti-HIV agents 41](#_Toc405329977)

[3. Conclusions 42](#_Toc405329978)

[References 43](#_Toc405329979)

1. Introduction

Malaria is the most lethal human parasitic infection; in 2012 malaria was transmitted in 103 countries, with 3.4 billion people at risk of infection, resulting in an estimated 207 million malaria cases and 627.000 deaths.[1](#_ENREF_1) About 80% of the estimated cases and 90% of the deaths occur in sub-Saharan Africa, mostly in children under the age of five, pregnant women or immuno-deficient people.[2-4](#_ENREF_2) Malaria is a protozoan disease that is transmitted to humans by bites of female *Anopheles* mosquitoes. There are five *Plasmodium* parasite species that are capable of human infection: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. The majority of malaria mortality in Africa occurs due to *P. falciparum* infections, while considerable morbidity can be caused by *P. vivax* infections, particularly in South America and Southeast Asia.[5](#_ENREF_5) Quinine **1** was the first effective treatment for malaria caused by *P. falciparum* and remained the drug of choice until the late 1940s, when other drugs such as chloroquine **2** and later on pyrimethamine **3**, artemisinin **4**, mefloquine **5**, *etc*. replaced it (Figure 1). Unfortunately, resistance of the *Plasmodium* parasite against frequently used antimalarial drugs such as chloroquine **2** and artemisinin **4** is ever-increasing and urges scientists to find new approaches to treat and prevent malaria infections. Since there is currently no licensed malaria vaccine available to make people immune,[1](#_ENREF_1) chemotherapy still offers the best solutions. Novel strategies in antimalarial treatment include the optimization of therapies with available drugs (*e.g.* artemisinin combination therapy), repurposing of medicines, developing analogs of existing drugs and the evaluation and use of chemosensitizers (drug-resistance reversers).[6-10](#_ENREF_6)



Figure 1

There is, however, another strategy that has gained much attention in the field of contemporary medicinal chemistry. It involves the combination of two biologically active molecules (pharmacophores) into one single hybrid entity with a dual mode of action. These novel hybrid molecules have the potential to enhance efficacy, improve safety, be cost-effective and reduce the propensity to elicit resistance relative to the parent drugs.[11-13](#_ENREF_11) Since this “molecular hybridization” approach is a hot topic in drug development, and not the least in antiplasmodial research, many contributions on this topic have appeared in the recent literature.

A few general reviews dealing with antimalarial hybrid drug synthesis have been published,[11-15](#_ENREF_11) but in this review, a specific literature overview of antimalarial hybrid molecules containing a quinoline core will be presented, covering publications between 2009 and 2014.

1. Classes of quinoline-containing antimalarial hybrids

Quinoline-based antimalarial hybrids can be categorized into four major classes. The first class contains quinolines which are connected to another well-known antimalarial drug, *i.e.* artemisinin or one of its derivatives. A second class involves the coupling of quinoline with a synthetic peroxide. Thirdly, quinolines can be linked to synthetic reversal agents (chemosensitizers) and lastly, the fourth class of quinoline hybrids consists of quinolines that are connected to new biologically active motifs.

* 1. Hybrids of quinoline and artemisinin (or derivatives)

One of the first antimalarial quinoline-artemisinin hybrids has been described by Walsh in 2007, and it was one of the simplest in terms of known individual drugs. Dihydroartemisinin (DHA) was coupled directly to the carboxylic acid derivative of quinine *via* an ester linkage, affording hybrid **6** (Figure 2). This hybrid had superior activity against chloroquine-sensitive (CQS) and chloroquine-resistant (CQR) strains of *P. falciparum* compared to quinine or artemisinin alone and compared to a 1:1 mixture of the two.[16](#_ENREF_16) This excellent activity suggested a palpable benefit from covalently binding these two molecules.

Prompted by these results, Lombard *et al.* combined 1-bromo-2-(10β-dihydroartemisinoxy)ethane with 7-chloro-4-aminoquinolines through different diamino linkers, resulting in hybrids **7** (Figure 2). All these compounds (except two) displayed a higher or comparable *in vitro* potency than chloroquine*.17-18* The most potent hybrids exhibited similar *in vivo* activities to chloroquine (20 nM) against the CQ-susceptible strain of *P. falciparum* and were superior against the resistant strain (20 vs 160 nM).[19](#_ENREF_19) Furthermore, it appeared that cyclic linkers should not be included and that the linker chain should be limited to two or three carbon atoms with or without methyl substituent.17-18



Figure 2

Since there is a wide range of aminoquinoline antimalarials available, Capela *et al.* decided to hybridize primaquine (PQ, an 8-aminoquinoline) with artemisinin. The synthesis started with the conversion of artelinic acid to the corresponding hydroxamate, which was then reduced to the aldehyde. Reductive amination using PQ afforded hybrid **8** (Figure 3). Further, hybrid **9** was obtained by oxidizing the allyl moiety of 10β-allyldeoxoartemisinin to the carboxylic acid, which was subsequently coupled to PQ in the presence of TBTU (*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate), a peptide coupling reagent, and triethylamine (Figure 3). Hybrids **8** and **9** were evaluated *in vitro* against a CQR *P. falciparum* strain W2. Their antiplasmodial activities (IC50 = 13 and 9 nM, respectively) were similar to artemisinin (8 nM) and superior to primaquine (3.3 µM). Interestingly, even though **9** had a lower *in vitro* IC50 value than compound **8**, it was more active *in vivo*. This suggested enhanced pharmacokinetic properties or stability, which was attributed to the replacement of the oxygen at the C-10 position of the artemisinin moiety with a carbon atom.[20](#_ENREF_20)



Figure 3

Another approach involved the use of the Ugi four-component condensation (U-4CC) reaction which utilizes an acid, amine, aldehyde and isocyanide, and converts them into an *α*-acetamidoamide in one step. Here the target Ugi adducts **10** have been synthesized by using artelinic acid, 4-amino-7-chloroquinoline, paraformaldehyde and cyclohexyl or *tert*-butyl isocyanide (Figure 4).[21](#_ENREF_21) These adducts **10** displayed *in vitro* antiplasmodial activities (IC50 values between 26 and 35 nM) that were comparable to chloroquine’s activity (20 nM) against the CQS D10 strain of *P. falciparum* and were more potent than CQ against the CQR K1 strain of *P. falciparum* (IC50 values of 19-23 nM and 219 nM, respectively). There was no evidence of hybrids **10** exhibiting cross-resistance with chloroquine.[21](#_ENREF_21)



Figure 4

A different strategy from the Lombard group involved the design of artemisinin-quinoline hybrid dimers **11**. Here two 1-bromo-2-(10β-dihydroartemisinoxy)ethane scaffolds were linked to a 4-amino-7-chloroquinoline scaffold *via* various spacers, affording conjugates **11** (Figure 5).[22](#_ENREF_22) The hybrids with a short chain diaminolinker (**11a** and **11b**) displayed excellent *in vitro* antiplasmodial activity against CQS (D10) and CQR (Dd2) strains (5-7 nM and 46-28 nM, respectively), exhibiting higher activity than CQ against both stains (22 and 158 nM). Hybrids with a chain length of more than three carbon atoms (**11c**) or with a cyclic linker (**11d**) were less active than CQ. However, all compounds were less active than dihydroartemisinin, but showed good selectivity towards *P. falciparum*.[22](#_ENREF_22) In a follow-up study by the same group, extra *in vitro* and *in vivo* antimalarial assessments of **11b** and **11d** have been performed.[23](#_ENREF_23) The *in vitro* antiplasmodial activities of hybrid dimers **11b** and **11d** against CQS (3D7) strain of *P. falciparum* were 9 and 30 nM, respectively, which were equipotent as compared to CQ’s activity of 20 nM. Furthermore, these dimers **11b** and **11d** were able to cure blood parasitemia of mice infected by *P. vinckei* at low doses (25-50 mg/kg), but recrudescence was usually observed within 7-18 days as was also the case with artesunate. Modifications to improve bioavailability are necessary for these dimers to be used as oral antimalarial treatment agents.[23](#_ENREF_23)



Figure 5

As mentioned before, the introduction of a carbon atom at the C-10 position of artemisinin has been shown to stabilize the hybrid molecule. The O’Neil group therefore converted DHA into its C-10 benzoate, which was allowed to react with allyltrimethylsilane, affording the C-10 allyl DHA derivative. Subsequent ozonolysis of the double bond and reductive work up resulted in the corresponding alcohol, which was oxidized to the aldehyde. Reductive amination of this aldehyde with various alkylaminoquinolines afforded hybrids **12** (Figure 6). However, oxidation of the alcohol to the carboxylic acid followed by treatment with oxalyl chloride and 4-(3-aminopropylamino)quinoline resulted in the formation of hybrid **13** (Figure 6). All hybrids displayed very good activities against a CQS (3D7) strain of *P. falciparum* (5-22 nM) and excellent activities against a CQR (K1) strain (8-16 nM), which are better than CQ (16 and 187 nM, respectively) and in the same order of magnitude as artemisinin (11 and 9 nM, respectively).[24](#_ENREF_24)



Figure 6

* 1. Hybrids of quinoline and a synthetic peroxide

The commercial availability of artemisinin (and consequently its semi-synthetic derivatives) is limited by the fact that it is a natural product isolated from the plant *Artemisia annua*. Fully synthetic peroxidic antimalarial drugs are only just reaching clinical application in India.25 Limitations associated with semi-synthetic artemisinins include chemical availability, purity, cost, bioavailability and pharmacokinetics, which all limit their therapeutical potential.26-27 Consequently, scientists have been engaged in extensive research into synthetic endoperoxide antimalarials in order to find structurally simplified molecules with better bioavailability that are also synthetically accessible and have a low overall production cost. This has led to the assembly of some totally synthetic peroxide analogs such as 1,2,4-trioxolanes, 1,2,4-trioxanes and 1,2,4,5-tetraoxanes, which all carry the critical endoperoxide bond that bestows activity to artemisinins.[28-32](#_ENREF_27)

An innovation in this field was the design of antimalarials specifically acting on multiple targets (covalent biotherapy) in which a trioxane or trioxolane motive was linked to a quinoline entity. These chimeric molecules were referred to as trioxaquines and trioxolaquines.24, 33 The first trioxaquine **14** has been synthesized by Meunier and co-workers in 2000 and showed high *in vitro* activity against a CQR strain of *P. falciparum* (Figure 7).



Figure 7

More recently, the O’Neill group produced synthetic 1,2,4-trioxolaquines **16**,[24](#_ENREF_24) in a three-step synthesis starting from adamantan-2-one. The first step involved the transformation of adamantanone to a methyl oxime, which in a second step underwent ozonolysis in the presence of 1,4-cyclohexadione toward intermediate **15**. Finally, reductive amination of **15** with aminoquinoline derivatives afforded trioxolaquines **16** (Figure 8). These hybrids **16** displayed significant antiplasmodial activity *in vitro* against a CQS (3D7) strain of *P. falciparum* (IC50 = 6-13 nM) and were equally active against a CQR (K1) strain (IC50 = 3-26 nM), which made them more potent than CQ (18 and 240 nM, respectively). Again, increasing the linker length or introducing cyclic linkers slightly reduced activity, but more interestingly, ketone **15** showed superior activity than conjugates **16** indicating that the presence of the additional hematin-binding unit (aminoquinoline) does not enhance antimalarial activity in this case.[24](#_ENREF_24)



Figure 8

Instead of coupling an aminoquinoline to a synthetic peroxide moiety in order to obtain trioxaquine hybrid antimalarials, Robert *et al.*34reported the synthesis of trioxaferroquines **18** and **19**, hybrids containing a 1,2,4-trioxane moiety that was covalently linked to ferroquine (FQ) **17** (Figure 9), a synthetic ferrocenyl quinoline. The synthesis involved an initial reduction of the *N*,*N*-dimethylamino substituent of FQ **17**, resulting in the primary amine derivative of FQ. This primary amine was then coupled to a trioxane moiety in different manners, affording trioxaferroquines **18** and **19** (Figure 9).The 1,2-disubstituted ferrocene moiety possesses planar chirality and hence trioxaferroquines are chiral compounds. The possibility of stereoisomerism complicates the development of trioxaferroquines as potential drugs, therefore *iso*-trioxaferroquine **20** was synthesized as well (Figure 9).[34](#_ENREF_33) *In vitro* antiplasmodial activity of trioxaferroquines **18** and **19** and *iso*-trioxaferroquine **20** was evaluated against two CQR strains (FcB1 and FcM29) of *P. falciparum*. All compounds showed IC50 values in the range from 16 to 71 nM, which makes them more active than CQ (145 and 735 nM against FcB1 and FcM29, respectively), equally active as artemisinin (10 and 18 nM, respectively), but slightly less active than FQ (6 and 7 nM, respectively). Furthermore, *in vivo* antimalarial evaluation of compound **18a** revealed that when administered orally at low dose (10 mg/kg/day), it was able to clear parasitemia below detectable level in *P. vinckei petteri* infected mice. [34](#_ENREF_33)



Figure 9

In order to prepare the fully synthetic derivative of the aforementioned artemisinin-PQ hybrids, the Lopes group linked synthetic 1,2,4,5-tetraoxane derivatives with PQ, using TBTU and methyl chloroformate as coupling agents, affording hybrids 21 and 22 (Figure 10). These chimeras were screened for antiplasmodial activity against a CQR (W2) strain of *P. falciparum* and they all inhibited the growth of the parasite with IC50 values ranging from 21 to 45 nM, suggesting that the linker length between the two active sites does not considerably affect activity. To evaluate the ability of hybrids 21 and 22 to inhibit liver cell infection by malaria parasites, they were evaluated using an *in vitro* infection model that utilizes a human hepatoma cell line (Huh7) and malaria parasite *P. berghei*. They displayed high potency against the liver forms of the parasite as well, exhibiting IC50 values between 330 and 1000 nM, which was significantly higher than PQ (7500 nM) and the equimolar mixture of PQ and artemisinin (9714 nM). Furthermore, none of the conjugates considerably affected Huh7 cell proliferation, indicating that the chimeras were selective and nontoxic antiplasmodial agents. The *in vivo* efficacy of compound 22a was evaluated using *P. berghei* infected mice; conjugate 22a was administered intraperitoneally at 30 mg/kg/day for 5 days and completely and irreversibly cleared the parasitemia by day 8. All treated mice survived until the end of the experiment.[35](#_ENREF_34)



Figure 10

* 1. Hybrids of quinoline and a synthetic reversal agent

CQR *Plasmodium falciparum* strains exhibit no changes in the process of heme detoxification, but resistance develops from mutations and alterations in the expression levels of membrane proteins located in the membrane of the parasitic digestive vacuole. Crucial to chloroquine resistance are mutant forms of a protein known as PfCRT.36-37 This protein transports chloroquine and lowers its concentration in the digestive vacuole, allowing hemozoin formation to resume unhindered and thereby causing resistance. It has been known for a long time that calcium channel blockers like verapamil **23**, nifedipine **24**, dibenzazepines **25** (Figure 11) and their analogs (imipramine, plant-derived alkaloids, phenothiazines, dibenzylmethylamines (dibemethins), dihydroanthracenes, primaquine, *etc*.) can restore chloroquine sensitivity in various resistant strains of *P. falciparum*,and these molecules are known as chemosensitizers or reversal agents.[38-41](#_ENREF_37) This knowledge resulted in the development of dual-function antimalarials that incorporate both, an active antimalarial (CQ) and a resistance reversing chemosensitizer. The covalent bonding of CQ to a reversal agent produced a single molecule that was termed ‘reversed-CQ’ (RCQ). 42-43



Figure 11

The first example **26** has been reported in 2006 and involved the merging of 4-amino-7-chloroquinoline to imipramine *via* an alkyl linker (Figure 12). Hybrid **26** was very effective against both CQS (D6) and CQR (Dd2) strains of *P. falciparum* (3 and 5 nM, respectively), and was able to eliminate parasitemia from a mouse model to less than 1% via oral dosing. However, compound **26** was not retained for further drug development because of its high lipophilicity.[44](#_ENREF_43)



Figure 12

In a follow-up study the linker and aromatic groups of RCQ have been varied, which involved the evaluation of the linker length and flexibility as well as the evaluation of the bridging between the two aromatic rings of the chemosensitizer. All hybrids **27**-**30** (Figure 13) were tested and displayed significant activity against CQS D6 (2-52 nM) and CQR Dd2 (5-115 nM) strains of *P. falciparum*. Noteworthy was the fact that changing terminal amines to amides reduced lipophilicity (cLogP) to values comparable to CQ (a factor that is important in improving solubility), as well as the fact that the reversal agent portion of the molecule could be considerably varied without severe loss of activity. All compounds **27**-**30** also exhibit large selectivity towards malaria parasites.[45](#_ENREF_44)



Figure 13

Subsequent research performed by the same team involved further variations to both the linker and the aromatic head groups of the reversal agent moiety. The linkage was now a piperazinyl ring which was supposed to make the compounds more stable to metabolic cleavage. Replacing the diphenyl- or dibenzylamino head group with groups such as benzhydryl, benzhydrylmethyl, adamantyl, triphenylmethyl, 9-fluorenyl and bis(pyridin-2-yl)methyl resulted in hybrids **31** and **32** (Figure 14). The *in vitro* testing results from hybrids **31** against CQS D6 (0.5-21 nM) and CQR Dd2 (1-15 nM) strains of *P. falciparum* were superior to CQ (7 and 102 nM, respectively). Interestingly, changing the head group had a relatively limited influence on the activity against either strain of the parasite. Remarkably, more fluctuation in activity was observed against the CQR 7G8 strain (2-56 nM) of *P. falciparum*; the activity against 7G8 was four- to five-fold weaker than against the D6 or Dd2 strains. This 7G8 strain stems from South-America and differs enough from the African D6 and Dd2 strains so that the chemosensitizer verapamil only has a weak influence on it, which could account for the decrease in activity. Also notable were derivatives **32** where the head group was replaced with pyridinyl groups. They were equally potent against all three tested strains but were substantially less lipophilic, which improved their solubility and potentially lowered their toxicity. Indeed, compounds **32** were found to have good oral activity in a *Plasmodium berghei* mouse model and reduced parasitemia by more than 99.9% with four doses of 44 or 46 mg/kg and cured three out of three and nine out of ten treated mice (hybrids **32a** and **32b**, respectively).43, 46



Figure 14

The astemizole scaffold **33** (Figure 15) possesses two aryl groups closely linked to each other causing it to resemble the initial reversal agent, imipramine. Another set of chimeras has been obtained by linking astemizole derivatives with an (amino)quinoline *via* a piperazine or an aminopiperidine linker. *In vitro* antiplasmodial activity of these hybrids **34**, **35** and **36** (Figure 15) was determined against a CQR (K1) strain of the *P. falciparum* parasite, and compounds **34b**, **35** and **36** were three to ten times more active than CQ (23-64 nM vs 230 nM), compound **34a** was less active (IC50 = 610 nM).[47](#_ENREF_47) Interestingly, the hybrids with conformationally constrained aminopiperidine linkers also delivered potent K1 activity, which is in contrast with previously described CQ derivatives where acyclic linkers were more potent than constrained cyclic linker.23-24 Furthermore, the hybrid analogs exhibited a good cytotoxicity profile and the *in vivo* antiplasmodial activity of compounds **35** and **36** against a *Plasmodium berghei* mouse malaria model was established. Both compounds showed *in vivo* activity (>80% clearance of parasitemia at doses of 20-50 mg/kg/day), although neither was as active as CQ.[47](#_ENREF_47)



Figure 15

An elevation of glutathione (GSH) content in *P. falciparum* appeared to lead to an increased resistance to CQ, while GSH depletion in resistant strains restored CQ sensitivity.[48](#_ENREF_48) Since GSH levels depend on the efficient reduction of glutathione disulfide by glutathione disulfide reductase (GR), novel GR inhibitors have been developed to reverse CQ resistance. Subsequently, the Biot group prepared secondary amine FQ analogs from FQ by nucleophilic substitution. The basic terminal nitrogen atom of FQ was quaternized with methyl iodide and the resulting quaternary ammonium unit was then replaced by the appropriate amine, resulting in the secondary amine FQ analogs. Subsequently, linking these ferroquine (FQ) derivatives to a GR inhibitor or GSH depletor afforded hybrids **37** and **38** (Figure 16). The antimalarial activity of all dual molecules **37**-**38** was assessed against both CQS (NF54) and CQR (K1) strains of *P. falciparum*. Compounds **37** and **38** were able to counter CQ resistance and showed good antimalarial activity with IC50<160 nM against both CQS and CQR strains. Compounds **38**, however, displayed decreased antimalarial activities (IC50 values between 36 and 445 nM) and could not counter CQ resistance. Overall, conjugates **37** were more active than CQ, but all hybrid molecules **37**-**38** were less active than FQ.[49](#_ENREF_49) The mechanism of action of these hybrids differs from the hybrids discussed earlier in this part since the CQ resistance is reversed by GR inhibitors and GSH depletors and not by the presence of calcium channel blockers.



Figure 16

The class of dual-function quinolines with resistance-reversing activity has been extended by dibemequines **39**-**41** which were synthesized in a single step by reaction of 4,7-dichloroquinoline with an appropriate dibemethin (dibenzylmethylamine) motif in the presence of potassium carbonate and triethylamine (Figure 17). The dibemethin side chain itself reversed chloroquine resistance and inhibited chloroquine transport by PfCRT. The *in vitro* antimalarial activity of hybrids **39**-**41** was evaluated against CQS (D10) and CQR (K1) strains of the parasite. All compounds exhibited activities between 20 and 180 nM against the D10 strain and activities between 26 and 1130 nM against the K1 strain. The whole series showed no significant cross-resistance with CQ. The three most active compounds (**40a**, **41a** and **41d**) were found to be very potent against both CQS and CQR strains, with IC50 values below 50 nM. The activity of the most potent compound **41a** against four CQR strains (K1, Dd2, W2 and RSA11) was similar to that of CQ against CQS strains. The three most active compounds were found to have low cytotoxicity and possessed significant *in vivo* antimalarial activity in the *P. berghei* mouse malaria model; two of the three compounds were therapeutic with three or four oral doses of 100 mg/kg, rendering parasites undetectable after 30 days of treatment with 100% survival of the mice.[50](#_ENREF_50)



Figure 17

In a study of Gemma *et al.* a trityl-aminoquinoline derivative **42** has been prepared, as well as some piperazine-tethered derivatives **43** and quinoline dimers **44** and **45** (Figure 18). Their *in vitro* antiplasmodial activity was evaluated against the aforementioned *P. falciparum* strains. Piperazine-tethered derivatives **43** displayed poor activity against all tested strains (IC50 values between 10 and 735 nM),[51](#_ENREF_51) confirming the theory that direct conjugation between the polyarylmethyl system and the iron-coordinating and electron-transfer moiety (4-aminoquinoline) is necessary for optimal activity.52-53 Dimers **44** and **45** displayed moderate activities (IC50 values between 10 and 190 nM) and trityl derivative **42** proved to be quite potent against the CQS strains of *P. falciparum* with IC50 values ranging from 10 to 26 nM and against the CQR strains with IC50 values between 8 and 52 nM. Hence, compound **42** was evaluated *in vivo* using the *P. berghei* mouse model but was unable to significantly improve survival of the mice.[51](#_ENREF_51)



Figure 18

Sulfonamides are competitive inhibitors of the DHPS enzyme (deoxyhypusine synthase),[54](#_ENREF_54) which catalyses the conversion of *para*-aminobenzoic acid to dihydropteroate, a fundamental step in folate synthesis.[55](#_ENREF_55) Sulfadoxine is a metabolically stable sulfonamide and can be used for malaria treatment in combination with pyrimethamine.[56](#_ENREF_56) Therefore, novel piperazine-tethered chloroquine-based sulfonamide hybrids **46** have been designed. They were synthesized by nucleophilic aromatic substitution of piperazine on the commercially available 4,7-dichloroquinoline. Subsequent addition of different sulfonyl chlorides, using triethylamine as a base, afforded hybrids **46** (Figure 19). Evaluation of their antiplasmodial activity against CQR FCR-3 strain of *P. falciparum* revealed that all compounds exhibited intrinsic *in vitro* antimalarial properties with IC50 values between 1.2 and 8.5 µM, but this is at least ten-fold less than quinine. Hybrid **46c** was the most potent and was able to inhibit β-hematin formation as potently as chloroquine. Although the antimalarial activity of most conjugates did not correlate with their ability to inhibit β-hematin formation, several compounds did display enough interesting properties to be considered as lead compounds in antimalarial drug development. [57](#_ENREF_57)



Figure 19

A number of CQ-related compounds are equally active against CQS and CQR strains, which can be attributed to the fact that these compounds are not recognized or translocated by the PfCRT-enzyme, and can thus evade the resistance mechanism caused by the mutant protein. An example of such an analog is piperaquine, a dimer that consists of two 7-chloroquinoline cores coupled *via* an amine-containing side chain. Piperaquine does not display cross-resistance with CQ and testing in an oocyte system showed that piperaquine was unable to inhibit transport of CQ *via* PfCRT. This indicated that piperaquine could bypass the CQ resistance mechanism because it doesn’t interact with CQR forms of PfCRT.58-59 This spurred the hypothesis that dimers of other quinoline drugs might also evade the CQ resistance mechanism, which led to the design and antiplasmodial evaluation of dimeric quinine agents **47**-**50** linked *via* ester, carbamate or amide bonds (Figure 20). The ability of these dimeric molecules to inhibit the transport of CQ *via* PfCRT was evaluated using the *Xenopus* oocyte system. All the compounds reduced the accumulation of CQ in oocytes to levels significantly below (1-6 µM) those measured in the presence of verapamil (30 µM), quinine (48 µM) or saquinavir (13 µM), indicating that the activity of quinine dimers **47**-**50** is not simply due to a doubling in amount of quinine in the digestive vacuole but is a consequence, at least in part, of an enhanced ability to inhibit PfCRT. The antiplasmodial activity of compounds **47a** and **50** was evaluated *in vitro* against the CQS HB3 strain of *P. falciparum* and CQR Dd2, FCB and P31 strains. The quinine dimers were significantly more active against the CQR strains than CQ (2- to 5-fold), but neither compound was more effective than quinine against the CQS strain. Compound **50** was also found to be a potent reverser of CQ resistance *in vitro*, while compound **47a** displayed an *in vivo* antimalarial activity comparable to quinine when orally administered to *P. berghei* infected mice.[60](#_ENREF_60)



Figure 20

* 1. Hybrids of quinoline and a new motif

Finally, the fourth class of antiplasmodial quinoline hybrids has been explored most frequently in the last years and involves the coupling of a quinoline unit to a novel motif with demonstrated biological (antimalarial) activity. This should lead to dual inhibitors or “double drugs” which could potentially inhibit hemozoin formation (activity caused by the CQ input) and another target within *P. falciparum* (activity caused by the novel motif) and would not be recognized by the proteins involved in drug efflux, making them very desirable for treatment of drug resistant strains.

* + 1. 7-Chloroquinoline-chalcone hybrids

Chalcones or 1,3-diarylprop-2-en-1-ones are bioprecursors of flavonoids and have been inspiring medicinal chemists for a long time. Their analogs exhibit a broad range of biological activities such as antifungal,[61](#_ENREF_96) antiparasitic,[62](#_ENREF_97) antitumor and antioxidant,[63](#_ENREF_98) immunomodulatory,[64](#_ENREF_99) antileishmanial,[65](#_ENREF_100) antimitotic,[66](#_ENREF_101) anti-invasive,67-68 anti-inflammatory[69-72](#_ENREF_104) and antimalarial activity.73-74 These systems display antiplasmodial activity by inhibiting either cysteine proteases or plasmodial aspartate proteases,[75](#_ENREF_110) and they also proved to inhibit the parasite-induced channels[76](#_ENREF_111) and cause severe membrane disruptions of the erythrocytes.[77](#_ENREF_112) Licochalcone-A was the first potent antimalarial chalcone with activity against CQR *P. falciparum*.[78](#_ENREF_113) This has led to the synthesis of new synthetic analogs and hybrid molecules.

In a first approach, chalcones have been connected to a quinoline core either *via* an oxo-linker or *via* an amino-linker. Nucleophilic substitution of 4-chloro- or 4,7-dichloroquinoline with 4-hydroxy- or 4-aminoacetophenone afforded quinoline intermediates which were subsequently condensed with different aldehydes by an aldol condensation reaction, yielding conjugates **51** (Figure 21). These compounds were screened *in vitro* against the CQS NF54 strain of *P. falciparum* and the 4-oxo-linked quinoline-chalcone hybrids were found to be inactive, while the 4-amino-linked derivatives displayed only very mild antimalarial activity.[79](#_ENREF_90)



Figure 21

Another group focused on the amino-linked derivatives but varied the substituents of the benzaldehydes used for the Claisen-Schmidt aldol condensation, thereby affording hybrid molecules **52** (Figure 22). These compounds were *in vitro* evaluated for their effects as inhibitors of β-hematin formation. Since inhibitions of more than 90% are considered significant (CQ: 94% inhibition), five hybrids **52a-e** were retained as they exhibited satisfactory inhibition (94-95%). However, none of them indicated effective inhibition of hemoglobin proteolysis in an *in vitro* assay which used trophozoyte-rich extract to digest the native hemoglobin of mice.[80](#_ENREF_114)



Figure 22

Hybridization of the chalcone moiety with a quinoline core via a triazole linker has been discussed by Guantai *et al*. Hybrids **53** and **54** were synthesized by a click reaction of acetylenic chalcones and 4-azido-7-chloroquinoline. The synthesis of the acetylenic chalcones involved the propargylation of vanillin and acetovanillone with propargyl bromide, followed by a base-catalyzed Claisen-Schmidt condensation with methoxylated acetophenone or benzaldehyde, respectively. Conjugates **53** and **54** (Figure 23) were evaluated for their *in vitro* antimalarial activity against the CQS D10 and the CQR Dd2 and W2 strains of *P. falciparum*. All compounds displayed moderate to good *in vitro* activity across all three strains, with IC50 values in the lower micromolar to high nanomolar range. Three conjugates **53b-c** and **54b** had submicromolar potency, compound **53b** was the most active with IC50 values of 40, 70 and 90 nM against the D10, Dd2 and W2 strains of *P. falciparum*, respectively. Hybrid **53b** was also evaluated for its cytotoxicity against the CHO (mammalian) cell line and no cytotoxicity was observed at the highest concentration tested (100 µM). [81](#_ENREF_115)



Figure 23

Inspired by these results, the Sashidhara group pursued a hybridization strategy that combined two known antiplasmodial moieties, CQ and ketoenamine chalcones. The Duff reaction on *ortho* alkyl- substituted phenols in the presence of hexamethylenetetraamine and TFA gave aromatic dicarbaldehydes, which on coupling with appropriate acetophenones afforded *para*-condensed chalcones. These chalcones were connected to appropriate 4-aminoquinolines, furnishing hybrids **55** (Figure 24). Antimalarial assessment of these compounds **55** against the CQS 3D7 strain of *P. falciparum* revealed that two hybrids (**55b** and **55g**) out of 28 derivatives displayed comparable activity (3.63 and 4.64 ng/mL, respectively) to CQ (2.45 ng/mL) and 5 compound showed IC50 values lower than 10 ng/mL. The difference in activity (3 to 380 ng/mL) in general could be attributed to different factors such as length and nature of the linker and substitutions on the chalcone ring. Furthermore, the 10 most potent compounds were also evaluated *in vivo* against the CQR N67 strain of *P. yoelii* in Swiss mice and results revealed that these derivatives were highly active and able to clear parasitemia below detectable levels in mice when orally administered in doses of 100 mg/kg. However, a complete cure was not obtained at the tested dose.[82](#_ENREF_116)



Figure 24

As a continuation of the previous research, the Sashidhara group reported on a new class of CQ-chalcone-based hybrid molecules **56** which were synthesized by substitution of 4-chloro- or 4,7-dichloroquinoline with hydrazine hydrate, followed by condenstation with 4-hydroxybenzaldehyde and nucleophilic substitution using 4-chlorophenacyl bromide. Finally, hybrids **56** were obtained by Claisen-Schmidt condensation with the appropriate aldehydes (Figure 25). The *in vitro* antiplasmodial activity of hybrids **56** was assessed against a CQS (3D7) and a CQR (K1) strain of *P. falciparum*. Most compounds exhibited potent antimalarial activity against the susceptible strain (IC50 values between 30 and 300 nM), but more importantly, all conjugates were more potent (IC50 values between 80 and 315 nM) than CQ (IC50 = 463 nM) against the resistant K1 *Plasmodium* strain. Compound **56c** was found to be the most potent against both strains. Cytotoxicity of hybrids **56** was evaluated against VERO cells and all compounds displayed SI values ranging between 387 and 6200. Since compounds with a SI value higher than 50 are generally considered as safe, these hybrids **56** are worth considering as promising lead compounds. Mechanistic studies also revealed that these hybrids interfered with heme polymerization.[83](#_ENREF_117)



Figure 25

The N’Da group continued this research by connecting a chalcone moiety (with 5-methylfuran as aromatic B-ring) to a 7-chloroquinoline pharmacophore through amide bond formation between the carboxylic acid of the chalcone and the free amine of the aminoquinolines, using CDI as a coupling agent, yielding chimeras **57** (Figure 26). *In vitro* antimalarial screens showed that all hybrids **57** proved to be active with IC50 values between 0.05-0.53 µM against the CQS 3D7 strain and IC50 values between 0.07-1.8 µM against the CQR W2 strain of the *Plasmodium* parasite. However, amide-hybrids **57** exhibited a loss of activity against the resistant strain compared to the CQ sensitive strain, which implied that chloroquine resistance was not overcome with these compounds. They also displayed moderate to high toxicity towards mammalian cells (WI-38 cell line, normal human fetal lung fibroblast). Hybrid **57c** was found to be the most potent against both strains and was up to two times more active than CQ against the resistant parasite strain.[84](#_ENREF_118)



Figure 26

* + 1. 7-Chloroquinoline-β/γ-lactam hybrids

Since their discovery β-lactam antibiotics have continued to be very effective chemotherapeutics combining a broad activity spectrum with low toxicity.[85](#_ENREF_119) Interest in this class of compounds has led to the design and synthesis of classical β-lactams such as penicillins and cephalosporins but also non-classical substrates like carbapenems and monobactams.[86-88](#_ENREF_120) More recently β-lactam research focused on modifications of the β-lactam ring in order to obtain compounds with very diverse pharmacological activities such as vasopressin V1a antagonist activity, cholesterol absorption inhibitory activity, thrombin and chymase inhibitory activity and antiparkinsonian, antidiabetic, antitubercular, anti-inflammatory and anti-HIV activity.[89-92](#_ENREF_123) A related class of compounds concerns the γ-lactams; these systems appear in many natural products and bioactive derivatives.[93-95](#_ENREF_127) Since β- and γ-lactams clearly represent biologically active scaffolds, they could serve as excellent motifs to include in hybrid molecules, where dual functionality could be beneficial for the overall activity.

This is exactly what the group of Kumar envisioned when they designed 1,2,3-triazole-tethered β-lactam and 7-chloroquinoline bifunctional hybrids **58** and **59**. Therefore, 3-amino-2-azetidinone was mono- or di-*N*-alkylated using propargyl bromide. The reaction products were treated with 4-azido-7-chloroquinoline, which afforded hybrids **58** and **59** after 1,3-dipolar cycloaddition (Figure 27). *In vitro* antimalarial activities of conjugates **58** and **59** were evaluated against a CQR (W2) strain of *P. falciparum*. These compounds were less active than CQ, but with the exception of **58a** and **58c**, all hybrids displayed moderate antiplasmodial activity with IC50 values ranging from 1 to 6 µM. The bis-quinoline compounds **59** mostly were more potent than the corresponding mono-quinoline scaffolds **58**. The increase in activity might be attributed to either solubility-enhancing properties of triazole rings or increased heme-binding of 7-chloroquinolines.[96](#_ENREF_130)



Figure 27

The Kumar group further focused on this strategy and synthesized a library of 4-aminoquinoline-β-lactam hybrids tethered via alkyl chain linkers (conjugates **60**) as well as trough amide functionalities (conjugates **61**). Compounds **60** and **61** (Figure 28) have been evaluated for their *in vitro* antimalarial profiles against the CQR W2 strain of *P. falciparum*. Most hybrids showed high nanomolar activities and when comparing the potencies among the alkyl chain and amide-tethered series, the alkyl chain-linked compounds displayed better efficacy in inhibiting *P. falciparum*. Again it seemed that varying the length of the alkyl linker chain had a distinct influence on the conjugate’s activity. Hybrids **60a**, **61b** and **61c** exhibited the best activity profiles with IC50 values ranging between 80 and 94 nM, which are comparable to the potency of CQ (IC50 = 99 nM) against the W2 parasite strain.[97](#_ENREF_131)



Figure 28

The Kumar group further extended this research toward the design of β-lactam-4-aminoquinoline conjugates **62** and **63** having urea/oxalamide linkers and a well-modulated alkyl chain length. Groups like amides, sulphonamides, ureas and thioureas have shown to improve pharmacological activities against both CQS and CQR strains of *P. falciparum*,16, 98-100 while oxalamide groups have proven to enhance antiplasmodial potency due to stronger hydrogen bonding ability.101-102 The 3-carbamic acid ethyl ester and 3-oxalamic acid ethyl ester 2-azetidinone intermediates were synthesized diastereoselectively by treating *cis*-3-amino-2-azetidinones with ethyl chloroformate or ethyl oxalylchloride. The desired hybrids **62** and **63** (Figure 29) were subsequently prepared by heating the latter intermediates in the presence of the appropriate aminoquinolines. The *in vitro* antimalarial potency of hybrids **62** and **63** was determined against the CQR W2 strain of *P. falciparum*. The urea-tethered compounds **62** displayed IC50 values ranging from 42 to 193 nM, while the conjugates **63**, linked through an oxalamido group, exhibited a slight improvement in activity with IC50 values ranging from 34-120 nM, which are good antiplasmodial activities (CQ: IC50 = 59 nM). A small SAR study clearly pointed out that an *N*-aryl substituent has a profound effect on the activity at shorter chain lengths (n = 2, 3), while the effect reverses in favor of the cyclohexyl substituent when higher alkyl chain lengths are considered (n = 4, 6). The cytotoxicity of the most potent compounds **62h** and **63d** was evaluated against HeLa cells and both hybrids displayed no apparent toxicitiy.[103](#_ENREF_137)



Figure 29

Aside from β-lactams, γ-lactams have also emerged as excellent substrates for molecular hybridization. Recent research reported on the synthesis of fluoroalkylated γ-hydroxy-γ-lactam-4-aminoquinoline hybrids **64** and **65**, also called quinolac hybrids. Therefore, γ-ketothioesters were treated with diisopropylamine to give rise to γ-lacton sulfides, which, after mCPBA oxidation, resulted in the corresponding sulfones. Coupling reaction of appropriate aminoquinolines with γ-lactones (lactamization) furnished the desired conjugates **64** and **65** (Figure 30). *In vitro* antimalarial assessment of derivatives **64** and **65** against CQS (3D7) and CQR (W2) strains of *P. falciparum* revealed eight compounds exhibiting reasonable potency (IC50<100 nM) against both strains. The citric acid salt of compounds **64b** and **65a** exhibited the highest activities (26 and 19 nM, respectively) against the 3D7 strain, which was comparable to CQ (IC50 = 30 nM) and potencies between 49 and 42 nM, respectively, against the resistant strain. Overall, the length of the spacer had a major impact on the antiplasmodial activity, with three carbon atoms being favored over four or six. Also, the insertion of a basic nitrogen in the spacer greatly improved the activity against both strains. The most active representatives were also evaluated against a mammalian cell line (HUVECs), but no significant cytotoxicity was determined at the tested concentrations (0.01-100 µM).[104](#_ENREF_138)



Figure 30

* + 1. 7-Chloroquinoline-cinnamic acid hybrids

Cinnamic acid is a naturally occurring organic acid in plants, has low toxicity and a broad biological activity spectrum. Many cinnamic acid derivatives, especially those with a phenolic hydroxyl group, are well-known antioxidants. Cinnamic acid derivatives, both isolated from plant material and synthesized, have been reported to display antibacterial, antiviral and antifungal properties,105-106 but have also proven to exhibit antimalarial activity.[107](#_ENREF_141) Cinnamic acid is thus a valuable motif to include in hybrid molecules.

Keeping this in mind, HEterocyclic-DIpeptide-CINnamic (HEDICIN) acid conjugates **66** (Figure 31) have been synthesized by linking a 4-amino-7-chloroquinoline core to a *trans*-cinnamic acid moiety through a dipeptide spacer. This was achieved by subsequently linking two amino acids to a 4-amino-7-chloroquinoline core, followed by coupling of this quinolinyldipeptide with cinnamic acid using PyBOP as a coupling agent. Analogs of these hybrids lacking the dipeptide spacer, HEterocyclic-CINnamic (HECIN) acid derivatives **67** (Figure 31) were also prepared by the Gomes group through direct coupling of aminoquinoline to cinnamic acid derivatives with PyBOP as a coupling agent. Compounds **66** and **67** were evaluated for their *in vitro* antimalarial activity against the blood-stage CQR W2 strain of *P. falciparum*. The resulting activity profile revealed a complete lack of activity for HECIN-hybrids **67**, which correlated with their inability to inhibit heme polymerization. Furthermore, HEDICIN-hybrids **66** inhibited heme polymerization *in vitro* and displayed IC50 values between 1 and 11 nM, suggesting that this inhibitory activity is at least in part accountable for their antimalarial activity. Hybrids **66** and **67** were also evaluated *in vitro* for inhibition of falcipains. HECINs **67** generally exhibited more potent inhibition of falcipain than HEDICINs **66** did, so these falcipain inhibition results do not allow the identification of a correlation between these inhibitory capacities and the hybrid’s antimalarial potency.[108](#_ENREF_142)



Figure 31

This research group continued their efford towards the design of *N*-cinnamoylated chloroquine analogs. Since the previous study proved that a spacer between the heterocycle and the cinnamoyl motif was required for antimalarial potency, the cinnamoyl moiety was linked to a 4-aminoquinoline core through a flexible and more hydrophobic butylamine/butyloxy chain, affording hybrids **68** (Figure 32). Since primaquine (an 8-aminoquinoline) remains the only drug in clinical use that acts against the liver stages of all *Plasmodium* species, the Gomes group also synthesized an *N*-cinnamoylated primaquine hybrid **69** (Figure 32) through a single amide coupling step between the parent drug PQ and cinnamic acid; cinnamic acid was first activated by TBTU in the presence of DIEA, followed by addition of PQ. These conjugates were evaluated for their *in vitro* antimalarial potency and hybrids **68** displayed activities between 15-141 nM against the sensitive 3D7 parasite strain and between 11-111 nM against the resistant W2 strain of *P. falciparum*, which are higher potencies than CQ (IC50 (W2) = 138 nM). The cinnamoyl core thus appears to be a valuable pharmacophore to enhance the antiplasmodial potency of chloroquine. The primaquine analog **69**, however, completely lacked activity. The compounds’ activities were also evaluated against liver stage *P. berghei* parasites and most conjugates displayed outstanding potency against both erythrocytic and liver stages of the parasite. They were found to be non-cytotoxic against Huh7 human hepatoma cells as well. The most potent compounds **68c** and **68e** were confirmed to be active *in vivo* against a blood-stage infection in a *P. berghei* rodent malaria model, as they extended survival with two to seven days when treated with doses of 30 mg/kg/day for two days. Hybrid **68c** was highly toxic when administered in doses of 100 mg/kg/day, while hybrid **68e** did not appear to be toxic at any tested dosage.[109](#_ENREF_143)



Figure 32

* + 1. Quinoline-HDAC inhibitor hybrids

Histone deacetylases (HDACs) are important zinc-dependent enzymes that affect post-translational modifications of proteins by altering the acetylation state of lysine side chains of histones.[110-112](#_ENREF_144) HDACs control the proliferation of transformed cells associated with many diseases as well as epigenetic variations that trigger cell transformations.113-114 These enzymes are validated drug targets since they have been widely evaluated for their cytotoxic, anticancer, antimalarial and other potential therapeutic properties.115-116 The malaria parasite *P. falciparum* contains at least five HDAC homologs and their presence raises the possibility that the parasite uses histone modulation to regulate gene expression, which makes them attractive targets for novel antimalarial drugs that could then act *via* a different mechanism than current antimalarial agents.

HDAC inhibitors normally possess a zinc binding group, a linker region and a cap group. Most alterations that have been made to HDAC inhibitors in connection to enhance their activity have involved altering the cap or linker region. Apicidin **70** (Figure 33) was one of the first HDAC inhibitors found to exhibit cytotoxic activity against *Plasmodium* species,[117](#_ENREF_151) and the Andrews group made derivatives of this compound by exchanging the tryptophan group by a quinoline group, affording hybrids **72** and **73** (Figure 33). Suberoylanilide hydroxamic acid **71** (Figure 33) is a simpler, achiral compound capable of inducing differentiation, cell growth arrest or apoptosis in a wide variety of cells at low concentrations.115, 118 2-Aminosuberic acid-quinoline conjugates **74** (Figure 33) have been designed in this study as derivatives with potentially better antimalarial potency. These hybrids were evaluated for their in vitro antimalarial activity against CQS (3D7) and CQR (Dd2) strains of *P. falciparum*. They proved to be very potent with IC50 values between 13-81 nM against the sensitive strain and between 33-71 nM against the resistant strain. This indicates that these derivatives are very valuable lead compounds and no cross-resistance was observed.[119](#_ENREF_153) In a later report of this group another quinoline-HDAC inhibitor hybrid **75** (Figure 34) was described, it exerted nanomolar activity (IC50 values between 10-40 nM) and displayed a reasonable selectivity index between 30 and 120.[120](#_ENREF_154)



Figure 33

* + 1. Quinoline-ferrocene hybrids

Since the work of Köpf-Maier reported on the anticancer activity of ferrocenium complexes,[121](#_ENREF_198) there has been a growing interest in metallocenes and their potential application in medicinal chemistry. Many ferrocene-containing compounds or functionalized ferrocenes have been designed and tested for their potential biological activity such as anticancer,[122-124](#_ENREF_199) antituberculosis,[125-127](#_ENREF_202) antimalarial activity,[128-131](#_ENREF_205) *etc*. Following these results a series of quinoline-ferrocene hybrids **76** with various spacers has been described. Condensation of various diamines with 4,7-dichloroquinoline afforded primary and secondary amino-functionalized quinolines. Subsequently, reductive amination of ferrocenic aldehyde with the functionalized quinolines furnished the desired hybrids **76** (Figure 34). These metallocenes **76** were screened against CQS (D10) and CQR (Dd2) strains of *P. falciparum*, and hybrids containing a flexible hydrocarbon spacer (**76a**, **76b**, **76f** and **76g**) were found to be the most active against both strains (IC50 between 0.09-0.13 µM for D10 and between 0.01-0.02 µM for Dd2). The compounds’ potency against the sensitive strain was comparable to that of CQ (0.05 nM), but was higher than CQ against the resistant strain (CQ: IC50 = 0.15 nM). Furthermore, all tested conjugates (except for **76a** and **76b**) displayed good selectivity towards Chinese Hamster Ovarium cell-types, implying low cytotoxicity.[132](#_ENREF_209)



Figure 34

* + 1. Quinoline-Rhodanine hybrids

The rhodanine scaffold is a known synthon for the synthesis of various heterocyclic units with a range of pharmacological activities.[133-137](#_ENREF_225) The combination of the two intrinsically bioactive moieties 4-aminoquinoline and rhodanine afforded hybrid molecules **77** and **78** (Figure 35). 4,7-Dichloroquinolines were condensed with various diamines, and addition-elimination reaction of these products with carbon disulfide and ethylbromo acetate provided cyclized intermediate 3-(7-chloroquinolin-4-yl)alkyl-2-thioxothiazolidin-4-ones **77**. Knoevenagel condensation with appropriate aldehydes furnished hybrids **78**. These compounds have been assessed for *in vitro* antiplasmodial efficacy against CQS (3D7) and CQR (K1) stains of *P. falciparum*. Derivatives **78** displayed promising activities against the sensitive *Plasmodium* strain (IC50 < 100 nM) and were even more potent than CQ (IC50 = 254 nM) against the resistant strain. Furthermore, all compounds were also assessed for their cytotoxicity toward the VERO cell line and all compounds exhibited high to very high selectivity indices (>2000), indicating no cytotoxicity.[138](#_ENREF_230)



Figure 35

* + 1. Quinoline-iron chelator hybrids

Iron plays an important role in the development of the malaria parasite, meaning that disruptions in the iron concentration can hamper parasite proliferation. 3-Hydroxypyridin-4-ones have been reported to chelate iron,[139](#_ENREF_235) which would lead to the loss of iron and cause the parasite to diminish, but only if the hydroxypyridinones are able to access the parasitic digestive vacuole, which would be possible using CQ transport systems. Therefore, 4-aminoquinoline-3-hydroxypyridin-4-one hybrid derivatives **79** (Figure 36) have been synthesized by Michael addition of *N*-(7-chloroquinolin-4-yl)diaminoalkanes to benzylated pyranones. These protected conjugates were deprotected by catalytic hydrogenolysis at high pressure or by acid hydrolysis. Hybrids **79** have been assessed for *in vitro* antiplasmodial efficacy against CQS 3D7 strain and CQR K1 and W2 strains of *P. falciparum*. Fifteen out of 20 compounds **79** displayed IC50 values < 1 µM against the sensitive strain, compound **79f** was more potent (IC50 = 4 nM) than CQ (IC50 = 10 nM). Nine compounds exhibited superior activity than CQ against the resistant strains (K1 and W2). Cytotoxicity studies in mammalian KB cell line revealed that most of the tested hybrids were not toxic up to concentrations of 30 µM.[140](#_ENREF_236)



Figure 36

An elevated iron level in some people (pregnant women and non-pregnant people on iron supplements) is a serious risk factor for human malaria.[141-144](#_ENREF_255) Therefore, the Chibale group chose to combine iron chelators (especially 3,4-hydroxypyridinones (3,4-HPO) which have also been proposed as potential antimalarial agents) with 4-aminoquinolines in order to obtain a hybrid molecule with increased therapeutical potential. In this approach, kojic acid was chosen as a precursor for the 3,4-HPO scaffold. The 5-hydroxyl group of kojic acid was chemoselectively *O*-benzylated, and subsequent Michael addition by methylamine or cyclopropylamine resulted in the formation of pyridinone derivatives which were then chlorinated to afford 2-(chloromethyl)pyridin-4-ones. Finally these pyridinones were linked with the appropriate *N*-(7-chloroquinolin-4-yl)diaminoalkanes, furnishing hybrid compounds **80** (Figure 37). Hybrids **80** were assessed for their *in vitro* antimalarial activity against a CQS (3D7) strain of *P. falciparum* and all compounds displayed nanomolar activity with IC50 values ranging from 4 to 670 nM, while antimalarial activity against a CQR (K1) strain of *P. falciparum* ranged from 30 nM to 2.5 µM. All deprotected compounds (R3 =H) had lower resistance indices than chloroquine, suggesting that they are likely to be active against resistant parasites.[145](#_ENREF_259)



Figure 37

* + 1. Quinoline-isatin hybrids

Since isatin is known for its broad biological activity spectrum and is well tolerated in humans,[146](#_ENREF_75) the Kumar group proposed to introduce 1*H*-1,2,3-triazole-tethered 7-chloroquinoline-isatin conjugates **81** and **82**. The triazole functionality was introduced because of its favorable properties (hydrogen bonding capacity, rigidity and stability under *in vivo* conditions, *etc*.). Conjugates **81** and **82** (Figure 38) were synthesized by Cu-mediated click chemistry of *N*-propargylated isatins with varied substitutions and 7-chloroquinoline-based azides with or without a well-modulated alkyl chain. Hybrids **81** and **82** have been evaluated for their *in vitro* antiplasmodial profiles against a CQR (W2) strain of *P. falciparum*. Hybrids **81** appeared to be inactive at tested concentrations, while compounds **82** displayed low micromolar activity against W2. The activity profiles indicated an influence of the length of the alkyl side chain as well as on the substituent at the C-5 position of isatin. Hybrid **82c** proved to be the most potent analog.[147](#_ENREF_76)



Figure 38

* + 1. Hybrids of quinolines and antimicrobial agents

Triclosan is a diarylether which is well established as an antibacterial agent with mild *in vitro* antimalarial potency,148-149 and this entity has been selected by Mishra *et al*. to be included in quinoline-based hybrids **83**. The synthesis commenced with the coupling of 2- or 4-fluoronitrobenzene with 2,5-dichlorophenol or 4-methoxyphenol, affording the diarylethers. Reducing the nitro group with iron and acetic acid furnished the respective substituted anilines, which were treated with different aryl isothiocyanates, affording the corresponding thioureides. Thiourea derivatives were transformed to the desired hybrids **83** (Figure 39) by reaction with different 4-aminoquinolines in the presence of mercury chloride and triethylamine. A total of 58 triclosan-4-amino-7-chloroquinoline derivatives **83** have been synthesized and assessed for their *in vitro* antiplasmodial activity against CQS (3D7) and CQR (K1) strains of *P. falciparum*. Thirty-six out of the 58 hybrids **83** displayed IC50 values lower than 100 nM against the sensitive 3D7 strain, but even the most active compound (IC50 = 20 nM) was less potent than CQ (IC50 = 7 nM). However, 28 conjugates **83** were more active (IC50 between 41 and 329 nM) than CQ (IC50 = 352 nM) against the resistant K1 strain. Overall, hybrids **83** exhibited significant antimalarial potency when compounds had the triclosan-ether linkage *para* to the guanidino group, a 3-chloro-substitution (R2) on the phenyl ring and a propyl spacer between the 4-aminoquinoline moiety and the guanidine unit. Further selectivity and toxicity studies should disclose whether or not more research should be performed toward this type of compounds.[150](#_ENREF_212)



Figure 39

Azithromycin has been the central compound in the hybridization study of the Perić group. Azithromycin is an azalide antibiotic, semi-synthetically derived from the macrolide erythromycin, that demonstrated *in vitro* and *in vivo* activity in malaria prophylaxis and experimental models.[151-153](#_ENREF_213) In the Starčević study a 4-amino-7-chloroquinoline moiety has been linked to a C-3’ modified 15-membered macrolide azalide, yielding hybrid molecules **84** (Figure 40). These compounds **84** were profiled for their *in vitro* antiplasmodial activity against CQS (3D7) and CQR (W2) strains of *P. falciparum*. The five most potent compounds displayed IC50 values between 3 and 104 nM against the susceptible parasite strain and between 2 and 48 nM against the resistant strain. The high *in vitro* activities and the high selectivity of these macrolides render them interesting lead compounds for further investigation.[154](#_ENREF_216)



Figure 40

Quinolone antibiotics are very well known for the treatment of life-threatening bacterial infections.[155](#_ENREF_246) Quinolones and fluoroquinolones have also been reported to exhibit antiplasmodial activity against CQS and CQR *P. falciparum*.[156-158](#_ENREF_247) Consequently, the Katritzky group looked into linking quinine-amino acid conjugates to quinolone antibiotics in order to obtain hybrids **85** (Figure 41) with potentially enhanced antimalarial activity. Quinine-amino acid conjugates were utilized because amino acids can be employed as carriers for drugs since they are able to be built into mammalian tissue later on. Hybrids **85** were assessed for *in vitro* antiplasmodial efficacy against a CQS (3D7) strain of *P. falciparum* and all compounds displayed nanomolar activity with IC50 values ranging from 12 to 207 nM, with compounds **85b** and **85c** (IC50 = 16 and 12 nM, respectively) being the most potent ones. This proves that conjugates **85** retained antimalarial activity, similar to quinine (IC50 = 18 nM).[159](#_ENREF_250)



Figure 41

The design of novel antimalarial hybrid drugs that combine the 4-aminoquinoline pharmacophore of chloroquine with that of antifungal clotrimazole-based compounds has been described by the Gemma group. The synthesis commenced with the substitution of 4-(bromomethyl)benzophenone with various heterocycles after which the carbonyl function was reduced with sodium borohydride, followed by activation of the resulting alcohols to the corresponding chlorides. These latter compounds were reacted with the appropriate 4-aminoquinolines, furnishing hybrids **86** and **87** bearing various heterocycles at the benzhydryl system (Figure 42). Heterocycles such as imidazole, piperazine, pyrrolidine and morpholine were employed because they are basic at the pH of the digestive vacuole (pH 5.5) and because they are able to coordinate metals such as iron. These hybrids **86** and **87** were *in vitro* assessed as racemates against the *P. falciparum* CQS strains D10 and NF54 and the CQR strains W2 and K1. Almost all compounds displayed IC50 values lower than 100 nM against all evaluated strains. The pyrrolidine and imidazole derivatives **86a** and **86c** appeared to exhibit low-level cross-resistance with CQ, which was determined by calculating their resistance index: RI = IC50(CQR strain)/IC50(CQS strain) (RI = 1.6 and 1.9). Piperazine derivative **86d** displayed more severe cross-resistance (RI = 2.8), indicating that not only the quinoline core but also the heterocyclic side chain influences cross-resistance with CQ. Hybrids carrying a pyrrolidine functionality proved to be more potent than compounds with the less basic morpholine skeleton in the side chain. Furthermore, introduction of an additional electron-withdrawing or -donating group (X = Cl, F, OMe) onto the benzhydryl side chain only had little effect on the antimalarial potency. Substitution of the quinoline core was found to be more pivotal for activity, 7-chloro-4-aminoquinolines issue greater antiplasmodial properties than 6-methoxy- or 7-trifluoromethyl-4-aminoquinolines. *In vivo* antimalarial activity of the most potent compounds (**86a**, **86b** and **86a**) was evaluated using a *P. berghei* mouse model. A single dose of **86a** or **87b** at 30 mg/kg substantially prolonged mouse survival and administration of three or four doses extended the survival of all mice until day 30.[51](#_ENREF_51)



Figure 42

* + 1. Hybrids of quinolines and antiparasitic agents

The 8-aminoquinoline primaquine (PQ) is active against liver-stage schizonts, it is also the only compound that eradicates hypnozoites and thus prevents relapses.[160-162](#_ENREF_194)Primaquine is active against the clinical silent liver stage and could obstruct the disease before symptoms appear. CQ and most other antimalarial drugs inhibit the blood stage of the *Plasmodium* parasite and act during the clinical phase of the disease. The perfect remedy would be a non-toxic compound that is active against all stages of the *Plasmodium* life cycle that can be used prophylactically. This train of thought led to the design of bifunctional hybrid **88** (Figure 43) where two approved antimalarial drugs CQ and PQ were combined in one dual compound by a neat coupling reaction at high temperature (120 °C). This conjugate **88** was tested for its antiplasmodial activity on the asexual blood stages of three *P. falciparum* strains: 3D7 (CQS), Dd2 (CQR) and K1 (CQR). Hybrid **88** was less efficient than CQ against 3D7 (640 vs 30 nM) and the combined application of CQ and PQ (1:1) also showed no additional effect, this implied that PQ had no synergistic effect on the 3D7 stain. However, compound **88** exhibited a moderate inhibitory effect against CQR strains Dd2 (IC50 = 580 nM) and significantly inhibited the resistant K1 strain (IC50 = 80 nM). The combined equimolar administration of CQ and PQ was slightly more potent than hybrid **88** against Dd2, but was less active against K1. This indicated a resistance-reversing effect of PQ. This conjugate **88** showed promising *in vitro* effects against the liver stages post-invasion in human hepatoma cells and was proven to be potent *in vivo* as well. This hybrid **88** thus inhibits the liver and blood stages of mammalian *Plasmodium* infection *in vitro* and *in vivo* and can be considered a very valuable lead in antiplasmodial research.[163](#_ENREF_197)



Figure 43

In the literature some examples of aminoquinoline-steroid conjugates have been reported to have good *in vitro* potencies against *Leishmania major* and *Mycobacterium tuberculosis,*[*164*](#_ENREF_217) which presented the incentive to design hybrids **89** of *Cinchona* alkaloids (quinine, quinidine, cinchonine and cinchonidine) and bile acids. The choice for bile acids was based on their easy accessibility, their role as drug transporters and the wide range of steroids that exhibit antiparasitic activity.[165-167](#_ENREF_218) Reaction of peracetylated chenodeoxycholic or lithocholic acids with 2-mercaptopyridine *N*-oxide and *N*,*N’*-dicyclohexylcarbodiimide (DCC) afforded Barton esters, which were subsequently subjected to photolytic decarboxylation in the presence of a large excess of a protonated *Cinchona* alkaloid. These peracetylated hybrids were finally treated with a sodium hydroxide solution, furnishing conjugates **89** (Figure 44). Hybrids **89** were assessed for their *in vitro* antiplasmodial activity against a CQS (3D7) strain of *P. falciparum* and cytotoxicity was evaluated against a human normal fibroblast cell line (WI38). Although none of the conjugates **89** were more active *in vitro* than the corresponding *Cinchona* alkaloids, they all exhibited activities with IC50 < 6 µg/mL, most of them even < 1 µg/mL. Moreover, hybrids **89** showed good selectivity indices.[168](#_ENREF_221)



Figure 44

Squaric acid has been identified in the literature as a compound with good antiplasmodial properties169-170 and was therefore utilized as active moiety in hybrid molecules. Linking squarate to 4-amino-7-chloroquinoline (CQ derivative) afforded hybrids **90** and **91** (Figure 45), while the connection of squarate and 8-amino-6-methoxyquinoline (PQ derivative) yielded conjugates **92** and **93** (Figure 45). These compounds were examined for their ability to inhibit a CQR (W2) strain of *P. falciparum*, and most of them displayed antiplasmodial activities in a range from 0.1 to 2 µM. Hybrids **91**, containing two CQ moieties, were clearly the most potent with IC50 values ranging from 0.1 to 0.2 µM. Therefore, the activity profiles of hybrids **90** and **91** were compared with those of *P. falciparum*-infected red blood cell that were incubated with a 1:1 and 2:1 mixture of CQ and squaric acid. The results revealed that the 1:1 mixture was equipotent to CQ (IC50 values of 138 and 140 nM, respectively), but considerably more active than conjugates **90**. The 2:1 mixture on the other hand exhibited potency comparable to that of hybrids **91**, implying that the 4-aminoquinoline moiety significantly contributes to the overall hybrid activity. The cytotoxicity was evaluated using NIH 3T3 and Hek 293T cell lines, most of the derivatives were non-cytotoxic at the tested concentrations (up to 50 µM).[171](#_ENREF_224)



Figure 45

*N*-acylhydrazones are a well-known group of antiparasitic agents which possess antiamoebic and antimalarial properties.172-173 In view of these characteristics, it was envisaged to link 4-aminoquinoline with *N*-acylhydrazone *via* an appropriate linker, resulting in hybrid molecules **94** (Figure 46). Nucleophilic aromatic substitution of 4,7-dichloroquinoline with piperazine afforded 7-chloro-4-piperazin-1-ylquinoline, which was subsequently reacted with methyl acrylate under neat conditions. The obtained ester was treated with hydrazine hydrate and further reacted with various aldehydes to give *N*-acylhydrazone hybrids **94**. All compounds **94** were screened for antimalarial activity against CQR W2 strain of *P. falciparum* and cytotoxicity was determined against mouse splenocytes. Only the compounds that showed *Plasmodium* inhibition higher than 90% were further evaluated, and they displayed IC50 values between 0.2 and 4.5 µM making them a lot less potent than the reference drug mefloquine (IC50 = 0.04 µM). These compounds were also not selective toward the parasite with selectivity indices between 0.03 and 0.7, which implies they are very cytotoxic.[174](#_ENREF_253)



Figure 46

The acridine skeleton possesses antiplasmodial activity175 and was therefore used as active moiety in the synthesis of hybrid structures.[176](#_ENREF_46) Acridine attached to quinoline with ethylene- and propylene-functionalized piperazine afforded hybrids **95** (Figure 47), while linkage *via* *meta*- or *para*-phenylenediamine resulted in conjugates **96** (Figure 47). These quinoline-acridine derivatives **95** and **96** were *in vitro* evaluated for their antimalarial activity against a CQS (NF54) strain of *P. falciparum*. Hybrids **95** and **96** displayed MIC values between 0.25 and 1 µg/mL, which were higher than CQ (MIC = 0.125 µg/mL). Compound **96b** was also tested *in vivo* against a CQR N67 strain of *P. yoelii* in Swiss mice and showed complete clearance of parasitemia on day 4 at doses of 50 mg/kg per day, but none of the mice survived beyond day 28.[176](#_ENREF_46)



Figure 47

4-Aminoquinolines carrying a single aromatic ring in the side chain have been proven to be considerably more active if they contain a hydrogen bond acceptor close to a basic nitrogen, which is the case in *e.g.* amodiaquine and isoquine. The recurrence of this hydrogen bonding motif and its importance for antiplasmodial activity inspired Gemma *et al.* to mimic this effect by means of the methylene spacer present in benzoxazines, quinazolines or febrifugine-based 1,3-quinozolin-4-ones.177 Benzoxazines or quinazolines linked to aminoquinolines afforded hybrids **97** (Figure 48), while the combination of aminoquinolines and febrifugine derivatives resulted in hybrids **98** (Figure 48). The antiplasmodial activities of conjugates **97** and **98** were determined *in vitro* against human red blood cells infected with either a CQS D10 or a CQR W2 strain of *P. falciparum*. Benzoxazine hybrids **97a−c** possessed excellent *in vitro* antiplasmodial activities (21-72 nM) but were unstable in acidic conditions. This aspect was addressed in a series of quinazoline hybrids **97a’-c’** which retained potent antimalarial activity, were chemically stable, and displayed significant oral *in vivo* activity against malaria-infected mice. Hybrids **98a-d** displayed poor activity against the tested *P. falciparum* strains (IC50>1000 nM); these low potencies were attributed to poor accumulation of the compounds in the digestive vacuole. However, addition of an extra protonatable moiety (compound **98e**) restored antimalarial activity against both *P. falciparum* strains (31-82 nM). Quinazoline hybrid **97c’** appeared to be the most promising analogue within this series and, in addition to its potency *in vivo* (EC50 = 15.7 mg/kg), compound **97c’** exhibited little or no *in vitro* cytotoxicity or mutagenicity.177



Figure 48

* + 1. Hybrids of quinolines and anticancer agents

Thiopurines, like 6-mercaptopurines, are cytotoxic prodrugs that hinder nucleic acid synthesis by inhibiting enzymes involved in the *de novo* purine synthetic pathway,[178](#_ENREF_231) and they are often used in cancer treatment and as immunosupressors.179-180 Conjugation of the sodium salt of 6-mercaptopurine with (7-chloroquinolin-4-ylamino)alkyl methanesulfonate afforded hybrids **99** and **100** (Figure 49), which were evaluated *in vivo* against *P. berghei* in a murine malaria model to determine their antiplasmodial efficacy. Compound **99** displayed the best antimalarial profile, after 7 days there was more than 70% inhibition of parasite multiplication (when using doses of 5 mg/kg/day for 4 days). Cytotoxicity evaluation was also performed in an *in vitro* peritoneal macrophage model and none of the tested compounds displayed toxicity for mammalian cells at the maximum concentration tested (100 µg/mL).[181](#_ENREF_234)



Figure 49

Paclitaxel (Taxol) is an antimicrotubular drug[182](#_ENREF_237) that also displays potential antiplasmodial efficacy,[183](#_ENREF_238) and consists of two structural moieties, (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine and baccatin III, thus it can be considered a hybrid molecule. It has been proven that both structural components are essential for the antimicrotubular potency, since individually they are devoid of any activity.[184](#_ENREF_239) As these structural nuclei act synergistically in Taxol, they suggest themselves as potential templates for the design of novel biologically active hybrid entities. In a study of Njogu *et al*., a (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine moiety has been coupled to a quinoline scaffold via ester, amide or triazole linkers, affording hybrid compounds **101** and **102** (Figure 50). All conjugates were evaluated *in vitro* for efficacy against two CQR (K1 and W2) strains of *P. falciparum*. Compounds **97** displayed IC50 values between 0.22 -1.00 µM against the K1 strain and between 0.13 and 0.56 µM against the W2 strain, while IC50 values of compounds **102** ranged from 0.39 to 3.24 µM and from 0.28 to 2.71 µM against K1 and W2, respectively. Hybrids **101c** and **101d** were the most potent against W2 (IC50 = 0.13 and 0.16 µM, respectively), but were still less active than CQ (IC50 = 0.05 µM). These results suggested that the inherent antimalarial activity of the 4-amino-7-chloroquinoline was retained, but hybridization with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine did not improve antimalarial potency as anticipated.[185](#_ENREF_240)



Figure 50

* + 1. Hybrids of quinolines and anti-HIV agents

Finally, reports have indicated that malaria and HIV co-infection may work synergistically in regions where they co-exist.[186-189](#_ENREF_241) The concept of hybrid drugs has led to the development of hybrid antimalarial and hybrid anti-HIV drugs, but a novel, interesting approach from the Chibale group consisted of the design of dual molecules targeting HIV and *P. falciparum* simultaneously. Therefore, hybrid molecules that incorporate derivatives of clinically approved antimalarial drugs (*e.g.* CQ) and anti-HIV drugs (azidothymidine) have been designed. 4-Aminoquinoline-based intermediates were reacted with silylated azidothymidine intermediates and afforded conjugates **103** and **104** (Figure 51). Quinoline-based hybrids **105** and **106** (Figure 51) were obtained by substitution with appropriate 4-aminoquinolines at the N-3 position of azidothymidine. This series of obtained compounds was evaluated for their inhibitory activity against CQS (3D7) and CQR (Dd2) strains of *P. falciparum* and were screened for cytotoxicity against HeLa cells at various concentrations (1-50 µM). Eleven of the hybrids displayed IC50 values in nanomolar range against both *Plasmodium* strains, while compounds **103a**, **103d** and **103d** showed significant reduction in the growth of HeLa cells. Compounds **103d** and **104d** appeared to be the most active (IC50 = 80 nM) against the resistant strain and they were 7- to 8-fold more potent than CQ (IC50 = 710 nM). Since the hybrids also exhibited moderate to strong inhibition of HIV-1 this study proved that the concept of using molecular hybrid molecules to inhibit two non-related organisms could find applications in the treatment of HIV/malaria co-infections.[190](#_ENREF_245)



Figure 51

1. Conclusions

The extent of this literature review demonstrates the high interest of organic and medicinal chemists in the field of quinoline hybrid formation. Hybridization of chemical entities has proven to be an extremely potent method to introduce structural diversity, which can result in molecules displaying less drug resistance, improved biological activities, improved safety, *etc*. In this review, some of the reported quinoline-containing chimeras exhibited excellent antiplasmodial potential against both sensitive and resistant *Plasmodium* species *in vitro* as well as *in vivo*, and displayed no cytotoxicity. This evinces that quinoline hybrid formation is a valuable approach in the development of novel antimalarial (lead) compounds. However, careful justification of the hybridization partners is essential, and the advantage(s) of the hybrid over the separate pharmacophores or their 1:1 combination should be verified as well to demonstrate the added value of the hybridization concept.

**Acknowledgements**

The authors are indebted to Ghent University (BOF) for financial support.

References

1. WHO. *WHO malaria Report* **2013**.

2. Brabin, B. J. *Bulletin of the World Health Organization* **1983,** *61*, 1005.

3. Menendez, C. *Parasitol. Today* **1995,** *11*, 178.

4. Flateau, C.; Le Loup, G.; Pialoux, G. *Lancet Infect. Dis.* **2011,** *11*, 541.

5. Baird, J. K. *Trends Parasitol.* **2007,** *23*, 533.

6. Schlitzer, M. *Arch. Pharm.* **2008,** *341*, 149.

7. Builders, M. I. *Int. J. Pharm.* **2013,** *3*, 40.

8. Biamonte, M. A.; Wanner, J.; Le Roch, K. G. *Bioorg. Med. Chem. Lett.* **2013,** *23*, 2829.

9. Klein, E. Y. *Int. J. Antimicrob. Ag.* **2013,** *41*, 311.

10. Muregi, F. W.; Kirira, P. G.; Ishih, A. *Curr. Med. Chem.* **2011,** *18*, 113.

11. Walsh, J. J.; Bell, A. *Curr. Pharm. Des.* **2009,** *15*, 2970.

12. Muregi, F. W.; Ishih, A. *Drug Dev. Res.* **2010,** *71*, 20.

13. Meunier, B. In *Polypharmacology in Drug Discovery;* Peters, J.-U., Ed.; John Wiley & Sons, Inc., 2012, 423.

14. Kouznetsov, V. V.; Gomez-Barrio, A. *Eur. J. Med. Chem.* **2009,** *44*, 3091.

15. Njogu, P. M.; Chibale, K. *Curr. Med. Chem.* **2013,** *20*, 1715.

16. Walsh, J. J.; Coughlana, D.; Heneghan, N.; Gaynor, C.; Bell, A. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 3599.

17. Lombard, M. C.; N'Da, D. D.; Breytenbach, J. C.; Smith, P. J.; Lategan, C. A. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 1683.

18. N'Da, D. D.; Breytenbach, J. C. *S. Afr. J. Chem.-S-Afr. T.* **2011,** *64*, 163.

19. Lombard, M. C.; N'Da, D. D.; Ba, C. T. V.; Wein, S.; Norman, J.; Wiesner, L.; Vial, H. *Malaria J.* **2013,** *12*.

20. Capela, R.; Cabal, G. G.; Rosenthal, P. J.; Gut, J.; Mota, M. M.; Moreira, R.; Lopes, F.; Prudencio, M. *Antimicrob. Agents Chemother.* **2011,** *55*, 4698.

21. Feng, T. S.; Guantai, E. M.; Nell, M.; van Rensburg, C. E.; Ncokazi, K.; Egan, T. J.; Hoppe, H. C.; Chibale, K. *Biochem. Pharmacol.* **2011,** *82*, 236.

22. Lombard, M. C.; N'Da, D. D.; Breytenbach, J. C.; Smith, P. J.; Lategan, C. A. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 6975.

23. Lombard, M. C.; N'Da, D. D.; Breytenbach, J. C.; Kolesnikova, N. I.; Van Ba, C. T.; Wein, S.; Norman, J.; Denti, P.; Vial, H.; Wiesner, L. *Eur. J. Pharm. Sci.* **2012,** *47*, 834.

24. Araujo, N. C. P.; Barton, V.; Jones, M.; Stocks, P. A.; Ward, S. A.; Davies, J.; Bray, P. G.; Shone, A. E.; Cristiano, M. L. S.; O'Neill, P. M. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 2038.

25. Abiodun, O. O.; Brun, R.; Wittlin, S. *Malaria J.* **2013,** *12*.

26. Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y. X.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Tomas, J. S.; Scheurer, C.; Scorneaux, B.; Tang, Y. Q.; Urwyler, H.; Wittlin, S.; Charman, W. N. *Nature* **2004,** *430*, 900.

27. Perry, C. S.; Charman, S. A.; Prankerd, R. J.; Chiu, F. C.; Dong, Y. X.; Vennerstrom, J. L.; Charman, W. N. *J. Pharm. Sci.* **2006,** *95*, 737.

28. O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004,** *47*, 2945.

29. Jefford, C. W. *Drug Disc. Today* **2007,** *12*, 487.

30. Biagini, G. A.; O'Neill, P. M.; Nzila, A.; Ward, S. A.; Bray, P. G. *Trends Parasitol.* **2003,** *19*, 479.

31. Vangapandu, S.; Jain, M.; Kaur, K.; Patil, P.; Patel, S. R.; Jain, R. *Med. Res. Rev.* **2007,** *27*, 65.

32. Sabbani, S.; Stocks, P. A.; Ellis, G. L.; Davies, J.; Hedenstrom, E.; Ward, S. A.; O'Neill, P. M. *Bioorg. Med. Chem. Lett.* **2008,** *18*, 5804.

33. Dechy-Cabaret, O.; Benoit-Vical, F.; Robert, A.; Meunier, B. *Chembiochem* **2000,** *1*, 281.

34. Bellot, F.; Cosledan, F.; Vendier, L.; Brocard, J.; Meunier, B.; Robert, A. *J. Med. Chem.* **2010,** *53*, 4103.

35. Miranda, D.; Capela, R.; Albuquerque, I. S.; Meireles, P.; Paiva, I.; Nogueira, F.; Amewu, R.; Gut, J.; Rosenthal, P. J.; Oliveira, R.; Mota, M. M.; Moreira, R.; Marti, F.; Prudencio, M.; O'Neill, P. M.; Lopes, F. *Med. Chem. Lett.* **2014,** *5*, 108.

36. Fidock, D. A.; Nomura, T.; Talley, A. K.; Cooper, R. A.; Dzekunov, S. M.; Ferdig, M. T.; Ursos, L. M. B.; Sidhu, A. B. S.; Naude, B.; Deitsch, K. W.; Su, X. Z.; Wootton, J. C.; Roepe, P. D.; Wellems, T. E. *Mol. Cell* **2000,** *6*, 861.

37. Sidhu, A. B. S.; Verdier-Pinard, D.; Fidock, D. A. *Science* **2002,** *298*, 210.

38. Krogstad, D. J.; Gluzman, I. Y.; Kyle, D. E.; Oduola, A. M. J.; Martin, S. K.; Milhous, W. K.; Schlesinger, P. H. *Science* **1987,** *238*, 1283.

39. Martin, S. K.; Oduola, A. M. J.; Milhous, W. K. *Science* **1987,** *235*, 899.

40. van Schalkwyk, D. A.; Egan, T. J. *Drug Resist. Update.* **2006,** *9*, 211.

41. Guantai, E.; Chibale, K. *Curr. Drug Deliv.* **2010,** *7*, 312.

42. Peyton, D. H. *Curr. Top. Med. Chem.* **2012,** *12*, 400.

43. Egan, T. J.; Kuter, D. *Future Microbiol.* **2013,** *8*, 475.

44. Burgess, S. J.; Selzer, A.; Kelly, J. X.; Smilkstein, M. J.; Riscoe, M. K.; Peyton, D. H. *J. Med. Chem.* **2006,** *49*, 5623.

45. Andrews, S.; Burgess, S. J.; Skaalrud, D.; Kelly, J. X.; Peyton, D. H. *J. Med. Chem.* **2010,** *53*, 916.

46. Burgess, S. J.; Kelly, J. X.; Shomloo, S.; Wittlin, S.; Brun, R.; Liebmann, K.; Peyton, D. H. *J. Med. Chem.* **2010,** *53*, 6477.

47. Musonda, C. C.; Whitlock, G. A.; Witty, M. J.; Brun, R.; Kaiser, M. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 481.

48. Ginsburg, H.; Famin, O.; Zhang, J. M.; Krugliak, M. *Biochem. Pharmacol.* **1998,** *56*, 1305.

49. Chavain, N.; Davioud-Charvet, E.; Trivelli, X.; Mbeki, L.; Rottmann, M.; Brun, R.; Biot, C. *Bioorg. Med. Chem.* **2009,** *17*, 8048.

50. Zishiri, V. K.; Joshi, M. C.; Hunter, R.; Chibale, K.; Smith, P. J.; Summers, R. L.; Martin, R. E.; Egan, T. J. *J. Med. Chem.* **2011,** *54*, 6956.

51. Gemma, S.; Camodeca, C.; Coccone, S. S.; Joshi, B. P.; Bernetti, M.; Moretti, V.; Brogi, S.; de Marcos, M. C. B.; Savini, L.; Taramelli, D.; Basilico, N.; Parapini, S.; Rottmann, M.; Brun, R.; Lamponi, S.; Caccia, S.; Guiso, G.; Summers, R. L.; Martin, R. E.; Saponara, S.; Gorelli, B.; Novellino, E.; Campiani, G.; Butini, S. *J. Med. Chem.* **2012,** *55*, 6948.

52. Gemma, S.; Campiani, G.; Butini, S.; Kukreja, G.; Coccone, S. S.; Joshi, B. P.; Persico, M.; Nacci, V.; Fiorini, I.; Novellino, E.; Fattorusso, E.; Taglialatela-Scafati, O.; Savini, L.; Taramelli, D.; Basilico, N.; Parapini, S.; Morace, G.; Yardley, V.; Croft, S.; Coletta, M.; Marini, S.; Fattorusso, C. *J. Med. Chem.* **2008,** *51*, 1278.

53. Gemma, S.; Campiani, G.; Butini, S.; Joshi, B. P.; Kukreja, G.; Coccone, S. S.; Bernetti, M.; Persico, M.; Nacci, V.; Fiorini, I.; Novellino, E.; Taramelli, D.; Basilico, N.; Parapini, S.; Yardley, V.; Croft, S.; Keller-Maerki, S.; Rottmann, M.; Brun, R.; Coletta, M.; Marini, S.; Guiso, G.; Caccia, S.; Fattorusso, C. *J. Med. Chem.* **2009,** *52*, 502.

54. Hong, Y. L.; Hossler, P. A.; Calhoun, D. H.; Meshnick, S. R. *Antimicrob. Agents Chemother.* **1995,** *39*, 1756.

55. Hitching, G. H. *J. Infect. Dis.* **1973,** *128*, S433.

56. Boison, J. O.; Nachilobe, P.; Cassidy, R.; Keng, L.; Thacker, P. A.; Peacock, A.; Fesser, A. C.; Lee, S.; Korsrud, G. O.; Bulmer, W. S. *Can. J. Vet. Res.* **1996,** *60*, 281.

57. Salahuddin, A.; Inam, A.; van Zyl, R. L.; Heslop, D. C.; Chen, C. T.; Avecilla, F.; Agarwal, S. M.; Azam, A. *Bioorg. Med. Chem.* **2013,** *21*, 3080.

58. Summers, R. L.; Nash, M. N.; Martin, R. E. *Cellular and Molecular Life Sciences* **2012,** *69*, 1967.

59. Martin, R. E.; Marchetti, R. V.; Cowan, A. I.; Howitt, S. M.; Broer, S.; Kirk, K. *Science* **2009,** *325*, 1680.

60. Hrycyna, C. A.; Summers, R. L.; Lehane, A. M.; Pires, M. M.; Namanja, H.; Bohn, K.; Kuriakose, J.; Ferdig, M.; Henrich, P. P.; Fidock, D. A.; Kirk, K.; Chmielewski, J.; Martin, R. E. *Chem. Biol.* **2014,** *9*, 722.

61. Lopez, S. N.; Castelli, M. V.; Zacchino, S. A.; Dominguez, J. N.; Lobo, G.; Charris-Charris, J.; Cortes, J. C. G.; Ribas, J. C.; Devia, C.; Rodriguez, A. M.; Enriz, R. D. *Bioorg. Med. Chem.* **2001,** *9*, 1999.

62. Konieczny, M. T.; Horowska, B.; Kunikowski, A.; Konopa, J.; Wierzba, K.; Yamada, Y.; Asao, T. *Synthesis*  **2001**, 1363.

63. Go, M. L.; Wu, X.; Liu, X. L. *Curr. Med. Chem.* **2005,** *12*, 483.

64. Barfod, L.; Kemp, K.; Hansen, M.; Kharazmi, A. *Int. Immunopharmacol.* **2002,** *2*, 545.

65. Tomar, V.; Bhattacharjee, G.; Kamaluddin; Rajakumar, S.; Srivastava, K.; Puri, S. K. *Eur. J. Med. Chem.* **2010,** *45*, 745.

66. Ducki, S.; Forrest, R.; Hadfield, J. A.; Kendall, A.; Lawrence, N. J.; McGown, A. T.; Rennison, D. *Bioorg. Med. Chem. Lett.* **1998,** *8*, 1051.

67. Parmar, V. S.; Sharma, N. K.; Husain, M.; Watterson, A. C.; Kumar, J.; Samuelson, L. A.; Cholli, A. L.; Prasad, A. K.; Kumar, A.; Malhotra, S.; Kumar, N.; Jha, A.; Singh, A.; Singh, I.; Himanshu; Vats, A.; Shakil, N. A.; Trikha, S.; Mukherjee, S.; Sharma, S. K.; Singh, S. K.; Kumar, A.; Jha, H. N.; Olsen, C. E.; Stove, C. P.; Bracke, M. E.; Mareel, M. M. *Bioorg. Med. Chem.* **2003,** *11*, 913.

68. Mukherjee, S.; Kumar, W.; Prasad, A. K.; Raj, H. G.; Bracke, M. E.; Olsen, C. E.; Jain, S. C.; Parmar, V. S. *Bioorg. Med. Chem.* **2001,** *9*, 337.

69. Ko, H. H.; Tsao, L. T.; Yu, K. L.; Liu, C. T.; Wang, J. P.; Lin, C. N. *Bioorg. Med. Chem.* **2003,** *11*, 105.

70. Hsieh, H. K.; Lee, T. H.; Wang, J. P.; Wang, J. J.; Lin, C. N. *Pharm. Res.* **1998,** *15*, 39.

71. Hsieh, H. K.; Tsao, L. T.; Wang, J. P.; Lin, C. N. *J. Pharm. Pharmacol.* **2000,** *52*, 163.

72. Herencia, F.; Ferrandiz, M. L.; Ubeda, A.; Dominguez, J. N.; Charris, J. E.; Lobo, G. M.; Alcaraz, M. J. *Bioorg. Med. Chem. Lett.* **1998,** *8*, 1169.

73. Gutteridge, C. E.; Nichols, D. A.; Curtis, S. M.; Thota, D. S.; Vo, J. V.; Gerena, L.; Montip, G.; Asher, C. O.; Diaz, D. S.; DiTusa, C. A.; Smith, K. S.; Bhattacharjee, A. K. *Bioorg. Med. Chem. Lett.* **2006,** *16*, 5682.

74. Liu, M.; Wilairat, P.; Go, M. L. *J. Med. Chem.* **2001,** *44*, 4443.

75. Dominguez, J. N.; Charris, J. E.; Lobo, G.; de Dominguez, N. G.; Moreno, M. M.; Riggione, F.; Sanchez, E.; Olson, J.; Rosenthal, P. J. *Eur. J. Med. Chem.* **2001,** *36*, 555.

76. Go, M. L.; Liu, M.; Wilairat, P.; Rosenthal, P. J.; Saliba, K. J.; Kirk, K. *Antimicrob. Agents Chemother.* **2004,** *48*, 3241.

77. Ziegler, H. L.; Hansen, H. S.; Staerk, D.; Christensen, S. B.; Hagerstrand, H.; Jaroszewski, J. W. *Antimicrob. Agents Chemother.* **2004,** *48*, 4067.

78. Chen, M.; Theander, T. G.; Christensen, S. B.; Hviid, L.; Zhai, L.; Kharazmi, A. *Antimicrob. Agents Chemother.* **1994,** *38*, 1470.

79. Sharma, M.; Chaturvedi, V.; Manju, Y. K.; Bhatnagar, S.; Srivastava, K.; Puri, S. K.; Chauhan, P. M. S. *Eur. J. Med. Chem.* **2009,** *44*, 2081.

80. Ferrer, R.; Lobo, G.; Gamboa, N.; Rodrigues, J.; Abramjuk, C.; Jung, K.; Lein, M.; Charris, J. E. *Sci. Pharm.* **2009,** *77*, 725.

81. Guantai, E. M.; Ncokazi, K.; Egan, T. J.; Gut, J.; Rosenthal, P. J.; Smith, P. J.; Chibale, K. *Bioorg. Med. Chem.* **2010,** *18*, 8243.

82. Sashidhara, K. V.; Kumar, M.; Modukuri, R. K.; Srivastava, R. K.; Soni, A.; Srivastava, K.; Singh, S. V.; Saxena, J. K.; Gauniyal, H. M.; Puri, S. K. *Bioorg. Med. Chem.* **2012,** *20*, 2971.

83. Sashidhara, K. V.; Avula, S. R.; Palnati, G. R.; Singh, S. V.; Srivastava, K.; Puri, S. K.; Saxena, J. K. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 5455.

84. Smit, F. J.; N'Da, D. D. *Bioorg. Med. Chem.* **2014,** *22*, 1128.

85. Wright, A. J. *Mayo Clin. Proc.* **1999,** *74*, 290.

86. Konaklieva, M. I. *Curr. Med. Chem. - Anti-Infecti. Ag.* **2002,** *1*, 215.

87. Cainelli, G.; Galletti, P.; Garbisa, S.; Giacomini, D.; Sartor, L.; Quintavalla, A. *Bioorg. Med. Chem.* **2003,** *11*, 5391.

88. Kazi, A.; Hill, R.; Long, T. E.; Kuhn, D. J.; Turos, E.; Dou, Q. P. *Biochem. Pharmacol.* **2004,** *67*, 365.

89. Slusarchyk, W. A.; Bolton, S. A.; Hartl, K. S.; Huang, M. H.; Jacobs, G.; Meng, W.; Ogletree, M. L.; Pi, Z. L.; Schumacher, W. A.; Seiler, S. M.; Sutton, J. C.; Treuner, U.; Zahler, R.; Zhao, G. H.; Bisacchi, G. S. *Bioorg. Med. Chem. Lett.* **2002,** *12*, 3235.

90. Guillon, C. D.; Koppel, G. A.; Brownstein, M. J.; Chaney, M. O.; Ferris, C. F.; Lu, S. F.; Fabio, K. M.; Miller, M. J.; Heindel, N. D.; Hunden, D. C.; Cooper, R. D. G.; Kaldor, S. W.; Skelton, J. J.; Dressman, B. A.; Clay, M. P.; Steinberg, M. I.; Bruns, R. F.; Simon, N. G. *Bioorg. Med. Chem.* **2007,** *15*, 2054.

91. Dubey, A.; Srivastava, S. K.; Srivastava, S. D. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 569.

92. Nivsarkar, M.; Thavaselvam, D.; Prasanna, S.; Sharma, M.; Kaushik, M. P. *Bioorg. Med. Chem. Lett.* **2005,** *15*, 1371.

93. Nay, B.; Riache, N.; Evanno, L. *Nat. Prod. Rep.* **2009,** *26*, 1044.

94. Osterhage, C.; Kaminsky, R.; Konig, G. M.; Wright, A. D. *J. Org. Chem.* **2000,** *65*, 6412.

95. Kontnik, R.; Clardy, J. *Org. Lett.* **2008,** *10*, 4149.

96. Singh, P.; Singh, P.; Kumar, M.; Gut, J.; Rosenthal, P. J.; Kumar, K.; Kumar, V.; Mahajan, M. P.; Bisetty, K. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 57.

97. Raj, R.; Biot, C.; Carrere-Kremer, S.; Kremer, L.; Guerardel, Y.; Gut, J.; Rosenthal, P. J.; Kumar, V. *Chem. Biol. Drug Des.* **2014,** *83*, 191.

98. Madapa, S.; Tusi, Z.; Sridhar, D.; Kumar, A.; Siddiqi, M. I.; Srivastava, K.; Rizvi, A.; Tripathi, R.; Puri, S. K.; Keshava, G. B. S.; Shukla, P. K.; Batra, S. *Bioorg. Med. Chem.* **2009,** *17*, 203.

99. Zhang, Y. Q.; Anderson, M.; Weisman, J. L.; Lu, M.; Choy, C. J.; Boyd, V. A.; Price, J.; Sigal, M.; Clark, J.; Connelly, M.; Zhu, F. Y.; Guiguemde, W. A.; Jeffries, C.; Yang, L.; Lemoff, A.; Liou, A. P.; Webb, T. R.; DeRisi, J. L.; Guy, R. K. *Med. Chem. Lett.* **2010,** *1*, 460.

100. Sunduru, N.; Srivastava, K.; Rajakumar, S.; Puri, S. K.; Saxena, J. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 2570.

101. Jiang, S. P.; Prigge, S. T.; Wei, L.; Gao, Y. E.; Hudson, T. H.; Gerena, L.; Dame, J. B.; Kyle, D. E. *Antimicrob. Agents Chemother.* **2001,** *45*, 2577.

102. Armelin, E.; Aleman, C.; Puiggali, J. *J. Org. Chem.* **2001,** *66*, 8076.

103. Singh, P.; Raj, R.; Singh, P.; Gut, J.; Rosenthal, P. J.; Kumar, V. *Eur. J. Med. Chem.* **2014,** *71*, 128.

104. Cornut, D.; Lemoine, H.; Kanishchev, O.; Okada, E.; Albrieux, F.; Beavogui, A. H.; Bienvenu, A. L.; Picot, S.; Bouillon, J. P.; Medebielle, M. *J. Med. Chem.* **2013,** *56*, 73.

105. Narasimhan, B.; Belsare, D.; Pharande, D.; Mourya, V.; Dhake, A. *Eur. J. Med. Chem.* **2004,** *39*, 827.

106. Sova, M. *Mini-Rev. Med. Chem.* **2012,** *12*, 749.

107. Wiesner, J.; Mitsch, A.; Wissner, P.; Jomaa, H.; Schlitzer, M. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 423.

108. Perez, B. C.; Teixeira, C.; Figueiras, M.; Gut, J.; Rosenthal, P. J.; Gomes, J. R. B.; Gomes, P. *Eur. J. Med. Chem.* **2012,** *54*, 887.

109. Perez, B. C.; Teixeira, C.; Albuquerque, I. S.; Gut, J.; Rosenthal, P. J.; Gomes, J. R. B.; Prudencio, M.; Gomes, P. *J. Med. Chem.* **2013,** *56*, 556.

110. Phillips, D. M. *Biochem. J.* **1963,** *87*, 258.

111. Allfrey, V. G.; Faulkner, R.; Mirsky, A. E. *P. Natl. Acad. Sci. USA* **1964,** *51*, 786.

112. Gershey, E. L.; Vidali, G.; Allfrey, V. G. *J. Biol. Chem.* **1968,** *243*, 5018.

113. Van Lint, C.; Emiliani, S.; Verdin, E. *Gene Expression* **1996,** *5*, 245.

114. Mitsiades, C. S.; Mitsiades, N. S.; McMullan, C. J.; Poulaki, V.; Shringarpure, R.; Hideshima, T.; Akiyama, M.; Chauhan, D.; Munshi, N.; Gu, X. S.; Bailey, C.; Joseph, M.; Libermann, T. A.; Richon, V. M.; Marks, P. A.; Anderson, K. C. *P. Natl. Acad. Sci. USA* **2004,** *101*, 540.

115. Gallinari, P.; Di Marco, S.; Jones, P.; Pallaoro, M.; Steinkuhler, C. *Cell Res.* **2007,** *17*, 195.

116. Rasheed, W. K.; Johnstone, R. W.; Prince, H. M. *Exp. Opin. Invest. Drugs* **2007,** *16*, 659.

117. Darkin-Rattray, S. J.; Gurnett, A. M.; Myers, R. W.; Dulski, P. M.; Crumley, T. M.; Allocco, J. J.; Cannova, C.; Meinke, P. T.; Colletti, S. L.; Bednarek, M. A.; Singh, S. B.; Goetz, M. A.; Dombrowski, A. W.; Polishook, J. D.; Schmatz, D. M. *P. Natl. Acad. Sci. USA* **1996,** *93*, 13143.

118. Rodriquez, M.; Aquino, M.; Bruno, I.; De Martino, G.; Taddei, M.; Gomez-Paloma, L. *Curr. Med. Chem.* **2006,** *13*, 1119.

119. Andrews, K. T.; Tran, T. N.; Wheatley, N. C.; Fairlie, D. P. *Curr. Top. Med. Chem.* **2009,** *9*, 292.

120. Andrews, K. T.; Tran, T. N.; Fairlie, D. P. *Curr. Pharm. Des.* **2012,** *18*, 3467.

121. Kopf-Maier, P.; Kopf, H.; Neuse, E. W. *J. Cancer Res. Clin. Oncol.* **1984,** *108*, 336.

122. Hottin, A.; Dubar, F.; Steenackers, A.; Delannoy, P.; Biot, C.; Behr, J. B. *Org. Biomol. Chem.* **2012,** *10*, 5592.

123. Lal, B.; Badshah, A.; Altaf, A. A.; Tahir, M. N.; Ullah, S.; Huq, F. *Dalton T.* **2012,** *41*, 14643.

124. Zhou, B. B.; Li, J.; Feng, B. J.; Ouyang, Y.; Liu, Y. N.; Zhou, F. M. *J. Inorg. Biochem.* **2012,** *116*, 19.

125. Mahajan, A.; Kremer, L.; Louw, S.; Gueradel, Y.; Chibale, K.; Biot, C. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 2866.

126. Kumar, K.; Singh, P.; Kremer, L.; Guerardel, Y.; Biot, C.; Kumar, V. *Dalton T.* **2012,** *41*, 5778.

127. Kumar, K.; Carrere-Kremer, S.; Kremer, L.; Guerardel, Y.; Biot, C.; Kumar, V. *Dalton T.* **2013,** *42*, 1492.

128. Quirante, J.; Dubar, F.; Gonzalez, A.; Lopez, C.; Cascante, M.; Cortes, R.; Forfar, I.; Pradines, B.; Biot, C. *J. Organomet. Chem.* **2011,** *696*, 1011.

129. Dubar, F.; Egan, T. J.; Pradines, B.; Kuter, D.; Ncokazi, K. K.; Forge, D.; Paul, J. F.; Pierrot, C.; Kalamou, H.; Khalife, J.; Buisine, E.; Rogier, C.; Vezin, H.; Forfar, I.; Slomianny, C.; Trivelli, X.; Kapishnikov, S.; Leiserowitz, L.; Dive, D.; Biot, C. *Chem. Biol.* **2011,** *6*, 275.

130. Biot, C.; Nosten, F.; Fraisse, L.; Ter-Minassian, D.; Khalife, J.; Dive, D. *Parasite* **2011,** *18*, 207.

131. Roux, C.; Biot, C. *Future Med. Chem.* **2012,** *4*, 783.

132. N'Da, D. D.; Smith, P. J. *Med. Chem. Res.* **2014,** *23*, 1214.

133. Takasu, K.; Inoue, H.; Kim, H. S.; Suzuki, M.; Shishido, T.; Wataya, Y.; Ihara, M. *J. Med. Chem.* **2002,** *45*, 995.

134. Habib, N. S.; Rida, S. M.; Badawey, E. A. M.; Fahmy, H. T. Y.; Ghozlan, H. A. *Eur. J. Med. Chem.* **1997,** *32*, 759.

135. Song, M. X.; Zheng, C. J.; Deng, X. Q.; Wang, Q.; Hou, S. P.; Liu, T. T.; Xing, X. L.; Piao, H. R. *Eur. J. Med. Chem.* **2012,** *54*, 403.

136. Sing, W. T.; Lee, C. L.; Yeo, S. L.; Lim, S. P.; Sim, M. M. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 91.

137. Sortino, M.; Delgado, P.; Juarez, S.; Quiroga, J.; Abonia, R.; Insuasty, B.; Nogueras, M.; Rodero, L.; Garibotto, F. M.; Enriz, R. D.; Zacchino, S. A. *Bioorg. Med. Chem.* **2007,** *15*, 484.

138. Chauhan, K.; Sharma, M.; Saxena, J.; Singh, S. V.; Trivedi, P.; Srivastava, K.; Puri, S. K.; Saxena, J. K.; Chaturvedi, V.; Chauhan, P. M. S. *Eur. J. Med. Chem.* **2013,** *62*, 693.

139. Dobbin, P. S.; Hider, R. C.; Hall, A. D.; Taylor, P. D.; Sarpong, P.; Porter, J. B.; Xiao, G. Y.; Vanderhelm, D. *J. Med. Chem.* **1993,** *36*, 2448.

140. Andayi, W. A.; Egan, T. J.; Gut, J.; Rosenthal, P. J.; Chibale, K. *Med. Chem. Lett.* **2013,** *4*, 77.

141. Weinberg, E. D.; Moon, J. *Drug Metab. Rev.* **2009,** *41*, 644.

142. Barrett, J. F. R.; Whittaker, P. G.; Williams, J. G.; Lind, T. *Brit. Med. J.* **1994,** *309*, 79.

143. Berger, J.; Dyck, J. L.; Galan, P.; Aplogan, A.; Schneider, D.; Traissac, P.; Hercberg, S. *Eur. J. Clin. Nutr.* **2000,** *54*, 29.

144. Murray, M. J.; Murray, A. B.; Murray, M. B.; Murray, C. J. *Brit. Med. J.* **1978,** *2*, 1113.

145. Andayi, W. A.; Egan, T. J.; Chibale, K. *Bioorg. Med. Chem. Lett.* **2014,** *24*, 3263.

146. Vine, K. L.; Matesic, L.; Locke, J. M.; Ranson, M.; Skropeta, D. *Anti-Cancer Ag. Med. Chem.* **2009,** *9*, 397.

147. Raj, R.; Singh, P.; Singh, P.; Gut, J.; Rosenthal, P. J.; Kumar, V. *Eur. J. Med. Chem.* **2013,** *62*, 590.

148. Surolia, N.; Surolia, A. *Nature Med.* **2001,** *7*, 167.

149. Rao, S. P. R.; Surolia, A.; Surolia, N. *Mol. Cell. Biochem.* **2003,** *253*, 55.

150. Mishra, A.; Batchu, H.; Srivastava, K.; Singh, P.; Shukla, P. K.; Batra, S. *Bioorg. Med. Chem. Lett.* **2014,** *24*, 1719.

151. Gingras, B. A.; Jensen, J. B. *Am. J. Trop. Med. Hyg.* **1992,** *47*, 378.

152. Gingras, B. A.; Jensen, J. B. *Am. J. Trop. Med. Hyg.* **1993,** *49*, 101.

153. Andersen, S. L.; Ager, A. L.; Mcgreevy, P.; Schuster, B. G.; Ellis, W.; Berman, J. *Antimicrob. Agents Chemother.* **1994,** *38*, 1862.

154. Starcevic, K.; Pesic, D.; Toplak, A.; Landek, G.; Alihodzic, S.; Herreros, E.; Ferrer, S.; Spaventi, R.; Peric, M. *Eur. J. Med. Chem.* **2012,** *49*, 365.

155. Liu, H.; Mulholland, S. G. *Am. J. Med.* **2005,** *118*, 14.

156. Divo, A. A.; Sartorelli, A. C.; Patton, C. L.; Bia, F. J. *Antimicrob. Agents Chemother.* **1988,** *32*, 1182.

157. Yeo, A. E. T.; Rieckmann, K. H. *J. Parasitology* **1994,** *80*, 158.

158. Pradines, B.; Rogier, C.; Fusai, T.; Mosnier, J.; Daries, W.; Barret, E.; Parzy, D. *Antimicrob. Agents Chemother.* **2001,** *45*, 1746.

159. Panda, S. S.; Bajaj, K.; Meyers, M. J.; Sverdrup, F. M.; Katritzky, A. R. *Org. Biomol. Chem.* **2012,** *10*, 8985.

160. Rodrigues, T.; Prudencio, M.; Moreira, R.; Mota, M. M.; Lopes, F. *J. Med. Chem.* **2012,** *55*, 995.

161. Bassat, Q.; Alonso, P. L. *Nature Med.* **2011,** *17*, 48.

162. Price, R. N.; Tjitra, E.; Guerra, C. A.; Yeung, S.; White, N. J.; Anstey, N. M. *Am. J. Trop. Med. Hyg.* **2007,** *77*, 79.

163. Lodige, M.; Lewis, M. D.; Paulsen, E. S.; Esch, H. L.; Pradel, G.; Lehmann, L.; Brun, R.; Bringmann, G.; Mueller, A. K. *Int. J. Med. Microbiol.* **2013,** *303*, 539.

164. Antinarelli, L. M. R.; Carmo, A. M. L.; Pavan, F. R.; Leite, C. Q. F.; Da Silva, A. D.; Coimbra, E. S.; Salunke, D. B. *Org. Med. Chem. Lett.* **2012,** *2*, 16.

165. Sievaen, E. *Molecules* **2007,** *12*, 1859.

166. Bhat, L.; Jandeleit, B.; Dias, T. M.; Moors, T. L.; Gallop, M. A. *Bioorg. Med. Chem. Lett.* **2005,** *15*, 85.

167. Bero, J.; Frederich, M.; Quetin-Leclercq, J. *J. Pharm. Pharmacol.* **2009,** *61*, 1401.

168. Leverrier, A.; Bero, J.; Frederich, M.; Quetin-Leclercq, J.; Palermo, J. *Eur. J. Med. Chem.* **2013,** *66*, 355.

169. Gloria, P. M. C.; Gut, J.; Goncalves, L. M.; Rosenthal, P. J.; Moreira, R.; Santos, M. M. M. *Bioorg. Med. Chem.* **2011,** *19*, 7635.

170. Kumar, S. P.; Gloria, P. M. C.; Goncalves, L. M.; Gut, J.; Rosenthal, P. J.; Moreira, R.; Santos, M. M. M. *Med. Chem. Commun.* **2012,** *3*, 489.

171. Ribeiro, C. J. A.; Kumar, S. P.; Gut, J.; Goncalves, L. M.; Rosenthal, P. J.; Moreira, R.; Santos, M. M. M. *Eur. J. Med. Chem.* **2013,** *69*, 365.

172. Melnyk, P.; Leroux, V.; Sergheraert, C.; Grellier, P. *Bioorg. Med. Chem. Lett.* **2006,** *16*, 31.

173. Specht, S.; Sarite, S. R.; Hauber, I.; Hauber, J.; Gorbig, U. F.; Meier, C.; Bevec, D.; Hoerauf, A.; Kaiser, A. *Parasitol. Res.* **2008,** *102*, 1177.

174. Inam, A.; Siddiqui, S. M.; Macedo, T. S.; Moreira, D. R. M.; Leite, A. C. L.; Soares, M. B. P.; Azam, A. *Eur. J. Med. Chem.* **2014,** *75*, 67.

175. Fernández-Calienes, A. *The Open Medicinal Chemistry Journal* **2011,** *5*, 11.

176. Kumar, A.; Srivastava, K.; Kumar, S. R.; Puri, S. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 7059.

177. Gemma, S.; Camodeca, C.; Brindisi, M.; Brogi, S.; Kukreja, G.; Kunjir, S.; Gabellieri, E.; Lucantoni, L.; Habluetzel, A.; Taramelli, D.; Basilico, N.; Gualdani, R.; Tadini-Buoninsegni, F.; Bartolommei, G.; Moncelli, M. R.; Martin, R. E.; Summers, R. L.; Lamponi, S.; Savini, L.; Fiorini, I.; Valoti, M.; Novellino, E.; Campiani, G.; Butini, S. *J. Med. Chem.* **2012,** *55*, 10387.

178. Kanemitsu, H.; Yamauchi, H.; Komatsu, M.; Yamamoto, S.; Okazaki, S.; Uchida, K.; Nakayama, H. *Neurotoxicol. Teratol.* **2009,** *31*, 198.

179. Miron, T.; Arditti, F.; Konstantinovski, L.; Rabinkov, A.; Mirelman, D.; Berrebi, A.; Wilchek, M. *Eur. J. Med. Chem.* **2009,** *44*, 541.

180. Petit, E.; Langouet, S.; Akhdar, H.; Nicolas-Nicolaz, C.; Guillouzo, A.; Morel, F. *Toxicol. in Vitro* **2008,** *22*, 632.

181. de Souza, N. B.; Carvalhaes, R.; do Carmo, A. M. L.; Alves, M. J. M.; Coimbra, E. S.; Cupolilo, S. M. N.; Abramo, C.; Da Silva, A. D. *Lett. Drug Des. Discov.* **2012,** *9*, 361.

182. Werbovetz, K. A. *Mini-Rev. Med. Chem.* **2002,** *2*, 519.

183. Koka, S.; Bobbala, D.; Lang, C.; Boini, K. M.; Huber, S. M.; Lang, F. *Cell. Physiol. Biochem.* **2009,** *23*, 191.

184. Jayasinghe, L. R.; Datta, A.; Ali, S. M.; Zygmunt, J.; Vandervelde, D. G.; Georg, G. I. *J. Med. Chem.* **1994,** *37*, 2981.

185. Njogu, P. M.; Gut, J.; Rosenthal, P. J.; Chibale, K. *Med. Chem. Lett.* **2013,** *4*, 72.

186. Kamya, M. R.; Gasasira, A. F.; Yeka, A.; Bakyaita, N.; Nsobya, S. L.; Francis, D.; Rosenthal, P. J.; Dorsey, G.; Havlir, D. *J. Infect. Dis.* **2006,** *193*, 9.

187. Whitworth, J.; Morgen, D.; Quigley, M.; Smith, A.; Mayanja, S.; Eotu, H.; Omoding, N.; Okongo, M.; Malamba, S.; Ojwiya, A. *Lancet* **2000,** *356*, 1051.

188. Hoffman, I. F.; Jere, C. S.; Taylor, T. E.; Munthali, P.; Dyer, J. R.; Wirima, J. J.; Rogerson, S. J.; Kumwenda, N.; Eron, J. J.; Fiscus, S. A.; Chakraborty, H.; Taha, T. E.; Cohen, M. S.; Molyneux, M. E. *Aids* **1999,** *13*, 487.

189. Kublin, J. G.; Patnaik, P.; Jere, C. S.; Miller, W. C.; Hoffman, I. F.; Chimbiya, N.; Pendame, R.; Taylor, T. E.; Molyneux, M. E. *Lancet* **2005,** *365*, 233.

190. Aminake, M. N.; Mahajan, A.; Kumar, V.; Hans, R.; Wiesner, L.; Taylor, D.; de Kock, C.; Grobler, A.; Smith, P. J.; Kirschner, M.; Rethwilm, A.; Pradel, G.; Chibale, K. *Bioorg. Med. Chem.* **2012,** *20*, 5277.

1. Corresponding author. tel.: +32 9 264 93 94; fax: +32 9 364 62 21

   E-mail address: Matthias.Dhooghe@UGent.be (M. D’hooghe). [↑](#footnote-ref-1)