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RECENT UPDATES IN THE DEVELOPMENT OF METTALLOCENES WITH ANTIMALARIAL ACTIVITY[†]

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Abstract. *Great progress in the fight against malaria has been made in the last decade. Nevertheless, the development of resistance to almost all commonly used antimalarial drugs poses a major threat to the sustainability of this progress and highlights the need for the discovery of novel potent and inexpensive antimalarials to stay one step ahead. After the finding of ferrocene-containing analog of chloroquine – ferroquine, that can overcome* Plasmodium *resistance, a "big-bang" in the metallocene antimalarials research has occurred. This review describes in detail the most recent advances in this important field of medicinal chemistry. Even though it is quite hard to beat ferroquine, it seems that this could be succeeded by suitable modifications in the structure of ferroquine, by the introduction of a second metal center or through joining metallocenes with two or more proven antimalarial motifs into a single molecule.*

Key words: *antimalarial agents,* Plasmodium *resistance, ferroquine, metallocenes*

1. INTRODUCTION

Malaria is an infectious disease caused by protozoan parasites of the genus *Plasmodium*, which is transmitted through the bite of an infected female *Anopheles* mosquito. Nearly one-half of the world's population lives under the constant threat of malaria, with the heaviest toll borne by the poorest and most vulnerable (WHO, 2011). From over 300 known species of *Plasmodium*, only five infect humans and cause the distinct disease patterns of malaria. *Plasmodium falciparum* is the most lethal among them and is considered responsible for approximately 90% of all reported cases. *Plasmodium vivax* is not nearly as lethal as is *P. falciparum* but persists for years in the dormant stage in the liver and could cause clinical relapses at regular intervals. Malaria infections with the parasites of

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the species *P. malariae*, *P. ovale*, and *P. knowlesi* are much less common (Salas et al., 2013b).

The complex life cycle of the malaria parasite involves different developmental stages taking place in different tissues of both human and mosquito hosts. When an infected mosquito stings a human host, it injects saliva containing sporozoites of the *Plasmodium* parasite into the bloodstream. Sporozoites then invade the host liver where they mature and multiply. Infected liver cells eventually burst, releasing *Plasmodium* merozoites back into the bloodstream, where they invade the erythrocytes. Merozoites reproduce asexually inside the erythrocytes, developing through the stages of rings, trophozoites, and schizonts. Each schizont typically divides into merozoites, which are released by lysis of the erythrocyte when they immediately invade new erythrocytes (**Fig. 1**; Salas et al., 2013b).

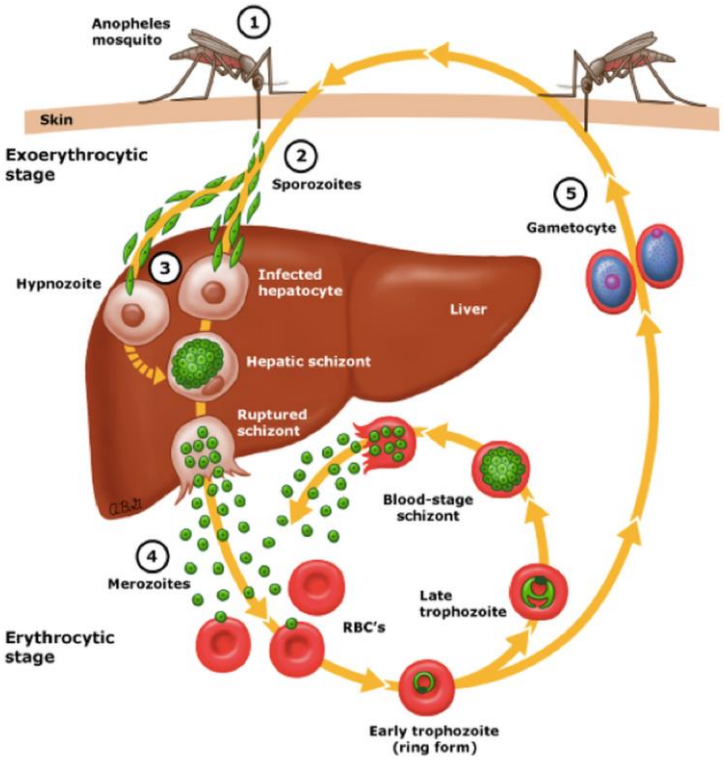


Fig. 1 Life cycle of the malaria parasite in humans (taken from Hill (2011))

A number of organic compounds have been used as antimalarial drugs, such as quinoline based agents: quinine (**1**), chloroquine (CQ; **2**), hydroxychloroquine (**3**), mefloquine (MQ; **4**), primaquine (**5**), and amodiaquine (**6**), then artemisinin derivatives, artemether (**7**) and artesunate (**8**), and some other compounds like proguanil (**9**), doxycycline (**10**), sulfadoxine (**11**), pyrimethamine (**12**) and lumefantrine (**13**; **Fig. 2**). Present-day treatments are based on a combination of two or three of these drugs. The CQ (**2**) was almost an ideal drug for antimalarial treatment due to its high efficacy, safety

(including during pregnancy), low cost, and oral application (Winstanley and Breckenridge, 1987). This quinoline-containing drug is known to accumulate in the food vacuole of the parasite and to cause parasite's death by blocking the polymerization of the toxic heme, into an insoluble and non-toxic (for the parasite) pigment (hemozoin), resulting in cell lysis and parasite cell autodigestion (**Fig. 3**; Kelly et al., 2009). However, resistance to CQ (**2**) is now widespread and this has been one of the crucial setbacks to the effective treatment and control of malaria (Trigg and Kondrachine, 1998). The use of oral artemisinin-based monotherapy is considered the main factor in the recent development and spread of resistance to artemisinins **7** and **8** (White, 2008). Hence, there is an urgent need to broaden the arsenal of available therapies well that extend the conventional purview of medicinal chemistry.

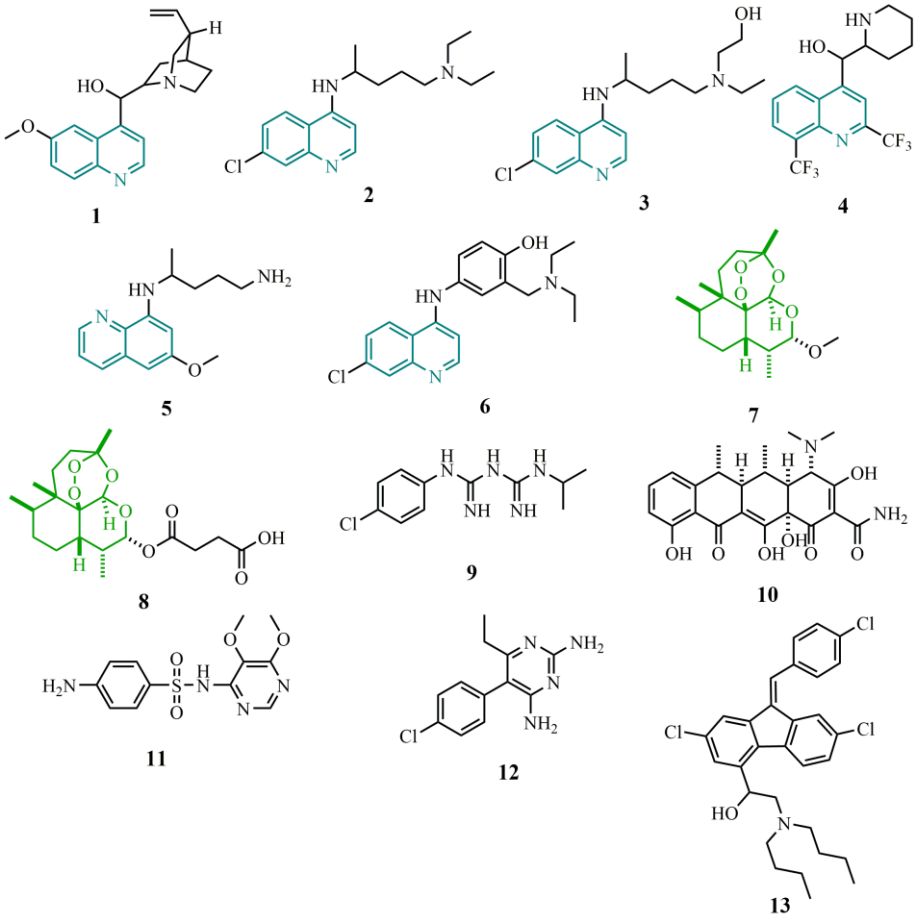


Fig. 2 Structures of organic molecules commonly used as antimalarials

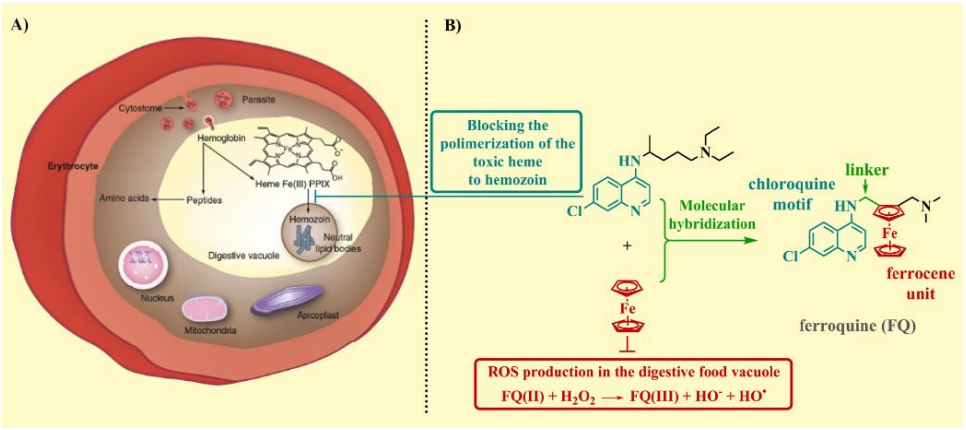
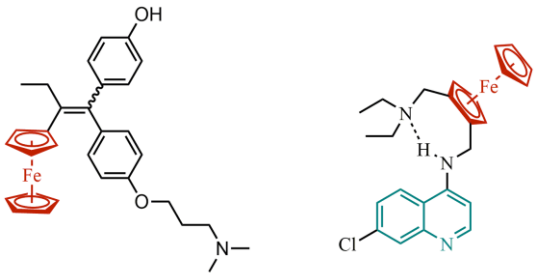


Fig. 3 (**A**) Proposed mechanism of hemozoin formation within the intraerythrocytic stage of *P. falciparum* life cycle[1] (taken from Fong and Wright, 2013) and (**B**) the mechanism(s) of action of CQ (**2**) and FQ (**15**)

Organometallic compounds, with a direct metal-carbon (σ or π) bond, have played an important role in medicinal chemistry in the last decades (Chavain and Biot, 2010). One well-known example is ferrocifen (**14**), the ferrocenyl (Fc) analog of 4-hydroxy-tamoxifen, which is the active metabolite of tamoxifen, the drug most widely prescribed for the treatment of hormone-dependent breast cancers. Ferrocifen (**14**) demonstrated not only greater potency than the parent drug but was also the first chemotherapeutic agent to be active in both hormone-dependent and hormone-independent breast cancer tissue (Jaouen et al., 2004; Top et al, 1996). Thus far thousands of structurally diverse organometallic compounds have been synthesized and their biological potential has been evaluated. The most outstanding results have been obtained for Fc-containing antimalarial agents where, in numerous cases, the presence of Fc improved the antiplasmodial activity compared to parent molecule and in some cases even enabled circumvention of the drug resistance in parasite strains. Ferrocene has specific properties such as stability under both aqueous and aerobic conditions, nontoxicity, high lipophilicity, small size, accessible redox potential, and its derivatization could be easily carried out, which makes it highly attractive for biological applications (Fouda et al., 2007; van Staveren and Metzler-Nolte, 2004). Combination of a 4-aminoquinoline moiety (that was known to target the parasite; see **Fig. 3**), with the Fc unit, has led to the design of ferroquine (FQ, **15**; **Fig. 4**) that is undoubtedly the most successful of all metallo-antimalarials synthesized and tested up to date (Biot et al., 1997). Following the success of FQ (**15**), many other structural analogs were synthesized to delineate structure-activity relationships (SAR) and to determine the mechanism of action. Subsequently, the research was directed towards the hybridization of ferrocene (and other metallocenes) with diverse antimalarial scaffolds resulting in the synthesis of a couple of hundreds of new metallo-antimalarials. Considering that the last review on the development of metallo-antimalarials was published seven years ago by

[1] Host hemoglobin is taken up by the parasite and transported to the digestive vacuole through the cytostome where is digested into small peptides and four toxic heme units (ferriprotoporphyrin IX (Fe(III) PPIX)). The detoxification of the heme byproduct is mediated by neutral lipid bodies through the formation of hemozoin.

Salas and coworkers (2013b), within this paper we want to pinpoint the progress in this important field of medicinal chemistry in the last 8 years. We narrowed down the focus of the present review to the metallocene antimalarials, as up to date this class of organometallic compounds achieved the biggest success in antimalarial metallotherapy, and divided them first into two groups depending on whether they contain Fc or other metallocenes in their structures. Among Fc-based compounds, we performed further subdivision on: (*i*) quinoline-containing derivatives, (*ii*) artemisinin-containing derivatives, (*iii*) chalcone and/or heterocycle-containing derivatives, and (*iv*) heterobimetallic compounds. These literature data are given in detail with special emphasis on the activity of compounds against both CQ-sensitive (CQS) and CQ-resistant (CQR) *Plasmodium* strains; the comparison of the observed activity with the activity of FQ (**15**) and conventional antimalarials; the results of SAR studies; and cytotoxicity of the studied compounds in some human cell line.



14 **15**

Fig. 4 Structures of the ferrocifen (**14**) and FQ (**15**). The intramolecular H-bond in FQ is indicated with the dashed line

2. FERROCENE-CONTAINING ANTIMALARIALS

The concept of grafting the Fc moiety inside an established antimalarial molecule was first applied during the mid-1990s, and these investigations are ongoing (Biot et al., 2011). Numerous Fc analogs of conventional or experimental antimalarials have been synthesized in the last 30 years. Results showed that incorporation of the Fc unit could lead to a substantial increase in antiplasmodial activity compared to the parent drug, and even to overcome the *Plasmodium* drug resistance (Salas et al., 2013b). It is supposed that this metallocene might act through modification of shape, volume, lipophilicity, basicity, and electronic profile of the parent molecule, which eventually alters its pharmacodynamic behavior. It is also possible that the Fc unit exerts a unique biological effect, not associated with other structural entities (Wu et al., 2002).

2.1. Ferrocene-quinoline hybrids

One of the most common strategies for new anti-plasmodial drug development is the molecular hybridization of the 4-aminoquinoline scaffold with other antimalarial pharmacophores. This is an extension of the concept of combination therapy by linking two pharmacophoric groups *via* a covalent bond to create a single entity instead of two

(or more) individual drugs (Soares et al., 2015). The success of quinoline-based hybrids in malaria chemotherapy could be exemplified by the molecule of FQ (**15**; **Fig. 4**).

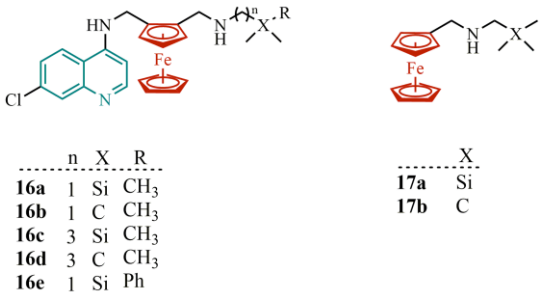
FQ (**15**) was firstly synthesized in 1997 and represents the result of the incorporation of Fc in the lateral side chain of CQ (**2**), between the two exocyclic nitrogens substituting two alkyl carbons by two cyclopentadienyl (Cp) carbons of ferrocene (Biot et al., 1997). FQ (**15**) is highly active in both CQS and CQR *P. falciparum* strains *in vitro* (Biot et al., 1997; Domarle et al., 1998). Against CQS strains, FQ (**15**) is as effective as the parent CQ (**2**; IC_{50} = 3.5 - 218 nM), while against CQR strains, FQ (**15**) is up to 20 times more potent than CQ (**2**; IC_{50} = 5 - 241 nM), maintaining the high observed activity from the CQS strains (Beagley et al., 2002; Biot et al., 2006 and 1999). FQ (**15**) displays some other outstanding properties such as: (*i*) greater *in vitro* and *in vivo* activity against CQS and CQR *P. falciparum* strains than any other quinoline-containing antimalarial drug that is even comparable to artemisinins; (*ii*) the *in vivo* activity against other *Plasmodium* strains (Sanchez-Delgado and Anzellotti, 2004); (*iii*) the inhibition of the *in vivo* development of both CQS and CQR *P. vinckei* strains and protection from lethal infection in mice, with a curative effect that was 5-20 times stronger than in case of CQ (**2**; Pradines et al., 2001; Zhou et al., 2009); (*iv*) high selectivity and therapeutic indexes (Biot, 2004; Biot and Dive, 2010); and (*v*) reduced risk of resistance development, so it can be used either as monotherapy or in combination with existent therapies (Daher et al., 2006). It seems that cytotoxicity, the acute toxicity and lethality of FQ (**15**) are dependent on gastric surfeit (Chibale and Biot, 2006). FQ (**15**; SSR97193) is now in phase IIb of clinical trials under the aegis of Sanofi-Aventis (Dive and Biot, 2008)

The mechanism of action of FQ (**15**) has been extensively studied, but it is only partially understood. Its therapeutic effectiveness has been attributed to its preferential accumulation in the parasite food vacuole by a factor higher than 50 in comparison to CQ (**2**; Dubar et al., 2008). It has been postulated that its weaker basic properties, its higher lipophilicity, and its unique conformation, influenced by the presence of an intramolecular hydrogen bond (**Fig. 4**), are key characteristics that play an important role in the elevated vacuolar accumulation (Biot et al., 2005; Dubar et al., 2011). The activity of FQ (**15**) can be ascribed to a dual mechanism: (*i*) FQ (**15**) is a strong inhibitor of β-hematin formation, more potent than CQ (**2**), and therefore able to halt more efficiently the detoxification mechanism of the parasite; and (*ii*), the redox activation from ferrocene to ferrocenium and consequent generation of reactive oxygen species (ROS) *via* a Fenton-like reaction, which likely irreversibly damages the parasite (**Fig. 3**; Dubar et al., 2011; Dubar et al., 2008). Thus far, the role of the Fc ring in the antimalarial activity of FQ (**15**) remains uncertain. The ring system was hypothesized to affect its interaction with PfCRT (*Plasmodium falciparum* Chloroquine Resistance Transporter) involved in CQ-resistance (Biot et al., 2005). Despite structural similarities to CQ (**2**) and FQ (**15**), none of the FQ (**15**) analogs were able to outdo it in performance and, possibly, more importantly, studies have not been able to explain unequivocally the role of the iron and how it contributes to the overcoming of resistance when Fc is bound to CQ (**2**). This has made apparent that exceptional structural characteristics of FQ (**15**) give this compound the specificity necessary to escape the mechanisms that encompass CQ-resistance (Salas et al., 2013b).

Previous SAR studies on CQ (**2**) analogs gave convincing pieces of evidence that significant and suitable structural changes on the side chain of the CQ (**2**) molecule (as the introduction of the Fc unit in FQ (**15**)) could circumvent *Plasmodium* CQ-resistance.

Therefore, several research groups continued their research in this direction and studied structural modification based on the (*i*) slight changes in the side chain of FQ (**15**) molecule, (*ii*) alteration of the structure and length of the linker between quinoline and the Fc unit, and/or (*iii*) through the introduction of novel structural motifs.

Adams and coworkers (2016b) prepared and fully spectrally characterized six new Fc-containing quinolines based on the incorporation of amine-terminated organosilanes, and their carbon bioisosteres (**16a-e**; **Fig. 5**), as well as two non-quinoline-based Fc-amines (**17a** and **17b**)**.** The quinolines **16a-d** (IC_{50} < 36 nM) displayed higher activities than the amines **17a-b**, confirming that the inclusion of the quinoline entity is essential to maintain good *in vitro* antiplasmodial activity and to act as an inhibitor of hemozoin formation. The carbon analogs (**16b** and **16d**) were slightly more active than the silicon analogs (**16a** and **16c**) against the CQS (NF54) strain. However, opposed to the carbon analogs, the silicon-containing hybrids were equipotent against both the sensitive and resistant strains (thus having resistance indexes[2] (RI) values ≤ 1). Incorporating organosilanes, therefore, appeared to improve activity, particularly in the CQR (Dd2) strain. All quinoline-based derivatives exhibited over 10-fold better activities than CQ (**2**) against the Dd2 strain. Moreover, compounds **16c**, **16d,** and FQ (**15**) displayed inhibition of β-haematin formation at similar IC_{50} levels (10 - 15 μM) and were considerably more effective when compared to CQ (**2**). According to these results, the authors proposed that these new quinoline-based derivatives may interact with the active site/target like that seen for FQ (**15**), while the silicon analogs, in particular, may act differently against the resistant strain. Moreover, all tested compounds displayed selectivity towards the parasite strains over the Chinese Hamster Ovarian (CHO) cell-line, with selectivity indices (SI)[3] ranging between 101 and 4643.



	n	X	R
16a	1	Si	CH_3
16b	1	C	CH_3
16c	3	Si	CH_3
16d	3	C	CH_3
16e	1	Si	Ph

	X
17a	Si
17b	C

Fig. 5 Structures of bioisosteric Fc-containing quinolines (**16a, 16c,** and **16e**) and amine (**17a**) with organosilane motif (**16b** and **16d**) and their carbon analogs (**17b**)

[2] The resistance index (RI = IC_{50}(CQR strain)/IC_{50}(CQS strain)) values are considered as a valuable tool for analysis of antimalarial drug candidates. Small RI values indicate the activity regardless of the susceptibility of the *Plasmodium* strain, while large values imply the loss of activity due to resistance development or likelihood of resistance development.

[3] Selectivity index (SI) corresponds to the ratio between cytotoxic IC_{50} value (against some human cell line) and parasitic IC_{50} value and it is used to estimate the potential of the molecules to inhibit *Plasmodium* growth without toxicity. Low SI indicates that the antiplasmodial activity is probably due to cytotoxicity rather than activity against the parasite themselves, while high SI offers the potential for safer therapy. In general, when SI is below 2.0 the compound should be regarded as a general toxin and should not be considered as a drug candidate regardless it is strong antimalarial agent.

Salas and coworkers (2013a) compared *in vitro* antiplasmodial activity of disubstituted Fc-CQ derivatives (**19a-e**; **Fig. 6**), in which the terminal *N* of the CQ derivative was bridged by the two Cp rings of Fc, with monosubstituted analogs, where the Fc moiety is covalently attached at the end of the *N*-alkylamino side chain (**18a-e**; **Fig. 6**). All derivatives were active against both CQS (D10; IC_{50} = 40.2 - 669 nM) and CQR (D2 and K1; IC_{50} = 16.1 - 1468 nM) *P. falciparum* strains, but neither of tested compounds was as potent as FQ (**15**; IC_{50} = 14 - 19 nM). On average bridged compounds **18a-d** were superior in the resistant strains *vs* the sensitive strain (thus having appealing RI values lower than 1), while the opposite was observed for monosubstituted derivatives. The growth of branching of the methylene spacer in the studied compounds caused the decrease or complete loss of the activity, while the length of the spacer had not such a strong influence. Association with hematin was observed for all derivatives but did not seem to be crucial for the activity. In this study, several biological and physical properties of tested compounds were correlated to their antiplasmodial activity as well. Although intramolecular hydrogen bonding was associated with increased antiplasmodial action, statistical analyses pointed out that a fine balance between lipophilicity and hydrophilicity of compounds had a greater influence on the activity they displayed.

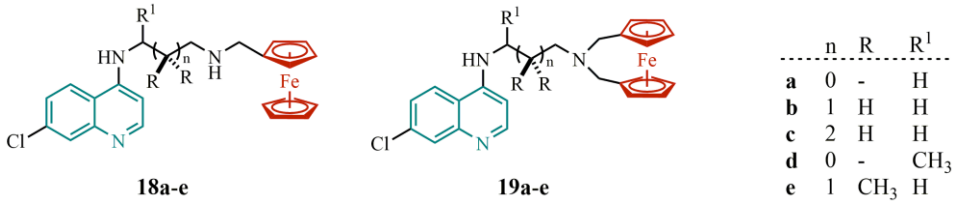


Fig. 6 Structures of monosubstituted chloroquine-Fc compounds (**18a-e**), and 1,1′-disubstituted bridged chloroquine-Fc conjugates (**19a-e**)

In 2015, Jacobs and coworkers reported the synthesis of four series of FQ (**15**) or phenylequine (PQ) derivatives (**20a-e** and **22a-e**, and **21a-e** and **23a-e**, respectively; **Fig. 7**) that contained either a diaminoalkyl or oxalamide linker between the aromatic moieties (Fc or phenylene, respectively) and the 7-chloroquinoline group. Also, they prepared a series of ethyl oxamate-PQ analogs (**24a-e**; **Fig. 7**). The hybrids in series **20**, except compound **20e**, were known and their antimalarial efficacy was previously determined (Chibale et a.l, 2000). Compound **21b** was previously reported as well (Blackie et al., 2007). Almost all hybrids manifested good activity toward CQS (NF54) strain compared to CQ (**2**; IC_{50} = 4.2 - 45.8 nM *vs.* IC_{50} = 22.1 nM). Moreover, the vast of compounds exhibited greater efficacy than CQ (**2**) in the CQR (Dd2) strain, although the efficacy of all tested compounds decreased toward this strain (RI values from 2.8 to 18), suggesting the possibility of some cross-resistance to CQ (**2**). Interestingly, there was no significant difference in activity between the Fc and phenylene series in the CQS strain since the activities of series **20** *vs.* **21** and **22** *vs.* **23** showed low variation, but it appears that the phenylene hybrids displayed less cross-resistance than the Fc-containing compounds. In both CQS and CQR strains, the oxalamides (series **23**) showed greater efficacy than the ethyl oxamate analogs (series **24**) indicating that the presence of the ethyl oxamate decreased their potency. The β-hematin inhibition assay pointed out that the inhibition of hemozoin

formation could be the primary target of the hybrids. The authors proposed that the observed activity may be attributed to their decreased efflux by PfCRT, resulting in a longer half-life within the digestive food vacuole, thus more effective hemozoin inhibition.

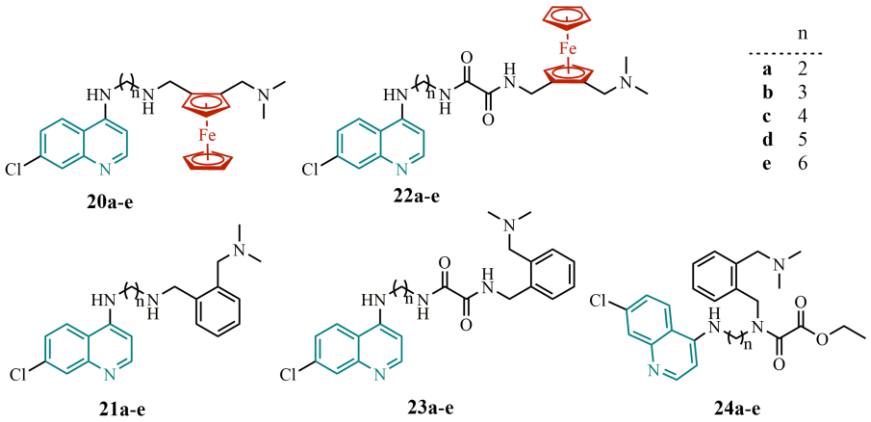


Fig. 7 Structures of Fc- (**20a-e** and **22a-e**) and phenylene derivatives (**21a-e**, **23a-e** and **24a-e**)

A series of seven quinoline-Fc hybrids (**25a-g**; **Fig. 8**) containing various (rigid or nonrigid) linkers were synthesized and screened for antimalarial activity by N'Da and Smith (2014). The hybrids **25d** and **25e** with rigid piperazine-based linker were found to be inactive (IC_{50} > 2 μM), while those with flexible spacers (**25a**, **25b**, **25f,** and **25g)** showed activity against both the CQS (D10) and CQR (Dd2) strains of *P. falciparum* (IC_{50} < 0.13 μM), and demonstrated a good selectivity towards these *Plasmodium* strains compared to CHO (SI ≥ 10). The hybrid **25g**, featuring a 3-aminopropylmethylamine linker, was the most active, exhibiting 15-folds better potency than CQ (**2**) against the Dd2 strain. Interestingly, hybrid **25c** with rigid (*p*-phenylenediamine) spacer, which only had a 4-*N* proton in this group, was also found to be active. Therefore, the authors proposed that, as in the case of FQ (**15**), the antiplasmodial activity of studied quinoline–Fc hybrids was greatly conformation-dependent, i.e. it was influenced by the possibility of the formation of the intramolecular hydrogen bond between the 4-*N* proton and the terminal *N* atom, which was favored by the flexibility of the spacer.

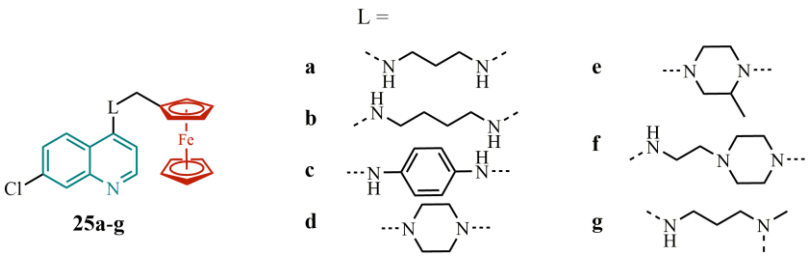


Fig. 8 Structures of quinoline–Fc hybrids containing rigid or non-rigid linkers (**25a-g**)

Antiplasmodial activity of derivatives in which the Fc unit was directly attached to quinoline or structurally related heterocycles was studied by Patti et al. (2012; **26a-c**, **27a-c**, and **28**; **Fig. 9**). All molecules achieved modest inhibition of the parasite growth (in μM range) with comparable activities against both CQS (D10) and CQR (W2) strains. The lowest values of IC_{50} (13.8 - 29.3 μM) were found for derivatives **26c** and **27c** containing a dimethylamino group as an additional substituent on heterocycle ring, but these values were still considerably higher than those obtained for CQ (**2**; IC_{50} = 0.03 and 0.4 μM). Corresponding phenyl analogs of **26a** and **27a**, **29** and **30**, were even less active, and these results confirmed the beneficial effect of the presence of the Fc unit in these molecules on their *in vitro* antiplasmodial activity.

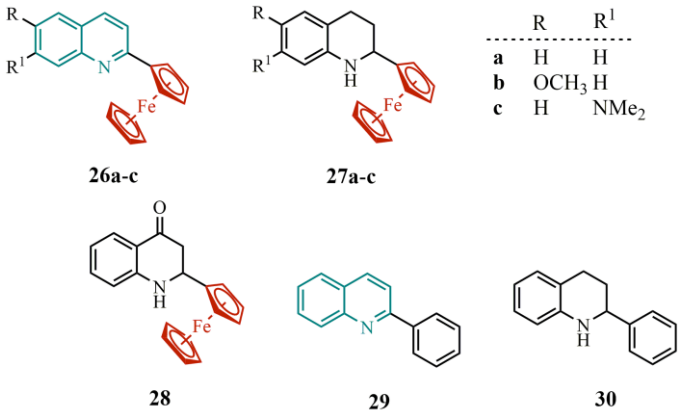


Fig. 9 Structures of quinoline-Fc derivatives (**26a-c**, **27a-c**, and **28**) and corresponding phenyl analogs (**29** and **30**)

Stringer and coworkers (2016) prepared a library of mono- (**31**-**35**, **Fig. 10A**), and multimeric (**36**-**39c**, **Figs. 10B** and **10C**) polyamine-containing Fc-quinoline hybrids. These derivatives were evaluated for *in vitro* antiplasmodial activity against both CQS (NF54) and CQR (K1) strains to identify any effects of the polyamine scaffold, multinuclearity, amine and imine functionalities on their activity. In general, the monomeric Fc hybrids (**31**-**35**) manifested enhanced activities compared to the dimeric (**36**-**38**) and trimeric (**39a-c**) derivatives against both *Plasmodium* strains. However, it was observed that the monomers display significantly higher RI values than dimeric and trimeric derivatives. All trimeric ferrocenes (**39a-c**), alongside dimeric derivative **38,** exhibited RI values very close to 1. Therefore, it seems that the incorporation of the polyamine backbone (specifically the DAB[4] scaffold) was beneficial for maintaining or enhancing activity in the resistant strain. Overall derivatives **33**, **38**, and **39c**, which did not possess the salicyl- and benzyl-moieties, displayed the highest activities against both strains (0.7 μM ≥ IC_{50} ≥ 0.08 μM). However, their IC_{50} values were still considerably higher than those determined for positive controls CQ (**2**) and FQ (**15**). Mechanistic studies revealed that hemozoin formation may be the target of these quinoline-based hybrids in the parasite. The trimeric Fc derivatives (**39a-c**) exhibited greater inhibition (IC_{50} = 10.4 - 16.8 μM) when compared to the monomeric (**31**-**35**) and dimeric (**36**-**38**) analogs, as well as to CQ (**2**; IC_{50} = 73.8 μM)

[4] *N*,*N*,*N*′,*N*′-Tetrakis(3-aminopropyl)-1,4-butanediamine.

and increased lipophilicity (higher log P values) which may be a reason for this enhanced activity. In addition to this, amines **34** and **35** manifested enhanced β-haematin inhibition compared to their corresponding imine derivatives (**31** and **33**). These data implied that enhancing the lipophilicity of the compounds as well as incorporating amino groups, positively affected the activity of the compounds in CQR strains.

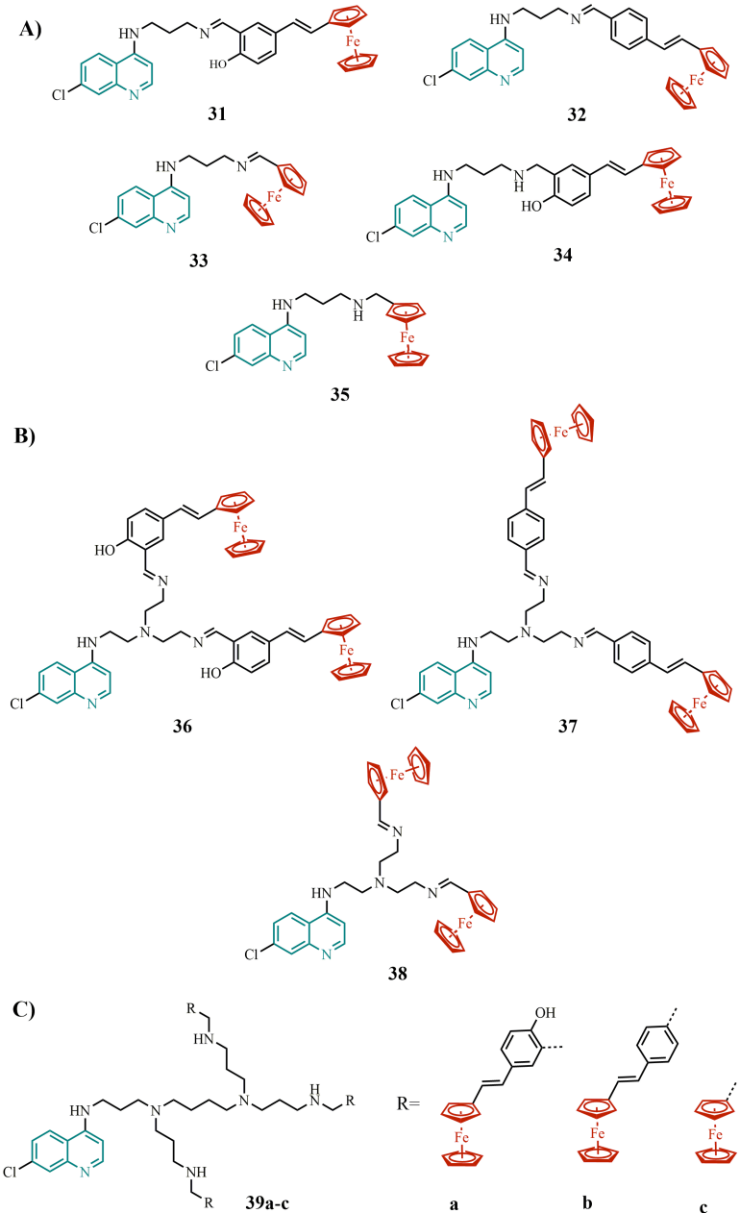


Fig 10 Structures of monomeric (**A**; **31-35**), dimeric (**B**; **36-38**) and trimeric (**C**; **39a-c**) Fc-quinoline hybrids

Three years later, the same research group, inspired by the previous results, made two additional ferroquine-derived polyamines, **40** and **41**, that showed good antiplasmodial activity in the CQS (NF54) strain (IC_{50} = 0.3 and 0.6 μM; Stringer et al., 2019) and were more active than their analogous polyamine CQ-type derivatives evaluated in the pearler study (Stringer et al., 2016). The trisamine-derived compound (**40**) was twice more active than the DAB-derived compound (**41**) possibly as a consequence of its greater cytotoxicity, as observed in the CHO cell line. Both compounds maintained their activity in the CQR strain (K1) as well (RI close to 1), which was comparable to CQ (**2**; IC_{50} = 0.28 μM), but inferior to FQ (**15**; IC_{50} = 0.024 μM). The mechanism of action for compound **40** appears not to involve the inhibition of hemozoin formation, since no increase in exchangeable haem was observed in treated parasites, suggesting that this compound has a distinct mechanism of action from CQ (**2**) and may, in part, be attributed to its ability to generate reactive oxygen species.

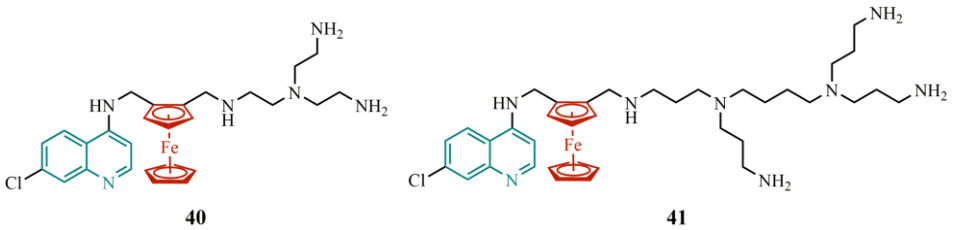
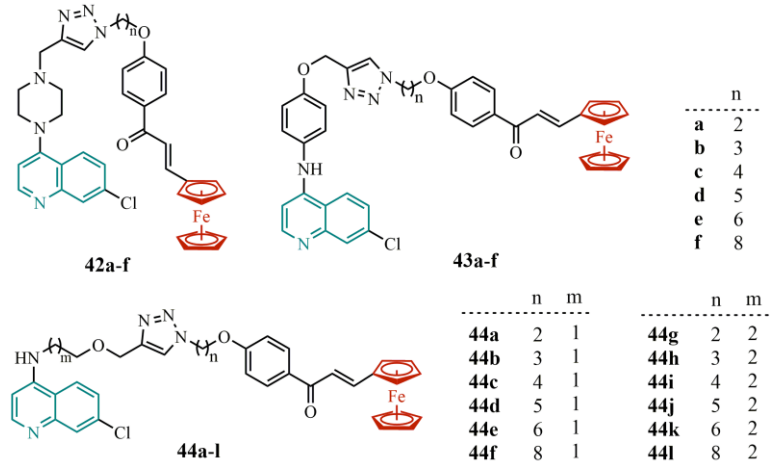


Fig. 11 Structures of FQ-derived polyamines (**40** and **41**)

Singh et al. (2017a) synthesized a library of 4-amino-quinoline-Fc-chalcone conjugates having aliphatic and aromatic substituted 1*H*-1,2,3-triazoles as a linker and evaluated them for antiplasmodial activity against CQR and MQ-sensitive (W2) strain (**42a-f**, **43a-f,** and **44a-l**; **Fig. 12**). The authors chose the 1*H*-1,2,3-triazole scaffold as a linker due to its stability under basic, acidic, reductive, and oxidative conditions, as well as favorable properties including high dipole moment, hydrogen bonding, and rigidity in binding with bio-molecular targets (Kolb and Sharpless, 2003). Alongside the length of the alkyl chain between the 7-chloroquinoline and Fc-chalcone pharmacophores, the nature of the substituent on the quinoline core was altered. The presence of a flexible chain as a substituent on the quinoline core in derivatives **44a-l** enhanced antiplasmodial activity compared to the presence of rigid piperazine/aminophenol functionalities (**42a-f** and **43a-f**) The conjugates **44a-l**, with amino-propanol as substituents, were non-cytotoxic against HeLa cells (SI > 29) and manifested activities in the sub-micromolar range (0.4 - 1.8 μM). Although these conjugates were less active than CQ (**2**) and FQ (**15**) they could be seen as useful templates for further design of new antiplasmodial scaffolds.



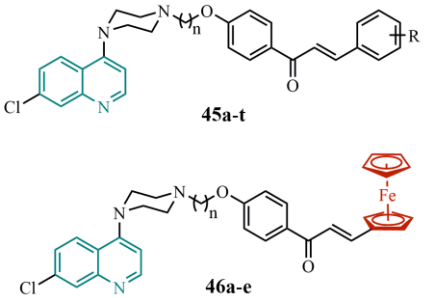
	n
a	2
b	3
c	4
d	5
e	6
f	8

	n	m
44a	2	1
44b	3	1
44c	4	1
44d	5	1
44e	6	1
44f	8	1

	n	m
44g	2	2
44h	3	2
44i	4	2
44j	5	2
44k	6	2
44l	8	2

Fig. 12 Structures of 4-aminoquinoline-Fc-chalcone conjugates (**42a-f**, **43a-f,** and **44a-l**)

Afterward, the same research group (Singh et al., 2017b) described the synthesis of 4-aminoquinoline-chalcone, as well as 4-aminoquinoline-Fc-chalcone conjugates (**45a-t** and **46a-e**, respectively; **Fig. 13**), linked *via* piperazine heterocycle, and the evaluation of their antimalarial potential against the same CQR strain (W2). Most of the hybrids showed activities at submicromolar level (IC_{50} = 0.4 - 2.4 μM). The SAR study revealed the improvement of antiplasmodial activities in both series with the increasing number of methylenes between the two pharmacophoric fragments. Overall, the most potent and non-cytotoxic (against HeLa cells) was conjugate **45e** with an optimal, hexyl chain as a linker (IC_{50} of 0.4 μM SI ~ 46.7). The compounds where the terminal aryl ring in the chalcone fragment was replaced with the Fc unit were less active (**46a-e**). The most potent hybrid in this Fc-containing series was also the one with the longest alkyl chain as a linker (**46e**; IC_{50} = 1.2 μM)**.**



	n	R
a	2	4-CH_3
b	3	4-CH_3
c	4	4-CH_3
d	5	4-CH_3
e	6	4-CH_3
f	2	4-F
g	3	4-F
h	4	4-F
i	5	4-F
j	6	4-F

	n	R
k	2	4-OCH_3
l	3	4-OCH_3
m	4	4-OCH_3
n	5	4-OCH_3
o	6	4-OCH_3
p	2	2,3,4-OCH_3
q	3	2,3,4-OCH_3
r	4	2,3,4-OCH_3
s	5	2,3,4-OCH_3
t	6	2,3,4-OCH_3

Fig. 13 Structures of 4-aminoquinoline-chalcone (**45a-t**) and Fc-chalcone conjugates (**46a-e**)

It has been previously observed that in *Plasmodium*-infected erythrocytes glucose uptake and metabolism are elevated at all stages of the parasite's life cycle (Roth, 1990). Motivated by these findings Herrmann and coworkers published three papers dealing with the antiplasmodial activity of a dozen of CQ and MQ derivatives in which they

introduced monosaccharide scaffold alongside the Fc moiety (Herrmann et al. 2012a, 2012b, and 2012c). Firstly, they compared the activity of the 1,2-disubstituted carbohydrate-CQ-Fc conjugates (**48a-c**; **Fig. 14**) and their regioisomeric 1,1′-heteroannular derivatives (**49a-c**; **Fig. 14**) to the activity of corresponding monosubstituted CQ-Fc counterparts previously designed by the Biot research group (**47a-c**; **Fig. 14**; 2006). In the monosubstituted series (**47a-c**) it was noted that the activity decreased with an increase in the alkyl chain length between the Fc and quinoline moiety (IC_{50} (Dd2) in the range from 36.2 to 1150 nM), while bifunctional conjugates **48a-c**, **49b**, and **49c** showed constant activity, outperforming CQ in the Dd2 strain ($IC_{50} \leq 173$ nM *vs.* $IC_{50} = 388$ nM). For the disubstituted conjugates **48a-c**, RIs were between 1.2 (**48b**) and 2.3 (**48c**) and were smaller than CQ's RI of 10, while the monosubstituted compounds **47a-c** showed RIs between 0.6 (**47a**) and 3.1 (**47c**), thus also surpassing CQ and in the case of **47a** even FQ (**15**; RI = 1.1).

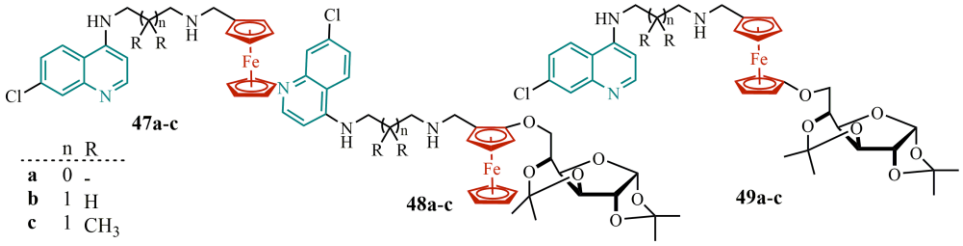


Fig. 14 Structures of monosubstituted CQ-Fc conjugates (**47a-c**; Biot et al., 2006), 1,2-disubstituted carbohydrate-CQ-Fc conjugates (**48a-c**) and their regioisomeric 1,1′-heteroannular derivatives (**49a-c**)

Moreover, the same research group reported the synthesis of a series of Fc compounds bearing ether-fused CQ (**2**) or MQ (**4**) derivatives and their analogs upgraded by an isopropylidene-protected carbohydrate (either glucofuranose or galactopyranose) in a homoannular (Sp)-1,2-substitution pattern (**50a-53b**; **Fig. 15**) or a 1,1′-heteroannular (**54a-c**; **Fig. 15**) substitution pattern. Their antiplasmodial activity was assessed *in vitro* in both the CQS (D10) and the CQR (Dd2) strains. Resistance indices (RI) for **50a-54c** compounds were < 1, indicating a high activity in the CQR strain in comparison to the CQS strain (from RI = 0.93 for **52a** to RI = 0.15 for **53a**). In general, the precursors, bearing the MQ or CQ moiety plus a protecting group, were less active than the final carbohydrate conjugates. This effect was the most dramatic for the pair **51a** and **52a**, where the IC_{50} value (for D10 strain) drops from >200 μM to 1.2 μM, showing an improvement by a factor of >160. The greatest activity, $IC_{50} = 0.8$ μM, was found for hybrid **52b** in the Dd2 strain.

Interestingly, the averaged IC_{50} value for **50a**, **53a**, and **53b** in D10 was 17.7 μM, in comparison to 2.1 μM in Dd2, leading to an average 8.4 times higher activity of these three compounds in the CQR strain. The authors highlighted that the possible cause of the observed differences in activities in these two *Plasmodium* strains was either the addition of the carbohydrate, which facilitates the uptake of the drug into the parasite, or the introduction of the additional amino group, which could potentially increase the uptake of the conjugate into the parasite's food vacuole.

Overall, these three studies by Herrmann et al. (2012a, 2012b and 2012c) revealed that the "inversely" substituted compounds **50a-b**, and **52a-54c** were more active in the

CQR (Dd2) strain in comparison to the CQS (D10) strain, whereas the 1,2- and 1,1′-disubstituted compounds with a carbohydrate attached *via* an ether linker and a CQ derivative linked through the secondary amine (**48a-c** and **49a-c**; **Fig. 14**) showed higher activity overall and were more active in the CQS (D10) strain.

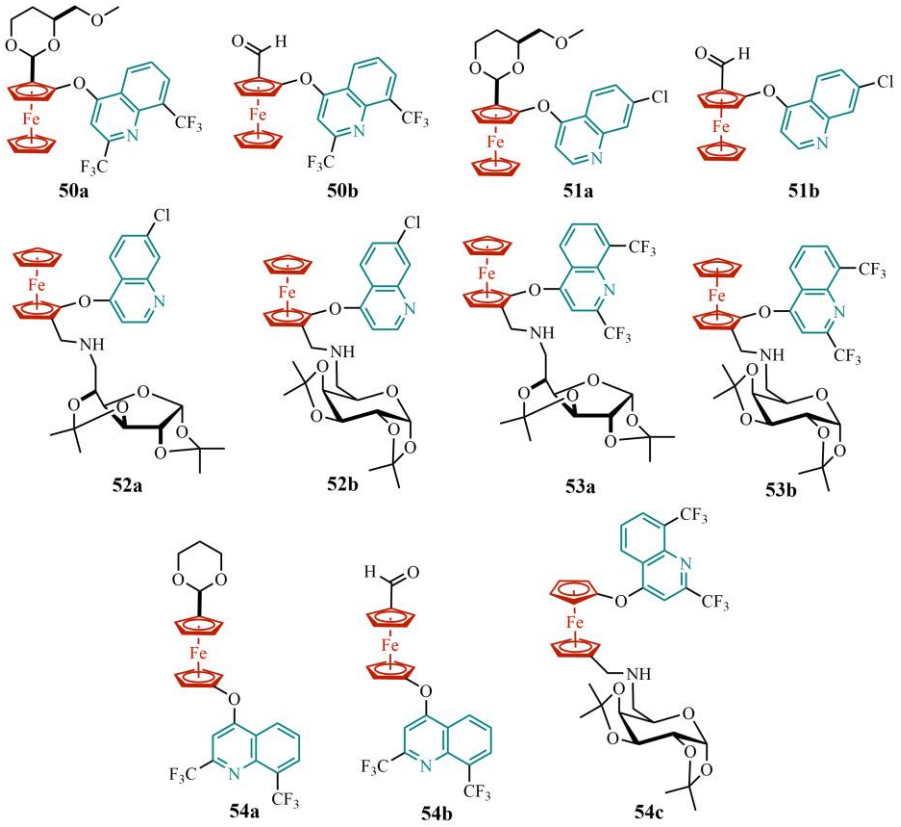


Fig. 15 Structures of Fc-containing compounds bearing ether-fused CQ (**2**) or MQ (**4**) derivatives upgraded by an isopropylidene protected carbohydrate (either glucofuranose or galactopyranose) in a 1,2-homoannular (**50a-53b**) or a 1,1′-heteroannular (**54a-c**) substitution pattern

2.2. Ferrocene-artemisinin derivatives

The artemisinin (ART; **55**; **Fig. 16**) and its derivatives have been used worldwide as a first-line treatment of *P. falciparum* malaria in the last 15 years (Fidock et al., 2004; Wani et al., 2015). ART (**55**) is a sesquiterpene lactone with an endoperoxide bridge in the seven-membered ring that is firstly isolated in 1972 from the Chinese sweet wormwood (*Artemisia annua* L.), a plant used for centuries to treat fever. (Klayman, 1985). ART derivatives are extremely efficient in killing parasites, act faster than any other antimalarial available, have a rapid symptomatic response, and are absorbed and eliminated rapidly from the host bloodstream ($t_{1/2}$ < 60 min; Price, 2000). These compounds are often

used in conjunction with other effective agents (for instance, in ACTs[5]) to improve antimalarial efficacy (Rathore et al., 2005). In contrast to other antimalarials, ART-based drugs show antiplasmodial effects at all stages of the malaria infection: both at the asexual pre-erythrocytic (liver) and erythrocytic (bloodstream) stages inside the host, as well as in the sexual stage as gametocytocidal agents (killing *Plasmodium* gametes inside the mosquito gut), thus lowering transmission rates (Price, 2000). Hence, this unrestricted action of artemisinins might be the key to their potency.

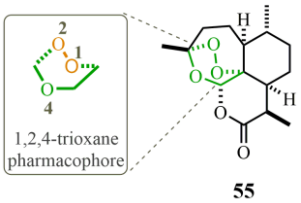


Fig. 16 Structure of ART (**55**)

Although the exact site and mechanism of action of the artemisinins are still being debated, SAR studies have indicated that the presence of the endoperoxide bridge within the sesquiterpene lactone is essential for antimalarial activity (Hien and White, 1993; Price, 2000). Opposite to CQ (**2**), ART (**55**) does not inhibit the formation of hemozoin but instead forms adducts with hemozoin and other biological macromolecules (Bhisutthibhan et al., 1998). This catalyzes the breakdown of the ART-labile peroxide bridge, generating free radicals that alkylate and oxidize important proteins within the parasite (such as a parasite-specific ATP-ase), causing lethal damage to the parasite membrane systems (Eckstein-Ludwig et al., 2003; **Fig. 17**). Unfortunately, ART-based therapy is not readily available and affordable everywhere because the constant growth in ACT demand caused numerous fluctuations in the availability and price of ART. Moreover, it is isolated in low yield from natural sources, while the production of semisynthetically artemisinins is costly (Enserink, 2010). In terms of toxicity, even though it appears to be safe in humans, it has been demonstrated to produce long-lived toxic metabolites in animal studies (Meshnick, 2002). Having in mind its radical-activated mechanism, neurotoxicity and cumulative toxicity can not be ruled out as well. Unfortunately, recent evidence indicates that ART resistance has emerged and spread within Southeast Asia (Fairhurst and Dondorp, 2016; Kung et al., 2018). The benefit of combining the Fc unit and the artemisinins could lie not only in the altering of the pharmacological properties but also in modifying the electrochemical properties, which could induce faster homolytic cleavage of the peroxide bond and stronger interaction with ferriprotoporphyrin IX Fe(III)PPIX (Salas et al., 2013b).

[5] The artemisinin-based combination therapy (ACT) represents a combination of artemisinin or an artemisinin derivative and a second drug with a different mechanism of action to enhance efficacy while diminishing the risk of resistance development (WHO, 2010).

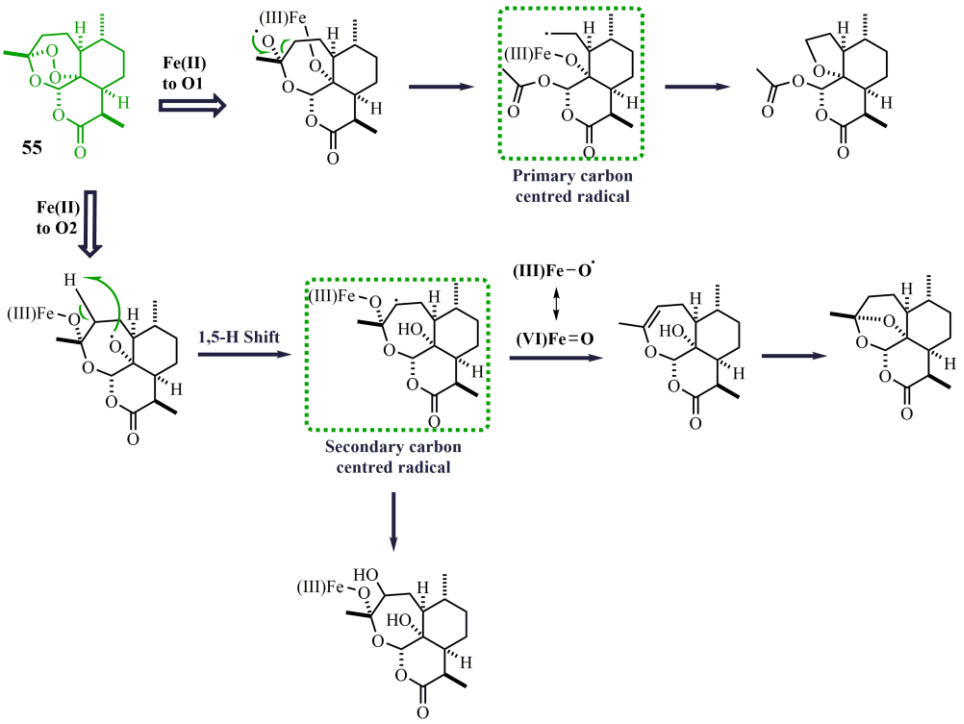


Fig. 17 Bioactivation of ART (**55**; taken from O'Neill et al., 2010)

Opposite to Fc-quinolines, the antiplasmodial activity of the hybrids of Fc and ART (**55**) derivatives have not been profoundly studied. In the last 8 years, only two research groups were involved in this kind of research. Reiter and coworkers (2014) prepared a series of novel 1,2,4-trioxane-based hybrids incorporating egonol[6] and/or Fc fragments and evaluated their *in vitro* activity against *P. falciparum*. Overall 4 derivatives with the Fc scaffold were synthesized either through esterification of ferrocene carboxylic acid (**56** and **57**) or ferrocene dicarboxylic acid (**58** and **59**) by egonol and/or 1,2,4-trioxane-derived alcohol (**Fig. 18**). Egonol-Fc hybrid **57** manifested a fivefold higher activity (IC_{50} of 5.1 μM) against CQR (3D7) strain than egonol itself. Interestingly, the introduction of the additional egonol unit in the egonol-Fc-egonol hybrid **59** resulted in the completed loss of the activity. Although 1,2,4-trioxane-Fc-egonol hybrid **58** was the most active among the tested molecules, its IC_{50} value (88 nM) was still 100-fold higher than the IC_{50} of artesunic acid. By comparing the antiplasmodial potential of hybrids with and without Fc unit (88 nM *vs.* 2.3 nM) it could be supposed that the introduction of the Fc moiety did not have a positive effect on the antimalarial activity of hybrids.

[6] Egonol is a natural benzofuran widely distributed in *Styrax* species that display interesting biological activities such as insecticidal, fungicidal, antimicrobial and anti-proliferative (Reiter et al., 2014).

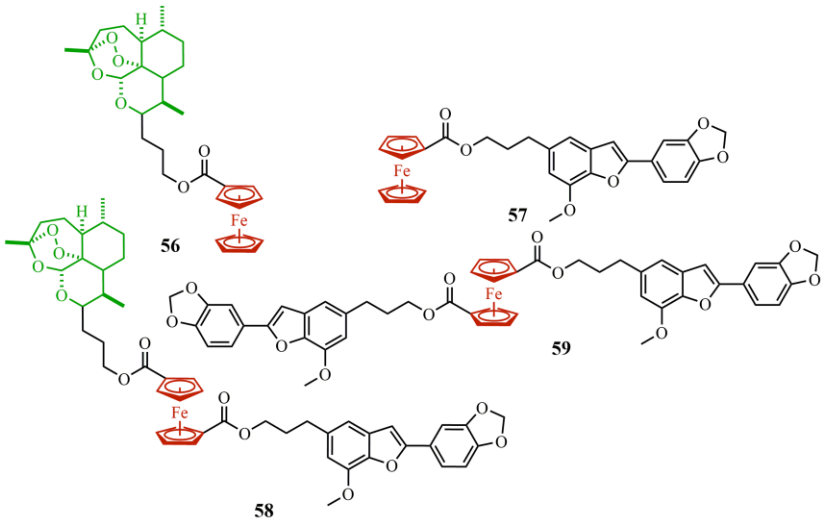


Fig. 18 Structures of 1,2,4-trioxane-based hybrids incorporating egonol and/or Fc fragments (**56**-**59**)

Motivated by the results of the above-mentioned study, only a year later, the same research group has designed the 2nd generation of anti-plasmodial 1,2,4-trioxane-Fc hybrids from ferrocene monocarboxylic acid or ferrocene dicarboxylic acid, and dihydroartemisinin (DHA) or DHA-derived precursors (**60**-**63**; **Fig. 19**; Reiter et al., 2015). All hybrids showed activity against *P. falciparum* 3D7 parasites in a low nanomolar range (IC_{50} of 7.2 - 30.2 nM) comparable to that of the parent compound DHA (IC_{50} of 2.4 nM). Although, the presence of the Fc fragment in these four new 1,2,4-trioxane-Fc hybrids did not enhance the antimalarial activity of the 1,2,4-trioxane counterpart, one of them (**61**) suppressed the activity CQ (**2**; IC_{50} = 9.8 nM). As hybrids **60** and **61** showed considerably higher inhibition of *Plasmodium* growth than **62** and **63**, it seems that the physical proximity of the Fc unit to the peroxide group/s influence the antiplasmodial activity of the hybrids.

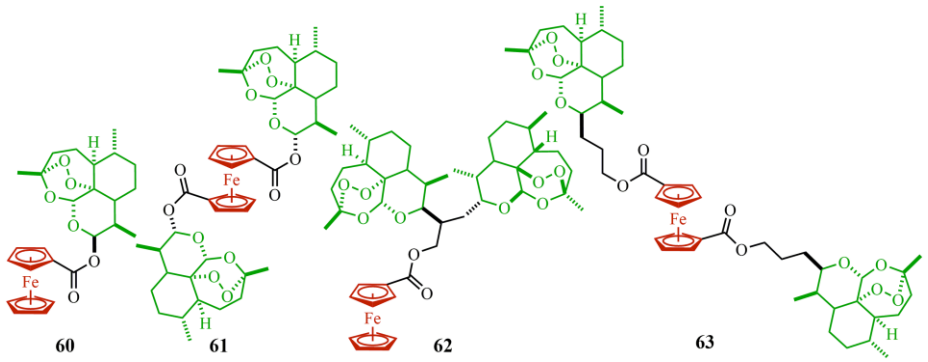


Fig. 19 Structures of 1,2,4-trioxane-Fc hybrids (**60**-**63**)

Additionally, they have reported the synthesis of nine new natural product-based hybrids comprising ART, thymoquinone[7], egonol, and/or homoegonol among which only three contained Fc moiety (**64**-**66**; **Fig. 20**). Most of the new hybrids surpassed their parent compounds regarding *in vitro* antimalarial activity towards the most fatal CQR strain (3D7). Hybrids **64** and **66** where only thymoquinone moiety was introduced through the esterification of Fc-di- and monocarboxylic acids, respectively, showed modest activity ($IC_{50} \geq 3.5$ μM), while ART-Fc-thymoquinone hybrid **65** displayed activity in the nanomolar range (IC_{50} = 11.8 nM) comparable to CQ and artesunic acid (Karagöz et al., 2018).

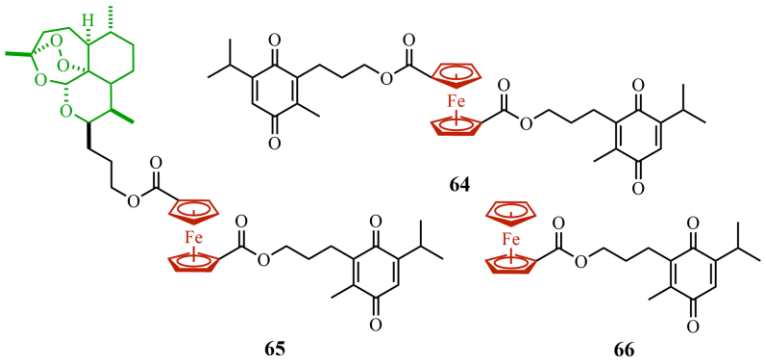


Fig. 20 Structures of ART- and/or thymoquinone-Fc hybrids (**64**-**66**)

In the search for effective bioactive hybrid molecules, which may possess improved properties compared to their parent compounds, the same research group designed and, synthesized a library of hybrids by linking betulinic acid/betulin based dimers with the Fc and/or artesunic acid moieties (Karagöz et al., 2019). They utilized betulin and its derivatives because of their wide spectrum of biological and pharmacological properties among which is antimalarial (Ziegler et al., 2004). Five Fc-containing hybrids were prepared in which the Fc unit represented a linker or subunit (**67**-**71**; **Fig. 21**). ART-betulin-Fc hybrid **69** was moderately active, showing IC_{50} of 1.5 μM against CQR strain (3D7), while betulin-Fc hybrid **67** (IC_{50} = 27.8 μM) was almost inactive so it could be stated that the ART moiety significantly enhanced the activity of compound **69**. Hybrids that did not contain the ART unit (**67**, **68**, **70**, and **71**) were more active than ferrocene monocarboxylic acid, but they did not outperform the activity of the betulin, betulinic, and artesunic acids. Since these hybrids did not reach at least the activity of the artesunic acid alone the authors supposed that they did not hydrolyze to artesunate or artesunic acid.

[7] Thymoquinone is a main bioactive constituent isolated from *Nigella sativa* seeds, that exhibits outstanding hepatoprotective, anti-inflammatory, antioxidant, cytotoxic and anti-cancer properties.

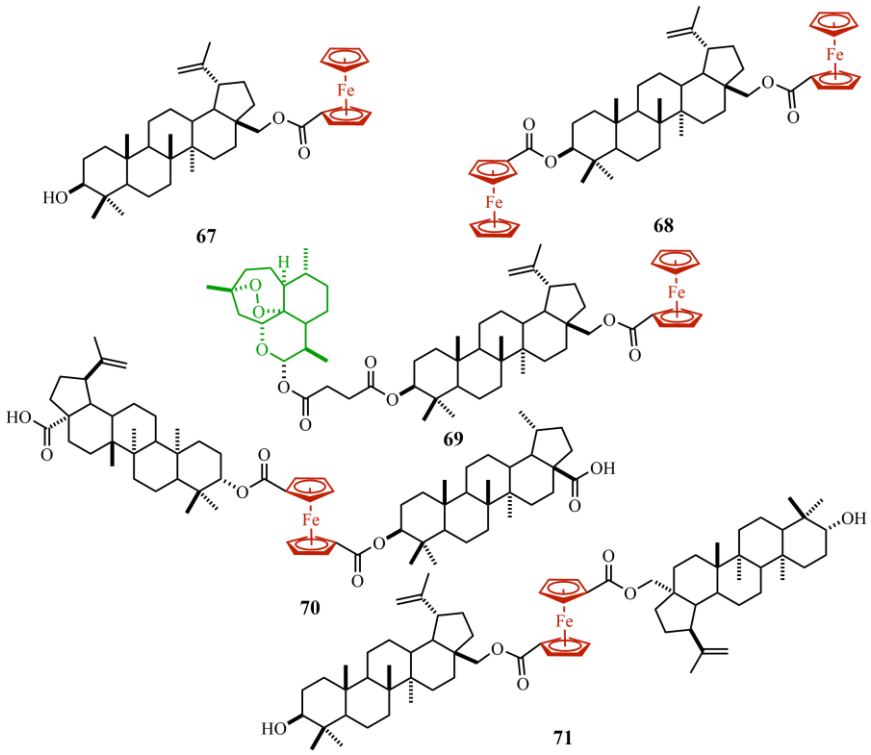


Fig. 21 Structures of hybrids containing betulinic acid/betulin based dimers linked to Fc and/or artesunic acid moieties (**67**-**71**)

In 2018, de Lange and coworkers published two papers on the synthesis of ten new amino-ART-Fc derivatives (**72a-c**, **73, 74a-c** and **75a-c**; **Fig. 22**), and the evaluation of their *in vitro* activity against both CQS (NF54) and CQR (K1 and W2) *P. falciparum* strains. In these derivatives, the Fc unit was attached *via* various piperazine-based linkers to the C-10 atom of the ART nucleus. In general, conjugates incorporating a 1,2-disubstituted Fc unit (analogous to that embedded in FQ (**15**)) were more potent than the corresponding ones where the Fc unit was monosubstituted. Compounds **75b** and **75c**, with additional piperidine or morpholine ring, overdid the effectiveness of conventional ART-based drugs towards the resistant K1 and W2 strains ($IC_{50} \leq 1.7$ nM *vs.* $IC_{50} \leq 9$ nM) but were slightly less active in the sensitive NF54 strain ($IC_{50} \leq 3.8$ nM *vs.* $IC_{50} \leq 3$ nM). Overall, the RI values of all studied amino-ART-Fc derivatives were smaller than 1 indicating a low potential for the occurrence of cross-resistance. It is considered that electron-withdrawing substituents attached to the Fc decrease the easiness of the oxidation of the Fe^{2+}, while the electron-donating groups should have the reverse effect (Kuwana et al., 1960). Even though the atom adjacent to the Fc ring comprised either electron-withdrawing carbonyl group in conjugates **72a-c** or electron-donating aminomethylene group in compound **73** (4.5; 2.7 and 3.2 nM) and methylene group in compounds **74a-c**, the observed activities of these derivatives did not vary significantly, indicating that these electronic effects were insignificant for hybrids activity (de Lange et al., 2018a and 2018b).

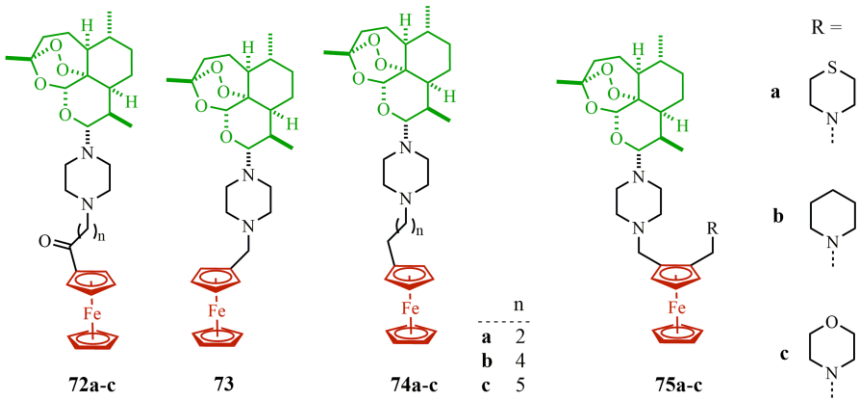


Fig. 22 Structures of amino-ART-Fc derivatives (**72a-c**, **73, 74a-c** and **75a-c**)

2.3. Ferrocene derivatives containing chalcone and/or heterocycles moieties

Chalcones (1,3-diaryl-2-propen-1-ones) are naturally occurring bioactive secondary metabolites that along with antimalarial activity could display antibacterial, antifungal, antiviral, anti-inflammatory, and antitumor properties (Sinha et al., 2013). The first reported chalcone with antimalarial activity was licochalcone A isolated from Chinese licorice roots, with an IC_{50} value of 6.5 µM against CQS (3D7) strain (Go et al., 2004; Larsen et al., 2005). This class of secondary metabolites manifests their activity through the inhibition of malarial cysteine proteases (Guantai et al., 2010) that could be explicitly targeted with minimal toxicity to the host. It is known that cysteine proteases facilitate the hydrolysis of hemoglobin in the food vacuole (Rosenthal, 2004) and it is also presumed that are involved in the rupture of the erythrocyte membrane (Aly and Matuschewski, 2005).

Although numerous studies have been carried on the Fc-containing chalcones, thus far the limited success has been achieved. For example, Wu et al. (2002) prepared more than 60 Fc–chalcone derivatives and found that all of them were less active than their aryl analogs. However, some researchers are persistent in their hunt for the Fc–chalcone hybrids that would show promising antimalarial properties.

Smit and coworkers (2016) synthesized a series of nine novel amino-Fc-chalcone amides (**76a-i**; **Fig. 23**) in which they linked the chalcone moiety (with a heterocyclic 5-methylfuran as ring B) to the Fc pharmacophore by aminoalkylene spacers of various lengths. In general, amides displayed retention of activity against the CQR (FCR3), compared to the CQS (3D7) strain, and among them, **76a** and **76g** had RI values lower or equal to 1. However, the observed antimalarial activities were modest (IC_{50} = 0.5 - 38.1 µM and IC_{50} = 2.1 - 32.4 µM against 3D7 and FCR3 strains, respectively) and the vast of the amides manifested low selective toxicity toward the parasitic cells in comparison to WI-38[8] mammalian cells (SI ≤ 1.4 for compounds **76a-f**). No conclusive trend was observed in terms of activity with increasing spacer chain length. It was, however, noted that the amides with lower electrochemical half-potential had lower cytotoxicity and higher selectivity toward parasitic cells. Overall, amide **76i** could be selected as the best drug candidate, due to its favorable drug-like and electrochemical properties, low

[8] The WI-38 cell line represents the normal human fetal lung fibroblast.

cytotoxicity, and high selectivity toward parasitic cells ($E_{1/2}$ = 0.55 V; IC_{50} = 3.5 and 4.9 μM against 3D7 and FCR3 strains, respectively; SI =16).

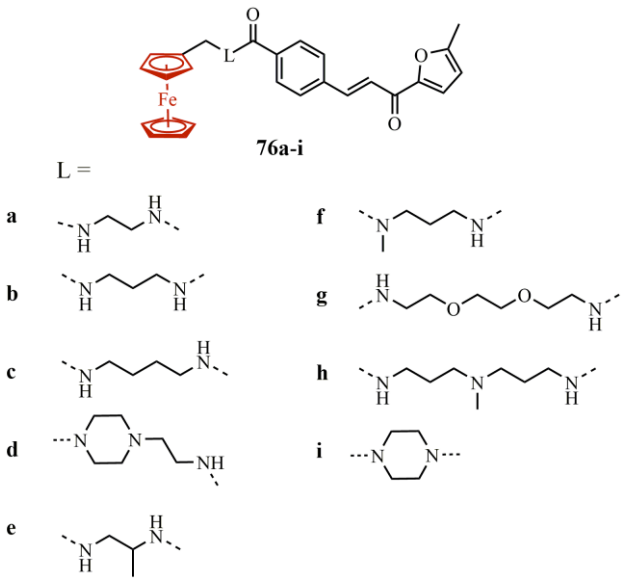


Fig. 23 Structures of amino-Fc-chalcone amides (**76a-i**)

In the past several decades, combinatorial chemistry has provided access to chemical libraries based on privileged heterocyclic motifs with proven efficacy in medicinal chemistry (Simpson et al., 2010). Thus far various heterocyclic moieties (such as 1*H*-1,2,3-triazole, pyrimidine, pyridine, imidazole, thiazole, benzimidazole, piperazine, pyrazine, etc.) were incorporated in the structure of some proven antimalarials to improve their activity. It was found that the introduction of some of the mentioned heterocycles enhanced the solubility and the oral bioavailability in some pre-clinical candidates (compared to their more lipophilic analogs) with no decrease in the antimalarial potency. This highlights the enormous potential of these promising scaffolds, especially those with five- and six-membered rings that could act on diverse molecular targets in the parasites (Gupta et al., 2005; Kalaria et al., 2018).

The discovery of penicillin as antibiotics of incomparable effectiveness after World War II has led to the identification of β-lactams as key structural motifs with broad pharmacological profile and minimal or no cytotoxicity. In the last few years, various modifications of β-lactams have been explored with the aim to prove/extend their diverse biological profile *e.g.* as antimalarial, anti-inflammatory, antidiabetic, anti-parkinsonian, anti-tubercular, and anti-HIV agents (Wright, 1999).

A library of 1*H*-1,2,3-triazole-tethered mono- and bis-Fc-chalcone-β-lactam conjugates (**77a-l** and **78a-l**, respectively; **Fig. 24**) were synthesized and evaluated for their antimalarial activity by Kumar and coworkers (2014b). They utilized 1*H*-1,2,3-triazole as a linker in these conjugates due to its moderate dipole character, hydrogen bonding capability, rigidity, and stability under *in vivo* conditions. Even though synthesized conjugates were

not as active as the CQ (**2**), the introduction of the Fc nucleus significantly enhanced the antimalarial efficacy of β-lactam core. The SAR revealed a strong dependence of activity on the nature of *N*-1 substituent of a β-lactam ring with a preference for *N*-cyclohexyl substituent, whereas the length of the linker and the presence of the mono- or bis-Fc-chalcones appeared not to be of vital importance. bis-Fc-chalcones bearing optimal *N*-1 cyclohexyl substituent (**78f** and **78l**) were the most effective against CQR (W2) exhibiting IC_{50} values of 2.36 and 2.43 µM, respectively.

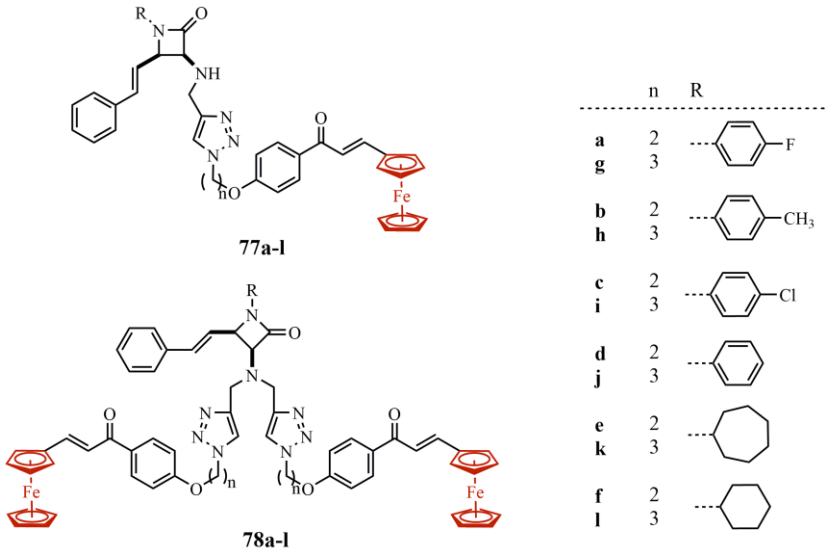
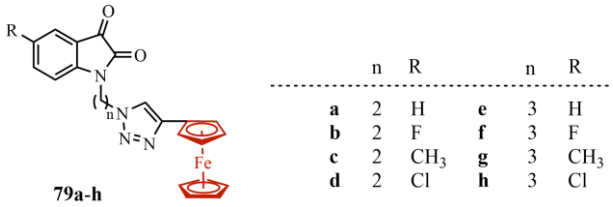


Fig. 24 Structures of mono- and bis-Fc-chalcone-β-lactam conjugates (**77a-l** and **78a-l**, respectively)

Kumar and coworkers (2014a) also published the paper on the synthesis of 1*H*-1,2,3-triazole tethered isatin[9]-Fc conjugates (**79a-h**; **Fig. 25**) and the evaluation of their antiplasmodial activities towards both CQS (3D7) and CQR (W2) strains. Authors noted that the change in chain length from ethyl to propyl had considerable influence on the activity as the conjugates **79e-h** displayed significantly higher potency (IC_{50} = 3.8 - 16.2 µM) compared to hybrids **79a-e** (IC_{50} = 24.4 - >100 µM). The most active and non-cytotoxic conjugates in the designed series were **79f** (IC_{50} = 3.8 and 6 µM against 3D7 and W2 strains, respectively) and **79h** (IC_{50} = 8.5 and 4.6 µM against 3D7 and W2 strains, respectively) with electron-withdrawing halogen substituent (F and Cl, respectively) at the C-5 position of isatin ring and the propyl chain as the linker.

[9] Isatin (1*H*-indole-2,3-dione) is a useful heterocyclic scaffold with vast possibility for synthetical modifications at C-3, C-5 and at N-1 position (Tripathy et al., 2006). This molecule manifests a wide range of biological activities such as anti-tumor, anti-HIV, antiviral, anti- antifungal, and anticonvulsants along with excellent tolerance in humans (Kumar et al., 2014b).



	n	R		n	R
a	2	H	**e**	3	H
b	2	F	**f**	3	F
c	2	CH_3	**g**	3	CH_3
d	2	Cl	**h**	3	Cl

Fig. 25 Structures of 1*H*-1,2,3-triazole tethered isatin-Fc conjugates (**79a-h**)

Chopra and coworkers (2015) synthesized six new Fc-pyrimidine derivatives (**80a-f**; **Fig. 26**) and assessed their *in vitro* antiplasmodial activity against CQS (NF54) strain. The Fc unit and pyrimidine moiety were linked through two five-membered heterocycles, 1,3-thiazole and 1*H*-1,2,3-triazole, which are known to have antimalarial properties. The authors noted that increasing lipophilicity resulted in the enhancement of antiplasmodial activity. For example, when a methyl ester group at the C-5 position of the pyrimidine ring in **80a** (IC_{50} = 28.2 µM) was replaced with ethyl or *iso*-propyl group, to obtain **80b** (IC_{50} = 17.6 µM) and **80c** (IC_{50} = 7.7 µM), respectively, both the lipophilicity and activity increased. Moreover, all hybrids showed a single electron reversible oxidation behavior similar to Fc.

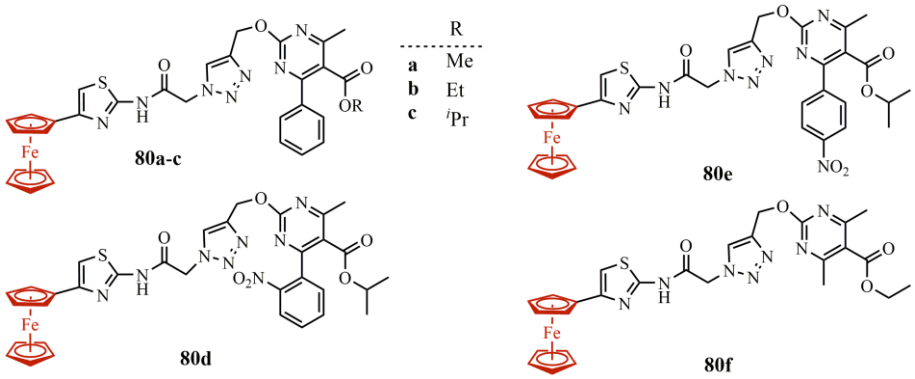


Fig. 26 Structures of Fc-pyrimidine derivatives (**80a-f**)

Very recently Mbaba and coworkers (2019) reported the synthesis of a series of novobiocin-Fc conjugates (**81a-b**, **82a-b**, and **83a-h**; **Fig. 27**) and assessment of their *in vitro* potency against CQS (3D7) strain. They chose novobiocin, an antibiotic isolated from *Streptomyces* bacteria since it is an inhibitor of the chaperone, heat shock protein 90 (Hsp90) that mediates various processes in the cells and hence plays a vital role in the life-cycle of the *P. falciparum* parasite (Kumar et al., 2003). They found that, in general, the presence of the Fc unit enhanced the potency and the selectivity of the novobiocin derivatives against *Plasmodium* species. Interestingly, derivatives that contained *N*-methyl substituent on the piperidine ring (**83a-c**) displayed moderate activity (IC_{50} values of 7.1, 9.2 and 0.9 µM, respectively) and reduced *P. falciparum* viability to below 25% without substantial HeLa cell cytotoxicity. The rest of the compounds in this series,

including parental novobiocin, were inactive as *P. falciparum* viability higher than 75% was observed at tested concentrations in most cases. Hence, the *N*-methyl group seemed to be beneficial for antiplasmodial activity since only these three Fc analogs (**83a-c**) with this group exhibited the activity.

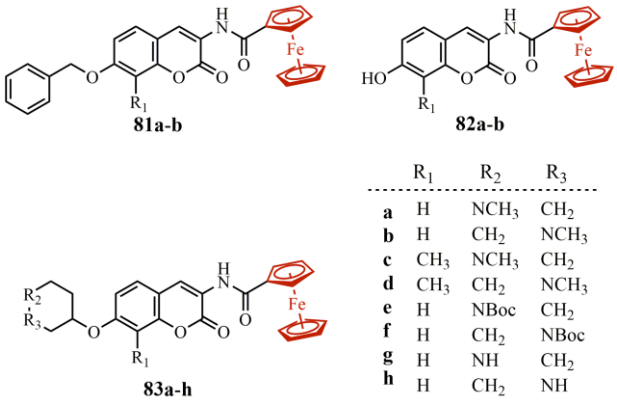


Fig. 27 Structures of novobiocin-Fc conjugates (**81a-b**, **82a-b**, and **83a-h**; Boc: *tert*-butoxycarbonyl)

2.4. Heterobimetallic compounds - ferrocene-derivatives bearing a second metal center

Along with organometallic derivatives of CQ, and other common antimalarials, some metal-CQ complexes showed also promising antiplasmodial potential. Unfortunately, the role of metal centers in these compounds is not yet completely understood. Two beneficial effects could result from the coordination of an organic drug to a metal ion: (*i*) the enhancement of the biological activity of the organic drug due to complexation, probably because of the prolongation of the residence time of the drug in the organism that allows it to reach the biological targets more efficiently; (*ii*) the decrease in the toxicity of the metal ion due to the fact that complexation with organic drugs carries the metal ion to the specific site of action and makes it less readily available for undesired reactions such as the inhibition of enzymes, or other damaging reactions leading to a malfunction in the organism. Moreover, the mechanisms by which the organometallics and coordination complexes operate are likely to be different (Sánchez-Delgado and Anzellotti, 2004). Hence, some research groups studied whether these two approaches are complementary and designed various heterobimetallic compounds of Fc-derivatives bearing a second metal center (Blackie et al., 2003).

Stringer and coworkers (2013) described the synthesis, spectral characterization, and activity against CQS (NF54) strain of six Fc-derived isoniazid and pyrazinamide conjugates and three isonicotinyl half-sandwich heterobimetallic complexes (**84**-**89** and **90**-**92**, respectively; **Fig. 28**). All of the tested compounds were inferior to CQ (**2**) and in most cases were more than 100-fold less active. The isoniazid-based hybrid **86** (IC_{50} = 1.6 μM) outdone pyrazinyl analog **89** (IC_{50} = 3.8 μM) and showed the highest activity overall. Both compounds in which the Fc unit was directly attached either to isoniazid or pyrazinamide scaffold (**84** and **87**) showed the lowest activity with IC_{50} values greater than 100 μM. The authors proposed that this may be a consequence of the lower

lipophilicity of these molecules compared to the rest of the compounds. Moreover, it seemed that incorporation of the salicyl-aldimine-Fc moiety was beneficial for antiplasmodial activity since compounds **86** and **89** were more active than **85** and **88** (IC_{50} = 31.5 μM and IC_{50} = 10.4 μM, respectively).

Among the heterobimetallic complexes the rhodium-Cp complex **91** (IC_{50} = 3 μM) showed greater activity compared to the ruthenium **92** (IC_{50} = 7.8 μM) and iridium **90** (IC_{50} = 5 μM) analogs. Most of the studied molecules exhibited higher activity compared to isoniazid at the tested concentration, suggesting a positive influence of the Fc moiety and the second metal on antiplasmodial activity. The weak cytotoxicity in CHO cells and the outcomes of β-haematin inhibition assay implied that this activity may be associated with their ability to target hemozoin in the digestive vacuole of the parasite.

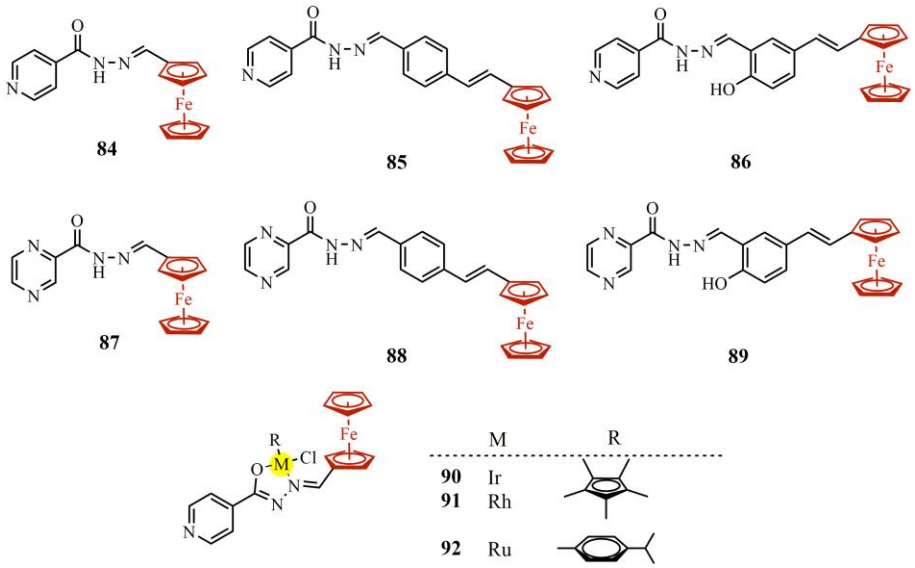


Fig. 28 Structures of Fc-derived isoniazid and pyrazinamide conjugates (**84**-**89**) and isonicotinyl half-sandwich heterobimetallic complexes (**90**-**92**)

Two years later, the same research group (Stringer et al., 2015) described the synthesis of new Fc-azines and their corresponding Rh(I) complexes (**93a-c** and **94a-c**, respectively; **Fig. 29**), as well as the assessment of their potency to inhibit the growth of both CQS (NF54) and CQR (K1) strains. The Fc-azines exhibited weak to moderate activity across both parasitic strains (IC_{50} in the range from 11 to 101 μM). Upon complexation, the activity of all compounds significantly improved (IC_{50} in the range from 3.9 to 18 μM). The SAR study revealed that compounds **93a** and **94a** possessing the 5-Cl substituent exhibited slightly higher activity compared to other hybrids. The enhanced activity of the complexes compared to the ligands may be a consequence of their higher lipophilicity due to the presence of the cyclooctadiene moiety that led to the overall increase in their logP values. Moreover, in the case of the resistant strain, the higher lipophilicity may result in the reduced efflux of these compounds by the mutated transmembrane transporter PfCRT. The Fc-azines demonstrated lower β-haematin inhibition activity (IC_{50} values

greater than 90 µM) compared to CQ (**2**) and FQ (**15**; IC_{50} = 73.8 and 14.5 µM, respectively) and this could be attributed to the fact that these compounds do not possess the quinoline moiety.

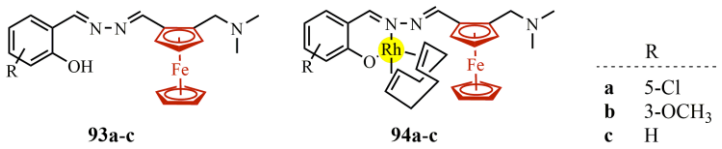


Fig. 29 Structures of Fc-azines (**93a-c**) and corresponding Rh(I) complexes (**94a-c**)

Furthermore, only a year later, the same research group reported the synthesis of a sodium sulfonate-salicylaldimine mononuclear Fc-based ligand (**95**; **Fig. 30**) and the corresponding Ru(II), Rh(III), and Ir(III) heterobimetallic complexes (**96-98**, **Fig. 30**). Compounds **95-97**[10] surpassed the metal-free parent salicylaldimine hydrazine against CQS (NF54) strain (IC_{50} = 47 - 57 µM *vs.* 222 µM) but were still inferior compared to CQ (**2**; IC_{50} = 0.02 µM). The Ru-complex (**96**) showed greater activity compared to both the Rh-complex (**97**) and Fc-containing sulfonated ligand (**95**). Neither of the studied molecules (**95-98**) inhibited the β-haematin formation at the tested concentration (100 µM), inferring that observed activities could be a result of an action on a different molecular target (Baartzes et al., 2016).

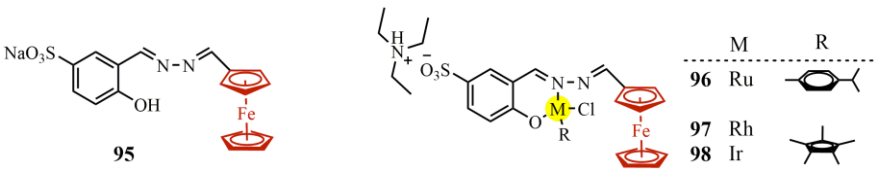


Fig. 30 Structures of the Fc-based ligand (**95**) and the corresponding ruthenium(II), rhodium(III), and iridium(III) heterobimetallic complexes (**96-98**)

The fact that several gold complexes possess antimalarial properties (Navarro et al., 1997) motivated Bjelosevic and coworkers (2012) to perform the synthesis of 1,2,1'-substituted bis(diphenylphosphino)-Fc- and ruthenocenyl-gold(I) complexes (**99**, **100a-b** and **101a-b**; **Fig. 31**) and to evaluate their activity against CQR (W2) strain. Complexes **100a-b** and **101b** exhibited low micromolar range activities, while complex **101a**, was not sufficiently stable in solution for reliable determination of biological data. The Fc-containing complex **100a** (IC_{50} = 1.8 µM) was two-fold more active than the Ru-containing analog **100b** (IC_{50} = 4.2 µM) but was slightly more cytotoxic to a human T-lymphoid cell line (CEM-SS; 17 *vs.* 21 µM).

[10] Iridium(III) complex (**98**) was not evaluated for antiplasmodial activity.

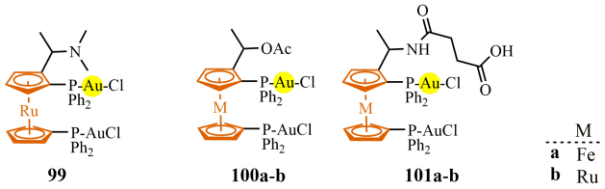


Fig. 31 Structures of ruthenocenyl- and Fc-gold(I) complexes (**99**, **100a-b** and **101a-b**)

In 2015 Adams and coworkers published a paper on the synthesis and antiplasmodial activity of a library of Fc- (**104a-b**; **Fig. 32**) and aryl-derived (**105a-c**; **Fig. 32**) thiosemicarbazones. They utilized thiosemicarbazones because of their acknowledged pharmacological properties, particularly as antiparasitic agents (Adams et al., 2013). Moreover, they incorporated an amine-terminated organosilane in some of the molecules, to confirm that the addition of the organosilane results in increased lipophilicity, and hence in improved efficacy. Overall, it was demonstrated that silicon-containing thiosemicarbazones were more effective towards *Plasmodium* strains ($IC_{50} \leq 8$ μM) and less cytotoxic against the CHO cell line than carbon-containing counterpart ($IC_{50} = 176$ μM). Also, they evaluated the effect of complexation of thiosemicarbazones with ruthenium or rhodium (**102a-b** and **103a-c**; **106a-b** and **107a-c**, respectively) on activity. It was found that both Ru and Rh complexes were slightly less active than the corresponding parent Si-containing thiosemicarbazones. On the other hand, the potency of the non-silicon thiosemicarbazone (**105c**) was significantly enhanced upon complexation either with Ru or Rh. Among studied complexes, the most potent was Rh-containing **106a** ($IC_{50} = 1.8$ and 2.3 μM against NF54 and Dd2 strains, respectively), which also manifested a moderate β-haematin inhibition ($IC_{50} = 150$ μM). The authors did not find any straight correlation between the presence of the Fc unit in the studied molecules and their antiplasmodial potency.

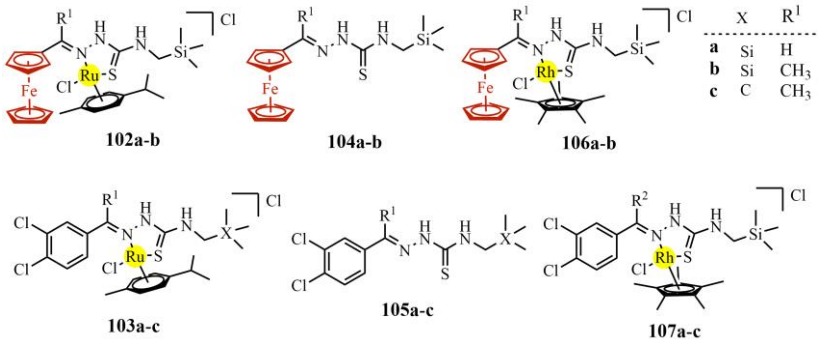


Fig. 32 Structures of the Fc- (**104a-b**) and aryl-derived (**105a-c**) thiosemicarbazones and their Ru- and Rh-complexes (**102a-b**, **103a-c**, **106a-b**, and **107a-c**)

In addition, the same research group studied the impact of the distance of the trimethylsilyl and *t*-butyl group from thiosemicarbazone moiety, as well as of the introduction of the cyclopalladated entity, on the antiplasmodial activity (Adams et al.,

2016a). Therefore, along with known Fc- (**104b**; **Fig. 32**) and aryl-derived (**105b** and **105c**; **Fig. 32**) thiosemicarbazones containing methylene spacer, they synthesized new analogs (**108-110**; **Fig. 33**) with propyl spacer, and afterward, they prepared corresponding cyclopalladated complexes *via* C–H activation of the ring (**111a-b**, **112a-b**, and **113a-b**; **Fig. 33**). It was found that the introduction of the cyclopalladated unit led to a general increment of activities in CQS (NF54) strain in comparison to the palladium-free thiosemicarbazones (IC_{50} = 0.55 - 1.6 μM *vs.* IC_{50} = 1.9 - 176 μM). Moreover, it was observed the slight improvement of the activity for the complexes against the CQR (Dd2) strain, whereas the thiosemicarbazones were equipotent or less active. The compounds containing a methylene spacer were generally more effective at killing parasitic cells, and therefore, only these compounds were further tested for their cytotoxicity against the CHO cell line. The highest SI values were found for thiosemicarbazone **105b** (13.1 and 12.2) and cyclopalladated complex **112a** (6.4 and 12.2). Interestingly, a preliminary β-haematin inhibition assay of the most potent, organosilane complex **112a** (IC_{50} = 0.55 and 0.29 μM against NF54 and Dd2, respectively) revealed that the formation of the synthetic hemozoin was not inhibited. Again, no straight conclusion about the impact of the Fc unit on the activity could be made.

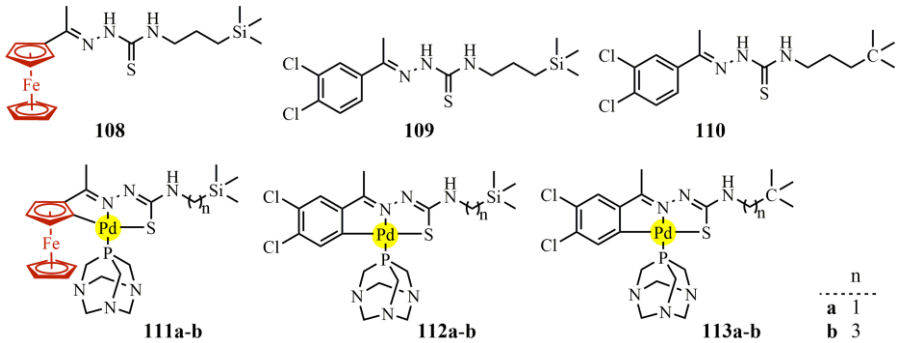


Fig. 33 Structures of Fc- (**108**) and aryl-derived (**109-110**) C- or Si-containing thiosemicarbazones and corresponding cyclopalladated complexes (**111a-b**, **112a-b**, and **113a-b**)

Guided by the same strategy, Li and coworkers (2014) reported the synthesis and spectral characterization of a carbosilane congener of FQ (**15**) and its corresponding heterobimetallic complexes (**114** and **115a-e**, respectively; **Fig. 34**) along with their *in vitro* antiplasmodial activities against both CQS (NF45) and CQR (Dd2) strains. Synthesized compounds inhibited the growth of the parasites in a low nanomolar range. Molecules **114**, **115b**, **115c**, and **115e** were the most active towards the NF54 strain, with IC_{50} values less than 10 nM, while the rest of the complexes displayed activities comparable to FQ (**15**; IC_{50} = 42.7 and 27.7 nM). In general, all compounds were less active in the Dd2 strain, suggesting that the cross-resistance could occur. Still, it is significant that these compounds surpassed CQ (**2**) in this strain which could be seen from both IC_{50} (34 - 77 nM *vs.* 108.4 nM) and RI (1 - 6 *vs.* 20) values. Overall, complex **115c** was the most potent with IC_{50} values of 4.9 and 36.6 nM against NF54 and the Dd2 strains, respectively. All studied heterobimetallic complexes inhibited the formation of synthetic hemozoin as well, and they were *ca.* 3-fold more potent in comparison to the FQ (**15**).

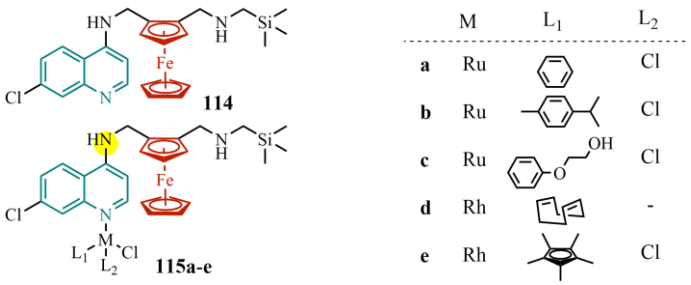
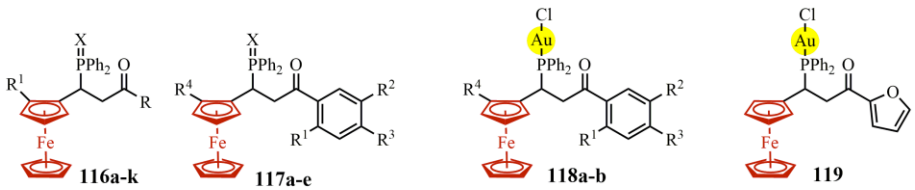


Fig. 34 Structures of a carbosilane congener of FQ (**15**) and its corresponding heterobimetallic complexes (**114** and **115a-e**, respectively)

Just recently, Subramanian and coworkers (2019) prepared a library of conjugates comprising of the phosphine oxide and phosphine sulfide derivatives of the Fc-enone substrates (**116a-k** and **117a-e**; **Fig. 35**), and they subsequently generated gold complexes of some selected conjugates (**118a-b** and **119**; **Fig. 35**). Stage-specific assays underlined the complex **119** as the one with consistent antiplasmodial activity (IC_{50} = 3.4 and 4.9 µM against 3D7 and K1, respectively), whereas the phosphine sulfides exhibited promising activity only in the mid and late stages (IC_{50} = 2.6 - 4.9 and 2.3 - 7.9 µM against 3D7 and K1, respectively). Moreover, superior inhibition of the parasite growth was observed for phosphine sulfides than oxide counterparts, most probably due to higher lipophilicity that alleviate the transport through the membrane of the digestive vacuole. Interestingly, the other two studied complexes (**118a-b**) did not exhibit the activity at all. Modification of the organic aryl/alkyl ketone moiety of the Fc-phosphine resulted in some variations of the antimalarial capability of the drug candidates, but no specific SAR was established.



	R_1	R_2	R_3	R_4
118a	H	H	CH_3	H
118b	CF_3	CF_3	H	H

	X	R_1	R_2	R_3	R_4
117a	S	H	H	CH_3	H
117b	S	CF_3	CF_3	H	H
117c	S	H	H	CH_3	CH_2OH
117d	O	H	H	CH_3	H
117e	O	CF_3	CF_3	H	H

	X	R	R_1
116a	S	furan	H
116b	S	thiophene	H
116c	S	benzofuran	H
116d	S	diisopropyl malonate	H
116e	S	dimethyl malonate	H
116f	S	furan	CH_2OH
116g	S	thiophene	CH_2OH
116h	O	furan	H
116i	O	thiophene	H
116j	O	CH_3	H
116k	O	diisopropyl malonate	H

Fig. 35 Structures of Fc-enone phosphine oxide and sulfide derivatives (**116a-k** and **117a-e**), and gold complexes (**118a-b** and **119**)

3. OTHER METALLOCENE-CONTAINING ANTIMALARIAL DRUGS

As iron and ruthenium both belonging to group 8 transition metals, ruthenocene analogs of FQ (**15**) were a rational extension (Salas et al., 2013b). Confirmed low toxicity makes Ru a very attractive choice for the development of new metallo-pharmaceuticals in particular for cancer and parasitic ailments (Bergamo and Sava, 2011). For example, the replacement of the Fe nucleus by the Ru nucleus resulted in ruthenoquine (RQ). Interestingly, it has been shown previously that the activities of FQ (**15**) and RQ in several *P. falciparum* strains are correlated with each other but not with CQ (**2**), confirming a similar mode of action for these metallocenes and a lack of cross-resistance (Dubar et al., 2011).

To establish the role that each pharmacophore might be playing in the overall antimalarial activity, Martínez and coworkers (2017) have synthesized a plausible multi-targeting hybrid **120** (**Fig. 36**) that incorporates the ruthenocene unit, the trioxane, and the 4-aminoquinoline moieties into a single molecular structure and compared its antimalarial potency with activities of the CQ (**2**), the ART (**55**), and three other related hybrids that contained one or two of the mentioned pharmacophores (**121**-**123**; **Fig. 36**). The antimalarial activity of hybrid **120,** as well as of compounds **121**-**122,** was assessed against the CQR (K1 and Dd2) strains under the experimental conditions of two independent laboratories (in Marseille and Paris). Bearing in mind that higher O_2 pressure could lead to increased efficacy of CQ (Briolant et al. 2007), an incubator with a fixed atmosphere of 10% O_2 was used in Marseille laboratory, while a candle jar with a 17% O_2 was employed in Paris laboratory. The obtained results unambiguously confirmed that the enhanced activity of hybrid **120** (IC_{50} = 16.9 - 65.3 nM) compared to that of CQ (**2**; IC_{50} = 35.1 - 1086 nM) was the result of the presence of the three different pharmacophores in a single compound. Interestingly, hybrid **122** containing only the Ru and trioxane motifs was significantly less active than hybrid **120**. The authors also noted that besides the O_2 tension, the variation of IC_{50} values between laboratories could also be due to other factors like different parasitemia and asynchronous or synchronous status of the culture. Importantly, hybrid **120** also showed low cytotoxicity toward healthy mammalian cells, which translated into a good selectivity index.

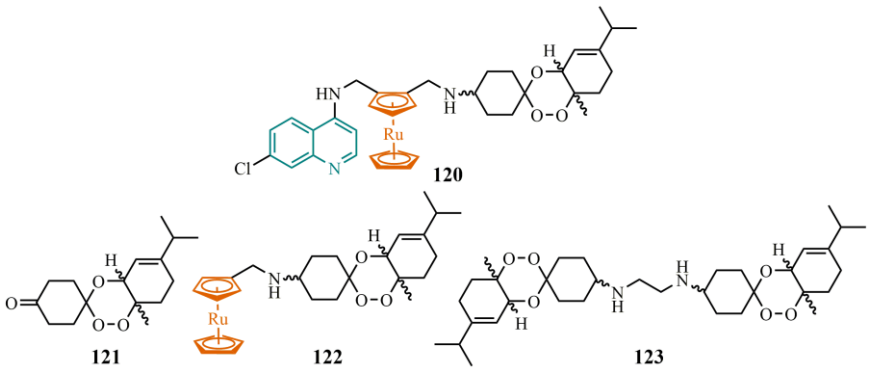
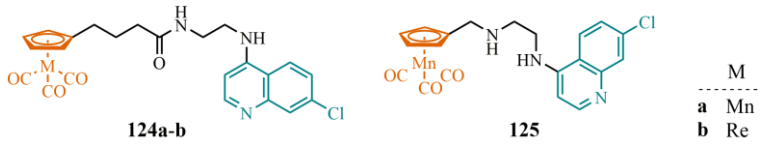


Fig. 36 Structures of ruthenocene-trioxane-4-aminoquinoline hybrid (**120**) and other three related hybrids (**121**-**123**)

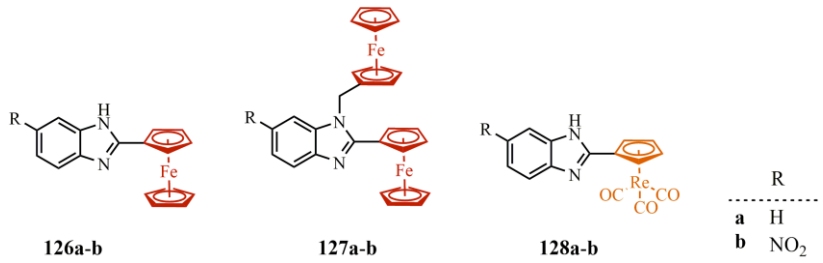
The cymantrene (Cp tricarbonyl manganese(I) half-sandwich) moiety is stable in water and air, making it suitable for incorporation into antimalarials. The corresponding rhenium half-sandwich compounds, cyrhetrene, have similar properties, although its application has been so far rather limited. Glans and coworkers (2012) reported the synthesis and characterization of new cymantrene ($CpMn(CO)_3$; **124a** and **125**; **Fig. 37**) and cyrhetrene ($CpRe(CO)_3$; **124b**; **Fig. 37**) 4-aminoquinoline conjugates with either an amine or amide linker, and the evaluation of their activity towards both CQS (D10) and CQR (Dd2) strains. Compounds **124a** and **125** were the first reported organometallic manganese-CQ analogs. All three compounds were active against the CQS strain at submicromolar concentrations (IC_{50} = 0.16 - 0.4 μM), while only conjugates with amide linker (**124a** and **124b**) maintained high potency against the CQR strain (IC_{50} = 0.28 and 0.37 μM, respectively) indicating a low risk for resistance occurrence (RI = 0.7 and 1.4, respectively).



124a-b 125

Fig. 37 Structures of cymantrene ($CpMn(CO)_3$) (**124a** and **125**) and cyrhetrene ($CpRe(CO)_3$) (**124b**) 4-aminoquinoline conjugates

To compare structural features and antimalarial potential of the Fc and cyrhetrene bioconjugates, Toro and coworkers (2013) reported the synthesis and characterization of new cyrhetrenyl benzimidazoles (**128a-b**; **Fig. 38**) and some previously described Fc-benzimidazoles (**126a-b** and **127a-b**; **Fig. 38**; Benito et al., 1995; Li et al., 1987). All compounds displayed micromolar range activity (IC_{50} = 10.4 - 48 μM and IC_{50} = 15 - 44.6 μM against 3D7 and W2 strains, respectively). In both strains, the cyrhetrenyl compounds (**128a** and **128b**; IC_{50} = 10.4 - 26.5 μM) were more potent than its Fc analogs (**126a** and **126b**; IC_{50} = 23.9 - 48 μM). The authors proposed that it could be related to the electron-withdrawing properties and higher lipophilicity of the cyrhetrenyl moiety present in **128a** and **128b** compared to the corresponding Fc derivatives (**126a** and **126b**). Moreover, molecules with only one organometallic moiety and nitro group at the position C-5 of the benzimidazole skeleton (**126b** and **128b**) were more potent than the unsubstituted analogs (**126a** and **128a**).



126a-b 127a-b 128a-b

Fig. 38 Structures of Fc- (**126a-b** and **127a-b**) and cyrhetrenyl benzimidazoles (**128a-b**)

4. CONCLUSION

With the recent emergence of *Plasmodium* resistance to current front-line artemisinin-based combination therapy, the need for the discovery of new chemical leads for the next-generation of antimalarials became an imperative of the scientific community. One of the most promising strategies in the design of new antimalarial agents is the molecular hybridization of the metallocenes, in particular, ferrocene, with the conventional antimalarial medicines. This approach could lead to new therapeutics with not only improved properties over those of the initial drug but also capable to act through some novel mechanisms of action. One such example is FQ (**15**), which is widely considered as the benchmark compound in this field, as it is the only metallo-drug that has entered clinical trials as an antimalarial.

According to SciFinder Scholar, 34 papers on antimalarial metallocenes were published in the last 8 years. In these studies, more than 200 novel metallocene-containing compounds have been synthesized, spectrally characterized, and evaluated for antiplasmodial activity against CQS and/or CQR strains. The main focus is still on the development of the Fc-containing CQ analogs that would surpass the FQ (**15**; *ca.* 40% of the metallocenes described in this review). The most noteworthy results were achieved in the case of the derivative **16b** (**Fig. 5**) that was more potent than CQ (**2**) in CQS (NF54) strain and FQ (**15**) in CQR (D2d) strain and only slightly more cytotoxic than FQ (**15**) in CHO cell line (Adams et al., 2016b). Structurally speaking, compound **16b** was obtained by formal replacement of two methyl groups on terminal nitrogen in the FQ molecule with one neopentyl group.

It seems that the linking of the Fc unit to artemisinin moiety could be the most advantageous strategy as it yielded dozens of molecules (**61**, **65**, **72a**, **73**, **74a**, and **75a-c**) that exhibited activities in the low nM range. The activities of derivatives **75a** and **75c** (**Fig. 22**) against asexual blood-stage parasites were even better than those of DHA, artesunate, and artemether towards the resistant K1 and W2 strains but were slightly less active towards the sensitive NF54 (de Lange et al., 2018b). Moreover, these two hybrids displayed superior RI and SI values to those of current clinical artemisinins. Both of these ART-Fc conjugates possessed 1,2-disubstituted ferrocene analogous to that embedded in the FQ (**15**) molecule but attached *via* a piperazine-based linker to C-10 of the artemisinin and an additional piperidine or morpholine ring.

A significant body of research has been carried out in recent years on the effect of the complexation of the second metal to various metallocene-containing compounds on their antiplasmodial activity. Although the introduction of the second metal ion (Ru(II), Rh(III), Ag(I), Ir(III) or Pd(II)) has lead in some cases to the improvement of the overall efficiency of the complex in comparison to parent ligands, the activities of these complexes were mainly in medium to low micromolar range. The only exception was Ru(II)-complexes **115b** and **115c** (**Fig. 34**) that displayed activities comparable to CQ (**2**) in CQS (NF54) strain (Li et al., 2014). Interestingly, the ligand **114** in these two complexes represented the Si-containing analog of compound **16b** (*i.e.* (trimethylsilyl)methyl motif was introduced in the lateral side chain of the FQ (**15**) molecule) and proved to be a very efficient inhibitor of the NF54 parasite's growth as well. However, neither of the herein described structural modifications have resulted in heterobimetallic derivatives with superior antiplasmodial activity relative to FQ (**15**) in CQR strains.

One of the newest approaches in the design and development of metallo antimalarials is based on the replacement of the Fc unit with other metallocenes such as ruthenocene, cymantrene, or cyrhetrene. The mentioned strategy has been implemented in several

studies since 2012 and obtained results indicated that it could have a beneficial effect on the antiplasmodial activity. For example, multi-targeting hybrid **120** (**Fig. 36**) that combined ruthenocene, the trioxane, and the 4-aminoquinoline motifs in a single molecular structure displayed higher antimalarial activity than CQ in two CQR (K1 and D2d) strains (Martínez et al., 2017). Although this molecule was slightly less potent than ART, it is worth mentioning that it was considerably less cytotoxic than ART towards mammalian cell lines (*ca*. 10-fold higher SI values).

Even though hybridization of the Fc unit with other scaffolds with plausible antimalarial properties, such as chalcones and various small aza containing heterocycles, did not result in the derivative that overcame the efficiency of the conventional antimalarial agents, some valuable information regarding SAR were provided by these studies.

The great potential of metallocene-containing compounds as antiplasmodial agents has not yet been explored. A few metallocenes more effective than CQ, FQ, and/or ART have been designed in the last 8 years, so these metallocene antimalarials may have an important role in malaria control in the foreseen future.

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PREGLED NAJNOVIJIH DOSTIGNUĆA U RAZVOJU METALOCENA SA ANTIMALARIJSKOM AKTIVNOŠĆU

U poslednjoj dekadi postignut je značajan napredak u borbi protiv malarije. Međutim, razvoj rezistencije na skoro sve dostupne antimalarike preti da uspori ovaj napredak i ukazuje na hitnu potrebu za novom, efektivnom i jeftinom terapijom. Otkriće ferohina, analoga hlorohina u čiju je strukturi uvedena ferocenska jedinica, a koji je sposoban da prevaziđe rezistenciju Plasmodium *parazita, dovelo je do nagle ekspanzije istraživanja u oblasti metalocena sa antimalarijskom aktivnošću. U ovom preglednom radu detaljno su opisana najnovija dostignuća u ovoj važnoj oblasti medicinske hemije. Iako je poprilično teško nadmašiti ferohin, čini se da bi to moglo biti postignuto odgovarajućom modifikacijom u strukturi ferohina, uvođenjem još jednog jona metala ili povezivanjem nekog od metalocena sa dve ili više farmakofore sa dokazanim antimalarijskim potencijalom u jedan molekul.*

Ključne reči: *antimalarici, rezistencija* Plasmodium *parazita, ferohin, metaloceni*