DOI: 10.1002/cmdc.201500349

Design, Synthesis, and Evaluation of Novel Ferroquine and Phenylequine Analogues as Potential Antiplasmodial Agents

Leon Jacobs,[a] Carmen de Kock,[b] Katherine A. de Villiers,[a] Peter J. Smith,[b] Vincent J. Smith,[a] Willem A. L. van Otterlo,[a] and Margaret A. L. Blackie*[a]

7-Chloroquinoline-based antimalarial drugs are effective in the inhibition of hemozoin formation in the food vacuole of the *Plasmodium* parasite, the causative agent of malaria. We synthesized five series of ferroquine (FQ) and phenylequine (PQ) derivatives, which display good in vitro efficacy toward both the chloroquine-sensitive (CQS) NF54 (IC_{50}: 4.2 nM) and chloroquine-resistant (CQR) Dd2 (IC_{50}: 33.7 nM) strains of *P. falciparum*. Several compounds were found to have good inhibitory activity against β-hematin formation in an NP-40 detergent assay, with IC_{50} values ranging between 10.4 and 19.2 μM.

Introduction

At present, more than 40% of the world's population is at risk of contracting malaria. The highest frequency of malaria infection occurs in developing countries situated in sub-Saharan Africa, Central and South America, and Asia. The 2014 World Health Organization Malaria Report documented 198 million cases of malaria in the previous year,[1] of which 90% originated from African regions. Malaria accounts for 10% of the mortality rate of children under the age of 15 in developing countries, with the vast majority of cases being children under the age of five.[2] Malaria is also associated with more than 200 000 maternal deaths annually in sub-Saharan Africa.[3] One of the most significant challenges to effective malaria chemotherapy is the emergence of drug resistance. Chloroquine (CQ), Figure 1, was one of the earliest synthetic antimalarial drugs;[4] however, resistance started to appear in the late 1950s.[5] This stimulated research into the development of new drugs, among them mefloquine, which was developed in the 1970s and introduced as an antimalarial drug in 1984. Unfortunately, within a period of six years, signs of mefloquine resistance had already started to appear in Thailand.[6]

A major cause for the development of drug resistance has been the use of monotherapy in controlling malaria.[7] In recent years this strategy has been replaced by combination therapy, in which two or more drugs are co-administered during treatment. The artemisinin-combination therapies (ACTs) are widely used today and include artemisinin, or one of its derivatives, together with a companion drug such as amodiaquine, mefloquine, or piperaquine.[8] In recent years there has been increasing evidence of mounting resistance to artemisinin throughout southeast Asia.[9] This is of great concern, given that since 2010, 84 countries have adopted ACTs as the treatment of choice for uncomplicated malaria.[10] With the threat of the emergence of resistance to combination therapies, the need for new antimalarial drugs is urgent.

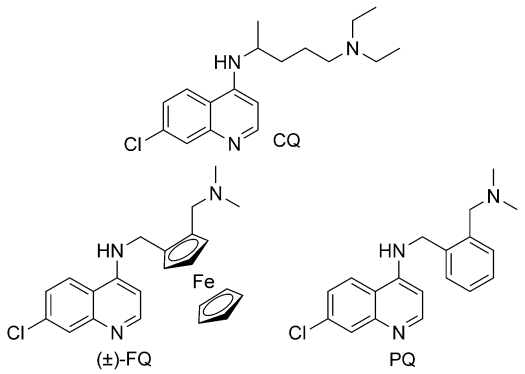


Figure 1. Structures of chloroquine (CQ), ferroquine (FQ), and phenylequine (PQ).

Early speculation concerning the mode of action of antimalarials containing quinoline-based scaffolds, such as CQ, suggested that these drugs target the formation of malaria pigment or hemozoin, an aggregate of iron(III) protoporphyrin IX.[11] β-Hematin is a synthetic form of hemozoin, which has been shown to be chemically and spectroscopically identical,[12] and compounds containing a 7-chloro-4-aminoquinoline moiety are efficient in inhibiting the formation of this synthetic material.[13] Hemozoin formation is not under the genetic control of the parasite, nor is there a similar process in human hosts; for this reason it represents a suitable antimalarial

[a] *L. Jacobs, Dr. K. A. de Villiers, Dr. V. J. Smith, Prof. W. A. L. van Otterlo, Dr. M. A. L. Blackie*
Department of Chemistry and Polymer Science
Stellenbosch University, Private Bag X1, Matieland 7602 (South Africa)
E-mail: mblackie@sun.ac.za

[b] *Dr. C. de Kock, Prof. P. J. Smith*
Department of Pharmacology, University of Cape Town
Private Bag X2, Rondebosch, Cape Town 7700 (South Africa)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cmdc.201500349.

target.[14] Resistance to CQ is thought to come about as a result of an efflux of the drug through the *P. falciparum* chloroquine-resistance transporter protein *Pf*CRT.[15] This then affords the possibility of developing a novel quinoline-based drug which retains activity against hemozoin formation, yet which evades recognition by *Pf*CRT.[16]

In 1997, a study that focused on introducing ferrocenyl moieties as substituents on known antimalarial pharmacophores such as the 4-amino-7-chloroquinoline scaffold afforded a novel drug known today as ferroquine (FQ), Figure 1.[17] It showed significant efficacy toward CQ-resistant and CQ-sensitive strains in preclinical in vitro and in vivo studies.[17] Studies have also shown that FQ is less affected by efflux through *Pf*CRT than CQ.[18] A detailed study of in vitro drug efficacy has demonstrated little-to-no cross-resistance between FQ and other drugs, including CQ.[19] Given that 1,2-disubstituted ferrocenes possess planar chirality, FQ is produced as a racemate of (+)-FQ and (−)-FQ. Both enantiomers are equipotent in vitro, although the racemate displays marginally better efficacy than the individual compounds.[20] Pharmacokinetic profiles emanating from the first-in-human phase 1a trial are favorable, and FQ has a long drug half-life as well as few side effects upon increased exposure and dosage.[19] A related compound, phenylequine (PQ), Figure 1, which is a phenylene analogue of FQ, has also been synthesized.[21] PQ was shown to have increased in vivo activity toward CQ-sensitive and CQ-resistant strains of *P. yoelii* and *P. berghei*.

The development of a dual-action drug that is potentially able to inhibit two or more targets could decrease the probability of cross-resistance emerging. A series of compounds based on an acridone skeleton was recently developed by Kelly et al.[4] These target the formation of hemozoin, and are also thought to interact with *Pf*CRT, thereby blocking its ability to actively pump CQ out of the digestive vacuole.

Our research aim was to synthesize various series of PQ and FQ analogues, which may demonstrate similar dual modes of action against *P. falciparum*. The molecules would have variations on four key features: The 7-chloroquinoline moiety would be retained as the active pharmacophore for the inhibition of hemozoin formation;[13] a terminal amine group which has been shown to be important for the pH trapping of the drug molecule in the food vacuole of the parasite;[22] the presence of the phenylene or ferrocenyl group which appears to evade the *Pf*CRT mechanism of resistance to a certain extent;[21] finally the incorporation of either an oxalamide or ethyl oxamate functional group which has been shown to increase antiplasmodial activity, although the mode of action has not yet been determined.[23]

This oxalamide or ethyl oxamate functionality was incorporated between the 7-chloroquinoline and arylmethyl moieties in order to retain the required terminal amine. The influence thereof would be investigated by determining whether the new analogues have increased or decreased efficacy relative to other PQ and FQ analogues.[23,24] In addition, the series were further varied by the inclusion of a linker of two to six methylene units between the 7-chloroquinoline and ferrocenyl/phenylene groups. The five series of compounds arising from these

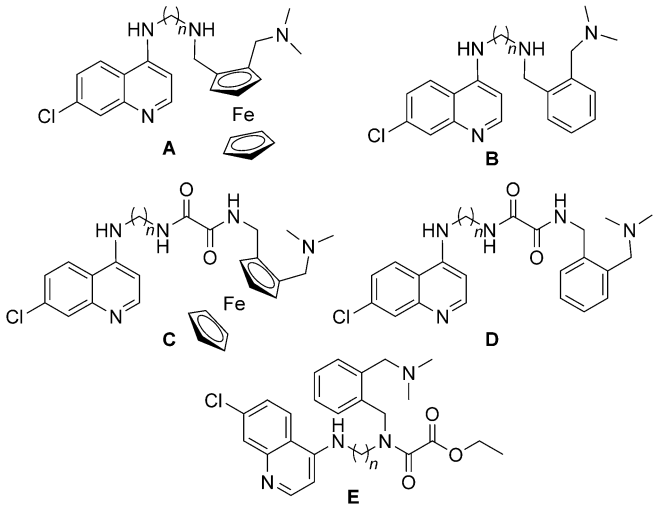
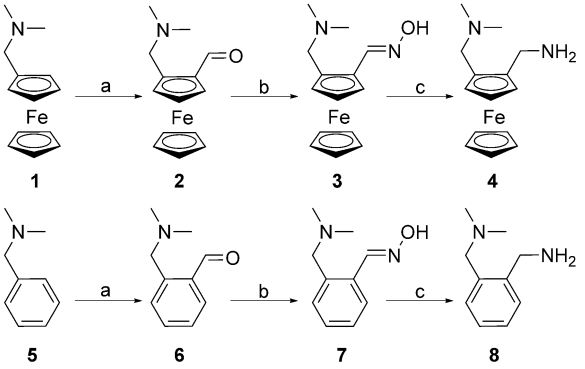


Figure 2. FQ and PQ analogues (**A**, **B**), oxalamide-FQ and oxalamide-PQ analogues (**C**, **D**), and ethyl oxamate-PQ analogues (**E**); $n = 2–6$.

structural variations are shown in Figure 2. Series **A** and **B** are FQ and PQ analogues that contain a diaminoalkyl linker between the aromatic group (ferrocenyl or phenylene, respectively) and the 7-chloroquinoline group. Series **C** and **D** have an oxalamide functional group included between the 7-chloroquinoline-bound linker and the aromatic group (ferrocenyl or phenylene, respectively). Series **E** is derived from series **B**, following further substitution of the secondary amine closest to the phenylene group with an ethyl 2-oxoacetate group to yield an ethyl oxamate substituent. It should be noted that compounds in series **A**, with the exception of compound **A5**, are known and their antimalarial efficacy was previously determined.[25] In addition, compound **B2** was reported previously.[26]

The influence of each of the structural components could be determined by comparison of efficacy between the following series:

1) Effect of ferrocenyl and phenylene moieties (series **A** vs. series **B** and series **C** vs. series **D**).
2) Effect of the inclusion of the oxalamide group (series **A** vs. series **C** and series **B** vs. series **D**). Notably, there is also an increase in chain length introduced here, so variation in efficacy may not be solely attributed to the presence of the oxalamide.
3) Effect of attachment of oxalyl group (series **D** vs. series **E**). It should be noted furthermore, that changing the position of the oxalyl group also changes the associated functional group from an amide (series **D**) to an ester (series **E**).
4) Effect of the methylene spacer length; within each series there is additional variation in the length of the methylene spacer from two to six carbons.



Scheme 1. Preparation of arylmethyl substituents. *Reagents and conditions*: a) *ortho*-lithiation of *N*,*N*-dimethylaminomethylferrocene or *N*,*N*-dimethylaminomethylbenzene: *t*BuLi, Et_2O, DMF, H_2O, 0 °C→RT, 1.75 h; b) aldoxime formation: $NH_2OH{\cdot}HCl$, $NaOH/H_2O$/EtOH, reflux, 12 h; c) reduction to form primary amine: $LiAlH_4$, Et_2O, reflux, 12 h.[21]

Results and Discussion

Chemistry

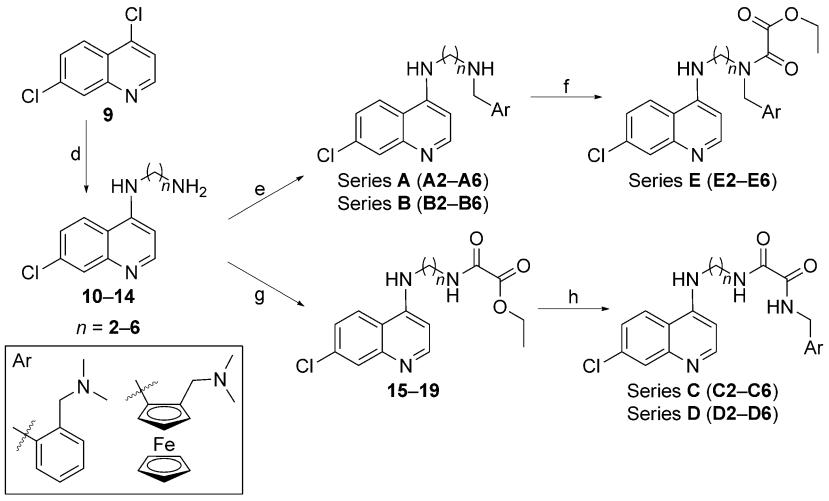
Scheme 1 shows the steps involved in the synthesis of the ferrocenic and phenylenic substituents. Step (a) involved the *ortho*-lithiation of *N*,*N*-dimethylaminomethylferrocene (**1**) or *N*,*N*-dimethylaminomethylbenzene (**5**) using *tert*-butyllithium as the lithiation base, after which the reaction was quenched with dimethylformamide to deliver the ferrocenyl (Fc) and phenylene (Ph) aldehydes **2** and **6**, respectively, in quantitative yields. The corresponding aldoxime products **3** and **7** were formed subsequently in step (b) by using hydroxylammonium chloride in a sodium hydroxide/water/ethanol mixture; yields of 83% for **3** (Fc) and >99% for **7** (Ph) were attained. The final reaction [step (c)] involved reduction of **3** and **7** with lithium aluminum hydride to give the primary amines **4** (Fc) and **8** (Ph) in >99 and 64% yields, respectively. In both the Fc and Ph cases, there is literature precedent for the aforementioned synthetic strategy.[21]

The general procedures for the synthesis of the 7-chloroquinoline-based ethyl oxamate precursors, the reductive amination coupling reaction for series **A** and **B**, and the formation of the FQ and PQ analogues containing an oxalamide moiety are shown in Scheme 2. Initially, an *ipso*-nucleophilic substitution reaction of 4,7-dichloroquinoline **9** with 4.5 equivalents of various diaminoalkanes[27] (ranging from ethylenediamine to 1,6-diaminohexane) led to compounds **10**–**14** in yields ranging from 54 to 93% [step (d)]. Subsequent reductive amination [step (e)] coupling of compounds **10**–**14** to either of the aldehydes (**2** or **6**) in methanol with sodium cyanoborohydride as the selective imine reducing agent led to series **A** and **B**. Yields for this reaction varied between 45–69% for series **A** (derived from **2**) and 30–74% for series **B** (derived from **6**). Compounds from series **B** were reacted further with ethyl chlorooxoacetate at the newly formed secondary amine to create series **E**, with yields varying between 59 and 99% [step (f)].

To obtain series **C** and **D**, the primary amine of compounds **10**–**14** was first acylated with ethyl chlorooxoacetate to give the ethyl oxamate precursors **15**–**19** in yields between 27 and 82%, with an average yield of ~60% [step (g)]. Compounds **15**–**19** were subsequently reacted with the aromatic amines **4** and **8** to obtain series **C** (Fc) and **D** (Ph), respectively [step (h)], with yields between 44 and 94% for series **C** and 22 and 79% for series **D**.

All compounds were fully characterized by standard NMR, IR, and MS techniques. Compounds of series **A** (with the exception of **A5**) were previously reported,[25] and all data are consistent with published values. It is also noted that the crystal structure of **A2** is known.[28] Compounds of series **A**, **C**, and **E** all showed characteristic signals of a 1,2-disubstituted phenylene ring. Likewise, compounds of series **B** and **D** showed the characteristic five-proton singlet of the unsubstituted ferrocenyl ring at ~4.06 ppm. The principle difference between series **A** and **B** can be observed in the signals arising from the methylene protons immediately adjacent to the ferrocenyl or phenylene rings.

In series **A**, the signals arising from the protons at positions a and b (Figure 3) appear as two doublets each having a coupling constant of 12–13 Hz due to the presence of the planar chirality inherent in an asymmetric 1,2-disubstituted ferrocenyl compound. In series **B**, these signals appear as two singlets at ~4.0 and at 3.6 ppm respectively, each integrating for two protons.



Scheme 2. General route for the synthesis of series **A**–**E**. *Reagents and conditions*: d) 4,7-dichloroquinoline, **1**, *n*-diaminoalkane, 80 °C, 1 h, 130–140 °C, 3–4 h; e) aromatic aldehyde (**2** or **6**), *p*TsOH (cat.), $NaCNBH_3$, MeOH, 18 h, RT; f), g) ClCOCOOEt, Et_3N, CH_2Cl_2, 2–5 h, 0 °C→RT; h) amine (**4** or **8**), EtOH, 40 °C, 18 h.

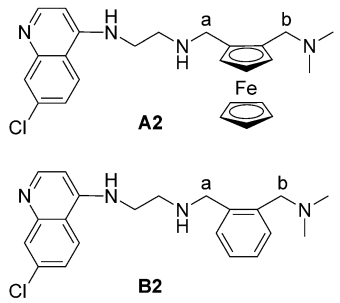


Figure 3. Structures of compounds **A2** and **B2**, showing the key protons (a and b) that exhibit different signals in the ^{1}H NMR spectra of the ferrocenyl and phenylene series.

For series **C**, **D**, and **E**, the ^{13}C NMR spectra show the presence of the two carbonyl carbon atoms of the oxalyl group at ~159 and 160 ppm. This was confirmed by the presence of the characteristic strong carbonyl stretching bands in the corresponding IR spectra at ~1650 cm^{-1}. High-resolution mass spectrometry was also carried out on all products, and the experimentally obtained results correlate well with calculated values.

Single-crystal X-ray diffraction was used to determine the molecular structure of compound **D2** (Figure 4; crystallographic data are provided in Supporting Information Table S1, and pertinent hydrogen bond lengths and angles are listed in Table S2). In the solid-state structure, the conformation of **D2** is "locked-in" by two intramolecular hydrogen bonds. The first intramolecular hydrogen bond is formed between the oxalamide proton (N4···H) and the nitrogen atom of the tertiary benzyl amine (N5). The second hydrogen bond is formed between the amino quinoline proton (N2···H) and the oxalamide oxygen atom (O1). These interactions result in the tertiary benzyl amine and the amino quinoline moieties being oriented on the same side of the oxalamide group. These interactions may constrain the flexibility of the molecule to some degree in solution. The remaining amine and carbonyl moieties of the oxalamide group are involved in intermolecular hydrogen bonding with the oxalamide group of a neighboring **D2** molecule. Finally, the structure of compound **D2** broadly confirms the proposed structures of compounds in series **C** and **D**.

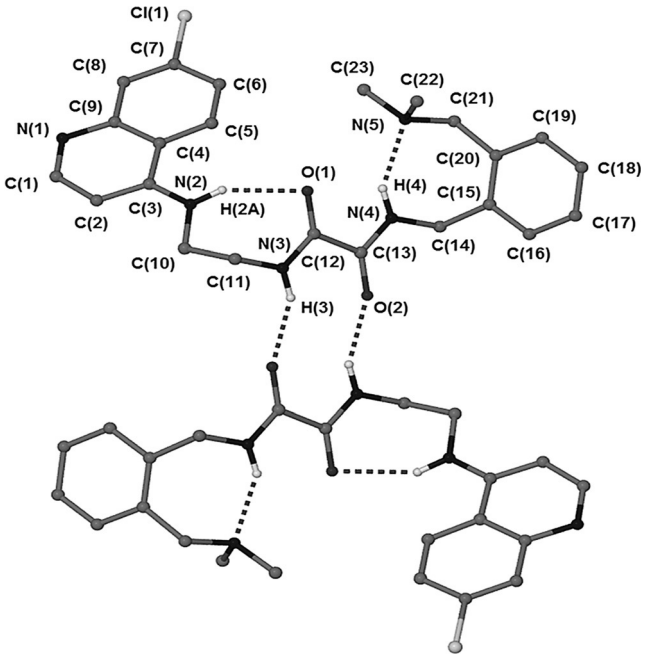


Figure 4. The centro-symmetric hydrogen bonded dimer of compound **D2** (CCDC 1032499). Intra- and intermolecular hydrogen bonds are indicated as dashed lines. Relevant hydrogen atoms are shown, whereas all others have been omitted for clarity.

Whole-cell screening against NF54 and Dd2

The whole-cell assays were conducted on the chloroquine-sensitive (CQS) NF54 and chloroquine-resistant (CQR) Dd2 strains of *P. falciparum*. The observed IC_{50} values for all compounds are listed in Table 1. There is an overall decrease in efficacy for all compounds against the CQR strain relative to the CQS strain. This suggests the possibility of some cross-resistance with respect to chloroquine. However, it is noted that the Dd2 strain shows a twofold decrease in susceptibility to artesunate relative to the NF54 strain, and therefore the observed decrease in efficacy for compounds in series **A**–**E** may not be wholly attributable to cross-resistance with chloroquine.

Table 1. Whole-cell and β-hematin inhibitory activity results for series **A**–**E**.[a]

Compd[b]	IC_{50} NF54 [nM]	IC_{50} Dd2 [nM]	IC_{50} β-H [μM]	RI[d]
A2	14.1 ± 2.3	–[c]	–	–
A3	34.8 ± 4.2	–[c]	17.8 ± 0.2	–
A4	25.4 ± 5.1	–[c]	13.3 ± 0.6	–
A5	4.2 ± 1.0	–[c]	–	–
A6	19.4 ± 2.3	–[c]	16.7 ± 0.2	–
B2	19.0 ± 3.2	53.7 ± 14.1	14.6 ± 1.8	2.8
B3	19.6 ± 4.5	69.5 ± 1.8	–	3.5
B4	32.7 ± 5.2	138.8 ± 16.9	–	4.2
B5	22.9 ± 4.1	130.9 ± 4.4	12.3 ± 1.7	5.7
B6	35.1 ± 3.1	200.9 ± 19.8	12.1 ± 0.8	5.7
C2	14.5 ± 2.9	–[c]	–	–
C3	9.4 ± 3.2	175.5 ± 19.9	16.3 ± 1.8	18
C4	14.2 ± 3.4	197.9 ± 59.7	–	14
C5	10.8 ± 2.5	57.9 ± 14.1	13.7 ± 0.6	5.4
C6	14.2 ± 5.3	40.2 ± 5.9	9.8 ± 0.4	2.8
D2	21.6 ± 6.1	68.2 ± 5.6	12.7 ± 2.8	3.2
D3	14.3 ± 3.6	62.4 ± 7.1	–	4.4
D4	9.8 ± 2.4	51.2 ± 9.3	15.6 ± 1.8	5.2
D6	7.4 ± 2.6	33.7 ± 1.2	19.2 ± 1.9	4.6
E2	185.5 ± 22.7	2008 ± 150	57.5 ± 1.2	11
E3	45.8 ± 10.1	670.8 ± 14.1	–	15
E4	22.7 ± 3.4	301.8 ± 49.9	29.0 ± 0.8	13
E5	8.7 ± 4.5	–[c]	14.3 ± 1.1	–
E6	14.1 ± 3.2	65.9 ± 14.7	–	4.7
CQ	22.1 ± 2.5	294.8 ± 74.4		13
artesunate	11.4 ± 1.9	24.2 ± 5.5		2.1

[a] IC_{50} values are the average ± SD of assays carried out in triplicate. [b] The length of the methylene spacer is given by the number in the compound code. [c] There were insufficient quantities of these compounds to submit for testing against the resistant strain. [d] Resistance index = [IC_{50} Dd2]/[IC_{50} NF4].

In the introduction, four points of comparison were stipulated for the series of compounds synthesized. 1) Effect of ferrocenyl versus phenylene moieties: In the CQS NF54 strain there was no significant difference in activity between the ferrocenyl and phenylene series. The efficacies of series **A** and **B** are all very similar, with the exception of compound **A5**, and fell within a 20 nM range. Series **C** and **D** show even less variation. Here the compounds range in efficacy from 7.4 to 21.6 nM. Greater variation in efficacy is observed in the CQR Dd2 strain. Comparing series **C** and **D**, it appears that the phenylene compounds show less cross-resistance than the ferrocenyl compounds. This is consistent with a previous study on ferroquine and phenylequine.[21] It is unfortunate that we were unable to obtain activity results for series **A** against the Dd2 strain, as we had insufficient sample. However, a previous study[25] of compounds **A2**, **A3**, **A4**, and **A6** against the CQS D10 strain and CQR K1 strain has shown that there is a similar erosion of efficacy as displayed in series **C** in moving from the sensitive to the resistant strain.

2) Effect of the oxalamide group: This does not have a clear trend. Series **A** and **C** have very similar efficacies in the CQS strain as do series **B** and **D**. However, series **D** is markedly more effective in the CQR strain. It is not clear whether this is an effect of the oxalamide or simply due to increasing distance between the quinoline and the terminal amine.

3) Effect of the attachment of the oxalyl group: In both CQS and CQR strains, the oxalamides (series **D**) show greater efficacy than the ethyl oxamate analogues (series **E**). This seems to indicate that the presence of the ethyl oxamate decreases the efficacy of these compounds.

4) Effect of the methylene spacer length: There is a variation in efficacy within each series. However, the observed variation is not consistent across series, or even within each series across the CQS and CQR strains.

β-Hematin inhibition

Each of the compounds tested contained the 7-chloroquinoline group, which has been shown to be essential for the inhibition of synthetic hemozoin formation.[13] A number of compounds showing good, mediocre, and poor in vitro efficacy against CQS NF54 strain were selected from each series to be tested for activity against β-hematin formation. The IC_{50} values for inhibition of β-hematin formation and the in vitro activity for compounds tested against the NF54 CQS strain of *P. falciparum* were compared, and inspection of the resultant correlation showed a conglomerate of compounds in the range of 10 to 20 μM that demonstrated good inhibitory activity against β-hematin formation, with the exception of two outliers [compound **E4** (28.97 μM β-H, 22.74 nM CQS) and **E2** (57.53 μM β-H, 185.51 nM CQS)]. These outliers (**E2** and **E4**) were removed from the data set shown (Figure 5) in order to highlight the observed activity in the remaining data.

A narrow range for inhibitory activity against β-hematin formation was observed between 10.4 and 19.2 μM. This is testament to the 7-chloroquinoline group, which is more than likely responsible for impeding the formation of β-hematin in the assay. The CQS IC_{50} values, however, were distributed over a wider range, between 4.0 and 35.1 nM.

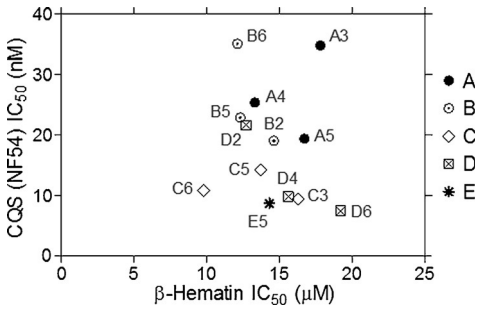


Figure 5. Plot of activity (IC_{50} values) of series **A**–**E** against whole-cell inhibition (CQS NF54 strain) and inhibition of β-hematin formation. Compounds **E2** and **E4** are omitted as outliers.

Conclusions

Five novel series of 4-amino-7-chloroquinoline compounds were synthesized. The β-hematin inhibition results indicate that the majority of these compounds show good activity in a narrow concentration range, thus indicating that hemozoin formation may be the primary inhibitory target. Notably, the majority of the compounds exhibited greater efficacy than CQ in the CQR Dd2 strain. This increased efficacy may be attributed to their decreased efflux by *Pf*CRT, resulting in a longer half-life within the digestive food vacuole, which in turn may result in more effective hemozoin inhibition. This, however, would require further investigation in a follow-up study. The fact that there is a small range of efficacy in the β-hematin inhibition assay, and that this is reflected in a small range of efficacy against the CQS NF54 strain, further supports the suggestion that the primary mode of action of these compounds is the inhibition of hemozoin formation. Unfortunately, it does appear that there is some cross-resistance with chloroquine.

Compounds of series **D** do warrant further investigation. The combination of both the oxalamide and phenylene moieties resulted in compounds that showed good activity against β-hematin formation, as well as good efficacy across both NF54 and Dd2 strains.

Experimental Section

All starting materials used were purchased from Merck, Fluka, or Sigma–Aldrich. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried over sodium wire/sand and distilled under nitrogen with benzophenone as an indicator. Dichloromethane was distilled over calcium hydride under nitrogen. Other solvents, such as ethyl acetate, *n*-hexane and triethylamine were purified according to standard procedures.[29] The molarity of *tert*-butyllithium was determined prior to use according to a standard titration method.[30] Reactions requiring anhydrous conditions were performed under nitrogen atmosphere. All ^1H and ^{13}C NMR spectra were obtained using a 300 MHz Varian VNMRS (75 MHz for ^{13}C), a 400 MHz Varian Unity Inova (100 MHz for ^{13}C) and a 600 MHz Varian Unity Inova (150 MHz for ^{13}C). Deuterated chloroform was used as standard solvent. Variable-temperature NMR spectroscopy was carried out on

a 400 MHz Varian Unity Inova (100 MHz for ^{13}C) and 600 MHz Varian Unity Inova (150 MHz for ^{13}C) using [D_6]DMSO as solvent. High-temperature NMR spectra were obtained at 130 °C. Thin-layer chromatography (TLC) was carried out on aluminum-backed Merck silica gel 60 F_{254} plates. Visualization was achieved with a UV lamp, iodine vapor, or by spraying with either a cerium ammonium molybdate (CAM) solution or a ninhydrin solution followed by heating. All column chromatography was carried out with Merck silica gel 60 (particle size: 0.040–0.063 mm). β-Hematin testing was carried out at the Department of Chemistry, University of Cape Town. Hemin (≥98%, Fluka), amodiaquine, dimethyl sulfoxide (DMSO), acetone, acetic acid, sodium acetate trihydrate, HEPES and pyridine were purchased from Sigma–Aldrich. NP-40 detergent was obtained from Pierce Biotechnology (Rockford, IL, USA); 96-well plates were purchased from Greiner Bio One (cat. no. 655 180, Cellstar).

[(2-Dimethylamino)methyl])ferrocenecarboxaldehyde (2):[17] [(Dimethylamino)methyl]ferrocene **1** (5.00 g, 20.6 mmol, 4.07 mL) and 60 mL dry Et_2O were added together after which 1.6 M *t*BuLi (19.3 mL, 1.5 equiv) was added to the mixture in a dropwise fashion and stirred for 1 h under N_2. Anhydrous *N*,*N*-dimethylformamide (DMF; 23.1 mmol, 1.79 mL, 1.2 equiv) was added to the mixture, which was further stirred for 1 h. The mixture was quenched with the addition of deionized H_2O (30 mL). The layers were separated and the aqueous phase washed with CH_2Cl_2 (3×80 mL). The organic fractions were combined, dried over Na_2SO_4 and the solvent removed under reduced pressure to give **2** as a red oil (3.37 g, quant). ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.21$ (s, 6H), 3.34 (d, $J=13.1$ Hz, 1H), 3.83 (d, $J=13.1$ Hz, 1H), 4.22 (s, 5H), 4.56 (br s, 1H), 4.61 (s, 1H), 4.78 (br s, 1H), 10.10 ppm (s, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta=44.8$, 56.6, 70.2, 70.3, 71.8, 75.8, 77.8, 86.7, 193.2 ppm.

2-[(Dimethylamino)methyl]benzaldehyde (6):[26] Compound **6** was synthesized in the manner described for **2**, however by starting from [(dimethylamino)methyl]benzene. The product was recovered as a pale-orange oil (1.92 g, quant). ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 2.20 (s, 6H), 3.70 (s, 2H), 7.32–7.35 (m, 1H), 7.38 (t, $J=1.0$ Hz, 1H), 7.47 (d, 1H), 7.84 (dd, $J=7.6$, 1.6 Hz, 1H), 10.38 ppm (s, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta=45.0$, 60.8, 127.6, 129.3, 130.3, 133.0, 134.9, 141.6, 192.0 ppm.

[(2-Dimethylamino)methyl]ferrocenecarboxaldehyde oxime (3):[17] Compound **2** (5.08 g, 17.7 mmol) was mixed with EtOH (190 mL), after which $NH_2OH{\cdot}HCl$ (3.33 g, 2.7 equiv) was added to the solution together with NaOH (51.0 mL, 2 M). The reaction was held at reflux (90 °C) overnight. The mixture was then cooled to room temperature, neutralized by the addition of excess CO_2(s), and diluted with H_2O. The product was extracted with CH_2Cl_2, and the organic fractions were combined and dried over Na_2SO_4, after which the solvent was removed under reduced pressure. The product **3** was recovered as a dark-red oil (4.43 g, 83%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=2.21$ (br s, 1H), 2.43 (br s, 6H), 3.46–3.55 (m, 1H), 3.93–3.99 (m, 1H) 4.13–4.23 (m, 5H), 4.42 (br s, 1H), 4.55 (br s, 1H), 8.05 ppm (br s, 1H).

2-[(Dimethylamino)methyl]benzaldehyde oxime (7):[26] Compound **7** was synthesized in the manner described for compound **3** starting from **6** to afford a pale-orange oil (2.09 g, quant). ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.22$ (s, 6H), 3.52 (s, 2H), 7.19–7.30 (m, 3H), 7.74–7.77 (m, 1H), 8.51–8.54 ppm (m, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta=45.1$, 61.2, 126.5, 127.4, 128.8, 130.7, 132.2, 136.4, 147.6 ppm.

[(2-Dimethylamino)methyl]ferrocenemethylamine (4):[17] Compound **3** (4.43 g, 15.6 mmol) was added to anhydrous THF (100 mL), followed by the addition of $LiAlH_4$ (1.95 g, 51.5 mmol). The reaction was stirred overnight at reflux (70 °C) under nitrogen. The reaction mixture was then diluted with Et_2O, and quenched with brine (60 mL). The layers were separated, and the aqueous phase washed with Et_2O (2×100 mL). The organic fractions were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure. The product **4** was purified by column chromatography over silica gel (80% CH_2Cl_2, 10% Et_3N, 10% EtOH) and recovered as a dark-red oil (2.69 g, 64%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=$ 2.03 (s, 6H), 2.75 (d, $J=12.5$ Hz, 1H), 3.05 (br s, 2H), 3.37 (d, $J=$ 13.5 Hz, 1H), 3.52 (d, $J=12.6$ Hz, 1H), 3.59 (d, $J=13.8$ Hz, 1H), 3.91 (br s, 1H), 3.94 (s, 5H), 4.00 (br s, 1H), 4.04 ppm (br s, 1H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$): $\delta=39.8$, 44.5, 57.6, 65.5, 68.2, 68.5, 70.5, 82.8, 88.8 ppm.

1-[2-(Aminomethyl)phenyl]-*N*,*N*-dimethylmethanamine (8):[26] Prepared from compound **7** in the same manner as described for compound **4**. Yellow oil (3.87 g, quant). ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.27$ (s, 6H), 3.50 (s, 2H), 3.90 (s, 2H), 7.25–7.38 ppm (m, 4H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta=44.7$, 57.0, 62.4, 126.7, 127.9, 129.0, 130.7, 136.6, 141.7 ppm.

***N*^{1}-(7-Chloroquinolin-4-yl)ethan-1,2-diamine (10)**:[27] 4,7-Dichloroquinoline (25.3 mmol, 5.00 g) was placed in a round-bottomed flask with ethylene diamine (4.5 equiv; 6.92 g, 7.71 mL, 113.6 mmol). The melt was stirred at 80 °C for 1 h after which the temperature was increased to 135--140 °C for a further 4 h. The reaction mixture was then cooled and neutralized with Et_3N (2.44 mL) after which it was added to a separating funnel containing 100 mL EtOAc and washed with 50 mL H_2O. The aqueous layer was washed with 100 mL EtOAc, the organic fractions were combined, dried over Na_2SO_4, and the solvent removed under vacuum. The product **10** was obtained as a yellow powder (3.67 g, 66%).

***N*^{1}-(7-Chloroquinolin-4-yl)propan-1,3-diamine (11)**:[27] Prepared in the same manner as described for compound **10** using appropriate starting materials. Yellow powder, 5.53 g, 93%.

***N*^{1}-(7-chloroquinolin-4-yl)butan-1,4-diamine (12)**:[27] Prepared in the same manner as described for compound **10** using appropriate starting materials. Yellow powder, 3.78 g, 60%.

***N*^{1}-(7-Chloroquinolin-4-yl)pentan-1,5-diamine (13)**:[27] Prepared in the same manner as described for compound **10** using appropriate starting materials. Yellow powder, 1.51 g, 54%.

***N*^{1}-(7-Chloroquinolin-4-yl)hexan-1,6-diamine (14)**:[27] Prepared in the same manner as described for compound **10** using appropriate starting materials. Yellow powder, 5.76 g, 82%.

Ethyl 2-[2-(7-chloroquinolin-4-ylamino)ethylamino]-2-oxoacetate (15): Compound **15** was prepared according to a published procedure.[22] Compound **9** (1.67 g, 7.53 mmol) was added to a solution of CH_2Cl_2 (40 mL) and Et_3N (1.10 mL) and cooled to 0 °C, followed by the dropwise addition of ethyl chlorooxoacetate (1.5 equiv). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with deionized H_2O (50 mL), and the product extracted with CH_2Cl_2 (2×100 mL). The organic fractions were collected, combined, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the product was purified by column chromatography over silica gel (90% EtOAc, 5% Et_3N, 5% EtOH) affording **15** as a white powder (0.65 g, 27%). $R_f=0.6$ (80% EtOAc, 15% Et_3N, 5% EtOH); ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.37$–1.45 (m, 3H) 3.48–3.55 (m, 2H) 3.78–3.86 (m, 2H) 4.39 (q, $J=7.1$ Hz, 2H) 6.36 (d, $J=5.4$ Hz, 1H) 7.41 (dd, $J=8.9$,

2.1 Hz, 1H) 7.76 (d, J=8.9 Hz, 1H) 7.96 (d, J=2.1 Hz, 1H) 8.53 ppm (d, J=5.4 Hz, 1H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ=14.0, 39.3, 44.9, 63.7, 98.5, 117.0, 121.6, 125.8, 128.5, 135.1, 148.9, 149.7, 151.8, 159.0, 160.2 ppm; IR (ATR): ν_{max}=3382 brm (NH), 2936 w, 1673 s (O=C–OEt), 1640 (O=C–N) vs, 1612 s (7-chloroquinoline), 1454 m, 1218 w, 759 w.

Ethyl 2-[3-(7-chloroquinolin-4-ylamino)propylamino]-2-oxoacetate (16): Prepared in the same manner as described for compound **15** using appropriate starting materials. The product was purified by column chromatography over silica gel (90% EtOAc, 5% Et_3N, 5% EtOH) affording **16** as a white powder (2.34 g, 82%). R_f=0.47 (90% EtOAc, 5% Et_3N, 5% EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43 (t, J=7.1 Hz, 3H), 1.93 (quint, J=6.1 Hz, 2H), 3.43 (q, J=6.1 Hz, 2H), 3.52 (q, J=6.4 Hz, 2H), 4.40 (q, J=7.1 Hz, 2H), 6.40 (d, J=5.5 Hz, 1H), 7.38 (dd, J=9.0, 2.1 Hz, 1H), 7.89 (d, J=9.0 Hz, 1H), 7.95 (d, J=2.1 Hz, 1H), 8.51 ppm (d, J=5.3 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ=14.0, 27.7, 36.8, 39.0, 63.7, 98.5, 117.4, 121.6, 125.5, 128.5, 135.0, 149.2, 149.6, 151.8, 158.0, 160.4 ppm; IR (ATR): ν_{max}=3373 brw (NH), 1726 w (O–C=O), 1631 vs (N–C=O), 1610 (7-chloroquinoline) vs, 1452 m, 1210 m, 758 m.

Ethyl 2-[4-(7-chloroquinolin-4-ylamino)butylamino]-2-oxoacetate (17): Prepared in the same manner as described for compound **15** using appropriate starting materials. The product was purified by column chromatography over silica gel (90% EtOAc, 5% Et_3N, 5% EtOH) affording **17** as a white powder (1.67 g, 60%). R_f=0.17 (90% CH_2Cl_2, 5% Et_3N, 5% MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.40 (t, J=1.0 Hz, 3H), 1.73–1.87 (m, 4H), 3.38 (q, J=1.0 Hz, 2H), 3.46 (q, J=6.7 Hz, 2H), 4.36 (q, J=1.0 Hz, 2H), 6.41 (d, J=5.5 Hz, 1H), 7.38 (dd, J=9.0, 2.2 Hz, 1H), 7.74 (d, J=9.0 Hz, 1H), 7.96 (d, J=2.2 Hz, 1H), 8.54 ppm (d, J=5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ=160.7, 156.9, 151.9, 149.6, 149.1, 134.9, 128.8, 125.4, 121.0, 117.2, 99.1, 63.4, 42.9, 39.4, 27.2, 25.7, 14.0 ppm; IR (ATR): ν_{max}=3377 brw (NH), 1753 w (O–C=O), 1672 m (N–C=O), 1611 vs (7-chloroquinoline), 1449 m, 1211 s, 760 w.

Ethyl 2-[5-(7-chloroquinolin-4-ylamino)pentylamino]-2-oxoacetate (18): Prepared in the same manner as described for compound **15** using appropriate starting materials. The product was purified by column chromatography over silica gel (90% EtOAc, 5% Et_3N, 5% EtOH) affording **18** as a white powder (1.76 g, 64%). R_f=0.35 (97.5% EtOAc, 2.5% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.37 (t, J=1.0 Hz, 3H), 1.50 (quint, J=1.0 Hz, 2H), 1.65 (quint, J=7.1 Hz, 2H), 1.81 (quint, J=1.0 Hz, 2H), 3.26–3.34 (m, 2H), 3.39 (q, J=6.7 Hz, 2H), 4.34 (q, J=1.0 Hz, 2H), 6.35 (dd, J=1.0 Hz, 1H), 7.33 (dd, J=1.0 Hz, 1H), 7.88–7.94 (m, 2H), 8.45 ppm (d, J=5.6 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ=14.0, 24.0, 27.8, 29.0, 39.2, 43.1, 63.3, 98.7, 117.0, 121.9, 125.4, 127.5, 135.2, 147.9, 150.4, 150.8, 157.0, 160.6 ppm; IR (ATR): ν_{max}=3272 brw (NH), 1730 w (O–C=O), 1644 vs (N–C=O), 1614 vs (7-chloroquinoline), 1455 m, 1208 s, 763 s.

Ethyl 2-[6-(7-chloroquinolin-4-ylamino)hexylamino]-2-oxoacetate (19): Prepared in the same manner as described for compound **15** using appropriate starting materials. The product was purified by column chromatography over silica gel (90% EtOAc, 5% Et_3N, 5% EtOH) affording **19** as a white solid (1.77 g, 65%). R_f=0.68 (90% EtOAc, 5% EtOH, 5% Et_3N); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (t, J=1.0 Hz, 3H), 1.41–1.48 (m, 2H), 1.48–1.56 (m, 2H), 1.62 (quint, J=7.2 Hz, 2H), 1.77 (quint, J=7.2 Hz, 2H), 3.32 (q, J=1.0 Hz, 2H), 3.38 (q, J=7.0 Hz, 2H), 4.35 (q, J=1.0 Hz, 2H), 6.40 (d, J=5.5 Hz, 1H), 7.37 (dd, J=9.0, 2.1 Hz, 1H), 7.72 (d, J=8.8 Hz, 1H), 7.96 (d, J=2.1 Hz, 1H), 8.52 ppm (d, J=5.3 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ=14.0, 26.3, 26.5, 28.6, 29.1, 39.5, 43.0, 63.3, 99.0, 117.1, 121.0, 125.3, 128.6, 134.9, 148.9, 149.8, 151.8, 156.7, 160.8 ppm; IR (ATR): ν_{max}=3360 w (NH), 1729 m (O–C=O), 1675 vs (N–C=O), 1609 m (7-chloroquinoline), 1456 m, 1209 s, 737 m.

***N*^{1}-(7-Chloroquinolin-4-yl)-*N*^{2}-{2-[(dimethylamino)methyl]ferrocenylmethyl}ethan-1,2-diamine (A2)**: Compound **A2** was synthesized according to a published procedure.[23] Compounds **2** (200 mg, 0.823 mmol), **10** (273 mg, 1.23 mmol), $NaCNBH_3$ (103.4 mg, 2 equiv), and *p*-toluenesulfonic acid (17.2 mg, 0.100 mmol) were added to 6 mL MeOH, and stirred for 18 h at room temperature under nitrogen. The reaction was quenched with 30 mL deionized H_2O. The product was extracted with 2× 50 mL CH_2Cl_2 and purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **A2** as a red solid (147 mg, 38%). R_f=0.20 (7% Et_3N, 93% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.04 (s, 6H), 2.80 (d, J=12.7 Hz, 1H), 2.94 (d, J=5.1 Hz, 2H), 3.27–3.42 (m, 2H), 3.44 (d, J=13.3 Hz, 1H), 3.70 (d, J=12.7 Hz, 1H), 3.92 (d, J=13.1 Hz, 1H), 4.06 (s, 5H), 4.06–4.07 (m, 1H), 4.11–4.15 (m, 1H), 4.17 (d, J=2.1 Hz, 1H), 6.34 (d, J=5.3 Hz, 1H), 7.35 (dd, J=8.8, 2.1 Hz, 1H), 7.86 (d, J=9.0 Hz, 1H), 7.93 (d, J=2.1 Hz, 1H), 8.50 ppm (d, J=5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ=43.6, 44.7, 46.2, 48.0, 58.1, 66.0, 69.1, 70.5, 71.3, 84.0, 97.8, 117.7, 123.0, 124.9, 128.1, 134.4, 149.1, 150.5, 151.9 ppm; IR (ATR): ν_{max}=2944 brw (NH), 1610 w (7-chloroquinoline), 1139 w, 1104 w (ferrocene); HRMS (EI) m/z $[M+H]^+$ 477.1519, $C_{25}H_{30}ClFeN_4$ requires 477.1508.

***N*^{1}-(7-Chloroquinolin-4-yl)-*N*^{3}-{2-[(dimethylamino)methyl]ferrocenylmethyl}propan-1,3-diamine (A3)**: Prepared in the same manner as described for compound **A2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **A3** as a red solid (112 mg, 28%). R_f=0.25 (3% Et_3N, 5% MeOH, 92% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.78–1.96 (m, 2H), 2.07–2.10 (m, 6H), 2.79 (d, J=12.7 Hz, 1H), 2.97 (brs, 2H), 3.35–3.42 (m, 2H), 3.46 (d, J=12.5 Hz, 1H), 3.75 (d, J=12.7 Hz, 1H), 3.89 (d, J=12.5 Hz, 1H), 4.06–4.08 (m, 5H), 4.12–4.14 (m, 1H), 4.17 (d, J=1.0 Hz, 1H), 4.19–4.22 (m, 1H), 6.23 (dd, J=5.4, 1.3 Hz, 1H), 7.12–7.17 (m, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.85–7.88 (m, 1H), 8.45 ppm (dd, J=5.4, 1.3 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ=26.5, 43.6, 44.7, 46.2, 48.0, 58.1, 66.0, 69.1, 70.5, 71.3, 84.0, 97.8, 117.7, 123.0, 124.9, 128.1, 134.4, 149.1, 150.6, 151.94 ppm; IR (ATR): ν_{max}=3365 brw (NH), 1610 w (7-chloroquinoline), 1132 w, 1104 w (ferrocene); HRMS (EI) m/z $[M+2H]^+$ 492.4088, $C_{26}H_{33}ClFeN_4$ requires 492.1745.

***N*^{1}-(7-Chloroquinolin-4-yl)-*N*^{4}-{2-[(dimethylamino)methyl]ferrocenylmethyl}butan-1,4-diamine (A4)**: Prepared in the same manner as described for compound **A2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **A4** as a red solid (313 mg, 69%). R_f=0.16 (5% Et_3N, 5% EtOH, 90% CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.60–1.75 (m, 2H), 1.75–1.91 (m, 2H), 2.14 (s, 6H), 2.61–2.72 (m, 2H), 2.80 (d, J=12.8 Hz, 1H), 3.20–3.35 (m, 2H), 3.46 (d, J=12.6 Hz, 1H), 3.74 (d, J=12.9 Hz, 1H), 3.99 (d, J=3.7 Hz, 1H), 4.05 (s, 6H), 4.12 (s, 1H), 4.16 (brs, 1H), 6.29 (d, J=5.3 Hz, 1H), 7.27 (d, J=6.7 Hz, 1H), 7.88 (s, 1H), 8.00 (d, J=8.2 Hz, 1H), 8.43 ppm (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.7, 26.4, 42.8, 44.9, 46.7, 47.4, 58.1, 66.7, 69.4, 71.0, 71.8, 82.7, 84.1, 98.7, 117.8, 123.1, 125.3, 128.3, 134.8, 149.3, 150.6, 152.2 ppm; IR (ATR): ν_{max}=3278 brw (NH), 1609 w (7-chloroquinoline), 1137 w, 1104 w (ferrocene); HRMS (EI) m/z $[M+H]^+$ 515.1820, $C_{27}H_{34}ClFeN_4$ requires 505.1821.

***N*¹-(7-Chloroquinolin-4-yl)-*N*⁵-{2-[(dimethylamino)methyl]ferrocenyl}pentan-1,5-diamine (A5)**: Prepared in the same manner as described for compound **A2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **A5** as a red solid (208 mg, 53%). R_f = 0.24 (92% CH_2Cl_2, 4% MeOH, 4% Et_3N); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.58 (br s, 2H), 1.70 (d, J = 5.5 Hz, 2H), 1.80 (br s, 2H), 2.08 (s, 6H), 2.61–2.77 (m, 2H), 2.84 (d, J = 12.9 Hz, 1H), 3.40 (br s, 2H), 3.83 (d, J = 12.9 Hz, 1H), 4.12 (s, 5H), 4.14–4.17 (m, 1H), 4.19 (br s, 1H), 4.27 (br s, 1H), 4.37 (d, J = 13.3 Hz, 1H), 6.33 (d, J = 5.5 Hz, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.86–7.92 (m, 1H), 8.37 (d, J = 9.0 Hz, 1H), 8.46 ppm (d, J = 5.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 23.3, 26.1, 26.9, 41.9, 44.2, 45.2, 46.6, 57.7, 66.9, 69.3, 69.6, 71.3, 71.7, 83.8, 98.4, 117.6, 123.4, 125.0, 128.0, 134.8, 149.1, 150.4, 151.6 ppm; IR (ATR): ν_{max} = 3273 brw (NH), 1609 w (7-chloroquinoline), 1137 w, 1104 w (ferrocene).

***N*¹-(7-Chloroquinolin-4-yl)-*N*⁶-{2-[(dimethylamino)methyl]ferrocenyl}hexane-1,6-diamine (A6)**: Prepared in the same manner as described for compound **A2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **A6** as a red solid (176 mg, 37%). R_f = 0.47 (92% CH_2Cl_2, 4% MeOH, 4% Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27–1.45 (m, 6H), 1.61–1.76 (m, 2H), 2.05–2.16 (m, 6H), 2.78 (d, J = 12.8 Hz, 1H), 3.16–3.32 (m, 2H), 3.44–3.59 (m, 2H), 3.80 (d, J = 12.8 Hz, 1H), 4.06 (s, 5H), 4.10–4.14 (m, 1H), 4.14–4.20 (m, 1H), 4.27 (d, J = 13.7 Hz, 1H), 6.30 (d, J = 5.5 Hz, 1H), 7.30 (dd, J = 8.9, 2.1 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.42 ppm (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7, 26.0, 26.7, 27.6, 42.4, 44.2, 44.7, 45.7, 57.6, 66.5, 69.3, 71.1, 71.5, 83.9, 98.5, 117.4, 122.6, 124.8, 127.9, 134.6, 148.9, 150.4, 151.5 ppm; HRMS (EI) m/z $[M+H]^+$ 533.2129, $C_{29}H_{38}ClFeN_4$ requires 533.2134.

***N*¹-(7-Chloroquinolin-4-yl)-*N*²-{2-[(dimethylamino)methyl]benzyl}ethan-1,2-diamine (B2)**: Compound **B2** was synthesized according to a published procedure.[24] Compounds **6** (200 mg, 1.2 mmol), **10** (247 mg, 1.1 mmol), $NaCNBH_3$ (140 mg, 2 equiv), and *p*-toluenesulfonic acid (21.0 mg, 0.122 mmol) were mixed in 6 mL anhydrous MeOH and stirred for 18 h at room temperature under nitrogen. The reaction was quenched with 30 mL deionized H_2O. The product was extracted with CH_2Cl_2 (2×50 mL). The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **B2** as a white powder (135 mg, 40%). R_f = 0.29 (6% Et_3N, 94% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 6H), 3.04 (t, J = 1.0 Hz, 2H), 3.53 (t, J = 5.5 Hz, 2H), 3.58 (s, 2H), 3.99 (s, 2H), 6.34 (d, J = 5.5 Hz, 1H), 7.22–7.26 (m, 1H), 7.28–7.38 (m, 4H), 7.88–7.93 (m, 2H), 8.47 ppm (d, J = 5.3 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ = 41.5 (2C), 44.2, 46.2), 51.8, 62.5, 98.7, 117.3, 122.1, 125.6, 128.4, 128.5, 128.9, 131.2, 131.6, 135.1, 135.7, 136.6, 149.0, 149.9, 151.8 ppm; IR (ATR): ν_{max} = 3252 brw (NH), 1610 w (7-chloroquinoline), 1577 vs (aromatic C–C); HRMS (EI) m/z $[M+H]^+$ 369.1852, $C_{21}H_{25}ClN_4$ requires 368.1846, $[M+Na^+]$ 391.2847.

***N*¹-(7-Chloroquinolin-4-yl)-*N*³-{2-[(dimethylamino)methyl]benzyl}propan-1,3-diamine (B3)**: Prepared in the same manner as described for compound **B2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **B3** as a white powder (228 mg, 54%). R_f = 0.47 (6% Et_3N, 94% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (quint, J = 10.7 Hz, 5H), 2.20 (s, 6H), 2.97 (t, J = 1.0 Hz, 2H), 3.38–3.43 (m, 2H), 3.47 (s, 2H), 3.84 (s, 2H), 6.26 (d, J = 5.5 Hz, 1H), 6.96 (dd, J = 9.0, 2.2 Hz, 1H), 7.28–7.38 (m, 4H), 7.42 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 8.47 ppm (d, J = 5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ = 26.9, 43.9, 44.9, 49.0, 52.9, 62.8, 97.9, 117.6, 122.7, 124.7, 127.5, 128.2, 131.0, 131.5, 134.4, 137.5, 138.7, 149.1, 150.6, 152.0 ppm; IR (ATR): ν_{max} = 3264 brw (NH), 1610 w (7-chloroquinoline), 1585 vs (aromatic C–C); HRMS (EI) m/z $[M+H]^+$ 383.2003, $C_{22}H_{27}ClN_4$ requires 383.2002.

***N*¹-(7-Chloroquinolin-4-yl)-*N*⁴-{2-[(dimethylamino)methyl]benzyl}butan-1,4-diamine (B4)**: Prepared in the same manner as described for compound **B2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **B4** as a white powder (250 mg, 52%). R_f = 0.40 (4% Et_3N, 5% MeOH, 91% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (quint, J = 6.7 Hz, 2H), 1.90 (quint, J = 6.6 Hz, 2H), 2.21 (s, 6H), 2.72 (t, J = 6.4 Hz, 2H), 3.31 (t, J = 6.2 Hz, 2H), 3.46 (s, 2H), 3.87 (s, 2H), 6.36 (d, J = 5.5 Hz, 1H), 7.17 (dd, J = 9.0, 2.2 Hz, 1H), 7.25–7.35 (m, 4H), 7.79 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 8.52 ppm (d, J = 5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ = 26.4, 27.7, 43.3, 45.2, 48.3, 52.5, 62.9, 98.8, 117.7, 122.5, 124.9, 127.4 127.9, 128.5, 130.7, 131.5, 134.7, 137.6, 139.1, 149.4, 150.5, 152.2 ppm; IR (ATR): ν_{max} = 3303 brw (NH), 1610 w (7-chloroquinoline), 1581 vs (aromatic C–C); HRMS (EI) m/z $[M+H]^+$ 397.2142, $C_{23}H_{29}ClN_4$ requires 397.2159, $[M+K]^+$ 436.2434.

***N*¹-(7-Chloroquinolin-4-yl)-*N*⁵-{2-[(dimethylamino)methyl]benzyl}pentan-1,5-diamine (B5)**: Prepared in the same manner as described for compound **B2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **B5** as a white powder (135 mg, 74%). R_f = 0.22 (7% Et_3N, 93% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (quint, J = 7.8 Hz, 2H), 1.64 (quint, J = 6.6 Hz, 2H), 1.72 (quint, J = 6.9 Hz, 2H), 2.10 (s, 6H), 2.63 (t, J = 6.5 Hz, 2H), 3.30 (q, J = 6.5 Hz, 2H), 3.41 (s, 2H), 3.89 (s, 2H), 6.29 (d, J = 5.5 Hz, 1H), 7.15–7.19 (m, 1H), 7.22–7.30 (m, 4H), 7.85 (d, J = 2.2 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 8.42 ppm (d, J = 5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ = 24.0, 27.7, 42.3, 44.7, 51.7, 62.5, 98.7, 117.4, 122.1, 125.1, 128.4, 128.5, 131.3, 131.5, 134.7, 137.1, 149.2, 150.0, 151.9 ppm; IR (ATR): ν_{max} = 3231 brw (NH), 1609 w (7-chloroquinoline), 1577 vs (aromatic C–C); HRMS (EI) m/z $[M+H]^+$ 411.2315, $C_{24}H_{31}ClN_4$ requires 411.2315.

***N*¹-(7-Chloroquinolin-4-yl)-*N*⁶-{2-[(dimethylamino)methyl]benzyl}hexan-1,6-diamine (B6)**: Prepared in the same manner as described for compound **B2** using appropriate starting materials. The product was purified by column chromatography over silica gel (95% CH_2Cl_2, 2.5% Et_3N, 2.5% EtOH) affording **B6** as a white powder (128 mg, 40%). R_f = 0.39 (3% Et_3N, 5% MeOH, 91% CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.34 (m, 4H), 1.44 (quint, J = 7.2 Hz, 2H), 1.58 (quint, J = 7.1 Hz, 2H), 2.27 (s, 6H), 2.72 (t, J = 7.2 Hz, 2H), 3.28 (t, J = 6.9 Hz, 2H), 3.53 (s, 2H), 3.95 (s, 2H), 6.36 (d, J = 5.5 Hz, 1H), 7.24–7.27 (m, 1H), 7.29–7.38 (m, 4H), 7.89 (d, J = 2.2 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.46 ppm (d, J = 5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ = 26.5, 28.1, 28.4, 42.7, 44.3, 45.9, 47.7, 51.4, 62.2, 98.5, 117.1, 122.1, 124.7, 127.6, 127.9, 128.1, 130.9, 131.1, 134.5, 136.1, 136.64, 148.6, 150.1, 151.4 ppm; IR (ATR): ν_{max} = 3229 brw (NH), 1609 w (7-chloroquinoline), 1576 vs (aromatic C–C); HRMS (EI) m/z $[M+H]^+$ 425.2478, $C_{25}H_{33}ClN_4$ requires 425.2472, $[M+K]^+$ 464.2778.

***N*¹-[2-(7-Chloroquinolin-4-ylamino)ethyl]-*N*²-{2-[(dimethylamino)-methyl]ferrocenylmethyl}oxalamide (C2)**: Compounds **15** (120 mg, 0.373 mmol) and **4** (203 mg, 0.746 mmol) were dissolved in 3 mL dry EtOH, and stirred at 40 °C for 18 h in a dry 50 mL round-bottomed flask under nitrogen. The solvent was then removed, and the resulting residue was dissolved in CH_2Cl_2. The product was purified by column chromatography over silica gel

(5% Et_3N, 5% EtOH, 90% EtOAc) affording **C2** as a red solid (204 mg, 64% yield). $R_f = 0.40$ (5% Et_3N, 5% EtOH, 90% EtOAc); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.33$ (s, 6H), 2.98 (d, $J = 12.8$ Hz, 1H), 3.07 (s, 1H), 3.16 (s, 1H), 3.47 (quint, $J = 5.3$ Hz, 1H), 3.75 (quint, $J = 6.2$ Hz, 1H), 3.88 (d, $J = 12.5$ Hz, 2H), 4.06 (t, $J = 2.5$ Hz, 1H), 4.11 (s, 5H), 4.14–4.17 (m, 1H), 4.19 (d, $J = 2.1$ Hz, 1H), 6.32 (d, $J = 5.4$ Hz, 1H), 7.25 (d, $J = 2.1$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.96 (d, $J = 2.1$ Hz, 1H), 8.49 ppm (d, $J = 5.4$ Hz, 1H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 38.3$, 38.9, 44.2, 45.0, 57.8, 66.3, 69.2, 70.0, 71.2, 83.4, 98.3, 117.1, 122.1, 125.4, 127.9, 135.2, 150.3, 151.2, 148.2, 158.5, 162.5 ppm; IR (ATR): $\nu_{max} = 3292$ brw, 1659 s (N–C=O), 1611 w (7-chloroquinoline), 1579 s (7-chloroquinoline), 1505 s (N–C=O), 1141 w, 1001 w (ferrocene); HRMS (EI) m/z $[M+H]^+$ 548.1509, $C_{27}H_{31}ClFeN_5O_2$ requires 548.1504.

***N*^{1}-[3-(7-Chloroquinolin-4-ylamino)propyl]-*N*^{3}-{2-[(dimethylamino)methyl]ferrocenylmethyl}oxalamide (C3)**: Prepared in the same manner as described for compound **C2** using appropriate starting materials. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **C3** as a red solid (92 mg, 44% yield). $R_f = 0.42$ (5% Et_3N, 5% EtOH, 90% EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.85$–1.93 (m, 2H), 2.24 (s, 6H), 2.88 (d, $J = 12.7$ Hz, 1H), 3.37 (d, $J = 5.5$ Hz, 2H), 3.42–3.50 (m, 2H), 3.81 (d, $J = 12.5$ Hz, 1H), 4.05 (t, $J = 2.4$ Hz, 1H), 4.11 (s, 5H), 4.12–4.17 (m, 2H), 4.20 (s, 1H), 4.53 (dd, $J = 14.3$, 8.6 Hz, 1H), 6.39 (d, $J = 5.5$ Hz, 1H), 7.32 (dd, $J = 8.9$, 2.0 Hz, 1H), 7.88 (d, $J = 8.9$ Hz, 1H), 7.95 (d, $J = 2.0$ Hz, 1H), 8.50 ppm (d, $J = 5.5$ Hz, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta = 27.8$, 36.4, 38.4, 38.8, 44.4, 57.9, 65.9, 69.2, 69.8, 71.2, 83.4, 84.3, 98.5, 117.6, 121.6, 125.1, 128.7, 134.8, 149.8, 151.9, 158.5, 161.5, 165.5 ppm; IR (ATR): $\nu_{max} = 3304$ brw (NH), 1659 s (N–C=O), 1610 w, 1578 s (7-chloroquinoline), 1505 s (N–C=O), 1138 w, 1104 w (ferrocene); HRMS (EI) m/z $[M+H]^+$ 562.1675, $C_{28}H_{33}ClFeN_5O_2$ requires 562.1672.

***N*^{1}-[4-(7-Chloroquinolin-4-ylamino)butyl]-*N*^{4}-{2-[(dimethylamino)methyl]ferrocenylmethyl}oxalamide (C4)**: Prepared in the same manner as described for compound **C2** using appropriate starting materials. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **C4** as a red solid (142 mg, 63% yield). $R_f = 0.44$ (5% Et_3N, 5% EtOH, 90% EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.71$–1.76 (m, 2H), 1.77–1.83 (m, 2H), 2.19 (s, 6H), 2.85 (d, $J = 12.7$ Hz, 1H), 3.32–3.38 (m, 2H), 3.41 (d, $J = 6.8$ Hz, 2H), 3.77 (d, $J = 12.7$ Hz, 1H), 4.03 (t, $J = 2.4$ Hz, 1H), 4.10 (s, 5H), 4.12 (d, $J = 2.2$ Hz, 2H), 4.19 (s, 1H), 4.51 (dd, $J = 14.4$, 8.5 Hz, 1H), 6.40 (d, $J = 5.5$ Hz, 1H), 7.35 (dd, $J = 8.9$, 2.3 Hz, 1H), 7.75 (d, $J = 8.9$ Hz, 1H), 7.96 (d, $J = 2.3$ Hz, 1H), 8.53 ppm (d, $J = 5.5$ Hz, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta = 25.6$, 27.6, 38.2, 39.0, 43.2, 44.4, 57.9, 65.9, 69.1, 69.7, 71.1, 83.6, 84.3, 99.1, 117.2, 121.1, 125.3, 128.8, 134.8, 149.1, 149.7, 152.0, 158.9, 160.5 ppm; IR (ATR): $\nu_{max} = 3303$ brw (NH), 1659 s (N–C=O), 1610 w, 1578 s (7-chloroquinoline), 1505 s (N–C=O), 1032 w, 1001 w (ferrocene); HRMS (EI) m/z $[M+H]^+$ 576.1831, $C_{29}H_{35}ClFeN_5O_2$ requires 576.1829.

***N*^{1}-[5-(7-Chloroquinolin-4-ylamino)pentyl]-*N*^{5}-{2-[(dimethylamino)methyl]ferrocenylmethyl}oxalamide (C5)**: Prepared in the same manner as described for compound **C2** using appropriate starting materials. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **C5** as a red solid (90 mg, 58% yield). $R_f = 0.49$ (5% Et_3N, 5% EtOH, 90% EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.47$–1.57 (m, 2H), 1.59–1.71 (m, 2H), 1.80 (quint, $J = 7.4$ Hz, 2H), 2.19 (s, 6H), 2.86 (d, $J = 12.5$ Hz, 1H), 3.28–3.32 (m, 2H), 3.33–3.37 (m, 2H), 3.76 (d, $J = 12.7$ Hz, 1H), 4.04 (t, $J = 2.5$ Hz, 1H), 4.10 (s, 5H), 4.11–4.13 (m, 2H), 4.19 (s, 1H), 4.50 (dd, $J = 14.3$, 8.6 Hz, 1H), 6.40 (d, $J = 5.5$ Hz, 1H), 7.35 (dd, $J = 8.8$, 2.2 Hz, 1H), 7.67 (d, $J = 8.8$ Hz, 1H), 7.96 (d, $J = 2.2$ Hz, 1H), 8.54 ppm (d, $J = 5.5$ Hz, 1H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$): $\delta = 24.3$, 28.4, 29.1, 38.2, 39.1, 43.1, 44.4, 58.0, 66.0, 69.2, 69.7, 71.1, 83.6, 84.2, 99.1, 117.1, 120.9, 125.3, 128.8, 134.9, 149.1, 149.7, 152.0, 159.0, 160.3 ppm; IR (ATR): $\nu_{max} = 3305$ brw (NH), 1659 s (N–C=O), 1609 w, 1578 s (7-chloroquinoline) 1505 s (N–C=O), 1033 w, 1001 w (ferrocene); HRMS (EI) m/z $[M+H]^+$ 590.1992, $C_{30}H_{37}ClFeN_5O_2$ requires 590.1985.

***N*^{1}-[6-(7-Chloroquinolin-4-ylamino)hexyl]-*N*^{6}-{2-[(dimethylamino)methyl]ferrocenylmethyl}oxalamide (C6)**: Prepared in the same manner as described for compound **C2** using appropriate starting materials. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **C6** as a red solid (239 mg, 94% yield). $R_f = 0.51$ (5% Et_3N, 5% EtOH, 90% EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$–1.46 (m, 2H), 1.49 (br s, 2H), 1.54–1.63 (m, 2H), 1.75 (t, $J = 7.0$ Hz, 2H), 2.17 (s, 6H), 2.84 (d, $J = 12.7$ Hz, 1H), 3.26–3.35 (m, 4H), 3.75 (d, $J = 12.7$ Hz, 1H), 4.02 (t, $J = 2.4$ Hz, 1H), 4.10 (s, 5H), 4.10–4.12 (m, 2H), 4.17–4.19 (m, 1H), 4.48 (d, $J = 8.6$ Hz, 1H), 6.40 (d, $J = 5.5$ Hz, 1H), 7.36 (dd, $J = 9.0$, 2.2 Hz, 1H), 7.70 (d, $J = 9.0$ Hz, 1H), 7.96 (d, $J = 2.2$ Hz, 1H), 8.53 ppm (d, $J = 5.5$ Hz, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta = 26.4$, 28.6, 29.2, 30.9, 38.1, 39.1, 42.9, 44.4, 58.0, 65.9, 69.1, 69.6, 71.0, 83.6, 84.4, 99.1, 117.1, 120.9, 125.2, 128.9, 134.8, 149.1, 149.6, 152.1, 159.0, 160.2 ppm; IR (ATR): $\nu_{max} = 3303$ brw, 2932 w (NH), 1659 s (N–C=O), 1610 w, 1578 s (7-chloroquinoline), 1504 s (N–C=O), 1032 w, 1011 w (ferrocene); HRMS (EI) m/z $[M+H]^+$ 604.2128, $C_{31}H_{39}ClFeN_5O_2$ requires 604.2142.

***N*^{1}-[2-(7-Chloroquinolin-4-ylamino)ethyl]-*N*^{2}-{2-[(dimethylamino)methyl]benzyl}oxalamide (D2)**: Compounds **15** (70.0 mg, 0.217 mmol) and **8** (70.6 mg, 0.43 mmol) were dissolved in 3 mL dry EtOH and stirred at 40 °C for 18 h in a dry 50 mL round-bottomed flask under nitrogen. The solvent was then removed, and the resulting residue was dissolved in CH_2Cl_2. The product was purified by column chromatography over silica gel. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **D2** as a white powder (48 mg, 50% yield). $R_f = 0.36$ (5% Et_3N, 5% EtOH, 90% EtOAc); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.35$ (s, 6H), 3.43–3.51 (m, 2H), 3.53 (s, 2H), 3.73–3.82 (m, 2H), 4.49 (d, $J = 5.9$ Hz, 2H), 6.31 (d, $J = 5.6$ Hz, 1H), 7.21–7.29 (m, 4H), 7.32–7.36 (m, 1H), 7.82 (d, $J = 9.0$ Hz, 1H), 7.97 (d, $J = 2.1$ Hz, 1H), 8.47 ppm (d, $J = 5.4$ Hz, 1H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) 38.9, 43.0, 44.4, 45.2, 62.9, 98.2, 116.9, 122.1, 125.4, 127.5, 127.5, 128.0, 128.5, 130.5, 131.5, 135.4, 137.0, 137.5, 150.6, 150.7, 158.6, 162.8 ppm; IR (ATR): $\nu_{max} = 3295$ brw, 2924 w (NH), 1656 s (N–C=O), 1610 w, 1582 s (7-chloroquinoline) 1537 s (N–C=O), 1514 s (aromatic C=C); HRMS (EI) m/z $[M+H]^+$ 440.1853, $C_{23}H_{27}ClFeN_5O_2$ requires 440.1842.

***N*^{1}-[3-(7-Chloroquinolin-4-ylamino)propyl]-*N*^{3}-{2-[(dimethylamino)methyl]benzyl}oxalamide (D3)**: Prepared in the same manner as described for compound **D2** using appropriate starting materials. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **D3** as a white powder (37 mg, 22% yield). $R_f = 0.37$ (5% Et_3N, 5% EtOH, 90% EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.93$ (quint, $J = 5.9$ Hz, 2H), 2.31 (s, 6H), 3.40–3.45 (m, 2H), 3.45–3.50 (m, 2H), 3.52 (s, 2H), 4.51 (d, $J = 5.9$ Hz, 2H), 6.41 (d, $J = 6.1$ Hz, 1H), 7.23–7.25 (m, 1H), 7.27–7.38 (m, 4H), 8.03 (d, $J = 2.2$ Hz, 1H), 8.07 (d, $J = 9.0$ Hz, 1H), 8.41 ppm (d, $J = 5.9$ Hz, 1H); $^{13}C\{H\}$ NMR (101 MHz, $CDCl_3$): $\delta = 30.1$, 36.7, 39.5, 43.2, 44.7, 63.0, 98.3, 117.2, 122.7, 126.1, 126.3, 128.3, 128.8, 130.8, 131.7, 136.5, 137.2, 137.7, 149.1, 151.8, 153.5, 159.1, 161.8 ppm; IR (ATR): $\nu_{max} = 3309$ brw, 2935 w (NH), 1650 s (N–C=O), 1611 w, 1578 s (7-chloroquinoline), 1544 s (N–C=O), 1510 s (aromat-

ic C=C); HRMS (EI) *m/z* $[M+H]^+$ 454.2006, $C_{24}H_{29}ClFeN_5O_2$ requires 454.2010.

***N*^{1}-[4-(7-Chloroquinolin-4-ylamino)butyl]-*N*^{4}-{2-[(dimethylamino)-methyl]benzyl}oxalamide (D4)**: Prepared in the same manner as described for compound **D2** using appropriate starting materials. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **D4** as a white powder (134 mg, 76% yield). R_f = 0.38 (5% Et_3N, 5% EtOH, 90% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71–1.76 (m, 2H), 1.76–1.81 (m, 2H), 2.27 (s, 6H), 3.32–3.38 (m, 2H), 3.41 (q, *J* = 6.5 Hz, 2H), 3.50 (s, 2H), 4.50 (d, *J* = 5.9 Hz, 2H), 6.39 (d, *J* = 5.5 Hz, 1H), 7.13–7.18 (m, 1H), 7.21–7.24 (m, 2H), 7.28–7.30 (m, 1H), 7.34 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.36–7.39 (m, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 2.2 Hz, 1H), 8.52 ppm (d, *J* = 5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ = 25.9, 27.9, 39.4, 43.1, 43.5, 44.8, 63.3, 99.4, 117.5, 121.5, 125.7, 128.2, 128.8, 129.0, 130.9, 131.7, 135.2, 137.4, 138.0, 150.1, 152.2, 159.6, 160.9 ppm; IR (ATR): ν_{max} = 3285 brw, 2937 w (NH), 1652 s (N–C=O), 1610 w, 1577 s (7-chloroquinoline), 1505 s (aromatic C=C); HRMS (EI) *m/z* $[M+H]^+$ 468.2156, $C_{25}H_{31}ClFeN_5O_2$ requires 468.2166.

***N*^{1}-[6-(7-Chloroquinolin-4-ylamino)hexyl]-*N*^{6}-{2-[(dimethylamino)-methyl]benzyl}oxalamide (D6)**: Prepared in the same manner as described for compound **D2** using appropriate starting materials. The product was purified by column chromatography over silica gel (5% Et_3N, 5% EtOH, 90% EtOAc) affording **D6** as a white powder (239 mg, 79% yield). R_f = 0.57 (5% Et3N, 5% EtOH, 90% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.51 (m, 4H), 1.56 (quint, *J* = 7.1 Hz, 2H), 1.72 (quint, *J* = 7.2 Hz, 2H), 2.25 (s, 6H), 3.29 (quint, *J* = 6.6 Hz, 4H), 3.47 (s, 2H), 4.49 (d, *J* = 6.1 Hz, 2H), 6.38 (d, *J* = 5.5 Hz, 1H), 7.19–7.22 (m, 1H), 7.24–7.28 (m, 2H), 7.33 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.35–7.38 (m, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 8.51 ppm (d, *J* = 5.5 Hz, 1H); ^{13}C{H} NMR (101 MHz, $CDCl_3$): δ = 26.2, 26.4, 28.46, 29.1, 39.1, 42.7, 42.8, 44.5, 63.0, 99.0, 117.1, 121.1, 125.2, 127.8, 128.4, 128.7, 130.5, 131.3, 134.8, 137.1, 137.6, 149.0, 149.7, 151.9, 159.4, 160.2 ppm; IR (ATR): ν_{max} = 3253 brw, 2928 w (NH), 1655 s (N–C=O), 1612 w, 1577 s (7-chloroquinoline), 1543 s (N–C=O), 1512 (aromatic C=C); HRMS (EI) *m/z* $[M+H]^+$ 496.2465, $C_{27}H_{35}ClFeN_5O_2$ requires 496.2479.

Ethyl 2-([2-(7-chloroquinolin-4-ylamino)ethyl]-{2-[(dimethylamino)methyl]benzyl}amino)-2-oxoacetate (E2): Compound **E2** was synthesized according to a published procedure.[22] **B2** (100 mg, 0.270 mmol) was dissolved in a mixture of dry CH_2Cl_2 (3 mL) and Et_3N (2 mL), followed by the dropwise addition of ethyl 2-chloro-2-oxoacetate (45.0 μL, 0.400 mmol) at 0 °C for 2 h under nitrogen. The product was purified by column chromatography over silica gel (96.5% CH_2Cl_2, 3.5% Et_3N) affording **E2** as a yellow semi-solid (126 mg, 99%). R_f = 0.64 (96.5% CH_2Cl_2, 3.5% Et_3N); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 130 °C): δ = 1.20 (q, *J* = 7.0 Hz, 3H), 2.13 (brs, 6H), 3.36–3.55 (m, 6H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.71 (s, 2H), 6.44 (d, *J* = 5.5 Hz, 1H), 7.16–7.31 (m, 4H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.39 ppm (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (151 MHz, [D$_6$]DMSO, 130 °C): δ = 12.7, 40.80, 43.8, 45.7, 47.8, 60.4, 61.0, 98.1, 116.9, 123.1, 123.7, 126.4, 126.7, 127.7, 129.7, 133.3, 134.4, 135.3, 136.3, 147.6, 150.0, 150.3, 162.4, 163.4 ppm; IR (ATR): ν_{max} = 2926 brw (NH), 1732 w (EtO–C=O), 1601 s, 1574 s (7-chloroquinoline), 1454 s (aromatic C=C); HRMS (EI) *m/z* $[M+H]^+$ 469.2018, $C_{25}H_{30}ClN_4O_3$ requires 469.2006.

Ethyl-2-([3-(7-chloroquinolin-4-ylamino)propyl]-{2-[(dimethylamino)methyl]benzyl}amino)-2-oxoacetate (E3): Prepared in the same manner as described for compound **E2** using appropriate starting materials. The product was purified by column chromatography over silica gel (96.5% CH_2Cl_2, 3.5% Et_3N) affording **E3** as a yellow semi-solid (160 mg, 88%). R_f = 0.70 (90% CH_2Cl_2, 5% Et_3N, 5% MeOH); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 130 °C): δ = 1.20 (brs, 3H), 1.95 (quint, *J* = 14.4 Hz, 2H), 2.07–2.16 (m, 6H), 3.29 (brs, 4H), 3.36 (brs, 2H), 4.18–4.26 (m, 2H), 4.74 (brs, 2H), 6.41 (d, *J* = 5.3 Hz, 1H), 7.23 (brs, 4H), 7.38 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 8.41 ppm (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (151 MHz, [D$_6$]DMSO, 130 °C): δ = 12.7, 25.6, 42.1, 44.0, 44.9, 47.2, 60.6, 61.0, 98.2, 117.2, 123.0, 123.4, 126.4, 126.6, 126.9, 129.6, 132.9, 134.5, 135.3, 136.4, 148.7, 149.5, 151.1, 161.6, 162.4 ppm; IR (ATR): ν_{max} = 2939 w, 2815 w (NH), 1737 m (EtO–C=O), 1644 s (N–C=O), 1609 m, 1577 vs (7-chloroquinoline), 1450 m (aromatic C=C); HRMS (EI) *m/z* $[M+H]^+$ 483.2178, $C_{26}H_{32}ClN_4O_3$ requires 483.2163.

Ethyl 2-([4-(7-chloroquinolin-4-ylamino)butyl]-{2-[(dimethylamino)methyl]benzyl}amino)-2-oxoacetate (E4): Prepared in the same manner as described for compound **E2** using appropriate starting materials. The product was purified by column chromatography over silica gel (96.5% CH_2Cl_2, 3.5% Et_3N) affording **E4** as a yellow semi-solid (186 mg, 59%). R_f = 0.34 (95% CH_2Cl_2, 5% Et_3N); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 130 °C): δ = 1.21 (brs, 3H), 1.67 (brs, 4H), 2.10–2.21 (m, 6H), 3.31 (d, *J* = 7.4 Hz, 4H), 3.41 (brs, 2H), 4.26 (brs, 2H), 4.72 (brs, 2H), 6.46 (d, *J* = 5.3 Hz, 1H), 7.15–7.29 (m, 4H), 7.40 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 8.41 ppm (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (151 MHz, [D$_6$]DMSO, 130 °C): δ = 12.9, 23.9, 24.9, 41.7, 44.0, 45.7, 46.4, 60.6, 60.9, 98.1, 117.1, 123.1, 123.3, 126.3, 126.6, 126.8, 129.6, 133.0, 134.6, 135.4, 136.5, 148.5, 149.8, 150.9, 161.5, 162.4 ppm; IR (ATR): ν_{max} 3271 brw, 2928 m (NH), 1736 m (EtO–C=O), 1651 s (N–C=O), 1602 s, 1578 s (7-chloroquinoline), 145 m (aromatic C=C); HRMS (EI) *m/z* $[M+H]^+$ 497.2340, $C_{27}H_{34}ClN_4O_3$ requires 497.2319.

Ethyl 2-([5-(7-chloroquinolin-4-ylamino)pentyl]-{2-[(dimethylamino)methyl]benzyl}amino)-2-oxoacetate (E5): Prepared in the same manner as described for compound **E2** using appropriate starting materials. The product was purified by column chromatography over silica gel (96.5% CH_2Cl_2, 3.5% Et_3N) affording **E5** as a yellow semi-solid (150 mg, 74%). R_f = 0.46 (95% CH_2Cl_2, 5% Et_3N); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 130 °C): δ = 1.18–1.32 (m, 3H), 1.37 (brs, 2H), 1.55–1.63 (m, 2H), 1.67 (brs, 2H), 2.15 (brs, 6H), 2.88 (brs, 2H) 3.26 (brs, 4H), 3.40 (brs, 2H), 4.28 (brs, 2H), 4.72 (brs, 2H), 6.43 (d, *J* = 4.9 Hz, 1H), 7.25 (brs, 4H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.78 (brs, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 8.39 ppm (d, *J* = 5.1 Hz, 1H) ^{13}C NMR (151 MHz, [D$_6$]DMSO, 130 °C): δ = 12.9, 23.2, 25.8, 27.0, 41.9, 44.0, 46.5, 60.6, 60.8, 98.1, 117.1, 123.1, 123.2, 126.2, 126.5, 126.8, 126.8, 129.6, 132.8, 134.6, 136.5, 148.6, 149.7, 150.9, 161.5, 162.4 ppm; IR (ATR): ν_{max} = 2938 brw, 2858 w (NH), 1737 m (EtO–C=O), 1651 s (N–C=O), 1609 w, 1577 vs (7-chloroquinoline), 1450 m (aromatic C=C); HRMS (EI) *m/z* $[M+H]^+$ 511.2493, $C_{28}H_{36}ClN_4O_3$ requires 511.2476.

Ethyl 2-([6-(7-chloroquinolin-4-ylamino)hexyl]-{2-[(dimethylamino)methyl]benzyl}amino)-2-oxoacetate (E6): Prepared in the same manner as described for compound **E2** using appropriate starting materials. The product was purified by column chromatography over silica gel (96.5% CH_2Cl_2, 3.5% Et_3N) affording **E6** as a yellow semi-solid (138 mg, 73%). R_f = 0.58 (95% CH_2Cl_2, 5% Et_3N)^{1}H NMR (400 MHz, [D$_6$]DMSO, 130 °C): δ = 1.22 (brs, 3H), 1.29 (brs, 2H), 1.39 (brs, 2H), 1.55 (m, 2H), 1.68 (m, 2H), 2.16 (s, 6H), 3.27 (brs, 4H), 3.41 (s, 2H), 4.29 (brs, 2H), 4.72 (brs, 2H), 6.44 (d, *J* = 5.3 Hz, 1H), 7.16–7.31 (m, 4H), 7.37 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 8.21 (d, *J* = 8.9 Hz, 1H), 8.40 ppm (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (151 MHz, [D$_6$]DMSO, 130 °C): δ = 12.9, 25.3, 25.5, 27.3, 42.0, 43.1, 44.0, 46.5, 47.0, 60.6, 60.8, 98.1, 117.1, 123.1, 123.2, 126.3, 126.5, 126.8, 129.6, 132.8, 134.6, 135.4, 136.4, 148.6, 149.8,

151.0, 161.5, 162.4 ppm; IR (ATR): $\nu_{max} = 2935$ brw, 2857 w (NH), 1737 m (EtO–C=O), 1651 s (N–C=O), 1609 w, 1577 vs (7-chloroquinoline), 1450 m (aromatic C=C); HRMS (EI) m/z $[M+H]^+$ 525.2610, $C_{29}H_{38}ClN_4O_3$ requires 525.2632.

Minimum inhibitory concentration determination: Samples were tested in triplicate on one occasion against the chloroquine-sensitive (CQS) NF54 and chloroquine-resistant (CQR) Dd2 strains of *P. falciparum*. Continuous in vitro cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[31] Quantitative assessment of antiplasmodial activity in vitro was determined by the parasite lactate dehydrogenase assay using a modified method described by Makler and Hinrichs.[32] The test samples were prepared to a 20 mg mL^{-1} stock solution in 100% DMSO, and were tested as a suspension if not completely dissolved. Stock solutions were stored at −20 °C. Further dilutions were prepared on the day of the experiment. Chloroquine (CQ) and artesunate were used as reference drugs in all experiments. A full dose–response profile was performed for all compounds to determine the concentration that inhibits parasite growth by 50% (IC_{50} value). Samples were tested at a starting concentration of 1000 μg mL^{-1}, and were then serially diluted (twofold per dilution) in complete medium to give ten test concentrations, with the lowest being 2 μg mL^{-1}. Reference drugs were tested at a starting concentration of 1000 ng mL^{-1}. The highest concentration of solvent to which the parasites were exposed had no measurable effect on their viability (data not shown). The IC_{50} values were obtained by nonlinear dose–response curve fitting analysis using GraphPad Prism software (version 4.0).

Detergent-mediated β-hematin formation assay: The β-hematin inhibition assay was developed at Vanderbilt University (USA) using a specific detergent (NP-40) to create the lipid–water interface at which hemozoin formation occurs naturally.[33] The assay we followed is the method described by Carter et al.[33] and was modified for manual liquid delivery using a multichannel pipette. Three stock solutions of the test compounds were made by dissolving each sample in DMSO: 10 mM (Stock 1), 2 mM (Stock 2), and 0.4 mM (Stock 3). The 10 mM solution (200 μL) was mixed with 800 μL DMSO to obtain the 2 mM solution, and 200 μL of that solution was mixed with 800 μL DMSO to obtain the 0.4 mM solution. In the 96-well plate, drugs were delivered in triplicate with concentrations ranging from 500 to 0 μM with a final DMSO volume of 10 μL in each well.

Well numbers 1–5 contained stock solution 3, well numbers 6–10 contained stock solution 2 and well numbers 11 and 12 contained stock solution 1. After the specific amount of stock solution has been added to a well and the corresponding volume of DMSO, 70 μL of distilled H_2O was added to each well, followed by 20 μL NP-40 (30.55 μM). Afterward, a 25 mM hemin stock solution in DMSO was prepared followed by sonication for complete dissolution. The hemin solution (177.76 μL) was added to 20 mL of a 2 M acetate buffer (pH 4.8) and vortexed to make the suspension as homogenous as possible; 100 μL of this solution was added to each well. The plate was then covered and incubated at 37 °C for 5–6 h. After the incubation time had elapsed, analysis of the plate was carried out using the pyridine–ferrichrome method.[34] A pyridine solution (32 μL: 50% pyridine, 20% acetone, 20% H_2O, and 10% 2 M HEPES) was added to each well. Finally 60 μL of acetone was added to each well to assist with mixing. The plate was read at λ 405 nm on a SpectraMax 340 PC384 plate reader, and the data were processed with GraphPad Prism ver. 6.01. Each compound's absorbance vs. concentration (nM) data were plotted, and then a sigmoidal dose–response curve (with variable slope) function was used to determine each compound's IC_{50} value.

X-ray crystallographic analysis: A single crystal was covered in a small amount of paratone oil and mounted on a glass fiber. X-ray intensity data were collected at 100 K on a Bruker SMART APEX CCD with 1.75 kW graphite monochromated Mo radiation. The detector-to-crystal distance was 60 mm. Data were collected by omega scans and were scaled and reduced using the APEXII software unit. Unit cell dimensions were refined on all the data, and the space group was assigned on the basis of systematic absences and intensity statistics. The structure was solved and refined using SHELX97.[35] Hydrogen atoms were placed in calculated positions and included in the model during later stages of the refinement. The program X-SEED,[36] an interface to SHELX, was used during the structure solution and refinements. CCDC 1032499 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Acknowledgements

This research was supported by grants from the National Research Foundation of South Africa (NRF) and Stellenbosch University, who provided the facilities. The authors thank Prof. T. J. Egan and K. Wicht (Department of Chemistry, University of Cape Town) for the use of facilities and assistance with the NP-40 β-hematin assay. Furthermore, we appreciate technical support from Dr. J. Brand and Ms. E. Malherbe (NMR).

Keywords: β-hematin · ferroquine · malaria · oxalamide · phenylequine

[1] *World Malaria Report 2014*, World Health Organization: http://www.who.int/malaria/publications/world_malaria_report_2014/en/ (accessed August 4, 2015).
[2] *Malaria*, UNICEF, **2014**: http://www.unicef.org/health/index_malaria.html (accessed August 4, 2015).
[3] T. K. Hartman, S. J. Rogerson, P. R. Fischer, *Ann. Tropical Paediatrics* **2010**, *30*, 271–282.
[4] J. X. Kelly, M. J. Smilkstein, R. Brun, S. Wittlin, R. A. Cooper, K. D. Lane, A. Janowsky, R. A. Johnson, R. A. Dodean, R. Winter, D. J. Hinrichs, M. K. Riscoe, *Nature* **2009**, *459*, 270–273.
[5] U. Farooq, J. C. Mahajan, *J. Vector Borne Dis.* **2004**, *41*, 45–53.
[6] R. N. Price, A.-C. Uhlemann, A. Brockman, R. McGready, E. Ashley, L. Phaipun, R. Patel, K. Laing, S. Looareesuwan, N. J. White, *Lancet* **2004**, *364*, 438–447.
[7] N. J. White, *Science* **2008**, *320*, 330–334.
[8] *Malaria Consortium*, **2015**: http://www.malariaconsortium.org/pages/malaria.html (accessed August 4, 2015).
[9] E. A. Ashley, M. Dhorda, R. M. Fairhurst, C. Amaratunga, P. Lim, S. Suon, S. Sreng, J. M. Anderson, S. Mao, B. Sam, *New Engl. J. Med.* **2014**, *371*, 411–423.
[10] K. Banek, M. Lalani, S. G. Staedke, D. Chandramohan, *Malar. J.* **2014**, *13*, 7.
[11] S. N. Cohen, K. O. Phifer, K. L. Yielding, *Nature* **1964**, *202*, 805.
[12] A. F. G. Slater, W. J. Swiggard, B. R. Orton, W. D. Flitter, D. E. Goldberg, A. Cerami, G. B. Henderson, *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 325–329.
[13] T. J. Egan, R. Hunter, C. H. Kaschula, H. M. Marques, A. Misplon, J. Walden, *J. Med. Chem.* **2000**, *43*, 283–291.
[14] D. J. Sullivan, *Curr. Pharm. Des.* **2013**, *19*, 282–289.
[15] D. A. Fidock, T. Nomura, A. K. Talley, R. A. Cooper, S. M. Dzekunov, M. T. Ferdig, L. M. Ursos, B. Naudé, K. W. Deitsch, X.-Z. Su, *Mol. Cell* **2000**, *6*, 861–871.
[16] A. F. G. Slater, *Pharmacol. Ther.* **1993**, *57*, 203–235.

[17] C. Biot, G. Glorian, L. A. Maciejewski, J. S. Brocard, O. Domarle, G. Blampain, P. Millet, A. J. Georges, H. Abessolo, D. Dive, *J. Med. Chem.* **1997**, *40*, 3715 – 3718.
[18] C. Biot, D. Taramelli, I. Forfar-Bares, L. A. Maciejewski, M. Boyce, G. Nowogrocki, J. S. Brocard, N. Basilico, P. Olliaro, T. J. Egan, *Mol. Pharmacol.* **2005**, *2*, 185 – 193.
[19] C. Supan, G. Mombo-Ngoma, M. P. Dal-Bianco, C. L. O. Salazar, S. Issifou, F. Mazuir, A. Filali-Ansary, C. Biot, D. Ter-Minassian, M. Ramharter, *Antimicrob. Agents Chemother.* **2012**, *56*, 3165 – 3173.
[20] L. Delhaes, C. Biot, L. Berry, P. Delcourt, L. A. Maciejewski, D. Camus, J. S. Brocard, D. Dive, *ChemBioChem* **2002**, *3*, 418 – 423.
[21] M. A. L. Blackie, V. Yardley, K. Chibale, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1078 – 1080.
[22] C. H. Kaschula, T. J. Egan, R. Hunter, N. Basilico, S. Parapini, D. Taramelli, E. Pasini, D. Montis, *J. Med. Chem.* **2002**, *45*, 3531 – 3539.
[23] S.-R. Choi, A. B. Beeler, A. Pradhan, E. B. Watkins, J. M. Rimoldi, B. Tekwani, M. A. Avery, *J. Comb. Chem.* **2007**, *9*, 292 – 300.
[24] N. Sunduru, M. Sharma, K. Srivastava, S. Rajakumar, S. Puri, J. Saxena, P. M. Chauhan, *Bioorg. Med. Chem.* **2009**, *17*, 6451 – 6462.
[25] K. Chibale, J. R. Moss, M. Blackie, D. van Schalkwyk, P. J. Smith, *Tetrahedron Lett.* **2000**, *41*, 6231 – 6235.
[26] M. A. L. Blackie, P. Beagley, S. L. Croft, H. Kendrick, J. R. Moss, K. Chibale, *Bioorg. Med. Chem.* **2007**, *15*, 6510 – 6516.
[27] D. De, F. M. Krogstad, L. D. Byers, D. J. Krogstad, *J. Med. Chem.* **1998**, *41*, 4918 – 4926.
[28] P. Beagley, M. A. L. Blackie, K. Chibale, C. Clarkson, R. Meijboom, J. R. Moss, P. J. Smith, H. Su, *Dalton Trans.* **2003**, 3046 – 3051.
[29] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals (3rd Ed.)*, Pergamon Press, Oxford, **1988**.
[30] A. F. Burchat, J. M. Chong, N. Nielsen, *J. Organomet. Chem.* **1997**, *542*, 281 – 283.
[31] W. Trager, J. B. Jensen, *Science* **1976**, *193*, 673 – 675.
[32] M. T. Makler, D. J. Hinrichs, *Am. J. Trop. Med. Hyg.* **1993**, *48*, 205 – 210.
[33] M. D. Carter, V. V. Phelan, R. D. Sandlin, B. O. Bachmann, D. W. Wright, *Combin. Chem. High Throughput Screen.* **2010**, *13*, 285.
[34] T. J. Egan, K. K. Ncokazi, *J. Inorg. Biochem.* **2005**, *99*, 1532 – 1539.
[35] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112 – 122.
[36] L. J. Barbour, *J. Supramol. Chem.* **2001**, *1*, 189 – 191.

Received: August 4, 2015
Published online on October 8, 2015