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ORIGINAL RESEARCH

Synthesis, in vitro antiplasmodial and antiproliferative activities of a series of quinoline–ferrocene hybrids

David D. N'Da · Peter J. Smith

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Abstract Series of quinoline–ferrocene hybrids containing various linkers were synthesized and evaluated for antimalarial and anticancer activities as well as cytotoxicity. The hybrids with rigid linkers were found to be inactive, while those with flexible spacers showed activity against both the D10 and Dd2 strains of *Plasmodium falciparum*, and demonstrated a good selectivity towards these parasitic cells in comparison with emetine. The hybrid **16**, featuring 3-aminopropyl methylamine linker, was the most antimalarial active compound, exhibiting a significantly better potency than chloroquine against the Dd2 strain (IC_{50} = 0.008 vs. 0.148 μM; 19-fold), and was also found to be significantly more active than the equimolar chloroquine–ferrocene combination (IC_{50} = 3.7 vs. 41 ng/ml, tenfold) against the Dd2 strain. Anticancer activity screening showed that all the antimalarial active hybrids also exhibited potent cytostatic (GI_{50} = 0.6–3.3 μM) and had good cytotoxic effects (LC_{50} = 6–8 μM) against all three cancer cell lines. The hybrid **11** possessing 1,4-butanediamine linker was distinctively the most antiproliferative of all. It was found to be more cytostatic (GI_{50}: 0.7 vs. 5.9 μM, eightfold) and (LC_{50}: 6.4 vs. 92.6 μM, 14-fold) more cytotoxic than etoposide against the TK10 (renal) cell line.

Keywords Malaria · Cancer · Quinoline · Ferrocene · Hybrids · Etoposide

Introduction

Overall, in the past decade, the incidence of malaria has slightly decreased, such that in 2011, there were approximately 216 million cases worldwide with 655,000 deaths (WHO, 2012). More than 80 % of reported cases and 90 % of all deaths are estimated to be in Africa, most of which are pregnant women and children under the age of 5 years (WHO, 2011). These figures exceed by far those due to other parasitic infections causing mortality in humans. The underlying main cause is the development of resistance of *Plasmodium falciparum* parasites against the widely used antimalarial drugs such as chloroquine and pyrimethamine/sulfadoxine (Petersen *et al.*, 2011).

The artemisinin class of compounds is currently the basis favoured by the World Health Organization (WHO) for the treatment of uncomplicated *P. falciparum*. Unfortunately, a cluster of alarming reports have been appearing over the increasing times taken for artemisinins to reduce parasitaemia; that is, the parasites are becoming increasingly tolerant to artemisinins (Dondorp *et al.*, 2009; Muller *et al.*, 2009; Noedl *et al.*, 2010; Phyo *et al.*, 2012). The emergence of resistance against the artemisinins will be catastrophic for malarial control. The global impact of this disease and the extraordinary ability of *Plasmodia* parasites to circumvent most efforts to counter them through chemotherapy justify the search for new drugs.

Cancer, accounting for ten millions of death worldwide, is a major disease and projected to continue rising (Beqa *et al.*, 2011). Efficient treatment of cancerous diseases is of crucial importance. Metal-based antitumour agents, such as

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D. D. N'Da (✉)
Department of Pharmaceutical Chemistry, School of Pharmacy, North-West University, Private Bag X 6001, Internal Box 304, Potchefstroom 2520, South Africa
e-mail: david.nda@nwu.ac.za

P. J. Smith
Department of Pharmacology, Groote Schuur Hospital, University of Cape Town, Observatory 7925, South Africa

cisplatin and carboplatin, are commonly used drugs for cancer treatment (Kelland *et al.*, 1999; Barnes and Lippard, 2004). However, many metal-based drugs would lead to serious side effects after administration. Thus, a numerous effort has been made to explore more efficient anticancer agents.

Since the pioneering work of Köpf-Maier and co-workers (Köpf-Maier *et al.*, 1984) reporting the anticancer activity of ferrocenium complex in Ehrlich ascites tumour, there has been an increasing interest in metallocenes and their potential use in the biomedical field. Ferrocene in particular has been extensively studied for potential biological and medicinal applications. Many functionalized ferrocenes or ferrocene-containing compounds have been prepared and tested in many research areas including cancer (Hottin *et al.*, 2012; Lal *et al.*, 2012; Zhou *et al.*, 2012; Acevedo-Morantes *et al.*, 2012), *Plasmodium* malaria (Quirante *et al.*, 2011; Dubar *et al.*, 2011; Biot *et al.*, 2011; Roux and Biot, 2012), tuberculosis therapy (Mahajan *et al.*, 2011; Kumar *et al.*, 2012, 2013) and *pneumocystis* infections (Matos *et al.*, 2010). From the extensive research carried out with the aim of generating metallocene-based antimalarials, ferroquine (FQ), a ferrocene–quinoline conjugate stands as the most promising organometallic drug candidate with a real potential to reach clinic. FQ is found to, like chloroquine (CQ), inhibit haemozoin formation (Biot *et al.*, 2011; Supan *et al.*, 2012) but is also remarkably active against both CQ-susceptible and CQ-resistant *P. falciparum* (Biot *et al.*, 2011; Supan *et al.*, 2012), against *Plasmodium vivax strains* (Leimanis *et al.*, 2010), isolates (Barends *et al.*, 2007; Daher *et al.*, 2006) and has displayed efficiency for the treatment of uncomplicated malaria in humans in phase IIb of clinical trials (http://clinicaltrials.gov/ct2/show/ NCT00988507). However, as for CQ and artemisinin, the mechanism of action of FQ is partially unknown.

In an attempt to elucidate the mechanism of action of ferroquine, Chavain *et al.* (2008) reported the ferrocene skeleton present in its structure to be able to generate reactive oxygen species under oxidizing conditions such as those estimated in the food vacuole of the parasite while other reports pointed out the presence of the intramolecular hydrogen bond to have a strong influence upon the antimalarial activity (Biot *et al.*, 2009, 2012).

Ferrocene nucleus has been directly linked to quinoline pharmacophore through various spacers (Biot *et al.*, 2004, 2006; N'Da *et al.*, 2010, 2011). Though, in general, none of the resulting compounds exhibited a global antimalarial either similar or better than FQ, some among these compounds displayed better activity than CQ especially against the CQ-resistant strains of *P. falciparum* (Biot *et al.*, 2004, 2006).

In this communication, we report the synthesis, in vitro antimalarial and anticancer activities as well as cytotoxicity of a series of quinoline–ferrocene hybrids in an attempt to highlight the influence of the linker between the two pharmacophores with regard to these activities.

Results and discussion

Chemistry

The hybrids **10–16** were synthesized in moderate to good yields (55–70 %) by reductive amination involving amino-functionalized quinolines and ferrocenic aldehyde. The two-step process started with the condensation of diamines with commercially available 4,7-dichloroquinoline **1** to afford the primary and secondary amino-functionalized quinolines **2–8**. Their IR spectra of the intermediates commonly showed absorption bands in the 3360–3250 cm^{-1} region due to the NH_2 and NH groups. The presence of these functional groups was also confirmed in the structures **8** by the singlet attributable to signal of the exchangeable NH_2 and NH protons ca $\sim$ 3.5 ppm in the ^1H spectra.

The IR spectra of hybrids **10–12**, **15** and **16** exhibited stretching vibrational bands in the 3100–3000 cm^{-1} region due to the NH group (s) in the linkers. The ^1H NMR spectra commonly display a broad singlet in the 4.39–3.9 ppm region assignable to protons of the ferrocenic moiety and a distinctive doublet in the 8.70–8.40 ppm region attributable to the heterocyclic H-2 protons of the quinoline ring. Comparing the intensities of the ferrocenic singlet and the doublet gives a 9:1 ratio. This indicates that one ferrocene moiety was linked to one quinoline ring, which is further confirmed by the presence of the broad singlet in the spectra of the hybrids as a result of the resonance methylene protons (CH_2–Fc) in the δ 3.75–3.50 ppm region. The HRMS-APCI data are in accordance with the structures of the compounds **10–16**.

It is noteworthy indicating that the synthesis of metallocenes **10** and **16** has previously been reported elsewhere (Biot *et al.*, 2006).

In vitro antimalarial activity

The metallocenes **10–16** commonly possess both quinoline and ferrocene skeletons and thus only differed structurally by the spacers. They were screened against the CQ-susceptible (D10) and CQ-resistant (Dd2) strains of *P. falciparum*. Hybrids **10**, **11**, **15** and **16** containing flexible hydrocarbon spacers and a 4-*N* proton were found to be active against both *P. falciparum* strains (Table 1). On contrary, compounds **13** and **14**, which possess rigid/non-flexible spacer and no 4-*N* proton, as well as ferrocene aldehyde **9**, were all inactive. Hybrid **12** also possesses a

rigid spacer but has a 4-*N* proton and was also found active. The equimolar combination **M** screened against the D10 and Dd2 strains also proved to be active. Overall, all the active hybrids and the combination **M** showed potency comparable to that of CQ against the CQS strains D10. Against the CQR strains, however, these hybrids and **M** were more potent than CQ. Compounds **10**, **11**, **15** and **16** were more active against the CQR than the CQS strains (RI < 1) while the combination showed a slight decrease in activity against Dd2 in comparison with D10 (RI $= 1.4$).

Previous study identified common structural features for active aminoquinolines against CQ-susceptible and CQ-resistant *P. falciparum* strains. These include (1) an aminoquinoline (AQ) ring without alkyl substitutions, (2) a halogen at position 7 of the AQ ring (Cl, Br or I but not F), (3) a protonatable nitrogen at position 1 of the AQ ring and (4) a second protonatable nitrogen at the other end of the side chain from the point of attachment to the AQ ring through the 4-aminonitrogen. Additional considerations such as latitude in the side chain (2–12 carbons) and terminal amines (diethylamine, piperidine, etc.) are also reported to influence antiparasitic activity of AQs (Hocart *et al*., 2011). The current active hybrids, though additionally contain a terminal ferrocenyl moiety, comply with these reported structural features.

Moreover, the structural characteristics of hybrids **10**, **11**, **15** and **16** confer the possibility of intramolecular hydrogen bonding between 4-*N* and the terminal N, which is favoured by the flexibility of the spacer. Such is not the case for the rigid or/and 4-*N* proton-depleted hybrids **12**–**14**. Thus, as for ferroquine, the antiplasmodial activity of these quinoline–ferrocene hybrids seems to be greatly conformation dependent.

Furthermore, all tested compounds (except **10**, **11** and **M**) showed good selectivity towards CHO *plasmodia* cell-types. Hybrids **15** and **16** with SI values of 1 782 and 1 378, respectively, appeared as the least cytotoxic of all the active hybrids. Hybrid **16** possessed IC_{50} values of 43.2 and 8.2 nM against the D10 and Dd2 strains, which translate into activities of 19.3 and 3.7 ng/ml, respectively, on mass basis. Thus, it showed activity comparable to that of the equimolar combination against the D10 strain (IC_{50}: 19.3 vs. 29 ng/ml) while possessing superior active than **M** against the Dd2 strain (IC_{50}: 3.7 vs. 41 ng/ml).

In vitro anticancer activity

The antiplasmodial active hybrids **10**, **11**, **15** and **16** were selected for antiproliferative activity screening against three different cell lines viz., renal (TK10), melanoma (UACC62) and breast (MCF7). They all exhibited potent growth inhibitory activity against the three cell-types as seen from the GI_{50} values less than 10 μM (Table 2). However, this was more pronounced against the TK10 and

Table 1 In vitro antimalarial activity and cytotoxicity of compounds

Compound	D10			Dd2				CHO[d]			
	n[a]	**IC_{50}** (μM)[b]	SD	n	**IC_{50}** (μM)[b]	SD	**RI**[c]	n[a]	**IC_{50}** (μM)[b]	SD	SI[e]
10	3	0.09	0.01	3	0.01	0.00	0.1	3	2.25	0.51	25
11	3	0.13	0.01	3	0.01	0.00	0.1	3	1.30	0.19	10
12	3	0.96	0.04	3	0.24	0.01	0.3	3	33.75	27.23	35
13	3	13.54[f]	2.89	3	2.13[f]	0.12	0.2	3	58.43	39.08	4
14	3	8.12[f]	1.07	3	2.98[f]	0.25	0.4	3	85.10	16.85	10
15	3	0.05	0.00	3	0.02	0.00	0.3	3	81.95	44.77	1 782
16	3	0.04	0.00	3	0.01	0.00	0.2	3	59.26	6.60	1 378
FcCHO	3	29.43[f]	3.27	3	19.47[f]	2.82	0.7	3	378.92	50.79	12
CQ	3	0.05	0.00	3	0.15	0.01	2.7		nd	nd	nd
M	3	0.03 μg/ml	0.00	3	0.04 μg/ml	0.00	1.4	3	69.93 μg/ml	14.97	2 412
Emetine								3	97.09	15.75	

Cells were incubated with compounds at various concentrations for 48 h; antimalarial activity and cytotoxicity were determined using parasite lactate dehydrogenase and MTT-assays, respectively

[a] Number of replicates

[b] Data represent the mean of three independent experiments, statistical significance $p < 0.05$

[c] Resistance index (RI) $= IC_{50}Dd2/IC_{50}D10$

[d] Chinese hamster ovarian (CHO)

[e] Selectivity index (SI) $= IC_{50}CHO/IC_{50}D10$

[f] IC_{50} value above maximum tested concentration therefore compound is considered inactive; not determined (nd)

MCF7 than against the UACC62 cells. Indeed, these hybrids were found to be twofold to tenfold more growth inhibitors of TK10 cell line than etoposide while comparable activities, against the UACC62 cells. Against the breast cancer cell line, hybrids **10** and **11** exhibited growth inhibitory activity similar while **15** and **16** were found to be up to threefold less active than etoposide. Hybrid **11** had the best growth inhibitory activity of all TK10 and MCF7 cells.

Comparison of the TGI concentrations revealed the hybrids to possess potent activity against all cell lines while etoposide showed potent, weak and inactivity against UACC62, TK10 and MCF7 cell lines, respectively. Hybrid **11** again displayed the highest total growth inhibitory power, being 15- and 50-fold more potent than etoposide against the TK10 and MCF7 cell lines, respectively.

The LC_{50} concentrations of the hybrids were also compared to that of etoposide to get a glimpse of the cytotoxic effects of these compounds against the three cell lines. The hybrids were found to possess equipotent cytotoxic effects against all cell lines (LC_{50} = 6–8 μM), whereas etoposide showed inactivity against both UACC62 and MCF7 while being 15-fold less cytotoxic to the TK10 line. Yet again, the compound **11** distinguished itself with lower LC_{50} values, an indication of slightly superior though negligible cytotoxicity over the other compounds. Thus, overall, hybrid **11** featuring 1,4-butanediamine linker exhibited better cytostatic (lower TGI concentration) and cytotoxic (lower LC_{50} concentration) effects as compared to all other compounds.

Small quinoline pharmacophore lowers DNA binding strength, which reduces nonspecific binding to other cell macromolecules like proteins and lipids (Atwell *et al*., 1988). Ferrocenyl moiety, on the other hand, inhibits cell growth through ROS generation (Acevedo-Morantes *et al*., 2012). Thus, the potent anticancer activity of these hybrids may be the result of synergism between the 4-aminoquinoline pharmacophore interacting favourably with the narrow minor groove of AT-rich sequences leading to DNA strand scission (Mcfadyen *et al*., 1988) and the ferrocenyl ring. In these hybrids, the spacers confer a region of flexibility between the quinoline and ferrocene pharmacophores, with the ionized secondary amines capable of increasing van der Waals interactions with the highly polar phosphate backbone and bases of DNA (Mcfadyen *et al*., 1988; Blagbrough *et al*., 1997).

Better antiproliferative activity was observed against TK10 and MCF7 than melanoma cells in comparison with etoposide. Hybrid **11** had the smallest TGI values against both tumour cell lines and thus appeared as the most active of all screened hybrids. However, the toxicity towards the CHO cells seems to militate against this fact. Indeed, this good displayed antiproliferative activity rather than being intrinsic, which is that, it solely emanates from its structural features, could well be the sum of both cytotoxicity and intrinsic activity. The hybrids **15** and **16**, on the other hand, are nontoxic to CHO cells suggesting that their anticancer activity may be intrinsic.

Overall, compounds **15** and **16** exhibited the most potent cytostatic and cytotoxic effects on the proliferation of all three cancer cell lines. These potent activities reveal an optimal distance of 3C atoms between two consecutive N atoms in the spacer, possibly allowing optimal interaction with the negatively charged phosphate groups of the DNA backbone. This ultimately may induce the external binding of these compounds to DNA and pull the AT-rich strains apart and result in the disruption of DNA transcription leading to tumour cell death.

Methods and materials

Materials

The reagents ethylenediamine and 1,3-diaminopropane, and the anhydrous solvents dichloromethane (DCM) and tetrahydrofuran (THF) and acetonitrile (ACN) were all purchased from Fluka (Johannesburg, South Africa).

Table 2 In vitro anticancer activity screening of selected hybrids against TK10 (renal), UACC62 (melanoma) and breast (MCF7) cancer cells expressed as GI_{50}, TGI and LC_{50} values (μM)

Compound	**TK10** (Renal)					**UACC62** (Melanoma)					**MCF7** (Breast)				
	GI_{50}	Activity	TGI	Activity	LC_{50}	GI_{50}	Activity	TGI	Activity	LC_{50}	GI_{50}	Activity	TGI	Activity	LC_{50}
10	1.5	*p*	4.4	*p*	7.3	2.6	*p*	5.1	*p*	7.6	0.8	*p*	3.5	*p*	7.1
11	0.7	*p*	2.8	*p*	6.4	2.4	*p*	4.9	*p*	7.5	0.6	*p*	1.7	*p*	6.2
15	2.6	*p*	5.2	*p*	7.7	3.3	*p*	5.6	*p*	7.9	2.7	*p*	5.3	*p*	8.2
16	1.7	*p*	4.6	*p*	7.4	2.5	*p*	5.1	*p*	7.6	2.7	*p*	5.3	*p*	8.0
Etoposide	5.9	*p*	43.3	*w*	92.6	3.4	*p*	4	p	>100	0.8	*p*	>100	*i*	>100

Inactive, *i* GI_{50} or TGI > 100 μM; weak activity, *w* 30 < GI_{50} or TGI < 100 μM; moderate activity, *m* 10 < GI_{50} or TGI < 30 μM; potent activity, *p* GI_{50} or TGI < 10 μM

Piperazine, para-phenylenediamine, 1,4-butanediamine, 1-methylpiperazine,1-(2-aminoethyl)piperazine, *N*-methyl-1,3-diaminopropane, sodium borohydride and sodium triacetoxyborohydride were purchased from Sigma-Aldrich (Johannesburg, South Africa). Ferrocene carboxyaldehyde was obtained from Dayangchem (Hangzhou, China). 4,7-Dichloroquinoline (CAS number: 86-98-6) was obtained from Leapchem (Hangzhou, China). All the reagents and chemicals were of analytical grade.

General procedures

Thin-layer chromatography (TLC) was performed using silica gel plates (60 F254), and purification of compounds was done by preparative flash column chromatography on silica gel (230–240 mesh, G60), all purchased from Merck (Johannesburg, South Africa).

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 600 spectrometer, cheIC50al shifts are reported in parts per million (ppm) from internal TMS and coupling constants (J) are measured in hertz. The splitting pattern abbreviations are as follows: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (double of triplets) and m (multiplet).

High resolution mass spectral measurements were performed on a Bruker microTOF-Q II 10390 instrument in the APCI mode. Positive ions M^+ and $[M + H]^+$ were recorded. IR spectra were recorded on a Bruker alpha-PFTIR Spectrometer. The melting points (mp) were determined in triplicate on a BÜCHI melting point B-545 instrument and are reported in degree Celsius (°C) uncorrected.

Experimental

Synthetic procedure for amine-functionalized quinolines

The amine-functionalized quinolines **2**, **3**, **7** and **8** were brought about following a general procedure (N'Da *et al*., 2011) and described as follows to exemplify the preparation of compound **2**: A mixture of 4,7-dichloroquinoline **1** (0.03 mol) and 1,3-propanediamine (0.13 mol, 5.2 eq.) were heated with stirring at 120 °C for 2 h. The mixture was allowed to cool to 50 °C, 1 M aqueous solution of NaOH (50 ml) was added, and then, stirring was continued until the mixture cooled to room temperature. The product was extracted with dichloromethane (3 × 150 ml). The combined organic fractions were washed with distilled water (4 × 150 ml) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was redissolved in boiling ethyl acetate and allowed to recrystallize at 0–5 °C to afford the target compound **2**.

For the synthesis of compounds **4**–**6**, each diamine and 4,7-dichloroquinoline in 4:1 molar ratio were dissolved in acetonitrile and refluxed for 4 h. Afterwards, the precipitate that formed during the reaction was filtered off. The filtrate was evaporated to dryness. The resulting residue was redissolved in boiling ethyl acetate and was successively washed with 1 M NaOH (3 × 150 ml) and with distilled water (4 × 150 ml). The organic layer was dried over $MgSO_4$, concentrated to half-volume and allowed to recrystallize at 0–5 °C to afford the target compound.

N-(3-aminopropyl)-7-chloroquinolin-4-amine ***2***

Yield: 65 %; off-yellow powder; mp: 125–129 °C; IR (ATR)/cm^{-1}: 3269, 1921, 1728; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.34 (*d*, $J = 5.2$ Hz, 1H, H-2), 8.10 (*d*, $J = 8.6$ Hz, 1H, H-5), 7.76 (*s*, 1H, H-5′), 7.38 (*d*, $J = 2.8$ Hz, 1H, H-8), 7.15 (*dd*, $J = 2.8$, 8.6 Hz, 1H, H-6), 6.51 (*d*, $J = 5.2$ Hz, 1H, H-3), 3.38 (*t*, $J = 7.5$ Hz, 2H, H-2′), 3.15 (*s*, 2H, H-4′), 2.82 (*t*, $J = 6.5$ Hz, 2H, H-4′), 2.2–1.85 (m, 2H, H-3′); ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 152.68 (C-2), 149.67 (C-4), 136.29 (C-7), 127.61 (C-8), 125.96 (C-5), 124.28 (C-6), 99.65 (C-3), 41.73 (C-11), 40.28 (C-9), 32.03 (C-10).

N-(4-aminobutyl)-7-chloroquinolin-4-amine ***3***

Yield: 68 %, off-white powder; mp: 115–120 °C; IR (ATR)/cm^{-1}: 3300, 1910, 1881, ^{1}H NMR (600 MHz, DMSO): δ (ppm) 8.37 (*d*, $J = 5.3$ Hz, 1H, H-2), 8.26 (*d*, $J = 9.0$ Hz, 1H, H-5), 7.76 (*d*, $J = 1.5$ Hz, 1H, H-8), 7.44 (*dd*, $J = 2.8$, 9.7 Hz, 1H, H-6), 6.43 (*d*, $J = 5.3$ Hz, 1H, H-3), 3.23 (*t*, $J = 25.72$ Hz, 2H, H-2′), 2.63–2.52 (*m*, 4H, H-3′, -5′), 1.77-157 (*m*, 2H, H-4′). ^{13}C NMR (600 MHz, DMSO): δ (ppm) 151.92 (C-2), 150.09 (C-4), 133.30 (C-7), 127.47 (C-8), 124.13 (C-5), 123.93 (C-6), 98.59 (C-3), 42.40 (C-2′), 41.45 (C-5′), 30.90 (C-3′), 25.34 (C-4′).

1-N-(7-chloroquinolinyl-yl) benzene-1,4-diamine ***4***

Yield: 55 %; dark-brown powder; mp: 183–185 °C; IR (ATR)/cm^{-1}: 3377, 1927, 1883; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.79 (*d*, $J = 5.9$ Hz, 1H, H-2), 8.39 (*d*, $J = 8.2$ Hz, 1H, H-5), 8.31 (*d*, $J = 1.5$ Hz, 1H, H-8), 7.81 (*dd*, $J = 1.5$, 8.2 Hz, 1H, H-6), 7.48 (*d*, $J = 8.8$ Hz, 2H, H-4′), 6.98 (*d*, $J = 5.9$ Hz, 2 H, H-3), 6.64 (*d*, $J = 8.8$ Hz, 2H, H-3′), 5.13 (*s*, 1H, H-6′), 3.37 (*s*, 2H, H-1′); ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 151.80 (H-2′), 150.05 (C-2), 149.46.10 (C-4), 133.60 (C-5′), 127.53 (C-7), 126.37 (C-8), 124.33 (C-5), 124.22 (C-6), 117.58 (C-3′), 114.54 (C-4′), 100.24 (C-3).

7-Chloro-4-(piperazin-1-yl) quinoline ***5***

Yield: 66 %; off-white powder; mp: 118–120 °C; IR (ATR)/cm^{-1}: 3253, 2939, 2823; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm)8.67 (*d*, *J* = 5.2 Hz, 1H, H-2), 7.79 (*d*, *J* = 9.0 Hz, 1H, H-5), 7.52 (*d*, *J* = 2.0 Hz, 1H, H-8), 7.45 (*dd*, *J* = 2.0, 9.0 Hz, 1H, H-6), 6.94 (*d*, *J* = 5.2 Hz, 1H, H-3), 3.5 (*s*, 1H, H-1′), 3.06 (*t*, *J* = 8.3 Hz, 4H, H-2′), 2.94 (4H, *t*, *J* = 8.3 Hz, H-3′); ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 156.88 (C-2), 152.18 (C-4), 133.46 (C-7), 128.03 (C-8), 126.10 (C-5), 125.58 (C-6), 109.22 (C-3), 54.21 (C-2′), 45.51 (C-3′).

7-Chloro-4-(3-methylpiperazin-1-yl) quinoline ***6***

Yield: 62 %; off-white powder; mp: 125–130 °C; IR (ATR)/cm^{-1}: 3255, 2960, 2818; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.66 (*d*, *J* = 5.0 Hz, 1H, H-2), 7.98 (*d*, *J* = 9.0 Hz, 1H, H-5), 7.89 (*d*, *J* = 2.0 Hz, 1H, H-8), 7.45 (*dd*, *J* = 2.0, 9.0 Hz, 1H, H-6), 6.77 (*d*, *J* = 5.0 Hz, 1H, H-3), 3.75 (*s*, 1H, H-1′), 3.52 (*t*, *J* = 7.5 Hz, 2H, H-2′), 3.27 (*t*, *J* = 7.5 Hz, 2H, H-3′), 2.49 (*dt*, *J* = 2.8, 11.5 Hz, 1H, H-4′a), 2.49 (*dt*, *J* = 10.5, 11.5 Hz, 1H, H-4′b), 1.92–1.61 (*m*, 1H, H-5′), 1.1 (*d*, *J* = 6.4 Hz, 3H, H-6′); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 157.05 (C-2), 151.89 (C-4), 134.74 (C-7), 128.79 (C-8), 126.01 (C-5), 125.16 (C-6), 108.97 (C-3), 77.22 (C-4′), 77.00 (C-2′ & C-3′), 58.00 (C-5′), 19.61 (C-6′).

7-Chloro-N-[2-(piperazin-1-yl)ethyl] quinolin-4-amine ***7***

Yield: 60 %; off-yellow powder; mp: 128–132 °C; IR (ATR)/cm^{-1}: 3210, 2939, 2424; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.70 (*d*, *J* = 5.2 Hz, 1H, H-2), 8.45 (*d*, *J* = 9.0 Hz, 1H, H-5), 7.77 (*d*, *J* = 2.1 Hz, 1H, H-8), 7.38 (*dd*, *J* = 2.1, 9.0 Hz, 1H, H-6), 6.74 (*d*, *J* = 5.2 Hz, 1H, H-3), 3.82 (*s*, 1H, H-6′), 3.42 (*t*, *J* = 6.5 Hz, H-4′), 2.64 (*t*, *J* = 4.1 Hz, 2H, H-3′), 2.57 (*t*, *J* = 4.1 Hz, 2H, H-2′), 2.57 (*t*, *J* = 6.5 Hz, 2H, H-5′); ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 151.96 (C-2), 150.00 (C-4), 133.41 (C-7), 127.53 (C-8), 127.53 (C-5), 124.14 (C-6), 98.73 (C-3), 53.21 (C-2′), 46.37 (C-3′), 45.51 (C-4′), 40.88 (C-5′).

{3-[(7-Chloroquinolin-4-yl)amino] propyl} (methyl) amine ***8***

Yield: 60 %; off-white powder; mp: 115–119 °C; IR (ATR)/cm^{-1}: 3220, 3103, 3060, 2947; ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 8.38 (*d*, *J* = 5.06 Hz, 1H, H-2), 8.25 (*d*, *J* = 9.2 Hz, 1H, H-5), 7.73 (*d*, *J* = 3.4 Hz, 1H, H-8), 7.39 (*dd*, *J* = 3.4, 9.2 Hz, 1H, H-6), 6.44 (*d*, *J* = 5.06 Hz, 1H, H-3), 3.8 (*s*, 1H, H-1′), 3.42 (*t*, *J* = 5.3 Hz, H-4′), 3.26 (*s*, 3H, H-6′), 2.57 (*t*, *J* = 4.0 Hz, 2H, H-2′), 1.71 (*dt*, *J* = 4.0, 5.3 Hz, 2H, H-3′); ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 151.92 (C-2), 150.13 (C-4), 133.31 (C-7), 127.50 (C-8), 124.00 (C-5), 123.85 (C-6), 98.73 (C-3), 72.28 (C-4′), 51.00 (C-2′), 36.15 (C-6′), 22.29 (C-3′).

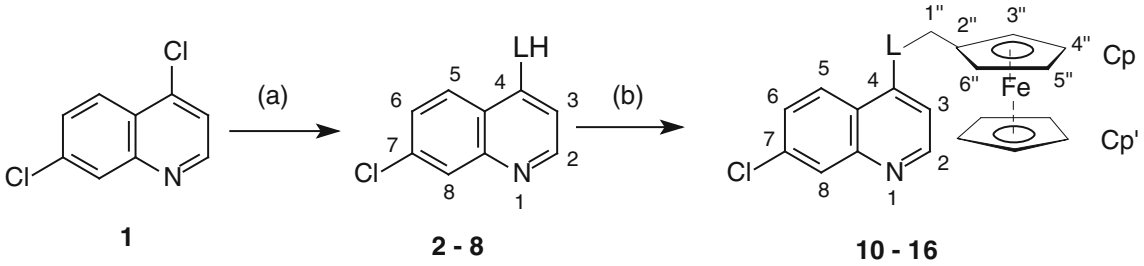
Synthesis of quinoline–ferrocene hybrids

The quinoline–ferrocene hybrids **10–12** were synthesized using a method reported (Biot *et al*., 2006) with slight modifications (Scheme 1) and described as follows: a mixture of primary aminoquinoline (**2–3**) (1 mmol) and ferrocenecarboxyaldehyde **9** (3 mmol, 3 equiv.) were thoroughly dissolved in 30 ml of anhydrous methanol and stirred for 4 h at room temperature. An excess of sodium borohydride (10 mmol, 20 eq.) was added portion wise, and the reaction mixture was stirred for an additional 2 h. After addition of 0.6 M hydrochloric acid (100 ml) and distilled water (100 ml), the aqueous layer was washed with diethyl ether (3 × 100 ml) then basified with saturated $NaHCO_3$ (pH 7) and extracted with dichloromethane (3 × 150 ml). The combined organic layers were dried over anhydrous $MgSO_4$. Afterwards, the solvent was evaporated *in vacuo,* and the residue was purified by flash chromatography on silica gel eluting with DCM–MeOH (4:1) to afford the desired compounds **10–12**.

For the synthesis of hybrids **13–16**, amine **5–8** (1 mmol), ferrocenecarboxyaldehyde **9** (3 mmol, 3 equiv.) and $NaHB(OAc)_3$ (5 mmol, 5 eq.) were dissolved in 30 ml of anhydrous tetrahydrofuran (THF), and the solution was stirred at room temperature for 24 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in 50 ml of anhydrous dichloromethane and 15 ml of 1 M NaOH solution was added and left for 20 min. The organic layer was washed with distilled water (3 × 20 ml) and was dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel eluting with DCM–MeOH (4:1) to afford the desired hybrids.

{3-[(7-Chloroquinolin-4-yl)amino]propyl} (ferrocenylmethyl) amine ***10***

Yield: 62 %, yellow powder; mp: 100–104 °C; IR (ATR)/cm^{-1}: 3309, 3079, 2928, 1733,1578; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.43 (*d*, *J* = 5.0 Hz, 1H, H-2), 7.93 (d, *J* = 8.8 Hz, 1H, H-5), 7.70 (*s*, 1H, H-5′), 7.59 (*d*, *J* = 2.1 Hz, 1H, H-8), 7.18 (*dd*, *J* = 2.1, 8.8 Hz, 1H, H-6), 6.23 (*d*, *J* = 5.0 Hz, 1H, H-3), 4.35–3.95 (*bs*, 9H, H-Cp, -Cp'), 3.80 (*s*, 1H, H-1′), 3.59 (*s*, 2H, H-1″), 3.21 (*t*, *J* = 7.0 Hz, 2H, H-2′), 3.06 (*t*, *J* = 7.0 Hz, 2H, H-4′), 2.02 (*m*, 2H, H-3′); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 151.86 (C-2), 150.62 (C-4), 134.61 (C-7), 128.15 (C-8), 124.92 (C-5), 122.57 (C-6), 98.06 (C-3), 48.27 (C-4′), 46.32



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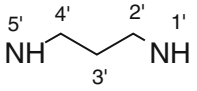
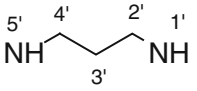
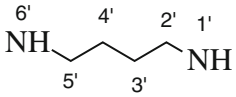
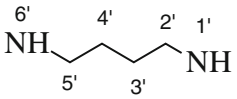
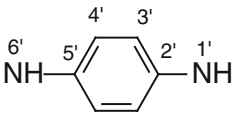
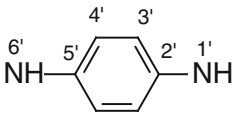
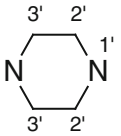
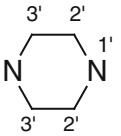
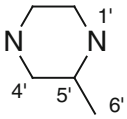
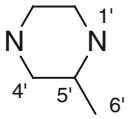
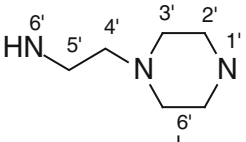
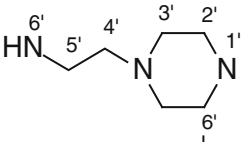
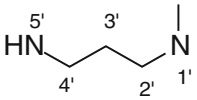
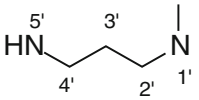
2		**10**	
3		**11**	
4		**12**	
5		**13**	
6		**14**	
7		**15**	
8		**16**	

Scheme 1 A general reaction illustrating the synthesis of aminoquinolines **2–8** and of quinoline–ferrocene hybrids **10–16**. Reagents and conditions: (*a*) 4,7-dichloroquinoline (**1**), diamine (liquid), neat, 120 °C, 2 h or (**1**), diamine (powder), acetonitrile, reflux, 4 h; (*b*) aminoquinoline (**2–4**), ferrocenecarboxyaldehyde **9**, MeOH, 4 h, rt then $NaBH_4$, 2 h, rt or (**5–8**), **9**, THF, 24 h, rt

(C-1″), 41.57 (C-2′), 27.00 (C-3′); HRMS-APCI m/z: 434.1066 $[M + H]^+$ ($[FeC_{23}H_{25}ClN_3$, $[M + H]^+$ 434.1535 calcd).

{4-[(7-Chloroquinolin-4-yl)amino]butyl} (ferrocenylmethyl) amine ***11***

Yield: 58 %, yellow powder; mp: 90–95 °C; IR (ATR)/ cm^{-1}: 3213, 3066, 2925, 1609, 1578; ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.50 (*d*, $J = 5.5$ Hz, 1H, H-2), 7.90 (*d*, $J = 8.4$ Hz, 1H, H-5), 7.70 (*d*, $J = 2.5$ Hz, 1H, H-8), 7.32 (*dd*, $J = 2.5$, 8.4 Hz, 1H, H-6), 6.28 (*d*, $J = 5.5$ Hz, H-3), 6.10 (*s*, 1H, H-6′), 4.35–4.1 (*bs*, 9H, H-Cp, -Cp'), 3.55 (*s*, 2H, H-1″), 3.25 (*t*, $J = 6.15$ Hz, 2H, H-5′), 2.75 (*t*, $J = 7.5$ Hz, 2H, H-2′), 1.9–1.65 (*m*, 2H, H-1′, -3′ and 4′); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 152.04 (C-2), 150.00 (C-4), 134.67 (C-7), 124.99 (C-8), 121.52 (C-5), 117.31 (C-6), 98.80 (C-3), 49.04 (C-5′), 48.47 (C-1″), 43.16 (C-2′); 27.69 (C-4′), 26.18 (C-3′); HRMS-APCI m/z: 447.1166 M^+ ($[FeC_{24}H_{26}ClN_3$, M^+ 447.1500 calcd].

1-N-(7-Chloroquinolin-4-yl)-4-N-(ferrocenylmethyl) benzene-1,4-diamine ***12***

Yield: 69 %, brown powder; mp: 104–107 °C; IR (ATR)/ cm^{-1}: 3374, 3194, 2954, 1885, 1572; ^1H NMR (600 MHz,

DMSO-d_6): δ (ppm)8.40 (*d*, $J = 4.8$ Hz, 1H, H-2), 7.95 (*d*, $J = 9.0$ Hz, 1H, H-5), 7.82 (*d*, $J = 1.8$ Hz, 1H, H-8), 7.68 (*dd*, $J = 1.8$, 9.0 Hz, 1H, H-6), 7.51 (*d*, $J = 8.5$ Hz, 1H, H-3′), 7.39 (*d*, $J = 8.5$ Hz, 2H, H-4′), 7.15 (*s*, 1H, H-6′), 6.75 (*d*, $J = 4.8$ Hz, 1H, H-3), 5.2 (*s*, 1H, H-1′), 4.5–4.20 (*bs*, 9H, H-Cp, -Cp'), 3.73 (2H, *s*, H-1″); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 151.80 (C-1′), 150.05 (C-2), 144.77 (C-4), 132.42 (C-4′), 128.79 (C-7), 126.54 (C-8), 126.54 (C-5), 125.67 (C-6), 117.35 (C-4′), 116.03 (C-3′), 101.26 (C-3), 46.32 (C-1″); HRMS-APCI m/z: 468.0907 $[M + H]^+$ $[FeC_{26}H_{23}ClN_3$, $[M + H]^+$ 468.1078 calcd].

7-Chloro-4-[4-(ferrocenylmethyl)piperazin-1-yl] quinoline ***13***

Yield: 55 %, brown powder; mp: 135–138 °C; IR (ATR)/ cm^{-1}: 3215, 3061, 2950, 1709, 1575; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.66 (*d*, $J = 4.9$ Hz, 1H, H-2), 8.0 (*d*, $J = 8.9$ Hz, 1H, H-5), 7.87 (*d*, $J = 1.5$ Hz, 1H, H-8), 7.37 (*dd*, $J = 1.5$, 8.9 Hz, 1H, H-6), 6.77 (*d*, $J = 4.9$ Hz, 1H, H-3), 4.34–3.92 (*bs*, 9H, H-Cp, -Cp'), 3.52 (*s*, 2H, H-1″), 3.19 (*t*, $J = 8.0$ Hz, 4H, H-2′), 2.69 (*t*, $J = 8.0$ Hz, 4H, H-3′); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 156.88 (C-2), 151.89 (C-4), 134.82 (C-7), 128.82 (C-8), 126.04 (C-5), 125.17 (C-6), 108.95 (C-3), 58.00 (C-2′), 53.27 (C-1″) and ppm 51.88 (C-3′); HRMS-APCI m/z: 446.1080 $[M + H]^+$ $[FeC_{24}H_{25}ClN_3$, $[M + H]^+$ 446.1642 calcd].

7-Chloro-4-[4-(ferrocenylmethyl)-3-methylpiperazin-1-yl] quinoline ***14***

Yield: 58 %, brown powder; mp: 142–145 °C; IR (ATR)/ cm^{-1}: 3071, 2971, 2876, 1724, 1563; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.65 (*d*, $J = 4.7$ Hz, 1H, H-2), 7.99 (*d*, $J = 8.9$ Hz, 1H, H-5), 7.84 (*d*, $J = 1.9$ Hz, 1H, H-8), 7.35 (*dd*, $J = 1.9$, 8.9 Hz, 1H, H-6), 6.75 (*d*, $J = 4.7$ Hz, 1H, H-3), 4.34–3.94 (*bs*, 9H, H-Cp, -Cp'), 3.75 (2H, *s*, H-1″), 3.61 (*t*, $J = 6.3$ Hz, 2H, H-3′), 3.27 (*t*, $J = 6.3$ Hz, 2H, H-4′), 3.08 (*dt*, $J = 2.5$, 11.5 Hz, 1H, H-5′a), 2.97 (*dt*, $J = 2.5$, 10.5 Hz, 1H, H-5′b), 2.64 (*d*, $J = 7.5$ Hz, 3H, H-5′); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 156.67 (C-2), 151.86 (C-4), 134.81 (C-7), 128.76 (C-8), 126.03 (C-5), 125.16 (C-6), 108.89 (C-3), 77.22 (C-3′), 77.00 (C-4′ and C-5′), 58.97 (C-1″), 50.55 (C-2′), 19.61 (C-6′); HRMS-APCI m/z: 460.1241 $[M + H]^+$ $[FeC_{25}H_{27}ClN_3$, $[M + H]^+$ 460.1907 calcd].

7-Chloro-N-{2-[4-(ferrocenylmethyl)piperazin-1-yl]ethyl} quinolin-4-amine ***15***

Yield: 68 %, brown powder; mp: 139–144 °C; IR (ATR)/ cm^{-1}: 3211, 3078, 2939, 1737, 1572; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.49 (*d*, $J = 5.2$ Hz, 1H, H-2), 7.91 (*d*, $J = 9.0$ Hz, 1H, H-5), 7.64 (*d*, $J = 2.1$ Hz, 1H, H-8), 7.36 (*dd*, $J = 2.1$, 9.0 Hz, 1H, H-6), 7.12 (*s*, 1H, H-6′), 6.30 (*d*, $J = 5.2$ Hz, 1H, H-3), 4.24–4.03 (*bs*, 9H, H-Cp, -Cp'), 3.37 (*s*, 2H, H-1″), 3.27 (*t*, $J = 7.2$ Hz, 2H, H-5′), 2.73 (*t*, $J = 7.2$ Hz, 2H, H-4′), 2.55 (*t*, $J = 5.7$ Hz, 4H, H-2′), 2.45 (*t*, $J = 5.7$ Hz, 4H, H-3′); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 151.76 (C-2), 149.92 (C-4), 134.97 (C-7), 128.46 (C-8), 125.41 (C-5), 121.21 (C-6), 99.22 (C-3), 77.22 (C-1″), 76.79 (C-2′), 70.32 (C-3′), 45.51 (C-4′), 40.88 (C-5′); HRMS-APCI m/z: 489.1498 $[M + H]^+$ $[FeC_{26}H_{30}ClN_4$, $[M + H]^+$ 489.1318 calcd].

{3-[(7-Chloroquinolin-4-yl)amino]propyl}(ferrocenylmethyl)methylamine ***16***

Yield: 70 %, brown powder; mp: 112–115 °C; IR (ATR)/ cm^{-1}: 3338, 3087, 2986, 1658, 1538; ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.43 (*d*, $J = 5.1$ Hz, 1H, H-2), 8.11 (*d*, $J = 9.2$ Hz, 1H, H-5), 7.89 (*d*, $J = 1.9$ Hz, 1H, H-8), 7.36 (*dd*, $J = 1.9$, 9.2 Hz, 1H, H-6), 7.05 (*s*, 1H, H-5′), 6.24 (*d*, $J = 5.1$ Hz, 1H, H-3), 4.39–3.9 (*bs*, 9H, H-Cp, -Cp'), 3.45 (*s*, 2H, H-1″), 3.39 (*t*, $J = 12.5$ Hz, H-4′), 3.25 (*s*, 3H, H-6′), 2.65 (*t*, $J = 9.0$ Hz, 2H, H-2′), 1.88 (*dt*, $J = 9.0$, 12.5 Hz, 2H, H-3′); ^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm) 151.54 (C-2), 149.52 (C-4), 134.76 (C-7), 127.89 (C-8), 125.06 (C-5), 122.51 (C-6), 98.05 (C-3), 77. 22 (C-1″), 77.00 (C-4′), 76.79 (C-2′), 70.37 (C-5′) and ppm 24.00 (C-3′); HRMS-APCI m/z: 448.1233 $[M + H]^+$ $[FeC_{24}H_{26}ClN_3$, $[M + H]^+$ 448.1879 calcd].

In vitro biological evaluation

Antimalarial activity

The hybrids **10–16** were screened in triplicate alongside ferrocenecarboxyaldehyde **9** and the equimolar mixture of chloroquine and **9**, on one occasion against chloroquine-sensitive (CQS) D10 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 (1976). The quantitative assessment of in vitro antimalarial activity was determined via the parasite lactate dehydrogenase assay using a modified method (Makler *et al*., 1993) reported elsewhere (van Heerden *et al*., 2012). The test samples were prepared from a 20 mg/ml stock solution in 10 % dimethylsulphoxide (DMSO) and sonicated to enhance solubility. Stock solutions were stored at −20 °C. Further dilutions were done on the day of the experiment. Chloroquine (CQ) was used as the reference drug in all experiments. A full dose–response was performed for all compounds to determine the concentration inhibiting 50 % of parasite growth (IC_{50}-value). The samples were tested at

a starting concentration of 100 ng/ml, which was then serially diluted twofold in complete medium to give 10 concentrations, with the lowest being 0.2 ng/ml. The same dilution technique was used for all samples. The IC_{50}-values were obtained using a nonlinear dose–response curve fitting analysis via GraphPad Prism v.4.0 software.

Cytotoxicity

The MTT-assay, a colorimetric assay, was used for cellular growth and survival and compares well with other available assays (Mosmann, 1983; Rubinstein *et al*., 1990). Mammalian cell line viz. CHO (Chinese Hamster Ovarian) was treated with the compounds, and the assay was used to measure all growth and chemosensitivity. The test samples were tested in triplicate on one occasion. The same stock solutions were used for both antimalarial activity and cytotoxicity tests, and dilutions were made on the day of the experiment. Emetine (EM) was used as the reference drug. The initial concentration of emetine was 100 μg/ml, which was serially diluted in complete medium with ten-fold dilutions to give 6 concentrations, the lowest being 0.001 μg/ml. The same dilution technique was applied to the all test samples. The highest concentration of solvent to which the cells were exposed to had no measurable effect on the cell viability. The 50 % inhibitory concentration values (IC_{50}-value) were obtained from full dose–response curves, using a nonlinear dose–response curve fitting analysis via GraphPad Prism v.4 software. All the antimalarial activity and cytotoxicity results are summarized in Table 1.

Antiproliferative activity

The growth inhibitory effects of the **10**, **11**, **15** and **16** were assessed in a panel of three cell lines recommended by the National Cancer Institute (NCI) for preliminary screens, using a sulforhodamine B (SRB) assay (Skehan *et al*., 1990). Screening was performed as previously reported (van Heerden *et al*., 2012). Etoposide, an anticancer agent, known to be an inhibitor of topoisomerase II and aids in DNA unwinding, which causes DNA strands to break, was used as a positive control (Wu *et al*., 2011). Three parameters were determined during the screening process. These included 50 % cell growth inhibition (GI_{50}), total cell growth inhibition (TGI) and the lethal concentration that kills 50 % of cells (LC_{50}). The TGI signifies a cytostatic effect, while LC_{50} indicates the cytotoxic effect of the tested agent. The biological activities were separated into 4 categories: inactive, *i* GI_{50} or TGI $>$ 100 μM), weak activity, *w* 30 μM $<$ GI_{50} or TGI $<$ 100 μM, moderate activity, *m* 10 μM $<$ GI_{50} or TGI $<$ 30 μM and potent activity, *p* TGI $<$ 10 μM. The results are reported in Table 2.

Conclusion

A series of seven quinoline–ferrocene hybrids were synthesized, and their structures confirmed by NMR and MS analyses. The hybrids **10**, **11**, **15** and **16** featuring flexible linkers and 4-*N* proton were active against both strains of *P. falciparum*, demonstrated good selectivity towards the parasitic cells and displayed potent anticancer activity against all three cell lines. The remaining three hybris with rigid or/and 4-*N* proton-depleted structures were found to be antimalarial inactive. This study confirms the antimalarial activity of this hybrid-type to be conformation dependent. Compound **16**, the most active hybrid, exhibited activity comparable to that of CQ against the CQ-susceptible strain D10 while being significantly more potent than CQ and the equimolar combination against the resistant strain Dd2 of *P. falciparum*. Hybrid **11**, on the other hand, was the most antiproliferative compound of all against the three human tumours cell lines.

On account of both the activity and selectivity, hybrids **11** and **16** stand as a good drug candidates to be further investigated in the search for safe and new therapies against malaria and renal cancer diseases, respectively.

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Conflict of interest The authors declare that they have no conflicts of interest.

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