# Synthesis and in vitro antiplasmodial evaluation of 7-chloroquinoline–chalcone and 7-chloroquinoline–ferrocenylchalcone conjugates

**ARTICLE** *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · MARCH 2015

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2015.03.045 · Source: PubMed

European Journal of Medicinal Chemistry 95 (2015) 230–239

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Preliminary communication

# Synthesis and *in vitro* antiplasmodial evaluation of 7-chloroquinoline–chalcone and 7-chloroquinoline–ferrocenylchalcone conjugates

Raghu Raj [a], Anu Saini [a], Jiri Gut [b], Philip J. Rosenthal [b], Vipan Kumar [a, *]

[a] Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India
[b] Department of Medicine, University of California, San Francisco, CA, USA

ARTICLE INFO

*Article history:*
Received 31 January 2015
Received in revised form
18 March 2015
Accepted 19 March 2015
Available online 20 March 2015

*Keywords:*
7-Chloroquinoline
Chalcone
Ferrocenylchalcone
Antiplasmodial activity
$IC_{50}$ value

ABSTRACT

The manuscript describes the synthesis of novel amide tethered 7-chloroquinoline–chalcone and 7-chloroquinoline–ferrocenylchalcone bifunctional hybrids and their evaluation as antimalarial agents against W2 resistant strain of *Plasmodium falciparum*. The antiplasmodial activity of 7-chloroquinoline–ferrocenylchalcones was found to be less than their corresponding simple chalcone conjugates. The presence of a methoxy substituent at *para* position of ring B on chalcones and longer alkyl chain length markedly improved the antiplasmodial profiles of the synthesized scaffolds with the most potent of the test compound exhibiting an $IC_{50}$ value of 17.8 nM.



## 1. Introduction

Malaria poses a major public health threat, especially in developing countries, where it has huge economic and social costs, with an estimated 207 million cases of infection and 627,000 deaths worldwide in 2012 [1]. In Africa alone, ~90% of malaria deaths occur, with the vast majority of them being young children under the age of five years [2]. Among Plasmodium species that cause disease in humans, *Plasmodium falciparum* is most fatal and responsible for majority of deaths. The major obstacle in the control of malaria is resistance of *P. falciparum* to common antimalarials including quinolines, antifolates, and artemisinin and its semi synthetic derivatives, potentially limiting the ability of artemisinin-based combination therapy (ACT) to contribute importantly to control and eventually eradicate the disease [3–8]. Thus, the synthesis of new antimalarials with the ability to overcome *P. falciparum* resistance is an urgent priority.

Since the discovery of quinine, the quinoline based drugs continued as the mainstay in the fight against malaria for many years. Among quinolines, chloroquine (CQ) has immense significance and extensively utilized in malaria chemotherapy due to its excellent clinical efficacy, limited host toxicity, simple and cost effective synthesis [9]. Unfortunately, emergence of resistant strains of *P. falciparum* to CQ led to its replacement by ACTs for the treatment of falciparum malaria [10,11]. However, recent studies have revealed that the resistance to CQ seems compound specific [12], and certain synthetic modifications around the quinoline nucleus have yielded many quinolines active against CQ-resistant parasites [13–17].

The quinoline hybridization strategy may allow us to circumvent quinoline resistance. The strategy involves covalently linking a quinoline nucleus with other drugs to result in a single hybrid molecule with improved efficacy compared to the parent drugs [18–21]. The potential of the hybridization strategy in malaria chemotherapy can be exemplified with the recent success of ferroquine (FQ) (7-chloroquinoline–ferrocene conjugate) and trioxaquine (7-chloroquinoline–trioxane conjugate). The hybrid FQ is an organometallic molecule active against CQ-sensitive as well as CQ-resistant strains of *P. falciparum* [22,23], and it has recently completed phase IIb clinical trials for the treatment of malaria [24]. Based on the success of FQ, a variety of ferrocenyl analogues of CQ have been synthesized [23,25] due to its favourable properties such as stability in aqueous and aerobic media and lipophilicity to

* Corresponding author.
*E-mail address:* vipan_org@yahoo.com (V. Kumar).

http://dx.doi.org/10.1016/j.ejmech.2015.03.045
0223-5234/

enhance penetration into cellular membranes. In addition to inhibition of hemozoin formation, ferrocene was shown to create oxidative stress due to the redox property of the ferrocene ($Fe^{2+}$)/ferricinium ($Fe^{3+}$) system, generating reactive oxygen species *via* a Fenton-like reaction in the parasite digestive vacuole, resulting in parasite death [26].

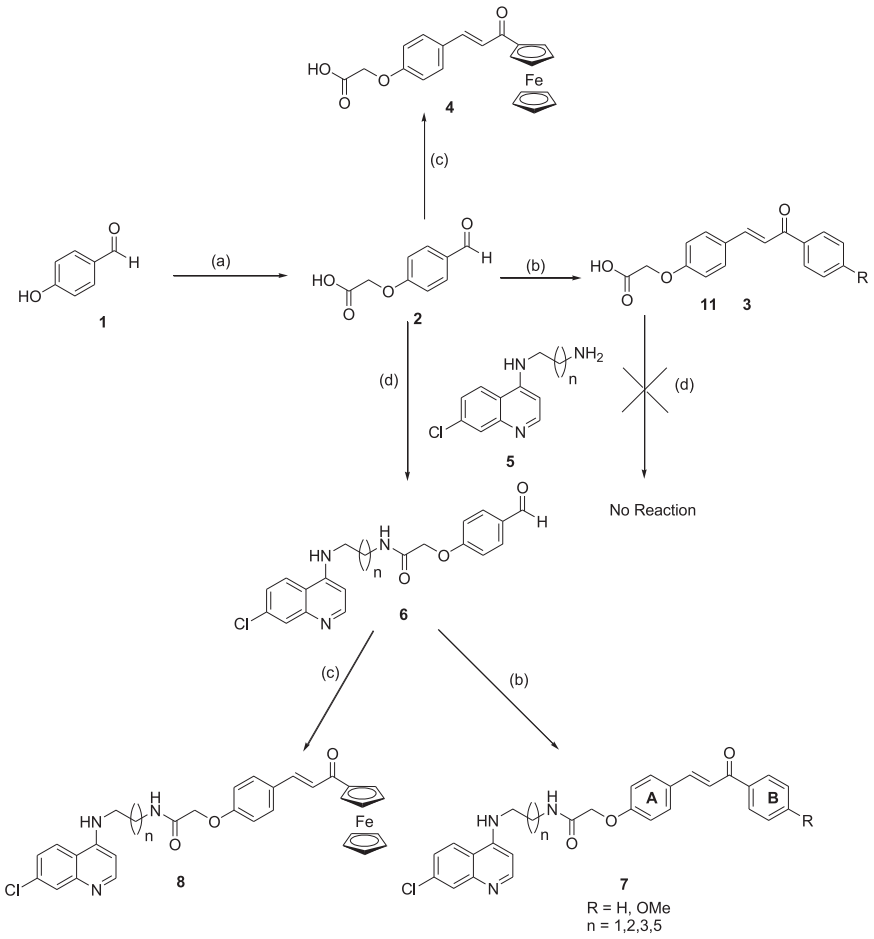
Chalcones represent key structural motifs among biologically active molecules, and they are key intermediates for combinatorial assembly of heterocyclic scaffolds. Synthetic manoeuvring of chalcones or their isolation from natural sources are being investigated because of their many relevant properties including antioxidant, antitumour, anti-inflammatory, antibacterial, and antiprotozoan activities [27,28]. The discovery of the oxygenated chalcone Licochalcone A as a potential antimalarial agent [29] encouraged researchers to design and synthesize variably functionalized chalcones and to assess their antimalarial efficacies. The antimalarial potential of chalcones is augmented by their ability to inhibit both plasmodial aspartate and cysteine proteases [30], which are potential novel chemotherapeutic targets [31]. Continuing our efforts in the synthesis of molecular conjugates and their antimalarial evaluation [32], we now describe the synthesis and characterization of amide tethered 7-chloroquinoline–chalcones and 7-chloroquinoline–ferrocenyl chalcones. The introduction of an amide as linker is based on its hydrogen bonding abilities, as this has been shown to enhance antimalarial efficacy against both CQ-sensitive and CQ-resistant strains of *P. falciparum* [33].

## 2. Result and discussion

### 2.1. Synthetic chemistry

The synthetic methodology involved an initial base-promoted treatment of 4-hydroxybenzaldehyde **1** with bromoacetic acid in water as solvent under refluxing conditions for 4–5 h to yield (4-Formyl-phenoxy)-acetic acid **2**. The aldol condensation of **2** with substituted acetophenones afforded the substituted chalcones **3** and **4**. These precursors were then utilized to provide an access to the desired amide tethered 7-chloroquinoline–chalcone conjugates. However, no significant reaction was observed, possibly because of the poor solubility of these chalcones in DMF. The approach was thus refined, with an initial DCC-HOBt promoted coupling of **2** with 4-diamino-7-chloroquinolines **5** having varied spacer length, to yield the corresponding amide **6**. Aldol condensation of **6** with varied acetophenones at room temperature for 0.5–2 h yielded the desired conjugates **7** and **8** in good to excellent yields (Scheme 1).

The structures of the synthesized conjugates were assigned on




Reagent and conditions: (a) $BrCH_2COOH$, $H_2O$, reflux, 3-5 h; (b) 40% KOH, Acetophenone/4-Methoxyacetophenone, EtOH, rt, 0.5-2 h; (c) 40% KOH, Acetylferrocene, EtOH, rt, 0.5-2 h; (d) **5**, HOBt, DCC, $Et_3N$, DCM:DMF (20:80) mix., rt, 10-12 h

**Scheme 1.** Synthesis of amide-tethered 7-chloroquinoline chalcone conjugates **7a**–**7h** and 7-chloroquinoline ferrocenylchalcone conjugates **8a**–**8d**.

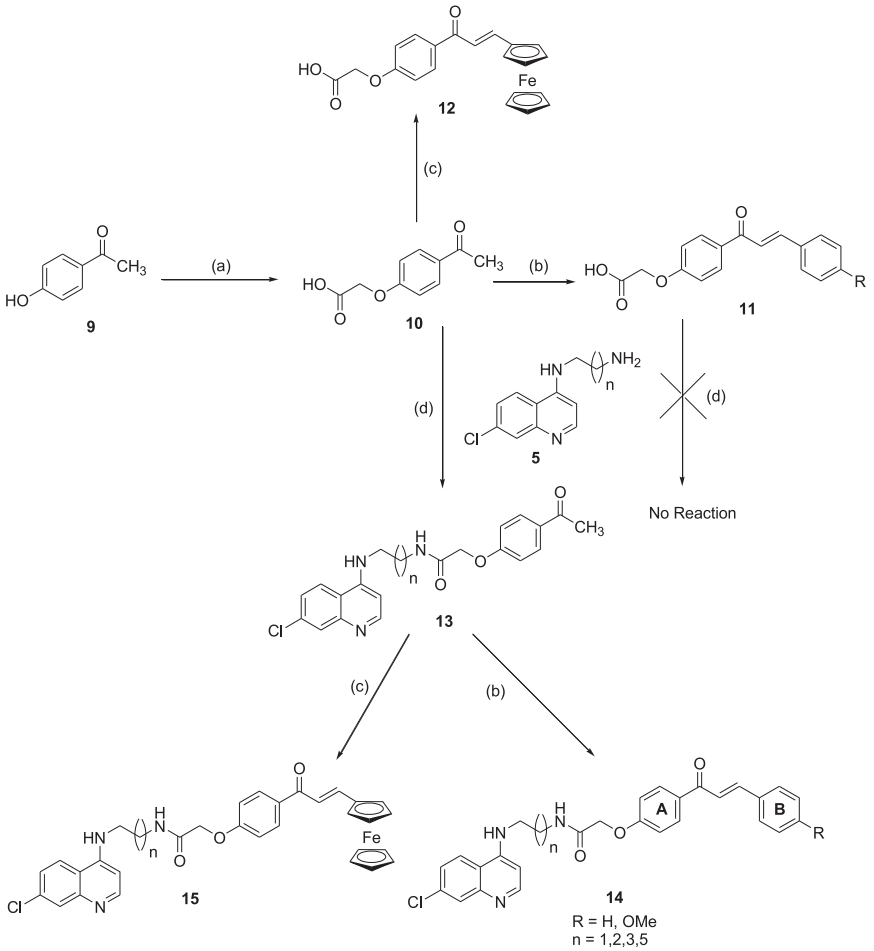
the basis of spectral data and analytical evidence. For example, **7c** showed a molecular ion peak $[M]^+$ at 513.1813 in its mass spectrum, while the $^1H$ NMR spectrum showed the presence of multiplets at δ 1.87 and 3.45 due to four methylene protons of the butyl diamine of chloroquinoline along with a singlet at δ 4.58 corresponding to methylene ether protons, and the characteristic quinoline ring protons. The presence of the required number of carbons in the $^{13}C$ NMR spectrum along with two carbonyls at δ 162.0 and 187.9 further confirmed the assigned the structure.

The approach was then extended using 4-hydroxyacetophenone **9** as the starting material. The initial treatment of **9** with bromoacetic acid led to the isolation of corresponding (4-Acetyl-phenoxy)-acetic acid **10**, which upon DCC-HOBt promoted coupling with 4-diamino-7-chloroquinolines **5** and subsequent aldol condensation with variedly substituted aldehydes led to the synthesis of 7-chloroquinoline–chalcone conjugates **14** and **15** in good to excellent yields (Scheme 2). Amide coupling was also attempted between **5** and chalcones **11** and **12**, but without success, likely due to solubility issues. The structures of the synthesized hybrids were assigned on the basis of spectral data and analytical evidence, discussed in detail in the experimental section, while some salient features include the appearance of two doublets at δ 7.86 and 8.15 with a *J* value of 15.7 Hz, corresponding to the *trans* protons of chalcone, confirming the structure assigned to the desired product **15b**.

### 2.2. In vitro antiplasmodial activity

The synthesized conjugates were assayed for their antimalarial activities against the CQ-resistant W2 strain of *P. falciparum* (Table 1). The synthesized conjugates were not as active as artemisinin, and few of the conjugates showed activity comparable to that of chloroquine. The substituted chalcones **3**, **11** and their ferrocenyl counterparts **4**, **12** were ineffective in inhibiting the growth of *P. falciparum* even at the highest tested concentrations. The precursors **6a**–**6d** with a 7-chloroquinoline nucleus, exhibited antimalarial activity dependent upon the length of the alkyl chain introduced as a linker. The conjugate **6b**, with propyl linker, proved to be the most potent of these precursors, exhibiting an $IC_{50}$ of 73.4 nM. Activity decreases substantially with increase in chain length.

Analysing the activity profiles among conjugates **7a**–**7h** revealed an interesting structure–activity relationship, with activity showing marked dependence upon the length of the alkyl chain as well as the nature of the substituent present. The conjugates **7a**–**7d** (R=H) showed improvement in activity profiles with




Reagent and Conditions: (a) $BrCH_2COOH$, $H_2O$, reflux, 3-5 h; (b) 40% KOH, Benzaldehyde/4-Methoxybenzaldehyde, EtOH, rt, 0.5-2 h; (c) 40% KOH, ferrocenecarboxyaldehyde, EtOH, rt, 0.5-2 h; (d) **5**, HOBt, DCC, $Et_3N$, DCM:DMF (20:80) mix., rt, 10-12 h

**Scheme 2.** Synthesis of amide-tethered 7-chloroquinoline chalcone conjugates **14a**–**14h** and 7-chloroquinoline ferrocenylchalcone conjugates **15a**–**15d**.

**Table 1**
Antimalarial activities of synthesized compounds.

| Compound | R | n | W2 (CQ-R)[a] $IC_{50}$(nM) ± Std. deviation |
|---|---|---|---|
| **3a** | H | – | >10,000 |
| **3b** | $OCH_3$ | – | >10,000 |
| **4** | – | – | >10,000 |
| **6a** | – | 1 | 419.4 ± 40.7 |
| **6b** | – | 2 | 73.4 ± 11.1 |
| **6c** | – | 3 | 443.7 ± 8.1 |
| **6d** | – | 5 | 875.2 ± 59.3 |
| **7a** | H | 1 | 905.3 ± 75.0 |
| **7b** | H | 2 | 109.4 ± 20.8 |
| **7c** | H | 3 | 139.4 ± 156.4 |
| **7d** | H | 5 | ND |
| **7e** | $OCH_3$ | 1 | 378.9 ± 1.1 |
| **7f** | $OCH_3$ | 2 | 221.1 ± 18.2 |
| **7g** | $OCH_3$ | 3 | 63.0 ± 2.9 |
| **7h** | $OCH_3$ | 5 | 35.4 ± 8.0 |
| **8a** | – | 1 | 1039.7 ± 96.5 |
| **8b** | – | 2 | 330.2 ± 177.1 |
| **8c** | – | 3 | 692.0 ± 50.3 |
| **8d** | – | 5 | 382.6 ± 41.9 |
| **11a** | H | – | >10,000 |
| **11b** | $OCH_3$ | – | >10,000 |
| **12** | – | – | >10,000 |
| **13a** | – | 1 | 558.0 ± 8.5 |
| **13b** | – | 2 | 173.2 ± 12.7 |
| **13c** | – | 3 | 147.6 ± 10.9 |
| **13d** | – | 5 | 71.1 ± 5.8 |
| **14a** | H | 1 | 840.2 ± 221.7 |
| **14b** | H | 2 | 46.3 ± 4.9 |
| **14c** | H | 3 | 398.3 ± 17.7 |
| **14d** | H | 5 | 4074.0 ± 502.0 |
| **14e** | $OCH_3$ | 1 | 2735.0 ± 338.0 |
| **14f** | $OCH_3$ | 2 | 50.5 ± 1.1 |
| **14g** | $OCH_3$ | 3 | 170.1 ± 21.1 |
| **14h** | $OCH_3$ | 5 | 17.8 ± 8.0 |
| **15a** | – | 1 | 3540.0 ± 328.1 |
| **15b** | – | 2 | 729.0 ± 122.8 |
| **15c** | – | 3 | 575.4 ± 166.3 |
| **15d** | – | 5 | 157.0 ± 0.7 |
| **CQ** | | | 15.9 ± 1.8 |
| **ART** | | | 6.5 ± 0.2 |

[a] CQ-R: Chloroquine-resistant strain.

increase in chain length. The introduction of a methoxy substituent on ring B resulted in considerable improvement in antimalarial efficacy, with conjugates **7e**–**7h** showing $IC_{50s}$ in the range of 35.5–378 nM. The activity improved considerably with chain length, with the most potent of the synthesized conjugates along with n = 5, exhibiting an $IC_{50}$ of 35.5 nM. The introduction of a ferrocene ring among synthesized conjugates **8a**–**8d** did not improve the activity profiles compared to their organic counterparts.

Similar comparison among the precursors **13a**–**13d** again revealed the dependence of activity profiles upon the length of the alkyl chain, with conjugate **13d** (n = 5) exhibiting an $IC_{50}$ of 71.1 nM. Structure activity relationship analysis among conjugates, **14a**–**14h** showed the dependence of activity on the length of the alkyl chain introduced as a spacer as well as the substituent on the ring. Among the conjugates **14a**–**14d** (R=H), compound **14b**, with propyl linker, displayed an $IC_{50}$ value of 46.3 nM. The introduction of a methoxy substituent enhanced the activity profiles, with conjugates **14f** (propyl linker) and **14h** (hexyl linker) exhibiting an $IC_{50s}$ of 50.5 and 17.8 nM. The introduction of a ferrocene nucleus again did not improve the antimalarial efficacy, except for conjugate **15d** (n = 5), with an $IC_{50}$ value of 157 nM.

Cytotoxicity of two most potent compounds *viz.* **7h** and **14h** were assessed against mammalian HeLa cells. As depicted in Table 2, compounds were non-cytotoxic against mammalian cells and therefore had selectivity for inhibition of *P. falciparum*.

**Table 2**
Cytotoxicity and Selective index of conjugates **7h** and **14h**.

| Compound | Cytotoxicity[a] (μM) | *P. falciparum*[b] $IC_{50}$(nM) | SI[c] |
|---|---|---|---|
| **7h** | 40 | 35.4 | 1129 |
| **14h** | 25 | 17.8 | 1404 |

[a] CQ-R: Chloroquine resistant strain.
[b] Cytotoxicity against HeLa cell line.
[c] SI: Selective index is ratio of $IC_{50}$ value of HeLa cell line to that of W2 resistant strain.

In conclusion, we describe herein the synthesis of amide tethered 7-chloroquinoline–chalcone and 7-chloroquinoline–ferrocenylchalcone conjugates along with their antimalarial evaluation against cultured *P. falciparum*. Antiplasmodial activity profiles of tested compounds showed the dependence of activity on the length of the alkyl chain. The 7-chloroquinoline–chalcone conjugates were more potent than their corresponding 7-chloroquinoline–ferrocenylchalcone counterparts. The most potent of the synthesized compounds, which had along alkyl chain (n = 5) and a methoxy substituent present on the *para* position of ring B, exhibited activity comparable to that of CQ, with an $IC_{50}$ value of 17.8 nM. Further work on the improvement of activity profiles of the reported amide-tethered 7-chloroquinoline chalcone conjugates is currently underway.

## 3. Experimental section

Melting points were determined by open capillary using a Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. $^1$H NMR spectra were recorded in deuterochloroform and dimethylsulfoxide-$d_6$ with a Jeol 300 (300 MHz) spectrometer using TMS as an internal standard. Chemical shift values are expressed as parts per million downfield from TMS and J values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. $^{13}$C NMR spectra were recorded on Bruker500 (125 MHz) spectrometer in dimethylsulfoxide using TMS as internal standard. High resolution mass spectra were recorded on Bruker-micrOTOF-Q II spectrometer.

### 3.1. General procedure for the synthesis of precursor **6**

To the stirred solution of (4-Formyl-phenoxy)-acetic acid (1 mmol), prepared by reacting *p*-salicyaldehyde and bromoacetic acid in presence of sodium hydroxide under refluxing conditions, and diaminochloroquinoline (1 mmol) in DCM:DMF (20:80) mixture was added triethylamine (1.5 mmol), HOBt (1.2 mmol) and DCC (1.1 mmol). The reaction mixture was allowed to stir overnight at room temperature and the progress was monitored using TLC. After usual workup in ethyl acetate and water, combined organic layers were collected, dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield crude product which was purified *via* coloumn chromatography in neutral alumina using 95:5 ($CHCl_3$: MeOH) mixture.

#### 3.1.1. *N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-2-(4-formyl-phenoxy)-acetamide (**6a**)*

Yield 85%; Off White Solid; $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 3.38–3.44 (m, 4H, 2× $-CH_2-$), 4.64 (s, 2H, $-O-CH_2-$), 6.58 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.11 (d, $J$ = 8.7 Hz, 2H, ArH), 7.44 (d, $J$ = 8.4 Hz, 2H, $H^4$ + −NH− exchangeable with $D_2O$), 7.78–7.83 (m, 3H, $H^5$ + 2ArH),

8.15 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.40 (d, $J$ = 5.4 Hz, 2H, $H^1$ + −NH− exchangeable with $D_2O$), 9.83 (s, 1H, −CHO); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 42.4, 47.9, 67.4, 99.0, 115.6, 117.8, 124.3, 124.6, 127.8, 130.5, 132.1, 149.2, 150.6, 152.1, 157.0, 162.9, 168.1, 191.7; HRMS: Calcd for $C_{20}H_{18}ClN_3O_3$ $[M]^+$ 383.1037, found 383.1030; Anal. Calcd (%) for: C, 62.58; H, 4.73; N, 10.95, found: C, 62.64; H, 4.78; N, 10.87.

### 3.1.2. N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-2-(4-formyl-phenoxy)-acetamide (**6b**)

Yield 76%; Off White Solid; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ1.80–1.86 (m, 2H, $-CH_2-$), 3.28–3.38 (s, 4H, 2× $-CH_2-$), 4.60 (s, 2H, $-O-CH_2-$), 6.59 (d, $J$ = 5.1 Hz, 1H, $H^2$), 7.14 (d, $J$ = 8.7 Hz, 2H, ArH),7.44 (d, $J$ = 8.4 Hz, 2H, $H^4$ + −NH− exchangeable with $D_2O$), 7.80–7.85 (m, 3H, $H^5$ + 2ArH), 8.12 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.40 (d, $J$ = 5.1 Hz, 2H, $H^1$ + −NH− exchangeable with $D_2O$), 9.80 (s, 1H, −CHO); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 29.8, 41.0, 47.3, 67.5, 99.2, 114.9, 117.4, 124.3, 124.7, 127.9, 130.8, 132.3, 149.1, 150.7, 152.3, 157.2, 162.8, 168.4, 191.5; HRMS: Calcd for $C_{21}H_{20}ClN_3O_3$ $[M]^+$ 397.1193, found 397.1202; Anal. Calcd (%) for: C, 63.40; H, 5.07; N, 10.56, found: C, 63.52; H, 5.15; N, 10.45.

### 3.1.3. N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-2-(4-formyl-phenoxy)-acetamide (**6c**)

Yield 81%; Off White Solid; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ1.65–1.71 (m, 2H, $-CH_2-$), 1.80–1.89 (m, 2H, $-CH_2-$),3.25–3.37 (s, 4H, 2× $-CH_2-$), 4.63 (s, 2H, $-O-CH_2-$), 6.57 (d, $J$ = 5.1 Hz, 1H, $H^2$), 7.13 (d, $J$ = 8.7 Hz, 2H, ArH),7.45 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.49 (s, 1H, −NH− exchangeable with $D_2O$), 7.79–7.84 (m, 3H, $H^5$ + 2ArH), 8.11 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.40 (d, $J$ = 5.1 Hz, 1H, $H^1$), 8.42 (s, 1H, −NH− exchangeable with $D_2O$), 9.82 (s, 1H, −CHO); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 25.4, 26.3, 41.6, 47.8, 67.4, 99.1, 115.2, 117.5, 124.5, 124.7, 127.8, 130.4, 132.7, 149.3, 150.4, 152.9, 157.0, 162.6, 168.1, 191.7; HRMS: Calcd for $C_{22}H_{22}ClN_3O_3$ $[M]^+$ 411.1350, found 411.1345; Anal. Calcd (%) for: C, 64.15; H, 5.38; N, 10.20, found: C, 64.07; H, 5.49; N, 10.26.

### 3.1.4. N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-(4-formyl-phenoxy)-acetamide (**6d**)

Yield 80%; Off White Solid; $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ1.42–1.59 (m, 6H, 3× $-CH_2-$), 1.76–1.85 (m, 2H, $-CH_2-$),3.30–3.45 (m, 4H, 2× $-CH_2-$), 4.65 (s, 2H, $-O-CH_2-$), 6.61 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.11 (d, $J$ = 8.7 Hz, 2H, ArH),7.45 (d, $J$ = 8.4 Hz, 2H, $H^4$ + −NH− exchangeable with $D_2O$), 7.82–7.87 (m, 3H, $H^5$ + 2ArH), 8.13 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.39 (d, $J$ = 5.4 Hz, 1H, $H^1$), 8.43 (s, 1H, −NH− exchangeable with $D_2O$), 9.87 (s, 1H, −CHO); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 25.4, 25.7, 28.9, 30.2, 41.9, 46.8, 67.4, 99.0, 115.0, 117.5, 124.1, 124.5, 127.7, 130.5, 132.6, 149.3, 150.9, 152.4, 157.2, 162.6, 168.1, 191.8; HRMS: Calcd for $C_{24}H_{26}ClN_3O_3$ $[M]^+$ 439.1663, found 439.1670; Anal. Calcd (%) for: C, 65.52; H, 5.96; N, 9.55, found: C, 65.66; H, 6.04; N, 9.62.

## 3.2. General procedure for the synthesis of amide-tethered 7-chloroquinoline chalcone conjugates **7** and 7-chloroquinoline ferrocenylchalcone conjugates **8**

To a well stirred solution of **6** (1 mmol) in ethanol, appropriate acetophenone (acetophenone/4-methoxyacetophenone/ferrocenylacetophenone) (1 mmol) along with 40% (w/v) sodium hydroxide solution was added sequentially into the reaction mixture. The progress of the reaction was monitored using TLC. The precipitates obtained were washed with dilute HCl solution, excess of water, dried in air and finally recrystallized with methanol to obtain conjugates **7** or **8**.

### 3.2.1. N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-2-[4-(3-oxo-3-phenyl-propenyl)-phenoxy]-acetamide (**7a**)

Yield 93%; Light Yellow Solid; $^1H$ NMR ($CDCl_3$, 300 MHz): δ3.36–3.46 (m, 4H, 2× $-CH_2-$), 4.20 (s, 1H, −NH− exchangeable with $D_2O$), 4.62 (s, 2H, $-O-CH_2-$), 6.40 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.85 (s, 1H, −NH− exchangeable with $D_2O$), 6.88–6.95 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.34 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.40 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.47–7.55 (m, 3H, ArH),7.81 (d, $J$ = 9.0 Hz, 2H, ArH),7.89 (s, 1H, $H^5$), 8.05 (d, $J$ = 8.7 Hz, 2H, ArH), 8.49 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 39.6, 46.5, 67.1, 99.0, 114.9, 117.3, 120.1, 123.8, 124.6, 125.1, 126.4, 127.8, 130.5, 131.2, 132.0, 135.1, 143.8, 147.1, 150.2, 151.6, 157.3, 162.1, 167.7, 188.0; HRMS: Calcd for $C_{28}H_{24}ClN_3O_3$ $[M]^+$ 485.1506 found 485.1516; Anal. Calcd (%) for: C, 69.20; H, 4.98; N, 8.65, found: C, 69.07; H, 4.91; N, 8.72.

### 3.2.2. N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-2-[4-(3-oxo-3-phenyl-propenyl)-phenoxy]-acetamide (**7b**)

Yield 85%; Light Yellow Solid; $^1H$ NMR ($CDCl_3$, 300 MHz): δ1.92–2.06 (m, 2H, $-CH_2-$), 3.35–3.47 (m, 4H, 2× $-CH_2-$), 4.22 (s, 1H, −NH− exchangeable with $D_2O$), 4.52 (s, 2H, $-O-CH_2-$), 6.40 (d, $J$ = 5.1 Hz, 1H, $H^2$), 6.81 (s, 1H, −NH− exchangeable with $D_2O$), 6.90–6.98 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.29 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.46 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.48–7.56 (m, 3H, ArH),7.80 (d, $J$ = 9.0 Hz, 2H, ArH),7.96 (s, 1H, $H^5$), 8.06 (d, $J$ = 8.7 Hz, 2H, ArH), 8.53 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 30.9, 37.0, 47.1, 67.5, 99.1, 115.3, 117.7, 119.9, 124.8, 125.4, 125.7, 126.4, 128.0, 130.9, 131.3, 132.2, 135.1, 143.6, 147.3, 150.6, 151.5, 157.3, 162.2, 167.5, 187.8; HRMS: Calcd for $C_{29}H_{26}ClN_3O_3$ $[M]^+$ 499.1663, found 499.1651; Anal. Calcd (%) for: C, 69.66; H, 5.24; N, 8.40, found: C, 69.75; H, 5.31; N, 8.50.

### 3.2.3. N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-2-[4-(3-oxo-3-phenyl-propenyl)-phenoxy]-acetamide (**7c**)

Yield 85%; Light Yellow Solid; $^1H$ NMR ($CDCl_3$, 300 MHz): δ1.70–2.05 (m, 4H, 2× $-CH_2-$), 3.40–3.51 (m, 4H, 2× $-CH_2-$), 4.25 (s, 1H, −NH− exchangeable with $D_2O$), 4.58 (s, 2H, $-O-CH_2-$), 6.37 (d, $J$ = 5.7 Hz, 1H, $H^2$), 6.77 (s, 1H, −NH− exchangeable with $D_2O$), 6.85–6.92 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.36 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.40 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.45–7.53 (m, 3H, ArH),7.81 (d, $J$ = 9.0 Hz, 2H, ArH),7.91 (s, 1H, $H^5$), 8.02 (d, $J$ = 8.7 Hz, 2H, ArH), 8.56 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 27.0, 28.2, 37.3, 47.8, 67.5, 99.3, 115.1, 117.6, 119.8, 124.5, 125.2, 125.6, 126.0, 127.9, 130.9, 131.2, 132.4, 134.9, 143.8, 147.2, 150.1, 151.7, 157.2, 162.0, 167.8, 187.9; HRMS: Calcd for $C_{30}H_{28}ClN_3O_3$ $[M]^+$ 513.1819, found 513.1813; Anal. Calcd (%) for: C, 70.10; H, 5.49; N, 8.17, found: C, 70.23; H, 5.41; N, 8.08.

### 3.2.4. N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-[4-(3-oxo-3-phenyl-propenyl)-phenoxy]-acetamide (**7d**)

Yield 89%; Light Yellow Solid; $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.52–1.72 (m, 6H, 3× $-CH_2-$), 1.90–2.03 (m, 2H, $-CH_2-$),3.36–3.47 (m, 4H, 2× $-CH_2-$), 4.18 (s, 1H, −NH− exchangeable with $D_2O$), 4.61 (s, 2H, $-O-CH_2-$), 6.39 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.82 (s, 1H, −NH− exchangeable with $D_2O$), 6.91–6.98 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.28 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.40 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.44–7.53 (m, 3H, ArH),7.77 (d, $J$ = 9.3 Hz, 2H, ArH),7.91 (s, 1H, $H^5$), 8.00 (d, $J$ = 8.7 Hz, 2H, ArH), 8.47 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): 26.1, 26.6, 29.2, 30.4, 37.5, 47.7, 67.1, 99.0, 115.0, 117.4, 120.1, 124.7, 125.3, 125.8, 126.1, 127.8, 130.9, 131.6, 132.3, 134.7, 143.9, 147.0, 150.1, 151.6, 157.3, 162.2, 167.6, 188.0; HRMS: Calcd for $C_{32}H_{32}ClN_3O_3$ $[M]^+$ 541.2132, found 541.2144; Anal. Calcd (%) for: C, 70.90; H, 5.95; N, 7.75, found: C, 70.97; H, 5.86; N, 7.83.

*3.2.5. N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-2-{4-[3-(4-methoxy-phenyl)-3-oxo-propenyl]-phenoxy}-acetamide (**7e**)*

Yield 89%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ3.37–3.48 (m, 4H, 2× $-CH_2-$), 3.89 (s, 3H, $-OCH_3$), 4.21 (s, 1H, –NH– exchangeable with $D_2O$), 4.58 (m, 2H, $-O-CH_2-$), 6.36 (d, $J$ = 5.7 Hz, 1H, $H^2$), 6.83 (s, 1H, –NH– exchangeable with $D_2O$), 6.90–6.97 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.30 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.42 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.58 (d, $J$ = 8.4 Hz, 2H, ArH),7.80 (d, $J$ = 9.0 Hz, 2H, ArH),7.94 (s, 1H, $H^5$), 8.02 (d, $J$ = 8.7 Hz, 2H, ArH), 8.46 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 39.2, 46.6, 55.9, 67.3, 99.1, 114.8, 117.2, 119.7, 123.9, 124.8, 125.2, 126.2, 127.7, 130.7, 131.3, 132.2, 135.0, 144.1, 147.4, 150.3, 151.5, 157.2, 162.0, 167.9, 187.9; HRMS: Calcd for $C_{29}H_{26}ClN_3O_4$ $[M]^+$ 515.1612 found 515.1605; Anal. Calcd (%) for: C, 67.50; H, 5.08; N, 8.14, found: C, 67.42; H, 5.20; N, 8.08.

*3.2.6. N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-2-{4-[3-(4-methoxy-phenyl)-3-oxo-propenyl]-phenoxy}-acetamide (**7f**)*

Yield 80%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ1.90–2.04 (m, 2H, $-CH_2-$), 3.40–3.51 (m, 4H, 2× $-CH_2-$), 3.85 (s, 3H, $-OCH_3$), 4.20 (s, 1H, –NH– exchangeable with $D_2O$), 4.56 (s, 2H, $-O-CH_2-$), 6.41 (d, $J$ = 5.1 Hz, 1H, $H^2$), 6.80 (s, 1H, –NH– exchangeable with $D_2O$), 6.88–6.95 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.30 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.42 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.57 (d, $J$ = 8.4 Hz, 2H, ArH),7.79 (d, $J$ = 9.0 Hz, 2H, ArH),7.97 (s, 1H, $H^5$), 8.03 (d, $J$ = 8.7 Hz, 2H, ArH), 8.50 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 30.5, 36.5, 47.8, 55.4, 67.6, 99.2, 115.1, 117.6, 119.8, 124.5, 125.3, 125.6, 126.2, 127.9, 130.6, 131.4, 132.1, 135.0, 144.1, 147.4, 150.3, 151.7, 157.2, 161.8, 167.7, 188.0; HRMS: Calcd for $C_{30}H_{28}ClN_3O_4$ $[M]^+$ 529.1768, found 529.1752; Anal. Calcd (%) for: C, 67.98; H, 5.32; N, 7.93, found: C, 68.08; H, 5.38; N, 7.78.

*3.2.7. N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-2-{4-[3-(4-methoxy-phenyl)-3-oxo-propenyl]-phenoxy}-acetamide (**7g**)*

Yield 86%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ1.66–2.07 (m, 4H, 2× $-CH_2-$), 3.33–3.47 (m, 4H, 2× $-CH_2-$), 3.88 (s, 3H, $-OCH_3$), 4.25 (s, 1H, –NH– exchangeable with $D_2O$), 4.54 (s, 2H, $-O-CH_2-$), 6.37 (d, $J$ = 5.7 Hz, 1H, $H^2$), 6.80 (s, 1H, –NH– exchangeable with $D_2O$), 6.91–6.98 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.32 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.43 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.58 (d, $J$ = 8.4 Hz, 2H, ArH),7.77 (d, $J$ = 9.0 Hz, 2H, ArH),7.92 (s, 1H, $H^5$), 8.01 (d, $J$ = 8.7 Hz, 2H, ArH), 8.49 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 26.8, 28.1, 36.7, 47.9, 55.8, 67.4, 99.0, 115.0, 117.4, 119.8, 124.7, 125.1, 125.4, 126.1, 127.8, 130.8, 131.1, 132.2, 134.8, 143.7, 147.1, 150.4, 151.6, 157.1, 161.9, 167.8, 187.7; HRMS: Calcd for $C_{31}H_{30}ClN_3O_4$ $[M]^+$ 543.1925, found 543.1938; Anal. Calcd (%) for: C, 68.44; H, 5.56; N, 7.72, found: C, 68.53; H, 5.48; N, 7.60.

*3.2.8. N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-{4-[3-(4-methoxy-phenyl)-3-oxo-propenyl]-phenoxy}-acetamide(**7h**)*

Yield 91%; Light Yellow Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.50–1.70 (m, 6H, 3× $-CH_2-$), 1.92–2.05 (m, 2H, $-CH_2-$),3.37–3.48 (m, 4H, 2× $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 4.23 (s, 1H, –NH– exchangeable with $D_2O$), 4.55 (s, 2H, $-O-CH_2-$), 6.36 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.84 (s, 1H, –NH– exchangeable with $D_2O$), 6.93–7.00 (m, 4H, $H^4$ + 2ArH + olefinic-H), 7.31 (d, $J$ = 7.8 Hz, 1H, $H^3$), 7.42 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.61 (d, $J$ = 8.4 Hz, 2H, ArH),7.76 (d, $J$ = 9.0 Hz, 2H, ArH),7.93 (s, 1H, $H^5$), 7.99 (d, $J$ = 8.7 Hz, 2H, ArH), 8.49 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 26.2, 26.7, 29.3, 30.1, 37.0, 47.8, 55.6, 67.5, 99.1, 114.9, 117.3, 120.0, 124.8, 125.2, 125.5, 126.2, 127.9, 130.8, 131.3, 132.5, 134.8, 143.6, 147.2, 150.3, 151.7, 157.4, 162.1, 167.4, 188.1; HRMS: Calcd for $C_{33}H_{34}ClN_3O_4$ $[M]^+$ 571.2238, found 571.2244; Anal. Calcd (%) for: C, 69.28; H, 5.99; N, 7.34, found: C, 69.36; H, 6.10; N, 7.49.

*3.2.9. N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-2-[4-(3-oxo-3-ferrocenyl-propenyl)-phenoxy]-acetamide (**8a**)*

Yield 79%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ 3.35–3.43 (m, 4H, 2× $-CH_2-$), 4.12 (s, 5H, Ferrocenyl-H), 4.49 (s, 2H, Ferrocenyl-H), 4.59 (s, 2H, Ferrocenyl-H), 4.70 (s, 2H, $-O-CH_2-$), 5.57 (s, 1H, –NH– exchangeable with $D_2O$), 6.42 (s, 1H, –NH– exchangeable with $D_2O$), 6.57 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.96–7.04 (m, 3H, 2ArH + olefinic-H),7.42 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.59 (d, $J$ = 15.9 Hz, olefinic-H), 7.86 (d, $J$ = 8.1 Hz, 2H, 2ArH), 8.02 (d, $J$ = 8.1 Hz, 1H, $H^3$), 8.13 (s, 1H, $H^5$), 8.33 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 42.0, 47.4, 67.6, 68.5, 69.5, 69.8, 71.6, 99.5, 115.6, 117.8, 120.3, 124.3, 125.0, 127.8, 130.5, 132.1, 144.5, 149.2, 150.6, 152.1, 157.0, 162.9, 167.2, 188.3; HRMS: Calcd for $C_{32}H_{28}ClFeN_3O_3$ $[M]^+$ 593.1169, found 593.1160; Anal. Calcd (%) for: C, 64.72; H, 4.75; N, 7.08, found: C, 64.84; H, 4.89; N, 7.01.

*3.2.10. N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-2-[4-(3-oxo-3-ferrocenyl-propenyl)-phenoxy]-acetamide(**8b**)*

Yield 84%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.99–2.08 (m, 2H, $-CH_2-$),3.38–3.46 (m, 4H, 2× $-CH_2-$), 4.15 (s, 5H, Ferrocenyl-H), 4.50 (s, 2H, Ferrocenyl-H), 4.61 (s, 2H, Ferrocenyl-H), 4.68 (s, 2H, $-O-CH_2-$), 5.53 (s, 1H, –NH– exchangeable with $D_2O$), 6.44 (s, 1H, –NH– exchangeable with $D_2O$), 6.56 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.95–7.03 (m, 3H, 2ArH + olefinic-H),7.41 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.59 (d, $J$ = 15.9 Hz, olefinic-H), 7.85 (d, $J$ = 8.1 Hz, 2H, 2ArH), 8.01 (d, $J$ = 8.1 Hz, 1H, $H^3$), 8.14 (s, 1H, $H^5$), 8.32 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 29.8, 37.2, 47.5, 67.4, 68.4, 69.3, 69.7, 71.5, 99.3, 115.0, 117.2, 120.1, 124.4, 125.1, 127.7, 130.4, 132.2, 143.9, 149.3, 150.5, 152.0, 157.1, 162.9, 167.6, 188.2; HRMS: Calcd for $C_{33}H_{30}ClFeN_3O_3$ $[M]^+$ 607.1325, found 607.1315; Anal. Calcd (%) for: C, 65.20; H, 4.97; N, 6.91, found: C, 65.32; H, 5.05; N, 6.82.

*3.2.11. N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-2-[4-(3-oxo-3-ferrocenyl-propenyl)-phenoxy]-acetamide(**8c**)*

Yield 76%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.66–1.91 (m, 4H, 2× $-CH_2-$), 3.32–3.41 (m, 4H, 2× $-CH_2-$), 4.17 (s, 5H, Ferrocenyl-H), 4.47 (s, 2H, Ferrocenyl-H), 4.60 (s, 2H, Ferrocenyl-H), 4.69 (s, 2H, $-O-CH_2-$), 5.59 (s, 1H, –NH– exchangeable with $D_2O$), 6.42 (s, 1H, –NH– exchangeable with $D_2O$), 6.54 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.99–7.06 (m, 3H, 2ArH + olefinic-H),7.45 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.58 (d, $J$ = 15.9 Hz, olefinic-H), 7.83 (d, $J$ = 8.1 Hz, 2H, 2ArH), 8.00 (d, $J$ = 8.4 Hz, 1H, $H^3$), 8.12 (s, 1H, $H^5$), 8.30 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 27.3, 28.2, 36.9, 47.3, 67.5, 68.3, 69.6, 69.9, 71.6, 99.1, 115.4, 117.8, 120.2, 124.4, 125.2, 127.9, 130.4, 132.2, 144.2, 149.3, 150.7, 152.2, 157.2, 162.7, 167.5, 187.9; HRMS: Calcd for $C_{34}H_{32}ClFeN_3O_3$ $[M]^+$ 621.1482, found 621.1490; Anal. Calcd (%) for: C, 65.66; H, 5.19; N, 6.76, found: C, 65.59; H, 5.30; N, 6.68.

*3.2.12. N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-[4-(3-oxo-3-ferrocenyl-propenyl)-phenoxy]-acetamide (**8d**)*

Yield 81%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.01–1.74 (m, 8H, 4× $-CH_2-$),3.24–3.33 (m, 4H, 2× $-CH_2-$), 4.13 (s, 5H, Ferrocenyl-H), 4.48 (s, 2H, Ferrocenyl-H), 4.54 (s, 2H, Ferrocenyl-H), 4.78 (s, 2H, $-O-CH_2-$), 5.56 (s, 1H, –NH– exchangeable with $D_2O$), 6.43 (s, 1H, –NH– exchangeable with $D_2O$), 6.51 (d, $J$ = 5.1 Hz, 1H, $H^2$), 6.98–7.05 (m, 3H, 2ArH + olefinic-H),7.40 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.58 (d, $J$ = 15.9 Hz, olefinic-H), 7.88 (d, $J$ = 8.1 Hz, 2H, 2ArH), 8.03 (d, $J$ = 8.1 Hz, 1H, $H^3$), 8.12 (s, 1H, $H^5$), 8.30 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 25.8, 26.6, 29.7, 30.8, 37.6, 47.4, 67.5, 68.0, 69.1, 69.6, 71.3, 99.2, 115.5, 117.7, 120.0, 124.2, 125.1, 127.6, 130.7, 132.4, 144.3, 149.0, 150.6, 152.4, 157.2, 162.7, 167.3, 188.1; HRMS: Calcd for $C_{36}H_{36}ClFeN_3O_3$ $[M]^+$ 649.1795, found 649.1809; Anal. Calcd (%) for: C, 66.52; H, 5.58; N,

6.46, found: C, 66.64; H, 5.61; N, 6.40.

### 3.3. General procedure for the synthesis of precursor **13**

To the stirred solution of (4-Acetyl-phenoxy)-acetic acid (1 mmol) and diaminochloroquinoline (1 mmol) in DCM:DMF (20:80) mixture was added triethylamine (1.5 mmol), HOBt (1.2 mmol) and DCC (1.1 mmol). The reaction mixture was allowed to stir overnight at room temperature. On the completion of reaction, as monitored by TLC, water (30 mL) was added into the reaction mixture and extracted with ethyl acetate (2 × 60 mL). Organic layers were collected, dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield the crude product which was purified *via* column chromatography on neutral alumina using 95:5 ($CHCl_3$: MeOH) mixture as eluent.

#### 3.3.1. 2-(4-Acetyl-phenoxy)-N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-acetamide (**13a**)

Yield 73%; Off White Solid; $^1$H NMR (DMSO-$d_6$, 300 MHz): δ2.45 (s, 3H, -$CH_3$), 3.36–3.44 (m, 4H, 2× −$CH_2$−), 4.66 (s, 2H, −O−$CH_2$−), 6.57 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.13 (d, $J$ = 8.7 Hz, 2H, ArH),7.43 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.47 (s, 1H, −NH− exchangeable with $D_2O$), 7.77–7.82 (m, 3H, $H^5$ + 2ArH), 8.18 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.40 (d, $J$ = 5.4 Hz, 1H, $H^1$), 8.42 (s, 1H, −NH− exchangeable with $D_2O$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 21.9, 42.6, 48.0, 67.6, 99.4, 115.5, 117.7, 124.2, 124.9, 127.6, 130.6, 132.3, 149.0, 150.5, 152.2, 157.4, 163.1, 168.4, 194.9; HRMS: Calcd for $C_{21}H_{20}ClN_3O_3$ $[M]^+$ 397.1193, found 397.1205; Anal. Calcd (%) for: C, 63.40; H, 5.07; N, 10.56, found: C, 63.56; H, 4.99; N, 10.47.

#### 3.3.2. 2-(4-Acetyl-phenoxy)-N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-acetamide(**13b**)

Yield 77%; Off White Solid; $^1$H NMR (DMSO-$d_6$, 300 MHz): δ1.81–1.88 (m, 2H, −$CH_2$−), 2.49 (s, 3H, -$CH_3$), 3.35–3.43 (m, 4H, 2× −$CH_2$−), 4.58 (s, 2H, −O−$CH_2$−), 6.60 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.16 (d, $J$ = 8.7 Hz, 2H, ArH),7.45 (d, $J$ = 8.4 Hz, 2H, $H^4$ + −NH− exchangeable with $D_2O$), 7.81–7.86 (m, 3H, $H^5$ + 2ArH), 8.09 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.38 (d, $J$ = 5.4 Hz, 1H, $H^1$), 8.41 (s, 1H, −NH− exchangeable with $D_2O$);$^{13}$C NMR (DMSO-$d_6$, 125 MHz): 21.8, 30.1, 41.2, 47.6, 67.8, 99.1, 115.2, 117.7, 124.2, 124.6, 127.8, 130.7, 132.4, 149.0, 150.6, 152.1, 157.4, 162.6, 168.5, 195.0; HRMS: Calcd for $C_{22}H_{22}ClN_3O_3$ $[M]^+$ 411.1350, found 411.1360; Anal. Calcd (%) for: C, 64.15; H, 5.38; N, 10.20, found: C, 64.22; H, 5.28; N, 10.08.

#### 3.3.3. 2-(4-Acetyl-phenoxy)-N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-acetamide(**13c**)

Yield 71%; Off White Solid; $^1$H NMR (DMSO-$d_6$, 300 MHz): δ1.60–1.70 (m, 2H, −$CH_2$−), 1.86–1.90 (m, 2H, 2× −$CH_2$−), 2.46 (s, 3H, -$CH_3$), 3.37–3.46 (m, 4H, 2× −$CH_2$−), 4.62 (s, 2H, −O−$CH_2$−), 6.59 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.12 (d, $J$ = 8.7 Hz, 2H, ArH),7.42 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.46 (s, 1H, −NH− exchangeable with $D_2O$), 7.78–7.83 (m, 3H, $H^5$ + 2ArH), 8.12 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.41 (d, $J$ = 5.1 Hz, 1H, $H^1$), 8.45 (s, 1H, −NH− exchangeable with $D_2O$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 22.1, 25.5, 26.3, 41.1, 47.7, 67.8, 99.0, 115.6, 117.4, 124.2, 124.8, 127.7, 130.5, 132.9, 149.2, 150.5, 153.1, 157.3, 162.8, 168.0, 195.2; HRMS: Calcd for $C_{23}H_{24}ClN_3O_3$ $[M]^+$ 425.1506, found 425.1520; Anal. Calcd (%) for: C, 64.86; H, 5.68; N, 9.87, found: C, 64.97; H, 5.74; N, 9.78.

#### 3.3.4. 2-(4-Acetyl-phenoxy)-N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-acetamide (**13d**)

Yield 80%; Off White Solid; $^1$H NMR (DMSO-$d_6$, 300 MHz): δ1.45–1.56 (m, 6H, 3× −$CH_2$−), 1.77–1.86 (m, 2H, −$CH_2$−), 2.48 (s, 3H, -$CH_3$), 3.34–3.42 (m, 4H, 2× −$CH_2$−), 4.62 (s, 2H, −O−$CH_2$−), 6.60 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.12 (d, $J$ = 8.7 Hz, 2H, ArH),7.43 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.46 (s, 1H, −NH− exchangeable with $D_2O$), 7.80–7.84 (m, 3H, $H^5$ + 2ArH), 8.16 (d, $J$ = 8.7 Hz, 1H, $H^3$), 8.42 (d, $J$ = 5.4 Hz, 1H, $H^1$), 8.46 (s, 1H, −NH− exchangeable with $D_2O$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 22.5, 25.3, 25.9, 29.1, 30.0, 42.1, 47.1, 67.7, 99.4, 115.3, 117.6, 124.7, 125.1, 127.8, 130.6, 132.7, 149.2, 151.0, 152.3, 157.4, 162.5, 168.2, 195.0; HRMS: Calcd for $C_{25}H_{28}ClN_3O_3$ $[M]^+$ 453.1819, found 453.1828; Anal. Calcd (%) for: C, 66.14; H, 6.22; N, 9.26, found: C, 66.26; H, 6.14; N, 9.35.

### 3.4. General procedure for the synthesis of amide-tethered 7-chloroquinoline chalcone conjugates **14** and 7-chloroquinoline ferrocenylchalcone conjugates **15**

To the well stirred solution of **13** (1 mmol) in ethanol, appropriate acetophenone (acetophenone/4-methoxyacetophenone/ferrocenylacetophenone) (1 mmol) was added followed by the addition of 40% (w/v) sodium hydroxide solution. The reaction mixture was stirred till completion of starting material as evidenced by TLC. The precipitates obtained were washed with dilute HCl solution and excess of water and finally recrystallized with methanol to obtain conjugates **14** or **15**.

#### 3.4.1. N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-2-[4-(3-phenyl-acryloyl)-phenoxy]-acetamide(**14a**)

Yield 88%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ3.39–3.48 (m, 4H, 2× −$CH_2$−), 4.20 (s, 1H, −NH− exchangeable with $D_2O$), 4.60 (s, 2H, −O−$CH_2$−), 6.38 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.01 (d, $J$ = 8.7 Hz, 2H, 2ArH), 7.24 (s, 1H, −NH− exchangeable with $D_2O$), 7.31 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.41–7.45 (m, 3H, ArH), 7.53 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.64 (d, $J$ = 8.4 Hz, 2H, ArH),7.79 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.92 (s, 1H, $H^5$), 7.99 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.03 (d, $J$ = 8.4 Hz, 2H, ArH), 8.42 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 40.7, 47.4, 67.4, 99.1, 115.2, 117.6, 119.8, 124.1, 125.2, 125.8, 126.4, 128.3, 130.7, 131.9, 132.4, 134.6, 143.6, 147.0, 150.3, 151.6, 157.5, 162.0, 167.9, 187.8; HRMS: Calcd for $C_{28}H_{24}ClN_3O_3$ $[M]^+$ 485.1506, found 485.1516; Anal. Calcd (%) for: C, 69.20; H, 4.98; N, 8.65, found: C, 69.29; H, 5.07; N, 8.80.

#### 3.4.2. N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-2-[4-(3-phenyl-acryloyl)-phenoxy]-acetamide(**14b**)

Yield 80%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.91–2.00 (m, 2H, −$CH_2$−),3.44–3.52 (m, 4H, 2× −$CH_2$−), 4.19 (s, 1H, −NH− exchangeable with $D_2O$), 4.62 (s, 2H, −O−$CH_2$−), 6.36 (d, $J$ = 5.7 Hz, 1H, $H^2$), 7.00 (d, $J$ = 8.7 Hz, 2H, 2ArH), 7.20 (s, 1H, −NH− exchangeable with $D_2O$), 7.32 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.42–7.46 (m, 3H, ArH), 7.51 (d, $J$ = 15.3 Hz, 1H, olefinic-H), 7.63 (d, $J$ = 8.4 Hz, 2H, ArH),7.81 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.91 (s, 1H, $H^5$), 7.99 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.04 (d, $J$ = 8.4 Hz, 2H, ArH), 8.38 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 28.1, 36.8, 47.9, 67.5, 99.1, 114.2, 114.4, 115.5, 117.9, 120.3, 124.5, 125.7, 127.9, 130.9, 131.0, 131.2, 133.8, 143.3, 149.5, 150.4, 152.3, 157.1, 163.5, 167.9, 187.7; HRMS: Calcd for $C_{29}H_{26}ClN_3O_3$ $[M]^+$ 499.1663, found 499.1670; Anal. Calcd (%) for: C, 69.66; H, 5.24; N, 8.40, found: C, 69.56; H, 5.29; N, 8.49.

#### 3.4.3. N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-2-[4-(3-phenyl-acryloyl)-phenoxy]-acetamide(**14c**)

Yield 82%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.71–2.10 (m, 4H, 2× −$CH_2$−), 3.40–3.50 (m, 4H, 2× −$CH_2$−), 4.21 (s, 1H, −NH− exchangeable with $D_2O$), 4.59 (s, 2H, −O−$CH_2$−), 6.36 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.00 (d, $J$ = 8.7 Hz, 2H, 2ArH), 7.22 (s, 1H, −NH− exchangeable with $D_2O$), 7.30 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.40–7.45 (m, 3H, ArH), 7.55 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.63 (d, $J$ = 8.4 Hz, 2H, ArH),7.80 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.90 (s, 1H, $H^5$), 7.97 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.02 (d, $J$ = 8.4 Hz, 2H, ArH), 8.40 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 27.3, 28.0, 36.9,

47.6, 67.3, 99.0, 115.1, 117.5, 119.9, 123.9, 125.2, 126.3, 128.4, 130.8, 131.3, 131.6, 132.5, 134.7, 143.5, 147.2, 150.1, 151.6, 157.4, 162.1, 168.1, 187.9; HRMS: Calcd for $C_{30}H_{28}ClN_3O_3$ $[M]^+$ 513.1819, found 513.1827; Anal. Calcd (%) for: C, 70.10; H, 5.49; N, 8.17, found: C, 70.01; H, 5.56; N, 8.30.

*3.4.4. N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-[4-(3-phenyl-acryloyl)-phenoxy]-acetamide(**14d**)*

Yield 79%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ1.52–1.70 (m, 6H, 3× $-CH_2-$), 1.93–1.99 (m, 2H, $-CH_2-$),3.41–3.51 (m, 4H, 2× $-CH_2-$), 4.15 (s, 1H, –NH– exchangeable with $D_2O$), 4.58 (s, 2H, $-O-CH_2-$), 6.35 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.01 (d, $J$ = 8.7 Hz, 2H, 2ArH), 7.18 (s, 1H, –NH– exchangeable with $D_2O$), 7.31 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.40–7.45 (m, 3H, ArH), 7.52 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.62 (d, $J$ = 8.4 Hz, 2H, ArH),7.80 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.88 (s, 1H, $H^5$), 7.98 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.02 (d, $J$ = 8.4 Hz, 2H, ArH), 8.41 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 25.9, 26.8, 29.1, 29.8, 37.1, 47.8, 67.4, 99.2, 115.0, 117.6, 120.1, 124.1, 125.1, 126.4, 128.3, 130.8, 131.3, 131.7, 132.6, 134.8, 144.0, 147.6, 150.3, 151.8, 157.5, 162.1, 167.7, 188.2; HRMS: Calcd for $C_{32}H_{32}ClN_3O_3$ $[M]^+$ 541.2132, found 541.2140; Anal. Calcd (%) for: C, 70.90; H, 5.95; N, 7.75, found: C, 70.80; H, 5.82; N, 7.82.

*3.4.5. N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenoxy}-acetamide(**14e**)*

Yield 90%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ3.36–3.47 (m, 4H, 2× $-CH_2-$), 3.89 (s, 3H, $-OCH_3$), 4.24 (s, 1H, –NH– exchangeable with $D_2O$), 4.56 (s, 2H, $-O-CH_2-$), 6.34 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.00 (d, $J$ = 8.7 Hz, 2H, 2ArH), 7.19 (s, 1H, –NH– exchangeable with $D_2O$), 7.33 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.42 (d, $J$ = 8.4 Hz, 2H, ArH), 7.52 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.66 (d, $J$ = 8.4 Hz, 2H, ArH),7.80 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.88 (s, 1H, $H^5$), 7.96 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.01 (d, $J$ = 8.4 Hz, 2H, ArH), 8.48 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 38.5, 47.5, 55.2, 67.3, 99.0, 115.1, 117.6, 119.9, 123.7, 125.2, 125.6, 126.5, 128.4, 130.6, 131.7, 132.2, 134.7, 143.7, 147.1, 150.4, 151.5, 157.4, 161.8, 167.4, 188.2; HRMS: Calcd for $C_{29}H_{26}ClN_3O_4$ $[M]^+$ 515.1612, found 515.1617; Anal. Calcd (%) for: C, 67.50; H, 5.08; N, 8.14, found: C, 67.58; H, 5.21; N, 8.20.

*3.4.6. N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenoxy}-acetamide(**14f**)*

Yield 80%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.95–2.01 (m, 2H, $-CH_2-$),3.32–3.41 (m, 4H, 2× $-CH_2-$), 3.92 (s, 3H, $-OCH_3$), 4.21 (s, 1H, –NH– exchangeable with $D_2O$), 4.57 (s, 2H, $-O-CH_2-$), 6.35 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.00 (d, $J$ = 8.7 Hz, 2H, 2ArH), 7.16 (s, 1H, –NH– exchangeable with $D_2O$), 7.31 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.41 (d, $J$ = 8.4 Hz, 2H, ArH), 7.53 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.62 (d, $J$ = 8.4 Hz, 2H, ArH),7.80 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.87 (s, 1H, $H^5$), 7.98 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.03 (d, $J$ = 8.4 Hz, 2H, ArH), 8.46 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 30.1, 37.0, 47.7, 55.0, 67.4, 99.1, 115.3, 117.4, 120.1, 124.1, 125.2, 125.8, 126.3, 128.2, 130.8, 131.9, 132.6, 135.0, 143.6, 147.2, 150.2, 151.8, 157.9, 161.9, 167.8, 187.9; HRMS: Calcd for $C_{30}H_{28}ClN_3O_4$ $[M]^+$ 529.1768, found 529.1760; Anal. Calcd (%) for: C, 67.98; H, 5.32; N, 7.93, found: C, 67.92; H, 5.45; N, 8.02.

*3.4.7. N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenoxy}-acetamide (**14g**)*

Yield 85%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.72–1.99 (m, 4H, 2× $-CH_2-$), 3.38–3.46 (m, 4H, 2× $-CH_2-$), 3.88 (s, 3H, $-OCH_3$), 4.26 (s, 1H, –NH– exchangeable with $D_2O$), 4.60 (s, 2H, $-O-CH_2-$), 6.37 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.98 (d, $J$ = 8.4 Hz, 2H, 2ArH), 7.19 (s, 1H, –NH– exchangeable with $D_2O$), 7.33 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.40 (d, $J$ = 8.4 Hz, 2H, ArH), 7.56 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.62 (d, $J$ = 8.4 Hz, 2H, ArH),7.82 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.89 (s, 1H, $H^5$), 7.99 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.05 (d, $J$ = 8.4 Hz, 2H, ArH), 8.44 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 27.2, 28.1, 36.8, 47.5, 55.2, 67.1, 99.3, 114.9, 117.6, 119.9, 124.0, 125.3, 125.8, 126.4, 128.6, 130.9, 131.9, 132.6, 134.8, 143.7, 147.3, 150.2, 151.6, 157.5, 162.2, 168.3, 188.0; HRMS: Calcd for $C_{31}H_{30}ClN_3O_4$ $[M]^+$ 543.1925, found 543.1937; Anal. Calcd (%) for: C, 68.44; H, 5.56; N, 7.72, found: C, 68.54; H, 5.49; N, 7.80.

*3.4.8. N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenoxy}-acetamide(**14h**)*

Yield 88%; Light Yellow Solid; $^1$H NMR ($CDCl_3$, 300 MHz): δ1.66–1.83 (m, 6H, 3× $-CH_2-$), 1.92–1.99 (m, 2H, $-CH_2-$),3.39–3.48 (m, 4H, 2× $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 4.20 (s, 1H, –NH– exchangeable with $D_2O$), 4.62 (s, 2H, $-O-CH_2-$), 6.40 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.04 (d, $J$ = 8.4 Hz, 2H, 2ArH), 7.22 (s, 1H, –NH– exchangeable with $D_2O$), 7.32 (d, $J$ = 9.0 Hz, 1H, $H^4$), 7.44 (d, $J$ = 8.4 Hz, 2H, ArH), 7.51 (d, $J$ = 15.6 Hz, 1H, olefinic-H), 7.62 (d, $J$ = 8.4 Hz, 2H, ArH),7.77 (d, $J$ = 15.6 Hz, 1H, olefinic-H),7.90 (s, 1H, $H^5$), 8.00 (d, $J$ = 9.0 Hz, 1H, $H^3$), 8.04 (d, $J$ = 8.4 Hz, 2H, ArH), 8.43 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 25.9, 26.7, 29.7, 30.5, 37.4, 47.6, 55.6, 67.3, 99.1, 115.1, 117.4, 120.2, 124.0, 125.2, 125.7, 126.4, 128.2, 131.3, 131.8, 132.5, 134.9, 144.2, 147.5, 150.1, 151.9, 157.7, 161.7, 167.5, 187.6; HRMS: Calcd for $C_{33}H_{34}ClN_3O_4$ $[M]^+$ 571.2238, found 571.2233; Anal. Calcd (%) for: C, 69.28; H, 5.99; N, 7.34, found: C, 69.36; H, 5.83; N, 7.44.

*3.4.9. N-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-acetamide(**15a**)*

Yield 80%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ 3.38–3.47 (m, 4H, 2× $-CH_2-$), 4.13 (s, 5H, Ferrocenyl-H), 4.51 (s, 2H, Ferrocenyl-H), 4.62 (s, 2H, Ferrocenyl-H), 4.69 (s, 2H, $-O-CH_2-$), 5.55 (s, 1H, –NH– exchangeable with $D_2O$), 6.46 (s, 1H, –NH– exchangeable with $D_2O$), 6.56 (d, $J$ = 5.4 Hz, 1H, $H^2$), 7.00–7.07 (m, 3H, 2ArH + olefinic-H),7.40 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.58 (d, $J$ = 15.9 Hz, olefinic-H), 7.87 (d, $J$ = 8.1 Hz, 2H, 2ArH), 8.05 (d, $J$ = 8.1 Hz, 1H, $H^3$), 8.12 (s, 1H, $H^5$), 8.31 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 42.4, 47.6, 67.5, 68.3, 69.4, 70.0, 71.8, 99.1, 115.4, 117.8, 120.5, 124.2, 125.1, 127.9, 130.4, 132.3, 144.2, 149.3, 150.7, 152.0, 157.2, 163.0, 167.4, 188.4; HRMS: Calcd for $C_{32}H_{28}ClFeN_3O_3$ $[M]^+$ 593.1169, found 593.1180; Anal. Calcd (%) for: C, 64.72; H, 4.75; N, 7.08, found: C, 64.64; H, 4.81; N, 7.17.

*3.4.10. N-[3-(7-chloro-quinolin-4-ylamino)-propyl]-2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-acetamide(**15b**)*

Yield 81%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.90–2.01 (m, 2H, $-CH_2-$),3.32–3.41 (m, 4H, 2× $-CH_2-$), 4.16 (s, 5H, Ferrocenyl-H), 4.49 (s, 2H, Ferrocenyl-H), 4.60 (s, 2H, Ferrocenyl-H), 4.67 (s, 2H, $-O-CH_2-$), 5.54 (s, 1H, –NH– exchangeable with $D_2O$), 6.43 (s, 1H, –NH– exchangeable with $D_2O$), 6.53 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.98–7.05 (m, 3H, 2ArH + olefinic-H),7.43 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.58 (d, $J$ = 15.9 Hz, olefinic-H), 7.84 (d, $J$ = 8.1 Hz, 2H, 2ArH), 8.04 (d, $J$ = 8.1 Hz, 1H, $H^3$), 8.10 (s, 1H, $H^5$), 8.34 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 30.1, 37.5, 47.6, 67.2, 68.5, 69.4, 69.8, 71.7, 99.5, 115.4, 117.6, 120.2, 124.6, 125.0, 127.8, 130.3, 132.1, 144.1, 149.2, 150.6, 152.1, 157.2, 162.8, 167.5, 187.8; HRMS: Calcd for $C_{33}H_{30}ClFeN_3O_3$ $[M]^+$ 607.1325, found 607.1319; Anal. Calcd (%) for: C, 65.20; H, 4.97; N, 6.91, found: C, 65.28; H, 4.86; N, 7.03.

*3.4.11. N-[4-(7-chloro-quinolin-4-ylamino)-butyl]-2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-acetamide(**15c**)*

Yield 78%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.71–1.92 (m, 4H, 2× $-CH_2-$), 3.37–3.46 (m, 4H, 2×

–$CH_2$–), 4.14 (s, 5H, Ferrocenyl-H), 4.48 (s, 2H, Ferrocenyl-H), 4.62 (s, 2H, Ferrocenyl-H), 4.71 (s, 2H, –O–$CH_2$–), 5.58 (s, 1H, –NH– exchangeable with $D_2O$), 6.41 (s, 1H, –NH– exchangeable with $D_2O$), 6.58 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.97–7.04 (m, 3H, 2ArH + olefinic-H),7.44 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.59 (d, $J$ = 15.9 Hz, olefinic-H), 7.81 (d, $J$ = 8.1 Hz, 2H, 2ArH), 8.03 (d, $J$ = 8.4 Hz, 1H, $H^3$), 8.15 (s, 1H, $H^5$), 8.31 (d, $J$ = 5.4 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 27.6, 28.3, 37.2, 47.5, 67.6, 68.2, 69.4, 70.1, 71.4, 99.0, 115.3, 117.7, 120.1, 124.5, 125.3, 127.8, 130.2, 132.1, 143.8, 149.4, 150.5, 152.2, 157.6, 162.6, 167.8, 188.0; HRMS: Calcd for $C_{34}H_{32}ClFeN_3O_3$ $[M]^+$ 621.1482, found 621.1477; Anal. Calcd (%) for: C, 65.56; H, 5.19; N, 6.76, found: C, 65.49; H, 5.10; N, 6.91.

#### 3.4.12. *N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-acetamide (**15d**)*

Yield 81%; Dark Red Solid; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$, 300 MHz): δ1.11–1.76 (m, 8H, 4× –$CH_2$–),3.30–3.39 (m, 4H, 2× –$CH_2$–), 4.19 (s, 5H, Ferrocenyl-H), 4.49 (s, 2H, Ferrocenyl-H), 4.58 (s, 2H, Ferrocenyl-H), 4.70 (s, 2H, –O–$CH_2$–), 5.55 (s, 1H, –NH– exchangeable with $D_2O$), 6.45 (s, 1H, –NH– exchangeable with $D_2O$), 6.49 (d, $J$ = 5.4 Hz, 1H, $H^2$), 6.99–7.06 (m, 3H, 2ArH + olefinic-H),7.41 (d, $J$ = 8.4 Hz, 1H, $H^4$), 7.57 (d, $J$ = 15.9 Hz, olefinic-H), 7.85 (d, $J$ = 8.1 Hz, 2H, 2ArH), 7.99 (d, $J$ = 8.4 Hz, 1H, $H^3$), 8.09 (s, 1H, $H^5$), 8.29 (d, $J$ = 5.1 Hz, 1H, $H^1$); $^{13}$C NMR (DMSO-$d_6$, 125 MHz): 25.6, 26.5, 29.8, 30.7, 37.5, 47.4, 67.6, 68.4, 69.5, 70.2, 71.6, 99.3, 115.6, 117.8, 120.0, 124.1, 125.3, 127.5, 130.7, 132.3, 144.1, 149.2, 150.4, 152.6, 157.1, 162.9, 167.4, 188.2; HRMS: Calcd for $C_{36}H_{36}ClFeN_3O_3$ $[M]^+$ 649.1795, found 649.1801; Anal. Calcd (%) for: C, 66.52; H, 5.58; N, 6.46, found: C, 66.65; H, 5.45; N, 6.58.

### 3.5. Biological evaluation

#### 3.5.1. Methods for assessment of antimalarial activity of test compounds

The W2 strain of *P. falciparum* was cultured in RPMI-1640 medium with 10% human serum, following standard methods, and parasites were synchronized with 5% D-sorbitol [34]. Beginning at the ring stage, microwell cultures were incubated with different concentrations of compounds for 48 h. The compounds were added from DMSO stocks; the maximum concentration of DMSO used was 0.1%. Controls without inhibitors included 0.1% DMSO. After 48 h when control cultures had progressed to new rings, the culture medium was removed, and cultures were incubated for 48 h with 1% formaldehyde in PBS, pH 7.4, at room temperature. Fixed parasites were then transferred to 0.1% Triton X-100 in PBS containing 1 nM YOYO-1 dye (Molecular Probes). Parasitemia was determined from dot plots (forward scatter *vs.* fluorescence) acquired on a FACSort flow cytometer using Cell Quest software (Beckton Dickinson). $IC_{50}$ values for growth inhibition were determined from plots of percent control parasitemia over inhibitor concentration using the Prism 3.0 program, (GraphPad Software), with data from duplicate experiments fitted by non linear regression [35].

#### 3.5.2. In vitro analysis of cytotoxicity on HeLa cells

HeLa cells were cultured in 60 mm × 15 mm tissue culture dishes containing 5 mL of Dulbecco's Modified Eagle's Medium (DMEM) supplemented with penicillin and streptomycin. Compounds were dissolved in DMSO to 100 μM concentrations. Once cell cultures reached 70%confluency, 5 μL of compound was added to the DMEM in the tissue culture dish for a final concentration of 100 μM. Cells were incubated for 24 h in a 37 °C $CO_2$ incubator. After 24 h incubation, the media was removed from the HeLa cells and the cells were then washed with 5 mL of 1× PBS. The cells were then cleaved off of the bottom of the plate *via* 5-min incubation with 0.5 mL of 0.25% trypsin. Cells were re-suspended in 1 mL of 1× PBS and transferred to a microcentrifuge tube. 100 μL of trypan blue solution were added to the re-suspended cells and allowed to incubate at room temperature for approximately 10 min. Viable and dead cells were visualized and counted with a hemacytometer. $IC_{50}$ values were determined using GraphPad PRISM.

## Acknowledgement

Financial assistance from Board of Research in Nuclear Sciences under DAE Research Award for Young Scientist Scheme (VK) is gratefully acknowledged.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.03.045.

## References

[1] WHO, World Malaria Report 2013, http://www.who.int/malaria/media/world_malaria_report_2013/en/.
[2] C.J.L. Murray, L.C. Rosenfeld, S.S. Lim, K.G. Andrews, K.J. Foreman, D. Haring, N. Fullman, M. Naghavi, R. Lozano, A.D. Lopez, Lancet 379 (2012) 413–431.
[3] U. Frevert, Trends Parasitol. 20 (2004) 417–424.
[4] A.J. Nzila, Antimicrob. Chemother. 57 (2006) 1043–1054.
[5] C. Wongsrichanalai, S.R. Meshnick, Emerg. Infect. Dis. 14 (2008) 716–719.
[6] M. Schlitzer, Curr. Med. Chem. 22 (2007) 944–986.
[7] C. O'Brien, P.P. Henrich, N. Passi, D.A. Fidock, Curr. Opin. Infect. Dis. 24 (2011) 570–577.
[8] M. Dondorp, F. Nosten, P. Yi, D. Das, A.P. Phyo, J. Tarning, K.M. Lwin, F. Ariey, W. Hanpithakpong, S.J. Lee, P. Ringwald, K. Silamut, M. Imwong, K. Chotivanich, P. Lim, T. Herdman, S.S. An, S. Yeung, P. Singhasivanon, N.P.J. Day, N. Lindegardh, D. Socheat, N.J. White, N. Engl. J. Med. 361 (2009) 455–467.
[9] S.R. Hawley, P.G. Bray, M. Mungthin, J.D. Atkinson, P.M. Ó Neill, S.A. Ward, Antimicrob. Agents Chemother. 42 (1998) 682–686.
[10] L.H. Miller, X. Su, Cell 146 (2011) 855–858.
[11] J.N. Burrows, K. Chibale, T.N.C. Wells, Curr. Top. Med. Chem. 11 (2011) 1226–1254.
[12] V.R. Solomon, W. Haq, M. Smilkstein, K. Srivastava, S. Rajakumar, S.K. Puri, S.B. Katti, Med. Chem. 4 (2008) 446–456.
[13] J.Y. Hwang, T. Kawasuji, D.J. Lowes, J.A. Clark, M.C. Connelly, F. Zhu, W.A. Guiguemde, M.S. Sigal, E.B. Wilson, J.L. DeRisi, R.K. Guy, J. Med. Chem. 54 (2011) 7084–7093.
[14] S. Manohar, U.C. Rajesh, S.I. Khan, B.L. Tekwani, D.S. Rawat, ACS Med. Chem. Lett. 3 (2012) 555–559.
[15] K.A. Ekoue-Kovi, K. Yearick, D.P. Iwaniuk, J.K. Natarajan, J. Alumasa, A.C. de Dios, P.D. Roepe, C. Wolf, Bioorg. Med. Chem. 17 (2009) 270–283.
[16] J.K. Natarajan, J.N. Alumasa, K. Yearick, K.A. Ekoue-Kovi, L.B. Casabianca, A.C. de Rios, C. Wolf, P.D. Roepe, J. Med. Chem. 51 (2008) 3466–3479.
[17] C. Biot, F. Nosten, L. Fraisse, D. Ter-Minassian, J. Khalife, D. Drive, Parasite 18 (2011) 207–214.
[18] B. Meunier, Acc. Chem. Res. 4 (2008) 69–77.
[19] F.W. Muregi, A. Ishih, Drug Dev. Res. 42 (2009) 1–13.
[20] C.A.M. Fraga, Expert Opin. Drug Discov. 4 (2009) 605–609.
[21] R. Morphy, Z. Rankovic, Curr. Pharm. Des. 15 (2009) 587–600.
[22] C. Biot, G. Glorian, L.A. Maciejewski, J.S. Brocard, O. Domarle, G. Blampain, P. Millet, A.J. Georges, H. Abessolo, D. Dive, J. Lebibi, J. Med. Chem. 40 (1997) 3715–3718.
[23] O. Domarle, G. Blampain, H. Agnaniet, T. Nzadiyabi, J. Lebibi, J. Brocard, L. Maciejewski, C. Biot, A.J. Georges, P. Millet, Antimicrob. Agents Chemother. 42 (1998) 540–544.
[24] G. Mombo-Ngoma, C. Supan, M.P. Dal-Bianco, M.A. Missinou, P.B. Matsiegui, C.L.O. Salazar, S. Issifou, D. Ter-Minassian, M. Ramharter, M. Kombila, P.G. Kremsner, B. Lell, Malar. J. 10 (2011) 53.
[25] (a) C. Biot, L. Delhaes, H. Abessolo, O. Domarle, L.A. Maciejewski, M. Mortuaire, P. Delcourt, P. Deloron, D. Camus, D. Dive, J.S. Brocard, J. Organomet. Chem. 589 (1999) 59–65;
(b) C. Biot, W. Daher, C.M. Ndiaye, P. Melnyk, B. Pradines, N. Chavain, A. Pellet, L. Fraisse, L. Pelinski, C. Jarry, J. Brocard, J. Khalife, I. Forfar-Bares, D. Dive, J. Med. Chem. 49 (2006) 4707–4714;
(c) M.A.L. Blackie, P. Beagley, S.L. Croft, H. Kendrick, J.R. Moss, K. Chibale, Bioorg. Med. Chem. 15 (2007) 6510–6516;
(d) P. Beagley, M.A.L. Blackie, K. Chibale, C. Clarkson, R. Meijboom, J.R. Moss, P.J. Smith, H. Su, Dalton Trans. 2003 (2003) 3046–3051;
(e) C. Biot, W. Daher, N. Chavain, T. Fandeur, J. Khalife, D. Dive, E. De Clercq, J. Med. Chem. 49 (2006) 2845–2849.
[26] (a) F. Dubar, J. Khalife, J. Brocard, D. Dive, C. Biot, Molecules 13 (2008) 2900–2907;

(b) F. Dubar, T.J. Egan, B. Pradines, D. Kuter, K.K. Ncokazi, D. Forge, J.F. Paul, C. Pierrot, H. Kalamou, J. Khalife, E. Buisine, C. Rogier, H. Vezin, I. Forfar, C. Slomianny, X. Trivelli, S. Kapishnikov, L. Leiserowitz, D. Dive, C. Biot, ACS Chem. Biol. 6 (2011) 275–287;
(c) N. Chavain, H. Vezin, D. Dive, N. Touati, J.F. Paul, E. Buisine, C. Biot, Mol. Pharm. 5 (2008) 710–716.
[27] S. Khatib, O. Nerya, R. Musa, M. Shmuel, S. Tamir, J. Vaya, Bioorg. Med. Chem. 13 (2005) 433–441.
[28] Z. Nowakowska, Eur. J. Med. Chem. 42 (2007) 125–137.
[29] M. Chen, T.G. Theander, S.B. Christensen, L. Hviid, L. Zhai, A. Kharazmi, Antimicrob. Agents Chemother. 38 (1994) 1470–1475.
[30] (a) N. Sriwilaijaroen, M. Liu, M.L. Go, P. Wilairat, Southeast Asian J. Trop. Med. Public Health 37 (2006) 607–612;
(b) J.N. Dominguez, J.E. Charris, G. Lobo, N.G. de Dominguez, M.M. Moreno, F. Riggione, E. Sanchez, J. Olson, P.J. Rosenthal, Eur. J. Med. Chem. 36 (2001) 555–560.
[31] P.J. Rosenthal, Int. J. Parasitol. 34 (2004) 1489–1499.
[32] (a) R. Raj, C. Biot, S. Carrère-Kremer, L. Kremer, Y. Guérardel, J. Gut, P.J. Rosenthal, V. Kumar, Chem. Biol. Drug Des. 83 (2014) 191–197;
(b) R. Raj, V. Mehra, J. Gut, P.J. Rosenthal, K.J. Wicht, T.J. Egan, M. Hopper, L.A. Wrischnik, K.M. Land, V. Kumar, Eur. J. Med. Chem. 84 (2014) 425–432;
(c) R. Raj, C. Biot, S. Carrère-Kremer, L. Kremer, Y. Guérardel, J. Gut, P.J. Rosenthal, D. Forge, V. Kumar, Chem. Biol. Drug Des. 83 (2014) 622–629;
(d) R. Raj, J. Gut, P.J. Rosenthal, V. Kumar, Bioorg. Med. Chem. Lett. 24 (2014) 756–759;
(e) P. Singh, R. Raj, P. Singh, J. Gut, P.J. Rosenthal, V. Kumar, Eur. J. Med. Chem. 71 (2014) 128–134;
(f) R. Raj, P. Singh, P. Singh, J. Gut, P.J. Rosenthal, V. Kumar, Eur. J. Med. Chem. 62 (2013) 590–596.
[33] J.N. Dominguez, C. Leon, J. Rodrigues, N.G. Dominguez, J. Gut, P.J. Rosenthal, J. Med. Chem. 48 (2005) 3654–3658.
[34] J.B. Jensen, D.L. Doolan (Eds.), Humana, Totowa, NJ (2002) 477–488.
[35] A. Singh, P.J. Rosenthal, Antimicrob. Agents Chemother. 45 (2001) 949–951.