1H-1,2,3-triazole tethered mono- and bis-ferrocenylchalcone-β-lactam conjugates: Synthesis and antimalarial evaluation

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · AUGUST 2014

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2014.08.053 · Source: PubMed

5 AUTHORS, INCLUDING:

Vipan Kumar
Guru Nanak Dev University
85 PUBLICATIONS **738** CITATIONS

European Journal of Medicinal Chemistry 86 (2014) 113–121

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Preliminary communication

1*H*-1,2,3-triazole tethered mono- and bis-ferrocenylchalcone-β-lactam conjugates: Synthesis and antimalarial evaluation

Kewal Kumar [a], Bruno Pradines [b, c, d], Marilyn Madamet [c, d, e], Rémy Amalvict [c, d, e], Vipan Kumar [a, *]

[a] Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India
[b] Unité de Parasitologie et d'Entomologie, Département de Microbiologie, Institut de Recherche Biomédicale des Armées, Brétigny sur Orge, France
[c] Aix Marseille Université, Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, UM 63, CNRS 7278, IRD 198, Inserm 1095, Marseille, France
[d] Centre National de Référence du Paludisme, Marseille, France
[e] Equipe Résidente de Recherche en Infectiologie Tropicale, Institut de Recherche Biomédicale des Armées, Hôpital d'Instruction des Armées Laveran, Marseille, France

ARTICLE INFO

Article history:
Received 11 June 2014
Received in revised form
11 August 2014
Accepted 15 August 2014
Available online 16 August 2014

Keywords:
Click chemistry
Ferrcenylchalcone-β-lactam conjugates
1*H*-1,2,3-triazoles
Structure–activity relationship
Plasmodium falciparum

ABSTRACT

A series of ferrocenylchalcone-β-lactam conjugates were synthesized and evaluated against 3D7 (CQ-Sensitive) and W2 (CQ-Resistant) strains of *Plasmodium falciparum*. The SAR studies revealed the dependence of activities at *N*-1 substituent of β-lactam ring with compounds being more potent on resistant strain. The compound **9f** and **9l** with *N*-cyclohexyl substituent proved to be the most potent and non-cytotoxic among the series exhibiting IC_{50} values of 2.36 and 2.43 μM respectively, against W2 strain of *P. falciparum*.

1. Introduction

After HIV and Cancer, Malaria still remains a major health problem particularly in the developing countries [1]. Five species of *Plasmodium* are responsible for the deadly disease, out of which *Plasmodium falciparum* is the most dangerous. According to the World Health Organization (WHO) factsheet, 3.4 billion people are at risk, of which 1.2 billion are at high risk and more than one malaria case occurs per 1000 population with transmission over 97 countries [2]. In 2012, malaria took 665,000 lives, which estimates around 1300 deaths per day or the death of one child per minute. The development of resistance across the existing drugs and the lack of vaccine have provided strong impetus for the discovery of new and effective antimalarials [3]. At present, WHO recommends an Artemisinin-based combination therapy (ACT), including an artemisinin derivative and a longer-acting partner drug for the treatment of malaria [4]. However the development of resistance to the present treatment in some parts of Southeast Asian regions is of great concern [5,6].

The successful amalgamation of the classical organometallic chemistry to biology, medicine, and molecular biotechnology has become a useful strategy in drug discovery research [7]. The introduction of the metal complexes to the biologically active organic pharmacophores has shown significant enhancement of their activity profiles. Among all the metallocenes used, ferrocenyl (Fc) moiety is considered as the most attractive because of its unique properties such as non-toxicity, neutral nature and chemical stability [8]. Many Fc based compounds display interesting cytotoxic [9], antimalarial [10], antifungal [11], antitoxoplasmic [12] and DNA-cleaving activity [13]. Ferroquine (FQ-SSR97193); the ferrocenyl analogue of chloroquine (CQ), is now under phase II clinical trials for the treatment of malaria [14]. Deciphering the mechanism of action of FQ revealed that in addition to the primary mechanism of action of quinoline (inhibition of the haem detoxification process); an important implication is the role of metallocenic moiety. Evidently, FQ could play a key role in the inhibition of merozoites reinvasion and clearly showed the advantage of an organometallic-based drug versus the purely organic parent drug

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

http://dx.doi.org/10.1016/j.ejmech.2014.08.053
0223-5234/

and hence the potential of organometallic chemistry for next generation of drug discovery [15].

The discovery of penicillin as antibiotics of incomparable effectiveness after World War II has led to the identification of β-lactams as key structural motifs with a broad range of pharmacological profiles and minimal or no cytotoxicity [16]. The recognition of non-classical β-lactams substrates such as carbapenems and monobactams along with classical β-lactams antibiotics rejuvenated a great interest in this field [17]. Last few years have witnessed the modification of β-lactam ring to prove their diverse biological properties *viz.* thrombin and chymase inhibitory activity, human tryptase, cholesterol absorption inhibitory activity, anti-inflammatory, vasopressin V1a antagonist activity, antidiabetic, antimalarial, antiparkinsonian, anti-tubercular and anti-HIV activity [16].

The naturally occurring bioactive 1,3-diaryl-2-propen-1-ones or Chalcones are another prominent secondary metabolite precursors of flavonoids and isoflavonoids in plants. The open-chain flavonoid consisting of two aromatic rings joined by a three-carbon-α, β-unsaturated carbonyl system exhibits a wide variety of biological properties such as anti-inflammatory anticancer, immunomodulatory, antimicrobial, antibacterial, and immunosuppressive as well as leishmanicidal, antimalarial, and trypanocidal activities [18]. The recent reports on the antimalarial profiles of chalcones have encouraged new developments and modifications of these structural units by both organic and medicinal chemists.

Recent reports from our group has shown the synthesis and antimalarial evaluation of 4-amino-quinoline-β-lactam conjugates tethered *via* 1,2,3-triazoles [19], amide [20], urea and oxalamide linkers [21]. Some of the synthesized conjugates exhibited promising antimalarial efficacy with activity profiles comparable to CQ against CQ resistant W2 strain of *P. falciparum*. In continuation with our interest to scrutinize the influence of Fc nucleus on the activity profile of organic ligands [22], the present manuscript explicates the synthesis of 1*H*-1,2,3-triazole-tethered β-lactam-ferrocenylchalcone conjugates and their *in vitro* antimalarial evaluation against CQ-susceptible 3D7 and CQ-resistant W2 strain of *P. falciparum* (Fig. 1).

The use of 1*H*-1,2,3-triazole as linker in the synthesized conjugates is based on its moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions.

2. Result and discussion

2.1. Synthetic chemistry

The precursors' *viz.* **3** and **4** were obtained *via* our recently reported mono- and dipropargyation of 3-amino-azetidin-2-ones **2** [23], prepared by Staudinger reaction of *N*-substituted 1-azadiene with azidoketene generated *in situ* from azidoacetic acid and *p*-toluenesulphonyl chloride in the presence of triethylamine with subsequent reduction using Zn/NH_4Cl, using 1.1 and 2.5 equivalents of propargyl bromide in the presence of K_2CO_3 in dry DMF at room temperature as shown in Scheme 1.

The second precursor **7**, was obtained *via* aldol-condensation of *O*-alkylazido-acetophenones with ferrocenecarboxaldehyde **6** in the presence of sodium hydroxide as a base in EtOH:H_2O (9:1) mixture (Scheme 2).

The precursors **3**, **4** and **7** were utilized for the synthesis of desired mono- and bis-1*H*-1,2,3-triazole-tethered β-lactam-ferrocenylchalcone conjugates *via* Cu-promoted azide-alkyne cycloaddition reaction in the presence of sodium ascorbate in EtOH:H_2O (10:1) mixture as depicted in Scheme 3.

2.2. Antimalarial evaluation

The synthesized β-lactam-ferrocenylchalcone conjugates were evaluated for their antimalarial profiles against the CQ-S 3D7 and CQ-R W2 strain of *P. falciparum* and the corresponding IC_{50} as well as 95% Cl values are listed in Table 1. The synthetic precursor *viz.* 3-amino-azetidin-2-ones were previously evaluated for their antimalarial potential and have exhibited IC_{50} values in the range of 18.59–38.06 μM against CQ-S strain of *P. falciparum* [27]. As evident from Table 1, although the synthesized conjugates were not as active as the standard drug CQ, the introduction of the ferrocene nucleus significantly improved the antimalarial efficacy of β-lactam nucleus. A closer inspection of Table 1 revealed an interesting Structure Activity Relationship (SAR) with activities strongly

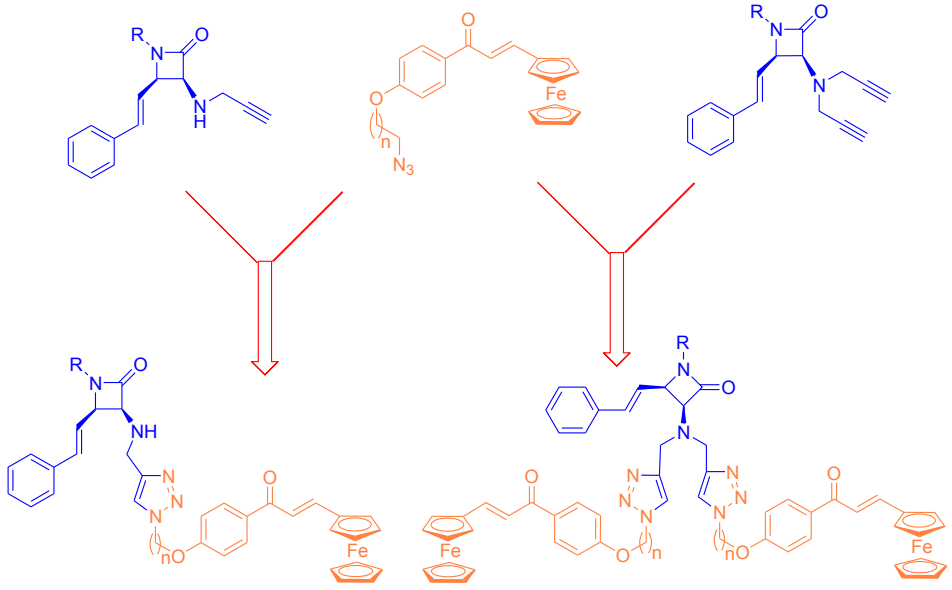
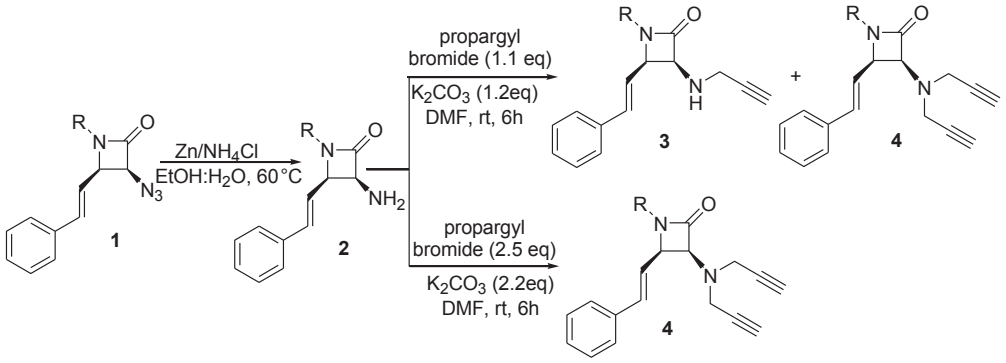
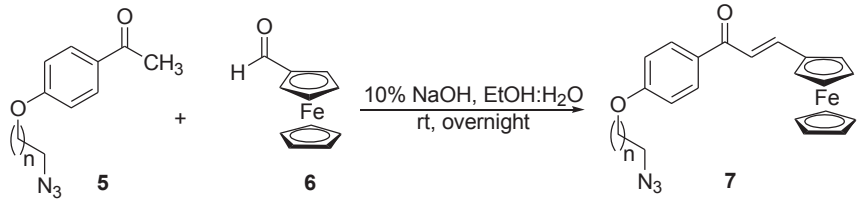


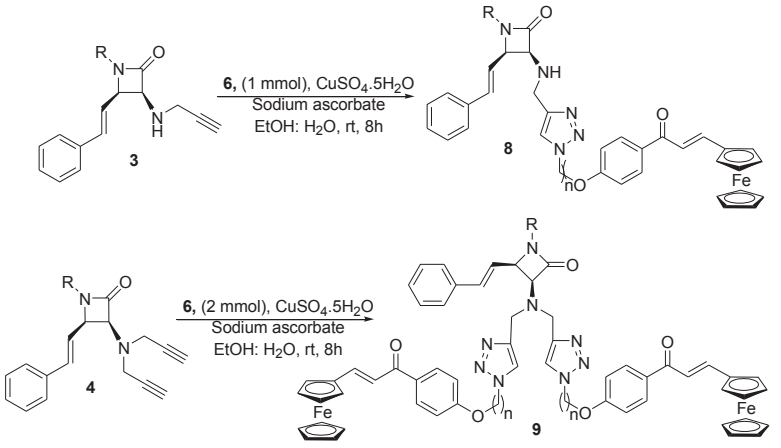
Fig. 1. Design of target hybrids.



Scheme 1. Synthesis of mono- and bis-propargylated precursors.



Scheme 2. Synthesis of *O*-alkylazido-ferrocenylchalcones.



Entry	n	R
8a/9a	2	4-FC_6H_4
8b9b	2	4-$CH_3C_6H_4$
8c/9c	2	4-ClC_6H_4
8d/9d	2	C_6H_5
8e/9e	2	Cycloheptyl
8f/9f	2	Cyclohexyl

Entry	n	R
8g/9g	3	4-FC_6H_4
8h/9h	3	4-$CH_3C_6H_4$
8i/9i	3	4-ClC_6H_4
8j/9j	3	C_6H_5
8k/9k	3	Cycloheptyl
8l/9l	3	Cyclohexyl

Scheme 3. Synthesis of desired target hybrids.

depending upon the nature of substituent at *N*−1 position of *β*-lactam while the length of alkyl chain introduced as linker and the presence of mono- and bis-ferrocenylchalcone have a little influence. On comparing the activity profiles among mono-ferrocenylchalcone-*β*-lactam conjugates **8a**–**l** against 3D7 strain, the presence of *N*-alkyl *viz.* cyclohexyl and cycloheptyl substituent improved the activity profiles compared to *N*-aryl substituents with **8f** proved to be the most potent among the series exhibiting an IC_{50} value of 5.81 μM.

Similar comparison among bis-ferrocenylchalcone-*β*-lactam conjugates **9a**–**l** against 3D7 strain revealed the dependence of activities only on the substituent at *N*−1 position of *β*-lactam ring while no improvement with the introduction of another ferrocenylchalcone unit was observed. The conjugates with *N*-aryl substituent at *N*−1 position of the *β*-lactam ring *viz.* **9a**–**d** and **9g**–**j** exhibited comparable activity profiles and are less potent compared to their *N*-alkyl counterparts *viz.* **9e**–**f** and **9k**–**l**. The compound **9l** with *N*-cyclohexyl substituent proved to be most potent among the series with an IC_{50} value of 4.80 μM.

A general comparison of activity profiles of synthesized conjugates **8a**–**l** and **9a**–**l** against CQ-S and CQ-R strains revealed that the scaffolds showed better antimalarial efficacy against CQ-R (W2) compared to CQ-S (3D7) strains. SAR studies among mono-ferrocenylchalcone-*β*-lactam conjugates **8a**–**l** against W2 strain showed activities to be independent upon the nature of substituent at *N*−1 position and the length of the linker. The compound **8e** with

Table 1
Antiplasmodial activity against 3D7 and W2 strains of *P. falciparum*.

Compound	R	*n*	Strains			
			3D7		W2	
			IC_{50} (μM)	95% CI	IC_{50} (μM)	95% CI
8a	p-F–C_6H_4	2	24.43	22.83–26.15	5.50	5.07–5.96
8b	p-CH_3–C_6H_4	2	26.85	24.54–29.39	4.72	4.45–5.01
8c	p-Cl–C_6H_4	2	20.00	18.03–22.19	6.81	5.53–8.38
8d	C_6H_5	2	20.18	18.19–22.39	14.45	12.45–16.78
8e	C_7H_{13}	2	8.26	7.86–8.68	2.89	2.49–3.35
8f	C_6H_{11}	2	5.81	5.03–6.71	5.07	4.63–5.55
8g	p-F–C_6H_4	3	18.58	17.44–19.79	4.48	3.35–5.98
8h	p-CH_3–C_6H_4	3	17.26	15.63–19.06	10.45	8.80–12.40
8i	p-Cl–C_6H_4	3	34.67	27.67–43.45	4.99	4.64–5.36
8j	C_6H_5	3	17.99	15.15–21.35	16.79	15.55–18.13
8k	C_7H_{13}	3	8.39	7.88–8.94	4.46	3.98–4.79
8l	C_6H_{11}	3	15.28	13.52–17.26	7.66	6.75–8.69
9a	p-F–C_6H_4	2	31.70	26.46–37.97	20.33	20.66–26.36
9b	p-CH_3–C_6H_4	2	23.44	20.75–26.48	14.06	11.69–16.92
9c	p-Cl–C_6H_4	2	21.23	19.31–23.34	11.09	10.00–12.30
9d	C_6H_5	2	13.77	12.99–14.60	15.14	13.10–17.49
9e	C_7H_{13}	2	5.75	4.76–6.96	3.33	3.04–3.64
9f	C_6H_{11}	2	6.79	5.77–7.99	2.36	2.04–2.73
9g	p-F–C_6H_4	3	>100	–	26.92	18.84–38.45
9h	p-CH_3–C_6H_4	3	11.51	9.02–14.68	17.50	18.88–18.14
9i	p-Cl–C_6H_4	3	26.55	25.26–27.90	14.29	12.58–16.21
9j	C_6H_5	3	15.96	14.78–17.23	15.67	12.90–19.02
9k	C_7H_{13}	3	5.38	4.58–6.33	6.97	6.63–7.32
9l	C_6H_{11}	3	4.80	4.51–5.12	2.43	2.19–2.70
CQ			0.021	0.018–0.025	0.49	0.37–0.63

IC_{50} values are means of 5 experiments. 95% CI: 95% confident interval.

cycloheptyl substituent at *N*–1 position of β-lactam ring proved to be the most active among this series and exhibited an IC_{50} value of 2.89 μM. The evaluation studies among bis-ferrocenylchalcone-conjugates **9a**–**l** confirmed them to be less potent than their mono-counterparts against CQ-R (W2) strain of *P. falciparum*. The activity profiles among this series were also shown to depend upon the nature of substituent at *N*–1 position of the β-lactam ring with a preference for *N*-alkyl (cyclohexyl) substituent. Further, studying the effect of nature of substituent at *N*–1 position of the triazole ring against CQ-S (3D-7) strain revealed a preference for ethyl linker among mono-conjugates as evident by **8e** and **8f** while no such dependence has been observed among bis-conjugates. Similar comparison of activity profiles against W2-strain showed independence over nature of substituent at *N*–1 position of triazole-functionality as evident by conjugates **8e**, **8f** **8k**, **8l**, **9e**, **9f**, **9k** and **9l**.

The conjugates **9f** and **9l** were the most potent among the series exhibiting IC_{50} values of 2.36 and 2.43 μM respectively. However, the *in vitro* antimalarial activity of the mono- and bis-ferrocenylchalcones-β-lactam conjugates is lower than ferroquine in laboratory strains (2.1–13.4 nM) [28] and in Senegalese or Gabonese field isolates (0.55–28.2 nM and 0.43–30.9 nM, respectively) [29,30], 4-*N*-substituted ferroquine analogues [31] and of ferrocenylmethyl-phenylindoles [32]. The antimalarial activities of the present conjugates against CQ-R W2 strain however are equivalent to ferrocene–ciprofloxacin complexes [10a,33] and ferrocenyl-chalcones such as 1-ferrocenyl-3-(4-nitrophenyl)prop-2-en-1-one [34,35].

Cytotoxicity of two most potent conjugates *viz.* **9f** and **9l** was determined against mammalian HeLa cells. As shown in Table 2, the conjugates were non-cytotoxic against mammalian cells and therefore had selectivity for inhibition of *P. falciparum*.

3. Conclusion

In conclusion, the present manuscript explicates the synthesis and antimalarial evaluation of mono- and bis-ferrocenylchalcones-β-lactam conjugates. The observed antimalarial profiles showed that these conjugates are more active against CQ-R W2 strain compared to CQ-S 3D7 strain of *P. falciparum*. SAR revealed a strong dependence of activity profiles at *N*–1 substituent of β-lactam ring while the length of the linker and the presence of the mono- and bis-ferrocenylchalcones seemed to play a secondary role. The compounds **9f** and **9l** with an optimum combination of *N*-alkyl (Cyclohexyl) substituent at *N*–1 position, a chain length of $n = 2$ and $n = 3$ and the presence of bis-ferrocenylchalcone unit proved to be the most potent among the series exhibiting IC_{50} values of 2.36 and 2.43 μM respectively.

Table 2
Cytotoxicity and selective index of conjugates **9f** and **9l**.

Compound	Strains				
	Cytotoxicity	3D7		W2	
	(IC_{50} μM)	(IC_{50} μM)	SI[a]	(IC_{50} μM)	SI[a]
9f	68.47	6.79	10.08	2.36	29.01
9l	75.04	4.80	15.63	2.43	30.88

[a] Selectivity index.

4. Experimental section

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. ^{1}H NMR spectra were recorded in deuterochloroform and DMSO-d_6 with Bruker B-ACS 120, 400 MHz and Bruker AVANCE III HD, 500 MHz spectrometer using TMS as 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 Bruker 500 MHz AVANCE III HD spectrometer in and DMSO-d_6 using TMS as internal standard. Mass spectra were recorded on a BRUCKER high resolution mass spectrometer (micrOTOF-QII). Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120 mesh) using ethyl acetate–hexane mixture as eluent.

4.1. General procedure for the synthesis of procedure for the preparation of β-lactam ferrocenylchalcone conjugates (*8* and *9*)

To a stirred solution of *O*-alkylazido ferrocenylchalcone **6** (1 mmol for **8** and 2 mmol for **9**) in EtOH:H_2O (10:1) was added appropriate acetylenic β-lactam **4** or **5** (1 mmol), copper sulphate (0.055 mmol for **8** and 0.1 mmol for **9**) and sodium ascorbate (0.13 mmol for **8** and 0.26 for **9**) in succession, at room temperature. The progress of the reaction was monitored using tlc and on completion, water (15 mL) was added to the reaction mixture and extracted with chloroform (2 × 50 mL). Combined organic layers were dried over anhydrous magnesium sulphate and concentrated under reduced pressure to result in the isolation of a crude product which was purified by silica gel chromatography using 4:6 (EtOAc:hexane) for **8** and 5.5:4.5 (EtOAc:hexane) for **9**.

4.1.1. 3-[(1-{2-[4-(3-Fereocenyl-acryloyl)-phenoxy]-ethyl}-1H [1,2,3]triazol-4-ylmethyl)-amino]-1-(4-fluoro-phenyl)-4-styryl-azetidin-2-one (*8a*)

Yield 80%; Brick Red Solid; mp. 112–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.16 (s, 5H, H^{13}), 4.37 (s, 2H, H^5), 4.47 (s, 2H, H^{12}), 4.57 (s, 2H, H^{11}), 4.64 (s, 2H, H^7), 4.89 (t, $J = 6.0$ Hz, –NH, exchangeable with D_2O), 5.16–5.30 (m, 3H, $H^1 + H^8$), 5.75 (dd, $J = 5.7$ Hz, 7.2 Hz,

1H, H^2), 6.19 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.71 (d, J = 15.9 Hz, 1H, H^4), 6.93–7.71 (m, 13H, 11ArH + H^9 + H^{10}), 7.76 (s, 1H, triazole-H^6), 7.94 (d, J = 8.4 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 49.6, 58.6, 60.5, 61.2, 63.3, 69.0, 69.8, 71.4, 79.3, 114.3, 115.8, 115.9, 116.2, 118.7, 118.8, 122.2, 125.1, 126.7, 126.8, 128.7, 128.8, 130.7, 132.4, 135.4, 135.5, 143.1, 146.5, 161.8, 188.4. HRMS (ESI-micrOTOF-QII) calcd for $C_{41}H_{36}FFeN_5O_3$ $[M+H]^+$ 722.3751, found 722.3749.

4.1.2. 3-[(1-{2-[4-(3-Fereocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-4-styryl-1-p-tolyl-azetidin-2-one (**8b**)

Yield 81%; Brick Red Solid; mp. 114–115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, 3H, $-CH_3$), 4.16 (s, 5H, H^{13}), 4.37 (s, 2H, H^5), 4.47 (s, 2H, H^{12}), 4.57 (s, 2H, H^{11}), 4.65 (s, 2H, H^7), 4.90 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.16–5.29 (m, 3H, H^1 + H^8), 5.72 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.17 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.72 (d, J = 15.9 Hz, 1H, H^4), 6.90–7.69 (m, 13H, 11ArH + H^9+H^{10}), 7.75 (s, 1H, triazole-H^6), 7.95 (d, J = 8.6 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.0, 49.7, 58.6, 60.1, 61.1, 66.3, 69.0, 69.8, 71.4, 79.3, 114.3, 117.2, 118.7, 122.4, 125.3, 126.7, 126.8, 128.8, 128.9, 129.6, 129.7, 130.7, 131.3, 132.4, 134.3, 136.5, 146.3, 146.4, 161.1, 188.6. HRMS (ESI-micrOTOF-QII) calcd for $C_{42}H_{39}FeN_5O_3$ $[M+H]^+$ 718.5279, found 718.5275.

4.1.3. 3-[(1-{2-[4-(3-Fereocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-(4-chloro-phenyl)-4-styryl-azetidin-2-one (**8c**)

Yield 79%; Brick Red Solid; mp. 117–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.14 (s, 5H, H^{13}), 4.36 (s, 2H, H^5), 4.46 (s, 2H, H^{12}), 4.58 (s, 2H, H^{11}), 4.63 (s, 2H, H^7), 4.88 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.14–5.31 (m, 3H, H^1 + H^8), 5.71 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.17 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.73 (d, J = 15.9 Hz, 1H, H^4), 6.89–7.67 (m, 13H, 11ArH + H^9 + H^{10}), 7.76 (s, 1H, triazole-H^6), 7.96 (d, J = 8.4 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 49.4, 58.5, 60.3, 61.1, 63.5, 69.2, 69.6, 71.5, 79.7, 114.4, 115.6, 115.8, 116.5, 118.4, 118.6, 122.4, 125.2, 126.6, 128.3, 128.5, 128.9, 130.5, 132.3, 135.2, 135.4, 143.5, 146.3, 161.2, 188.9. HRMS (ESI-micrOTOF-QII) calcd for $C_{41}H_{36}ClFeN_5O_3$ $[M+H]^+$ 738.6192, found 738.6184.

4.1.4. 3-[(1-{2-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-phenyl-4-styryl-azetidin-2-one (**8d**)

Yield 82%; Brick Red Solid; mp. 116–117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.14 (s, 5H, H^{13}), 4.35 (s, 2H, H^5), 4.48 (s, 2H, H^{12}), 4.55 (s, 2H, H^{11}), 4.63 (s, 2H, H^7), 4.92 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.14–5.28 (m, 3H, H^1 + H^8), 5.70 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.19 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.74 (d, J = 15.9 Hz, 1H, H^4), 6.93–7.66 (m, 14H, 12ArH + H^9+H^{10}), 7.78 (s, 1H, triazole-H^6), 7.93 (d, J = 8.6 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 49.4, 58.8, 60.6, 66.3, 69.8, 69.9, 71.5, 76.8, 79.6, 114.9, 117.3, 118.6, 126.7, 126.8, 126.9, 128.3, 128.5, 128.7, 129.5, 129.7, 130.5, 131.9, 132.7, 134.8, 136.8, 146.4, 146.6, 161.8, 188.4. HRMS (ESI-micrOTOF-QII) calcd for $C_{41}H_{37}FeN_5O_3$ $[M+H]^+$ 704.6415, found 704.6411.

4.1.5. 3-[(1-{2-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cycloheptyl-4-styryl-azetidin-2-one (**8e**)

Yield 79%; Brick Red Solid; mp. 115–116 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33–2.26 (m, 12H, cycloheptyl); 3.55–3.59 (m, 1H, cycloheptyl H), 4.16 (s, 5H, H^{13}), 4.39 (s, 2H, H^5), 4.46 (s, 2H, H^{12}), 4.58 (s, 2H, H^{11}), 4.63 (s, 2H, H^7), 4.92 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.14–5.29 (m, 3H, H^1 + H^8), 5.71 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.16 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.72 (d, J = 15.9 Hz, 1H, H^4), 6.93–7.68 (m, 9H, 7ArH + H^9 + H^{10}), 7.77 (s, 1H, triazole-H^6), 7.94 (d, J = 8.6 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 23.6, 28.4, 32.7, 48.6, 49.7, 58.5, 60.2, 66.7, 69.2, 69.5, 71.1, 76.4, 79.7, 114.9, 117.4, 118.6, 126.3, 126.5, 126.8, 128.2, 129.5, 131.9, 132.5, 134.8, 136.6, 146.4, 146.8, 161.9, 188.5. HRMS (ESI-micrOTOF-QII) calcd for $C_{42}H_{45}FeN_5O_3$ $[M+H]^+$ 724.5272, found 724.5267.

4.1.6. 3-[(1-{2-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cyclohexyl-4-styryl-azetidin-2-one (**8f**)

Yield 82%; Brick Red Solid; mp. 116–117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.43–2.25 (m, 10H, cyclohexyl); 3.52–3.55 (m, 1H, cyclohexyl H), 4.17 (s, 5H, H^{13}), 4.37 (s, 2H, H^5), 4.45 (s, 2H, H^{12}), 4.58 (s, 2H, H^{11}), 4.67 (s, 2H, H^7), 4.91 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.11–5.27 (m, 3H, H^1 + H^8), 5.74 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.17 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.71 (d, J = 15.9 Hz, 1H, H^4), 6.91–7.66 (m, 9H, 7ArH + H^9 + H^{10}), 7.75 (s, 1H, triazole-H^6), 7.94 (d, J = 8.4 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.1, 27.3, 31.5, 47.4, 49.6, 58.7, 60.4, 66.5, 69.6, 69.8, 71.2, 76.7, 79.3, 114.8, 117.1, 118.5, 126.2, 126.4, 126.7, 128.6, 129.2, 131.8, 132.4, 134.6, 136.9, 146.1, 146.9, 161.4, 188.3. HRMS (ESI-micrOTOF-QII) calcd for $C_{41}H_{43}FeN_5O_3$ $[M+H]^+$ 710.7537, found 710.7531.

4.1.7. 3-[(1-{3-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-(4-fluoro-phenyl)-4-styryl-azetidin-2-one (**8g**)

Yield 85%; Brick Red Solid; mp. 118–119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.34–2.36 (m, 2H, H^8), 4.00 (s, 2H, H^5), 4.16 (s, 5H, H^{13}), 4.46 (s, 4H, H^7 + H^{14}), 4.58 (s, 2H, H^{12}), 4.89 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.15–5.28 (m, 3H, H^1 + H^9), 5.81 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.20 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.74 (d, J = 15.9 Hz, 1H, H^4), 6.89–6.98 (m, 4H, –ArH), 7.14 (d, J = 15.9 Hz, 1H, H^{10}), 7.25–7.55 (m, 7H, –ArH), 7.64 (s, 1H, triazole-H^6), 7.72 (d, J = 15.9 Hz, 1H, H^{11}), 7.98 (d, J = 8.9 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.2, 47.0, 58.7, 60.5, 64.3, 69.0, 69.8, 71.3, 71.8, 79.4, 114.2, 115.9, 116.2, 118.7, 118.8, 122.5, 124.4, 126.7, 126.8, 128.7, 128.8, 130.7, 131.9, 132.7, 135.5, 136.8, 143.0, 146.2, 161.9, 188.2. HRMS (ESI-micrOTOF-QII) calcd for $C_{42}H_{38}FFeN_5O_3$ $[M+H]^+$ 736.1041, found 736.1037.

4.1.8. 3-[(1-{3-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-4-styryl-1-p-tolyl-azetidin-2-one (**8h**)

Yield 84%; Brick Red Solid; mp. 112–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.30–2.34 (m, 2H, H^8), 2.32 (s, 3H, $-CH_3$), 4.01 (s, 2H, H^5), 4.17 (s, 5H, H^{13}), 4.44 (s, 4H, H^7 + H^{14}), 4.59 (s, 2H, H^{12}), 4.88 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.16–5.27 (m, 3H, H^1 + H^9), 5.80 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.22 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.75 (d, J = 15.9 Hz, 1H, H^4), 6.86–6.95 (m, 4H, –ArH), 7.13 (d, J = 15.9 Hz, 1H, H^{10}), 7.23–7.53 (m, 7H, –ArH), 7.62 (s, 1H, triazole-H^6), 7.71 (d, J = 15.9 Hz, 1H, H^{11}), 7.98 (d, J = 8.9 Hz, 2H, –ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.5, 21.4, 47.6, 58.4, 60.3, 64.7, 69.3, 69.5, 71.6, 71.8, 79.7, 114.1, 115.5, 116.4, 118.6, 118.7, 122.3, 124.5, 126.6, 126.9, 128.5, 128.9, 130.5, 131.8, 132.4, 135.6, 136.9, 143.2, 146.1, 161.4, 188.1. HRMS (ESI-micrOTOF-QII) calcd for $C_{43}H_{41}FeN_5O_3$ $[M+H]^+$ 732.0409, found 732.0401.

4.1.9. 3-[(1-{3-[4-(3-Fereocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-(4-chloro-phenyl)-4-styryl-azetidin-2-one (**8i**)

Yield 80%; Brick Red Solid; mp. 119–120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32–2.36 (m, 2H, H^8), 4.02 (s, 2H, H^5), 4.14 (s, 5H, H^{13}), 4.48 (s, 4H, H^7 + H^{14}), 4.59 (s, 2H, H^{12}), 4.88 (t, J = 6.0 Hz, –NH, exchangeable with D_2O), 5.17–5.29 (m, 3H, H^1 + H^9), 5.80 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.21 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.73 (d, J = 15.9 Hz, 1H, H^4), 6.88–6.96 (m, 4H, –ArH), 7.14 (d, J = 15.9 Hz, 1H, H^{10}), 7.23–7.54 (m, 7H, –ArH), 7.66 (s, 1H, triazole-H^6),7.74 (d,

J = 15.9 Hz, 1H, H^{11}), 7.96 (d, J = 8.9 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.1, 47.4, 58.5, 60.3, 64.7, 69.3, 69.9, 71.5, 71.9, 79.6, 114.3, 115.8, 116.3, 118.6, 118.9, 122.3, 124.5, 126.6, 126.9, 128.5, 128.9, 130.5, 131.7, 132.6, 135.4, 136.6, 143.3, 146.4, 161.8, 188.1. HRMS (ESI-micrOTOF-QII) calcd for $C_{42}H_{38}ClFeN_5O_3$ $[M+H]^+$ 752.0713, found 752.0710.

4.1.10. 3-[(1-{3-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-phenyl-4-styryl-azetidin-2-one (**8j**)

Yield 80%; Brick Red Solid; mp. 110–111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31–2.37 (m, 2H, H^8), 4.01 (s, 2H, H^5), 4.14 (s, 5H, H^{13}), 4.47 (s, 4H, H^7 + H^{14}), 4.57 (s, 2H, H^{12}), 4.87 (t, J = 6.0 Hz, −NH, exchangeable with D_2O), 5.15–5.27 (m, 3H, H^1 + H^9), 5.83 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.21 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.72 (d, J = 15.9 Hz, 1H, H^4), 6.88–6.96 (m 4H, −ArH), 7.12 (d, J = 15.9 Hz, 1H, H^{10}), 7.23–7.51 (m, 8H, −ArH), 7.63 (s, 1H, triazole-H^6), 7.75 (d, J = 15.9 Hz, 1H, H^{11}), 7.97 (d, J = 8.9 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.4, 47.3, 58.6, 60.1, 64.8, 69.2, 69.8, 71.4, 71.8, 79.2, 114.6, 115.5, 116.7, 118.1, 118.5, 122.6, 124.2, 126.6, 126.8, 128.3, 128.8, 130.3, 131.5, 132.8, 135.7, 136.9, 143.4, 146.2, 161.6, 188.2. HRMS (ESI-micrOTOF-QII) calcd for $C_{42}H_{39}FeN_5O_3$ $[M+H]^+$ 718.4291, found 718.4288.

4.1.11. 3-[(1-{3-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cycloheptyl-4-styryl-azetidin-2-one (**8k**)

Yield 81%; Brick Red Solid; mp. 118–119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.37–2.33 (m, 14H, H^8 + cycloheptyl); 3.53–3.55 (m, 1H, cycloheptyl H), 4.01 (s, 2H, H^5), 4.16 (s, 5H, H^{13}), 4.45 (s, 4H, H^7 + H^{14}), 4.56 (s, 2H, H^{12}), 4.87 (t, J = 6.0 Hz, −NH, exchangeable with D_2O), 5.16–5.29 (m, 3H, H^1 + H^9), 5.83 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.21 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.75 (d, J = 15.9 Hz, 1H, H^4), 6.87–6.95 (m, 2H, −ArH), 7.16 (d, J = 15.9 Hz, 1H, H^{10}), 7.24–7.49 (m, 5H, −ArH), 7.62 (s, 1H, triazole-H^6), 7.70 (d, J = 15.9 Hz, 1H, H^{11}), 7.97 (d, J = 8.4 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.2, 22.5, 27.7, 31.9, 47.3, 49.4, 58.7, 60.2, 66.5, 69.6, 69.9, 71.2, 76.6, 79.8, 114.2, 117.1, 118.7, 126.2, 126.5, 126.7, 128.5, 129.9, 131.5, 132.0, 134.2, 136.4, 146.2, 146.6, 161.2, 188.6. HRMS (ESI-micrOTOF-QII) calcd for $C_{43}H_{47}FeN_5O_3$ $[M+H]^+$ 738.2419, found 738.2416.

4.1.12. 3-[(1-{3-[4-(3-Ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cyclohexyl-4-styryl-azetidin-2-one (**8l**)

Yield 83%; Brick Red Solid; mp. 113–114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46–2.32 (m, 12H, H^8 + Cyclohexyl), 3.54–3.55 (m, 1H, cyclohexyl H), 4.02 (s, 2H, H^5), 4.17 (s, 5H, H^{13}), 4.47 (s, 4H, H^7 + H^{14}), 4.59 (s, 2H, H^{12}), 4.88 (t, J = 6.0 Hz, −NH, exchangeable with D_2O), 5.14–5.28 (m, 3H, H^1 + H^9), 5.81 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.22 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.72 (d, J = 15.9 Hz, 1H, H^4), 6.87–6.99 (m, 2H, −ArH), 7.13 (d, J = 15.9 Hz, 1H, H^{10}), 7.26–7.49 (m, 5H, −ArH), 7.64 (s, 1H, triazole-H^6), 7.73 (d, J = 15.9 Hz, 1H, H^{11}), 7.99 (d, J = 8.9 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.4, 22.2, 27.4, 31.6, 47.4, 49.7, 58.3, 60.5, 66.9, 69.0, 69.8, 71.5, 76.2, 79.5, 114.5, 117.1, 118.0, 126.0, 126.1, 126.6, 128.1, 129.7, 131.9, 132.2, 134.7, 136.8, 146.5, 146.6, 161.6, 188.1. HRMS (ESI-micrOTOF-QII) calcd for $C_{42}H_{45}FeN_5O_3$ $[M+H]^+$ 724.1053, found 724.1047.

4.1.13. 3-[Bis-(1-{2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-(4-fluoro-phenyl)-4-styryl-azetidin-2-one (**9a**)

Yield 82%; Brick Red Solid; mp. 107–108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.01 (s, 4H, H^5), 4.14 (s, 10H, H^{13}), 4.36 (s, 4H, H^7), 4.48 (s, 4H, H^{12}), 5.51–5.24 (m, 4H, H^8), 4.56 (s, 4H, H^{11}), 4.75 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 4.96 (d, J = 5.1 Hz, 1H, H^1) 6.24 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.66 (d, J = 15.9 Hz, 1H, H^4), 6.90 (d, J = 8.6 Hz, 4H, −ArH), 7.10 (d, J = 15.9 Hz, 2H, H^9), 7.23–7.37 (m, 9H, −ArH), 7.71 (d, J = 15.9 Hz, 2H, H^{10}), 7.87 (s, 2H, triazole-H^6), 7.95 (d, J = 8.6 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 45.4, 49.6, 58.3, 62.2, 66.1, 69.3, 69.4, 71.8, 79.4, 114.1, 117.7, 118.5, 124.8, 126.9, 128.5, 129.7, 130.4, 132.6, 133.3, 134.7, 135.3, 135.6, 138.2, 138.5, 139.9, 143.5, 146.4, 161.2, 188.7. HRMS (ESI-micrOTOF-QII) calcd for $C_{65}H_{57}FFe_2N_8O_5$ $[M+H]^+$ 1161.3211, found 1161.3206.

4.1.14. 3-[Bis-(1-{2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-4-styryl-1-p-tolyl-azetidin-2-one (**9b**)

Yield 83%; Brick Red Solid; mp. 105–106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.27 (s, 3H, $-CH_3$), 4.00 (s, 4H, H^5), 4.16 (s, 10H, H^{13}), 4.34 (s, 4H, H^7), 4.46 (s, 4H, H^{12}), 4.50–4.52 (m, 4H, H^8), 4.57 (s, 4H, H^{11}), 4.76 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 4.97 (d, J = 5.1 Hz, 1H, H^1), 6.26 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.64 (d, J = 15.9 Hz, 1H, H^4), 6.91 (d, J = 8.6 Hz, 4H, −ArH); 7.09 (d, J = 15.9 Hz, 2H, H^9), 7.25–7.34 (m, 9H, −ArH), 7.72 (d, J = 15.9 Hz, 2H, H^{10}), 7.86 (s, 2H, triazole-H^6), 7.97 (d, J = 8.6 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 21.0, 45.3, 49.4, 58.5, 62.2, 66.3, 69.0, 69.8, 71.3, 79.3, 114.3, 117.2, 118.8, 124.9, 126.7, 128.8, 129.6, 130.7, 132.3, 133.8, 134.9, 135.0, 135.4, 138.5, 138.6, 139.8, 143.9, 146.7, 161.3, 188.0. HRMS (ESI-micrOTOF-QII) calcd for $C_{66}H_{60}Fe_2N_8O_5$ $[M+H]^+$ 1157.1352, found 1157.1348.

4.1.15. 3-[Bis-(1-{2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-(4-chloro-phenyl)-4-styryl-azetidin-2-one (**9c**)

Yield 83%; Brick Red Solid; mp. 102–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.02 (s, 4H, H^5), 4.15 (s, 10H, H^{13}), 4.33 (s, 4H, H^7), 4.47 (s, 4H, H^{12}), 4.50–4.53 (m, 4H, H^8), 4.57 (s, 4H, H^{11}), 4.74 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 4.98 (d, J = 5.1 Hz, H^1), 6.27 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.63 (d, J = 15.9 Hz, 1H, H^4), 6.93 (d, J = 8.6 Hz, 4H, −ArH), 7.07 (d, J = 15.9 Hz, 2H, H^9), 7.24–7.37 (m, 9H, −ArH), 7.74 (d, J = 15.9 Hz, 2H, H^{10}), 7.84 (s, 2H, triazole-H^6), 7.96 (d, J = 8.6 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 45.2, 49.4, 58.2, 62.3, 66.4, 69.5, 69.7, 71.6, 79.3, 114.4, 117.6, 118.3, 124.6, 126.7, 128.3, 129.6, 130.2, 132.4, 133.1, 134.4, 135.2, 135.5, 138.1, 138.5, 139.6, 143.2, 146.6, 161.5, 188.4. HRMS (ESI-micrOTOF-QII) calcd for $C_{65}H_{57}ClFe_2N_8O_5$ $[M+H]^+$ 1177.5307, found 1177.5302.

4.1.16. 3-[Bis-(1-{2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-phenyl-4-styryl-azetidin-2-one (**9d**)

Yield 85%; Brick Red Solid; mp. 114–115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.03 (s, 4H, H^5), 4.17 (s, 10H, H^{13}), 4.36 (s, 4H, H^7), 4.45 (s, 4H, H^{12}), 4.51–4.54 (m, 4H, H^8), 4.57 (s, 4H, H^{11}), 4.77 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 4.95 (d, J = 5.1 Hz, 1H, H^1), 6.23 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.75 (d, J = 15.9 Hz, 1H, H^4), 6.90 (d, J = 8.6 Hz, 4H, −ArH), 7.08 (d, J = 15.9 Hz, 2H, H^9), 7.23–7.37 (m, 10H, −ArH), 7.73 (d, J = 15.9 Hz, 2H, H^{10}), 7.87 (s, 2H, triazole-H^6), 7.98 (d, J = 8.4 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 49.6, 58.7, 60.3, 66.7, 69.5, 69.6, 71.4, 76.6, 79.3, 114.7, 117.2, 118.7, 126.2, 126.4, 126.7, 128.1, 128.4, 128.9, 129.4, 129.9, 130.8, 131.7, 132.8, 134.6, 136.4, 146.6, 146.8, 161.7, 188.9. HRMS (ESI-micrOTOF-QII) calcd for $C_{65}H_{58}Fe_2N_8O_5$ $[M+H]^+$ 1143.6244, found 1143.6437.

4.1.17. 3-[Bis-(1-{2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cycloheptyl-4-styryl-azetidin-2-one (**9e**)

Yield 78%; Brick Red Solid; mp. 102–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34–2.24 (m, 12H, cycloheptyl); 3.51–3.56 (m, 1H, cycloheptyl H), 4.03 (s, 4H, H^5), 4.18 (s, 10H, H^{13}), 4.35 (s, 4H, H^7),

4.46 (s, 4H, H^{12}), 4.52–4.55 (m, 4H, H^8), 4.55 (s, 4H, H^{11}), 4.73 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 4.95 (d, J = 5.1 Hz, 1H, H^1), 6.25 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.66 (d, J = 15.9 Hz, 1H, H^4), 6.90 (d, J = 8.6 Hz, 4H, −ArH), 7.10 (d, J = 15.9 Hz, 2H, H^9), 7.23–7.32 (m, 5H, −ArH), 7.75 (d, J = 15.9 Hz, 2H, H^{10}), 7.83 (s, 2H, triazole-H^6), 7.95 (d, J = 8.6 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 23.5, 28.7, 32.6, 48.8, 49.5, 58.7, 60.1, 66.4, 69.3, 69.7, 71.0, 76.2, 79.5, 114.6, 117.1, 118.3, 126.3, 126.5, 126.6, 128.1, 129.3, 131.4, 132.2, 134.6, 136.8, 146.1, 146.5, 161.6, 188.7. HRMS (ESI-micrOTOF-QII) calcd for $C_{66}H_{66}Fe_2N_8O_5$ $[M+H]^+$ 1162.8946, found 1162.8940.

4.1.18. 3-[Bis-(1-{2-[4-(3-ferrocenyl-acryloyl)-phenoxy]-ethyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cyclohexyl-4-styryl-azetidin-2-one (**9f**)

Yield 81%; Brick Red Solid; mp. 103–104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44–2.23 (m, 10H, cyclohexyl); 3.51–3.53 (m, 1H, cyclohexyl H), 4.00 (s, 4H, H^5), 4.15 (s, 10H, H^{13}), 4.33 (s, 4H, H^7), 4.47 (s, 4H, H^{12}), 4.51–4.54 (m, 4H, H^8), 4.55 (s, 4H, H^{11}), 4.75 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 4.96 (d, J = 5.1 Hz, 1H, H^1), 6.27 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.62 (d, J = 15.9 Hz, 1H, H^4), 6.94 (d, J = 8.6 Hz, 4H, −ArH), 7.08 (d, J = 15.9 Hz, 2H, H^9), 7.24–7.36 (m, 5H, −ArH), 7.69 (d, J = 15.9 Hz, 2H, H^{10}), 7.83 (s, 2H, triazole-H^6), 7.96 (d, J = 8.6 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 22.3, 27.6, 31.7, 47.5, 49.8, 58.4, 60.3, 66.8, 69.2, 69.7, 71.0, 76.3, 79.6, 114.7, 117.3, 118.4, 126.2, 126.3, 126.7, 128.2, 129.6, 131.7, 132.6, 134.4, 136.6, 146.3, 146.8, 161.1, 188.8. HRMS (ESI-micrOTOF-QII) calcd for $C_{65}H_{64}Fe_2N_8O_5$ $[M+H]^+$ 1148.1147, found 1148.1142.

4.1.19. 3-[Bis-(1-{3-[4-(3-ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-(4-fluoro-phenyl)-4-styryl-azetidin-2-one (**9g**)

Yield 81%; Brick Red Solid; mp. 104–105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32–2.37 (m, 4H, H^8), 4.03 (s, 4H, H^5), 4.14 (s, 10H, H^{13}), 4.47 (s, 8H, H^7 + H^{14}), 4.57 (s, 4H, H^{12}), 5.13–5.29 (m, 5H, H^1 + H^9), 5.82 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.22 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.76 (d, J = 15.9 Hz, 1H, H^4), 6.88–6.99 (m, 8H, −ArH), 7.12 (d, J = 15.9 Hz, 2H, H^{10}), 7.27–7.58 (m, 5H, −ArH), 7.65 (s, 2H, triazole-H^6), 7.73 (d, J = 15.9 Hz, 2H, H^{11}), 7.97 (d, J = 8.9 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.5, 45.3, 49.4, 58.6, 62.7, 66.4, 69.1, 69.6, 71.9, 79.8, 114.3, 117.5, 118.4, 124.7, 126.5, 128.4, 129.4, 130.6, 132.5, 133.3, 134.6, 135.5, 135.7, 138.1, 138.6, 139.8, 143.2, 146.7, 161.2, 188.3. HRMS (ESI-micrOTOF-QII) calcd for $C_{67}H_{61}FFe_2N_8O_5$ $[M+H]^+$ 1189.2590, found 1189.2584.

4.1.20. 3-[Bis-(1-{3-[4-(3-ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-4-styryl-1-p-tolyl-azetidin-2-one (**9h**)

Yield 80%; Brick Red Solid; mp. 104–105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.91–2.24 (m, 4H, H^8), 2.35 (s, 3H, $-CH_3$), 4.02 (s, 4H, H^5), 4.14 (s, 10H, H^{13}), 4.45 (s, 8H, H^7 + H^{14}), 4.51 (s, 4H, H^{12}), 5.12–5.28 (m, 5H, H^1 + H^9), 5.76 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.24 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.74 (d, J = 15.9 Hz, 1H, H^4), 6.89–6.97 (m, 5H, −ArH), 7.14 (d, J = 15.9 Hz, 2H, H^{10}), 7.25–7.56 (m, 8H, −ArH), 7.73 (d, J = 15.9 Hz, 2H, H^{11}), 7.91 (s, 2H, triazole-H^6), 7.93 (d, J = 9.0 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.3, 21.5, 47.4, 58.5, 60.1, 64.8, 69.2, 69.5, 71.7, 71.9, 79.6, 114.4, 115.7, 116.6, 118.2, 118.8, 122.2, 124.2, 126.1, 126.3, 128.6, 128.8, 130.7, 131.6, 132.3, 135.4, 136.4, 143.1, 146.4, 161.5, 188.5. HRMS (ESI-micrOTOF-QII) calcd for $C_{68}H_{64}Fe_2N_8O_5$ $[M+H]^+$ 1185.6373, found 1185.6369.

4.1.21. 3-[Bis-(1-{3-[4-(3-ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-(4-chloro-phenyl)-4-styryl-azetidin-2-one (**9i**)

Yield 84%; Brick Red Solid; mp. 101–102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.33–2.39 (m, 4H, H^8), 4.04 (s, 4H, H^5), 4.12 (s, 10H, H^{13}), 4.45 (s, 8H, H^7 + H^{14}), 4.56 (s, 4H, H^{12}), 5.11–5.31 (m, 5H, H^1 + H^9), 5.81 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.21 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.78 (d, J = 15.9 Hz, 1H, H^4), 6.86–6.97 (m, 8H, −ArH), 7.14 (d, J = 15.9 Hz, 2H, H^{10}), 7.26–7.55 (m, 5H, −ArH), 7.66 (s, 2H, triazole-H^6), 7.74 (d, J = 15.9 Hz, 2H, H^{11}), 7.98 (d, J = 8.9 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.3, 45.4, 49.6, 58.5, 62.4, 66.7, 69.3, 69.5, 71.8, 79.9, 114.2, 117.4, 118.1, 124.6, 126.4, 128.6, 129.5, 130.3, 132.2, 133.7, 134.3, 135.5, 135.7, 138.5, 138.8, 139.6, 143.0, 146.5, 161.5, 188.9. HRMS (ESI-micrOTOF-QII) calcd for $C_{67}H_{61}ClFe_2N_8O_5$ $[M+H]^+$ 1205.8463, found 1205.8459.

4.1.22. 3-[Bis-(1-{3-[4-(3-ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-phenyl-4-styryl-azetidin-2-one (**9j**)

Yield 78%; Brick Red Solid; mp. 106–107 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.29–2.35 (m, 4H, H^8), 4.01 (s, 4H, H^5), 4.15 (s, 10H, H^{13}), 4.47 (s, 8H, H^7 + H^{14}), 4.56 (s, 4H, H^{12}), 5.13–5.26 (m, 5H, H^1 + H^9), 5.80 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.24 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.74 (d, J = 15.9 Hz, 1H, H^4), 6.89–6.98 (m, 8H, −ArH), 7.11 (d, J = 15.9 Hz, 2H, H^{10}), 7.24–7.55 (m, 6H, −ArH), 7.65 (s, 2H, triazole-H^6), 7.74 (d, J = 15.9 Hz, 2H, H^{11}), 7.98 (d, J = 8.9 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.2, 47.5, 58.2, 60.7, 64.3, 69.7, 69.9, 71.5, 71.6, 79.3, 114.1, 115.7, 116.2, 118.6, 118.9, 122.3, 124.5, 126.6, 126.9, 128.1, 128.4, 130.4, 131.2, 132.5, 135.8, 136.8, 143.3, 146.4, 161.1, 188.6. HRMS (ESI-micrOTOF-QII) calcd for $C_{67}H_{62}Fe_2N_8O_5$ $[M+H]^+$ 1171.5113, found 1171.5117.

4.1.23. 3-[Bis-(1-{3-[4-(3-ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cycloheptyl-4-styryl-azetidin-2-one (**9k**)

Yield 80%; Brick Red Solid; mp. 102–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32–2.32 (m, 16H, H^8 + cycloheptyl); 3.54–3.58 (m, 1H, cycloheptyl H), 4.01 (s, 4H, H^5), 4.15 (s, 10H, H^{13}), 4.46 (s, 8H, H^7 + H^{14}), 4.55 (s, 4H, H^{12}), 5.14–5.27 (m, 5H, H^1 + H^9), 5.84 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.24 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.76 (d, J = 15.9 Hz, 1H, H^4), 6.88–6.97 (m, 6H, −ArH), 7.13 (d, J = 15.9 Hz, 2H, H^{10}), 7.26–7.54 (m, 3H, −ArH), 7.63 (s, 2H, triazole-H^6),7.71 (d, J = 15.9 Hz, 2H, H^{11}), 7.97 (d, J = 8.9 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.4, 22.1, 27.4, 31.5, 47.7, 49.2, 58.4, 60.5, 66.7, 69.5, 69.7, 71.3, 76.7, 79.7, 114.6, 117.2, 118.6, 126.3, 126.7, 126.9, 128.4, 129.7, 131.4, 132.3, 134.1, 136.6, 146.4, 146.5, 161.5, 188.8. HRMS (ESI-micrOTOF-QII) calcd for $C_{68}H_{71}Fe_2N_8O_5$ $[M+H]^+$ 1190.1983, found 1190.1978.

4.1.24. 3-[Bis-(1-{3-[4-(3-ferrocenyl-acryloyl)-phenoxy]-propyl}-1H-[1,2,3]triazol-4-ylmethyl)-amino]-1-cyclohexyl-4-styryl-azetidin-2-one (**9l**)

Yield 84%; Brick Red Solid; mp. 104–105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45–2.35 (m, 14H, H^8 + Cyclohexyl), 3.51–3.53 (m, 1H, cyclohexyl H), 4.00 (s, 4H, H^5), 4.15 (s, 10H, H^{13}), 4.46 (s, 8H, H^7 + H^{14}), 4.57 (s, 4H, H^{12}), 5.13–5.27 (m, 5H, H^1 + H^9), 5.81 (dd, J = 5.7 Hz, 7.2 Hz, 1H, H^2), 6.21 (dd, J = 7.2 Hz, 15.9 Hz, 1H, H^3), 6.75 (d, J = 15.9 Hz, 1H, H^4), 6.87–6.97 (m, 6H, −ArH), 7.14 (d, J = 15.9 Hz, 2H, H^{10}), 7.26–7.59 (m, 3H, −ArH), 7.63 (s, 2H, triazole-H^6), 77.2 (d, J = 15.9 Hz, 2H, H^{11}), 7.98 (d, J = 8.9 Hz, 4H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 19.2, 22.4, 27.5, 31.7, 47.2, 49.6, 58.1, 60.7, 66.8, 69.5, 69.9, 71.3, 76.4, 79.2, 114.2, 117.6, 118.3, 126.2, 126.3, 126.7, 128.2, 129.8, 131.8, 132.1, 134.8, 136.9, 146.2, 146.5, 161.4, 188.0. HRMS (ESI-micrOTOF-QII) calcd for $C_{67}H_{68}Fe_2N_8O_5$ $[M+H]^+$ 1176.4863, found 1176.4858.

4.2. Methods for assessment of antimalarial activity of test compounds

The two strains *viz.* 3D7, the CQ-susceptible strain (isolated in West Africa; obtained from MR4, VA, USA), and W2 (isolated in Indochina; obtained from MR4, VA, USA), the CQ-resistant strain, were maintained in culture in RPMI 1640 (Invitrogen, Paisley, United Kingdom), supplemented with 10% human serum (Abcys S.A. Paris, France) and buffered with 25 mM HEPES and 25 mM $NaHCO_3$. Parasites were grown in A-positive human blood (Etablissement Français du Sang, Marseille, France) under controlled atmospheric conditions that consisted of 10% O_2, 5% CO_2 and 85% N_2 at 37 °C with a humidity of 95%.

The two strains were synchronized twice with sorbitol before use [24], and clonality was verified every 15 days through PCR genotyping of the polymorphic genetic markers *msp1* and *msp2* and microsatellite loci [25,26]; additionally, clonality was verified each year by an independent laboratory from the Worldwide Antimalarial Resistance Network (WWARN).

Chloroquine diphosphate (CQ) was purchased from Sigma (Saint Louis, MO). CQ was resuspended in water in concentrations ranging between 5 and 3200 nM. The synthetic compounds were resuspended in DMSO and then diluted in RPMI-DMSO (99v/1v) to obtain final concentrations ranging from 1 nM to 100 μM.

For *in vitro* isotopic microtests, 25 μL/well of antimalarial drug and 200 μL/well of the parasitized red blood cell suspension (final parasitaemia, 0.5%; final haematocrit, 1.5%) were distributed into 96 well plates. Parasite growth was assessed by adding 1 μCi of tritiated hypoxanthine with a specific activity of 14.1 Ci/mmol (Perkin–Elmer, Courtaboeuf, France) to each well at time zero. The plates were then incubated for 48 h in controlled atmospheric conditions. Immediately after incubation, the plates were frozen and thawed to lyse erythrocytes. The contents of each well were collected on standard filter microplates (Unifilter GF/B; Perkin–Elmer) and washed using a cell harvester (Filter-Mate Cell Harvester; Perkin–Elmer). Filter microplates were dried, and 25 μL of scintillation cocktail (Microscint O; Perkin–Elmer) was placed in each well. Radioactivity incorporated by the parasites was measured with a scintillation counter (Top Count; Perkin–Elmer).

The IC_{50}, the drug concentration able to inhibit 50% of parasite growth, was assessed by identifying the drug concentration corresponding to 50% of the uptake of tritiated hypoxanthine by the parasite in the drug-free control wells. The IC_{50} value was determined by non-linear regression analysis of log-based dose–response curves (Riasmart™, Packard, Meriden, USA). IC_{50} are expressed as geometric means of 5 experiments.

4.3. In vitro analysis of cytotoxicity on HeLa cells

HeLa cells were cultured in 60 × 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 1X 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 1X PBS and transferred to a micro-centrifuge tube. 100 μL of trypan blue solution was 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 haemacytometer. IC_{50} values were determined using GraphPad PRISM.

Acknowledgements

Financial assistance from Department of Science and Technology, New Delhi under Innovation in Science Pursuit for Inspired Research (INSPIRE) Fellowship with code IF-10482 (KK) is gratefully acknowledged. We are also thankful to Professor Christophe Biot for his valued guidance during the course of this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.08.053.

References

[1] (a) S. Hurtley, C. Ash, L. Roberts, Science 328 (2010) 841;
(b) V. Kumar, A. Mahajan, K. Chibale, Bioorg. Med. Chem. 17 (2009) 2236.
[2] Factsheet on the World Malaria Report, 2013. http://www.who.int/malaria/media/world_malaria_report_2013/en/.
[3] M. Schlitzer, Curr. Med. Chem. 2 (2007) 944.
[4] R.T. Eastman, D.A. Fidock, Nat. Rev. Microbiol. 7 (2009) 864.
[5] C. Wongsrichanalai, S.R. Meshnick, Emerg. Infect. Dis. 14 (2008) 716.
[6] A.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. Day, N. Lindegardh, D. Socheat, N.J.N. White, Engl. J. Med. 361 (2009) 455.
[7] G. Gasser, N. Metzler-Nolte, Curr. Opin. Chem. Biol. 16 (2012) 84.
[8] D.R. Staveren, N. Metzler-Nolte, Chem. Rev. 104 (2004) 5931.
[9] (a) O. Payen, S. Top, A. Vessières, E. Brulé, M.A. Plamont, M.J. McGlinchey, H. Müller- Bunz, G. Jaouen, J. Med. Chem. 51 (2008) 1791;
(b) G. Gasser, I. Ott, N. Metzler-Nolte, J. Med. Chem. 54 (2011) 3.
[10] (a) F. Dubar, G. Anquetin, B. Pradines, D. Dive, J. Khalife, C. Biot, J. Med. Chem. 52 (2009) 7954;
(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;
(c) C. Biot, F. Nosten, L. Fraisse, D. Ter-Minassian, J. Khalife, D. Dive, Parasite 18 (2011) 207.
[11] C. Biot, N. Francois, L. Maciejewski, J. Brocard, D. Poulain, Bioorg. Med. Chem. Lett. 10 (2000) 839.
[12] A. Baramee, A. Coppin, M. Mortuaire, L. Pelinski, S. Tomavo, J. Brocard, Bioorg. Med. Chem. 14 (2006) 1294.
[13] P.J. Higgins, A.M. Gellett, Bioorg. Med. Chem. Lett. 19 (2009) 1614.
[14] (a) W. Daher, C. Biot, T. Fandeur, H. Jouin, L. Pelinski, E. Viscogliosi, L. Fraisse, B. Pradines, J. Brocard, J. Khalife, D. Dive, Malar. J. 5 (2006) 11;
(b) C. Supan, G. Mombo-Ngoma, M.P. Dal-Bianco, C.L. Ospina-Salazar, S. Issifou, F. Mazuir, A. Filali-Ansary, C. Biot, D. Ter-Minassian, M. Ramharter, Antimicrob. Agents Chemother. 56 (2012) 3165;
(c) D. Dive, C. Biot, ChemMedChem 3 (2008) 383.
[15] F. Dubar, C. Slomianny, J. Khalife, D. Dive, H. Kalamou, Y. Guérardel, P. Grellier, C. Biot, Angew. Chem. 125 (2013) 7844.
[16] A.J. Wright, Mayo Clin. Proc. 74 (1999) 290.
[17] (a) G. Cainelli, P. Galletti, S. Garbisa, D. Giacomini, L. Sartor, A. Quintavalla, Bioorg. Med. Chem. 11 (2003) 5391;
(b) A. Kazi, R. Hill, T.E. Long, D.J. Kuhn, E. Turos, Q.P. Dou, Biochem. Pharmacol. 67 (2004) 365.
[18] (a) Z. Nowakowska, Eur. J. Med. Chem. 42 (2007) 125;
(b) A. Boumendjel, J. Boccard, P.A. Carrupt, E. Nicolle, M. Blanc, A. Geze, L. Choisnard, D. Wouessidjewe, E.L. Matera, C. Dumontet, J. Med. Chem. 51 (2008) 2307;
(c) M. Cabrera, M. Simoens, G. Falchi, M.L. Lavaggi, O.E. Piro, E.E. Castellano, A. Vidal, A. Azqueta, A. Monge, A. Lopez de Cerain, G. Sagrera, G. Seoane, H. Cerecetto, M. Gonzalez, Bioorg. Med. Chem. 15 (2007) 3356;
(d) O. Sabzevari, G. Galati, M.Y. Moridani, A. Siraki, P.J. O'Brien, Chem. Biol. Interact. 148 (2004) 57;
(e) Y.K. Rao, S.H. Fang, Y.M. Tzeng, Bioorg. Med. Chem. 12 (2004) 2679.
[19] R. Raj, J. Gut, P.J. Rosenthal, V. Kumar, Bioorg. Med. Chem. Lett. 24 (2014) 756.
[20] R. Raj, C. Biot, S. Carrere-Kremer, L. Kremer, Y. Guérardel, J. Gut, P.J. Rosenthal, V. Umar, Chem. Biol. Drug Des. 83 (2014) 191.
[21] P. Singh, R. Raj, P. Singh, J. Gut, P.J. Rosenthal, V. Kumar, Eur. J. Med. Chem. 71 (2014) 128.
[22] (a) K. Kumar, S. Carrère-Kremer, L. Kremer, Y. Guérardel, C. Biot, V. Kumar, Organometallics 32 (2013) 5713;
(b) K. Kumar, C. Biot, S. Carrère-Kremer, L. Kremer, Y. Guérardel, P. Roussel, V. Kumar, Organometallics 32 (2013) 7386.
[23] P. Singh, P. Singh, M. Kumar, J. Gut, P.J. Rosenthal, K. Kumar, V. Kumar, M.P. Mahajan, K. Bisetty, Bioorg. Med. Chem. Lett. 22 (2012) 57.
[24] C. Lambros, J.P. Vanderberg, J. Parasitol. 65 (1979) 418.

[25] H. Bogreau, F. Renaud, H. Bouchiba, P. Durand, S.B. Assi, M.C. Henry, E. Garnotel, B. Pradines, T. Fusai, B. Wade, E. Adehossi, P. Parola, M.O. Kamil, O. Puijalon, C. Rogier, Am. J. Trop. Med. Hyg. 74 (2006) 953.
[26] M. Henry, I. Diallo, J. Bordes, S. Ka, B. Pradines, B. Diatta, P.S. M'Baye, M. Sane, M. Thiam, P.M. Gueye, B. Wade, J.E. Touze, J.M. Debonne, C. Rogier, T. Fusai, Am. J. Trop. Med. Hyg. 75 (2006) 146.
[27] P. Singh, S. Sachdeva, R. Raj, V. Kumar, M.P. Mahajan, S. Nasser, L. Vivas, J. Gut, P.J. Rosenthal, T.-S. Feng, K. Chibale, Bioorg. Med. Chem. Lett. 21 (2011) 4561.
[28] M. Henry, S. Briolant, A. Fontaine, J. Mosnier, E. Baret, R. Amalvict, T. Fusai, L. Fraisse, C. Rogier, B. Pradines, Antimicrob. Agents Chemother. 52 (2008) 2755.
[29] B. Pradines, A. Tall, T. Fusai, A. Spiegel, R. Hienne, C. Rogier, J.F. Trape, D. Parzy, Antimicrob. Agents Chemother. 43 (1999) 418.
[30] B. Pradines, T. Fusai, W. Daries, V. Laloge, C. Rogier, P. Millet, E. Panconi, M. Kombila, D. Parzy, J. Antimicrob. Chemother. 48 (2001) 179.
[31] C. Biot, N. Chavain, F. Dubar, B. Pradines, X. Trivelli, J. Brocard, I. Forfar, D. Dive, J. Organomet. Chem. 694 (2009) 545–854.
[32] J. Quirante, F. Dubar, A. Gonzalez, C. Lopez, M. Cascante, R. Cortes, I. Forfar, B. Pradines, C. Biot, J. Org. Chem. 696 (2011) 1011.
[33] F. Dubar, R. Wintjens, E.S. Martins-Duarte, R.C. Vommaro, W. Souza, D. Dive, C. Pierrot, B. Pradines, A. Wohlkonig, J. Khalife, C. Biot, MedChemCom 2 (2011) 430.
[34] X. Wu, P. Wilairat, M.L. Go, Bioorg. Med. Chem. Lett. 12 (2002) 2299.
[35] X. Wu, E.R. Tiekink, I. Kostetski, N. Kochorginsky, A.L. Tan, S.B. Khoo, P. Wilairat, M.L. Go, Eur. J. Pharm. Sci. 27 (2006) 175.