Bioorganic & Medicinal Chemistry 19 (2011) 4562–4573

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and antimalarial activity of new heterocyclic hybrids based on chloroquine and thiazolidinone scaffolds

Fernando A. Rojas Ruiz [a], Rory N. García-Sánchez [b,c], Santiago Villabona Estupiñan [a], Alicia Gómez-Barrio [b], Diego F. Torres Amado [a], Berta Martín Pérez-Solórzano [b], Juan J. Nogal-Ruiz [b], Antonio R. Martínez-Fernández [b], Vladimir V. Kouznetsov [a,*]

[a] Laboratorio de Química Orgánica y Biomolecular, Escuela de Química, Universidad Industrial de Santander, A. A. 678, Bucaramanga, Colombia
[b] Departamento de Parasitología, Facultad de Farmacia, Universidad Complutense de Madrid, 28040 Madrid, España, Spain
[c] Laboratorio de Investigación de Productos Naturales Antiparasitarios de la Amazonía, Universidad Nacional de la Amazonía Peruana, Iquitos, Perú

ARTICLE INFO

Article history:
Received 17 March 2011
Revised 31 May 2011
Accepted 5 June 2011
Available online 15 June 2011

Keywords:
Chloroquine
Thiazolidin-4-ones
Heterocyclic hybrids
Synthesis
Antimalarial activity

ABSTRACT

A series of new 21 chloroquine heterocyclic hybrids containing either benzylamino fragment or *N*-(aminoalkyl)thiazolidin-4-one moiety were synthesized and screened for their antimalarial activity against chloroquine (CQ)-sensitive 3D7 and multidrug-resistance Dd2 strains of *Plasmodium falciparum*. Although no compounds more active than CQ against 3D7 was found; against Dd2 strain, six compounds, four of them with benzylamino fragment, showed an excellent activity, up to 3-fold more active than CQ. Non specific cytotoxicity on J774 macrophages was observed in some compounds whereas only two of them showed liver toxicity on HepG2 cells. In addition, all active compounds inhibited the ferriprotoporphyrin IX biocrystalization process in concentrations around to CQ. In vivo preliminary results have shown that at least two compounds are as active as CQ against *Plasmodium berghei* ANKA.

1. Introduction

Despite decades of fighting malaria, the disease is gaining ground as the parasite's resistance to drugs and the parasite-carrying mosquito's resistance to insecticides expands. The increasing spread of malaria together with the emergence of resistance against conventional drugs has put enormous pressure on public health systems to introduce new malaria treatments.[1] Quinoline containing compounds are still attractive models for treatment of malaria (Fig. 1). The success of the antimalarial aminoquinoline drug, chloroquine (CQ), has been based on its excellent clinical efficacy, limited host toxicity, ease to use and simple cost-effective synthesis. However, the use of this drug has been seriously eroded in recent years, mainly as a result of the development of parasite resistance to CQ. Amodiaquine (AQ), another drug based on 7-chloro-4-aminoquinoline nucleus, is effective against many CQ-resistant strains of *Plasmodium falciparum*.

However, its clinical use has been restricted because of associations with hepatotoxicity and agranulocytosis due to the toxic quinone–imine metabolite. Its isomeric analogue, isoquine (IsoQ) showed excellent oral in vivo ED_{50} activity and did not undergo in vivo bioactivation.[2] These drugs are also important templates for target-based antimalarial drug discovery. The structure–activity relationship studies on 4-aminoquinoline antimalarial compounds suggest that 7-chloro-4-aminoquinoline skeleton is obligatory for antimalarial activity, particularly, inhibition of β-hematin formation and accumulation of the drug at the target site.[3] New potent leads such as AQ-13 and GSK369796 were developed by modifying aminoalkyl side chain or amino function of CQ and IsoQ, respectively.[4,5]

Nowadays, double drug development and/or multi-therapeutic strategies, which utilize new chemical entities with two (or more than two) different N-heterocyclic skeletons, are also valid and perspective to create new antimalarial drugs.[2] These strategies have the potential to overcome the drug resistant parasites problem. So, the design and synthesis of aminoquinoline-containing dual inhibitors or 'double drugs' that would potentially inhibit haemozoin formation and another target within *P. falciparum*, and will not be recognized by the proteins involved in drug efflux, are very productive in the generation of new chemical entities that are effective against drug resistant parasites in the long term. The success of this hybridization approach has wonderful examples as trioxaquines[6] or artemisinin–quinine hybrid.[7]

Among these nitrogen containing heterocyclic skeletons, thiazolidin-4-ones, rigid molecules, are considered as a biologically privileged scaffold well-tolerated in human subjets[8] and could be perspective models for the designing of new antimalarial CQ-hybrids.[9]

* Corresponding author.
E-mail address: kouznet@uis.edu.co (V.V. Kouznetsov).

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.06.025

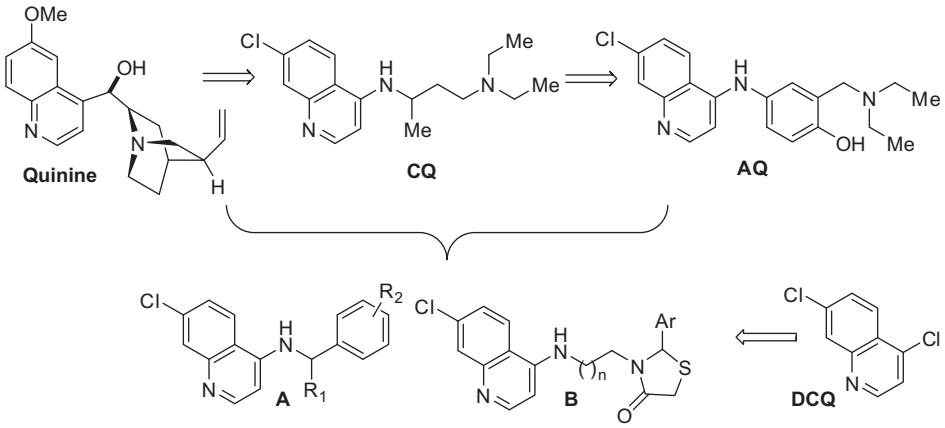


Figure 1. Aminoquinoline drugs and structures of the investigated compounds.

Keeping in view the above facts and continuing our program on the development of efficient methods to generate drug-like nitrogen-containing molecules, we were interested in a simple synthesis of CQ or AQ analogues containing the *N*-(aminoalkyl)thiazolidin-4-one moiety or the benzylamino fragment and their evaluation as potentially active compounds against *Plasmodium* malaria parasite.

Now, we report the biological results of a new series of chloroquine heterocyclic hybrids that contain benzylamino fragment and *N*-(aminoalkyl)thiazolidin-4-one moiety at C-4 position (molecules **A** and **B**) (Fig. 1). We expected at the outset that these chemical functions at C-4 will alter the biological activity of new quinoline compounds and may help in developing structure–activity relationships.

2. Results and discussion

2.1. Chemistry

The target compounds **1–4** and key intermediate molecules **5–7** were synthesized employing straightforward and efficient procedures.[13] Benzylamino fragments were attached to the 4,7-chloroquinoline ring (DCQ) by nucleophilic substitution S_NAr using commercial benzylamines to give compd **1–4**. This reaction was carried out in the presence of DMF at elevated temperature 140 °C. Amino side functions were introduced in compd **5–7** by interaction of DCQ and α,ω-diaminoalkane excess refluxing without any solvent.

Finally, target compounds **8–24** were prepared by one-pot three component reaction of diamines **5–7**, furfuraldehyde (2-FuCHO), thiophencarboxyaldehyde (2-ThieCHO) or benzaldehydes (ArCHO) and α-mercaptoacetic acid with ratios 1:2.5:2.5 respectively, in refluxing dry toluene for 4–5 h to get solid products, which can be filtered and recrystallized in ethanol from the reaction mixture (Scheme 1).

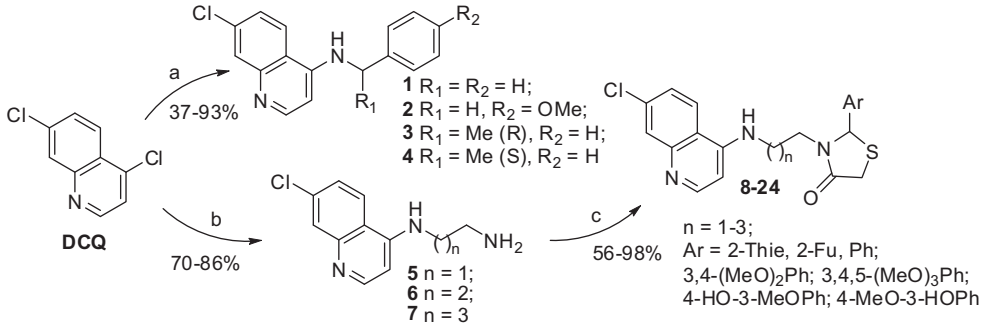
Almost all target compounds were obtained in good yields (56–98%); conversely synthesis of aminoquinolines **3**,**4** was less effective (37%), probably due to steric hindrance of methyl group in α-methylbenzylamines. All aminoquinoline derivatives were purified by column chromatography and obtained as powdered stable substances with well-defined melting points.

Calculated log *P* values, using commercially available ACD LAB 6.0 program, for all 21 aminoquinolines **1–4**, **8–24** ranged from 3.25 (compd **9**) to 4.64 (compd **3, 4**). Since this estimation is considered to be a well established lipophilicity parameter, these data allow predicting the good absorption and transport properties across cell membranes for the obtained molecules.

2.2. Biological activity

Initially, all 21 compounds were tested for their activity against CQ-sensitive 3D7 strain of *P. falciparum*, under in vitro conditions described in Experimental. Subsequently, compounds that showed an IC_{50} value less than 2 μM (Table 1) were evaluated against multidrug-resistance Dd2 strain.

No compound more active than CQ against 3D7 strain was found. In fact, the activity shown by the most active compounds was 9- to 15-fold minor than CQ. Nonetheless, against Dd2 strain, 4-benzylamino-7-chloroquinolines **1**, **2**, **3,** and 4-amino-7-chloroquinoline-thiazolidinone hybrid **19,** were more active than CQ (IC_{50} = 0.50 μM), with IC_{50} values between 0.30 and 0.44 μM. Other



Scheme 1. Reagents and conditions: (a) 4,7-dichloroquinoline (2.5 mmol), *N*-benzylamine (5.10 mmol), and K_2CO_3 (5.01 mmol), DMF, 140 °C, 10 h; (b) 4,7-dichloroquinoline (20.2 mmol), α,ω-diaminoalkane (101 mmol), 80 °C for 1 h, 140–150 °C for 6–7 h; (c) amine **5–7**, ArCHO, $HSCH_2COOH$, PhMe, 4–5 h reflux.

Table 1
Structure and antimalarial activity of quinolines **1–4, 8–24** against *P. falciparum* 3D7 and Dd2 strains and cytotoxicity data

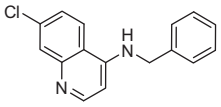
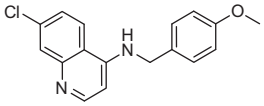
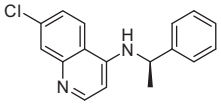
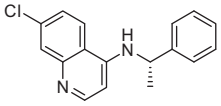
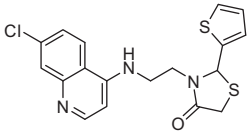
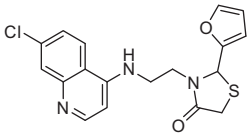
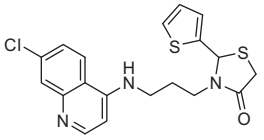
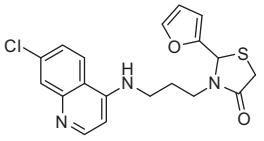
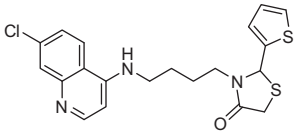
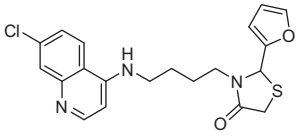
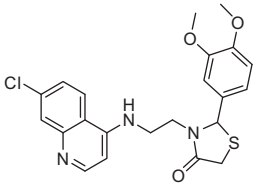
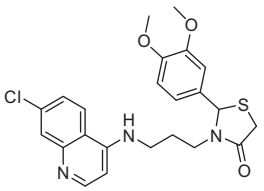
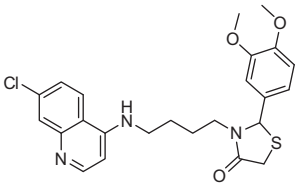
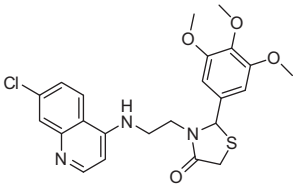
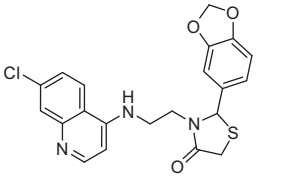
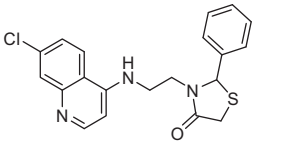
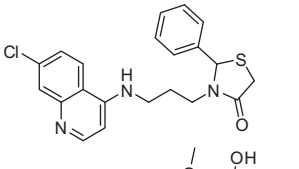
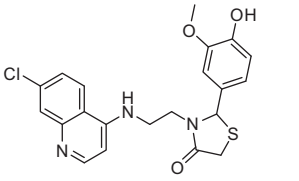
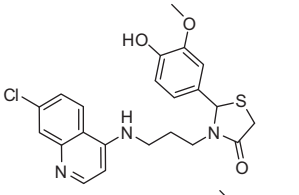
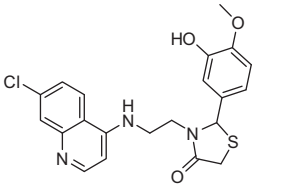
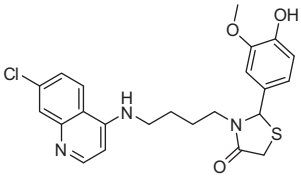
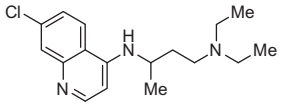
Compd	Structure	Log P^c	*P. falciparum* (μM)				FBIT(μM)		Cytotoxicity				
			3D7		Dd2				μM	MØJ774		HepG2	
			IC_{50}[a]	±SD	IC_{50}[a]	±SD	IC_{50}[b]	±SD		%	±SD	%	±SD
1		4.08	0.30	0.04	0.33	0.05	46.52	2.98	37	0.00	0.0	46.58	2.5
2		4.14	0.25	0.03	0.30	0.02	39.32	1.84	33	28.31	0.9	10.13	0.8
3		4.64	0.30	0.03	0.35	0.02	44.20	1.15	35	34.02	2.0	10.94	0.4
4		4.64	0.35	0.05	0.58	0.04	44.20	1.41	35	53.77	2.4	45.51	2.1
8		3.58	10.54	0.23	nt[d]		nt[d]		nt[d]	nt[d]		nt[d]	
9		2.94	1.82	0.09	1.59	0.07	200.59	3.08	27	56.6	4.5	16.96	1.1
10		3.85	14.16	0.36	nt[d]		nt[d]		nt[d]	nt[d]		nt[d]	
11		3.21	0.53	0.03	0.80	0.05	83.78	4.19	26	43.65	3.3	8.14	0.6
12		4.12	5.93	0.16	nt[d]		nt[d]		nt[d]	nt[d]		nt[d]	
13		3.48	8.16	0.19	nt[d]		nt[d]		nt[d]	nt[d]		nt[d]	
14		3.64	0.92	0.06	1.76	0.10	91.80	2.93	23	28.38	1.8	2.21	0.1
15		3.91	1.18	0.12	1.77	0.07	158.33	3.33	22	34.61	2.2	0.03	0

Table 1 (*continued*)

Compd	Structure	Log *P*[c]	*P. falciparum* (μM)				FBIT(μM)		Cytotoxicity				
			3D7		Dd2				μM	MØJ774		HepG2	
			IC_{50}[a]	±SD	IC_{50}[a]	±SD	IC_{50}[b]	±SD		%	±SD	%	±SD
16		4.18	0.39	0.05	0.75	0.04	79.45	2.33	21	45.22	1.7	13.26	1.2
17		3.62	1.56	0.09	1.87	0.07	121.33	2.95	21	9.16	1.1	1.64	0.1
18		3.88	0.51	0.04	0.75	0.05	58.42	1.93	23	47.93	3.2	25.53	1.7
19		4.46	0.36	0.02	0.44	0.02	54.70	2.21	26	2.01	0.1	0	0
20		4.56	2.19	0.14	nt[d]		nt[d]		nt[d]	nt[d]		nt[d]	
21		3.33	0.72	0.06	0.93	0.06	52.92	2.38	23	3.1	0.2	1.65	0.1
22		3.60	> 22.00		nt[d]		nt[d]		nt[d]	nt[d]		nt[d]	
23		3.33	0.40	0.03	0.54	0.03	52.34	1.51	23	1.8	0.0	14.71	1.3
24		3.87	10.94	0.17	nt[d]		nt[d]		nt[d]	nt[d]		nt[d]	

(*continued on next page*)

Table 1 (*continued*)

Compd	Structure	Log *P*[c]	*P. falciparum* (μM)				FBIT(μM)		Cytotoxicity				
			3D7		Dd2				μM	MØJ774		HepG2	
			IC_{50}[a]	±SD	IC_{50}[a]	±SD	IC_{50}[b]	±SD		%	±SD	%	±SD
CQ		3.27	0.027	0.004	0.50	0.03	22.29	0.58	19	0.0	0.0	0.0	0

IC_{50} values, concentration inhibiting 50% of the parasite growth[a] or β-hematine formation[b], are expressed as means ± SD from two different experiments in triplicate.
[a] in vitro IC_{50} values for *P. falciparum* strains 3D7 and Dd2.
[b] in vitro IC_{50} values for inhibition of β-hematine.
[c] Theoretical values log *P* were calculated using commercially available ACD LAB 6.0 program.
[d] Not tested, because compounds showed an IC_{50} value more than 2 μM.

two compounds, **4** and **23**, showed IC_{50} values comparable than CQ, 0.58 and 0.54 μM respectively.

In general, the activity showed by 4-benzylamino-7-chloroquinolines **1–4** was greater than 4-amino-7-chloroquinoline-thiazolidinone hybrids **8–24**. Previously reported results have shown that benzylamino chloroquinolines[5,10,11] are better than the 4-amino-7-chloroquinoline-thiazolidinone hybrids with 4-chlorophenyl or 2,6-dichlorophenyl substituents at C-2 of thiazolidinone[9] as potential antimalarial agents.

Another important fact to highlight is that the activity showed by compounds against both *P. falciparum* strains, 3D7 and Dd2, was in most cases not significantly different or slightly lower against Dd2.

Ferriprotoporphyrin IX (FPIX) biocrystallization is a *Plasmodium*-specific process in which the toxic FPIX derived from the digestion of ingested hemoglobin is converted into an insoluble non-toxic crystalline species called hemozoin. The inhibition of this process is the main mechanism of action associated to chloroquine and other 4-amino-7-chloroquinolines; consequently it was essential to verify if the prepared compounds also act by this mechanism of action.

As expected, all in vitro active compounds showed the capability to block the β-hematine formation process on FPIX biocrystallization inhibition assay (FBIT) at concentrations lower than 500 μM. In fact, the most in vitro active benzylaminoquinolines **1**, **2**, **3**, and **4** were the most active on FBIT as well, showing IC_{50} values between 39.32 and 46.52 μM, which are only 1.76- to 2.1-fold lower than CQ (IC_{50} = 22.29 μM). Moreover, a direct relationship between the activity against the parasite and the capability to inhibit β-hematine formation was observed (Fig. 2).

Based on the in vitro and FBIT results, the association with thiazolidin-4-one moiety and the addition of a benzylamino fragment to the 4-amino-7-cloroquinoline skeleton prevent the action of the mechanisms of resistance associated to CQ derivatives, allowing the compounds to reach its target in the food vacuole inhibiting the crystallization process of FPIX.

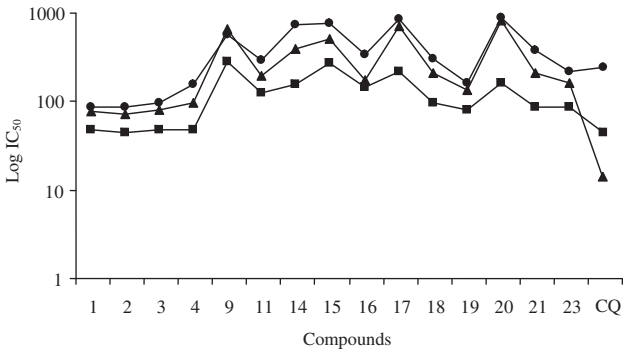


Figure 2. Relationship between the activity against *P. falciparum* and FBIT. IC_{50} values against 3D7 (–▲–) and Dd2 (–●–) in μM and FBIT in μM (–■–).

A nonspecific cytotoxicity assay on J774 murine macrophages at concentrations between 19 and 37 μM was performed in order to know the selectivity degree of the active compounds. In addition, under similar conditions, the effect of the aminoquinoline derivatives on HepG2 cells (human hepatocellular carcinoma cell line), which is widely used as a liver toxicity marker, was measured. Cytotoxicity on J774 murine macrophages was observed in seven compounds, whereas only two showed to be cytotoxic for HepG2 cells.

Given that the concentrations tested on both cytotoxicity assays are far enough from the limit accepted as active against the parasite, we could consider that four of the more active compounds, compd **1**,**2, 19** and **23**, showing no more that 30% of cytotoxicity, have a selective activity against the parasite, and therefore good candidates for the in vivo test.

The structure-activity relationship studies for the series **1–4** suggest that the presence of methyl (compd **3**,**4**) or methoxy (compd **2**) functional groups on the benzylamino fragment did not improve their activity and increased the cytotoxicity of these compounds.

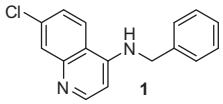
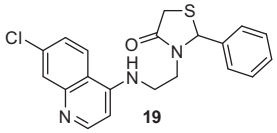
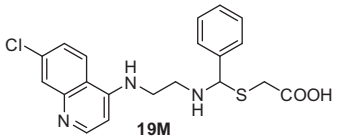
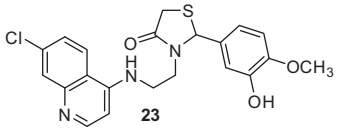
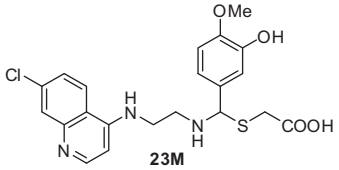
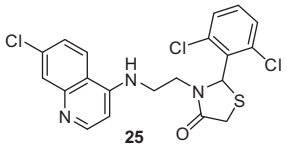
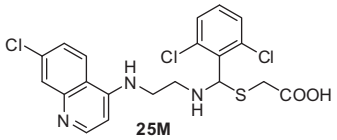
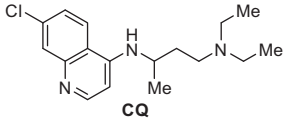
Regarding to thiazolidinone-based CQ hybrids **8–24**, it was observed a critical decrease in activity when a α-thienyl ring is attached to the thiazolidinone skeleton at position C-2 (compd **8,10** and **12**). On the other hand, if a α-furanyl group is present at same position (compd **9,11** and **13**); the activity is increased, provided that the length of the aminoalkyl side chain was 2 or 3 carbons. Nevertheless, these compounds showed high cytotoxicity levels on J774 macrophages.

Another modification performed on hybrids **8–24** structures was the introduction of an aryl ring in the same position of thiazolidinone skeleton, with and without substituents. The presence of a phenyl group in this skeleton with two carbons length of aminoalkyl side chain (compd **19**) increased considerably the activity, but when the length of aminoalkyl side chain was increased in three carbons (compd **20**), the activity decreased.

Although the presence of 4-hydroxy-3-methoxyphenyl (compd **21,22** and **24**) or 3-hydroxy-4-methoxyphenyl (compd **23**) radicals did not modify significantly the activity in comparison with unsubstituted aryl ring, the effect of the length of aminoalkyl side chain in these compounds was evident, as the activity decreased notoriously or even disappeared with 3 or 4 carbons length. According to our results, an optimal length of two carbons in aminoalkyl side chain is also necessary in order to maintain the antimalarial activity of thiazolidinone-based hybrids.

Several research groups have studied the appropriate length and size of the aminoalkyl side chain. Solomon et al. synthesized and evaluated the antimalarial activity of 4-amino-7-chloroquinoline-thiazolidinone hybrids with 4-chlorophenyl and 4,6-dichlorophenyl substitutions at C-2 of thiazolidinone and 2, 3 and 4 carbons chain length, showing that 4,6-dichlorophenyl substitution and 2

Table 2
In vivo assay (4-day suppressive test) against *P. berghei* ANKA using compd **1**, **19** and **23** at a dose of 10 mg/kg/day[a]

Tested compd	% Inhibition	Log *P*[b]	Log $D_{5.2}$[c]	Log $D_{7.4}$[c]
 **1**	25	4.08	2.44	4.27
 **19**	80	4.46	1.72	3.59
 **19M**	nt[d]	3.81	0.21	0.23
 **23**	100	3.33	1.28	3.13
 **23M**	nt[d]	3.15	0.04	0.05
 **25**	76[e]	5.25	3.86	4.95
 **25M**	nt[d]	5.07	1.56	1.36
 **CQ**	100	3.27	−1.42	1.92

[a] Each group of mice was treated intraperitoneally ip.
[b] Theoretical values log P were calculated using commercially available ACD LAB 6.0 program.
[c] Theoretical values log *D* were calculated using the on line available SPARC V4.5 program.
[d] Not tested in vivo assay.
[e] In vivo assay (4-day suppressive test) against *Plasmodium yoelli* (N-67 strain), data from the Ref.9.

carbons chain length (compd 25) is the best and more active than CQ combination against NF-54 strain of *P. falciparum*.[9] However, their nonspecific cytotoxicity has not been reported and discussed.

De et al. suggested that both shortening and lengthening produce compounds that retain the activity.[12] Stocks et al. synthesized novel short chain chloroquine analogues which retained the activity against CQ resistant K1 *P. falciparum* and Natarajan et al. have shown that the most active 4-aminoquinoline derivatives were those having two carbons in the aminoalkyl side chain.[13,14]

Finally, the presence of two methoxy groups (compd **14–16**) on phenyl ring reduced the activity and increased cytotoxicity.

A preliminary in vivo assay (4-day suppressive test) against *P. berghei* ANKA using benzylaminoquinoline **1**, and the 7-chloroquinoline-thiazolidinone hybrids **19** and **23** at a dose of 10 mg/kg/day was carried out (Table 2). These compounds were selected because they were three of the most active compounds and, at the same time, did not showed nonspecific cytotoxicity.

Compounds **19** and **23** inhibited 80% and 100% respectively the parasite growth in infected mice, whereas compound **1** only 25%. CQ used as positive control showed 100% of inhibition at the same dose. As the variation of log *P* for tested compd **1**, **19** and **23** did not appear to play a role in the in vivo antimalarial activity, we addressed to another quantitative parameter. Log *D* can predict gastro intestinal (GI) track absorption and lipophilic properties as it is a pH dependent function. Calculated values demonstrated the high GI track absorption (pH 3–7) and lipophilic properties. It was observed a good correlation between the calculated distribution coefficients at pH 7.4 and pH 5.2 (log $D_{5.2}$ and log $D_{7.4}$ parameters), and the found inhibition percentages for the tested compds Moreover, conversely to the compd **25**[9], these ADME properties are enhanced by replacing the two chlorine atoms on the aryl moiety. In addition, metabolic opening of the thiazolidinone ring of hybrids **19**, **23,** and **25** could provide the more active metabolites **19M**, **23M**, and **25M** (Table 2). Comparing their calculated parameters,

it can be confirmed that possible metabolite **23M** has better lipophilic properties. In contrast to this, compd **1** cannot be metabolized in this way which explains its low in vivo activity.

According to these theoretical values, our most active and lipophilic compound **23** may have an improved absorption and distribution comparable to CQ, observed on its in vivo antimalarial activity, in addition to the in vitro activity against the Dd2 strain.

3. Conclusion

Designing compounds based on 4-amino-7-chloroquinoline scaffolds is an alternative pathway in order to obtain new and promising antimalarial entities. Especially, some heterocyclic hybrids containing benzylamino fragments or *N*-(aminoalkyl)thiazolidin-4-one moiety, as compounds **1**, **19** or **23** described in this study, showed excellent in vitro and in vivo antimalarial activity and low cytotoxicity levels to be considered as potential antimalarial agents.

4. Experimental

4.1. Chemistry

The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. The IR spectra were recorded on a Lumex Infralum FT-02 spectrophotometer in KBR. ^{1}H MNR spectra were recorded on Bruker AM-400 spectrometer. Chemical shifts are reported in ppm (δ relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for protons). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; dt, doublet of triplets; td, triplet of doublets; q, quartet; quint., quintet; m, multiplet; br, broad. On DEPT-135 spectra, the signals of CH_3, CH_2, and CH carbons are shown as positive (+), negative (−), and positive (+), respectively, and quaternary carbons are not shown. A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS Chemstation Data system was used for ms identification at 70 ev using a 60 m capillary column coated with HP-5 [5%-phenyl-poly(dimethyl-siloxane)]. Elemental analyses were performed on a Perkin Elmer 2400 Series II analyzer and were within ±0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminum sheet.

4.1.1. Group A. General procedure for synthesis of 4-*N*-benzylaminoquinolines 1–4

Under nitrogen atmosphere 0.50 g of DCQ (2.5 mmol), benzylamine 0.70 g (5.10 mmol), and K_2CO_3 0.70 g (5.01 mmol) were dissolved in 8 mL de DMF. The mixture was stirred under reflux during 10 h (TLC) and cooled to ambient temp. After, the reaction mass was diluted with water and extracted with dichloromethane (2 × 30 mL). The organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by flash column chromatography using petroleum ether (P.E) and ethyl acetate (E.A) mixes, obtaining the 4-*N*-benzylamino substituted quinolines **1–4.**

4.1.1.1. *N*-Benzyl-7-chloroquinolin-4-amine (1)[15]. White crystals; yield 80% from DCQ and benzylamine; R_f = 0.5 (P.E/E.A 1:1), mp 175–178 °C; IR (KBr): 3220 (N–H), 2928–3013 (CH_2), 1575 (C═N), 1448 (N–H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si), δ (ppm): 5.62 (1H, s, –NH), 4.51 (2H, d, J = 4.7 Hz, –CH_2), 8.51 (1H, d, J = 5.0 Hz, 2-H), 6.40 (1H, d, J = 5.1 Hz, 3-H), 7.72 (1H, d, J = 8.9 Hz, 6-H), 7.33 (1H, d, J = 8.5 Hz, 7-H), 7.93 (1H, s, 9-H), 7.32–7.38 (5H, dd, J = 8.9, 2.0 Hz, 2-H_{Ar}–6-H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si), δ (ppm): 152.1, 149.6, 149.2, 137.3, 134.9, 129.4, 128.9 (2C), 127.9 (2C), 127.5, 125.5, 121.2, 117.2, 99.7, 47.5; GC–MS: t_R = 25.3 min, m/z (%): 268 ($M^{+\cdot}$, 50), 91 (100), 232 (15). Anal. Calcd. for $C_{16}H_{13}N_2Cl$: C, 71.51; H, 4.88; N, 10.42. Found: C 71.43; H 4.56; N 10.26.

4.1.1.2. 7-Chloro-*N*-[(4-methoxyphenyl)methyl]quinolin-4-amine (2). White crystals; yield 93% from DCQ and *p*-methoxybenzylamine; R_f = 0.3 (P.E/E.A 1:1), mp 165–168 °C; IR (KBr): 3220 (N–H), 2928–3018 (CH_2), 1573 (C═N), 1510 (N–H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si), δ (ppm): 5.62 (1H, s, -NH), 4.51 (2H, d, J = 4.7 Hz, –CH_2), 3.82 (3H, s, –OCH_3), 8.51 (1H, d, J = 5.3 Hz, 2-H), 6.45 (1H, d, J = 5.3 Hz, 3-H), 7.69 (1H, d, J = 8.9 Hz, 6-H), 7.34 (1H, d, J = 8.3 Hz, 7-H), 7.95 (1H, d, J = 1.7 Hz, 9-H), 7.31 (2H, d, J = 8.6 Hz, 2-H_{Ar}–6-H_{Ar}), 6.91 (2H, d, J = 8.5 Hz, 3-H_{Ar}–5H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si), δ (ppm): 160.9, 159.4, 152.1, 149.5, 149.1, 134.9, 129.2, 128.9, 128.8, 125.4, 121.1, 117.2, 114.4, 114.2, 99.6, 55.4, 47.1; GC–MS: t_R = 28.4 min, m/z (%): 298 ($M^{+\cdot}$, 15), 121 (100), 191 (8). Anal. Calcd. for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06; N, 9.38. Found: C 68.13; H 5.28; N 9.11.

4.1.1.3. (*R*)-7-Chloro-*N*-(1-phenylethyl)quinolin-4-amine (3). White crystals; yield 37% from DCQ and (*R*)-α-methylbenzylamine; R_f = 0.6 (P.E/E.A 1:1), mp 115–118 °C; IR (KBr): 3327 (N–H), 2918 (CH_2), 1573 (C═N), 1445 (N–H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si), δ (ppm): 5.34 (1H, s, -NH), 4.71 (1H, t, J = 5.8 Hz, –CH), 1.68 (3H, d, J = 6.4 Hz, –CH_3) 8.39 (1H, d, J = 4.9 Hz, 2-H), 6.22 (1H, d, J = 4.9 Hz, 3-H), 7.39 (1H, d, J = 9.0 Hz, 6-H), 7.91 (1H, d, J = 8.8 Hz, 5-H), 7.96 (1H, s, 8-H), 7.26–7.35 (5H, m, 2-H_{Ar}–6-H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si), δ (ppm): 154.5, 152.7, 149.3, 143.5, 134.9, 129.4, 128.5, 126.9, 126.7 (2C), 124.8 (2C), 121.6, 117.5, 99.2, 60.6, 21.6. GC–MS: t_R = 24.8 min, m/z (%): 282 ($M^{+\cdot}$, 48), 178 (40), 267 (35), 105 (100). Anal. Calcd. for $C_{17}H_{15}N_2Cl$: C, 72.21; H, 5.35; N, 9.91. Found: C 72.45; H 5.19; N 9.76.

4.1.1.4. (*S*)-7-Chloro-*N*-(1-phenylethyl)quinolin-4-amine (4). White crystals; yield 37% from DCQ and (*S*)-α-methylbenzylamine; R_f = 0.6 (P.E: E.A 1:1), mp 115–118 °C; IR (KBr): 3327 (N–H), 2918–2973 (CH_2), 1573 (C═N), 1445 (N–H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si), δ (ppm): 5.34 (1H, s, -NH), 4.71 (1H, t, J = 5.8 Hz, –CH), 1.68 (3H, d, J = 6.4 Hz, –CH_3) 8.39 (1H, d, J = 4.9 Hz, 2-H), 6.22 (1H, d, J = 4.9 Hz, 3-H), 7.39 (1H, d, J = 9.0 Hz, 6-H), 7.91 (1H, d, J = 8.8 Hz, 5-H), 7.96 (1H, s, 8-H), 7.26–7.35 (5H, m, 2-H_{Ar}–6-H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si), δ (ppm): 154.5, 152.7, 149.3, 143.5, 134.9, 129.4, 128.5, 126.9, 126.7 (2C), 124.8 (2C), 121.6, 117.5, 99.2, 60.6, 21.6. GC–MS: t_R = 24.8 min, m/z (%): 282 ($M^{+\cdot}$, 48), 178 (40), 267 (35), 105 (100). Anal. Calcd. for $C_{17}H_{15}N_2Cl$: C, 72.21; H, 5.35; N, 9.91. Found: C 72.35; H 5.21; N 9.76.

4.1.2. General procedure for synthesis of 4-amino7-chloroquinoline precursors 5–7

A mixture of DCQ (4.0 g, 20.2 mmol) and α,ω-diaminoalkane (101 mmol) was heated at 80 °C for 1 h with stirring and subsequently at 140–150 °C for 6–7 h with continued stirring. The reaction mixture was cooled to room temp and basified with 10% NaOH (70 mL). The resultant mixture was extracted with chloroform-methanol (20:1, 4 × 50 mL). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue (10 mL) was precipitated by the addition of 70 mL *n*-heptane. The solid was purified by washing with 40 mL ethyl ether.

4.1.2.1. N^1-(7-Chloroquinolin-4-yl)-ethane-1,2-diamine (5). Yellowish white solid, yield 75% from DCQ and 1,2-diaminoethane; mp 143–145 °C; IR (KBr): 3248 (N–H), 2893 (CH_2), 1589 (N–H), 1142 (C–N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ (ppm): 8.51 (1H, d,, J = 5.4 Hz, 2-H), 7.94 (1H, d, J = 2.0 Hz, 5-H), 7.75 (1H, d, J = 8.9 Hz, 8-H), 7.34 (1H, dd, J = 8.8, 1.8 Hz, 6-H), 6.39 (1H, d,

J = 5.4 Hz, 3-H), 5.82 (1H, br s, NH), 3.27 (2H, br s, NH_2), 3.11–3.18 (4H, m, 1′-Hab, 2′-Hab); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δ (ppm): 156.1, 144.7, 140.5, 138.4, 127.4, 126.6, 120.7, 117.1, 99.4, 42.9, 38.1. GC–MS: t_R = 22.13 min, *m/z* (%): 221 ($M^{+\cdot}$, 29),192 (55), 191 (100), 179 (17), 163 (25), 156 (87), 155 (44), 128 (18). Anal. Calcd. for $C_{11}H_{12}ClN_3$: C, 59.60; H, 5.46; N, 18.95. Found: C 59.83; H 5.25; N 18.74.

4.1.2.2. *N*[1]-(7-Chloroquinolin-4-yl)-propane-1,3-diamine (6).

Yellowish white solid, yield 86% from DCQ and 1,3-diaminopropane; mp 130–132 °C; IR (KBr): 3278 (N–H), 2871 (CH_2), 1589 (N–H), 1141 (C–N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ (ppm): 8.47 (1H, d,, J = 5.3 Hz, 2-H), 7.92 (1H, d, J = 1.9 Hz, 5-H), 7.71 (1H, d, J = 8.9 Hz, 8-H), 7.37 (1H, br s, NH), 7.28 (1H, dd, J = 8.8, 1.9 Hz, 6-H), 6.34 (1H, d, J = 5.4 Hz, 3-H), 3.47–3.28 (2H, m, 1′-Hab), 3.11–3.02 (2H, m, 3′-Hab), 2.74 (2H, br s, NH_2), 1.97–1.93 (2H, m, 2′-Hab); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δ (ppm): 155.9, 144.4, 140.3, 138.2, 127.2, 126.4, 120.4, 117.3, 98.7, 42.2, 40.6, 30.6. GC–MS: t_R = 23.23 min, *m/z* (%): 235 ($M^{+\cdot}$, 93), 219 (21), 218 (44), 217 (52), 205 (35), 203 (36), 192 (95), 191 (100), 179 (92), 163 (25), 156 (87), 155 (67), 128 (26). Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.15; H, 5.99; N, 17.83. Found: C 61.23; H 5.76; N 17.65.

4.1.2.3. *N*[1]-(7-Chloroquinolin-4-yl)-butane-1,4-diamine (7).

Yellowish white solid, yield 70% from DCQ and 1,4-diaminobutane; mp 115–117 °C; IR (KBr): 3278 (N–H), 2871 (CH_2), 1589 (N–H), 1141 (C–N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ (ppm): 8.47 (1H, d,, J = 5.3 Hz, 2-H), 7.92 (1H, d, J = 1.9 Hz, 5-H), 7.71 (1H, d, J = 8.9 Hz, 8-H), 7.37 (1H, br s, NH), 7.28 (1H, dd, J = 8.8, 1.9 Hz, 6-H), 6.34 (1H, d, J = 5.4 Hz, 3-H), 3.47–3.28 (2H, m, 1′-Hab), 3.11–3.02 (2H, m, 3′-Hab), 2.74 (2H, br s, NH_2), 1.97–1.93 (2H, m, 2′-Hab), 1.83–1.78 (2H, m, 4′-Hab); ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si) δ (ppm): 155.6, 144.3, 140.3, 138.1, 127.2, 126.3, 120.4, 117.1, 98.8, 42.2, 40.6, 38.8, 30.5. GC–MS: t_R = 24.27 min, *m/z* (%): 249 ($M^{+\cdot}$, 34), 219 (5), 205 (99), 203 (36), 192 (25), 191 (100), 179 (91), 163 (18), 156 (80), 155 (62), 128 (21). Anal. Calcd. for $C_{13}H_{16}ClN_3$: C, 62.52; H, 6.46; N, 16.83. Found: C 62.48; H 6.57; N 16.69.

4.1.3. Group B. General procedure for synthesis of 4-amino-7-chloroquinoline-thiazolidin-4-ones 8–24

A mixture of the amine **5** (**6** or **7**) (4.51 mmol), aldehyde (5.41 mmol) and α-mercaptoacetic acid (5.41 mmol) was stirred and heated to boiling and refluxed for 4–5 h while collecting water distilled as an azeotropic mixture of toluene/water in a Dean-Stark trap. The reaction mixture was cooled to room temp and the toluene was removed by vacuum distillation. The obtained mass was dissolved in a mixture of ethyl acetate-methanol (10:1, 150 mL), successively basified with 10% $NaHCO_3$ (50 mL) and then washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using petroleum ether and ethyl acetate. The products **8–24** were obtained as viscous oils then solidified by adding *n*-heptane.

4.1.3.1. 3-(2-(7-Chloroquinolin-4-ylamino)ethyl)-2-(thiophen-2-yl)thiazolidin-4-one (8).

This compound was obtained as a beige solid in 85% yield, from 1,2-diamine **5**, 2-thiophencarboxaldenyde and α-mercaptoacetic acid; mp178–180 °C; IR (KBr): 3379, 2924, 1682, 1605, 1574, 656 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.37 (1H, d, J = 5.4 Hz, 2-H), 8.14 (1H, d, J = 9.1 Hz, 5-H), 7.79 (1H, d, J = 2.2 Hz, 8-H), 7.64 (1H, d, J = 5.1 Hz, 5-H_{Thie}), 7.46 (1H, s, N-H), 7.46 (1H, dd, J = 9.0 Hz, J = 2.2 Hz, 6-H), 7.22 (1H, dd, J = 3.4, 0.9 Hz, 3-H_{Thie}), 7.00 (1H, dd, J = 5.1, 3.5 Hz, 4-H_{Thie}), 6.38 (1H, d, J = 5.5 Hz, 3-H), 6.28 (1H, s, 2-H_{Thiaz}), 3.81 (1H, dd, J = 15.6 Hz, J = 1.3 Hz, 5-Ha_{Thiaz}), 3.72 (1H, d, J = 15.5 Hz, 5-Hb_{Thiaz}), 3.65–3.58 (1H, m, 2′-Ha), 3.50–3.42 (1H, m, 1′-Ha), 3.27–3.19 (1H, m, 1′-Hb), 3.10–3.03 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 170.4, 151.5 (+), 149.7, 148.7, 143.9, 133.5 (+), 128.3 (+, 2C), 127.3 (+), 126.7 (+), 124.3 (+), 123.7 (+), 117.3, 98.4 (+), 58.2 (+) 40.6 (−), 39.3 (−), 32.0 (−). GC–MS: t_R = 23.71 min, *m/z* (%): 389 ($M^{+\cdot}$, 10), 356 (9), 205 (62), 204 (51), 203 (49), 192 (15), 178 (11), 156 (51), 155 (35). Anal. Calcd. for $C_{18}H_{16}ClN_3OS_2$: C, 55.45; H, 4.14; N, 16.45. Found: C 55.67; H 4.01; N 16.33.

4.1.3.2. 3-(2-(7-Chloroquinolin-4-ylamino)ethyl)-2-(furan-2-yl)thiazolidin-4-one (9).

This compound was obtained as a yellowish white solid in 60% yield, from *N*[1]-(7-chloroquinolin-4-yl)-ethane-1,2-diamine **5**, 2-furancarboxaldenyde and α-mercaptocetic acid; mp 158–160 °C; IR (KBr): 3379, 2908, 1666, 1612, 1581, 640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.40 (1H, d, J = 5.5 Hz, 2-H), 8.16 (1H, d, J = 9.0 Hz, 5-H), 7.80 (1H, d, J = 2.0 Hz, 8-H), 7.71 (1H, s, 5-H_{Fu}), 7.56 (1H, t, J = 5.0 Hz, NH), 7.46 (1H, dd, J = 9.0, 2.1 Hz, 6-H), 6.54 (1H, d, J = 3.2 Hz, 3-H_{Fu}), 6.46 (1H, d, J = 5.0 Hz, 4-H_{Fu}), 6.46 (1H, s, 3-H), 6.10 (1H, s, 2-H_{Thiaz}), 3.80 (1H, d, J = 15.6 Hz, 5-Ha_{Thiaz}), 3.66 (1H, d, J = 15.6 Hz, 5-Hb_{Thiaz}), 3.65–3.61 (1H, m, 2′-Ha), 3.50–3.41 (1H, m, 1′-Ha), 3.23–3.15 (1H, m, 1′-Hb), 3.11–3.05 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 170.8, 151.1 (+), 150.9, 150.0, 148.2, 144.1 (+), 133.7 (+), 126.9 (+), 124.4 (+), 123.8 (+), 117.2, 110.7 (+), 109.7 (+), 98.4 (+), 55.7 (+), 41.0 (−), 39.3 (−), 31.6 (−). GC–MS: t_R = 48.88 min, *m/z* (%): 373 ($M^{+\cdot}$, 10), 344 (2), 205 (51), 204 (52), 203 (51), 192 (12), 191 (100), 178 (7), 156 (53), 155 (34). Anal. Calcd. for $C_{18}H_{16}ClN_3O_2S$: C, 57.83; H, 4.31; N, 11.24. Found: C 57.74 H 4.54; N 11.02.

4.1.3.3. 3-(3-(7-Chloroquinolin-4-ylamino)propyl)-2-(thien-2-yl)thiazolidin-4-one (10).

This compound was obtained as a yellowish white solid in 64% yield, from *N*[1]-(7-chloroquinolin-4-yl)-propane-1,3-diamine **6** (4.24 mmol), 2-thiophencarboxaldenyde (5.09 mmol) and α-mercaptoacetic acid (5.09 mmol); mp 160–162 °C; IR (KBr): 3332, 3032, 2846, 1666, 1612, 1574, 648 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.39 (1H, d, J = 5.4 Hz, 2-H), 8.19 (1H, d, J = 9.1 Hz, 5-H), 7.79 (1H, d, J = 2.2 Hz, 8-H), 7.57 (1H, d, J = 5.0 Hz, 5-H_{Thie}), 7.46 (1H, dd, J = 9.0 Hz, J = 2.2 Hz, 6-H), 7.29 (1H, t, J = 5.3 Hz, NH), 7.19 (1H, dd, J = 3.4, 0.8 Hz, 3-H_{Thie}), 6.88 (1H, dd, J = 5.0, 3.5 Hz, 4′-H_{Thie}), 6.39 (1H, d, J = 5.5 Hz, 3-H), 6.20 (1H, s, 2-H_{Thiaz}), 3.80 (1H, dd, J = 15.7, 1.2 Hz, 5-Ha_{Thiaz}), 3.70 (1H, d, J = 15.6 Hz, 5-Hb_{Thiaz}), 3.58–3.51 (1H, m, 3′-Ha), 3.20 (2H, q, J = 6.1 Hz, 1′-Ha, 1′-Hb), 2.93–2.86 (1H, m, 3′-Hb), 1.86–1.76 (1H, m, 2′-Ha), 1.74–1.64 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 170.0, 151.6 (+), 149.9, 148.7, 144.3, 133.4 (+), 127.8 (+), 127.7 (+), 127.2 (+), 126. 7 (+), 124.1 (+), 123.8 (+), 117.3, 98.6 (+), 57.9 (+), 40.4 (−), 39.7 (−), 31.9 (−), 25.2 (−). GC–MS: t_R = 112.18 min, *m/z* (%): 403 ($M^{+\cdot}$, 7), 370 (13), 219 (48), 218 (5), 217 (20), 192 (100), 191 (78), 178 (12), 156 (35), 155 (29). Anal. Calcd for $C_{19}H_{18}ClN_3OS_2$: C, 56.49; H, 4.49; N, 10.40. Found: C 56.32; H 4.61; N 10.45.

4.1.3.4. 3-(3-(7-Chloroquinolin-4-ylamino)propyl)-2-(furan-2-yl)thiazolidin-4-one (11).

This compound was obtained as a yellowish white solid in 62% yield, from *N*[1]-(7-chloroquinolin-4-yl)-propane-1,3-diamine **6** (4.24 mmol), 2-furancarboxaldenyde (5.09 mmol) and α-mercaptocetic acid (5.09 mmol); mp 125–127 °C; IR (KBr): 3356, 2885, 1666, 1612, 1589, 633 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.39 (1H, d, J = 5.4 Hz, 2-H), 8.20 (1H, d, J = 9.1 Hz, 5-H), 7.79 (1H, d, J = 2.1 Hz, 8-H), 7.67 (1H, s, 5-H_{Fu}), 7.46 (1H, dd, J = 9.0, 2.2 Hz, 6-H), 7.28 (1H, t, J = 5.2 Hz, NH), 6.48 (1H, dd, J = 3.2, 0.6 Hz, 3-H_{Fu}), 6.43–6.38 (2H, m, 4-H_{Fu}, 3-H), 6.00 (1H, s, 2-H_{Thiaz}), 3.78 (1H, d, J = 15.4 Hz, 5-Ha_{Thiaz}), 3.64 (1H, d, J = 15.4 Hz, 5-Hb_{Thiaz}), 3.59–3.50 (1H, m,

3′-Ha), 3.20 (2H, q, Hz, J = 6.4 Hz, 1′-Ha, 1′-Hb), 2.94–2.87 (1H, m, 3′-Hb), 1.87–1.74 (1H, m, 2′-Ha), 1.74–1.61 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.2, 154.5 (+), 152.7, 151.5, 149.3, 142.1 (+), 134.9, 129.4, 124.8 (+), 121.6 (+), 117.5, 110.6 (+), 107.0 (+), 99.2 (+), 62.6 (+), 41.2 (−), 40.3 (−), 31.5 (−), 25.6 (−). GC–MS: t_R = 60.29 min, m/z (%): 387 ($M^{+\cdot}$, 15), 354 (9), 219 (44), 217 (23), 205 (50), 192 (100), 191 (91), 178 (15), 156 (42), 155 (31). Anal. Calcd for $C_{19}H_{18}ClN_3O_2S$: C, 58.83; H, 4.68; N, 10.83. Found: C 58.95; H 4.53; N 10.65.

4.1.3.5. 3-(4-(7-Chloroquinolin-4-ylamino)butyl)-2-(thien-2-yl)thiazolidin-4-one (12). This compound was obtained as a yellowish white solid in 80% yield, from N^1-(7-chloroquinolin-4-yl)-butane-1,4-diamine **7** (4.00 mmol), 2-thiophencarboxaldenyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 173–175 °C; IR (KBr): 3363, 2862, 1666, 1605, 1574, 656 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.38 (1H, d, J = 5.4 Hz, 2-H), 8.25 (1H, d, J = 9.1 Hz, 5-H), 7.78 (1H, d, J = 2.2 Hz, 8-H), 7.57 (1H, d, J = 5.1 Hz, 5-H_{Thie}), 7.45 (1H, dd, J = 9.0, 2.2 Hz, 6-H), 7.32 (1H, br s, NH), 7.24 (1H, dd, J = 3.4, 0.8 Hz, 3-H_{Thie}), 6.95 (1H, dd, J = 5.0, 3.5 Hz, 4-H_{Thie}), 6.43 (1H, d, J = 5.5 Hz, 3-H), 6.19 (1H, s, 2-H_{Thiaz}), 3.79 (1H, dd, J = 15.7, 1.1 Hz, 5-Ha_{Thiaz}), 3.69 (1H, d, J = 15.6 Hz, 5-Hb_{Thiaz}), 3.55–3.48 (1H, m, 4′-Ha), 3.21 (2H, c, J = 5.8 Hz, 1′-Ha, 1′-Hb), 2.82–2.75 (1H, m, 4′-Hb), 1.59–1.42 (4H, m, 2′-Ha, 2′-Hb, 3′-Ha, 3′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 169.8, 151.5 (+), 150.1, 148.6, 144.5, 133.4 (+), 127.7 (+), 127.5 (+), 127.1 (+), 126.7 (+), 124.0 (+), 124.0 (+), 117.3, 98.5 (+), 57.6 (+), 41.9 (−), 41.8 (−), 31.9 (−), 24.9 (−), 24.0 (−). Anal. Calcd for $C_{20}H_{20}ClN_3OS_2$: C, 57.47; H, 4.82; N, 10.05. Found: C 57.32; H 4.67; N 10.23.

4.1.3.6. 3-(4-(7-Chloroquinolin-4-ylamino)butyl)-2-(furan-2-yl)thiazolidin-4-one (13). This compound was obtained as a yellowish white solid in 56% yield, from N^1-(7-chloroquinolin-4-yl)-butane-1,4-diamine **7** (4.00 mmol), 2-furancarboxaldenyde (4.80 mmol) and α-mercaptocetic acid (4.80 mmol); mp 179–181 °C; IR (KBr): 3356, 2862, 1666, 1605, 1574, 656 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.38 (1H, d, J = 5.4 Hz, 2-H), 8.25 (1H, d, J = 9.1 Hz, 5-H), 7.78 (1H, d, J = 2.2 Hz, 8-H), 7.58 (1H, d, J = 5.1 Hz, 5-H_{Fu}), 7.44 (1H, dd, J = 9.0, 2.2 Hz, 6-H), 7.29 (1H, t, J = 5.0 Hz, NH), 7.24 (1H, dd, J = 3.4, 0.9 Hz, 3-H_{Fu}), 6.95 (1H, dd, J = 5.1, 3.5 Hz, 4-H_{Fu}), 6.43 (1H, d, J = 5.5 Hz, 3-H), 6.19 (1H, s, 2-H_{Thiaz}), 3.79 (1H, d, J = 15.7 Hz, 5-Ha_{Thiaz}), 3.69 (1H, d, J = 15.6 Hz, 5-Hb_{Thiaz}), 3.55–3.48 (1H, m, 4′-Ha), 3.21 (2H, q, J = 5.7 Hz, 1′-Ha, 1′-Hb), 2.82–2.75 (1H, m, 4′-Hb), 1.61–1.41 (4H, m, 2′-Ha, 2′-Hb, 3′-Ha, 3′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 170.0, 151.7 (+), 150.0, 148.9, 144.5, 133.3 (+), 127.7 (+), 127.5 (+), 127.2 (+), 126.7 (+), 124.0 (+), 123.9 (+), 117.3, 98.5 (+), 57.6 (+), 41.8 (−), 41.8 (+), 31.9 (−), 24.9 (−), 24.0 (−). Anal. Calcd for $C_{20}H_{20}ClN_3O_2S$: C, 59.77; H, 5.02; N, 10.46. Found: C 59.59 H 5.17; N 10.55.

4.1.3.7. 3-(2-(7-Chloroquinolin-4-ylamino)ethyl)-2-(3,4-dimethoxyphenyl) thiazolidin-4-one (14). This compound was obtained as a beige solid in 81% yield, from N^1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine **5** (4.24 mmol), 3,4-dimetoxybenzaldehyde (5.09 mmol) and α-mercaptocetic acid (5.09 mmol); mp 210–212 °C; IR (KBr): 3348, 2831, 1651, 1605, 1574, 1265, 648 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.30 (1H, d, J = 5.4 Hz, 2-H), 8.12 (1H, d, J = 8.3 Hz, 5-H), 7.78 (1H, s, 8-H), 7.46–7.44 (1H, m, 6-H), 7.46–7.44 (1H, m, NH), 6.93 (1H, s, 2-H_{Ar}), 6.93 (2H, s, 6-H_{Ar}, 5-H_{Ar}), 6.26 (1H, d, J = 3.5 Hz, 3-H), 5.85 (1H, s, 2-H_{Thiaz}), 3.88–3.71 (2H, m, 5-Ha_{Thiaz}, 5-Hb_{Thiaz}), 3.75 (1H, s, 3-H_{Ar}), 3.69 (1H, s, 4-H_{Ar}), 3.55–3.53 (1H, m, 2′-Ha), 3.45–3.44 (1H, m, 1′-Ha), 3.20–3.19 (1H, m, 1′-Hb), 3.01–2.97 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.0, 151.6 (+), 149.6, 149.3, 148.9, 148.9 (+), 133.4, 131.3, 127.5 (+), 124.2 (+), 123.7 (+), 120.1 (+), 117.3, 111.5 (+), 110.7 (+), 98.3 (+), 62.9 (+), 55.5 (+), 55.4 (+), 40.6 (−), 32.1 (−), 24.8 (−). Anal. Calcd for $C_{22}H_{22}ClN_3O_3S$: C, 59.52; H, 4.99; Cl, 7.99; N, 9.47. Found: C 59.43; H 5.06; N 9.35.

4.1.3.8. 3-(3-(7-Chloroquinolin-4-ylamino)propyl)-2-(3,4-dimethoxyphenyl) thiazolidin-4-one (15). This compound was obtained as a beige solid in 88% yield, from N^1-(7-chloroquinolin-4-yl)-propane-1,3-diamine **6** (4.24 mmol), 3,4-dimetoxybenzaldehyde (5.09 mmol) and α-mercaptoacetic acid (5.09 mmol); mp 145–147 °C; IR (KBr): 3232, 2839, 1606, 1612, 1581, 1265, 640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.37 (1H, d, J = 5.3 Hz, 2-H), 8.16 (1H, d, J = 9.0 Hz, 5-H), 7.79 (1H, s, 8-H), 7.44 (1H, dd, J = 8.9, 1.7 Hz, 6-H), 7.22 (1H, t, J = 4.6 Hz, NH), 6.93 (1H, s, 2-H_{Ar}), 6.86 (1H, d, J = 8.3 Hz, 6-H_{Ar}), 6.81 (1H, d, J = 8.3 Hz, 5-H_{Ar}), 6.37 (1H, d, J = 5.4 Hz, 3-H), 5.78 (1H, s, 2-H_{Thiaz}), 3.87 (1H, d, J = 15.5 Hz, 5-Ha_{Thiaz}), 3.71 (1H, s, 3-H_{Ar}), 3.70 (1H, s, 4-H_{Ar}), 3.67 (1H, d, J = 15.5 Hz, 5-Hb_{thiaz}), 3.59–3.52 (1H, m, 3′-Ha), 3.23–3.14 (2H, m, 1′-Ha, 1′-Hb), 2.82–2.76 (1H, m, 3′-Hb), 1.83–1.67 (2H, m, 2′-Ha, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 170.6, 151.7 (+), 149.7, 149.1, 148.9, 148.9 (+), 133.3, 131.8, 127.4 (+), 123.9 (+), 123.7 (+), 119.6 (+), 117.3, 111.4 (+), 110.3 (+), 98.5 (+), 62.3 (+), 55.4 (+), 55.4 (+), 40.3 (−), 34.7 (−), 32.0 (−), 25.1 (−). Anal. Calcd for $C_{23}H_{24}ClN_3O_3S$: C, 60.29; H, 5.30; N, 9.21. Found: C 60.42; H 5.18; N 9.35.

4.1.3.9. 3-(4-(7-Chloroquinolin-4-ylamino)butyl)-2-(3,4-dimethoxyphenyl) thiazolidin-4-one (16). This compound was obtained as a beige solid in 70% yield, from N^1-(7-chloroquinolin-4-yl)-butane-1,4-diamine **7** (4.00 mmol), 3,4-dimetoxybenzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 185–187 °C; IR (KBr): 3371, 2870, 1666, 1612, 1574, 1257, 648 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.38 (1H, d, J = 5.4 Hz, 2-H), 8.25 (1H, d, J = 9.1 Hz, 5-H), 7.78 (1H, d, J = 2.1 Hz, 8-H), 7.44 (1H, dd, J = 9.0, 2.1 Hz, 6-H), 7.27 (1H, t, J = 5.0 Hz, NH), 6.93 (1H, s, 2-H_{Ar}), 6.91–6.86 (2H, m, 5-H_{Ar}, 6-H_{Ar}), 6.41 (1H, d, J = 5.5 Hz, 3-H), 5.77 (1H, s, 2-H_{Thiaz}), 3.86 (1H, dd, J = 15.6, 0.9 Hz, 5-Ha_{Thiaz}), 3.73 (1H, s, 3-H_{Ar}), 3.72 (1H, s, 4-H_{Ar}), 3.66 (1H, d, J = 15.4 Hz, 5-Hb_{thiaz}), 3.59–3.52 (1H, m, 4′-Ha), 3.23–3.18 (2H, m, 1′-Ha, 1′-Hb), 2.69–2.62 (1H, m, 4′-Hb), 1.61–1.50 (4H, m, 2′-Ha, 2′-Hb, 3′-Ha, 3′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 170.4, 151.7 (+), 149.9, 149.1, 149.0, 149.0 (+), 133.3, 131.9, 127.3 (+), 124.0 (+), 123.9 (+), 119.4 (+), 117.3, 111.5 (+), 110.3 (+), 98.5 (+), 62.0 (+), 55.5 (+), 55.4 (+), 41.9 (−), 41.7 (−), 32.0 (−), 24.8 (−), 23.8 (−). Anal. Calcd for $C_{24}H_{26}ClN_3O_3S$: C, 61.07; H, 5.55; N, 8.90. Found: C 61.23; H 5.67; N 8.97.

4.1.3.10. 3-(2-(7-Chloroquinolin-4-ylamino)ethyl)-2-(3,4,5-trimethoxyphenyl) thiazolidin-4-one (17). This compound was obtained as a withe solid in 71% yield, from N^1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine **5** (4.00 mmol), 3,4,5-trimethoxybenzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 182–184 °C; IR (KBr): 3356, 2862, 1670, 1605, 1574, 656 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.31 (1H, d, J = 5.4 Hz, 2-H), 8.14 (1H, d, J = 9.1 Hz, 5-H), 7.78 (1H, d, J = 2.2 Hz, 8-H), 7.45 (1H, dd, J = 9.0, 2.2 Hz, 6-H), 7.42 (1H, s, NH), 6.66 (2H, s, 2-H_{Ar}, 6-H_{Ar}), 6.30 (1H, d, J = 5.5 Hz, 3-H), 5.85 (1H, s, 2-H_{Thiaz}), 3.90 (1H, dd, J = 15.3, 1.6 Hz, 5-Ha_{Thiaz}), 3.71 (6H, s, –OCH_3), 3.70 (1H, d, J = 15.1, 5-Hb_{Thiaz}), 3.65 (3H, s, –OCH_3), 3.63–3.56 (1H, m, 2′-Ha), 3.53–3.42 (1H, m, 1′-Ha), 3.28–3.20 (1H, m, 1′-Hb), 3.06–2.99 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.2, 153.5 (+), 152.8, 152.8, 152.7, 149.3 (+), 137.6, 134.9, 133.4 (+), 129.4, 124.6 (+), 127.6 (+), 117.5, 106.1 (+), 106.0 (+), 99.2 (+), 71.1 (+), 60.8 (+), 56.5 (+),

56.3 (+), 52.1 (−), 46.9 (−), 33.9 (−). Anal. Calcd for $C_{23}H_{24}ClN_3O_4S$: C, 58.28; H, 5.10; N, 8.87. Found: C 58.12; H 5.23; N 8.63.

4.1.3.11. 2-(3,4-(Methylendioxy)phenyl)-3-(2-((7-chloroquinolin-4-yl)amino)ethyl)thiazolidin-4-one (18). This compound was obtained as a withe solid in 82% yield, from N^1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine **5** (4.00 mmol), 3,4-(methylendioxy)-benzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 238–240 °C; IR (KBr): 3390, 2862, 1659, 1615, 1569, 656 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.33 (1H, d, J = 5.4 Hz, 2-H), 8.12 (1H, d, J = 9.0 Hz, 5-H), 7.78 (1H, d, J = 1.9 Hz, 8-H), 7.45 (1H, dd, J = 9.0, 2.0 Hz, 6-H), 7.41 (1H, t, J = 5.7 Hz, NH), 6.98 (1H, s, 2-H_{Ar}), 6.86 (2H, s, 5-H_{Ar},6-H_{Ar}), 6.34 (1H, d, J = 5.4 Hz, 3-H), 6.02 (2H, d, J = 4.9 Hz, –OCH_2O–), 5.84 (1H, s, 2-H_{Thiaz}), 3.88 (1H, dd, J = 15.1, 1.0 Hz, 5-Ha_{Thiaz}), 3.66 (1H, d, J = 15.3 Hz, 5-Hb_{Thiaz}), 3.57–355 (1H, m, 2′-Ha), 3.52–3.47 (1H, m, 1H, m, 1′-Ha), 3.27–3.18 (1H, m, 1′-Hb), 3.01- 2.92 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.2, 154.5 (+), 152.7, 149.3, 148.7, 147.2 (+), 134.9, 132.5, 129.4 (+), 124.8 (+), 122.0 (+), 121.6 (+), 117.5, 113.8 (+), 112.3 (+), 101.2 (+), 99.2 (+), 70.8 (−), 52.0 (−), 46.5 (−), 33.9 (−). Anal. Calcd for $C_{21}H_{18}ClN_3O_3S$: C, 58.94; H, 4.24; N, 9.82. Found: C 58.90; H 4.28; N 9.73.

4.1.3.12. 3-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-phenylthiazolidin-4-one (19). This compound was obtained as a withe solid in 93% yield, from N^1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine **5** (4.00 mmol), benzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 120–122 °C; IR (KBr): 3356, 2862, 1666, 1605, 1574, 656 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.31 (1H, d, J = 5.4 Hz, 2-H), 8.12 (1H, d, J = 9.1 Hz, 5-H), 7.79 (1H, d, J = 2.2 Hz, 8-H), 7.44 (1H, dd, J = 9.0, 2.3 Hz, 6-H), 7.41–7.38 (6H, m, 2-H_{Ph}-6-H_{Ph}, NH), 6.26 (1H, d, J = 5.5 Hz, 3-H), 5.92 (1H, J = 1.5 Hz, 2-H_{Thiaz}), 3.88 (1H, dd, J = 15.5, 1.8 Hz, 5-Ha_{Thiaz}), 3.71 (1H, d, J = 15.5 Hz, 5-Hb), 3.65–3.58 (1H, m, 2′-Ha), 3.50–3.41 (1H, m, 1′-Ha), 3.25–3.17 (1H, m, 1′-Hb), 2.98–2.91 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.2, 154.5 (+), 152.7, 149.3, 143.8, 134.9 (+), 129.4 (+), 128.6 (+), 128.6 (+), 127.1 (+), 126.9 (+), 124.8 (+), 121.6 (+), 117.5 (+), 99.3 (+), 70.5 (+), 52.0 (+), 46.5 (−), 34.8 (−), 33.9 (−). Anal. Calcd for $C_{20}H_{18}ClN_3OS$: C, 62.57; H, 4.73; N, 10.95; Found: C 62.44; H 4.89; N 10.76.

4.1.3.13. 3-(3-((7-Chloroquinolin-4-yl)amino)propyl)-2-phenylthiazolidin-4-one (20). This compound was obtained as a beige solid in 65% yield, from N^1-(7-chloroquinolin-4-yl)-propane-1,3-diamine **6** (4.24 mmol), benzaldehyde (5.09 mmol) and α-mercaptoacetic acid (5.09 mmol); mp 128–130 °C; IR (KBr): 3348, 2846, 1666, 1612, 1581, 640 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.38 (1H, d, J = 5.4 Hz, 2-H), 8.17 (1H, d, J = 9.1 Hz, 5-H), 7.79 (1H, d, J = 1.9 Hz, 8-H), 7.45 (1H, dd, J = 8.9, 1.7 Hz, 6-H), 7.37–7.27 (5H, m, 2-H_{Ph}-6-H_{Ph}), 7.25 (1H, t, J = 4.8 Hz, NH), 6.37 (1H, d, J = 5.4 Hz, 3-H), 5.84 (1H, s, 2-H_{Thiaz}), 3.88 (1H, d, J = 15.4 Hz, 5-Ha_{Thiaz}), 3.69 (1H, d, J = 15.4 Hz, 5-Hb_{Thiaz}), 3.63–3.56 (1H, m, 3′-Ha), 3.19 (2H, d, J = 5.8 Hz, 1′-Ha, 1′-Hb), 2.77–2.70 (1H, m, 3′-Hb), 1.84–1.67 (2H, m, 2′-Ha, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.2, 149.3 (+), 154.5, 152.7, 143.8, 134.9, 129.4 (+), 128.6 (2C, +), 127.1 (+), 126.9 (2C, +), 124.8 (+), 121.6 (+), 117.5, 99.2 (+), 70.8 (+), 42.7 (−), 41.2 (−), 33.9 (−), 26.2 (−). GC–MS: t_R = 109.55 min, m/z (%): 397 ($M^{+\cdot}$, 4), 324 (6), 219 (48), 218 (6), 217 (15), 205 (54), 192 (100), 191 (80), 178 (21), 156 (37), 155 (24). Anal. Calcd for $C_{21}H_{20}ClN_3OS$: C, 63.39; H, 5.07; N, 10.56. Found: C 63.21; H 5.19; N 10.43.

4.1.3.14. 3-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (21). This compound was obtained as a withe solid in 92% yield, from N^1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine **5** (4.00 mmol), 4-hydroxy-3-methoxybenzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 233–236 °C; IR (KBr): 3400, 3382, 3020, 1665, 1614, 1581, 665 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.29 (1H, d, J = 5.4 Hz, 2-H), 8.12 (1H, d, J = 9.2 Hz, 5-H), 7.78 (1H, d, J = 2.2 Hz, 8-H), 7.45 (1H, dd, J = 9.0, 2.2 Hz, 6-H), 7.44–7.41(1H, m, NH), 6.90 (1H, s, 2-H_{Ar}), 6.84–6.73 (2H, m, 5-H_{Ar}, 6-H_{Ar}), 6.22 (1H, d, J = 5.5 Hz, 3-H), 5.81 (1H, s, 2-H_{Thiaz}), 3.83 (1H, d, J = 15.3, 5-Ha_{Thiaz}), 3.69 (3H, s, –OCH_3), 3.68 (1H, d, J = 15.0, 5-Hb_{Thiaz}), 3.55–3.43 (2H, m, 2′-Ha,1′-Ha), 3.39 (1H, s, –OH), 3.21–3.13 (1H, m, 1′-Hb), 3.03–2.96 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 170.4, 154.7 (+), 152.9, 149.3, 149.4, 149.1 (+), 133.3, 131.9, 129.3 (+), 122.0 (+), 123.9 (+), 121.4 (+), 117.3, 115.5 (+), 114.3 (+), 98.5 (+), 62.0 (+), 56.5 (+), 55.4 (−), 46.9 (−), 41.7 (−). Anal. Calcd for $C_{21}H_{20}ClN_3O_3S$: C, 58.67; H, 4.69; N, 9.77. Found: C 58.55; H 4.86; N 9.64.

4.1.3.15. 3-(3-((7-Chloroquinolin-4-yl)amino)propyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (22). This compound was obtained as a withe solid in 98% yield, from N^1-(7-chloroquinolin-4-yl)-propane-1,3-diamine **6** (4.00 mmol), 4-hydroxy-3-methoxybenzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 180–183 °C; IR (KBr): 3420, 2862, 3356, 2934, 1664, 1612, 1541, 1150, 656 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.38 (1H, d, J = 5.3 Hz, 2-H), 8.17 (1H, d, J = 9.0 Hz, 5-H), 7.78 (1H, d, J = 2.1 Hz, 8-H), 7.44 (1H, dd, J = 9.0, 2.2 Hz, 6-H), 7.21(1H, t, NH), 6.91 (1H, d, J = 1.7 Hz, 2-H_{Ar}), 6.78 (1H, dd, J = 8.2, 1.7 Hz, 6-H_{Ar}), 6.73 (1H, d, J = 8.1 Hz, 5-H_{Ar}), 6.37 (1H, d, J = 5.4 Hz, 3-H), 5.74 (1H, s, 2-H_{Thiaz}), 3.84 (1H, d, J = 15.3 Hz, 5-Ha_{Thiaz}), 3.71 (3H, s, –OCH_3), 3.66 (1H, d, J = 15.5 Hz, 5-Hb_{Thiaz}), 3.57–3.50 (1H, m, 3′-Ha), 3.40 (1H, s, –OH), 3.22–3.13 (2H, m, 1′-Ha, 1′-Hb), 2.84–2.77 (1H, m, 3′-Hb), 1.81–1.67 (2H, m, 2′-Ha, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.4, 154.7 (+), 150.9, 149.3, 147.1, 147.4 (+), 134.3, 131.9, 128.3 (+), 124.8 (+), 123.9 (+), 121.4 (+), 117.5, 115.5 (+), 113.9 (+), 98.5 (+), 72.0 (+), 55.5 (+), 42.9 (−), 41.7 (−), 32.0 (−), 26.8 (−). Anal. Calcd for $C_{22}H_{22}ClN_3O_3S$: C, 59.52; H, 4.99; N, 9.47 Found: C 59.43; H 5.06; N 9.17.

4.1.3.16. 3-(2-((7-Chloroquinolin-4-yl)amino)ethyl)-2-(3-hydroxy-4-methoxyphenyl)thiazolidin-4-one (23). This compound was obtained as a bagie solid in 56% yield, from N^1-(7-chloroquinolin-4-yl)-ethane-1,2-diamine **5** (4.00 mmol), 3-hydroxy-4-methoxybenzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 250–253 °C; IR (KBr): 3371, 2870, 1666, 1612, 1574, 1257, 648 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.33 (1H, d, J = 5.5 Hz, 2-H), 8.14 (1H, d, J = 9.0 Hz, 5-H), 7.80 (1H, d, J = 2.1 Hz, 8-H), 7.55(1H, t, NH), 7.46 (1H, dd, J = 9.0, 2.0 Hz, 6-H), 6.88 (1H, d, J = 8.3 Hz 5-H_{Ar}), 6.84 (1H, d, J = 2.0, 2-H_{Ar}), 6.77 (1H, dd, J = 8.2, 1.8 Hz, 5-H_{Ar}) 6.29 (1H, d, J = 5.6 Hz, 3-H), 5.79 (1H, s, 2-H_{Thiaz}), 3.76 (3H, s, –OCH_3) 3.82–3.62 (2H, m, 5-Ha_{Thiaz}, 5-Hb_{Thiaz}), 3.59–3.52 (1H, m, 2′-Ha), 3.50–3.42 (1H, m, 1′-Ha), 3.25–3.18 (1H, m, 1′-Hb), 3.39 (1H, s, –OH), 3.01–2.94 (1H, m, 2′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 171.0, 151.6 (+), 149.6, 149.3, 147.9, 148.9 (+), 133.4, 131.3, 127.5 (+), 124.2 (+), 123.7 (+), 120.1 (+), 117.3, 111.5 (+), 110.7 (+), 98.3 (+), 62.9 (+), 55.5 (+), 55.4 (−), 40.6 (−), = 32.1 (−). Anal. Calcd for $C_{21}H_{20}ClN_3O_3S$: C, 58.67; H, 4.69; N, 9.77; Found: C 58.58; H 4.79; N 9.54.

4.1.3.17. 3-(4-((7-Chloroquinolin-4-yl)amino)butyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (24). This

compound was obtained as a bagie solid in 98% yield, from N^1-(7-chloroquinolin-4-yl)-butane-1,4-diamine **7** (4.00 mmol), 4-hydroxy-3-methoxybenzaldehyde (4.80 mmol) and α-mercaptoacetic acid (4.80 mmol); mp 180–183 °C; IR (KBr): 3333, 3224, 2947, 1658, 1612, 1581, 1137, 602. ^{1}H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 8.38 (1H, d, J = 5.5 Hz, 2-H), 8.25 (1H, d, J = 9.2 Hz, 5-H), 7.77 (1H, d, J = 2.2 Hz, 8-H), 7.43 (1H, dd, J = 8.9, 1.9 Hz, 6-H), 7.27 (1H, t, J = 5.2 Hz, NH), 6.97–6.91 (3H, m, 2-H_{Ar}, 5-H_{Ar}, 6-H_{Ar}), 6.42 (1H, d, J = 5.5 Hz, 3-H), 5.75 (1H, s, 2-H_{Thiaz}), 3.83 (1H, d, J = 15.7 Hz, 5-Ha_{Thiaz}), 3.73 (3H, s, –OCH_3), 3.64 (1H, d, J = 15.4 Hz, 5-Hb_{Thiaz}), 3.58–3.49 (1H, m, 4′-Ha), 3.23–3.18 (2H, m, 1′-Ha, 1′-Hb), 3.40 (1H, s, –OH), 2.69–2.64 (1H, m, 4′-Hb), 1.62–1.42 (4H, m, 2′-Ha, 2′-Hb, 3′-Ha, 3′-Hb). ^{13}C NMR (100 MHz, DMSO-d_6, Me_4Si), δ (ppm): 172.4, 151.7 (+), 149.9, 149.5, 149.1, 149.0 (+), 133.3, 131.9, 127.3 (+), 124.0 (+), 123.9 (+), 119.4 (+), 117.3, 111.5 (+), 110.3 (+), 98.5 (+), 62.0 (+), 55.5 (+), 55.4 (+), 41.9 (−), 41.7 (−), 32.0 (−), 23.8 (−). Anal. Calcd for $C_{23}H_{24}ClN_3O_3S$: C, 60.32; H, 5.28; N, 9.18. Found: C 60.43; H 5.35; N 9.02.

4.2. Biology

4.2.1. In vitro antimalarial activity screening against *Plasmodium falciparum*

The SYBR©GreenI-based micromethod described by Smilkstein et al[16] was followed for testing antimalarial activity. Erythrocytic stages of *P. falciparum* 3D7 chloroquine-sensitive and Dd2 multidrug-resistance strains were maintained according to method of Trager and Jensen,[17] with minor modifications. RPMI 1640 culture medium supplemented with 0.5% Albumax II at 37 °C in an atmosphere with 5% CO_2. An erythrocyte suspension, with initial 1% parasitemia and 4% hematocrit, was prepared using the aforementioned culture and then distributed in a 96-well plate (50 μL per well). Next, stock solutions of each compound were prepared in DMSO and diluted in RPMI medium in order to obtain concentrations from 10 to 0.01 μg/mL. The final DMSO concentration was never higher than 0.1%. 50 μL of each prepared concentration were added per well. DMSO, chloroquine and mefloquine were included as a negative and positive control, respectively.

All compounds and controls were placed in triplicate. The plate was incubated under the same conditions. After 48 h, the plate was removed from the incubator and frozen for at least 1 h at -70 °C and then thawed. Finally, 100 μL of SYBR©GreenI in lysis buffer (0.2 μL/mL) was added per well and shaken for 5 minutes or until no erythrocyte precipitated was observed. The plate was left to stand in the dark for 1 h at room temperature. The fluorescence intensity (F.I.) for each well was measured at 485 nm of excitation and 530 nm of emission. The background fluorescence for the no parasitized erythrocytes was subtracted to each well tested. Percentage inhibition of the parasite growth for each concentration was calculated by using the following formula:

$$\%\text{inhibition} = 100 \times [(\text{F.I.control} - \text{F.I.comp})/(\text{F.I.control})]$$

IC_{50} values were estimated by plotting drug concentration versus percentage inhibition.

4.2.2. Hepatotoxicity and nonspecific cytotoxicity assays

Murine J774 macrophages and human hepatocarcinoma cells (HepG2) were maintained on RPMI 1640 medium supplemented with 10% FBS at 37 °C in a 5% CO_2 atmosphere. The same MTT-based method, according to Hattori and Nakanishi[18], was used to measure the cytotoxicity level on both cell lines. In a flat bottom 96-well microplate, 100 μL of cell suspension in RPMI medium, containing 5×10^4 cells, were distributed per well. The cells were allowed to attach for 24 h at 37 °C. Then, the medium was replaced by 200 μL of the compound solution in medium at the selected concentration, or DMSO at the same concentration of the control. The cells were exposed to compound solutions for another 24 h. Afterwards, the medium was eliminated and 100 μL/well of 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution, 0.4 mg/mL in PBS, was added and the plates were returned to incubator for 1 h. The suspension was removed and the toxic effect of the compounds was assessed by the reduction of MTT to formazan crystals (as a cell viability indicator). Crystals were solubilized by adding 100 μL of DMSO after discarding the supernatant and the optical density of the final solution (O.D.) was measured at 595 nm. The cytotoxicity percentages were calculated as follows:

$$\%\text{toxicity} = [(\text{O.D.control} - \text{O.D.comp})/(\text{O.D.control})] \times 100$$

4.2.3. Ferriprotoporphyrin IX biomineralization inhibition test (FBIT)

The procedure for testing FP biomineralization was performed according to the method described by Deharo et al.[19] A mixture containing: 50 μL of a 10 mg/mL compound solution or 50 μL of solvent (for control), 50 μL of 0.5 mg/ml of haemin chloride (Sigma H 5533) freshly dissolved in dimethylsulphoxide (DMSO) and 100 μL of 0.5 M sodium acetate buffer pH 4.4, was incubated in a non-sterile flat bottom 96-well plate at 37 °C for 18–24 hrs. After incubation, the plate was centrifuged at 1600 g for 5 min and the supernatant was discarded. The remaining pellet was resuspended with 200 μL of DMSO in order to remove unreacted FP. The plate was then centrifuged once again and the supernatant discarded. The pellet (precipitate of ß-haematin), was dissolved in 150 μL of 0.1 M NaOH and the absorbance quantified at 405 nm with a microplate reader. The data were expressed as the percentage of inhibition of FP biomineralization calculated using the following equation:

$$\%\text{inhibition} = 100 \times [(\text{O.D.control} - \text{O.D.drug})/(\text{O.D.control})]$$

4.2.4. In vivo antimalarial activity assessment

The in vivo antimalarial activity of the compounds was measured by the classical 4-day suppressive test.[20] Briefly, on day 0, groups of five NMRI male mice, with weight of 20 ± 2 g, were inoculated with 2×10^7 red blood cells RBCs infected by erythrocytic stages of rodent malaria parasite *P. berghei* ANKA strain. Two hours later, each group of mice was treated intraperitoneally i.p. with a dose of 10 mg/kg/day of the selected compound, which were previously prepared in DMSO. Treatment was continued from day 1 to 3, always at similar times. On the day 4, Giemsa-stained thin blood smears from the tail of the mice were made and microscopically examined with 1000× magnification. The mean of the parasitemia (Par.) of each group was calculated in a total of 1000 RBCs, and the growth inhibition percentage of parasite was estimated in relation to the control group, which received only the solvent of the compounds.

$$\%\text{inhibition} = [(\text{Par. control} - \text{Par. comp})/(\text{Par. control})] \times 100$$

Acknowledgments

The authors are grateful to the Research Center of Excellence, CENIVAM (contract no 432–2004) and Ministerio de Ciencia e Innovación (Project SAF 2009–10399), and Ministerio de Asuntos Exteriores y Cooperación (A/024093/09) of Spain.

References and notes

1. Ridley, R. G. *Nature* **2002**, *415*, 686–693.
2. Kouznetsov, V. V.; Gómez-Barrio, A. *Eur. J. Med. Chem.* **2009**, *44*, 3091–3113.
3. Ridley, R. G. *Nature* **1995**, *374*, 269–271.

4. Thayer, A. M. *Chem. Eng. News* **2005**, *83*, 69–82.
5. O'Neill, P. M.; Park, B. K.; Shone, A. E.; Maggs, J. L.; Roberts, P.; Stocks, P. A.; Biagini, G. A.; Bray, P. G.; Gibbons, P.; Berry, N.; Winstanley, P. A.; Mukhtar, A.; Bonar-Law, R.; Hindley, S.; Bambal, R. B.; Davis, C. B.; Bates, M.; Hart, T. K.; Gresham, S. L.; Lawrence, R. M.; Brigandi, R. A.; Gomez-Delas-Heras, F. M.; Gargallo, D. V.; Ward, S. A. *J. Med. Chem.* **2009**, *52*, 1408–1415.
6. (a) Meunier, B. *Acc. Chem. Res.* **2008**, *41*, 69–77; (b) Bellot, F.; Coslédan, F.; Vendier, L.; Brocard, J.; Meunier, B.; Robert, A. *J. Med. Chem.* **2010**, *53*, 4103–4109.
7. Walsh, J. J.; Coughlan, D.; Heneghan, N.; Gaynor, C.; Bell, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3599–3602.
8. (a) Lesyk, R. B.; Zimenkovsky, B. *Curr. Org. Chem.* **2004**, *8*, 1547–1577; (b) Prabhakar, Y. S.; Solomon, V. R.; Gupta, M. K.; Katti, S. B. In *Topics in Heterocyclic Chemistry*; Gupta, S. P., Ed.; Springer: Berlin, 2006; 4, pp 161–249.
9. Solomon, V. R.; Haq, W.; Srivastava, K.; Puri, S. K.; Katti, S. B. *J. Med. Chem.* **2007**, *50*, 394–398.
10. O'Neill, P. M.; Shone, A. E.; Stanford, D.; Nixon, G.; Asadollahy, E.; Park, B. K.; Maggs, J. L.; Roberts, P.; Stocks, P. A.; Biagini, G.; Bray, P. G.; Davies, J.; Berry, N.; Hall, C.; Rimmer, K.; Winstanley, P. A.; Hindley, S.; Bambal, R. B.; Davis, C. B.; Bates, M.; Gresham, S. L.; Brigandi, R. A.; Gomez-Delas-Heras, F. M.; Gargallo, D. V.; Parapini, S.; Vivas, L.; Lander, H.; Taramelli, D.; Ward, S. A. *J. Med. Chem.* **2009**, *52*, 1828–1844.
11. Madrid, P. B.; Liou, A. P.; DeRisi, J. L.; Guy, R. K. *J. Med. Chem.* **2006**, *49*, 4535–4543.
12. De, D.; Krogstad, F. M.; Byers, L. D.; Krogstad, D. *J. Med. Chem.* **1998**, *41*, 4918.
13. Stocks, P. A.; Raynes, K. J.; Bray, P. G.; Park, B. K.; O'Neill, P. M.; Ward, S. A. *J. Med. Chem.* **2002**, *45*, 4975–4983.
14. Natarajan, J. K.; Alumasa, J. N.; Yearick, K.; Ekoue-Kovi, K. A.; Casabianca, L. B.; de Dios, A. C.; Wolf, C.; Roepe, P. D. *J. Med. Chem.* **2008**, *51*, 3466–3479.
15. Motiwala, H. F.; Kumar, R.; Chakraborti, A. K. *Aust. J. Chem.* **2007**, *60*, 369–374.
16. Smilkstein, M.; Sriwilaijaroen, N.; Kelly, J. X.; Wilairat, P.; Riscoe, M. *Antimicrob. Agents Chemother.* **2004**, *48*, 1803–1806.
17. Trager, W.; Jensen, J. *Science* **1976**, *193*, 673–675.
18. Hattori, Y.; Nakanishi, N. *Cell. Immunology* **1995**, *165*, 7–11.
19. Deharo, E.; García, R. N.; Oporto, P.; Gimenez, A.; Sauvain, M.; Jullian, V.; Ginsburg, H. *Exp. Parasitology* **2002**, *100*, 252–256.
20. Peters, W. *Chemotherapy and drug resistance in malaria*, second ed.; Academic Press: London, 1987.