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# Facile synthesis of antimalarial 1,2-disubstituted 4-quinolones from 1,3-bisaryl-monothio-1,3-diketones†

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A new strategy was developed to synthesize 1,2-disubstituted 4-quinolones in good yield starting from 1,3-bisaryl-monothio-1,3-diketone substrates. The synthesized compounds were evaluated for antimalarial activity using *Plasmodium falciparum* strains. All compounds, except for two, showed good activity. Of these, seven compounds exhibited an excellent antimalarial activity ($IC_{50}$, <2 μM). More importantly, all seven compounds were equally effective in inhibiting the growth of both chloroquine-sensitive and chloroquine-resistant strains. The cytotoxicity assessment using carcinoma and non-carcinoma human cell lines revealed that almost all synthesized compounds were minimally cytotoxic ($IC_{50}$, >50 μM).



## 1. Introduction

Malaria, caused by the *Plasmodium* family of protozoan parasites, particularly *P. falciparum*, is a devastating disease, exerting enormous morbidity and mortality in many countries around the world.[1,2] Nearly half the world's population is at risk of contracting malaria and, in 2012 alone, there have been an estimated 207 million clinical cases and 627 000 malaria deaths, mostly in children.[1,2] In the past, quinine derivatives such as chloroquine, mefloquine and primaquine have been very effective in treating and controlling malaria. However, parasites have developed a widespread resistance against these commonly used drugs.[3] Hence, artemisinin-based combination therapy (ACT) has been deployed as a front-line treatment. ACT has been very effective in reducing malaria. However, parasites have already started developing resistance to ACT in Southeast Asia.[4,5] In view of this, the development of new drugs is an urgent necessity to control and eradicate malaria.

Although malaria parasites have developed resistance to widely used quinolines, new synthetic compounds containing quinoline and quinolone scaffolds have been shown to possess potent antimalarial activity.[6–8] For instance, recently, endochin related 3-substituted and 2,3-disubstituted 4(1*H*)-quinolones have been shown to be promising antimalarial drugs because some of these compounds can efficiently inhibit both *P. falciparum* and *P. vivax* parasites.[8] Additionally, they effectively target the liver stage, the blood stage including gametocytes, and all developmental forms of parasites in mosquitoes,[8] thereby making it difficult for parasites to develop drug resistance. Accordingly, more recently there have been substantial efforts to exploit this class of compounds for malaria treatment and control.[7,8] Considering the potential usefulness of variously substituted 4-quinolones as antimalarial agents, it is of interest to determine whether 1,2-disubstituted 4-quinolones possess antimalarial activity. Towards this goal, we synthesized a series of 1,2-disubstituted 4-quinolones through a simple, novel approach and tested their capacity to control *P. falciparum* growth.

Many strategies, involving Camp cyclization, have been employed to synthesize 4-quinolones.[9] Of these, some notable approaches include condensation of isatoic anhydride with aryl ketones,[10] α-imino ester with ethyltrimethylsilyl acetate,[11] intramolecular cyclization of phenacylanthranilate,[12] anthranilamide,[13] and cyclization of substituted aryl amine with the 2-fluorobenzoylvinylonio system.[14] Most of these methods afforded 1- and 3-substituted, and 1,3-di-substituted 4-quinolones. In comparison, only a limited number of studies have been reported on 1,2-disubstituted 4-quinolones that include palladium or copper catalyzed cyclization of alkynones[15–18] or chalcones[19] as depicted in Scheme 1. However, these methods are associated with significant disadvantages. For one, the

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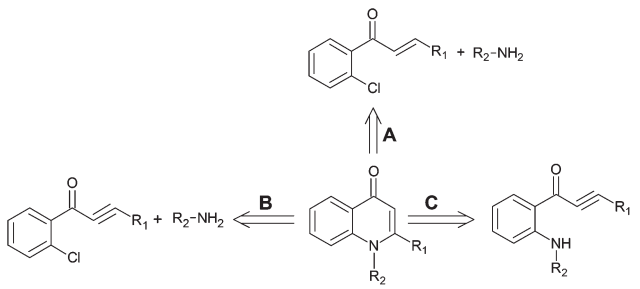
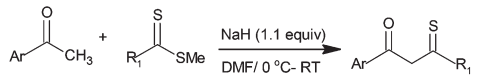


Scheme 1 Strategies that have been used for the synthesis of 1,2-disubstituted 4-quinolones.[15–19]



Scheme 2 Synthesis of 1,3-bisaryl-monothio-1,3-diketones.[21]

preparation of alkynone substrates required for the synthesis of 1,2-disubstituted 4-quinolones is cumbersome as the reaction has to be carried out at −78 °C in the presence of *n*-BuLi (Scheme 1, **A** and **B**). In the case of chalcones, the yield of 4-quinolone products markedly varies from very low to good yield depending on the nature of substituents on the phenyl ring (Scheme 1, **C**). Moreover, the phosphine oxide formed from $Ph_3P$ used in the cyclization of alkynones or chalcones, in addition to being hazardous, interferes with the purification of products by silica gel chromatography, resulting in a decreased yield.[20]

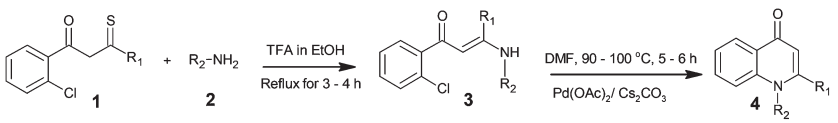
To overcome the above problems, in the present study, we developed a novel approach to synthesize 1,2-disubstituted 4-quinolones starting from 1,3-bisaryl-monothio-1,3-diketones. Unlike the case with alkynones, these monothiodiketone substrates can be prepared in good yield by a facile reaction at room temperature (Scheme 2).[21] Our approach involves a facile condensation of monothio-β-diketones with aryl amines that results in the formation of enaminones in almost quantitative yield followed by cyclization of enaminones into the desired 4-quinolone products. Furthermore, in view of our long-term interest in developing antimalarial drugs, we have tested the synthesized compounds for their ability to inhibit chloroquine-sensitive and chloroquine-resistant malaria parasite strains.

## 2. Results and discussion

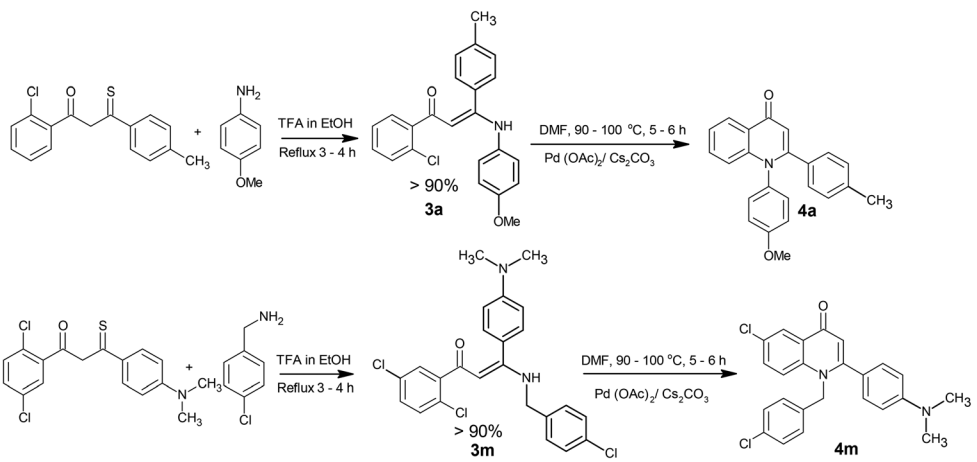
### 2.1. Synthesis of 1,2-disubstituted 4-quinolones

The overall approach that we have used for the synthesis of 1,2-disubstituted 4-quinolones involves two reaction steps (Scheme 3).

In the first step, an equimolar mixture of monothiodiketone substrates **1** and arylamines **2** in ethanol containing trifluoroacetic acid as a catalyst was refluxed for 3–4 h. The reaction was facile, forming exclusively 1-(2-chloroaryl)-3-aryl/aralkylamino-2-en-1-ones **3** in >90% yield. In the second step, the enaminones were cyclized using the $Pd(OAc)_2$ catalyst, the $Cs_2CO_3$ base, and DMF as a solvent to obtain 1,2-disubstituted 4-quinolones **4**. To demonstrate that enaminones are the exclusive products of the condensation reaction, in two typical examples (Scheme 4), wherein $R_1$ is either *p*-MePh or *N*,*N*-$(Me)_2$Ph and $R_2$ is either *p*-OMePh or *p*-chlorobenzyl, the enaminone intermediate products **3a** and **3m** (Scheme 4) were purified on silica gel columns and characterized by $^1H$ and $^{13}C$ NMR. Since in both cases, enaminones **3** were exclusive products of the condensation reaction, henceforth, they were cyclized directly to form 1,2-disubstituted 4-quinolones after evaporating ethanol solvent under vacuum.



Scheme 3 Approach to the synthesis of 1,2-disubstituted 4-quinolones.



Scheme 4 Confirmation that enaminones are the exclusive products (**3a** and **3m**) of the condensation reaction.

**Table 1** Optimization of reaction conditions for the cyclization of 1,2-disubstituted 4-quinolones

| Entry | Catalyst | Ligand | Base | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | — | $K_2CO_3$ | 12 | 10 |
| 2 | $Pd_2(dba)_3$ | $PPh_3$ | $K_2CO_3$ | 10 | 38 |
| 3 | $Pd_2(dba)_3$ | $PCy_3$ | $K_2CO_3$ | 10 | 32 |
| 4 | $Pd_2(dba)_3$ | $PPh_3$ | $Cs_2CO_3$ | 10 | 46 |
| 5 | $Pd_2(OAc)_2$ | — | $K_2CO_3$ | 8 | 65 |
| **6** | **$Pd_2(OAc)_2$** | — | **$Cs_2CO_3$** | **5** | **83** |
| 7 | $Pd_2(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | 6 | 75 |
| 8 | $Pd_2(OAc)_2$ | $PCy_3$ | $Cs_2CO_3$ | 6 | 56 |
| 9 | — | — | $Cs_2CO_3$ | 24 | 40 |

Having established the above synthetic strategy to access 1,2-disubstituted-4-quinolones, the reaction conditions were optimized for maximum product yield by carrying out cyclization of a model enaminone in which $R_1$ is Ph and $R_2$ is *p*-OMePh under different reaction conditions (Table 1). The cyclization using the $Pd_2(dba)_3$ catalyst in the presence of $K_2CO_3$ afforded the product in ~10% yield (Table 1, entry 1). The addition of a ligand, either $PPh_3$ or $PCy_3$, increased the yield to 38% and 32%, respectively (Table 1, entries 2 and 3). When $K_2CO_3$ was replaced by $Cs_2CO_3$ and $PPh_3$ was used as a ligand, the yield increased to 46% (Table 1, entry 4). Replacement of $Pd_2(dba)_3$ with $Pd(OAc)_2$ increased the yield substantially even in the absence of a ligand (Table 1, entry 5). However, the reaction performed using the $Pd(OAc)_2$ catalyst in the presence of $Cs_2CO_3$ without any ligand furnished 83% yield (Table 1, entry 6). The reaction was also carried out in the presence $PPh_3$ or $PCy_3$, but the yield decreased (Table 1, entries 7 and 8). Therefore, the use of a ligand was deemed undesirable. The enaminones can also be cyclized in the absence of a Pd catalyst by carrying out the reaction for 24 h, but the yield of the product was only 40% (Table 1, entry 9). Thus, $Pd(OAc)_2$ in the presence of the $Cs_2CO_3$ base without a ligand (Table 1, entry 6) was determined to be the optimal reaction conditions for the cyclization of enaminones to access 1,2-disubstituted 4-quinolones.

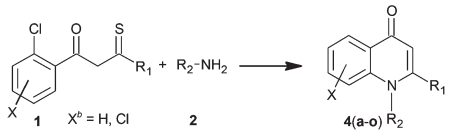
Using these optimal reaction conditions, several 1,2-disubstituted 4-quinolones were synthesized (Table 2). In all cases, the yields were in the range of 70–85%, suggesting that the substituents have little or no effect on the cyclization reaction. The products were purified by silica gel chromatography and were characterized by NMR and liquid chromatography-mass spectrometry.

### 2.2. Antimalarial activity and cytotoxicity

All the synthesized 1,2-disubstituted 4-quinolones (Table 2, **4a–o**) were initially tested for their antimalarial activity using the chloroquine drug-sensitive *P. falciparum* 3D7 strain at concentrations ranging from 0.25 μM to 100 μM. The inhibition of parasite growth was measured by the SYBR Green assay.[22] All compounds, except two (Table 2, **4g** and **4o**), showed good antimalarial activity. Of these, the $IC_{50}$ values (the concentrations required for the inhibition of parasite growth by 50%) of seven compounds, **4d**, **4f**, **4i**, **4h**, **4l**, **4m** and **4n** were less than 2 μM. These compounds were further assessed for their ability to inhibit the chloroquine-sensitive D6 strain and chloroquine-resistant W2 and 7G8 strains. Each of all seven compounds was almost equally effective irrespective of whether parasite strains are drug-sensitive or drug-resistant (Table 3), indicating that this class of 4-quinolones can be exploited for malaria treatment.

Furthermore, we tested all the synthesized compounds (**4a–o**) for cytotoxicity using human lung cancer A549 cells and human kidney HEK 293 cells using the MTS assay.[24] All compounds, except two (**4f** and **4i**), showed minimal cytotoxicity ($IC_{50}$ > 50 μM, Table 4). For these compounds to be useful as drugs against the blood stage malaria parasite, it is necessary that they should not cause lysis of red blood cells. Therefore, all compounds were tested for their effect on red blood cells at concentrations ranging from 2.5 μM to 40 μM. None of the compounds caused lysis of red blood cells at <20 μM. Together these results demonstrate that the 4-quinolones synthesized here are selectively inhibitory to malaria parasites.

**Table 2** Synthesis of 1,2-disubstituted 4-quinolones and their antimalarial activity[a]




| | $R_1$ | $R_2$ | Product | Yield (%) | $IC_{50}$ μM ± SD |
|---|---|---|---|---|---|
| 1 | Ph | *p*-OMePh | **4a** | 83 | 3.92 ± 0.22 |
| | | *m*-OMePh | **4b** | 79 | 2.18 ± 0.30 |
| 2 | *p*-MePh | *p*-OMePh | **4c** | 81 | 5.15 ± 1.71 |
| | | *p*-F-Ph | **4d** | 72 | 0.82 ± 0.11 |
| | | *m*-Br-Ph | **4e** | 76 | 6.21 ± 0.33 |
| | | 1-Naphthyl | **4f** | 80 | 1.53 ± 0.16 |
| 3 | *p*-OMePh | Ph | **4g** | 83 | 16.61 ± 3.20 |
| | | *m*-OMePh | **4h** | 82 | 1.25 ± 0.32 |
| | | *p*-OMePh | **4i** | 85 | 1.91 ± 0.16 |
| | | *o*-Br-Ph | **4j** | 76 | 2.23 ± 0.34 |
| | | *p*-F-Ph | **4k** | 70 | 5.61 ± 0.84 |
| | | 1-Naphthyl | **4l** | 83 | 1.53 ± 0.49 |
| 4 | *p-NN*-$(CH_3)_2$Ph | *p*-Cl-Ph-$CH_2$ | **4m** | 82 | 0.75 ± 0.15 |
| | | *m*,*p*-$(OMe)_2$ | **4n** | 79 | 1.26 ± 0.20 |
| 5 | Thiophenyl | *p*-OMePh | **4o** | 81 | 71.86 ± 5.37 |

[a] Against the *P. falciparum* 3D7 strain. [b] **4a** and **4b**, *p*-Cl; **4m** and **4n**, *m*-Cl.

**Table 3** Antimalarial activity of 1,2-disubstituted 4-quinolones against drug-sensitive and drug resistant parasites

| | Parasite growth inhibition ($IC_{50}$ μM ± SD) | | | |
|---|---|---|---|---|
| | 3D7 | D6 | W2 | 7G8 |
| **4d** | 0.82 ± 0.11 | 0.94 ± 0.12 | 0.85 ± 0.08 | 0.63 ± 0.22 |
| **4f** | 1.50 ± 0.16 | 1.20 ± 0.16 | 1.10 ± 0.31 | 1.00 ± 0.17 |
| **4i** | 1.90 ± 0.16 | 1.45 ± 0.44 | 1.59 ± 0.22 | 1.12 ± 0.20 |
| **4h** | 1.20 ± 0.32 | 1.30 ± 0.34 | 1.45 ± 0.50 | 0.94 ± 0.20 |
| **4l** | 1.50 ± 0.49 | 1.61 ± 0.53 | 1.32 ± 0.16 | 1.14 ± 0.31 |
| **4m** | 0.75 ± 0.15 | 1.03 ± 0.16 | 1.19 ± 0.20 | 0.80 ± 0.47 |
| **4n** | 1.26 ± 0.20 | 1.63 ± 0.56 | 1.54 ± 0.34 | 1.10 ± 0.36 |

Table 4 Cytotoxicity assay of 1,2-disubstituted 4-quinolones against human cell lines

| Compound | $IC_{50}$ μM ± SD[a] | |
|---|---|---|
| | A549 cells | HEK 293 cells |
| **4a** | 63.6 ± 2.5 | 56.2 ± 6.2 |
| **4b** | 80.4 ± 4.1 | 79.8 ± 3.1 |
| **4c** | 60.6 ± 3.1 | 56.6 ± 4.6 |
| **4d** | 81.0 ± 4.2 | 70.6 ± 5.6 |
| **4e** | 89.6 ± 2.6 | 61.0 ± 5.3 |
| **4f** | 45.0 ± 2.4 | 33.2 ± 2.4 |
| **4g** | 67.3 ± 2.4 | 59.1 ± 3.3 |
| **4h** | 63.6 ± 3.5 | 71.3 ± 2.6 |
| **4i** | 68.15 ± 4.4 | 23.4 ± 3.1 |
| **4j** | 61.2 ± 2.3 | 48.1 ± 1.9 |
| **4k** | 83.1 ± 5.5 | 75.0 ± 3.6 |
| **4l** | 45.0 ± 2.1 | 60.0 ± 4.1 |
| **4m** | 62.8 ± 3.4 | 56.6 ± 2.8 |
| **4n** | 88.5 ± 5.2 | 72.7 ± 3.2 |
| **4o** | 82.9 ± 2.3 | 70.6 ± 1.9 |

[a] The absorbances were measured using a micro plate reader at 72 h.

# 3. Conclusion

In conclusion, we have established a novel approach to obtain in high yield 1,2-disubstituted 4-quinolones from 1,3-bisaryl-monothio-1,3-diketone and arylamine substrates in two simple steps. In the first step, the substrates were condensed using TFA as a catalyst to form enaminones. In the second step, after evaporating the solvent of the first reaction, the enaminones were cyclized using the $Pd(OAc)_2$ catalyst and the $Cs_2CO_3$ base without a ligand. Several of the synthesized 4-quinolones showed an excellent activity against both chloroquine-sensitive and chloroquine-resistant parasites and exhibited minimal cytotoxicity. These results provide impetus to undertake further studies for exploiting this group of 4-quinolones as effective anti-malarial drugs.

# 4. Experimental

## 4.1. General information

Unless otherwise stated, all reagents and solvents were purchased and used without further purification. DMF and *n*-hexane were dried by standard procedures and stored over 3 Å molecular sieves. All reactions were carried out under an inert atmosphere in round-bottomed flasks. Precoated aluminum plates (SIL G/UV 254) were used for thin-layer chromatography. Column chromatography was performed with silica gels (60–120 mesh) using *n*-hexane and ethyl acetate eluents. $^1$H NMR and $^{13}$C NMR spectra were recorded on an Agilent 400 MHz NMR spectrometer at ambient temperature. Chemical shifts are expressed in ppm in relative to tetramethylsilane and residual solvent protons ($^1$H) or solvent carbons ($^{13}$C) were used as internal standards. IR spectra were recorded using a Shimadzu FT-IR model 8300 spectrophotometer. Elemental analysis was performed on a CE 400 CHN analyzer. Mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer. All melting points were recorded using Selaco melting point apparatus and are uncorrected.

## 4.2. General procedure for the preparation of 1,3-enaminones 3

To solutions of 1-(2-haloaryl)-3-(het)aryl-monothiodiketones **1** (3.1 mmol) and arylamines **2** (3.1 mmol) in EtOH (10 mL), trifluoroacetic acid (0.5 mmol) was added and heated at 80 °C while stirring for 3–4 h. The formation of enaminones was monitored by TLC. Then the solvent was evaporated under reduced pressure. The residual materials were dissolved in ethyl acetate (20 mL) and water (10 mL) and thoroughly mixed. The ethyl acetate layer was washed with brine solution (10 mL), dried over anhydrous $Na_2SO_4$, concentrated to obtain enaminones **3** and purified by silica gel column chromatography using *n*-hexane and EtOAc (2 : 8, vol/vol). The purified enaminones were characterized using IR, $^1$H NMR, and $^{13}$C NMR techniques. The results showed that enaminones were the exclusive products in the above reaction and were cyclized to obtain the final products.

**4.2.1. 1-(2-Chlorophenyl)-3-[(4-methoxyphenyl)amino]-3-(4-methylphenyl)prop-2-en-1-one 3a.** Yellow solid; mp: 115–117 °C; yield: 95%.

IR (KBr) cm$^{-1}$: 3421, 1589, 1512, 1509, 1316, 1272, 1120; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 11.5 (s, 1H, NH), 7.51 (d, $J$ = 7.2 Hz, 1H, ArH), 7.22–7.33 (m, 8H, ArH), 6.68 (d, $J$ = 8.4 Hz, 3H, ArH) 5.5 (s, 1H, HC═C–), 4.6 (s, 3H, OMe), 3.0 (s, 3H, Me); $^{13}$C NMR (100 MHz, $CDCl_3$): 190.1, 162.2, 156.6, 145.9, 141.1, 139.9, 132.3, 132.2, 130.9, 130.2, 129.4, 129.1, 128.5, 126.6, 125.1, 113.9, 99.9, 55.3, 21.4.

**4.2.2. 3-(*N*,*N*-Dimethylamino)phenyl-3-[(4-chlorobenzyl)-amino]-1-(2,5-dichlorophenyl)prop-2-en-1-one 3m.** Yellow solid; mp: 120–122 °C; yield: 92%.

IR (KBr) cm$^{-1}$: 3466, 1610, 1578, 1530, 1426, 1303, 744, 690; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.65 (s, 1H, NH), 6.68–7.56 (m, 11H, ArH), 5.72 (s, 1H, HC═C–), 3.74 (s, 2H, $PhCH_2$), 2.33 (s, 6H, $N(CH_3)_2$); $^{13}$C NMR (100 MHz, $CDCl_3$): 187.1, 163.6, 155.0, 154.0, 141.1, 140.0, 132.4, 132.1, 131.0, 130.2, 129.4, 128.9, 128.5, 126.6, 125.1, 113.9, 95.1, 48.2, 40.2.

## 4.3. General procedure for the cyclization of enaminones 4a–o

Having proved that the substrates were almost quantitatively converted into enaminones, the solvent used in the first reaction step was removed under reduced pressure and the residual matter was directly cyclized. $Cs_2CO_3$ (1.6 mmol) and $Pd(OAc)_2$ (0.02 mmol) were added to the solutions of enaminones **3** (0.8 mmol) dissolved in DMF (4 mL). The mixture was stirred at 90–100 °C for 5–6 h and the reaction was monitored by TLC. Upon completion, the reaction mixture was filtered through a pad of celite, the residual material was extracted with EtOAc (3 × 10 mL), washed with brine and then with water. The combined extract was dried over anhydrous $Na_2SO_4$, filtered, and concentrated by evaporating under vacuum. The product was purified by silica gel column chromatography using *n*-hexane and EtOAc (6 : 4, vol/vol) to obtain 1,2-disubstituted 4-quinolones **4a–o**.

# 5. Analytical data

## 5.1. Characterization of 1,2-disubstituted 4-quinolones 4(a–o)

**5.1.1. 7-Chloro-1-(4-methoxyphenyl)-2-phenylquinolin-4(1*H*)-one (4a).** White solid; m.p. 222–224 °C; IR (KBr) $cm^{-1}$: 3048, 1631, 1586, 1516, 1464, 1382, 1318, 1157, 1086, 834; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.42 (d, $J$ = 8.8 Hz, 1H, ArH), 7.04–7.33 (m, 8H, ArH), 6.85–6.92 (m, 3H, ArH), 6.42 (s, 1H, CH), 3.80 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.3, 165.5, 159.6, 154.9, 143.6, 138.3, 135.4, 131.1, 130.7, 129.0, 128.7, 128.0, 127.9, 124.5, 117.7, 114.8, 112.9, 55.5; MS $m/z$: 362 $[M + H]^+$; Anal. Calcd for $C_{22}H_{16}ClNO_2$: C 73.03, H 4.46, N 3.87. Found: C 73.06, H 4.52, N 3.94.

**5.1.2. 7-Chloro-1-(3-methoxyphenyl)-2-phenylquinolin-4(1*H*)-one (4b).** Yellow solid; m.p. 114–116 °C; IR (KBr) $cm^{-1}$: 3056, 1673, 1547, 1498, 1398, 1278, 1247, 1121, 876; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.42 (d, $J$ = 9.2 Hz, 1H, ArH), 7.05–7.33 (m, 5H, ArH), 6.78–7.05 (m, 6H, ArH), 6.42 (s, 1H, CH), 3.73 (s, 1H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 178.0, 160.5, 159.6, 153.9, 142.6, 140.3, 131.9, 130.5, 130.2, 128.1, 126.2, 126.0, 123.7, 122.3, 118.0, 115.6, 114.6, 113.4, 112.7, 55.5; MS $m/z$: 362 $[M + H]^+$; Anal. Calcd for $C_{22}H_{16}ClNO_2$: C 73.03, H 4.46, N 3.87. Found: C 73.10, H 4.55, N 3.95.

**5.1.3. 1-(4-Methoxyphenyl)-2-(4-methylphenyl)quinolin-4(1*H*)-one (4c).** Brown solid; m.p. 216–218 °C; IR (KBr) $cm^{-1}$: 3078, 1614, 1603, 1458, 1402, 1318, 1275, 1063, 834; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.50 (d, 1H, $J$ = 7.2 Hz, ArH), 7.48–7.34 (m, 2H, ArH), 7.06–6.85 (m, 9H, ArH), 6.41 (s, 1H, CH), 3.80 (s, 3H, OMe), 2.27 (s, 3H, ArMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.9, 159.4, 154.5, 142.9, 138.4, 132.9, 131.9, 131.7, 130.9, 129.0, 128.6, 126.2, 126.1, 123.6, 118.1, 114.6, 112.5, 55.4, 21.2; MS $m/z$: 342 $[M + H]^+$; Anal. Calcd for $C_{23}H_{19}NO_2$: C 80.92, H 5.61, N 4.10. Found: C 80.96, H 5.68, N 4.17.

**5.1.4. 1-(4-Fluorophenyl)-2-(4-methylphenyl)quinolin-4(1*H*)-one (4d).** White solid; m.p. 234–336 °C; IR (KBr) $cm^{-1}$: 1618, 1594, 1562, 1488, 1421, 1341, 1172, 1068, 789; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.51 (d, $J$ = 8.0 Hz, 1H, ArH), 7.50–7.37 (m, 2H, ArH), 7.16–7.02 (m, 8H, ArH), 6.87 (d, $J$ = 8.4 Hz, 1H, ArH), 6.42 (s, 1H, CH), 2.28 (s, 3H, ArMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 178.5, 160.0, 158.8, 144.2, 139.9, 134.0, 132.9, 132.1, 131.4, 130.1, 129.7, 127.4, 127.1, 124.5, 119.0, 115.9, 113.5, 23.01; MS $m/z$: 330 $[M + H]^+$; Anal. Calcd for $C_{22}H_{16}FNO$: C 80.23, H 4.90, N 4.25. Found: C 80.29, H 4.96, N 4.31.

**5.1.5. 1-(3-Bromophenyl)-2-(4-methylphenyl)quinolin-4(1*H*)-one (4e).** White solid; m.p. 208–210 °C; IR (KBr) $cm^{-1}$: 1631, 1587, 1492, 1463, 1394, 1261, 1123, 767; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.50 (d, 1H, $J$ = 8.0 Hz, ArH), 7.51–7.48 (t, 2H, $J$ = 7.6 Hz, ArH), 7.40–7.37 (t, 2H, $J$ = 7.6 Hz, ArH), 7.27–7.23 (t, 1H, $J$ = 8.4 Hz, ArH), 7.12–6.87 (m, 6H, ArH), 6.41 (s, 1H, CH), 2.28 (s, 3H, ArMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.9, 153.8, 142.3, 140.5, 138.9, 133.2, 132.4, 132.2, 132.0, 130.7, 128.9, 128.8, 128.8, 126.4, 125.9, 123.9, 122.8, 117.7, 112.8, 21.2; MS $m/z$: 390, 392 $[M + H]^+$; Anal. Calcd for $C_{22}H_{16}BrNO$: C 67.71, H 4.13, N 3.59. Found: C 67.78, H 4.18, N 3.62.

**5.1.6. 2-(4-Methylphenyl)-1-(naphthalen-1-yl)quinolin-4(1*H*)-one (4f).** Brown solid; m.p. 236–238 °C; IR (KBr) $cm^{-1}$: 1623, 1607, 1534, 1481, 1436, 1279, 1236, 1191, 1031, 842; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.54 (d, $J$ = 8.0 Hz, 1H, ArH), 7.87–6.86 (m, 14H, ArH), 6.48 (s, 1H), 2.17 (s, 3H, Me); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.9, 159.4, 154.0, 149.1, 142.7, 136.6, 133.1, 132.5, 131.7, 130.5, 129.6, 129.1, 128.0, 127.9, 127.8, 127.3, 127.0, 126.2, 126.1, 123.7, 118.2, 113.4, 122.7, 21.4; MS $m/z$: 362 $[M + H]^+$; Anal. Calcd for $C_{26}H_{19}NO$: C 86.40, H 5.30, N 3.88. Found: 86.48, H 5.36, N 3.93.

**5.1.7. 2-(4-Methoxyphenyl)-1-phenylquinolin-4(1*H*)-one (4g).** White solid; m.p. 208–210 °C; IR (KBr) $cm^{-1}$: 3065, 1628, 1614, 1521, 1484, 1402, 1248, 1186, 1025, 841; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.43 (d, $J$ = 8.0 Hz, 1H, ArH), 7.30–7.45 (m, 3H, ArH), 6.67–7.19 (m, 9H, ArH), 6.53 (s, 1H, CH), 3.83 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$175.8, 164.0, 157.8, 144.4, 141.2, 135.9, 133.2, 128.9, 128.3, 126.7, 126.4, 125.6, 125.5, 122.1, 115.5, 112.3, 110.5, 53.6; MS $m/z$: 328 $[M + H]^+$; Anal. Calcd for $C_{22}H_{17}NO_2$: C 80.71, H 5.23, N 4.28. Found: C 80.76, H 5.32, N 4.35.

**5.1.8. 1-(3-Methoxyphenyl)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (4h).** White solid; m.p. 214–216 °C; IR (KBr) $cm^{-1}$: 3054, 1630, 1598, 1521, 1474, 1412, 1348, 1175, 1048, 838; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.50 (d, $J$ = 7.6 Hz, 1H, ArH), 7.49–7.11 (m, 5H, ArH), 6.98–6.67 (m, 6H, ArH), 6.42 (s, 1H, CH), 3.76 (s, 3H, OMe), 3.73 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.9, 160.4, 159.6, 153.8, 142.5, 140.2, 131.8, 130.4, 130.2, 128.0, 126.2, 125.9, 123.7, 122.2, 118.1, 115.6, 114.6, 113.3, 112.6, 55.5, 55.2; MS $m/z$: 358 $[M + H]^+$; Anal. Calcd for $C_{23}H_{19}NO_3$; C 77.29, H 5.36, N 3.92. Found: C 77.31, H 5.39, N 3.98.

**5.1.9. 1,2-Bis(4-methoxyphenyl)quinolin-4(1*H*)-one (4i).** Yellow solid; m.p. 222–224 °C; IR (KBr) $cm^{-1}$: 3068, 1628, 1614, 1532, 1464, 1436, 1261, 1163, 1087, 774; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.50 (d, $J$ = 7.60 Hz, 1H, ArH), 7.48–7.33 (m, 2H, ArH), 7.10–6.71 (m, 9H, ArH), 6.41 (s, 1H, CH), 3.81 (s, 3H, OMe), 3.75 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.9, 159.4, 159.3, 154.2, 142.9, 131.8, 131.7, 130.8, 130.5, 128.1, 126.1, 125.9, 123.5, 118.1, 114.6, 113.3, 112.5, 55.2, 55.1; MS $m/z$: 358 $[M + H]$; Anal. Calcd for $C_{23}H_{19}NO_3$: C 77.29, H 5.36, N 3.92. Found: C 77.31, H 5.39, N 3.98.

**5.1.10. 1-(2-Bromophenyl)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (4j).** White solid; m.p. 212–214 °C; IR (KBr) $cm^{-1}$: 3059, 1631, 1627, 1591, 1482, 1423, 1268, 1157, 1120, 846; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.51 (d, $J$ = 7.6 Hz, 1H, ArH), 7.61 (d, $J$ = 8.0 Hz, 1H, ArH), 7.48 (t, $J$ = 7.6 Hz, 1H, ArH), 7.38 (q, 2H, $J$ = 8.5 Hz, ArH), 7.21–7.30 (m, 4H, ArH), 6.45 (s, 1H, CH), 3.75 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 178.2, 159.9, 153.6, 141.5, 138.4, 134.0, 132.3, 132.1, 130.7, 130.3, 128.5, 127.4, 126.4, 125.9, 124.5, 123.9, 117.3, 113.2, 112.9, 55.2; MS $m/z$: 406, 408 $[M + H]$; Anal. Calcd for $C_{22}H_{16}BrNO_2$: C 65.04, H 3.97, N 3.45. Found: C 65.10, H 3.99, N 3.53.

**5.1.11. 1-(4-Fluorophenyl)-2-(4-methoxyphenyl)quinolin-4(1*H*)-one (4k).** White solid; m.p. 228–230 °C; IR (KBr) $cm^{-1}$: 3063, 1622, 1583, 1511, 1486, 1417, 1326, 1161, 1018, 845; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.50 (d, $J$ = 7.6 Hz, 1H, ArH), 7.48–7.34 (m, 2H, ArH), 7.16–7.03 (m, 5H, ArH), 6.71–6.95 (m, 4H, ArH), 6.42 (s, 1H, CH), 3.76 (s, 3H, OMe); $^{13}C$ NMR

(100 MHz, $CDCl_3$): $\delta$ 178.9, 159.6, 154.3, 143.0, 142.6, 131.9, 131.7, 130.8, 128.2, 126.3, 123.8, 118.1, 117.7, 116.8, 116.6, 113.4, 113.3, 55.2; MS *m*/*z*: 346 [M + H]; Anal. Calcd for $C_{22}H_{16}FNO_2$: C 76.51, H 4.67, N 4.06. Found: C 76.58, H 4.73, N 4.14.

**5.1.12. 2-(4-Methoxyphenyl)-1-(naphthalen-1-yl)quinolin-4(1*H*)-one (4l).** Yellow solid; m.p. 242–244 °C; IR (KBr) $cm^{-1}$: 3084, 1631, 1624, 1573, 1563, 1426, 1356, 1287, 778; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.52 (d, *J* = 7.6 Hz, 1H, ArH), 7.87–7.85 (d, *J* = 8.4 Hz, 2H, ArH), 7.77–7.24 (m, 7H, ArH), 7.15–7.13 (d, *J* = 8.8 Hz, 2H, ArH), 6.89–6.87 (d, *J* = 8.4 Hz, 1H, ArH), 6.64–6.61 (d, *J* = 8.8 Hz, 2H, ArH), 6.47 (s, 1H), 3.66 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.9, 159.5, 154.1, 148.8, 142.8, 136.7, 133.1, 132.6, 131.8, 130.5, 129.7, 129.1, 128.0, 127.9, 127.8, 127.3, 127.1, 126.2, 126.0, 123.7, 118.1, 113.3, 112.7, 55.1; MS *m*/*z*: 378 [M + H]; Anal. Calcd for $C_{26}H_{19}NO_2$: C 82.74, H 5.07, N 3.71. Found: C 82.79, H 5.12, N 3.78.

**5.1.13. 6-Chloro-1-(4-chlorobenzyl)-2-(4-(dimethylamino)-phenyl)quinolin-4(1*H*)-one (4m).** White solid; m.p. 208–210 °C; IR (KBr) $cm^{-1}$: 3052, 1676, 1552, 1486, 1385, 1285, 1254, 1126, 868; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.46 (s, 1H, ArH), 7.42 (t, *J* = 7.6 Hz, 1H, ArH), 7.17–7.30 (m, 5H, ArH), 6.95 (d, *J* = 8.4 Hz, 2H, ArH), 6.64 (d, *J* = 8.0 Hz, 2H, ArH), 6.37 (s, 1H, ArH), 5.31 (s, 2H, $ArCH_2$), 2.99 (s, 6H, $NMe_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 176.5, 156.3, 151.1, 139.5, 135.0, 133.5, 132.3, 129.9, 129.3, 129.2, 128.3, 126.9, 126.1, 122.1, 119.0, 113.3, 111.6, 51.9, 40.1; MS *m*/*z*: 423 [M + H]; Anal. Calcd for $C_{24}H_{20}Cl_2N_2O$: C 68.09, H 4.76, N 6.62. Found: C 68.16, H 4.82, N 6.73.

**5.1.14. 6-Chloro-1-(3,4-dimethoxyphenyl)-2-(4-(dimethylamino)phenyl)quinolin-4(1*H*)-one (4n).** Yellow solid; m.p. 214–216 °C; IR (KBr) $cm^{-1}$: 3042, 1656, 1565, 1485, 1385, 1282, 1252, 1135, 882; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.43 (s, 1H, ArH), 7.37 (d, *J* = 8.8 Hz, 1H, Ar-H), 6.78–7.04 (m, 5H, Ar-H), 6.61 (s, 1H, Ar-H), 6.43–6.48 (m, 3H, Ar-H), 3.90 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.92 (s, 6H, $NMe_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 176.7, 154.3, 150.2, 149.6, 149.0, 141.4, 132.0, 131.7, 130.1, 129.7, 126.1, 125.4, 122.7, 122.2, 119.9, 112.8, 112.5, 111.0, 110.8, 56.1, 55.9, 40.0; MS *m*/*z*: 435 [M + H]; Anal. Calcd for $C_{25}H_{23}ClN_2O_3$: C 69.04, H 5.33, N 6.44. Found: C 69.09, H 5.39, N 6.49.

**5.1.15. 1-(4-Methoxyphenyl)-2-(thiophen-2-yl)quinolin-4(1*H*)-one (4o).** White solid; m.p. 196–198 °C; IR (KBr) $cm^{-1}$: 2930, 1589, 1572, 1428, 1235, 1124; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.47 (d, *J* = 8.0 Hz, 1H, ArH), 7.49–7.17 (m, 5H, ArH), 6.99–6.87 (m, 5H, ArH), 6.67 (s, 1H), 3.87 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 178.0, 159.2, 155.0, 141.2, 135.0, 133.0, 132.5, 132.0, 132.0, 130.0, 129.5, 128.0, 126.0, 123.5, 122.5, 114.0, 110.5, 56.5; MS *m*/*z*: 334 [M + H]; Anal. Calcd for $C_{20}H_{15}NO_2S$: C 72.05, H 4.53, N 4.20. Found: C 72.13, H 4.58, N 4.25.

### 5.2. Assessment of antimalarial activity and cytotoxicity

**5.2.1. Antimalarial activity.** *P. falciparum* parasites were cultured according to the method of Trager and Jensen.[23] Briefly, 3D7, D6, W2 and 7G8 parasite strains were cultured in RPMI 1640 medium (Gibco) supplemented with 25 mM HEPES, 29 mM sodium bicarbonate, 0.005% hypoxanthine, *p*-aminobenzoic acid (2 mg per liter), gentamycin sulfate (50 mg per liter) and 5% AlbuMAX II (Invitrogen) using fresh O-positive human red blood cells at 2% hematocrit. The cultures were maintained at 37 °C under 5% $O_2$, 5% $CO_2$, and 90% $N_2$ atmosphere. The antimalarial activity of quinolone compounds was determined by a fluorometric method using SYBR Green I.[22] Briefly, stock solutions of quinolones were prepared in DMSO (10 mM) and were diluted to 400 μM with DMSO. The solutions were then 1 : 2 serially diluted with complete culture medium to give concentrations ranging from 0.5 to 200 μM; the final concentration of DMSO was less than 0.1%. 100 μL of each testing solution was mixed with 100 μL of 0.2% parasitized red blood cells in the ring stage at 2% hematocrit in complete medium and dispensed into 96-well plates. Untreated- and DMSO (0.1%) vehicle-treated parasites were used as controls. The plates were incubated at 37 °C for 72 h and the experiment was performed in triplicate. To each well, 100 μL of lysis buffer (20 mM Tris-HCl, pH 7.5, 5 mM EDTA, 0.008% saponin, 0.08% Triton X-100) containing 0.2 μL $mL^{-1}$ of SYBR Green I (Life Technology) was added. The plates were wrapped with an aluminum foil and incubated in the dark at room temperature for 1 h. The fluorescence intensity was measured using a multi-well plate fluorescence reader at an excitation and emission wavelengths of 485 and 535 nm, respectively. The absorption values were expressed as relative fluorescence units. The $IC_{50}$ values (the effective concentrations that inhibit parasite growth by 50%) of three independent experiments were plotted using the nonlinear regression (Sigmoidal dose response) equation (GraphPad Prism, version 4.01, GraphPad Software, La Jolla, CA).

**5.2.2. Cytotoxicity assay.** The toxicity of quinolones against human cells was assessed by the MTS assay using human embryonic kidney cells (HEK 293 cell line) and human adenocarcinoma epithelial cells (A549 cell line).[24] Briefly, $5 \times 10^3$ cells per well in 100 μL of DMEM medium supplemented with 10% bovine fetal serum were plated in 96-well plates. After 24 h, the stock solutions of quinolones in DMSO that were diluted to obtain concentrations ranging from 0.5 μM to 200 μM in 100 μl complete medium were added to each well and incubated at 37 °C for 72 h. The wells treated with DMSO (1%) alone were used as vehicle controls. To each well was added 20 μl of the MTS/PMS reagent (Promega, Madison, WI), incubated for 3 h at 37 °C and the absorbance was measured at 490 nm. The assay was performed in triplicate and the values from three independent experiments were used to calculate the $IC_{50}$ values (GraphPad Prism, version 4.01).

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