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A trio of quinoline-isoniazid-phthalimide with promising antiplasmodial potential: Synthesis, *in-vitro* evaluation and heme-polymerization inhibition studies

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ABSTRACT

Quinoline-isoniazid-phthalimide triads have been synthesised to assess their antiplasmodial efficacy and cytotoxicity against chloroquine-resistant W2 strain of *P. falciparum* and Vero cells, respectively. Most of the synthesized compounds displayed IC_{50} in lower nM range and appeared to be approximately five to twelve fold more active than chloroquine. Heme-binding studies were also carried out to delineate the mode of action. The promising compounds with IC_{50s} in range of 11–30 nM and selectivity index >2800, may act as promising template for the design of new antiplasmodials.

1. Introduction

Malaria continues to be a public health challenge worldwide. *Plasmodium falciparum* is the most fatal and contributory species responsible for highest malaria morbidity and is responsible for half a million deaths every year.[1] WHO world malaria report-2019 estimated 228 million malaria cases and 405,000 malaria related deaths in 2018, which is an increase of ~9 million cases compared to the previous year. These numbers confirm that malaria is still one of the world's most lethal parasitic infection. Around two-thirds of the affected population globally are infants under the age of five and expectant mothers.[2] The currently available anti-malarial drugs invariably suffer from lower effectiveness, and development of resistant parasitic strains thus limiting their therapeutic efficacy.[3] Most of the previously used antimalarial treatments such as quinine, chloroquine, mefloquine, amodiaquine, piperaquine, sulfadoxine-pyrimethamine and halofantrine, suffered from the above mentioned problems.[1,4] Among the currently employed antimalarials, artemisinin combination therapies (ACTs) proved to be the most effective, especially against *P. falciparum*.[5–8] However, no present-day first line antimalarial match the favorable efficacy, safety, and affordability once held by CQ.[9,10] The increasing malaria related morbidity/mortality along with the lack of a suitable vaccine, therefore provide a strong impetus for the identification and development of new therapeutic frameworks with low incidence of resistance.[11–13]

In the development of antimalarial therapy, quinoline-core has played a prominent role as shown by drugs like quinine, chloroquine, mefloquine, amodiaquine, primaquine, piperaquine and while few scaffolds are under clinical trials (Fig. 1).[14] 4-aminoquinoline-hybridization involving the fusion of various pharmacophores with 4-aminoquinoline core is considered as one of the novel approaches for affording new molecular structures with promising anti-plasmodial potential.[15–18]

Iron (Fe) is considered as crucial for cellular proliferation, and Fe-chelators are known to inhibit the growth of the malarial parasite in cell culture, in animal and human studies.[19] A number of heterocyclic scaffolds, including the pyridine core act as iron chelators and display promising antimalarial activities (Fig. 2). 4-isonicotinic hydrazide (isoniazid), a pyridine analogue is a first line drug in treatment of tuberculosis (TB). It is an enoyl-ACP reductase inhibitor, an important enzyme in the biosynthesis of fatty acids (Fig. 2).[20]

Phthalimide-based moieties have recently gained medicinal chemists' attention to afford antitumor, antitubercular, antimalarial, antioxidant, anti-microbial, and anti-inflammatory drug candidates.[21] Recently, we have disclosed the anti-plasmodial potential of 4-aminoquinoline linked functionalized phthalimides, with the compounds exhibiting promising activities in nanomolar range against chloroquine-resistant (CQR) W2 strain of *P. falciparum* (Fig. 3).[22] In continuation,[23] the present paper is a logical extension and includes the synthesis and

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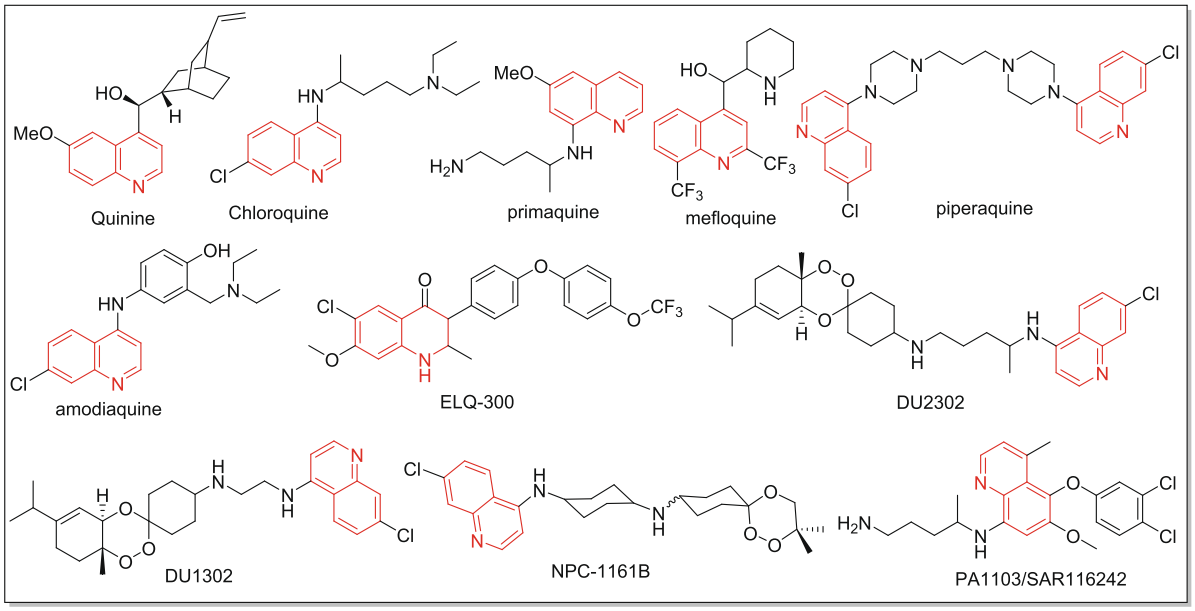


Fig. 1. Quinoline based clinically approved/under clinical trial antimalarials.

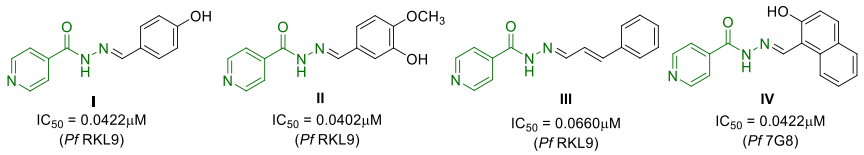


Fig. 2. Isoniazid-derivatives with promising antimalarial activity.

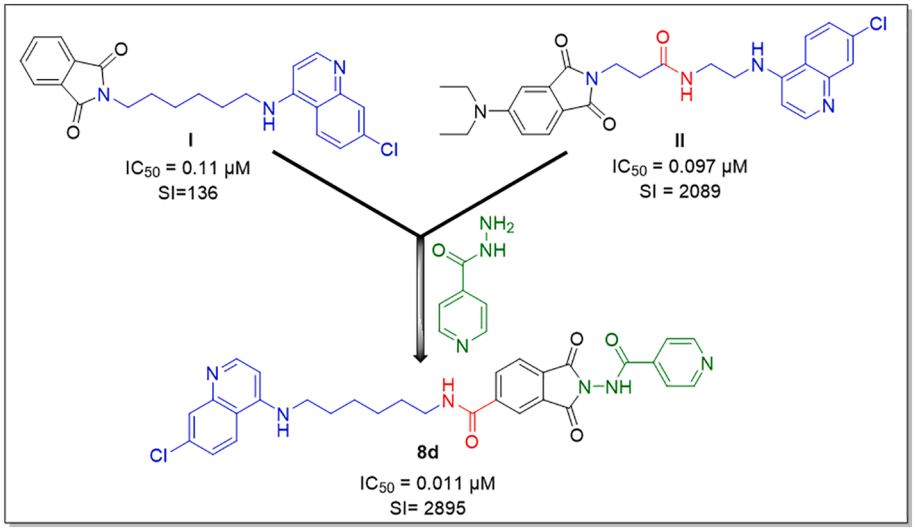


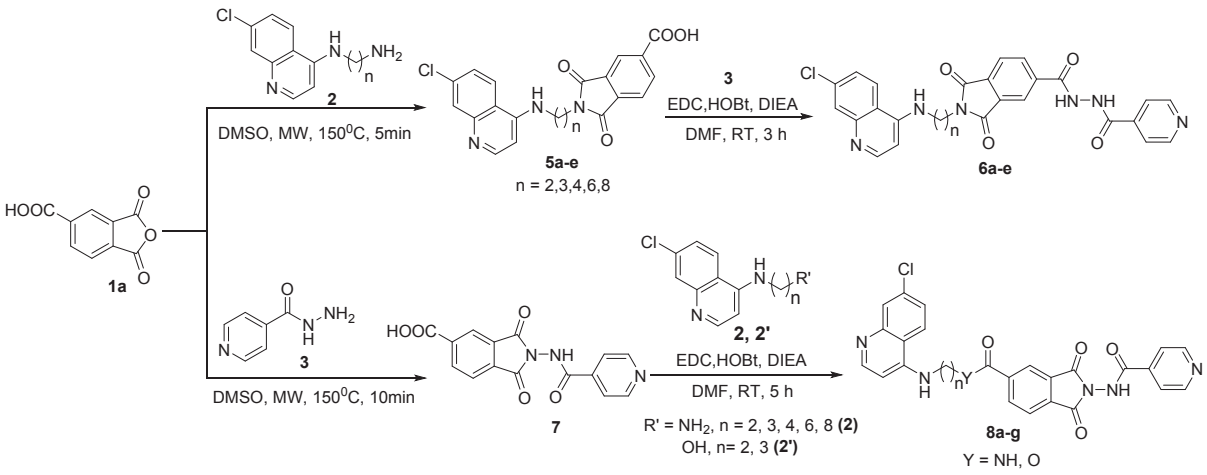
Fig. 3. Design and comparison of the antiplasmodial activity of most potent compound **8d** with previously reported scaffolds **I** and **II**.

anti-plasmodial activities of quinoline-isoniazid hybrids linked *via* phthalimide-core. The length of spacer between the pharmacophores along with their positions around phthalimide core were meticulously altered to study antiplasmodial-Structure-Activity Relationship (SAR). Additionally, mechanistic studies were performed in order to equate the findings with the biological data and to endorse the validity of the hybrid design model.

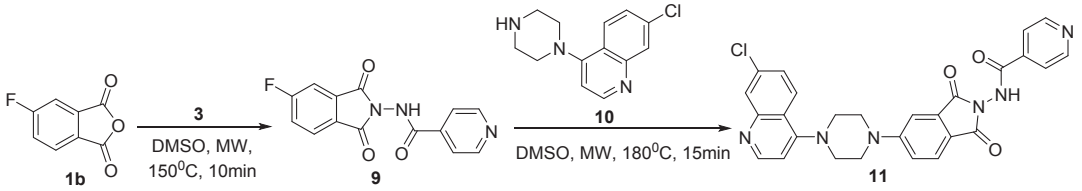
2. Results and discussion

For the synthesis of quinoline-isoniazid-phthalimide triads **6a-e**, the initial treatment of phthalic anhydride **1** with 4-aminoquinoline-diamines **2** in DMSO at 150 °C for 5 min was carried out in a microwave synthesizer to afford the precursors' 4-aminoquinoline-phthalimides **5a-e** followed by their amide coupling with isoniazid (INH) (Scheme 1).[24]

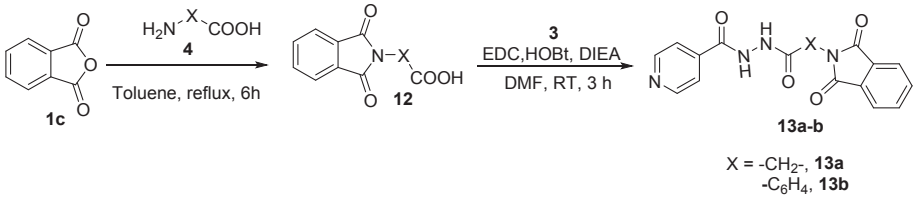
Another set of triads *viz.* quinoline-isoniazid-phthalimides **8a-g** were



Scheme 1. Synthesis of amide-tethered quinoline-isoniazid-phthalimide triads **6a-e** and **8a-g**.



Scheme 2. Synthesis of piperazinyl tethered triads **11.**



Scheme 3. Synthesis of amino acid linked isoniazid-phthalimide conjugates **13a-b**.

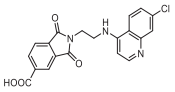
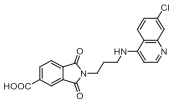
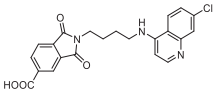
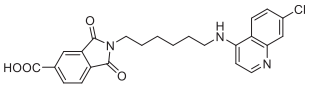
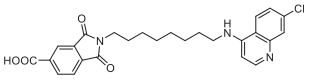
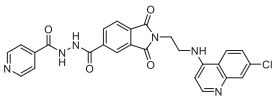
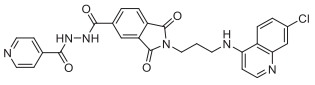
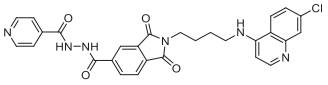
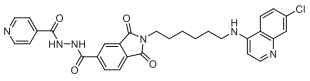
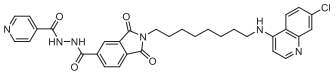
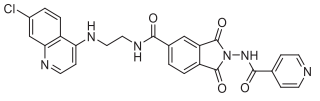
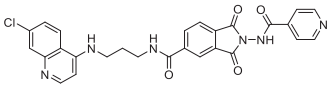
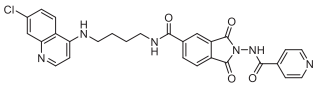
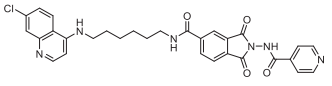
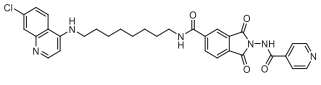
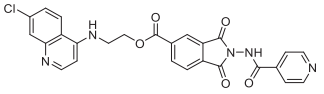
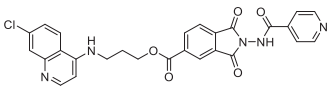
synthesized by initial treatment of substituted phthalic anhydride **1** with INH in microwave to afford INH-phthalimides **7**. EDC promoted amide/ester coupling between **7** and 4-aminoquinoline diamines **2**/quinoline based alcohol **2′** afforded **8a-g** (Scheme 1). Further, a piperazyl analogue **11** was also synthesized so as to access the influence of flexible alkyl chain on anti-plasmodial activity (Scheme 2). Additionally, amide-tethered isoniazid-phthalimides **13a-b** were synthesized to vindicate the antiplasmodial effect of quinoline core in the designed hybrids (Scheme 3). The structures of the synthesized triads were confirmed based on the spectral and analytical evidence. For example, the compound **6b** showed a molecular ion peak $[M + H]^+$ at 529.1334 in its high-resolution mass spectrum (HRMS). The significant features of its ^{1}H NMR spectrum involved the presence of a triplet at δ_H 3.72 because of methylene (N—CH_2—) protons; doublets at δ_H 7.79 (J = 5.6 Hz) and 8.76 (J = 5.2 Hz) corresponding to INH protons along with doublets of quinoline ring protons at δ_H 6.44 (J = 5.5 Hz) and 8.35 (J = 5.4 Hz). The ^{13}C NMR spectrum signals at δ_C 164.6, 164.8, 167.92, and 167.93 correspondings to carbonyl carbons, along with methylenes carbons at δ_C 27.1, 36.4 and 40.6 further validated the assigned structure.

3. Antiplasmodial activity and Structure–Activity relationships (SARs)

The synthesized triads were assayed for their antiplasmodial activities on CQR-W2 strain of *P. falciparum*, while cytotoxicities were evaluated on mammalian Vero cell line. Table 1 enlists the antiplasmodial and cytotoxic activities of synthesized triads using CQ as the reference compound. A closer inspection of Table 1 revealed an interesting SAR with activity showing dependence upon the length of the spacer between the pharmacophores as well as their positions around the phthalimide core. Among the 4-aminoquinoline-phthalimides **5a-e**, the antiplasmodial activity increases with the increase in spacer length, as evident by **5c** (n = 4), **5d** (n = 6) and **5e** (n = 8) exhibiting IC_{50s} of 50.8, 30.2 and 43.2 nM respectively.

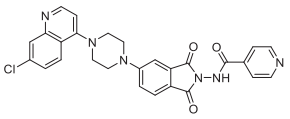
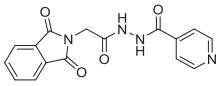
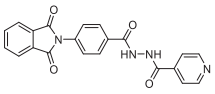
The Inclusion of INH at the free carboxylic acid end did not show any regular trend with some of the synthesized triads, **6c** (n = 4) and **6e** (n = 8) displaying IC_{50s} of 26.3 and 43.3 nM, respectively. The triad **6d,** having hexyl as a spacer was unable to inhibit the growth of *P. falciparum* even at the highest tested concentration, 10 μM. Exchanging the position of quinolone with INH around the phthalimide core led to the triads **8a-e**, where the activities improved considerably with the increase in spacer length. This exchange resulted in the identification of most promising compound of the series, **8d** (n = 6) with an IC_{50} 11 nM. The inclusion of piperazyl-ring in place of alkylamines as in **11**, led to the reduction in antiplasmodial activity. In compounds **8f-g** having an ester linkage, the anti-plasmodial activity decreased substantially thus showing the significance of the amide bond in the present series of synthesized compounds. The compounds **13a** and **13b** without quinoline core, exhibited no antiplasmodial activity, confriming the worth of proposed design of quinoline-isoniazid-phthalimide trio to

Table 1
In vitro antiplasmodial activity (IC_{50}) against the W2 strain of *P. falciparum* and cytotoxicity (IC_{50}) on Vero cells, selectivity index (SI) and ClogP values.

Code	Structure	% Yield	IC_{50} (nM) Antiplasmodial	IC_{50} (μM) Cytotoxicity	SI value	ClogP[a]
5a		81	424.4 ± 12.7	>252.6	601.4	3.78
5b		76	495.7 ± 10.3	241.5	487.1	4.05
5c		77	50.8 ± 4.1	40.1	789.3	4.33
5d		**76**	**30.2 ± 0.5**	**24.3**	**804.63**	**5.34**
5e		79	43.2 ± 5.6	>208.3	4821.7	6.35
6a		81	1402.0 ± 452.5	>194.2	138.5	2.57
6b		76	412.1 ± 9.3	119.1	289.0	2.84
6c		**82**	**26.3 ± 4.8**	**16.5**	**627.3**	**3.11**
6d		78	>10000	127.8	12.7	4.12
6e		79	43.3 ± 7.9	128.5	2967.6	5.13
8a		79	445.0 ± 41.2	64.0	143.8	2.57
8b		77	438.6 ± 39.2	160.7	366.3	2.84
8c		74	252.8 ± 64.5	14.7	58.1	3.11
8d		**76**	**11.5 ± 1.6**	**33.3**	**2895.6**	**4.12**
8e		72	93.5 ± 6.9	>167.0	1786.0	5.13
8f		85	811.5 ± 40.0	>193.8	238.8	3.55
8g		84	3773 ± 168.3	>188.7	50.0	3.82

(*continued on next page*)

Table 1 (*continued*)

Code	Structure	% Yield	IC_{50} (nM) Antiplasmodial	IC_{50} (μM) Cytotoxicity	SI value	ClogP[a]
11		83	1295.5 ± 228.4	>437.8	337.9	3.59
13a		83	>10000	>308.3	30.8	0.14
13b		85	>10000	>258.8	25.8	0.41
CQ		–	141.9 ± 0.7			5.00

[a] ClogP calculated from molinspiration.[25]

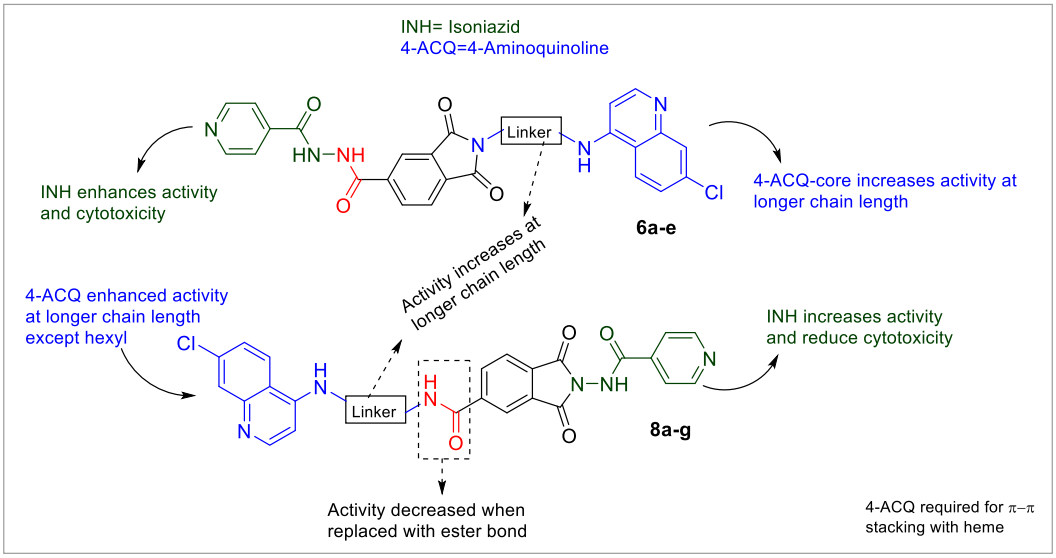


Fig. 4. Generalized antiplasmodial SAR of the synthesized triads **6a-e** and **8a-g**.

evoke antiplasmodial activity. The inclusion of INH at C5 of phthalimide improved antiplasmodial activity up to hundred folds if we compare the activity of currently synthesized most active analog (**8d**) with the one report earlier (**I-II**) (Fig. 3).[21]

The cytotoxicity of the synthesized compounds was assessed in order to confirm their inherent antiplasmodial activities. As evident from Table 1, most of the scaffolds with promising antiplasmodial activities were not cytotoxic and exhibited selectivity indices ranging from 627 to 4821.

The general antiplasmodial SAR/cytotoxicity of the synthesized triads is elucidated in Fig. 4.

4. Mechanistic insights

CQ is a diprotic weak base. Its accumulation in the parasite can be explained by trapping of the positively-charged CQH^{2+} inside the acidic digestive vacuole. In unprotonated form, it passes through the membranes of the infected erythrocyte and moves down the pH gradient to

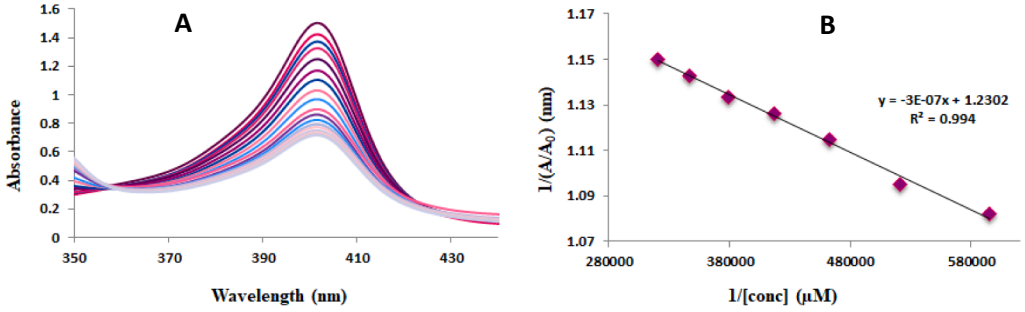


Fig. 5. (A) Change in absorbance on titration of monomeric heme with compound **8d** at pH 7.4; (B) (Inset: plot of A402 nm vs. concentration of **8d**).

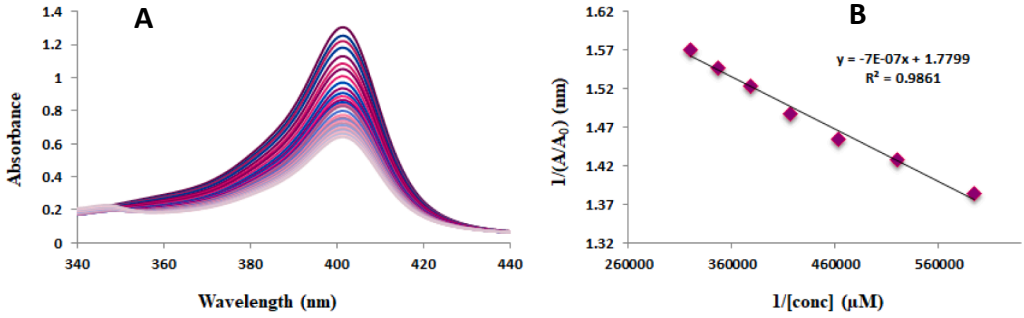


Fig. 6. (A) Change in absorbance on titration of monomeric heme with compound **8d** at pH 5.6; (B) (Inset: plot of A402 nm vs. concentration of **8d**).

Table 2
Binding constants (log *K*) for **8d** and **CQ**.

Compound	Monomeric Heme log *K*	
	pH 5.6 (MES Buffer)	pH 7.4 (HEPES Buffer)
8d	6.39	6.66
CQ	5.18	5.10

accumulate in the acidic food vacuole (pH 5–5.2). Once protonated inside the vacuole; it becomes membrane-impermeable and starts accumulating. This process is based on pK_as and ClogP of CQ.[25] The reported ClogP value of CQ (free base) is 5.06, while the calculated ClogP of the promising compounds range from 3.11 to 6.35. Under physiological conditions, ClogP value further decreases, which is entirely suitable from the viewpoint of bioavailability.[26]

Blocking hemozoin formation is critical for the heme-detoxification process in malarial parasites and it is proposed that compounds that exhibit high affinity for heme may help to achieve the goal. To assess the mode of action of synthesized scaffolds, heme binding studies were performed with **8d**. Binding stoichiometry was established using the method described in the literature.[27] A band at 402 nm was observed for a solution of hemin in 40% DMSO in water at pH 5.6 (0.02 M MES buffer) and pH 7.4 (0.02 M HEPES buffer) confirm the presence of monomeric heme at both the pH values. Compound **8d** (0–18 μM, 40% DMSO) was titrated with the monomeric heme (12 μM) at pH of parasite's food vacuole (pH 5.6) and physiological pH (pH 7.4). This has resulted in a substantial decrease in the absorbance, with no shift in the absorption maximum (Figs. 5 and 6); indicating the interaction of **8d** with heme. Solvent (40% DMSO) had no effect on the binding of **8d** with heme at either pH (Fig. S3, Supplementary Information). The binding constants (Table 2) were calculated by analyzing the titration curves using HypSpec, a nonlinear least-squares fitting program. For comparison purposes, titrations of CQ with heme were performed under same conditions, and binding constants were calculated (Fig. S1-2, Supplementary Information). As evident, the binding constants for the complexes formed between monomeric heme and compound **8d** were better than CQ (Table 2).

Additionally, HRMS analysis of an equimolar of hemin chloride and **8d** showed a molecular ion peak at 1185.6672 Da (Fig. 7), corresponding to the molecular formula $C_{64}H_{59}ClFeN_{10}O_8$, verifying the formation of a 1:1 complex.

In conclusion, the present paper describes the synthesis and antiplasmodial activities of quinoline-isoniazid-phthalimides on W2 strain (CQ-R) of *P. falciparum*. The synthesized second generation (tri-pharmacophore) inhibitors were rationally designed from previously reported first generation (bi-pharmacophore) inhibitors and resuted in the gain in potency. Most of the triads reported herein showed good to excellent activities with the most potent and non-cytotoxic scaffold **8d** exhibiting ~12-fold more potency than the standard drug CQ. Heme-binding studies further delineate the mechanism of action of synthesized triads. Further, the merits and demerits of tri-pharmacophore approach especially its cross-resistance on CQ-Susceptible (CQ-S) strain will be assessed and communicated.

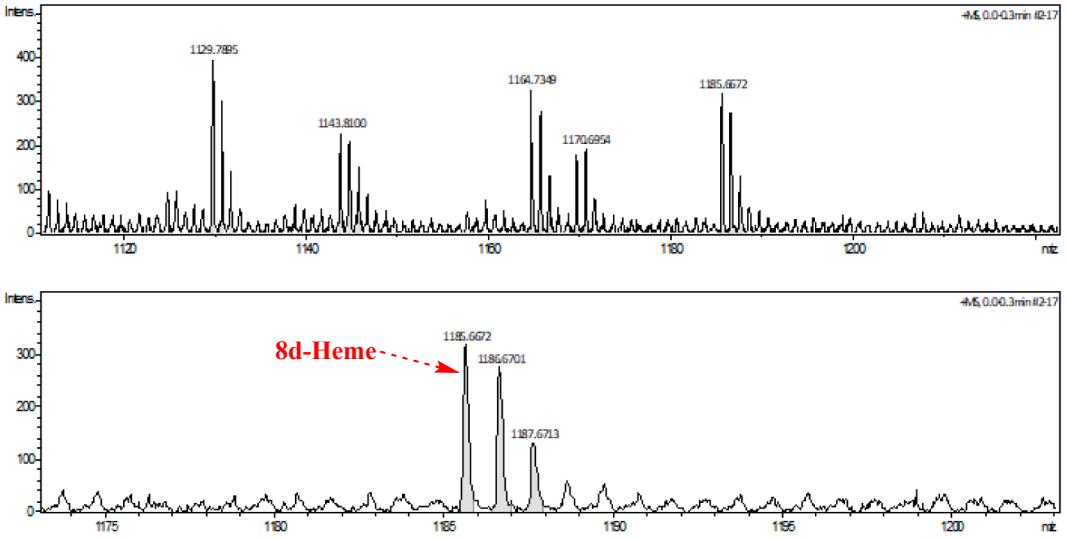


Fig. 7. The solution phase spectra of **8d** (5 μmol) upon addition of monomeric heme (5 μmol) in 40% DMSO-water solution.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2021.116159.

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