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Original article

The design, synthesis, *in silico* ADME profiling, antiplasmodial and antimycobacterial evaluation of new arylamino quinoline derivatives

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ABSTRACT

A series of new arylamino quinoline derivatives was designed based on the quinine and mefloquine scaffolds and evaluated *in vitro* for antiplasmodial and antimycobacterial activities. A number of these compounds exhibited significant activity against the drug-sensitive 3D7 and drug-resistant K1 strains of *Plasmodium falciparum*. Furthermore, two compounds, **4.12b** and **4.12d**, also showed 94 and 98% growth inhibitory activity against non-replicating and replicating *Mycobacterium tuberculosis* strains, respectively.

1. Introduction

Malaria and tuberculosis (TB) are ancient diseases that continue to have devastating impact on mankind, killing over 2.5 million people annually [1]. The recent widespread emergence of multi-drug resistant (MDR) strains of *Plasmodium falciparum* and *Mycobacterium tuberculosis* to clinically available drugs puts further impetus to the urgent need for the discovery of new and effective antimalarial and anti-TB agents with novel mechanisms of action. The TB problem is further exacerbated by extensively drug-resistant (XDR) and totally drug-resistant (TDR) forms [1b]. Compounds containing the quinoline scaffold exhibit a wide-spectrum of biological actions, including antiviral [2], anticancer [3], antibacterial [4], antifungal [5] and anti-inflammatory activities [6]. The diarylquinoline drug, TMC 207 (**1**) (Fig. 1), currently in phase IIB TB clinical trials, is active against drug-sensitive and drug-resistant *M. tuberculosis*, and has a bactericidal effect against dormant tubercle *bacilli* [7,8]. Moreover, this compound functions by inhibiting ATP synthase subunit C, an energy source for the bacterium [9], thus exhibiting a new mechanism of action. The majority of the quinoline-based antimalarial drugs, including the arylamino alcohols, have been shown to possess moderate anti-TB activity [10–12].

Members of the arylamino alcohol family of quinolines, which includes quinine (**2**) and mefloquine (**3**), possess potent activity against multi-drug resistant *P. falciparum* [13]. The mechanism of action of these drugs against the plasmodial parasite is not clearly understood. However, recent studies [14,15] suggest that these compounds exert their activity through (i) π-stacking of the quinoline ring with the porphyrin ring of haeme moieties (green), (ii) coordination with the iron centre of haeme *via* alkoxide formation on the benzylic alcohol (red), and (iii) intermolecular hydrogen-bonding interactions with the propionate side-chain of haeme (blue) (Fig. 2; for interpretation of the references to colour in this figure, the reader is referred to the web version of this article).

Recently, Egan and co-workers described the coordinating ability of various nitrogen donor ligands such as imidazoles, pyridines and amines, which contain sp^2 hybridized nitrogen(s), with haeme [15].

Abbreviations: ADME, adsorption, distribution, metabolism and excretion; ATP synthase, adenosine triphosphate synthase; CQ, chloroquine; IC_{50}, 50% inhibitory concentration; MIC_{90}, 90% minimum inhibitory concentration; MABA, microplate Alamar blue assay; MCR, multi-component reactions; LORA, low oxygen recovery assay; PLS, partial least square; SAR, structure activity relationship; $TMSN_3$, trimethylsilane azide.

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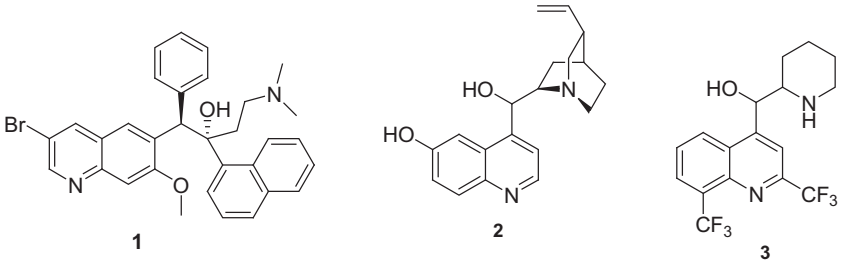


Fig. 1. TMC 207 (**1**), quinine (**2**) and mefloquine (**3**).

The above studies prompted us to investigate whether the introduction of *N*-donor atoms on arylamino quinolines enhances antiplasmodial and/or antimycobacterial activity. In designing the new arylamino quinoline derivatives, the *O*-donor hydroxyl group was replaced with an *N*-donor tetrazole ring that contains sp^2 hybridized nitrogen atoms, while the heterocyclic ring systems containing a basic nitrogen in quinine and mefloquine were in turn replaced by various tertiary amines (Fig. 3). The ability of the tetrazole ring to coordinate with the iron centre of haeme was exploited by Roman et al. [16] in the design of haeme oxygenase inhibitors, and by Adachi et al. [17] in ligand binding studies of tetrazole–myoglobin complexes, justifying the use of this heterocyclic system in our work. The substituent on the tetrazole ring was limited to the *t*-butyl isocyanide (a cleavable isocyanide) and hydrogen atom, the result of the de-*tert*-butylation of the former.

Herein, we describe the synthesis, *in silico* ADME profiling and biological evaluation of a series of new arylamino quinoline derivatives.

2. Results and discussion

2.1. Synthesis

The first step in the synthesis of the designed arylamino quinoline derivatives involved the respective synthesis of the quinine and mefloquine nuclei, *i.e.* 6-methoxyquinoline-4-carbaldehyde (**4.8**) and 2,8-bis(trifluoromethyl)quinoline-4-carbaldehyde (**4.11**). Preparation of **4.8** (Scheme 1) commenced with the four-step synthesis of 4-bromo-6-methoxyquinoline (**4.7**) according to the procedure described by Daines et al. [18]. Treatment of **4.7**, and 4-bromo-2,8-*bis*(trifluoromethyl)quinoline prepared from commercially available alcohol precursor, with 2-equivalents of *n*-BuLi at −78 °C and subsequent formylation by DMF to afford the corresponding aldehydes **4.8** and **4.11** in 86 and 29% yields, respectively [19].

With the desired nuclei (**4.8** and **4.11**) in hand, the modified $TMSN_3$-Ugi MCR procedure described by Dömling et al. [20] and Mayer et al. [21] was followed. The quinoline aldehydes (**4.8** and **4.11**) were allowed to react at ambient temperature with various commercially available secondary amines and *t*-butyl isocyanide in the presence of $TMSN_3$ in anhydrous MeOH for 24 h to obtain the desired target compounds, **4.12a**–**f** and **4.13a**–**b**, in low to excellent yields after column chromatographic purification. Post-modification (de-*tert*-butylation) of these compounds then furnished the de-*tert*-butylated compounds, **4.14a**–**f**, in low yields after purification (Scheme 2, Table 1). The purity of all synthesized compounds was determined to be >95% by HPLC. Post-modification of the mefloquine derivatives was not attempted due to the insufficient amounts obtained of the precursor compounds. All the intermediates and target compounds were characterized fully by analytical and spectroscopic techniques.

2.2. In silico profiling

The small series of the synthesized arylamino quinoline derivatives was profiled *in silico* for various physico-chemical properties of interest such as aqueous solubility, metabolic stability, and blood–brain barrier (BBB) permeation using Volsuf+ software [22]. Mefloquine and its derivatives accumulate in the central nervous system (CNS) [23], while quinine has been shown to have dose-related CNS effects following excessive infusion or from accumulation following oral administration [24]. Therefore, designing compounds with reduced permeation through the BBB is likely of importance in avoiding adverse CNS effects. Figs. 4 and 5 show predicted aqueous solubility (log S) of arylamino quinoline derivatives plotted against the predicted *n*-octanol–water partition coefficient (log D) at pH 5.0 and 7.5, and 2D PLS plots of metabolic stability and BBB permeation, respectively. In the 2D PLS plots the blue and the red zones indicate good and poor predicted properties, respectively, while the block dots represents a dataset of compounds that the program is built on [25] (For interpretation of the references to colour, the reader is referred to the web version of this article.). At both pH 5 and 7.5, the majority of the de-*tert*-

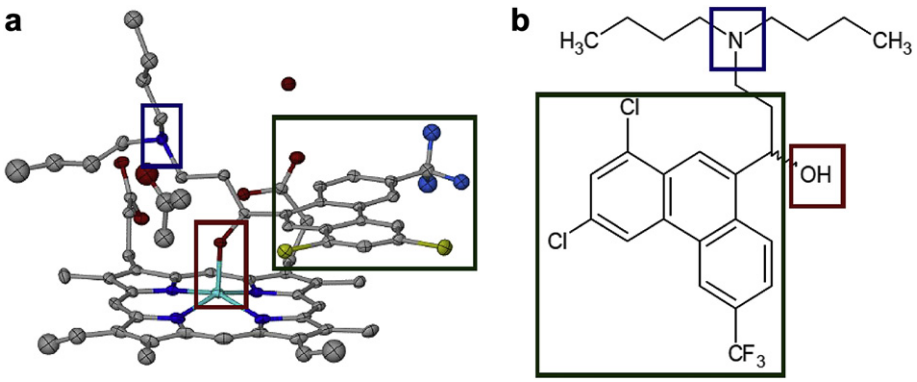


Fig. 2. (a) Crystal structure of the haeme-halofantrine complex; and (b) highlighted halofantrine structural features responsible for the interaction with the haeme (reproduced from Ref. [14]).

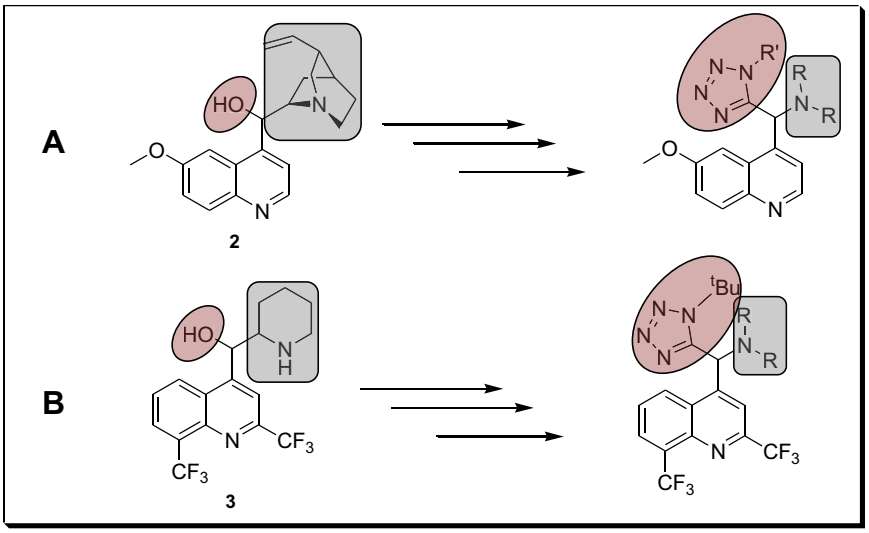
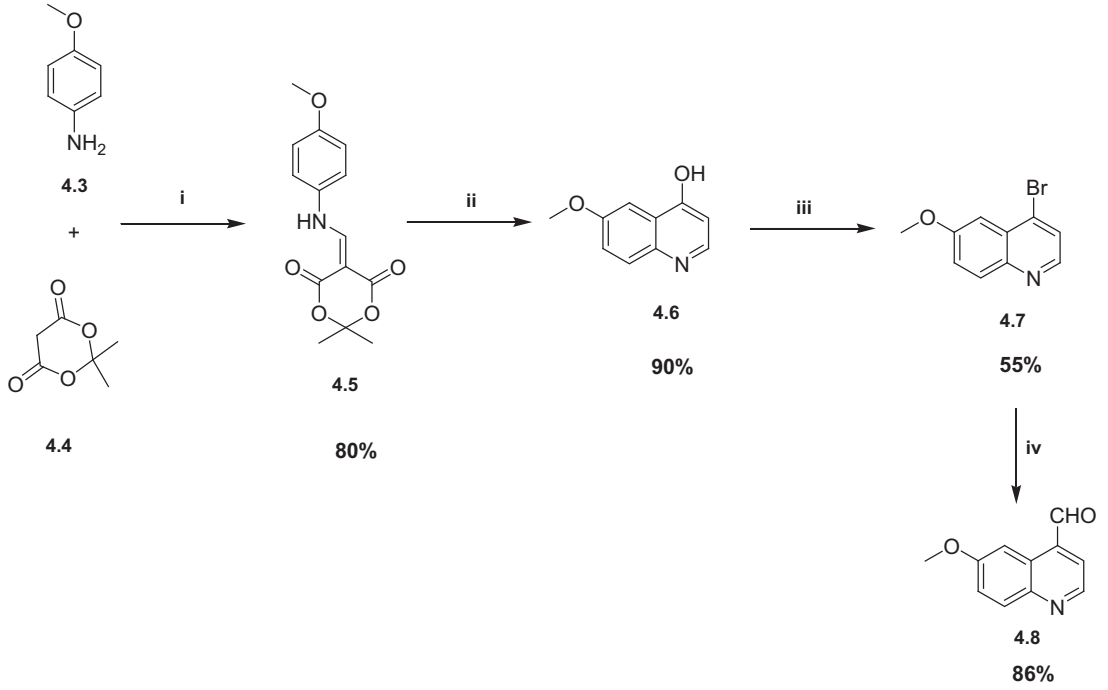


Fig. 3. Substructure replacement in the design of quinine- and mefloquine-based target compounds.

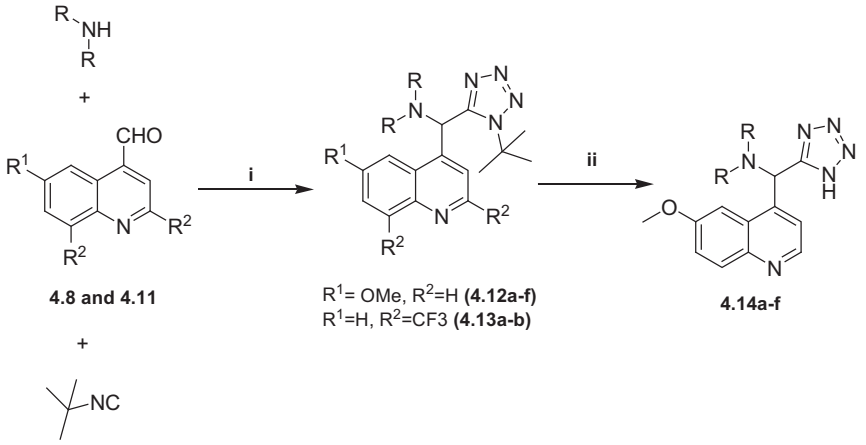
butylated quinine derivatives were predicted to be more soluble than quinine, while the *t*-butyl protected analogues were predicted to be less so (Fig. 4). This was expected, since unsubstituted tetrazoles are known to exhibit amphoteric characteristics [26]. Mefloquine was predicted to be more soluble than its two derivatives (**4.13a** and **4.13b**) but less soluble than quinine at both pHs (Fig. 4). This was also anticipated, since mefloquine and its derivatives are more lipophilic than quinine. Furthermore, the de-*tert*-butylated derivatives were predicted to be more metabolically stable compared to quinine and the *t*-butyl protected analogues (Fig. 5). However, the metabolic stability of mefloquine and its derivatives could not be reliably quantified, as these fell outside the 99% confidence interval [27], *i.e.* outside the solid ellipsoid. With regards to BBB permeation, mefloquine, quinine and its *t*-butyl protected derivatives were predicted to have higher, and the de-*tert*-butylated quinine derivatives to have lower permeation (Fig. 5). These *in silico* predictions are consistent with the observed CNS effects caused by mefloquine and quinine.

2.3. Biological evaluation

Synthesized target compounds were also evaluated for antiplasmodial activity against chloroquine (CQ)-sensitive (3D7) and CQ-resistant (K1 and W2) strains of *P. falciparum*, and for antimycobacterial activity against replicating and non-replicating cultures of *M. tuberculosis* $H_{37}Rv$. It is important to note that for comparison purposes only one of the de-*tert*-butylated compounds (**4.14f**) was evaluated for its biological activity. The most active antiplasmodial compound in this series, **4.12f** ($IC_{50} = 1.228$ μM against the K1 strain), was 60 times less active than quinine, and the quinine derivatives appeared to be generally more active than the two mefloquine derivatives (**4.13a**–**b**) (Table 2). Against the W2



Scheme 1. Reagents and conditions: (i) triethyl orthorformate, EtOH, reflux, 4 h; (ii) Dowtherm A, 250 °C, 20 min; (iii) PBr_3, DMF, N_2, 2 h, rt; (iv) Et_2O, *n*-BuLi, DMF, −78 °C, 3 h.



Scheme 2. Reagents and conditions: (i) $TMSN_3$, MeOH, 26 °C, 24 h; (ii) neat 32% HCl, 120 °C, 8–12 h.

strain, none of the tested compounds exhibited significant activity. The compounds were more active against the CQ-sensitive 3D7 strain when compared to the two resistant strains, and the most active of these, **4.12d** ($IC_{50} = 0.647$ μM), was about 900-fold less active than quinine. With regards to antimycobacterial activity, the majority of the compounds did not exhibit activity against the drug-sensitive H_{37}Rv *M. tuberculosis* strain at the highest tested concentrations (MIC_{90} >128 and >160), except for compound **412b**, which inhibited 94% ($MIC_{90} = 123.2$ μM) of non-replicating bacteria and **4.12d**, which showed 98% inhibition ($MIC_{90} = 92.5$ μM) of replicating bacteria (Table 2). The lack of antimycobacterial activity exhibited by the majority of the compounds is not surprising considering the fact that Kozikowski et al. [28] observed in their SAR studies that the replacement of the hydroxyl group of 4-quinoline methanols was accompanied by complete loss of activity. The predicted metabolically stable compounds (de-*tert*-butylated) showed poor biological activity while the ones that were predicted to be BBB permeable (*t*-butylated) showed notable activity. In terms of predicted solubilities, compounds that were predicted to be less soluble at pH 7.5 exhibited better biological activity than those predicted to be highly soluble.

Furthermore, five compounds were then selected for *in vitro* solubility determination. All these showed comparable kinetic solubility to quinine, with the de-*tert*-butylated compound, **4.14f** (201 μM), slightly more soluble than reference drug at pH 7.5, corroborating *in silico* predictions.

In summary, we have designed and synthesized a small number of new arylamino quinoline tetrazole derivatives using the modified $TMSN_3$-Ugi MCR, and these were screened for antiplasmodial and antimycobacterial activities. The majority of these compounds exhibited modest activity against the 3D7 and K1 strains of *P. falciparum,* with IC_{50} values ranging from 0.647 to 6.737 μM. However, none of these compounds inhibited the growth of the W2 strain. Against the drug-sensitive H_{37}Rv *M. tuberculosis* strain, the majority of these compounds did not exhibit significant activity except for compounds **4.12b** and **4.12d**, which inhibited 94 and 98% of non-replicating and replicating bacteria, respectively.

3. Materials and methods

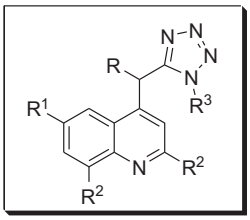
3.1. Chemistry

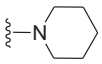
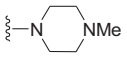
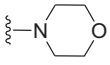
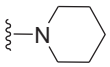
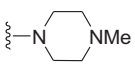
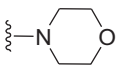
All chemical reagents used were supplied by either Sigma–Aldrich® or Merck and were used without further purification. Unless otherwise stated, all the solvents used were anhydrous and were purchased from Sigma–Aldrich, with the exception of THF and diethyl ether which were dried by appropriate techniques. Chromatographic solvents such as ethyl acetate, dichloromethane and hexane were purchased from Kimix or Protea Chemicals and were distilled prior to use. Column chromatography was carried out using Merck Kieselgel 60: particle size 70–230 mesh as a stationary phase. Analytical TLC was carried out using Merck PF_{254} aluminium-packed pre-coated silica gel plates and visualized under UV light or iodine vapour. Melting points were determined on a Reichert–Jung Thermovar hot-stage microscope and are uncorrected. Low-resolution mass spectra were obtained by flow-injection (5 mM NH_4 formate pH 3 in H_2O:ACN, no column used) on an AB SCIEX 4000 QTRAP Hybrid triple quadrupole linear ion trap mass spectrometer, coupled with an Agilent 1200 Rapid Resolution (600 bar) HPLC system consisting of a binary pump, degasser, auto-sampler and temperature controlled column compartment. Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer in the 4000–450 cm^{-1} range, with samples either as dichloromethane solution or as KBr discs. NMR spectra were recorded on Bruker 400 MHz or Varian Unity 400 MHz and/or Varian Mercury 300 MHz spectrometers, all chemical shifts are reported in ppm and were referenced using solvent signals (2.50 and 39.4 ppm for DMSO-d_6 and 7.26 and 77.0 ppm for $CDCl_3$). Chemical shifts (δ) are recorded in parts per million (ppm). Coupling constants, *J*, are measured in Hertz (Hz) and rounded off to one decimal place. Abbreviations used in the assignment of the ^{1}H NMR spectra are as follows: br (broad), d (doublet), dd (doublet of doublets), m (multiplets), s (singlet) and t (triplet). ^{13}C NMR chemical shifts are listed without assignment to specific carbon atoms. Purity was determined by HPLC, and all compounds were confirmed to have purity >95%. Sample solutions for purification were prepared at *ca.* 100 mg/mL in 50% methanol. Injection volumes ranged between 50 μL and 1 mL, the mobile phase flow rate was 20 mL/min for all purifications and the column heater was set at 30 °C. A mobile phase gradient was used, where mobile phase A, an aqueous solution of 0.1% formic acid, was mixed online with mobile phase B, a 0.1% formic acid solution in methanol.

3.1.1. General procedure for preparation of compounds ***4.12*** *and* ***4.13***

Aldehydes **4.8** and **4.11** (1.6 mmol) with various amines (2.12 mmol) were stirred in anhydrous methanol at 26 °C for 5 min. Thereafter, $TMSN_3$ (2.12 mmol) was added, followed by the addition of *tert*-butyl isocyanide (2.12 mmol) and the resulting mixture

Table 1
Yields, melting points and HPLC purity of the target compounds.



Code	R	R^1	R^2	R^3	Yield [%]	HPLC purity [%]	Melting point [°C]
4.12a		OMe	H	Bu^t	65	95.2	101–103
4.12b		OMe	H	Bu^t	80	99	118–121
4.12c		OMe	H	Bu^t	46	96.6	–
4.12d		OMe	H	Bu^t	87	95.5	117–119
4.12e		OMe	H	Bu^t	56	98.9	140–144
4.12f		OMe	H	Bu^t	75	93.8	110–112
4.13a		H	CF_3	Bu^t	22	98.9	171–173
4.13b		H	CF_3	Bu^t	12	95.3	76–78
4.14a		OMe	H	H	33	95.8	159–162
4.14b		OMe	H	H	15	96.7	168–171
4.14c		OMe	H	H	13	95.1	211–214
4.14d		OMe	H	H	28	95.2	131–134
4.14e		OMe	H	H	34	95.6	176–179
4.14f		OMe	H	H	21	99.1	137–140

was further stirred for 24 h. On completion of the reaction, the solvent was removed *in vacuo* to afford crude tetrazole products **4.12a**–**f** and **4.13a**–**b**, which were then purified by column chromatography to give the desired compounds with HPLC purity greater than 95%.

*3.1.1.1. (1-Tert-butyl-1H-tetrazol-5-yl)(6-methoxyquinolin-4-yl)-N,N-dimethylmethanamine (**4.12a**).* Yield 65%; white solid; m. p. 101–103 °C, R_f (EtOAc:Hex, 1:1) 0.41; IR ν_{max} (DCM)/cm^{-1} 1621 (Ar C=C), 1374 (N=N), 1318 (C=N), 1278 (C–N), 1230 (C–O Ester); δ_H (400 MHz; $CDCl_3$) 8.64 (1H, d, *J* 4.5 Hz, H2), 8.07 (1H, d, *J* 9.2 Hz, H8), 7.67 (1H, d, *J* 2.7 Hz, H5), 7.43 (1H, dd, *J* 9.2 and 2.7 Hz, H7), 6.89 (1H, d, *J* 4.5 Hz, H3), 6.13 (1H, s, H9), 3.99 (3H, s, OCH_3), 2.48 (6H, s, 2× H10), 1.56 (9H, s, 3× H11); δ_C (101 MHz; $CDCl_3$) 158.4, 152.5, 147.2, 144.8, 140.6, 131.8, 127.9, 122.0, 121.4, 102.6, 61.3, 60.5, 55.5, 41.3 (2C) and 30.1 (3C); MS (ESI) *m*/*z* 341.3 ($M^+ + H$); HPLC purity: 95.2%; $t_{r'} = 6.52$ min.

*3.1.1.2. N-[(1-tert-butyl-1H-tetrazol-5-yl)(6-methoxyquinolin-4-yl) methyl]-N-ethylethanamine (**4.12b**).* Yield 80%; pale-yellow solid; m.p. 118–121 °C, R_f (DCM:MeOH, 19:1) 0.59; IR ν_{max} (DCM)/cm^{-1} 1619 (Ar C=C), 1376 (N=N), 1316 (C=N), 1290 (C–N), 1236 (C–O Ester); δ_H (300 MHz; $CDCl_3$) 8.60 (1H, d, *J* 4.6 Hz, H2), 8.05 (1H, d, *J* 9.2 Hz, H8), 7.86 (1H, d, *J* 2.8 Hz, H5), 7.42 (1H, dd, *J* 9.2 and 2.8 Hz, H7), 6.60 (1H, d, *J* 4.6 Hz, H3), 6.30 (1H, s, H9), 3.98 (3H, s, OCH_3), 2.89 (4H, m, 2×x H10), 1.52 (9H, s, 3× H12), 0.91 (6H, t, *J* 5.4 Hz, 2× H11); δ_C (75 MHz; $CDCl_3$) 158.6, 153.1, 147.2, 145.1, 142.6, 131.7, 127.9, 122.5, 122.4, 102.6, 62.1, 58.6, 55.9, 46.3 (2C), 30.1 (3C) and 15.3 (2C); MS (ESI) *m*/*z* 369.3 ($M^+ + H$); HPLC purity: 99.0%; $t_{r'} = 9.46$ min.

*3.1.1.3. 4-[(1-Tert-butyl-1H-tetrazol-5-yl)(pyrrolidin-1-yl)methyl]-6-methoxyquinoline (**4.12c**).* Yield 46%; thick brown oil; R_f (DCM:MeOH, 19:1) 0.61; IR ν_{max} (DCM)/cm^{-1} 1618 (Ar C=C), 1372 (N=N), 1309 (C=N), 1279 (C–N), 1238 (C–O Ester); δ_H (400 MHz; $CDCl_3$) 8.62 (1H, d, *J* 4.5 Hz, H2), 8.05 (1H, d, *J* 9.2 Hz, H8), 7.90 (1H, d, *J* 2.4 Hz, H5), 7.43 (1H, dd, *J* 9.2 and 2.4 Hz, H7), 6.79 (1H, d, *J* 4.5 Hz, H3), 6.16 (1H, s, H9), 4.03 (3H, s, OCH_3), 3.01 (2H, m, *H10a*), 2.50 (2H, m, *H10b*), 1.59 (9H, s, 3× H12), 1.44 (4H, m, 2× H11); δ_C (101 MHz; $CDCl_3$) 158.2, 152.6, 147.3, 145.0, 140.3, 131.7, 128.0, 122.0, 121.7, 102.7, 62.8, 61.3, 55.5, 50.3 (2C), 30.1 (3C) and 26.8 (2C); MS (ESI) *m*/*z* 367.2 ($M^+ + H$); HPLC purity: 96.6%; $t_{r'} = 7.09$ min.

*3.1.1.4. 4-[(1-Tert-butyl-1H-tetrazol-5-yl)(piperidin-1-yl)methyl]-6-methoxyquinoline (**4.12d**).* Yield 87%; light-brown solid; m.p. 117–119 °C, R_f (DCM:MeOH, 19:1) 0.39; IR ν_{max} (DCM)/cm^{-1} 1617 (Ar C=C), 1374 (N=N), 1314 (C=N), 1260 (C–N), 1241 (C–O Ester); δ_H (400 MHz; $CDCl_3$) 8.65 (1H, d, *J* 4.5 Hz, H2), 8.06 (1H, d, *J* 9.2 Hz, H8), 7.73 (1H, d, *J* 2.2 Hz, H5), 7.42 (1H, dd, *J* 9.2 and 2.2 Hz, H7), 7.06 (1H, d, *J* 4.6 Hz, H3), 6.29 (1H, s, H9), 4.00 (3H, s, OCH_3), 3.14 (2H, m, H*10a*), 2.45 (2H, m, H*10b*), 1.80 (2H, m, H12), 1.73 (4H, m, 2× H11), 1.60 (9H, s, 3× H13); δ_C (101 MHz; $CDCl_3$) 158.3, 153.6, 147.5, 144.8, 140.9, 131.8, 127.7, 121.4 (2C), 102.3, 61.3, 57.2, 55.5, 49.5 (2C), 30.1 (3C), 29.9 and 24.2 (2C); MS (ESI) *m*/*z* 381.5 ($M^+ + H$); HPLC purity: 95.5%; $t_{r'} = 9.50$ min.

*3.1.1.5. 4-[(1-Tert-butyl-1H-tetrazol-5-yl)(4-methylpiperazin-1-yl) methyl]-6-methoxyquinoline (**4.12e**).* Yield 56%; pale-yellow solid; m.p. 140–144 °C, R_f (DCM:MeOH, 19:1) 0.32; IR ν_{max} (DCM)/cm^{-1} 1619 (Ar C=C), 1374 (N=N), 1318 (C=N), 1275 (C–N), 1223 (C–O Ester); δ_H (300 MHz; $CDCl_3$) 8.62 (1H, d, *J* 4.5 Hz, H2), 8.04 (1H, d, *J* 9.2 Hz, H8), 7.81 (1H, d, *J* 2.7 Hz, H5), 7.41 (1H, dd, *J* 9.2 and 2.7 Hz, H7), 6.93 (1H, d, *J* 4.5 Hz, H3), 6.12 (1H, s, H9), 3.99 (3H, s, OCH_3), 3.00 (2H, m, H*10a*), 2.45 (2H, m, H*10b*), 2.38 (2H, m, H*11a*), 2.31 (2H, m, H*11b*), 2.20 (3H, s, H12), 1.56 (9H, s, 3× H13); δ_C (75 MHz; $CDCl_3$) 158.3, 152.4, 147.4, 145.0, 140.0, 131.9, 127.9, 122.3, 121.8, 102.6, 61.4, 61.0, 55.6 (3C), 49.5 (2C), 46.0 and 30.2 (3C); MS (ESI) *m*/*z* 396.1 (M^+); HPLC purity: 98.9%; $t_{r'} = 5.38$ min.

*3.1.1.6. 4-[(1-Tert-butyl-1H-tetrazol-5-yl)(morpholino)methyl]-6-methoxyquinoline (**4.12f**).* Yield 75%; pale-yellow solid; m.p. 110–112 °C, R_f (DCM:MeOH, 19:1) 0.45; IR ν_{max} (DCM)/cm^{-1} 1619 (Ar C=C), 1372 (N=N), 1321 (C=N), 1276 (C–N), 1239 (C–O Ester); δ_H

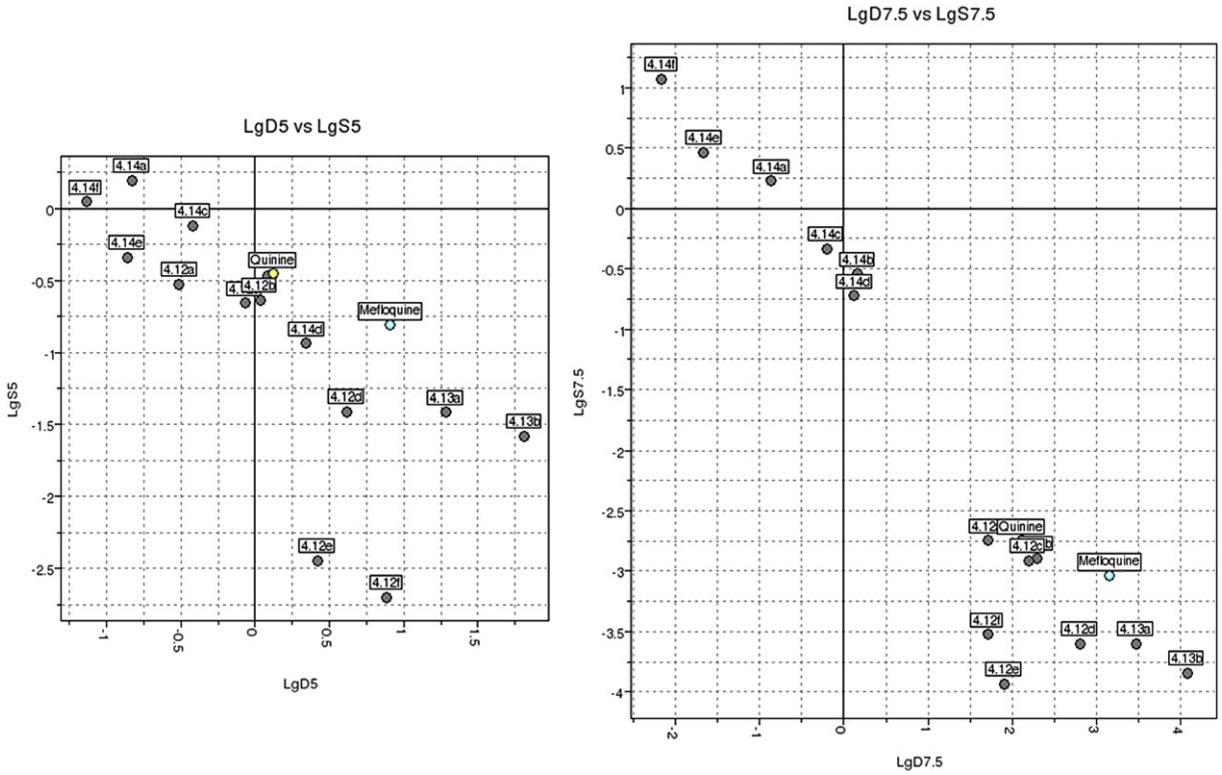


Fig. 4. Plots of predicted aqueous solubility (log S) against *n*-octanol–water partition coefficient (log D) at pH 5.0 and 7.5.

(400 MHz; $CDCl_3$) 8.65 (1H, d, *J* 4.5 Hz, H2), 8.08 (1H, d, *J* 9.2 Hz, H8), 7.83 (1H, d, *J* 2.6 Hz, H5), 7.45 (1H, dd, *J* 9.2 and 2.6 Hz, H7), 6.90 (1H, d, *J* 4.5 Hz, H3), 6.15 (1H, s, H9), 4.02 (3H, s, OCH_3), 3.67 (2H, m, H*11a*), 3.57 (2H, m, H*11b*), 3.06 (2H, m, H*10a*), 2.54 (2H, m, H*10b*), 1.58 (9H, s, 3× H13); δ_C (101 MHz; $CDCl_3$) 158.4, 152.3, 147.3, 145.0, 139.1, 132.0, 127.7, 122.3, 121.6, 102.6, 67.4 (2C), 61.4, 61.2, 55.6, 49.8 (2C) and 30.2 (3C); MS (ESI) *m/z* 383.3 ($M^+ + H$); HPLC purity: 93.8%; $t_{r'} = 8.35$ min.

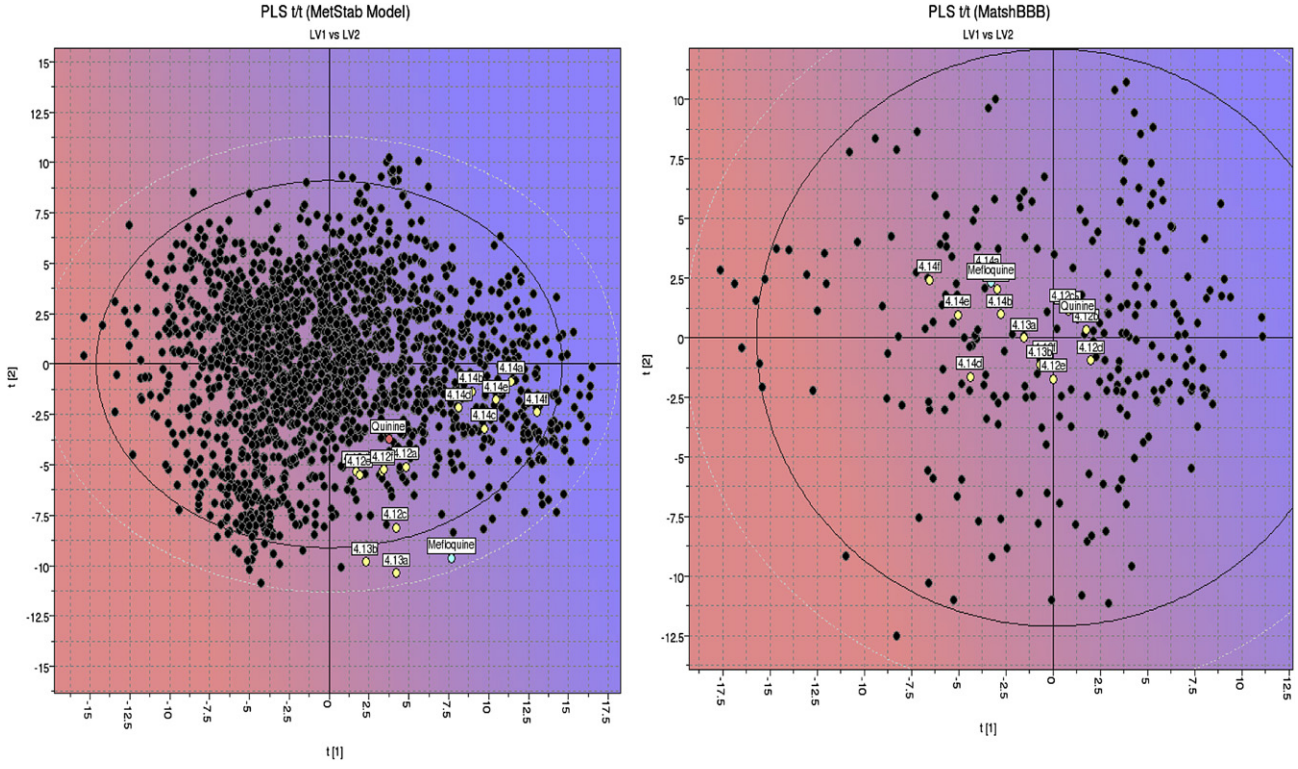


Fig. 5. Plots showing the designed target compounds projected onto PLS models used to predict metabolic stability and blood–brain barrier permeation.

Table 2
In vitro antiplasmodial and antimycobacterial activity of the target compounds.

Product	*P. falciparum* IC_{50} [μM (μg/mL)]			*M. tuberculosis* $H_{37}Rv$ strain				Solubility
				MABA (μM)		LORA (μM)		
	3D7	K1	W2	%Inh	MIC_{90}	%Inh	MIC_{90}	pH 7.4 (μM)
4.12a	1.310	1.310	>10	16	>128	42	>128	189.45
4.12b	2.393	2.393	>10	83	>128	94	123.2	136.84
4.12c	13.84	13.80	>10	24	>128	30	>128	ND
4.12d	0.647	2.633	>10	98	92.5	64	>128	114.44
4.12e	16.790	7.947	8.393	0	>128	0	>128	ND
4.12f	0.980	1.228	>10	0	>128	32	>128	178.54
4.14f	8.625	6.737	>10	0	>128	1	>128	201.86
4.13a	ND	4.525 (2.02)	ND	ND	>160[a]	ND	ND	ND
4.13b	ND	2.318 (1.1)	ND	ND	>160[a]	ND	ND	ND
Quinine	0.0007	0.0204	0.0187	95	119.7	98	122.0	186.68
Mefloquine	–	–	–	–	10	–	–	ND
RMP	–	–	–	100	0.05	98	1.93	ND
INH	–	–	–	92	0.23	64	>128	ND
PA-824	–	–	–	99	0.12	100	3.78	ND
Kanamycin	–	–	–	–	3.125	–	–	ND
Streptomycin	–	–	–	–	0.4	–	–	ND

Antiplasmodial and solubility assays performed in triplicates and antimycobacterial in duplicates; ND = not determined.
[a] Testing was only done on the replicating bacteria at a different laboratory to the one that tested compounds **4.12a**–**f**, **4.14f**.

*3.1.1.7. [2,8-Bis(trifluoromethyl)quinolin-4-yl](tert-butyl-1H-tetrazol-5-yl)-N,N-dimethylmethanamine (**4.13a**).* Yield 22%; white powder; m.p. 171–173 °C, R_f (EtOAc:Hex, 1:1) 0.35; IR ν_{max} (DCM)/cm^{-1} 1602 (Ar C=C), 1423 (N=N), 1314 (C=N), 1271 (C–N), 1090 (C–F); δ_H (400 MHz; $CDCl_3$) 8.70 (1H, d, *J* 8.5 Hz, H7), 8.23 (1H, d, *J* 7.1 Hz, H5), 7.84 (1H, t, *J* 7.9 Hz, H6), 7.40 (1H, s, H3), 6.29 (1H, s, H8), 2.46 (6H, s, 2× H9), 1.62 (9H, s, 3× H10); δ_C (101 MHz; $CDCl_3$) 151.4, 145.2, 144.2, 129.4, 129.3, 129.2, 128.2, 128.1, 127.8, 124.8, 122.0, 118.0, 61.6, 60.3, 41.3 (2C) and 30.2 (3C); MS (ESI) *m*/*z* 447.2 ($M^+ + H$); HPLC purity: 98.9%; $t_{r'} = 8.60$ min.

*3.1.1.8. N-{[2,8-bis(trifluoromethyl)quinolin-4-yl](tert-butyl-1H-tetrazol-5-yl)metyhyl}-N-ethylethanamine (**4.13b**).* Yield 22%; light-brown solid; m.p. 76–78 °C, R_f (EtOAc:Hex, 1:1) 0.35; IR ν_{max} (DCM)/cm^{-1} 1602 (Ar C=C), 1424 (N=N), 1309 (C=N), 1279 (C–N), 1112 (C–F); δ_H (400 MHz; $CDCl_3$) 8.82 (1H, d, *J* 8.6 Hz, H7), 8.23 (1H, d, *J* 7.2 Hz, H5), 7.84 (1H, t, *J* 7.7 Hz, H6), 7.11 (1H, s, H3), 6.43 (1H, s, H8), 2.88 (4H, q, *J* 7.2 Hz, 2× H9), 1.62 (9H, s, 3× H11), 0.93 (6H, t, *J* 7.2 Hz, 2× H10); δ_C (101 MHz; $CDCl_3$) 152.5, 146.6, 143.1, 129.4, 129.3, 129.2, 128.4, 128.0, 127.8, 124.8, 122.1, 118.1, 61.9, 58.4, 45.8 (2C), 30.2 (3C) and 14.7 (2C); MS (ESI) *m*/*z* 475.4 ($M^+ + H$); HPLC purity: 95.3%; $t_{r'} = 8.93$ min.

*3.1.2. General procedure for preparation of compounds (**4.14a**–**f**)*

To the corresponding *tert*-butylated tetrazole **4.12** (0.51 mmol) in a round-bottom flask was added 32% hydrochloric acid (10 ml), and the resulting mixture refluxed at 120 °C for 4–8 h. On complete consumption of the starting material, as shown by TLC, the reaction mixture was allowed to cool to room temperature, water (30 ml) added and the pH adjusted to 12 by the addition of 5% $NaHCO_3$. The basified mixture was then washed with EtOAc (2 × 100 ml), the aqueous layer neutralized to pH 7 by drop-wise addition of 32% HCl acid and allowed to stand in the fume hood overnight. The precipitate which had formed was filtered and washed with cold Et_2O to afford a crude product which was then purified by column chromatography (on silica gel; elution with DCM:MeOH: 25% aqueous NH_4OH; 19:1:0.1) and preparative HPLC to give the desired product (**4.14**) in greater than 95% purity.

*3.1.2.1. (6-Methoxyquinolin-4-yl)-N,N-dimethyl(1H-tetrazol-5-yl)methanamine (**4.14a**).* Yield 33% (8 h); pale-yellow solid; m.p. 159–162 °C, R_f (DCM:MeOH:NH_4OH; 19:1:0.1) 0.12; IR ν_{max} (KBr)/cm^{-1} 1588 (Ar C=C), 1369 (N=N), 1314 (C=N), 1276 (C–O Ester), 1245(C–O Ester); δ_H (400 MHz; DMSO-d_6) 8.65 (1H, d, *J* 4.5 Hz, H2), 7.86 (1H, d, *J* 9.2 Hz, H8), 7.82 (1H, d, *J* 2.8 Hz, H5), 7.76 (1H, d, *J* 4.5 Hz, H3), 7.33 (1H, dd, *J* 9.2 and 2.8 Hz, H7), 5.37 (1H, s, H9), 3.87 (3H, s, OCH_3), 2.14 (6H, s, 2× H10); δ_C (101 MHz; DMSO-d_6) 159.5, 156.4, 147.3, 146.0, 143.9, 130.6, 127.7, 120.9, 120.5, 103.7, 63.3, 55.2 and 43.2 (2C); MS (ESI) *m*/*z* 285.1 ($M^+ + H$); HPLC purity: 95.8%; $t_{r'} = 6.33$ min.

*3.1.2.2. N-ethyl-N-[(6-methoxyquinolin-4-yl)(1H-tetrazol-5-yl)methyl]ethanamine (**4.14b**).* Yield 15% (8 h); yellow solid; m.p. 168–171 C, R_f (DCM:MeOH:NH_4OH; 19:1:0.1) 0.11; IR ν_{max} (KBr)/cm^{-1} 1600 (Ar C=C), 1368 (N=N), 1319 (C=N), 1269 (C–N), 1225 (C–O Ester); δ_H (400 MHz; DMSO-d_6) 8.61 (1H, d, *J* 4.5 Hz, H2), 7.91 (1H, d, *J* 2.8 Hz, H5), 7.86 (1H, d, *J* 9.2 Hz, H8), 7.52 (1H, d, *J* 4.5 Hz, H3), 7.32 (1H, dd, *J* 9.2 and 2.8 Hz, H7), 5.87 (1H, s, H9), 3.85 (3H, s, OCH_3), 2.63 (2H, q, *J* 7.1 Hz, H*10a*), 2.27 (2H, q, J 7.1 Hz, H*10b*), 0.91 (6H, t, *J* 7.1 Hz, 2× H11); δ_C (100 MHz; DMSO-d_6) 159.6, 156.6, 147.8, 146.1, 144.6, 131.1, 127.8, 122.1, 121.2, 104.4, 58.8, 55.8, 44.3 (2C) and 13.5 (2C); MS (ESI) *m*/*z* 313.2 ($M^+ + H$); HPLC purity: 96.7%; $t_{r'} = 7.38$ min.

*3.1.2.3. 6-Methoxy-4-[(pyrrolidin-1-yl)(1H-tetrazol-5-yl)methyl]quinoline (**4.14c**).* Yield 13% (8 h); light-brown solid; m.p. 211–214 °C; R_f (DCM:MeOH:NH_4OH; 19:1:0.1) 0.09; IR ν_{max} (KBr)/cm^{-1} 1579(Ar C=C), 1366 (N=N), 1326 (C=N), 1274 (C–N), 1215 (C–O Ester); δ_H (300 MHz; DMSO-d_6) 8.66 (1H, d, *J* 4.4 Hz, H2), 7.96 (1H, d, *J* 2.6 Hz, H8), 7.84 (1H, d, *J* 9.2 Hz, H5), 7.79 (1H, d, *J* 4.4 Hz, H3), 7.30 (1H, dd, *J* 9.2 and 2.6 Hz, H7), 5.40 (1H, s, H9), 3.86 (3H, s, OCH_3), 2.54 (2H, m, H*10a*), 2.35 (2H, m, H*10b*), 1.65 (4H, m, 2× H11); δ_C (75 MHz; DMSO-d_6) 159.0, 156.2, 147.2, 146.5, 130.3, 130.1, 129.1, 127.2, 120.3, 103.7, 61.9, 58.5, 51.6 (2C) and 23.0 (2C); MS (ESI) *m*/*z* 311.4 ($M^+ + H$); HPLC purity: 95.1%; $t_{r'} = 7.12$ min.

*3.1.2.4. 6-Methoxy-4-[(piperidin-1-yl)(1H-tetrazol-5-yl)methyl]quinoline (**4.14d**).* Yield 28% (6 h); pale-yellow crystalline solid; m.p. 131–134 °C, R_f (DCM:MeOH:NH_4OH; 19:1:0.1) 0.10; IR ν_{max} (KBr)/cm^{-1} 1630 (Ar C=C), 1368 (N=N), 1309 (C=N), 1251 (C–N), 1223 (C–O Ester);δ_H (300 MHz; DMSO-d_6) 8.62 (1H, d, *J* 4.5 Hz, H2), 7.99 (1H, d, *J* 2.8 Hz, H5), 7.85 (1H, d, *J* 9.2 Hz, H8), 7.69 (1H, d, *J* 4.5 Hz, H3), 7.31 (1H, dd, *J* 9.2 and 2.8 Hz, H7), 5.43 (1H, s, H9), 3.88

(3H, s, OCH_3), 2.45 (2H, m, H*10a*), 2.25 (2H, m, H*10b*), 1.44 (4H, m, 2× H11), 1.35 (2H, m, H12); δ_C (101 MHz; DMSO-d_6) 159.2, 156.1, 147.1, 145.9, 143.9, 130.3, 127.8, 120.8, 120.4, 104.0, 63.5, 55.0, 51.6 (2C), 25.8 (2C) and 24.0; MS (ESI) *m*/*z* 325.1 ($M^+ + H$); HPLC purity: 95.2%; $t_{r'} = 6.98$ min.

*3.1.2.5. 6-Methoxy-4-[(4-methylpiperazin-1-yl)(1H-tetrazol-5-yl) methyl]quinoline (**4.14e**).* Yield 34% (4 h); cream-coloured solid; m.p. 176–179 °C, R_f (DCM:MeOH:NH_4OH; 19:1:0.1) 0.12; IR ν_{max} (KBr)/cm^{-1} 1590 (Ar C═C), 1368 (N═N), 1299 (C═N), 1259 (C–N), 1219 (C–O Ester);δ_H (400 MHz; DMSO-d_6) 8.60 (1H, d, *J* 4.5 Hz, H2), 7.96 (1H, d, *J* 2.5 Hz, H5), 7.81 (1H, d, *J* 9.2 Hz, H8), 7.68 (1H, d, *J* 4.5 Hz, H3), 7.27 (1H, dd, *J* 9.2 and 2.5 Hz, H7), 5.36 (1H, s, H9), 3.84 (3H, s, OCH_3), 2.46 (2H, m, H*10a*), 2.39 (2H, m, H*10b*), 2.26 (4H, m, 2× H11), 2.09 (3H, s, H12); δ_C (100 MHz; DMSO-d_6) 159.5, 156.3, 147.4, 145.6, 144.0, 130.5, 127.7, 120.9, 120.8, 103.9, 63.2, 55.3, 55.0 (3C), 50.5 and 45.6; MS (ESI) *m*/*z* 340.4 ($M^+ + H$); HPLC purity: 95.6%; $t_{r'} = 7.22$ min.

*3.1.2.6. 6-Methoxy-4-[morpholino(1H-tetrazol-5-yl)methyl]quinoline (**4.14f**).* Yield 21% (8 h); light-brown solid; m.p. 137–140 °C, R_f (DCM:MeOH:NH_4OH; 19:1:0.1) 0.23; IR ν_{max} (KBr)/cm^{-1} 1598 (Ar C═C), 1368 (N═N), 1330 (C═N), 1273 (C–N), 1220 (C–O Ester);δ_H (300 MHz; DMSO-d_6) 8.64 (1H, d, *J* 4.5 Hz, H2), 8.03 (1H, d, *J* 2.8 Hz, H5), 7.85 (1H, d, *J* 9.2 Hz, H8), 7.74 (1H, d, *J* 4.5 Hz, H3), 7.32 (1H, dd, *J* 9.2 and 2.8 Hz, H7), 5.44 (1H, s, H9), 3.90 (3H, s, OCH_3), 3.56 (4H, m, 2× H11), 2.44 (2H, m, H*10a*), 2.29 (2H, m, H*10b*); δ_C (75 MHz; DMSO-d_6) 158.9, 156.3, 147.2, 145.1, 144.0, 130.4, 127.7, 121.0, 120.6, 104.0, 66.4 (2C), 63.4, 55.2 and 51.2 (2C); MS (ESI) *m*/*z* 327.3 ($M^+ + H$); HPLC purity: 99.1%; $t_{r'} = 6.66$ min.

3.2. Biology

3.2.1. In vitro antiplasmodial evaluation

The *in vitro* antiplasmodial activities of compounds were evaluated against 3D7, K1 and W2 strains of *P. falciparum*. For the 3D7 and K1 strains, the cultures are naturally asynchronous (65–75% ring stage) and were maintained in continuous log phase growth in RPMI 1640 supplemented with 5% washed human A+ erythrocytes, 25 mM HEPES, 32 nM $NaHCO_3$ and AlbuMAXII (lipid rich bovine serum albumin) (GIBCO, Grand Island, NY) (CM). The assays were conducted at 37 °C under an atmosphere of 5% CO_2 and 5% O_2, with a balance N_2. Furthermore, these assays were performed in various stages, i.e. the primary and secondary screens, using sterile 96-well microtitre plates, each plate containing 100 μl of parasite culture (0.5% parasitemia, 2.5% haematocrit). The test compounds were tested in triplicate and parasite growth compared to the control and blank (uninfected erythtocytes) wells. After 24 h of incubation at 37 °C, 3.7 Bq of [^{3}H]hypoxanthine was added to each well. Cultures were incubated for a further 24 h before they were harvested onto glass-fibre filter mats. The radioactivity was counted using a Wallac Microbeta 1450 scintillation counter. The results were recorded as counts per minute (CPM) per well at each compound concentration, control and blank wells. Percentage inhibition was calculated from comparison to blank and control wells, and IC_{50} values calculated using GraphPad Prism 4.0.

3.2.1.1. Primary screen. The primary screen used the 3D7 strain. The test compounds were tested at 6 concentrations (30, 10, 3, 1, 0.3, and 0.1 μg/mL). Compounds that did not affect parasite growth at 10 μg/mL are considered inactive, between 10 and 1 μg/mL are designated as partially active and if <1 μg/mL the compound was classified as active and was further evaluated by threefold serial dilutions in a repeat test.

3.2.1.2. Secondary screen. In this screen both 3D7 and K1 were used. The test drug was diluted threefold over at 12 different concentrations with an appropriate starting concentrations based on the primary screen. The IC_{50} values were determined by sigmoidal dose response analysis using Microsoft XLFit (IDBS, UK). For each assay, the IC_{50} values for each parasite line were determined against CQ and other standard compounds appropriate for the assay [29].

3.2.1.3. For the W2 assay. The protocol to this assay is as described by Rosenthal et al. [30]. The W2 (CQ-resistant) strain of *P. falciparum* (1% parasitemia, 2% hematocrit) were cultured in 0.5 ml of medium in 48-well culture dishes. Stock solutions of inhibitors (10 mM) in DMSO were added to cultured parasites to a final concentration of 20 μM. From the 48-well plates, 125 μM of culture was transferred to two 96-well plates (duplicates). Serial dilutions (1%) of inhibitors were made to final concentrations of 10 μM, 2 μM, 0.4 μM, 80 nM, 16 nM and 3.2 nM. Cultures were maintained at 37 °C for 2 days after which the parasites were washed and fixed with 1% formaldehyde in PBS. After 2 days parasitemia was measured by flow cytometry using the DNA stain YOYO-1 as a marker of cell survival.

3.2.2. In vitro antimycobacterial evaluation

The MICs for *in vitro* antimycobacterial activities were determined using *M. tuberculosis* H_{37}Rv strain in MABA and LORA assays according to the published procedure [31,32]. Rifampin (RMP), isoniazid (INH), PA-824, kanamycin and streptomycin were used as positive controls.

3.2.2.1. MABA. Briefly, all compounds were evaluated for MIC vs. *M. tuberculosis* H_{37}Rv (ATCC 27294) using the microplate Alamar Blue assay (MABA) as previously described [31] except that we now use 7H12 media (3) (instead of 7H9 + glycerol + casitone + OADC). In the case of compounds exhibiting significant background fluorescence, luciferase reporter strains of *M. tuberculosis* H_{37}Rv were utilized as well as measurement of intracellular adenosine triphosphate. Cultures were incubated in 200 μl medium in 96-well plates for 7 days at 37 °C. Alamar Blue and Tween 80 are added and incubation continued for 24 h at 37 °C. Fluorescence is determined at excitation/emission wavelengths of 530/590 nm, respectively. The MIC is defined as the lowest concentration effecting a reduction in fluorescence (or luminescence) of 90% relative to controls. Six control compounds are run in each experiment including isoniazid, rifampin, moxifloxacin, streptomycin, PA-824 and metronidazole. The reported MIC values are an average of two individual experiments.

3.2.2.2. LORA. This low oxygen recovery assay (LORA) was designed to detect compounds which may have the potential for shortening the duration of therapy through (more) efficient killing of the non-replicating persistor (NRP) population [32]. The assay involves (1) adaptation of *M. tuberculosis* to low oxygen through gradual, monitored, self-depletion of oxygen during culture in a sealed flask with slow stirring, (2) exposure for 10 days of the low-oxygen adapted culture to test compounds in microplates that are maintained under an anaerobic environment using an Anoxomat system, thus precluding growth and (3) subsequent evaluation of *M. tuberculosis* viability as determined by the ability to recover. Recovery/viability is determined by the extent to which a luciferase-expressing strain can recover the ability to produce luminescence. This assay is high-throughput screening (HTS)-compatible. Compounds such as isoniazid and ethambutol which are considered to be devoid of "sterilizing activity", are inactive in this assay. Confirmation of new classes with activity was made by immediate subculture (without recovery phase) onto solid, drug-

free media and determination of colony forming units. While the rifamycins and the more potent fluoroquinolones, which do appear to eliminate some proportion of the persistor population and thus can affect treatment duration, are active, albeit at concentrations higher than the MICs for replicating cultures. Correlation between the cfu and luminescence readout has been good with the exception of the fluoroquinolone class for which luminescence underestimates absolute activity but not relative activity. The reported MIC values are an average of two individual experiments.

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Appendix A. Supporting information

Supporting information related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.08.047. These data include MOL files and InChiKeys of the most important compounds described in this article.

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