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SHORT COMMUNICATION

Design, synthesis and characterization of quinoline–pyrimidine linked calix[4]arene scaffolds as anti-malarial agents

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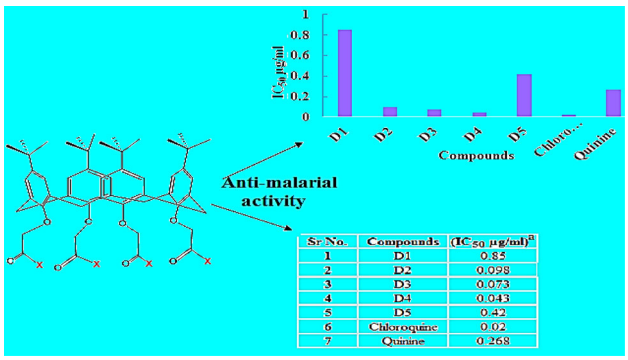
Abstract In this paper, we report a series of quinoline-pyrimidine linked calix[4]arene derivatives functionalized with 8-amino quinoline, 5-amino quinoline, 8-hydroxy quinoline, 2-amino pyrimidine and 4-amino 3-methyl quinoline. The synthesized compounds were purified and characterized by elemental analysis, FT-IR, ^{1}H NMR and ESI-MS and screened for their anti-malarial activity against plasmodium falciparum strains. Two synthesized compounds with 8-hydroxy quinoline and 2-amino pyrimidine substituents showed good antimalarial activity with IC_{50} 0.073 and 0.043 μg/ml respectively which is comparable with the standard drug chloroquine. The present study provides valuable information for developing calix[4]arene conjugates quinoline-pyrimidine based derivatives as an effective antimalarial agents.

Graphical Abstract In this paper, we report a series of quinoline-pyrimidine linked calix [4]arenes derivatives functionalised with 8-amino quinoline, 5-amino quinoline, 8-hydroxy quinoline, 2- amino pyrimidine and 4-amino 3-methyl quinoline and screened for antimalarial activity. Two synthesized compounds with 8-hydroxy quinoline and 2-amino pyrimidine substituents showed good antimalarial activity with IC_{50} 0.073 and 0.043 μg/mL respectively, which is comparable with the standard drug chloroquine. The present study provides valuable information for developing calix[4]arene conjugates quinoline-pyrimidine derivatives.



Sr.No.	Compounds	(IC_{50} μg/ml)[a]
1	D1	0.85
2	D2	0.098
3	D3	0.073
4	D4	0.043
5	D5	0.42
6	Chloroquine	0.02
7	Quinine	0.268

Keywords Calix[4]arene · Quinoline · Pyrimidine · *Plasmodium falciparum* strains · Anti-malarial activity

Introduction

Calixarenes, with their unique three-dimensional surface, are one of the best known host molecules along with cyclodextrins, cucurbiturils, cryptands, and crown ethers. By their availability and easy functionalization at either the upper or lower rim of the molecular skeleton among potential building blocks, calixarenes have become important receptors in synthesis and applications as supramolecular platforms for molecular recognition, sensing and self-assembly, catalysis, nanotechnology and drug discovery.

It is well known that the toxicity is a barrier to the discovery and development of potent drug molecules. Most calixarene derivatives showed low or no toxicity in the

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animal models [1]. Calixarenes have shown antiviral [2] antibacterial [3], antifungal, antitubercular [4] and anticancer activities [5-7]. In 2009, Fátima et al. [8] has reviewed the use of calixarenes as new chemical entitiesof distinct biological activities or as host for bioactive guest molecules.

Malaria is a parasitic infection of the red blood cells, transmitted by the female anopheles mosquito through biting and transfer of plasmodium parasites by saliva. According to the WHO, over 198 million people worldwide live under the threat of malaria infection and in 2009, nearly 584,000 people lost their lives to the disease [9, 10]. Malaria is caused by infection with four species of the family *Plasmodium*; *plasmodium falciparum* (*Pf*), *Plasmodium malariae* (*Pm*), *Plasmodium ovale* (*Po*) and *Plasmodium vivax* (*Pv*) of which *Pf* is responsible for the most severe and fatal form of the disease. Most of the drugs currently used in the treatment of malaria target either the haem detoxification system (e.g. chloroquine and mefloquine) or the biosynthesis of nucleotide bases by inhibiting dihydrofolate reductase (DHFR) or dihydropteroate reductase (DHPR) (e.g. pyrimethamine/sulfadoxine). The primary chemotherapeutic drugs, such as chloroquine (CQ) and pyrimethamine, are of little or no use because the malarial parasite developed resistance against them [11]. Recent reports of resistance to artemisinin, the only effective antimalarial drug at present, have become the cause of concern [12, 13]. Therefore, it is important to search for new antimalarial drugs and also to test the efficacies of some of the old drugs whose antimalarial potential has not been verified in depth.

It is well known that quinoline-based molecules are effective anti malarials; in fact the readily available and inexpensive chloroquine, mefloquine and quinine are all quinoline derivatives. Recently, Solomon et al. [14] reported the synthesis of a new series of side-chain modified 4-aminoquinolines which were found active against *P. falciparumin vitro* and *P. yoelli* in vivo. These analogs form a complex with hematin and inhibit the β-hematin formation, suggesting that this class of compounds act on a heme polymerization target. Twenty-four new 4-aminoquinoline–pyrimidine hybrids containing a terminal aliphatic amino-alcohol chain were also synthesized and assessed for their antimalarial activity against chloroquine-sensitive (D_6) andchloroquine-resistant (W_2) strains of *Plasmodium falciparum* [15].

Ferroquine is a derivative of chloroquine that have shown promising potential as new generation antimalarial agents of clinical interest [16]. A series of new 4-amidino quinoline (4-AMQ) and 10-amidinobenzonaphthyridine (10-AMB) derivatives were synthesized and displayed high activity in vitro and in vivo against D_6, W_2 and C_{235} strains of *Plasmodium falciparum*(*Pf* clones) [17]. A series of novel triazine–pyrimidine hybrids have been synthesized and evaluated for their in vitro antimalarial activity [18]. Pandey and co-workers synthesized a novel series of tetrazole derivatives of 4-aminoquinoline and screened for their antimalarial activities against both chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *Plasmodium falciparum* as well as for cytotoxicity against VERO cell lines [19]

Recently our research group reported [20, 21] calixarene based thiadiazole-oxadiazole derivatives and calix[4]resorcinarene with curcumin interactions and their biological evaluations, which showed excellent anti-microbial, antitubercular and anti-oxidant activities. However, since no work has been reported on the antimalarial activities, in the present investigation we functionalized calix[4]arene with 8-amino quinoline, 5-amino quinoline, 8-hydroxy quinoline, 2-amino pyrimidine and 4-amino 3-methyl quinoline at the lower rim to study the antimalarial activity against *P. falciparum* strain.

Experimental

Chemical and reagents

All the chemicals and reagents used are of analytical grade of BDH, Aldrich and Merck unless and otherwise specified.

Apparatus

Melting points were taken on Opti-Melt (Automated melting point system). The FTIR spectra were recorded on Bruker TENSOR-27 in the range of 4000–400 cm^{-1} using KBr pellet. GmbH Vario Micro cube elemental analyzer was used for elemental analysis. ^1H NMR spectra was scanned on 400 MHz FT-NMR Bruker Avance—400 in the range of 0.5–15 ppm using internal standard tetramethylsilane (TMS) and DMSO-d_6 as a solvent. ESI Mass spectra were taken on a Shimadzu GCMS-QP 2000A.

Synthesis of compound A: microwave synthesis of *p*-tert butyl calix[4]arene

A mixture of *p*-tert-butyl phenol (4.0 g, 0.0266 mol) sodium hydroxide (NaOH) (1 g) and formaldehyde(1.8 ml, 0.0641 mol) solution was taken in an open vessel and was irradiated with 100 W power in a microwave synthesizer discover(CEM) by stirring for 3 min. Cooling for 10 min, resulted yellow solid mass. Added, 4 ml of toluene and 30 ml of diphenyl ether to this yellow solid, again irradiated with microwave power of 100 W for 5 min with stirring and obtained a dark brown solution. Further, this solution was added into 75 ml of ethyl acetate and kept for

2 h. Finally, white precipitate was obtained which was filtered and washed with ethyl acetate and finally dried. Yield, 3.5 g (96 %). Elemental analysis for $C_{44}H_{56}O_4$ calcd. C; 81.44 %, H; 8.70 %, Found: C; 81.11 %, H; 8.261 %. ^{1}HNMR: (DMSO, 400 MHZ) δH: 1.18 (36H, tbutyl, s), 3. 81 (8H, $ArCH_2Ar$, s), 7.12 (8H, Ar–H, s), 9.71(4H, Ar–OH, s), ESI–MS (m/z) 648 (M+1).

Synthesis of compound B

In a solution of *p-tert*-butylcalix[4]arene (**A**) (1.296 g, 2 mmol) in freshly distilledacetone (80 mL), ethylbromo acetate (0.764 g, 4. 5 mmol) and K_2CO_3 (0.345 g, 2.5 mmol) were added and the reaction mixture was heated at 57 °C for 20 h under inert atmosphere. The solution was then allowed to cool to room temperature and evaporated to dryness by rotary evaporation. The residue was then triturated three times with methanol (25 mL each time) and filtered off the white solid. The desired white solid was kept in high vacuum overnight. Yield: 1.124 g, (71 %). Elemental analysis for $C_{60}H_{80}O_8$ calcd: C, 77.55; H, 8.68. Found: C, 77.35; H, 8.42. FT-IR, (KBr pellet)/cm^{-1} 1759 (–C=O); ^{1}H NMR (400 MHz, DMSO): δ 7.03 (s, 4H, Ar–H), 6.81 (s, 4H, Ar–H), 4.73 (s, 4H, $–OCH_2CO$), 4.43 (d, 4H, $ArCH_2Ar$), 3.85 (s, 6H, $–CH_3$), 3.32 (d, 4H, $ArCH_2Ar$), 1.27 (s, 36H, $–C(CH_3)_3$), ESI MS (*m/z*): 929.23 (M+1).

Synthesis of compound C

A solution of **B** (0.794 g, 0.799 mmol) and KOH (0.6 g, 10.69 mmol) in a mixture of THF (10 ml), methanol (20 ml) and water (10 mL) was heated at reflux for 15 h. The solution was then allowed to cool to room temperature and evaporated to dryness by rotary evaporation. The residue was dissolved in EtOAc (150 ml), and the solution was washed thrice with 20 % HCl (60 ml each time). After that this solution was washed thrice by water (100 ml each time). The organic layer was separated, dried over $MgSO_4$ and evaporated in vacuum to give compound **C** as white solid. Yield: 0.762 g, (90 %). Elemental analysis for $C_{52}H_{64}O_{12}$ calcd: C, 70.89; H, 7.32. Found: C, 70.33; H, 7.17. FT-IR: 3434 cm^{-1} (–OH), 1742 cm^{-1} (–C=O); ^{1}H NMR (400 MHz, DMSO): δ 7.06 (s, 4H, Ar), 6.95 (s, 4H, Ar–H), 4.68 (s, 4H, $–OCH_2CO$), 4.15 (d, 8H, $ArCH_2Ar$), 1.25 (s, 36H, C $(CH_3)_3$). ESI MS (*m/z*): found 881 (M+1).

Synthesis of compound D

A mixture of compound **C** (1 g, 1.13 mmol) and different quinoline and pyrimidine moiety (**X**) (0.6 g) were dissolved in anhydrous dichloromethane (20–25 ml) and stirred this solution for 15 min. Then *N*,*N*′-dicyclohexylcarbodiimide (DCC) (0.93 g, 0.004 mol) and catalytic amount of 4-dimethylaminopyridine (DMAP) were added into the reaction mixture. This reaction mixture was stirred at room temperature for 48 h. The reaction progress was monitored by TLC using mixture of chloroform:methanol (7:3). After the completion of reaction, solvent was evaporated. The crude product was then wash with 1 N HCl followed by $NaHCO_3$for the removal of unreacted quinoline and pyrimidine compounds and unreacted compound **C**. The product was then crystalized with dichloromethane, solubility: soluble in $CHCl_3$, CH_2Cl_2, CH_3CN and insoluble in H_2O.

Compound D1

Yield 78 %, mp > 280 °C. Anal. calc: $C_{88}H_{88}N_8O_8$: C, 76.28; H, 6.40; N, 8.09; O, 9.24 % Found: C, 75.88; H, 6.12; N, 7.90; O, 10.10 % FT-IR (KBr)υ: 3180 cm^{-1} (–NH), 3320 cm^{-1} (–CH), 1710 cm^{-1} (–C=O). ^{1}H NMR(DMSO-d_6) 1.31 (s, $C(CH_3)_{12}$, 36H), 3.82 (s, $Ar–CH_2–Ar$, 8H), 7.67 (s, Ar–H, 8H), 4.09 (s, $–OCH_2$, 8H), 8.22 (s, –NH, 4H), 8.10 (s, Ar–H, 4H), 8.06 (s, Ar–H, 4H), 7.88 (s, Ar–H, 4H), 7.38 (s, Ar–H, 4H), 7.32 (s, Ar–H, 4H), 7.40(s, Ar–H, 4H), ESI–MS: (*m/z*) 1386 (M+1).

Compound D2

Yield 79 %, mp > 290 °C. Anal. calc: $C_{88}H_{88}N_8O_8$: C, 76.28; H, 6.40; N, 8.09; O, 9.24 % Found: C, 75.88; H, 6.12; N, 7.90; O, 10.10 % FT-IR (KBr)υ: 3180 cm^{-1} (–NH), 3320 cm^{-1} (–CH), 1710 cm^{-1} (–C=O). ^{1}H NMR(DMSO-d_6) 1.31 (s, $C(CH_3)_{12}$, 36H), 3.81 (s, $Ar–CH_2–Ar$, 8H), 7.14 (s, Ar–H, 8H), 4.68 (s, $–OCH_2$, 8H), 10.02 (s, –NH, 4H), 8.99 (d, Ar–H, 4H), 8.73(d, Ar–H, 4H), 8.59 (d, Ar–H, 4H), 7.87 (d, Ar–H, 4H), 7.84(d, Ar–H, 4H), 7.71 (d, Ar–H, 4H), ESI–MS: (*m/z*) 1386 (M+1).

Compound D3

Yield 69 %, mp > 290 °C. Anal. calc: $C_{88}H_{84}N_4O_{12}$: C, 76.06; H, 6.09; N, 4.03; O, 13.82 % Found: C, 76.00; H, 6.12; N, 4.08; O, 13.80 % FT-IR (KBr)υ: 3320 cm^{-1} (–CH), 1710 cm^{-1} (–C=O) 1730 cm^{-1} (–COO). ^{1}H NMR(DMSO-d_6) 1.31 (s, $C(CH_3)_{12}$, 36H), 3.81 (s, $Ar–CH_2–Ar$, 8H), 7.14 (s, Ar–H, 8H), 5.15 (s, $–OCH_2$, 8H), 8.87 (d, Ar–H, 4H), 8.43(d, Ar–H, 4H), 7.95 (d, Ar–H, 4H), 7.81 (d, Ar–H, 4H), 7.44(d, Ar–H, 4H), 7.19 (d, Ar–H, 4H), ESI–MS: (*m/z*) 1389 (M+1).

Compound D4

Yield 86 %, mp > 260 °C. Anal. calc: $C_{68}H_{76}N_{12}O_8$: C, 68.67; H, 6.44; N, 14.13; O, 10.76 % Found: C, 68.61; H, 6.51; N, 14.18; O, 10.70 % FT-IR (KBr)υ: 3180 cm^{-1} (–NH), 3320 cm^{-1} (–CH), 1710 cm^{-1} (–C=O). ^{1}H

NMR(DMSO-d_6) 1.31 (s, $C(CH_3)_{12}$, 36H), 3.81 (s, Ar–CH_2–Ar, 8H), 7.14 (s, Ar–H, 8H), 4.63 (s, –OCH_2, 8H), 10.30 (s, –NH, 4H), 8.58 (s, Ar–H, 8H), 7.17(d, Ar–H, 4H), ESI–MS: (*m*/*z*) 1190 (M+1).

Compound D5

Yield 82 %, mp > 290 °C. Anal. calc: $C_{92}H_{96}N_8O_8$: C, 76.64; H, 6.71; N, 7.77; O, 8.88 % Found: C, 76.61; H, 6.76; N, 7.69; O, 8.94 % FT-IR (KBr)υ: 3180 cm^{-1} (–NH), 3320 cm^{-1} (–CH), 1710 cm^{-1} (–C=O), 1370 cm^{-1} (–CH_3). ^{1}H NMR(DMSO-d_6) 1.31 (s, $C(CH_3)_{12}$, 36H), 3.81 (s, Ar–CH_2–Ar, 8H), 7.14 (s, Ar–H, 8H), 4.63 (s, –OCH_2, 8H), 9.92 (s, –NH, 4H), 8.77 (s, Ar–H, 4H), 8.06(d, Ar–H, 4H), 7.93 (d, Ar–H, 4H), 7.81 (d, Ar–H, 4H), 7.48(d, Ar–H, 4H), 1.96 (s, –CH_3, 12H), ESI–MS: (*m*/*z*) 1442 (M+1).

In vitro antimalarial assay

The novel synthesized calix[4]arene conjugates quinoline and pyrimidine based derivatives (**D1**–**D5**) were evaluated for their antimalarial activity against the *P. falciparum* in vitro *assay* according to the reported procedure in the literature [22]. Briefly, The cultures of *P. falciparum* strain weremaintained in medium RPMI1640 supplemented with 25 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), 1 % D-glucose, 0.23 % sodium bicarbonate and 10 % heat inactivated human serum. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5 % at 3 % haematocrit in a total volume of 200 µl of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and uniformly maintained with 50 % RBCs. A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µl volume were added to the test wells so as to obtain final concentrations (at fivefold dilutions) ranging between 0.4 and 100 µg/ml in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37 °C in a candle jar. After 36–40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Chloroquine and quinine were used as the reference drugs.

Results and discussion

The synthesis of hydroxy and amino series was carried out in 4 steps from commercially available starting materials as well as all quinoline–pyrimidine moieties (see Fig. 1). All the quinoline–pyrimidine moieties (**D1**–**D5**), conjugates at the lower rim of calix[4]arene in the presence of DCC and DMAP in dichloromethane which gave the desired calix[4]arene conjugates quinoline–pyrimidine scaffolds (**D1**–**D5**) in excellent yields. The structure of final derivatives were determined on the basis of several spectral analysis viz., FT-IR, ^{1}H-NMR and Mass. The spectroscopic data are in good arrangement with the proposed structures.

In vitro antimalarial activity

In this research work, we have identified the *p*-hydroxy and amino substituents on the D-series ring having good antimalarial activity. Analysis of the in vitro antimalarial data reveals that good activity can be achieved by the introduction of a hydroxy group in quinoline analogues (**D3**) in the 8-position and amino group pyrimidine analogues (**D4**) in the 2-position. The six-membered ring containing two nitrogen analogue (**D4**) was much more effective. While a clear trend is seen in the amino group based quinoline compound (**D2**) in the 5-position provide optimum activity. In contrast, 8 and 4- amino quinoline analogues of **D1** and **D5** resulted in a complete less in antimalarial activity compared to standard drugs against *P. falciparum* strain. The IC_{50} values are calculated from experiments carried out in triplicate. Among the tested compounds, compounds **D3** and **D4** showed an IC_{50} values of 0.073 and 0.043 µg/ml respectively. Moreover, compounds **D2** and **D5** have an IC_{50}valuesof 0.098 and 0.42 µg/ml respectively (Table 1; Fig. 2).

The quinoline and pyrimidine analogues **D3** and **D4** are well known antimalarial agents; their mechanism of action is to inhibit hemazoin (β-hematin) formation by the malarial parasites. Here, the difference in the IC_{50} values can be recognized to features such as hydroxy as well as amino group's position, ring size and substitutions on the ring at distal amino groups.

One of the major goals of this study is to synthesize a potent, safe and long-acting antimalarial compound to replace chloroquine as malaria prophylactic drug. Among the **D1**–**D5** analogs, compounds **D3** and **D4** showed good in vitro antimalarial activities against *P. falciparum* strains (Table 1; Fig. 2). Regarding structure activity relationship (SAR), antimalarial activity data suggested that the compounds with 8-hydroxy quinoline and 2-amino pyrimidine based calix[4]arene derivatives are more potent than the other compounds. These results indicates that 2- amino pyrimidine with additional nitrogen atom in the ring significants increase the π-deficiency there by increasing the electronegativity, which has a remarkable effect on the antimalarial activity. Further, -NH_2 group substitution at 2-position in phenyl ring will increase the electronegativity

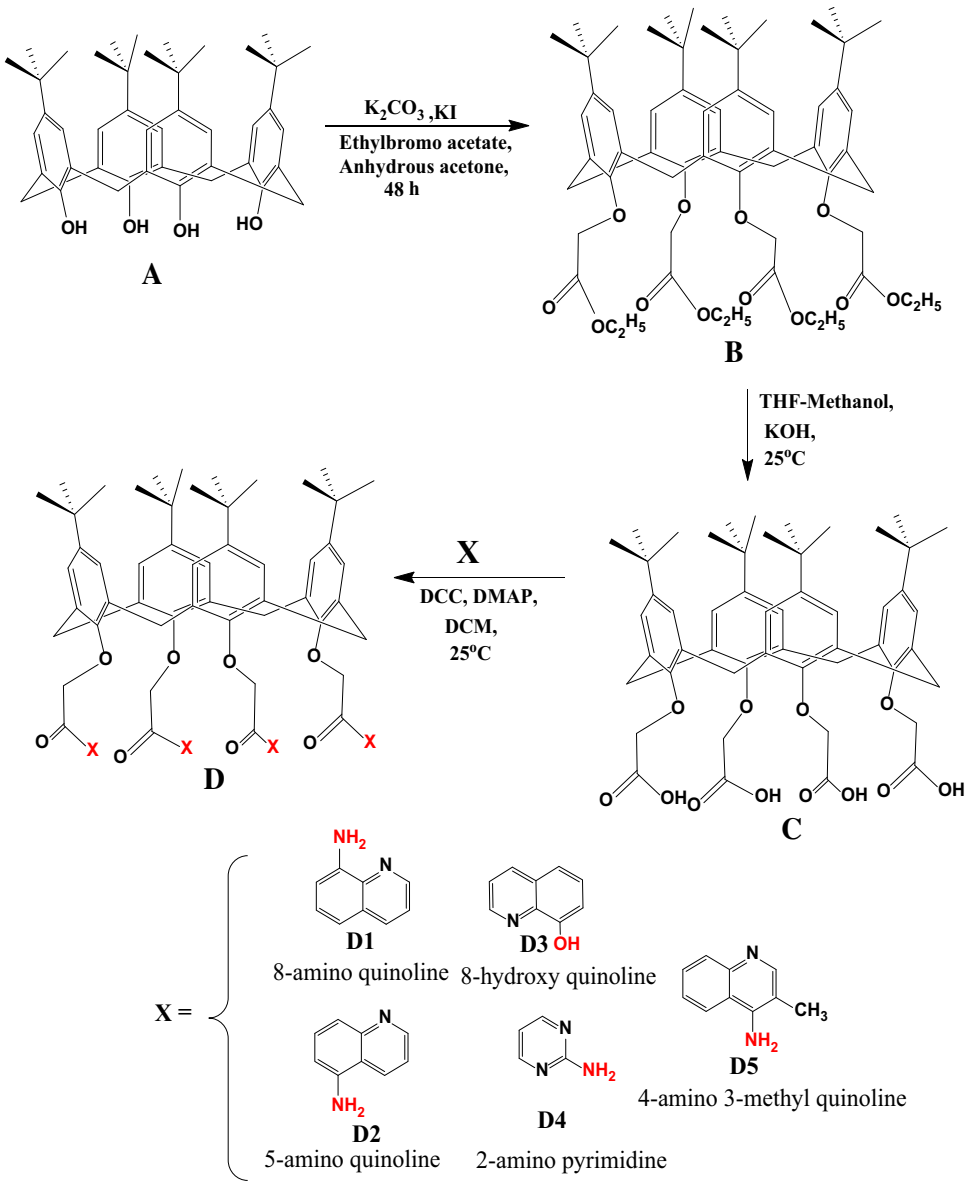

Fig. 1 Scheme of synthesis of quinoline–pyrimidine based calix[4]arene derivatives

Table 1 Antimalarial activity of calix[4]arene conjugates quinolone-pyrimidine based derivatives (**D1–D5**)

Sr. No.	Compounds	(IC_{50} µg/ml)[a]
1	**D1**	0.85
2	**D2**	0.098
3	**D3**	0.073
4	**D4**	0.043
5	**D5**	0.42
6	Chloroquine	0.02
7	Quinine	0.268

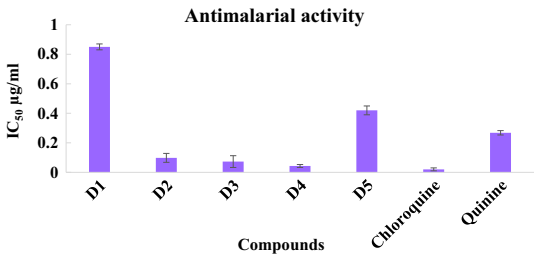

Fig. 2 Antimalarial activity of compounds **D1–D5** with standard drugs

there by increasing the antimalarial activity of the compound (**D4**) compared to the $-NH_2$ substituted quinoline derivatives, **D1**, **D2** and **D5**. Large substituents like 4-amino 3-methyl quinoline (**D5**) may significantly degrade activity against *P. falciparum* strain due to steric factor. The substitution of electron donating group -OH at

the 8-position of quinoline also showed an enhancement in the antimalarial activity due to increase in the electronegativity of the quinoline scaffold.

Conclusion

The present study is on a series of calix[4]arene conjugates quinoline- pyrimidine based derivatives that have been successfully synthesized and screened for antimalarial activity. Two of the synthesized compounds, 5, 11, 17, 23 tetra tert butyl-25, 26, 27, 28 tetra (8- hydroxy quinolate) calix[4]arene (**D3**) and 5, 11, 17, 23 tetra tert butyl-25, 26, 27, 28 tetra (2- amino pyrimidine) calix[4]arene (**D4**), showed good antimalarial activity against *P. falciparum* strain. The results indicates that 8-hydroxy quinoline and 2-amino pyrimidine substituted compounds exhibited good antimalarial activity with IC_{50} 0.073 and IC_{50} 0.043 μg/ml respectively which was comparable with the standard drug chloroquine. Thus the present study provides valuable information for developing calix[4]arene conjugates quinoline-pyrimidine based derivatives as an effective antimalarial agents.

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