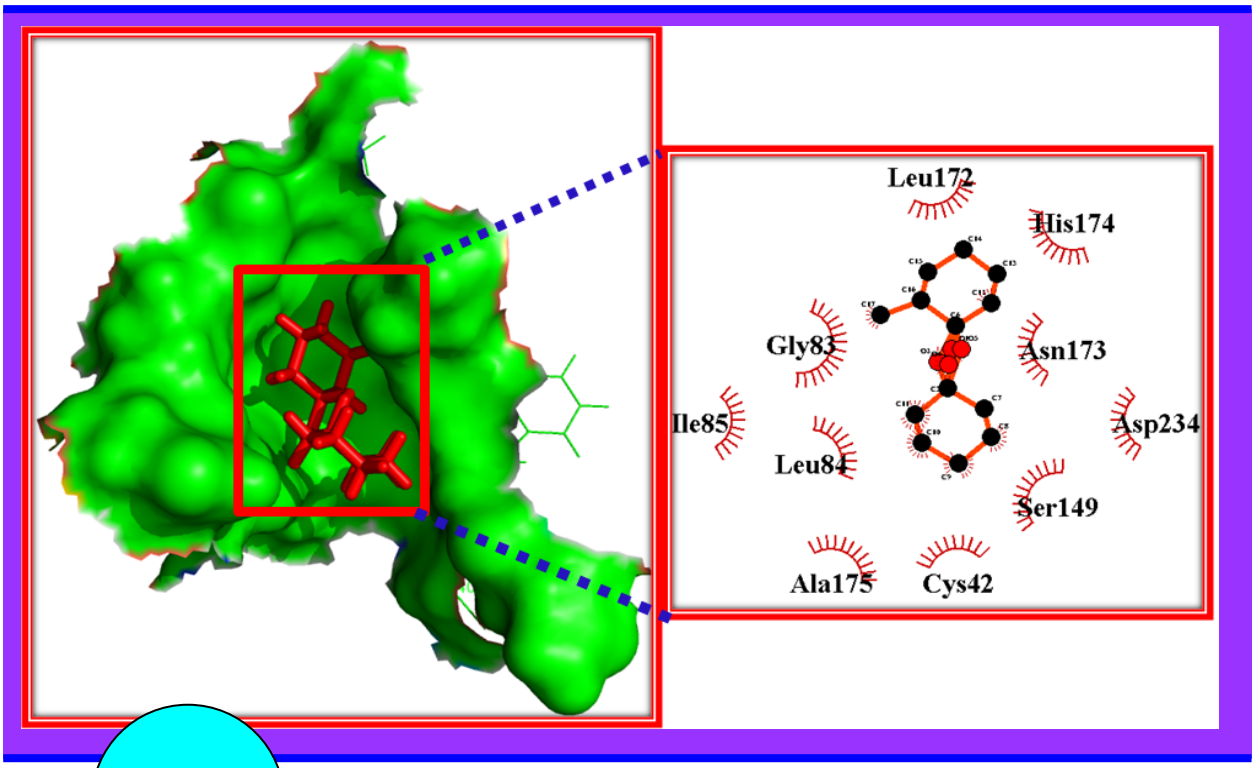

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Synthesis, antimalarial activity evaluation and molecular docking studies of some novel dispiro-1,2,4,5-tetraoxanes

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Abstract

Seven novel dispiro-1,2,4,5-tetraoxane derivatives were synthesized and characterized by a number of analytical and spectroscopic techniques. The molecules were subsequently screened for *in vitro* antimalarial activity against chloroquine resistant strain of *Plasmodium falciparum* (RKL-9). At antimalarial activity screening, two compounds, namely **5d** (MIC = 15.6 µg/mL or 64.5 µM) and **5f** (MIC = 15.6 µg/mL or 54.6 µM) were found to be about 1.5 times more potent against chloroquine resistant strain-RKL-9 compared to chloroquine (MIC = 25.0 µg/mL or 78.3 µM). Molecular docking studies of potent ligands were also performed in cysteine protease binding pocket residues of falcipain-2 as a target protein.

Introduction

Human malaria is a life-threatening disease transmitted by female *Anopheles* mosquitoes. It is caused by four parasite species of the genus *Plasmodium; P. vivax, P. malariae, P. ovale* and *P. falciparum*. *P. falciparum* is the most pernicious, causing the majority of malaria related morbidity and mortality (Kumawat et al., 2011). WHO reported that 207 million cases of malaria and 627,000 deaths occurred globally in 2012. Most cases (80%) and deaths (90%) occurred in Africa, and most deaths (77%) were in children under 5 years of age.

The growing drug resistance towards *P. falciparum* and the lack of an effective antimalarial vaccine emphasize the need to develop a novel, safe, affordable antimalarial drug effective against multi drug-resistant malaria (Casteel, 1997; O'Neill et al., 2010). Tetraoxanes are believed to have a similar mode of activity as the naturally occurring endoperoxides such as artemisinin ((O'Neill et al., 2008; Vennerstrom et al., 1992, 2000). 1,2,4,5-tetraoxanes have been proven to be superior to other synthetic endoperoxides such as 1,2,4- trioxolanes in terms of stability and to trioxane analogues in terms of both stability and activity (Dong et al., 1999; Amewu et al., 2013).

In the present study, seven molecules of dispiro-1,2,4,5-tetraoxanes were synthesized and subsequently screened for their *in vitro* antimalarial activity against laboratory cultured *P. falciparum*. These molecules were also tested for their inhibitory potency against falcipain-2 (FP-2).

Materials and Methods

Chemistry

All the chemicals used in the work were procured either from Sigma–Aldrich Corporation, USA or Merck Specialties Pvt. Ltd., Mumbai and were used without further purification. The melting points of the synthesized compounds, including intermediate were determined by using Veego-MPI melting point apparatus. The progress of the reactions was monitored on silica gel-G TLC plate using various solvent combinations. The spots were detected with iodine vapors and by observing under UV-light. The UV–visible spectra of

the synthesized compounds were recorded on UV–visible spectrophotometer (Shimadzu *UV*-1800). Infra-red spectra were recorded on an FT-IR Perkin-Elmer spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker Avance-*II* 400 NMR spectrometer using either DMSO-d_6 or $CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a Waters Q-TOF MICROMA SS LC mass spectrometer. Elemental analyses (CHN and O) were carried out on Eager Xperience Elemental analyzer (Coates, 2000; Pasto et al., 1992; Mathieson, 1965; Silverstein and Webster, 1963).

General Procedure

Synthesis of intermediate dihydroperoxides (Step I)

Cyclic aldehyde/ketone (1 mL, 10 mmol) was dissolved at room temperature in a CH_2Cl_2/CH_3CN mixture (20 mL, 1:3 v/v) followed by 30% H_2O_2 (10.4 mL, 0.1 mol) and 0.5 mL of concentrated HCl. The reaction mixture was stirred for 2 hours at room temperature and quenched with saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, and the water layer was filtered and dried (O'Neill et al., 2008; Opsenica et al., 2008; Terent'ev et al., 2012).

Synthesis of targeted dispiro-1,2,4,5-tetraoxanes 5 (a-g) (Step II)

Cyclic ketone/aldehyde (0.36 g, 2.3 mmol) was added to a cooled solution (ice bath) of dihydroperoxide (0.34 g, 2.3 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 30 min at the same temperature, and then a cooled H_2SO_4/CH_3CN mixture (1.66 mL, 1:10, v/v) was added drop wise. After an additional 50 min of stirring, the reaction was quenched with saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was separated, and the water layer was filtered and dried (O'Neill et al., 2008; Opsenica et al., 2008; Terent'ev et al., 2012).

6,7,14,15-tetraoxa-dispiro[4.2.5.2]pentadecane; 5a

Brownish semisolid with a characteristic odor; soluble in dichloromethane, DMSO, chloroform; %yield 43.98; R_f value 0.81 (petroleum ether: acetone: 1:4); spectroscopic analysis: λ_{max} (in $CHCl_3$) 242.72 nm; FTIR (ν_{max}, in cm^{-1}, film) 2934.34-2863.53 (C-H stretching, cycloalkyl), 1453.03-1392.73 (C-H bending, cycloalkyl), 1096.82 (C-C-O stretching), 736.74 (peroxide, C-O-O- stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm) 1.22-1.43 (m, 6H, 3x>CH_2, cyclohexyl), 1.46-1.78 (m, 2H, 2x>CH_2, cyclopentyl), 1.81-1.84 (t, 4H, J=12Hz, 2x>CH_2, cyclohexyl), 2.50-2.51 (t, 4H, J=4Hz, 2x>CH_2, cyclopentyl); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm) 24.96, 25.29 (2xC, cyclohexyl), 27.52, 27.61, 27.79, 27.85, 28.46, 29.26 (2xC, cyclopentyl), 30.38, 30.84, 32.08, 33.01, 33.11, 33.68, 33.49 (2xC, cyclohexyl), 38.92 (1xC, cyclohexyl), 39.12, 39.33, 39.54, 39.75, 39.96, 40.17 (2xC, cyclopentyl), 53.93, 60.59, 63.16, 63.38, 63.43, 78.42, 78.75, 79.08 (1xC, tetraoxane), 172.41, 172.54, 174.09, 174.24 (1xC, tetraoxane); mass (m/z) calculated 214.26; observed 246.2 (100%), 260.2 (94.14%), 165.2 (79.03%), 196.2 (73.92%).

7,8,16,17-tetraoxa-dispiro[5.2.6.2]heptadecane; 5b

Reddish brown semisolid with a characteristic odor; soluble in dichloromethane, DMSO, chloroform; %yield 15.28; R_f value (petroleum ether: acetone: 1:3) 0.79; spectroscopic analysis: λ_{max} (in $CHCl_3$) 242.41 nm; FTIR (ν_{max}, in cm^{-1}, film) 2933.37-2862.09 (C-H stretching, cycloalkyl), 1455.48-1349.89 (C-H bending, cycloalkyl), 1044.19 (C-C-O stretching), 855.70-735.23 (peroxide, C-O-O- stretching); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) 1.18-1.40 (m, 8H, 4x>CH_2, cycloheptyl), 1.48-1.88 (m, 6H, 3x>CH_2, cyclohexyl), 1.97-1.99 (dd, 4H, J=8Hz, 2x>CH_2, cycloheptyl), 2.00-2.02 (t, 4H, J=8Hz, 2x>CH_2, cyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm) 24.35, 24.58 (2xC, cyclohexyl), 25.53, 28.31(2xC, cycloheptyl), 30.44, 34.14, 43.90 (3xC, cyclohexyl), 64.09, 64.18 (2xC, cycloheptyl), 76.70 (2xC, cycloheptyl), 77.02 (1xC, tetraoxane), 77.34 (1xC, tetraoxane).

6,7,15,16-tetraoxa-dispiro[4.2.6.2]hexadecane, 5c

Brownish yellow solid with characteristic odor; soluble in DMSO, dichloromethane, chloroform; melting range 96-97°C; %yield 09.96; R_f value (petroleum ether: acetone: 1:2) 0.65; spectroscopic analysis: λ_{max} (in $CHCl_3$) 269.30 nm; FTIR (ν_{max}, in cm^{-1}, film) 2924.12-2855.05 (C-H stretching, cycloalkyl), 1491.98-1372.76 (C-H bending, cycloalkyl), 1027.81 (C-C-O stretching), 906.12-749.87 (peroxide, C-O-O- stretching); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) 1.18-1.49 (m, 8H, 4x>CH_2, cycloheptyl), 1.67-1.74 (m, 4H, 2x>CH_2, cyclopentyl), 2.32-2.46 (m, 4H, 2x>CH_2, cycloheptyl), 2.57-2.60 (t, 4H, J=12Hz, 2x>CH_2, cyclopentyl); ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm) 25.62 (2xC, cyclopentyl), 28.01, 28.10 (2xC, cycloheptyl), 29.71, 40.40 (2xC, cyclopentyl), 76.72, 77.04, 77.36 (2xC, cycloheptyl), 125.50, 125.64 (2xC, cycloheptyl), 127.65 (1xC, tetraoxane), 127.97 (1xC, tetraoxane).

1-methyl-7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane; 5d

Creamy semisolid with a characteristic odor; soluble in dichloromethane, chloroform; %yield 52.12; R_f value (isopropyl alcohol: benzene: 1:1) 0.78; spectroscopic analysis: λ_{max} (in $CHCl_3$) 253.48 nm; FTIR (ν_{max}, in cm^{-1}, film) 2935.02-2861.33 (C-H stretching, methyl and cycloalkyl), 1447.56-1344.27 (C-H bending, methyl and cycloalkyl), 1064.69-952.83 (C-C-O stretching), 846.91-758.74 (peroxide, C-O-O- stretching); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) 0.90-0.93 (dd, 3H, J=12Hz, -CH_3, methylcyclohexyl), 1.02-1.10 (m, 6H, 3x>CH_2, cyclohexyl), 1.20-1.32 (m, 6H, 3x>CH_2, methylcyclohexyl), 1.38-1.48(m, 4H, 2x>CH_2, cyclohexyl), 1.52-1.94 (m, 2H, >CH_2, methylcyclohexyl), 2.27-2.40 (m, 2H,

>CH_2, methylcyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm) 13.66, 14.88 (1xC, -CH_3, methylcyclohexyl), 20.43, 22.59, 22.63 (2xC, cyclohexyl), 22.73, 22.76 (1xC, methylcyclohexyl), 22.82, 23.15 (1xC, methylcyclohexyl), 24.57, 25.26, 25.39 (1xC, methylcyclohexyl), 25.54, 25.57, 25.62 (1xC, methylcyclohexyl), 28.31, 29.48, 29.84, 30.17, 30.40, 30.48, 30.65, 30.89 (3xC, cyclohexyl), 31.09, 31.92, 32.88, 34.15 (1xC, methylcyclohexyl), 76.70, 77.02, 77.34 (1xC, tetraoxane), 107.53, 107.60, 107.66, 108.04, 108.17, 109.26, 109.72 (1xC, tetraoxane); mass (m/z) calculated 242.31; observed 129.1 (100%), 411.2 (77.20%), 525.2 (64.55%), 115.1 (60.78%), 539.3 (51.53%), 503.3 (47.94%), 243.1 (47.09%) $[M+H]^+$; elemental analysis calculated C, 64.44; H, 9.15; O, 26.41; Observed C, 64.654; H, 9.462; O, 26.620.

9-methyl-6,7,14,15-tetraoxadispiro[4.2.5.2]pentadecane; 5e

Brown semisolid with a characteristic odor; soluble in dichloromethane, chloroform; %yield 10.67; R_f value (isopropyl alcohol: benzene: 1:1) 0.74; spectroscopic analysis: λ_{max} (in $CHCl_3$) 240.51 nm; FTIR (ν_{max}, in cm^{-1}, Film) 2927.77-2860.43 (C-H stretching, methyl and cycloalkyl), 1457.38-1375.93 (C-H bending, methyl and cycloalkyl), 1039.11-933.44 (C-C-O stretching), 843.84-736.33 (peroxide, C-O-O- stretching).

Ethyl 6,7,14,15-tetraoxadispiro[4.2.5.2]pentadecane-1-carboxylate; 5f

Orange liquid with a characteristic odor; soluble in dichloromethane, chloroform; boiling range 104-105°C; %yield 40.35; R_f value (benzene: carbon tetrachloride: 2:1) 0.51; spectroscopic analysis: λ_{max} (in $CHCl_3$) 253.48 nm; FTIR (ν_{max}, in cm^{-1}, Film) 2940.15-2869.23 (C-H stretching, cycloalkyl), 1721.64 (C=O stretching, C_2H_5COO-), 1455.05-1337.93 (C-H bending, cycloalkyl), 1234.61-1107.91 (-C-O stretching, C_2H_5COO-), 1025.47 (C-C-O stretching), 855.46-735.67 (peroxide, C-O-O-stretching); ^1H NMR (400 MHz, $CDCl_3$, δ in ppm) 1.20-1.22 (t, 3H, J=8Hz, -CH_3, ethylcarboxylate), 1.25-1.33 (m, 6H, 3x>CH_2, cyclohexyl), 1.35-1.47 (m, 2H, >CH_2, cyclopentyl), 1.57-1.76 (m, 4H, 2x>CH_2, cyclohexyl), 1.84-1.92 (m, 2H, >CH_2, cyclopentyl), 1.96-1.99 (m, 2H, >CH_2, cyclopentyl), 2.28-2.40 (m, 2H, >CH_2, cyclopentyl), 4.09-4.38 (m, 2H, >CH_2, ethylcarboxylate); ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm) 14.24 (1xC, -CH_3, ethylcarboxylate), 20.96 (1xC, cyclopentyl), 23.23 (2xC, cyclohexyl), 24.58 (1xC, cyclopentyl), 25.51, 27.39, 28.33 (3xC, cyclohexyl), 34.18 (1xC, cyclopentyl), 38.08 (1xC, cyclopentyl), 38.36 (1xC, -C_2H_5, ethylcarboxylate), 54.80 (1xC, tetraoxane), 76.71 (1xC, tetraoxane), 77.02, 77.34 (1xC, -C=O, ethylcarboxylate); mass (m/z) calculated 286.32; Observed 143.1 (100%), 115.1 (78.27%), 111.0 (52.78%), 157.1 (47.48%), 407.2 (32.10%), 129.1 (26.54%); elemental analysis calculated C, 58.73; H, 7.74; O, 33.53; observed C, 58.784; H, 7.746; O, 33.581.

1-chloro-7,8,15,16-tetraoxadispiro[5.2.5.2]hexadecane; 5g

Yellowish pink semisolid with a characteristic; soluble in methanol, dichloromethane, chloroform; %yield 09.92; R_f value 0.82 (petroleum ether: *n*-butanol: 2:1); spectroscopic analysis: λ_{max} (in $CHCl_3$) 242.72 nm; FTIR (ν_{max}, in cm^{-1}, film) 2940.10-2866.00 (C-H stretching, cycloalkyl), 1435.76-1363.54 (C-H bending, cycloalkyl), 1062.74-961.13 (C-C-O stretching), 809.83-738.60 (peroxide, C-O-O- stretching), 706.26 (-C-Cl stretching, aliphatic-Cl).

Antimalarial activity

All the synthesized compounds were evaluated for *in vitro* antimalarial activity against chloroquine resistant strain-RKL-9 of *P. falciparum* (*Pf*) using 96 well-micro-titre plates at the Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India. The laboratory adapted strain of *Pf* was routinely cultured at 37°C temperature and 5% CO_2 environment in RPMI 1640 medium supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. For antimalarial testing, the asynchronous parasites of *Pf* were synchronized to obtain only the ring stage parasitized cells by 5% D-sorbitol treatment. For carrying out the assay, the initial ring stage parasitemia of 0.8–1.5% at 3% hematocrit in a total volume of 100 mL of medium RPMI-1640 was uniformly maintained. A stock solution (1 mg/mL) of sample was prepared by dissolving the test compounds in DMSO and subsequent dilutions were made with the culture medium. Hundred microlitres of the test compounds at 100 µg/mL concentrations in triplicate was incubated with parasitized cell preparation at 37°C and 5% CO_2 in a CO_2 incubator. After an incubation period of 36–40 hours, blood smears were prepared from each well and stained with 3% Giemsa stain. The slides were microscopically observed and the percent dead rings and schizonts were scored against 200 asexual parasites with respect to the control group. Chloroquine was used as the standard reference drug (Trager and Jensen, 1976).

Molecular docking studies

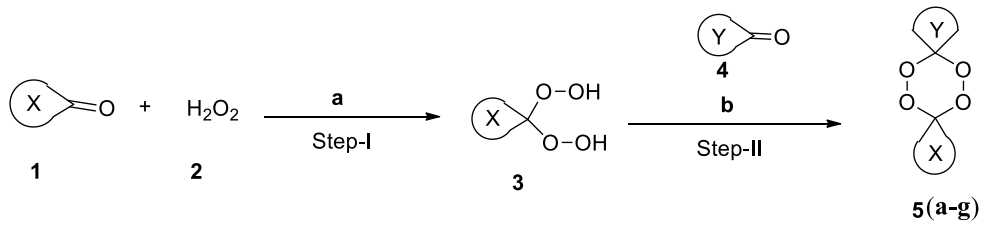
The three dimensional (3D) crystal structure of falcipain -2 (PDB code 3BPF) was retrieved from the protein data bank (PDB) (Source:www.rcsb.org/pdb). The native autoinducer and all water molecules were removed. The CHARMm force field (FF) was used to add atom types and hydrogens in the proteins. 3D structures of all synthesized compounds were constructed and energy minimized using the Discovery Studio 2.5/ Builder module. Docking studies were performed using the CDOCKER module of Discovery Studio 2.5. CDOCKER is a grid-based molecular docking method where the receptor is held rigid while the ligands are allowed to flex during the refinement. The CHARMm

force field was used as an energy grid force field for docking and scoring function calculations. Random ligand conformations were generated from the initial structure through high temperature molecular dynamics, followed by random rotations which were further refined by grid-based (GRID 1) simulated annealing and a final grid-based minimization. Of the 10 best poses, one (conformation) having a highest docking score (-CDOCKER energy) was used for the binding energy calculations and further analysis. The higher negative value of CDOCKER energy represents more favorable binding of the complex. This means that ligands with high docking scores are able to fit snugly in the active site pocket with the minimal steric clashes. CDOCKER score (-CDOCKER Energy) includes internal ligand strain energy and receptor-ligand interaction energy, and is used to sort the different conformations of each input ligand (Oliveira et al., 2013; Liu et al., 2012).

Results

Chemistry

The targeted compounds were prepared as outlined in Scheme 1 (Steps 1 and 2). The step 1 involved the preparation of intermediates dihydroperoxide (**3**) by the acid-catalyzed addition of hydrogen peroxide (**2**) to cyclic carbonyl compounds (1). The step 2 involved the preparation of targeted dispiro-1,2,4,5-tetraoxanes (**5**)



Wherein

S. N.	Compound Code	X	Y
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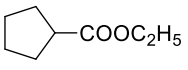
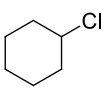
2.	5b		
3.	5c		
4.	5d		
5.	5e		
6.	5f		
7.	5g		

Scheme 1: Synthesis of targeted compounds **5** (**5a** to **5g**): *Reagents and condition* (a,b): Step I: Synthesis of dihydroperoxide (3): a; CH_3CN, CH_2CI_2, Concentrated HCI, stirring at room temperature; Step II: Synthesis of dispiro–1,2,4,5-tetraoxanes (5): b; CH_3CN, CH_2CI_2, Concentrated H_2SO_4, stirring at 0-10°C

Table I

***In vitro* antimalarial activity of the synthesized dispirotetraoxanes**

Compound code	MIC (μM)	MIC (μg/mL)	IC_{50} (μg/mL)	IC_{90} (μg/mL)
5a	1166.6	250.0	3.9	9.1
5b	257.9	62.5	3.9	6.5
5c	273.8	62.5	3.9	38.5
5d	64.5	15.6	3.9	12.0
5e	547.6	125.0	3.9	88.2
5f	54.6	15.6	3.9	3.9
5g	958.7	250.0	4.9	146.8
Chloroquine	78.3	25.0	0.4	1.2

*MIC, IC_{50} and IC_{90} values were means of three independent experiments

via cyclization between dihydroperoxide (**3**) and cyclic carbonyl compounds (**4**) in the presence of conc. sulfuric acid. The reaction yielded desired pure products though the yields were low.

FT-IR spectra showed the stretching frequency range between region 2850–2950 cm^{-1} due to aliphatic cycloalkyl –C–H stretching, 1250-1000 cm^{-1} due to C-C-O stretching and 900-750 cm^{-1} due to peroxide, C-O-O-stretching. ^1H NMR spectra of the compounds showed a triplet or multiplet at δ (ppm) 1.00–2.50 due to cycloalkyl –C-H which further confirmed the formation of the desired compounds. The analytical and spectral data of the compounds were in conformity with the structure of the synthesized compounds.

Antimalarial activity

Among the seven compounds, four compounds **5b**, **5c**, **5d** and 5f showed good activity against chloroquine resistant *Pf* strain RKL-9 with MIC 62.5 μg/mL, 62.5 μg/mL, 15.6 μg/mL, 15.6 μg/mL, respectively and IC_{50} 3.9 μg/mL compared to chloroquine (MIC 25.0 μg/mL and IC_{50} 0.4 μg/mL). Compounds **5d** (MIC = 15.6 μg/mL or 64.5 μM) and **5f** (MIC = 15.6 μg/mL or 54.6 μM) were observed to be about 1.5 times more potent than CQ (MIC = 25.0 μg/mL or 78.3 μM) (Table I).

Table II

Molecular docking interaction results

Compound code	CDOCKER energy (kcal/mol)	CDOCKER interaction energy (kcal/moL)
5a	-1.69	-28.65
5b	-14.75	-28.15
5c	-23.13	-28.73
5d	-11.06	-28.10
5e	-2.75	-34.81
5f	-12.96	-26.82
5g	-8.56	-37.87

Molecular docking studies

A molecular docking study was undertaken to gain insight into the key structural requirements and the basis of the distinct activity profile of the test compounds in *P. falciparum* parasite. The docking studies of the target compounds were performed into the binding pocket of falcipain-2 (PDB code 3BPF). The results and docked conformations of the ligands in the active site are illustrated in Table II and Figure 1, respectively.

Discussion

Seven novel dispiro-1,2,4,5-tetraoxane derivatives were synthesized and characterized by a number of analytical and spectroscopic techniques. Two compounds, namely **5d** (MIC = 15.6 μg/mL or 64.5 μM) and 5f (MIC = 15.6 μg/mL or 54.6 μM) were found to be about 1.5 times more potent against chloroquine resistant strain-RKL-9 compared to chloroquine (MIC = 25.0 μg/mL or 78.3 μM) on antimalarial activity screening. Molecular docking study results showed that the targeted molecules were snugly fitted into the active site with considerable and diverse CDOCKER energy (-1.6870 to -23.1300) with FP-2 along with the formation of numerous hydrogen bonds and hydrophobic interactions.

Vennerstrom and co-workers (1992) reported that high

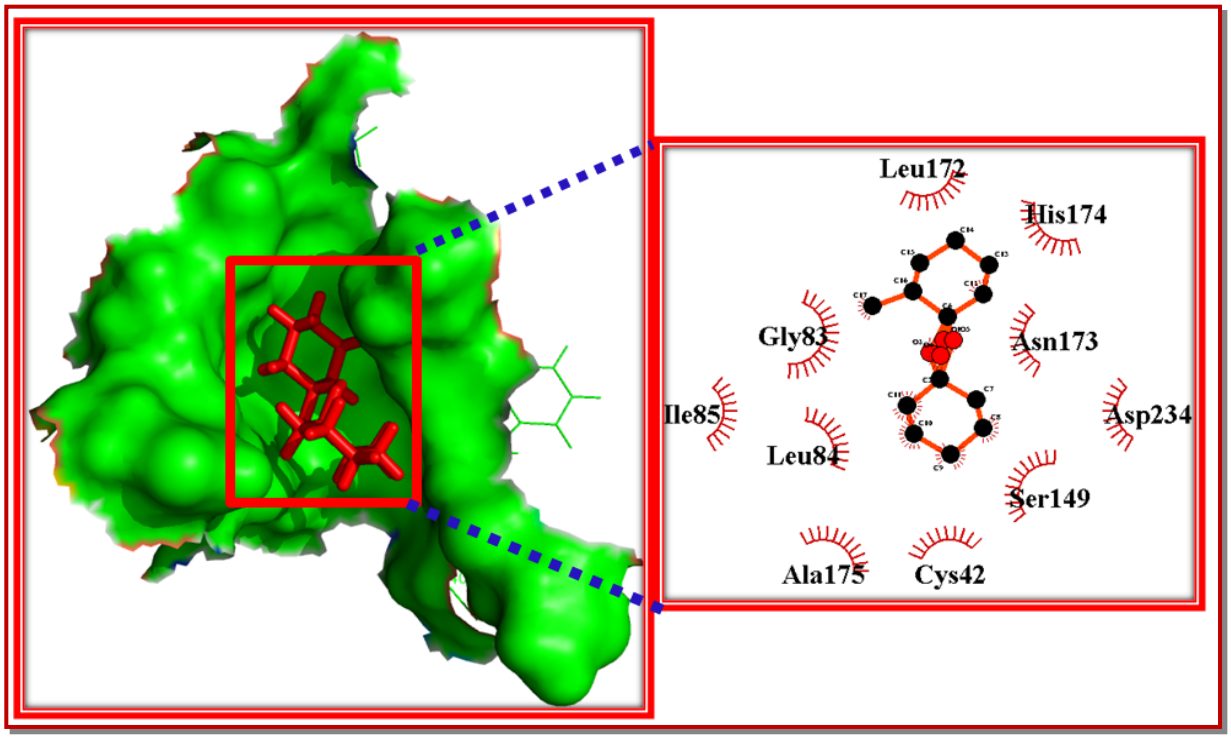


Figure 1: Docked complex of compound 5c in the binding pocket of FP-2

steric hindrance close to the peroxide ring is unfavorable for activity in dispirotetraoxanes. Amewu and coworkers (Amewu et al., 2013) reported that dispirotetraoxane compounds was found to be equally potent as artemisinin.

Antimalarial activity results reflect that the dispirotetraoxanes are found to be potent compounds against chloroquine resistant *Pf* strain RKL-9. Substitution on dispirocycloalkane-tetraoxane with methyl and ethyl carboxylic acid groups make more active tetraoxanes than CQ against RKL-9 as observed with **5d** and **5f**, due to desirable lipophilicity to tetraoxane. Attachment of higher cycloalkanes e.g. six and seven member dispirocycloalkane ring (cyclo-hexane or cycloheptane) to tetraoxane ring enhanced effectiveness of tetraoxanes than that of lower cycloalkanes e.g. five member dispirocycloalkane ring (cyclopentane) towards their antimalarial activity. Chloro group substituted dispirotetraoxane become less active than corresponding unsubstituted dispirotetraoxanes.

Conclusion

A novel series of compounds with potent antimalarial activity has been developed. Designed molecules have the possibility to introduce chemical diversity around the core skeleton to generate newer and potent molecules.

Conflict of Interest

Authors declare no conflict of interest

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