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SYNTHESIS AND *IN SILICO* ANALYSIS OF SOME DIHYDROARTEMISININ ESTERS WITH SEBACOYL CHLORIDE AND SOME ACID ANHYDRIDES AS POTENTIAL ANTI-PLASMODIAL AGENTS

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Abstract

The emergence of drug-resistant malarial parasites has seriously threatened malaria therapy. Scientists have developed many semi-synthetic derivatives of artemisinin to combat the limitations of the ACTs via rational synthetic drug modification strategies. However, a significant proportion of these derivatives, which showed optimum therapeutic activities, has been limited due to poor pharmacokinetic profiles, including poor lipid solubility, short half-lives and an increased rate of metabolism have further strengthened the grounds for the development of drug resistance. In this work, dihydroartemisinin (a reduced form of artemisinin) was used to prepare three (3) semi-synthetic derivatives with sebacoyl chloride, maleic and phthalic anhydrides via the Einhorn's method of esterification. A comparative *in-silico* clog P determination using five (5) different pharmacokinetic software, reveals that the sebacoyl ester product gave a clog P value of 6.02 while the maleic and phthalic ester products gave clog P- values of 2.81 and 3.90. In comparison with dihydroartemisinin (2.63) and artesunate (2.65), it was observed that the maleic and phthalic ester products gave clog P values that are higher in lipophilicity and membrane permeability, but still within the Lipinski's cut off for orally viable drug candidates (< 5). The sebacoyl ester did not show appreciable oral viability.

Keywords: Dihydroartemisinin, Ester, cLogP, malaria, *in-silico*

1.1 INTRODUCTION

Malaria is one of the most important public health problems worldwide, with almost half of the global population exposed to the risk of infection. Malaria is caused by a unicellular apicomplexan parasite of the genus *Plasmodium*. (WHO, 2018).

The discovery of artemisinin 1, as the active principle of the Chinese traditional herb against malaria, *Artemisia annua*, is a breakthrough in malaria chemotherapy. The derivatives of artemisinin, e.g. dihydroartemisinin 2, artemether 3, arteether 4, and artesunic acid 5 (figure 1), are more active than the parent compound and are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *P. falciparum* (Shyamlal *et al*., 2016; Chaudhary *et al*., 2016),

While these compounds show high efficacy when administered by systemic routes, recent studies showed that they are comparatively less active when given by oral route (Shyamlal *et al*., 2016). This led to several efforts being made by researchers to improve the antimalarial activity of artemisinin derivatives by oral route (Shyamlal *et al*., 2016).

However, the newer artemisinin derivatives have been found to be just slightly more potent than artemether and artesunic acid. Therefore, the search for the next generation artemisinin analogues continues to define an active area of scientific research.

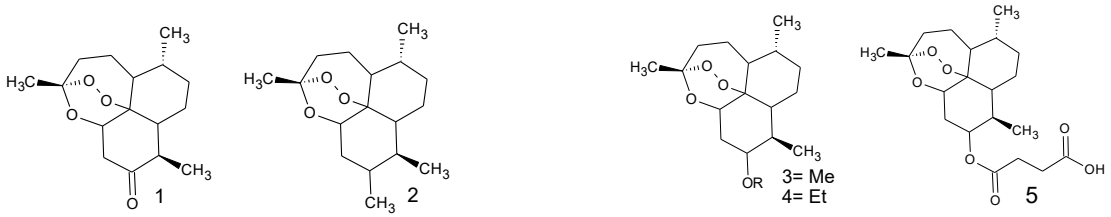

Figure 1. Artemisinin and its clinically useful derivatives

Herein, we report the synthesis, characterization, and computational prediction of ester derivatives of dihydroartemisinin, 2, using sebacoyl chloride, maleic and phthalic anhydrides. We used Einhorn's classical esterification method in this work to synthesize the ester derivatives

(Clark, 2000; Tsakos, *et al.*, 2014). Chemical literature (Harold & Zavod, 2014; DeRuiter, 2005; Bissantz et al., 2010) reveals that the ester functional group possesses more hydrogen bond acceptors, is more lipophilic than the OH function of 2; and these can favour drug transport and penetration, ultimately improving drug bioavailability and minimizing the chances for the development of drug resistance.

1.2 MATERIALS AND METHOD

1.2.1 Synthesis (6R,9R)-3,6,9-trimethyldecahydro-12H -3,12-epoxypyrano[4,3-j][1,2]benzodioxepin-10-yl 10-chloro-10-oxodecanoate (9a): To a solution of DHA **2** (0.145 g, 1 mmol) and sebacoyl chloride **6** (0.67 ml, 3 mmol) in dry CH_2Cl_2 (30 ml) was added Et_3N (0.4 ml, 3 equiv, 3 mmol) dropwise at 0°C. The mixture was stirred for 10 h at the same 0°C. The reaction was quenched with saturated $NaHCO_3$ solution (25 ml) and extracted with CH_2Cl_2 (3×25 ml). The organic layer was washed with 10% aq. HCl (2×20 ml), then with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was run on column chromatography over silica gel using EtOAc/C_6H_{12} (1:25) to give **9a.**

The structure was confirmed using FTIR (Shimadzu, 8400S), EIMS (Shimadzu), ^{1}H NMR, and ^{13}C NMR as follows:

FT-IR (neat) characteristics bands (cm^{-1}): 2800, 1735, 1450, 1373, and 848.

MS major fragments (m/z): 234[M^+], 199, 166, 149, 138, 125, and 55

^{1}H NMR: δ 0.87-1.03 (6H, 0.93 (d, *J* = 6.9 Hz), 0.97 (d, *J* = 6.9 Hz)), 1.18-1.38 (11H, 1.25 (tt, *J* = 7.7, 7.0 Hz), 1.25 (tt, *J* = 7.7, 7.0 Hz), 1.25 (tt, *J* = 7.7, 6.9 Hz), 1.25 (tt, *J* = 7.7, 6.9 Hz), 1.26 (tt, *J* = 7.0, 6.9 Hz), 1.26 (tt, *J* = 7.0, 6.9 Hz), 1.26 (quint, *J* = 7.0 Hz), 1.26 (quint, *J* = 7.0 Hz), 1.33 (s)), 1.42-2.41 (20H, 1.50 (dddd, *J* = 13.0, 7.9, 5.8, 1.6 Hz), 1.56 (tt, *J* = 7.7, 7.4 Hz), 1.56 (tt, *J* = 7.7, 7.4 Hz), 1.58 (dddd, *J* = 13.0, 7.3, 6.1, 1.4 Hz), 1.57 (tt, *J* = 7.7, 7.4 Hz), 1.57 (tt, *J* = 7.7, 7.4 Hz), 1.59 (dddd, *J* = 13.0, 3.6, 3.5, 2.5 Hz), 1.60 (dddd, *J* = 13.2, 7.9, 6.1, 3.9 Hz), 1.67 (ddd, *J* = 14.8, 3.5, 2.2 Hz), 1.77 (dddd, *J* = 13.0, 10.2, 10.0, 2.2 Hz), 1.93 (dddd, *J* = 13.2, 5.8, 2.4, 1.4 Hz), 2.05 (ddd, *J* = 7.8, 3.9, 2.4 Hz), 2.08 (dqdd, *J* = 7.3, 6.9, 2.4, 1.6 Hz), 2.15 (ddd, *J* = 10.0, 3.6, 2.4 Hz), 2.24 (ddd, *J* = 14.8, 10.2, 2.5 Hz), 2.31 (dquint, *J* = 7.8, 6.8 Hz), 2.32 (t, *J* = 7.4 Hz), 2.32 (t, *J* = 7.4 Hz), 2.35 (t, *J* = 7.4 Hz), 2.35 (t, *J* = 7.4 Hz)), 5.33 (1H, s), 6.38 (1H, d, *J* = 6.8 Hz).

^{13}C NMR: δ 19.0 (1C, s), 19.3 (1C, s), 22.2 (1C, s), 24.1 (1C, s), 24.3 (1C, s), 24.8 (1C, s), 25.2 (1C, s), 29.3-29.4 (4C, 29.4 (s), 29.4 (s), 29.4 (s), 29.4 (s)), 32.9 (1C, s), 33.9 (1C, s), 35.1 (1C, s), 36.8 (1C, s), 40.7 (1C, s), 44.5 (1C, s), 46.7 (1C, s), 49.1 (1C, s), 79.1 (1C, s), 93.7 (1C, s), 96.8 (1C, s), 104.8 (1C, s), 171.8 (1C, s), 173.2 (1C, s).

1.2.2 Synthesis of (2E)-4-oxo-4-{[(6R,9R)-3,6,9-trimethyldecahydro-12H-3,12-epoxypyrano[4,3-j][1,2]benzodioxepin-10-yl]oxy}but-2-enoic acid (9b): DHA **2** (0.58 g, 1 mmol) was suspended in ethyl acetate (40 ml) and cooled in an ice bath. Afterward, Et_3N (0.33 ml) was added and the mixture was stirred vigorously. To the cooled suspension, maleic anhydride **7** (0.40 g, 3 mmol) was added step by step in small portions over a period of 30 min. After a further 10 min, the ice bath was removed and the solution was stirred for 7 h at room temperature. The reaction was monitored using TLC (CH_2Cl_2: MeOH: C_6H_{12}; 6.5:0.5:3) to ensure a complete reaction. The product was detected by spraying the TLC plate with vanillin-sulphuric acid. For the workup, distilled water (50 ml cooled) was added to the reaction mixture and then neutralized (pH = 5) with 2N H_2SO_4. The aqueous phase was then extracted three times with about 20 ml of ethyl acetate until no product could be found in the extracting agent as monitored using TLC. The combined ethyl acetate extracts were washed once with water. Afterward, the extract was dried

with anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure and the yield (**9b**) was determined (Presser and Von, 2007).

The structure was confirmed using FT-IR (Shimadzu, 8400S), EIMS (Shimadzu), ^{1}H NMR, and ^{13}C NMR as follows:

FT-IR (neat) characteristics bands (cm^{-1}): 3363, 2947, 2862, 1442, 1373, and 1712. MS major fragments (m/z): 212[base peak], 209,182, 165, 152, and 43. ^{1}H-NMR: δ 0.87-1.03 (6H, 0.93 (d, *J* = 6.9 Hz), 0.97 (d, *J* = 6.8 Hz)), 1.33 (3H, s), 1.48-2.20 (11H, 1.56 (dddd, *J* = 13.1, 8.2, 5.8, 4.0 Hz), 1.58 (dddd, *J* = 13.0, 8.2, 5.5, 1.8 Hz), 1.60 (dddd, *J* = 13.0, 7.5, 5.8, 1.5 Hz), 1.60 (dddd, *J* = 13.0, 3.7, 3.2, 2.1 Hz), 1.75 (dqdd, *J* = 7.5, 6.9, 2.9, 1.8 Hz), 1.83 (dddd, *J* = 13.0, 10.2, 10.1, 2.0 Hz), 1.85 (ddd, *J* = 14.8, 3.7, 2.0 Hz), 1.94 (dddd, *J* = 13.1, 5.5, 2.4, 1.5 Hz), 2.03 (ddd, *J* = 7.9, 4.0, 2.4 Hz), 2.12 (ddd, *J* = 14.8, 10.1, 2.1 Hz), 2.12 (ddd, *J* = 10.2, 3.2, 2.9 Hz)), 2.39 (1H, ddq, *J* = 7.9, 7.2, 6.8 Hz), 5.41 (1H, s), 6.36 (1H, d, *J* = 7.2 Hz), 6.83-7.08 (2H, 6.90 (d, *J* = 16.8 Hz), 7.01 (d, *J* = 16.8 Hz)). ^{13}C NMR: δ 19.0 (1C, s), 19.3 (1C, s), 22.2 (1C, s), 24.1 (1C, s), 25.2 (1C, s), 32.9 (1C, s), 35.1 (1C, s), 36.8 (1C, s), 40.7 (1C, s), 44.5 (1C, s), 49.1 (1C, s), 79.1 (1C, s), 93.7 (1C, s), 96.8 (1C, s), 104.8 (1C, s), 132.0 (1C, s), 134.2 (1C, s), 167.8 (1C, s), 170.1 (1C, s).

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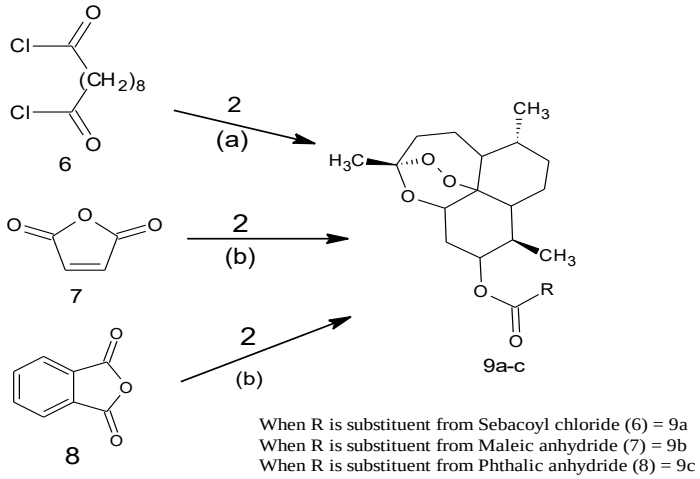

Scheme 1. Synthesis of esters of dihydroartemisinin, 2, (a) Et_3N, dry CH_2Cl_2, 0°C, 10 h. (b) Et_3N, EtOAc, 0°C→25°C, 7 h

1.2.3 Synthesis of 2-({[(6R,9R)-3,6,9-trimethyldecahydro-12H -3,12-epoxypyrano[4,3-j][1,2]benzodioxepin-10-yl]oxy}carbonyl)benzoic acid (9c): DHA **2** (0.58 g, 1 mmol) was suspended in ethyl acetate (40 ml) and cooled in an ice bath. Afterward, Et_3N (0.33 ml) was added and the mixture was stirred vigorously. To the cooled suspension, phthalic anhydride **8** (0.61 g, 3 mmol) was added step by step in small portions over a period of 30 min. After a further 10 min, the ice bath was removed and the solution was stirred for 7 h at room temperature. The reaction was monitored with TLC (CH_2Cl_2: MeOH: C_6H_{12}; 6.5:0.5:3) to ensure a complete reaction. The product was detected by spraying the TLC plate with vanillin-sulphuric acid. For the workup, distilled water (50 ml cooled) was added to the reaction mixture and then neutralized (pH = 5) with 2N H_2SO_4. The aqueous phase was then extracted three times with about 20 ml of ethyl acetate until no product could be found in the extracting agent as monitored with TLC. The combined ethyl acetate extracts were washed once with water. Afterward, the extract was dried with anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure and the yield (**9c**) was determined. (Presser and Von, 2007).

The structure was confirmed using FTIR (Shimadzu, 8400S), EIMS (Shimadzu), ^{1}H NMR, and ^{13}C NMR as follows:

FT-IR (neat) characteristics bands (cm^{-1}):3379, 2931, 2862, and 1651, 1435-1396.

MS major fragments (m/z): 266[base peak], 228, 213, 195, 93, 69, and 43.

^{1}H NMR: δ 0.87-1.02 (6H, 0.93 (d, *J* = 6.9 Hz), 0.96 (d, *J* = 6.9 Hz)), 1.33 (3H, s), 1.48-2.20 (11H, 1.57 (dddd, *J* = 13.1, 8.2, 5.8, 4.0 Hz), 1.58 (dddd, *J* = 13.0, 8.2, 5.5, 1.8 Hz), 1.60 (dddd, *J* = 13.0, 3.7, 3.2, 2.1 Hz), 1.60 (dddd, *J* = 13.0, 7.5, 5.8, 1.5 Hz), 1.75 (dqdd, *J* = 7.5, 6.9, 2.9, 1.8 Hz), 1.83 (dddd, *J* = 13.0, 10.2, 10.1, 2.0 Hz), 1.85 (ddd, *J* = 14.8, 3.7, 2.0 Hz), 1.93 (dddd, *J* = 13.1, 5.5, 2.4, 1.5 Hz), 2.04 (ddd, *J* = 7.9, 4.0, 2.4 Hz), 2.12 (ddd, *J* = 14.8, 10.1, 2.1 Hz), 2.12 (ddd, *J* = 10.2, 3.2, 2.9 Hz)), 2.40 (1H, ddq, *J* = 7.9, 7.2, 6.9 Hz), 5.41 (1H, s), 6.35 (1H, d, *J* = 7.2 Hz), 7.64-7.83 (4H, 7.71 (ddd, *J* = 7.8, 7.7, 1.3 Hz), 7.74 (ddd, *J* = 7.8, 7.7, 1.3 Hz), 7.76 (ddd, *J* = 7.8, 1.3, 0.5 Hz), 7.77 (ddd, *J* = 7.8, 1.3, 0.5 Hz)).

^{13}C NMR: δ 19.0 (1C, s), 19.3 (1C, s), 22.2 (1C, s), 24.1 (1C, s), 25.2 (1C, s), 32.9 (1C, s), 35.1 (1C, s), 36.8 (1C, s), 40.7 (1C, s), 44.5 (1C, s), 49.1 (1C, s), 79.1 (1C, s), 93.7 (1C, s), 96.8 (1C,

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s), 104.8 (1C, s), 128.3-128.5 (2C, 128.4 (s), 128.4 (s)), 129.3-129.4 (2C, 129.3 (s), 129.3 (s)), 131.4 (1C, s), 132.4 (1C, s), 166.2 (1C, s), 167.5 (1C, s).

1.2.4 *In-silico* cLogP Calculation: The SMILES notations for the chemical structures of **2, 5, 9a, 9b,** and **9c** were generated using ACD/Chemsketch software and then loaded into the online platforms of Molinspiration, Molsoft, SwissADME, and VCCL to calculate their cLogP values. The cLogP was also obtained directly from ACD/Chemsketch software.

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1.3 RESULTS & DISCUSSION

1.3.1 Synthesis Output: Products **9b** and **9c** were obtained in higher yields of 43.27% and 47.06% respectively compared to **9a**. This is consistent with the yield obtained when succinic anhydride was employed (Presser *et al.*, 2017). The absence of alcoholic -OH stretch in 9a explains the successful esterification process that substituted the hydroxyl group with an acyl (ester) group. All the products showed characteristic carbonyl ester stretches (-RCOOR) around 1700 to 1740 cm^{-1} which leads to saying that the esterification process was successful.

1.3.2 In silico pharmacokinetic and molecular properties

See Table 2

1.3.3 Computational Pharmacokinetic/ Molecular Properties

The mean octanol/water partition coefficient (clog P) was calculated for all the products synthesized using four (4) computational software as shown in Table 3. This was to strengthen the validity of the clogP values. The clog P measures the extent of hydrophilicity or lipophilicity of a solute. The partition coefficient is an important measurement of the physical nature of a substance and thereby a predictor of its behavior in different environments. A negative value for log P means the compound has a higher affinity for the aqueous phase (it is more hydrophilic); when log P = 0 the compound is equally partitioned between the lipid and aqueous phases; a positive value for log P denotes a higher concentration in the lipid phase (i.e., the compound is more lipophilic). Drug candidates are often screened according to log P, among other criteria, to help guide drug selection and analog optimization. This is because lipophilicity is a major determining factor in a compound's absorption, distribution in the body, penetration across vital membranes and biological barriers, metabolism, and excretion (ADME properties). According to 'Lipinski's Rule of 5' the log P of a compound intended for oral administration should be < 5 (Bhal, 2007).

From Table 2, Products 9b and 9c had to mean calculated log P (clog P) values of 2.72 and 3.70. When compared to that of dihydroartemisinin and artesunate, 2.48 and 2.54 respectively, it can be seen that Products 9b and 9c have better lipophilicity profiles and still obey Lipinski's rule of 5. This affords a higher drug distribution and penetration into cell membranes when administered. Notwithstanding, the product can be condensed with a suitable salt-forming anion to improve its water solubility and optimize log D values while still retaining their optimized lipophilicity profiles. However, Product 9a had mean clog P values of 5.85. This precludes its qualification for oral administration. Notwithstanding, it is a potential drug candidate for parenteral formulations (excluding the intravenous route) as they will deliver the active moiety of the antimalarial into desired areas of the body at a faster rate, reduce the frequency of drug administration and improve patient compliance. Table 3 shows the evaluation of the molecular properties of the products synthesized for oral viability, comparing them with dihydroartemisinin and a standard drug reference, artesunate. Due to the necessity of screening very large real or virtual libraries, on the order of a million compounds or more, to derive acceptable molecular/physicochemical properties of drug candidates, approaches were investigated that would significantly speed the evaluation of each compound while maintaining the accuracy (Pajouhesh & Lenz, 2005).

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Lipinski's rules predict that a molecule is likely to be orally bioavailable if the following criteria are met (Pajouhesh & Lenz, 2005): Molecular weight is < 500, log P is < 5, < 5 H-bond donors (sum of NH and OH) and < 10 H-bond acceptors (sum of Nitrogen and Oxygen atoms). An additional rule was proposed by Veber of < 10 rotatable bonds (Pajouhesh & Lenz, 2005). Ertl has also developed a topological polar surface area (TPSA) to explore drug distribution which holds that TPSA of < 140 Å for oral drugs and < 90 Å for CNS-penetrating drugs (Pajouhesh & Lenz, 2005).

From Table 3, products 9b and 9c are seen to possess the necessary criteria for oral viability together with dihydroartemisinin and artesunate. However, Product 9a did not meet the necessary criteria for oral viability. In drug distribution, (calculated as TPSA), Products 9b and 9c were found to distribute appreciably in the systemic circulation only with TPSA < 140 Å while Product 9a was found to possess a potential CNS penetrating ability with a TPSA of 80.29 Å.

Table 1. Physical Properties of the Ester derivatives obtained

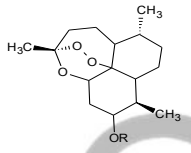
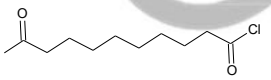
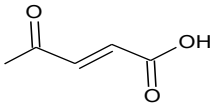
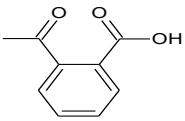
Compound/Physical appearance	Chemical Structure	% Yield (%)	Melting Point (◦C)
	 R=		
2 *White amorphous powder*	H	-	148-152
9a *Yellow crystalline solid*		14.19	82-86
9b *Pink Crystalline powder*		43.27	133-136
9c *White Crystalline Needles*		47.06	139-142

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Table 2: Computational prediction of octanol/water partition coefficient (clog P)

Compound No.	Calculated Log P (clog P)				Mean clog P
	Molinspiration	(VCCL 2.0) [a]	ACD/Chem Sketch[b]	Swiss ADME[c]	
2	2.78	2.25	2.60	2.27	2.48
5	2.75	2.35	2.94	2.13	2.54
9a	7.02	5.26	6.22	4.88	5.85
9b	3.04	2.17	3.60	2.05	2.72
9c	4.39	3.94	4.28	2.17	3.70

[a]VCCL 2.0: Virtual Computational Chemistry Laboratory 2.0
[b]ACD/Chem Sketch: Advanced Chemistry Development/ Chem Sketch
[c]ADME: Absorption, Distribution, Metabolism, Excretion.

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Table 3. Comparison of parameters for assessment of oral viability of the synthesized compounds

Compound	Mol. Wt.[a] (< 500 g/mol)	TPSA[b] (<140 Å^2)	No. HBA[c] (<10)	No. HBD[d] (< 5)	Mean clog P[e] (< 5)	No. RB[f] (<10)	Remark
2	284.35	57.15	5	1	2.48	0	Orally viable
5	384.42	100.52	8	1	2.54	5	Orally viable
9a	487.03	80.29	12	0	5.85	11	Not orally viable
9b	382.40	100.52	8	1	2.72	4	Orally viable
9c	432.46	100.52	8	1	3.70	4	Orally viable

[a]Mol. Wt.: Molecular weight
[b]TPSA: Total Polar Surface Area
[c]No. HBA: Number of hydrogen bond acceptors
[d]No. HBD: Number of hydrogen bond donors
[e]Mean clog P: Mean of calculated log P values
[f]No. RB: Number of rotatable bonds

1.4 CONCLUSION

In conclusion, three (3) products (9a, 9b, and 9c) were synthesized using standard procedures, and their molecular and physicochemical properties were predicted using computational software. Products 9b and 9c were found to be potential orally viable drug candidates while Products 9a was found to be a potential parenterally acting antimalarial.

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1.6 CONFLICT OF INTEREST: All authors declare no any conflict of interest.

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