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SHORT COMMUNICATION

Synthesis of Lapachol and 4-Hydroxyquinazoline Derivatives as Candidates for Antimalarial Activity

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Abstract:

Malaria is a disease that still plagues many tropical countries, affecting around 228 million people and with approximately 430 thousand deaths worldwide. The resistance of the causative protozoan against the existing antimalarials has been increasing, including for combination therapies based on artemisinin, a first-line treatment against malaria. Therefore, the search for new antimalarial agents becomes essential. Lapachol and febrifugine are substances with antimalarial activity with the potential for the development of new antimalarials, but with relevant cytotoxicity. In this work, we propose the synthesis of two derivatives, one from lapachol and the other from febrifugine, aiming at an improvement in antimalarial activity and a decrease in cytotoxicity. Lapachol was isolated from the sawdust of purple ipe and derivatized in a twostep synthesis, providing an unprecedented derivative in 25% yield overall. The febrifugine derivative was synthesized from 4-hydroxyquinazoline in 61% yield (2 steps). Both were purified by column chromatography and characterized by ^{1}H, ^{13}C NMR, HSQC and HMBC. Also, the parameters as clogP, the presence of atoms capable of acting as acceptors or donors of hydrogen bonds, molecular mass, topological surface area, rotatable bonds were determined in order to predict the solubility and bioavailability of this compounds as drug candidates.

Keywords: febrifugine; quinazoline; lapachol; malaria

1. Introduction

Malaria is an infectious disease caused by protozoa of the genus *Plasmodium*, which are transmitted to humans by mosquitoes of the genus *Anopheles*, occurring exclusively through the bite of the infected female [1,2]. In 2018, the number of malaria cases in the world was estimated at 228 million, higher than the 219 million cases registered in 2017 [3]. This increase in the number of cases occurs due to the appearance of an increasing resistance of the parasite to almost all existing antimalarials. The treatment recommended by the World Health Organization (WHO), since 2006, consists of combination therapies, where two or more antimalarials are used simultaneously. However, the treatment has been facing the emergence of resistance. Therefore, the discovery of new drugs for the treatment of malaria is essential [4].

The substances that have the quinone core such as lapachol (Figure 1) are of great interest to medicinal chemistry, as they are related to diverse biological activities as antiprotozoal, antifungal, anticancer and antibacterial among others. [5]. Despite being considered an antimalarial agent, lapachol (**1**) has low activity against *Plasmodium berghei* in mice (20% inhibition of schizogony) and *P. falciparum* in vitro [6].

Some naphthoquinones also face problems of bioavailability and lack of selectivity, so structural changes of quinones are necessary to achieve greater activity and decrease their cytotoxicity. Changes in the prenyl side chain linked to carbon 3 in lapachol (**1**, Figure 1) carried out by

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Kopa et al. [7] and Pérez-Sacau et al. [8] suggest that its presence is crucial for antimalarial activity, since its absence or modifications result in a drastic reduction in activity.

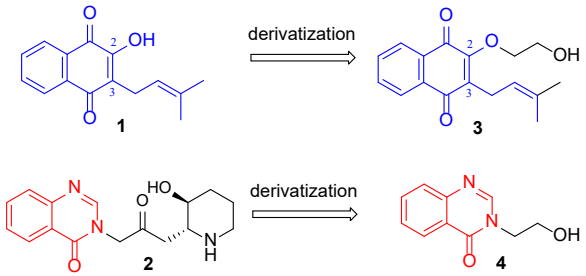


Figure 1. Derivatization proposal for Lapachol (**1**) and Febrifugine (**2**). The pharmacophoric groups of the molecules are emphasized in blue and red.

Still in the context of natural products with antimalarial activity, the roots of the Chinese herb *Dichroa febrifuga* Lour. have been used by local residents since the past to fight fever caused by malaria, even though it is a plant classified as poisonous by the Chinese book of herbs [9].

Only in 1942 the plant began to be the subject of scientific studies, when Jang et al. isolated an alkaloid (Dichroin B), later called febrifugine (**2**, Figure 1). It turned out that part of the toxic effect was not due to it, but to its isomer and intermediate, which are formed from an equilibrium in solution [9].

Therefore, based on the precedents that lapachol (**1**) and febrifugine (**2**) are compounds that have antimalarial activity, having different mechanisms of action, we saw an opportunity to create two derivatives of these compounds, as shown in Figure 1. This work intended to maintain the prenyl chain of lapachol (**1**) and add a hydroxyethyl substituent in position 2 (**3**). In addition to increasing hydrophobicity, the new group allows later derivatization and/or hybridization of lapachol with other pharmacophoric groups. Likewise, the proposed modification of febrifugine (**2**) was to replace the group responsible for its toxicity with a hydroxyethyl substituent group (**4**), which will also allow further derivatization of this molecule, if necessary.

In addition to the synthesis, important pharmacokinetic parameters were calculated in order to predict the solubility and bioavailability of compounds **3** and **4** as drug candidates in comparison with compounds **1** and **2**.

2. Results and Discussion

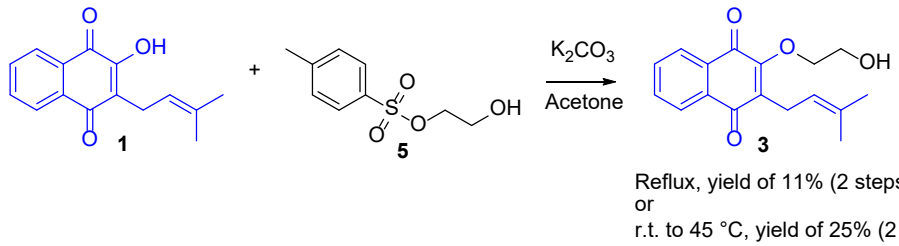
2.1 Synthesis of lapachol derivative 3

Lapachol was obtained after acid-base extraction from the sawdust of purple ipê and purification by chromatographic column with 0.08% yield [10-12]. The ^{1}H NMR spectrum of the isolated material showed all the signals of lapachol (**1**): the double doublets (8.11 and 8.06ppm) and the triplets (7.74 and 7.67 ppm) corresponding to the aromatic hydrogens and the singlet (7.33 ppm) referring to hydroxyl hydrogen, the multiplet (5.20 ppm) of methyline hydrogen, the doublet (3.30 ppm) of methylene hydrogens, and the signals of six methyl hydrogens (1.79 and 1.68 ppm). All signs were in accordance with data in the literature [11].

Subsequently, the nucleophilic substitution reaction of lapachol (**1**) with **5** (previously prepared [13]) in the presence of potassium carbonate in acetone under reflux [14], led to the formation of the desired product in 11% yield for two steps (preparation of **5** and nucleophilic substitution, Scheme 1). However, the formation of unwanted by-products led us to adjust the reaction temperature, with the reaction starting at room temperature and reaching a maximum of 45 °C for 1 week. Thus, the desired product **3** was obtained in the higher yield of 25% overall, and lapachol was recovered as remaining starting material (Scheme 1).

After product isolation and characterization, the structure of **3** was confirmed by ^{1}H, ^{13}C, HSQC and HMBC NMR analyses. The ^{1}H NMR spectrum of the isolated material presented, in addition to the characteristic signals of the lapachol precursor (**1**), two triplets 4.40 and 3.91 ppm), referring to the methylene hydrogens of the new side chain. The ^{13}C NMR spectrum of **3** shows a separation of 3 ppm between the carbonyl groups signals, a difference also presents in the lapachol carbonyl groups (**1**) (Figure 2). The permanence of this difference in the chemical shift of the carbonyl groups is an indication that the substitution occurred in the

oxygen atom linked to 2, since the 1,2-quinones, such as compound **6** (Figure 2), do not present this difference [15].



Scheme 1. Synthesis of 2-(2-hydroxyethoxy)-3-(3-methylbut-2-en-1-yl)naphthalene-1,4-dione (**3**).

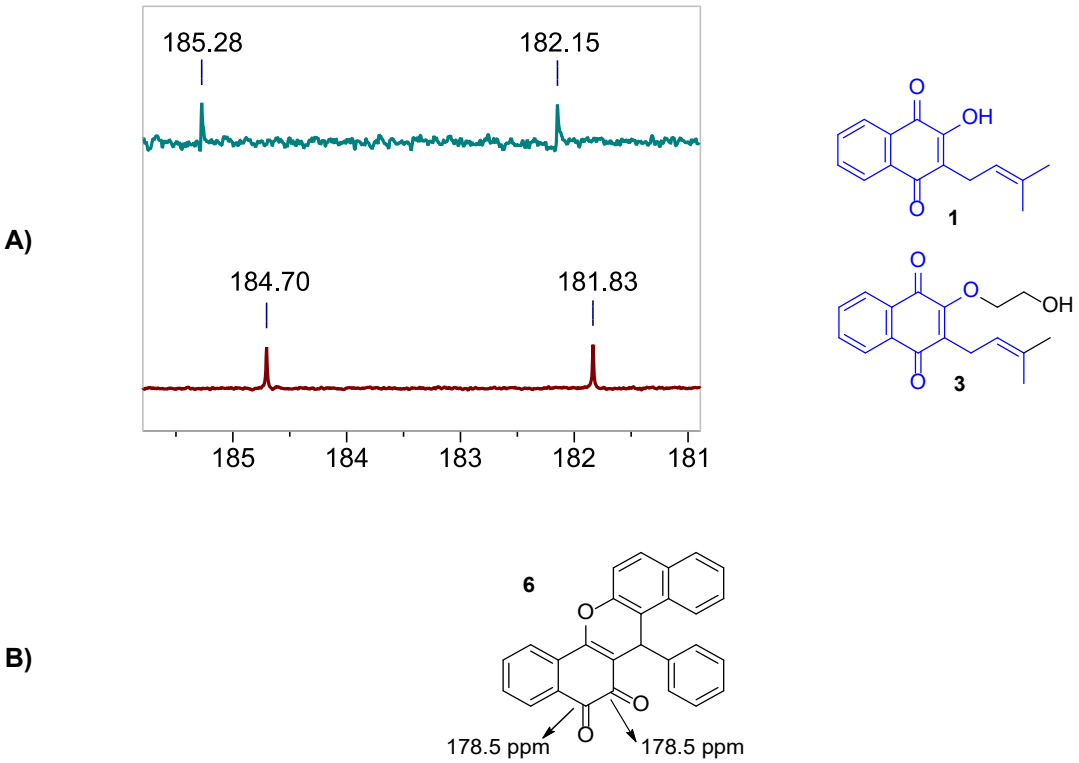


Figure 2. A) Difference in the ^{13}C NMR chemical shifts of the carbonyl groups of lapachol (**1**, a 1,4-quinone) and derivative **3** (1,4-quinone) and B), chemical shifts of carbonyl groups of a 1,2-quinone (**6**) reported in the literature [15].

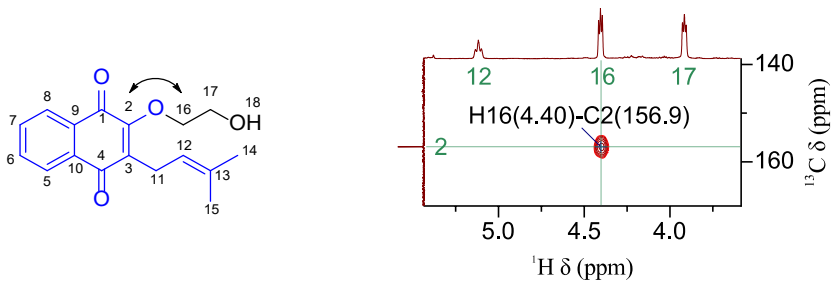


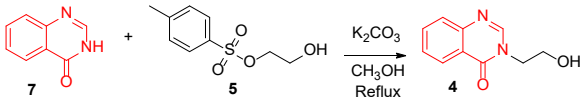
Figure 3. Correlation between H-16 and C-2 observed in the HMBC spectrum of compound **3**.

The unambiguous elucidation of the structure was completed with the aid of two-dimensional NMR techniques. After determining which carbons were linked to which hydrogens in the structure by HSQC experiment, the HMBC displayed the correlation between H-16 at

4.40 ppm and C-2 at 156.9 ppm (Figure 3), confirming the position of substitution and allowing the characterization of compound **3**, unprecedented in the literature.

2.2 Synthesis of Febrifugine analogue 4

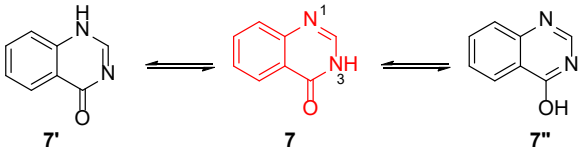
Compound **4** was prepared similarly to compound **3**, by a nucleophilic substitution reaction between commercially available 4-quinazolinone (**7**) and **5** (previously prepared [13]) in the presence of potassium carbonate, under reflux in methanol (Scheme 2).



Scheme 2. Synthesis of 3-(2-hydroxyethyl)quinazolin-4(3H)-one (**4**).

The 4-quinazolinone **7** has three possible tautomers (4(3H)-quinazolinone (**7**), 4(1H)-quinazolinone (**7'**) and 4-hydroxyquinazoline (**7"**)) and three atoms capable of carrying out nucleophilic substitution reaction, *N*-1, *N*-3 and oxygen (Scheme 3). Špulák et al. [16] reported that the literature describes several procedures for preferential alkylation of one nucleophilic center over the others. However, they observe contradictory information when analyzing works that use the same substrate and similar reaction conditions resulting in different proportions of produtcs. In addition, Špulák et al. indicate a lack of consistency in the literature probably due to the erroneous attribution of the structures.

The simultaneous formation of products by alternative nucleophilic sites can lead to the formation of regioisomers with similar ^{1}H NMR spectra, making impossible to differentiate them by this technique alone. This led to the incorrect characterization of many structures and their replication in the literature [16]. Špulák et al. emphasize that a reliable indicator that the alkylation reaction has occurred at *N*-3, is the observation, in the ^{13}C NMR, of a signal in the range of 45-55 ppm.



Scheme 3. 4-quinazolinone **7** and its tautomers.

The ^{1}H NMR spectrum of product **4** shows the signals of aromatic hydrogens (ddd, 8.14, 7.67, 7.57 and 7.41 ppm), the singlet of methyline hydrogen at 8.10 ppm, and two triplets of the methylene hydrogens at 3.85 and 7.07 ppm. The structural characterization of product **4** was in accordance with the ^{1}H NMR data in the literature [17] and was also consistent with the observation of Špulák et al. [16], since a ^{13}C NMR signal at 49.51 ppm was observed. However, due to the lack of consistency of data available in the literature, two-dimensional NMR experiments were performed in order to confirm the structure. By using the HSQC, to determining which carbons were linked to which hydrogens in the structure, and HMBC, another two-dimensional NMR technique, the electrophile entry position was confirmed by the correlations between H-11 4.04 ppm), and C-2 148.6 ppm) and C-4(160.3 ppm) (Figure 4).

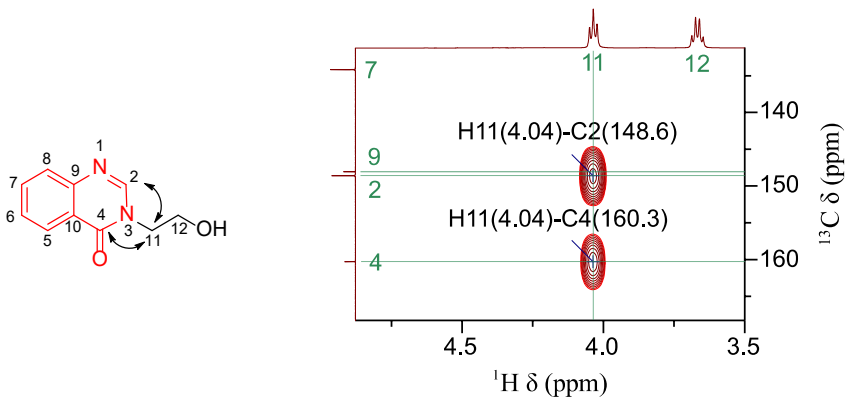


Figure 4. Correlations between H-11, C-2 and C-4 in the HMBC spectrum that allowed to confirm the substitution position in derivative **4**.

The exclusive formation of the product by *N*-3 substitution can be explained in part by the proportion of the tautomers. Hearn et al. [18] estimated that the proportion between **7'**:**7**:**7"**, in neutral medium (95% ethanol), should be close to 1:7:2. Špulák et al. [16] performed computational studies to report the preference for *N*-3 between the three nucleophilic sites in a substitution reaction with methyl bromide, as it has the lowest activation energy of the transition state (9.34 kcal mol^{-1}) when compared to *N*-1 and O (13.34 and 11.53 kcal mol^{-1}, respectively).

2.3 In Silico Analysis of Physical and Chemical Properties of Synthetized Substances

The hydrophilicity of the substances is an important parameter for pharmacokinetic studies and can be calculated by predicting the Octanol/Water Partition Coefficient (clogP) [19]. Other parameters can also be evaluated to determine the solubility and permeability of the substances, making, consequently, the prediction of its bioavailability will become a drug. In addition to clogP, the presence of atoms capable of acting as acceptors (HBA) or donors (HBD) of hydrogen bonds, molecular mass (MM), topological surface area (TPSA) , rotatable bonds (RB) are important to determine what the chances of certain substances will become drugs [20,21].

These calculated data can be used in the framework of Lipinski's rules and their extensions. This rule, also called the "Rule of 5", is the result of computational research carried out by Christopher A. Lipinski and collaborators in 1997, in a library with more than 2000 drugs, of which the physical and chemical properties and these were associated with good solubility in an aqueous environment and intestinal permeability. Finally, the rule is that low oral absorption will be observed in molecules that have MM> 500 units, clogP> 5, HBA> 5 and HBD> 10 [22, 23].

In a position to extend these postulated rules, under similar concepts, in order to improve estimates of bioavailability and toxicity, Veber et al. [24] evaluated a library of 1,100 drug candidates. Among their findings, it was possible to predict/determine an association of molecular permeation with the number of 10 or less rotatable bonds (RB), as well as low TPSA. An optimum TPSA value was also determined in this work for the absorption of the compound in the intestine (less than or equal to 140 Å). [24]

In general, it is argued that a molecule should not have two or more violations of Lipinski's rules (including Veber's extension) for its cell permeation characteristics to be adequate. And yet, it is necessary to observe the compliance with these rules, so that the designed compounds can be appropriately adapted to clinical trials and the conveniences of using the oral route. [23]

Thus, in this work the values of clogP were estimated on the SwissADME online platform. On this platform, values can be obtained by different methodologies. Here we use the value of "consensual clogP", that is, an arithmetic average between the values predicted in all methodologies [25]. For the derivatives synthesized in this work, the data are promising, since they all fall within the optimization range of -0.4 and +5.6 (Table 1, entry 2).

Using a methodology validated in the work of Ertl et al. [26], the SwissADME platform also makes prediction of TPSA by the sum of the polar fragments in order to indicate a better absorption (resulting from dissolution in a hydrophilic environment) and membrane permeation. [25]

TPSA is related to a prediction of substance transport and, in general, correlates very well with human intestinal absorption. Therefore, it is possible to infer that the compounds presented would have a good absorption, with values of 63.60 for derivative **3** and 53.23 for derivative **5** (table 1, entry 3).

Other values obtained on the platform are the Molecular Mass (MM, Table 1, entry 4) and the amount of Hydrogen Donors and Acceptors (HBD, entry 7 and HBA, entry 6) which, as discussed by Veber et al. [24], signal a relative solubility in aqueous medium and the possibility of hydrogen bonding occurring in the compound fitting with a molecular target. In the case of derivative **3**, it has one more acceptor than lapachol **1** and derivative **4**, although less acceptors and hydrogen bond donors, still contribute positively to the water solubility of

substances.

When considering the Rotatable Connections (RB), which, as described by Veber et al. [24], works as an assessment of molecular flexibility, evaluated as an increase in the bioavailability description of the compound. Derivative **3** has three more rotatable bonds than its precursor lapachol **1**.

In general, the data obtained are promising. For all compounds, the clogP values fall within the optimization range of -0.4 and +5.6; as well as the molecular weight between 180 and 500 units and the number of rotatable connections less than ten. Still, compounds **3** and **4** have no escape from the rules of Lipinski or even to the extension of Veber. [23]

In addition, compounds that meet the criteria stated by Lipinski and Veber are commonly referred to as drug-like. [23] The Druglikeness score assessment can be obtained in the OsirisProperty program, in an evaluative approach that verifies the structural similarity of the compound designed with a library of fragments of 3300 commercial drugs and other 15000 chemicals [27]. The similarity values to these compounds are evaluated and reveal a numerical variation by the program, in which the positive values indicate the predominance of chemical fragments present in commercial drugs.

The Drug-Score calculation is done by OsirisProperty, in order to mathematically combine the properties of the designed compound (such as druglikeness, water solubility and octanol/water distribution coefficient, molecular weight, etc.) in a single value that can be used to classify the potential of the compound in its use as a drug [28]. The score, ranging from 0 to 1, represents the reduction of risks related to the use of this compound

Compound **4** has interesting subsidies from the point of view of drug planning, since the positive druglikeness score announces a degree of similarity of the compound with drugs available on the market and yet, the drug-score data is close to number one, demonstrating the likelihood of very low health risk during use.

Table 1. Physico-chemical properties for compounds **1** - **4**.

Entry	Compound	1	2	3	4
1	Violations	0	0	0	0
2	LogP	2.61	0.83	2.57	0.83
3	TPSA	54.37	84.22	63.60	53.23
4	MM	242.27	301.34	286.32	190.20
5	RB	2	4	5	2
6	HBA	3	5	4	3
7	HBD	1	2	1	1
11	Druglikeness	-2.02	5.18	-2.1	4.04
12	Drug-Score	0.28	0.92	0.46	0.96

3. Material and Methods

All reactions were monitored by thin layer chromatography (TLC, Merck®, silica gel 60) and developed with ultraviolet light (UV, 254 nm) and/or phosphomolybdic acid solution (10% w/v).

The product purification procedure was performed by recrystallization or column chromatography (CC) using silica gel (0.060-0.200 mm Acros Organics® or 0.040-0.063 mm Merck®) as a stationary phase and mixtures of ethyl acetate/hexane as a mobile phase.

The products were characterized by Nuclear Magnetic Resonance of Hydrogen (^{1}H NMR at 400 MHz) and carbon-13 (^{13}C NMR at 100 MHz) in a Bruker Ascend III spectrometer equipped with 5 mm multinuclear probes from the multi-user Spectroscopy Laboratory (ESPEC) of Universidade Estadual de Londrina. The spectra were calibrated with tetramethylsilane (δH, 0.00 ppm), deuterated chloroform (δH, 7.26 ppm; δC, 77.16 ppm) or deuterated DMSO (δH, 2.50 ppm).

The multiplicity of ^{1}H NMR signals were denoted as singlet (s), doublet (d), double doublet (dd), double double doublet (ddd), triplet (t) and multiplet (m). When necessary, the indication of large (l) was added, followed by the

multiplicity. Coupling constants (*J*) are described in hertz (Hz).

Synthesis of 2-hydroxyethyl 4-methylbenzenesulfonate (5): The reaction was performed according to Davis and Bull [13]. In a round bottom flask, a solution of 4-toluenesulfonyl chloride (6.0 g, 31.6 mmol) in pyridine (30 mL; 11.8 eq.) was added dropwise over ethylene glycol (26.7 mL; 474.2 mmol; 15 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After consumption of the starting material, followed by TLC, the mixture was transferred to a separatory funnel with 25 mL of CH_2Cl_2 and washed with three portions of saturated aqueous NH_4Cl solution (25 mL). The organic phase was washed with 25 mL of brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The product was purified by silica gel column chromatography using 6:4 ethyl acetate:hexane as the eluent, providing a light yellow oil (3.0 g; 45%). Rf = 0.51 (7:3 ethyl acetate:hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.81 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.14 (t, *J* = 4.3 Hz, 2H), 3.82 (t, *J* = 4.5 Hz, 2H), 2.45 (s, 3H), 2.08 (s, 1H). ^{1}H NMR ([13], 400 MHz, $CDCl_3$) δ (ppm): 7.86-7.80 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 4.18-4.13 (m, 2H), 3.86-3.80 (m, 2H), 2.47 (s, 3H), 1.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.2, 132.8, 130.1, 128.1, 71.8, 60.1, 21.8. ^{13}C NMR ([13], 101 MHz, $CDCl_3$) δ (ppm): 145.1, 132.6, 129.9, 127.9, 71.6, 60.6, 21.6.

Isolation of Lapachol (1): The extraction procedure was performed according to Brandão et al. [11] with modifications. 250 g of ipê sawdust were kept for one week in 1 L of 1% aqueous Na_2CO_3 solution. The dark colored suspension was filtered through cotton and acidified with 1 M HCl solution until the dark collor became light yellow. The precipitate formed was vacuum filtered and oven dried at 45 °C. The solid material was extracted with 110 mL of CH_2Cl_2 in a Sohxlet extractor for 6 h and purified by silica gel column chromatography (1:9 ethyl acetate:hexane), yielding yellow lapachol crystals (193.1 mg; 0.08%). Rf = 0.55 (3:7 ethyl acetate:hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (dd, *J* = 7.7, 1.0 Hz, 1H), 8.06 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.74 (td, *J* = 7.6, 1.4 Hz, 1H), 7.67 (td, *J* = 7.5, 1.3 Hz, 1H); 7.33 (s, 1H), 5.20 (m, 1H,), 3.30 (d, *J* = 7.3 Hz, 2H), 1.79 (s, 3H), 1,68 (s, 3H). ^{1}H NMR ([11] 200 MHz, $CDCl_3$) δ (ppm): 8.13-8.05 (m, 2H), 7.78-7.63 (m, 2H), 7.34 (s, 1H), 5.21 (m, 1H), 3.30 (d, 3H, *J* = 6.6 Hz), 1.79 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 184.7, 181.8, 152.8, 134.9, 133.9, 133.0, 133.0, 129.6, 126.9, 126.2, 123.6, 119.8, 25.9, 22.8, 18.0. ^{13}C NMR ([11] 50 MHz, CDCl3) δ (ppm): 184.5, 181.7, 152.7, 134.8, 133.7, 133.0, 132.8, 129.5, 126.8, 126.0, 123.6, 119.7, 25.7, 22.7, 17.9.

Synthesis of 2-(2-hydroxyethoxy)-3-(3-methylbut-2-en-1-yl)naphthalene-1,4-dione (3): The reaction was performed according to Fiorito et al. [14] with modifications. In a round-bottom flask containing a solution of lapachol (**1**) (96.5 mg; 0.398 mmol) in acetone (3.6 mL), K_2CO_3 (110.1 mg; 0.797 mmol; 2 eq) was added. After 5 min, a solution of **5** (258.5 mg; 1.195 mmol; 3 eq.) dissolved in acetone (6.8 mL) was slowly added and the reaction mixture was kept at 45 °C for 1 week. The reaction mixture was poured into 10 mL of distilled water, transferred to a separatory funnel and extracted with three portions of ethyl ether (10 mL). The organic phase was washed with brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The product was purified by silica gel column chromatography (2:8 ethyl acetate:hexane) , providing a yellow oil (29.2 mg; 25.6%). Rf = 0.34 (3:7 ethyl acetate:hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 – 8.01 (m, 2H), 7.76 – 7.65 (m, 2H), 5.12 (t, *J* = 7.1 Hz, 1H), 4.40 (t, *J* = 4.3 Hz, 1H), 3.91 (t, *J* = 4.3 Hz, 2H), 3.34 (d, *J* = 7.1 Hz, 2H), 1.79 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 185.3, 182.2, 157.0, 135.8, 134.3, 134.2, 133.5, 132.2, 131.5, 126.5, 126.4, 120.2, 75.5, 62.5, 25.9, 23.3, 18.1.

Synthesis of 3-(2-hydroxyethyl)quinazolin-4(3H)-one (4): The reaction was performed according to Okuda et al. [17] with modifications. In a round-bottom flask containing 4-quinazolinone (500.0 mg; 3.4 mmol) dissolved in methanol (8.6 mL), K_2CO_3 (1.8913 g; 13.6 mmol; 4 eq.) was added and, after 5 min, **5** was added slowly at room temperature (2.5894 g; 11.9 mmol; 3.5 eq.). The reaction mixture was brought to reflux and maintained for 40 h. After

evaporating the solvent under reduced pressure, the reaction mixture was diluted with 10 mL of distilled water and extracted with three portions of $CHCl_3$ (10 mL) in a separatory funnel. The organic phase was washed with 10 mL of brine, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The reaction product was purified by recrystallization from ethyl acetate, resulting in a white solid (398.0 mg; 61%). Rf = 0.19 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$ and CD_3OD (1:1) δ (ppm): 8.14 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1H), 8.10 (s, 1H), 7.67 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.2, 1.1, 0.5 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 4.07 (t, *J* = 5.2 Hz, 2H), 3.85 (t, *J* = 5.3 Hz, 2H). ^{1}H NMR ([17] 400 MHz, $CDCl_3$) δ (ppm): 8.15 (dd, *J* = 7.8, 1.4, 1H), 8.07 (s, 1H), 7.72 (td, *J* = 7.6, 1.4 Hz, 1H), 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.43 (td, *J* = 7.6, 1.5 Hz, 1H), 4.16 (t, *J* = 4.9 Hz, 2H), 4.01 (t, *J* = 4.9 Hz, 2H), 3.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ and CD_3OD (1:1) δ (ppm): 161.4; 147.8; 147.4; 134.5; 127.4; 126.7; 126.5; 121.7; 59.7; 49.5. ^{13}C NMR ([29] 100 MHz, $CDCl_3$) δ (ppm): 160.2, 148.6, 148.0, 134.2, 127.1, 126.8, 126.0, 121.6, 58.2, 48.6.

4. Conclusions

We achieved the synthesis of two new candidates for antimalarials, **3** and **4**, in 25% and 61% yield over two steps, respectively. Associated with this, the structure of the lapachol derivative, unprecedented in the literature, was confirmed by one- and two-dimensional NMR techniques. The structure of the febrifugine analogue, although already reported in the literature, had its unequivocally determined by the same NMR techniques. Both products, **3** and **4**, can be subsequently derivatized, since their structure have a primary hydroxyl available for further reactions, such as oxidation, esterification, etherification, elimination and aliphatic nucleophilic substitution.

The pharmacokinetic parameters for the synthesized compounds are promising, since all clogP values fall within the optimization range of -0.4 and +5.6. In addition, molecular weights are between 180 and 500 units, with numbers of rotatable bonds (RB) less than 10. Also, compounds **3** and **4** have no escape from the rules of Lipinski or even the extension of Veber. Compound **4** has interesting subsidies from the point of view of drug design, since the positive druglikeness score announces a degree of similarity of the compound with drugs available on the market and yet, the drug-score data is close to number 1, demonstrating the likelihood of very low health risk during use.

Supporting Information

^{1}H, ^{13}C, HSQC and HMBC spectra for the prepared compounds are available.

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