New Orally Active Derivatives of Artemisinin with High Efficacy against Multidrug-Resistant Malaria in Mice[1]

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A new series of ether derivatives of dihydroartemisinin have been prepared and evaluated for their antimalarial activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in mice by oral route. These new derivatives **7**−**17** are highly lipophilic (log P in the range of 5.51 to 7.19) as compared with β-arteether (log P 3.84), and several of them are two- to four-fold more active than β-arteether. Among the ether derivatives, α-isomers are more active than the β-isomers. The ether derivatives **12**α and **14**α, the most active compounds of the series, provided 100% protection to infected mice at 12 mg/kg × 4 days. In this model β-arteether provides 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively.

Introduction

Malaria is endemic in many parts of the world. Around 300−500 million clinical cases of malaria are reported every year of which more than a million die due to complicated malaria.[2] The malaria situation is getting worse with rapid spread of multidrug-resistant *Plasmodium falciparum*. Against this background, isolation of artemisinin **1** as the active principle of the Chinese traditional drug against malaria, *Artemisia annua*, is a major breakthrough in malaria chemotherapy.[3] Artemisinin owes its antimalarial activity due to the presence of 1,2,4-trioxane system and is active against both chloroquine-sensitive and chloroquine-resistant malaria. The semisynthetic derivatives of artemisinin such as dihydroartemisinin **2**, artemether **3**, arteether **4**, and artesunic acid **5** are more active than artemisinin and are currently the drugs of choice for the treatment of malaria caused by multidrug- resistant *Plasmodium falciparum*.[4] While these compounds show high efficacy when administered by intramuscular or subcutaneous route, they exhibit poor activity when given by oral route.[5] In recent years, several attempts have been made to improve the antimalarial activity of artemisinin derivatives by oral route.[6] However, these new derivatives are only marginally more active than artemether and artesunic acid. Thus, there is a need to develop new artemisinin derivatives with better oral absorption and improved antimalarial activity. Herein, we report the synthesis and antimalarial activity of a series of new ether derivatives of dihydroartemisinin, several of which are orally 2- to 4-fold more active than β-arteether against multidrug-resistant *P. yoelii nigeriensis* in mice.[7]

Synthesis. Dihydroartemisinin **2** was prepared by $NaBH_4$ reduction of artemisinin using the known procedure.[8] $BF_3{\cdot}OEt_2$-catalyzed reaction of **2** with alcohols **6a**−**k** (Figure 2) in CH_2Cl_2 at subzero temperature (−10 °C to −5 °C) furnished the corresponding ether derivatives **7**−**17** in 65−99% yields as diastereomeric mixtures of α and β isomers, with β-isomers as the major products (Table 1). In all these cases, except ether derivatives **7**, **9**, **11**, and **17**, the α and β isomers appeared as two distinct spots on TLC and were separated by column chromatography, and the pure isomers were evaluated for antimalarial activity. Ether **11**β was obtained by crystallization of mixture of **11**α and **11**β in hexane; the pure α isomer could not be obtained. Ether derivatives **7**, **9**, and **17** which were obtained as inseparable mixture of α- and β-isomers were used as such for bioevaluation.

Antimalarial Activity. Antimalarial drug β-arteether, when given orally at 48 mg/kg × 4 days provides 100% protection to the mice infected with multidrug-resistant *P. yoelii nigeriensis*. At 24 mg/kg × 4 days, it provides only 20% protection. Since the objective of the study was to select compounds having activity profile better than that of β-arteether, all the newly prepared ether derivatives **7**−**17** were initially screened against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice at 48 mg/kg × 4 days by oral route using Peter's procedure.[9] All the ethers derivatives except **8**β and **14**β provided 100% protection at this dose and these active compounds were screened at 24 mg/kg × 4 days. Compounds **8**α, **10**α, **12**α, **14**α, **15**α, **16**α, **16**β, and **17**(as mixtures of α and β isomer) which showed 100% protection at 24 mg/kg × 4 days were further tested at 12 mg/kg × 4 days. Only compounds **12**α and **14**α, which showed 100% protection at 12 mg/kg × 4 days, were further tested at 6 mg/kg × 4 days. Both these compounds showed only partial suppression of parasitaemia on day 4 at 6 mg/kg × 4 days and none of the treated mice survived. The results are summerized in Table 2.

Results and Discussion

Artemisinin derivatives such as artemether **3**, arteether **4**, and artesunic acid **5** have excellent antimalarial activity when given by systemic routes. They are fast acting drugs and are increasingly being used for the treatment of complicated cases of malaria caused by multidrug-resistant *P. falciparum*. These drugs, however, have serious limitation such as short half-life and poor bioavailability when given by oral route.[5] Both the short half-life and poor oral bioavailability are believed to be due to the poor stability of C_{10}−O linkage which is prone to acid hydrolysis and P450-catalyzed oxidation.[10] Since C-10 acetal derivatives are unstable, several workers have in recent past prepared C_{10}−C linked derivatives which are more stable and have shown improved antimalarial activity by oral route.[6] In a parallel program on synthetic antimalarial 1,2,4-trioxanes, we had observed that molecules built around adamantane, biphenyl, and flourene scaffold show promising antimalarial activity by oral routes.[11] Also there are several reports in the literature wherein compounds having these substructures as part

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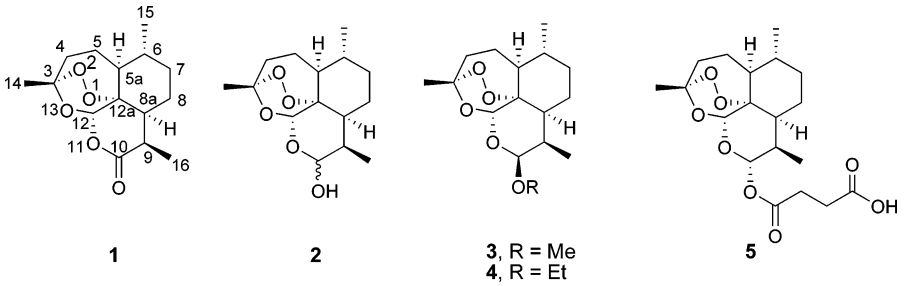


Figure 1. Artemisinin and its derivatives.

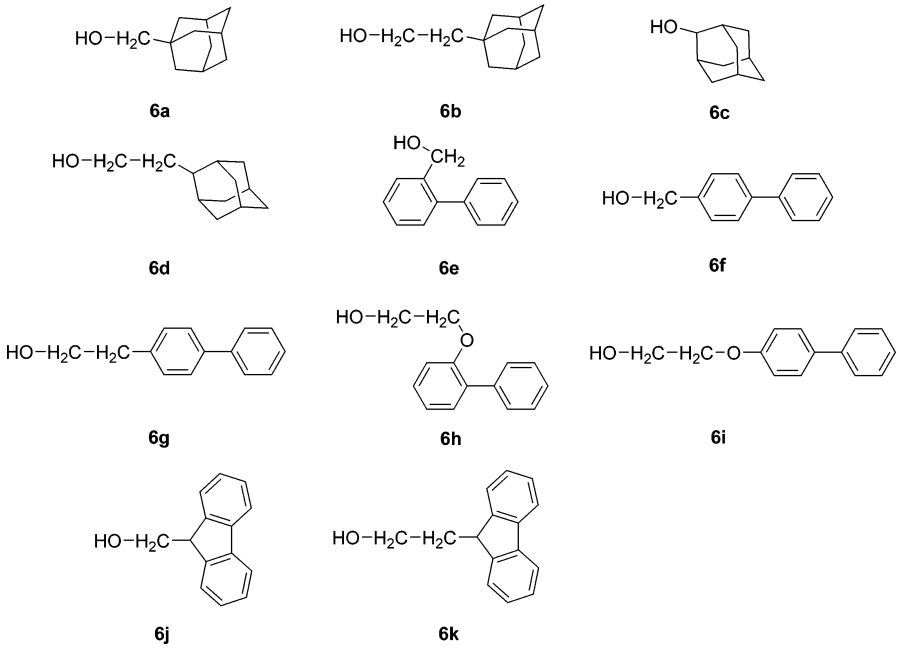


Figure 2. Structure of alcohols **6a**−**k**.

of molecular architecture show promising biological activities.[12] On the basis of these considerations, we have prepared ether derivatives **7**−**17** and evaluated them for antimalarial activity using β-arteether as positive control. Compounds **7**,[13] **9**, and **17** were obtained as inseparable mixtures of α- and β-isomers and were tested as mixtures. Compounds **7** and **9**, both being adamantane-based derivatives, showed 100% protection at 48 mg/kg × 4 days and 70% protection at 24 mg/kg × 4 days while **17**, a flourene-based compound, showed 100% protection both at 48 mg/kg × 4 days and 24 mg/kg × 4 days. In case of compounds **11** and **13**, only β-isomers were isolated; the α-isomers could not be obtained as pure compounds. Both these β-isomers showed 100% protection at 48 mg/kg and partial protection at 24 mg/kg and 12 mg/kg. For the rest of ether derivatives, where both pure α- and β-isomers were available, α-isomers were more active than the corresponding β-isomers. Thus, **8**α provided 100% protection at 24 mg/kg; while **8**β showed no protection at 24 mg/kg and only partial protection (60%) at 48 mg/kg. This is in sharp contrast to the activity profile of arteether, where β-isomer showed better activity than the α-isomer. The isomeric derivative **10**α also showed 100% protection at 24 mg/kg while the corresponding β-isomer showed only partial protection at this dose and 100% protection at 48 mg/kg. Ethers **12**α and **14**α, the two most active compounds of the series, showed 100% protection at 12 mg/kg × 4 days. Both these compounds were 4 times as active as β-arteether. The corresponding β-isomers were comparatively less active; **12**β provided 100% protection only at 48 mg/kg while **14**β was ineffective even at this dose. **15**α, a positional isomer of **14**α, was slightly less active than **14**α; it showed 100% protection at 24 mg/kg and 70% protection at 12 mg/kg. **15**β was half as active as **15**α but was much more active than its positional isomer **14**β. It showed 100% protection at 48 mg/kg and 80% protection at 24 mg/kg. In contrast to the above trend, both **16**α and **16**β showed similar level of activity. Both these isomers provided 100% protection at 24 mg/kg, and 20−40% protection at 12 mg/kg. In this case β-isomer appears to be marginally more active than the α-isomer. Overall, the ether derivatives containing the biphenyl moieties showed better activity profile than the adamantane- and flourene-based derivatives. All these ether derivatives have log *P* value above 6 (with exception of **9** which has log *P* value 5.51) and are more lipophilic than β-arteether which have log *P* values 3.84, indicating thereby that increased lipophilicity is accompanied by increase in oral bioavailability. Highly hydrophobic/lipophilic compounds are known to show good oral bioavailability, and Janssen et al. have proposed a model to explain this phenomenon. According to this model, hydrophobic compounds form aggregates of appropriate size in the aqueous environment of the gastrointestinal tract where they are taken up by microvilli (M) cells and then drained into lymphatic circulation and emptied into systemic compartments.[14]

Conclusion

We have prepared a new series of orally active ether derivatives of dihydroartemisinin, many of which show better activity profile than that of β-arteether. Ether derivatives **12**α and **14**α, the most active compounds of the series, are four times

Table 1. Ether Derivatives **7**−**17**

Compd. No.	α - isomer / β-isomer	α / β[a] ratio	% yield (α+β)
7.	R = −H$_2$C−	1: 3	91
8.	R = −H$_2$C·H$_2$C−	1: 5	79
9.	R =	1: 3	97
10.	R = −H$_2$C−H$_2$C−	1: 5	81
11.	R = −CH$_2$−	1: 4	90
12.	R = −H$_2$C−	1: 4	71
13.	R = −H$_2$C−H$_2$C−	1: 5	82
14.	R = −H$_2$C−H$_2$C−O−	1: 3	94
15.	R = −H$_2$C−H$_2$C−O−	1: 3	67
16.	R = −H$_2$C−	1: 3	76
17.	R = −H$_2$C−H$_2$C−	1: 4	99

[a] α/*β* ratio were calculated from ^{1}H NMR of α and *β* mixtures.

more active than *β*-arteether. The high order of antimalarial activity combined with ease of preparation of these compounds qualifies these compounds as candidates for further drug development studies.

Experimental Section

General. All glass apparatus were oven dried prior to use. Melting points were taken in open capillaries on Complab melting point apparatus and are presented uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 and 300 MHz respectively for ^{1}H; 50 and 75 MHz respectively for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (*δ* 0 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (*δ* 77.0 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). In NMR, numbering of atoms is presented according to the usual numbering in artemisinin as indicated in the text. Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (HR-EIMS) were obtained on JEOL MS route 600H instrument. Elemental analyses were performed on Vario EL-III C H N S analyzer (Germany), and values were within ±0.4% of the calculated values except where noted. Column chromatography was performed over Merck silica gel (particle size: 60−120 Mesh) procured from Qualigens (India), or flash silica gel (particle size: 230−400 Mesh). All chemicals and reagents were obtained from Aldrich (Milwaukee, WI), Lancaster (England), or Spectrochem (India) and were used without further purification. Log *P* values of the compounds were calculated using Chem Draw Ultra 7.0 software.

General Procedure for Etherification of Dihydroartemisinin 7−17 (compound 12 as representative). To a solution of dihydroartemisinin (1.5 g, 5.28 mmol) and biphenyl-4-yl-methanol (1.0 g, 5.43 mmol) in dichloromethane (50 mL) was added BF_3·OEt_2 (0.25 mL) at −10 °C to −5 °C. The reaction mixture was stirred at the same temperature for 2 h, neutralized with saturated sodium bicarbonate solution (25 mL), and extracted with dichloromethane (3 × 25 mL). The organic layer was washed with water (10 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The resultant crude product, upon column chromatography over silica gel using ethyl acetate/hexane (1:49) as eluant, gave pure **12***β* (1.26 g), a mixture of **12**α and **12***β* (0.23 g), and pure **12**α (0.18 g), the combined yield of **12**α and **12***β* being 71%.

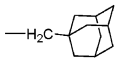
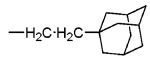
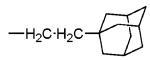
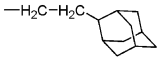
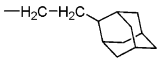
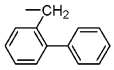
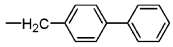
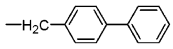
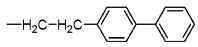
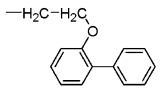
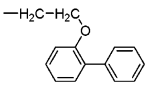
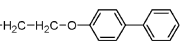
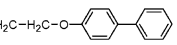
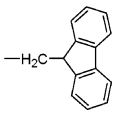
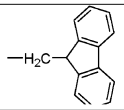
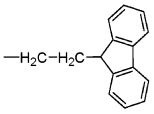
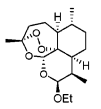
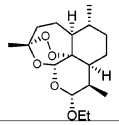
1-Adamantan-1-ylmethyl Ether of Dihydroartemisinin (7). This was obtained as white solid in 91% yield as an inseparable mixture of 7α and 7*β* (α/*β* ratio: 1:3).

7: White Solid; mp 146−147 °C; FT-IR (KBr, cm^{-1}) 2913.3, 2852.0, 1107.0, 1026.3, 761.4; ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 0.91-(d, 3H, *J* = 7.4 Hz, CH_3), 0.96(d, 3H, *J* = 5.8 Hz, CH_3), 1.21−2.09(m, 25H), 1.43(s, 3H, CH_3), 2.29−2.38(m, 1H), 2.60−2.66(m, 1H), 2.87 and 2.93(2 × d, *J* = 9.1 and 12.5 Hz respectively, together integrating for 1H), 3.48 and 3.60(2 × d, *J* = 9.1 and 9.8 Hz respectively, together integrating for 1H), 4.36 and 4.72(2 × d, 1H, *J* = 9.0 and 3.3 Hz respectively, together integrating for 1 C_{10}-H), 5.30 and 5.35(2 × s, together integrating for 1 C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 13.26(CH_3), 13.48(CH_3), 20.69(CH_3), 20.81(CH_3), 24.91(CH_2), 25.06(CH_2), 26.46(CH_3), 26.64(CH_3), 28.63(3 × CH_3), 31.62(CH), 33.32(C), 34.29(CH_2), 34.63(CH_2), 35.14(CH_2), 36.86(CH_2), 37.62(3 × CH), 37.92(CH), 40.14(3 × CH_2), 44.92(CH), 45.77(CH), 52.14(CH), 53.08(CH), 79.90(CH_2), 80.52(CH_2), 80.78(C), 81.54(C), 88.25(CH), 91.58(CH), 101.53-(CH), 102.71(CH), 104.41(C); FABMS(*m*/*z*): 433[M + H]$^+$; Anal. for ($C_{26}H_{40}O_5$): Calcd C 72.18 H 9.32; Found C 71.92 H 9.33.

2-Adamantan-1-ylethyl Ether of Dihydroartemisinin (8). This was obtained as white solid in 79% yield as a mixture of 8α and 8*β* (α/*β* ratio: 1:5) which were separated by column chromatography.

8*β*(higher R_f): White solid; mp 65−67 °C; FT-IR (KBr, cm^{-1}) 2906.9, 1218.5; ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 0.89(d, 3H, *J* = 7.3 Hz, CH_3), 0.95(d, 3H, *J* = 5.9 Hz, CH_3), 1.28−2.08(m, 27H), 1.44(s, 3H, CH_3), 2.29−2.38(m, 1H), 2.56−2.62(m, 1H), 3.32−3.44(m, 1H), 3.83−3.95(m, 1H), 4.75(d, 1H, *J* = 3.3 Hz, C_{10}-H), 5.39(s, 1H, C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 13.50(CH_3), 20.77(CH_3), 24.82(CH_2), 25.09(CH_2), 26.64(CH_3), 29.09(3 × CH), 31.29(CH), 32.07(C), 35.09(CH_2), 36.88(CH_2), 37.52(3 × CH_2),

Table 2. Blood Schizontocidal Activity of Ethers **7**−**17** against Multidrug-Resistant (MDR) Strain *P. yoelii* in Swiss Mice via Oral Route

Compd.	Structure R=	Log P	Dose mg/kg x 4 days	% Suppression of Parasitaemia on day 4[a,b]	Cured / Treated
7(α +β)		6.02	48 24 12	100 100 100	5/5 7/10 3/5
8α		6.29	48 24 12 6	100 100 97.43 61.25	5/5 5/5 0/5 0/5
8β		6.29	48 24	100 100	3/5 0/5
9(α +β)		5.51	48 24 12	100 100 100	5/5 7/10 2/5
10α		6.15	48 24 12	100 100 100	5/5 5/5 0/5
10β		6.15	48 24	100 100	5/5 2/5
11β		6.91	48 24 12	100 100 100	5/5 5/10 3/5
12α		6.91	48 24 12 6	100 100 100 86.33	5/5 10/10 10/10 0/5
12β		6.91	48 24 12	100 100 100	5/5 6/10 2/5
13β		7.19	48 24 12	100 100 100	5/5 6/10 3/5
14α		6.85	48 24 12 6	100 100 100 64.44	5/5 10/10 10/10 0/5
14β		6.85	48 24	100 100	0/5 0/5
15α		6.85	48 24 12 6	100 100 100 44.33	5/5 10/10 7/10 0/5
15β		6.85	48 24 12	100 100 100	5/5 8/10 2/5
16α		6.75	48 24 12	100 100 100	5/5 5/5 1/5
16β		6.75	48 24 12 6	100 100 100 92.95	5/5 5/5 2/5 0/5
17(α + β)		7.10	48 24 12	100 100 100	5/5 5/5 0/5
β-Arteether		3.84	48 24	100 100	5/5 1/5
α-Arteether		3.84	48 24	100 100	0/5 0/5

[a] Percent suppression= [(C − T)/*C*] × 100; where *C* = parasitaemia in control group, and *T* = parasitaemia in treated group. [b] 100% suppression of parasitaemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[15]

37.83(CH), 43.17(3 × CH_2), 44.20(CH_2), 44.91(CH_2), 53.02(CH), 64.94(CH_2), 81.57(C), 88.34(CH), 102.49(CH), 104.41(C); FABMS-(*m*/*z*): 447[M + H]$^+$; ESMS (*m*/*z*) 469 [M + Na]$^+$, 485 [M + K]$^+$; Anal. for ($C_{27}H_{42}O_5$·0.1H_2O): Calcd C 72.61 H 9.48; Found C 72.31 H 9.48.

8α(lower R_f): Viscous Oil; FT-IR (KBr, cm^{-1}) 2906.9, 1218.5; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87(d, 3H, J = 7.1 Hz, CH_3), 0.95-(d, 3H, J = 5.6 Hz, CH_3), 1.18−2.07(m, 27H), 1.44(s, 3H, CH_3), 2.30−2.45(m, 2H), 3.38−3.50(m, 1H), 3.46−4.10(m, 1H), 4.40(d, 1H, J = 9.1 Hz, C_{10}-H), 5.33(s, 1H, C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.15(CH_3), 20.68(CH_3), 22.63(CH_2), 25.12(CH_2), 26.46-(CH_3), 29.10(3 × CH), 32.05(C), 33.03(CH), 34.68(CH_2), 36.76-(CH_2), 37.54(3 × CH_2), 37.79(CH), 43.12(3 × CH_2), 43.85(CH_2), 45.79(CH), 52.09(CH), 65.56(CH_2), 80.78(C), 91.60(CH), 100.58-(CH), 104.64(C); ESMS (*m*/*z*) 469 [M + Na]$^+$ (60%); Anal. for ($C_{27}H_{42}O_5$·0.05H_2O): Calcd C 72.61 H 9.48; Found C 72.46 H 9.48.

2-Adamantanyl Ether of Dihydroartemisinin (9). This was obtained as white solid in 97% yield as an inseparable mixture of 9α and 9β (α/β ratio: 1:3).

9: White solid; mp 136−138 °C; FT-IR (KBr, cm^{-1}) 2906.3, 1102.9, 1013.7; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92(d, 3H, J = 7.5 Hz, CH_3), 0.96(d, 3H, J = 5.9 Hz, CH_3), 1.22−2.08(m, 24H), 1.44(s, 3H, CH_3), 2.29−2.45(m, 1H), 2.61−2.63(m, 1H), 3.86 and 3.96(2 × m, together integrating for 1H), 4.56 and 4.93(2 × d, J = 9.1 and 3.2 Hz respectively, together integrating for 1 C_{10}-H), 5.31 and 5.44(2 × s, together integrating for 1 C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.56(CH_3), 13.75(CH_3), 20.72(CH_3), 20.78-(CH_3), 24.94(CH_2), 25.06(CH_2), 26.44(CH_3), 26.66(CH_3), 27.69-(CH), 27.89(CH), 30.85(CH), 31.33(CH), 31.39(CH), 31.81(CH_2), 32.03(CH_2), 32.68(CH_2), 33.27(CH_2), 33.66(CH_2), 34.35(CH), 34.69(CH_2), 35.19(CH_2), 36.67(CH_2), 36.91(CH_2), 37.00(CH_2), 37.76(CH), 37.98(CH_2), 45.00(CH), 45.91(CH), 52.19(CH), 53.11-(CH), 78.88(CH_2), 79.70(CH_2), 81.62(C), 88.57(CH), 91.61(CH), 96.72(CH), 100.34(CH), 104.40(C); FABMS(*m*/*z*): 419[M + H]$^+$; Anal. for ($C_{25}H_{38}O_5$): Calcd C 71.73 H 9.15; Found C 71.40 H 9.28.

2-Adamantan-2-ylethyl Ether of Dihydroartemisinin (10). This was obtained as white solid in 81% yield as a mixture of 10α

and 10β (α/β ratio: 1:5) which were separated by column chromatography.

10β(higher R_f): White solid; mp 50−52 °C; FT-IR (KBr, cm^{-1}) 2906.9, 1218.5; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89(d, 3H, J = 7.3 Hz, CH_3), 0.95(d, 3H, J = 5.2 Hz, CH_3), 1.25−2.04(m, 27H), 1.43(s, 3H, CH_3), 2.29−2.43(m, 1H), 2.57−2.62(m, 1H), 3.34−3.41(m, 1H), 3.85−3.90(m, 1H), 4.76(d, 1H, J = 3.3 Hz, C_{10}-H), 5.38(s, 1H, C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.41(CH_3), 20.78(CH_3), 24.82(CH_2), 25.09(CH_2), 26.60(CH_3), 28.62(CH), 31.34(CH), 31.92(CH), 32.04(CH), 32.12(CH_2), 32.45(CH), 32.85(CH_2), 35.11(CH_2), 36.86(CH_2), 37.88(CH), 38.75(CH_2), 39.66(3 × CH_2), 41.75(CH), 44.90(CH), 53.01(CH), 67.48(CH_2), 81.52(C), 88.31(CH), 102.39(CH), 104.40(C); ESMS (*m*/*z*) 469 [M+Na]$^+$, 485 [M + K]$^+$; Anal. for ($C_{27}H_{42}O_5$): Calcd C 72.61 H 9.48; Found C 72.82 H 9.48.

10α(lower R_f): White solid; mp 75−77 °C; FT-IR (KBr, cm^{-1}) 2906.9, 1218.5; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87(d, 3H, J = 7.3 Hz, CH_3), 0.98(d, 3H, J = 5.2 Hz, CH_3), 1.17−2.05(m, 27H), 1.44(s, 3H, CH_3), 2.36−2.43(m, 2H), 3.40−3.59(m, 1H), 3.98−4.10(m, 1H), 4.41(d, 1H, J = 9.2 Hz, C_{10}-H), 5.33(s, 1H, C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.99(CH_3), 20.67(CH_3), 22.61(CH_2), 25.12(CH_2), 26.43(CH_3), 28.48(CH), 28.64(CH), 31.90(CH), 32.07(CH_2), 32.13(CH), 32.36(CH), 32.53(CH_2), 32.79(CH), 33.02(CH_2), 34.67(CH_2), 36.75(CH_2), 37.77(CH), 38.80(CH_2), 39.57(CH_2), 41.32(CH), 45.76(CH), 52.09(CH), 68.29(CH_2), 80.74(C), 91.58(CH), 100.59(CH), 104.62(C); ESMS (*m*/*z*) 469 [M + Na]$^+$, 485 [M + K]$^+$; Anal. for ($C_{27}H_{42}O_5$): Calcd C 72.61 H 9.48; Found C 72.41 H 9.47.

2-Biphenylmethyl Ether of Dihydroartemisinin (11). This was obtained as white solid in 90% yield as an inseparable mixture of **11**α and **11**β (α/β ratio: 1:4) which on crystallization in CH_2Cl_2/hexane gave pure **11**β as a white crystalline solid.

11β: White solid; mp 130−132 °C; FT-IR (KBr, cm^{-1}) 2933.2, 2863.0,1627.9, 1451.7, 1374.0, 1100.2, 1020.0; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89(d, 3H, J = 7.3 Hz, CH_3), 0.94(d, 3H, J = 5.8 Hz, CH_3), 1.19−2.06(m, 10H), 1.42(s, 3H, CH_3), 2.28−2.37(m, 1H), 2.61−2.65(m, 1H), 4.33(d, 1H, J = 11.7 Hz, benzylic H), 4.83(d, 1H, J = 3.2 Hz, C_{10}−H), 4.87(d, 1H, J = 11.7 Hz, benzylic H), 5.32(s, 1H, C_{12}-H), 7.29−7.51(m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.51(CH_3), 20.75(CH_3), 24.87(CH_2), 25.09(CH_2), 26.59(CH_3), 31.37(CH), 35.01(CH_2), 36.85(CH_2), 37.76(CH), 44.81(CH), 52.98(CH), 69.15(CH_2), 81.51(C), 88.43(CH), 102.41(CH), 104.47(C), 127.58(CH), 127.77(CH), 127.98(CH), 128.55(CH), 129.53(CH), 130.46(CH), 135.93(C), 141.21(C), 142.18(C); FABMS(*m*/*z*): 451-[M + H]$^+$; Anal. for ($C_{28}H_{34}O_5$·0.1H_2O): Calcd C 74.63 H 7.60; Found C 74.34 H 7.62.

4-Biphenylmethyl Ether of Dihydroartemisinin (12). This was obtained as white solid in 71% yield as a mixture of 12α and 12β (α/β ratio: 1:4) which were separated by column chromatography.

12β(higher R_f): White solid; mp 51 °C; FT-IR (KBr, cm^{-1}) 2928.3, 1596.5, 1020.1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94(d, 3H, J = 4.8 Hz, CH_3), 0.97(d, 3H, J = 6.9 Hz, CH_3), 1.23−2.08(m, 10H), 1.46(s, 3H, CH_3), 2.31−2.39(m, 1H), 2.67−2.71(m, 1H), 4.57(d, 1H, J = 12.4 Hz, benzylic H), 4.94(d, 1H, J = 3.5 Hz, C_{10}−H), 4.95(d, 1H, J = 12.3 Hz, benzylic H), 5.49(s, 1H, C_{12}-H), 7.33−7.61(m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.58(CH_3), 20.81(CH_3), 25.00(CH_2), 25.16(CH_2), 26.67(CH_3), 31.41(CH), 35.09(CH_2), 36.91(CH_2), 37.87(CH), 44.90(CH), 53.05(CH), 69.98(CH_2), 81.59(C), 88.50(CH), 101.91(CH), 104.58(C), 127.49(CH), 127.68(CH), 128.10(CH), 129.20(CH), 137.89(C), 140.75(C), 141.33(C); FABMS(*m*/*z*): 451[M + H]$^+$; Anal. for ($C_{28}H_{34}O_5$·0.1H_2O): Calcd C 74.63 H 7.60; Found C 74.34 H 7.62.

12α(lower R_f): White solid; mp 79−80 °C; FT-IR (KBr, cm^{-1}) 2929.7, 1628.6, 1029.0; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93(d, 3H, J = 7.1 Hz, CH_3), 0.95(d, 3H, J = 5.3 Hz, CH_3), 1.25−2.07(m, 10H), 1.47(s, 3H, CH_3), 2.32−2.58(m, 2H), 4.55(d, 1H, J = 9.2 Hz, C_{10}−H), 4.68(d, 1H, J = 12.5 Hz, benzylic H), 5.01(d, 1H, J = 12.5 Hz, benzylic H), 5.35(s, 1H, C_{12}−H), 7.33−7.61(m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.18(CH_3), 20.68(CH_3), 22.64(CH_2), 25.16(CH_2), 26.50(CH_3), 33.10(CH), 34.65(CH_2), 36.79(CH_2), 37.76(CH), 45.84(CH), 52.10(CH), 69.95(CH_2), 80.80(C), 91.71(CH), 99.36(CH), 104.72(C), 127.40(CH), 127.47(CH), 127.63(CH), 128.52(CH), 129.16(CH), 137.77(C), 140.72(C), 141.37(C); FABMS-(*m*/*z*): 451[M + H]$^+$; ES-MS (*m*/*z*) 468 [M + NH_4]$^+$; HR-EIMS for C_{28} H_{34} O_5: Measured 450.2381 Calculated 450.2406; Anal. for (C_{28} H_{34} O_5· 0.1 H_2O): Calcd C 74.63 H 7.60; Found C 74.34 H 7.67.

4-Biphenylethyl Ether of Dihydroartemisinin (13). This was obtained as white solid in 82% yield as a mixture of 13α and 13β (α/β ratio: 1:5) which were separated by column chromatography.

13β(lower R_f): White shiny solid; mp110−112 °C; FT-IR (KBr, cm^{-1}) 2928.0, 2874.6, 1600.7, 1451.6, 1104.2,1021.9; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.77(d, 3H, J = 5.6 Hz, CH_3), 0.85(d, 3H, J = 7.3 Hz, CH_3), 1.09−2.01(m, 10H), 1.41(s, 3H, CH_3), 2.23−2.32(m, 1H), 2.56−2.58(m, 1H), 2.87−2.94(m, 2H, benzylic H), 3.63−3.67(m, 1H), 4.12−4.17(m,1H), 4.78(d, 1H, J = 3.4 Hz, C_{10}-H), 4.99(s, 1H, C_{12}-H), 7.25−7.60(m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.39(CH_3), 20.69(CH_3), 24.55(CH_2), 25.03(CH_2), 26.61(CH_3), 31.27(CH), 34.94(CH_2), 36.28(CH_2), 36.82(CH_2), 37.47(CH), 44.65(CH), 52.86(CH), 68.99(CH_2), 81.45(C), 88.20(CH), 101.95(CH), 104.34(C), 127.22(CH), 127.34(CH), 127.47(CH), 129.11(CH), 129.86(CH), 139.16(C), 139.40(C), 141.34(C); FABMS(*m*/*z*): 464-[M + H]$^+$; HR-EIMS for $C_{29}H_{36}O_5$: Measured 464.25548 Calculated 464.25627; Anal. for ($C_{29}H_{36}O_5$·0.1 H_2O): Calcd C 74.96 H 7.81; Found C 74.68 H 7.57.

2-(Biphenyl-2-yloxy)ethyl Ether of Dihydroartemisinin (14). This was obtained as white solid in 94% yield as a mixture of 14α and 14β (α/β ratio: 1:3) which were separated by column chromatography.

14β(higher R_f): White solid; mp 90−92 °C; FT-IR (KBr, cm^{-1}) 2928.1, 2874.7, 1636.5, 1479.9, 1455.8, 1260.9, 1111.2, 1030.6, 753.2; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82(d, 3H, J = 7.3 Hz, CH_3), 0.90(d, 3H, J = 5.7 Hz, CH_3), 1.05−2.07(m, 10H), 1.43(s, 3H, CH_3), 2.27−2.36(m, 1H), 2.53−2.61(m, 1H), 3.66−3.76(m, 1H), 4.06−4.16(m, 3H), 4.78(d, 1H, J = 3.7 Hz, C_{10}−H), 5.30(s, 1H, C_{12}−H), 6.95−7.59(m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.23(CH_3), 20.77(CH_3), 24.75(CH_2), 25.01(CH_2), 26.59(CH_3), 31.21(CH), 35.00(CH_2), 36.87(CH_2), 37.54(CH), 44.86(CH), 52.95(CH), 67.39(CH_2), 68.07(CH_2), 81.47(C), 88.31(CH), 102.78(CH), 104.44(C), 112.71(CH), 121.45(CH), 127.22(CH), 128.24(CH), 128.87(CH), 129.88(CH), 131.20(C), 131.42(C), 138.84(C), 156.15(C); FABMS(*m*/*z*): 481[M + H]$^+$; Anal. for ($C_{29}H_{36}O_6$): Calcd C 72.47 H 7.55; Found C 72.32 H 7.71.

14α(lower R_f): White solid; mp 103−105 °C; FT-IR (KBr, cm^{-1}) 2931.7, 2875.0, 1594.0, 1444.6, 1227.9, 1158.6, 1024.5, 759.3; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85(d, 3H, J = 7.2 Hz, CH_3), 0.95(d, 3H, J = 5.6 Hz, CH_3), 1.18−2.04(m, 10H), 1.43(s, 3H, CH_3), 2.29−2.42(m, 1H), 3.88−3.99(m, 1H), 4.11−4.17(m, 3H), 4.44(d, 1H, J = 9.2 Hz, C_{10}−H), 5.18(s, 1H, C_{12}-H), 6.96−7.59(m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.76(CH_3), 20.69(CH_3), 22.31(CH_2), 25.16(CH_2), 26.50(CH_3), 33.02(CH), 34.65(CH_2), 36.77(CH_2), 37.61(CH), 45.64(CH), 52.02(CH), 67.40(CH_2), 68.78(CH_2), 80.78(C), 91.60(CH), 100.81(CH), 104.68(C), 112.61(CH), 121.43(CH), 127.10(CH), 128.25(CH), 129.04(CH), 130.06(CH), 130.95(C), 131.40(C), 139.10(C), 156.09(C); FABMS(*m*/*z*): 481[M + H]$^+$; HR-EIMS for $C_{29}H_{36}O_6$: Measured 480.2510 Calculated 480.2512; Anal. for ($C_{29}H_{36}O_6$): Calcd C 72.47 H 7.55; Found C 72.21 H 7.76.

2-(Biphenyl-4-yloxy)ethyl Ether of Dihydroartemisinin (15). This was obtained as white solid in 67% yield as a mixture of 15α and 15β (α/β ratio: 1:3) which were separated by column chromatography.

15β(higher R_f): White solid; mp 111−112° C; FT-IR (KBr, cm^{-1}) 2930.1, 2875.7, 1608.5, 1484.8, 1455.9 1246.3,1031.1, 761.4; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92(d, 6H, J = 6.9 Hz, 2 × CH_3), 1.19−2.07(m, 10H), 1.45(s, 3H, CH_3), 2.29−2.38(m, 1H), 2.62−2.68(m, 1H), 3.77−3.86(m, 1H), 4.11−4.27(m,3H), 4.91(d, 1H, J = 3.4 Hz, C_{10}-H), 5.49(s, 1H, C_{12}−H), 6.95−6.99(m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.41(CH_3), 20.78(CH_3), 24.84(CH_2), 25.14(CH_2), 26.63(CH_3), 31.33(CH), 35.06(CH_2), 36.86(CH_2), 37.84(CH), 44.88(CH), 52.99(CH), 66.96(CH_2), 67.86(CH_2), 81.56(C), 88.35(CH), 102.58(CH), 104.50(C), 127.12(CH), 128.54(CH),

129.15(CH), 134.30(C), 141.19(C), 158.88(C); FABMS(*m*/*z*): 481-[M + H]$^+$; Anal. for (C_{29} H_{36} O_6): Calcd C 72.53 H 7.55; Found C 72.18 H 7.56.

15α(lower R_f): White solid; mp108−109 °C; FT-IR (KBr, cm^{-1}) 2936.8, 2875.7, 1610.8, 1451.5, 1125.0,1027.0, 762.2; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92(d, 3H, J = 7.1 Hz, CH_3), 0.95(d, 3H, J = 5.6 Hz, CH_3), 1.25−2.06(m, 10H), 1.45(s, 3H, CH_3), 2.31−2.45-(m, 2H), 3.89−3.95(m, 1H), 4.17−4.27(m, 1H), 4.60(d, 1H, J = 9.3 Hz, C_{10}-H), 5.37(s, 1H, C_{12}−H), 6.96−7.01(m, 2H), 7.28−7.62(m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.91(CH_3), 20.68-(CH_3), 22.60(CH_2), 25.13(CH_2), 26.45(CH_3), 32.94(CH), 34.66-(CH_2), 36.74(CH_2), 37.80(CH), 45.74(CH), 52.05(CH), 67.66(CH_2), 68.10(CH_2), 80.76(C), 91.66(CH), 101.02(CH), 104.72(C), 115.41-(CH), 127.13(CH), 128.51(CH), 129.10(CH), 134.28(C), 141.24-(C), 158.86(C); FABMS(*m*/*z*): 481[M + H]$^+$; HR-EIMS for $C_{29}H_{36}O_6$: Measured 480.2515 Calculated 480.2512; Anal. for (C_{29} H_{36} O_6): Calcd C 72.53 H 7.55; Found C 72.23 H 7.56.

(9*H*-Fluoren-9-yl)methyl Ether of Dihydroartemisinin (16). This was obtained as white solid in 76% yield as a mixture of 16α and 16β (α/β ratio: 1:4) which were separated by column chromatography.

16α(higher R_f): White solid; mp 100−102 °C; FT-IR (KBr, cm^{-1}) 2928.6, 2872.0, 1601.8, 1450.1, 1374.0, 1150.3, 1026.4, 745.1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91(d, 3H, J = 7.2 Hz, CH_3), 0.94(d, 3H, J = 5.8 Hz, CH_3), 1.46(s, 3H, CH_3), 1.16−2.06-(m, 10H), 2.31−2.58(m, 2H), 3.44(t, 1H, J = 9.1 Hz, benzylic H), 4.27(dd, 1H, J = 8.4 Hz and 5.7 Hz), 4.44(d, 1H, J = 9.2 Hz, C_{10}−H), 4.55(dd, 1H, J = 9.3 Hz and 5.6 Hz), 5.30(s, 1H, C_{12-}H), 7.28−7.76(m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.27(CH_3), 20.66(CH_3), 22.54(CH_2), 25.11(CH_2), 26.46(CH_3), 33.23(CH), 34.63(CH_2), 36.76(CH_2), 37.75(CH), 45.88(CH), 48.47(CH), 52.06-(CH), 71.93(CH_2), 80.79(C), 91.68(CH), 100.84(CH), 104.72(C), 120.09(CH), 120.18(CH), 125.54(CH), 126.43(CH), 127.16(CH), 127.24(CH), 127.67(CH), 127.80(CH), 141.56(C), 141.76(C), 144.61-(C), 146.18(C);ESMS (*m*/ *z*) 485 [M + Na]$^+$; Anal. for (C_{29} H_{34} O_5): Calcd C 75.30 H 7.41; Found C 75.46 H 7.59.

16β(lower R_f): White solid; mp136−138 °C; FT-IR (KBr, cm^{-1}) 2925.7, 1587.1, 1448.6, 1218.2, 1020.0, 766.7; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.62(d, 3H, J = 7.3 Hz, CH_3), 0.88(d, 3H, J = 4.0 Hz, CH_3), 1.04−2.03(m,10H), 1.41(s, 3H, CH_3), 2.23−2.32(m, 1H), 2.46−2.50(m, 1H), 3.76(dd, 1H, J = 9.1 Hz, 5.5 Hz), 4.10−4.15-(dd, 1H, J = 5.0 Hz, benzylic H), 4.46(dd, 1H, J = 9.1 Hz, 4.6 Hz), 4.72(d, 1H, J = 3.3 Hz, C_{10}-H), 5.05(s, 1H, C_{12}-H), 7.24−7.72(m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.07(CH_3), 20.61-(CH_3), 24.23(CH_2), 25.04(CH_2), 26.58(CH_3), 31.22(CH), 34.95-(CH_2), 36.82(CH_2), 37.44(CH), 44.53(CH), 48.72(CH), 52.83(CH), 70.20(CH_2), 81.41(C), 88.33(CH), 102.11(CH), 104.37(C), 120.09-(CH), 124.81(CH), 125.01(CH), 127.23(CH), 127.62(CH), 141.98-(C), 142.16(C), 145.23(C), 145.86(C); ESMS (*m*/*z*) 485 [M + Na]$^+$; Anal. for (C_{29} H_{34} O_5): Calcd C 75.30 H 7.41; Found C 75.25 H 7.40.

2-(9*H*-fluoren-9-yl)ethyl Ether of Dihydroartemisinin (17). This was obtained as white solid in 99% yield as an inseparable mixture of 17α and 17β (α/β ratio: 1:4).

17: White solid; mp 131−133 °C; FT-IR (KBr, cm^{-1}) 2927.4, 2872.0, 1601.8, 1450.1, 1374.0, 1150.3, 1026.4, 745.1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86(d, 3H, J = 7.3 Hz, CH_3), 0.87(d, 3H, J = 7.0 Hz, CH_3), 0.92−0.95(m, 6H, 2 × CH_3), 1.22−2.07(m, 10H), 1.43(s, 3H, CH_3), 2.15−2.44(m, 6H), 2.60(m, 1H), 3.46−3.58(m, 2H), 3.91−4.15(m, 4H), 4.43 and 4.78(2 × d, 1H, J = 3.4 Hz and 9.2 Hz respectively, together integrating for 1C_{10}-H), 5.31 and 5.37-(2 × s, together integrating for 1C_{12-}H), 7.29−7.77(m, 13H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.10(CH_3), 13.46(CH_3), 20.77(CH_3), 24.87(CH_2), 25.10(CH_2), 26.62(CH_3), 31.31(CH), 33.10(CH_2), 33.90(CH_2), 34.68(CH_2), 35.07(CH_2), 36.87(CH_2), 37.85(CH), 44.86(CH), 44.93(CH), 45.76(CH), 52.07(CH), 52.98(CH), 66.65-(CH_2), 81.49(C), 88.39(CH), 91.58(CH), 100.61(CH), 102.67(CH), 104.48(C), 120.33(CH), 124.92(CH), 125.30(CH), 127.35(CH), 127.46(CH), 128.29(CH), 129.99(CH), 141.33(C), 147.52(C); ESMS (*m*/*z*) 499 [M + Na]$^+$; Anal. for (C_{30} H_{36} O_5): Calcd C 75.60 H 7.61; Found C 75.45 H 7.38.

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Supporting Information Available: Elemental analysis data and ^{1}H NMR and ^{13}C NMR spectral data of compounds **7**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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groundnut oil so as to contain the required amount of the drug (0.6 mg/kg for a dose of 48 mg/kg, 0.3 mg for a dose of 24 mg/kg, 0.15 mg for a dose of 12 mg/kg, and 0.075 mg for a dose of 6 mg/kg) in 0.1 mL and administered orally for each dose. Parasitaemia level were recorded from thin blood smears on day 4 and subsequently twice a week till day 28. The animals which did not develop patent infection till day 28 were recorded as cured.[16] Mice treated with β-arteether served as positive control.

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