Antimalarial Activity of Novel Ring-Contracted Artemisinin Derivatives

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Received September 8, 1994®

Bromoacetal **2** undergoes a novel ring-contracted reaction to give the aldehyde **3** in the presence of DBU or triethylamine. The aldehyde **3** is reduced to the alcohol **4** and oxidized to the carboxylic acid **5**. The alcohol **4** reacts with dihydroartemisinin to give the two diastereoisomers **38** and **39**. All the compounds were tested for antimalarial activity in mice infected with chloroquine sensitive *Plasmodium berghei*. If the activity of a compound was comparable to that of the standard compound, such as arteether, it was tested against chloroquine resistant NS strain infection in mice. Initially the compounds were administered subcutaneously, and if found to be active, they were tested by oral route. The antimalarial activity of compounds **19**, **38**, and **39** was found to be comparable to that of arteether when tested in K-173-infected mice. They were also active against chloroquine resistant NS strain infection in mice.

Artemisinin (quinghaosu, arteannuin), an antimalarial agent isolated from the plant Artemisia annua, is an endoperoxide containing sesquiterpene lactone.[1-5] It showed very potent activity especially in the case of cerebral malaria.[2] The use of artemisinin as an antimalarial agent however is hampered by its poor solubility in oil and water and its poor efficacy on oral administration. In this connection, synthesis of new structural modifications of artemisinin becomes essential.[6-10]

Chemistry

Treatment of dehydroartemisinin (**1**) with bromine in carbon tetrachloride and then quenching with water gave the bromoacetal[11] **2**. Reaction of the bromoacetal **2** with DBU in methylene chloride at room temperature gave a solid, **3**, mp 100 °C, in 85% yield. Its IR indicated the presence of a carbonyl group and a peroxide group. Further, the signals at δ 5.8 (H_{11}), 1.66 (3-CH_3), 1.52 (9-CH_3), and 1.0 (6-CH_3) indicated the presence of the artemisinin ring system.[6] Use of triethylamine in place of DBU in the above reaction also gave the same product, **3** (Scheme 1).

As the aldehyde **3** was found to be relatively unstable, it was reduced with sodium borohydride to give the alcohol **4** as a solid. The ^{13}C-NMR of the alcohol **4** showed signals for C-3 (δ 103.59) and C-12 (δ 25.3) comparable with those of compound[12] **A** (Scheme 2). The signal due to the 15α-methyl group in compound **A** appears downfield (δ 28.12) as compared with that of the 15β-methyl group in compound **B** (δ 22.66). The signal due to the 13β-methyl group in the ring-contracted compound **C** appears at δ 21.88. In a similar type of ring-contracted compound such as **4**, the corresponding 14α-methyl group should appear downfield compared with that in compound **C** (δ 21.88). The observed downfield chemical shift (δ 25.13) for the 14α-methyl group supports the α-stereochemistry for the 14-methyl group in compound **4**. The differences in the ^{13}C-NMR shifts for C-11 (δ 97.09), C-11a (δ 84.73), and C-8a (δ 49.30) in compound **4** compared with those in **A** are a result of the contraction from a six- to five-membered ring. Further, irradiation of the OCH_2 signal at δ 3.55 displayed (~4%) NOE on the signal due to H_{11} at δ 5.6, thus confirming the relative configuration of the OCH_2 group is β, since the configuration of H_{11} is β as in the case of artemisinin.[3] Yagen et al.[12] reported a silica gel-catalyzed rearrangement of β-epoxide to give D-ring-contracted product **C**, which was devoid of a peroxide group. The formation of the aldehyde **3** in the presence of anhydrous base may presumably involve an equilibrium of the hemiacetal **2** with the ring-opened form **D** (Scheme 2). Nucleophilic attack by the hydroxyl group would then produce the desired product **3** with the peroxide group intact.

Derivatization of the aldehyde **3** and the alcohol **4** was done in order that a series of artemisinin derivatives could be prepared for screening of their antimalarial properties. Oxidation of the aldehyde **3** with aqueous silver nitrate and sodium hydroxide in ethanol gave the acid **5**. The alcohol **4** underwent alkylation in the presence of sodium hydroxide and an alkyl halide to give the products **6–9**. The alcohol **4** reacted with either acid chlorides or alkyl- and arylsulfonyl chlorides in the presence of 4-(dimethylamino)pyridine to give the esters **10–13** and the sulfonates **15–17**. The ester **14** was prepared by the treatment of the alcohol **4** with formic acid. Reaction of the alcohol **4** with isocyanates or isothiocyanates gave the carbamates and thiocarbamates **18–24**. The acid **5** on treatment first with thionyl chloride followed with amine gave the amides **25–27**. Similarly the esters **28**, **29**, and **34–37** were prepared. Quenching of the acid chloride derived from the acid **5** with thiophenol gave the thioester **33**. Reaction of the aldehyde **3** with ethyl acetate, diethyl malonate, or phosphonium ylides derived from the substituted benzyl bromide, gave compounds **30–32**, respectively. Treatment of dihydroartemisinin (DHA) with the alcohol **4** in the presence of BF_3Et_2O gave the two diastereoisomers **38** and **39** in a 2:1 ratio (Scheme 3). The structures **38** and **39** were assigned on NMR spectral ground.[6] The large $^3J_{H_{10}H_9}$ (9.2 Hz) observed in **39** is indicative of a trans diaxial coupling between H_{10} and H_9; hence H_{10} was assigned to a β-configuration. The

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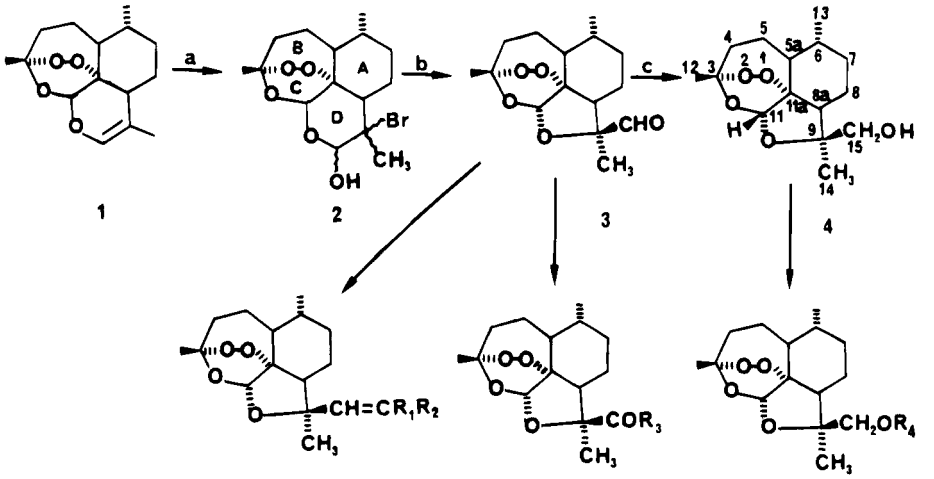
® Abstract published in *Advance ACS Abstracts*, April 1, 1995.

0022-2623/95/1838-1922$09.00/0

Scheme 1[a]



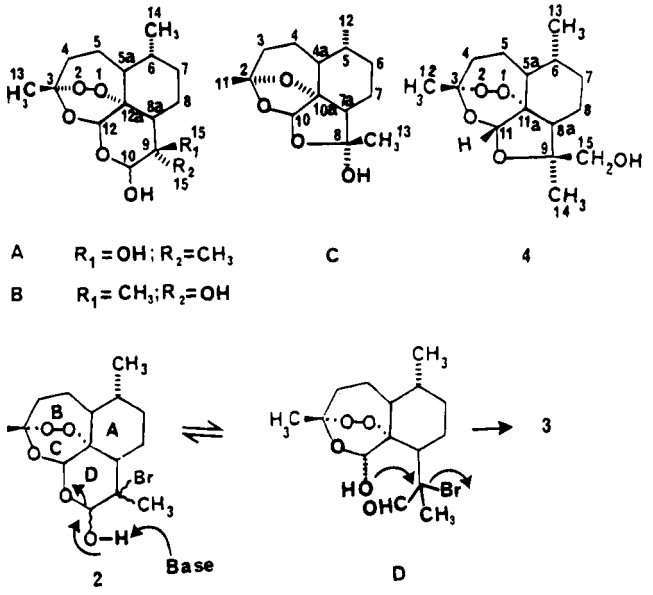
R_1	R_2		
H	COOEt	cis	30
COOEt	COOEt	cis	31
H	4-$CF_3C_6H_4$	cis	32

R_3	
OH	5
SC_6H_5	33
OEt	37

R_4	
$CH_2CH_2NEt_2$	6
$CH_2CH{=}CH$	7
$COCH_2Cl$	10
$SO_2C_6H_5$	16
4-ClC_6H_4NHCO	18
4-ClC_6H_4NHCS	19

[a] (a) Br_2/H_2O; (b) DBU; (c) $NaBH_4$.

Scheme 2



$^3J_{H_{10}H_9}$ value of 3.6 Hz in the NMR spectrum of compound **38**, on the other hand, suggests an α-configuration for H_{10}. The physical data of all the compounds described herein are given in Table 1.

Results and Discussion

All the compounds were initially tested for their antimalarial activity in mice infected with *Plasmodium berghei*. The screening procedure is described in the experimental section, and the antimalarial activity of all the compounds described herein is given in Table 2. The reference compound against which their activities are given is arteether. Out of 37 compounds tested, only 14 compounds showed moderate to good antimalarial activity. Compounds **12**, **15**, **18**, **27**, and **33** showed moderate activity, and compounds **3**, **7**, **8**, **21**, **24**, and **32** displayed 100% activity but were less active than arteether.[6] The thiocarbamate **19** showed 100% activity at 2.5 mg/kg × 5, sc and 45% at 1 mg/kg × 5, sc. It also showed 100% and 82% activity at 25 and 10 mg/kg × 5, po, respectively. Against chloroquine resistant NS strain, it was 100% active at 5 mg/kg × 5, sc and 25 mg/kg × 5, po. At a lower dose of 2.5 mg/kg × 5, sc, it displayed 91% activity. The ether **38** showed 100% activity at 1.25 mg/kg × 5, sc and 73% activity at 0.625 mg/kg × 5, sc. On oral administration at 25 mg/kg × 5, it displayed 83% activity. Against NS strain, it displayed 100% activity at 7.5 mg/kg × 5, sc and 78% activity at 2.5 mg/kg × 5, sc. By oral route, the compound was inactive against NS strain at 25 mg/kg × 5. The other diastereoisomer, **39**, displayed excellent activity. It was 100% active at 0.625 mg/kg × 5, sc and 25 mg/kg × 5, po. Against NS strain, it showed 100% activity at 2.5 mg/kg × 5, sc and 25 mg/kg × 5, po.

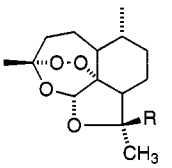
In conclusion, compounds **19**, **38**, and **39** showed better activity than the other derivatives, and the activity is comparable to that of arteether. Further evaluation of the activity of these compounds is underway.

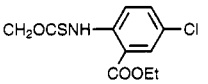
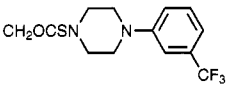
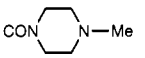
Experimental Section

Chemistry. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra of solid samples were obtained in KBr discs on a Perkin-Elmer model spectrophotometer. ^1H- and ^{13}C-NMR spectra were run on a JOEL FX 90Q spectrophotometer using trimethylsilane as an internal standard. Elemental analyses were performed on a Heraeus microelemental analyzer.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]-benzodioxepin-9β-carboxaldehyde (3). Diazabicycloun-

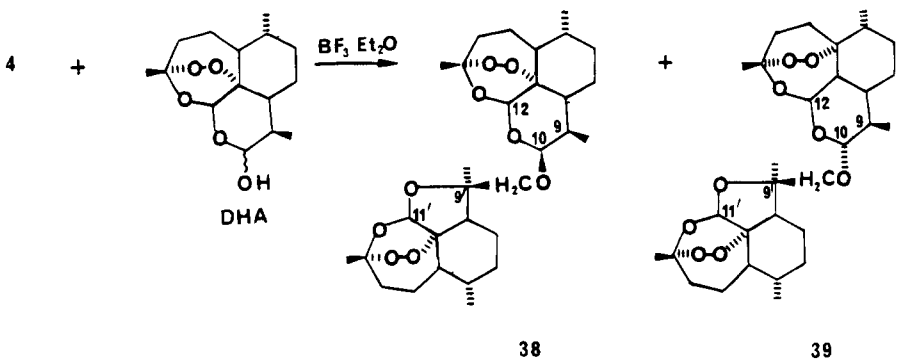
Table 1. Ring-Contracted Artemisinin Derivatives



compd no.	R	mp (°C)	solvent[a]	yield (%)	formula
3	CHO	100	E	85	$C_{15}H_{22}O_5$
4	CH_2OH	135–136	C	72	$C_{15}H_{24}O_5$
5	COOH	166–167	B	76	$C_{15}H_{22}O_6$
6	$CH_2OCH_2CH_2N(Et)_2$	oil		47	$C_{21}H_{37}NO_5$
7	$CH_2OCH_2C{\equiv}CH$	105	A	71	$C_{18}H_{26}O_5$
8	$CH_2OCH_2CH{=}CH_2$	oil		45	$C_{18}H_{28}O_5$
9	$CH_2OCH_2CH{=}CHC_6H_5$	oil		43	$C_{24}H_{32}O_5$
10	CH_2OCOCH_2Cl	oil		42	$C_{17}H_{25}ClO_6$
11	$CH_2OCO(CH_2)_3Cl$	oil		36	$C_{19}H_{29}ClO_6{\cdot}H_2O$
12	4-$NO_2C_6H_4COOCH_2$-	158–159	D	64	$C_{22}H_{27}NO_8$
13	$CH_2OCOCOOH$	98–99	E	36	$C_{17}H_{24}O_8$
14	CH_2OCHO	84	D	33	$C_{16}H_{24}O_6$
15	4-$CH_3C_6H_4SO_2OCH_2$-	oil		33	$C_{22}H_{30}O_7S$
16	$CH_2OSO_2C_6H_5$	oil		27	$C_{21}H_{28}O_7S$
17	$CH_2OSO_2CH_3$	123	A	42	$C_{16}H_{26}O_7S$
18	4-$ClC_6H_4NHCOOCH_2$-	160	D	42	$C_{22}H_{28}ClNO_6$
19	4-$ClC_6H_4NHCSOCH_2$-	189–190	D	42	$C_{22}H_{28}ClNO_5S$
20		oil		36	$C_{25}H_{32}ClNO_7S$
21	4-$FC_6H_4NHCSOCH_2$-	79–80	D	37	$C_{22}H_{28}FNO_5S$
22	$CH_2OCSNHCH_2CH{=}CH_2$	oil		22	$C_{19}H_{29}NO_5S$
23		69–71	D	22	$C_{27}H_{35}F_3N_2O_5S$
24	$CH_2OCSNHC_6H_5$	81–82	D	44	$C_{22}H_{29}NO_5S{\cdot}{}^1/_2H_2O$
25		oil		43	$C_{19}H_{29}NO_6{\cdot}{}^1/_2H_2O$
26		93	A	43	$C_{20}H_{32}N_2O_5{\cdot}{}^1/_2H_2O$
27	4-$CF_3C_6H_4CH_2NHCO$-	170–172	A	25	$C_{23}H_{28}F_3NO_5$
28	$COOCH_2CH_2Cl$	112	A	46	$C_{17}H_{25}ClO_6$
29	$COOCH_2CH{=}CH_2$	85	A	38	$C_{18}H_{26}O_6$
30	CH=CHCOOEt (cis)	oil		54	$C_{19}H_{28}O_6$
31	$CH{=}C(COOEt)_2$	oil		22	$C_{22}H_{32}O_8$
32	4-$CF_3C_6H_4CH{=}CH$-	oil		27	$C_{23}H_{27}F_3O_4$
33	$COSC_6H_5$	oil		26	$C_{21}H_{25}O_5S$
34	$COOCH_2CH_2Br$	oil		47	$C_{17}H_{25}BrO_6$
35	$COOCH_2CH_2CH_2Cl$	oil		24	$C_{18}H_{27}ClO_6{\cdot}{}^1/_2H_2O$
36	$COOCH_2(CH_2)_6CH_2Cl$	oil		21	$C_{23}H_{37}ClO_6$
37	COOEt	oil		29	$C_{17}H_{26}O_6$
38	(see Scheme 3)	154–156	D	34	$C_{30}H_{46}O_9$
39	(see Scheme 3)	100	D	21	$C_{30}H_{46}O_9$

[a] Solvent: A; petroleum ether (60–80 °C); B, isopropyl ether/ether; C, $CHCl_3$/ether (60–80 °C); D, EtOAc/petroleum ether (60–80 °C); E, $CHCl_3$.

Scheme 3



decene (0.2 mL, 1.31 mmol) was added to a solution of 0.19 g (0.52 mmol) of the bromoacetal[11] **2** in 5 mL of chloroform at room temperature. After being stirred for 45 min, the solvent was removed and the residue was purified by column chro-

Table 2. Blood Schizonticidal Activity of Ring-Contracted Artemisinin Derivatives against *P. berghei* (K-173 and NS strains) in the Mouse Model

compd no.	dose (mg/kg × 5)	route	cured/treated (% cured) on D+7 K-173 strain	NS strain
arteether	1.25	sc	23/35 (65)	
	2.5	sc	36/36 (100)	
	5	sc		16/18 (88)
	20	po	34/34 (100)	
	25	po		7/12 (58)
3	10	sc	0/6	
	25	sc	4/4 (100)	
4	10	sc	0/6	
5	10	sc	0/6	
6	5	sc	0/6	
	20	po	0/6	
7	5	sc	0/6	
	10	sc	6/6 (100)	
8	2.5	sc	0/6	
	5	sc	10/10 (100)	
	25	po	0/6	
9	5	sc	0/6	
10	5	sc	0/6	
11	5	sc	0/6	
12	5	sc	1/6 (16)	
13	10	sc	0/6	
14	10	sc	0/5	
15	5	sc	5/6 (83)	
16	10	sc	0/6	
17	5	sc	0/6	
18	5	sc	1/6 (16)	
	20	po	0/6	
19	1	sc	10/22 (45)	2.5, sc, 11/12 (91)
	1.25	sc	26/34 (76)	5, sc, 22/22 (100)
	2.5	sc	28/28 (100)	20, po, 8/12 (66)
	10	po	34/39 (82)	25, po, 6/6 (100)
	15	po	19/22 (86)	
	25	po	16/16 (100)	
20	10	sc	0/6	
21	2.5	sc	0/6	
	5	sc	6/6 (100)	
	25	po	0/6	
22	10	sc	0/6	
23	5	sc	0/6	
24	5	sc	6/6 (100)	
25	10	sc	0/6	
26	10	sc	0/6	
27	5	sc	4/6 (66)	
28	5	sc	0/6	
	25	po	0/6	
29	10	sc	0/6	
30	5	sc	0/5	
31	10	sc	0/5	
32	2.5	sc	0/4	
	5	sc	5/5 (100)	
33	5	sc	2/6 (33)	
34	5	sc	0/6	
35	5	sc	0/6	
36	10	sc	0/4	
37	10	sc	0/4	
38	0.625	sc	14/19 (73)	2.5, sc, 11/14 (78)
	1.25	sc	30/30 (100)	5, sc, 19.20 (95)
	10	po	0/6	7.5, sc, 8/8 (100)
	20	po	4/12 (33)	25, po, 0/6
	25	po	10/12 (83)	
39	0.625	sc	6/6 (100)	2.5, sc, 6/6 (100)
	12.5	po	3/6 (50)	12.5, po, 2/6 (33)
	25	po	6/6 (100)	25, po, 6/6 (100)

matography on silica gel using chloroform as an eluant to give 0.124 g (85%) of **3** as a white solid, mp 100 °C. IR (KBr, cm^{-1}): 1740 (CO), 830, 885, 1130 (peroxide). ^{1}H-NMR ($CDCl_3$): δ 9.7 (s, 1H, CHO), 5.8 (s, 1H, H_{11}), 1.66 (s, 3H, 3-CH_3), 1.52 (s, 3H, 9-CH_3), 1.0 (s, 3H, 6-CH_3). Anal. $C_{15}H_{22}O_5$) C, H.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9β-(hydroxymethyl)-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]benzodioxepin (4). Sodium borohydride (1.0 g, 2.64 mmol) was added to a solution of 1 g (3.54 mmol) of **3** in 60 mL of ethanol. After being stirred for 30 min, the solvent was removed under vacuum and the residue was extracted with dichloromethane, washed with water, dried, and concentrated. The crude product obtained was purified by flash chromatography on silica gel using 8% ethyl acetate in chloroform as eluant to give 0.72 g (72%) of **4** as a white solid, mp 135–136 °C. ^{1}H-NMR ($CDCl_3$): δ 5.6 (s, 1H, H_{11}), 3.55 (two d, J = 4.5 Hz, 2H, OCH_2), 1.6 (s, 3H, 3-CH_3), 1.5 (s, 3H, 9-CH_3), 1.0 (s, 3H, 6-CH_3). ^{13}C-NMR ($CDCl_3$): δ 19.38 (C-13), 24.2 (C-8), 24.5 (C-5), 25.13 (C-14), 25.3 (C-12), 32.7 (C-7), 36.95 (C-4), 37.38 (C-6), 49.30 (C-8a), 51.79 (C-5a), 67.50 (C-15), 84.73 (C-11a), 87.01 (C-9), 97.09 (C-11), 103.59 (C-3). Anal. ($C_{15}H_{24}O_5$) C, H.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]-benzodioxepin-9β-carboxylic Acid (5). A solution of 1.8 g (11 mmol) of silver nitrate in 3 mL of water was added to a solution of 0.9 g (3.2 mmol) of **3** in 5 mL of ethanol followed by a solution of 0.4 g (10 mmol) of sodium hydroxide in 2 mL of water. After being stirred for 2 h at room temperature, the reaction mixture was filtered and washed with 5 mL of aqueous alcohol. The filtrate was concentrated, neutralized with acetic acid, and extracted with methylene chloride. The methylene chloride extract was then concentrated to give the crude product. Crystallization from isopropyl ether/petroleum ether gave 0.72 g (76%) of **5** as a white solid, mp 166–167 °C. ^{1}H-NMR ($CDCl_3$): δ 5.76 (s, 1H, H_{11}), 1.86 (s, 3H, 3-CH_3), 1.50 (s, 3H, 9-CH_3), 1.04 (s, 3H, 6-CH_3). Anal. ($C_{15}H_{22}O_6$) C, H.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9β-[(2-propynoxy)methyl]-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]benzodioxepin (7). Propargyl bromide (0.1 mL, 1.12 mmol) and 60 mg (0.21 mmol) of alcohol **4** were added to a suspension of 20 mg (0.83 mmol) of NaH in 0.5 mL of DMF at 5 °C. The reaction mixture was slowly brought to room temperature and stirred for 2 h. The reaction mixture was extracted with petroleum ether (60–80 °C), washed with water, dried, and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using petroleum ether as an eluant to give 47 mg (71%) of **7** as a white solid, mp 105 °C. ^{1}H-NMR ($CDCl_3$): δ 5.58 (s, 1H, H_{11}), 4.40 (d, J = 2.5 Hz, 2H, OCH_2), 3.80 (two d, J = 4.5 Hz, 2H, OCH_2), 2.40 (t, J = 2.5 Hz, 1H, CH), 1.60 (s, 3H, 3-CH_3), 1.46 (s, 3H, 9-CH_3), 1.0 (s, 3H, 6-CH_3). Anal. ($C_{18}H_{26}O_5$) C, H. Similarly compounds **6**, **8**, and **9** were prepared.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9β-[(α-chloroacetoxy)methyl]-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]benzodioxepin (10). α-Chloroacetyl chloride (0.1 mL, 0.88 mmol) was added to a stirred solution of 1 g (0.81 mmol) of 4-(dimethylamino)pyridine in 5 mL of chloroform at room temperature. The resulting mixture was stirred for additional 20 min, and 0.07 g (0.35 mmol) of the alcohol **4** was added. After being stirred for 3 h, the reaction mixture was extracted with petroleum ether. The petroleum ether extract was washed with water, dried, and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using petroleum ether as eluant to give 34 mg (42%) of **10** as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 5.6 (s, 1H, H_{11}), 4.16 (s, 2H, OCH_2), 4.08 (s, 2H, CH_2Cl), 1.66 (s, 3H, 3-CH_3), 1.48 (s, 3H, 9-CH_3), 1.40 (s, 3H, 6-CH_3). Anal. ($C_{17}H_{25}ClO_6$) C, H, Cl. Similarly the esters **11–13** and the sulfonates **15–17** were prepared.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,11,11a-undecahydro-9β-[[[[(4-chlorophenyl)amino]thiocarbonyl]-oxy]methyl]-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]-benzodioxepin (19). A mixture of 0.1 g (0.35 mmol) of the alcohol **4** and 0.15 g (0.88 mmol) of 4-chlorophenyl isothiocyanate in 5 mL of pyridine was heated at 60 °C for 14 h. The reaction mixture was extracted with petroleum ether, washed with ice cold dilute HCl and water, dried, and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using 1% of ethyl acetate in

petroleum ether as eluant to give 0.081 g (65%) of **19** as a white solid, mp 89–90 °C. ^{1}H-NMR ($CDCl_3$): δ 7.12 (d, J = 7.2 Hz, 2H, ArH), 7.38 (d, J = 7.2 Hz, 2H, ArH), 5.6 (s, 1H, H_{11}), 4.12 (s, 2H, OCH_2), 2.88 (s, 3H, 3-CH_3), 2.66 (s, 3H, 9-CH_3), 2.48 (s, 3H, 6-CH_3). Anal. ($C_{22}H_{28}ClNO_5S$) C, H, Cl, N, S. Similarly the carbamate **18** and the thiocarbamates **20–24** were prepared.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,11,11a-undecahydro-9β-[[[[4-(trifluoromethyl)phenyl]methyl]-amino]carbonyl]-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]-benzodioxepin (27). Thionyl chloride (0.1 mL, 0.84 mmol) was added to a stirred solution of 0.07 g (0.23 mmol) of the carboxylic acid **5** in 2.5 mL of dry ethyl acetate. After the mixture was stirred for 1 h, a solution of 0.2 mL (1.14 mmol) of 4-(trifluoromethyl)benzylamine in 2 mL of dry ethyl acetate was added at 0–5 °C. The reaction mixture was stirred further for an additional 30 min at 60–70 °C, extracted with petroleum ether, washed with water, dried, and concentrated to give 26 mg (25%) of **27** as a white solid, mp 170–172 °C. ^{1}H-NMR ($CDCl_3$): δ 7.18 (d, J = 10 Hz, 2H, ArH), 7.52 (d, J = 10 Hz, 2H, ArH), 5.6 (s, 1H, H_{11}), 4.38 (d, J = 5 Hz, 2H, NCH), 1.76 (s, 3H, 3-CH_3), 1.56 (s, 3H, 9-CH_3), 1.40 (s, 3H, 6-CH_3). Anal. ($C_{23}H_{28}F_3NO_5$) C, H, N. Similarly the amides **25** and **26** were prepared.

Preparation of 2-Chloroethyl 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9α-trimethylfurano-[3,4-*j*][1,2]benzodioxepin-9β-carboxylate (28). A solution of 0.1 mL of thionyl chloride in 2 mL of dry ethyl acetate and 0.2 mL of pyridine was added to a stirred solution of 0.05 g (0.16 mmol) of the carboxylic acid **5** in 2 mL of dry ethyl acetate at 5 °C. After the mixture was stirred for 15 min, 0.2 mL of 2-chloroethanol was added. The reaction mixture was stirred for an additional 1 h, extracted with dichloromethane, washed with cold dilute HCl and water, dried, and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using petroleum ether as eluant to give 27 mg (46%) of **28** as a white solid, mp 112 °C. ^{1}H-NMR ($CDCl_3$): δ 5.70 (s, 1H, H_{11}), 4.36 (m, 2H, OCH_2), 3.70 (t, J = 7 Hz, 2H, CH_2Cl), 1.80 (s, 3H, 3-CH_3), 1.62 (s, 3H, 9-CH_3), 1.46 (s, 3H, 6-CH_3). Anal. ($C_{17}H_{25}ClO_6$) C, H, Cl. Similarly compounds **29** and **34–37** were prepared.

Preparation of 1-(3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]-benzodioxepin-9β-yl)-2,2-dicarbethoxyethylene (31). A mixture of 0.08 g (0.28 mmol) of the aldehyde **3**, 0.3 mL (1.27 mmol) of diethyl malonate, 0.3 mL (3.77 mmol) of pyridine, and 1 mL of piperidine was heated with stirring at 80 °C for 16 h. The reaction mixture was neutralized with dilute HCl, extracted with petroleum ether, washed with water, dried, and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using EtOAc/petroleum ether (1:9) as eluant to give 26 mg (22%) of **31** as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 6.68 (s, 1H, olefinic H), 5.45 (s, 1H, H_{11}), 4.24 (two q, 4H, OCH_2), 1.68 (s, 3H, 3-CH_3), 1.6 (s, 3H, 9-CH_3), 1.44 (s, 3H, 6-CH_3). Anal. ($C_{22}H_{32}O_8$) C, H. Similarly compounds **30** was prepared.

Preparation of 3α,11α-Epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-9β-[*cis*-4-(trifluoromethyl)styryl]-3β,6α,9α-trimethylfurano[3,4*j*][1,2]benzodioxepin (32). Sodium hydride (0.03 g, 0.75 mmol) was added to a stirred solution of 0.18 g (0.38 mmol) of (trifluoromethylbenzyl)phosphonium bromide in 2 mL of dry tetrahydrofuran. The reaction mixture was stirred for 30 min at room temperature. The aldehyde **3** (0.09 g, 0.31 mmol) was then added, and the reaction mixture was stirred at room temperature for an addition 2 h. The reaction mixture was extracted with chloroform, washed with water, dried, and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using chloroform as eluant to give 34 mg (26%) of **32** as a viscous oil. ^{1}H-NMR ($CDCl_3$): δ 7.51 (d, J = 9 Hz, 2H, ArH), 7.34 (d, J = 9 Hz, 2H, ArH), 6.36 (d, J = 12.6 Hz, 1H, C=CHAr), 5.7 (d, J = 12.6 Hz, 1H, CH=C), 5.32 (s, 1H, H_{11}), 1.68 (s, 9-CH_3), 1.72 (s, 3-CH_3), 1.44 (s, 6-CH_3). Anal. ($C_{23}H_{27}F_3O_4$) C, H.

Preparation of 3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,12β,12α-dodecahydro-10-[(3α,11α-epoxy-3,4,5,5aα,6,7,8,8a,9,11,11a-undecahydro-3β,6α,9α-trimethylfurano[3,4-*j*][1,2]-benzodioxepin-9β-methylene)oxy]-3β,6α,9β-trimethylpyrano[4,3-*j*][1,2]benzodioxepin (38 and 39). Boron trifluoride etherate (0.2 mL) was added dropwise to a solution of 0.49 g (1.7 mmol) of the alcohol **4** and 0.35 g (1.23 mmol) of dihydroartemisinin in 10 mL of dry methylene chloride at 0 °C. The reaction mixture was stirred for 15 min and then diluted with water. The organic layer was separated, dried, filtered, and concentrated. The crude product obtained was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluant to give the α-isomer **39** followed by the β-isomer **38**. Compound **38**: white solid, mp 154–156 °C, yield 317 mg (34%). ^{1}H-NMR ($CDCl_3$): δ 5.54 (s, 1H, $H_{11'}$), 5.32 (s, 1H, H_{12}), 4.70 (d, J = 3.6 Hz, 1H, H_{10}), 3.77 (d, J = 7 Hz, 1H, OC*H*H), 3.4 (d, J = 7 Hz, 1H, OCH*H*), 1.64 (s, CH_3), 1.60 (s, CH_3), 1.44 (s, CH_3). Anal. ($C_{30}H_{46}O_9$) C, H. Compound **39**: white solid, mp 100 °C, yield 158 mg (17%). ^{1}H-NMR ($CDCl_3$): δ 5.54 (s, 1H, $H_{11'}$), 5.24 (1H, H_{12}), 4.36 (d, J = 7 Hz, 1H, OC*H*H), 4.04 (d, J = 7 Hz, 1H, OCH*H*), 3.21 (d, J = 9 Hz, 1H, H_{10}), 1.68 (s, CH_3), 1.44 (s, CH_3), 1.40 (s, CH_3). Anal. ($C_{30}H_{46}O_9$) C, H.

Biology. Materials and Methods. In vivo studies were carried out in Swiss mice model, following the method described by Peters.[13–15] Interesting compounds were also tested in mice infected with a chloroquine resistant strain of *Plasmodium yoelii* nigeriensis (NS).

Inoculum for infection was prepared from the previously infected donor mouse with rising parasitemia (20%). Blood was drawn from the heart of an infected mouse under anesthesia in a sterile, heparinized disposable syringe. The blood was then diluted in sterile RPMI 1640 medium so that 0.25 mL contained about 5×10^6 infected red blood corpuscles. Infection was given by intravenous route. The compounds were first dissolved in 2–3 drops of kardi oil followed by 2–3 drops of Tween 80 and then finally reconstituted in 5% tylose in water for oral administration. For subcutaneous administration, the compounds were first dissolved in 2–3 drops of kardi oil followed by 2–3 drops of Tween 80 and then finally reconstituted in sterile distilled water. The test compounds were administered on 5 consecutive days. The first dose was administered after 2 h postinfection. The rest of the doses were given once daily for 4 days. Blood smears were prepared on D+7, fixed in methanol, and stained with Giemsa. The slides were observed under an oil immersion (1000x) lens. The slides where parasites were detected were considered as positive and those without the parasite as cured. The slides that were found to be negative for malaria parasite were critically examined in a minimum of 25 fields.

Acknowledgment. Our thanks are due to Dr. Inamdar for the spectral and analytical data and to Dr. Miss Shah for providing the plant extract.

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JM9405957