Cambridge, U.K., in 1983 and maintained by intramuscular inoculation of a tumor brei for up to 12 consecutive passages and then reestablished from frozen stocks. For experimentation, 2–4 × 10⁵ viable tumor cells were injected subcutaneously in the middorsal pelvic region of the mice. Treatments were initiated 10–14 days later when tumors reached a maximum diameter of 6–8 mm.

Prior to injection, compounds were usually dissolved at 20 °C in PBS at pH 7.0 by means of sonication for up to 5 min. Compounds 9 and 10 were dissolved in phosphate buffer at pH 5 to minimize cyclization to 3. All solutions were administered within 10 min of preparation. Solutions were administered by the intraperitoneal route in a volume of 0.5 mL per 25 g of mouse body weight, with the exception of 14, 16, and 18, which were administered in a volume of 1 mL per 25 g owing to their dose-limiting solubility. Escalating doses of each of the test compounds were administered to groups of two or three tumor-bearing mice to establish the maximum tolerated dose (MTD). The MTD is defined as the highest single dose which does not produce severe or persistent clinical signs or death of the animals within 24 h.

The responses of KHT sarcomas to therapy administered in vivo were measured by means of a soft agar clonogenic assay in vitro,[34] as described recently.[35] Tumors were excised 18–24 h after treatment and each was assayed individually. Surviving fractions were calculated as the ratios of the numbers of colonies scored to the number of viable cells plated, relative to the plating efficiency of a control tumor processed at the same time. The mean plating efficiency of cells from 66 untreated tumors was 49.5

± 1.8% (mean ± SE) and the yield of cells ranged between 8.9 × 10⁶ and 7.6 × 10⁷ cells g⁻¹ of tumor tissue. A Pantac X-ray set was used to produce 250 kV X-rays (15 mA) at a dose rate of 3.8 Gy min⁻¹ with a half-value layer (HVL) equivalent to 1.33 mm Cu. Radiation doses were monitored with an air chamber corrected for ambient temperature and pressure. Unanesthetized mice were restrained in polyvinyl jigs with Pb shielding and a cutaway section to allow local irradiation of tumor by the unilateral beam.[36] A dose of 10 Gy of X-rays was used to test the efficiency of each compound as a hypoxic cell radiosensitizer. Each experiment included mice exposed to a 10 Gy dose of X-rays without drug and mice treated with drug without radiation. There is a minimum of three tumors in each group; most points were determined from the geometric mean of surviving fractions from at least four to six tumors from two separate experiments. Initially, the optimum time of administration before irradiation for maximum radiosensitization was determined for each of the compounds by administering the MTD. Subsequently a range of single doses of the compounds were administered at the optimum time (45–60 min in each case) before exposure to X-rays to obtain a drug dose/response curve for radiosensitization. Where appropriate, direct comparisons of radiosensitization by equimolar doses of chemically related compounds were made in a single experiment.

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Antimalarial Activity of New Water-Soluble Dihydroartemisinin Derivatives. 3.[1,2] Aromatic Amine Analogues

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A series of artemisinin (1) derivatives containing bromo and heterocyclic or aromatic amine functions was prepared in the search for analogues with good water solubility and high antimalarial activity. Treatment of dihydroartemisinin (2a) with boron trifluoride etherate at room temperature gave the key intermediate, 9,10-dehydrodihydroartemisinin (3), which, on reaction with bromine, gave the dibromide 4. The latter was condensed with amines in anhydrous CH₂Cl₂ at <–10 °C to give the desired products in 25–55% yield. The new derivatives, tested in vitro against *Plasmodium falciparum*, were found to be more effective against W-2 than D-6 clones and were not cross-resistant with existing antimalarials. Compound 6b, 3-fluoroaniline derivative, was the most active of the series, with the IC₅₀ ≤ 0.16 ng/mL, making it several fold more potent than 1. However, no significant in vivo antimalarial activity against *Plasmodium berghei* was observed in any of the new compounds tested.

Artemisinin (qinghaosu, arteannuin, 1), an antimalarial agent isolated from the plant *Artemisia annua*, is an endoperoxide-containing sesquiterpene lactone.[3–7] The unusual chemical structure of artemisinin coupled with its low toxicity and proven antimalarial efficacy have attracted attention from both chemists and parasitologists since its discovery in 1972. The practical use of artemisinin as an antimalarial agent, however, is impaired by (a) its insolubility in both water and oil,[8] (b) its poor efficacy by oral administration,[9] and (c) the rate of recrudescence in treated patients.[9]

The lactol form of 1, dihydroartemisinin (2a), prepared by the sodium borohydride reduction of the parent com-

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‡ Naval Research Laboratory.

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Table I. Physical Properties of 9-Bromo-10-aminated Dihydroartemisinin Derivatives

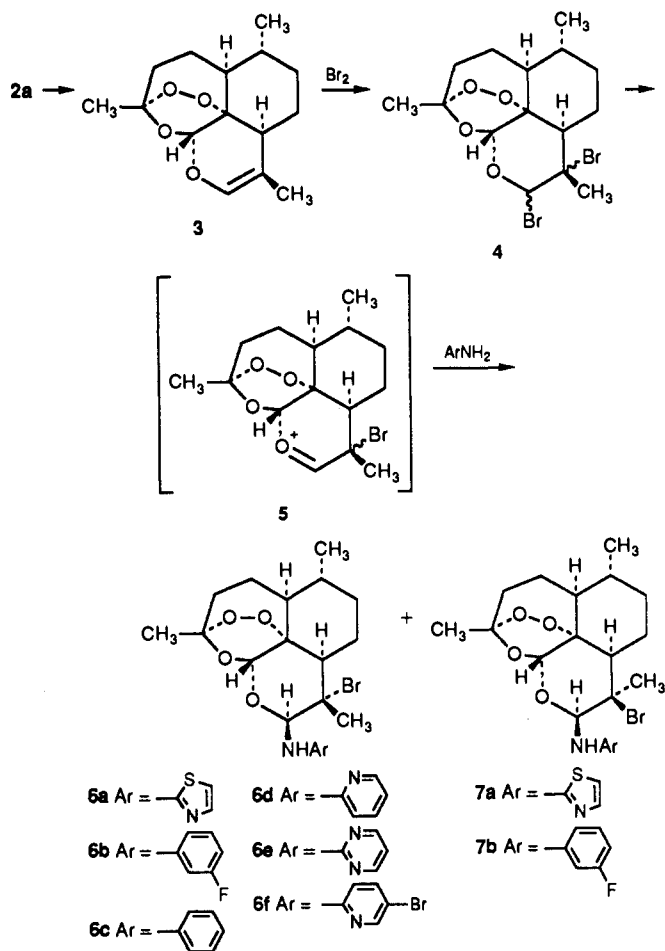| compd	mp, °C	recrystn solvent	TLC solvent (v/v)	R_f	% yield
6a	162–164	hexane + EtOAc	hexane/EtOAc (12:1)	0.41	30
7a	154–156	hexane + EtOAc	hexane/EtOAc (12:1)	0.35	10
6b	141–142	hexane + EtOAc	hexane/EtOAc (5:1)	0.38	25
7b	137–139	hexane + EtOAc	hexane/EtOAc (5:1)	0.35	10
6c	151–152	hexane + EtOAc	hexane/EtOAc (5:1)	0.54	35
6d	155–157	acetone + hexane	hexane/EtOAc (1:3)	0.52	36
6e	165–166	acetone + hexane	5% MeOH/CHCl$_3$	0.62	54

pound, was shown to be more active than 1.[4,8] But, because of its hemiacetal structure, the compound is believed to have lower stability than 1.

Chemical modifications of dihydroartemisinin to improve its efficacy and solubility have been reported by several laboratories. Artemether[8-12] and arteether,[8,10-12] the methyl and ethyl ethers of **2a**, respectively, are more lipophilic and more effective than artemisinin. Sodium artesunate (**2b**), a water soluble derivative of **2a**, was demonstrated to be particularly useful in the treatment of cerebral malaria.[8,9,13] A half ester of succinic acid, sodium artesunate is, however, not stable in aqueous solution, a property that is detrimental to its practical utility as an antimalarial agent.[1]

Recently, we prepared a series of derivatives of dihydroartemisinin (**2a**) in which the solubilizing group, carboxylate, was coupled to dihydroartemisinin by an alkyl ether rather than an ester linkage.[1,2] Among the water soluble derivatives that we prepared, the sodium salt of artelinic acid (**2c**) was found to be equally active as the parent artemisinin and sodium artesunate (**2b**) in vitro and more active than 1 and **2b** in rodent *Plasmodium berghei* test systems.[1] Furthermore, sodium artelinate is sub-

1

2a: R = –OH

b: R = α –OCCH$_2$CH$_2$COOH

c: R = β –OCH$_2$–⟨⟩–COOH
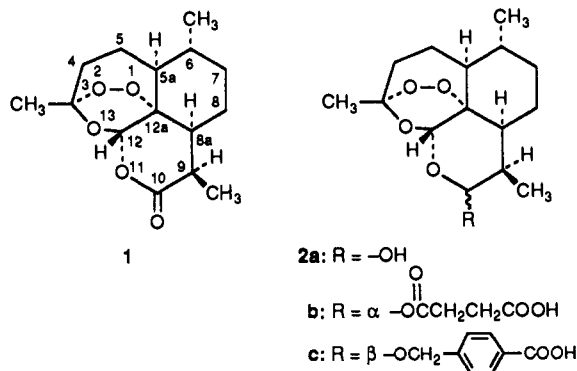
stantially more stable than sodium artesunate in weakly alkaline aqueous solution, an important physical property for the preparation of an intravenous injection dosage form. Antimalarial studies have shown that sodium artelinate totally eliminated the parasitemia in mice infected with *P. berghei* when administered in their drinking water.[14]

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Scheme I

6a Ar = ⟨thiazole⟩   **6d** Ar = ⟨pyridine⟩   **7a** Ar = ⟨thiazole⟩

6b Ar = ⟨C$_6$H$_4$F⟩   **6e** Ar = ⟨pyrimidine⟩   **7b** Ar = ⟨C$_6$H$_4$F⟩

6c Ar = ⟨phenyl⟩   **6f** Ar = ⟨pyridine⟩–Br

In our continuing search for new artemisinin analogues with good water solubility and high antimalarial efficacy, we report here the preparation and antimalarial studies of additional dihydroartemisinin derivatives which contain bromo and heterocyclic or aromatic amine functions. Water solubility, it was anticipated, would be achieved through salt formation.

Chemistry

The starting material, dihydroartemisinin (**2a**), was prepared by sodium borohydride reduction of 1 according to a modified literature procedure.[2] Experiments have shown that proper adjustment of the pH of the reaction mixture before workup is critical to obtaining acceptable yields of product.

Dihydroartemisinin, upon treatment with boron trifluoride etherate at room temperature, gave a key intermediate, 9,10-dehydrodihydroartemisinin (**3**) in 75–80% yield (Scheme I). Compound **3** was reported earlier to be a minor product when dihydroartemisinin was treated with alcohols under the boron trifluoride etherate catalysis and is probably formed by tautomerization of the oxonium intermediate, as discussed in the previous report.[2]

Table II. ^{1}H NMR Data for Compounds **6a–f** and **7a–b** (δ)

compd	C_9-Me	C_{10}-NH	C_{12}-H	C_{10}-H	aromatic protons
6a	2.07	6.42	5.46	5.61 (d) J = 10.8 Hz	7.20 (d, 1 H, J = 3.6 Hz), 6.63 (d, 1 H, J = 3.6 Hz)
6b	2.05	5.20	5.45	5.61 (d) J = 10.8 Hz	7.16–6.40 (m, 4 H)
6c	2.06	5.07	5.46	5.66 (d) J = 10.8 Hz	7.22–6.81 (m, 5 H)
6d	1.89	5.22	5.40	6.58 (d) J = 10.8 Hz	8.14 (m, 1 H), 7.46 (m, 1 H), 6.95 (d, 1 H, J = 8.1 Hz), 6.75 (m, 1 H)
6e	1.87	5.65	5.36	7.18 (d) J = 10.8 Hz	8.35 (d, 2 H, J = 4.5 Hz), 6.70 (t, 1 H, J = 4.5 Hz)
6f	1.87	5.24	5.39	6.53 (d) J = 10.8 Hz	8.18 (d, 1 H, J = 1.8 Hz), 7.66 (dd, 1 H, J = 1.8 and 9 Hz), 6.76 (d, 1 H, J = 9 Hz)
7a	2.28	5.79	5.49	5.54 (d) J = 4.5 Hz	7.19 (d, 1 H, J = 3.6 Hz), 6.58 (d, 1 H, J = 3.6 Hz)
7b	2.31	4.62	5.47	5.14 (d) J = 5.4 Hz	7.17 (m, 2 H), 6.52 (m, 2 H)

Treatment of **3** with bromine at low temperature gave a good yield of the corresponding dibromide (**4**). Inasmuch as two asymmetric carbons atoms are created during the bromination, four possible dibromide isomers are theoretically possible. However, **4** was found to be unstable at room temperature and, therefore, was used for reactions with amines without purification.

Condensation of dibromide **4** with amines was carried out in anhydrous dichloromethane at <–10 °C. Because this reaction involves the formation of 1 equiv of HBr, 2 equiv of amine were necessary for each equivalent of dibromide employed. Purification of the crude product was achieved through silica gel chromatography and yields ranged from 25–55% (Table I).

In contrast to aromatic amines, aliphatic amines such as benzylamine, butylamine, and N,N-diethylethylenediamine, gave no desired product under identical conditions. Instead, the major isolable product was 9,10-dehydrodihydroartemisinin (**3**) which was also found to be the minor product of reactions between aromatic amines and **4**.

Since two asymmetric carbon centers (C_9 and C_{10}) are created during the process of conversion from **3** to **6** and **7**, four stereoisomers are possible in the final products of each reaction. However, only two isomers were isolated in reactions when 3-fluoroaniline and 2-aminothiazole were used, and only one isomer was separated when aniline, 2-aminopyridine, and 2-aminopyrimidine were employed as reactants. In addition to **6d**, a byproduct was also isolated from the reaction mixture which contained 2-aminopyridine and was identified as 5-bromopyridine analogue **6f** by NMR (Table II). Compound **6f** presumably was derived from the bromination of the starting amine, 2-aminopyridine, or the product, **6d**. The source of the bromine atom was most likely from the oxidation of bromide anion by the hydroperoxide which is derived from the partial decomposition of the starting dibromide **4** during the reaction.

That there is little or no difference in chemical shift of C_{12}-H of all products suggests that compounds **6** and **7** have the same configuration at C_{10} (Table II). This leaves the structural differences between **6** and **7** to occur at C_9. Notably, C_{10}-H of **6a–e** are deshielded by C_9-Br to cause a greater downfield shift than **7a–b**, whereas C_9-CH$_3$ of compounds **7a–b** resonates at lower field ($\Delta\delta$ 0.2–0.3 ppm) than compounds **6a–f**, due to the deshielding effect of the peroxide group. A molecular model shows that the methyl group and the peroxide function are in close proximity in compounds **7a–b**. These results suggest that the bromine in compounds **7a–b** is in the β configuration (i.e., on the same side as the C_{12}-H), whereas the bromine in compounds **6a–f** assumes an α configuration. Only one bromo group was displaced by an amino function when dibromide **4** was treated with amine at <–10 °C. This suggests that the C_{10}-Br and not the C_9-Br is displaced by amine. Since C_{10}-Br of **4** is attached to the same carbon as C_{10}-O, electron delocalization from oxygen will lead to formation of a reactive oxonium ion **5** which is then reacted with amines
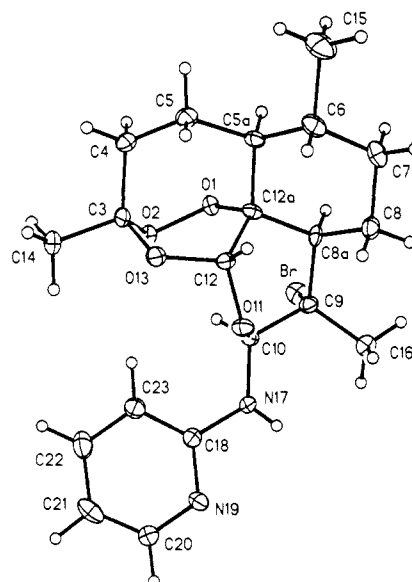

Figure 1. Thermal ellipsoid plot drawing of **6d** at 20% probability level from experimental coordinates.

to give the observed products **6a–e** and **7a–b**. Steric hindrance of the α side of the intermediate **5** caused the preferential attack by the amine from β side which accounts for the observation that compound **6** is the major or the sole product of the condensation reactions. Like the ether formation of dihydroartemisinin with an alcohol under the catalysis of boron trifluoride etherate which gave mainly the β isomer and was also involved the oxonium ion as the intermediate,[2] the C_{10}-N configuration is also β in both products **6** and **7**.

A molecular model indicated that, due to steric hindrance by the surrounding functional groups, the rotation of the bulky heterocyclic or aromatic ring of the new compounds along the C_{10} and N bond is restricted and, thus, only two conformations are possible for N-H, with the amine proton skewed between both protons at C_8 (α-H and β-H) or between the C_{12}-H and the β-C_8-H. The latter conformation gave larger J value than the former conformation due to larger dihedral angle between C_{10}-H and the N-H. The J value on C_{10}-H (Table II) suggested that compounds **6a–f** assume the latter conformation whereas compounds **7a–b** have the former conformation. The chemical shift and the coupling constant of C_{10}-H and C_{10}-NH of the final products were established by D$_2$O exchange technique.

The structure assignment of **6d** was confirmed by X-ray study. The results of the study are illustrated in Figure 1. The absolute configuration of **6d** (C_{5a}, C_9, and C_{10} are S and C_3, C_{12}, C_{12a}, and C_{8a} are R) agrees with that found for artemisinin (**1**).[15] With the exception that the brominated six-membered ring is more boat-shaped than

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Table III. In Vitro Antimalarial Activity of Dihydroartemisinin Derivatives against *Plasmodium falciparum*

	IC$_{50}$, ng/mL	
compd	African clone (D-6)	Indochina clone (W-2)
6a	0.91	0.21
6b	0.16	<0.16
6c	3.42	0.63
6d	7.72	1.19
6e	25.96	5.56
1	0.56	0.61

chair-shaped, the overall conformation of the fused ring system in **6d** is similar to that found for both artemisinin and its derivatives such as artemether and dihydroartemisinin (**2a**).[16] There is no hydrogen bonding in this structure with the closest N$_{17}$ intermolecular approach being N$_{17}$···O$_{13}$ at 3.21 Å. The closest intermolecular approach to the Br atom is a van der Waal's distance of 3.40 Å to a neighboring O$_2$ atom.

Results and Discussion

The new derivatives were tested in vitro against clones of human malaria, *P. falciparum* D-6 (Sierra Leone clone) and W-2 (Indochina clone). The former clone is a strain that is resistant to mefloquine and the latter, to chloroquine, pyrimethamine, sulfadoxine, and quinine.

The results (Table III) indicate that the new derivatives, like the parent agent 1, are not cross-resistant with any of the antimalarial agents mentioned. As was observed with other water soluble dihydroartemisinin derivatives, these new agents are more effective against W-2 than D-6. Compound **6b**, 3-fluoroaniline derivative, was the most active compound of the series, with the IC$_{50}$ (50% inhibitory concentration) $\leq$ 0.16 ng/mL making it several fold more potent than artemisinin. Compounds **6a** and **6c** showed activity comparable to artemisinin, whereas **6d** and **6e** are less active than the parent compound.

Despite the in vitro activities against *P. falciparum* observed with **6a–c**, no significant antimalarial activity against rodent malaria *P. berghei* in vivo was observed in any of the new compounds tested. No antimalarial testing was conducted on **7a–b** due to insufficient supply of these isomers.

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 disks on a Nicolet 20SXB FT-IR spectrometer. NMR spectra were determined on a JEOL FX90Q spectrometer with Me$_4$Si as an internal standard. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, and the results are within 0.4% of the theoretical values, except where noted.

Synthesis of 9,10-Dehydrodihydroartemisinin (3). Dihydroartemisinin (**2a**)[2] (5 g, 17.6 mmol) was dissolved in 30 mL of anhydrous Et$_2$O and cooled to 0–5 °C. Boron trifluoride etherate (5 mL in 50 mL of anhydrous Et$_2$O) was added dropwise to the solution with stirring. The solution was allowed to stand at room temperature overnight, washed first with aqueous NaHCO$_3$, followed by saturated aqueous NaCl solution, and dried over MgSO$_4$. The solvent was evaporated to dryness under the reduced pressure. The residue was chromatographed on a silica gel column using hexane/EtOAc (3:1 v/v) as eluent to give 4.0 g (85%) of colorless crystals of **3**: mp 96–98 °C (lit.[2] mp 95–97 °C), R_f = 0.74 (silica gel, hexane/EtOAc 3:1 v/v).

Bromination of 9,10-Dehydrodihydroartemisinin (3). To the solution of compound **3** (100 mg, 0.38 mmol) in 5 mL of anhydrous CCl$_4$ was added dropwise with stirring a 5% solution

of bromine in anhydrous CCl$_4$ at 0 °C until the mixture turned pale orange in color. After the mixture was stirred for an additional hour, the solvent was removed under reduced pressure at <40 °C and was used in the succeeding step without further purification. The bromo products (**4**) gradually turned to a black tar on standing at room temperature.

General Procedure for the Condensation of 4 with Amines. An amine (2 mmol) was dissolved in 10 mL of anhydrous CH$_2$Cl$_2$ and cooled to –10 °C with a ice/salt bath. To the amine solution was added dibromo compound **4** (1 mmol) in 10 mL of CH$_2$Cl$_2$ dropwise with stirring. After the addition was completed, the solution was allowed to stand at room temperature overnight. The reaction mixture was washed with saturated aqueous NaHCO$_3$ solution, dried over MgSO$_4$, and evaporated to dryness under reduced pressure. The crude product was purified by silica gel column chromatography using hexane and EtOAc mixed solvent as eluent to give the desired final products (Table I).

X-ray Crystallographic Data for 6d. C$_{20}$H$_{27}$N$_2$O$_4$Br, molecular weight = 546.48, clear colorless data crystal (0.18 × 0.32 × 0.48 mm), orthorhombic, space group $P2_12_12_1$, a = 10.113 (3), b = 10.663 (4), c = 18.461 (5) Å, d_{calc} = 1.82 mg mm^{-3}, Z = 4, μ = 2.1 mm^{-1}, 2620 independent reflections were measured out to $2\theta_{max}$ = 45.0° with a Nicolet R3m/V diffractometer using Mo Kα radiation (λ = 0.70169 Å) with a graphite monochromator in the incident beam. The data were collected at room temperature by using the $\theta/2\theta$ scan technique with a variable scan rate ranging from 10°/min minimum to 30°/min maximum, depending upon the intensity of a reflection. Data were corrected for Lorentz and polarization effects, and an empirical absorption correction was applied (maximum and minimum transmission factors were 0.786 and 0.695, respectively). The structure was solved by direct methods as implemented by the SHELXTL system of programs.[17] Full-matrix least-squares refinement on 249 parameters (coordinates and anisotropic thermal parameters for nonhydrogen atoms; hydrogen atoms originally placed at calculated positions and then allowed to ride on covalently bonded atoms, that is, C–H distances set 0.96 Å and coordinate shifts of attached C atom also applied to H atom, C–C–H angles set as close to idealized values as possible) used the 2270 reflections for which $|F_o| > 3\sigma(F_o)$. The absolute configuration of **6d** was determined from the difference in R factors on the basis of the anomalous scattering of the Br atom by using Friedel's pairs as suggested by Rogers.[18] The final R factors for the configuration shown in Figure 1 were R = 0.043 and R_w = 0.042 (for the "wrong" hand these values were R = 0.070 and R_w = 0.075). The goodness of fit parameter was 1.4, and the final difference map was featureless.

Biology. (a) In Vitro Antimalarial Studies. The in vitro assays were conducted with use of the semiautomated microdilution technique of Desjardins et al.[19] as modified by Milhous et al.[20] Two *P. falciparum* malaria parasite clones, designated as Indochina (W-2) and Sierra Leone (D-6), were utilized in susceptibility testing. They were derived by direct visualization and micromanipulation from patient isolates obtained by the Centers for Disease Control, Atlanta, GA in 1980 and 1982, respectively. The patients had acquired infections either in Vietnam or Sierra Leone. The Indochina clone is resistant to the antimalarials chloroquine, sulfadoxine, pyrimethamine, and quinine, whereas the Sierra Leone, is resistant to mefloquine but susceptible to chloroquine, quinine, sulfadoxine, and pyrimethamine. Test compounds were initially dissolved in DMSO and 70% ethanol and diluted in RPMI 1640 culture medium with 10% human plasma to 400-fold. Drugs were subsequently further diluted by using the Cetus Pro/Pette (Perkin-Elmer Corp., Norwalk, CT) over a range of 1.56–100 × 10^{-9} molar. Parasite inocula (at 0.5% parasitemia and a 1% hematocrit) were incubated for 24 h and added to equimolar concentrations of each test compound prior to the addition of ^{3}H-hypoxanthine. After a further incubation

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of 18 h, particulate matter was harvested from each microtiter well with use of an automated cell harvester (Skatron, Inc., Sterling, VA). Uptake of ^{3}H-hypoxanthine was measured by using a scintillation spectrophotometer (Model LS3801, Beckman Instruments, Irvine, CA). Concentration–response data were analyzed by nonlinear regression and the IC$_{50}$ values (50% inhibitory concentrations) for each compound were calculated.

(b) In Vivo Antimalarial Studies. The suppressive blood schizonticidal and curative activities of these new compounds were measured in a test where mice were infected with 5.98×10^5 *P. berghei* parasitized cells intraperitoneally on day 0. Test compounds were dissolved in peanut oil and were administered subcutaneously once a day for three consecutive days commencing on day 3. The dose levels of compounds given were 640, 160, and 40 mg/kg per day. Blood films were taken on days 6, 13, and 20. Blood schizonticidal activity was determined by monitoring blood films for the appearance of parasites and for extended survival times compared to infected untreated controls. Mice surviving 60 days were considered cured. The infected untreated control mice (negative controls) died on either day 6 or 7. Compounds was considered active when the survival time of the treated mice was greater than twice the control mice, i.e., 12–14 days.

Synthesis and Antineoplastic Properties of Ether-Linked Thioglycolipids

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Ether-linked glycero-α- and β-D-glucopyranosides and glycero-1-thio-α- and β-D-glucopyranosides have been synthesized by modifications of the Königs–Knorr procedure, and their antitumor activities have been evaluated. The bioactivities of these compounds have been evaluated in five different cell lines (WEHI 3B, C653, X63/OMIL3, R6X-B15, and HL-60) and compared with the activities of 1-*O*-hexadecyl-2-*O*-methyl-*sn*-3-glycerophosphocholine (GPC) and its enantiomer, 3-*O*-hexadecyl-2-*O*-methyl-*sn*-1-GPC. The results indicate that a α-D-thioglucopyranoside [1-*O*-hexadecyl-2-*O*-methyl-3-*S*-(α-D-1′-thioglucopyranosyl-*sn*-glycerol)] is selective with respect to its action on target cells, with high activity for killing of WEHI 3B and C653 cells as determined by inhibition of [^{3}H]thymidine incorporation into DNA and HL-60 cell cytotoxicity, but unable to induce aggregation of rabbit platelets at 10^{-5} M. The corresponding β-linked thioglycolipid was ineffective with respect to cytotoxicity against each cell line tested, indicating the importance of configuration at the anomeric position; the β-thioglycoside was also ineffective with respect to inducing platelet aggregation. 1-*O*-Hexadecyl-2-*O*-methyl-*sn*-3-GPC and 3-*O*-hexadecyl-2-*O*-methyl-*sn*-1-GPC were potent inhibitors of growth of each cell line tested but also caused rabbit platelet aggregation at concentrations $\geq 10^{-7}$ M. Thus, 3-*S*-(α-thioglycopyranosyl)-*sn*-glycerols bearing a long-chain *O*-alkyl group at the *sn*-1 position and a methoxy group at the *sn*-2 position of glycerol appear to be a promising class of antineoplastic agents with lower risk of inducing thrombosis than the widely studied platelet activating factor analogue, 1-*O*-octadecyl-2-*O*-methyl-*rac*-3-GPC.

A synthetic glucosyl diglyceride containing a long alkyl chain at the *sn*-1 position of glycerol, a methoxy group at the *sn*-2 position, and a β-linked glucosyl moiety at the *sn*-3 position (1-*O*-hexadecyl-2-*O*-methyl-3-*O*-(β-D-glucopyranosyl)-*sn*-glycerol (1); see Figure 1) possesses cancerostatic activities.[1] "Alkyl lysophospholipids" that have a 16- or 18-carbon alkyl chain at the *sn*-1 position, a methoxy group at the *sn*-2 position, and a phosphocholine moiety at the *sn*-3 position (4) have been shown to specifically inhibit the growth of tumor cells, inhibit tumor cell invasion and metastasis, and enhance the tumoricidal capacity of macrophages.[2] Although the mechanisms responsible for the cytotoxic action of the alkyl lysophospholipids are not known, the possibility of a metabolite being the active component has been raised.[3] In Ehrlich ascites cells *rac*-1-*O*-[^{3}H]octadecyl-2-*O*-methyl-glycerophosphocholine (GPC) was converted to *rac*-1-*O*-[^{3}H]octadecyl-2-*O*-methylglycerol at a rate of 70 pmol/10^6 cells/h.[1a] The significance of this observation is not yet known, however, since it is not clear whether the viability

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