Synthesis and Antimalarial Activity of 2-Aziridinyl- and 2,3-Bis(aziridinyl)-1,4-naphthoquinonyl Sulfonate and Acylate Derivatives[1]

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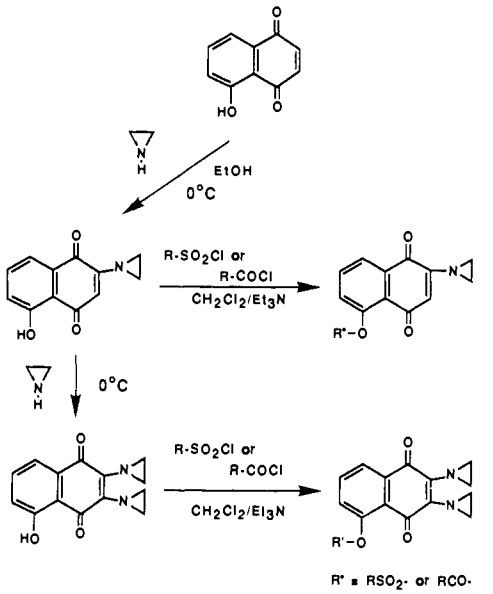
A series of 2-aziridinyl- and 2,3-bis(aziridinyl)-1,4-naphthoquinonyl sulfonate and acylate derivatives has been synthesized and evaluated for antimalarial activity in vitro against the human malaria parasite, *Plasmodium falciparum* (Vietnam Smith strain, chloroquine-resistant at the R_3 level). The most active compounds, 2-aziridinyl-1,4-naphthoquinon-5-yl *p*-ethylbenzenesulfonate (13), 2-aziridinyl-1,4-naphthoquinon-5-yl *p*-*tert*-butylbenzenesulfonate (48), and 2-aziridinyl-5-hydroxy-1,4-naphthoquinone (5) produced 50% inhibition of the growth of *P. falciparum* at 9.6×10^{-8}, 2.4×10^{-8}, and 8.8×10^{-8} M, respectively.

Introduction

Factors responsible for the continued rise in the incidence of disease due to malaria infection include, in addition to adverse socioeconomic conditions, the spread of drug-resistant parasites[3-6] and problems associated with vector control.[6,7] Although an emphasis has been placed upon vaccine development, this approach has not yet contributed to the control of this disease. Thus, since, at best, modest prospects appear to exist for the development of an efficacious vaccine in the near future,[8-10] the need for new drugs which are effective against drug resistant *P. falciparum* is obvious.

An antimalarial effect has been observed for numerous compounds which produce elevated levels of oxidative stress within the parasitized erythrocyte.[11] There is evidence which suggests that malaria parasites rely upon the defense mechanisms that exist within the host erythrocyte for protection against this type of insult.[11] An antiplasmodial effect was described almost 50 years ago for naphthoquinones.[12] Although no agents of this class have been developed as useful antimalarials, a number of naphthoquinones and quinone-containing compounds have displayed significant antimalarial activity when tested against *P. falciparum* in animal models[12-14] and in vitro.[14-17] In addition, compounds of this class were found to be active against other sporozoan parasites of veterinary importance.[15,18,19]

Scheme I



Two mechanisms of action, redox cycling[11] and inhibition of the enzyme dihydroorotate dehydrogenase, have been proposed to account for the antimalarial activity of the naphthoquinones.[13,20] There is evidence in support of both mechanisms and each site may contribute to the antiparasitic activity of these compounds. In an effort to develop agents that are irreversibly bound and are capable of redox cycling in malaria-infected cells, we have synthesized a series of 2-aziridinyl- and 2,3-bis(aziridinyl)-1,4-naphthoquinonyl sulfonate and acylate derivatives and have measured their activity against chloroquine-resistant *P. falciparum*.

Chemistry

Treatment of 2-aziridinyl-5-hydroxy-1,4-naphthoquinone (5),[21] 2,3-bis(aziridinyl-5-hydroxy)-1,4-naphthoquinone (6),[21] 2-(methylamino)-5-hydroxy-1,4-naphthoquinone (8), and 2-[(2-chloroethyl)amino]-5-hydroxy-1,4-naphthoquinone (10) with RSO_2Cl or RCOCl, in the presence of Et_3N, produced the respective sulfonates and acylates.

(1) This paper has been presented in part, see: Lin, T. S.; Xu, S. P.; Divo, A. A.; Sartorelli, A. C. In Abstracts of Papers; 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 7-12, 1986; American Chemical Society: Washington, DC, 1986; MEDI 91.
(2) Visiting Scientists from the Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, The People's Republic of China.
(3) Geary, T. G.; Edgar, S. A.; and Jensen, J. B. In *Chemotherapy of Parasitic Diseases*; Campbell, W. C., Rew, R. S., Eds.; Plenum: New York, 1986; pp 209-236.
(4) Peters, W. *Parasitology* **1985**, *90*, 705.
(5) Moran, J. S.; Bernard, K. W. *J. Am. Med. Assoc.* **1989**, *262*, 245.
(6) Wyler, D. J. *N. Engl. J. Med.* **1983**, *308*, 875.
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(9) Marshall, E. *Science* **1990**, *247*, 399.
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(13) Wan, Y.-P.; Portor, T. H.; Folkers, K. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 952.
(14) Hudson, A. T.; Randall, A. W.; Fry, M.; Ginger, C. D.; Hill, B.; Latter, V. S.; McHardy, N.; Williams, R. B. *Parasitology* **1985**, *90*, 45.
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(16) Percy, M.; Howells, R. E. *Ann. Trop. Med. Parasitol.* **1986**, *80*, 359.
(17) Heiga, L. A. E.; Kathendler, J.; Gean, K. F.; Bachrach, U. *Biochem. Pharmacol.* **1990**, *39*, 1620.
(18) McHardy, N.; Hudson, A. T.; Morgan, D. W. T.; Rae, D. G. *Res. Vet. Sci.* **1983**, *35*, 347.
(19) Zaugg, J. L. *Am. J. Vet. Res.* **1989**, *50*, 782.
(20) Skelton, F. S.; Rietz, R. E. *Ann. Trop. Med. Parasitol.* **1970**, *13*, 602.
(21) Lin, T. S.; Xu, S. P.; Zhu, L. Y.; Cosby, L. A., Sartorelli, A. C. *J. Med. Chem.* **1989**, *32*, 1467.

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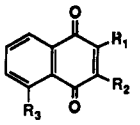
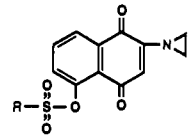
Table I. Effect of 2,3,5-Substituted 1,4-Naphthoquinone Derivatives on the in Vitro Growth of *P. falciparum*

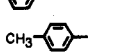
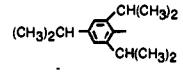
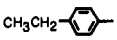
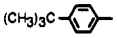
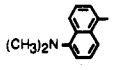
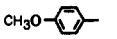
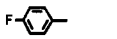
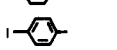


no.[a]	R_1	R_2	R_3	IC_{50},[b] M
1	H	H	OH	3.7×10^{-6}
2	CH_3	H	OH	2.4×10^{-6}
3	CH_3	H	H	3.4×10^{-6}
4	OH	H	H	1.0×10^{-4}
5		H	OH	8.8×10^{-8}
6			OH	1.6×10^{-6}
7	CH_3		OH	1.5×10^{-6}
8	$NHCH_3$	H	OH	3.7×10^{-6}
9	$N(CH_3)_2$	H	OH	1.6×10^{-6}
10	$NHCH_2CH_2Cl$	H	OH	4.3×10^{-6}

[a] Compounds 1–4 were obtained from Aldrich Chemical Co. [b] All agents were initially dissolved in dry dimethyl sulfoxide at a concentration of 10^{-2} M. The 50% inhibitory concentrations (IC_{50} values) are defined as the concentrations resulting in a 50% decrease in [^{3}H]hypoxanthine incorporation compared with drug-free controls; values were obtained as described previously from simple graphic extrapolation[40] and, therefore, are only estimates. IC_{50} values are the means of two to four observations. In every case, standard errors were ≤10% of the mean.

Table II. Effect of 2-Aziridinyl-1,4-naphthoquinonyl Sulfonate Derivatives on the in Vitro Growth of *P. falciparum*

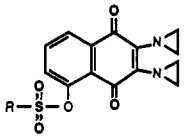


no.	R	IC_{50}, M	no.	R	IC_{50}, M
11		2.3×10^{-7}	18		1.7×10^{-7}
12		2.0×10^{-7}	19		2.8×10^{-7}
13		9.6×10^{-8}	20		1.3×10^{-7}
14		2.4×10^{-8}	21		2.9×10^{-7}
15		1.6×10^{-7}	22		4.3×10^{-7}
16		1.4×10^{-7}	23		4.7×10^{-7}
17		3.3×10^{-7}			

The synthetic routes for these compounds are depicted in Scheme I.

2-(Methylamino)-5-hydroxy-1,4-naphthoquinone (**8**) was prepared by reaction of 5-hydroxy-1,4-naphthoquinone (1, juglone; Aldrich Chemical Co.) with an ethanolic solution of methylamine (33%, w/v). 2-(Dimethylamino)-5-hydroxy-1,4-naphthoquinone (**9**) was obtained by treatment of juglone (1) with aqueous dimethylamine solution (26%, w/v). Treatment of 2-methyl-5-hydroxy-1,4-naphthoquinone with ethylenimine in ethanol afforded the 3-aziridinyl derivative **7**. 2-[(2-Chloroethyl)amino]-5-hydroxy-1,4-naphthoquinone (**10**) was fabricated by reacting 2-aziridinyl-5-hydroxy-1,4-naphthoquinone (**5**) with dry methanolic HCl. 2,3-Bis(aziridinyl)-1,4-naphthoquinon-5-yl sulfonate derivatives **24–42** were synthesized by previously described methodology.[21]

Table III. Effect of 2,3-Bis(aziridinyl)-1,4-naphthoquinonyl Sulfonate Derivatives on the in Vitro Growth of *P. falciparum*



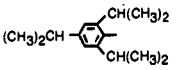
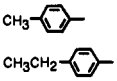
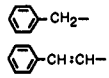
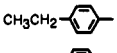
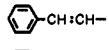
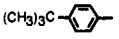
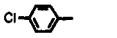
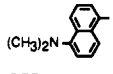
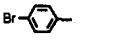
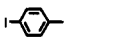
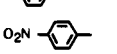
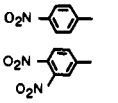
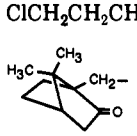
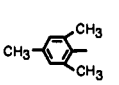
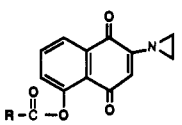
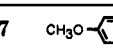
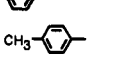
no.	R	IC_{50}, M	no.	R	IC_{50}, M
24		5.8×10^{-6}	34		3.0×10^{-6}
25		4.6×10^{-6}	35		2.4×10^{-6}
26		4.0×10^{-6}	36		5.8×10^{-6}
27		4.6×10^{-6}	37		3.4×10^{-6}
28		3.2×10^{-6}	38		3.0×10^{-6}
29		3.7×10^{-6}	39	CH_3–	3.2×10^{-6}
30		4.1×10^{-6}	40	$CH_3(CH_2)_{14}CH_2$–	2.0×10^{-5}
31		7.6×10^{-6}	41	$ClCH_2CH_2CH_2$–	3.0×10^{-6}
32		2.4×10^{-6}	42		6.0×10^{-6}
33		3.9×10^{-6}			

Table IV. Effect of 2-Aziridinyl-1,4-naphthoquinonyl Acylate Derivatives on the in Vitro Growth of *P. falciparum*



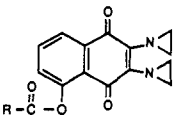
no.	R	IC_{50}, M	no.	R	IC_{50}, M
43		4.5×10^{-7}	47		5.4×10^{-7}
44		6.2×10^{-7}	48		1.6×10^{-7}
45		4.9×10^{-7}	49		4.9×10^{-7}
46		5.3×10^{-7}	50		4.7×10^{-7}

Results and Discussion

The synthesized compounds were evaluated in vitro for antimalarial activity against the human malaria parasite, *P. falciparum*[22-24] (Vietnam Smith strain, chloroquine-resistant at the R_3 level), and the results are shown in Tables I–VI. In general, the 2-aziridinyl-substituted compounds were more active than the 2,3-bis(aziridinyl) substituted derivatives, and the sulfonates were more active than the acylate derivatives. The most active compounds in the 2-aziridinyl-1,4-naphthoquinone series, *p-tert*-butylbenzenesulfonate **14**, *p*-ethylbenzenesulfonate **13**, and 3′,4′,5′-trimethoxybenzoyl ester (**48**) produced IC_{50} values of 2.4×10^{-8}, 9.6×10^{-8}, and 1.6×10^{-7} M, respectively. The most active compounds in the 2,3-bis(aziri-

(22) Jensen, J. B.; Trager, W. *J. Parasitol.* **1977**, *63*, 883.
(23) Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. B. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.
(24) Geary, T. G.; Divo, A. A.; Jensen, J. B. *J. Parasitol.* **1983**, *69*, 577.

Table V. Effect of 2,3-Bis(aziridinyl)-1,4-naphthoquinonyl Acylate Derivatives on the in Vitro Growth of *P. falciparum*



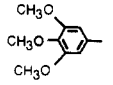
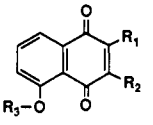
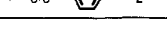
no.	R	IC_{50}, M	no.	R	IC_{50}, M
51		2.6×10^{-6}	56		3.4×10^{-6}
52		4.4×10^{-6}	57		4.6×10^{-6}
53		4.4×10^{-6}	58		2.6×10^{-6}
54		1.7×10^{-6}	59		3.9×10^{-6}
55		3.7×10^{-6}	60		5.4×10^{-6}

Table VI. Effect of 2-[(Chloroethyl)amino]-1,4-naphthoquinonyl Sulfonate and 2-Methyl-3-aziridinyl-1,4-naphthoquinone Derivatives on the in Vitro Growth of *P. falciparum*



no.	R_1	R_2	R_3	IC_{50}, M
61	$ClCH_2CH_2NH$	H	CH_3SO_2	8.5×10^{-6}
62	$ClCH_2CH_2NH$	H	$(CH_3)_2NSO_2$	2.2×10^{-5}
63	$ClCH_2CH_2NH$	H		6.5×10^{-6}
64	$ClCH_2CH_2NH$	H		2.9×10^{-6}
65	CH_3			3.6×10^{-6}

dinyl)-1,4-naphthoquinone series, β-styrenesulfonate (**36**) and the *p*-chlorobenzoyl ester (**54**) gave respective IC_{50} values of 5.8×10^{-7} and 1.7×10^{-6} M. In the aliphatic sulfonate series, 2,3-bis(aziridinyl)-5-[(methylsulfonyl)-oxy]-1,4-naphthoquinone (**39**) produced an IC_{50} value of 3.2×10^{-6} M. A lengthening of the aliphatic chain resulted in a decrease in antimalarial activity.

The structure–activity relationships demonstrate that the antimalarial effect was consistently increased by the presence of an aziridinyl substituent at the 2-position of the naphthoquinone ring. Since it has been postulated that naphthoquinones act as antimalarials by a redox cycling mechanism,[11] the relative rates of redox cycling for juglone (**1**), 2-aziridinyl-5-hydroxy-1,4-naphthoquinone (**5**), 2,3-bis(aziridinyl)-5-hydroxy-1,4-naphthoquinone (**6**), and 2-aziridinyl-5-[[(4′-*tert*-butylphenyl)sulfonyl]oxy]-1,4-naphthoquinone (**14**) were compared in uninfected and parasitized red blood cells. The rate of redox cycling did not significantly differ in uninfected and parasitized red blood cells (data not shown). Incubation of these compounds at 10^{-4} M in the presence of 3-amino-1,2,4-triazole for 90 min at 37 °C resulted in a 90% decrease in catalase activity; in the presence of H_2O_2, 3-aminotriazole irreversibly inactivates catalase.[25] The IC_{50} values for compounds **1**, **5**, **6**, and **14** were 3.7×10^{-6}, 8.8×10^{-6}, 1.6×10^{-6}, and 2.4×10^{-6} M, respectively, which do not correlate with their relative rates of redox cycling. The IC_{50} values for the 2,3-bis(aziridinyl) series, the 3-aziridinyl analogues (**7** and **65**), and the compounds which did not contain an aziridinyl moiety were all found to be similar ($>10^{-6}$ M) in vitro against *P. falciparum*. These agents probably share a common mechanism of action, most likely by the generation of H_2O_2 through a redox cycling mechanism. The increased potency of the 2-aziridinyl analogues does not appear to be due to elevated rates of redox cycling.

The enhancement of antiplasmodial activity observed for the 2-aziridinyl analogues appears to be specific. The IC_{50} values of compounds **8–10** and **61–64**, which possess a non-aziridinyl nitrogen-containing substituent at the 2-position, of compounds **7** and **65**, which contain a 3-aziridinyl substituent, and of the 2,3-bis(aziridinyl) substituted derivatives were approximately a log higher than those of the corresponding 2-aziridinyl analogues. Since the corresponding 2-aziridinyl derivatives were much more potent than 2-(dimethylamino)-5-hydroxy-1,4-naphthoquinone (**9**), it appears that alkylation is important for the observed increase in antimalarial activity. Although the 2,3-bis(aziridinyl)-1,4-naphthoquinones were found to be more efficacious as anticancer agents than the corresponding 2-aziridinyl analogues,[21] these derivatives were no more potent as antimalarials than the parent compound, juglone (**1**). The 2,3-bis(aziridinyl) derivatives have been postulated to be bioreductive alkylating agents that act in malignant cells by cross-linking DNA[21,26] and that these bifunctional alkylating agents are more efficacious than their monofunctional counterparts.[27,28] Since the potency as antimalarials of compounds **7** and **65**, which contain a 3-aziridinyl substituent, and the 2,3-bis(aziridinyl)-substituted derivatives (**6**, **24–42**, **51–60**) was found to be similar to compounds which do not have the capacity to alkylate, it appears unlikely that the enhanced antiplasmodial activity of the 2-aziridinyl analogues is solely due to alkylation of DNA. It is possible that dihydroorotate dehydrogenase (DHO) may be a target site for these agents.[29-32] Previous studies have demonstrated that DHO is inhibited by menoctone,[33] and if the 2-aziridinyl-1,4-naphthoquinones can be reduced by this enzyme, two possible consequences may ensue. First, a localized increase in the generation of H_2O_2 and, second, alkylation of DHO or other nucleophiles within the mitochondrial compartment may occur; both of these actions should be deleterious to the parasite. Aziridines as such would not appear to be the most suitable class of drugs to employ in the treatment of chloroquine-resistant strains of *P. falciparum*, but it may be possible to develop effective prodrugs of these agents. Although the 2-chloroethylamine prodrugs examined (**10**, **61–64**) were not as active as the 2-aziridinyl derivatives, it may be possible to generate the aziridinyl functionality in situ from ethylamines which possess a better leaving group such as bromine or iodine.[34,35]

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Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded at 500 MHz on a Brucker WM-500 spectrometer with Me_4Si as the internal reference. IR spectra were recorded on a Perkin-Elmer-21 spectrophotometer. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

2-Methyl-3-aziridinyl-5-hydroxy-1,4-naphthoquinone (7). Ethylenimine (1.2 g, 27.8 mmol, 1 mL) in 8 mL of ethanol was added slowly to a stirred solution of 2-methyl-5-hydroxy-1,4-naphthoquinone (0.5 g, 2.7 mmol) in 4 mL of CH_2Cl_2 and 150 mL of ethanol. The solution was stirred at room temperature for 72 h, then concentrated to dryness in vacuo. The resulting solid residue was chromatographed on a silica gel column (EtOAc–hexane, 2:3, v/v) to afford 0.3 g (61%) of pure product: R_f 0.59 (EtOAc–hexane, 2:3, v/v); mp 175–177 °C; NMR ($CDCl_3$) δ 2.20 (s, 3 H, 2-CH_3), 2.39 (s, 4 H, 3-aziridinyl), 7.19 (d, 1 H, 6-H), 7.57 (t, 1 H, 7-H), 7.61 (d, 1 H, 8-H), 11.97 (s, 1 H, 5-OH, D_2O exchangeable). Anal. ($C_{13}H_{11}NO_3$) C, H, N.

2-(Methylamino)-5-hydroxy-1,4-naphthoquinone (8). Ethanolic methylamine solution (33%, w/v, 0.2 mL) was added to a suspension of 5-hydroxy-1,4-naphthoquinone (0.2 g, 1.40 mmol). The reaction mixture was stirred vigorously at room temperature for 1 h and the solution was then extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried with anhydrous Na_2SO_4. The solution was concentrated to a small volume under reduced pressure and chromatographed on a silica gel column (EtOAc–hexane, 1:1, v/v) to afford 0.15 g (65%) of product: R_f 0.38 (EtOAc–hexane, 1:1, v/v); mp 214–215 °C; NMR ($CDCl_3$) δ 2.96 (d, 3 H, 2-NCH_3), 5.63 (s, 1 H, 2-NH), 6.12 (brs, 1 H, 3-H), 7.25 (d, 1 H, 6-H), 7.47 (t, 1 H, 7-H), 7.61 (d, 1 H, 8-H), 13.1 (s, 1 H, 5-OH, D_2O exchangeable). Anal. ($C_{11}H_9NO_3$) C, H, N.

2-(Dimethylamino)-5-hydroxy-1,4-naphthoquinone (9). Aqueous dimethylamine solution (26%, w/v, 3 mL) was added to a suspension of 5-hydroxy-1,4-naphthoquinone (1; 1 g, 5.74 mmol) in 50 mL of water with vigorous stirring. The transient violet color of the suspension became red immediately and then dark brown. After stirring for 2 h at room temperature, the reaction mixture was extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo. The resulting residue was then chromatographed on a silica gel column (EtOAc–hexane, 1:1, v/v; R_f 0.65) to give 0.43 g (34%) of red-brown product: mp 140–143 °C (lit.[21] mp 147 °C); NMR ($CDCl_3$) δ 3.26 [s, 6 H, 2-$N(CH_3)_2$], 5.72 (s, 1 H, 3-H), 7.20 (d, 1 H, 6-H), 7.45 (t, 1 H, 7-H), 7.51 (d, 1 H, 8-H), 12.9 (s, 1 H, 5-OH).

2-[(2-Chloroethyl)amino]-5-hydroxy-1,4-naphthoquinone (10). A solution of dry HCl/CH_3OH (3.3 mol, 3 mL) was added slowly to a stirred solution of 0.1 g (0.46 mmol) of 2-aziridinyl-5-hydroxy-1,4-naphthoquinone (5) in 20 mL of CH_2Cl_2. The reaction mixture was stirred for 30 min at room temperature and the color of the solution changed from yellow to red immediately. After the reaction was completed (monitored by TLC), the solvent was evaporated to dryness in vacuo. The residue was triturated with water and alcohol to give an orange product (0.12 g, 90%): mp 160–162 °C; R_f 0.59 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 3.59 (q, 2 H, 2-NCH_2), 3.77 (t, 2 H, 2-CH_2Cl), 5.75 (s, 1 H, NH), 6.15 (m, 1 H, 3-H), 7.17 (t, 1 H, 7-H), 7.63 (d, 2 H, 6- and 8-H). Anal. ($C_{12}H_{10}ClNO$) C, H, N.

2-Aziridinyl-5-[[(4′-*tert*-butylphenyl)sulfonyl]oxy]-1,4-naphthoquinone (14). A solution of 4-*tert*-butylbenzenesulfonyl chloride (0.98 g, 4.18 mmol) and triethylamine (1.45 g, 14.4 mmol, 2 mL) in 10 mL of CH_2Cl_2 was added to a stirred solution of 2-aziridinyl-5-hydroxy-1,4-naphthoquinone (5; 0.3 g, 1.4 mmol) in 10 mL of CH_2Cl_2. The reaction mixture was stirred for 15 h at room temperature. The solution was concentrated to a small volume and then chromatographed on a silica gel column (EtOAc–hexane–CH_2Cl_2, 3:4:5, v/v) to give 0.25 g (43%) of the product: mp 206–208 °C; R_f 0.67 (EtOAc–hexane–CH_2Cl_2 3:4:5, v/v); NMR ($CDCl_3$) δ 1.35 [s, 9 H, 4′-$C(CH_3)_3$], 2.25 (s, 4 H, 2-aziridinyl), 6.22 (s, 1 H, 3-H), 7.26 (d, 1 H, 6-H), 7.45 (d, 2 H, 3′- and 5′-H), 7.67 (t, 1 H, 7-H), 7.92 (d, 2 H, 2′- and 6′-H), 8.07 (d, 1 H, 8-H). Anal. ($C_{22}H_{21}NO_5S$) C, H, N.

Compounds 11–13 and 15–20 were synthesized by methodology similar to that described for the synthesis of compound 14.

2-Aziridinyl-5-[(phenylsulfonyl)oxy]-1,4-naphthoquinone (11): mp 152–154 °C; R_f 0.37 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.25 (s, 4 H, 2-aziridinyl), 6.22 (s, 1 H, 3-H), 7.40 (d, 1 H, 6-H), 7.58 (t, 2 H, 7- and 4′-H), 7.66 (m, 2 H, 3′- and 5′-H), 7.99 (d, 2 H, 2′- and 6′-H), 8.06 (d, 1 H, 8-H). Anal. ($C_{18}H_{13}NO_5S$) C, H, N.

2-Aziridinyl-5-[(*p*-tolylsulfonyl)oxy]-1,4-naphthoquinone (12): mp 152–154 °C; R_f 0.48 (EtOAc–CH_2Cl_2–hexane, 2:5:3, v/v); NMR ($CDCl_3$) δ 2.36 (s, 4 H, 2-aziridinyl), 2.47 (s, 3 H, 4′-CH_3), 6.23 (s, 1 H, 3-H), 7.37 (d, 2 H, 3′- and 5′-H), 7.41 (d, 1 H, 6-H), 7.66 (t, 1 H, 7-H), 7.88 (d, 2 H, 2′- and 6′-H), 8.07 (d, 1 H, 8-H). Anal. ($C_{19}H_{15}NO_5S$·EtOAc) C, H, N.

2-Aziridinyl-5-[[(4′-ethylphenyl)sulfonyl]oxy]-1,4-naphthoquinone (13): mp 174–176 °C; R_f 0.51 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 1.27 (t, 3 H, 4′-CH_2CH_3), 2.25 (s, 4 H, 2-aziridinyl), 2.75 (q, 2 H, 4′-CH_2), 6.22 (s, 1 H, 3-H), 7.38 (d, 2 H, 3′- and 5′-H), 7.42 (d, 1 H, 6-H), 7.67 (t, 1 H, 7-H), 7.90 (d, 2 H, 2′- and 6′-H), 8.06 (d, 1 H, 8-H). Anal. ($C_{20}H_{17}NO_5S$) C, H, N.

2-Aziridinyl-5-[[(4′-methoxyphenyl)sulfonyl]oxy]-1,4-naphthoquinone (15): mp 197–198 °C; R_f 0.56 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.25 (s, 4 H, 2-aziridinyl), 3.89 (s, 3 H, 4′-OCH_3), 6.22 (s, 1 H, 3-H), 6.99 (d, 2 H, 3′- and 5′-H), 7.44 (d, 1 H, 6-H), 7.66 (t, 1 H, 7-H), 7.92 (d, 2 H, 2′- and 6′-H), 8.06 (d, 1 H, 8-H). Anal. ($C_{19}H_{15}NO_6S$) C, H, N.

2-Aziridinyl-5-[[(4′-fluorophenyl)sulfonyl]oxy]-1,4-naphthoquinone (16): mp 185–187 °C; R_f 0.48 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.26 (s, 4 H, 2-aziridinyl), 6.24 (s, 1 H, 3-H), 7.24 (d, 2 H, 3′- and 5′-H), 7.46 (d, 1 H, 6-H), 7.69 (t, 1 H, 7-H), 8.06 (d, 1 H, 8-H), 8.09 (d, 2 H, 2′- and 6′-H). Anal. ($C_{18}H_{12}FNO_5S$) C, H, N.

2-Aziridinyl-5-[[(4′-iodophenyl)sulfonyl]oxy]-1,4-naphthoquinone (17): mp 156–158 °C; R_f 0.47 (EtOAc–hexane, 1:3, v/v); NMR ($CDCl_3$) δ 2.25 (s, 4 H, 2-aziridinyl), 6.23 (s, 1 H, 3-H), 7.46 (d, 1 H, 6-H), 7.68 (t, 1 H, 7-H), 7.71 (d, 2 H, 3′- and 5′-H), 7.93 (d, 2 H, 2′- and 6′-H), 8.09 (d, 1 H, 8-H). Anal. ($C_{18}H_{12}INO_5S$) C, H, N.

2-Aziridinyl-5-[(β-styrenesulfonyl)oxy]-1,4-naphthoquinone (18): mp 111–113 °C; R_f 0.44 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.26 (s, 4 H, 2-aziridinyl), 6.24 (s, 1 H, 3-H), 7.19 (d, 1 H, α-H), 7.42 (d, 2 H, 3′- and 5′-H), 7.45 (d, 1 H, 6-H), 7.52 (d, 2 H, 2′- and 6′-H), 7.56 (d, 1 H, β-H), 7.67 (d, 1 H, 4′-H), 7.74 (d, 1 H, 7-H), 8.07 (d, 1 H, 8-H). Anal. ($C_{20}H_{15}NO_5S$) C, H, N.

2-Aziridinyl-5-[[(2′,4′,6′-triisopropylphenyl)sulfonyl]oxy]-1,4-naphthoquinone (19): mp 139–141 °C; R_f 0.52 (EtOAc–hexane, 1:3, v/v); NMR ($CDCl_3$) δ 1.21 and 1.23 [d, 12 H, 2′- and 6′-$CH(CH_3)_2$], 1.28 and 1.30 [d, 6 H, 4′-$CH(CH_3)_2$], 2.28 (s, 4 H, 2-aziridinyl), 2.85 (m, 1 H, 4′-CH), 4.08 (m, 2 H, 2′- and 6′-CH), 6.26 (s, 1 H, 3-H), 7.02 (d, 1 H, 6-H), 7.24 (s, 2 H, 3′- and 5′-H), 7.56 (t, 1 H, 7-H), 8.03 (d, 1 H, 8-H). Anal. ($C_{27}H_{31}NO_5S$) C, H, N.

2-Aziridinyl-5-[(1′-naphthalenylsulfonyl)oxy]-1,4-naphthoquinone (20): mp 144–146 °C; R_f 0.43 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.25 (s, 4 H, 2-aziridinyl), 6.23 (s, 1 H, 3-H), 6.80 (d, 1 H, 5′-H), 7.47 (t, 1 H, 6′-H), 7.52 (t, 1 H, 7′-H), 7.68 (t, 1 H, 7-H), 7.99 (t, 1 H, 3′-H), 8.01 (d, 2 H, 6- and 8-H), 8.14 (d, 1 H, 4′-H), 8.19 (d, 1 H, 8′-H), 8.89 (d, 1 H, 2′-H). Anal. ($C_{22}H_{15}NO_5$) C, H, N.

2-Aziridinyl-5-[[[5′-(dimethylamino)-1′-naphthalenyl]sulfonyl]oxy]-1,4-naphthoquinone (21): mp 141–142 °C; R_f 0.71 (CH_2Cl_2–EtOAc–hexane, 1.5:1.5:1, v/v); NMR ($CDCl_3$) δ 2.26 (s, 4 H, 2-aziridinyl), 2.91 (s, 6 H, 5′-$N(CH_3)_2$), 6.23 (s, 1 H, 3-H), 6.78 (d, 1 H, 6′-H), 7.24 (d, 1 H, 6-H), 7.44 (t, 1 H, 7′-H), 7.52 (t, 1 H, 7-H), 7.65 (t, 1 H, 3′-H), 8.01 (d, 1 H, 8-H), 8.12 (d, 1 H, 8′-H), 8.52 (d, 1 H, 4′-H), 8.65 (d, 1 H, 2′-H). Anal. ($C_{24}H_{20}N_2O_5S$) C, H, N.

2-Aziridinyl-5-[(8-quinolinylsulfonyl)oxy]-1,4-naphthoquinone (22): mp 170–172 °C; R_f 0.56 (EtOAc); NMR ($CDCl_3$)

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δ 2.13 (s, 4 H, 2-aziridinyl), 6.20 (s, 1 H, 3-H), 7.39 (d, 1 H, 6-H), 7.56 (m, 1 H, 3-H), 7.60 (t, 1 H, 7-H), 7.70 (t, 1 H, 6'-H), 8.05 (d, 1 H, 8-H), 8.18 (d, 1 H, 4'-H), 8.29 (d, 1 H, 5'-H), 8.56 (d, 1 H, 2'-H), 9.02 (d, 1 H, 7'-H). Anal. ($C_{21}H_{14}N_2O_5S$) C, H, N.

2-Aziridinyl-5-[(2'-thiophene-ylsulfonyl)oxy]-1,4-naphthoquinone (23): mp 125–126 °C; R_f 0.39 (EtOAc–hexane, 2:3, v/v); NMR ($CDCl_3$) δ 2.26 (s, 4 H, 2-aziridinyl), 6.24 (s, 1 H, 3-H), 7.15 (t, 1 H, 4'-H), 7.42 (d, 1 H, 6-H), 7.68 (t, 1 H, 7-H), 7.75 (d, 1 H, 5'-H), 7.78 (d, 1 H, 3'-H), 8.09 (d, 1 H, 8-H). Anal. ($C_{16}H_{11}NO_5S_2$) C, H, N.

2-Aziridinyl-5-(benzoyloxy)-1,4-naphthoquinone (43): A solution of 0.26 g (1.85 mmol) of benzoyl chloride in 15 mL of CH_2Cl_2 was added slowly to a solution of 2-aziridinyl-5-hydroxy-1,4-naphthoquinone (5; 0.2 g, 0.92 mmol) and triethylamine (1 mL) in 20 mL of CH_2Cl_2. The solution was stirred at 0 °C (ice–water bath) for 30 min. The solvent was removed in vacuo to give a yellow solid which was recrystallized from EtOH to yield 1.5 g (52%) of product: mp 138–140 °C; R_f 0.37 (EtOAc–hexane, 3:7, v/v); NMR ($CDCl_3$) δ 2.22 (s, 4 H, 2-aziridinyl), 6.26 (s, 1 H, 3-H), 7.44 (d, 1 H, 6-H), 7.56 (t, 2 H, 3'- and 5'-H), 7.66 (t, 1 H, 4'-H), 7.68 (t, 1 H, 7-H), 8.09 (d, 1 H, 8-H), 8.27 (d, 1 H, 2'- and 6'-H); IR (KBr) 1730 cm^{-1} (R–COOR'). Anal. ($C_{19}H_{13}NO_4$) C, H, N.

2-Aziridinyl-5-[(4'-methylbenzoyl)oxy]-1,4-naphthoquinone (44): mp 182–184 °C; R_f 0.33 (EtOAc–hexane, 2:3, v/v); NMR ($CDCl_3$) δ 2.23 (s, 4 H, 2-aziridinyl), 2.48 (s, 3 H, 4'-CH_3), 6.26 (s, 1 H, 3-H), 7.35 (d, 2 H, 3'- and 5'-H), 7.44 (d, 1 H, 6-H), 7.76 (t, 1 H, 7-H), 8.07 (d, 1 H, 8-H), 8.16 (d, 2 H, 2'- and 6'-H); IR (KBr) 1730 cm^{-1} (R–COOR'). Anal. ($C_{20}H_{15}NO_4$) C, H, N.

2-Aziridinyl-5-[(4'-fluorobenzoyl)oxy]-1,4-naphthoquinone (45): mp 179–181 °C; R_f 0.31 (EtOAc–hexane, 3:7, v/v); NMR ($CDCl_3$) δ 2.23 (s, 4 H, 2-aziridinyl), 6.27 (s, 1 H, 3-H), 7.26 (t, 2 H, 3'- and 5'-H), 7.45 (d, 1 H, 6-H), 7.78 (t, 1 H, 7-H), 8.08 (t, 1 H, 8-H), 8.28 (t, 2 H, 2'- and 6'-H); IR (KBr) 1725 cm^{-1} (R–COOR'). Anal. ($C_{19}H_{12}FNO_4$) C, H, N.

2-Aziridinyl-5-[(4'-chlorobenzoyl)oxy]-1,4-naphthoquinone (46): mp 191–193 °C; R_f 0.35 (EtOAc–hexane, 1:3, v/v); NMR ($CDCl_3$) δ 2.23 (s, 4 H, 2-aziridinyl), 6.27 (s, 1 H, 3-H), 7.45 (d, 1 H, 6-H), 7.54 (d, 2 H, 3'- and 5'-H), 7.78 (t, 1 H, 7-H), 8.09 (d, 1 H, 8-H), 8.21 (d, 2 H, 2'- and 6'-H); IR (KBr) 1725 cm^{-1} (R–COOR'). Anal. ($C_{19}H_{12}ClNO_4$) C, H, N.

2-Aziridinyl-5-[(4'-methoxybenzoyl)oxy]-1,4-naphthoquinone (47): mp 180–182 °C; R_f 0.29 (EtOAc–hexane, 2:3, v/v); NMR ($CDCl_3$) δ 2.22 (s, 4 H, 2-aziridinyl), 3.93 (s, 3 H, 4'-OCH_3), 6.26 (s, 1 H, 3-H), 7.03 (d, 2 H, 3'- and 5'-H), 7.46 (d, 1 H, 6-H), 7.76 (t, 1 H, 7-H), 8.06 (d, 1 H, 8-H), 8.23 (d, 2 H, 2'- and 6'-H), IR (KBr) 1711 cm^{-1} (R–COOR'). Anal. ($C_{20}H_{15}NO_5$) C, H, N.

2-Aziridinyl-5-[(3',4',5'-trimethoxybenzoyl)oxy]-1,4-naphthoquinone (48): mp 180–182 °C; R_f 0.32 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.24 (s, 4 H, 2-aziridinyl), 3.98 (s, 9 H, 3'-, 4'-, and 5'-OCH_3), 6.28 (s, 1 H, 3-H), 7.45 (d, 1 H, 6-H), 7.53 (s, 2 H, 2'- and 6'-H), 7.78 (t, 1 H, 7-H), 8.01 (d, 1 H, 8-H); IR (KBr) 1725 cm^{-1} (R–COOR'). Anal. ($C_{22}H_{19}NO_7$) C, H, N.

2-Aziridinyl-5-(2'-furoyloxy)-1,4-naphthoquinone (49): mp 209–211 °C; R_f 0.15 (CH_2Cl_2): NMR ($CDCl_3$) δ 2.24 (s, 4 H, 2-aziridinyl), 6.27 (s, 1 H, 3-H), 6.55 (t, 1 H, 4'-H), 7.44 (d, 1 H, 6-H), 7.48 (d, 1 H, 3'-H), 7.76 (d, 1 H, 5'-H), 7.90 (t, 1 H, 7-H), 8.10 (d, 1 H, 8-H); IR (KBr) 1725 cm^{-1} (R–COOR'). Anal. ($C_{17}H_{11}NO_5$) C, H, N.

2-Aziridinyl-5-[(2'-thiophene-ylcarbonyl)oxy]-1,4-naphthoquinone (50): mp 149–151 °C; R_f 0.43 (EtOAc–hexane–CH_2Cl_2, 1:2:1, v/v); NMR ($CDCl_3$) δ 2.23 (s, 4 H, 2-aziridinyl), 6.26 (s, 1 H, 3-H), 7.26 (t, 1 H, 4'-H), 7.46 (d, 1 H, 6-H), 7.76 (d, 1 H, 5'-H), 7.78 (t, 1 H, 7-H), 8.06 (d, 1 H, 3'-H), 8.08 (d, 1 H, 8-H); IR (KBr) 1710 cm^{-1} (R–COOR'). Anal. ($C_{17}H_{11}NO_4S$) C, H, N.

2,3-Bis(aziridinyl)-5-(benzoyloxy)-1,4-naphthoquinone (51). A solution of benzoyl chloride (1 mL) and triethylamine (1 mL) in 20 mL of CH_2Cl_2 was added gradually to a solution of 2,3-bis(aziridinyl)-1,4-naphthoquinone (6; 0.3 g, 1.2 mmol). The reaction mixture was stirred at 0 °C (ice–water bath) for 30 min. The solution was evaporated to dryness in vacuo. The residue was then chromatographed on a silica gel column (EtOAc–hexane, 1:1, v/v; R_f 0.45) to afford 0.24 g (57%) of product: mp 140–142 °C; NMR ($CDCl_3$) δ 2.32 and 2.37 (2 s, 8 H, 2- and 3-aziridinyl), 7.36 (d, 1 H, 6-H), 7.54 (t, 2 H, 3'- and 5'-H), 7.66 (t, 2 H, 7- and 4'-H), 8.02 (d, 1 H, 8-H), 8.24 (d, 2 H, 2'- and 6'-H); IR (KBr) 1725 cm^{-1} (R–COOR'). Anal. ($C_{21}H_{16}N_2O_4$) C, H, N.

Compounds **52–60** were prepared by the methodology described for the synthesis of compound 51.

2,3-Bis(aziridinyl)-5-[(4'-methylbenzoyl)oxy]-1,4-naphthoquinone (52): mp 167–168 °C; R_f 0.14 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.32 and 2.37 (2 s, 8 H, 2- and 3-aziridinyl), 2.47 (s, 3 H, 4'-CH_3), 7.35 (d, 2 H, 3'- and 5'-H), 7.36 (d, 1 H, 6-H), 7.65 (t, 1 H, 7-H), 8.02 (d, 1 H, 8-H), 8.14 (d, 2 H, 2'- and 6'-H); IR (KBr) 1715 cm^{-1} (R–COOR'). Anal. ($C_{22}H_{18}N_2O_4$) C, H, N.

2,3-Bis(aziridinyl)-5-[(4'-fluorobenzoyl)oxy]-1,4-naphthoquinone (53): mp 141–143 °C; R_f 0.19 (EtOAc–hexane, 3:7, v/v); NMR ($CDCl_3$) δ 2.32 and 2.37 (2 s, 8 H, 2- and 3-aziridinyl); 7.26 (t, 2 H, 3'- and 5'-H), 7.36 (d, 1 H, 6-H), 7.66 (t, 1 H, 7-H), 8.02 (d, 1 H, 8-H), 8.26 (t, 2 H, 2'- and 6'-H); IR (KBr) 1730 cm^{-1} (R–COOR'). Anal. ($C_{21}H_{15}FN_2O_4 \cdot 0.25EtOAc$) C, H, N.

2,3-Bis(aziridinyl)-5-[(4'-chlorobenzoyl)oxy]-1,4-naphthoquinone (54): mp 186–187 °C; R_f 0.41 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.32 and 2.37 (2 s, 8 H, 2- and 3-aziridinyl), 7.37 (d, 1 H, 6-H), 7.51 (d, 2 H, 3'- and 5'-H), 7.67 (t, 1 H, 7-H), 8.02 (d, 1 H, 8-H), 8.19 (d, 2 H, 2'- and 6'-H); IR (KBr) 1727 cm^{-1} (R–COOR'). Anal. ($C_{21}H_{15}ClN_2O_4$) C, H, N.

2,3-Bis(aziridinyl)-5-[(4'-methoxybenzoyl)oxy]-1,4-naphthoquinone (55): mp 174–176 °C; R_f 0.15 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.32 and 2.37 (2 s, 8 H, 2- and 3-aziridinyl), 3.91 (s, 3 H, 4'-OCH_3), 7.06 (d, 2 H, 3'- and 5'-H), 7.37 (d, 1 H, 6-H), 7.65 (t, 1 H, 7-H), 8.02 (d, 1 H, 8-H), 8.26 (d, 2 H, 2'- and 6'-H); IR (KBr) 1715 cm^{-1} (R–COOR'). Anal. ($C_{22}H_{18}N_2O_5$) C, H, N.

2,3-Bis(aziridinyl)-5-[(3',4',5'-trimethoxybenzoyl)oxy]-1,4-naphthoquinone (56): mp 181–183 °C; R_f 0.21 (EtOAc–hexane, 1:1, v/v); NMR ($CDCl_3$) δ 2.36 and 2.39 (2 s, 8 H, 2- and 3-aziridinyl), 3.97, (s, 6 H, 3'- and 5'-OCH_3), 3.98 (s, 3 H, 4'-OCH_3), 7.39 (d, 1 H, 6-H), 7.52 (s, 2 H, 2'- and 6'-H), 7.68 (t, 1 H, 7-H), 8.04 (d, 1 H, 8-H); IR (KBr) 1730 cm^{-1} (R–COOR'). Anal. ($C_{24}H_{22}N_2O_7$) C, H, N.

2,3-Bis(aziridinyl)-5-(2'-furoyloxy)-1,4-naphthoquinone (57): mp 169–170 °C; R_f 0.31 (EtOAc–hexane–CH_2Cl_2, 1:1:1, v/v); NMR ($CDCl_3$) δ 2.35 and 2.38 (2 s, 8 H, 2- and 3-aziridinyl), 6.65 (t, 1 H, 4'-H), 7.36 (d, 1 H, 6-H), 7.46 (d, 1 H, 3'-H), 7.66 (t, 1 H, 7-H), 7.72 (d, 1 H, 5'-H), 8.04 (d, 1 H, 8-H); IR (KBr) 1725 cm^{-1} (R–COOR'). Anal. ($C_{19}H_{14}N_2O_5$) C, H, N.

2,3-Bis(aziridinyl)-5-[(2'-thiophene-ylcarbonyl)oxy]-1,4-naphthoquinone (58): mp 88–90 °C; R_f 0.19 (EtOAc–hexane, 2:3, v/v); NMR ($CDCl_3$) δ 2.32 and 2.37 (2 s, 8 H, 2- and 3-aziridinyl), 7.21 (t, 1 H, 4'-H), 7.38 (d, 1 H, 6-H), 7.65 (t, 1 H, 7-H), 7.69 (d, 1 H, 5'-H), 8.037 (d, 1 H, 8-H), 8.039 (d, 1 H, 3'-H); IR (KBr) 1715 cm^{-1} (R–COOR'). Anal. ($C_{19}H_{14}N_2O_4S$) C, H, N.

2,3-Bis(aziridinyl)-5-[(2',5'-dichlorothiophene-3'-ylcarbonyl)oxy]-1,4-naphthoquinone (59): mp 174–176 °C; R_f 0.51 (CH_2Cl_2–EtOAc, 4:1, v/v); NMR ($CDCl_3$) δ 2.36 and 2.38 (2 s, 8 H, 2- and 3-aziridinyl), 7.34 (d, 1 H, 6-H), 7.45 (s, 1 H, 4'-H), 7.66 (t, 1 H, 7-H), 8.03 (d, 1 H, 8-H); IR (KBr) 1730 cm^{-1} (R–COOR'). Anal. ($C_{19}H_{12}Cl_2N_2O_4$) C, H, N.

2,3-Bis(aziridinyl)-5-[(1'-adamantanylcarbonyl)oxy]-1,4-naphthoquinone (60): mp 152–154 °C; R_f 0.43 (EtOAc–hexane, 2:3, v/v); NMR ($CDCl_3$) δ 1.8 (s, 6 H, 4'-, 6'-, and 10'-H), 2.11 (s, 3 H, 3'-, 5'-, and 7'-H), 2.18 (s, 6 H, 2'-, 8'-, and 9'-H), 2.36 (s, 8 H, 2- and 3-aziridinyl), 7.16 (d, 1 H, 6-H), 7.59 (t, 1 H, 7-H), 7.94 (d, 1 H, 8-H); IR (KBr) 1720 cm^{-1} (R–COOR'). Anal. ($C_{25}H_{26}N_2O_4$) C, H, N.

Compounds **61–64** and **65** were fabricated from compounds **10** and **7**, respectively, by the methodology described for the preparation of compound 11.

2-[(2-Chloroethyl)amino]-5-[(methylsulfonyl)oxy]-1,4-naphthoquinone (61): mp 145–146 °C; R_f 0.23 (EtOAc–hexane–CH_2Cl_2, 1:2:2, v/v); NMR ($CDCl_3$) δ 3.42 (s, 3 H, 5-SCH_3), 3.56 (q, 2 H, 2-NCH_2), 3.75 (t, 2 H, 2-CH_2Cl), 5.79 (s, 1 H, NH), 6.21 (m, 1 H, 3-H), 7.61 (d, 1 H, 6-H), 7.78 (t, 1 H, 7-H), 8.17 (d, 1 H, 8-H). Anal. ($C_{13}H_{12}ClNO_5S$) C, H, N.

2-[(2-Chloroethyl)amino]-5-[[(dimethylamino)sulfonyl]oxy]-1,4-naphthoquinone (62): mp 175–176 °C; R_f 0.42 (EtOAc–hexane–CH_2Cl_2, 1:1:1, v/v); NMR ($CDCl_3$) δ 3.16 [s, 6 H, 5-$SN(CH_3)_2$], 3.57 (q, 2 H, 2-NCH_2), 3.75 (t, 2 H, CH_2Cl), 5.76

(s, 1 H, 2-NH), 6.22 (m, 1 H, 3-H), 7.74 (m, 2 H, 6- and 7-H), 8.08 (d, 1 H, 8-H). Anal. ($C_{14}H_{16}ClN_2O_5S$) C, H, N.

2-[(2-Chloroethyl)amino]-5-[(α-tolylsulfonyl)oxy]-1,4-naphthoquinone (63): mp 117–118 °C; R_f 0.28 (EtOAc–hexane, 2:3, v/v); NMR ($CDCl_3$) δ 3.58 (q, 2 H, 2-NCH_2), 3.76 (t, 2 H, 2-CH_2Cl), 4.83 (s, 2 H, $C_6H_5CH_2$), 5.78 (s, 1 H, 3-H), 6.23 (br, 1 H, NH), 7.43 (m, 3 H, 3'-, 4'-, and 5'-H), 7.47 (d, 1 H, 6-H), 7.55 (br, 2 H, 2'- and 6'-H), 7.69 (t, 1 H, 7-H), 8.11 (d, 1 H, 8-H). Anal. ($C_{19}H_{16}ClNO_5S$) C, H, N.

2-[(2-Chloroethyl)amino]-5-[[[5'-(dimethylamino)-1'-naphthalenyl]sulfonyl]oxy]-1,4-naphthoquinone (64): mp 205–206 °C; R_f 0.62 (CH_2Cl_2–EtOAc–hexane, 1.5:1.5:1, v/v); NMR ($CDCl_3$) δ 2.93 [s, 6 H, 5'-$N(CH_3)_2$], 3.55 (m, 2 H, 2-NCH_2), 3.74 (t, 2 H, 2-CH_2Cl), 5.75 (s, 1 H, 2-NH), 6.23 (m, 1 H, 3-H), 6.68 (d, 1 H, 6'-H), 7.25 (d, 1 H, 6-H), 7.47 (t, 1 H, 7'-H), 7.53 (t, 1 H, 7-H), 7.66 (t, 1 H, 3'-H), 8.05 (d, 1 H, 8-H), 8.07 (d, 1 H, 8'-H), 8.50 (d, 1 H, 4'-H), 8.66 (d, 1 H, 2'-H). Anal. ($C_{24}H_{21}ClN_2O_5S$) C, H, N.

2-Methyl-3-aziridinyl-5-[[(*p*-*tert*-butylphenyl)sulfonyl]oxy]-1,4-naphthoquinone (65): mp 124–126 °C; R_f 0.55 (EtOAc–hexane, 2:4, v/v); NMR ($CDCl_3$) δ 1.36 [s, 9 H, 4'-$C(CH_3)_3$], 2.16 (s, 3 H, 2-CH_3), 2.34 (s, 4 H, 3-aziridinyl), 7.35 (d, 1 H, 6-H), 7.56 (d, 2 H, 3'- and 5'-H), 7.58 (t, 1 H, 7-H), 7.92 (d, 2 H, 2'- and 6'-H), 8.07 (d, 1 H, 8-H). Anal. ($C_{23}H_{23}NO_5S$) C, H, N.

Antimalarial Activity. Stock cultures of *P. falciparum* were maintained in a candle jar system with minor modifications.[22,36,37] Parasites used were of the Vietnam Smith strain, an R_3 chloroquine-resistant organism (obtained from Dr. L. Perrin, University of Geneva, Geneva, Switzerland). Experiments were performed in 96-well microtiter plates (Linbro) as previously described;[23,24] [^{3}H]hypoxanthine (10 Ci/mmol; New England Nuclear Corp.) incorporation was used to measure the effects of synthesized agents. Each well contained 2 μL of infected erythrocytes, 200 μL of RPMI 1640 medium (GIBCO Laboratories) supplemented with 25 mM HEPES (Sigma Chemical Co.), sodium bicarbonate, 5% pooled calf serum,[37] and various drug concentrations. Parasites were exposed to synthesized agents over a 48-h period. Using semisynchronized cultures,[38,39] initial parasitemias were 1–3%, depending upon the ratio of trophozoites:schizonts. To each well, 1 μCi of [^{3}H]hypoxanthine was added and incorporation of radiolabel was measured for the entire 48-h incubation period. Cells were collected on glass-fiber filters with a Skatron cell harvester. The filters were dried and added to scintillation fluid (Opti-fluor; United Technologies Packard), and radioactivity was determined with a Beckman LS 7500 scintillation spectrometer.[24]

All agents were initially dissolved in dry dimethyl sulfoxide at a concentration of 10^{-2} M. The 50% inhibitory concentrations (IC_{50} values) were defined as the levels that produced a 50% decrease in [^{3}H]hypoxanthine incorporation compared to drug-free controls; values were obtained as the means of two to four observations from simple graphic extrapolation as described previously[40] and, therefore, are only estimates. In every case, standard errors were ≤10% of the mean.

Determination of the Relative Rates of Redox Cycling by Indirect Measurement of the Generation of Hydrogen Peroxide. The relative rates of redox cycling were determined by indirectly measuring the formation of H_2O_2 in uninfected and parasitized erythrocytes; this was accomplished by measuring residual catalase activity after incubation with compounds 1, 5, 6, or 14 in the presence of 3-amino-1,2,4-triazole,[25] which irreversibly inactivates catalase in the presence of H_2O_2. Red blood cells were always freed from white blood cell contaminants by centrifugation onto a 64% Percol cushion before being placed into culture. Mature parasites were concentrated by gel flotation before use; under these conditions, ca. 90% of the red blood cells were parasitized.[38] Control or parasitized erythrocytes were incubated at 37 °C for 90 min in RPMI 1640 medium supplemented with 25 mM HEPES, sodium bicarbonate, and 5% calf serum, in the presence of 10^{-4} M synthesized agent and 50 μM 3-aminotriazole. After incubation, the control and parasitized cells were washed three times with ice-cold RPMI 1640 medium supplemented only with $NaHCO_3$. To measure residual catalase activity, 0.1 μL of uninfected or parasitized erythrocytes were suspended in 2 mL of RPMI 1640 medium supplemented with $NaHCO_3$ placed into a Gilson Oxygraph and warmed to 37 °C. Oxygen was purged from the cell suspension by bubbling with N_2, and catalase activity was determined by measuring the evolution of O_2 after the addition of 10 mM H_2O_2. The relative rates of redox cycling were ascertained by comparing the slopes of the O_2 evolution curves.

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