= 6.5 Hz, $J_{2'a,3'}$ = 3.5 Hz, 2'-H_a), 2.47 (ddd, 1, $J_{2'b,1'}$ = 7.0 Hz, $J_{2'b,3'}$ = 7.0 Hz, 2'-H_b), 2.95 (br s, 1, 5'-OH, D_2O-exchangeable, 5'-OH), 3.72 (dd, 1, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 3.0 Hz, 4'-H), 4.04 (m, 1, 5'-H), 4.35 (dt, 1,3'-H), 5.94 (dd, 1, 1'-H), 7.25 (d, 1, 6-H), 9.10 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.453, 19.098, 36.971, 59.314, 67.152, 86.953, 88.123, 111.350, 137.057, 150.363, 163.693. IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

1-(3'-Azido-2',3',6'-trideoxy-α-L-talofuranosyl)thymine (6): FC EA; yield 80%; colorless crystals, mp 110–111 °C (EA–PE); R_f = 0.51 (EA); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, 3, J (CH_3, 5') = 6.2 Hz, CH_3), 1.92 (d, 3, J (5-CH_3, 6) = 1.0 Hz, 5-CH_3), 2.36 (ddd, 1, $J_{2'a,2'b}$ = 14.0 Hz, $J_{2'a,1'}$ = 7.0 Hz, $J_{2'a,3'}$ = 5.0 Hz, 2'-H_a), 2.54 (ddd, 1, $J_{2'b,1'}$ = 7.0 Hz, $J_{2'b,3'}$ = 7.0 Hz, 2'-H_b), 3.75 (dd, 1, $J_{3',4'}$ = 5.0 Hz, $J_{4',5'}$ = 3.0 Hz, 4'-H), 3.99 (dq, 1, 5'-H), 4.34 (dt, 1, 3'-H), 6.07 (t, 1, 1'-H), 7.43 (d, 1, 6-H), 9.00 (br s, 1, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$ δ 12.513, 20.256, 36.901, 61.121, 67.476, 86.538, 87.366, 111.268, 136.854, 150.250, 163.640; IR (CH_2Cl_2) 2115 (N_3) cm^{-1}. Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

Anti-HIV Assays. The HIV cytopathicity assay in human T-lymphocyte MT-4 cells has been described previously.[32,33] Briefly, MT-4 cells, subcultured 1 day before the start of the experiment, were adjusted to 5×10^5 cells/mL and infected with HIV ($HTLV\text{-}III_B$) at 400 $CCID_{50}$/mL. Then, 100 μL of the infected cell suspension was transferred to wells of a microtiter tray containing 100 μL of varying dilutions of the test compounds. After 5 days of incubation at 37 °C, the number of viable cells was recorded microscopically in a hematocytometer following the trypan blue exclusion procedure.

Acknowledgment. This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich—Project No. 7177 and P6537C (400 MHz NMR), the AIDS Basic Research Programme of the European Community, and the Belgian Fonds voor Geneeskundig Wetenschappelijk Onderzoek (Project No. 3.0097.87). We thank Ann Absillis, Wolfgang Binder, Frieda Demeyer, Martina Drescher, Judith Humpelstetter, Dirk Trauner and Anita Van Lierde for technical assistance and Hanspeter Kählig for 400-MHz spectra.

Registry No. 1, 30516-87-1; 2, 130481-61-7; 3, 136011-36-4; 4, 142003-05-2; 5, 134018-71-6; 6, 141980-84-9; 7, 2595-05-3; 8, 14728-80-4; 9, 64993-88-0; 10, 130481-52-6; 11, 130481-53-7; 12, 89128-39-2; 13, 114978-51-7; 14, 141980-85-0; 15, 141980-86-1; 16a, 130481-54-8; 16b, 141980-87-2; 16c, 141980-88-3; 16d, 141980-89-4; 16e, 141980-90-7; α-17a, 130481-55-9; β-17a, 130481-62-8; α-17b, 142036-32-6; β-17b, 142036-33-7; α-17c, 142036-34-8; β-17c, 142036-35-9; α-17d, 141980-91-8; β-18d, 141980-92-9; α-17e, 141980-93-0; β-17e, 141980-94-1; 18a, 130481-56-0; 18b, 141980-95-2; 18c, 141980-96-3; 18d, 141980-97-4; 18e, 141980-98-5; 19a, 130481-57-1; 19b, 141980-99-6; 19c, 142036-36-0; 19d, 141981-00-2; 19e, 142036-37-1; 19f, 141981-01-3; 20a, 130481-58-2; 20b, 141981-02-4; 20c, 142036-38-2; 20d, 141981-03-5; 20e, 142128-33-4; 21a, 130481-59-3; 21b, 141981-04-6; 21c, 142036-39-3; 21d, 141981-05-7; 21e, 142036-40-6; 22a, 130481-60-6; 22b, 142003-12-1; 22c, 141981-06-8; 22d, 141981-07-9; 22e, 141981-08-0; 22f, 141981-09-1; 22g, 141981-10-4; ClC(S)OC_7H_7, 937-63-3; thymine, 65-71-4.

Supplementary Material Available: Full experimental details and ^1H NMR data of compounds 8–11, 14, 15, 16A–E, 17Aα/β–17Eα/β, and 20A–20E and ^{13}C NMR data of 17Aα/β–17Eα/β (8 pages). Ordering information is given on any current masthead page.

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Dispiro-1,2,4,5-tetraoxanes: A New Class of Antimalarial Peroxides[1]

Jonathan L. Vennerstrom,*[,†] Hong-Ning Fu,[†] William Y. Ellis,[‡] Arba L. Ager, Jr.,[§] James K. Wood,[∥] Steven L. Andersen,[‡] Lucia Gerena,[‡] and Wilbur K. Milhous[‡]

College of Pharmacy, University of Nebraska Medical Center, 600 South 42nd Street, Omaha, Nebraska 68198-6025, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC 20307-5100, Department of Chemistry, University of Nebraska at Omaha, 60th and Dodge Street, Omaha, Nebraska 68182-0109, and Center for Tropical Parasitic Diseases, Department of Microbiology and Immunology, University of Miami School of Medicine, 12500 Southwest 152nd Street, Miami, Florida 33177. *Received March 16, 1992*

Dispiro-1,2,4,5-tetraoxanes 2–4 were synthesized as potential peroxide antimalarial drugs. They had curative activity against *Plasmodium berghei* in vivo at single doses of 320 and 640 mg/kg which confirms earlier unpublished data. Moreover, artemisinin (1) and 4 had equivalent ED_{50}'s against *P. berghei* in vivo in the multiple-dose Thompson test; neither showed any evidence of acute toxicity at total doses of more than 12 g/kg. Dispiro-1,2,4,5-tetraoxane 4 had IC_{50}'s comparable to those of 1 against *Plasmodium falciparum* clones in vitro. These results confirm the potential of dispiro-1,2,4,5-tetraoxanes as a new class of inexpensive peroxide antimalarial drugs.

As a result of an apparent association between the peroxide functional group and antimalarial activity,[2] a substantial effort has been devoted to developing new peroxide antimalarials. Our early attempts[3,4] in this regard led us to conclude that an endoperoxide ketal is a minimum but insufficient structural requirement for an effective peroxide-containing antimalarial. Most work, however, has centered around artemisinin (1), the proto-

† University of Nebraska Medical Center.
‡ Walter Reed Army Institute of Research.
§ University of Miami.
∥ University of Nebraska at Omaha.

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Table I. Antimalarial Activity of Dispiro-1,2,4,5-tetraoxanes 2–4 Compared to Artemisinin (1)

	P. falciparum IC_{50} (nM)			*P. berghei* T – C[a] (days) at the following doses (mg/kg)[c]					
compd	D-6	W-2	resistance index[b]	20	40	80	160	320	640
1	4.7	2.2	0.47	1.5	1.7	2.3	3.9	5.1	C-2[d]
2	50	13	0.26	1.5	1.3	2.4	5.5	C-1	NA
				0.6	1.0	3.8	5.8	7.4A	C-2[e]
3	8.2	58	7.1	0.1	0.4	0.1	2.4	1.9	C-1
				0.3	0.5	2.0	3.2	13.0A	C-1[e]
4	6.9	3.4	0.49	0.2	1.8	1.6	9.6A	C-1	C-3
				0.7	1.2	5.0	12.0A	C-3	C-5[e]

[a] T – C is the mean survival time of the treated mice beyond that of the control animals. This value must be ≥ twice the mean survival time (6.2 days) of the control animals to be considered active (A). Survival beyond 60 days is considered curative (C), and deaths from 0–2 days postinfection are attributed to toxicity (T). [b] IC_{50} (W-2)/IC_{50}(D-6) ratio. [c] Single dose administered sc 3 days postinfection, $n = 5$. [d] T – C values for 1 represent averages of eight data sets from WRAIR. [e] Unpublished data.[12]

type peroxide antimalarial, in an effort to discern its structure–activity relationship (SAR).[5] These investigations identify the 1,2,4-trioxane heterocycle as the critical pharmacophore, and suggest that an intact ABC ring system is required for maximum potency.

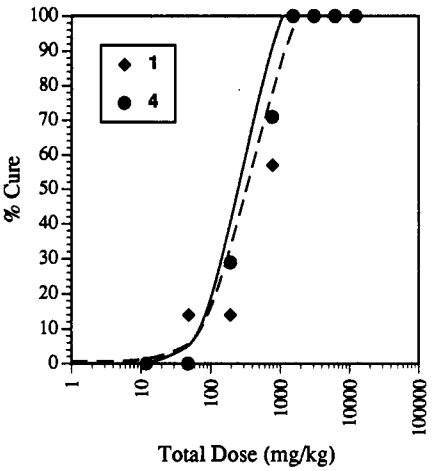
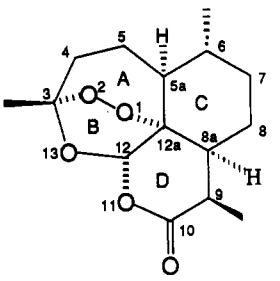


Figure 1. Dose–response curves for 1 (hatched line) and 4 (solid line) in the Thompson test. Doses of 1 and 4 were administered sc twice daily for 3 days, starting at day 3 postinfection.



1

Others[6-9] have synthesized structurally diverse 1,2,4-trioxanes which show mixed results when screened for

(4) We found that two tricyclic peroxy ketals (7-acetyl-1,4,6-trimethyl-2,3,5,10-tetraoxatricyclo[4.3.1.0^{4,9}]decane and 1,4,6-trimethyl-2,3,5,7,8-pentaoxatricyclo[4.2.2.0^{4,9}]decane described by Bischoff, C.; Rieche, A. Über die Bildung cyclischer Peroxide aus Mehrfachketonen. *Liebigs Ann. Chem.* **1969**, *725*, 87–92, have IC_{50}'s >300 nM against *P. falciparum* in vitro and are inactive against *P. berghei* with toxicity observed at a 640 mg/kg dose. We thank Prof. Christophe Morin, of the Universite de Grenoble, St.-Martin D'Heres, France for bringing these peroxides to our attention as potential antimalarials.

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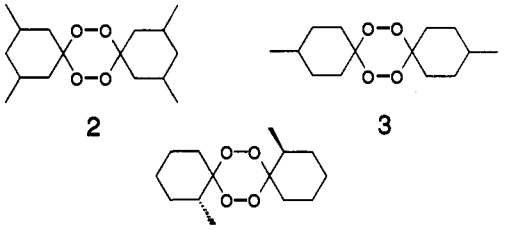
antimalarial activity. For example, Kepler et al.[6] synthesized 10 1,2,4-trioxanes that were inactive against *P. berghei* in vivo; the most active compounds in this series had IC_{50}'s between 24 and 100 ng/mL against *P. falciparum* in vitro. Singh[7] synthesized several 1,2,4-trioxanes with IC_{50}'s ranging from 3 to 222 ng/mL against *P. falciparum* in vitro. Jefford et al.[8] reported that 10 1,2,4-trioxanes were either inactive or much less active than was 1 against *P. berghei* in mice. More recently, however, Jefford et al.[9] described excellent in vitro and in vivo antimalarial activity for numerous 1,2,4-trioxanes, many of which were more potent than 1.

It must be noted that 1 is curative against *P. berghei* only at 640 mg/kg in the single-dose Rane screen[10] (Table I); its curative activity improves dramatically, however, when a multiple-dose protocol is followed.[11] In this light, unpublished data[12] that indicates several dispiro-1,2,4,5-tetraoxanes[13] are curative at single doses of 320 and 640 mg/kg is remarkable. We now confirm this curative in vivo activity and show that dispiro-1,2,4,5-tetraoxanes are also active against *P. falciparum* in vitro.

Chemistry

From this unpublished data,[12] we chose three of the more active dispiro-1,2,4,5-tetraoxanes (2–4) which were obtained via acid-catalyzed peroxyketalization between a 1:1 mole ratio of the substituted cyclohexanone and hydrogen peroxide. A modified procedure of Braunworth and Crosby[14] using 30% H_2O_2 and H_2SO_4 in aqueous EtOH at 0 °C afforded 2[12] and 3.[15,16] We found the procedure of



2

3

4

Sanderson et al.[15] using 30% H_2O_2, HCl, and $HClO_4$ in acetic acid at room temperature to be the best method for the synthesis of 4.[15,16] ^1H and ^{13}C NMR spectroscopy indicate that 2 and 3 are each mixtures of meso and d,l stereoisomers, whereas 4 is a single stereoisomer. For example, 4 has a seven-line ^{13}C NMR spectrum consistent with the presence of a single stereoisomer, whereas 2 and 3 each have 2–3-fold the number of lines expected for that of a single diastereomer. Furthermore, ^1H NMR spectra show a single doublet for the methyl groups in 4, and closely overlapping doublets for the methyl groups in 2 and 3. Previous X-ray crystallographic structural analysis of 4[17] has shown that it exists as a single meso stereoisomer.

Antimalarial Activity

In vivo antimalarial activity for 2–4 against a drug-sensitive strain (KBG 173) of *P. berghei* in the single-dose Rane screen[10] was comparable (Table I) to unpublished data[12] with cures seen at doses of 320 and 640 mg/kg. A multiple-dose Thompson test[18] against *P. berghei* (Figure 1) revealed no significant difference between ED_{50}'s of 1 (607 mg/kg) and 4 (382 mg/kg) at the 95% confidence intervals using nonlinear regression.[19] Both drugs demonstrated a remarkable lack of acute toxicity; no deaths were observed at total doses of more than 12 g/kg.

In vivo antimalarial activity against the D-6 and W-2 clones of *P. falciparum* (Table I) using a semiautomated microdilution technique[20,21] indicates that 2 and 3 are 2- to 26-fold less potent than is 1; curiously, 3, in contrast to 1, 2, and 4, has a high resistance index. Dispiro-1,2,4,5-tetraoxane 4 is only 1.5-fold less potent than is 1 against both *P. falciparum* clones. The excellent potency of 4 against *P. falciparum* in vitro is consistent with its superior single-dose in vivo activity in comparison to 2 and 3. The range of in vitro potencies for 2–4 is also consistent with unpublished data of Doorenbos and Decker[12a] who noted considerable changes in in vivo antimalarial activity with relatively small structural modifications.

Discussion

Even though an overlay of energy-minimized structures of 1 and 4[22] using PCMODEL reveals substantial structural

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(13) Antimalarial data (*P. berghei*) from WRAIR indicates that several 1,2,4,5-tetraoxanes derived from cyclic ketones are curative, whereas those derived from acyclic ketones and aldehydes are not. Cyclic triperoxides (1,2,4,5,7,8-hexaoxonanes) which are kinetic products (Story, P. R.; Lee, B.; Bishop, C. E.; Denson, D. D.; Busch, P. Macrocyclic Synthesis. II. Cyclohexanone Peroxides. *J. Org. Chem.* **1970**, *35*, 3059–3062) of acid-catalyzed peroxyketalization between hydrogen peroxide and ketones are without activity.

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(19) The % cure versus dose data from the Thompson test were fit to a Hill Equation using nonlinear regression (PCNONLIN SCI, Lexington, KY). Hill Equation: $R = R_{max} \cdot D^H/ED_{50} + D^H$ where R_{max} is the maximum effect (100% cure), ED_{50} is the dose at which 50% cure occurs, H is the Hill coefficient or slope factor, and D is the dose.

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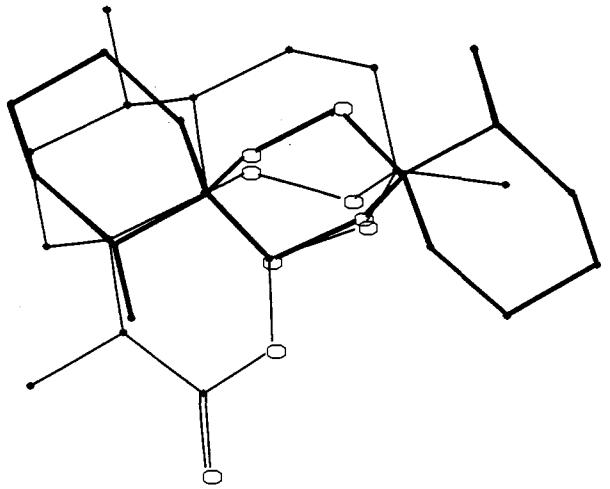
dissimilarity between the two as exemplified by the boat 1,2,4-trioxane in 1 and the chair 1,2,4,5-tetraoxane in 4, structural correlations between artemisinin and 4 are of interest. For example, VT ^{13}C NMR experiments[17b] in-



dicate that 4, like 1, exists as a relatively rigid structure. If one speculates that the 1,2,4-trioxane in 1 corresponds with the 1,2,4,5-tetraoxane in 4, several correlations are evident: (1) the oxygen-substituted carbon atom (C-12) in 1 is replaced with an oxygen atom in 4; (2) the C-3 methyl and 4,5-ethano bridge (which forms the A-ring in 1) are replaced with a methyl-substituted spirocyclohexane in 4; and (3) the C-ring, a substituted spirocyclohexane with respect to the 1,2,4-trioxane (B-ring) in 1 may correspond to the other spirocyclohexane ring in 4. These correlations are consistent with the observation that full potency is seen with certain ABC ring analogs of 1.[5i,5o]

As the peroxide bond is absolutely essential for antimalarial activity in 1,[23] it is likely that at least one of the peroxide bonds in 4 is required. To partially address this question, work is in progress to screen the analogous dispiro-1,2,4-trioxolanes[24] and dispiro-1,2,4-trioxanes which differ from dispiro-1,2,4,5-tetraoxanes by removal of one oxygen atom or by replacement of an oxygen atom by a methylene carbon, respectively.

In summary, we suggest that the potency observed with 4 against *P. falciparum* in vitro confirms the potential of dispiro-1,2,4,5-tetraoxanes as a new class of peroxide antimalarial drugs. An expected advantage of these compounds with respect to 1 and its semisynthetic derivatives is a one-step synthesis using inexpensive starting materials vs a multistep synthesis or isolation from *Artemisia annua*. Work is in progress to synthesize additional dispiro-1,2,4,5-tetraoxanes to define SAR and optimize antimalarial activity.

Experimental Section

Molecular modeling experiments were performed with PCMODEL 4.0 (Serena Software). Melting points were taken with a Mel-Temp capillary apparatus. IR spectra were run as KBr discs on a Perkin Elmer 1420 spectrophotometer. NMR spectra were obtained with Varian XL-300 or Bruker AC-200 spectrometers using deuteriated chloroform and TMS as an internal standard. Microanalyses were performed by M-H-W Laboratories, Phoenix, AZ. Analytical HPLC of 2–4 was performed on a 5-μm silica column (Alltech Spherisorb 250 × 4.6 mm) using a 97:3 heptane *tert*-butyl methyl ether mobile phase with detection at 220 nm. All reagents are commercially available from Aldrich Chemical Co. with the exception of 3,5-dimethylcyclohexanone. The latter was prepared by Jones oxidation of 3,5-dimethylcyclohexanol.

Synthesis. 2,4,11,13-Tetramethyl-7,8,15,16-tetraoxodispiro[5.2.5.2]hexadecane (2). Thirty percent H_2O_2 (23.8 mmol, 0.810 g) and 3,5-dimethylcyclohexanone (23.8 mmol, 3.00 g) were added by consecutive dropwise addition to a stirred solution of water (25 mL), EtOH (27 mL), and H_2SO_4 (50 mL) at 0 °C. Stirring was continued for 14 h at 0 °C. The resulting white precipitate was filtered, washed with water, and air-dried to afford 2 (2.64 g, 78%): mp 172–173 °C (CH_3CN) (lit.[12] mp 172–173 °C); IR 2980, 2920, 2900, 2840, 1445 cm^{-1}; ^1H NMR δ 0.45–0.75 (m, 2 H), 0.77–1.22 (m, 16 H), 1.49–1.93 (m, 8 H), 2.05–2.34 (m, 2 H); ^{13}C NMR δ 21.87, 21.94, 22.02, 28.29, 28.63, 28.93, 36.40, 36.50, 40.12, 43.23, 43.38, 108.68, 109.05. Anal. ($C_{18}H_{28}O_4$) C, H.

3,12-Dimethyl-7,8,15,16-tetraoxodispiro[5.2.5.2]hexadecane (3): 0.78 g, 70%; mp 71–72 °C (6:4 MeOH/H_2O) (lit.[12,15,16] mp 71–72 °C); IR 2950, 2930, 2860, 1445 cm^{-1}; ^1H NMR δ 0.75–1.02 (m, 6 H), 1.03–1.80 (m, 14 H), 2.01–2.41 (m, 4 H); ^{13}C NMR δ 21.51, 21.60, 21.63, 28.50, 28.57, 30.78, 30.93, 30.96, 31.06, 31.11, 31.16, 31.65, 31.73, 31.76, 31.83, 107.51, 107.58, 107.71. Anal. ($C_{14}H_{24}O_4$) C, H.

1(*S*),1(*R*)-Dimethyl-7,8,15,16-tetraoxodispiro[5.2.5.2]hexadecane (4). Thirty percent H_2O_2 (0.1 mol, 3.40 g) was added by slow dropwise addition to a stirred mixture of 2-methylcyclohexanone (0.1 mol, 11.22 g) and 2 N HCl (1 mL) at room temperature. Stirring was continued for 12 h at room temperature at which time glacial AcOH (75 mL) and 10% $HClO_4$ (4 mL) were added. Stirring was continued for an additional 12 h at room temperature. Water (150 mL) was added, and 4 (7.70 g, 60%) was collected as a white solid after filtration and washing with water: mp 105–106 °C (MeOH) (lit.[15,16] mp 105–106 °C); IR 2940, 2860, 1460, 1440 cm^{-1}; ^1H NMR δ 1.01 (d, J = 6.9 Hz, 6 H), 1.19–1.98 (m, 16 H), 2.73–3.05 (m, 2 H); ^{13}C NMR δ 13.65, 22.46, 24.54, 29.41, 30.71, 38.21, 109.17. Anal. ($C_{14}H_{24}O_4$) C, H.

Screening Methods. In vitro activity against *P. falciparum* was determined using a modification of the semiautomated microdilution technique of Desjardins et al.[20] and Milhous et al.[21] Two *P. falciparum* malaria parasite clones, designated as Sierra Leone (D-6) and Indochina (W-2), were used in susceptibility testing. The former was resistant to mefloquine, and the latter to chloroquine (CQ), pyrimethamine, sulfadoxine, and quinine. Test compounds were dissolved in dimethyl sulfoxide and solutions serially diluted with culture media. Erythrocytes with 0.25–0.5% parasitemia were added to each well of a 96-well microdilution plate to give a final hematocrit of 1.5%. Inhibition of uptake of tritiated hypoxanthine was used as an index of antimalarial activity. Results were reported as IC_{50} (ng/mL) values.

In vivo activity against *P. berghei* was obtained against a drug-sensitive strain of *P. berghei* (strain KBG 173).[10] Each test compound was administered to five male mice per dilution in a single subcutaneous (sc) dose 3 days after infection. Results were expressed in T – C values which indicate the mean survival time

(22) Models of 1 and *trans*-3,6-dimethoxy-1,2,4,5-tetraoxane were constructed and minimized using PCMODEL. Since a comparison of bond angles (±0.70°, ±1.57°), and bond length (±0.019 Å, ±0.013 Å) of 1 and the modeled tetraoxane, respectively, with published X-ray data (Leban, I.; Golič, L.; Japelj, M. Crystal and Molecular Structure of Qinghaosu: a Redetermination. *Acta Pharm. Jugosl.* 1988, *38*, 71–77. Chiang, C.-Y.; Butler, W.; Kuczkowski, R. L. The Synthesis, X-Ray Structural Analysis, and Anomeric Effect in *trans*-3,6-Dimethoxy-1,2,4,5-tetroxane. *J. Chem. Soc. Chem. Comm.* 1988, 465–466) was excellent, models of the two d,l and two meso stereoisomers of 4 were also constructed and minimized. Meso isomer 4, or 1(*S*),10(*R*)-dimethyl-7,8,15,16-tetraoxodispiro[5.2.5.2]-hexadecane was found to be the more stable stereoisomer. This result is consistent with unpublished X-ray crystallographic data noted in ref 17(b).

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(24) We have synthesized and screened several aza analogs of dispiro-1,2,4-trioxolanes, namely 1,2-dioxa-4-azacyclopentanes with spirocyclohexane rings at the 3 and 5 positions (Hawkins, E. G. E. Reactions of Organic Peroxides. Part X. Aminoperoxides from Cyclohexanone. *J. Chem. Soc. C* 1963, 2663–2670), and found them to be without antimalarial activity.

of the treated mice beyond that of the control animals; untreated mice survive on average 6.2 days. Compounds were classified as active (A) when the mean survival time of the treated mice is twice that of the controls (>12.4 days), and curative (C) when one or more test animals live 60 days postinfection. Deaths from 0–2 days post-treatment were attributed to toxicity (T).

A slight modification of the Thompson test[16] was used to further quantify antimalarial activity and toxicity. Five week old CD-1 mice were inoculated on day 0 with 5×10^6 trophozoites of *P. berghei* (strain KBG 173) obtained from an infected mouse at 60% parasitemia, diluted with uninfected mouse blood, and injected intraperitonealy. On days 3–5, each group of seven mice were treated sc with the compound to be tested in eight total doses, twice a day for 3 days. A range of doses sufficient to generate a dose–response curve was used. Blood films were taken 1 day after completion of drug treatment (day 6) and weekly thereafter until day 60. Parasitemia values were determined from Giemsa-stained blood films. Drug activity was evaluated by suppression of parasitemia, extension of survival time, and curative activity. Mice living 60 days postinfection and blood film negative were considered cured. A drug was considered to be toxic if the mice died before the untreated control mice. An advantage of this method of evaluation is the ability to assess efficacy and acute toxicity at the same time in the same model.

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Thieno[2,3-*b*]furan-2-sulfonamides as Topical Carbonic Anhydrase Inhibitors

George D. Hartman,* Wasyl Halczenko, John D. Prugh, Robert L. Smith, Michael F. Sugrue, Pierre Mallorga, Stuart R. Michelson, William C. Randall, Harvey Schwam, and John M. Sondey

Merck Research Laboratories, Departments of Medicinal Chemistry and Ocular Pharmacology, West Point, Pennsylvania 19486. *Received March 9, 1992*

Novel 5-[(alkylamino)methyl]thieno[2,3-*b*]furan-2-sulfonamides were prepared and evaluated in vitro for inhibition of human carbonic anhydrase II (CA II) and ex vivo for their ability to inhibit CA II in the albino rabbit eye after topical administration. Compound **11a** was found to lower intraocular pressure (IOP) in both the α-CT ocular hypertensive albino rabbit and the normal albino rabbit, but was ineffective at lowering IOP in a hypertensive, pigmented monkey model. Since **11a** was highly bound to ocular pigment, a series of less basic analogs was prepared. Examples in this series were both less extensively bound to ocular pigment and more active at reducing IOP in pigmented rabbits after topical dosing. Key examples displayed moderate reactivity toward glutathione.

Introduction

Topically effective carbonic anhydrase inhibitors that minimize systemic side effects[1] are a potentially important therapeutic advance in the treatment of open-angle glaucoma.[2] Recently, several novel classes of inhibitors, including sulfonamides of benzo[*b*]thiophene,[3] benzo[*b*]furan,[4] 4-aminothienothiopyran,[5] thieno[2,3-*b*]thiophene,[6] and 5-[(hydroxyalkyl)sulfonyl]thiophene,[7] have been reported. Leading representatives in these classes demonstrate nanomolar level potency for inhibition of human carbonic anhydrase II (CA II) in vitro, ocular hypotensive efficacy in animals after topical dosing, minimal sensitization potential, and appropriate solubility at or near physiological pH to allow for dosing as a suspension or a solution. As part of our continuing work in this area we wish to report on the biological evaluation of a series of

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