dissolved in 50 mL of CH_3CN containing 5.6 g (16.9 mmol) of 2,2,3,3,3-pentafluoropropyl trichloromethanesulfonate and 1.5 g (10.9 mmol) of anhydrous K_2CO_3. The mixture was stirred at 80 °C overnight. After solvent removal, the residue was treated with 30 mL of H_2O and extracted with ether. This extract was washed with H_2O and dried with $MgSO_4$. After filtration, the methanesulfonic acid in ether was dropped into the filtrate. The methanesulfonate salt of **23** was collected by filtration to afford 1.4 g of white solid: 43%; mp 204–205 °C; mass spectra m/z 417 (M^+); ^1H NMR ($CDCl_3$, TMS) δ = 6.82 (d, 1 H, ArH), 6.7 (d, 1 H, ArH), 5.8 (d, 1 H, CH=), 5.4 (d, 1 H, CH=), 5.0 (d, 1 H), 4.6–4.3 (m, 3 H), 3.9 (s, 3 H, OCH_3), 3.6 (q, 1 H), 3.45 (m, 1 H), 3.35 (m, 2 H), 3.2 (m, 1 H), 3.15 (m, 1 H), 2.75 (s, 3 H, CH_3SO), 2.5 (m, 1 H), 2.15 (q, 1 H). Anal. ($C_{20}H_{20}NO_3 \cdot CH_3SO_3H \cdot 0.5H_2O$) C, H, N.

***N*-(2,2,3,3,3-Pentafluoro-*n*-propyl)norapocodeine (24).** The methanesulfonate of **23** (1 g, 1.95 mmol) was converted to **24** with 5 mL of methanesulfonic acid by following the procedure for the arrangement of **21** to **22**. The crude free base was purified by flash column ($CHCl_3$/MeOH, 20:1) to afford 300 mg (39%) of clear oil of **24**, which showed a single spot on TLC ($CHCl_3$/MeOH, 9:1 vol): ^1H NMR ($CDCl_3$, TMS) δ = 8.2 (d, 1 H, 1-H), 7.1 (t, 1 H, 2-H), 6.9 (d, 1 H, 3-H), 6.7 (d, 1 H, 8-H), 6.6 (d, 1 H, 9-H), 3.8 (s, 3 H, OCH_3), 3.4 (q, 1 H, $CHCF_2$), 3.23 (m, 1 H), 3.1–2.9 (m, 3 H), 2.75 (q, 1 H), 2.62 (m, 2 H), 2.33 (t, 1 H).

***N*-(2,2,3,3,3-Pentafluoro-*n*-propyl)norapomorphine Hydrobromide (11·HBr).** The free base of **24** (0.2 g, 0.5 mmol) was converted to **11** by using the procedure for **10** to yield 140 mg of **11** (60%); mp 238–239 °C. The HCl salt of **11** also was obtained by treatment of the free base of **11** in ether with HCl/ether solution: mp 149–153 °C; mass spectra m/z 385 (M^+); ^1H NMR (CD_3OD, TMS) δ = 8.3 (d, 1 H, 1-H), 7.25 (t, 1 H, 2-H), 7.05 (d, 1 H, 3-H), 6.62 (m, 2 H, 8-, 9-H), 4.3 (q, 1 H, $CHCF_2$), 4.15 (d, 1 H), 3.96 (q, 1 H, $CHCF_2$), 3.7 (q, 1 H), 3.5–3.1 (m, 3 H), 2.92 (d, 1 H), 2.65 (t, 1 H). Anal. ($C_{19}H_{16}NO_2F_5 \cdot HCl$) C, H, N.

Acknowledgment. This work was supported by USPHS Grants NS-15439 (J.L.N.) and MH-47370 and MH-34006 (R.J.B.) and an award from the Bruce J. Anderson Foundation (R.J.B.). We also wish to thank Mallinckrodt, Inc. for the generous gift of codeine alkaloid and Research Biochemicals, Inc. for gifts of (-)-norapomorphine hydrochloride, (-)-apomorphine hydrochloride, (-)-*N*-*n*-propylnorapomorphine hydrochloride, (-)-*N*-allylnorapomorphine hydrobromide, and (-)-*N*-(2-hydroxyethyl)norapomorphine. We also wish to thank Dr. J.-H. Guan for preparation of the *N*-ethylnorapomorphine hydrobromide (**3**), as well as Dr. John Hyttel of Lundbeck Laboratories for the generous gift of *cis*-(*Z*)-flupenthixol.

Registry No. 1, 478-76-2; 1·HCl, 20382-69-8; 2, 58-00-4; 2·HCl, 314-19-2; 3, 18426-16-9; 3·HBr, 123240-93-7; 4, 18426-20-5; 4·HCl, 20382-71-2; 5, 123241-06-5; 5·HBr, 115017-81-7; 6, 123241-07-6; 6·HBr, 115017-82-8; 7, 18426-18-1; 7·HCl, 63907-00-6; 8, 18426-17-0; 8·HBr, 123240-94-8; 9, 79640-90-7; 9·HCl, 75846-02-5; 10, 123241-08-7; 10·HCl, 123240-95-9; 10·HBr, 123241-10-1; 11, 123241-09-8; 11·HCl, 123240-96-0; 11·HBr, 123241-11-2; 12, 76-57-3; 13, 467-15-2; 14, 478-77-3; 15, 115017-67-9; 15·HCl, 115017-68-0; 16, 115017-69-1; 16·HCl, 115017-70-4; 17, 115017-65-7; 17·HCl, 115017-66-8; 18, 57933-97-8; 19·HBr, 123240-97-1; 20, 123240-98-2; 21, 123241-12-3; 21·HCl, 123240-99-3; 22, 123241-04-3; 22·HCl, 123241-00-9; 23, 123241-01-0; 23·CH_3SO_3H, 123241-02-1; 24, 123241-03-2; CF_3CH_2OH, 75-89-8; CCl_3SO_2Cl, 2547-61-7; $CF_3CH_2OSO_2CCl_3$, 23199-56-6; $CF_3CH_2CH_2OSO_2CCl_3$, 123241-05-4.

Synthesis, Structure, and Antiparasitic Activity of Sulfamoyl Derivatives of Ribavirin

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The triazole nucleoside derivatives 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (**2**), 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (**3**), and 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)-[1,2,4]triazole-3-carbonitrile (**4**) were synthesized. Suitably protected triazole nucleosides were converted to their corresponding 5′-sulfamoyl derivatives, which on subsequent deprotection gave the desired compounds in good yields. The structures of compounds **2–4** were confirmed by X-ray crystallographic analysis. All three compounds showed significant antiparasitic activity in vitro, while **2** showed significant activity in vivo against *Leishmania donovani* and *Trypanosoma brucei*.

Certain nucleosides have been known to exhibit antiparasitic properties.[1-5] We have previously synthesized several nucleosides that have shown activity against a variety of parasites.[6-9] Robins et al. reported the chemical synthesis of the first sulfamoyl nucleoside, 5′-*O*-sulfamoyladenosine.[10,11] 5′-Sulfamoyladenosine, while active in vitro against a wide variety of parasites, is also extremely toxic. Ribavirin, 1-β-D-ribofuranosyl[1,2,4]-triazole-3-carboxamide, first synthesized by Robins et al.,[12] is a relatively nontoxic broad-spectrum antiviral agent.[13,14] It has also been shown[15] to be a substrate for adenosine kinase in certain human cell lines in vitro. Thus, as part of our ongoing program of the synthesis of nucleosides as potential antiparasitic agents, the 5′-*O*-sulfamoyl nucleoside derivatives of ribavirin **2–4** were synthesized, their

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[∥] Cornell Medical Center.

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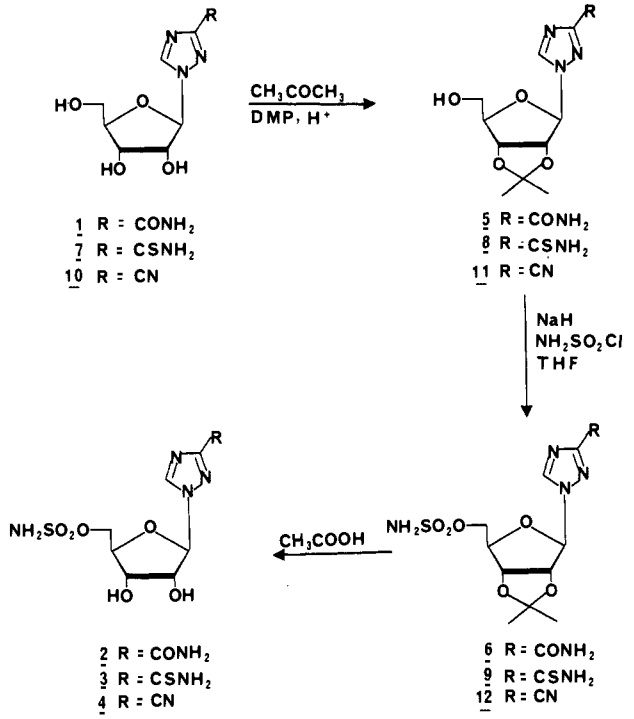
Scheme I



chemical structures studied and confirmed by X-ray crystallography, and they were evaluated for antiparasitic activity in vitro and in vivo.

Results and Discussion

Chemistry. The synthesis of 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (**2**) was accomplished as shown in Scheme I. Ribavirin was converted to its 2′,3′-di-*O*-isopropylidene derivative **5** by treatment with dimethoxypropane and acetone under acid-catalyzed conditions in 58% yield. Treatment of **5** with sulfamoyl chloride and sodium hydride in dry THF yielded the 5′-*O*-sulfamoyl derivative 1-(5′-*O*-sulfamoyl-2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (**6**) in 80% yield. The protected nucleoside **6** was subsequently deblocked by treatment with 80% acetic acid to give compound **2** in 79% yield.

Scheme I also outlines the synthesis of the thioamide sulfamate 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (**3**). In a manner similar to the synthesis of **2**, 1-β-D-ribofuranosyl[1,2,4]triazole-3-thiocarboxamide (**7**) was converted to the corresponding isopropylidene derivative 1-(2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (**8**). Subsequent treatment with sulfamoyl chloride resulted in the protected sulfamate 1-(5′-*O*-sulfamoyl-2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (**9**), which was then deblocked by treatment with aqueous acetic acid to give thioamide sulfamate **3**.

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Table I. Crystal Data for Compounds **2**, **3**, and **4**

	2	3	4
formula	$C_8H_{13}N_5O_7S$	$C_8H_{13}N_5O_6S_2$	$C_8H_{11}N_5O_6S$
M_r	323.28	339.34	305.26
a, Å	4.9405 (4)	8.5583 (10)	6.2993 (13)
b, Å	9.1804 (11)	9.0779 (11)	7.8161 (13)
c, Å	14.124 (2)	17.360 (3)	25.420 (5)
β, deg	93.973 (6)	90	90
V, Å^3	639.06 (13)	1348.7 (3)	1251.6 (4)
system	monoclinic	orthorhombic	orthorhombic
space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
Z	2	4	4
wavelength, Å	1.54178	1.54178	1.54178
R	0.0224	0.0243	0.0282
reflections ($F \geq 4\sigma_F$)	2629	2701	2394
total reflections	2658	2814	2600

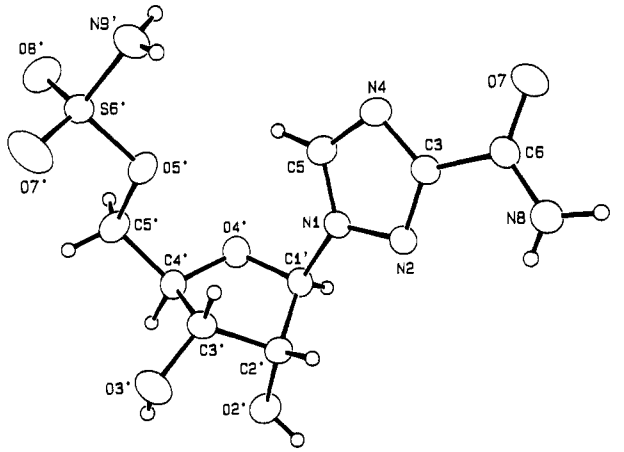

Figure 1. Perspective illustration of **2** giving atom labeling and the molecular conformation. Thermal ellipsoids are drawn at the 50% probability level.

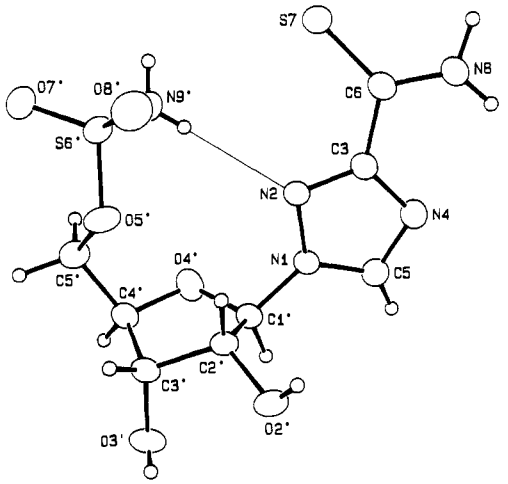

Figure 2. Perspective drawing of **3** showing the atom labeling. The intramolecular hydrogen bond is indicated by a thin line between the hydrogen on N9′ and N2 of the triazole ring. Thermal ellipsoids are drawn at the 50% probability level.

1-(5′-*O*-Sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile (**4**) was synthesized according to Scheme I. 1-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile[16] was deblocked under acidic conditions to yield 1-β-D-ribofuranosyl[1,2,4]triazole-3-carbonitrile (**10**). Subsequent treatment with acetone and dimethoxypropane in the presence of perchloric acid resulted in the isopropylidene 1-(2′,3′-di-*O*-isopropylidene-β-D-ribo-

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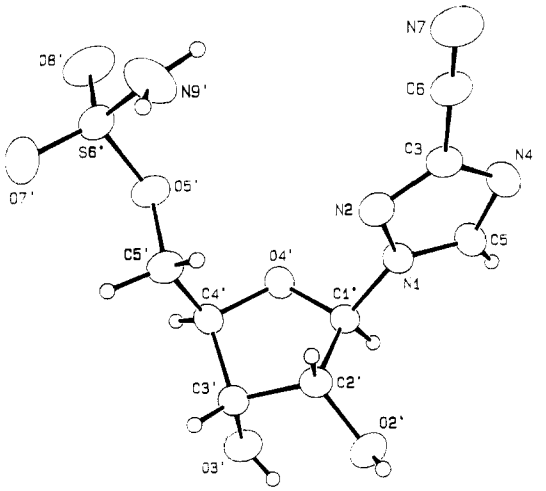

Figure 3. Perspective illustration of 4 indicating the atom labeling and molecular conformation. Thermal ellipsoids are drawn at the 50% probability level.

Table II. In Vitro Antiparasitic Activity Data

organism	ED_{50}, μg/mL 2,[a]	3	4
L. donovani	0.03	2.5	1–5
T. cruzi	>50	>50	>50
T. gambiense	0.01–0.05	0.5	1–5
G. lamblia	5–10	>25	>25
T. vaginalis	>25	15	>25

[a] 2 is toxic to U-937 cells (10% control at 1 μg/mL).

furanosyl)[1,2,4]triazole-3-carbonitrile (**11**), which was then converted to the sulfamate 1-(5′-*O*-sulfamoyl-2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile (**12**) by treatment with sulfamoyl chloride. Deblocking with aqueous acetic acid gave cyanotriazole-sulfamate **4** in nearly quantitative yield.

Nucleosides **2**–**4** were found to crystallize readily from appropriate solvents, yielding crystals suitable for X-ray crystallography.

X-ray Crystallography. Compound **2** crystallized as thick, colorless, transparent plates from a slowly cooled hot ethanol/water solution. Compound **3** crystallized from a slowly cooled hot methanol solution as transparent yellowish square pyramids. Slow cooling of a warm methanol/ether solution of **4** produced colorless, transparent, pentagonally cross-sectioned needles. Crystal data for these compounds are given in Table I. ORTEPII[17] plots of **2**, **3**, and **4** are shown in Figures 1, 2, and 3, respectively.

The sugar conformations are C3′ endo/C2′ exo for **2**, C2′ endo for **3**, and C3′ exo for **4** with pseudorotation angles of 3°, 156°, and 192°, respectively. The C4′–C5′ conformations are *gg* for **2** and **3** and *gt* for **4**. The glycosidic torsion angle, O4′–C1′–N1–N2, in each structure is 175.0 (1)° for **2**, 50.6 (2)° for **3**, and 64.2 (2)° for **4**. Despite these differences in the three structures, the sulfamoyl moiety is similarly situated with respect to the ribose ring with the NH_2 group over the ring. Every NH and OH in each structure is involved in hydrogen bonding. The amino group of the sulfamoyl moiety in **3** is intramolecularly hydrogen bonded to N2 of the triazole ring. Details of the X-ray structural studies will be published elsewhere.[18]

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Table III. In Vivo Antiparasitic Activity against *T. brucei* EATRO 110[a]

compd	dose, mg/kg (route)	average survival time, days	range of survival	% cured
–	–	3.4	3–5	0
2	1 (ip)	4.6	4–5	0
	5 (ip)	4.8	4–6	0
	10 (ip)	7.4	4–11	0
	20 (ip)	7.4	4–11	0
	50 (ip)	6.4	4–10	0
	50 (po)	11.6	10–14	0
	50 (iv)	6.4	4–12	0
9-deazainosine	25 (ip)	35	35	100

[a] Mice (groups of five) were infected with 2×10^5 trypanosomes and treatment commenced 24 h postinoculation. Drugs were given once daily by the route indicated for 3 days.

Table IV. In Vivo Antileishmanial Data

compd	no. of animals	dose, mg/kg per day	LDUs in liver	% suppression
none	3		1515 ± 477	0
pentostam	3	50	411 ± 245	73
2	3	10	1244 ± 469	18
2	3	20	765 ± 133	50
2	3	50	501 ± 276	67
3	3	10	1039 ± 446	0
3	2	20	1143 ± 91	0
3	3	50	1514 ± 225	0

[a] % suppression = 100 − 100(LDUs of experimental/LDUs of control).

Antiparasitic Activity. The antiparasitic activities of the sulfamoyl derivatives of ribavirin were investigated in a series of in vitro experiments. The organisms studied were the pathogenic hemoflagellates *L. donovani*, *Trypanosoma cruzi*, and *Trypanosoma gambiense*. The enteric protozoan pathogens *Giardia lamblia* and *Trichomonas vaginalis* also were studied. As shown in Table II, compound **2** was the most active and had the lowest ED_{50} against those organisms which were sensitive to the agents. *T. cruzi* was uniformly resistant to the sulfamoyl nucleosides but *T. gambiense* was quite sensitive. *L. donovani* also was killed by low concentrations of **2**. The mucosal pathogen *G. lamblia* responded to concentrations of **2** which could be achieved by nonabsorbable compound. It is ineffective against *T. vaginalis*. Compounds **3** and **4** have similar activity profiles in that *T. cruzi* is resistant, but the other organisms are sensitive to the same relative degree. The concentrations required for activity are higher; ED_{50} = 0.5 and 1–5 μg/mL against *T. gambiense* and 2.5 and 1–5 μg/mL against *L. donovani*. For the mucosal pathogens, the concentrations needed are about the same as that for compound **2**.

Because of the good activity of compound **2** against *T. gambiense* it was studied in vivo against *T. brucei*. As shown in Table III, there was moderate in vivo activity against the latter pathogen except when it was given orally. It prolonged survival but did not cure any of the animals. The purine analogue 9-deazainosine, which was used as a positive control, was 100% effective in this system.

Table IV shows the activity of compounds **2** and **3** in a mouse model of visceral leishmaniasis. Compound **3** was ineffective but compound **2** showed good suppression of the parasites in the livers of the animals. A dose of 20 mg/kg per day decreased the infection by 50% at 7 days of treatment.

(18) Larson, S. B.; Henry, E. M.; Kini, G. D.; Robins, R. K. Manuscript in preparation.

Of the three compounds, the antiparasitic activity of compound **2** is particularly interesting. Its antileishmanial activity, which is good in vitro (Table II), is supported by animal studies (Table IV). In the latter system, it is as active as pentavalent antimony, the only therapeutic modality generally available in the clinic. At comparable mg/kg doses (not equimolar) it was as active as Pentostam (Burroughs Wellcome, Beckenham, England). The in vivo activity against *T. brucei* was moderate as opposed to the very excellent in vitro activity against *T. gambiense*. It is significant, however, that the compound is active when administered orally. This animal model for African trypanosomiasis has proven very useful for the study of other compounds (ref 19 and op. cit.).

The mechanism of action of compounds **2**–**4** is not known at this time and the reason for the striking antileishmanial activity of compound **2** as compared to those of compounds **3** and **4** is unclear. Studies on the structure–activity relationships among various antileishmanial compounds are only beginning. It is clear, however, that inosine analogues which have antileishmanial activity and whose metabolism has been studied in detail are active to the degree to which they are converted to the amino derivative.[20] Thus, there is a direct relationship between the amination to analogues of adenosine and their toxicities to the cell. It also has been shown that 5′-*O*-sulfamoyladenosine has significant antiparasitic activity.[10] It is very likely that compound **2**, exhibiting properties of both of the foregoing compounds, interferes with the adenosine metabolism in the parasite.

The activity of compound **2** against *T. gambiense* in vitro did not correlate with studies in the animal model. Since the clearance of this compound from the animal in either the kidneys or the liver is not known, it is conceivable that an intravenous or intraperitoneal dose, both of which would produce rather high blood levels in a short period of time, could be rapidly removed from the body. Oral administration of the same compound, if absorbed relatively slowly, could produce lower blood levels albeit sustained over a longer period of time.

Although the relationship of amination of inosine analogues to their antiprotozoan activity is clear (ref 20 and op. cit.), the specifics of metabolism and activity of compound **2** are far from complete. Future studies will be necessary to determine if compound **2** is aminated by the parasite and if this is in fact the active form. Nevertheless, the sulfamoyl derivative of ribavirin represents a new and unique antiparasitic nucleoside and significantly broadens our perspective. Heretofore the data in the literature suggested that pyrazolo[3,4-*d*]- or [4,3-*d*]pyrimidines,[1] guanosine analogues,[6] and inosine analogues[2,7] have the most significant potential for antiprotozoan activity. This investigation demonstrates that the sulfamoyl derivative of ribavirin, a 1,2,4-triazole nucleoside, has good activity both in vitro and in vivo and holds significant promise as an antileishmanial compound. The antiparasitic acitivity of compounds **2**–**4** is under further investigation.

Experimental Section

Chemistry. Proton NMR data were obtained at 300 MHz on an IBM NR-300 spectrometer in $(CD_3)_2SO$ or $CDCl_3$ solvents using the residual proton as internal reference. Melting points were obtained in open capillaries with a Haake-Buchler apparatus and are uncorrected. Combustion analyses were performed by Robertson Laboratories, Florham Park, NJ.

Culture Techniques. *T. cruzi* (Peru strain, obtained from S. M. Krassner, University of California, Irvine, CA), *L. donovani* (ATCC #30142)), and *T. gambiense* (TH114, obtained from R. Brun, Schweizer Tropeninstitut, Basel, Switzerland) were grown in THOSMEM, HOSMEM, and PPDM-79 media respectively as previously described.[21–23] For drug-sensitivity studies, these organisms were grown in 10 mL of their respective media in 25 cm^2 tissue-culture flasks. Cultures were inoculated to a cell density of $\sim 10^5$/mL and incubated for 5 days at 26 °C in a 5% CO_2 atmosphere. Final cell density was determined by counting the cells on a Coulter counter (Model ZBI); control cultures reached a final density of $\sim 2 \times 10^7$/mL. *G. lamblia* (P1, ATCC #30888) and *T. vaginalis* (ATCC #3301) were grown in modified TYI medium in 13 × 100 mm screw-cap tubes as previously described.[24] Cultures were inoculated at a density of 10^4 and incubated for 3 days at 37 °C; control cultures reached densities of ~ 1–2×10^6 for *G. lamblia* and 6–7 × 10^6 for *T. vaginalis*. These parasites were counted by chilling tubes on ice for 30 min and then reading the optical density at 650 nm in a Gilford 300-N microsample spectrophotometer. Their cell number was obtained by comparing the absorbance to a standard curve constructed from numbers obtained by counting cells in a hemocytometer.[24] Drug stock solutions were prepared by dissolving the analogue in 0.1 N NaOH and adjusting the final concentration to 2 mg/mL on the basis of extinction coefficients. Drug was added to respective culture media (<2% v/v) and the media was filter sterilized. Doses effective against 50% (ED_{50}) and 90% (ED_{90}) were determined by triplicate counting of organisms exposed to various drug concentrations and determining a mean value. Results were expressed as a percentage of control.

Animal Models. The mouse model for the study[25] of compounds against *T. brucei* EATRO 110 has been described previously.[19] The mouse experiments with *L. donovani* were similar to those previously described[26] for a hamster model. Briefly, mice were infected with 5 × 10^7 stationary-phase promastigotes subcultured in Schneider's drosophila medium with 15% heat-inactivated fetal-bovine serum. Compounds **2** and **3** were administered by gavage 9 days after infection and continued for 1 week. Positive controls received Pentostam intraperitoneally. Infected, untreated controls received water orally but no intraperitoneal sham injections. Mice were necropsied 16 days after infection (7 days after the beginning of drug treatment).

1-(2′,3′-Di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (5). A suspension of 1-β-D-ribofuranosyl[1,2,4]triazole-3-carboxamide (**1**, 5.0 g, 20.5 mmol) in a mixture of acetone (100 mL) and dimethoxypropane (50 mL) was cooled to 0 °C in an ice bath. Perchloric acid (0.34 mL, 70%) was added dropwise with stirring. The resulting clear solution was stirred at 0 °C for 1.5 h and neutralized to pH 7 by dropwise addition of 1 N aqueous sodium hydroxide in the cold. The mixture was concentrated in vacuo and the residue was chromatographed over silica gel (flash chromatography) with 10% acetone in chloroform as eluent to yield **5** (3.38 g, 58%) as an analytically pure oil, which crystallized from methanol; mp 163–165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.31, 1.49 (2 s, 6 H, isopropylidene methyls), 3.40 (m, 2 H, C_5H), 4.23 (t, 1 H, C_4H), 4.96 (t, 1 H, OH), 4.90, 5.18 (2 d, 2 H, C_2H and C_3H), 6.20 (s, 1 H, C_1H), 7.67, 7.87 (2s, 2 H, $CONH_2$), 8.81 (s, 1 H, triazole ring proton). Anal. ($C_{11}H_{16}N_4O_5$) C, H, N.

1-(5′-*O*-Sulfamoyl-2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (6). A solution of 1-(2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (**5**, 10.0 g, 34.9 mmol) in dry tetrahydrofuran (200 mL) was cooled to 0 °C in an ice bath. Sodium hydride (4.2 g, 60% suspension in oil) was added and the mixture was stirred

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for 15 min. A solution of sulfamoyl chloride (9.3 g, 80.5 mmol) in dry tetrahydrofuran (50 mL) was added dropwise and the resulting mixture was stirred at 0 °C for 2 h and at room temperature for 4 h. The mixture was cooled, after which ethanol (20 mL) and saturated aqueous ammonium chloride (20 mL) were added in succession. The mixture was concentrated in vacuo and chromatographed over silica gel (flash chromatography) with 20% acetone in chloroform to yield **6** (7.8 g, 61.5%) as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.33, 1.51 (2 s, 6 H, isopropylidene methyls), 4.11 (m, 2 H, C_5H), 4.44 (m, 1 H, C_4H), 5.02, 5.17 (m, 1 H, d, 1 H, C_2H and C_3H), 6.36 (s, 1 H, C_1H), 7.59 (s, 2 H, SO_2NH_2), 7.72, 7.88 (2 s, 2 H, $CONH_2$), 8.82 (s, 1 H, triazole ring proton). Anal. ($C_{11}H_{17}N_5O_7S$) C, H, N, S.

1-(2′,3′-Di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (8). A suspension of 1-β-D-ribofuranosyl[1,2,4]triazole-3-thiocarboxamide[27] (**7**, 5.8 g, 22.3 mmol) in a mixture of acetone (100 mL) and dimethoxypropane (50 mL) was treated in a manner identical with the synthesis of compound **5** to yield 8 (5.9 g, 88%) as an analytically pure oil: ^{1}H NMR (DMSO-d_6) δ 1.32, 1.50 (2 s, 6 H, isopropylidene methyls), 3.40 (m, 2 H, C_5H), 4.98 (t, 1 H, OH), 4.90, 5.17 (2 d, 2 H, C_2H and C_3H), 6.18 (s, 1 H, C_1H), 8.80 (s, 1 H, triazole ring proton), 9.55, 10.01 (2 s, 2 H, $CSNH_2$). Anal. ($C_{11}H_{16}N_4O_4S$) C, H, N, S.

1-(5′-*O*-Sulfamoyl-2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (9). A solution of 1-(2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (8, 2.0 g, 6.7 mmol) in dry tetrahydrofuran (50 mL) was cooled to 0 °C in an ice bath. Sodium hydride (0.80 g, 60% suspension in oil) was added and the mixture was stirred for 15 min. A solution of sulfamoyl chloride (1.55 g, 13.4 mmol) in dry tetrahydrofuran (10 mL) was added dropwise and the resulting mixture was stirred at 0 °C for 2 h and at room temperature for 1 h. The mixture was cooled; ethanol (5 mL) and saturated aqueous ammonium chloride (5 mL) were added in succession. The mixture was concentrated in vacuo and chromatographed over silica gel (flash chromatography) with 20% acetone in chloroform to yield **9** (1.8 g, 70%) as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 1.33, 1.52 (2 s, 6 H, isopropylidene methyls), 4.11 (m, 2 H, C_5H), 4.44 (m, 1 H, C_4H), 5.02, 5.16 (d, m, 2 H, C_2H and C_3H), 6.35 (s, 1 H, C_1H), 7.58 (s, 2 H, SO_2NH_2), 8.81 (s, 1 H, triazole ring proton), 9.55, 10.05 (2 s, 2 H, $CSNH_2$). Anal. ($C_{11}H_{17}N_5O_6S_2$) C, H, N, S.

1-β-D-Ribofuranosyl[1,2,4]triazole-3-carbonitrile (10). A solution of 1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile[16] (20 g, 56.8 mmol) in ice-cold methanolic HCl (0.5 N, 250 mL) was kept at 0 °C for 24 h. Solvent was removed in vacuo and the resulting oil (12.0 g, 91%), which was homogeneous on TLC, was used directly for the next step without purification; ^{1}H NMR (DMSO-d_6) δ 3.60 (m, 2 H, C_5H), 3.96 (m, 1 H, C_4H), 4.11, 4.32 (2 m, 2 H, C_2H and C_3H), 4.96, 5.26, 5.68 (t, 2 d, 3 H, OH), 5.89 (d, 1 H, J = 3.54 Hz, C_1H), 9.15 (s, 1 H, triazole ring proton).

1-(2′,3′-Di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile (11). A suspension of 1-β-D-ribofuranosyl[1,2,4]triazole-3-carbonitrile (**10**, 12.0 g, 52.1 mmol) in a mixture of acetone (200 mL) and dimethoxypropane (100 mL) was treated in a manner identical with the synthesis of compound **5** to yield 11 (10.78 g, 76.3%) as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.32, 1.49 (2 s, 6 H, isopropylidene methyls), 3.44 (m, 2 H, C_5H), 4.32 (m, 1 H, C_4H), 4.96 (t, 1 H, OH), 4.88, 5.19 (2 m, 2 H, C_2H and C_3H), 6.25 (s, 1 H, C_1H), 9.07 (s, 1 H, triazole ring proton). Anal. ($C_{11}H_{14}N_4O_4$) C, H, N.

1-(5′-*O*-Sulfamoyl-2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile (12). To a solution of 1-(2′,3′-di-*O*-isopropylidene-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile (11, 13.81 g, 51.8 mmol) in dry tetrahydrofuran (200 mL) cooled to 0 °C in an ice/salt bath was added sodium hydride (8.3 g, 60% dispersion in oil). The suspension was stirred at 0 °C for 10 min and a solution of sulfamoyl chloride (11.91 g, 103.1 mmol) in dry tetrahydrofuran (50 mL) was added dropwise, while the temperature of the reaction mixture was maintained at 0 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 4 h. The mixture was cooled to 0 °C, and ethanol (25 mL) was added, followed by a saturated aqueous solution of ammonium chloride (25 mL). The mixture was concentrated in vacuo and chromatographed over silica gel (flash chromatography) using 15% acetone in chloroform to yield **12** (8.8 g, 50%) as an oil: ^{1}H NMR (DMSO-d_6) δ 1.32, 1.50 (2 s, 6 H, isopropylidene methyls), 4.10 (m, 2 H, C_5H), 4.50, 4.95, 5.21 (3 m, 3 H, C_2, C_3 and C_4 protons), 6.41 (s, 1 H, C_1H), 7.58 (s, 2 H, SO_2NH_2), 9.07 (s, 1 H, triazole ring proton). Anal. ($C_{11}H_{15}N_5O_6S$) C, H, N, S.

1-(5′-*O*-Sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (2). A solution of **6** (5.43 g, 14.9 mmol) in 80% acetic acid was heated to 100 °C for 2 h. The mixture was concentrated to dryness in vacuo, and the residue was crystallized from ethanol to yield **2** (4.48 g, 93%) as an analytically pure crystalline solid: mp 160 °C dec; ^{1}H NMR (DMSO-d_6) δ 5.48, 5.76 (2 d, 2 H, OH), 5.92 (d, 1 H, J = 3.2 Hz, C_1H), 7.59 (s, 2 H, SO_2NH_2), 7.68, 7.88 (2 s, 2 H, $CONH_2$), 8.83 (s, 1 H, triazole ring proton) and other sugar protons. Anal. ($C_8H_{13}N_5O_7S$) C, H, N, S.

1-(5′-*O*-Sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (3). A solution of **9** (1.7 g, 4.5 mmol) in 80% aqueous acetic acid was heated to 100 °C for 4 h. The mixture was concentrated to dryness in vacuo, and the residue was chromatographed over silica gel (flash chromatography) using 10% methanol in dichloromethane as eluent to yield **3** (0.95 g, 62.5%) as a yellow solid: mp 173–175 °C dec; ^{1}H NMR (DMSO-d_6) δ 4.0–4.33 (3 m, 5 H, sugar protons), 5.46, 5.77 (2 d, 2 H, OH), 5.89 (d, 1 H, J = 2.7 Hz, C_1H), 7.58 (s, 2 H, SO_2NH_2), 8.80 (s, 1 H, triazole ring proton), 9.54, 10.02 (2 s, 2 H, $CSNH_2$). Anal. ($C_8H_{13}N_5O_6S_2$) C, H, N, S.

1-(5′-*O*-Sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carbonitrile (4). A solution of **12** (7.7 g, 22.3 mmol) in 80% aqueous acetic acid was heated to 100 °C for 2 h. The mixture was concentrated to dryness in vacuo, and the residue was dissolved in methanol (50 mL). The resulting solution was concentrated to dryness in vacuo and the residue was crystallized from methanol/ether to yield **4** (6.47 g, 95%) as a crystalline solid: mp 153–154 °C; ^{1}H NMR (DMSO-d_6) δ 4.0–4.40 (3 m, 5 H, sugar protons), 5.53, 5.83 (2 d, 2 H, OH), 6.0 (d, 1 H, J = 2.9 Hz, C_1H), 7.58 (s, 2 H, SO_2NH_2), 9.10 (s, 1 H, triazole ring proton). Anal. ($C_8H_{11}N_5O_6S$) C, H, N, S.

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