2235 cm^{-1} (CN); ^1H NMR [$(CD_3)_2SO$ + CD_3OD (1:1), 200 MHz] δ 3.64, 3.83 (2 dd, 2 H, H-5'a, H-5'b, $J_{5'a,5'b}$ = 12.6 Hz), 3.85 (dd, 1 H, H-3', $J_{2',3'}$ = 5.7, $J_{3',4'}$ = 8.9 Hz), 4.42 (m, 1 H, H-4'), 4.83 (dd, 1 H, H-2', $J_{1',2'}$ = 2.3 Hz), 5.97 (d, 1 H, H-1'), 8.25, 8.10 (2 s, 2 H, H-8, H-2); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 35.82 (C-3'), 60.54 (C-5'), 74.13, 81.92 (C-2', C-4'), 90.55 (C-1'), 117.07 (CN), 119.10 (C-5), 139.28 (C-8), 148.80 (C-4), 152.57 (C-2), 156.06 (C-6). Anal. ($C_{11}H_{12}N_6O_3$) C, H, N.

Antiviral Assay Procedures. Human immunodeficiency virus (HIV) infection was carried out with the HTLV-III_B strain. The virus was prepared from the culture supernatant of a persistently HTLV-III_B-infected HUT-78 cell line. The antiviral assays were based on an inhibition of HIV-induced cytopathogenicity in human MT-4 lymphocytes as described previously.[30]

Transformation of C3H mouse embryo cells by Moloney murine sarcoma virus (MSV) was carried out into 48-well Costar tissue culture cluster plates. C3H cells were seeded at 20 000 cells/mL per well and grown for 24 h. Cell cultures were then infected by 80 foci-forming units of MSV during 90 min, whereafter medium was replaced by 1 mL of fresh culture medium containing different concentrations of the test compounds. After 6–7 days, the transformation of the cell culture was examined microscopically.[30]

The antiviral assays, other than those for HIV and MSV, were based on the inhibition of virus-induced cytopathogenicity in either HeLa cells or Vero cells of primary rabbit kidney cell cultures, following established procedures.[32] Briefly, confluent cell cultures in microtiter trays were inoculated with 100 $CCID_{50}$ of virus. After 1 h of virus adsorption, residual virus was removed and the cell cultures were incubated in the presence of varying concentrations of the test compounds. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures.

Acknowledgment. We thank Dr. R. C. Gallo [National Cancer Institute, National Institutes of Health (NIH), Bethesda, MD] for providing HTLV-III_B and Dr. N. Yamamoto (Yamaguchi University, Yamaguchi, Japan) for providing the MT-4 cells. The investigations were supported by the Consejo Superior de Investigaciones Cientificas and the Comisión Asesora de Investigación Cientifica y Técnica, the AIDS Basic Research Programme of the European Community, and grants from the Belgian FGWO (Fonds voor Geneeskundig Wetenschappelijk Onderzoek; Projects 3.0040.83 and 3.0097.87) and the Belgian GOA (Geconcerteerde Onderzoeksacties; Project 85/90-79). We thank María Jesús Moreno Guerrero, Ann Absillis, Frieda De Meyer, Lizette van Berckelaer, and Anita Van Lierde for their excellent technical help with the biological experiments and Christiane Callebaut for her dedicated editorial assistance.

Registry No. **5c**, 121055-61-6; **6c**, 121055-62-7; **7b**, 90813-54-0; **7c**, 121055-63-8; **7e**, 86734-95-4; **10b**, 121055-64-9; **10c**, 121055-65-0; **10e**, 121055-66-1; **11b**, 121055-67-2; **11d**, 121055-68-3; **11e**, 121055-69-4; **12a**, 117174-35-3; **12b**, 121123-89-5; **12e**, 121153-18-2; **13b**, 121123-90-8; **13c**, 121055-71-8; **13d**, 121055-70-7; **13e**, 121123-91-9; **14**, 117174-38-6; **15**, 117174-39-7; **16**, 116195-58-5; **17**, 118222-08-5; *N*-acetylcytidine, 3768-18-1.

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Prodrugs of the Selective Antiherpesvirus Agent 9-[4-Hydroxy-3-(hydroxymethyl)but-1-yl]guanine (BRL 39123) with Improved Gastrointestinal Absorption Properties

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Potential oral prodrugs of the antiherpesvirus acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine (**1**, BRL 39123) have been synthesized and evaluated for bioavailability of **1** in the blood of mice. Reduction of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-amino-6-chloropurine (**13**) using ammonium formate and 10% palladium on carbon afforded the 2-aminopurine **14**, which was hydrolyzed to the monoacetate **15** and to 2-amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine (**5**). The 2-aminopurine **5** was subsequently converted to additional monoester (**17**, **21–23**) and diester (**16**, **24**) derivatives and to its di-*O*-isopropylidene derivative **18**. Both **5** and its esters (**14–17**, **21**, **22**) and also **18** were well absorbed after oral administration and converted efficiently to **1**, the diacetyl (**14**) and dipropionyl (**16**) esters providing concentrations of **1** in the blood that were more than 15-fold higher than those observed after dosing either **1** or its esters (**25–27**). Some 6-alkoxy-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purines (**8–10**), the preparation of which has been reported previously, also showed improved absorption properties, but their conversion to **1** was less efficient than for the 2-aminopurine derivatives. On the basis of these results and subsequent experiments involving determinations of rates of conversion to **1** in the presence of rat and human tissue preparations, 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (**14**, BRL 42810) was identified as the preferred prodrug of **1**. Oral bioavailability studies in healthy human subjects confirmed **14** as an effective prodrug, and this compound is now being evaluated in clinical trials.

The acyclonucleoside 9-[4-hydroxy-3-(hydroxymethyl)-but-1-yl]guanine (**1**, BRL 39123)[1,2] possesses potent and selective activity against herpes simplex virus types 1 and 2, varicella zoster virus, and Epstein–Barr virus in cell cultures[3] and in animals,[4] and its clinical efficacy in the treatment of herpetic infections is presently being evaluated.

However, after oral administration of **1** to mice only relatively low concentrations of the antiviral acyclonucleoside were detectable in the blood. The gastrointestinal absorption of acyclovir (**2**), which is also an acyclic analogue of guanosine, has similarly been reported[5,6] to be

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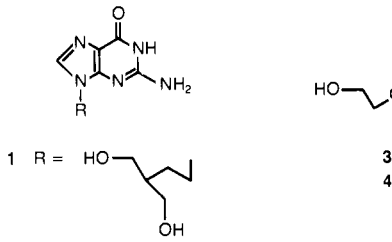
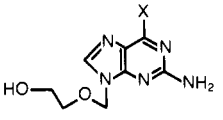
relatively poor in both rats and man. Higher concentrations of acyclovir in the blood have been obtained following oral administration of both its 6-amino-6-deoxy (**3**) and 6-deoxy (**4**) congeners which, after absorption, are converted to acyclovir by the enzymes adenosine deaminase and xanthine oxidase, respectively.[6]

We have investigated a similar approach to development of prodrugs of **1** with improved gastrointestinal absorption properties. In this publication we report the preparation of the 6-deoxy congener (**5**) of **1** and its *O*-acyl and other derivatives and present data from experiments using mice which contributed to the selection of 9-[4-acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (**14**) for progression to clinical studies. Additionally, similar investigations of gastrointestinal absorption properties and conversion to **1** are described for the 6-amino-6-deoxy congener (**6**) and a series of 6-*O*-alkyl derivatives (**7–12**) of **1**, the preparation of which has been reported previously.[2] Some 6-*O*-alkyl derivatives (**8**, **9**) are also of interest as novel prodrugs of antiviral guanine derivatives.

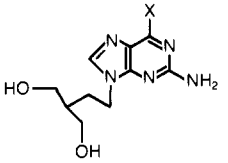


1 R = HO–CH(CH₂OH)–CH₂CH₂–

2 R = HO–CH₂CH₂–O–CH₂–



3 X = NH_2
4 X = H



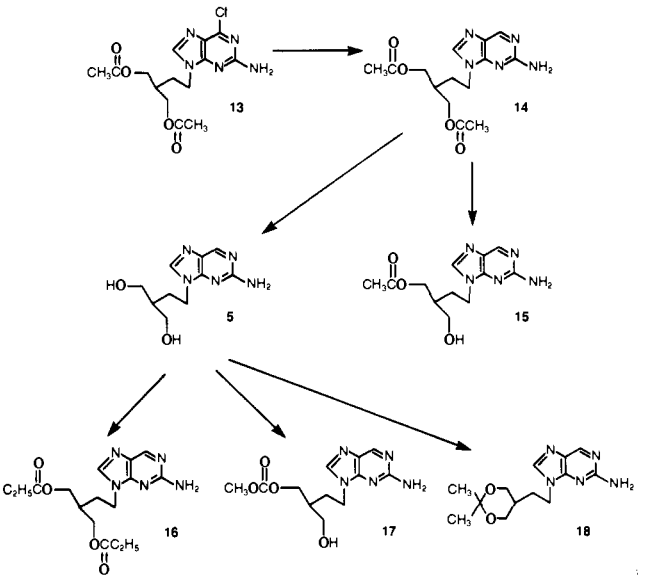
5 X = H
6 X = NH_2
7 X = CH_3O
8 X = C_2H_5O
9 X = $(CH_3)_2CHO$
10 X = $CH_3(CH_2)_3O$
11 X = C_6H_5O
12 X = $C_6H_5CH_2O$

Chemistry

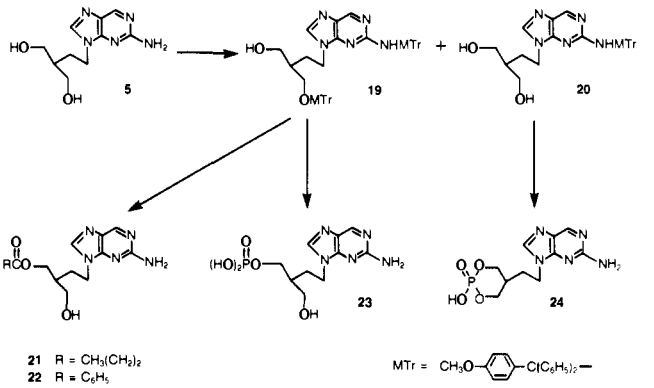
Reduction of the diacetylated 2-amino-6-chloropurine **13**[7] by catalytic hydrogen transfer from ammonium formate afforded the 2-aminopurine **14** in 78% yield after recrystallization (Scheme I). Deacetylation of **14** with methanolic ammonia gave **5**[2] in 90% yield. Compound **14** could also be deacetylated with catalytic potassium carbonate in methanol, and by stopping this reaction partway, the monoacetate **15** was obtained in 30% yield. Reaction of **5** with propionic anhydride and 4-(dimethylamino)-pyridine (DMAP) in DMF afforded the dipropionate **16** (71% yield). Treatment of **5** with tetramethyl orthocarbonate followed by aqueous workup did not give a cyclic carbonate, but rather the methoxycarbonyl ester **17**, presumably due to ring opening of the cyclic orthoester intermediate rather than exocyclic hydrolysis. Acid-catalyzed reaction of **5** with 2,2-dimethoxypropane gave the isopropylidene derivative **18** in 94% yield.

Selective protection of **5** was achieved with monomethoxytrityl chloride in DMF to give the N-protected (**20**) and N,O-diprotected (**19**) derivatives (Scheme II). Reaction

Scheme I



Scheme II

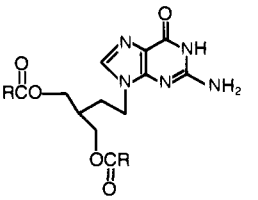


21 R = $CH_3(CH_2)_2$
22 R = C_6H_5

MTr = CH_3O–C_6H_4–$C(C_6H_5)_2$–

of **19** with butyryl chloride resulted in degradation of the purine base, but by using the corresponding anhydride selective O-acylation was obtained. Deprotection with 80% acetic acid at 70 °C afforded the monobutyrate **21** in 68% yield. The monobenzoate **22** was obtained similarly in 76% yield. The monophosphate **23** and cyclic phosphate **24** were prepared by treatment of **19** and **20** with 1 equiv of phosphorus oxychloride followed by aqueous workup and acetic acid deprotection and were obtained in yields of 25% and 75%, respectively.

The aqueous solubilities of the 2-aminopurines **5**, **14**, and **16**, measured at 25 °C, are 120, >300, and 19 mg/mL, respectively, as compared with 3.0, 6.7, and 1.2 mg/mL for the corresponding guanines (**1**, **25**, and **26**). The outstandingly high solubility of the diacetate **14** is particularly notable. However, a crystalline monohydrate deposits from concentrated aqueous solutions. The solubility of this monohydrate in water is 20 mg/mL. The 2-aminopurines are also considerably more soluble in organic solvents than are the guanines.



25 R = CH_3
26 R = C_2H_5
27 R = $CH_3(CH_2)_4$

(6) Krenitsky, T. A.; Hall, W. W.; de Miranda, P.; Beauchamp, L. M.; Schaeffer, H. J.; Whiteman, P. D. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3209.
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Table I. Concentrations of 9-[4-Hydroxy-3-(hydroxymethyl)but-1-yl]guanine (1) and 2-Amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine (5) in the Blood following Oral Administration[a] of 5 and Its Derivatives to Mice

compd[b] administered	concn, μM, in blood at time, h, after dosing					
	1[c]			5[c]		
	0.25	1	3	0.25	1	3
1	4.9	4.0	1.1			
5	16	13	3.2	8	4	1
14	74	17	1.1	69	3	<1
15	51	20	1.2	38	3	<1
16	79	26	2.1	92	9	<1
17	54	22	2.6	55	4	<1
18[d]	33	11	3.2	33	4	1
21	64	28	2.0	57	7	<1
22	63	26	1.1	71	8	<1
23	8.7	17	5.2	4	8	1
24	1.0	1.0	2.6	<1	<1	<1

[a] Compounds were administered as single doses of 0.2 mmol/kg in 0.1 mL of 1% (carboxymethyl)cellulose by oral gavage to female Balb/c mice weighing 20 g, from which food had been withheld for 18 h. Blood was collected at 0.25, 1, and 3 h after dosing by cardiac puncture using heparinized syringes. Equal aliquots from three mice per time point were pooled, and an equal volume of 16% trichloroacetic acid was added. Following centrifugation, 0.1 mL of saturated aqueous $NaHCO_3$ was added to 0.5 mL of supernatant and the solution analyzed by HPLC, in duplicate. [b] The results quoted for 1 and 5 are the mean values from 20 and 4 experiments, respectively. For other compounds the results of a single experiment are given. [c] Minimum limit of detection was 0.8 μM for 1 and 1 μM for 5. [d] Compound 18 was unstable in the presence of trichloroacetic acid. The concentrations of 5 quoted are therefore from 5 in the blood and 5 liberated from 18 during assay.

Results and Discussion

Gastrointestinal Absorption and Conversion to 1 in Mice. Esters (25–27) of 1, its 2,6-diaminopurine analogue (6), 2-amino-6-alkoxypurines 7–12, and the 2-aminopurine 5 and its derivatives (14–18, 21–24) were administered orally to mice and concentrations of 1 and its prodrugs in the blood determined by using HPLC.

Although the dihexanoate ester 27 is more active than 1 in antiviral tests carried out in cell cultures,[2] neither it nor any other ester (25, 26) tested provided concentrations of 1 in the blood that were higher than those achieved after administration of the equivalent dose of 1. Since in no case were appreciable concentrations of the administered ester detected in the blood, the gastrointestinal absorption of these derivatives does not appear to be significantly improved in comparison with that of 1. They may also be susceptible to hydrolysis by esterases in the gut prior to absorption. It has been suggested that diesters of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (ganciclovir), particularly the dipropionate derivative, are of potential interest as orally active prodrugs of the antiviral acyclonucleoside.[8] However, this conclusion was based on dissolution rates, partition coefficients, and in vitro studies on rates of hydrolysis in mammalian tissues, and in no species was the gastrointestinal absorption of the prodrugs studied. In accordance with our results, esters of acyclovir also failed to provide higher concentrations of the antiviral acyclonucleoside in the blood.[6]

In contrast to data reported for the 2,6-diaminopurine analogue (3) of acyclovir, the 2,6-diaminopurine 6 was not well absorbed following oral administration to mice. Additionally, we have observed that 6 is a relatively poor substrate for adenosine deaminase.

Table II. Concentrations of 9-[4-Hydroxy-3-(hydroxymethyl)but-1-yl]guanine (1) and Administered Compound in the Blood following Oral Administration[a] of 6-Alkoxy-2-aminopurines to Mice

compd administered	concn, μM, in blood at time, h, after dosing					
	1[b]			unchanged 6-alkoxy-2-aminopurine[b]		
	0.25	1	3	0.25	1	3
7	0.6	0.9	<0.5	8	7	2
8	6.8	8.0	0.9	25	11	<1
9	9.2	3.8	<0.5	43	12	1
10	5.7	5.2	<0.5	19	11	1
11	<0.5	<0.5	<0.5	8	7	<1
12	1.8	2.1	0.5	3	2	<1

[a] See footnote a in Table I. [b] Minimum limit of detection was 0.5 μM for 1 and 1 μM for 7–12.

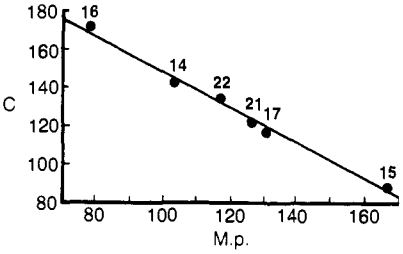

Figure 1. Plot of total concentrations of acyclonucleosides in the blood (C, μM) at 15 min after oral administration of esters of 5 (14–17, 21, 22) against their melting points (M.p., °C). The solid line is given by the equation $C = 240 - 0.924M$ ($r = 0.994$).

The 2-aminopurine 5 showed improved absorption in comparison with 1 and was efficiently converted to the antiviral guanine derivative. The corresponding analogue (4) of acyclovir (2) has similarly been reported[6] to be better absorbed in rats than is 2. Thus, the maximum concentrations of 1 detected in the blood after oral administration of 5 were more than 3 times higher than those obtained after administration of the equivalent oral dose of 1 (Table I). Ester derivatives (14–17, 21, 22) of 5 and its isopropylidene derivative 18 were, however, absorbed much more efficiently and provided maximum concentrations of 1 in the blood that were from 7 to 16 times higher than those obtained after administration of the equivalent oral dose of 1. The monophosphate (23) and cyclic phosphate (24) derivatives of 5 were less well absorbed than was 5.

Several 6-alkoxy congeners (7–10) of 1 were also more efficiently absorbed after oral administration to mice than was 1. Thus, the maximum total concentrations of 6-alkoxy prodrug and 1 detected in the blood were up to 11 times higher than those achieved after administration of the equivalent dose of 1 (Table II). However, conversion of the 6-alkoxypurines to 1 was less efficient than was conversion of the 6-deoxy congener 5. Consequently, the highest concentrations of 1 achieved in the blood, obtained after oral administration of the 6-ethoxy (8) and 6-isopropoxy (9) derivatives, were only about 2 times the concentrations achieved with the equivalent oral dose of 1. The mechanism for conversion of 2-amino-6-alkoxypurines to guanines has not yet been elucidated, but the more efficient conversion of the ethoxy (8), isopropoxy (9), and *n*-butoxy (10) derivatives in comparison with the methoxy (7) derivative is consistent with enzymatic oxidative dealkylation.

Correlation of Gastrointestinal Absorption and Physical Properties. It has been postulated[9] that for certain high-melting crystalline compounds disruption of

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(9) Yamaoka, Y.; Roberts, R. D.; Stella, V. J. *J. Pharm. Sci.* **1983**, *72*, 400.

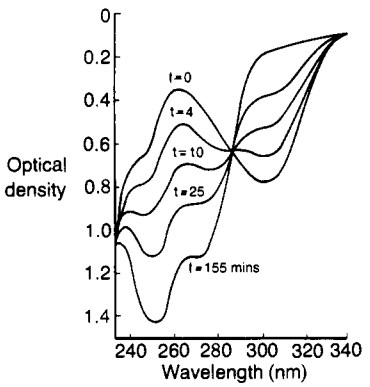

Figure 2. UV spectra during the oxidation of **5** by xanthine oxidase. Standards: **5**, λ_{max} 302 nm; **1**, λ_{max} 254 nm, shoulder 270 nm. To an aqueous solution of **5** (0.5 mM, 0.7 mL; pH 7) was added cows' milk xanthine oxidase (20 μL, 0.4 unit). Dissolved atmospheric oxygen was allowed to act as electron acceptor, and changes in the UV spectrum were measured. After 4 min 25% conversion had occurred, and after 2.5 h conversion was essentially complete. In the absence of xanthine oxidase, under the same conditions, no change in the UV spectrum was observed after 2.5 h. The oxidation product was identical with authentic 9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]guanine by UV, TLC (silica gel), and HPLC (reverse phase).

intermolecular hydrogen bonding, for example, by making bioreversible adducts, may concomitantly lower the melting point and increase lipid solubility, thereby improving gastrointestinal absorption. These workers showed experimentally that the melting point and the logarithm of solubility in lipids of certain phenytoin derivatives were linearly correlated.[9] In the present work with esters (**14–17**, **21**, **22**) of 2-amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine (**5**) we found that as the melting point decreased, the compounds showed improved gastrointestinal absorption in mice. Indeed, the total concentration of acyclonucleosides in the blood 15 min after oral administration of the prodrug had a highly significant linear dependence on its melting point (Figure 1).

Disruption of the crystal lattice by ester formation has effects on solubility both in lipids and in water, and these two vary in quite different ways. In order to assess the dependence of gastrointestinal absorption on lipophilicity, the total concentration of acyclonucleosides in the blood 15 min after oral administration of esters of **5** was also correlated with calculated log *P* values.

Although the correlation coefficient with log *P* was much lower (0.790 as compared to 0.994 with melting points), it does indicate that a major contribution to increasing absorption in this series is due to increase in lipophilicity. Another component in the superior correlation with melting point could be rate of dissolution, which may vary with changes in lattice energy.

Enzymic Oxidation. Confirmation that xanthine oxidase is the enzyme involved in the oxidation of **5** was obtained by incubation of the 2-aminopurine **5** with xanthine oxidase (cows' milk) in the presence of dissolved oxygen. The reaction was monitored by UV (Figure 2). The enzyme catalyzed an efficient and specific oxidation at the 6-position leading to exclusive formation of guanine **1**.

Summary. In this publication we have described syntheses of 2-amino-9-[4-hydroxy-3-(hydroxymethyl)-but-1-yl]purine (**5**) and a series of its derivatives (**14–18**, **21–24**). The potential utility of these compounds and their previously reported[2] 2,6-diaminopurine (**6**) and 6-alkoxy-2-aminopurine (**7–12**) analogues as oral prodrugs of the antiviral guanine derivative **1** has been evaluated. Several derivatives (**14–18**, **21**, **22**) of **5** are very well absorbed and efficiently converted to **1** after oral administration to mice. Interestingly, a highly significant correlation between the extent of gastrointestinal absorption and the melting points of esters of **5** was observed. Consideration of these data and additional factors, such as ease of synthesis and stability at acidic pH's, led to selection of the diesters **14** and **16** for further evaluation. A brief summary of these subsequent studies has been presented in a preliminary communication.[10] The diacetate **14** was more stable than the dipropionate **16** in rat and human duodenal contents, yet was readily converted to **1** in intestinal wall and liver preparations. When **14** was administered orally to rats, the bioavailability of **1** in the blood was about 25 times that following an equivalent oral dose of **1**. Following oral administration of **14** to healthy human subjects,[11] more than half the dose was absorbed and converted to **1**. Peak plasma concentrations of **1** were observed within 1 h and were over 10-fold higher than those detected following an equivalent oral dose of **1**.

In conclusion, from a series of 2-aminopurines and 6-alkoxy-2-aminopurines, 9-[4-acetoxy-3-(acetoxymethyl)-but-1-yl]-2-aminopurine (**14**) and 2-amino-9-[4-(propionyloxy)-3-[(propionyloxy)methyl]but-1-yl]purine (**16**) were selected as potential oral prodrugs of the antiviral acyclonucleoside **1** (BRL 39123). Subsequent evaluation identified **14** (BRL 42810) as the preferred prodrug for oral administration to humans, and this compound is now being evaluated in clinical trials.

Experimental Section

Melting points were determined on a Reichert Kofler apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM-390 90-MHz or a Jeol GX-270 270-MHz spectrometer. Infrared spectra were recorded with a Perkin-Elmer 580 spectrometer and ultraviolet spectra with a Cary 219 spectrometer. Mass spectra were recorded on a VG 70-70 instrument, and accurate masses were measured on a VG ZAB spectrometer. Microanalyses were performed on a Carlo-Erba Model 1106 analyzer and, where only the symbols for the elements are recorded, were within ±0.4% of the calculated values. Upon TLC of analytical samples using silica gel $60G_{254}$ precoated aluminium sheets (Merck Art. 5554), in each case only a single component was detected. Xanthine oxidase (cows' milk) was purchased from Boehringer Mannheim. Aqueous solubilities were measured at 25 °C by ultraviolet absorption of appropriately diluted samples. Calculated log *P* values were derived by using the Medchem program, copyright of Medicinal Chemistry Project, Pomona College, Claremont, CA.

Determination of acyclonucleoside concentrations was by HPLC as previously described.[4] Briefly, a Waters Nova-Pak C_{18} cartridge (10 cm by 8 or 5 mm) fitted in a Z-module and protected with a C_{18} Guard-Pak was used in conjunction with two M45 pumps, a WISP autosampler, an M720 controller, an M 730 data module, and a Kratos Spectroflow 757 detector. For most analyses the buffer used was 5 mM KH_2PO_4, and each sample was eluted at a linear flow rate of 40 mm/min. Guanine and 2-amino-6-alkoxypurine derivatives were detected by monitoring the eluate at 254 nm and 2-aminopurine derivatives by monitoring at 310 nm.

9-[4-Acetoxy-3-(acetoxymethyl)but-1-yl]-2-aminopurine (14). A suspension of **13** (0.36 g, 1.0 mmol) and 10% palladium on charcoal (30 mg) in methanol containing ammonium formate (400 mM; 10 mL) was heated under reflux for 30 min. The mixture was allowed to cool and filtered and the solvent removed. The residue was taken up in water and the solution extracted twice with chloroform. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed to afford **14** (0.29 g, 90%).

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Recrystallization from ethyl acetate–hexane gave white shiny plates (0.25 g, 78%): mp 102–104 °C; UV (MeOH) λ_{max} 222 (ϵ 27 500), 244 (4890), and 309 (7160) nm; IR (KBr) ν_{max} 3340, 3170, 1745, 1730, 1660, 1615, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90–2.05 (3 H, m, $CHCH_2CH_2$), 2.07 (6 H, s, 2 × CH_3), 4.15 (4 H, d, J 5.2 Hz, 2 × CH_2O) 4.21 (2 H, t, J 7.2 Hz, CH_2N), 5.16 (2 H, br s, 2-NH_2), 7.79 (1 H, s, 8-H), and 8.70 (1 H, s, 6-H). Anal. ($C_{14}H_{18}N_5O_4$) C, H, N.

2-Amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine (5).[2] A solution of the diacetate **14** (6.5 g, 20 mmol) in methanol saturated with ammonia at 0 °C (200 mL) was left to stand at room temperature for 18 h. The solvent was removed, and the residue was suspended in chloroform and filtered off. The solid was recrystallized from ethanol–methanol–water to give **5**, (4.07 g, 86%). A further 0.50 g was obtained from the mother liquors (total 4.57 g, 96%).

(*R*,*S*)-9-[4-Acetoxy-3-(hydroxymethyl)but-1-yl]-2-aminopurine (15). To a solution of **14** (0.48 g, 1.5 mmol) in methanol (9 mL) was added anhydrous potassium carbonate (14 mg, 0.1 mmol), and the solution was stirred for 20 min. Two drops of glacial acetic acid were added, the solution was filtered and the solvent removed. The residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (15:1, 10:1) to afford **15** as a white crystalline solid (124 mg, 30%): mp 166–168 °C; IR (KBr) ν_{max} 3440, 3220, 1720, 1650, 1615, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.68 (1 H, m, $CHCH_2CH_2$), 1.82 (2 H, m, $CHCH_2CH_2$), 1.98 (3 H, s, CH_3), 3.41 (2 H, t, J 4.8 Hz, D_2O exchange gives d, CH_2OH), 3.9–4.05 (2 H, AB part of ABX, J_{AB} 10.9 Hz and J_{AX} = J_{BX} 5.8 Hz, CH_2OCO), 4.12 (2 H, t, J 7.2 Hz, CH_2N), 4.62 (1 H, t, J 5.0 Hz, D_2O exchangeable, OH), 6.44 (2 H, s, D_2O exchangeable, 2-NH_2), 8.07 (1 H, s, 8-H), and 8.56 (1 H, s, 6-H). Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

2-Amino-9-[4-(propionyloxy)-3-[(propionyloxy)methyl]but-1-yl]purine (16). A solution of **5** (0.24 g, 1.0 mmol), DMAP (10 mg), and propionic anhydride (0.64 mL, 5.0 mmol) in DMF (5 mL) was stirred for 10 min. Methanol (1 mL) was added and the solvent was removed. The residue was partitioned between aqueous $NaHCO_3$ (8 mL) and chloroform (8 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed. Trituration with ether afforded **16** as a white crystalline solid which was recrystallized from ethyl acetate–hexane (247 mg, 71%): mp 78.5–80 °C; UV (EtOH) λ_{max} 222 (ϵ 27 300), 244 (5020), and 309 (7110) nm; IR (KBr) ν_{max} 3390, 3210, 1735, 1650, 1605, 1580, 1525, 1475, and 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (6 H, t, J 7.6 Hz, 2 × CH_3), 1.96 (3 H, m, $CHCH_2CH_2$), 2.34 (4 H, q, J 7.6 Hz, 2 × CH_2CH_3), 4.15 (4 H, d, J 5.5 Hz, 2 × CH_2OCO), 4.21 (2 H, t, J 7.0 Hz, CH_2N), 5.05 (2 H, s, D_2O exchangeable, 2-NH_2), 7.77 (1 H, s, 8-H), and 8.69 (1 H, s, 6-H). Anal. ($C_{16}H_{23}N_5O_4$) C, H, N.

(*R*,*S*)-2-Amino-9-[3-(hydroxymethyl)-4-[(methoxycarbonyl)oxy]but-1-yl]purine (17). To a suspension of **5** (237 mg, 1.0 mmol) in tetrahydrofuran (3 mL) were added *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol) and tetramethyl orthocarbonate (0.53 mL, 4.0 mmol), and the mixture was stirred for 100 min. Water (0.8 mL) was added, and after a further 15 min the solution was neutralized by addition of aqueous $NaHCO_3$. The solvent was removed and the residue was extracted with chloroform–methanol (3:1). The solvent was removed and the residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (10:1) to afford **17**, which was obtained as a white crystalline solid after trituration with ethyl acetate (65 mg, 22%): mp 129–132 °C; IR (KBr) ν_{max} 3440, 3220, 1745, 1650, 1615, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.73 (1 H, m, $CHCH_2CH_2$), 1.81 (2 H, m, $CHCH_2CH_2$), 3.41 (2 H, t, J 5.1 Hz, D_2O exchange gives d, CH_2OH), 3.68 (3 H, s, CH_3), 4.0–4.2 (4 H, m, CH_2OCO and CH_2N), 4.65 (1 H, t, J 5.2 Hz, D_2O exchangeable, OH), 6.44 (2 H, s, D_2O exchangeable, 2-NH_2), 8.06 (1 H, s, 8-H), and 8.55 (1 H, s, 6-H). HRMS: calcd for $C_{12}H_{17}N_5O_4$ 295.1280; found 295.1286. Anal. ($C_{12}H_{17}N_5O_4 \cdot 0.15H_2O$) C, H, N.

2-Amino-9-[2-(2,2-dimethyl-1,3-dioxan-5-yl)ethyl]purine (18). To a suspension of **5** (240 mg, 1.0 mmol) in DMF (3 mL) were added *p*-toluenesulfonic acid monohydrate (210 mg, 1.1 mmol) and 2,2-dimethoxypropane (0.62 mL, 5.0 mmol), and the solution was stirred for 30 min. Potassium carbonate (110 mg, 0.8 mmol) was added, and the solution was stirred for a further 30 min. Water (10 mL) was added and the solution was extracted with chloroform (3 × 8 mL). The organic layers were combined and dried ($MgSO_4$) and the solvent removed. Trituration with toluene–ether afforded **18** as a white crystalline solid (262 mg, 94%) which was recrystallized from ethyl acetate–hexane (216 mg, 78%): mp 118–120 °C; UV (MeOH) λ_{max} 221 (ϵ 27 200), 244 (4920), and 308 (7130) nm; IR (KBr) ν_{max} 3450, 3140, 1635, 1615, 1580, and 1435 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.26 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 1.58 (1 H, m, $CHCH_2CH_2$), 1.74 (2 H, q, J 7.1 Hz, $CHCH_2CH_2$), 3.54 (2 H, dd, J 11.8 and 8.5 Hz, 2 × H_{ax}), 3.78 (2 H, dd, J 11.8 and 4.4 Hz, 2 × H_{eq}), 4.07 (2 H, t, J 7.2 Hz, CH_2N), 6.46 (2 H, s, D_2O exchangeable, 2-NH_2), 8.09 (1 H, s, 8-H), and 8.56 (1 H, s, 6-H). Anal. ($C_{13}H_{19}N_5O_3$) C, H, N.

(*R*,*S*)-9-[3-(Hydroxymethyl)-4-[(monomethoxytrityl)oxy]but-1-yl]-2-[(monomethoxytrityl)amino]purine (19) and 9-[4-Hydroxy-3-(hydroxymethyl)but-1-yl]-2-[(monomethoxytrityl)amino]purine (20). To a suspension of **5** (2.37 g, 10 mmol) in DMF (40 mL) containing DMAP (30 mg) and triethylamine (4.2 mL) was added a solution of monomethoxytrityl chloride (6.8 g, 22 mmol) in DMF (60 mL) over a period of 40 min. The solution was stirred for further 40 min, methanol (1 mL) was added, and the solvent was removed. The residue was taken up in chloroform and washed with water and dilute aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was purified by column chromatography on silica gel, eluting with chloroform–methanol mixtures (40:1 to 6:1).

The first product to elute was **19**, which was further purified by a second silica gel column, eluting with chloroform–methanol (40:1), and obtained as a colorless foam (3.34 g, 43%): UV (EtOH) λ_{max} 227 (ϵ 47 400) and 312 (6450) nm; IR (KBr) ν_{max} 3430, 1615, 1580, 1510, 1490, and 1415 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.37 (2 H, m, $CHCH_2CH_2$), 1.49 (1 H, m, $CHCH_2CH_2$), 2.8–2.9 (2 H, m, CH_2OC), 3.2–3.4 (2 H, m, CH_2OH), 3.64 (5 H, m, CH_2N and OCH_3), 3.73 (3 H, s, OCH_3), 4.40 (1 H, t, J 5.0 Hz, D_2O exchangeable, OH), 6.7–7.4 (28 H, m, Ar-H), 7.46 (1 H, s, D_2O exchangeable, 2-NH), 7.88 (1 H, s, 8-H), and 8.53 (1 H, s, 6-H). Anal. H, N; C: calcd, 76.80; found, 77.28.

The second product to elute was **20**, which was obtained as a white crystalline solid after trituration and filtration from ether (2.07 g, 41%): mp 181–183 °C; UV (EtOH) λ_{max} 227 (ϵ 36 000) and 312 (6780) nm; IR (KBr) ν_{max} 3390, 1615, 1580, 1525, 1510, 1490, and 1420 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.30 (1 H, m, $CHCH_2CH_2$), 1.39 (2 H, q, J 6.8 Hz, $CHCH_2CH_2$), 3.15–3.35 (4 H, m, 2 × CH_2O), 3.70 (3 H, s, OCH_3), 3.76 (2 H, t, J 7.2 Hz, CH_2N), 4.33 (2 H, t, J 5.1 Hz, D_2O exchangeable, 2 × OH), 6.8–7.4 (14 H, m, Ar-H), 7.52 (1 H, s, D_2O exchangeable, 2-NH), 7.97 (1 H, s, 8-H), and 8.52 (1 H, s, 6-H). Anal. C, H, N.

(*R*,*S*)-2-Amino-9-[4-(butyryloxy)-3-(hydroxymethyl)but-1-yl]purine (21). To a solution of **19** (0.70 g, 0.9 mmol) and DMAP (10 mg) in DMF (5 mL) was added butyric anhydride (0.29 mL, 1.8 mmol), and the solution was stirred for 15 min. Methanol (1 mL) was added and the solvent was removed. The residue was taken up in 80% acetic acid (9 mL), and the solution was stirred at 70 °C for 30 min. Water (2 mL) was added and the solution was extracted with hexane (2 × 10 mL). The aqueous layer was retained and the solvent was removed. The residue was partitioned between saturated aqueous $NaHCO_3$ and chloroform, and the organic layer was dried ($MgSO_4$) and the solvent removed. The residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (16:1) to afford **21**, which was obtained as a white crystalline solid after trituration with methanol (188 mg, 68%): mp 125–127 °C; UV (MeOH) λ_{max} 222 (ϵ 27 600), 243 (4830), and 308 (6950) nm; IR (KBr) ν_{max} 3190, 1730, 1640, 1620, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.85 (3 H, t, J 7.4 Hz, CH_3), 1.50 (2 H, sextet, J 7.3 Hz, $CH_2CH_2CH_3$), 1.68 (1 H, m, $CHCH_2CH_2$), 1.82 (2 H, m, $CHCH_2CH_2$), 2.23 (2 H, t, J 7.4 Hz, $CH_2CH_2CH_3$), 3.42 (2 H, t, J 5.2 Hz, D_2O exchange gives d, CH_2OH), 3.95–4.1 (2 H, AB of ABX, J_{AB} 11.0 Hz, J_{AX} = J_{BX} 5.8 Hz, CH_2OCO), 4.12 (2 H, t, J 7.3 Hz, CH_2N), 4.62 (1 H, t, J 4.9 Hz, D_2O exchangeable, OH), 6.44 (2 H, s, D_2O exchangeable, 2-NH_2), 8.06 (1 H, s, 8-H), and 8.56 (1 H, s, 6-H). Anal. ($C_{14}H_{21}N_5O_3$) C, H, N.

(*R*,*S*)-2-Amino-9-[4-(benzoyloxy)-3-(hydroxymethyl)but-1-yl]purine (22). To a solution of **19** (0.70 g, 0.9 mmol) and DMAP (10 mg) in DMF (5 mL) was added benzoic anhydride (0.61 g, 2.7 mmol), and the solution was stirred for 1 h. Methanol (1

mL) was added and the solvent was removed. The residue was taken up in 80% acetic acid (9 mL), and the solution was stirred at 80 °C for 20 min. Water (3 mL) was added and the solution was extracted with hexane (2 × 10 mL). The aqueous layer was retained and the solvent was removed. The residue was partitioned between saturated aqueous $NaHCO_3$ and chloroform, and the organic layer was dried ($MgSO_4$) and the solvent removed. The residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (14:1) to afford **22**, which was obtained as a white crystalline solid after trituration with methanol (235 mg, 76%): mp 116–118 °C; UV (MeOH) λ_{max} 223 (ϵ 36 700) and 309 (6680) nm; IR (KBr) ν_{max} 3320, 1710, 1610, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.83 (1 H, m, C*H*CH_2CH_2), 1.93 (2 H, q, J 7.1 Hz, CHC*H*$_2$$CH_2$), 3.52 (2 H, t, J 5.3 Hz, D_2O exchange gives d, C*H*$_2$OH), 4.19 (2 H, t, J 7.0 Hz, CH_2N), 4.2–4.3 (2 H, ABX, J_{AB} 11.0 Hz, $J_{AX} = J_{BX}$ 5.6 Hz, CH_2OCO), 4.69 (1 H, t, J 5.2 Hz, D_2O exchangeable, OH), 6.43 (2 H, s, D_2O exchangeable, 2-NH_2), 7.5–7.9 (5 H, m, C_6H_5), 8.10 (1 H, s, 8-H), and 8.55 (1 H, s, 6-H). Anal. ($C_{17}H_{19}N_5O_3$) C, H, N.

(*R*,*S*)-2-Amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine Phosphate (23). To an ice-cooled solution of phosphorus oxychloride (0.10 mL, 1.1 mmol) in pyridine (2 mL) was added dropwise over 15 min a solution of **19** (0.78 g, 1.0 mmol) in pyridine (2 mL). The solution was stirred for a further 30 min at room temperature and was then added dropwise to a solution of $NaHCO_3$ (0.5 g, 6.0 mmol) in water (7 mL). The solvent was removed, the residue was taken up in 80% acetic acid (10 mL), and the solution was stirred at 70 °C for 25 min. The solvent was removed, and the residue was taken up in water and brought to pH 6 by addition of ammonia. The solution was extracted twice with chloroform, and the solvent was removed. The residue was purified by preparative high-pressure liquid chromatography on a C_{18} reverse-phase μBondapak column eluting with 3% methanol in ammonium acetate buffer (pH 4.5; 50 mM) to afford **23** as a hygroscopic white powder (85 mg, 25%): UV (H_2O) λ_{max} 220 (ϵ 26 100), 241 (3860), and 303 (6350) nm; IR (KBr) ν_{max} 3410, 1660, 1620, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.57 (1 H, m, C*H*CH_2CH_2), 1.77 (2 H, m, CHC*H*$_2$$CH_2$), 3.37 (2 H, d, J 4.4 Hz, C*H*$_2$OH), 3.77 (2 H, t, J 5.6 Hz, CH_2OP), 4.12 (2 H, t, J 7.4 Hz, CH_2N), 6.48 (2 H, s, D_2O exchangeable, 2-NH_2), 8.08 (1 H, s, 8-H), and 8.54 (1 H, s, 6-H). Anal. ($C_{10}H_{16}N_5O_5P$·0.5NH_3·H_2O) H, N; C: calcd, 34.94; found, 35.53.

2-Amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine Cyclic Phosphate (24). To an ice-cooled solution of phosphorus oxychloride (93 μL, 1.0 mmol) in pyridine (2 mL) was added dropwise over 45 min a solution of **20** (0.46 g, 0.9 mmol) in pyridine (4 mL). The solution was stirred for a further 20 min at room temperature and was then added dropwise to a solution of $NaHCO_3$ (0.34 g, 4.0 mmol) in water (6 mL). The solvent was removed, the residue was taken up in 80% acetic acid (9 mL), and the solution was stirred at 70 °C for 25 min. The solvent was removed, and the residue was taken up in water and brought to pH 6 by addition of ammonia. The solution was extracted twice with chloroform, and the solvent was removed. The residue was purified by preparative high-pressure liquid chromatography on a C_{18} reverse-phase μBondapak column, eluting with 4% methanol in ammonium acetate buffer (pH 4.5, 50 mM) to afford **24** as a white powder (225 mg, 75%): UV (H_2O) λ_{max} 220 (ϵ 25 600), 242 (3900), and 303 (6270) nm; IR (KBr) ν_{max} 2900–3200 (br), 1705, 1615, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.63 (1 H, m, C*H*CH_2CH_2), 1.74 (2 H, q, J 7.0 Hz, CHC*H*$_2$$CH_2$), 3.80 (2 H, q, J 9.2 Hz, 2 × H_{ax}), 3.98 (2 H, ddd, J 14.3, 10.9, and 3.5 Hz, 2 × H_{eq}), 4.08 (2 H, t, J 7.1 Hz, CH_2N), 6.51 (2 H, s, D_2O exchangeable, 2-NH_2), 8.10 (1 H, s, 8-H), and 8.56 (1 H, s, 6-H). Anal. ($C_{10}H_{14}N_5O_4P$·0.3NH_3·1.5H_2O) C, H, N.

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3′-Fluoro-2′,3′-dideoxy-5-chlorouridine: Most Selective Anti-HIV-1 Agent among a Series of New 2′- and 3′-Fluorinated 2′,3′-Dideoxynucleoside Analogues

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A series of 2′- and 3′-fluorinated 2′,3′-dideoxynucleosides and 3′-azido-2′,3′-dideoxynucleosides were synthesized and evaluated for their inhibitory activity against human immunodeficiency virus-1 (HIV-1) replication in MT-4 cells. Neither conversion of 3′-fluoro- or 3′-azido-2′,3′-dideoxyadenosine to the corresponding inosine derivatives nor 8-bromination of 2′,3′-dideoxyadenosine resulted in increased anti-HIV-1 activity. Nor did introduction of a 2′-fluorine in the erythro or threo configuration lead to improved anti-HIV-1 activity of the parent 2′,3′-dideoxynucleosides. 1-(2-Fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)cytosine and 1-(2-fluoro-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine were only marginally active. However, 3′-fluoro-2′,3′-dideoxyuridine (FddUrd) proved to be potent and a relatively nontoxic inhibitor of HIV-1. 5-Halogenated derivatives of FddUrd were prepared in attempts to further increase its anti-HIV potency and selectivity. Of these 5-halogenated derivatives, 3′-fluoro-2′,3′-dideoxy-5-chlorouridine emerged as the most selective inhibitor of HIV-1 replication. Its selectivity index was comparable to that of azidothymidine when evaluated under the same conditions.

The discovery of the human immunodeficiency virus (HIV) as the causative agent of AIDS[1,2] and the identification of HIV as a retrovirus have prompted the search for agents that would be able to block the HIV replication process. Our efforts have mainly focused on the design and synthesis of reverse transcriptase inhibitors.[3-6] 2′,3′-Dideoxynucleoside analogues (for a recent review see

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