Anticancer and Antiviral Effects and Inactivation of *S*-Adenosyl-L-homocysteine Hydrolase with 5′-Carboxaldehydes and Oximes Synthesized from Adenosine and Sugar-Modified Analogues[1]

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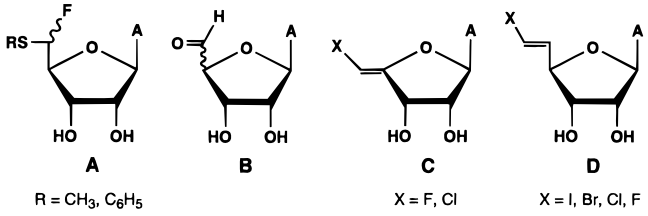
Selectively protected adenine nucleosides were converted into 5′-carboxaldehyde analogues by Moffatt oxidation (dimethyl sulfoxide/dicyclohexylcarbodiimide/dichloroacetic acid) or with the Dess−Martin periodinane reagent. Hydrolysis of a 5′-fluoro-5′-*S*-methyl-5′-thio (α-fluoro thioether) arabinosyl derivative also gave the 5′-carboxaldehyde. Treatment of 5′-carboxaldehydes with hydroxylamine [or *O*-(methyl, ethyl, and benzyl)hydroxylamine] hydrochloride gave *E*/*Z* oximes. Treatment of purified oximes with aqueous trifluoroacetic acid and acetone effected trans-oximation to provide clean samples of 5′-carboxaldehydes. Adenosine (Ado)-5′-carboxaldehyde and its 4′-epimer are potent inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase. They bind efficiently to the enzyme and undergo oxidation at C3′ to give 3′-keto analogues with concomitant reduction of the NAD^+ cofactor to give an inactive, tightly bound NADH−enzyme complex (type I cofactor-depletion inhibition). Potent type I inhibition was observed with 5′-carboxaldehydes that contain a ribo *cis*-2′,3′-glycol. Their oxime derivatives are "proinhibitors" that undergo enzyme-catalyzed hydrolysis to release the inhibitors at the active site. The 2′-deoxy and 2′-epimeric (arabinosyl) analogues were much weaker inhibitors, and the 3′-deoxy compounds bind very weakly. Ado-5′-carboxaldehyde oxime had potent cytotoxicity in tumor cell lines and was toxic to normal human cells. Analogues had weaker cytotoxic and antiviral potencies, and the 3′-deoxy compounds were essentially devoid of cytotoxic and antiviral activity.

Introduction

S-Adenosyl-L-methionine (AdoMet, SAM) is the ubiquitous methyl donor for most biological methylation reactions, and the byproduct, *S*-adenosyl-L-homocysteine (AdoHcy), is a potent feedback inhibitor of various transmethylation enzymes. AdoHcy hydrolase (EC 3.3.1.1) is the cellular enzyme that catalyzes hydrolytic cleavage of AdoHcy to adenosine (Ado) and L-homocysteine (Hcy).[2a] Inhibition of AdoHcy hydrolase results in increased ratios of AdoHcy/AdoMet which diminishes transmethylation processes that are crucial for cell division and viral maturation. Therefore, the design of inhibitors of AdoHcy hydrolase provides a rational approach to mechanism-based chemotherapy of cancer and viral diseases.[2]

Several years ago we reasoned that 5′-*S*-(alkyl and aryl)-5′-fluoro-5′-thioadenosines **A** (Chart 1) might function as alternative substrates of AdoHcy hydrolase and be mechanism-based (suicide) inhibitors.[3a] Such α-fluoro thioethers of 5′-thioadenosine underwent spontaneous chemical hydrolysis in aqueous buffer to give 4′-epimeric "adenosine-5′-carboxaldehyde" species (*e.g.*, **B**) that caused inactivation of AdoHcy hydrolase.[3,4] McCarthy *et al.*[5] employed similar chemistry to prepare 4′,5′-didehydro-5′-deoxy-5′(*Z*)-fluoroadenosine (**C**, X = F) and other *exo*-vinyl halides. Fluorovinyl compound **C**

Chart 1



(X = F) was a potent inhibitor of AdoHcy hydrolase with significant biological activity,[5] and Borchardt's group elucidated the mechanism of enzyme inactivation.[6] Catalyzed attack of water at C5′ of **C** (X = F) and loss of fluoride resulted in generation of the adenosine-5′-carboxaldehydes **B** which were synthesized and shown to be potent inhibitors of AdoHcy hydrolase.[7] It is noteworthy that the adenosine-5′-carboxaldehyde epimers were not detected during analogous time-dependent inhibition of AdoHcy hydrolase[3c,8] with the 5′(*Z*)-chloro analogue **C** (X = Cl).

We have recently developed stereocontrolled syntheses of 6′(*E* and *Z*)-halohomovinyl nucleosides[4,9] that inhibit AdoHcy hydrolase and have anticancer and antiviral activity.[9b] The 6′(*E*)-(halohomovinyl)adenosine derivatives **D** were shown to inactivate AdoHcy hydrolase by catalyzed addition of water to the 5′,6′-double bond and generation of the labile homoadenosine-6′-carboxaldehyde (loss of a proton and halide from C6′).[10] Other 4′/5′-modified inhibitors include 5′-azido- and 5′-cyano-5′-deoxyadenosine,[11] the 4′-ethynyl (acetylenic) analogue,[12] and amide or ester derivatives of adenosine-

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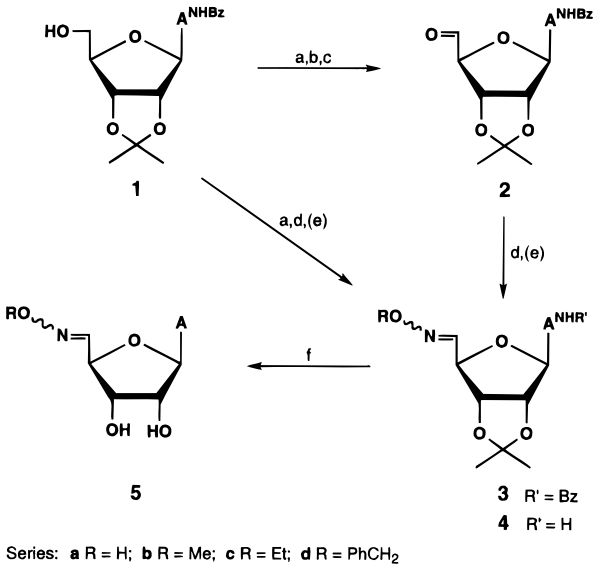
Scheme 1[a]



[a] (a) DMSO/DCC/Cl_2CHCO_2H; (b) $(PhNHCH_2)_2$; (c) (i) Dowex (H^+)/THF/H_2O, (ii) Dean−Stark trap benzene/Δ; (d) NH_2OR·HCl/pyridine; (e) NH_3/MeOH; (f) TFA/H_2O.

5′-carboxylic acid.[13] Detailed mechanisms of inactivation were not determined,[11−13] but no evidence for enzyme-mediated hydrolysis of the amide or ester compounds was observed.[13] Porter recently showed that 9-(α-L-lyxofuranosyl)adenine, the 4′-hydroxymethyl epimer of Ado, is a substrate for AdoHcy hydrolase.[14]

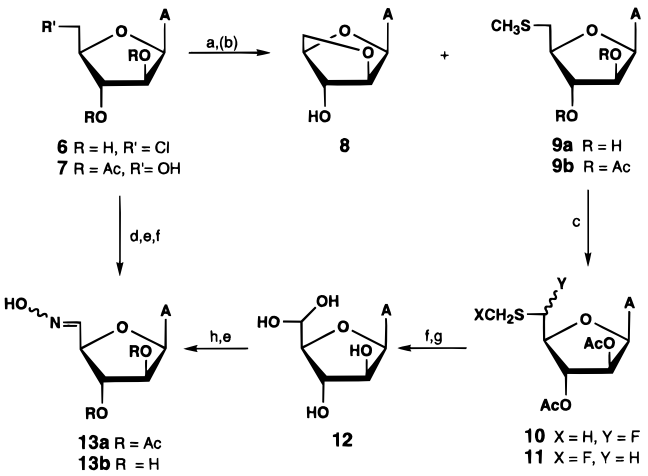
Few oxime derivatives of nucleosides have been reported.[15] The epimeric adenosine-5′-carboxaldehydes are potent inhibitors of AdoHcy hydrolase,[2e,f] but they are somewhat unstable and are difficult to purify and characterize.[16] We considered that their oxime derivatives might serve as AdoHcy hydrolase-activated prodrugs that would undergo hydrolysis to the 5′-carboxaldehydes within the enzyme active site. We now report syntheses of crystalline adenosine-5′-carboxaldehyde oximes and their arabino, 2′-deoxy, and 3′-deoxy analogues. Several of these compounds inhibited AdoHcy hydrolase and had in vitro cytotoxic and antiviral activity.

Chemistry

Adenosine-5′-carboxaldehyde oximes[15c,d] have been dehydrated to give 4′-cyano products,[15d] and 2′- and 3′-ketouridine derivatives have been converted to oximes.[15a,b] Moffatt oxidation[16] of 6-*N*-benzoyl-2′,3′-*O*-isopropylideneadenosine (**1**; Scheme 1) gave adenosine-5′-carboxaldehyde (**2**). Purified **2**[16a] was treated with hydroxylamine hydrochloride in pyridine to give the oximes **3a** (*E*/*Z* ∼2.4:1; 67%) plus debenzoylated **4a** (*E*/*Z* ∼9:1; 8%). Chromatographic separation of the *E* and *Z* isomers of **3** or **4** (or deprotected **5**) did not occur readily. However, early fractions from a silica gel flash column contained **3a**(*E*), and following fractions were enriched in this major isomer. Acid-catalyzed deprotection resulted in an elevated *E*/*Z* ratio. Stereochemical assignments are based on deshielding[17] of hydrogen (H5′) cis to OH (*E*) relative to trans H5′ and OH in the *Z* isomer.

Debenzoylation (NH_3/MeOH) of **3a**(*E*/*Z*) and acid-catalyzed removal of the isopropylidene group [CF_3CO_2H (TFA)/H_2O] gave **5a**(*E*/*Z*), and deprotection of

Scheme 2[a]



[a] (a) NaSMe/DMF; (b) Ac_2O/pyridine; (c) DAST/$SbCl_3$/CH_2Cl_2; (d) DMSO/DCC/Cl_2CHCO_2H; (e) NH_2OH·HCl/pyridine; (f) NH_3/MeOH; (g) TFA/H_2O; (h) Dean−Stark trap/benzene/Δ.

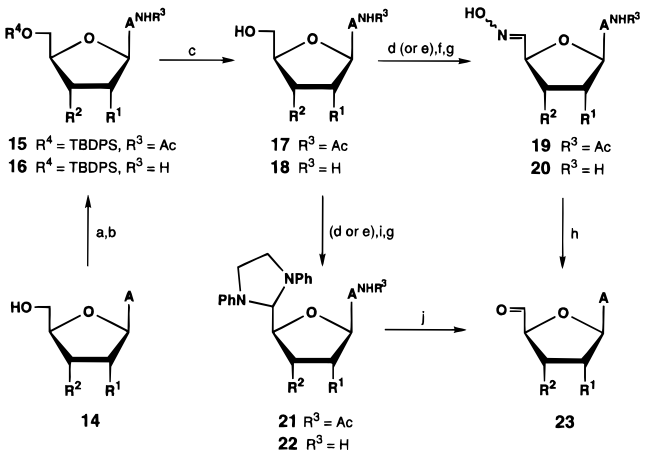
3a(*E*) gave **5a**(*E*). Treatment of **1** by a four-stage sequence [(i) oxidation (DMSO/DCC/dichloroacetic acid), (ii) treatment with NH_2OH·HCl, (iii) debenzoylation, (iv) deacetonization] without purification of intermediates gave **5a** (*E*/*Z* ∼4.5:1; 67%). Treatment of **2** with the *O*-(methyl, ethyl, and benzyl)hydroxylamines in pyridine gave **3b**−**d**, respectively, plus the debenzoylated derivatives **4b**−**d** (*E*/*Z* 2.5−3.5:1; combined yields 73−83%). Deprotection of **3b**−**d**/**4b**−**d** gave **5b**−**d** (*E*/*Z* 9−19:1) in high yields.

Synthesis of the 5′-carboxaldehydes of 2′- and 3′-deoxyadenosine and 9-(β-D-arabinofuranosyl)adenine (AraA) and their oximes required different protection strategies. Treatment of 9-(5-chloro-5-deoxy-β-D-arabinofuranosyl)adenine[18] (**6**; Scheme 2) with sodium thiomethoxide in DMF[19] gave the 5′-*S*-methyl-5′-thio product[20] **9a** (46%) plus the 2′,5′-anhydro byproduct[21] **8** (26%) resulting from intramolecular displacement of 5′-chloride by O2′. Treatment of the 2′,3′-di-*O*-acetyl derivative **9b** with (diethylamino)sulfur trifluoride (DAST)/$SbCl_3$[22] gave quantitative conversion to diastereomeric 5′-fluoro-5′-*S*-methyl-5′-thio **10** and its regioisomer, 5′-*S*-(fluoromethyl)-5′-thio **11** [**10** (5′*R*/*S* ∼1:1.2)/**11**, 3.2:1; ^{19}F NMR[3b]]. Immediate deacetylation (NH_3/MeOH) of **10**/**11**, treatment with aqueous acid[3b,7] to effect hydrolysis to the aldehyde hydrate, and RP-HPLC purification gave **12** (42% from **8**).

Dehydration (benzene/Dean−Stark trap) of **12** and treatment with hydroxylamine hydrochloride in pyridine gave oximes **13b** (*E*/*Z* ∼1:1.6) in low yield. Alternatively, selective protection of AraA with *tert*-butyldiphenylsilyl chloride (TBDPSCl), acetylation, O5′-desilylation [tetrabutylammonium fluoride (TBAF)/acetic acid[23]], oxidation of 2′,3′-di-*O*-acetyl-AraA[23] (**7**), treatment with hydroxylamine, and deacetylation gave **13b** (*E*/*Z* ∼1.2:1) in low yield. Acetyl migration occurred during O5′-desilylation with TBAF in the absence of equimolar acetic acid to give 3′,5′-di-*O*-acetyl-AraA[23] in high yield.

The 3′-*O*-acetyl-2′-dAdo[24a] (**18d**; Scheme 3) and 2′-*O*-acetyl-3′-dAdo (**18c**) isomers were selected for syntheses of the 5′-carboxaldehydes[24b] and oximes. One-flask treatment of 3′-dAdo (**14a**) with TBDPSCl/pyridine followed by Ac_2O gave **16c** plus diacetylated **15c** (∼1:1,

Scheme 3[a]



Series: **a** R^1 = OH, R^2 = H (3′-dAdo); **d** R^1 = H, R^2 = OAc (2′-dAdo)
b R^1 = H, R^2 = OH (2′-dAdo); **e** R^1 = R^2 = OH (Ado)
c R^1 = OAc, R^2 = H (3′-dAdo)

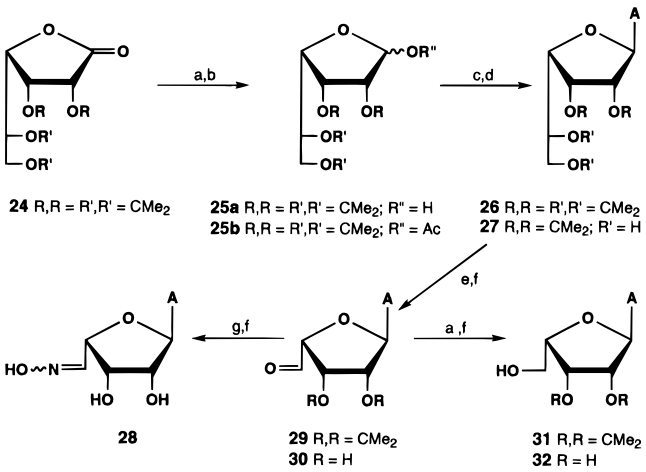
[a] (a) TBDPSCl/pyridine; (b) Ac_2O/pyridine; (c) TBAF/THF or NH_4F/MeOH/Dowex (H^+)/Δ or TFA/H_2O; (d) DMSO/DCC/Cl_2-$CHCO_2H$; (e) Dess−Martin periodinane/CH_2Cl_2; (f) NH_2OH·HCl/pyridine; (g) NH_3/MeOH; (h) TFA/Me_2CO/H_2O; (i) $(PhNHCH_2)_2$; (j) (4)$CH_3C_6H_4SO_3H$·H_2O/CH_2Cl_2.

82% combined) which were separated by chromatography. Removal of the TBDPS group from **16c** and **15c** [TBAF/THF or ammonium fluoride/MeOH[25a] with added Dowex 50 (H^+)[25b] or TFA/H_2O[25c]] gave **18c** and its 6-*N*-acetyl derivative **17c**. One-flask Moffatt oxidation of **17c** and treatment with hydroxylamine hydrochloride gave oximes **19c** (*E*/*Z* ∼2.1:1; 67%) which were deacetylated and chromatographed to give the 3′-dAdo-5′-carboxaldehyde oximes **20a** (*E*/*Z* ∼9:1).

Parallel treatment of 2′-dAdo (**14b**) and oxidation of 3′-*O*-acetyl-2′-dAdo (**18d**) gave the oximes **20b** (*E*/*Z* ∼5:1) in low yield [adenine was detected (TLC) during workup]. Oxidation of **18d** with the Dess−Martin periodinane reagent[26] also afforded **20b** in low yield. Treatment of the 5′-carboxaldehyde from **18d** with 1,2-dianilinoethane gave the 1,3-diphenylimidazolidine derivative **22d** (∼32%). The unstable 5′-carboxaldehyde **23b** (obtained by deacetylation of **22d** and hydrolysis of crystalline **22b**) was purified by repetitive RP-HPLC. Analogous treatment of **17c** gave the 1,3-diphenylimidazolidine derivative **21c** which was deacetylated to **22a** and hydrolyzed to give 3′-dAdo-5′-carboxaldehyde (**23a**). Mild hydrolysis (TFA/acetone/water) of the crystalline oximes provided an alternative procedure for isolation of clean 5′-carboxaldehydes.

A recent report that 9-(α-L-lyxofuranosyl)adenine (**32**, the 4′-epimer of Ado) functioned as an alternative substrate for AdoHcy hydrolase[14] supported our finding that **30** (the 4′-epimer of adenosine-5′-carboxaldehyde) is a potent inhibitor of the enzyme.[7] This is noteworthy since an unusual spatial leniency within the active site of AdoHcy hydrolase in the region occupied by C4′ substituents is indicated. The epimeric 5′-carboxaldehyde and oximes were prepared to further probe this observation. Known procedures[27−29] were modified to convert D-gulonic γ-lactone via its 2,3:5,6-di-*O*-isopropylidene derivative **24** (Scheme 4) into anomeric **25b** (∼9:1) which was coupled with adenine to give the protected 9-(β-D-gulofuranosyl)adenine **26** plus its α-anomer (40%, ∼3:1). Selective removal of the 5′,6′-*O*-isopropylidene group and periodate cleavage of diol **27**

Scheme 4[a]



[a] (a) $NaBH_4$; (b) Ac_2O/DMAP/pyridine; (c) adenine/$SnCl_4$/CH_3CN; (d) HOAc/H_2O (7:3); (e) $NaIO_4$/H_2O; (f) TFA/H_2O; (g) NH_2OH·HCl/pyridine.

Table 1. Inhibition of AdoHcy Hydrolase by Adenine Nucleoside 5′-Carboxaldehyde and Oxime Analogues

	enzyme activity remaining (%)						
conctn (μM)	**12**	**13b**	**20a**	**20b**	**23a**	**23b**	**23e**
0.01	99.2	92.3	98.0	80.8	99.9	95.8	41.6
0.1	93.1	88.5	110.2	79.9	92.8	89.6	12.2
1.0	85.8	80.1	108.3	76.1	91.0	83.2	5.3
10.0	66.4	45.3	101.2	74.3	90.2	80.1	*a*
100.0	39.1	21.1	64.8	38.6	68.2	57.8	*a*

[a] No activity detected.

Table 2. Kinetic Constants for Inhibition of AdoHcy Hydrolase by Ado-5′-Carboxaldehyde and Oxime Analogues

inhibitors	K_i (nM)	k_2 (min^{-1})	k_2/K_i (M^{-1} min^{-1})
5a	670	0.16	2.4×10^5
5b	94.6	0.048	5.1×10^5
5c	111	0.037	3.4×10^5
5d	101	0.036	3.6×10^5
23e	39.0	0.65	1.7×10^5
28	224	0.13	5.8×10^5
30	43.0	0.22	5.1×10^5

gave the protected 5′-carboxaldehyde **29**.[27] In situ reduction ($NaBH_4$) and deprotection gave 9-(α-L-lyxofuranosyl)adenine **32**.[27] Deprotection of **29** gave **30**, the 4′-epimer of Ado-5′-carboxaldehyde, by independent synthesis.[7] Treatment of **29** with hydroxylamine hydrochloride in pyridine and deprotection gave the somewhat unstable oximes **28** (*E*/*Z* ∼7:3) in low yield.

Inhibition of *S*-Adenosyl-L-homocysteine Hydrolase

Ado-5′-carboxaldehyde and oxime analogues were evaluated as potential inhibitors of purified recombinant human placental AdoHcy hydrolase. Compounds lacking 2′- or 3′-hydroxyl groups in the ribo configuration were weak inhibitors of the enzyme and not time-dependent inactivators (Table 1). In contrast, analogues with an intact *cis*-2′,3′-glycol unit were potent inhibitors of AdoHcy hydrolase and produced both concentration- and time-dependent inhibition of the enzyme (Table 2 contains kinetic constants determined by the Kitz and Wilson method[30]). Results summarized in Tables 1 and 2 indicate that both the 2′- and 3′-hydroxyl groups of Ado-5′-carboxaldehydes and oximes are essential for proper binding with AdoHcy hydrolase and subsequent

Table 3. Cytostatic Activity of Adenine Nucleoside 5′-Carboxaldehyde and Oxime Analogues against Murine and Human Tumor Cell Lines

	IC_{50}[a] (μg/mL)			
compd	L1210	FM3A	Molt-4/clone 8	CEM
5a	1.8 ± 0.07	2.3 ± 0.11	5.4 ± 0.3	2.9 ± 1.0
5b	271 ± 30	19 ± 9.9	218 ± 25	330 ± 130
5c	295 ± 18	≥500	≥500	≥500
5d	187 ± 125	340 ± 216	118 ± 64	136 ± 69
12	156 ± 7	125 ± 25	>200	118 ± 8
13b	10.5 ± 0.4	12.7 ± 0.8	16.4 ± 0.4	15.0 ± 0.9
20a	180 ± 0	≥200	≥200	185 ± 21
20b	4.60 ± 0.29	11.2 ± 1.5	17.0 ± 0.2	13.8 ± 1.1
23a	≥200	≥200	≥200	≥200
23b	6.64 ± 0.05	50.9 ± 25.0	4.96 ± 0.8	17.8 ± 1.8
23e	9.71 ± 0.68	15.0 ± 4.0	41.5 ± 0.2	7.30 ± 0.49

[a] 50% inhibitory concentration (concentration of compound required to inhibit tumor cell proliferation by 50%).

3′-oxidative and/or 5′-hydrolytic reactions. Alterations at either C2′ or C3′ result in significant reductions of enzyme inhibitory activity. Oximes listed in Table 2 had similar inhibitory activities with k_2/K_i values of 2.4−5.8 × 10^5 M^{-1} min^{-1}. However, comparisons of individual kinetic constants (K_i and k_2) for oximes **5a** and its 4′-epimer **28** with those of analogues **5b**−**d** show that the former have K_i values that are 2−6 times larger than the latter, and k_2 values for **5a** and **28** are about 3 times larger than those for **5b**−**d**. This suggests that C5′ atoms of **5a** and **28** are in more favorable proximity as electrophilic centers for nucleophilic attack by water sequestered in the enzyme active site than C5′ of **5b**−**d**.[2e,f]

The mechanism of inactivation of AdoHcy hydrolase with oxime **5a** has recently been studied in greater detail.[31] It has been found that **5a** (and 4′,5′-didehydro-5′-*O*-methyladenosine) inactivates the enzyme in the same manner as fluorovinyl compound **C** and thus functions as a "proinhibitor" of Ado-5′-carboxaldehyde.[6] Incubation of the AdoHcy hydrolase apoprotein with **5a** generated Ado-5′-carboxaldehyde **23e** and its 4′-epimer **30**.[31] Inclusion of the NAD^+ cofactor afforded 3′-keto products that had HPLC profiles identical to those with radiolabeled 3′-keto-Ado-5′-carboxaldehydes generated from incubation of [8-^{3}H]**C** (the labeled fluorovinyl compound) with the NAD^+ form of AdoHcy hydrolase, and the rate of inhibition of the enzyme with **5a** was the same as for inhibitor-induced NAD^+ depletion.[31] Thus, inhibition of AdoHcy hydrolase by these oximes involves their enzyme-catalyzed hydrolysis to give Ado-5′-carboxaldehydes, which then inactivate the enzyme via the established type I mechanism.[6] This rationalizes why the parent 5′-carboxaldehydes **23e** and **30** are more potent inhibitors than their oximes **5a** and **28**. The more rapidly the "proinhibitor" is converted into the inhibitor (aldehyde) in the active site, the more potent the enzyme inhibitory activity.

Cytostatic Activity

Compounds were evaluated for cytostatic activity against murine leukemia L1210, murine mammary carinoma FM3A, and human lymphocyte Molt 4/clone 8 and CEM cells (Table 3). Only Ado-5′-carboxaldehyde oxime (**5a**) was markedly cytostatic against all cell lines included in this study. The *O*-(methyl, ethyl, and benzyl) oximes **5b**−**d** were 10−(>100)-fold less inhibitory to tumor cell proliferation. The arabinosyl (**13b**) and 2′-deoxy (**20b**) oxime compounds were 4−5-fold less cytostatic than **5a**, whereas the 3′-deoxy (cordycepin) oxime analogue **20a** was very weakly cytostatic (IC_{50} 180−200 μg/mL). Ado-5′-carboxaldehyde (**23e**) and its 2′-deoxy analogue **23b** were cytostatic with efficacies comparable to those of **13b** and **20b**, whereas the 3′-deoxy (**23a**) and arabinosyl (**12**) 5′-carboxaldehydes were weakly inhibitory.

Antiviral Activity

Only **5a** (EC_{50} 0.25−0.30 μg/mL against cytomegalovirus), **20b** (EC_{50} 0.6−1 μg/mL against cytomegalovirus), and **5d** (EC_{50} 2 μg/mL against vaccinia virus) had significant anti-DNA virus activity (Table 4). Low anti-CMV selectivity index values of 2−3 and 14−25, respectively, result since **5a** and **20b** were also the most toxic to HEL cell proliferation. Compounds **12**, **13b**, and **20a** showed moderate activity against vaccinia virus and cytomegalovirus, respectively. The compounds were inactive against vesicular stomatitis virus (VSV), Sindbis virus, Coxsackie virus B4, parainfluenzavirus-3, reovirus-1, and Punta Toro virus in Vero cell cultures (Tables 5 and 6). Compounds **5a**−**d** were inactive against VSV, Coxsackie virus B4, and RSV in HeLa cell cultures (Table 6). Interestingly, **5a**−**c** were quite active against influenza A and B in MDCK cell cultures (EC_{50} 0.8−4 μg/mL), but their marked toxicity to MDCK cells resulted in low selectivity index values of 1 (**5a**), 5−25 (**5b**), and 3−5 (**5c**). Compound **5d** (selectivity index 5) was less toxic to MDCK cells but also 5−20-fold less inhibitory to influenza A and B.

In summary, we have employed four procedures to obtain nucleoside 5′-carboxaldehyde derivatives [Moffatt oxidation, Dess−Martin oxidation, hydrolysis of 5′-(α-fluoro thioethers), and acid-catalyzed trans-oximation]. The 5′-carboxaldehyde analogues have been converted to their oximes by standard procedures. Ado-5′-carboxaldehyde oxime is a potent inhibitor of AdoHcy hydrolase and is cytotoxic against several tumor cell lines. The *O*-alkyloximes investigated had lower activities. Removal of the 2′-hydroxyl group (2′-dAdo derivatives) or 2′-epimerization (AraA derivatives) resulted in reduced activity, whereas removal of the 3′-hydroxyl (3′-dAdo derivatives) abolished activity. These trends are in harmony with a mode of action involving binding in the enzyme active site (ribo *cis*-glycol unit required for good binding), enzyme-catalyzed hydrolysis of oximes to give active aldehyde inhibitors, and oxidation at C3′ to give 3′-keto derivatives with concomitant reduction of the NAD^+ cofactor to give inactive, tightly bound NADH forms (type I inhibition). It appears that the 3′-hydroxyl group is essential for adequate binding, as well as for the mandatory oxidation to produce type I inhibition.

Experimental Section

Uncorrected melting points were determined with a capillary apparatus. UV spectra of solutions in MeOH were recorded on a Hewlett Packard 8951 spectrophotometer. NMR spectra [^{1}H (200 MHz, Table 7) and ^{13}C (50 MHz, Table 8)] of solutions in Me_2SO-d_6 unless otherwise noted were recorded on a Varian Gemini-200 spectrometer. Low- and high-resolution electron-impact and chemical ionization (CI) mass spectra (MS) were obtained with a Finnigan MAT 8430 instrument.

Table 4. Anti-DNA Virus Activity of Adenine Nucleoside 5′-Carboxaldehyde and Oxime Analogues in E_6SM and HEL Cell Cultures

	EC_{50}[a] (μg/mL)								
	HSV-1	HSV-2	HSV-1 (TK$^-$)		CMV				
compd	KOS	G	B2006	VMW 1837	AD-169	Davis	VV	MIC[b] (E_6SM)	CC_{50}[c] (HEL)
5a	>4	>4	>4	>4	0.25	0.30	>4	7	0.7
5b	>200	>200	>200	>200	>10	>10	100	400	>50
5c	>200	>200	>200	>200	>10	>4	100	≥200	>50
5d	>40	>40	>40	>40	>10	>10	2	100	33
12	300	>400	>400	>400	>40	>40	20	>400	>50
13b	70	>100	70	>100	>10	≥10	20	≥200	34
20a	>400	>400	>400	>400	10	40	300	>400	>50
20b	>100	>100	>100	>100	0.6	1	>100	200	14
23a	>400	>400	>400	>100	>40	>40	>400	>400	>50
23b	>400	>400	>400	>400	>40	>40	>400	>400	>50
23e	>400	>400	>400	>400	>40	>40	70	>400	>50
BVDU	0.04	>400	10	>400	>40	>40	0.7	>400	>40
C-c^{3}Ado	>400	>400	40	>400			0.7	>400	
(*S*)-DHPA	>400	>400	>400	>400			20	>400	

[a] 50% effective concentration (concentration of compound required to reduce virus-induced cytopathicity by 50%). [b] Minimal inhibitory concentration (concentration of compound required to effect a microscopically visible change of cell morphology). [c] 50% cytostatic concentration (concentration of compound required to inhibit HEL cell proliferation by 50%).

Table 5. Anti-RNA Virus Activity of Adenine Nucleoside 5′-Carboxaldehyde and Oxime Analogues in Vero Cell Cultures[a]

	EC_{50}[a] (μg/mL) Vero				
compd	VSV	Sindbis	Coxsackie virus B4	para-influenza-3	reo-virus-1
5a	>1	>0.4	>0.4	>1	>1
5b	150	>100	>100	>100	>100
5c	>200	>100	>100	>100	>100
5d	>40	>100	>100	>100	>100
12	>400	>200	>200	150	300
13b	>100	>40	>40	>40	>40
20a	>400	>400	>400	>400	300
20b	>100	>100	>100	>100	>100
23a	≥400	>200	>200	>400	>200
23b	>400	>200	>200	70	>200
23e	300	>200	>200	>200	>200
BVDU	>400	>400	>400	>400	>400
C-c^{3}Ado	0.7	4	>400	0.2	4
(*S*)-DHPA	20	>400	>400	70	70

[a] 50% effective concentration (concentration of compound required to reduce virus-induced cytopathicity by 50%).

Elemental analyses were determined by M-H-W Laboratories, Phoenix, AZ. Reagents and solvents were of reagent quality, and solvents were purified and dried before use. "Diffusion crystallization" was performed with the noted solvent combinations as described.[32] TLC was performed on Merck Kieselgel 60 F_{254} sheets with S_1 (EtOAc/*i*-PrOH/H_2O, 4:1:2, upper layer), S_2 (MeOH/$CHCl_3$, 1:6), and S_3 (EtOAc/MeOH, 12:1) with sample observation under 254 nm light. Column chromatography was performed with Merck Kieselgel 60 (230−400 mesh). Preparative and analytical RP-HPLC were performed with a Spectra Physics SP 8800 ternary pump system and Dynamax C_{18} columns. "Oximes" refer to the *E*/*Z* mixtures, and the "unstable" carboxaldehydes can be stored as amorphous glasses (or in aqueous solutions for a few days) after RP-HPLC purification. Some undergo decomposition and become colored with time. General procedures A−D are illustrated with specific compounds but can be applied to different syntheses as noted throughout the Experimental Section.

Procedure A. 6-*N*-Benzoyl-9-(2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanosyl)adenine Oximes [3a(*E*/*Z*)]. NH_2OH·HCl (521 mg, 7.5 mmol) was added to a solution of carboxaldehyde **2** [prepared[16a] from 320 mg (0.75 mmol) of **2** hydrate] in pyridine (15 mL) under N_2 at ambient temperature, and stirring was continued for 14 h. Volatiles were evaporated, the residue was partitioned (1% AcOH/H_2O// $CHCl_3$), and the aqueous layer was extracted (3 × $CHCl_3$). The combined organic phase was washed ($NaHCO_3$/H_2O, brine), dried ($MgSO_4$), concentrated, and chromatographed (2% → 4% MeOH/EtOAc) to give **3a**(*E*) (90 mg, 28%), **3a** (*E*/*Z* ∼1:1; 108 mg, 34%) [MS *m*/*z* 424 (2, M^+), 406 (20, M − 18), 377 (100)], and **3a** (*E*/*Z* ∼2:5; 15 mg, 5%). Further elution gave **4a** (*E*/*Z* ∼9:1; 19 mg, 8%): MS *m*/*z* 320 (62, M^+), 303 (26, M − 17), 164 (100). Similar yields and ratios of **3a**(*E*/*Z*) and **4a**(*E*/*Z*) were obtained beginning with the **2** hydrate.[16a]

Procedure B. 9-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)-adenine Oximes (Adenosine-5′-carboxaldehyde Oximes) [5a(*E*/*Z*)]. Method A. The 6-*N*-benzoyl group was removed by addition of NH_3/MeOH [20 mL, saturated at ∼0 °C (ice bath)] to a solution of **3a** (*E*/*Z* 3:1; 127 mg, 0.3 mmol) in MeOH (5 mL) at ∼0 °C, and stirring was continued overnight at ambient temperature. Volatiles were evaporated to give **4a** (*E*/*Z* ∼3:1; 130 mg of white solid). The 2′,3′-*O*-isopropylidene group was removed by addition of CF_3CO_2H/H_2O (9:1, 5 mL) to the crude **4a** (130 mg), and stirring was continued at ∼0 °C for 1 h. Volatiles were evaporated, and the residue was coevaporated (EtOH), column chromatographed (EtOAc → EtOAc/S_1, 1:1), and crystallized (MeOH) to give **5a** (*E*/*Z* ∼3:1; 60 mg, 71%): mp 198−201 °C dec; UV max 260 (ε 14 300), min 230 nm (ε 3500); MS *m*/*z* 280 (12, M^+), 263 (8, M − 17), 178 (22), 164 (68), 136 (100, BH_2). Anal. ($C_{10}H_{12}N_6O_4$·0.5CF_3CO_2H) C,H,N. Analogous sequential deprotection of **3a**(*E*) (50 mg, 0.12 mmol) gave **5a**(*E*) (25 mg, 74%): mp 228−229 °C dec.

Procedure C. Method B. Oxidation[16a] (2 h, ambient

Table 6. Anti-RNA Virus Activity of Ado-5′-Carboxaldehyde Oxime Analogues in Vero, MDCK, and HeLa Cell Cultures

	EC_{50}[a] (μg/mL)								
	Vero	MDCK		HeLa			MIC[b]		
compd	Punta Toro	influenza A (Ishiwara)	influenza B (Singapore)	VSV	Coxsackie B4	RSV	Vero	HeLa	MDCK
5a	>0.4	0.8	≥0.8	>4	>40	<4	≥1	≥4	0.8
5b	>100	0.8	4.0	>200	>200	>200	≥200	≥200	20
5c	>100	0.8	1.2	>200	>200	>200	≥200	≥200	4
5d	>100	20	20	>200	>200	>200	≥200	≥200	100

[a] 50% effective concentration (concentration of compound required to reduce virus-induced cytopathicity by 50%). [b] Minimal inhibitory concentration (concentration of compound required to effect a microscopically visible change of cell morphology).

Table 7. ^{1}H NMR Spectral Data[a,b]

compd	H1′ [c] ($J_{1'-2'}$)	H2′ [d] ($J_{2'-3'}$)	H3′ [d] ($J_{3'-4'}$)	H4′ [d] ($J_{4'-5'or5'',5''}$)	H5′ [c] or H5′,5″ [d] ($J_{5'-5''}$)	N−OR[e]	NH[e] or NH_2[e]	H2[f]	H8[f]	others[f]
3a(*E*)[g]	6.21 (1.0)	5.61 (5.9)	5.26 (2.1)	4.83 (4.7)	7.33	10.15	9.25	8.11	8.73	1.40, 1.60 (CH_3's), 7.40−7.60,[h] 7.97[c] (Bz)
3a(*Z*)[g,i]	6.18 (1.0)	5.50 (5.7)	5.30−5.37[h]	5.30−5.37[h] (4.2)	6.26	10.80	9.30	8.11	8.71	1.40, 1.62 (CH_3's), 7.38−7.60,[h] 7.98[c] (Bz)
3b(*E*)[g,i]	6.20 (1.4)	5.58 (6.1)	5.38 (2.7)	4.87 (5.9)	7.33	3.75	9.00	8.06	8.78	1.40, 1.61 (CH_3's), 7.42−7.61,[h] 8.00[c] (Bz)
3b(*Z*)[g,i]	6.15 (1.5)	5.58 (6.1)	5.27−5.33[h]	5.27−5.33[h] (4.6)	6.48	3.93	9.00	8.07	8.76	1.40, 1.61 (CH_3's), 7.42−7.61,[h] 8.00[c] (Bz)
3c(*E*)[g,i]	6.17 (1.4)	5.51 (6.0)	5.34 (2.5)	4.83 (6.1)	7.32	3.95,[j] 1.10[k] (7.0[l])	9.38	8.02	8.68	1.38, 1.58 (CH_3's), 7.40−7.58,[h] 7.96[c] (Bz)
3c(*Z*)[g,i]	6.11 (1.5)	5.53 (6.0)	5.23 (2.1)	5.27 (4.6)	6.44	4.12,[j] 1.21[k] (7.0[l])	9.46	8.03	8.65	1.38, 1.58 (CH_3's), 7.40−7.58,[h] 7.96[c] (Bz)
4a(*E*)	6.25 (1.5)	5.50 (6.1)	5.28 (3.1)	4.65 (7.0)	7.34	11.14	7.38	8.17	8.27	1.33, 1.54 (CH_3's)
4a(*Z*)[i]	6.27 (1.2)	5.50 (6.1)	5.13−5.21[h]	5.13−5.21[h] (4.72)	6.33	11.37	7.37	8.15	8.31	1.33, 1.53 (CH_3's)
4d(*E*)[g,i]	6.11 (1.4)	5.53 (6.1)	5.36 (2.6)	4.85 (6.2)	7.45	4.97 7.23−7.39[h]	5.67	7.80	8.30	1.40, 1.60 (CH_3's)
4d(*Z*)[g,i]	6.07 (1.5)	5.53 (6.1)	5.28 (2.1)	5.34 (4.6)	6.53	5.16 7.23−7.39[h]	5.67	7.82	8.22	1.40, 1.60 (CH_3's)
5a(*E*)	5.94 (5.4)	4.75[m] (4.7)	4.35[m] (4.1)	4.40 (7.4)	7.62	11.08	7.32	8.30	8.52	5.53[c] (5.2,[n] OH3′), 5.61[c] (5.8,[n] OH2′)
5a(*Z*)[i]	5.93 (7.4)	4.88[m] (4.4)	4.13[m] (1.5)	5.01 (5.5)	7.22	11.32	7.32	8.31	8.57	5.53[c] (5.2,[n] OH3′), 5.63[c] (5.8,[n] OH2′)
5b(*E*)[i,o]	5.94 (5.5)	4.75[m] (4.6)	4.32[m] (3.8)	4.37 (7.3)	7.71	3.78	7.35	8.17	8.38	5.58[c] (5.0,[n] OH3′), 5.64[c] (5.9,[n] OH2′)
5c(*E*)[i,p]	5.95 (5.5)	4.76[m] (4.7)	4.34[m] (3.8)	4.38 (7.4)	7.70	4.04,[j] 1.17[k] (7.0[l])	7.35	8.18	8.38	5.58[c] (5.1,[n] OH3′), 5.63[c] (5.9,[n] OH2′)
5d(*E*)[i,q]	5.94 (5.7)	4.75[m] (4.6)	4.33[m] (3.8)	4.38 (7.5)	7.80	5.06 7.27−7.40[h]	7.35	8.16	8.36	5.59[c] (5.1,[n] OH3′), 5.64[c] (6.0,[n] OH2′)
12[r]	6.38 (4.4)	4.41−4.49[h]	4.41−4.49[h] (4.7)	3.92 (5.2)	5.28			8.16	8.30	
13b(*E*)[i]	6.33 (4.6)	3.96−4.34[h]	3.96−4.34[h]	3.96−4.34[h] (7.9)	7.58	11.05	7.30	8.16	8.20	5.82−5.90[h] (OH2′,3′)
13b(*Z*)[i]	6.39 (2.6)	3.96−4.34[h]	3.96−4.34[h]	4.92[c] (5.1)	7.08	11.18	7.30	8.16	8.35	5.82−5.90[h] (OH2′,3′)
15c[g,s]	6.19 (1.5)	5.68[h] (5.6)	2.71[m] (9.9)	4.45−4.58[h] (3.3, 4.0)	4.03, 3.77 (11.6)		8.90	8.30	8.65	1.02 (*t*-Bu), 2.14, 2.62 (Ac's), 7.25−7.65[h] (Ph's)
16c[g,t]	6.16 (1.5)	5.66[h] (5.8)	2.69[m] (10.0)	4.43−4.55[h] (3.3, 3.8)	4.02, 3.77 (11.6)		5.85	8.12	8.31	1.06 (*t*-Bu), 2.13 (Ac), 7.28−7.65[h] (Ph's)
17c[u]	6.18 (1.9)	5.64[h] (6.3)	2.54[m] (9.8)	4.31−4.43[h] (3.4, 4.4)	3.68,[m] 3.52[m] (12.2)		10.80	8.78	8.80	2.06, 2.25 (Ac's), 5.08[k] (5.5,[v] OH5′)
18c[w]	6.07 (2.3)	5.62[h] (6.6)	2.52[m] (9.3)	4.30−4.43[h] (3.4, 4.4)	3.65,[m] 3.49[m] (12.2)		7.32	8.17	8.36	2.04 (Ac), 5.15[k] (5.3,[v] OH5′)
20a(*E*)[i,x]	5.95 (1.8)	4.73[h] (5.1)	2.52[m] (9.6)	4.81[m] (7.3)	7.56	11.08	7.30	8.18	8.29	5.81[c] (4.2,[n] OH2′)
20b(*E*)[i,y]	6.40[k] (6.8)	2.93[m] (5.6)	4.56[h] (3.0)	4.37 (7.6)	7.57	11.07	7.30	8.19	8.38	5.61[c] (4.3,[n] OH3′)
23a[r]	6.04 (2.8)	4.72−4.79[h]	2.10−2.48[h] (also 3″)	4.42−4.50[h] (4.2)	5.12			8.21	8.31	
23b[r]	6.52[k] (7.1)	2.45−2.90[h] (also 2″)	4.61−4.72[h]	4.02−4.07[h] (3.7)	5.15			8.26	8.37	
28(*E*)[i,z]	5.99 (6.6)	4.92−5.02[h]	4.21−4.27[h]	4.92−5.02[h] (8.0)	7.37	11.12	7.35	8.30	8.62	5.20−5.70[e] (OH2′,3′)
32	5.88 (6.9)	5.04[m] (4.1)	4.14−4.20[h]	4.42−4.51[h] (5.1, 6.4)	3.67,[m] 3.53[m] (11.0)		7.30	8.18	8.39	4.64[k] (5.7,[s] OH5′) 5.12[c] (4.0,[n] OH3′) 5.46[c] (6.9,[n] OH2′)

[a] Chemical shifts (δ) in Me_2SO-d_6 at 200 MHz (unless otherwise noted). [b] "Apparent" first-order coupling constant (Hz, in parentheses). [c] Doublet (unless otherwise noted). [d] Doublet of doublets (unless otherwise noted). [e] Broad singlet. [f] Singlet (unless otherwise noted). [g] In $CDCl_3$. [h] Multiplet. [i] From mixture of *E* and *Z* isomers (assignments based on integration). [j] Quadruplet. [k] Triplet. [l] $J_{CH_3-CH_2}$. [m] Doublet of doublets of doublets. [n] J_{CH-OH}. [o] Minor **5b**(*Z*) had δ 7.32[c] ($J_{5'-4'}$ = 5.6 Hz, H5′). [p] Minor **5c**(*Z*) had δ 7.32[c] ($J_{5'-4'}$ = 5.5 Hz, H5′). [q] Minor **5d**(*Z*) had the H5′ signal in the aromatic proton envelope δ 7.30−7.40.[h] [r] In D_2O. [s] Also δ 2.15[m] ($J_{3''-3'}$ = 13.9 Hz, $J_{3''-2'}$ = 1.7 Hz, $J_{3''-4'}$ = 5.6 Hz, H3″). [t] Also δ 2.07−2.19[h] ($J_{3''-3'}$ = 13.9 Hz, H3″). [u] Also δ 2.13[m] ($J_{3''-3'}$ = 14.1 Hz, $J_{3''-2'}$ = 1.9 Hz, $J_{3''-4'}$ = 5.9 Hz, 1, H3″). [v] $J_{CH_2-OH_5}$. [w] Also δ 2.11[m] ($J_{3''-3'}$ = 13.8 Hz, $J_{3''-2'}$ = 2.4 Hz, $J_{3''-4'}$ = 6.3 Hz, H3″). [x] From *E*/*Z* ~90:10. Also δ 2.14[m] ($J_{3''-3'}$ = 13.3 Hz, $J_{3''-2'}$ =1.9 Hz, $J_{3''-4'}$ = 5.9 Hz, H3″); minor *Z* isomer had δ 7.07[c] ($J_{5'-4'}$ = 5.1 Hz, 0.10, H5′). [y] From *E*/*Z* 83:17. Also δ 2.36[m] ($J_{2''-2'}$ = 13.5 Hz, $J_{2''-1'}$ = 6.3 Hz, $J_{2''-3'}$ = 3.7 Hz, 1, H2″); minor *Z* isomer had δ 7.12[c] ($J_{5'-4'}$ = 5.6 Hz, 0.17, H5′). [z] From *E*/*Z* ~70:30. Minor *Z* isomer had δ 6.75[c] ($J_{5'-4'}$ = 4.6 Hz, 0.3, H5′).

temperature) of **1** (206 mg, 0.5 mmol) with DMSO (3 mL)/DCC (3.5 equiv)/Cl_2CHCO_2H (0.5 equiv) gave carboxaldehyde **2**. Pyridine (1 mL) and NH_2OH·HCl (347 mg, 5 mmol) were added, and stirring was continued at ambient temperature overnight. Volatiles were evaporated, the precipitated dicyclohexylurea (DCU) was filtered, and the solution was processed as described in procedure A. Column chromatography (2% MeOH/$CHCl_3$) gave **3a** (*E*/*Z* ~3:2; 172 mg, 81%) plus the more polar **4a** (*E*/*Z* ~3:2; 8 mg, 5%). Treatment of **3a** by procedure B gave a light yellow solid. Chromatography [EtOAC → EtOAc/S_1 (1:1)] and crystallization (MeOH) gave **5a** (*E*/*Z* ~11:2; 74 mg, 53% from **1**): mp 218−221 °C; UV max 259 (ϵ 14 500), min 228 nm (ϵ 3500). The mother liquor was concentrated and diffusion crystallized (MeOH/EtOAc) to give **5a** (*E*/*Z* ~7:3; 20 mg, 14%).

9-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)adenine *O*-Me-

Table 8. ^{13}C NMR Spectral Data[a,b]

compd	C2	C4	C5	C6	C8	C1′	C2′[c]	C3′[c]	C4′	C5′
5a(*E*/*Z*)[d]	153.66	149.61[c]	119.27	159.20	141.49	87.99	73.36	72.72	82.03	148.02[c]
	153.83	148.72[c]	119.60	158.53	142.21	87.32	73.27	73.08	79.02	149.26[c]
5b(*E*)[e,f]	153.05	149.67	119.40	156.31	140.35	87.96	72.88	72.78	81.37	149.03
5c(*E*)[e,g]	153.06	149.69	119.50	156.30	140.30	87.88	72.91	72.78	81.50	148.71
5d(*E*)[e,h]	153.07	149.55[c]	119.36	156.29	140.29	87.90	72.90	72.76	81.40	149.68[c]
8	152.92	149.66	118.41	155.85	139.62	86.97	75.13[c]	73.08	80.48	76.86[c]
9a[i]	152.82	149.46	118.17	155.84	140.79	83.94[c]	77.94	75.36	82.86[c]	36.05
12[j]	153.39	149.99	119.75	156.60	141.98	88.37	77.09	76.92	86.32	90.41
13b(*E*/*Z*)[d]	153.72	149.51[c]	118.36	159.17	142.05	84.71	78.37	75.42	81.77	148.53[c]
	153.72	150.84[c]	119.98	158.51	142.29	85.94	79.21	74.32	80.02	149.09[c]
20a(*E*)[e]	152.93	149.21	119.19	156.13	139.31	91.10	74.71	37.25	77.41	149.01
20b(*E*)[e]	152.87	149.28	119.80	156.13	140.08	84.39	*k*	73.08	84.05	148.41
32	150.81	149.50	119.00	154.33	141.46	87.84	74.95	70.95	82.75	60.05

[a] Chemical shifts (δ) in Me_2SO-d_6 at 50 MHz. [b] Proton-decoupled singlets. [c] Assignments may be reversed. [d] From *E*/*Z* mixture (tentatively assigned by peak intensities with *E* isomer in upper row). [e] From *E*/*Z* mixture (only major *E* isomer listed). [f] Peak also at δ 61.48 (MeO). [g] Peaks also at δ 14.31, 69.02 (EtO). [h] Peaks also at δ 75.39 (CH_2O), 128.18, 128.45, 128.67, 137.71 (Ph). [i] Peak also at δ 15.87 (CH_3S). [j] In D_2O (Me_2SO-d_6 as internal standard, δ 39.5). [k] Peak for C2′ in Me_2SO-d_6 envelope (δ 39.0−40.2).

thyloximes [5b(*E*/*Z*)]. Treatment of **2**[16a] (500 mg, 1.22 mmol) with CH_3ONH_2·HCl (713 mg, 8.5 mmol; 8 h) by procedure A gave a light yellow solid that was column chromatographed (2% MeOH/$CHCl_3$) to give **3b** (*E*/*Z* ~3:1; 210 mg, 39%) [MS *m*/*z* 438 (100, M^+), 409 (82)] plus the more polar **4b** (*E*/*Z* ~2:1; 180 mg, 39%). [The ^1H NMR spectrum ($CDCl_3$) of **4b** was similar to that of **3b** except for isomer ratios: δ 7.38 (d, $J_{5'-4'}$ = 6.3 Hz, 0.67, H5′(*E*)), 6.48 (d, $J_{5'-4'}$ = 4.7 Hz, 0.33, H5′(*Z*)); MS *m*/*z* 334 (100, M^+).] Treatment of **3b** (*E*/*Z* ~3:1; 150 mg, 0.34 mmol) by procedure B and crystallization (MeOH) gave **5b** (*E*/*Z* ~9:1; 70 mg, 70%): mp 115−117 °C; UV max 260 (ϵ 14 700), min 230 nm (ϵ 3900); MS *m*/*z* 294 (70, M^+), 263 (41, M − OCH_3), 164 (71), 136 (100, BH_2). Anal. ($C_{11}H_{14}N_6O_4$) C,H,N. Analogous treatment of **2** hydrate gave **3b** and **4b** with similar ratios and yields. The **3b**/**4b** mixture can be subjected directly to procedure B.

9-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)adenine *O*-Ethyloximes [5c(*E*/*Z*)]. Treatment of **2**[16a] (500 mg, 1.22 mm) with $EtONH_2$·HCl (714 mg, 7.32 mmol; 12 h) by procedure A [chromatography (EtOAc → 2% MeOH/EtOAc)] gave *N*-ethoxybenzamide followed by **3c** (*E*/*Z* ~3:1; 270 mg, 49%) [MS *m*/*z* 452 (100, M^+), 423 (78, M − 28), 348 (88), 303 (62)] plus the more polar **4c** (*E*/*Z* ~2:1; 102 mg, 24%). [The ^1H NMR spectrum ($CDCl_3$) of **4c** was similar to that of **3c** except for isomer ratios: δ 7.42 (d, $J_{5'-4'}$ = 6.3 Hz, 0.66, H5′(*E*)), 6.47 (d, $J_{5'-4'}$ = 4.7 Hz, 0.34, H5′(*Z*)); MS *m*/*z* 348 (100, M^+), 303 (64).] Treatment of **3c** (*E*/*Z* ~3:1; 200 mg, 0.44 mmol) by procedure B and crystallization (MeOH) gave **5c** (*E*/*Z* ~9:1; 103 mg, 76%; two crops): mp 144−147 °C; UV max 260 (ϵ 14 300), min 231 nm (ϵ 4400); MS *m*/*z* 308 (34, M^+), 263 (28, M − OC_2H_5), 164 (52), 135 (100, BH). Anal. ($C_{12}H_{16}N_6O_4$) C,H,N.

9-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)adenine *O*-Benzyloximes [5d(*E*/*Z*)]. Treatment of **2**[16a] (409 mg, 1 mmol) with $BnONH_2$·HCl (1.12 g, 7 mmol; 14 h) by procedure A gave **3d** (*E*/*Z* ~4:1; 200 mg, 39%) plus the more polar **4d** (*E*/*Z* ~3:1; 180 mg, 44%) [MS *m*/*z* 410 (46, M^+), 289 (100)]. [The ^1H NMR spectrum ($CDCl_3$) of **4d** was similar to that of **3d** except for isomer ratios: δ 7.41 (d, $J_{5'-4'}$ = 6.2 Hz, 0.80, H5′(*E*)), 6.52 (d, $J_{5'-4'}$ = 4.4 Hz, 0.20, H5′(*Z*)); MS *m*/*z* 514 (90, M^+), 393 (100), 289 (66).] Treatment of **4d** (*E*/*Z* ~3:1; 140 mg, 0.34 mmol) with CF_3CO_2H/H_2O by procedure B gave a colorless solid that was crystallized (MeOH) directly to give **5d** (*E*/*Z* ~11:1; 73 mg, 58%). The mother liquor was concentrated, chromatographed ($CHCl_3$ → 5% MeOH/$CHCl_3$), and diffusion crystallized (EtOH/EtOAc) to give additional **5d** (*E*/*Z* ~19:1; 25 mg, 20%): mp 153−154 °C; UV max 258 (ϵ 14 700), min 232 nm (ϵ 5300); MS (CI, CH_4) *m*/*z* 371 (100, MH^+), 136 (92, BH_2). Anal. ($C_{17}H_{18}N_6O_4$) C,H,N.

9-(5-*S*-Methyl-5-thio-β-D-arabinofuranosyl)adenine (9a). NaH (14 mg, 0.3 mmol; 50% in mineral oil, washed twice with dried Et_2O) was added to a suspension of $NaSCH_3$ (340 mg, 4.62 mmol; Aldrich 95% reagent) in dried DMF (30 mL) under N_2 at ambient temperature, and stirring was continued for 15 min. The solution was cooled (−20 °C), and 9-(5-chloro-5-deoxy-β-D-arabinofuranosyl)adenine[18] [**6**; 1.2 g, 4.20 mmol; R_f 0.47 (S_2), 0.45 (S_1)] was added. After 2 h, the mixture was allowed to warm to ambient temperature, stirred for 10 h, and evaporated (<30 °C, in vacuo). The residue was adsorbed (silica gel, ~3 g), applied to a silica gel column, and chromatographed (2% → 10% MeOH/$CHCl_3$) to give 9-(2,5-anhydro-β-D-arabinofuranosyl)adenine [**8**; 271 mg, 26% after crystallization (MeOH): mp 275−277 °C dec (lit.[21] mp 220 °C dark, 300 °C dec); UV max 259 (ϵ 14 800), min 228 nm (ϵ 2300); MS (CI, CH_4) *m*/*z* 250 (100, MH^+); R_f 0.56 (S_2), 0.36 (S_1); ^1H NMR data as reported[21]] plus the more polar **9a** [587 mg, 46% after crystallization (H_2O/MeOH, ~4:1): mp 198−200 °C dec (lit.[20] mp 202−204 °C); MS *m*/*z* 297 (4, M^+), 282 (8, M − CH_3), 250 (22, M − SCH_3), 194 (74), 164 (100), 136 (95, BH_2); R_f 0.49 (S_2), 0.44 (S_1); other data as reported[20]].

9-(β-D-*arabino*-Pentodialdo-1,4-furanosyl)adenine (12). Dried pyridine (8 mL) was added to a suspension of **9a** (356 mg, 1.2 mmol) in Ac_2O (0.453 mL, 490 mg, 4.8 mmol) at ~0 °C (ice−H_2O bath), and stirring was continued for 8 h (~0 °C). MeOH (10 mL) was added, stirring was continued for 30 min, and volatiles were evaporated. The residue was partitioned (1% HCl/H_2O//$CHCl_3$), and the organic phase was washed ($NaHCO_3$/H_2O, brine), dried ($MgSO_4$), and chromatographed ($CHCl_3$ → 2% MeOH/$CHCl_3$) to give **9b** (430 mg, 94%; TLC homogenous white solid): ^1H NMR ($CDCl_3$) δ 1.90, 2.18, 2.20 (3 × s, 3 × 3, 2 × Ac, SCH_3), 3.01 (d, $J_{5',5''-4'}$ = 5.1 Hz, 2, H5′,5″), 4.20−4.28 (m, 1, H4′), 5.45−5.51 (m, 2, H2′,3′), 6.25 (br s, 2, NH_2), 6.56 (d, $J_{1'-2'}$ = 4.3 Hz, 1, H1′), 8.10 (s, 1, H2), 8.38 (s, 1, H8); MS *m*/*z* 381 (3, M^+), 136 (100, BH_2).

DAST (0.165 mL, 201 mg, 1.25 mmol) was added to a solution of **9b** (200 mg, 0.52 mmol) and $SbCl_3$ (15 mg, 0.06 mmol) in dried CH_2Cl_2 (10 mL) under Ar at ambient temperature, and stirring was continued for 2.75 h. The mixture was poured into ice-cold, saturated $NaHCO_3$/H_2O and extracted ($CHCl_3$). The combined organic phase was washed (brine), dried ($MgSO_4$), and evaporated (<30 °C) to give **10** (5′*R*/*S* ~1:1.2)/**11** (~3.2:1, 250 mg) (yellow foam): ^{19}F NMR CCl_3F/$CDCl_3$ δ −164.24 (dd, $^2J_{F-5'}$ = 51.5 Hz, $^3J_{F-4'}$ = 11.3 Hz, 0.34, F5′*R*), −167.32 (dd, $^2J_{F-5'}$ = 51.5 Hz, $^3J_{F-4'}$ = 16.9 Hz, 0.42, F5′*S*), −185.49 (t, $^2J_{F-CH_2}$ = 54.3 Hz, 0.24, SCH_2F); MS *m*/*z* 399 (4, M^+), 385 (25), 164 (62), 136 (100, BH_2).

This mixture (250 mg) was treated immediately with saturated NH_3/MeOH (20 mL) at ~0 °C for 30 min, and volatiles were evaporated (<30 °C). The brown residue was dissolved (MeOH/H_2O, 1:3, 20 mL), and the solution was cooled (~0 °C, ice bath); CF_3CO_2H/H_2O (3:1, 4 mL) was added, and the mixture was stirred at ~0 °C for 2 h [TLC (S_1 and S_2) showed mainly the polar aldehyde **12**]. Volatiles were evaporated in vacuo, and the residue was coevaporated (2 × EtOH) to give a product that was dissolved (H_2O/CH_3CN, 3:1, 2 mL), filtered, and purified [RP-HPLC (20% CH_3CN/H_2O for 30 min followed by a gradient of 20% → 30% CH_3CN/H_2O for 30 min at a flow rate of 3.0 mL/min)]. Appropriate fractions (t_R 25−31 min) were evaporated, and the residue was dried in vacuo at ambient temperature to give hydrate **12** (65 mg, 44% from **9b**): mp 143−147 °C dec; UV max 259 (ϵ 13 300), min 229 nm

(ϵ 3000); MS (CI, CH_4) *m/z* 283 (8, M^+), 207 (100). Anal. ($C_{10}H_{13}N_5O_5 \cdot 1.5H_2O \cdot 0.1Et_2O$) C,H,N. ^{1}H NMR verified ~0.1 equiv of Et_2O.

9-(β-D-*arabino*-Pentodialdo-1,4-furanosyl)adenine Oximes [13b(*E/Z*)]. Method A. A suspension of **12** (71 mg, 0.25 mmol) in dried benzene (30 mL) was refluxed (10 min with a Dean−Stark trap), and volatiles were evaporated. The residue was dried in vacuo and dissolved in dried pyridine (5 mL) under Ar, and $NH_2OH \cdot HCl$ (261 mg, 3.75 mmol) was added. The mixture was stirred overnight at ambient temperature and heated (~40 °C, 2 h), and volatiles were evaporated. The residue was dissolved (MeOH, 10 mL), silica (~1 g) was added, volatiles were evaporated, and the impregnated silica was added to a silica gel column (packed in EtOAc). Elution [EtOAc → EtOAc/S_1 (1:1)] and crystallization (MeOH) gave **13b** (*E/Z* ~1:1.6; 18 mg, 26%): mp 156−159 °C dec; UV max 258 (ϵ 14 300), min 229 nm (ϵ 2600); MS *m/z* 280 (12, M^+), 263 (8), 262 (7), 164 (100), 135 (88, BH). Anal. ($C_{10}H_{12}N_6O_4 \cdot 0.5H_2O$) C,H,N.

Method B. Oxidation of 9-(2,3-di-*O*-acetyl-β-D-arabinofuranosyl)adenine [**7**; 88 mg, 0.25 mmol; prepared[23] (68%, white foam) as described for **15c**/**16c** from AraA with TBDPSCl in place of TBDMSCl] and treatment of the 5′-carboxaldehyde with $NH_2OH \cdot HCl$ by procedure C gave the 2′,3′-di-*O*-acetyl oximes **13a** (*E/Z* ~2:1; 48 mg, ~45%) [^{1}H NMR ($CDCl_3$) δ 7.07 (d, $J_{5'-4'}$ = 7.5 Hz, 0.66, H5′(*E*)), 6.58 (d, $J_{5'-4'}$ = 4.4 Hz, 0.33, H5′(*Z*)); MS *m/z* 364 (10, M^+), 135 (100, BH)]. This material was dissolved (MeOH, 5 mL) and treated with saturated NH_3/MeOH (10 mL) at ~5 °C for 2 h. Volatiles were evaporated, and the residue was chromatographed [EtOAc → EtOAc/S_1 (1:1)] and diffusion crystallized (MeOH/EtOAc) to give **13b** (*E/Z* ~1:1; 12 mg, 17% from **7**): mp 157−159 °C. The mother liquor was concentrated to give 10 mg (14%) of **13b** (*E/Z* ~3:2): mp 154−156 °C.

6-*N*-Acetyl-9-[2-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]adenine (15c) and 9-[2-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]adenine (16c). TBDPSCl (0.88 mL, 0.96 g, 3.3 mmol) was added to a suspension of 3′-deoxyadenosine (**14a**; 753 mg, 3 mmol) in dried pyridine (10 mL), and the mixture was stirred at ambient temperature for 24 h. TLC (S_2, S_3) showed the less polar 5′-*O*-TBDPS product and traces of **14a**. The mixture was cooled (~3 °C, ice bath), Ac_2O (0.8 mL, 865 mg, 8.5 mmol) was added, stirring was continued for 7 h, and MeOH (3 mL) was added. After 1 h, volatiles were evaporated, and the residue was partitioned (ice-cold 2% HCl/H_2O//$CHCl_3$). The organic phase was washed ($NaHCO_3/H_2O$, brine), dried ($MgSO_4$), and evaporated, and the residue was chromatographed ($CHCl_3$ → 2% MeOH/$CHCl_3$) to give **15c** [460 mg, 27%; MS (CI) *m/z* 574 (100, MH^+), 516 (44, M − 57)], **15c**/**16c** (~1:1; 380 mg, 24%), and **16c** [500 mg, 31%; MS (CI) *m/z* 532 (100, MH^+), 474 (38, M − 57)] of sufficient purity for use in subsequent reactions.

Procedure D. 6-*N*-Acetyl-2′-*O*-acetyl-3′-deoxyadenosine (17c). TBAF/THF (1 M, 1.0 mL, 1.0 mmol) was added to a solution of **15c** (400 mg, 0.7 mmol) in THF (20 mL) at ~5 °C, and stirring was continued for 2 h. Volatiles were evaporated, and the residue was partitioned ($NaHCO_3/H_2O$//$CHCl_3$). The aqueous layer was extracted ($CHCl_3$, 3 × 25 mL), and the combined organic phase was dried ($MgSO_4$), evaporated, and chromatographed ($CHCl_3$ → 5% MeOH/$CHCl_3$) to give **17c** (166 mg, 71%; white foam). Crystallization (EtOH) gave **17c**: mp 85−88 °C softened, 115−120 °C resolidified, 140−142 °C; UV max 271 (ϵ 15 100), min 231 nm (ϵ 2400); MS *m/z* 335 (80, M^+), 207 (92), 159 (100). Anal. ($C_{14}H_{17}N_5O_5$) C,H,N. Treatment of **15c** (120 mg, 0.21 mmol) with TFA/H_2O (9:1, 5 mL; 0 °C, 2 h) gave **17c** (48 mg, 68%) after similar workup and purification.

2′-*O*-Acetyl-3′-deoxyadenosine (18c). Method A. Treatment of **16c** (280 mg, 0.53 mmol) by procedure D (TBAF/THF), evaporation, and chromatography ($CHCl_3$ → 8% MeOH/$CHCl_3$) of the residue without aqueous workup gave **18c** (120 mg, 70%; white foam). Crystallization (MeOH) gave **18c**: mp 231−232 °C; UV max 259 (ϵ 14 100), min 226 nm (ϵ 2400); MS *m/z* 293 (18, M^+), 164 (42), 159 (100), 135 (32, BH). Anal. ($C_{12}H_{15}N_5O_4$) C,H,N.

Method B. A solution of **16c** (159 mg, 0.3 mmol) or **15c**/**16c** (~1:2; 164 mg, 0.3 mmol), NH_4F (167 mg, 4.5 mmol), and Dowex 50 × 8 (H^+) (200−400 mesh, ~0.8 g of dry resin) in MeOH (10 mL) was refluxed for 2.5 h. Chromatographic purification as in method A gave **18c** [70 mg (79%) or 60 mg (68%); white foam], respectively.

3′-*O*-Acetyl-2′-deoxyadenosine (18d). Treatment of 2′-deoxyadenosine (**14b**; 1.01 g, 4.0 mmol) with TBDPSCl and Ac_2O (as described for **15c/16c)** gave **16d** (1.61 g, 76%; white foam): MS *m/z* 531 (6, M^+), 474 (100, M − 57), 414 (84), 279 (35). Treatment of **16d** (700 mg, 1.32 mmol) by procedure D [TBAF/THF (1 M, 1.5 mL, 1.5 mmol; 1 h, ~0 °C)], evaporation of volatiles, and diffusion crystallization (MeOH/Et_2O) of the residue gave **18d** (286 mg, 74%; white crystals): mp 209−212 °C (lit.[24a] mp 203−207 °C); MS *m/z* 293 (8, M^+), 234 (16), 135 (100, BH). The mother liquor was evaporated and the residue worked up and chromatographed ($CHCl_3$ → 5% MeOH/$CHCl_3$) to give **18d** (69 mg, 18%; white solid).

9-(3-Deoxy-β-D-*erythro*-pentodialdo-1,4-furanosyl)adenine Oximes (3′-Deoxyadenosine-5′-carboxaldehyde Oximes) [20a(*E/Z*)]. Oxidation of **17c** (130 mg, 0.39 mm) and treatment with $NH_2OH \cdot HCl$ as described for **5a**(*E/Z*) (procedure C) and chromatography gave **19c** (*E/Z* ~7:3; 71 mg, 52%): ^{1}H NMR δ 2.15, 2.61 (2 × s, 2 × 3, Ac's), 2.35−2.95 (m, 2, H3′,3″), 5.03−5.15 (m, 0.7, H4′(*E*)), 5.47−5.56 (m, 0.3, H4′(*Z*)), 5.72−5.79 (m, 1, H2′), 6.12 (d, $J_{1'-2'}$ = 1.2 Hz, 0.3, H1′(*Z*)), 6.17 (d, $J_{1'-2'}$ = 1.0 Hz, 0.7, H1′(*E*)), 7.14 (d, $J_{5'-4'}$ = 4.6 Hz, 0.3, H5′(*Z*)), 7.65 (d, $J_{5'-4'}$ = 6.1 Hz, 0.7, H5′(*E*)), 8.14 (s, 0.3, H2), 8.23 (s, 0.7, H2), 8.70 (s, 1, H8), 9.35 (br s, 1, NH); MS *m/z* 348 (18, M^+), 178 (82, BH_2), 172 (95), 135 (100).

Further elution gave **19c** (*E/Z* ~3:2; 20 mg, 15%) contaminated (~15%) with **20c**. Combined product (91 mg) was dissolved in MeOH (5 mL) and treated with NH_3/MeOH (10 mL; 20 h, ambient temperature). Evaporation of volatiles, chromatography (EtOAc → S_1), and crystallization (MeOH) gave **20a** (*E/Z* ~9:1; 46 mg, 45% from **17c**): mp 229−232 °C dec; UV max 260 (ϵ 14 900), min 227 nm (ϵ 2600); MS *m/z* 264 (28, M^+), 247 (22, M − 17), 164 (74), 135 (100, BH). Anal. ($C_{10}H_{12}N_6O_3$) C,H,N. A second crop of **20a** (*E/Z* ~3:1; 8 mg, 8%) was obtained from the mother liquor. Oxidation of **18c** (100 mg, 0.34 mmol) with the Dess−Martin periodinane reagent, oximation, and deacetylation (as described for **20b**, method B; without aqueous workup) gave **20a** (37 mg, 41%).

9-(2-Deoxy-β-D-*erythro*-pentodialdo-1,4-furanosyl)adenine Oximes (2′-Deoxyadenosine-5′-carboxaldehyde Oximes) [20b(*E/Z*)]. Method A. Oxidation of **18d** (175 mg, 0.60 mmol) and oximation (procedure C), deacetylation (NH_3/MeOH; 2 h, ~5 °C), purification (as described for **20a**), and diffusion crystallization (MeOH/EtOAc//hexane) gave **20b** (*E/Z* ~5:1; 24 mg, 15% from **18d**): mp 167−169 °C; UV max 259 (ϵ 14 600), min 227 nm (ϵ 2700); MS *m/z* 264 (20, M^+), 247 (10), 164 (41), 162 (38), 135 (100, BH). Anal. ($C_{10}H_{12}N_6O_3 \cdot 0.6H_2O \cdot 0.1$EtOAc) C,H,N. EtOAc (~0.1 equiv) was verified by ^{1}H NMR. Major amounts of adenine were detected [TLC (S_1, S_2)] in the water layer (workup, procedure C), and it was necessary to back-extract the water layer (3 × $CHCl_3$, 3 × EtOAc) to recover **20d**.

Method B. A solution of **18d** (147 mg, 0.5 mmol) in dried CH_2Cl_2 (10 mL) was added to the Dess−Martin periodinane reagent[26] (424 mg, 1 mmol) in CH_2Cl_2 (5 mL) at ~0 °C (ice bath) under Ar, and stirring was continued at 0 °C for 1 h. The solution was allowed to warm to ambient temperature (90 min), and volatiles were evaporated. Dried pyridine (3 mL) and $NH_2OH \cdot HCl$ (70 mg, 5 mmol) were added to the oily residue, and the mixture was stirred at ambient temperature for 10 h. Volatiles were evaporated in vacuo, the residue was partitioned ($NaHCO_3/H_2O$//$CHCl_3$), and the water layer was extracted (3 × $CHCl_3$, 3 × EtOAc). The combined organic phase was dried ($MgSO_4$), evaporated, and chromatographed [EtOAc → EtOAc/S_1 (1:1)] to give **20d** (~70 mg) which was deacetylated (NH_3/MeOH, 15 mL; 1 h, ~5 °C), chromatographed (EtOAc → S_1), and diffusion crystallized (MeOH/EtOAc) to give **20b** (*E/Z* ~5.7:1; 24 mg, 18% from **18d**): mp 168−171 °C. RP-HPLC (preparative C_{18} column; 10% CH_3CN/H_2O for 20 min followed by a gradient of 10% → 40% CH_3-

CN/H_2O for 30 min at 3 mL/min; t_R 35−39 min) of the mother liquor gave 12 mg (9%) of **20b** (E/Z ∼4.5:1).

2′,5′-Dideoxy-5′,5′-(*N*,*N*′-diphenylethylenediamino)-adenosine (22b). Oxidation (1 h at 0 °C, 2 h at ambient temperature) of **18d** (147 mg, 0.5 mmol) with the Dess−Martin periodinane reagent (as described for **20b**, method B) was followed by stirring the crude 5′-carboxaldehyde with 1,2-dianilinoethane (159 mg, 0.75 mmol) for 1 h at ambient temperature and for 15 h at ∼5 °C. Volatiles were evaporated, and the residue was worked up by procedure D [unreacted **18d** was present (TLC, S_3) in the water layer] and chromatographed ($CHCl_3$ → 2% MeOH/$CHCl_3$) to give **22d** (87 mg, 36%): ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3, Ac), 2.36 (ddd, $J_{2''-3'}$ = 2.4 Hz, $J_{2''-2'}$ = 13.7 Hz, $J_{2''-1'}$ = 5.4 Hz, 1, H2″), 2.57 (ddd, $J_{2'-3'}$ = 6.5 Hz, $J_{2'-1'}$ = 8.7 Hz, 1, H2′), 3.56−3.85 (m, 4, CH_2-CH_2), 4.58−4.62 (m, 1, H4′), 5.55−5.62 (m, 1, H3′), 5.88 (s, 1, H5′), 6.11 (br s, 2, NH_2), 6.37 (dd, 1, H1′), 6.71−7.32 (m, 10, Arom), 7.49 (s, 1, H2), 8.32 (s, 1, H8); MS m/z 485 (2, M^+), 290 (21), 223 (100), 135 (40, BH). [Oxidation of **18d** (88 mg, 0.3 mmol) by procedure C, treatment with oxalic acid dihydrate, filtration of DCU,[16a] and analogous treatment of the mother liquor with 1,2-dianilinoethane gave **22d** (45 mg, 31%).]

Deacetylation (NH_3/MeOH, 10 mL; 2 h, ∼0 °C) of **22d** (97 mg, 0.2 mmol) and crystallization (MeOH) of the residue gave **22b** (60 mg, 67%): mp 128−132 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.10 (br s, 1, OH3′), 2.37−2.64 (m, 2, H2′,2″), 3.53−3.80 (m, 4, CH_2CH_2), 4.47 (dd, $J_{4'-3'}$ = 4.8 Hz, $J_{4'-5'}$ = 2.1 Hz, 1, H4′), 4.72−4.92 (m, 1, H3′), 5.61 (br s, 2, NH_2), 5.77 (d, 1, H5′), 6.38 (t, $J_{1'-2',2''}$ = 6.1 Hz, 1, H1′), 6.74−7.28 (m, 10, Arom), 7.48 (s, 1, H2), 8.28 (s, 1, H8); MS (CI) m/z 444 (20, MH^+), 223 (100), 135 (40, BH); HRMS (CI) m/z 444.2140 (100), calcd for MH^+ ($C_{24}H_{26}N_7O_2$) 444.2148.

9-(3-Deoxy-β-D-*erythro*-pentodialdo-1,4-furanosyl)-adenine (23a). Method A. Oximes **20a** (40 mg, 0.15 mmol) were dissolved in Me_2CO/H_2O (5:1, 6 mL), TFA (0.115 mL, 171 mg, 1.5 mmol) was added dropwise at ambient temperature, and stirring was continued overnight. TLC (S_1) showed that **20a** had been converted into more polar products that migrated faster than adenine. Evaporation of volatiles and purification of the residue by RP-HPLC (10% CH_3CN/H_2O for 30 min followed by a gradient of 10% → 30% CH_3CN/H_2O for 40 min at a flow rate of 2.7 mL/min; t_R 31−36 min) gave **23a** hydrate (16 mg, 40%). Trituration with Et_2O gave a white solid: mp 135−143 °C dec; UV max 260 (ϵ 10 600), min 227 nm (ϵ 1600); MS (CI) m/z 268 (14, MH^+ − hydrate), 250 (22, MH^+), 178 (81), 135 (100, BH).

Method B. Oxidation of **17c** (100 mg, 0.3 mmol) with the Dess−Martin periodinane reagent,[26] treatment of the 5′-carboxaldehyde with 1,2-dianilinoethane, deacetylation (NH_3/MeOH; 14 h, ∼0 °C), and chromatography (EtOAc → 4% MeOH/EtOAc) (as described for **22b**) gave **22a** (58 mg, 44%): ^{1}H NMR ($CDCl_3$) δ 1.95 (br s, 1, OH2′), 2.01−2.45 (m, 2, H3′,3″), 3.60−3.83 (m, 4, CH_2CH_2), 4.44−4.50 (m, 1, H4′), 4.96−5.05 (m, 1, H2′), 5.70 (br s, 2, NH_2), 5.80 (s, 1, H1′), 5.88 (s, 1, H5′), 6.72−7.38 (m, 10, Arom), 7.70 (s, 1, H2), 8.20 (s, 1, H8); MS (CI) m/z 444 (10, MH^+), 223 (100), 135 (15, BH). Treatment of **22a** (88 mg, 0.2 mmol) with TsOH·H_2O (as described for **23b**) and RP-HPLC purification gave **23a** hydrate (16 mg, 28%; white solid).

9-(2-Deoxy-β-D-*erythro*-pentodialdo-1,4-furanosyl)-adenine (23b). TsOH·H_2O (85 mg, 0.45 mmol) was added to a solution of **22b** (88 mg, 0.2 mmol) in CH_2Cl_2/Me_2CO (1:1, 10 mL) at ∼0 °C, and stirring was continued for 1 h. TLC (S_2) showed conversion of **22b** to more polar products. NH_3/MeOH was added dropwise (to pH ∼7), and volatiles were evaporated. Preparative RP-HPLC (10% CH_3CN/H_2O for 30 min, then a gradient of 10% → 25% CH_3CN/H_2O for 25 min at 2.8 mL/min) gave **23b** (t_R 38−43 min) contaminated with NH_4OTs. RP-HPLC (20% MeOH/H_2O for 40 min, then a gradient of 20% → 40% MeOH/H_2O; t_R 42−46 min) gave the unstable **23b** hydrate (12 mg, 21%; white solid, precipitated from CH_3CN and dried in vacuo at ambient temperature): mp 165−180 °C dec; UV max 260 (ϵ 10 100), min 228 nm (ϵ 3000); MS (CI) m/z 267 (3, MH^+), 135 (100, BH).

9-(β-D-*ribo*-Pentodialdo-1,4-furanosyl)adenine (Adenosine-5′-carboxaldehyde) (23e). Hydrolysis of oximes **5a** (56 mg, 0.2 mmol) in Me_2CO/H_2O/TFA and RP-HPLC purification (as described for **23a**, method A) gave **23e** hydrate (29 mg, 51%; white solid with data as reported[7]).

9-(2,3:5,6-Di-*O*-isopropylidene-β-D-gulofuranosyl)adenine (26). Adenine (594 mg, 4.4 mmol) was added to a solution of **25b** [1.21 g, 4 mmol; prepared from D-gulonic γ-lactone via **24** and **25a** as described[27] and acetylation (Ac_2O/DMAP/pyridine)] in dried CH_3CN (150 mL). $SnCl_4$ (2.29 g, 1.03 mL, 8.8 mmol) was added dropwise to the stirred suspension at ambient temperature. After 1 h, the resulting solution was heated (∼35 °C) for 2 h, stirred at ambient temperature for 14 h, refluxed for 3 h [TLC (S_1, S_2) showed two products with higher R_f values than adenine], and concentrated (∼10 mL). $NaHCO_3$ (∼3 g) and water (∼15 mL) were added (vigorous evolution of CO_2), and the emulsion was partitioned ($NaHCO_3/H_2O$//$CHCl_3$). The aqueous layer was extracted (3 × $CHCl_3$), and the combined organic phase was washed (NaCl/H_2O, brine), dried ($MgSO_4$), concentrated, and chromatographed (EtOAc → 30% S_1/EtOAc) to give **26** (450 mg, 30%; off-white solid): ^{1}H NMR δ 1.26, 1.28, 1.35, 1.51 (4 × s, 4 × 3, Me's), 3.75−3.82 (m, 1, H5′), 4.06−4.38 (m, 3, H4′,6′,6″), 5.22 (dd, $J_{3'-4'}$ = 3.5 Hz, $J_{3'-2'}$ = 5.8 Hz, 1, H3′), 5.43 (d, 1, H2′), 6.25 (s, 1, H1′), 7.38 (br s, 2, NH_2), 8.19 (s, 1, H2), 8.28 (s, 1, H8); MS m/z 377 (18, M^+), 362 (84, M − 15), 302 (61), 218 (100), 164 (72), 136 (86, BH_2); HRMS (CI) m/z 378.1767 (100), calcd for MH^+ ($C_{17}H_{24}N_5O_5$) 378.1777. Also eluted was 9-(2,3:5,6-di-*O*-isopropylidene-α-D-gulofuranosyl)-adenine (135 mg, 9%; off-white solid): ^{1}H NMR δ 1.25, 1.30, 1.38, 1.50 (4 × s, 4 × 3, Me's), 3.79−3.93 (m, 2, H6′,6″), 4.08−4.16 (m, 1, H4′), 4.31−4.43 (m, 1, H5′), 4.85 (dd, $J_{3'-4'}$ = 3.5 Hz, $J_{3'-2'}$ = 6.0 Hz, 1, H3′), 4.93 (dd, $J_{2'-1'}$ = 3.4 Hz, 1, H2′), 6.15 (d, 1, H1′), 7.33 (br s, 2, NH_2), 8.18 (s, 1, H2), 8.19 (s, 1, H8); MS m/z 377 (12, M^+), 362 (83, M − 15), 319 (100), 164 (84), 136 (50, BH_2).

9-(α-L-*lyxo*-Pentodialdo-1,4-furanosyl)adenine Oximes [28(*E*/*Z*)]. The aqueous eluent containing **29** [prepared as described for **32** from **27** (68 mg, 0.2 mmol)] was concentrated in vacuo (<30 °C), coevaporated (CH_3CN, 2 × 5 mL), and dissolved in dried pyridine (5 mL). NH_2OH·HCl (139 mg, 2 mmol) was added, and stirring was continued overnight at ambient temperature [TLC (S_1) showed less polar products]. Evaporation and deprotection (2 h, procedure B and RP-HPLC as for **20b**; precipitation from MeOH with CH_3CN) gave **28** (E/Z ∼7:3; 18 mg, 32%): mp 102−105 °C dec; UV max 258 (ϵ 12 800), min 230 nm (ϵ 3000); MS m/z 280 (12, M^+), 135 (100, BH); HRMS (CI) m/z 281.0995 (16), calcd for MH^+ ($C_{10}H_{13}N_6O_4$) 281.0998. Treatment of crude **30** with NH_2OH·HCl/pyridine gave **28** (∼15%), but treatment of the aqueous eluent containing **29** with NH_2OH·HCl/$NaHCO_3$/MeOH gave traces of oximes.

9-(α-L-*lyxo*-Pentodialdo-1,4-furanosyl)adenine (30). The aqueous eluent containing **29** [prepared as described for **32** from **27** (169 mg, 0.5 mmol)] was concentrated in vacuo (<30 °C) and treated with TFA/H_2O (4:1, 5 mL) at 0 °C (ice bath) for 2 h. Evaporation, coevaporation (EtOH), and RP-HPLC (as described for **20b**) gave **30** (43 mg, 33%; white solid with data as reported[7]).

9-(α-L-Lyxofuranosyl)adenine (32). Treatment of **27** [169 mg, 0.5 mmol; prepared by hydrolysis (AcOH/H_2O, 7:3) of **26** as described[27] and chromatography ($CHCl_3$ → 10% MeOH/$CHCl_3$)] with $NaIO_4/H_2O$ (0.5 M, 1.3 mL) and chromatography (Amberlite IR-45 resin)[27,29] gave **29**. $NaBH_4$ (303 mg, 8 mmol) was immediately added to the combined aqueous eluent, and the mixture was allowed to stand for 1 h at ambient temperature and worked up as described[27,29] to give **31** (80 mg, 52% from **27**; white foam): ^{1}H NMR δ 1.33, 1.48 (2 × s, 2 × 3, Me's), 3.57 (ddd, $J_{5''-5'}$ = 11.8 Hz, $J_{5''-4'}$ = 7.0 Hz, $J_{5',5''-OH5'}$ = 5.5 Hz, 1, H5″), 3.71 (ddd, $J_{5'-4'}$ = 4.5 Hz, 1, H5′), 4.31−4.39 (m, 1, H4′), 4.76 (t, 1, OH5′), 5.15 (dd, $J_{3'-4'}$ = 3.6 Hz, $J_{3'-2'}$ = 5.8 Hz, 1, H3′), 5.42 (d, 1, H2′), 6.18 (s, 1, H1′), 7.35 (br s, 2, NH_2), 8.18 (s, 1, H2), 8.28 (s, 1, H8); MS m/z 307 (8, M^+), 292 (28, M − 15), 218 (100), 135 (82, BH).

Treatment of **31** (61 mg, 0.2 mmol) with TFA/H_2O (9:1, 5 mL) by procedure B, RP-HPLC (as described for **20b**), and crystallization (MeOH, two crops) gave **32** (39 mg, 73%): mp 226−228 °C dec (lit.[27] mp 246−249 °C); UV max 259 (ϵ 13 500),

min 227 nm (ϵ 1500); MS (CI) m/z 268 (10, MH^+), 192 (20), 135 (100, BH). The TLC (S_1, S_2) R_f values for **32** were lower than those for adenosine.

Determination of Kinetic Constants for Inhibition of AdoHcy Hydrolase. Kinetic constants for time-dependent inhibition of AdoHcy hydrolase by the 5′-carboxaldehydes and oximes were determined by methods described previously.[9b]

Inhibition of L1210, FM3A, Molt, and CEM Cell Proliferation. Assays were performed in flat-bottomed 96-well microtiter plates as described.[33] Briefly, cells were suspended in growth medium and added to microplate wells at a density of 5×10^4 L1210 or FM3A cells/well (200 μL) or 7.5×10^4 Molt or CEM cells/well in the presence of varying concentrations of test compounds. Cells were allowed to proliferate for 48 h (L1210, FM3A) or 72 h (Molt, CEM) at 37 °C in a humidified, CO_2-controlled atmosphere. At the end of the incubation period, cells were counted in a Coulter counter. IC_{50} is defined as the concentration of compound that reduced the number of viable cells by 50%.

Antiviral Assays. Assays were based on inhibition of virus-induced cytopathicity in HeLa, Vero, E_6SM (human embryonic skin-muscle), or MDCK (Madin-Darby canine kidney) cell cultures with established procedures.[34] Briefly, confluent cell cultures in microtiter trays were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ is the virus dose required to infect 50% of the cell cultures). Residual virus was removed after a 1-h virus adsorption period, and cell cultures were incubated in the presence of varying concentrations (1, 10, 100, ... μg/mL) of test compounds. Viral cytopathogenicity was recorded as soon as it reached completion in the control virus-infected cell cultures.

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