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2-Amino-9-(3-Azido-2,3-Dideoxy-β-D-*Erythro*-Pentofuranosyl)-6-Substituted-9*H*-Purines: Synthesis and Anti-HIV Activity

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Abstract—A series of 2-amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-substituted-9*H*-purines was synthesized and tested for the ability to protect MT4 cells from the cytopathic effect of HIV-1_{IIIB}. These compounds were prepared by a combination of chemical and enzymatic reactions. Some of the nucleoside analogs with 6-alkoxy, 6-alkylamino, or 6-arylamino substitutents were active against HIV-1_{IIIB}. Their IC_{50} values were in the range of 2–60 μM. In contrast, analogs with 6-thio, 6-alkylthio, 6-methyl, or 6-carbonitrile substitutents did not protect cells from the cytopathic effect of HIV infection.

Introduction

3'-Azido-3'-deoxythymidine (1) (AZT, Retrovir®) is an effective antiviral agent for the treatment of AIDS. Replacement of the 3'-hydroxyl of thymidine with an azido group results in an alternate substrate for cellular kinases, allowing for production of 3'-azido-3'-deoxythymidine-5'-triphosphate (AZTTP).[1] AZTTP inhibits DNA synthesis catalyzed by HIV reverse transcriptase (HIV RT) more than it inhibits DNA synthesis mediated by the host cell's polymerases.[1] The triphosphate serves as both an inhibitor of HIV reverse transcription and as an alternate substrate, resulting in chain termination of the nascent DNA chain.[2,3] Following the discovery of the antiviral activity of the azidothymidine analog, and the activity of the 3'-azido-2',3'-dideoxyguanosine analog reported by Hartmann *et al.*,[4] we undertook the synthesis of a series of 2-amino-6-substituted-(3'-azido-2',3'-dideoxy-β-D-*erythro*-pentofuranosyl)purine analogs to explore the structure–activity relationships. Substitutents exemplified at the 6-position of the purine ring include hydroxy, alkoxy, amino, mono- and disubstituted-amino, thio, alkylthio, methyl, and carbonitrile groups. The synthesis of these novel nucleoside analogs was accomplished by a combination of chemical and enzymatic reactions.

Chemical synthesis of 3'-azido-2',3'-dideoxyguanosine was first accomplished by Eckstein and Imazawa utilizing a chemical transglycosylation reaction.[5] Their procedure resulted in the formation of both 7- and 9-isomers as well as α- and β-anomers. An alternative synthesis reported by Almond *et al.* utilized a TMS triflate catalyzed coupling of a carbohydrate precursor with the 9-TMS derivative of 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine.[6] Only the 9-isomer was reported and the stereochemistry was controlled during the coupling by a 2-*O*-acetyl group on the carbohydrate resulting in the formation of the β-anomer exclusively. The chemical synthesis reported here starts with triacetylguanosine and thereby avoids the problems of regio- and stereochemistry of the nucleoside bond. The 6-position was modified before conversion of the ribosyl to the 3'-azido-2',3'-dideoxypentofuranosyl moiety. The key step in the transformation of the sugar moiety was a lithium triethylborohydride deoxygenation of the 2'-position with concomitant inversion of the stereochemistry at the 3'-position,[7] in a manner analogous to the method used by Herdewijn *et al.*[8] Subsequent conversion to the desired azido-sugar was carried out using standard reactions.

The enzymatic transformations were catalyzed by the *Lactobacillus trans-N*-deoxyribosylase [nucleoside: purine(pyrimidine) deoxyribosyltransferase, EC 2.4.2.6]. The normal function of the enzyme in *Lactobacillus* is to transfer a 2'-deoxyribose moiety between purine and pyrimidine nucleobases. We investigated the possibility of transferring a 3'-azido-2',3'-dideoxyribose moiety from a thymidine donor to a variety of 2-amino-6-substituted purine bases. We found that the reactions proceeded smoothly in contrast to earlier reports[9] and provided the 9-substituted β-anomer exclusively.

The compounds were tested for their ability to protect MT4 cells from the cytopathic effect of HIV-1_{IIIB}.[10] The anti-HIV activity and cytotoxicity of these analogs are reported here.

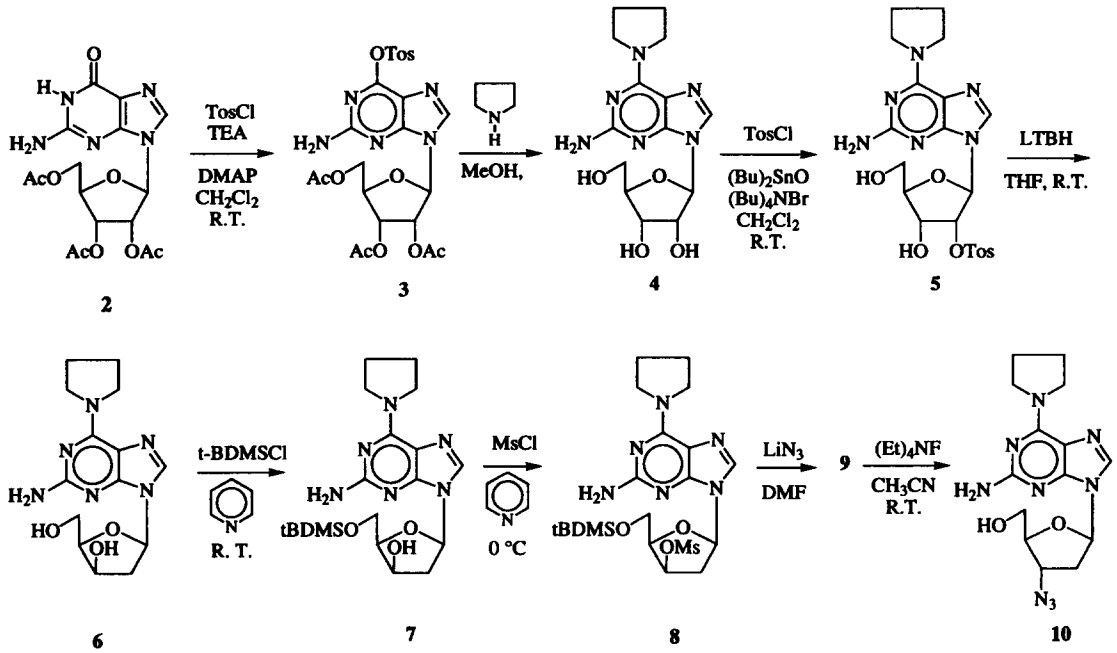
Results

Chemistry

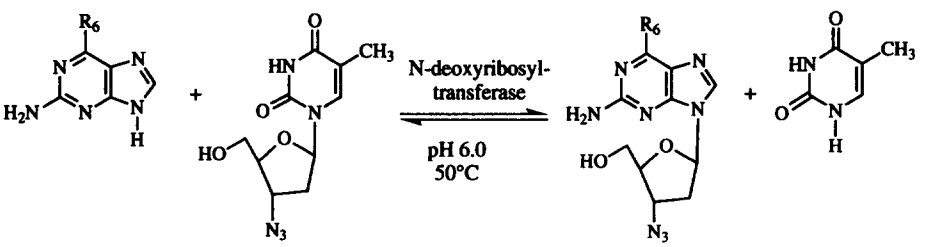
Synthesis of 2-amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-(1-pyrrolidinyl)-9*H*-purine (**10**) was accomplished as outlined in Scheme 1. Starting with commercially available 2',3',5'-triacetylguanosine

(2) the 6-position was functionalized by introduction of a tosyl group to give an uncharacterized 6-tosyl intermediate (3).[11] Introduction of a pyrrolidinyl group was accomplished by heating **3** *in situ* with pyrrolidine in methanol. Subsequent removal of the acetyl groups gave the 6-pyrrolidinyl intermediate (**4**). Following the reaction sequence originally developed by Verheyden and Moffatt[12] and modified by Grouiller *et al.*[13] conversion of the 2'-hydroxyl to a 2'-tosylate proceeded through a 2',3'-dibutyltin adduct, giving the 2'-tosylribose derivative (**5**). Deoxygenation of the 2'-position and inversion of the stereochemistry at the 3'-position was accomplished in one step by reaction of **5** with lithium triethylborohydride, giving the *threo*-2'-deoxyribose compound (**6**), in a manner analogous to that reported by Hansske and Robins.[7] Protection of the 5'-hydroxyl of **6** was achieved with a *t*-butyldimethylsilyl group, giving **7**. Functionalization of the 3'-hydroxyl with a methanesulfonyl group was accomplished in standard fashion, giving the *threo*-5'-*O*-*t*-butyldimethylsilyl-2'-deoxy-3'-mesylribose intermediate (**8**). Introduction of the azido substituent was accomplished by heating **8** in a 90 °C oil bath with lithium azide in dimethylformamide, producing the 3'-azido-5'-*O*-*t*-butyldimethylsilyl-2'-deoxyribose intermediate (**9**). The 5'-position of **9** was deblocked with tetrabutyl-ammonium fluoride, yielding the target compound (**10**). The conversion of 2',3',5'-triacetylguanosine to **10** was accomplished in eight steps with an 8% overall yield.

To provide a more direct route to these compounds, synthesis of 3'-azido-2',3'-dideoxypurine ribosides utilizing *trans*-*N*-deoxyribosyltransferase was investigated. Carson and Wasson reported no product formation using deoxyribosyltransferase, purified from *Lactobacillus helveticus*, when 3'-azido-3'-deoxythymidine (AZT) was used as the donor and adenine as the acceptor base.[9] In contrast to these results, we found that deoxyribosyltransferase, expressed in *Escherichia coli* and purified as described,[14] catalyzed the transfer of the 3'-azido-2',3'-dideoxyribose moiety from AZT to a series of 2-amino-6-substituted purine bases (Scheme 2). To prepare analogs **10**–**19**, **27**, and **32**–**39**, the 2-aminopurine bases (final concentration, 1 mM) and AZT (final concentration, 5 mM) were dissolved in 50 mM sodium citrate buffer at pH 6.0 and deoxyribosyltransferase was added to give a concentration of 75 units of enzyme per milliliter. The reactions were incubated at 50 °C. The purine bases were added as necessary to maintain a 1 mM concentration over the time course of the reactions. The reaction times averaged 21–28 days. The products were isolated in 100 to 200 mg amounts, giving yields in the 50% range for most compounds.



Scheme 1.



Scheme 2.

The 2-amino-6-chloro analog (**38**), was used to prepare 10 additional analogs, **20–26** and **28–30**, by straightforward nucleophilic displacement reactions. The yields ranged from 20 to 80%. The NMR spectrum of the 2,6-diaminopurine analog (**20**), prepared here was compared to previously published NMR data for the 2,6-diaminopurine analog and was found to be in close agreement.[15]

3'-Azido-2',3'-dideoxyguanosine (**31**), was prepared by demethylation of the 6-methoxy analog, (**11**), with calf intestine adenosine deaminase at room temperature. The 6-thioguanosine analog, (**42**), was prepared by oxidation of the 6-methylthio analog (**19**) with oxone[16] in 1 N potassium acetate buffer at 0 °C to give the sulfone (**41**). Nucleophilic displacement of the 6-sulfone moiety of **41** with sodium hydrosulfide hydrate in acetone/water at room temperature gave **42**.

Anti-HIV-1_{IIIB} activity in MT4 cells

The anti-HIV activity determined in MT4 cells utilizing the HIV-1_{IIIB} strain of the virus for compounds **10–40** and **42** is given in Table 1. The IC_{50}s reported for most of these compounds represent an average of at least two determinations. The activity of 3'-azido-3'-deoxythymidine (**1**), (AZT), is included for comparison. The IC_{50} value of **1** was in the range of 0.060–0.068 μM. The guanosine analog, **31**, was much less active than **1**; its average IC_{50} was 5 μM. Activity comparable to **31** was found for most of the 6-alkoxy compounds. Alkyl groups from C-1 to C-4, including straight chain, branched, and cyclic analogs all gave IC_{50}s in the same range. The straight chain alkyl groups from C-1 to C-4, **11–13**, gave IC_{50}s in the 5–27 μM range. The isopropoxy (**14**) and isobutoxy (**15**) analogs gave IC_{50}s in the 19–22 μM range. The cyclobutoxy analog (**16**) gave an average IC_{50} of 10 μM. The phenoxy analog (**17**) gave a somewhat higher average IC_{50} of 36 μM. However, the benzyloxy analog (**18**) with an average IC_{50} of 8 μM, was in the same range as **31**.

Some variation was seen among the 2-amino-6-monosubstituted amino analogs. Analogs with alkyl groups C-2–C-4, including straight chain, branched, and cyclic structures, were investigated. The 2,6-diamino analog (**20**) gave an average IC_{50} of 2 μM, which is comparable to the IC_{50} of **31**. The methylamino-derivative (**21**) was significantly less active than **20** with an average IC_{50} of 52 μM. The straight chain analogs, ethyl- (**22**), propyl- (**23**) and butylamino (**24**) analogs were more active than **21** having an average IC_{50} value of approximately 17 μM; they were slightly less active than **20**. The phenyl- (**27**) and benzylamino (**28**) analogs were both inactive. In contrast, spacing the aryl group out from the nitrogen by two methylene units, giving the phenethylamino analog (**29**) restored activity to the same range as noted for **22–24**. A *trans*-2-phenylcyclo-propylamino analog (**30**) was prepared. An accurate assessment of antiviral potency could not be made because of toxicity to the MT4 cells. The 2-amino-6-disubstituted amino analogs (**32–35**) gave average IC_{50} values slightly higher than the 2,6-diamino analog (**20**). Disubstitutions included one methyl group and straight chain alkyl groups of C-1–C-3 (**32–34**). In addition, disubstitutions included a methyl group and a cyclopropyl group (**35**). Cyclic analogs included four- and five-membered ring compounds **37** and **10**. Their average IC_{50} values were close to the values found for the 2-amino-6-monosubstituted amino compounds, with the exception of the 6-diethylamino compound (**36**) which was inactive at 200 μM.

The 2-amino-6-thio (**42**), 6-methylthio (**19**), 6-methyl (**39**) and 6-carbonitrile (**40**) analogs were all inactive at 200 μM.

Toxicity assessment in MT4 cells

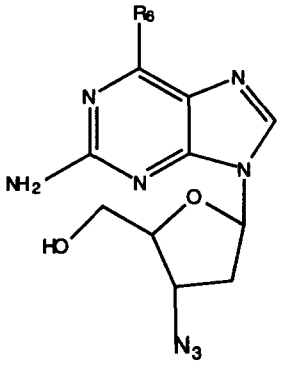
The toxicity of these compounds was assessed in the MT4 assay by comparing the growth of cells treated with compound and without virus to the growth of untreated control cells. Among the 2-amino-6-alkoxy analogs, relatively little inhibition of cell growth was seen until the chain length reached four carbon atoms. The cyclobutyl (**16**), phenyl (**17**) and benzyl (**18**) analogs all demonstrated some toxicity in a range of 13–80 μM. Among the 2,6-diamino analogs, only the *trans*-cyclopropyl-2-phenyl analog (**30**) consistently demonstrated inhibition of cell growth.

Discussion

The chemical synthesis of 2-amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-(1-pyrrolidinyl)-9*H*-purine (**10**) was accomplished through an eight-step reaction sequence. The yields for most of the steps were in the range of 60–70%. The overall yield was 8%. The low overall yield can be accounted for by the length of the sequence combined with the average yield obtained for each step.

An enzymatic synthesis of the 2-amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-substituted-9*H*-purines was investigated. *N*-Deoxyribosyltransferase is known to catalyze the transfer of the 2'-deoxyribose moiety between the 2'-deoxyribonucleosides and their conjugate bases.[14] The transfer takes place by a ping pong bi–bi mechanism. First, the donor nucleoside is bound to the enzyme followed by formation of an enzyme–deoxyribose complex with loss of the conjugate nucleobase. The product is formed by interaction of the new nucleobase with the enzyme–deoxyribose complex. Both steps are reversible. We demonstrated that *N*-deoxyribosyltransferase could also catalyze the transfer of the 3-azido-2,3-dideoxy-pentofuranosyl moiety from **1** to a variety of 2-amino-6-substituted purine bases. The transfer was regiospecific to the 9-position and stereospecific for formation of the beta-anomer. In these transfer reactions, the initial concentrations of the donor nucleoside and the purine acceptor were 5 and 1 mM, respectively. These concentrations were chosen to drive the reaction to completion in light of the transfer mechanism.

Table 1. Anti-human immunodeficiency virus activity and celluar toxicity in MT4 cells of some 2-amino-9-(3-azido-2,3-dideoxy-pentofuranosyl)-6-substituted-9*H*-purines



no.	R_6	Average IC_{50}(μM)	% growth of MT4 cells compared to untreated controls[a]
1	AZT	0.064	TC IC_{50} = 27 μM
31	OH	5	100[b]
11	OCH_3	9	100
12	OCH_2CH_3	23	100
13	$OCH_2CH_2CH_3$	9	65
14	$OCH(CH_3)_2$	22	54
15	$O(CH_2)_3CH_3$	19	25
16	O-cyclobutyl	5	60[c]
		15	28
17	OC_6H_5	28	86[d]
		43	48
18	$OCH_2C_6H_5$	8	74, 33[d]
19	SCH_3	8% I at 200	100
42	SH	20% I at 32	47[d]
20	NH_2	2	79
21	$HNCH_3$	52	86
22	$HNCH_2CH_3$	17	90
23	$HN(CH_2)_2CH_3$	12	84[d]
		23	61
24	HN-cyclopropyl	18	37
25	$HN(CH_2)_3CH_3$	29	23
26	HN-cyclobutyl	14	23
		16	66[d]
27	HNC_6H_5	112	24
		Inactive at 200	100
28	$HNCH_2C_6H_5$	Inactive at 200	58[d]
29	$HN(CH_2)_2$-phenyl	21	12
30	*trans* -HN-cyclo-propyl-2-phenyl	-	50[e]
		-	8[d]
32	CH_3NCH_3	12	77
33	$CH_3NCH_2CH_3$	11	78
34	$CH_3N(CH_2)_2CH_3$	12	69
35	CH_3N-cyclopropyl	4	41
36	$N(CH_2CH_3)_2$	Inactive at 200	100
37	$N(CH_2)_3$	9	100
10	$N(CH_2)_4$	8	not determined
38	Cl	6	24, 100
39	CH_3	Inactive at 200	100
40	C N	Inactive at 200	75

[a] All concentrations were 200 μM unless otherwise noted. [b] 100 μM. [c] 13 μM. [d] 80 μM. [e] 32 μM.

The progress of the reactions was monitored by HPLC. The concentration of the purine base was maintained at approximately 1 mM by addition of subsequent amounts as indicated by HPLC. In a typical transfer reaction, 2–4 weeks were required to allow maximum concentration of product to be reached. The isolated yields, based on amount of purine base added, averaged 50%. Fifty-two per cent yield of the 6-(1-pyrrolidinyl) analog (**10**) was achieved by enzymatic synthesis, compared to 8% yield by chemical synthesis.

The activity of the guanosine analog (**31**) against HIV has been reported by other workers to be in the range of 1–3 μM when evaluated in a system similar to the MT4 assay used in this study.[17] The average IC_{50} for **31** reported here is 9 μM and is close to the previously reported values. The diaminopurine analog (**20**) has been reported by other workers to give an IC_{50} of 0.3 μM when tested in an MT4 cell system.[18] The average IC_{50} of 2 μM reported here is somewhat higher than the previouly reported value. None of the 2-amino-6-substituted purine analogs gave a lower IC_{50} than the value reported for **31**. However, selected 2-amino-6-alkoxy- as well as 2-amino-6-substituted amino analogs gave average IC_{50}s in the range of 6–15 μM and are equivalent to the average value determined for **31**. Further work is needed to determine if the activities of the compounds reported here are the result of metabolism to the guanosine analog (**31**) or if some undergo anabolic conversion to their distinct mono-, di- and triphosphate forms. The 2,6-diamino analog (**20**) and as well as analogs with 6-alkoxy groups might be partially converted to **31** by adenosine deaminase. A slow rate of conversion of 6-alkoxypurine-2',3'-dideoxynucleosides to ddI has been reported by our laboratories.[19] In addition, the monophosphates of these analogs might be converted to the monophosphate of **31** by AMP deaminase via a mechanism similar to that proposed for the conversion of the 6-alkoxypurine-2',3'-dideoxyribo-nucleotides to ddI monophosphate.[19] If some of the 6-substituted analogs are converted to their triphosphate form and these triphosphates are inhibitors of HIV-RT, either as competitive inhibitors or as chain terminators, insight into the size and shape of the purine nucleoside binding site on RT could be gained.

The IC_{50} of AZT (**1**) is, on average, 18 times lower than the IC_{50} of **31**. Dideoxyinosine, ddI, has an average IC_{50} of 23 μM when tested under these conditions.[19] No purine analog is as active as AZT in the MT4 assay. However, the IC_{50} of **31** and some 2-amino-6-substituted analogs are about one-half the value reported for ddI. While it is not clear what *in vitro* antiviral potency a compound should have to be a clinically effective anti-HIV agent, some of the compounds reported here are active against HIV and represent potential antiviral agents.

Experimental

^{1}H NMR spectra were recorded with a Varian 300 MHz spectrometer. TLC was performed with Merck HPTLC 60 F_{254} plates. Flash chromatography was performed on Merck silica gel G60 40–63 μm mesh. HPLC was performed using Waters Expert Ease software for data control and a Hewlett Packard 1040M diode array detector. Mobile phase was generated with two Waters 510 pumps. A Waters 712 WISP was used as the autosampler. The separations were performed on either a Hamilton PRP-1 column, 4.6 mm by 15 cm, 5 μM particles, or a Supelco C_{18}, 3.3 cm by 4.6 mm, deactivated base column packed with 3 μm spherical particles. The flow rate was 1 mL min^{-1}. 2',3',5'-Triacetylguanosine was purchased from U.S. Biochemical. Adenosine deaminase from calf intestine was purchased from Boehringer Mannheim Biochemicals.

HIV-1 assay

The human T-cell lymphotropic virus type 1 transformed cell line MT4 was infected with HIV-1 (strain IIIB) at 100 times the amount necessary to cause a 50% reduction in cell growth. The infected cells were incubated for 5 days in the presence of various concentrations of each test compound. HIV-mediated cytopathic effect (CPE) was expressed as inhibition of MT4 cell growth. A compound that expressed anti-HIV activity reversed the CPE. The extent of CPE reversal was monitored by a propidium iodide stain for DNA.[5]

2-Amino-6-(1-pyrrolidinyl)-9-β-D-ribofuranosyl-9H-purine (4). 2',3',5'-Triacetylguanosine (**2**) (50 g, 0.12 mol) and 4-dimethylamino-pyridine (1.9 g, 0.016 mol, 0.13 eq.) were combined and dried by azeotropic removal of H_2O with toluene. The toluene was removed *in vacuo* and CH_2Cl_2 (1 L) was added. Triethylamine (30.6 mL, 0.22 mol, 1.8 eq.) and *p*-toluenesulfonyl chloride (32.6 g, 0.17 mol, 1.4 eq.) were added. The reaction was stirred at room temperature overnight. TLC on silica gel eluted with $CHCl_3$:MeOH (95:5, v/v) indicated a complete reaction. Approximately half of the CH_2Cl_2 was removed *in vacuo*. The remaining solution was stirred for 30 min with an equal volume of saturated aqueous sodium bicarbonate. The phases were separated and the organic phase was washed two times with saturated aqueous sodium bicarbonate then once with H_2O. The organic phase was dried with $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the crude intermediate **3**, which was converted to **4** by refluxing in MeOH (500 mL) and pyrrolidine (25.5 mL, 0.3 mol, 2.5 eq.) overnight. The solvent and pyrrolidine were removed *in vacuo*. Water (300 mL) was added and the mixture was filtered. The pH was adjusted to 8 and H_2O was removed *in vacuo*. The residue was stirred in acetonitrile. The product was collected by filtration and dried *in vacuo* to give 37.1 g, 90% yield. UV (nm): pH 1 λ_{max} = 297, 257 (ε = 13,800, 12,000), pH 13 λ_{max} = 283, 228 (ε = 17,700, 20,900); ^{1}H NMR (DMSO-d_6): δ 7.91 (*s*, 1H, H-8), 5.75 (*m*, 3H, NH_2, H-1'), 5.42–5.35 (*m*, 2H, 5'-OH, 2'-OH), 5.11 (*d*, *J* = 4.56 Hz, 1H, 3'-OH), 4.51–4.45 (*m*, 1H, H-2'), 4.12–4.07 (*m*, 1H, H-3'),

4.07–3.40 (*m*, 7H, H-4', H-5', 2 × CH_2), 1.91 (*br s*, 4H, 2 × CH_2). Anal. ($C_{14}H_{20}N_6O_4$) C,H,N.

2-Amino-6(1-pyrrolidinyl)-9-(2-O-tosyl-β-D-ribofuranosyl)-9H-purine (5). Compound **4** (18.4 g, 55 mmol) and tetrabutylammonium bromide (17.6 g, 55 mmol, 1 eq.) were dried by azeotropic removal of H_2O with toluene. The toluene was removed *in vacuo*. Dichloromethane (800 mL) was added followed by dibutyltin oxide (13.6 g, 0.055 mol, 1 eq.). *p*-Toluenesulfonyl chloride (12.5 g, 0.066 mol, 1.2 eq.) was added last and the reaction was stirred overnight at room temperature. The solvent was removed *in vacuo*, and the residue was stirred with acetonitrile for 1 h. The resulting product was filtered. After stirring with EtOAc, refiltering, and drying *in vacuo*, 17.2 g of product, 64% yield, was collected. UV (nm): pH 1 λ_{max} 301, 258 (ε = 11,600, 11,200), pH 13 λ_{max} 284 (ε = 12,900); ^{1}H NMR (DMSO-d_6): δ 7.68 (*s*, 1H, H-8), 7.41–7.01 (*m*, 4H, phenyl), 5.97–5.88 (*m*, 3H, H-1', H-2', 3'-OH), 5.64 (*s*, 2H, NH_2), 5.43–5.39 (*m*, 1H, 5'-OH), 4.30–4.27 (*t*, *J* = 5.0 Hz, 1H, H-3'), 4.00–3.48 (*m*, 7H, H-4', H-5', 2 × CH_2), 2.20 (*s*, 3H, CH_3), 1.98–1.92 (*br s*, 4H, 2 × CH_2). Anal. ($C_{21}H_{26}N_6O_6S$) C,H,N,S.

*2-Amino-9-(2-deoxy-β-D-*threo*-pentofuranosyl)-6-(1-pyrrolidinyl)-9H-purine (6).* A 1 M solution of lithium triethyl-borohydride in tetrahydrofuran (67 mL, 67 mmol, 10 eq.) was placed in a 500 mL round bottom flask and covered with a N_2 blanket. Compound **5** (3.3 g, 6.7 mmol) was dissolved in tetrahydrofuran (125 mL) and added in a steady stream over 5 min. The reaction was stirred at room temperature for 2.5 h. Water (125 mL) was carefully added. The pH was adjusted to 8 with 1 N HCl. The resulting layers were separated. The aqueous phase contained the product. The pH was adjusted to 11 with 1 N NaOH, and the product was extracted with chloroform (3 × 200 mL). The product was chromatographed on silica gel eluted with $CHCl_3$:MeOH (95:5 v/v). The fractions containing the product were combined, and solvents were removed *in vacuo*, giving 1.3 g, a 60% yield. UV (nm): pH 1 λ_{max} 295, 256 (ε = 13,600, 11,900), pH 13 λ_{max} 283 (ε = 16,000); ^{1}H NMR (DMSO-d_6): δ 7.92 (*s*, 1H, H-8), 6.07 (*dd*, *J* = 2.30 Hz, 8.60 Hz, 1H, H-1'), 5.97 (*m*, 1H, 3'-OH), 5.79 (*s*, 2H, NH_2), 4.65 (*t*, *J* = 5.70 Hz, 1H, 5'-OH), 4.29–4.27 (*m*, 1H, H-3'), 4.10–3.40 (*m*, 7H, H-4', H-5', 2 × CH_2), 2.70–2.67 (*m*, 1H, H-2'), 2.19–2.14 (*m*, 1H, H-2'), 1.90 (*m*, 4H, 2 × CH_2). Anal. ($C_{14}H_{20}N_6O_3$) C,H,N.

*2-Amino-9-(5-O-(tert-butyldimethylsilyl)-2-deoxy-β-D-*threo*-pentofuranosyl)-6-(1-pyrrolidinyl)-9H-purine (7).* Compound **6** (3.12 g, 9.74 mmol) was dissolved in 30 mL of pyridine. The solution was heated until the temperature of the vapor coming off reached 112 °C to remove residual H_2O. The solution was cooled to room temperature. *t*-Butyldimethylsilyl chloride (3 g, 19.9 mmol, 2 eq.) was added. The reaction was stirred at room temperature for 30 min. Methanol, 30 mL, was added, and the solvents were removed *in vacuo*. The residue was boiled first with toluene and then with nitromethane to remove pyridine. The residual gum was dissolved in H_2O, 20 mL, and the pH was adjusted to 9 with 1 N NaOH. The aqueous phase was extracted with EtOAc (3 × 20 mL). The EtOAc fractions were combined and dried with $MgSO_4$. After filtering, the solvent was removed *in vacuo* to give 3.36 g of product, 79% yield, as a yellow foam. A portion of the product was purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (95:5 v/v) to give an analytical sample. UV (nm): pH 1 λ_{max} 295 (ε = 13,300), pH 13 λ_{max} 283, 256 (ε = 14,800, 11,700); ^{1}H NMR (DMSO-d_6): δ 7.91 (*s*, 1H, H-8), 6.08 (*m*, 2H, H-1', 3'-OH), 5.77 (*s*, 2H, NH_2), 4.33–4.28 (*m*, 1H, H-4'), 4.00–3.56 (*m*, 6H, H-5', 2 × CH_2), 2.80–2.60 (*m*, 1H, H-2'), 2.20–2.12 (*m*, 1H, H-2'), 1.91–1.84 (*m*, 4H, 2 × CH_2), 0.86 (*s*, 9H, 3 × CH_3), 0.04 (*s*, 6H, 2 × CH_3). Anal. ($C_{20}H_{34}N_6O_3Si$) C,H,N.

*2-Amino-9-(5-O-(tert-butyldimethylsilyl)-2-deoxy-3-O-mesyl-β-D-*threo*-pentofuranosyl)-6-(1-pyrrolidinyl)-9H-purine (8).* Compound **7** (0.14 g, 0.32 mmol) was dissolved in dry pyridine (15 mL) and chilled to 0 °C in an ice bath. Methanesulfonyl chloride (27 mL, 0.35 mmol, 1.1 eq.) was added, and the reaction stirred for 30 min and then poured onto ice H_2O. A yellow precipitate formed and was collected by filtration. The product, 0.11 g, was obtained in 67% yield. UV (nm): pH 1 λ_{max} 296 (ε = 13,800), pH 13 λ_{max} 283, 257 (ε = 14,700, 11,800); ^{1}H NMR (DMSO-d_6): δ 7.74 (*s*, 1H, H-8), 6.20 (*dd*, *J* = 3.0 Hz, 8.2 Hz, 1H, H-1'), 5.86 (*s*, 2H, NH_2), 5.38 (*t*, *J* = 3.5 Hz, 1H, H-3'), 4.21–4.16 (*m*, 1H, H-4'), 3.99–3.50 (*m*, 6H, H-5', 2 × CH_2), 3.28 (*s*, 3H, SCH_3), 3.10–2.93 (*m*, 1H, H-2'), 2.62–2.51 (*m*, 1H, H-2'), 2.00–1.80 (*m*, 4H, 2 × CH_2), 0.87 (*s*, 9H, 3 × CH_3), 0.06 (*s*, 6H, 2 × CH_3). Anal. ($C_{21}H_{36}N_6O_5SSi$•1.35 H_2O) C,H,N,S.

*2-Amino-9-(3-azido-5-O-(tert-butyldimethylsilyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-(1-pyrrolidinyl)-9H-purine (9).* Compound **8** (1.3 g, 2.6 mmol) was dissolved in dimethylformamide (20 mL) and placed in a 70–80 °C oil bath. Lithium azide (0.38 g, 7.8 mmol, 3 eq.) was added. The reaction was heated for 3 h. The solution was poured onto 125 mL of ice and a brown gum resulted. The water was decanted and the gum dissolved in EtOAc. After removal of the solvent, 0.79 g of product was collected. A portion of the product was purified by chromatograhpy on silica gel eluted with EtOAc:$CHCl_3$ (4:1 v/v). UV (nm): pH 1 λ_{max} 297, 256 (ε = 14,200, 12,500), pH 13 λ_{max} 284 (ε = 14,800); ^{1}H NMR (DMSO-d_6): δ 7.86 (*s*, 1H, H-8), 6.15 (*t*, *J* = 6.3 Hz, 1H, H-1'), 5.86 (*s*, 2H, NH_2), 4.60–4.54 (*m*, 1H, H-3'), 3.92–3.58 (*m*, 7H, H-4', H-5', 2 × CH_2), 2.85–2.78 (*m*, 1H, H-2'), 2.49–2.38 (*m*, 1H, H-2'), 1.89 (*br s*, 4H, 2 × CH_2), 0.86 (*s*, 9H, 3 × CH_3), 0.03 (*s*, 6H, 2 × CH_3). Anal. ($C_{20}H_{33}N_9O_2Si$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-(1-pyrrolidinyl)-9H-purine (10).* Compound **9** (0.096 g, 0.21 mmol) was dissolved in acetonitrile (5 mL). Tetraethylammonium fluoride (0.038 g, 0.26 mmol, 1.2 eq.) was added. The reaction was stirred at room temperature for 2 h. A precipitate formed which

was collected by filtration. The solid was stirred in H_2O then filtered. After drying, the product, 0.049 g, was obtained in 68% yield. UV (nm): pH 1 λ_{max} 296, 256 (ε = 17,500, 15,100), pH 13 λ_{max} 283 (ε = 20,600); ^{1}H NMR (DMSO-d_6): δ 7.90 (*s*, 1H, H-8), 6.10 (*t*, *J* = 6.6 Hz, 1H, H-1'), 5.80 (*s*, 2H, NH_2), 5.30 (*br s*, 1H, 5'-OH), 4.61–4.56 (*m*, 1H, H-3'), 3.91–3.87 (*m*, 1H, H-4'), 3.63–3.52 (*m*, 6H, H-5', 2 × CH_2), 2.86–2.77 (*m*, 1H, H-2'), 2.49–2.39 (*m*, 1H, H-2'), 1.90 (*br s*, 4H, 2 × CH_2). Anal. ($C_{14}H_{19}N_9O_2$•1.0 CH_3CN and 0.75 H_2O) C,H,N.

Enzymatic reactions to prepare analogs **10–19**, **27**, and **32–39** were conducted by the same method on either a 500 or 800 mL scale. The reaction solvent was an aqueous pH 6.0 50 mM citrate buffer solution prepared by adding 8.41 g of citric acid to 800 mL of distilled deionized H_2O and adjusting the final pH to 6.0 with NaOH. The purine bases were dissolved to give a 1 mM concentration. The source of the 3'-azido-2',3'-dideoxyribofuranosyl moiety, i.e. the donor molecule AZT, was dissolved to give a 5 mM concentration. A sample was withdrawn to serve as a control for HPLC analysis. *trans-N*-Deoxyribosylase was added to give a concentration of 75 units of enzyme mL^{-1}. The reactions were placed in a shaker bath and heated to 50 °C. Each reaction was followed by HPLC, and concentrations of substrates were maintained near the starting level by addition of starting materials when appropriate. The reactions were continued for an average of 21–28 days.

The reactions were worked up by one of two methods. Method One: the enzyme was inactivated by heating to 80 °C and removed by filtration through Celite. The product was extracted from the aqueous phase with EtOAc. The EtOAc solution was washed with 1 M K_2CO_3 two times. The product was purified by chromatography on silica gel or basic alumina. Method Two: when the product precipitated during the reaction, the mixtures were chilled to 0 °C and the precipitate was collected by filtration. The product from each reaction was purified by chromatography on silica gel or basic alumina.

The 2-amino-6-substituted purine bases were made by heating 2–5 equivalents of the appropriate nucleophile with 2-amino-6-chloropurine dissolved in either methanol or acetonitrile. Synthesis of 2-amino-6-azetidinyl-9-*H*-purine is given as an example.

2-Amino-6-azetidinyl-9H-purine. 2-Amino-6-chloropurine (1.0 g, 5.8 mmol) was suspended in 50 mL acetonitrile. Azetidine (1.0 g, 17.5 mmol, 3 eq.) was added and the reaction was stirred at 60 °C for 24 h. The solvent was evaporated to give a white solid, which was recrystallized from MeOH to give the product in 65% yield. ^{1}H NMR (DMSO-d_6): δ 12.07 (*br s*, 1H, NH) 7.62 (*s*, 1H, H-8), 5.74 (*s*, 2H, NH_2), 4.36–4.09 (*br m*, 4H, $N(CH_2)_2$), 2.42–2.27 (*m*, 2H, CH_2).

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-(1-pyrrolidinyl)-9H-purine (10).* Enzymatic synthesis: the enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (60:40 v/v) at 1 mL min^{-1} for thymine, purine base, and AZT. The product eluted by 6 min with 100% MeOH. The reaction was allowed to continue for 33 days. The product was isolated by Method 1. Purification was accomplished by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99:1 v/v). A 52% yield was obtained. UV (nm): pH 1 λ_{max} 298, 257 (ε = 17,800, 15,500), pH 13 λ_{max} 284 (ε = 20,000); ^{1}H NMR (DMSO-d_6): δ 7.90 (*s*, 1H, H-8), 6.12 (*t*, *J* = 6.64 Hz, 1H, H-1'), 5.81 (*s*, 2H, NH_2), 5.30 (*t*, *J* = 5.63 Hz, 1H, 5'-OH), 4.60–4.52 (*m*, 1H, H-3'), 4.00–3.4 (*m*, 7H, H-4', H-5', $2CH_2$), 2.90–2.73 (*m*, 1H, H-2'), 2.44–2.35 (*m*, 1H, H-2'), 1.88 (*br s*, 4H, $2CH_2$). Anal. ($C_{14}H_{19}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methoxy-9H-purine (11).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (70:30 v/v) for 8 min. The reaction was allowed to continue for 21 days. The product was isolated by Method 1. Purification was accomplished by chromatography on silica gel eluted with $CHCl_3$:MeOH (99:1 v/v). A 41% yield was obtained. UV (nm): pH 1 λ_{max} 287, 243 (ε = 10,300, 7800), pH 13 λ_{max} 279, 247 (ε = 9400, 9600); ^{1}H NMR (DMSO-d_6): δ 8.08 (*s*, 1H, H-8), 6.49 (*s*, 2H, NH_2), 6.14 (*t*, *J* = 6.5 Hz, 1H, H-1'), 5.13 (*t*, *J* = 5.5 Hz, 1H, 5'-OH), 4.60–4.57 (*m*, 1H, H-3'), 3.93 (*s*, 1H, 6-OCH_3), 3.90–3.83 (*m*, 1H, H-4'), 3.58–3.47 (*m*, 2H, H-5'), 2.86–2.76 and 2.46–2.39 (*m*, 2H, H-2'). Anal. ($C_{11}H_{14}N_8O_3$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-ethoxy-9H-purine (12).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (70:30 v/v) for 12 min. The reaction was allowed to continue for 11 days. The product was isolated by Method 1. Purification was accomplished by chromatography on silica gel eluted with $CHCl_3$:MeOH (98:2 v/v). A 55% yield was obtained. UV (nm): pH 1 λ_{max} 287, 243 (ε = 9500, 6700), pH 13 λ_{max} 280, 247 (ε = 9400, 9400); ^{1}H NMR (DMSO-d_6): δ 8.09 (*s*, 1H, H-8), 6.45 (*s*, 2H, NH_2), 6.14 (*t*, *J* = 6.5 Hz, 1H, H-1'), 4.63–4.54 (*m*, 1H, H-3'), 4.43 (*q*, *J* = 7.0 Hz, 2H, 6-OCH_2), 3.91–3.83 (*m*, 1H, H-4'), 3.57–3.48 (*m*, 2H, H-5'), 2.86–2.76 and 2.47–2.39 (*m*, 2H, H-2'), 1.34 (*t*, *J* = 7.0 Hz, 3H, 6-$OCH_2\underline{CH_3}$). Anal. ($C_{12}H_{16}N_8O_3$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-propoxy-9H-purine (13).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (60:40 v/v) for thymine, purine base, and AZT. The product was eluted using MeOH:H_2O (80:20 v/v). The reaction was allowed to continue for 11 days. The product was isolated by Method 1 and purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (98:2 v/v). A 56% yield was obtained. UV (nm): pH 1 λ_{max} 287, 243 (ε = 9800, 7000), pH 13 λ_{max} 280, 247 (ε = 9900, 9900); ^{1}H NMR (DMSO-d_6): δ 8.09 (*s*, 1H, H-8), 6.46 (*s*, 2H, NH_2), 6.16 (*t*, *J* = 6.2 Hz, 1H, H-1'), 5.15 (*t*, *J* = 5.3 Hz, 1H, 5'-OH), 4.63–4.58 (*m*, 1H, H-3'), 4.35 (*t*, *J* = 6.7 Hz, 2H, 6-OCH_2-), 3.91–3.87 (*m*, 1H, H-4'), 3.65–3.53 (*m*, 2H, H-5'), 2.89–2.80 and 2.51–2.40

(*m*, 2H, H-2'), 1.82–1.70 (*m*, 2H,-$CH_2\underline{CH_2}CH_3$), 0.97 (*t*, *J* = 7.3 Hz,3H,-$CH_2\underline{CH_3}$). Anal. ($C_{13}H_{18}N_8O_3$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro-*pentofuranosyl)-6-isopropoxy-9H-purine (14).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (40:60 v/v) for thymine, purine base, and AZT. The product was eluted using MeOH:H_2O (90:10 v/v). The reaction was allowed to continue for 33 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (95:5 v/v). A 28% yield was obtained. UV (nm): pH 1 λ_{max} 287 (ε = 17,700), pH 13 λ_{max} 280 (ε = 17,600); ^{1}H NMR (DMSO-d_6): δ 8.06 (*s*, 1H, H-8), 6.4 (*br s*, 2H, NH_2), 6.14 (*t*, *J* = 6.44 Hz, 1H, H-1'), 5.5–5.4 (*m*, 1H, CH), 5.14 (*t*, *J* = 5.6 Hz, 1H, 5'-OH), 4.6–4.5 (*m*, 1H, H-3'), 3.9–3.8 (*m*, 1H, H-4'), 3.6–3.47 (*m*, 2H, H-5'), 2.89–2.76 and 2.5–2.4 (*m*, 2H, H-2'), 1.3 (*d*, *J* = 6.25 Hz, 6H, $(CH_3)_2$). Anal. ($C_{13}H_{18}N_8O_3$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro-*pentofuranosyl)-6-butyloxy-9H-purine (15).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (80:20 v/v). The reaction was allowed to continue for 26 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (95:5 v/v). A 48% yield was obtained. UV (nm): pH 1 λ_{max} 285 (ε = 11,900), pH 13 λ_{max} 279, 246 (ε = 8300, 8600); ^{1}H NMR (DMSO-d_6): δ 8.07 (*s*, 1H, H-8), 6.44 (*s*, 2H, NH_2), 6.14 (*t*, *J* = 6.29 Hz, 1H, H-1'), 5.13 (*t*, *J* = 5.47 Hz, 1H, 5'-OH), 4.63–4.55 (*m*, 1H, H-3'), 4.38 (*t*, 2H, OCH_2), 3.90–3.84 (*m*, 1H, H-4'), 3.58–3.53 (*m*, 2H, H-5'), 2.89–2.76 and 2.49–2.36 (*m*, 2H, H-2'), 1.79–1.64 (*m*, 2H, CH_2), 1.49–1.31 (*m*, 2H, CH_2), 0.92 (*t*, 3H, CH_3). Anal. ($C_{14}H_{20}N_8O_3$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro-*pentofuranosyl)-6-cyclobutyloxy-9H-purine (16).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (80:20 v/v). The reaction was allowed to continue for 26 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (95:5 v/v). A 32% yield was obtained. UV(nm): pH 1 λ_{max} 288, 243 (ε = 10,000, 7100), pH 13 λ_{max} 281, 247 (ε = 11,000, 10,600); ^{1}H NMR (DMSO-d_6): δ 8.06 (*s*, 1H, H-8), 6.4 (*br s*, 2H, NH_2), 6.14 (*t*, *J* = 6.44 Hz, 1H, H-1'), 5.35–5.2 (*m*, 1H, CH), 5.14 (*t*, *J* = 5.6 Hz, 1H, 5'-OH), 4.6–4.5 (*m*, 1H, H-3'), 3.9–3.8 (*m*, 1H, H-4'), 3.6–3.50 (*m*, 2H, H-5'), 2.89–2.76 and 2.5–2.34 (*m*, 2H, H-2'), 2.20–2.00 (*m*, 2H, CH_2), 1.9–1.6 (*m*, 2H, CH_2). Anal. ($C_{14}H_{18}N_8O_3$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro-*pentofuranosyl)-6-phenoxy-9H-purine (17).* The enzymatic reaction was followed by HPLC on a Supelco C_{18} column eluted with MeOH:H_2O (40:60 v/v). The reaction was allowed to continue for 33 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99:1 v/v). A 54% yield was obtained. UV (nm): pH 1 λ_{max} 293, 243 (ε = 10,300, 8900), pH 13 λ_{max} 286, 246 (ε = 13,500, 12,900); ^{1}H NMR (DMSO-d_6): δ 8.22 (*s*, 1H, H-8), 7.5–7.2 (*m*, 5H, phenyl), 6.5 (*s*, 2H, NH_2), 6.20 (*t*, *J* = 6.34 Hz, 1H, H-1'), 5.15 (*s*, 1H, 5'-OH), 4.7–4.6 (*m*, 1H, H-3'), 3.95–3.85 (*m*, 1H, H-4'), 3.65–3.50 (*m*, 2H, H-5'), 2.9–2.8 (*m*, 1H, H-2'), 2.5–2.4 (*m*, 1H, H-2', obscured by DMSO-d_6). Anal. ($C_{16}H_{16}N_8O_3$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro-*pentofuranosyl)-6-benzyloxy-9H-purine (18).* The enzymatic reaction was followed by HPLC on a Supelco C_{18} column eluted with MeOH:H_2O (40:60 v/v). The reaction was allowed to continue for 26 days. The product was isolated by Method 2 and purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (98:2, v/v) followed by chromatography on basic alumina eluted with $CHCl_3$:MeOH (98:2 v/v). A 26% yield was obtained. UV (nm): pH 1 λ_{max} 289, 243 (ε = 9800, 7100), pH 13 λ_{max} 281, 247 (ε = 11,200, 10,800); ^{1}H NMR (DMSO-d_6): δ 8.08 (*s*, 1H, H-8), 7.50–7.30 (*m*, 5H, Ph), 6.52 (*s*, 2H, NH_2), 6.15 (*t*, *J* = 6.3 Hz, 1H, H-1'), 5.48 (*s*, 2H,-$O\underline{CH_2}$Ph), 5.11 (*t*, *J* = 5.5 Hz, 1H, 5'-OH), 4.63–4.54 (*m*, 1H, H-3'), 3.91–3.84 (*m*, 1H, H-4'), 3.58–3.45 (*m*, 2H, H-5'), 2.89–2.76 and 2.47–2.36 (*m*, 2H, H-2'). Anal. ($C_{17}H_{18}N_8O_3$•0.2 H_2O) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro-*pentofuranosyl)-6-methylthio-9H-purine (19).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (60:40 v/v) for thymine, purine base and AZT. The column was eluted with MeOH:H_2O (80:20 v/v) for product. The reaction was allowed to continue for 10 days. The product was isolated by Method 1 and purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (98:2 v/v). A 46% yield was obtained. UV (nm): pH 1 λ_{max} 324, 249 (ε = 20,200, 18,000), pH 13 λ_{max} 310, 245 (ε = 15,600, 17,600); ^{1}H NMR (DMSO-d_6): δ 8.15 (*s*, 1H, H-8), 6.56 (*s*, 2H, NH_2), 6.15 (*t*, *J* = 6.44 Hz, 1H, H-1'), 5.11 (*t*, *J* = 5.47 Hz, 1H, 5'-OH), 4.65–4.58 (*m*, 1H, H-3'), 3.88–3.84 (*m*, 1H, H-4'), 3.58–3.52 (*m*, 2H, H-5'), 2.92–2.78 (*m*, 1H, H-2'), 2.55 (*s*, 3H, CH_3), 2.51–2.38 (*m*, 1H, H-2'). Anal. ($C_{11}H_{14}N_8O_2S$ H_2O) C,H,N,S.

*2,6-Diamino-9-(3-azido-2,3-dideoxy-β-D-*erythro-*pentofuranosyl)-9H-purine (20).* Compound **38** (0.5 g, 1.6 mmol) was dissolved in 25 mL of MeOH saturated with ammonia. The solution was heated in a sealed tube in a 60 °C oil bath for 4 days. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel eluted with EtOAc. UV (nm): pH 1 λ_{max} 290, 252 (ε = 9500, 10,900), pH 13 λ_{max} 279, 255 (ε = 11,200, 10,300); ^{1}H NMR (DMSO-d_6): δ 7.93 (*s*, 1H, H-8), 6.75 (*s*, 2H, NH_2), 6.12 (*t*, *J* = 6.48 Hz, 1H, H-1'), 5.80 (*s*, 2H, NH_2), 5.35 (*t*, *J* = 5.75 Hz, 1H, 5'-OH), 4.62–4.57 (*m*, 1H, H-3'), 3.92–3.88 (*m*, 1H, H-4'), 3.65–3.51 (*m*, 2H, H-5'), 2.89–2.79 (*m*, 1H, H-2'), 2.47–2.36 (*m*, 1H, H-2'). Anal. ($C_{10}H_{13}N_9O_2$•0.3 H_2O) C,H,N.

Lit. NMR (DMSO-d_6): 7.91 (*s*, 1H, H-8), 6.73 (*br s*, NH_2), 6.12 (*t*, *J* = 7.0 Hz, 1H, H-1'), 5.78 (*br s*, NH_2),

5.32 (*t*, 1H, 5'-OH), 4.59 (*m*, 1H, H-3'), 3.90 (*br q*, 1H, H-4'), 3.62 (*m*, 2H, H-5'), 2.68–3.04 (*m*, 1H, H-2'a), 2.22–2.58 (*m*, 1H, H-2'b).[18]

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methylamino-9H-purine (21).* Compound **38** (0.35 g; 1.13 mmol) was refluxed in 88 mL methylamine (40% in H_2O) for 15 min. The reaction was cooled and the solvent evaporated to give a foam. The product was purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99:1 v/v). A 61% yield was obtained. UV (nm): pH 1 λ_{max} 290, 255 (ε = 12,000, 12,300), pH 13 λ_{max} 280 (ε = 14,400); ^{1}H NMR (DMSO-d_6): δ 7.88 (*s*, 1H, H-6), 7.22 (*s*, 1H, NH), 6.14–6.07 (*m*, 1H, H-1'), 5.81 (*s*, 2H, NH_2), 5.3–5.2 (*m*, 1H, 5'-OH), 4.61–4.53 (*m*, 1H, H-3'), 3.90–3.88 (*m*, 1H, H-4'), 3.6–3.5 (*m*, 2H, H-5'), 2.9–2.7 (*m*, 4H, H-2' and CH_3), 2.46–2.31 (*m*, 1H, H-2'). Anal. ($C_{11}H_{15}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-ethylamino-9H-purine (22).* Compound **38** (0.23 g, 0.74 mmol) was dissolved in 20 mL anhydrous acetonitrile and placed in a sealed tube. The solution was cooled to 0 °C, saturated with ethylamine and sealed. The reaction was heated in a 70 °C oil bath for 16 h. The solvent was removed *in vacuo* and the product was purified by chromatography on silica gel and eluted with $CHCl_3$:MeOH (95:5 v/v). A 58% yield was obtained. UV (nm): pH 1 λ_{max} 291, 254 (ε = 11,500, 11,600), pH 13 λ_{max} 281, 243 (ε = 13,800, 6300); ^{1}H NMR (DMSO-d_6): δ 7.91 (*s*, 1H, H-8), 6.12 (*t*, *J* = 6.61 Hz, 1H, H-1'), 5.85 (*br s*, 2H, NH_2), 5.35 (*t*, *J* = 5.77 Hz, 1H, 5'-OH), 4.61–4.57 (*m*, 1H, H-3'), 3.92–3.87 (*m*, 1H, H-4'), 3.61–3.38 (*m*, 4H, H-5', NCH_2), 2.89–2.79 (*m*, 1H, H-2'), 2.44–2.36 (*m*, 1H, H-2'), 1.13 (*t*, 3H, CH_3). Anal. ($C_{12}H_{17}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-propylamino-9H-purine (23).* Compound **38** (0.24 g, 0.87 mmol) and propylamine (0.257 g, 4.36 mmol, 5 eq.) were heated in 10 mL anhydrous acetonitrile at 70 °C for 8 h. The solvents were evaporated and the product purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (98:2 v/v). The product was obtained as an oil. Evaporation from EtOAc yielded the product as a foam in 76% yield. UV (nm): pH 1 λ_{max} 293 (ε = 13,000), pH 13 λ_{max} 281, 255 (ε = 15,200); ^{1}H NMR (DMSO-d_6): δ 7.9 (*s*, 1H, H-8), 7.3 (*s*, 1H, NH), 6.1 (*t*, *J* = 6.49 Hz, 1H, H-1'), 5.8 (*s*, 2H, NH_2), 5.3 (*t*, *J* = 6.04 Hz, 1H, 5'-OH), 4.6–4.55 (*m*, 1H, H-3'), 3.9–3.85 (*m*, 1H, H-4'), 3.6–3.54 (*m*, 2H, H-5'), 2.9–2.76 (*m*, 1H, H-2'), 2.5–2.3 (*m*, 1H, H-2'), 1.6–1.5 (*m*, 2H, CH_2), 0.8 (*t*, 3H, CH_3). Anal. ($C_{13}H_{19}N_9O_2$•0.2 H_2O) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-cyclopropylamino-9H-purine (24).* Compound **38** (0.35 g, 1.13 mmol) and cyclopropylamine (0.78 g, 11.5 mmol, 10 eq.) were combined with 88 mL anhydrous MeOH in a 150 mL stainless steel bomb. The bomb was sealed and placed in a 75 °C oven for 24 h. After cooling, the solvent was evaporated and the product purified by chromatography on silica gel eluted with EtOAc:MeOH (98:2, v/v). A 67% yield was obtained. UV (nm): pH 1 λ_{max} 295, 255 (ε = 14,000, 11,000), pH 13 λ_{max} 283, 263 (ε = 14,900, 10,000); ^{1}H NMR (DMSO-d_6): δ 7.89 (*s*, 1H, H-6), 7.36 (*d*, *J* = 4.34 Hz, 1H, NH), 6.1 (*t*, 1H, H-1'), 5.85 (*s*, 2H, NH_2), 5.29 (*t*, 1H, 5'-OH), 4.65–4.50 (*m*, 1H, H-3'), 3.90–3.82 (*m*, 1H, H-4'), 3.68–3.50 (*m*, 2H, H-5'), 2.99 (*s*, 1H, CH), 2.9–2.8 (*m*, 1H, H-2'), 2.46–2.30 (*m*, 1H, H-2'), 0.7–0.6 [*m*, 4H, $(CH_2)_2$]. Anal. ($C_{13}H_{17}N_9O_2$•0.25 H_2O) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-butylamino-9H-purine (25).* Compound **38** (0.4 g, 1.29 mmol) and *n*-butylamine (0.94 g, 12.9 mmol, 10 eq.) were combined with 25 mL anhydrous MeOH in a sealed tube. The reaction was placed in a 60 °C oil bath for 18 h. The solvent was removed *in vacuo* and the product purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (98:2 v/v). A 76% yield was obtained. UV (nm): pH 1 λ_{max} 295, 253 (ε = 14,500, 13,600), pH 13 λ_{max} 281 (ε = 14,300); ^{1}H NMR (DMSO-d_6): δ 7.89 (*s*, 1H, H-8), 7.20 (*br s*, 1H, NH), 6.10 (*t*, *J* = 6.44 Hz, 1H, H-1'), 5.80 (*s*, 2H, NH_2), 5.32 (*t*, *J* = 5.47 Hz, 1H, 5'-OH), 4.61–4.52 (*m*, 1H, H-3'), 3.90–3.85 (*m*, 1H, H-4'), 3.60–3.30 (*m*, 4H, H-5', CH_2), 2.90–2.75 (*m*, 1H, H-2'), 2.47–2.30 (*m*, 1H, H-2'), 1.60–1.20 (*m*, 4H, 2 × CH_2), 0.87 (*t*, *J* = 7.23 Hz, 3H, CH_3). Anal. ($C_{14}H_{21}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-cyclobutylamino-9H-purine (26).* Compound **38** (0.24 g, 0.77 mmol) and cyclobutylamine (0.55 g, 7.7 mmol, 10 eq.) were combined in 50 mL anhydrous acetonitrile and heated in a 75 °C oil bath for 16 h. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (95:5 v/v) followed by chromatography on basic alumina eluted with $CHCl_3$:MeOH (19:1 v/v). Evaporation of product fractions yielded an oil. Evaporation with EtOAc gave a foam. A 19% yield was obtained. UV (nm): pH 1 λ_{max} 295, 256 (ε = 12,300, 11,000), pH 13 λ_{max} 283 (ε = 14,500); ^{1}H NMR (DMSO-d_6): δ 7.92 (*s*, 1H, H-8), 7.53 (*br s*, 1H, NH), 6.10 (*t*, *J* = 6.49 Hz, 1H, H-1'), 5.84 (*br s*, 2H, NH_2), 5.31 (*t*, *J* = 5.51 Hz, 1H, 5'-OH), 4.80–4.54 (*m*, 2H, H-3', NCH), 3.89–3.84 (*m*, 1H, H-4'), 3.60–3.50 (*m*, 2H, H-5'), 2.85–2.75 (*m*, 1H, H-2'), 2.48–2.34 (*m*, 1H, H-2'), 2.30–1.95 (*m*, 4H, 2 CH_2), 1.70–1.50 (*m*, 2H, CH_2). Anal. ($C_{14}H_{19}N_9O_2$•0.35 $C_4H_8O_2$ and 0.35 HCl) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-anilino-9H-purine (27).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (70:30 v/v) for thymine, purine base, and AZT and neat MeOH for product. The reaction was allowed to continue for 24 days. The product was isolated by Method 2 and purified by recrystallization from MeOH. A 35% yield was obtained. UV (nm): pH 1 λ_{max} 304, 255 (ε = 17,500, 12,600), pH 13 λ_{max} 303, 250 (ε = 22,600, 13,100); ^{1}H NMR (DMSO-d_6): δ 9.38 (*s*, 1H, H-8), 8.07 (*s*, 1H, NH), 7.99 (*d*, *J* = 7.73 Hz, 2H, phenyl), 7.26 (*t*, *J* = 8.21 Hz, 2H, phenyl), 6.96 (*t*, *J* =

7.23 Hz, 1H, phenyl), 6.22–6.13 (*m*, 3H, NH_2, H-1'), 5.22 (*t*, *J* = 5.62 Hz, 1H, 5'-OH), 4.65–4.57 (*m*, 1H, H-3'), 3.93–3.86 (*m*, 1H, H-4'), 3.63–3.55 (*m*, 2H, H-5'), 2.93–2.80 (*m*, 1H, H-2'), 2.50–2.39 (*m*, 1H, H-2'). Anal. ($C_{16}H_{17}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-benzylamino-9H-purine (28).* Compound **38** (0.40 g, 1.3 mmol) and benzylamine (1.4 mL, 13 mmol, 10 eq.) were combined in 25 mL anhydrous MeOH in a sealed tube. The reaction was heated in a 50°C oil bath overnight. The solvent was removed *in vacuo* and the product purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99:1 v/v) followed by chromatography on silica gel eluted with $CHCl_3$:MeOH (20:1 v/v). A 13% yield was obtained. UV (nm): EtOH λ_{max} 283, 259 (ε = 15,100, 10,700); ^{1}H NMR (DMSO-d_6): δ 7.92 (*s*, 1H, H-8), 7.80 (*br s*, 1H, NH), 7.33–7.17 (*m*, 5H, phenyl), 6.11 (*t*, *J* = 6.49 Hz, 1H, H-1'), 5.87 (*s*, 2H, NH_2), 5.29 (*t*, *J* = 5.43 Hz, 1H, 5'-OH), 4.75–4.52 (*m*, 3H, H-3', CH_2), 3.91–3.84 (*m*, 1H, H-4'), 3.60–3.52 (*m*, 2H, H-5'), 2.90–2.75 (*m*, 1H, H-2'), 2.50–2.31 (*m*, 1H, H-2'). Anal. ($C_{17}H_{19}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-phenethylamino-9H-purine (29).* Compound **38** (0.40 g, 1.3 mmol) and phenethylamine (0.82 mL, 6.5 mmol, 5 eq.) were combined in 15 mL anhydrous MeOH and refluxed overnight. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel eluted with EtOAc:MeOH (4:1 v/v). A 96% yield was obtained. UU (nm): pH 1 λ_{max} 292 (ε = 14,400), pH 13 λ_{max} 282 (ε = 18,800); ^{1}H NMR (DMSO-d_6): δ 7.79 (*s*, 1H, H-8), 7.40–7.10 (*m*, 6H, NH, phenyl), 6.10 (*t*, *J* = 6.6 Hz, 1H, H-1'), 5.80 (*br s*, 2H, NH_2), 5.30 (*t*, *J* = 5.8 Hz, 1H, 5'-OH), 4.60–4.50 (*m*, 1H, H-3'), 3.90–3.80 (*m*, 1H, H-4'), 3.60–3.50 (*m*, 4H, H-5',CH_2), 2.90–2.70 (*m*, 3H, H-2', CH_2), 2.40–2.30 (*m*, 1H, H-2'). Anal. ($C_{18}H_{21}N_9O_2$•0.3 $C_4H_8O_2$ and 0.2 H_2O) C,H,N.

trans-*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-[(2-phenylcyclopropyl)amino]-9H-purine (30).* 2-Phenylcyclopropylamine hydrochloride (2.5 g, 14.7 mmol, 10 eq.) was dissolved in 5 mL H_2O and the pH adjusted to 12 with 5 N NaOH. The amine was extracted with EtOAc. The solvent was removed *in vacuo*. The free amine and compound **38** (0.4 g, 1.3 mmol) were combined in 25 mL of EtOH and heated in a 50°C oil bath overnight. The solvent was removed *in vacuo*. The product was purified by chromatography two times on basic alumina eluted with $CHCl_3$ and $CHCl_3$:MeOH (99:1 v/v) followed by chromatography on silica gel eluted $CHCl_3$:MeOH (20:1 v/v) and finally by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99.5:0.5 v/v). A 16% yield was obtained. UV (nm): pH 1 λ_{max} 297, 253 (ε = 15,500, 13,000), pH 13 λ_{max} 286, 260 (ε = 21,700, 14,000); ^{1}H NMR (DMSO-d_6): δ 7.92 (*s*, 1H, H-8), 7.62 (*br d*, *J* = 5.47 Hz, 1H, NH), 7.30–7.10 (*m*, 5H, phenyl), 6.11 (*t*, *J* = 6.53 Hz, 1H, H-1'), 5.82 (*s*, 2H, NH_2), 5.28 (*t*, *J* = 5.7 Hz, 1H,5'-OH), 4.60–4.56 (*m*, 1H, H-3'), 3.89–3.82 (*m*, 1H, H-4'), 3.59–3.53 (*m*, 2H, H-5'), 2.90–2.79 (*m*, 1H, H-2'), 2.50–2.36 (*m*, 1H, H-2'), 2.20–2.08 (*m*, 1H, CH), 1.40–1.15 (*m*, 2H, CH_2). Anal. ($C_{18}H_{21}N_9O_2$•0.75 CH_4O) C,H,N.

3'-Azido-2',3'-dideoxyguanosine (31). Compound **11** (1.42 g, 4.64 mmol) was dissolved in 150 mL H_2O. Adenosine deaminase (10 mG mL^{-1}, 3.5 mL) was added and the reaction stirred at ambient temperature for 3.5 h. The resulting suspension was filtered. The product was washed with H_2O and dried. A 86% yield was obtained. UV (nm): pH 1 λ_{max} 255 (ε = 13,500), pH 13 λ_{max} 265 (ε = 12,700); ^{1}H NMR (DMSO-d_6): δ 10.67 (*s*, 1H, NH), 7.92 (*s*, 1H, H-8), 6.51 (*br s*, 2H, NH_2), 6.05 (*t*, *J* = 6.49 Hz, 1H, H-1'), 5.11 (*t*, *J* = 5.27 Hz, 1H, 5'-OH), 4.59–4.51 (*m*, 1H, H-3'), 3.89–3.82 (*m*, 1H, H-4'), 3.60–3.46 (*m*, 2H, H-5'), 2.82–2.68 (*m*, 1H, H-2'), 2.50–2.37 (*m*, 1H, H-2'). Anal. ($C_{10}H_{12}N_8O_3$•0.25 H_2O) C,H,N. Lit. NMR (DMSO-d_6) 10.63 (*s*, 1H, NH), 7.93 (*s*, 1H, H-8), 6.49 (*br s*, 2H, NH_2), 6.08 (*t*, 1H, H-1'), 5.12 (*t*, 1H, 5'-OH), 4.57 (*m*, 1H, H-3'), 3.90 (*q*, $J_{3',4'}$–$J_{4',5'}$ = 4.5 Hz, 1H, H-4'), 3.60 (*m*, 2H, H-5'), 2.83 (*m*, 1H, $J_{1',2'a}$ = $J_{2'a,3'}$ = 6.5 Hz, H-2'a), 2.40 (*m*,1H, $J_{1',2'b}$ = 6.5 Hz, $J_{2'b,3'}$ = 5 Hz, $J_{2'a,2'b}$ = 13 Hz, H-2'b).[6]

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-dimethylamino-9H-purine (32).* The enzymatic reaction was followed by HPLC on a PRP-1 column eluted with MeOH:H_2O (60:40 v/v) for thymine, purine base, and AZT and MeOH:H_2O (90:10 v/v) for product. The reaction was allowed to continue for 14 days. The product was isolated by Method 1 and purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (97:3, v/v). Chromatography a second time on silica gel eluted with $CHCl_3$:MeOH (98:2, v/v) gave pure product in 41% yield. UV (nm): pH 1 λ_{max} 293, 257 (ε = 8900, 9300), pH 13 λ_{max} 284 (ε = 12,700); ^{1}H NMR (DMSO-d_6): δ 7.93 (*s*, 1H, H-8), 6.13 (*t*, *J* = 6.5 Hz, 1H, H-1'), 5.84 (*br s*, 2H, NH_2), 5.26 (*t*, *J* = 5.6 Hz, 1H, 5'-OH), 4.61–4.53 (*m*, 1H, H-3'), 3.91–3.84 (*m*, 1H, H-4'), 3.59–3.53 (*m*, 2H, H-5'), 3.33 [*br s*, 6H, $N(CH_3)_2$], 2.86–2.73 and 2.45–2.36 (*m*, 2H, H-2'). Anal. ($C_{12}H_{17}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-ethylmethylamino-9H-purine (33).* The enzymatic reaction was followed by HPLC on a PRP-1 column. Thymine, purine base, and AZT were eluted with MeOH:H_2O (50:50 v/v). Product was eluted with MeOH. The reaction was allowed to continue for 33 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99:1, v/v). A 16% yield was obtained. UV (nm): pH 1 λ_{max} 295, 257 (ε = 13,200, 13,100), pH 13 λ_{max} 284 (ε = 16,600); ^{1}H NMR: (DMSO-d_6): δ 7.93 (*s*, 1H, H-8), 6.13 (*t*, *J* = 6.59 Hz, 1H, H-1'), 5.82 (*s*, 2H, NH_2), 5.27 (*t*, *J* = 5.37 Hz, 1H, 5'-OH), 4.61–4.53 (*m*, 1H, H-3'), 4.05–3.84 (*m*, 3H, H-4', NCH_2), 3.59–3.53 (*m*, 2H, H-5'), 3.25 (*br s*, 3H, CH_3) 2.87–2.74 (*m*, 1H, H-2'), 2.47–2.33 (*m*, 1H, H-2'), 1.11 (*t*, *J* = 7.04 Hz, 3H, CH_3). Anal. ($C_{13}H_{19}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methylpropylamino-9H-purine (34).* The enzymatic reaction was followed by HPLC on a PRP-1 column. Thymine, purine base, and AZT were eluted with MeOH:H_2O (70:30 v/v) at 1 mL min^{-1}. Product was eluted with MeOH. The reaction was allowed to continue for 33 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99:1, v/v). A 30% yield was obtained. UV (nm): pH 1 λ_{max} 295, 257 (ε = 12,600, 12,300), pH 13 λ_{max} 284 (ε = 16,200); ^{1}H NMR: (DMSO-d_6): δ 7.93 (*s*, 1H, H-8), 6.13 (*t*, *J* = 6.64 Hz, 1H, H-1'), 5.81 (*s*, 2H, NH_2), 5.27 (*t*, *J* = 5.37 Hz, 1H, 5'-OH), 4.61–4.53 (*m*, 1H, H-3'), 4.00–3.80 (*m*, 3H, H-4', NCH_2), 3.59–3.53 (*m*, 2H, H-5'), 3.23 (*br s*, 3H, CH_3), 2.87–2.73 (*m*, 1H, H-2'), 2.45–2.32 (*m*, 1H, H-2'), 1.64–1.53 (*m*, 2H, CH_2), 0.84 (*t*, *J* = 7.37 Hz, 3H, CH_3). Anal. ($C_{14}H_{21}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-cyclopropylmethylamino-9H-purine (35).* The enzymatic reaction was followed by HPLC on a PRP-1 column. Thymine, purine base, and AZT were eluted with MeOH:H_2O (50:50 v/v) at 1 mL min^{-1}. Product was eluted with MeOH. The reaction was allowed to continue for 33 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (97:3, v/v). A 29% yield was obtained. UV (nm): pH 1 λ_{max} 303, 256 (ε = 16,600, 13,100), pH 13 λ_{max} 287, 264 (ε = 23,100, 14,400); ^{1}H NMR (DMSO-d_6): δ 7.96 (*s*, 1H, H-8), 6.16 (*t*, *J* = 6.58 Hz, 1H, H-1'), 5.89 (*s*, 2H, NH_2), 5.28 (*s*, 1H, 5'-OH), 4.63–4.58 (*m*, 1H, H-3'), 3.92–3.88 (*m*, 1H, H-4'), 3.62–3.58 (*m*, 2H, H-5'), 3.24–3.21 (*m*, 4H, NH, NCH_3), 2.88–2.80 (*m*, 1H, H-2'), 2.46–2.38 (*m*, 1H, H-2'), 0.85–0.65 (*m*, 4H, 2 CH_2). Anal. ($C_{14}H_{19}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-diethylamino-9H-purine (36).* The enzymatic reaction was followed by HPLC on a PRP-1 column. Thymine, purine base, and AZT were eluted with MeOH:H_2O (80:20 v/v) at 1 mL min^{-1}. Product was eluted with MeOH. The reaction was allowed to continue for 32 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (98:2, v/v). A 43% yield was obtained. UV (nm): pH 1 λ_{max} 296, 257 (ε = 12,900, 12,600), pH 13 λ_{max} 284 (ε = 16,400); ^{1}H NMR (DMSO-d_6): δ 7.93 (*s*, 1H, H-8), 6.13 (*t*, *J* = 6.48 Hz, 1H, H-1'), 5.80 (*br s*, 2H, NH_2), 5.30 (*t*, *J* = 5.43 Hz, 1H, 5'-OH), 4.62–4.54 (*m*, 1H, H-3'), 3.96–3.72 (*m*, 5H, H-4', 2 × CH_2), 3.63–3.54 (*m*, 2H, H-5'), 2.88–2.74 (*m*, 1H, H-2'), 2.45–2.32 (*m*, 1H, H-2'), 1.14 (*t*, *J* = 7.0 Hz, 6H, 2 × CH_3). Anal. ($C_{14}H_{21}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-(1-azetidinyl)-9H-purine (37).* The enzymatic reaction was followed by HPLC on a PRP-1 column. Thymine, purine base, and AZT were eluted with MeOH:H_2O (50:50 v/v). Product was eluted with MeOH. The reaction was allowed to continue for 33 days. The product was isolated by Method 1 and purified by chromatography on basic alumina eluted with $CHCl_3$:MeOH (99:1, v/v). A 56% yield was obtained. UV (nm): pH 1 λ_{max} 298, 257 (ε = 15,900, 14,000), pH 13 λ_{max} 285 (ε = 17,400); ^{1}H NMR (DMSO-d_6): δ 7.89 (*s*, 1H, H-8), 6.10 (*t*, *J* = 6.64 Hz, 1H, H-1'), 5.93 (*s*, 2H, NH_2), 5.26 (*t*, *J* = 5.62 Hz, 1H, 5'-OH), 4.61–4.53 (*m*, 1H, H-3'), 4.23 (*br s*, 4H, $2CH_2$), 3.90–3.84 (*m*, 1H, H-4'), 3.61–3.52 (*m*, 2H, H-5'), 2.87–2.74 (*m*, 1H, H-2'), 2.44–2.28 (*m*, 1H, H-2'). Anal. ($C_{13}H_{17}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-chloro-9H-purine (38).* The enzymatic reaction was followed by HPLC on a PRP-1 column. Thymine, purine base, and AZT were eluted with MeOH:H_2O (50:50 v/v). Product was eluted with MeOH:H_2O (60:40 v/v). The reaction was allowed to continue for 14 days. The product was isolated by Method 1 and purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (96:4, v/v). A 46% yield was obtained. UV (nm): pH 1 λ_{max} 310, 246 (ε = 8000, 7100), pH 13 λ_{max} 306, 246 (ε = 8800, 8200); ^{1}H NMR (DMSO-d_6): δ 8.34 (*s*, 1H, H-8), 6.98 (*s*, 2H, NH_2), 6.17 (*t*, *J* = 6.3 Hz, 1H, H-1'), 5.09 (*t*, *J* = 5.6 Hz, 1H, 5'-OH), 4.64–4.56 (*m*, 1H, H-3'), 3.92–3.85 (*m*, 1H, H-4'), 3.65–3.47 (*m*, 2H, H-5'), 2.93–2.80 and 2.53–2.40 (*m*, 2H, H-2'). Anal. ($C_{10}H_{11}ClN_8O_2$•0.25 H_2O) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methyl-9H-purine (39).* The enzymatic reaction was followed by HPLC on a PRP-1 column. Thymine, purine base, and AZT were eluted with MeOH:H_2O (40:60 v/v). Product was eluted with methanol/water (70:30 v/v). The reaction was allowed to continue for 12 days. The product was isolated by Method 1 and purified by recrystallization from H_2O. A 53% yield was obtained. UV (nm): pH 1 λ_{max} 310, 246 (ε = 6800, 6100), pH 13 λ_{max} 299, 244 (ε = 9200, 7600); ^{1}H NMR (DMSO-d_6): δ 8.21 (*s*, 1H, H-8); 6.46 (*s*, 2H, NH_2), 6.19 (*t*, *J* = 6.21 Hz, 1H, H-1'), 5.13 (*t*, *J* = 5.50 Hz, 1H, 5'-OH), 4.65–4.59 (*m*, 1H, H-3'), 3.92–3.88 (*m*, 1H, H-4'), 3.65–3.51 (*m*, 2H, H-5'), 2.92–2.83 (*m*, 1H, H-2'), 2.54–2.42 (*m*, 4H, H-2', CH_3). Anal. ($C_{11}H_{14}N_8O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-carbonitrile-9H-purine (40).* Compound **38** (0.50 g, 1.6 mmol) and tetrabutylammonium cyanide (0.864 g, 3.2 mmol, 2 eq.) were combined in 15 mL anhydrous acetonitrile. The solution was cooled to 0°C. Trimethylamine was bubbled into the solution for 10 min. The reaction was stirred at room temperature overnight. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel eluted with EtOAc:$CHCl_3$ (3:1 v/v). A 27% yield was obtained. UV (nm): pH 1 λ_{max} 351 (ε = 6400), pH 13 λ_{max} 345 (ε = 5600); ^{1}H NMR (DMSO-d_6): δ 8.57 (*s*, 1H, H-8), 7.19 (*s*, 2H, NH_2), 6.22 (*t*, *J* = 6.01 Hz, 1H, H-1'), 5.12 (*t*, *J* = 5.48 Hz, 1H, 5'-OH), 4.67–4.61 (*m*, 1H, H-3'), 3.93–3.89 (*m*, 1H, H-4'), 3.63–3.56 (*m*, 2H, H-5'), 2.94–2.86 (*m*, 1H, H-2'), 2.55–2.46 (*m*, 1H, H-2'). Anal. ($C_{11}H_{11}N_9O_2$) C,H,N.

*2-Amino-9-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-1,9-dihydro-4H-purine-6-thione (42).* Compound **19** (0.27 g, 0.82 mmol) was suspended in 10 mL of a pH 4.2 1 N KOAc buffer and chilled to 0°C. Oxone (1 g, 1.64 mmol, 2 eq.) was added and the reaction stirred at 0°C for 48 h. The solution was neutralized to pH 7 with 1 N NaOH. The solvents were removed *in vacuo*. The product was extracted from the residue with MeOH, filtered and the methanol removed *in vacuo*. The sulfone intermediate **41** was purified by chromatography on silica gel eluted first with EtOAc then EtOAc:$CHCl_3$ (10:1 v/v) followed by EtOAc:MeOH (4:1 v/v). The sulfone **41** (0.076 g, 0.2 mmol) was dissolved in 4 mL Me_2CO:H_2O (3:1 v/v) at room temperature. Sodium hydrosulfide hydrate (0.02 g) was added three times over 15 min. The reaction was stirred another 5 min. The solvents were removed *in vacuo*. The product was purified by chromatography on silica gel eluted with $CHCl_3$:MeOH (9:1 v/v). A 23% overall yield was obtained. UV (nm): pH 1 λ_{max} 344, 262 (ε = 25,700, 9800), pH 13 λ_{max} 319, 270, 251 (ε = 24,400, 9100, 17,800); ^{1}H NMR: (DMSO-d_6): δ 11.96 (*br s*, 1H, NH), 8.13 (*s*, 1H, H-8), 6.82 (*br s*, 2H, NH_2), 6.10–6.03 (*m*, 1H, H-1'), 5.14–5.08 (*m*, 1H, 5'-OH), 4.62–4.53 (*m*, 1H, H-3'), 3.92–3.84 (*m*, 1H, H-4'), 3.60–3.52 (*m*, 2H, H-5'), 2.86–2.74 (*m*, 1H, H-2'), 2.50–2.42 (*m*, 1H, H-2'). Anal. ($C_{10}H_{12}N_8O_2S$•0.1$CHCl_3$ and 0.5 CH_4O) C,H,N.

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