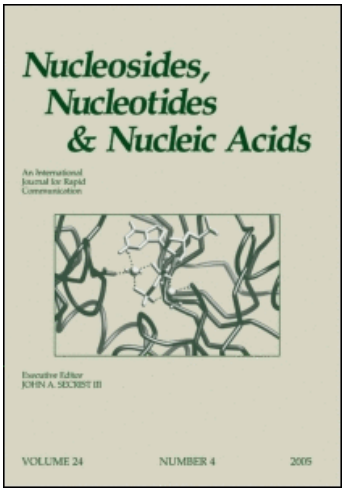


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Base-Functionalized Carbocyclic Nucleosides: Design, Synthesis, and Mechanism of Antiviral Activity

Vasu Nair[a]; Fan Zhang[a]; Xiaohui Ma[a]; Eric Bonsu[a]
[a] Department of Pharmaceutical and Biomedical Sciences and the Center for Drug Discovery, University of Georgia, Athens, Georgia, USA

To cite this Article Nair, Vasu , Zhang, Fan , Ma, Xiaohui and Bonsu, Eric(2009) 'Base-Functionalized Carbocyclic Nucleosides: Design, Synthesis, and Mechanism of Antiviral Activity', Nucleosides, Nucleotides and Nucleic Acids, 28: 5, 408 — 423
To link to this Article: DOI: 10.1080/15257770903044465
URL: http://dx.doi.org/10.1080/15257770903044465

Nucleosides, Nucleotides and Nucleic Acids, 28:408–423, 2009

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770903044465

Taylor & Francis
Taylor & Francis Group

BASE-FUNCTIONALIZED CARBOCYCLIC NUCLEOSIDES: DESIGN, SYNTHESIS, AND MECHANISM OF ANTIVIRAL ACTIVITY

Vasu Nair, Fan Zhang, Xiaohui Ma, and Eric Bonsu

Department of Pharmaceutical and Biomedical Sciences and the Center for Drug Discovery, University of Georgia, Athens, Georgia, USA

□ *New carbocyclic ribonucleosides with unsaturated groups at the C-2 position of the nucleobase were designed as potential RNA antiviral compounds. The design was based on the expectation that the monophosphates of these compounds would be inhibitors of the enzyme, IMPDH. Appropriate methodologies were developed to achieve the target molecules. Results from the initial in vitro antiviral studies are mentioned. The IMPDH-associated mechanism of the antiviral activity of the most active compound is supported by enzyme inhibition studies.*

Keywords Carbocyclic nucleosides; synthesis; antiviral; IMPDH inhibitor

INTRODUCTION

Inosine 5′-monophosphate dehydrogenase (IMPDH, EC 1.1.1.205) catalyzes NAD (nicotinamide adenine dinucleotide)-dependent oxidation of inosine 5′-monophosphate (IMP) into xanthosine 5′-monophosphate (XMP), which is the rate-limiting reaction in the de novo biosynthesis of GTP.[1] Two distinct but nearly identical IMPDH isoforms (Type I and II) exist in mammalian cells sharing 85% sequence identity. IMPDH Type I is ubiquitous and is present in normal cells, whereas IMPDH Type II is upregulated in malignant cells, including human neoplastic cells[2–4] and human leukemic cells.[5] Inhibition of IMPDH causes the reduction of guanine nucleotide pools, impeding DNA and RNA synthesis, guanine nucleotide-coupled signaling and oncogene expression. IMPDH inhibition suppresses cell proliferation and induces cell differentiation and

Received 2 February 2009; accepted 20 March 2009.
This project was supported by NIAID (NIH) through research award number U19 AI 056540.
Dedicated to Dr. Morris J. Robins on the occasion of his 70th birthday.
Address correspondence to Vasu Nair, Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, GA, 30602–2352, USA. E-mail: mail: vnair@rx.uga.edu

apoptosis.[6] As the demand for purine nucleotides needed for RNA and DNA synthesis increases significantly in virus-infected cells, inhibition of IMPDH may also lead to antiviral activity.[7] Thus, IMPDH has emerged as an important target enzyme for the development of chemotherapeutic agents and extensive efforts have been directed towards the discovery of IMPDH inhibitors.[8–11]

The mechanism of the biochemical conversion of IMP to XMP catalyzed by IMPDH is initiated by nucleophilic attack of the active-site residue, Cys-331, on IMP to form a covalent bond between the 2-position of IMP and the sulfhydryl group of Cys-331.[12,13] A hydride is then transferred to the cofactor, NAD^+, to produce NADH and E-XMP*. Subsequently, the resulting intermediate, E-XMP,* is subject to hydrolysis, which liberates XMP via a tetrahedral intermediate E-XMP.† Based on this mechanism, some nucleoside 5′-monophosphate derivatives containing modified purines as base moieties such as 3-deazaguanosine[14] and 2-vinylinosine[15] (Figure 1) have been identified as potent IMPDH inhibitors. 3-Deazaguanosine has been reported to possess broad spectrum antiviral activity against a variety of DNA and RNA viruses, as well as antitumor activity against the L1210 leukemia and several mammary adenocarcinomas in mice.[16,17] 2-Vinylinosine is a modified nucleoside with broad-spectrum RNA antiviral activity against a number of virus including JEV, PIC, PT, VEE, and YF.[18]

Compared to conventional nucleosides with natural sugar moieties, carbocyclic nucleosides are chemically more stable with respect to cellular degradation, particularly with respect to cleavage by nucleoside phosphorylases, because of the alteration of the N-glycosidic linkage. For example, 2-vinylinosine is a substrate for mammalian purine nucleoside phosphorylase,[19] while isonucleosides, where the base is translocated from the 1′-position to the non-glycosidic 2′-position, are not cleaved by nucleoside phosphorylases.[20] In the search for new ribonucleosides with RNA antiviral activity, we have synthesized new carbocyclic ribonucleosides functionalized at the C-2 position of the hypoxanthine nucleobase (Figure 2). This article reports on the methodologies for the synthesis of these

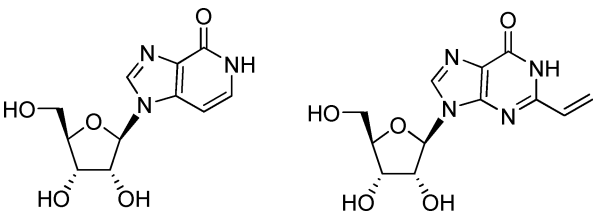


FIGURE 1 3-Deazaguanosine and 2-vinylinosine are IMPDH inhibitors as their monophosphates.

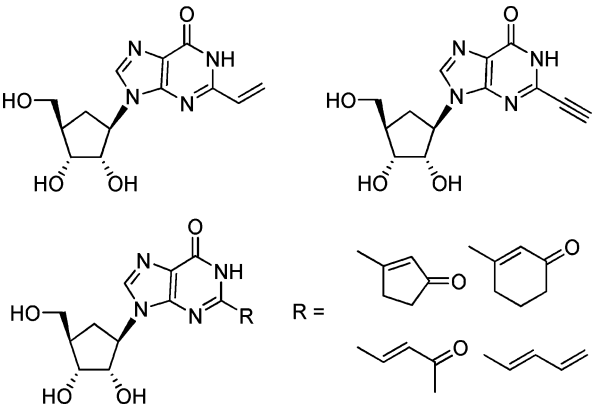


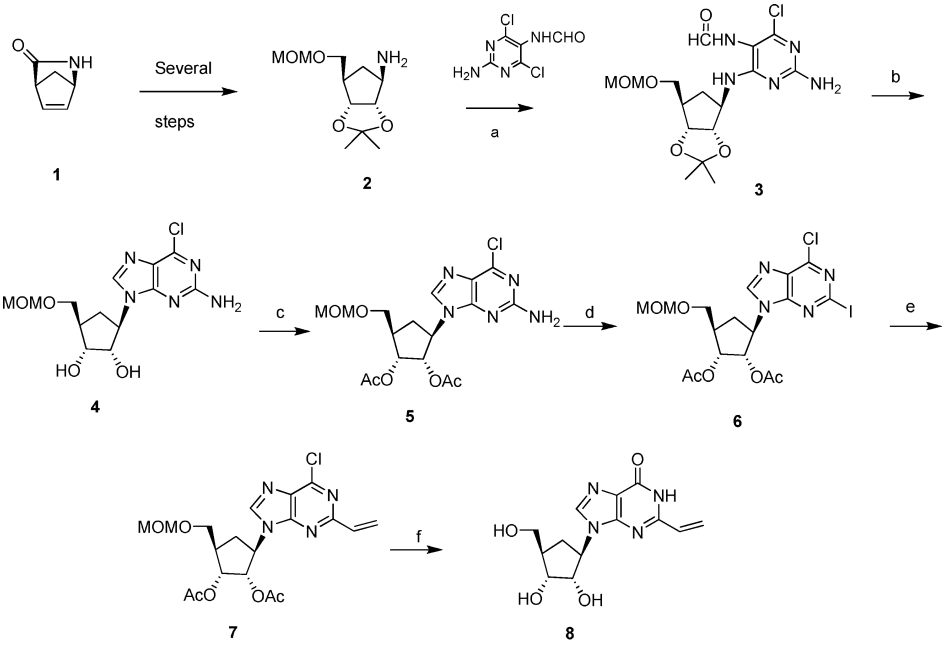
FIGURE 2 Structures of target compounds.

compounds, their antiviral activities and the IMPDH inhibition data and mechanism of antiviral activity of the most active compound.

RESULTS AND DISCUSSION

There are two general approaches to this class of compounds, which can be described as linear or convergent. In terms of chemical regioselectivity, the approach that may be preferable is the linear approach rather than the convergent approach because the former avoids side products arising from alkylation at different nitrogens on the purine base. This also simplifies purifications. However, both approaches were used in this article, depending on the target molecule. The bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one, in its racemic or chiral form, has been shown to be a versatile synthon for the preparation of carbocyclic nucleosides.[21] We used the commercially available chiral building block, (-)-2-azabicyclo[2.2.1]hept-5-en-3-one **1**, as the starting material for these syntheses (Scheme 1). In several steps (cis-hydroxylation, isopropylidene and Boc protection, reduction, MOM protection, and Boc removal), compound **1** was converted to the starting compound **2**,[22] on which the nucleobase was constructed and elaborated at the C-2 position. We had also attempted protection of the primary hydroxyl group of **2** through formation of the corresponding tert-butyldimethylsilyl ether, but this protecting group could not be removed successfully under aqueous conditions due to the poor solubility of the compound in water.

With intermediate **2** in hand as the building intermediate for the carbocyclic moiety, the strategy of first constructing carbocyclic guanosine and then modifying it was adopted for synthesis of target compounds. For carbocyclic 2-vinylinosine, the amine **2** and 2-amino-4,6-dichloro-5-formamidopyrimidine (prepared according to a literature method[23])

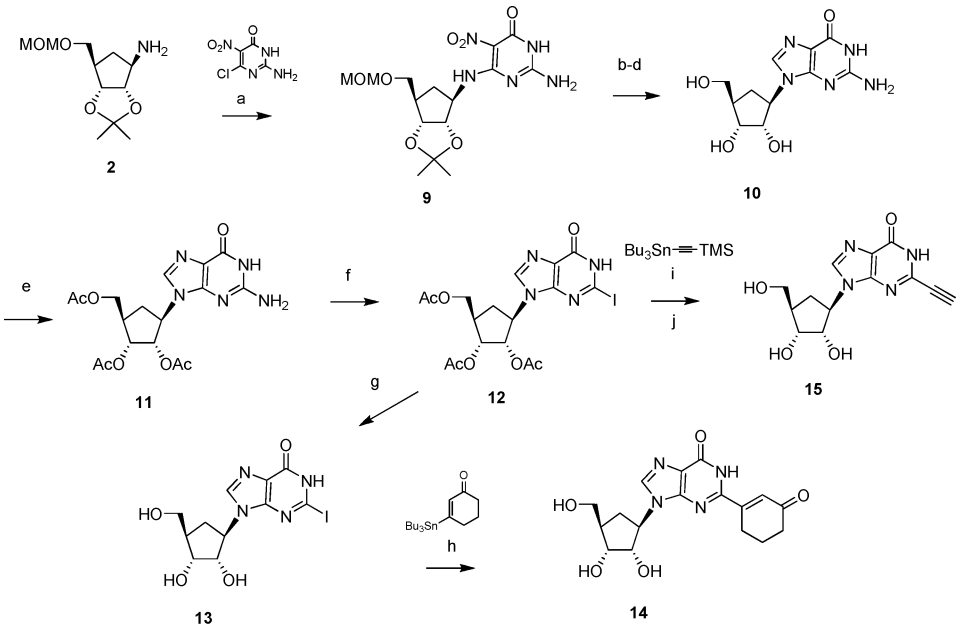


Reagents and conditions: (a) Et_3N, EtOH, reflux, 7h; (b) conc. HCl, $CH(OEt)_3$, overnight, r.t.; (c) Ac_2O, Py,CH_3CN, overnight, r.t.; (d) isoamyl nitrite, CH_2I_2, CH_3CN, relux, 5h; (e) tributylvinylstannane, $Pd(CH_3CN)_2Cl_2$, CH_3CN, reflux, 2h; (f) 1N HCl, reflux, 1h, then NH_3 H_2O, r.t., 30min.

SCHEME 1 Synthesis of a carbocyclic analog of 2-vinylinosine.

in ethanol in the presence of triethylamine was heated under reflux to afford compound **3**. The chloropurine **4** was obtained by treating **3** with 4 equivalents of concentrated HCl in triethylorthoformate.[24] However, under these acidic conditions, the cyclization reaction was accompanied by removal of the isopropylidene protecting group. Thus, continuation of the synthesis began with the diacetate **5**, which underwent deamination-halogenation[25] on treatment with isoamyl nitrite in the presence of diiodomethane at 75°C to afford the 2-iodo derivative **6**. Cross coupling of **6** with tributylvinylstannane catalyzed by $Pd(CH_3CN)_2Cl_2$ was carried out in CH_3CN under reflux conditions[26] to introduce the vinyl group at the C-2 position of the purine ring. The product, **7**, was subjected first to acidic hydrolysis conditions (removal of MOM protecting group) and the resulting product was treated with ammonium hydroxide to disconnect the acetate protecting groups to afford target compound **8.**

While compound **8** and its precursor, **7**, are relatively stable with respect to the C-2 vinyl substituent under the harsh acidic conditions used for the hydrolysis of compound **7**, target compounds and their precursors with reactive Michael acceptors at C-2 (e.g., α,β-unsaturated carbonyls) were found to be less stable under these conditions. So a new synthetic route based on radical deamination-iodination of partially protected carbocyclic



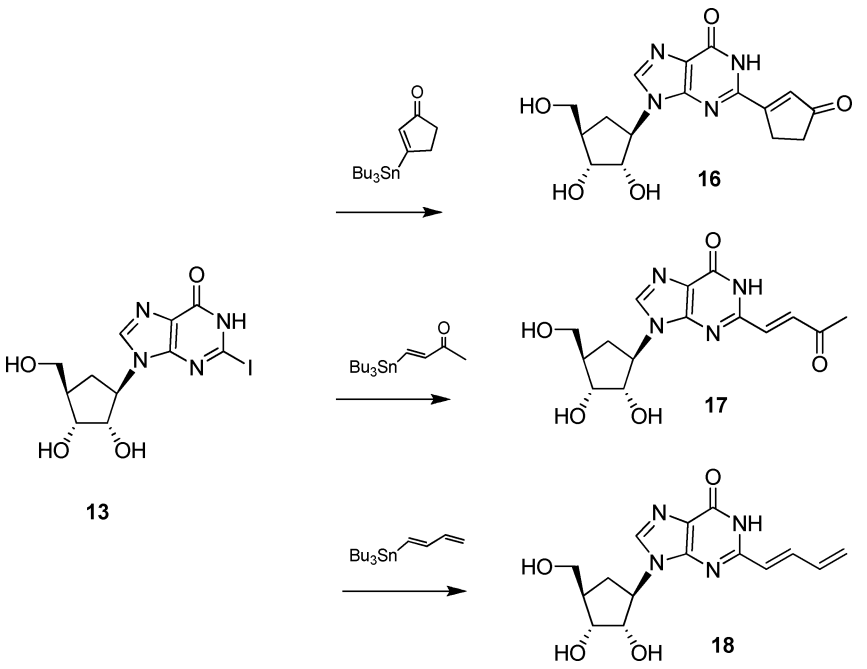
Reagents and conditions: (a) 4A molecular sieves, EtOH, reflux, 6h; (b) H_2, 10% Pt/C, MeOH, r.t., 3h; (c) $HCONH_2$, 220 °C, 2h; (d) 1N HCl, 80 °C, 0.5 h; (e) Ac_2O, Et_3N, CH_3CN, 55 °C, 1h; (f) isoamyl nitrite, CHI_3, CH_3CN, reflux, 2h; (g) NH_3, CH_3OH, r.t., 12 h; (h) tributylcyclohexenyl stannane, $Pd(PPh_3)_2Cl_2$, DMF, 95 °C, 6h; (i) $Pd(PPh_3)_2Cl_2$, DMF, 95 °C, 6h; (j) NH_3, CH_3OH, r.t., 12h.

SCHEME 2 Methodology to purine carbocyclic nucleosides with Michael acceptors at C-2.

guanosine and palladium-catalyzed cross-coupling between unprotected carbocyclic 2-iodoinosine and appropriate tin reagents was designed in which those substituents susceptible to nucleophilic attack were introduced into the purine ring in the final step. In this way, deprotection under acidic conditions was avoided and the sequence of protection and deprotection were necessary to achieve the target compounds described below.

Protected carbocyclic guanosine precursor **9** was synthesized from **2** in one step[22,23,27] and then converted in three further steps[24] to provide **10** (Scheme 2). Compound **10** was treated with acetic anhydride and triethylamine and the resulting triacetate, **11**, subjected to aprotic diazotization-halogenation[28] with isoamyl nitrite in the presence of iodoform in refluxing CH_3CN to afford the 2-iodopurine **12**. After formation of the 2-iodo compound, the protective groups of compound **12** were removed to provide the deprotected coupling precursor **13**. The 3-oxocyclohex-1-enyl functionality was introduced at C-2 through cross-coupling of **13** with 3-(tributylstannyl)cyclohex-2-enone under catalysis with $Pd(PPh_3)_2Cl_2$ in DMF to directly afford target compound **14**. Synthesis of the 2-ethynyl compound **15** required two steps[29] from precursor intermediate **12**.

A synthetic strategy similar to that used for **14** was adopted for the synthesis of compounds with other Michael acceptors at C-2: **16** (3-



SCHEME 3 Carbocyclic hypoxanthine nucleosides with other Michael acceptors.

oxocyclopent-1-enyl), **17** [(E)-3-oxobut-1-enyl] and **18** [(E)-buta-1,3-dienyl] (Scheme 3).

The compounds synthesized in this article were submitted for initial antiviral assays against a number of RNA viruses. The most active compound in this series was compound **8**, which is moderately active against Flu A (H5N1), [$EC_{50} = 3\mu g/$ mL, CC_{50} 74 $\mu g/$ mL, TI = 23 (MDCK, NR Assay)]. It also exhibits low activity against the Punta Toro virus [$EC_{50} = 7\mu g/$ mL, CC_{50} 28 $\mu g/$ mL TI = 4 (LLC-MK2), NR Assay]. The mechanism of the antiviral activity of compound **8** may be associated with the inherent ability of its monophosphate to inhibit IMPDH through blocking the formation of the ternary complex normally formed between the enzyme, the substrate IMP and the cofactor, NAD^+.[7] Support for this comes from our observation of the inhibition of *E. coli* IMPDH by the monophosphate of **8** (graphical data shown below in Figures 3 and 4). We found that **8-MP** was a strong inactivator of IMPDH with a k_{on} of 2.12×10^4 $M^{-1}s^{-1}$ (the second-order rate constant, $k_{on} = k_{inact}/K_i$, is a measure of the potency of the inhibition). In comparison, 2-vinylinosine 5′-monophosphate exhibited a k_{on} of 0.73×10^4 $M^{-1}s^{-1}$ and 6-chloropurine ribonucleoside 5′-monophosphate had a k_{on} of 1.55×10^2 $M^{-1}s^{-1}$ (*E. coli* IMPDH).[12,15]

The activity/toxicity of two other compounds of the series synthesized need to be mentioned. Compound **15** shows some toxicity and it was difficult to determine whether any observed activity (e.g., against the West Nile

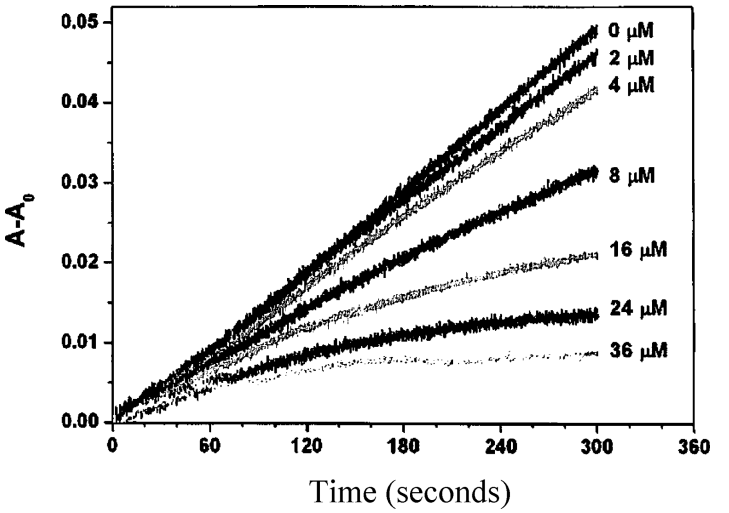


FIGURE 3 Progress curves for the inhibition of IMPDH by inhibitor **8-MP** monitored by the UV absorption of cofactor product, NADH, at 340 nM (see reference 15 for detailed procedure for inhibition studies).

virus) was due to activity or was a manifestation of the toxicity of this compound. Target compound **18** exhibited low activity against SARS (Vero cells). Further antiviral studies are in progress.

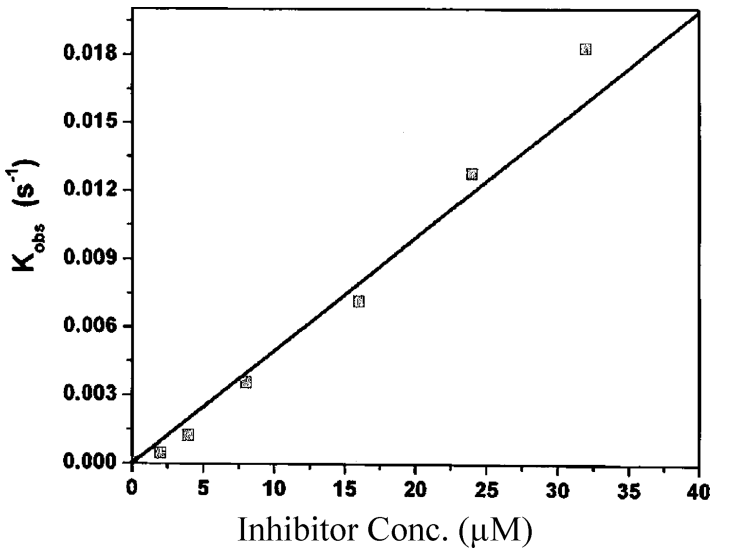


FIGURE 4 Plot of K_{obs} versus inhibitor concentration derived from progress curves of Figure 3. The relevant equations are: $A—A_o = V_o/K_{obs}[1\text{-}\exp(-K_{obs}t)$ and $K_{obs} = k_{on}[I]/(1 + [IMP]/K_m$.

SUMMARY AND CONCLUSIONS

In summary, six new carbocyclic hypoxanthine ribonucleosides, **8** and **14–18**, with different unsaturated groups at the C-2 position of the nucleobase were designed as inhibitors of IMPDH as their monophosphates. Because of the reactivity of the exocyclic groups at C-2, the multi-step syntheses of these compounds were challenging but appropriate methodologies were developed to achieve the target molecules. Evaluation of the compounds for in vitro RNA antiviral activity revealed that one of the compounds (**8**) had good activity against the FluA (H5N1) virus. The mechanism of the antiviral activity of compound **8** may be associated with the inherent ability of its monophosphate to inhibit IMPDH and experimental support for this came from inhibition studies, which showed that the monophosphate of this compound was a strong inactivator of IMPDH.

EXPERIMENTAL SECTION

(1R,2S,3R,4R)-1-[(2-Amino-6-chloro-5-formamido-4-pyrimidinyl) amino] -2,3-isopropyl -idenedioxy-4-(methoxymethoxymethyl) cyclopentane (3)

A mixture of compound **2** (1.32 g, 5.70 mmol), [22] 2-amino-4,6-dichloro-5-formamidopyrimidine (1.18g, 5.70 mmol) and triethylamine (2 mL) in ethanol (15 mL) was heated under reflux for 7h. After cooling to 5°C, the mixture was filtered and washed with ethanol (50 mL). The combined filtrate was concentrated and the residue was purified on a silica gel column using chloroform/methanol (97:3) as eluent to give compound **3** (1.18 g, 51.5%): ^{1}H NMR (500MHz, DMSO-d_6) δ 9.05 and 8.66 (s and d, J = 11Hz, total 1H), 8.17 and 7.81 (s and d, J = 11Hz, total 1H), 7.11 and 6.82 (two d, J = 8, 8Hz, total 1H), 6.64 and 6.53 (two br.s, total 2H), 4.60 (s, 2H), 4.54–4.51 (m, 1H), 4.42–4.39 (m, 2H), 3.51–3.48 (m, 2H), 3.27 (s, 3H), 2.23–2.16 (m, 2H), 1.47–1.43 (m, 1H), 1.42 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (125MHz, CD_3OD) δ 167.4, 162.5, 161.3, 159.9, 155.4, 111.3, 96.3, 86.0, 83.0, 69.0,.56.7, 54.4, 45.0, 33.0, 26.1,23.6; UV λ_{max} (MeOH) 212 nm (ε 33500), 241 nm (ε 16000), 289 nm (ε 10100); HRMS (ESI) calcd for $C_{16}H_{25}Cl\,N_5O_5$ $[M+H]^+$ for 402.1544, found 402.1531.

(1R,2S,3R,5R)-3-(2-Amino-6-chloro-9H-purin-9-yl)-5-[(methoxymethoxy)methyl] cyclopentane-1,2-diol (4)

A solution of compound **3** (100 mg, 0.25 mmol) and triethylorthoformate (60 mL) was stirred while conc. HCl (37%, 1.8 mL) was added in one portion. A clear, light yellow solution resulted within one minute. After 4 hours, the solution was neutralized with saturated $NaHCO_3$, extracted

with EtOAc, washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dissolved in 0.6 N HCl. After stirring for 30 minutes at room temperature, the pH of the reaction mixture was adjusted to 10 with ammonium hydroxide. The solution was concentrated to dryness and the residue was dissolved in acetone and filtered. The filtrate was evaporated to give the crude product, which was purified by silica gel chromatography to afford pure compound **4** (70 mg, 81.4%): ^{1}H NMR (500MHz, DMSO-d_6) δ 8.28 (s, 1H), 6.89 (br.s, 2H), 5.05 (d, J = 6Hz, 1H), 4.78 (d, J = 4Hz, 1H), 4.68–4.61 (m,3H), 4.35–4.31 (m, 1H), 3.83–3.81 (m, 1H), 3.60–3.57(m, 1H), 3.52–3.48 (m, 1H), 3.29 (s, 3H), 2.28–2.26 (m, 1H), 2.20–2.16 (m, 1H), 1.64–1.61 (m, 1H); ^{13}C NMR (125MHz, CD_3OD) δ 159.9, 154.1, 150.1, 142.5, 124.0, 96.2, 74.5, 72.5, 69.0, 60.2, 54.2, 43.2, 28.6; UV λ_{max} (MeOH) 225 nm (ε 34300), 248 nm (ε 6800), 310 nm (ε 9700); HRMS (ESI) calcd for $C_{13}H_{19}ClN_5O_4$ $[M+H]^+$ for 344.1126, found 344.1107.

(1R,2S,3R,5R)-3-(2-Amino-6-chloro-9H-purin-9-yl)-5-[(methoxymethoxy)methyl] cyclo- pentane-1,2-diol diacetate (5)

A solution of compound **4** (100 mg, 0.29 mmol) in acetonitrile (5 mL) was treated with acetic anhydride (0.15 mL, 1.60 mmol) in the presence of pyridine (5 mL) and stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the title compound **5** (98 mg, 0.23 mmol, 79.3%):^{1}H NMR (500MHz, DMSO-d_6) δ 8.34 (s, 1H), 6.99 (br. s, 2H), 5.65–5.62 (m, 1H), 5.25–5.23 (m, 1H), 4.99–4.93 (m, 1H), 4.65 (s, 2H), 3.66–3.62 (m, 2H), 3.30 (s, 3H), 2.47–2.38 (m, 2H), 2.10 (s, 3H), 2.01–1.93 (m, 1H), 1.91 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ 170.0, 169.9, 159.0, 153.7, 151.4, 141.2, 125.6, 96.6, 74.4, 73.3, 67.9, 57.3, 55.6, 41.2, 28.7, 20.9, 20.5; UV λ_{max} (MeOH) 221 nm (ε 23200), 247 nm (ε 5800), 308 nm (ε 6030); HRMS (ESI) calcd for $C_{17}H_{23}Cl\ N_5O_6$ $[M+H]^+$ for 428.1337, found 428.1346.

(1R,2S,3R,5R)-3-(2-Iodo-6-chloro-9H-purin-9-yl)-5-[(methoxymethoxy) methyl]cyclo- pentane-1,2-diol diacetate (6)

A dry, one-necked round bottom flask equipped with a magnetic stirring bar and an argon bubble was charged with compound **5** (235 mg, 0.55 mmol) and acetonitrile (25 mL). The solution was stirred under the argon atmosphere and cooled to about 5°C in an ice/water bath. To the solution was added diiodomethane (735 mg, 2.75 mmol) and isoamyl nitrite (332 mg, 2.75 mmol). The solution was purged with argon for 30 minutes and then heated at 90°C under an argon atmosphere for 5 hours. After removal of solvent under reduced pressure, the residue was purified on a silica gel

column to give compound **6** (135 mg, 45.6%): ^{1}H NMR (500MHz, $CDCl_3$) δ 8.22 (s, 1H), 5.75–5.72 (m, 1H), 5.42–5.40 (m, 1H), 5.22–5.16 (m, 1H), 4.78–4.74 (m, 2H), 3.85–3.82 (m,1H), 3.69–3.66 (m, 1H), 3.45 (s, 3H), 2.74–2.69 (m, 1H), 2.57–2.54 (m, 1H), 2.18 (s, 3H), 2.17–2.13 (m, 1H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 125MHz) δ 170.0, 169.9, 152.7, 150.7, 143.6, 132.0, 116.6, 96.8, 74.8, 73.7, 67.8, 57.8, 55.7, 41.3, 29.3, 20.9, 20.5; UV λ_{max} (MeOH) 277nm (ε 11300); HRMS (ESI) calcd for $C_{17}H_{21}Cl\,IN_4O_6$ $[M+H]^+$ for 539.0194, found 539.0199.

(1R,2S,3R,5R)-3-(2-Vinyl-6-chloro-9H-purin-9-yl)-5-[(methoxymethoxy)methyl]cyclo- pentane-1,2-diol diacetate (7)

Compound **6** (260 mg, 0.48 mmol), $Pd(CH_3CN)_2Cl_2$ (8 mg, 0.031 mmol) and tributylvinylstannane (780 mg, 2.46 mmol) in anhydrous CH_3CN (18 mL) was heated under reflux for 2 hours. The solution was evaporated to dryness under reduced pressure and the residue was purified by silica gel column chromatography to afford compound **7** (140 mg, 66.5%): ^{1}H NMR (500MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.93–6.88 (m, 1H), 6.71–6.68 (m, 1H), 5.81–5.76 (m, 2H), 5.47–5.45 (m, 1H), 5.12–5.08 (m,1H), 4.71 (s, 2H), 3.80–3.77 (m 1H), 3.70–3.67 (m, 1H), 3.41 (s, 3H), 2.64–2.60 (m,1H), 2.56–2.54 (m,1H), 2.29 (s, 3H), 2.15–2.11 (m, 1H), 1.95 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ169.9, 169.8, 158.9, 152.2, 150.9, 144.0, 135.4, 130.6, 124.4, 96.7, 74.6, 73.3, 67.8, 58.0, 55.6, 41.3, 29.0, 20.9, 20.5; UV λ_{max} (MeOH) 229 nm (ε 21500), 276 nm (ε 12400); HRMS (ESI) calcd for $C_{19}H_{24}\,Cl\,N_4O_6$ $[M+H]^+$ for 439.1384, found 439.1383.

9-[(1′R,2′S,3′R,4′R)-2′,3′-Dihydroxy-4′-(hydroxymethyl) cyclopentyl]-2-vinyl-1H-purin-6(9H)-one (8)

Compound **7** (140 mg, 0.31 mmol) was heated under reflux in 1N HCl (10 mL) for 1 hour. After cooling to room temperature, the reaction mixture was treated with ammonium hydroxide (10 mL, pH 10–11). Then the solvent was removed under reduced pressure and the residue was purified initially by silica gel column chromatography and then by HPLC to provide compound **8** (43 mg, 47.5%): ^{1}H NMR (500MHz, CD_3OD) δ 8.16 (s, 1H), 6.69–6.60 (m, 2H), 5.85 (dd, J = 9, 2Hz, 1H), 4.91–4.87 (m, 1H), 4.58–4.55 (m,1H), 4.10–4.09 (m,1H), 3.74–3.72 (m, 2H), 2.49–2.45 (m, 1H), 2.27 (m, 1H), 2.04–1.99 (m, 1H); ^{13}C NMR (125MHz, CD_3OD) δ 157.9, 151.7, 149.4, 140.4, 129.2, 124.5, 123.2, 75.2, 72.3, 63.2, 60.6, 45.4, 29.0; UV (H_2O) λ_{max} 295 nm (ε 7100), 262 nm (ε 7700); HRMS (ESI) calcd for $C_{13}H_{17}N_4O_4$ $[M+H]^+$ for 293.1250, found 293.1222.

2-Amino-6-[(1′R,2′S,3′R,4′R)-2′,3′-isopropylidenedioxy-4′-(methoxymethoxymethyl)- cyclopentylamino]-5-nitropyrimidin-4(3H)-one (9)

2-Amino-6-chloro-5-nitropyrimidin-4(3H)-one (2.65 g, 13.9 mmol) and the amine **2** (1.34g, 5.79 mmol) were suspended in dry EtOH (100 mL) and stirred for 1 hour over 4A molecular sieves. The reaction mixture was subsequently heated under reflux for 2 hours. After cooling to room temperature, the mixture was filtered and the residue was washed with (3 × 10 mL). The combined filtrate was evaporated to dryness and the residue was purified by silica gel column chromatography to give compound **9** (1.53g, 65.7%): ^{1}H NMR (500MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.74 (d, J = 8Hz, 1H), 7.95 (br.s, 1H), 6.61 (br.s, 1H), 4.68–4.66 (m, 1H), 4.64–4.61 (m, 2H), 4.56–4.54 (m, 1H), 4.48–4.47 (m,1H), 3.55–3.48 (m, 2H), 3.26 (s, 3H), 2.41–2.37 (m, 1H), 2.28–2.26 (m,1H), 1.59–1.54 (m,1H), 1.42 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125MHz, DMSO-d_6) δ 159.0, 156.7, 154.5, 111.3, 110.9, 96.1, 86.2, 83.1, 69.2, 57.3, 55.1, 44.9, 34.3, 27.6, 25.1; UV (MeOH) λ_{max} 215 nm (ε 31500), 238 nm (ε 21900), 283 nm (ε 7600), 330 nm (ε 16300); HRMS (ESI) calcd for $C_{15}H_{24}N_5O_7$ $[M+H]^+$ for 386.1676, found 386.1675.

2-Amino-9-[(1′R,2′S,3′R,4′R)-2′,3′-dihydroxy-4′-(hydroxymethyl)cyclopentyl]-1H-purin -6(9H)-one (10)

The nitro product from the previous step (1000 mg, 2.60 mmol) was dissolved in dry methanol (50 mL). Under an argon atmosphere, 10% Pt/C (1000 mg) was added and the reaction mixture was stirred under a H_2 atmosphere (14 psi). After 30 minutes, diisopropylethylamine (1 mL) was added and the hydrogenation was continued for 3 hours. The solvent was removed under reduced pressure, and the crude product was dissolved in formamide (10 mL) under argon, and the solution was heated under reflux for 2 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was condensed to dryness under reduced pressure and the residue was purified by silica gel column chromatography to give the cyclized protected nucleoside (670 mg, 70.5% for two steps): ^{1}H NMR (500MHz, DMSO-d_6) δ10.61 (s, 1H), 7.89 (s, 1H), 6.64 (br.s, 2H), 4.65–4.62 (m, 1H), 4.61(s, 2H), 4.54–4.52 (m, 1H), 4.46–4.44 (m,1H), 3.56–3.54 (m, 2H), 3.28 (s, 3H), 2.31–2.28 (m, 2H), 2.03–2.00 (m,1H), 1.50 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (125MHz, DMSO-d_6) δ 161.9, 157.3, 153.9, 151.5, (137.5), 117.3, 113.1, 96.2, 83.8, 81.6, 68.8, 59.5, 55.1, 43.8, 35.1, 27.9, 25.5; UV λ_{max} (MeOH) 254 nm (ε 12600); HRMS (ESI) calcd for $C_{16}H_{24}N_5O_5$ $[M+H]^+$ for 366.1777, found 366.1761.

The protected nucleoside from the previous step (300 mg, 0.82 mmol) was heated to 80°C in 1N HCl for 20 minutes. After cooling to room temperature, the solution was neutralized by saturated $NaHCO_3$. The solvent was then removed and the residue was dissolved in methanol and filtered. The filtrate was concentrated and purified by HPLC to give compound **10** (166 mg, 71.3%):^{1}H NMR (500MHz, CD_3OD) δ 7.84 (s,1H), 4.71–4.66 (m, 1H), 4.47–4.44 (m, 1H), 4.05–4.03 (m, 1H), 3.72–3.69 (m, 2H), 2.42–2.39 (m, 1H), 2.24–2.22 (m, 1H), 1.91–1.88 (m, 1H); ^{13}C NMR (125MHz, CD_3OD) δ 158.0, 153.5, 152.0, 137.4, 116.7, 75.1, 72.3, 63.2, 59.9, 45.4, 28.8; UV λ_{max} (MeOH) 254nm (ε 9600); HRMS (ESI) calcd for $C_{11}H_{16}N_5O_4$ $[M+H]^+$ for 282.1202, found 282. 1190.

2-Amino-9-[(1′R,2′S,3′R,4′R)-2′,3′-diacetoxy-4′-(acetoxymethyl)cyclopentyl]-1H-purin-6(9H)-one (11)

Compound **10** (127 mg, 0.45 mmol), triethylamine (1010 mg, 10 mmol) and DMAP (10 mg, 0.08 mmol) were suspended in dry acetonitrile (10 mL). To the solution was added acetic anhydride (163 mg, 1.6 mmol) and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give compound **11** (135 mg, 73.1%): ^{1}H NMR (500MHz, CD_3OD) δ 7.77 (s, 1H), 5.72–5.68 (m,1H), 5.37–5.34 (m, 1H), 4.94–4.91 (m, 1H), 4.29–4.26 (m, 2H), 2.66–2.63 (m,1H), 2.45–2.42 (m, 1H), 2.11–2.07 (m,1H), 2.09 (s, 3H), 2.07 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (125MHz, CD_3OD) δ171.4, 170.3, 170.2, 158.0, 153.8, 151.7, 137.6, 116.8, 74.4, 72.4, 64.4, 57.8, 40.6, 28.2, 19.5, 19.4, 19.1; UV λ_{max} (MeOH) 254nm (ε 10000); HRMS (ESI) calcd for $C_{17}H_{22}N_5O_7$ $[M+H]^+$ for 408.1519, found 408.1509.

9-[(1′R,2′S,3′R,4′R)-2′,3′-Diacetoxy-4′-(acetoxymethyl) cyclopentyl]-2-iodo-1H-purin-6(9H)-one (12)

To a solution of compound **11** (135 mg, 0.33 mmol) and iodoform (1299 mg, 3.3 mmol) in dry acetonitrile (15 mL) under argon was added isoamyl nitrite (387 mg, 3.3 mmol) at 5°C. The solution was purged with argon for 30 minutes and then heated under reflux under argon for 2 hours. After removal of solvent under reduced pressure, the residue was purified by silica gel column chromatography to give compound **12** (25 mg, 14.6%): ^{1}H NMR (500MHz, CD_3OD) δ 8.06 (s, 1H), 5.70–5.66 (m, 1H), 5.40–5.38 (m, 1H), 5.09–5.07 (m, 1H), 4.32–4.30 (m, 2H), 2.64–2.61 (m,1H), 2.55–2.52 (m, 1H), 2.15–2.13 (m,1H), 2.14 (s, 3H), 2.13 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 171.0, 169.8, 169.7, 158.7, 148.9, 139.0, 124.9, 105.0, 74.3, 72.2, 64.1, 58.3, 40.5, 29.0, 21.0, 20.9, 20.5; UV λ_{max} (MeOH) 254nm (ε

12900); HRMS (ESI) calcd for $C_{17}H_{20}IN_4O_7$ $[M+H]^+$ for 519.0377, found 519.0376.

9-[(1′R,2′S,3′R,4′R)-2′,3′-Dihydroxy-4′-(hydroxymethyl)-cyclopentyl]-2-iodo-1H-purin-6(9H)-one (13)

A solution of compound **12** (20 mg, 0.038 mmol) in methanolic ammonia (10 mL) was stirred under room temperature for 12 hours. After the reaction was complete, the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography to give compound 1**3** (11 mg, 71.1%): ^{1}H NMR (500MHz, CD_3OD) δ 8.05 (s, 1H), 4.86–4.81 (m, 1H), 4.50–4.47 (m, 1H), 4.08–4.06 (m, 1H), 3.74–3.69 (m, 2H), 2.50–2.46 (m, 1H), 2.28–2.25 (m, 1H), 1.91–1.86 (m, 1H); ^{13}C NMR (125MHz, CD_3OD) δ160.3, 149.4, 138.9, 124.0, 109.7, 75.5, 72.4, 63.2, 60.2, 45.4, 29.2; UV λ_{max} (MeOH) 254nm (ε 12900); HRMS (ESI) calcd for $C_{11}H_{14}IN_4O_4$ $[M+H]^+$ for 393.0060, found 393.0008.

9-[(1′R,2′S,3′R,4′R)-2′,3′-Dihydroxy-4′-(hydroxymethyl) cyclopentyl]-2-(3-oxocyclohex-1-enyl)-1H-purin-6(9H)-one (14)

To a solution of compound **13** (50 mg, 0.13 mmol) and $Pd(PPh_3)_2Cl_2$ (14 mg, 0.01 mmol) in anhydrous DMF (5 mL) was added 3-(tributylstannyl)cyclohex-2-enone (120 mg, 0.30 mmol). The reaction mixture was stirred at 95°C under argon for 24 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound **14** (20 mg, 42.2%): ^{1}H NMR (500MHz,DMSO-d_6) δ 12.28 (s, 1H), 8.17 (s, 1H), 6.75 (s, 1H), 4.92 (m, 1H), 4.68–4.64 (m, 3H), 4.27–4.25 (m, 1H), 3.78 (m, 1H), 3.42–3.36 (m, 2H), 2.77–2.74 (m, 2H), 2.37–2.35 (m, 2H), 2.20–2.15 (m, 1H), 1.98–1.93 (m, 3H), 1.68–1.65 (m, 1H); ^{13}C NMR (125MHz, DMSO-d_6) δ 199.6, 157.5, 151.9, 151.7, 148.5, 141.5, 129.5, 125.0, 75.3, 72.2, 63.6, 60.2, 45.7, 37.6, 29.9, 25.7, 22.4; UV λ_{max} (MeOH) 243nm (ε 15500), 328 (ε 7400); HRMS (ESI) calcd for $C_{17}H_{21}N_4O_5$ $[M+H]^+$ for 361.1512, found 361.1519.

Preparation of 9-[(1′R,2′S,3′R,4′R)-2′,3′-dihydroxy-4′-(hydroxymethyl)cyclo pentyl]-2-ethynyl-1H-purin-6(9H)-one (15)

To a solution of compound **12** (130 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) in anhydrous DMF (5 mL) was added 2-(tributylstannyl)ethynyl)trimethylsilane (387 mg, 1.00 mmol). The reaction mixture was stirred at 95°C under argon for 24 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the title compound **15** (86 mg, 70.4%): ^{1}H NMR (500MHz, $CDCl_3$) δ 11.54 (br.s, 1H), 7.85 (s, 1H), 5.68–5.65 (m,

1H), 5.35–5.33 (m, 1H), 5.00–4.98 (m,1H), 4.27–4.20 (m,2H), 2.55–2.52 (m, 2H), 2.13 (s, 3H), 2.10 (s, 3H), 2.09–2.07 (m,1H), 1.96 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) 171.6, 170.5, 170.4, 158.3, 149.3, 140.2, 138.4, 126.6, 101.7, 96.7, 74.7, 73.0, 65.0, 58.5, 41.3, 29.7, 21.7, 21.6, 21.2; UV λ_{max} (MeOH) 254nm (ε 6400), 261nm (ε 6300), 301nm (ε 9300) HRMS (ESI) calcd for $C_{22}H_{29}N_4O_7Si$ $[M+H]^+$ for 489.1806, found 489.1801.

The aforementioned coupled product (86 mg, 0.17 mmol) was treated with NH_3/MeOH (saturated at 0°C, 20 mL) at 0°C for 6 hours. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography and HPLC to afford the title compound **33** (24 mg, 48.6%): ^{1}H NMR (500MHz, DMSO-d_6) δ 12.84 (br.s, 1H), 8.19 (s, 1H), 4.92 (m, 1H), 4.69–4.58 (m, 4H), 4.17–4.15 (m,1H), 3.75 (m,1H), 3.52–3.36 (m, 2H), 2.19–2.17 (m, 1H), 1.97–1.95 (m,1H), 1.54–1.50 (m, 1H); ^{13}C NMR (125MHz, DMSO-d_6) 157.4, 148.6, 140.4, 137.6, 125.5, 83.3, 77.5, 75.6, 72.1, 63.4, 59.5, 45.8, 30.3; UV λ_{max} (MeOH) 252nm (ε 2900), 260nm (ε 2800), 297nm (ε 3800); HRMS (ESI) calcd for $C_{13}H_{15}N_4O_4$ $[M+H]^+$ for 291.1093, found 291.1060.

9-[(1′R,2′S,3′R,4′R)-2′,3′-Dihydroxy-4′-(hydroxymethyl) cyclopentyl]-2-(3-oxocyclo- pent-1-enyl)-1H-purin-6(9H)-one (16)

Compound **13** (60 mg, 0.15 mmol) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.01 mmol) in anhydrous DMF (5 mL) was treated with 3-(tributylstannyl)cyclopent-2-enone (174 mg, 0.45 mmol) and the reaction mixture was stirred at 95°C under argon for 24 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give compound **16** (22 mg, 43.1%): ^{1}H NMR (500MHz, CD_3OD) δ 8.23 (s, 1H), 7.04 (s, 1H), 4.93–4.89 (m, 1H), 4.62–4.60 (m, 1H), 4.12–4.10 (m, 1H), 3.75–3.72 (m, 2H), 3.23–3.20 (m, 2H), 2.64–2.62 (m, 2H), 2.49–2.46 (m, 1H), 2.28–2.26 (m, 1H), 2.11–2.09 (m, 1H); ^{13}C NMR (125MHz, DMSO-d_6) δ 209.4, 166.7, 157.8, 149.0, 148.5, 142.1, 133.6, 125.7, 75.2, 72.2, 63.6, 60.7, 45.7, 35.4, 29.7, 28.2; UV λ_{max} (MeOH) 240nm (ε 22800), 332nm (ε 14500); HRMS (ESI) calcd for $C_{16}H_{19}N_4O_5$ $[M+H]^+$ for 347.1355, found 347.1351.

9-[(1′R,2′S,3′R,4′R)-2′,3′-Dihydroxy-4′-(hydroxymethyl)cyclo- pentyl]-2-[(E)-3-oxobut-1-enyl]-1H-purin-6(9H)-one (17)

To a solution of compound **13** (30 mg, 0.08 mmol) and $Pd(PPh_3)_2Cl_2$ (6 mg, 0.008 mmol) in anhydrous DMF (5 mL) was added (E)-4-(tributylstannyl)but-3-en-2-one (41.2 mg, 0.12 mmol). The reaction mixture was stirred at 95°C under argon for 24 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give compound **17** (11 mg, 41.2%): ^{1}H NMR (500MHz,

CD_3OD) δ 8.24 (s, 1H), 7.39 (d, J = 16Hz, 1H), 7.34 (d, J = 16Hz, 1H), 4.92–4.90 (m, 1H), 4.57–4.54 (m, 1H), 4.11–4.09 (m, 1H), 3.75–3.74 (m, 2H), 2.49–2.46 (m,1H), 2.45 (s, 3H), 2.29–2.27 (m, 1H), 2.05–2.02 (m, 1H); ^{13}C NMR (125MHz, CD_3OD) δ 198.1, 157.8, 150.1, 149.1, 141.0, 134.6, 133.4, 124.2, 75.3, 72.3, 63.1, 60.6, 45.4, 29.0, 26.8; UV λ_{max} (MeOH) 233nm (ε 26100), 337nm (ε 9900); HRMS (ESI) calcd for $C_{15}H_{19}N_4O_5$ $[M+H]^+$ for 335.1355, found 335.1345.

2-[(E)-Buta-1,3-dienyl]-9-[(1′R,2′S,3′R,4′R)-2′,3′-dihydroxy-4′-(hydroxymethyl)cyclo- pentyl] -1H-purin-6(9H)-one (18)

Compound **13** (60 mg, 0.15 mmol) and $Pd(PPh_3)_2Cl_2$ (8 mg, 0.01 mmol) in anhydrous DMF (5 mL) was treated with (E)-buta-1,3-dienyltributylstannane (172 mg, 0.50 mmol). This reaction mixture was then stirred at 95°C under argon for 24 hours. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give compound **18** (21 mg, 44.3%):^{1}H NMR (500MHz, CD_3OD) δ 8.15 (s, 1H), 7.64–7.59 (m, 1H), 6.67–6.63 (m, 1H), 6.48–6.45 (m, 1H), 5.73–5.70 (m, 1H), 5.55–5.53 (m, 1H), 4.92–4.88 (m, 1H), 4.58–4.55 (m, 1H), 4.12–4.10 (m, 1H), 3.76–3.75 (m, 2H), 2.49–2.44 (m, 1H), 2.30–2.27 (m, 1H), 2.08–2.05 (m, 1H); ^{13}C NMR (125MHz, CD_3OD) δ 158.0, 152.1, 149.6, 140.3, 140.0, 135.4, 123.5, 123.1, 122.9, 75.3, 72.4, 63.1, 60.5, 45.4, 28.9; UV λ_{max} (MeOH) 236 nm (ε 34000), 260 nm (ε 29400), 321 nm (ε 22900); HRMS (ESI) calcd for $C_{15}H_{19}N_4O_4$ $[M+H]^+$ for 319.1406, found 319.1404.

REFERENCES

1. Weber, G.; Nakamura, H.; Natsumeda, Y.; Szekeres, T.; Nagai, M. Regulation of GTP biosynthesis. *Adv. Enzyme Regu.* **1992**, 32, 57–69.
2. Natsumeda, Y.; Ohno, S.; Kawasaki, H.; Konno, Y.; Weber, G.; Suzuki, K. Two distinct cDNAs for human IMP dehydrogenase. *J. Biol. Chem.* **1990**, 265, 5292–5295.
3. Collart, F.R.; Huberman, E. Cloning and sequence analysis of the human and Chinese hamster inosine-5′-monophosphate dehydrogenase cDNAs. *J. Biol. Chem.* **1988**, 263, 15769–15772.
4. Senda, M.; Natsumeda, Y. Tissue-differential expression of two distinct genes for human IMP dehydrogenase (E.C.1.1.1.205). *Life Sciences* **1994**, 54, 1917–1926.
5. Nagai, M.; Natsumeda, Y.; Konno, Y.; Hoffman, R.; Irino, S.; Weber, G. Selective up-regulation of type II inosine 5′-monophosphate dehydrogenase messenger RNA expression in human leukemias. *Cancer Res.* **1991**, 51, 3886–3890.
6. Weber, G.; Prajda, N.; Abonyi, M.; Look, K.Y.; Tricot, G. Tiazofurin: molecular and chemical action. *Anticancer Res.* **1996**, 16, 3313–3322.
7. Nair, V.; Shu, Q. Inosine monophosphate dehydrogenase as a probe in antiviral drug discovery. *Antiviral Chem. & Chemother.* **2007**, 18, 245–258.
8. Franchetti, P.; Cappellacci, L.; Grifantini, M. IMP dehydrogenase as a target of antitumor and antiviral chemotherapy. *Farmaco* **1996**, 51, 457–469.
9. Ratcliffe, A.J. Inosine 5′-monophosphate dehydrogenase inhibitors for the treatment of autoimmune diseases. *Current Opin. Drug Discov. Develop.* **2006**, 9, 595–605.

10. Shu, Q.; Nair, V. Inosine monophosphate dehydrogenase (IMPDH) as a target in drug discovery. *Med. Res. Rev.* **2007**, 28, 219–232.
11. Nair, V. IMPDH inhibitors: discovery of antiviral agents against emerging diseases, in *Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats*, ed. P. F. Torrence, Wiley & Sons, Hoboken, NJ, 2005, pp 179–202.
12. Kerr, K.M.; Hedstrom, L. Asp338 controls hydride transfer in Escherichia coli IMP dehydrogenase. *Biochemistry* **2000**, 39, 9804–9810.
13. Link, J.O.; Straub, K. Trapping of an IMP dehydrogenase-substrate covalent intermediate by mycophenolic acid. *J. Am. Chem. Soc.* **1996**, 118, 2091–2092.
14. Cook, P.D.; Rousseau, R.J.; Mian, A.M.; Dea, P.; Meyer, R.B.; Robins, R.K. Synthesis of 3-deazaguanine, 3-deazaguanosine, and 3-deazaguanylic acid by a novel ring closure of imidazole precursors. *J. Am. Chem. Soc.* **1976**, 98, 1492–1498.
15. Pal, S.; Bera, B.; Nair, V. Inhition of inosine monophosphate dehydrogenase (IMPDH) by the antiviral compound, 2-vinylinosine monophosphate. *Bioorg. Med. Chem.* **2002**, 10, 3615–3618.
16. Allen, L.B.; Huffman, J.H.; Cook, P.D.; Meyer, R.B., Jr.; Robins, R.K.; Sidwell, R.W. Antiviral activity of 3-deazaguanine, 3-deazaguanosine, and 3-deazaguanylic acid. *Antimicrob. Agents Chemother.* **1977**, 12, 114–119.
17. Revankar, G.R.; Gupta, P.K.; Adams, A.D.; Dalley, N.K.; McKernan, P.A.; Cook, P.D.; Canonico, P.G.; Robins, R.K. Synthesis and antiviral/antitumor activities of certain 3-deazaguanine nucleosides and nucleotides. *J. Med. Chem.*, 1984, 27, 1389–1396.
18. Nair, V.; Ussery, M.A. New hypoxanthine nucleosides with RNA antiviral activity. *Antiviral Res.* **1992**, 19, 173–178.
19. Pal, S.; Nair, V. Phosphorylation of the anti-HIV compound,(S,S)-isodideoxyadenosine by human recombinant deoxycytidine kinase. *Biochem. Pharmacol.* **2000**, 60, 1505–1508.
20. Guenther, S.; Balzarini, J.; DeClercq, E.; Nair, V. A thymidine-phosphorylase stable analogue of BVDU with significant antiviral activity. *J. Med. Chem.* **2002**, 45, 5426–5429.
21. Daluge, S.; Vince, R. Synthesis of carbocyclic aminonucleosides. *J. Org. Chem.*, **1978**, 43, 2311–2320.
22. Hutchinson, E.J.; Taylor, B.F.; Blackburn, G.M. Synthesis of carbocyclic NAD+ containing a methylenebisphosphonate linkage for the investigation of ADP-ribosyl cyclase. *Chem.Commun.* **1996**, 24, 2765–2766.
23. Daluge, S.M.; Martin, M.T.; Sickle, B.R.; Livingston, D.A. An efficient, scalable synthesis of the HIV reverse transcriptase inhibitor Ziagen. *Nucleosides, Nucleotides Nucleic Acids* **2000**, 19, 297–327.
24. Pickering, L.; Nair, V. Synthesis of novel bicyclic nucleosides related to griseolic acids. *Nucleosides Nucleotides* **1996**, 15, 1751–1769.
25. Nair, V.; Richardson, S.G. Utility of purinyl radicals in the synthesis of base-modified nucleosides and alkylpurines: 6-amino group replacement by hydrogen, chlorine, bromine, and iodine. *J. Org. Chem.*, **1980**, 45, 3969–3974.
26. Nair, V.; Turner, G.A.; Chamberlain, S.D. Novel approaches to functionalized nucleosides *via* palladium-catalyzed cross-coupling with organostannanes. *J. Am Chem. Soc.* **1987**, 109, 7223–7224.
27. Burgdorf, L.T.; Carell, T. Synthesis, stability and conformation of the formamidopyrimidine G DNA lesion. *Chem. Eur. J.*, **2002**, 8, 293–301.
28. Bonsu, E.T. *Synthesis of C-2 and C-6 functionalized ribofuranosyl purine analogues as potential antiviral agents targeting inhibition of inosine monophosphate dehydrogenase. Ph.D. thesis*, University of Georgia, USA, 2005.
29. Purdy, D.F.; Nair, V. Synthetic approaches to new doubly modified nucleosides: congeners of cordycepin and related 2′-deoxyadenosine. *Tetrahedron* **1991**, 47, 365–382.