Bioorganic & Medicinal Chemistry 19 (2011) 5648–5669

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and biological evaluation of 2′,4′- and 3′,4′-bridged nucleoside analogues

K. C. Nicolaou [a,b,c,*], Shelby P. Ellery [a], Fatima Rivas [a], Karen Saye [d], Eric Rogers [d], Tyler J. Workinger [e], Mark Schallenberger [a], Rommel Tawatao [e], Ana Montero [a], Ann Hessell [d], Floyd Romesberg [a], Dennis Carson [e], Dennis Burton [d]

[a] Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
[b] Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
[c] Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA
[d] Department of Immunology and Microbial Science and International AIDS Vaccine Initiative Neutralizing Antibody Center, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
[e] Moores UCSD Cancer Center, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA

ARTICLE INFO

Article history:
Received 20 May 2011
Revised 12 July 2011
Accepted 13 July 2011
Available online 23 July 2011

Keywords:
Nucleosides
Synthesis
Antiviral
Cytotoxic

ABSTRACT

Most nucleosides in solution typically exist in equilibrium between two major sugar pucker forms, N-type and S-type, but bridged nucleosides can be locked into one of these conformations depending on their specific structure. While many groups have researched these bridged nucleosides for the purpose of determining their binding affinity for antisense applications, we opted to look into the potential for biological activity within these conformationally-locked structures. A small library of 2′,4′- and 3′,4′-bridged nucleoside analogues was synthesized, including a novel 3′,4′-carbocyclic bridged system. The synthesized compounds were tested for antibacterial, antitumor, and antiviral activities, leading to the identification of nucleosides possessing such biological activities. To the best of our knowledge, these biologically active compounds represent the first example of 2′,4′-bridged nucleosides to demonstrate such properties. The most potent compound, nucleoside **33**, exhibited significant antiviral activity against pseudoviruses SF162 (IC_{50} = 7.0 μM) and HxB2 (IC_{50} = 2.4 μM). These findings render bridged nucleosides as credible leads for drug discovery in the anti-HIV area of research.

1. Introduction

The first antiviral antisense oligodeoxynucleotides were discovered in 1978 by Zamecnik and Stephenson.[1] Since then, interest in antisense technologies has been on the rise due to these molecules having the potential to treat diseases that small molecule drugs are incapable of targeting. Perhaps the most promising candidates for antisense drug therapy have been the 2′,4′-bridged nucleic acids (BNAs), as they have recently entered human clinical trials.[2] Their success is due to their more rigid structures, which translate into higher affinities for their biological targets. Most sugars and nucleosides exist in solution in a fast equilibrium between two major sugar pucker forms, North (N-type) and South (S-type),[3] but bridged nucleosides are locked into one conformation: 2′,4′-bridged systems such as **1a** exist in the C3′-*endo* (N-type) form **1b**, while 3′,4′-systems such as **2a** exist in the C2′-*endo* (S-type) conformation **2b** (Fig. 1). Therefore, 2′,4′-BNAs with the N-type conformation and 3′,4′-BNAs with the S-type conformation have a high binding affinity for complementary single-stranded RNA and DNA, respectively, giving the 2′,4′-BNAs a special advantage as promising antisense drug candidates.

Due to this fact, several groups have directed their research efforts toward the synthesis of novel bridged nucleosides in an attempt to determine the best bridged nucleic acid for antisense drug therapy. Following the synthesis and evaluation of the 2′-*O*,4′-*C*-[4] and 3′-*O*,4′-*C*-[5] bridged nucleic acids, there have been reports on the synthesis of 2′-*NO*,4′-*C* systems,[6] 2′-*N*,4′-*C*-bridged systems,[7] 2′,4′-propylene-BNAs,[8] carbocyclic-BNAs,[9] and more.[10] However, only a few groups have explored the biological activities of bridged nucleoside analogues themselves (see Fig. 2 for selected

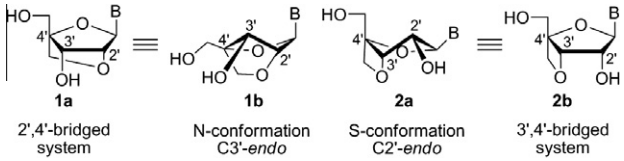


Figure 1. Locked conformations of 2′,4′-bridged system **1a**/**1b** and 3′,4′-bridged system **2a**/**2b**.

* Corresponding author. Tel.: +1 858 284 2400; fax: +1 858 284 2469.
E-mail address: kcn@scripps.edu (K.C. Nicolaou).

0968-0896/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2011.07.022

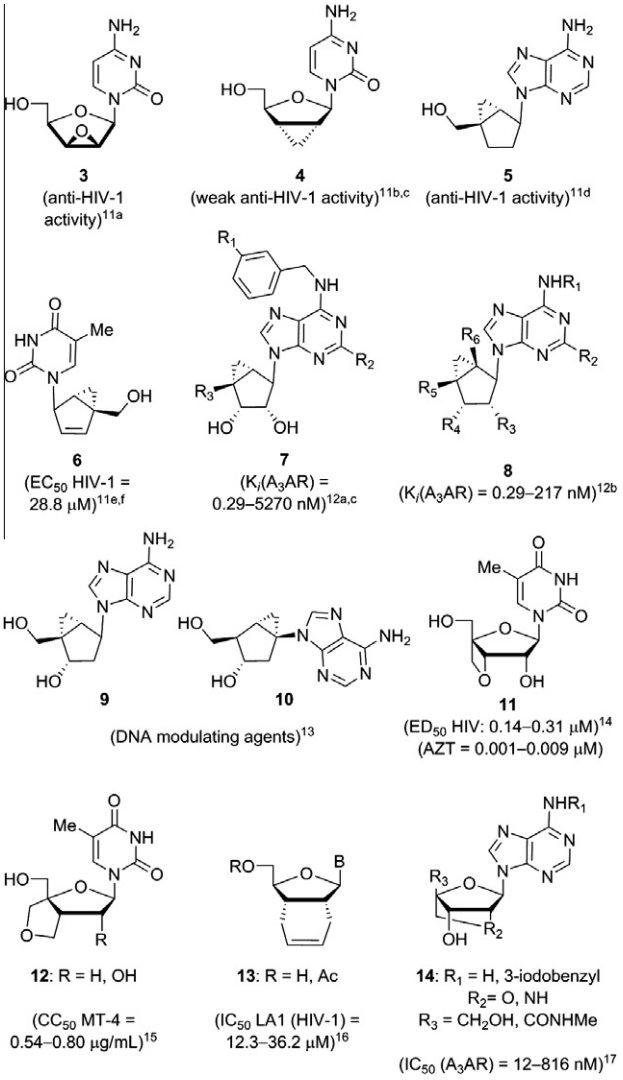


Figure 2. Previously synthesized bridged nucleoside analogues **3**–**14** and their biological activities. A_3AR = adenosine A_3 receptor. CC_{50} = Concentration at which compound is cytotoxic to half the amount of cells. MT-4 = metallothionein 4, a human T cell line. LA1 = lymphocytotropic strain of HIV-1.

examples). This appears to be a research area that warrants further attention, for what has been published does show potential for medicinal applications. Thus, and as shown in Figure 2, select epoxide- and cyclopropane-bridged systems have been shown to have significant antiviral activity (**3**–**6**),[11] and act as adenosine A_3 receptor inhibitors (**7** and **8**)[12] and DNA polymerase modulating agents (**9** and **10**).[13] Also reported were antiviral 3′,4′-oxetane bridged nucleoside analogue **11**,[14] cytotoxic 3′,4′-tetrahydrofuran bridged nucleoside derivative **12**,[15] and antiviral 2′,3′-hexahydroisobenzofuran bridged nucleosides **13**.[16] Additionally, a number of 2′,4′-bridged nucleoside analogues such as compounds **14** have demonstrated the ability to act as adenosine A_3 receptor antagonists (see Fig. 2),[17] while other 2′,4′-bridged derivatives have shown no significant antiviral[18] or anticancer[19] activity.

Since there are a number of nucleoside analogue drugs currently in clinical use and in clinical trials, we felt it was important to further probe the biological activity of these bridged nucleoside systems while simultaneously developing new synthetic strategies for their continued development. Herein, we describe the synthesis of a library of 2′,4′- and 3′,4′-bridged nucleoside analogues which not only differ by the structure of the bridge, but also by the substitution on the adenine base (see compounds **15**–**51**, Fig. 3). Additionally, a new type of 3′,4′-bridged nucleoside was synthesized through a novel [2+2] cycloaddition pathway (see compounds **52** and **53**, Fig. 3). All compounds were tested for antibacterial, antitumor, and antiviral activities, with some compounds displaying significant biological activities.

2. Results and discussion

2.1. Synthesis of 2′,4′-bridged nucleoside analogues

Beginning from commercially available diacetone D-glucose, oxidation, then reduction to invert the secondary alcohol, and subsequent benzylation afforded literature-known diacetonide **54** (Scheme 1).[20] One-pot selective acetonide removal and oxidative cleavage with periodic acid furnished aldehyde **55** in 98% yield, from which differentially protected sugar **56** was prepared through a known sequence of steps.[5c,21] Vorbrüggen coupling[22] with 2,6-diaminopurine then installed the base onto diacetate **56**; however, two different products resulted, depending on the specific conditions employed. The use of only 2 equiv of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) resulted in a quantitative yield of the thermodynamic product *N*9-isomer **57**. Increasing the amount of BSA to 5 equiv caused the formation of compound **57** plus the kinetic product unnatural *N*7-isomer **58** in a 1.6:1 ratio and 95% total yield. This appears to be due to the fact that excess BSA further silylates the 2,6-diaminopurine, resulting in a species that can attack the diacetate with either the *N*9 or *N*7 purine positions.[23]

2′,4′-Bridged compound **59** was constructed through base-induced cyclization of *N*9-isomer **57** (aq 2 M NaOH, 94% yield, Scheme 2). From this point, the synthesis diverged to produce a number of substituted amino analogues as shown in Scheme 2. Cyclization product **59** was peracylated with benzoyl chloride to afford tetrabenzoate **60** in 52% yield, along with a number of less substituted side products which were not isolated or characterized. Desilylation of compound **60** (HF·py) then led to the targeted nucleoside **15** in 50% yield. Compound **59** was also deprotected directly with HF·py to give diamino compound **16** in 85% yield. The use of boron trichloride to remove the benzyl ether from this intermediate furnished the expected β-nucleoside **17** in 85% yield, along with a 10% yield of the corresponding α-nucleoside (**18**), the mixture being a result of oxonium formation at the anomeric position. Additionally, the difference in the nucleophilicity of the amine groups in intermediate **59** was exploited to furnish, through reductive alkylation, mono-substituted derivatives **61**–**64** with ethyl, *n*-octyl, *n*-butyl, and isobutyl groups, respectively (see Scheme 2).[24] The yields in this step were moderate (48%, 29%, 57%, and 52%, respectively) due to incomplete reactions and decomposition of the alkyl aldehyde components. Desilylation (TBAF) of these products afforded compounds **19**–**21** and **23** in good yields. Further debenzylation of *n*-butylamine **21** and isobutylamine **23** with BCl_3 furnished butylamine diol **22** and isobutylamine diol **24** in 71% and 64% yield, respectively. Due to the lack of biological activity of nucleosides **22** and **24**, it was decided not to proceed with the deprotection of compounds **19** and **20**.

With *N*7-isomer **58** in hand, bridged nucleoside analogues with unnatural bases attached became synthetically accessible. Thus, in a similar fashion to the *N*9-isomer **57**, *N*7-isomer **58** was cyclized with aqueous sodium hydroxide to produce 2′,4′-bridged tetrahydrofuran ring system **65** in 85% yield (Scheme 3). Reductive alkylation of the latter compound with isobutyraldehyde formed isobutylamine **66**, which furnished targeted nucleoside **25** upon desilylation (TBAF) in 34% yield over the two steps. Alternatively, intermediate **65** could be desilylated directly with HF·py to generate analogue **26**. Debenzylation (BCl_3) then furnished nucleoside **27** in 46% yield over the two steps. Further explorations into these

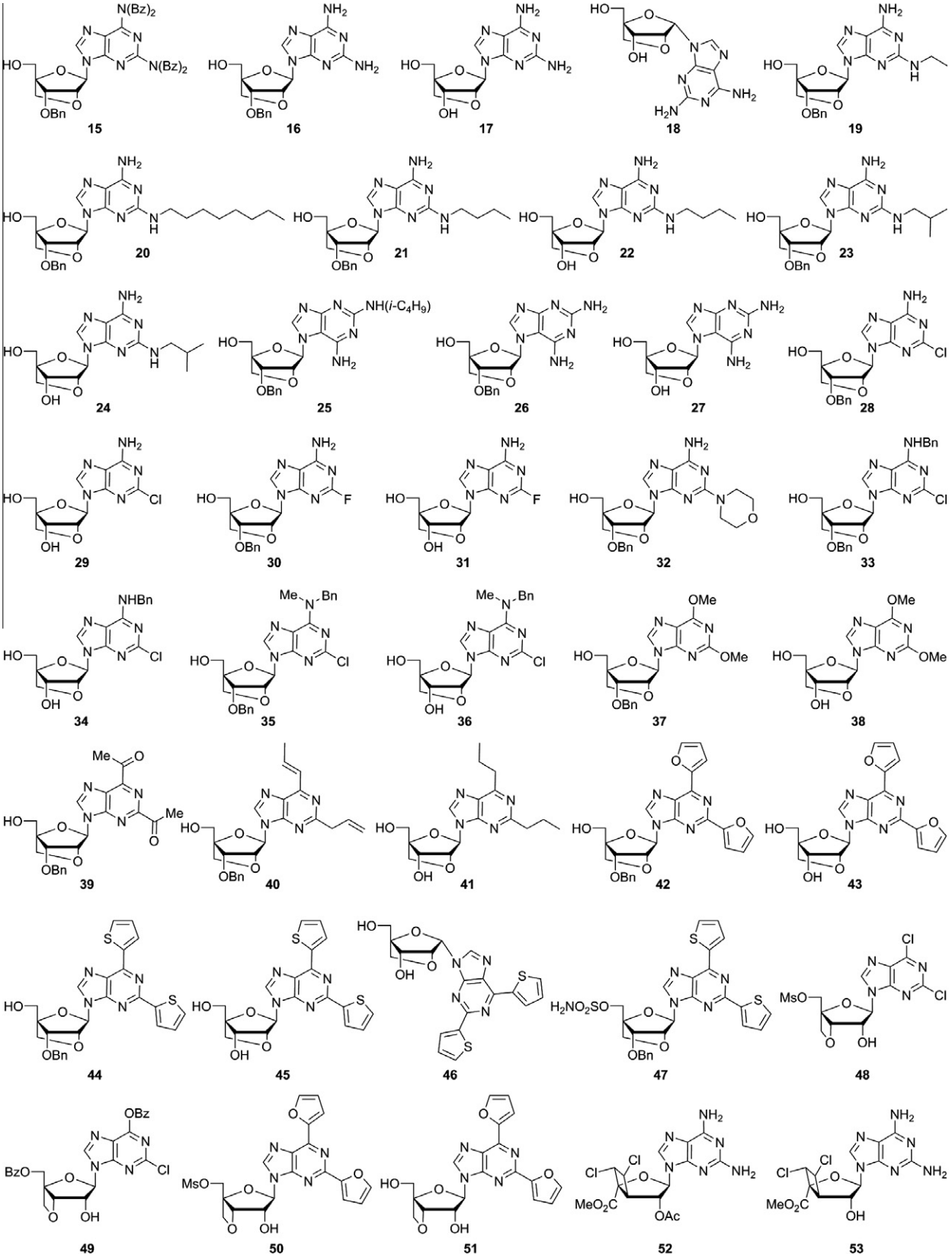
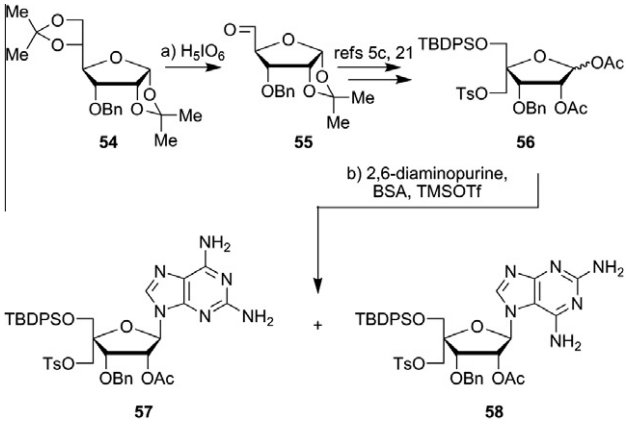


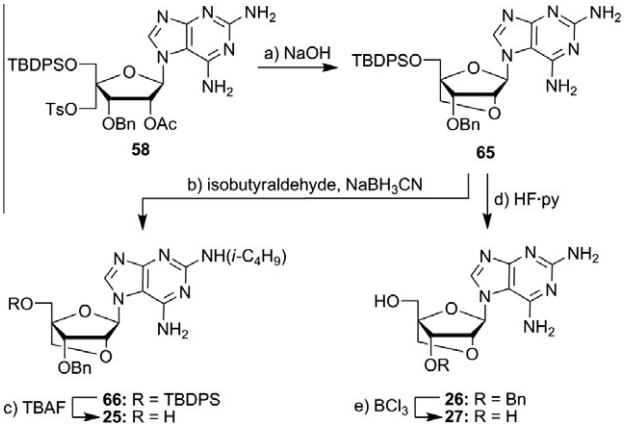
Figure 3. Synthesized compound library of bridged nucleoside analogues (**15**–**53**).

unnatural *N*7-isomeric analogues were not pursued due to instability problems with the nucleoside base during chemical transformations, which suggested that these compounds may also be too labile for biological applications.

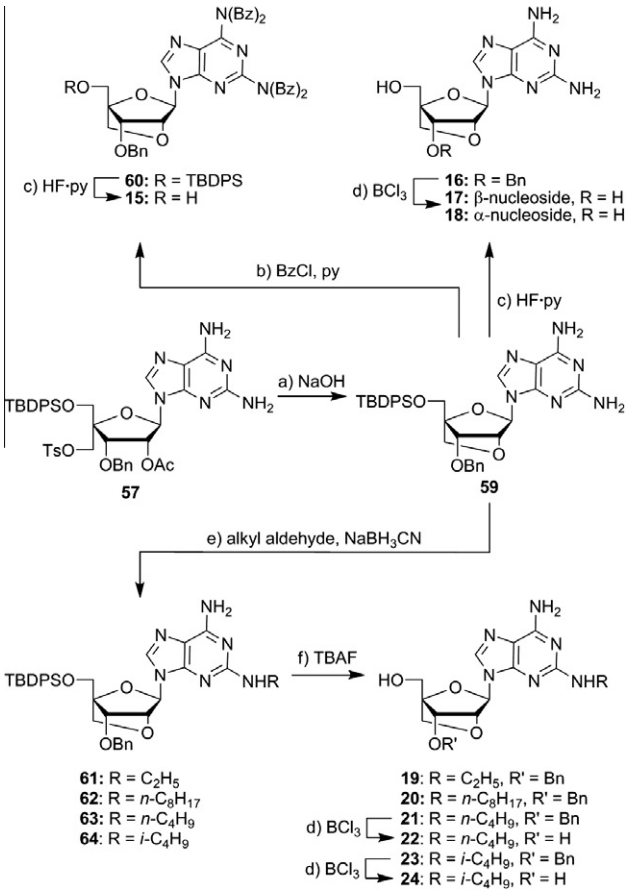
Bridged nucleoside analogues were also synthesized using nucleobases other than 2,6-diaminopurine (see Scheme 4). Vorbrüggen reaction of 2-chloroadenine with diacetate **56** produced nucleoside **67** as a single isomer in 85% yield. Deacetylation



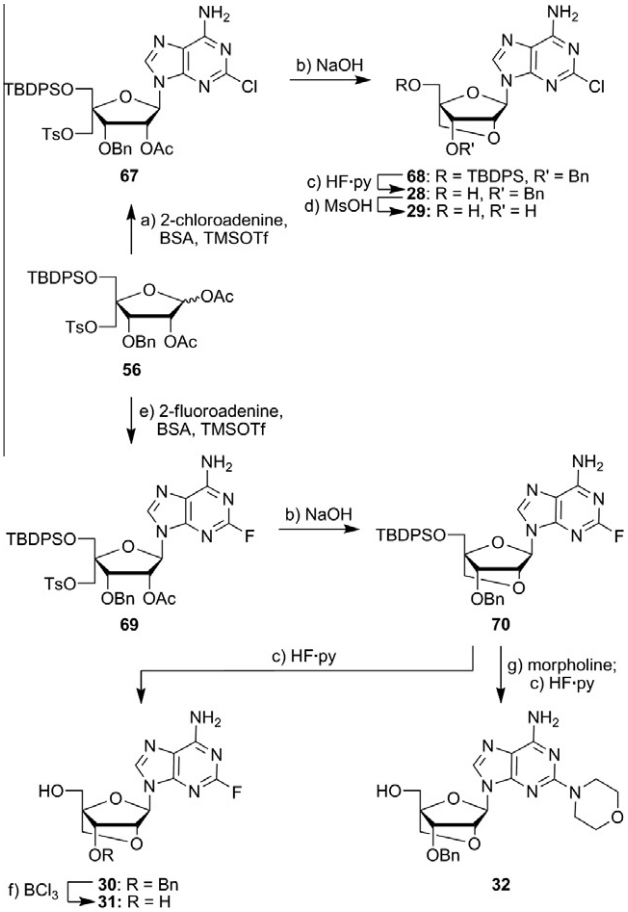
Scheme 1. Synthesis of compounds **57** and **58**. Reagents and conditions: (a) H_5IO_6 (1.2 equiv), EtOAc, 25 °C, 1 h, 98%; (b) 2,6-diaminopurine (1.5 equiv), BSA (2.3 or 5.0 equiv), MeCN, 65 °C, 1.5 h; then TMSOTf (2.0 or 2.8 equiv), 65 °C, 3 h, 100% of **57** or 59% of **57** + 36% of **58**. H_5IO_6 = periodic acid; EtOAc = ethyl acetate; MeCN = acetonitrile; Bn = benzyl; TBDPS = *tert*-butyldiphenylsilyl; Ts = *para*-toluenesulfonyl; Ac = acetyl; BSA = *N*,*O*-bis(trimethylsilyl)acetamide; TMSOTf = trimethylsilyl trifluoromethylsulfonate.



Scheme 3. Synthesis of compounds **25**–**27**. Reagents and conditions: (a) aq 2 M NaOH, THF, 25 °C, 2 h, 85%; (b) isobutyraldehyde (8.0 equiv), $NaBH_3CN$ (6.0 equiv), MeOH, 25 °C, 48 h, 44%; (c) TBAF (2.0 equiv), THF, 25 °C, 16 h, 77%; (d) HF·py (5.0 equiv), THF, 25 °C, 12 h; (e) BCl_3 (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 46% over the two steps.



Scheme 2. Synthesis of compounds **15**–**24**. Reagents and conditions: (a) aq 2 M NaOH, THF, 25 °C, 2 h, 94%; (b) BzCl (4.0 equiv), py, 25 °C, 18 h, 52%; (c) HF·py (5.0 equiv), THF, 25 °C, 12 h, 50% for **15**, 85% for **16**; (d) BCl_3 (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 85% of **17** + 10% of **18**, 71% for **22**, 64% for **24**; (e) alkyl aldehyde (8.0 equiv), $NaBH_3CN$ (6.0 equiv), MeOH, 25 °C, 48 h, 48% for **61**, 29% for **62**, 57% for **63**, 52% for **64**; (f) TBAF (2.0 equiv), THF, 25 °C, 16 h, 79% for **19**, 77% for **20**, 77% for **21**, 98% for **23**. Bz = benzoyl; py = pyridine; THF = tetrahydrofuran; TBAF = tetra-*n*-butylammonium fluoride.



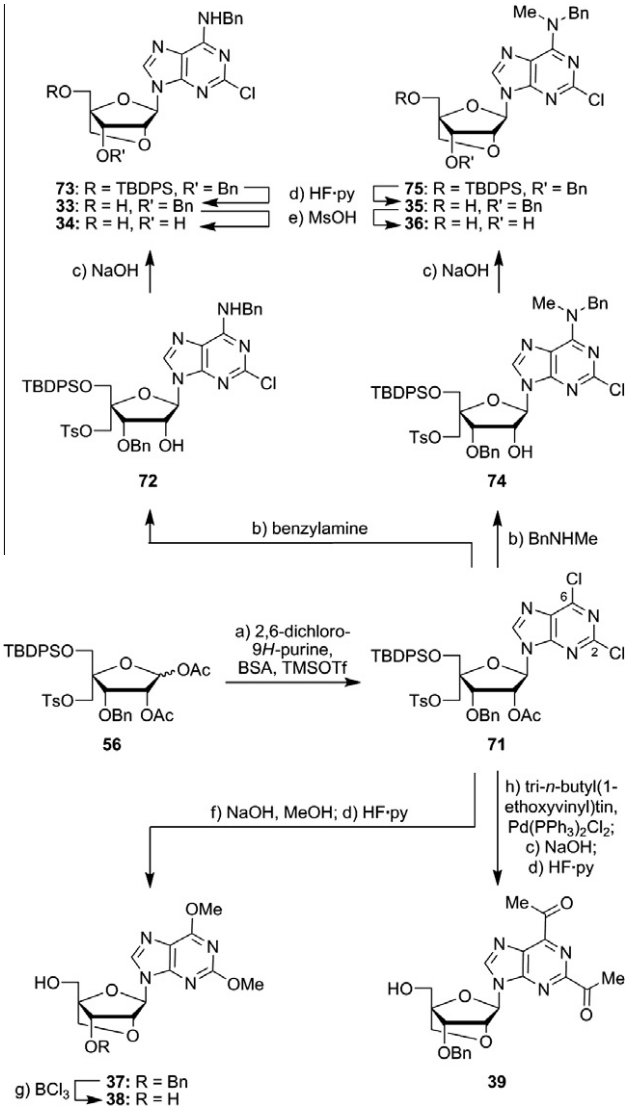
Scheme 4. Synthesis of compounds **28**–**32**. Reagents and conditions: (a) 2-chloroadenine (1.5 equiv), BSA (2.3 equiv), MeCN, 65 °C, 1.5 h; then TMSOTf (2.0 equiv), 65 °C, 3 h, 85%; (b) aq 2 M NaOH, THF, 25 °C, 15 h, 87% for **68**, 81% for **70**; (c) HF·py (5.0 equiv), THF, 25 °C, 12 h, 61% for **28**, 85% for **30**; (d) MsOH (78 equiv), CH_2Cl_2, 0 °C, 1.5 h, 46%; (e) 2-fluoroadenine (2.0 equiv), BSA (2.5 equiv), MeCN, 65 °C, 1.5 h; then TMSOTf (2.0 equiv), 65 °C, 3 h, 78%; (f) BCl_3 (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 69%; (g) morpholine (2.0 equiv), DMSO, 95 °C, 24 h, 76% over the two steps. MsOH = methanesulfonic acid; DMSO = dimethyl sulfoxide.

followed by cyclization to bridged intermediate **68** was effected with aq NaOH; desilylation with HF·py then gave nucleoside **28** in 53% overall yield from compound **67**. The use of methanesulfonic acid as a debenzylation agent was crucial to the successful generation of aminochloride diol **29** (46% yield),[17] as the typical boron trichloride conditions proved to be too harsh for this analogue.

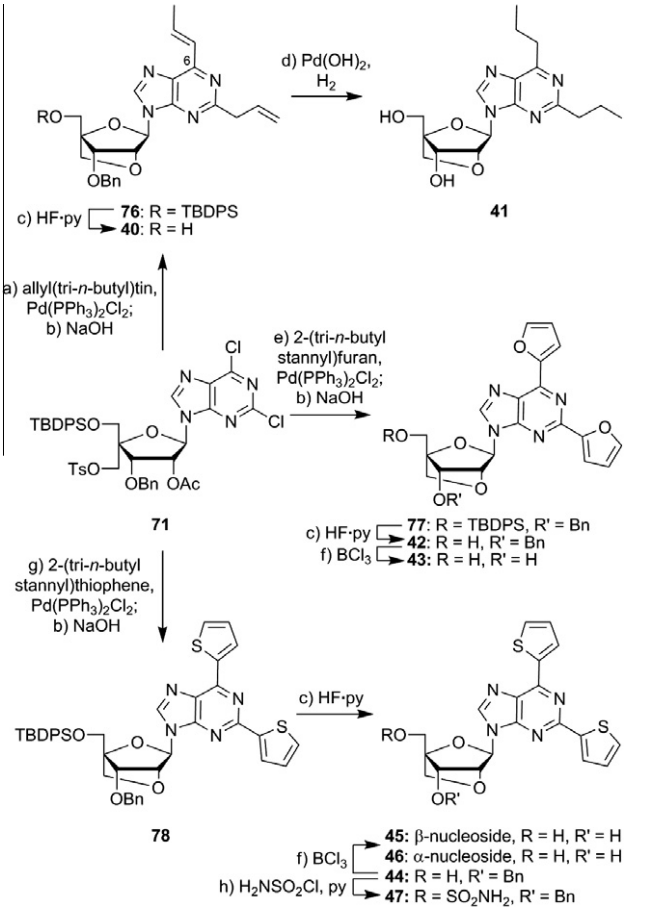
Amino fluoride derivative **31** could also be prepared in a similar manner (see Scheme 4). Vorbrüggen coupling with diacetate **56** and 2-fluoroadenine led to nucleoside **69** (78% yield), which could then be deacetylated and cyclized with NaOH to produce intermediate **70** in 81% overall yield. Desilylation (HF·py), followed by debenzylation (BCl_3) under the standard conditions, then furnished, sequentially, hydroxy benzyl ether **30** and diol **31** in 59% yield over the two steps. Intermediate **70** was converted into bridged analogue **32** through morpholine displacement of the fluoride moiety and desilylation (HF·py) in 76% yield over the two steps (see Scheme 4).

2,6-Dichloropurine nucleoside **71** was synthesized in 64% yield through Vorbrüggen reaction of diacetate **56** and 2,6-dichloro-9*H*-purine as shown in Scheme 5. This compound proved to be one of the most derivatizable intermediates in this study (see Scheme 5). The difference in the electrophilicity between the C2 and C6 carbons of nucleoside **71** was exploited to synthesize aminochloride **72**, in 93% yield, via displacement of the C6 chlorine residue with benzylamine.[25] Cyclization induced by NaOH then afforded locked nucleoside **73** in 68% yield. Desilylation of the latter compound produced alcohol **33** (HF·py, 96% yield), and subsequent debenzylation of compound **33** (MsOH) furnished diol analogue **34** (61% yield). A similar sequence of steps could also be employed to synthesize nucleoside **36**. Thus, compound **71** was reacted with *N*-methylbenzylamine to afford intermediate **74** lacking the acetoxy group in 82% yield (see Scheme 5). Cyclization of compound **74** through the action of NaOH then produced the bridged intermediate **75** (98% yield), followed by desilylation (HF·py) to form alcohol **35** (75% yield). Debenzylation (MsOH) of the latter compound then generated dihydroxy derivative **36** (75% yield). Displacement of both chlorine residues of intermediate **71** and concurrent ring closure were effected by exposure to NaOH in MeOH to afford locked nucleoside derivative **37** upon desilylation (HF·py), in 69% overall yield. Finally, debenzylation of the latter compound with BCl_3 furnished dimethoxy nucleoside diol **38** (77% yield).

Stille coupling reactions were employed to synthesize additional derivatives from dichloro compound **71** as shown in Schemes 5 and 6.[26] Reaction of intermediate **71** with tri-*n*-butyl(1-ethoxyvinyl)tin and bis(triphenylphosphine)palladium(II) chloride, followed immediately by base-induced deacetylation/



Scheme 5. Synthesis of compounds **33**–**39**. Reagents and conditions: (a) 2,6-dichloro-9*H*-purine (2.0 equiv), BSA (2.5 equiv), MeCN, 95 °C, 1.5 h; then TMSOTf (2.0 equiv), 80 °C, 3 h, 64%; (b) benzylamine (5.0 equiv) or *N*-methylbenzylamine (5.0 equiv), MeOH, 55 °C, 12 h, 93% for **72**, 82% for **74**; (c) aq 2 M NaOH, THF, 25 °C, 15 h, 68% for **73**, 98% for **75**; (d) HF·py (5.0 equiv), THF, 25 °C, 12 h, 96% for **33**, 75% for **35**, 77% for **37**, 31% over the three steps for **39**; (e) MsOH (78 equiv), CH_2Cl_2, 0 °C, 1.5 h, 61% for **34**, 75% for **36**; (f) NaOH (15 equiv), MeOH/THF (1:1), 25 °C, 12 h, 90%; (g) BCl_3 (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 77%; (h) tri-*n*-butyl(1-ethoxyvinyl)tin (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.10 equiv), DMF, 95 °C, 18 h. DMF = dimethylformamide.



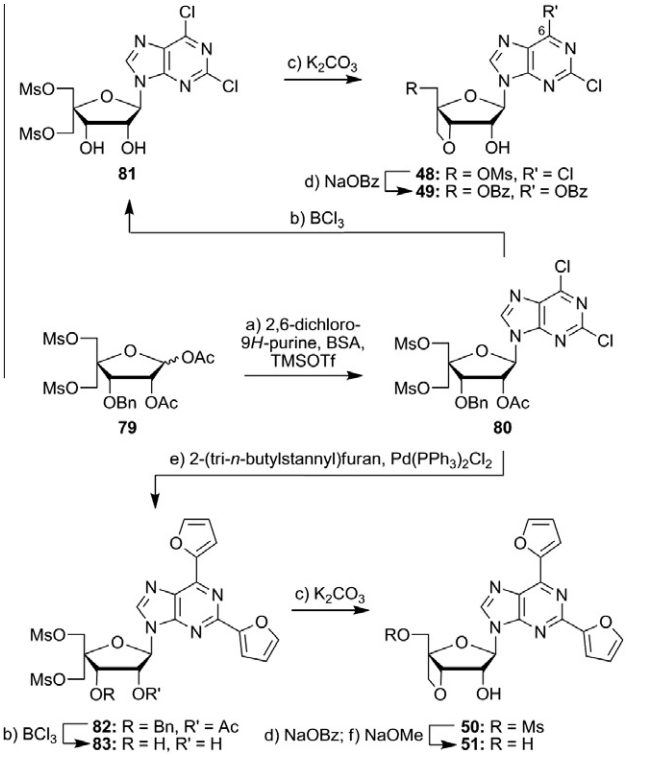
Scheme 6. Synthesis of compounds **40**–**47**. Reagents and conditions: (a) allyl(tri-*n*-butyl)tin (3.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.10 equiv), DMF, 95 °C, 6 h; (b) aq 2 M NaOH, THF, 25 °C, 12 h, 42% over the two steps for **76**, 76% for **77**, 98% for **78**; (c) HF·py (5.0 equiv), THF, 25 °C, 12 h, 87% for **40**, 100% for **42**, 99% for **44**; (d) H_2, $Pd(OH)_2$ (10% w/w), EtOH, 50 °C, 12 h, 50%; (e) 2-(tri-*n*-butylstannyl)furan (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.075 equiv), DMF, 95 °C, 7 h, 99%; (f) BCl_3 (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 90% for **43**, 40% of **45** + 33% of **46**; (g) 2-(tri-*n*-butylstannyl)thiophene (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.12 equiv), DMF, 80 °C, 7 h, 72%; (h) chlorosulfonyl isocyanate (4.3 equiv), formic acid (4.3 equiv), py (5.8 equiv), CH_2Cl_2, 25 °C, 24 h, 35%.

cyclization and desilylation (HF·py), generated diketone nucleoside **39** in 31% yield over the three steps (Scheme 5). Intermediate **71** also underwent reaction with allyl(tri-*n*-butyl)tin to afford, upon subsequent cyclization with NaOH, compound **76** in 42% overall yield for the two steps (see Scheme 6). Formation of the conjugated olefin at the C6 position of the purine within compound **76** was presumed to have occurred as a result of palladium- and base-induced isomerization of the coupled allyl moiety. Desilylation of compound **76** (HF·py) furnished intermediate **40** (87% yield), which was converted to dipropyl derivative **41** (50% yield) by reduction and concomitant debenzylation with hydrogen and Pearlman's catalyst. Stille reaction of dichloride **71** with 2-(tri-*n*-butylstannyl)furan, followed by ring closure (NaOH), afforded bridged product **77** (75% over the two steps) (Scheme 6). Sequential desilylation (HF·py) and debenzylation (BCl_3) of compound **77** then produced, through the intermediacy of alcohol **42**, difuran diol **43** in 90% yield over the two steps. Dichloride **71** was also reacted with 2-(tri-*n*-butylstannyl)thiophene to furnish the corresponding bis-thiophene derivative, which was converted to the bridged nucleoside **78** by reaction with NaOH in 71% overall yield (Scheme 6). Desilylation of the latter with HF·py gave intermediate **44** (99% yield), which was debenzylated (BCl_3) to afford β-nucleoside **45** (40% yield), along with its α-anomer **46** (33% yield). Intermediate **44** was also converted to sulfamoyl derivative **47** in 35% yield by reaction with freshly prepared sulfamoyl chloride in the presence of pyridine.[27]

2.2. Synthesis of 3′,4′-bridged nucleoside analogues

The synthesis of the 3′-*O*,4′-*C*-bridged nucleoside analogues began with conversion of literature-known dimesylate **79**[4e] to dichloro nucleoside **80** through Vorbrüggen reaction with 2,6-dichloro-9*H*-purine (Scheme 7). The standard Vorbrüggen coupling procedure that had been employed in the synthesis of the other nucleosides mentioned above led to nucleoside **80** in low yield; however, an 84% yield of this nucleoside was achieved by the use of microwave irradiation instead of moderate heating.[28] Debenzylation and concomitant deacetylation of compound **80** with boron trichloride led to a 90% yield of intermediate **81**. Treatment of the latter compound with potassium carbonate in THF then caused smooth cyclization to afford compound **48** in 79% yield. At this point, all that remained to reach the targeted dichloro-locked nucleoside was manipulation of the mesyl group to form the 5′-hydroxyl functionality. However, attempts to accomplish this goal by reaction with NaOBz (followed by benzoate cleavage) resulted in additional displacement of the C6 chloride residue, producing dibenzoate **49** in 82% yield (see Scheme 7). The 5′-benzoate could not be cleaved without causing decomposition, thus an alternate route to these 3′,4′-bridged systems that did not involve chloride residues on the nucleobase was implemented as described below.

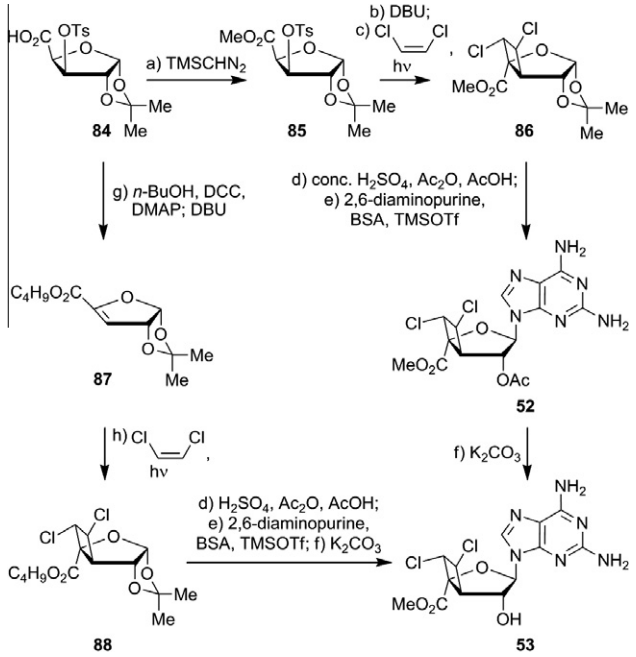
Dichloride **80** was converted to difuran compound **82** via a Stille reaction with 2-(tri-*n*-butylstannyl)furan (84% yield), and the latter compound was deprotected (BCl_3) to give diol **83** in 82% yield (see Scheme 7). Treatment of compound **83** with potassium carbonate in THF afforded intermediate **50** in 91% yield. This compound was successfully converted into diol **51** through the intermediacy of the corresponding 5′-benzoate (NaOBz; then NaOMe, 69% yield over the two steps). Other studies directed toward a number of different bridged nucleosides were thwarted, primarily due to difficulties in bringing about the desired oxetane formation. The ability of the nucleoside to undergo ring closure to the oxetane derivative was found to be strongly dependent on the actual substituents on the nucleobase. Additionally, after cyclization of the intermediate, the oxetane ring was found to be unstable to typical reaction conditions as well as general handling, causing concern about its stability during biological evaluation.



Scheme 7. Synthesis of compounds **48**–**51**. Reagents and conditions: (a) 2,6-dichloro-9*H*-purine (2.0 equiv), BSA (3.5 equiv), MeCN, −40 °C, 5 min; then TMSOTf (1.5 equiv), μ-waves, 80 °C, 5 min, 84%; (b) BCl_3 (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 90% for **81**, 82% for **83**; (c) K_2CO_3 (4.0 equiv), THF, 25 °C, 18 h, 79% for **48**, 91% for **50**; (d) NaOBz (2.0 equiv), DMF, 90 °C, 4.5 h, 82% for **49**; (e) 2-(tri-*n*-butylstannyl)furan (4.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.091 equiv), DMF, 95 °C, 3 h, 84%; (f) aq NaOMe, MeOH, 25 °C , 30 min, 69% over the two steps for **51**.

Faced with these difficulties, we opted to synthesize analogues with an alternate 3′,4′-bridged ring system which would be more stable than those containing the 3′,4′-oxetane bridge, and could be constructed through a flexible route to afford a variety of analogues. These analogues were synthesized via a [2+2] cycloaddition reaction as shown in Scheme 8. Esterification of known compound **84**[29] with trimethylsilyl diazomethane formed methyl ester **85** (88% yield). Elimination of the tosyl group (DBU) to form the α,β-unsaturated ester, followed by [2+2] cycloaddition of the resulting product with 1,2-*cis*-dichloroethylene under photoirradiation conditions, generated compound **86** in 18% yield over the two steps as the major product, in addition to two other diastereomers (ca. 4:2:1) differing in the orientation of the chlorine residues. In all three diastereomers of compound **86**, the cyclobutane ring occuppied the position opposite the acetonide moiety as expected on steric grounds. The *trans* relationship of the chlorine atoms within isomer **86**, proven by NMR spectroscopy (ROESY), confirmed the radical nature of the [2+2] photocycloaddition. The stereochemistry of the two diastereomers of compound **86** was not determined. Following chromatographic separation of compound **86**, its acetonide moiety was cleaved and the resulting compound peracetylated in a one-pot reaction (AcOH, concd H_2SO_4, Ac_2O) to afford the corresponding bis-acetate. Subsequent Vorbrüggen reaction of the latter product with 2,6-diaminopurine and BSA provided bridged nucleoside **52** in 36% yield over the two steps. Deacetylation with potassium carbonate in methanol then provided the desired alcohol **53** in 83% yield.

Although the targeted product **53** was accessed by this method, the yield of the key [2+2] cycloaddition reaction was disappointing. It was reasoned that the inefficiency of this process was, in part, due to the volatility of both the elimination product from



Scheme 8. Synthesis of compound **53**. Reagents and conditions: (a) $TMSCHN_2$ (1.2 equiv), Et_2O/MeOH (1:1), 0 °C, 30 min, 88%; (b) DBU (1.2 equiv), benzene, 25 °C, 5 h; (c) 1,2-*cis*-dichloroethylene (15.9 equiv), MeCN, *hν*, 25 °C, 3.5 d, 18% over the two steps; (d) concd H_2SO_4, Ac_2O (12 equiv), AcOH, 25 °C, 16 h; (e) 2,6-diaminopurine (1.5 equiv), BSA (2.3 equiv), MeCN, 65 °C, 1.5 h; then TMSOTf (2.0 equiv), 65 °C, 3 h, 36% over the two steps for **52**; (f) K_2CO_3 (0.30 equiv), MeOH, 25 °C, 30 min, 83% over one step or 38% over the three steps from compound **86**; (g) *n*-BuOH (1.2 equiv), DCC (1.2 equiv), DMAP (0.15 equiv), CH_2Cl_2, 25 °C, 24 h; then DBU (1.2 equiv), 25 °C, 24 h, 67%; (h) 1,2-*cis*-dichloroethylene (16.9 equiv), MeCN, *hν*, 25 °C, 6.5 d, 33% based on 12% recovered starting material. $TMSCHN_2$ = trimethylsilyl diazomethane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Ac_2O = acetic anhydride; AcOH = acetic acid; DCC = *N*,*N*′-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine.

compound **85** (step b) and the cycloaddition product **86**. To circumvent the problem, a larger ester group was employed. Thus, substrate **84** was esterified with *n*-BuOH, DCC, and DMAP, and the resulting product was treated with DBU, leading to unsaturated *n*-butyl ester **87** in 67% yield (see Scheme 8). Light-induced [2+2] cycloaddition of compound **87** with 1,2-*cis*-dichloroethylene gave product **88** in an improved 33% yield (based on 12% recovered starting material), along with the other two diastereomers (27% combined yield). Intermediate **88** was then exposed to the same one-pot acetonide cleavage–bis-acetylation procedure and Vorbrüggen coupling to afford, upon potassium carbonate-induced deacetylation, desired product **53** in 38% overall yield for the three steps. This approach provided a more efficient and reliable access to these new 3′,4′-carbocyclic bridged nucleoside analogues.

2.3. Biological evaluation

The library of bridged nucleoside analogues **15**–**53** (Fig. 3) were tested for antibacterial, antitumor, and antiviral properties. Of these thirty-nine compounds, six demonstrated significant biological activities (see Table 1 and Fig. 4). Compound **36** was the only compound to demonstrate antibacterial activity, showing moderate potency against both *Escherichia coli* (MIC = 16 μM) and *Staphylococcus aureus* (MIC = 8 μM). It is interesting to note that several other compounds with very similar structures displayed no significant biological activity. The *N*-methylbenzylamine structural motif specifically appears to be essential, as compound **36** differs from compound **34** (Fig. 3) only by a methyl group, and compound **29** (Fig. 3) differs from nucleoside **36** by having no substituents on the C6 amino group. Neither of these two compounds (i.e., **34**

Table 1
Antibacterial, anticancer, and antiviral activities of bridged nucleoside analogues

Compound	Antibacterial activity MIC[a] (μM)		Anticancer activity IC_{50}[b] (μM)		Antiviral activity IC_{50}[c] (μM)	
	E. coli	*S. aureus*	CCRF-CEM	Raji	SF162	HxB2
15	NA	NA	0.36	0.25	NA	NA
19	NA	NA	NA	NA	60.0	NA
21	NA	NA	NA	NA	68.0	28.0
33	NA	NA	NA	NA	7.0	2.4
36	16	8	NA	NA	27.9	24.9
40	NA	NA	7.6	5.8	—[d]	2.4[e]
Cladribine[30]	—	—	0.0005	0.009	—	—
AZT	—	—	—	—	0.078	0.037

[a] Minimum inhibitory concentration.
[b] Concentration that causes 50% of cell growth inhibition.
[c] Concentration that causes 50% neutralization of virus.
[d] While an IC_{50} below 100 μM was calculated, this was determined to be from toxicity to the TZM-bl cells, not neutralization of the virus.
[e] Compound **40** is toxic to the TZM-bl cells, however, below the toxicity limit it did display antiviral activity. If the activities due to toxicity at higher concentration of **40** are ignored, an IC_{50} of 2.4 μM can be determined. CCRF-CEM = Human T leukemic lymphoblasts derived from acute lymphoblastic leukemia. Raji = Human B lymphocytes derived from Burkitt's lymphoma. SF162 and HxB2 = HIV-1 pseudoviruses. NA = not active at the highest concentration tested (64 μM for the antibacterial assay, 10 μM for the cytotoxicity assay, and 100 μM for the antiviral assay).

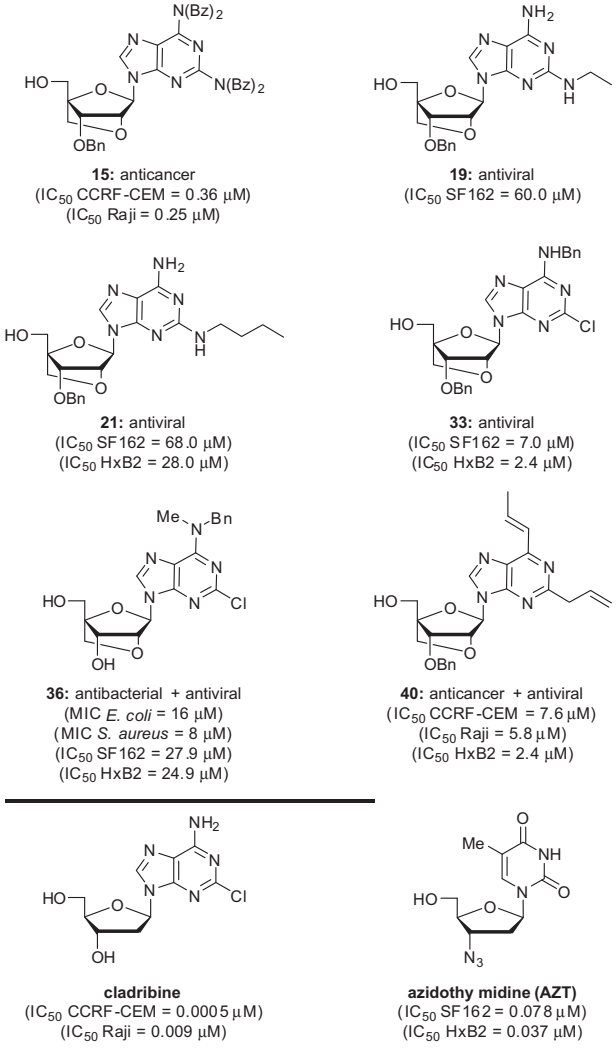


Figure 4. Structures of biologically active, bridged nucleoside analogues **15**, **19**, **21**, **33**, **36**, and **40** as compared to those of cladribine and azidothymidine (AZT).

and **29**) displayed significant antibacterial activity. Additionally, benzylation of the 3′-hydroxyl group of compound **36** also results in complete loss of its biological activity since the resulting nucleoside (i.e., **35**, Fig. 3) is inactive against *E. coli* and *S. aureus*.

Two bridged nucleosides were found to exhibit significant antitumor activity: compound **15** and compound **40** (see Table 1 and Fig. 4). Nucleoside **15** was found to possess the most potent activity of the two against CEM (IC_{50} = 0.36 μM) and Raji (IC_{50} = 0.25 μM) cancer cell lines. However, these activities are considerably lower than those of the anticancer nucleoside agent cladribine (CEM: IC_{50} = 0.5 nM; Raji: IC_{50} = 9 nM). Compound **40** (Fig. 4) showed less potent activities than compound **15**, with an IC_{50} of 7.6 μM against the T cell line CEM and an IC_{50} of 5.8 μM against the B cell line Raji. Important to note is the fact that the 2′,4′-bridged nucleoside analogue corresponding to the structure of cladribine, compound **29** (Fig. 3), was also synthesized, but did not exhibit significant cytotoxicity below 10 μM. It appears that the act of locking the conformation of cladribine, or the addition of an extra CH_2O moiety, changes the structure of the molecule enough to deplete its antitumor properties.

The most promising biological activities of the synthesized bridged nucleosides were discovered from screening the library against HIV-1 (see Table 1). Thus, compound **36** (Fig. 4), which had also demonstrated antibacterial activity, showed moderate activity against both the SF162 (IC_{50} = 27.9 μM) and HxB2 (IC_{50} = 24.9 μM) pseudoviruses. Compound **19** (Fig. 4), with an ethylamine functionality, also showed moderate activity, but only against SF162 (IC_{50} = 60.0 μM). Similarly, *n*-butylamine nucleoside **21** (Fig. 4) displayed moderate activity against both pseudoviruses (SF162 IC_{50} = 68.0 μM; HxB2 IC_{50} = 28.0 μM). However, octyl analogue **20** (Fig. 3) and isobutyl nucleoside **23** (Fig. 3) did not exhibit any significant antiviral activities against the viruses. This suggests that an alkyl amine containing approximately two to four carbon atoms with no branching is an essential structural motif for antiviral properties.

The highest antiviral activities were demonstrated by compounds **33** and **40** (see Table 1). Nucleoside **40** (Fig. 4), which had also displayed moderate antitumor activity, was found to be toxic to the TZM-bl cells used in the antiviral assay at concentrations at or above 33 μM. However, compound **40** (Fig. 4) did exhibit some actual antiviral activity against pseudovirus HxB2 below the concentration at which it was causing cell death. Therefore, an IC_{50} was approximated by ignoring the higher concentrations at which it was toxic; this approximation led to an IC_{50} against HxB2 of 2.4 μM for this analogue (**40**). Nucleoside **33** (Fig. 4) exhibited the most potent antiviral activity without concomitant cellular toxicity (SF162: IC_{50} = 7.0 μM; HxB2: IC_{50} = 2.4 μM). Analogue **35** (Fig. 3), which contains a *N*-methylbenzylamine moiety instead of a benzylamine substituent, did not display any antiviral activity. While compounds **33** (Fig. 4) and **40** (Fig. 4) still remain less potent than the antiviral nucleoside AZT (SF162: IC_{50} = 0.078 μM; HxB2: IC_{50} = 0.037 μM), these activities suggest considerable potential for these bridged nucleosides as possible lead compounds for further optimization.

3. Conclusion

In conclusion, we have synthesized a focused compound library of both 2′,4′- and 3′,4′-bridged nucleoside analogues with various modifications on the purine base. This study included the development of a [2+2] cycloaddition strategy to synthesize novel 3′,4′-carbocyclic bridged systems expediently and with the flexibility to target considerable molecular diversity. Some of the compounds synthesized were found to exhibit diverse but selective biological activities, with the best compounds displaying potent antiviral properties (e.g., compound **33**, SF162 IC_{50} = 7.0 μM; HxB2 IC_{50} = 2.4 μM). While the mechanism of action of these nucleosides remains unknown, it has been shown that the biological activity is dependent on not only the bridged system on the sugar, but the specific modifications of the purine residue. These compounds are, to the best of our knowledge, the first examples of 2′,4′-bridged nucleosides exhibiting antibacterial, anticancer, or antiviral activity.

4. Experimental methods

4.1. Chemical synthesis

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et_2O), *N*,*N*′-dimethylformamide (DMF), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of anisaldehyde and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254 for normal silica, RF-18 F-254 for C_{18}-silica).

NMR spectra were recorded on Bruker AV-400, DRX-500, or DRX-600 instruments and calibrated using residual undeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; acetone-d_6: δ_H = 2.05 ppm, δ_C = 29.84 ppm; CD_3CN: δ_H = 1.94 ppm, δ_C = 1.32 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.00 ppm; D_2O: δ_H = 4.79 ppm)[31] as an internal reference. The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. Infrared (IR) spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF (time of flight) mass spectrometer using MALDI (matrix-assisted laser desorption ionization) or ESI (electrospray ionization). Optical rotations were recorded on a Perkin-Elmer Model 343 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

4.1.1. (2*R*,3*S*,5*S*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)-methyl)-2-(2,6-diamino-9*H*-purin-9-yl)-5-(tosyloxymethyl)-tetrahydrofuran-3-yl acetate (57)

Compound **56** (1.35 g, 1.81 mmol) and 2,6-diaminopurine (407 mg, 2.71 mmol) were suspended in MeCN (17.4 mL), and BSA (1.06 mL, 4.14 mmol) was added. The mixture was heated at 65 °C for 1.5 h, after which the mixture was cooled to 0 °C and TMSOTf (0.72 mL, 3.62 mmol) was added dropwise. The solution was then stirred at 65 °C for 3 h. The reaction mixture was quenched with cold satd aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2. The organics were washed with satd aq $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica, EtOAc) to give compound **57** (1.51 g, 1.81 mmol, 100%). Compound **57**: white foam; R_f = 0.50 (silica, EtOAc); $[\alpha]_D^{25}$ = −7.0 (MeCN, *c* 1.57); FT-IR (film) ν_{max} 3371, 2932, 1735, 1599, 1472, 1427, 1409, 1371, 1238, 1189, 1176, 1095, 1042, 975, 915, 813, 790, 741, 601, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.70

(d, J = 8.3 Hz, 2H), 7.64–7.59 (m, 4H), 7.44 (s, 1H), 7.44–7.31 (m, 7H), 7.28–7.25 (m, 4H), 7.18 (d, J = 8.0 Hz, 2H), 6.04 (t, J = 5.7 Hz, 1H), 5.83 (d, J = 5.8 Hz, 1H), 5.53 (s, 2H), 4.78 (d, J = 5.5 Hz, 1H), 4.58 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.42 (d, J = 10.5 Hz, 1H), 4.35 (d, J = 10.6 Hz, 1H), 4.27 (s, 2H), 3.88 (d, J = 10.8 Hz, 1H), 3.74 (d, J = 10.9 Hz, 1H), 2.37 (s, 3H), 2.03 (s, 3H), 0.99 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 170.05, 159.58, 155.88, 151.61, 144.72, 137.39, 137.39, 137.19, 135.71, 135.65, 133.01, 132.85, 132.27, 130.08, 130.06, 129.74, 128.68, 128.31, 128.14, 128.09, 128.05, 127.99, 115.00, 86.21, 86.14, 78.26, 74.72, 73.57, 68.75, 63.86, 26.88, 21.71, 20.76, 19.22 ppm; HRMS (ESI-TOF) (m/z): [M+H]$^+$ calcd for $C_{45}H_{49}N_6O_8SSi^+$ 837.3096, found 837.3100.

4.1.2. (2*R*,3*R*,4*S*,5*S*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)-methyl)-2-(2,6-diamino-7*H*-purin-7-yl)-5-(tosyloxymethyl)-tetrahydrofuran-3-yl acetate (58)

Compound **56** (200 mg, 0.268 mmol) and 2,6-diaminopurine (61.8 mg, 0.412 mmol) were suspended in MeCN (2.6 mL), and BSA (0.34 mL, 1.33 mmol) was added. The reaction mixture was heated at 65 °C for 1 h, after which the mixture was cooled to 0 °C and TMSOTf (0.15 mL, 0.753 mmol) was added dropwise. The solution was then stirred at 65 °C for 3.5 h. The reaction was quenched with cold satd aq $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2. The organics were washed with satd aq $NaHCO_3$ (2 × 2 mL) and brine (2 × 2 mL), dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica, EtOAc) to give compound **58** (81.1 mg, 0.0964 mmol, 36%) along with isomer **57** (133 mg, 0.158 mmol, 59%). Compound **58**: white foam; R_f = 0.21 (silica, EtOAc); $[\alpha]_D^{25}$ = −40.1 ($CHCl_3$, c 1.85); FT-IR (film) ν_{max} 3342, 3191, 2932, 1735, 1668, 1625, 1576, 1470, 1428, 1359, 1234, 1189, 1176, 1105, 1045, 972, 812, 792, 741, 701, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.67 (s, 1H), 7.67–7.64 (m, 2H), 7.53–7.51 (m, 2H), 7.50–7.48 (m, 2H), 7.45–7.41 (m, 2H), 7.35–7.31 (m, 7H), 7.22 (d, J = 8.6 Hz, 2H), 7.19 (dd, J = 3.8, 1.8 Hz, 2H), 5.87 (d, J = 7.1 Hz, 1H), 5.50 (s, 2H), 5.45 (dd, J = 7.0, 5.8 Hz, 1H), 4.92 (s, 2H), 4.54 (d, J = 5.7 Hz, 1H), 4.46 (dd, J = 11.1, 2.7 Hz, 2H), 4.41 (d, J = 11.3 Hz, 1H), 4.09 (d, J = 11.1 Hz, 1H), 3.62 (s, 2H), 2.39 (s, 3H), 2.04 (s, 3H), 0.99 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 159.95, 151.75, 145.11, 141.00, 136.26, 135.43, 135.25, 132.39, 131.73, 131.66, 130.13, 129.75, 128.60, 128.43, 127.93, 127.88, 127.69, 86.82, 85.84, 77.53, 75.21, 73.27, 67.64, 64.15, 26.72, 21.51, 20.30, 18.97 ppm; HRMS (ESI-TOF) (m/z): [M+H]$^+$ calcd for $C_{45}H_{49}N_6O_8SSi^+$ 837.3096, found 837.3096.

4.1.3. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-9*H*-purine-2,6-diamine (59)

Compound **57** (1.12 g, 1.34 mmol) was dissolved in THF (56 mL) at 0 °C, and 2 M NaOH (56 mL) was added. The reaction solution was warmed to rt and stirred for 2 h. The solution was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$, filtered, and concentrated to give compound **59** (780 mg, 1.26 mmol, 94%). Compound **59**: white foam; R_f = 0.50 (silica, EtOAc); $[\alpha]_D^{25}$ = +13.0 ($CHCl_3$, c 0.5); FT-IR (film) ν_{max} 3330, 3187, 2931, 2857, 1591, 1471, 1427, 1408, 1363, 1279, 1198, 1111, 1038, 939, 791, 743, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.75 (s, 1H), 7.71–7.67 (m, 3H), 7.45–7.37 (m, 4H), 7.34 (t, J = 7.4 Hz, 3H), 7.29 (dd, J = 5.4, 1.7 Hz, 2H), 7.26–7.24 (m, 3H), 5.92 (s, 1H), 5.48 (s, 2H), 4.75 (s, 2H), 4.72 (s, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.28 (s, 1H), 4.06 (d, J = 7.7 Hz, 1H), 4.03 (d, J = 11.9 Hz, 1H), 3.97 (d, J = 12.0 Hz, 1H), 3.91 (d, J = 7.7 Hz, 1H), 1.08 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 159.70, 155.67, 151.05, 137.20, 135.77, 135.68, 135.48, 132.74, 132.72, 130.08, 128.63, 128.17, 128.03, 127.98, 127.80, 114.85, 88.27, 86.44, 77.27, 77.03, 72.73, 72.49, 59.41, 26.91, 19.37 ppm; HRMS (ESI-TOF) (m/z): [M+H]$^+$ calcd for $C_{34}H_{39}N_6O_4Si^+$ 623.2796, found 623.2795.

4.1.4. *N*,*N*′-(9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-9*H*-purine-2,6-diyl)bis(*N*-benzoylbenzamide) (60)

Compound **59** (30 mg, 0.0483 mmol) was co-evaporated twice with anhydrous pyridine (2 × 0.6 mL) and then dissolved in anhydrous pyridine (0.6 mL). The solution was cooled to 0 °C, benzoyl chloride (0.023 mL, 0.193 mmol) was added, and the mixture was stirred at rt for 18 h. The mixture was diluted with EtOAc (4 mL) and washed with H_2O (2 mL). The organics were dried over $MgSO_4$, filtered, concentrated, and purified by preparative-plate chromatography (silica, hexanes:EtOAc 2:1) to give compound **60** (26 mg, 0.0251 mmol, 52%). Compound **60**: yellow oil; R_f = 0.49 (silica, hexanes:EtOAc 2:1); $[\alpha]_D^{25}$ = +27.3 ($CHCl_3$, c 1.20); FT-IR (film) ν_{max} 3068, 2932, 2858, 1704, 1599, 1576, 1491, 1449, 1428, 1365, 1244, 1177, 1112, 1048, 1027, 1001, 976, 932, 909, 864, 823, 794, 733, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.13 (s, 1H), 7.79 (dd, J = 8.4, 1.2 Hz, 4H), 7.67–7.62 (m, 8H), 7.51 (dd, J = 10.6, 4.3 Hz, 2H), 7.43–7.30 (m, 19H), 7.20 (dd, J = 6.8, 2.7 Hz, 2H), 5.79 (s, 1H), 4.47 (d, J = 11.3 Hz, 1H), 4.38 (d, J = 11.3 Hz, 1H), 4.16 (s, 1H), 4.03 (d, J = 8.2 Hz, 2H), 3.97 (d, J = 12.1 Hz, 1H), 3.91 (d, J = 12.1 Hz, 1H), 3.87 (d, J = 7.9 Hz, 1H), 1.04 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 172.44, 172.30, 152.97, 152.58, 143.01, 137.31, 135.97, 135.86, 134.80, 134.44, 133.39, 133.01, 132.95, 132.90, 130.39, 130.36, 129.83, 129.58, 129.12, 129.04, 128.92, 128.50, 128.32, 128.26, 127.98, 126.17, 88.95, 87.19, 77.62, 77.00, 73.06, 72.68, 59.87, 27.23, 19.63 ppm; HRMS (ESI-TOF) (m/z): [M+H]$^+$ calcd for $C_{62}H_{55}N_6O_8Si^+$ 1039.3845, found 1039.3826.

4.1.5. *N*,*N*′-(9-((1*S*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-9*H*-purine-2,6-diyl)bis(*N*-benzoylbenzamide) (15)

Compound **60** (91 mg, 0.0880 mmol) was dissolved in THF (0.55 mL) and cooled to 0 °C. HF·pyridine (0.011 mL, 0.440 mmol) was added and the reaction solution stirred at rt for 12 h. The reaction solution was poured into cold satd aq $NaHCO_3$ (1 mL) and stirred for 1 h. The resulting mixture was filtered through Celite and washed with CH_2Cl_2. The aqueous was extracted with CH_2Cl_2, and then the organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by preparative-plate chromatography (silica, EtOAc:hexanes 3:1) to give compound **15** (35.2 mg, 0.0440 mmol, 50%). Compound **15**: white foam; R_f = 0.46 (silica, EtOAc:hexanes 3:1); $[\alpha]_D^{25}$ = +37.1 ($CHCl_3$, c 1.24); FT-IR (film) ν_{max} 3506, 2947, 1702, 1598, 1577, 1491, 1449, 1407, 1365, 1244, 1177, 1143, 1052, 1002, 977, 932, 905, 864, 830, 795, 774, 732, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.12 (s, 1H), 7.81–7.75 (m, 4H), 7.66–7.60 (m, 4H), 7.51 (dd, J = 10.6, 4.3 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.34 (dt, J = 22.9, 7.7 Hz, 11H), 7.25–7.22 (m, 2H), 5.77 (s, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.20 (s, 1H), 4.12 (s, 1H), 4.06 (d, J = 8.0 Hz, 1H), 3.90 (d, J = 12.6 Hz, 1H), 3.84 (dd, J = 10.3, 7.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 172.18, 172.01, 154.18, 152.75, 143.07, 137.10, 134.39, 134.02, 133.23, 132.75, 129.52, 129.30, 128.90, 128.77, 128.67, 128.29, 127.74, 125.61, 88.17, 86.92, 77.30, 76.95, 72.49, 72.47, 57.96 ppm; HRMS (ESI-TOF) (m/z): [M+H]$^+$ calcd for $C_{46}H_{37}N_6O_8^+$ 801.2667, found 801.2687.

4.1.6. ((1*S*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-3-(2,6-diamino-9*H*-purin-9-yl)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (16)

From compound **59**, using the same procedure as for compound **15**, compound **16** was obtained and purified by flash column chromatography to give nucleoside **16** (409 mg, 1.06 mmol, 85%). Compound **16**: white powder; R_f = 0.18 (C_{18} silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = +31.0 (MeOH, c 0.62); FT-IR (film) ν_{max} 3332, 3195, 2927, 1595, 1455, 1407, 1280, 1201, 1036, 932, 908, 881, 809, 789, 740, 698 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ = 7.86 (s, 1H),

7.31–7.22 (m, 5H), 5.85 (s, 1H), 4.63 (s, 2H), 4.58 (s, 1H), 4.22 (s, 1H), 4.05 (d, J = 7.8 Hz, 1H), 3.93 (d, J = 1.8 Hz, 2H), 3.87 (d, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 161.60, 157.34, 151.72, 138.80, 136.59, 129.39, 129.14, 128.99, 114.44, 89.49, 87.48, 78.44, 77.96, 73.49, 73.27, 58.15 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{18}H_{21}N_6O_4^+$ 385.1619, found 385.1614.

4.1.7. (1*S*,3*R*,4*R*,7*S*) and (1*S*,3*S*,4*R*,7*S*)-3-(2,6-Diamino-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (17and 18)

Compound **16** (640 mg, 1.67 mmol) was partially dissolved in CH_2Cl_2 (3.3 mL) at 0 °C. Boron trichloride (3.33 mL, 1.0 M in DCM, 3.33 mmol) was slowly added dropwise and the solution was stirred at rt for 1 h. The reaction was quenched with MeOH (4 mL) and allowed to stir for 1.5 h, after which the mixture was evaporated and azeotroped with MeOH. Purification by flash column chromatography (C_{18} silica, 4% H_2O/MeCN) was completed to give compound **17** (416 mg, 1.42 mmol, 85%) and epimer **18** (50 mg, 0.167 mmol, 10%). Compound **17**: characterization previously reported.[32] Compound **18**: white powder; R_f = 0.33 (C_{18} silica, 4% H_2O/MeCN); $[\alpha]_D^{25}$ = −1.7 (DMSO, c 0.2); FT-IR (film) ν_{max} 3318, 3142, 2922, 1632, 1594, 1481, 1460, 1410, 1386, 1286, 1226, 1178, 1140, 1119, 1035, 1009, 965, 941, 916, 872, 832, 808, 785 cm^{-1}; ^{1}H NMR (D_2O, 600 MHz) δ = 7.94 (s, 1H), 5.92 (s, 1H), 4.63 (s, 1H), 4.47 (s, 1H), 4.07 (d, J = 8.5 Hz, 1H), 4.01 (d, J = 10.2 Hz, 3H) ppm; ^{13}C NMR (D_2O, 151 MHz) δ = 151.00, 137.32, 113.80, 89.21, 85.78, 80.29, 72.30, 71.07, 57.62 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{11}H_{15}N_6O_4^+$ 295.1149, found 295.1154.

4.1.8. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-*N*2-ethyl-9*H*-purine-2,6-diamine (61)

Compound **59** (70 mg, 0.112 mmol) and $NaBH_3CN$ (42 mg, 0.668 mmol) were suspended in MeOH (1.4 mL), and acetaldehyde (0.05 mL, 0.899 mmol) was added. The mixture was stirred at rt for 48 h. The solvent was evaporated and the residue was purified by preparative-plate chromatography (silica, hexanes:EtOAc:MeOH 1:1:0.1) to give compound **61** (35 mg, 0.0538 mmol, 48%) along with recovered starting material **59** (6.4 mg, 0.0101 mmol, 9%). Compound **61**: white foam; R_f = 0.42 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +54.5 ($CHCl_3$, c 1.03); FT-IR (film) ν_{max} 3328, 3178, 3071, 2931, 2858, 1733, 1630, 1595, 1536, 1485, 1472, 1427, 1409, 1373, 1345, 1324, 1255, 1199, 1109, 1036, 938, 910, 885, 865, 823, 805, 789, 737, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.73 (s, 1H), 7.70 (t, J = 6.6 Hz, 4H), 7.47–7.37 (m, 4H), 7.34 (t, J = 7.5 Hz, 2H), 7.28 (dd, J = 5.3, 1.9 Hz, 3H), 7.23 (dd, J = 6.9, 2.5 Hz, 2H), 5.95 (s, 1H), 5.47 (d, J = 0.7 Hz, 2H), 4.83 (t, J = 5.5 Hz, 1H), 4.80 (s, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.27 (s, 1H), 4.07 (d, J = 7.7 Hz, 1H), 4.04 (d, J = 12.0 Hz, 1H), 3.98 (d, J = 11.9 Hz, 1H), 3.92 (d, J = 7.7 Hz, 1H), 3.44–3.38 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 1.08 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 159.66, 155.61, 151.27, 137.28, 135.87, 135.77, 134.98, 132.89, 132.84, 130.16, 128.68, 128.23, 128.12, 128.06, 127.88, 114.43, 88.28, 86.66, 77.46, 77.15, 72.87, 72.62, 59.62, 36.79, 27.01, 19.46, 15.31 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{36}H_{43}N_6O_4Si^+$ 651.3109, found 651.3103.

4.1.9. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-*N*2-octyl-9*H*-purine-2,6-diamine (62)

Compound **59** (70 mg, 0.112 mmol) and $NaBH_3CN$ (42 mg, 0.668 mmol) were suspended in MeOH (1.4 mL), and octyl aldehyde (0.14 mL, 0.899 mmol) was added. The mixture was stirred at rt for 48 h. The solvent was evaporated and the residue was purified by preparative-plate chromatography (silica, hexanes:EtOAc:MeOH 1:1:0.1) to give compound **62** (29 mg, 0.0325 mmol, 29%) along with recovered starting material **59** (21 mg, 0.0336 mmol, 30%). Compound **62**: yellow oil; R_f = 0.70 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +50.4 ($CHCl_3$, c 0.81); FT-IR (film) ν_{max} 3325, 2927, 2855, 1635, 1599, 1537, 1470, 1427, 1408, 1362, 1324, 1263, 1198, 1112, 1036, 939, 911, 885, 862, 805, 789, 740, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.75 (s, 1H), 7.69 (dd, J = 8.0, 6.7 Hz, 4H), 7.45–7.38 (m, 3H), 7.35–7.27 (m, 6H), 7.23 (dd, J = 6.8, 2.8 Hz, 2H), 5.93 (s, 1H), 5.69 (s, 2H), 5.12 (s, 1H), 4.77 (s, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.25 (s, 1H), 4.06 (d, J = 7.7 Hz, 1H), 4.03 (d, J = 12.0 Hz, 1H), 3.97 (d, J = 12.0 Hz, 1H), 3.91 (d, J = 7.7 Hz, 1H), 3.37 (td, J = 7.0, 1.7 Hz, 2H), 1.59–1.57 (m, 2H), 1.29–1.25 (m, 10H), 1.08 (s, 9H), 0.88 (d, J = 5.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 151.90, 138.37, 137.83, 136.50, 136.40, 133.46, 133.40, 130.82, 129.39, 129.32, 128.90, 128.76, 128.71, 128.65, 128.53, 88.98, 87.27, 73.47, 73.28, 63.98, 60.14, 42.66, 33.68, 32.69, 30.52, 30.27, 30.14, 27.89, 27.63, 23.53, 20.08, 14.98 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{42}H_{55}N_6O_4Si^+$ 735.4048, found 735.4053.

4.1.10. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-*N*2-butyl-9*H*-purine-2,6-diamine (63)

Compound **59** (145 mg, 0.234 mmol) and $NaBH_3CN$ (87 mg, 1.38 mmol) were suspended in MeOH (2.9 mL), and butyraldehyde (0.17 mL, 1.82 mmol) was added. The mixture was stirred at rt for 48 h. The solvent was evaporated and the residue was purified by flash column chromatography (silica, hexanes:EtOAc 1:1 then hexanes:EtOAc:MeOH 1:1:0.1) to give compound **63** (90 mg, 0.133 mmol, 57%) along with recovered starting material **59** (35 mg, 0.056 mmol, 24%). Compound **63**: yellow oil; R_f = 0.22 (silica, hexanes:EtOAc 1:1); $[\alpha]_D^{25}$ = +61.2 ($CHCl_3$, c 0.20); FT-IR (film) ν_{max} 3322, 2930, 2858, 1633, 1600, 1537, 1471, 1427, 1408, 1362, 1324, 1267, 1199, 1112, 1036, 938, 911, 823, 789, 740, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.73–7.66 (m, 5H), 7.46–7.36 (m, 4H), 7.33 (dd, J = 9.0, 5.9 Hz, 2H), 7.27 (dd, J = 5.2, 1.9 Hz, 3H), 7.25–7.21 (m, 2H), 5.93 (s, 1H), 5.32 (s, 2H), 4.82–4.75 (m, 2H), 4.62 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.26 (s, 1H), 4.06 (d, J = 7.7 Hz, 1H), 4.02 (d, J = 11.9 Hz, 1H), 3.97 (d, J = 11.9 Hz, 1H), 3.91 (d, J = 7.7 Hz, 1H), 3.38 (d, J = 6.9 Hz, 1H), 3.36 (d, J = 7.0 Hz, 1H), 1.60–1.52 (m, 2H), 1.40 (dq, J = 14.2, 7.2 Hz, 2H), 1.07 (s, 9H), 0.94 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 159.78, 155.52, 151.19, 137.17, 135.78, 135.69, 134.83, 132.77, 132.73, 130.07, 128.59, 128.14, 128.03, 127.97, 127.80, 114.39, 88.16, 86.55, 77.31, 77.05, 72.77, 72.52, 59.49, 41.60, 32.05, 26.91, 20.29, 19.36, 14.07 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{38}H_{46}N_6O_4Si^+$ 679.3422, found 679.3417.

4.1.11. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-*N*2-isobutyl-9*H*-purine-2,6-diamine (64)

Compound **59** (140 mg, 0.225 mmol) and $NaBH_3CN$ (84 mg, 1.34 mmol) were suspended in MeOH (2.8 mL), and isobutyraldehyde (0.17 mL, 1.82 mmol) was added. The mixture was stirred at rt for 48 h. The solvent was evaporated and the residue was purified by flash column chromatography (silica, hexanes:EtOAc 1:1 then hexanes:EtOAc:MeOH 1:1:0.1) to give compound **64** (80 mg, 0.117 mmol, 52%) along with recovered starting material **59** (8 mg, 0.0135 mmol, 6%). Compound **64**: yellow oil; R_f = 0.38 (silica, 1:1 hexanes:EtOAc); $[\alpha]_D^{25}$ = +40.6 ($CHCl_3$, c 2.0); FT-IR (film) ν_{max} 3323, 2956, 1602, 1536, 1471, 1427, 1364, 1253, 1199, 1112, 1037, 939, 910, 789, 739, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.73 (s, 1H), 7.72–7.68 (m, 4H), 7.45–7.37 (m, 5H), 7.33 (t, J = 7.5 Hz, 2H), 7.28 (dt, J = 4.6, 2.4 Hz, 2H), 7.25–7.22

(m, 2H), 5.94 (s, 1H), 5.49 (s, 2H), 4.96 (s, 1H), 4.79 (s, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 4.25 (s, 1H), 4.06 (d, J = 7.7 Hz, 1H), 4.03 (d, J = 11.9 Hz, 1H), 3.97 (d, J = 12.0 Hz, 1H), 3.92 (d, J = 7.7 Hz, 1H), 3.21 (t, J = 6.3 Hz, 2H), 1.85 (m, 1H), 1.08 (s, 9H), 0.96 (d, J = 6.7 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 155.45, 151.12, 137.14, 135.78, 135.69, 134.84, 132.76, 132.71, 130.07, 128.60, 128.16, 128.03, 127.98, 127.80, 114.22, 88.18, 86.54, 77.27, 77.03, 72.77, 72.55, 59.47, 49.45, 28.70, 26.91, 20.50, 19.36 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{38}H_{47}N_6O_4Si^+$ 679.3422, found 679.3424.

4.1.12. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-(ethylamino)-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (19)

Compound **61** (30 mg, 0.0461 mmol) was dissolved in THF (0.46 mL) at 0 °C, and tetra-*n*-butylammonium fluoride (0.092 mL, 0.0922 mmol, 1.0 M in THF) was slowly added dropwise. The reaction was allowed to warm to rt and stirred for 16 h. The solution was quenched with H_2O (0.5 mL) and stirred for 10 min. The aqueous layer was extracted with 5% MeOH/DCM and the organics dried over $MgSO_4$, filtered, and concentrated. Purification by preparative-plate chromatography (silica, hexanes:EtOAc:MeOH 1:1:0.1) was completed to give compound **19** (15 mg, 0.0364 mmol, 79%). Compound **19**: white foam; R_f = 0.21 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +13.7 ($CHCl_3$, *c* 0.50); FT-IR (film) ν_{max} 3344, 2928, 1631, 1598, 1540, 1473, 1409, 1345, 1260, 1212, 1143, 1035, 935, 909, 789, 752, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.55 (s, 1H), 7.34–7.27 (m, 5H), 5.89 (s, 1H), 5.66 (s, 2H), 4.93 (s, 1H), 4.67 (d, J = 11.7 Hz, 2H), 4.63 (d, J = 11.7 Hz, 1H), 4.49 (s, 1H), 4.12 (d, J = 7.7 Hz, 1H), 4.04 (d, J = 12.6 Hz, 1H), 3.96 (d, J = 12.6 Hz, 1H), 3.91 (d, J = 7.7 Hz, 1H), 3.43–3.36 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 159.37, 155.53, 151.17, 137.31, 135.11, 128.62, 128.20, 127.82, 114.02, 88.31, 86.99, 77.80, 72.58, 72.50, 57.76, 53.57, 36.70, 15.20 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{20}H_{25}N_6O_4^+$ 413.1932, found 413.1938.

4.1.13. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-(octylamino)-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (20)

From compound **62**, using the same procedure as for compound **19**, compound **20** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc:MeOH 1:1:0.1) was completed to give nucleoside **20** (15 mg, 0.0302 mmol, 77%). Compound **20**: white foam; R_f = 0.33 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +27.0 ($CHCl_3$, *c* 1.30); FT-IR (film) ν_{max} 3335, 2924, 2854, 1634, 1598, 1539, 1467, 1408, 1366, 1326, 1264, 1206, 1143, 1034, 935, 909, 881, 809, 788, 738, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.56 (s, 1H), 7.32–7.27 (m, 5H), 5.89 (s, 1H), 5.54 (s, 2H), 4.82 (t, J = 5.3 Hz, 1H), 4.75 (s, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.45 (s, 1H), 4.12 (d, J = 7.8 Hz, 1H), 4.03 (d, J = 12.7 Hz, 1H), 3.94 (d, J = 12.8 Hz, 1H), 3.91 (d, J = 7.7 Hz, 1H), 3.38–3.32 (m, 2H), 1.59–1.52 (m, 2H), 1.37–1.25 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 160.03, 155.94, 151.51, 137.62, 135.30, 128.89, 128.47, 128.10, 114.38, 100.01, 88.58, 87.28, 78.06, 72.87, 72.80, 58.08, 42.28, 32.25, 30.22, 29.83, 29.69, 27.47, 23.08, 14.52 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{26}H_{37}N_6O_4^+$ 497.2871, found 497.2872.

4.1.14. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-(butylamino)-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (21)

From compound **63**, using the same procedure as for compound **19**, compound **21** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc:MeOH 1:1:0.1) was completed to give nucleoside **21** (5 mg, 0.0114 mmol, 77%). Compound **21**: yellow oil; R_f = 0.30 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +19.0 ($CHCl_3$, *c* 0.45); FT-IR (film) ν_{max} 3337, 2928, 2871, 1634, 1600, 1542, 1466, 1409, 1365, 1326, 1273, 1207, 1144, 1036, 935, 909, 882, 789, 736, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.56 (s, 1H), 7.34–7.27 (m, 5H), 5.89 (s, 1H), 5.82–5.66 (s, 1H), 4.99 (dd, J = 3.5, 1.7 Hz, 1H), 4.72 (s, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.64–4.60 (m, 1H), 4.43 (s, 1H), 4.15–4.10 (m, 1H), 4.03 (d, J = 12.8 Hz, 1H), 3.95 (d, J = 12.7 Hz, 1H), 3.91 (d, J = 7.8 Hz, 1H), 3.36 (dt, J = 7.2, 4.7 Hz, 2H), 2.08 (s, 1H), 1.56 (dd, J = 8.5, 6.3 Hz, 2H), 1.44–1.35 (m, 2H), 0.94 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 159.43, 155.53, 151.13, 137.25, 135.00, 128.63, 128.23, 127.85, 113.76, 88.26, 86.95, 77.73, 77.30, 72.61, 72.50, 57.84, 41.60, 31.96, 20.28, 14.05 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{22}H_{29}N_6O_4^+$ 441.2245, found 441.2249.

4.1.15. (1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-(butylamino)-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (22)

From compound **21**, using the same procedure as for compound **64**, compound **22** was obtained and purification by preparative-plate chromatography (C_{18} silica, 5% MeOH/DCM) was completed to give nucleoside **22** (18 mg, 0.0514 mmol, 71%). Compound **22**: yellow oil; R_f = 0.13 (C_{18} silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = +11.1 (MeOH, *c* 0.93); FT-IR (film) ν_{max} 3258, 2957, 1683, 1624, 1512, 1463, 1416, 1367, 1327, 1222, 1130, 1031, 924, 902, 875, 833, 809, 762, 722, 675 cm^{-1}; ^{1}H NMR (CD_3OD, 600 MHz) δ = 8.07 (s, 1H), 5.86 (s, 1H), 4.51 (s, 1H), 4.32 (s, 1H), 4.05 (d, J = 7.9 Hz, 1H), 3.95 (s, 2H), 3.87 (d, J = 8.0 Hz, 1H), 3.45 (td, J = 6.9, 4.9 Hz, 2H), 1.65 (dd, J = 10.0, 4.9 Hz, 2H), 1.45 (dd, J = 15.0, 7.5 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 152.90, 152.84, 139.61, 139.59, 112.88, 90.21, 87.51, 80.92, 72.85, 71.40, 58.08, 42.29, 32.09, 21.04, 14.12 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{15}H_{23}N_6O_4^+$ 351.1775, found 351.1781.

4.1.16. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-(isobutylamino)-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)-methanol (23)

From compound **64**, using the same procedure as for compound **19**, compound **23** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc:MeOH 1:1:0.1) was completed to give nucleoside **23** (38 mg, 0.0863 mmol, 98%). Compound **23**: white foam; R_f = 0.22 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +20.7 ($CHCl_3$, *c* 1.83); FT-IR (film) ν_{max} 3339, 2956, 1633, 1601, 1542, 1485, 1467, 1409, 1384, 1354, 1277, 1207, 1143, 1036, 935, 909, 863, 807, 789, 734, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.61 (s, 1H), 7.32–7.26 (m, 5H), 5.88 (s, 1H), 5.84 (s, 2H), 5.10 (s, 1H), 4.77 (s, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.38 (s, 1H), 4.12 (d, J = 7.7 Hz, 1H), 4.03 (d, J = 12.9 Hz, 1H), 3.94 (d, J = 12.9 Hz, 1H), 3.91 (d, J = 7.8 Hz, 1H), 3.19 (dd, J = 9.2, 3.3 Hz, 2H), 2.07 (s, 1H), 1.84 (dp, J = 13.4, 6.8 Hz, 1H), 0.94 (d, J = 6.7 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 159.73, 155.58, 151.09, 137.31, 134.99, 128.60, 128.17, 127.79, 113.77, 99.72, 88.38, 86.82, 77.38, 72.59, 72.54, 57.63, 49.44, 28.63, 20.46 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{22}H_{29}N_6O_4^+$ 441.2245, found 441.2242.

4.1.17. (1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-(isobutylamino)-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (24)

Compound **23** (19.8 mg, 0.0449 mmol) was dissolved in CH_2Cl_2 (0.45 mL) at 0 °C, and boron trichloride (0.09 mL, 1.0 M in DCM, 0.0899 mmol) was added slowly dropwise. The solution was allowed to stir at rt for 16 h. The reaction was quenched with

MeOH (1 mL) and allowed to stir for 1.5 h, after which the solution was evaporated and azeotroped with MeOH. Purification by flash column chromatography (C_{18} silica, 5% MeOH/DCM) was completed to give compound **24** (10.2 mg, 0.0287 mmol, 64%). Compound **24**: white powder; R_f = 0.29 (C_{18} silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = +3.9 (MeOH, *c* 0.17); FT-IR (film) ν_{max} 3274, 2958, 1684, 1627, 1575, 1512, 1465, 1420, 1385, 1283, 1223, 1175, 1132, 1032, 928, 904, 808 cm^{-1}; ^1H NMR (CD_3OD, 600 MHz) δ = 7.90 (s, 1H), 5.85 (s, 1H), 4.52 (s, 1H), 4.36 (s, 1H), 4.04 (d, *J* = 7.8 Hz, 1H), 3.93 (s, 2H), 3.88 (d, *J* = 7.8 Hz, 1H), 3.19 (ddd, *J* = 26.4, 13.1, 6.9 Hz, 2H), 1.94–1.88 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 6H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 152.05, 136.47, 114.05, 89.82, 87.30, 81.06, 72.88, 71.56, 58.35, 50.21, 29.63, 20.66 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{23}N_6O_4^+$ 351.1775, found 351.1781.

4.1.18. 7-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-7*H*-purine-2,6-diamine (65)

From compound **58**, using the same procedure as for compound **59**, compound **65** (636 mg, 1.02 mmol, 85%) was obtained. Compound **65**: white foam; R_f = 0.21 (silica, EtOAc); $[\alpha]_D^{25}$ = −119.1 ($CHCl_3$, *c* 1.15); FT-IR (film) ν_{max} 3330, 3182, 2931, 2857, 1574, 1470, 1427, 1401, 1361, 1217, 1105, 1036, 923, 883, 856, 823, 792, 744, 699, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.56 (dd, *J* = 10.4, 3.8 Hz, 4H), 7.44–7.30 (m, 13H), 5.75 (s, 1H), 5.45 (s, 2H), 4.81 (d, *J* = 0.9 Hz, 2H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.54 (s, 1H), 4.14 (d, *J* = 7.5 Hz, 2H), 3.98 (t, *J* = 6.9 Hz, 3H), 0.95 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 160.34, 151.92, 139.19, 136.80, 135.57, 135.52, 132.86, 132.54, 130.13, 130.09, 128.95, 128.76, 128.13, 127.96, 106.10, 89.93, 86.19, 78.07, 76.64, 73.10, 72.95, 59.59, 26.70, 19.34 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{34}H_{39}N_6O_4Si^+$ 623.2796, found 623.2778.

4.1.19. 7-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-*N*2-isobutyl-7*H*-purine-2,6-diamine (66)

From compound **65**, using the same procedure as for compound **17**, compound **66** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 1:1 then hexanes:EtOAc:MeOH 1:1:0.1) was completed to give nucleoside **66** (43 mg, 0.0634 mmol, 44%). Compound **66**: white foam; R_f = 0.22 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = −67.6 ($CHCl_3$, *c* 2.13); FT-IR (film) ν_{max} 3331, 2956, 1629, 1588, 1470, 1427, 1385, 1361, 1233, 1112, 1039, 910, 856, 823, 791, 736, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.58 (td, *J* = 8.4, 1.3 Hz, 4H), 7.45–7.31 (m, 12H), 5.77 (s, 1H), 5.68 (d, *J* = 0.4 Hz, 2H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.63–5.59 (m, 2H), 4.14 (dd, *J* = 7.0, 2.2 Hz, 2H), 4.00 (d, *J* = 1.8 Hz, 2H), 3.98 (d, *J* = 8.0 Hz, 1H), 3.31–3.24 (m, 2H), 2.04 (s, 1H), 1.91 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.99–0.95 (m, 15H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 151.86, 139.01, 136.86, 135.60, 132.91, 132.64, 130.16, 130.14, 129.00, 128.81, 128.25, 128.01, 128.00, 105.38, 99.74, 90.08, 86.29, 78.03, 76.70, 73.17, 73.00, 59.61, 49.37, 28.58, 26.78, 20.42, 19.40 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{38}H_{47}N_6O_4Si^+$ 679.3422, found 679.3421.

4.1.20. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-(isobutylamino)-7*H*-purin-7-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)-methanol (25)

From compound **66**, using the same procedure as for compound **19**, compound **25** was obtained and purification by preparative-plate chromatography (silica, 5% MeOH/DCM) was completed to give nucleoside **25** (20 mg, 0.0454 mmol, 77%). Compound **25**: white foam; R_f = 0.11 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = −131.8 ($CHCl_3$, *c* 0.98); FT-IR (film) ν_{max} 3351, 2956, 1630, 1579, 1530, 1488, 1467, 1411, 1362, 1229, 1147, 1095, 1039, 911, 856, 790, 733, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.39 (ddd, *J* = 27.1, 17.2, 7.2 Hz, 5H), 7.07 (s, 1H), 5.63 (s, 1H), 5.48 (s, 2H), 4.97–4.90 (m, 1H), 4.87 (d, *J* = 12.1 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.57 (s, 1H), 4.15 (d, *J* = 7.9 Hz, 1H), 4.05 (d, *J* = 13.3 Hz, 1H), 3.97 (d, *J* = 13.3 Hz, 1H), 3.91 (d, *J* = 7.9 Hz, 1H), 3.21 (dt, *J* = 12.8, 6.2 Hz, 1H), 3.14–3.07 (m, 1H), 2.15 (s, 1H), 1.82 (dt, *J* = 13.5, 6.7 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 159.67, 151.56, 138.80, 137.58, 128.87, 128.54, 128.17, 105.58, 99.74, 90.76, 85.89, 77.91, 77.04, 73.08, 57.57, 49.37, 28.49, 20.45, 20.41 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{29}N_6O_4^+$ 441.2245, found 441.2245.

4.1.21. ((1*S*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-3-(2,6-diamino-7*H*-purin-7-yl)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (26)

From compound **65**, using the same procedure as for compound **15**, compound **26** was obtained and purification for characterization was completed by preparative-plate chromatography (C_{18} silica, MeCN/H_2O 10:1). Compound **26**: white semi-solid; R_f = 0.12 (C_{18} silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = −62.8 (MeOH, *c* 1.11); FT-IR (film) ν_{max} 3115, 1648, 1545, 1455, 1389, 1316, 1219, 1143, 1047, 937, 884, 858, 733, 696, 676 cm^{-1}; ^1H NMR (D_2O, 600 MHz) δ = 7.83 (s, 1H), 7.37 (s, 5H), 6.03 (s, 1H), 4.75 (s, 1H), 4.70 (s, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.11 (s, 1H), 4.09 (d, *J* = 8.5 Hz, 1H), 4.04 (d, *J* = 8.5 Hz, 1H), 4.01 (d, *J* = 13.4 Hz, 1H), 3.96 (d, *J* = 13.4 Hz, 1H) ppm; ^{13}C NMR (D_2O, 151 MHz) δ = 153.65, 153.35, 150.03, 140.93, 136.10, 128.77, 128.75, 104.92, 89.66, 85.90, 77.11, 76.27, 72.70, 72.16, 56.43 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{21}N_6O_4^+$ 385.1619, found 385.1624.

4.1.22. (1*S*,3*R*,4*R*,7*S*)-3-(2,6-Diamino-7*H*-purin-7-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (27)

From compound **26**, using the same procedure as for compound **17**, compound **27** was obtained and purification by flash column chromatography (C_{18} silica, 4% H_2O/MeCN) was completed to give nucleoside **27** (100 mg, 0.469 mmol, 46% over two steps). Compound **27**: white semi-solid; R_f = 0.39 (C_{18} silica, 20% H_2O/MeOH); $[\alpha]_D^{25}$ = −95.1 (MeOH, *c* 0.21); FT-IR (film) ν_{max} 3129, 1648, 1466, 1392, 1224, 1172, 1091, 1039, 1012, 975, 929, 874, 832, 764 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ = 8.16 (s, 1H), 6.02 (s, 1H), 4.97 (s, 1H), 4.42 (s, 1H), 4.07 (d, *J* = 10.6 Hz, 2H), 3.97 (s, 2H) ppm; ^{13}C NMR (D_2O, 126 MHz) δ = 154.29, 153.86, 150.48, 142.01, 141.78, 90.69, 86.27, 79.34, 72.06, 70.81, 57.03 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{15}N_6O_4^+$ 295.1149, found 295.1157.

4.1.23. (2*R*,3*R*,4*S*,5*S*)-2-(6-Amino-2-chloro-9*H*-purin-9-yl)-4-(benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-5-(tosyloxymethyl)tetrahydrofuran-3-yl acetate (67)

Compound **56** (400 mg, 0.526 mmol) and 2-chloroadenine (136 mg, 0.803 mmol) were dissolved in MeCN (5.2 mL), and BSA (0.30 mL, 1.23 mmol) was added. The mixture was heated to 65 °C for 1.5 h. The reaction mixture was then cooled to 0 °C and TMSOTf (0.24 mL, 1.07 mmol) was added, after which the reaction was heated at 65 °C for 3 h. The reaction solution was quenched with cold satd aq $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2. The organics were washed with satd aq $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL), dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (silica, hexanes:EtOAc 1:1) to give compound **67** (390 mg, 0.447 mmol, 85%). Compound **67**: white foam; R_f = 0.44 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = −5.6 ($CHCl_3$, *c* 1.64); FT-IR (film) ν_{max} 3320, 3174, 2931, 2858, 1745, 1643, 1593, 1497, 1461, 1428, 1360, 1308, 1227, 1189, 1175, 1105, 978, 936, 909, 813, 790, 731, 700, 666 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.75 (s, 1H), 7.71–7.67 (m, 2H), 7.58–7.52 (m, 4H), 7.45–7.27 (m, 11H), 7.20 (d, J = 8.0 Hz, 2H), 6.06 (s, 2H), 5.94 (d, J = 4.9 Hz, 1H), 5.71 (dd, J = 5.7, 5.0 Hz, 1H), 4.71 (d, J = 5.8 Hz, 1H), 4.54 (s, 1H), 4.51 (s, 1H), 4.36 (d, J = 10.7 Hz, 1H), 4.28 (d, J = 10.7 Hz, 1H), 3.76 (d, J = 11.0 Hz, 1H), 3.73 (d, J = 11.1 Hz, 1H), 2.38 (s, 3H), 2.04 (s, 3H), 1.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 169.99, 156.22, 154.35, 147.46, 144.85, 139.78, 137.03, 135.72, 135.58, 132.92, 132.63, 132.32, 130.09, 130.07, 129.83, 128.67, 128.38, 128.27, 128.13, 128.00, 127.90, 86.79, 86.54, 78.15, 74.86, 74.67, 68.68, 64.75, 27.01, 21.73, 20.74, 19.31 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{43}H_{47}ClN_5O_8SSi^+$ 856.2598, found 856.2587.

4.1.24. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-2-chloro-9*H*-purin-6-amine (68)

Compound **67** (29 mg, 0.0339 mmol) was dissolved in THF (3.42 mL) at 0 °C, and 2 M NaOH (0.28 mL) was added. The mixture was allowed to warm to rt with stirring over 15 h. The reaction solution was worked up by extraction with CH_2Cl_2, drying over $MgSO_4$, filtration, and concentration. Purification by flash column chromatography was completed to produce compound **68** (19 mg, 0.0285 mmol, 87%). Compound **68**: white foam; R_f = 0.53 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +33.0 ($CHCl_3$, c 1.55); FT-IR (film) ν_{max} 3314, 3170, 2931, 2858, 1645, 1592, 1571, 1498, 1456, 1427, 1345, 1310, 1245, 1202, 1112, 1038, 937, 909, 857, 823, 804, 735, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.01 (s, 1H), 7.69 (ddd, J = 8.0, 3.7, 1.4 Hz, 4H), 7.48–7.32 (m, 7H), 7.29–7.27 (m, 2H), 7.26–7.22 (m, 2H), 6.09 (s, 2H), 6.02 (s, 1H), 4.79 (s, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.24 (s, 1H), 4.07 (d, J = 7.8 Hz, 1H), 4.04 (d, J = 11.9 Hz, 1H), 3.98 (d, J = 12.0 Hz, 1H), 3.90 (d, J = 7.8 Hz, 1H), 1.08 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 156.18, 154.34, 138.69, 137.03, 135.75, 135.64, 132.74, 132.66, 130.12, 128.59, 128.23, 128.06, 128.00, 127.88, 88.62, 86.72, 77.36, 76.88, 72.71, 72.56, 59.31, 26.92, 19.38 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{34}H_{36}ClN_5O_4Si^+$ 642.2298, found 642.2280.

4.1.25. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-chloro-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (28)

From compound **68**, using the same procedure as for compound **15**, compound **28** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc:MeOH 1:1:0.1) was completed to give nucleoside **28** (28 mg, 0.0695 mmol, 61%). Compound **28**: white semi-solid; R_f = 0.18 (silica, hexanes:EtOAc:MeOH 1:1:0.1); $[\alpha]_D^{25}$ = +18.0 ($CHCl_3$, c 0.56); FT-IR (film) ν_{max} 3322, 3176, 2926, 2248, 1644, 1593, 1572, 1497, 1455, 1347, 1309, 1249, 1203, 1182, 1143, 1097, 1035, 987, 933, 907, 883, 821, 789, 729, 697, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.84 (s, 1H), 7.34–7.27 (m, 5H), 6.49 (s, 2H), 5.96 (s, 1H), 4.78 (s, 1H), 4.72 (d, J = 11.8 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.43 (s, 1H), 4.13 (d, J = 7.9 Hz, 1H), 4.04 (d, J = 12.2 Hz, 2H), 3.96 (d, J = 7.8 Hz, 1H), 3.91 (d, J = 7.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 156.19, 154.45, 138.83, 137.25, 128.63, 128.26, 127.88, 99.71, 88.57, 87.08, 77.56, 77.27, 72.52, 57.69 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{18}H_{19}ClN_5O_4^+$ 404.1120, found 404.1120.

4.1.26. (1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-chloro-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (29)

Compound **28** (5 mg, 0.0124 mmol) was dissolved in CH_2Cl_2 (0.13 mL) at 0 °C, and methanesulfonic acid (0.06 mL, 0.963 mmol) was added. The reaction was stirred at this temperature for 1.5 h. The reaction was neutralized with concentrated aq NaOH (0.13 mL, 0.963 mmol) and the mixture concentrated. The residue was diluted with CH_2Cl_2 (2 mL) and MeOH (0.5 mL) then filtered through Celite to remove most salts. Purification by preparative-plate chromatography (C_{18} silica, EtOAc) was completed to give compound **29** (1.8 mg, 0.00570 mmol, 46%). Compound **29**: white powder; R_f = 0.61 (C_{18} silica, EtOAc); $[\alpha]_D^{25}$ = +1.8 (MeOH, c 0.15); FT-IR (film) ν_{max} 3179, 2925, 1667, 1597, 1571, 1498, 1460, 1445, 1354, 1311, 1265, 1204, 1180, 1131, 1034, 1009, 934, 900, 877, 848, 821, 786, 749, 725, 678 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ = 8.20 (s, 1H), 5.92 (s, 1H), 4.48 (s, 1H), 4.30 (s, 1H), 4.03 (d, J = 7.9 Hz, 1H), 3.92 (s, 2H), 3.86 (d, J = 7.9 Hz, 1H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 158.08, 155.48, 139.99, 90.18, 87.55, 81.01, 72.82, 71.36, 58.16 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{11}H_{13}ClN_5O_4^+$ 314.0651, found 314.0657.

4.1.27. (2*R*,3*R*,4*S*,5*S*)-2-(6-Amino-2-fluoro-9*H*-purin-9-yl)-4-(benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-5-(tosyloxymethyl)tetrahydrofuran-3-yl acetate (69)

Acetylated compound **56** (200 mg, 0.268 mmol) was dissolved in dry MeCN (2.0 mL) along with 2-fluoro-9*H*-purine-6-amine (81 mg, 0.530 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.17 mL, 0.670 mmol). The reaction mixture was heated to 80 °C for 1.5 h. The reaction mixture was cooled to 0 °C and TMSOTf (0.132 mL, 0.530 mmol) was slowly added. Heating was resumed for an additional 3 h at 80 °C. The reaction mixture was quenched with satd aq $NaHCO_3$ (2 mL) and extracted with EtOAc. The combined organic extracts were washed with brine (2 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, hexanes:EtOAc 4:1) was completed to give compound **69** (176 mg, 0.210 mmol, 78%). Compound **69**: light yellow oil; R_f = 0.49 (silica, hexanes:EtOAc 2:3); $[\alpha]_D^{25}$ = −6.9 (MeCN, c 0.30); FT-IR (film) ν_{max} 3459, 2931, 1652, 1496, 1438, 1410, 1387, 1255, 1224, 1094, 1062, 865, 659 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.74 (s, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.55 (dd, J = 11.5, 6.8 Hz, 4H), 7.42–7.30 (m, 9H), 7.26–7.23 (m, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.89 (d, J = 4.8 Hz, 1H), 5.74–5.71 (m, 1H), 4.78 (s, 2H), 4.73 (d, J = 5.8 Hz, 1H), 4.54 (d, J = 11.3 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.36 (d, J = 10.7 Hz, 1H), 4.26 (d, J = 10.7 Hz, 1H), 3.77 (d, J = 11.0 Hz, 1H), 3.71 (d, J = 11.0 Hz, 1H), 2.37 (s, 3H), 2.02 (s, 3H), 0.99 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 176.75, 169.98, 144.91, 139.65, 139.63, 136.96, 135.70, 135.54, 132.77, 132.57, 132.27, 130.09, 130.08, 129.83, 128.65, 128.35, 128.24, 128.20, 128.13, 128.10, 127.99, 127.90, 86.64, 86.48, 77.95, 74.78, 74.46, 68.64, 64.58, 26.95, 21.73, 20.74, 19.29 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{43}H_{47}N_5O_8SSi^+$ 840.2893, found 840.2892.

4.1.28. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-2-fluoro-9*H*-purin-6-amine (70)

From compound **69**, using the same procedure as for compound **30**, compound **70** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 4:1) was completed to give nucleoside **70** (6 mg, 0.00964 mmol, 81%). Compound **70**: colorless foam; R_f = 0.60 (silica, hexanes:EtOAc 2:3); $[\alpha]_D^{25}$ = +12.9 (MeCN, c 0.30); FT-IR (film) ν_{max} 3490, 2293, 2253, 1443, 1375, 1039, 918, 749 cm^{-1}; ^{1}H NMR (CD_3CN, 600 MHz) δ = 7.95 (s, 1H), 7.71–7.65 (m, 4H), 7.49–7.43 (m, 2H), 7.42–7.35 (m, 4H), 7.32–7.25 (m, 5H), 6.32 (s, 2H), 5.92 (s, 1H), 4.70 (s, 1H), 4.65 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.38 (s, 1H), 4.08–4.01 (m, 2H), 3.98 (d, J = 7.9 Hz, 1H), 3.87 (d, J = 7.9 Hz, 1H), 1.02 (s, 9H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 160.56, 159.19, 158.48, 158.34, 139.07, 139.05, 138.59, 136.35, 136.29, 133.67, 133.60, 130.89, 129.23, 128.76, 128.68, 128.58, 88.97, 87.00, 78.11, 77.69, 73.09, 72.70, 60.22, 27.01, 19.66 ppm; HRMS (ESI-TOF) (m/z): $[M+Na]^+$ calcd for $C_{34}H_{36}FN_5O_4SiNa^+$ 648.2413, found 648.2411.

4.1.29. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-fluoro-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (30)

From compound **70**, using the same procedure as for compound **15**, compound **30** was obtained and purification by flash column chromatography (silica, EtOAc:hexanes 8:1) was completed to give nucleoside **30** (21 mg, 0.0543 mmol, 85%). Compound **30**: colorless oil; R_f = 0.25 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = −8.0 (MeCN, *c* 0.10); FT-IR (film) ν_{max} 3311, 2949, 2837, 1646, 1408, 1113, 1014 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ = 8.13 (s, 1H), 7.29–7.24 (m, 5H), 5.92 (s, 1H), 4.97 (s, 1H), 4.63 (s, 2H), 4.22 (s, 1H), 4.06 (d, *J* = 7.8 Hz, 1H), 3.94 (d, *J* = 1.8 Hz, 2H), 3.89 (d, *J* = 7.8 Hz, 1H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 161.19, 159.80, 159.10, 139.81, 138.73, 129.35, 129.16, 129.00, 89.70, 87.69, 78.38, 78.03, 73.52, 73.30, 58.08 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{19}FN_5O_4^+$ 388.1416, found 388.1411.

4.1.30. (1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-fluoro-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (31)

From compound **30**, using the same procedure as for compound **12**, compound **31** was obtained and purification by flash column chromatography (silica, 5% MeOH/DCM) was completed to give nucleoside **31** (5.3 mg, 0.0178 mmol, 69%). Compound **31**: white foam; R_f = 0.12 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = −3.5 (MeCN, *c* 0.10); FT-IR (film) ν_{max} 3343, 2948, 2836, 2502, 2238, 2073, 1655, 1449, 1119, 1021, 977 cm^{-1}; ^1H NMR (CD_3OD, 600 MHz) δ = 8.21 (s, 1H), 5.92 (s, 1H), 4.50 (s, 1H), 4.34 (s, 1H), 4.05 (d, *J* = 7.9 Hz, 1H), 3.94 (s, 2H), 3.88 (d, *J* = 7.9 Hz, 1H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 161.30, 159.91, 139.83, 90.14, 87.50, 80.97, 72.84, 71.42, 58.18 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{13}FN_5O_4$ 298.0946, found 298.0945.

4.1.31. ((1*S*,3*R*,4*R*,7*S*)-3-(6-Amino-2-morpholino-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (32)

Compound **70** (18 mg, 0.0288 mmol) was dissolved in dry DMSO (0.30 mL) along with morpholine (0.0050 mL, 0.0570 mmol). The reaction mixture was heated to 95 °C for 24 h. The mixture was placed under vacuum to remove solvent, and the residue was dissolved in dry THF (0.2 mL). The solution was cooled to 0 °C and treated with HF·pyridine (0.03 mL, 0.280 mmol). After 1 h at 0 °C, the reaction mixture was quenched with satd aq $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed brine (2 × 1 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, 5% MeOH/DCM) was completed to give compound **32** (10 mg, 0.0220 mmol, 76% over two steps). Compound **32**: light yellow oil; R_f = 0.54 (silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = +50.0 (MeCN, *c* 0.10); FT-IR (film) ν_{max} 3399, 2962, 1605, 1474, 1408, 1293, 1056, 1017 cm^{-1}; ^1H NMR (CD_3CN, 500 MHz) δ = 7.69 (s, 1H), 7.34–7.25 (m, 5H), 5.83 (s, 1H), 5.73 (s, 2H), 4.67 (s, 1H), 4.61 (s, 2H), 4.29 (s, 1H), 3.99 (d, *J* = 7.9 Hz, 1H), 3.88 (dd, *J* = 7.7, 3.2 Hz, 2H), 3.84 (d, *J* = 7.9 Hz, 1H), 3.67 (s, 8H), 3.19–3.15 (m, 1H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 160.12, 156.51, 152.08, 138.84, 136.40, 129.26, 128.70, 128.60, 88.78, 86.85, 78.39, 78.12, 73.06, 72.73, 67.34, 58.23, 45.72 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{27}N_6O_5^+$ 455.2037, found 455.2050.

4.1.32. (2*R*,3*R*,4*S*,5*S*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-2-(2,6-dichloro-9*H*-purin-9-yl)-5-(tosyloxymethyl)tetrahydrofuran-3-yl acetate (71)

Peracetylated compound **56** (500 mg, 0.669 mmol) was dissolved in dry MeCN (5.0 mL) along with 2,6-dichloro-9*H*-purine (240 mg, 1.33 mmol) and BSA (0.41 mL 1.67 mmol). The reaction mixture was heated to 95 °C for 1.5 h. After cooling to 0 °C, TMSOTf (0.33 mL, 1.33 mmol) was slowly added and heating was resumed for 3 h at 80 °C. The reaction mixture was brought to rt, quenched with satd aq $NaHCO_3$ (5 mL) and extracted with EtOAc. The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, hexanes:EtOAc:acetone 8:1:1) was completed to give compound **71** (374 mg, 0.428 mmol, 64%). Compound **71**: yellow foam; R_f = 0.51 (silica, 10% MeOH/ DCM); $[\alpha]_D^{25}$ = −2.8 ($CHCl_3$, *c* 0.10). FT-IR (film) ν_{max} 2932, 1750, 1595, 1557, 1428, 1360, 1227, 1189, 1177, 1112, 980, 883, 814, 744, 702, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ = 8.09 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.55–7.49 (m, 4H), 7.40–7.32 (m, 8H), 7.28 (d, *J* = 5.8 Hz, 2H), 7.22–7.19 (m, 3H), 6.02 (d, *J* = 5.2 Hz, 1H), 5.67 (t, *J* = 6.0 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 4.26 (d, *J* = 10.7 Hz, 1H), 3.76 (d, *J* = 10.8 Hz, 1H), 3.71 (d, *J* = 10.8 Hz, 1H), 2.38 (s, 3H), 2.05 (s, 3H), 0.99 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 176.98, 170.23, 153.42, 152.57, 152.49, 145.20, 144.80, 135.92, 135.77, 133.04, 132.60, 132.35, 131.71, 130.39, 130.08, 128.97, 128.77, 128.55, 128.32, 128.23, 128.09, 87.60, 87.28, 77.99, 77.58, 74.77, 68.68, 64.86, 27.22, 21.99, 20.92, 19.49 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{43}H_{45}Cl_2N_4O_8SSi^+$ 875.2099, found 875.2097.

4.1.33. ((3*S*,4*R*,5*R*)-5-(6-(Benzylamino)-2-chloro-9*H*-purin-9-yl)-3-(benzyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)-4-hydroxytetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (72)

Compound **71** (104 mg, 0.119 mmol) was dissolved in MeOH (7.0 mL) and treated with benzylamine (0.065 mL, 0.594 mmol). The reaction mixture was heated at 55 °C for 12 h. The solvent was evaporated and purification of the residue by flash column chromatography (silica, hexanes:EtOAc 1:1) was completed to give compound **72** (100 mg, 0.111 mmol, 93%). Compound **72**: white foam; R_f = 0.48 (silica, hexanes:EtOAc 1:1); $[\alpha]_D^{25}$ = −7.7 ($CHCl_3$, *c* 1.07); FT-IR (film) ν_{max} 3325, 3069, 2931, 2858, 1619, 1581, 1533, 1496, 1472, 1454, 1428, 1354, 1310, 1189, 1176, 1103, 1029, 1019, 977, 910, 813, 788, 736, 701, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.75–7.71 (m, 2H), 7.54 (ddd, *J* = 17.0, 8.0, 1.4 Hz, 5H), 7.42–7.28 (m, 16H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.36 (s, 1H), 5.65 (d, *J* = 4.9 Hz, 1H), 4.77 (s, 2H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.59 (dd, *J* = 11.3, 6.0 Hz, 1H), 4.48 (d, *J* = 5.9 Hz, 1H), 4.38 (q, *J* = 10.5 Hz, 2H), 3.77 (d, *J* = 10.8 Hz, 1H), 3.71 (d, *J* = 6.7 Hz, 1H), 3.66 (d, *J* = 10.8 Hz, 1H), 2.39 (s, 3H), 1.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 144.93, 139.28, 136.88, 135.68, 135.58, 132.86, 132.69, 132.31, 130.07, 129.88, 128.89, 128.84, 128.58, 128.44, 128.17, 128.14, 127.97, 127.89, 127.86, 89.73, 86.91, 79.47, 74.82, 74.55, 69.08, 64.92, 26.99, 21.75, 19.30 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{48}H_{51}ClN_5O_7SSi^+$ 904.2961, found 904.2961.

4.1.34. *N*-Benzyl-9-((1*R*,3*R*,4*R*,7*S*)-7-(benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-2-chloro-9*H*-purin-6-amine (73)

From compound **72**, using the same procedure as for compound **68**, compound **73** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 7:3) was completed to afford nucleoside **73** (59 mg, 0.0806 mmol, 68%). Compound **73**: white foam; R_f = 0.87 (silica, hexanes:EtOAc 1:1); $[\alpha]_D^{25}$ = +18.0 (MeCN, *c* 0.10); FT-IR (film) ν_{max} 2930, 1619, 1577, 1455, 1428, 1346, 1311, 1208, 1112, 1046, 937, 858, 824, 741, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.94 (s, 1H), 7.68 (ddd, *J* = 8.0, 3.6, 1.4 Hz, 4H), 7.46–7.26 (m, 15H), 7.25–7.23 (m, 1H), 6.32 (s, 1H), 6.02 (s, 1H), 4.81 (d, *J* = 9.3 Hz, 3H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.23 (s, 1H), 4.07 (d, *J* = 7.8 Hz, 1H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.97 (d, *J* = 12.0 Hz, 1H), 3.90 (d, *J* = 7.8 Hz, 1H), 1.07 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 137.99, 137.10, 135.75, 135.65, 132.75, 132.68, 130.10, 128.91, 128.59, 128.25,

128.19, 128.04, 127.99, 127.92, 127.87, 99.72, 88.54, 86.67, 77.41, 76.91, 72.71, 72.53, 59.36, 26.90, 19.35 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{41}H_{43}ClN_5O_4Si^+$ 732.2767, found 732.2765.

4.1.35. ((1*S*,3*R*,4*R*,7*S*)-3-(6-(Benzylamino)-2-chloro-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (33)

From compound **73**, using the same procedure as for compound **15**, compound **33** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 7:3) was completed to give nucleoside **33** (39 mg, 0.0790 mmol, 96%). Compound **33**: light yellow oil; R_f = 0.17 (silica, hexanes:EtOAc 1:1); $[\alpha]_D^{25}$ = +10.0 (MeCN, *c* 0.50); FT-IR (film) ν_{max} 3316, 2930, 1703, 1618, 1578, 1496, 1454, 1348, 1310, 1212, 1145, 1097, 1050, 931, 883, 857, 787, 739, 698, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ = 7.73 (s, 1H), 7.38–7.28 (m, 10H), 6.56 (s, 1H), 5.95 (s, 1H), 4.80 (s, 2H), 4.70 (d, *J* = 13.3 Hz, 2H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.40 (s, 1H), 4.11 (d, *J* = 7.8 Hz, 1H), 3.98 (d, *J* = 12.5 Hz, 1H), 3.88 (d, *J* = 7.7 Hz, 2H), 3.38 (d, *J* = 0.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 155.08, 154.97, 149.05, 138.05, 137.69, 137.21, 128.92, 128.63, 128.28, 128.22, 127.99, 127.95, 119.09, 88.47, 87.19, 77.83, 77.16, 72.59, 72.47, 57.84, 44.95 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{25}ClN_5O_4^+$ 495.1589, found 495.1591.

4.1.36. (1*S*,3*R*,4*R*,7*S*)-3-(6-(Benzylamino)-2-chloro-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (34)

From compound **33**, using the same procedure as for compound **39**, compound **34** was obtained and purification by preparative-plate chromatography (C_{18} silica, EtOAc) was completed to give nucleoside **34** (10 mg, 0.0248 mmol, 61%). Compound **34**: yellow oil; R_f = 0.71 (C_{18} silica, EtOAc); $[\alpha]_D^{25}$ = −8.3 (MeOH, *c* 0.86); FT-IR (film) ν_{max} 3269, 2926, 1619, 1577, 1533, 1453, 1351, 1300, 1205, 1138, 1094, 1040, 930, 876, 847, 821, 786, 694, 678 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ = 8.25 (s, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.02 (s, 1H), 4.82 (s, 2H), 4.57 (s, 1H), 4.40 (s, 1H), 4.12 (d, *J* = 7.9 Hz, 1H), 4.02 (s, 2H), 3.95 (d, *J* = 7.9 Hz, 1H) ppm; ^{13}C NMR (CD_3OD, 126 MHz) δ = 149.14, 138.90, 138.55, 128.55, 127.84, 127.80, 127.34, 89.15, 86.53, 80.06, 71.83, 70.41, 57.19 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{19}ClN_5O_4^+$ 404.1120, found 404.1122.

4.1.37. ((2*S*,3*S*,4*R*,5*R*)-5-(6-(Benzyl(methyl)amino)-2-chloro-9*H*-purin-9-yl)-3-(benzyloxy)-2-((*tert*-butyldiphenylsilyloxy)-methyl)-4-hydroxytetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (74)

Compound **71** (107 mg, 0.122 mmol) was dissolved in MeOH (2.14 mL), and *N*-benzylmethylamine (0.08 mL, 0.610 mmol) was added. The solution was heated to 55 °C for 3 h. Evaporation and purification by flash column chromatography (silica, hexanes:EtOAc 3:1) were completed to give compound **74** (95 mg, 0.100 mmol, 82%). Compound **74**: white foam; R_f = 0.3 (silica, hexanes:EtOAc 2:1); $[\alpha]_D^{25}$ = −6.3 ($CHCl_3$, *c* 0.70); FT-IR (film) ν_{max} 2930, 2858, 1592, 1454, 1427, 1402, 1359, 1313, 1237, 1210, 1189, 1176, 1095, 974, 941, 908, 812, 730, 699, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.60 (s, 1H), 7.57–7.51 (m, 4H), 7.43–7.28 (m, 15H), 7.23 (d, *J* = 8.0 Hz, 3H), 5.65 (d, *J* = 4.8 Hz, 1H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.58 (dd, *J* = 11.5, 6.0 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 1H), 4.38 (d, *J* = 10.5 Hz, 1H), 4.36 (d, *J* = 10.5 Hz, 1H), 3.77 (d, *J* = 10.8 Hz, 1H), 3.65 (dd, *J* = 8.7, 4.7 Hz, 3H), 3.17 (s, 1H), 2.39 (s, 3H), 0.99 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ 144.94, 136.94, 135.71, 135.60, 132.83, 132.70, 132.34, 130.07, 129.89, 128.85, 128.80, 128.56, 128.46, 128.21, 127.99, 127.88, 127.70, 119.42, 89.85, 86.93, 79.58, 74.83, 74.68, 69.16, 64.93, 27.00, 21.79, 19.31 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{49}H_{53}ClN_5O_7SSi^+$ 918.3124, found 918.3110.

4.1.38. *N*-Benzyl-9-((1*R*,3*R*,4*R*,7*S*)-7-(benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-2-chloro-*N*-methyl-9*H*-purin-6-amine (75)

From **74**, using the same procedure as for **68**, compound **75** was obtained (73 mg, 0.0979 mmol, 98%). Compound **75**: white foam; R_f = 0.77 (silica, hexanes:EtOAc 2:1); $[\alpha]_D^{25}$ = +13.1 ($CHCl_3$, *c* 1.18); FT-IR (film) ν_{max} 3030, 2930, 2857, 1590, 1582, 1524, 1495, 1472, 1454, 1427, 1402, 1354, 1314, 1241, 1207, 1110, 1037, 939, 910, 885, 856, 824, 806, 784, 736, 701, 677 cm^{-1}; ^1H NMR (CD_3CN, 500 MHz) δ = 7.92 (s, 1H), 7.66 (dd, *J* = 9.3, 8.1 Hz, 4H), 7.43 (dd, *J* = 10.6, 4.2 Hz, 2H), 7.40–7.24 (m, 14H), 5.94 (s, 1H), 4.73 (s, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.35 (s, 1H), 4.06 (d, *J* = 12.1 Hz, 1H), 4.03 (d, *J* = 12.1 Hz, 1H), 3.98 (d, *J* = 8.0 Hz, 1H), 3.88 (d, *J* = 7.9 Hz, 1H), 3.64 (s, 1H), 3.12 (s, 1H), 1.00 (s, 9H) ppm; ^{13}C NMR (CD_3CN, 126 MHz) δ = 138.66, 137.49, 136.43, 136.38, 133.81, 133.77, 130.98, 130.96, 129.61, 129.33, 128.86, 128.80, 128.69, 128.37, 120.10, 89.12, 87.12, 78.31, 77.80, 73.23, 72.87, 60.36, 27.16, 19.80 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{42}H_{45}ClN_5O_4Si^+$ 746.2929, found 746.2922.

4.1.39. ((1*S*,3*R*,4*R*,7*S*)-3-(6-(Benzyl(methyl)amino)-2-chloro-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)-methanol (35)

From compound **75**, using the same procedure as for compound **15**, compound **35** was obtained and preparative-plate chromatography (silica, EtOAc) was completed to give nucleoside **35** (36 mg, 0.0710 mmol, 75%). Compound **35**: white foam; R_f = 0.67 (silica, EtOAc); $[\alpha]_D^{25}$ = −13.3 ($CHCl_3$, *c* 1.13); FT-IR (film) ν_{max} 3378, 2942, 1592, 1454, 1403, 1354, 1313, 1211, 1145, 1039, 938, 910, 856, 783, 751, 700, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.75 (s, 1H), 7.35–7.26 (m, 10H), 5.99 (s, 1H), 5.53 (s, 1H), 5.00 (s, 1H), 4.72–4.63 (m, 3H), 4.42 (s, 1H), 4.13 (d, *J* = 7.8 Hz, 1H), 4.05–3.99 (m, 1H), 3.98–3.93 (m, 1H), 3.92 (t, *J* = 5.5 Hz, 1H), 3.65 (s, 1H), 3.21 (s, 1H), 2.78 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 155.12, 154.13, 137.24, 136.52, 128.82, 128.62, 128.25, 127.97, 127.72, 119.39, 88.21, 87.12, 77.89, 77.36, 77.29, 72.58, 72.47, 58.12 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{26}H_{27}ClN_5O_4^+$ 508.1746, found 508.1750.

4.1.40. (1*S*,3*R*,4*R*,7*S*)-3-(6-(Benzyl(methyl)amino)-2-chloro-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (36)

From compound **35**, using the same procedure as for compound **29**, compound **36** was obtained and purification by preparative-plate chromatography (silica, EtOAc) was completed to give nucleoside **36** (36 mg, 0.0863 mmol, 75%). Compound **36**: white semi-solid; R_f = 0.34 (silica, EtOAc); $[\alpha]_D^{25}$ = −7.8 (MeOH, *c* 0.80); FT-IR (film) ν_{max} 3354, 2928, 1592, 1453, 1403, 1356, 1313, 1215, 1131, 1038, 936, 905, 874, 845, 820, 783, 738, 701, 676 cm^{-1}; ^1H NMR (CD_3OD, 600 MHz) δ = 8.15 (s, 1H), 7.35–7.22 (m, 5H), 5.96 (s, 1H), 5.56 (s, 2H), 4.49 (s, 1H), 4.32 (s, 1H), 4.05 (d, *J* = 7.9 Hz, 1H), 3.94 (s, 2H), 3.88 (d, *J* = 7.9 Hz, 1H), 3.65 (s, 3H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 156.23, 155.04, 138.25, 129.68, 129.35, 129.17, 128.81, 128.55, 120.20, 90.10, 87.48, 81.03, 72.81, 71.37, 58.16 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{20}ClN_5O_4^+$ 418.1277, found 418.1280.

4.1.41. ((1*S*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-3-(2,6-dimethoxy-9*H*-purin-9-yl)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (37)

Compound **71** (150 mg, 0.171 mmol) was dissolved in MeOH (2.0 mL) and THF (2.0 mL) and solid NaOH (100 mg, 2.50 mmol) was added. The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine (2 × 4 mL), dried over $MgSO_4$, filtered, and concentrated to give the cyclic compound (10 mg, 0.153 mmol, 90%), which was taken to the next

step without further purification. The oil (10 mg, 0.153 mmol) was dissolved in dry THF (2.0 mL) along with HF·pyridine (0.20 mL, 2.00 mmol) at 0 °C. The reaction mixture was stirred at rt for 12 h. The reaction was quenched with satd aq $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine (2 × 4 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, 7:3 hexanes:acetone) was completed to afford compound **37** (49 mg, 77%). Compound **37**: colorless semi-solid; R_f = 0.41 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = +28.0 ($CHCl_3$, *c* 0.50); FT-IR (film) ν_{max} 3300, 2951, 1594, 1480, 1397, 1363, 1255, 1144, 1040, 791, 742, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ = 7.85 (d, *J* = 8.5 Hz, 1H), 7.35–7.27 (m, 5H), 6.01 (d, *J* = 3.2 Hz, 1H), 4.68–4.57 (m, 3H), 4.33 (s, 1H), 4.19–4.12 (m, 4H), 4.06–3.97 (m, 5H), 3.93 (dd, *J* = 7.8, 3.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 162.42, 162.19, 152.48, 138.35, 137.27, 128.89, 128.57, 128.19, 118.07, 88.48, 87.02, 77.90, 72.93, 72.70, 58.15, 55.65, 54.76 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{23}N_4O_6^+$ 415.1612, found 415.1629.

4.1.42. (1*S*,3*R*,4*R*,7*S*)-3-(2,6-Dimethoxy-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (38)

From compound **37**, using the same procedure as for compound **17**, compound **38** was obtained and purification by flash column chromatography (silica, DCM:MeOH 99:1) was completed to give nucleoside **38** (18 mg, 0.0555 mmol, 77%). Compound **38**: colorless oil; R_f = 0.18 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = +25.6 (MeCN, *c* 0.20); FT-IR (film) ν_{max} 3341, 2951, 1594, 1507, 1480, 1397, 1362, 1255, 1240, 1138, 1082, 1034, 1012, 959, 937, 905, 875, 829, 806, 791, 770, 742, 722, 677 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 7.96 (s, 1H), 5.90 (s, 1H), 4.48 (s, 1H), 4.40 (s, 1H), 4.08 (s, 3H), 4.01–3.95 (m, 4H), 3.84 (dt, *J* = 17.7, 6.1 Hz, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 162.32, 162.17, 153.15, 139.10, 89.39, 86.95, 80.46, 72.43, 71.60, 58.11, 55.56, 54.77 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{17}N_4O_6^+$ 325.1143, found 325.1151.

4.1.43. 1,1′-(9-((1*S*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-9*H*-purine-2,6-diyl)-diethanone (39)

Compound **71** (65 mg, 0.0742 mmol) was dissolved in dry, degassed DMF (2.0 mL) along with tributyl(1-ethoxyvinyl)tin (0.050 mL, 0.148 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mg, 0.00713 mmol). The reaction mixture was stirred at 95 °C for 18 h. It was then allowed to cool down and directly passed through a silica gel plug, affording a mixture of inseparable compounds that was taken to the next step without further purification. The oil was dissolved in THF (3.3 mL) along with 2 M NaOH (0.30 mL) and stirred at rt for 12 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc. The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated to afford a yellow foam, which was dissolved in dry THF (0.50 mL) along with HF·pyridine (0.10 mL, 0.860 mmol) at 0 °C. The reaction mixture was stirred at rt for 6 h. It was then quenched with satd aq $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine (2 × 3 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, hexanes:EtOAc:acetone 5:4:1) was completed to give compound **39** (10 mg, 0.0228 mmol, 31% over three steps). Compound **39**: colorless oil; R_f = 0.44 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = +24.0 (MeOH, *c* 0.10); FT-IR (film) ν_{max} 3408, 2925, 1708, 1580, 1363, 1210, 1138, 1054, 1033, 700 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.66 (s, 1H), 7.32–7.23 (m, 5H), 6.16 (s, 1H), 4.75 (s, 1H), 4.60 (s, 2H), 4.30 (s, 1H), 4.07–4.02 (m, 1H), 3.93 (m, 3H), 2.86 (s, 3H), 2.81 (s, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 199.20, 197.38, 177.55, 149.42, 148.99, 138.77, 129.23, 128.69, 128.62, 89.53, 87.59, 78.22, 78.09, 73.21, 72.78, 57.99, 28.45, 27.58 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{23}N_4O_6^+$ 439.1612, found 439.1612.

4.1.44. 2-Allyl-9-((1*R*,3*R*,4*R*,7*S*)-7-(benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-6-((*E*)-prop-1-enyl)-9*H*-purine (76)

Compound **71** (150 mg, 0.171 mmol) was dissolved in dry, degassed DMF (0.50 mL) along with allyl(tri-*n*-butyl)tin (0.16 mL, 0.513 mmol) and $Pd(PPh_3)_2Cl_2$ (12 mg, 0.0171 mmol). The reaction mixture was stirred at 95 °C for 6 h. It was allowed to cool down and directly passed through a silica gel plug, affording a mixture of inseparable compounds that were taken to the next step without further purification. The yellow oil residue was dissolved in THF (0.60 mL) along with 2 M NaOH (0.10 mL) and stirred at rt for 12 h. The reaction mixture was diluted with H_2O (1 mL) and extracted with EtOAc. The combined organic extracts were washed with brine (2 × 2 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, 4:1 hexanes:EtOAc) was completed to give compound **76** (48 mg, 0.0714 mmol, 42% over two steps). Compound **76**: light yellow oil; R_f = 0.90 (silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = +35.5 (MeOH, *c* 0.20); FT-IR (film) ν_{max} 2931, 1579, 1428, 1365, 1211, 1112, 1038, 911, 823, 741, 702 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.20 (s, 1H), 7.68 (dd, *J* = 6.7, 4.9 Hz, 4H), 7.66–7.60 (m, 1H), 7.47–7.42 (m, 2H), 7.37 (dt, *J* = 12.8, 7.4 Hz, 4H), 7.29–7.23 (m, 5H), 6.90 (dd, *J* = 15.7, 1.7 Hz, 1H), 6.22 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 6.04 (s, 1H), 5.16 (dd, *J* = 17.2, 1.9 Hz, 1H), 5.09 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.82 (s, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.44 (s, 1H), 4.08 (d, *J* = 12.1 Hz, 1H), 4.04 (d, *J* = 12.1 Hz, 1H), 4.00 (d, *J* = 7.9 Hz, 1H), 3.90 (d, *J* = 7.9 Hz, 1H), 3.71 (dt, *J* = 6.8, 1.5 Hz, 2H), 2.04 (dd, *J* = 6.9, 1.7 Hz, 3H), 1.01 (s, 9H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 163.74, 154.46, 152.40, 142.59, 140.85, 138.66, 136.71, 136.40, 136.35, 133.74, 133.69, 130.94, 130.00, 129.27, 128.82, 128.81, 128.72, 128.57, 127.63, 116.70, 89.02, 87.15, 78.46, 77.79, 73.22, 72.80, 60.35, 44.52, 27.08, 19.73, 19.18 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{40}H_{45}N_4O_4Si^+$ 673.3204, found 673.3211.

4.1.45. ((1*S*,3*R*,4*R*,7*S*)-3-(2-Allyl-6-((*E*)-prop-1-enyl)-9*H*-purin-9-yl)-7-(benzyloxy)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (40)

From compound **76**, using the same procedure as for compound **40**, compound **40** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 1:1) was completed to give nucleoside **40** (28 mg, 0.0645 mmol, 87%). Compound **40**: colorless oil; R_f = 0.31 (silica, 5% MeOH/chloroform); $[\alpha]_D^{25}$ = +22.0 (MeOH, *c* 0.70); FT-IR (film) ν_{max} 3347, 2941, 1653, 1578, 1492, 1454, 1368, 1288, 1213, 1142, 1096, 1054, 1033, 976, 909, 882, 860, 811, 738, 698 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.19 (s, 1H), 7.68–7.58 (m, 1H), 7.32–7.22 (m, 5H), 6.92–6.85 (m, 1H), 6.21 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 6.02 (s, 1H), 5.16 (ddd, *J* = 17.2, 3.4, 1.6 Hz, 1H), 5.10 (ddd, *J* = 10.1, 1.9, 1.4 Hz, 1H), 4.71 (s, 1H), 4.64–4.56 (m, 2H), 4.34 (s, 1H), 4.02 (d, *J* = 7.8 Hz, 1H), 3.93–3.87 (m, 3H), 3.70 (dd, *J* = 6.8, 1.5 Hz, 2H), 3.46 (s, 1H), 2.04 (dd, *J* = 6.9, 1.7 Hz, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 163.64, 154.47, 152.52, 142.83, 140.88, 138.81, 136.70, 130.09, 129.24, 128.68, 128.59, 127.62, 116.76, 89.17, 87.41, 78.31, 78.29, 73.13, 72.73, 58.13, 44.47, 19.17 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{27}N_4O_4^+$ 435.2027, found 435.2015.

4.1.46. (1*S*,3*R*,4*R*,7*S*)-3-(2,6-Dipropyl-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (41)

Protected compound **40** (10 mg, 0.0230 mmol) was dissolved in wet ethanol (1.2 mL) along with $Pd(OH)_2$ (1 mg, 0.00712 mmol). The mixture was degassed and put under hydrogen atmosphere. The reaction mixture was heated to 50 °C for 12 h. The mixture

was filtered and the solvent was concentrated under reduced pressure. Purification by flash column chromatography (silica, DCM:MeOH 95:5) was completed to give compound **41** (4 mg, 0.0115 mmol, 50%). Compound **41**: colorless oil; R_f = 0.19 (silica, hexanes:acetone 7:3); $[\alpha]_D^{25}$ = +13.0 (MeCN, *c* 0.10); FT-IR (film) ν_{max} 3300, 2927, 1592, 1490, 1368, 1050, 810, 738, 698 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.20 (s, 1H), 5.99 (s, 1H), 4.47 (s, 1H), 4.43 (s, 1H), 4.00 (d, *J* = 7.9 Hz, 1H), 3.88 (d, *J* = 4.6 Hz, 2H), 3.84 (d, *J* = 8.0 Hz, 1H), 3.06–3.03 (m, 2H), 2.92–2.88 (m, 2H), 1.88–1.82 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 6H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 165.96, 162.85, 151.35, 142.25, 131.84, 89.23, 86.70, 80.49, 72.49, 71.74, 58.27, 41.80, 35.63, 22.95, 22.44, 14.28, 13.95 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{25}N_4O_4^+$ 349.187, found 349.1884.

4.1.47. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-2,6-di(furan-2-yl)-9*H*-purine (77)

Compound **71** (83 mg, 0.0948 mmol) was dissolved in dry, degassed DMF (2.0 mL) along with 2-(tributylstannyl)furan (0.060 mL, 0.189 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mg, 0.00712 mmol). The reaction mixture was stirred at 95 °C for 13 h. It was then allowed to cool to rt and directly passed through a silica gel plug, affording the compound as a yellow oil (88 mg, 0.0937 mmol, 99%), which was taken to the next step without further purification. The yellow oil (85 mg, 0.0905 mmol) was dissolved in THF (5.0 mL) along with 2 M NaOH (0.40 mL) and stirred at rt for 12 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc. The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, hexanes:EtOAc 4:1) was completed to give compound **77** (50 mg, 0.0690 mmol, 76%). Compound **77**: yellow foam; R_f = 0.94 (silica, hexanes:EtOAc 7:3); $[\alpha]_D^{25}$ = +52.0 (MeOH, *c* 1.00); FT-IR (film) ν_{max} 3602, 2937, 1584, 1053, 1033, 1012, 702 cm^{-1}; ^1H NMR (CD_3CN, 500 MHz) δ = 8.31 (s, 1H), 7.92–7.86 (m, 2H), 7.72 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.71–7.66 (m, 4H), 7.46–7.42 (m, 2H), 7.41–7.34 (m, 6H), 7.27–7.23 (m, 4H), 6.75 (dt, *J* = 2.9, 1.4 Hz, 1H), 6.65 (dt, *J* = 2.9, 1.4 Hz, 1H), 6.13 (s, 1H), 4.91 (s, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.48 (s, 1H), 4.09 (q, *J* = 12.1 Hz, 2H), 4.03 (d, *J* = 7.9 Hz, 1H), 3.94 (d, *J* = 7.9 Hz, 1H), 1.03 (s, 9H) ppm; ^{13}C NMR (CD_3CN, 126 MHz) δ = 153.68, 152.84, 152.61, 150.49, 147.13, 146.62, 145.89, 143.67, 138.74, 136.45, 136.40, 133.83, 133.76, 130.97, 129.30, 128.86, 128.74, 128.61, 128.46, 118.75, 113.72, 113.69, 113.19, 89.23, 87.34, 78.51, 77.90, 73.30, 72.88, 60.45, 27.14, 19.79 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{42}H_{41}N_4O_6Si^+$ 725.2790, found 725.2798.

4.1.48. ((1*S*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-3-(2,6-di(furan-2-yl)-9*H*-purin-9-yl)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (42)

From compound **77**, using the same procedure as for compound **15**, compound **42** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 7:3) was completed to give nucleoside **42** (27 mg, 0.0552 mmol, 100%). Compound **42**: light yellow foam; R_f = 0.38 (silica, hexanes:EtOAc 7:3); $[\alpha]_D^{25}$ = +64.0 (MeOH, *c* 0.50); FT-IR (film) ν_{max} 3375, 2943, 1584, 1487, 1367, 1208, 1144, 1102, 1050, 1012, 938, 895, 885, 827, 801, 747, 698 cm^{-1}; ^1H NMR (1% D_2O/CD_3CN, 400 MHz) δ = 8.34 (s, 1H), 7.90 (dd, *J* = 3.5, 0.8 Hz, 1H), 7.87 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.73 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.35 (dd, *J* = 3.4, 0.9 Hz, 1H), 7.29–7.22 (m, 5H), 6.75 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.65 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.10 (s, 1H), 4.80 (s, 1H), 4.62 (s, 2H), 4.34 (s, 1H), 4.06–4.04 (m, 1H), 3.93–3.91 (m, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 153.54, 152.67, 152.48, 150.32, 147.00, 146.44, 145.78, 143.71, 138.74, 129.17, 128.60, 128.52, 118.68, 113.59, 113.09, 89.21, 87.23, 78.26, 78.08, 73.13, 72.70, 58.05 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{26}H_{23}N_4O_6^+$ 487.1612, found 487.1623.

4.1.49. (1*S*,3*R*,4*R*,7*S*)-3-(2,6-Di(furan-2-yl)-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (43)

From compound **42**, using the same procedure as for compound **12**, compound **43** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 7:3) was completed to afford nucleoside **43** (11 mg, 0.0278 mmol, 90%). Compound **43**: off-white foam; R_f = 0.15 (silica, hexanes:EtOAc 7:3); $[\alpha]_D^{25}$ = +26.0 (MeOH, *c* 0.25); FT-IR (film) ν_{max} 3340, 2949, 2838, 1647, 1407, 1113, 1014, 550, 530 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ = 8.57 (s, 1H), 7.91 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.83 (dd, *J* = 3.5, 0.7 Hz, 1H), 7.75 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.40 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.76 (dd, *J* = 3.5, 1.7 Hz, 1H), 6.65 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.18 (s, 1H), 4.70 (s, 1H), 4.45 (s, 1H), 4.10 (d, *J* = 7.9 Hz, 1H), 3.99 (s, 2H), 3.94 (d, *J* = 7.9 Hz, 1H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 153.68, 153.57, 151.15, 147.59, 147.23, 146.10, 144.57, 118.24, 114.21, 113.68, 113.26, 90.27, 87.64, 81.06, 72.91, 71.58, 58.18 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{17}N_4O_6^+$ 397.1143, found 397.1148.

4.1.50. 9-((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-2,6-di(thiophen-2-yl)-9*H*-purine (78)

Compound **71** (40 mg, 0.0457 mmol) was dissolved in dry, degassed DMF (1.0 mL) along with 2-(tributylstannyl)thiophene (0.029 mL, 0.091 mmol) and $Pd(PPh_3)_2Cl_2$ (4 mg, 0.00570 mmol). The reaction mixture was stirred at 80 °C for 7 h. It was then allowed to cool to rt and directly passed through a silica gel plug, affording the compound as yellow oil (32 mg, 0.0330 mmol, 72%), which was advanced to the next chemical transformation without further purification. The yellow oil (28 mg, 0.0289 mmol) was dissolved in THF (2.4 mL) along with 2 M NaOH (0.20 mL) and stirred at rt for 13.5 h. The reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc. The combined organic extracts were washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, hexanes:EtOAc 7:3) was completed to give compound **78** (21.3 mg, 0.0282 mmol, 98%). Compound **78**: white foam; R_f = 0.97 (silica, hexanes:EtOAc 7:3); $[\alpha]_D^{25}$ = +38.0 (MeOH, *c* 1.00); FT-IR (film) ν_{max} 3477, 2979, 1709, 1422, 1360, 1221, 1066, 903 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.70–8.68 (m, 1H), 8.34 (s, 1H), 8.08–8.06 (m, 1H), 7.80–7.78 (m, 1H), 7.74–7.70 (m, 4H), 7.61–7.59 (m, 1H), 7.49–7.44 (m, 3H), 7.41 (ddd, *J* = 21.6, 11.2, 3.8 Hz, 5H), 7.35–7.33 (m, 1H), 7.27–7.25 (m, 3H), 7.23–7.20 (m, 1H), 6.16 (s, 1H), 4.97 (s, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.46 (s, 1H), 4.15 (d, *J* = 12.0 Hz, 1H), 4.11 (d, *J* = 12.1 Hz, 1H), 4.06 (d, *J* = 7.8 Hz, 1H), 3.97 (d, *J* = 7.8 Hz, 1H), 1.06 (s, 9H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 177.49, 156.17, 152.74, 150.31, 144.42, 143.53, 140.94, 138.61, 136.42, 136.36, 133.79, 133.68, 132.33, 130.95, 130.58, 129.91, 129.43, 129.28, 129.25, 128.85, 128.83, 128.70, 128.58, 89.20, 87.40, 78.38, 77.87, 73.27, 72.85, 60.46, 27.12, 19.76 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{42}H_{41}N_4O_4S_2Si$ 757.2333, found 757.2332.

4.1.51. ((1*S*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-3-(2,6-di(thiophen-2-yl)-9*H*-purin-9-yl)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methanol (44)

From compound **78**, using the same procedure as for compound **15**, compound **44** was obtained and purification by flash column chromatography (silica, hexanes:EtOAc 7:3) was completed to give nucleoside **44** (27 mg, 0.0521 mmol, 99%). Compound **44**: white foam; R_f = 0.43 (silica, hexanes:EtOAc 7:3); $[\alpha]_D^{25}$ = +64.0 (MeOH, *c* 0.50); FT-IR (film) ν_{max} 3338, 2951, 1642, 1572, 1428, 1391,

1327, 1206, 1032, 1015, 820, 591, 541, 528 cm^{-1}; ^1H NMR (CD_3CN, 400 MHz) δ = 8.68 (dd, J = 3.8, 1.2 Hz, 1H), 8.34 (s, 1H), 8.05 (dd, J = 3.7, 1.3 Hz, 1H), 7.76 (dd, J = 5.0, 1.2 Hz, 1H), 7.58 (dd, J = 5.0, 1.3 Hz, 1H), 7.31 (dt, J = 6.1, 3.0 Hz, 1H), 7.29–7.25 (m, 4H), 7.25–7.21 (m, 1H), 7.20 (dd, J = 5.0, 3.7 Hz, 1H), 6.10 (s, 1H), 4.85 (s, 1H), 4.61 (m, 2H), 4.34 (s, 1H), 4.05 (d, J = 8.0 Hz, 1H), 3.98–3.90 (m, 3H), 3.27 (t, J = 6.0 Hz, 1H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 156.12, 152.74, 150.25, 144.42, 143.67, 140.93, 138.76, 133.64, 132.29, 130.55, 129.89, 129.40, 129.28, 129.22, 128.67, 128.59, 128.58, 89.28, 87.35, 78.32, 78.12, 73.19, 72.79, 58.15 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{26}H_{22}N_4O_4S_2$ 519.1155, found 519.1151.

4.1.52. (1*S*,3*R*,4*R*,7*S*)-3-(2,6-Di(thiophen-2-yl)-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (45) and (1*S*,3*S*,4*R*,7*S*)-3-(2,6-di(thiophen-2-yl)-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,5-dioxabicyclo[2.2.1]heptan-7-ol (46)

From compound **44**, using the same procedure as for compound **17**, compounds **45** and **46** were obtained. Purification by flash column chromatography (silica, hexanes:EtOAc 7:3) was completed to give compounds **45** (4.0 mg, 0.00934 mmol, 40%) and **46** (3.3 mg, 0.00770 mol, 33%). Compound **45**: white foam; R_f = 0.14 (silica, hexanes:EtOAc 7:3); $[\alpha]_D^{25}$ = +51.2 (MeOH, *c* 0.20); FT-IR (film) ν_{max} 3361, 1572, 1535, 1443, 1426, 1376, 1222, 1038, 907, 823, 799, 711 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ = 8.61 (d, J = 3.7 Hz, 1H), 8.50 (s, 1H), 8.04 (d, J = 3.5 Hz, 1H), 7.75 (d, J = 5.0 Hz, 1H), 7.56 (d, J = 4.9 Hz, 1H), 7.32–7.25 (m, 1H), 7.18–7.13 (m, 1H), 6.13 (s, 1H), 4.73 (s, 2H), 4.48 (s, 1H), 4.12 (d, J = 7.8 Hz, 1H), 3.99 (s, 2H), 3.96 (d, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 156.93, 152.85, 150.98, 144.73, 144.09, 141.36, 133.66, 132.29, 130.54, 129.61, 129.03, 128.54, 90.19, 87.63, 81.10, 72.97, 71.76, 58.30 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{19}H_{17}N_4S_2O_4$ 429.0686, found 429.0691. Compound **46**: colorless oil; R_f = 0.54 (silica, hexanes:EtOAc 7:3); $[\alpha]_D^{25}$ = −26.4 (MeOH, *c* 0.40); FT-IR (film) ν_{max} 3330, 2982, 1574, 1444, 1426, 1378, 1212, 1057, 1033, 800, 723 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ = 8.68 (s, 1H), 8.64 (dd, J = 3.7, 1.2 Hz, 1H), 8.08 (dd, J = 3.7, 1.2 Hz, 1H), 7.79 (dd, J = 5.0, 1.1 Hz, 1H), 7.60 (dd, J = 5.0, 1.2 Hz, 1H), 7.30 (dd, J = 5.0, 3.8 Hz, 1H), 7.19 (ddd, J = 5.3, 3.7, 1.6 Hz, 1H), 6.82 (d, J = 7.4 Hz, 1H), 4.76 (dd, J = 7.4, 3.5 Hz, 1H), 4.29 (d, J = 9.6 Hz, 1H), 4.12 (d, J = 9.5 Hz, 1H), 4.04 (d, J = 9.5 Hz, 1H), 3.90–3.86 (m, 2H) ppm; ^{13}C NMR (CD_3OD, 151 MHz) δ = 157.51, 153.16, 151.41, 144.91, 144.41, 141.01, 133.95, 132.67, 130.94, 129.96, 129.77, 129.13, 111.74, 89.41, 88.39, 77.81, 76.31, 67.80, 66.35 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{19}H_{17}N_4O_4S_2$ 429.0686, found 429.0688.

4.1.53. ((1*R*,3*R*,4*R*,7*S*)-7-(Benzyloxy)-3-(2,6-di(thiophen-2-yl)-9*H*-purin-9-yl)-2,5-dioxabicyclo[2.2.1]heptan-1-yl)methyl sulfamate (47)

Formic acid (0.055 mL, 1.45 mmol) was added to chlorosulfonyl isocyanate (0.13 mL, 1.45 mmol) at 0 °C with stirring. The resulting white solid was dissolved in CH_2Cl_2 (1.4 mL) and the solution warmed to rt and stirred for 14 h. The solution was cooled to 0 °C and a portion of this reagent (0.04 mL) was added dropwise to a solution of compound **44** (5 mg, 0.00964 mmol) in CH_2Cl_2 (0.08 mL) at 0 °C. Pyridine (0.005 mL, 0.0556) was added dropwise and the reaction mixture was warmed to rt and stirred 24 h. The solvent was evaporated and purification by preparative-plate chromatography (silica, hexanes:EtOAc 1:1) was completed to give compound **47** (2 mg, 0.00337 mmol, 35%). Compound **47**: white semi-solid; R_f = 0.37 (silica, hexanes:EtOAc 1:1); $[\alpha]_D^{25}$ = +33.6 (acetone, *c* 0.15); FT-IR (film) ν_{max} 2925, 1572, 1535, 1487, 1443, 1426, 1376, 1245, 1183, 1148, 1094, 1039, 994, 911, 855, 818, 800, 782, 724 cm^{-1}; ^1H NMR (acetone-d_6, 600 MHz) δ = 8.73 (dt, J = 3.7, 1.1 Hz, 1H), 8.49 (d, J = 1.1 Hz, 1H), 8.07 (dt, J = 3.6, 1.2 Hz, 1H), 7.86 (dt, J = 5.0, 1.2 Hz, 1H), 7.66 (dt, J = 5.0, 1.2 Hz, 1H), 7.36–7.30 (m, 3H), 7.25 (ddd, J = 7.1, 4.3, 1.1 Hz, 2H), 7.21 (ddd, J = 6.1, 3.9, 1.2 Hz, 2H), 7.01 (s, 2H), 6.25 (s, 1H), 5.09 (s, 1H), 4.73 (ddd, J = 28.3, 14.7, 6.4 Hz, 3H), 4.65 (d, J = 11.3 Hz, 2H), 4.22 (d, J = 7.8 Hz, 1H), 4.05 (d, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (acetone-d_6, 151 MHz) δ = 156.11, 152.60, 150.22, 144.37, 143.70, 140.96, 138.60, 133.70, 132.25, 130.47, 129.67, 129.33, 129.09, 129.02, 128.58, 128.54, 128.46, 87.55, 86.32, 78.78, 78.03, 73.06, 72.74, 65.93 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{26}H_{24}N_5O_6S_3^+$ 598.0883, found 598.0885.

4.1.54. (2*R*,3*R*,4*S*)-4-(Benzyloxy)-2-(2,6-dichloro-9*H*-purin-9-yl)-5,5-bis((methylsulfonyloxy)methyl)tetrahydrofuran-3-yl acetate (80)

Literature-known compound **79** (290 mg, 0.569 mmol) was dissolved in dry MeCN (1.5 mL) along with 2,6-dichloropurine (214 mg, 1.13 mmol) and BSA (0.51 mL, 1.99 mmol). After 5 min, the reaction mixture was cooled to −40 °C followed by slow addition of TMSOTf (0.21 mL, 0.850 mmol), and then heated to 80 °C in the microwave (CEM Discover, 300 W). The reaction mixture was brought to rt, quenched with satd aq $NaHCO_3$ (2 mL), and extracted with EtOAc. The combined organic extracts were washed with brine (3 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, hexanes:EtOAc 4:1) was completed to give compound **80** (30 mg, 0.478 mmol, 84%). Compound **80**: yellow foam; R_f = 0.56 (silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = +13.0 ($CHCl_3$, *c* 0.10); FT-IR (film) ν_{max} 3019, 1749, 1595, 1560, 1496, 1357, 1226, 1175, 1030, 963, 883, 826, 755, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 8.18 (s, 1H), 7.43–7.32 (m, 5H), 6.17 (d, J = 3.6 Hz, 1H), 5.87 (dd, J = 5.9, 3.7 Hz, 1H), 4.97 (d, J = 6.0 Hz, 1H), 4.71–4.59 (m, 3H), 4.42 (d, J = 10.9 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 10.9 Hz, 1H), 3.04 (s, 3H), 2.93 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 207.26, 169.83, 153.77, 152.49, 151.89, 145.32, 136.39, 128.94, 128.82, 88.40, 84.96, 77.26, 75.08, 73.66, 67.48, 67.38, 38.00, 37.71, 31.10 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{22}H_{25}Cl_2N_4O_{10}S_2^+$ 639.0389, found 639.0388.

4.1.55. ((3*S*,4*R*,5*R*)-5-(2,6-Dichloro-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2,2-diyl)bis(methylene) dimethanesulfonate (81)

From compound **80**, using the same procedure as for compound **17**, compound **81** was obtained and purification by flash column chromatography (silica, hexanes:acetone 7:3) was completed to give nucleoside **81** (270 mg, 0.534 mmol, 90%). Compound **81**: colorless semi-solid; R_f = 0.40 (silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = +2.5 (MeCN, *c* 0.10); FT-IR (film) ν_{max} 3368, 1726, 1660, 1596, 1561, 1355, 1252, 1174, 1031, 999, 965, 884, 830 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.47 (d, J = 2.2 Hz, 1H), 6.08 (dd, J = 6.3, 2.1 Hz, 1H), 4.97–4.93 (m, 1H), 4.57–4.54 (m, 2H), 4.45 (ddd, J = 15.6, 13.0, 6.5 Hz, 3H), 4.21–4.09 (m, 2H), 3.09 (t, J = 2.6 Hz, 6H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 153.97, 152.71, 151.45, 146.37, 132.10, 99.58, 89.05, 85.08, 73.50, 72.25, 69.17, 37.53, 29.24 ppm; HRMS (ESI-TOF) (m/z): $[M+H]^+$ calcd for $C_{13}H_{17}Cl_2N_4O_9S_2^+$ 506.9814, found 506.9810.

4.1.56. ((1*R*,3*R*,4*R*,5*S*)-3-(2,6-Dichloro-9*H*-purin-9-yl)-4-hydroxy-2,6-dioxabicyclo[3.2.0]heptan-1-yl)methyl methanesulfonate (48)

Compound **81** (200 mg, 0.364 mmol) was dissolved in wet THF (15 mL) along with K_2CO_3 (200 mg, 1.45 mmol). The reaction mixture was stirred at rt for 18 h. The reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, hexanes:acetone 1:1) was completed to

afford compound **48** (118 mg, 0.288 mmol, 79%). Compound **48**: colorless semi-solid; R_f = 0.48 (silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = −42.0 (MeCN, *c* 0.30); FT-IR (film) ν_{max} 3615, 2293, 2253, 1443, 1375, 1039, 918, 750 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.51 (s, 1H), 6.43 (d, *J* = 7.3 Hz, 1H), 5.21 (dd, *J* = 16.9, 4.6 Hz, 1H), 4.94–4.86 (m, 1H), 4.67 (ddd, *J* = 21.2, 12.0, 6.5 Hz, 2H), 4.54 (tt, *J* = 7.2, 3.5 Hz, 2H), 3.75 (dd, *J* = 7.7, 1.4 Hz, 1H), 3.07 (s, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 154.49, 153.31, 151.76, 146.28, 132.77, 89.19, 85.10, 84.51, 78.45, 75.12, 69.06, 37.78 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{13}Cl_2N_4O_6S^+$ 410.9933, found 410.9937.

4.1.57. ((1*R*,3*R*,4*R*,5*S*)-3-(6-(Benzoyloxy)-2-chloro-9*H*-purin-9-yl)-4-hydroxy-2,6-dioxabicyclo[3.2.0]heptan-1-yl)methyl benzoate (49)

Compound **48** (100 mg, 0.244 mmol) was dissolved in dry DMF (0.50 mL) along with sodium benzoate (70 mg, 0.486 mmol). The reaction mixture was heated to 90 °C for 4.5 h. Direct purification of the mixture by flash column chromatography (silica, 7:3 hexanes:EtOAc) was completed to give compound **49** (105 mg, 0.201 mmol, 82%). Compound **49**: white foam; R_f = 0.45 (silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = −65.7 (MeCN, *c* 0.30); FT-IR (film) ν_{max} 3618, 2293, 2253, 1443, 1375, 1038, 918, 749 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.08–7.99 (m, 5H), 7.68–7.62 (m, 2H), 7.52 (dt, *J* = 19.1, 7.7 Hz, 4H), 6.74 (d, *J* = 6.8 Hz, 1H), 5.68 (dt, *J* = 9.9, 4.6 Hz, 2H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.78 (d, *J* = 8.3 Hz, 1H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.69 (d, *J* = 12.2 Hz, 1H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 166.75, 166.03, 157.89, 149.13, 145.52, 139.43, 134.70, 134.42, 130.53, 130.51, 130.39, 129.75, 129.69, 129.64, 124.93, 87.16, 85.69, 84.48, 79.14, 77.35, 64.33 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{20}ClN_4O_7^+$ 523.1015, found 523.1015.

4.1.58. (2*R*,3*R*,4*S*)-4-(Benzyloxy)-2-(2,6-di(furan-2-yl)-9*H*-purin-9-yl)-5,5-bis((methylsulfonyloxy)methyl)tetrahydrofuran-3-yl acetate (82)

Compound **80** (50 mg, 0.0781 mmol) was dissolved in dry, degassed DMF (0.20 mL) along with 2-(tributylstannyl)furan (0.098 mL, 0.310 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mg, 0.0071 mmol). The reaction mixture was stirred at 95 °C for 3 h, quenched with a solution of potassium fluoride (4 mL), and extracted with EtOAc. The combined organic extracts were washed with brine (2 × 2 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, EtOAc:hexanes 4:1) was completed to give compound **82** (46 mg, 0.0655 mol, 84%). Compound **82**: yellow foam; R_f = 0.58 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = −6.5 (MeOH, *c* 0.20); FT-IR (film) ν_{max} 1748, 1585, 1488, 1357, 1226, 1176, 966, 825, 753 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.31 (s, 1H), 7.92 (d, *J* = 3.5 Hz, 1H), 7.88 (d, *J* = 1.7 Hz, 1H), 7.74 (d, *J* = 0.8 Hz, 1H), 7.45–7.32 (m, 6H), 6.76 (dd, *J* = 3.5, 1.7 Hz, 1H), 6.65 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.34 (d, *J* = 3.4 Hz, 1H), 6.16 (dd, *J* = 5.9, 3.4 Hz, 1H), 5.28 (d, *J* = 5.9 Hz, 1H), 4.75 (s, 2H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 10.6 Hz, 1H), 4.49 (d, *J* = 10.7 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 3.07 (s, 3H), 2.91 (s, 3H), 2.08 (s, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 170.51, 153.48, 152.78, 152.67, 150.19, 147.25, 146.83, 146.06, 145.76, 137.85, 129.28, 129.16, 129.09, 118.98, 113.74, 113.22, 88.77, 85.17, 79.59, 75.66, 74.33, 69.20, 69.14, 37.77, 37.34, 20.71 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{30}H_{31}N_4O_{12}S_2^+$ 703.1374, found 703.1374.

4.1.59. ((3*S*,4*R*,5*R*)-5-(2,6-Di(furan-2-yl)-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2,2-diyl)bis(methylene) dimethanesulfonate (83)

From compound **82**, using the same procedure as for compound **17**, compound **83** was obtained and purification by flash column chromatography (silica, DCM:MeOH 95:5) was completed to give nucleoside **83** (20 mg, 0.0351 mmol, 82%). Compound **83**: white foam; R_f = 0.36 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = −17.0 (MeOH, *c* 0.10); FT-IR (film) ν_{max} 3300, 2922, 1586, 1489, 1354, 1174, 1054, 1033, 1001, 832, 754 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.37 (s, 1H), 7.94 (dd, *J* = 11.6, 3.5 Hz, 1H), 7.88 (m, 1H), 7.75 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.58 (s, 1H), 7.38 (s, 1H), 6.76 (ddd, *J* = 3.5, 1.7, 0.7 Hz, 1H), 6.66 (ddd, *J* = 3.4, 1.7, 0.7 Hz, 1H), 6.15 (d, *J* = 6.4 Hz, 1H), 5.21 (d, *J* = 11.6 Hz, 1H), 4.68 (s, 1H), 4.60 (dd, *J* = 24.0, 10.8 Hz, 2H), 4.50 (t, *J* = 11.1 Hz, 2H), 4.12 (d, *J* = 12.5 Hz, 1H), 3.10 (s, 3H), 3.03 (s, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 153.56, 153.28, 152.86, 150.39, 147.21, 146.95, 146.11, 145.69, 128.69, 118.98, 113.80, 113.76, 113.22, 90.16, 89.38, 85.09, 73.69, 72.78, 69.34, 69.23, 37.69, 37.64 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{23}N_4O_{11}S_2^+$ 571.0805, found 571.0801.

4.1.60. ((1*R*,3*R*,4*R*,5*S*)-3-(2,6-Di(furan-2-yl)-9*H*-purin-9-yl)-4-hydroxy-2,6-dioxabicyclo[3.2.0]heptan-1-yl)methyl methanesulfonate (50)

From compound **83**, using the same procedure as for compound **64**, compound **50** was obtained and purification by flash column chromatography (silica, EtOAc:hexanes 8:1) was completed to give nucleoside **50** (7 mg, 0.0148 mmol, 91%). Compound **50**: slightly yellow foam; R_f = 0.31 (silica, 10% MeOH/DCM); $[\alpha]_D^{25}$ = −18.0 (MeOH, *c* 0.10); FT-IR (film) ν_{max} 3300, 2922, 1586, 1354, 1175, 1054, 1033, 1001, 832 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 8.45 (s, 1H), 7.94 (d, *J* = 3.5 Hz, 1H), 7.89 (s, 1H), 7.75 (s, 1H), 7.40 (d, *J* = 3.3 Hz, 1H), 6.77 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.66 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.53 (d, *J* = 7.2 Hz, 1H), 5.30 (d, *J* = 4.6 Hz, 1H), 4.94 (d, *J* = 8.4 Hz, 1H), 4.84 (td, *J* = 7.1, 4.6 Hz, 1H), 4.67 (d, *J* = 8.4 Hz, 1H), 4.59 (q, *J* = 11.5 Hz, 1H), 3.92 (d, *J* = 7.1 Hz, 1H), 3.62–3.54 (m, 1H), 3.10–2.94 (m, 3H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 153.72, 153.59, 153.05, 150.42, 147.21, 146.94, 146.06, 145.10, 126.37, 118.98, 113.84, 113.76, 113.24, 88.96, 85.60, 84.54, 78.60, 75.33, 69.40, 37.73 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{19}N_4O_8S^+$ 475.0918, found 475.0927.

4.1.61. (1*S*,3*R*,4*R*,5*S*)-3-(2,6-Di(furan-2-yl)-9*H*-purin-9-yl)-1-(hydroxymethyl)-2,6-dioxabicyclo[3.2.0]heptan-4-ol (51)

Compound **50** (15 mg, 0.0316 mmol) was dissolved in dry DMF (0.20 mL) along with sodium benzoate (9.1 mg, 0.0630 mmol). The reaction mixture was heated to 90 °C for 4.5 h. The resulting white mixture was passed through a silica plug to give a white solid compound (15.3 mg, 0.0306 mmol, 97%). The benzoyl derivative (5 mg, 0.00999 mmol) was dissolved in MeOH (0.40 mL), and 0.1 M NaOMe (0.20 mL) was added. The mixture was stirred at rt for 30 min and quenched with a solution of 0.1 M HCl (1 mL). The reaction mixture was extracted with 10% MeOH:DCM, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica, DCM:MeOH 9:1) was completed to give compound **51** (2.8 mg, 0.00707 mmol, 71%). Compound **51**: white semi-solid; R_f = 0.15 (silica, hexanes:acetone:MeOH 5:4:1); $[\alpha]_D^{25}$ = −28.0 (MeOH, *c* 0.10); FT-IR (film) ν_{max} 3300, 2926, 1680, 1354, 1175, 1054, 1033, 1001, 830 cm^{-1}; ^1H NMR (CD_3CN, 400 MHz) δ = 8.45 (s, 1H), 7.97 (dd, *J* = 3.5, 0.8 Hz, 1H), 7.91 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.76 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.42 (dd, *J* = 3.4, 0.9 Hz, 1H), 6.79 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.68 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.47 (d, *J* = 7.3 Hz, 1H), 5.25 (d, *J* = 4.5 Hz, 1H), 4.89 (d, *J* = 8.1 Hz, 1H), 4.80 (dd, *J* = 7.3, 4.5 Hz, 1H), 4.60 (d, *J* = 7.6 Hz, 1H), 3.90 (d, *J* = 12.3 Hz, 1H), 3.81 (d, *J* = 12.3 Hz, 1H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) δ = 153.44, 153.41, 152.90, 150.37, 147.26, 147.00, 145.98, 145.68, 129.43, 119.10, 113.82, 113.78, 113.26, 90.33, 88.09, 86.33, 78.78, 75.55, 62.57 ppm; HRMS

(ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{17}N_4O_6^+$ 397.1143, found 397.1145.

4.1.62. (3a*R*,5*S*,6*R*,6a*R*)-Methyl 2,2-dimethyl-6-(tosyloxy)tetrahydrofuro[2,3-d][1,3]dioxole-5-carboxylate (85)

Literature-known compound **84** (770 mg, 2.15 mmol) was dissolved in dry Et_2O (10 mL) and MeOH (10 mL) at 0 °C, and trimethylsilyldiazomethane (1.29 mL, 2.58 mmol, 2.0 M in hexanes) was slowly added. The reaction solution was stirred at this temperature for 30 min, then the solvent was evaporated. Purification by flash column chromatography (silica, hexanes:EtOAc 3:1) was completed to give compound **85** (700 mg, 1.88 mmol, 88%). Compound **85**: white foam; R_f = 0.67 (silica, hexanes:EtOAc 1:1); $[\alpha]_D^{25}$ = −28.8 ($CHCl_3$, *c* 0.82); FT-IR (film) ν_{max} 2988, 1769, 1741, 1597, 1495, 1440, 1372, 1294, 1215, 1190, 1176, 1163, 1094, 1063, 1034, 964, 901, 866, 846, 816, 772, 740, 704, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.07 (d, *J* = 3.5 Hz, 1H), 5.13 (d, *J* = 3.3 Hz, 1H), 4.83 (d, *J* = 3.4 Hz, 1H), 4.77 (d, *J* = 3.5 Hz, 1H), 3.58 (s, 3H), 2.46 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 166.73, 145.95, 133.22, 130.35, 128.42, 113.57, 105.78, 83.11, 82.45, 78.46, 52.81, 27.16, 26.72, 22.13 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{21}O_8S^+$ 373.0952, found 373.0957.

4.1.63. (1*R*,3*S*,4*S*,5*S*,6*S*,7*S*)-Methyl 6,7-dichloro-3,4-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-2-oxabicyclo[3.2.0]heptane-1-carboxylate (86)

Compound **85** (254 mg, 0.682 mmol) was dissolved in benzene (6.8 mL), and DBU (0.12 mL, 0.818 mmol) was added. The reaction solution was stirred at rt for 5 h. The mixture was worked up by evaporation to half volume, then elution through a silica gel plug with EtOAc. This residue was dissolved in MeCN (8 mL) under argon in a Quartz test tube tightly capped with a septum. 1,2-*Cis*-dichloroethylene (0.51 mL, 6.82 mmol) was added and the reaction degassed with argon for 20 min. The reaction solution was exposed to UV light (Hanovia 400 W high-pressure Hg lamp) for 36 h. Additional 1,2-*cis*-dichloroethylene (0.3 mL, 4.0 mmol) was added and the solution degassed for 20 min. The reaction solution was exposed to UV light for an additional 48 h, then worked up by evaporation. Purification by flash column chromatography (hexanes:EtOAc 5:1) was completed to give compound **86** (36 mg, 0.123 mmol, 18% over two steps) along with a mix of two other diastereomers (27 mg, 0.0887 mmol, 13% over two steps). Compound **86**: yellow oil; R_f = 0.50 (silica, hexanes:EtOAc 4:1); $[\alpha]_D^{25}$ = +3.0 ($CHCl_3$, *c* 2.70); FT-IR (film) ν_{max} 2992, 1738, 1439, 1375, 1337, 1211, 1161, 1124, 1053, 990, 934, 899, 783, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 6.08 (d, *J* = 3.8 Hz, 1H), 5.08 (d, *J* = 3.8 Hz, 1H), 4.50 (dd, *J* = 9.5, 6.4 Hz, 1H), 4.17 (d, *J* = 6.6 Hz, 1H), 3.87 (d, *J* = 0.7 Hz, 3H), 3.79 (d, *J* = 9.7 Hz, 1H), 1.41 (d, *J* = 15.5 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 167.03, 114.98, 109.11, 88.90, 81.99, 65.55, 54.11, 53.04, 50.48, 27.93, 27.34 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+Na]^+$ calcd for $C_{11}H_{14}Cl_2O_5Na^+$ 319.0110, found 319.0103.

4.1.64. (1*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-Methyl 4-acetoxy-6,7-dichloro-3-(2,6-diamino-9*H*-purin-9-yl)-2-oxabicyclo[3.2.0]heptane-1-carboxylate (52)

Compound **86** (20 mg, 0.0675 mmol) was dissolved in acetic acid (0.72 mL) and acetic anhydride (0.08 mL, 0.810 mmol). Two drops of sulfuric acid were added and the reaction solution stirred at rt for 16 h. The reaction solution was poured into ice water (4 mL) and stirred for 30 min. Satd aq NH_4Cl (4 mL) was added and the aqueous phase extracted with 5% MeOH/DCM. The combined organics were dried over $MgSO_4$, filtered, and concentrated to give a residue. This crude material was exposed to the same procedure as for compound **57**, and compound **52** was obtained as a crude oil. Purification by preparative-plate chromatography (C_{18} silica, 5% MeOH/DCM) was completed to give the title compound **52** (10.5 mg, 0.0243 mmol, 36% over two steps). Compound **52**: yellow oil; R_f = 0.71 (C_{18} silica, 5% MeOH/DCM); $[\alpha]_D^{25}$ = −30.4 (MeCN, *c* 0.90); FT-IR (film) ν_{max} 3335, 3193, 2958, 1747, 1686, 1644, 1528, 1420, 1333, 1282, 1208, 1180, 1159, 1110, 1044, 1031, 884, 794, 760, 711 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ = 7.84 (s, 1H), 7.40 (s, 2H), 6.58–6.55 (m, 1H), 6.25 (s, 2H), 6.09 (d, *J* = 7.1 Hz, 1H), 5.45 (d, *J* = 8.1 Hz, 1H), 4.72 (t, *J* = 8.4 Hz, 1H), 3.95–3.91 (m, 1H), 3.82 (s, 3H) ppm; ^{13}C NMR (CD_3CN, 600 MHz) δ = 170.47, 167.75, 155.10, 152.99, 152.74, 92.08, 87.27, 74.26, 66.18, 54.79, 53.42, 51.22, 20.73 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{16}Cl_2N_6O_5^+$ 431.0632, found 431.0630.

4.1.65. (3a*R*,6a*R*)-Butyl 2,2-dimethyl-3a,6a-dihydrofuro[2,3-*d*][1,3]dioxole-5-carboxylate (87)

Literature-known compound **84** (470 mg, 1.31 mmol) and anhydrous *n*-butanol (0.14 mL, 1.57 mmol) were dissolved in CH_2Cl_2 (11.8 mL), and DCC (325 mg, 1.57 mmol) and DMAP (24 mg, 0.196 mmol) were added. The reaction solution was stirred at rt for 24 h. DBU (0.22 mL, 1.57 mmol) was added and the solution stirred at rt for 24 h. The reaction solution was evaporated and purification by flash column chromatography (silica, hexanes:EtOAc 5:1) was completed to give compound **87** (200 mg, 0.878 mmol, 67%). Compound **87**: white semi-solid; R_f = 0.70 (silica, hexanes:EtOAc 2:1); $[\alpha]_D^{25}$ = −17.7 (MeOH, *c* 0.26); FT-IR (film) ν_{max} 2993, 2957, 2935, 2873, 1722, 1639, 1627, 1575, 1458, 1397, 1381, 1371, 1332, 1320, 1305, 1256, 1248, 1234, 1213, 1156, 1127, 1082, 1039, 1009, 970, 897, 886, 852, 835, 805, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 6.17 (d, *J* = 5.4 Hz, 1H), 6.06 (d, *J* = 2.5 Hz, 1H), 5.36 (dd, *J* = 5.4, 2.5 Hz, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 1.68 (dd, *J* = 9.9, 5.2 Hz, 2H), 1.39 (dt, *J* = 14.8, 7.5 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 159.88, 150.48, 113.22, 110.31, 106.84, 82.93, 65.74, 30.60, 28.10, 27.84, 19.18, 13.79 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{18}O_5Na^+$ 265.1046, found 265.1034.

4.1.66. (1*R*,3*S*,4*S*,5*S*,6*S*,7*S*)-Methyl 6,7-dichloro-3,4-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-2-oxabicyclo[3.2.0]heptane-1-carboxylate (88)

Compound **87** (200 mg, 0.826 mmol) was dissolved in MeCN (16 mL) under argon in a Quartz test tube tightly capped with a septum. 1,2-*Cis*-dichloroethylene (0.86 mL, 8.86 mmol) was added and the reaction solution degassed with argon for 30 min. The mixture was exposed to UV light (Hanovia 400 W high-pressure Hg lamp) for 108 h. Additional 1,2-*cis*-dichloroethylene (0.50 mL, 5.14 mmol) was added and the solution degassed for 30 min. The reaction mixture was exposed to UV light for an additional 48 h and then worked up by evaporation. Purification by flash column chromatography (silica, hexanes:EtOAc 20:1) was completed to give compound **76** (59 mg, 0.174 mmol, 21%) along with two other diastereomers (76 mg, 0.224 mmol, 27%) and recovered starting material **87** (23 mg, 0.0949 mmol, 12%). Compound **88**: yellow oil; R_f = 0.75 (silica, hexanes:EtOAc 4:1); $[\alpha]_D^{25}$ = +16.0 ($CHCl_3$, *c* 1.00); FT-IR (film) ν_{max} 2961, 2937, 2875, 1757, 1731, 1459, 1384, 1374, 1325, 1270, 1244, 1190, 1160, 1122, 1052, 987, 933, 899, 852, 782, 746, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ = 6.08 (d, *J* = 3.8 Hz, 1H), 5.08 (d, *J* = 3.8 Hz, 1H), 4.49 (dd, *J* = 9.7, 6.8 Hz, 1H), 4.31–4.24 (m, 2H), 4.16 (dd, *J* = 6.8, 1.2 Hz, 1H), 3.77 (d, *J* = 9.7 Hz, 1H), 1.69 (dq, *J* = 13.6, 6.7 Hz, 2H), 1.43–1.38 (m, 8H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz) δ = 166.61, 114.90, 109.03, 88.68, 81.95, 66.21, 65.58, 54.09, 50.56, 30.62, 27.90, 27.37, 19.14, 13.77 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{21}Cl_2O_5^+$ 339.0760, found 339.0768.

4.1.67. (1*R*,3*R*,4*R*,5*R*,6*S*,7*S*)-Methyl 6,7-dichloro-3-(2,6-diamino-9*H*-purin-9-yl)-4-hydroxy-2-oxabicyclo[3.2.0]heptane-1-carboxylate (53)

Method 1: Compound **88** (4.3 mg, 0.00986 mmol) was dissolved in MeOH (0.47 mL), and K_2CO_3 (0.40 mg, 0.00296 mmol) was added. The reaction was stirred at rt for 30 min. The reaction mixture was quenched with one drop AcOH and purification by preparative-plate chromatography (C_{18} silica, 5% MeOH/DCM) was completed to give compound **53** (3.2 mg, 0.00818 mmol, 83%). Method 2: From compound **88**, using the same procedures as for compound **52**, a crude residue was obtained. This residue was then dissolved in MeOH (0.3 mL), and K_2CO_3 (0.26 mg, 0.00190 mmol) was added. The reaction mixture was stirred at rt for 1 h. The mixture was quenched with one drop AcOH and purification by preparative-plate chromatography (C_{18} silica, 5% MeOH/DCM) was completed to give compound **53** (2.2 mg, 0.00564 mmol, 38% over three steps). Compound **53**: white powder; $R_f = 0.10$ (silica, 5% MeOH/DCM); $[\alpha]_D^{25} = -17.7$ (MeOH, *c* 0.26); FT-IR (film) ν_{max} 3333, 2925, 1742, 1688, 1643, 1528, 1414, 1331, 1281, 1208, 1157, 1100, 1031, 959, 888, 791, 707 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) $\delta = 7.93$ (s, 1H), 7.30 (s, 2H), 6.32 (s, 2H), 5.89 (d, $J = 7.8$ Hz, 1H), 5.43 (t, $J = 7.3$ Hz, 1H), 5.20 (dd, $J = 8.0$, 1.0 Hz, 1H), 4.72–4.68 (m, 1H), 4.21 (s, 1H), 3.81 (s, 3H), 3.66 (ddd, $J = 6.8$, 5.0, 1.1 Hz, 1H) ppm; ^{13}C NMR (CD_3CN, 151 MHz) $\delta = 168.07$, 154.25, 153.11, 152.15, 141.45, 125.82, 93.25, 86.46, 74.31, 66.88, 55.22, 53.30, 52.41 ppm; HRMS (ESI-TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{15}Cl_2N_6O_4^+$ 389.0526, found 389.0534.

4.2. Biological assays

4.2.1. Bacterial minimum inhibitory concentration (MIC) assays

Minimum inhibitory concentrations (MIC) were determined by CLSI micro-broth dilution guidelines.[33] Briefly, compounds were serially diluted in 96-well plates containing 100 μL of cation-adjusted Mueller-Hinton broth (MHB) per well. *E. coli* MG1655 and *S. aureus* 8325 were inoculated into MHB from a fresh overnight plate scrape on Mueller-Hinton agar (MHA) plates to a final concentration of 1×10^7 colony forming units ml^{-1}, and 5 μL of this suspension was added to each well. The plates were incubated at 37 °C and the MIC determined after 24 h of growth. MICs were defined as the lowest concentration of the compound that yielded no observable growth, and reported values were the median value of at least three independent replicates with an error of no greater than two-fold.

4.2.2. Cytotoxicity assays

Raji and CEM cells were incubated for 72 h in 96-well plates with the test compounds. Cell proliferation by reduction of the yellow dye MTT [i.e., 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] to a blue formazan product was used to test viability. The amount of formazan dye formed is a direct indication of the number of metabolically active cells in the culture. The optical density of the blue formazan product was measured at 570 nm with an Infinite M200 (Tecan, Switzerland) and analyzed using one-way ANOVA using GraphPad Prism version 5.0b for OSX (GraphPad Software, San Diego, CA).

4.2.3. Pseudovirus neutralization assays

Pseudoviruses were generated in 293T cells and neutralization with single-round infectious pseudovirus was performed using TZM-bl cells as targets for infection as described previously.[34] Briefly, pseudovirus was titrated on TZM-bl cells and a predetermined amount of virus that produces $\sim 1 \times 10^6$ RLUs was incubated for 1 h at 37 °C with serially diluted samples and controls. TZM-bl cells were resuspended in media, washed, counted and plated at 1×10^5 cells per well over the incubated solution of virus and samples for an additional 48 h. The degree of virus neutralization by each sample was achieved by measuring luciferase activity. The wells were aspirated and washed once with PBS, and 60 μL of luciferase cell culture lysis reagent (Promega, Madison, WI) was added. The lysate is mixed by pipetting, and 50 μL was transferred to a round-bottom plate (Corning), and the plate is centrifuged at 1800*g* for 10 min at 4 °C. Then 20 μL was transferred to an opaque assay plate (Corning, Corning, NY), and the luciferase activity was measured on a luminometer (EG&G Berthold LB 96 V; Perkin Elmer, Gaithersburg, MD) by using luciferase assay reagent (Promega, Madison, WI).

Acknowledgments

We thank Dr. D. H. Huang and Dr. L. Pasternack for NMR spectroscopic assistance and Dr. G. Siuzdak for mass spectrometric assistance. Financial support for this work was provided by the National Institutes of Health (USA) and the Skaggs Institute for research, along with fellowships from Novartis (to S.P.E.) and UCSD/SDSU IRACDA (to F.R.).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.07.022.

References and notes

1. Zamecnik, P. C.; Stephenson, M. L. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 280.
2. Reviews: (a) Petersen, M.; Wengel, J. *Trends Biotechnol.* **2003**, *21*, 74; (b) Kurreck, J. *Eur. J. Biochem.* **2003**, *270*, 1628; (c) Kaur, H.; Babu, B. R.; Maiti, S. *Chem. Rev.* **2007**, *107*, 4672; (d) Rahman, S. M. A.; Imanishi, T.; Obika, S. *Chem. Lett.* **2009**, *38*, 512; (e) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Chem. Biodivers.* **2011**, *8*, 373.
3. (a) Altona, C.; Sunderalingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205; (b) Altona, C.; Sunderalingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333.
4. (a) Koshkin, A. A.; Singk, S. K.; Nielsen, P.; Rajwanshi, V. K.; Kumar, R.; Meldgaard, M.; Olsen, C. E.; Wengel, J. *Tetrahedron* **1998**, *54*, 3607; (b) Koshkin, A. A.; Rajwanshi, V. K.; Wengel, J. *Tetrahedron Lett.* **1998**, *39*, 4381; (c) Rajwanshi, V. K.; Håkansson, A. E.; Sørensen, M. D.; Pitsch, S.; Singh, S. K.; Kumar, R.; Nielsen, P.; Wengel, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1656; (d) Obika, S.; Uneda, T.; Sugimoto, T.; Nanbu, D.; Minami, T.; Doi, T.; Imanishi, T. *Bioorg. Med. Chem.* **2001**, *9*, 1001; (e) Koshkin, A. A.; Fensholdt, J.; Pfundheller, H. M.; Lomholt, C. *J. Org. Chem.* **2001**, *66*, 8504.
5. (a) Obika, S.; Morio, K.-i.; Nanbu, D.; Imanishi, T. *Chem. Commun.* **1997**, 1643; (b) Obika, S.; Morio, K.-i.; Hari, Y.; Imanishi, T. *Chem. Commun.* **1999**, 2423; (c) Obika, S.; Morio, K.-i.; Nanbu, D.; Hari, Y.; Itoh, H.; Imanishi, T. *Tetrahedron* **2002**, *58*, 3039.
6. Rahman, S. M. A.; Seki, S.; Obika, S.; Yoshikawa, H.; Miyashita, K.; Imanishi, T. *J. Am. Chem. Soc.* **2008**, *130*, 4886.
7. (a) Umemoto, T.; Wengel, J.; Madsen, A. S. *Org. Biomol. Chem.* **2009**, *7*, 1793; (b) Astakhova, I. V.; Lindegaard, D.; Korshun, V. A.; Wengel, J. *Chem. Commun.* **2010**, *46*, 8362.
8. Liu, Y.; Xu, J.; Karimiahmadabadi, M.; Zhou, C.; Chattopadhyaya, J. *J. Org. Chem.* **2010**, *75*, 7112.
9. Seth, P. P.; Allerson, C. R.; Berdeja, A.; Siwkowski, A.; Pallan, P. S.; Gaus, H.; Prakash, T. P.; Watt, A. T.; Egli, M.; Swayze, E. E. *J. Am. Chem. Soc.* **2010**, *132*, 14942.
10. Review: Mathé, C.; Périgaud, C. *Eur. J. Org. Chem.* **2008**, 1489.
11. (a) Webb, T. R.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1988**, *31*, 1475; (b) Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *30*, 2203; (c) Beard, A. R.; Butler, P. I.; Mann, J.; Partlett, N. K. *Carbohydr. Res.* **1990**, *205*, 87; (d) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi, J. J., Jr. *J. Med. Chem.* **1994**, *37*, 3389; (e) Park, A.-Y.; Moon, H. R.; Kim, K. R.; Chun, M. W.; Jeong, L. S. *Org. Biomol. Chem.* **2006**, *4*, 4065; (f) Moon, H. R.; Park, A.-Y.; Kim, K. R.; Chun, M. W.; Jeong, L. S. *Nucleosides, Nucleotides Nucleic Acids* **2007**, *26*, 1653.
12. (a) Tchilibon, S.; Joshi, B. V.; Kim, S.-K.; Duong, H. T.; Gao, Z.-G.; Jacobson, K. A. *J. Med. Chem.* **2005**, *48*, 1745; (b) Jacobson, K. A.; Joshi, B. V.; Tchilibon, S. International Patent WO 031505 A1, 2006; (c) Tosh, D. K.; Chinn, M.; Ivanov, A. A.; Klutz, A. M.; Gao, Z.-G.; Jacobson, K. A. *J. Med. Chem.* **2009**, *52*, 7580.
13. Eoff, R. L.; McGrath, C. E.; Maddukuri, L.; Salamanca-Pinzón, S. G.; Marquez, V. E.; Marnett, L. J.; Guengerich, F. P.; Egli, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1.
14. O-Yang, C.; Kurz, W.; Eugui, E. M.; McRoberts, M. J.; Verheyden, J. P. H.; Kurz, L. J.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 41.
15. Kim, M. J.; Kim, H. O.; Kim, H.-D.; Kim, J. H.; Jeong, L. S.; Chun, M. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3499.
16. Díaz-Rodríguez, A.; Sanghvi, Y. S.; Fernández, S.; Schinazi, R. F.; Theodorakis, E. A.; Ferrero, M.; Gotor, V. *Org. Biomol. Chem.* **2009**, *7*, 1415.

17. (a) Ravn, J.; Qvortrup, K.; Rosenbohm, C.; Koch, T. *Bioorg. Med. Chem.* **2007**, *15*, 5440; (b) Ravn, J.; Rosenbohm, C.; Qvortrup, K.; Koch, T. International Patent WO 006369 A1, 2008.
18. (a) Olsen, A. G.; Nielsen, C.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 900; (b) Bryld, T.; Sørensen, M. H.; Nielsen, P.; Koch, T.; Nielsen, C.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1655; (c) Nair, V.; Jeon, G.-S. *ARKIVOC* **2004**, 133.
19. (a) Chun, M. W.; Kim, M. J.; Kim, H. O.; Kim, H.-D.; Kim, J. H.; Moon, H. R.; Jeong, L. S. *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 915; (b) Hrdlicka, P. J.; Jepsen, J. S.; Wengel, J. *Nucleosides, Nucleotides Nucleic Acids* **2005**, *24*, 397.
20. (a) Fleet, G. W. J.; Ramsden, N. G.; Dwek, R. A.; Rademacher, T. W.; Fellows, L. E.; Nash, R. J.; Green, St. C. D.; Winchester, B. *Chem. Commun.* **1988**, 483; (b) Yoshikawa, M.; Okaichi, Y.; Cha, B. C.; Kitagawa, I. *Tetrahedron* **1990**, *46*, 7459.
21. Youssefyeh, R. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 1301.
22. Niedballa, U.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 461.
23. Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256.
24. Hirota, K.; Kazaoka, K.; Sajiki, H. *Bioorg. Med. Chem.* **2003**, *11*, 2715.
25. Geng, B.; Breault, G.; Comita-Prevoir, J.; Petrichko, R.; Eyerman, C.; Lundqvist, T.; Doig, P.; Gorseth, E.; Noonan, B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4368.
26. Langli, G.; Gundersen, L.-L.; Rise, F. *Tetrahedron* **1996**, *52*, 5625.
27. Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434.
28. Bookser, B. C.; Raffaele, N. B. *J. Org. Chem.* **2007**, *72*, 173.
29. (a) Timoshchuk, V. A. *Carbohydr. Res.* **1985**, *145*, 131; (b) Mezzina, E.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 845.
30. Wilson, P. K.; Szabados, E.; Mulligan, S. P.; Christopherson, R. I. *Int. J. Biochem. Cell Biol.* **1998**, *30*, 833.
31. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J.Org. Chem.* **1997**, *62*, 7512.
32. (a) Koshkin, A. A. *J. Org. Chem.* **2004**, *69*, 3711; Ramsing, N. B.; Nielsen, A. T.; Koshkin, E. A.; Tolstrup, N.; Pfundheller, H. M.; Lomholdt, C. U.S. Patent 0,147,924, A1, 2006.; (c) Pasternack, A.; Kierzek, E.; Pasternack, K.; Turner, D. H.; Kierzek, R. *Nucleic Acids Res.* **2007**, *35*, 4055.
33. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. CLSI, Wayne, PA, USA, 2006.
34. Zwick, M. B.; Wang, M.; Poignard, P.; Stiegler, G.; Katinger, H.; Burton, D. R.; Parren, P. W. *J. Virol.* **2001**, *75*, 12198.