

Synthesis of C6-substituted purine nucleoside analogues via late-stage photoredox/nickel dual catalytic cross-coupling

James J. Perkins[‡], Valerie W. Shurtleff[‡], Alayna M. Johnson and Abdellatif El Marrouni^{*}

Merck & Co., Inc. 770 Sumneytown Pike, West Point, Pennsylvania, 19486, USA

Table of Contents	Page
1. General information	S-2
2. Experimental procedures and characterization data	S-3
A. Optimization/Screening (Table 1)	S-3
B. Synthesis of compounds 3-17 (Table 2)	S-4
3. ¹H and ¹³C-NMR spectra	S-14

General Information:

Unless otherwise noted, all reactions were performed in capped vials (1-dram or 2-dram or scintillation vial) and under inert atmosphere. Nonaqueous reagents were transferred using syringe techniques. N,N-dimethylformamide (DMF), dimethoxyethane (DME), and acetonitrile (MeCN), were obtained in sealed, anhydrous bottles from Aldrich or Acros Organics. Bulk solvents used for reverse phase chromatographic purifications (MeCN, 0.1% TFA in MeCN and 0.1% TFA in water) were acquired in 4L bottles from Fisher and used without further treatment. Commercial reagents were obtained at the highest commercial quality and used without further purification, unless otherwise stated. Catalysts Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ was purchased from Strem Chemicals (CAS no. 870987-63-6) and 4CzIPN was purchased from Synnovator, Inc (CAS no. 1416881-52-1). [Ni(dtbbpy)(H₂O)₄]Cl₂ was prepared according to the literature procedure¹. (2*R*,3*R*,4*S*,5*R*)-2-(6-chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol **1** was sourced from Alfa Aesar (CAS no. 2004-06-0). Yields refer to chromatographically and spectroscopically (¹H-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by LC-MS techniques using Waters Acquity UPLC, water/MeCN gradient and 0.1% v/v TFA as modifier. Chromatographic separations were performed using ISCO ACCQPrep HP125 with Waters SunFire C18 OBD 5 μm 30 × 150 mm prep column or Phenomenex Gemini-NX C18 5 μm 30 × 100 mm prep column. Infrared spectra (IR) were recorded on a PerkinElmer Spectrum 100 Optica FT-IR spectrometer. Only the strongest and/or structurally important absorption of infrared (IR) spectra are reported in reciprocal centimeters (ν, cm⁻¹). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance NEO 500 MHz NMR spectrometer and chemical shifts are reported relative to internal tetramethylsilane [0.00 ppm] for ¹H NMR and residual undeuterated solvent for ¹³C NMR [δ 49.00 (CD₃OD) or 39.52 (DMSO-*d*₆) ppm]. ³¹P NMR spectra were recorded at 202.45 MHz at ambient temperature with CD₃OD as solvent. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; qd = quartet of doublet; ddd = doublet of doublet of doublet; dtd = doublet of triplet of doublet; m = multiplet or nonequivalent resonances. NMR coupling constants are reported as J values in Hz and δ values in parts per million (ppm). High resolution mass measurements (HRMS) were obtained on Waters Synapt G1 QTOF instrument (ESI+ mode, source temperature: 130 °C) connected to Waters Acquity UPLC (column: Acquity UPLC BEH C18 1.7μm 1.0 x 50 mm).

(1) Gutiérrez-Bonet, Á.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. 1,4-Dihydropyridines as Alkyl Radical Precursors: Introducing the Aldehyde Feedstock to Nickel/Photoredox Dual Catalysis. *ACS Catal.* **2016**, *6*, 8004.

Experimental procedures and characterization data:

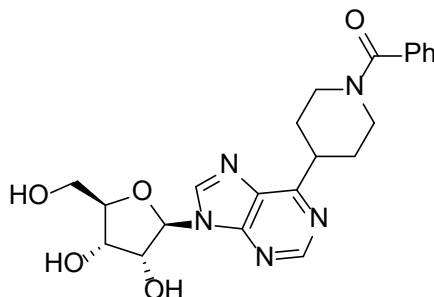
General procedure for optimization (Table 1).

A 2-dram vial equipped with a magnetic stirring bar was charged with (2R,3R,4S,5R)-2-(6-chloro-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**1**) (20 mg, 0.070 mmol, 1.0 equiv.), (4-bromopiperidin-1-yl)(phenyl)methanone (**2**) (37.4 mg, 0.14 mmol, 2.0 equiv.), Na₂CO₃ (22 mg, 0.21 mmol, 3.0 equiv.), [Ni(dtbbpy)(H₂O)₄]Cl₂ (3.3 mg, 0.007 mmol, 0.1 equiv.) and the appropriate photocatalyst (0.0014 mmol, 0.02 equiv.). Solvent was added to the vials (698 μ L) followed by tris(trimethylsilyl)silanol (21.5 μ L, 0.07 mmol, 1.0 equiv.). The mixtures were sparged with nitrogen for 10 minutes and then sealed. The reactions were irradiated on the PennOC Photoreactor® (wavelength: 450 nm; LED intensity: 100%; fan speed: ~5000 rpm; stir: ~1000 rpm) for 12 hours. Mesitylene (internal standard) (9.71 μ L, 0.070 mmol) was added and the crude mixture was analyzed by ¹H NMR.

General procedure for preparation of compounds 3-17:

A 2-dram vial equipped with a magnetic stirring bar was charged with (2R,3R,4S,5R)-2-(6-chloro-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**1**) (50 mg, 0.174 mmol, 1.0 equiv.), alkyl bromide (0.35 mmol, 2.0 equiv.), Na₂CO₃ (56 mg, 0.52 mmol, 3.0 equiv.), [Ni(dtbbpy)(H₂O)₄]Cl₂ (8.2 mg, 0.017 mmol, 0.1 equiv.) and Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (3.91 mg, 0.004 mmol, 0.02 equiv.). DMF was added to the vials (1745 μ L) followed by tris(trimethylsilyl)silanol (54 μ L, 0.174 mmol, 1.0 equiv.). The mixtures were sparged with nitrogen for 10 minutes. The reaction was irradiated on the PennOC Photoreactor® (wavelength: 450 nm; LED intensity: 100%; fan speed: ~5000 rpm; stir: ~1000 rpm) for 4 hours. After the reaction was stopped, DMSO (2 mL) was added to the mixture, which was filtered and the filtrate purified by reverse phase (C-18) HPLC (30 x 150 mm, Waters SunFire® OBD™ 5 μ m) eluting with a gradient of 5-50% Acetonitrile/Water + 0.1% TFA over 15 minutes at 43 ml/min. The fractions were concentrated to provide the final products.

Synthesis of (4-(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)piperidin-1-yl)(phenyl)methanone (3)



A 2-dram vial equipped with a magnetic stirring bar was charged with (2R,3R,4S,5R)-2-(6-chloro-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**1**) (50 mg, 0.174 mmol, 1.0 equiv.), (4-bromopiperidin-1-yl)(phenyl)methanone (**2**) (94 mg, 0.35 mmol, 2.0 equiv.), Na₂CO₃ (56 mg, 0.52 mmol, 3.0 equiv.), [Ni(dtbbpy)(H₂O)₄]Cl₂ (8.2 mg, 0.017 mmol, 0.1 equiv.) and Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (3.91 mg, 0.004 mmol, 0.02 equiv.). DMF was added to the vial (1745 μL) followed by tris(trimethylsilyl)silanol (54 μL, 0.174 mmol, 1.0 equiv.). The mixtures were sparged with nitrogen for 10 minutes. The reaction was irradiated on the PennOC Photoreactor® (wavelength: 450 nm; LED intensity: 100%; fan speed: ~5000 rpm; stir: ~1000 rpm) for 4 hours. After the reaction was stopped, DMSO (2 mL) was added to the mixture, which was filtered and the filtrate purified by reverse phase (C-18) HPLC (30 x 150 mm, Waters SunFire® OBD™ 5 μm) eluting with a gradient of 5-50% Acetonitrile/Water + 0.1% TFA over 15 minutes at 43 ml/min. The fractions were concentrated to provide product **3** as a colorless foam (45 mg, 0.10 mmol, 59% yield).

tR (UPLC): 0.69 min

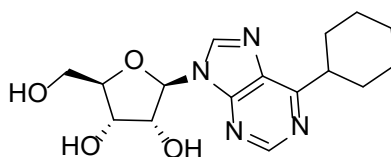
IR (neat) 3346, 2931, 1672, 1600, 1448, 1200, 1136 cm⁻¹.

¹H NMR (500 MHz, DMSO-d₆) δ 8.89 (s, 1H), 8.80 (s, 1H), 7.48 – 7.44 (m, 3H), 7.43 -7.40 (m, 2H), 6.03 (d, *J* = 5.8 Hz, 1H), 4.65 (t, *J* = 5.4 Hz, 1H), 4.62 (m, 1H), 4.21 – 4.16 (m, 1H), 3.98 (q, *J* = 3.8 Hz, 1H), 3.77 – 3.64 (m, 2H), 3.68 (dd, *J* = 12.0, 4.0 Hz, 2H), 3.57 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.29 (m, 1H), 3.06 (m, 1H), 2.09 – 1.82 (m, 4H) ppm.

¹³C NMR (126 MHz, DMSO-d₆) δ 169.1, 163.0, 151.8, 150.7, 144.3, 136.3, 131.7, 129.4, 128.5, 126.7, 87.6, 85.8, 73.6, 70.4, 61.3 ppm.

HR-MS (ESI⁺): *m/z* calcd. for C₂₂H₂₅N₅O₅ [M+H]⁺ 440.1928, found 440.1908.

(2*R*,3*R*,4*S*,5*R*)-2-(6-cyclohexyl-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**4**)



Synthesized according to the general procedure using bromocyclohexane (57 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **4** : 50% (29 mg, 0.087 mmol).

tR (UPLC): 0.69 min

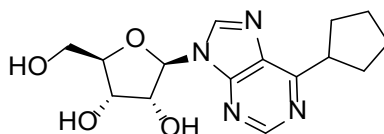
IR (neat) 3320, 2931, 1595, 1460, 1394, 1332, 1214, 1051 cm^{-1} .

^1H NMR (500 MHz, CD_3OD) δ 8.90 (s, 1H), 8.82 (s, 1H), 6.16 (d, $J = 5.5$ Hz, 1H), 4.73 (t, $J = 5.3$ Hz, 1H), 4.37 (dd, $J = 5.0, 3.8$ Hz, 1H), 4.17 (q, $J = 3.1$ Hz, 1H), 3.90 (dd, $J = 12.3, 3.0$ Hz, 1H), 3.79 (dd, $J = 12.3, 3.0$ Hz, 1H), 3.46 (dt, $J = 11.6, 5.8$ Hz, 1H), 1.99 – 1.97 (m, 6H), 1.87 – 1.79 (m, 1H), 1.59 – 1.47 (m, 2H), 1.46 – 1.38 (m, 1H).

^{13}C NMR (126 MHz, CD_3OD) δ 166.2, 152.5, 151.8, 146.6, 133.1, 90.7, 87.7, 75.9, 72.1, 62.9, 42.8, 32.2, 27.2, 26.9.

HR-MS (ESI+): m/z calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 335.1714, found 335.1710.

(2*R*,3*R*,4*S*,5*R*)-2-(6-cyclopentyl-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**5**)



Synthesized according to the general procedure using bromocyclopentane (52 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **5** : 53.7% (30 mg, 0.094 mmol).

tR (UPLC): 0.62 min

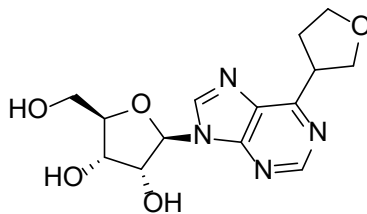
IR (neat) 3310, 2947, 1676, 1594, 1466, 1324, 1202, 1086 cm^{-1} .

^1H NMR (500 MHz, CD_3OD) δ 8.91 (s, 1H), 8.83 (s, 1H), 6.17 (d, $J = 5.5$ Hz, 1H), 4.72 (t, $J = 5.3$ Hz, 1H), 4.37 (dd, $J = 5.0, 3.8$ Hz, 1H), 4.17 (q, $J = 3.1$ Hz, 1H), 3.90 (dd, $J = 12.3, 2.9$ Hz, 1H), 3.88 – 3.82 (m, 1H), 3.79 (dd, $J = 12.3, 3.1$ Hz, 1H), 2.24 – 2.15 (m, 2H), 2.14 – 2.05 (m, 2H), 2.03 – 1.92 (m, 2H), 1.88 – 1.76 (m, 2H).

^{13}C NMR (126 MHz, CD_3OD) δ 166.1, 152.3, 151.6, 146.6, 133.6, 90.8, 87.7, 76.0, 72.1, 62.8, 43.5, 33.87, 33.86, 27.32, 27.29.

HR-MS (ESI+): m/z calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 321.1557, found 321.1560.

(2*R*,3*S*,4*R*,5*R*)-2-(hydroxymethyl)-5-(6-(tetrahydrofuran-3-yl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (**6**)



Synthesized according to the general procedure using 3-bromotetrahydrofuran (53 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **6** : 96% (54 mg, 0.168 mmol). Major diastereoisomer.

tR (UPLC): 0.84 min

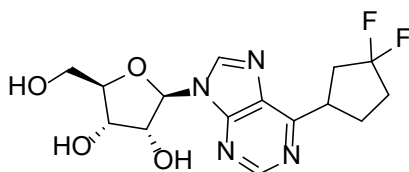
IR (neat) 3325, 2932, 1676, 1594, 1464, 1415, 1330, 1203, 1119, 1084, 1054 cm^{-1} .

$^1\text{H NMR}$ (500 MHz, CD_3OD) δ 8.87 (s, 1H), 8.75 (s, 1H), 6.14 (d, $J = 5.6$ Hz, 1H), 4.74 (t, $J = 5.3$ Hz, 1H), 4.37 (dd, $J = 5.0, 3.7$ Hz, 1H), 4.28 – 4.22 (m, 2H), 4.17 (q, $J = 3.1$ Hz, 1H), 4.15 – 4.08 (m, 2H), 4.01 – 3.95 (m, 1H), 3.90 (dd, $J = 12.3, 3.1$ Hz, 1H), 3.78 (dd, $J = 12.3, 3.1$ Hz, 1H), 2.46 (q, $J = 6.8$ Hz, 2H).

$^{13}\text{C NMR}$ (126 MHz, CD_3OD) δ 163.1, 152.8, 151.9, 146.2, 133.9, 90.8, 87.7, 75.8, 73.3, 72.2, 69.8, 63.0, 43.0, 33.2.

HR-MS (ESI+): m/z calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$ 323.1350, found 323.1347.

(2*R*,3*R*,4*S*,5*R*)-2-(6-(3,3-difluorocyclopentyl)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**7**)



Synthesized according to the general procedure using 3-bromo-1,1-difluorocyclopentane (64.5 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **7** : 72.4% (45 mg, 0.126 mmol). Major diastereoisomer.

tR (UPLC): 0.69 min

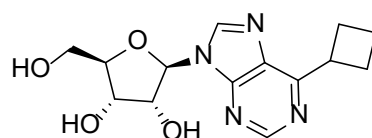
IR (neat) 3329, 2955, 1597, 1337, 1211, 1131 cm^{-1} .

¹H NMR (500 MHz, CD₃OD) δ 8.89 (s, 1H), 8.76 (s, 1H), 6.14 (d, *J* = 5.6 Hz, 1H), 4.74 (t, *J* = 5.3 Hz, 1H), 4.37 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.20 – 4.11 (m, 2H), 3.90 (dd, *J* = 12.3, 2.9 Hz, 1H), 3.78 (dd, *J* = 12.3, 3.2 Hz, 1H), 2.84 – 2.70 (m, 1H), 2.63 – 2.51 (m, 1H), 2.47 – 2.31 (m, 2H), 2.31 – 2.20 (m, 2H).j

¹³C NMR (126 MHz, CD₃OD) δ 163.2, 152.9, 152.0, 146.2, 133.6, 133.4 (t, *J* = 247 Hz), 90.8, 87.7, 75.8, 72.2, 63.0, 41.4 (m), 40.5 (dd, *J* = 6.1, 2.3 Hz), 36.6 (t, *J* = 25.4 Hz), 30.2 (d, *J* = 12.9 Hz).

HR-MS (ESI+): *m/z* calcd. for C₁₅H₁₈F₂N₄O₄ [M+H]⁺ 357.1369, found 357.1376.

(2R,3R,4S,5R)-2-(6-cyclobutyl-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**8**)



Synthesized according to the general procedure using bromocyclobutane (47 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **8** : 37.4% (20 mg, 0.065 mmol).

tR (UPLC): 0.55 min

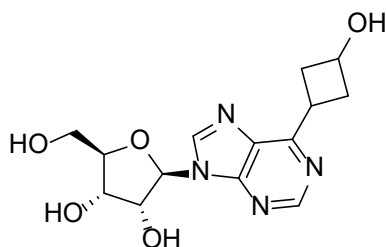
IR (neat) 3320, 2946, 1675, 1594, 1466, 1415, 1329, 1202, 1132, 1084 cm⁻¹.

¹H NMR (500 MHz, CD₃OD) δ 8.94 (s, 1H), 8.83 (s, 1H), 6.16 (d, *J* = 5.4 Hz, 1H), 4.72 (t, *J* = 5.3 Hz, 1H), 4.37 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.32 (q, *J* = 8.5 Hz, 1H), 4.18 (q, *J* = 3.1 Hz, 1H), 3.90 (dd, *J* = 12.3, 2.9 Hz, 1H), 3.79 (dd, *J* = 12.3, 3.1 Hz, 1H), 2.69 (pd, *J* = 9.5, 2.3 Hz, 2H), 2.54 – 2.46 (m, 2H), 2.30 – 2.19 (m, 1H), 2.11 – 2.00 (m, 1H).

¹³C NMR (126 MHz, CD₃OD) δ 164.1, 152.4, 151.7, 146.7, 133.1, 90.8, 87.7, 75.6, 72.1, 62.8, 38.1, 28.61, 28.60, 19.5.

HR-MS (ESI+): *m/z* calcd. for C₁₄H₁₈N₄O₄ [M+H]⁺ 307.1401, found 307.1403.

(2*R*,3*R*,4*S*,5*R*)-2-(6-(3-hydroxycyclobutyl)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**9**)



Synthesized according to the general procedure using *cis*-3-bromocyclobutan-1-ol (52.7 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **9** : 53.4% (30 mg, 0.093 mmol).

tR (UPLC): 0.38 min

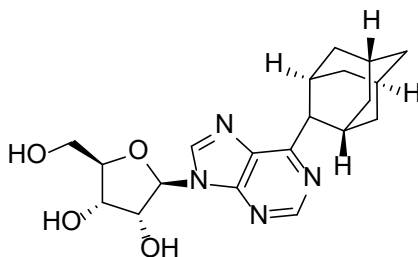
IR (neat) 3319, 2934, 1680, 1596, 1337, 1210, 1135, 1086 cm⁻¹.

¹H NMR (500 MHz, CD₃OD) δ 8.91 (s, 1H), 8.78 (s, 1H), 6.15 (d, *J* = 5.5 Hz, 1H), 4.73 (t, *J* = 5.3 Hz, 1H), 4.40 – 4.30 (m, 2H), 4.17 (q, *J* = 3.1 Hz, 1H), 3.90 (dd, *J* = 12.3, 2.9 Hz, 1H), 3.78 (dd, *J* = 12.3, 3.1 Hz, 1H), 3.73 (m, 1H), 3.02 – 2.85 (m, 1H), 2.85 – 2.75 (m, 2H), 2.58 – 2.48 (m, 2H) ppm.

¹³C NMR (126 MHz, CD₃OD) δ 163.8, 152.4, 152.0, 146.3, 133.4, 90.8, 87.7, 75.8, 72.1, 64.1, 62.9, 39.57, 39.56, 28.8 ppm.

HR-MS (ESI+): *m/z* calcd. for C₁₄H₁₈N₄O₅ [M+H]⁺ 323.1350, found 323.1365.

(2*R*,3*R*,4*S*,5*R*)-2-(6-((1*R*,3*R*,5*R*,7*R*)-adamantan-2-yl)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (**10**)



Synthesized according to the general procedure using 2-bromoadamantane (75 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **10** : 30% (20 mg, 0.052 mmol).

tR (UPLC): 0.96 min

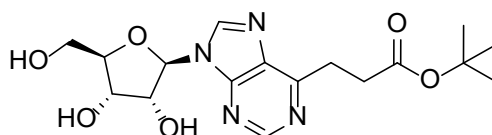
IR (neat) 3322, 2905, 2850, 1676, 1588, 1451, 1203, 1102 cm⁻¹.

¹H NMR (500 MHz, CD₃OD) δ 8.91 (s, 1H), 8.76 (s, 1H), 6.16 (d, *J* = 5.6 Hz, 1H), 4.74 (t, *J* = 5.3 Hz, 1H), 4.37 (dd, *J* = 5.0, 3.6 Hz, 1H), 4.18 (q, *J* = 3.0 Hz, 1H), 3.90 (dd, *J* = 12.3, 2.8 Hz, 1H), 3.82 – 3.76 (m, 2H), 2.83 (br s, 1H), 2.16 – 2.08 (m, 4H), 2.07 – 2.00 (m, 4H), 1.88 – 1.82 (m, 3H), 1.67 (d, *J* = 12.6 Hz, 2H).

¹³C NMR (126 MHz, CD₃OD) δ 165.5, 152.2, 151.6, 145.6, 133.8, 90.8, 87.7, 75.8, 72.2, 62.9, 39.9, 38.7, 33.9, 32.2, 32.1, 29.3, 29.1.

HR-MS (ESI+): *m/z* calcd. for C₂₀H₂₆N₄O₄ [M+H]⁺ 387.2027, found 387.2022.

tert-butyl 3-(9-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9*H*-purin-6-yl)propanoate (**11**)



Synthesized according to the general procedure using *tert*-butyl 3-bromopropanoate (73 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **11** : 75% (50 mg, 0.131 mmol).

tR (UPLC): 0.71 min

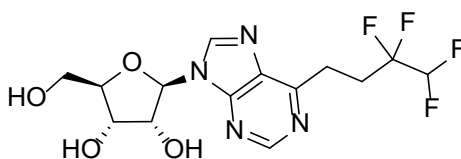
IR (neat) 3298, 2978, 2932, 1725, 1597, 1459, 1393, 1329, 1203, 1156 cm⁻¹.

¹H NMR (500 MHz, CD₃OD) δ 8.88 (s, 1H), 8.80 (s, 1H), 6.15 (d, *J* = 5.5 Hz, 1H), 4.73 (t, *J* = 5.3 Hz, 1H), 4.37 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.17 (q, *J* = 3.1 Hz, 1H), 3.90 (dd, *J* = 12.3, 2.9 Hz, 1H), 3.78 (dd, *J* = 12.3, 3.2 Hz, 1H), 3.50 – 3.41 (m, 2H), 2.93 (m, 2H), 1.36 (d, *J* = 3.6 Hz, 9H).

¹³C NMR (126 MHz, CD₃OD) δ 173.3, 161.5, 152.1, 151.9, 146.5, 134.0, 90.8, 87.7, 81.8, 75.9, 72.1, 62.9, 33.6, 33.5, 28.2.

HR-MS (ESI+): *m/z* calcd. for C₁₇H₂₄N₄O₆ [M+H]⁺ 381.1769, found 381.1787.

(2*R*,3*S*,4*R*,5*R*)-2-(hydroxymethyl)-5-(6-(3,3,4,4-tetrafluorobutyl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (**12**)



Synthesized according to the general procedure using 4-bromo-1,1,2,2-tetrafluorobutane (73 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **12** : 51.3% (34 mg, 0.089 mmol).

tR (UPLC): 0.67 min

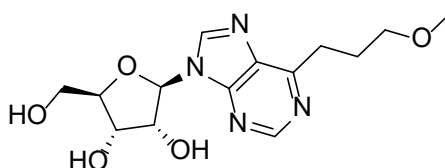
IR (neat) 33294, 2935, 1673, 1599, 1466, 1403, 1333, 1204, 1102 cm^{-1} .

^1H NMR (500 MHz, CD_3OD) δ 8.88 (s, 1H), 8.78 (s, 1H), 6.15 (d, $J = 5.6$ Hz, 1H), 6.13 (tt, $J = 53.2, 3.8$, 2H), 4.74 (t, $J = 5.3$ Hz, 1H), 4.40 – 4.31 (m, 1H), 4.17 (q, $J = 3.1$ Hz, 1H), 3.90 (dd, $J = 12.3, 2.8$ Hz, 1H), 3.78 (dd, $J = 12.3, 3.2$ Hz, 1H), 3.48 (dd, $J = 9.0, 6.9$ Hz, 2H), 2.68 (m, 2H).

^{13}C NMR (126 MHz, CD_3OD) δ 160.6, 152.7, 151.9, 146.4, 134.1, 119.10 (tt, $J = 244.2, 28.2$ Hz), 111.8 (tt, $J = 247.7, 38.5$ Hz), 90.8, 87.7, 75.8, 72.2, 62.9, 29.1 (m), 24.8 (t, $J = 4.4$ Hz).

HR-MS (ESI+): m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_4\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 381.1180, found 381.1190.

(2R,3S,4R,5R)-2-(hydroxymethyl)-5-(6-(3-methoxypropyl)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (13)



Synthesized according to the general procedure using 1-bromo-3-methoxypropane (53.4 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **13** : 80% (45 mg, 0.139 mmol).

tR (UPLC): 0.49 min

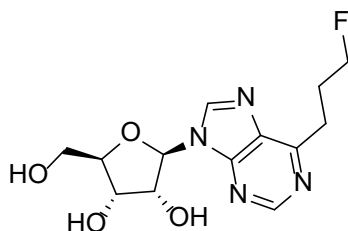
IR (neat) 3346, 2937, 1675, 1600, 1418, 1335, 1202, 1132 cm^{-1} .

^1H NMR (500 MHz, CD_3OD) δ 8.95 (s, 1H), 8.88 (s, 1H), 6.18 (d, $J = 5.4$ Hz, 1H), 4.72 (t, $J = 5.2$ Hz, 1H), 4.38 (dd, $J = 5.0, 3.9$ Hz, 1H), 4.18 (d, $J = 3.5$ Hz, 1H), 3.90 (dd, $J = 12.3, 2.9$ Hz, 1H), 3.79 (dd, $J = 12.3, 3.2$ Hz, 1H), 3.49 (t, $J = 6.1$ Hz, 2H), 3.36 – 3.29 (m, 2H), 3.27 (s, 3H), 2.20 – 2.13 (m, 2H).

^{13}C NMR (126 MHz, CD_3OD) δ 162.1, 152.4, 151.2, 147.2, 134.0, 90.7, 87.7, 76.0, 72.8, 72.1, 62.8, 58.8, 30.0, 29.4.

HR-MS (ESI+): m/z calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$ 325.1506, found 325.1514.

(2*R*,3*R*,4*S*,5*R*)-2-(6-(3-fluoropropyl)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol
(14)



Synthesized according to the general procedure using 1-bromo-3-fluoropropane (49.2 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **14** : 90% (49 mg, 0.157 mmol).

tR (UPLC): 0.47 min

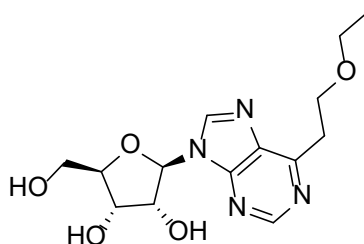
IR (neat) 3320, 2929, 1673, 1600, 1500, 1417, 1200, 1132, 1084, 1056 cm^{-1} .

^1H NMR (500 MHz, CD_3OD) δ 8.93 (s, 1H), 8.86 (s, 1H), 6.17 (d, $J = 5.4$ Hz, 1H), 4.73 (t, $J = 5.3$ Hz, 1H), 4.59 (t, $J = 5.8$ Hz, 1H), 4.49 (t, $J = 5.8$ Hz, 1H), 4.38 (dd, $J = 4.9, 3.8$ Hz, 1H), 4.18 (q, $J = 3.1$ Hz, 1H), 3.90 (dd, $J = 12.3, 2.9$ Hz, 1H), 3.79 (dd, $J = 12.3, 3.2$ Hz, 1H), 3.39 – 3.33 (m, 2H), 2.36 – 2.22 (m, 2H).

^{13}C NMR (126 MHz, CD_3OD) δ 161.7, 152.3, 151.7, 147.0, 134.0, 90.7, 87.7, 84.1 (d, $J = 164.9$ Hz), 76.0, 72.1, 62.8, 30.1 (d, $J = 20.1$ Hz), 29.2 (d, $J = 5.3$ Hz).

HR-MS (ESI+): m/z calcd. for $\text{C}_{13}\text{H}_{17}\text{FN}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 313.1307, found 313.1305.

(2*R*,3*R*,4*S*,5*R*)-2-(6-(2-ethoxyethyl)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol
(15)



Synthesized according to the general procedure using 1-bromo-2-ethoxyethane (53.4 mg, 0.35 mmol, 2.0 equiv.). Purified by reverse phase (C-18) HPLC (30 x 100 mm, Phenomenex Gemini-NX 5 μm) eluting with a gradient of 5-50% Acetonitrile/Water + 0.1% NH_4OH over 15 minutes at 30 ml/min. Colorless foam. Yield **15** : 88% (50 mg, 0.154 mmol).

tR (UPLC): 0.56 min

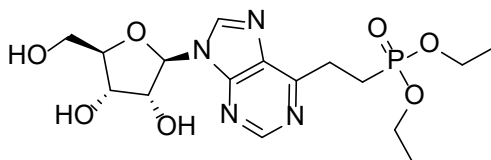
IR (neat) 3340, 2940, 1674, 1601, 1416, 1202, 1131 cm^{-1} .

^1H NMR (500 MHz, CD_3OD) δ 8.82 (s, 1H), 8.72 (s, 1H), 6.13 (d, $J = 5.7$ Hz, 1H), 4.76 (t, $J = 5.4$ Hz, 1H), 4.37 (dd, $J = 5.0, 3.6$ Hz, 1H), 4.17 (q, $J = 3.1$ Hz, 1H), 3.98 (t, $J = 6.6$ Hz, 2H), 3.90 (dd, $J = 12.3, 2.9$ Hz, 1H), 3.78 (dd, $J = 12.3, 3.2$ Hz, 1H), 3.51 (q, $J = 7.0$ Hz, 2H), 3.43 (t, $J = 6.6$ Hz, 2H), 1.09 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 161.3, 152.9, 151.7, 146.0, 134.8, 90.7, 87.6, 75.7, 72.2, 69.4, 67.2, 63.0, 34.4, 15.3.

HR-MS (ESI+): m/z calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$ 325.1506, found 325.1505.

Diethyl (2-(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)ethyl)phosphonate (16)



Synthesized according to the general procedure using ethyl (2-bromoethyl)(propyl)phosphinate (85 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **16** : 84% (61 mg, 0.147 mmol).

tR (UPLC): 0.59 min

IR (neat) 3322, 2932, 1676, 1599, 1399, 1205, 1138, 1051 cm^{-1} .

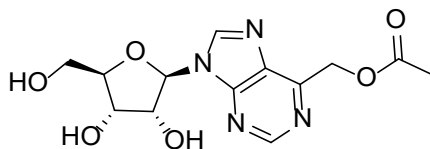
^1H NMR (500 MHz, CD_3OD) δ 8.87 (s, 1H), 8.76 (s, 1H), 6.14 (d, $J = 5.6$ Hz, 1H), 4.74 (t, $J = 5.2$ Hz, 1H), 4.37 (dd, $J = 5.0, 3.7$ Hz, 1H), 4.17 (q, $J = 3.1$ Hz, 1H), 4.10 (p, $J = 7.1$ Hz, 4H), 3.90 (dd, $J = 12.3, 2.9$ Hz, 1H), 3.78 (dd, $J = 12.3, 3.2$ Hz, 1H), 3.52 – 3.43 (m, 2H), 2.53 – 2.43 (m, 2H), 1.35 – 1.26 (m, 1H), 1.29 (t, $J = 7.1$ Hz, 6H).

^{13}C NMR (126 MHz, CD_3OD) δ 161.1 (dd, $J = 15.1, 2.7$ Hz), 152.6, 152.0, 134.0, 90.7, 87.6, 75.8, 72.2, 63.4 (d, $J = 6.6$ Hz), 63.0, 26.6 (d, $J = 4.2$ Hz), 24.3 (d, $J = 7.0$ Hz), 23.2 (d, $J = 6.9$ Hz), 16.6 (d, $J = 6.0$ Hz).

^{31}P NMR (202.45 MHz, CD_3OD) δ 31.2 ppm.

HR-MS (ESI+): m/z calcd. for $\text{C}_{16}\text{H}_{25}\text{N}_4\text{O}_7\text{P}$ $[\text{M}+\text{H}]^+$ 417.1534, found 417.1521.

(9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)methyl acetate (**17**)



Synthesized according to the general procedure using bromomethyl acetate (53.4 mg, 0.35 mmol, 2.0 equiv.). Colorless foam. Yield **17** : 37.1% (21 mg, 0.065 mmol).

tR (UPLC): 0.46 min

IR (neat) 3302, 2940, 1740, 1680, 1596, 1400, 1340, 1205, 1135, 1080 cm^{-1} .

^1H NMR (500 MHz, CD_3OD) δ 8.89 (s, 1H), 8.78 (s, 1H), 6.16 (d, $J = 5.5$ Hz, 1H), 5.59 (s, 2H), 4.74 (t, $J = 5.3$ Hz, 1H), 4.38 (dd, $J = 5.0, 3.8$ Hz, 1H), 4.17 (q, $J = 3.2$ Hz, 1H), 3.90 (dd, $J = 12.3, 2.9$ Hz, 2H), 3.78 (dd, $J = 12.3, 3.3$ Hz, 1H), 2.18 (s, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 172.4, 156.7, 152.9, 152.5, 146.8, 133.1, 90.7, 87.6, 75.8, 72.1, 63.2, 62.9, 20.6.

HR-MS (ESI+): m/z calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$ 325.1143, found 325.1131.

3. ¹H and ¹³C-NMR spectra

