

**Supporting information for “Efficient Synthesis of an Adenosine A2a Agonist:
Glycosylation of 2-Haloadenines and a *N*²-alkyl-6-chloroguanine”**

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Experimental Section

General Procedures:

All reactions were run under nitrogen unless otherwise specified. Heating was provided through a heating mantle and temperature was controlled by a thermocouple. Unless otherwise specified, concentration by rotary evaporation or distillation was carried out under house vacuum of 12-20 torr. NMR spectra were recorded in a 300 MHz spectrometer. Melting points were uncorrected. HPLC analysis was performed as follows. Columns: Zorbax XDB-C18, 250 mm x 4.0 mm, 5 micron; column temperature: 35 C; solvent A: 97.5% water, 2.5% MeCN, 0.05% TFA; solvent B: 60% water, 40% MeCN, 0.05% TFA; gradient: 0-100% B over 30 min; flow rate: 1.5 ml/min; run time: 40 min; detection wavelength: 254 nm; injection volume: 5-20 ul.

5-[(3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(methyloxy)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-2-ethyl-2*H*-tetrazole (6). To a mixture of 1.00 kg (4.13 mol) of tetrazole **5** and 370 g (2.68 mol) of K₂CO₃ in 7.00 L of acetone was added with vigorous stirring 430 mL (5.37 mol) of iodoethane at room temperature. The addition was accompanied by a mild exotherm of 2-3°C. The reaction mixture was heated to 45-50 °C for 12-14 h. Weight based assay analysis by HPLC showed a 2.4:1 ratio of **6** and **7**. After being cooled to room temperature, the mixture was treated with 10 L of cyclohexane and distilled *in vacuo* to remove 11.9 L of distillate. Additional cyclohexane (6.9 L) was added and the distillation was continued to remove 5.0 L of distillate. The resultant slurry was stirred

overnight at room temperature, filtered and washed with 2.0 L of cyclohexane. The filtrate was concentrated *in vacuo* to remove 7.6 L of distillate and diluted with 4.0 L of MeOH. Concentration was continued to remove 2.5 L of distillate and the resulting solution was used in next step. A 6.00 g portion of this solution was concentrated *in vacuo* to 769 mg of oil which was analyzed by weight based assay analysis by HPLC. The analysis indicated that there was 692 g (62%) of product as a 92:8 mixture of **6** and **7** in this methanolic solution. The ratio was confirmed by ¹H NMR. The small sample was chromatographed on silica gel. Elution with 50% EtOAc-hexanes afforded a pure sample of N2 ethyltetrazole **6** for analysis. The solid from the filtration provided pure N1 ethyltetrazole as a crystalline solid. ¹H NMR (CDCl₃) **6**: δ 1.31 (s, 3H), 1.47 (s, 3H), 1.55 (t, J = 7.5 Hz, 3H), 3.02 (s, 3H), 4.54 (q, J = 7.5 Hz, 2H), 4.64 (d, J = 7.0 Hz, 1H), 5.02 (s, 1H), 5.35 (s, 1H), 5.50 (d, J = 7.0 Hz, 1H). **7**: δ 1.32 (s, 3H), 1.49 (s, 3H), 1.55 (t, J = 7.5 Hz, 3H), 2.95 (s, 3H), 4.50 (q, J = 7.5 Hz, 2H), 4.72 (d, J = 6.0 Hz, 1H), 5.00 (s, 1H), 5.23 (s, 1H), 5.81 (d, J = 6.0 Hz, 1H). Anal. Calcd for C₁₁H₁₈N₄O₄: C, 48.88%; H, 6.71%; N, 20.73. Found: C, 48.98%; H, 6.69%; N, 20.78.

(2S,3R,4R,5R)-5-(2-Ethyl-2H-tetrazol-5-yl)tetrahydrofuran-2,3,4-triyl triacetate (3), as a mixture with 2R- or α-epimer. The 98:2 mixture of **6** and **7** in MeOH (equivalent of 681 g of **6**) as above was treated with 100 mL (1.41 mole) of AcCl in 5.8 L of MeOH. The mixture was concentrated *in vacuo* at 45-50°C to remove 2,2-dimethoxypropane and MeOH was replenished as needed over a period of 11 h. The mixture was diluted with 2.5 L of pyridine and MeOH was removed by atmospheric distillation to ≤1% w/w by GC. The resultant diol intermediate as a solution in pyridine

was diluted with 3.9 L of EtOAc, cooled to 5 °C, and treated with 950 ml (4.97 mole) of Ac₂O over 20 min while the temperature was maintained below 15 °C. After being stirred at room temperature overnight, the mixture was cooled to 5 °C and neutralized with 7.6 L of 8.5% H₂SO₄ while the temperature was maintained below 25 °C. The organic layer was washed with 0.7% H₂SO₄ (3 x 1L) until the aqueous layer was at pH < 4. The organic layer was then washed successively with 1.0 L of saturated KHCO₃ and 1.0 L of water. The solvent was removed *in vacuo* and the mixture was diluted with EtOAc and concentrated interactively until the water level was <250ppm. Weight based assay analysis by HPLC on the resulting oil indicated there was 806 g of the diacetate intermediate present. This crude diacetate was diluted with 4.6 L of EtOAc and treated with 308 mL (3.27 moles) of Ac₂O. After being heated to 60-65°C, the mixture was treated with 39.5 mL (741 mmol) of concentrated H₂SO₄ with vigorous stirring over 10 min. There was immediate formation of solids and a 3-5°C exotherm was observed. The reaction was stirred at 60-65°C for 4 h, cooled to 10-15°C and quenched with 3.8 L of saturated KHCO₃. The organic layer was separated and the solvent was evaporated *in vacuo*. The resultant oil was diluted with 2.84 L of anhydrous MeCN, providing 698 g (amount determined by weight based assay analysis through HPLC, 81% for three steps from **6**) of triacetate **3** as a solution in MeCN. HPLC analysis showed > 99:1 N2/N1 ratio. Analysis by both HPLC and ¹H NMR indicated 85:15 β/α ratio. A small sample was chromatographed on silica gel. Elution with 50% EtOAc-hexanes afforded an analytical sample. ¹H NMR (CDCl₃) β-epimer: δ 1.26 (t, J = 7.2 Hz, 3H), 1.62 (s, 3H), 1.65 (s, 3H), 1.68 (s, 3H), 4.65 (q, J = 7.2 Hz, 2H), 5.46 (d, J = 7.0 Hz, 1H), 5.57 (d, J =

4.8 Hz, 1H), 5.91 (dd, $J = 7.0, 4.8$ Hz, 1H), 5.27 (s, 1H). Anal. Calcd for $C_{13}H_{18}N_4O_7$: C, 45.62; H, 5.30; N, 16.37. Found: C, 45.55; H, 5.34; N, 16.18.

2-[(1*S*)-1-Benzyl-2-hydroxyethylamino]-1,9-dihydro-6*H*-purin-6-one (4e). A mixture of 78.0 g (360 mmol) of 2-bromohypoxanthine and 110 g (730 mmol) of L-phenylalaninol in 310 mL of 2-methoxyethanol stirred in a 2 L round bottom flask was heated and refluxed overnight. The mixture was cooled to ambient temperature resulting in the precipitation of solids. Additional precipitation was generated by addition of 780 mL of water. After being stirred for 1 h, the suspension was filtered and the filtering cake was washed with 195 mL of water and dried under vacuum to afford 76.7 g (74%) of 2-alkylaminopurine **4e** as a yellow solid. The product was a mixture of two tautomers by ^1H NMR and was contaminated by residual amount of 2-methoxyethanol. ^1H NMR (DMSO- d_6) major tautomer: δ 2.76-2.98 (m, 2H), 3.49 (m, 2H), 4.09 (br s, 1H), 5.04 (s, 1H), 6.36 (d, $J = 8.1$ Hz, 1H), 7.19-7.38 (m, 5H), 7.66 (s, 1H), 10.5 (s, 1H), 12.5 (s, 1H). MS (ES $^-$): m/z 284 [(M-1) $^-$], calcd for $C_{14}H_{15}N_5O_2$, 285].

(2*S*)-2-[(6-Chloro-9*H*-purin-2-yl)amino]-3-phenyl-1-propanol (4d). To a suspension of 12.1 g (42.0 mmol) of dihydroxy compound **4e** in 85 mL of DMF in a 2 L round bottom flask was successively added 16.0 mL (168 mmol) of Ac_2O , 0.1 g (catalytic) of 4-dimethylaminopyridine and 23.6 mL (168 mmol) of Et_3N at ambient temperature. The mixture was stirred at ambient temperature overnight. After being quenched with 365 mL of water and stirred for 2 h, the suspension was filtered and the filtering cake was washed with 240 mL of water and dried *in vacuo* at 70-100 $^\circ\text{C}$ to

afford 10.7 g (68%) of the diacetate intermediate as an off-white powder: MS (ES⁻): m/z 368 (M-1)⁻, 326 (M-1-Ac)⁻; ¹H NMR (DMSO-*d*₆) δ 1.96 (s, 3H), 2.80 (s, 3H), 2.90 (m, 2H), 4.16 (m, 2H), 4.37 (m, 1H), 6.70 (br s, 1H), 7.16-7.31 (m, 5H), 8.16 (s, 1H), 10.8 (s, 1H). To a suspension of 19.1 g (52.0 mmol) of the diacetate intermediate in 100 mL of MeCN in a 500 mL round bottom flask was successively added 17.1 g (104 mmol) of tetraethylammonium chloride, 6.86 mL (0.05 mol) of *N,N*-dimethylaniline and 28.9 mL of POCl₃ at ambient temperature. The mixture was heated at reflux for 70 min, stirred at ambient temperature overnight, and added dropwise to a solution of 170 g (2.10 mol) of NaOAc in 510 mL of water at 0°C. The resulting mixture was stirred at ambient temperature for 3 h, then extracted with EtOAc (2 x 150 mL). The organic extract was washed with saturated NaHCO₃ (4 x 100 mL) and brine (100 mL) and concentrated *in vacuo*. The resultant oil was dissolved in 150 mL MeOH, treated with 0.7 g (catalytic) of K₂CO₃ and stirred at ambient temperature overnight. The mixture was concentrated to an oil and dissolved in 280 mL of 35% EtOAc/H₂O. Concentrated HCl was added until the aqueous phase had been adjusted to pH 6-7 and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with 100 mL of brine and concentrated *in vacuo* to a total volume of 150 mL. After being cooled to 5°C and held overnight, the product was filtered, washed with 25 mL EtOAc, and dried under vacuum at 50°C to afford 9.4 g (60%) of chloropurine **4d** as a beige solid: IR 1643, 1515 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.78-2.98 (m, 2H), 3.20 (s, 1H), 3.39-3.58 (m, 2H), 4.16 (m, 1H), 4.81 (m, 1H), 7.10-7.38 (m, 5H), 8.09 (s, 1H), 12.9 (s, 1H); MS (ES⁻): m/z 302 [(M-1)⁻, calcd for C₁₄H₁₄ClN₅O, 303]. Anal. Calcd for C₁₄H₁₄ClN₅O: C, 55.36; H, 4.65; N, 23.06. Found: C, 55.59; H, 4.75; N, 23.01.

(2S)-2-[(6-Amino-9H-purin-2-yl)amino]-3-phenyl-1-propanol (4c). A 20 mL Teflon liner in a Parr pressure reactor was charged with 980 mg (3.23 mmol) of 6-chloropurine **4d** and 10 mL (70.0 mmol) of 7M NH₃ in methanol. The reactor was sealed and heated in an oven of 90-100 °C for 24 h. After being cooled to ambient temperature, the solvent and excess ammonia were evaporated under vacuum. The resultant oil was chromatographed on silica gel. Elution with 10-15% MeOH in CH₂Cl₂ afforded 777 mg (85%) of diaminopurine **4c** as an off-white crystalline solid: ¹H NMR (DMSO-*d*₆) δ 2.61-2.80 (m, 2H), 3.30-3.45 (m, 2H), 3.95 (m, 1H), 4.70 (s, 1H), 5.65 (d, J = 8.0 Hz), 6.41 (s, 2H), 6.99-7.26 (m, 5H), 7.52 (s, 1H), 12.1 (s, 1H). Anal. Calcd for C₁₄H₁₆N₆O: C, 59.14; H, 5.67; N, 29.56. Found: C, 59.29; H, 5.58; N, 29.59.

(2R,3R,4R,5R)-2-(6-Amino-2-fluoro-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (9a). To a mixture of 65.0 g (190 mmol) of triacetate **3** and 24.1 g (157 mmol) of 2-fluoroadenine **4a** in 372 mL of MeCN was successively added 58.5 mL (238 mmol) of *N,O*-bis(trimethylsilyl)acetamide (BSA) and 34.5 mL (190 mmol) of TMSOTf at ambient temperature. The yellow suspension was heated at reflux and for 5 h. After being cooled to ambient temperature, the reaction was quenched with 390 mL of 10% KHCO₃ and extracted with CH₂Cl₂ (3 x 300 mL). The combined organic layers were washed with 400 mL of 10% brine, filtered through a short pad of Celite and partially concentrated *in vacuo* to 300 mL. The resultant white slurry was treated with 500 mL of EtOH and concentrated to 350 mL. The product was filtered off and dried *in vacuo* at 50 °C to afford 51.9 g (76%) of 2-fluoroadenosine **9a** as a white

crystalline solid. Before the reaction was quenched, an aliquot was taken and diluted with H₂O-MeCN (1:9). This crude mixture was analyzed by HPLC-MS. The analysis indicated 90% of desired product **9a** along with 3.1% total of five isomeric impurities. The ratio of the desired 9 β product and isomers was thus 29:1. **9a**: mp 208-210 °C (dec); $[\alpha]_D^{20} -35^\circ$ (c 1.1, MeOH); IR 1763, 1673, 1610 cm⁻¹; ¹H NMR (CDCl₃) δ 1.69 (t, J = 7.5 Hz, 3H), 2.07 (s, 3H), 2.21 (s, 3H), 4.74 (q, J = 7.5 Hz, 2H), 5.58 (s, 1H), 5.78 (dd, J = 4.8, 2.4 Hz, 1H), 5.93 (br s, 2H), 6.16 (dd, J = 6.7, 4.8 Hz, 1H), 6.46 (d, J = 6.7 Hz, 1H), 8.39 (s, 1H). Anal. Calcd for C₁₆H₁₈FN₉O₅: C, 44.14; H, 4.17; N, 28.95. Found: C 44.09; H, 4.13; N, 28.78.

(2R,3R,4R,5R)-2-(6-Amino-2-chloro-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diol (9b). To a mixture of 688 g (2.01 mol) of triacetate **3** and 282 g (1.67 mol) of 2-chloroadenine **4b** in 2.43 L of MeCN was successively added 826 mL (3.42 mol) of BSA and 255 mL (1.41 mol) of TMSOTf at ambient temperature. The yellow suspension was heated to reflux and held for 5 h. After being cooled to ambient temperature, the reaction was quenched with 415 mL of 10% KHCO₃ and extracted with CH₂Cl₂ (1 x 1.5 L, 2 x 1 L). The combined organic layers were washed with 1 L of 10% brine, filtered through a short pad of Celite and partially concentrated *in vacuo* to 2.2 L. The mixture was treated with 2.9 L of MeOH and partially concentrated again to 2.6 L. The resultant 2-chloroadenosine diacetate solution was treated with 13.8 g (100 mmol) of K₂CO₃ and the mixture was stirred at ambient temperature for 2 days. The resultant slurry was treated with 585 mL of water, cooled in an ice bath for 2 h, and filtered. The

filter cake was washed with MeOH (3 x 140 mL) and dried *in vacuo* at 50 °C to afford 479 g (78%) of the 2,3-dihydroxy product **9b** as an off-white solid in the first crop. The filtrate was partially concentrated to about 1 L and the resultant solid was processed the same way as for the first crop to yield 30.8 g (5%) of product in the second crop. The overall yield for two steps from **4b** was 83% for the two crops combined. Before the glycosylation reaction was quenched, an aliquot was taken and diluted with H₂O-MeCN (1:9). This crude mixture was analyzed by HPLC-MS. The analysis indicated 91.4% of desired product along with 3.9% of five isomeric impurities. The ratio of the desired 9 β product and isomers was thus 23:1. **9b**: IR 1717, 1593 cm⁻¹; ¹H NMR (MeOH-*d*₄): δ 1.52 (t, J = 7.4 Hz, 3H), 4.66 (m, 1H), 4.76 (q, J = 7.4 Hz, 2H), 4.83 (m, 1H), 5.38 (d, J = 4.5 Hz, 1H), 6.24 (d, J = 5.8 Hz, 1H), 8.50 (s, 1H). Anal. Calcd for C₁₂H₁₄ClN₉O₃: C, 39.19; H, 3.84; N, 34.28. Found: C 39.16; H, 3.85; N, 33.99.

(2R,3R,4R,5R)-2-(6-Amino-2-[[[(1S)-2-hydroxy-1-(phenylmethyl)ethyl]amino]-9H-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (9c). To a mixture of 480 mg (1.41 mmol) of triacetate **3** and 334 mg (1.18 mmol) of diaminopurine **4c** in 7 mL of MeCN was successively added 0.59 mL (2.38 mmol) of BSA and 0.25 mL (1.41 mmol) of TMSOTf at ambient temperature. The homogeneous solution was heated to reflux overnight. The mixture was cooled to ambient temperature, quenched with 7 mL of 10% aqueous KHCO₃ and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with 10 mL of brine, dried over Na₂SO₄ and concentrated *in vacuo*. The resultant foam (998 mg) was chromatographed on silica gel. Elution with 4-6% MeOH in CH₂Cl₂ afforded 520 mg (78%) of 6-aminoguanosine **9c** as a yellow solid.

This product was contaminated with a small amount of impurities related to trimethylsilyl group by ^1H NMR and was used for the next step without further purification. Before the glycosylation reaction was quenched, an aliquot was taken and diluted with H_2O -MeCN (1:2). This crude mixture was analyzed by HPLC-MS. The analysis showed three isomeric impurities. The ratio of the desired 9β product and isomers was 9:1. 9β isomer: IR: 1699, 1597 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.52 (t, $J = 7.4$ Hz, 3H), 1.96 (s, 3H), 2.04 (s, 3H), 2.46 (s, 1H), 2.83 (m, 2H), 3.47 (m, 3H), 4.20 (m, 1H), 4.56 (q, $J = 7.4$ Hz, 2H), 5.40 (d, $J = 3.6$ Hz, 1H), 5.73 (m, 1H), 6.06 (m, 1H), 6.15 (m, 1H), 7.04-7.18 (m, 5H), 7.92 (s, 1H).

(2R,3R,4R,5R)-2-(6-Chloro-2-[[*(1S)*-2-hydroxy-1-(phenylmethyl)ethyl]amino]-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (9d). To a mixture of 6.76 g (19.7 mmol) of triacetate **3** and 5.00 g (16.5 mmol) of 6-chloropurine **4d** in 35 mL of MeCN in a 200 mL round bottom flask was successively added 9.76 mL (39.5 mmol) of BSA and 3.57 mL (19.7 mmol) of TMSOTf at ambient temperature. The homogeneous solution was heated to reflux and held for 4.5 h. The mixture was cooled to ambient temperature, quenched with 67 mL of water and stirred for 30 min. The mixture was then neutralized with 35 mL of 10% aqueous KHCO_3 and extracted with EtOAc (1 x 300 mL, 2 x 150 mL). The combined organic phases were washed with brine (67 mL) and concentrated *in vacuo* to 11.2 g of a yellow foam. Part of the crude product (1.04 g) was chromatographed on silica gel. Elution with EtOAc afforded 634 mg (71%) of 6-chloroguanosine **9d**. Before the glycosylation reaction was quenched, an aliquot was taken and diluted with H_2O -MeCN (1:9). This crude mixture was analyzed by HPLC-

MS. The analysis indicated 94.5% of desired product **9d** along with 0.8% of two isomeric impurities. The ratio of the desired 9 β product and isomers was thus 93:1. IR: 1612, 1591, 1525 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.67 (t, $J = 7.3$ Hz, 3H), 2.20 (s., 3H), 2.21 (s, 3H), 3.01 (m, 2H), 3.73 (m, 2H), 4.52 (br s, 1H), 4.69 (q, $J = 7.3$ Hz, 2H), 5.48 (m, 1H), 5.56 (d, $J = 4.5$ Hz, 1H), 6.10-6.28 (m, 2H), 6.30 (m, 1H), 7.19-7.38 (m, 5H), 8.09 (s, 1H). Anal. Calcd for $\text{C}_{25}\text{H}_{28}\text{ClN}_9\text{O}_6$: C, 51.24; H, 4.82; N, 21.51. Found: C, 51.17; H, 4.89; N, 21.30.

(2R,3R,4R,5R)-2-(2-Ethyl-2H-tetrazol-5-yl)-5-(2-([(1S)-2-hydroxy-1-(phenylmethyl)ethyl]amino)-6-oxo-1,6-dihydro-9H-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (9e). To a suspension of 1.00 g (3.51 mmol) of **4e** in 8 mL of MeCN was added 4.34 mL of BSA at room temperature. The resultant solution was heated to reflux and held for 1 h. After being cooled to room temperature, the mixture was treated with 1.56 g (17.5 mmol) of triacetate **3** as a solution in 4 mL of MeCN, followed by 0.96 mL (5.26 mmol) of TMSOTf in three portions over 2 h. The mixture was heated to reflux and held overnight. After cooling the mixture to room temperature, the solvent was evaporated *in vacuo* and the resultant residue was diluted with 20 mL of CH_2Cl_2 and poured into 30 mL of water. The organic layer was removed and the aqueous layer was back-extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with 15 mL of brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo* to give crude product containing 1.8:1 mixture of compound **9e** and an isomer by ^1H NMR. The crude product was chromatographed on silica gel. Elution with 5-15% MeOH in CH_2Cl_2 afforded 1.01 g (47%) of **9e** as a yellow solid. The structure assignment for **9e** was

accomplished by subsequent conversion of **9e** to target **1** through acetyl protection of the primary OH group, chlorination at C6 position, amino displacement of the chloride and *in situ* deacetylation at the 2' and 3' positions. The minor isomer was presumably the N7 isomer. **9e**: IR: 1612, 1592, 1525 cm^{-1} ; ^1H NMR ($\text{DMSO-}d_6$): δ 1.53 (t, $J = 7.3$ Hz, 3H), 2.10 (s., 3H), 2.19 (s, 3H), 2.89 (m, 2H), 3.46 (m, 2H), 4.14 (br s, 1H), 4.79 (q, $J = 7.3$ Hz, 2H), 5.04 (m, 1H), 5.57 (d, $J = 4.3$ Hz, 1H), 5.80 (s, 1H), 6.04 (m, 2H), 6.30 (m, 1H), 6.51 (d, $J = 6.5$ Hz, 1H), 7.22-7.38 (m, 5H), 8.35 (s, 1H). Anal. Calcd for $\text{C}_{25}\text{H}_{29}\text{N}_9\text{O}_7$: C, 52.91; H, 5.15; N, 22.21. Found: C, 52.77; H, 5.18; N, 22.06.

(2R,3R,4R,5R)-2-(2,6-Dichloro-9H-purin-9-yl)-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydrofuran-3,4-diyl diacetate (9f). To a mixture of 3.24 g (9.46 mmol) of triacetate **3** and 1.48 g (7.86 mmol) of 2,6-dichloropurine in 16 mL of MeCN was successively added 2.92 mL (11.8 mmol) of BSA and 1.72 mL (9.46 mmol) of TMSOTf at ambient temperature. The mixture was heated to reflux and held for 6 h. After being cooled to ambient temperature, the reaction was quenched with 10 mL of 10% KHCO_3 and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with 15 mL of 10% brine and concentrated *in vacuo* to 4.0 g of residue. The mixture was chromatographed on silica gel. Elution with 5-10% MeOH in CH_2Cl_2 afforded 2.88 g (78%) of **9f** as a yellow foam. Before the reaction was quenched, an aliquot was taken and diluted with H_2O -MeCN (1:9). This crude mixture was analyzed by HPLC-MS. The analysis showed product **9f** along with two isomeric impurities. The ratio of the desired β product and isomers was 14:1. ^1H NMR (CDCl_3) δ 1.70 (t, $J = 7.3$ Hz, 3H), 2.09 (s, 3H), 2.24 (s, 3H), 4.73 (q, $J = 7.3$ Hz, 2H), 5.63 (s, 1H), 5.77 (d, $J = 1.6$ Hz, 1H), 6.20(dd,

J = 6.7, 1.7 Hz, 1H), 6.56 (d, J = 6.7Hz, 1H), 6.17 (br s, 2H), 6.36 (d, J = 6.8 Hz, 1H), 8.29 (s, 1H). Anal. Calcd for C₁₆H₁₆Cl₂N₈O₅: C, 40.78; H, 3.42; Cl, 15.05; N, 23.78. Found: C, 40.65; H, 3.49; Cl, 14.98; N, 23.89.

(2R,3R,4S,5R)-2-(6-Amino-2-[[[(1S)-2-hydroxy-1-(phenylmethyl)ethyl]amino]-9H-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)tetrahydro-3,4-furandiol Maleate Salt (2).

From **9a**: A mixture of 23.1 g (53.1 mmol) of 2-fluoroadenosine **9a** and 14.7 g (106 mmol) of K₂CO₃ in 215 mL of MeOH was stirred at ambient temperature overnight. The resultant slurry was diluted with 300 mL of EtOAc and poured into 250 mL of water. The aqueous layer was extracted with EtOAc (4 x 200 mL). The combined organic layers were dried with anhydrous Na₂SO₄, concentrated *in vacuo* and dried at 60 °C to give 18.5 g (99%) of the 2,3-dihydroxy derivative of 2-fluoroadenosine **9b** as a white solid. A mixture of 18.2 g (52.0 mmol) of this solid and 16.5 g (109 mmol) L-phenylalaninol in 40 mL of DMSO and 120 mL of *i*-Pr₂NEt was heated at 100 °C overnight. The mixture was cooled to 40 °C, diluted with 200 mL of water and extracted with 20:1 EtOAc-MeOH (4 x 200 mL). The combined organic layers were washed with 200 mL of brine and concentrated *in vacuo*. The resultant crude product (39 g) was chromatographed on silica gel. Elution with 10% MeOH in CH₂Cl₂ afforded 21.2 g (85%) of **1** as a light yellow solid. A solution of 1.29 g (2.68 mmol) of free base **1** and 311 mg (2.68 mmol) of maleic acid in 16 mL of 95:5 EtOH-MeOH was stirred at ambient temperature for 4 h. The resultant white solid was filtered, washed with 3 mL of EtOH and dried *in vacuo* at 60 °C to provide 1.42 g (89%) of maleate salt **2** as a white crystalline solid: mp 169 °C (dec); [α]_D²⁵ -30.0° (c 1.0, MeOH); IR 1705, 1663, 1628,

1508 cm^{-1} ; ^1H NMR ($\text{MeOH-}d_4$) δ 1.63 (t, $J = 7.3$ Hz, 3H), 2.97 (m, 2H), 3.33 (m, 1H), 3.68 (m, 2H), 4.38 (m, 1H), 4.68 (m, 1H), 4.72 (q, $J = 7.3$ Hz, 2H), 4.83 (m, 1H), 5.36 (d, $J = 4.5$ Hz, 1H), 6.12 (d, $J = 5.8$ Hz, 1H), 6.30 (s, 2H), 7.13-7.34 (m, 5H), 8.27 (s, 1H).
Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{N}_{10}\text{O}_8$: C, 50.16; H, 5.07; N, 23.40. Found: C 50.04; H, 5.07; N, 23.33.

From 9b: A 2 L round bottom flask was charged with 855 g (5.65 mol) of L-phenylalaninol. The flask was heated to 90 °C. Stirring was slowly initiated as melting occurred. Once the solid was completely melted, 415 g (1.13 mol) of 2-chloroadenosine diol **9b** was added and the reaction mixture was stirred at 110°C for two days. The reaction mixture was cooled to 90°C and successively diluted with 415 mL of 2-methoxyethanol, 3.9 L of EtOAc (9.5 vol), 4.0 L of water and 2.8 L of 1N HCl. The layers were separated and the aqueous layer was extracted with 2 L of EtOAc. The aqueous layer was treated with 580 mL of 1N NaOH and extracted with EtOAc (2 x 2 L). The combined organic layers were washed with 600 mL of brine and concentrated *in vacuo* to 2.0 L at 50 °C. The mixture was treated with 4.0 L of EtOH and further concentrated to 2.0 L to provide free base **1** as a concentrated ethanol solution. This solution was diluted with 125 mL of MeOH and 375 mL of EtOH. This generated a 95:5 EtOH-MeOH mixture by ^1H NMR. To the mixture was added 187 g (1.24 mol) of maleic acid as a solution in 830 mL of 95:5 EtOH-MeOH. The mixture was stirred at room temperature overnight. The resultant solids were filtered, washed with 415 mL of EtOH

and dried *in vacuo* for at 55°C to give 398 g (59%) of product **2** as a white crystalline solid.

From 9c: A mixture of 475 mg of diacetate **9c** and 12 mg (0.084 mmol) anhydrous K₂CO₃ in 4 mL of methanol was stirred at ambient temperature overnight. The mixture was diluted with 8 mL of water and extracted with 5:95 MeOH-CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with 20 mL of 10% brine, dried with Na₂SO₄ and concentrated *in vacuo* to provide 378 mg (94% based on crude **1**) of free base **1** as a yellow solid. A solution of 360 mg (0.746 mmol) of free base **1** and 87 mg (0.746 mmol) of maleic acid in 5 mL of 95:5 EtOH-MeOH was stirred at ambient temperature for 6 h. The resultant white solid was filtered, washed with 2 x 2 mL of EtOH and dried *in vacuo* to provide 281 mg (63%) of product **2** as a white crystalline solid.

From 9d: A mixture of 624 mg (1.06 mmol) of 6-chloroguanosine diacetate **9d** and 14 mL (24 mmol) of 2M NH₃ in *i*-PrOH was sealed in a Teflon reaction vessel and heated at 100 °C for 4 days. After being cooled to ambient temperature, the mixture was concentrated *in vacuo*. The resultant oily mixture was dissolved in 30 mL of 10% MeOH-CH₂Cl₂ and washed with 10 mL water. The aqueous layer was back extracted with MeOH-CH₂Cl₂ (2 x 10 mL) and the combined organic layers were concentrated *in vacuo* to give 514 mg (quantitative based on crude product) of crude free base **1**. To 475 mg (0.984 mmol) of the above free base **1** in 5 mL of 95:5 EtOH-MeOH was added 125 mg (1.08 mmol) of maleic acid in 2 mL of the solvent at ambient temperature overnight.

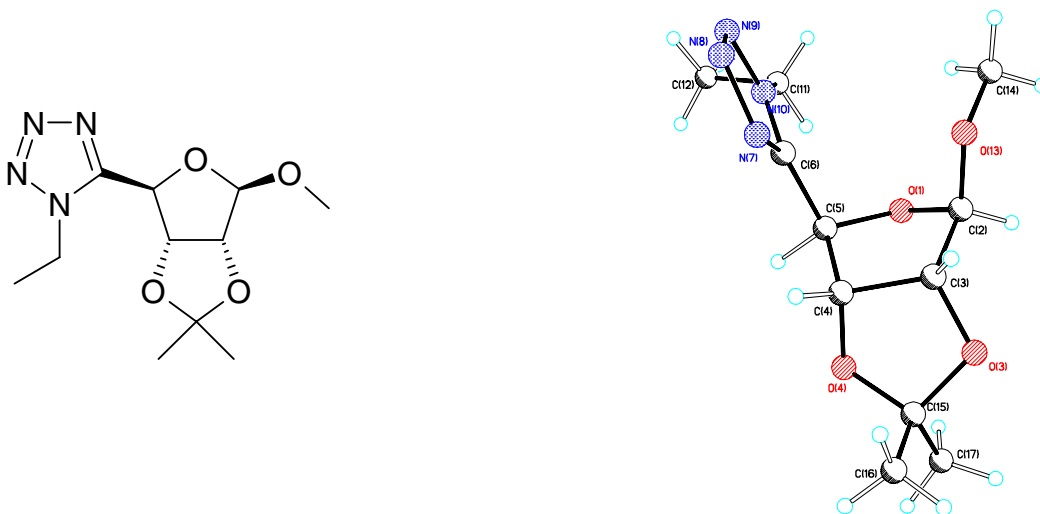
The resultant solids were filtered, washed with 2 x 1 mL of EtOH and dried *in vacuo* at 65 °C to provide 387 mg (66%) of **2** as white crystalline solid.

Crystallographic data for compound **7**

(note: separate numbering for figures and tables for the data provided here)

Structure:

5-[(3*aR*,4*R*,6*R*,6*aR*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-1-ethyl-1*H*-tetraazole



The absolute stereochemistry was not determined, the relative stereochemistry is as shown in the diagram.

The simulated powder pattern is shown in Figure 4.

Final R1 [$I > 2\sigma(I)$] = 7.00%. This figure represents a medium precision data set, and is indicative of a reliable structure.

Table 1. Crystal data and structure refinement 7.

X-Ray Number	X2911
Empirical formula	C11 H18 N4 O4
Formula weight	270.29
Temperature	293 (2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 6.1683(12) Å alpha = 90
deg.	b = 8.697(2) Å beta = 90
deg.	c = 25.428(5) Å gamma = 90
deg.	
Volume	1364.1(5) Å ³
Z	4
Density (calculated)	1.316 Mg/m ³
Absorption coefficient	0.853 mm ⁻¹
F(000)	576
Crystal size	0.8 x 0.4 x 0.4 mm
Theta range for data collection	3.48 to 57.08 deg.
Index ranges	0 ≤ h ≤ 6, 0 ≤ k ≤ 9, 1 ≤ l ≤ 27
Reflections collected	1030
Independent reflections	1030 [R(int) = 0.0000]
Absorption correction	None
Refinement method	Full-matrix least-squares on
F ²	

Data / restraints / parameters	1028 / 0 / 192
Goodness-of-fit on F^2	1.604
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0700, wR2 = 0.1840
R indices (all data)	R1 = 0.0768, wR2 = 0.1915
Absolute structure parameter	0.8(9)
Largest diff. peak and hole	0.230 and -0.246 e. \AA^{-3}

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **7**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	-1386(7)	-7481(5)	-1325(1)	58(1)
C(2)	-2008(11)	-6855(7)	-829(2)	55(2)
O(3)	-4222(9)	-8807(6)	-425(2)	79(2)
C(3)	-4317(11)	-7453(8)	-735(2)	62(2)
O(4)	-5066(10)	-9612(5)	-1237(1)	80(2)
C(4)	-5094(12)	-8020(7)	-1277(2)	60(2)
C(5)	-3295(10)	-7541(7)	-1645(2)	59(2)
C(6)	-3721(10)	-6044(8)	-1915(2)	58(2)
N(7)	-5419(9)	-5175(7)	-1863(2)	72(2)
N(8)	-5112(11)	-3927(7)	-2173(2)	79(2)
N(9)	-3270(10)	-4046(7)	-2415(2)	74(2)
N(10)	-2390(8)	-5380(6)	-2265(2)	62(1)
C(11)	-264(14)	-5855(10)	-2462(3)	82(2)
C(12)	-268(14)	-6127(11)	-3047(3)	93(2)
O(13)	-2075(8)	-5275(4)	-840(2)	62(1)
C(14)	-21(14)	-4603(9)	-910(3)	84(2)
C(15)	-5288(13)	-10020(8)	-697(2)	69(2)
C(16)	-7620(14)	-10103(10)	-541(3)	89(2)
C(17)	-4113(17)	-11466(9)	-603(3)	100(3)

Table 3. Bond lengths [Å] and angles [deg] for 7.

O(1)-C(2)	1.426(6)
O(1)-C(5)	1.433(7)
C(2)-O(13)	1.375(7)
C(2)-C(3)	1.535(10)
O(3)-C(3)	1.417(8)
O(3)-C(15)	1.423(9)
C(3)-C(4)	1.542(8)
O(4)-C(4)	1.388(7)
O(4)-C(15)	1.424(7)
C(4)-C(5)	1.509(9)
C(5)-C(6)	1.495(8)
C(6)-N(7)	1.299(8)
C(6)-N(10)	1.341(8)
N(7)-N(8)	1.354(8)
N(8)-N(9)	1.296(8)
N(9)-N(10)	1.337(7)
N(10)-C(11)	1.463(9)
C(11)-C(12)	1.508(10)
O(13)-C(14)	1.407(9)
C(15)-C(17)	1.471(11)
C(15)-C(16)	1.494(12)
C(2)-O(1)-C(5)	107.1(4)
O(13)-C(2)-O(1)	111.8(5)
O(13)-C(2)-C(3)	108.3(6)
O(1)-C(2)-C(3)	105.0(5)
C(3)-O(3)-C(15)	109.1(4)
O(3)-C(3)-C(2)	109.2(5)
O(3)-C(3)-C(4)	104.1(5)
C(2)-C(3)-C(4)	104.9(5)
C(4)-O(4)-C(15)	108.6(5)
O(4)-C(4)-C(5)	108.2(6)
O(4)-C(4)-C(3)	104.3(5)
C(5)-C(4)-C(3)	103.7(5)
O(1)-C(5)-C(6)	111.9(5)
O(1)-C(5)-C(4)	105.3(4)
C(6)-C(5)-C(4)	113.3(5)
N(7)-C(6)-N(10)	108.1(5)
N(7)-C(6)-C(5)	127.0(6)
N(10)-C(6)-C(5)	124.9(6)
C(6)-N(7)-N(8)	107.1(5)
N(9)-N(8)-N(7)	109.6(6)
N(8)-N(9)-N(10)	106.8(5)
N(9)-N(10)-C(6)	108.3(5)
N(9)-N(10)-C(11)	120.7(6)
C(6)-N(10)-C(11)	130.9(6)
N(10)-C(11)-C(12)	112.4(6)
C(2)-O(13)-C(14)	113.0(6)
O(3)-C(15)-O(4)	103.8(5)
O(3)-C(15)-C(17)	109.1(6)
O(4)-C(15)-C(17)	108.8(6)
O(3)-C(15)-C(16)	110.6(6)

O(4)-C(15)-C(16) 111.1(6)
 C(17)-C(15)-C(16) 113.0(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **7**.
 The anisotropic displacement factor exponent takes the form:
 $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	
U12						
O(1)	59(2)	69(3)	47(2)	-2(2)	-3(2)	
11(2)						
C(2)	72(4)	60(4)	34(3)	-4(2)	-5(3)	
10(3)						
O(3)	103(4)	79(3)	54(2)	15(2)	-13(2)	-
17(3)						
C(3)	75(4)	65(4)	44(3)	-2(3)	-4(3)	-
1(3)						
O(4)	124(4)	66(3)	49(2)	-2(2)	7(3)	-
14(3)						
C(4)	78(4)	65(4)	37(3)	-5(2)	-8(3)	-
7(4)						
C(5)	65(4)	62(3)	50(3)	-1(3)	-4(3)	
1(3)						
C(6)	58(3)	72(4)	42(3)	0(3)	-6(2)	
5(4)						
N(7)	69(4)	90(4)	57(3)	9(3)	-6(3)	
15(3)						
N(8)	77(4)	78(4)	80(4)	17(3)	-8(3)	
14(4)						
N(9)	76(4)	70(3)	76(3)	22(3)	-11(3)	
0(3)						
N(10)	57(3)	73(3)	55(3)	11(2)	-2(2)	
4(3)						
C(11)	71(4)	103(5)	72(4)	19(4)	12(3)	
3(5)						
C(12)	97(6)	119(6)	62(4)	-1(4)	3(4)	
1(6)						
O(13)	77(3)	53(2)	57(2)	-7(2)	0(2)	
1(2)						
C(14)	88(5)	80(5)	85(4)	-5(4)	2(4)	-
20(5)						
C(15)	84(4)	68(4)	56(3)	3(3)	3(3)	
4(4)						
C(16)	93(5)	94(6)	81(4)	6(4)	13(4)	-
9(5)						
C(17)	108(7)	84(5)	106(6)	20(4)	19(5)	
18(5)						

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) **7**.

	x	y	z	U(eq)
H(2)	-793 (85)	-7315 (62)	-587 (18)	44 (14)
H(3)	-5078 (119)	-6672 (78)	-544 (24)	70 (21)
H(4)	-6902 (89)	-7544 (54)	-1355 (19)	48 (14)
H(5)	-3584 (135)	-8447 (90)	-1954 (28)	100 (25)
H(11A)	173 (14)	-6793 (10)	-2284 (3)	99
H(11B)	792 (14)	-5066 (10)	-2378 (3)	99
H(12A)	1191 (19)	-6290 (72)	-3166 (5)	139
H(12B)	-868 (96)	-5247 (35)	-3222 (3)	139
H(12C)	-1128 (89)	-7018 (48)	-3126 (3)	139
H(14A)	-152 (18)	-3504 (9)	-897 (19)	127
H(14B)	556 (38)	-4905 (47)	-1245 (9)	127
H(14C)	936 (26)	-4942 (46)	-636 (12)	127
H(16A)	-7728 (15)	-10452 (61)	-184 (8)	134
H(16B)	-8366 (24)	-10809 (49)	-768 (14)	134
H(16C)	-8264 (27)	-9103 (16)	-572 (21)	134
H(17A)	-4962 (53)	-12314 (11)	-730 (25)	149
H(17B)	-3860 (104)	-11588 (42)	-233 (4)	149
H(17C)	-2751 (53)	-11440 (34)	-786 (23)	149

Figure 2: X-Ray Structure of **7**.

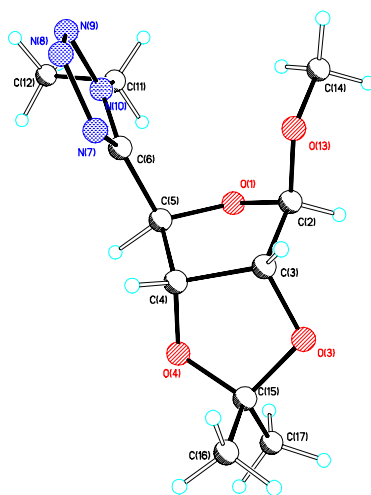
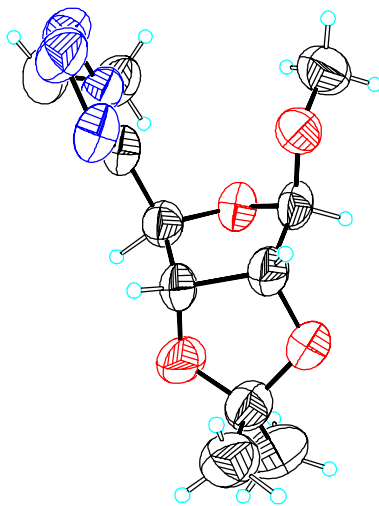
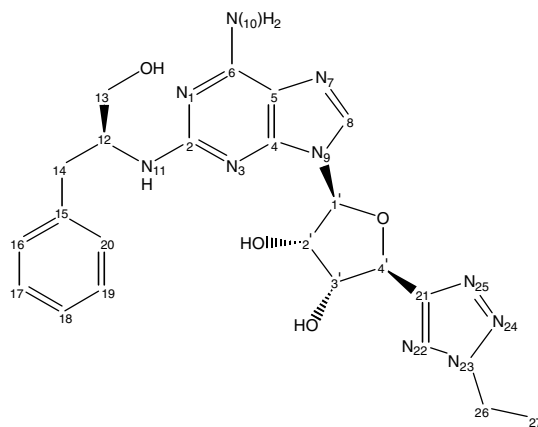


Figure 3: 50% Thermal Ellipsoid Plot for **7**.



Nuclear Magnetic Resonance Analysis for **2**



¹H NMR Data for Maleate 2 in DMSO-*d*₆

Chemical Shift (δ)*	Multiplicity**	No. of H Atoms	Assignment
8.136	s	1	8
7.319	AA'BB'C	2	16,20
7.270	AA'BB'C	2	17,19
7.174	AA'BB'C	1	18
6.189	s	2	Maleic acid
6.005	dd	1	1'
5.205	dd	1	4'
4.799	m	1	2'
4.708	q	2	26
4.614	m	1	3'
4.111	m	1	12
3.478	dd	2	13
2.865	m	2	14
2.506			dmsO-d5
1.520	t	3	27
0.000	s		TMS

* referenced to TMS at 0.000 ppm; H₂O appears at 3.476 ppm and DMSO-*d*₅ appears at 2.523 ppm

**s = singlet; d = doublet; dd = doublet of doublets of doublets; d_{AA'BB'C} = non first-order doublet; m = multiplet

¹³C NMR Data for 2 in DMSO-*d*₆

Chemical Shift (δ)*	Assignment
166.97	Maleic Acid
164.07	21
151.54	4
139.09	15
137.53	8
132.67	Maleic acid
129.36	16,18
128.20	17,19
126.00	18
87.43	1'
77.01	4'
73.83	3'
73.38	2'
61.73	13
54.39	12
48.20	25
39.86	dmsO-d6
36.56	14
14.05	20
0.00	TMS

* referenced to TMS at 0.00 ppm; DMSO-*d*₆ heptet is centered at 39.40 ppm

† chemical shift taken from HSQC spectrum

Data Interpretation

The NMR data for compound **2** was recorded in XXXXXX (GSK internal electronic notebook system). Full details of the analysis are included there. The critical NMR features that distinguish the molecule as drawn are described below.

The ^1H and ^{13}C NMR spectra are fully concordant with the structure shown. The broadening of the H8 peak is characteristic of this type of spin system as is the broadening of the H2' and H3' peaks in the THF ring. Note also that no ^{13}C signal was observed for C2. This is likely due to the same type of broadening that affected C8. This nucleus most likely has a very long relaxation time which would also greatly diminish its signal intensity.

The stereochemistry on this ring was confirmed by nOe measurements. The data confirmed that the protons on C1' and C4' are on the same side of the ring and that the protons on C2' and C3' are on the opposite side.

The linkage of the "phenylalanine" moiety through the nitrogen rather than the hydroxyl group is confirmed by ^{13}C chemical shift arguments.

The attachment of the THF ring to the hetero-bicyclic system was confirmed via ^1H - ^{13}C HMBC experiments. The chemical shifts of C4 and C5 are very distinct at 151.54 and 112.14ppm. A correlation from H1' to C4 and C8 show that N9 is the attachment point.