Supporting Information:

Optimization of Adenosine 5'-Carboxamide Derivatives as Adenosine Receptor Agonists Using Structure-Based Ligand Design and Fragment-Based Searching

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Contents: page

Table S1. List of 5’ substituents in high-affinity $hA_{2A}AR$ binding compounds found in ChEMBL database. Ki values of the highest affinity compound with this substituent are shown. Calculated ICM docking scores for adenosine 5’-substituted with this group are shown in the last column.

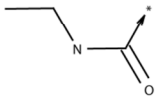
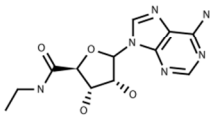
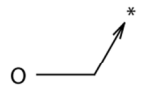
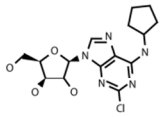
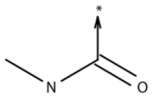
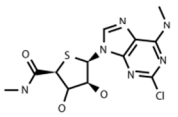
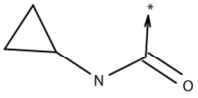
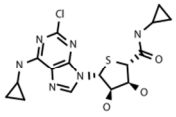
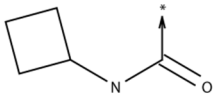
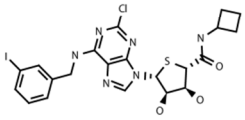
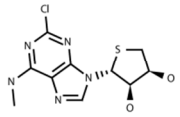
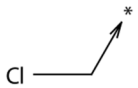
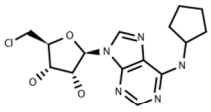
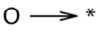
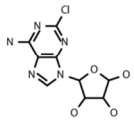
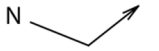
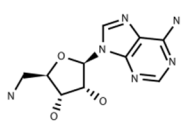
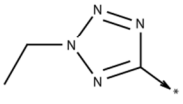
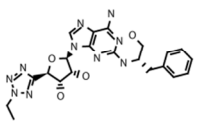
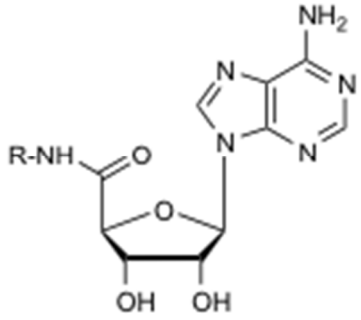
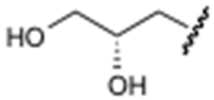
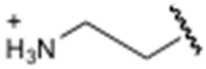
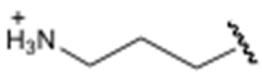
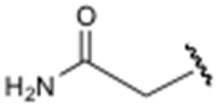
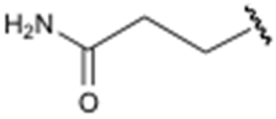
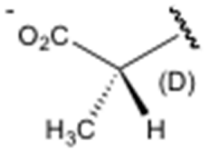
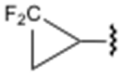
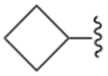
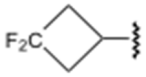
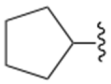
5’-substituent	Compound	CHEBI ID	*Ki* best, nM	ICM Score
		140422	1.	-46.
		152990	0.8	-32.
		304469	20.	-45.
		435266	202.	-46.
		435244	549.	-42.
		482271	45.	-31.
		598812	837.	-30.
		171264	120.	-29.
		205934	52.	-26.
		411899	1.	-34.

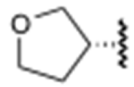
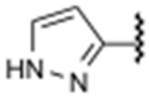
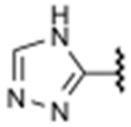
Table S2. Docking scores for the series of adenosine 5'-carboxamide derivatives in Table 1 in four different docking models.



1, 3–25

Compd	R =	Binding score of compounds (kJ/mol)			
		$hA_{2A}AR$-inactive (PDB:3EML)	$hA_{2A}AR$-activated (3EML-based model)	$hA_{2A}AR$-activated (PDB:3QAK)	hA_1AR-activated (3QAK-based model)
1	CH_3CH_2	-21.1*	-29.4	**-46.5**	**-48.8**
3	CH_2FCH_2	-21.6*	-31.	**-46.6**	**-48.3**
4	CHF_2CH_2	-25.6*	-27.2	**-48.8**	**-47.7**
5	CF_3CH_2	-20.6*	-25.6	**-46.4**	**-45.6**
6	CH_2ClCH_2	-14.7*	-28.4	**-46.6**	**-47.2**
7	$CH_3(CH_2)_2$	-20.7*	-28.	**-45.6**	**-47.3**
8	$F(CH_2)_3$	-18.9*	-26.5*	**-45.3**	**-45.8**
9	$HO\text{-}CH_2CH_2$	-18.7*	-29.6	**-51.7**	**-57.3**

10		-14.2*	-20.8*	**-54.7**	**-51.**
11		-17.2*	-25.6*	-36.	-34.2
12		-20.*	-21.2*	-33.3	-37.1
13		-15.3*	-41.1	**-51.5**	***-55.***
14		-22.34*	-27.4*	***-50.7***	***-47.2***
15		-12.7*	-28.6	-38.8	-37.2
16		-21.7*	-28.2	**-46.1**	**-45.**
17		-21.2*	-31.7	**-46.3**	**-46.3**
18		-18.4*	-19.6*	**-42.3**	**-45.6**
19		-18.9*	-18.8*	**-44.1**	**-44.0**
20		-18.6*	-20.5*	**-42.7**	**-45.3**
21		-19.5*	-30.6	**-46.8**	**-50.3**
22		-18.8*	-18.1*	**-42.**	**-43.7**

23		-19.9*	-19.7*	**-46.6**	**-42.6**
24		-22.9*	-32.7	**-46.8**	**-43.9**
25		-10.4*	-30.5	**-48.3**	***-49.***

* The binding pose not consistent with NECA pose ($RMSD_{NECA}$ >3. Å)

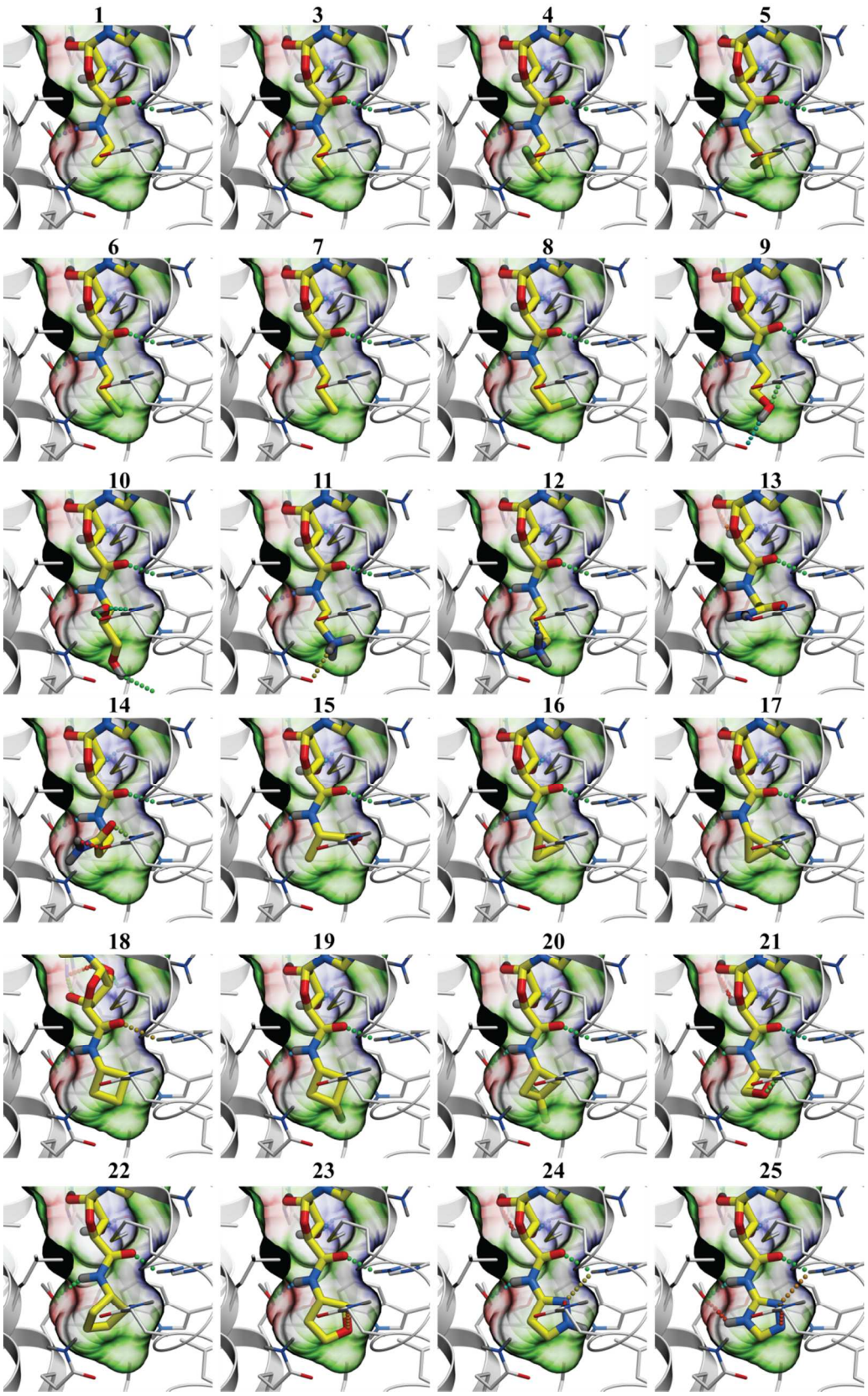


Figure S1. Predicted binding poses of all 5'-Carboxamide Derivatives from Table 1.

Synthetic procedures for the nucleoside derivatives and their characterization.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-(2-fluoroethyl)-3,4-dihydroxytetrahydrofuran-2-carboxamide (3)

Yield 23 mg (18%). ^{1}H NMR (DMSO-D_6, 400 MHz) d 9.32 (t, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 7.43 (br s, 2H), 5.95 (d, 1H), 5.78 (d, 1H), 5.56 (d, 1H), 4.59 (m, 1H), 4.47 (dm, J_{HF}=47 Hz, 2H), 4.35 (s, 1H), 4.14 (t, 1H), 3.53 (dm, J_{HF}=27 Hz, 2H). ^{19}F NMR (DMSO-D_6, 376 MHz) d -221.2 (tt, $^{2}J_{FH}$=47, $^{3}J_{FH}$=27 Hz). (HRMS: calculated for $C_{12}H_{16}N_6O_4F$ (M+H) 327.1217, found 327.1220.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-(2,2-difluoroethyl)-3,4-dihydroxytetrahydrofuran-2-carboxamide (4)

Yield 31 mg (23%). ^{1}H NMR (DMSO-D_6, 400 MHz) d 9.58 (t, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 7.46 (br s, 2H), 6.08 (tt, J_{HF}=56 Hz, 1H), 5.97 (d, 1H), 5.83 (d, 1H), 5.60 (d, 1H), 4.58 (m, 1H), 4.39 (s, 1H), 4.15 (t, 1H), 3.75-3.62 (m, 2H). ^{19}F NMR (DMSO-D_6, 376 MHz) d -121.5 (dt, $^{2}J_{FH}$=56, $^{3}J_{FH}$=16s Hz). HRMS: calculated for $C_{12}H_{15}N_6O_4F_2$ (M+H) 345.1123, found 345.1118.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxy-*N*-(2,2,2-trifluoroethyl)tetrahydrofuran-2-carboxamide (5)

Yield 38 mg (26%). ^{1}H NMR (DMSO-D_6, 400 MHz) d 10.0 (br t, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 7.50 (br s, 2H), 5.97 (d, 1H), 5.89 (d, 1H), 5.63 (d, 1H), 4.55 (m, 1H), 4.43 (s, 1H), 4.24-4.03 (m, 3H). ^{19}F NMR (DMSO-D_6, 376 MHz) d -70.3 (t, $^{3}J_{FH}$=10 Hz). Lit.[38] reported: ^{1}H NMR (DMSO-D_6) d 10.0 (t, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 7.47 (s, 2H), 5.97 (d, 1H), 5.87 (d, 1H), 5.60 (d, 1H), 4.53 (dd, 1H), 4.42 (s, 1H), 4.12 (m, 3H).

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxy-*N*-propyltetrahydrofuran-2-carboxamide (7)

EDC (24.05 mg, 0.12 mmol) was added to a solution of compound **26** (20.15 mg, 0.06 mmol) in pyridine (0.8 mL), in the presence of propylamine hydrochloride (7.19 mg, 0.07 mmol) and stirred at room temperature overnight. Solvent was evaporated under vacuum, and the residue was roughly purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 8:1). The resulting product was dissolved in dioxane (1.5 mL) and 1 N HCl (1.5 mL) and heated at 50 ^{o}C for 5 h. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 8:1) to give compound **7** (14.3 mg, 71%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) d 8.31 (s, 1H), 8.25 (s, 1H), 6.03 (d, *J* = 7.6 Hz, 1H), 4.79-4.76 (m, 1H), 4.95 (d, *J* = 1.6 Hz, 1H), 4.33-4.32 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 1H), 1.65-1.59 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{13}H_{19}N_6O_4$ $(M + H)^+$: 323.1468; found 323.1467.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-(3-fluoropropyl)-3,4-dihydroxytetrahydrofuran-2-carboxamide (8)

Yield 36 mg (26%). ^{1}H NMR (DMSO-D_6, 400 MHz) d 9.08 (t, 1H), 8.37 (s, 1H), 8.18 (s, 1H), 7.43 (br s, 2H), 5.94 (d, 1H), 5.76 (d, 1H), 5.55 (d, 1H), 4.61 (m, 1H), 4.56 (dt, J_{HF}=47 Hz, 2H), 4.32 (s, 1H), 4.14 (t, 1H), 3.18-3.12 (m, 2H), 1.85 (dm, J_{HF}=27 Hz, 2H). ^{19}F NMR (DMSO-D_6, 376 MHz) d -

218.7 (tt, $^{2}J_{FH}$=47, $^{3}J_{FH}$=27 Hz). HRMS: calculated for $C_{13}H_{18}N_6O_4F$ (M+H) 341.1374, found 341.1384.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-((S)-2,3-dihydroxypropyl)-3,4-dihydroxytetrahydrofuran-2-carboxamide (10)

1 N HCl (0.6 mL) was added to a solution of compound **32** (6.32 mg, 0.016 mmol) in dioxane (0.8 mL) and stirred at room temperature overnight. Solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 3:1) to give compound **10** (3.5 mg, 61%) as a solid. ^{1}H NMR (CD_3OD, 400 MHz) d 8.35 (s, 1H), 8.31 (s, 1H), 6.04 (d, *J* = 7.6 Hz, 1H), 4.81-4.80 (m, 1H), 4.52 (d, *J* = 1.2 Hz, 1H), 4.35 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 1H), 3.79-3.74 (m,1H), 3.79-3.74 (m, 1H), 3.57-3.53 (m, 3H), 3.39-3.35 (m, 1H). HRMS calculated for $C_{13}H_{19}N_6O_6$ $(M + H)^+$: 355.1366; found 355.1357.

(2*S*,3*S*,4*R*,5*R*)-*N*-(2-Amino-2-oxoethyl)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxy tetrahydrofuran-2-carboxamide (13)

Compound **13** (74%) was prepared from compound **13a** following the same method for compound **10**. ^{1}H NMR (DMSO-D_6, 400 MHz) d 9.03 (t, J = 6.0 Hz, 1H), 8.43 (s, 1H), 8.16 (s, 1H), 7.39 (s, 3H), 7.07 (s, 1H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.76 (d, *J* = 4.4 Hz, 1H), 5.57 (d, *J* = 6.4 Hz, 1H), 4.67-4.63 (m, 1H), 4.38 (s, 1H), 4.20 (t, *J* = 4.0 Hz, 1H), 3.76 (t, *J* = 6.8 Hz, 1H), 3.17 (d, *J* = 5.2 Hz, 1H). HRMS calculated for $C_{12}H_{16}N_7O_5$ $(M + H)^+$: 338.1213; found 338.1209.

(2*S*,3*S*,4*R*,5*R*)-*N*-(3-Amino-3-oxopropyl)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxy tetrahydrofuran-2-carboxamide (14)

Compound **14** (71%) was prepared from compound **34** following the same method for compound **10**. ^{1}H NMR (DMSO-D_6, 400 MHz) d 9.11 (t, J = 6.0 Hz, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.40 (s, 2H), 7.37 (s, 1H), 6.80 (s, 1H), 5.94 (d, *J* = 8.0 Hz, 1H), 4.56-4.53 (m, 1H), 4.30 (s, 1H), 4.13 (d, *J* = 3.6 Hz, 1H), 3.46-3.45 (m, 2H), 3.41-3.38 (m, 2H), 2.29 (t, *J* = 6.8 Hz, 2H). HRMS calculated for $C_{13}H_{18}N_7O_5$ $(M + H)^+$: 352.1369; found 352.1388.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-(D-alanyl)-3,4-dihydroxytetrahydrofuran-2-carboxamide (15)

Yield 48 mg (34%). ^{1}H NMR (DMSO-D_6, 400 MHz) d 9.05 (d, 1H), 8.51 (s, 1H), 8.22 (s, 1H), 7.90 (br s, 2H), 6.00 (d, 1H), 5.62 (br s, 2H), 4.60 (m, 1H), 4.40 (s, 1H), 4.31 (m, 1H), 4.15 (d, 1H), 1.35 (d, 6H). HRMS: calculated for $C_{13}H_{15}N_6O_6$ (M+H) 351.1053, found 351.1051.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-(2,2-difluorocyclopropyl)-3,4-dihydroxy tetrahydrofuran-2-carboxamide (17)

DIPEA (10 µL, 0.06 mmol) was added to a solution of compound **26** (13.33 mg, 0.04 mmol) in dry DMF (0.8 mL) in the presence of 2,2-difluorocyclopropylamine hydrochloride (6.45 mg, 0.05 mmol) and COMU (26.66 mg, 0.06 mmol) and stirred at room temperature overnight. Solvent was evaporated under vacuum and the residue was roughly purified on flash silica gel column chromatography. The resulting product was dissolved in dioxane (1 mL) and 1 N HCl (1 mL) was

added into it and stirred overnight at room temperature. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 6:1) to give compound **17** (10.0 mg, 68%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) d 8.33 (d, *J* = 12.4 Hz, 1H), 8.23 (s, 1H), 6.07-6.04 (m, 1H), 4.76-4.71 (m, 2H), 4.70 (s, 1H), 4.54 (t, *J* = 1.2 Hz, 1H), 2.00-1.90 (m, 1H), 1.60-1.52 (m, 1H). HRMS calculated for $C_{13}H_{15}N_6O_4F_2$ (M + H) $^+$: 357.1123; found 357.1114.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-cyclobutyl-3,4-dihydroxy tetrahydro furan-2-carboxamide (18)

Compound **18** (67%) was prepared from compound **37** following the same method for compound **10**. ^{1}H NMR (CD_3OD, 400 MHz) d 8.33 (s, 1H), 8.28 (s, 1H), 6.03 (d, *J* = 7.6 Hz, 1H), 4.80-4.76 (m, 1H), 4.46-4.45 (m, 2H), 4.32 (d, *J* = 1.2 Hz, 1H), 2.43-2.30 (m, 2H), 2.16-2.02 (m, 2H), 1.86-1.82 (m, 2H). HRMS calculated for $C_{14}H_{19}N_6O_4$ (M + H) $^+$: 335.1454; found 335.1458.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-(3-fluorocyclobutyl)-3,4-dihydroxy tetrahydrofuran-2-carboxamide (19)

Compound **19** (72%) was prepared from compound **38** following the same method for compound **10**. ^{1}H NMR (CD_3OD, 400 MHz) d 8.40 (s, 1H), 8.26 (s, 1H), 6.07 (d, *J* = 7.2 Hz, 1H), 5.29-5.26 (m, 1H), 4.80-4.77 (m, 1H), 4.59-4.58 (m, 1H), 4.47 (d, *J* = 1.6 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 1H), 2.65-2.51 (m, 2H), 2.46-2.40 (m, 2H). HRMS calculated for $C_{14}H_{18}N_6O_4F$ (M + H) $^+$: 353.1374; found 353.1368.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-(3,3-difluorocyclobutyl)-3,4-dihydroxy tetrahydrofuran-2-carboxamide (20)

Compound **20** (77%) was prepared from compound **39** following the same method for compound **10**. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.34 (s, 1H), 8.26 (s, 1H), 6.05 (d, *J* = 7.2 Hz, 1H), 4.81-4.78 (m, 1H), 4.49 (d, *J* = 1.6 Hz, 1H), 4.37 (d, *J* = 1.6 Hz, 1H), 4.33-4.28 (m, 1H), 3.06-2.96 (m, 2H), 2.76-2.62 (m, 2H). HRMS calculated for $C_{14}H_{17}N_6O_4F_2$ (M + H) $^+$: 371.1279; found 371.1295.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxy-*N*-(oxetan-3-yl)tetrahydro furan-2-carboxamide (21)

EDC (11.1 mg, 0.057 mmol) was added to a suspension of adenosine 5'-carboxylic acid **45** (8.14 mg, 0.028 mmol) and oxetanamine (2.11 mg, 0.034 mmol) in pyridine (0.8 mL) and stirred overnight at room temperature. The solvent was evaporated, and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 10:1) to give compound **21** (6.7 mg, 69%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.41 (s, 1H), 8.31 (s, 1H), 6.05 (d, *J* = 7.6 Hz, 1H), 5.03-4.95 (m, 2H), 4.84-4.78 (m, 2H), 4.72 (t, *J* = 6.4 Hz, 1H), 4.63 (t, *J* = 6.4 Hz, 1H), 4.51 (d, *J* = 1.2 Hz, 1H), 4.33 (dd, J_1 = 3.6 Hz, J_2 = 1.2 Hz, 1H). HRMS calculated for $C_{13}H_{17}N_6O_5$ (M + H) $^+$: 337.1260; found 337.1264.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-*N*-cyclopentyl-3,4-dihydroxytetrahydro furan-2-carboxamide (22)

Compound **22** (79%) was prepared from compound **41** following the same method for compound **10**. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.34 (s, 1H), 8.21 (s, 1H), 6.04 (d, *J* = 7.6 Hz, 1H), 4.80-4.77 (m, 1H), 4.49 (s, 1H), 4.47 (d, *J* = 1.6 Hz, 1H), 4.34-4.32 (m, 1H), 2.09-1.98 (m, 2H), 1.82-1.69 (m, 2H), 1.67-1.50 (m, 4H). HRMS calculated for $C_{15}H_{21}N_6O_4$ (M + H) $^+$: 349.1624; found 349.1629.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxy-*N*-((*R*)-tetrahydrofuran-3-yl)tetrahydrofuran-2-carboxamide (23)

Compound **23** (71%) was prepared from **26** following the same method for compound **17**. ^{1}H NMR (DMSO-D_6, 400 MHz) δ 8.96 (d, *J* = 7.2 Hz, 1H), 8.39 (s, 1H), 8.20 (s, 1H), 7.44 (br s, 2H), 5.95 (d, *J* = 7.6 Hz, 1H), 5.78 (br s, 1H), 5.56 (br s, 1H), 4.62-4.59 (m, 1H), 4.40-4.37 (m, 1H), 4.34 (d, *J* =1.2 Hz, 1H), 4.14 (d, *J* = 4.4 Hz, 1H), 3.86-3.69 (m, 3H), 3.52 (dd, J_1 = 5.6 Hz, J_2 = 3.6 Hz, 1H), 2.21-2.16 (m, 1H), 1.85-1.81 (m, 1H). HRMS calculated for $C_{14}H_{19}N_6O_5$ (M + H) $^+$: 351.1417; found 351.1409.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxy-*N*-(1*H*-pyrazol-3-yl)tetra hydrofuran-2-carboxamide (24)

Compound **24** (66%) was prepared from compound **43** following the same method for compound **10**.^{1}H NMR (CD_3OD, 400 MHz) δ 8.57 (s, 1H), 8.29 (s, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 6.69 (s, 1H), 6.08 (d, *J* = 7.6 Hz, 1H), 4.80-4.77 (m, 1H), 4.67 (s, 1H), 4.42 (d, *J* = 4.4 Hz, 1H). HRMS calculated for $C_{13}H_{15}N_8O_4$ (M + H) $^+$: 347.1216; found 347.1216.

(2*S*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxy-*N*-(4*H*-1,2,4-triazol-3-yl)tetrahydrofuran-2-carboxamide (25)

A solution of compound **44** (2.28 mg, 0.005 mmol) in dioxane (0.8 mL) and 1 N HCl (0.5 mL) was stirred for 2 h at room temperature. Solvent was evaporated, and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 4:1) to give compound **25** (1.4 mg, 72%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.7 (s, 1H), 8.29 (s, 2H), 6.14 (d, *J* = 8.0 Hz, 1H), 4.75-4.72 (m, 2H), 4.44 (d, *J* = 4.4 Hz, 1H). HRMS calculated for $C_{12}H_{14}N_9O_4$ (M + H) $^+$: 348.1169; found 348.1177.

(3a*S*,4*S*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-*N*-((*S*)-2,3-dihydroxypropyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (32)

EDC (18.38 mg, 0.095 mmol) was added to a solution of compound **26** (15.4 mg, 0.047 mmol) in pyridine (1 mL), in the presence of (*S*)-(-)-3-amino-1,2-propanediol and stirred overnight at room temperature. Solvent was evaporated under vacuum, and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 8:1) to give the desired compound **32** (14.5 mg, 77%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.26 (s, 1H), 8.21 (s, 1H), 6.35 (d, *J* = 2.0 Hz, 1H), 5.56 (dd, J_1 = 4.0 Hz, J_2 = 2 Hz, 1H), 5.45 (dd, J_1 = 4.0 Hz, J_2 = 2 Hz, 1H), 4.70 (d, *J* = 2.0 Hz, 1H), 3.38-3.37 (m, 1H), 3.30-3.18 (m, 3H), 2.69-2.64 (m, 1H), 1.61 (s, 3H), 1.41 (s, 3H). HRMS calculated for $C_{16}H_{23}N_6O_6$ (M + H) $^+$: 395.1679; found 395.1680.

(3a*S*,4*S*,6*R*,6a*R*)-N-(2-Amino-2-oxoethyl)-6-(6-amino-9*H*-purin-9-yl)-2,2-dimethyl tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (33)

DIPEA (15 µL, 0.06 mmol) was added to a solution of **26** (13.34 mg, 0.04 mmol) in dry DMF (1 mL) in the presence of glycinamide hydrochloride (5.51 mg, 0.05 mmol) and COMU (26.68 mg, 0.06 mmol), and the mixture was stirred at room temperature overnight. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 6:1) to give compound **33** (12.8 mg, 82%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.27 (s, 1H), 8.17 (s, 1H), 6.37 (d, J = 1.6 Hz, 1H), 5.60 (dd, J_1 = 4.4 Hz, J_2 = 2 Hz, 1H), 5.45 (dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, 1H), 4.78 (d, J = 2.0 Hz, 1H), 3.64 (d, J = 17.2 Hz, 1H), 3.23 (d, J = 17.2 Hz, 1H), 1.61 (s, 3H), 1.41 (s, 3H). HRMS calculated for $C_{15}H_{20}N_7O_5$ $(M + H)^+$: 378.1526; found 378.1518.

(3a*S*,4*S*,6*R*,6a*R*)-*N*-(3-Amino-3-oxopropyl)-6-(6-amino-9*H*-purin-9-yl)-2,2-dimethyl tetrahydrofuro[3,4-d][1,3]dioxole-4-carboxamide (34)

Compound **34** (80%) was prepared from **26** following the same method for compound **33**. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.25 (s, 1H), 8.20 (s, 1H), 6.36 (d, J = 1.2 Hz, 1H), 5.60 (dd, J_1 = 4.0 Hz, J_2 = 2.0 Hz, 1H), 5.45 (dd, J_1 = 4.0 Hz, J_2 = 2 Hz, 1H), 4.67 (d, J = 1.6 Hz, 1H), 3.15-3.01 (m, 2H), 2.16-2.08 (m, 1H), 1.87-1.80 (m, 1H), 1.60 (s, 3H), 1.41 (s, 3H). HRMS calculated for $C_{16}H_{22}N_7O_5$ $(M + H)^+$: 392.1682; found 392.1673.

(3a*S*,4*S*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-*N*-cyclobutyl-2,2-dimethyl tetrahydrofuro [3,4-*d*][1,3]dioxole-4-carboxamide (37)

Compound **37** (78%) was prepared from **26** following the same method for compound **33**. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.25 (s, 1H), 8.15 (s, 1H), 6.37 (s, 1H), 5.64 (dd, J_1 = 4.4 Hz, J_2 = 1.2 Hz, 1H), 5.53-5.50 (m, 1H), 4.63 (d, J = 1.6 Hz, 1H), 3.95-3.91 (m, 1H), 2.18-2.13 (m, 2H), 1.95-1.63 (m, 2H), 1.58 (s, 3H), 1.57-1.49 (m, 2H), 1.41 (s, 3H). HRMS calculated for $C_{17}H_{23}N_6O_4$ $(M + H)^+$: 375.1703; found 375.1711.

(3a*S*,4*S*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-*N*-(3-fluorocyclobutyl)-2,2-dimethyl tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (38)

Compound **38** (84%) was prepared from **26** following the same method for compound **33**. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.25 (s, 1H), 8.15 (s, 1H), 6.38 (s, 1H), 5.68 (d, J = 4.4 Hz, 1H), 5.55 (d, J = 6.4 Hz, 1H), 4.65 (d, J = 1.6 Hz, 1H), 4.13-4.10 (m, 1H), 3.03-2.99 (m, 1H), 2.37-2.26 (m, 2H), 2.21-1.96 (m, 2H), 1.59 (s, 3H), 1.42 (s, 3H). HRMS calculated for $C_{17}H_{22}N_6O_4F$ $(M + H)^+$: 393.1687; found 393.1691.

(3a*S*,4*S*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyl-*N*-(oxetan-3-yl)tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (40)

EDC (24 mg, 0.12 mmol) was added to a solution of **26** (20.15 mg, 0.06 mmol) in pyridine (1 mL) and stirred at room temperature for overnight. Solvent was evaporated, and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 20:1) to give compound **40** (12.8 mg, 85%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.25 (s, 1H), 8.14 (s, 1H), 6.39 (s, 1H), 5.68 (d, J_1= 4.4 Hz, J_2= 1.6 Hz,

1H), 5.53-5.50 (m, 1H), 4.68 (d, *J* = 1.6 Hz, 1H), 4.67-4.60 (m, 2H), 4.37-4.29 (m, 2H), 3.69-3.66 (m, 1H), 1.59 (s, 3H), 1.42 (s, 3H). HRMS calculated for $C_{16}H_{21}N_6O_5$ (M + H) $^+$: 377.1573; found 377.1569. The deprotection of this compound failed due to decomposition.

(3a*S*,4*S*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-*N*-cyclopentyl-2,2-dimethyl tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (41)

Compound **40** (81%) was prepared from **26** following the same method for compound **33**.^{1}H NMR (CD_3OD, 400 MHz) δ 8.25 (s, 1H), 8.20 (s, 1H), 6.36 (s, 1H), 5.65 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H), 5.52 (d, *J* = 6.4 Hz, 1H), 4.67 (d, *J* = 2.0 Hz, 1H), 4.02-3.99 (m, 1H), 3.68-3.66 (m, 1H), 3.58-3.49 (m, 2H), 3.41-3.40 (m, 1H), 1.74-1.69 (m, 1H), 1.59 (s, 3H), 1.42 (s, 3H), 0.96-0.93 (m, 1H). HRMS calculated for $C_{17}H_{23}N_6O_5$ (M + H) $^+$: 391.1730; found 391.1744.

(3a*S*,4*S*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyl-*N*-(1*H*-pyrazol-3-yl) tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (43)

EDC (13.8 mg, 0.03 mmol) was added to a solution of **26** (20.15 mg, 0.06 mmol) in pyridine (1 mL) in the presence of 1*H*-pyrazol-3-amine (3 mg. 0.04 mmol) and stirred at room temperature for 4 h. Solvent was evaporated, and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 20:1) to give compound **42** (12.0 mg, 87%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.28 (s, 1H), 8.16 (s, 1H), 7.46 (s, 1H), 6.41-6.39 (m, 2H), 5.50 (s, 1H), 5.43 (d, *J* = 1.6 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 1.64 (s, 3H), 1.42 (s, 3H). HRMS calculated for $C_{16}H_{19}N_8O_4$ (M + H) $^+$: 387.1529; found 387.1524.

(3a*S*,4*S*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyl-N-(4*H*-1,2,4-triazol-3-yl)tetrahydrofuro[3,4-*d*][1,3]dioxole-4-carboxamide (44)

Compound **43** (15%) was prepared from **26** following the same method for compound **42**. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.28 (s, 2H), 8.16 (s, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 5.64 (d, *J* = 5.2 Hz, 1H), 5.40 (dd, J_1 = 4.0 Hz, J_2 = 2.0 Hz, 1H), 4.92 (s, 1H), 1.64 (s, 3H), 1.43 (s, 3H). HRMS calculated for $C_{15}H_{18}N_9O_4$ (M + H) $^+$: 388.1482; found 388.1476.