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Note

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Visible-Light-Mediated Mono-Selective Ortho C-H Arylation of 6-Arylpurine Nucleosides with Diazonium Salts

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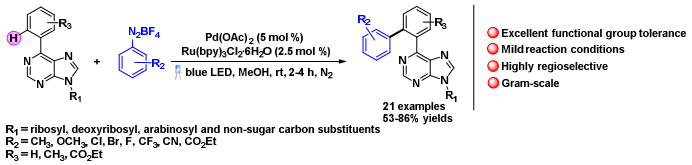


ABSTRACT

A combined palladium- and photoredox-catalyzed mono-selective arylation of 6-arylpurine nucleosides has been developed by employing purine as a directing group *via* the photoredox reaction and many functional groups are well tolerated in this direct C–H arylation condition. Various of functionalized purines (nucleosides) which are potentially of great importance in medicinal chemistry could be obtained under visible light irradiation at room temperature within 4 hours.

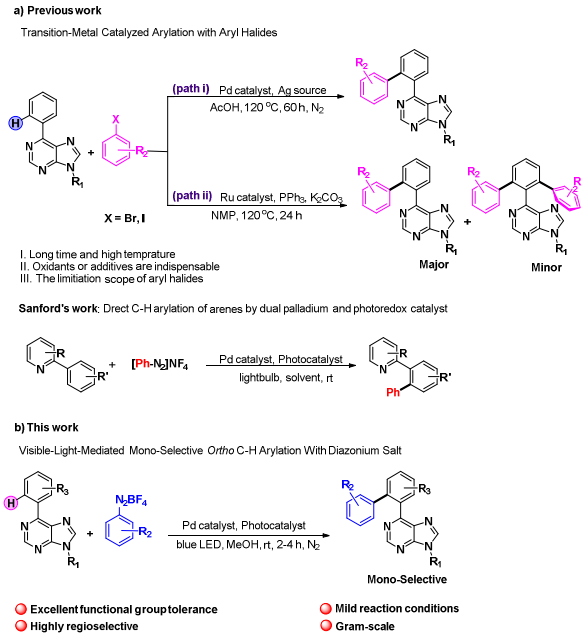
As the universal structural units in RNA and DNA, purine bases and nucleosides have displayed unique biological activities such as cytostatic,[1] anti-HCV,[2] antiviral and antimicrobacterial[3]

activities. In particular, C6 aryl- and heteroaryl purine analogues possess high inhibitory activity against *Mycobacterium tuberculosis*.[4] Nowdays, nitrogen-based directed C–H bond arylation has been regarded as an efficient method to construct biaryl compounds which are ubiquitous building blocks in biological and pharmaceutical sciences.[5] Our group firstly described purine as the new directing group (DG) for Pd-catalyzed Csp^2–H bond arylation (Scheme 1, path i), but, the reaction could not be regarded as an efficient method because of the high temperature (120 ^oC) and long reaction time (48-60 hours). Later, the Lakshman's group utilized the identical directing group for the arylation of Csp^2–H bonds under ruthenium catalysis (Scheme 1, path ii).[6] Although their condition provides a broader substrate scope (especially deoxyribonucleosides), its practical application in synthesis has been limited due to its lower regioselectivity (mono/diarylation), long reaction time (24 hours) and high temperature (120 ^oC). Thus, exploring an efficient route to obtain C6-arylated purines (nucleosides) with high regioselectivity under mild condition is challenging and fascinating.

Recently, many efforts have been devoted to direct C–H functionalization using combined transmetal with photoredox catalyst.[7] The concept of visible-light-mediated direct C–H functionalizations has received significant attention as a promising strategy for the cross coupling reactions including cycloaddition,[8] radical addition,[9] alkylation,[10] arylation[11] and others.[12] At first, Sanford and co-workers reported ligand-directed C-H arylation reactions by using aryl diazonium salts and diaryliodonium salts as cross partners under visible light irradiation, which provided a new strategy for the construction of biaryl compounds (Scheme 1).[7a-b] Different directing groups (such as amides, pyrazoles, pyrimidines, and oxime ethers) were examined. However, no example of photocatalyzed purine modifucation has been reported up to now. Based on our long standing

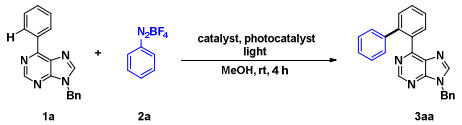
goals on the selective modification of nucleoside analogues and the established work on the arylation reaction,[13] we describe a mild and highly regioselective method for the direct arylation of 6-aryl-purines (nucleosides) using photoredox catalyst, palladium and diazonium salts under visible light irradiation.

Scheme 1. Strategies for the *ortho* arylation of 6–arylpurine (nucleoside).



Initially, we began our study by using 6-phenyl-9-benzyl-purine **1a** and phenyldiazonium tetrafluoroborate **2a** as model substrates to optimize the reaction conditions (Table 1). The finding that photoredox catalyst can be used to enable a Pd(IV)/Pd(II) catalytic cycle,[7a] the dual palladium/photoredox catalytic system was firstly used to test the arylation reaction. As shown in Table 1, white LED irradiation of a mixture of 6-aryl-9-benzyl-purine, aryl diazonium salt, $Ru(bpy)_3Cl_2 \cdot 6H_2O$ and $Pd(OAc)_2$ in MeOH at room temperature under air provided **3aa** as a product in trace amounts (Table 1, entry 1). When the reaction was carried out in an inert atmosphere and irradiated with blue LED bulb, the yield of product **3aa** was obviously increased (Table 1, entries 1-3). Subsequently, other palladium sources and transition-mental-catalysts were also screened, which revealed $Pd(OAc)_2$ to be the suitable catalyst for this reaction (Table 1, entries 4-7).

Table 1. Optimization of the reaction conditions.[a]



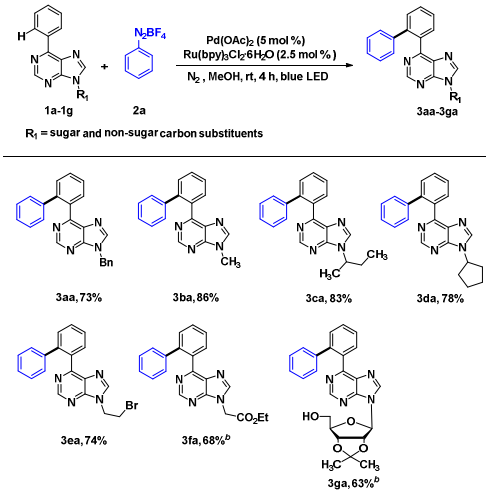
entry	catalyst	photocatalyst	yield (%)[b]
1[c,d]	$Pd(OAc)_2$	$Ru(bpy)_3Cl_2·6H_2O$	trace
2[d]	$Pd(OAc)_2$	$Ru(bpy)_3Cl_2·6H_2O$	21
3	$Pd(OAc)_2$	$Ru(bpy)_3Cl_2·6H_2O$	73
4	$PdCl_2$	$Ru(bpy)_3Cl_2·6H_2O$	69
5	$Pd_2(dba)_3$	$Ru(bpy)_3Cl_2·6H_2O$	N.R.
6	$Cu(OTf)_2$	$Ru(bpy)_3Cl_2·6H_2O$	N.R.
7	$[\{RuCl_2(C_6H_6)\}_2]$	$Ru(bpy)_3Cl_2·6H_2O$	N.R.
8	$Pd(OAc)_2$	$Ru(bpy)_3(PF_6)_2$	62
9	$Pd(OAc)_2$	Eosin Y	41
10	$Pd(OAc)_2$	$Ir(ppy)_3$	N.R.[e]
11	$Pd(OAc)_2$		N.R.[e]
12		$Ru(bpy)_3Cl_2·6H_2O$	N.R.[e]
13[f]	$Pd(OAc)_2$	$Ru(bpy)_3Cl_2·6H_2O$	trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 mmol), catalyst (5 mol %), and photoredox catalyst (2.5 mol %) in MeOH (2 mL) at room temperature irradiation with 4*7W blue LED bulb under N_2. [b] Isolated yield. [c] Without N_2 protection. [d] Irradiation with 4*7W white LED bulb. [e] N.R.= No Reaction. [f] In the absence of light.

$Ru(bpy)_3Cl_2·6H_2O$ was the best photoredox catalyst that gave the optimal reaction effect (Table 1, entries 3, 8-10). Control reactions confirmed that both $Pd(OAc)_2$, $Ru(bpy)_3Cl_2·6H_2O$ and light played a crucial role for significant conversion to the product (Table 1, entries 11-13). Thus, the optimal reaction conditions were 5 mol % $Pd(OAc)_2$, 2.5 mol % $Ru(bpy)_3Cl_2·6H_2O$ in MeOH at room temperature under N_2 irradiation with blue LED bulb (Table 1, entry 3).

Under the optimized reaction conditions (Table 1, entry 3), the substrate scope of C–H arylation reaction was examined. As shown in Scheme 2, the reaction of N9-substituted substrates (including alkyl, benzyl, ester, sugar) with $Pd(OAc)_2/Ru(bpy)_3Cl_2·6H_2O$ catalytic system afforded the corresponding arylation products in 63%-86% yields (Scheme 2). The N9 alkyl or cycloalkyl

Scheme 2. Direct C–H monophenylation of various purines (nucleoside) with ArN_2BF_4.[a]



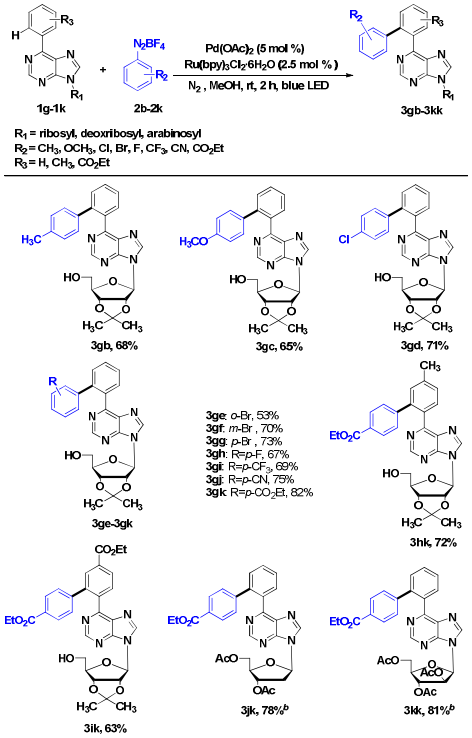
[a] Unless otherwise mentioned, all of the reactions were carried out with **1a-1e** (0.2 mmol), **2a (**1.2 mmol), $Pd(OAc)_2$ (5 mol %), $Ru(bpy)_3Cl_2·6H_2O$ (2.5 mol %) in MeOH (2 mL) at room temperature irradiation with 4*7W blue LED bulb for 4 h under N_2. [b] **2a** (1.6 mmol), 2 h.

substituted substrates reacted smoothly and gave the desired products in higher yields (Scheme 2, **3ba-3da**), while substrates bearing some active groups such as –bromine, –ester or –sugar resulted in slightly lower yields (Scheme 2, **3ea-3ga**). It was worth mentioning that the reaction time of substrate with ester and sugar should be shortened to 2 hours in order to avoid generating excessive byproducts (not the diarylation products), and it was necessary to increase the amount of aryl diazonium for their conversion (Scheme 2, **3fa-3ga**).

Subsequently, the tolerance of this reaction to a range of aryldiazonium salts and the electronic effect on the 6-arylpurines were examined (Scheme 3). Firstly, purine nucleoside was reacted with various substituted aryldiazonium salts, and the corresponding biaryl-purine nucleosides were obtained in moderate to good yields (see Supporting Information for competition reactions). The reaction proceeded smoothly with diazonium salts having bromine substituted at each position of the aryl ring, giving acceptable yields of desired products (Scheme 3, **3ge-3gg**) except that the yield of the desired product **3gf** was somewhat low. This might be due to the steric hindrance of

o-Br. Both electron-withdrawing and electron-donating groups at the C6-Ar of purine lead to subtle decrease in reaction yields (scheme 3, **3gk-3ik**). Notably, some strong electron-withdrawing groups such as –F, $–CF_3$ and –CN were well tolerated in this photoreaction that is not feasible in the previous ways[6] (Scheme 3, **3gh-3gj**). Moreover, a range of functional groups (–Cl, –Br, $–CO_2Et$) could successfully remain in the products, which were useful for the further modifications (Scheme 3, **3gd-3gg** and **3gk-3kk**). Therefore, **2k** was selected as the cross partner to react with challenge purine nucleosides. Deoxyribosyl purine nucleoside and arabinoribosyl purine nucleoside show well anti-HIV/HBV activity,[14] and its derivatives (**1j** and **1k**) proceeded well and afforded the corresponding products with good yields at 0 °C (Scheme 3, **3jk** and **3kk**).

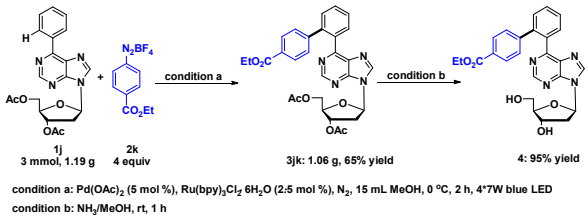
Scheme 3. Substrates scope of purine nucleosides.[a]



[a] Reaction conditions: **1g-1i** (0.2 mmol), **2b-2k** (1.6 mmol), $Pd(OAc)_2$ (5 mol %), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.5 mol %) in MeOH (2 mL) at room temperature irradiation with 4*7W blue LED bulb for 2 h under N_2. [b] At 0 °C.

To further evaluate the prospect of the methodology in synthesis, a gram-scale synthesis of nucleoside analogue **3jk** was performed. As shown in Scheme 4, **3jk** was obtained in 65 % yield (1.06 g) by treatment of 3 mmol of deoxyribosyl purine nucleoside **1j** in the presence of 5 mol % $Pd(OAc)_2$, 2.5 mol % of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ and *p*-ethoxycarbonylbenzenediazonium tetrafluoroborate **2k**. After that, in the present of NH_3/MeOH solution, the deprotection of the product **3jk** could be carried out, affording the biaryl-purine nucleoside with free hydroxyl group **4** in 95% yield which can be directly used as active fragment in bological test.

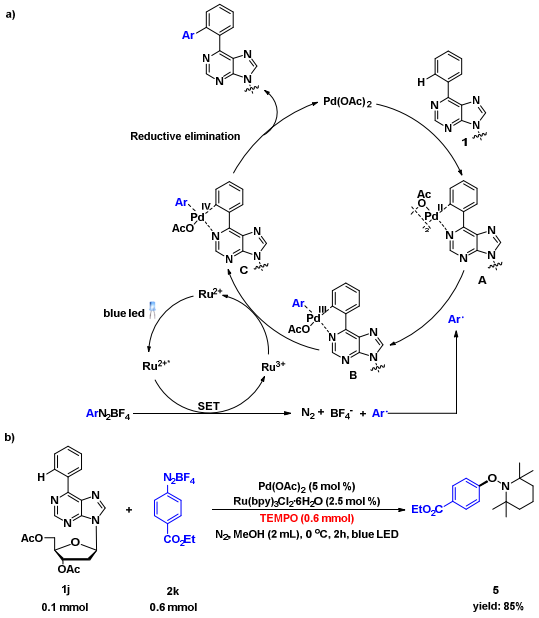
Scheme 4. Gram-scaled synthesis of 3jk and deprotection of **3jk**.



On the basis of the previous work and our experimental results,[7a, 13] a plausible mechanism was outlined in Scheme 5, **a**. i) photoexcitation of Ru^{2+} generated Ru^{2+*}, and aryl radical was formed by SET (single electron transfer) from the Ru^{2+*}, ii) purine-directed abstraction of **1** with $Pd(OAc)_2$ gave the N1 atom-mediated palladacycle intermediate **A** (Intermediate **A** was prepared, see Supporting Information for more details), iii) addition of aryl radical to intermediate **A** afforded the Pd^{III} intermediate **B**, iv) one-electron oxidation of **B** by Ru^{3+} regenerated the photocatalyst and formed Pd^{IV} intermediate **C**, v) the following step involved aryl-aryl bond

formation and the regeneration of $Pd(OAc)_2$ *via* reductive elimination. In order to trap the aryl radical generated in the reaction, TEMPO was added to the reaction mixture. Only trace amounts of the target product **1jk** was detected and the radical-trapping product **5** was isolated in 85% yield (Scheme 5, **b**).

Scheme 5. Plausible mechanism for monophenylation reaction.



In summary, a combined photoredox- and palladium-catalyzed system for mono-selective C_{Ar}–H bond arylation of purine nucleoside has been reported for the first time. The reaction operates at room temperature in only 2-4 hours and is mediated by visible light from household blue LED. Catalytic amounts of photoredox catalyst can generate aryl radical and enable a Pd(II)-Pd(III)-Pd(IV)-Pd(II) catalytic cycle, so that external oxidants can be avoided. This C–H arylation approach provided a broad substrate scope reaction condition to a variety of functionalized purines (nucleosides) which are potentially of great importance in medicinal chemistry.

EXPERIMENTAL SECTION

General information:

^{1}H NMR spectra were recorded on commercial instruments (400/600 MHz). Chemical shifts are recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal

standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quaternary, m = multiplet, br = broad), coupling constants (Hz), integration. ^{13}C NMR data were collected on commercial instruments (100/150 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. High-resolution mass spectra were taken with electrospray ionization (ESI) as the ionization method used for the HRMS measurement. For column chromatography silica gel (200-300 mesh) was used as the stationary phase. All regents and solvents were purchased from commercial sources and purified commonly before used. Experiments upon visible-light irradiation were carried out using household blue LED lamps (λmax = 465 nm, 4*7 W).

Synthesis of starting materials

Synthesis of 6-aryl-9-substitudent-purine 1a-1k.

Staring materials **1a-1k** were synthesized by Suzuki cross-coupling reactions of 6-chloro-9-substituted purine with aryl boronic acid according to the corresponding reference. [15] 6-chloro-9-substitudent-purine (3 mmol), boronic acid (4.5 mmol), K_2CO_3 (6 mmol), toluene (20 mL) were added in a 100 mL tube. The tube was refluxed in a 110 ^oC bath and stirred for 8-12 h under N_2 gas. The mixture was then allowed to cool to room temperature. The mixture was diluted with water then extracted with ethyl acetate. The extracts were combined, washed with brine, and then dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography on silica gel (V_{PE}/V_{EA} = 3:1 as eluent) to give the 6-aryl-9-substitudent-purine.

Synthesis of diazonium tetrafluoroborate salts 2a-2k.

Aniline (10 mmol) was dissolved in a mixture of 4 mL of distilled water and 3.4 mL of 50 % hydrofluoroboric acid. After cooling the reaction mixture to 0° C, sodium nitrite (0.69 g) dissolved in 1.5 mL of water, was added dropwise. The resulting mixture was stirred for 1 h and the precipitate was collected by filtration, washed with water and redissolved in minimum amount of acetone. Diethyl ether was added until precipitation of the corresponding diazonium tetrafluoroborate, which was filtered, washed several times with diethyl ether and dried under vacuum.

General procedure for the mono-selective *ortho* C-H arylation

In a 25 mL sealed tube was charged with **1a-1e** (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (3.7 mg, 0.005 mmol) and phenyldiazonium tetrafluoroborate **2a** (1.2 mmol), then MeOH (2 mL) were added and the reaction mixture was irradiation with 4*7W blue led bulb for 4 hours at room temperature under a N_2 atmosphere via several vacuum-N_2 exchanges. In a 25 mL sealed tube was charged with **1f-1i** (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (3.7 mg, 0.005 mmol) and phenyldiazonium tetrafluoroborate **2a-2k** (1.6 mmol), then MeOH (2 mL) were added and the reaction mixture was irradiation with 4*7W blue led bulb for 2 hours at room temperature under a N_2 atmosphere via several vacuum-N_2 exchanges. In a 25 mL sealed tube was charged with **1j-1k** (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (3.7 mg, 0.005 mmol) and phenyldiazonium tetrafluoroborate **2k** (1.6 mmol), then MeOH (2 mL) were added and the reaction mixture was irradiation with 4*7W blue led bulb for 2 hours at 0 ^oC under a N_2 atmosphere via several vacuum-N_2 exchanges. After completion of the reaction, the mixture was then diluted with brine (10 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was collected and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (V_{PE}/V_{EA} = 1:1 as eluent) to give the desired products **3aa-3kk**.

Deprotection of diacetyl deoxy-purine nucleoside analogues

In the present of NH_3/MeOH solution (7 mol/L), the deprotection of the product **3jk** (81 mg, 0.15 mmol) could be carried out, affording the biaryl-purine nucleoside with free hydroxyl group **4** (66 mg) in 95 % yield.

The background reaction with TEMPO

In a 25 mL sealed tube was charged with **1j** (39.6mg, 0.1 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1.3 mg, 0.0025 mmol) and phenyldiazonium tetrafluoroborate **2k** (158.4mg, 0.6 mmol), TEMPO (93.8 mg, 0.6 mmol), then MeOH (2 mL) were added and the reaction mixture was irradiation with 4*7W blue led bulb for 4 hours at 0 ^oC under a N_2 atmosphere via several vacuum-N_2 exchanges. After completion of the reaction, the mixture was

then diluted with brine (10 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was collected and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (V_{PE}/V_{EA} = 10:1 as eluent) to give the desired products **5** (155 mg, 85%).

Characterization of compounds

6-([1,1'-Biphenyl]-2-yl)-9-benzyl-9*H*-purine (3aa)

Light yellow oil. Yield 53 mg (73%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.87 (s, 1H), 7.80 (d, *J* =8.0 Hz, 1H), 7.57–7.49 (m, 3H), 7.39–7.34 (m, 3H), 7.22–7.20 (dd, *J* =8.0 Hz, 2 Hz, 2H), 7.15–7.11 (m, 5H), 5.41 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.1, 152.5, 151.6, 144.2, 142.0, 141.3, 135.2, 134.4, 132.2, 130.9, 130.7, 129.9, 129.2, 129.1, 128.6, 127.8, 127.6, 127.4, 126.5, 47.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{19}N_4$ 363.1604; Found 363.1609.

6-([1,1'-Biphenyl]-2-yl)-9-methyl-9*H*-purine (3ba)

Light yellow oil. Yield 49 mg (86%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.91 (s, 1H), 7.78 (d, *J* =7.2 Hz, 1H), 7.57–7.50 (m, 3H), 7.16–7.12 (m, 5H), 3.87 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.9, 151.2, 150.8, 143.9, 140.9, 140.3, 133.3, 131.2, 130.0, 129.8, 128.8, 128.2, 126.8, 126.3, 125.5, 28.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{14}N_4Na$ 309.1111; Found 309.1101.

6-([1,1'-Biphenyl]-2-yl)-9-(sec-butyl)-9*H*-purine (3ca)

Brown oil. Yield 54 mg (83%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.91 (s, 1H), 7.80 (d, *J* =7.6 Hz, 1H), 7.56–7.49 (m, 3H), 7.15–7.09 (m, 5H), 4.64 (m, 1H), 2.05–1.88 (m, 2H), 1.59 (d, *J* =6.8 Hz, 3H), 0.80 (t, *J* =7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9,

151.9, 151.4, 142.6, 141.9, 141.3, 134.5, 132.5, 130.9, 130.7, 129.8, 129.2, 127.8, 127.3, 126.4, 53.0, 29.5, 20.4, 10.6. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{20}N_4Na$ 351.1580; Found 351.1579.

6-([1,1'-Biphenyl]-2-yl)-9-cyclopentyl-9*H*-purine (3da)

Brown oil. Yield 53 mg (78%) at 0.2 mmol scale. NMR (600 MHz,) δ 8.82 (s, 1H), 7.97 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.55-7.49 (m, 3.0 Hz), 7.16–7.12 (m, 5H), 4.97 (m, 1H), 2.32–2.29(m, 2H), 2.04–1.99 (m, 2H), 1.95–1.93 (m, 2H), 1.83 – 1.81 (m, 2H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.9, 150.8, 150.6, 141.6, 140.8, 140.3, 133.4, 131.7, 130.0, 129.8, 128.7, 128.2, 126.8, 126.3, 125.4, 55.1, 31.6, 22.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{21}N_4$ 341.1761; Found 341.1756.

6-([1,1'-Biphenyl]-2-yl)-9-(2-bromoethyl)-9*H*-purine (3ea)

Light brown oil. Yield 56 mg (74%) at 0.2 mmol scale. ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.99 (s, 1H), 7.82 (d, *J* =7.2 Hz, 1H), 7.58–7.52 (m, 3H), 7.16–7.12 (m, 5H), 4.65 (t, *J* =5.8 Hz, 2H), 3.79 (t, *J* =6.0 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 152.3, 151.3, 144.5, 142.0, 141.2, 134.2, 132.4, 131.0, 130.8, 129.9, 129.2, 127.9, 127.4, 126.5, 45.6, 29.6. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{15}BrN_4Na$ 401.0372; Found 401.0376.

Ethyl 2-(6-([1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)acetate (3fa)

Yellow oil. Yield 49 mg (68%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.99 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.58–7.50 (m, 3H), 7.17–7.13 (m, 5H), 5.01 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.9, 159.2, 152.4, 151.6, 144.6, 141.9, 141.2, 134.2, 131.8, 131.1, 130.8, 129.9, 129.2, 127.9, 127.4, 126.5, 62.5, 44.1, 14.1. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{18}N_4O_2Na$ 381.1322; Found 381.1322.

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-([1,1'-Biphenyl]-2-yl)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3ga)

Light rellow oil. Yield 56 mg (63%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.02 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.58–7.50 (m, 3H), 7.16 (s, 5H), 5.91 (d, *J* = 4.8 Hz, 1H), 5.76 (d, *J* = 9.6, 1H), 5.24 (t, *J* = 5.2 Hz, 1H), 5.11 (d, *J* = 5.2, 1H), 4.54 (s, 1H), 3.96 (d, *J* = 12.4 Hz, 1H), 3.78 (t, *J* = 11.0 Hz, 1H), 1.65 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.4, 151.6, 150.2, 144.1, 142.0, 141.0, 133.9, 133.8, 131.2, 131.0, 130.1, 129.2, 128.0, 127.4, 126.7, 114.3, 94.1, 86.1, 82.9, 81.6, 63.3, 27.6, 25.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{25}N_4O_4$ 445.1870; Found 445.1875.

((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(6-(4'-methyl-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3gb)

Light brown oil. Yield 62 mg (68%) at 0.2 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.01 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.57–7.53 (m, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 7.8

Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 5.91 (d, *J* = 4.8 Hz, 1H), 5.79 (d, *J* = 10.8 Hz, 1H), 5.25 (t, *J* = 5.1 Hz, 1H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.56 (s, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 3.81 (t, *J* = 12.0 Hz, 1H), 2.28 (s, 3H), 1.66 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.8, 151.7, 150.3, 144.2, 142.1, 138.2, 136.5, 134.2, 133.9, 131.3, 131.1, 130.3, 129.2, 128.9, 127.3, 114.4, 94.4, 86.2, 83.0, 81.8, 63.5, 27.8, 25.4, 21.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{26}N_4NaO_4$ 481.1846; Found 481.1851.

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3gc)

Light yellow oil. Yield 62 mg (65%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.00 (s, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.57–7.46 (m, 3H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 5.90 (d, *J* = 4.8 Hz, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 5.25 (t, *J* = 5.4 Hz, 1H), 5.13 (d, *J* = 5.6 Hz, 1H), 4.56 (s, 1H), 3.99 (d, *J* = 12.4 Hz, 1H), 3.81 (t, *J* = 11.2 Hz, 1H), 3.75 (s, 3H), 1.66 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.7, 157.5, 150.6, 149.1, 143.0, 140.6, 133.0, 132.7, 132.5, 130.1, 129.8, 129.3, 129.1, 126.0, 113.3, 112.5, 93.2, 85.1, 81.8, 80.6, 62.3, 54.1, 26.6, 24.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{26}N_4NaO_5$ 497.1795; Found 497.1795.

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(4'-Chloro-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3gd)

Brown oil. Yield 68 mg (71%) at 0.2 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.02 (s, 1H), 7.80–7.78 (m, 1H), 7.60–7.50 (m, 3H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 5.92 (d, *J* = 4.8 Hz, 1H), 5.66 (d, *J* = 10.4 Hz, 1H), 5.26 (t, *J* = 5.4 Hz, 1H), 5.13 (d, *J* = 6.0 Hz,

1H), 4.56 (s, 1H), 3.99 (d, *J* = 12.8 Hz, 1H), 3.81 (d, *J* = 11.2 Hz, 1H), 1.66 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 150.6, 149.2, 143.2, 139.8, 138.6, 132.8, 132.7, 131.8, 130.4, 129.8, 129.5, 129.2, 129.0, 127.7, 127.2, 126.7, 113.3, 93.1, 85.1, 81.9, 80.6, 62.3, 26.6, 24.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}ClN_4O_4$ 479.1481; Found 479.1481.

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(2'-Bromo-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3ge)

Light brown oil. Yield 55 mg (53%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.07 (s, 1H), 8.05–8.01 (m, 1H), 7.60–7.56 (m, 2H), 7.46–7.42 (m, 2H), 7.26–7.23 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.93 (d, *J* = 4.9 Hz, 1H), 5.68 (t, *J* = 11.2 Hz, 1H), 5.24 (q, *J* =5.2 Hz, 1H), 5.13–5.10 (m, 1H), 4.55 (s, 1H), 4.00–3.91 (m, 1H), 3.79 (t, *J* = 11.2 Hz, 1H), 1.66 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.1, 151.1, 150.3, 144.1, 142.0, 141.1, 132.3, 131.8, 131.5, 129.9, 128.4, 128.0, 126.8, 114.3, 94.3, 94.2, 81.6, 63.4, 27.7, 25.2. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{23}B_rN_4NaO_4$ 545.0795; Found 545.0791.

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(3'-Bromo-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3gf)

Brown oil. Yield 73 mg (70%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.02 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.57–7.53 (m, 3H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.04-6.94 (m, 2H), 5.92 (d, *J* = 4.8 Hz, 1H), 5.56 (d, *J* = 10.4 Hz, 1H), 5.25 (t, *J* = 5.2 Hz,1H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.55 (s, 1H), 3.98 (d, *J* = 12.4 Hz, 1H), 3.81 (t, *J* = 11.4 Hz, 1H), 1.66 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 151.7, 150.3, 144.3, 140.8, 140.1, 133.7, 131.4, 131.2,

130.8, 130.8, 130.3, 128.7, 128.3, 127.7, 126.5, 121.1, 114.3, 94.2, 86.1, 82.9, 81.6, 63.4, 27.6, 25.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}B_rN_4O_4$ 523.0975; Found 523.0979.

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(4'-Bromo-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3gg)

Light brown oil. Yield 76 mg (73%) at 0.2 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.02 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.59–7.50 (m, 3H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 7.8 Hz, 2H), 5.92 (d, *J* = 4.8 Hz, 1H), 5.54 (d, *J* = 10.8 Hz, 1H), 5.26 (t, *J* = 5.4 Hz, 1H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.56 (s, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 3.81 (t, *J* = 11.4 Hz, 1H), 1.66 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.9, 151.7, 150.3, 140.8, 140.1, 133.9, 133.7, 131.4, 131.2, 130.8, 130.8, 130.3, 127.8, 121.1, 114.3, 94.2, 86.1, 82.9, 63.4, 27.6, 25.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}B_rN_4O_4$ 523.0975; Found 523.0973.

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(4'-Fluoro-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3gh)

Brown oil. Yield 62 mg (67%) at 0.2 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.00 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.11 (dd, *J* = 8.2, 5.6 Hz, 2H), 6.86 (t, *J* = 8.4 Hz, 2H), 5.91 (d, *J* = 4.8 Hz, 1H), 5.59 (d, *J* = 10.8 Hz, 1H), 5.25 (t, *J* = 5.4 Hz, 1H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.55 (s, 1H), 3.98 (d, *J* = 12.6 Hz, 1H), 3.80 (t, *J* = 11.7 Hz, 1H), 1.65 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7, 161.1, 160.1, 151.6, 150.2, 144.2, 141.0, 137.1, 133.9, 133.8, 131.3, 130.9, 130.8, 130.7, 130.2, 129.2, 128.0, 127.5, 115.0, 114.3, 94.2, 86.1, 82.9, 81.6, 63.3, 27.6, 25.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{24}FN_4O_4$ 463.1776; Found 463.1779.

((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(6-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (3gi)

Light yellow oil. Yield 71 mg (69%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.01 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.61–7.49 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.24 (s, 2H), 5.90 (d, *J* = 5.2 Hz, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 5.22 (t, *J* = 5.2 Hz, 1H), 5.10 (d, *J* = 5.2 Hz, 1H), 4.53 (s, 1H), 3.97 (d, *J* = 12.8 Hz, 1H), 3.79 (t, *J* = 11.2 Hz, 1H), 1.63 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.5, 151.6, 150.4, 144.9, 144.3, 140.7, 133.9, 133.8, 131.6, 131.0, 130.4, 129.5, 128.1, 125.0, 124.9, 114.4, 94.2, 86.1, 82.9, 81.6, 63.3, 27.6, 25.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{24}F_3N_4O_4$ 513.1744; Found 513.1747.

2'-(9-((3a*R*,4*R*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-9*H*-purin-6-yl)-[1,1'-biphenyl]-4-carbonitrile (3gj)

Yellow oil. Yield 70 mg (75%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.02 (s, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.64–7.57 (m, 2H), 7.51 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.27 (s, 1H), 7.25 (s, 1H), 5.92 (d, *J* = 4.8 Hz, 1H), 5.43 (d, *J* = 9.6 Hz, 1H), 5.24 (t, *J* = 5.2 Hz, 1H), 5.12 (d, *J* = 4.8 Hz, 1H), 4.55 (s, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 3.81 (t, *J* = 11.2 Hz, 1H), 1.66 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.1, 151.7, 150.4, 146.1, 144.4, 140.2, 133.8, 131.8, 131.8, 130.8, 130.5, 129.9, 128.5, 118.9, 114.4, 110.5, 94.1, 86.1, 63.33. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{24}N_5O_4$ 470.1823; Found 470.1826.

Ethyl 2'-(9-((3a*R*,4*R*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro [3,4-d][1,3]dioxol-4-yl)-9*H*-purin-6-yl)-[1,1'-biphenyl]-4-carboxylate (3gk)

Light brown oil. Yield 85 mg (82%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.01 (s, 1H), 7.86–7.81 (m, 3H), 7.62–7.53 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.91 (d, *J* = 4.8 Hz, 1H), 5.61 (d, *J* = 9.6 Hz, 1H), 5.25 (t, *J* = 5.4 Hz, 1H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.55 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.98 (d, *J* = 12.8 Hz, 1H), 3.80 (t, *J* = 11.2 Hz, 1H), 1.65 (s, 3H), 1.39–1.35(m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 159.7, 151.6, 150.3, 145.9, 144.2, 141.1, 133.9, 132.1, 132.1, 132.0, 131.4, 130.8, 130.3, 129.3, 129.2, 128.7, 128.6, 128.5, 128.0, 114.3, 94.2, 86.2, 82.9, 63.3, 60.9, 27.6, 25.2, 14.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{28}N_4NaO_6$ 539.1901; Found 539.1900.

Ethyl 2'-(9-((3a*R*,4*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro [3,4-d][1,3]dioxol-4-yl)-9*H*-purin-6-yl)-5'-methyl-[1,1'-biphenyl]-4-carboxylate (3hk)

Brown oil. Yield 76 mg (72%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.98 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.90 (d, *J* = 4.8 Hz, 1H), 5.58 (d, *J* = 10.8 Hz, 1H), 5.25 (t, *J* = 5.4 Hz, 1H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.54 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.97 (d, *J* = 12.8 Hz, 1H), 3.80 (t, *J* = 11.4 Hz, 1H), 2.48 (s, 3H), 1.65 (s, 3H), 1.39–1.35 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 159.8, 151.6, 150.2, 146.1, 144.0, 141.0, 140.5, 133.9, 131.6, 131.5, 131.1, 129.2, 129.2, 128.8, 128.6, 114.3, 94.2, 86.1, 82.8, 81.6, 63.4, 60.9, 27.6, 25.2, 21.5, 14.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{31}N_4O_6$ 531.2238; Found 531.2237.

Diethyl 6-(9-((3a*R*,4*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro

[3,4-d][1,3]dioxol-4-yl)-9*H*-purin-6-yl)-[1,1'-biphenyl]-3,4'-dicarboxylate (3ik)

Light yellow oil. Yield 74 mg (63%) at 0.2 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.22–8.21 (s, 2H), 8.01 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 5.91 (d, *J* = 4.8 Hz, 1H), 5.36 (d, *J* = 11.4 Hz, 1H), 5.24 (t, *J* = 5.1 Hz, 1H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.55 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.97 (d, *J* = 12.6 Hz, 1H), 3.80 (t, *J* = 11.7 Hz, 1H), 1.65 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.39–1.36 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 165.9, 158.6, 151.7, 150.4, 144.9, 144.5, 141.4, 137.9, 133.9, 129.4, 129.2, 114.4, 94.1, 86.2, 82.9, 81.6, 63.3, 61.4, 61.0, 30.9, 27.6, 25.2, 14.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{33}N_4O_8$589.2293; Found 589.2295.

Ethyl 2'-(9-((2*R*,4*S*,5*R*)-4-acetoxy-5-(acetoxymethyl)tetrahydrofuran-2-yl)-9*H*-purin-6-yl)-[1,1'-biphenyl]-4-carboxylate (3jk)

Colorless oil. Yield 85 mg (78%) at 0.2 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.11 (s, 1H), 7.83 (t, *J* = 7.8 Hz, 3H), 7.60–7.54 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.48 (t, *J* = 7.2 Hz, 1H), 5.44 (d, *J* = 6.0 Hz, 1H), 4.40 (q, *J* = 6.0 Hz, 1H), 4.36–4.31 (m, 4H), 3.00–2.95 (m, 1H), 2.67–2.63 (m, 1H), 2.14 (s, 3H), 2.06 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 170.3, 166.6, 158.8, 152.3, 151.1, 146.0, 142.6, 140.9, 134.2, 132.9, 131.3, 130.8, 130.1, 129.2, 129.2, 128.6, 128.0, 84.7, 82.7, 74.5, 63.7, 60.9, 37.5, 20.9, 20.7, 14.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{28}N_4NaO_7$ 567.1850; Found 567.1849.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-5-(6-(4'-(ethoxycarbonyl)-[1,1'-biphenyl]-2-yl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3kk)

Colorless oil. Yield 98 mg (81%) at 0.2 mmol scale. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.08 (s, 1H), 7.83–7.79 (m, 3H), 7.60–7.53 (m, 3H), 7.23 (s, 1H), 7.21 (s, 1H), 6.62 (d, *J* = 4.4 Hz, 1H), 5.48 (t, *J* = 3.8 Hz, 1H), 5.43 (t, *J* = 3.6 Hz 1H), 4.45 (t, *J* = 4.8 Hz, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.26 (m, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.78 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 169.6, 168.5, 166.5, 158.7, 152.6, 150.9, 146.0, 143.3, 140.9, 134.1, 131.9, 129.2, 128.6, 128.1, 83.1, 80.0, 75.8, 74.9, 62.9, 60.9, 20.8, 20.7, 20.1, 14.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{30}N_4NaO_9$ 625.1905; Found 625.1903.

Ethyl 2'-(9-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9*H*-purin-6-yl)-[1,1'-biphenyl]-4-carboxylate (4)

White solid. Yield 68 mg (95%) at 0.2 mmol scale of **3j**. M.p. 62-64 ^{o}C ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.00 (s, 1H),7.84 (m, 3H), 7.61–7.54 (t, *J* = 8.4 Hz , 3H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.36 (q, *J* = 5.2 Hz, 1H), 5.62 (s, 1H), 4.80 (d, *J* = 4.8 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.23 (s, 1H), 3.98 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.88 (s, 1H), 3.80 (d, *J* = 11.4 Hz, 1H), 3.12–3.08 (m, 1H), 2.35 (q, *J* = 5.4 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 159.6, 151.4, 150.4, 145.9, 144.3, 141.1, 134.1, 134.0, 131.4, 130.8, 130.3, 129.3, 129.2, 128.7, 128.0, 89.6, 87.7, 73.5, 63.4, 61.0, 40.7, 14.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{24}N_4NaO_5$ 483.1639; Found 483.1632.

Ethyl 4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)benzoate (5)

Browm solid. Yield 155 mg (85%) at 0.6 mmol scale. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 7.20 (br, 2H), 4.33 (q, J = 7.2 Hz, 2H), 4.06 (br, 1H), 1.94–1.91 (m, 3H), 1.63 (t, J = 12.0 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.27 (s, 6H), 1.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 166.6, 131.1, 122.6, 113.7, 62.9, 60.9, 60.6, 48.2, 32.5, 21.3, 14.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{28}NO_3$ 306.2064; Found 306.2067.

ASSOCIATED CONTENT

Supporting Information

Verification test, copies of all spectral and full characterization for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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