

6-ALKYNYLPURINES BEARING ELECTRONACCEPTOR SUBSTITUENTS: PREPARATION, REACTIVITY IN CYCLOADDITION REACTIONS AND CYTOSTATIC ACTIVITY

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While direct Sonogashira coupling of 6-halopurines with methyl propiolate and with propargyl aldehyde was not successful, the corresponding orthoester and propargyl aldehyde diethylacetal reacted smoothly. Such prepared orthoester was then converted to the desired methylester by methanolysis, the acetal was too stable to be hydrolyzed. The obtained 6-ethynylpurines, bearing orthoester, acetal, methoxycarbonyl and for comparison also the phenyl substituent on the ethynyl group, were subjected to the cycloaddition reaction with cyclopentadiene, diazomethane and phenylazide. Electron deficient alkynylpurines were considerably more reactive in this reaction compared to the not activated phenylethynyl derivative. The prepared alkynylpurines exhibited medium cytostatic activity ($IC_{50} = 2.6\text{--}15\text{ }\mu\text{M}$), while the cycloadducts were inactive.

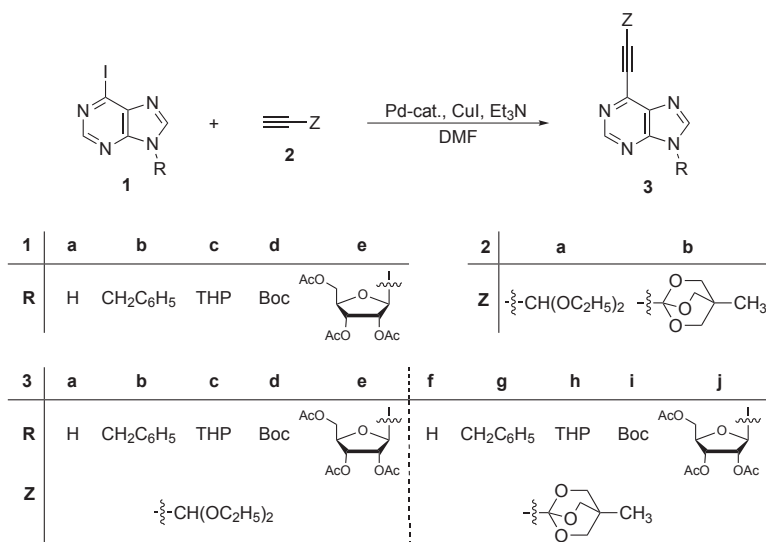
Keywords: Alkynylpurines; Cytotoxicity; Cycloaddition reactions.

Purine bases bearing C-6 substituent exhibit wide range of biological effects, mainly cytostatic¹, antiviral² and antimycobacterial³. Bis(purin-6-yl)-acetylenes and diacetylenes designed as covalent analogues of DNA base-pairs display significant cytostatic activity in vitro⁴ and high cytotoxicity was found in the case of 6-alkynyl-2-oxopurines⁵ and 6-alkynyl purines⁶. This high cytotoxicity was ascribed⁶ to the ability of 6-alkynyl-

purines to undergo easily conjugate additions of wide range of O, N and S-nucleophiles⁷. Therefore, we assumed, that the introduction of the ethynyl moiety bearing electron withdrawing substituent may further enhance the cytotoxicity. For that reason we attempted to synthesize purine derivatives substituted in the position 6 with ethynyl group bearing ester and aldehyde groups in conjugation with the triple bond.

However, all attempts to prepare derivatives of the propiolic acid bearing 9-protected purin-6-yl group at the position 3 using the Sonogashira coupling of the ethyl propiolate or the propiolic acid itself with 9-protected 6-iodopurines **1** have failed. Also attempts to prepare these compounds by the Negishi coupling, reaction of the lithium salt of the 6-ethynylpurine with CO₂ or by an oxidation of the 3-(purin-6-yl)propargyl alcohol have failed.

Therefore, a different strategy consisting in the protection of the carboxylic and aldehyde functionalities was used. Thus, diethyl acetal of propargylaldehyde (**2a**) and the orthoester **2b** were used for the coupling reactions. These alkynes were reacted with 6-iodopurine (**1a**), 9-benzyl-6-iodopurine (**1b**), with the derivatives with removable protecting group at the position 9 (6-iodo-9-tetrahydropyranylpurine (**1c**) and 9-Boc-6-iodopurine (**1d**)) and with acetylated riboside **1e** (Scheme 1). After some experimentation, it was found that the best results can be obtained using PdCl₂(PPh₃)₂ (method A) or Pd(dba)₂ in the presence of tris(2-furyl)phosphine (method B).



SCHEME 1

The unsubstituted 6-iodopurine (**1a**) reacted only with propargylaldehyde diethylacetal (**2a**) in low yield (Table I, entry 1), while no reaction with the orthoester **2b** (Table I, entry 7) was observed. On the opposite, all the 9-substituted 6-iodopurines gave the desired 6-alkynylpurines **3**. Generally, the method *B* using Pd(dba)₂ in the presence of tris(2-furyl)phosphine gave somewhat better yields compared to the method *A*. This is especially the case of 9-Boc derivative **1d** (Table I, entries 10, 11), where the yield of the desired **3i** using method *A* was only 6%, while the method *B* furnished the same product in 86% (Table I, entries 10, 11). In this case, the very low yield of **3i** using the method *A* is most probably due to the thermal instability of the Boc derivative **1d** in prolonged reaction time. 9-Unsubstituted orthoester **3f**, which is not accessible by direct coupling of 6-iodopurine (**1a**) with **2b**, was obtained in 69% yield by the thermolysis of the 9-Boc de-

TABLE I
The Sonogashira reaction of **1** with alkynes **2**

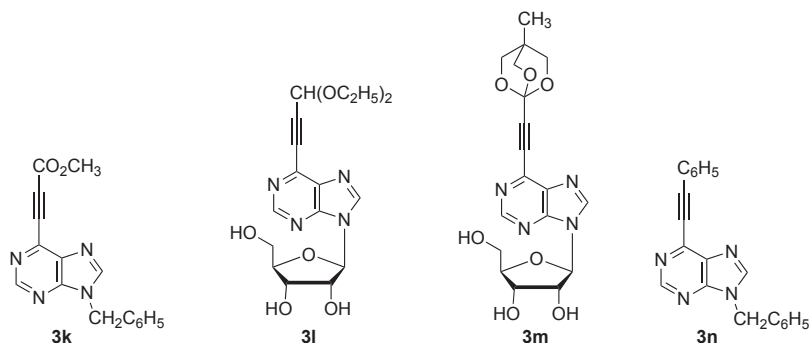
Entry	Purine 1	Alkyne 2	Method ^a	Reaction time, h	3 , Yield, %
1	1a	2a	A	8	3a , 32 ^c
2	1b	2a	A	4	3b , 84
3	1c	2a	A	12	3c , 84
4	1d	2a	B ^b	12	3d , 77
5	1e	2a	A	4	3e , 50
6	1e	2a	B	3	3e , 73
7	1a	2b	A, B	24	3f , 0
8	1b	2b	A	12	3g , 75
9	1c	2b	A	12	3h , 79
10	1d	2b	A	12	3i , 6
11	1d	2b	B ^b	17	3i , 72
12	1e	2b	A	15	3j , 50
13	1e	2b	B	3	3j , 68

^a Method A: A mixture of 6-iodopurine **1**, alkyne (1.5 equiv.), PdCl₂(PPh₃)₂ (2 mole %), CuI (5 mole %), triethylamine (3 equiv.) and DMF (2 ml per mmol of iodopurine) was stirred at 65 °C; Method B: A mixture of 6-iodopurine **1**, alkyne (1.5 equiv.), Pd(dba)₂ (2 mole %), tris(2-furyl)phosphine (4 mole %), CuI (5 mole %), triethylamine (3 equiv.) and DMF (2 ml per mmol of iodopurine) was stirred at 50 °C. ^b The reaction was performed at a laboratory temperature due to the thermal instability of the Boc group. ^c The compound was alternatively prepared in 58% yield by acidolysis of **3c**.

rivative **3i** in DMF. The orthoester group remains untouched under these conditions.

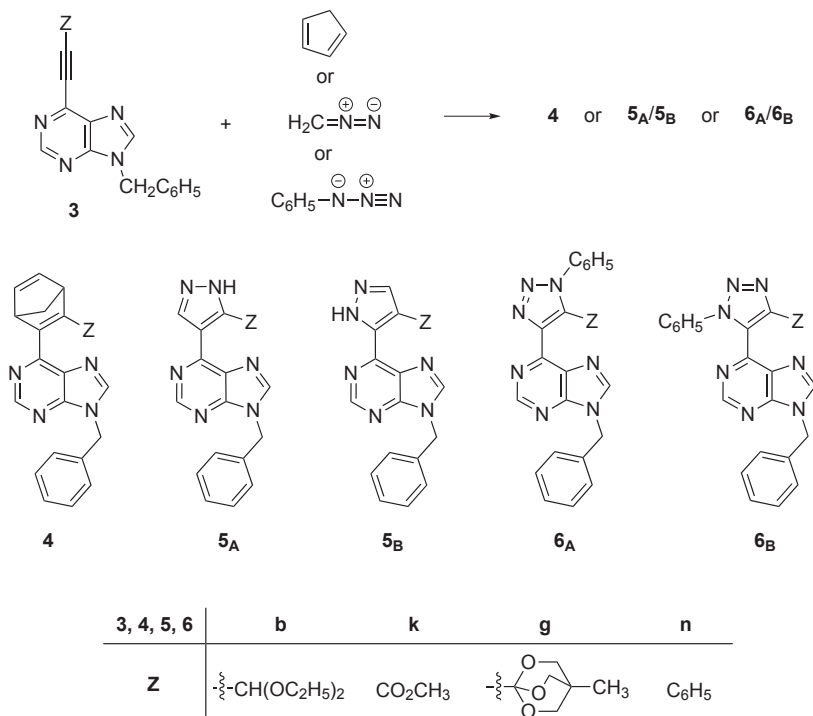
The removing of the protective groups was addressed next. All attempts of the hydrolysis of the propargyl acetal **3b** ($\text{CF}_3\text{COOH}/\text{H}_2\text{O}/\text{DCM}$, $\text{TsOH}/\text{H}_2\text{O}/\text{acetone}$, $\text{LiBF}_4/\text{CH}_3\text{CN}/\text{H}_2\text{O}$) were not successful, also no reaction or full decomposition of the starting **3b** was observed.

On the opposite, the conversion of the orthoester **3g** to the corresponding methyl ester **3k** proceeded smoothly. The best results were obtained in a two-step process. At first the orthoester **3g** was converted in THF –methanol– H_2O mixture under acid catalysis to the monoester of 1,1,1-tris-(hydroxymethyl)ethane which was then without isolation converted to the methylester **3k** by methanolysis giving the desired compound in 82% isolated yield. Also the removal of the acetoxy groups of the ribosides **3e** and **3j** by methanolysis gave the corresponding nucleosides **3l** and **3m** in 90% and 78% yield, respectively.



Reactivity of the title 6-alkynylpurines was studied on the reaction with cyclopentadiene and 1,3-dipoles – diazomethane and phenylazide. From the alkynylpurines the acetal **3b**, the orthoester **3g** and the methylester **3k** were used as the representative examples together with the unactivated 9-benzyl-6-(phenylethynyl)purine (**3n**) which was used for the comparison (Scheme 2).


Cycloaddition reaction of alkynylpurines **3b**, **3k**, **3d** and **3n** with cyclopentadiene was carried out in dichloromethane in a sealed glass tube at 60°C (Table II, entries 1–4). While the reactions of the ester **3k** and the orthoester **3g** were finished within hours in quantitative yield, the acetal **3b** reacted repeatedly incompletely even after overnight heating, giving the expected product **4b** in 56% yield. The phenylethynyl derivative **3n** did not react with cyclopentadiene under these conditions.



SCHEME 2

The reaction with diazomethane was accomplished in THF at room temperature (Table II, entries 5–8). The alkynes **3b**, **3k** and **3d** were consumed during several hours giving the expected products **5k**, **5b** and **5g** in practically quantitative yields. In contrast, the less activated **3n** gave only low yield of the **5n** after prolonged reaction time (Table II, entry 8). In the reaction with diazomethane formation of two regioisomers of the product is possible. This was really observed in the reaction of the ester derivative **3k**, where the mixture of regioisomers **5k_A** and **5k_B** in approximately 3:1 ratio was obtained. The structure assignment was done by NMR. The minor isomer in contrast to the major one showed NOE between the ester methyl group and the CH of the pyrazole ring. Therefore, the major isomer was assigned as **5k_A** and the minor as **5k_B**. The other alkynes gave single isomers of the product **5b_B**, **5g_B** and **5n_B**, respectively. The structure of the **5b_B** was unambiguously determined using HMBC after transformation to the corresponding dimethylacetal **7** to avoid presence of diastereotopic CH₂ groups. The structure of **5g_B** was obtained after transformation to the correspond-

TABLE II
Cycloaddition reactions of the purinylalkynes **3** with the cyclopentadiene, diazomethane and phenylazide

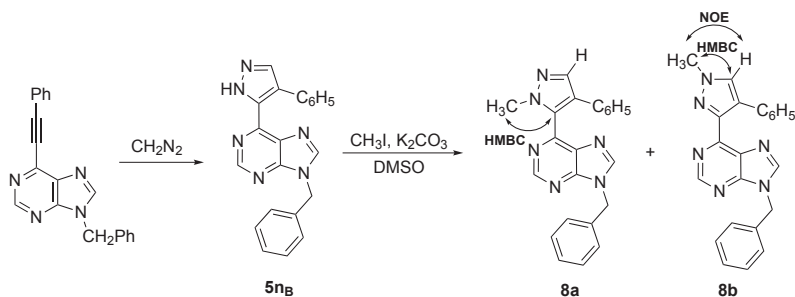
Entry	Alkyne, Z	Reagent	Solvent, temp., °C	Time, h	Product, Yield, %		
1	3k		CH ₂ Cl ₂ , 60	1	4k, 100		
2	3b		CH ₂ Cl ₂ , 60	16	4b, 56		
3	3g		CH ₂ Cl ₂ , 60	4	4g, 99		
4	3n		CH ₂ Cl ₂ , 60	16	— ^a		
5	3k	CH ₂ N ₂	THF, r.t.	1	5k _A , 61		
					5k _B , 18		
6	3b				5b _B , 100		
7	3g				5g _B , 100		
8	3n	C ₆ H ₅ N ₃	THF, r.t.	72	5n _B , 27 ^b		
9	3k				2	6k _A , 30	
						6k _B , 55	
10	3b				28	6b _A , 27	
						6b _B , 67	
11	3g	DMF, 100	8	6g _A , 26			
				6g _B , 38			
12	3n			48	6n _A , 40		
					6n _B , 40		

^a No reaction; ^b 66% of the starting material was recovered.

ing methylester by methanolysis. The resulting compound appeared to be identical with **5k_B** obtained previously.

The structure assignment of **5n_B** by NMR was complicated by very low solubility of this compound in CDCl₃ and by formation of mixture of tautomers in DMSO (not observed in CDCl₃). Therefore this compound was N-methylated by CH₃I in DMSO in the presence of K₂CO₃ giving approximately 1:1 mixture of two regioisomers **8a** and **8b**. The structure of these compounds was then unambiguously determined using HMBC and NOE (Scheme 3).

The cycloaddition of the above alkynylpurines with phenylazide required somewhat harsher conditions compared to the previous reactions (Table II, entries 9–12). This reaction was done in DMF at 100 °C. Again the methylester **3k** was the most reactive and full conversion of the starting material was observed within 2 h. The acetal **3b** and the orthoester **3g** required 8 h



SCHEME 3

at these conditions to achieve full conversion and with **3n** even after 48 h the conversion was only about 80%. All alkynes furnished chromatographically separable mixtures of both possible regioisomers. Their structure was assigned on the basis of NOE experiments. The NOE effect was observed between the triazole phenyl group and the ester methyl group in the case of **6k_A**, between the phenyl group and the purine H-2 in the case of **6k_B**, between the phenyl group and CH of the acetal moiety of **6b_A**, and between the phenyl group and the CH_2 moiety of the orthoester in **6g_A**. This approach was not successful with **6n**, however the structure of **6n_A** was assigned using X-ray analysis (Fig. 1).

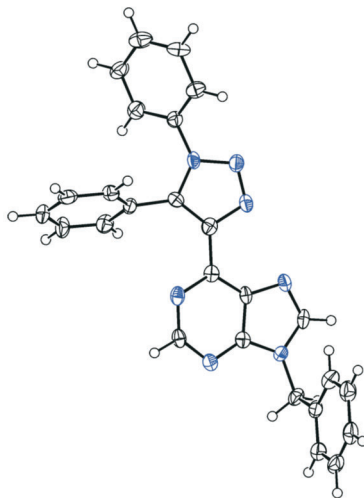


FIG. 1
X-ray structure of **6n_A**

The representative examples of the alkynes **3** and the cycloadducts **5** and **6** were tested on their in vitro inhibition of the cell growth in the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 219), human promyelocytic leukemia HL 60 cells (ATCC CCL 240), human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2), and human T lymphoblastoid CCR_F-CEM cell line (ATCC CCL 119). The results in Table III show that the ethynyl derivatives **3** exhibited a medium cytostatic activity in these assays ($IC_{50} = 2.4\text{--}15\text{ }\mu\text{M}$) which is lower than that previously reported for phenylethynyl-purines⁶ and bis(purinyl)ethynes⁴. In contrast, the cycloadducts **5** and **6** were entirely inactive.

TABLE III
Cytostatic activity of compounds **3**, **5** and **6**

Compound	IC_{50} , μM^a			
	L1210	HL60	HeLa S3	CCRF-CEM
3a	5.0 (\pm 0.20)	2.9 (\pm 0.21)	10 (\pm 0.6)	7.5 (\pm 0.61)
3b	6.5 (\pm 0.39)	4.7 (\pm 0.22)	15.4 (\pm 1.2)	5.4 (\pm 0.35)
3c^b	13.7 (\pm 0.92)	4.4 (\pm 0.25)	8.0 (\pm 0.6)	2.6 (\pm 0.15)
3g	7.3 (\pm 0.48)	3.7 (\pm 0.21)	9.4 (\pm 0.56)	3.4 (\pm 0.21)
3h	8.6 (\pm 0.56)	5.7 (\pm 0.33)	15 (\pm 1.1)	7.2 (\pm 0.42)
3l^b	>12	>15	>15	12 (\pm 0.8)
3m^b	12 (\pm 1.1)	10.8 (\pm 0.8)	4.0 (\pm 0.2)	15 (\pm 1.4)
3k	4.8 (\pm 0.29)	4.7 (\pm 0.32)	15 (\pm 1.1)	2.4 (\pm 0.15)
5b_B	na ^c	na	na	na
5g_B	na	na	na	na
5k_A	na	na	>20	na
6b_A	na	na	na	na
6b_B	>12	na	na	na

^a Values are means of four experiments, standard deviation is given in parentheses; ^b the solution is not stable in time (THP derivative and the nucleosides); ^c na, not active (inhibition of cell growth at 10 μM was lower than 30%).

In conclusion, while the attempts to accomplish the Sonogashira coupling of methyl propiolate or propargylaldehyde with 9-protected-6-halo-purines have not been successful, the coupling of the compounds with protected carbonyl group – the acetal **2a** and the orthoester **2b** proceeds

smoothly. The orthoesters can be easily converted to the corresponding methylesters, while the acetals **3a–3d** are too stable to be hydrolyzed. The resulting electron-deficient alkynes are more reactive towards cycloaddition reactions compared to the non-activated 6-phenylethynyl purines. According to our expectations, the compound **3b**, bearing the carbonyl group in the conjugation with the triple bond, is the most reactive, but both the orthoester **3g** and acetal **3b** are still considerably more reactive compared to the 6-phenylethynylpurine **3n**. The ethynylpurines showed moderate cytotoxicity, in contrast with their cycloadducts **5** and **6** which were completely inactive.

EXPERIMENTAL

Unless stated otherwise, all reaction were performed in flame-dried flasks under an argon atmosphere. NMR spectra were measured on a Varian Gemini 300 (^1H , 300.07 MHz; ^{13}C , 75.46 MHz), a Bruker AMX3 400 (^1H , 400.13 MHz; ^{13}C , 100.62 MHz) or a Bruker DRX 500 Avance (^1H , 500.13 MHz; ^{13}C , 125.77 MHz) spectrometer at 298 K. Unambiguous assignment of the NMR signals is based on $^{13}\text{C}\{^1\text{H}\}$, ^{13}C APT, COSY, HMQC and ^{13}C HMBC spectra. Chemical shifts are given in ppm (δ -scale), coupling constants (J) in Hz. IR spectra (ν , cm^{-1}) were recorded on Nicolet 740 FT-IR. High resolution mass spectra were recorded on LTQ Orbitrap Velos spectrometer (Thermo Scientific). Melting points were measured on a Koffler block and are uncorrected. The solvents were dried and degassed by standard procedures; silica gel (ICN SiliTech, 32–63) was used for column chromatography. 6-Iodopurine⁸, 9-benzyl-6-iodopurine⁹, 6-iodo-9-(tetrahydropyran-2-yl)purine¹⁰, 9-(*O,O*,*O*-triacetyl- β -D-ribofuranosyl)-6-iodopurine¹¹ and 9-benzyl-6-phenylethynylpurine¹² were prepared via procedures described in literature. Cyclopentadiene was freshly prepared from dicyclopentadiene by cracking¹³. Other compounds were purchased.

Cytostatic activity tests were performed according to literature procedure^{1b}.

9-(*tert*-Butyloxycarbonyl)-6-iodopurine (**1d**)

To a suspension of thoroughly powdered 6-iodopurine (12.3 g, 50 mmol) in THF (100 ml), di-*tert*-butyldicarbonate (10.9 g, 1 equiv.) and triethylamine (7 ml, 1 equiv.) were added. The resulting mixture was stirred at the room temperature until the solid was completely dissolved. Then the solvent was evaporated and the residue was dissolved in a minimum amount of dichloromethane, the solution was filtered through silica gel, which was subsequently eluted with a mixture of ethyl acetate and hexane (2:1). The eluate was dried with Na_2SO_4 and evaporated to dryness in vacuum. The crystallization (ethyl acetate–hexane, 1:2) yielded **1d** (15.58 g, 90%) as white crystals; m.p. > 100 °C (dec.). ^1H NMR (300 MHz, CDCl_3): 1.66 (s, 9 H, CH_3), 8.51 (s, 1 H, H-8), 8.72 (s, 1 H, H-2). ^{13}C NMR (75 MHz, CDCl_3): 28.1 (CH_3), 88.2 ($\text{C}(\text{CH}_3)_3$), 123.1 (C-5), 139.5 (C-6), 143.4 (C-8), 145.8 (C=O), 147.6 (C-4), 154.1 (C-2). IR (ATR): 3119 (w), 3010 (w), 2975 (m), 2934 (w), 1917 (w), 1829 (w), 1784 (m), 1756 (s), 1581 (m), 1549 (s), 1488 (w), 1435 (m), 1372 (m), 1344 (m), 1293 (m), 1256 (m), 1218 (m), 1204 (m), 1164 (s), 1088 (w), 963 (w), 914 (m), 838 (m), 822 (m), 789 (w), 764 (m), 662 (w). HRMS (EI): m/z [M]⁺ calculated for $\text{C}_{10}\text{H}_{11}\text{IN}_4\text{O}_2$: 345.9927; found: 345.9937.

Preparation of 6-Alkynylpurines. General Procedure

Method A: A mixture of 6-iodopurine **1**, alkyne (1.5 equiv.), $\text{PdCl}_2(\text{PPh}_3)_2$ (2 mole %), CuI (5 mole %), triethylamine (3 equiv.) and DMF (2 ml per mmol of iodopurine) was stirred at 65 °C for the amount of time given in Table I. After the removal of volatiles in vacuo, the product was isolated using column chromatography on silica gel.

Method B: A mixture of 6-iodopurine **1**, alkyne (1.5 equiv.), $\text{Pd}(\text{dba})_2$ (2 mole %), tris(2-furyl)phosphine (4 mole %), CuI (5 mole %), triethylamine (3 equiv.) and DMF (2 ml per mmol of iodopurine) was stirred at 50 °C for the amount of time given in Table I. After the removal of volatiles, the product was isolated using column chromatography on silica gel.

6-(3,3-Diethoxyprop-1-yn-1-yl)purine (**3a**)

Method A, starting from 6-iodopurine (**1a**; 246 mg, 1.0 mmol) afforded after column chromatography (ethyl acetate) **3a** (79 mg, 32%) as a white crystalline solid; m.p. 118–122 °C. Alternatively, **3a** was prepared in higher yield via acidolysis of **3c**. 6-(3,3-Diethoxyprop-1-yn-1-yl)-9-(tetrahydropyran-2-yl)purine (**3c**; 55 mg, 0.17 mmol) was dissolved in ethanol (4 ml), anhydrous CuCl_2 (2.9 mg, 13 mole %) was added and the reaction mixture was stirred at 50 °C for 4 h. The solvent was then evaporated and the residue was column chromatographed (ethyl acetate) to obtain 24 mg (58%) of white crystalline **3a** (m.p. 118–122 °C) and 8 mg (15%) of the starting material. ^1H NMR (300 MHz, CDCl_3): 1.25 (t, $J = 7.0$, 6 H, CH_3), 3.65–3.90 (m, 4 H, CH_2), 5.58 (s, 1 H, $\text{CH-C}\equiv\text{C}$), 8.53 (s, 1 H, H-8), 9.04 (s, 1 H, H-2). ^{13}C NMR (75 MHz, CDCl_3): 15.2 (CH_2CH_3), 61.8 (CH_2CH_3), 79.5 ($\text{C}\equiv\text{C}$), 91.7 ($\text{CH-C}\equiv\text{C}$), 93.4 ($\text{C}\equiv\text{C}$), 132.3 (C_q^{Pur}), 138.7 (C_q^{Pur}), 146.2 (CH^{Pur}), 152.7 (CH^{Pur}), 154.4 (C_q^{Pur}). IR (CHCl_3): 3434 (w), 3111 (w), 3061 (w), 2935 (w), 2891 (w), 2827 (w), 2717 (w), 1583 (s), 1477 (w), 1443 (w), 1428 (w), 1392 (m), 1353 (w), 1324 (s), 1299 (w), 1119 (s), 1083 (m), 1051 (s), 1014 (w), 924 (w), 892 (w), 860 (w), 828 (w), 639 (w), 606 (w). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{10}\text{H}_9\text{N}_4\text{O}$ ($\text{M} - \text{C}_2\text{H}_5\text{O}$): 201.0776; found: 201.0779.

9-Benzyl-6-(3,3-diethoxyprop-1-yn-1-yl)purine (**3b**)

Method A, starting from 9-benzyl-6-iodopurine (**1b**; 1.01 g, 3.0 mmol), column chromatography (ethyl acetate–hexane, 2:1) afforded 848 mg (84%) of **3b** as a brown solid. Crystallization (ethyl acetate–hexane) yielded 736 mg (73%) of light brown needles; m.p. 77–78 °C. ^1H NMR (500 MHz, CDCl_3): 1.27 (t, $J = 7.0$, 6 H, CH_3), 3.70–3.90 (m, 4 H, $2 \times \text{CH}_2\text{-CH}_3$), 5.45 (s, 2 H, $\text{CH}_2\text{-Ph}$), 5.62 (s, 1 H, $\text{CH-C}\equiv\text{C}$), 7.28–7.37 (m, 5 H, Ph), 8.09 (s, 1 H, H-8), 8.97 (s, 1 H, H-2). ^{13}C NMR (125 MHz, CDCl_3): 15.0 (CH_3), 47.4 ($\text{CH}_2\text{-Ph}$), 61.4 ($\text{CH}_2\text{-CH}_3$), 79.6 ($\text{C}\equiv\text{C}$), 91.6 ($\text{C}\equiv\text{C-CH}$), 93.0 ($\text{C}\equiv\text{C}$), 127.8 (CH^{Ph}), 128.7 (CH^{Ph}), 129.2 (CH^{Ph}), 134.6 (C_q^{Ph}), 134.8 (C-5), 140.8 (C-6), 145.4 (C-8), 151.8 (C-4), 152.7 (C-2). IR (CHCl_3): 3068 (w), 2983 (w), 2935 (w), 2897 (w), 1582 (s), 1497 (w), 1444 (w), 1404 (w), 1354 (w), 1328 (m), 1297 (w), 1149 (w), 1114 (m), 1101 (m), 1048 (m), 1017 (w), 948 (w), 894 (w), 669 (w), 645 (w). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{17}\text{H}_{15}\text{N}_4\text{O}$ ($\text{M} - \text{CH}_3\text{CH}_2\text{O}$): 291.1246; found: 291.1249.

6-(3,3-Diethoxyprop-1-yn-1-yl)-9-(tetrahydropyran-2-yl)purine (**3c**)

Method A, starting from 9-(tetrahydropyran-2-yl)-6-iodopurine (**1c**; 672 mg, 2.0 mmol) afforded after column chromatography (ethyl acetate–hexane, 2:1) 598 mg (84%) of **3c** as a

light brown viscous liquid. ^1H NMR (500 MHz, CDCl_3): 1.29 (t, $J = 7.0$, 6 H, CH_3), 1.65–1.86 (m, 3 H, $2 \times \text{H-5}' + \text{H-4}'$), 2.03–2.21 (m, 3 H, $2 \times \text{H-3}' + \text{H-4}'$), 3.70–3.94 (m, 5 H, $2 \times \text{CH}_2\text{CH}_3 + \text{H-6}'$), 4.20 (m, 1 H, H-6'), 5.64 (s, 1 H, $\text{CH-C}\equiv\text{C}$), 5.81 (m, 1 H, H-2'), 8.35 (s, 1 H, H-8), 8.92 (s, 1 H, H-2). ^{13}C NMR (125 MHz, CDCl_3): 15.1 (CH_3), 22.7 (C-4'), 24.8 (C-5'), 31.8 (C-3'), 61.3 (CH_2CH_3), 68.8 (C-6'), 79.5 ($\text{C}\equiv\text{C}$), 82.1 (C-2'), 91.6 ($\text{CH-C}\equiv\text{C}$), 92.9 ($\text{C}\equiv\text{C}$), 134.7 (C-5), 140.7 (C-6), 143.4 (C-8), 150.9 (C-4), 152.5 (C-2). IR (CHCl_3): 2982 (w), 2951 (w), 2898 (w), 2869 (w), 1583 (s), 1492 (w), 1443 (w), 1403 (w), 1354 (w), 1326 (m), 1290 (w), 1267 (w), 1186 (w), 1160 (w), 1089 (m), 1047 (s), 1017 (w), 994 (w), 949 (w), 912 (w), 878 (w), 823 (w), 642 (w). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_3$: 330.1692; found: 330.1691.

6-(3,3-Diethoxyprop-1-yn-1-yl-9-(*tert*-butyloxycarbonyl)purine (**3d**)

Method *B* (reaction performed at a laboratory temperature), starting from 9-(*tert*-butyloxycarbonyl)-6-iodopurine (**1d**; 346 mg, 1.0 mmol) gave after column chromatography (ethyl acetate–hexane, 1:1) 266 mg (77%) of **3d** as a pale yellow viscous liquid. ^1H NMR (300 MHz, CDCl_3): 1.25 (t, 3 H, $J = 7.0$, CH_2CH_3), 1.68 (s, 9 H, $\text{C}(\text{CH}_3)_3$), 3.65–3.75 (m, 2 H, CH_2), 3.80–3.91 (m, 2 H, CH_2), 5.59 (s, 1 H, $\text{CH-C}\equiv\text{C}$), 8.52 (s, 1 H, H-8), 9.05 (s, 1 H, H-2). ^{13}C NMR (75 MHz, CDCl_3): 15.3 (CH_2CH_3), 28.1 ($\text{C}(\text{CH}_3)_3$), 61.6 (CH_2CH_3), 79.2 ($\text{C}\equiv\text{C}$), 87.9 ($\text{C}(\text{CH}_3)_3$), 91.7 ($\text{CH-C}\equiv\text{C}$), 94.0 ($\text{C}\equiv\text{C}$), 135.6 (C-5), 141.8 (C-6), 144.3 (C-8), 145.8 (C=O), 151.3 (C-4), 154.7 (C-2). IR (ATR): 3123 (w), 3061 (w), 2979 (m), 2933 (w), 2889 (w), 2242 (w), 1778 (m), 1758 (s), 1579 (s), 1496 (w), 1478 (w), 1440 (m), 1389 (m), 1372 (m), 1342 (m), 1327 (m), 1294 (s), 1262 (m), 1230 (m), 1196 (m), 1165 (s), 1148 (m), 1114 (s), 1053 (m), 1017 (m), 941 (w), 894 (w), 839 (m), 806 (w), 769 (w), 728 (w), 664 (w). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{15}\text{H}_{17}\text{N}_4\text{O}_3$ ($\text{M} - \text{C}_2\text{H}_5\text{O}$): 301.1301; found: 301.1286.

9-(2',3',5'-Tri-*O*-acetyl- β -D-ribofuranosyl)-6-(3,3-diethoxyprop-1-yn-1-yl)purine (**3e**)

Method *A*, starting from 9-(2',3',5'-tri-*O*-acetyl- β -D-ribofuranosyl)-6-iodopurine (**1e**; 504 mg, 1.0 mmol) afforded after column chromatography (ethyl acetate–hexane, 2:1) 252 mg (50%) of **3e** as a brown viscous liquid. Method *B*, starting from 9-(2',3',5'-tri-*O*-acetyl- β -D-ribofuranosyl)-6-iodopurine (**1e**; 252 mg, 0.5 mmol) afforded after column chromatography (ethyl acetate–hexane, 2:1) 184 mg (73%) of **3e** as a light brown viscous liquid. ^1H NMR (300 MHz, CDCl_3): 1.26 (t, 6 H, CH_2CH_3), 2.06 (s, 3 H, COCH_3), 2.10 (s, 3 H, COCH_3), 2.14 (s, 3 H, COCH_3), 3.65–3.92 (m, 4 H, $2 \times \text{CH}_2\text{CH}_3$), 4.33–4.49 (m, 3 H, $2 \times \text{H-5}' + \text{H-4}'$), 5.60 (s, 1 H, $\text{CH-C}\equiv\text{C}$), 5.64 (t, $J = 5.3$, 1 H, H-3'), 5.93 (t, $J = 5.6$, 1 H, H-2'), 6.22 (d, $J = 5.3$, 1 H, H-1'), 8.27 (s, 1 H, H-8), 8.93 (s, 1 H, H-2). ^{13}C NMR (75 MHz, CDCl_3): 15.3 (CH_2CH_3), 20.6 (COCH_3), 20.7 (COCH_3), 20.9 (COCH_3), 61.6 (CH_2CH_3), 63.1 (C-5'), 70.7 (C-3'), 73.2 (C-2'), 79.4 ($\text{C}\equiv\text{C}$), 80.7 (C-4'), 86.7 (C-1'), 91.7 ($\text{CH}(\text{OEt})_2$), 93.8 ($\text{C}\equiv\text{C}$), 135.4 (C-5), 141.3 (C-6), 144.3 (C-8), 151.4 (C-4), 153.0 (C-2), 169.6 (C=O), 169.8 (C=O), 170.5 (C=O). IR (ATR): 2978 (w), 2935 (w), 2890 (w), 1752 (m), 1582 (m), 1495 (w), 1442 (w), 1402 (w), 1373 (w), 1333 (w), 1242 (s), 1164 (w), 1104 (m), 1056 (m), 1018 (w), 899 (w), 823 (w), 806 (w), 732 (w). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{21}\text{H}_{23}\text{N}_4\text{O}_8$ ($\text{M} - \text{C}_2\text{H}_5\text{O}$): 459.1516; found: 459.1507.

1-(2-(Purin-6-yl)ethynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**3f**)

A solution of 1-(2-(9-(*tert*-butoxycarbonyl)purin-6-yl)ethynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**3i**; 90 mg, 0.24 mmol) in 1.5 ml DMF was heated at 100 °C for 1 h. After removal of DMF, the residue was column chromatographed (ethyl acetate–methanol, 20:1), yielding 45 mg (69%) of a white powder, m.p. > 340 °C (dec.). ¹H NMR (500 MHz, DMSO, 373 K): 0.83 (s, 3 H, CH₃), 4.01 (s, 6 H, 3 × OCH₂), 8.58 (s, 1 H, H-8), 8.88 (s, 1 H, H-2). ¹³C NMR (125 MHz, DMSO, 373 K): 13.0 (CH₃), 29.3 (C-CH₃), 72.1 (OCH₂), 75.5 (C≡C), 88.7 (C≡C), 101.2 (C(OR)₃), 131.4 (C-5), 135.7 (C-6), 146.2 (C-8), 151.5 (C-2), 153.5 (C-4). IR (ATR): 3101 (w), 3063 (w), 2957 (m), 2883 (m), 2803 (m), 2691 (m), 2539 (w), 1818 (w), 1723 (w), 1596 (s), 1583 (s), 1465 (w), 1455 (w), 1395 (m), 1335 (s), 1319 (s), 1272 (w), 1246 (m), 1234 (m), 1192 (m), 1151 (w), 1112 (w), 1076 (m), 1044 (w), 1025 (m), 1000 (s), 939 (w), 921 (w), 867 (w), 807 (w), 766 (w), 724 (w). HRMS (EI): *m/z* [M]⁺ calculated for C₁₃H₁₂N₄O₃: 295.0807; found: 295.0817.

1-(2-(9-Benzylpurin-6-yl)ethynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**3g**)

Method A, starting from 9-benzyl-6-iodopurine (**1b**; 672 mg, 2.0 mmol) afforded after column chromatography (ethyl acetate–hexane, 2:1) 544 mg (75%) of **3g** as a light brown solid. Crystallization (ethyl acetate–hexane) yielded 500 mg (69%) of white crystals; m.p. 194–208 °C. Another crystallization from chloroform yielded an analytic sample with m.p. 214–215 °C. ¹H NMR (300 MHz, CDCl₃): 0.85 (s, 3 H, CH₃), 4.03 (s, 6 H, 3 × OCH₂), 5.44 (s, 2 H, CH₂-Ph), 7.27–7.36 (m, 5 H, Ph), 8.09 (s, 1 H, H-8), 8.95 (s, 1 H, H-2). ¹³C NMR (300 MHz, CDCl₃): 14.4 (CH₃), 30.4 (C-CH₃), 47.4 (CH₂Ph), 73.1 (OCH₂), 75.9 (C≡C), 90.0 (C≡C), 102.4 (C(OR)₃), 127.8 (CH^{Ph}), 128.6 (CH^{Ph}), 129.2 (CH^{Ph}), 134.8 + 135.0 (C^{q Ph} + C-5), 140.0 (C-6), 145.6 (C-8), 151.8 (C-4), 152.6 (C-2). IR (CHCl₃): 3067 (w), 2969 (w), 2945 (w), 2885 (w), 1581 (s), 1497 (w), 1456 (w), 1444 (w), 1405 (w), 1395 (w), 1338 (s), 1327 (s), 1272 (w), 1148 (w), 1135 (w), 1078 (w), 1051 (m), 995 (s), 889 (w), 869 (w), 698 (w), 640 (w). HRMS (EI): *m/z* [M]⁺ calculated for C₂₀H₁₈N₄O₃: 362.1379; found: 362.1363.

1-(2-(9-(Tetrahydropyran-2-yl)purin-6-yl)ethynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**3h**)

Method A, starting from 9-(tetrahydropyran-2-yl)-6-iodopurine (**1c**; 447 mg, 1.35 mmol) gave after column chromatography (ethyl acetate–hexane, 2:1) 382 mg (79%) of **3h** as pale yellow crystals; m.p. 223.5–225 °C. ¹H NMR (500 MHz, CDCl₃): 0.84 (s, 3 H, CH₃), 1.62–1.85 (m, 3 H, H-4' + 2 × H-5'), 2.02–2.17 (m, 3 H, 2 × H-3' + H-4'), 3.76 (t, *J* = 10.5, 1 H, H-6'), 4.01 (s, 6 H, 3 × OCH₂), 4.15 (d, *J* = 11.0, 1 H, H-6'), 5.76 (d, *J* = 10.0, 1 H, H-2'), 8.30 (s, 1 H, H-8), 8.91 (s, 1 H, H-2). ¹³C NMR (125 MHz, CDCl₃): 14.4 (CH₃), 22.6 (C-4'), 24.7 (C-5'), 30.4 (C-CH₃), 31.7 (C-3'), 68.8 (C-6'), 73.1 (OCH₂), 75.8 (C≡C), 82.1 (C-2'), 89.9 (C≡C), 102.2 (C(OR)₃), 135.2 (C-5), 139.9 (C-6), 143.6 (C-8), 150.9 (C-4), 152.4 (C-2). IR (CHCl₃): 2949 (w), 2883 (w), 1731 (w), 1582 (s), 1520 (w), 1491 (w), 1469 (w), 1442 (w), 1408 (w), 1397 (w), 1338 (s), 1323 (m), 1304 (w), 1275 (w), 1155 (w), 1088 (m), 1048 (s), 996 (s), 927 (w), 914 (w), 873 (w), 848 (w), 642 (w), 627 (w). HRMS (EI): *m/z* [M]⁺ calculated for C₁₈H₂₀N₄O₄: 356.1485; found: 356.1500.

1-(2-(9-(*tert*-Butyloxycarbonyl)purin-6-yl)ethynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**3i**)

Method A, starting from 9-(*tert*-butyloxycarbonyl)-6-iodopurine (**1d**; 692 mg, 2.0 mmol) afforded after column chromatography (ethyl acetate–hexane, 2:1) 296 mg (60%) of 9-*H*-6-iodopurine and 47 mg (6%) of **3i** as a pale yellow solid; m.p. > 100 °C (dec.). Method B, reaction performed at laboratory temperature, starting from 9-(*tert*-butyloxycarbonyl)-6-iodopurine (**1d**; 346 mg, 1.0 mmol) afforded after column chromatography (ethyl acetate–hexane, 2:1) 268 mg (72%) of **3i** as white crystals; m.p. > 100 °C (dec.). ¹H NMR (300 MHz, CDCl₃): 0.81 (s, 3 H, CH₃), 1.64 (s, 9 H, C(CH₃)₃), 3.98 (s, 6 H, 3 × OCH₂), 8.50 (s, 1 H, H-8), 9.01 (s, 1 H, H-2). ¹³C NMR (75 MHz, CDCl₃): 14.6 (CH₃), 28.1 (C(CH₃)₃), 30.6 (C-CH₃), 73.4 (CH₂), 75.5 (C≡C), 87.8 (C(CH₃)₃), 90.8 (C≡C), 102.5 (C(OR)₃), 135.9 (C-5), 141.0 (C-6), 144.6 (C-8), 145.7 (C=O), 151.3 (C-4), 154.5 (C-2). IR (ATR): 3478 (w), 3156 (w), 3124 (m), 3077 (s), 2992 (m), 2970 (m), 2937 (m), 2879 (s), 2686 (w), 2583 (w), 2444 (w), 1960 (w), 1796 (w), 1738 (s), 1706 (w), 1630 (w), 1575 (s), 1499 (m), 1459 (m), 1440 (m), 1384 (m), 1335 (s), 1309 (s), 1290 (m), 1262 (m), 1243 (m), 1190 (m), 1145 (m), 1130 (s), 1100 (m), 1041 (s), 974 (s), 893 (m), 869 (w), 840 (m), 806 (m), 770 (s), 752 (m), 721 (m), 667 (m). HRMS (EI): *m/z* [M]⁺ calculated for C₁₇H₂₀N₄O₃ (M – CO₂): 328.1535; found: 328.1527.

9-(2',3',5'-Tri-*O*-acetyl-β-*D*-ribofuranosyl)-6-(2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethynyl)purine (**3j**)

Method A, starting from 9-(2',3',5'-tri-*O*-acetyl-β-*D*-ribofuranosyl)-6-iodopurine (**1e**; 378 mg, 0.75 mmol) gave after column chromatography (ethyl acetate–hexane, 2:1) 199 mg (50%) of **3j** as a pale yellow amorphous solid. Method B, starting from 9-(2',3',5'-tri-*O*-acetyl-β-*D*-ribofuranosyl)-6-iodopurine (**1e**; 252 mg, 0.5 mmol) gave after column chromatography (ethyl acetate–hexane, 2:1) 180 mg (68%) of **3j** as a pale yellow amorphous solid. ¹H NMR (500 MHz, CDCl₃): 0.85 (s, 3 H, CH₃), 2.06 (s, 3 H, COCH₃), 2.10 (s, 3 H, COCH₃), 2.14 (s, 3 H, COCH₃), 4.03 (s, 6 H, 3 × OCH₂), 4.35–4.46 (m, 3 H, 2 × H-5' + H-4'), 5.65 (t, *J* = 4.9, 1 H, H-3'), 5.94 (t, *J* = 5.4, 1 H, H-2'), 6.22 (d, *J* = 5.0, 1 H, H-1'), 8.25 (s, 1 H, H-8), 8.94 (s, 1 H, H-2). ¹³C NMR (CDCl₃): 14.4 (CH₃), 20.3 (COCH₃), 20.5 (COCH₃), 20.7 (COCH₃), 30.4 (C-CH₃), 62.9 (C-5'), 70.5 (C-3'), 73.0 (C-2'), 73.3 (OCH₂), 75.6 (C≡C), 80.5 (C-4'), 86.4 (C-1'), 90.4 (C≡C), 102.4 (C(OR)₃), 135.7 (C-5), 140.6 (C-6), 144.1 (C-8), 151.2 (C-4), 152.7 (C-2), 169.3 (C=O), 169.5 (C=O), 170.3 (C=O). IR (CHCl₃): 2969 (w), 2947 (w), 2885 (w), 1751 (s), 1582 (m), 1493 (w), 1444 (w), 1409 (w), 1394 (w), 1374 (w), 1340 (m), 1142 (w), 1098 (w), 1050 (s), 999 (s), 924 (w), 894 (w), 823 (w), 638 (w). HRMS (EI): *m/z* [M]⁺ calculated for C₂₄H₂₆N₄O₁₀: 530.1649; found: 530.1649.

9-Benzyl-6-(2-methoxycarbonylethynyl)purine (**3k**)

A mixture of 1-(2-(9-benzylpurin-6-yl)ethynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**3g**; 200 mg, 0.138 mmol), TsOH (20 mg), THF (20 ml), methanol (20 ml) and water (0.2 ml) was stirred at laboratory temperature for 3 h. The solution was then filtered through 5 g of anhydrous MgSO₄ for the removal of water, the dissicant was washed with methanol (5 ml) and to the combined filtrates it was added MeONa (2 ml of 0.1 M solution in MeOH). The mixture was stirred at r.t. until the methanolysis of the intermediate ester was complete according to TLC (ca. 1 h). After removal of the volatiles, the residue was column chromatog-

raphed on silica gel (ethyl acetate–hexane, 1:1). It was obtained 126 mg (78%) of **3k** as a white solid; m.p. 101–105 °C. ^1H NMR (500 MHz, CDCl_3): 3.88 (s, 3 H, CH_3), 5.47 (s, 2 H, $\text{CH}_2\text{-Ph}$), 7.32–7.40 (m, 5 H, Ph), 8.16 (s, 1 H, H-8), 9.03 (s, 1 H, H-2). ^{13}C NMR (125 MHz, CDCl_3): 47.6 (CH_2), 53.1 (CH_3), 78.7 ($\text{C}\equiv\text{C-CO}$), 86.0 ($\text{C}\equiv\text{C-CO}$), 127.9 (CH^{Ph}), 128.9 (CH^{Ph}), 129.2 (CH^{Ph}), 134.5 (C_q^{Ph}), 135.1 (C-5), 138.6 (C-6), 146.2 (C-8), 152.0 (C-4), 152.7 (C-2), 153.2 (C=O). IR (CHCl_3): 2956 (w), 1720 (s), 1581 (s), 1497 (w), 1455 (w), 1440 (m), 1403 (w), 1330 (m), 1303 (m), 1261 (m), 1149 (w), 1134 (w), 1080 (w), 967 (w), 889 (w), 848 (w), 646 (w). HRMS (EI): m/z $[\text{M}]^+$ calculated for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$: 292.0960; found: 292.0964.

9-(β -D-Ribofuranosyl)-6-(3,3-diethoxyprop-1-yn-1-yl)purine (**3l**)

To the solution of 9-(2',3',5'-tri-*O*-acetyl- β -D-ribofuranosyl)-6-(3,3-diethoxyprop-1-yn-1-yl)-purine (**3e**; 89 mg, 0.18 mmol) in dry methanol (10 ml), 0.01 M sodium methoxide in methanol (1.8 ml, 0.1 equiv.) was added. After 24-h stirring at the laboratory temperature, 1 M AcOH in methanol (0.1 ml) was added and the solution was evaporated to dryness. Column chromatography (ethyl acetate–methanol, 9:1) afforded 60 mg (90%) of **3l** as a pale yellow amorphous solid. ^1H NMR (500 MHz, DMSO): 1.21 (t, $J = 7.1$, 6 H, CH_3), 3.56–3.80 (m, 6 H, $2 \times \text{H-S}' + 2 \times \text{CH}_2\text{CH}_3$), 3.99 (m, 1 H, H-4'), 4.20 (m, 1 H, H-3'), 4.61 (m, 1 H, H-2'), 5.08 (t, $J = 5.5$, 1 H, OH-5'), 5.23 (d, $J = 5.1$, 1 H, OH-3'), 5.54 (d, $J = 5.8$, 1 H, OH-2'), 5.72 (s, 1 H, $\text{CH}(\text{OEt})_2$), 6.05 (d, $J = 5.3$, 1 H, H-1'), 8.93 (s, 1 H, H-8), 8.95 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO): 15.1 (CH_3), 60.9 (CH_2CH_3), 61.1 (C-5'), 70.2 (C-3'), 73.9 (C-2'), 79.4 ($\text{C}\equiv\text{C}$), 85.7 (C-4'), 87.9 (C-1'), 91.0 ($\text{CH-C}\equiv\text{C}$), 92.6 ($\text{C}\equiv\text{C}$), 134.8 (C-5), 139.1 (C-6), 146.2 (C-8), 151.5 (C-4), 152.2 (C-2). IR (ATR): 3312 (m), 2976 (w), 2930 (w), 1585 (s), 1493 (w), 1445 (w), 1399 (w), 1332 (m), 1210 (m), 1090 (s), 1048 (s), 901 (w), 865 (w), 804 (w), 732 (w). HRMS (EI): m/z $[\text{M}]^+$ calculated for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{NaO}_6$ (MNa^+): 401.1437; found: 401.1456.

9-(β -D-Ribofuranosyl)-6-(2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-ethynyl)purine (**3m**)

To the solution of 9-(2',3',5'-tri-*O*-acetyl- β -D-ribofuranosyl)-6-(2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethynyl)purine (**3j**; 30 mg, 0.056 mmol) in dry methanol (3 ml), 0.01 M sodium methoxide in methanol (0.56 ml, 0.1 equiv.) was added. After 24-h stirring at the laboratory temperature, 1 M AcOH in methanol (0.1 ml) was added and the solution was evaporated to dryness. Column chromatography (ethyl acetate–methanol, 9:1) afforded 18 mg (78%) of **3m** as white crystalline solid; m.p. 183–186 °C. ^1H NMR (500 MHz, DMSO): 0.82 (s, 3 H, CH_3), 3.55–3.61 (m, 1 H, H-5'), 3.66–3.72 (m, 1 H, H-5'), 3.99 (m, 1 H, H-4'), 4.01 (s, 6 H, OCH_2), 4.19 (m, 1 H, H-3'), 4.6 (m, 1 H, H-2'), 5.08 (t, $J = 5.5$, 1 H, OH-5'), 5.23 (d, $J = 5.1$, 1 H, OH-3'), 5.54 (d, $J = 5.8$, 1 H, OH-2'), 6.04 (d, $J = 5.4$, H-1'), 8.95 (s, 1 H, H-8), 8.96 (s, 1 H, H-2). ^{13}C NMR (125 MHz, DMSO): 13.5 (CH_3), 29.8 (C- CH_3), 61.0 (C-5'), 70.1 (C-3'), 72.4 (OCH_2), 73.8 (C-2'), 75.5 ($\text{C}\equiv\text{C}$), 85.7 (C-4'), 87.8 (C-1'), 89.5 ($\text{C}\equiv\text{C}$), 101.6 ($\text{C}(\text{OR})_3$), 134.9 (C-5), 138.1 (C-6), 146.4 (C-8), 151.6 (C-4), 152.1 (C-2). IR (ATR): 3393 (m), 2925 (w), 2884 (w), 1584 (s), 1492 (w), 1442 (w), 1399 (m), 1334 (s), 1304 (m), 1245 (m), 1208 (m), 1190 (w), 1081 (w), 1043 (m), 988 (s), 867 (w), 725 (w). HRMS (EI): m/z $[\text{M}]^+$ calculated for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{NaO}_7$ (MNa^+): 427.1230; found: 427.1243.

Diels–Alder Reaction of 6-Alkynylpurines with Cyclopentadiene. General Procedure

6-Alkynylpurine was dissolved in DCM (0.5 ml per 0.1 mmol of alkyne) and cyclopentadiene (same volume) was added. The mixture was placed in a sealed glass tube and heated at 60 °C for the period of time given in Table II. Volatiles were evaporated and the residue was column chromatographed.

9-Benzyl-6-(3-(methoxycarbonyl)bicyclo[2.2.1]hepta-2,5-dien-2-yl)purine (**4k**)

The reaction of compound **3k** (20 mg, 0.07 mmol) with cyclopentadiene, after column chromatography (ethyl acetate–hexane, 1:1), afforded 25 mg (~100%) of **4k** as a colorless oil. ¹H NMR (300 MHz, CDCl₃): 2.21 (m, 1 H, H-7'), 2.52 (m, 1 H, H-7'), 3.60 (s, 3 H, CH₃), 4.11 (m, 1 H, H-3' or H-6'), 4.34 (m, 1 H, H-3' or H-6'), 5.43 (s, 2 H, CH₂Ph), 7.04 (m, 2 H, H-4' + H-5'), 7.25–7.36 (m, 5 H, Ph), 8.00 (s, 1 H, H-8), 8.98 (s, 1 H, H-2). ¹³C NMR (75 MHz, CDCl₃): 47.5 (CH₂Ph), 51.8, 54.0, 56.3, 72.9, 128.1 (CH^{Ph}), 128.8 (CH^{Ph}), 129.4 (CH^{Ph}), 131.4, 135.3, 142.9, 143.5, 144.5, 150.2, 151.9, 152.6, 153.6, 157.7, 166.5. IR (ATR): 3060 (w), 2998 (w), 2946 (w), 2871 (w), 1717 (s), 1622 (w), 1581 (s), 1498 (m), 1438 (m), 1405 (m), 1326 (s), 1294 (m), 1241 (s), 1215 (m), 1197 (m), 1153 (m), 1098 (m), 1048 (s), 1020 (w), 868 (w), 949 (w), 876 (w), 823 (w), 774 (w), 727 (m), 698 (w). HRMS (EI): *m/z* [M]⁺ calculated for C₂₁H₁₈N₄O₂: 358.1430; found: 358.1429.

9-Benzyl-6-(3-(diethoxymethyl)bicyclo[2.2.1]hepta-2,5-dien-2-yl)purine (**4b**)

The reaction of compound **3b** (50 mg, 0.15 mmol) with cyclopentadiene, after column chromatography (ethyl acetate–hexane, 1:1), afforded 34 mg (56%) of **4b** as a pale yellow viscous liquid. Also, 16 mg (32%) of the starting material was recovered. ¹H NMR (500 MHz, CDCl₃): 1.00 (t, *J* = 7.0, 3 H, CH₃), 1.22 (t, *J* = 7.0, 3 H, CH₃), 2.03 (d, *J* = 6.5, 1 H, H-7'), 2.18 (d, *J* = 6.5, 1 H, H-7'), 3.12 (m, 1 H, OCH₂), 3.31 (m, 1 H, OCH₂), 3.64 (m, 1 H, OCH₂), 3.79 (m, 1 H, OCH₂), 3.95 (s, 1 H, H-4'), 4.71 (s, 1 H, H-1'), 5.37 (d, *J* = 6.4, 2 H, CH₂Ph), 6.24 (s, 1 H, CH(OEt)₂), 6.83 (m, 1 H, H-5' or H-6'), 6.93 (m, 1 H, H-5' or H-6'), 7.22–7.32 (m, 5 H, Ph), 7.94 (s, 1 H, H-8), 8.83 (s, 1 H, H-2). ¹³C NMR (125 MHz, CDCl₃): 15.1 (CH₃), 15.4 (CH₃), 47.2 (CH₂Ph), 51.4 (C-4'), 53.6 (C-1'), 62.2 (CH₂CH₃), 62.9 (CH₂CH₃), 70.4 (C-7'), 98.0 (CH(OEt)₂), 127.8 (CH^{Ph}), 128.5 (CH^{Ph}), 129.1 (CH^{Ph}), 130.6 (C-5), 135.2 (C_q^{Ph}), 142.4 (C-5' or C-6'), 142.8 (C-5' or C-6'), 143.4 (C-8), 147.2 (C-2' or C-3'), 152.2 (C-2), 152.3 (C-4), 153.6 (C-6), 160.9 (C-2' or C-3'). IR (ATR): 3064 (w), 2973 (m), 2931 (m), 2870 (w), 1690 (w), 1625 (w), 1578 (s), 1566 (s), 1496 (m), 1448 (m), 1403 (m), 1372 (m), 1320 (s), 1247 (w), 1214 (m), 1137 (m), 1103 (w), 1058 (m), 996 (w), 888 (w), 812 (w), 770 (w), 728 (w), 698 (w). HRMS (ESI): *m/z* [M + Na]⁺ calculated for C₂₄H₂₆N₄NaO₂: 425.1953; found: 425.1964.

9-Benzyl-6-(3-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octane-1-yl)bicyclo[2.2.1]hepta-2,5-dien-2-yl)purine (**4g**)

The reaction of compound **3g** (34 mg, 0.094 mmol) with cyclopentadiene, after column chromatography (ethyl acetate–hexane, 1:1), afforded 40 mg (~100%) of **4g** as a pale yellow viscous oil. The product is prone to acid hydrolysis. Therefore, both TLC and column chromatography require non-acidic sorbent (alumina or Et₃N pre-treated silica). Also, the CDCl₃ for NMR must not be acidic, otherwise the compound degrades rapidly. ¹H NMR (300 MHz,

CDCl_3): 0.71 (s, 3 H, CH_3), 2.04 (m, 1 H, H-7'), 2.43 (m, 1 H, H-7'), 3.77 (s, 6 H, $3 \times \text{OCH}_2$), 3.94 (m, 1 H, H-1' or H-4'), 4.03 (m, 1 H, H-1' or H-4'), 5.42 (s, 2 H, CH_2Ph), 7.01 (m, 1 H, H-5' or H-6'), 7.07 (m, 1 H, H-5' or H-6'), 7.24–7.36 (m, 5 H, Ph), 7.98 (s, 1 H, H-8), 8.94 (s, 1 H, H-2). ^{13}C NMR (75 MHz, CDCl_3): 14.8 (CH_3), 30.6 (C- CH_3), 47.3 (CH_2Ph), 52.9 (C-1' or C-4'), 56.9 (C-1' or C-4'), 72.0 (C-7'), 72.7 (OCH_2), 107.3 (C(OR) $_3$), 127.9 (CH^{Ph}), 128.7 (CH^{Ph}), 129.3 (CH^{Ph}), 132.0 (C-5), 135.7 (C_q^{Ph}), 143.3 (C-5' or C-6'), 143.4 (C-5' or C-6'), 143.8 (C-8), 148.4 (C-2' or C-3'), 151.5 + 152.2 + 153.3 (C-2 + C-4 + C-6), 156.4 (C-2' or C-3'). IR (ATR): 2964 (w), 2933 (w), 2873 (w), 1663 (w), 1578 (m), 1497 (w), 1455 (w), 1395 (w), 1363 (w), 1348 (w), 1325 (m), 1293 (m), 1252 (w), 1214 (m), 1195 (w), 1148 (w), 1097 (m), 1036 (m), 969 (m), 747 (s), 723 (s), 698 (m). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_3$: 428.1848; found: 428.1835.

Reaction of 6-Alkynylpurines with Diazomethane. General Procedure

To a solution of 6-alkynylpurine in THF (1 ml per 0.1 mmol of alkyne) was added diazomethane (2 equiv., as 0.5 M solution in Et_2O) and the mixture was stirred at r.t. for the period of time given in Table II. Volatiles were evaporated and the residue was column chromatographed (unless stated otherwise).

9-Benzyl-6-(3-(methoxycarbonyl)pyrazol-4-yl)purine (**5k_A**) and

9-Benzyl-6-(4-(methoxycarbonyl)pyrazol-3-yl)purine (**5k_B**)

The reaction of compound **3k** (208 mg, 0.71 mmol) with diazomethane, after column chromatography (ethyl acetate), afforded 217 mg (92%) of a white solid. The product turned out to be a 3:1 mixture of regioisomers **5k_A** and **5k_B**. Repetitive chromatography on chromatotron (EtOAc-MeOH , 40:1) finally lead to a complete resolution of the regioisomers. There were obtained 145 mg (61%) of **5k_A** and 42 mg (18%) of **5k_B**. The correct identities were assigned using NOE experiments.

5k_A (higher R_f). ^1H NMR (300 MHz, CDCl_3): 3.84 (s, 3 H, OCH_3), 5.47 (s, 2 H, CH_2), 7.30–7.40 (m, 5 H, Ph), 8.08 (s, 1 H, H-8), 8.34 (s, 1 H, CH^{PyT}), 9.03 (s, 1 H, H-2), 12.95 (br s, 1 H, NH). ^{13}C NMR (75 MHz, CDCl_3): 47.4 (CH_2Ph), 52.4 (CH_3), 118.6, 128.0 (CH^{Ph}), 128.7 (CH^{Ph}), 129.2 (CH^{Ph}), 131.4, 135.0, 135.6, 139.5, 144.3, 150.1, 151.6, 152.6, 162.1 (C=O). IR (ATR): 3137 (w), 2951 (w), 1726 (w), 1596 (m), 1496 (w), 1455 (w), 1402 (w), 1362 (w), 1324 (w), 1271 (w), 1215 (w), 1133 (w), 1067 (w), 945 (w), 915 (w), 851 (w), 808 (w), 726 (s), 696 (m). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_2$: 334.1178; found: 334.1180.

5k_B (lower R_f). ^1H NMR (300 MHz, CDCl_3): 3.83 (s, 3 H, CH_3), 5.48 (s, 2 H, CH_2), 7.35 (m, 5 H, Ph), 8.11 (s, 1 H, H-8 or CH^{PyT}), 8.13 (s, 1 H, H-8 or CH^{PyT}), 9.14 (s, 1 H, H-2), 12.42 (br s, 1 H, NH). ^{13}C NMR (75 MHz, CDCl_3): 47.8 (CH_2Ph), 52.0 (CH_3), 114.7, 128.2 (CH^{Ph}), 129.0 (CH^{Ph}), 129.5 (CH^{Ph}), 131.2, 135.0, 139.6, 144.4, 145.3, 147.2, 152.4, 153.2, 163.6 (C=O). IR (ATR): 2949 (w), 2923 (w), 1719 (s), 1597 (s), 1585 (s), 1496 (m), 1454 (m), 1436 (m), 1399 (m), 1363 (m), 1329 (s), 1282 (m), 1266 (s), 1210 (s), 1198 (s), 1135 (m), 1103 (w), 1074 (s), 1028 (w), 953 (m), 936 (m), 922 (m), 784 (m), 754 (m), 731 (s), 693 (m). HRMS (EI): m/z [M] $^+$ calculated for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_2$: 334.1178; found: 334.1183.

9-Benzyl-6-(4-(diethoxymethyl)pyrazol-3-yl)purine (**5b_B**)

The reaction of compound **3b** (34 mg, 0.1 mmol) with diazomethane, without chromatography, afforded 38 mg (100%) of **5b_B** as a pale yellow powder, pure according to ^1H and

^{13}C NMR. ^1H NMR (300 MHz, CDCl_3): 1.24 (t, $J = 7.3$, 6 H, CH_3), 3.65–3.82 (m, 4 H, CH_2CH_3), 5.48 (s, 2 H, CH_2Ph), 6.67 (s, 1 H, $\text{CH}(\text{OEt})_2$), 7.28–7.40 (m, 5 H, Ph), 7.92 (s, 1 H, CH^{PYT}), 8.08 (s, 1 H, H-8), 9.05 (s, 1 H, H-2), 12.75 (br s, 1 H, NH). ^{13}C NMR (75 MHz, CDCl_3): 15.5 (CH_3), 47.6 (CH_2Ph), 62.2 (CH_2CH_3), 96.7 ($\text{CH}(\text{OEt})_2$), 122.6, 128.1 (CH^{Ph}), 129.0 (CH^{Ph}), 129.5 (CH^{Ph}), 129.8, 135.1, 137.2, 138.7, 144.7 (C-8), 147.0, 152.0, 153.2 (C-2). IR (ATR): 3158 (m), 2974 (m), 1659 (w), 1588 (s), 1550 (m), 1517 (w), 1485 (w), 1453 (m), 1368 (w), 1324 (m), 1214 (w), 1115 (w), 1059 (m), 955 (w), 820 (w), 728 (m), 696 (m). HRMS (EI): m/z $[\text{M}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{N}_6\text{NaO}_2$ (MNa^+): 401.1702; found: 401.1712.

The identity of the compound was assigned using HMBC after previous transformation to a corresponding dimethyl acetal 7.

Compound **5b_B** (20 mg, 0.05 mmol) and TsOH (3 mg) was dissolved in methanol (2 ml) and the solution was stirred at room temperature for 1 h. Triethylamine (5 mg) was then added and the reaction mixture was evaporated to dryness. The crude product was purified by column chromatography (DCM–methanol, 20:1). There were obtained 16 mg (86%) of white amorphous 7. ^1H NMR (500 MHz, CDCl_3): 3.45 (s, 6 H, CH_3), 5.48 (s, 2 H, CH_2), 6.59 (s, 1 H, $\text{CH}(\text{OMe})_2$), 7.29–7.40 (m, 5 H, Ph), 7.91 (s, 1 H, CH^{PYT}), 8.09 (s, 1 H, H-8), 9.07 (s, 1 H, H-2), 12.65 (br s, 1 H, NH). ^{13}C NMR (125 MHz, CDCl_3): 47.4 (CH_2Ph), 53.2 (CH_3), 98.0 ($\text{CH}(\text{OMe})_2$), 121.1 (C-5'), 127.9 (CH^{Ph}), 128.8 (CH^{Ph}), 129.2 (CH^{Ph}), 129.5 (C-5), 134.8 (C_q^{Ph}), 136.7 (C-4'), 138.9 (C-3'), 144.5 (C-8), 146.3 (C-6), 151.9 (C-4), 153.2 (C-2). IR (ATR): 3166 (s), 3029 (w), 2938 (w), 2831 (w), 1751 (w), 1671 (w), 1588 (s), 1546 (w), 1517 (w), 1485 (w), 1454 (w), 1438 (w), 1367 (w), 1324 (m), 1281 (w), 1217 (m), 1198 (w), 1167 (w), 1075 (s), 966 (s), 930 (w), 885 (m), 827 (m), 809 (m), 738 (w), 732 (s), 696 (m). HRMS (EI): calculated for $\text{C}_{18}\text{H}_{18}\text{N}_6\text{NaO}_2$ (MNa^+): 373.1389; found: 373.1376.

9-Benzyl-6-(4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octane-1-yl)pyrazol-3-yl)purine (**5g_B**)

The reaction of compound **3g** (36 mg, 0.1 mmol) with diazomethane, without chromatography, afforded 40 mg (100%) of **5g_B** as a white amorphous solid. The compound exists in a DMSO solution as a mixture of two tautomers A and B in approximately 6:5 ratio (according to ^1H NMR). The structure of the **5g_B** was confirmed after methanolysis by comparison of the NMR spectra of obtained **5k_B** with the spectra of authentic sample of **5k_B**. ^1H NMR (300 MHz, DMSO): 0.69 (m, 3 H, CH_3), 3.75 (m, 6 H, OCH_2), 5.51 (m, 2 H, CH_2Ph), 7.35 (m, 5 H, Ph), 7.6 (s, CH^{B}), 7.84 (s, CH^{A}), 8.62 (s, CH^{A}), 8.78 (s, CH^{B}), 8.89 (s, CH^{A}), 8.97 (s, CH^{B}), 13.16 (bs, NH^{A}), 13.32 (bs, NH^{B}). IR (ATR): 3118 (m), 2927 (m), 2882 (m), 1762 (w), 1601 (s), 1565 (m), 1526 (m), 1456 (w), 1434 (w), 1395 (m), 1364 (m), 1329 (m), 1250 (w), 1193 (m), 1148 (w), 1074 (s), 1048 (w), 1005 (s), 922 (m), 885 (w), 834 (w), 725 (m), 695 (m), 677 (w). HRMS (EI): m/z $[\text{M}]^+$ calculated for $\text{C}_{21}\text{H}_{20}\text{N}_6\text{NaO}_3$ (MNa^+): 427.1495; found: 427.1501.

9-Benzyl-6-(4-phenylpyrazol-3-yl)purine (**5n_B**)

The reaction of compound **3n** (62 mg, 0.2 mmol) with diazomethane, after column chromatography (DCM–MeOH, 20:1), afforded 41 mg (66%) of the starting material and 19 mg (27%) of white amorphous **5n_B**. The compound exists in a DMSO solution as a mixture of two tautomers in ca. 1:1 ratio (according to ^1H NMR). The identity of the compound was confirmed after N-methylation and identification of two obtained N-methyl derivatives **8a**

and **8b**. ^1H NMR (500 MHz, DMSO): 5.51 (s, 2 H, CH_2), 7.28–7.45 (m, 8 H, Ph), 7.63–7.68 (m, 2 H, Ph), 8.7 (m, CH), 13.45 (s, NH), 13.53 (s, NH). IR (ATR): 3110 (m), 2906 (m), 1594 (s), 1490 (m), 1459 (m), 1443 (m), 1401 (m), 1342 (s), 1327 (s), 1249 (m), 1216 (m), 1142 (m), 1067 (w), 912 (w), 848 (w), 772 (w), 730 (m), 698 (m). HRMS (EI): m/z $[\text{M}]^+$ calculated for $\text{C}_{21}\text{H}_{16}\text{N}_6\text{Na}$ (MNa^+): 375.1334; found: 375.1327.

9-Benzyl-6-(4-phenyl-1-methylpyrazol-5-yl)purine (**8a**) and
9-Benzyl-6-(4-phenyl-1-methylpyrazol-3-yl)purine (**8b**)

To a solution of compound **5n_B** (10 mg, 0.028 mmol) in DMSO (0.5 ml) was added iodomethane (40 mg, 10 equiv.) and anhydrous K_2CO_3 (46 mg, 12 equiv.) and the suspension was stirred at r.t. for 17 h. It was then diluted with EtOAc (20 ml) and washed with 5% NaCl (3 × 20 ml). The organic layer was dried with MgSO_4 and evaporated to dryness. There were obtained 10 mg (~100%) of a pale yellow wax. According to ^1H NMR, the mixture contained **8a** and **8b** in a 7:6 ratio. Column chromatography (EtOAc–hexane, 2:1) afforded 4 mg (~40%) of pure **8a** (R_F 0.5) and 4 mg (~40%) of pure **8b** (R_F 0.37), both isomers as colourless amorphous solids. The assignment of the corresponding structures was possible using ^1H (^{13}C) HMBC and ^1H NOE experiments.

8a (higher R_F). ^1H NMR (500 MHz, CDCl_3): 3.81 (s, 3 H, NCH_3), 5.42 (s, 2 H, CH_2Ph), 7.26–7.36 (m, 6 H, Ph), 7.41–7.47 (m, 4 H, Ph), 7.98 (s, 1 H, H-8), 8.62 (s, 1 H, H-2), 8.78 (s, 1 H, H-3'). ^{13}C NMR (125 MHz, CDCl_3): 37.4 (NCH_3), 47.1 (CH_2Ph), 116.4 (C-4'), 127.8 (CH^{Ph}), 128.3 (CH^{Ph}), 128.5 (CH^{Ph}), 128.8 (CH^{Ph}), 129.1 (CH^{Ph}), 130.3 (CH^{Ph}), 130.4 (C_q^{Ph}), 130.6 (C-5), 135.4 (C_q^{Ph}), 141.8 (C-3'), 143.2 (C-8), 143.6 (C-5'), 151.3 (C-4 or C-6), 151.5 (C-4 or C-6), 152.5 (C-2). IR (ATR): 2921 (s), 2851 (m), 1581 (m), 1486 (m), 1465 (m), 1451 (m), 1435 (m), 1382 (m), 1325 (m), 1255 (w), 1204 (m), 1182 (w), 1072 (w), 966 (w), 915 (w), 850 (m), 809 (w), 773 (w), 729 (m), 693 (w), 659 (w). HRMS (ES): m/z $[\text{M}]^+$ calculated for $\text{C}_{22}\text{H}_{18}\text{N}_6\text{Na}$ (MNa^+): 389.1491; found: 389.1489

8b (lower R_F). ^1H NMR (500 MHz, CDCl_3): 4.05 (s, 3 H, CH_3), 5.46 (s, 2 H, CH_2), 7.31–7.40 (m, 8 H, Ph), 7.73 (m, 2 H, Ph), 8.00 (s, 1 H, H-8), 8.67 (s, 1 H, H-5'), 8.81 (s, 1 H, H-2). ^{13}C NMR (125 MHz, CDCl_3): 39.1 (CH_3), 47.2 (CH_2), 115.0 (C-4'), 127.8 (CH^{Ph}), 127.9 (CH^{Ph}), 128.0 (CH^{Ph}), 128.6 (CH^{Ph}), 129.2 (CH^{Ph}), 129.3 (CH^{Ph}), 130.1 (C-5), 133.6 (C_q^{Ph}), 135.3 (C_q^{Ph}), 135.5 (C-5'), 143.3 (C-8), 151.4 (C-4 or C-6), 151.5 (C-4 or C-6), 151.9 (C-3'), 152.7 (C-2). IR (ATR): 2922 (s), 2852 (s), 1580 (s), 1539 (m), 1495 (m), 1454 (m), 1395 (m), 1326 (m), 1249 (m), 1183 (m), 1134 (w), 1074 (w), 915 (w), 849 (w), 808 (w), 772 (w), 724 (m), 695 (m), 644 (w). HRMS (ES): m/z $[\text{M}]^+$ calculated for $\text{C}_{22}\text{H}_{18}\text{N}_6\text{Na}$ (MNa^+): 389.1491; found: 389.1501.

Reaction of 6-Alkynylpurines with Phenyl Azide. General Procedure

To a solution of 6-alkynylpurine in DMF (2 ml per mmol of alkyne) was added phenyl azide (10 equiv.) and the mixture was stirred at 100 °C for the period of time given in Table II. The reaction mixture was subsequently diluted with ethyl acetate (triple volume) and washed 3× with equal volume of 5% brine. The organic layer was dried with MgSO_4 and after the evaporation of volatiles the residue was column chromatographed.

9-Benzyl-6-(3-phenyl-4-methoxycarbonyl-1,2,3-triazol-5-yl)purine (**6k_A**) and
9-Benzyl-6-(1-phenyl-5-methoxycarbonyl-1,2,3-triazol-4-yl)purine (**6k_B**)

The reaction of compound **3k** (47 mg, 0.16 mmol) with phenyl azide, after column chromatography (DCM–methanol, 40:1), afforded 56 mg (85%) of the mixture of **6k_A** and **6k_B**. Chromatography on chromatotron (DCM–methanol, 40:1) yielded 20 mg (30%) of **6k_A** and 36 mg (55%) of **6k_B** as colourless amorphous solids.

6k_A (higher R_f). ^1H NMR (500 MHz, CDCl_3): 3.81 (s, 3 H, CH_3), 5.53 (s, 2 H, CH_2), 7.32–7.42 (m, 5 H, Ph), 7.58 (m, 3 H, Ph), 7.65 (m, 2 H, Ph), 8.19 (s, 1 H, H-8), 9.11 (s, 1 H, H-2). ^{13}C NMR (125 MHz, CDCl_3): 47.4 (CH_2), 53.2 (CH_3), 125.0 (CH^{Ph}), 127.8 (CH^{Ph}), 128.7 (CH^{Ph}), 129.2 (CH^{Ph}), 129.4 (CH^{Ph}), 130.2 (CH^{Ph}), 130.3 (C-5'), 131.0 (C-5), 135.0 ($\text{C}_q^{\text{Ph-Bn}}$), 136.1 ($\text{C}_q^{\text{Ph-triaz.}}$), 143.8 (C-4'), 145.4 (C-8), 147.1 (C-6), 152.6 (C-4), 152.7 (C-2), 160.3 (C=O). IR (ATR): 3064 (w), 3033 (w), 2993 (w), 2952 (w), 1740 (s), 1595 (s), 1547 (w), 1498 (s), 1455 (m), 1403 (w), 1376 (w), 1328 (s), 1285 (m), 1244 (m), 1221 (m), 1202 (m), 1170 (m), 1077 (w), 1007 (w), 955 (w), 923 (w), 859 (w), 810 (w), 760 (m), 728 (m), 694 (m), 645 (m), 605 (w), 554 (w). HRMS (ES): m/z $[\text{M}]^+$ calculated for $\text{C}_{22}\text{H}_{17}\text{N}_7\text{NaO}_2$ (MNa^+): 434.1341; found: 434.1342.

6k_B (lower R_f). ^1H NMR (500 MHz, CDCl_3): 3.86 (s, 3 H, CH_3), 5.47 (s, 2 H, CH_2), 7.33–7.44 (m, 10 H, Ph), 8.07 (s, 1 H, H-8), 9.04 (s, 1 H, H-2). ^{13}C NMR (75 MHz, CDCl_3): 47.7 (CH_2), 52.3 (CH_3), 125.1 (CH^{Ph}), 128.2 (CH^{Ph}), 128.9 (CH^{Ph}), 129.2 (CH^{Ph}), 129.3 (CH^{Ph}), 129.8 (CH^{Ph}), 133.3 (C-5), 134.4 ($\text{C}_q^{\text{Ph-Bn}}$), 135.3 (C-5'), 135.8 ($\text{C}_q^{\text{Ph-triaz.}}$), 139.3 (C-4'), 145.2 (C-6), 146.0 (C-8), 152.2 (C-4), 152.4 (C-2), 160.9 (C=O). IR (ATR): 3065 (w), 2952 (w), 2849 (w), 1730 (m), 1592 (m), 1558 (m), 1498 (s), 1453 (m), 1400 (w), 1367 (w), 1328 (s), 1213 (s), 1169 (m), 1085 (m), 1005 (m), 920 (m), 818 (m), 791 (m), 751 (s), 727 (s), 692 (s), 643 (m), 566 (w), 532 (w), 510 (w). HRMS (ES): m/z $[\text{M}]^+$ calculated for $\text{C}_{22}\text{H}_{17}\text{N}_7\text{NaO}_2$ (MNa^+): 434.1341; found: 434.1349.

9-Benzyl-6-(1-phenyl-4-(diethoxymethyl)-1,2,3-triazol-5-yl)purine (**6b_A**) and
9-Benzyl-6-(1-phenyl-5-(diethoxymethyl)-1,2,3-triazol-4-yl)purine (**6b_B**)

The reaction of compound **3b** (101 mg, 0.3 mmol) with phenyl azide, after column chromatography (DCM–methanol, 80:1), afforded 128 mg (94%) of the mixture of **6b_A** and **6b_B**. Chromatography on chromatotron (DCM–methanol, 80:1) yielded 37 mg (27%) of **6k_A** and 91 mg (67%) of **6k_B** as colourless amorphous solids.

6b_A (lower R_f). ^1H NMR (500 MHz, CDCl_3): 1.05 (t, $J = 7.0$, 6 H, CH_3), 3.48–3.55 (m, 2 H, CH_2CH_3), 3.67–3.73 (m, 2 H, CH_2CH_3), 5.53 (s, 2 H, CH_2Ph), 6.78 (s, 1 H, $\text{CH}(\text{OEt})_2$), 7.32–7.40 (m, 5 H, Ph), 7.48–7.53 (m, 3 H, Ph), 7.74–7.78 (m, 2 H, Ph), 8.26 (s, 1 H, H-8), 9.05 (s, 1 H, H-2). ^{13}C NMR (125 MHz, CDCl_3): 14.8 (CH_3), 47.3 (CH_2Ph), 63.7 (OCH_2), 95.4 ($\text{CH}(\text{OEt})_2$), 126.2 (CH^{Ph}), 127.7 (CH^{Ph}), 128.4 (CH^{Ph}), 128.6 (CH^{Ph}), 129.1 (CH^{Ph}), 129.3 (CH^{Ph}), 130.7 (C-5), 135.1, 136.6, 137.9, 141.8, 145.4 (C-8), 148.9 (C-6), 152.1 (C-2), 152.6 (C-4). IR (ATR): 3063 (w), 2976 (m), 2928 (m), 1717 (w), 1596 (s), 1546 (m), 1500 (s), 1454 (m), 1404 (w), 1380 (m), 1326 (s), 1257 (m), 1210 (m), 1191 (m), 1117 (s), 1062 (s), 1028 (m), 931 (m), 863 (w), 811 (w), 764 (m), 728 (m), 693 (m). HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{25}\text{H}_{25}\text{N}_7\text{NaO}_2$: 478.1967; found: 478.1980.

6b_B (higher R_f). ^1H NMR (300 MHz, CDCl_3): 0.91 (t, $J = 7.2$, 6 H, CH_3), 3.44–3.66 (m, 4 H, CH_2CH_3), 5.43 (s, 2 H, CH_2Ph), 6.06 (s, 1 H, CH), 7.22–7.38 (m, 10 H, Ph), 8.04 (s, 1 H, H-8), 8.93 (s, 1 H, H-2). ^{13}C NMR (75 MHz, CDCl_3): 15.1 (CH_3), 47.7 (CH_2Ph), 61.3 (OCH_2), 96.2 ($\text{CH}(\text{OEt})_2$), 125.2 (CH^{Ph}), 128.3 (CH^{Ph}), 129.0 (CH^{Ph}), 129.3 (CH^{Ph}), 129.39 (CH^{Ph}),

129.44 (CH^{Ph}), 130.6, 133.2, 134.9, 136.9, 145.7, 146.5, 146.8, 152.2, 152.5. IR (ATR): 3394 (w), 3379 (m), 3062 (w), 3030 (w), 2927 (w), 2858 (w), 1693 (w), 1600 (s), 1572 (s), 1543 (m), 1502 (m), 1454 (m), 1448 (m), 1376 (w), 1328 (m), 1288 (w), 1227 (m), 1188 (m), 1146 (m), 1106 (m), 1079 (m), 1026 (m), 991 (w), 941 (m), 821 (w), 791 (w), 759 (w), 733 (m), 694 (w). HRMS (ESI): m/z [M + Na]⁺ calculated for C₂₅H₂₅N₇NaO₂: 478.1967; found: 478.1969.

9-Benzyl-6-(1-phenyl-5-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octane-1-yl)-1,2,3-triazol-4-yl)purine (**6g_A**) and 9-Benzyl-6-(1-phenyl-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octane-1-yl)-1,2,3-triazol-5-yl)purine (**6g_B**)

The reaction of compound **3g** (72 mg, 0.2 mmol) with phenyl azide, after column chromatography (DCM–ethyl acetate, 1:1), afforded 8 mg (11%) of the starting material and 78 mg (82%) of a mixture of two regioisomers **6g_A** and **6g_B**. Repeated chromatography on chromatotron (hexane–ethyl acetate, 2:1 with 3% MeOH and 2% Et₃N) yielded 25 mg (26%) of **6g_A** and 36 mg (38%) of **6g_B** as colourless waxes, prone to acid-catalyzed hydrolysis.

6g_A (higher R_F). ¹H NMR (500 MHz, CDCl₃): 0.73 (s, 3 H, CH₃), 3.77 (s, 6 H, OCH₂), 5.51 (s, 2 H, CH₂Ph), 7.33–7.40 (m, 5 H, Ph^{Bn}), 7.47–7.52 (m, 3 H, Ph^{triaz}), 7.69–7.73 (m, 2 H, Ph^{triaz}), 8.18 (br s, 1 H, H-8), 9.14 (s, 1 H, H-2). ¹³C NMR (125 MHz, CDCl₃): 14.14 (CH₃), 30.5 (C-CH₃), 47.3 (CH₂Ph), 72.6 (OCH₂), 105.1 (C(OR)₃), 126.0 (CH^{Ph}), 127.8 (CH^{Ph}), 128.3 (CH^{Ph}), 128.6 (CH^{Ph}), 129.1 (CH^{Ph}), 129.2 (CH^{Ph}), 132.3 (C-5), 135.1 (C_q^{Ph-Bn}), 138.1 (C_q^{Ph-triaz}), 141.6 (C-4' or C-5'), 145.1 (C-8), 149.6 (C-6), 152.0 (C-4), 152.3 (C-2). IR (ATR): 3063 (w), 2966 (w), 2935 (w), 2881 (w), 1595 (m), 1583 (m), 1563 (m), 1498 (m), 1469 (w), 1456 (m), 1396 (w), 1376 (w), 1350 (w), 1328 (m), 1304 (w), 1238 (w), 1209 (w), 1192 (m), 1167 (m), 1064 (m), 1047 (m), 1022 (s), 998 (s), 923 (w), 854 (w), 814 (w), 755 (s), 729 (m), 693 (m). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₆H₂₃N₇NaO₃: 504.1760; found: 504.1752.

6g_B (lower R_F). ¹H NMR (500 MHz, CDCl₃): 0.80 (s, 3 H, CH₃), 3.93 (s, 6 H, OCH₂), 5.44 (s, 2 H, CH₂Ph), 7.24–7.40 (m, 10 H, 2 × Ph), 7.97 (s, 1 H, H-8), 9.06 (s, 1 H, H-2). ¹³C NMR (125 MHz, CDCl₃): 14.4 (CH₃), 30.6 (C-CH₃), 47.4 (CH₂Ph), 72.9 (OCH₂), 105.5 (C(OR)₃), 125.1 (CH^{Ph}), 127.8 (CH^{Ph}), 128.7 (CH^{Ph}), 128.9 (CH^{Ph}), 129.1 (CH^{Ph}), 129.2 (CH^{Ph}), 130.3 (C-4' or C-5'), 133.4 (C-5), 134.8 (C_q^{Ph-Bn}), 136.4 (C_q^{Ph-triaz}), 144.2 (C-4' or C-5'), 145.3 (C-8), 146.9 (C-6), 151.9 (C-4), 152.2 (C-2). IR (ATR): 3065 (w), 2933 (w), 2879 (w), 1617 (w), 1585 (m), 1568 (m), 1499 (m), 1456 (w), 1431 (w), 1399 (m), 1351 (w), 1329 (m), 1226 (m), 1195 (m), 1093 (w), 1075 (m), 1047 (m), 1016 (s), 994 (s), 922 (w), 850 (w), 813 (w), 753 (s), 728 (m), 693 (m). HRMS (ESI⁺): m/z [M + Na]⁺ calculated for C₂₆H₂₃N₇NaO₃: 504.1760; found: 504.1745.

9-Benzyl-6-(1,5-diphenyl-1,2,3-triazol-4-yl)purine (**6n_A**) and
9-Benzyl-6-(1,4-diphenyl-1,2,3-triazol-5-yl)purine (**6n_B**)

The reaction of compound **3n** (93 mg, 0.3 mmol) with phenyl azide, after column chromatography (DCM–ethyl acetate, 4:1), afforded 18 mg (19%) of the starting material and 103 mg (80%) of the mixture of regioisomers **6n_A** and **6n_B**. Separation on chromatotron (DCM–ethyl acetate, 4:1) yielded 52 mg (40%) of **6n_A** as a white powder and 51 mg (40%) of **6n_B** as a colourless wax. Crystallization of **6n_A** (ethyl acetate) afforded colourless crystals; m.p. 192.2–192.5 °C.

6n_A (lower *R_F*). ¹H NMR (300 MHz, CDCl₃): 5.46 (s, 2 H, CH₂), 7.21–7.40 (m, 15 H, 3 × Ph), 8.12 (s, 1 H, H-8), 8.85 (s, 1 H, H-2). ¹³C NMR (75 MHz, CDCl₃): 47.5 (CH₂Ph), 125.8, 127.0, 128.0, 128.5, 128.8, 129.3, 129.5, 129.6, 130.9, 131.6, 135.4, 136.5, 138.3, 141.6, 145.5, 149.2, 152.6. IR (ATR): 3380 (w), 3062 (w), 2920 (w), 2850 (w), 1591 (s), 1548 (m), 1496 (s), 1453 (m), 1400 (m), 1325 (s), 1216 (w), 1189 (m), 1149 (w), 1069 (w), 996 (w), 923 (m), 857 (m), 812 (w), 749 (s), 727 (s), 694 (s), 664 (m), 645 (m), 609 (m), 554 (w). HRMS (EI⁺): calculated for C₂₆H₁₉N₇: 429.1702; found: 429.1713.

6n_B (higher *R_F*). ¹H NMR (300 MHz, CDCl₃): 5.40 (s, 2 H, CH₂), 7.20–7.41 (m, 13 H, Ph), 7.64–7.70 (m, 2 H, Ph), 7.87 (s, 1 H, H-8), 9.07 (s, 1 H, H-2). ¹³C NMR (75 MHz, CDCl₃): 47.7 (CH₂Ph), 125.1, 127.9, 128.1, 128.6, 128.7, 128.8, 129.1, 129.27, 129.32, 129.5, 130.6, 133.3, 134.7, 137.0, 145.9, 147.4, 147.7, 152.5, 153.0. IR (ATR): 3064 (w), 3006 (w), 1599 (m), 1553 (w), 1499 (m), 1456 (w), 1400 (w), 1366 (w), 1328 (m), 1250 (w), 1211 (w), 1159 (w), 1145 (w), 1073 (w), 1001 (m), 921 (w), 851 (w), 813 (w), 754 (s), 726 (m), 696 (s), 644 (w), 572 (w), 517 (w). HRMS (EI⁺): calculated for C₂₆H₁₉N₇: 429.1702; found: 429.1706.

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