# NOVEL METHOD FOR PREPARATION OF HIGHLY SUBSTITUTED 6-ARYLPURINES BY REACTIONS OF 6-ALKYNYLPURINES WITH ZIRCONACYCLOPENTADIENES

Pavel TUREK[a,b], Martin KOTORA[a1,b,*], Michal HOCEK[b1,*] and Ivan VOTRUBA[b2]

[a] *Department of Organic and Nuclear Chemistry, Faculty of Science, Charles University, Hlavova 8, 128 43 Prague 2, Czech Republic; e-mail:* [1] *kotora@natur.cuni.cz*

[b] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic; e-mail:* [1] *hocek@uochb.cas.cz,* [2] *votruba@uochb.cas.cz*

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Reactions of various zirconacyclopentadienes bearing alkyl and aryl groups with 6-alkynylpurines in the presence of $NiBr_2(PPh_3)_2$ afforded the corresponding 6-arylpurines with highly hydrophobic aryl moieties in low to moderate yields. Some of the title purines showed interesting cytostatic activity.

**Keywords**: Purines; Nucleosides; Alkynes; Cyclotrimerizations; Zirconium; Nickel; Cytostatic activity.

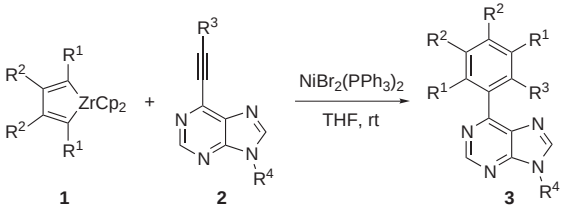
6-Arylpurine derivatives display diverse types of biological activity: some substituted 6-arylpurine bases are antagonists of corticotropin-releasing hormone[1] or possess antimycobacterial and antibacterial activity[2], while 6-arylpurine ribonucleosides are potent cytostatics[3]. Moreover, 6-arylpurines were used as unnatural nucleobases in artificial base-pairs[4] and as covalent base-pair analogues[5]. So far, biological activity screening and other applications (e.g. in chemical biology) have been limited to easily available purines bearing simple aryl groups, while those bearing highly substituted and/or functionalized aryl moieties still remain to be explored. As recently many bulky and hydrophobic aryl *C*-nucleosides were also used[6] as potential nucleobase surrogates in extension of the genetic alphabet, also 6-arylpurines bearing bulky hydrophobic substituents are of particular interest. 6-Arylpurines have been efficiently prepared by cross-coupling reactions[7] of 6-halopurines with various organometallics. Recently, we have reported[8] an alternative method for preparation of 6-arylpurines based on a transition metal complex catalyzed [2+2+2]-co-cyclotrimerization of diynes with 6-alkynylpurines. 6-Alkynylpurines are easily available and also cytostatic

compounds[9] and therefore we have further explored their applicability in the synthesis of modified purine derivatives. Herein, we would like to disclose a novel procedure for preparation of highly alkylated 6-arylpurines starting from 6-alkynylpurines and to report on their cytostatic activity.

Among a number of cyclotrimerization methods, one of the most convenient and general method for the construction of highly substituted benzene rings is based on the reaction of zirconacyclopentadienes[10] with alkynes in the presence of a stoichiometric amount of $NiBr_2(PPh_3)_2$ (lit.[11,12]). This approach has been successfully applied to the synthesis of benzoheterocycles containing group 14 elements[13], haloterphenyls[14] and ferrocenylarynes[15]. There are several factors that favor the above mentioned method: first, zirconacyclopentadienes are easily prepared with a great variety of substituents and they are stable at room temperature and, second, alkynylpurines can be easily prepared from commonly accessible starting material. Moreover, $NiBr_2(PPh_3)_2$ is a stable and cheap compound.

## RESULTS AND DISCUSSION

Reactions of zirconacyclopentadienes **1** with alkynylpurines **2** in the presence of $NiBr_2(PPh_3)_2$ were carried out under standard conditions[11] (Scheme 1). The zirconacyclopentadienes bearing Et, Pr and Ph groups **1a**–**1c** and the bicyclic zirconacyclopentadiene **1d** prepared from 1,8-diphenylocta-1,7-diyne were tested in the cyclotrimerization reactions. As to 6-alkynylpurines[16], those bearing hex-1-yn-1-yl, 2-phenylethynyl and 2-trimethylsilylethynyl moieties with benzyl **2aa**–**2ca** or THP **2ab**, **2bb** protective groups in position 9 were selected. The obtained results are summarized in Table I.



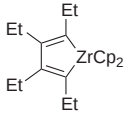
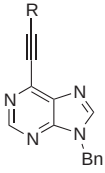
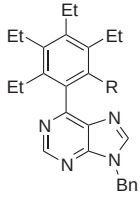
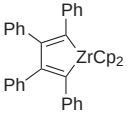
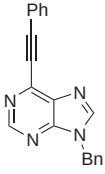
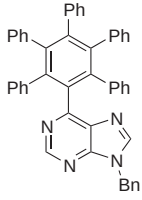
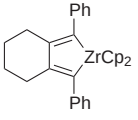
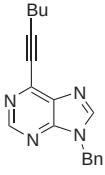
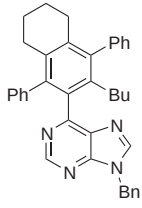
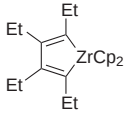
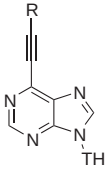
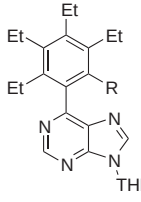
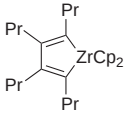
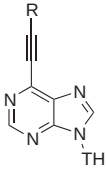
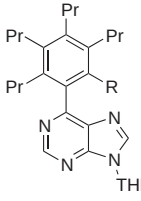
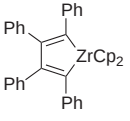
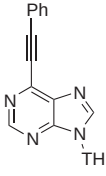
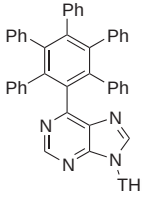

**1** **2** **3**

| **1** | $R^1$ | $R^2$ | **2** | $R^3$ | $R^4$ |
|---|---|---|---|---|---|
| **a** | Et | Et | **aa** | Bu | Bn |
| **b** | Pr | Pr | **ba** | Ph | Bn |
| **c** | Ph | Ph | **ca** | TMS | Bn |
| **d** | Ph | $-(CH_2)_4-$ | **ab** | Bu | THP |
| | | | **bb** | Ph | THP |

**3*xyz***
***x*** denotes $R^1$, $R^2$
***y*** denotes $R^3$
***z*** denotes $R^4$

SCHEME 1

TABLE I
Reaction of zirconacyclopentadienes **1** with alkynylpurines **2**

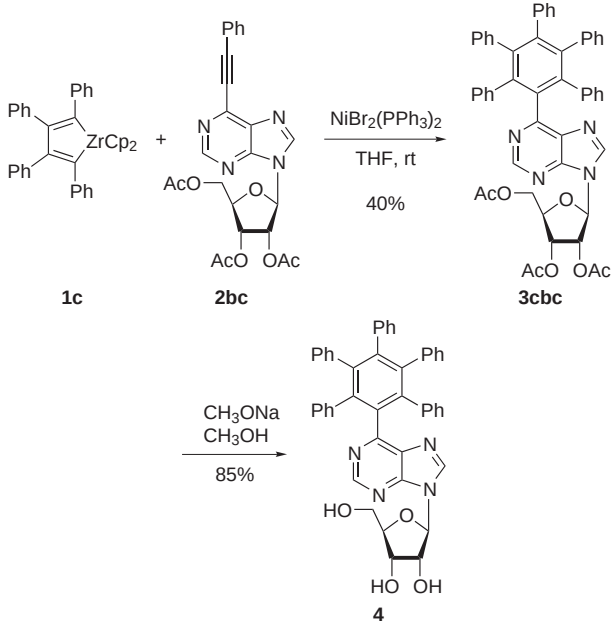
| Zirconacycle | Alkyne | Product | Isolated yield (%) |
|---|---|---|---|
|  **1a** |  **2aa** **2ba** **2ca** |  **3aaa**; R = Bu<br>**3aba**; R = Ph<br>**3aca**; R = $SiMe_3$ | 25<br>24<br>21 |
|  **1c** |  **2ba** |  **3cba** | 24 |
|  **1d** |  **2aa** |  **3daa** | 12 |
|  **1a** |  **2ab** **2bb** |  **3aab**; R = Bu<br>**3abb**; R = Ph | 19<br>17 |
|  **1b** |  **2ab** **2bb** |  **3bab**; R = Bu<br>**3bbb**; R = Ph | 21<br>21 |
|  **1c** |  **2bb** |  **3cbb** | 18 |

Generally, the obtained yields of the corresponding 6-arylpurines **3** were rather low. Thus the reactions of tetraethylzirconacyclopentadiene **1a** with benzyl-protected alkynes **2aa**, **2ba** and **2ca** afforded the corresponding arylpurines **3aaa**, **3aba** and **3aca** in 25, 24 and 21% yields, respectively. The reaction of tetraphenylzirconacyclopentadiene **1c** with **2ba** afforded pentaphenylphenylpurine **3cba** in 24% yield. A disappointingly low yield of the product **3daa** (12%) was obtained in the reaction of the bicyclic zirconacyclopentadiene **1d** with **2aa**. Previously, we observed that the change of a protective group from benzyl to tetrahydropyranyl had positive effect on the yield of cyclotrimerization in catalytic reactions[8b]. We hoped that the exchange of the protective group might have the same effect in this reaction as well. Unfortunately, our expectations were not materialized. The yields of the reaction with THP-protected alkynylpurines were in the same range as with the benzyl-protected ones. Thus the reaction of tetraethylzirconacyclopentadiene **1a** with THP-protected alkynes **2ba** and **2bb** afforded the corresponding arylpurines in 19 and 17% yields. The use of tetrapropylzirconacyclopentadiene **1b** with the same alkynes furnished arylpurines in 21% yields. Similarly, the reaction of tetraphenylzirconacyclopentadiene **1c** with **2bb** furnished the pentaphenylphenyl-derivative **3cbb** in 18% yield. The unsymmetrically substituted arylpurines **3aab**–**3dbb**, except for the symmetrical **3cbb**, were obtained as 1:1 mixtures of diastereoisomers, because of the presence of a chiral center in THP moiety and axial chirality caused by restricted rotation along the C–C bond connecting the aryl and the purine rings.

In addition, an applicability of this approach in the synthesis of modified nucleosides was demonstrated. The reaction of tetraphenylzirconacyclopentadiene **1c** with acetylated 9-(phenylethynyl)purine ribonucleosides **2bc** was carried out to afford the corresponding protected 6-(pentaphenylphenyl)purine nucleoside **3cbc** in reasonable yield of 40%. Its deprotection using sodium methoxide in methanol proceeded smoothly to give 6-(pentaphenylphenyl)purine ribonucleoside **4** in 85% yield (Scheme 2).

The relatively low isolated yields of the cyclotrimerizations could be mainly attributed to difficulties encountered during separation of the products in reasonable purity from the reaction mixture. In addition, a part of the alkynylpurines must have been also consumed by side-reactions, because analyses of the reaction mixtures (NMR, TLC) indicated that the starting alkynylpurines **2** underwent in all of the cases total conversion. In this regard, one of the possible explanations may lie in the reaction mechanism of the whole process. It has been shown that in the course of the reaction the zirconacyclopentadienes are transmetallated into nickelacyclopenta-

dienes that in turn react with alkynes to give the benzenes. In this step Ni(0) species is also released[11]; therefore we assume that the Ni(0) species partially oligomerized the alkynylpurines. This assumption was supported by the observation and isolation of a tar-like material which, according to NMR spectra, seemed to be a complex mixture of products containing purine rings. Nevertheless, despite the low to moderate yields, this approach is very straightforward and enables the synthesis of a highly substituted benzene ring containing a purine or nucleoside moiety in a single step. Moreover, the starting compounds are relatively simple and easily available. Therefore we believe that this methodology will find further applications in the synthesis of highly substituted hydrophobic nucleobases and nucleosides.




**1c** **2bc** **3cbc** **4**

SCHEME 2

Preliminary in vitro cytostatic activity tests of some representative examples of title compounds were performed using the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 219), human promyelocytic leukemia HL60 cells (ATCC CCL 240), human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2) and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). The most active was **3aba** ($IC_{50}$ = 7.0, 6.4 and 10.9 μM against L1210, HL60 and CCRF-CEM cell-lines, respectively). Slightly lower activities were found with **3aaa** ($IC_{50}$ = 23.0, 10.0 and 10.0 μM, respectively) and

**3aca** ($IC_{50}$ = 7.7, 14.0 and 21.0 μM, respectively), while purine **3cba** and nuclerosides **3cbc** and **4** were entirely inactive. Though the activities in micromolar range are probably below the therapeutically useful level, this novel type of compounds definitely represents a new structural lead in the search of antiproliferative drugs.

In summary, the reaction of zirconacyclopentadienes with 6-alkynylpurines constitutes the first application of zirconocene-based cyclotrimerization method for synthesis of biologically active compounds, namely a simple and straightforward method for the preparation of 6-arylpurines with highly substituted hydrophobic aryl moieties. In addition, preliminary tests showed interesting antiproliferative activity of some of the title compounds in culture cells of leukemia and cancer. Further investigations will focus both on the optimization of conditions in order to improve yields and on extension of the series of this promising class of compounds for SAR (structure–activity relationship) study.

## EXPERIMENTAL

All reactions were carried out under inert atmosphere (Ar). THF was distilled from benzophenone and sodium prior to use. $NiBr_2(PPh_3)_2$ (lit.[17]) and alkynylpurines[9,16] were prepared according to previously published procedures. Hex-3-yne, oct-4-yne, diphenylacetylene, zirconocene dichloride and butyllithium (1.6 M solution in hexanes) were purchased from Aldrich. All other chemicals and solvents were of commercial purity and were used without further purification.

Melting points were determined on a Kofler block. Optical rotations were measured on an Autopol III polarimeter; $[\alpha]_D$ values are given in $10^{-1}$ deg $cm^2$ $g^{-1}$. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Varian Unity Inova 400 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) are given in Hz. Infrared spectra (wavenumbers in $cm^{-1}$) were recorded on a PE-640 Perkin–Elmer spectrometer. Mass spectra were obtained on a ZAB-SEQ VG Analytical spectrometer. Elemental analyses were obtained on a Perkin–Elmer 2400 elemental analyser. TLC was performed on Merck Silica Gel 60 $F_{254}$ aluminium sheets and column chromatography was performed on Fluka Silica Gel 60.

6-(Phenylethynyl)-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine (**2bc**)

DMF (8 ml) and $Et_3N$ (2 ml) were added through a septum to an argon purged flask containing 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (1.3 g, 3.15 mmol), phenylacetylene (1.2 g, 10 mmol), CuI (100 mg, 0.53 mmol) and $Pd(PPh_3)_4$ (100 mg, 0.087 mmol). The mixture was stirred at 120 °C for 7 h. The solvents were evaporated and the residue was chromatographed on a silica gel column (200 g, ethyl acetate/petroleum ether 1:2 to 2:1) to give the product (1.2 g, 80%) as brownish oil. $^1$H NMR ($CDCl_3$): 2.09, 2.13 and 2.16 3 × s, 3 × 3 H ($CH_3$); 4.36–4.50 m, 3 H (H-4′ and 2 × H-5′); 5.69 dd, 1 H, *J* = 4.6 and 5.1 (H-3′); 5.99 t, 1 H, *J* = 5.1 (H-2′); 6.26 d, 1 H, *J* = 5.1 (H-1′); 7.39–7.44 m, 3 H (H-arom.); 7.73–7.75 m,

2 H (H-arom.); 8.30 s, 1 H (H-8); 8.98 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 20.33, 20.49 and 20.71 (3 × $CH_3$); 62.98 ($CH_2$-5′); 70.61 (CH-3′); 73.10 (CH-2′); 80.53 (CH-4′); 83.98 (C≡); 86.55 (CH-1′); 99.00 (C≡); 121.30 (C-*i*-arom.); 128.45, 130.03, 132.73 (3 × CH-arom.); 134.87 (C-5); 142.47 and 151.17 (C-4 and C-6); 148.53 (CH-8); 152.89 (CH-2); 169.30, 169.52 and 170.25 (3 × CO). IR ($CHCl_3$): 2215, 1751, 1599, 1582, 1489, 1443, 1374, 1334, 1232. FAB MS, *m/z* (rel.%): 479 (6) [M + H], 221 (62), 139 (88), 97 (100). Exact mass (FAB HR MS) calculated for $C_{24}H_{23}N_4O_7$ [M + H]: 479.1567; found: 479.1551.

Reactions of 6-Alkynylpurines with Zirconacyclopentadienes. General Procedure

Alkynylpurine **2** (1 mmol) and $NiBr_2(PPh_3)_2$ (742 mg, 1 mmol) were added into a solution of zirconacyclopentadiene **1** (1 mmol) in THF (5 ml) under Ar atmosphere and the reaction mixture was stirred at 20 °C overnight. Then it was quenched with 3 M HCl and extracted with EtOAc (3 × 5 ml). Combined organic extracts were washed with saturated solutions of $NaHCO_3$, NaCl, and dried over anhydrous $MgSO_4$. Column chromatography on silica gel was used to obtain the products.

*9-Benzyl-6-(2-butyl-3,4,5,6-tetraethylphenyl)-9H-purine* (**3aaa**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 113 mg (25%) of **3aaa** as a colorless solid. M.p. 96–97 °C (hexane). $^1$H NMR ($CDCl_3$): 0.43 t, 3 H, *J* = 7.3 ($CH_3$); 0.86 t, 3 H, *J* = 7.3 ($CH_3$); 1.17 t, 3 H, *J* = 7.3 ($CH_3$); 1.19 t, 6 H, *J* = 7.3 (2 × $CH_3$); 2.08–2.15 m, 2 H ($CH_2$); 2.15–2.35 m, 2 H ($CH_2$); 2.62–2.76 m, 6 H (3 × $CH_2$); 5.45 d, 1 H, *J* = 15.1 (C**H**$_2$Ph); 5.56 d, 1 H, *J* = 15.1 (C**H**$_2$Ph); 7.3–7.4 m, 5 H (Ph); 8.02 s, 1 H (H-8); 9.09 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 13.08, 15.41, 15.74, 15.78, 21.08, 21.93, 22.13, 22.86, 23.69, 25.48, 30.27, 32.87, 47.13, 67.82, 127.61, 128.43, 129.02, 133.29, 133.31, 135.19, 136.09, 137.06, 137.68, 137.87, 141.11, 144.05, 151.34, 152.47, 161.81. IR ($CHCl_3$): 2967, 1589, 1455, 1327. Exact mass (EI HR MS) calculated for $C_{30}H_{38}N_4$: 454.3096; found: 454.3081. $R_F$ 0.50 (hexane/EtOAc 1:1).

*9-Benzyl-6-(6-phenyl-2,3,4,5-tetraethylphenyl)-9H-purine* (**3aba**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 56 mg (24%) of a white solid. M.p. 174–175 °C (hexane). $^1$H NMR ($CDCl_3$): 0.90 t, 3 H, *J* = 7.2 ($CH_3$); 0.93 t, 3 H, *J* = 7.2 ($CH_3$); 1.24 t, 3 H, *J* = 7.2 ($CH_3$); 1.28 t, 3 H, *J* = 7.2 ($CH_3$); 2.38–2.56 m, 2 H ($CH_2$); 2.44 q, 2 H, *J* = 7.2 ($CH_2$); 2.78 q, 2 H, *J* = 7.2 (2 × $CH_2$); 5.25 d, 1 H, *J* = 15.5 (C**H**$_2$Ph); 5.44 d, 1 H, *J* = 15.5 (C**H**$_2$Ph); 6.76–7.06 m, 7 H (Ph); 7.30–7.40 m, 3 H (Ph); 7.87 s, 1 H (H-8); 8.81 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 15.49, 15.52, 15.79, 15.81, 21.92, 22.20, 23.01, 23.66, 46.63, 125.51, 126.05, 126.49, 126.93, 128.20, 128.90, 129.76, 130.42, 132.92, 133.12, 135.33, 136.69, 137.80, 139.16, 139.47, 140.29, 140.96, 143.68, 150.93, 151.75, 161.13. IR ($CHCl_3$): 2973, 1593, 1498, 1455, 1330, 1221. EI MS, *m/z* (rel.%): 474 (27) [$M^+$], 383 (100). Exact mass (EI HR MS) calculated for $C_{32}H_{34}N_4$: 474.2783; found: 474.2763. $R_F$ 0.42 (hexane/EtOAc 1:1).

*9-Benzyl-6-[2,3,4,5-tetraethyl-6-(trimethylsilyl)phenyl]-9H-purine* (**3aca**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 50 mg (21%) of a white solid. M.p. 128–129 °C (hexane). $^1$H NMR ($CDCl_3$): –0.28 s, 9 H ($Si(CH_3)_3$); 0.79 t, 3 H, *J* = 7.5 ($CH_3$); 1.17 t, 3 H, *J* = 7.5 ($CH_3$); 1.18 t, 3 H, *J* = 7.2 ($CH_3$); 1.20 t, 3 H, *J* = 7.2 ($CH_3$); 2.16–2.32 m, 2 H ($CH_2$); 2.71 q, 2 H, *J* = 7.5 ($CH_2$); 2.78 q, 2 H, *J* = 7.5 ($CH_2$); 2.89 q, 2 H, *J* = 7.5 ($CH_2$); 5.44 d, 1 H, *J* = 15.3 (C**H**$_2$Ph); 5.54 d, 1 H, *J* = 15.3 (C**H**$_2$Ph); 7.25–7.29 m, 2 H (Ph); 7.33–7.40 m, 3 H (Ph); 8.02 s, 1 H (H-8); 9.04 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 2.88, 15.25, 15.61, 16.07, 17.43, 21.72, 22.04, 23.24, 26.46, 47.13, 127.46, 128.44, 129.08, 133.95, 134.42, 135.28, 136.92, 139.41, 141.27, 141.64, 144.03, 146.54, 151.16, 152.07, 162.63. IR ($CHCl_3$): 2974, 2938, 2907, 2877, 1589, 1578, 1499, 1455, 1378, 1331, 1250, 1222, 1218, 861, 844. EI MS, *m/z*

(rel.%): 470 (9) [$M^+$], 455 (28), 441 (28), 397 (16), 379 (11), 91 (100). Exact mass (EI HR MS) calculated for $C_{29}H_{38}N_4Si$: 470.2866; found: 470.2893. For $C_{29}H_{38}N_4Si$ (470.7) calculated: 74.00% C, 8.14% H, 11.90% N; found: 73.90% C, 8.29% H, 11.53% N. $R_F$ 0.53 (hexane/EtOAc 1:1).

*9-Benzyl-6-(2,3,4,5,6-pentaphenylphenyl)-9H-purine* (**3cba**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 80 mg (24%) of a white solid. M.p. 265–266 °C (hexane). $^1$H NMR ($CDCl_3$): 5.28 s, 2 H (C**H**$_2$Ph); 6.62–6.70 m, 27 H (Ph); 7.25–7.30 m, 3 H (Ph); 7.80 s, 1 H (H-8); 8.62 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 46.53, 125.33, 125.53, 126.36, 126.58, 128.17, 128.90, 130.36, 130.81, 131.15, 131.21, 131.24, 131.38, 133.15, 134.56, 135.40, 139.49, 139.85, 140.01, 140.28, 140.43, 142.14, 144.02, 150.68, 151.52, 159.91. IR ($CHCl_3$): 2975, 1593, 1498, 1329. EI MS, *m/z* (rel.%): 666 (56) [$M^+$], 575 (15), 91 (100). Exact mass (EI HR MS) calculated for $C_{48}H_{34}N_4$: 666.2783; found: 666.2769. $R_F$ 0.39 (hexane/EtOAc 1:1).

*9-Benzyl-6-(3-butyl-1,4-diphenyl-5,6,7,8-tetrahydro-2-naphthyl)-9H-purine* (**3daa**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 32 mg (12%) of a white solid. M.p. 85–86 °C (hexane). $^1$H NMR ($CDCl_3$): 0.23 t, 3 H, $J$ = 7.2 ($CH_3$); 0.56–0.72 m, 2 H ($CH_2$); 0.94–1.06 m, 1 H ($CH_2$); 1.18–1.30 m, 1 H ($CH_2$); 1.54–1.68 m, 4 H ($CH_2$); 1.96–2.04 m, 1 H ($CH_2$); 2.14–2.22 m, 1 H ($CH_2$); 2.30–2.40 m, 3 H ($CH_2$); 2.44–2.52 m, 1 H ($CH_2$); 5.33 d, 1 H, $J$ = 15.5 (C**H**$_2$Ph); 5.41 d, 1 H, $J$ = 15.5 (C**H**$_2$Ph); 6.87–7.13 m, 7 H (Ph); 7.25–7.45 m, 8 H (Ph); 7.88 s, 1 H (H-8); 8.84 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 12.92. 22.52, 22.95, 23.09, 28.79, 29.45, 30.66, 32.79, 46.76, 125.86, 126.47, 126.64, 126.94, 127.09, 128.07, 128.16, 128.30, 128.99, 129.57, 129.60, 129.64, 130.07, 132.14, 132.76, 133.16, 135.45, 135.61, 136.50, 139.88, 140.36, 140.87, 141.09, 143.88, 151.01, 151.92, 160.56. IR ($CHCl_3$): 2936, 1590, 1496, 1328. EI MS, *m/z* (rel.%): 548 (16) [$M^+$], 457 (60), 414 (8), 91 (100). Exact mass (EI HR MS) calculated for $C_{38}H_{36}N_4$: 548.2940; found: 548.2966. $R_F$ 0.47 (hexane/EtOAc 1:1).

*6-(2-Butyl-3,4,5,6-tetraethylphenyl)-9-(tetrahydropyran-2-yl)-9H-purine* (**3aab**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 42 mg (19%) of a yellow liquid. $^1$H NMR ($CDCl_3$): 0.46 t, 1.5 H, $J$ = 7.4 ($CH_3$); 0.52 t, 1.5 H, $J$ = 7.4 ($CH_3$); 0.84 t, 1.5 H, $J$ = 7.5 ($CH_3$); 0.85 t, 1.5 H, $J$ = 7.5 ($CH_3$); 0.88–1.00 m, 2 H (2 × $CH_2$); 1.16–1.22 m, 9 H (6 × $CH_3$); 1.30–1.40 m, 1 H ($CH_2$); 1.66–1.90 m, 4 H (4 × $CH_2$); 2.00–2.30 m, 7 H (7 × $CH_2$); 2.62–2.75 m, 6 H (6 × $CH_2$); 3.80–3.88 m, 1 H (2 × $CH_2$-O); 4.19–4.25 m, 1 H (2 × $CH_2$-O); 5.85–5.92 m, 1 H (2 × CH-O); 8.25 s, 0.5 H (H-8); 8.27 s, 0.5 H (H-8); 9.04 s, 0.5 H (H-2); 9.05 s, 0.5 H (H-2). $^{13}$C NMR ($CDCl_3$): 13.12, 13.26, 15.48, 15.84, 21.86, 21.97, 22.18, 22.80, 22.88, 22.96, 23.71, 24.83, 30.31, 30.38, 31.66, 31.75, 32.91, 33.08, 133.24, 133.49, 136.06, 136.19, 137.04, 137.16, 137.68, 137.77, 137.87, 137.94, 141.19, 141.89, 142.05, 150.50, 152.31, 152.36, 161.92, 161.95. IR ($CHCl_3$): 2968, 1590, 1454, 1043. EI MS, *m/z* (rel.%): 448 (8) [$M^+$], 363 (100), 335 (20), 321 (14), 85 (28). Exact mass (EI HR MS) calculated for $C_{28}H_{40}N_4O$: 448.320212; found: 448.318209. $R_F$ 0.44 (hexane/EtOAc 1:1).

*6-(6-Phenyl-2,3,4,5-tetraethylphenyl)-9-(tetrahydropyran-2-yl)-9H-purine* (**3abb**). Column chromatography on silica gel (hexane/EtOAc 2:1) afforded 40 mg (17%) of a yellow liquid. $^1$H NMR ($CDCl_3$): 0.88 t, 1.5 H, $J$ = 7.5 ($CH_3$); 0.89 t, 1.5 H, $J$ = 7.5 ($CH_3$); 0.90 t, 3 H, $J$ = 7.5 (2 × $CH_3$); 1.24 t, 3 H, $J$ = 7.5 (2 × $CH_3$); 1.26 t, 1.5 H, $J$ = 7.5 ($CH_3$); 1.27 t, 1.5 H, $J$ = 7.5 ($CH_3$); 1.60–1.67 m, 1 H ($CH_2$); 1.67–1.80 m, 2 H (2 × $CH_2$); 1.95–2.12 m, 3 H (3 × $CH_2$); 2.30–2.48 m, 2 H (2 × $CH_2$); 2.43 q, 2 H, $J$ = 7.5 (2 × $CH_2$); 2.77 q, 4 H, $J$ = 7.5 (8 × $CH_2$); 3.70–3.80 m, 1 H (2 × $CH_2$-O); 4.12–4.18 m, 1 H (2 × $CH_2$-O); 5.65–5.71 m, 1 H (2 × CH-O); 6.78–7.08 m, 5 H (2 × Ph); 8.12 s, 0.5 H (H-8); 8.13 s, 0.5 H (H-8); 8.76 s, 0.5 H (H-2); 8.77 s, 0.5 H (H-2). $^{13}$C NMR ($CDCl_3$): 15.53, 15.84, 21.95, 22.23, 22.70, 23.03, 23.64, 24.79, 31.55,

31.71, 68.70, 81.45, 81.94, 125.62, 125.82, 126.10, 126.47, 126.51, 126.55, 129.55, 129.68, 130.44, 133.08, 133.17, 133.22, 136.71, 136.80, 137.82, 137.94, 139.10, 139.42, 139.52, 140.19, 140.30, 141.00, 141.37, 141.66, 150.00, 151.59, 161.18. IR ($CHCl_3$): 2971, 1590, 1495, 1084, 1042. EI MS, *m/z* (rel.%): 468 (3) [$M^+$], 383 (65), 43 (100). Exact mass (EI HR MS) calculated for $C_{30}H_{36}N_4O$: 468.288912; found: 468290024. $R_F$ 0.34 (hexane/EtOAc 1:1).

*6-(2-Butyl-3,4,5,6-tetrapropylphenyl)-9-(tetrahydropyran-2-yl)-9H-purine* (**3bab**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 52 mg (21%) of a yellow liquid. $^1$H NMR ($CDCl_3$): 0.46 t, 1.5 H, *J* = 7.5 ($CH_3$); 0.53 t, 1.5 H, *J* = 7.5 ($CH_3$); 0.54 t, 1.5 H, *J* = 7.5 ($CH_3$); 0.58 t, 1.5 H, *J* = 7.5 ($CH_3$); 0.84–0.98 m, 2 H (2 × $CH_2$); 1.01 t, 1.5 H, *J* = 7.2 ($CH_3$); 1.02 t, 3 H, *J* = 7.2 (2 × $CH_3$); 1.03 t, 1.5 H, *J* = 7.2; 1.06 t, 3 H, *J* = 7.2 (2 × $CH_3$); 1.14–1.28 m, 2 H (2 × $CH_2$); 1.28–1.42 m, 2 H (2 × $CH_2$); 1.48–1.60 m, 6 H (6 × $CH_2$); 1.66–1.72 m, 1 H ($CH_2$); 1.72–1.90 m, 2 H (2 × $CH_2$); 1.98–2.22 m, 7 H (7 × $CH_2$); 2.50–2.60 m, 6 H (6 × $CH_2$); 3.80–3.90 m, 1 H (2 × $CH_2$-O); 4.19–4.26 m, 1 H (2 × $CH_2$-O); 5.85–5.92 m, 1 H (2 × CH-O); 8.25 s, 0.5 H (H-8); 8.26 s, 0.5 H (H-8); 9.04 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 13.10, 13.25, 14.69, 14.74, 15.05, 15.10, 15.13, 22.78, 22.88, 22.97, 24.43, 24.82, 24.88, 30.41, 30.50, 31.65, 31.79, 31.89, 32.17, 32.87, 33.04, 33.32, 68.83, 81.86, 81.93, 133.17, 133.41, 136.06, 136.18, 136.65, 136.69, 136.74, 140.16, 141.89, 142.00, 150.41, 150.46, 152.27, 162.02. IR ($CHCl_3$): 2958, 1587, 1457, 1086. EI MS, *m/z* (rel.%): 504 (2) [$M^+$], 419 (48), 85 (65), 83 (100). Exact mass (EI HR MS) calculated for $C_{32}H_{48}N_4O$: 504.382813; found: 504.3874638. $R_F$ 0.54 (hexane/EtOAc 1:1).

*6-(2-Phenyl-3,4,5,6-tetrapropylphenyl)-9-(tetrahydropyran-2-yl)-9H-purine* (**3bbb**). Column chromatography on silica gel (hexane/EtOAc 3:1) afforded 54 mg (21%) of a yellow liquid. $^1$H NMR ($CDCl_3$): 0.58 t, 1.5 H, *J* = 7.3 ($CH_3$); 0.62 t, 1.5 H, *J* = 7.3 ($CH_3$); 0.66 t, 3 H, *J* = 7.3 (2 × $CH_3$); 1.07 t, 1.5 H, *J* = 7.3 ($CH_3$); 1.08 t, 4.5 H, *J* = 7.3 (3 × $CH_3$); 1.20–1.34 m, 4 H (4 × $CH_2$); 1.54–1.80 m, 7 H (7 × $CH_2$); 1.90–2.14 m, 3 H (3 × $CH_2$); 2.14–2.42 m, 4 H (4 × $CH_2$); 2.60–2.68 m, 4 H (4 × $CH_2$); 3.70–3.80 m, 1 H (2 × $CH_2$-O); 4.12–4.18 m, 1 H (2 × $CH_2$-O); 5.64–5.70 m, 1 H (2 × CH-O); 6.76–7.05 m, 5 H (2 × Ph); 8.10 s, 0.5 H (H-8); 8.12 s, 0.5 H (H-8); 8.75 s, 0.5 H (H-2); 8.76 s, 0.5 H (H-2). $^{13}$C NMR ($CDCl_3$): 14.67, 14.74, 15.12, 22.63, 24.45, 24.76, 24.83, 24.90, 31.63, 31.85, 32.14, 32.57, 33.12, 68.65, 81.47, 81.89, 125.49, 125.72, 125.96, 126.38, 126.46, 129.52, 129.68, 130.35, 133.00, 133.06, 133.13, 135.67, 135.73, 136.63, 136.77, 138.34, 138.44, 139.10, 139.97, 140.22, 140.32, 141.29, 141.59, 149.89, 151.46, 161.23. IR ($CHCl_3$): 2958, 1590, 1457, 1082, 1049. EI MS, *m/z* (rel.%): 524 (2) [$M^+$], 439 (100), 411 (8). Exact mass (EI HR MS) calculated for $C_{34}H_{44}N_4O$: 524.351512; found: 524.351352. $R_F$ 0.46 (hexane/EtOAc 1:1).

*6-(Pentaphenylphenyl)-9-(tetrahydropyran-2-yl)-9H-purine* (**3cbb**). Column chromatography on silica gel (hexane/EtOAc 2:1) afforded 58 mg (18%) of a white solid. M.p. > 350 °C ($CH_2Cl_2$/hexane). $^1$H NMR ($CDCl_3$): 1.59–1.77 m, 3 H (1.5 × $CH_2$); 1.83–2.04 m, 3 H (1.5 × $CH_2$); 3.70 dt, 1 H, *J* = 11.6, 2.7 ($CH_2O$); 4.06–4.14 m, 1 H ($CH_2O$); 5.58 dd, 1 H, *J* = 9.6, 3.3 (CH-O); 6.60–7.04 m, 25 H (5 × Ph); 8.05 s, 1 H (H-8); 8.58 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 22.58, 24.77, 31.65, 68.66, 81.72, 125.29, 125.44, 125.70, 126.22, 126.45, 130.12, 130.39, 130.66, 130.83, 131.14, 131.20, 131.23, 131.25, 131.34, 133.37, 134.46, 139.31, 139.40, 139.87, 139.96, 140.07, 140.30, 140.33, 140.49, 141.63, 142.08, 149.602, 151.20, 159.82. IR ($CHCl_3$): 2955, 1593, 1442, 1086, 1046. EI MS, *m/z* (rel.%): 660 (2) [$M^+$], 576 (18), 55 (100). Exact mass (EI HR MS) calculated for $C_{28}H_{40}N_4O$: 660.288912; found: 660.287432. $R_F$ 0.52 (hexane/EtOAc 1:2).

*6-(Pentaphenylphenyl)-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-9H-purine* (**3cbc**). Column chromatography on silica gel (toluene/EtOAc 5:2) afforded 167 mg (40%) of a white solid. M.p.

137–138 °C, $[\alpha]_D$ –13.6 (*c* 0.14, $CHCl_3$). $^1$H NMR ($CDCl_3$): 2.02 s, 3 H ($CH_3$); 2.09 s, 3 H ($CH_3$); 2.12 s, 3 H ($CH_3$); 4.24 m, 1 H (H-5′b); 4.37–4.44 m, 2 H (H-4′, H-5′a); 5.55 m, 1 H (H-3′); 5.65 t, $J_{2',3'}$ = 5.4, $J_{2',1'}$ = 5.2, 1 H (H-2′); 6.06 d, $J_{1',2'}$ = 5.2, 1 H (H-1′); 6.65–6.98 m, 25 H (5 × Ph); 7.98 s, 1 H (H-8); 8.60 s, 1 H (H-2). $^{13}$C NMR ($CDCl_3$): 20.25, 20.50, 20.72, 62.89, 70.40, 73.19, 80.27, 86.01, 125.37, 125.65, 125.73, 126.34, 126.47, 126.51, 126.62, 130.30, 130.72, 130.79, 131.14, 131.21, 131.25, 131.37, 133.87, 134.28, 139.30, 139.32, 139.80, 139.81, 140.00, 140.06, 140.25, 140.49,140.51, 141.93, 142.29, 149.95, 151.56, 160.43, 168.99, 169.49, 170.20. IR ($CHCl_3$): 1752, 1595, 1578, 1496, 1443, 1374, 1227, 700. FAB MS, *m/z* (rel.%): 835 (10) [M + H], 577 (12), 279 (43). FAB HR MS calculated for $C_{52}H_{43}N_4O_7$ [M + H]: 835.3132; found: 835.3105. $R_F$ 0.51 (toluene/EtOAc 1:1).

6-(Pentaphenylphenyl)-9-(β-D-ribofuranosyl)-9*H*-purine (**4**)

Compound **3cbc** (150 mg, 0.18 mmol) in methanol (9 ml) was treated with 1 M solution of MeONa in MeOH (36 µl, 0.036 mmol) at room temperature for 1 h. The reaction mixture was extracted with $CH_2Cl_2/H_2O$ and dried over anhydrous $Na_2SO_4$. Evaporation afforded a white solid 108 mg (85%). M.p. > 360 °C, $[\alpha]_D$ –46.9 (*c* 0.15, MeOH). $^1$H NMR (DMSO-$d_6$): 3.50 ddd, $J_{gem}$ = 12.0, $J_{5'b,OH}$ = 5.6, $J_{5'b,4'}$ = 4.1, 1 H (H-5′b); 3.62 ddd, $J_{gem}$ = 12.0, $J_{5'a,OH}$ = 5.6, $J_{5'a,4'}$ = 4.0, 1 H (H-5′a); 3.88 q, $J_{4',5'}$ = 4.1, 4.0, $J_{4',3'}$ = 4.0, 1 H (H-4′); 4.05 td, $J_{3',OH}$ = 5.2, $J_{3',2'}$ = 5.0, $J_{3',4'}$ = 4.0, 1 H (H-3′); 4.30 bq, $J_{2',OH}$ = 6.4, $J_{2',1'}$ = 5.6, $J_{2',3'}$ = 5.0, 1 H (H-2′); 5.07 t, $J_{OH,5'}$ = 5.6, 1 H (OH-5′); 5.21 d, $J_{OH,3'}$ = 5.2, 1 H (OH-3′); 5.40 d, $J_{OH,2'}$ = 6.4, 1 H (OH-2′); 5.81 d, $J_{1',2'}$ = 5.6, 1 H (H-1′); 6.61–6.98 m, 25 H (5 × Ph); 8.51 s, 1 H (H-2); 8.64 s, 1 H (H-8). $^{13}$C NMR (DMSO-$d_6$): 61.30, 70.14, 73.89, 85.51, 87.15, 125.69, 126.00, 126.04, 126.33, 126.45, 126.78, 129.80, 130.64, 130.73, 130.90, 130.98, 131.14, 133.66, 134.85, 138.97, 139.63, 139.69, 140.02, 140.17, 141.56, 144.17, 150.28, 150.74, 158.59. IR (KBr): 3368, 1593, 1578, 1496, 1442, 1331. FAB MS, *m/z* (rel.%): 709 (26) [M + H], 619 (12), 577 (100), 279 (7). FAB HR MS calculated for $C_{46}H_{37}N_4O_4$ [M + H]: 709.2815; found: 709.2836.

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