COVALENT ANALOGUES OF DNA BASE-PAIRS AND TRIPLETS IV*. SYNTHESIS OF TRISUBSTITUTED BENZENES BEARING PURINE AND/OR PYRIMIDINE RINGS BY CYCLOTRIMERIZATION OF 6-ETHYNYLPURINES AND/OR 5-ETHYNYL-1,3-DIMETHYLURACIL

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Ni-Catalyzed cyclotrimerizations of 6-ethynylpurines 3 or 5-ethynyl-1,3-dimethyluracil (4) afforded the 1,2,4-tris(purin-6-yl)benzenes 7 or 1,2,4-tris(1,3-dimethyluracil-5-yl)benzene (9), respectively. The symmetrical 1,3,5-tris(purin-6-yl)benzenes 8 were also formed as minor products in very low yields. Co-cyclotrimerization of 9-benzyl-6-ethynylpurine (3a) with 4 afforded the tris(purinyl)benzene 7a as a major product along with 1,2-bis(9-benzylpurin-6-yl)-4-(1,3-dimethyluracil-5-yl)benzene (10) and a complex mixture of other derivatives and isomers. Compounds 7–10 are analogues of Hoogsteen base-triplets.

Keywords: Purines; Pyrimidines; Nucleobases; Hoogsteen triplets; Cyclotrimerizations; Nickel; Alkynes; [2+2+2] Cycloadditions.

Two main hydrogen bonding motifs exist in DNA: the Watson–Crick motif in duplexes and the Hoogsteen motif in triplexes. Hydrogen bonding is crucial to the ability of the two strands to stay annealed to each other but equally important is the ability to separate from one another in the right moment. Therefore the effect of many clinically used antitumor agents is based on DNA cross-linking1 or on intercalation2 into DNA. Numerous models and analogues of Watson–Crick base pairs consisting of annelated3 or cross-linked4 purine and pyrimidine heterocycles or even more simple aromatic rings5,6 have been prepared. Such base-pair analogues may interact with DNA (e.g. by intercalation); if incorporated into single-stranded

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DNA, they are complementary to abasic site of a damaged DNA strand; or alternatively, if incorporated to a duplex, they form permanent cross-links. On the other hand, no systematic research on covalent analogues of another important DNA H-bonding motif, Hoogsteen triplets (Fig. 1), has been reported so far, tripurinylamines being the only known example.\(^7\)

Very recently, we have prepared a new type of covalent base-pair analogues consisting of various purine dimers and purine-pyrimidine conjugates linked through positions 6 and 6' (or position 5 of pyrimidine) by acetylene, diacetylene, vinylene and ethylene\(^6\) as well as para- or meta-phenylene\(^9\) linkers. Such carbon linkers connected to carbon atoms of the heterocycles were expected to be stable towards enzymatic degradation. Significant cytostatic activity has been found\(^8\) in some bis(purin-6-yl)-acetylenes and diacetylenes, while the partially and fully saturated derivatives, phenylene-linked analogues as well as the purine-pyrimidine conjugates were inactive. Taking also into account the high cytostatic activity of

![Natural nucleobase-triplets (examples):](image)

![Covalent triplet analogues:](image)

**Fig. 1**

Structure of natural Hoogsteen triplets and their covalent analogues under study

\(^{1224}\) Hocek, Stará, Starý, Dvořáková:

6-arylpurine ribonucleosides, we have decided to prepare a new type of Hoogsteen triplets analogues consisting of benzene rings bearing three nucleobases (purines or pyrimidines). A preliminary communication on the synthesis of 1,3,4- and 1,3,5-tris(purin-6-yl)benzenes has recently been published. The present full-paper gives the results in full details and extends the study towards the analogues bearing purine and/or pyrimidine rings (Fig. 1).

Our original approach to the triplet analogues relies on cyclotrimerization of properly functionalized alkynes. Substituted 6-ethynylpurines are readily available by the Sonogashira coupling of 6-chloropurine derivatives with alkynes (analogy to the known procedure for 6-alkynyl-9-phenylpurine derivatives). The terminal acetylenes were prepared in good yields in two steps consisting in the coupling of with (trimethylsilyl)acetylene followed by desilylation using methanolic ammonia (Scheme 1). Analogous approach has been applied to the synthesis of 5-ethynyl-1,3-dimethyluracil starting from 5-ido-1,3-dimethyluracil (Scheme 2). While the coupling of with (trimethylsilyl)acetylene to give the known TMS-protected acetylene proceeded quite well, subsequent desilylation of using methanolic ammonia did not lead to the terminal acetylene but to a complex mixture of oligo- and/or polymers. Equally unsuccessful were attempts using KF/methanol or K₂CO₃/methanol. Finally we have succeeded making use of TBAF in THF which gave the desired acetylene in a moderate yield of 51%.
The 9-substituted 6-ethynylpurines 3a and/or 3b were used as model substrates for a series of cyclotrimerization experiments varying transition metal catalysts and reaction conditions according to literature protocols14–19 (Scheme 3). While TaCl₅ in benzene, the Grubbs catalyst PhCH=Ru(PCy₃)Cl₂ in dichloromethane, Pd(PPh₃)₄ or Ni(CO)₂(PPh₃)₂ in tetrahydrofuran, and the Wilkinson catalyst RhCl(PPh₃)₃ in ethanol left the starting alkynes 3a and/or 3b untouched even under reflux for a prolonged reaction period, the use of CpCo(CO)₂ in decane at 140 °C with the concomitant visible light irradiation led to a very complex mixture containing only traces of the target products 7 or 8 (according to the MS analysis of the crude reaction mixture). The observed low reactivity of these alkynes towards cyclotrimerization might be explained in terms of a substantial decrease of the electron density at the triple bond due to the presence of the electron-deficient purine moiety.

The situation dramatically changed when applying a highly reactive Ni(COD)₂ (COD = cycloocta-1,4-diene) complex to enforce the trimerization (Scheme 3, Table I). The THP-protected 3b with a catalytic amount of Ni(COD)₂ and PPh₃ afforded an 8:1 mixture of tris(purin-9-yl)benzenes 7b and 8b in good yield (74%; Table I, Entry 2). Both regioisomers were successfully separated by column chromatography. The use of a stoichiometric amount of Ni(COD)₂ (1/3 equivalent) without PPh₃ as a stabilizing ligand gave a 4:1 mixture of 7b and 8b in moderate yield (41%; Table I, Entry 3). Compound 7b was deprotected by means of wet Dowex 50X8 (H⁺ form) in methanol20 to give the free purine derivative 7f in 70% yield.

Analogously, the reaction of the Bn-protected compound 3a with Ni(COD)₂ and PPh₃ afforded the unsymmetrical 1,2,4-tris(purin-9-yl)benzene 7a in 50% yield, while the symmetrical product 8a could not be isolated in a pure form (Table I, Entry 1). Similarly, the reaction of 6-ethynyl-9-methylpurine (3c) gave the unsymmetrical trimer 7c in 43% yield, while the symmetrical trimer 8c was just detected in spots and could not be isolated (Table I, Entry 4).
The disubstituted acetylenes 1d and 1e were also subjected to the cyclotrimerization using catalytic amount of Ni(COD)₂ and PPh₃. However, the reaction was very sluggish to form the trimers in trace amounts only (MS detection) even after prolonged reaction times and/or at elevated temperature (up to 60 °C).

Analogously to the purines, the 5-ethynyl-1,3-dimethyluracil (4) was also cyclotrimerized using Ni(COD)₂ to give the unsymmetrical trimer 9 in 25% yield. Compound 8a was not isolated in a pure form (yield estimated from ¹H NMR of the crude reaction mixture).

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yield (Scheme 4). This reaction was much slower than those of purine derivatives, probably due to low solubility of the starting compound 4 in THF. Furthermore, we have also tried a co-cyclotrimerization of purine 3a with pyrimidine 4 in order to get mixed purine-pyrimidine conjugates linked by a benzene ring. The co-cyclotrimerization of 3a and 4 in the 1:1 ratio gave the unsymmetrical purine homo-trimer 7a as major product (25% yield), accompanied by the unreacted 4 (30%) and a complex mixture of homo- and heterotrisubstituted benzenes. Out of this mixture, only 1,2-bis-(9-benzylpurin-6-yl)-4-(1,3-dimethyluracil-5-yl)benzene (10) was successfully isolated in pure form in 5% yield. This result was not surprising when taking into account the lower solubility and/or reactivity of 4. Nevertheless, compound 10 could be considered as the first analogue of the real Pu-Py-Pu Hoogsteen triplet.

Recently, the use of stable nickelocene (NiCp₂) instead of extremely air-sensitive Ni(COD)₂ in coupling and cyclization reactions has been described. In analogy, we have used NiCp₂/PPh₃ catalytic system for the cyclotrimerization of 3a to obtain the unsymmetrical trimer 7a in 35% yield (Table I, Entry 7). Though the yield was somewhat lower, due to much easier handling of NiCp₂ in comparison to Ni(COD)₂, this alternative method could be also advantageously used for the trimerization of 6-ethynylpurines.
While the NMR spectra of the 1,3,5-trisubstituted benzene 8b displayed very simple patterns due to their high symmetry, the spectra of the 1,2,4-trisubstituted derivatives 7a–7c and 7f contained distinct sets of signals belonging to each purine ring. Possessing chirality centers at the THP protecting groups, compounds 7b and 8b have to occur as mixtures of diastereoisomers. In spite of this, these materials were chromatographically homogeneous. Although in the 1H and 13C NMR spectra of 7b some signals of the proximal purines were split, the spectra of 8b exhibited a perfect symmetry. Furthermore, no hindered rotation was observed in dynamic NMR experiments with compounds 7a, 7b and 8b even at low temperatures (down to –70 °C) indicating that these compounds could easily adopt a planar conformation which is necessary for intercalation into DNA.

In conclusion, the Ni-catalyzed cyclotrimerizations of 6-ethynylpurines 3 provided the unsymmetrical (major) and symmetrical (minor) tri(purin-6-yl)benzenes 7 and 8 as the novel Hoogsteen-triplet analogues. This method is especially suitable for the synthesis of 1,2,4-tris(purin-6-yl)-benzenes from terminal ethynylpurines. Analogous cyclotrimerization of 5-ethynyl-1,3-dimethyluracil (4) gave also the unsymmetrical trimer 9. The co-trimerization of 3a and 4 led to a complex mixture containing the unsymmetrical purine homo-trimer 7a as a major product and, therefore, it is not applicable for the preparative synthesis of mixed trimers containing both purine and pyrimidine substituents. The target triplet-analogues 7–10 were tested for their cytostatic activity (inhibition of cell growth of the following cell cultures: mouse leukemia L1210 cells (ATCC CCL 219), murine L929 cells (ATCC CCL 1), human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2) and human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119)). None of the compounds exhibited any considerable activity in these assays.

**EXPERIMENTAL**

Unless stated otherwise, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 60 °C/2 kPa over P2O5. Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Bruker AMX-3 400 (400 MHz for 1H and 100.6 MHz for 13C), a Bruker DRX 500 (500 MHz for 1H and 125.8 MHz for 13C). Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. TMS was used as internal standard. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol matrix). Toluene was degassed in vacuo and stored over molecular sieves under argon. DMF was distilled from P2O5, degassed in vacuo and stored over
molecular sieves under argon. THF was refluxed with Na and benzophenone under argon and freshly distilled prior to use.

Sonogashira Reactions of 6-Chloropurines with (Trimethylsilyl)acetylene.

General Procedure

DMF (10 ml) and Et3N (4 ml) were added through septum to an argon purged flask containing a 6-chloropurine 2 (6 mmol), TMSC≡CH (980 mg, 10 mmol), CuI (100 mg, 0.5 mmol) and Pd(PPh3)4 (100 mg, 0.087 mmol). The mixture was then stirred at 120 °C for 7 h and left at ambient temperature overnight. The solvents were evaporated in vacuo and the products isolated by column chromatography on silica gel (150 g, ethyl acetate/light petroleum 1:2).

9-Benzyl-6-[(trimethylsilyl)ethynyl]purine (1a). White crystals, yield 70%; m.p. 126–128 °C (heptane/CH2Cl2). EI MS, m/z (rel.%): 306 (60) [M], 291 (42) [M – Me], 91 (100). 1H NMR (400 MHz, CDCl3): 0.33 (s, 9 H, (CH3)3Si); 5.44 (s, 2 H, CH2); 7.27–7.36 (m, 5 H, H-arom.); 8.09 (s, 1 H, H-8); 8.95 (s, 1 H, H-2). 13C NMR (100 MHz, CDCl3): –0.44 ((CH3)3Si); 47.38 (CH2); 98.47, 105.46 (C≡C); 127.74, 128.68, 129.16 (CH-arom.); 134.22 (C-arom.); 134.84 (C-5); 141.30 (C-6); 145.21 (C-8); 151.82 (C-4); 152.70 (C-2). For C17H18N4 (306.4) calculated: 66.63% C, 5.92% H, 18.28% N; found: 66.48% C, 6.01% H, 18.26% N.

9-(Tetrahydropyran-2-yl)-6-[(trimethylsilyl)ethynyl]purine (1b). White crystals, yield 78%; m.p. 129–131 °C (heptane/CH2Cl2). EI MS, m/z (rel.%): 300 (37) [M], 272 (20), 217 (100) [M + H – THP], 98.47, 105.46 (C≡C); 127.74, 128.68, 129.16 (CH-arom.); 134.22 (C-arom.); 134.84 (C-5); 141.30 (C-6); 145.21 (C-8); 151.82 (C-4); 152.70 (C-2). For C15H20N4OSi (300.4) calculated: 59.97% C, 6.71% H, 18.65% N; found: 59.61% C, 6.74% H, 18.41% N.

9-Methyl-6-[(trimethylsilyl)ethynyl]purine (1c). Brownish crystals, yield 75%; m.p. 155–158 °C (heptane/CH2Cl2). EI MS, m/z (rel.%): 230 (42) [M], 215 (100). IR (KBr): ν = 2960, 2157, 1581, 1505, 1443 cm–1. 1H NMR (400 MHz, CDCl3): 0.32 (s, 9 H, (CH3)3Si); 3.90 (s, 3 H, CH3); 8.08 (s, 1 H, H-8); 8.91 (s, 1 H, H-2). 13C NMR (100.6 MHz, CDCl3): –0.45 ((CH3)3Si); 29.84 (CH3); 76.05, 101.65 (C≡C); 127.79, 128.66, 129.16, 129.88, 132.66 (CH-arom.); 134.22, 134.84 (C-arom.); 141.90, 151.66 (C-4 and C-6); 145.00 (CH-8); 152.77 (CH-2). EI HRMS, found: 310.1215; C20H14N4 [M] requires: 310.1218. For C20H14N4 (310.4) calculated: 77.40% C, 4.55% H, 18.05% N; found: 77.23% C, 4.68% H, 17.70% N.

9-Benzyl-6-(phenylethynyl)purine (1d). Brownish oil that solidified to crystals on drying, yield 71%; m.p. 114–117 °C. EI MS, m/z (rel.%): 310 (73) [M], 272 (20), 217 (100) [M + H – THP], 201 (63), 85 (95) [THP]. 1H NMR (400 MHz, CDCl3): 0.33 (s, 9 H, (CH3)3Si); 1.75–2.17 (m, 6 H, CH2); 3.79 (dt, 1 H, J = 2.5, 11.7, H-5′a); 4.19 (m, 1 H, H-5′b); 5.80 (dd, 1 H, J = 10.4, 2.4, H-1′); 8.34 (s, 1 H, H-6); 8.92 (s, 1 H, H-2). 13C NMR (100 MHz, CDCl3): 47.38 (CH2Ph); 84.13, 98.41 (C≡C); 121.38 (C-arom.); 127.81, 128.39, 128.70, 129.19, 129.88, 132.66 (CH-arom.); 134.22, 134.84 (C-arom.); 141.90, 151.66 (C-4 and C-6); 145.00 (CH-8); 152.77 (CH-2). EI HRMS, found: 310.1215; C20H14N4 [M] requires: 310.1218. For C20H14N4 (310.4) calculated: 77.40% C, 4.55% H, 18.05% N; found: 77.23% C, 4.68% H, 17.70% N.
129.16 (CH-arom.); 134.19, 134.90 (C-5 and C-arom.); 142.54, 151.45 (C-4 and C-6); 144.73 (CH-8); 152.75 (CH-2). EI HRMS, found: 290.1512; C$_{18}$H$_{18}$N$_{4}$ [M] requires: 290.1531. For C$_{18}$H$_{18}$N$_{4}$ (290.4) calculated: 76.46% C, 6.25% H, 19.30% N; found: 74.19% C, 6.32% H, 18.92% N.

Desilylation of 6-[(Trimethylsilyl)ethynyl]purines. General Procedure

A TMS derivative 1a–1c (10 mmol) was treated with saturated ethanolic ammonia (100 ml) for 3 h, the solvent was evaporated and the products were isolated by column chromatography on silica gel (150 g, ethyl acetate).

9-Benzyl-6-ethynylpurine (3a). White crystals, yield 65%; m.p. 158–160 °C (heptane/CH$_2$Cl$_2$). EI MS, m/z (rel.%) 234 (84) [M]; 91 (100). $^1$H NMR (500 MHz, CDCl$_3$): 3.72 (s, 1 H, ≡CH); 5.46 (s, 2 H, CH$_2$); 7.30–7.37 (m, 5 H, H-arom.); 8.12 (s 1 H, H-8); 8.99 (s, 1 H, H-2). $^{13}$C NMR (125 MHz, CDCl$_3$): 47.47 (CH$_2$); 77.94 (C≡CH); 86.08 (≡CH); 127.89, 128.78, 129.23 (CH-arom.); 134.70 (C-5); 140.68 (C-6); 145.46 (C-8); 151.75 (C-4); 152.73 (C-2). For C$_{14}$H$_{10}$N$_{4}$ (234.2) calculated: 71.78% C, 4.30% H, 23.92% N; found: 71.46% C, 4.37% H, 23.79% N.

6-Ethynyl-9-(tetrahydropyran-2-yl)purine (3b). White crystals, yield 70%; m.p. 105–108 °C (heptane/CH$_2$Cl$_2$). EI MS, m/z (rel.%) 228 (26) [M], 200 (18) [M + H – THP], 145 (48), 85 (100) [THP]. $^1$H NMR (400 MHz, CDCl$_3$): 1.69–2.19 (m, 6 H, CH$_2$); 3.72 (s, 1 H, ≡CH); 3.80 (dt, 1 H, J = 2.6, 11.5, H-5’a); 4.16–4.22 (m, 1 H, H-5’b); 5.81 (dd, 1 H, J = 10.2, 2.4, H-1’); 8.36 (s, 1 H, H-8); 8.95 (s, 1 H, H-2). $^{13}$C NMR (75 MHz, CDCl$_3$): 23.31, 25.44, 32.46 (CH$_2$); 69.51 (CH$_2$-5’a); 78.59 (=C); 82.83 (CH-1’); 86.75 (=CH); 135.67 (C-5); 141.30 (C-6); 144.19 (C-8); 151.55 (C-4); 153.16 (C-2). For C$_{12}$H$_{12}$N$_{4}$O (228.3) calculated: 63.15% C, 5.30% H, 24.55% N; found: 63.19% C, 5.01% H, 24.26% N.

6-Ethynyl-9-methylpurine (3c). White crystals, yield 77%; m.p. 220–222 °C (heptane/CH$_2$Cl$_2$). EI MS, m/z (rel.%) 158 (100) [M]. IR (KBr): ν = 3 155, 3 097, 2 101, 1 579, 1 504, 1 437, 1 425, 1 345 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): 0.19 (s, 9 H, SiMe$_3$); 3.15, 3.30 (2 × s, 2 × 3 H, N-Me); 8.16 (s, H-6). $^{13}$C NMR (100 MHz, CDCl$_3$): 27.68, 36.57 (N-Me); 96.03, 96.42, 98.11 (C≡C and C-5); 134.78 (C-5); 140.55 (C-6); 146.11 (CH-8); 152.03 (C-4); 152.57 (CH-2). For C$_{8}$H$_{6}$N$_{4}$ (158.1) calculated: 60.75% C, 3.82% H, 35.42% N; found: 60.49% C, 3.79% H, 35.09% N.

1,3-Dimethyl-5-[(trimethylsilyl)ethynyl]pyrimidine-2,4-(1H,3H)-dione (6) DMF (9 ml) and Et$_3$N (3 ml) were added to an argon purged flask containing 5 (2.66 g, 10 mmol), TMSC≡CH (2.1 g, 21 mmol), CuI (160 mg, 5.2 mmol) and Pd(PPh$_3$)$_4$ (160 mg, 0.14 mmol). The mixture was stirred under argon at 100 °C for 8 h. Then the solvents were evaporated and the residue chromatographed on a column of silica gel (150 g, light petroleum/ethyl acetate 1 : 1 to 1 : 2) to give 6 (1.794 g, 76%). M.p. – slow decomposition over 180 °C (ref.$^{13}$ gives m.p. 160–162 °C, no spectral data were given). EI MS, m/z (rel.%): 236 (36) [M], 221 (100). $^1$H NMR (400 MHz, CDCl$_3$): 0.19 (s, 9 H, SiMe$_3$); 3.15, 3.30 (2 × s, 2 × 3 H, N-Me); 8.16 (s, H-6). $^{13}$C NMR (100 MHz, CDCl$_3$): -0.15 (SiMe$_3$); 27.68, 36.57 (N-Me); 96.03, 96.42, 98.11 (C≡C and C-5); 148.81 (CH-6); 150.47, 161.20 (C=O-2 and C=O-4).
A 1 M solution of TBAF·3H₂O in THF (10 ml, 10 mmol) was added to silyl derivative 6 (470 mg, 2 mmol) at 0 °C and the mixture was stirred at room temperature for 5 h. Then the solvent was evaporated, the residue was applied onto a column of silica gel (50 g) and the product was eluted with a gradient of ethyl acetate/MeOH (10:0 to 8:2). The crude product was crystallized from dichloromethane/heptane. Yield 166 mg (51%); m.p. 218–221 °C. EI MS, m/z (rel.%): 164 (100) [M], 107 (25), 79 (28), 66 (15), 42 (93). ¹H NMR (400 MHz, CDCl₃): 3.17 (s, 1 H, ≡CH); 3.38, 3.42 (2 × s, 2 × 3H, 2 × CH₃); 7.50 (H-6).

¹³C NMR (100 MHz, CDCl₃): 28.38, 37.37 (N-CH₃); 74.92 (C≡CH); 142.5 (very weak, C-5); 146.39 (CH-6); 150.85 (C=O-2); 151.79 (C=O-4). For C₈H₈N₂O₂ (164.2) calculated: 58.53% C, 4.91% H, 17.06% N; found: 58.79% C, 4.98% H, 16.74% N.

Ni-Catalyzed Cyclotrimerizations of Acetylenes. General Procedure

**Method A**: A 0.065 M solution of Ni(COD)₂ in THF (6 ml, 0.4 mmol) was added dropwise through a septum to a stirred solution of an acetylene (500 mg, 2 mol) and PPh₃ (262 mg, 1 mol) in THF (10 ml) under argon (CAUTION! exothermic reaction). The mixture was stirred at room temperature for 5 h and then the solvent was evaporated. Products were separated by column chromatography of the residue on silica gel (50 g, light petroleum/ethyl acetate/methanol (1:1:0 → 0:1:0 → 0:9:1)). For yields of the particular products, see Table I.

**Method B**: THF (10 ml) was added to an argon purged flask containing acetylene 3a (1 mmol), NiCp₂ (76 mg, 0.4 mmol) and PPh₃ (420 mg, 1.6 mmol). The mixture was stirred at room temperature overnight. The work-up and isolation was performed in the same way as in method A to afford product 7a in 35% yield.

1,3,4-Tris(9-benzylpurin-6-yl)benzene (7a). Yellow microcrystals; m.p. 155–158 °C (EtOH/toluene). FAB MS, m/z (rel.%): 703 (15) [M + H], 91 (100). ¹H NMR (500 MHz, CDCl₃): 5.40 (s, 4 H, CH₂Ph); 5.49 (s, 2 H, CH₃Ph); 7.24–7.36 (m, 15 H, H-Ph); 8.14, 8.16, 8.18, 8.20 (4 × s, 4 × 1 H, H-8-Pu); 8.28 (d, 1 H, J = 8.2, H-6-benzene); 8.36 (s, 1/2 H), 8.38 (s, 1 H) and 8.40 (s, 1/2 H, H-8-PuA,B); 8.46 (d, 1 H, J = 8.2, H-5-benzene); 8.68, 8.70, 8.72, 8.74 (4 × s, 4 × 1/2 H, H-2-PuA,B); 9.07 (s, 1 H, H-2-PuC); 9.21 (d, 1 H, J = 8.2, H-5-benzene); 9.60 (s, 1 H, H-3-benzene). ¹³C NMR (100 MHz, CDCl₃): 47.15 (CH₂); 127.70, 128.47, 129.06, 131.06, 132.52, 133.23 (CH-arom.); 131.93, 135.19, 136.14, 136.94, 137.79 (CH-arom. and C-5); 141.16, 144.16, 144.50 (CH-8); 151.96, 152.54 (CH-2); 151.71, 153.50, 157.36, 157.94 (C-4 and C-6). FAB HRMS, found: 703.2778; C₄₂H₃₁N₁₂ [M + H] requires: 703.2795. For C₄₂H₃₀N₁₂·1/2 toluene (748.8) calculated: 72.98% C, 4.58% H, 22.45% N; found: 72.65% C, 4.55% H, 22.26% N.

1,2,4-Tris[9-(tetrahydropyran-2-yl)purin-6-yl]benzene (7b). Yellow amorphous solid. FAB MS, m/z (rel.%): 685 (9) [M + H], 601 (3) [M + H – THP], 517 (7) [M + 2 H – 2 THP], 433 (100) [M + 3 H – 3 THP], 85 (42) [THP]. ¹H NMR (500 MHz, CDCl₃, particular purine rings designated as A, B and C): 1.60–2.20 (m, 18 H, CH₂); 3.80, 4.19 (2 × m, 6 H, CH₂O); 5.79 (d, 2 H, J = 9.6, OCHN); 5.88 (d, 1 H, J = 9.9, OCHN); 8.14 (s, 1/2 H), 8.16 (s, 1 H) and 8.19 (s, 1/2 H, H-8-PuA,B); 8.36 (d, 1 H, H-8-PuC); 8.46 (d, 1 H, J = 8.2, H-6-benzene); 8.68, 8.70, 8.72, 8.74 (4 × s, 4 × 1/2 H, H-2-PuA,B); 9.07 (s, 1 H, H-2-PuC); 9.21 (d, 1 H, J = 8.2, H-5-benzene); 9.60 (s, 1 H, H-3-benzene). ¹³C NMR (100 MHz, CDCl₃): 69.48 (CH₂O); 82.60, 82.67, 82.76 (OCHN); 131.87 (C-5-benzene); 132.25, 132.81 (C-5-PuA,B,C); 133.37 (C-6-benzene); 134.11 (C-3-benzene); 134.94 (C-1-benzene); 136.88 (C-2-benzene); 137.67 (C-4-benzene); 138.54 (C-1-benzene); 142.84, 142.90, 143.12 (C-8-PuA,B,C); 151.79 (C-4-PuA,B,C); 152.58 (C-2-PuA,B); 153.13 (C-2-PuC); 154.36 (C-3-PuC).
1,3,5-Tris[9-(tetrahydropyran-2-yl)purin-6-yl]benzene (8b). Yellow amorphous solid. FAB MS, m/z (rel.%) 685 (27) [M + H - THP], 517 (14) [M + 2 H - 2 THP], 433 (100) [M + 3 H - 3 THP]. ¹H NMR (400 MHz, CDCl₃): 1.65-2.22 (m, 18 H, CH₂); 3.84 (dt, 3 H, J = 2.2, 11.5, CH₂Oa); 4.22 (d, 3 H, J = 11.3, CH₂Ob); 5.90 (dd, 3 H, J = 10.2, 2.4, OCHN); 8.43 (s, 3 H, H-8-Pu); 9.15 (s, 3 H, H-2-Pu); 10.36 (s, 3 H, H-benzene). ¹³C NMR (100 MHz, APT, CDCl₃): 23.54, 25.64, 32.65 (3 × CH₂); 69.55 (CH₂O); 82.77 (OCHN); 132.21 (C-5-Pu); 134.51 (CH-benzene); 137.51 (C-benzene); 143.29 (C-8-Pu); 152.62 (C-6-Pu); 153.33 (C-2-Pu); 155.13 (C-4-Pu). FAB HRMS, found: 685.3135; C₃₆H₃₇N₁₂O₃ [M+H] requires: 685.3112.

1,3,4-Tris(9-methylpurin-6-yl)benzene (7c). Yellowish powder; m.p. 195–199 °C (EtOH/toluene). EI MS, m/z (rel.%) 474 (18) [M], 446 (17), 210 (15), 129 (35), 57 (100). ¹H NMR (500 MHz, CDCl₃): 3.87 (s, 6 H, CH₃); 3.95 (s, 3 H, CH₃); 7.91 (d, 1 H, J = 9.5, H-benzene); 8.12, 8.20, 8.67, 8.72, 9.07, 9.59 (6 × s, 6 × 1 H, H-Pu); 8.43 (d, 1 H, J = 7.9, H-benzene); 9.16-9.21 (m, 1 H, H-benzene). ¹³C NMR (100 MHz, CDCl₃): 29.74, 29.86 (CH₃); 131.15, 132.57, 133.23 (CH-benzene); 131.32, 131.88, 131.93 (C-5-Pu); 136.14, 136.96, 137.81 (C-benzene); 144.97, 145.17, 145.36 (CH-8-Pu); 151.85, 151.93, 152.45 (CH-2-Pu); 152.01, 152.09, 153.03, 153.46, 157.30, 157.89 (C-4 and C-6). EI HRMS, found: 474.1759; C₂₄H₁₈N₁₂ [M] requires: 474.1777.

1,2,4-Tris(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)benzene (9). Obtained in 43% yield from 4 (reaction time 12 h). Yellow amorphous solid. FAB MS, m/z (rel.%) 493 (21) [M + H], 279 (30), 75 (100). ¹H NMR (500 MHz, CDCl₃): 3.87 (s, 6 H, CH₃); 3.95 (s, 3 H, CH₃); 3.30 (s, 3 H); 3.32 (s, 6 H); 3.40 (s, 3 H, al CH₃); 7.30 (d, 1 H, J = 7.8, H-arom.); 7.51 (s, 1 H, H-6-U); 7.60–7.64 (m, 3 H, 2 × H-arom. and H-6-U); 8.05 (s, 1 H, H-6-U). ¹³C NMR (125.8 MHz, CDCl₃): 27.63, 27.72, 36.30, 36.32, 36.47 (all CH₃); 110.73, 111.86, 112.21, 112.45, 132.73, 133.39, 150.87, 151.09, 161.54, 161.60, 161.66 (C-arom.); 127.03, 130.29, 130.66, 142.64, 142.85 (CH-arom.). FAB HRMS, found: 493.1864; C₂₄H₂₅N₆O₆ [M+H] requires: 493.1836.

Co-cyclotrimerization of 3a and 4. Co-cyclotrimerization of 3a (234 mg, 1 mmol) and 4 (164 mg, 1 mmol) in presence of Ni(COD)₂ and PPh₃ was performed in the same way as described above (method A). A column chromatography gave 7a (59 mg, 25%), unreacted 4 (49 mg, 30%) and a complex mixture of other products which was re-chromatographed to give compound 10 (16 mg, 5%).

1,2-Bis(9-benzylpurin-6-yl)-4-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)benzene (10). Yellowish amorphous solid. FAB MS, m/z (rel.%) 633 (9) [M + H], 279 (12), 91 (100). ¹H NMR (500 MHz, CDCl₃): 3.43, 3.48 (2 × s, 2 × 3 H, CH₃-U); 5.39 (s, 4 H, CH₂Ph); 7.25-36 (m, 10 H, H-arom.); 7.54 (s, 1 H, H-6-U); 7.83, 7.85 (2 × s, 2 × 1 H, H-8-Pu); 7.95 (dd, 1 H, J = 8.2, 1.3, H-5-benzene); 8.29 (d, 2 H, J = 8.2, H-6-benzene); 8.31 (d, 2 H, J = 1.3, H-3-benzene); 8.65, 8.70 (2 × s, 2 × 1 H, H-2-Pu). ¹³C NMR (125.8 MHz, CDCl₃): 28.28, 37.20 (CH₃); 47.19 (CH₂Ph); 113.23 (C-5-U); 127.73, 128.52, 129.09 (CH-arom.-Bn); 129.53 (C-5-benzene); 131.32 (C-3-benzene); 131.77 (C-5-Pu); 134.52, 135.00, 135.21, 135.91 (C-arom-Br); 141.19 (CH-6-U); 144.12 (CH-8-Pu); 151.71 (C=O-2-U and C-4-Pu); 152.01 (CH-2-Pu); 157.42, 157.85 (C-6-Pu); 161.97 (C=O-4-U). FAB HRMS, found: 633.2457; C₃₆H₂₉N₁₀O₂ [M + H] requires: 633.2475.
1,2,4-Tris(purin-6-yl)benzene (7e)

Dowex 50X8 (H+ form, 50 mg) was added to a solution of compound 7b (120 mg, 0.18 mmol) in 96% aqueous EtOH (20 ml) and the mixture was refluxed for 3 h (TLC showed completion of the reaction). Then the resin was filtered off and washed with hot EtOH (20 ml), saturated ethanolic ammonia (10 ml) and EtOH (10 ml). The collected filtrates were evaporated and the residue crystallized from EtOH. Yield 70 mg (90%). White microcrystals; m.p. 319–322 °C. FAB MS, m/z (rel.%) 433 (100) [M + H]. 1H NMR (500 MHz, DMSO- d6): 8.36 (d, 1 H, J = 8.1, H-6′′); 8.40 (s, 1 H, H-8A); 8.45 (s, 1 H, H-8B); 8.51 (s, 1 H, H-2A); 8.59 (s, 1 H, H-8C); 8.61 (s, 1 H, H-2B); 8.97 (s, 1 H, H-8C); 9.21 (dd, 1 H, J = 1.3, 8.1, H-5′′); 9.50 (d, 1 H, J = 1.2, H-3′′). 13C NMR (125 MHz, DMSO- d6): 129.27 (C-5A,B); 129.85 (C-5′′); 130.64 (C-5C); 132.00 (C-6′′); 132.19 (C-3′′); 136.29 (C-2′′); 137.09 (C-1′′); 137.51 (C-4′′); 145.46 (C-8A); 145.74 (C-8B); 148.12 (C-8C); 149.80 (C-6C); 150.86 (C-2A); 151.10 (C-2B,C); 154.27 (C-6A); 154.61 (C-4A); 154.85 (C-4B); 155.12 (C-6B); 156.46 (C-4C).

For C21H12N21·2EtOH (524.5) calculated: 57.24% C, 4.61% H, 32.04% N; found: 57.37% C, 4.25% H, 31.78% N. FAB HRMS, found: 433.1337; C21H13N12 [M + H] requires: 433.1386.

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