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-dimetyhyluracil-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-linking[1] or on intercalation[2] into DNA. Numerous models and analogues of Watson–Crick base pairs consisting of annelated[3] or cross-linked[4] purine and pyrimidine heterocycles or even more simple aromatic rings[5,6] have been prepared. Such base-pair analogues may interact with DNA (*e.g.* by intercalation); if incorporated into single-stranded

+ For Part III see ref.[9]

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[8] 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

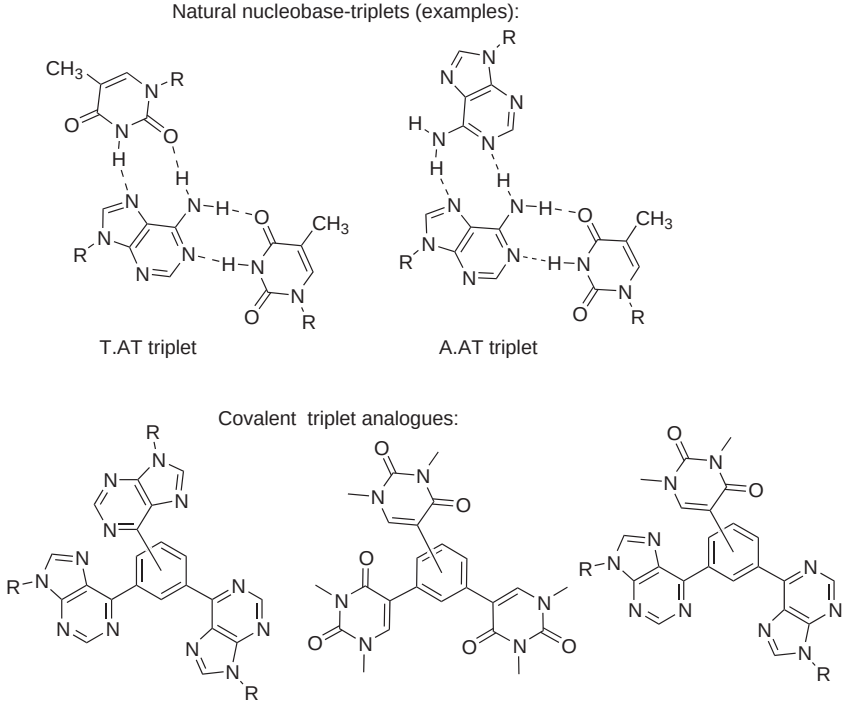
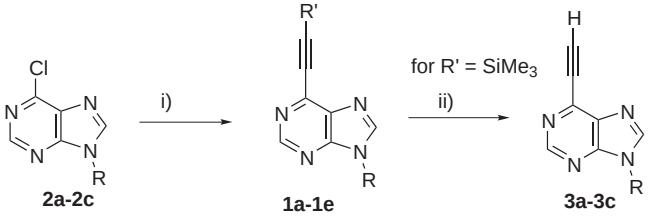


FIG. 1
Structure of natural Hoogsteen triplets and their covalent analogues under study

6-arylpurine ribonucleosides[10], 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[11]. 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).



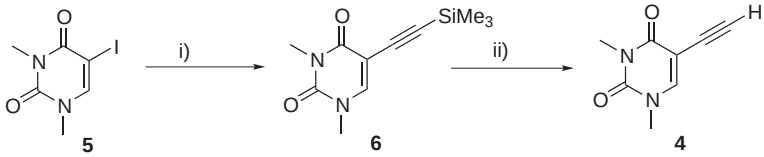
1	R	R'
a	Bn	$SiMe_3$
b	THP	$SiMe_3$
c	Me	$SiMe_3$
d	Bn	Bu
e	Bn	Ph

2,3	R
a	Bn
b	THP
c	Me

i) R'C≡CH, $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 120 °C, 7 h;
ii) NH_3/MeOH, r.t., 3 h

SCHEME 1

Our original approach[11] to the triplet analogues relies on cyclotrimerization of properly functionalized alkynes. Substituted 6-ethynylpurines **1** are readily available by the Sonogashira coupling of 6-chloropurine derivatives **2** with alkynes (analogy to the known[12] procedure for 6-alkynyl-9-phenylpurine derivatives). The terminal acetylenes **3** were prepared in good yields in two steps consisting in the coupling of **2** with (trimethylsilyl)acetylene followed by desilylation using methanolic ammonia[12] (Scheme 1). Analogous approach has been applied to the synthesis of 5-ethynyl-1,3-dimethyluracil (**4**) starting from 5-iodo-1,3-dimethyluracil (**5**) (Scheme 2). While the coupling of **5** with (trimethylsilyl)acetylene to give the known[13] TMS-protected acetylene **6** proceeded quite well, subsequent desilylation of **6** using methanolic ammonia did not lead to the terminal acetylene **4** but to a complex mixture of oligo- and/or polymers. Equally unsuccessful were attempts using KF/methanol or K_2CO_3/methanol. Finally we have succeeded making use of TBAF in THF which gave the desired acetylene **4** in a moderate yield of 51%.



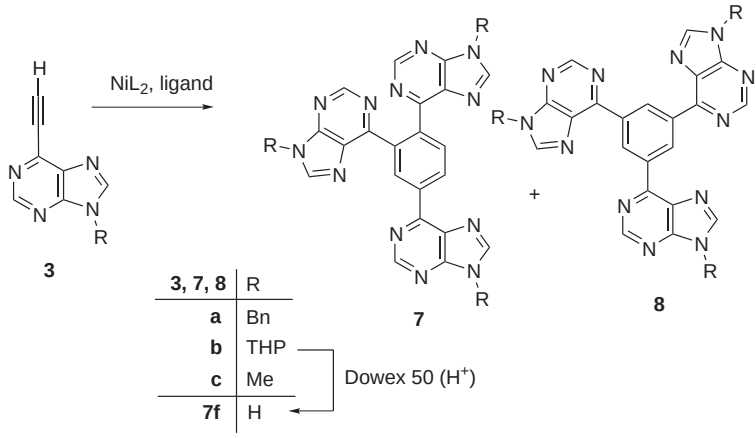
i) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 100 °C, 8h; ii) TBAF,THF, 0 °C then r.t., 5 h

SCHEME 2

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 protocols[14–19] (Scheme 3). While $TaCl_5$ in benzene, the Grubbs catalyst $PhCH{=}Ru(PCy_3)Cl_2$ in dichloromethane, $Pd(PPh_3)_4$ or $Ni(CO)_2(PPh_3)_2$ in tetrahydrofuran, and the Wilkinson catalyst $RhCl(PPh_3)_3$ 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 PPh_3 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 PPh_3 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 methanol[20] to give the free purine derivative **7f** in 70% yield.

Analogously, the reaction of the Bn-protected compound **3a** with $Ni(COD)_2$ and PPh_3 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).



SCHEME 3

TABLE I
Cyclotrimerizations of 6-ethynylpurines **1** and **3**

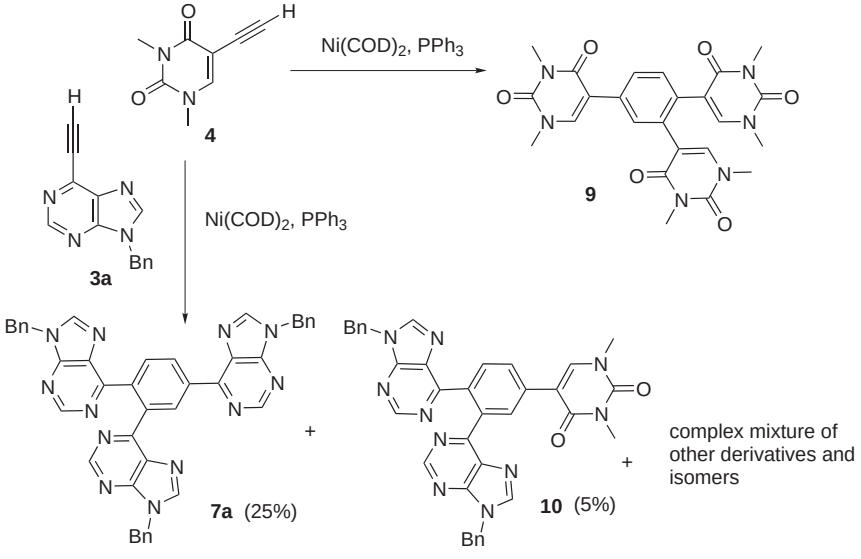
Entry	Starting compound	Catalyst, ligand (mole %)	Yield, %	
			7	**8**
1	**3a**	$Ni(COD)_2$ (20), PPh_3 (50)	50	5[a]
2	**3b**	$Ni(COD)_2$ (20), PPh_3 (50)	66	8
3	**3b**	$Ni(COD)_2$ (33)	33	8
4	**3c**	$Ni(COD)_2$ (20), PPh_3 (50)	43	traces
5	**1d**	$Ni(COD)_2$ (20), PPh_3 (50)	only traces of cyclotrimers	
6	**1e**	$Ni(COD)_2$ (20), PPh_3 (50)	only traces of cyclotrimers	
7	**3a**	$NiCp_2$ (20), PPh_3 (50)	35	traces

[a] Compound **8a** was not isolated in a pure form (yield estimated from ^{1}H NMR of the crude reaction mixture).

The disubstituted acetylenes **1d** and **1e** were also subjected to the cyclotrimerization using catalytic amount of $Ni(COD)_2$ and PPh_3. 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 (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 surprizing 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.



SCHEME 4

Recently, the use of stable nickelocene ($NiCp_2$) instead of extremely air-sensitive $Ni(COD)_2$ in coupling and cyclization reactions has been described[21]. In analogy, we have used $NiCp_2/PPh_3$ 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 $NiCp_2$ 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 ^{1}H and ^{13}C 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 intercallation 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[22].

EXPERIMENTAL

Unless stated otherwise, solvents were evaporated at 40 °C/2 kPa and compounds were dried at 60 °C/2 kPa over P_2O_5. Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Bruker AMX-3 400 (400 MHz for ^{1}H and 100.6 MHz for ^{13}C), a Bruker DRX 500 (500 MHz for ^{1}H and 125.8 MHz for ^{13}C). 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 P_2O_5, 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 Et_3N (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 $Pd(PPh_3)_4$ (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/CH_2Cl_2). EI MS, *m/z* (rel.%): 306 (60) [M], 291 (42) [M – Me], 91 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.33 (s, 9 H, $(CH_3)_3Si$); 5.44 (s, 2 H, CH_2); 7.27–7.36 (m, 5 H, H-arom.); 8.09 (s, 1 H, H-8); 8.95 (s, 1 H, H-2).^{13}C NMR (100 MHz, $CDCl_3$): –0.44 ($(CH_3)_3Si$); 47.38 (CH_2); 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 $C_{17}H_{18}N_4$ (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/CH_2Cl_2). EI MS, *m/z* (rel.%): 300 (37) [M], 272 (20), 217 (100) [M + H – THP], 201 (63), 85 (95) [THP]. ^{1}H NMR (500 MHz, $CDCl_3$): 0.34 (s, 9 H, $(CH_3)_3Si$); 1.75–2.17 (m, 6 H, CH_2); 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-8); 8.92 (s, 1 H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): 0.225 ($(CH_3)_3Si$); 23.31, 25.44, 32.46 (CH_2); 69.47 (CH_2-5′); 82.77 (CH-1′); 99.07, 106.08 (C≡C); 135.02 (C-5); 141.88 (C-6); 143.88 (C-8); 151.58 (C-4); 153.11 (C-2). For $C_{15}H_{20}N_4OSi$ (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/CH_2Cl_2). EI MS, *m/z* (rel.%): 230 (42) [M], 215 (100). IR (KBr): ν = 2 960, 2 157, 1 581, 1 505, 1 443, 1 394, 1 326 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 0.32 (s, 9 H, $(CH_3)_3Si$); 3.90 (s, 3 H, CH_3); 8.08 (s, 1 H, H-8); 8.91 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): –0.45 ($(CH_3)_3Si$); 29.84 (CH_3); 98.45, 105.31 (C≡C); 134.15 (C-5); 141.10 (C-6); 145.86 (CH-8); 152.06 (C-4); 152.52 (CH-2). For $C_{11}H_{14}N_4Si$ (230.3) calculated: 57.36% C, 6.13% H, 24.32% N; found: 57.04% C, 6.16% H, 24.23% N.

9-Benzyl-6-(phenylethynyl)purine[23] (**1d**). Brownish oil that solidified to crystals on drying, yield 71%; m.p. 114–117 °C. EI MS, *m/z* (rel.%): 310 (73) [M], 91 (89), 57 (100), 43 (86). ^{1}H NMR (400 MHz, $CDCl_3$): 5.48 (s, 2 H, CH_2Ph); 7.26–7.75 (m, 10 H, H-arom.); 8.13 (s, 1 H, H-8); 9.00 (s, 1 H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): 47.41 (CH_2Ph); 84.13, 98.41 (C≡C); 121.38 (C-arom.); 127.81, 128.39, 128.70, 129.19, 129.88, 132.66 (CH-arom.); *ca* 134, 134.83 (C-5 and C-arom.); 141.90, 151.66 (C-4 and C-6); 145.00 (CH-8); 152.77 (CH-2). EI HRMS, found: 310.1215; $C_{20}H_{14}N_4$ [M] requires: 310.1218. For $C_{20}H_{14}N_4$ (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-(hex-1-yn-1-yl)purine (**1e**). Brownish oil that solidified to crystals on drying, yield 77%; m.p. 71–73 °C. EI MS, *m/z* (rel.%): 290 (40) [M], 261 (20), 248 (56), 199 (22), 91 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.95 (t, 3 H, *J* = 7.3, CH_3); 1.48–1.56 (m, 2 H, CH_2); 1.65–1.73 (m, 2 H, CH_2); 2.60 (t, 2 H, *J* = 7.1, CH_2C≡); 5.44 (s, 2 H, CH_2Ph); 7.26–7.37 (m, 5 H, H-arom.); 8.06 (s, 1 H, H-8); 8.93 (s, 1 H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): 13.56 (CH_3); 19.61, 22.10, 30.13 (CH_2); 47.34 (CH_2Ph); 76.05, 101.65 (C≡C); 127.79, 128.66,

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_2Cl_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≡); 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_2Cl_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′); 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 $C_{12}H_{12}N_4O$ (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_2Cl_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, $CDCl_3$): 3.71 (s, 1 H, ≡CH); 3.94 (s, 3 H, CH_3); 8.13 (s, 1 H, H-8); 8.97 (s, 1 H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): 29.87 (CH_3); 77.95 (C≡); 85.96 (≡CH); 134.78 (C-5); 140.55 (C-6); 146.11 (CH-8); 152.03 (C-4); 152.57 (CH-2). For $C_8H_6N_4$ (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-(1*H*,3*H*)-dione (**6**)

DMF (9 ml) and Et_3N (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).

5-Ethynyl-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (**4**)

A 1 M solution of TBAF·3H_2O 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). ^{1}H NMR (400 MHz, $CDCl_3$): 3.17 (s, 1 H, ≡CH); 3.38, 3.42 (2 × s, 2 × 3 H, 2 × CH_3); 7.50 (H-6). ^{13}C NMR (100 MHz, $CDCl_3$): 28.38, 37.37 (N-CH_3); 74.92 (C≡); 81.52 (≡CH); *ca* 142.5 (very weak, C-5); 146.39 (CH-6); 150.85 (C=O-2); 161.74 (C=O-4). For $C_8H_8N_2O_2$ (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 PPh_3 (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), $NiCp_2$ (76 mg, 0.4 mmol) and PPh_3 (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). ^{1}H NMR (500 MHz, $CDCl_3$): 5.40 (s, 4 H, CH_2Ph); 5.49 (s, 2 H, CH_2Ph); 7.24–7.36 (m, 15 H, H-Ph); 7.84, 7.88, 8.11 (3 × s, 3 × 1 H, H-8-Pu); 8.47 (d, 1 H, *J* = 8.2, H-6-benzene); 8.69, 8.73, 9.08 (3 × s, 3 × 1 H, H-2-Pu); 9.20 (dd, 1 H, *J* = 8.2, 1.8, H-5-benzene); 9.64 (d, 1 H, *J* = 1.6, H-3-benzene). ^{13}C NMR (100 MHz, $CDCl_3$): 47.15 (CH_2); 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); 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; $C_{42}H_{31}N_{12}$ [M + H] requires: 703.2795. For $C_{42}H_{30}N_{12}$·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]. ^{1}H NMR (500 MHz, $CDCl_3$, particular purine rings designated as A, B and C): 1.60–2.20 (m, 18 H, CH_2); 3.80, 4.19 (2 × m, 6 H, CH_2O); 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 (s, 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).^{13}C NMR (100 MHz, APT, $CDCl_3$): 23.51, 25.60, 32.43, 32.58 (4 × CH_2); 69.48 (CH_2O); 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); 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-6-PuC); 158.13 (C-6-PuA); 158.77 (C-6-PuB). FAB HRMS, found: 685.3128; $C_{36}H_{37}N_{12}O_3$ [M + H] requires: 685.3112.

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], 601 (12) [M + H – THP], 517 (13) [M + 2 H – 2 THP], 433 (100) [M + 3 H – 3 THP]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.65–2.22 (m, 18 H, CH_2); 3.84 (dt, 3 H, *J* = 2.2, 11.5, CH_2Oa); 4.22 (d, 3 H, *J* = 11.3, CH_2Ob); 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).^{13}C NMR (100 MHz, APT, $CDCl_3$): 23.54, 25.64, 32.65 (3 × CH_2); 69.55 (CH_2O); 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; $C_{36}H_{37}N_{12}O_3$ [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). ^{1}H NMR (500 MHz, $CDCl_3$): 3.87 (s, 6 H, CH_3); 3.95 (s, 3 H, CH_3); 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). ^{13}C NMR (100 MHz, $CDCl_3$): 29.74, 29.86 (CH_3); 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; $C_{24}H_{18}N_{12}$ [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). ^{1}H NMR (500 MHz, $CDCl_3$): 3.25 (s, 3 H); 3.29 (s, 3 H); 3.30 (s, 3 H); 3.32 (s, 6 H); 3.40 (s, 3 H, all CH_3); 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). ^{13}C NMR (125.8 MHz, $CDCl_3$): 27.63, 27.72, 36.30, 36.32, 36.47 (all CH_3); 110.73, 111.86, 112.21, 132.45, 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; $C_{24}H_{25}N_6O_6$ [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 PPh_3 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). ^{1}H NMR (500 MHz, $CDCl_3$): 3.43, 3.48 (2 × s, 2 × 3 H, CH_3-U); 5.39 (s, 4 H, CH_2Ph); 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). ^{13}C NMR (125.8 MHz, $CDCl_3$): 28.28, 37.20 (CH_3); 47.19 (CH_2Ph); 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.); 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; $C_{36}H_{29}N_{10}O_2$ [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]. ^{1}H NMR (500 MHz, DMSO-d_6): 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″). ^{13}C NMR (125 MHz, DMSO-d_6): 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 $C_{21}H_{12}N_{21}$·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; $C_{21}H_{13}N_{12}$ [M + H] requires: 433.1386.

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