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Synthesis of carba-analogues of myoseverin by regioselective cross-coupling reactions of 2,6-dichloro-9-isopropylpurine

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Abstract—A series of 9-isopropylpurine derivatives bearing 4-methoxyphenyl, 4-methoxybenzyl, (4-methoxyphenyl)ethynyl and 2-(4-methoxyphenyl)ethyl groups in positions 2 and 6 were prepared as carba-analogues of antimitotic myoseverin. Cross-coupling reactions of 2,6-dichloro-9-isopropylpurine (**1**) with one equivalent of (4-methoxyphenyl)boronic acid or (4-methoxybenzyl)zinc chloride gave regioselectively the 6-substituted 2-chloropurines which were used for another cross-coupling reaction with a second equivalent of the organometallic reagent. The Sonogashira reaction of **1** with 4-(methoxyphenyl)ethyne gave 2,6-bis[(4-methoxyphenyl)ethynyl]-9-isopropylpurine that was hydrogenated to 2,6-bis[2-(4-methoxyphenyl)ethyl]-9-isopropylpurine. Regioselectivity of the couplings was proved by means of $^{1}H-^{15}N$ HMBC experiments. 2,6-Bis[(4-methoxyphenyl)ethynyl]-9-isopropylpurine showed considerable cytostatic activity, while the other compounds were inactive.

1. Introduction

In the last decade, several biological activities of 9-alkyl-2,6-bis(alkyl or benzylamino)purines were reported: inhibition of CDK,[1] estrogen sulfotransferase[2] and inositol-1,4,5-triphosphate-3-kinase.[3] Recently, a novel cytostatic compound myoseverin, 2,6-bis[(4-methoxybenzyl)amino]-9-isopropylpurine, has been discovered by screening of a purine library.[4] This compound blocks tubulin polymerization with moderate activity. Later on, some 9-cycloalkyl derivatives[5] as well as analogously substituted triazines[6] were found to exhibit a somewhat better activity. Myoseverin also affects cultures of hybridoma cells producing monoclonal antibodies.[7]

6-Aryl-,[8] 6-benzyl-[9] and 6-alkynylpurine[10] derivatives were also recently reported to possess cytostatic activity. A combination of the structural features of these two classes of antineoplastic compounds led us to the design of carba-analogues of myoseverin (Fig. 1) consisting of 9-isopropylpurine derivatives bearing 4-methoxyphenyl, 4-methoxybenzyl, (4-methoxyphenyl)ethynyl and isosteric 2-(4-methoxyphenyl)ethyl groups in the positions 2 and 6. The replacement of the (4-methoxybenzyl)amino groups by C–C linked 4-methoxyphenyl groups should prevent catabolic degradation by deaminases and also test the role of the NH group in the binding with a biological target; on the other hand it will definitely decrease water-solubility of the compounds. The synthesis of these carba-analogues is the subject of this paper.

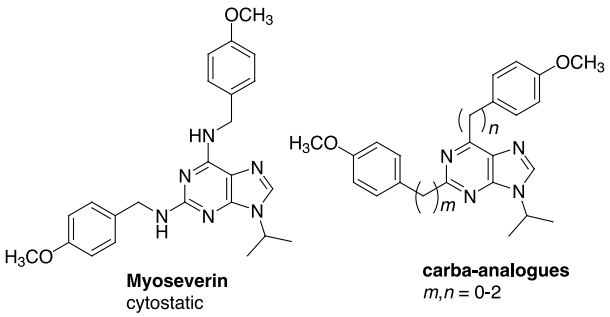

Figure 1.

2. Results and discussion

In order to prepare the abbreviated analogues, regioselective cross-coupling reactions[11] of 2,6-dichloropurines have been employed.[12] Thus the reaction of 2,6-dichloro-9-isopropylpurine (**1**)[13] with one equivalent of (4-methoxyphenyl)-boronic acid gave selectively the substitution at position 6 to form 2-chloro-6-(4-methoxyphenyl)purine **2** in 83% yield. Analogously the reaction of 2,6-dichloropurine **1** with one equivalent of (4-methoxybenzyl)zinc chloride gave regioselectively 2-chloro-6-(4-methoxybenzyl)purine **3** in 76%

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yield. Another cross-coupling reaction of **2** with (4-methoxybenzyl)zinc chloride or of **3** with (4-methoxyphenyl)boronic acid furnished the heterodisubstituted purines **4** or **5** in 91 and 96% yields, respectively. Cross-coupling of **1** with three equivalents of (4-methoxyphenyl)boronic acid or (4-methoxybenzyl)zinc chloride afforded the 2,6-bis(4-methoxyphenyl or 4-methoxybenzyl)purines **6** and **7** in high yields of 94 and 90%, respectively (Scheme 1).

The Sonogashira cross-coupling reaction of **1** with 2 equiv. of (4-methoxyphenyl)acetylene gave the 2,6-bis[(4-methoxyphenyl)ethynyl]purine **8** in a moderate yield of 39%. Catalytic hydrogenation of **8** on Pd/C afforded the 2,6-bis(4-methoxyphenethyl)purine **9** in a low isolated yield of 14% accompanied by a complex mixture of partly hydrogenated and oligo/polymeric by-products. The yield of **9** could probably be improved by optimization of conditions and selection of other catalysts (Pt or Ni). Nevertheless, despite the lower yields, the compounds **8** and **9** were prepared in sufficient amounts and purity for the biological activity screening.

Though the cross-coupling reactions of 2,6-dichloro-9-isopropylpurine (**1**) should follow the same regioselectivity as reported earlier,[12] we have decided to make an independent proof by direct NMR methods. In order to distinguish between the 2-benzyl-6-phenylpurine **4** and 6-benzyl-2-phenylpurine **5** derivatives, standard $^{1}H-^{13}C$ HMBC experiments were used. However, the crucial cross-peaks affording three-bond correlations between the CH_2 and C-5 were overlapped with aromatic signals. Therefore, for the assignment of these compounds we utilized $^{1}H-^{15}N$ HMBC experiments (Table 1, Fig. 2). Using this standard procedure optimized for long-range couplings of 7–10 Hz (50–60 ms delay) two- and three-bond correlations were observed. The assignment of compound **4** was based on the presence of cross-peaks between methylene protons and nitrogens N-1 and N-3,

Table 1. ^{15}N NMR chemical shifts and $^{3}(^{1}H,^{15}N)$ connectivities from $^{1}H-^{15}N$ HMBC spectra of compounds **4**, **5** and **7** in $CDCl_3$ at 298 K

Compound	^{15}N shifts, δ				$^{3}(^{1}H,^{15}N)$ connectivities	
	N-1	N-3	N-7	N-9	2-C**H**$_2$Ar	6-C**H**$_2$Ar
4	267.3	242.9	238.7	172.7	N-1, N-3	–
5	270.6	n.o.[a]	236.8	174.7	–	N-1
7	277.4	245.6	237.7	174.6	N-1, N-3	N-1

[a] Not observed.

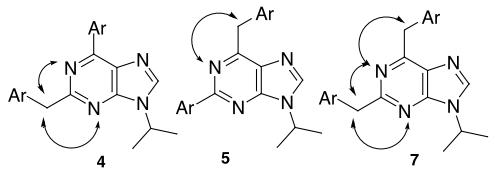
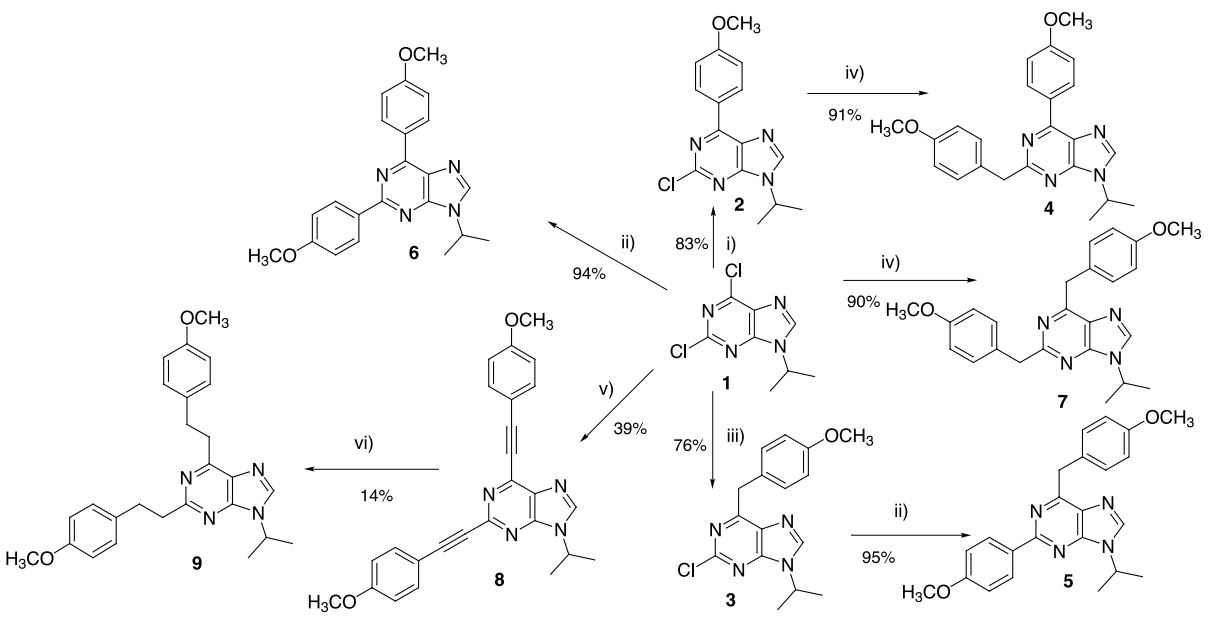


Figure 2. $^{1}H-^{15}N$ HMBC connectivities in compounds **4**, **5** and **7**.

while in the case of compound **5** only one cross-peak, indicating a connectivity between methylene protons and nitrogen N-1 was observed. Accordingly, in $^{1}H-^{15}N$ HMBC spectrum of compound **7** we found three-bond correlation signals between both methylene groups and corresponding nitrogens.

In conclusion, abbreviated carba-analogues of myoseverin were regioselectively and efficiently prepared by cross-coupling reactions of 2,6-dichloro-9-isopropylpurine (**1**) with (4-methoxyphenyl)boronic acid and/or (4-methoxybenzyl)zinc chloride. Much less efficient was the coupling of **1** with (4-methoxyphenyl)acetylene followed by catalytic hydrogenation leading to 2,6-bis(4-methoxyphenethyl)-purine **9**.

The target compounds **2–9** were tested on their in vitro inhibition of the cell growth in the following cell cultures:



Scheme 1. (i) 4-MeOC$_6$H$_4$B(OH)$_2$ (1 equiv.), K_2CO_3, Pd(PPh$_3$)$_4$; (ii) 4-MeOC$_6$H$_4$B(OH)$_2$ (2 equiv.), K_2CO_3, Pd(PPh$_3$)$_4$; (iii) 4-MeOC$_6$H$_4$CH$_2$ZnCl (1 equiv.), K_2CO_3, Pd(PPh$_3$)$_4$; (iv) 4-MeOC$_6$H$_4$CH$_2$Zncl (2 equiv.), K_2CO_3, Pd(PPh$_3$)$_4$; (v) 4-CH$_3$OC$_6$H$_4$C≡CH, CuI, Et$_3$N, Pd(PPh$_3$)$_4$, DMF; (vi) H_2, Pd/C, dioxane/EtOH.

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 results showed that the 2,6-bis[(4-methoxyphenyl)ethynyl]purine **8** exhibits considerable activity (IC_{50}=0.6, 1.6 and 3.1 μM against L1210, HL60 and CCRF-CEM cell-lines, respectively; for comparison: myoseverin[6] IC_{50}=10 μM for U937 cell line). Compound **5** showed a moderate activity against L1210 (IC_{50}~5 μM—low water solubility), while the other compounds of this series were inactive (IC_{50}>20 μM) in these assays. The lack of activity in most of the compounds could be caused by the lower water solubility and/or limited transport into the cells.

3. Experimental

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Bruker AMX3 400 (^{1}H, 400.13 MHz and ^{13}C, 100.62 MHz) or a Bruker DRX 500 Avance (^{1}H, 500.13 MHz and ^{13}C, 125.77 MHz) spectrometer at 298 K. Standard ^{1}H–^{15}N HMBC experiments were recorded in $CDCl_3$ using a Bruker Avance DRX 500 spectrometer operating at frequencies of 500.13 MHz (^{1}H) and 50.68 MHz (^{15}N). ^{15}N NMR resonances were referenced to the signal of liquid CH_3NO_2 (381.7 ppm). Unambiguous assignment of the NMR signals is based on ^{13}C{^{1}H}, ^{13}C APT, COSY and ^{1}H–^{13}C and ^{1}H–^{15}N HMBC spectra. IR spectra were recorded on Nicolet 750 FT-IR. Mass spectra were measured on ZAB-SEQ (VG Analytical). Microanalyses were performed on a Perkin–Elmer 240-II CHN Analyser. Silica gel (ICN SiliTech, 32-63) was used for column chromatography. 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. (4-Methoxyphenyl)boronic acid and Rieke® (4-methoxybenzyl)zinc chloride were supplied by Aldrich. Starting compound **1** was prepared according to known[13] procedure. Cytostatic activity tests were performed as described in Ref. 8.

3.1. Cross-coupling reactions with (4-methoxyphenyl)boronic acid—general procedure A

Toluene (10 ml) was added to an argon-purged flask containing the chloropurine (1 mmol), K_2CO_3 (200 mg, 1.5 mmol), (4-methoxyphenyl)boronic acid (1 or 3 mmol) and $Pd(PPh_3)_4$ (59 mg, 0.05 mmol) and the mixture was stirred under argon at 100°C for 8 h. After cooling to ambient temperature the solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (100 g, ethyl acetate–light petroleum 1:2 to 9:1). Evaporation and drying of the product containing fractions afforded the (4-methoxyphenyl)purines as foams or amorphous solids.

3.2. Cross-coupling reactions with (4-methoxybenzyl)zinc chloride—general procedure B

THF (10 ml) was added to an argon-purged flask containing the chloropurine (1 mmol) and $Pd(PPh_3)_4$ (59 mg, 0.05 mmol). The mixture was stirred at ambient temperature for 10 min and, after dissolution of the solids, a solution of (4-methoxybenzyl)zinc chloride (Rieke® organozinc reagent, 0.5 M solution in THF, 2 or 6 ml, 1 or 3 mmol) was added dropwise (within 10 min) at ambient temperature. Stirring at ambient temperature was continued for 15 min followed by stirring at 60°C for 8 h. Then the reaction mixture was allowed to stand overnight at ambient temperature and poured into saturated aqueous NH_4Cl (10 ml). To this mixture, saturated aqueous Na_2EDTA (10 ml) was added and the mixture was stirred for 10 min. Then the reaction mixture was extracted with ethyl acetate (3×20 ml) and the collected organic layers were washed with saturated aqueous Na_2EDTA (20 ml) and brine (20 ml), dried with anhydrous $MgSO_4$ and evaporated in vacuo. Column chromatography of the residue on silica gel (100 g, ethyl acetate–light petroleum 1:2 to 9:1) afforded, after evaporation and drying, the (4-methoxybenzyl)purines as amorphous solids.

3.2.1. 2-Chloro-9-isopropyl-6-(4-methoxyphenyl)purine (2). Prepared from **1** by procedure A (1 equiv. of boronic acid) in 83%. Colorless crystals, mp 210–214°C (CH_2Cl_2/heptane). EI MS, *m/z*: 302 (78) [M], 260 (100). IR (KBr), ν=1607, 1586, 1570, 1518, 1460, 1405, 1325 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.64 (d, 6H, *J*=6.7 Hz, $CH(CH_3)_2$); 3.90 (s, 3H, OCH_3); 4.95 (sept., 1H, *J*=6.7 Hz, $CH(CH_3)_2$); 7.05 (d, 2H, *J*=8.7 Hz, H-arom.); 8.13 (s, 1H, H-8); 8.82 (d, 2H, *J*=8.7 Hz, H-arom.). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.62 ($CH(CH_3)_2$); 47.25 ($CH(CH_3)_2$); 55.41 (OCH_3); 114.10 and 131.93 (CH-arom.); 127.39 (C-*i*-arom.); 129.81 (C-5); 141.89 (CH-8); 153.55, 153.89 and 156.22 (C-2, C-4 and C-6); 162.56 (*C*-OMe). Exact mass (EI HR MS) found: 302.0943; for $C_{15}H_{15}ClN_4O$ calculated: 302.0934. Anal. calcd for $C_{15}H_{15}ClN_4O$ (302.8): C, 59.50; H, 4.99; N, 18.51; found: C, 59.50; H, 4.97; N, 18.40.

3.2.2. 2-Chloro-9-isopropyl-6-(4-methoxybenzyl)purine (3). Prepared from **1** by procedure B (1 equiv. of organozinc reagent) in 76%. Colorless oil. EI MS, *m/z*: 316 (18) [M], 274 (10), 259 (12), 121 (8), 28 (100). IR ($CHCl_3$), ν=1552, 1483, 1435, 1348, 1206 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.60 (d, 6H, *J*=6.8 Hz, $CH(CH_3)_2$); 3.75 (s, 3H, OCH_3); 4.41 (s, 2H, CH_2); 4.87 (sept., 1H, *J*=6.8 Hz, $CH(CH_3)_2$); 6.82 (d, 2H, *J*=8.6 Hz, H-arom.); 7.42 (d, 2H, *J*=8.6 Hz, H-arom.); 8.09 (s, 1H, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.50 ($CH(CH_3)_2$); 38.68 (CH_2); 47.46 ($CH(CH_3)_2$); 55.18 (OCH_3); 113.99 and 130.35 (CH-arom.); 129.28 (C-*i*-arom.); 131.74 (C-5); 142.36 (CH-8); 152.45, 153.75 and 158.50 (C-2, C-4 and C-6); 163.08 (*C*-OMe). Exact mass (EI HR MS) found: 316.1084; for $C_{16}H_{17}ClN_4O$ calculated: 316.1091.

3.2.3. 9-Isopropyl-2-(4-methoxybenzyl)-6-(4-methoxyphenyl)purine (4). Prepared from **2** by procedure B (1.5 equiv. of organozinc reagent) in 91%. Colorless oil. EI MS, *m/z*: 388 (61) [M], 345 (20), 277 (15), 149 (100). IR (KBr), ν=1608, 1577, 1513, 1464, 1391, 1372, 1302, 1253 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.62 (d, 6H, *J*=6.7 Hz, $CH(CH_3)_2$); 3.77 and 3.88 (2×s, 2×3H, 2×OCH_3); 4.33 (s, 2H, CH_2); 4.94 (sept., 1H, *J*=6.7 Hz,

C*H*(CH_3)$_2$); 6.84 (d, 2H, *J*=8.2 Hz, H-arom.); 7.05 (d, 2H, *J*=8.4 Hz, H-arom.); 7.42 (d, 2H, *J*=8.2 Hz, H-arom.); 8.07 (s, 1H, H-8); 8.78 (d, 2H, *J*=8.4 Hz, H-arom.). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.57 (CH(*C*H_3)$_2$); 45.15 (CH_2); 46.79 (*C*H(CH_3)$_2$); 55.21 and 55.33 (2×OCH_3); 113.67, 113.91, 130.15 and 131.43 (CH-arom.); 128.93, 128.99 and 131.68 (2×C-*i*-arom. and C-5); 140.96 (CH-8); 152.64, 154.06 and 158.09 (C-2, C-4 and C-6); 161.72 and 163.39 (2×*C*-OMe). Exact mass (EI HR MS) found: 388.1907; for $C_{23}H_{24}N_4O_2$ calculated: 388.1899.

3.2.4. 9-Isopropyl-6-(4-methoxybenzyl)-2-(4-methoxyphenyl)purine (5). Prepared from **3** by procedure A (1.5 equiv. of boronic acid) in 95%. Colorless oil. EI MS, *m*/*z*: 388 (100) [M], 345 (45), 277 (15), 149 (40). IR (KBr), ν=1610, 1593, 1511, 1494, 1465, 1438, 1389, 1375, 1302, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.66 (d, 6H, *J*=6.8 Hz, CH(C*H*$_3$)$_2$); 3.75 and 3.88 (2×s, 2×3H, 2×OCH_3); 4.47 (s, 2H, CH_2); 4.95 (sept., 1H, *J*=6.8 Hz, C*H*(CH_3)$_2$); 6.83 (d, 2H, *J*=8.6 Hz, H-arom.); 7.00 (d, 2H, *J*=8.8 Hz, H-arom.); 7.48 (d, 2H, *J*=8.6 Hz, H-arom.); 8.03 (s, 1H, H-8); 8.50 (d, 2H, *J*=8.8 Hz, H-arom.). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.56 (CH(*C*H_3)$_2$); 38.76 (CH_2); 47.12 (*C*H(CH_3)$_2$); 55.17 and 55.34 (2×OCH_3); 113.68, 113.79, 129.79 and 130.36 (CH-arom.); 130.41, 130.86 and 131.26 (2×C-*i*-arom. and C-5); 141.46 (CH-8); 151.69 (C-4); 158.19, 158.44, 160.29 and 161.19 (C-2, C-6, 2×*C*-OMe). Exact mass (EI HR MS) found: 388.1911; for $C_{23}H_{24}N_4O_2$ calculated: 388.1899.

3.2.5. 9-Isopropyl-2,6-bis(4-methoxyphenyl)purine (6). Prepared from **1** by procedure A (3 equiv. of boronic acid) in 94%. Colorless crystals, mp 175–176°C (CH_2Cl_2/heptane). EI MS, *m*/*z*: 374 (80) [M], 332 (59), 149 (100). IR (KBr), ν=1609, 1588, 1565, 1513, 1433, 1372, 1246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.64 (d, 6H, *J*=6.6 Hz, CH(C*H*$_3$)$_2$); 3.84 and 3.85 (2×s, 2×3H, 2×OCH_3); 4.97 (sept., 1H, *J*=6.6 Hz, C*H*(CH_3)$_2$); 6.98 (d, 2H, *J*=8.5 Hz, H-arom.); 7.04 (d, 2H, *J*=8.5 Hz, H-arom.); 8.03 (s, 1H, H-8); 8.56 (d, 2H, *J*=8.5 Hz, H-arom.); 8.88 (d, 2H, *J*=8.5 Hz, H-arom.). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.59 (CH(*C*H_3)$_2$); 47.00 (*C*H(CH_3)$_2$); 55.34 (2×OCH_3); 113.69, 113.90, 129.77 and 131.43 (CH-arom.); 129.19 and 129.31 (2×C-*i*-arom.); 131.50 (C-5); 141.28 (CH-8); 152.96, 153.72 and 158.02 (C-2, C-4 and C-6); 161.24 and 161.75 (2×*C*-OMe). Exact mass (EI HR MS) found: 374.1754; for $C_{22}H_{22}N_4O_2$ calculated: 374.1743. Anal. calcd for $C_{22}H_{22}N_4O_2$ (374.4): C, 70.57; H, 5.92; N, 14.96; found: C, 70.56; H, 5.92; N, 14.95.

3.2.6. 9-Isopropyl-2,6-bis(4-methoxybenzyl)purine (7). Prepared from **1** by procedure B (3 equiv. of organozinc reagent) in 90%. Colorless oil. EI MS, *m*/*z*: 402 (100) [M], 359 (34), 345 (11), 149 (21). IR (KBr), ν=1611, 1594, 1513, 1496, 1464, 1442, 1391, 1382, 1325, 1301, 1249 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (d, 6H, *J*=6.7 Hz, CH(C*H*$_3$)$_2$); 3.74 and 3.77 (2×s, 2×3H, 2×OCH_3); 4.27 and 4.40 (2×s, 2×2H, 2×CH_2); 4.85 (sept., 1H, *J*=6.7 Hz, C*H*(CH_3)$_2$); 6.79 (d, 2H, *J*=9.0 Hz, H-arom.); 6.81 (d, 2H, *J*=8.9 Hz, H-arom.); 7.32 (d, 2H, *J*=8.3 Hz, H-arom.); 7.39 (d, 2H, *J*=8.3 Hz, H-arom.); 8.00 (s, 1H, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.51 (CH(*C*H_3)$_2$); 38.65 and 44.93 (2×CH_2); 46.95 (*C*H(CH_3)$_2$); 55.17 and 55.22 (2×OCH_3); 113.63, 113.78, 130.11 and 130.32 (CH-arom.); 130.73, 131.50 (2×C-*i*-arom. and C-5); 141.19 (CH-8); 151.49, 158.11 and 158.23 (C-2, C-4 and C-6); 160.50 and 163.71 (2×*C*-OMe). Exact mass (EI HR MS) found: 402.2064; for $C_{24}H_{26}N_4O_2$ calculated: 402.2056. Anal. calcd for $C_{24}H_{26}N_4O_2$ (402.5): C, 71.62; H, 6.51; N, 13.92; found: C, 71.24; H, 6.58; N, 13.63.

3.2.7. 9-Isopropyl-2,6-bis[(4-methoxyphenyl)ethynyl]purine (8). DMF (5 ml) and Et_3N (2 ml) were added through septum to an argon purged flask containing 2,6-dichloropurine **1** (690 mg, 3 mmol), (4-methoxyphenyl)-acetylene[14] (1.32 g, 10 mmol), CuI (200 mg, 1 mmol) and $Pd(PPh_3)_4$ (200 mg, 0.174 mmol). The mixture was then stirred at 120°C for 12 h and left overnight at ambient temperature. The solvents were evaporated in vacuo and the residue was chromatographed on a silica gel column (150 g, ethyl acetate–light petroleum 1:2) to give compound **8** as yellow amorphous solid (500 mg, 39%). FAB MS, *m*/*z*: 423 (20) [M], 279 (18), 135 (100). IR ($CHCl_3$), ν=2211, 1605, 1569, 1512, 1487, 1465, 1379, 1295, 1252 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.66 (d, 6H, *J*=6.8 Hz, CH(C*H*$_3$)$_2$); 3.84 and 3.85 (2×s, 2×3H, 2×OCH_3); 5.03 (sept., 1H, *J*=6.8 Hz, C*H*(CH_3)$_2$); 6.90 (d, 2H, *J*=8.4 Hz, H-arom.); 6.92 (d, 2H, *J*=8.2 Hz, H-arom.); 7.65 (d, 2H, *J*=8.7 Hz, H-arom.); 7.71 (d, 2H, *J*=8.7 Hz, H-arom.); 8.24 (s, 1H, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.70 (CH(*C*H_3)$_2$); 47.21 (*C*H(CH_3)$_2$); 55.28 and 55.32 (2×OCH_3); 83.38, 87.01, 87.65 and 99.38 (C≡); 113.45 and 113.74 (2×C-*i*-arom.); 114.03, 114.12, 134.16 and 134.51 (CH-arom.); 133.01 (C-5); 143.23 (CH-8); 142.43, 146.74 and 151.32 (C-2, C-4 and C-6); 160.48 and 160.99 (2×*C*-OMe). Exact mass (FAB HR MS) found: 423.1819; for $C_{26}H_{23}N_4O_2$ [M+H] calculated: 423.1821.

3.2.8. 9-Isopropyl-2,6-bis[2-(4-methoxyphenyl)ethyl]purine (9). A solution of compound **8** (395 mg, 0.94 mmol) in dioxane (120 ml and EtOH (50 ml) was hydrogenated under atmospheric pressure in the presence of 5% Pd/C (200 mg) for 24 h at ambient temperature. The catalyst was filtered off on Celite and the solvents were evaporated. Column chromatography of the complex mixture gave compound **9** as yellow oil (55 mg, 14%). EI MS, *m*/*z*: 430 (37) [M], 387 (11), 277 (15), 149 (20), 121 (100). IR ($CHCl_3$), ν=1610, 1592, 1513, 1497, 1392, 1246 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.61 (d, 6H, *J*=6.8 Hz, CH(C*H*$_3$)$_2$); 3.13–3.16 (m, 4H, 2×CH_2); 3.30–3.34 (m, 2H, CH_2); 3.43–3.46 (m, 2H, CH_2); 3.77 (s, 6H, 2×OCH_3); 4.90 (sept., 1H, *J*=6.8 Hz, C*H*(CH_3)$_2$); 6.80 (d, 2H, *J*=8.6 Hz, H-arom.); 6.81 (d, 2H, *J*=8.5 Hz, H-arom.); 7.17 (d, 2H, *J*=8.5 Hz, H-arom.); 7.22 (d, 2H, *J*=8.5 Hz, H-arom.); 8.02 (s, 1H, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): 22.54 (CH(*C*H_3)$_2$); 33.50, 34.11, 35.17 and 41.08 (CH_2); 46.90 (*C*H(CH_3)$_2$); 55.12 and 55.21 (2×OCH_3); 113.66, 113.72, 129.40 and 129.43 (CH-arom.); 133.62, 133.95 and 136.82 (2×C-*i*-arom. and C-5); 140.86 (CH-8); 151.00, 157.79, 157.86, 161.17 and 164.08 (C-2, C-4 and C-6 and 2×*C*-OMe). Exact mass (EI HR MS) found: 430.2358; for $C_{26}H_{30}N_4O_2$ calculated: 430.2369.

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