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# Preparation and Crystal Structures of Purine 2,2′-, 6,6′-, and 8,8′-Dimers

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Treatment of 9- or 7-substituted 6-, 2-, or 8-iodopurine derivatives with copper(I) thiophene-2-carboxylate or copper(I) 3-methylsalicylate in *N*,*N*-dimethylformamide affords the corresponding 6,6′-, 2,2′-, and 8,8′-purine dimers in high yield. Cross-dimerization reactions of different iodo derivatives were attempted, but only mixtures containing the cross-coupled products, homodimers, or dehalogenation products were obtained. The crystal structures of 9,9′-dibenzyl- (**1a**) and 9,9′-bis(1-methylethyl)-9*H*,9′*H*-[6,6′]bipurinyl (**1c**) and the salt [**1a**$H_2$]$Br_2$ were determined by single-crystal X-ray diffraction analysis, which revealed extensive hydrogen bonding and π···π stacking interactions.


## Introduction

The effect of many clinically used antitumor agents relies on their ability to crosslink[1] or intercalate[2] DNA. With an aim of extending the scope of antitumor-active compounds, a number of diverse purine–purine conjugates were designed and synthesized featuring linkages (9–9, 8–8, 9–8, 9–7, 9–6, and 6–6) of various lengths and with various connecting groups, including all-carbon chains attached to the carbon atoms of the purine and pyrimidine heterocycles.[3] In contrast, directly connected purine C–C dimers still remain practically unknown.

Nucleoside C–C 8,8′-dimers were reported as products of oxidative DNA damage.[4] The synthesis of some C–C 6,8′-purine dimers, 6,8′,6′,8′′-purine trimers, 6,8′,6′,8′′,6′′,8′′-purine tetramers, and a Pd complex of the corresponding cyclic tetramer based on Negishi cross-coupling reaction has been described.[5] Recently, we reported the formation of 6,6′-purine dimers in an attempted Heck reaction involving 6-iodopurines.[6] Although this methodology can be utilized for the preparation of purine 6,6′-dimers, the reaction is complicated by the formation of difficult-to-remove byproducts, the separation of which results in substantial decrease in the yield of the coupling products. This led us to search for a more convenient and general approach to C–C purine dimers. To the best of our knowledge, neither a practical preparative method nor the biological evaluation of simple purine dimers connected directly by a C–C bond between the ring carbon atoms (6–6′, 2–2′, 8–8′) have been reported. Moreover, as the purine bases are known to coordinate transition metals,[7] the purine dimers may serve as interesting donors for metal ions.

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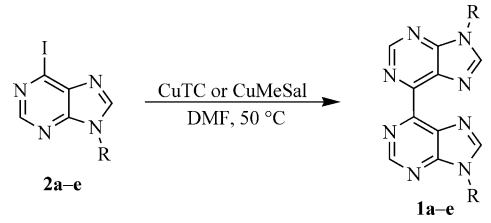
## Results and Discussion

Our observation that traces of 9,9′-dibenzyl-9*H*,9′*H*-[6,6′]bipurinyl (**1a**) are formed during the preparation of (9-benzylpurine-6-yl)magnesium halides[8] encouraged us to study dimerization of magnesiated purines. Unfortunately, attempts at $Pd^0$- and $Ni^0$-catalyzed coupling of 9-benzyl-6-iodopurine (**2a**) with (9-benzylpurin-6-yl)magnesium chloride were unsuccessful. For instance, the $Cu^I$-mediated dimerization of (9-benzylpurin-6-yl)magnesium chloride afforded a modest yield (42%) of dimer **1a** and so did the simple thermal decomposition of (9-benzylpurin-6-yl)magnesium chloride at 50 °C in THF (yield of **1a**: 28%).

Finally, we found that copper(I) thiophene-2-carboxylate (CuTC) introduced by Liebeskind for Ullmann reductive coupling of aromatic iodides and bromides[9] is a suitable reagent for purine coupling. Heating of **2a** in DMF at 50 °C in the presence of CuTC (3 equiv.) gave the desired dimer **1a** in excellent isolated yield (Scheme 1; Table 1, Entry 1). High yields of symmetrical dimers were also obtained with other 9-substituted 6-iodopurines (Table 1). In contrast, CuTC was completely inactive in the case of riboside **2d**. However, copper(I) 3-methylsalicylate (CuMeSal),[10] which was also reported to be active in this coupling, afforded the corresponding purine dimer **1d** in good yield (Table 1, Entry 4). 7-Benzyl-6-iodopurine furnished the corresponding dimer **3** in only moderate yield regardless of the catalyst used (CuTC or CuMeSal).

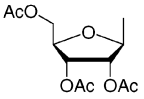
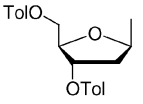
The same methodology was also applied for the dimerization of 2- and 8-iodopurine. Thus, 2-iodo-9-isopropyl-6-methoxypurine (**4**) afforded the corresponding 2,2′-dimer **5**



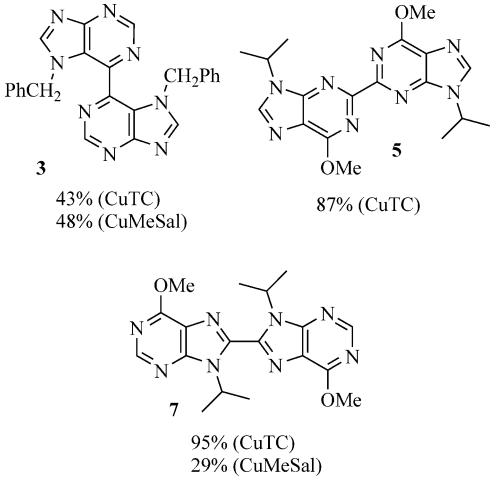

Scheme 1. Dimerization of 9-substituted 6-iodopurines.

Table 1. Preparation of purine 6,6′-dimers (Scheme 1).

| Entry | R | Product (Yield)[a] |
|---|---|---|
| 1 | $CH_2Ph$ | **1a** (90)[b] |
| 2 | $CH_2CH{=}CH_2$ | **1b** (83)[b] |
| 3 | $CH(CH_3)_2$ | **1c** (84)[b] |
| 4 |  | **1d** (0)[b] (78)[c] |
| 5 |  | **1e** (61)[b] |

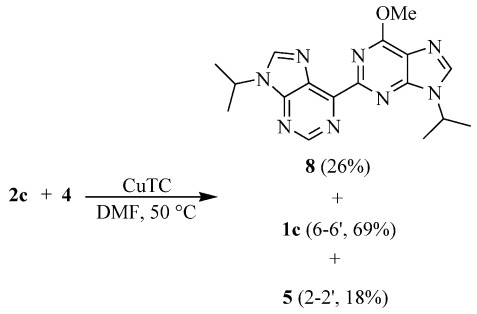
[a] Isolated yields. [b] With CuTC. [c] With CuMeSal.

in 87% yield with both catalysts (CuTC or CuMeSal). On the contrary, CuTC gave significantly better results in the dimerization of 8-iodo-9-isopropyl-6-methoxypurine (**6**) and provided the 8,8′-dimer **7** in almost quantitative yield, whereas the CuMeSal-catalyzed reaction resulted in only 29% isolated yield (Scheme 2).

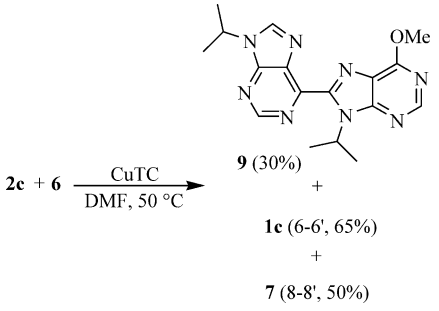



Scheme 2. Products and yields of the dimerization of 7-benzyl-6-iodopurine, 2-iodopurine **4**, and 8-iodopurine **6**.

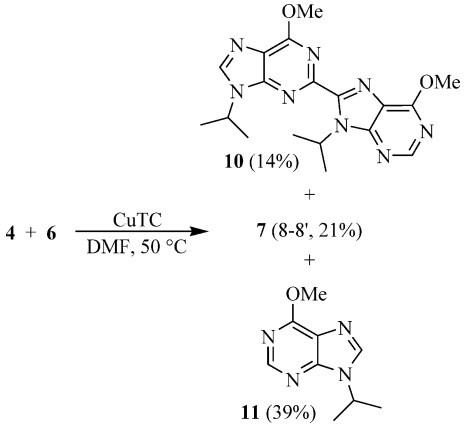
Cross-coupling of two different iodopurine derivatives under the above conditions was addressed next. Generally, such cross-coupling reactions gave mixtures of all possible regioisomers with only low selectivity for the mixed product, which could be isolated by tedious chromatography. For example, the reaction of equimolar amounts of 6-iodo-9-isopropylpurine (**2c**) and 2-iodo-9-isopropyl-6-methoxypurine (**4**) gave − besides the mixed 2–6′ bis(purine) derivative **8** (26%) – the symmetrical dimers **1c** (69%) and **5** (18%) (Scheme 3). Similarly, the mixture of 6-iodo-9-isopropylpurine (**2c**) and 2-iodo-9-isopropyl-6-methoxypurine (**6**) afforded the unsymmetrical 6–8′ dimer **9** (30%) together with the homocoupling products **1c** (65%) and **7** (50%) (Scheme 4). Interestingly, when 8-iodo-9-isopropyl-6-methoxypurine (**6**) and 2-iodo-9-isopropyl-6-methoxypurine (**4**) were submitted to reductive cross-coupling in the presence of CuTC, only formation of the 2,8′-mixed dimer (14%) together with the symmetrical 8,8′-dimer **7** (21%) was ob-




Scheme 3. Mixed dimerization of 6-iodopurine **2c** and 2-iodopurine **4**.




Scheme 4. Mixed dimerization of 6-iodopurine **2c** and 8-iodopurine **6**.




Scheme 5. Mixed dimerization of 2-iodopurine **4** and 8-iodopurine **6**.

served. The 2,2′-dimer was not detected in this case but instead a product of dehalogenation of **4**, viz. 9-isopropyl-6-methoxypurine (**11**) was isolated in 39% yield (Scheme 5).

## X-ray Crystallography

The solid-state structures of **1a**, **1c**, and the salt [**1a**$H_2$]-$Br_2$ were determined by single-crystal X-ray diffraction. The molecular structures shown in Figures 1, 2, and 3 are rather unexceptional as far as molecular geometry is concerned. In all cases, the imposed crystallographic symmetry results in *anti* arrangement of the purine moieties and renders the dimers planar. Far more interesting, however, are the crystal assemblies that may serve as a unique example of variable and synergic cooperation between C–H···X hydrogen bonding, π···π stacking of the heterocyclic rings, and hydrophobic interactions.

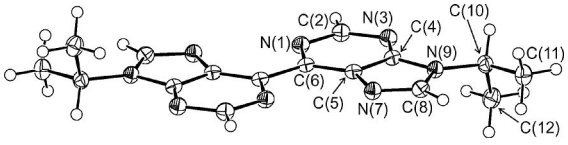



Figure 1. Molecular structure of **1c**. Displacement ellipsoids are shown with 30% probability. Selected distances [Å] and angles [°]: N(1)–C(2) 1.336(2), N(1)–C(6) 1.350(2), N(3)–C(2) 1.337(2), N(3)–C(4) 1.334(2), N(7)–C(5) 1.387(2), N(7)–C(8) 1.315(2), N(9)–C(4) 1.372(2), N(9)–C(8) 1.375(2), N(9)–C(10) 1.476(2), C(4)–C(5) 1.414(2), C(5)–C(6) 1.401(2), C(6)–C(6$^{i}$) 1.4818(2). Inner ring angles: six-membered ring, from 111.4(1) [C(2)–N(3)–C(4)] to 128.8(1) [N(1)–C(2)–N(3)]; five-membered ring, from 106.2(1) [N(9)–C(4)–C(5)] to 114.3(1) [N(7)–C(8)–N(9)]. Symmetry code: *i*. 1/2 – *x*, 1/2 – *y*, – *z*.

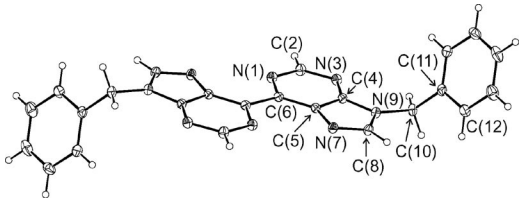



Figure 2. Molecular structure of **1a**. Displacement ellipsoids are shown with 30% probability. Selected distances [Å] and angles [°]: N(1)–C(2) 1.337(2), N(1)–C(6) 1.348(2), N(3)–C(2) 1.337(2), N(3)–C(4) 1.325(2), N(7)–C(5) 1.391(2), N(7)–C(8) 1.319(2), N(9)–C(4) 1.368(2), N(9)–C(8) 1.365(2), N(9)–C(10) 1.475(2), C(4)–C(5) 1.411(2), C(5)–C(6) 1.403(2), C(6)–C(6$^{ii}$) 1.489(2). Inner ring angles: six-membered ring, from 111.4(1) [C(2)–N(3)–C(4)] to 128.2(1) [N(1)–C(2)–N(3)]; five-membered ring, from 104.1(1) [C(5)–N(7)–C(8)] to 114.3(1) [N(7)–C(8)–N(9)]. Symmetry code: *ii*. 1 –*x*, 1 – *y*, 1 – *z*.

The molecules of **1c** assemble into tilted columns through graphite-like π···π interactions of their aromatic rings. The interacting purine moieties are parallel but offset and mutually rotated by 180° (crystallographic inversion operation; Figure 4a), which ensues in $1^5\cdots2^6/1^6\cdots2^5$ pairing of the fused heterocyclic rings ($X^n$: X is used to distinguish the purine units and *n* the rings therein). The distance of the centroids of the interacting five- and six-membered rings Cg(5)···Cg(6$^{iv}$) is 3.6876(7) Å, and the perpendicular

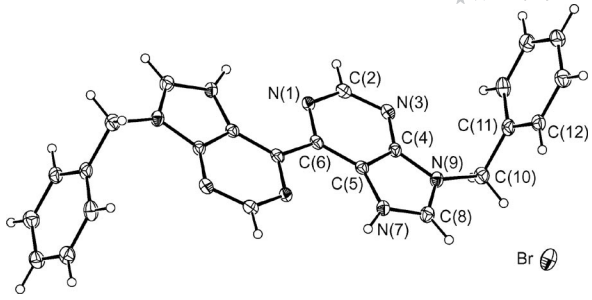



Figure 3. A view of the molecular structure of [**1a**$H_2$]$Br_2$ showing only one, structurally independent bromide ion. Displacement ellipsoids are shown with 30% probability. Selected distances [Å] and angles [°]: N(1)–C(2) 1.335(6), N(1)–C(6) 1.337(6), N(3)–C(2) 1.338(6), N(3)–C(4) 1.330(6), N(7)–C(5) 1.374(6), N(7)–C(8) 1.324(6), N(9)–C(4) 1.380(6), N(9)–C(8) 1.344(6), N(9)–C(10) 1.479(6), C(4)–C(5) 1.392(6), C(5)–C(6) 1.400(6), C(6)–C(6$^{iii}$) 1.462(6); N(9)–C(10)–C(11) 111.0(4). Inner ring angles: six-membered ring, from 118.8(4) [C(2)–N(3)–C(4)] to 128.4(4) [N(1)–C(2)–N(3)]; five-membered ring, from 106.9(4) [N(9)–C(4)–C(5)] to 111.6(4) [N(7)–C(8)–N(9)]. Symmetry code: *iii*. 1/2 – *x*, 1/2 – *y*, 1/2 – *z*.

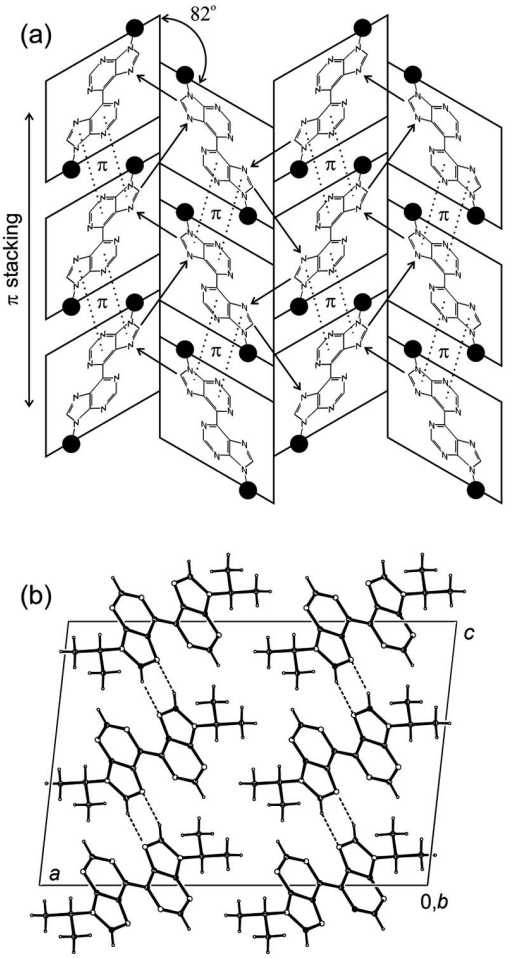



Figure 4. (a) Schematic drawing of the crystal assembly of **1c** showing π interactions of the aromatic rings (dotted lines) and hydrogen bonds (C–H → N). The isopropyl groups are shown as black circles. (b) Projection of the unit cell onto the *ac* plane (i.e., along the π-stacked columns) showing the hydrogen bonds as dashed lines.

distance of the ring planes separation is ca. 3.5 Å, which corresponds with an offset of about 1.3 Å (*iv.* 1/2 – *x*, –1/2 – *y*, –*z*).

The unit cell contains two pairs of such stacks differing in orientation (Figure 4b); molecules in the neighboring stacks are mutually rotated at a dihedral angle of 82°. Individual columns are interconnected by C–H···N hydrogen bonds: C(8)–H(8)···N(7$^{v}$), C(8)···N(7$^{v}$) 3.253(2) Å, angle at H(8) 161°, *v.* 1/2 – *x*, –1/2 + *y*, 1/2 – *z* (Figure 4a and Figure 4b). Hydrogen-bond formation brings the nonpolar substituents at N(9) into proximity, which leads to the formation of alternating polar and hydrophobic domains (Figure 4b). It is also worth noting that the structure can alternatively be looked upon as if consisting of zig–zag folded ribbons involving hydrogen-bonded, mutually rotated molecules that are piled up at distances corresponding to the π···π stacking interactions and interlinked by hydrogen bonds (see horizontal slices in Figure 4a).

Although the interactions operating in crystals of **1a** are similar to those in **1c**, the crystal assemblies differ. In the structure of **1a**, each purine moiety takes part in three-centered hydrogen bonds from C(8)–H(8) to N(1) and N(5) in an adjacent bis(purine) molecule (Figure 5a): C(8)···N(7$^{vi}$) 3.269(2) Å, angle at H(8) 129°; C(8)···N(1$^{vii}$) 3.258(2) Å, angle at H(8) 155° (*vi.* 1 – *x*, –1/2 + *y*, 1/2 – *z*; *vii.* *x*, 1/2 – *y*, –1/2 + *z*). Because the purine units forming one molecule are rotated by 180° along the 6–6′ line, the bis(purine) molecules act as bridges between four other proximal molecules: two as twofold hydrogen-bond donors [from H(8) and H(8′)] and two as twofold acceptors [to N(1)/N(5′) and to N(1′)/N(5)]. This gives rise to infinite folded sheets that are layered at the distances dictated by π···π stacking interactions of the purine units, which similar are to that in **1c** (Figure 5b): Cg(5)···Cg(6$^{viii}$) 3.7031(8) Å, interplanar distance 3.29 Å (*viii.* 1 – *x*, –*y*, 1 – *z*). The formed molecular assembly is further aided by relatively weaker C–H(phenyl)···π-ring(purine) interactions [C(14)–H(14)···Cg(6$^{ix}$): C(14)···Cg(6$^{ix}$) 3.567(2) Å, angle at H(14) 143°; and C(15)–H(15)···Cg(5$^{ix}$): C(15)···Cg(5$^{ix}$) 3.518(2) Å, angle at H(15) 127°; *ix.* –*x*, –1/2 + *y*, 1/2 – *z*].

The salt [**1a**H$_2$]Br$_2$ crystallizes with the symmetry of the tetragonal space group $I4_1/a$ (Figure 6). The bis(purine) units are doubly protonated at both N(7) atoms and form three-centered hydrogen bridges from N(7)–H(7) to neighboring bromide ions [intermolecular; N(7)–H(7)···Br$^{x}$, N(7)···Br$^{x}$ 3.258(4) Å, angle at H(7) 155°; *x.* 1/4 – *y*, 1/4 + *x*, 5/4 – *z*] and to the N(1) atom in the second bonded purine moiety [intramolecular; N(7)–H(7)···N(1$^{xi}$), N(7)···N(1$^{xi}$) 2.927(5) Å, angle at H(7) 110°; *xi.* 1/2 – *x*, 1/2 – *y*, 1/2 – *z*]. Thus, each bis(purine) unit behaves as a fourfold hydrogen-bond donor and a twofold hydrogen-bond acceptor.[11] This leads to the formation of hollow helical assemblies along the crystallographic fourfold axes. Albeit the cylindrical channels are nearly 5 Å wide, they do not host other molecules (e.g., the solvents), very likely due to saturation of the groups prone to hydrogen bonding.[12,13]

In addition to the mentioned polar interactions, the six-membered ring of the protonated bis(purine) units in

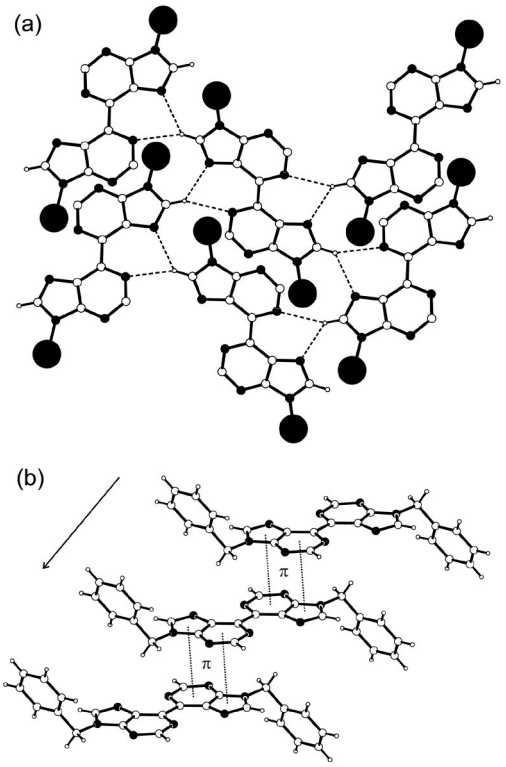



Figure 5. (a) A view of the hydrogen bonded sheets in the structure of **1a** along the columnar stacks. The hydrogen bonds are shown as dashed lines. For clarity, the phenyl groups were replaced with black circles. (b) A side view of the π-stacked columns. The arrow indicating how the tilted columnar assembly propagates is identical to the viewing direction used to obtain the diagram shown in Figure 5a.

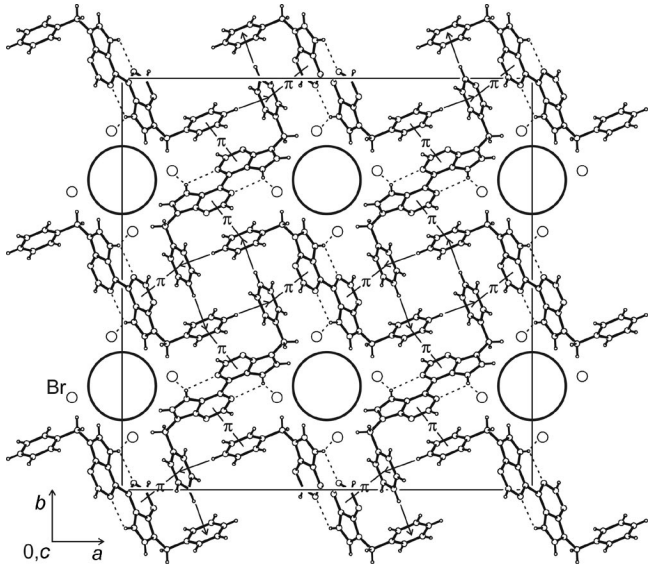



Figure 6. Projection of the unit cell of [**1a**H$_2$]Br$_2$ onto the *ab* plane showing important intermolecular interactions [hydrogen bonds (dashed lines), π···π stacking of the aromatic rings (–π–), and C–H···π-ring interactions (→)] and structural voids (large empty circles).

[**1a**$H_2$]$Br_2$ take part in π···π stacking with phenyl rings from adjacent molecules: the ring centroid distance Cg(6)···Cg($Ph^{xii}$) is 3.652(3) Å and the interplanar separation is about 3.5 Å (*xii*. 1/4 + *y*, 1/4 – *x*, 1/4 + *z*); the least-squares ring planes are rotated by ca. 6°. Finally, each phenyl ring enters into C–H···π-system interaction as both the donor and acceptor (see Figure 4); the parameters are as follows: C(14)–H(14)···Cg($Ph^{xiii}$), C(14)···Cg($Ph^{xiii}$) 3.609(6) Å, angle at H(14) 150° (*xiii*. 1/4 – *y*, – 1/4 + *x*, –1/4 + *z*).

## Conclusions

Symmetrical 6,6′-, 2,2′-, and 8,8′-purine dimers can be conveniently prepared by CuTC- or CuMeSal-mediated dimerization of the corresponding iodopurines. Cross dimerization is also possible but lacks selectivity and gives mixtures of all the possible products. Complexation behavior of the purine dimers is currently under study in our laboratories.

## Experimental Section

**General Comments:** NMR spectra were measured with a Varian Gemini 300 ($^1$H, 300.07 MHz; $^{13}$C, 75.46 MHz), Bruker AMX3 400 ($^1$H, 400.13 MHz and $^{13}$C, 100.62 MHz), or Bruker DRX 500 Avance ($^1$H, 500.13 MHz and $^{13}$C, 125.77 MHz) spectrometers at 298 K. The assignment of the NMR signals is based on $^{13}$C{$^1$H}, $^{13}$C APT, COSY, $^{13}$C HMQC, and $^{13}$C HMBC spectra. IR spectra were recorded with a Nicolet 750 FTIR spectrometer. Mass spectra were measured with a ZAB-SEQ (VG Analytical).

The solvents were dried and degassed by standard procedures; silica gel (ICN SiliTech, 32–63 mesh) was used for column chromatography. 9-Benzyl-6-iodopurine[14] (**2a**), 6-iodo-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine[15] (**2d**), 9-(3,5-di-*O*-p-toluoyl-2-deoxy-β-D-erythro-pentofuranosyl)-6-iodopurine[16] (**2e**), and 7-benzyl-6-iodopurine[14] were prepared by the reported procedures. 9-Allyl-6-iodopurine (**2b**) and 9-isopropyl-6-iodopurine (**2c**) were prepared by alkylation of 6-iodopurine[17] with allyl bromide or 2-iodopropane, respectively. 9-Isopropyl-2-iodo-6-methoxypurine (**4**) was prepared from 2-amino-6-chloro-9-isopropylpurine.[18] It was at first converted into 2-amino-9-isopropyl-6-methoxypurine by the reaction with $CH_3OH$ in the presence of $K_2CO_3$, and the amino group was subsequently replaced with iodine. Preparation of 8-iodo-9-isopropyl-6-methoxypurine (**6**) started from 6-chloro-9-isopropylpurine,[19] which was converted into 9-isopropyl-6-methoxypurine and then iodinated. Other compounds were purchased.

**9-Allyl-6-iodopurine (2b):** Dry acetonitrile was added to a mixture of 6-iodopurine (246 mg, 1 mmol) and $K_2CO_3$ (3 mmol, 415 mg) followed by the addition of allyl bromide (181 mg, 1.5 mmol). The resulting mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, evaporated with silica, and purified by flash chromatography (hexane/ethyl acetate, 1:2) to afford **2b** (220 mg, 77%) as white solid. Formation of the 7-isomer was not observed. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.89 (m, 2 H, $CH_2$), 5.27 (d, $J$ = 17.3 Hz, 1 H, =$CH_2$), 5.38 (d, $J$ = 10.3 Hz, 1 H, =$CH_2$), 6.04 (m, 1 H, -CH=), 8.13 (s, 1 H, 8-H), 8.65 (s, 1 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 46.0, 119.7, 121.9, 130.7, 138.1, 144.1, 144.8, 147.6, 151.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3000, 1583, 1554, 1491, 1428, 1400, 1333 cm$^{-1}$. HRMS (EI): calcd. for $C_8H_7IN_4$ 285.9715; found 285.9713.

**9-Isopropyl-6-iodopurine (2c):**[20] 6-Iodopurine[17] (5.24 g, 21.3 mmol) was added to a suspension of dry $K_2CO_3$ (8.83 g, 63.9 mmol) in dry DMF (100 mL). The mixture was stirred at room temperature for 30 min and then treated with 2-iodopropane (4.3 mL, 42.6 mmol). After stirring for 16 h, the mixture was filtered through Celite, which was subsequently washed with dry acetone. Evaporation of the solvents in vacuo and chromatography on silica (hexane/ethyl acetate, 2:1) afforded **2c** (4.52 g, 74%) as a white solid. M.p. 94–98 °C (toluene). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.66 (d, $J$ = 6.9 Hz, 6 H, $CH_3$), 4.91 [m, 1 H, C$H$($CH_3$)$_2$], 8.18 (s, 1 H, 8-H), 8.62 (s, 1 H, 2-H) ppm. The data agree with those in ref.[24] Formation of the 7-isomer was not observed.

**2-Amino-9-isopropyl-6-methoxypurine:** Sodium (0.274 g, 10.74 mmol) was added to MeOH (20 mL), and the resulting mixture was stirred until sodium disappeared. 2-Amino-6-chloro-9-isopropylpurine (1.894 g, 8.95 mmol) was then added, and stirring was continued at ambient temperature. After 2 h, the reaction mixture was evaporated with silica and purified by flash chromatography (ethyl acetate/methanol, 9:1) to the product (1.84 g, 99%). M.p. 166–169 °C. $^1$H NMR (300 MHz, DMSO): $\delta$ = 1.47 (d, $J$ = 6.6 Hz, 6 H, $CH_3$), 3.96 (s, 3 H, $OCH_3$), 4.58 [m, 1 H, C$H$($CH_3$)$_2$], 6.38 (s, 2 H, $NH_2$), 7.97 (s, 1 H, 8-H) ppm. $^{13}$C NMR (75 MHz, DMSO): $\delta$ = 22.0 ($CH_3$), 45.8 [$CH(CH_3)_2$], 53.1 ($OCH_3$), 114.1 (C-5), 137.5 (C-8), 153.6 (C-4), 159.5 (C-4), 160.6 (C-6) ppm. IR (KBr): $\tilde{\nu}$ = 3338, 3189, 1644, 1606, 1586, 1517, 1480, 1463, 1409, 1395, 1254, 1052 cm$^{-1}$. $C_9H_{13}N_5O$ (207.23): calcd. C 52.16, H 6.32, N 33.79; found C 52.42, H 6.59, N 34.17.

**2-Iodo-9-isopropyl-6-methoxypurine (4):** A mixture of 2-amino-9-isopropyl-6-methoxypurine (0.525 g, 2.53 mmol), iodine (0.642 g, 2.53 mmol), $Cu_2I_2$ (0.506 g, 2.65 mmol), $CH_2I_2$ (2.1 mL, 26.1 mmol), isoamyl nitrite (1.1 mL, 7.8 mmol), and THF (10 mL) was heated at reflux for 2 h. After cooling, the reaction mixture was washed with a saturated solution of $Na_2S_2O_3$. The water layer was washed with $CH_2Cl_2$ (3 × 15 mL), and the combined organic portion was dried with $Na_2SO_4$. Chromatography on silica with hexane removed the excess amount of $CH_2I_2$. A subsequent elution with hexane/ethyl acetate (1:2) furnished **4** (0.371 g, 46%) as a white solid. M.p. 140–146 °C (toluene). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.59 (d, $J$ = 6.8 Hz, 6 H, $CH_3$), 4.16 (s, 3 H, $OCH_3$), 4.86 [m, 1 H, C$H$($CH_3$)$_2$], 7.88 (s, 1 H, 8-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 22.7 ($CH_3$), 47.4 [$CH(CH_3)_2$], 54.9 ($OCH_3$), 139.6 (C-8), 117.3, 121.7, 159.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2999, 1595, 1564, 1464, 1376, 1328, 1308, 1282, 1222, 1202, 1159, 1146, 1040, 900 cm$^{-1}$. HRMS (EI): calcd. for $C_9H_{11}IN_4O$ 317.9978; found 317.9991.

**9-Isopropyl-6-methoxypurine:** 6-Chloro-9-isopropylpurine[19] (1.76 g, 8.95 mmol) was added to a solution of sodium (0.274 g, 10.74 mmol) in dry methanol (20 mL), and the reaction mixture solution was stirred for 2 h at room temperature. Methanol was then evaporated in vacuo, and the residue was purified by chromatography on silica (hexane/ethyl acetate, 1:2) to give 9-isopropyl-6-methoxypurine (1.71 g, 99%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.61 (d, $J$ = 6.77 Hz, 6 H, $CH_3$), 4.17 (s, 3 H, $OCH_3$), 4.87 [m, 1 H, C$H$($CH_3$)$_2$], 7.97 (s, 1 H, 8-H), 8.56 (s, 1 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 22.5 ($CH_3$), 47.4 and 54.0 [$CH(CH_3)_2$ and $OCH_3$], 121.9 (C-5), 139.7 (C-8), 151.5 (C-4), 151.7 (C-2), 161.1 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2988, 1604, 1575, 1479, 1402, 1350, 1323, 1306, 1197, 1042 cm$^{-1}$. HRMS (EI): calcd. for $C_9H_{12}N_4O$ 192.1011; found 192.1016.

**8-Iodo-9-isopropyl-6-methoxypurine (6):** BuLi (1.6 M in hexanes, 3.8 mL, 6.03 mmol) was added to a stirred solution of diisopropylamine (0.85 mL, 6.03 mmol) in THF (5 mL) at –80 °C. After 5 min,

9-isopropyl-6-methoxypurine (0.58 g, 3.02 mmol) dissolved in THF (5 mL) was added dropwise. After 80 min at –80 °C, a solution of iodine (2.30 g, 9.05 mmol) in THF (10 mL) was introduced, and the mixture was stirred for another 10 min. It was then quenched by the addition of a saturated solution of $Na_2S_2O_3$ (20 mL). The water layer was separated and washed with $CH_2Cl_2$ (3 × 10 mL). The combined organic extract was dried with $MgSO_4$ and evaporated in vacuo. Chromatography on silica (hexane/ethyl acetate, 1:2) gave **6** (0.719 g, 74%) as white crystals. M.p. 156–162 °C (toluene). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.72 (d, $J$ = 6.9 Hz, 6 H, $CH_3$), 4.14 (s, 3 H, $OCH_3$), 4.78 [m, 1 H, C*H*$(CH_3)_2$], 8.42 (s, 1 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 20.9 ($CH_3$), 53.5 and 54.1 [$CH(CH_3)_2$ and $OCH_3$], 151.1 (C-2), 102.5, 125.0, 152.8, 159.6 (C-6, C-5, C-4, C-8) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2996, 1602, 1573, 1484, 1443, 1335, 1318, 1290, 1270, 1221, 1215, 1086, 1041 cm$^{-1}$. HRMS (EI): calcd. for $C_9H_{11}IN_4O$ 317.9978; found 317.9974.

**General Procedure for the Dimerization of Iodopurines:** Iodopurine (1 equiv.) and CuTC or CuMeSal (3 equiv.) were placed in a flask equipped with a rubber septum. After three vacuum/argon cycles, dry DMF was added, and the resulting mixture was stirred under an argon atmosphere at 50 °C overnight (14–16 h). It was then cooled to room temperature and quenched by the addition of a mixture of a saturated aqueous solution of $NH_4Cl$ and concentrated ammonia. The resulting mixture was stirred at ambient temperature for 30 min. The organic phase was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extract was dried with $MgSO_4$, the solvents were removed in vacuo, and the solid residue was purified by flash chromatography on silica.

**9,9′-Dibenzyl-9*H*,9′*H*-[6,6′]bipurinyl (1a):** General procedure starting from **2a** (67 mg, 0.20 mmol) and CuTC (114 mg, 0.60 mmol) in dry DMF (5 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) gave dimer **1a** (38 mg, 90%) as a yellow solid. M.p. 236–240 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 5.54 (s, 4 H, $CH_2Ph$), 7.36 (br. s, 10 H, ArH), 8.23 (s, 2 H, 8-H), 9.31 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 47.5, 127.8, 128.6, 129.1, 132.2, 134.7, 146.2, 151.8, 153.1, 152.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2992, 1578, 1568, 1498, 1457, 1438, 1397, 1329, 1254, 1201, 1174 cm$^{-1}$. HRMS (EI): calcd. for $C_{24}H_{18}N_8$ 418.1654; found 418.1643.

**Preparation of [1a$H_2$]$Br_2$:** Compound **1a** (42 mg, 0.10 mmol) was dissolved in a mixture of water (10 mL), ethanol (5 mL), and HBr (47%, 1 mL). The mixture was briefly boiled, whereupon most of the solid dissolved; the formed solution was filtered while hot. Subsequent crystallization induced by slow cooling to room temperature and then completed by storing at +4 °C for several days gave crystalline product, which was filtered off, washed with 50% ethanol and water (2 × 2 mL each), and dried in air. Yield: 47 mg (81%), yellow solid. MS (ESI): $m/z$ = 441 [**1a** + Na]$^+$. The compound gives erratic elemental analyses, probably due to incomplete combustion.

**9,9′-Diallyl-9*H*,9′*H*-[6,6′]bipurinyl (1b):** General procedure starting from **2b** (280 mg, 0.98 mmol) and CuTC (561 mg, 2.94 mmol) in dry DMF (5 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) furnished dimer **1b** (130 mg, 83%) as yellow solid. M.p. 183–188 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 5.00 (d, $J$ = 4.69 Hz, 4 H, $CH_2$), 5.32 (d, $J$ = 16.8 Hz, 2 H, =$CH_2$), 5.39 (d, $J$ = 10.8 Hz, 2 H, =$CH_2$), 6.10 (m, 2 H, C*H*CH=), 8.29 (s, 2 H, 8-H), 9.32 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 45.9, 119.7, 131.1, 132.3, 146.3, 151.9, 152.7, 153.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2991, 1734, 1579, 1567, 1488, 1422, 1397, 1329 cm$^{-1}$. HRMS (EI): calcd. for $C_{16}H_{14}N_8$ 318.1341; found 318.1324.

**9,9′-Diisopropyl-9*H*,9′*H*-[6,6′]bipurinyl (1c):** General procedure starting from **2c** (308 mg, 1.06 mmol) and CuTC (606 mg, 3.18 mmol) in dry DMF (5 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) afforded dimer **1c** (143 mg, 84%) as yellow solid. M.p. 187–192 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.71 (d, $J$ = 6.7 Hz, 12 H, $CH_3$), 5.05 [m, 2 H, C*H*$(CH_3)_2$], 8.33 (s, 2 H, 8-H), 9.28 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 22.5, 47.6, 132.8, 144.1, 151.9, 152.3 152.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2986, 1590, 1576, 1490, 1483, 1460, 1407, 1391, 1375, 1331 cm$^{-1}$. HRMS (EI): calcd. for $C_{16}H_{18}N_8$ 322.1654; found 322.1644.

**9,9′-Bis(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*,9′*H*-[6,6′]bipurinyl (1d):** General procedure starting from **2d** (101 mg, 0.20 mmol) and CuMeSal (129 mg, 0.60 mmol) in dry DMF (3 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) gave dimer **1d** (59 mg, 78%) as a yellow foam. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.09 (s, 6 H, $COCH_3$), 2.14 (s, 6 H, $COCH_3$), 2.17 (s, 6 H, $COCH_3$), 4.44 (m, 4 H, $OCH_2$), 4.51 (m, 2 H, $CH_2CHO$), 5.68 (m, 2 H, C*H*OAc), 6.01 (t, $J$ = 5.8 Hz, 2 H, C*H*OAc), 6.37 (d, $J$ = 5.8 Hz, 2 H, CH), 8.45 (s, 2 H, 8-H), 9.30 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 20.3, 20.5,20.7, 63.0, 70.7, 73.0, 80.6, 86.1, 133.0, 144.7, 152.0, 152.8, 152.9, 169.2, 169.5, 170.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2869, 1752, 1673, 1581, 1491, 1437, 1388, 1330, 1266, 1226 cm$^{-1}$. HRMS (EI): calcd. for $C_{32}H_{34}N_8O_{14}$ 754.2194; found 754.2168.

**9,9′-Bis(3,5-di-*O*-p-toluoyl-2-deoxy-β-D-ribofuranosyl)-9*H*,9′*H*-[6,6′]-bipurinyl (1e):** General procedure starting from **2e** (50 mg, 0.08 mmol) and CuTC (48 mg, 0.25 mmol) in dry DMF (3 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) gave dimer **1e** (23 mg, 14%) as a brown amorphous solid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 2.38 (s, 6 H, $CH_3$), 2.44 (s, 6 H, $CH_3$), 2.91 (dd, $J_1$ = 4.3 Hz, $J_2$ = 13.2 Hz, 2 H, 2-$H_a$), 3.18 (m, 2 H, 2-$H_b$), 4.68 (m, 4 H, 4-H, 5-$H_b$), 4.78 (m, 2 H, 5-$H_a$), 5.85 (d, $J$ = 6.3 Hz, 2 H, 3-H), 6.71 (m, 2 H, 1-H), 7.22 (d, $J$ = 7.9 Hz, 4 H, ArH), 7.30 (d, $J$ = 7.9 Hz, 4 H, ArH), 7.91 (d, $J$ = 7.9 Hz, 4 H, ArH), 7.99 (d, $J$ = 7.9 Hz, 4 H, ArH), 8.43 (s, 2 H, 8-H), 9.22 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.65, 21.74, 38.0, 64.0, 75.1, 83.2, 84.9, 126.3, 126.6, 129.3, 129.3, 129.6, 129.8, 133.0, 144.2, 144.6, 144.7, 151.9, 152.7, 165.9, 166.1 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2929, 2853, 1721, 1612, 1578, 1489, 1441, 1409, 1329, 1271, 1179, 1101 cm$^{-1}$. HRMS (ES): calcd. for $C_{52}H_{47}N_8O_{10}$ [M+ H]$^+$ 943.3415; found 943.3591.

**7,7′-Dibenzyl-7*H*,7′*H*-[6,6′]bipurinyl (3):** General procedure starting from 6-iodo-7-benzylpurine (67 mg, 0.20 mmol) and CuTC (114 mg, 0.6 mmol) in dry DMF (5 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 4:1) gave dimer **3** (18 mg, 43%) as a yellow foam. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 5.18 (s, 4 H, $CH_2$), 6.57 (d, $J$ = 6.7 Hz, 4 H, ArH), 7.07 (m, 6 H, ArH), 8.18 (s, 2 H, 8-H), 9.25 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 123.2, 126.8, 128.4, 128.8, 133.8, 146.3, 149.9, 151.8, 162.9 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2934, 1605, 1580, 1553, 1497, 1479, 1455, 1371, 1334, 1173 cm$^{-1}$. HRMS (EI): calcd. for $C_{24}H_{18}N_8$ 418.1654; found 418.1664.

By following the same procedure and by using CuMeSal (161 mg, 0.60 mmol) and 6-iodo-7-benzylpurine (84 mg, 0.25 mmol) in dry DMF (5 mL) gave, after quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL) followed by flash chromatog-

raphy (EtOAc/MeOH, 9:1) a mixture (53 mg) of **3** and 7-benzylpurine contaminated with dimer **3** (25 mg, 48%; on the basis of NMR spectroscopic data).

**9,9′-Diisopropyl-6,6′-dimethoxy-9*H*,9′*H*-[2,2′]bipurinyl (5):** General procedure starting from **4** (64 mg, 0.20 mmol) and CuTC (114 mg, 0.60 mmol) in dry DMF (5 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) gave 2,2′-dimer **5** (33 mg, 87%) as a yellow solid. M.p. 172–176 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.68 (d, $J$ = 6.7 Hz, 12 H, $CH_3$), 4.36 (s, 6 H, $OCH_3$), 5.14 [m, 2 H, C*H*$(CH_3)_2$], 8.11 (s, 2 H, 8-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 23.0, 46.9, 54.2, 121.5, 140.8, 152.5, 156.7, 161.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2987, 1597, 1575, 1464, 1392, 1380, 1327, 1244 cm$^{-1}$. HRMS (EI): calcd. for $C_{18}H_{22}N_8O_2$ 382.1866; found 382.1851.

**9,9′-Diisopropyl-6,6′-dimethoxy-9*H*,9′*H*-[8,8′]bipurinyl (7):** General procedure starting from **6** (50 mg, 0.16 mmol) and CuTC (90 mg, 0.47 mmol) in dry DMF (3 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) gave dimer **7** (29 mg, 95%) as a white solid. M.p. 223–225 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.78 (d, $J$ = 7.1 Hz, 12 H, $CH_3$), 4.24 (s, 6 H, $OCH_3$), 5.48 [m, 2 H, C*H*$(CH_3)_2$], 8.62 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.3, 50.4, 54.3, 121.8, 141.6, 152.1, 153.0, 161.5 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2947, 1598, 1573, 1485, 1422, 1325, 1294, 1266 cm$^{-1}$. HRMS (EI): calcd. for $C_{18}H_{22}N_8O_2$ 382.1866; found 382.1862.

By following the same procedure and by using CuMeSal (129 mg, 0.60 mmol) and **6** (64 mg, 0.20 mmol) in dry DMF (3 mL) gave, after quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL) and flash chromatography (EtOAc/MeOH, 9:1) dimer **7** (11 mg, 29%) as a white solid.

**9,9′-Diisopropyl-6-methoxy-9*H*,9′*H*-[2,6′]bipurinyl (8):** General procedure starting from **4** (92 mg, 0.29 mmol), **2c** (83 mg, 0.29 mmol), and CuTC (343 mg, 1.8 mmol) in dry DMF (5 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/MeOH, 9:1) gave successively 2,2′-dimer **5** (10 mg, 18%) and 2,6′-dimer **8** (27 mg, 26%) as yellow amorphous solids. Subsequent elution (EtOAc/MeOH, 3:2) afforded 6,6′-dimer **1c** (65 mg, 69%). Data for **8**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.65 (m, 12 H, $CH_3$), 4.36 (s, 3 H, $OCH_3$), 5.01 [m, 1 H, C*H*$(CH_3)_2$], 5.17 [m, 1 H, C*H*$(CH_3)_2$], 8.12 (s, 2 H, 8-H), 8.28 (s, 2 H, 8-H), 9.18 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 22.5, 23.1, 46.9, 47.5, 54.6, 121.5, 132.3, 152.2, 152.3, 153.0, 153.4, 155.4, 161.1 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2987, 2935, 1707, 1599, 1578, 1493, 1467, 1395, 1376, 1332, 1262 cm$^{-1}$. HRMS (EI): calcd. for $C_{17}H_{20}N_8O$ 352.1760; found 352.1764.

**9,9′-Diisopropyl-6′-methoxy-9*H*,9′*H*-[6,8′]bipurinyl (9):** General procedure starting from **2c** (58 mg, 0.20 mmol), **6** (64 mg, 0.20 mmol), and CuTC (229 mg, 1.20 mmol) in dry DMF (3 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/Hexane, 2:1) gave 8,8′-dimer **7** (19 mg, 50%). Subsequent elution (EtOAc/MeOH, 9:1) afforded 6,8′-dimer **9** (21 mg, 30%) as a colorless oil. Subsequent elution (EtOAc/MeOH, 3:2) gave 6,6′-dimer **1c** (21 mg, 65%). Data for **9**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.69 (d, $J$ = 6.9 Hz, 6 H, $CH_3$), 1.79 (d, $J$ = 6.9 Hz, 6 H, $CH_3$), 4.17 (s, 3 H, $OCH_3$), 5.01 [m, 1 H, C*H*$(CH_3)_2$], 5.64 [m, 1 H, C*H*$(CH_3)_2$], 8.29 (s, 2 H, 8-H), 8.58 (s, 2 H, 2-H), 9.08 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.3, 22.5, 47.6, 50.3, 53.8, 122.8, 133.1, 144.3, 146.1, 147.3, 151.3, 151.9, 152.6, 153.2, 161.8 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3053, 2946, 1610, 1580, 1486, 1459, 1449, 1350, 1334, 1266 cm$^{-1}$. HRMS (EI): calcd. for $C_{17}H_{20}N_8O$ 352.1760; found 352.1766.

**9,9′-Diisopropyl-6,6′-dimethoxy-9*H*,9′*H*-[2,8′]bipurinyl (10):** General procedure starting from **6** (64 mg, 0.20 mmol), **4** (64 mg, 0.20 mmol), and CuTC (229 mg, 1.20 mmol) in dry DMF (3 mL). After quenching with a saturated solution of $NH_4Cl$ (15 mL) and ammonia (2 mL), flash chromatography (EtOAc/Hexane, 2:1) gave 8,8′-dimer **7** (8 mg, 14%). Subsequent elution (EtOAc/MeOH, 9:1) afforded successively 9-isopropyl-6-methoxypurine (**11**; 30 mg, 39%) and 2,8′-dimer **10** (11 mg, 14%) as white amorphous solid. Data for **10**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 1.65 (d, $J$ = 6.9 Hz, 6 H, $CH_3$), 1.83 (d, $J$ = 6.9 Hz, 6 H, $CH_3$), 4.20 (s, 6 H, $OCH_3$), 4.27 (s, 6 H, $OCH_3$), 5.07 [m, 1 H, C*H*$(CH_3)_2$], 5.59 [m, 1 H, C*H*$(CH_3)_2$], 8.11 (s, 2 H, 8-H), 8.58 (s, 2 H, 2-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 21.2, 22.9, 47.4, 50.5, 54.0, 54.6, 121.5, 121.9, 141.2, 149.0, 150.8, 151.7, 152.0, 153.2, 160.7, 161.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 2853, 1601, 1575, 1484, 1470, 1394, 1363, 1331, 1299, 1266, 1239 cm$^{-1}$. HRMS (EI): calcd. for $C_{18}H_{22}N_8O_2$ 382.1866, found 382.1870.

**X-ray Crystallography:** Crystals suitable for single-crystal X-ray diffraction analysis were selected directly from the reaction batch ([**1a**$H_2$]$Br_2$: yellow needle, $0.03 \times 0.05 \times 0.28$ mm$^3$) or grown by recrystallization from toluene (**1c**: yellowish needle, $0.12 \times 0.20 \times 0.35$ mm$^3$). Crystals of **1a** were obtained from attempted preparation of a zinc–halide adduct by crystallization of a **1a**–$ZnCl_2$ mixture from aqueous ethanol (colorless bar, $0.10 \times 0.12 \times 0.40$ mm$^3$). Full-set diffraction data ($\pm h \pm k \pm l$; **1c**: $\theta \leq 27.5°$, **1a**: $\theta \leq 27.1°$, and [**1a**$H_2$]$Br_2$: $\theta \leq 26.0°$) were collected with a Nonius KappaCCD diffractometer equipped with a Cryostream Cooler (Oxford Cryosystems) by using graphite monochromatized Mo-$K_\alpha$ radiation ($\lambda$ = 0.71073 Å) and analyzed with the HKL program package.[21] The data were corrected for absorption by a Gaussian routine incorporated in the diffractometer software ([**1a**$H_2$]$Br_2$); the range of the transmission factors is given in Table 2.

Table 2. Crystallographic data, data collection, and structure refinement parameters for **1c**, **1a**, and [**1a**$H_2$]$Br_2$.

| | **1c** | **1a** | [**1a**$H_2$]$Br_2$ |
|---|---|---|---|
| Formula | $C_8H_9N_4$ | $C_{24}H_{18}N_8$ | $C_{24}H_{20}Br_2N_8$ |
| $M$ [g mol$^{-1}$] | 506.27 | 418.46 | 580.30 |
| Crystal system | monoclinic | monoclinic | tetragonal |
| Space group | $C2/c$ (no. 15) | $P2_1/c$ (No. 14) | $I4_1/a$ (no. 88) |
| $a$ [Å] | 20.2888(6) | 10.0120(5) | 28.6321(6) |
| $b$ [Å] | 5.4443(2) | 6.6310(2) | 28.6321(6) |
| $c$ [Å] | 13.8576(5) | 14.8380(8) | 5.9260(2) |
| β [°] | 96.313(2) | 99.054(2) | – |
| $Z$ | 8 | 2 | 8 |
| $V$ [Å$^3$] | 1521.41(9) | 972.81(8) | 4858.1(2) |
| $D_{calcd.}$ [g mL$^{-1}$] | 1.407 | 1.429 | 1.578 |
| $T$ [K] | 150(2) | 150(2) | 150(2) |
| $\mu$(Mo-$K_\alpha$) [mm$^{-1}$] | 0.093 | 0.091 | 3.367[d] |
| Diffrns. total | 12248 | 12399 | 23866 |
| $R_{int}$ [%][a] | 3.3 | 4.9 | 9.5 |
| Unique/obsd.[b] diffrns. | 1737/1456 | 2146/1577 | 2388/1718 |
| $R$ (obsd. data) [%][c] | 3.96 | 4.16 | 4.80 |
| $R$, w$R$ (all data) [%][c] | 4.96, 10.0 | 6.77, 9.89 | 7.80, 15.1 |
| $\Delta\rho$ [e Å$^{-3}$] | 0.21, –0.23 | 0.15, –0.20 | 0.93, –0.43 |

[a] $R_{int} = \Sigma|F_o^2 - F_o^2(\text{mean})|/\Sigma F_o^2$, where $F_o^2$(mean) is the average intensity of symmetry equivalent diffractions. [b] Diffractions with $I_o > 2\sigma(I_o)$. [c] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, w$R = [\Sigma\{w(F_o^2 - F_c^2)^2\}/\Sigma\, w(F_o^2)^2]^{1/2}$. [d] Corrected for absorption; the range of transmission coefficients: 0.378–0.937.

The structures were solved by direct methods (SIR97[22]) and refined by weighted full-matrix least-squares procedure on $F^2$ (SHELXL97[23]). All non-hydrogen atoms were refined with aniso-

tropic thermal motion parameters. The H(7) atom in the structure of [**1a**$H_2$]$Br_2$ was identified from the difference electron density maps and refined as a riding atom. All other hydrogen atoms were included in the calculated positions and refined by using the riding model. Relevant crystallographic data are given in Table 2. Geometric parameters and structural drawing were obtained by using a recent version of the Platon program.[24] Values involving hydrogen atoms in the calculated positions are given without estimated standard deviations.

CCDC-672184 (for **1c**), -672185 (for **1a**), and -672186 (for [**1a**$H_2$]-$Br_2$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] Review: S. R. Rajski, R. M. Williams, *Chem. Rev.* **1998**, *98*, 2723–2796.
[2] Review: B. C. Baguley, *Anti-Cancer Drugs. Des.* **1991**, *6*, 1–35.
[3] a) F. Nagatsugi, K. Uemura, S. Nakashima, M. Maeda, S. Sasaki, *Tetrahedron Lett.* **1995**, *36*, 421–424; b) F. Nagatsugi, K. Uemura, S. Nakashima, M. Maeda, S. Sasaki, *Tetrahedron* **1997**, *53*, 3035–3044; c) F. Nagatsugi, T. Kawasaki, D. Usui, M. Maeda, S. Sasaki, *J. Am. Chem. Soc.* **1999**, *121*, 6753–6754; d) F. Nagatsugi, D. Usui, T. Kawasaki, M. Maeda, S. Sasaki, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 343–345.
[4] N. J. Duker, J. Sperling, K. J. Soprano, D. P. Druin, A. Davis, R. Ashworth, *J. Cell Biochem.* **2001**, *81*, 393–400 and references cited therein.
[5] H. Guthmann, M. Könemann, T. Bach, *Eur. J. Org. Chem.* **2007**, 632–638.
[6] T. Tobrman, D. Dvořák, *Collect. Czech. Chem. Commun.* **2007**, *72*, 1365–1374.
[7] Review: B. Lippert, *Coord. Chem. Rev.* **2000**, *200–202*, 487.
[8] T. Tobrman, D. Dvořák, *Org. Lett.* **2003**, *5*, 4289–4291.
[9] S. Zhang, D. Zhang, L. S. Liebeskind, *J. Org. Chem.* **1997**, *62*, 2312–2313.
[10] See the Supporting Information accompanying: C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2001**, *3*, 91–93.
[11] Additional interactions of the bromide ions with the H(8) atom: C(8)–H(8)···Br, C(8)···Br 3.604(5) Å, angle at H(8) 143°; were not considered, as the C(8)···Br distance exceeds the sum of the contact radii (ca. 3.55 Å).
[12] A search in Cambridge Structural Database (version 5.24 of November 2004 with updates of February, May and August 2005) revealed a rather low ability of bromide ions to attract water molecules into the "organic" crystals. Among 3923 structures of bromide salts with organic cations, only about 8% feature water molecules in distances suitable for O–H···Br hydrogen bond formation.
[13] The corresponding hydrogensulfate salt, which was obtained as described for the bromide except that 1 mL of 96% $H_2SO_4$ was used, crystallizes with one water molecule per diprotonated bis(purine) unit. However, in regard to the arrangement of the organic part and distribution of the anions, the structures of both salts can be considered isostructural. Crystallographic data for [**1a**$H_2$]$(HSO_4)_2 \cdot H_2O \equiv (C_{24}H_{20}N_8)(HSO_4)_2 \cdot H_2O$: tetragonal, $I4_1/a$ (no. 88), $a = b = 30.364(1)$ Å, $c = 5.9130(1)$ Å; $V = 5451.6(3)$ Å$^3$, $Z = 8$. CCDC-672187.
[14] L.-L. Gundersen, A. K. Bakkestuen, A. J. Aasen, H. Øverås, F. Rise, *Tetrahedron* **1994**, *50*, 9743–9756.
[15] V. Nair, S. G. Richardson, *J. Org. Chem.* **1980**, *45*, 3969–3974.
[16] P. Čapek, R. Pohl, M. Hocek, *J. Org. Chem.* **2004**, *69*, 7985–7987.
[17] G. B. Elion, G. H. Hitchings, *J. Am. Chem. Soc.* **1956**, *78*, 3508–3510.
[18] M. Česnek, A. Holý, M. Masojídková, Z. Zídek *Bioorg. Med. Chem.* **2005**, *13*, 2917–2926
[19] B. Y. Kim, J. B. Ahn, H. W. Lee, S. K. Kang, J. H. Lee, J. S. Shin, S. K. Ahn, C. I. Hong, S. S. Yoon, *Eur. J. Med. Chem.* **2004**, *39*, 433–437.
[20] A. Toyota, N. Katagiri, C. Kaneko, *Synth. Commun.* **1993**, *23*, 1295–1305.
[21] Z. Otwinowski, W. Minor, *HKL Denzo and Scalepack Program Package*, Nonius BV, Delft, The Netherlands. For a reference, see: Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326.
[22] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
[23] G. M. Sheldrick, *SHELXL97: Program for Crystal Structure Refinement from Diffraction Data*, University of Goettingen, Germany, **1997**.
[24] A. L. Spek, *Platon: A Multipurpose Crystallographic Tool*, Utrecht University, The Netherlands, **2003** and updates. Distributed via: http://www.cryst.chem.uu.nl/platon/

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