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Synthesis of 6,8,9-Tri- and 2,6,8,9-Tetrasubstituted Purines by a Combination of the Suzuki Cross-coupling, N-Arylation, and Direct C−H Arylation Reactions

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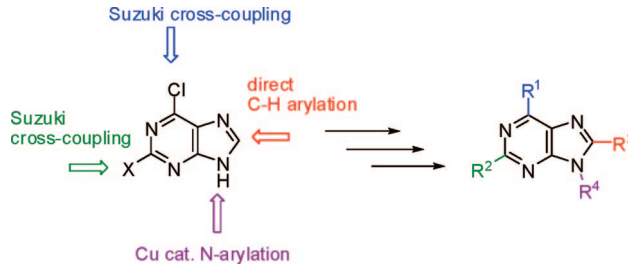

Novel practical methodology of synthesis of a several types of di-, tri-, and tetraarylpurine derivatives by a combination of regioselective Suzuki cross-coupling reactions and/or Cu-catalyzed N-arylation with direct C−H arylations was developed. 6,8-Diaryl- and 2,6,8-triaryl-9-isopropylpurines were prepared by one or two cross-couplings of 6-chloro- or 2,6-dichloro-9-isopropylpurine with arylboronic acids followed by Pd-catalyzed C−H arylation by aryl halides to position 8. 6-Chloropurine and adenine underwent Cu-catalyzed N-arylation to position 9 with boronic acids, followed by cross-coupling with $AlMe_3$ and/or C−H arylation to obtain 8,9-diaryl-6-methylpurines or 8,9-diaryladenines (accompanied by products of partial N-arylation of adenine in position 6). The methodology is suitable for construction of small libraries of modified purines.

Introduction

2,6,9- or 6,8,9-Trisubstituted and 2,6,8,9-tetrasubstituted purines display a wide range of biological activities,[1] such as inhibition of protein kinases[2] or tubulin polymerization,[3] and antagonist effects to receptors,[4] etc. Reversine is a purine derivative causing a dedifferentiation of muscle cells to progenitor cells[5] and inducing polyploidization[6] of cancer cells via inhibition of Aurora kinases. 6-Arylpurines are of particular importance due to anti-HCV, cytostatic, and antimycobacterial activities.[7] Large combinatorial libraries of several types of tri- and tetrasubstituted purines have been prepared by heterocyclizations[8] or by regioselective nucleophilic substitutions of dihalopurines with amines (sometimes in combination with one cross-coupling reaction).[9,10] In contrast to simple, efficient, and

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regioselective introduction of N- or C-substituents,[10] regioselective introduction of C-substituents by cross-coupling reactions[11] is more problematic. Although 2,6- and 6,8-dihalopurines give regioselective cross-couplings with most types of organometallics and were used for the synthesis of series of several types of disubstituted purine bases and nucleosides,[12] reactions of 2,6,8-trichloropurine proceed unselectively, giving mixtures of products.[13] Therefore, we have started out developing the methodology of direct C−H arylation[14,15] in purines as a new strategy complementary to the cross-couplings applicable for regioselective multiple substitutions of purine. Recently, we have reported[16] on the new C−H arylations of 6,9-disubstituted purines to position 8 by diverse aryl halides under Pd catalysis in absence of ligands (in analogy to Bellina's protocol[15]). As a proof of principle, this method was applied[15] in combination with two regioselective cross-coupling reactions to get two examples of 2,6,8-trisubstituted purines. Later on, we[17] and others[18] have further developed the C−H arylation for modification of unprotected nucleosides (i.e., adenosine).

Several types of cytostatic natural products (e.g., colchicine, podophyllotoxin, and combretastatine) displaying antimitotic effect through inhibition of tubulin polymerization possess a common structural feature of two heavily methoxylated aromatic rings in the vicinity. Many diverse non-natural compounds of such and related structures (diarylpyrroles,[19] -triazoles,[20] -imidazoles,[21] -thiophenes[22] etc.) were prepared and were also found to be potent inhibitors of tubulin polymerization. Myoseverin[3] is a related cytostatic purine derivative, 2,6-bis[(4-methoxybenzyl)amino]-9-isopropylpurine, with the same mechanism of action. Our own study[23] on analogous 2,6-diaryl- and -dibenzylpurines did not show significant activities except for 2,6-diarylethynylpurines. Now, we have decided to further combine the stuctural features of three classes of cytostatic compounds—2,6,9-trisubstituted purines, 6-arylpurines, and combretastatine analogues—and use a purine ring as a scaffold for attachment of two or three methoxylated phenyl groups in other positions and their combinations. Therefore, our target compounds were novel 9-isopropyl-6,8-diarylpurines, -2,6,8-triarylpurines, 6-methyl-8,9-diarylpurines, and 8,9-diaryladenines, and our synthetic methodology of choice involved a combination of the cross-coupling reactions in positions 2 and/or 6, N-arylations in position 9, and C−H arylation in position 8.

Results and Discussion

As mentioned above, our synthetic strategy toward the target compounds was based on a combination of the Pd-catalyzed Suzuki−Miyaura cross-coupling reactions of (di)halopurines with arylboronic acids, Pd-calatyzed C−H arylations of purines with aryl halides, and Cu-catalyzed N-arylations of 9*H*-purines with arylboronic acids. Therefore a set of five methoxylated phenylboronic acids (**1a**−**e**) and four methoxylated phenyl iodides and bromides (**2a**−**d**) has been chosen (Chart 1) as the reagents for the particular arylations in different position.

The first class of compounds of our interest were 9-isopropyl-6,8-diarylpurines envisaged to be prepared by a two-step sequence of the Suzuki reaction in position 6 followed by the C−H arylation in position 8. Thus 6-chloro-9-isopropylpurine (**3**) underwent the Pd-catalyzed Suzuki-Miyaura cross-coupling reactions with four arylboronic acids **1a**−**d** under classical conditions[12c,23] in toluene in presence of $Pd(PPh_3)_4$ and K_2CO_3 to get a series of 6-aryl-9-isopropylpurines (**4a**−**d**, Scheme 1) isolated in good yields (except for the 3,4,5-trimethoxyphenyl derivative **4d** isolated in rather moderate yield of 66%). In the second step, each of these intermediates **4a**−**d** was used in a series of C−H arylation[16] experiments with methoxyphenyl halides (**2a**−**d**) to generate a small library of 16 6,8-diarylpu-

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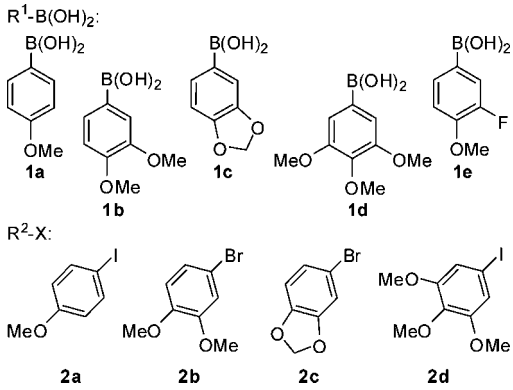
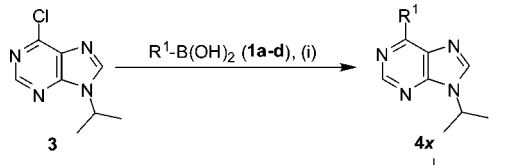
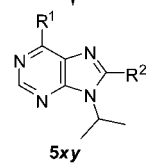
CHART 1. Set of arylboronic acids and aryl halides

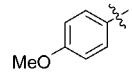
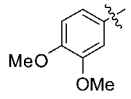
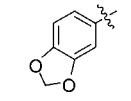
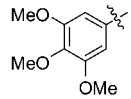


SCHEME 1. Preparation of 6,8-disubstituted-9-isopropyl-9*H*-purines



4*x*	R^1	Yield
4a	4-MeO-Ph	98 %
4b	3,4-$(MeO)_2$-Ph	75 %
4c	3,4-(OCH_2O)-Ph	81 %
4d	3,4,5-$(MeO)_3$-Ph	66 %



5*xy*	R^1	R^2	Yield
5aa		4-MeO-Ph	64 %
5ab		3,4-$(MeO)_2$-Ph	72 %
5ac		3,4-(OCH_2O)-Ph	58 %
5ad		3,4,5-$(MeO)_3$-Ph	40 %
5ba		4-MeO-Ph	80 %
5bb		3,4-$(MeO)_2$-Ph	75 %
5bc		3,4-(OCH_2O)-Ph	58 %
5bd		3,4,5-$(MeO)_3$-Ph	31 %
5ca		4-MeO-Ph	45 %
5cb		3,4-$(MeO)_2$-Ph	35 %
5cc		3,4-(OCH_2O)-Ph	43 %
5cd		3,4,5-$(MeO)_3$-Ph	31 %
5da		4-MeO-Ph	48 %
5db		3,4-$(MeO)_2$-Ph	54 %
5dc		3,4-(OCH_2O)-Ph	58 %
5dd		3,4,5-$(MeO)_3$-Ph	23 %

(i) R^1-$B(OH)_2$ (**1a-1d**, 1.3 equiv), $Pd(PPh_3)_4$ (0.024 equiv), K_2CO_3 (1.25 equiv), Toluene, 19 h, 100°C.
(ii) R^2-X (**2a-2d**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), Cs_2CO_3 (2.5 equiv), CuI (3 equiv), DMF, 60 h, 160°C.

rines (**5xy**, Scheme 1). The direct C−H arylation reactions were performed under the previously reported[16] optimized conditions in the presence of $Pd(OAc)_2$ (without any ligand) and excess of CuI and Cs_2CO_3 in DMF at 160 °C for 60 h. The yields of the second step varied between 23 and 80% depending on the aryl halide used. Somewhat surprisingly we did not observe significant differences in reactivity between substituted phenyl iodides and bromides, but the least reactive was the most electron-rich 3,4,5-trimethoxyphenyl iodide (yields 23−40%). The moderate yields were mostly caused by incomplete conversion of the starting materials rather than by formation of side-products.[16] Formation of minor 8,8′-bis(purine) side-products[16] has been observed in several cases with yields of <5%, but in the case of reaction of **4a** or **4b** with **2a**, the bis(purines) were isolated in 24 and 10%, respectively (see Supporting Information), in addition to the desired major products **5aa** (64%) and **5ba** (80%). The overall yields of the desired title 6,8-diarylpurines **5xy** over the two steps ranged from moderate (15%) to excellent (71%), and the methodology was quite efficient for a facile generation of the 4 × 4 library of derivatives.

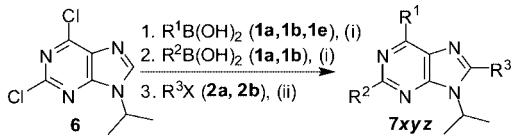
The second class of compounds under study were 9-isopropyl-2,6,8-triarylpurines. To access these compounds, we decided to combine two regioselective Suzuki−Miyaura cross-couplings with direct C−H arylation. In our previous communication, we have demonstrated, as a proof-of-principle, on two examples that, starting from 9-substituted 2,6-dichloropurine, one can perform consecutively two cross-couplings followed (without isolation of intermediates) by the C−H arylation. We have now applied the approach for the synthesis of our target 2,6,8,9-tetrasubstituted purines. Thus, the starting 2,6-dichloro-9-isopropylpurine **6** was reacted successively in one pot with two arylboronic acids, and then, without isolation, the reaction mixture was just filtered through a pad of celite, evaporated, and directly used for C−H arylation reaction (Scheme 2). Both reactions were performed under the same conditions as discussed above in the previous series of compounds. The first aryl group was regioselectively introduced to position 6 (using arylboronic acids **1a**, **1b**, and **1e**), the second to position 2 (using **1a** and **1b**), and the third one to position 8 (using aryl halides **2a** and **2b**). Using this methodology, we prepared 9 examples of desired 2,6,8,9-tetrasubstituted purines (**7xyz**) in very good total yields (average yield 48% over three steps). Reactions proceeded relatively cleanly with only one major product, easily separable from minor impurities (presumably mono- and diarylated purines) by column chromatography.

In the third series of compounds, 6-methyl-8,9-diarylpurines, we used a combination of N^9-arylation, cross-coupling with trimethylaluminum, and direct C−H arylation. This time the intermediates after each step were isolated from the reaction mixture on a pad of silica gel due to incompatible reagents used in each step. The N^9-arylations of 6-chloropurine **8** with arylboronic acids (**1a**, **1b**) were performed according to the Gundersen procedure[24] in presence of anhydrous $Cu(OAc)_2$, phenanthroline and molecular sieves in dichloromethane gave desired products **9a** and **9b** in ca. 50% yields (Scheme 3). Methylation of intermediates **9a** and **9b** with trimethylaluminum was performed in analogy to literature[25] in the presence of $Pd(PPh_3)_4$ in THF to give the 6-methyl-9-arylpurines **10a** and **10b** in 63 and 80% yields, respectively. The last step, C−H arylation in position 8 of **10a**,**b** with aryl halides **2a**, **2b**, and **2d** proceeded smoothly under the same conditions as above to give six examples of the target compounds **11x,y** in 52−97%

(24) Bakkestuen, A. K.; Gundersen, L. L. *Tetrahedron Lett.* **2003**, *44*, 3359–3362.

(25) (a) Hirota, K.; Kitade, Y.; Kanbe, Y.; Maki, Y. *J. Org. Chem.* **1992**, *57*, 5268–5270. (b) Česnek, M.; Hocek, M.; Holý, A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1357–1373.

SCHEME 2. Consecutive synthesis of 2,6,8-trisubstituted-9-isopropyl-9*H*-purines



7xyz	R^1	R^2	R^3	Yield
7aaa	MeO	MeO	MeO	56 %
7aab	MeO	MeO	MeO, OMe	54 %
7aba	MeO	MeO, OMe	MeO	43 %
7abb	MeO	MeO, OMe	MeO, OMe	41 %
7baa	MeO, OMe	MeO	MeO	42 %
7bab	MeO, OMe	MeO	MeO, OMe	39 %
7bba	MeO, OMe	MeO, OMe	MeO	61 %
7bbb	MeO, OMe	MeO, OMe	MeO, OMe	61 %
7eaa	MeO, F	MeO	MeO	36 %

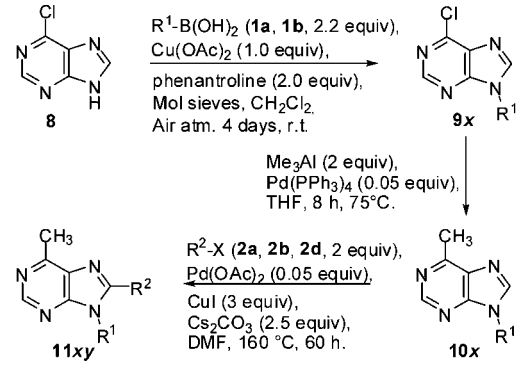
(i) 1. $R^1B(OH)_2$ (**1a,1b, 1e,** 1.05 equiv), $Pd(PPh_3)_4$ (0.05 equiv), K_2CO_3 (3 equiv), Toluene, 100°C, 18h. 2. $R^2B(OH)_2$ (**1a,1b,** 2 equiv) 100°C, 12h.
(ii) R^2-X (**2a,2b**, 2 equiv), $Pd(OAc)_2$ (0.05 equiv), Cs_2CO_3 (2.5 equiv), CuI (3 equiv), DMF, 60 h, 160°C.

yields of the third step. Again, reactions with 5-iodo-1,2,3-trimethoxybenzene **2d** gave lower conversions to give the products **11ad** and **11bd** in 53 and 52%, respectively.

In the last series we focused on synthesis of 8,9-disubstituted-adenines. The first step was N^9-arylation of adenine with arylboronic acids **1a** and **1b** according to the literature[26] in presence of $Cu(OAc_2)\cdot H_2O$ and TMEDA (Scheme 4). These reactions proceeded very slowly to give the 9-aryladenines **12a,b** in moderate yields of 37 and 28%, respectively (Table 2), after separation from unreacted starting material by a simple filtration through a short pad of silica gel. Considering the low cost of the starting adenine and simple separation of products, the low-

(26) Yue, Y.; Zheng, Z.-G.; Wu, B.; Xia, C.-Q.; Yu, X.-Q *Eur. J. Org. Chem.* **2005**, *515*, 4–5157.

SCHEME 3. Synthesis of 8,9-disubstituted-6-methyl-9*H*-purines

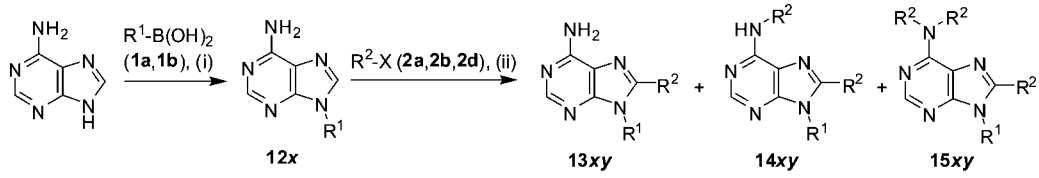


R^1	9x (yield)	10x (yield)	11xy	R^2	yield
MeO	9a (47 %)	10a (63 %)	11aa	4-MeO-Ph	78 %
			11ab	3,4-$(MeO)_2$-Ph	97 %
			11ad	3,4,5-$(MeO)_3$-Ph	53 %
MeO, OMe	9b (46 %)	10b (80 %)	11ba	4-MeO-Ph	76 %
			11bb	3,4-$(MeO)_2$-Ph	79 %
			11bd	3,4,5-$(MeO)_3$-Ph	52 %

yielding procedure was still quite practical. The second step, C−H arylation of **12a** with **2a**, led to complex mixture of three major products. Besides the desired 8-arylated adenine **13aa**, two byproducts were also isolated arising from single (**14aa**) and double (**15aa**) Cu-mediated N^6-arylation of **13aa** (Scheme 4). This phenomenon was also observed in direct C−H arylation on adenosine,[17] where partial (in this case only one-fold) N^6-arylation of the product also took place. Under the standard conditions mentioned above, we isolated 45% of desired product **13aa** and 29 (**14aa**) and 17% (**15aa**) of the byproducts (Table 1, entry 1), which were easily separable from each other by flash chromatography. Several optimization experiments have been performed in order to suppress the side reaction. Shortened reaction time led to lower conversion (entry 2), whereas a lower temperature (120 °C, Table 1, entry 3) slighty increase the yield of desired product **13aa**. Decreasing or increasing of the amount of copper iodide did not bring any improvements (Table 1, entries 4 and 5). The use of piperidine as base (entry 6) gave the best selectivity and yield of formation of 8-aryladenine **13aa** (79%), accompanied only by 10% of minor product **14aa** (**15aa** was not observed). We took advantage of the good separation of the three products (**13**, **14**, and **15**) to diversity-oriented synthesis of several derivatives in parallel and used the conditions giving good yields of all of them (Table 1, entry 3) in arylation of **12a,b** with a series of aryl halides **2a**, **2b**, and **2d**. These six arylation reactions gave 18 compounds (Scheme 4, Table 2). The yields of the 8,9-diaryladenines **13x,y** ranged from 21 to 50%, whereas the N-arylated products **14** and **15** were isolated in 5−31% yields. It is interesting to mention that although the arylation of **12** with mono- and dimethoxyphenyl halides **2a** and **2b** produced the 8-aryladenines **13** as major products, the reaction with trimethoxyphenyl iodide **2d** led to preferential formation of N^6,8-diarylated products **14ad** and **14bd** (Table 2, entries 3 and 6).

All the intermediates and final compounds were fully characterized by NMR spectroscopy (including C,H-HSQC and C,H-HMBC experiments for complete assignment of all signals,

SCHEME 4. Synthesis of 8,9-disubstituted-adenines



(i) R^1-B(OH)$_2$ (**1a**,**1b**, 2 equiv), Cu(OAc)$_2$.H$_2$O (1.0 equiv), TMEDA (2 equiv), CH$_3$OH:H$_2$O=4:1, air atm. 24h, r.t.
(ii) R^2-X (**2a**,**2b**,**2d**, 2 equiv), Pd(OAc)$_2$ (0.05 equiv),CuI (3 equiv), Cs$_2$CO$_3$ (2.5 equiv), DMF, 120°C, 42 h.

TABLE 1. Reaction of 12a with 2a. Optimization of conditions

Entry	T (°C)	t (h)	base	CuI (equiv)	**13aa** (%)	**14aa** (%)	**15aa** (%)
1	160	48	Cs_2CO_3	3	45	29	17
2	160	21	Cs_2CO_3	3	39	27	15
3	120	42	Cs_2CO_3	3	46	24	16
4	120	42	Cs_2CO_3	1	37	28	24
5	120	42	Cs_2CO_3	6	21	17	18
6	150	14	piperidine	3	79	10	0

see Supporting Information). Selected examples of compounds were also characterized by single-crystal X-ray diffraction. Figure 1 shows the ORTEP plots for structures of compounds **7eaa**, **13ad**, and **15aa**. It demonstrates a low steric hindrance in the 2,6,8-arylpurines, where in **7eaa** all the three aryl groups are nearly coplanar to the purine ring. On the other hand, in 8,9-diarylpurines, the two bulky adjacent aryl groups cannot adopt planar conformation, and the one in position 9 is perpendicular to the purine plane (**13ad** and **15aa**), similarly to the two aryl groups of diarylamino group in compound **15aa**.

All the title substituted purines **4**, **5**, **7**, **10**, **11**, **13**, **14**, and **15** were subjected to biological activity screening. The cytostatic activity in vitro (inhibition of cell growth)[7a] was studied on the following cell cultures: (i) mouse leukemia L1210 cells (ATCC CCL 219); (ii) human promyelocytic leukemia HL60 cells (ATCC CCL 240); (iii) human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2), and (iv) human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119). The cytostatic activities of compounds were determined by XTT analysis. None of the studied compounds showed any significant cytostatic effect at $c = 1-10\ \mu$M (depending on the solubility in water). In addition, inhibition of polymerization of tubulin[27] was performed on all the compounds and again, no significant effect was found. The very limited solubility in water was definitely a limitation for this class of compounds.

In conclusion, we have developed the synthetic strategy for the preparation of several novel classes of tri- and tetrasubstituted purines by a combination of the Suzuki−Miyaura cross-coupling reactions of (di)chloropurines with arylboronic acids in position(s) 6 (and 2), the Cu-catalyzed N-arylation in position 9 and direct C−H arylation in position 8. The 2−3 step synthetic sequences in principle can be performed without isolation of intermediates (but not one-pot due to incompatibility of the reagents and solvents in each step). The approach is efficient and suitable for parallel synthesis of combinatorial libraries of purines bearing several aryl groups in different position. The compounds under study were inactive in cytostatic activity screening and in tubulin assay; however, the cross-couplings, N and C−H arylations should be suitable for combination with amination(s) in position(s) 6 (and/or 2) to generate the second generation of compounds with a better solubility in water.

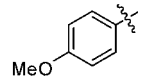
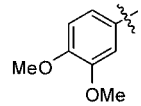
Experimental Section

General Procedure for Suzuki Cross-coupling Reactions of 3 with 1a−d. Toluene (5 mL) was added through a septum to an argon-purged vial containing 6-chloro-9-isopropyl-9*H*-purine (**3**, 196.6 mg, 1 mmol), Pd(PPh$_3$)$_4$ (27.7 mg, 0.024 mmol), arylboronic acid (**1a−d**, 1.3 mmol), and K$_2$CO$_3$ (172.7 mg, 1.25 mmol). The reaction mixture was heated to 100 °C for 19 h. The solvent was evaporated under reduced pressure. Products were isolated by flash column chromatography (gradient elution hexanes → ethyl acetate/hexanes 1:1).

9-Isopropyl-6-(4-methoxyphenyl)-9*H*-purine (4a). Yield 98%, white crystals from CHCl$_3$/heptane, 89−92 °C. ^{1}H NMR (600 MHz, CDCl$_3$): 1.68 (d, 6H, J_{vic} = 6.8, (C*H*$_3$)$_2$CH); 3.91 (s, 3H, CH$_3$O); 4.98 (h, 1H, J_{vic} = 6.8, C*H*(CH$_3$)$_2$); 7.08 (m, 2H, H-3′,5′); 8.16 (s, 1H, H-8); 8.81 (m, 2H, H-2′,6′); 8.97 (s, 1H, H-2). ^{13}C NMR (151 MHz, CDCl$_3$): 22.6 ((*C*H$_3$)$_2$CH); 47.1 (*C*H(CH$_3$)$_2$); 55.4 (CH$_3$O); 114.0 (CH-3′,5′); 128.4 (C-1′); 130.9 (C-5); 131.4 (CH-2′,6′); 141.4 (CH-8); 151.9 (C-4); 152.0 (CH-2); 154.4 (C-6); 161.9 (C-4′). MS (FAB), *m*/*z* (% relative intensity): 184 (10), 227 (40), 269 (MH$^+$, 100). HR MS (MH$^+$) 269.140558 (calcd for C$_{15}$H$_{16}$N$_4$O 269.140236). Anal. calcd for C$_{15}$H$_{16}$N$_4$O: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.07; H, 5.90; N, 20.69.

General Procedure for C−H Arylation of 6-Aryl-9-isopropylpurines 4a−d with 2a−d. DMF (6 mL) was added through a septum to an argon-purged vial containing a 6-aryl-9-isopropyl-

TABLE 2. Synthesis of 8,9-disubstituted-adenines

Entry	R^1	**12*x*** (Yield)	R^2	Product (Yield) **13*xy***	**14*xy***	**15*xy***
1		**12a** (37%)	4-MeO-Ph	**13aa** (46 %)	**14aa** (24 %)	**15aa** (16 %)
2			3,4-(MeO)$_2$-Ph	**13ab** (26 %)	**14ab** (12 %)	**15ab** (18 %)
3			3,4,5-(MeO)$_3$-Ph	**13ad** (21 %)	**14ad** (24 %)	**15ad** (15 %)
4		**12b** (28%)	4-MeO-Ph	**13ba** (50 %)	**14ba** (27 %)	**15ba** (18 %)
5			3,4-(MeO)$_2$-Ph	**13bb** (26 %)	**14bb** (5 %)	**15bb** (9 %)
6			3,4,5-(MeO)$_3$-Ph	**13bd** (23 %)	**14bd** (31 %)	**15bd** (10 %)

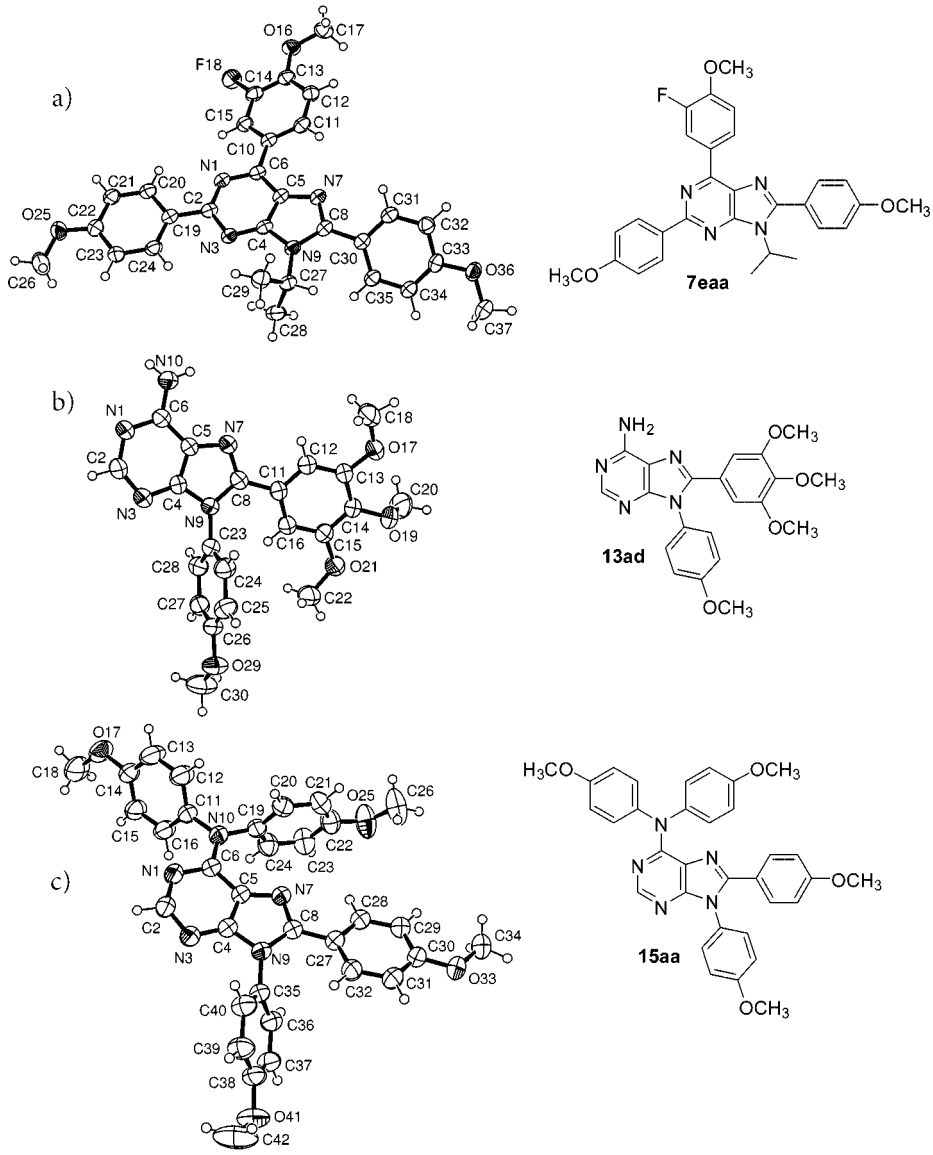


FIGURE 1. ORTEP drawings of crystal structures of **7eaa** (a), **13ad** (b), and **15aa** (c) with atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

9*H*-purine (1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %), CuI (571.3 mg, 3 mmol), aryl halide (**2a**−**d**, 2 mmol), and Cs_2CO_3 (814.6 mg, 2.5 mmol). Reaction mixture was stirred at 160 °C for 60 h and, after cooling to rt, it was diluted with chloroform (20 mL) and solvents were evaporated under reduced pressure. Products were isolated by flash column chromatography (gradient elution hexanes → ethyl acetate/hexanes 1:1).

9-Isopropyl-6,8-bis(4-methoxyphenyl)-9*H*-purine (5aa). Yield 52%, white crystals from $CHCl_3$/heptane, mp 151−152 °C. ^{1}H NMR (600 MHz, $CDCl_3$): 1.78 (d, 6H, J_{vic} = 6.9, $(CH_3)_2CH$); 3.89 (s, 3H, CH_3O-4′); 3.91 (s, 3H, CH_3O-4″); 4.83 (h, 1H, J_{vic} = 6.9, $CH(CH_3)_2$); 7.06 (m, 2H, H-3′,5′); 7.09 (m, 2H, H-3″,5″); 7.68 (m, 2H, H-2″,6″); 8.88 (m, 2H, H-2′,6′); 8.93 (s, 1H, H-2). ^{13}C NMR (151 MHz, $CDCl_3$): 21.1 ($(CH_3)_2CH$); 49.7 ($CH(CH_3)_2$); 55.3 (CH_3O-4′); 55.5 (CH_3O-4″); 113.9 (CH-3′,5′); 114.3 (CH-3″,5″); 122.4 (C-1″); 128.8 (C-1′); 130.9 (C-5); 131.0 (CH-2″,6″); 131.4 (CH-2′,6′); 151.0 (CH-2); 153.3 (C-6); 153.9 (C-4); 154.5 (C-8); 161.3 (C-4″); 161.6 (C-4′). MS (FAB), *m*/*z* (% relative intensity): 134 (35), 290 (5), 303 (6), 319 (5), 333 (59), 345 (6), 359 (5), 375 (MH^+, 100). HR MS (MH^+) 375.183958 (calcd for $C_{22}H_{22}N_4O_2$ 375.182101). Anal. calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.59; H, 5.84; N, 14.64.

General Procedure for Consecutive Synthesis of 2,6,8,9-Tetrasubstituted Purines 7xyz. Toluene (3 mL) was added through a septum to an argon-purged vial containing a 2,6-dichloro-9-isopropyl-9*H*-purine (**6**, 231.1 mg, 1 mmol), arylboronic acid (**1a**,**1b**,**1e**, 1.05 mmol), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 5 mol %), and K_2CO_3 (414.6 mg, 3 mmol). Reaction mixture was heated to 100 °C for 18 h. After cooling to rt, the second arylboronic acid (**1a**,**1b**, 2 mmol) and toluene (6 mL) were added. The reaction mixture was heated to 100 °C for 12 h, and after being cooled to rt it was diluted with $CHCl_3$ (100 mL) and filtered through a pad of celite. The solvents were evaporated, and the residue was dried at room temperature under vacuum for 14 h. The crude reaction mixture was transferred into a vial and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %), CuI (571.3 mg, 3 mmol), aryl halide (**2a**,**2b**, 2 mmol), and Cs_2CO_3 (814.6 mg, 2.5 mmol) were added. The vial was closed with a pressure cap, evacuated and filled with argon. Then DMF (6 mL) was added under argon atmosphere, and the reaction mixture was heated to 160 °C for 60 h. The crude mixture was diluted with $CHCl_3$ (50 mL), and the solvents were evaporated

(27) (a) Castoldi, M.; Popov, A. V. *Protein Expr. Purif.* **2003**, *32*, 83–88. (b) Hamel, E. *Cell Biochem. Biophys.* **2003**, *38*, 1–21.

under reduced pressure. Products **7xyz** were isolated by flash column chromatography (gradient elution 5% ethyl acetate in hexanes → 30% ethyl acetate in hexanes).

8-(3,4-Dimethoxyphenyl)-9-isopropyl-2,6-bis(4-methoxyphenyl)-9*H*-purine (7aab). Yield 54%, white crystals from $CHCl_3$/heptane, mp 198−201 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 1.85 (d, 6H, J_{vic} = 6.8, $(CH_3)_2CH$); 3.90 (s, 3H, CH_3O-4″); 3.91 (s, 3H, CH_3O-4′); 3.98 (s, 3H, CH_3O-4‴); 3.99 (s, 3H, CH_3O-3‴); 4.86 (h, 1H, J_{vic} = 6.8, $CH(CH_3)_2$); 7.04 (d, 1H, $J_{5‴,6‴}$ = 8.2, H-5‴); 7.05 (m, 2H, H-3′,5′); 7.08 (m, 2H, H-3″,5″); 7.27 (dd, 1H, $J_{6‴,5‴}$ = 8.2, $J_{6‴,2‴}$ = 2.0, H-6‴); 7.31 (d, 1H, $J_{2‴,6‴}$ = 2.0, H-2‴); 8.64 (m, 2H, H-2′,6′); 9.01 (m, 2H, H-2″,6″). ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.3 ($(CH_3)_2CH$); 49.6 ($CH(CH_3)_2$); 55.35 and 55.38 (CH_3O-4′,4″); 56.09 and 56.13 (CH_3O-3‴,4‴); 111.1 (CH-5‴); 112.7 (CH-2‴); 113.7 (CH-3′,5′); 113.8 (CH-3″,5″); 122.3 (CH-6‴); 122.9 (C-1‴); 129.3 (C-5); 129.4 (C-1″); 129.7 (CH-2′,6′); 131.5 (CH-2″,6″); 131.8 (C-1′); 149.3 (C-3‴); 150.8 (C-4‴); 152.8 (C-6); 154.3 (C-8); 154.9 (C-4); 157.0 (C-2); 161.1 (C-4′); 161.5 (C-4‴). IR (KBr): 2937, 2909, 2839, 1608, 1566, 1513, 1462, 1376, 1305, 1248, 1165, 1027, 867, 619. MS (ESI), *m*/*z* (% relative intensity): 316.4 (3), 469.3 (2), 511.2 (MH^+, 100). HR MS (MH^+) 511.23368 (calcd for $C_{30}H_{31}N_4O_4$ 511.23453). Anal. calcd for $C_{30}H_{30}N_4O_4$: C, 70.57; H, 5.92; N, 10.97. Found: C, 70.37; H, 6.09; N, 10.62.

General Procedure for C−H Arylation of 9-Aryl-adenines 12a,b with 2a, 2b, and 2d. DMF (6 mL) was added through a septum to an argon-purged vial containing a 9-aryl-adenine (1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %), CuI (571.3 mg, 3 mmol), aryl halide (2 mmol), and Cs_2CO_3 (814.6 mg, 2.5 mmol), and the reaction mixture was heated to 120 °C for 42 h. The crude mixture was diluted with $CHCl_3$ (50 mL), and the solvents were evaporated under reduced pressure. Products **13xy**, **14xy**, and **15xy** were isolated by flash chromatography on silica gel (gradient elution 40% ethyl acetate in hexanes → ethyl acetate).

8,9-Bis(4-methoxyphenyl)-adenine (13aa). Yield 46%, white crystals from $CHCl_3$/heptane, R_f 0.17 (EtOAc), mp 127−130 °C. ^{1}H NMR (600 MHz, $CDCl_3$): 3.80 (s, 3H, CH_3O-4′); 3.86 (s, 3H, CH_3O-4″); 6.09 (bs, 2H, NH_2); 6.83 (m, 2H, H-3′,5′); 7.00 (m, 2H, H-3″,5″); 7.22 (m, 2H, H-2″,6″); 7.46 (m, 2H, H-2′,6′); 8.33 (s, 1H, H-2). ^{13}C NMR (151 MHz, $CDCl_3$): 55.3 (CH_3O-4′); 55.6 (CH_3O-4″); 113.9 (CH-3′,5′); 115.0 (CH-3″,5″); 119.0 (C-5); 121.4 (C-1′); 127.6 (C-1″); 128.5 (CH-2″,6″); 130.6 (CH-2′,6′); 150.5 (C-8); 152.3 (C-4); 152.9 (CH-2); 154.8 (C-6); 159.7 (C-4″); 160.8 (C-4′). IR (KBr): 3490, 3288, 3151, 2976, 2910, 2841, 1639, 1598, 1567, 1515, 1469, 1449, 1416, 1331, 1304, 1254, 1173, 1102, 1031, 839, 812, 684. MS (ESI), *m*/*z* (% relative intensity): 288.3 (20), 316.4 (9), 348.2 (MH^+, 100). HR MS (MH^+) 348.14454 (calcd for $C_{19}H_{18}N_5O_2$ 348.14550). Anal. calcd for $C_{19}H_{17}N_5O_2 \cdot 1CHCl_3$: C, 51.47; H, 3.89; N, 15.0. Found: C, 51.13; H, 3.83; N, 14.86.

***N*^{6},8,9-Tris(4-methoxyphenyl)-adenine (14aa).** Yield 24%, brownish crystals from $CHCl_3$/heptane, R_f 0.79 (EtOAc), mp 94−98 °C. ^{1}H NMR (600 MHz, $CDCl_3$): 3.82 (s, 3H, CH_3O-4″); 3.83 (s, 3H, CH_3O-4′); 3.87 (s, 3H, CH_3O-4‴); 6.86 (m, 2H, H-3′,5′); 6.96 (m, 2H, H-3′,5′); 7.02 (m, 2H, H-3‴,5‴); 7.27 (m, 2H, H-2‴,6‴); 7.51 (m, 2H, H-2″,6″); 7.70 (m, 2H, H-2′,6′); 7.75 (bs, 1H, NH); 8.48 (s, 1H, H-2). ^{13}C NMR (151 MHz, $CDCl_3$): 55.3 (CH_3O-4″); 55.5 and 55.5 (CH_3O-4′,4‴); 114.0 (CH-3″,5″); 114.3 (CH-3′,5′); 115.0 (CH-3‴,5‴); 119.7 (C-5); 121.6 (C-1″); 122.4 (CH-2′,6′); 127.8 (C-1‴); 128.6 (CH-2‴,6‴); 130.6 (CH-2″,6″); 131.7 (C-1′); 150.3 (C-8); 151.96 and 151.97 (C-4,6); 153.0 (CH-2); 156.0 (C-4′); 159.7 (C-4‴); 160.8 (C-4″). IR (KBr): 3417, 3075, 3038, 2934, 2909, 2834, 1620, 1590, 1513, 1465, 1346, 1300, 1229, 1173, 1079, 1031, 971, 916, 834, 802, 739. MS (ESI), *m*/*z* (% relative intensity): 288.3 (14), 316.4 (5), 454.3 (MH^+, 100). HR MS (MH^+) 454.18611 (calcd for $C_{26}H_{24}N_5O_3$ 454.18737). Anal. calcd for $C_{26}H_{23}N_5O_3 \cdot 1CHCl_3$: C, 56.61; H, 4.22; N, 12.22. Found: C, 56.61; H, 4.19; N, 12.08.

***N*^{6},*N*^{6},8,9-Tetrakis(4-methoxyphenyl)adenine (15aa).** Yield 16%, colorless crystals from $CHCl_3$/heptane, R_f 0.73 (EtOAc), mp 215−218 °C. ^{1}H NMR (600 MHz, $CDCl_3$): 3.77 (s, 3H, CH_3O-4″); 3.85 (s, 6H, CH_3O-4′); 3.87 (s, 3H, CH_3O-4‴); 6.71 (m, 2H, H-3″,5″); 6.94 (m, 4H, H-3′,5′); 7.02 (m, 2H, H-3‴,5‴); 7.23 (m, 2H, H-2″,6″); 7.25 (m, 2H, H-2‴,6‴); 7.29 (m, 4H, H-2′,6′); 8.43 (s, 1H, H-2). ^{13}C NMR (151 MHz, $CDCl_3$): 55.2 (CH_3O-4″); 55.5 (CH_3O-4′); 55.6 (CH_3O-4‴); 113.6 (CH-3″,5″); 114.3 (CH-3′,5′); 115.0 (CH-3‴,5‴); 121.0 (C-5); 122.0 (C-1″); 128.3 (C-1‴); 128.4 (CH-2′,6′); 128.7 (CH-2‴,6‴); 130.4 (CH-2″,6″); 138.1 (C-1′); 148.8 (C-8); 152.6 (CH-2); 154.0 and 154.6 (C-4,6); 157.6 (C-4′); 159.7 (C-4‴); 160.5 (C-4″). IR (KBr): 2835, 1609, 1574, 1508, 1455, 1418, 1341, 1293, 1250, 1179, 1107, 1091, 1030, 838, 745, 712, 634. MS (ESI), *m*/*z* (% relative intensity): 288.3 (5), 316.4 (3), 376.3 (2), 560.3 (MH^+, 100). HR MS (MH^+) 560.2286 (calcd for $C_{33}H_{30}N_5O_4$ 560.2292). Anal. calcd for $C_{33}H_{29}N_5O_4 \cdot 0.1\ CHCl_3$: C, 69.56; H, 5.13; N, 12.25. Found: C, 69.83; H, 5.10; N, 12.29.

Single Crystal X-ray Structure Analysis. X-ray crystallographic analysis of single crystals of **7eaa** (colorless, 0.14 × 0.19 × 0.44 mm), **15aa** (colorless, 0.18 × 0.29 × 0.60 mm), and **13ad** (light brown, 0.18 × 0.31 × 0.50 mm) was performed with Xcalibur X-ray diffractometr with $Cu_{K\alpha}$ (λ=1.54180 Å), data collected at 150K (**7eaa**) and 298 K (**15aa**, **13ad**). All three structures were solved by direct methods with SIR92[28] and refined by full-matrix least-squares on F with CRYSTALS.[29] The hydrogen atoms were located in a difference map, but those attached to carbon atoms were repositioned geometrically and then refined with riding constraints, and all non-hydrogen atoms were refined anisotropically in all three cases.

Crystal Data − 7eaa. $C_{29}H_{27}F_1N_4O_3$, orthorhombic, space group $P2_12_121$, a = 7.1004(1) Å, b = 17.4319(2) Å, c = 19.7015(2) Å, V = 2438.52(5) Å^3, Z = 4, M = 498.55, 38154 reflections measured, 4993 independent reflections. Final R = 0.0317, wR = 0.0430, GoF = 1.0768 for 3587 reflections with $I > 2\sigma(I)$ and 336 parameters. CCDC 698313.

Crystal Data − 13ad. $C_{21}H_{21}N_5O_4.CHCl_3$, monoclinic, space group $P2_1/c$, a = 10.1515(12) Å, b = 13.1309(11) Å, c = 18.5570(17) Å, β = 91.195(9) °, V = 2473.1(4) Å^3, Z = 4, M = 526.80, 29663 reflections measured, 5219 independent reflections. Final R = 0.0488, wR = 0.0780, GoF = 1.1339 for 2510 reflections with $I > 2\sigma(I)$ and 308 parameters. CCDC 698558.

Crystal Data − 15aa. $C_{33}H_{29}N_5O_4$, triclinic, space group $P1^-$, a = 9.8920(8) Å, b = 10.9199(7) Å, c = 15.2855(9) Å, α = 97.982(5)°, β = 101.901(6)°, γ = 112.999(7)°, V = 1442.4(2) Å^3, Z = 2, M = 559.61, 44274 reflections measured, 6065 independent reflections. Final R = 0.0403, wR = 0.0554, GoF = 1.0621 for 4137 reflections with $I > 2\sigma(I)$ and 380 parameters. CCDC 698314.

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Supporting Information Available: Complete experimental part and characterization of all compounds, copies of all NMR spectra and cif files for **7eaa**, **13ad**, and **15aa** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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