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New Approach to the Synthesis of N^7-Arylguanines and N^7-Aryladenines

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The copper-mediated arylation of 7-methylpyrimido[1,2-*a*]-purin-10(3*H*)-one (**1**) in dichloromethane or of N^2-(dimethylamino)methyleneguanine (**2**) in methanol in the presence of TMEDA as a base/ligand led to the preferential formation of 1-aryl-7-methylpyrimido[1,2-*a*]purin-10(3*H*)-ones (**4**) and 7-aryl-N^2-(dimethylamino)methyleneguanines (**7**), respectively. These compounds can be easily hydrolysed to the corresponding 7-arylguanines. Similar arylation of N^6-(dimethylamino)methyleneadenine (**15**) in the presence of *o*-phenanthroline instead of TMEDA afforded mainly 7-aryladenines after hydrolysis.

Introduction

Substituted purines, including *N*-arylpurines, have recently attracted much interest as therapeutics, molecular tools and probes for investigating biological systems.[1] N^9-Arylpurines have been reported to serve as agonists or antagonists for adenosine receptors,[2a–2c] corticotropin-releasing hormone receptors[2d–2f] and folic acid receptors[2g] as inhibitors of enzymes like phosphatidylinositol 4-kinase,[2h] adenosine[2i] and guanine[2j] deaminase and xanthine oxidase.[2k–2n] Also N^9-arylpurines have been reported to exhibit antimicrobial activity.[2g,2o] Arylguanines may be formed in vivo by the interaction of arene oxides formed by the metabolic activation of mutagenic and carcinogenic arenes such as benzene[3] or PAH with cellular DNA followed by cleavage of the modified nucleobases from the DNA.[4] N^7-Arylpurines have been, probably due to their poor availability, much less studied. 7-Phenylguanine itself has been suggested as a potential biological marker of exposure to benzene[5] and is therefore needed (and possibly other N^7-arylguanines) as an analytical standard for biological monitoring studies.

Whereas *N*-alkylpurines are available by the direct *N*-alkylation of purines,[6] the synthesis of *N*-arylpurines relied until recently on the cyclization of suitable pyrimidine precursors.[7] Recently, the direct *N*-arylation of purine derivatives with arylboronic acids in the presence of cupric acetate and a base under anhydrous conditions was reported. Thus, the successful N^9-arylation of purine,[8] 6-chloropurine,[9] 6-methylthiopurine,[9] 6-mercaptopurine[9] (with partial *S*-arylation), 6-(2-thienyl)purine,[9] 2-amino-6-chloropurine[9] and 2,6-dichloropurine[9,10] has been published. Also, the microwave-assisted N^9-arylation of 2-substituted amino-6-chloropurines has been recently reported.[11] Direct arylation of adenine was not possible under these conditions, probably due to the low solubility of adenine. This problem was overcome by using CH_3OH/H_2O as the solvent[12] or by the arylation of N^6,N^6-bis-BOC-adenine, which was then deprotected.[13] Similarly, the direct arylation of guanine, due to its insolubility in most solvents, has not been reported. However, the arylguanines may be prepared indirectly by the arylation of N^2,N^2-bis-BOC-6-chloropurine followed by acid hydrolysis.[13] TBS-protected inosine and guanosine (in which the N^9 position is occupied),[14] as well as unprotected guanosine and inosine,[15] have been reported to arylate selectively at the N^1 position. Adenosine[15] and 2-amino-9-benzyl-6-chloropurine[16] may be arylated at the NH_2 group to give N^6- or N^2-aryl derivatives, respectively. So far copper-mediated arylation of purine bases with arylboronic acids is highly regioselective, giving exclusively N^9-arylated products. Only Schultz and coworkers have reported the formation of small amounts (<10%) of the N^7-arylated isomer in the arylation of 2,6-dichloropurine.[10] Therefore heterocyclization remains the only method for the preparation of N^7-arylpurines. To the best of our knowledge, the only described N^7-arylpurines are N^7-phenylguanine and several N^7-arylhypoxanthines prepared by cyclization of 4-amino-1-aryl-5-imidazolecarboxylates with cyanamide,[17] which is laborious and inefficient.

Recently we observed that under specific reaction conditions and with the choice of an appropriate substrate, N^7-arylated purines are the main products of the arylation with arylboronic acids in the presence of cupric acetate. Herein we describe the application of this methodology to the

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preparation of N^7-arylguanine and -adenine derivatives, respectively. To overcome the low solubility of guanine, its derivatives, 7-methylpyrimido[1,2-*a*]purin-10(3*H*)-one (**1**)[18] and N^2-(dimethylamino)methyleneguanine (**2**),[19] which can easily be converted to unprotected guanine derivatives, were used as the starting compounds (Figure 1).

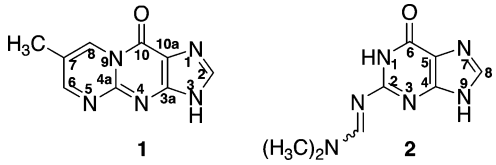
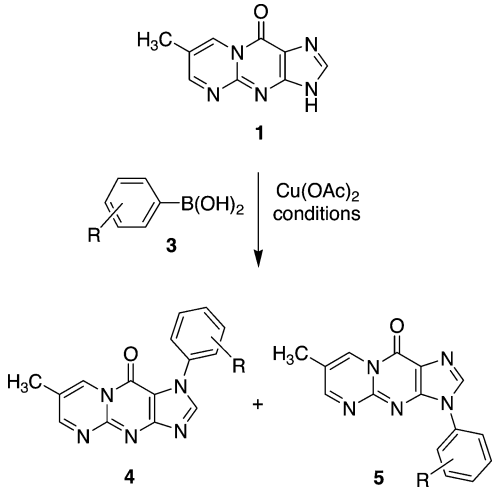


Figure 1. The starting purine derivatives and their numbering.

Results and Discussion

N-Arylation of 7-Methylpyrimido[1,2-*a*]purin-10(3*H*)-one (1)

First, phenylboronic acid (**3a**) was used. The reaction was carried out in the presence of 3 equiv. of **3a**, a stoichiometric amount of copper(II) acetate and 2 equiv. of a base/ligand. In contrast to the results reported for the *N*-arylation of other purine derivatives, a mixture of both regioisomers **4a** (corresponding to the desired N^7 isomer of unprotected guanine) and **5a** (corresponding to the N^9 isomer of unprotected guanine) were obtained (Scheme 1, R = H). The mixture of **4a** and **5a** was easily separated by column chromatography.



Scheme 1. Arylation of 7-methylpyrimido[1,2-*a*]purin-10(3*H*)-one (**1**).

The ratio of the arylated products was strongly dependent on the reaction conditions, especially on the base/ligand and solvent (Table 1). In dichloromethane in the presence of triethylamine or pyridine only traces of the *N*-arylated products were formed. In contrast, in the presence of 2,2′-bipyridine or *o*-phenanthroline, the mixture of **4a** and **5a**, in which the undesired regioisomer **5a** prevailed (Table 1, entries 1 and 2), was obtained in a moderate yield. When TMEDA was used as the base/ligand (Table 1, entry 3), **4a** and **5** were obtained in a 1:1 ratio in high yield (79%). The same ratio of **4a** and **5a**, but in a somewhat higher overall yield, was observed when 1,2-dichloroethane was used as the solvent at room temperature. Increasing the reaction temperature resulted in a substantial lowering of the yield in this case (entries 4 and 5). A 1:1 ratio of regioisomers was also obtained in THF at room temperature (entry 6). In polar solvents like CH_3OH, CH_3CN and DMF, the yields of the *N*-arylated products were generally low, although the desired N^1-arylated isomer **4a** becomes the main product. In the case of DMF the reaction was also accomplished at 80 °C, but led to a lowering of the yield (entries 7–10). Therefore, for preparative purposes, it is preferable to use dichloromethane or 1,2-dichloroethane as the solvent as it gives a higher overall yield of the desired regioisomer **4**. Low yields of the reaction at higher temperatures (entries 5 and 10) are presumably due to a low stability of the substrate at elevated temperatures under the reaction conditions.

Table 1. Optimization of the reaction conditions for the *N*-arylation of **1** with phenylboronic acid (**3a**; Scheme 1, R = H).[a]

Entry	Base/ligand	Solvent	Temp.	Ratio **4a**/**5a**[b]	% Yield[c]
1	2,2′-bipyridine	CH_2Cl_2	room temp.	1:2	46
2	*o*-phenanthroline	CH_2Cl_2	room temp.	1:2	66
3	TMEDA	CH_2Cl_2	room temp.	1:1	79
4	TMEDA	$Cl(CH_2)_2Cl$	room temp.	1:1	85
5	TMEDA	$Cl(CH_2)_2Cl$	70 °C	1:1	36
6	TMEDA	THF	room temp.	1:1	71
7	TMEDA	CH_3OH	room temp.	3:1	44
8	TMEDA	CH_3CN	room temp.	2:1	37
9	TMEDA	DMF	room temp.	1:1	35
10	TMEDA	DMF	80 °C	2:1	15

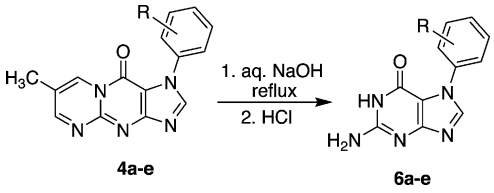
[a] Reaction conditions: $PhB(OH)_2$ (3 equiv.), $Cu(OAc)_2$ (1 equiv.), base (2 equiv.). [b] Established by ^1H NMR spectroscopy. [c] Isolated yield of the mixture of regioisomers **4a** and **5a**.

The yields obtained by using TMEDA in dichloromethane and 1,2-dichloroethane were similar and the best results were obtained at room temperature. Therefore, the more common dichloromethane in combination with TMEDA at room temperature (Table 1, entry 3) was used for the arylation of **1** with all three isomers **3b**–**d** of tolylboronic acid and also with 4-styrylboronic acid (**3e**), which would lead to possible metabolites of toluene and styrene (Table 2). With only 2 equiv. of boronic acid the corresponding *N*-arylated products were obtained in high isolated yields with higher N^1/N^3 arylation ratios than that obtained with unsubstituted phenylboronic acid. The highest N^1/N^3 ratio of the arylation was obtained with *o*-tolylboronic acid. After isolation by column chromatography the desired N^1 isomer **4** was converted into the corresponding N^7-arylguanine **6** by alkaline hydrolysis followed by acidification (Scheme 2, Table 2).

Table 2. Synthesis of substituted N^7-arylguanines (see Schemes 1 and 2).[a]

Boronic acid	R	% Yield of **4** + **5**[b]	Ratio[c] **4/5**	Hydrolysis product (% yield)[d]
3a	H	66	1.4:1	**6a** (68)
3b	2-CH_3	69	5:1	**6b** (72)
3c	3-CH_3	60	2:1	**6c** (60)
3d	4-CH_3	63	2:1	**6d** (65)
3e	4-CH_2=CH	70	2:1	**6e** (89)

[a] Reaction conditions: $ArB(OH)_2$ (**3**) (2 equiv.), $Cu(OAc)_2$ (1 equiv.), TMEDA (2 equiv.), CH_2Cl_2, room temp. [b] Sum of the isolated yields of the N^1 and N^3 isomers. [c] Established by ^1H NMR spectroscopy of the crude reaction mixture. [d] Isolated yield of the hydrolysis of the N^1 isomer.

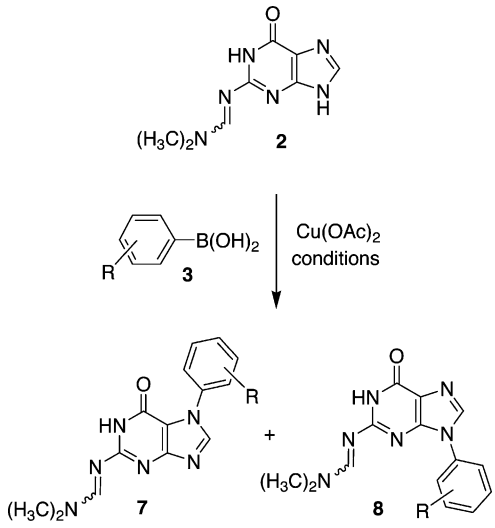


Scheme 2. Hydrolysis of 1-aryl-7-methylpyrimido[1,2-*a*]purin-10(3*H*)-ones **4**.

N-Arylation of N^2-(Dimethylamino)methyleneguanine (2)

N^2-(Dimethylamino)methyleneguanine (**2**), which can be easily prepared by condensation of guanine with DMF dineopentyl acetal, was reported to produce mainly the N^7 derivative by alkylation.[20] Moreover, the (dimethylamino)-methylene protecting group can be easily removed by hydrolysis. Therefore, we chose this substrate for the copper-mediated *N*-arylation with arylboronic acids.

Similarly to **1**, a mixture of N^7- and N^9-arylated isomers was formed in the arylation of **2** (Scheme 3). Generally, the yields were somewhat lower than the reactions of **1**, but the ratio of N^7/N^9 isomers was substantially higher (Table 3). The highest overall yield (83%), but with a low selectivity (1:1), was obtained with *o*-phenanthroline in dichloromethane at room temperature (Table 3, entry 1). The same regioselectivity, but with a lower yield, was also obtained when 2,2′-bipyridine in dichloromethane was used (entry 2). The application of TMEDA in dichloromethane, the conditions that gave the best results in the arylation of **1**, afforded high N^7 selectivity (6:1), but only a very low overall yield (11%) (entry 4). The same N^7/N^9 selectivity and an acceptable yield (62%) was obtained with TMEDA in methanol at room temperature (entry 5). A higher temperature resulted, similarly to the arylation of **1**, in a lowering of the yield (entry 6). In a mixture of methanol/acetonitrile or methanol/dichloromethane the N^7/N^9 ratio was very high (10:1), but the overall yield was low (entries 7 and 8). Therefore, methanol in the presence of TMEDA was used for the arylation of **2** with other boronic acids. The yields of the *N*-arylation products were comparable, but the selectivities were higher than those obtained with **1** (Scheme 3, Table 4). The N^7 isomer was isolated by chromatography and subsequent acid-catalyzed hydrolysis afforded the desired N^7-arylated guanines in high yields (Scheme 4, Table 4).



Scheme 3. Arylation of N^2-(dimethylamino)methyleneguanine (**2**).

Table 3. Optimization of the reaction conditions for the *N*-arylation of **2** with phenylboronic acid (**3a**; Scheme 3, R = H).

Entry	Base/Ligand	Solvent	Temp.	Ratio **7a/8a**[a]	% Yield[b]
1	*o*-phenanthroline	CH_2Cl_2	room temp.	1:1	83
2	2,2′-bipyridine	CH_2Cl_2	room temp.	1:1	56
3	*o*-phenanthroline	CH_3OH	room temp.	4:1	38
4	TMEDA	CH_2Cl_2	room temp.	6:1	11
5	TMEDA	CH_3OH	room temp.	6:1	62
6	TMEDA	CH_3OH	60 °C	6:1	38
7	TMEDA	CH_2Cl_2/CH_3OH (5:1)	room temp.	10:1	43
8	TMEDA	CH_3CN/CH_3OH (5:1)	room temp.	10:1	48

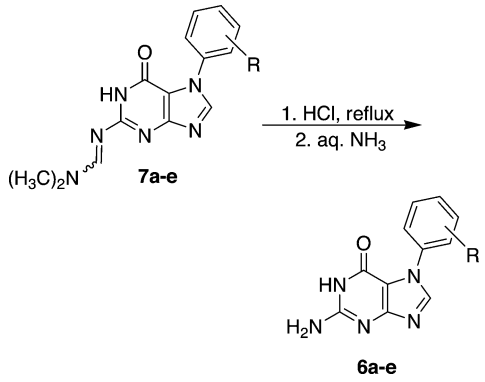
[a] Established by ^1H NMR spectroscopy. [b] Isolated yield of the mixture of regioisomers **7a** and **8a**.

Table 4. Synthesis of the substituted N^7-arylguanines **6** (see Schemes 3 and 4).[a]

Boronic acid	R	% Yield of **7** + **8**[b]	Ratio[c] **7/8**	Hydrolysis product (% yield)[d]
3a	H	62	6:1	**6a** (80)
3b	2-CH_3	58	9:1	**6b** (94)
3c	3-CH_3	63	4:1	**6c** (86)
3d	4-CH_3	69	3:1	**6d** (89)
3e	4-CH_2=CH	52	2:1	**6e** (95)

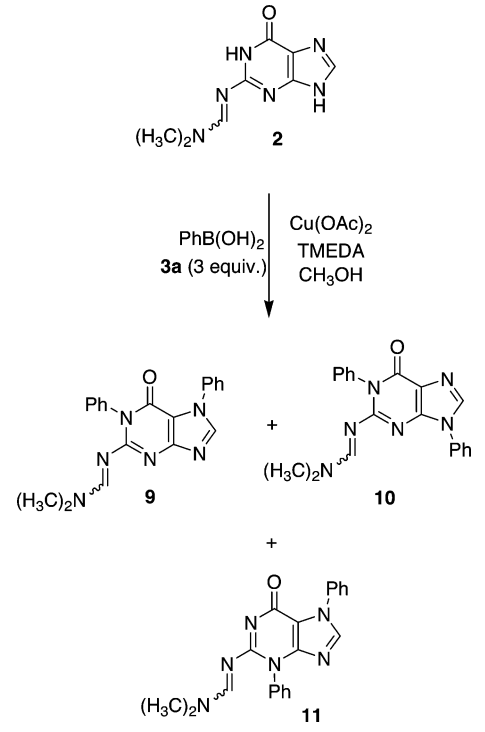
[a] Reaction conditions: $ArB(OH)_2$ (**3**) (1.5 equiv.), $Cu(OAc)_2$ (1 equiv.), TMEDA (2 equiv.), CH_3OH, room temp. [b] Sum of the isolated yields of the N^7 and N^9 isomers. [c] Established by ^1H NMR spectroscopy. [d] Isolated yield of the hydrolysis of the N^7 isomer.

N^2-(Dimethylamino)methyleneguanine (**2**) was diarylated when an excess of boronic acid and a prolonged reaction time were used. Thus, reaction of **2** with 3 equiv. of phen-

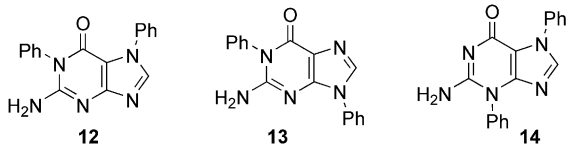


Scheme 4. Hydrolysis of 7-aryl-N^2-(dimethylamino)methyleneguanines (**7**).

ylboronic acid (**3a**) in methanol in the presence of TMEDA and a prolonged reaction time afforded a mixture of N^1,N^7- (**9**), N^1,N^9- (**10**) and N^3,N^7- (**11**) diarylated products in a ratio of 5:1:1. The formation of N^3,N^9-diarylated guanine derivatives was not observed, probably for steric reasons (Scheme 5). The structures of the diarylated compounds were verified by the arylation of pure N^7-phenyl-N^2-(dimethylamino)methyleneguanine (**7a**), which gave a mixture of **9** and **11** (overall yield 79%), and by the arylation of the N^9 isomer **8a**, which afforded only the N^1,N^9-diarylated derivative **10** in 72% yield. Acid hydrolysis of the obtained (dimethylamino)methylene derivatives **9**–**11** then smoothly afforded the unprotected N^1,N^7-diphenylguanine (**12**), N^1,N^9-diphenylguanine (**13**) and N^3,N^7-diphenylguanine (**14**) in 77, 73 and 64% yields, respectively.

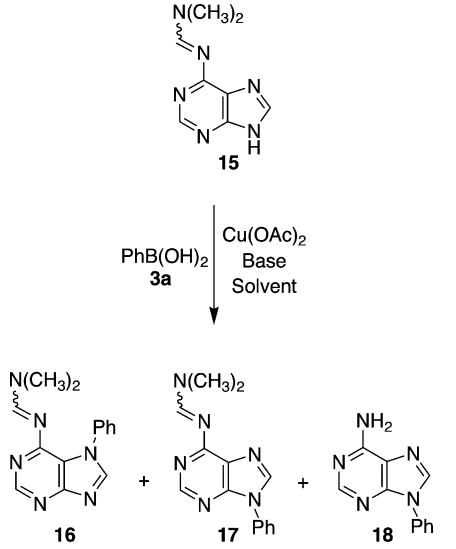


Scheme 5. Diarylation of N^2-(dimethylamino)methyleneguanine (**2**).



N-Arylation of N^6-(Dimethylamino)methyleneadenine (15)

Encouraged by the smooth arylation of N^2-(dimethylamino)methyleneguanine (**2**), the *N*-arylation of N^6-(dimethylamino)methyleneadenine (**15**) was also attempted. This compound is easily accessible by the condensation of adenine with DMF dineopentyl acetal,[21] and its high N^7 selectivity in alkylation reactions has been reported.[22] Again, copper-mediated *N*-arylation with phenylboronic acid (**3a**) gave a mixture of the N^7 (**16**) and N^9 (**17**) isomers with the former prevailing (Scheme 6). In contrast to the guanine derivatives, *o*-phenanthroline as the base/ligand gave a better yield and higher N^7 selectivity than TMEDA (Table 5). We also observed the presence of 15% N^9-phenyladenine (**18**) in the reaction mixture when methanol was used as the solvent. The formation of N^3-arylated adenine was not detected. Acid hydrolysis of **16** smoothly afforded N^7-phenyladenine in 78% yield.



Scheme 6. Arylation of N^6-(dimethylamino)methyleneadenine (**15**).

Table 5. Optimization of the reaction conditions for the *N*-arylation of **15** with phenylboronic acid (**3a**; Scheme 6).

Base/ligand	Solvent	Temp.	Ratio **16/17**[a]	% Yield[b]
Phenanthroline	CH_2Cl_2	room temp.	5:1	71
Phenanthroline	CH_3OH	room temp.	6:1	75[c]
TMEDA	CH_2Cl_2	room temp.	–	trace
TMEDA	CH_3OH	room temp.	3:2	57[c]

[a] Established by ^{1}H NMR spectroscopy. [b] Isolated yield of the mixture of regioisomers **16** and **17**. [c] The formation of **18** (15%) was observed.

Identification of Products and Determination of the Regioselectivity

The products obtained were characterized by the usual spectral methods, for example, ^{1}H and ^{13}C NMR and IR spectroscopy. As the products give erratic elemental analyses, probably due to incomplete combustion, HRMS was used instead. The structures of the obtained compounds were determined by NMR spectroscopy. The ^{1}H, ^{13}C and 2D NMR (HMQC and HMBC) techniques were used for the assignment of all the protons and carbons in heterocyclic rings of the compounds **4**, **5**, **7**, **8**, **16** and **17**.[23] The rules formulated by Kjellberg and Johansson[24] were used to distinguish between the N^7 and N^9 isomers on the basis of their ^{1}H and ^{13}C NMR shifts. (It is important to note that these rules are valid only for spectra measured in $CDCl_3$; in [D_6]DMSO the rules cannot be used.) The 8-H signals of the N^9 isomers were reported to be shifted upfield relative to the corresponding signals of the N^7 isomers. The signals of C-5 and C-8 should be very distinctive in the ^{13}C NMR spectra: the signals of C-5 in the N^9 isomers should be deshielded relative to those of the N^7 isomers, whereas the ^{13}C NMR signals of C-8 of the N^9 isomers should be shifted upfield relative to the corresponding signals of the N^7 isomers. We also noticed that the shifts of the C-4 signals could be used to distinguish between the N^7 and N^9 isomers. The C-4 signals of the N^7 isomers are deshielded relative to those of the N^9 isomers. All these trends can be seen in Table 6. In the case of (dimethylamino)methylene derivatives **7** and **8** (Figure 2), in which theoretically reaction on the pyrimidine ring is possible, substitution on the imidazole part was confirmed by HMBC experiments by the detection of a three-bond interaction between 8-H and the *ipso*-carbon of the aromatic ring. As 7-phenylguanine[12] (**6a**), 9-phenylguanine[11] and 9-phenyladenine[10] (**18**) have been described, the above assignment was confirmed after hydrolysis of the corresponding protected derivatives by comparison of their spectra with published data.

As far as the diphenylated compounds are concerned, the position of one phenyl ring was unambiguously given by their preparation starting from the *N*^{7}- or *N*^{9}-phenyl derivative. The chemical shifts of C-8 and C-5 follow the pattern of the previously discussed *N*^{7}- and *N*^{9}-monoarylated compounds and do not significantly differ from them. The only difference can be found at C-4; one of the compounds obtained by phenylation of the *N*^{7}-phenyl derivative has a similar chemical shift at C-4 as that obtained by arylation of the N^9 isomer (and as other *N*^{9}-aryl derivatives; Table 6). The influence of the aryl ring attached to the N^9 position should be very similar to that having an aryl ring attached to N^3. Moreover, it can be expected that the formation of the 3,9-diphenylguanine derivative would be disfavoured for steric reasons and that this compound will not be formed. Therefore, the structure of the 1,9-diphenyl derivative **10** [δ(C-4) = 148.2 ppm] was assigned to the compound prepared by the arylation of 9-phenyl-*N*^{2}-[(dimethylamino)-methylene]guanine (**8a**). On the other hand, the 1,7-diphenyl derivative **9** was determined as that isomer having a ^{13}C NMR shift at C-4 of 158.7 ppm and the 3,7-disubstituted compound **11** to that having C-4 at δ = 150.5 ppm.

Table 6. Important ^{1}H and ^{13}C NMR shifts of the *N*^{7}- and *N*^{9}-arylated purine derivatives in $CDCl_3$ (Figure 1).

Comp.	R	2-H/8-H	C-3a/C-4	C-10a/C-5	C-2/C-8
4a	H	8.28	159.7	110.0	146.7
5a	H	8.21	149.5	118.9	141.0
4b	2-Me	8.13	159.2	–[a]	147.2
5b	2-Me	8.00	–[b]	–[b]	–[b]
4c	3-Me	8.28	159.6	–[a]	–[a]
5c	3-Me	8.17	149.5	119.0	141.2
4d	4-Me	8.26	159.4	–[a]	–[a]
5d	4-Me	8.18	149.6	119.0	141.2
4e	4-CH_2=CH	8.30	159.5	109.6	146.5
5e	4-CH_2=CH	8.19	149.5	119.0	140.8
7a	H	7.95	160.7	111.1	143.0
8a	H	7.83	150.0	121.1	137.4
7b	2-Me	7.73	159.7	112.5	143.3
8b	2-Me	7.65	150.9	120.4	138.6
7c	3-Me	7.91	160.5	111.1	143.0
8c	3-Me	7.83	150.0	121.0	137.7
7d	4-Me	7.91	160.5	111.2	143.0
8d	4-Me	7.81	150.1	121.0	137.6
7e	4-CH_2=CH	7.92	–[a]	–[a]	142.9
8e	4-CH_2=CH	7.84	–[a]	121.2	137.5
9	1,7-DiPh	7.97	158.7	111.3	143.1
10	1,9-DiPh	7.81	148.2	120.8	137.1
11	3,7-DiPh	7.69	150.5	112.5	140.0

[a] Not detected. [b] Due to a small amount of sample the ^{13}C NMR spectrum was not recorded.

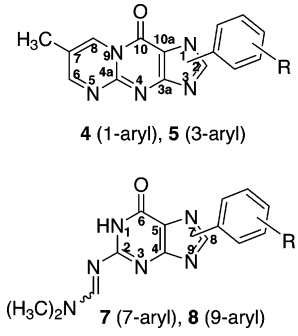


Figure 2. Numbering of the ring atoms of the prepared purine derivatives.

Conclusions

N^7-Arylated guanine and adenine derivatives can be easily prepared by Cu-mediated arylation of 7-methylpyrimido[1,2-*a*]purin-10(3*H*)-one (**1**) or *N*^{2}-(dimethylamino)-methyleneguanine (**2**) with boronic acids and subsequent hydrolysis. For guanine derivatives **1** and **2** the highest N^7 selectivities were obtained in methanol by using TMEDA as the base/ligand, whereas *N*^{6}-(dimethylamino)methyleneadenine (**15**) gave the best results when *o*-phenanthroline was used as the base/ligand in methanol. This methodology allows the preparation of *N*^{7}-arylpurines that are otherwise hard to access and that may be used, for example, as analytical standards for biological monitoring studies.

Experimental Section

General: Dichloromethane was dried by distillation from calcium hydride, methanol was dried by distillation from magnesium and stored over molecular sieves. Other chemicals of analytical or synthetic grade were obtained from commercial sources and were used as received. The starting compounds **1**,[13] **2**[14] and **15**[16] were prepared according to published procedures. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance DRX500 (500 MHz) or Varian Mercury 300 (300 MHz) spectrometer with Fourier transformation. HMQC and HMBC NMR spectra were recorded with a Bruker Avance DRX500 (500 MHz) spectrometer. Mass spectra were measured with a Autospec Ultima (Waters, Great Britain) magnetic segment mass spectrometer by using the ionization by electron impact technique. IR spectra were recorded with a Nicolet 740 FTIR spectrometer with a Bruker IFS 66 microscope by using the ATR technique. Column chromatography was performed on silica gel 60 obtained from Fluka: particle size 0.063–0.200 mm or, for flash chromatography, 0.035–0.070 mm.

General Procedure for the *N*-Arylation of Purine Derivatives 1 and 2: A mixture of purine derivative (0.33 mmol), arylboronic acid (0.66 mmol, for diarylation 1.00 mmol), base/ligand (0.66 mmol) (TMEDA for **1** and **2**, *o*-phenanthroline for **15**), anhydrous copper(II) acetate (0.33 mmol) and dried (4-Å molecular sieves, 250 mg) in dry solvent (CH_2Cl_2 for **1**, CH_3OH for **2** and **15**; 5 mL) in a 50 mL round-bottomed flask connected to a reflux condenser and with an anhydrous calcium chloride tube was stirred at ambient temperature for 24 h (compounds **9**–**11** for 48 h). Then methanol (15 mL) was added and the resulting mixture was filtered through Celite, evaporated and purified by flash chromatography on silica gel. Acetone/ethyl acetate (1:1) was used for the separation of **4** and **5** (*N*3 isomers **5** eluted first), for the separation of (dimethylamino)methylene derivatives **7** and **8** a mixture of chloroform/methanol (10:1) was used (*N*7 isomer **7** eluted first). The diphenyl derivatives **9**–**11** were prepared on a 0.1 mmol scale and separated by using chloroform/methanol (20:1). The order of elution was **9**, **10** and **11**.

7-Methyl-1-phenylpyrimido[1,2-*a*]purin-10(3*H*)-one (4a): Yellow powder; yield 36 mg (39%); m.p. 211–214 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3), 7.45–7.70 (m, 5 H, Ph-H), 8.28 (s, 1 H, 2-H), 8.87 (s, 1 H, 6-H), 9.03 (s, 1 H, 8-H) ppm. ^{13}C NMR (600 MHz, $CDCl_3$): δ = 15.7 (CH_3), 110.0 (C-10a), 119.8 (C-7), 125.4 (CH-Ph), 129.2 (CH-Ph), 129.7 (CH-Ph), 135.4 (Cq-Ph), 133.0 (C-8), 146.7 (C-2), 148.3 (C-4a), 149.9 (C-10), 159.7 (C-3a), 163.1 (C-6) ppm. IR: $\tilde{\nu}$ = 3102, 2924, 1710, 1554, 1534, 1511, 1495, 1470, 1457, 1377, 1340, 1214, 955, 779 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{11}N_5O$ 277.0964; found 277.0977.

7-Methyl-3-phenylpyrimido[1,2-*a*]purin-10(3*H*)-one (5a): Yellow powder; yield 24 mg (27%); m.p. 179–184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 7.47–7.76 (m, 5 H, Ph-H), 8.21 (s, 1 H, 2-H), 8.85 (s, 1 H, 6-H), 9.28 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 15.3 (CH_3), 118.9 (C-10a), 119.8 (C-7), 124.0, 128.5, 129.9, 132.4, 134.2 (C-8), 141.0 (C-2), 148.5 (C-4a), 149.5 (C-3a), 152.6 (C-10), 163.2 (C-6) ppm. IR: $\tilde{\nu}$ = 3384, 3128, 3097, 2921, 1722, 1530, 1481, 1378, 1313, 1209, 1112, 908, 779 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{11}N_5O$ 277.0964; found 277.0962.

7-Methyl-1-(2-methylphenyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (4b): Yellow powder; yield 60 mg (58%); m.p. 276–282 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.10 (s, 3 H, CH_3Ar), 2.37 (s, 3 H, CH_3), 7.37–7.49 (m, 4 H, Ar-H), 8.64 (br. s, 1 H, 2-H), 8.90 (s, 2 H, 6-H and 8-H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 14.6 (CH_3), 17.1 (CH_3Ph), 119.3 (C-5), 126.6, 127.7, 129.3, 130.6, 132.5, 134.9, 135.0, 132.5 (C-8), 147.5 (C-4a), 149.2 (C-3a), 158.2 (C-10), 163.2 (C-6) ppm. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 7.32 (d, *J* = 9.4 Hz, 1 H, Ar-H), 7.37 (t, *J* = 8.8 Hz, 1 H, Ar-H), 7.42 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.47 (t, *J* = 9.4 Hz, 1 H, Ar-H), 8.13 (s, 1 H, 2-H), 8.87 (s, 1 H, 6-H), 8.98 (s, 1 H, 8-H) ppm. ^{13}C NMR (600 MHz, $CDCl_3$): δ = 15.7 (CH_3), 17.9 (CH_3), 119.6 (C-7), 127.2 (CH-Ar), 127.7 (CH-Ar), 130.4 (CH-Ar), 131.5 (CH-Ar), 132.9 (C-8), 134.9 (Cq-Ar), 135.7 (Cq-Ar), 147.2 (C-2), 148.4 (C-4a), 150.0 (C-10), 159.2 (C-3a), 162.6 (C-6) ppm. IR: $\tilde{\nu}$ = 3411, 3111, 2924, 1706, 1537, 1512, 1495, 1470, 1375, 1330, 1248, 1299.1070, 957, 779 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{13}N_5O$ 291.1120; found 291.1124.

7-Methyl-3-(2-methylphenyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (5b): Yellow powder; yield 7 mg (11%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3) 2.46 (s, 3 H, CH_3Ar), 7.34–7.42 (m, 4 H, Ar-H), 8.00 (s, 1 H, 2-H), 8.82 (s, 1 H, 6-H), 9.29 (s, 1 H, 8-H) ppm.

7-Methyl-1-(3-methylphenyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (4c): Yellow powder; yield 38 mg (39%); m.p. 252–258 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3Ar), 7.31–7.32 (m, 1 H, Ar-H), 7.45–7.50 (m, 3 H, Ar-H), 8.79 (br. s, 1 H, 2-H), 8.97 (s, 1 H, 6-H), 9.08 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 14.6 (CH_3), 20.9 (CH_3Ar), 119.4 (C-10a), 122.2 (C-7), 125.6, 128.7, 132.8, 135.1, 138.5 (C-8), 147.5 (C-4a), 149.2 (C-3a), 158.9 (C-10), 163.3 (C-6) ppm. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 7.31–7.36 (m, 3 H, Ar-H), 7.45 (t, *J* = 9.4 Hz, 1 H, Ar-H), 8.28 (s, 1 H, 2-H), 8.88 (s, 1 H, 6-H), 9.07 (s, 1 H, 8-H) ppm. ^{13}C NMR (600 MHz, $CDCl_3$): δ = 15.6 (CH_3), 21.6 (CH_3), 119.5 (C-7), 122.4 (CH-Ar), 125.8 (CH-Ar), 129.3 (CH-Ar), 129.9 (CH-Ar), 132.8 (C-8), 135.2 (Cq-Ar), 139.7 (Cq-Ar), 148.1 (C-4a), 149.7 (C-10), 159.6 (C-3a), 162.8 (C-6) ppm. IR: $\tilde{\nu}$ = 3106, 3043, 2921, 2852, 1712, 1512, 1465, 1375, 1325, 1263, 1221, 780, 691 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{13}N_5O$ 291.1120; found 291.1115.

7-Methyl-3-(3-methylphenyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (5c): Yellow powder; yield 20 mg (21%); m.p. 219–224 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3Ar), 7.29–7.55 (m, 4 H, Ar), 8.17 (s, 1 H, 2-H), 8.86 (s, 1 H, 6-H), 9.29 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 15.3 (CH_3), 21.5 (CH_3Ar), 119.0 (C-10a), 119.7 (C-7), 121.3, 125.6, 129.3, 129.7, 134.2, 134.2 (C-8), 141.2 (C-2), 148.5 (C-4a), 149.5 (C-3a), 152.7 (C-10), 163.1 (C-6) ppm. IR: $\tilde{\nu}$ = 3129, 3099, 2918, 1719, 1708, 1526, 1480, 1369, 1321, 1206, 1108, 910, 779 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{13}N_5O$ 291.1120; found 291.1115.

7-Methyl-1-(4-methylphenyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (4d): Yellow powder; yield 40 mg (42%); m.p. 281–284 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.46 (s, 6 H, CH_3, CH_3Ar), 7.35–7.44 (m, 4 H, Ar-H), 8.31 (br. s, 1 H, 2-H), 8.90 (s, 1 H, 6-H), 9.05 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 14.6 (CH_3), 20.6 (CH_3Ar), 119.3 (C-10a), 124.9, 129.3, 132.7, 132.8 (C-8), 137.7 (C-2), 147.4 (C-4a), 149.1 (C-3a), 158.9 (C-10), 163.2 (C-6) ppm. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.45 and 2.46 (2 s, 6 H, 2CH_3), 7.36 (d, *J* = 9.9 Hz, 2 H, Ar-H), 7.43 (d, *J* = 9.9 Hz, 2 H, Ar-H), 8.26 (s, 1 H, 2-H), 8.87 (s, 1 H, 6-H), 9.04 (s, 1 H, 8-H) ppm. ^{13}C NMR (600 MHz, $CDCl_3$): δ = 15.4 (CH_3), 21.2 (CH_3), 119.4 (C-7), 125.0 (CH-Ar), 130.0 (CH-Ar), 132.7 (C-8), 139.2 (Cq-Ar), 147.9 (C-4a), 149.6 (C-3a), 159.4 (C-10), 162.7 (C-6) ppm. IR: $\tilde{\nu}$ = 3100, 2924, 2863, 1706, 1652, 1533, 1516, 1376, 1330, 1214, 954, 779 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{13}N_5O$ 291.1120; found 291.1126.

7-Methyl-3-(4-methylphenyl)pyrimido[1,2-*a*]purin-10(3*H*)-one (5d): Yellow powder; yield 20 mg (21%); m.p. 225–230 °C. ^{1}H NMR

(500 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3Ar), 7.35–7.37 (m, 2 H, Ar-H), 7.61–7.63 (m, 2 H, Ar-H), 8.18 (s, 1 H, 2-H), 8.85 (s, 1 H, 6-H), 9.28 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 15.3 (CH_3), 21.1 (CH_3Ar), 119.0 (C-10a), 119.6 (C-7), 123.9, 130.4, 132.7, 138.6, 134.2 (C-8), 141.2 (C-2), 148.5 (C-4a), 149.6 (C-10), 152.7 (C-3a), 163.1 (C-6) ppm. IR: $\tilde{\nu}$ = 3088, 2924, 2526, 1729, 1532, 1487, 1379, 1328, 1310, 1221, 1111, 985, 911, 779 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{13}N_5O$ 291.1120; found 291.1129.

1-(4-Ethenylphenyl)-7-methylpyrimido[1,2-*a*]purin-10(3*H*)-one (4e): Yellow powder; yield 44 mg (44%); m.p. 275–280 °C. ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3 H, CH_3), 5.37 (d, J = 11.0 Hz, 1 H, CH=CH_2), 5.97 (d, J = 17.5 Hz, 1 H, CH=CH_2), 6.84 (dd, J = 11.0, J = 17.5 Hz, 1 H), 7.65–7.67 (m, 4 H, Ar-H), 8.80 (s, 1 H, 2-H), 8.98 (s, 1 H, 6-H), 9.07 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 14.6 (CH_3), 115.6 (CH_2=CH), 119.5 (C-10a), 125.2, 126.6, 134.5, 137.0, 132.7 (C-8), 135.6 (CH_2=CH), 147.6 (C-4a), 149.2 (C-3a), 158.9 (C-10), 163.4 (C-6) ppm. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 5.39 (d, J = 10.9 Hz, 1 H, *cis* CH=CH_2), 5.85 (d, J = 17.6 Hz, 1 H, *trans* CH=CH_2), 6.80 (dd, J = 10.9, 17.6 Hz, 1 H, CH=CH_2), 7.52 (d, J = 8.5 Hz, Ar-H), 7.60 (d, J = 8.4 Hz, Ar-H), 8.30 (s, 1 H, 2-H), 8.89 (s, 1 H, 6-H), 9.06 (s, 1 H, 8-H) ppm. ^{13}C NMR (600 MHz, $CDCl_3$): δ = 15.5 (CH_3), 109.6 (10a), 115.8 (=CH_2), 119.5 (C-7), 125.2 (CH-Ar), 127.1 (CH-Ar), 132.7 (C-8), 134.3 (Cq-Ar), 135.5 (CH=), 138.3 (Cq-Ar), 146.5 (C-2), 148.0 (C-4a), 149.6 (C-10), 159.5 (C-3a), 162.9 (C-6) ppm. IR: $\tilde{\nu}$ = 3099, 2919, 1715, 1556, 1534, 1517, 1470, 1379, 1332, 1254, 1214, 955, 779 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{13}N_5O$ 303.1120; found 303.1119.

3-(4-Ethenylphenyl)-7-methylpyrimido[1,2-*a*]purin-10(3*H*)-one (5e): Yellow powder; yield 26 mg (26%); m.p. 186–191 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 5.34 (d, J = 10.9 Hz, 1 H, CH=CH_2), 5.81 (d, J = 17.6 Hz, 1 H, CH=CH_2), 6.76 (dd, J = 10.9, J = 17.6 Hz, 1 H), 7.56–7.58 (m, 2 H, Ar-H), 7.70–7.72 (m, 2 H, Ar-H), 8.19 (br. s, 1 H, 2-H), 8.84 (s, 1 H, 6-H), 9.26 (br. s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 15.3 (CH_3), 115.4 (CH$_2$=CH), 119.0 (C-10a), 119.8 (C-7), 123.9, 127.5, 133.5, 134.6 (C-8), 135.4 (CH_2=CH), 137.7, 140.8 (C-2), 148.4 (C-4a), 149.5 (C-3a), 152.6 (C-10), 163.2 (C-6) ppm. IR: $\tilde{\nu}$ = 3378, 3101, 2926, 1731, 1532, 1488, 1377, 1331, 1221, 1110, 987, 912, 781 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{13}N_5O$ 303.1120; found 303.1118.

***N*^{2}-[(Dimethylamino)methylene]-7-phenylguanine (7a):** White powder; yield 50 mg (53%); m.p. 278–284 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.08 and 3.16 (2 s, 6 H, 2 CH_3), 7.40–7.57 (m, 5 H, Ar-H), 7.95 (s, 1 H, 8-H), 8.84 (s, 1 H, 11-H), 9.60 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 35.0 and 41.2 (2 CH_3), 111.1 (C-5), 124.6, 128.1, 129.1, 135.7, 143.0 (C-8), 155.0 (C-6), 156.5 (C-2), 158.3 (C-11), 160.7 (C-4) ppm. IR: $\tilde{\nu}$ = 3122, 3076, 3032, 2921, 1669, 1635, 1555, 1520, 1433, 1385, 1341, 1267, 1240, 1147, 1112, 759 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{14}N_6O$ 282.1229; found 282.1225.

***N*^{2}-[(Dimethylamino)methylene]-9-phenylguanine (8a):** Amorphous solid; yield 8 mg (9%). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.11 and 3.16 (2 s, 6 H, 2 CH_3), 7.41–7.62 (m, 5 H, Ph-H), 7.83 (s, 1 H, 8-H), 8.55 (s, 1 H, 11-H), 9.63 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 35.2 and 41.4 (2 CH_3), 121.1 (C-5), 123.8, 127.8, 129.5, 135.1, 137.4 (C-8), 150.0 (C-4), 156.9 (C-2), 158.0 (C-11), 158.2 (C-6) ppm. IR: $\tilde{\nu}$ = 3093, 2925, 2850, 1691, 1637, 1545, 1430, 1356, 1154, 1116, 962, 765, 691 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{14}N_6O$ 282.1229; found 282.1226.

***N*^{2}-[(Dimethylamino)methylene]-7-(2-methylphenyl)guanine (7b):** White powder; yield 51 mg (52%); m.p. 254–257 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, CH_3Ar), 3.02 and 3.12 (2 s, 6 H, 2 CH_3), 7.26–7.36 (m, 4 H, Ar-H), 7.73 (s, 1 H, 8-H), 8.79 (s, 1 H, 11-H), 9.80 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 17.5 (CH_3Ar), 34.9 and 41.1 (2 CH_3), 112.5 (C-5), 126.5, 127.2, 129.2, 130.9, 135.1, 135.2, 143.3 (C-8), 155.0 (C-6), 156.5 (C-2), 158.1 (C-11), 159.7 (C-4) ppm. IR: $\tilde{\nu}$ = 3102, 2923, 2852, 1686, 1635, 1557, 1516, 1430, 1348, 1321, 1206, 1107, 979, 783, 765 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{16}N_6O$ 296.1386; found 296.1372.

***N*^{2}-[(Dimethylamino)methylene]-9-(2-methylphenyl)guanine (8b):** Amorphous solid; yield 6 mg (6%). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.18 (s, 3 H, CH_3Ar), 3.06 and 3.10 (2 s, 6 H, 2 CH_3), 7.27–7.44 (m, 4 H, Ar-H), 7.65 (s, 1 H, 8-H), 8.43 (s, 1 H, 11-H), 9.01 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 18.7 (CH_3Ar), 35.1 and 41.3 (2 CH_3), 120.4 (C-5), 126.9, 127.7, 129.3, 131.3, 133.7, 135.5, 138.6 (C-8), 150.9 (C-4), 156.8 (C-2), 157.9 (C-11) ppm.

***N*^{2}-[(Dimethylamino)methylene]-7-(3-methylphenyl)guanine (7c):** White powder; yield 49 mg (50%); m.p. 243–247 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3Ar), 3.06 and 3.14 (2 s, 6 H, 2 CH_3), 7.19–7.21 (m, 1 H, Ar-H), 7.32–7.35 (m, 3 H, Ar-H), 7.91 (s, 1 H, 8-H), 8.82 (s, 1 H, 11-H), 9.59 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 21.3 (CH_3Ar), 34.9 and 41.2 (2 CH_3), 111.1 (C-5), 121.9, 125.1, 128.8, 128.9, 135.6, 139.1, 143.0 (C-8), 154.8 (C-6), 156.5 (C-2), 158.3 (C-11), 160.5 (C-4) ppm. IR: $\tilde{\nu}$ = 3098, 2966, 2920, 2815, 1671, 1627, 1550, 1513, 1427, 1380, 1344, 1321, 1271, 1241, 1140, 1101, 781, 684 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{16}N_6O$ 296.1386; found 296.1374.

***N*^{2}-[(Dimethylamino)methylene]-9-(3-methylphenyl)guanine (8c):** Amorphous solid; yield 12 mg (13%). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3Ar), 3.10 and 3.15 (2 s, 6 H, 2 CH_3), 7.23–7.26 (m, 1 H, Ar-H), 7.39–7.42 (m, 3 H, Ar-H), 7.83 (s, 1 H, 8-H), 8.54 (s, 1 H, 11-H), 9.00 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 18.7 (CH_3Ar), 35.2 and 41.4 (2 CH_3), 121.0 (C-5), 121.2, 124.5, 128.7, 129.3, 134.9, 139.7, 137.7 (C-8), 150.0 (C-4), 156.8 (C-2), 157.8 (C-6), 158.0 (C-11) ppm. IR: $\tilde{\nu}$ = 3102, 2955, 2925, 2856, 1684, 1628, 1519, 1426, 1344, 1112 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{16}N_6O$ 296.1386; found 296.1402.

***N*^{2}-[(Dimethylamino)methylene]-7-(4-methylphenyl)guanine (7d):** White powder; yield 52 mg (53%); m.p. >300 °C (dec.). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3Ar), 3.08 and 3.16 (2 s, 6 H, 2 CH_3), 7.26–7.28 (m, 2 H, Ar-H), 7.41–7.43 (m, 2 H, Ar-H), 7.91 (s, 1 H, 8-H), 8.83 (s, 1 H, 11-H), 9.20 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 21.1 (CH_3Ph), 34.9 and 41.2 (2 CH_3), 111.2 (C-5), 124.5, 129.7, 133.2, 138.2, 143.0 (C-8), 154.7 (C-6), 156.4 (C-2), 158.3 (C-11), 160.5 (C-4) ppm. IR: $\tilde{\nu}$ = 3109, 3031, 2921, 1679, 1639, 1553, 1529, 1389, 1384, 1332, 1266, 1237, 1147, 1109, 848, 820, 782 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{16}N_6O$ 296.1386; found 296.1394.

***N*^{2}-[(Dimethylamino)methylene]-9-(4-methylphenyl)guanine (8d):** Amorphous solid; yield 15 mg (16%). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3Ar), 3.11 and 3.16 (2 s, 6 H, 2 CH_3), 7.32–7.34 (m, 2 H, Ar-H), 7.48–7.49 (m, 2 H, Ar-H), 7.81 (s, 1 H, 8-H), 8.55 (s, 1 H, 11-H), 9.26 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 21.1 (CH_3Ph), 35.2 and 41.4 (2 CH_3), 121.0 (C-5), 123.8, 130.1, 132.5, 137.9, 137.6 (C-8), 150.1 (C-4), 156.8 (C-2), 157.9 (C-11), 158.0 (C-6) ppm. IR: $\tilde{\nu}$ = 3092, 3029, 2927, 2861, 1678, 1641, 1552, 1436, 1371, 1274, 1171, 1121, 996, 824, 784 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{16}N_6O$ 296.1386; found 296.1371.

***N*^{2}-[(Dimethylamino)methylene]-7-(4-ethenylphenyl)guanine (7e):** White powder; yield 35 mg (35%); m.p. 266–272 °C. ^1H NMR

(500 MHz, $CDCl_3$): δ = 3.05 and 3.15 (2 s, 6 H, 2 CH_3), 5.29 (d, J = 11.1 Hz, 1 H, CH=CH_2), 5.77 (d, J = 17.1 Hz, 1 H, CH=CH_2), 6.68 (dd, J = 10.8, J = 17.6 Hz, 1 H) 7.45–7.52 (m, 4 H, Ar-H), 7.92 (br. s, 1 H, 8-H), 8.76 (s, 1 H, 11-H), 9.61 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 35.0 and 41.3 (2 CH_3), 115.2 (CH_2=CH), 124.6, 126.9, 134.9, 137.6, 135.7 (CH_2=CH), 142.9 (C-8), 154.5 (C-6), 156.4 (C-2), 158.3 (C-11) ppm. HRMS (EI): calcd. for $C_{17}H_{13}N_5O$ 308.1386; found 308.1369.

N^2-[(Dimethylamino)methylene]-9-(4-ethenylphenyl)guanine (8e): Amorphous solid; yield 17 mg (17%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.11 and 3.16 (2 s, 6 H, 2 CH_3), 5.35 (d, J = 11.1 Hz, 1 H, CH=CH_2), 5.81 (d, J = 17.6 Hz, 1 H, CH=CH_2), 6.76 (dd, J = 10.8, J = 17.3 Hz, 1 H, CH=CH_2), 7.55–7.56 (m, 4 H, Ar-H), 7.84 (br. s, 1 H, 8-H), 8.55 (s, 1 H, 11-H), 9.36 (br. s, 1 H, 1-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 35.2 and 41.4 (2 CH_3), 115.2 (CH_2=CH), 121.2 (C-5), 123.9, 127.2, 134.4, 137.3, 135.6 (CH_2=CH), 137.5 (C-8), 156.8 (C-2), 157.9 (C-6), 158.0 (C-11) ppm. IR: $\tilde{\nu}$ = 3473, 3091, 2922, 2852, 1668, 1658, 1625, 1522, 1427, 1343, 1167, 1118, 966, 849, 785 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{13}N_5O$ 308.1386; found 303.1396.

N^2-[(Dimethylamino)methylene]-1,7-diphenylguanine (9): White powder; yield 23 mg (63%); m.p. 255–260 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.08 and 3.16 (2 s, 6 H, 2 CH_3), 7.18–7.55 (m, 10 H, 2 Ph-H), 7.97 (s, 1 H, 8-H), 8.66 (s, 1 H, 11-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 34.5 and 40.8 (2 CH_3), 111.3 (C-5), 124.9, 127.5, 128.0, 128.5, 128.7, 129.0, 135.6, 138.0, 143.1 (C-8), 155.4 (C-6), 156.8 (C-11), 157.0 (C-2), 158.7 (C-4) ppm. IR: $\tilde{\nu}$ = 3081, 3060, 2926, 1693, 1624, 1532, 1490, 1424, 1384, 1337, 1261, 1119, 779 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{18}N_6O$ 358.1542; found 358.1545.

N^2-[(Dimethylamino)methylene]-1,9-diphenylguanine (10): White powder; yield 21 mg (59%); m.p. 214–218 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.63 and 3.03 (2 s, 6 H, 2 CH_3), 7.18–7.64 (m, 10 H, 2 Ph-H), 7.81 (s, 1 H, 8-H), 8.35 (s, 1 H, 11-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 34.6 and 40.9 (2 CH_3), 120.8 (C-5), 123.6, 127.4, 127.7, 128.5, 128.7, 129.5, 135.1, 138.2, 137.1 (C-8), 148.2 (C-4), 156.4 (C-11), 157.2 (C-2), 158.3 (C-6) ppm. IR: $\tilde{\nu}$ = 2924, 2853, 1694, 1624, 1503, 1484, 1371, 1343, 1122, 726 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{18}N_6O$ 358.1542; found 358.1561.

N^2-[(Dimethylamino)methylene]-3,7-diphenylguanine (11): White powder; yield 5 mg (16%); m.p. 158–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.78 and 3.09 (2 s, 6 H, 2 CH_3), 7.39–7.60 (m, 10 H, 2 Ph-H), 7.69 (s, 1 H, 8-H), 8.80 (s, 1 H, 11-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 34.8 and 41.0 (2 CH_3), 112.5 (C-5), 124.9, 128.3, 128.4, 128.0, 128.5, 128.7, 129.0, 135.6, 138.0, 140.0 (C-8), 150.5 (C-4), 156.2 (C-2), 158.8 (C-11), 161.7 (C-6) ppm. IR: $\tilde{\nu}$ = 3105, 3060, 2921, 2851, 1651, 1640, 1600, 1494, 1467, 1432, 1420, 1369, 1350, 1151, 1122, 1042, 780, 764 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{18}N_6O$ 358.1542; found 358.1559.

Preparation of the Arylguanines

Method A. Hydrolysis of the Arylated Pyrimidopurines: The pyrimidopurine derivative (0.1 mmol) was heated at reflux in 0.1 M NaOH (5 mL) for 4–6 h. After neutralization with 1 M hydrochloric acid, the white precipitate was collected by filtration. An analytical sample was crystallized from DMF and washed with water.

Method B. Hydrolysis of the Arylated (Dimethylamino)methylenepurine Derivatives: The (dimethylamino)methylenepurine derivative (0.1 mmol) was heated at reflux in 1.0 M HCl (5 mL) for 1–2 h. After neutralization with ammonia (24% aqueous solution), the white precipitate was collected by filtration.

7-Phenylguanine (6a):[12] White powder; yield 15 mg (68%, Method A), 18 mg (80%, Method B); m.p. > 300 °C. ^{1}H NMR (300 MHz, DMSO): δ = 6.22 (br. s, 2 H, NH_2), 7.41–7.60 (m, 5 H, Ph-H), 8.23 (s, 1 H, 8-H), 10.83 (br. s, 1 H, NH) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 107.6 (CH_3), 124.4, 127.5, 128.8, 135.7, 143.3 (C-5), 153.1 (C-2), 153.8 (C-6), 161.2 (C-4) ppm. IR: $\tilde{\nu}$ = 3311, 3162, 2922, 2852, 2767, 1670, 1558, 1496, 1471, 1390, 1334, 1240, 1141, 1110, 981, 761, 690 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_9N_5O$ 227.0807; found 227.0810.

7-(2-Methylphenyl)guanine (6b): White powder; yield 17 mg (72%, Method A), 23 mg (94%, Method B); m.p. >300 °C. ^{1}H NMR (300 MHz, DMSO): δ = 2.08 (s, 3 H, CH_3), 6.21 (br. s, 2 H, NH_2), 7.30–7.40 (m, 4 H, Ar-H), 7.99 (s, 1 H, 8-H), 11.32 (br. s, 1 H, NH) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 17.1 (CH_3), 109.3 (C-5), 126.5, 127.3, 128.8, 130.5, 134.7, 135.5, 143.5 (C-8), 153.1 (C-2), 153.8 (C-6), 160.1 (C-4) ppm. IR: $\tilde{\nu}$ = 3319, 3142, 3049, 2811, 1690, 1639, 1556, 1496, 1463, 1403, 1322, 1238, 1146, 1107, 981, 762, 694 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}N_5O$ 241.0964; found 241.0969.

7-(3-Methylphenyl)guanine (6c): White powder; yield 15 mg (60%, Method A), 20 mg (86%, Method B); m.p. >300 °C. ^{1}H NMR (300 MHz, DMSO): δ = 2.37 (s, 3 H, CH_3), 6.22 (br. s, 2 H, NH_2), 7.23–7.40 (m, 4 H, Ar-H), 8.20 (s, 1 H, 8-H), 10.81 (br. s, 1 H, NH) ppm. ^{13}C NMR (600 MHz, DMSO): δ = 20.9 (CH_3), 107.7 (C-5), 121.6, 124.8, 128.1, 128.6, 135.7, 138.4, 143.3 (C-8), 153.1 (C-2), 153.8 (C-6), 161.1 (C-4) ppm. IR: $\tilde{\nu}$ = 3297, 3116, 2928, 2859, 2784, 2721, 1689, 1601, 1554, 1496, 1478, 1389, 1323, 1271, 1250, 1199, 1116, 912, 857, 772, 684 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}N_5O$ 241.0964; found 241.0957.

7-(4-Methylphenyl)guanine (6d): White powder; yield 16 mg (65%, Method A), 21 mg (89%, Method B); m.p. >300 °C. ^{1}H NMR (600 MHz, DMSO): δ = 2.37 (s, 3 H, CH_3), 6.26 (br. s, 2 H, NH_2), 7.30–7.46 (m, 4 H, Ar-H), 8.22 (s, 1 H, 8-H), 10.88 (br. s, 1 H, NH) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 20.6 (CH_3), 107.7 (C-5), 124.3, 129.2, 133.2, 137.1, 143.2 (C-8), 153.0 (C-2), 153.7 (C-6), 162.3 (C-4) ppm. IR: $\tilde{\nu}$ = 3321, 3156, 2894, 2762, 1681, 1659, 1610, 1550, 1512, 1473, 1393, 1328, 1243, 1147, 1110, 983, 884, 855, 818, 774, 691 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}N_5O$ 241.0964; found 241.0969.

7-(4-Ethenylphenyl)guanine (6e): White powder; yield 22 mg (89%, Method A), 24 mg (95%, Method B); m.p. >300 °C. ^{1}H NMR (300 MHz, DMSO): δ = 5.31 (d, J = 10.8 Hz, 1 H, CH=CH_2), 5.89 (d, J = 17.6 Hz, 1 H, CH=CH_2), 6.20 (br. s, 2 H, NH_2), 6.78 (dd, J = 10.8, J = 17.9 Hz, 1 H), 7.40–7.56 (m, 4 H, Ar-H), 8.18 (br. s, 1 H, 8-H), 10.85 (br. s, 1 H, NH) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 114.5 (C-5), 115.1 (CH_2=CH), 124.4, 127.6, 135.1, 136.3, 135.6 (CH_2=CH), 143.2 (C-8), 153.3 (C-2), 153.9 (C-6), 161.2 (C-4) ppm. IR: $\tilde{\nu}$ = 3489, 3324, 3107, 1701, 1631, 1544, 1508, 1495, 1389, 1331, 1111, 756, 694 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{11}N_5O$ 253.0964; found 253.1000.

1,7-Diphenylguanine (12): White powder; yield 23 mg (77%, Method B); m.p. 289–292 °C. ^{1}H NMR (500 MHz, DMSO): δ = 6.14 (br. s, 2 H, NH_2), 7.31–7.56 (m, 10 H, Ph-H), 8.30 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 107.5 (C-5), 124.6, 127.6, 128.6, 129.1, 129.9, 135.6, 143.9 (C-8), 153.1 (C-2), 153.7 (C-6), 159.6 (C-4) ppm. IR: $\tilde{\nu}$ = 3489, 3108, 1700, 1614, 1544, 1506, 1454, 1434, 1389, 1336, 1269, 1114, 756, 695 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{13}N_5O$ 303.1120; found 303.1125.

1,9-Diphenylguanine (13): White powder; yield 22 mg (73%, Method B); m.p. 295–298 °C. ^{1}H NMR (500 MHz, DMSO): δ = 6.13 (br. s, 2 H, NH_2), 7.31–7.56 (m, 10 H, Ph-H), 8.30 (s, 1 H, 8-

H) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 107.4 (C-5), 124.5, 127.5, 128.6, 129.0, 129.8, 135.5, 143.8 (C-8), 153.0 (C-2), 153.6 (C-6), 159.5 (C-4) ppm. IR: $\tilde{\nu}$ = 3484, 3290, 3107, 3061, 1705, 1618, 1547, 1508, 1391, 1337, 1230, 1114, 757, 693 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{13}N_5O$ 303.1120; found 303.1120.

3,7-Diphenylguanine (14): White powder; yield 19 mg (64%, Method B); m.p. 285–290 °C. ^{1}H NMR (500 MHz, DMSO): δ = 6.40 (br. s, 2 H, NH_2), 7.30–7.32 (m, 2 H, Ph-H), 7.45–7.58 (m, 6 H, Ph-H), 7.77–7.79 (m, 2 H, Ph-H), 8.11 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 116.7 (C-5), 123.8, 127.7, 129.0, 129.1, 129.4, 130.0, 135.1, 135.7, 136.7 (C-8), 149.6 (C-4), 153.9 (C-2), 156.9 (C-6) ppm. HRMS (EI): calcd. for $C_{17}H_{13}N_5O$ 303.1120; found 303.1120.

Arylation of N^6-(Dimethylamino)methyleneadenine (15): A mixture of **15** (0.33 mmol), phenylboronic acid (0.66 mmol), *o*-phenanthroline (0.66 mmol), anhydrous copper(II) acetate (0.33 mmol) and dried 4 Å molecular sieves (250 mg) in dry CH_3OH (5 mL) in a 50 mL round-bottomed flask connected to a reflux condenser and with an anhydrous calcium chloride tube was stirred at ambient temperature for 24 h. Then methanol (15 mL) was added and resulting mixture was filtered through Celite, evaporated and purified by flash chromatography on silica gel. Besides the arylated (dimethylamino)methylene derivatives **16** and **17**, the formation of deprotected 9-phenyladenine (**18**; 15%) was also observed. Although the separation of **18** was without problems using chloroform/methanol (10:1), chromatographic separation of **16** and **17** (first eluted) turned out to be difficult and laborious. Acid hydrolysis (Method B) of a mixture of **16** and **17** (0.1 mmol), which was obtained in 71% yield, followed by chromatographic separation of **18** and **19** using chloroform/methanol (5:1) was much more effective.

***N*^{6}-[(Dimethylamino)methylene]-7-phenyladenine (16):** White powder; yield 52 mg (59%); m.p. 145–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 and 3.06 (2 s, 6 H, 2 CH_3), 7.41–7.47 (m, 5 H, Ph-H), 8.13 (s, 1 H, 2-H), 8.64 (s, 1 H, 8-H), 8.67 (s, 1 H, 11-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 34.7 and 40.8 (2 CH_3), 117.6, 126.7, 128.1, 128.3, 136.5, 145.6, 153.0, 154.8, 155.6, 161.5 ppm. IR: $\tilde{\nu}$ = 3107, 3050, 2923, 1631, 1573, 1540, 1499, 1453, 1422, 1394, 1355, 1331, 1313, 1211, 1059, 878 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{14}N_6$ 266.1280; found 266.1300.

***N*^{6}-[(Dimethylamino)methylene]-9-phenyladenine (17):** Amorphous solid; yield 11 mg (12%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.25 and 3.30 (2 s, 6 H, 2 CH_3), 7.41–7.48 (m, 1 H, Ph-H), 7.55–7.61 (m, 2 H, Ph-H), 7.70–7.73 (m, 2 H, Ph-H), 8.20 (s, 1 H, 2-H), 8.64 (s, 1 H, 8-H), 9.11 (s, 1 H, 11-H) ppm.

9-Phenyladenine (18):[10] White powder; overall yield 17 mg (25%); m.p. 245–246 °C (ethanol) [lit.:[25] 245–246 °C (ethanol)]. ^{1}H NMR (500 MHz, DMSO): δ = 7.40–7.47 (m, 3 H, Ph-H, NH_2), 7.58–7.61 (m, 2 H, Ph-H), 7.90–7.92 (m, 2 H, Ph-H), 8.23 (s, 1 H, 2-H), 8.61 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 119.3 (C-5), 122.9, 127.4, 129.5, 135.1, 139.7 (C-8), 149.1 (C-2), 153.0 (C-6), 156.3 (C-4) ppm. IR: $\tilde{\nu}$ = 3287, 3148, 3040, 1676, 1601, 1510, 1447, 1417, 1374, 1333, 1310, 1300, 1187, 964, 758, 715 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_9N_5$ 211.0858; found 211.0853.

7-Phenyladenine (19): Light-yellow powder; yield 17 mg (78%, Method B); m.p. 264–267 °C. ^{1}H NMR (500 MHz, DMSO): δ = 6.15 (br. s, 2 H, NH_2), 7.57–7.66 (m, 5 H, Ph-H), 8.33 (s, 1 H, 2-H), 8.53 (s, 1 H, 8-H) ppm. ^{13}C NMR (500 MHz, DMSO): δ = 107.6 (C-5), 124.4, 127.5, 128.8, 135.7, 143.3 (C-8), 153.1 (C-2), 153.8 (C-6), 161.2 (C-4) ppm. IR: $\tilde{\nu}$ = 3467, 3288, 3120, 3092, 1641, 1599, 1553, 1495, 1476, 1405, 1343, 1305, 1233, 1177, 777 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_9N_5$ 211.0858; found 211.0855.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **6a–e**, **12–14**, **18** and **19**.

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[23] In several cases (**5a**, **5c**, **4c**–**e**, **7e**, **8e**, **12** and **13**) some base signals in ^{13}C NMR were missing due to broadening. This was also evident in the ^{1}H NMR spectra in which the signals of the base protons were broadened. Such phenomena are usually the result of some dynamic process. However, in the case of compounds **4** and **5** this is not the case. We found that the broadening of the base signals is due to the coordination of trace amounts of paramagnetic Cu^{2+} ion. The broadening disappeared after treatment of the dichloromethane solutions of the compounds **4** and **5** with Divergan® HM (BASF), an insoluble vinylimidazole/vinylpyrrolidone copolymer, which efficiently removes traces of metal ions.

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