A site selective C–H arylation of free-(NH_2) adenines with aryl chlorides: Application to the synthesis of 6,8-disubstituted adenines†

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An efficient site selective method for the direct arylation of free-(NH_2) adenines **1** to provide a range of C-8 arylated adenines **3** in excellent yields is described. This process based on the use of $Pd(OH)_2/C$ as the catalyst and a stoichiometric amount of CuI under ligandless conditions is general. It allows the coupling to proceed with a variety of aryl halides, including for the first time cheaper and less reactive aryl chlorides. The extension of this process for the sequential preparation of non-symmetrical C8/N^6-arylated adenines **4** is also reported.

Introduction

Substituted purines have attracted much interest as therapeutics, molecular tools and probes for investigating biological systems.[1] In addition, they represent a large family of biologically active molecules and constitute the scaffold for a wide variety of promising drugs, including kinase inhibitors,[2] modulators of multidrug resistance[3] and antineoplastic agents.[4] In recent years, several substituted purines, such as PU24FCl, PU24S, as well as their 8-arylsulfanyl analogues,[5] have been found to be potent inhibitors of chaperone hsp90, an exciting new target in cancer drug discovery (Fig. 1).[6] This wide range of biological activity displayed by purines has made them popular synthetic targets.[7]

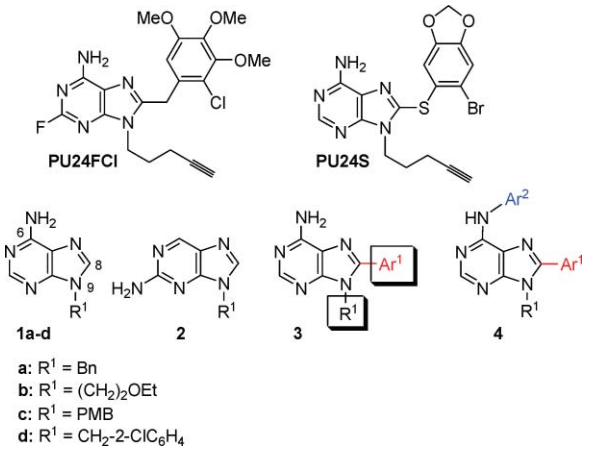

Fig. 1 Adenines used in this study and target structures **3** and **4**.

In support of an ongoing medicinal chemistry program toward hsp90,[8] a rapid and versatile access to 8-aryladenines of type **3**, which includes two centers for introduction of diversity into adenine molecule, was required (Fig. 1). Conventional methods for the synthesis of substituted adenines **3** are based on the construction of the heteroaryl–aryl bond at the 8-position of these heterocycles by Pd-catalyzed cross-coupling reactions between organometallic reagents with *N*-protected 8-bromoadenines.[9] While these reactions are suitable methods, they suffer from being multistep syntheses requiring the preparation of either or both reagents and are therefore time-consuming and economically inefficient. New synthetic strategies such as the direct functionalization of sp2 C–H bonds are now emerging as viable alternatives to traditional cross-coupling reactions. In these instances, the need for preactivating one of the reaction components is circumvented. Several reviews highlight the broad scope of this strategy, as well as high functional group tolerance and atom economy.[10] However, this straightforward approach is hindered by the regioselectivity difficulties particularly with free-(NH_2) adenines. Hocek and Fairlamb described the direct aryl functionalization of free-(NH_2) adenine nucleosides with aryl iodides which give in moderate to good yields C8-arylated adenosine derivatives together with a small amount of N^6-arylation products.[11] This C–H activation process was further extended by Hocek to N^9-protected free-(NH_2) adenines and optimal conditions reported led to a complex mixture of three major products.[12] Besides the desired 8-arylated adenines formed in low to moderate yields (21–50%), two by-products were also isolated arising from single and double Pd/Cu-mediated N^6-arylation of starting adenine. Therefore, the site selective direct arylation of free-(NH_2) adenines still remains a significant synthetic challenge. For this purpose, we sought to use aryl chlorides in palladium mediated C–H arylation reactions[13] as these substrates have traditionally been the least successful partners in the *N*-arylation reactions.[14]

Results and discussion

Recently, we described a regioselective and direct C–H arylation of free-(NH_2) adenines to prepare a variety of 8-aryladenines **3** from aryl bromides and iodides under ligandless microwave activation.[15] In this preliminary study, we reported three examples where the new developed catalyst system also enabled, for the first time, efficient reaction with cheap and the less reactive aryl chlorides. Encouraged by this initial discovery, the scope of this catalyst system with various aryl chlorides as substrates was more

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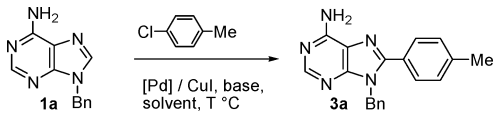
† Electronic supplementary information (ESI) available: General, experimental procedures for starting materials and ^1H and ^{13}C spectra for all new compounds. See DOI: 10.1039/b912033e

Table 1 Optimization C-8 arylation of **1a** with 4-tolyl chloride[a]



Entry	[Pd][b]	Base	Solvent	T (°C) / Time (h)	Yield (%)[c]
1	Pd_2dba_3	Cs_2CO_3	NMP	160/16	0
2	Pd/C	Cs_2CO_3	NMP	160/16	0
3	$Pd(OAc)_2$	Cs_2CO_3	NMP	160/16	73
4	$Pd(OH)_2/C$	Cs_2CO_3	NMP	160/16	90
5	$Pd(OAc)_2$	Cs_2CO_3	DMF	120 /42	0[d]
6	$Pd(OH)_2/C$	K_2CO_3	NMP	160/16	51
7	$Pd(OH)_2/C$	Na_2CO_3	NMP	160/16	8
8	$Pd(OH)_2/C$	K_3PO_4	NMP	160/16	25
9	$Pd(OH)_2/C$	piperidine	NMP	160/16	0
10	$Pd(OH)_2/C$	Cs_2CO_3	DMF	160/16	27
11	$Pd(OH)_2/C$	Cs_2CO_3	DMA	160/16	85
12	$Pd(OH)_2/C$	Cs_2CO_3	Dioxane	160/16	0
13	$Pd(OH)_2/C$	Cs_2CO_3	NMP	160 /4	91

[a] **1a** (1 equiv), 4-tolyl chloride (1.5 equiv), $Pd(OH)_2/C$ (5 mol%), CuI (1 equiv), Cs_2CO_3 (2 equiv), NMP, 160 °C. [b] No reaction occurred without palladium catalyst or copper salt. [c] Isolated yields. [d] Hocek conditions.[11]

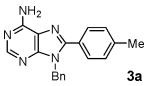
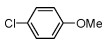
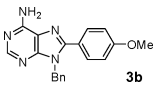
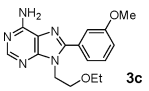
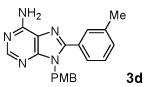
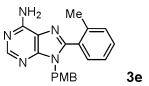
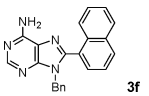
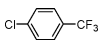
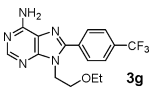
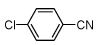
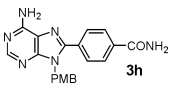
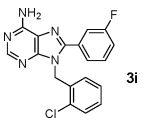
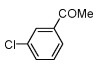
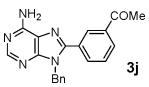
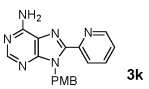
deeply investigated. Moreover, the development of this method on the regiocontrolled C-8 (hetero)arylation of **1** followed by a N^6-(hetero)arylation with various hetero(aryl) halides to furnish **4** will be reported.

Initial studies were performed by using adenine **1a** and 4-tolyl chloride as model substrates. As summarized in Table 1, the screening conditions revealed that the source of palladium used has an important influence on the outcome of the present reaction. Thus, the use of Pd/C or $Pd_2(dba)_3$ did not promote the C–H arylation reaction (entries 1 and 2), while in the presence of $Pd(OAc)_2$ the reaction led to **3a** in a satisfactory 73% yield (entry 3). We were delighted to find that the catalytic activity of $Pd(OH)_2/C$[16] proved to be superior to $Pd(OAc)_2$ leading to **3a** with an excellent 90% yield (entry 4). It should be noted that no reaction occurred when **1a** was reacted with 4-tolyl chloride under Hocek conditions (entry 5); only starting material was recovered. The screening reactions were continued with respect to the base and solvent. Evaluation of bases revealed that Cs_2CO_3 is superior to all other choices (entries 6–9). Optimization with respect to the solvent showed that the reaction proceeds best in NMP. In the presence of other polar solvents such as DMA, the C–H arylation also proved to be effective providing **3a** in a similar yield (85%, entry 11). Finally, the best conditions were found to require: 4-tolyl chloride (1.5 equiv), $Pd(OH)_2/C$ (5 mol%), CuI (1 equiv) and Cs_2CO_3 (2 equiv) at 160 °C for 4 h furnishing **3a** in 91% yield (entry 13).

With an effective catalytic system in hand, we probed its scope in the direct C8-arylation of various N^9-substituted adenines **1**. The results summarized in Table 2, show that the optimized conditions described above proved to be general for the coupling with a large variety of electron-rich and electron-deficient aryl chlorides. In addition, there was little effect of the substitution pattern of the aryl chloride with respect to yield or selectivity. One can note that 4-chlorobenzonitrile reacted with **1c** to provide concomitantly **3h** in a good yield as the arylated adenine with hydration of the nitrile function (entry 8). Running the reaction from **1d** bearing an sp2-carbon–chlorine bond, the C–H arylation gave selectively **3i** in 54% yield (entry 9).

As depicted in entry 11, heteroaromatic chlorides could be employed in this direct arylation reaction as well. Thus, 2-chloropyridine gave rise to the heteroarylated adenine **3k** in 55% yield. Finally, as demonstrated in entries 1, 2, 6 and 11, microwave heating is also effective for direct arylation of adenines **1**. The expected coupling products **3** were isolated in similar yields as those of conventional heating but with shorter reaction times (~1 h). The lower yield observed with 4-chloroanisole (entry 2, 60%

Table 2 Direct C-8 arylation of adenines **1** with aryl chlorides[a]

Entry	Adenine	ArCl	Time (h)	Product **3**	Yield (%)[b]
1	**1a**		4	 **3a**	91(86)[c]
2	**1a**		16	 **3b**	83(60)[c,d]
3	**1b**		16	 **3c**	77
4	**1c**		16	 **3d**	94
5	**1c**		16	 **3e**	93
6	**1a**		4	 **3f**	90(85)[c]
7	**1b**		16	 **3g**	64
8	**1c**		16	 **3h**	77
9	**1d**		24	 **3i**	54
10	**1a**		32	 **3j**	62
11	**1c**		4	 **3k**	55(56)[c]

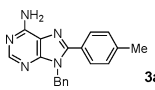
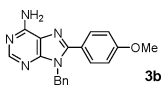
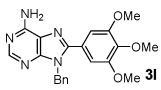
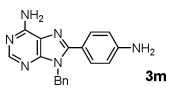
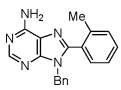
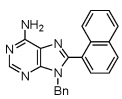
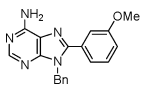
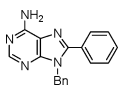
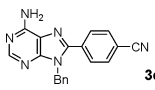
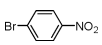
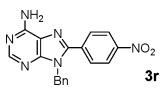
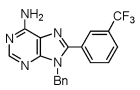
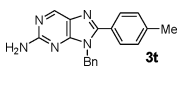
[a] Substrate (1 equiv), ArCl (1.5 equiv), Cs_2CO_3 (2 equiv), $Pd(OH)_2/C$ (5 mol %), CuI (1 equiv), 160 °C. [b] Isolated yields. [c] Yield between brackets refers to C–H arylation under MWI. See ESI† for details. [d] A 22% of methoxy substituent deprotection product was isolated as side product.

vs. 83%) is due to the formation of side product (22%) resulting from deprotection of the methoxy substituent.

Attention was next focused on this direct arylation using aryl iodides and bromides as arene coupling partners. As shown in Table 3, this method was equally efficient with electron-rich and electron-deficient aryl bromides and iodides, suggesting that the substrate scope of this method is high. A variety of 8-aryladenines **3** were thus obtained in 33–95% yields. One can note that the lower yield observed with ortho and meta substituted aryl iodides (entries 5 and 7) is due to the formation of the C-8 arylation compound together with a notable amount of N^6-arylated byproduct. These results clearly demonstrate that aryl chlorides are more suitable partners than the corresponding iodo and bromo derivatives for the site selective direct arylation of free-(NH_2) adenines (Table 2, entries 3–5).

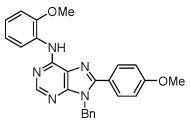
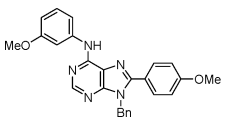
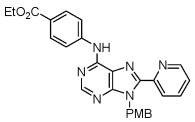
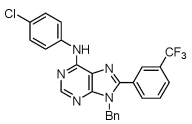
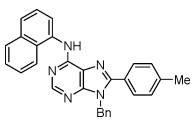
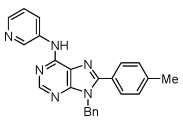
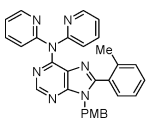
Being given the high efficiency of the synthesis of C8-substituted adenines **3**, we expected that the newly developed procedure would serve as an extremely useful and quick route to obtain N^6-arylated adenine derivatives **4**. These classes of substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as biologically active compounds.[1] In this context, we were pleased to observe that optimal reaction conditions for the *N*-arylation of adenines **3** were found to be similar than those of the C–H arylation reaction, using $Pd(OH)_2/C$ as the palladium source, Xantphos as the ligand, Cs_2CO_3 as the base and NMP as the solvent. These conditions proved to be effective with a wide range of aryl bromides and iodides furnishing non-symmetrical adenines **4a–g** in good yields (Table 4).

Table 3 Arylation of **1a** and **2a** with aryl iodides and bromides[a]

Entry	Adenine	ArX	Product	Yield (%)[b]
1	**1a**		 **3a**	78
2	**1a**		 **3b**	90
3	**1a**		 **3l**	55
4	**1a**		 **3m**	80
5	**1a**		 **3n**	42[c]
6	**1a**		 **3f**	95
7	**1a**		 **3o**	33[c]
8	**1a**		 **3p**	44
9	**1a**		 **3q**	68
10	**1a**		 **3r**	43
11	**1a**		 **3s**	82
12	**2a**		 **3t**	61

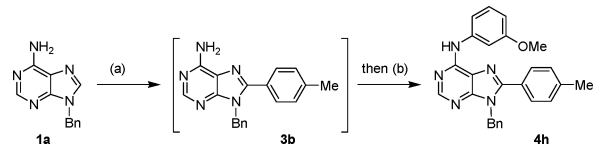
[a] Substrate (1 equiv), ArX (1.5 equiv), Cs_2CO_3 (2 equiv), $Pd(OH)_2/C$ (5 mol%), CuI (1 equiv), NMP, 160 °C, MWI. See the ESI for details.† [b] Isolated yields. [c] Accompanied by 35% of C8/N^6-diarylated byproduct.

Table 4 N^6-arylation of adenines **3** with aryl halides[a]

Entry	Adenine	ArX	Product **4**	Yield (%)[b]
1	**3b**		 **4a**	60
2	**3b**		 **4b**	58
3	**3k**		 **4c**	44
4	**3s**		 **4d**	87
5	**3a**		 **4e**	61
6	**3a**		 **4f**	66
7	**3e**		 **4g**	60[c]

[a] Substrate (1 equiv), ArX (1.05 equiv), Cs_2CO_3 (2 equiv), $Pd(OH)_2/C$ (5 mol%), Xantphos (10 mol%), NMP, 160 °C, 16 h. See the ESI for details.† [b] Isolated yields. [c] Run with 2 equiv of ArBr.

To obviate direct manipulation and purification of **3**, we next examined a one-pot Pd-catalyzed C-arylation/N^6-amination coupling sequence as it would be economically and environmentally advantageous over multistep syntheses (Scheme 1). In a typical experiment, we achieved this transformation in a one-pot way by mixing, in the first step, **1a** with 4-tolyl chloride as partner under optimal reaction conditions. After completion of the C8-arylation step, 3-iodoanisole (1.05 equiv) and Xantphos (10 mol%) in NMP were introduced and heated at 160 °C for 16 h. Thus, under this protocol, we were pleased to observe that the reaction worked well and provided the desired **4h** in a 49% yield, despite the fact that the reaction conditions had never been optimized.



Scheme 1 One-pot synthesis of C8, N^6-disubstituted adenine **4h**. (a): **1a** (1.0 equiv), 4-chlorotoluene (1.5 equiv), $Pd(OH)_2/C$ (5 mol %), CuI (1 equiv), Cs_2CO_3 (2.0 equiv), NMP, 160 °C, 4 h. (b): 3-iodoanisole (1.05 equiv), Xantphos (10 mol%), NMP (2 mL), 160 °C, 12 h.

Conclusion

In summary, we demonstrated that N^6-free-(NH_2) adenines can be selectively arylated at the 8-position with a variety of aryl halides including cheaper and generally more available aryl chlorides in the presence of $Pd(OH)_2/CuI$ system, with Cs_2CO_3 as the base and NMP as the solvent under ligandless conditions. This is the first general method for N^6-free adenines arylation with aryl chlorides to provide C-8 arylated adenines in good to excellent yields. Sequential combination of C8-direct arylation using aryl chlorides and N^6-arylation reaction using aryl bromides and iodides proved to be useful for the rapid construction of disubstituted adenines in good yields. We believe that this methodology should find broad applications in synthetic organic chemistry, as well as the combinatorial and pharmaceutical sciences. The synthesis of a library of new adenine derivatives **3** as well as **4** as potential hsp90 inhibitors will be reported in due course.

Experimental details

General experimental

General procedure for direct arylation of N^9-substituted adenines 1 with aryl chlorides. A flame-dried resealable 2–5 mL Pyrex reaction vessel was charged with the solid reactant(s): $Pd(OH)_2/C$ (20% on carbon) (5.0 mol%), CuI (1.0 mmol), N^9-substituted adenine **2** (1.0 mmol), aryl chloride (1.5 mmol) and Cs_2CO_3 (2.0 mmol). The reaction vessel was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The liquid reactant(s) and NMP (6 mL per mmol) were added through the septum. The septum was replaced with a Teflon screwcap. The reaction vessel was sealed, and then heated at 160 °C; time: (see Table 2). The resulting suspension was cooled to room temperature and filtered through a pad of Celite eluting with CH_2Cl_2/MeOH (7 : 3), and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

General procedure for direct arylation of N^9-substituted adenines 1 with aryles halides under microwave irradiation. A flame-dried resealable 2–5 mL Pyrex reaction vessel was charged with the solid reactant(s): $Pd(OH)_2/C$ (20% on carbon) (5.0 mol%), CuI (1.0 mmol), N^9-substituted adenine (1.0 mmol), aryl halide (1.5 mmol) and Cs_2CO_3 (2.0 mmol). The reaction vessel was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The liquid reactant(s) and NMP (6 mL per mmol) were added through the septum. The septum was replaced with a Teflon screwcap. The reaction vessel was sealed, then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature: 160 °C; time: (see tables); fixed hold time: on; sample absorption: high; pre-stirring: 60 s. The resulting suspension was cooled to room temperature and filtered through a pad of Celite eluting with CH_2Cl_2/MeOH (7 : 3), and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Compound 3a. Yield: 91% (287 mg); white solid; mp: 188–190 °C; TLC: R_f 0.32 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3145, 2357, 1639, 1597, 1453, 1329, 1298, 1184, 1108, 1074, 1022, 826, 729, 694; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.46 (d, 2H, J = 8.1 Hz),7.27 (m, 3H), 7.23 (d, 2H, J = 8.0 Hz), 7,07 (m, 2H), 5,97 (s, 2H, N*H*), 5,45 (s, 2H), 2,40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 153.0, 151.8, 151.8, 140.6, 136.4, 129.5 (2C), 128.9 (2C), 128.8 (2C), 127.8, 126.6 (2C), 126.5, 119.1, 46.9, 21.4; m/z MS (ES+) (M+H$^+$) 316; Anal. Calcd for $C_{19}H_{17}N_5$ (315,15): C 72.36, H 5.43, N 22.21; found: C 72.64, H 5.69, N 22.65.

Compound 3b. Yield: 83% (275 mg); beige solid; mp: 104–106 °C; TLC: R_f 0.29 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3157, 1661, 1606, 1530, 1458, 1332, 1298, 1266, 1179, 1031, 834, 727, 694; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.53 (d, 2H, J = 8.5 Hz), 7.28 (m, 3H), 7.09 (m, 2H), 6.96 (d, 2H, J = 8.5 Hz), 5.92 (s, 2H, N*H*), 5.47 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO d^6): δ 160.3, 155.5, 152.4, 151.3, 150.0, 137.0, 130.1 (2C), 128.6 (2C), 127.3, 126.1 (2C), 121.9, 118.4, 114.1 (2C), 55.2, 46.0; m/z MS (ES+) (M+H)$^+$ 332; Anal. Calcd for $C_{19}H_{17}N_5O$ (331,14): C 68.87, H, 5.17, N, 21.13; found: C 69.01, H, 5.34, N, 21.24.

Compound 3c. Yield: 77% (241 mg); white solid; mp: 139–141 °C; TLC: R_f 0.26 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3308, 3119, 2931, 1661, 1594, 1572, 1479, 1350, 1322, 1257, 1219, 1116, 1023, 883, 787, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, 3H, J = 7.0 Hz), 3.37 (q, 2H, J = 7.0 Hz), 3.86 (m, 5H), 4.42 (t, 2H, J = 5.4 Hz), 6.26 (s, 2H, N*H*), 7,04 (m, 1H), 7,39 (m, 3H), 8,34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9, 44.0, 55.4, 66.6, 68.0, 114.9, 116.2, 119.3, 121.9, 129.8, 130.9, 151.5, 151.8, 152.5, 155.3, 159.7; m/z MS (ES+) (M+ h)$^+$ 314; Anal. Calcd for $C_{16}H_{19}N_5O_2$ (313,15): C 61.33, H 6.11, N 22.35; found: C 61.61, H 6.24, N 22.67.

Compound 3d. Yield: 94% (325 mg); beige solid; mp: 157–159 °C; TLC: R_f 0.45 (CH_2Cl_2/MeOH: 9/1); IR (neat): ν(cm^{-1}) 3321, 3139, 1664, 1647, 1597, 1565, 1513, 1302, 1246, 1178, 1030,

846; ^{1}H NMR (300 MHz, DMSO-d^6): δ 8.36 (bs, 1H), 7.40 (m, 4H), 7.17 (s, 2H, N*H*), 6.94 (d, 2H, *J* = 8.4 Hz), 6.81 (d, 2H, *J* = 8.3 Hz), 5.40 (s, 2H), 3.69 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 158.2, 137.4, 129.9, 129.5, 129.0, 128.6, 128.0, 127.5 (2C), 125.4, 113.6 (2C), 54.7, 45.3, 20.3; *m/z* MS (ES+) (M+H)$^+$ 346; Anal. Calcd for $C_{20}H_{19}N_5O_1$ (345,16): C, 69.55, H 5.54, N 20.28; found: C, 69.62, H 5.74, N 20.32.

Compound 3e. Yield: 93% (321 mg); beige solid; mp: 238–240 °C; TLC: R$_f$ 0.44 (CH_2Cl_2/MeOH: 9/1); IR (neat): ν(cm^{-1}) 3313, 1638, 1611, 1584, 1480, 1335, 1301, 1243, 1182, 1035, 779, 735, 657; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.32 (m, 4H),6.85 (d, 2H, *J* = 8.6 Hz), 6.69 (d, 2H, *J* = 8.5 Hz), 5.93 (s, 2H, N*H*), 5.15 (s, 2H), 3.73 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 155.1, 152.8, 151.0, 150.9, 138.3, 130.6, 130.3, 130.0, 129.4, 129.2 (2C), 128.2, 125.8, 119.0, 113.8 (2C), 55.2, 46.0, 19.4; *m/z* MS (ES+) (M+H)$^+$ 346; Anal. Calcd for $C_{20}H_{19}N_5O$ (345,16): C 69.55, H 5.54, N 20.28; found: C 69.70, H 5.72, N 20.31.

Compound 3f. Yield: 90% (316 mg); beige solid; mp: 184–186 °C; TLC: R$_f$ 0.30 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3337, 3164, 1610, 1606, 1572, 1496, 1454, 1450, 1432, 1322, 1315, 800, 775, 722, 695; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.99 (d, 1H, *J* = 8.1 Hz), 7.92 (d, 1H, *J* = 8.2 Hz),7.47 (m, 5H), 7.07 (m, 3H), 6.78 (m, 2H), 6.18 (s, 2H, N*H*), 5.21 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 153.1, 151.3, 150.3, 136.0, 133.5, 131.9, 130.7, 128.8, 128.4, 128.4 (2C), 127.7, 127.4 (3C), 127.1, 126.5,124.8 (2C), 119.3, 46.8; *m/z* MS (ES+) (M+ h)$^+$ 352; Anal. Calcd for $C_{220}H_{17}N_5$ (351,15): C 75.19, H 4.88, N 19.93; found: C 75.22, H 4.96, N 20.10.

Compound 3g. Yield: 64% (225 mg); white solid; mp: 170–172 °C; TLC: R$_f$ 0.27 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3381, 3156, 2893, 2204, 1645, 1599, 1582, 1462, 1411, 1323, 1169, 1119, 1070, 1019, 899, 854, 839; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.05 (d, 2H, *J* = 8.0 Hz), 7,77 (d, 2H, *J* = 8.1 Hz), 6.17 (s, 2H, N*H*), 4.41 (t, 2H, *J* = 5.1 Hz), 3.89 (t, 2H, *J* = 5.1 Hz), 3.38 (q, 2H, *J* = 7.0 Hz), 1.06 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4; 152.9, 151.6, 150.6, 133.4, 131.8 (q, *J* = 32.8 Hz), 130.2 (2C), 125.6 (2C), 123.8 (q, *J* = 272.4 Hz), 119.5, 68.1, 66.7, 44.3, 14.9; *m/z* MS (ES+) (M+ h)$^+$ 352; Anal. Calcd for $C_{16}H_{16}F_3N_5O$ (351,13): C 54.70, H 4.59, N 19.93; found: C 54.81, H 4.63, N 20.10.

Compound 3h. Yield: 77% (288 mg); white solid; mp: 173–175 °C; TLC: R$_f$ 0.10 (CH_2Cl_2/MeOH: 95/5)); IR (neat): ν(cm^{-1}) 3314, 3139, 2918, 2187, 1640, 1600, 1513, 1459, 1330, 1288, 1247, 1177, 1030, 862, 722; ^{1}H NMR (300 MHz, DMSO-d6): δ 8.22 (s, 1H), 8.09 (s, 1H, CON*H*), 8.00 (d, 2H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 8.4 Hz), 7,51 (s, 1H, CON*H*), 7.41 (s, 2H, N*H*),6.92 (d, 2H, *J* = 8.7 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 5.46 (s, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6): δ 167.1, 158.4, 155.8, 152.9, 151.3, 148.9, 135.0, 132.3, 128.7, 128.5 (2C), 127.7 (4C), 118.6, 114.0 (2C), 54.9, 45.6; *m/z* MS (ES+) (M+ h)$^+$ 375; Anal. Calcd for $C_{20}H_{18}N_6O_2$ (374,15): C 64.16, H 4.85, N 22.45; found: C 64.21, H 4.99, N 22.52.

Compound 3i. Yield: 54% (191 mg); white solid; mp: 198–200 °C; TLC: R$_f$ 0.28 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3315, 3140, 2188, 2066, 1656, 1595, 1586, 1458, 1373, 1348, 1323, 1299, 1202, 1051, 886, 881; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H); 7.30 (m, 7H), 6.74 (d, 1H, *J* = 7.5 Hz), 6.27 (s, 2H, N*H*), 5.58 (s, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7 (d, *J* = 248.1 Hz), 155.5, 153.4, 152.0, 150.1, 133.6, 132.0, 131.2 (d, *J* = 8.1 Hz), 130.7 (d, *J* = 8.3 Hz), 129.8, 129.1, 127.4, 127.0, 124.2, 119.3,117.4 (d, *J* = 21.1 Hz), 116.0 (d, *J* = 23.4 Hz), 44.9; *m/z* MS (ES+) (M+ h)$^+$ 354; Anal. Calcd for $C_{18}H_{13}ClFN_5$ (353,08): C 61.11, H 3.70, N 19.80; found: C 61.22, H 3.83, N 19.98.

Compound 3j. Yield: 62% 213 mg); beige solid; mp: 169–171 °C; TLC: R$_f$ 0.28 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3832, 3464, 3382, 3303, 3113, 2204, 1663, 1591, 1575, 1495, 1448, 1407, 1357, 1329, 1283, 1237, 1013, 955, 846, 816, 721, 692; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8,43 (s, 1H), 8,12 (s, 1H), 8,08 (d, 1H, *J* = 7.8 Hz), 7,82 (d, 1H, *J* = 7.7 Hz), 7,57 (dd, 1H, *J* = 7.7 Hz, *J* = 7.8 Hz), 7,29 (m, 3H),7.01 (m, 2H), 6.05 (s, 2H, N*H*), 5.50 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 155.4, 153.3, 152.1, 150.5, 137.5, 136.2, 133.4, 130.1, 129.7, 129.3, 129.0 (3C), 128.0, 126.4 (2C), 119.4, 47.0, 26.4; *m/z* MS (ES+) (M+H)$^+$ 344; Anal. Calcd for $C_{20}H_{17}N_5O$ (343,14): C 69.96, H 4.99, N 20.40; found: C 70.12, H 5.13, N 20.61.

Compound 3k. Yield: 55% (183 mg); beige solid; mp: 161–163 °C; TLC: R$_f$ 0.34 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3354, 3105, 2926, 2204, 2150, 1656, 1592, 1586, 1504, 1500,1462, 1427, 1336, 1300, 1286, 1253, 1175, 1096, 1035, 818, 794; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (brd, 1H, *J* = 4.8 Hz), 8.42 (s, 1H), 8.21 (d, 1H, *J* = 8.0 Hz), 7.78 (td, 1H, *J* = 7.9 Hz, *J* = 1.4 Hz),7.33 (dd, 1H, *J* = 7.5 Hz, *J* = 4.9 Hz), 7.20 (d, 2H, *J* = 8.6 Hz), 6.71 (d, 2H, *J* = 8.6 Hz), 6.08 (s, 2H), 5.94 (s, 2H, N*H*), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 155.4,153.4, 152.3, 150.0, 148.7, 147.9, 136.8, 129.7, 129.2 (2C), 124.1, 123.9, 119.4, 113.7 (2C), 55.1, 46.9; *m/z* MS (ES+) (M+H)$^+$ 333; Anal. Calcd for $C_{18}H_{16}N_6O_1$ (332,14): C 65.05, H 4.85, N 25.29; found: C 65.18, H 4.98, N 25.37.

Compound 3l. Yield: 55% (215 mg); beige brown solid; mp: 189–191 °C; TLC: R$_f$ 0.22 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3155, 1662, 1589, 1461, 1417, 1356, 1326, 1298, 1241, 1124, 1025, 992, 852; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 6H), 3.88 (s, 3H), 5.50 (s, 2H), 6.00 (s, 2H, N*H*), 6.78 (s, 2H), 7.13 (m, 2H), 7.31 (m, 3H), 8.42 (s, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.0, 55.9 (2C), 60.9, 106.2 (2C), 124.5, 126.1 (2C), 127.8, 129.0 (2C), 136.7, 139.7, 151.9, 153.4 (2C); *m/z* MS (ES+) (M+H)$^+$ 392; Anal. Calcd for $C_{21}H_{21}N_5O_3$ (391,16): C 64.44, H 5.41, N 17.89; found: C 64.61, H 5.56, N 17.98.

Compound 3m. Yield: 80% (253 mg); beige solid; mp: 170–172 °C; TLC: R$_f$ 0.19 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3127, 1654, 1606, 1451, 1331, 1300, 1184, 835, 729, 695; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.36 (d, 2H, *J* = 8.4 Hz), 7.25 (m, 5H), 7,01 (d, 2H, *J* = 7.3 Hz), 6.59 (d, 2H, *J* = 8.4 Hz), 5.58 (s, 2H), 5.45 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.2, 152.0, 151.3, 150.9, 150.3, 137.3, 129.7 (2C), 128.6 (2C), 127.2, 126.2 (2C), 118.3, 116.3, 113.3 (2C), 46.1; *m/z* MS (ES+) (M+H)$^+$ 317; Anal. Calcd for $C_{18}H_{16}N_6$ (316,14): C 68.34, H 5.10, N 26.56; found: C 68.64, H 5.19, N 26.70.

Compound 3n. Yield: 33% (109 mg); beige solid; mp: 145–147 °C; TLC: R$_f$ 0.28 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3141, 2355, 1650, 1596, 1580, 1454, 1327, 1300, 1261, 1220, 1041,

869, 864, 726, 696; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.31 (m, 4H), 7.09 (m, 5H), 6.49 (s, 2H, N*H*), 5.48 (s, 2H), 3.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 155.4, 153.0, 151.7, 151.4, 136.4, 130.5, 129.9, 128.8 (2C), 127.7, 126.5 (2C), 121.3, 119.1, 116.7, 113.8, 55.1, 46.1; *m/z* MS (ES+) $(M+H)^+$ 332; Anal. Calcd for $C_{19}H_{16}N_5O$ (331,14): C 68.87, H 5.17, N 21.13; found: C 68.98, H 5.31, N 21.30.

Compound 3o. Yield: 42% (132 mg); white solid; mp: 160–162 °C; TLC: R_f 0.29 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3163, 1650, 1595, 1475, 1455, 1370, 1323, 1068, 723, 696, 657; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.42 (m, 1H), 7.22 (m, 6H), 6.91 (m, 2H), 6.34 (s, 2H, N*H*), 5.22 (s, 2H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 152.9, 150.9, 150.8, 138.3, 135.9, 130.5, 130.3, 129.9, 129.2, 128.4 (2C), 127.8, 127.6 (2C), 125.8, 118.9, 46.5, 19.3; *m/z* MS (ES+) $(M+H)^+$ 316; Anal. Calcd for $C_{19}H_{17}N_5$ (315,15): C 72.36, H 5.43, N 22.21; found: C 72.63, H 5.54, N 22.32.

Compound 3p. Yield: 44% (132 mg); light brown solid; mp: 138–140 °C; TLC: R_f 0.29 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3314, 2926, 1654, 1596, 1455, 1372, 1332, 1296, 1074, 1032, 727, 696, 664; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.58 (m, 2H), 7.45 (m, 3H), 7.28 (m, 3H), 7.07 (m, 2H), 6.53 (s, 2H, N*H*), 5.47 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 153.0, 151.7, 151.5, 136.3, 130.2, 129.4, 129.0 (2C), 128.8 (4C), 127.8, 126.6 (2C), 119.1, 46.9; *m/z* MS (ES+) $(M+H)^+$ 302; Anal. Calcd for $C_{18}H_{15}N_5$ (301,13): C 71.74, H 5.02, N 23.24; found: C 71.96, H 5.11, N 23.31.

Compound 3q. Yield: 68% (222 mg); white solid; mp: 215–217 °C; TLC: R_f 0.31 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3373, 3168, 2228, 1648, 1593, 1580, 1527, 1490, 1461, 1408, 1310, 1302, 1277, 1110, 1065, 1019, 849, 720, 714, 694; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.73 (s, 4H), 7.29 (m, 3H), 7.05 (m, 2H), 6.07 (s, 2H, N*H*), 5.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 153.6, 152.1, 149.4, 135.8, 133.9, 132.5 (2C), 129.6 (2C), 129.1 (2C), 128.1, 126.4 (2C), 118.0, 113.9, 47.1; *m/z* MS (ES+) $(M+H)^+$ 327; Anal. Calcd for $C_{19}H_{14}N_6$ (326,13): C 69.92, H 4.32, N 25.75; found: C 69.99, H 4.42, N 25.83.

Compound 3r. Yield: 43% (149 mg); yellow solid; mp: 236–238 °C; TLC: R_f 0.30 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3479, 3070, 2158, 1665, 1593, 1568, 1520, 1341, 1292, 1105, 1064, 975, 856, 734, 707; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, 2H, J = 8.9 Hz), 8.23 (s, 1H), 7.99 (d, 2H, J = 8.9 Hz), 7.55 (s, 2H, N*H*), 7.24 (m, 3H), 6.99 (m, 2H), 5.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 156.1, 153.3, 151.5, 147.7, 147.4, 136.5, 135.8, 129.8 (2C), 128.6 (2C), 127.5, 126.3 (2C), 123.8 (2C), 118.8, 46.1; *m/z* MS (ES+) $(M+H)^+$ 347; Anal. Calcd for $C_{18}H_{14}N_6O_2$ (346,12): C 62.42, H 4.07, N 24.27; found: C 62.60, H 4.19, N 24.19.

Compound 3s. Yield: 82% (303 mg); beige solid; mp: 172–174 °C; TLC: R_f0.31 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3140, 2927, 2359, 1659, 1601, 1570, 1497, 1452, 1420, 1377, 1356, 1325, 1300, 1242, 1167, 1122, 1099, 1076, 982, 914, 840, 821, 727, 695, 681; ^{1}H NMR (300 MHz, Acetone-d_6): δ 8.29 (s, 1H), 8.00 (m, 2H), 7.84 (d, 1H, J = 7.9 Hz), 7.73 (dd, 1H, J = 8.1 Hz, J = 8.0 Hz), 7.28 (m, 3H), 7.11 (m, 2H),6.83 (s, 2H, N*H*), 5.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.4, 153.5, 152.0, 150.0, 136.0, 132.2, 131.4 (q, J = 33.0 Hz), 130.5; 129.4; 129.0 (2C), 128.1; 126.9 (d, J = 3.1 Hz), 126.6 (2C), 126.1 (d, J = 3.3 Hz), 123.5 (q, J = 272.5 Hz), 47.1; RMN ^{13}C (100 MHz, $CDCl_3$): δ (ppm): 155.5, 153.2, 152.0, 150.1, 136.0, 130.5, 129.4, 129.0 (2C), 132.2, 131.4 (q, J = 32.9 Hz), 128.1, 126.8 (d, J = 3.0 Hz), 126.6 (2C), 126.1 (d, J = 3.4 Hz),123.5 (q, J = 272.7 Hz), 47.1; *m/z* MS (ES+H)$^+$ 370; Anal. Calcd for $C_{19}H_{14}F_3N_5$ (369,12): C 61.79, H 3.82, N 18.96; found: C 61.96, H 3.96, N 19.16.

Compound 3t. Yield: 61% (192 mg); beige solid; mp: 163–165 °C; TLC: R_f 0.28 (CH_2Cl_2/MeOH: 95/5); IR (neat): ν(cm^{-1}) 3314, 3188, 1615, 1586, 1497, 1474, 1431, 1423, 1359, 1265, 1140, 909, 826, 798, 727; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.49 (d, 2H, J = 7.9 Hz),7.29 (m, 3H), 7.23 (d, 2H, J = 7.8 Hz), 7.09 (m, 2H), 5.38 (s, 2H), 5.1 (s, 2H, N*H*), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 156.1, 159.8, 155.3, 153.5, 148.8, 140.5, 136.4, 129.4 (2C), 128.8 (4C),127.8, 127.7, 126.5 (2C), 46.4, 21.3; *m/z* MS (ES+) $(M+H)^+$ 316; Anal. Anal. Calcd for $C_{19}H_{17}N_5$ (315,15): C 72.36, H 5.43, N 22.21; found: C 72.63, H 5.75, N 22.41.

General procedure for *N*-arylation of adenines 3 with various bromides and iodides

A flame-dried resealable Schlenk tube was charged with the solid reactant(s): $Pd(OH)_2/C$ (5 mol%), Xantphos (10 mol%), 1.05 mmol of the aryl iodides/bromides, 1.0 mmol of adenines 3 and Cs_2CO_3 (2 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The liquid reactant(s) and NMP (6 mL) were added through the septum. The septum was replaced with a teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 160 °C for 16 h. The resulting suspension was cooled to room temperature and filtered through celite eluting with ethyl acetate, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Compound 4a. Yield: 60% (262 mg); white solid; mp: 188–190 °C; TLC: R_f 0.30 (EtOAc/*c*-hexane: 7/3); IR (neat): ν(cm^{-1}) 3406, 3027, 2944, 2840, 1610, 1577, 1522, 1482, 1453, 1423, 1375, 1353, 1330, 1312, 1292, 1255, 1180, 1168, 1105, 1049, 1024, 831; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (m, 1H),. 8,59 (s, 1H), 8.30 (s, 1H), 7.59 (d, 2H, J = 8.6 Hz), 7.29 (m, 3H), 7.08 (m, 4H), 6.98 (m, 1H), 6.98 (d, 2H, J = 8.6 Hz),5.51 (s, 2H), 3.95 (s, 3H), 3.87 (s, 3H); RMN ^{13}C (75 MHz, $CDCl_3$): δ 161.1, 152.5, 151.7, 151.6, 151.4, 148.5, 136.5, 130.6 (2C), 128.9 (2C), 128.5, 127.7, 126.5 (2C), 122.6, 121.9, 120.8, 120.6, 120.0, 114.3 (2C), 110.0, 55.6, 55.4, 46.9; *m/z* MS (ES+) $(M+H)^+$ 438; Anal. Calcd for $C_{26}H_{23}N_5O_2$ (437,19): C 71.38, H 5.30, N 16.01; found: C 71.57, H 5.43, N 16.21.

Compound 4b. Yield: 58% (253 mg); beige solid; mp: 148–150 °C; TLC: R_f 0.29 (EtOAc/*c*-hexane: 7/3); IR (neat): ν(cm^{-1}) 3396, 2920, 1626, 1608, 1578, 1536, 1495, 1470, 1455, 1420, 1380, 1357, 1336, 1306, 1280, 1256, 1198, 1175, 1157, 1116, 1078, 1029, 981, 956, 934, 844, 822, 791, 777, 734; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.86 (s, 1H), 7.68 (s, 1H), 7.60 (d, 2H, J = 8.4 Hz), 7.34 (m, 5H),7.14 (d, 1H, J = 6.5 Hz), 7.01 (d, 2H, J = 8.4 Hz), 6.70 (d, 2H, J = 7.9 Hz), 5.54 (s, 2H), 3.90 (s, 6H); RMN ^{13}C (75 MHz, $CDCl_3$): δ 161.3, 160.2, 152.6, 151.9, 151.6,

151.5, 140.1, 136.4, 130.6 (2C), 129.7, 128.9 (2C), 127.8, 126.6 (2C), 121.6, 120.0, 114.4 (2C), 112.4, 108.8, 106.1, 55.4, 55.3, 47.0; *m/z* MS (ES+) $(M+H)^+$ 438; Anal. Calcd for $C_{26}H_{23}N_5O_2$ (437,19): C 71.38, H 5.30, N 16.01; found: C 71.65, H 5.43, N 16.21.

Compound 4c. Yield: 44% (211 mg); beige solid; mp: 171–173 °C; TLC: R_f 0.16 (EtOAc/*c*-hexane: 7/3); IR (neat): ν(cm^{-1}) 3568, 3411, 2985, 1703, 1624, 1607, 1578, 1512, 1462, 1421, 1404, 1379, 1339, 1274, 1240, 1189, 1174, 1103, 1030, 938, 901, 852, 823, 793, 766; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (brs, 1H), 8.64 (s, 1H), 8.24 (d, 1H, J = 7.5 Hz), 8.06 (m, 3H), 7.95 (d, 2H, J = 8.6 Hz), 7.79 (t, 1H, J = 7.7 Hz), 7.35 (m, 1H), 7.24 (d, 2H, J = 8.5 Hz), 6.73 (d, 2H, J = 8.5 Hz), 6.12 (s, 2H),4.37 (q, 2H, J = 7.1 Hz), 3.59 (s, 3H),1.40 (t, 3H, J = 7.1 Hz); RMN ^{13}C (75 MHz, $CDCl_3$): δ 166.2, 158.9, 152.9, 152.1, 151.4, 149.7, 148.7, 148.3, 143.1, 136.8, 130.8 (2C), 129.4, 129.2 (2C), 124.6, 124.3, 124.0, 120.4, 118.7 (2C), 113.7 (2C), 60.7, 55.1, 47.0, 14.3; *m/z* MS (ES+) $(M+H)^+$ 481; Anal. Calcd for $C_{27}H_{24}N_6O_3$ (480,19): C 67.49, H 5.03, N 17.49; found: C 67.60, H 5.13, N 17.51.

Compound 4d. Yield: 87% (417 mg); white solid; mp: 162–164 °C; TLC: R_f 0.48 (EtOAc/*c*-hexane: 7/3); IR (neat): ν(cm^{-1}) 3392, 3037, 2205, 1965, 1621, 1579, 1526, 1492, 1476, 1383, 1352, 1323, 1298, 1248, 1163, 1136, 1088, 1071, 1038, 910, 846, 822, 797, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.83 (m, 6H), 7.59 (t, 1H, J = 7.7 Hz),7.31 (m, 5H), 7.11 (m, 2H), 5.52 (s, 2H); RMN ^{13}C (75 MHz, $CDCl_3$): δ 153.2; 151.8, 151.7, 150.2, 137.3, 135.9, 132.2, 131.5 (q, J = 32.9 Hz), 129.5; 129.0 (2C), 129.0 (2C), 128.4, 128.1, 127.0 (d, J = 3.2 Hz), 126.6 (2C), 126.1 (d, J = 3.5 Hz), 123.5 (q, J = 272.8 Hz), 121.7, 121.4 (2C), 120.1, 47.2; *m/z* MS (ES+) $(M+H)^+$ 480; Anal. Calcd for $C_{25}H_{17}ClF_3N_5$ (479,11): C 62.57, H 3.57, N 14.59; found: C62.60, H 3.63, N 14.60.

Compound 4e. Yield: 61% (269 mg); white solid; mp: 172–174 °C; TLC: R_f 0.55 (EtOAc/*c*-hexane: 7/3); IR (neat): ν(cm^{-1}) 3751, 3559, 3427, 3028, 2356, 1631, 1608, 1593, 1573, 1536, 1502, 1471, 1407, 1374, 1358, 1327, 1275, 1185, 1114, 1094, 1031, 977, 827, 789, 772, 724, 693; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.29 (s, 1H), 8.13 (m, 2H),7.91 (m, 1H), 7.76 (d, 1H, J = 8.2 Hz), 77.54 (m, 5H),.29 (m, 5H), 7.13 (d, 2H, J = 7.6 Hz), 5.52 (s, 2H), 2.43 (s, 3H); RMN ^{13}C (75 MHz, $CDCl_3$): δ 153.0, 152.9, 152.1, 151.7, 140.5, 136.4, 134.4, 133.2, 129.5 (2C), 129.0 (2C), 128.9 (2C), 128.6, 128.2, 127.8, 126.6 (2C), 126.5, 126.1, 126.0, 125.7, 125.5, 121.7, 121.1, 120.2, 47.0, 21.4; *m/z* MS (ES+) $(M+H)^+$ 442; Anal. Calcd for $C_{29}H_{23}N_5$ (441,2): C 78.89, H 5.25, N 15.86; found: C 79.01 H 5.43, N15.89.

Compound 4f. Yield: 66% (259 mg); white solid; mp: 200–202 °C; TLC: R_f 0.21 (EtOAc/*c*-hexane: 7/3); IR (neat): ν(cm^{-1}) 3030, 2785, 2372, 1633, 1576, 1533, 1479, 1457, 1413, 1377, 1326, 1290, 1031, 1023, 824, 794, 727, 696, 615, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.52 (s, 2H), 7.10 (m, 2H), 7.32 (m, 6H), 7.51 (d, 2H, J = 8.2 Hz), 7.92 (s, 1H), 8.36 (brs, 1H), 8.52 (m, 1H), 8.59 (s, 1H), 8.94 (brs, 1H); RMN ^{13}C (75 MHz, $CDCl_3$): δ 21.4, 47.1, 120.2, 123.6, 126.3, 126.6 (2C), 127.1, 127.9, 128.9 (2C), 129.0 (2C), 129.6 (2C), 136.0, 136.2, 140.8, 141.3, 143.9, 151.4, 151.8, 152.4, 152.5; *m/z* MS (ES+) $(M+H)^+$ 393; Anal. Calcd for $C_{24}H_{20}N_6$ (392,17): C 73.45, H 5.14, N 21.41; found: C 73.63, H 5.25, N 21.87.

Compound 4g. Yield: 61% (304 mg); light brown solid; mp: 92–94 °C; TLC: R_f 0.36 (CH_2Cl_2/MeOH: 9/1); IR (neat): ν(cm^{-1}) 2361, 1611, 1563, 1513, 1470, 1427, 1336, 1304, 1281, 1249, 1177, 1091, 1033, 908, 850; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.39 (brs, 2H), 7.68 (t, 2H, J = 7.5 Hz), 7.23 (m, 8H), 6.87 (d, 2H, J = 8.4 Hz), 6.70 (d, 2H, J = 8.5 Hz), 5.22 (s, 2H), 3.74 (s, 3H), 1.86 (s, 3H); RMN ^{13}C (75 MHz, $CDCl_3$): δ 159.1, 156.2, 153.6, 153.3, 152.0, 151.9, 148.7, 138.7, 137.7 (2C), 130.6, 130.0, 129.7, 129.2 (3C), 129.0, 128.1, 125.3, 124.1, 120.6, 120.3, 113.8 (4C), 55.2, 46.1, 19.6; *m/z* MS (ES+) $(M+H)^+$ 500; Anal. Calcd for $C_{30}H_{25}N_7O_1$ (499,21): C 72.13, H 5.04, N 19.63; found:. C 72.35, H 5.23, N 19.91.

General procedure for one-pot synthesis of C8, N^6-disubstituted adenine 4h

A flame-dried resealable 2–5 mL Pyrex reaction vessel was charged with the solid reactant(s): $Pd(OH)_2/C$ (20% on carbon) (5.0 mol %), CuI (1.0 mmol), N^9-substituted adenine (1.0 mmol), aryl chloride (1.5 mmol) and Cs_2CO_3 (2.0 mmol). The reaction vessel was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. NMP (6 mL) was added through the septum. The septum was replaced with a Teflon screwcap. The reaction vessel was sealed, and then heated at 160 °C for 4 h. Then, the resulting suspension was cooled to room temperature and a solution of $Pd(OH)_2/C$ (5 mol%) and Xantphos (10 mol%) in NMP (1 mL) was added through the septum. The septum was replaced with a Teflon screwcap and the reaction vessel was sealed, and then heated at 160 °C for 16 h. The resulting suspension was cooled to room temperature and filtered through a pad of celite eluting with CH_2Cl_2/MeOH (7 : 3), and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Compound 4h. Yield: 40% (169 mg); white solid; mp: 112–114 °C; TLC: R_f 0.27 (EtOAc/*c*-hexane: 7/3); IR (neat): ν(cm^{-1}) 3376, 1721, 1691, 1603, 1515, 1390, 1250, 1221, 1192, 1022, 996, 941, 889, 826; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.84 (brs, 1H), 7.65 (m, 1H), 7.50 (d, 2H, J = 8.0 Hz),7.31 (m, 7H), 7.1 (m, 2H), 6.67 (m, 1H), 5.50 (s, 2H), 3.86 (s, 3H), 2.42 (s, 3H); RMN ^{13}C (75 MHz, $CDCl_3$): δ 160.1, 152.7, 151.8, 151.5, 151.2, 140.8, 140.1, 138.8, 136.2, 129.6, 129.5, 129.0, 128.8 (2C), 127.9, 126.6 (2C), 126.2, 123.4, 120.3, 112.5, 109.0, 106.1, 55.3, 47.0, 21.4; *m/z* MS (ES+) $(M+H)^+$ 422; Anal. Calcd for $C_{26}H_{23}N_5O_1$ (421,19): C 74.09, H 5.50, N 16.62; found: C 74.26, H 5.43, N16.51

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