Palladium-Catalyzed Cross-Coupling between 8-Substituted 6-Thiophenylpurines and Boronic Acids

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Abstract: A palladium(II)-catalyzed, copper(I)-mediated Liebeskind–Srogl cross-coupling for the C-6 arylation/alkenylation on purine scaffold is reported. Various boronic acids reacted readily with 8-substituted 6-thiophenylpurines.

Key words: purine, cross-coupling, sulfur, copper, palladium

Purine is the most widely distributed N-heterocycle scaffold in nature and its synthetic derivatives are well known for their biological and more recently fluorescent properties.[1] These characteristics are linked to the diversity of substituents that can be introduced, especially on the C-2, C-6, C-8, and N-9 positions. Although many strategies have been described for the elaboration and functionalization of purines, the development of new methods for rapid functionalization is still of great synthetic interest.[2]

During our precedent work on functionalization at the C-8 position of purines, a major drawback was the undesired reactivity of the C–Cl bond at the 6-position of the purine scaffold during Buchwald–Hartwig and direct C–H alkenylation reactions.[3] Indeed, 6-chloropurines are well known to be reactive under various conditions such as S_NAr and metal-catalyzed cross-coupling reactions.[4] To circumvent this problem, we chose to replace the chloro atom at the 6-position of the purine ring by a thiophenyl group that would be initially inert under the studied reaction conditions to allow the C-8 functionalization of purines, but that would be subsequently reactive enough to introduce various substituents on the C-6 position of the purine ring.

Over the last decade, the reactivity of the C–S bond has gained significant attention as organosulfur compounds provide a good alternative to the use of halogenated reagents in metal-catalyzed reactions[5] including cross-coupling reactions between thioethers and alkynyl,[6] organotin,[7] organomagnesium,[8] organozinc,[9] organosilicon,[10] organoindium,[11] and to a larger extent organoboron[12] compounds.

In purine chemistry, the reactivity of C–S bond has been mostly studied through sulfur atom oxidation of 6-thioaryl(alkyl)purines followed by nucleophilic aromatic substitution.[3a,13] Regarding C–S bond functionalization for the formation of C–C bond on the purine ring, a few examples have been reported. In 1985, Takei reported a cross-coupling between 6-(methylsulfanyl)purine derivatives and Grignard reagents with a nickel-phosphine complex.[14] Robins later described a reaction between 6-sulfanylpurine and boronic acids, using $Pd(OAc)_2$, a carbene ligand [1,3-bis(2,6-diisopropylphenyl)imidazoline-2-ylidene], and K_3PO_4 in toluene at 90 °C for eight hours.[15] Good yields were obtained but only three examples were presented. Fukuyama detailed a single example of a cross-coupling reaction between a 6-sulfanylpurine and an organozinc compound using $Pd(dppf)Cl_2$ in toluene at 50 °C over two hours.[16] Very recently, Hocek described the cross-coupling reaction of a 8-(phenylsulfanyl)purine with phenylboronic acid or stannanes.[17]

In our previous work on Pd-catalyzed amidation and amination of 8-iodopurine, the first example of Liebeskind–Srogl reaction between 6-thiophenyl-8-phenylaminopurine and (4-methoxyphenyl)boronic acid using Pd(0) and Cu(I) complexes as catalysts under neutral conditions was also disclosed.[3b,18] Thus, we were keen to optimize this method in order to discover the scope of reactivity of various 8-substituted 6-thioetherpurines in the Liebeskind–Srogl reaction.

In this context, we report the palladium-catalyzed cross-coupling of various 8-substituted 6-thioetherpurines with a range of boronic acids that widens the type of reactions, which can be used to functionalize the purine ring. We also took advantage of the stability of the C–S bond under a variety of metal-catalyzed reactions including Suzuki, Buchwald–Hartwig, and direct C–H alkenylation and alkynylation conditions to synthesize 6,8,9-trisubstituted purines, with an efficient Liebeskind–Srogl cross-coupling as the last step.

The Liebeskind–Srogl cross-coupling optimization was initially performed with an easily accessible substrate, purine **1**, and the commercially available (4-methoxyphenyl)boronic acid (Table 1). The first attempt was carried out using the standard Liebeskind–Srogl conditions, with copper(I) thiophene-2-carboxylate (CuTC), $Pd_2(dba)_3$, and tri(2-furyl)phosphine as the ligand in THF at 50 °C (Table 1, entry 1).[18b] After 16 hours of reaction, the product **2a** was obtained in a promising yield of 50%. When this catalyst system was replaced by $Pd(PPh_3)_4$, a similar yield of 42% was observed (entry 2).[18c] But when $Pd(dppf)Cl_2$ was used in 1,4-dioxane, the isolated yield

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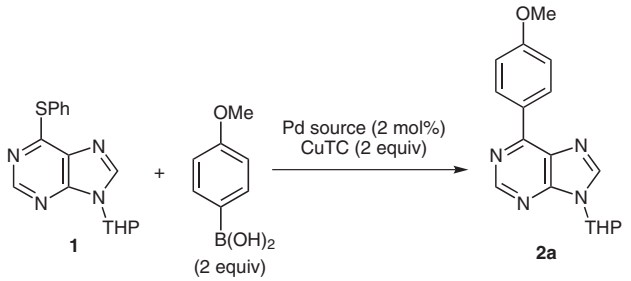
leapt to 79% (entry 3).[19] It is clear that the reaction proceeds very rapidly, since a comparable yield of 73% was observed when the heating time was reduced to only 15 minutes (entry 4). Heating under microwave irradiation raised the yield of **2a** to 83% (entry 5); however, fewer equivalents of CuTC resulted in a considerable decrease of the yield (entry 6). As there was no significant microwave effect, the influence of the reaction temperature was investigated under thermal heating. The yield dramatically decreased when the reaction was performed at room temperature even after 24 hours (entry 7). Indeed, the higher the temperature of the reaction, the better the yield was (entries 4, 8 and 9) peaking at 86% for reaction at 120 °C (entry 9). However, reducing the amount of boronic acid decreased the yield by half (entry 10). Finally, only traces of product were observed when CuTC was replaced with copper(I) 3-methylsalicylate (CuMeSal) and complete absence of CuTC was fatal to the reaction (entries 11, 12). Thus, the optimum conditions were found to be $Pd(dppf)Cl_2$ (2 mol%) and CuTC (2 equiv) in 1,4-dioxane at 120 °C for 15 minutes under classical heating.

Table 1 Optimization of Liebeskind–Srogl Conditions with Purine **1** and (4-Methoxyphenyl)boronic Acid[a]



Entry	Pd source	Solvent	Temp/Time	Yield (%)[b]
1	$Pd_2(dba)_3$	THF	50 °C, 16 h	50[c]
2	$Pd(PPh_3)_4$	THF	50 °C, 16 h	42[d]
3	$Pd(dppf)Cl_2$	1,4-dioxane	80 °C, 16 h	79
4	$Pd(dppf)Cl_2$	1,4-dioxane	80 °C, 15 min	73
5	$Pd(dppf)Cl_2$	1,4-dioxane	80 °C, 15 min	83[e]
6	$Pd(dppf)Cl_2$	1,4-dioxane	80 °C, 15 min	63[e,f]
7	$Pd(dppf)Cl_2$	1,4-dioxane	25 °C, 15 min	16[g]
8	$Pd(dppf)Cl_2$	1,4-dioxane	100 °C, 15 min	79
9	**$Pd(dppf)Cl_2$**	**1,4-dioxane**	**120 °C, 15 min**	**86**
10	$Pd(dppf)Cl_2$	1,4-dioxane	120 °C, 15 min	42[h]
11	$Pd(dppf)Cl_2$	1,4-dioxane	120 °C, 15 min	<5[i]
12	$Pd(dppf)Cl_2$	1,4-dioxane	120 °C, 15 min	0[j]

[a] Substrate **1** (1 equiv), 4(-methoxyphenyl)boronic acid (2 equiv), and CuTC (2 equiv) were heated in a sealed tube in the presence of [Pd] (2 mol%).
[b] Isolated yields.
[c] Four mol% of $Pd_2(dba)_3$ and 16 mol% of TFP.
[d] Five mol% of Pd source.
[e] Microwave heating.
[f] CuTC used: 1.2 equiv.
[g] Yield obtained when the reaction was run for 24 h: 24%.
[h] (4-Methoxyphenyl)boronic acid used: 1.2 equiv.
[i] CuMeSal was used.
[j] No CuTC.

In order to explore the scope of this method, these optimized conditions were next applied to couple 8-substituted purines with a range of boronic acids (Table 2). 8-Unsubstituted purines were efficiently reactive as electron-deficient and electron-rich aromatic and vinyl groups were introduced from the corresponding boronic acids in yields ranging from 59 to 86% (Table 2, entries 1–3). In the case of 8-chloropurine, the reaction was chemoselective but a low yield was observed despite total conversion (entry 4). Unfortunately, the reaction did not take place with 8-iodopurine (entry 5). In spite of total conversion, only traces of 8,8′-purine dimer (~10%) and product derived from a Suzuki reaction in position 8 (<5%) were isolated. In this case, the carboxylate counterion (from CuTC) could act as a base allowing the Suzuki reaction to proceed. Thus, under Liebeskind–Srogl conditions, the C–I bond seems to interfere with the reactivity of the C–S bond. This behavior was in agreement with the work of Dvorak on the dimerization of iodopurines in the presence of CuTC.[20] However, it was quite in contrast with the work of Neumann or Wipf on the orthogonal selectivity of the Liebeskind–Srogl coupling versus the Suzuki–Miyaura reaction on bromopyrimidinones[18c] and quinazolines,[18c,21] respectively. Noteworthy was the C–S bond, which was stable under metal-catalyzed reaction conditions including the Buchwald–Hartwig coupling used during the synthesis of starting material **9** and direct C–H bond alkenylation and alkynylation for the synthesis of compounds **10** and **11**. Whilst phenylamino, styryl, and alkynyl[22] groups were well tolerated on the position 8 of the purine scaffold under the optimized Liebeskind–Srogl conditions (entries 6–9) it should be noted, however, that some purines were degraded at 120 °C and required a lower heating temperature of 80 °C (entries 4, 6–8). Regrettably, boronic acids bearing a simple alkyl substituent were unreactive.

Then, we were interested in studying the scope of our optimized Liebeskind–Srogl conditions on 8-styrylpurine **10** that has been previously developed in our laboratory via a direct C–H bond functionalization reaction (Table 3).[3a,23] Compound **1** reacted with bromostyrene through direct alkenylation, using a Pd/Cu co-catalysis under microwave irradiation, to afford compound **10**. Then, the Liebeskind–Srogl reaction proceeded well with a range of electron-rich and electron-poor boronic acids. These optimized conditions are compatible with functional groups such as nitro or halogen that can undergo subsequent transformations. Nevertheless, in the case of (4-cyanophenyl)boronic acid and propenylboronic acid, purification problems were encountered and the products were contaminated with starting material **10**. It should be noted that products **5c**, **5e**, and **5g**, were inclined to isomerization on silica gel,

a phenomenon previously observed by Lakshman during a Heck reaction on nucleosides.[24] Finally, a two-step sequence involving direct C–H bond functionalization followed by the optimized Liebeskind–Srogl reaction led to new 6-aryl/alkenyl-8-stryrylpurines.

Table 2 Scope of Palladium-Catalyzed Copper-Mediated Cross-Coupling between 6-Thioetherpurines and Boronic Acids under Classical Heating

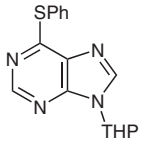
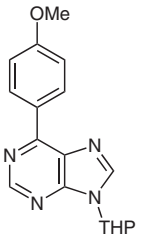
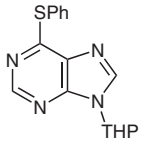
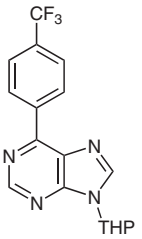
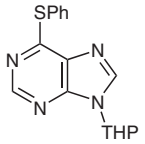
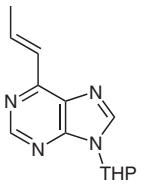
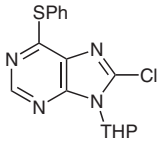
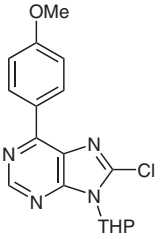
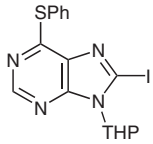
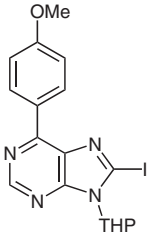
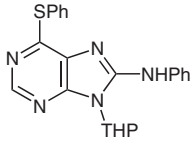
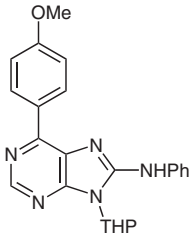
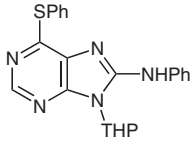
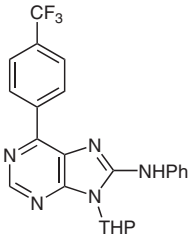
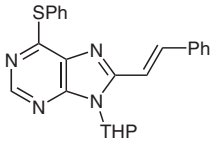
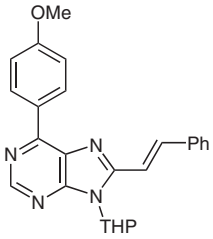
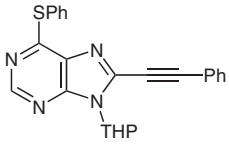
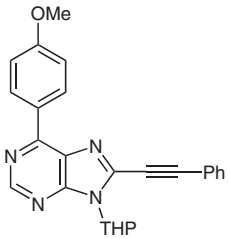
Entry	Substrate		Product		Yield (%)[a]
1		**1**		**2a**	86
2		**1**		**2b**	65
3		**1**		**2c**	59
4		**8a**		**3a**	30[b]
5		**8b**		**3b**	0
6		**9**		**4a**	54[b]

Table 2 Scope of Palladium-Catalyzed Copper-Mediated Cross-Coupling between 6-Thioetherpurines and Boronic Acids under Classical Heating (continued)

Entry	Substrate		Product		Yield (%)[a]
7		**9**		**4b**	47[c,d]
8		**10**		**5a**	72[d]
9		**11**		**6**	55[22]

[a] Isolated yields. Average of two runs.
[b] Conditions: 80 °C, 15 min.
[c] Starting material recovered: 30%.
[d] Conditions: 80 °C, 30 min.

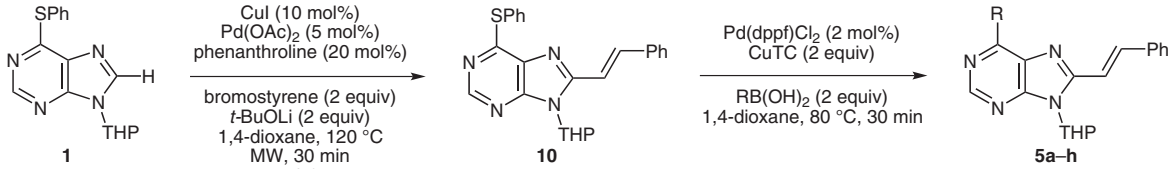
Having in hand the 8-iodo-6-thiophenylpurine **8b**, we further tested its useful synthetic application. First, Suzuki conditions, using phenylboronic acid, $Pd(PPh_3)_4$, and K_2CO_3 in 1,4-dioxane–water, were successfully applied to give 8-phenylpurine **12**. Interestingly, the C–S bond was not reactive as only traces of 6,8-diphenylpurine were detected. Thus, the C–I bond appears to be more reactive than the C–S bond regardless of the conditions applied, highlighting the orthogonal reactivity of compound **8b** as already observed in other heterocyclic series.[21,25] Then, purine **12** reacted smoothly with both electron-rich and electron-poor boronic acids at the 6-position with moderate to good yields to give 6,8-diarylpurines **7a**–**h** (Table 4). As with the 8-styrylpurine, reaction with phenylboronic acid led to an average 39% yield and separation between the product and the substrate **12** remained difficult when (4-cyanophenyl)boronic acid was used. However, 6-propenylpurine was obtained in a good yield of 75%.

Although 6,8-diarylpurines can be potentially synthesized in a two-step sequence by regioselective Suzuki coupling from 6,8-dihalogenated purines as already described for compound **7g**[4d] or by combination of Suzuki coupling/direct C–H arylation,[26] the purine derivatives **7a**–**f** and **7h** were newly synthesized. Therefore, these double C–I/C–S cross-coupling reactions represent a viable chemoselective alternative for the rapid, stepwise functionalization of purine derivatives.

In conclusion, optimized Liebeskind–Srogl cross-coupling conditions could be applied to various 8-substituted 6-thiophenylpurines with boronic acids, expanding the scope of the limited described examples. The functional group tolerance and the speed of this optimized Liebeskind–Srogl reaction render this method suitable for the combinatorial synthesis of new polyfunctionalized purines that is complementary to existing methods.

Commercially available reagents and solvents were used without further purification, unless otherwise stated. Yields refer to isolated and purified products. Reactions were monitored by TLC carried out on silica gel plates (60F-254) and visualized under UV light. Column chromatography was performed on silica gel 60, 40–63 μm. Chemical shifts of ^{1}H NMR and ^{13}C NMR were reported in ppm (δ units) and residual nondeuterated solvent was used as internal reference. Standard abbreviations were used to designate the multiplicities. Microwave irradiation was performed on CEM Explorer (CEM Corporation). Temperature measurement of the reaction mixture within the Discovery series was achieved by an IR sensor. The method was set with maximum power of 150 W, with maximum pressure of 17 bar, and used without powermax. Reaction times refer to the hold time at the desired set temperature. Reaction cooling was performed by compressed air after the heating period was over.

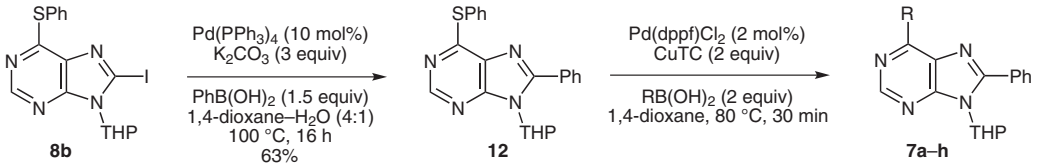
Table 3 Scope of 8-Styrylpurines



Product	R	Yield (%)[a]
5a	4-$MeOC_6H_4$	72
5b	4-$Me_2NC_6H_4$	66
5c	4-$F_3CC_6H_4$	68[b,c]
5d	4-NCC_6H_4	54[d]
5e	3-$O_2NC_6H_4$	81[e,f]
5f	3-ClC_6H_4	54
5g	Ph	46[g]
5h	(*E*)-MeCH=CH	60[d]

[a] Isolated yields. Average of two runs.
[b] Reaction time: 15 min.
[c] Isolated as an *E*/*Z* 8:2 mixture.
[d] NMR yield.
[e] Reaction time: 1 h.
[f] Isolated as an *E*/*Z* 95:5 mixture.
[g] Isolated as an *E*/*Z* 86:14 mixture.

Table 4 Scope of 8-Phenylpurines



Product	R	Yield (%)[a]
7a	4-$MeOC_6H_4$	60
7b	4-$Me_2NC_6H_4$	43[b]
7c	4-$F_3CC_6H_4$	56
7d	4-NCC_6H_4	20[c]
7e	3-$O_2NC_6H_4$	56
7f	3-ClC_6H_4	57
7g	Ph	39
7h	(*E*)-MeCH=CH	75

[a] Isolated yields. Average of two runs.
[b] Reaction time: 1 h.
[c] NMR yield.

Compounds **1**,[3b] **4a**,[3b] **7g**,[4d] **8b**,[3b] and **9**[3b] showed satisfactory spectroscopic data in agreement with those reported in the literature. ^{1}H NMR for compound **2a** was already described.[27]

Thioether-Boronic Acid Coupling; 6-(4-Methoxyphenyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (2a); Typical Procedure

A flame-dried tube filled with argon was charged with **1** (80 mg, 0.256 mmol, 1 equiv), Pd(dppf)Cl_2 (3.7 mg, 0.005 mmol, 2 mol%), CuTC (97.7 mg, 0.512 mmol, 2 equiv), and 4-methoxyphenylboronic acid (77.8 mg, 0.512 mmol, 2 equiv) in anhydrous 1,4-dioxane (1.5 mL). The sealed tube was placed in a preheated oil bath at 120 °C for 15 min. The reaction mixture was taken up in EtOAc (20 mL), washed with 10% NH_4OH (10 mL), and the organic layer was dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2–EtOH (100:0 → 99:1). The title compound was obtained as a beige solid (68.3 mg, 86%); mp 154–156 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97 (s, 1 H), 8.81 (d, *J* = 9.0 Hz, 2 H), 8.31 (s, 1 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 5.84 (dd, *J* = 9.9, 2.6 Hz, 1 H), 4.20 (d, *J* = 13.2 Hz, 1 H), 3.90 (s, 3 H), 3.85–3.77 (m, 1 H), 2.29–2.02 (m, 3 H), 1.89–1.65 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 154.7, 152.5, 151.6, 141.6, 131.6, 130.6, 128.4, 114.2, 82.0, 69.0, 55.5, 32.0, 25.0, 22.9.

MS (ES+): *m*/*z* (%) = 311.1 (100, $[M + H]^+$), 227.1 $[M – THP]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{19}N_4O_2$ $[(M + H)^+]$: 311.1508; found: 311.1505.

9-(Tetrahydro-2*H*-pyran-2-yl)-6-[4-(trifluoromethyl)phenyl]-9*H*-purine (2b)

Reaction conditions: 120 °C, 15 min; yield: 43.8 mg (65%); white solid; mp 170–172 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 8.93 (d, *J* = 8.1 Hz, 2 H), 8.38 (s, 1 H), 7.81 (d, *J* = 8.3 Hz, 2 H), 5.87 (dd, *J* = 10.0, 2.3 Hz, 1 H), 4.22 (d, *J* = 11.2 Hz, 1 H), 3.87–3.78 (m, 1 H), 2.22–2.04 (m, 3 H), 1.90–1.67 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1, 152.5, 152.1, 142.8, 139.0, 132.6, 132.2, 131.5, 130.2, 125.9, 125.61, 125.56, 122.3, 82.2, 69.0, 32.0, 25.0, 22.9.

MS (ES+): *m*/*z* (%) = 349.1 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}F_3N_4O$ $[(M + H)^+]$: 349.1276; found: 349.1271.

(*E*)-6-(Prop-1-en-1-yl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (2c)

Reaction conditions: 120 °C, 15 min; yield: 27.8 mg (59%); dark yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.86 (s, 1 H), 8.25 (s, 1 H), 7.68–7.56 (m, 1 H), 7.02 (d, *J* = 15.5 Hz, 1 H), 5.80 (dd, *J* = 9.6, 2.3 Hz, 1 H), 4.19 (d, *J* = 12.2 Hz, 1 H), 3.80 (td, *J* = 11.4, 2.6 Hz, 1 H), 2.17–2.06 (m, 3 H), 1.89–1.68 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 152.5, 151.0, 141.7, 140.2, 130.6, 126.6, 81.9, 68.9, 31.9, 24.9, 22.9, 19.3.

MS (ES+): *m*/*z* (%) = 245.1 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{17}N_4O$ $[(M + H)^+]$: 245.1402; found: 245.1398.

8-Chloro-6-(4-methoxyphenyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (3a)

Reaction conditions: 80 °C, 15 min; yield: 24.3 mg (30%); brown solid; mp 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 8.73 (d, *J* = 8.9 Hz, 2 H), 7.06 (d, *J* = 8.9 Hz, 2 H), 5.81 (dd, *J* = 11.3, 2.2 Hz, 1 H), 4.23 (d, *J* = 11.4 Hz, 1 H), 3.89 (s, 3 H), 3.75 (t, *J* = 11.8 Hz, 1 H), 3.03 (qd, *J* = 12.5, 4.0 Hz, 1 H), 2.15 (m, 1 H), 1.93–1.66 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 153.5, 153.1, 152.4, 142.1, 131.6, 129.4, 127.9, 114.2, 84.0, 69.5, 55.5, 29.0, 24.8, 23.4.

MS (ES+): *m*/*z* (%) = 345.3 (100, $[M + H]^+$), 261.2 (60, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}ClN_4O_2$ $[(M + H)^+]$: 345.1118; found: 345.1117.

***N*-Phenyl-9-(tetrahydro-2*H*-pyran-2-yl)-6-[4-(trifluoromethyl)phenyl]-9*H*-purin-8-amine (4b)**

Reaction conditions: 80 °C, 30 min; yield: 25.4 mg (47%); white solid; mp 146–148 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 8.1 Hz, 2 H), 8.79 (s, 1 H), 8.22 (s, 1 H), 7.79 (t, *J* = 7.9 Hz, 4 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 6.01 (dd, *J* = 9.9, 3.1 Hz, 1 H), 4.39 (d, *J* = 11.3 Hz, 1 H), 3.86 (br s, 1 H), 2.03 (m, 3 H), 1.78 (br s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 150.7, 149.7, 146.6, 139.8, 138.6, 129.5, 129.4, 125.5, 125.4, 123.4, 118.8, 83.7, 69.9, 30.8, 25.4, 22.5.

MS (ES+): *m*/*z* (%) = 440.2 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}F_3N_5O$ $[(M + H)^+]$: 440.1698, found: 440.1717.

(*E*)-6-(4-Methoxyphenyl)-8-styryl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (5a)

Reaction conditions: 80 °C, 30 min; yield: 71.6 mg (72%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.92 (d, *J* = 9.1 Hz, 2 H), 8.89 (s, 1 H), 8.10 (d, *J* = 16.0 Hz, 1 H), 7.68–7.65 (m, 2 H), 7.57 (d, *J* = 16.0 Hz, 1 H), 7.46–7.37 (m, 3 H), 7.10 (d, *J* = 9.0 Hz, 2 H), 6.08 (dd, *J* = 11.2, 2.4 Hz, 1 H), 4.32 (dd, *J* = 11.1, 3.2 Hz, 1 H), 3.83–3.78 (s, 3 H), 3.83 (m, 1 H), 2.39–2.26 (m, 1 H), 2.11–2.04 (m, 1 H), 1.87–1.68 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 153.0, 152.9, 152.2, 151.7, 138.8, 136.1, 131.7, 130.5, 129.6, 129.1, 128.8, 127.8, 115.7, 114.2, 82.7, 69.5, 55.5, 31.9, 25.4, 23.4.

MS (ES+): *m*/*z* (%) = 413.1 (100, $[M + H]^+$), 429.1 (50, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{25}N_4O_2$ $[(M + H)^+]$: 413.1978; found: 413.1978.

(*E*)-*N*,*N*-Dimethyl-4-[8-styryl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl]aniline (5b)

Reaction conditions: 80 °C, 30 min; yield: 67.7 mg (66%); dark green solid; mp 202–204 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.89–8.84 (m, 3 H), 8.08 (d, *J* = 16.0 Hz, 1 H), 7.66 (d, *J* = 7.1 Hz, 2 H), 7.57 (d, *J* = 16.0 Hz, 1 H), 7.47–7.36 (m, 3 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 6.07 (d, *J* = 9.2 Hz, 1 H), 4.32 (d, *J* = 11.1 Hz, 1 H), 3.83 (t, *J* = 11.1 Hz, 1 H), 3.09 (s, 6 H), 2.38–2.25 (m, 1 H), 2.09 (s, 1 H), 1.96–1.71 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6, 152.5, 152.2, 151.6, 151.3, 138.1, 136.1, 131.3, 129.9, 129.4, 129.0, 127.6, 123.6, 115.8, 111.7, 82.5, 69.4, 40.2, 31.8, 25.4, 23.3.

MS (ES+): *m*/*z* (%) = 426.3 (100, $[M + H]^+$), 342.2 (35, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{28}N_5O$ $[(M + H)^+]$: 426.2294; found: 426.2276.

(*E*)-8-Styryl-9-(tetrahydro-2*H*-pyran-2-yl)-6-[4-(trifluoromethyl)phenyl]-9*H*-purine (5c)

Reaction conditions: 80 °C, 15 min; yield: 73.9 mg (68%); *E*/*Z* = 8:2; light brown solid; mp 122–124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.03–8.97 (m, 3 H, *E*), 8.77 (d, *J* = 7.8 Hz, 0.54 H, *Z*), 8.13 (d, *J* = 15.8 Hz, 1 H, *E*), 7.84 (d, *J* = 8.3 Hz, 2 H, *E*), 7.68 (d, *J* = 7.0 Hz, 2 H, *E*), 7.58 (d, *J* = 16.0 Hz, 1 H, *E*), 7.49–7.41 (m, 3 H, *E*), 7.18 (d, *J* = 12.9 Hz, 0.27 H, *Z*), 6.96 (d, *J* =

12.5 Hz, 0.27 H, *Z*), 6.10 (d, *J* = 11.1 Hz, 1 H, *E*), 5.89 (d, *J* = 11.4 Hz, 0.27 H, *Z*), 4.34 (d, *J* = 10.4 Hz, 1 H, *E*), 4.23 (d, *J* = 10.3 Hz, 0.27 H, *Z*), 3.84 (t, *J* = 11.2 Hz, 1 H, *E*), 3.76–3.69 (m, 0.27 H, *Z*), 2.65–2.53 (m, 0.27 H, *Z*), 2.41–2.30 (m, 1 H, *E*), 2.12 (m, 1 H, *E*), 1.96 (d, *J* = 14.2 Hz, 1 H, *E*), 1.89–1.63 (m, 4 H, *E*/*Z*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 153.3, 152.1, 151.7, 151.6, 151.2, 140.4, 139.6, 139.4, 135.8, 132.3, 131.9, 131.4, 130.1, 130.0, 129.8, 129.7, 129.1, 128.9, 128.2, 127.8, 126.1, 125.5, 125.3, 122.5, 116.9, 115.3, 83.2, 82.8, 69.5, 31.8, 30.7, 25.3, 25.0, 23.3.

MS (ES+): *m*/*z* (%) = 473.2 (100, $[M + Na]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}F_3N_4O$ $[(M + H)^+]$: 451.1746; found: 451.1753.

(*E*)-6-(3-Nitrophenyl)-8-styryl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (5e)

Reaction conditions: 80 °C, 1 h; yield: 50.3 mg (81%); *E*/*Z* = 95:5; yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 9.29 (d, *J* = 7.9 Hz, 1 H), 8.96 (s, 1 H), 8.34 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 15.9 Hz, 1 H), 7.76–7.67 (m, 3 H), 7.56 (d, *J* = 16.0 Hz, 1 H), 7.49–7.41 (m, 3 H), 6.10 (d, *J* = 10.8 Hz, 1 H), 4.35 (d, *J* = 10.9 Hz, 1 H), 3.85 (t, *J* = 10.5 Hz, 1 H), 2.42–2.30 (m, 1 H), 2.13 (m, 1 H), 2.00–1.76 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6, 151.6, 149.9, 148.8, 140.0, 137.9, 135.6, 131.3, 130.0, 129.7, 129.1, 127.9, 125.1, 124.8, 115.1, 82.8, 69.6, 31.8, 25.4, 23.3.

MS (ES+): *m*/*z* (%) = 428.4 (80, $[M + H]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}N_5O_3$ $[(M + H)^+]$: 428.1723; found: 428.1732.

(*E*)-6-(3-Chlorophenyl)-8-styryl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (5f)

Reaction conditions: 80 °C, 30 min; yield: 54.3 mg (54%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 8.88–8.85 (m, 2 H), 8.13 (d, *J* = 16.0 Hz, 1 H), 7.67 (d, *J* = 6.7 Hz, 2 H), 7.60–7.40 (m, 6 H), 6.09 (dd, *J* = 11.2, 2.1 Hz, 1 H), 4.33 (d, *J* = 10.9 Hz, 1 H), 3.83 (t, *J* = 10.4 Hz, 1 H), 2.39–2.28 (m, 1 H), 2.12 (m, 1 H), 1.97–1.75 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 153.1, 151.5, 151.4, 139.5, 137.9, 135.8, 134.7, 131.1, 130.7, 130.0, 129.7, 129.6, 129.0, 128.3, 128.2, 127.8, 115.3, 82.7, 69.5, 53.6, 31.8, 25.3, 23.3.

MS (ES+): *m*/*z* (%) = 417.2 (100, $[M + H]^+$), 333.1 (50, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}ClN_4O$ $[(M + H)^+]$: 417.1482; found: 417.1475.

(*E*)-6-Phenyl-8-styryl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (5g)

Reaction conditions: 80 °C, 30 min; yield: 42.4 mg (46%); *E*/*Z* = 86:14; yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.95–8.87 (m, 3 H, *E*), 8.67 (s, 0.30 H), 8.13 (d, *J* = 16.0 Hz, 1 H, *E*), 7.68–7.36 (m, 9 H, *E*), 7.14 (d, *J* = 12.4 Hz, 0.30 H, *Z*), 6.95 (d, *J* = 13.1 Hz, 0.15 H, *Z*), 6.09 (d, *J* = 11.0 Hz, 1 H, *E*), 5.86 (d, *J* = 11.6 Hz, 0.15 H, *Z*), 4.33 (d, *J* = 10.8 Hz, 1 H, *E*), 4.21 (d, *J* = 14.3 Hz, 0.15 H, *Z*), 3.84 (t, *J* = 10.4 Hz, 1.15 H, *E*/*Z*), 2.65–2.53 (m, 0.15 H, *Z*), 2.40–2.28 (m, 1 H, *E*), 2.11 (m, 1.15 H, *E*/*Z*), 1.95 (d, *J* = 14.2 Hz, 1.15 H, *E*/*Z*), 1.88–1.68 (m, 3.45 H, *E*/*Z*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 153.1, 152.7, 151.6, 139.1, 136.1, 135.9, 130.8, 130.0, 129.9, 129.8, 129.6, 129.0, 128.7, 128.6, 128.4, 128.2, 127.8, 115.5, 82.7, 69.5, 31.8, 29.8, 25.4, 23.3.

MS (ES+): *m*/*z* (%) = 383.4 (70, $[M + H]^+$), 299.3 (50, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{23}N_4O$ $[(M + H)^+]$: 383.1872; found: 383.1863.

6-(4-Methoxyphenyl)-8-(phenylethynyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (6)

Reaction conditions: 120 °C, 15 min; yield: 16.6 mg (55%); light brown solid; mp 130–132 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.98 (s, 1 H), 8.83 (d, *J* = 8.5 Hz, 2 H), 7.71–7.68 (m, 2 H), 7.46 (m, 3 H), 7.07 (d, *J* = 8.5 Hz, 2 H), 5.98 (dd, *J* = 11.3, 2.3 Hz, 1 H), 4.28 (d, *J* = 11.9 Hz, 1 H), 3.90 (s, 3 H), 3.80 (t, *J* = 11.7 Hz, 1 H), 3.07 (qd, *J* = 12.6, 4.4 Hz, 1 H), 2.17–2.14 (m, 1 H), 1.98–1.65 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 154.5, 153.1, 152.0, 137.5, 132.3, 131.8, 130.6, 130.4, 128.8, 128.3, 121.0, 114.2, 96.7, 83.8, 79.5, 69.5, 55.5, 29.7, 25.1, 23.6.

MS (ES+): *m*/*z* (%) = 411.1 (100, $[M + H]^+$), 327.1 (90, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_4O_2$ $[(M + H)^+]$ 411.1821; found: 411.1811.

6-(4-Methoxyphenyl)-8-phenyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (7a)

Reaction conditions: 80 °C, 30 min; yield: 38.5 mg (60%); beige solid; mp 158–160 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 8.89 (d, *J* = 9.0 Hz, 2 H), 7.96–7.93 (m, 2 H), 7.59–7.57 (m, 3 H), 7.06 (d, *J* = 9.0 Hz, 2 H), 5.64 (d, *J* = 9.3 Hz, 1 H), 4.28 (d, *J* = 9.4 Hz, 1 H), 3.89 (s, 3 H), 3.70 (t, *J* = 11.3 Hz, 1 H), 3.13 (qd, *J* = 13.1, 4.0 Hz, 1 H), 2.08–2.01 (m, 1 H), 1.86–1.61 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.9, 154.9, 154.0, 152.0, 131.7, 130.8, 130.6, 130.2, 130.1, 128.8, 128.6, 114.1, 84.2, 69.1, 55.5, 28.7, 24.3, 23.6.

MS (ES+): *m*/*z* (%) = 387.1 (100, $[M + H]^+$), 303.1 (40, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}N_4O_2$ $[(M + H)^+]$: 387.1821; found: 387.1808.

***N*,*N*-Dimethyl-4-[8-phenyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl]aniline (7b)**

Reaction conditions: 80 °C, 1 h; yield: 44.2 mg (43%); dark green solid; mp 208–210 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 (s, 1 H), 8.86 (d, *J* = 9.1 Hz, 2 H), 7.97–7.93 (m, 2 H), 7.58–7.56 (m, 3 H), 6.82 (d, *J* = 9.2 Hz, 2 H), 5.64 (dd, *J* = 11.3, 2.1 Hz, 1 H), 4.27 (d, *J* = 9.6 Hz, 1 H), 3.70 (t, *J* = 10.9 Hz, 1 H), 3.07 (s, 6 H), 2.05–2.01 (m, 1 H), 1.86–1.61 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 154.2, 153.7, 152.3, 152.1, 131.4, 130.6, 130.5, 130.1, 128.8, 123.6, 111.7, 84.2, 69.1, 40.3, 29.8, 28.7, 24.9, 23.6.

MS (ES+): *m*/*z* (%) = 400.4 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{26}N_5O$ $[(M + H)^+]$: 400.2137; found: 400.2140.

8-Phenyl-9-(tetrahydro-2*H*-pyran-2-yl)-6-[4-(trifluoromethyl)phenyl]-9*H*-purine (7c)

Reaction conditions: 80 °C, 30 min; yield: 61.2 mg (56%); white solid; mp 142–144 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.08 (s, 1 H), 9.00 (d, *J* = 8.4 Hz, 2 H), 7.96–7.93 (m, 2 H), 7.80 (d, *J* = 8.1 Hz, 2 H), 7.61–7.59 (m, 3 H), 5.66 (d, *J* = 11.7 Hz, 1 H), 4.29 (d, *J* = 8.9 Hz, 1 H), 3.71 (t, *J* = 11.2 Hz, 1 H), 3.22–3.11 (m, 1 H), 2.08 (s, 1 H), 1.89–1.63 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 154.5, 152.4, 152.0, 139.3, 132.4, 132.0, 131.5, 131.1, 130.2, 130.1, 129.9, 128.9, 126.0, 125.6, 125.5, 122.4, 84.4, 69.1, 28.6, 24.8, 23.6.

MS (ES+): *m*/*z* (%) = 425.3 (100, [M + H]$^+$), 341.2 (70, [M – THP]$^+$).

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{20}F_3N_4O$ [(M + H)$^+$]: 425.1589; found: 425.1577.

6-(3-Nitrophenyl)-8-phenyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (7e)

Reaction conditions: 80 °C, 30 min; yield: 57.9 mg (56%); brown solid; mp 150–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.75 (s, 1 H), 9.30 (d, *J* = 7.8 Hz, 1 H), 9.09 (s, 1 H), 8.34 (d, *J* = 8.1 Hz, 1 H), 7.97 (m, 2 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.62–7.57 (m, 3 H), 5.67 (dd, *J* = 11.2, 2.0 Hz, 1 H), 4.29 (d, *J* = 11.4 Hz, 1 H), 3.72 (t, *J* = 11.1 Hz, 1 H), 3.25–3.11 (m, 1 H), 2.08–2.05 (m, 1 H), 1.90–1.63 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 154.6, 151.9, 151.0, 148.6, 137.6, 135.8, 131.1, 130.0, 129.6, 128.9, 125.0, 124.5, 84.4, 69.1, 28.6, 24.8, 23.5.

MS (ES+): *m*/*z* (%) = 402.3 (85 [M + H]$^+$), 318.3 [M – THP]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{20}N_5O_3$ [(M + H)$^+$]: 402.1566; found: 402.1563.

6-(3-Chlorophenyl)-8-phenyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (7f)

Reaction conditions: 80 °C, 30 min; yield: 57.7 mg (57%); beige solid; mp 126–128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.05 (s, 1 H), 8.84 (m, 2 H), 7.95 (m, 2 H), 7.60 (m, 3 H), 7.48 (m, 2 H), 5.65 (dd, *J* = 11.3, 2.1 Hz, 1 H), 4.28 (d, *J* = 10.1 Hz, 1 H), 3.71 (t, *J* = 11.0 Hz, 1 H), 3.23–3.09 (m, 1 H), 2.08–2.05 (m, 1 H), 1.89–1.62 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 154.4, 152.6, 151.9, 137.7, 134.8, 131.2, 131.0, 130.8, 130.1, 130.0, 129.9, 129.6, 128.9, 128.4, 84.4, 69.1, 28.6, 24.8, 23.6.

MS (ES+): *m*/*z* (%) = 391.3 (100, [M + H]$^+$), 307.2 (90, [M – THP]$^+$).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}ClN_4OS$ [(M + H)$^+$]: 391.1326; found: 391.1320.

6,8-Diphenyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (7g)

Reaction conditions: 80 °C, 30 min; yield: 35.8 mg (39%); white solid; mp 162–164 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.05 (s, 1 H), 8.86 (d, *J* = 6.5 Hz, 1 H), 7.96–7.93 (m, 2 H), 7.59–7.50 (m, 6 H), 5.65 (dd, *J* = 11.3, 2.1 Hz, 1 H), 4.28 (d, *J* = 9.4 Hz, 1 H), 3.70 (t, *J* = 11.0 Hz, 1 H), 3.15 (qd, *J* = 12.9, 4.2 Hz, 1 H), 2.06–2.02 (m, 1 H), 1.88–1.61 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 154.3, 154.2, 152.0, 135.9, 131.2, 130.9, 130.1, 130.0, 128.9, 128.7, 84.3, 69.1, 28.7, 24.8, 23.6.

MS (ES+): *m*/*z* (%) = 357.3 (90, [M + H]$^+$).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}N_4O$ [(M + H)$^+$]: 357.1715; found: 357.1705.

(*E*)-8-Phenyl-6-(prop-1-en-1-yl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (7h)

Reaction conditions: 80 °C, 30 min; yield: 61.9 mg (75%); light brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.88 (s, 1 H), 7.88 (m, 2 H), 7.66–7.56 (m, 4 H), 7.10 (d, *J* = 15.7 Hz, 1 H), 5.57 (dd, *J* = 11.2, 1.9 Hz, 1 H), 4.26 (d, *J* = 9.4 Hz, 1 H), 3.68 (t, *J* = 11.1 Hz, 1 H), 3.12 (qd, *J* = 12.7, 3.7 Hz, 1 H), 2.07–2.01 (m, 4 H), 1.85–1.59 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.1, 153.7, 153.4, 152.1, 139.5, 130.8, 130.0, 129.9, 128.8, 126.5, 84.2, 69.0, 28.6, 24.8, 23.5, 19.2.

MS (ES+): *m*/*z* (%) = 321.3 (80, [M + H]$^+$), 237.3 (100, [M – THP]$^+$).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{21}N_4O$ [(M + H)$^+$]: 321.1715; found: 321.1705.

8-Chloro-6-(phenylthio)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (8a)

In a dry flask, a solution of lithium diisopropylamide (LDA) was prepared in situ from 1.6 M *n*-BuLi in hexane (5 mL, 8 mmol, 5 equiv) and *i*-Pr_2NH (1.1 mL, 8 mmol, 5 equiv) in freshly distilled THF (10 mL) and stirred for 30 min at –78 °C under argon. A solution of **1** (500 mg, 1.6 mmol, 1 equiv) in freshly distilled THF (10 mL) was added dropwise and the solution was stirred at –78 °C for 1 h. Then, a solution of hexachloroethane (0.91 mL, 8 mmol, 5 equiv) in freshly distilled THF (10 mL) was added dropwise and the solution was stirred at –78 °C for 15 min, warmed to r.t., and stirred for 1 h. Sat. aq NH_4Cl (10 mL) was added and the resulting mixture was extracted with EtOAc (2 × 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with cyclohexane–EtOAc (100:0 → 90:10) to afford the title compound as a beige solid; yield: 456.3 mg (82%); mp 128–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 7.56–7.53 (m, 2 H), 7.38–7.36 (m, 3 H), 5.64 (dd, *J* = 11.2, 1.9 Hz, 1 H), 4.11 (d, *J* = 11.6 Hz, 1 H), 3.64 (t, *J* = 11.7 Hz, 1 H), 2.89 (qd, *J* = 12.4, 3.9 Hz, 1 H), 2.05–1.96 (m, 1 H), 1.81–1.51 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 152.3, 149.6, 141.4, 135.7, 129.6, 129.9, 129.4, 126.9, 84.1, 69.4, 29.0, 24.7, 23.3.

MS (ES+): *m*/*z* (%) = 347.2 (80, [M + H]$^+$), 263.1 (100, [M – THP]$^+$).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{16}ClN_4OS$ [(M + H)$^+$]: 347.0733; found: 347.0730.

(*E*)-6-(Phenylthio)-8-styryl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (10)

A flame-dried tube filled with argon was charged with **1** (450 mg, 1.44 mmol, 1 equiv), CuI (27.4 mg, 0.144 mmol, 10 mol%), phenanthroline (51.9 mg, 0.288 mmol, 20 mol%), $Pd(OAc)_2$ (16.2 mg, 0.072 mmol, 5 mol%), *t*-BuOLi (57.8 mg, 0.722 mmol, 2 equiv), and a solution of distilled β-bromostyrene (527.5 mg, 2.88 mmol, 2 equiv) in 1,4-dioxane (3 mL). The tube was sealed with a rubber cap and heated to 120 °C for 30 min under microwave irradiation. The reaction mixture was taken up in EtOAc (15 mL) and washed with H_2O (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with cyclohexane–EtOAc (100:0 → 90:10). The title compound was obtained as a white solid; yield: 325.4 mg (54%); mp 210–212 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1 H), 8.06 (d, *J* = 16.0 Hz, 1 H), 7.69–7.62 (m, 4 H), 7.49–7.38 (m, 6 H), 5.97 (d, *J* = 11.2 Hz, 1 H), 4.31 (d, *J* = 12.3 Hz, 1 H), 3.80 (t, *J* = 11.5 Hz, 1 H), 2.32 (m, 1 H), 2.07 (m, 1 H), 1.92–1.81 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 151.6, 151.4, 149.3, 138.9, 135.7, 135.5, 130.5, 129.4, 129.3, 129.2, 128.8, 127.5, 114.9, 82.6, 69.2, 31.5, 25.1, 23.1.

MS (ES+): *m*/*z* (%) = 415.1 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{23}N_4OS$ [(M + H)$^+$]: 415.1593; found: 415.1589.

8-(Phenylethynyl)-6-(phenylthio)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (11)

A flame-dried tube filled with argon was charged with **1** (100 mg, 0.320 mmol, 1 equiv), $CuBr·SMe_2$ (9.9 mg, 0.048 mmol, 15 mol%), DPEPhos (25.9 mg, 0.048 mmol, 15 mol%), *t*-BuOLi (51.3 mg, 0.640 mmol, 2 equiv), and a solution of bromophenylacetylene (144.9 mg, 0.800 mmol, 2.5 equiv) in 1,4-dioxane (2 mL). The tube was placed in a preheated oil bath at 120 °C for 1 h. The reaction mixture was taken up in EtOAc (15 mL), washed with H_2O (10 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrat-

ed. The residue was purified by flash chromatography on silica gel eluting with cyclohexane–EtOAc (100:0 → 80:20). The title compound was obtained as a beige solid; yield: 49.3 mg (37%); mp >230 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 7.67 (m, 4 H), 7.45 (m, 6 H), 5.90 (d, *J* = 11.3 Hz, 1 H), 4.26 (d, *J* = 13.0 Hz, 1 H), 3.77 (t, *J* = 11.8 Hz, 1 H), 3.01 (qd, *J* = 12.3, 4.0 Hz, 1 H), 2.14 (d, *J* = 11.0 Hz, 1 H), 1.95–1.64 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 152.9, 148.6, 136.8, 135.7, 132.3, 130.7, 130.4, 129.7, 129.4, 128.8, 127.2, 120.8, 96.8, 84.0, 79.0, 69.4, 29.7, 25.0, 23.4.

MS (ES+): *m*/*z* (%) = 413.1 (100, $[M + H]^+$), 329.1 (750, $[M – THP]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{21}N_4OS$ $[(M + H)^+]$: 413.1436; found. 413.1437.

8-Phenyl-6-(phenylthio)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (12)

In a 100 mL round-bottomed flask were introduced **8b** (1.41 g, 3.22 mmol, 1 equiv), phenylboronic acid (588.9 mg, 4.83 mmol, 1.5 equiv), K_2CO_3 (1.34 g, 9.66 mmol, 3 equiv), $Pd(PPh_3)_4$ (372 mg, 0.322 mmol, 10 mol%), and 1,4-dioxane–H_2O (4:1, 33 mL). The mixture was placed in a preheated oil bath at 100 °C and stirred overnight. Then, the reaction mixture was diluted with EtOAc (10 mL) and washed with H_2O (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel eluting with cyclohexane–EtOAc (100:0 → 85:15) to afford a beige solid; yield: 782 mg (63%); mp 186–188 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1 H), 7.88 (m, 2 H), 7.68 (m, 2 H), 7.57–7.46 (m, 6 H), 5.55 (dd, *J* = 11.2, 1.7 Hz, 1 H), 4.25 (d, *J* = 8.6 Hz, 1 H), 3.66 (t, *J* = 11.1 Hz, 1 H), 3.10 (qd, *J* = 13.0, 4.1 Hz, 1 H), 2.05–2.00 (m, 1 H), 1.84–1.58 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 154.5, 152.0, 150.5, 135.7, 130.8, 130.0, 129.8, 129.5, 129.4, 128.8, 127.6, 84.4, 69.0, 28.7, 24.8, 23.5.

MS (ES+): *m*/*z* (%) = 389.1 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}N_4OS$ $[(M + H)^+]$: 389.1436; found: 389.1437.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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