Supporting Information

Direct $N^9$-arylation of purines with aryl halides

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General Methods
All commercial solvents and reagents were used as obtained without further purification, except for CH$_2$Cl$_2$ which was distilled before use. Water was purified by a Milli-Q system and degassed by letting through nitrogen gas. All reactions were carried out under a nitrogen atmosphere. Semi-automatic flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm), on a Biotage HPFC SP4 Flash Purification System. $^1$H and $^{13}$C NMR spectra were recorded at 300 K on a Bruker Avance III 400 operating at 400 MHz and 101 MHz, respectively, with chemical shifts calibrated relative to solvent residual peaks ($^1$H NMR (DMSO-$d_6$): $\delta$ 2.50 ppm; $^1$H NMR (CDCl$_3$): $\delta$ 7.26 ppm; $^{13}$C NMR (DMSO-$d_6$): $\delta$ 39.52 ppm; $^{13}$C NMR (CDCl$_3$): $\delta$ 77.16 ppm). Assignments are based on chemical shifts and/or COSY, HSQC and NOESY spectra. Mass spectra were recorded on a Bruker MicroTOF-Q II (ESI) spectrometer. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV-light and HPLC using a Dionex 120A C18 column (5µ, 4.6x150 mm) with gradient elution of MeCN and water, both solvents containing 0.05% trifluoroacetic acid (TFA), at a flow rate of 1 mL min$^{-1}$ and UV detection at 230, 254 and 320 nm. HPLC purification was performed by using a Phenomenex Luna C18 5µ column (250x21.20 mm) with gradient elution of MeCN and water, both solvents containing 0.05% TFA, at a flow rate of 20 mL min$^{-1}$.

Synthesis of phenanthroline ligands
Ligands L1(DPPhen)$^1$ and G$^2$ were prepared as described previously.

$^{N^4,N^7}$-Dimethyl-1,10-phenanthroline-4,7-diamine (Ligand L2)

A sealed vial containing 4,7-dichloro-1,10-phenanthroline (300 mg, 1.2 mmol) and methylamine (5.0 mL, 33% in EtOH, 40 mmol) was heated in a microwave reactor (Emrys Creator) at 150 °C for 40 min to give an orange mixture with a precipitate. The precipitate was isolated by filtration, washed with water, ethanol and diethyl ether, and dried under vacuum to give the title compound as a pale yellow solid (255 mg, 89% yield). m.p. > 250 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.73 (s, 2H), 8.53 (d, $J$ = 6.2 Hz, 2H), 8.36 (s, 2H), 6.84 (d, $J$ = 6.3 Hz, 2H), 3.04 ppm (d, $J$ = 4.4 Hz, 6H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 153.6, 145.8, 137.3, 118.2, 117.0, 101.1, 29.7 ppm. HRMS-ESI: m/z calcd for C$_{14}$H$_{15}$N$_4$+: 239.1291 [M+H$^+$], found: 239.1298.

$^{N^4,N^7}$-Bis(2-hydroxyethyl)-1,10-phenanthroline-4,7-diamine (Ligand L3, BHPhen)

A sealed vial containing 4,7-dichloro-1,10-phenanthroline (747 mg, 3.0 mmol), 2-aminoethanol (1.81 mL, 30.0 mmol) and anhydrous EtOH (15.0 mL) was heated in a microwave reactor (Biotage Initiator + EU) at 140 °C for 3 hours to give a red mixture with a precipitate. The precipitate was isolated by filtration, washed sequentially with water, ethanol and diethyl ether, and dried under vacuum to give the title compound as a pale yellow solid (795 mg, 89% yield). m.p. > 250 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.48 (d, $J$ = 5.3 Hz, 2H), 8.06 (s, 2H), 7.19–7.03 (m, 2H), 6.67 (d, $J$ = 5.4 Hz, 2H), 4.91 (s, 2H), 3.70 (t, $J$ = 5.7 Hz, 6H), 3.42–3.35 ppm (m, 4H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 150.2, 149.4, 146.3, 117.4, 117.2, 118.2, 117.0, 101.1, 29.7 ppm. HRMS-ESI: m/z calcd for C$_{16}$H$_{19}$N$_4$O$_2$: 299.1503 [M+H$^+$], found: 299.1514.
Table S1: Ligand screening for the coupling of adenine and iodobenzene

![Chemical structures](https://via.placeholder.com/150)

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Reaction conditions: 1 (0.60 mmol), iodobenzene (0.50 mmol), ligand (10 mol %), CuBr (5 mol %), KOH (1.0 mmol), EtOH/H₂O (1.0 mL, 4:1), heated in a sealed vial to 100 °C or 120 °C for 18 h. <sup>b</sup> Determined from integration of the area under the signal of 2 (HPLC; UV absorption at 254 nm) as the percentage of the total area of the signals corresponding to 1 and 2. <sup>c</sup> Yield of isolated product. ND: not determined.
**Reaction optimisation**

**Entry 1:** A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (L1, 15.9 mg, 0.05 mmol), adenine (1, 81 mg, 0.60 mmol) and KOH (56.1 mg, 1.0 mmol). The tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. EtOH/H2O (4:1 v/v, 1 mL) and iodobenzene (56 µL, 0.50 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 21 hours, the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography (Biotage SNAP 10 g, MeOH in CH2Cl2 (3% → 5%)), to provide 49 mg (46%) of 9-phenyladenine (2).3

Entries 2-19 were performed by the same procedure, but with the modifications indicated in Table 1.

**General procedure for N9-arylation of adenine (Table 2)**

A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (L3, 14.9 mg, 0.05 mmol), sodium ascorbate (10 mg, 0.05 mmol), adenine (67.6 mg, 0.50 mmol), KOH (56.1 mg, 1.0 mmol) and aryl halide (if solid, 0.75 mmol). The reaction tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. DMF/H2O (4:1 v/v, 1 mL) and aryl halide (if liquid, 0.75 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 21 hours (for aryl bromides 48 hours), the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography. In some cases an inorganic iodide salt eluted with the product on the column, which was removed by recrystallisation from H2O or MeOH. Known compounds exhibited 1H and 13C NMR in agreement with previously reported data cited below and ESI-MS was in agreement with the predicted molecular mass.

3-(6-Aminopurin-9-yl)phenol (3a)

Following the general procedure using 3-iodophenol (165 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH2Cl2 (4% → 7%)), followed by a recrystallisation from water. Yield: 101 mg (89%). m.p. >250 °C; 1H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.54 (s, 1H), 8.22 (s, 1H), 7.45–7.29 (m, 4H), 7.29–7.24 (m, 1H), 6.88–6.78 ppm (m, 1H); 13C NMR (101 MHz, DMSO-d6) δ 158.1, 156.3, 153.1, 149.1, 139.6, 136.1, 130.3, 119.4, 114.4, 113.2, 110.0 ppm; HRMS-ESI: m/z calcd for C11H10N5O+: 228.0880 [M+H+], found: 228.0884.
9-(4-Aminophenyl)purin-6-amine (3b)

Using 4-iodoaniline: Following the general procedure using 4-iodoaniline (164 mg, 0.75 mmol) and heating for 21 hours provided the title compound as a pale tan solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (6% → 10%)), followed by a recrystallisation from water. Yield: 100 mg (88%).

Using 4-bromoaniline: Following the general procedure using 4-bromoaniline (129 mg, 0.75 mmol) and heating for 48 hours provided the title compound as a pale tan solid after semi-automated flash chromatography (Biotage SNAP 25 g, 10% MeOH in CH₂Cl₂). Yield: 86 mg (76%).

9-(4-Aminophenyl)purin-6-amine (3b): m.p. > 250 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.32 (s, 1H), 8.14 (s, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.26 (s, 2H), 6.69 (d, J = 8.6 Hz, 2H), 5.36 ppm (s, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.1, 152.7, 149.3, 148.4, 140.0, 124.6, 123.5, 119.0, 113.8 ppm; HRMS-ESI: m/z calcd for C₁₁H₁₁N₆⁺: 227.1040 [M+H⁺], found: 227.1042.

3-(6-Aminopurin-9-yl)benzoic acid (3c)

Following the general procedure using 3-iodobenzoic acid (186 mg, 0.75 mmol) provided the title compound as a tan solid after semi-automated flash chromatography (Biotage SNAP 25 g, MeOH/AcOH 2:1 in CH₂Cl₂ (6% → 12%)), followed by a recrystallisation from MeOH. Yield: 84 mg (66%), m.p. >250 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 13.32 (s, 1H), 8.68 (s, 1H), 8.51 (s, 1H), 8.32–8.20 (m, 1H), 8.19–8.11 (m, 1H), 8.07–7.94 (m, 1H), 7.81–7.68 (m, 1H), 7.42 ppm (s, 2H); HRMS-ESI: m/z calcd for C₁₂H₁₀N₅O₂⁺: 256.0829 [M+H⁺], found: 256.0831.
3-(6-Aminopurin-9-yl)benzonitrile (3d)

Following the general procedure using 3-iodobenzonitrile (172 mg, 0.75 mmol) provided the title compound as an off-white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (4% → 8%)), followed by a recrystallisation from H₂O. Yield: 91 mg (77%). m.p. >250 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.71 (s, 1H), 8.48 (t, J = 1.7 Hz, 1H), 8.40–8.32 (m, 1H), 8.25 (s, 1H), 7.95–7.87 (m, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.47 ppm (s, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.4, 153.4, 149.0, 139.3, 135.9, 130.8, 130.8, 127.2, 125.8, 119.3, 118.1, 112.3 ppm; HRMS-ESI: m/z calcld for C₁₂H₉N₆⁺: 237.0883 [M+H⁺], found: 237.0881.

9-(3-(Trifluoromethyl)phenyl)purin-6-amine (3e)

Following the general procedure using 1-iodo-3-(trifluoromethyl)benzene (204 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (4% → 6%)). Yield: 116.5 mg (83%). m.p. 226-228°C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.74 (s, 1H), 8.40 (s, 1H), 8.33–8.26 (m, 1H), 8.25 (s, 1H), 7.88–7.76 (m, 2H), 7.46 ppm (s, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.4, 153.4, 149.1, 139.5, 135.9, 130.8, 130.2 (q, J = 32.2 Hz), 126.4, 123.8 (q, J = 272.5 Hz), 123.8 (q, J = 3.6 Hz), 119.3, 119.2 ppm (q, J = 3.9 Hz); HRMS-ESI: m/z calcld for C₁₂H₉F₃N₅⁺: 280.0805 [M+H⁺], found: 280.0818.

9-(3-Nitrophenyl)purin-6-amine (3f)

Following the general procedure using 1-iodo-3-nitrobenzene (187 mg, 0.75 mmol) provided the title compound as a yellow solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 5%)), followed by a recrystallisation from water. Yield: 104 mg (81%). m.p. >250 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.96 (t, J = 2.2 Hz, 1H), 8.80 (s, 1H), 8.48–8.40 (m, 1H), 8.31–8.24 (m, 2H), 7.89 (t, J = 8.2 Hz, 1H), 7.49 ppm (s, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.4, 153.4, 149.1, 148.3, 139.4, 136.2, 131.0, 128.4, 121.7, 119.3, 117.1 ppm; HRMS-ESI: m/z calcld for C₁₁H₉N₆O₂⁺: 257.0781 [M+H⁺], found: 257.0794.
9-(2-Chlorophenyl)purin-6-amine (3g)

Following the general procedure using 1-chloro-2-iodobenzene (179 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 5%)). Yield: 2.2 mg (2%). m.p. 233-234 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.33 (s, 1H), 8.11 (s, 1H), 7.79–7.73 (m, 1H), 7.69–7.64 (m, 1H), 7.64–7.53 (m, 2H), 7.39 ppm (s, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.2, 153.2, 150.2, 140.6, 132.1, 131.0, 130.7, 130.2, 130.1, 128.3, 118.2 ppm; HRMS-ESI: m/z calcd for C₁₁H₉ClN₅+: 246.0541 [M+H⁺], found: 246.0553.⁴

9-(o-Tolyl)purin-6-amine (3h)

Following the general procedure using 2-iodotoluene (164 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 5%). Yield: 7.5 mg (7%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.26 (s, 1H), 8.11 (s, 1H), 7.49–7.45 (m, 2H), 7.40–7.37 (m, 2H), 7.35 (s, 2H), 2.08 ppm (s, 3H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.3, 153.0, 150.1, 140.8, 134.9, 133.7, 131.0, 129.2, 127.8, 126.8, 118.4, 17.5 ppm; HRMS-ESI: m/z calcd for C₁₂H₁₂N₅+: 226.1087 [M+H⁺], found: 226.1088.⁵

9-(Pyridin-2-yl)purin-6-amine (3i)

Following the general procedure using 2-bromopyridine (118 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (4% → 6%)). Yield: 87 mg (82%). m.p. 230-231 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.88 (s, 1H), 8.62–8.53 (m, 2H), 8.29 (s, 1H), 8.15–8.07 (m, 1H), 7.54–7.40 ppm (m, 3H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.4, 153.3, 148.7, 148.7, 148.2, 139.5, 138.0, 122.7, 119.9, 115.1 ppm; HRMS-ESI: m/z calcd for C₁₀H₉N₅+: 213.0883 [M+H⁺], found: 213.0876.

* ¹H NMR is not in agreement with that reported by Tao et al.⁵ No ¹³C NMR has been reported previously.
9-(6-Methylpyridin-3-yl)purin-6-amine (3j)

Following the general procedure using 5-bromo-2-methylpyridine (129 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 6%)). Yield: 92 mg (81%). m.p. 259-260 °C (dec.); ¹H NMR (400 MHz, DMSO-d₆) δ 8.95 (d, J = 2.4 Hz, 1H), 8.61 (s, 1H), 8.27 – 8.16 (m, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.43 (s, 2H), 2.55 ppm (s, 3H); ¹³C NMR (101 MHz, DMSO-d₆) δ 157.0, 156.4, 153.3, 149.2, 143.1, 139.4, 130.9, 129.6, 123.4, 119.1, 23.7 ppm; HRMS-ESI: m/z calcd for C₁₁H₁₁N₆⁺: 227.1040 [M+H⁺], found: 227.1029.

9-(Thiophen-3-yl)purin-6-amine (3k)

Following the general procedure using 3-bromothiophene (122 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (4% → 8%)). Yield: 83 mg (76%). m.p. 218-219 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.65 (s, 1H), 8.24 (s, 1H), 8.16 – 8.08 (m, 1H), 7.84 – 7.73 (m, 2H), 7.40 ppm (s, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.3, 153.3, 148.7, 139.3, 133.3, 127.1, 121.8, 119.0, 114.5 ppm; HRMS-ESI: m/z calcd for C₉H₈N₅S⁺: 218.0495 [M+H⁺], found: 218.0487.

4-(6-Aminopurin-9-yl)phenol (3l)

Following the general procedure using 4-bromophenol (130 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 25 g, 10% MeOH in CH₂Cl₂). Yield: 72 mg (63%). m.p. 303-305 °C (dec.); ¹H NMR (400 MHz, DMSO-d₆) δ 9.79 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.31 (s, 2H), 6.93 ppm (d, J = 8.8 Hz, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 156.8, 156.3, 153.0, 149.2, 139.9, 126.6, 124.9, 119.0, 115.8 ppm; HRMS-ESI: m/z calcd for C₁₁H₁₀N₅O⁺: 228.0873 [M+H⁺], found: 228.0873.
1-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-one (3m)

Following the general procedure using 4'-bromoacetophenone (149 mg, 0.75 mmol) provided the title compound as a yellow solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 5%). Yield: 98 mg (77%). m.p. >250 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.74 (s, 1H), 8.25 (s, 1H), 8.19–8.14 (m, 4H), 7.45 (s, 2H), 2.64 ppm (s, 3H); ¹³C NMR (101 MHz, DMSO-d₆) δ 197.0, 156.4, 153.4, 149.1, 139.3, 139.0, 135.1, 129.6, 122.0, 119.5, 26.8 ppm; HRMS-ESI: m/z calcd for C₁₃H₁₂N₅O+: 254.1036 [M+H⁺], found: 254.1047.

9-(4-Fluorophenyl)purin-6-amine (3n)

Following the general procedure using 1-bromo-4-fluorobenzene (131 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 5%)). Yield: 96 mg (84%). m.p. 255-256 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.56 (s, 1H), 8.20 (s, 1H), 7.96–7.90 (m, 2H), 7.47–7.42 (m, 2H), 7.39 ppm (s, 2H); ¹³C NMR (101 MHz, DMSO-d₆) δ 160.9 (d, J = 244.4 Hz), 156.3, 153.2, 149.1, 139.7, 131.5 (d, J = 2.8 Hz), 125.2 (d, J = 8.6 Hz), 119.1, 116.3 ppm (d, J = 22.9 Hz); HRMS-ESI: m/z calcd for C₁₁H₉FN₅+: 230.0836 [M+H⁺], found: 230.0836.

2-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-ol (3o)

Following the general procedure using 4-bromophenylethyl alcohol (151 mg, 0.75 mmol) provided the title compound as a white solid after semi-automated flash chromatography (Biotage SNAP 25 g, MeOH in CH₂Cl₂ (5% → 8%)), followed by recrystallisation from H₂O. Yield: 105 mg (82%). m.p. >250 °C; ¹H NMR (400 MHz, DMSO-d₆) δ 8.53 (s, 1H), 8.20 (s, 1H), 7.80–7.73 (m, 2H), 7.44–7.40 (m, 2H), 7.37 (s, 2H), 4.70 (t, J = 5.2 Hz, 1H), 3.65 (td, J = 6.9, 5.3 Hz, 2H), 2.80 ppm (t, J = 6.9 Hz, 2H); ¹³C NMR (101 MHz, DMSO-
\[ \delta 156.3, 153.1, 149.2, 139.6, 139.1, 133.1, 129.9, 122.8, 119.2, 62.0, 38.5 \text{ ppm; HRMS-ESI: } m/z \text{ calcd for } C_{13}H_{14}N_5O^+: 256.1193 \left[ M+H^+ \right], \text{ found: 256.1204.} \]

9-(4-(2-Aminoethyl)phenyl)purin-6-amine (3p)

Following the general procedure using 4-bromophenethyl amine (151 mg, 0.75 mmol) and EtOH/H_2O (1 mL, 4:1 v/v) as solvent provided the title compound as a pale yellow solid after semi-automated flash chromatography (Biotage SNAP 10 g, 24% NH_3(aq)/MeOH 1:9 in CH_2Cl_2 (5% \rightarrow 8%)). Yield: 101 mg (79%). m.p. 219-220 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta 8.53 \text{ (s, 1H), 8.19 \text{ (s, 1H), 7.82–7.74 \text{ (m, 2H), 7.42–7.38 \text{ (m, 2H), 7.37 \text{ (s, 2H), 7.21 \text{ (t, } J = 6.9 \text{ Hz, 2H), 2.71 \text{ (t, } J = 7.0 \text{ Hz, 2H), 1.47 pp}} \text{ (s br, 2H); }^{13}C \text{ NMR (101 MHz, DMSO-}d_6\text{)} \delta 156.3, 153.01, 149.1, 139.9, 139.6, 133.0, 129.6, 122.9, 119.2, 43.6, 39.3 \text{ ppm (merged with DMSO); HRMS-ESI: } m/z \text{ calcd for } C_{13}H_{15}N_6^+: 255.1353 \left[ M+H^+ \right], \text{ found: 255.1355.} \]

N-(4-(6-Aminopurin-9-yl)phenethyl)formamide

Following the general procedure using 4-bromophenethyl amine (151 mg, 0.75 mmol) and DMF/H_2O (1 mL, 4:1 v/v) as solvent provided N-(4-(6-aminopurin-9-yl)phenethyl)formamide as a pale yellow solid after semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH_2Cl_2 (5% \rightarrow 9%)). Yield: 112 mg (79%). m.p. 169-170 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta 8.55 \text{ (s, 1H), 8.21 \text{ (s, 1H), 8.11 \text{ (s, 1H), 8.02 \text{ (d, } J = 1.6 \text{ Hz, 1H), 7.81 \text{ (d, } J = 8.5 \text{ Hz, 2H), 7.46–7.40 \text{ (m, 2H), 7.37 \text{ (s, 2H), 3.42–3.38 \text{ (m, 2H, 2.82 pp}} \text{ (t, } J = 7.1 \text{ Hz, 2H); }^{13}C \text{ NMR (101 MHz, DMSO-}d_6\text{)} \delta 161.1, 156.3, 153.1, 149.1, 139.6, 138.7, 133.3, 129.7, 122.9, 119.3, 38.6, 34.5 \text{ ppm. HRMS-ESI: } m/z \text{ calcd for } C_{14}H_{15}N_6O^+: 283.1302 \left[ M+H^+ \right], \text{ found: 283.1295.} \]
Synthetic procedure for N-arylation of various purines (Table 3)

Preparation of 8-methyltheophylline (4d)

A sealed vial containing 5,6-diamino-1,3-dimethyluracil hydrate (565 mg, 3.0 mmol), acetic anhydride (0.31 mL, 3.3 mmol) and pyridine (6 mL) was heated in a microwave reactor (Emrys Creator) at 110 °C for 20 min to give a red mixture with a precipitate. The solvent was evaporated under vacuum to dryness. The resulting amide was converted to benzimidazole by treatment with t-BuOK (1.01 g, 9.0 mmol) in isopropyl alcohol (14 mL) at 60 °C. After 16 hours, the reaction mixture was cooled to RT, silica (5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography (Biotage SNAP 25 g, MeOH in CH₂Cl₂ (3% → 4.5%)), to provide 382 mg (66%) of 8-methyltheophylline (4d). m.p. 322-324 °C (lit. 325 °C 7); ¹H NMR (400 MHz, DMSO) δ 3.39 (s, 3H), 3.21 (s, 3H), 2.36 ppm (s, 3H); ¹³C NMR (101 MHz, DMSO-d₆) δ 153.9, 151.2, 150.4, 106.1, 29.7, 27.6, 14.3 ppm. HRMS-ESI: m/z calcld for C₁₄H₁₅N₆O⁺: 283.1302 [M+H⁺], found: 283.1295.

General procedure A - purine, 2,6-diaminopurine, theophylline and 8-methyltheophylline (4a-d): A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (L₃, 14.9 mg, 0.05 mmol), sodium ascorbate (10 mg, 0.05 mmol), the purine substrate (4a, 4b, 4c or 4d, 0.50 mmol) and KOH (56.1 mg, 1.0 mmol). The tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. Then DMF/H₂O (4:1 v/v, 1 mL) and aryl halide (0.75 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 21 hours or 48 hours, the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture was concentrated to dryness on a rotary evaporator. The dry residue was purified by semi-automated flash column chromatography.

General procedure B - guanine and hypoxanthine (4e and 4f): A reaction tube equipped with a magnetic stirring bar was charged with CuBr (3.6 mg, 0.025 mmol), ligand (L₃, 14.9 mg, 0.05 mmol), the purine substrate (4e or 4f, 0.50 mmol) and KOH (56.1 mg, 1.0 mmol). The tube was sealed with a rubber septum, evacuated and back-filled with nitrogen three times. Then DMSO/H₂O (4:1 v/v, 1 mL) and aryl halide (0.75 mmol) was added by syringe. The rubber septum was exchanged with a cap designed to withstand moderate pressure under a stream of nitrogen and the reaction tube was placed in a preheated oil bath at 120 °C. After 6-48 hours, the reaction mixture was cooled to RT, silica (1.5 g) was added and the mixture concentrated to dryness on a rotary evaporator at 60 °C. The dry residue was purified by semi-automated flash column chromatography.
9-Phenylpurine (5a) and 7-phenylpurine (6a)

Using iodobenzene: Synthesised by general procedure A using iodobenzene (153 mg, 0.75 mmol) and heating for 21 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH\textsubscript{2}Cl\textsubscript{2} (2% → 3%)) gave 61 mg (62%) of 9-phenylpurine (5a) and 7 mg (7%) of 7-phenylpurine (6a), both products as pale brown solids.

Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH\textsubscript{2}Cl\textsubscript{2} (2% → 3%)) gave 63 mg (64%) of 9-phenylpurine (5a) and 3 mg (3%) of 7-phenylpurine (6a), both products as pale brown solids.

9-phenylpurine (5a): \( ^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta 9.24 \text{ (s, 1H), 9.05 \text{ (s, 1H), 8.38 \text{ (s, 1H), 7.78–7.67 \text{ (m, 2H), 7.66–7.55 \text{ (m, 2H), 7.53–7.44 \text{ ppm (m, 1H).} \) \( ^{13}\text{C NMR (101 MHz, CDCl}_3 \) \( \delta 153.5, 151.2, 149.4, 144.3, 134.7, 134.3, 130.2, 128.7, 123.6 \text{ ppm; HRMS-ESI: } m/z \text{ caleld for C}_{11}\text{H}_{9}\text{N}_4^+: 197.0822 [M+H]^+, \text{ found: 197.0823.}^{†}\)

7-phenylpurine (6a): \( ^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta 9.21 \text{ (s, 1H), 9.06 \text{ (s, 1H), 8.47 \text{ (s, 1H), 7.68–7.62 \text{ (m, 2H), 7.59–7.51 \text{ ppm (m, 3H).} ^{13}\text{C NMR (101 MHz, CDCl}_3 \) \( \delta 161.3, 154.0, 146.9, 140.8, 135.0, 130.8, 129.4, 125.3, 123.7 \text{ ppm; HRMS-ESI: } m/z \text{ caleld for C}_{11}\text{H}_{9}\text{N}_4^+: 197.0822 [M+H]^+, \text{ found: 197.0826.}^{†}\)

9-Phenylpurine-2,6-diamine (5b)

Using iodobenzene: Synthesised by general procedure A using iodobenzene (153 mg, 0.75 mmol) and heating for 21 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH\textsubscript{2}Cl\textsubscript{2} (4% → 5%) gave 106 mg (94%) of the title compound as a white solid.

Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH\textsubscript{2}Cl\textsubscript{2} (4% → 5%) gave 68 mg (60%) of the title compound as a white solid.

\( ^{†} \text{ In accordance with the } ^1\text{H-NMR reported by Hayashi et al. No } ^{13}\text{C-NMR has been reported previously.}^{†}\)

\( ^{‡} \text{ H-NMR reported by Laufer et al. used DMSO-}d_6 \text{ as solvent. No } ^{13}\text{C-NMR has been reported previously.}^{†}\)
7-Phenyltheophylline (6c)

Using iodosobenzene: Synthesised by general procedure A using iodosobenzene (153 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (50% → 100%)) gave 101 mg (79%) of the title compound as a white solid.10

Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (50% → 100%)) gave 100 mg (78%) of the title compound as a white solid.

8-methyl-7-phenyltheophylline (6d)

Using iodosobenzene: Synthesised by general procedure A using iodosobenzene (153 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (60% → 100%)) gave 16 mg (12%) of the title compound as a white solid.

Using bromobenzene: Synthesised by general procedure A using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, EtOAc in PE (60% → 100%)) gave 13 mg (10%) of the title compound as a white solid.

m.p. 230-231 °C (lit. 235 °C 11); 1H NMR (400 MHz, CDCl 3) δ 7.57 – 7.49 (m, 3H), 7.38 – 7.28 (m, 2H), 3.63 (s, 3H), 3.34 (s, 3H), 2.36 ppm (s, 3H). 13C NMR (101 MHz, CDCl 3) δ 154.3, 151.8, 151.2, 148.6, 135.0, 129.6, 129.5, 127.1, 108.3, 29.9, 28.1, 13.9 ppm; HRMS-ESI: m/z calced for C 14H15N4O2 +: 271.1190 [M+H+] , found: 271.1184.

9-Phenylguanine (5e) and 7-phenylguanine (6e)

Using iodosobenzene: Synthesised by general procedure B using iodosobenzene (153 mg, 0.75 mmol) and heating for 21 hours. Purification by semi-automated flash chromatography (Biotage SNAP 25 g, MeOH in CH2Cl2 (4% → 8%)) gave a mixture of two isomers: 9-phenylguanine (5e) and 7-phenylguanine (6e) that were separated on HPLC (5-22% MeCN in H2O (0-5 min), R6(6e) = 3.9 min, R6(5e) = 4.7 min) to give 68 mg (60%) of 5e as a white solid and 24 mg (21%) of 6e as a pale yellow solid.3,12
Using bromobenzene: Synthesised by general procedure B using bromobenzene (118 mg, 0.75 mmol) and heating for 48 hours. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (5% → 10%)) gave a mixture of two isomers: 9-phenylguanine (5e) and 7-phenylguanine (6e) that were separated on HPLC (5-22% MeCN in H₂O (0-5 min), Rₜ(6e) = 3.9 min, Rₜ(5e) = 4.7 min) to give 67 mg (59%) of 5e as a white solid and 15 mg (13%) of 6e as a pale yellow solid.

9-Phenylhypoxanthine (5f) and 7-phenylhypoxanthine (6f)

Using iodobenzene: Synthesised by general procedure B using iodobenzene (153 mg, 0.75 mmol) and heating for 3 hours, after which the starting material was almost consumed, and diarylated products had started to form. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 5%)) gave a mixture of two isomers: 9-phenylhypoxanthine (5f) and 7-phenylhypoxanthine (6f) that were separated on HPLC (10-21% MeCN in H₂O (0-6 min), Rₜ(6f) = 4.4 min, Rₜ(5f) = 5.3 min) to give 46 mg (43%) of 5f and 15 mg (14%) of 6f, both as white solids.

Using bromobenzene: Synthesised by general procedure B using bromobenzene (118 mg, 0.75 mmol) and heating for 32 hours, after which the starting material was almost consumed, and diarylated products had started to form. Purification by semi-automated flash chromatography (Biotage SNAP 10 g, MeOH in CH₂Cl₂ (3% → 5%)) gave a mixture of two isomers: 9-phenylhypoxanthine (5f) and 7-phenylhypoxanthine (6f) that were separated on HPLC (10-21% MeCN in H₂O (0-6 min), Rₜ(6f) = 4.4 min, Rₜ(5f) = 5.3 min) to give 51 mg (48%) of 5f and 12 mg (11%) of 6f, both as white solids.

9-phenylhypoxanthine (5f): m.p. 317-318 °C (lit. 316-318 °C); ¹H NMR (400 MHz, DMSO-d₆) δ 12.47 (s, 1H), 8.47 (s, 1H), 8.09 (s, 1H), 7.83–7.69 (m, 2H), 7.67–7.55 (m, 2H), 7.55–7.44 ppm (m, 1H). ¹³C NMR (101 MHz, DMSO-d₆) δ 156.7, 147.9, 146.1, 139.4, 134.5, 129.5, 128.1, 124.8, 123.8 ppm; HRMS-ESI: m/z calcd for C₁₁H₉N₄O+: 213.0771 [M+H⁺], found: 213.0761.

7-phenylhypoxanthine (6f): m.p. 295-296 °C (lit. 295-297 °C); ¹H NMR (400 MHz, DMSO-d₆) δ 12.43 (s, 1H), 8.51 (s, 1H), 8.06 (s, 1H), 7.68–7.59 (m, 2H), 7.57–7.51 (m, 2H), 7.51–7.44 ppm (m, 1H). ¹³C NMR (101 MHz, DMSO-d₆) δ 158.2, 153.6, 145.2, 144.0, 135.4, 128.9, 128.2, 125.2, 114.6 ppm; HRMS-ESI: m/z calcd for C₁₁H₉N₄: 213.0771 [M+H⁺], found: 213.0761.

References
NMR-spectra

$N^4,N^7$-dimethyl-1,10-phenanthroline-4,7-diamine (Ligand L2)
$N^4,N^7$-Bis(2-hydroxyethyl)-1,10-phenanthroline-4,7-diamine (Ligand L3).
9-phenyladenine (2)
3-(6-Aminopurin-9-yl)phenol (3a)
3-(6-Aminopurin-9-yl)benzoic acid (3c)
3-(6-Aminopurin-9-yl)benzonitrile (3d)
9-(3-(Trifluoromethyl)phenyl)purin-6-amine (3e)
9-(3-Nitrophenyl)purin-6-amine (3f)
9-(2-Chlorophenyl)purin-6-amine (3g)
9-(o-Tolyl)purin-6-amine (3h)
9-(Pyridin-2-yl)purin-6-amine (3i)
9-(6-Methylpyridin-3-yl)purin-6-amine (3j)
9-(Thiophen-3-yl)purin-6-amine (3k)

![NMR Spectra](image)

**NMR Data:**
- **Resonance Peaks:**
  - 8.65 ppm
  - 8.12 ppm
  - 8.11 ppm
  - 7.70 ppm
  - 7.79 ppm
  - 7.76 ppm
  - 7.40 ppm
- **Chemical Shifts:**
  - N 114.5 ppm
  - N 119.0 ppm
  - N 121.8 ppm
  - S 127.1 ppm
  - S 129.0 ppm
  - S 134.5 ppm
- **Additional Observations:**
  - NH2: 3.36 ppm, 2.50 ppm
4-(6-Aminopurin-9-yl)phenol (3l)
1-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-one (3m)
9-(4-Fluorophenyl)purin-6-amine (3n)
2-(4-(6-Aminopurin-9-yl)phenyl)ethan-1-ol (3o)
9-(4-(2-Aminoethyl)phenyl)purin-6-amine (3p)
HSQC of 3p:

\[
\text{Structure Image}
\]

{7.78,122.88}, {7.41,129.56}, {8.53,139.63}, {8.19,153.10}, {2.82,43.59}, {2.72,39.34}, {2.50,39.52}
N-(4-(6-Aminopurin-9-yl)phenethyl)formamide
9-Phenylpurine (5a)
NOESY of 5a
9-Phenylpurine-2,6-diamine (5b)
9-Phenylguanine (5e)
9-Phenylhypoxanthine (5f)
HMBC of 5f
NOESY of 6a
7-Phenytheophylline (6c)
8-methyl-7-phenyltheophylline (6d)
7-phenylguanine (6e)
7-Phenylhypoxanthine (6f)