Supporting Information

“A One-Pot Two-Step Microwave Assisted Reaction in Constructing 4,5-Disubstituted Pyrazolopyrimidines”

Tom Y.H. Wu, Peter G. Schultz*, Sheng Ding*

The Scripps Research Institute, La Jolla, CA 92037, USA.

General. All reagents and solvents were purchased at highest commercial quality and used without further purification. Purity of compounds was assessed by reverse-phase liquid chromatography mass spectrometry (4 minutes elution using 5% to 95% acetonitrile in water) with an UV detector at $\lambda = 255$ nm and an electrospray ionization source. All microwave reactions were carried out in sealed tubes in an Emrys Optimizer microwave reactor (Personal Chemistry Inc). NMR spectra were recorded on Bruker-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Preparation of 4 (and 6).

4-Chloropyrazolopyrimidine **5** (400 mg, 2.60 mmol) and *N*-bromosuccinimide (509 mg, 2.86 mmol) were suspended in acetonitrile (4.5 mL). The reaction vessel was sealed and heated in a microwave reactor to 100°C for 10 minutes. After cooling to ambient temperature, the solvent was evaporated in *vacuo*. The resulting solids were taken up in ethyl acetate and washed once with water, once with brine, dried over anhydrous MgSO_4 , and concentrated in *vacuo*. The white solid (600 mg, 99%) was used in the subsequent reactions without further purification.

Compound **4**: ^1H NMR (500 MHz, *d*-DMSO) δ 14.84 (s, 1H), 8.85 (s, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 232.9 (calcd 231.9).

Compound **6**: ^1H NMR (500 MHz, *d*-DMSO) δ 12.91 (s, 1H), 8.56 (s, 1H), 7.88 (s, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 231.9 (calcd 230.9).

Representative preparation of 5 (and 7) using the one-pot two-step microwave assisted reaction.

5-Bromo-4-chloropyrazolopyrimidine **4** (15 mg, 0.649 mmol), 1,3-phenyldiamine (11 mg, 0.0974 mmol, entry 17), and glacial acetic acid (4 μL) were suspended in dioxane (0.7 mL). The reaction vessel was sealed and heated in a microwave reactor to 150°C for ten minutes. After cooled to ambient temperature, 3-aminophenylboronic acid (26 mg, 0.195 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$ (9 mg, 0.013 mmol), and K_3PO_4 (41 mg, 0.195 mmol) were added to the reaction mixture as solids. The vessel was sealed and heat to 180°C for

another 10 minutes. After cooling to ambient temperature, the crude reaction mixture was subjected to HPLC purification using a C18 reverse phase column with a ten minute 0 to 70% AcCN/H₂O gradient. The fraction(s) containing the desired product was evaporated in *vacuo* to give 19 mg of solids (89%).

Compound **5** (Table 1):

Entry 1: ¹H NMR (500 MHz, *d*-MeOH) δ 8.55 (s, 1H), 7.78 (s, 1H), 7.54-7.58 (m, 2H), 7.49 (t, J = 7.3 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.32-7.37 (m, 2H), 7.21 (d, J = 7.0 Hz, 1H), 2.46 (s, 3H). LC-ESMS observed [M+H]⁺ 336.1 (calcd 335.1).

Entry 2: ¹H NMR (500 MHz, *d*-MeOH) δ 8.54 (s, 1H), 7.84 (s, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.33-7.39 (m, 2H), 7.21-7.22 (m, 2H), 7.16 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H). LC-ESMS observed [M+H]⁺ 338.1 (calcd 337.1).

Entry 3: ¹H NMR (500 MHz, *d*-DMSO) δ 8.49 (s, 2H), 7.88 (s, 1H), 7.77-7.79 (m, 2H), 7.54-7.57 (m, 2H), 7.44-7.50 (m, 2H), 7.33 (t, J = 8.1 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H). LC-ESMS observed [M+H]⁺ 322.1 (calcd 321.1).

Entry 4: ¹H NMR (500 MHz, *d*-MeOH) δ 8.48 (s, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.74 (s, 1H), 7.69 (s, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H). LC-ESMS observed [M+H]⁺ 406.1 (calcd 405.1).

Entry 5: ¹H NMR (500 MHz, *d*-MeOH) δ 8.49 (s, 1H), 7.79 (s, 1H), 7.61-7.67 (m, 3H), 7.29-7.33 (m, 2H), 7.31 (t, J = 8.1 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H). LC-ESMS observed [M+H]⁺ 337.1 (calcd 336.1).

Entry 6: ¹H NMR (500 MHz, *d*-DMSO) δ 8.61 (s, 1H), 8.50 (s, 1H), 8.32 (s, 1H), 8.10 (s, 1H), 7.97-7.99 (m, 2H), 7.90 (d, J = 7.9 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 9.7 Hz, 1H), 7.44 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H). LC-ESMS observed [M+H]⁺ 365.1 (calcd 364.1).

Entry 7: ¹H NMR (500 MHz, *d*-DMSO) δ 8.80 (s, 1H), 8.51 (s, 1H), 8.31 (s, 1H), 8.01-8.03 (m, 2H), 7.81 (s, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 2.58 (s, 3H). LC-ESMS observed [M+H]⁺ 364.1 (calcd 363.1).

Entry 8: ¹H NMR (500 MHz, *d*-DMSO) δ 8.77 (s, 1H), 8.51 (s, 1H), 8.05 (s, 1H), 7.83 (s, 1H), 7.76-7.80 (m, 2H), 7.68-7.70 (m, 2H), 7.63 (t, J = 7.7 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.40-7.43 (m, 2H), 7.36 (t, J = 7.1 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H). LC-ESMS observed [M+H]⁺ 398.1 (calcd 397.1).

Entry 9: ¹H NMR (500 MHz, *d*-MeOH) δ 8.52 (s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 7.42-7.47 (m, 2H), 7.31 (t, J = 8.1 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 3.90 (s, 3H). LC-ESMS observed [M+H]⁺ 395.1 (calcd 394.1).

Entry 10: ^1H NMR (500 MHz, *d*-DMSO) δ 8.49 (s, 1H), 8.47 (s, 1H), 7.88 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.27 (s, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.07-7.11 (m, 2H), 6.10 (s, 2H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 366.1 (calcd 365.1).

Entry 11: ^1H NMR (500 MHz, *d*-DMSO) δ 8.79 (s, 1H), 8.50 (s, 1H), 7.84 (s, 1H), 7.78 (s, 1H), 7.71 (d, J = 7.0 Hz, 1H), 7.48-7.56 (m, 4H), 7.33 (t, J = 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 356.1 (calcd 355.1).

Entry 12: ^1H NMR (500 MHz, *d*-MeOH) δ 8.49 (s, 1H), 8.21 (s, 1H), 7.81-7.84 (m, 2H), 7.60-7.69 (m, 3H), 7.48 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 347.1 (calcd 346.1).

Entry 13: ^1H NMR (500 MHz, *d*-MeOH) δ 8.44 (s, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.23-7.25 (d, J = 6.8 Hz, 1H), 7.14-7.20 (m, 2H), 6.93 (d, J = 9.1 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 319.1 (calcd 318.1).

Entry 14: ^1H NMR (500 MHz, *d*-MeOH) δ 8.50 (s, 1H), 8.10 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.59-7.61 (m, 2H), 7.57 (s, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 6.2 Hz, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 371.1 (calcd 370.1).

Entry 15: ^1H NMR (500 MHz, *d*-MeOH) δ 8.47 (s, 1H), 8.03 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.51-7.53 (m, 2H), 7.47 (s, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 346.1 (calcd 345.1).

Entry 16: ^1H NMR (500 MHz, *d*-MeOH) δ 8.43 (s, 1H), 7.94 (s, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.48 (d, J = 7.3 Hz, 1H), 7.43 (s, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.21-7.28 (m, 3H), 2.11 (s, 3H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 360.1 (calcd 359.1).

Entry 17: ^1H NMR (500 MHz, *d*-MeOH) δ 8.47 (s, 1H), 8.02 (s, 1H), 7.58-7.61 (m, 3H), 7.32-7.43 (m, 3H), 7.05 (d, J = 7.7 Hz, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 318.1 (calcd 317.1).

Entry 18: ^1H NMR (500 MHz, *d*-MeOH) δ 9.26 (s, 1H), 8.88 (s, 1H), 8.51 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 6.8 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.69-7.73 (m, 2H), 7.64 (s, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 9.4 Hz, 1H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 354.1 (calcd 353.1).

Entry 19: ^1H NMR (500 MHz, *d*-MeOH) δ 8.52 (s, 1H), 7.68 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.49-7.59 (m, 3H), 7.37-7.38 (m, 2H), 7.25 (d, J = 8.5 Hz, 1H), 4.95 (s, 2H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 385.1 (calcd 384.1).

Entry 20: ^1H NMR (500 MHz, *d*-MeOH) δ 8.49 (s, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.21-7.23 (m, 2H), 7.16 (d, J = 7.9 Hz, 1H), 4.53-4.59 (m, 1H), 2.09-2.13 (m, 2H), 1.56-1.72 (m, 6H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 295.1 (calcd 294.1).

Entry 21: ^1H NMR (500 MHz, *d*-MeOH) δ 8.47 (s, 1H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.18-7.28 (m, 3H), 4.04-4.34 (m, 2H), 3.20-3.23 (m, 1H), 2.45-2.47 (m, 1H), 1.92-1.96 (m, 1H), 1.45-1.75 (m, 4H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 338.1 (calcd 337.1).

Entry 22: ^1H NMR (500 MHz, *d*-MeOH) δ 8.51 (s, 1H), 7.47 (t, $J = 7.8$ Hz, 1H), 7.12-7.20 (m, 3H), 4.42-4.46 (m, 1H), 1.49-1.59 (m, 3H), 1.31-1.37 (m, 2H), 1.26-1.27 (m, 3H), 1.16-1.22 (m, 2H), 0.85-0.88 (m, 6H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 339.1 (calcd 338.1).

Compound 7: ^1H NMR (500 MHz, *d*-MeOH) δ 8.37 (s, 1H), 7.74 (s, 1H), 7.52 (t, $J = 7.7$ Hz, 1H), 7.39-7.42 (m, 2H), 7.30-7.33 (m, 3H), 7.15-7.19 (m, 2H). LC-ESMS observed $[\text{M}+\text{H}]^+$ 336.1 (calcd 335.1).