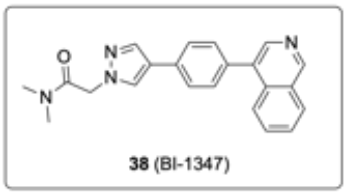
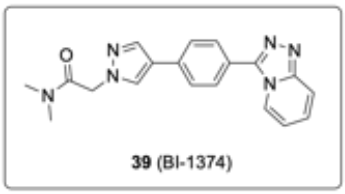
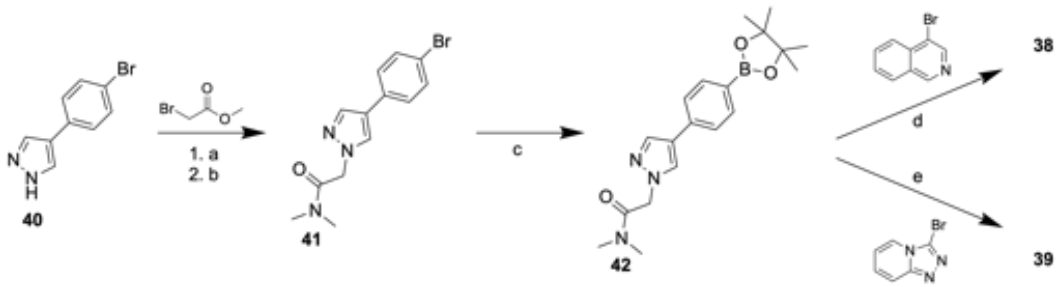
CDK8 Inhibitor | BI-1347

Synthesis of BI-1347 (Patent No. WO 2017/202719)

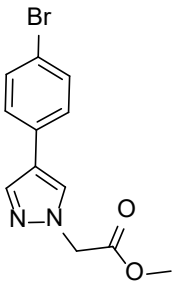
The compound numbers mentioned herein are a reference to the numbering system employed in: Gollner A., Heine C., Hofbauer K. S. Kinase Degraders, Activators, and Inhibitors: Highlights and Synthesis Routes to the Chemical Probes on opnMe.com, Part 1. *ChemMedChem* **2023**, 18, e202300031. DOI: 10.1002/cmdc.202300031, PubMed.





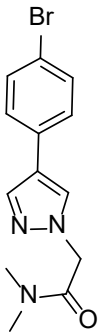


Synthesis of CDK8 inhibitor, BI-1347and its negative control, BI-1374. Reaction Conditions: (a) NaH, DMF, RT, 18 h; (b) dimethylamine, THF, 140°C MW, 4 h; (c) B_2Pin_2, KOAc, Pd(dppf)Cl_2xDCM, dioxane, 100°C, 18 h; (d) Cs_2CO_3, Pd(dppf)Cl_2xDCM, DME/water, 90°C MW, 30 min; (e) Cs_2CO_3, Pd(dppf)Cl_2xDCM, DMF/water, 110°C MW, 1 h.

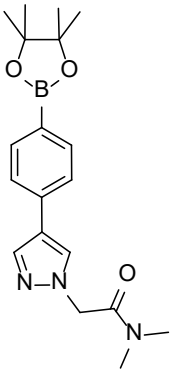


4-(4-Bromo-phenyl)-1H-pyrazole (1.00 g. 4.39 mmol) was dissolved in DMF (15 mL) and sodium hydride (150 mg, 5.94 mmol) was added. The reaction mixture was stirred for 30 min and then bromo-acetic acid methyl ester (500 µL, 5.39 mmol) was added at 25 °C. After 18 h, the reaction mixture was quenched with aqueous NH_4CI solution and to extracted with DCM twice. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified using normal phase

chromatography (DCM/MeOH: 100:0 -> 90:10) to afford the desired intermediate. Yield: 72 % (955 mg; 3.17 mmol)
HPLC-MS: (M+H)+ = 295/297.

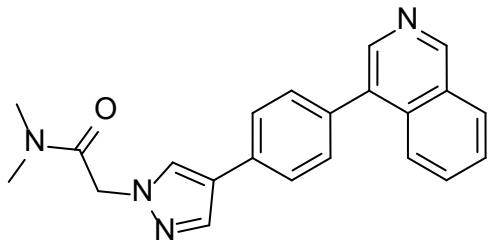


The product from the former step (500 mg; 1.61 mmol) was dissolved in a 2 M solution of dimethylamine in THF (5 mL; 10 mmol) and heated in a microwave reactor to 140 °C for 4 h. The solvents were evaporated and the crude product was diluted with water, the precipitate was collected by filtration to afford the desired intermediate. Yield: 51 % (252 mg; 0.82 mmol)



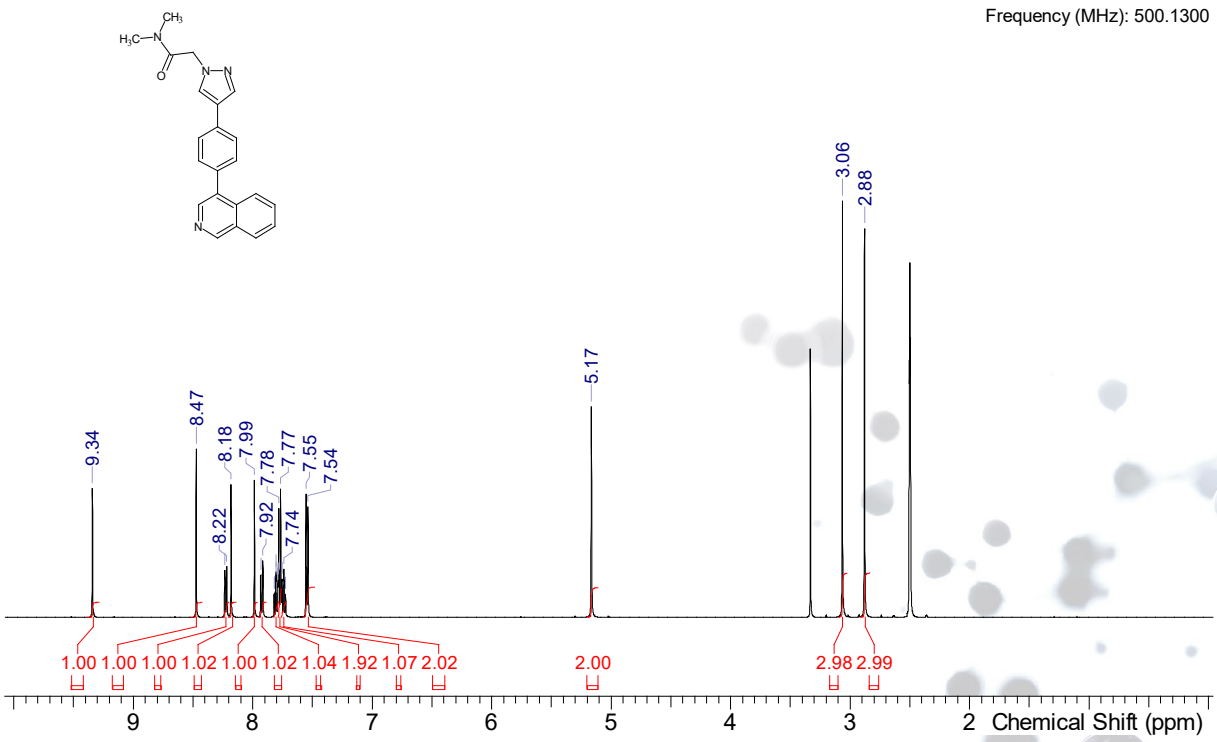
Bis(pinacolato)biboron (710 mg; 2.80 mmol) and KOAc (1.37 g; 13.97 mmol) were added to a stirring solution of intermediate **compound 41** (550 mg; 1.86 mmol) in dioxane (20 ml) and degassed with argon for 20 min. [1,1 '-Bis[diphenylphosphino]ferrocene]dichloropaliadium[0] dichloromethane (61 mg; 0.075 mmol) was added. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was diluted with $NaHCO_3$ solution and then extracted with DCM twice. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified using normal phase chromatography (cyclohexan/EtOAc: 85:15) to afford the desired intermediate.
Yield: 89 % (570 mg; 1.66 mmol), HPLC-MS: (M+H)+ = 343.

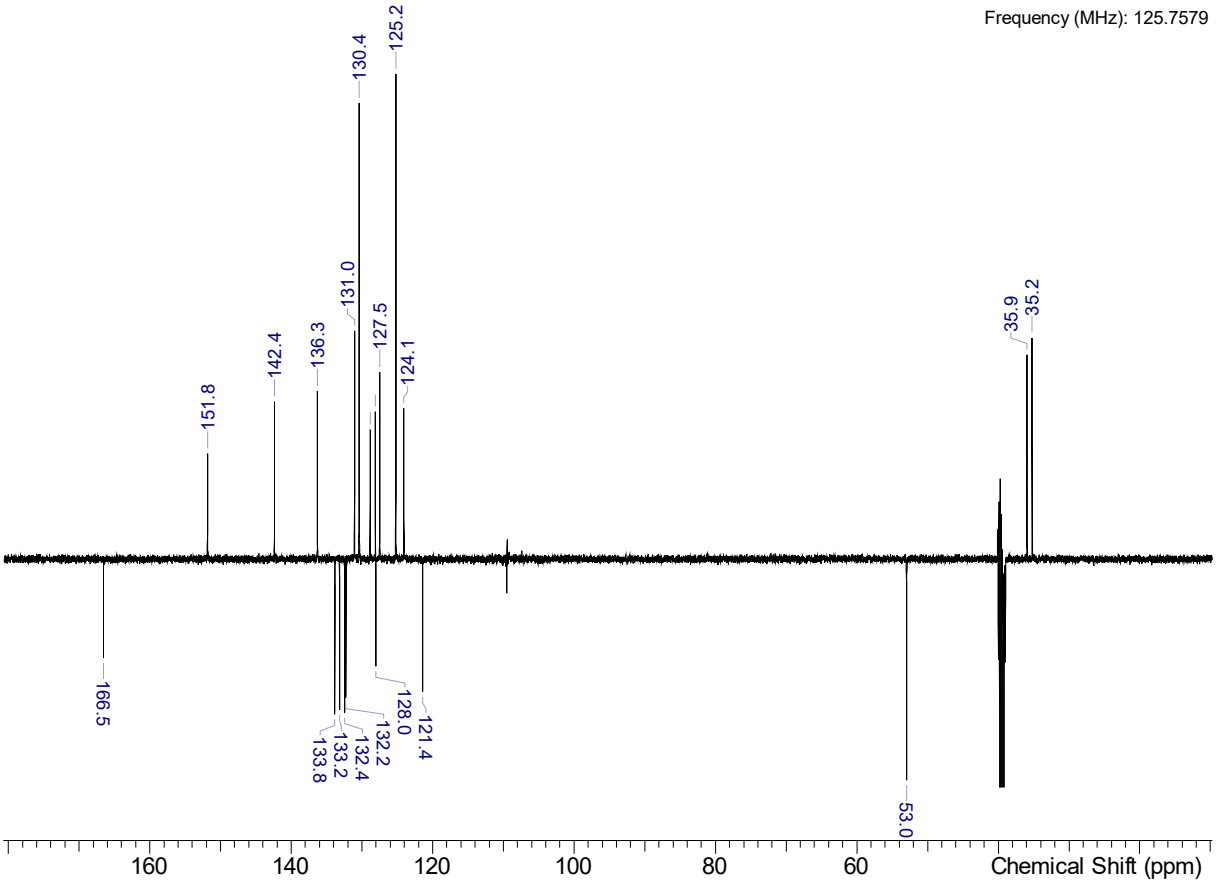
BI-1347 (Compound 38)



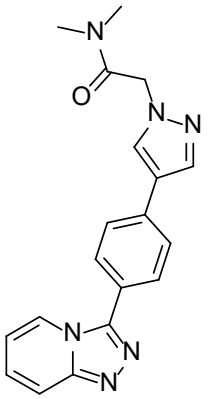
4-Bromoisoquinoline (15 mg; 0.07 mmol), **compound 42** (30 mg; 0,08 mmol) and caesium carbonate (75 mg; 0.23 mmol) were suspended in a mixture of 1,2-dimethoxyethane (3 ml) and water (1 ml). The reaction mixture was purged with argon, [1,1´-Bis[diphenylphosphino]-ferrocene]dichloropalladium[0], complex with dichloromethane (5 mg; 0.006 mmol) was added and stirred for 30 min in a micro wave reactor at 90 °C. The solvents were evaporated and the crude product I-003 was purified using reversed phase chromatography.
Yield: 57 % (14 mg; 0.04 mmol). HPLC-MS: (M+H)+ = 357.

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.34 (s, 1H), 8.47 (s, 1H), 8.23 (d, 1H, *J*=7.9 Hz), 8.18 (s, 1H), 7.99 (s, 1H), 7.92 (d, 1H, *J*=8.2 Hz), 7.8-7.8 (m, 1H), 7.77 (d, 2H, *J*=8.2 Hz), 7.7-7.8 (m, 1H), 7.55 (d, 2H, *J*=8.2 Hz), 5.17 (s, 2H), 3.06 (s, 3H), 2.88 (s, 3H)
^{13}C NMR (DMSO-d_6, 125 MHz) δ 166.5, 151.8, 142.4, 136.3, 133.8, 133.2, 132.4, 132.2, 131.0, 130.4, 128.8, 128.1, 128.0, 127.5, 125.2, 124.1, 121.4, 53.0, 35.9, 35.2
HRMS (*m/z*): $[M+H]^+$ calculated for C22H20N4O, 357.17099; found, 357.17161;





BI-1374 (Compound 39)



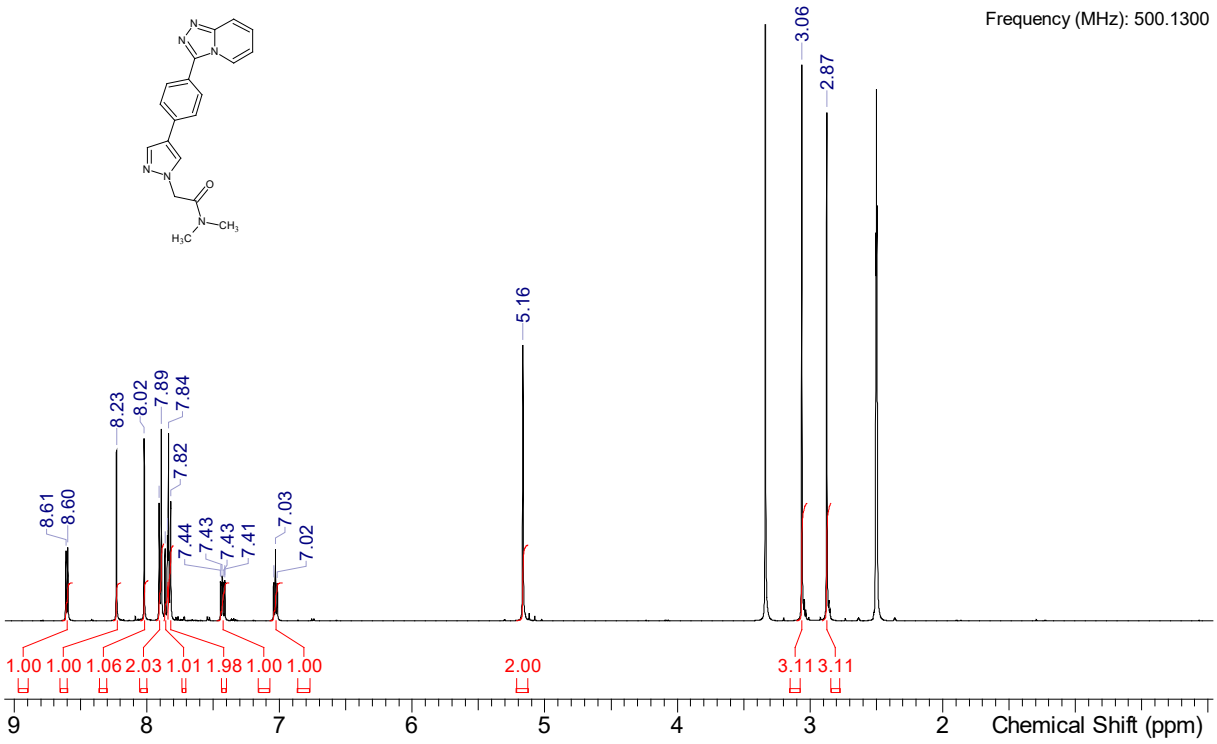
3-bromo-[1,2,4]triazolo[4,3-a]pyridine (0.60 g; 3.03 mmol), **compound 42** (1.61 g; 4.55 mmol) and caesium carbonate (2.96 g; 9.10 mmol) were suspended in a mixture of DMF (30 ml) and water (5 ml). The reaction mixture was purged with argon, [1,1´-Bis[diphenylphosphino]-ferrocene]dichloropalladium[0], complex with dichloromethane (0.33 g; 0.45 mmol) was added and

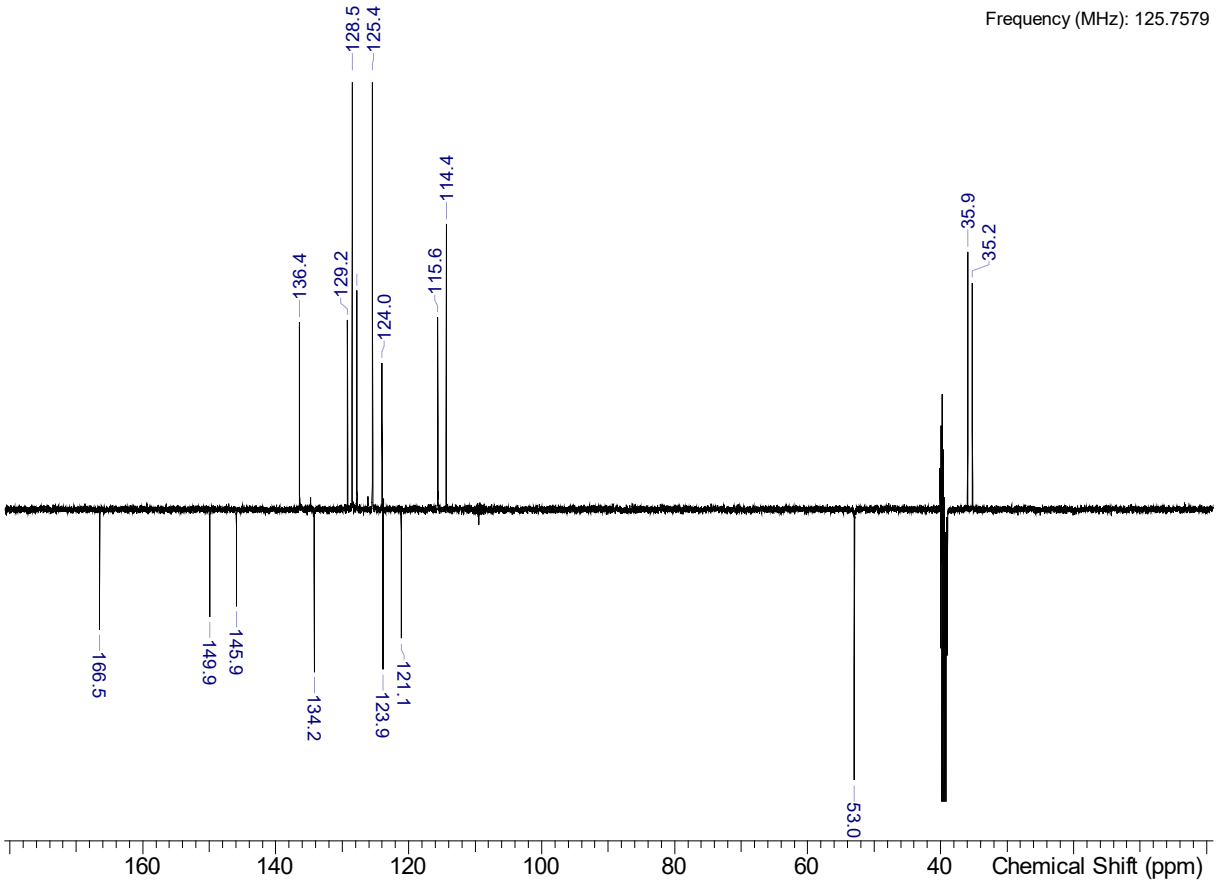
irradiated for 1 hour in a micro wave reactor at 110 °C. The reaction mixture was diluted with DCM and water, filtered and the aqueous layer was extracted with DCM 3 times. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified using reversed phase chromatography (basic conditions) to afford the desired **compound 39**, BI-1347. Yield: 65% (0.68 g, 1.98 mmol).

^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.60 (d, 1H, *J*=7.3 Hz), 8.23 (s, 1H), 8.02 (s, 1H), 7.90 (d, 2H, *J*=1.0 Hz), 7.85 (d, 1H, *J*=9.5 Hz), 7.83 (d, 2H, *J*=1.0 Hz), 7.4-7.5 (m, 1H), 7.0-7.1 (m, 1H), 5.16 (s, 2H), 3.06 (s, 3H), 2.87 (s, 3H);

^{13}C NMR (DMSO-d_6, 125 MHz) δ 166.5, 149.9, 145.9, 136.4, 134.2, 129.2, 128.5, 127.8, 125.4, 124.0, 123.9, 121.1, 115.6, 114.4, 53.0, 35.9, 35.2;

HRMS (*m/z*): $[M+H]^+$ calculated for C19H18N6O, 347.16149; found, 347.16207;

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