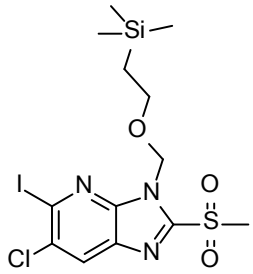
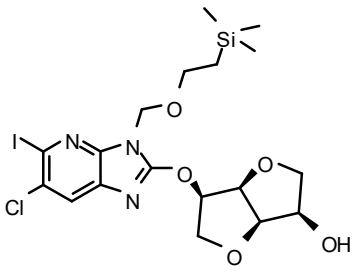
AMPK Activator | BI-9774

Synthesis of BI-9774 (Patent No. WO 2015/007669)

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.

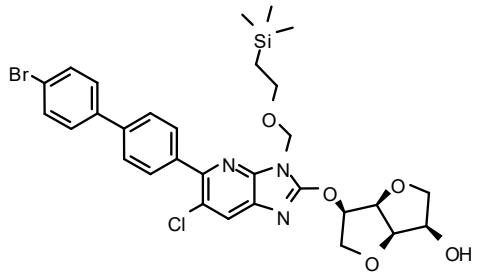


6-Chloro-5-iodo-2-methanesulfonyl-1H-imidazo[4,5-b]pyridine (1.0 g, 2.80 mmol) and triethylamine (0.59 mL, 4.24 mmol) were dissolved in THF (20 mL), cooled to 0°C and treated with SEM-Cl (0.51 mL, 2.90 mmol). The mixture was stirred for 30min while warming to room temperature. The mixture was partitioned between saturated aqueous NH_4Cl and ethyl acetate. The organic phase was washed with water and brine. After drying over $MgSO_4$, the solvents were evaporated in vacuo to give the title compound (0.76 g, yield 56 %).

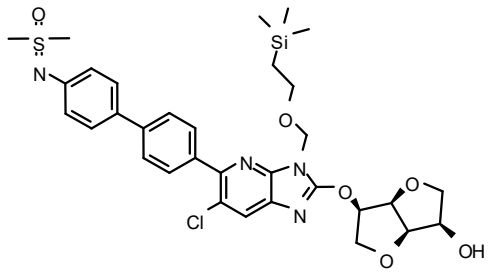


Isomannide (29.3 g, 22.49 mmol) was dissolved in N,N-dimethylformamide (120 mL) and treated with 1,8-diazabicyclc[5.4.0]undec-7-ene (DBU; 30.9 mL). A solution of 6-Chloro-5-iodo-2-methanesulfonyl-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazo[4,5-b]pyridine (32.6 g, 66.83 mmol) in N,N-dimethylformamide (180 mL) was added dropwise and the mixture is stirred for 2 hours at room temperature. The mixture was partitioned between water and ethyl acetate and the organic

phase was washed with brine and dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was chromatographed on silica gel cyclohexane/ethyl acetate 30:70-0:100) to give the title compound (27.0 g, yield 73%).

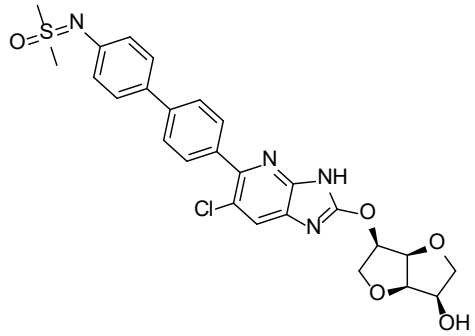


A mixture of (3R,3aR,6R,6aR)-6-(6-chloro-5-iodo-3-(2-trimethylsilanyl-ethoxymethyl)- 3H-imidazo[4,5-b]pyridin-2-yloxy)hexahydrofuro[3,2-b]furan-3-ol (1.0 g, 1.81 mmol), 4´Bromo-4-biphenylboronic acid (550 mg, 1.99 mmol), Na_2CO_3 (2 M aqueous solution, 2.71 mL), and 1,4-dioxane (10 mL) was purged for 5 minutes with argon. [1,1'-Bis(diphenylphosphino)- ferrocene]-dichloropalladium(II)-CH2Cl2-complex (PdCI2(dppf)xDCM) (103 mg, 0.13 mmol) was added and the mixture was stirred for 3 h at 90 °C. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate 40:60-0:100) to give the desired compound (0.94 g, yield: 79%)



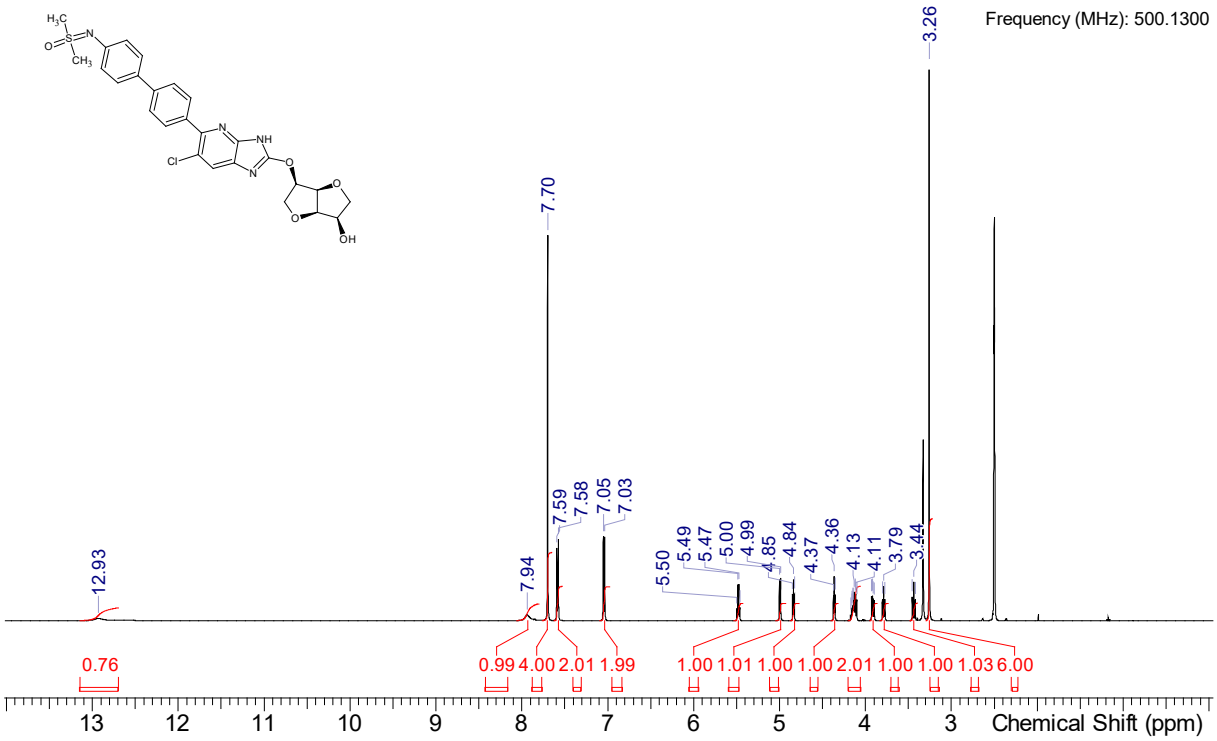
A microwave vial was charged with a stir bar, (3R,3aR,6R,6aR)-6-[(5-{4'-bromo-[1,1'-biphenyl]-4-yl}-6-chloro-3-{[2-(trimethylsilyl)ethoxy]methyl}-3H-imidazo[4,5-b]pyridin-2-yl)oxy]-hexahydrofuro[3,2-b]furan-3-ol (0.94 g, 1.43 mmol), S,S-dimethylsulfoximine (159 mg, 1.71 mmol) and Caesium carbonate (744 mg, 2.28 mmol) in toluene (10 mL). The mixture was purged with argon for 5min, then Palladium(II)-acetate (32 mg, 0.14 mmol) and RuPhos (67 mg, 0.14 mmol) were added and stirred over night at 75°C. After cooling to room temperature, the mixture was filtered through a pad of celite and the pad was rinsed with dichloromethane. The combined filtrates were concentrated in vacuo and the residue was chromatographed on silica gel (ethyl acetate/methanol 95:5-80:20) to give the desired compound (0.62 g, yield: 65%).

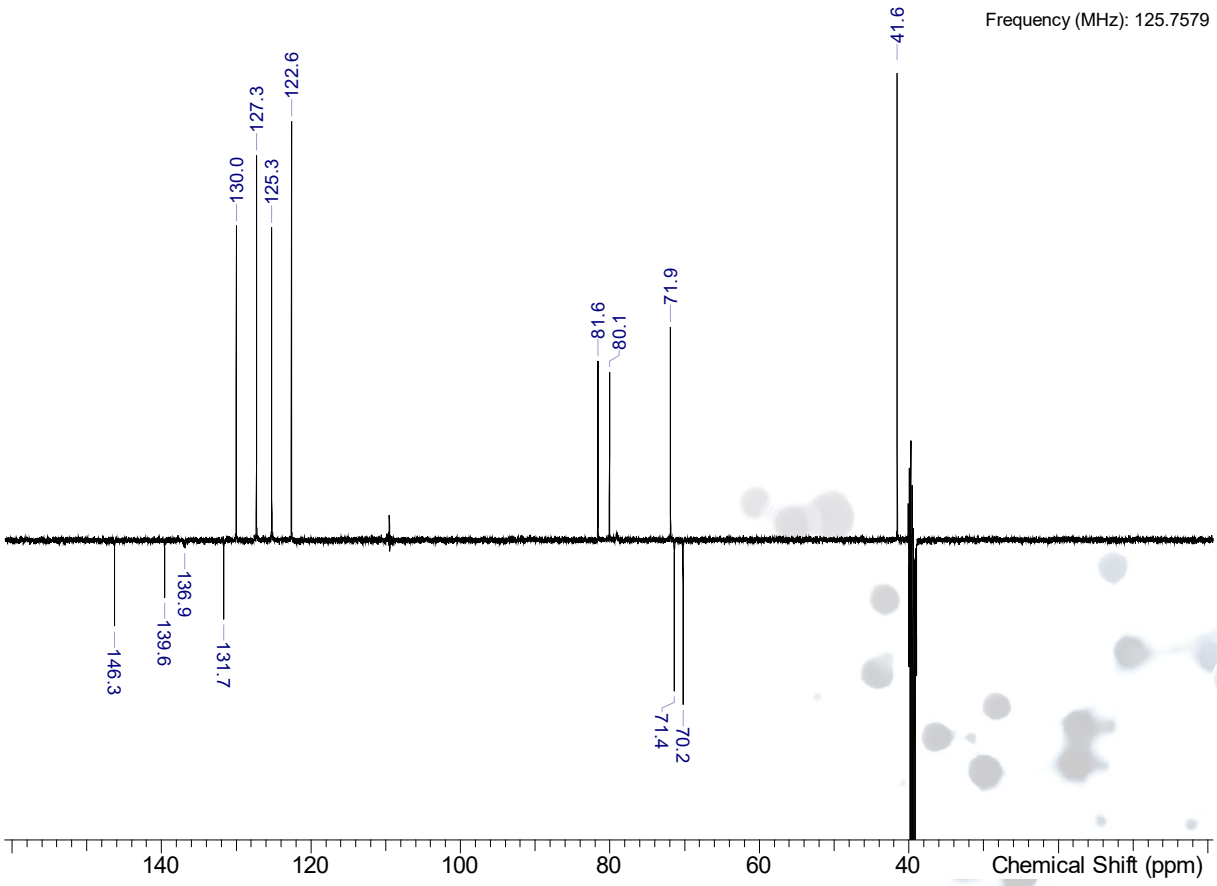
BI-9774 (Compound 25)



A mixture of N-(4-(6-chloro-2-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazo[4,5-b]pyridin-5-yl)phenyl)- S,S-dimethylsulfoximide (290 mg, 0.43 mmol) and KHSO4 (2 M aqueous solution, 302 µL, 0.61 mmol) in formic acid (5 mL) was stirred for 2 h at 60°C. The mixture was cooled to 0°C in an ice bath and the pH was adjusted to 11 by adding NaOH (10 M aqueous solution). Tetrahydrofurane (3 mL) was added and the mixture was stirred for 1 h at room temperature. Hydrochloric acid (4 N) was added until the pH reaches 6. The mixture was diluted with ethyl acetate, washed with water and brine, and dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by HPLC on reversed phase to give **BI-9774** (143 mg, yield: 61%).

^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.93 (br s, 1H), 7.94 (br s, 1H), 7.70 (s, 4H), 7.58 (d, 2H, *J*=8.5 Hz), 7.04 (d, 2H, *J*=8.5 Hz), 5.48 (q, 1H, *J*=5.9 Hz), 5.00 (d, 1H, *J*=6.6 Hz), 4.84 (t, 1H, *J*=5.0 Hz), 4.36 (t, 1H, *J*=4.9 Hz), 4.1-4.2 (m, 2H), 3.91 (dd, 1H, *J*=6.0, 9.5 Hz), 3.79 (t, 1H, *J*=7.4 Hz), 3.44 (t, 1H, *J*=8.5 Hz), 3.26 (s, 6H).
^{13}C NMR (DMSO-d_6, 125 MHz) δ 146.3, 139.6, 136.9, 131.7, 130.0, 127.3, 125.3, 122.6, 81.6, 80.1, 79.1, 71.9, 71.4, 70.2, 41.6, appr.147.5 (HSQC), 5 Carbons not detected.
HRMS (*m/z*): $[M+H]^+$ calculated for C26H25ClN4O5S, 541.13069; found, 541.13123;


Frequency (MHz): 500.1300
3.26
7.70
7.59
7.58
7.05
7.03
12.93
7.94
5.50
5.49
5.47
5.00
4.99
4.85
4.84
4.37
4.36
4.13
4.11
3.79
3.44
0.76
0.99 4.00 2.01 1.99
1.00 1.01 1.00 1.00 2.01 1.00 1.00 1.03 6.00
13 12 11 10 9 8 7 6 5 4 3
Chemical Shift (ppm)


Frequency (MHz): 125.7579
41.6
122.6
127.3
130.0
125.3
81.6
80.1
71.9
146.3
139.6
136.9
131.7
71.4
70.2
140 120 100 80 60 40
Chemical Shift (ppm)