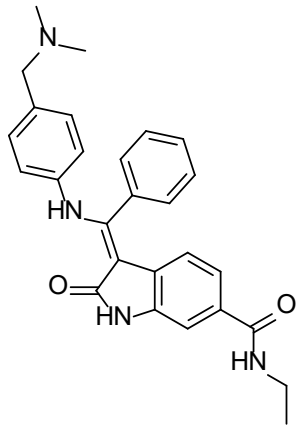
ALK5 Inhibitor | BI-4659

Synthesis of BI-4659[1]

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.

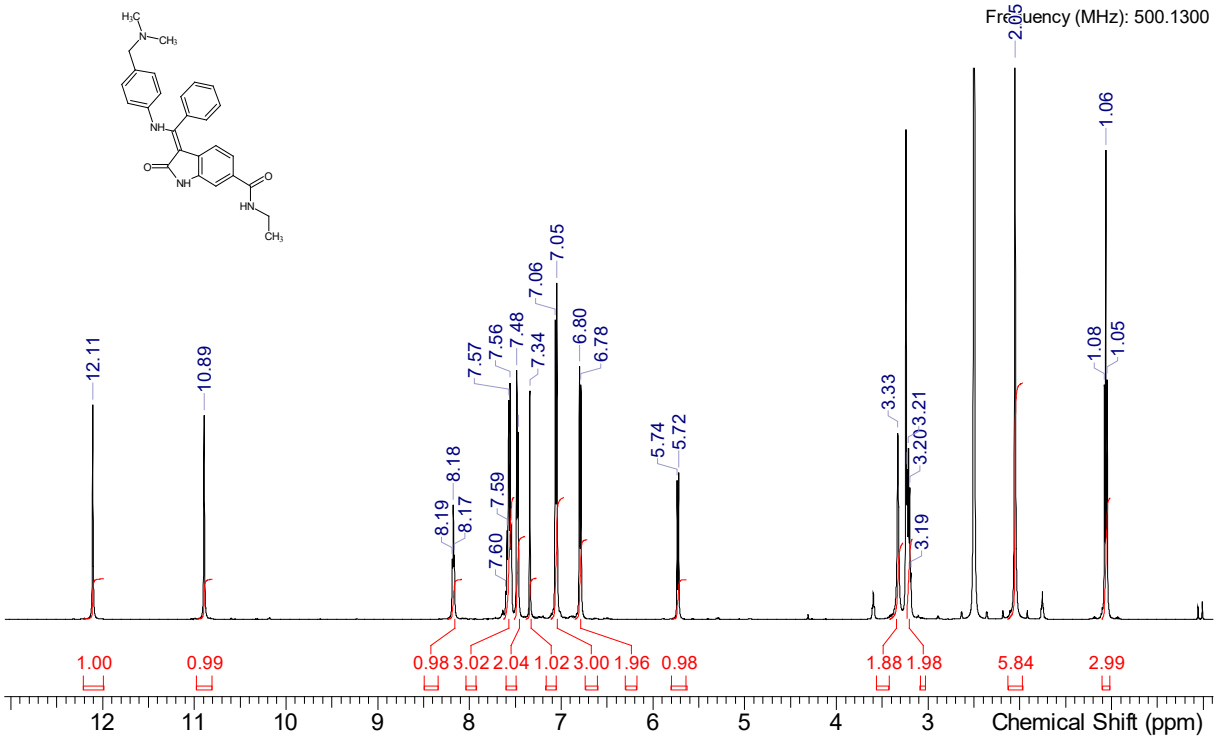
ALK Inhibitor, BI-4659 (Compound 17)

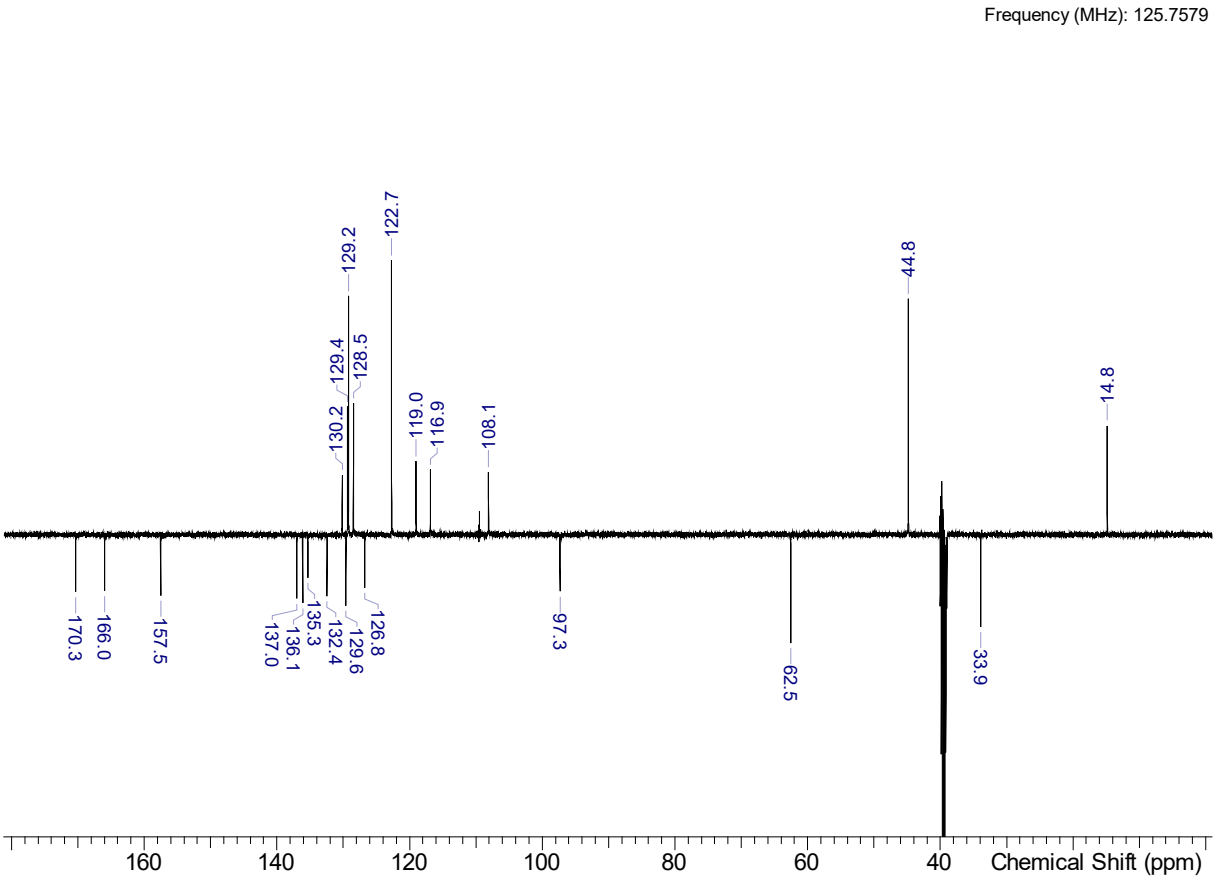


(E)-3-(Hydroxy-phenyl-methylene)-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid ethylamide (200 mg, 0.65 mmol) was dissolved in THF (3.0 mL) and 4-(dimethylamino)methyl]aniline (293 mg, 1.95 mmol, 3 equiv) and trimethylsilylimidazole (0.48 mL, 3.25 mmol, 5 equiv) were added. The mixture was stirred for 15 min at 170 °C under microwave irradiation. After that time, the solvent was removed and ethyl acetate was added. The organic layer was washed with water twice and dried over sodium sulfate. The solvent was removed by evaporation, and the residue was triturated with diethyl ether, filtered off and dried in vacuum at 70°C to give 220 mg (77%) of **BI-4659**.

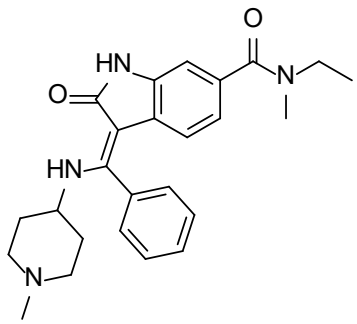
[1] Roth G. J., Heckel A., Brandl T., Grauert M., Hoerer S., Kley J. T., Schnapp G., Baum P., Mennerich D., Schnapp A., Park, J. E. Design, synthesis, and evaluation of indolinones as inhibitors of the transforming growth factor β receptor I (TGFβRI). *J Med Chem* **2010**, 53(20), 7287-7295. DOI: 10.1021/jm100812a, Pubmed.

^{1}H NMR (DMSO-d6, 500 MHz) δ 12.11 (s, 1H), 10.89 (s, 1H), 8.18 (br t, 1H, J=5.4 Hz), 7.5-7.6 (m, 3H), 7.48 (br d, 2H, J=6.9 Hz), 7.34 (s, 1H), 7.0-7.1 (m, 3H, J=8.5 Hz), 6.79 (br d, 2H, J=8.2 Hz), 5.73 (d, 1H, J=8.2 Hz), 3.33 (br s, 2H), 3.2-3.2 (m, 2H), 2.05 (s, 6H), 1.06 (t, 3H, J=7.3 Hz); ^{13}C NMR (DMSO-d6, 125 MHz) δ 170.3, 166.0, 157.5, 137.0, 136.1, 135.3, 132.4, 130.2, 129.6, 129.4, 129.2, 128.5, 126.8, 122.7, 119.0, 116.9, 108.1, 97.3, 62.5, 44.8, 33.9, 14.8; HRMS (m/z): [M+H]+ calculated for C27H28N4O2, 441.22850; found, 441.22922;



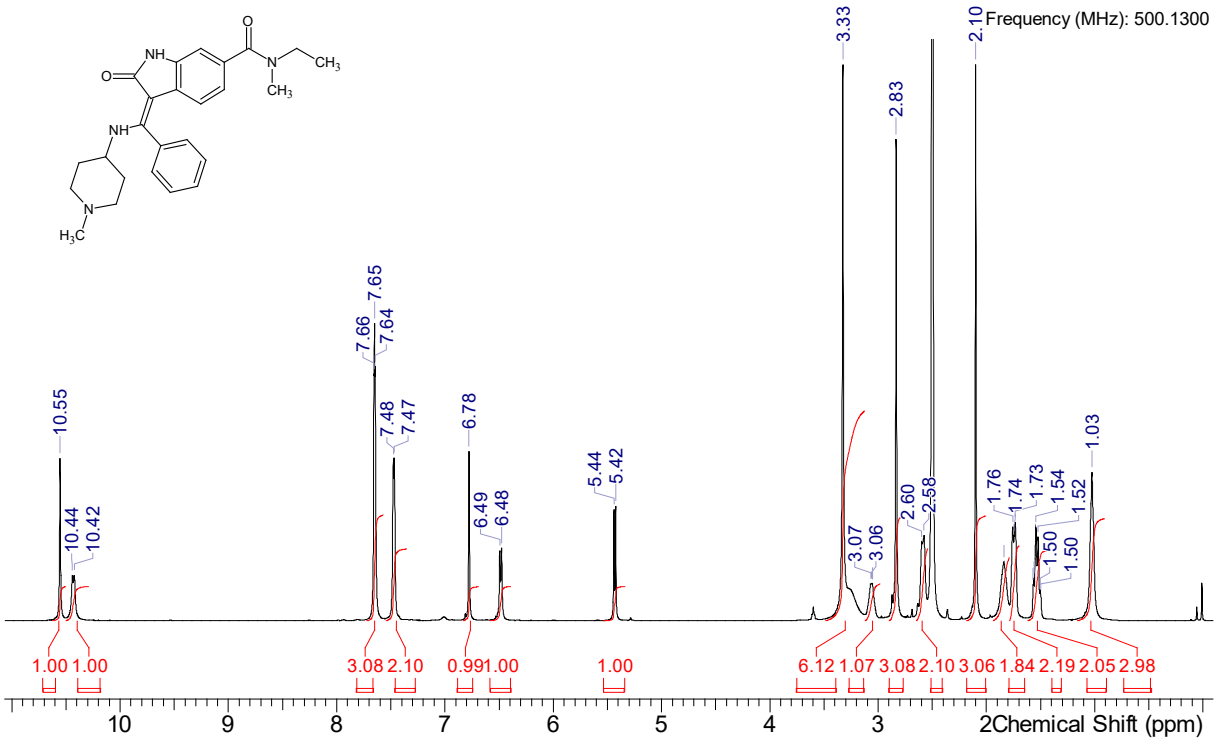


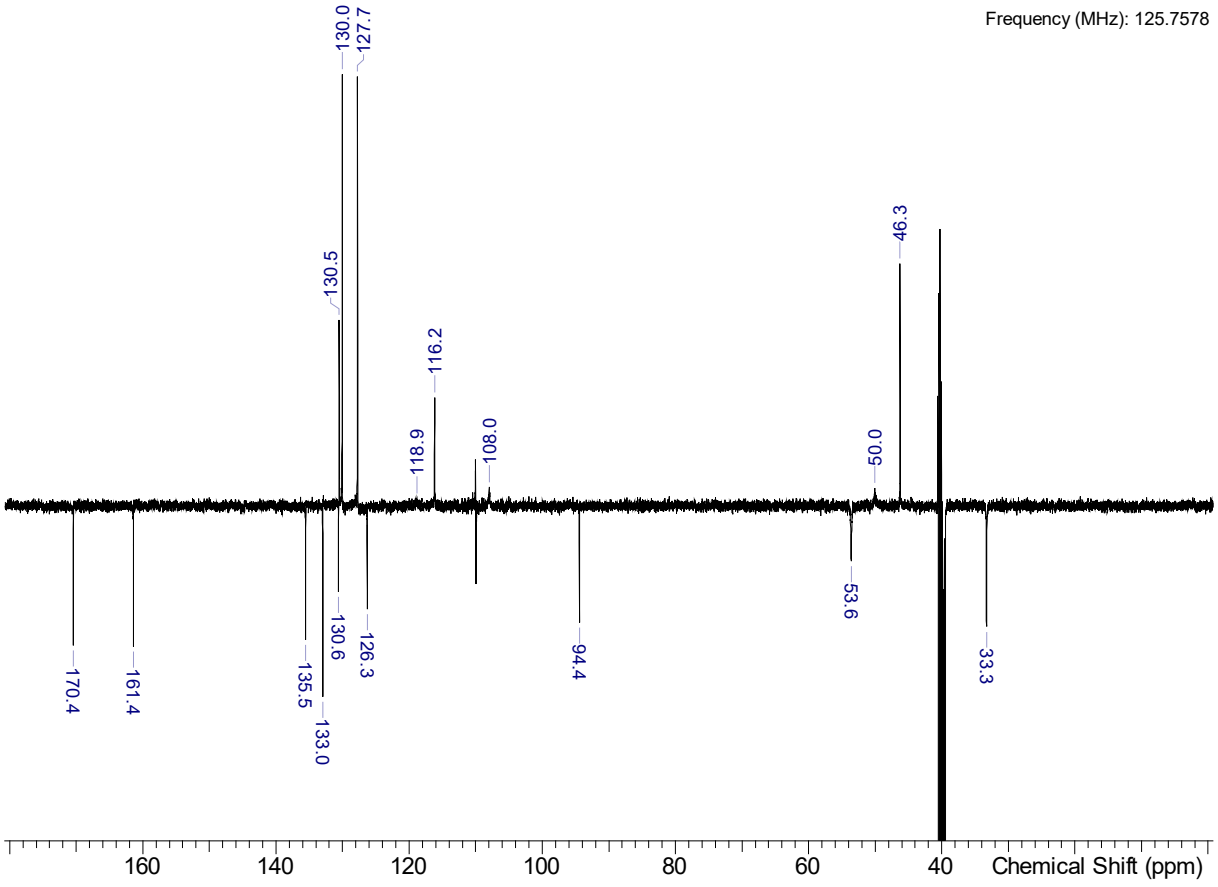
ALK Inhibitor Negative Control, BI-4101 (Compound 18)



(3Z)-3-{[(1-methylpiperidin-4-yl)amino](phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid (0.25 g, 0.66 mmol), TBTU (0.26 g, 0.79 mmol), HOBt (0.12 g, 0.79 mmol) and ethyl-diisopropylamine (0.58 mL, 3.31 mmol) were suspended in DMF (8 mL) and stirred for 0.5 h at ambient temperature. After that time, methylethylamine (90 µL, 1.01 mmol) was added and stirring was continued for 24 h at ambient temperature. After that time, water was added, the precipitate was filtered off and dried at 100 °C under vacuum to give 0.17 g (61%) of **BI-4101**.

^{1}H NMR (DMSO-d6, 500 MHz) δ 10.55 (s, 1H), 10.43 (br d, 1H, J=8.8 Hz), 7.6-7.7 (m, 3H), 7.47 (br d, 2H, J=3.5 Hz), 6.78 (s, 1H), 6.49 (br d, 1H, J=7.9 Hz), 5.43 (d, 1H, J=8.2 Hz), 3.33 (br s, 2H), 3.0-3.1 (m, 1H), 2.83 (s, 3H), 2.59 (br d, 2H, J=10.7 Hz), 2.10 (s, 3H), 1.7-2.0 (m, 4H), 1.4-1.6 (m, 2H), 1.03 (br s, 3H)
^{13}C NMR (DMSO-d6, 125 MHz) δ 170.4, 161.4, 135.5, 133.0, 130.6, 130.5, 130.0, 127.7, 126.3, 118.9, 116.2, 108.0, 94.4, 53.6, 50.0, 46.3, 33.3, appr. 13 (HSQC), 3 carbons not detected
HRMS (m/z): [M+H]+ calculated for C25H30N4O2, 419.24415; found, 419.24491;

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53.6
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161.4
135.5
133.0
130.6
126.3
94.4
33.3
160
140
120
100
80
60
40
Chemical Shift (ppm)