

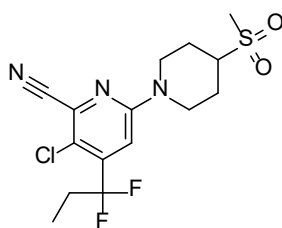


IKK β Inhibitor | BI 605906

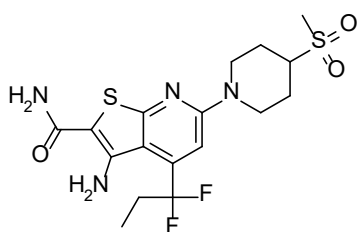
Synthesis of BI 605906 (Patent No. US 2007/0293533)

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](https://doi.org/10.1002/cmdc.202300031), [PubMed](#).

IKK β Inhibitor, BI 605906 (51)



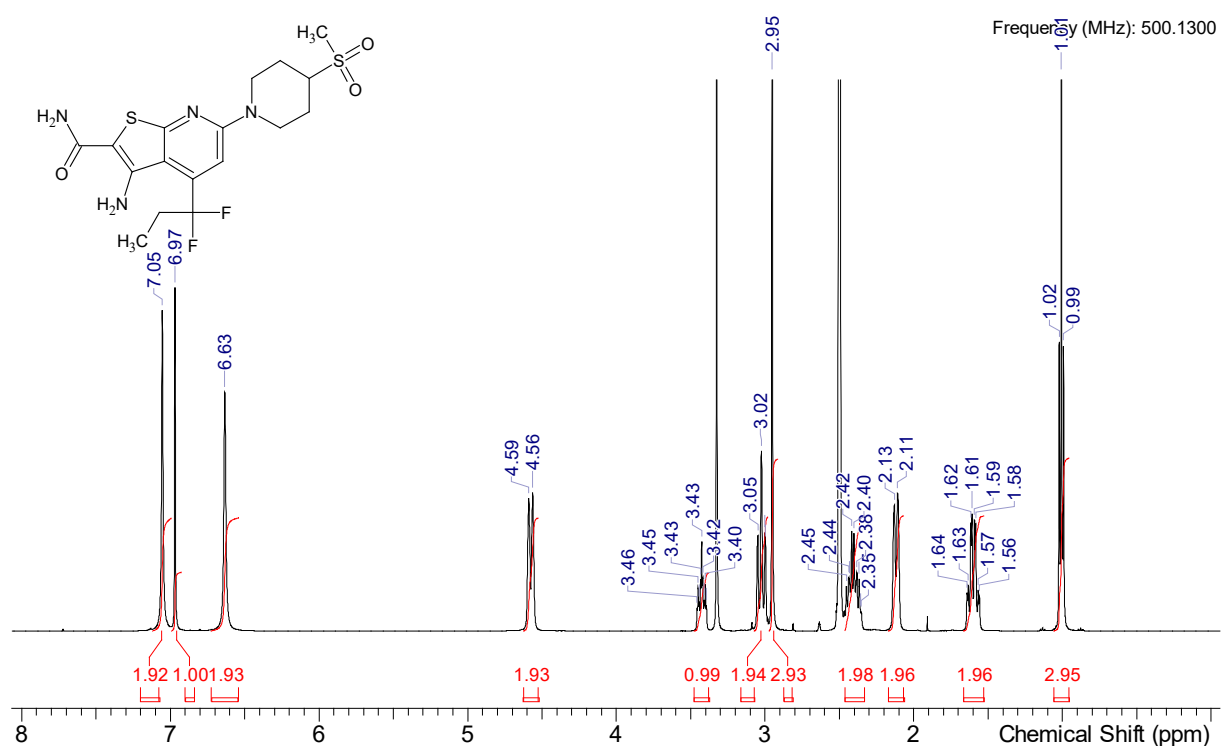
A suspension of 4-(methylsulfonyl)-piperidine trifluoroacetate (2.08 g, 7.5 mmol), nicotinonitrile (1.88 g, 7.5 mmol), and potassium carbonate (5.18 g, 37.5 mmol) in DMF (20 mL) were stirred at room temperature overnight. The crude reaction mixture was used for next step with 100% assumed yield.

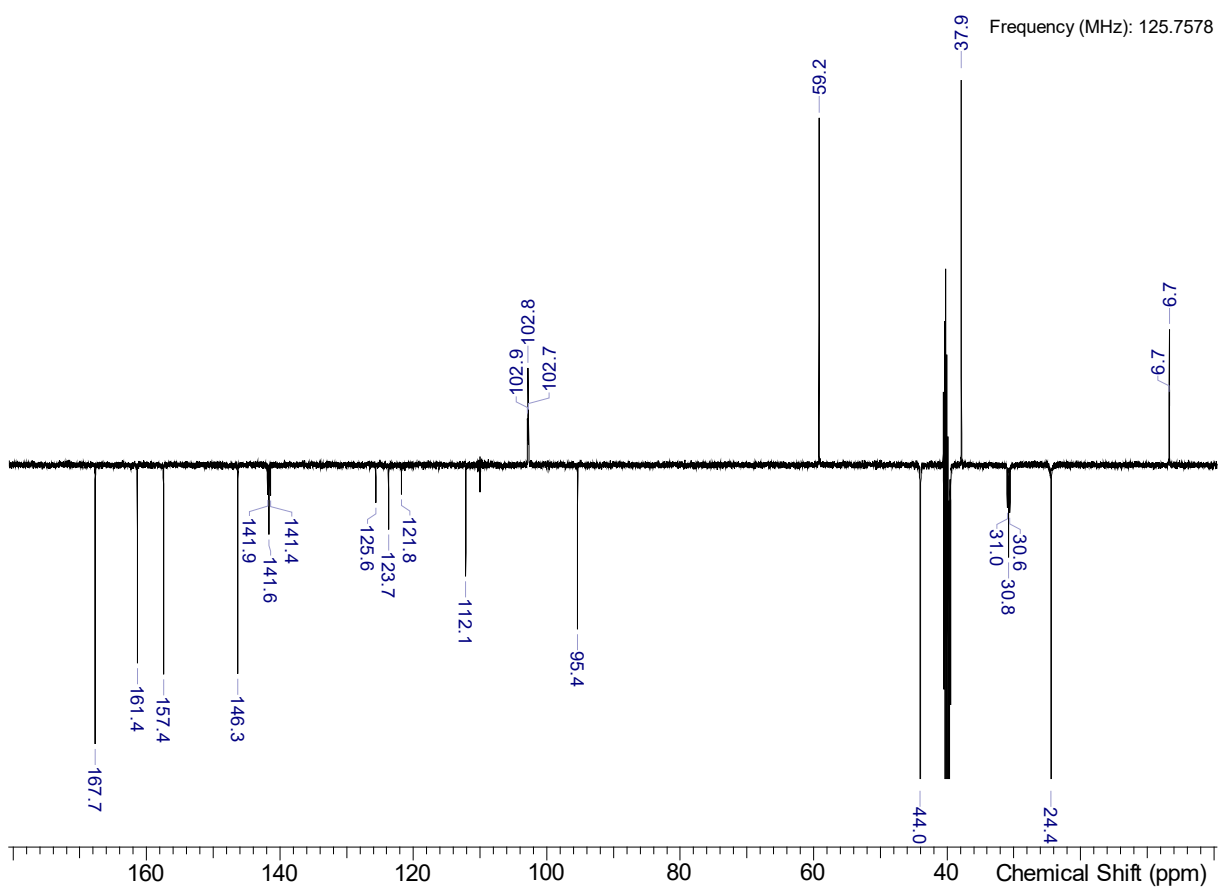


3-chloro-4-(1,1-difluoropropyl)-6-(4-methanesulfonylpiperidin-1-yl)pyridine-2-carbonitrile was diluted with additional DMF (20 mL) and purged with nitrogen as 2-mercaptoacetamide was added (7.5 mmol as a 2M solution in methanol). After stirring for 3 h at room temperature the reaction mixture was heated to 80°C overnight to affect the intramolecular thiophen cyclization reaction. The dark coloured reaction was poured into water, filtered, and washed with additional water to provide 2.24 g (69%) **BI 605906** as a yellow-brown solid.

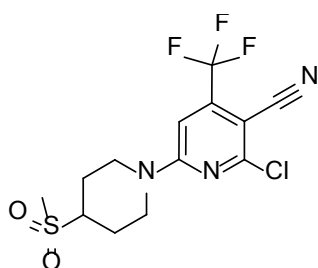
^1H NMR (DMSO- d_6 , 500 MHz) δ 7.05 (s, 2H), 6.97 (s, 1H), 6.63 (br s, 2H), 4.58 (br d, 2H, $J=13.2$ Hz), 3.43 (tt, 1H, $J=3.6, 12.0$ Hz), 3.0-3.1 (m, 2H), 2.95 (s, 3H), 2.3-2.5 (m, 2H), 2.12 (br d, 2H, $J=11.0$ Hz), 1.60 (dq, 2H, $J=4.1, 12.4$ Hz), 1.01 (t, 3H, $J=7.3$ Hz);

^{13}C NMR (DMSO- d_6 , 125 MHz) δ 167.7, 161.4, 157.4, 146.3, 141.6 (t, $J(\text{CF})=26.8$ Hz), 123.7 (t, $J(\text{CF})=241.6$ Hz), 112.1, 102.8 (t, $J(\text{CF})=10.0$ Hz), 95.4, 59.2, 44.0, 37.9, 30.8 (t, $J(\text{CF})=25.4$ Hz), 24.4, 6.7 (t, $J(\text{CF})=4.1$ Hz); HRMS (m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{22}\text{F}_2\text{N}_4\text{O}_3\text{S}_2$, 433.11741; found, 433.11809;

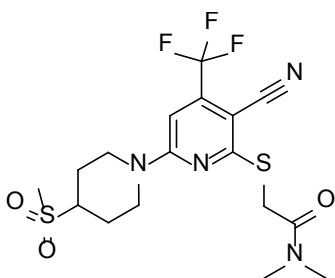




IKK β Inhibitor Negative Control, BI-5026 (Compound 52)

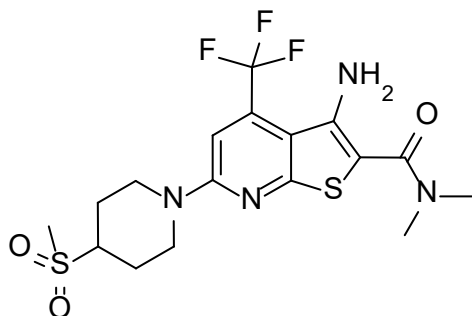


A suspension of 2,6-Dichloro-4-(trifluoromethyl)-nicotinonitrile (2.0 g, 8.30 mmol), 4-(methylsulfonyl)-piperidine (1.35 g, 8.30 mmol) and DIPEA (0.7 mL, 4.05 mmol) in ethanol (20 mL) was stirred at ambient temperature overnight. The reaction mixture was diluted with water and the product is collected by filtration. The solids were dried in vacuum to afford 1.87 g (61%) desired compound.



A mixture of 2-chloro-6-(4-methanesulfonylpiperidin-1-yl)-4-(trifluoromethyl)pyridine-3-carbonitrile (1.0 g, 2.72 mmol), N,N-dimethyl-2-sulfanylacetamide (0.65 g, 5.44 mmol) and potassium carbonate (1.13 g, 8.16 mmol) was stirred in dimethylsulfoxid (30 mL) at ambient temperature overnight. The reaction mixture was diluted with water and the product was collected by filtration. The solids were dried under air to afford 1.1 g solid product (90%).

BI-5026



To a mixture of 2-[[3-cyano-6-(4-methanesulfonylpiperidin-1-yl)-4-(trifluoromethyl)pyridin-2-yl]-sulfanyl]-N,N-Dimethylacetamide (1.1 g, 2.44 mmol) in ethanol (20 mL), potassium carbonate (1.13 g, 8.16 mmol) was added. The reaction mixture was stirred while refluxing for 2 hours, then added to stirred water. The desired compound was collected by filtration, washed with water and dried under air to afford 1.0g (82%) **BI-5026**.

^1H NMR (DMSO- d_6 , 500 MHz) δ 7.28 (s, 1H), 5.88 (s, 2H), 4.62 (br d, 2H, $J=13.2$ Hz), 3.44 (tt, 1H, $J=3.7$, 11.9 Hz), 3.0-3.1 (m, 8H), 2.95 (s, 3H), 2.12 (br d, 2H, $J=10.7$ Hz), 1.60 (dq, 2H, $J=4.1$, 12.5 Hz);

^{13}C NMR (DMSO- d_6 , 125 MHz) δ 166.8, 161.9, 156.9, 143.3, 132.7 (q, $J(\text{CF})=32.7$ Hz), 123.4 (q, $J(\text{CF})=273.4$ Hz), 110.7, 103.6 (q, $J(\text{CF})=6.4$ Hz), 97.2, 59.2, 44.1, 37.9, 37.9, 24.4, appr. 40 (under DMSO);

HRMS (m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{21}\text{F}_3\text{N}_4\text{O}_3\text{S}_2$, 451.10799; found, 451.10877;

