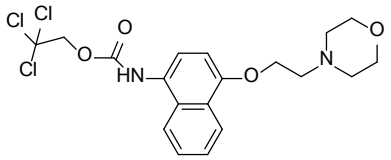
p38 MAPK Inhibitor | BIRB 796

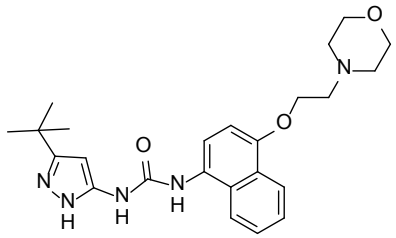
Synthesis of BIRB 796 (Patent No. WO 02/066442 AL)

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.



To a solution of 4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-ylamine (10.9 g, 40 mmol) and N, N-diisopropylethylamine (10 mL, 57 mmol) in THF (80 mL), cooled to -10°C under argon, was added 2,2,2-trichloroethyl chloroformate (5.6 mL, 40 mmol) via syringe over 10 min. Upon stirring at -10°C for 40 min, EtOAc (100 mL) and water (100 mL) were added. The organic layer was washed with brine, dried (MgSO4), filtered and concentrated in vacuo. The crude product was triturated (ether), filtered, washed (ether) and air-dried to give a first crop as a slightly pink solid (11.1 g). The filtrate was concentrated in vacuo, triturated (ether), filtered, washed (ether) and dried, providing a second crop of 4.6 g. A total of 15.7 g (88%) of [4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-carbamic acid 2,2,2-trichloroethyl ester was obtained as a pink solid.

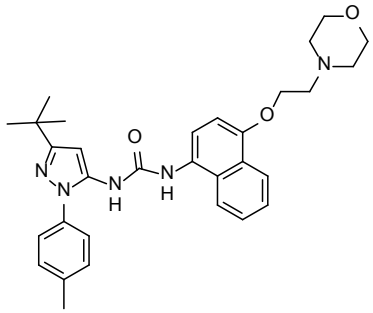
1HNMR (CDCl3) δ 2.66(t, 4H), 2.97(t, 2H), 3.75(t, 4H), 4.3l(t, 3H), 4.88(s, 2H), 6.80(d, 1H), 6.94(s, 1H), 7.58(m, 3H), 7.87(d, 1H), 8.29(d, 1H); MS (Cl) 447(M+ +H). m.p. 124 -125 °C.



A solution of the above trichloroethyl carbamate (4.5 g, 10 mmol), 5-tert-butyl-2-aminopyrazole (1.4 g, 10 mmol), and N, N-diisopropylethylamine (1.8 mL, 10 mmol) in DMSO (100 mL) was heated at 80°C for 14 h. The mixture was cooled to room temperature, EtOAc (100 mL) and water (100 mL) were added. The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated in vacuo, triturated (ether), washed (hexane) and dried in air to give 1-(5-tert-butyl-2H-pyrazol-3-yl)-3-[4-(2-morphohn-4-yl-ethoxy)-naphthalen-1-yl]-urea as a pale pink solid (3.7g, 84%)

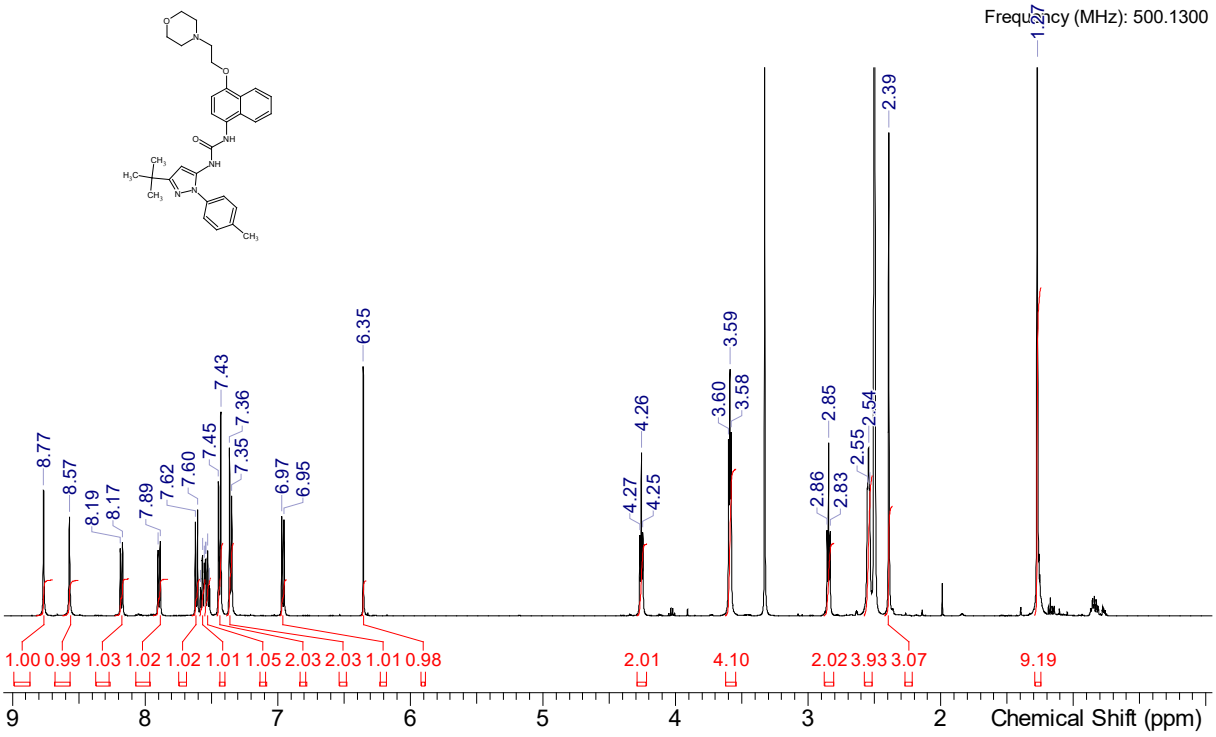
mp 206-207 °C,1H NMR (DMSO) δ 1.25(s, 9H), 2.53(t, 4H), 2.83(t, 2H), 3.58(t, 4H), 4.25(t, 2H), 5.87(s, 1H), 6.96(d, 1H), 7.56(m, 2H), 7.82(d, 1H), 8.03(d, 1H), 8.18(d, 1H), 9.17(s, 1H), 12.06(s, 1H); MS (CI) 438(M+ +H).

BIRB 796 (Compound 60)



A mixture of 1-(5-tert-butyl-2H-pyrazol-3-yl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea (0.022 g, 0.050 mmol), p-tolylboronic acid (0.014 g, 0.1 mmol), copper (II) acetate (0.014 g, 0.075 mmol), pyridine (0.01 mL, 0.1 mmol), molecular sieves (4°A activated, 0.030 g) and methylene chloride (2 mL) was stirred at room temperature for 14 h under air. After filtration through diatomaceous earth, the filtrate was concentrated in vacuo and purified by flash chromatography (EtOAc 100% to EtOH 100%). The title compound **BIRB 796** was obtained as a yellow-white solid (0.013 g, 50%)

mp 144 -146 °C;
^{1}H NMR (400 MHz, DMSO-d_6, 30ºC): δ = 8.76 (s, 1H), 8.57 (s, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.55 (dddd, *J* = 15.3, 8.3, 6.8, 1.4 Hz, 2H), 7.39-7.47 (m, 2H), 7.33-7.37 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.35 (s, 1H), 4.26 (t, *J* = 5.6 Hz, 2H), 3.56-3.62 (m, 4H), 2.85 (t, *J* = 5.6 Hz, 2H), 2.52-2.58 (m, 4H), 2.39 (s, 3H), 1.27 ppm (s, 9H)
^{13}C NMR (101 MHz, DMSO-d_6, 30ºC): δ = 160.5, 152.7, 150.9, 137.5, 136.7, 136.2, 129.6, 128.5, 126.6, 126.3, 125.3, 125.2, 124.3, 121.9, 120.6, 105.1, 95.1, 66.2, 57.0, 53.6, 40.2, 32.0, 30.2, 20.6 ppm
HRMS (m/z): [M+H]+ calculated for C31H37N5O3, 528.29692; found, 528.29762;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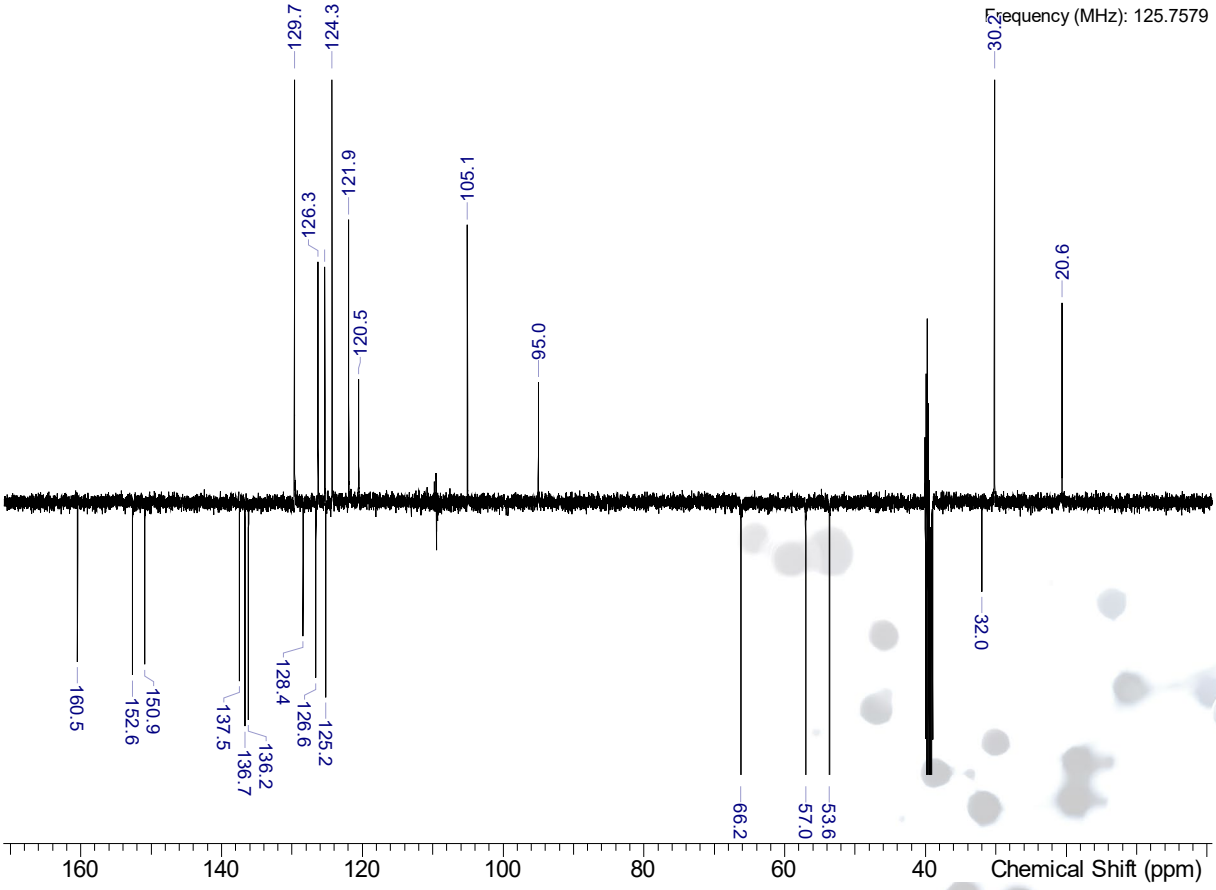
4.26
4.25
3.60
3.59
3.58
2.86
2.85
2.83
2.55
2.54
2.39
1.27
1.00 0.99 1.03 1.02 1.02 1.01 1.05 2.03 2.03 1.01 0.98
2.01
4.10
2.02 3.93 3.07
9.19
Chemical Shift (ppm)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136.2
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126.6
125.2
69.2
57.0
53.6
32.0
Chemical Shift (ppm)