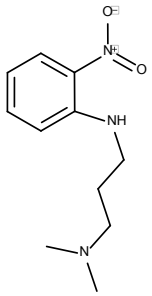
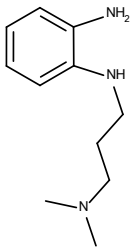
RSK Inhibitor | BIX 02565

Synthesis of BIX 02565 (Patent No. US 2010/058271)

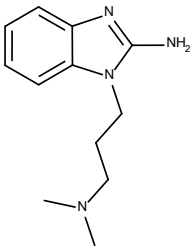
The compound numbers mentioned herein are a reference to the numbering system employed in: Gollner A., Heine C., Hofbauer K. S. Kinase Degraders, Activators, and Inhibitors: Highlights and Synthesis Routes to the Chemical Probes on opnMe.com, Part 1. *ChemMedChem* **2023**, 18, e202300031. DOI: 10.1002/cmdc.202300031,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



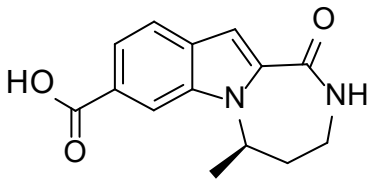
A flask was charged with 3g (21.3 mmol) 2-fluoronitrobenzene, 3.2mL (25.5 mmol) propylamine, 5.5 mL (31.9 mmol) Hunig's base and 40 mL of DMSO. The vial was warmed to 80 °C and stirred overnight. The reaction was poured into 150 mL of ice water and extracted with ethylacetate. The combined extracts were washed four times with water, brine, dried over Na2SO4, filtered and concentrated to afford 4.67g of an orange oil (98%). NMR was consistent with desired product.



To a solution of 4.67g (20.9mmol) N-[3-(dimethylamino)propyl]-2-nitroaniline in 150 mL of EtOH under N_2, 250mg (10 mol%) Pd on carbon was carefully added. The reaction was placed under an atmosphere of H_2 and stirred overnight, the yellow color was gone after several hours, and LC-MS showed the reaction complete. The reaction was carefully filtered through a bed of celite and the filtrate was concentrated in vacuo to afford 4.0g as a dark oil (99%). NMR was consistent with desired product.

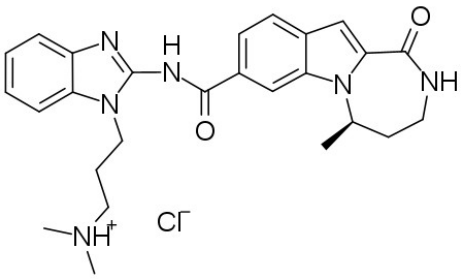


To a solution of diamine (4.0 g, 20.6 mmol) in 100 mL of EtOH, 3.55 mL (62. 08mmol) of formic acid was added, followed by 8.6 mL (25.8 mmol) of 3M cyanogen bromide in CH_2Cl_2 and the reaction was stirred at room temperature. After 1 hour, LC-MS showed the reaction was complete. The reaction was concentrated in vacuo, dissolved in water, basified with 2M aqueous K_2CO_3 and extracted with ethylacetate. The combined extracts were dried over Na_2SO_4, filtered and concentrated to afford a brown solid. The resulting solids were triturated with acetone and isolated by filtration to get 1.45 g (32%) as title compound.



To a solution of 3.65 g (11.4 mmol) (5R)-5-methyl-1-oxo-2,3,4,5-tetrahydro-1H-[1,4]diazepino[1,2-a]indole-8-carboxylate in 30 mL of EtOH, 13.8 mL of 1M aqueous NaOH was added. The reaction mixture was refluxed for 2h. The reaction mixture was acidified with 1M HCl and ethanol was removed under vacuum. The resulting slid was collected by filtration, washed with water and dried to afford 2.1g title compound (41% for three steps).

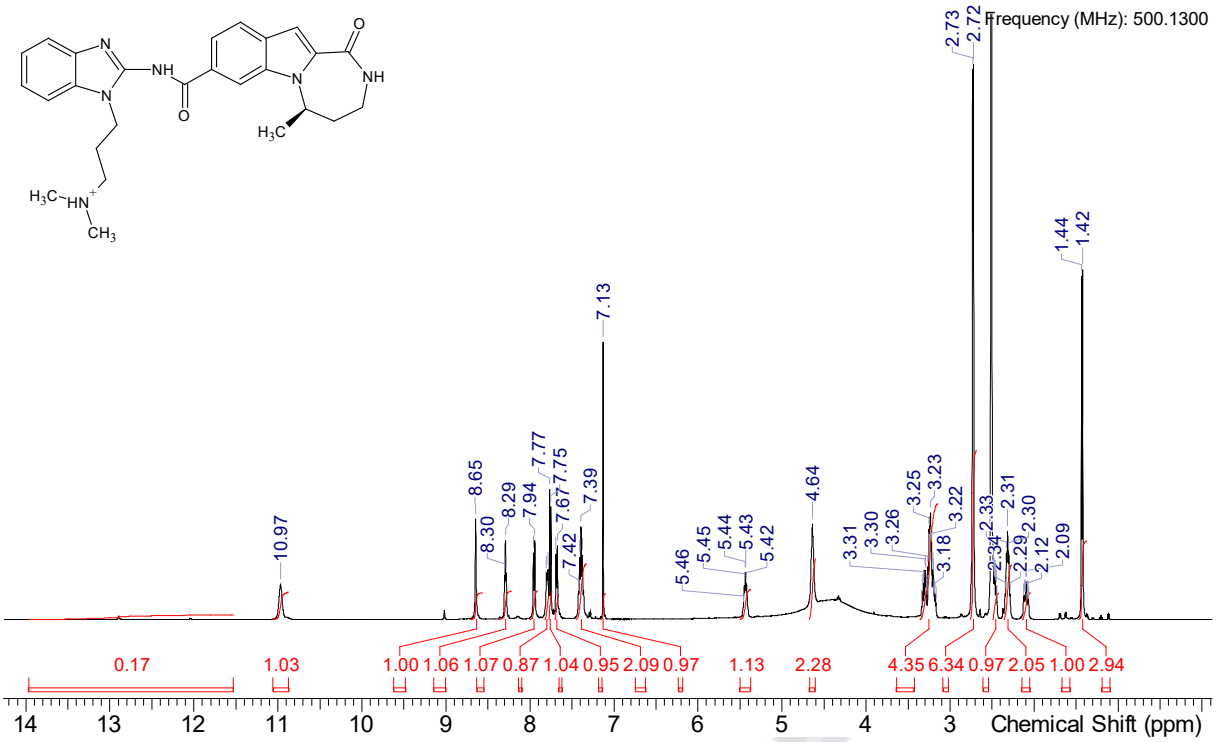
BIX 02565 (Compound 73)

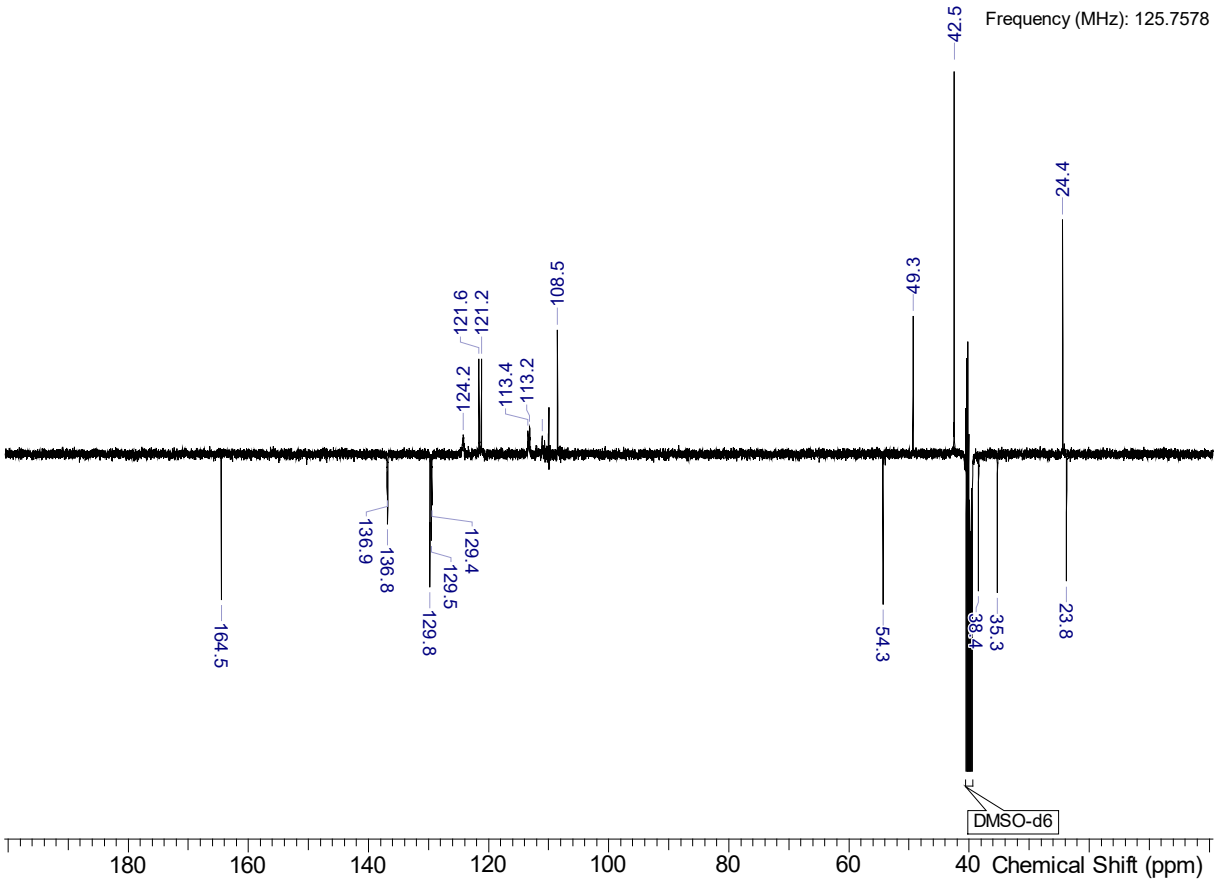


To a solution of 680mg (2.6 mmol) chiral acid in 15 mL DMF, 1.01g (3.9 mmol) TBTU, 632.2mg (1.1 equiv., 2.9 mmol) aminobenzimidazole and 550 µL triethylamine were added. The solution was stirred at 40°C for 24h. The solution was diluted with ethyl acetate and washed in turn with Na_2CO_3, twice

with water and brine. The organic layer was dried over $MgSO_4$ and evaporated to give a pale yellow gum. It was triturated with diethylether, which gave an off-white solid that was collected by filtration, washed well with diethylether and dried to give 776mg **BIX 02565** (64%).

^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.5-14.0 (m, 1H), 10.97 (br s, 1H), 8.65 (s, 1H), 8.29 (br t, 1H, *J*=5.0 Hz), 7.95 (br d, 1H, *J*=8.2 Hz), 7.80 (br d, 1H, *J*=7.6 Hz), 7.76 (d, 1H, *J*=8.2 Hz), 7.68 (br d, 1H, *J*=7.6 Hz), 7.3-7.4 (m, 2H), 7.13 (s, 1H), 5.4-5.5 (m, 1H), 4.64 (br s, 2H), 3.1-3.4 (m, 4H), 2.73 (br d, 6H, *J*=4.4 Hz), 2.4-2.5 (m, 1H), 2.32 (td, 2H, *J*=7.3, 14.7 Hz), 2.0-2.1 (m, 1H), 1.43 (d, 3H, *J*=6.9 Hz);
^{13}C NMR (DMSO-d_6, 125 MHz) δ 164.5, 136.9, 136.8, 129.8, 129.5, 129.4, 124.2, 124.2, 121.6, 121.2, 113.4, 113.2, 111.1, 108.5, 54.3, 49.3, 42.5, 38.4, 35.3, 24.4, 23.8, appr. 40 (under DMSO), appr. 172 (HMBC), 3 carbons not detected;
HRMS (*m/z*): $[M+H]^+$ calculated for C26H30N6O2, 459.25030; found, 459.24968;

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121.6
121.2
124.2
113.4
113.2
136.9
136.8
129.4
129.5
129.8
164.5
54.3
38.4
35.3
23.8
DMSO-d6
180
160
140
120
100
80
60
40
Chemical Shift (ppm)