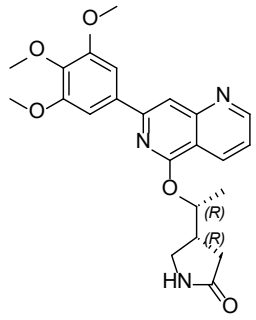
SYK Inhibitor | BI 1002494

Synthesis of BI 1002494 (Patent No. WO2011/92128)

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.

BI 1002494 (81)

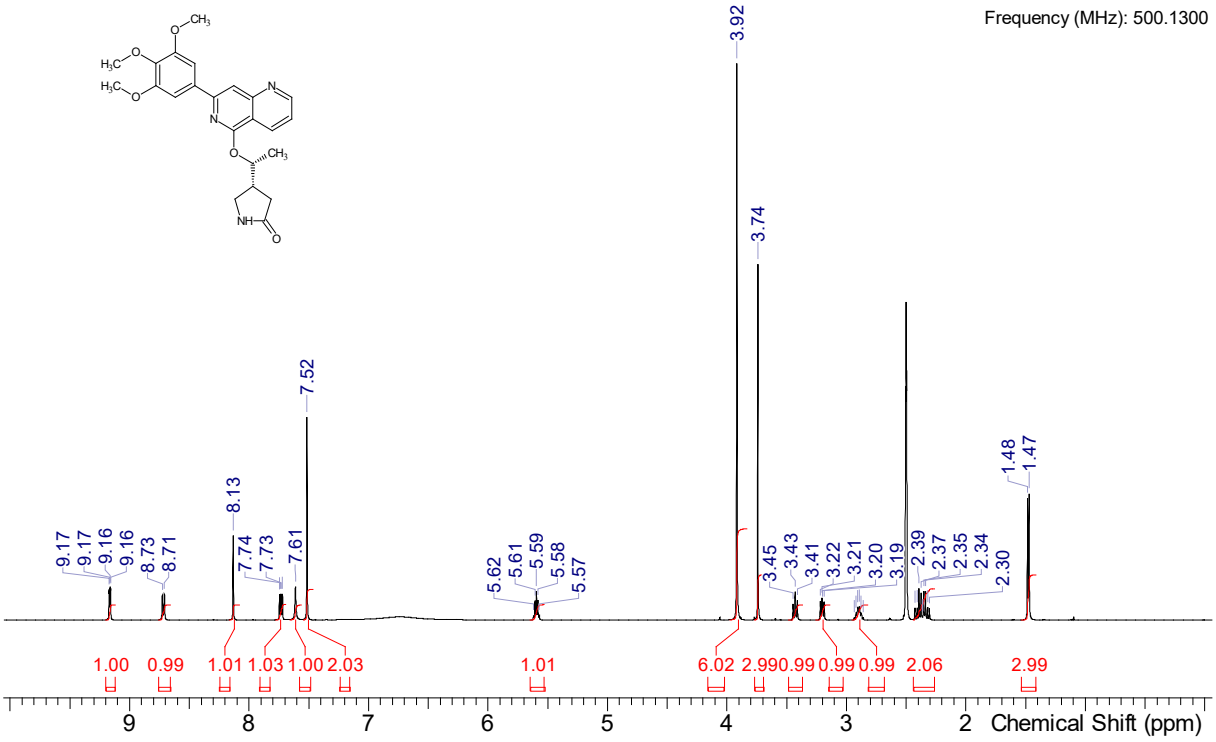


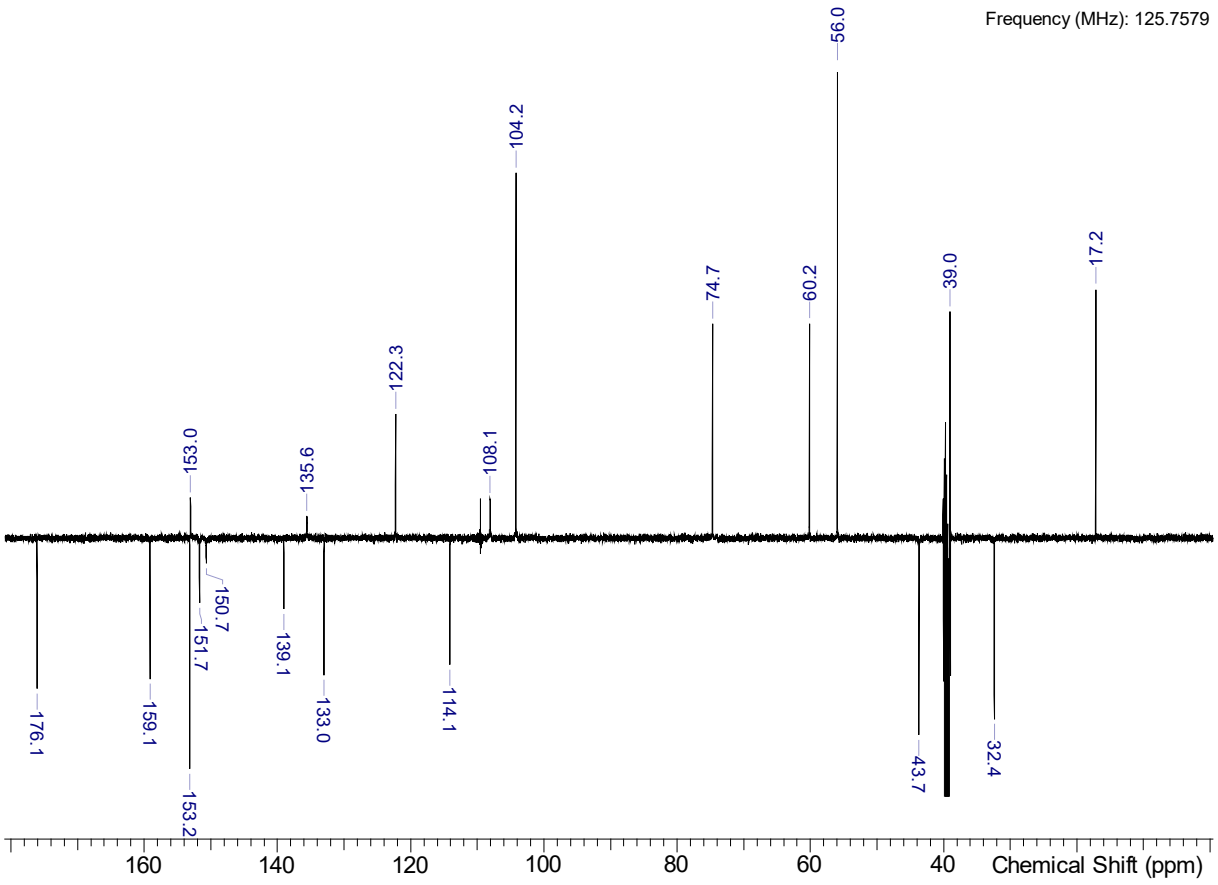
152 g 1 -[(S)-1 -(4-Methoxy-phenyl)-ethyl]-(R)-4-[(R)-1 -[7-(3,4,5-trimethoxy-phenyl)-[1,6]naphthyridine-5-yloxy]-ethyl]-pyrrolidin-2-one was suspended in 1.5 L of toluene. At 20°C 0.86 L of 1 N sodium hydroxide solution was added under vigorous mixing. The toluene phase was separated and the solvent was evaporated. 1.5 L toluene were added to the residue and evaporation was repeated. 176 g of the free base was obtained as an oil. Under inert gas atmosphere the oil was dissolved in 0.5 L trifluoroacetic acid. The solution was stirred for 40 hours at 55°C to 60°C. 2.8 L tert-butylmethylether was added at 45 °C to 50 °C. The suspension was stirred for 1 hour at 20°C and 3 hours at 0 °C. The precipitate was filtered, washed with 2 L of tert.-butylmethylether and dried at 40°C. 165 g (quantitative) crude product as trifluoroacetic acid salt was obtained.

326 g of the trifluoroacetic acid salt were suspended in 2.6 L 2-methyltetrahydrofurane. 0.6 L of a 2 N sodium hydroxide solution was added under vigorous mixing. The organic phase was separated and the aqueous phase was extracted twice with 0.4 L of 2-methyltetrahydrofurane. The combined organic phases were washed several times with 0.6 L of sodium hydroxide solution. The organic phase was dried and the solvent was evaporated under reduced pressure. 240 g (94 %) of the free base was obtained as a foam.

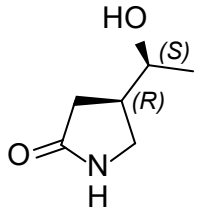
240 g of the base was dissolved in 1 L of ethanol at 40°C to 45 °C. After clarification 72.3 mL of chlorotrimethylsilane was added. Crystallization started. After 5 minutes 1 L of tert- butylmethylether was added. The suspension was stirred for 2 hours at 20 °C. The precipitate was filtered, washed with tert-butylmethylether and dried at 50 °C. 204 g (73 %) yellow solid as hydrochloride salt was obtained from BI-2494.

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.17 (dd, 1H, *J*=1.6, 4.7 Hz), 8.72 (d, 1H, *J*=8.2 Hz), 8.13 (s, 1H), 7.73 (dd, 1H, *J*=4.7, 8.2 Hz), 7.61 (s, 1H), 7.52 (s, 2H), 5.59 (quin, 1H, *J*=6.1 Hz), 3.92 (s, 6H), 3.74 (s, 3H), 3.43 (t, 1H, *J*=9.0 Hz), 3.20 (dd, 1H, *J*=6.3, 9.8 Hz), 2.8-3.0 (m, 1H), 2.3-2.4 (m, 2H), 1.48 (d, 3H, *J*=6.3 Hz);
^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.1, 159.1, 153.2, 153.0, 151.7, 150.7, 139.1, 135.6, 133.0, 122.3, 114.1, 108.1, 104.2, 74.7, 60.2, 56.0, 43.7, 39.0, 32.4, 17.2;
HRMS (*m/z*): $[M+H]^+$ calculated for C23H25N3O5, 424.18670; found, 424.18702;

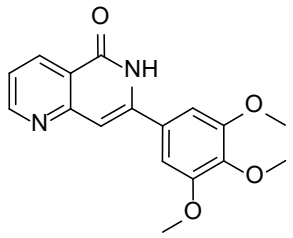




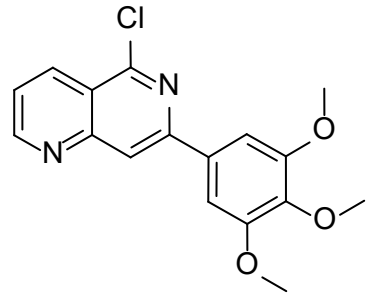
BI-2492 (Compound 82)



0.63 g (4*R*)-4-[(1*S*)-1-hydroxyethyl]-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]pyrrolidin-2-one was dissolved in 3 mL Trifluoroacetic acid and irradiated at 90°C for 1 hour in the microwave. The solvent was evaporated under reduced pressure. The residue was dissolved in warm water and the impurities were extracted with DCM. The aqueous layer was freeze dried to afford 0.4 g (4*R*)-4-[(1*S*)-1-hydroxyethyl]pyrrolidin-2-one. It was used as such in the next step.

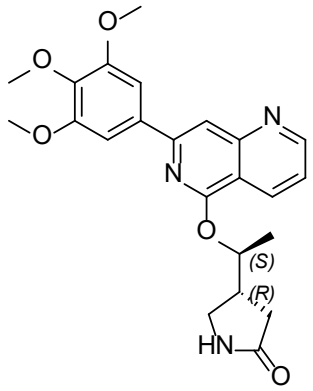


The reaction was carried out under an argon atmosphere. 7 g 2-Methyl-nicotinic acid was suspended in 150 ml of tetrahydrofuran and cooled to -70°C with a bath of ethanol/dry ice. 80 ml lithium diisopropylamide (2.0 M in tetrahydrofuran/n-heptane/ethylbenzene) was added dropwise over 10 min and the mixture was stirred for 2 h at 0°C. It was cooled to -73°C and a solution of 10 g 3,4,5-trimethoxy-benzonitrile in 50 ml tetrahydrofuran was added. The reaction mixture was warmed overnight to ambient temperature. 30 ml water was added and the solvent was distilled off before 200 ml ethyl acetate was added and the precipitate formed was collected. 7.3 g of a solid were obtained (46%).



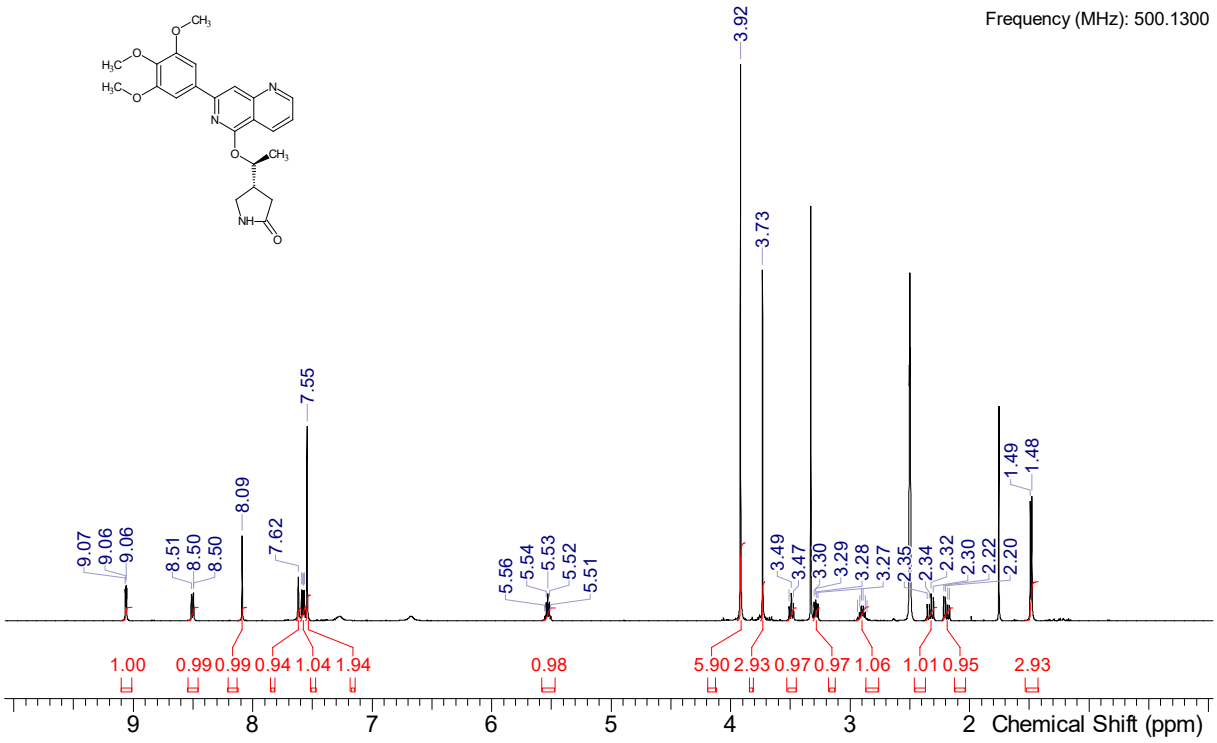
565 mg 7-(3,4,5-Trimethoxy-phenyl)-[1,6]-naphthyridine (5.2) and 15 µL N,N-diethylaniline were stirred into 4 mL phosphorus oxychloride overnight at 100°C and at ambient temperature over 2 days. The reaction mixture was evaporated down, and a small amount of ethyl acetate was added. Upon scratching a precipitate was formed. Methyl-tert-butylether was added and the precipitate was isolated and dried overnight at 50°C under vacuo. 700mg 5-chloro-7-(3,4,*S*-trimethoxy-phenyl)-[1,6]-naphthyridine was obtained (99%).

BI-2492 (Compound 82)



To a solution of 470 mg (4*R*)-4-[(1*S*)-1-hydroxyethyl]pyrrolidin-2-one in 6 mL Dimethylacetamide, 260 mg sodium hydride (60% dispersion) was added at ambient temperature. After 30 min 1.0 g 5-chloro-7-(3,4,*S*-trimethoxy-phenyl)-[1,6]-naphthyridine was added and the reaction mixture was stirred at 40°C for 4 hours. 1 N hydrochloric acid and ethylacetate were added and the layers were separated. The organic layer was washed with sat. $NaHCO_3$ solution and dried over $MgSO_4$. The crude product was purified via normal phase (EtOAc/DCM/MeOH 10/5/1) to afford 480 mg desired product **BI-2492** (38%).

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.06 (dd, 1H, *J*=1.7, 4.3 Hz), 8.50 (dd, 1H, *J*=0.6, 8.2 Hz), 8.09 (s, 1H), 7.62 (s, 1H), 7.58 (dd, 1H, *J*=4.3, 8.4 Hz), 7.55 (s, 2H), 5.53 (quin, 1H, *J*=6.3 Hz), 3.92 (s, 6H), 3.73 (s, 3H), 3.49 (t, 1H, *J*=9.0 Hz), 3.28 (dd, 1H, *J*=6.5, 9.6 Hz), 2.90 (qd, 1H, *J*=7.9, 15.5 Hz), 2.3-2.4 (m, 1H), 2.19 (dd, 1H, *J*=7.9, 16.7 Hz), 1.48 (d, 3H, *J*=6.3 Hz);
^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.0, 159.1, 155.1, 153.6, 153.1, 150.2, 138.6, 133.5, 132.2, 122.1, 113.6, 110.9, 104.0, 74.6, 60.1, 55.9, 43.7, 33.1, 17.4, appr. 40 (under DMSO);
HRMS (*m/z*): $[M+H]^+$ calculated for C23H25N3O5, 424.18670; found, 424.18748;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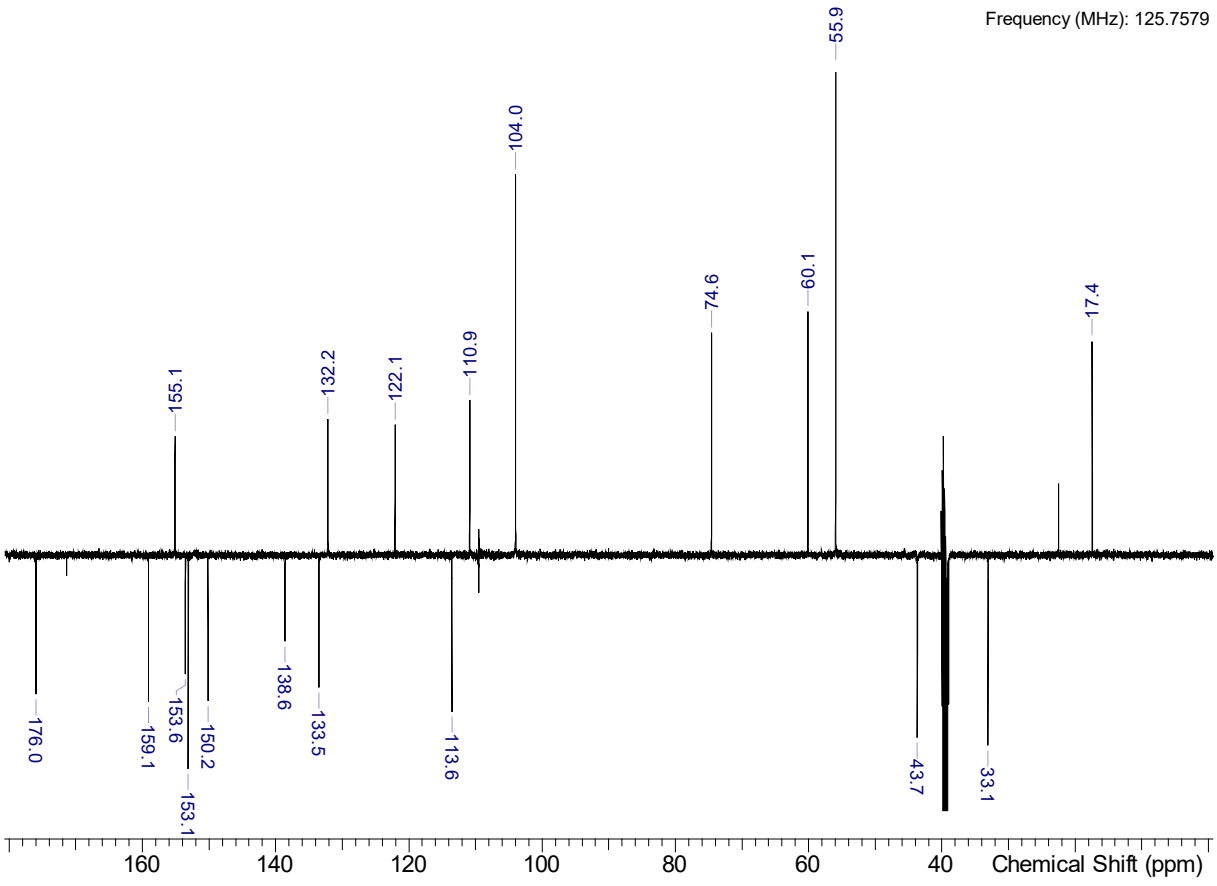
Chemical Shift (ppm)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133.5
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80
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40
Chemical Shift (ppm)