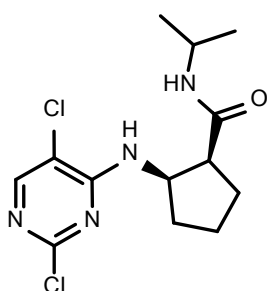




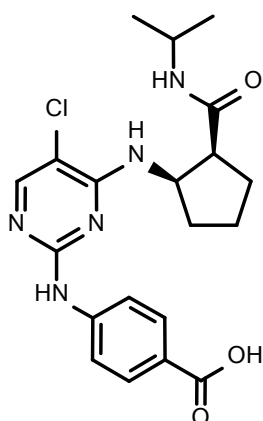
# Aurora B Inhibitor | BI 831266

## Synthesis of BI 831266

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](#).

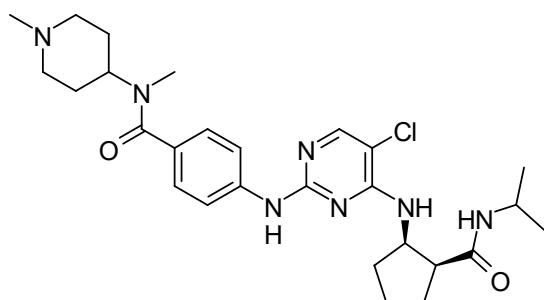


2,4,5-trichloropyrimidine (2.56 g, 13.94 mmol) and (1S,2R)-2-aminocyclopentanecarboxylic acid isopropylamide (2.37 g, 13.94 mmol) were dissolved in DCM (50 mL) and cooled to 0°C. Then DIPEA (4.87 mL, 27.88 mmol) was added dropwise. The reaction mixture was stirred at RT until completion of the reaction. The reaction mixture was washed twice with sat. NH<sub>4</sub>Cl solution. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to yield the desired compound (4.36 g, 13.75 mmol) as a slightly colored solid, MS-ESI+: 317 (M+H)+.



The final compound from last step (2.18 g, 6.87 mmol) and 4-amino-benzoic acid (0.95 g, 6.87 mmol) were suspended in 1-butanol (21.8 mL). After the addition of dioxanic hydrochloric acid (4 M, 0.22 mL, 0.89 mmol) the mixture was refluxed for 2 hours with stirring. After cooling the precipitate formed was filtered off and washed with cold 1-butanol (2x 3mL). After drying in vacuo, the title compound was obtained as a colorless solid (1.77 g, 4.23 mmol).

## BI 831266 (Compound 30)

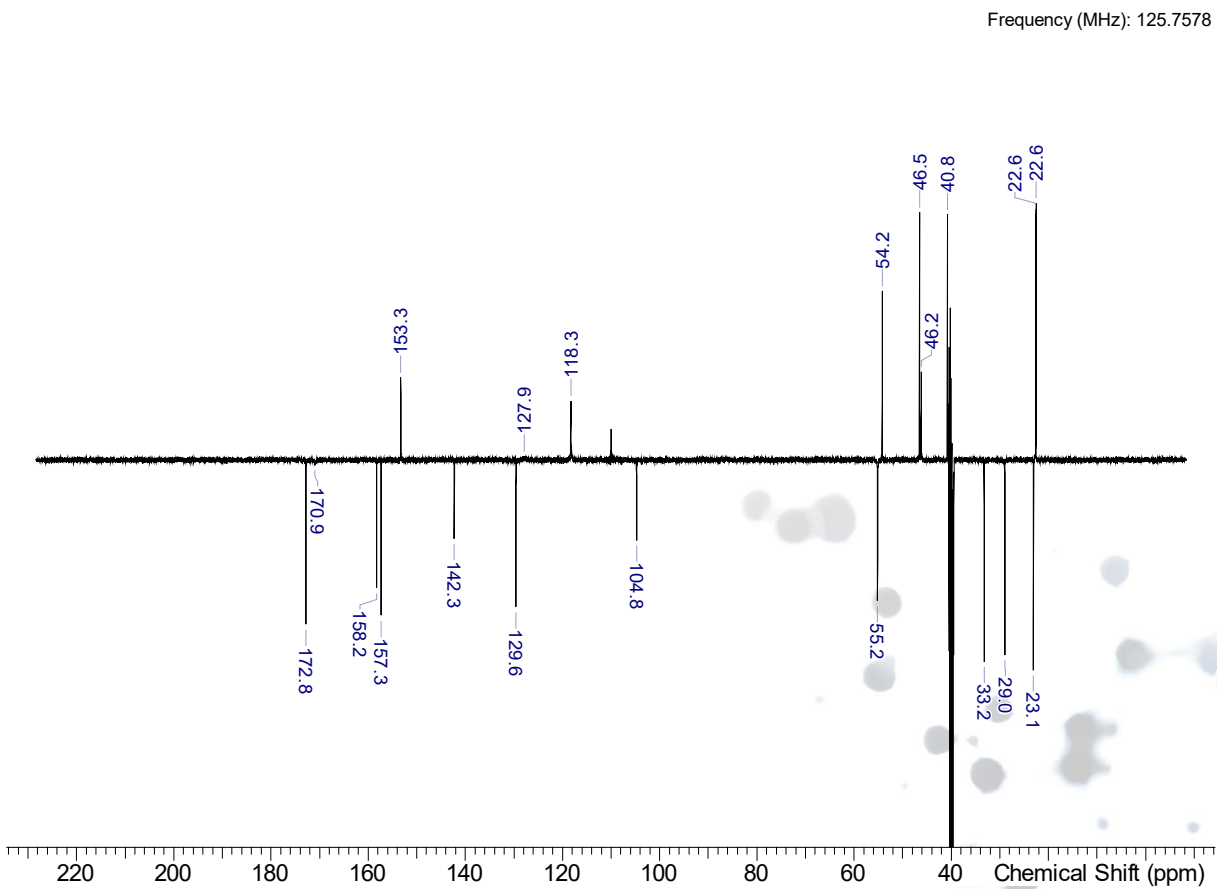
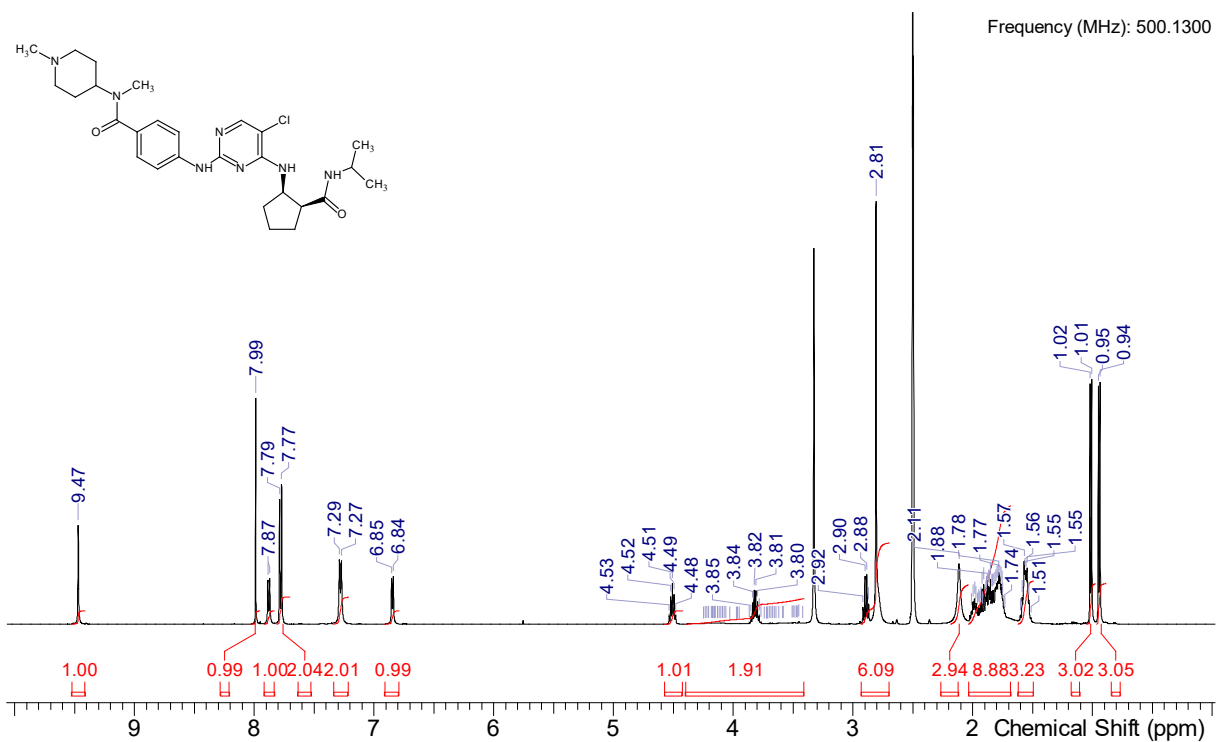


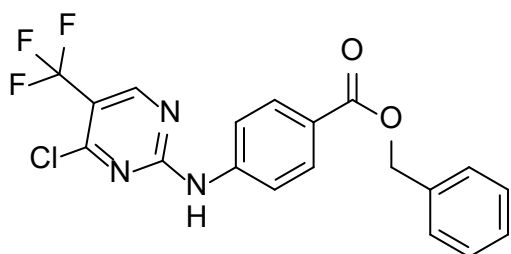
4-[(5-chloro-4-[(1R,2S)-2-[(propan-2-yl)carbamoyl]cyclopentyl]amino]pyrimidin-2-yl)amino]benzoic acid (3.99 g, 9.55 mmol), TBTU (4.47 g, 13.37 mmol) and DIPEA (8.34 mL, 47.74 mmol) were dissolved in DMF (55 mL) and stirred at RT for 30min. 1-Methyl-4-(methylamino)piperidine (1.67 mL, 11.46 mmol) was added. After completion of the reaction the mixture was filtered over AloxB and washed with methanol. The volatiles were removed in vacuo and the crude product was purified via RP-chromatography under acidic conditions. The desired product fractions were pooled and hydrochloric acid (37%, 0.79 mL, 9.55 mmol) was added. After freeze-drying **BI 831266** (4.21 g, 6.93 mmol) was obtained as a colorless HCl salt.

$^1\text{H}$  NMR (DMSO- $d_6$ , 500 MHz)  $\delta$  9.47 (s, 1H), 7.99 (s, 1H), 7.88 (d, 1H,  $J=7.6$  Hz), 7.78 (d, 2H,  $J=8.5$  Hz), 7.28 (d, 2H,  $J=8.2$  Hz), 6.85 (d, 1H,  $J=6.9$  Hz), 4.51 (quin, 1H,  $J=6.9$  Hz), 3.7-3.9 (m, 1H,  $J=6.7, 6.7, 6.7, 13.6$  Hz), 3.4-4.4 (m, 1H), 2.89 (q, 1H,  $J=7.9$  Hz), 2.81 (s, 5H), 2.11 (br s, 3H), 1.7-2.0 (m, 9H), 1.5-1.6 (m, 3H), 1.01 (d, 3H,  $J=6.6$  Hz), 0.94 (d, 3H,  $J=6.6$  Hz).

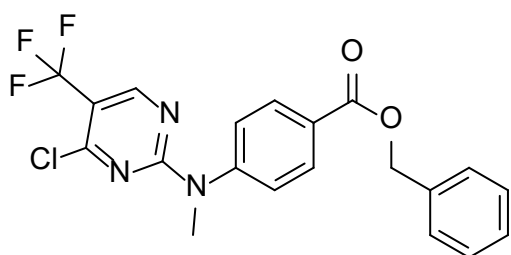
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 125 MHz)  $\delta$  172.8, 170.9, 158.2, 157.3, 153.3, 142.3, 129.6, 127.7, 118.3, 104.8, 55.2, 54.2, 46.5, 46.2, 40.8, 33.2, 29.0, 23.1, 22.6, 22.6; appr. 40 (under DMSO), 2 Carbons not detected.

HRMS ( $m/z$ ):  $[M+H]^+$  calculated for  $\text{C}_{27}\text{H}_{38}\text{ClN}_7\text{O}_2$ , 528.28483; found, 528.28573;

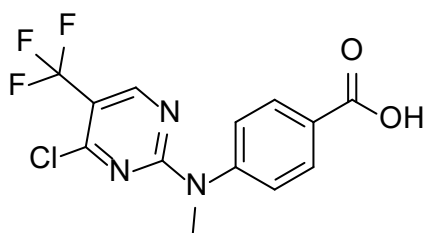




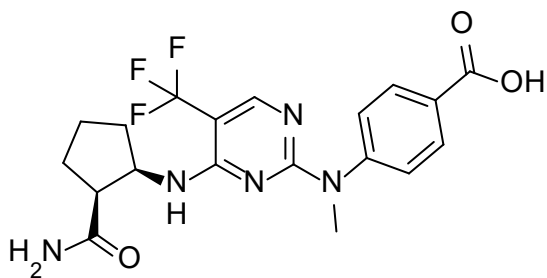
Zinc chloride (31.0 g, 0.23 mol) was cooled to 0°C under inert gas. A solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (50.1 g, 0.23 mol) in acetone (400 mL) was added over a period of 30 min. Then DIPEA (75.5 mL, 0.43 mol), followed by addition of a solution of 4-aminobenzoic acid benzyl ester (50.0 g, 0.23 mol) in acetone (100 mL) was added. The reaction mixture was stirred at 0°C for 60 hours. The reaction was quenched by addition of methanol (500 mL) and water (250 mL). The mixture was stirred at RT for 30 min, then filtered and the precipitate is dissolved in warm THF (850 mL). This solution was added to ice water (850 mL) and stirred for 30 min. The crystals were collected by filtration, washed with MeOH (3x 100 mL) and dried at 45°C to yield compound 1 (63.7 g, 0.16 mol) as a yellow solid.



The product from the last step (200 mg, 0.49 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 24 mg, 0.59 mmol) in DMF (4 mL) under inert gas, at RT. After 30 min methyl iodide (37 µl, 0.59 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the mixture was poured in ice water (100 mL) and extracted with EtOAc (3x 50 mL). The combined organic layers were washed with sat. NaCl solution, dried over MgSO<sub>4</sub> and the volatiles were evaporated to yield title compound (206 mg, 0.49 mmol) as a yellow solid.

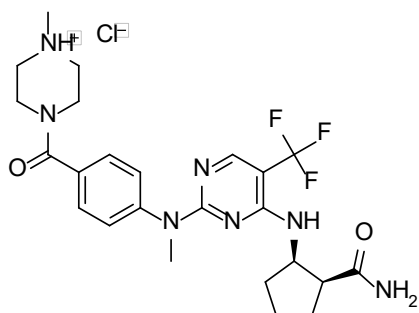


To a solution of the product from the last step (302 mg, 0.72 mmol) in THF (30 mL), 20% Palladium hydroxide on carbon (40 mg) was added and the reaction mixture was stirred under 6 bar H<sub>2</sub> at 40°C for 24 hours. After completion of the reaction the catalyst was removed by filtration over a pad of Celite and washed with THF (3x 30 mL). The volatiles were removed under reduced pressure to yield the title compound (230 mg, 0.69 mmol) as a yellow solid. Crude was used as such for the next step.



To a solution of product from the last step (230 mg, 0.69 mmol) in DMA (1.0 mL), DIPEA (0.30 mL, 1.73 mmol) followed by *cis*-2-Amino-1-cyclopentancarboxamid (racemate) (89 mg, 0.69 mmol) were added. The reaction mixture was stirred at 70°C for 20 hours. The product was purified via RP chromatography under acidic conditions to yield the desired compound (141 mg, 0.33 mmol) as a colorless solid.

## BI-1282 (Compound 31)



To a solution of product from the last step (140 mg, 0.33 mmol) in DMF (9.0 mL), DIPEA (0.33 mL, 1.92 mmol) followed by TBTU (155 mg, 0.46 mmol) were added at RT. After 40min N-methylpiperazine (56  $\mu$ l, 0.50 mmol) was added and the reaction mixture was stirred for further 1 hour. After completion the product was purified via NP chromatography (DCM/ NH<sub>3</sub> in MeOH). The desired product fraction was acidified with 4 M HCl in dioxane and concentrated under reduced pressure to yield **BI-1282** (138 mg, 0.26 mmol) as a colourless HCl salt.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz)  $\delta$  11.45 (br s, 1H), 8.10 (s, 1H), 7.9-8.2 (m, 1H), 7.75 (br s, 1H), 7.5-7.6 (m, 4H), 7.26 (br s, 1H), 4.31 (br s, 1H), 3.5-3.5 (m, 3H), 3.2-3.7 (m, 6H), 3.0-3.2 (m, 2H), 2.82 (q, 1H,  $J=7.9$  Hz), 2.76 (d, 3H,  $J=4.4$  Hz), 1.8-2.0 (m, 3H), 1.6-1.8 (m, 2H), 1.4-1.6 (m, 1H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 125 MHz)  $\delta$  ppm 176.8, 169.2, 156.9, 144.9, 133.4, 128.6, 127.3, 124.5 (d,  $J(CF)=269.8$  Hz), 98.6 (q,  $J(CF)=33.5$  Hz), 54.6, 52.3, 45.2, 42.5, 39.1, 33.0, 29.7, 22.8, 3 Carbons not detected.

HRMS ( $m/z$ ):  $[M+H]^+$  calculated for C<sub>24</sub>H<sub>30</sub>F<sub>3</sub>N<sub>7</sub>O<sub>2</sub>, 506.24858; found, 506.24942;

