Supporting Information

Discovery of BLU-945, a Reversible, Potent, and Wild-Type Sparing Next-Generation EGFR Mutant Inhibitor for Treatment Resistant NSCLC

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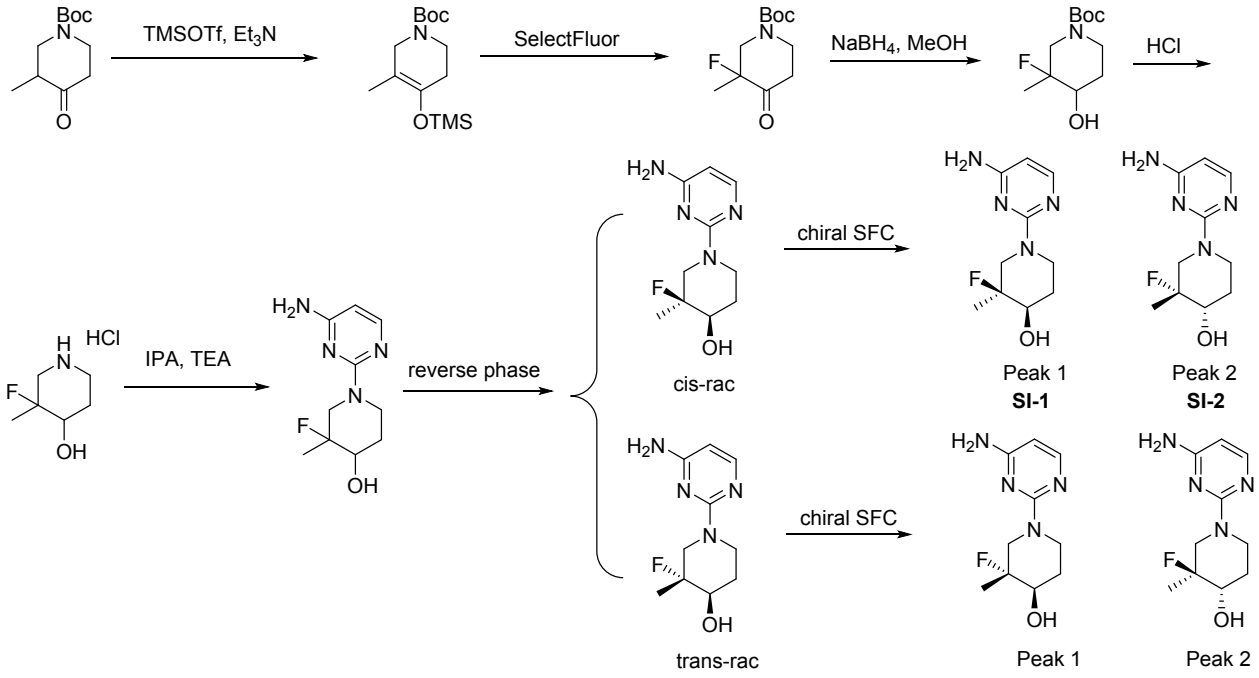
1. General Considerations: Synthesis

All solvents employed were commercially available anhydrous grade, and reagents were used as received unless otherwise noted. Compound purity of all compounds was assessed by HPLC to confirm >95% purity. The liquid chromatography-mass spectrometry (LC-MS) data were obtained with an Agilent model-1260 LC system using an Agilent model 6120 mass spectrometer utilizing ES-API ionization fitted with an Agilent Poroshel 120 (EC-C18, 2.7 µm particle size, 3.0 x 50 mm dimensions) reverse-phase column. The mobile phase consisted of a mixture of solvent 0.1% formic acid in water and 0.1% formic acid in acetonitrile. A constant gradient from 95% aqueous/5% organic to 5% aqueous/95% organic mobile phase over the course of 4 minutes was utilized. The flow rate was constant at 1 mL/min. Alternatively, the LC-MS data were obtained with a Shimadzu LCMS system using an Shimadzu LCMS mass spectrometer utilizing ESI ionization fitted with an Agilent (Poroshel HPH-C18 2.7 µm particle size, 3.0 x 50 mm dimensions) reverse-phase column. The mobile phase consisted of a mixture of solvent 5 mM NH_4HCO_3 (or 0.05% TFA) in water and acetonitrile. A constant gradient from 90% aqueous/10% organic to 5% aqueous/95% organic mobile phase over the course of 2 minutes was utilized. The flow rate was constant at 1.5 mL/min. Preparative HPLC was performed on a Shimadzu Discovery VPR Preparative system fitted with a Luna 5 µm C18(2) 100 Å, AXIA packed, 250 x 21.2 mm reverse-phase column. Alternatively, the preparative HPLC was performed on a Waters Preparative system fitted with Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5 µm; the mobile phase consisted of a mixture of solvent water (10 mmol/L NH_4CO_3 + 0.05% $NH_3•H_20$) and acetonitrile. A constant gradient from 95% aqueous/5% organic to 5% aqueous/95% organic mobile phase over the course of 11 minutes was utilized. The flow rate was constant at 60 mL/min. Reactions carried out in a microwave were performed in a Biotage Initiator microwave unit. Silica gel chromatography was performed on a Teledyne Isco CombiFlash Rf unit, a BiotageR Isolera Four unit, or a BiotageR Isolera Prime unit. ^{1}H NMR spectra were obtained with a Varian 400 MHz Unity Inova 400 MHz NMR instrument, Avance 400 MHz Unity Inova 400 MHz NMR instrument or an Avance 300 MHz Unity Inova 300 MHz NMR instrument. Unless otherwise indicated, all protons were reported in DMSO-d_6 solvent as parts-per million (ppm) with respect to residual DMSO (2.50 ppm). Chiral-HPLC was performed on an Agilent 1260 Preparative system. Chiral-SFC purification was performed with a Waters preparative system.

2. Synthesis & Characterization of Key Intermediates

Synthesis of (3S,4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (peak1, SI-1)



*Step 1: Synthesis of tert-butyl 3-methyl-4-(trimethylsilyloxy)-5,6-dihydropyridine-l(2H)-carboxylat*e. Trimethylsilyl trifluoromethanesulfonate (12.50 g, 56.25 mmol, 1.20 equiv.) was added drop wise to a pre-cooled solution of tert-butyl3-methyl-4-oxopiperidine-l-carboxylate (10 g, 46.88 mmol, 1 equiv.) and TEA (11.38 g, 112.5 mmol, 2.40 equiv.) in toluene (100 mL) at 0 °C. The resulting mixture was stirred for 4 h at 0 °C. The solution was quenched with water (50 mL) and extracted twice with EA. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuum to afford the title compoud the title compound (10.5 g, 78.5 %) as yellow oil. IH-NMR (400 MHz, 6d-DMSO) δ ppm 3.68-3.66 (m, 2H), 3.43 (t, 2H, J = 5.8 Hz), 2.05 (tq, 2H, J = 6.0, 2.0 Hz), 1.53 - 1.47 (m, 3H), 1.41 (s, 9H), 0.15 (s, 9H).

Step 2: Synthesis oftert-butyl 3-fluoro-3-methyl-4-oxopiperidine-l-carboxylate. A mixture of tert-butyl 5-methyl-4-[(trimethylsilyl)oxy]-l,2,3,6-tetrahydropyridine-l-carboxylate (10 g, 35.0 mmol, 1 equiv.) and SelectFluor (13.6 g, 38.5 mmol, 1.10 equiv.) in acetonitrile (100 mL) and stirred for 1 h at 0 °C. The solution was diluted with water (100 mL) and extracted with EA. The organic layers were washed with brine, dried over anhydrous sodium sulfate, fdtered and concentrated in vacuum. This resulted in 8 g (98.8 %) of the title compound as light-yellow oil.

*Step 3: Synthesis oftert-butyl 3-fluoro-4-hydroxy-3-methylpiperidine-l-carboxylat*e. The mixture of tert-butyl 3-fluoro-3-methyl-4-oxopiperidine-l-carboxylate (7 g, 30.2 mmol, 1 equiv.) and $NaBH_4$ (1.37 g, 36.2 mmol, 1.12 equiv.) in methanol (70 mL) was stirred for 3 h at rt. The solution was extracted with EA. The organic layers were washed with brine, dried over anhydrous sodium sulfate, fdtered and concentrated in vacuum. This resulted in the crude compound 7 g (99.4 %) of the title compound light-yellow oil.

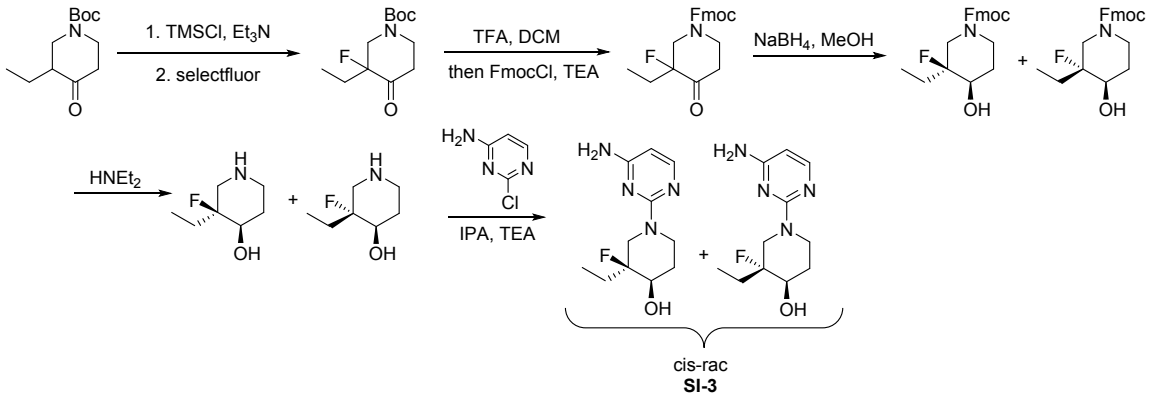
Step 4: Synthesis of 3-fluoro-3-methylpiperidin-4-ol hydrochloride: To a reaction vessel was added tert-butyl 3 -fluoro-4-hydroxy-3-methylpiperidine- 1-carboxylate (7 g, 30.0 mmol), DCM (70 mL) and hydrochloric (4 M in dioxane, 50 mL). The resulting mixture was stirred at rt for 3 h. The reaction precipitate was collected by filtration to afford the title compound the title compound (4.5 g) as a white solid.

Step 5: Synthesis of l-(4-aminopyrimidin-2-yl)-3 -fluoro-3 -methylpiperidin-4-ol: The mixture of 2-chloropyrimidin-4-amine (2.7 g, 20.8 mmol, 1 equiv.), 3-fluoro-3-methylpiperidin- 4-ol hydrochloride (3.86 g, 22.8 mmol, 1.10 equiv.) and TEA (6.30 g, 62.4 mmol, 3 equiv.) in isopropyl alcohol (45 mL) stirred for 5 h at 130 °C in a sealed vial. The reaction mixture was cooled to rt. The solids were fdtered out. The fdtrate was concentrated under vacuum to give the crude compound the title compound (6 g) as a yellow oil. The crude product l-(4-aminopyrimidin-2-yl)-3 -fluoro-3 -methylpiperidin-4-ol was purified by HPFLASH with the following conditions (Column: XBridge Prep OBD C18 Column 30x 150mm 5um;Mobile Phase A:Water(3 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 100 mL/min; Gradient: 10% B to 30% B in 35 min; 254/220 nm; Rt: 21.12 min). The fractions containing the desired compound were evaporated to dryness to afford cis racemate (1.3 g, 26.1 %) as a white solid and trans racemate (500 mg, 10.0 %) as a white solid.

The cis racemate (3S,4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol was separated by Prep-Chiral-SFC-HPLC with the following conditions (Column: Phenomenex Lux 5u Cellulose-3, 5*25cm,5um;Mobile Phase A:C02: 50, Mobile Phase B: MEOH (0.1% DEA): 50; Flow rate: 170 mL/min; 220 nm). The fractions containing the desired compound were evaporated to dryness to afford (3S,4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (peak 1, **SI-1**) (Stereochemistry assigned by xray crystallography of Compound **24**) as a white solid and (3R,4S)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (500 mg, peak 2, **SI-2**) as a white solid. Analytical Data: LC-MS: (ES, m/z) = 227 [M+1]; 1H-NMR (400 MHz, 6d-DMSO) δ ppm 7.71 (d, 1H,J = 5.6 Hz), 6.37 (s, 2H), 5.69 (d, 1H,J = 5.6 Hz), 4.93 (d ,1H, J = 6.5 Hz), 4.66 (ddd, 1H,J = 14.1, 9.1, 2.2 Hz), 4.60 - 4.50 (m, 1H), 3.44 (ddt, 1H,J = 24.8, 11.0, 5.6 Hz), 3.02 - 2.78 (m, = 2H),1.69- 1.53 (m, 2H), 1.31 (d, 3H, J= 21.2 Hz).

The trans racemate was separated by Prep-Chiral-SFC with the following conditions (Column: CHIRALPAK AD-H-TC001 SFC, 2*25cm,5um;Mobile Phase A:C02: 70, Mobile Phase B: MeOH Preparative: 30; Flow rate: 40 mL/min; 220 nm) The fractions containing the desired compound were evaporated to dryness to afford (3R,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol or (3S,4S)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (180 mg) as a white solid (peak 1) and (3S,4S)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol or (3R,4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (190 mg) as a white solid (peak 2). Analytical Data: LC-MS: (ES, m/z) = 227 [M+1]; 1H-NMR (300 MHz, 6d-DMSO) δ ppm 7.72 (d, 1H, J= 5.7 Hz), 6.40 (s, 2H), 5.70 (d, 1H, J= 5.6 Hz), 5.24 (d, 1H, J= 4.5 Hz), 3.83 - 3.56 (m, 5H), 1.78 (ddt, 1H, J= 12.9, 10.0, 4.7 Hz), 1.48- 1.36 (m, 1H), 1.24 (d, 3H, J= 22.5 Hz).

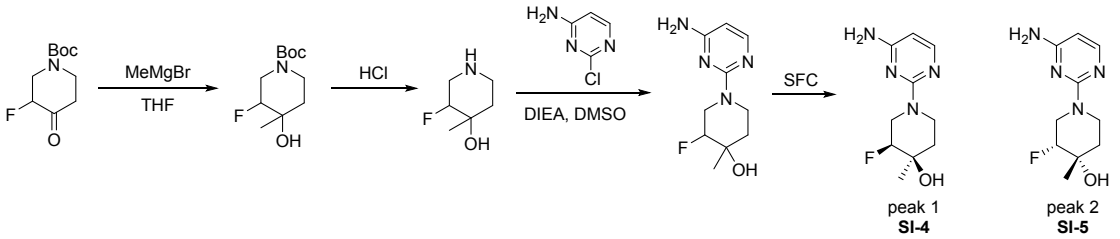
Synthesis of rac-(cis)-l-(4-aminopyrimidin-2-yl)-3-ethyl-3-fluoropiperidin-4-ol (SI-3).



Step1: rac-tert-butyl 3-ethyl-3-fluoro-4-oxopiperidine-l-carboxylate. A solution of tert-butyl 3-ethyl-4-oxopiperidine-l-carboxylate (7.95 g, 35 mmol, 1 equiv.) in DMF (35 mL) was added TEA (7.07 g, 70.0 mmol, 2 equiv.), followed by TMSCl (5.67 g, 52.5 mmol, 1.50 equiv.) at rt. The reaction was carried on at 120 °C for 18 h before quenching with sat. NaHCCE. The mixture was extracted with MTBE. The organic layer was combined and concentrated. The residue was dissolved in DMF (70 mL), Selectfluor (12.3 g, 35 mmol, 1 equiv) was added at O °C. The mixture was stirred for 2h at rt and then quenched with brine. The mixture was extracted with EA. The organic layer was combined and concentrated to afford a mixture of tert-butyl 3-ethyl-3-fluoro-4-oxopiperidine-l-carboxylate, tert-butyl 3-ethyl-5-fluoro-4-oxopiperidine-l-carboxylate and tert-butyl-3- ethyl-4-oxopiperidine-l-carboxylate as yellow oil (6.5 g).

Step2: rac-(9H-fluoren-9-yl)methyl 3-ethyl-3-fluoro-4-oxopiperidine-l-carboxylate. A solution of tert-butyl 3-ethyl-3-fluoro-4-oxopiperidine-l-carboxylate (6.5 g, 26.4 mmol, 1 equiv.) in TFA (20 mL) and DCM (60 mL) was stirred at rt for 2 h. The mixture was concentrated and redissolved in DCM (120 mL), TEA (13.3 g, 132 mmol, 5.00 equiv.) was added, followed by (9H-fluoren-9-yl)methyl carbonochloridate (10.2 g, 39.5 mmol, 1.50 equiv.). The reaction was carried on at rt for 2h. Sat. NaHCO3 was added. The mixture was extracted with DCM. The organic layer was combined and concentrated. The residue was purified by silica gel column chromatography (DCM/EA=30:1) to afford the title compound **SI-3** (3.7 g, 30.5% over 2 steps) as a colorless syrup. LC-MS: (ES, m/z) = 390 [M+23].

Synthesis of (3S, 4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-4-methylpiperidin-4-ol (SI-4, peak 1)



Step1: rac-cis-tert-butyl 3-fluoro-4-hydroxy-4-methylpiperidine-1-carboxylate. MeMgBr (9.2 mL, 27.6 mmol) was added to a solution of tert-butyl 3-fluoro-4-oxopiperidine-lcarboxylate (5 g, 2.3 mmol) in THF (50 mL) at -78 °C. The mixture was stirred overnight at rt. The reaction mixture was carefully diluted with sat. NH4CI (aq), then extracted with EA and washed with brine. The organic layer was dried over NaaSCE, fdtered, evaporated to afford the title compound 4.8 g (crude) as a yellow solid. LC-MS: (ES, m/z) = 178 [M+l-56].

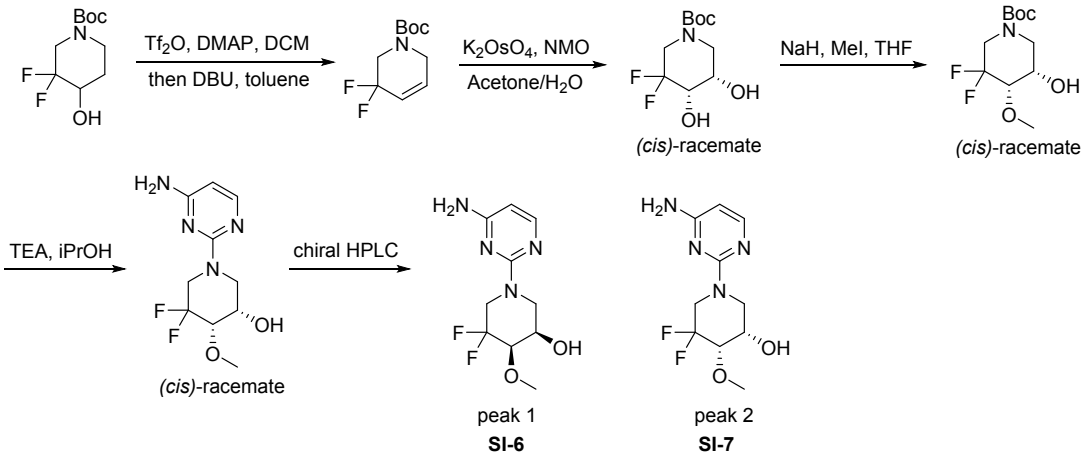
Step 2: rac-cis-3-fluoro-4-methylpiperidin-4-ol. Tert-butyl 3-fluoro-4-hydroxy-4-methylpiperidine-l-carboxylate (4.8 g, 20 mmol) in HCl/dioxane (50 mL) was stirred at rt for 4h. The reaction mixture was evaporated to afford 3-fluoro-4-methylpiperidin-4-ol 3 g (crude) as a yellow solid. The crude product was used directly for next step. LC-MS: (ES, m/z) = 134 [M+l].

Step 3: rac-cis-l-(4-aminopyrimidin-2-yl)-3-fluoro-4-methylpiperidin-4-ol. The mixture of 2-chloropyrimidin-4-amine (1.5 g, 11.5 mmol), 3-fluoro-4-methylpiperidin-4-ol (3 g, crude) and DIPEA (11.9 g, 92.3 mmol) in DMSO (40 mL) was stirred overnight at 120 °C. The reaction mixture was diluted with water, extracted with EA and washed with brine. The organic layer was dried over Na_2SO_4, filtered, evaporated, purified by column chromatography (PE:EA=1:1) to afford the title compound (1.3 g) as a light-yellow solid. LC-MS: (ES, m/z) = 227 [M+l].

Step 4: Synthesis of (3S,4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-4-methylpiperidin-4-ol. Rac-cis l-(4-aminopyrimidin-2-yl)-3-fluoro-4-methylpiperidin-4-ol was separated by preparative SFC with following conditions: Column: CHIRAL Cellulose-SJ

(4.6* 150mm,5um); Mobile Phase: CO2/MeOH(0.1%DEA); Flow Rate: 4 g/min); to afford peak 1: (3S,4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-4-methylpiperidin-4-ol (450 mg, **SI-4**, Stereochemistry assigned by xray crystallography) as a white solid and peak 2: (3R,4S)-l-(4-aminopyrimidin-2-yl)-3-fluoro-4-methylpiperidin-4-ol (**SI-5**, 470 mg) as a white solid. peak 1: (3 S, 4R)-l-(4-aminopyrimidin-2-yl)-3-fluoro-4-methylpiperidin-4-ol, ^{1}H-NMR (300 MHz, DMSO-*6d*) δ ppm 7.73 (d, IH J = 5.6 Hz), 6.40 (s, 2H), 5.72 (d, 1H, J = 5.6 Hz), 4.71 (s, 1H), 4.39 - 3.92 (m, 3H), 3.38 (dddd, 2H, J = 40.5, 13.6, 10.3, 4.6 Hz), 1.62 (q, 1H, J = 6.2 Hz), 1.42 (td, 1H, J = 13.6, 12.0, 4.3 Hz,), 1.20 (s, 3H).

Synthesis of (3R,4R)-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol (SI-6, peak 1)



Step 1: Synthesis oftert-butyl 5,5-difluoro-5,6-dihydropyridine-l(2H)-carboxylate. A solution oftert-butyl 3,3-difluoro-4-hydroxypiperidine-l-carboxylate (355 mg, 1.5 mmol, 1 equiv.) in DCM (6 mL) was added DMAP (274 mg, 2.25 mmol, 1.5 equiv.), followed by trifluoromethanesulfonyl trifluoromethanesulfonate (550 mg, 1.95 mmol, 1.3 equiv.) at O °C. The reaction was carried on at O °C for Ih before quenching with sat. NaHCO3 (30 mL). The mixture was extracted with DCM (10 mL*3). The organic layer was combined and concentrated. The residue was dissolved in toluene (5 mL). DBU (569 mg, 3.75 mmol, 2.5 equiv) was added. The reaction was carried on at 70 °C for 18h. After cooling down to r.t., the mixture was dilluted with MTBE (50 mL). The mixture was washed with water (10 mL). The organic layer was combined and concentrated. The residue was purified by silica gel column chromatography (PE/EA=10:1) to afford the title compound (260 mg, 79.3%) as a light-yellow oil. ^{1}H-NMR (400 MHz, CD3Cl) δ ppm 6.23 - 6.17 (m, 1H), 5.98 - 5.92 (m, 1H), 4.06 -4.00 (m, 2H), 3.91-3.65 (m, 2H), 1.51 (s, 9H).

Step 2: Synthesis oftert-butyl cis-3,3-difluoro-4,5-dihydroxypiperidine-l-carboxylate. A mixture of tert-butyl 3,3-difluoro-l,2,3,6-tetrahydropyridine-l-carboxylate (153 mg, 700 pmol, 1 equiv.) in acetone (4 mL) and H2O (1 mL) was added K2OSO4. 2H2O (12.8 mg, 35 pmol, 0.05 equiv.). and NMO (244 mg, 2.1 mmol, 3 equiv.) at rt. The reaction was carried on at 40 °C for 18 h. After cooling down to rt, the mixture was diluted with EA (50 mL), washed with 10% Na2S203 solution (10 mL) and water (10 mL). The organic layer was concentrated, the residue was purified by silica gel column chromatography (DCM/EA=2:1) to afford the title compound (71 mg, 40.1%) as a white solid. ^{1}H-NMR (400 MHz, 6d-DMSO) δ ppm 5.88 (d, 1H, J=5.1 Hz), 5.18 (d, 1H, J=5.9 Hz), 3.96-3.60 (m, 3H), 3.60 - 3.44 (m, 1H), 3.34 - 3.19 (m, 1H), 3.10 - 2.76 (m, 1H), 1.40 (s, 9H).

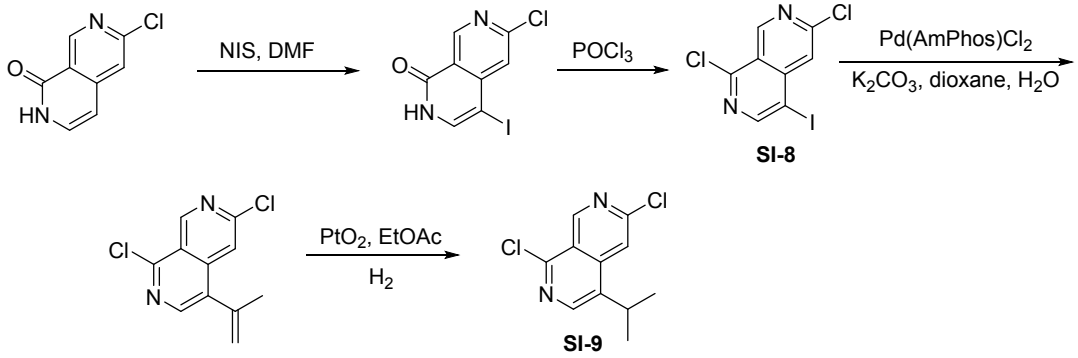
Step 3: Synthesis oftert-butyl cis-3,3-difluoro-5-hydroxy-4-methoxypiperidine-l-carboxylate. A solution oftert-butyl cis-3,3-difluoro-4,5-dihydroxypiperidine-l-carboxylate (69.6 mg, 275 pmol, 1 equiv.) in THF (2 mL) was added NaH (10.9 mg, 275 pmol, 1 equiv., 60%) at 0 °C. After 30 min, MeI (39.0 mg, 275 pmol, 1 equiv.) was added. The reaction was carried on at 0 °C for Ih and at rt for 18h. After quenching with sat. NH4CI (10 mL), the mixture was extracted with EA (5 mL*3). The organic layer was combined and concentrated. The residue was purified by silica gel column chromatography (DCM/EA=2:1) to afford the title compound (22 mg, 30%) as a colourless syrup.

Step 4: Synthesis of cis-5,5-difluoro-4-methoxypiperidin-3-ol. A solution of tert-butyl cis-3,3-difluoro-5-hydroxy-4-methoxypiperidine-l-carboxylate (240 mg, 900 pmol, 1 equiv.) in TFA (1 mL) and DCM (3 mL) was stirred at rt for 3 h and concentrated to afford the title compound (220 mg, crude) as colorless oil. LC-MS: (ES, m/z) = 168 [M+l].

Step 5: Synthesis of cis-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol and (3S,4S)-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol. 220 mg of cis-5,5-difluoro-4-methoxypiperidin-3-ol was dissolved in IPA (2 mL). 2-chloropyrimidin- 4-amine (116 mg, 900 pmol, 1 equiv.) was added, followed by TEA (454 mg, 4.50 mmol, 5 equiv.). The reaction was carried on at 100 °C for 18h. After cooling down to rt, the mixture was concentrated. The residue was purified by prep-TLC (DCM/MeOH=20:1) to afford (3S,4S)-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol (50

mg, 21.36%) as a white solid. The compound was separated by prep-chiral-HPLC with following conditions: CHIRAL Cellulose-SB4.6* 100mm 3um; mobile phase: Hex(0.1%DEA):IPA=70:30;Flow : 1.0 mL/min; to afford peak 1: (3R,4R)-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol or (3S,4S)-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol (20 mg) as pale-yellow solid (**SI-6**) and peak 2: (3R,4R)-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol or (3S,4S)-l-(4-aminopyrimidin-2-yl)-5,5-difluoro-4-methoxypiperidin-3-ol (20 mg) as pale-yellow solid (**SI-7**). LC-MS: (ES, m/z) = 261 [M+1]; IH-NMR (300 MHz, CD_3Cl) δ ppm 7.95 (d, 1H,J=5.6 Hz), 5.82 (d, 1H, J=5.6 Hz), 4.87 - 4.70 (m, 1H), 4.67 - 4.48 (m, 3H), 3.91 (s, 1H), 3.67 (d, 3H, J=10 Hz), 3.67- 3.60 (m, 1H), 3.51 (ddd, 1H, J=29.0, 14.0, 1.8 Hz), 3.12 (dd, 1H, J=12.9, 10.1 Hz), 2.41 (s, 1H).

Synthesis of l,6-dichloro-4-isopropyl-2,7-naphthyridine (SI-9).



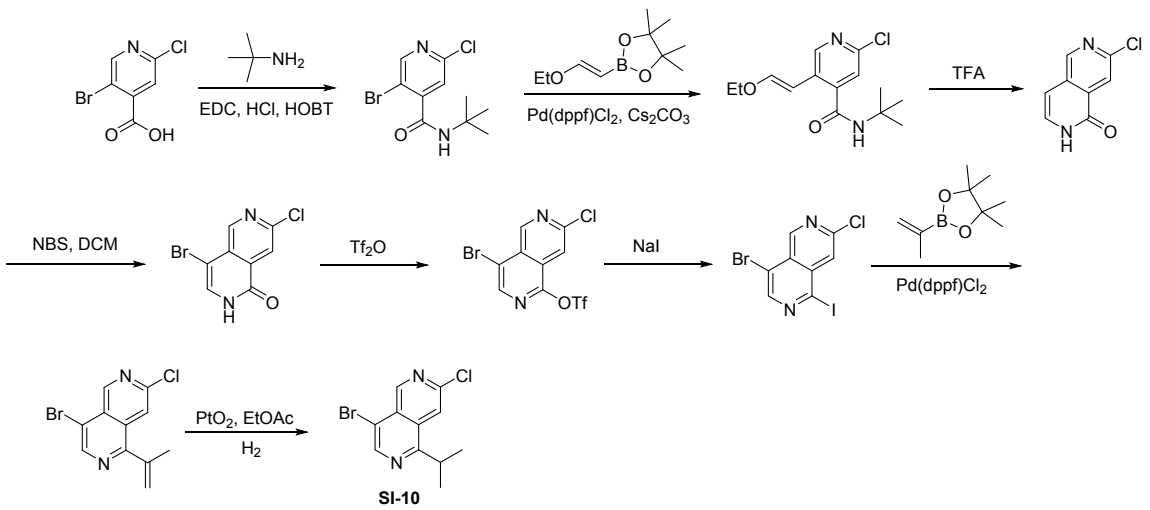
Step 1: Synthesis of 6-chloro-4-iodo-2,7-naphthyridin-l(2H)-one. To a solution of 6-chloro-l,2-dihydro-2,7-naphthyridin-l-one (50 g, 0.276 mol) in DMF (300 mL), NIS (74 g, 0.33 mol) was added at O °C and the mixture was stirred overnight at rt. The reaction mixture was filtered and the filtered cake was washed by water and dried under vacuum to afford the title compound (60 g, 70%) as a light-yellow solid. LC-MS: (ES, m/z) = 307 [M+l], ^{1}H NMR (300 MHz, DMSO-d6) δ 12 (s, 1H), 9.02 (s, 1H), 7.89 (d, 1H, J = 6.0 Hz), 7.44 (s, 1H).

Step 2: Synthesis of l,6-dichloro-4-iodo-2,7-naphthyridine. A mixture of 6-chloro-4-iodo-l,2-dihydro-2,7-naphthyridin-l-one (60 g, 0.196 mol) in $POCl_3$ (320 mL) was stirred at 100 °C for 1.5 h. LCMS showed the starting material was consumed. The mixture was concentrated and neutralized with cooled saturated aq. $NaHCO_3$. The mixture was extracted with EA 3*300 mL. The combined organic layers were dried over Na_2SO_3. filtered and concentrated in reduced pressure to give l,6 dichloro-4-iodo-2,7-naphthyridine (**SI-8**, 53 g, 84%) as a yellow solid. LC-MS: (ES, m/z) = 325 [M+l].

Step 3: Synthesis of l,6-dichloro-4-(prop-l-en-2-yl)-2,7-naphthyridine. To a solution of l,6-dichloro-4-iodo-2,7-naphthyridine (30 g, 92.5 mmol) in 1,4-dioxane/$H_2$0 (300/70 mL) was added 4,4,5,5-tetramethyl-2-(prop-l-en-2-yl)-l,3,2-dioxaborolane (15 g, 93 mmol), K2CO3 (37.8 g, 276 mmol) and PdAMPhosCl_2/ Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (3 g, 4.2 mmol). The resulting solution was stirred for 0.5 h at 50 °C. LCMS showed the reaction is complete. The mixture was cooled to rt and diluted with 200 mL of water. The resulting solution was extracted with 2x300 mL of EA and the organic layers combined. The resulting mixture was washed with 200 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The product was purified by chromatography with EA: PE (1: 10). This resulted in 15 g (68.1%) of l,6-dichloro-4-(prop-l-en-2-yl)-2,7-naphthyridine as white solid. LC-MS: (ES, m/z) = 239 [M+l].

Step 4: Synthesis of l,6-dichloro-4-isopropyl-2,7-naphthyridine. To a solution of l,6-dichloro-4-(prop-l-en-2-yl)-2,7-naphthyridine (4 g, 16.8 mmol) in EA (300 mL) was added Pt_2O (5 g, 22 mmol). The resulting mixture was stirred at 25 °C for 24 h under H_2 atmosphere. The solid was filtered out. The filtrate was concentered under vacuum. The residue was purified by chromatography (EA:PE=1:8) to give (**SI-9**, 3 g, 75%) of l,6-dichloro-4-(propan-2-yl)-2,7-naphthyridine as a white solid. LC-MS: (ES, m/z) = 241 [M+l], IH NMR (300 MHz, DMSO-d6) δ 9.47 (d, 1H, J = 0.8 Hz), 8.47 (d, 1H, J = 0.7 Hz), 8.26 (d, 1H, J = 0.8 Hz), 3.64 (p, 1H, J = 6.8 Hz), 1.33 (d, 6H, J = 6.9 Hz).

Synthesis of 4-bromo-7-chloro-l-isopropyl-2,6-naphthyridine (SI-10)



SI-10

Step 1: Synthesis of 5-bromo-N-tert-butyl-2-chloroisonicotinamide. Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 5-bromo-2-chloropyridine-4-carboxylic acid (4 g, 16.9 mmol) in DMF (30 mL), 2- methylpropan-2-amine (1.47 g, 20.2 mmol), EDC HCl (4.85 g, 25.3 mmol) and HOBT (3.41 g, 25.3 mmol). The resulting solution was stirred overnight at rt. The resulting solution was added water and suspension was extracted with EA, and then the organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by FLASH with PE/EA (2:1). This resulted in 3 g (60.9 %) of 5-bromo-N-tert-butyl-2-chloropyridine-4-carboxamide as a white solid. LC-MS: (ES, m/z) = 293 [M+1]; ^{1}H NMR (300 MHz, DMSO-d6) δ 8.64 (s, 1H), 8.30 (s, 1H), 7.58 (s, 1H), 1.36 (s, 9H).

Step 2: Synthesis of (E)-N-tert-butyl-2-chloro-5-(2-ethoxyvinyl)isonicotinamide. Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 5-bromo-N-tert-butyl-2-chloropyridine-4-carboxamide (2 g, 6.85 mmol) in dioxane (30 mL) and H2O (6 mL), 2-[(E)-2-ethoxyethenyl]-4,4,5,5-tetramethyl-l,3,2-dioxaborolane (1.49 g, 7.53 mmol), CS2CO3 (4.46 g, 13.7 mmol) and Pd(dppf)Cl_2 (501 mg, 685 μmol). The resulting solution was stirred for 2 h at 80 °C. The resulting solution was diluted with water and extracted with EA, and then the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by FLASH with PE/EA (2:1). This resulted in 1.2 g (62.1 %) of N-tert-butyl-2-chloro-5-[(E)-2-ethoxyethenyl]pyridine-4-carboxamide as a yellow solid. LC-MS: (ES, m/z) = 283 [M+1]; ^{1}H NMR (300 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.20 (s, 1H), 7.35 (d, 1H, J = 13.0 Hz), 7.28 (s, 1H), 5.79 (d, 1H, J = 13.0 Hz), 3.90 (q, 2H, J = 7.0 Hz), 1.35 (s, 9H), 1.26 (t, 3H, J = 7.0 Hz).

Step 3: Synthesis of 7-chloro-2,6-naphthyridin-l(2H)-one. Into a 20-mL vial was placed N-tert-butyl-2-chloro-5-[(E)-2-ethoxyethenyl]pyridine-4-carboxamide (1.2 g, 4.24 mmol) in TFA (20 mL). The resulting solution was stirred overnight at 100 °C. The resulting mixture was concentrated under vacuum. This resulted in 600 mg (91.5 %) of 7-chloro-1,2-dihydro-2,6-naphthyridin-1-one as a red solid. The crude product was used directly for next step without any further purification. LC-MS: (ES, m/z) = 181 [M+1].

Step 4: Synthesis of 4-bromo-7-chloro-2,6-naphthyridin-1(2H)-one. Into a 250-mL round-bottom flask was placed 7-chloro-1,2-dihydro-2,6-naphthyridin-1-one (3 g, 16.6 mmol) in DCM (40 mL) and NBS (3.54 g, 19.9 mmol). The resulting solution was stirred for 1 h at rt. The solid was collected by filtration. This resulted in 3 g (69.7 %) of the title compound as a white solid. LC-MS: (ES, m/z) = 261 [M+1]; H NMR (300 MHz, DMSO-d6) δ 12.09 (s, 1H), 8.93 (s, 1H), 8.04 (s, 1H), 7.70 (d, 1H, J= 6.0 Hz).

Step 5: Synthesis of 4-bromo-7-chloro-2,6-naphthyridin-l-yl trifluoromethanesulfonate. Into a 50-mL three-necked bottle was placed 4-bromo-7-chloro-l,2-dihydro-2,6-naphthyridin-l-one (1 g, 3.85 mmol) in DCM (15 mL) and TEA (777 mg, 7.70 mmol). The resulting mixture was cooled to -78 °C, and then Tf_2O (4.34 g, 15.4 mmol) was added drop wise over 10 min. The resulting solution was stirred for 0.5 h at -78 °C. Then the mixture was warmed to room temperature and stirred at this temperature for 0.5 h. The reaction was then quenched by the addition of 2 mL of water/ice,extracted with DCM, and then the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with EA/PE (0-10 %). This resulted in 1 g (66.6 %) of the title compound as a white solid. LC-MS: (ES, m/z) = 393 [M+1]; ^{1}H NMR (300 MHz, DMSO-d6) δ 9.47 (s, 1H), 8.78 (s, 1H), 8.14 (d, 1H, J = 0.9 Hz).

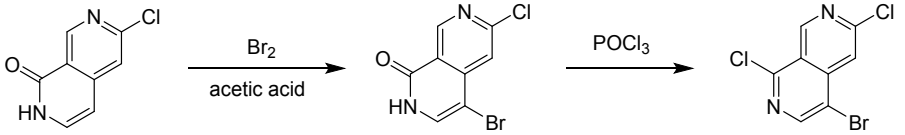
Step 6: Synthesis of 4-bromo-7-chloro-l-iodo-2,6-naphthyridine. Into a 50-mL three-necked bottle was placed 4-bromo-7-chloro-2,6-naphthyridin-l-yl trifluoromethanesulfonate (500 mg, 1.27 mmol) in ACN (9 mL) and NaI (952 mg, 6.35 mmol). The resulting mixture was cooled to 0 °C and trifluoromethanesulfonate acid (381 mg, 2.54 mmol) in ACN (1 mL) was added

drop wise over 10 min. The mixture was then stirred at rt for 1.5 h. After that, the resulting solution was extracted with EA, and then the organic layers combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 500 mg of the title compound as a dark solid. The crude compound was used directly for next without further purification. LC-MS: (ES, m/z) = 369 [M+1].

Step 7: Synthesis of 4-bromo-7-chloro-l-(prop-l-en-2-yl)-2,6-naphthyridine. Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-bromo-7-chloro-l-iodo-2,6-naphthyridine (500 mg,1.35 mmol) was added in dioxane (5 mL) and H_2O (1 mL), 4,4,5,5-tetramethyl-2-(prop-l-en-2-yl)-l,3,2-dioxaborolane (226 mg, 1.35 mmol), K_2CO_3 (372 mg, 2.7 mmol) and $Pd(dppf)Cl_2$ (0.99 mg, 0.135 mmol). The resulting solution was stirred for 2 h at 80 °C. The resulting solution was extracted with EA, and then the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC withPE/EA (8:1). This resulted in 200 mg (52.3 %) of the title compound as a light-yellow oil. LC-MS: (ES, m/z) = 285 [M+1].

Step 8: Synthesis of 4-bromo-7-chloro-l-isopropyl-2,6-naphthyridine. Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of hydrogen, was placed 4-bromo-7-chloro-l-(prop-l-en-2-yl)-2,6-naphthyridine (160 mg, 564 pmol) in EA (6 mL) and PtO_2 (166 mg, 733 pmol). The resulting solution was stirred for 3 h at rt. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in (100 mg, 62.1 %) of the title compound **SI-10** as a yellow solid. LC-MS: (ES, m/z) = 287 [M+1].

Synthesis of 4-bromo-1,6-dichloro-2,7-naphthyridine (SI-11),

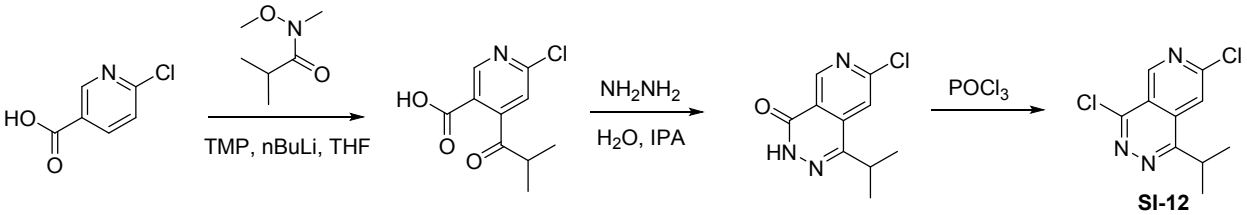


SI-11

Step1: synthesis of 4-bromo-6-chloro-2,7-naphthyridin-1(2H)-one. To a mixture of 6-chloro-2,7-naphthyridin-1(2H)-one (220.0 mg, 1.22 mmol, 1.00 eq) in CH3COOH (4 mL) was added Br_2 (194.68 mg, 1.22 mmol, 62.80 uL, 1.00 eq) dropwise. The mixture was stirred at 25°C for 1 hr. LCMS showed the reaction was complete. The mixture was concentrated. Then EtOAc (10 mL) was added to the mixture and the mixture was filtered. The filter cake was wash with EtOAc (5 mL) and dried to yield the title compound (310 mg, 1.19 mmol, yield: 98%) as a light yellow solid. LC-MS: (ES, m/z) = 180 [M+1].

Step2: 4-bromo-1,6-dichloro-2,7-naphthyridine. A mixture of 4-bromo-6-chloro-2,7-naphthyridin-1(2H)-one (310 mg, 1.19 mmol, 1.00 eq) in $POCl_3$ (10.0 mL) was stirred at 100 °C for 1.5 hrs. TLC (PE/EtOAc = 3/1) showed the reaction was complete. The mixture was concentrated and cooled saturated aq.NaHCO3 (10 mL) was added. Then, the mixture was extracted by EtOAc (10 mL*2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in reduced pressure to yield the title compound (**SI-11**, 320 mg, 1.15 mmol, yield: 96%) was got as white solid. LC-MS: (ES, m/z) = 259 [M+1];

Synthesis of 4,7-dichloro-l-isopropylpyrido[4,3-d]pyridazine (SI-12)



SI-12

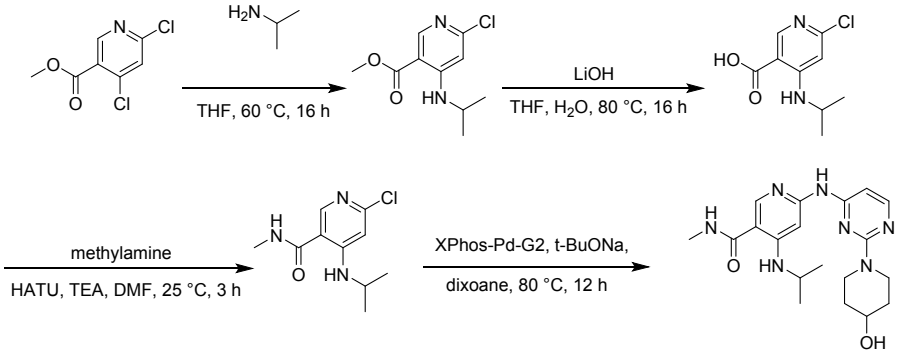
Step 1: Synthesis of 6-chloro-4-isobutyrylnicotinic acid. To a stirred solution of n-BuLi (100 mL) in THF was added dropwise TMP (40.1 g, 285 mmol) at -78°C . The mixture was allowed to warm to O °C and stirred for Ih and then recooled to -78°C. And then a solution of 6-chloropyridine-3-carboxylic acid (15 g, 95.2 mmol) in THF was added dropwise and the reaction was left to stir for 1.5 h. Then N-methoxy- N,2-dimethylpropanamide (37.3 g 285 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 4 h. The mixture was quenched by aq. NH_4Cl and pH was adjusted to 5-6 with citric acide, and then extracted with EA. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the target product as yellow oil without further purification. LC-MS: (ES, m/z) = 228 [M+l].

Step 2: Synthesis of 7-chloro-l-isopropylpyrido[3,4-d]pyridazin-4(3H)-one. To a solution of 6-chloro-4-(2-methylpropanoyl)pyridine-3-carboxylic acid (11 g, 48.3 mmol) in IPA was added $NH_2NH_2{\cdot}H_2O$ (3.62 g, 72.4 mmol), the mixture was stirred at 70 °C for 3 h. The mixture was filtered and the solid was collected, the filtrate was concentrated to 10 mL, and then filtered. The solid was combined to get target product as yellow solid (6 g, crude). LC-MS: (ES, m/z) = 224 [M+l].

Step 3: Synthesis of 4,7-dichloro-l-isopropylpyrido[4,3-d]pyridazine. To a solution of $POCl_3$ (5 mL) was added 7-chloro-l-(propan-2-yl)-3H,4H-pyrido [3,4-d]pyridazin-4-one (100 mg, 447 umol). The mixture was stirred overnight at 100 °C. The mixture was concentrated and the product **SI-12** and used directly without further purification. LC-MS: (ES, m/z) = 242 [M+1].

3. Synthesis & Characterization of Compounds 4-23

Synthesis of 6-((2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl)amino)-4-(isopropylamino)-N-methylnicotinamide (Compound 4)



Step1: methyl 6-chloro-4-(isopropylamino)nicotinate. To the solution of methyl 4,6-dichloronicotinate (10.0 g, 48.5 mmol) in tetrahydrofuran (20 mL) was added propan-2-amine (8.61 g, 146 mmol, 12.48 mL), the mixture was heated to 60 °C for 16 hours. The reaction was monitored by TLC. The reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1) to give the title compound (8.50 g, 77% yield) as a white solid. LC-MS: (ES, m/z) = 229 [M+1].

Step2: 6-chloro-4-(isopropylamino)nicotinic acid. To the solution of methyl 6-chloro-4-(isopropylamino)nicotinate (5.00 g, 21.9 mmol) in tetrahydrofuran (15 mL) and H_2O (5 mL) was added lithium hydroxide (628 mg, 26.2 mmol), the mixture was stirred at 80 °C for 16 hours. The reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure to give the title compoun (4.00 g, 85% yield) was given as a white solid. LC-MS: (ES, m/z) = 215 [M+1].

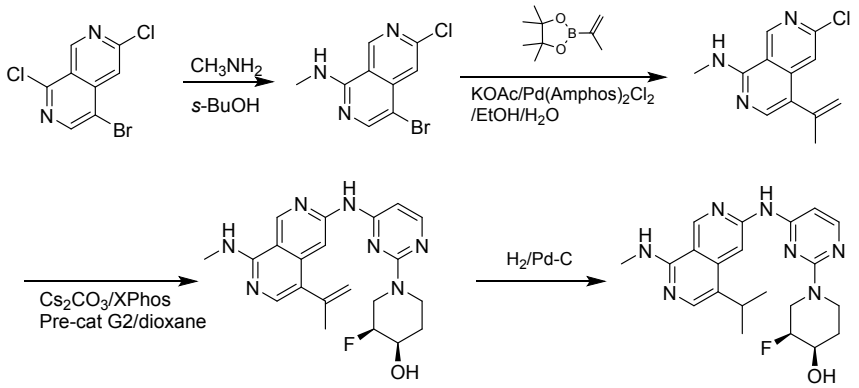
Step3: 6-chloro-4-(isopropylamino)-N-methylnicotinamide. To the solution of 6-chloro-4-(isopropylamino)nicotinic acid (2.00 g, 9.32 mmol) and methylamine (944 mg, 14.0 mmol, HCl) in N,N-dimethyl formamide (10 mL) was added HATU (5.32 g, 13.98 mmol) and triethylamine (1.41 g, 14.0 mmol, 1.94 mL), the mixture was stirred at 25 °C for 3 hours. The reaction was monitored by LCMS. The reaction mixture was diluted with 10 mL water and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with water (3 mL × 3), dried over sodium sulfate, filtered and concentrated under reduced pressure and purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 1:1) to yeild the title compound (2.00 g, 94% yield) as a white solid. LC-MS: (ES, m/z) = 278 [M+1].

Step4: 6-((2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl)amino)-4-(isopropylamino)-N-methylnicotinamide. To a solution of 6-chloro-4-(isopropylamino)-N-methylnicotinamide (50.0 mg, 257 μmol) and 1-(4-aminopyrimidin-2-yl)piperidin-4-ol (70.0 mg, 309 μmol) in dioxane (3 mL) was added t-BuONa (74.2 mg, 772 μmol) and XPhos-Pd-G2 (9.51 mg, 12.9 μmol) under nitrogen. Then the solution was warmed to 80 °C and stirred for 12 hours. The reaction was monitored by LCMS. The residue was diluted with water (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL × 3).The combined organic phase was washed with brine (50 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum and purified by prep-TLC (silica dichloromethane : methanol = 10:1) to yield the title compound **4** (40.00 mg, 40% yield) as a light yellow solid. LC-MS: (ES, m/z) = 386 [M+1].^{1}H-NMR (400 MHz, CD3OD): δ ppm 8.27 (s, 1H), 8.03 (d, J = 5.2 Hz, 1H), 7.24 (s, 1H), 6.37 (d, J = 4.8 Hz, 1H), 4.45-4.30 (m, 2H), 3.92 (s, 1H), 3.85-3.75 (m, 1H), 3.43-3.35 (m, 2H), 2.88 (s, 3H), 2.00-1.90 (m, 2H), 1.60-1.47 (m, 2H), 1.32 (d, J = 5.6 Hz, 6H).

*The following compound was synthesized following procedures similar to that described for compound **4**.*

Synthesis of 6-((2-((3S,4R)-3-fluoro-4-hydroxypiperidin-1-yl)pyrimidin-4-yl)amino)-4-(isopropylamino)-N-methylnicotinamide (Compound 5). Using (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoropiperidin-4-ol in step 4 yielded the title compound (57.0 mg, 64 % yield). LC-MS: (ES, m/z) = 404 [M+1]. 1H-NMR (400 MHz, CD_3OD): δ ppm 8.38 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.87-4.85 (m, 1H), 4.74-4.73 (m, 1H), 4.53-4.46 (m, 1H), 4.30-4.27 (s, 1H), 4.04-3.96 (m, 1H), 3.90-3.84 (m, 1H), 3.70-3.59 (m, 1H), 3.46-3.40 (m, 1H), 3.31-3.29 (m, 2H), 2.88 (s, 3H), 1.96-1.87 (m, 2H), 1.35 (dd, J = 4.0 Hz, 6H).

Synthesis of (3S,4R)-3-fluoro-1-(4-((5-isopropyl-8-(methylamino)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)piperidin-4-ol (Compound 6)



Step1: 4-bromo-6-chloro-N-methyl-2,7-naphthyridin-1-amine. To a mixture of 4-bromo-1,6-dichloro-2,7-naphthyridine (**SI-11**, 0.20 g, 719.60 umol, 1.00 eq) and methanamine (72.88 mg, 1.08 mmol, 1.50 eq, HCl) in S-BuOH (5.00 mL) was added Et_3N (218.45 mg, 2.16 mmol, 300.48 uL, 3.00 eq) at 25°C, the reaction mixture was stirred at 110°C for 16 hrs under N2. LCMS showed starting material was consumed and the desired ms of the product was detected. The reaction mixture was concentrated and residue was purified by acidic prep-HPLC (TFA) to yeild the title compound (0.15 g, 388.05 umol, yield: 54%, TFA) was obtained as a yellow solid. LC-MS: (ES, m/z) = 271 [M+1]

Step2: 6-chloro-N-methyl-4-(prop-1-en-2-yl)-2,7-naphthyridin-1-amine. To a mixture of 4-bromo-6-chloro-N-methyl-2,7-naphthyridin-1-amine (0.07 g, 181.09 umol, 1.00 eq, TFA) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.43 mg, 181.09 umol, 1.00 eq) in EtOH (10.00 mL) and H_2O (1.50 mL) was added KOAc (35.54 mg, 362.18 umol, 2.00 eq) and $Pd(Amphos)_2Cl_2$ (12.82 mg, 18.11 umol, 12.82 uL, 0.10 eq) at 25°C, the reaction mixture was stirred at 80°C for 16 hrs under N_2. LCMS showed starting material was consumed and the desired ms of the product was detected. The reaction mixture was concentrated. The residue was purified by acidic prep-HPLC (TFA) to yeild the title compound (0.06 g, 172.55 umol, yield: 47%, TFA) as a yellow solid. LC-MS: (ES, m/z) = 234 [M+1]

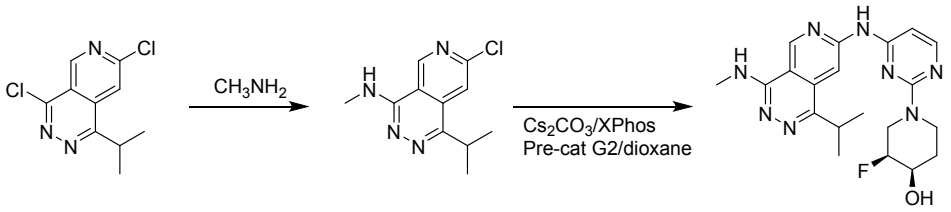
Step3: (3S,4R)-3-fluoro-1-(4-((8-(methylamino)-5-(prop-1-en-2-yl)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)piperidin-4-ol. To a mixture of 6-chloro-N-methyl-4-(prop-1-en-2-yl)-2,7-naphthyridin-1-amine (0.06 g, 172.55 umol, 1.00 eq, TFA) and (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoropiperidin-4-ol (36.62 mg, 172.55 umol, 1.00 eq) in dioxane (5.00 mL) was added Cs_2CO_3 (112.44 mg, 345.11 umol, 2.00 eq) and XPhos-Pd-G2 (13.58 mg, 17.26 umol, 0.10 eq) at 25°C, the reaction mixture was stirred at 120°C for 16 hrs under N_2. TLC (PE:EtOAc = 0:1) showed reaction was completed, the reaction mixture was concentrated and purified by prep-TLC (PE:EtOAc = 0:1, Rf = 0.4) to give the title compound (0.05 g, 122.11 umol, yield: 70.77%) as a brown oil. LC-MS: (ES, m/z) = 410 [M+1]

*Step4: (3S,4R)-3-fluoro-1-(4-((5-isopropyl-8-(methylamino)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)piperidin-4-ol. T*o a mixture of (3S,4R)-3-fluoro-1-(4-((8-(methylamino)-5-(prop-1-en-2-yl)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)piperidin-4-ol (0.05 g, 122.11 umol, 1.00 eq) in MeOH (5.00 mL) was added 10%Pd/C (0.05 g, 48.84 umol, 50% purity) at 25°C, the reaction mixture was stirred at 25°C for 16 hrs under H_2 (15 psi). Once reaction determined complete by LCMS the reaction mixture was concentrated and purified by basic prep-HPLC (column: Waters Xbridge Prep OBD C18 150*30 10u; mobile phase: [water (0.04% NH_3H_2O)-ACN]; B%: 25%-55%,10min) to yeild the title compound **6** (4.80 mg, 11.49 umol, yield: 9%)as a brown solid. LC-MS: (ES, m/z) = 412 [M+1]; ^{1}H-NMR (400MHz, CH_3OD) δ ppm 9.13 (s, 1H), 8.52 (s, 1H), 7.98 (d, 1H, J = 6.0 Hz), 7.81 (s, 1H), 6.38 (d, 1H, J = 5.6 Hz), 4.78-4.77 (m, 1H), 4.65-4.60 (m, 2H), 4.40-4.36 (m, 1H), 3.99-3.94 (m, 1H), 3.70-3.60 (m, 1H), 3.48-3.34 (m, 2H), 3.03 (s, 3H), 1.93-1.82 (m, 2H), 1.36 (dd, 1H, J = 6.4, 5.2 Hz).

*The following compound was synthesized following procedures similar to that described for compound **6** above:*

Synthesis of (3S,4R)-3-fluoro-1-(4-((5-isopropyl-8-(methylamino)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (Compound 8). (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1**) was used as the aminopyrimined in step 3, step 4 was conducted as stated and yeilded the title compound **8** as a gray solid (8.7 mg, 20.45 umol, 12% yield). LC-MS: (ES, m/z) = 426 [M+1];^{1}H-NMR (400MHz, CD_3OD) δ ppm 9.19 (s, 1H), 8.51 (s, 1H), 8.01 (d, 1H, J = 5.7 Hz), 7.79 (s, 1H), 6.44 (d, 1H, J = 5.7 Hz), 4.76 - 4.68 (m, 2H), 3.73 - 3.68 (m, 1H), 3.42 - 3.37 (m, 1H), 3.28 - 3.12 (m, 2H), 3.07 (s, 3H), 1.96-1.86 (m, 2H), 1.48 (d, 3H, J = 20.8 Hz), 1.39 (d, 6H, J = 6.8 Hz).

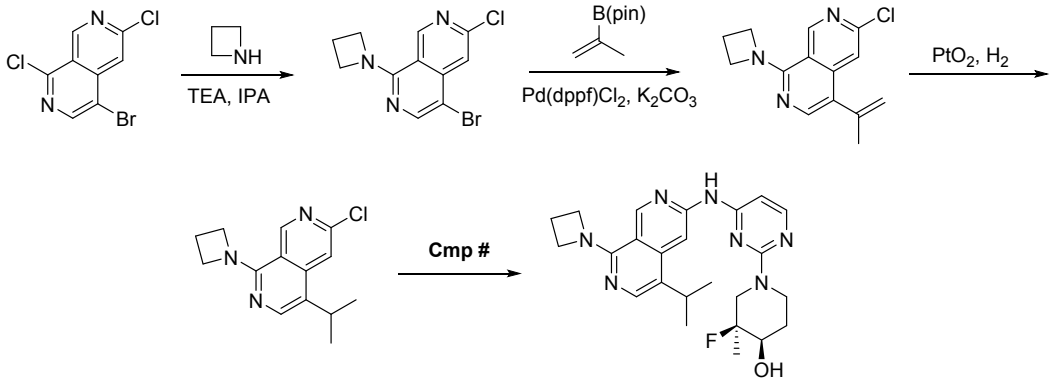
Synthesis of (3S,4R)-3-fluoro-1-(4-((1-isopropyl-4-(methylamino)pyrido[3,4-d]pyridazin-7-yl)amino)pyrimidin-2-yl)piperidin-4-ol (Compound 7)



Step1: 7-chloro-1-isopropyl-N-methylpyrido[3,4-d]pyridazin-4-amine. A mixture of 4,7-dichloro-1-isopropylpyrido[3,4-d]pyridazine (**SI-12**, 34.00 mg, 140.44 umol, 1.00 eq), methanamine hydrochloride (9.48 mg, 140.44 umol, 1.00 eq) and Et_3N (28.42 mg, 280.87 umol, 39.09 uL, 2.00 eq) in sec-butyl alcohol (1.00 mL) was stirred at 90°C for 16 hrs. Once reaction complete the mixture was concentrated under reduced pressure and purified by acidic prep-HPLC (TFA) to give the title compound (20.00 mg, 57.03 umol, yield: 40.61%, TFA) as a light brown oil. LC-MS: (ES, m/z) = 237 [M+1].

Step2: (3S,4R)-3-fluoro-1-(4-((1-isopropyl-4-(methylamino)pyrido[3,4-d]pyridazin-7-yl)amino)pyrimidin-2-yl)piperidin-4-ol. A mixture of 7-chloro-1-isopropyl-N-methylpyrido[3,4-d]pyridazin-4-amine (20.00 mg, 57.03 umol, 1.00 eq, TFA), (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-piperidin-4-ol (14.52 mg, 68.43 umol, 1.20 eq), Cs_2CO_3 (37.16 mg, 114.05 umol, 2.00 eq) and XPhos-Pd-G2 (4.49 mg, 5.70 umol, 0.10 eq) in dioxane (2.00 mL) was stirred at 120°C for 16 hrs under N2. The next day the reaction was filtered and concentrated to give the crude product. The crude product was purified by acidic prep-HPLC (column: Nano-micro Kromasil C18 100*30mm 5um; mobile phase: [water (0.225%FA)-ACN]; B%: 1%-30%,15min) to yield the title compound **7** (12.00 mg, 25.34 umol, yield: 44%) obtained as a yellow gum. LC-MS: (ES, m/z) = 413 [M+1]; ^{1}H-NMR (400 MHz, CD3OD) δ ppm 9.31 (s, 1H), 8.68 (s, 1H), 8.06 (d, 1H, J = 5.6 Hz), 6.44 (d, 1H, J = 5.6 Hz), 4.80-4.67 (m, 1H), 4.61-4.57 (m, 1H), 4.35 (d, 1H, J = 13.2 Hz), 4.08-3.94 (m, 1H), 3.71-3.58 (m, 2H), 3.47 (t, 1H, J = 9.6 Hz), 3.16 (s, 3H), 1.94-1.82 (m, 2H), 1.42 (t, 6H, J = 6.4 Hz).

Synthesis of (3S,4R)-1-(4-((8-(azetidin-1-yl)-5-isopropyl-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (Compound 9)



Step1: synthesis of 1-(azetidin-1-yl)-4-bromo-6-chloro-2,7-naphthyridine. A solution of 4-bromo-1,6-dichloro-2,7-naphthyridine (**SI-11**, 2.78 g, 10 mmol), azetidine (628 mg, 11 mmol) and TEA (2.02 g, 20 mmol) in IPA (20 mL) was stirred at 100 °C for 2 h. The mixture was filtered, the solid washed with IPA, and dried in vacuo to afford the title compound, 2.7 g, 90.8% yield, as a yellow solid. LCMS m/z = 297 $[M+H]^+$

Step2: synthesis of 1-(azetidin-1-yl)-6-chloro-4-(prop-1-en-2-yl)-2,7-naphthyridine. 1-(Azetidin-1-yl)-4-bromo-6-chloro-2,7-naphthyridine (2.39 g, 8 mmol), 4,4,5,5-tetramethyl-2-(prop-1 -en-2-yl)-1,3,2-dioxaborolane (1.61 g, 9.6 mmol), $Pd(dppf)Cl_2$ (585 mg, 0.80 mmol), and K_2CO_3 (1.63 g, 12 mmol) were dissolved in dioxane-H_2O (4:1) (50 mL) and the

reaction stirred at 80 °C for 4 h. The cooled mixture was concentrated in vacuo and the crude product was purified by silica gel column eluting with MeOH-DCM (2:1) to give the title compound, 1.8 g, 86.5%, as a yellow solid. LCMS m/z = 260 $[M+H]^+$

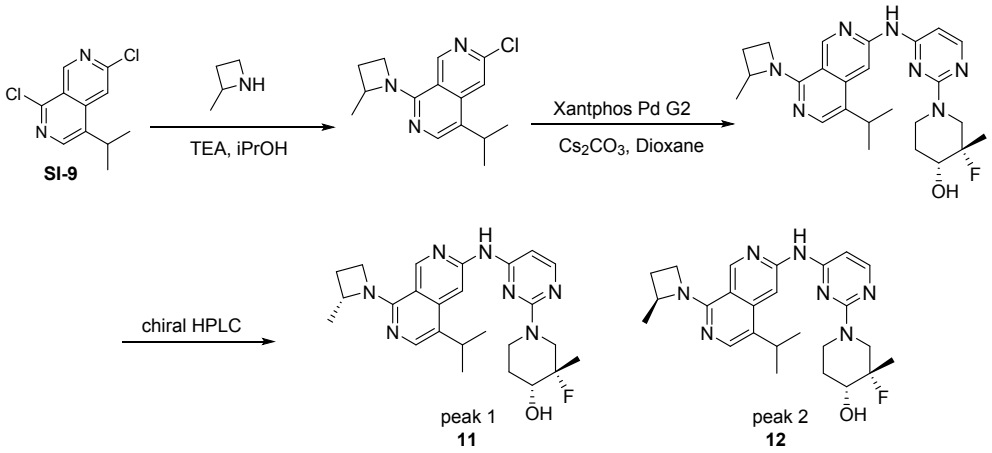
Step 3: synthesis of 1-(azetidin-1-yl)-6-chloro-4-isopropyl-2,7-naphthyridine. PtO_2 (1.57 g, 2.68 mmol) was added to a solution of 1-(azetidin-1-yl)-6-chloro-4-(prop-1-en-2-yl)-2,7-naphthyridine (1.8 g, 6.92 mmol) in EtOAc (200 mL) and the reaction stirred under H_2 at 25 °C for 24 h. The reaction mixture was filtered through Celite®, the filtrate concentrated in vacuo and the product purified by column chromatography (PE-EtOAc (1:5)) to provide the title compound, 1.7 g. 93.8% as a light yellow solid. LCMS m/z = 262 $[M+H]^+$

Step 4: (3S,4R)-1-(4-((8-(azetidin-1-yl)-5-isopropyl-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol. 1-(azetidin-1-yl)-6-chloro-4-isopropyl-2,7-naphthyridine (400 mg, 153 µmol), (3S,4R)-1-(4-aminopyri-midin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1,** 380 mg, 168 µmol), BrettPhos Pd-G3 (112 mg, 15.3 µmol), Cs_2CO_3 (748 mg, 230 µmol) were dissolved in 20 mL of dioxane. The mixture was stirred at 100 °C for 4h. LCMS showed the reaction was OK. The crude product was purified by column and the eluted with MeOH-DCM (1:10) and the product was further purified by prep-HPLC Column: XBridge Prep OBD C18 Column 19*250mm,5um;Mobile Phase A:Water(10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 35% B to 60% B in 7 min; 254/220 nm; Rt: 6.63 min and obtained 167.4 mg of title compound **9** as a light yellow solid. LC-MS: (ES, m/z) = 452[M+1]; 1H-NMR (300 MHz, 6d-DMSO) δ ppm 10.02 (s, 1H), 9.03 (s, 1H), 8.45 (s, 1H), 8.03 (d, 1H, J = 5.6 Hz), 7.97 (s, 1H), 6.55 – 6.45 (m, 1H), 5.02 (d, 1H, J = 6.4 Hz), 4.79 – 4.61 (m, 2H), 4.38 (t, 4H, J = 7.5 Hz), 3.68 – 3.49 (m, 1H), 3.28 (s, 1H), 3.15 (q, 2H, J = 13.8 Hz), 2.40 (p, 2H, J = 7.5 Hz), 1.73 (s, 2H), 1.46 – 1.22 (m, 9H).

*The following compound was synthesized following procedures similar to that described for compound **9** above.*

Synthesis of (3S,4R)-3-fluoro-1-(4-((5-isopropyl-8-(pyrrolidin-1-yl)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (Compound 10). Using pyrrolidine in step 1 and step 4 performed at 130 °C in a microwave to yield the title compound as a white solid (9.9 mg, 8% yield). LCMS m/z = 466 [M+H]. ^{1}HNMR (400 MHz, DMSO-d6) δ: 10.01 (s, 1H), 9.31 (s, 1H), 8.43 (s, 1H), 8.03 (d, 1H), 7.96 (s, 1H), 6.52 (d, 1H), 5.03 (d, 1H), 4.80-4.49 (m, 2H), 3.87-3.67 (m, 4H), 3.64-3.49 (m, 1H), 3.26-3.02 (m, 2H), 2.03-1.86 (m, 4H), 1.79-1.70 (m, 2H), 1.45-1.21 (m, 9H).

Synthesis of (3S,4R)-3-fluoro-1-(4-((5-isopropyl-8-((S)-2-methylazetidin-1-yl)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (**Compound 12**) and **(3S,4R)-3-fluoro-1-(4-((5-isopropyl-8-((R)-2-methylazetidin-1-yl)-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol** (**Compound 11**).



Step 1: 6-chloro-1-(2-methylazetidin-1-yl)-4-(propan-2-yl)-2,7-naphthyridine. A mixture of 2-methylazetidine (44.2 mg, 622 µmol), 1,6-dichloro-4-(propan-2-yl)-2,7-naphthyridine (**SI-9**, 150 mg, 622 µmol), triethylamine (188 mg, 1.86 mmol) in iPrOH (3 mL) was stiried at 100 °C for 4 hours. The resulting solution was concentrated under vacuum, the residue was purifiled by Prep-TLC with PE/EA(8:1). This resulted in 95mg of 6-chloro-1-(2-methylazetidin-1-yl)-4-(propan-2-yl)-2,7-naphthyridine as light yellow solid. LC-MS: (ES, m/z) = 276 [M+1].

Step 2: (3S,4R)-3-fluoro-3-methyl-1-(4-{[8-(2-methylazetidin-1-yl)-5-(propan-2-yl)-2,7-naphthyridin-3-yl]amino}pyrimidin-2-yl)piperidin-4-ol. A mixture of 6-chloro-1-(2-methylazetidin-1-yl)-4-(propan-2-yl)-2,7-naphthyridine (80 mg, 289.6 µmol), (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1**,65.4mg, 289.6µmol), caesium carbonate (187.2 mg, 579.2µmol), XantPhos Pd G2 (77.2 mg, 86.9µmol) in dioxane(15 mL) stirred at 100°C for 16 hours. The solvent

was purified by preparative TLC (DCM: MeOH = 10: 1), to afford Reactant (3S,4R)-3-fluoro-3-methyl-1-(4-{[8-(2-methylazetidin-1-yl)-5-(propan-2-yl)-2,7-naphthyridin-3-yl]amino}pyrimidin-2-yl)piperidin-4-ol (100 mg, 99.0%) as a light-yellow solid. The solid was furthur purified by CHIRAL HPLC: Column: CHIRALPAK IA, 2*25cm,5um;Mobile Phase A:Hex(8mmol/L NH3.MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30 B to 30 B in 11 min; 254/220 nm ; Fractions containing the desired compound were evaporated to dryness to afford (3S,4R)-3-fluoro-3-methyl-1-[4-({8-[(2S)-2-methylazetidin-1-yl]-5-(propan-2-yl)-2,7-naphthyridin-3-yl}amino)pyrimidin-2-yl]piperidin-4-ol (**11**, 42 mg, 97%, peak 1); LC-MS: (ES, m/z) = 465 [M+1];1H-NMR (300 MHz, 6d-DMSO) δ ppm 10.04 (s, 1H), 9.01 (s, 1H), 8.45 (s, 1H), 8.05 – 7.94 (m, 2H), 6.48 (d, 1H, J = 5.7 H,), 5.02 (d, 1H, J = 6.5 Hz), 4.74 (d, 4H, J = 8.1Hz), 4.08 (d, 1H, J = 6.8 Hz), 3.48 (s, 1H), 3.31 (s, 1H), 3.16 (s, 2H), 2.48 (d, 1H, J = 1.7 Hz), 2.05 (s, 1H), 1.71 (s, 2H), 1.45 – 1.35 (m, 3H), 1.34 – 1.25 (m,9H) and (3S,4R)-3-fluoro-3-methyl-1-[4-({8-[(2R)-2-methylazetidin-1-yl]-5-(propan-2-yl)-2,7-naphthyridin-3-yl}amino)pyrimidin-2-yl]piperidin-4-ol (**12**, 48 mg, 99%, peak 2); LC-MS: (ES, m/z) = 465 [M+1];[1]H-NMR (400 MHz, 6d-DMSO) δ ppm 10.06 (s, 1H), 9.04 (s, 1H), 8.47 (s, 1H), 8.07 – 7.97 (m, 2H), 6.51 (d, 1H, J = 5.6 Hz), 5.05 (d, 1H, J = 6.4 Hz), 4.83 - 4.73 (m,2H), 4.69 - 4.62 (m, 2H), 4.12 (q, 1H, J = 7.6 Hz), 3.23 – 3.11 (m, 4H), 2.51 (s, 2H), 1.47 – 1.38 (m, 3H), 1.37 – 1.29 (m, 9H).

The following compound was synthesized following procedures similar to that described for compound **11** *above.*

Synthesis of (3S,4R)-3-fluoro-1-(4-((8-(3-hydroxyazetidin-1-yl)-5-isopropyl-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (Compound 15). azetidin-3-ol was used as the nucelophile in step 1 and step 2 was performed using BrettPhos Pd G3 (10 mol%) heating at 100 °C for 3 hours to yield the title compound **15** after purification as an off-white solid (34.7 mg, 14% yield). LC-MS: (ES, m/z) = 468[M+1]; [1]H-NMR (400 MHz, 6d-DMSO) δ ppm 10.05 (s, 1H), 9.03 (d, 1H, J=0.7 Hz), 8.46 (s, 1H), 8.03 (d, 1H, J=5.6 Hz), 7.97 (s, 1H), 6.51 (d, 1H, J=5.6 Hz), 5.69 (d, 1H, J=6.0 Hz), 5.04 (d, 1H, J=6.4 Hz), 4.76 – 4.44 (m, 5H), 4.17 – 4.04 (m, 2H), 3.66 – 3.43 (m, 1H), 3.13 (t, 2H, J=14.4 Hz), 1.81 – 1.61 (m, 2H), 1.42 – 1.28 (m, 9H).

Synthesis of (3S,4R)-3-fluoro-1-(4-((8-((2R,3S)-3-hydroxy-2-methylazetidin-1-yl)-5-isopropyl-2,7-naphthyridin-3-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (Compound 16). (2R,3S)-2-methylazetidin-3-ol was used as the nucelophile in step 1 and step 2 was performed using BrettPhos Pd G3 (10 mol%) heating at 100 °C for 3 hours to yield the title compound **16** after purification as a light yellow solid (22 mg, 27% yield). LC-MS: (ES, m/z) = 482[M+1]; [1]H-NMR (300 MHz, 6d-DMSO) δ ppm 10.06 (s, 1H), 9.04 (s, 1H), 8.47 (s, 1H), 8.08 – 7.94 (m, 2H), 6.48 (d, 1H, J = 5.6 Hz), 5.62 (d, 1H, J = 6.7 Hz), 5.05 (d, 1H, J = 6.4Hz), 4.84 (t, 1H, J = 7.4 Hz), 4.79 – 4.58 (m, 2H), 4.37 (q, 1H, J = 5.9 Hz), 4.15 (t, J = 5.7 Hz, 1H), 3.75 (dd, 1H, J = 8.0, 5.2 Hz), 3.54 (dq, 2H, J = 26.3, 7.7 Hz), 3.31 – 3.01 (m, 2H), 1.73 (d, 2H, J = 8.6 Hz), 1.45 – 1.25 (m, 12H).

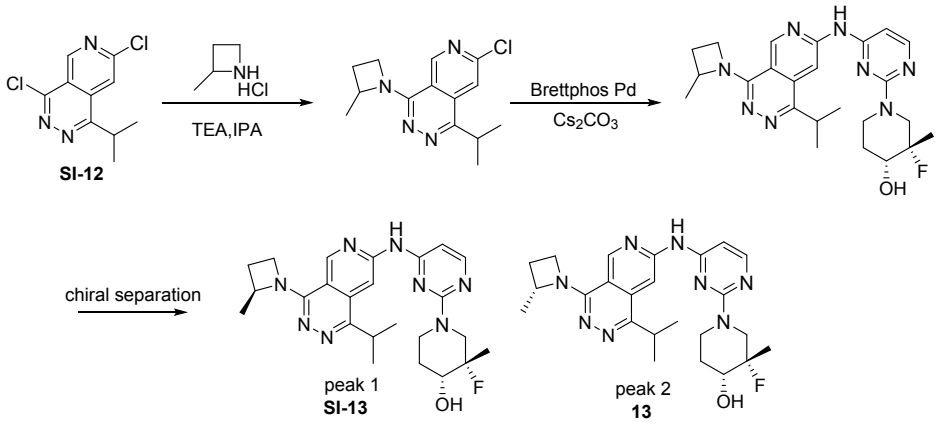
Synthesis of (3S,4R)-3-fluoro-1-(4-{[8-(3-methoxyazetidin-1-yl)-5-(propan-2-yl)-2,7-naphthyridin-3-yl]amino}pyrimidin-2-yl)-3-methylpiperidin-4-ol (Compound 19). 3-methoxyazetidine was used as the nucelophile in step 1 and step 2 was performed using BrettPhos Pd G3 (10 mol%) heating at 100 °C for 3 hours to yield the title compound **19** after purification as a white solid (75 mg, 37% yield). LC-MS: (ES, m/z) = 482[M+1]; [1]H-NMR (300 MHz, 6d-DMSO) δ ppm 10.03 (s, 1H), 9.03 (s, 1H), 8.45 (s, 1H), 8.02 (d, 1H, J=5.6 Hz), 7.96 (s, 1H), 6.51 (d, 1H, J=5.6 Hz), 5.01 (d, 1H, J=6.3 Hz), 4.86 – 4.42 (m, 4H), 4.40 – 4.27 (m, 1H), 4.18 (dd, 2H, J=9.5, 3.9 Hz), 3.65 – 3.46 (m, 1H), 3.37 – 3.29 (m, 4H), 3.20 – 2.91 (m, 2H), 1.84 – 1.62 (m, 2H), 1.45 – 1.26 (m, 9H).

Synthesis of (3S,4R)-3-fluoro-1-[4-({8-[3-(methoxymethyl)azetidin-1-yl]-5-(propan-2-yl)-2,7-naphthyridin-3-yl}amino)pyrimidin-2-yl]-3-methylpiperidin-4-ol (Compound 20). 3-(methoxymethyl)azetidine hydrochloride was used as the nucelophile in step 1 and step 2 was performed performed using BrettPhos Pd G3 (10 mol%) heating at 100 °C for 2 hours to yield the title compound **20** after purification as an off-white solid (20 mg, 11% yield). LC-MS: (ES, m/z) = 496[M+1]; [1]H-NMR (300 MHz, 6d-DMSO) δ ppm 10.06 (s, 1H), 9.02 (s, 1H), 8.45 (s, 1H), 8.01 (d, 1H, J=5.5 Hz), 7.95 (s, 1H), 6.48 (d, 1H, J=5.6 Hz), 5.03 (d, 1H, J=6.4 Hz), 4.80 – 4.54 (m, 2H), 4.41 (t, 2H, J=8.4 Hz), 4.08 (dd, 2H, J=8.5, 5.6 Hz), 3.64 – 3.42 (m, 3H), 3.31 (s, 3H), 3.18 – 2.92 (m, 3H), 1.88 – 1.56 (m, 2H), 1.42 – 1.21 (m, 9H).

Synthesis of 1-[6-([2-[(3S,4R)-3-fluoro-4-hydroxy-3-methylpiperidin-1-yl]pyrimidin-4-yl]amino)-4-(propan-2-yl)-2,7-naphthyridin-1-yl]azetidine-3-carbonitrile (Compound 21). Azetidine-3-carbonitrile hydrochloride was used as the nucelophile in step 1 and step 2 was performed using BrettPhos Pd G3 (10 mol%) and heated in a microwave reactor at 130 °C for 2 hours to yield the title compound **21** after purification as a white solid. LC-MS: (ES, m/z) = 477[M+1]; [1]H-NMR (300 MHz, 6d-DMSO) δ ppm 10.11 (s, 1H), 9.02 (s, 1H), 8.50 (s, 1H), 8.06 – 7.97 (m, 2H), 6.55 – 6.45 (m, 1H), 5.03 (d, 1H, J = 6.4 Hz), 4.71 (s, 1H), 4.62 (t, 3H, J = 8.8 Hz), 4.52 (t, 2H, J = 7.2 Hz), 3.92 (ddd, 1H, J = 14.6, 8.7, 5.7 Hz), 3.6 (s,2H), 3.2 (s,2H), 1.72 (s, 2H), 1.41 – 1.26 (m, 9H).

Synthesis of 1-[6-({2-[(3S,4R)-3-fluoro-4-hydroxy-3-methylpiperidin-1-yl]pyrimidin-4-yl}amino)-4-(propan-2-yl)-2,7-naphthyridin-1-yl]-N,N-dimethylazetidine-3-carboxamide (Compound 23). N,N-dimethylazetidine-3-carboxamide hydrochloride was used as the nucelophile in step 1 and step 2 was performed using BrettPhos Pd G3 (10 mol%) heating at 100 °C for 3 hours to yield the title compound **23** after purification as an off-white soli (64 mg, 33% yield). LC-MS: (ES, m/z) = 523 [M+1]; ^{1}H-NMR (300 MHz, 6d-DMSO) δ ppm 10.09 (s, 1H), 9.05 (s, 1H), 8.49 (s, 1H), 8.04 (d, 1H, J=5.6 Hz), 7.98 (s, 1H), 6.52 (d, 1H, J=5.6 Hz), 5.05 (d, 1H, J=6.4 Hz), 4.82 – 4.62 (m, 2H), 4.56 (d, 2H, J=8.4 Hz), 4.44 (t, 2H, J=7.2 Hz), 3.92 (d, 1H, J=8.0 Hz), 3.68 – 3.46 (m, 1H), 3.22 – 3.04 (m, 2H), 2.94 (s, 3H), 2.87 (s, 3H), 1.82 – 1.70 (m, 2H), 1.44 – 1.27 (m, 9H)

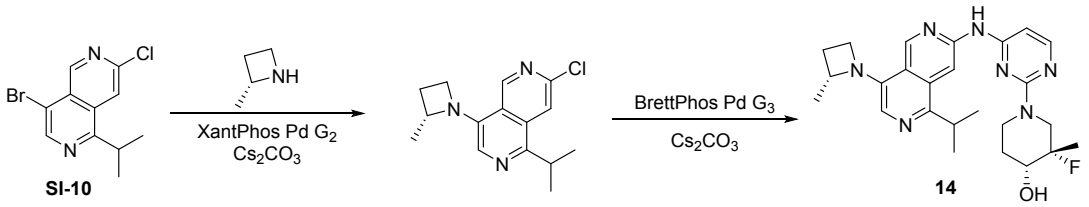
Synthesis of (3S,4R)-3-fluoro-1-(4-((1-isopropyl-4-((R)-2-methylazetidin-1-yl)pyrido[3,4-d]pyridazin-7-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (Compound 13, peak 2)



Step 1: 1-[7-chloro-1-(propan-2-yl)pyrido[3,4-d]pyridazin-4-yl]-2-methylazetidine. Into a 40 mL of reaction tube was added 4,7-dichloro-1-(propan-2-yl)pyrido[3,4-d]pyridazine (**SI-12**, 200 mg, 826 umol), 2-methylazetidine (70.4 mg, 991 umol) and TEA (166 mg, 1.65 mmol) in IPA. The mixture was stirred for 2 h at 100 °C. The mixture was concentrated and the residue was purified by Prep-TLC with petroleum ether/ethyl acetate (10:1). This resulted in 200 mg (70%) of 1-[7-chloro-1-(propan-2-yl)pyrido[3,4-d]pyridazin-4-yl]-2-methylazetidine as a light yellow solid. LCMS m/z = 465 $[M+H]^+$

Step 2: (3S,4R)-3-fluoro-1-(4-((1-isopropyl-4-((R)-2-methylazetidin-1-yl)pyrido[3,4-d]pyridazin-7-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol and (3S,4R)-3-fluoro-1-(4-((1-isopropyl-4-((S)-2-methylazetidin-1-yl)pyrido[3,4-d]pyridazin-7-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol. Into a 40 mL reaction tube was added 1-[7-chloro-1-(propan-2-yl)pyrido[3,4-d]pyridazin-4-yl]-2-methylazetidine (140 mg, 505 umol), (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1**, 125 mg, 555 umol), Brettphos Pd (91.5 mg, 101 umol) and Cs_2CO_3 (329 mg, 1.01 mmol) in dioxane under N2. The mixture was stirred at 100°C for 2 h. The mixture was concentrated and extracted with EA and water. The organic layer was dried by Na_2SO_4 and concentrated. The product was purified by Column: Kinetex EVO C18 Column 30*150,5um;Mobile Phase A:, Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 50% B in 7 min; 254;220 nm; Rt: 6.42 min, This resulted in 60 mg of product as a light yellow solid. The compound was furthur purified by Column: (R,R)-WHELK-O1-Kromasil, 5cm*25cm(5um);Mobile Phase A:MTBE(10mM NH_3-MEOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 5 B to 5 B in 10 min; 220/254 nm ; RT1:6.378 ; RT2:8.076 This resulted in 21 mg of (3S,4R)-3-fluoro-1-(4-((1-isopropyl-4-((S)-2-methylazetidin-1-yl)pyrido[3,4-d]pyridazin-7-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (**SI-13**, Peak 1), and 19 mg of (3S,4R)-3-fluoro-1-(4-((1-isopropyl-4-((R)-2-methylazetidin-1-yl)pyrido[3,4-d]pyridazin-7-yl)amino)pyrimidin-2-yl)-3-methylpiperidin-4-ol (**13**, Peak 2) as light yellow solid.

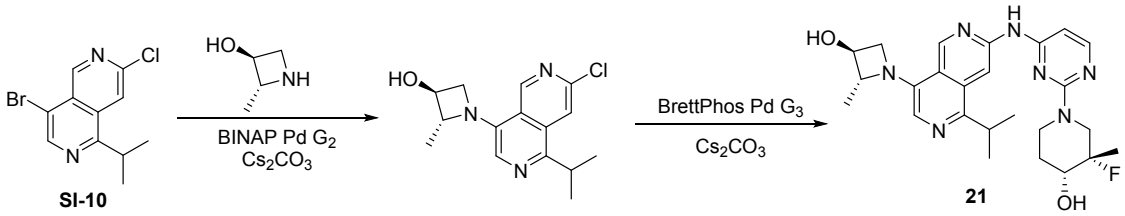
Syntheiss of (3S,4R)-3-fluoro-3-methyl-1-[4-({8-[(2R)-2- methylazetidin-1-yl]-5-(propan-2-yl)-2,6-naphthyridin-3-yl}amino)pyrimidin-2-yl]piperidin-4-ol (Compound 14).



Step1: 7-chloro-4-[(2R)-2-methylazetidin-1-yl]-1-(propan-2-yl)- 2,6-naphthyridine. A mixture of 4-bromo-7-chloro-1-(propan-2-yl)-2,6-naphthyridine (**SI-10,** 100 mg, 350 μmol), (2R)-2-methylazetidine (24.8 mg, 350 μmol), XantPhos Pd G2 (46.6 mg, 52.5 μmol), Cs_2CO_3 (228 mg, 700 μmol) in dioxane (20 mL) was stirred at 100°C for 16 hours. The mixture was concentrated to dryness. The residue was purified on prep-TLC (EA:PE=1:2) to afford 7-chloro-4-[(2R)-2-methylazetidin-1-yl]-1-(propan-2-yl)- 2,6-naphthyridine (70 mg) as a yellow oil. LC-MS: (ES, m/z) = 276 [M+1].

Step 2: (3S,4R)-3-fluoro-3-methyl-1-[4-({8-[(2R)-2- methylazetidin-1-yl]-5-(propan-2-yl)-2,6-naphthyridin-3-yl}amino)pyrimidin-2-yl]piperidin-4-ol. A mixture of 7-chloro-4-[(2R)-2-methylazetidin-1-yl]-1-(propan-2-yl)-2,6-naphthyridine (60 mg, 217 μmol), (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1**, 49.0 mg, 217 μmol), BrettPhos Pd G3 (39.3 mg, 43.4 μmol), Cs_2CO_3 (141 mg, 434 μmol) in Dioxane (20 mL) was stirred at 130oC for 2 hours. The mixture was concentrated to dryness. The residue was purified on prep-TLC (DCM:MeOH=25:1). The resulted crude product was purified on prep-HPLC, Column: XBridge Prep OBD C18 Column 30×150mm 5um;Mobile Phase A:Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 60% B in 7 min; 254;220 nm; Rt: 5.68 min to afford (3S,4R)-3-fluoro-3-methyl-1-[4-({8-[(2R)-2- methylazetidin-1-yl]-5-(propan-2-yl)-2,6-naphthyridin-3-yl}amino)pyrimidin-2-yl]piperidin-4-ol (**14**, 14.9 mg) as a yellow solid. LC-MS: (ES, m/z) = 466 [M+1]; 1H NMR(300 MHz , DMSO-d6): δ = 10.07 (s, 1H), 9.10 (s, 1H), 8.69 (s, 1H), 8.00 (d, 1H, J=5.6 Hz), 7.68 (s, 1H), 6.43 (d, 1H, J=5.6 Hz), 5.03 (d, 1H, J=6.4 Hz), 4.81 – 4.61 (m, 2H), 4.58 – 4.40 (m, 2H), 3.87 (d, 1H, J=7.6 Hz), 3.74 – 3.43 (m, 1H), 3.11 (s, 2H), 1.73 (s, 3H), 1.38 (d, 5H, J=5.9 Hz), 1.34 – 1.24 (m, 7H).

Synthesis of (3S,4R)-3-fluoro-1-[4-([8-[(2R,3S)-3-hydroxy-2-methylazetidin-1-yl]-5-(propan-2-yl)-2,6-naphthyridin-3-yl]amino)pyrimidin-2-yl]-3-methylpiperidin-4-ol (Compound 17).

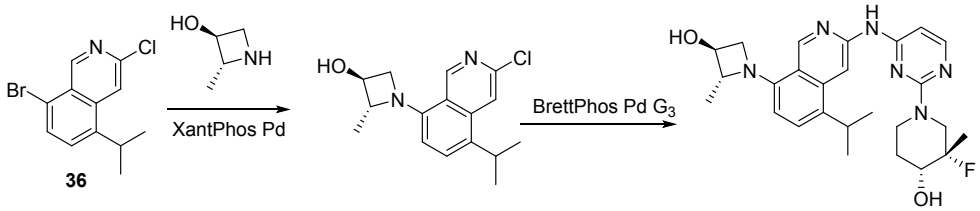


Step1: (2R,3S)-1-[7-chloro-1-(propan-2-yl)-2,6-naphthyridin-4-yl]-2-methylazetidin-3-ol. Into a 8-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen, was placed (2R,3S)-2-methylazetidin-3-ol (110 mg, 1.263 mmol, 1 equiv), 4-bromo-7-chloro-1-(propan-2-yl)-2,6-naphthyridine (**SI-10**, 360 mg, 1.26 mmol, 1 equiv), caesio methaneperoxoate caesium (1237mg, 3.8 mmol, 3 equiv), dioxane (2 mL), BINAP Pd G3 (115.8 mg, 0.126 mmol, 0.1 equiv). The resulting solution was stirred for 3 hr at 90 degrees C. The reaction was then quenched by the addition of 1 mL of $Na_2S_2O_3$. The solids were filtered out. The resulting solution was extracted with 3x2 mL of ethyl acetate The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (3:1). This resulted in 70 mg (19%) of (2R,3S)-1-[7-chloro-1-(propan-2-yl)-2,6-naphthyridin-4-yl]-2-methylazetidin-3-ol as a light yellow solid. LC-MS: (ES, m/z) = 292[M+1].

Step 2: (3S,4R)-3-fluoro-1-[4-([8-[(2R,3S)-3-hydroxy-2-methylazetidin-1-yl]-5-(propan-2-yl)-2,6-naphthyridin-3-yl]amino)pyrimidin-2-yl]-3-methylpiperidin-4-ol. Into a 8-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen, was placed (2R,3S)-1-[7-chloro-1-(propan-2-yl)-2,6-naphthyridin-4-yl]-2-methylazetidin-3-ol (100 mg, 0.343 mmol, 1 equiv), (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1**, 77 mg, 0.34 mmol, 1 equiv), caesio methaneperoxoate caesium (336 mg, 1.0 mmol, 3 equiv), BrettPhos Pd G3 (31 mg, 0.034 mmol, 0.1 equiv), dioxane (2 mL). The resulting solution was stirred for 3 hr at 130 degrees C. The reaction was then quenched by the addition of 1 mL of water. The solids were filtered out. The resulting solution was extracted with 3x2 mL of ethyl acetate The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (3:1). The crude product was purified by Prep-HPLC with the following conditions; Column: XBridge Shield RP18 OBD Column 19*250mm, 10um;Mobile Phase

A:Water(10 mmol/L NH_4HCO_3+0.1%NH3.H2O), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% B to 57% B in 9 min; 254/210 nm; Rt: 8.30 min; This resulted in **17** (15 mg, 9 %) of (3S,4R)-3-fluoro-1-[4-([8-[(2R,3S)-3-hydroxy-2-methylazetidin-1-yl]-5-(propan-2-yl)-2,6-naphthyridin-3-yl]amino)pyrimidin-2-yl]-3-methylpiperidin-4-ol as a light yellow solid. LC-MS: (ES, m/z) = 482[M+1]; ^{1}H-NMR (400 MHz, 6d-DMSO) δ ppm 10.06 (s, 1H), 9.12 (s, 1H), 8.79(s, 1H), 8.01 (d, 1H, J = 5.6 Hz), 7.74 (s, 1H), 6.41 (d, 1H, J = 5.7 Hz), 5.64 (d, 1H, J = 6.6 Hz),5.01(d,1H), 4.73 (t, 3H, J = 6.8 Hz), 4.15 (ddd, 2H, J = 25.1, 11.8, 5.9 Hz), 3.89 (s, 1H), 3.79 (s, 2H), 3.27 – 3.06 (m, 2H), 1.64 (d, 2H, J = 10.8 Hz), 1.41 (d, 6H, J = 6.1 Hz), 1.30 (dd, 6H, J = 6.6, 2.7 Hz).

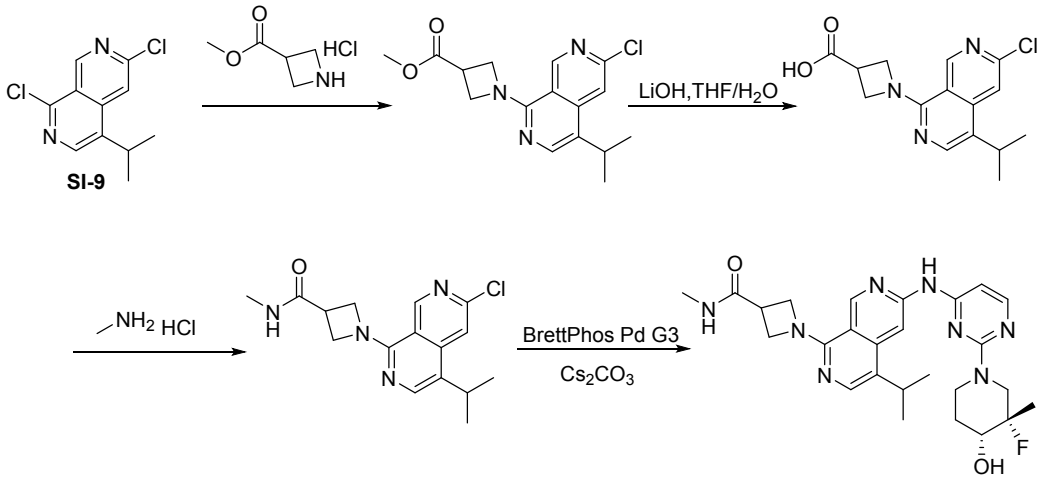
(3S,4R)-3-fluoro-1-[4-({8-[(2R,3S)-3-hydroxy-2-methylazetidin-1-yl]-5-(propan-2-yl)isoquinolin-3-yl}amino)pyrimidin-2-yl]-3-methylpiperidin-4-ol (Compound 18).



Step 1: (2R,3S)-1-[3-chloro-5-(propan-2-yl)isoquinolin-8-yl]-2-methylazetidin-3-ol. Cs_2CO_3 (544 mg, 1.67 mmol) was added to (2R,3S)-2-methylazetidin-3-ol; {7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl}methanesulfonic acid (447 mg, 1.40 mmol, 8-bromo-3-chloro-5-(propan-2-yl)isoquinoline (36, 400 mg, 1.40 mmol) and XantPhos Pd G3 (124 mg,140 μmol) in dioxane (15 mL) at rt. The resulting mixture was stirred at 85 °C for 4hrs under N2 atmosphere. The mixture was diluted with EA 100 mL and washed with brine. The organic layer was dried with Na2SO4 and concentrated under vacuum. The residue was purified by a Prep-TLC with DCM:MeOH=30:1 to afford 210 mg (2R,3S)-1-[3-chloro-5-(propan-2-yl)isoquinolin-8-yl]-2-methylazetidin-3-ol as a yellow solid. LC-MS: (ES, m/z) = 291 [M+1].

Step 2: (3S,4R)-3-fluoro-1-[4-({8-[(2R,3S)-3-hydroxy-2-methylazetidin-1-yl]-5-(propan-2-yl)isoquinolin-3-yl}amino)pyrimidin-2-yl]-3-methylpiperidin-4-ol. Cs_2CO_3 (235 mg, 722 μmol) was added to BrettPhos Pd G3 (65.4 mg, 72.2 μmol), (2R,3S)-1-[3-chloro-5-(propan-2-yl)isoquinolin-8-yl]-2-methylazetidin-3-ol (210 mg, 722 μmol) and (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1**, 179 mg, 794 μmol) in dioxane (15 mL) at rt. The resulting mixture was stirred at 100 °C for 4h under N2 atmosphere. The mixture was diluted with EA 100 mL and washed with brine. The organic layer was dried with Na2SO4 and concentrated under vaccum. The redisue was purified by a Prep-HPLC with the condition: Column: XBridge Prep OBD C18 Column 30×150mm 5um;Mobile Phase A:Water(10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 34% B to 44% B in 7 min; 254;220 nm; Rt: 5.90 min. The title compound **18** was obtained as a yellow solid (105 mg). LC-MS: (ES, m/z) = 481 [M+1]; ^{1}H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.06 (s, 1H), 8.62 (s, 1H), 7.99 (d, 1H, J = 5.6 Hz), 7.43 (d, 1H ,J = 8.0 Hz), 6.60 (d, 1H, J = 8.1 Hz), 6.45 (d, 1H, J = 5.7 Hz), 5.62 (d, 1H, J = 6.6 Hz), 5.05 (d, 1H, J = 6.4 Hz), 4.92 – 4.45 (m, 3H), 4.16 (p, 1H, J = 6.1 Hz), 4.00 (t, 1H, J = 5.9 Hz), 3.53 (m, 2H), 3.43 (t, 1H, J = 6.4 Hz), 3.10 - 3.20 (m, 2H), 1.74 (s, 2H), 1.34 (ddd, 12H, J = 18.5, 12.8, 7.2 Hz).

1-[6-({2-[(3S,4R)-3-fluoro-4-hydroxy-3-methylpiperidin-1-yl]pyrimidin-4-yl}amino)-4-(propan-2-yl)-2,7-naphthyridin-1-yl]-N-methylazetidine-3-carboxamide (Compound 22).



Step1: methyl 1-[6-chloro-4-(propan-2-yl)-2,7-naphthyridin-1-yl]azetidine-3-carboxylate. To a solution of methyl azetidine-3-carboxylate hydrochloride (224 mg, 1.48 mmol) in IPA (10mL) were added 1,6-dichloro-4-(propan-2-yl)-2,7-naphthyridine (**SI-9**, 300 mg, 1.24 mmol) and TEA (375 mg, 3.72 mmol) at 100 °C. The organic concentrated and was purified by FLASH (5% MeOH in DCM). It obtained methyl 1-[6-chloro-4-(propan-2-yl)-2,7-naphthyridin-1-yl]azetidine-3-carboxylate of 320 mg. LC-MS: (ES, m/z) = 320 [M+1].

Step 2: 1-[6-chloro-4-(propan-2-yl)-2,7-naphthyridin-1-yl]azetidine-3-carboxylic acid. To a solution of methyl 1-[6-chloro-4-(propan-2-yl)-2,7-naphthyridin-1-yl]azetidine-3-carboxylate (27 mg, 84.4 μmol) in THF and water were added LiOH (5.81 mg, 253 μmol) at 0 °C and warmed to room temperature for 2 h. The mixture was acidified by aq. HCl and extracted with EtOAc. The organic concentrated and was purified by FLASH (5% MeOH in DCM). It obtained 1-[6-chloro-4-(propan-2-yl)-2,7-naphthyridin-1-yl]azetidine-3-carboxylic acid of 180 mg. LC-MS: (ES, m/z) = 306 [M+1].

Step 3: 1-(6-chloro-4-isopropyl-2,7-naphthyridin-1-yl)-N-methylazetidine-3-carboxamide. To a mixture of 1-[6-chloro-4-(propan-2-yl)-2,7-naphthyridin-1-yl]azetidine-3-carboxylic acid (150 mg, 490 μmol), HOBT (99.2 mg, 735 μmol) and EDC·HCl (93.9 mg, 490 μmol) in DCM was stirred at 0 °C for 1h. CH_3NH_2·HCl (49.2 mg, 735 μmol) added it and stirred at r.t. for 12h. After aqueous work up, the organic concentrated and was purified by FLASH (5% MeOH in DCM). It obtained the title product, 100 mg. LC-MS: (ES, m/z) = 319 [M+1].

Step 4: -[6-({2-[(3S,4R)-3-fluoro-4-hydroxy-3-methylpiperidin-1-yl]pyrimidin-4-yl}amino)-4-(propan-2-yl)-2,7-naphthyridin-1-yl]-N-methylazetidine-3-carboxamide. To a solution of 1-[6-chloro-4-(propan-2-yl)-2,7-naphthyridin-1-yl]-N-methylazetidine-3-carboxamide (80 mg, 250 μmol) in dry dioxane were added (3S,4R)-1-(4-aminopyrimidin-2-yl)-3-fluoro-3-methylpiperidin-4-ol (**SI-1**, 56.5 mg, 250 μmol) and Cs_2CO_3 (163 mg, 500 μmol). Then BrettPhos Pd G3 (22.6 mg, 25.0 μmol) was added, the solution was stirred at 100 °C for 2 h under N2. LCMS showed the reaction was complete. After aqueous work, the residue was purified by Prep-HPLC. Column: XBridge Shield RP18 OBD Column, 19*150 mm, 5μm; Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 20% B to 38% B in 7 min, 38% B; Wave Length: 254; 220 nm; RT1(min): 6.33; to afford the title compound **22** as a yellow solid (25.9 mg). LC-MS: (ES, m/z) =509 [M+1]; ^{1}H-NMR (300 MHz, 6d-DMSO) δ ppm 10.06 (s, 1H), 9.01 (s, 1H), 8.46 (s, 1H), 8.10 – 7.84 (m, 3H), 6.48 (d, 1H, J=5.7 Hz), 5.02 (d, 1H, J=6.4 Hz), 4.79 – 4.55 (m, 2H), 4.41 (dt, 4H, J=36.0, 8.1 Hz), 3.64 – 3.40 (m, 2H), 3.22 – 2.94 (m, 3H), 2.61 (d, 3H, J=4.6 Hz), 1.86 – 1.62 (m, 2H), 1.47 – 1.19 (m, 9H)

4. Purity Analysis for Key Compounds 26-27, 29-31

Compound 26

Acquired by	: System Administrator
Sample Name	: LCMS69-PH-BPM-792-0-1(1018-013Q1)1T
Injection Volume	: 3
Data File	: LCMS69-PH-BPM-792-0-1(1018-013Q1)1T.lcd
Report Format File	: LCMS2020-PDA+ELSD+TIC+MS.lsr
Date Acquired	: 8/13/2018 12:16:27 PM
Comment	: Mobile phaseA:Water/0.04%NH4OH; Mobile phaseB:Acetonitrile

Instrument Name:Shimadzu LCMS-2020

<<Pump>>

Mode	: Binary gradient
Pump A	: LC-20ADXR
Pump B	: LC-20ADXR
Total Flow	: 1.2000 mL/min
B Conc.	: 10.0 %

<<Oven>>

Oven Temperature	: 40 C

<<PDA>>

PDA Model	: SPD-M20A
Lamp	: D2
Start Wavelength	: 190 nm
End Wavelength	: 400 nm

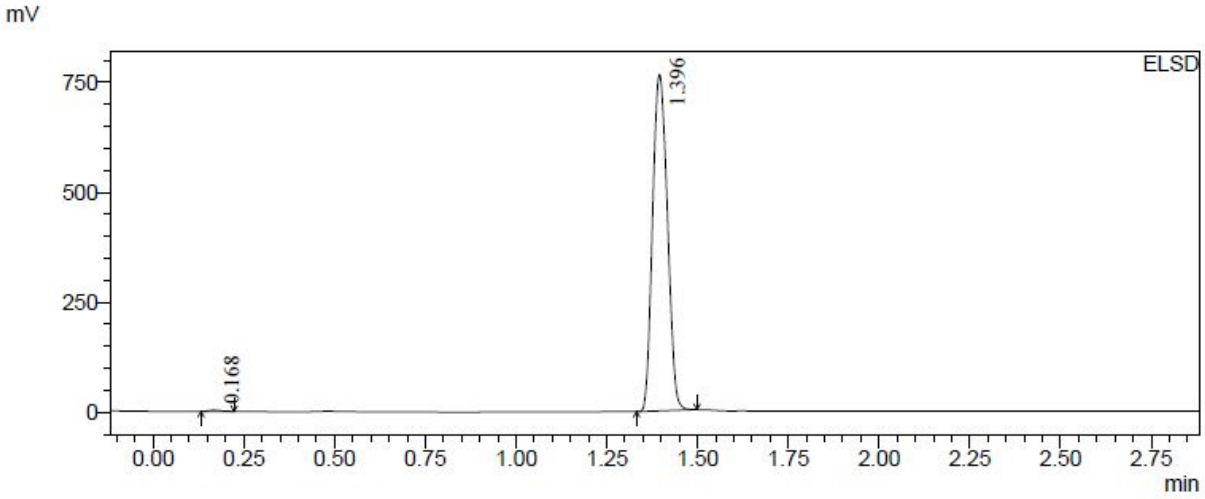
<<Interface>>

Interface	:ESI
DL Temperature	:250 C
Nebulizing Gas Flow	:1.50 L/min
Heat Block	:300 C
Drying Gas	:On
	12.00 L/min

<<MS Parameter>>

--Segment 1 Event 1--	
Start Time	:0.00 min
End Time	:3.00 min
Acquisition Mode	:Scan
Polarity	:Positive
Event Time	:0.50 sec
Detector Voltage	:+0.95 kV
Threshold	:0
Start m/z	:90.00
End m/z	:900.00
Scan Speed	:1667 u/sec
Interface Volt.	:Use the Data in the Tuning File
DL Volt.	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File

System Configuration



Peak Table

ELSD

Peak#	Ret. Time	Height	Height%	Area	Area%
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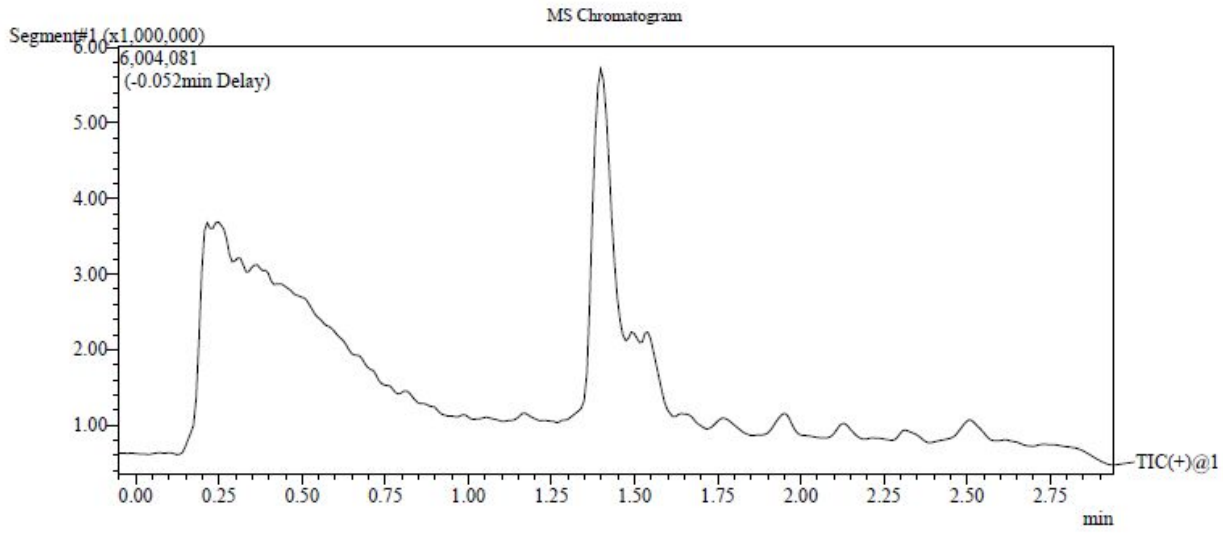
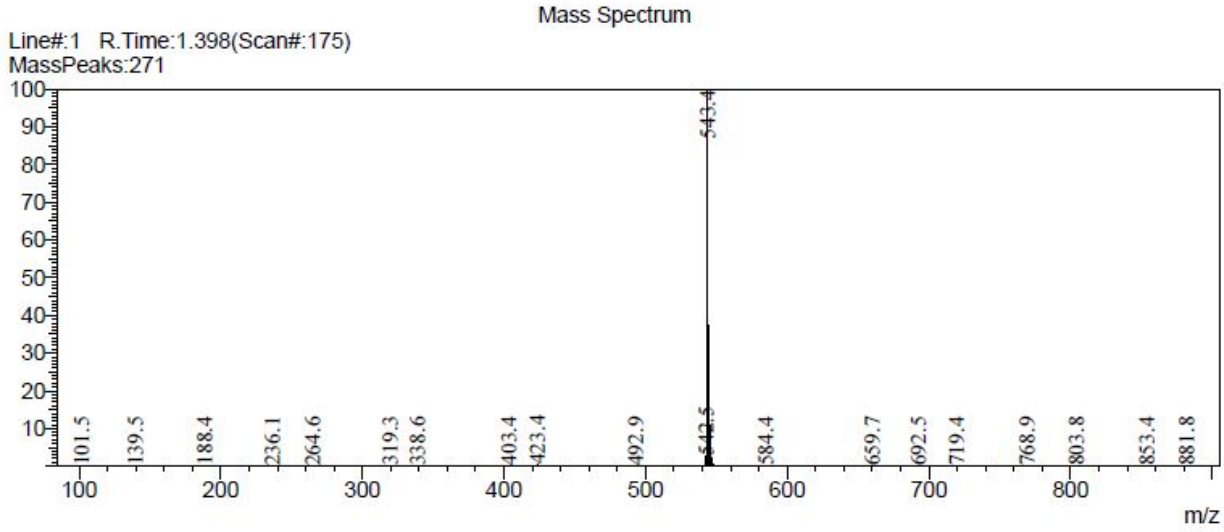
2	1.396	759279	99.593	2174272	99.635
Total		762380	100.000	2182242	100.000





Compound 27

Acquired by	: System Administrator
Sample Name	: LCMS69-PH-BPM-983-0-2(1011-410Q1)1T
Injection Volume	: 0.6
Data File	: LCMS69-PH-BPM-983-0-2(1011-410Q1)1T.lcd
Report Format File	: LCMS2020-PDA+ELSD+TIC+MS.lsr
Date Acquired	: 12/14/2018 4:27:54 PM
Comment	: Mobile phaseA:Water/0.04%NH4OH; Mobile phaseB:Acetonitrile

Instrument Name:Shimadzu LCMS-2020

<<Pump>>

Mode	: Binary gradient
Pump A	: LC-20ADXR
Pump B	: LC-20ADXR
Total Flow	: 1.2000 mL/min
B Conc.	: 10.0 %

<<Oven>>

Oven Temperature	: 40 C

<<PDA>>

PDA Model	: SPD-M20A
Lamp	: D2
Start Wavelength	: 190 nm
End Wavelength	: 400 nm

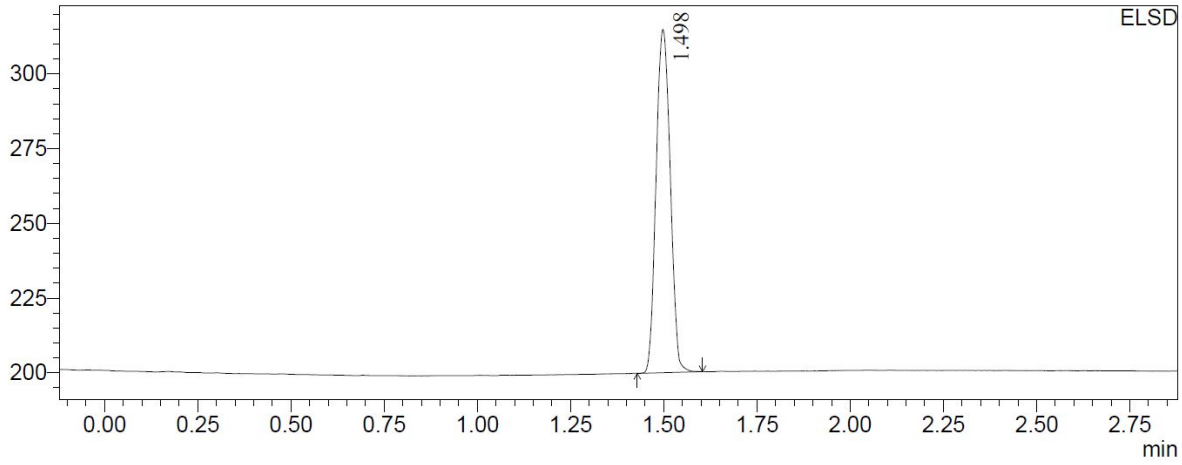
<<Interface>>

Interface	:ESI
DL Temperature	:250 C
Nebulizing Gas Flow	:1.50 L/min
Heat Block	:300 C
Drying Gas	:On
	12.00 L/min

<<MS Parameter>>

--Segment 1 Event 1--	
Start Time	:0.00 min
End Time	:3.00 min
Acquisition Mode	:Scan
Polarity	:Positive
Event Time	:0.50 sec
Detector Voltage	:+0.95 kV
Threshold	:0
Start m/z	:90.00
End m/z	:900.00
Scan Speed	:1667 u/sec
Interface Volt.	:Use the Data in the Tuning File
DL Volt.	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File

System Configuration



Peak Table

ELSD

Peak#	Ret. Time	Height	Height%	Area	Area%
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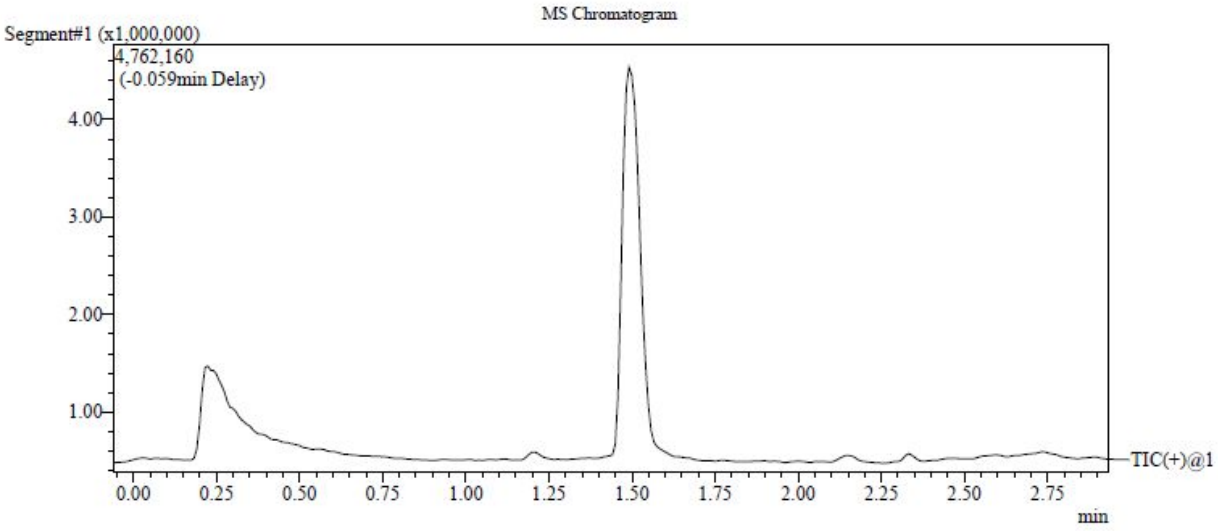
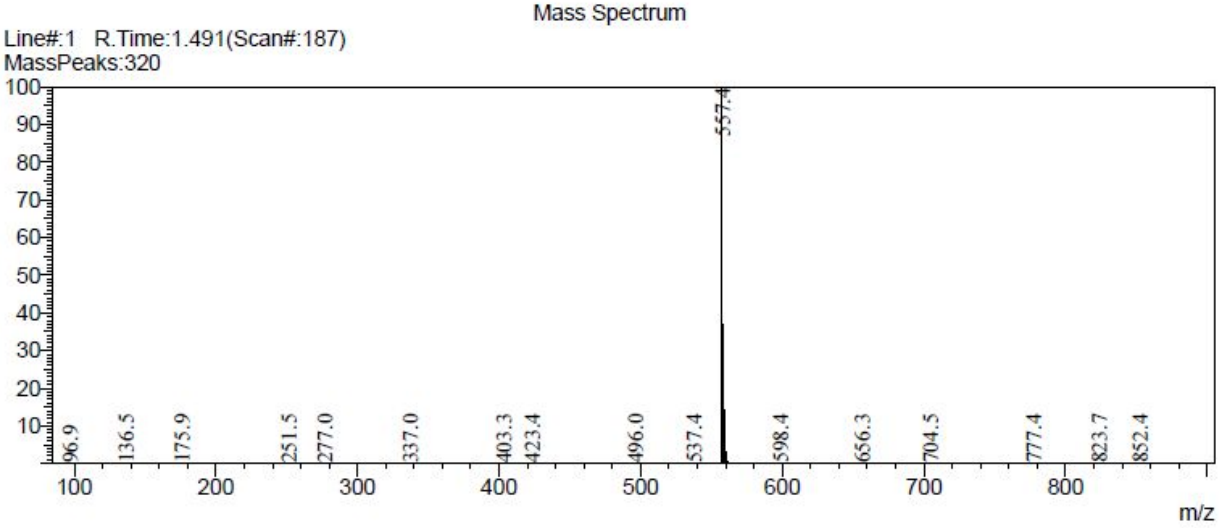




Compound 29

Chemical Formula: $C_{28}H_{37}FN_6O_3S$
Exact Mass: 556
Molecular Weight: 557

Acquired by	: System Administrator
Sample Name	: LCMS27-PH-BPM-1252-0-1(1009-520Q1)1T
Injection Volume	: 1
Method File	: ACN-Water-6.5mM NH4HCO3pH10-10%B-1.0-3.0MIN(90-900).lcm
Data File	: LCMS27-PH-BPM-1252-0-1(1009-520Q1)1T.lcd
Report Format File	: LCMS2020-PDA+ELSD+TIC+MS.lsr
Date Acquired	: 2019/4/1 11:59:33
Comment	: Mobile Phase A:Water+6.5mM NH4HCO3pH10 Mobile Phase B:Acetonitrile

Instrument Name:Shimadzu LCMS-2020

<<Pump>>

Mode	: Binary gradient
Pump A	: LC-30AD
Pump B	: LC-30AD
Total Flow	: 1.0000 mL/min
B Conc.	: 10.0 %

<<Oven>>

Oven Temperature	: 35 C

<<PDA>>

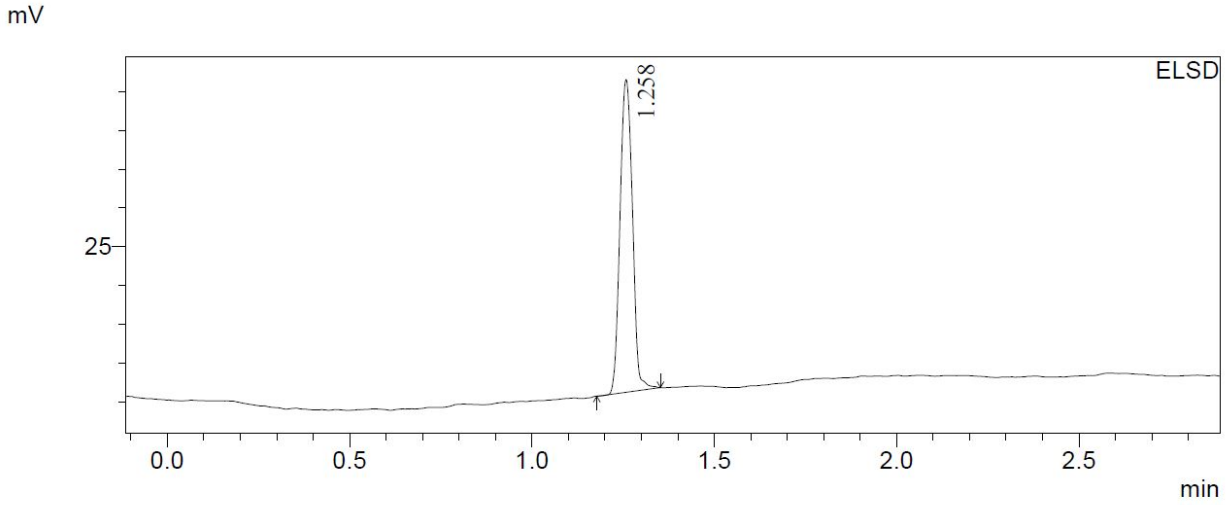
PDA Model	: SPD-M20A
Lamp	: D2
Start Wavelength	: 190 nm
End Wavelength	: 400 nm

<<Interface>>

Interface	:ESI
DL Temperature	:250 C
Nebulizing Gas Frow	:1.50 L/min
Heat Block	:200 C
Drying Gas	:On
	12.00 L/min

<<MS Parameter>>

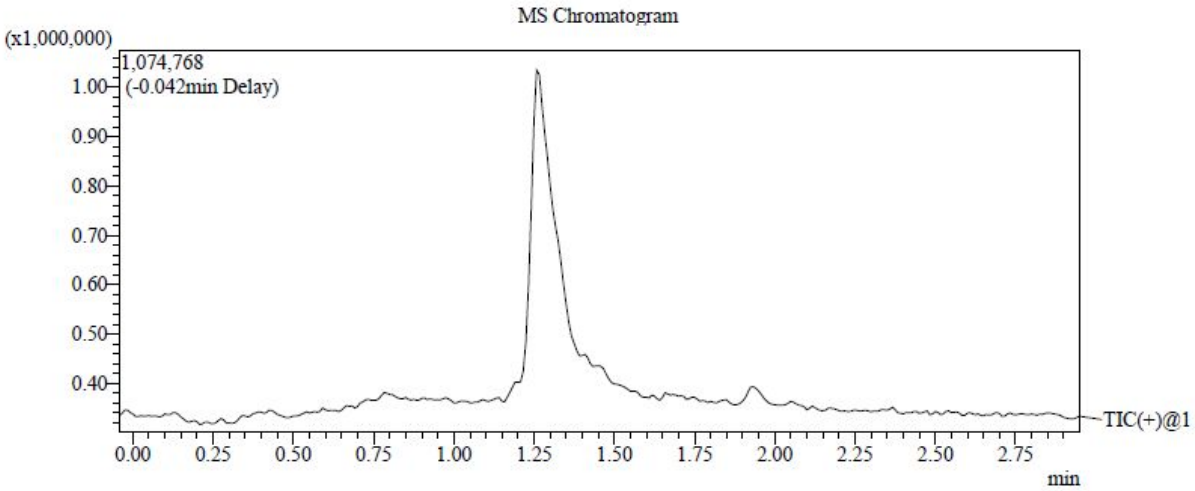
Initial Valve Position	:-
--Segment 1 Event 1--	
Start Time	:0.00 min
End Time	:3.00 min
Acquisition Mode	:Scan
Polarity	:Positive
Event Time	:0.50 sec
Detector Voltage	:+0.80 kV
Threshold	:0
Start m/z	:90.00
End m/z	:900.00
Scan Speed	:1667 u/sec
Interface Volt.	:Use the Data in the Tuning File
DL Volt.	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File

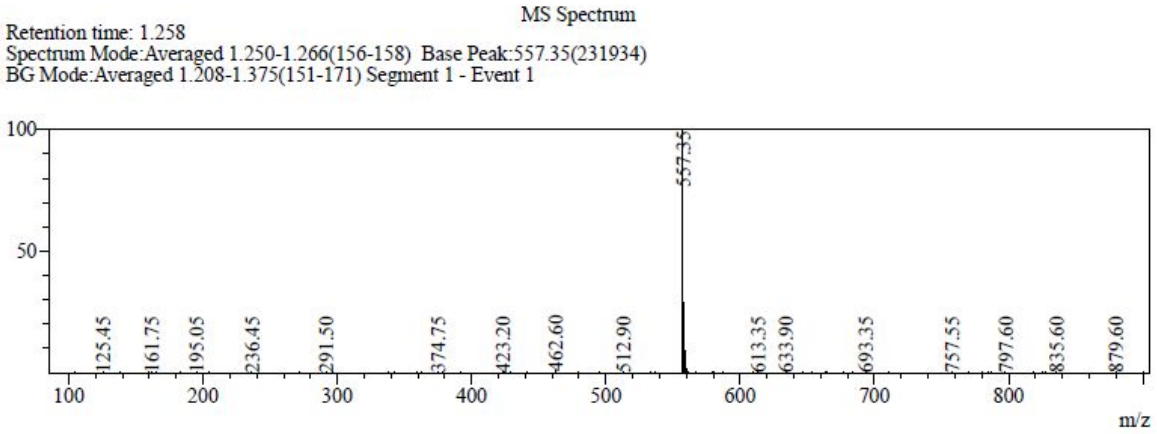


Peak Table

ELSD

Peak#	Ret. Time	Height	Height%	Area	Area%
1	1.258	39947	100.000	95507	100.000
Total		39947	100.000	95507	100.000





Compound 30

Acquired by	: System Administrator
Sample Name	: LCMS31-PH-BPM-1527-0-1(1015-594A1)1T
Injection Volume	: 1
Data File	: LCMS31-PH-BPM-1527-0-1(1015-594A1)1T.lcd
Report Format File	: LCMS2020-PDA+ELSD+TIC+MS.lsr
Date Acquired	: 2019/11/15 11:36:45
Comment	: Mobile phaseA:water/0.05%TFA Mobile phaseB:ACN/0.05%TFA

Instrument Name:Shimadzu LCMS-2020

<<Pump>>

Mode	: Binary gradient
Pump A	: LC-20AD
Pump B	: LC-20AD
Total Flow	: 1.2000 mL/min
B Conc.	: 5.0 %

<<Oven>>

Oven Temperature	: 40 C

<<PDA>>

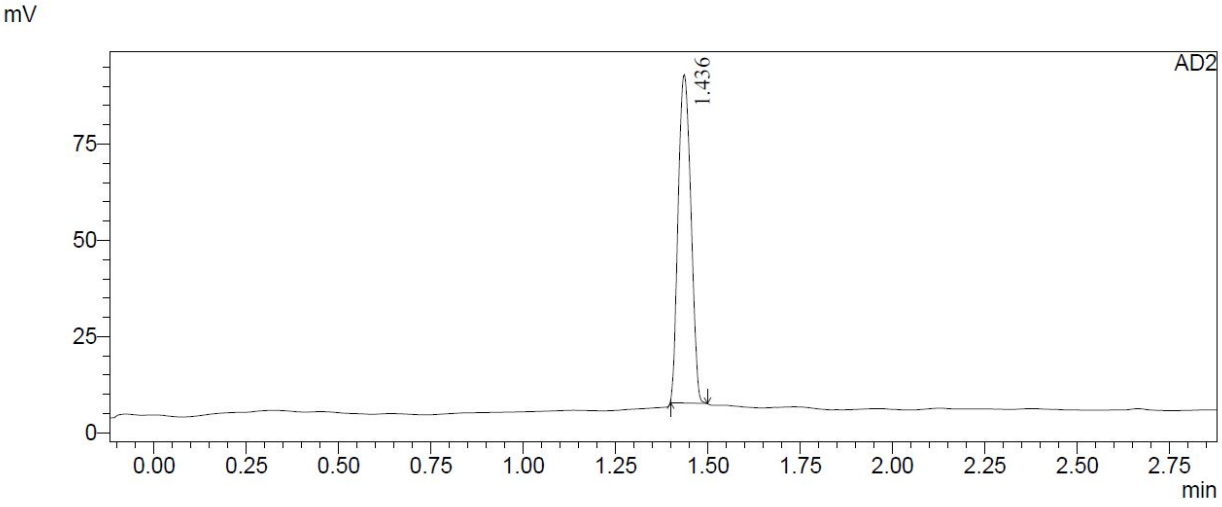
PDA Model	: SPD-M20A
Lamp	: D2
Start Wavelength	: 190 nm
End Wavelength	: 400 nm

<<Interface>>

Interface	:ESI
DL Temperature	:250 C
Nebulizing Gas Frow	:1.50 L/min
Heat Block	:250 C
Drying Gas	:On
	15.00 L/min

<<MS Parameter>>

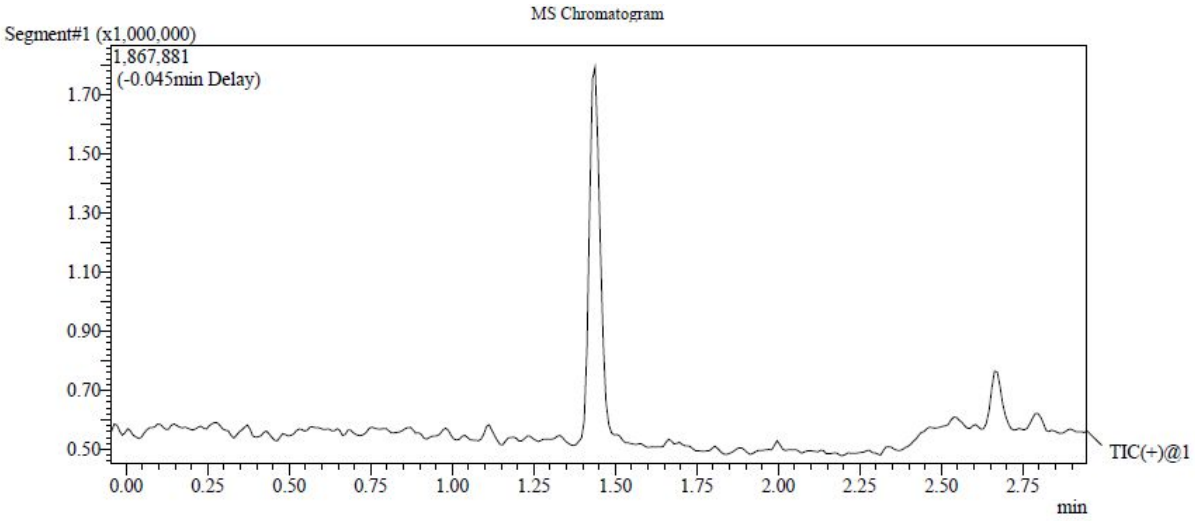
Initial Valve Position	:-
--Segment 1 Event 1--	
Start Time	:0.00 min
End Time	:3.00 min
Acquisition Mode	:Scan
Polarity	:Positive
Event Time	:0.50 sec
Detector Voltage	:+0.85 kV
Threshold	:0
Start m/z	:90.00
End m/z	:900.00
Scan Speed	:1667 u/sec
Interface Volt.	:Use the Data in the Tuning File
DL Volt.	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File



Peak Table

AD2

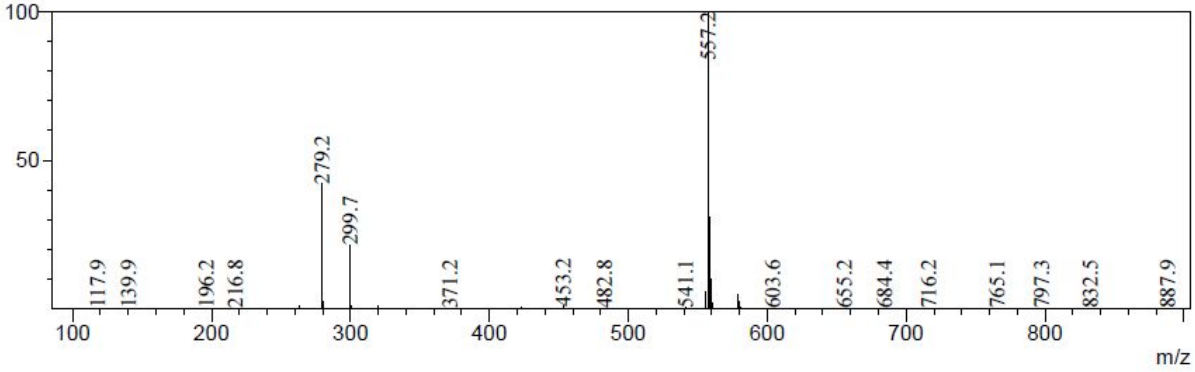
Peak#	Ret. Time	Height	Height%	Area	Area%
1	1.436	84571	100.000	204908	100.000
Total		84571	100.000	204908	100.000



Mass Spectrum

Retention time: 1.438

Spectrum Mode:Single 1.438(179) Base Peak:557.2(458597)
BG Mode:Averaged 1.388-1.538(173-191) Segment 1 - Event 1



Compound 31

Acquired by	: System Administrator
Sample Name	: LCMS31-PH-BPM-1290-0-1(1006-1009Q1)1T
Injection Volume	: 1
Data File	: LCMS31-PH-BPM-1290-0-1(1006-1009Q1)1T.lcd
Report Format File	: LCMS2020-PDA+ELSD+TIC+MS.lsr
Date Acquired	: 2019/5/30 16:07:39
Comment	: Mobile phaseA:water/0.05%TFA Mobile phaseB:ACN/0.05%TFA

Instrument Name:Shimadzu LCMS-2020

<<Pump>>

Mode	: Binary gradient
Pump A	: LC-20AD
Pump B	: LC-20AD
Total Flow	: 1.2000 mL/min
B Conc.	: 5.0 %

<<Oven>>

Oven Temperature	: 40 C

<<PDA>>

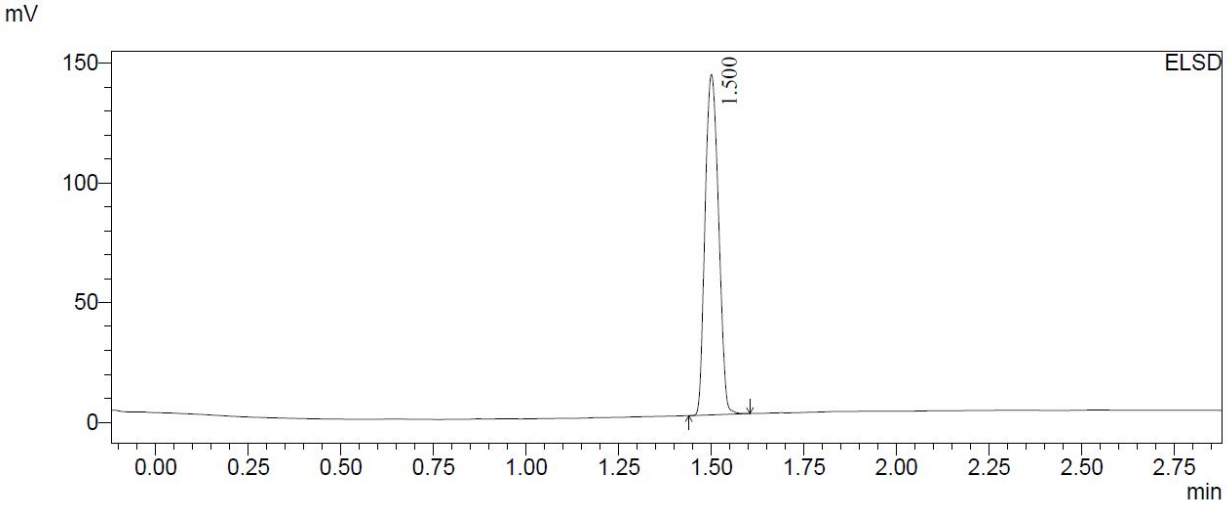
PDA Model	: SPD-M20A
Lamp	: D2
Start Wavelength	: 190 nm
End Wavelength	: 400 nm

<<Interface>>

Interface	:ESI
DL Temperature	:250 C
Nebulizing Gas Frow	:1.50 L/min
Heat Block	:250 C
Drying Gas	:On
	15.00 L/min

<<MS Parameter>>

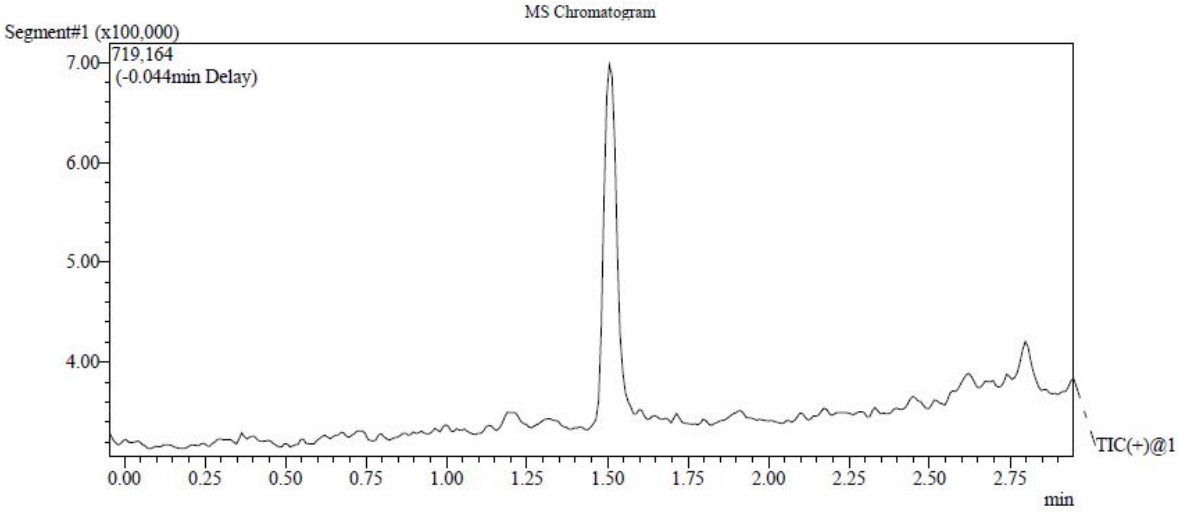
Initial Valve Position	:-
--Segment 1 Event 1--	
Start Time	:0.00 min
End Time	:3.00 min
Acquisition Mode	:Scan
Polarity	:Positive
Event Time	:0.50 sec
Detector Voltage	:+0.90 kV
Threshold	:0
Start m/z	:90.00
End m/z	:900.00
Scan Speed	:1667 u/sec
Interface Volt.	:Use the Data in the Tuning File
DL Volt.	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File
Qarray DC Voltage	:Use the Data in the Tuning File

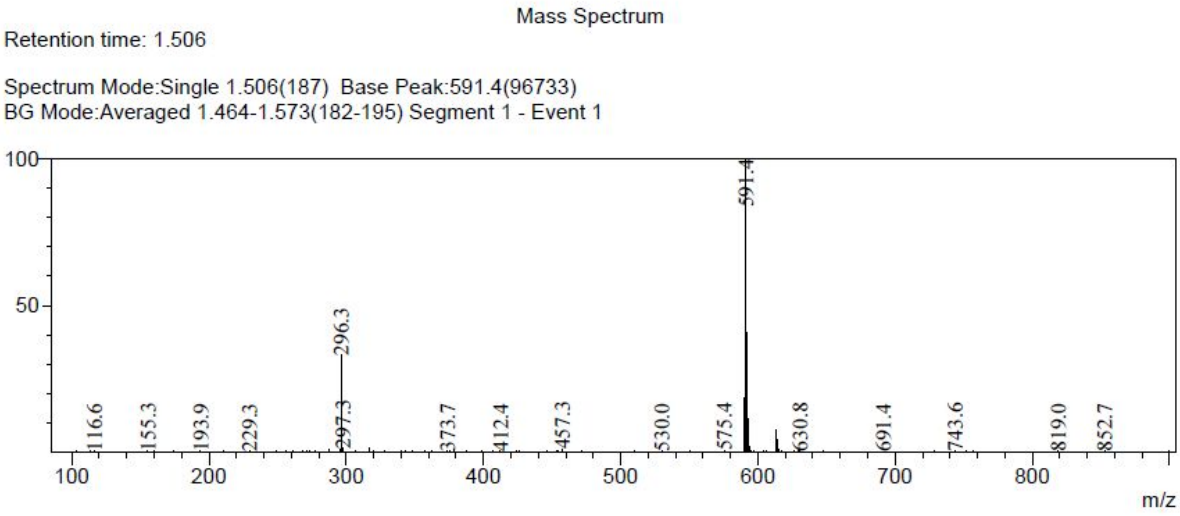


Peak Table

ELSD

Peak#	Ret. Time	Height	Height%	Area	Area%
1	1.500	140867	100.000	359653	100.000
Total		140867	100.000	359653	100.000





5. X-ray data collection and refinement statistics for compounds 7 and 24

	Compound 7	Compound 24
Accession Code	**8D73**	**8D76**
Data collection:		
Wavelength	0.966	0.916
Resolution range (Å)	29.79 – 2.17 (2.29 – 2.17)	48.71 – 2.39 (2.43 – 2.39)
Space group	P1	P1
Unit cell	41.7 49.5 86.1 103.2 101.6 90.1	41.5 50.3 85.9 104.2 101.7 90.1
Unique reflections	31680 (4458)	25531 (1289)
Multiplicity	1.7 (1.7)	3.5 (3.5)
Completeness (%)	91.4 (88.5)	98.0 (96.9)

Mean I/sigma(I)	4.9 (1.6)	10.8 (2.2)
R-meas	0.130 (0.660)	0.080 (0.630)
Refinement:		
Resolution range (Å)	29-79 – 2.17 (2.23 – 2.17)	30.0 – 2.40 (2.46 – 2.40)
Reflections used in refinement	30146 (2160)	23969 (1723)
Reflections used for R-free	1531 (125)	1260 (104)
Completeness (%)	91.4 (89.2)	97.9 (96.9)
R-work	0.191 (0.383)	0.156
R-free	0.285 (0.424)	0.260
Number of non-hydrogen atoms	5809	5833
r.m.s.d. bonds (Å)	0.010	0.006
r.m.s.d. angles (°)	1.41	1.36