Supporting Information

Asymmetric Synthesis of Heterocyclic Analogs of a CGRP Antagonist for Treating Migraine

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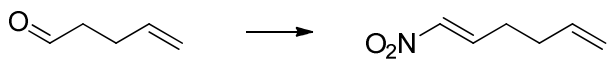
Experimental section

Chemistry. **General Details**. All commercially available reagents and solvents were used without further purification unless otherwise stated. All reactions were carried out under an inert atmosphere of dry nitrogen in oven-dried glassware unless otherwise stated. Flash column chromatography was performed using 40-60 μm Silica Gel 60 (EMD Chemicals, Inc.) as the stationary phase, or pre-packed columns from ISCO Inco., Biotage, or Thomson Instrument Co. ^{1}H NMR spectra were recorded on a Bruker 400 or 500 MHz machine with tetramethylsilane or residual protiated solvent used as a reference. ^{13}C NMR were recorded on a Bruker DRX-500 instrument operating at 125 MHz with residual ^{12}C solvent used as a reference. Low resolution mass spectra were recorded using a Waters Micromass ZQ with electrospray ionization. High resolution mass spectra were recorded using a Waters Micromass LCT time of flight mass spectrometer with electrospray ionization.

Synthesis and characterization of intermediates 11, 12, 10, and 9

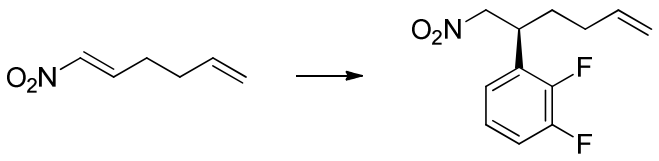
Intermediate **11**



(E)-1-nitrohexa-1,5-diene. In an oven-dried 1 L round-bottomed flask pent-4-enal (11.3 g, 134 mmol) was dissolved in toluene (300 mL) to give a colorless solution. After cooling to 0 °C, nitromethane (72.4 mL, 1343 mmol) and 1,1,3,3-tetramethylguanidine (1.685 mL, 13.43 mmol) were added. After the mixture was stirred at 0 °C for 60 min, TLC showed a major product (4:1 hexane/ethyl acetate). Methanesulfonyl chloride (15.7 mL, 202 mmol) and triethylamine (28 mL, 202 mmol) were added. The cooling bath was removed and the mixture was stirred at r.t. for 1 h. After 1 h, a further 0.5 equiv. of methanesulfonyl chloride (5.2 mL) and triethylamine (9.3 mL) were added to the mixture and the reaction continued for another h. It was quenched with saturated sodium bicarbonate solution and diluted with diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl

ether. The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated under high vacuum to give a tan oil. The residue was purified by flash column chromatography up to 20% ethyl acetate/hexanes. The major uv-active fraction was pooled and concentrated to a light yellow oil (further dried under house vac over 3 days: 12.30 g, 72%): ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.24 (ddd, *J*=13.74, 7.15, 6.96 Hz, 1 H) 6.98 (d, *J*=13.55 Hz, 1 H) 5.67 - 5.86 (m, 1 H) 4.98 - 5.14 (m, 2 H) 2.37 (q, *J*=7.03 Hz, 2 H) 2.27 (q, *J*=6.94 Hz, 2 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 140.82 - 141.82, 139.50, 135.60, 115.56 - 116.67, 30.49 - 31.82, 26.73 - 27.94.

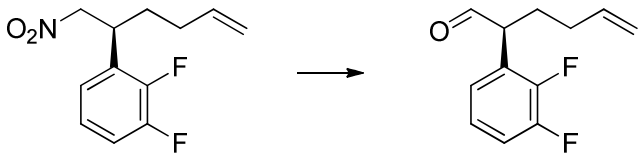
Intermediate **12**



(S)-1,2-Difluoro-3-(1-nitrohex-5-en-2-yl)benzene. In a 1 L round-bottom flask was dissolved (E)-1-nitrohexa-1,5-diene (12.30 g, 97 mmol) and 2,3-difluorophenylboronic acid (38.2 g, 242 mmol) in dioxane (315 mL) to give a colorless suspension. Water (6.1 mL, 340 mmol) was added. The mixture was degassed with nitrogen and in a sonicator for 20 min. Sodium bicarbonate (4.06 g, 48.4 mmol) and (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.807 g, 2.90 mmol) and acetylacetonatobis(ethylene)rhodium (I) (0.749 g, 2.90 mmol) were added to the solution under nitrogen. The mixture was stirred at rt for 2 min, and then heated to 35 °C for 6 h under nitrogen. Reaction was continued for another 8 h at 35 °C. The mixture was diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated to a tan oil. Flash column chromatography up to 15% ethyl acetate/hexane afforded a major peak which was pooled and concentrated to the product as a colorless oil (22.38 g, 96%): ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ

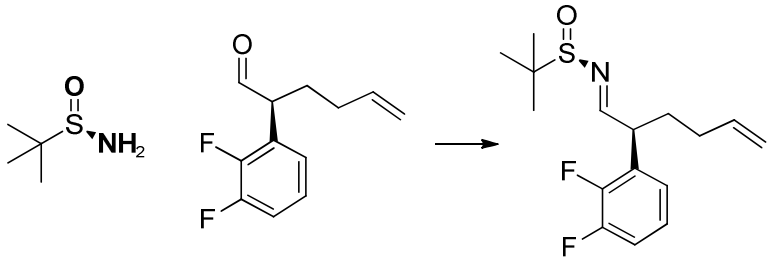
ppm 7.03 - 7.17 (m, 2 H) 6.91 - 7.02 (m, 1 H) 5.70 – 5.80 (m, 1 H) 4.94 - 5.05 (m, 2 H) 4.66 – 4.68 (m, 2 H) 3.78 – 3. 85 (m, 1 H) 1.94 - 2.08 (m, 2 H) 1.77 - 1.94 (m, 2 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 151.74 - 149.14 (dd, J = 13.13 and 249.47 Hz), 150.15 - 147.55, (dd, J = 13.13 and 249.47 Hz), 136.32 (d, *J*=10.02 Hz), 128.18 (d, *J*=10.79 Hz), 124.15, 123.68 (d, *J*=3.85 Hz) 115.82 - 117.00, 115.54, 78.49, 37.85 (d, *J*=11.56 Hz), 30.63, 30.54; ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -137.24, -142.38.

Intermediate **10**



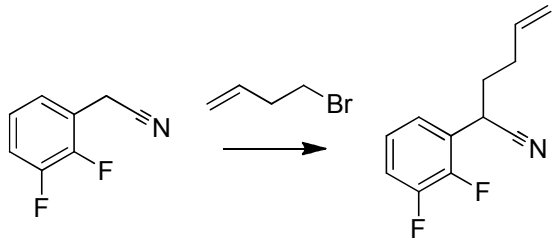
(S)-2-(2, 3-Difluorophenyl)hex-5-enal. In a 250 mL round-bottomed flask was dissolved (S)-1, 2-difluoro-3-(1-nitrohex-5-en-2-yl)-benzene (4.14 g, 17.2 mmol) in methanol (21 mL) under nitrogen. After cooling to 0 °C, sodium methoxide (4.12 mL, 18.0 mmol) was added via syringe. After stirring at 0 °C for 30 min, the temperature was lowered to -60 °C. Conc. sulfuric acid (2.93 mL, 54.9 mmol) in 21 mL methanol was added dropwise. The resulting milky mixture was stirred at -60 to -20 °C for 4 h. It was diluted with ethyl acetate and saturated ammonium chloride solution. The layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine, dried, and concentrated to a give tan oil (4.8 g), which was dissolved in chloroform (124 mL). Water (31 mL) was added followed by slow addition of trifluoroacetic acid (31 mL). The mixture was stirred at rt overnight for 18 h. The layers were separated. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried and concentrated to give a light yellow oil (5 g, 100%), which was directly carried onto next reaction immediately.

Intermediates 9



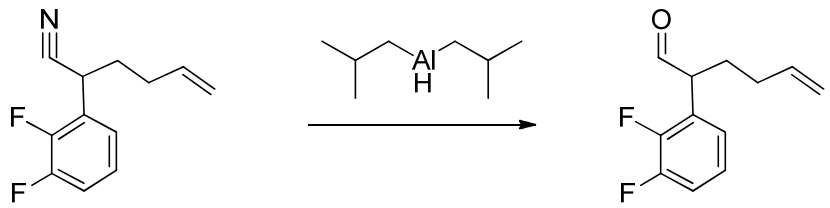
(R,E)-N-((S)-2-(2,3-difluorophenyl)hex-5-enylidene)-2-methylpropane-2-sulfinamide. In a 500 mL round-bottomed flask was dissolved (S)-2-(2,3-difluorophenyl)hex-5-enal (3.61 g, 17.2 mmol) (freshly azeotroped with dry benzene) and (R)-2-methylpropane-2-sulfinamide (2.08 g, 17.2 mmol) in tetrahydrofuran (100 mL) to give a yellow solution. Titanium(IV) ethoxide (36.0 mL, 34.3 mmol) was added dropwise, and the mixture was stirred at rt under nitrogen for 6 h. It was transferred to a stirred solution of brine (90 mL) and a white solid was formed. This was filtered through a plug of celite and washed with ethyl acetate. The eluent was concentrated to give a tan oil. The residue was purified by flash column chromatography up to 40% ethyl acetate/hexane afforded the desired product (3.94 g, 73% for 2 steps) as a light yellow oil: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.09 (d, J=4.52 Hz, 1 H) 7.02 - 7.14 (m, 2 H) 6.97 (d, J=8.28 Hz, 1 H) 5.68 - 5.87 (m, 1 H) 5.02 (d, J=13.05 Hz, 2 H) 4.07 - 4.18 (m, 1 H) 2.19 (dt, J=13.30, 6.65 Hz, 1 H) 2.05 - 2.13 (m, 2 H) 1.90 - 2.03 (m, 1 H) 1.17 (s, 9 H); ^{19}F NMR (376 MHz, CHLOROFORM-d) δ ppm -137.55 (br. s., 1 F) -142.03 (br. s., 1 F); ^{13}C NMR (101 MHz, CHLOROFORM-d) δ ppm 167.94, 150.37 (dd, (dd, *J* = 248.9, 13.2 Hz), 148.56 (dd, *J* = 247.8, 12.8 Hz), 136.73, 128.40 (d, *J* = 11.8 Hz), 123.79 (d, *J* = 25.4 Hz), 115.76 (d, *J* = 16.8 Hz), 115.38, 109.63, 56.74 , 43.92 (d, *J* = 12.0 Hz), 30.81 , 30.38 , 21.96/21.93.

Synthesis and characterization of racemic 10, 9, and 7a:



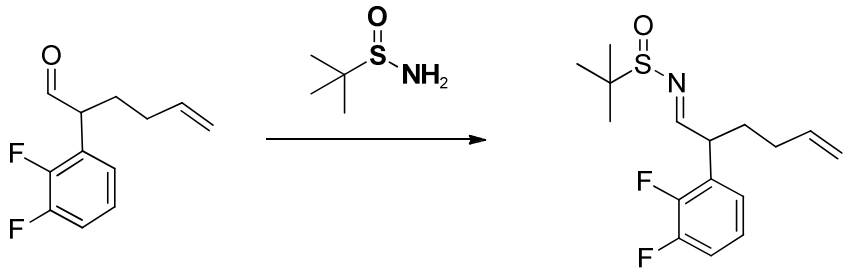
2-(2,3-Difluorophenyl)hex-5-enenitrile. To a 100 mL round bottom flask was added 2-(2,3-difluorophenyl)acetonitrile (5.455 g, 35.6 mmol) and N-benzyl-N,N-diethylethanaminium chloride (0.811 g, 3.56 mmol). This reaction mixture was added NaOH (1.710 g, 42.7 mmol) in Water (2 mL) at room temperature. 4-bromobut-1-ene (3.62 mL, 35.6 mmol) was added to the above reaction mixture at 50 °C slowly. The reaction mixture was stirring at 50 °C for 6.5 h and was stirred at room temperature overnight. TLC showed still has some starting material left. Another 10% (0.4 mL) of 4-bromobut-1-ene was added to the reaction mixture and the reaction was stirred at 50 °C for 4 hours. The reaction was diluted with water and extract with ethyl acetate. The ethyl acetate layer was washed with 1N HCl before dried (Na_2SO_4), filtered and concentrated. Flash column by ethyl acetate in hexane from 0 to 10% gave the desired product (5.62 g, 67%, 88% purity by LCMS): ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.13 - 7.30 (3 H, m), 5.80 (1 H, ddt, *J*=17.0, 10.4, 6.7, 6.7 Hz), 5.09 - 5.19 (2 H, m), 4.12 - 4.19 (1 H, m), 2.24 - 2.35 (2 H, m), 1.94 - 2.13 (2 H, m).

Racemic **10**



In a 100 mL round-bottomed flask was 2-(2,3-difluorophenyl)hex-5-enenitrile (575 mg, 2.77 mmol) (azeotroped with dry benzene) in Toluene (20 mL) to give a colorless solution. After cooling to 0 °C, DIBAL-H (4.16 mL, 4.16 mmol) (1.0M in toluene) was added via syringe, and the mixture was stirred at rt for 2 h. The mixture was diluted with ether and slowly quenched with 30ml 1M citric acid. After stirring for 5 min, the layers were separated. The organic layer was washed with brine, dried and concentrated to a colorless oil. Purification by FCC up to 10% EtOAc/hexane afforded the desired product (430 mg, 74%) as a colorless oil: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.71 (d, *J*=1.26 Hz, 1 H) 7.03 - 7.17 (m, 2 H) 6.85 - 6.97 (m, 1 H) 5.68 - 5.86 (m, 1 H) 4.95 - 5.06 (m, 2 H) 3.88 (dd, *J*=8.78, 6.02 Hz, 1 H) 2.17 - 2.33 (m, 1 H) 2.06 (ddd, *J*=13.80, 6.78, 6.53 Hz, 2 H) 1.74 - 1.90 (m, 1 H); ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -137.41 - -137.05, -142.09.

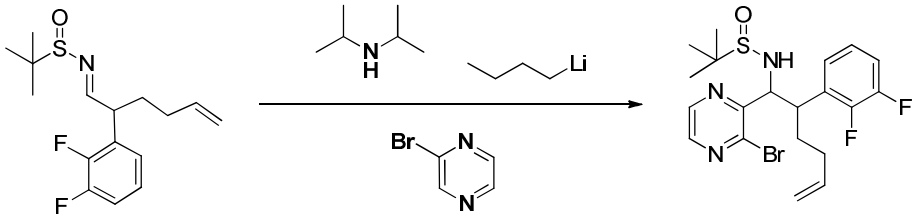
Racemic **9**



In a 250 mL round-bottomed flask was 2-(2,3-difluorophenyl)hex-5-enal (430 mg, 2.045 mmol) (azeotroped with dry benzene) and 2-Methyl-2-propanesulfinamide (248 mg, 2.045 mmol) in THF (12 mL to give a yellow solution. Titanium(IV) ethoxide (4.29 mL, 4.09 mmol) was added, and the mixture was stirred at rt under nitrogen for 6 h. It was transfered to a stirring 16 ml brine and white solids were formed. It was filtered through a plug of celite and washed with EtOAc. The elute was concentrated to a tan oil. The residue was purified by FCC up to 20% EtOAc/hexane afforded the desired product (507 mg, 79%) as a colorless oil (a diastereomeric mixture): ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.09 (dd, *J*=13.68, 4.39 Hz, 1 H) 7.00 - 7.11 (m, 2 H) 6.91 - 6.99 (m, 1 H) 5.69 - 5.87 (m, 1 H) 4.94 -

5.04 (m, 2 H) 3.99 - 4.18 (m, 1 H) 2.13 - 2.26 (m, 1 H) 2.07 (dt, *J*=13.24, 6.56 Hz, 2 H) 1.87 - 2.02 (m, 1 H) 1.12 - 1.21 (m, 9 H); ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -137.59 - -137.24 (m, 1 F) -142.18 - -141.83 (m, 1 F); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 168.31/167.93, 150.36 (dd, *J* = 248.8, 13.0 Hz), 148.57 (ddd, *J* = 248.0, 12.7, 6.3 Hz), 136.74 , 128.40 (dd, *J* = 11.6, 2.8 Hz), 123.81 (d, *J* = 20.0 Hz), 116.34 – 115.52 (m), 115.35, 56.70/56.55, 44.14 – 43.84, 30.79/30.73, 30.34, 22.03-21.88.

Racemic **7a**

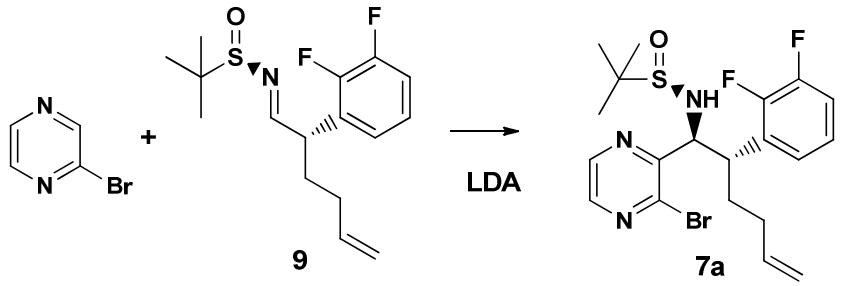


In an oven-dried 100 mL round-bottomed flask was diisopropylamine (0.149 mL, 1.053 mmol) in THF (3 mL) to give a colorless solution under nitrogen. After cooling to -30 °C, BuLi (0.383 mL, 0.957 mmol) was added, and the mixture was gradually warmed up to 0 °C for 10 min. After cooling down to -78 °C, 2-bromopyrazine (0.088 mL, 0.957 mmol) was added in one portion. The resulted yellow solution was stirred at -78 °C for 25 min (turned to dark). (E)-N-(2-(2,3-difluorophenyl)hex-5-enylidene)-2-methylpropane-2-sulfinamide (150 mg, 0.479 mmol) in 1 ml anhydrous THF (plus 1 ml rinse) was added via canuula, and the mixture was stirred for 2 h while the temperature gradually warmed upt to -40 °C. 2.5 h later, the reaction was quenched by saturated $NaHCO_3$ solution and diluted with EtOAc. The layers were separated. The organic layer was washed with brine, dried, and concentrated to a tan oil. FCC up to 70% EtOAc/hexane afforded the more polar desired product (overlapping two peaks, 158 mg, 70%, ^{1}H NMR showed two diasteromers with ratio of 5/2) as a dense yellow oil: ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.09 - 8.47 (m, 2 H) 6.84 - 7.24 (m, 3 H)

5.65 - 5.84 (m, 1 H) 5.11 - 5.28 (m, 1 H) 4.85 - 5.02 (m, 2 H) 4.30 (d, *J*=9.29 Hz, 1 H) 3.51 - 3.79 (m, 1 H) 2.40 (dd, *J*=8.03, 3.51 Hz, 1 H) 1.92 - 2.06 (m, 2 H) 1.75 - 1.91 (m, 1 H) 1.02 - 1.12 (2s, 9 H).

Synthesis and Characterization of 7a, 13 and Heck reactions of 13:

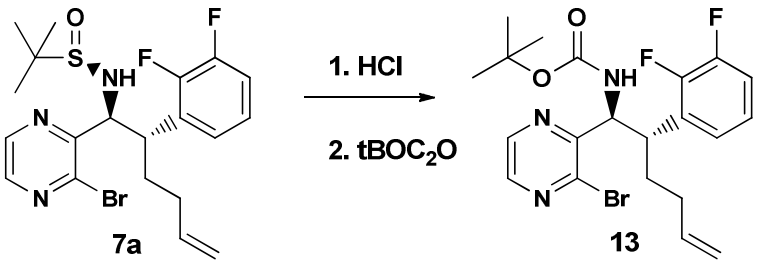
Intermediates 7a



(R)-N-((1S,2S)-1-(3-bromopyrazin-2-yl)-2-(2,3-difluorophenyl)hex-5-enyl)-2-methylpropane-2-sulfinamide. In an oven-dried 250 mL round-bottomed flask was dissolved diisopropylamine (1.7 mL, 12 mmol) in tetrahydrofuran (40 mL) to give a colorless solution under nitrogen. After cooling to -30 °C, n-BuLi (4.3 mL, 11 mmol) was added, and the mixture was briefly warmed up to rt for 3 min. After cooling down to -78 °C, 2-bromopyrazine (0.98 mL, 10.7 mmol) was added dropwise via syringe. The resulting yellow solution was stirred at -78 °C for 5 min. (R,E)-N-((S)-2-(2,3-difluorophenyl)hex-5-enylidene)-2-methylpropane-2-sulfinamide (2.089 g, 6.67 mmol) in 4 mL anhydrous tetrahydrofuran (plus 3 mL rinse) was added via canuula, and the mixture was stirred for 2 h at -75 °C. The reaction was quenched with saturated sodium bicarbonate solution and diluted with ethyl acetate. The layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated to give a tan oil. Flash column chromatography up to 80% ethyl acetate/hexane afforded the desired product (1.964 g, 62%) as a dense tan oil: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.33 (d, J=2.26 Hz, 1 H) 8.26 (d, J=2.26 Hz, 1

H) 6.99 - 7.22 (m, 3 H) 5.74 (d, J=6.53 Hz, 1 H) 5.18 (dd, J=9.29, 5.27 Hz, 1 H) 4.85 - 4.99 (m, 2 H) 4.30 (d, J=9.54 Hz, 1 H) 3.66 - 3.77 (m, 1 H) 2.17 (br. s., 1 H) 1.80 - 2.04 (m, 3 H) 1.05 (s, 9 H); ^{19}F NMR (376 MHz, CHLOROFORM-d) δ ppm -138.41 (d, J=15.61 Hz, 1 F) -144.20 - -143.20 (m, 1 F).

Intermediate 13

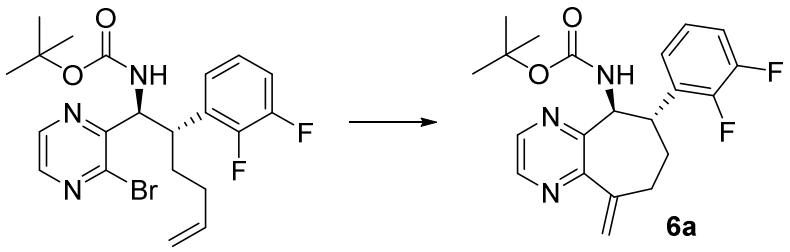


tert-Butyl (1S,2S)-1-(3-bromopyrazin-2-yl)-2-(2,3-difluorophenyl)hex-5-enylcarbamate. In a 250 mL round-bottomed flask was (R)-N-((1S)-1-(3-bromopyrazin-2-yl)-2-(2,3-difluorophenyl)hex-5-enyl)-2-methylpropane-2-sulfinamide (1.96 g, 4.16 mmol) in methanol (17 mL) to give a tan solution. HCl (4M in dioxane, 4.2 mL, 17 mmol) was added, and the mixture was stirred at rt for 1h. Volatiles were removed in vacuo and the tan residue was diluted with ether and concentrated. The remaining tan foam was directly used in the next reaction.

In the same round-bottomed flask was dissolved (1S,2S)-1-(3-bromopyrazin-2-yl)-2-(2,3-difluorophenyl)hex-5-en-1-amine (1.532 g, 4.16 mmol) (crude HCl salt) and t-butylpyrocarbonate (1.449 mL, 6.24 mmol) in methylene chloride (22 mL) to give a tan solution. Triethylamine (1.28 mL, 9.15 mmol) was added dropwise, and the mixture was stirred at rt for 2 h. LCMS showed complete conversion. It was concentrated to dryness, and directly subject to flash column chromatography up to 40% ethyl acetate/hexane to afford the desired product (1.80 g, 92% for 2 steps) as colorless oil: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.27 (d, J=17.07 Hz, 2 H) 6.92 - 7.14 (m, 3 H) 5.69 (dd,

J=10.29, 5.77 Hz, 1 H) 5.63 (dd, J=9.41, 5.90 Hz, 1 H) 5.41 (d, J=9.54 Hz, 1 H) 4.84 - 4.95 (m, 2 H) 3.65 (br. s., 1 H) 1.88 - 2.08 (m, 3 H) 1.81 (br. s., 1 H) 1.30 - 1.41 (m, 9 H). A slightly more polar diastereomer (generally <10% if there was minimum epimerization at the aldehyde stage) could be removed at this stage: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.46 (d, J=2.26 Hz, 1 H) 8.20 (d, J=2.51 Hz, 1 H) 6.88 - 7.11 (m, 3 H) 5.66 - 5.81 (m, 1 H) 5.60 (t, J=8.91 Hz, 1 H) 5.51 (d, J=9.29 Hz, 1 H) 4.83 - 5.00 (m, 2 H) 3.55 (d, J=6.53 Hz, 1 H) 1.87 - 2.06 (m, 3 H) 1.73 - 1.86 (m, 1 H) 1.44 (s, 9 H).

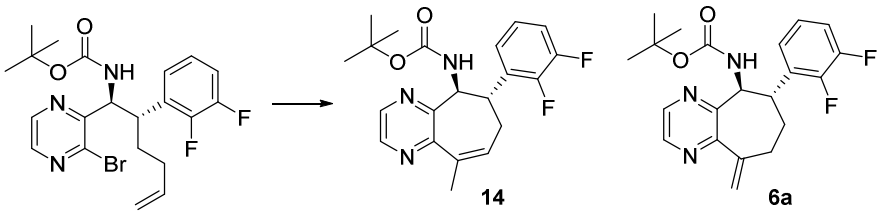
Intermediates 6a



tert-Butyl ((5S,6S)-6-(2,3-difluorophenyl)-9-methylene-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-yl)carbamate. In a 5 mL microwave tube was tert-butyl (1S,2S)-1-(3-bromopyrazin-2-yl)-2-(2,3-difluorophenyl)hex-5-enylcarbamate (23.6 mg, 0.050 mmol), and Bis(tri-t-butylphosphine)palladium(0) (0.773 mg, 1.512 μmol) in dioxane (Volume: 1.5 mL) (degassed) to give a yellow solution under nitrogen. Methyl dicyclohexylamine (0.012 mL, 0.055 mmol) was added, and the reaction was sealed under nitrogen. The mixture was stirred at rt for 1h then at 70 °C (microwave) for 20 h. It was diluted with EtOAc and water. The layers were separated and the organic layer was washed with brine, dried, and concentrated to a tan oil. FCC up to 60% EtOAc/hexane afforded the recovered SM (5.1 mg, 22%) and the more polar desired product (3.9 mg, 20%): ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.50 (d, J=2.51 Hz, 1 H) 8.46 (d, J=2.51 Hz, 1 H) 7.29 - 7.35 (m, 1 H) 7.02 - 7.12 (m, 2 H) 5.87 (d, J=9.29 Hz, 1 H) 5.76 (s, 1 H) 5.54 (d, J=1.51 Hz, 1 H) 5.25 - 5.34 (m, 1 H) 3.30 -

3.43 (m, 1 H) 2.94 (d, J=7.78 Hz, 1 H) 2.54 (br. s., 1 H) 2.15 - 2.28 (m, 1 H) 1.96 - 2.07 (m, 1 H) 1.25 - 1.28 (m, 9 H).

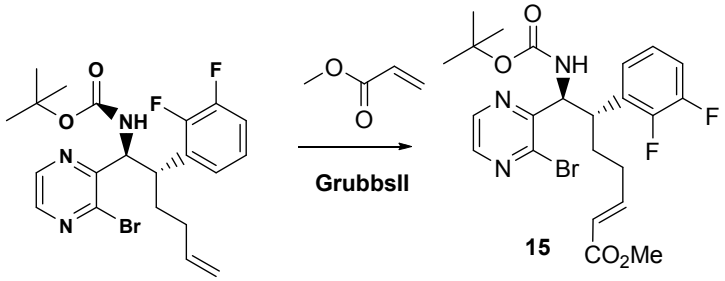
Compound 14



tert-Butyl (5S,6S)-6-(2,3-difluorophenyl)-9-methyl-6,7-dihydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate. In a 150 mL pressure bottle was tert-butyl (1S,2S)-1-(3-bromopyrazin-2-yl)-2-(2,3-difluorophenyl)hex-5-enylcarbamate (810 mg, 1.730 mmol), and Bis(tri-t-butylphosphine)palladium(0) (44.2 mg, 0.086 mmol) in dioxane (24 mL, degassed) to give a yellow solution under nitrogen. Methyl dicyclohexylamine (0.407 mL, 1.902 mmol) was added, and the reaction was sealed under nitrogen. The mixture was stirred at rt for 5 min and then 100°C (preheated oil bath) for 20 h. It was diluted with EtOAc and water. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated to a tan oil. TLC (1/1 EtOAc/hexane) showed a major more polar blue spot (with a small spot right above/overlapping with this spot). After purification by FCC up to 60% EtOAc/hexane, and ^{1}H NMR analysis, the major blue spot turned out to be likely the isomerized product (328 mg, 49%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (q, *J* = 2.4 Hz, 2H), 7.27 – 7.02 (m, 4H), 5.12 (t, *J* = 10.4 Hz, 1H), 5.05 – 4.88 (m, 1H), 3.47 (ddd, *J* = 12.8, 11.2, 3.8 Hz, 1H), 3.08 (dd, *J* = 16.1, 3.8 Hz, 1H), 2.78 (ddt, *J* = 15.4, 12.9, 2.3 Hz, 1H), 1.87 (dd, *J* = 7.3, 1.7 Hz, 3H), 1.34 (s, 9H). The spot right above the blue spot turned out to be the desired product (89 mg, 13%, ^{1}H NMR matched that of **6a**).

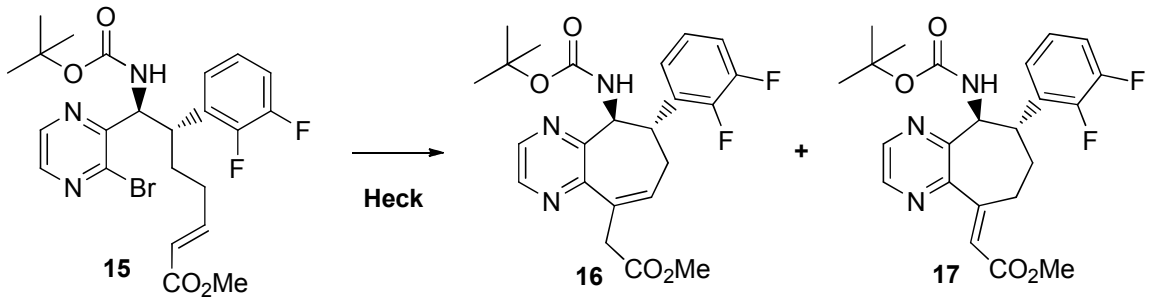
Synthesis and characterization of intermediates 15-19 and 4a:

Intermediate 15



(6S,7S,E)-Methyl 7-(3-bromopyrazin-2-yl)-7-(tert-butoxycarbonylamino)-6-(2,3-difluorophenyl)hept-2-enoate. In a 250 mL round-bottomed flask was dissolved tert-butyl (1S,2S)-1-(3-bromopyrazin-2-yl)-2-(2,3-difluorophenyl)hex-5-enylcarbamate (354.6 mg, 0.757 mmol) in methylene chloride (16 mL) to give a colorless solution. Methyl acrylate (0.21 mL, 2.3 mmol) and Grubbs-II catalyst (32.1 mg, 0.038 mmol) were added, and the mixture was stirred under reflux for 3 h under nitrogen. TLC showed complete conversion. Volatile components were removed in vacuo and the residue was purified by flash column chromatography up to 50% ethyl acetate/hexane to afford the desired product (335 mg, 84%) as a colorless oil: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.31 (s, 1 H) 8.28 (s, 1 H) 6.98 - 7.14 (m, 3 H) 6.80 - 6.94 (m, 1 H) 5.76 (d, J=16.56 Hz, 1 H) 5.59 - 5.71 (m, 1 H) 5.42 (d, J=9.54 Hz, 1 H) 3.71 (s, 3 H) 3.59 - 3.69 (m, 1 H) 2.09 - 2.29 (m, 2 H) 1.96 - 2.04 (m, 1 H) 1.83 - 1.95 (m, 1 H) 1.37 (s, 9 H).

Intermediates 16 and 17

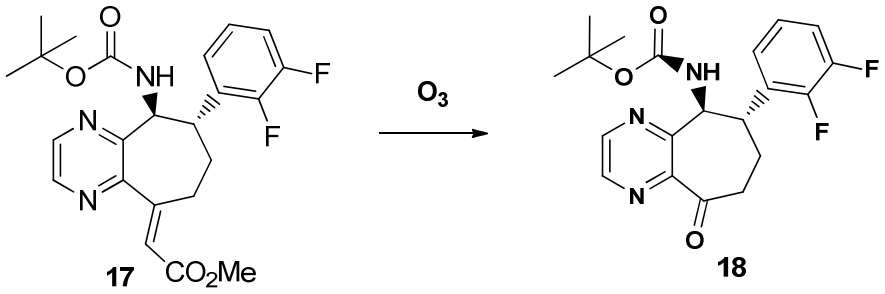


Methyl 2-((5S,6S,Z)-5-(tert-butoxycarbonylamino)-6-(2,3-difluorophenyl)-6,7-dihydro-5H-cyclohepta[b]pyrazin-9-yl)acetate (16) and (E)-methyl 2-((8S,9S)-9-(tert-butoxycarbonylamino)-8-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylidene)acetate (17). In a 25 mL microwave tube was dissolved (6S,7S,E)-methyl 7-(3-bromopyrazin-2-yl)-7-(tert-butoxycarbonylamino)-6-(2,3-difluorophenyl)hept-2-enoate (335 mg, 0.636 mmol), and bis(tri-t-butylphosphine)palladium (16.3 mg, 0.032 mmol) in dioxane (14 mL) (degassed) to give a yellow solution under nitrogen. Methyl dicyclohexylamine (0.15 mL, 0.70 mmol) was added, and the reaction was sealed under nitrogen. The mixture was stirred at rt for 1 min then at 160 °C under microwave irradiation for 2 h. TLC (1/1 ethyl acetate/hexane) showed little starting material and mainly the desired isomer. The mixture was partitioned between water and ethyl acetate. The layers were separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated. The residue was purified by flash column chromatography up to 70% ethyl acetate to afford the cyclized product **17** (153 mg, 54%) as a white solid, as well as the isomer (**16**, 69.5 mg, 24.5%) as a colorless oil. **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 - 8.52 (m, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.13 - 7.06 (m, 2H), 6.49 (s, 1H), 5.70 (d, *J* = 9.5 Hz, 1H), 5.40 - 5.30 (m, 1H), 3.79 (s, 3H), 3.51 - 3.37 (m, 2H), 3.09 (dd, *J* = 19.1, 6.7 Hz, 1H), 2.05 (s, 1H), 1.95 - 1.80 (m, 1H), 1.29 (s, 9H).

Isomer **16:** ^{1}H NMR (400 MHz, CDCl3) δ 8.51 (d, J = 2.4 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.13 - 7.03 (m, 2H), 6.51 (t, J = 6.8 Hz, 1H), 5.87 (d, J = 9.4 Hz, 1H), 5.42 (t, J = 9.7 Hz,

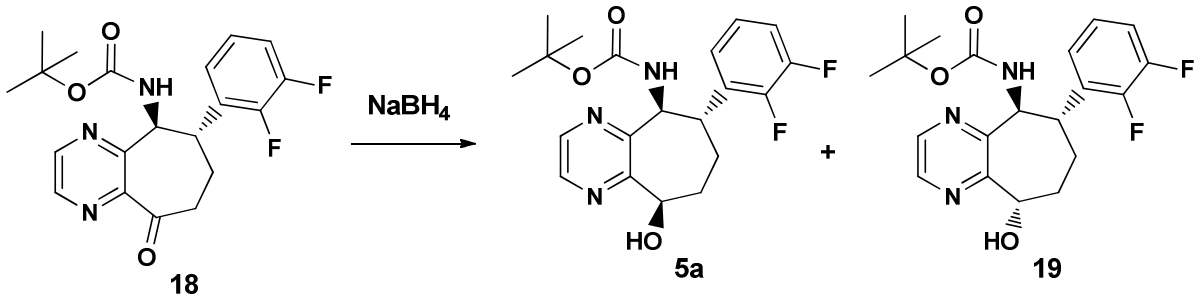
1H), 3.95 - 3.76 (m, 2H), 3.69 (s, 3H), 3.65 - 3.54 (m, 1H), 2.42 (t, J = 5.8 Hz, 2H), 1.28 (d, J = 5.3 Hz, 9H).

Intermediate 18



tert-Butyl (5S,6S)-6-(2,3-difluorophenyl)-9-oxo-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate. In a 250 mL round-bottomed flask was dissolved (E)-methyl 2-((8S,9S)-9-(tert-butoxycarbonylamino)-8-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylidene)acetate (153 mg, 0.343 mmol) in methylene chloride (50 mL) to give a colorless solution. After cooling to -78 °C, ozone was bubbled through the solution for 5 min. TLC (1/1 ethyl acetate/hexane) showed a new more polar peak. Nitrogen was then bubbled through the solution for 5 min, and a few drops of dimethylsulfide were added. Volatiles were removed in vacuo. The residue was directly purified by flash column chromatography up to 60% ethyl acetate/hexane to afford the desired product (88 mg, 66%) as a colorless oil: ^{1}H NMR (400 MHz, CDCl3) δ 8.71 (d, J = 2.3 Hz, 1H), 8.69 (d, J = 2.4 Hz, 1H), 7.28 (s, 1H), 7.13 - 7.06 (m, 2H), 5.76 (d, J = 9.0 Hz, 1H), 5.61 - 5.46 (m, J = 7.5 Hz, 1H), 3.58 - 3.44 (m, 1H), 3.18 - 3.03 (m, 1H), 2.88 (dd, J = 17.1, 3.3 Hz, 1H), 2.18 - 2.10 (m, J = 5.0 Hz, 2H), 1.26 (s, 9H); ^{19}F NMR (376 MHz, CDCl3) δ -137.90 (d, J = 17.8 Hz), -142.15 (d, J = 16.9 Hz); ^{13}C NMR (101 MHz, CDCl3) δ 201.00 (s), 154.80 (s), 152.87 (s), 150.69 (dd, J = 174.1, 13.3 Hz), 148.30 (dd, J = 160.0, 12.4 Hz), 147.27 (s), 145.56 - 145.00 (m), 143.97 (d, J = 6.7 Hz), 130.66 (d, J = 10.8 Hz), 123.74 (s), 122.57 (s), 115.67 (s), 79.73 (s), 52.93 (s), 39.58 (s), 36.88 (s), 28.61 - 26.78 (m), 26.11 (s).

Intermediates 5a and 19

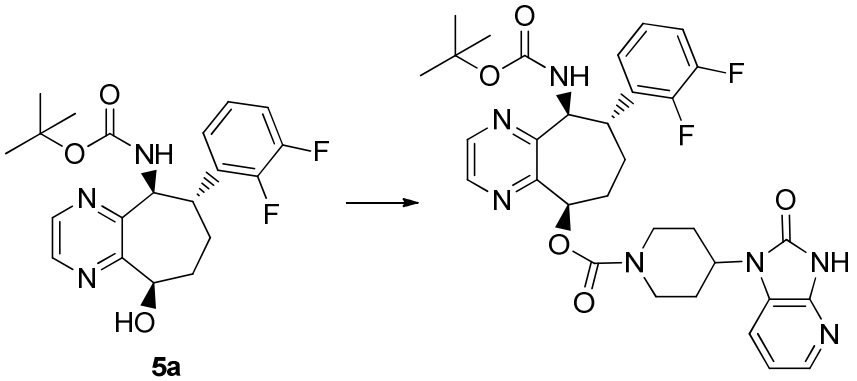


tert-Butyl (5S,6S,9R)-6-(2,3-difluorophenyl)-9-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (5a) and tert-butyl (5S,6S,9S)-6-(2,3-difluorophenyl)-9-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (19). In a 100 mL round-bottomed flask was dissolved tert-butyl (5S,6S)-6-(2,3-difluorophenyl)-9-oxo-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (88 mg, 0.23 mmol) in methanol (4 mL) to give a colorless solution. Sodium borohydride (25.6 mg, 0.678 mmol) was added, and the mixture was stirred at rt for 2 h, methanol was removed in vacuo and the residue was partitioned between water and ethyl acetate. The layer was separated. The organic layer was washed with brine, dried with sodium sulfate and concentrated. The residue was purified by flash column chromatography up to 70% ethyl acetate/hexane to afford the less polar product (**5a**, 41 mg, 46%) as a white solid and the more polar product (**19**, 35 mg, 40%) as a colorless oil. **5a:** ^{1}H NMR (400 MHz, CDCl3) δ 8.52 (d, J = 2.5 Hz, 1H), 8.47 (d, J = 2.6 Hz, 1H), 7.24 (dd, J = 7.7, 5.0 Hz, 1H), 7.11 - 6.98 (m, 2H), 6.19 (d, J = 9.1 Hz, 1H), 5.23 (d, J = 4.2 Hz, 1H), 5.16 (t, J = 9.6 Hz, 1H), 5.12 - 5.06 (m, 1H), 3.02 (t, J = 10.9 Hz, 1H), 2.55 (td, J = 14.7, 2.9 Hz, 1H), 2.48 - 2.38 (m, 1H), 2.24 - 2.14 (m, 1H), 1.54 (ddd, J = 16.0, 14.1, 3.0 Hz, 1H), 1.22 (s, 9H); ^{19}F NMR (376 MHz, CDCl3) δ -139.00 - -139.52 (m), -142.39 (s); ^{13}C NMR (101 MHz, CDCl3) δ 154.66 (s), 154.40 (s), 152.82 (s), 150.22 (dd, J = 163.2, 13.4 Hz), 147.77 (dd, J = 160.1, 13.2

Hz), 141.41 (s), 140.15 (s), 131.55 (s), 131.44 (s), 123.32 (d, J = 15.1 Hz), 114.84 (d, J = 17.1 Hz), 79.10 (s), 70.18 (s), 55.40 (s), 41.19 (s), 35.54 (s), 32.54 (s), 27.71 (d, J = 4.6 Hz).

19: ^{1}H NMR (400 MHz, CDCl3) δ 8.40 (d, J = 2.5 Hz, 1H), 8.32 (d, J = 2.5 Hz, 1H), 7.31 (s, 1H), 7.04 (dt, J = 7.4, 5.8 Hz, 2H), 5.97 (d, J = 9.3 Hz, 1H), 5.89 (t, J = 9.6 Hz, 1H), 5.17 (d, J = 6.8 Hz, 1H), 4.08 (s, 1H), 3.16 (t, J = 9.7 Hz, 1H), 2.91 (dd, J = 23.6, 11.5 Hz, 1H), 2.40 - 2.28 (m, 1H), 1.99 - 1.88 (m, 1H), 1.81 (t, J = 13.3 Hz, 1H), 1.24 (d, J = 5.9 Hz, 9H); ^{19}F NMR (376 MHz, CDCl3) δ -139.45 (d, J = 20.1 Hz), -143.03 (s); ^{13}C NMR (101 MHz, CDCl3) δ 155.16 (s), 154.85 (s), 154.66 (s), 150.17 (dd, J = 171.9, 13.1 Hz), 147.73 (dd, J = 170.2, 14.0 Hz), 141.71 (s), 140.81 (s), 132.49 (s), 132.38 (s), 123.41 (d, J = 35.2 Hz), 114.50 (s), 78.94 (s), 74.08 (s), 54.72 (s), 41.38 (s), 31.15 (s), 28.72 (s), 27.77 (d, J = 4.5 Hz).

Intermediate

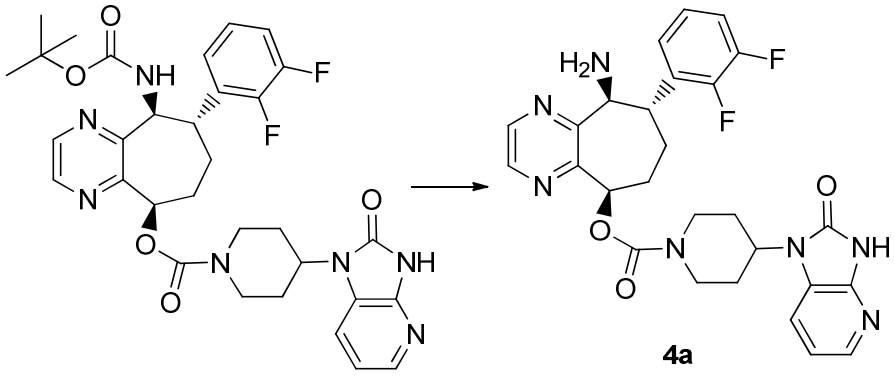


5a

(5R,8S,9S)-9-(tert-butoxycarbonylamino)-8-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate. In a 100 mL round-bottomed flask was dissolved tert-butyl (5S,6S,9R)-6-(2,3-difluorophenyl)-9-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (40 mg, 0.102 mmol) (azeotroped with dry benzene) and 1-(1-(1H-imidazole-1-carbonyl)piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (41.5 mg, 0.133 mmol) in dimethylformamide (1 mL) to give a

colorless suspension under nitrogen. After cooling to -15°C (ice/methanol bath), NaHMDS (0.378 mL, 0.378 mmol) was added dropwise. The cooling bath was removed and the resulting tan solution was stirred under nitrogen at rt for 2 h. LCMS showed complete conversion. The reaction was quenched with sodium bicarbonate solution, and diluted with ethyl acetate. The layers were separated. The organic layer was washed with brine, dried with sodium sulfate, and concentrated to give a slightly tan oil. Purification by flash column chromatography up to 10% methanol (with 2M ammonia)/methylene chloride afforded the desired product (39.5mg, 61%) as a white solid: ^{1}H NMR (400 MHz, CDCl3) δ 11.17 (s, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 8.12 (d, J = 5.0 Hz, 1H), 7.43 (d, J = 6.0 Hz, 1H), 7.33 - 7.26 (m, 1H), 7.05 (dt, J = 7.8, 5.9 Hz, 3H), 6.34 (d, J = 8.8 Hz, 1H), 6.15 (d, J = 11.0 Hz, 1H), 5.36 - 5.25 (m, 1H), 4.63 (t, J = 12.4 Hz, 2H), 4.46 (s, 1H), 3.07 (t, J = 9.7 Hz, 3H), 2.62 (dd, J = 23.9, 11.8 Hz, 1H), 2.49 - 2.26 (m, 3H), 2.21 (d, J = 12.0 Hz, 1H), 2.03 - 1.78 (m, 3H), 1.23 (s, 9H).

Product 4a



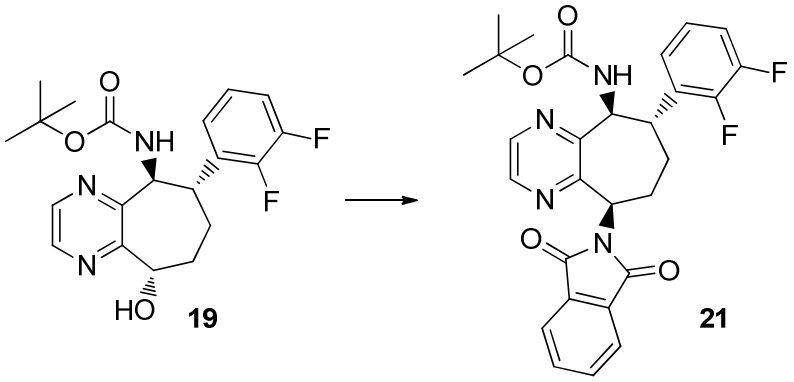
4a

(5R,8S,9S)-9-amino-8-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate. In a 50 mL round-bottomed flask was dissolved (5R,8S,9S)-9-(tert-butoxycarbonylamino)-8-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (38.1 mg, 0.060 mmol) in methylene chloride (1 mL) to give a colorless solution. trifluoroacetic acid (0.5 mL) was added, and the mixture was stirred at rt for 1 h. LCMS

showed complete conversion. Volatiles were removed in vacuo, and the residue was partitioned between ethyl acetate/0.5N sodium hydroxide/saturated sodium bicarbonate solution. The layers were separated. The organic layer was dried and concentrated to give a tan oil. flash column chromatography up to 10% methanol (2M ammonia) in methylene chloride afforded the desired product (22 mg, 69%) as a white solid: MS(ESI)[M+H$^+$] = 536.2; ^{1}H NMR (400 MHz, CDCl3) δ 8.50 (s, 2H), 8.11 (d, J = 4.9 Hz, 1H), 7.42 (s, J = 16.5 Hz, 1H), 7.17 - 6.95 (m, 4H), 6.24 - 5.97 (m, 2H), 4.69 - 4.34 (m, 4H), 3.31 - 2.81 (m, 3H), 2.37 (dd, J = 23.5, 13.6 Hz, 4H), 2.17 - 1.67 (m, 6H); ^{19}F NMR (376 MHz, CDCl3) δ -137.10 - -137.50 (m), -142.45 (d, J = 20.6 Hz).

Synthesis and characterization of intermediates 21-24 and 25:

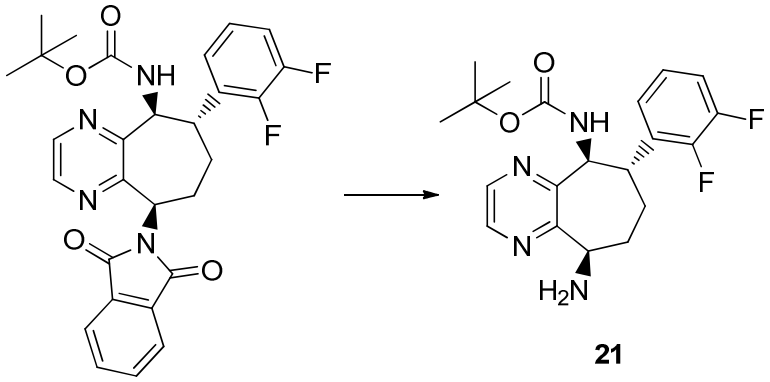
Intermediate 21



tert-butyl (5S,6S,9R)-6-(2,3-difluorophenyl)-9-(1,3-dioxoisoindolin-2-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate. In an oven-dried 100 mL round-bottomed flask was dissolved tert-butyl (5S,6S,9S)-6-(2,3-difluorophenyl)-9-hydroxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (35.3 mg, 0.090 mmol) (1**9**, azeotroped with dry benzene) in methylene chloride (3 mL) to give a colorless solution. isoindoline-1,3-dione (26.5 mg, 0.180 mmol) and triphenylphosphine (47.3 mg, 0.180 mmol) were added, followed by diisopropylazodicarboxylate (0.026 mL, 0.135 mmol). The mixture was stirred at rt under nitrogen. After 22 h, the mixture was

directly subject to flash column chromatography up to 50% ethyl acetate/hexane afforded one major peak. Concentration afforded the desired product as a colorless oil. ^{1}H NMR indicated that some elimination product might also be present. This was carried onto next reaction without further purification and characterization.

Intermediate 21

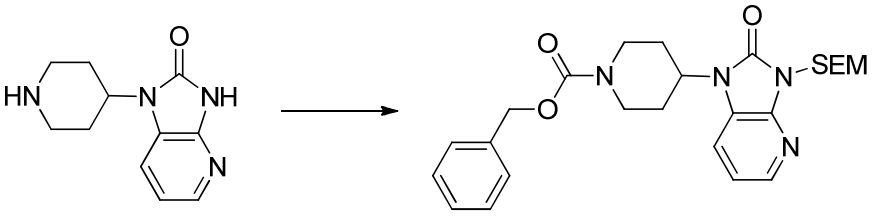


21

tert-butyl (5S,6S,9R)-9-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate. In a 100 mL round-bottomed flask was dissolved tert-butyl (5S,6S,9R)-6-(2,3-difluorophenyl)-9-(1,3-dioxoisoindolin-2-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (46.8 mg, 0.090 mmol) in methanol (1 mL) to give a white suspension. Hydrazine hydrate (0.1 mL, 3.2 mmol) was added, and the mixture was stirred in a preheated oil bath at 70 °C under nitrogen for 2 h. LCMS indicated the desired product. Methanol was removed in vacuo and the residue was partitioned between 0.5N sodium hydroxide and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. Flash column chromatography up to 10% methanol (with 2M ammonia) in methylene chloride afforded the desired product as a colorless oil (26.9 mg, 77% for two steps): ^{1}H NMR (400 MHz, CDCl3) δ 8.48 (d, J = 2.3 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 6.4 Hz, 1H), 7.12 - 6.98 (m, 2H), 6.24 (d, J = 8.6 Hz, 1H), 5.25 (t, J = 9.5 Hz, 1H),

4.50 (d, J = 10.2 Hz, 1H), 3.03 (t, J = 10.7 Hz, 1H), 2.60 - 2.43 (m, 1H), 2.39 - 2.07 (m, 4H), 1.61 - 1.40 (m, 1H), 1.23 (s, 9H); ^{19}F NMR (376 MHz, CDCl3) δ -138.95 - -139.53, -142.46.

Synthesis of Intermediate 23:

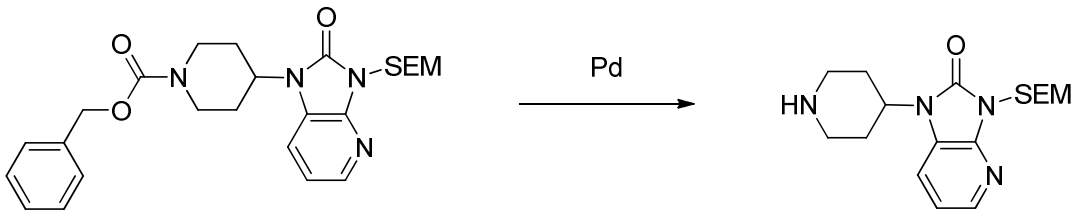


Benzyl 4-(2-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate. In an oven-dried 500 mL round-bottomed flask was 1-(piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one dihydrochloride (2.91 g, 9.99 mmol) in CH_2Cl_2 (50 mL) to give a tan suspension. Et_3N (5.57 mL, 40.0 mmol) was added under nitrogen. Benzyl chloroformate (1.421 mL, 9.99 mmol) was added dropwise via syringe. The mixture was stirred at rt overnight. LCMS showed good conversion. The mixture was diluted with EtOAc and water. The layers were separated. The organic layer was washed with brine, dried and concentrated. The residue was purified by FCC up to 8% MeOH/CH_2Cl_2 to afford the desired product as a colorless oil (2.17 g, 62%). LCMS showed >95% purity (M + H = 353.3). It was carried on to the next step without further characterizations.

In a 500 mL round-bottomed flask was benzyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (1.62 g, 4.60 mmol) in THF (40 mL) to give a colorless solution. NaH (0.552 g, 22.99 mmol) (excess) was added. After stirring for 5 min under nitrogen, SEM-Cl (0.897 mL, 5.06 mmol) was added. The mixture was stirred at rt overnight for 16 h. LCMS showed good converson. The reaction mixture was diluted with EtOAc and slowly quenched with water (gas evolves!). The layers were separated. The organic layer was washed with brine, dried and concentrated to a slightly

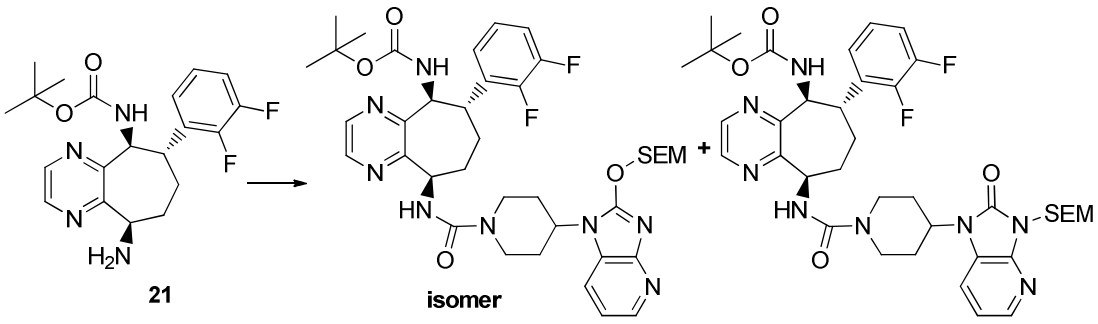
green oil. TLC (10% MeOH/CH_2Cl_2) showed a major blue spot (Rf ~ 0.25) (slightly less polar than SM). Purification by FCC up to 10% MeOH/CH_2Cl_2 afforded the desired product as a colorless oil (1.92 g, 87%) (M + H = 483.3). It was carried on to the next reaction without further characterization.

Intermediate 23



tert-butyl (5S,6S,9R)-9-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate. In a 500 mL round-bottomed flask was benzyl 4-(2-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (1.85 g, 3.83 mmol) in MeOH (30 mL) to give a colorless solution. Pd/C (0.408 g, 0.383 mmol) was added, and the mixture was stirred under hydrogen balloon overnight for 17 h. LCMS indicated complete conversion to the desired product (M + H = 349.3). It was filtered, washed, and concentrated under high vac to a colorless foam (1.31 g, 100%). It was used without further purification and characterizations.

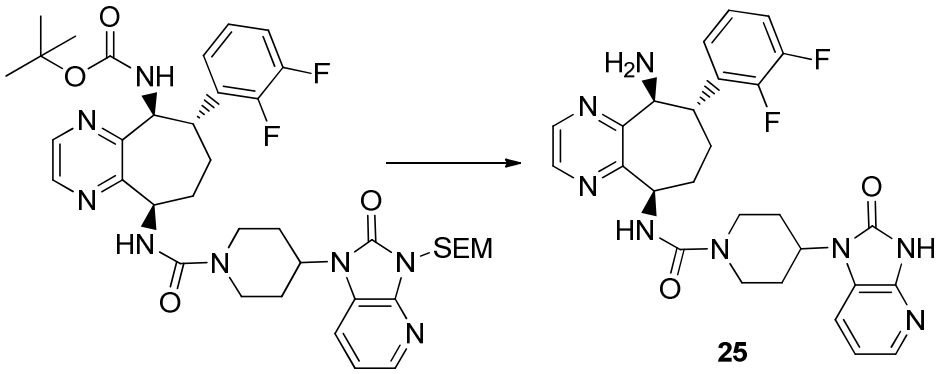
Intermediates



tert-butyl (5S,6S,9R)-6-(2,3-difluorophenyl)-9-(4-(2-((2-(trimethylsilyl)ethoxy)methoxy)-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamido)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (the isomer) and tert-butyl (5S,6S,9R)-6-(2,3-difluorophenyl)-9-(4-(2-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamido)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate. In an oven-dried 100mL round-bottomed flask was dissolved 1-(piperidin-4-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (36.0 mg, 0.103 mmol) in methylene chloride (2 mL) to give a colorless solution. Triethylamine (0.029 mL, 0.207 mmol) was added under nitrogen and the mixture was cooled to -20°C. Trichloromethyl chloroformate (8 µl, 0.07 mmol) was added dropwise. The mixture was gradually warmed up with stirring to 10 °C for 1 h, during which time the solution became slightly yellow. The mixture was concentrated to dryness under house vacuum and further dried under high vacuum. Tert-butyl (5S,6S,9R)-9-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (26.9 mg, 0.069 mmol) and triethylamine (0.029 mL, 0.207 mmol) dissolved in 1 mL tetrahydrofuran was added via canuula at rt. The resulting faint yellow suspension was stirred under nitrogen for 3 days. The residue was partitioned between ethyl acetate/0.5 N sodium hydroxide. The organic layer was separated. TLC (10% methanol/methylene chloride) showed two spots: a less polar dark spot and a faint, more polar blue spot. The organic layer was separated and washed with brine, dried with sodium sulfate, and concentrated. The residue was purified by flash column chromatography up to 10% methanol/methylene chloride afforded two products **the expected** (32 mg, 61%) and **the isomer** (7.0 mg, 13%). **The expected**: MS(ESI)[$M+H^+$] = 765.5; ^{1}H NMR (400 MHz, CDCl3) δ 8.50 (d, J = 2.4 Hz, 1H), 8.43 (d, J = 2.6 Hz, 1H), 8.07 (dd, J = 5.2, 1.2 Hz, 1H), 7.34 (dd, J = 7.9, 1.2 Hz, 1H), 7.28 (s, J = 5.2 Hz, 1H), 7.11 - 6.94 (m, 4H), 6.14 (d, J = 9.2 Hz, 1H), 5.43 (s, J = 3.6 Hz, 2H), 5.40 - 5.32 (m, 2H), 4.63 (tt, J = 12.4, 3.9 Hz, 1H), 4.33 (t, J = 13.9 Hz, 2H), 3.77 - 3.69 (m, 2H), 3.13 - 2.94 (m, 3H), 2.69 (dd, J = 25.5, 13.2 Hz, 1H),

2.57 (d, J = 13.5 Hz, 1H), 2.30 (qd, J = 12.4, 4.1 Hz, 2H), 2.14 (ddd, J = 8.4, 5.0, 2.5 Hz, 1H), 1.95 (d, J = 12.2 Hz, 1H), 1.88 (s, 1H), 1.43 (dd, J = 23.7, 11.0 Hz, 1H), 1.23 (s, 9H), 1.03 - 0.95 (m, 2H), -0.02 (s, 9H); ^{19}F NMR (376 MHz, CDCl3) δ -139.05 - -139.63 (m), -142.98 (s). **The isomer**: MS(ESI)[M+H$^+$] = 765.5; ^{1}H NMR (400 MHz, CDCl3) δ 8.51 (d, J = 2.3 Hz, 1H), 8.45 (d, J = 2.6 Hz, 1H), 7.40 (dd, J = 6.9, 0.7 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.12 - 6.99 (m, 4H), 6.67 (t, J = 7.1 Hz, 1H), 6.13 (d, J = 9.1 Hz, 1H), 5.74 (s, 2H), 5.37 (t, J = 9.3 Hz, 2H), 4.76 - 4.55 (m, 1H), 4.42 - 4.23 (m, 2H), 3.73 - 3.65 (m, 2H), 3.14 - 2.94 (m, 3H), 2.79 - 2.63 (m, 1H), 2.58 (d, J = 13.6 Hz, 1H), 2.36 - 2.09 (m, 2H), 1.97 (s, 2H), 1.75 (s, 1H), 1.52 - 1.36 (m, 1H), 1.24 (s, 9H), 1.01 - 0.93 (m, 2H), -0.00 (s, 9H); ^{19}F NMR (376 MHz, CDCl3) δ -139.38 (d, J = 17.6 Hz), -142.93 (s).

Product 25



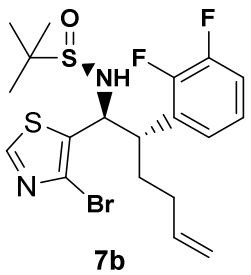
25

N-((5R,8S,9S)-9-amino-8-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-yl)-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide. In a 50 mL round-bottomed flask was dissolved tert-butyl (5S,6S,9R)-6-(2,3-difluorophenyl)-9-(4-(2-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamido)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazin-5-ylcarbamate (31 mg, 0.041 mmol) in methylene chloride (1 mL) to give a colorless solution. trifluoroacetic acid (0.5 mL) was added, and the mixture was stirred at rt for 1.5 h: LCMS showed complete conversion. The solvent was removed in vacuo, and the residue was partitioned between ethyl acetate/0.5N sodium hydroxide/saturated sodium bicarbonate solution.

The layers were separated. The organic layer was dried and concentrated to give a tan oil. flash column chromatography up to 10% methanol (2M ammonia) in methylene chloride afforded the desired product (12 mg, 55%) as a white solid: MS(ESI)[M+H$^+$] = 535.3; ^{1}H NMR (400 MHz, CDCl3) δ 10.98 - 9.87 (m, 1H), 8.56 (d, J = 2.5 Hz, 1H), 8.42 (d, J = 2.5 Hz, 1H), 8.07 (dd, J = 5.3, 1.2 Hz, 1H), 7.35 (dd, J = 7.9, 1.2 Hz, 1H), 7.21 - 7.05 (m, 4H), 6.98 (dd, J = 7.9, 5.3 Hz, 1H), 5.29 (dd, J = 10.4, 5.1 Hz, 1H), 4.71 - 4.55 (m, 2H), 4.35 (d, J = 13.6 Hz, 2H), 3.05 (t, J = 13.0 Hz, 2H), 2.94 (t, J = 9.3 Hz, 1H), 2.53 (t, J = 11.7 Hz, 2H), 2.41 - 2.23 (m, 2H), 2.16 - 1.69 (m, 6H); ^{19}F NMR (376 MHz, CDCl3) δ -137.32 (ddd, J = 21.4, 9.6, 4.5 Hz), -142.66 (d, J = 19.5 Hz).

Synthesis and characterization of intermediates 7b, 26-30, 5b and 4b:

Intermediate 7b

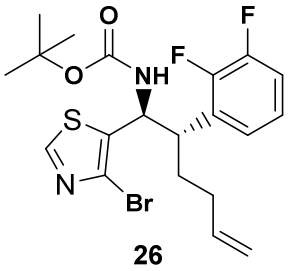


7b

(R)-N-((1S,2S)-1-(4-bromothiazol-5-yl)-2-(2,3-difluorophenyl)hex-5-enyl)-2-methylpropane-2-sulfinamide. To a 250 mL round bottom flask was added tetrahydrofuran (10 mL) and diisopropylamine (1.04 mL, 7.33 mmol) under nitrogen. The flask was cooled down to -20 °C before addition of n-BuLi (2.93 mL, 7.33 mmol). The reaction was stirred at this temperature for 5 min before being cooled to -78 °C. 2, 4-dibromothiazole (1.782 g, 7.33 mmol) was added at once to the reaction mixture. After stirring at -78 °C for 10 min, (R,E)-N-((S)-2-(2,3-difluorophenyl)hex-5-enylidene)-2-methylpropane-2-sulfinamide (1.1494 g, 3.67 mmol) in 5 mL tetrahydrofuran was added to the reaction mixture via cannula. The reaction was allowed to continue to stir while it was gradually warmed up to -60 °C (4 h). The reaction was cooled down to -78 °C and n-BuLi (2.93 mL, 7.33 mmol) was added at -

78 °C. The reaction was stirred for 20 min. Methanol (0.44 mL, 11.0 mmol) l was added to quench the reaction. The reaction was stirred at rt for 0.5 h. The solvent was removed under vacuum and the crude mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, dried (sodium sulfate), filtered and concentrated. Flash chromatography using ethyl acetate in hexane from 0 to 50% to 85% gave the desired product (1.08 g, 62 %) as a brown oil, which was solidified upon standing at room temperature overnight: MS(ESI)[M+H$^+$] = 479.12. ^{1}H NMR showed a mixture of two diastereomers with a ratio of 3/1 (partially epimerized **9** from previous reactions). It was carried on.

Intermediate 26



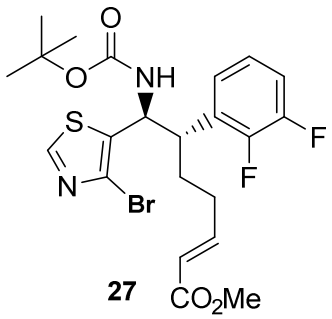
26

***tert*-Butyl (1S,2S)-1-(4-bromothiazol-5-yl)-2-(2,3-difluorophenyl)hex-5-enylcarbamate.** 2M HCl in diethyl ether (4.82 mL, 9.63 mmol) was added to a methanol (10 mL) solution of (R)-N-((1S,2S)-1-(4-bromothiazol-5-yl)-2-(2,3-difluorophenyl)hex-5-enyl)-2-methylpropane-2-sulfinamide (1.15 g, 2.409 mmol) at rt. The reaction was stirred for 2.5 h before removal of the solvent. The crude mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The ethyl acetate layer was separated, dried (sodium sulfate), filtered and concentrated. Flash chromatography using ethyl acetate in hexane from 0 to 45% to 65% gave the desired free amine intermediate: MS(ESI)[M+H$^+$] = 375.08. ^{1}H NMR showed inseparable diastereomers with a ratio of 3:1.

(1S,2S)-1-(4-bromothiazol-5-yl)-2-(2,3-difluorophenyl)hex-5-en-1-amine (600 mg, 1.607 mmol) was dissolved in methylene chloride (10 mL). Boc_2O (3.5 g) was added to the reaction mixture at rt. The reaction was put in the refrigerator overnight. The solvent was removed and the crude mixture was

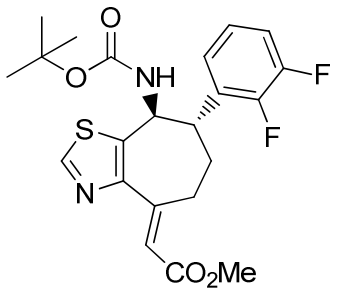
purified by silica gel flash chromatography, eluting with ethyl acetate in hexane from 0 to 45% to afford the desired product (722 mg, 95%): MS(ESI)[M+H$^+$] = 475.10. ^{1}H NMR showed inseparable diastereomers with a ratio of 3/1. It was carried on.

Intermediate 27



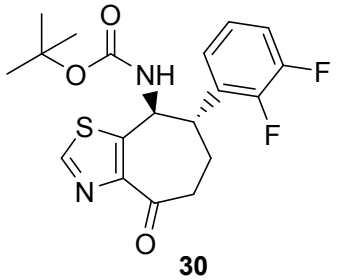
(6S,7S,E)-methyl 7-(4-bromothiazol-5-yl)-7-(tert-butoxycarbonylamino)-6-(2,3-difluorophenyl)hept-2-enoate. A mixture of methyl acrylate (0.16 mL, 1.80 mmol), GrubbsII catalyst (0.025 g, 0.030 mmol) and tert-butyl (1S,2S)-1-(4-bromothiazol-5-yl)-2-(2,3-difluorophenyl)hex-5-enylcarbamate (0.2842 g, 0.600 mmol) in methylene chloride (20 mL) was heat to reflux for 3 h under nitrogen. The solvent was removed under vacuum and the crude product was puridied by silica gel chromatography, eluting with ethyl acetate in hexane from 0 to 45% to give the desired product (273.2 mg, 86 %): MS(ESI)[M+H$^+$] = 533.13. ^{1}H NMR showed inseparable diastereomers with a ratio of 3.5:1. It was carried on.

Intermediate 29



(E)-methyl 2-((7S,8S)-8-(tert-butoxycarbonylamino)-7-(2,3-difluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-ylidene)acetate. A mixture of (6S,7S,E)-methyl 7-(4-bromothiazol-5-yl)-7-(tert-butoxycarbonylamino)-6-(2,3-difluorophenyl)hept-2-enoate (0.217 g, 0.409 mmol), bis(tri-t-butylphosphine)palladium (0) (0.021 g, 0.041 mmol) and methyl dicyclohexylamine (0.096 mL, 0.450 mmol) in dioxane (10 mL) (degassed with nitrogen) was heated at 140 °C under microwave radiation for 1 h under nitrogen. The solvent was removed under vaccum and the product was purified by flash chromatography eluting with ethyl acetate in hexane from 0 to 45% to afford the desired product (53.4 mg, 29%), (M + H = 451.20), as well as the isomerized product (double bond moved into the ring) (108.8 mg, 59%) as the major component.

Intermediate 30



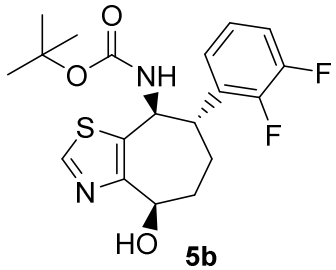
30

tert-butyl (7S,8S)-7-(2,3-difluorophenyl)-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-8-ylcarbamate. A solution of (E)-methyl 2-((7S,8S)-8-(tert-butoxycarbonylamino)-7-(2,3-difluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-ylidene)acetate (68 mg, 0.15 mmol) in methylene chloride (5 mL) was treated with ozone under -78 °C for 2 min. The reaction mixture was

purged with nitrogen and quenched with dimethyl sulfide. The solvent was removed under vacuum and the product was purified by flash chromatography, eluting with ethyl acetate in hexane from 0 to 100% to afford the desired product (34.5 mg, 58 %): ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.73 (s, 1H), 7.16 - 7.09 (m, 3H), 5.62 - 5.53 (m, 1H), 5.13 - 5.05 (m, 1H), 3.64 - 3.53 (m, 1H), 3.13 - 3.02 (m, 1H), 3.01 - 2.92 (m, 1H), 2.38 - 2.24 (m, 2H), 1.33 (s, 9H); ^{19}F NMR (400MHz, CHLOROFORM-d) δ -137.33, -141.96.

The minor diastereomer (12.1 mg, 20 %) was separated at this step: ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.77 (s, 1H), 7.19 - 7.09 (m, 1H), 7.05 - 6.97 (m, 1H), 6.54 (br. s., 1H), 5.84 - 5.76 (m, 1H), 4.79 - 4.70 (m, 1H), 4.14 (d, *J*=7.0 Hz, 1H), 3.08 - 2.89 (m, 2H), 2.53 - 2.43 (m, 1H), 2.04 - 1.92 (m, 1H), 1.44 (s, 9H); ^{19}F NMR (400MHz, CHLOROFORM-d) δ -136.00, -141.64.

Intermediate 5b

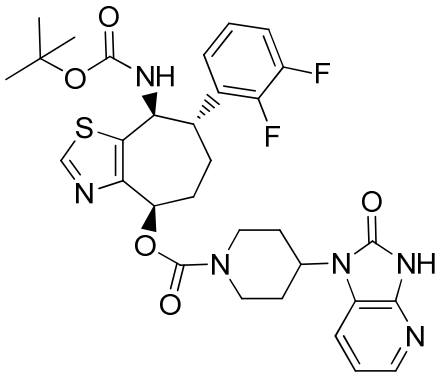


5b

tert-butyl (4R,7S,8S)-7-(2,3-difluorophenyl)-4-hydroxy-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-8-ylcarbamate. Sodium borohydride (9.93 mg, 0.262 mmol) was added to a methanol (5 mL) solution of tert-butyl (7S,8S)-7-(2,3-difluorophenyl)-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-8-ylcarbamate (34.5 mg, 0.087 mmol) at rt. The reaction was stirred for 0.5 h. The solvent was removed under vacuum and the product was purified by prep TLC developed with ethyl acetate in hexane (50%). There were two bands collected. The less polar was the desired product (20.1 mg. 58%): LCMS: M+H=397.24; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.57 (1 H, s), 7.03 -

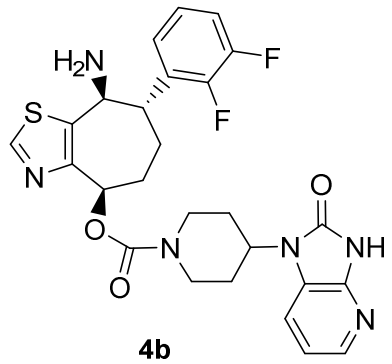
7.09 (3 H, m), 5.16 - 5.23 (1 H, m), 4.94 - 5.00 (1 H, m), 4.85 - 4.91 (1 H, m), 4.26 (1 H, s), 3.28 - 3.36 (1 H, m), 2.19 - 2.36 (3 H, m), 1.64 - 1.69 (1 H, m), 1.26 - 1.29 (8 H, m).

Intermediate



(4R,7S,8S)-8-(tert-butoxycarbonylamino)-7-(2,3-difluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate. NaHMDS (0.228 mL, 0.228 mmol) was added to a dimethylformamide (1 mL) solution of tert-butyl (4R,7S,8S)-7-(2,3-difluorophenyl)-4-hydroxy-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-8-ylcarbamate (20.1 mg, 0.051 mmol) and 1-(1-(1H-imidazole-1-carbonyl)piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (**20**, 23.7 mg, 0.076 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h and rt for 2 h before quenching with water. The reaction was diluted with ethyl acetate and the organic layer was separated, washed with water and brine and then dried (sodium sulfate), filtered and concentrated. Flash chromatography, eluting with methanol in methylene chloride from 0 to 10% gave the desired product (18.2 mg, 56 %): LCMS (M+H=641.38); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.64 (1 H, s), 8.07 (1 H, d, *J*=5.0 Hz), 7.31 - 7.56 (1 H, m), 6.93 - 7.12 (4 H, m), 6.22 (1 H, d, *J*=7.5 Hz), 5.24 - 5.34 (1 H, m), 4.96 - 5.07 (1 H, m), 4.32 - 4.71 (3 H, m), 3.61 - 3.77 (1 H, m), 2.88 - 3.15 (2 H, m), 2.29 (4 H, d, *J*=10.5 Hz), 1.83 - 1.97 (4 H, m), 1.30 (9 H, s).

Product 4b

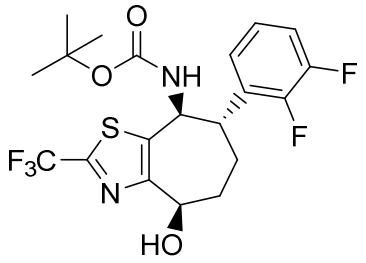


4b

(4R, 7S, 8S)-8-amino-7-(2,3-difluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate. A mixture of trifluoroacetic acid (0.986 mL, 12.80 mmol) and (4R,7S,8S)-8-(tert-butoxycarbonylamino)-7-(2,3-difluorophenyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (16.4 mg, 0.026 mmol) in methylene chloride (10 mL) was stirred at rt from for 2.5 h. The solvent was removed under vacuum and the crude product was taken up in ethyl acetate and washed with saturated sodium bicarbonate. The ethyl acetate layer was separated, dried (sodium sulfate), filtered and concentrated. Flash chromatography, eluting with methanol in methylene chloride from 0 to 10% gave the desired product (13 mg, 89%) as a white solid: LCMS (M + H = 541.40); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.98 (1 H, br. s), 8.64 (1 H, s), 8.08 (1 H, d, *J*=4.8 Hz), 7.31 - 7.64 (1 H, m), 6.94 - 7.19 (4 H, m), 6.11 - 6.21 (1 H, m), 4.42 (4 H, m), 3.23 - 3.43 (1 H, m), 2.85 - 3.16 (2 H, m), 2.24 (6 H, m), 1.83 - 1.98 (2 H, m), 1.56 (2 H, br. m).

Synthesis and characterization of intermediate 31 and 4c:

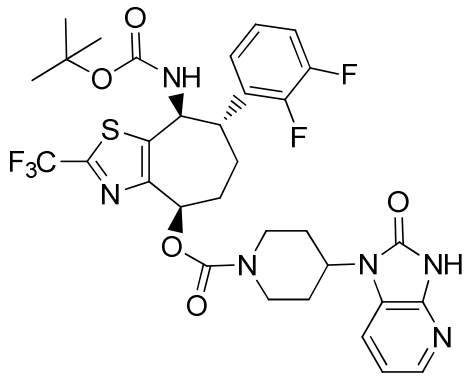
Intermediate 31



31

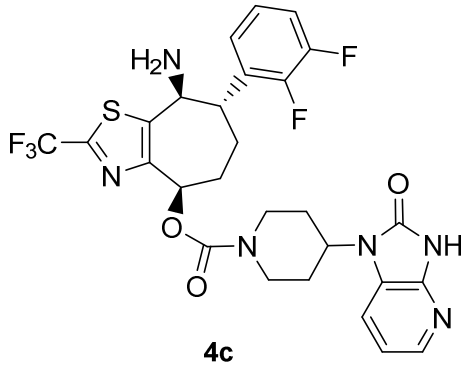
tert-Butyl (4R,7S,8S)-7-(2,3-difluorophenyl)-4-hydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-8-ylcarbamate. Trifluoromethyliodide gas was bubbled through 4 mL of dimethylsulfoxide for 3 min at rt. In this way, approximately 0.9 g of trifluoromethyliodide was dissolved in this solution. Dicyclopentadienyliron(II) (21.9 mg, 0.114 mmol) and tert-butyl (4R,7S,8S)-7-(2,3-difluorophenyl)-4-hydroxy-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-8-ylcarbamate (45.3 mg, 0.114 mmol) was dissolved in 2 mL of the trifluoromethyliodide- dimethylsulfoxide solution described above. Hydrogen peroxide (0.012 mL, 0.114 mmol) was added to the reaction mixture. The reaction was stirred at rt for 1 h. Aqueous sodium carbonate was added and the reaction was extracted with ethyl acetate. The ethyl acetate layer was washed with water (2 x) and dried (sodium sulfate). The product was purified by flash chromatography, eluting with ethyl acetate in hexane from 0 to 30% to 45% to give the desired product (12.5 mg, 24%): LCMS (M + H = 465.08); ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.15 – 7.00 (m, 3H), 5.23 (t, *J* = 10.2 Hz, 1H), 4.91 (t, *J* = 11.2 Hz, 2H), 3.86 (d, *J* = 2.2 Hz, 1H), 3.41 – 3.28 (m, 1H), 3.06 – 2.83 (m, 2H), 2.38 – 2.27 (m, 2H), 1.90 – 1.78 (m, 1H), 1.28 (s, 9H).

Intermediate



(4R,7S,8S)-8-(tert-butoxycarbonylamino)-7-(2,3-difluorophenyl)-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate. NaHMDS (0.1 mL, 0.100 mmol) was added to a dimethylformamide (1 mL) solution of tert-butyl (4R,7S,8S)-7-(2,3-difluorophenyl)-4-hydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-8-ylcarbamate (12.5 mg, 0.027 mmol) and 1-(1-(1H-imidazole-1-carbonyl)piperidin-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one (12.61 mg, 0.040 mmol) at -20 °C. The reaction was stirred at -20 °C for 1 h and rt for 2 h before being quenched with water. The reaction was diluted with ethyl acetate and the organic layer was separated, washed with water, brine, water, and then dried (sodium sulfate), filtered and concentrated in vacuo. Flash chromatography, eluting with methanol in methylene chloride from 0 to 10% gave the desired product (3.5 mg, 18%): LCMS (M + Na = 731.06).

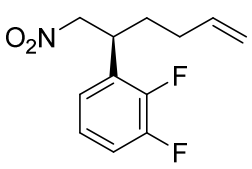
Product 4c

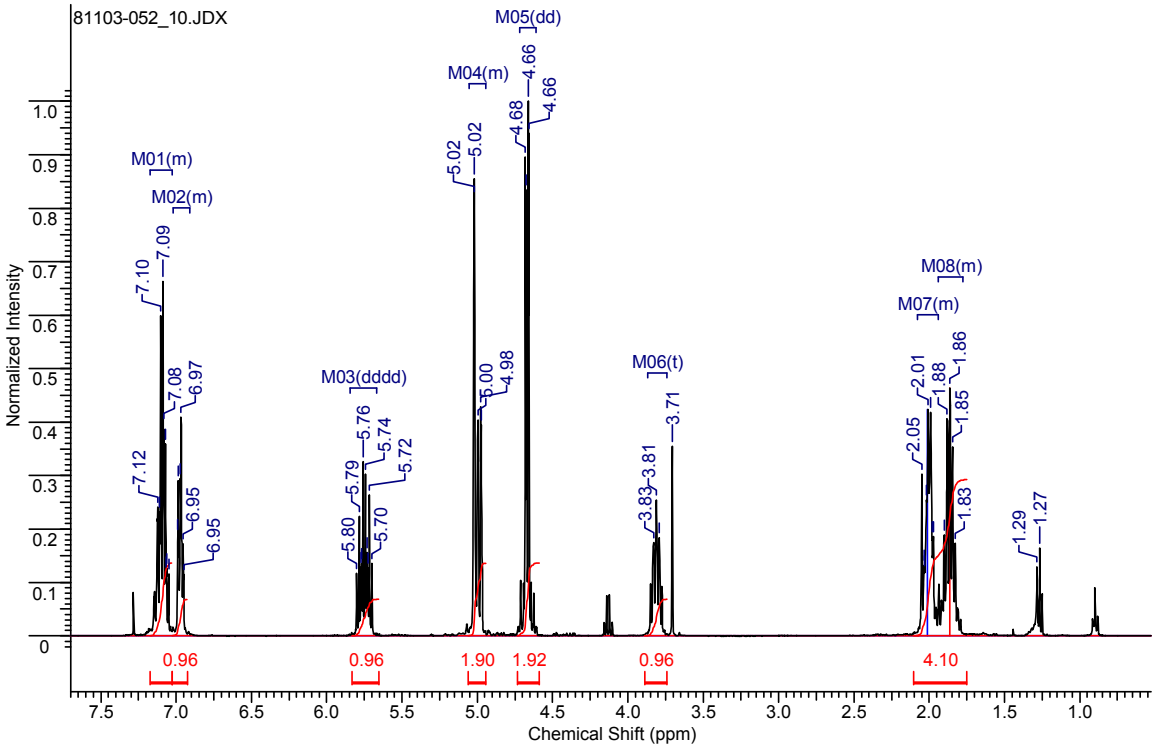


4c

(4R,7S,8S)-8-amino-7-(2,3-difluorophenyl)-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate. (4R,7S,8S)-8-(tert-butoxycarbonylamino)-7-(2,3-difluorophenyl)-2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-cyclohepta[d]thiazol-4-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (3.5 mg, 4.94 μmol) in methylene chloride (2 mL) was treated with trifluoroacetic acid (0.5 mL, 6.49 mmol) at rt. The reaction was stirred for 2 h. The solvent was removed under vacuum and the crude product was partitioned between sodium bicarbonate (sat.) and ethyl acetate. The organic layer was separated, dried (sodium sulfate), filtered and concentrated in vacuo. Flash chromatography, eluting with methanol in methylene chloride from 0 to 10% gave the desired product (2.7 mg, 90%) as a white solid: LCMS (M + Na = 631.04).

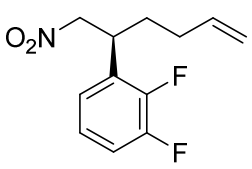
^{1}H NMR of 12:

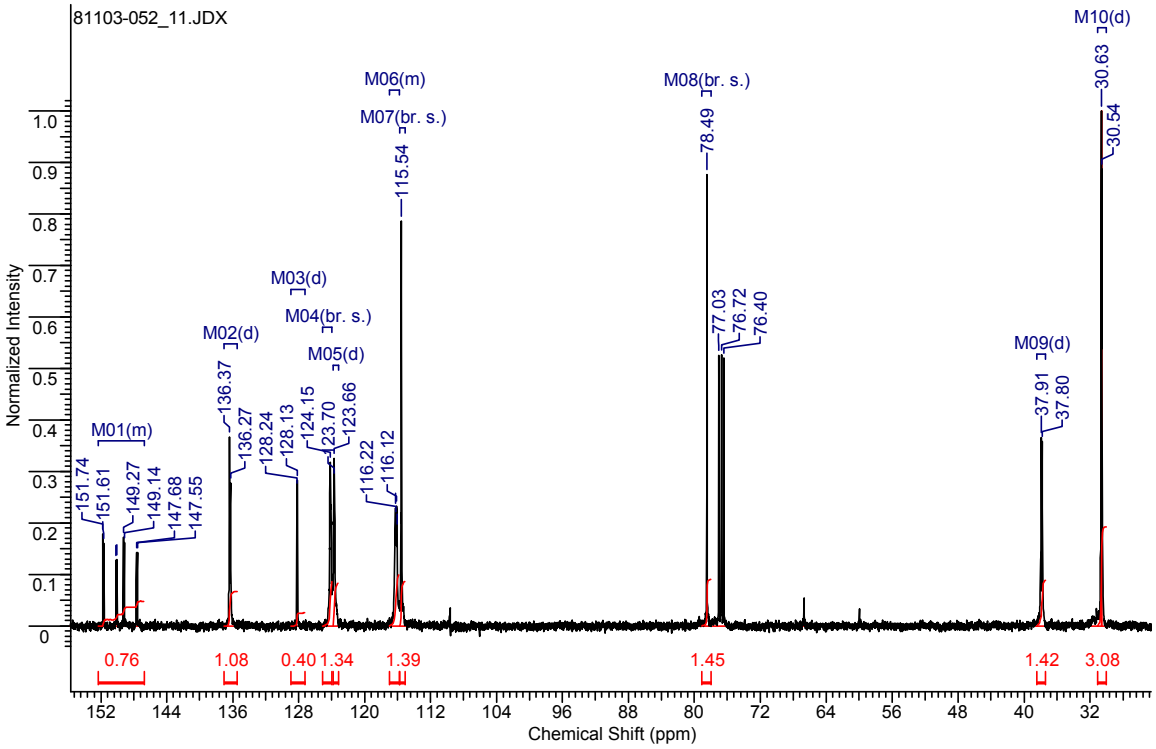




^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.03 - 7.17 (m, 2 H) 6.91 - 7.02 (m, 1 H) 5.70 – 5.80 (m, 1 H) 4.94 - 5.05 (m, 2 H) 4.66 – 4.68 (m, 2 H) 3.78 – 3. 85 (m, 1 H) 1.94 - 2.08 (m, 2 H) 1.77 - 1.94 (m, 2 H).

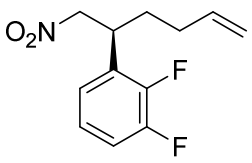
^{13}C NMR of 12:

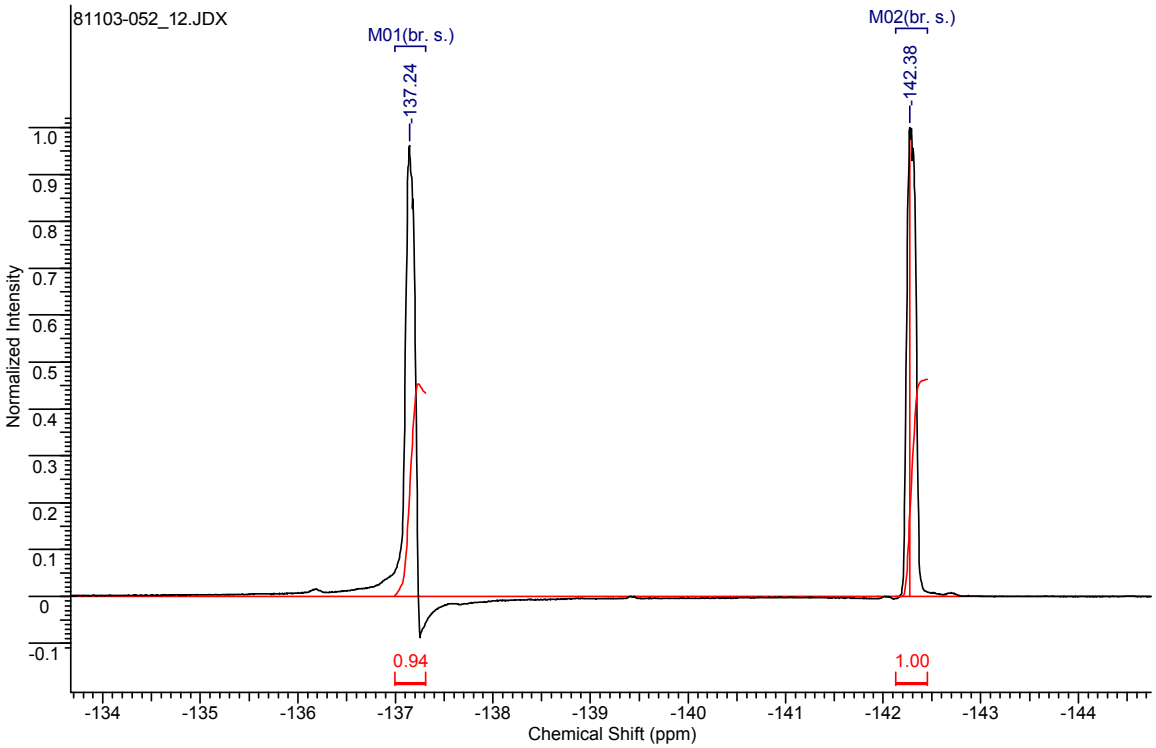




^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 151.74 - 149.14 (dd, J = 13.13 and 249.47 Hz), 150.15 - 147.55, (dd, J = 13.13 and 249.47 Hz), 136.32 (d, *J*=10.02 Hz), 128.18 (d, *J*=10.79 Hz), 124.15, 123.68 (d, *J*=3.85 Hz) 115.82 - 117.00, 115.54, 78.49, 37.85 (d, *J*=11.56 Hz), 30.63, 30.54.

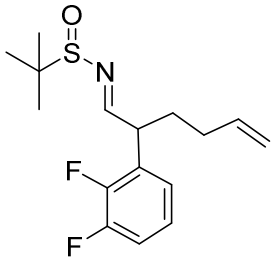
^{19}F NMR of 12:

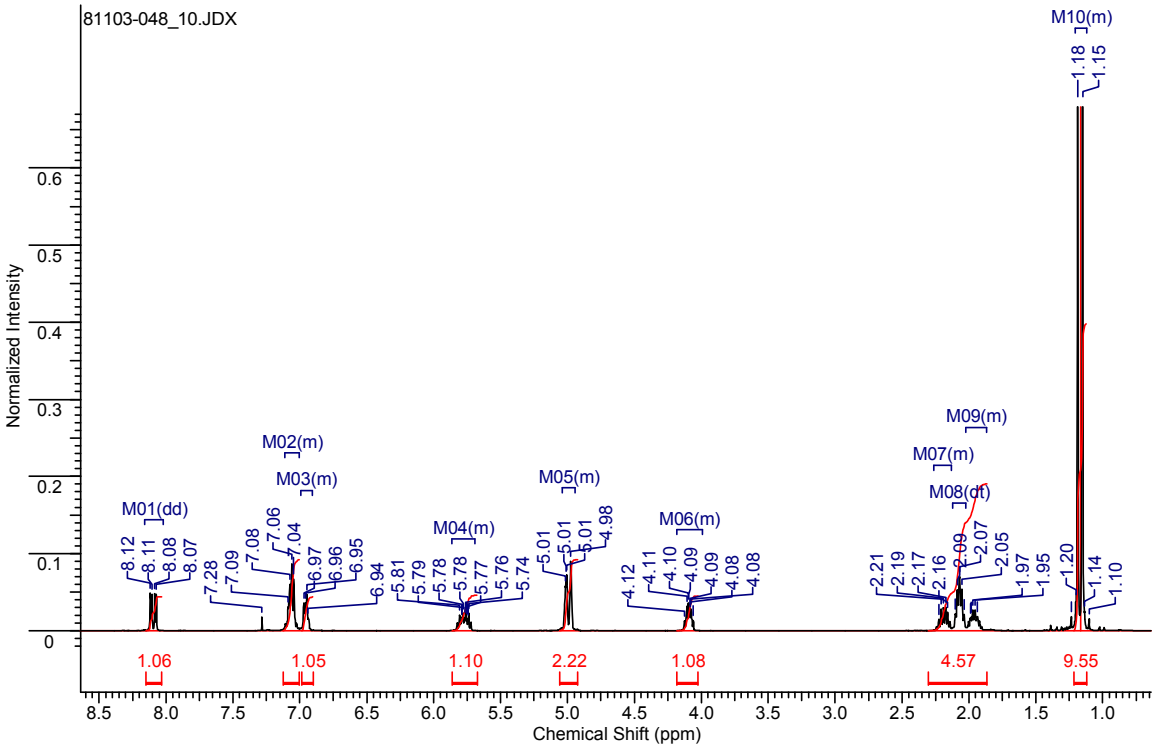




^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -137.24, -142.38.

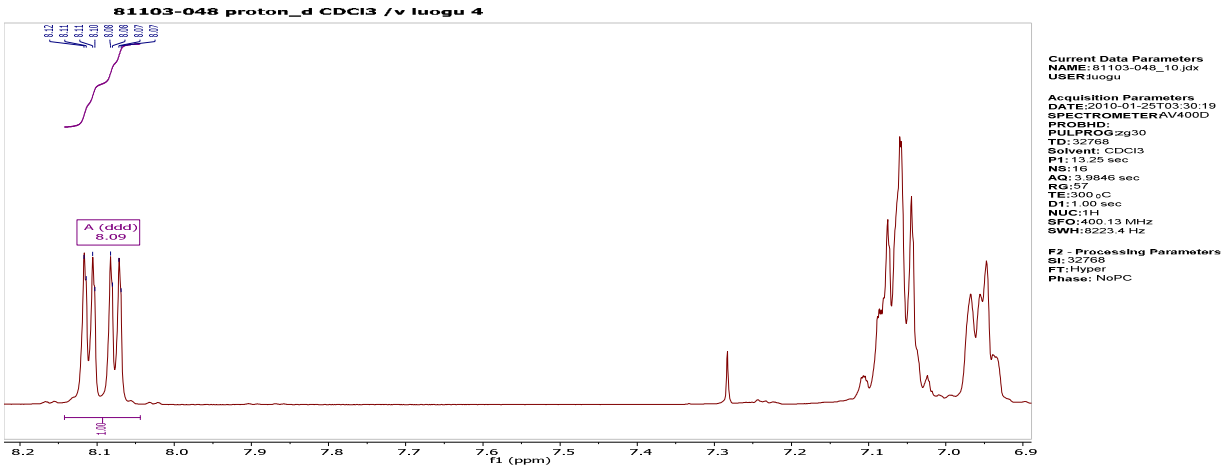
^{1}H NMR of Racemic 9:



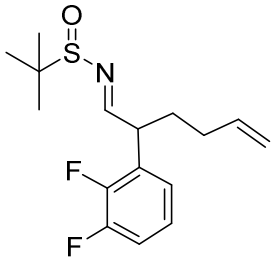


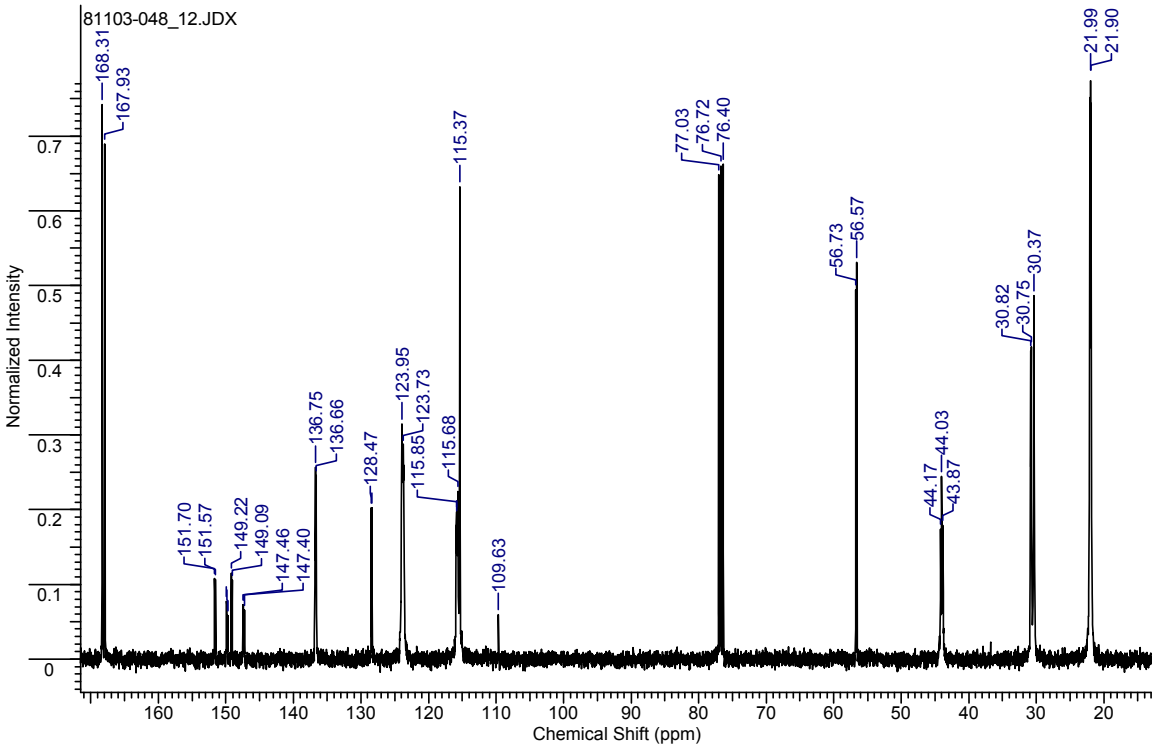
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.09 (dd, *J*=13.68, 4.39 Hz, 1 H) 7.00 - 7.11 (m, 2 H) 6.91 - 6.99 (m, 1 H) 5.69 - 5.87 (m, 1 H) 4.94 - 5.04 (m, 2 H) 3.99 - 4.18 (m, 1 H) 2.13 - 2.26 (m, 1 H) 2.07 (dt, *J*=13.24, 6.56 Hz, 2 H) 1.87 - 2.02 (m, 1 H) 1.12 - 1.21 (m, 9 H).

Imine proton of Racemic 9:



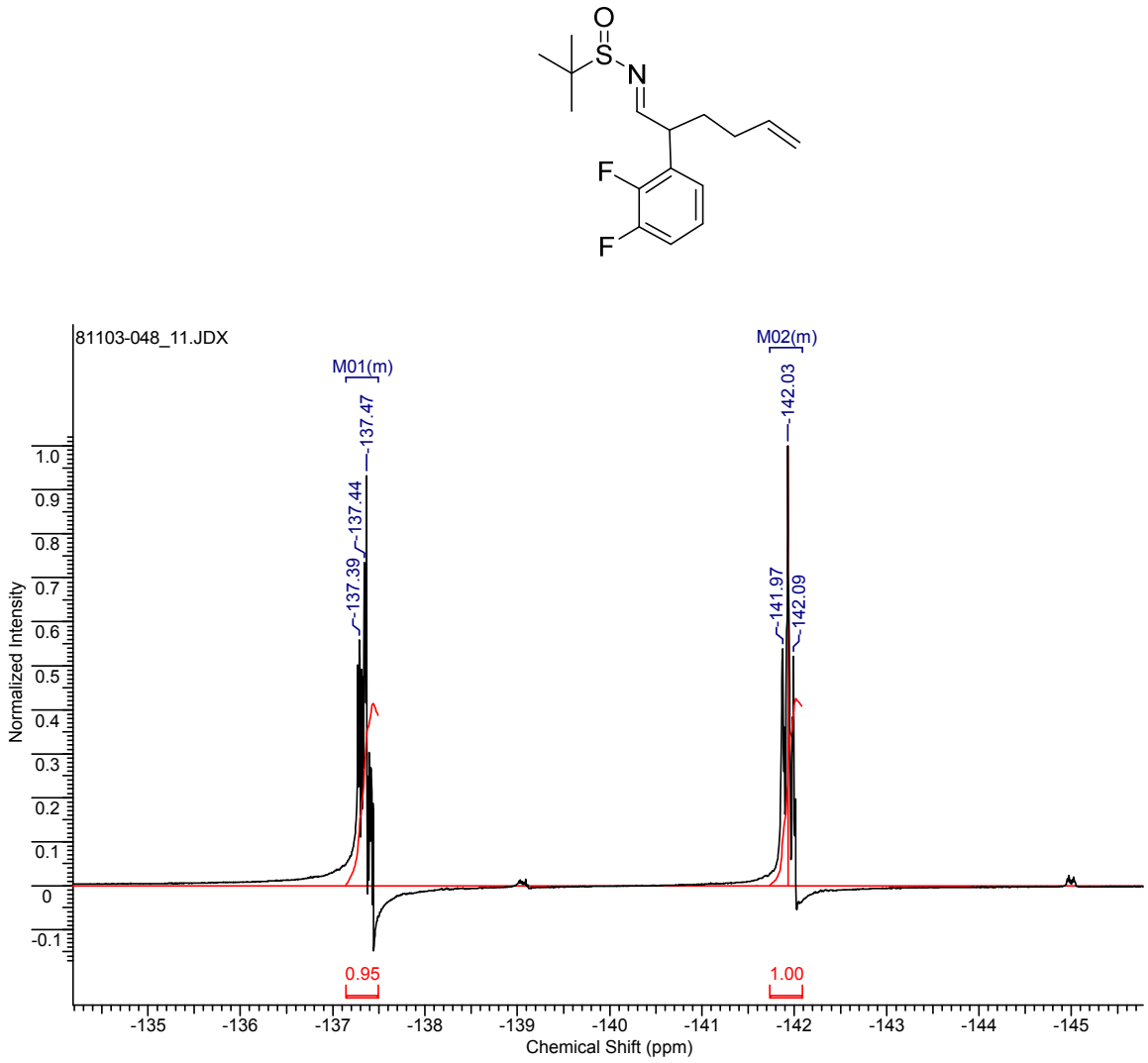
^{13}C NMR of Racemic 9:





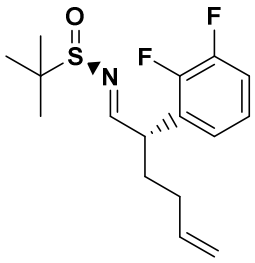
^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 168.31/167.93, 150.36 (dd, *J* = 248.8, 13.0 Hz), 148.57 (ddd, *J* = 248.0, 12.7, 6.3 Hz), 136.74 , 128.40 (dd, *J* = 11.6, 2.8 Hz), 123.81 (d, *J* = 20.0 Hz), 116.34 – 115.52 (m), 115.35, 56.70/56.55, 44.14 – 43.84, 30.79/30.73, 30.34, 22.03- 21.88.

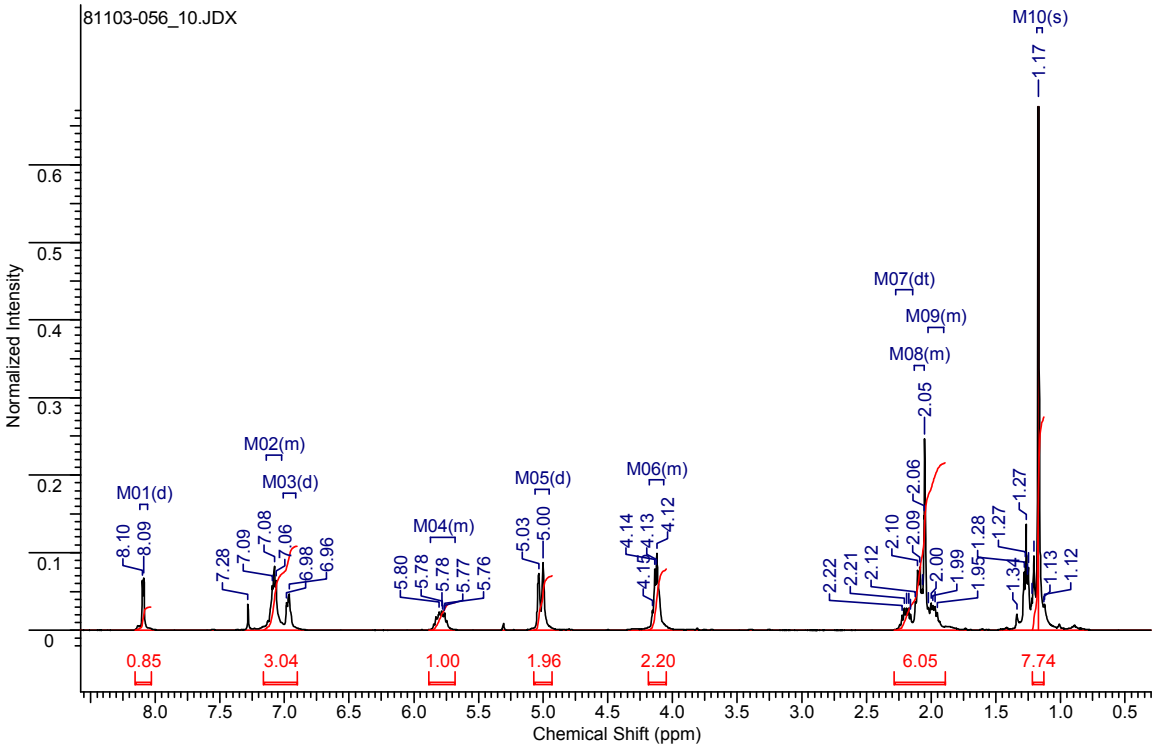
^{19}F NMR of Racemic 9:



19F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -137.59 - -137.24 (m, 1 F) -142.18 - -141.83 (m, 1 F).

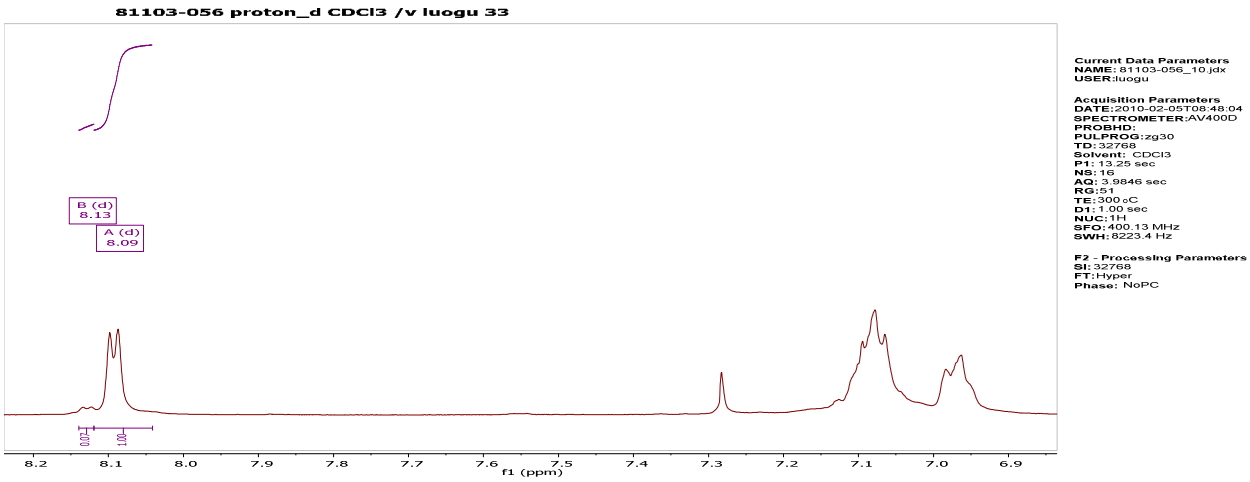
^{1}H NMR of 9:



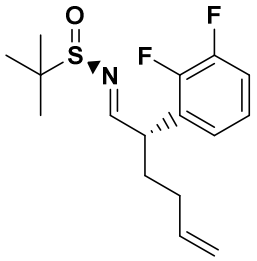


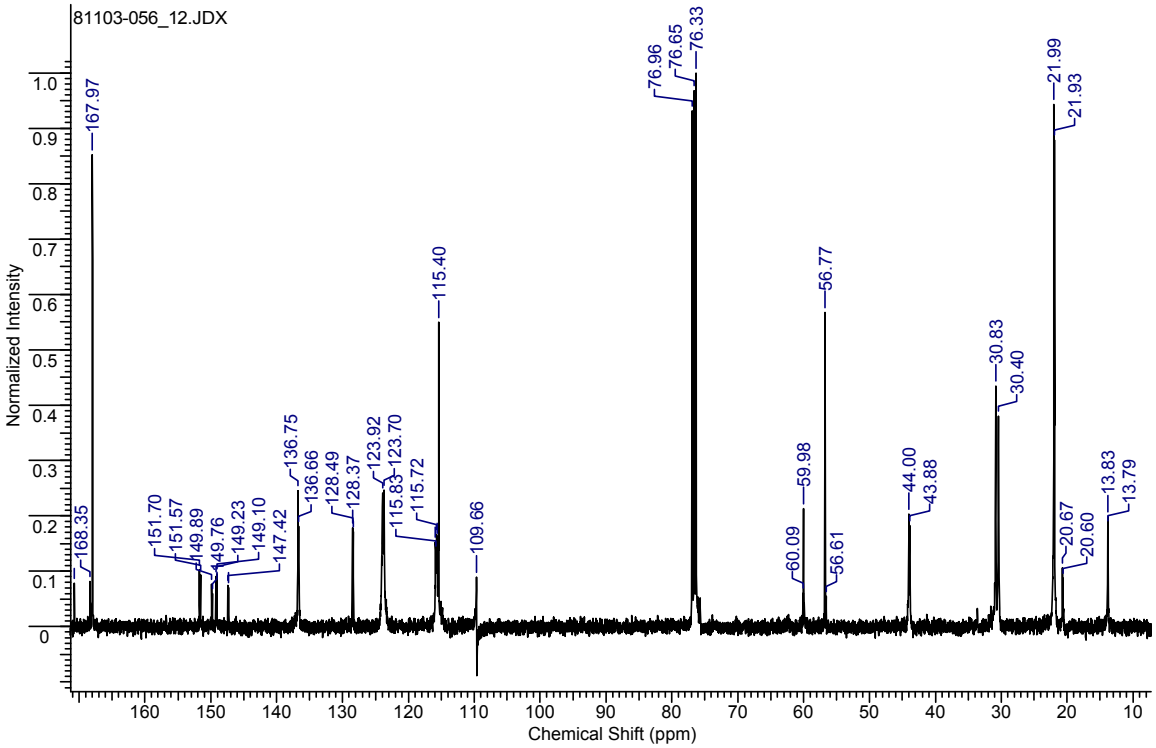
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.09 (d, *J*=4.52 Hz, 1 H) 7.02 - 7.14 (m, 2 H) 6.97 (d, *J*=8.28 Hz, 1 H) 5.68 - 5.87 (m, 1 H) 5.02 (d, *J*=13.05 Hz, 2 H) 4.07 - 4.18 (m, 1 H) 2.19 (dt, *J*=13.30, 6.65 Hz, 1 H) 2.05 - 2.13 (m, 2 H) 1.90 - 2.03 (m, 1 H) 1.17 (s, 9 H).

Imine proton of 9:


81103-056 proton_d CDCl3 /v luogu 33
B (d)
8.13
A (d)
8.09
0.02
1.00
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
f1 (ppm)
Current Data Parameters
NAME: 81103-056_10.jdx
USER:luogu
Acquisition Parameters
DATE:2010-02-05T08:48:04
SPECTROMETER:AV400D
PROBHD:
PULPROG:zg30
TD: 32768
Solvent: CDCl3
P1: 13.25 sec
NS: 16
AQ: 3.9846 sec
RG:51
TE:300 oC
D1: 1.00 sec
NUC:1H
SFO:400.13 MHz
SWH:8223.4 Hz
F2 - Processing Parameters
SI: 32768
FT:Hyper
Phase: NoPC

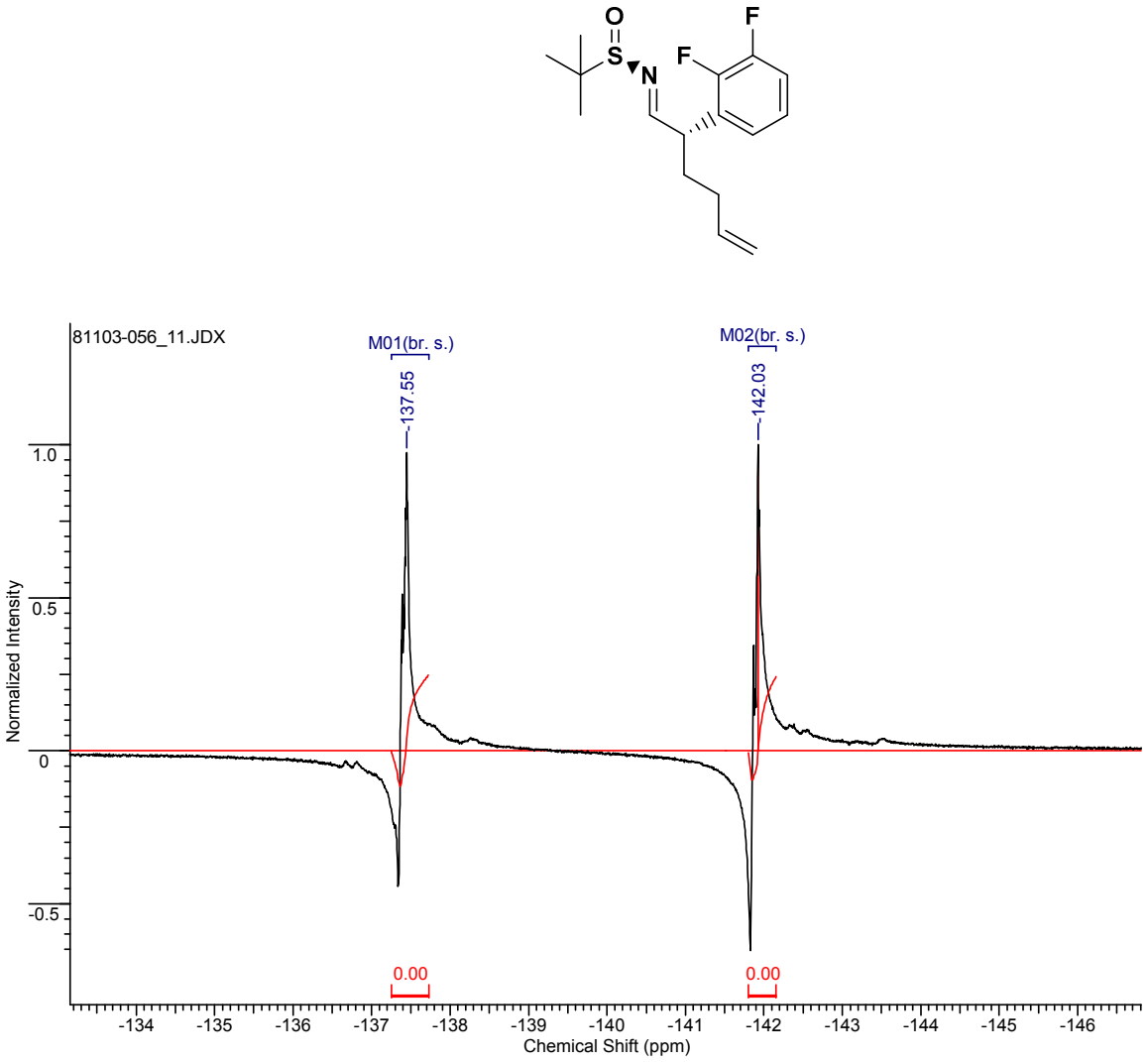
^{13}C NMR of 9:


O
S
N
F
F


81103-056_12.JDX
Normalized Intensity
Chemical Shift (ppm)
167.97
168.35
151.70
151.57
149.89
149.76
149.23
149.10
147.42
136.75
136.66
128.49
128.37
123.92
123.70
115.83
115.72
115.40
109.66
76.96
76.65
76.33
60.09
59.98
56.77
56.61
44.00
43.88
30.83
30.40
21.99
21.93
20.67
20.60
13.83
13.79

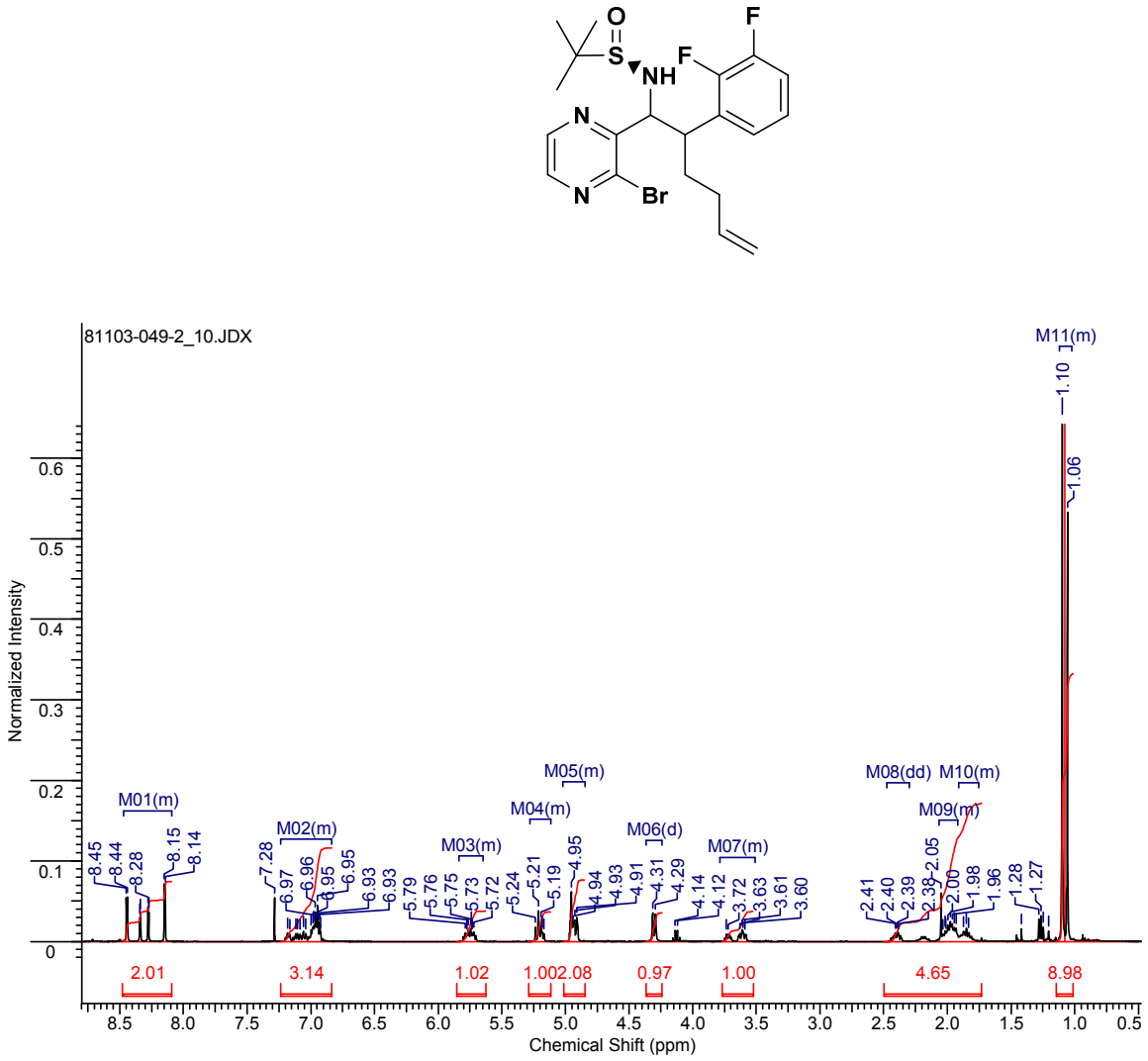
^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 167.94, 150.37 (dd, (dd, *J* = 248.9, 13.2 Hz), 148.56 (dd, *J* = 247.8, 12.8 Hz), 136.73, 128.40 (d, *J* = 11.8 Hz), 123.79 (d, *J* = 25.4 Hz), 115.76 (d, *J* = 16.8 Hz), 115.38, 109.63, 56.74, 43.92 (d, *J* = 12.0 Hz), 30.81 , 30.38 , 21.96/21.93.

^{19}F NMR of 9:



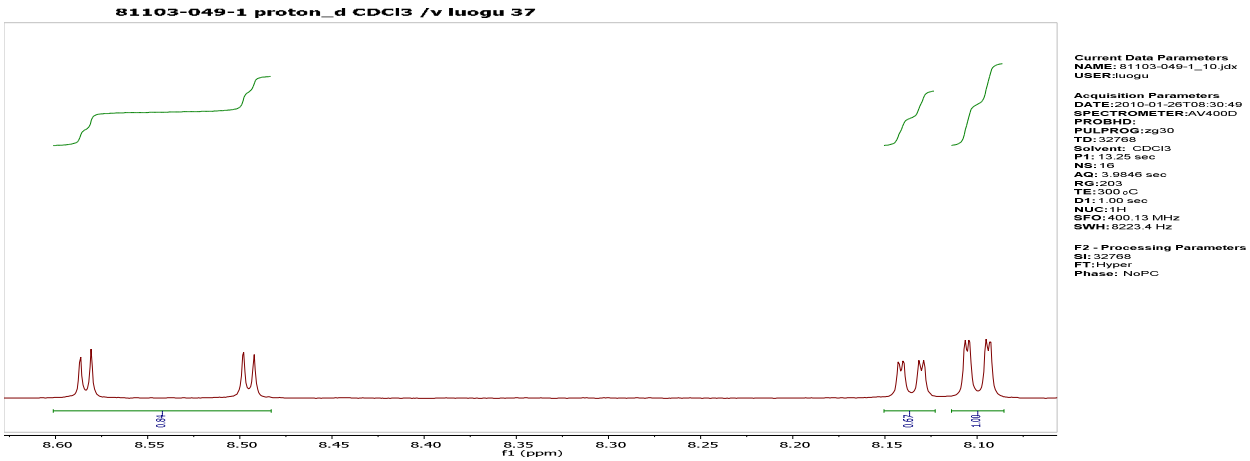
19F NMR (376 MHz, CHLOROFORM-*d*) □ ppm -137.55 (br. s., 1 F) -142.03 (br. s., 1 F).

^{1}H NMR of diastereomeric 7a:

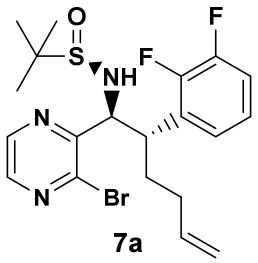


^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.09 - 8.47 (m, 2 H) 6.84 - 7.24 (m, 3 H) 5.65 - 5.84 (m, 1 H) 5.11 - 5.28 (m, 1 H) 4.85 - 5.02 (m, 2 H) 4.30 (d, *J*=9.29 Hz, 1 H) 3.51 - 3.79 (m, 1 H) 2.40 (dd, *J*=8.03, 3.51 Hz, 1 H) 1.92 - 2.06 (m, 2 H) 1.75 - 1.91 (m, 1 H) 1.02 - 1.12 (m, 9 H).

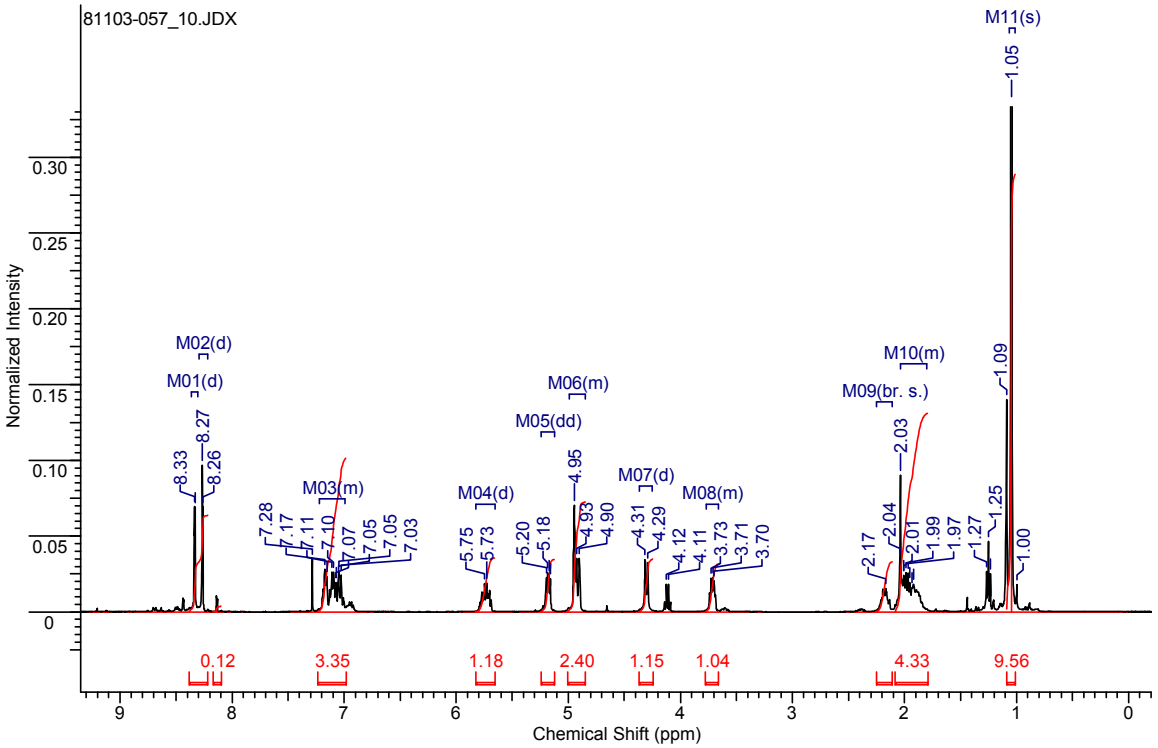
8.7 – 8.1 ppm of diastereomeric 7a:



^{1}H NMR of 7a:

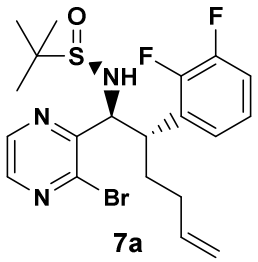


7a

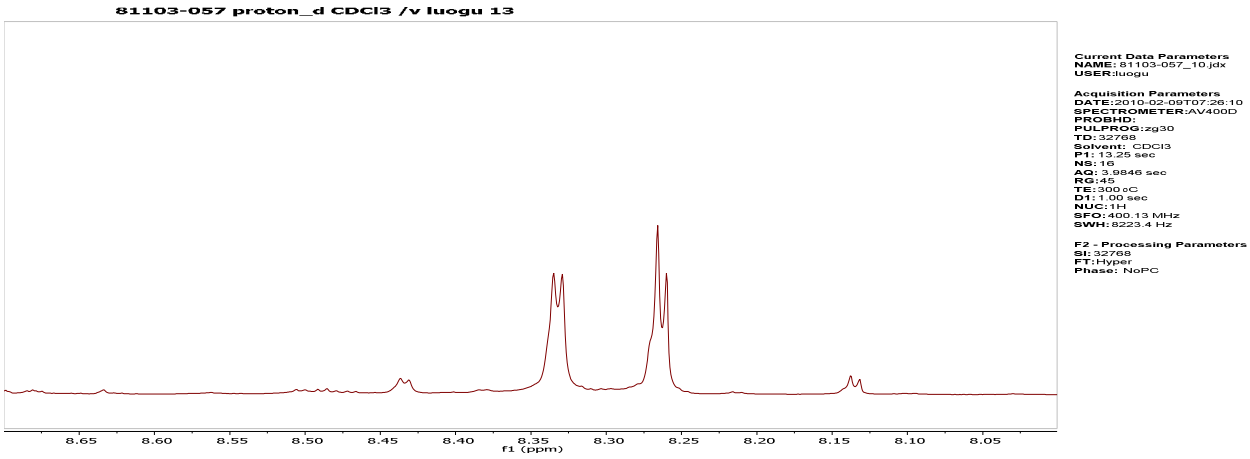


^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.33 (d, *J*=2.26 Hz, 1 H) 8.26 (d, *J*=2.26 Hz, 1 H) 6.99 - 7.22 (m, 3 H) 5.74 (d, *J*=6.53 Hz, 1 H) 5.18 (dd, *J*=9.29, 5.27 Hz, 1 H) 4.85 - 4.99 (m, 2 H) 4.30 (d, *J*=9.54 Hz, 1 H) 3.66 - 3.77 (m, 1 H) 2.17 (br. s., 1 H) 1.80 - 2.04 (m, 3 H) 1.05 (s, 9 H).

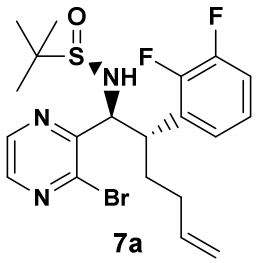
8.7 – 8.1 ppm of 7a:



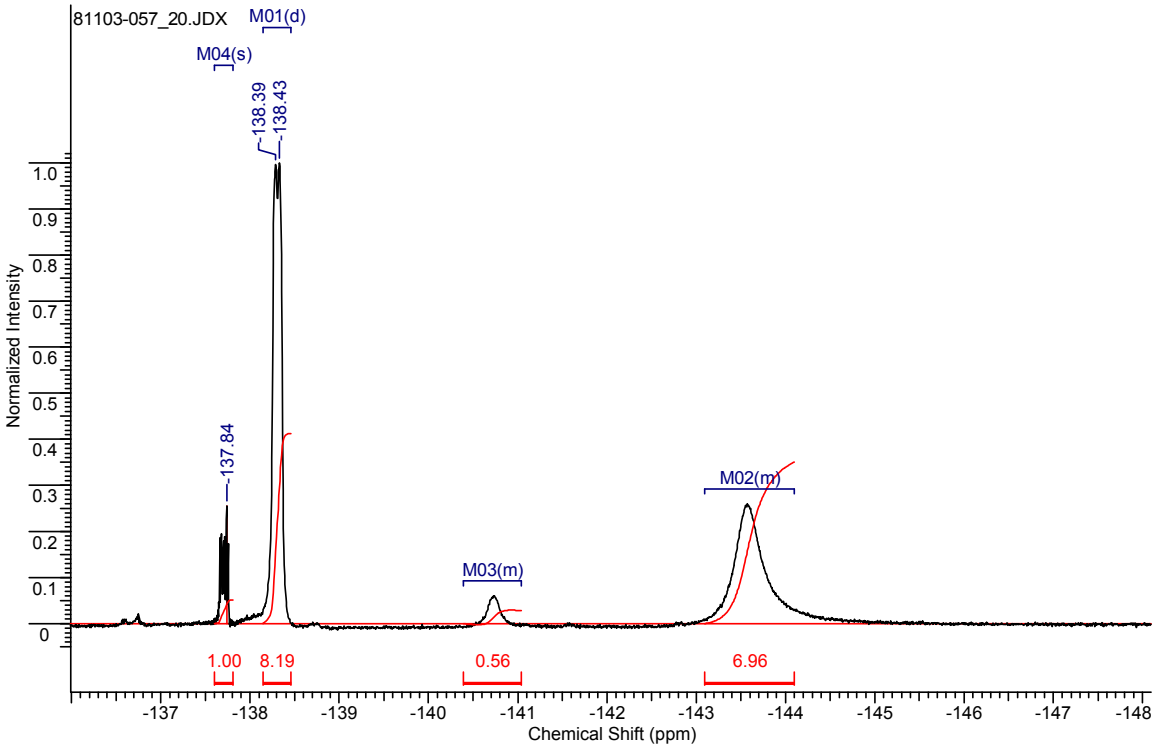
7a



^{19}F NMR of 7a:

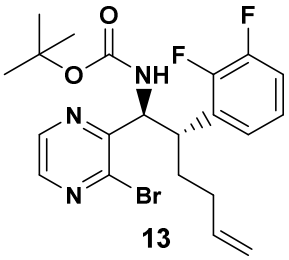


7a

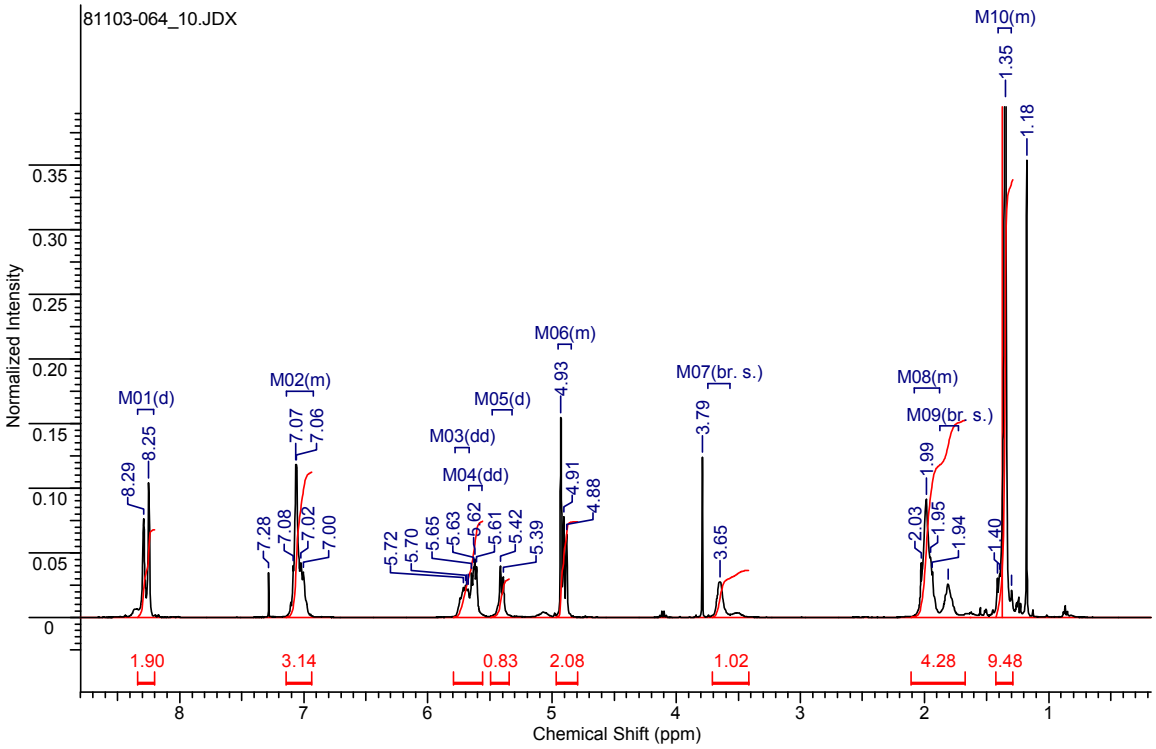


^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -138.41 (d, *J*=15.61 Hz, 1 F) -144.20 - -143.20 (m, 1 F).

^{1}H NMR of 13:

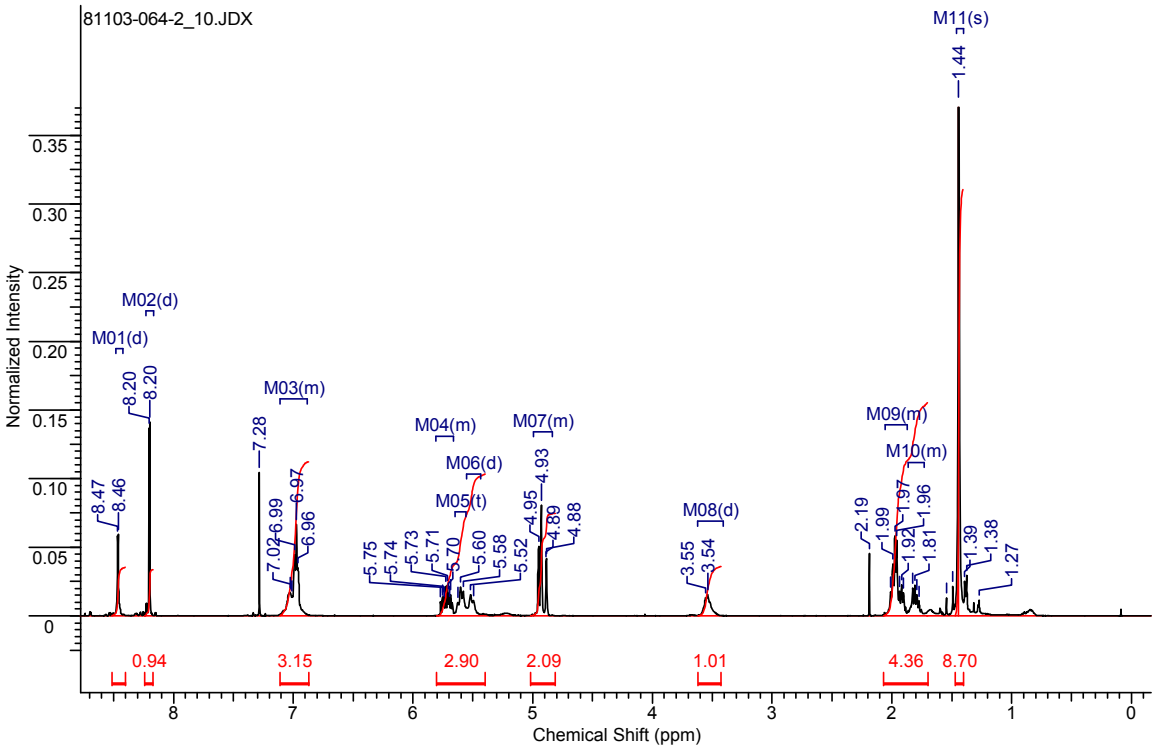


13



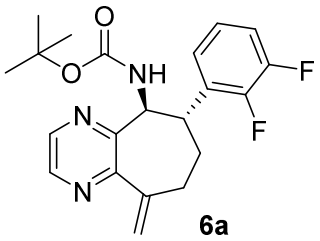
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.27 (d, *J*=17.07 Hz, 2 H) 6.92 - 7.14 (m, 3 H) 5.69 (dd, *J*=10.29, 5.77 Hz, 1 H) 5.63 (dd, *J*=9.41, 5.90 Hz, 1 H) 5.41 (d, *J*=9.54 Hz, 1 H) 4.84 - 4.95 (m, 2 H) 3.65 (br. s., 1 H) 1.88 - 2.08 (m, 3 H) 1.81 (br. s., 1 H) 1.30 - 1.41 (m, 9 H).

[1]H NMR of diastereomeric 13:

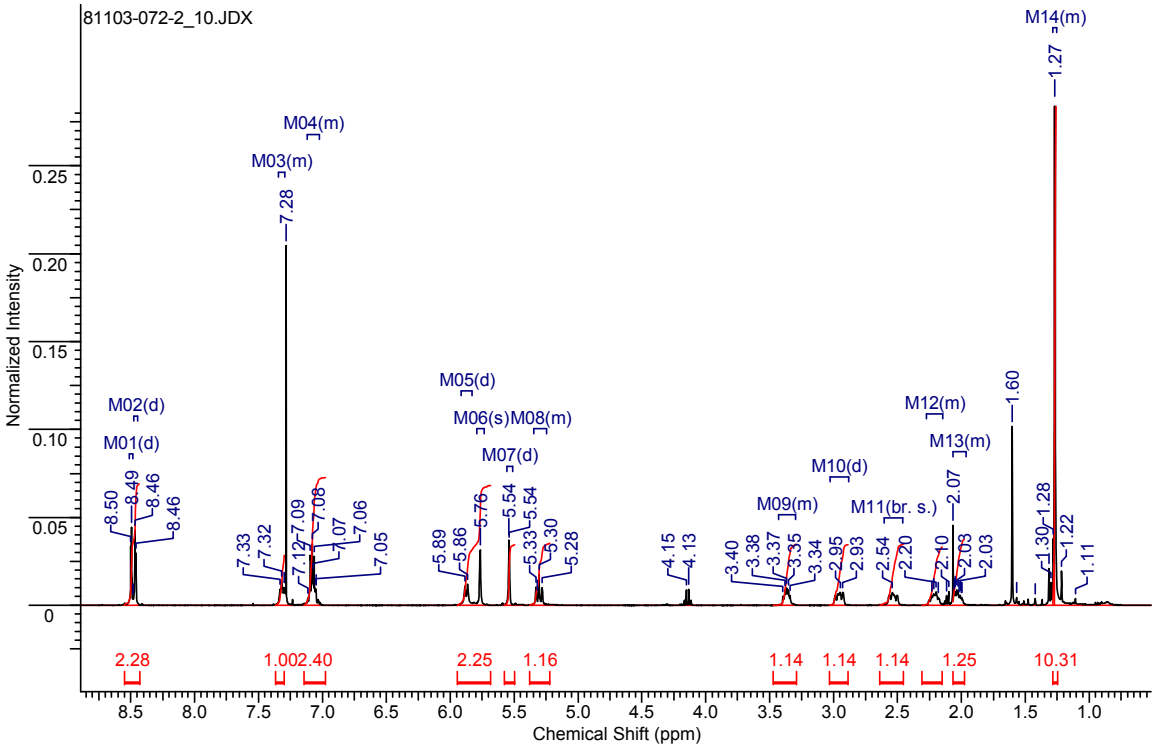


[1]H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.46 (d, *J*=2.26 Hz, 1 H) 8.20 (d, *J*=2.51 Hz, 1 H) 6.88 - 7.11 (m, 3 H) 5.66 - 5.81 (m, 1 H) 5.60 (t, *J*=8.91 Hz, 1 H) 5.51 (d, *J*=9.29 Hz, 1 H) 4.83 - 5.00 (m, 2 H) 3.55 (d, *J*=6.53 Hz, 1 H) 1.87 - 2.06 (m, 3 H) 1.73 - 1.86 (m, 1 H) 1.44 (s, 9 H).

[1]H NMR of 6a:

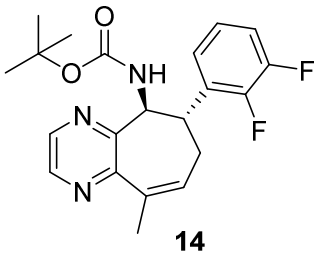


6a

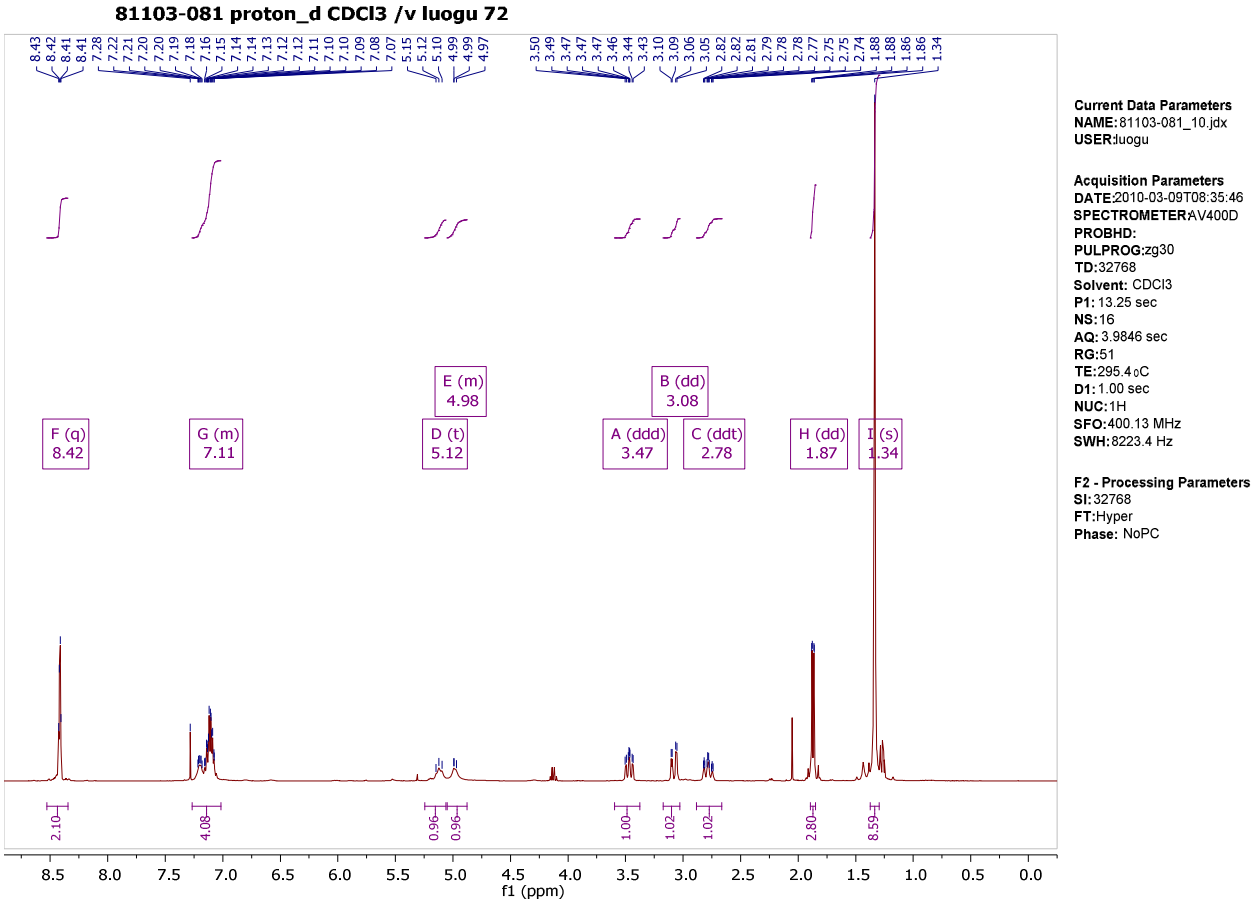


[1]H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.50 (d, *J*=2.51 Hz, 1 H) 8.46 (d, *J*=2.51 Hz, 1 H) 7.29 - 7.35 (m, 1 H) 7.02 - 7.12 (m, 2 H) 5.87 (d, *J*=9.29 Hz, 1 H) 5.76 (s, 1 H) 5.54 (d, *J*=1.51 Hz, 1 H) 5.25 - 5.34 (m, 1 H) 3.30 - 3.43 (m, 1 H) 2.94 (d, *J*=7.78 Hz, 1 H) 2.54 (br. s., 1 H) 2.15 - 2.28 (m, 1 H) 1.96 - 2.07 (m, 1 H) 1.25 - 1.28 (m, 9 H).

^{1}H NMR of 14:

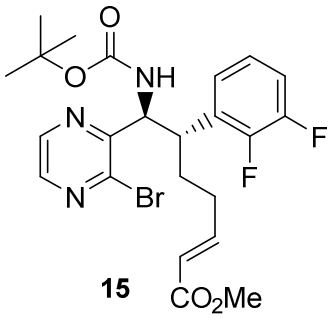


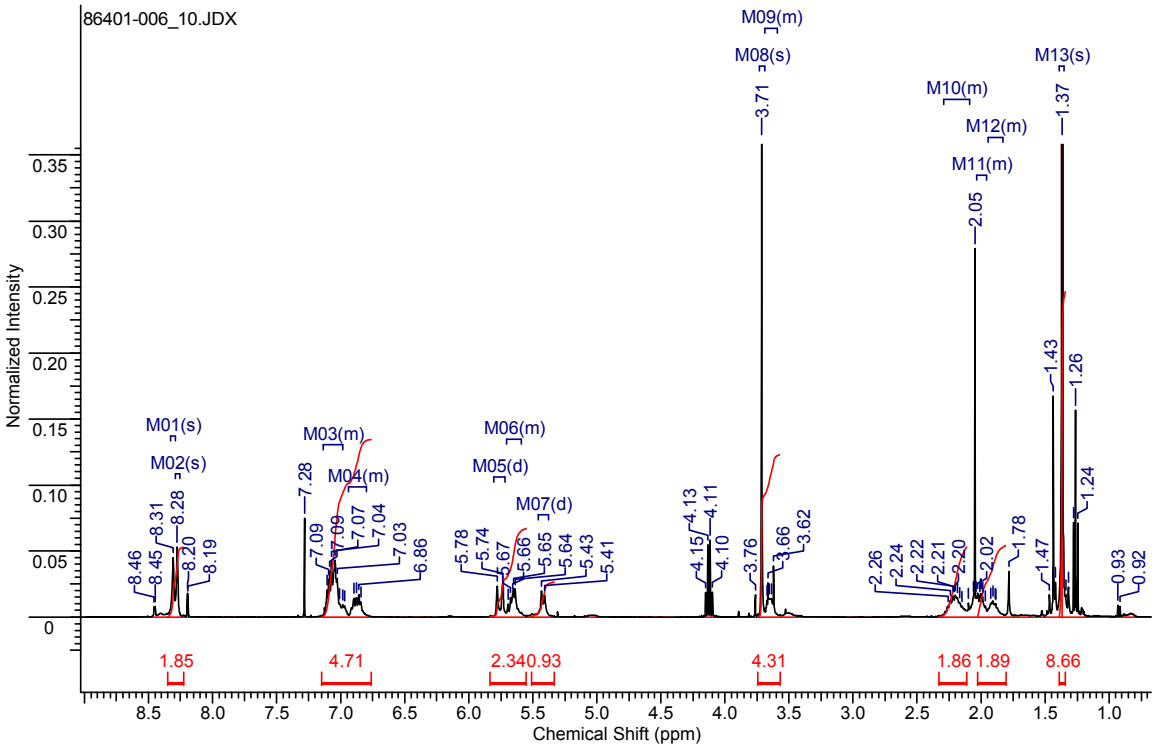
14



^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (q, *J* = 2.4 Hz, 2H), 7.27 – 7.02 (m, 4H), 5.12 (t, *J* = 10.4 Hz, 1H), 5.05 – 4.88 (m, 1H), 3.47 (ddd, *J* = 12.8, 11.2, 3.8 Hz, 1H), 3.08 (dd, *J* = 16.1, 3.8 Hz, 1H), 2.78 (ddt, *J* = 15.4, 12.9, 2.3 Hz, 1H), 1.87 (dd, *J* = 7.3, 1.7 Hz, 3H), 1.34 (s, 9H).

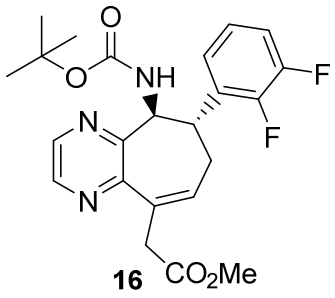
^{1}H NMR of 15:

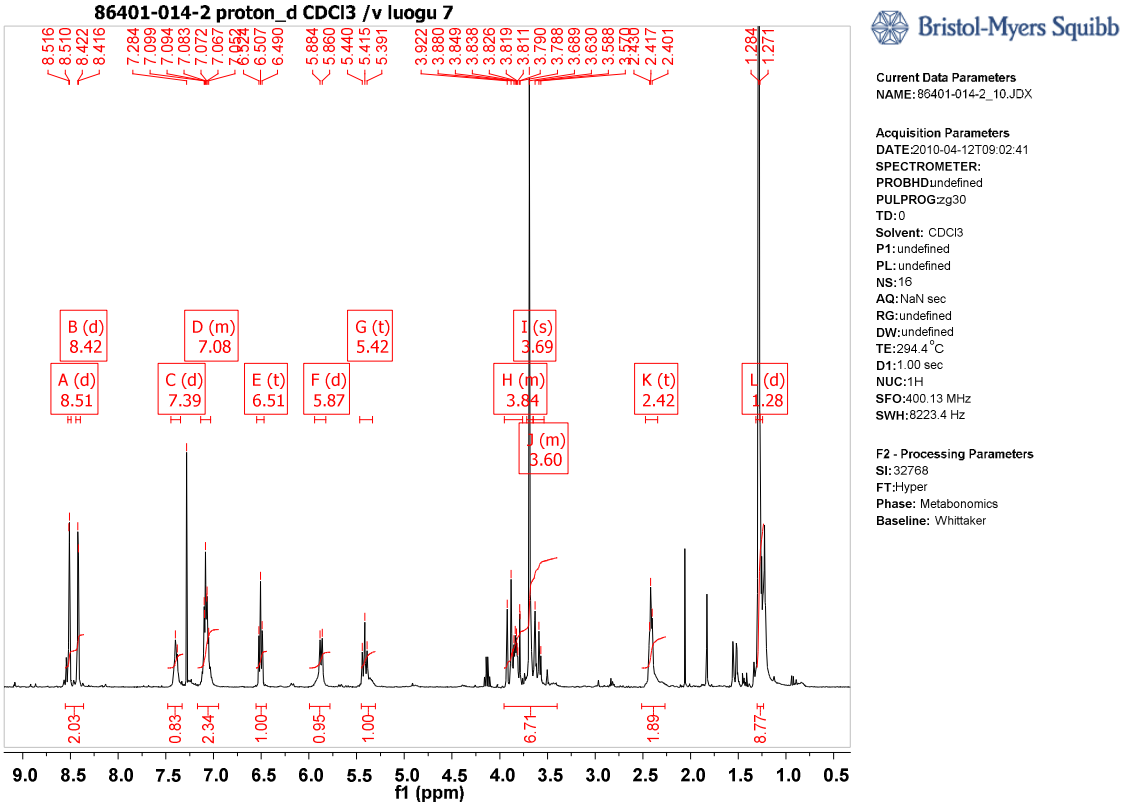




^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.31 (s, 1 H) 8.28 (s, 1 H) 6.98 - 7.14 (m, 3 H) 6.80 - 6.94 (m, 1 H) 5.76 (d, *J*=16.56 Hz, 1 H) 5.59 - 5.71 (m, 1 H) 5.42 (d, *J*=9.54 Hz, 1 H) 3.71 (s, 3 H) 3.59 - 3.69 (m, 1 H) 2.09 - 2.29 (m, 2 H) 1.96 - 2.04 (m, 1 H) 1.83 - 1.95 (m, 1 H) 1.37 (s, 9 H).

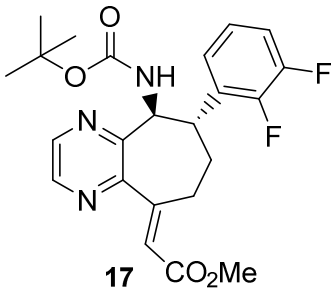
^{1}H NMR of 16:

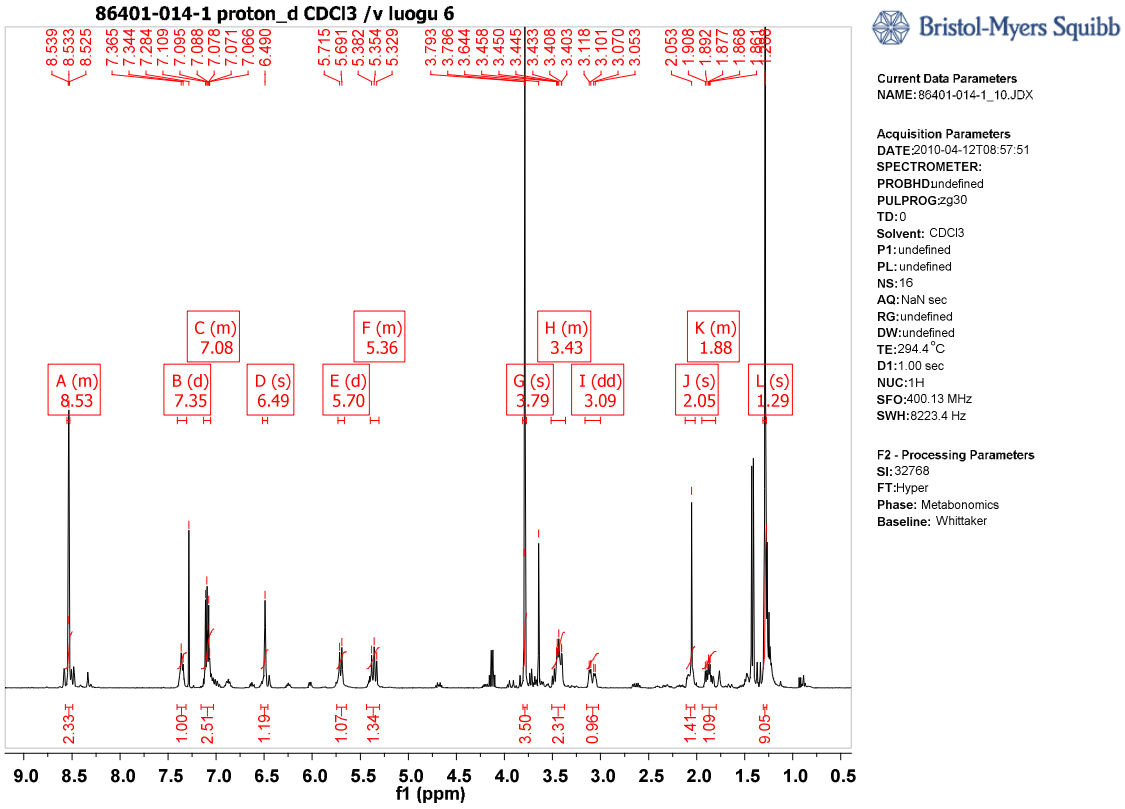




^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.4 Hz, 1H), 8.42 (d, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.13 – 7.03 (m, 2H), 6.51 (t, *J* = 6.8 Hz, 1H), 5.87 (d, *J* = 9.4 Hz, 1H), 5.42 (t, *J* = 9.7 Hz, 1H), 3.95 – 3.76 (m, 2H), 3.69 (s, 3H), 3.65 – 3.54 (m, 1H), 2.42 (t, *J* = 5.8 Hz, 2H), 1.28 (d, *J* = 5.3 Hz, 9H).

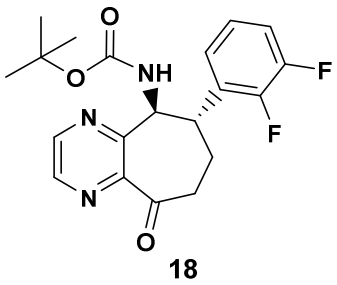
^{1}H NMR of 17:



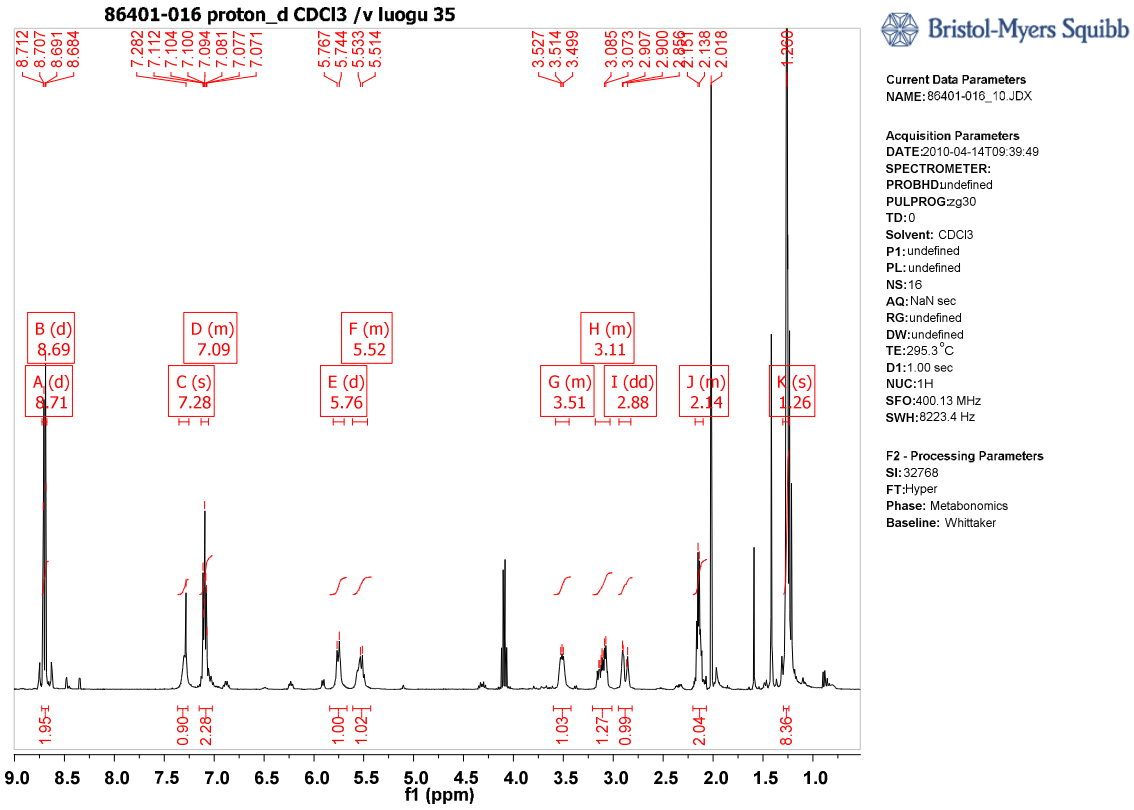


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.52 (m, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.49 (s, 1H), 5.70 (d, *J* = 9.5 Hz, 1H), 5.40 – 5.30 (m, 1H), 3.79 (s, 3H), 3.51 – 3.37 (m, 2H), 3.09 (dd, *J* = 19.1, 6.7 Hz, 1H), 2.05 (s, 1H), 1.95 – 1.80 (m, 1H), 1.29 (s, 9H).

^{1}H NMR of 18:

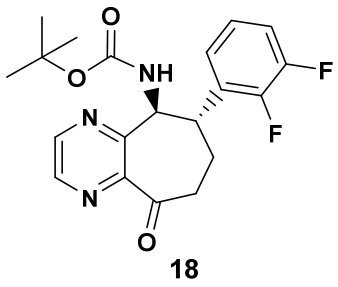


18

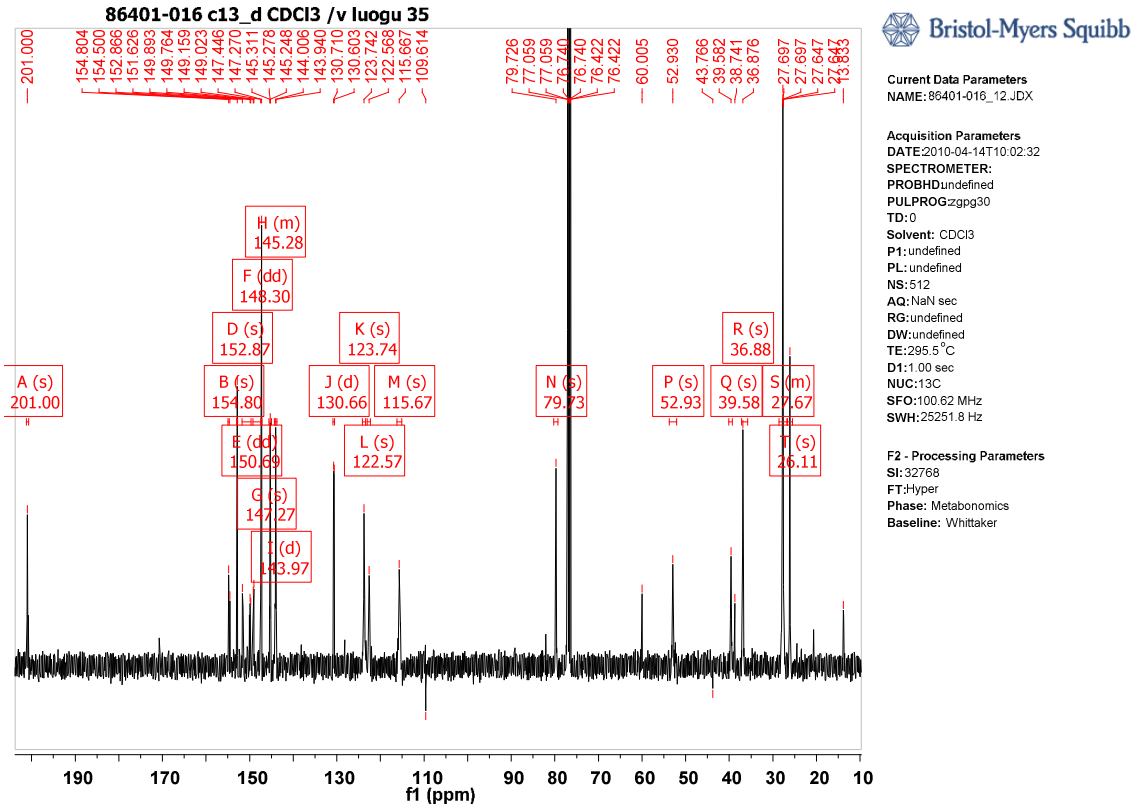


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 2.3 Hz, 1H), 8.69 (d, J = 2.4 Hz, 1H), 7.28 (s, 1H), 7.13 – 7.06 (m, 2H), 5.76 (d, J = 9.0 Hz, 1H), 5.61 – 5.46 (m, J = 7.5 Hz, 1H), 3.58 – 3.44 (m, 1H), 3.18 – 3.03 (m, 1H), 2.88 (dd, J = 17.1, 3.3 Hz, 1H), 2.18 – 2.10 (m, J = 5.0 Hz, 2H), 1.26 (s, 9H).

^{13}C NMR of 18:

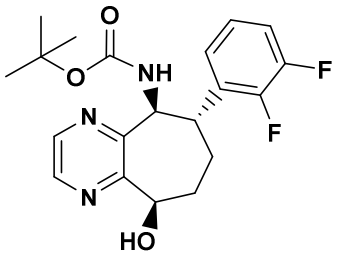


18

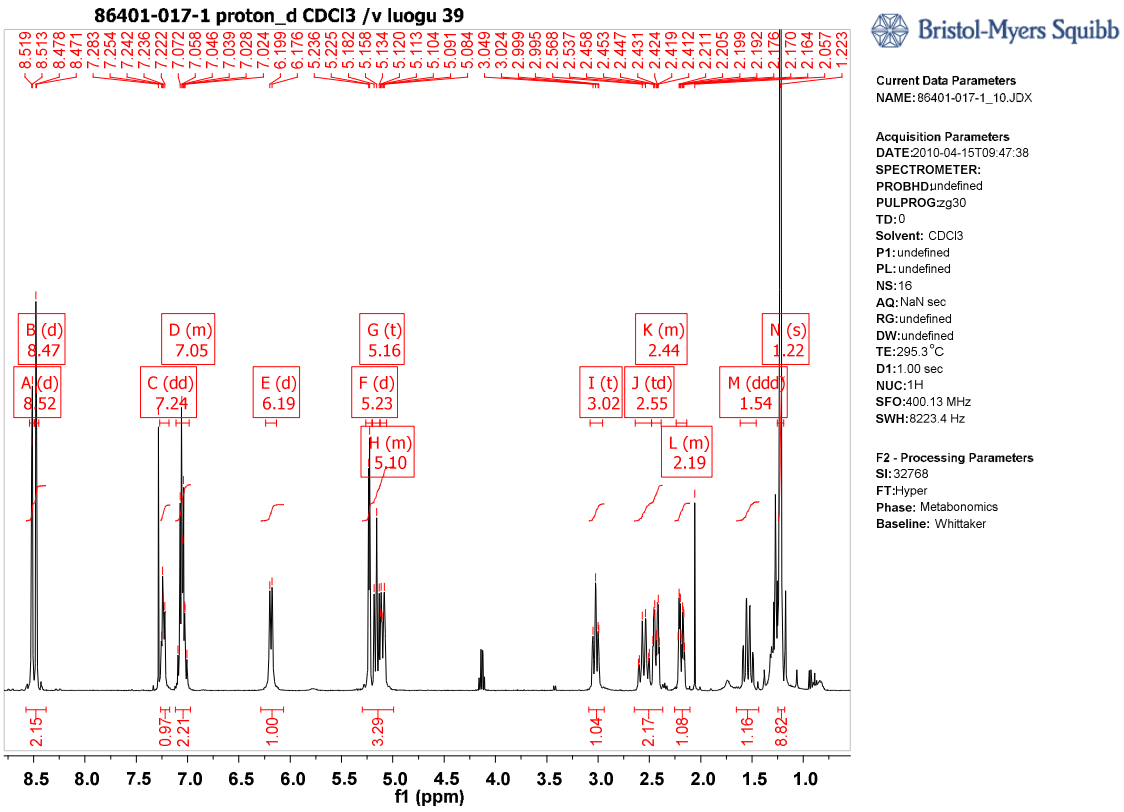


^{13}C NMR (101 MHz, $CDCl_3$) δ 201.00 (s), 154.80 (s), 152.87 (s), 150.69 (dd, J = 174.1, 13.3 Hz), 148.30 (dd, J = 160.0, 12.4 Hz), 147.27 (s), 145.56 – 145.00 (m), 143.97 (d, J = 6.7 Hz), 130.66 (d, J = 10.8 Hz), 123.74 (s), 122.57 (s), 115.67 (s), 79.73 (s), 52.93 (s), 39.58 (s), 36.88 (s), 28.61 – 26.78 (m), 26.11 (s).

^{1}H NMR of 5a:



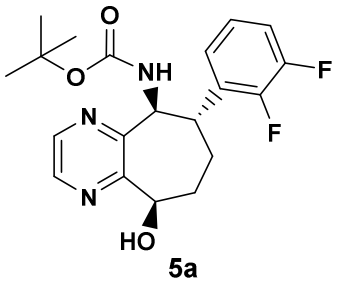
5a



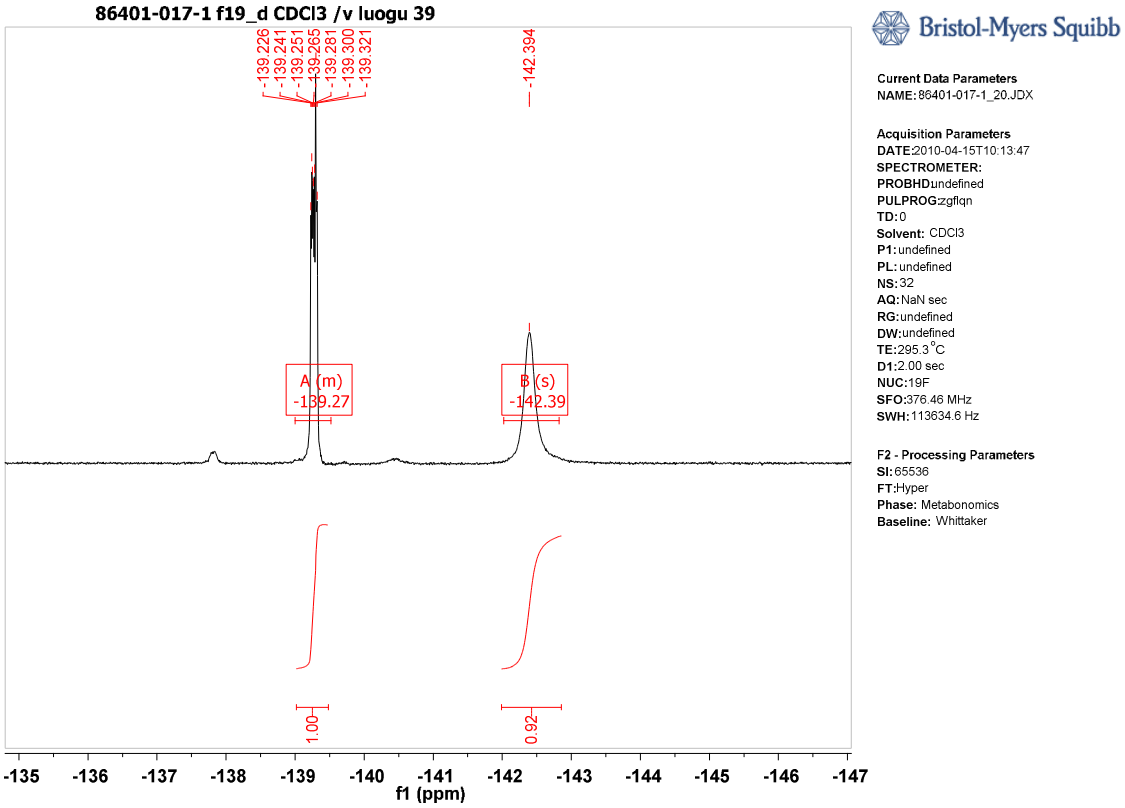
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 2.5 Hz, 1H), 8.47 (d, J = 2.6 Hz, 1H), 7.24 (dd, J = 7.7, 5.0 Hz, 1H), 7.11 – 6.98 (m, 2H), 6.19 (d, J = 9.1 Hz, 1H), 5.23 (d, J = 4.2 Hz, 1H), 5.16 (t, J = 9.6 Hz, 1H),

5.12 – 5.06 (m, 1H), 3.02 (t, J = 10.9 Hz, 1H), 2.55 (td, J = 14.7, 2.9 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.24 – 2.14 (m, 1H), 1.54 (ddd, J = 16.0, 14.1, 3.0 Hz, 1H), 1.22 (s, 9H).

^{19}F NMR of 5a:

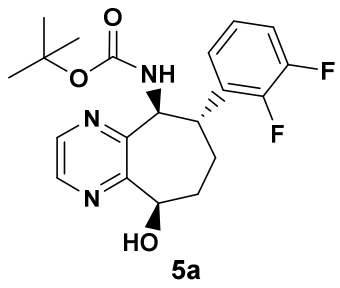


5a

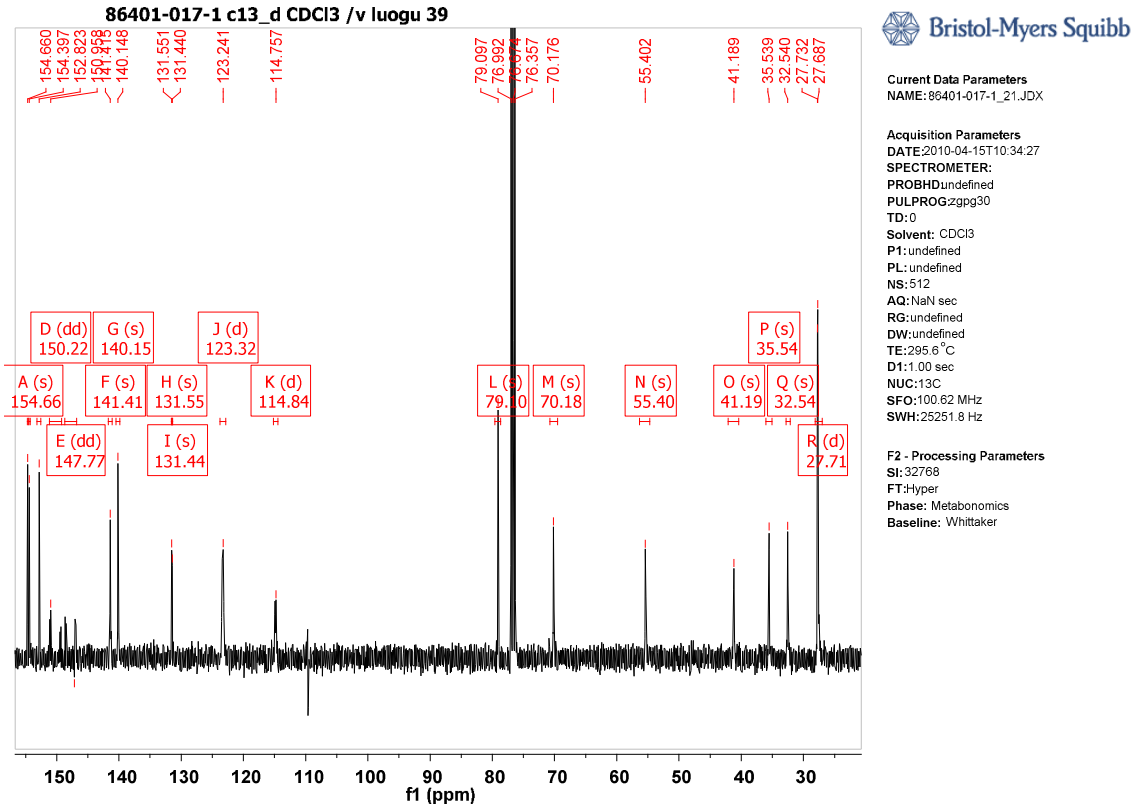


^{19}F NMR (376 MHz, $CDCl_3$) δ -139.00 – -139.52 (m), -142.39 (s).

^{13}C NMR of 5a:



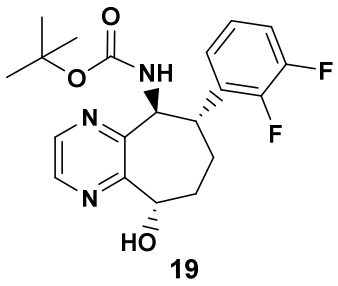
5a



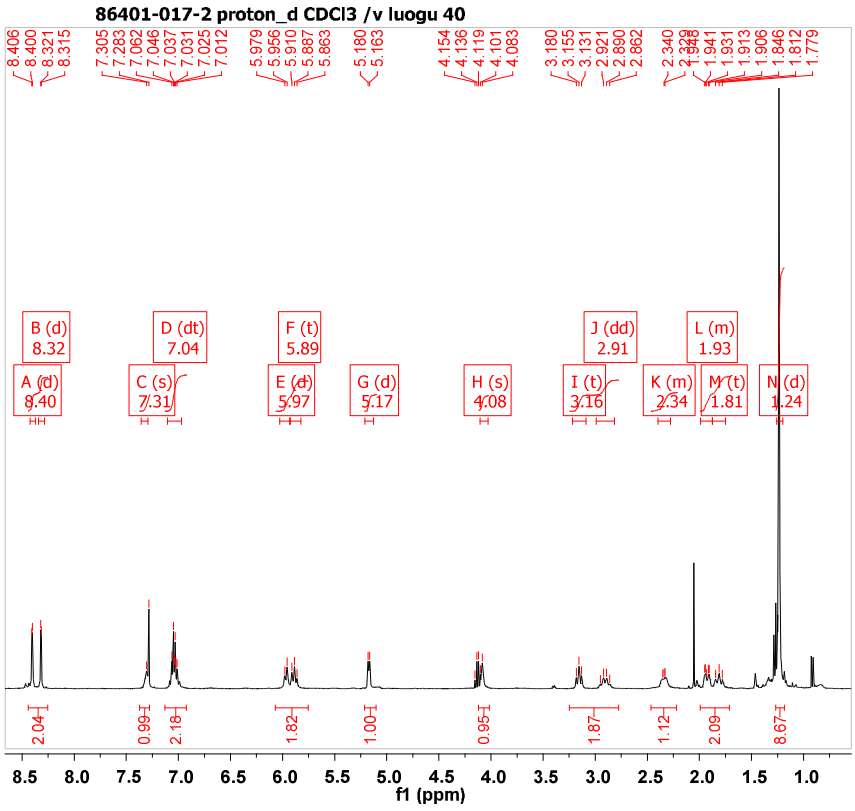
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.66 (s), 154.40 (s), 152.82 (s), 150.22 (dd, J = 163.2, 13.4 Hz), 147.77 (dd, J = 160.1, 13.2 Hz), 141.41 (s), 140.15 (s), 131.55 (s), 131.44 (s), 123.32 (d, J = 15.1 Hz),

114.84 (d, J = 17.1 Hz), 79.10 (s), 70.18 (s), 55.40 (s), 41.19 (s), 35.54 (s), 32.54 (s), 27.71 (d, J = 4.6 Hz).

^{1}H NMR of 19:



19



Bristol-Myers Squibb

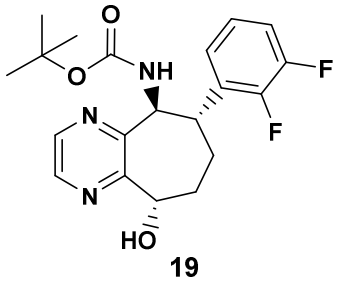
Current Data Parameters
NAME: 86401-017-2_10.JDX

Acquisition Parameters
DATE: 2010-04-15T09:52:22
SPECTROMETER:
PROBHD: undefined
PULPROG: zg30
TD: 0
Solvent: CDCl3
P1: undefined
PL: undefined
NS: 16
AQ: NaN sec
RG: undefined
DW: undefined
TE: 295.3 °C
D1: 1.00 sec
NUC: 1H
SFO: 400.13 MHz
SWH: 8223.4 Hz

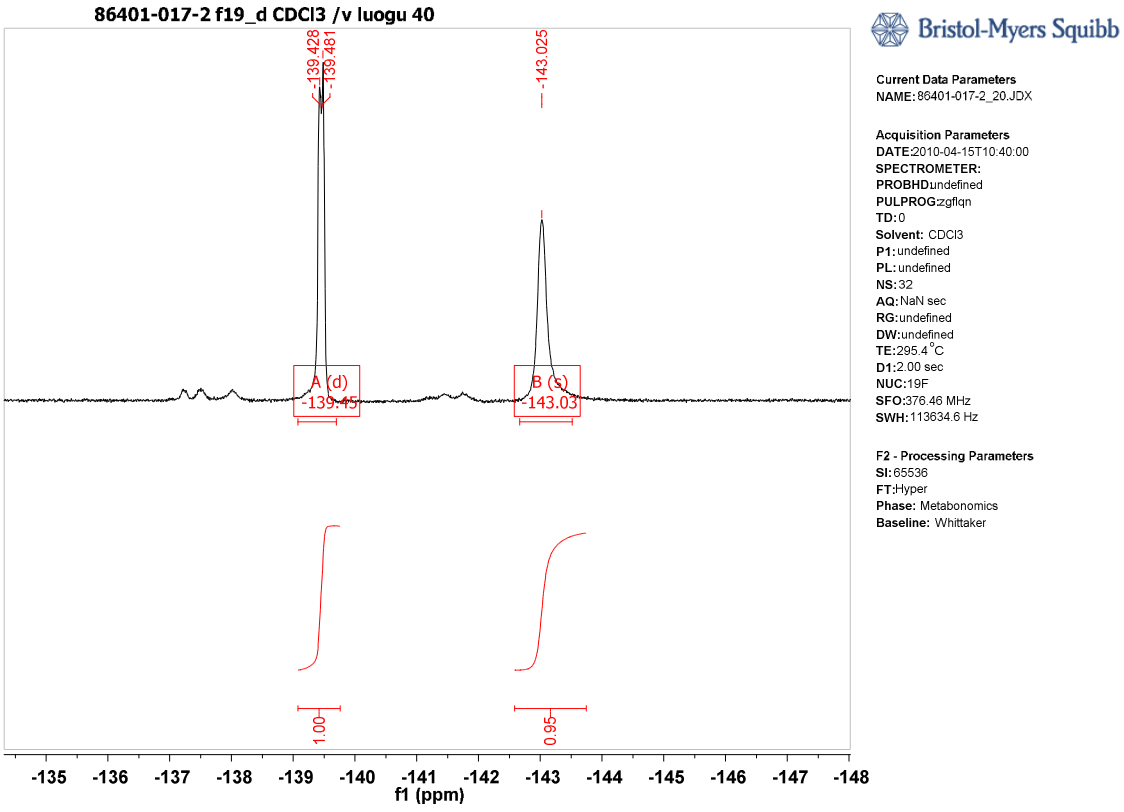
F2 - Processing Parameters
SI: 32768
FT: Hyper
Phase: Metabonomics
Baseline: Whittaker

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.5 Hz, 1H), 8.32 (d, *J* = 2.5 Hz, 1H), 7.31 (s, 1H), 7.04 (dt, *J* = 7.4, 5.8 Hz, 2H), 5.97 (d, *J* = 9.3 Hz, 1H), 5.89 (t, *J* = 9.6 Hz, 1H), 5.17 (d, *J* = 6.8 Hz, 1H), 4.08 (s, 1H), 3.16 (t, *J* = 9.7 Hz, 1H), 2.91 (dd, *J* = 23.6, 11.5 Hz, 1H), 2.40 – 2.28 (m, 1H), 1.99 – 1.88 (m, 1H), 1.81 (t, *J* = 13.3 Hz, 1H), 1.24 (d, *J* = 5.9 Hz, 9H).

^{19}F NMR of 19:

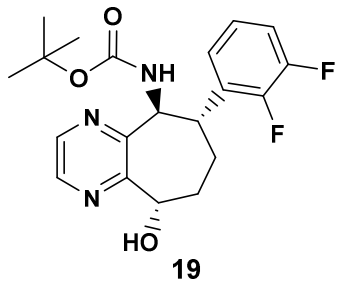


19

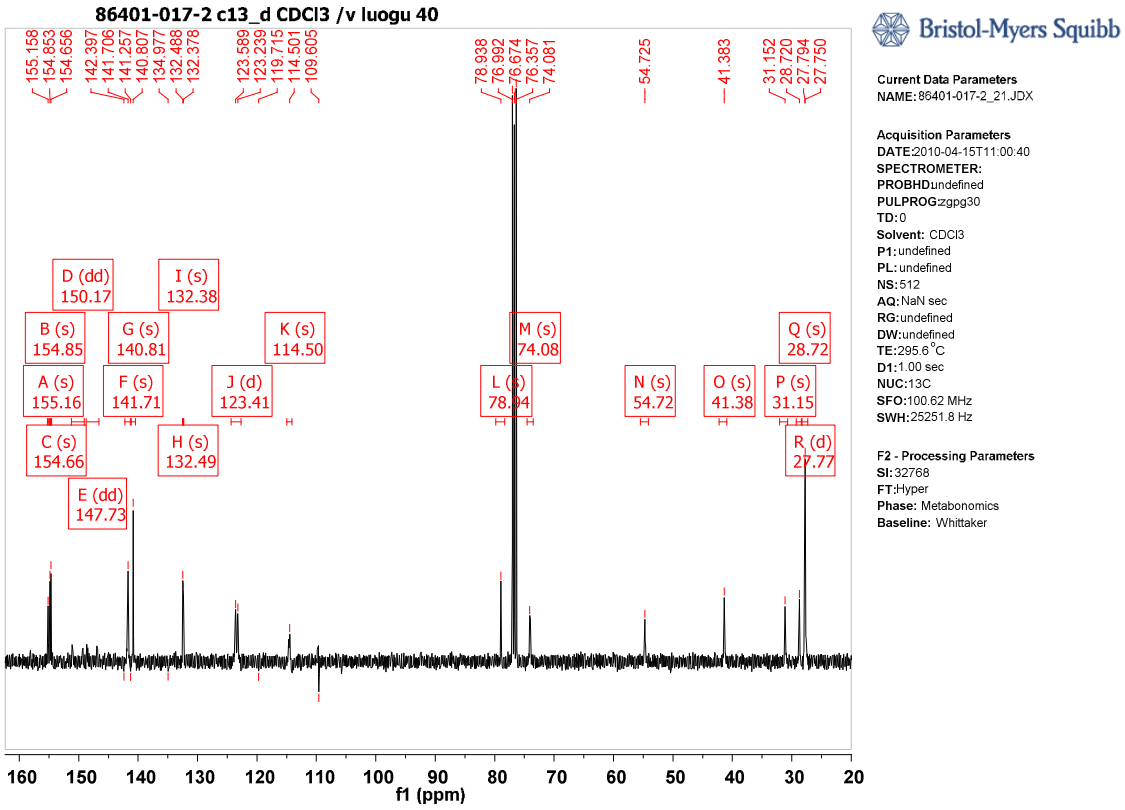


^{19}F NMR (376 MHz, $CDCl_3$) δ -139.45 (d, J = 20.1 Hz), -143.03 (s).

^{13}C NMR of 19:

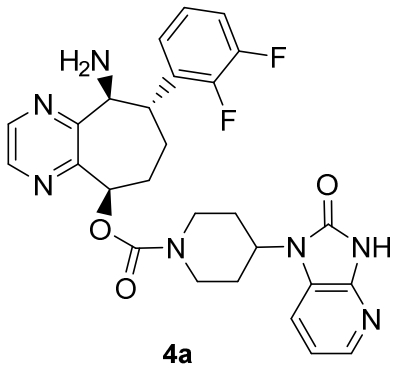


19

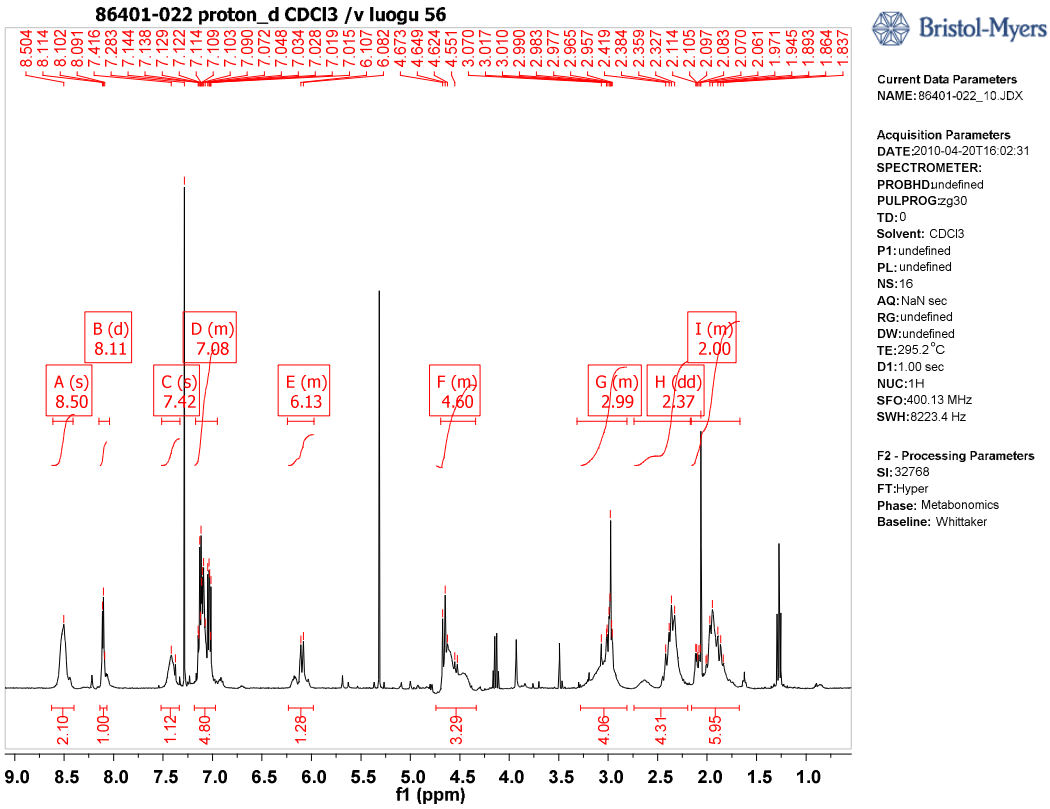


^{13}C NMR (101 MHz, $CDCl_3$) δ 155.16 (s), 154.85 (s), 154.66 (s), 150.17 (dd, *J* = 171.9, 13.1 Hz), 147.73 (dd, *J* = 170.2, 14.0 Hz), 141.71 (s), 140.81 (s), 132.49 (s), 132.38 (s), 123.41 (d, *J* = 35.2 Hz), 114.50 (s), 78.94 (s), 74.08 (s), 54.72 (s), 41.38 (s), 31.15 (s), 28.72 (s), 27.77 (d, *J* = 4.5 Hz).

^{1}H NMR of 4a:

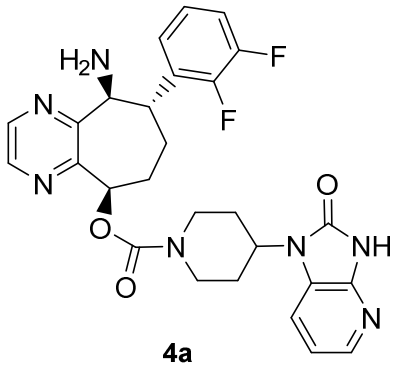


4a



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 2H), 8.11 (d, J = 4.9 Hz, 1H), 7.42 (s, J = 16.5 Hz, 1H), 7.17 – 6.95 (m, 4H), 6.24 – 5.97 (m, 2H), 4.69 – 4.34 (m, 4H), 3.31 – 2.81 (m, 3H), 2.37 (dd, J = 23.5, 13.6 Hz, 4H), 2.17 – 1.67 (m, 6H).

Analytical HPLCs for 4a (6 pages):



4a

HPLC Report

Sample Name: 86401-022

Method Description: File = 2010_0420_2018.025
User = guanglin.luo
Instrument = WFD-489C-HPLC1
Vial = 5 Inj. Vol. = 5 uL
Start % B = 10
Final % B = 100
Gradient Time = 15 min
Flow Rate = 1 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = 0.1%TFA/H2O/MeCN
Solvent A = 0.1% TFA/95%H2O/5%acetonitrile
Solvent B = 0.1% TFA/5%H2O/95%acetonitrile
Column 1 = (TFA/WATER/MeCN)SunFire C18 & Xbridge Phe

86401-022

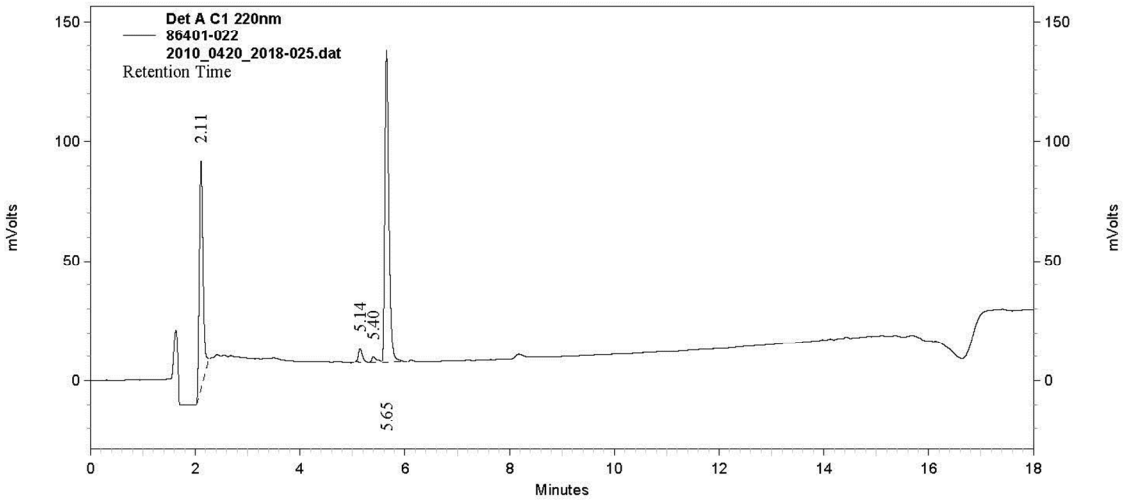
Filename:
c:\shimadzu\data\public\guanglin.luo\20100420\2010_0420_2018-025.dat
Analysis Time: 4/20/2010 8:31:32 PM

Parallel HPLC:
Low pH analysis:
UV detector A (220/254nm): Column#1: Sunfire C18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#2: Xbridge Phenyl 3.5um, 3.0x150mm

High pH analysis:
UV detector A (220/254nm): Column#3: XbridgeC18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#4: Xbridge Phenyl 3.5um, 3.0x150mm

Flow=0.5mL/min on each column

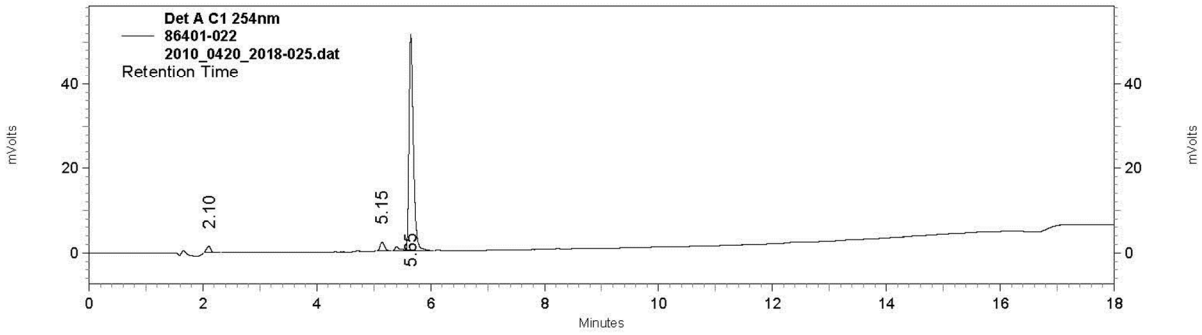
Det A C1 (220nm)



Det A C1 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	2.11	472997	38.93	0.146
2	5.14	28910	2.38	0.155
3	5.40	15222	1.25	0.000
4	5.65	697853	57.44	0.156
Totals		1214982	100.00	

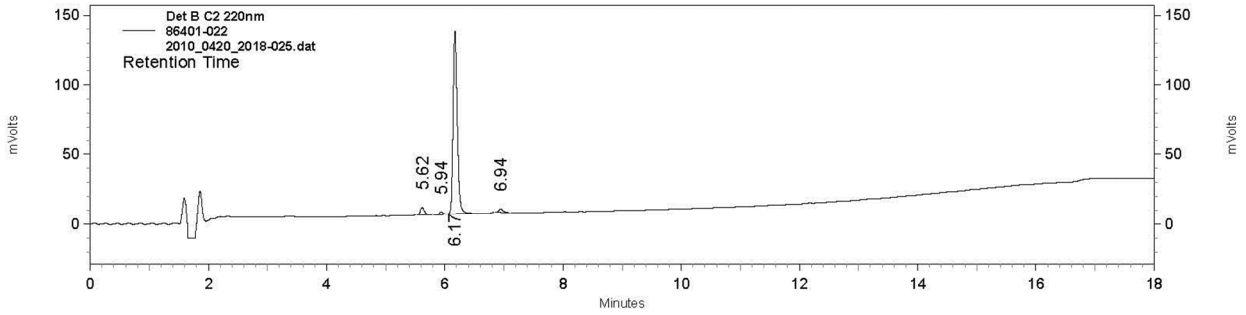
Det A C1 (254nm)



Det A C1
254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	2.10	7603	2.56	0.147
2	5.15	11183	3.77	0.152
3	5.65	277952	93.67	0.155
Totals		296738	100.00	

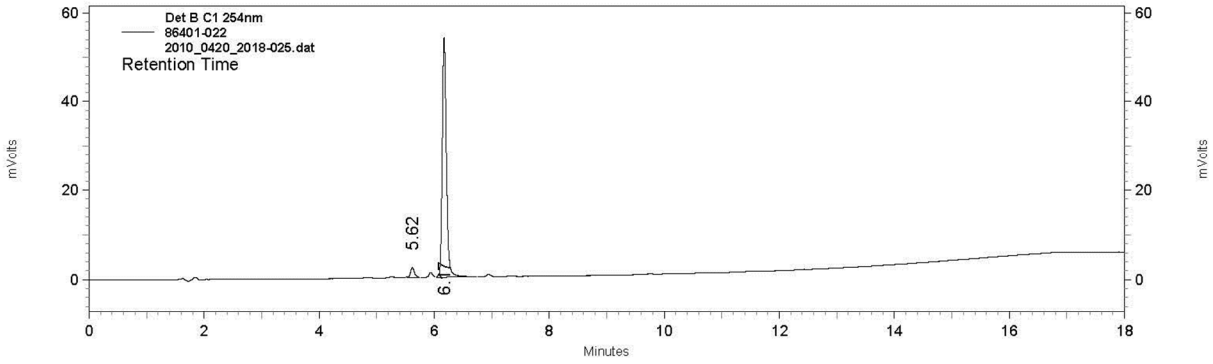
Det B C2 (220 nm)



Det B C2 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	5.62	27169	3.92	0.138
2	5.94	9943	1.44	0.129
3	6.17	640878	92.56	0.141
4	6.94	14383	2.08	0.185
Totals		692373	100.00	

Det B C2 (254 nm)



Det B C1 254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	5.618	10063	3.6	0.134
2	6.171	269079	96.4	0.142
Totals		279142	100.0	

HPLC Report

Sample Name: 86401-022

Method Description: File = 2010_0420_2049.026
User = guanglin.luo
Instrument = WFD-489C-HPLC1
Vial = 5 Inj. Vol. = 5 uL
Start % B = 10
Final % B = 100
Gradient Time = 15 min
Flow Rate = 1 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = 10mM amm. bicarb/H2O/MeOH
Solvent A = 10mM amm. bicarbonate (pH=9.5)/95%H2O/5%methar
Solvent B = 10mM amm. bicarbonate (pH=9.5)/5%H2O/95%methar
Column 2 = (AMMBICARB/WATER/MeOH) Xbridge C18 & 2

86401-022

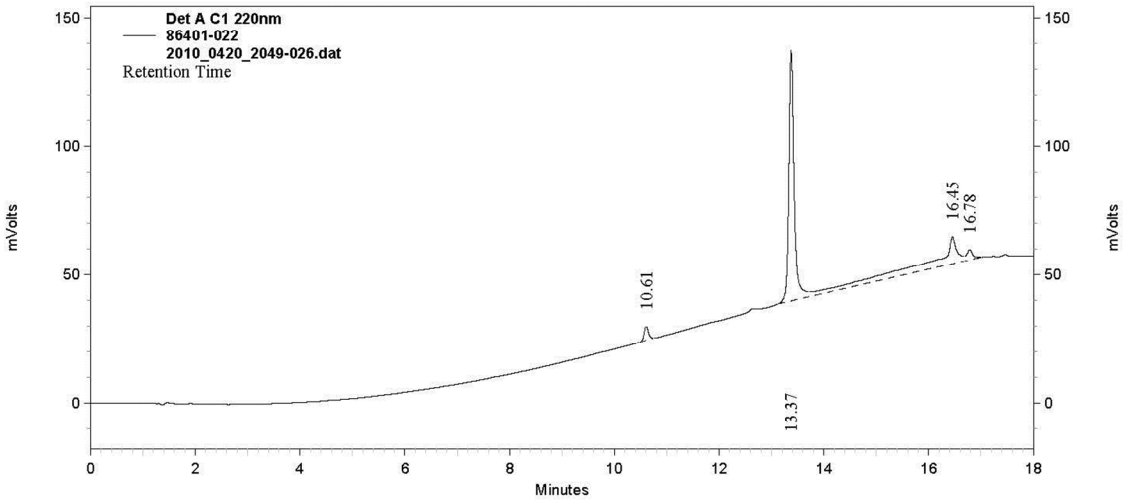
Filename:
c:\shimadzu\data\public\guanglin.luo\20100420\2010_0420_2049-026.dat
Analysis Time: 4/20/2010 8:58:57 PM

Parallel HPLC:
Low pH analysis:
UV detector A (220/254nm): Column#1: Sunfire C18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#2: Xbridge Phenyl 3.5um, 3.0x150mm

High pH analysis:
UV detector A (220/254nm): Column#3: XbridgeC18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#4: Xbridge Phenyl 3.5um, 3.0x150mm

Flow=0.5mL/min on each column

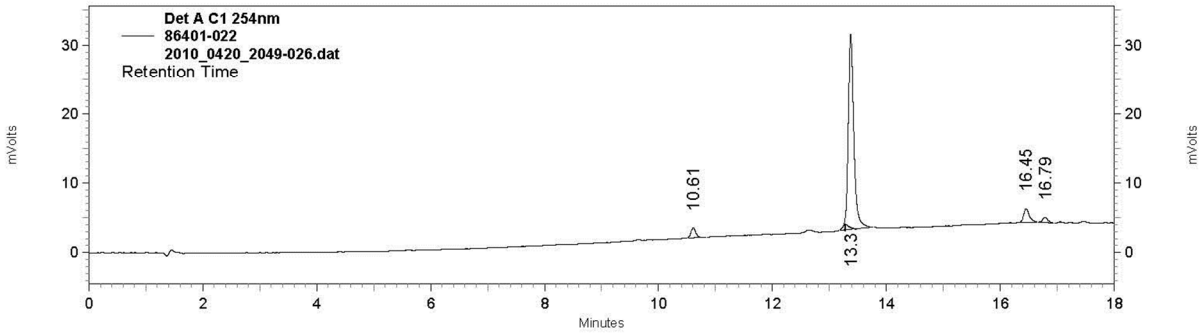
Det A C1 (220nm)



Det A C1 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	10.61	30527	2.59	0.167
2	13.37	687777	58.31	0.209
3	16.45	427441	36.24	0.000
4	16.78	33815	2.87	0.000
Totals		1179560	100.00	

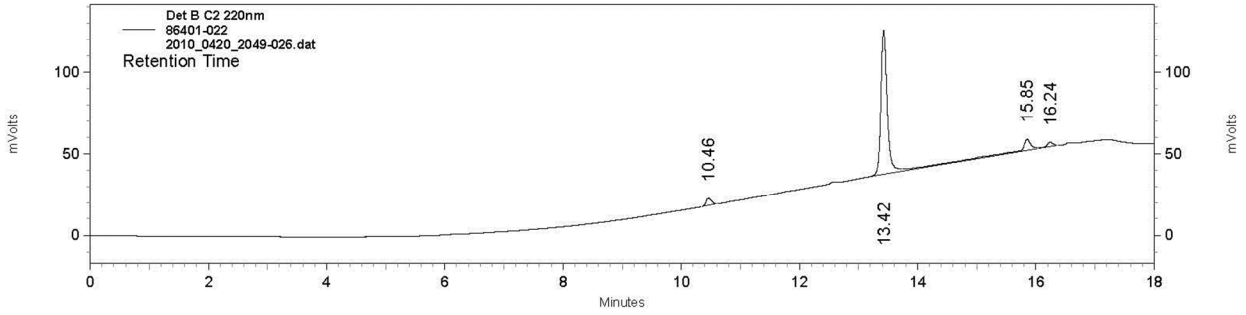
Det A C1 (254nm)



Det A C1
254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	10.61	8511	3.90	0.177
2	13.37	191472	87.64	0.202
3	16.45	13454	6.16	0.215
4	16.79	5046	2.31	0.222
Totals		218483	100.00	

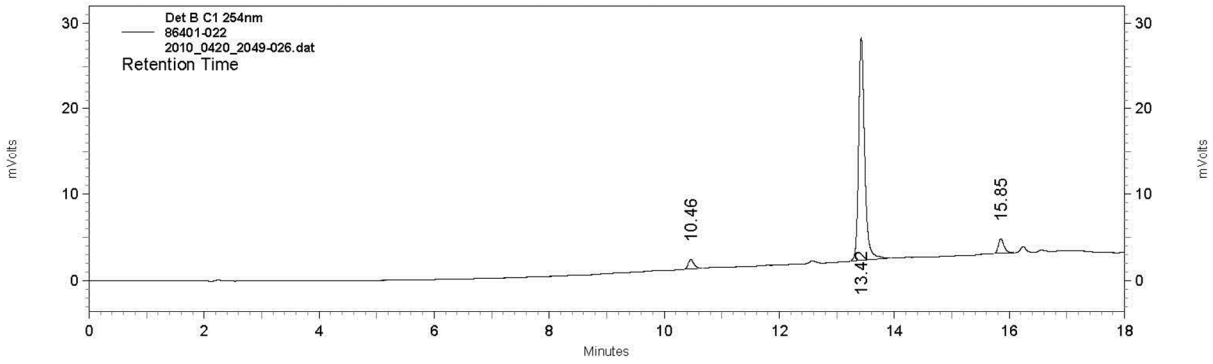
Det B C2 (220 nm)



Det B C2 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	10.46	27165	3.30	0.184
2	13.42	647175	78.64	0.215
3	15.85	128881	15.66	1.206
4	16.24	19724	2.40	0.202
Totals		822945	100.00	

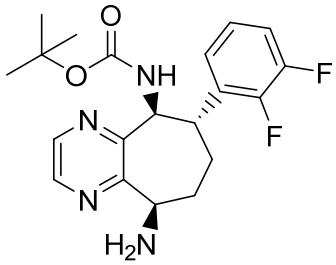
Det B C2 (254 nm)



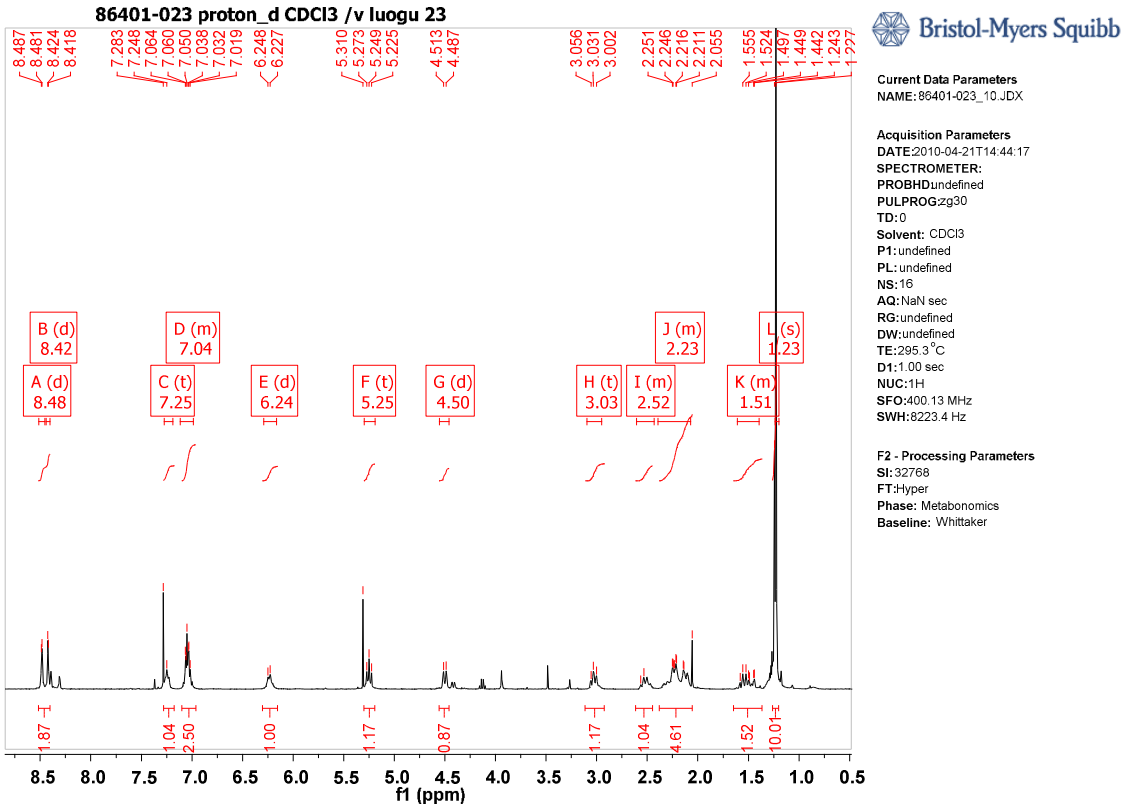
Det B C1 254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	10.461	7375	3.5	0.197
2	13.422	189233	91.0	0.212
3	15.849	11397	5.5	0.208
Totals		208005	100.0	

^{1}H NMR of 21:

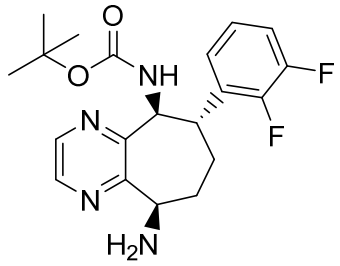


21

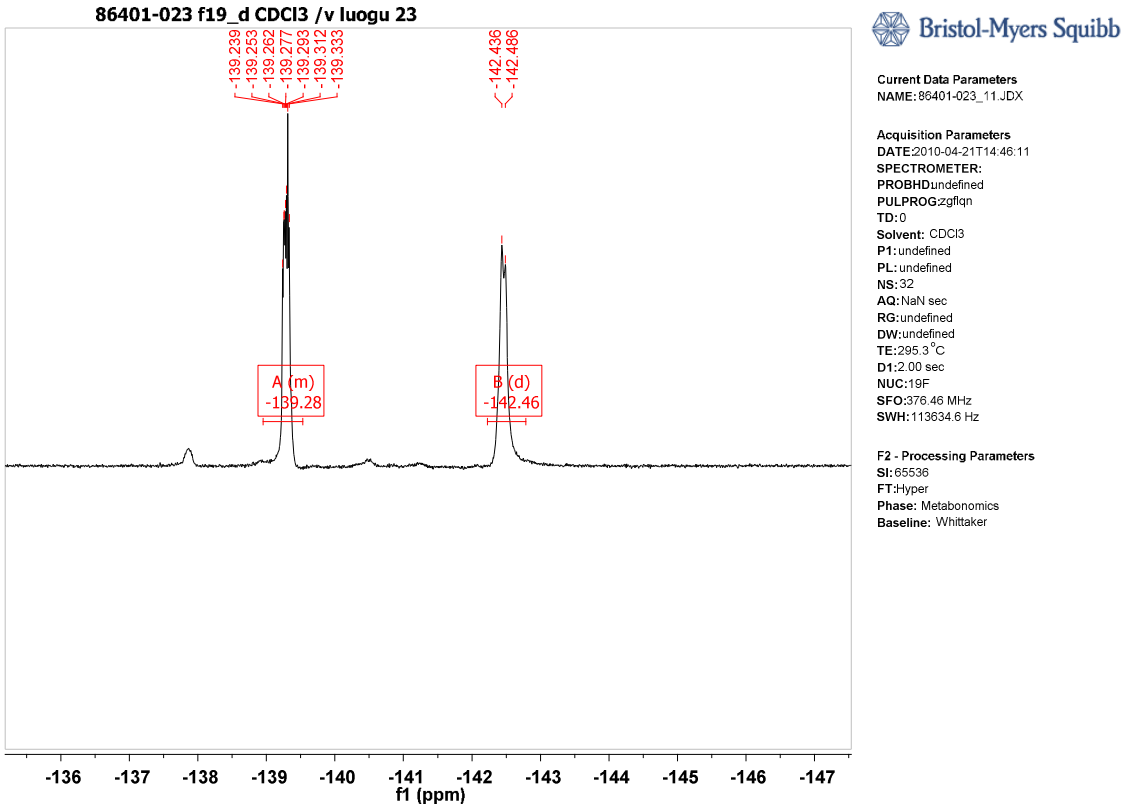


^{1}H NMR (400 MHz, CDCl3) δ 8.48 (d, J = 2.3 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 6.4 Hz, 1H), 7.12 – 6.98 (m, 2H), 6.24 (d, J = 8.6 Hz, 1H), 5.25 (t, J = 9.5 Hz, 1H), 4.50 (d, J = 10.2 Hz, 1H), 3.03 (t, J = 10.7 Hz, 1H), 2.60 – 2.43 (m, 1H), 2.39 – 2.07 (m, 4H), 1.61 – 1.40 (m, 1H), 1.23 (s, 9H).

^{19}F NMR of 21:

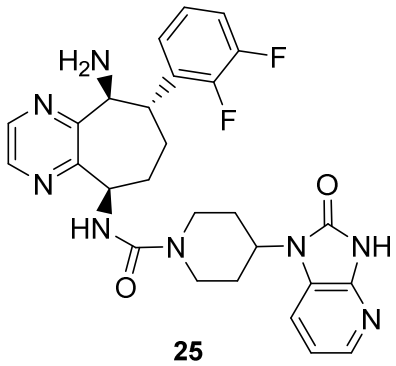


21

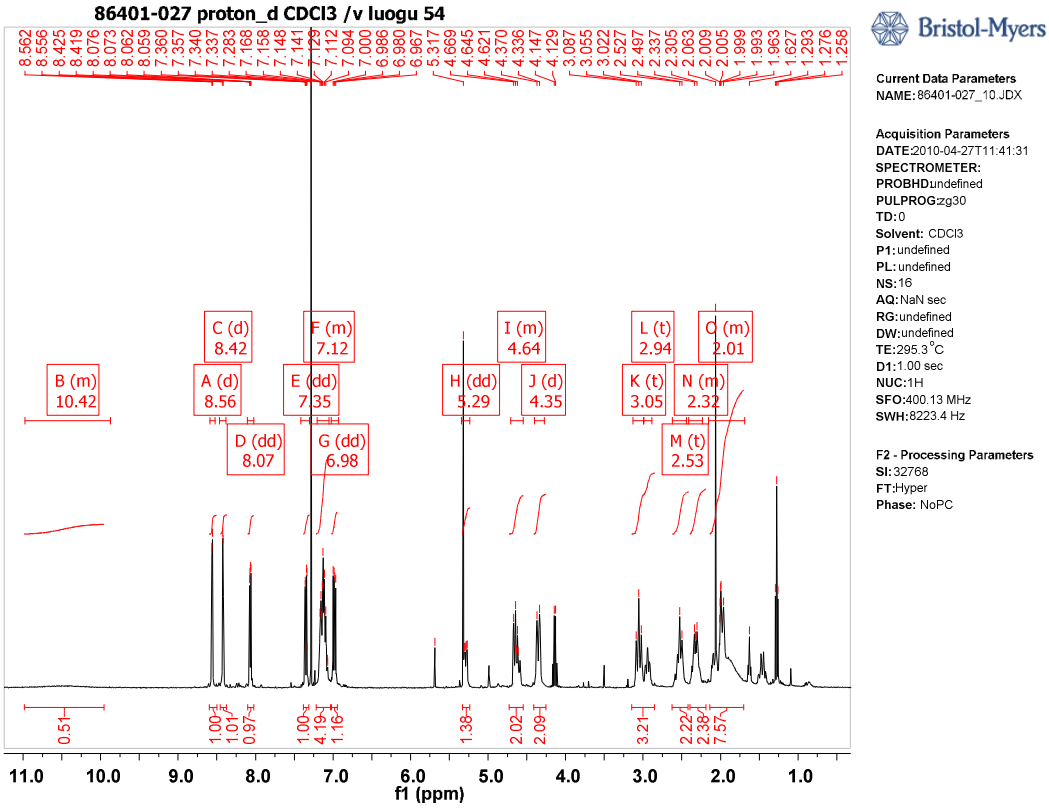


^{19}F NMR (376 MHz, $CDCl_3$) δ -138.95 – -139.53 (m), -142.46 (d, J = 18.8 Hz).

^{1}H NMR of 25:

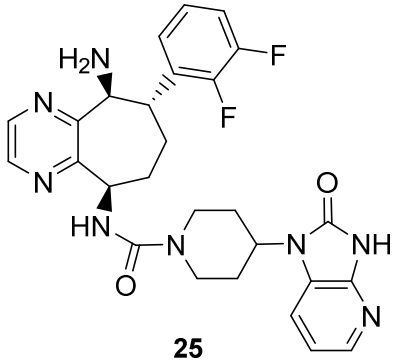


25



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 – 9.87 (m, 1H), 8.56 (d, *J* = 2.5 Hz, 1H), 8.42 (d, *J* = 2.5 Hz, 1H), 8.07 (dd, *J* = 5.3, 1.2 Hz, 1H), 7.35 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.21 – 7.05 (m, 4H), 6.98 (dd, *J* = 7.9, 5.3 Hz, 1H), 5.29 (dd, *J* = 10.4, 5.1 Hz, 1H), 4.71 – 4.55 (m, 2H), 4.35 (d, *J* = 13.6 Hz, 2H), 3.05 (t, *J* = 13.0 Hz, 2H), 2.94 (t, *J* = 9.3 Hz, 1H), 2.53 (t, *J* = 11.7 Hz, 2H), 2.41 – 2.23 (m, 2H), 2.16 – 1.69 (m, 6H).

Analytical HPLC for 25 (6 pages):



25

HPLC Report

Sample Name: 86401-027

Method Description: File = 2010_0427_1417.010
User = guanglin.luo
Instrument = WFD-489C-HPLC1
Vial = 2 Inj. Vol. = 5 uL
Start % B = 10
Final % B = 100
Gradient Time = 15 min
Flow Rate = 1 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = 0.1%TFA/H2O/MeCN
Solvent A = 0.1% TFA/95%H2O/5%acetonitrile
Solvent B = 0.1% TFA/5%H2O/95%acetonitrile
Column 1 = (TFA/WATER/MeCN)SunFire C18 & Xbridge Phe

86401-027

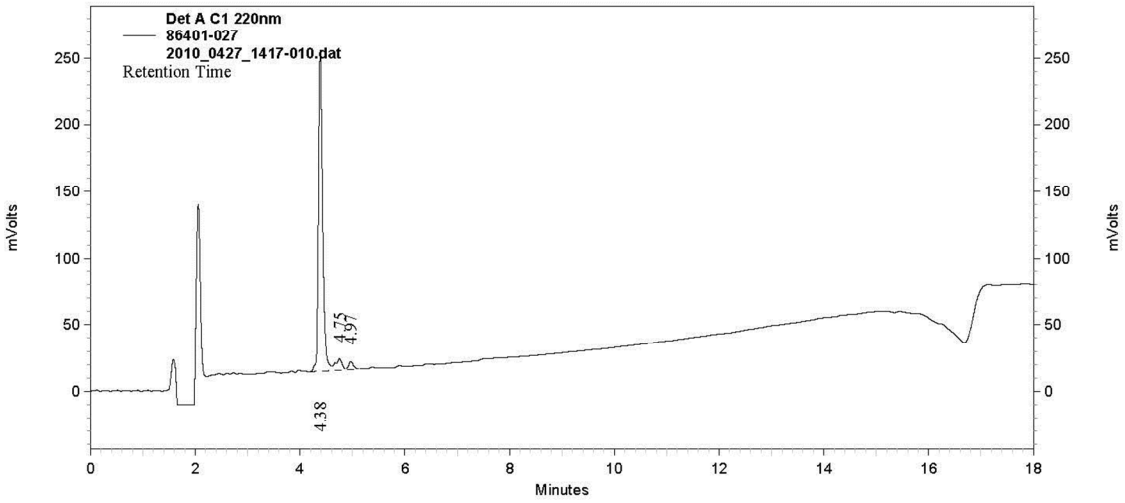
Filename:
c:\shimadzu\data\public\guanglin.luo\20100427\2010_0427_1417-010.dat
Analysis Time: 4/27/2010 2:25:59 PM

Parallel HPLC:
Low pH analysis:
UV detector A (220/254nm): Column#1: Sunfire C18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#2: Xbridge Phenyl 3.5um, 3.0x150mm

High pH analysis:
UV detector A (220/254nm): Column#3: XbridgeC18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#4: Xbridge Phenyl 3.5um, 3.0x150mm

Flow=0.5mL/min on each column

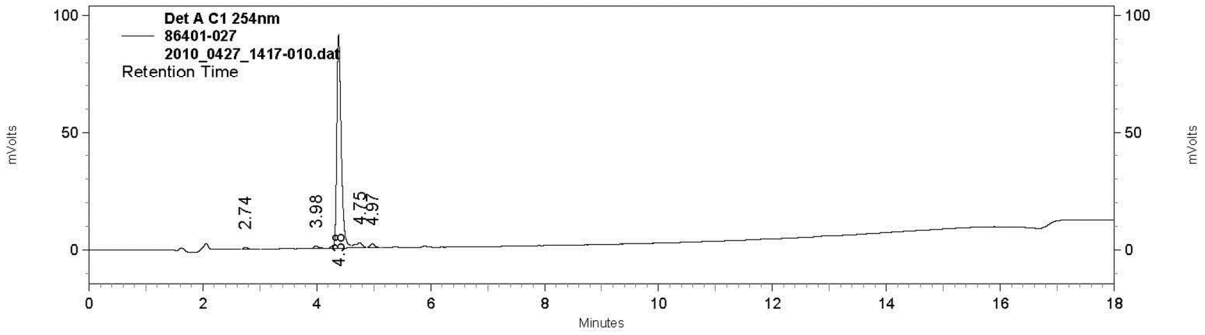
Det A C1 (220nm)



Det A C1 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	4.38	1340657	92.39	0.161
2	4.75	74070	5.10	0.000
3	4.97	36346	2.50	0.000
Totals		1451073	100.00	

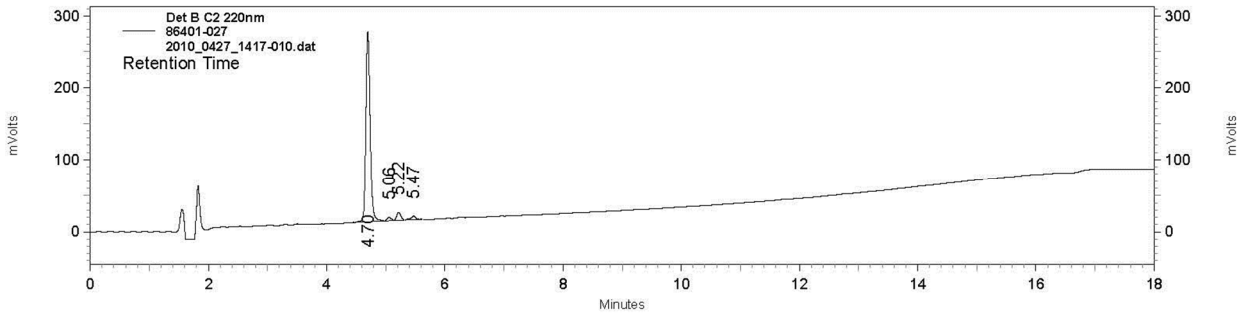
Det A C1 (254nm)



Det A C1
254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	2.74	4512	0.84	0.209
2	3.98	6231	1.16	0.201
3	4.38	494891	92.42	0.158
4	4.75	19894	3.72	0.000
5	4.97	9932	1.85	0.180
Totals		535460	100.00	

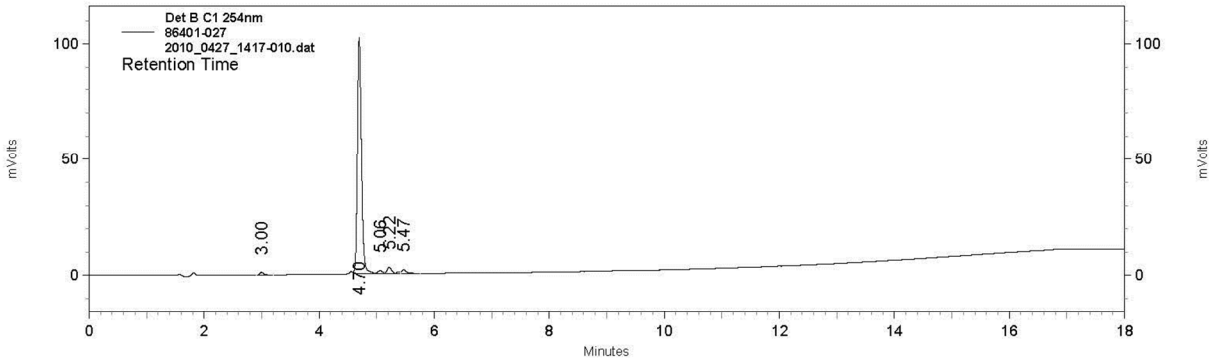
Det B C2 (220 nm)



Det B C2 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	4.70	1326619	92.37	0.144
2	5.06	24483	1.70	0.000
3	5.22	52701	3.67	0.147
4	5.47	32437	2.26	0.203
Totals		1436240	100.00	

Det B C2 (254 nm)



Det B C1 254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	2.998	6079	1.1	0.160
2	4.696	503506	92.6	0.141
3	5.058	8181	1.5	0.000
4	5.218	15034	2.8	0.000
5	5.471	10859	2.0	0.000

Totals				
		543659	100.0	

HPLC Report

Sample Name: 86401-027

Method Description: File = 2010_0427_1444.011
User = guanglin.luo
Instrument = WFD-489C-HPLC1
Vial = 2 Inj. Vol. = 5 uL
Start % B = 10
Final % B = 100
Gradient Time = 15 min
Flow Rate = 1 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = 10mM amm. bicarb/H2O/MeOH
Solvent A = 10mM amm. bicarbonate (pH=9.5)/95%H2O/5%methar
Solvent B = 10mM amm. bicarbonate (pH=9.5)/5%H2O/95%methar
Column 2 = (AMMBICARB/WATER/MeOH) Xbridge C18 & 2

86401-027

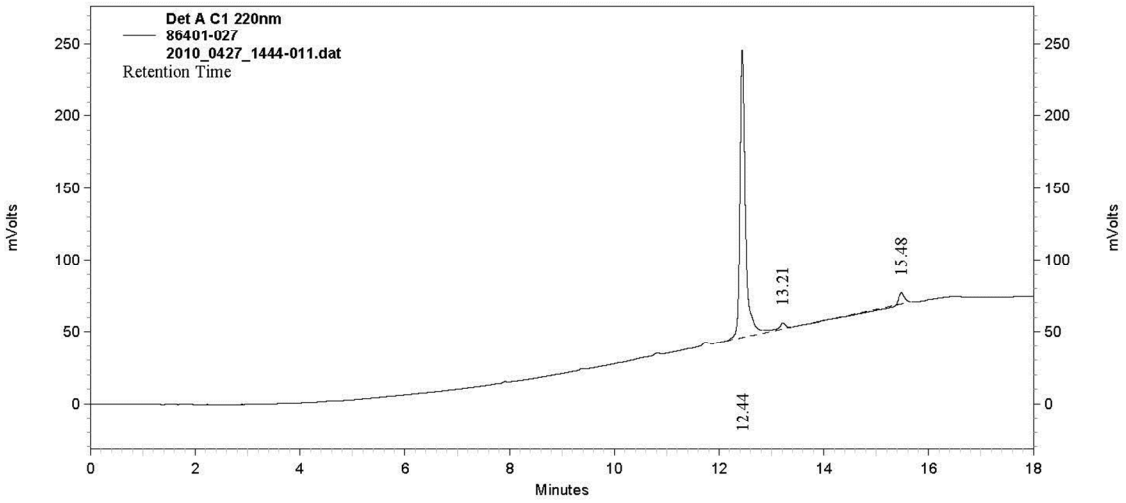
Filename:
c:\shimadzu\data\public\guanglin.luo\20100427\2010_0427_1444-011.dat
Analysis Time: 4/27/2010 2:53:18 PM

Parallel HPLC:
Low pH analysis:
UV detector A (220/254nm): Column#1: Sunfire C18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#2: Xbridge Phenyl 3.5um, 3.0x150mm

High pH analysis:
UV detector A (220/254nm): Column#3: XbridgeC18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#4: Xbridge Phenyl 3.5um, 3.0x150mm

Flow=0.5mL/min on each column

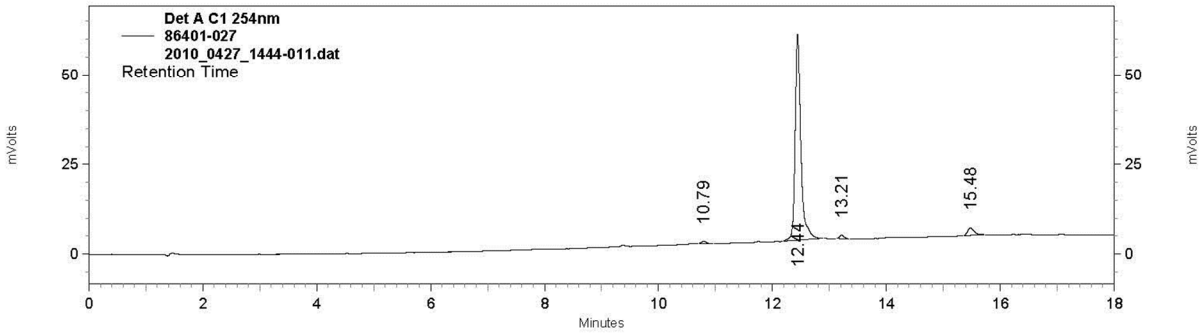
Det A C1 (220nm)



Det A C1 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	12.44	1451235	95.28	0.216
2	13.21	54674	3.59	0.000
3	15.48	17261	1.13	0.222
Totals		1523170	100.00	

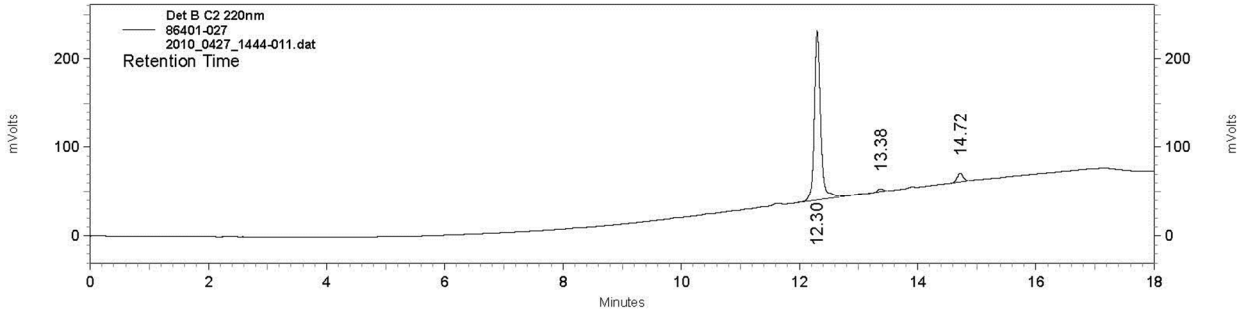
Det A C1 (254nm)



Det A C1
254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	10.79	4338	1.01	0.189
2	12.44	401499	93.73	0.207
3	13.21	5484	1.28	0.163
4	15.48	17039	3.98	0.239
Totals		428360	100.00	

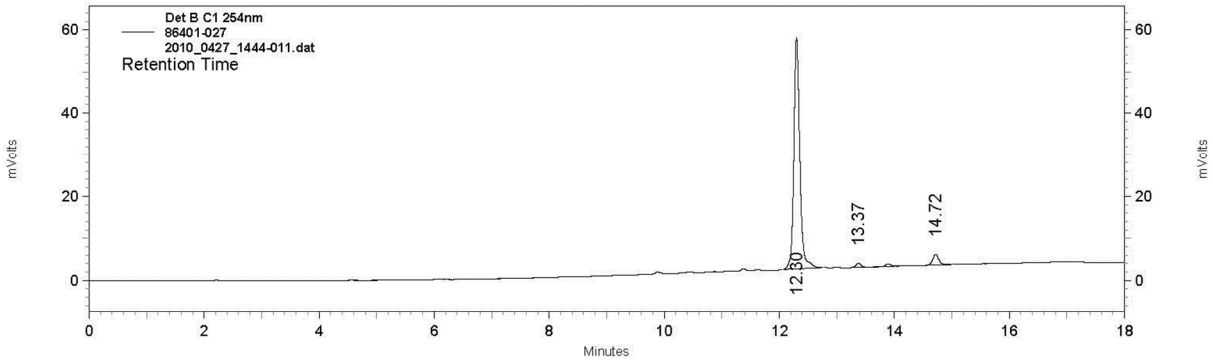
Det B C2 (220 nm)



Det B C2 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	12.30	1409283	93.26	0.212
2	13.38	34796	2.30	0.168
3	14.72	67129	4.44	0.204
Totals		1511208	100.00	

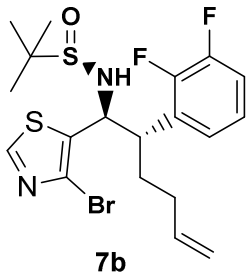
Det B C2 (254 nm)



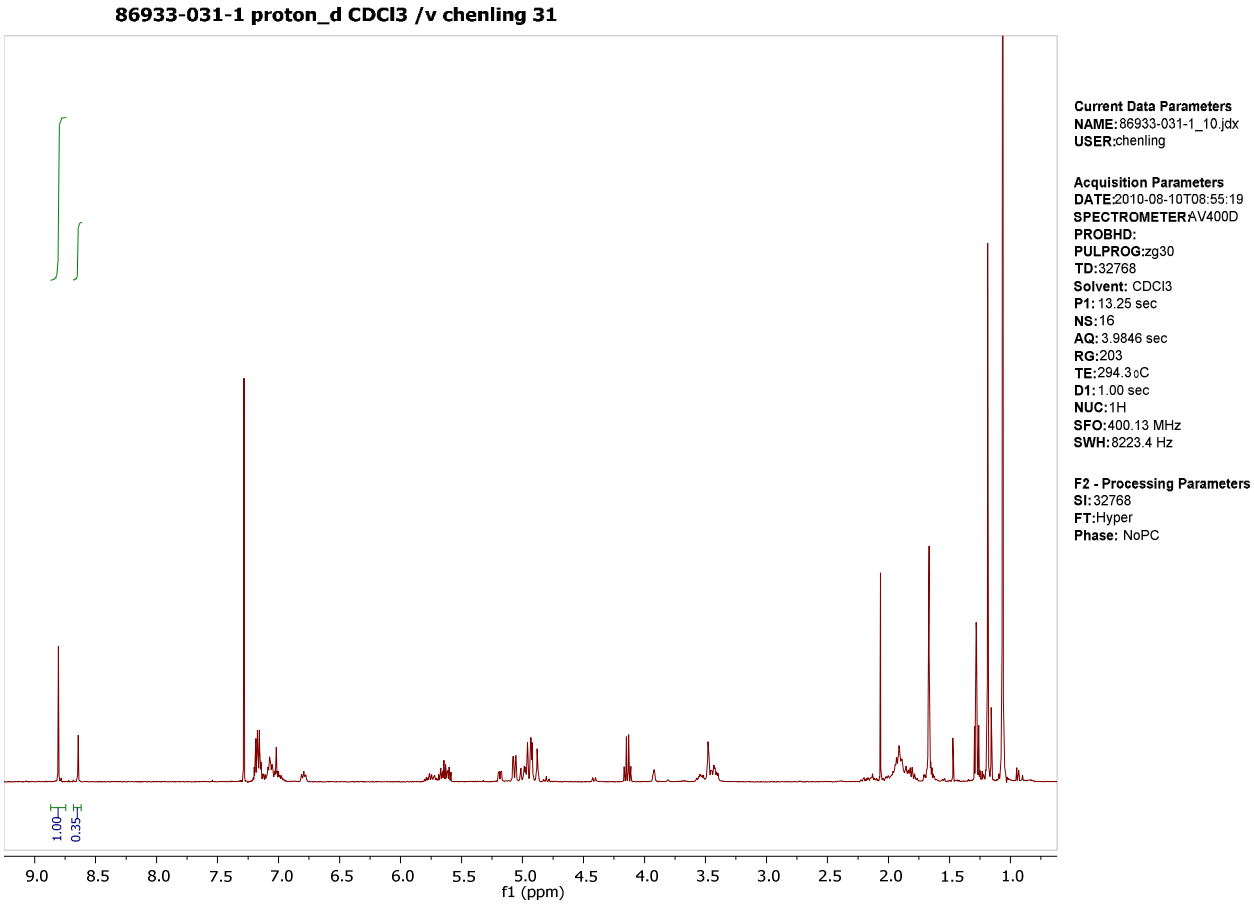
Det B C1 254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	12.299	395031	94.1	0.206
2	13.369	6000	1.4	0.183
3	14.716	18826	4.5	0.218
Totals		419857	100.0	

^{1}H NMR of 7b:

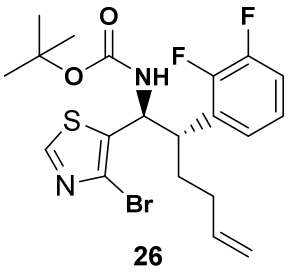


7b

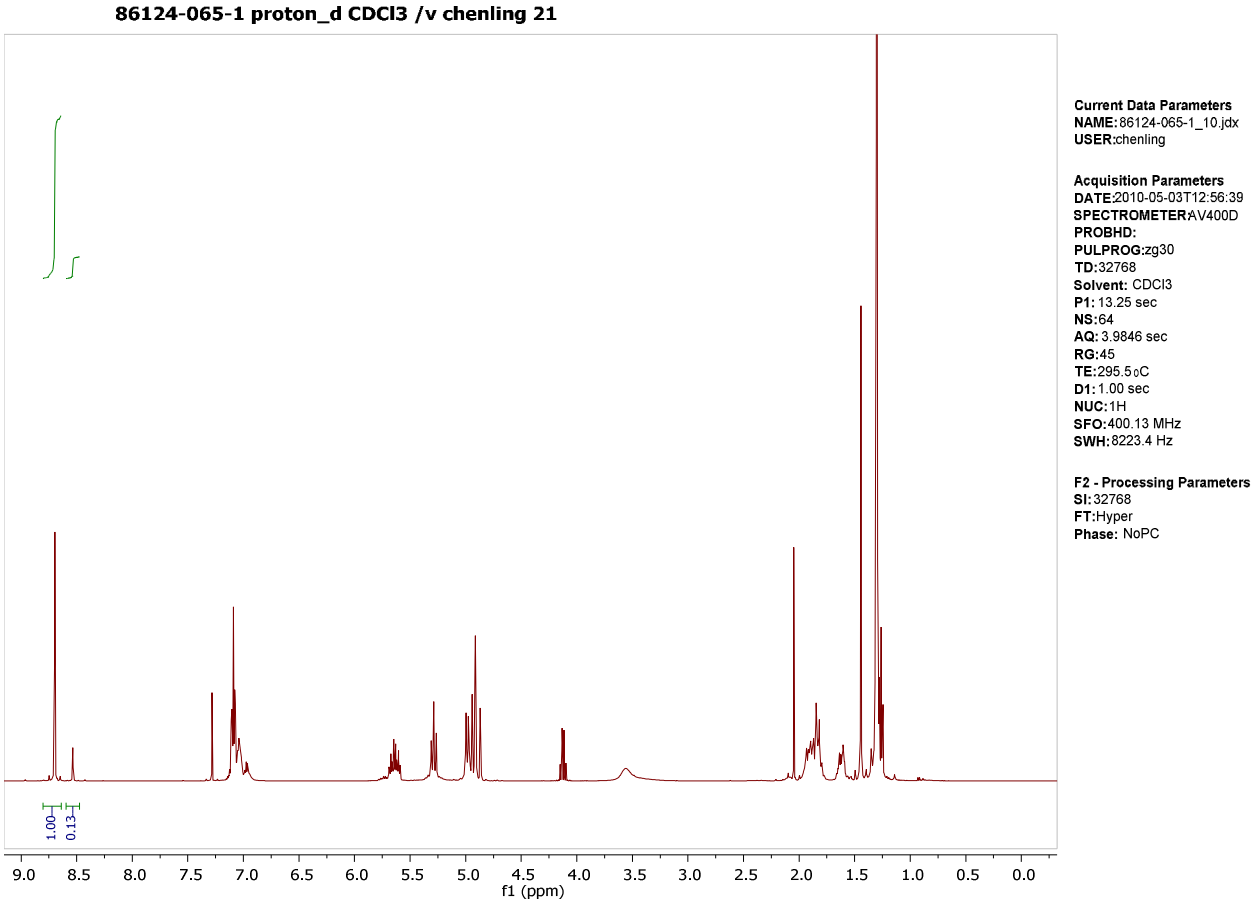


Diastereomeric ratio was roughly estimated based on the thiazole proton.

^{1}H NMR of 26:

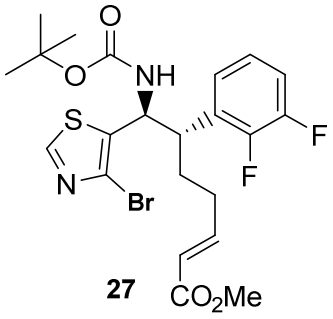


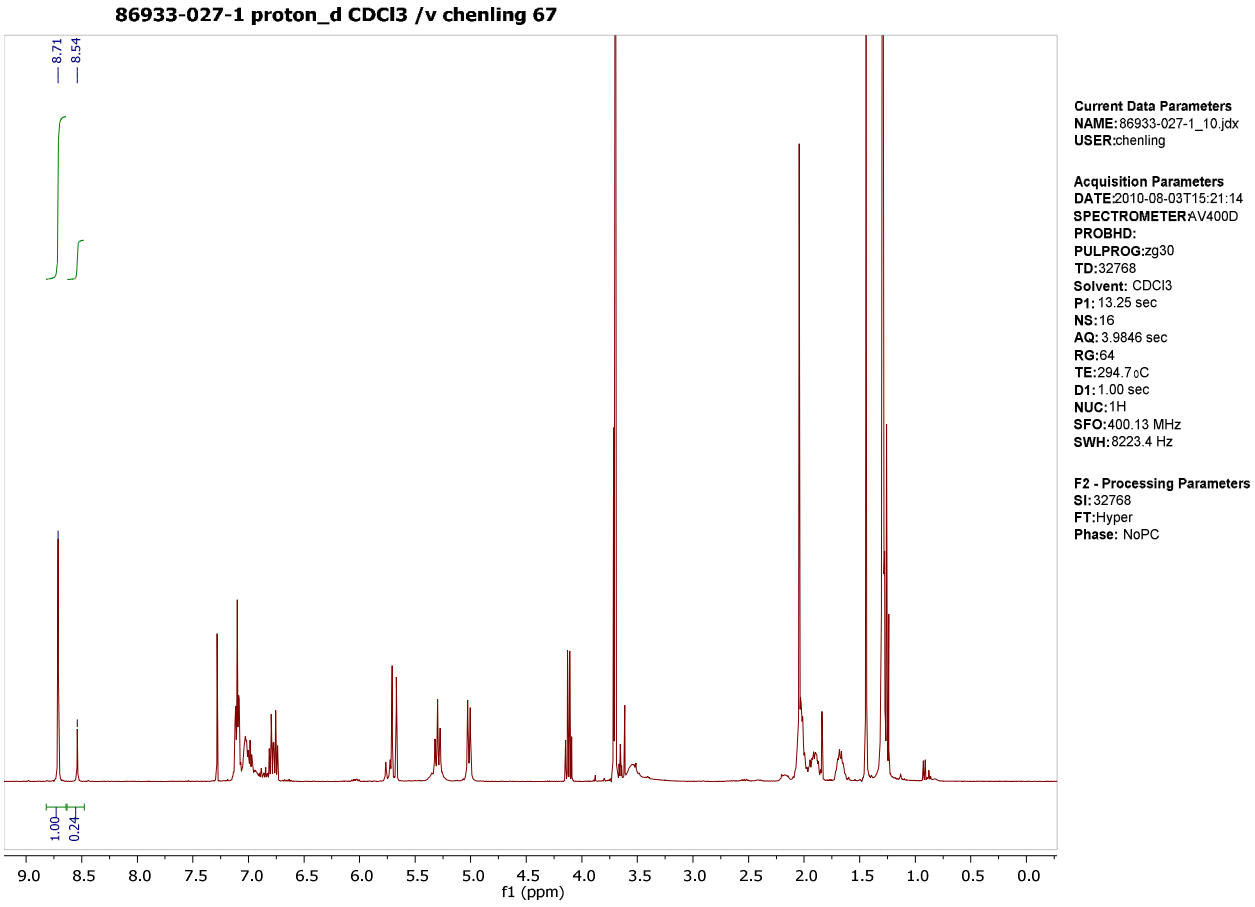
26



Diastereomeric ratio was roughly estimated based on the thiazole proton.

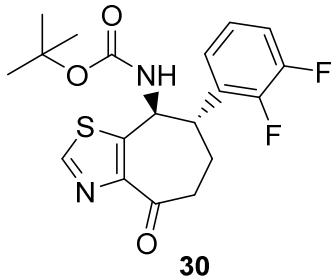
^{1}H NMR of 27:



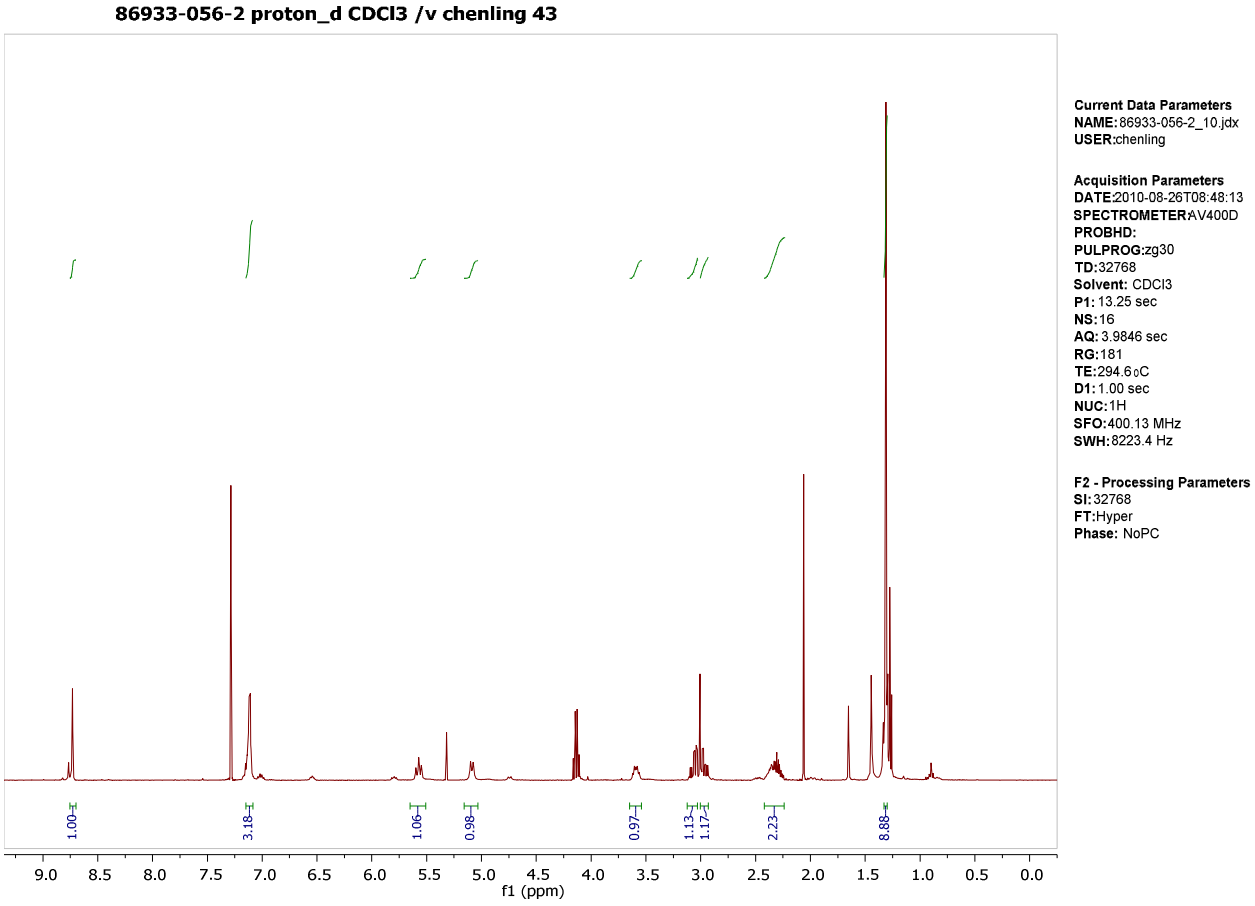


Diastereomeric ratio was roughly estimated based on the thiazole proton.

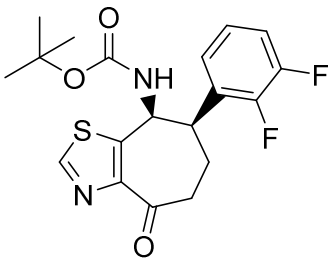
^{1}H NMR of 30:

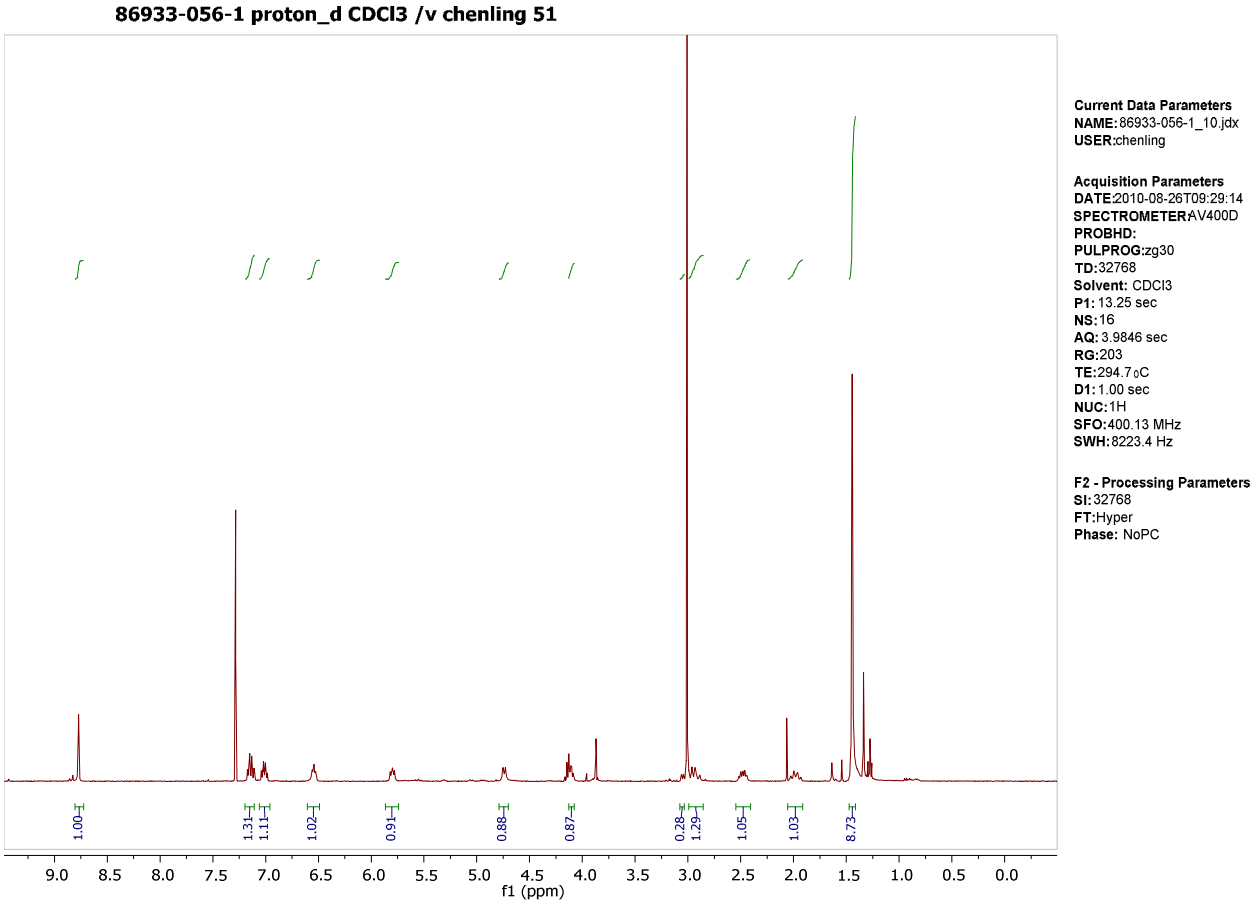


30

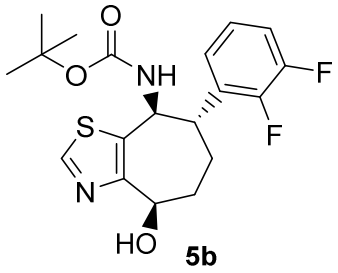


^{1}H NMR of diastereomeric 30:

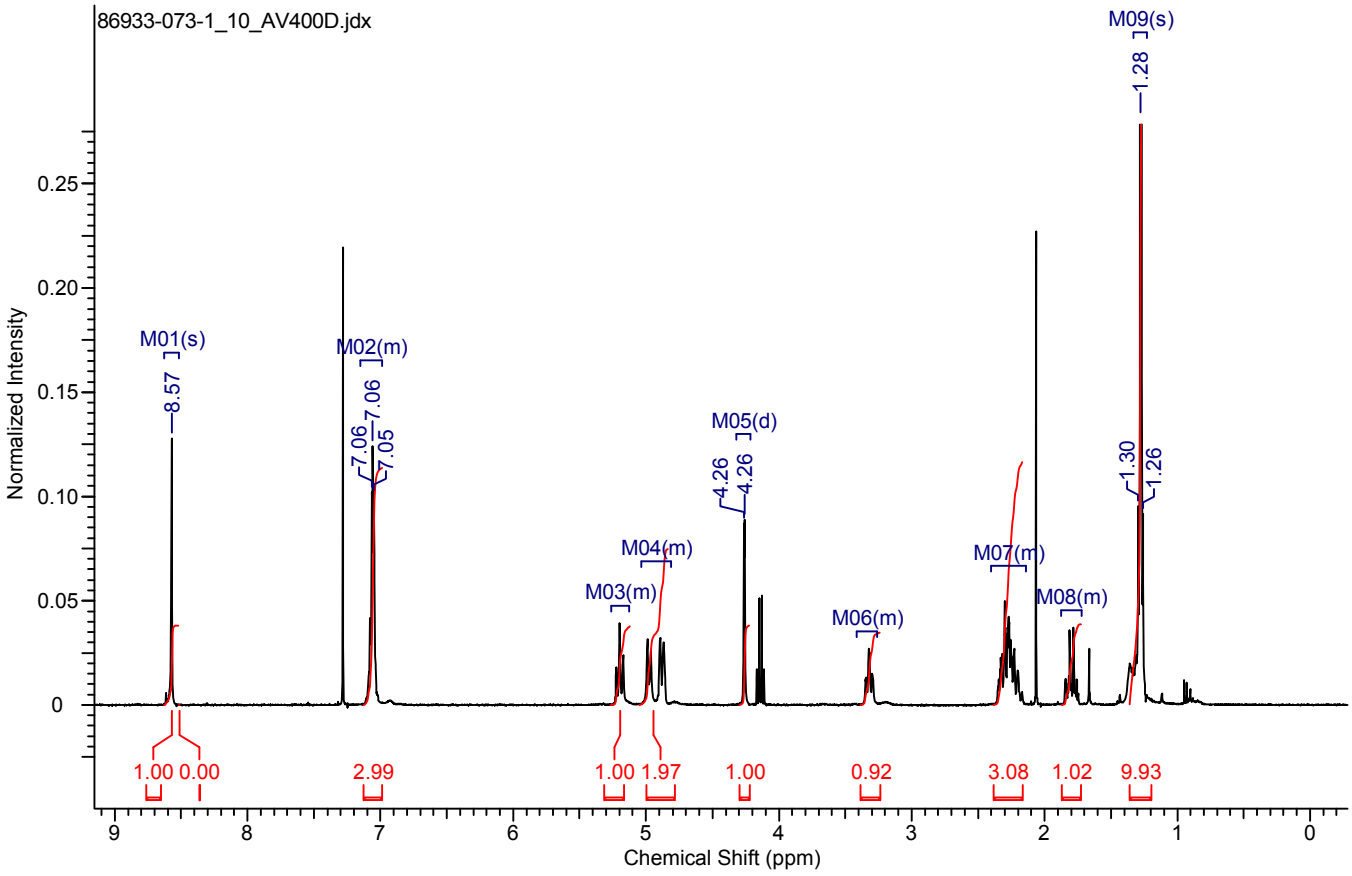




[1]H NMR of 5b:

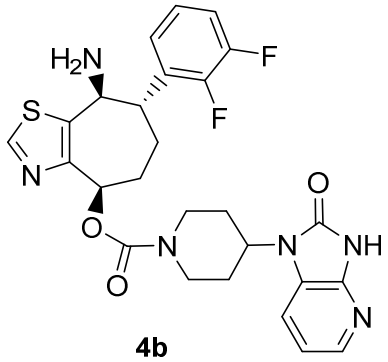


5b

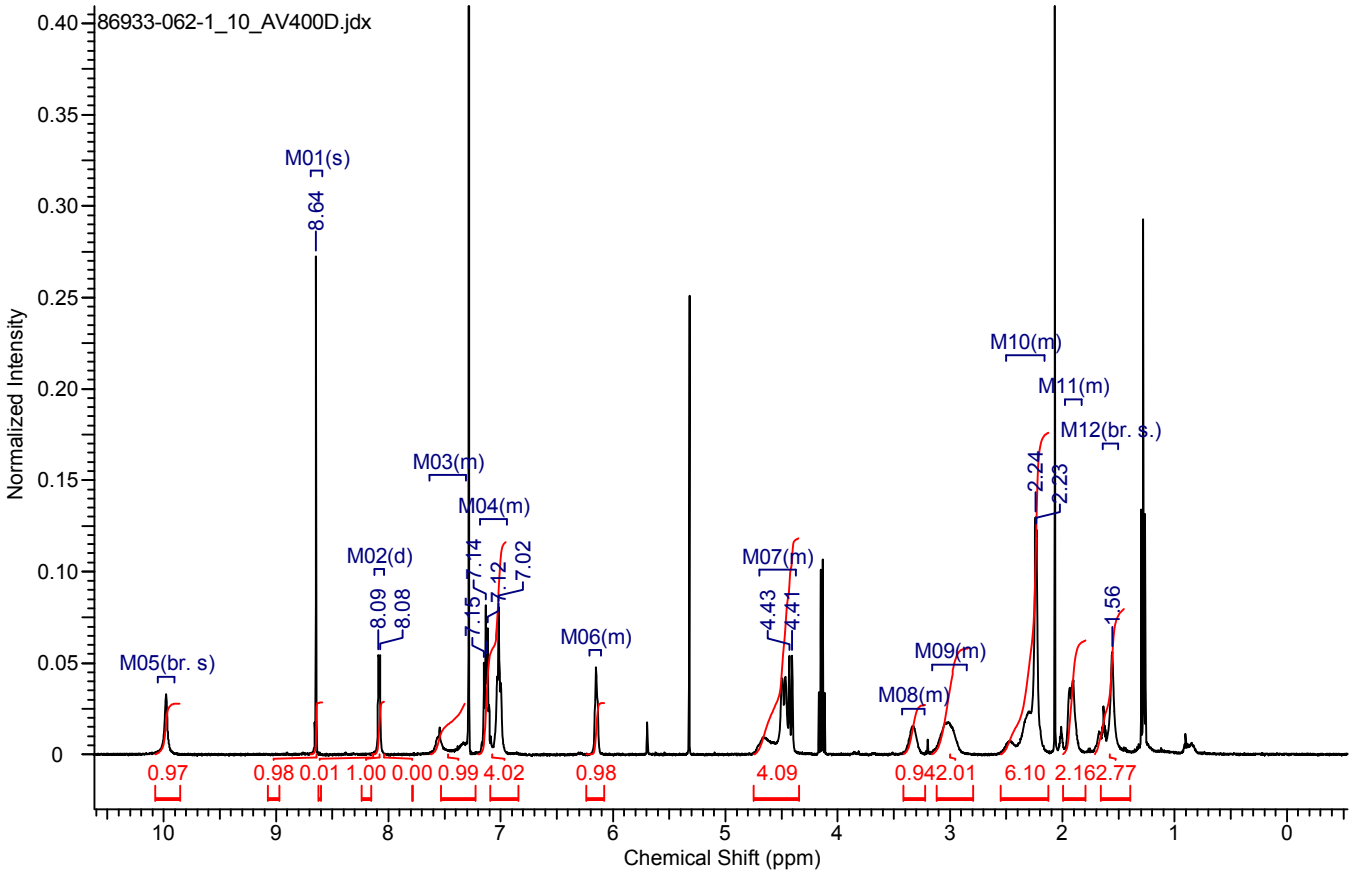


[1]H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.57 (1 H, s), 6.99 - 7.15 (3 H, m), 5.13 - 5.26 (1 H, m), 4.81 - 5.03 (2 H, m), 4.26 (1 H, d, *J*=2.0 Hz), 3.26 - 3.42 (1 H, m), 2.14 - 2.40 (3 H, m), 1.72 - 1.88 (1 H, m), 1.28 (9 H, s).

[1]H NMR of 4b:

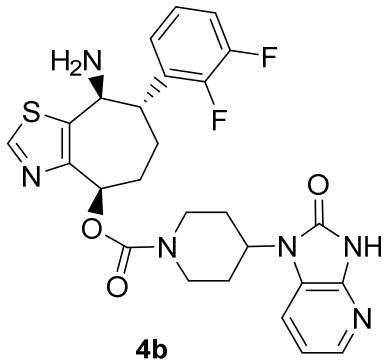


4b



[1]H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.98 (1 H, br. s), 8.64 (1 H, s), 8.08 (1 H, d, *J*=4.8 Hz), 7.31 - 7.64 (1 H, m), 6.94 - 7.19 (4 H, m), 6.11 - 6.21 (1 H, m), 4.42 (4 H, m), 3.23 - 3.43 (1 H, m), 2.85 - 3.16 (2 H, m), 2.24 (6 H, m), 1.83 - 1.98 (2 H, m), 1.56 (2 H, br. m).

Analytical HPLC for 4b (6 pages):



4b

HPLC Report

Sample Name: 86933-062-1

Method Description: File = 2010_0902_1613.005
User = ling.chen1
Instrument = WFD-489C-HPLC1
Vial = 3 Inj. Vol. = 5 uL
Start % B = 10
Final % B = 100
Gradient Time = 15 min
Flow Rate = 1 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = 0.1%TFA/H2O/MeCN
Solvent A = 0.1% TFA/95%H2O/5%acetonitrile
Solvent B = 0.1% TFA/5%H2O/95%acetonitrile
Column 1 = (TFA/WATER/MeCN)SunFire C18 & Xbridge Phe

86933-062-1

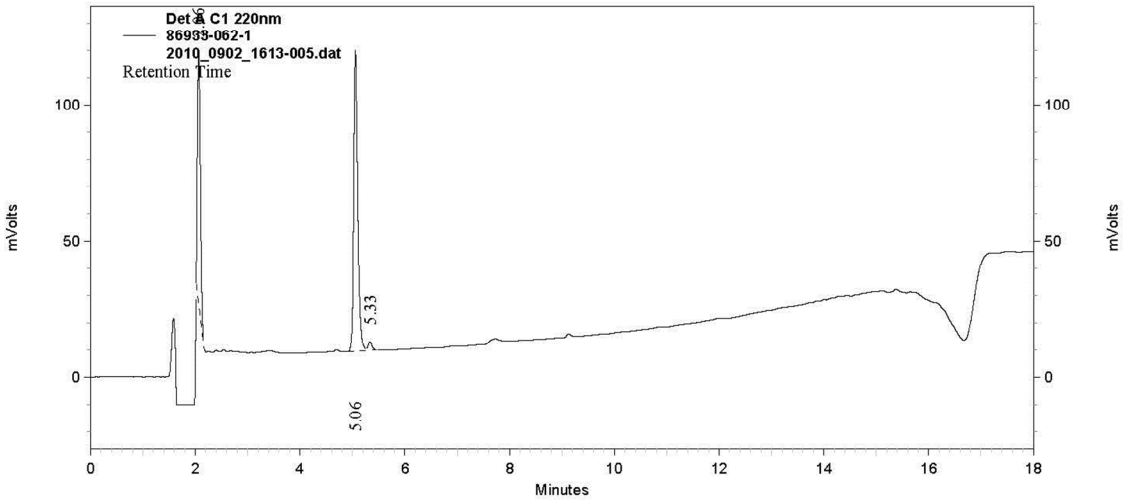
Filename:
c:\shimadzu\data\public\ling.chen1\20100902\2010_0902_1613-005.dat
Analysis Time: 9/2/2010 4:21:36 PM

Parallel HPLC:
Low pH analysis:
UV detector A (220/254nm): Column#1: Sunfire C18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#2: Xbridge Phenyl 3.5um, 3.0x150mm

High pH analysis:
UV detector A (220/254nm): Column#3: XbridgeC18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#4: Xbridge Phenyl 3.5um, 3.0x150mm

Flow=0.5mL/min on each column

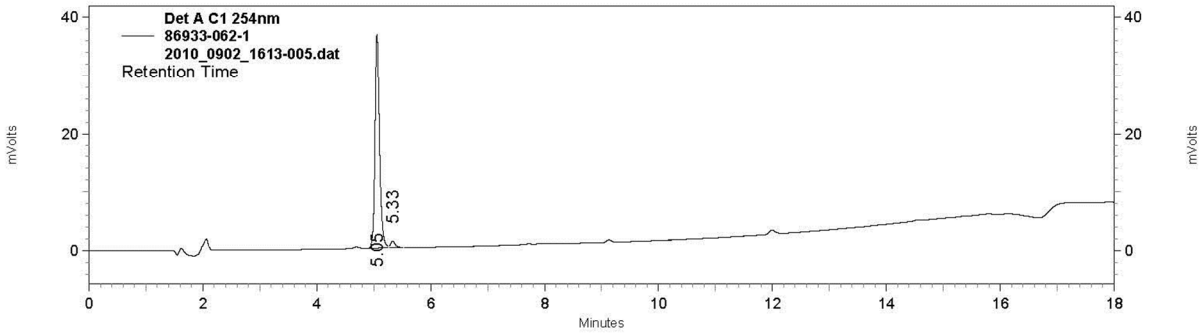
Det A C1 (220nm)



Det A C1
220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	2.06	372802	37.91	0.110
2	5.06	593610	60.37	0.159
3	5.33	16865	1.72	0.000
Totals		983277	100.00	

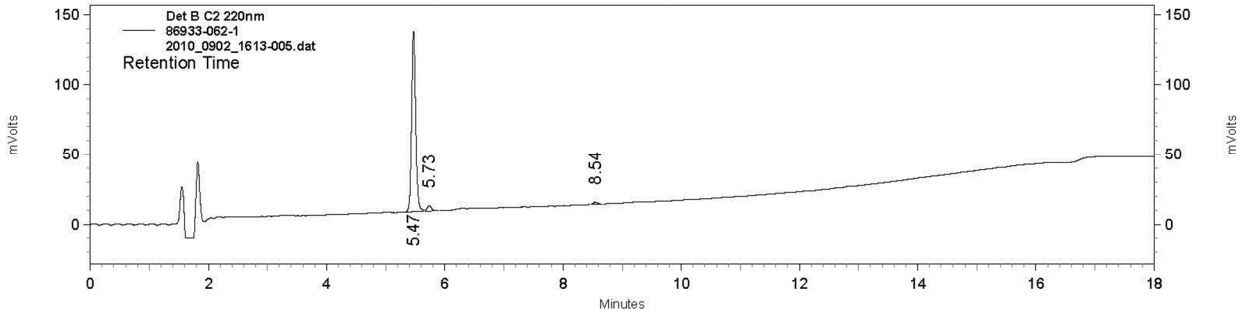
Det A C1 (254nm)



Det A C1
254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	5.05	201238	97.00	0.165
2	5.33	6223	3.00	0.000
Totals		207461	100.00	

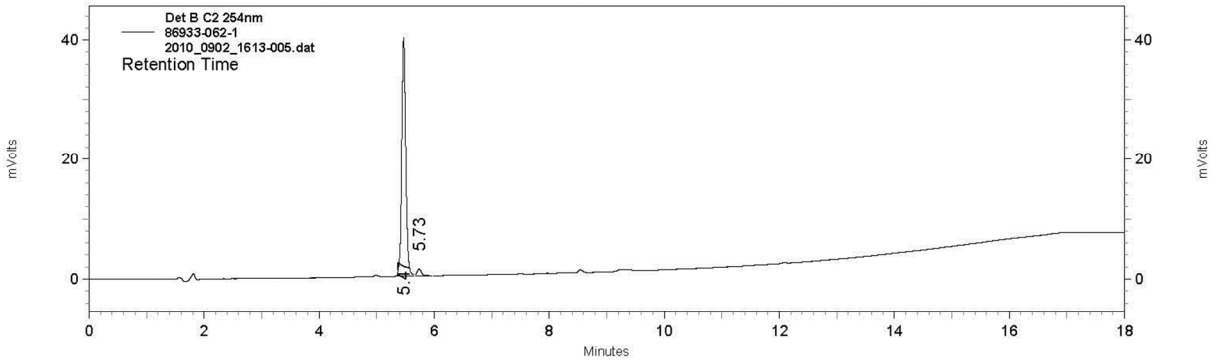
Det B C2 (220 nm)



Det B C2 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	5.47	618699	95.82	0.139
2	5.73	19962	3.09	0.000
3	8.54	7049	1.09	0.142
Totals		645710	100.00	

Det B C2 (254 nm)



Det B C2 254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	5.468	195369	96.9	0.145
2	5.735	6338	3.1	0.000
Totals		201707	100.0	

HPLC Report

Sample Name: 86933-062-1

Method Description: File = 2010_0902_1639.006
User = ling.chen1
Instrument = WFD-489C-HPLC1
Vial = 3 Inj. Vol. = 5 uL
Start % B = 10
Final % B = 100
Gradient Time = 15 min
Flow Rate = 1 ml/min
Wavelength1 = 220
Wavelength2 = 254
Solvent Pair = 10mM amm. bicarb/H2O/MeOH
Solvent A = 10mM amm. bicarbonate (pH=9.5)/95%H2O/5%methar
Solvent B = 10mM amm. bicarbonate (pH=9.5)/5%H2O/95%methar
Column 2 = (AMMBICARB/WATER/MeOH) Xbridge C18 & 2

86933-062-1

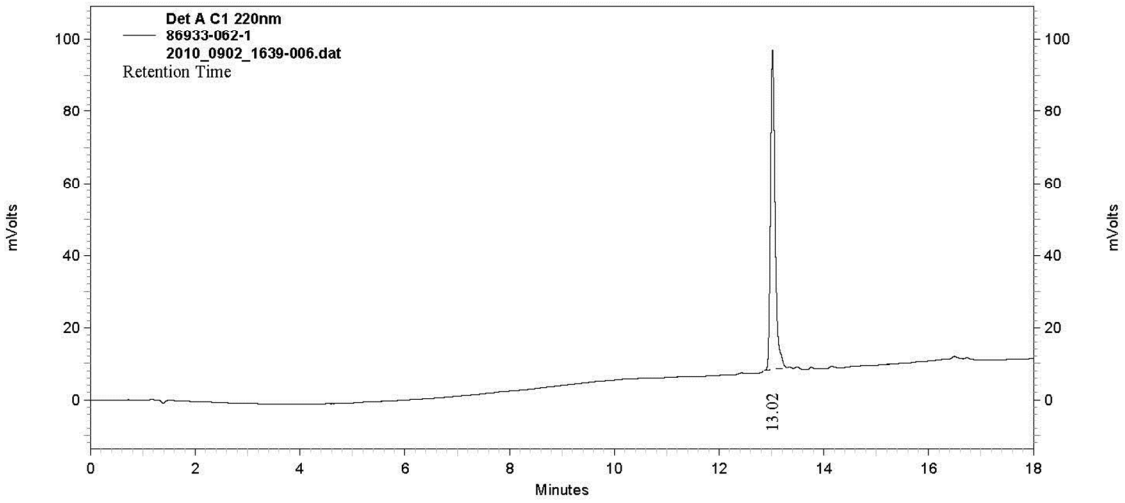
Filename:
c:\shimadzu\data\public\ling.chen1\20100902\2010_0902_1639-006.dat
Analysis Time: 9/2/2010 4:47:35 PM

Parallel HPLC:
Low pH analysis:
UV detector A (220/254nm): Column#1: Sunfire C18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#2: Xbridge Phenyl 3.5um, 3.0x150mm

High pH analysis:
UV detector A (220/254nm): Column#3: XbridgeC18 3.5um, 3.0x150mm
UV detector B (220/254nm): Column#4: Xbridge Phenyl 3.5um, 3.0x150mm

Flow=0.5mL/min on each column

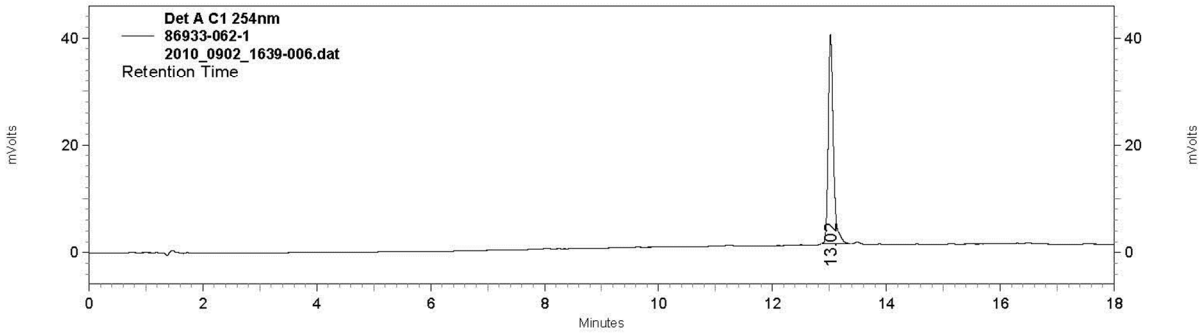
Det A C1 (220nm)



Det A C1 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	13.02	545615	100.00	0.180
Totals		545615	100.00	

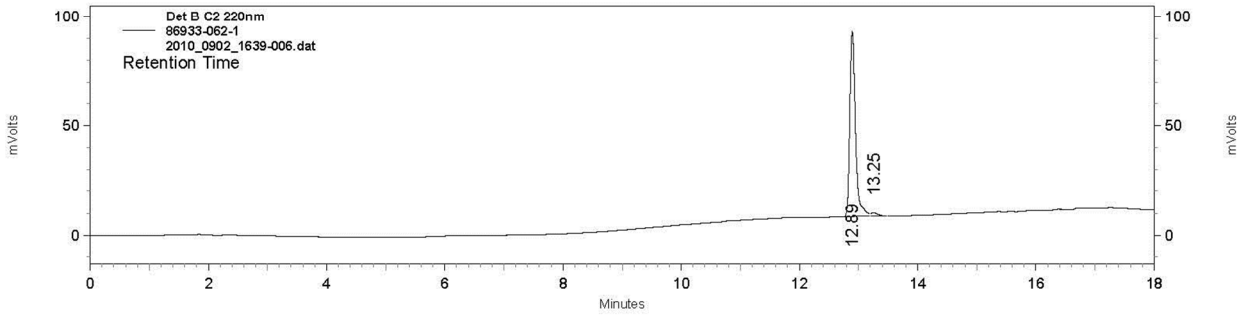
Det A C1 (254nm)



Det A C1
254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	13.02	241914	100.00	0.180
Totals		241914	100.00	

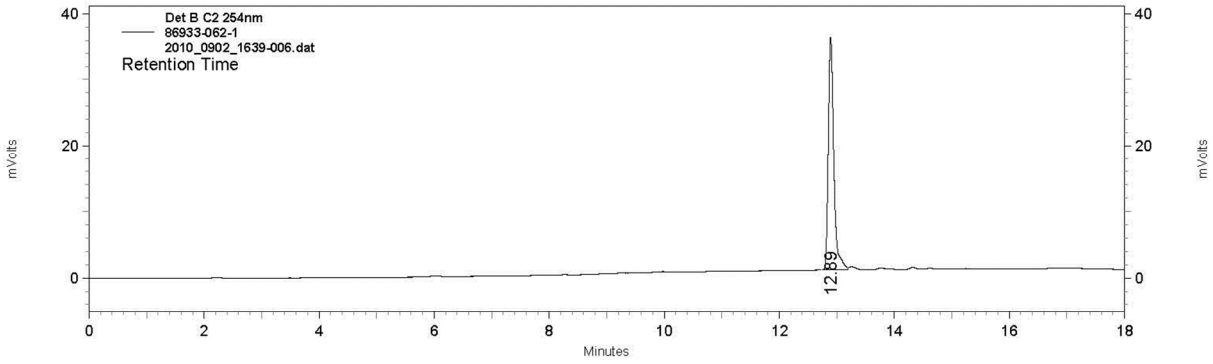
Det B C2 (220 nm)



Det B C2 220nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	12.89	562077	97.82	0.189
2	13.25	12518	2.18	0.000
Totals		574595	100.00	

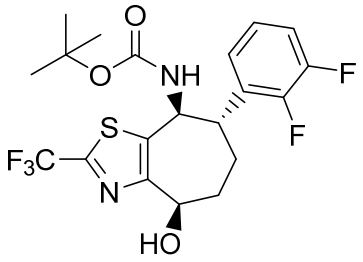
Det B C2 (254 nm)



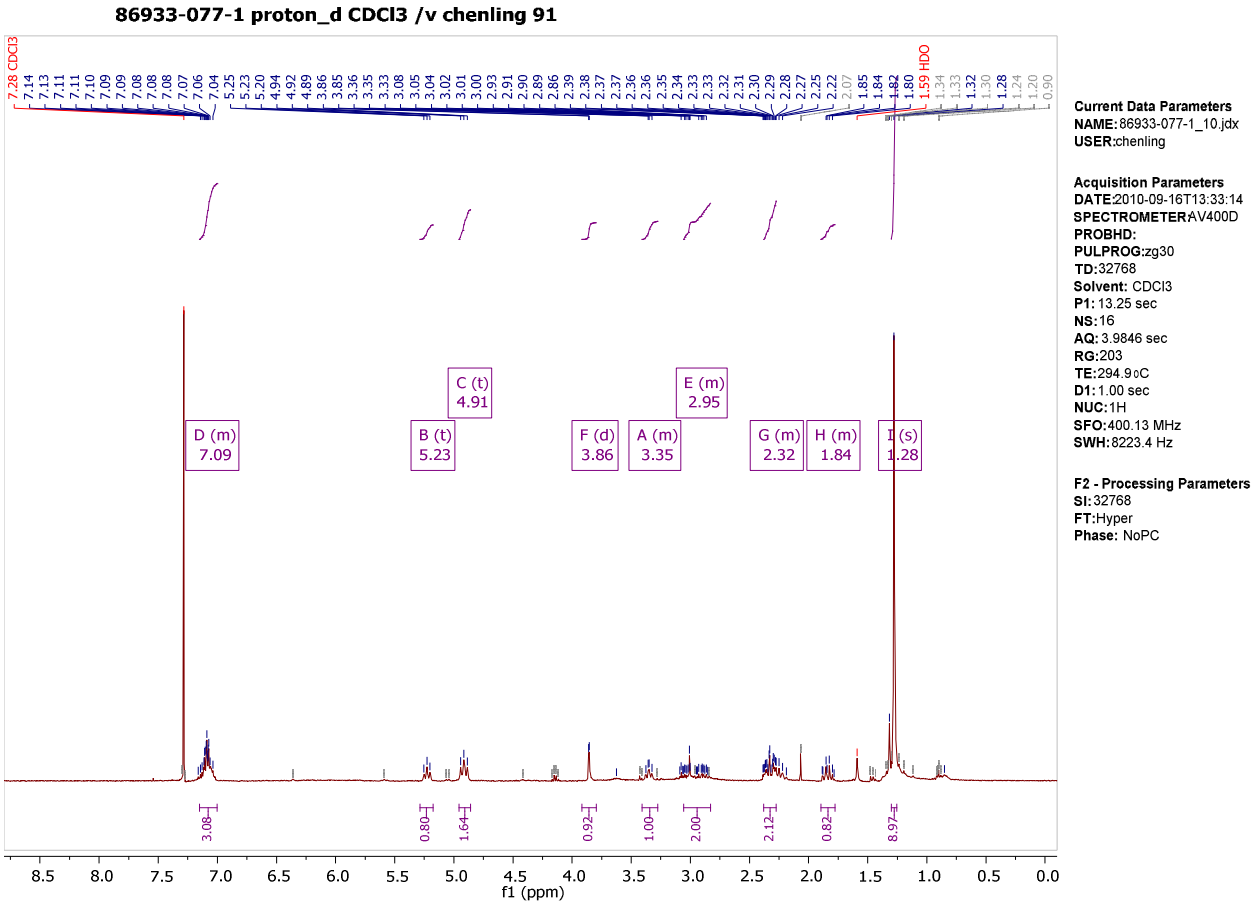
Det B C2 254nm Results

Pk #	Retention Time	Area	Area Percent	Width at 10% height
1	12.893	233121	100.0	0.189
Totals		233121	100.0	

^{1}H NMR of 31:

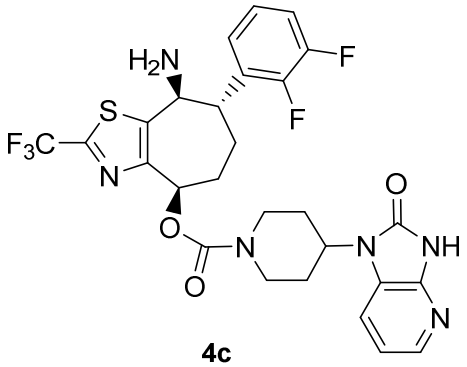


31



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 7.00 (m, 3H), 5.23 (t, *J* = 10.2 Hz, 1H), 4.91 (t, *J* = 11.2 Hz, 2H), 3.86 (d, *J* = 2.2 Hz, 1H), 3.41 – 3.28 (m, 1H), 3.06 – 2.83 (m, 2H), 2.38 – 2.27 (m, 2H), 1.90 – 1.78 (m, 1H), 1.28 (s, 9H).

Analytical HPLC/LCMS for 4c (3 pages):

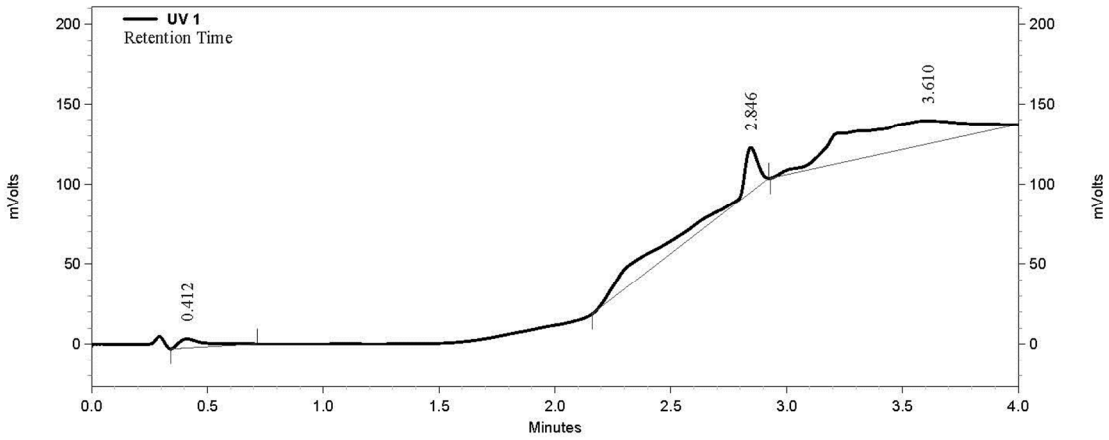


4c

Analytical HPLC Report

```
File:         =
c:\shimadzu\data\public\ling.chen1\20100920\2010_0920_1640-036.dat
Sample ID:    = 86933-082
Acquired:     = 9/20/2010 4:45:24 PM
File          = 2010_0920_1640.036
User          = ling.chen1
Instrument    = WFD-489C-LCMS1
Well          =  190          Inj. Vol. = 3 uL
Start % B     =  0
Final % B     =  100
Gradient Time =  3 min
Flow Rate     =  .8 ml/min
Wavelength    =  220
Solvent Pair  = MeOH:H2O:TFA
Solvent A = 10% MeOH - 90% H20 - 0.1% TFA
Solvent B = 90% MeOH - 10% H20 - 0.1% TFA
Column 3       = 3.) Xbridge Phenyl 2.1 X 50 mm 2.5um
MW1 = 132+
Oven Temp.    =  40

86933-082
```



UV 1 Results

Pk #	RT	Area	Area %	Height (uV)	Plates
1	0.412	46973	4.431	5628	78
2	2.846	369149	34.819	27769	1172
3	3.610	644076	60.751	14531	262

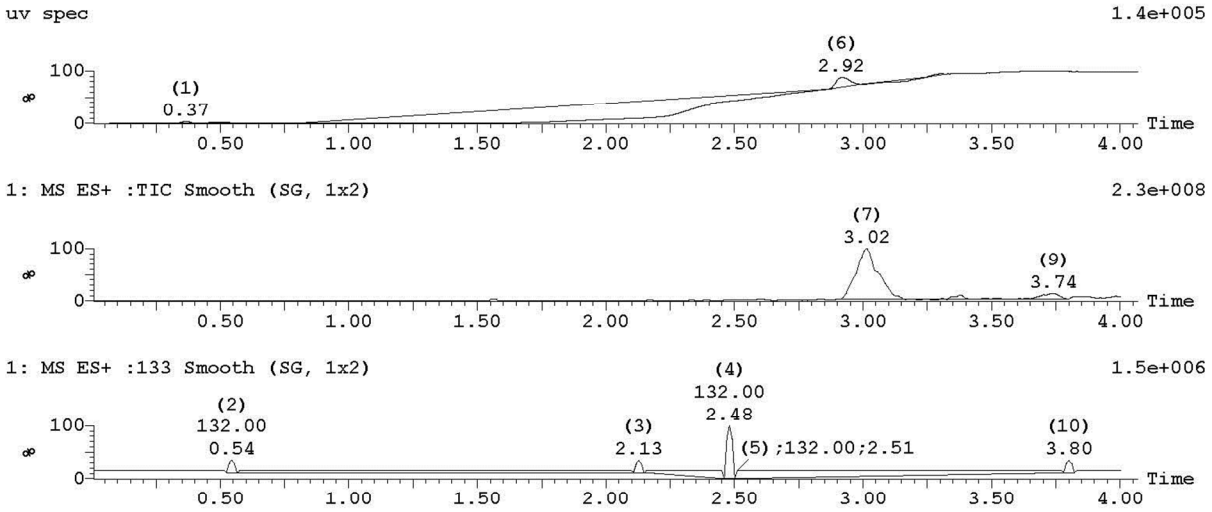
Totals					
		1060198	100.000	47928	

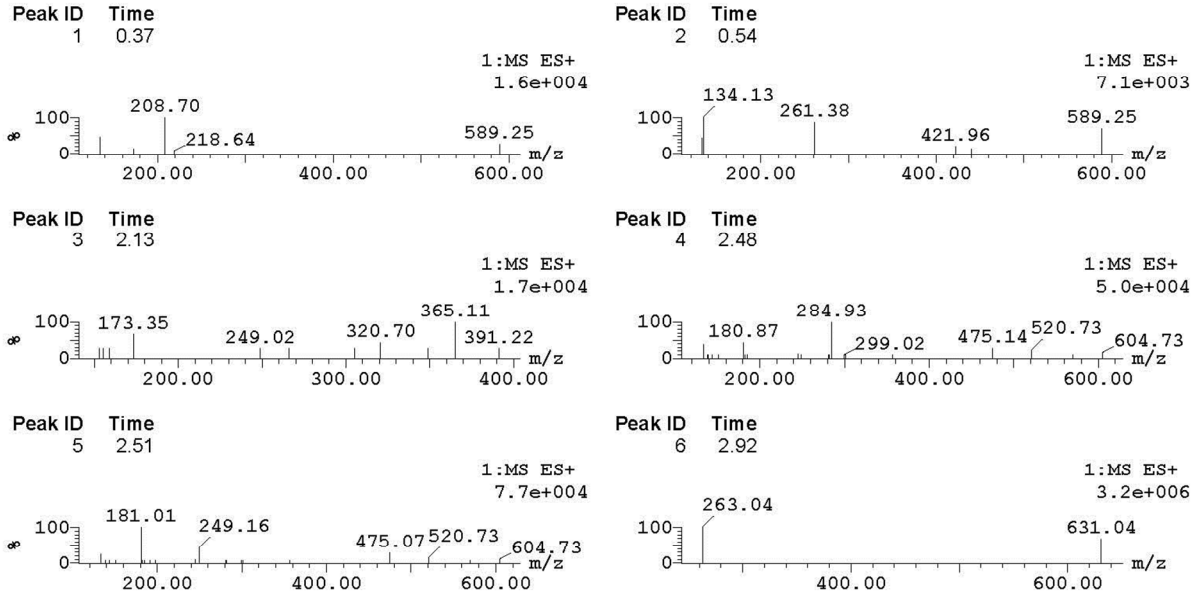
Openlynx Report BMS LCMS Report- ling.chen1 Page 1

Sample: 1 Vial:1:A,1 ID:86933-082
File:2010_0920_1640-036 Date:20-Sep-2010 Time:16:35:17
Description:

Printed: Mon Sep 20 16:42:59 2010

Sample Report:



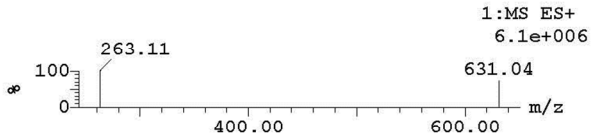


Sample: 1 Vial:1:A,1 ID:86933-082
File:2010_0920_1640-036 Date:20-Sep-2010 Time:16:35:17
Description:

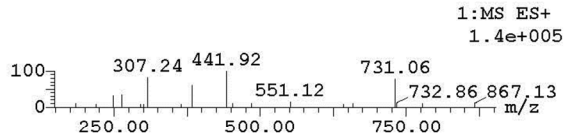
Printed: Mon Sep 20 16:42:59 2010

Sample Report (continued):

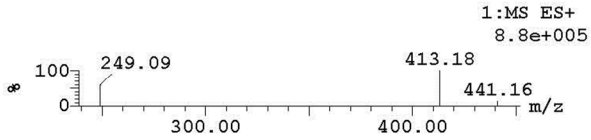
Peak ID **Time**
7 3.01



Peak ID **Time**
8 3.29



Peak ID **Time**
9 3.74



Peak ID **Time**
10 3.80