Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Highly Efficient Ruthenium-Catalyzed Asymmetric Hydrogenation of N-Heteroaryl Vinyl Ethers

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Experimental Section

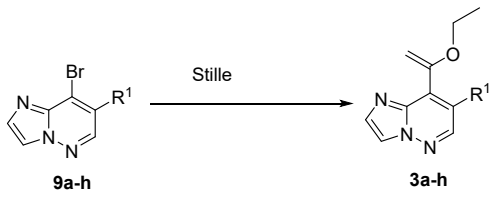
General Information

Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on Bruker ADVANCE III HD (300 MHz)/ BRUKER AVANCE NEO (400 MHZ) spectrometers for ^{1}H NMR and ^{13}C NMR. $CDCl_3$/DMSO-d_6 was the solvent used for the NMR analysis, with tetramethylsilane as the internal standard. Chemical shifts were reported upfield to TMS (0.00 ppm) for ^{1}H NMR and relative to $CDCl_3$ (77.0 ppm) for ^{13}C NMR. HPLC analysis was conducted on an Agilent 1260 Series instrument. Column Chromatography was performed with silica gel (Rushanshi Shuangbang Xincailiao Co., Ltd). All new products were further characterized by HRMS. A positive ion mass spectrum of sample was acquired on an Agilent 6135 mass spectrometer with an electrospray ionization source.

General Procedure for the Synthesis of Vinyl ether substrates 3a-h, 5a, 7a-d

Vinyl ether derivatives were prepared according to previously reported procedures with some modifications:

The synthesis of 3e :



entry	R^1
1	-COOEt (**3a/4a**)
2	-COO^{t}Bu (**3b/4b**)
3	-COOMenthol (**3c/4c**)
4	-COOMenthol (**3d/4d**)
5	-NHBoc (**3e/4e**)

To a solution of tert-butyl N-(8-bromoimidazo[1,2-b]pyridazin-7-yl)carbamate (**9a**, 10.36 g, 33.08 mmol) in N,N-dimethylformamide (50 mL) was added tributyl(1-ethoxyvinyl)stannane (23.90 g, 66.17 mmol, 22.33 mL) at room temperature. Then bis(triphenylphosphine)palladium(II) chloride (2.32 g, 3.31 mmol) was added under N_2. The resulting reaction mixture was stirred at 100 °C for 3 h. After the reaction was completed, the mixture was concentrated and the residue was purified by flash column chromatography (Petroleum ether: Ethyl acetate 3:1) to give tert-butyl N-[8-(1-ethoxyvinyl)imidazo[1,2-b]pyridazin-7-yl]carbamate (**3e**, 10.06 g, 99 % yield) as a yellow oil.

LC/MS: m/z 305 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.71 (s, 1H), 8.19 (d, J = 1.3 Hz, 1H), 7.66 (d, J = 1.3 Hz, 1H), 5.27 (d, J = 2.5 Hz, 1H), 4.88 (d, J = 2.6 Hz, 1H), 3.93 (q,

J = 7.0 Hz, 2H), 1.47 (s, 9H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 153.22, 151.98, 142.48, 137.47, 133.66, 126.05, 117.04, 94.01, 80.59, 63.65, 28.41, 14.65.

The synthesis of 3a-c, 5a is similar to 3e.

The characterization of 3a:

LC/MS: m/z 262 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.48 (d, J = 1.3 Hz, 1H), 7.95 (s, 1H), 5.32 (d, J = 2.7 Hz,1H), 4.92 (d, J = 2.7 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.91 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H),1.26 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.15, 151.30, 142.66, 135.61, 135.38, 132.10, 118.64, 118.03, 93.20,63.46, 61.54, 13.91, 13.82.

The characterization of 3b:

LC/MS: m/z 290 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.45 (d, J = 1.1 Hz, 1H), 7.93 (d, J = 1.2 Hz, 1H), 4.92 (d, J= 2.8 Hz, 1H), 4.82 (d, J = 2.8 Hz, 1H), 3.93 (q, J = 7.0 Hz, 2H), 1.53 (s, 9H), 1.27 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.13, 152.11, 143.54, 136.33, 136.21, 133.47, 119.41, 119.09, 91.98,82.82, 63.91, 28.04, 14.44.

The characterization of 3c/3d:

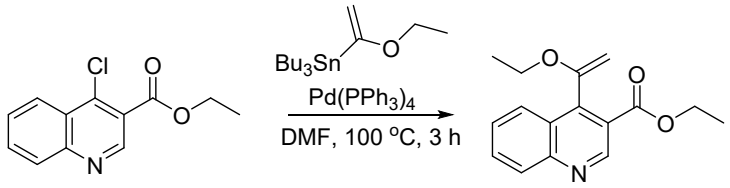
LC/MS: m/z 372.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.49 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 4.92 –4.86 (m, 1H), 4.82 (dd, J = 5.8, 3.7 Hz, 2H), 3.92 (q, J = 6.9 Hz, 2H), 2.13 – 2.03 (m, 1H), 1.91 (pd, J =6.9, 2.5 Hz, 1H), 1.67 (dt, J = 13.4, 3.9 Hz, 2H), 1.55 – 1.40 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.17 – 1.02(m, 2H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.35, 152.12, 143.28, 136.47, 136.42, 134.03, 119.28, 118.08, 91.88, 75.87, 64.03, 46.90, 34.09, 31.27, 26.15, 23.28, 22.36, 21.10, 16.63, 14.42.

The characterization of 5a:

LC/MS: m/z 291.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.73 (s, 1H), 8.20 (d, J = 1.3 Hz, 1H), 7.68(d, J = 1.3 Hz, 1H), 5.30 (d, J = 2.5 Hz, 1H), 4.80 (d, J = 2.6 Hz, 1H), 3.65 (s, 3H), 1.47 (s, 9H), ^{13}C NMR (101 MHz, DMSO) δ 153.22, 151.98, 142.48, 137.47, 133.66, 126.05, 117.04, 94.01, 80.59, 63.65, 28.41.

The synthesis of 7a, 7b

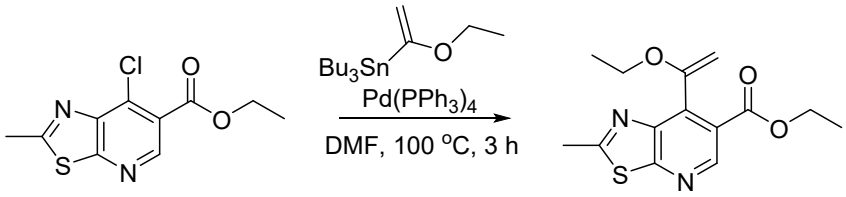
Synthesis report of ethyl 4-(1-ethoxyvinyl)quinoline-3-carboxylate (7a)



7a

To a suspension of ethyl 4-chloroquinoline-3-carboxylate (500 mg, 2.12 mmol), tributyl(1-ethoxyvinyl) stannane (766.2 mg, 2.12 mmol, 716.11 µL) and Tetrakis(triphenylphosphine)palladium(0)(490.10 mg, 424.33 umol) in DMF (10 mL) was stirred at 100 °C for 3 hours, then brought to room temperature and poured out into ice water. Ethyl acetate (50 mL) was added. The mixture was filtered over celite. Celite was washed with Ethyl acetate (50 mL). The filtrate was extracted with Ethyl acetate (50 mL). The organic layer was washed with water (30 mL), dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (eluting with ethyl acetate/ petroleum ether from 0 to 50%) to give ethyl 4-(1-ethoxyvinyl)quinoline-3-carboxylate (105 mg, 387.01 umol, 18.24% yield) as colorless oil. Chemical Formula: $C_{16}H_{17}NO_3$. LC/MS(ESI+) [$(M+H)^+$]: 271.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.19 (dd, J = 8.4, 1.2 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.91 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H), 7.74 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 4.74 (d, J = 2.8 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.28 (d, J = 2.8 Hz, 1H), 4.02 (q, J = 7.2 Hz, 2H), 1.31 (dt, J = 12.4, 7.2 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.32, 155.00, 149.66, 149.15, 143.85, 131.89, 129.69, 128.49, 126.94, 125.25, 123.62, 89.42, 64.14, 61.82, 14.66, 14.34.

Synthesis report of ethyl 4-(1-ethoxyvinyl)-6-fluoroquinoline-3-carboxylate (7b)

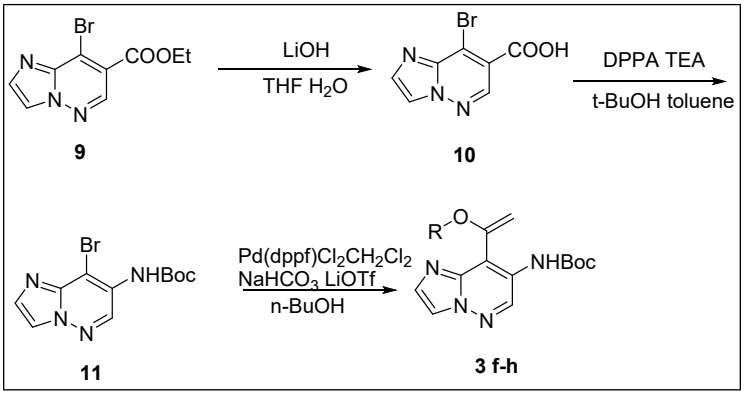


7b

To a suspension of ethyl 7-chloro-2-methyl-thiazolo[5,4-b]pyridine-6-carboxylate (500 mg, 1.95 mmol), tributyl(1-ethoxyvinyl)stannane (703.4 mg, 1.95 mmol, 657.41 µL) and Tetrakis(triphenylphosphine)palladium(0) (449.9 mg, 389.55 umol) in DMF (10 mL) was stirred at 100 °C for 3 hours, then brought to room temperature and poured out into ice water. Ethyl acetate (50 mL) was added. The mixture was filtered over celite. Celite was washed with Ethyl acetate (50 mL). The filtrate was extracted with Ethyl acetate (50 mL). The organic layer was washed with water (30 mL), dried ($MgSO_4$), filtered and the solvent was evaporated. The

residue was purified by flash column chromatography on silica gel (eluting with ethyl acetate/ petroleum ether from 0 to 50%) to give ethyl 4-(1-ethoxyvinyl) quinoline-3-carboxylate (105 mg, 387.01 umol, 18.24% yield) as colorless oil. Chemical Formula: $C_{14}H_{16}N_2O_3S$. LC/MS(ESI+) [$(M+H)^+$]: 292.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 4.78 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 3.89 (q, J = 7.2 Hz, 2H), 2.87 (s, 3H), 1.33 – 1.23 (m, 6H). ^{13}C NMR (101 MHz, DMSO) δ 169.53, 166.15, 161.38, 153.21, 146.15, 142.65, 136.64, 124.32, 91.23, 63.46, 61.36, 20.98, 14.05, 13.88.

The synthesis of 3f-h.

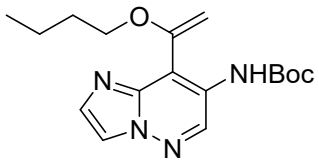


To a stirred solution of ethyl 8-bromoimidazo[1,2-b]pyridazine-7-carboxylate (30.0 g, 111.08 mmol) in THF (300 mL) was added LiOH (5.32 g, 222.15 mmol) in H_2O (300 mL), the resulting mixture was allowed to stir at 0°C for 2 hours and monitored by the LCMS until the reaction was completed. MTBE (600 mL, 20 v/w) was charged to the reaction mixture at 10 °C, separated and the aqueous phase was collected. After cooling to 0 °C, the solution was added HCl solution (3 M) at 0 °C until pH=3~4, filtered , the filter cake was dried in vacuo to afford 8-bromoimidazo[1,2-b]pyridazine-7-carboxylic acid (26.6 g, 109.90 mmol, 98.94% yield) as an off white solid, LC/MS(ESI$^+$) [$(M+H)^+$]:243, which was directly used to the next step without further purification.

To a solution of 8-bromoimidazo[1,2-b]pyridazine-7-carboxylic acid (24.0 g, 99.16 mmol) in t-BuOH (240 mL) and toluene (240 mL) was added TEA (14.05 g, 138.83 mmol, 19.35 mL) under N_2 atmosphere. The resulting mixture was added DPPA (26.53 g, 109.08 mmol), heated to 100°C and stirred for 2.5 hours. After cooling to room temperature, and concentrated *in vacuo*, the residue was diluted with EtOAc (48 mL, 2 v/w) and water (96 mL, 4 v/w). After agitating for 30 minutes at room temperature, the mixture was filtered, and the solid was slurried in THF (12mL, 0.5 v/w), filtered and the solid was dried in vacuum to afford tert-butyl N-(8-bromoimidazo[1,2-b]pyridazin-

7-yl)carbamate (21.5 g, 68.66 mmol, 69.24% yield) as a yellow solid, LC/MS(ESI$^+$) [(M+H)$^+$]: 313, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.56 (s, 1H), 8.34 (d, J = 1.0 Hz, 1H), 7.75 (d, J = 0.9 Hz, 1H), 1.49 (s, 9H).

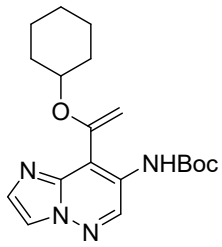
The synthesis of 3f



3f

To a stirred solution of tert-butyl N-(8-bromoimidazo[1,2-b]pyridazin-7-yl)carbamate (400 mg, 1.28 mmol) in n-BuOH (4 mL) were added $NaHCO_3$(321.9 mg, 3.83 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (208.6 mg, 255.47 umol), lithium trifluoromethanesulfonate(199.3 mg, 1.28 mmol), and 1-vinyloxybutane (511.8 mg, 5.11 mmol), the reaction mixture was degassed and refilled with N_2 three times, heated at 90°C and stirred for 20 hours, then cooled to room temperature, diluted with EA and washed with brine, and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude mixture was purified by silica gel column chromatography using EA/PE=1:10 as eluent to give tert-butyl N-[8-(1-butoxyvinyl)imidazo[1,2-b]pyridazin-7-yl]carbamate (115 mg, 345.97 umol, 27.09% yield) as a yellow solid, LCMS(ESI$^+$) [(M+H)$^+$]: 333, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.78 (s, 1H), 8.18 (d, J = 1.1 Hz, 1H), 7.66 (d, J = 0.9 Hz, 1H), 5.32 (d, J = 2.1 Hz, 1H), 4.92 (d, J = 2.4 Hz, 1H), 3.89 (t, J = 6.3 Hz, 2H), 1.75 – 1.65 (m, 3H), 1.47 (s, 9H), 1.44 (s, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.04, 152.02, 137.43, 133.64, 126.08, 117.02, 94.32, 80.69, 67.77, 30.99, 28.36, 19.43, 14.27.

The synthesis of 3g

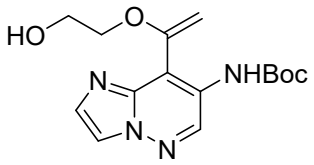


3g

To a stirred solution of tert-butyl N-(8-bromoimidazo[1,2-b]pyridazin-7-yl)carbamate (400 mg, 1.28 mmol) in n-BuOH (4 mL) were added $NaHCO_3$ (321.9 mg, 3.83 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (208.6 mg, 255.47 umol), lithium trifluoromethanesulfonate(199.3 mg, 1.28 mmol), and vinyloxycyclohexane

(644.8 mg, 5.11 mmol) , the reaction mixture was degassed and refilled with N_2 three times, heated at 90°C and stirred for 20 hours, then cooled to room temperature, diluted with EA and washed with brine, and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude mixture was purified by silica gel column chromatography using EA/PE=1:10 as eluent to give tert-butyl N-[8-[1-(cyclohexoxy)vinyl]imidazo[1,2-b]pyridazin-7-yl]carbamate (110 mg, 306.89 umol, 24.03% yield) as a yellow solid, LC/MS(ESI$^+$) [(M+H)$^+$]: 359, ^{1}HNMR(400MHz, DMSO-d_6) δ 8.83 (s, 2H), 8.19 (d, J = 1.1Hz, 1H), 7.66 (d, J = 0.9Hz, 1H), 5.38 (s, 1H), 4.99 (d, J = 2.4Hz, 1H), 4.34 – 4.24 (m, 1H), 1.98 – 1.89 (m, 2H), 1.74 – 1.63 (m, 2H), 1.53 (dd, J = 10.7, 6.7Hz, 2H), 1.47 (s, 9H), 1.44 – 1.36 (m, 2H), 1.31 – 1.20 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.95, 149.80, 137.51, 133.68, 126.05, 117.07, 96.11, 80.80, 74.96, 31.01, 28.36, 25.63, 23.29.

The synthesis of 3h

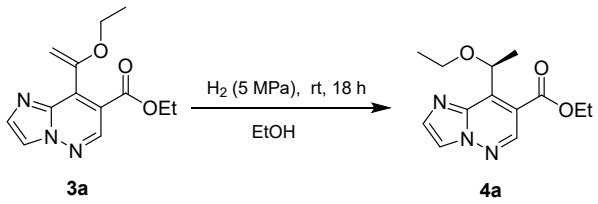


3h

To a stirred solution of tert-butyl N-(8-bromoimidazo[1,2-b]pyridazin-7-yl)carbamate (1.0 g, 3.19 mmol) in n-BuOH (10 mL) were added sodium hydrogen carbonate (804.8 mg, 9.58 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (260.78 mg, 319.34 umol), lithium trifluoromethanesulfonate (498.2 mg, 3.19 mmol), and 2-vinyloxyethanol (1.13 g, 12.77 mmol) , the reaction mixture was degassed and refilled with N_2 three times, heated at 90°C and stirred for 20 hours, then cooled to room temperature, diluted with EA and washed with brine, and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude mixture was purified by silica gel column chromatography using MeOH/DCM=1:10 as eluent to give tert-butyl N-[8-[1-(2-hydroxyethoxy)vinyl]imidazo[1,2-b]pyridazin-7-yl]carbamate (140 mg, 437.03 umol, 13.69% yield) as a yellow solid, LC/MS(ESI$^+$) [(M+H)$^+$]: 321, ^{1}HNMR(400MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.83 (s, 1H), 8.20 (d, J = 1.0Hz, 1H), 7.66 (s, 1H), 5.19 (d, J = 2.4Hz, 2H), 4.93 (d, J = 2.6Hz, 1H), 3.99 (t, J = 4.7Hz, 2H), 3.73 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.33, 151.61, 142.06, 137.53, 133.57, 126.47, 116.98, 94.06, 80.72, 69.92, 59.21, 28.36.

General Procedure for the Asymmetric Hydrogenation: 4a-h, 6a, 8c-d

The synthesis of **4a**



3a **4a**

Typical procedure: Charged compound **3a** (8.9 g, 34.1 mmol) into a 300 mL three-necked flask at r.t. under N_2, then EtOH (90 mL, 30 v/w) , (S)-Ru(OAC)$_2$(BINAP) (0.43 g, 0.51 mmol, 0.015 eq) and (S)-RuCl$_2$(BINAP) (0.51 mmol, 0.015 eq) into the flask at r.t.. The resulting mixture was agitated for 48 h under H_2 (5 Mpa). After that the mixture was filtered and collected the filtrate. After concentration of the filtrate, the residue was purified by column of chromatography using PE/EtOAc= 1:0~5:1 as eluent. Compound **4a** was obtained as a gray solid. (yield 90%, purity 99.0%) , LC/MS(ESI) m/z: 264.1 [M+1]) ,

^{1}H NMR(400 MHz, CDCl$_3$-d_1) δ 8.85(s, 1H), 8.66(s, 1H), 8.15(d, *J*=4 Hz, 1H), 4.68 (q, *J*= 6.8 Hz, 1H), 4.29(q, 2H), 3.88 (q, *J* = 8.0Hz, 2H), 1.53(d, 3H), 1.49(d, *J*=6.8 Hz, 3H), 1.30(t, *J*=7.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.05, 142.46, 140.05, 135.85, 134.76, 118.46, 117.99, 71.74, 64.76,61.63, 20.75, 14.79, 13.81.

The characteration of **4b**:

LC/MS: m/z 292 [M+H]$^+$. 1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.39 (d, *J* = 1.2 Hz, 1H), 7.87 (d, *J* = 1.2 Hz, 1H), 5.32 (q, *J*= 6.6 Hz, 1H), 3.41 – 3.36 (m, 1H), 3.33 – 3.26 (m, 1H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.57 (s, 9H), 1.07 (t, *J*= 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.12, 142.71, 139.24, 135.96, 134.69, 119.81, 117.88, 82.69, 71.80, 64.94, 27.66, 20.62, 14.87.

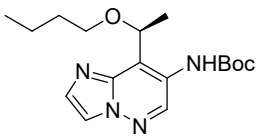
The characterization of **4c/4d**:

LC/MS: m/z 374.2 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.42 (q, *J* = 1.9 Hz, 1H), 7.90 (d, *J* = 1.2 Hz, 1H), 5.36 (p, *J*= 6.6 Hz, 1H), 4.87 (tt, *J* = 10.9, 4.1 Hz, 1H), 3.39 (ddd, *J* = 14.9, 7.4, 2.2 Hz, 1H), 3.28 (dddd, *J* = 13.7,6.9, 5.2, 1.9 Hz, 1H), 2.17 (dtd, *J* = 11.8, 7.9, 3.0 Hz, 1H), 1.90 – 1.74 (m, 1H), 1.72 – 1.67 (m, 1H), 1.64(dd, *J* = 6.7, 4.6 Hz, 4H), 1.52 – 1.39 (m, 2H), 1.08 – 1.03 (m, 3H), 0.93 (s, 1H), 0.92 – 0.90 (m, 3H),0.89 – 0.84 (m, 3H), 0.79 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.58, 142.52, 140.04, 135.83, 134.90, 118.66, 118.02, 75.60, 71.67, 64.86, 46.54, 40.31, 33.63, 30.83, 25.95, 23.07, 21.93, 20.68, 16.37, 14.91.

The characterization data of **4e :**

LC/MS: m/z 307.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.83 (s, 1H), 8.18 (d, J = 1.3 Hz, 1H), 7.65 (d, J = 1.3 Hz, 1H), 5.30 (q, J = 6.7 Hz, 1H), 3.52 – 3.44 (m, 1H), 3.41 – 3.36 (m, 1H), 1.53 (d, J = 6.6 Hz, 3H), 1.49 (s, 9H), 1.15 (t, J = 7.0 Hz, 3H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.01, 140.65, 138.00, 133.56, 126.40, 116.71, 81.10, 72.40, 64.90, 28.37, 20.15, 15.44.

The characterization data of **4f**

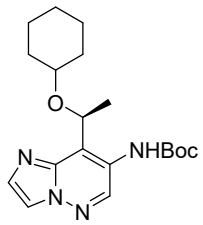


4f

gray solid, yield 96%, 93.4% ee, LCMS(ESI) m/z: 335.2 [M+1]

^1H NMR (300 MHz, $CDCl_3$-d_1) δ 9.38 (s, 1H), 8.78 (s, 1H), 7.84 (d, *J*=1.2 Hz, 1H), 7.60 (d, *J*=1.2 Hz, 1H), 5.48 (q, *J*=6 Hz, 1H), 3.41~3.62 (m, 2H), 1.58 (d, *J*=6 Hz, 3H), 1.54 (s, 9H), 1.38~1.66 (m, 4H), 0.93 (t, *J*=6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 152.4, 138.4 (d, *J*=90 Hz), 132.7, 127.5, 121.3, 115.9, 81.3, 73.3, 69.8, 31.7, 29.6 (d, *J*=12 Hz), 28.2, 19.4 (d, *J*=81 Hz), 13.8.

The characterization data of **4g**

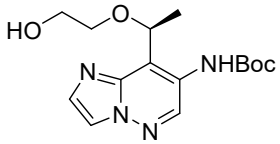


4g

gray solid, yield 90.5%, 95.5% ee, LC/MS(ESI) m/z: 361.3 [M+1]

^1H NMR (300 MHz, $CDCl_3$-d_1) δ 9.40 (s, 1H), 9.05 (s, 1H), 7.84 (d, *J*=1.2 Hz, 1H), 7.62 (d, *J*=1.2 Hz, 1H), 5.68 (q, *J*=6 Hz, 1H), 3.41~3.48 (m, 1H), 1.56 (d, *J*=6 Hz, 3H), 1.53 (s, 9H), 1.33~1.75 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 152.4, 138.4 (d, *J*=258 Hz), 134.1, 128.1, 120.3, 115.9, 81.4, 77.2, 70.1, 32.3, 31.6, 29.6, 28.2, 25.2, 23.5 (d, *J*=33 Hz), 20.5.

The characterization data of **4h**



4h

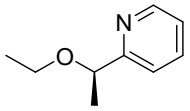
gray solid, yield 96%, 90.6% ee, LCMS(ESI) m/z: 323.2 [M+1]

^{1}H NMR (300 MHz, $CDCl_3$-d_1) δ 9.29 (s, 1H), 8.55 (s, 1H), 7.85 (d, *J*=1.2 Hz, 1H), 7.60 (d, *J*=1.2 Hz, 1H), 5.56 (q, *J*=6 Hz, 1H), 3.54~3.90 (m, 4H), 1.62 (d, *J*=6 Hz, 3H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 152.4, 138.6 (d, J=213 Hz), 132.6, 127.4, 121.4, 116.0, 81.6, 73.4, 71.0, 61.6, 28.2, 19.6.

The synthesis of 6a.

Charge compound **5a** (89.7 g, 3.45 mmol) into a 2 L three-necked flask at r.t. under N_2, then dichloromethan (897 mL, 10 v/w) , (S)-RuCl[(p-cymene)(binap)Cl] (2.87g, 32.5 mmol, 0.01 eq) into the flask at r.t.. The mixture was agitated for 48 h under H_2 (5 Mpa). After remaining starting material≤0.5%, the mixture was filtered and collected the filtrate. After concentration of the filtrate, the residue was purified by column of chromatography using PE/EtOAc= 1:0~5:1 as eluent. Compound **6a** was obtained as a gray solid. (82.5g, yield: 93%, purity 99%, 97 % ee, LCMS(ESI) m/z: 293.2 [M+1]) ^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 8.85 (s, 1H), 8.66 (s, 1H), 8.15 (d, *J*=4 Hz, 1H), 7.64 (d, *J*=4 Hz, 1H), 5.17 (q, *J*=8 Hz, 1H), 3.23 (s, 3H), 1.53 (d, 3H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.01, 140.65, 138.00, 133.56, 126.40, 116.71, 81.10, 72.40, 64.90, 28.37, 20.15.

The characterization data of **8c**



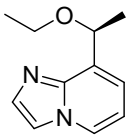
8c

gray solid, yield 87%, 61.6% *ee*, LCMS(ESI) m/z: 152.2 [M+1]

^{1}H NMR (300 MHz, $CDCl_3$-d_1) δ 8.85 (dq, *J*1=6 Hz, *J*2=1.2 Hz, 1H), 7.65 (dt, *J*1==6 Hz, *J*2=9 Hz, 1H), 7.40 (dt, *J*1==9 Hz, *J*2=1.2 Hz, 1H), 710~7.16 (m, 1H), 4.50 (q, *J*=6 Hz, 1H), 3.53 (q, *J*=6 Hz, 2H), 1.59 (d, *J*=6 Hz, 3H), 1.26 (t, *J*=6 Hz, 3H). ^{13}C NMR (101 MHz MHz, $CDCl_3$-

d_1) δ 163.8, 148.9(d, *J*=60 Hz), 136.4 (d, *J*=180 Hz), 122.3 (d, *J*=90 Hz), 119.7, 78.9, 64.4, 22.6, 15.3 (d, *J*=24 Hz).

The data of **8d**



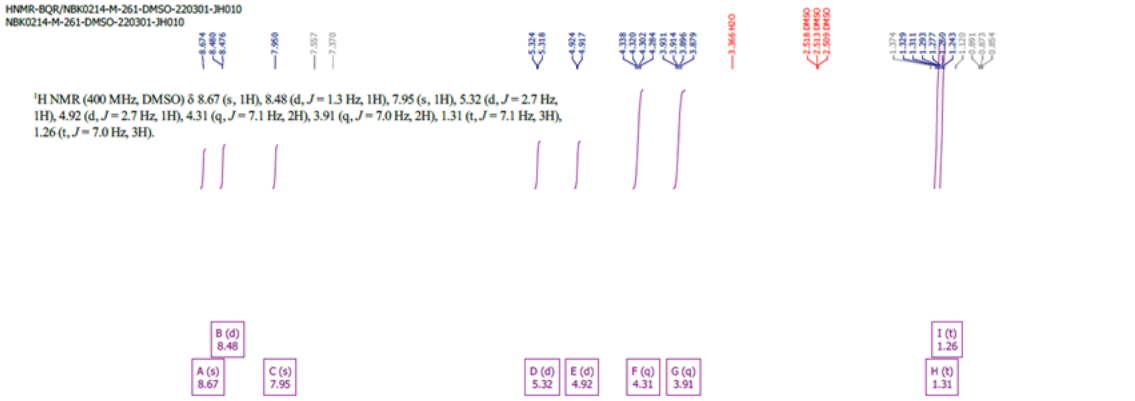
8d

gray solid, yield 97%, 63.6% *ee*, LCMS(ESI) m/z: 191.1 [M+1]

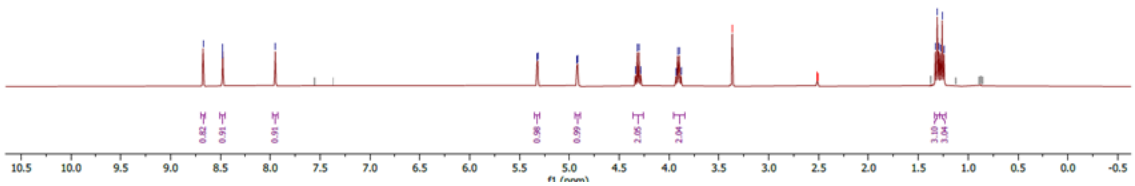
^{1}H NMR (300 MHz, $CDCl_3$-d_1) δ 8.06 (dd, *J*1=9 Hz, *J*2=3 Hz, 1H), 7.62 (dd, *J*1=9 Hz, *J*2=3 Hz, 1H), 7.28 (dt, *J*1=6 Hz, *J*2=1.2 Hz, 1H), 6.83 (t, *J*=6 Hz, 1H), 5.24 (q, *J*=6 Hz, 1H), 3.27~3.55 (m, 2H), 1.43 (d, *J*=6 Hz, 3H), 1.18 (t, *J*=6 Hz, 3H). ^{13}C NMR (101 MHz , $CDCl_3$-d_1) δ 144.1, 133.8, 132.9, 124.2, 119.2, 112.5 (d, *J*=42 Hz), 72.5, 64.5, 22.5, 15.5.

NMR and chiral HPLC Spectra

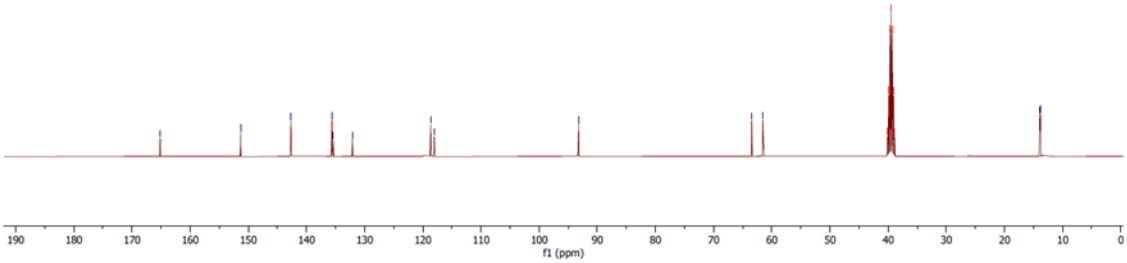
Ethyl 8-(1-ethoxyvinyl)imidazo[1,2-b]pyridazine-7-carboxylate(3a)



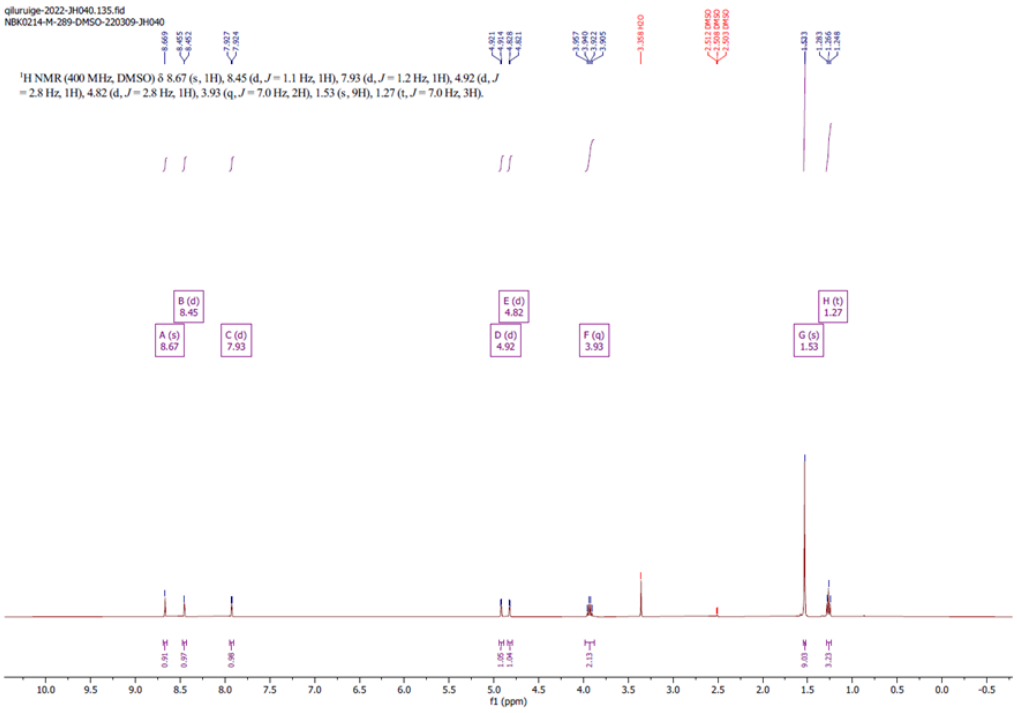
^{1}H NMR (400 MHz, DMSO) δ 8.67 (s, 1H), 8.48 (d, *J* = 1.3 Hz, 1H), 7.95 (s, 1H), 5.32 (d, *J* = 2.7 Hz, 1H), 4.92 (d, *J* = 2.7 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.91 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H).



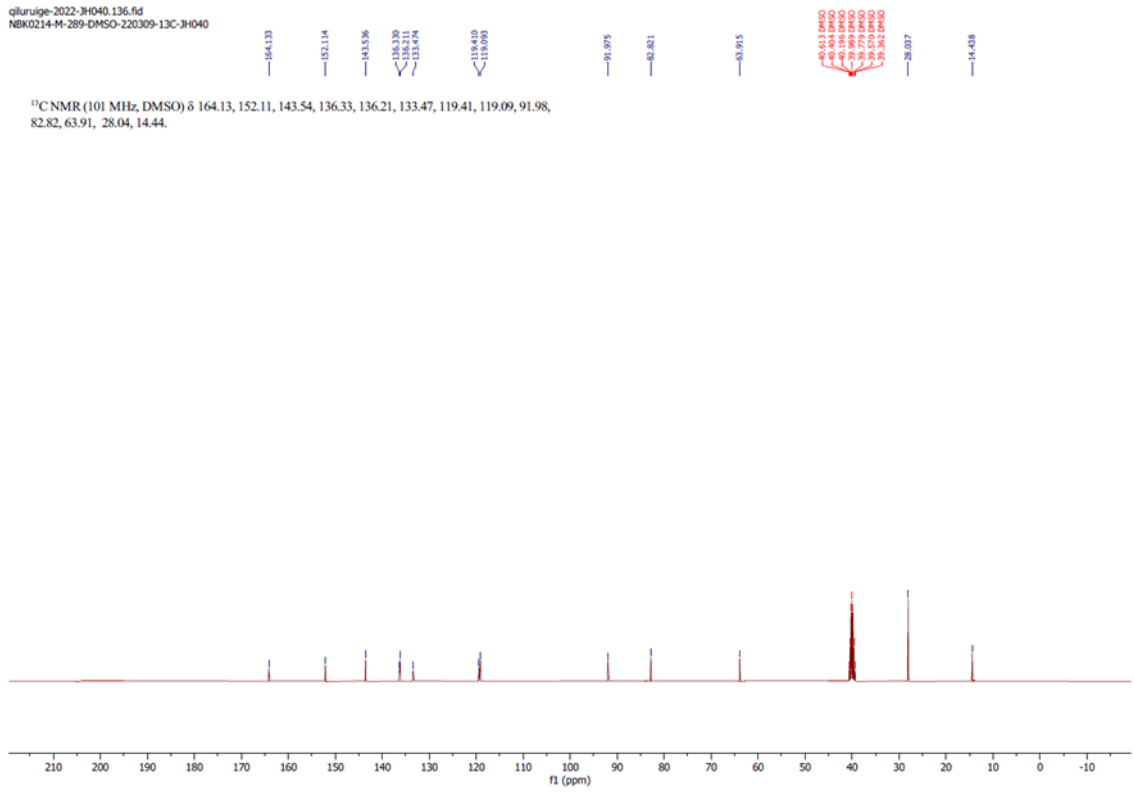
^{13}C NMR (101 MHz, DMSO) δ 165.15, 151.30, 142.66, 135.61, 135.38, 132.10, 118.64, 118.03, 93.20, 63.46, 61.54, 13.91, 13.82.



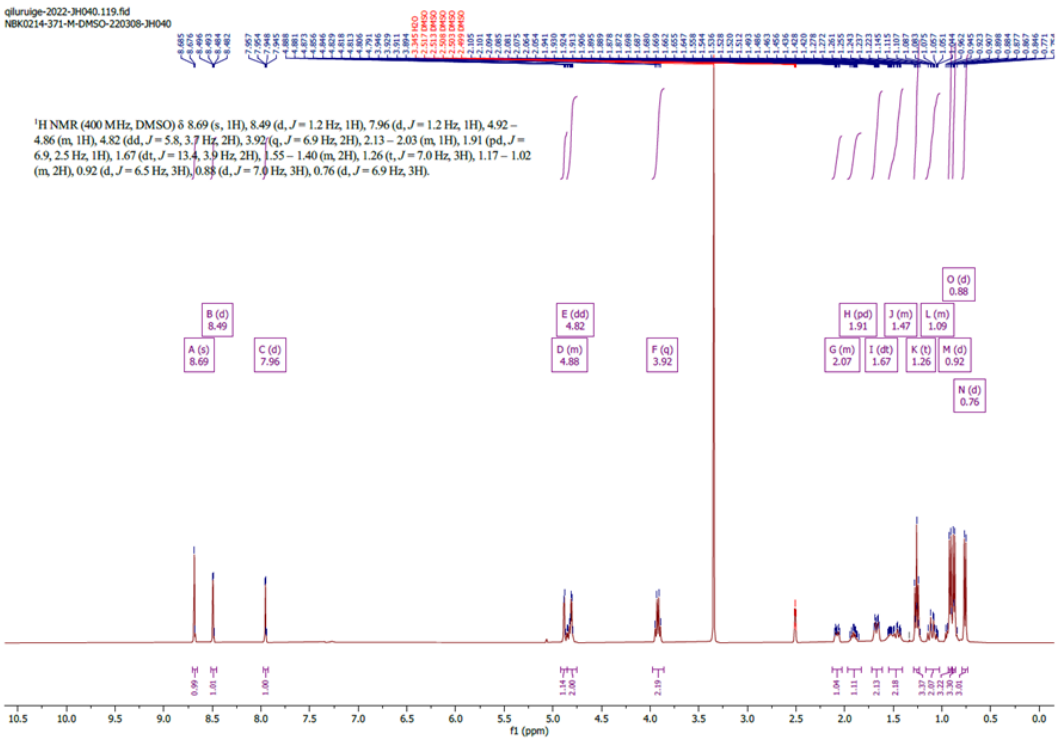
Tert-butyl 8-(1-ethoxyvinyl)imidazo[1,2-b]pyridazine-7-carboxylate(3b)



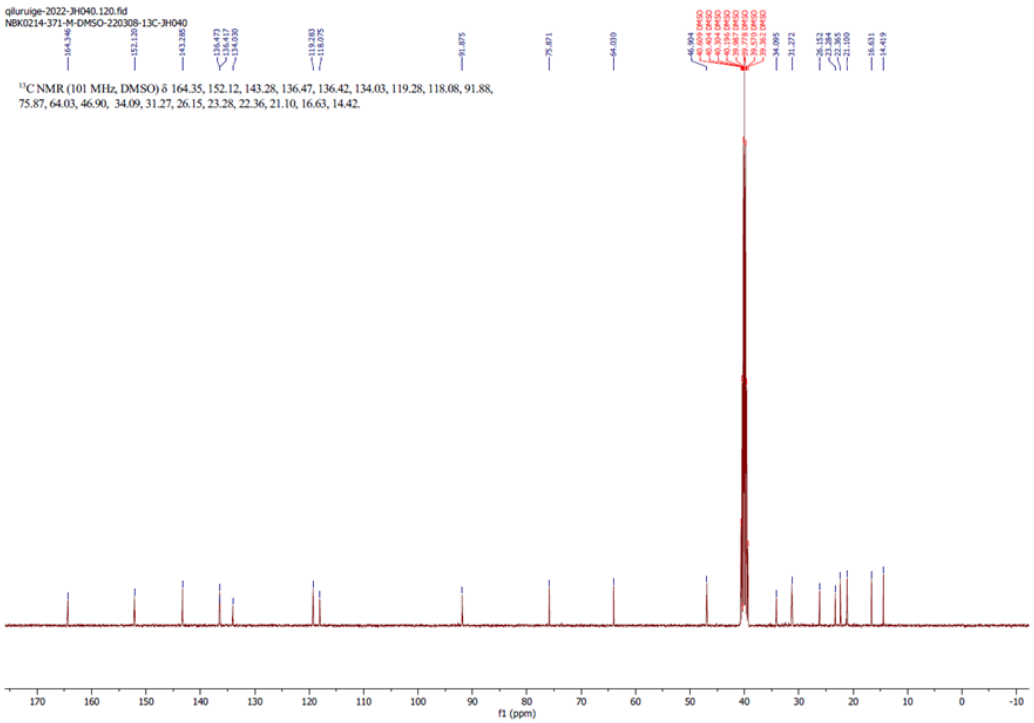
^{1}H NMR (400 MHz, DMSO) δ 8.67 (s, 1H), 8.45 (d, *J* = 1.1 Hz, 1H), 7.93 (d, *J* = 1.2 Hz, 1H), 4.92 (d, *J* = 2.8 Hz, 1H), 4.82 (d, *J* = 2.8 Hz, 1H), 3.93 (q, *J* = 7.0 Hz, 2H), 1.53 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H).

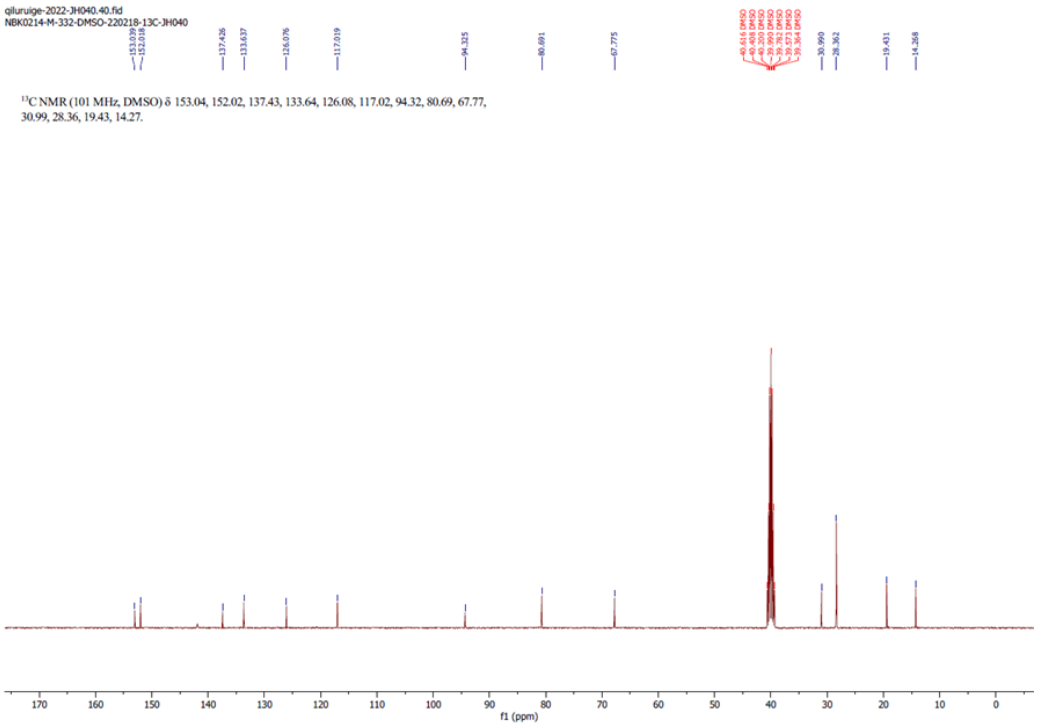


^{13}C NMR (101 MHz, DMSO) δ 164.13, 152.11, 143.54, 136.33, 136.21, 133.47, 119.41, 119.09, 91.98, 82.82, 63.91, 28.04, 14.44.



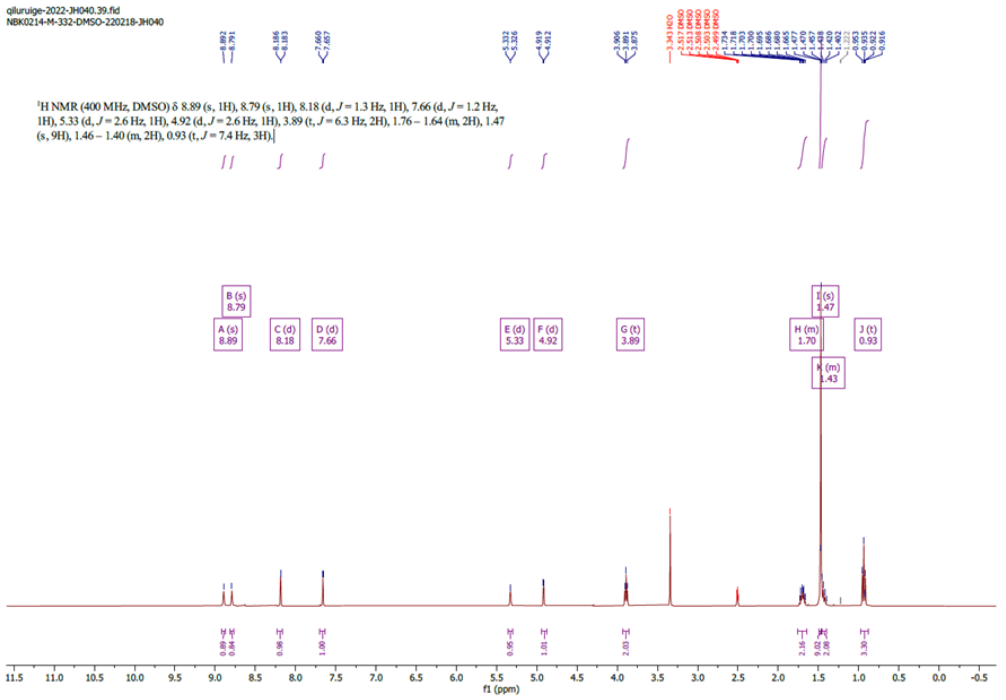
2-isopropyl-5-methylcyclohexyl 8-(1-ethoxyvinyl)imidazo[1,2-b]pyridazine-7-carboxylate(3c)



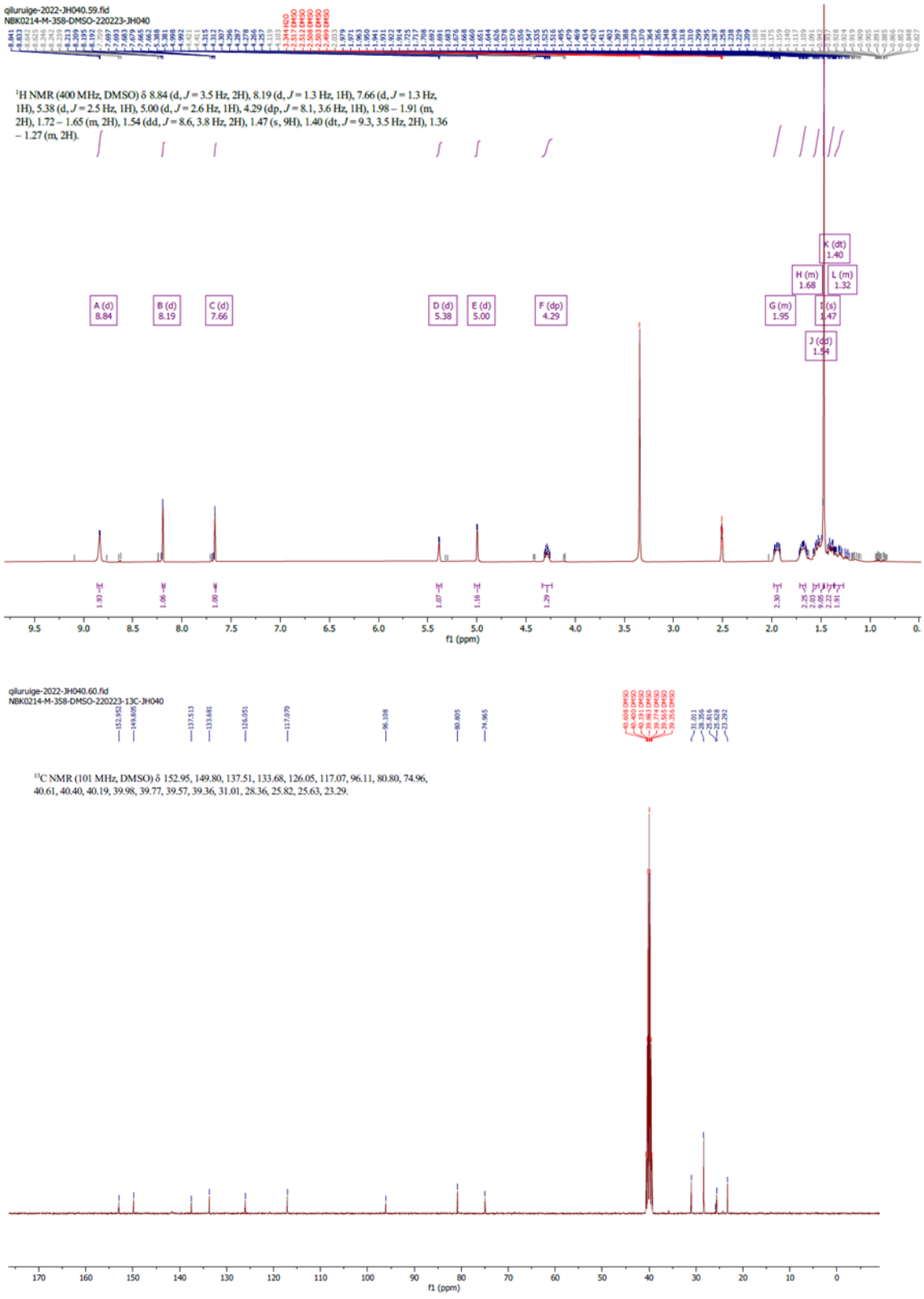


^{13}C NMR (101 MHz, DMSO) δ 153.04, 152.02, 137.43, 133.64, 126.08, 117.02, 94.32, 80.69, 67.77, 30.99, 28.36, 19.43, 14.27.

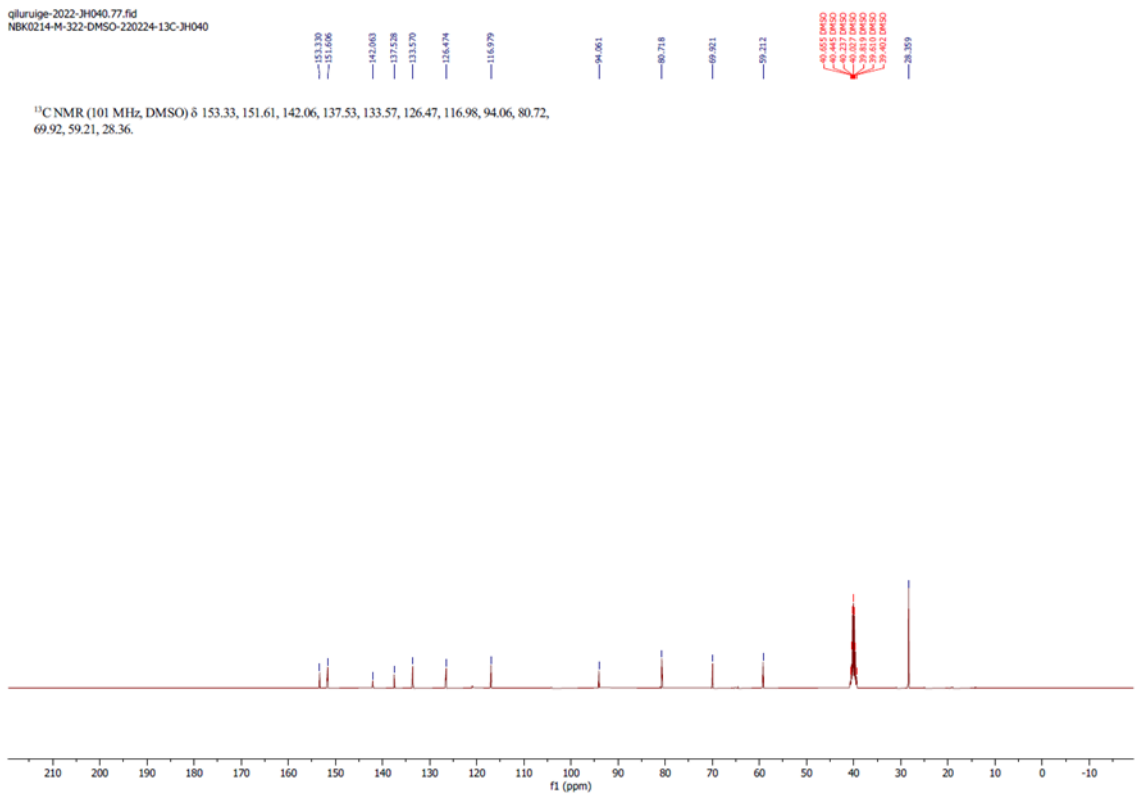
Tert-butyl (8-(1-butoxyvinyl)imidazo[1,2-b]pyridazin-7-yl)carbamate(3f)



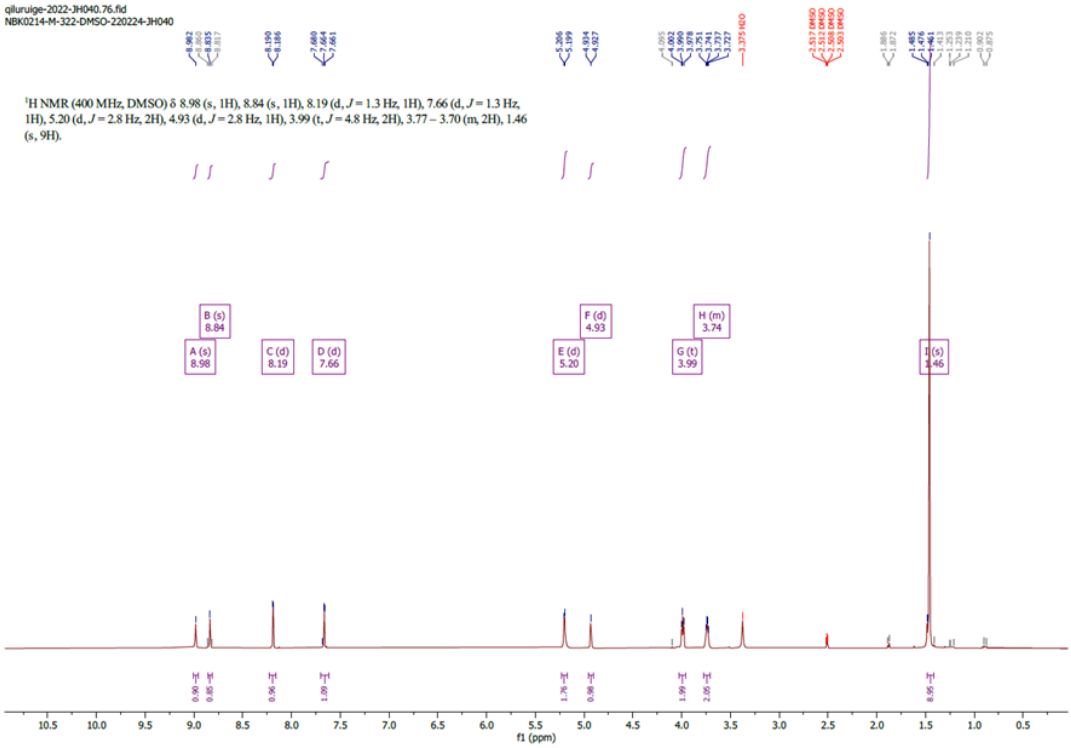
^{1}H NMR (400 MHz, DMSO) δ 8.89 (s, 1H), 8.79 (s, 1H), 8.18 (d, *J* = 1.3 Hz, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 5.33 (d, *J* = 2.6 Hz, 1H), 4.92 (d, *J* = 2.6 Hz, 1H), 3.89 (t, *J* = 6.3 Hz, 2H), 1.76 – 1.64 (m, 2H), 1.47 (s, 9H), 1.46 – 1.40 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).



Tert-butyl (8-(1-(cyclohexyloxy)vinyl)imidazo[1,2-b]pyridazin-7-yl)carbamate(3g)



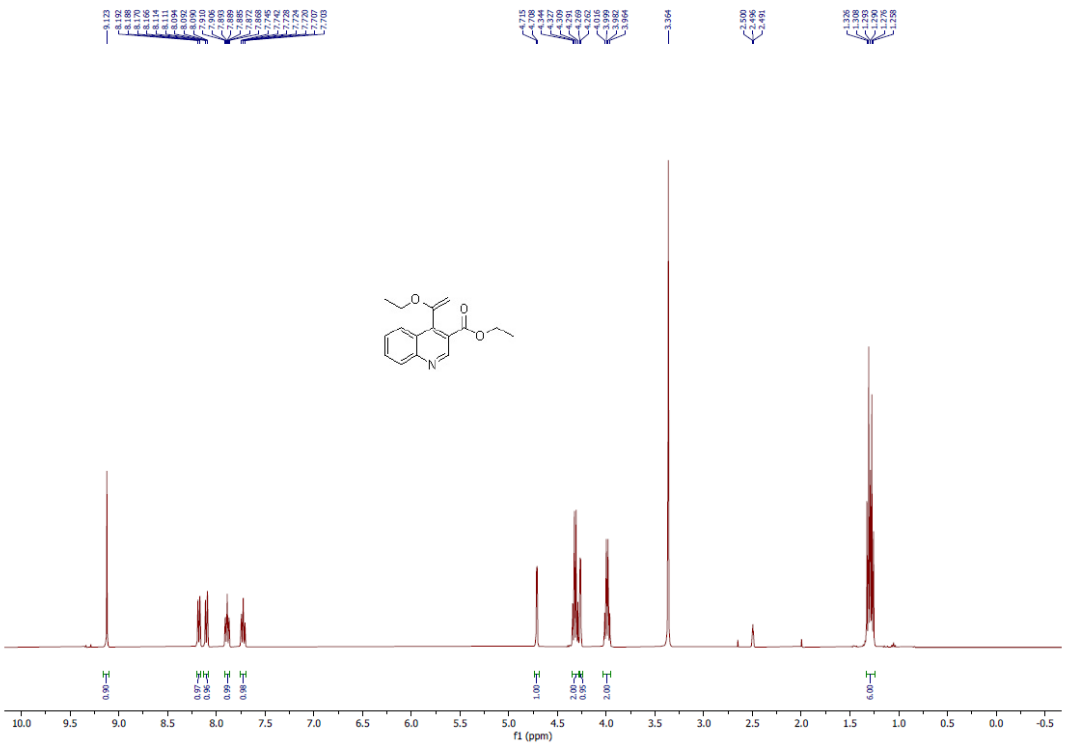
^{13}C NMR (101 MHz, DMSO) δ 153.33, 151.61, 142.06, 137.53, 133.57, 126.47, 116.98, 94.06, 80.72, 69.92, 59.21, 28.36.



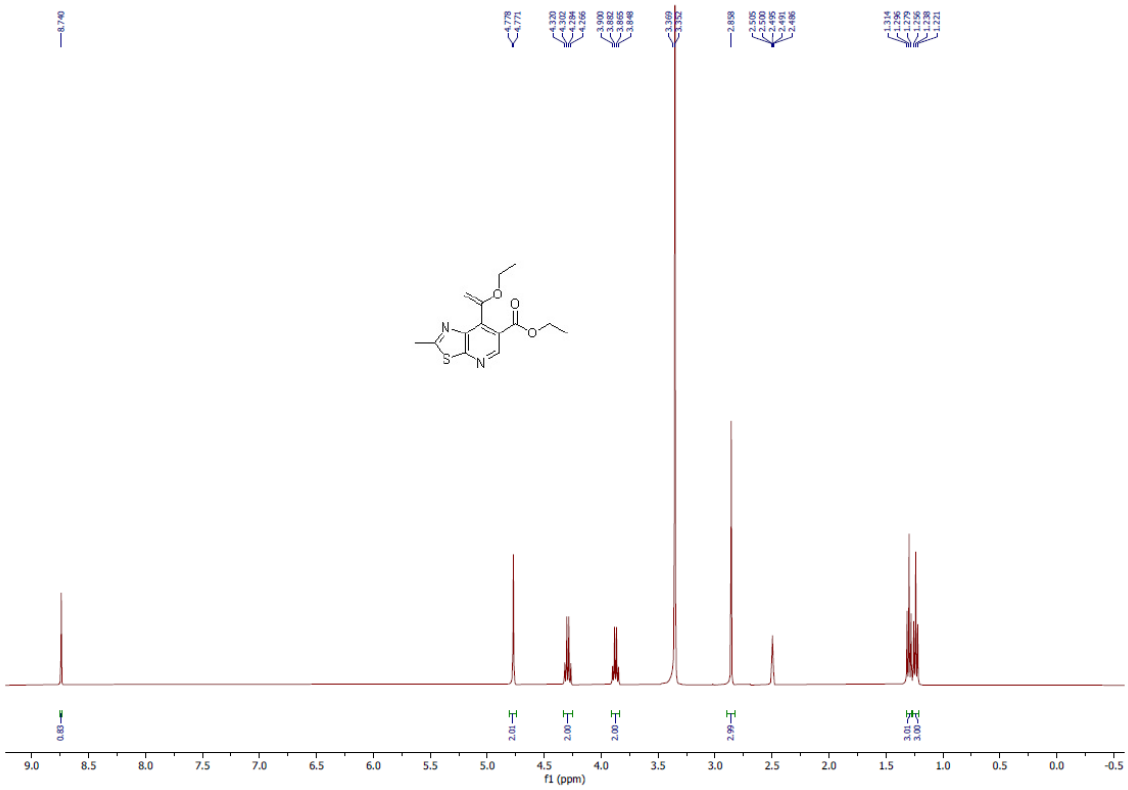
^{1}H NMR (400 MHz, DMSO) δ 8.98 (s, 1H), 8.84 (s, 1H), 8.19 (d, *J* = 1.3 Hz, 1H), 7.66 (d, *J* = 1.3 Hz, 1H), 5.20 (d, *J* = 2.8 Hz, 2H), 4.93 (d, *J* = 2.8 Hz, 1H), 3.99 (t, *J* = 4.8 Hz, 2H), 3.77 – 3.70 (m, 2H), 1.46 (s, 9H).

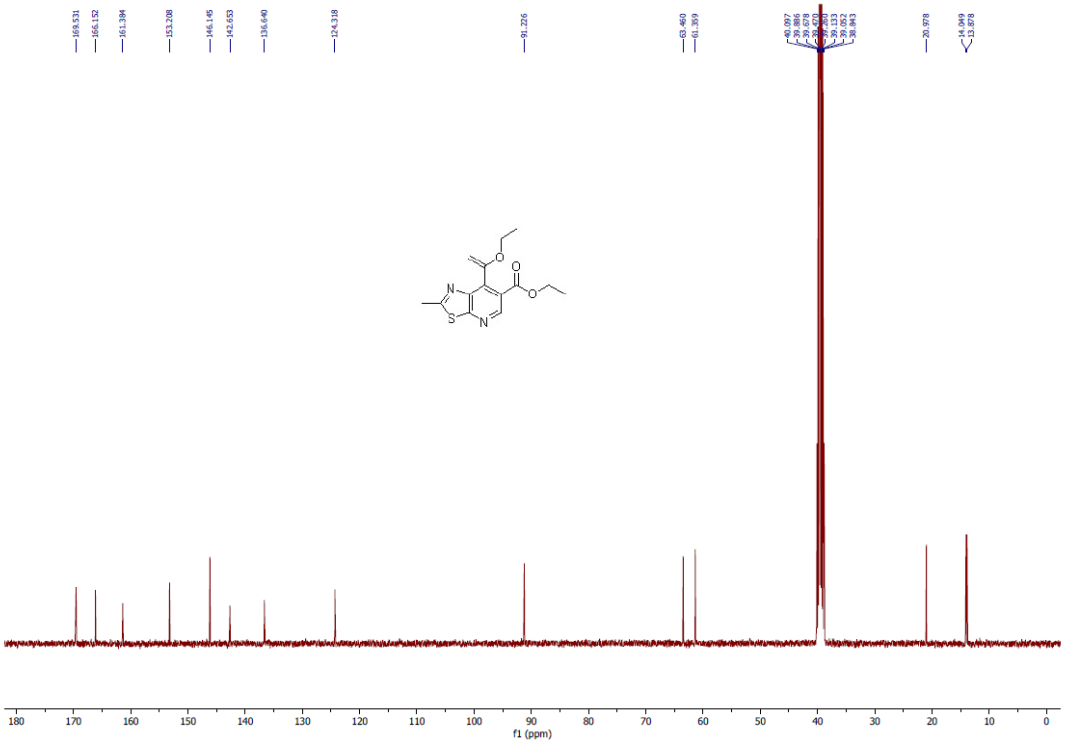
Tert-butyl (8-(1-(2-hydroxyethoxy)vinyl)imidazo[1,2-b]pyridazin-7-yl)carbamate(3h)

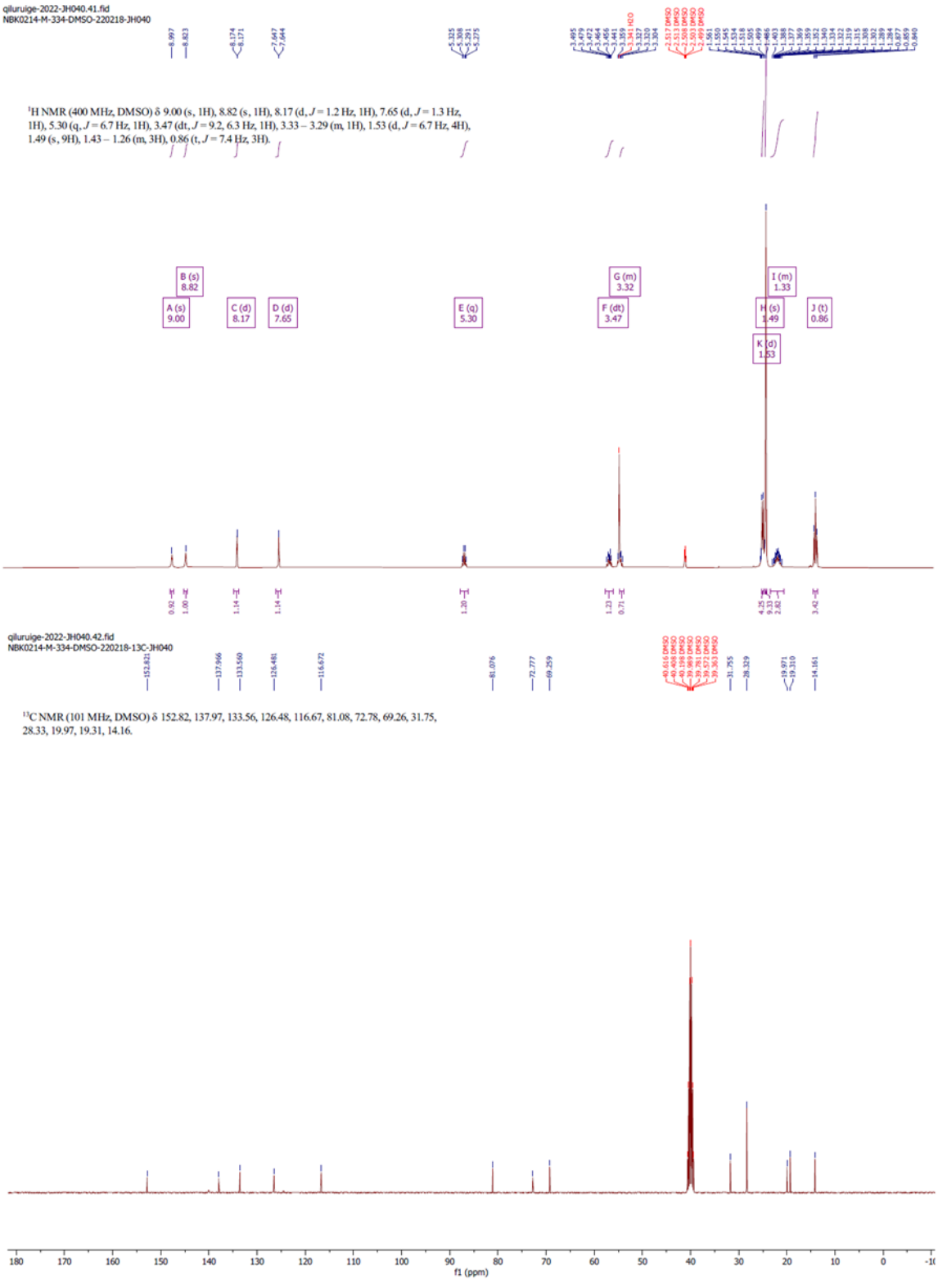
Synthesis report of ethyl 4-(1-ethoxyvinyl)quinoline-3-carboxylate (7a)



Synthesis report of ethyl 4-(1-ethoxyvinyl)-6-fluoroquinoline-3-carboxylate (7b)

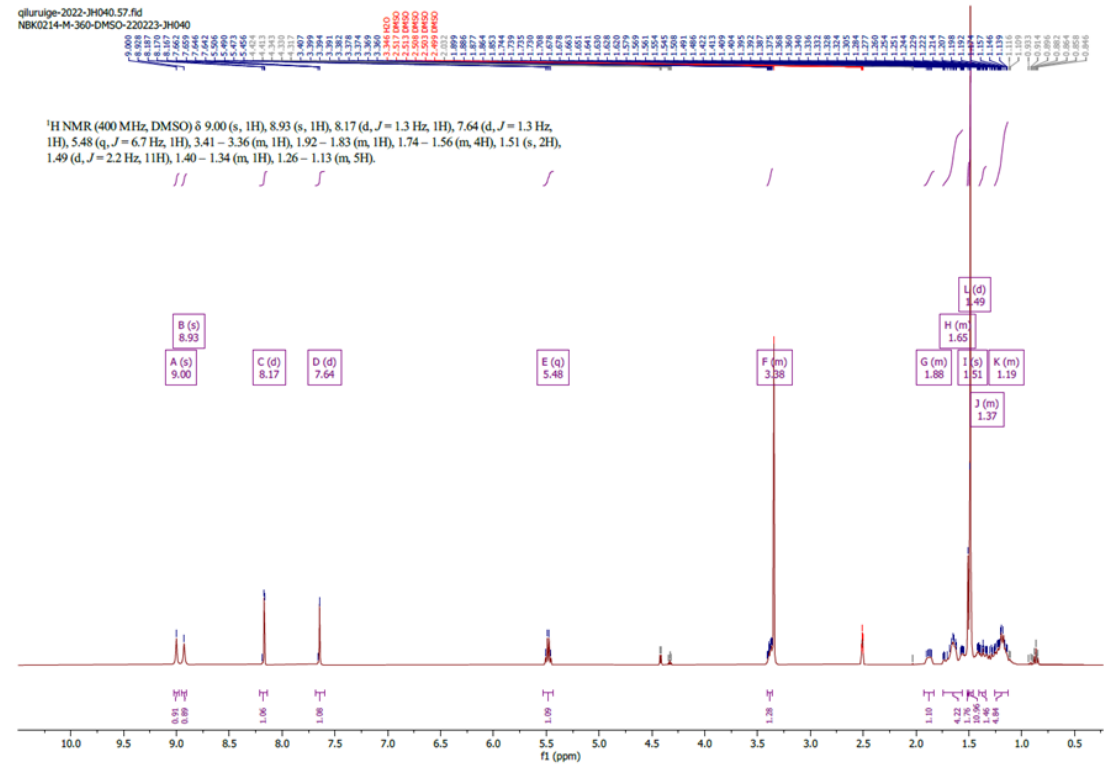






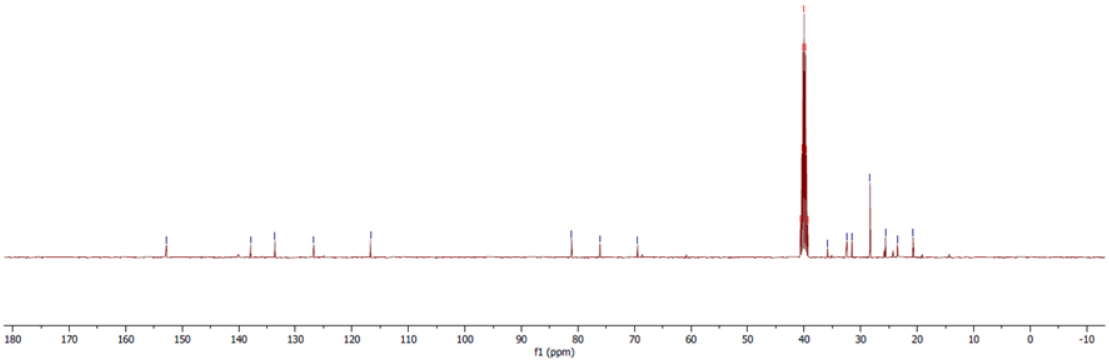
Tert-butyl (R)-(8-(1-butoxyethyl)imidazo[1,2-b]pyridazin-7-yl)carbamate(4f)

Tert-butyl (R)-(8-(1-(cyclohexyloxy)ethyl)imidazo[1,2-b]pyridazin-7-



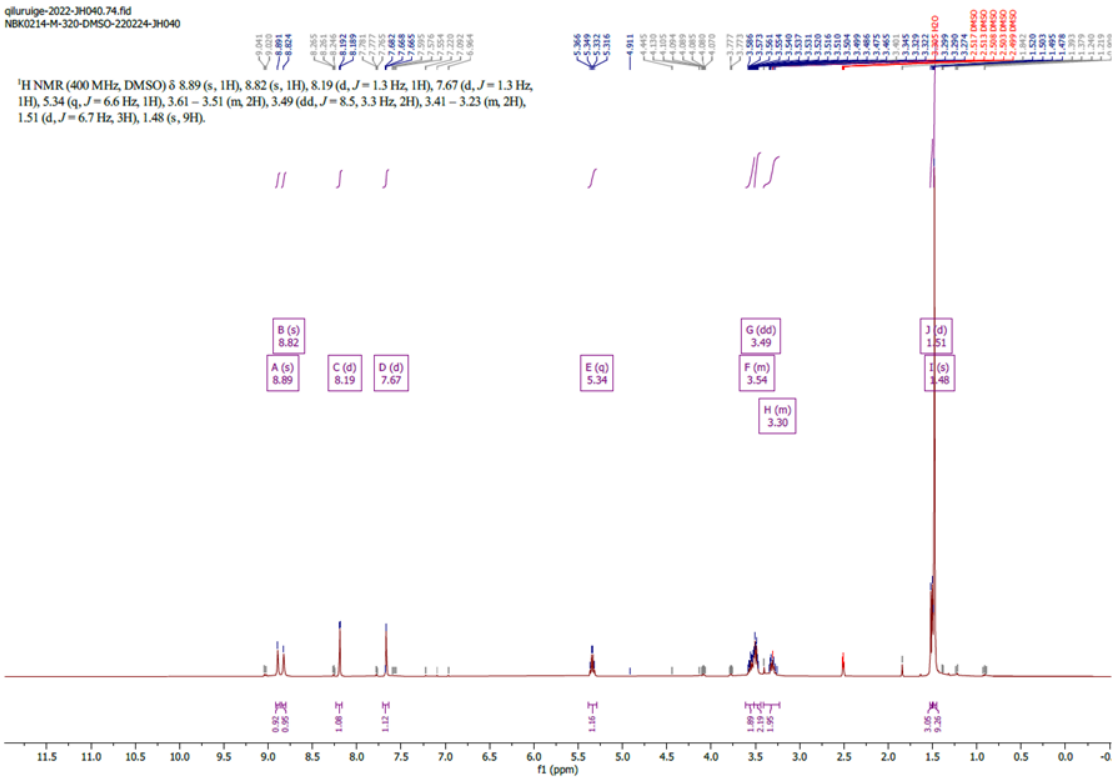
^{1}H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 8.93 (s, 1H), 8.17 (d, *J* = 1.3 Hz, 1H), 7.64 (d, *J* = 1.3 Hz, 1H), 5.48 (q, *J* = 6.7 Hz, 1H), 3.41 – 3.36 (m, 1H), 1.92 – 1.83 (m, 1H), 1.74 – 1.56 (m, 4H), 1.51 (s, 2H), 1.49 (d, *J* = 2.2 Hz, 11H), 1.40 – 1.34 (m, 1H), 1.26 – 1.13 (m, 5H).

^{13}C NMR (101 MHz, DMSO) δ 152.76, 137.88, 133.59, 126.72, 116.68, 81.12, 76.11, 69.44,35.83, 32.41, 31.52, 28.34, 25.60, 23.50, 23.44, 20.71.



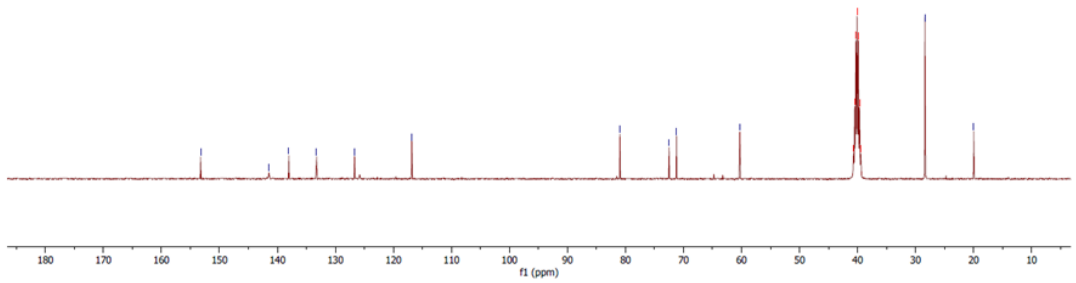
yl)carbamate(4g)

Tert-butyl (R)-(8-(1-(2-hydroxyethoxy)ethyl)imidazo[1,2-b]pyridazin-7-



^{1}H NMR (400 MHz, DMSO) δ 8.89 (s, 1H), 8.82 (s, 1H), 8.19 (d, *J* = 1.3 Hz, 1H), 7.67 (d, *J* = 1.3 Hz, 1H), 5.34 (q, *J* = 6.6 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.49 (dd, *J* = 8.5, 3.3 Hz, 2H), 3.41 – 3.23 (m, 2H), 1.51 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 9H).

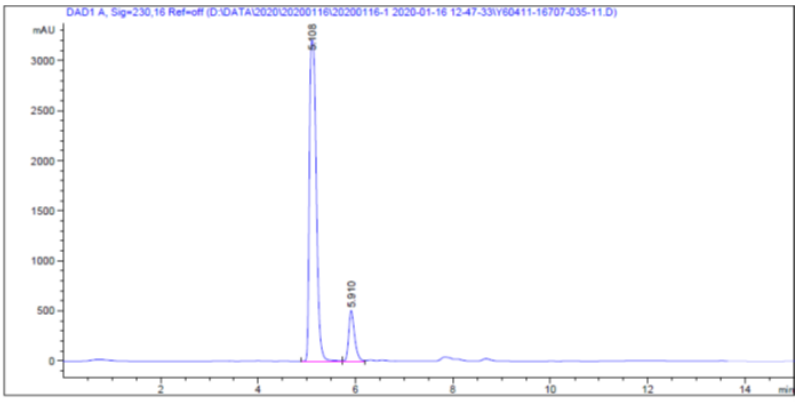
^{13}C NMR (101 MHz, DMSO) δ 153.23, 141.45, 138.04, 133.26, 126.69, 116.84, 80.94, 72.48, 71.21, 60.30, 28.38, 19.97.



yl)carbamate(4h)

The chiral HPLC spectra

The chiral HPLC spectra of 4a-4e

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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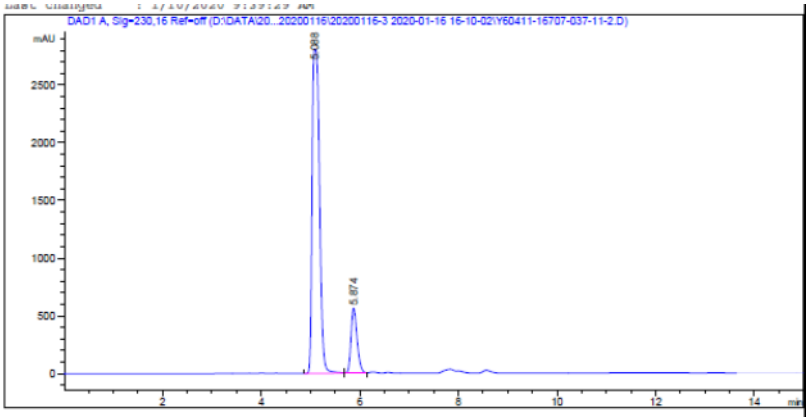


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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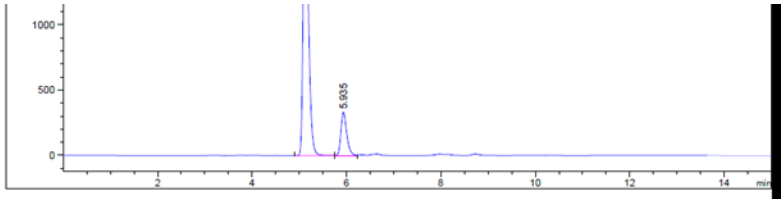


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Date Processed	: 2/20/2020 10:52:40 AM	Processed by	: System Administrator
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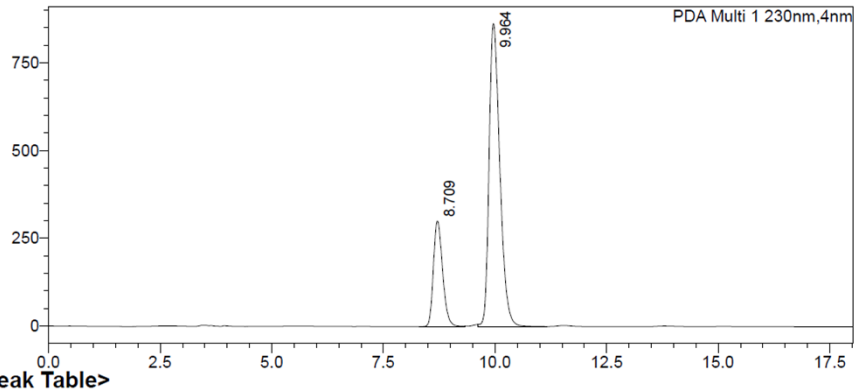

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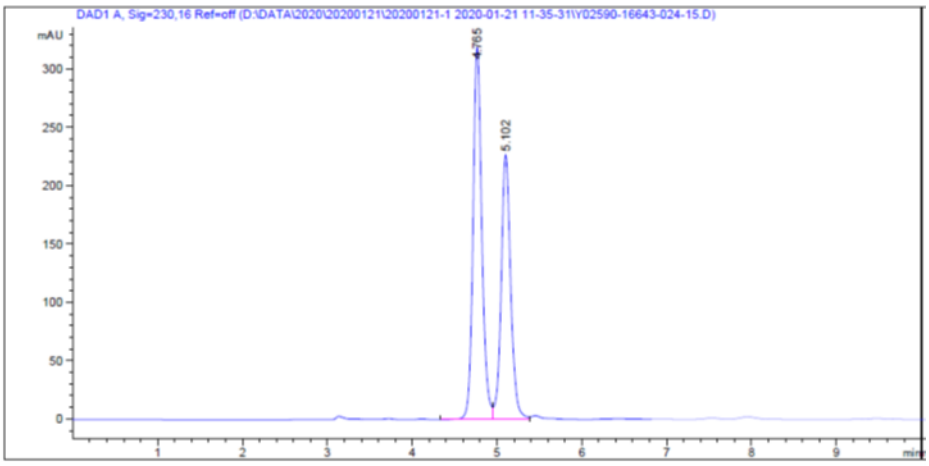
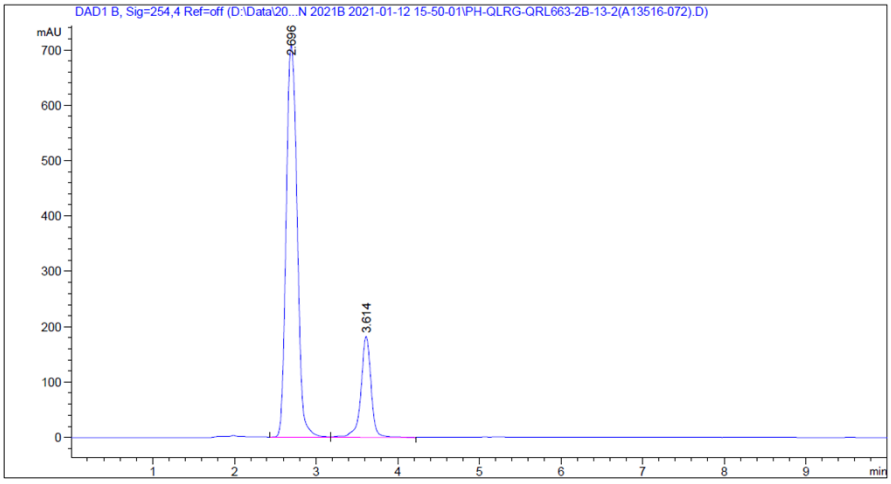
2	9.964	14479733	863100	0.000	M	76.895	3.032
Total		18830562	1164212			100.000	



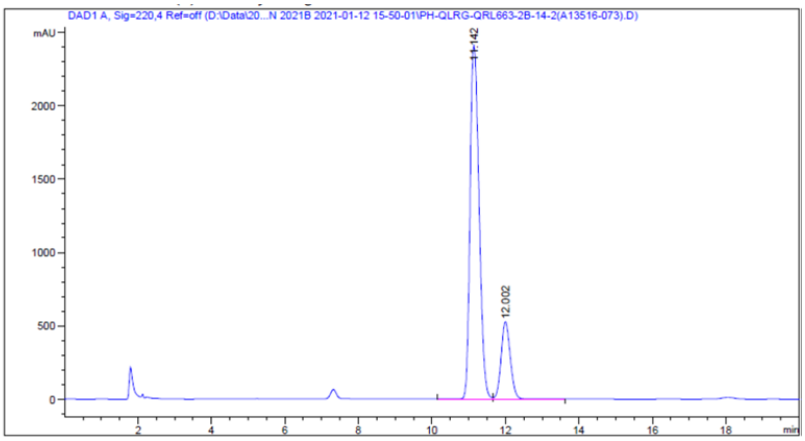

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=230,16 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.765 BV    0.1102 2306.23120  319.55765  56.4232
   2   5.102 VV    0.1195 1781.14673  227.10828  43.5768
```

The chiral HPLC spectra of 8c

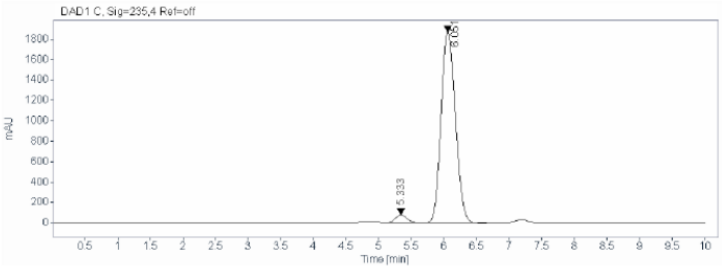


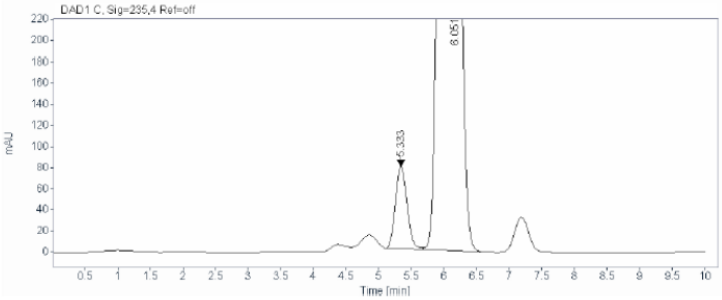

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   2.696 BV    0.1507 6592.55811  707.80090  80.7998
   2   3.614 VB    0.1304 1566.56580  182.11533  19.2002
```

The chiral HPLC spectra of 8d




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.142 BV    0.2713 4.12348e4  2414.04663  81.7860
   2  12.002 VB    0.2692 9183.09180  527.29913  18.2140
```

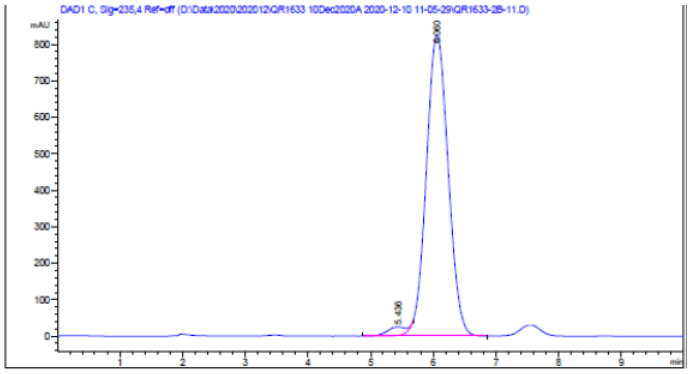




Compound Name	RT	Height	Area	Area%	Peak Resolution USP
	5.333	78.27	974.3297	3.295	
	6.051	1869.76	28599.6328	96.705	1.95703
		Sum	29573.96246		

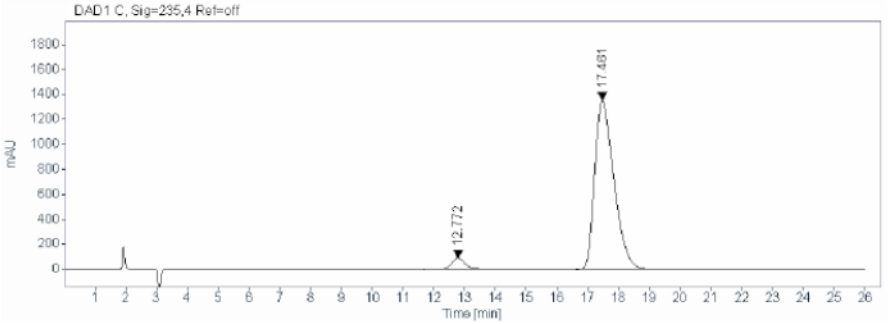
The chiral HPLC of 4f

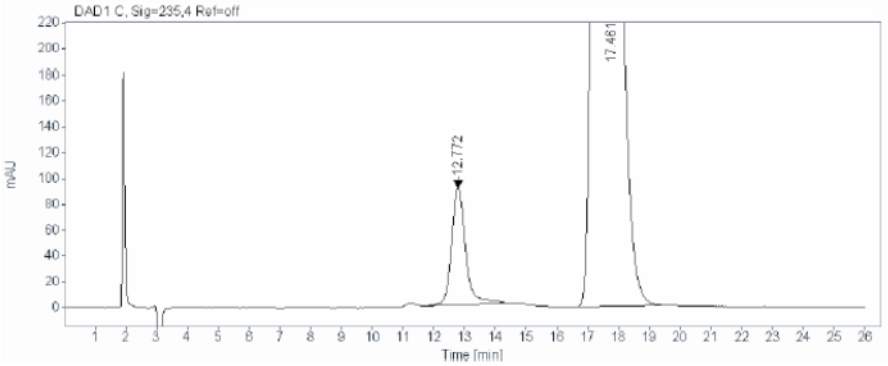
The chiral HPLC of 4g




```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 C, Sig=235,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.436 BV E  0.2987  464.01730   23.66582   2.2562
   2   6.060 VB R  0.3822 2.01025e4   825.34137  97.7438
```

Chiral HPLC spectra of 4h





Compound Name	RT	Height	Area	Area%	Peak Resolution USP
	12.772	90.72	2913.4082	4.721	
	17.461	1357.78	58795.6367	95.279	4.83186
		Sum	61709.04492		