

Adventures in Atropisomerism: Total Synthesis of a Complex Active Pharmaceutical Ingredient with Multiple Atropisomeric Bonds

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EXPERIMENTAL SECTION

General Considerations. All reagents were purchased from commercial sources. Standard benchtop techniques were employed for handling air-sensitive reagents. Melting points (°C) are uncorrected. NMR spectra were recorded on a 400 or 500 MHz spectrometer. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz) and integration. HRMS samples were run on the Thermo LTQ-Orbitrap with Acquity Classic inlet

Procedure for the preparation of (S)-3-(prop-1-en-2-yl)cyclohexan-1-one (7). A 20 L jacketed Chemglass reactor equipped with an overhead agitator, a thermocouple, nitrogen sparging tube, a sampling port, a condenser connected to the glycol supply, and a nitrogen outlet connected sequentially to a bubbler, flow meter and an oxygen meter, was inerted using a vigorous nitrogen sweep. Heptane (4.0 L), 2-cyclohexen-1-one (1 kg, 10.4 M) in heptane (1.0 L), isopropenyl pinacol boronate (1.92 kg, 11.4 M, 1.1 eq) in heptane (1.0 L), DIPEA (0.91 L, 0.67 kg, 0.50 eq), a solution of 2,2-dimethyl-1,3-propanediol (1.19 kg, 1.1 eq) and methanol (0.12L) in water (3 L), and additional heptane (2.55L) were sequentially charged to the reactor via vacuum. Nitrogen sparging subsurface through the agitated biphasic mixture continued after the charges until <300 ppm oxygen level was reached in the headspace prior to the catalyst charge, then the nitrogen flow was reduced to maintain a slight positive pressure in the reactor

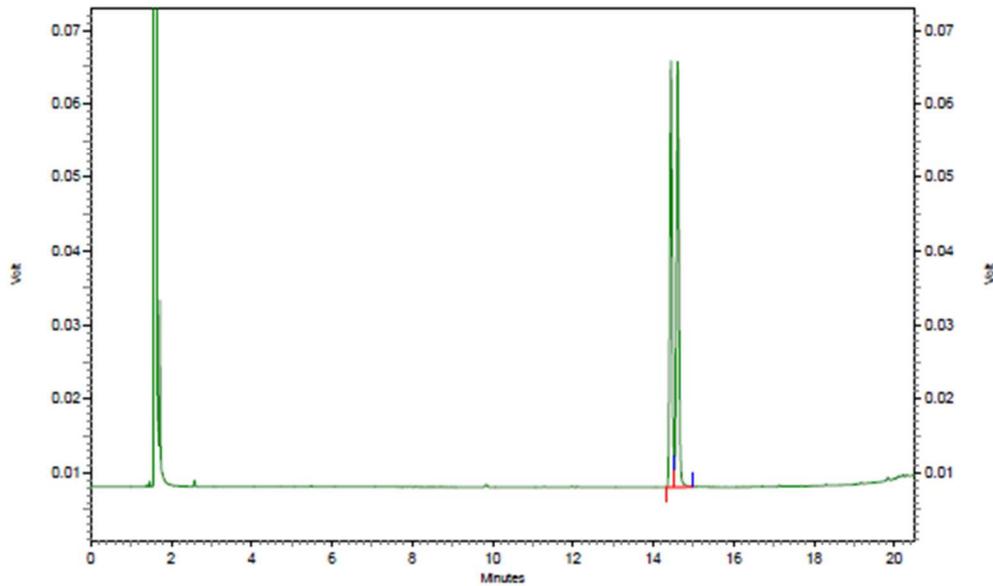
To a 0.5 L jacketed Chemglass reactor equipped with an overhead agitator, nitrogen sparging tube and an outlet connected to an oxygen meter was added methanol (320 mL). The reactor was inerted by sparging nitrogen subsurface through methanol until <300 ppm O₂ was detected in the headspace. S-(+) DTBM-SEGPHOS (77.3 g, 65.6 mmol) and [Rh(cod)Cl]₂ (15.4 g, 31 mmol) were charged and the nitrogen sparging continued until <300 ppm O₂ was detected in the headspace. The mixture was agitated at RT under constant positive nitrogen pressure for 30 min by sweeping low flow of nitrogen through the headspace. The catalyst slurry was transferred from the 0.5 L reactor to the 20L reactor through inerted teflon tubing by applying slight positive pressure of nitrogen. The jacket was set to 60°C on the 20 L reactor, and the biphasic mixture was vigorously heated and agitated under nitrogen. After 26 h the reaction mixture was cooled to 20-25°C. The phases were separated. The bottom aq phase was transferred to a carboy, and the organic phase was washed with 1N HCl (5.6 kg). The organic phase was then washed with water (2.5 L). Two back-extractions with heptane (2 x 2L) from the original aq phase were performed. The combined organic phases were combined (total volume ~15 L) and the solution was polished filtered back to the cleaned reactor. Heptane was removed under reduced pressure (30-40 °C at 45-55 torr, jacket at 40-60 °C) to give the product as a solution in heptane (~20 wt %, 1.207 kg product, 84% yield).

Chiral GC Analysis:

Method Description:

Column: Supelco AlphaDEX 120 30m x 0.25mm x 0.25um, SN=53705-03A (Tmax 230°C)
 Inlet (front): 125C, split ratio 30:1, gas saver 15ml/min at 2min
 Carrier Gas: Helium, constant flow 1.9 mL/min (40 cm/sec)
 Oven Program: 80C for 0min, then 2C/min to 110C for 0min, then 20C/min to 220 for 0min
 (20.5 min run time)
 Detector (front): FID, 250C, 35/350/30 Hydrogen/Air/Makeup (He), 20 Hz acquisition, auto
 zero on
 Needle Rinse Vials: A) MeOH, B) MeOH

Racemic 7:

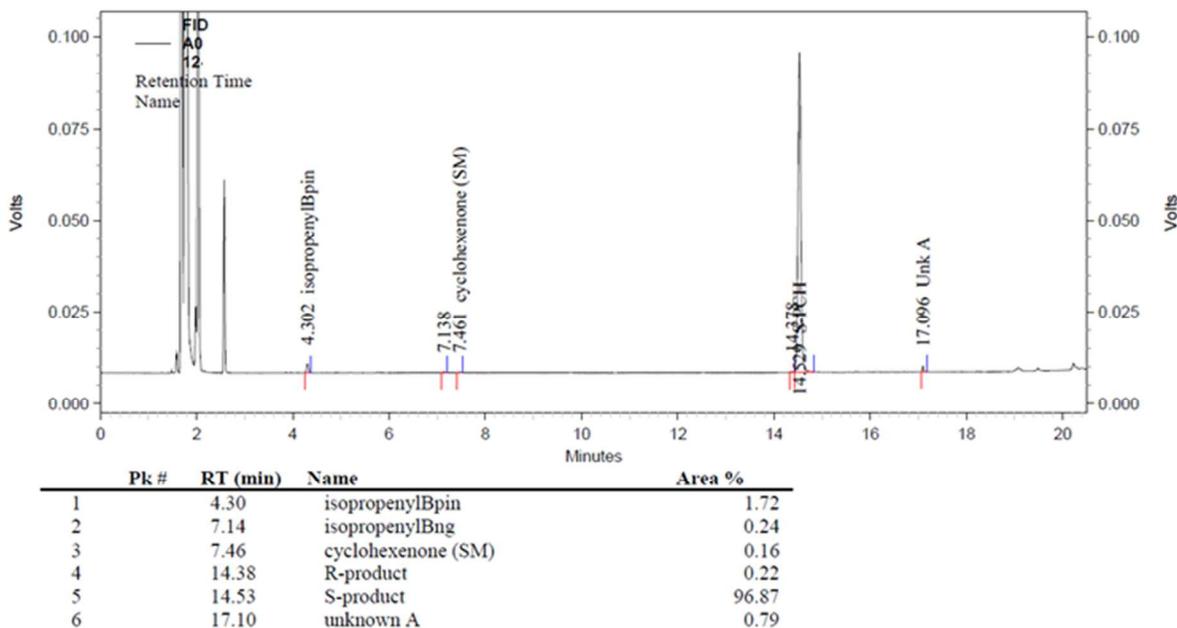


FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	14.442	241802	49.256	R-Product
2	14.608	249103	50.744	S-Product

Totals		490905	100.000	
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GC trace from 20 L reaction:



Procedure for the preparation of (S,E)-4-bromo-5-fluoro-2-(2-(3-(prop-1-en-2-yl)cyclohexylidene)hydrazineyl)benzoic acid (10). A heptane solution of **7** (50 mL, ~20 wt % **9**), was added to a 250 mL Chemglass reactor with overhead agitator. MeOH (75 mL) was added, and a constant vacuum distillation was performed (60 torr vacuum and 50 °C jacket temperature) during the addition of MeOH (300 mL). The batch was then cooled to 20 °C. **6** (8.54g, 29.9 mmol) was added, and the batch stirred at 20 °C for 2 h. Water (25 mL) was added over 25 min under slow agitation (RPM = 100). After agitating for an additional 1.0 h, the resultant slurry was filtered. The cake was washed the cake with 3:2 MeOH/H₂O (2x25mL), and dried overnight at 55 °C under vacuum for overnight to afford **10** as an off-white solid (10.57 g; 96 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ 13.54 (s, 1H), 10.76 (d, J = 26.5 Hz, 1H), 7.73 (appt triplet, J = 6.32 Hz, 1H), 7.64 (dd, J = 9.35, 1.26 Hz, 1H), 4.77-4.75 (m, 2H), 2.68-2.61 (m, 1H), 2.46-2.44 (m, 1H), 2.27-2.12 (m, 2H), 2.06-1.97 (m, 1H), 1.96-1.86 (m, 1H), 1.82-1.80 (m, 1H), 1.75-1.74 (m, 3H), 1.50-1.41 (m, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ 168.7, 152.8, 152.7, 150.7, 148.4, 148.4, 148.2, 145.1, 117.5, 117.2, 116.5, 116.4, 115.8, 115.7, 115.5, 115.5, 109.6, 109.4, 108.9, 108.8, 108.8, 108.8, 44.8, 43.7, 34.2, 30.9, 30.1, 30.1, 25.4, 25.4, 24.2, 20.6, 20.4. mp 170-172 °C. IR (neat) 3317, 2941, 2858, 1668, 1504, 1236, 1186, 884 cm⁻¹; HRMS (ESI) m/z: calcd for C₁₆H₁₈BrFN₂O₂ [M+H]⁺ 369.0608, found 369.0608.

Procedure for the preparation of (S)-5-bromo-6-fluoro-2-(prop-1-en-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (11). To a 250 mL Chemglass reactor with overhead agitator, was added zinc chloride (8.79g, 64.46 mmol), and **10** (17.00 g, 46.05 mmol) followed by isopropyl acetate (170 mL). The batch was heated to 69.5 °C for 71 h and then cooled to rt. 2-Methyltetrahydrofuran (205 mL) was added followed by 1N HCl (85 mL). The

batch stirred at rt for 0.5 h. The layers were separated, and the organic layer was then washed with water (85 mL). The organic layer was polish filtered. The batch was distilled (220 torr vacuum and 70 °C jacket temperature) to 85 mL. A constant volume distillation (220 torr vacuum and 70 °C jacket temperature) was then performed with the continuous addition of acetonitrile (350 mL). Acetonitrile was then added (153 mL). The resultant slurry was then heated to 82 °C for 3 h and then cooled to 20 °C over 2.0 h, where it stirred for an additional 14 h. The slurry was filtered. The cake was washed with acetonitrile (2x17 mL), and dried in a vacuum oven at 50-55 °C overnight affording **11** as a yellow solid (8.66 g; 53% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 13.41 (s, 1H), 11.03 (s, 1H), 7.45 (d, J = 9.85 Hz, 1H), 4.79 (appt d, J = 4.55 Hz, 2H), 3.21-3.17 (m, 1H), 2.95 (dd, J = 17.18, 4.80 Hz, 1H), 2.91-2.83 (m, 1H), 2.61 (dd, J = 16.93, 10.61 Hz, 1H), 2.41-2.35 (m, 1H), 2.01-1.95 (m, 1H), 1.79 (s, 3H), 1.67-1.57 (m, 1H). ¹³C NMR (100 MHz, DMSO-d₆) δ 166.6, 166.6, 152.7, 150.42, 148.4, 134.0, 131.9, 127.4, 127.4, 112.4, 112.3, 109.7, 109.5, 109.4, 109.2, 109.1, 28.3, 27.8, 22.2, 20.7. mp >250 °C. IR (neat) 3444, 3074, 2937, 2919, 2854, 1670, 1225 cm⁻¹; HRMS (ESI) m/z: calcd for C₁₆H₁₅BrFNO₂ [M+H]⁺ 352.0333, found 352.0343.

Procedure for the preparation of (S)-5-bromo-6-fluoro-2-(prop-1-en-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (12). To a 250 mL Chemglass reactor was added acetonitrile (70 mL) followed by **11** (7.02 g) and 1,1-carbonyldiimidazole (4.22 g, 26.0 mmol). The resultant slurry stirred at 20 °C for 5 h and then cooled to 3 °C. Aqueous ammonia (30 mL, 20 mmol, 30 mass %) was added. The batch stirred at 3 °C for 17.5 h. Water (70 mL) was then added, and the slurry stirred for an additional 3 h. The slurry was filtered. The wet cake was washed with 1:1 MeCN/H₂O (2x50 mL), and dried at 55 °C under vacuum affording **12** as a light yellow solid (6.64 g; 95% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 11.05 (s, 1H), 8.11 (s, 1H), 7.59 (d, J = 10.36 Hz, 1H), 7.55 (br s, 1H), 4.78 (br s, 2H), 3.18 (br d, J = 14.65 Hz, 1H), 2.94 (dd, J = 16.93, 4.80 Hz, 1H), 2.88-2.82 (m, 1H), 2.62 (dd, J = 16.93, 10.61 Hz, 1H), 2.40-2.34 (m, 1H), 1.98 (d, J = 11.87 Hz, 1H), 1.78 (s, 3H), 1.66-1.56 (m, 1H). ¹³C NMR (100 MHz, DMSO-d₆) δ 167.6, 152.7, 150.4, 148.5, 139.5, 131.7, 127.0, 127.0, 115.4, 115.3, 109.5, 108.7, 108.6, 107.5, 107.2, 28.2, 27.9, 22.2, 20.7. mp 180-182 °C. IR (neat) 3496, 3433, 3388, 2928, 2902, 2880, 2852, 1607, 1283, 890, 655 cm⁻¹; HRMS (ESI) m/z: calcd for C₁₆H₁₆BrFN₂O [M+H]⁺ 351.0503, found 351.0499.

Procedure for the preparation of (S)-5-bromo-6-fluoro-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (5). To a 250 mL Chemglass reactor was added dichloromethane (100 mL) and **12** (10.00g, 28.48 mmol). The slurry was cooled to 5 °C. Trifluoroacetic acid (14.68 g, 128.7 mmol) was added over 0.5 h (keeping the internal temperature < 10 °C) under agitation (RPM = 250). The batch was warmed to 14 °C over 0.5 h and held for 17.5 h with agitation. Methanol (60 mL) was then added. The batch was cooled to -10 °C. The batch was distilled (80 torr vacuum, increasing the jacket temperature to 20 °C) to 60 mL resulting in a slurry formation. The batch was then distilled at constant volume (60-80 torr vacuum and 20 °C jacket temperature) during the addition of methanol (120 mL). Methanol (20 mL) and aqueous ammonia (30 mL) was then added, and the batch stirred at 20 °C for 0.5 h. The batch was then heated to 70 °C. Water (40 mL) was added over 15 min to yield a clear solution. The batch was seeded with **5** (0.005 g). The batch continued to heat at 70 °C for 0.5 h

and was then cooled down to 20 °C in 0.5 h. The batch stirred at 20 °C for 65 h. The slurry was filtered. The cake was washed with 1:1 MeOH/H₂O (2x15 mL), and dried in the oven at 65 °C under vacuum for 24 h, giving **5** as an off-white solid (9.17 g, 87% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 10.99 (s, 1H), 8.10 (s, 1H), 7.57 (d, J = 10.36 Hz, 1H), 7.54 (br s, 1H), 4.27 (s, 1H), 3.26 (dd, J = 15.66, 4.29 Hz, 1H), 2.93 (dd, J = 17.18, 4.55 Hz, 1H), 2.76-2.68 (m, 1H), 2.44 (dd, J = 16.17, 11.87 Hz, 1H), 2.12 (br d, J = 11.12 Hz, 1H), 1.69-1.62 (m, 1H), 1.31 (ddd, J = 25.01, 12.38, 5.31 Hz, 1H), 1.14 (s, 6H). ¹³C NMR (100 MHz, DMSO-d₆) δ 167.7, 152.6, 150.3, 140.5, 131.8, 127.0, 127.0, 115.3, 115.2, 109.1, 109.1, 107.3, 107.0, 101.4, 101.2, 70.4, 45.0, 27.2, 26.7, 24.9, 24.4, 22.9. mp 218-222 °C. IR (neat) 3427, 3420, 3349, 3200, 2969, 2930, 2985, 1564, 1279 cm⁻¹; HRMS (ESI) m/z: calcd for C₁₆H₁₈BrFN₂O₂ [M+H]⁺ 369.0608, found 369.0608.

Procedure for the preparation of 2-amino-4-bromo-5-fluorobenzoic acid. 5% Pt/C (50% water-wet) (60 g, 6 wt%) was charged to a nitrogen blanketed 100 L reactor containing isopropyl acetate (22 L) and 4-bromo-5-fluoro-2-nitrobenzoic acid (1.00 kg, 3.79 mol). The headspace was exchanged three times with nitrogen and followed three times with hydrogen. The reaction mixture was stirred at 20-30 °C under an atmosphere of hydrogen. After 24-40 hours, the reaction vessel headspace was exchanged three times with nitrogen. The reaction mixture was filtered. The reaction vessel and filter train were rinsed with isopropyl acetate (5 L). The combined organic layers were concentrated under reduced pressure to about 5.0 L. The solvent then was exchanged to toluene under reduced pressure constant volume distillation. The resulting solids were isolated by filtration, washed with toluene and dried at 50 °C under reduced pressure to afford 2-amino-4-bromo-5-fluorobenzoic acid as a white to off-white crystalline solid (0.59 kg, 66% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.62 (d, J=9.6 Hz, 1H), 7.21-6.5 (m, 3H), 3.8-3.3 (br s, 1H). ¹³C NMR (100 MHz, DMSO-d₆) δ 170.5, 149.6, 147.6, 147.3, 120.4, 118.1, 118.0, 109.2, 109.0, 99.5. mp >250 °C. IR (neat) 3494, 3351, 3053, 3038, 1521, 774 cm⁻¹; HRMS (ESI) m/z: calcd for C₇H₅BrFNO₂ [M+H]⁺ 233.9560, found 233.9551.

Procedure for the preparation of 4-bromo-5-fluoro-2-hydrazineylbenzoic acid hydrochloride (6b). Slowly charged was a solution of sodium nitrite (100.0 g, 6.38 mol) and water (1.8 L) to a cold slurry of 2-amino-4-bromo-5-fluorobenzoic acid (1.00 kg, 4.27 mol) in water (2.2 L) containing 35% HCl (2.1 kg, 20.15 mol) in a 5 L reactor. Caution: reaction is exothermic and produces an acidic gas; maintain the internal batch temperature at -5 – 5 °C during the addition of sodium nitrite. The reaction mixture slurry was stirred at 0 °C for 3-5 hours. The cold diazonium salt slurry was charged over 3-5 hours to a cold solution of sodium bisulfite (2.66 kg, 25.0 mol in water (7.5 L). Caution this reaction is exothermic; maintain the internal batch temperature at -5 – 5 °C during the addition. The diazonium reaction vessel was rinsed with cold water (2.5 L) and transferred water rinse slowly to the reaction mixture. After 40 min the reaction mixture was warmed to 20 °C over one hour. The reaction mixture slurry was stirred at 20 °C for 3 h. The batch was then slowly transferred to a 55-60 °C solution of 35% HCl (15.0 kg, 144.0 mol) and water (3.0 L). Slow agitation during the transfer is necessary in order to minimize excessive foaming during the hydrolysis step. Caution: endothermic reaction produces an acidic off-gas. The transfer vessel was rinsed with water (2.5 L) and transferred to the reaction vessel. The reaction mixture was stirred at 60-65 °C for 2 hours. The reaction mixture slurry was cooled to 0 °C. The product was isolated by filtration and washed, via

reaction vessel, with water (3.0 L). The wet cake was charged back to the reactor and was slurried with isopropyl acetate (9.0 L) for 2 hours at 20 °C. The product was isolated by filtration, washed with isopropyl acetate (1.0 L), and dried at 45-50 °C under reduced pressure to afford **6** (0.856 kg, 70% yield) as an off-white crystalline solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.04 (br s, 3H), 9.03 (br s, 1H), 7.76 (d, *J*=9.1 Hz, 1H), 7.63 (d, *J*=5.8 Hz, 1H). ¹³C NMR (100 MHz, DMSO-d₆) δ 167.2, 152.8, 150.5, 144.6, 144.6, 119.0, 118.1, 117.9, 114.4, 114.4. mp >250 °C. IR (neat) 3213, 3002 (br), 1692, 1483, 1238, 743 cm⁻¹; HRMS (ESI) *m/z*: calcd for C₇H₆BrFN₂O₂ [M+H]⁺ 248.9669, found 248.9660.

Procedure for the preparation of (2S,5R)-5-(3-amino-2-methylphenyl)-6-fluoro-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (3). To vessel 1 was charged water (6.0 L, 6.0 L/kg), potassium phosphate tribasic anhydrous powder (3.45 kg, 6.00 eq), which was then aged with agitation to dissolve for 15 min. To vessel 2, was charged 2-methyl tetrahydrofuran (5.0 L, 5.0 L/kg), (R)-BINAP catalyst (0.093 kg, 0.055 eq), palladium (II) acetate (0.030 kg, 0.050 eq), which was then aged with agitation to dissolve for 15 min. To vessel 2 was charged **5** (0.10 kg, 0.10 eq, LR), 2-methyl tetrahydrofuran (0.5 L, 0.5 L/kg), water (0.5 L, 0.5 L/kg). Vessel 2 was then inerted with vacuum/N₂ swings [O₂] < 400 ppm. Vessel 2 was heated to 70 °C, aged for 3 h with agitation, and then cooled to 20 °C. To a 20 L Chemglass reactor (Vessel 2) with an overhead agitator, a thermocouple, nitrogen sparging tube, a sampling port, a condenser connected to the glycol supply, and a nitrogen outlet was charged **5** (0.90 kg, 0.90 eq, LR), tetrahydrofuran (2.5 L, 2.5 L/kg), **4** (0.584 kg, 1.15 eq), and methanol (2.0 L, 2.0 L/kg). Vessels 1 and 2 were inerted with vacuum/N₂ swings [O₂] < 400 ppm and cooled to -15 °C. The phosphate solution from vessel 1 was transferred to vessel 2. Vessel 2 was heated to 5 °C and aged for 3 h with agitation. Vessel 2 was heated to 25 °C and aged for 1 h with agitation. To vessel 2 was charged water (2.5 L, 2.5 L/kg) and N-acetyl-L-cysteine (1.0 kg, 2.3 eq). The batch was then heated to 40 °C, aged for 3 h with agitation, and cooled to 20 °C. Agitation was stopped. The layers settle, and the lower aqueous layer was split. To vessel 2 was charged tetrahydrofuran (1.0 L, 1.0 L/kg) and brine [sodium chloride 13% w/w] (7.0 L, 7.0 L/kg). The batch agitated for 0.5 h. Agitation was stopped. The layers settle, and the lower aqueous layer was split. The batch was then transferred to vessel 3 via a polish filter. Vessel 2 was rinsed with tetrahydrofuran (1.0 L, 1.0 L/kg) which was then transferred to vessel 3 via a polish filter. The batch was distilled to 8.0 L at 200 mbar. The batch was then heated to 50 °C. n-Butanol (4.0 L, 4.0 L/kg) was charged followed by **3** seed (0.011 kg, 0.010 eq). The slurry aged for 4 h at 50 °C with agitation. A constant volume distillation was then performed at 100 mbar during the addition of n-butanol (9.0 L). The batch was then cooled to 50 °C and aged for 1 h with agitation. The batch was then cooled to 20 °C and filtered. n- Butanol (2.0 L, 2.0 L/kg) was charged to rinse vessel 3 and filtered. The wet cake was washed with n-heptane (2x4.0 L) and dried in the oven under vacuum at 50 °C to afford **3** as an off-white solid (0.93 kg, 87%). ¹H NMR (500 MHz, DMSO-d₆) δ 10.76 (s, 1H), 8.09 (br s, 1H), 7.54 (d, *J*=10.7 Hz, 1H), 7.47 (br s, 1H), 6.96 (t, *J*=7.7 Hz, 1H), 6.72 (d, *J*=7.9 Hz, 1H), 6.41 (d, *J*=7.3 Hz, 1H), 4.90 (s, 2H), 4.19 (s, 1H), 2.91 (br dd, *J*=16.6, 4.0 Hz, 1H), 2.50 - 2.39 (m, 1H), 2.05 - 1.93 (m, 1H), 1.88 - 1.75 (m, 5H), 1.64 - 1.53 (m, 1H), 1.21 - 1.11 (m, 1H), 1.09 (s, 6H). ¹³C NMR (125.8 MHz, DMSO-d₆) δ 169.0 (d, *J*=2.7 Hz), 152.5 (d, *J*=229.8 Hz), 146.7, 139.1, 134.4, 132.0, 127.7 (d, *J*=4.5 Hz), 125.6, 123.3 (d, *J*=20.0 Hz), 120.5, 119.2, 115.1 (d, *J*=7.3 Hz), 114.3, 109.5 (d, *J*=4.5 Hz), 107.2 (d, *J*=27.3 Hz), 70.9, 45.9, 27.6, 27.2, 25.3, 25.0, 22.7, 14.7. mp >250 °C. IR (neat) 3490, 3436,

3386, 2958, 1649, 1565, 1290, 941, 778 cm^{-1} ; HRMS (ESI) m/z : calcd for $\text{C}_{23}\text{H}_{26}\text{FN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 396.2082, found 396.2082.

Chiral HPLC Analysis:

Gradient: Complex

Start % B: 5

4 Min. 30%

41 Min. 95%

42 Min. 95%

Stop Time: 42 min

Flow Rate: .7 ml/min

Wavelength1: 230

Wavelength2: 240

Solvent Pair: ZY5361/ZY5362

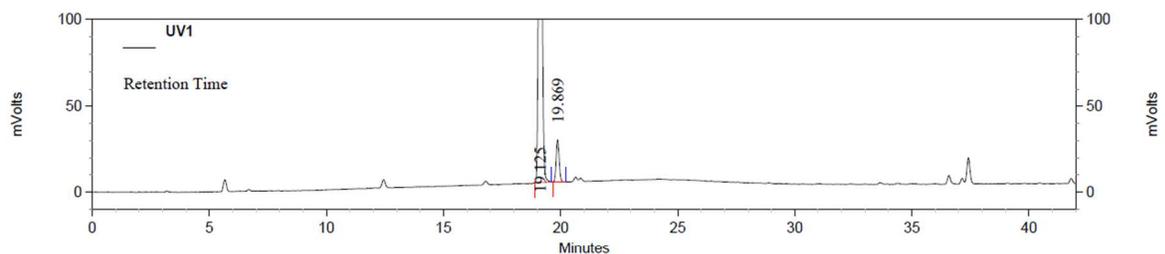
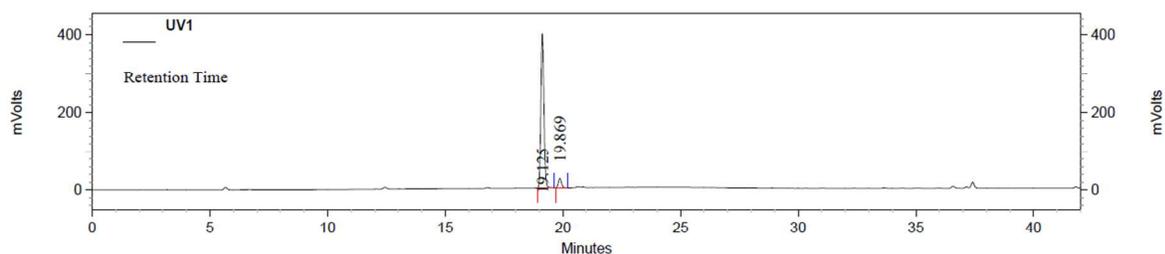
Solvent A: A1: 10 mM sodium phosphate buffer pH7

Solvent B: B1: $\text{CH}_3\text{CN}:\text{MeOH}$ (50:50)

Column 3 : 3: Waters XBridge BEH C18 S-2.5um 150 X 4.6mm SN:01553602618021

Oven Temperature: 30

Standard Mixture of Atropisomers:

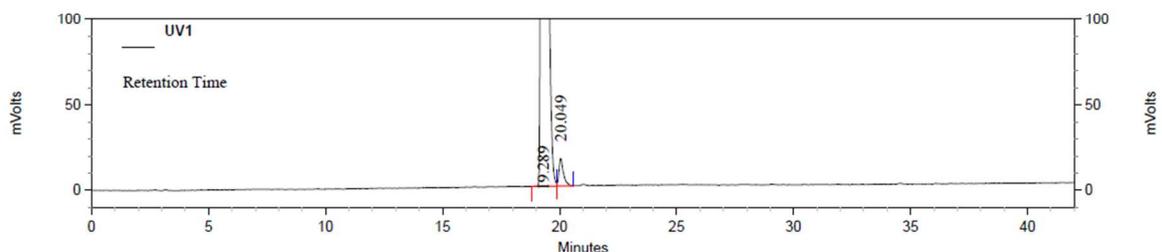
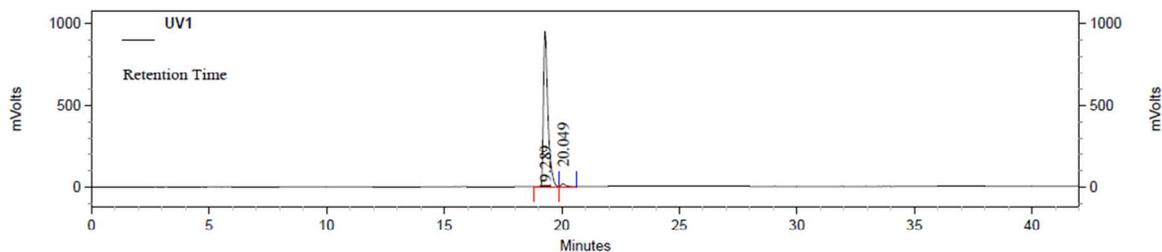


UV1 Results

PK #	RT (min)	Area	Area Percent	Relative RT	Name
1	19.13	3524666	94.16	0.00	3
2	19.87	218760	5.84	0.00	3-Atropisomer

Totals		3743426	100.00		
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Isolated 3:



UV1 Results						
Pk #	RT (min)	Area	Area Percent	Relative RT	Name	
1	19.29	12630570	98.32	0.00	3	
2	20.05	216331	1.68	0.00	3-Atropisomer	
Totals		12846901	100.00			

Procedure for the preparation of 3-fluoro-2-(methyl(propoxycarbonyl)amino)benzoic acid (21). A 20 L jacketed glass reactor with an overhead mechanical agitator, a thermocouple, a nitrogen inlet, a glass baffle, and a condenser rinsed with dichloromethane (4 L) followed by nitrogen sweeping through bottom valve overnight. To the reactor was charged 3-fluoro-2-(methylamino)benzoic acid (1004.7 g, 5939.7 mmol,) followed by dichloromethane (6000 mL) to form an off-white-colored suspension. Cesium carbonate (1035.2 g, 3170 mmol) was added followed the addition of water (6000 g) at ambient temperature. Gas evolution was observed during the water charging. The colorless biphasic mixture was stirred for NLT 15 min. n-Propyl chloroformate (806.0 g, 6445.4 mmol) was charged to the reactor over 1 h with agitation, maintaining the batch temperature between 15 and 20 °C. The white milky reaction mixture was agitated for 90 minutes at 20 °C. The agitation was stopped, and the reaction mixture was allowed to settle for phase split. The organic layer was split from the aqueous layer and was transferred to a carboy. Anhydrous Na₂SO₄ (1000 g) and 60-200 mesh silica gel (100 g) was added to the dichloromethane solution in the carboy, and it aged overnight. The dichloromethane solution was transferred to a clean 20 L reactor via a 10 micron filter. The carboy was rinsed dichloromethane (2 x 1 L) and transferred to the reactor. The batch was distilled (200-253 torr and a jacket temperature of 32 °C) to a volume of 3 L. Dichloromethane (3 L) was charged to the reactor, and the batch was distilled (200-253 torr and a jacket temperature of 32 °C) to a volume of 3 L. Dichloromethane (1 L) was then charged to the reactor, which was then into a carboy. Dichloromethane (2 x 500 mL) was charged to the reactor and rinsed through the filter. The organic solution was then transferred to a 20 L reactor via a polish filter. The carboy was rinsed

with dichloromethane (3 x 300 mL) and transferred to the reactor via the polish filter. Dichloromethane (500 mL) was added to the reactor. The batch was distilled under reduced pressure (200-253 torr and a jacket temperature of 32 °C) to a volume of 2 L. After setting the batch to 30 °C, cyclohexane (2.0 L) was added followed by **21** crystalline seed (5.0 g). The mixture was allowed to stir at 30 °C for 5-10 min to form a thick slurry. Additional cyclohexane (2.0 L) was added over 2 minutes. The jacket temperature was lowered to 25 °C. The mixture was allowed to stir for 40 min. Additional cyclohexane (2.0 L) was added over 2 minutes. The jacket temperature was lowered to 23 °C. The suspension was maintained at 23 °C for 60 min. Additional cyclohexane (2.0 L) was added over 2 minutes. The suspension was stirred for 20 min. The jacket temperature was lowered to 19.0 °C. The suspension was maintained at 19.0-21.0 °C for 10 hrs. The slurry was filtered. The wet cake was washed with cyclohexane (3 x 2.0 L), and dried in a vacuum oven at 35-40 °C for 12 h to afford **21** as a white crystalline solid (1182 g, 78%). ¹H NMR (400 MHz, DMSO-d₆) (3:1 mixture of rotamers) δ 13.3 (br s, 1H), 7.72 - 7.67 (m, 1H), 7.58 - 7.52 (m, 1H), 7.49 - 7.43 (m, 1H), 4.06 - 3.95 (m, 0.50H), 3.90 - 3.80 (m, 1.50H), 3.12 (s 0.75H), 3.12 (s 2.25H), 1.67 - 1.58 (m, 0.50H), 1.42 - 1.34 (m, 1.50H), 0.93 (t, *J*=7.5 Hz, 0.75H), 0.67 (t, *J*=7.5 Hz, 2.25H). ¹³C NMR (100 MHz, DMSO-d₆) (mixture of rotamers) δ 165.9, 159.2, 156.8, 154.5, 131.8, 131.2, 128.8, 128.8, 126.5, 126.4, 120.0, 119.8, 66.7, 66.6, 36.8, 36.6, 36.4, 21.9, 21.6, 10.20, 9.9. mp 70-72 °C. IR (neat) 3054 (br), 2969, 2943, 1666, 1256, 759 cm⁻¹; HRMS (ESI) *m/z*: calcd for C₁₂H₁₄FNO₄ [M+H]⁺ 256.0980, found 256.0975.

Procedure for the preparation of propyl (2-((3-((2*S*,5*R*)-8-carbamoyl-6-fluoro-2-((*S*)-1-hydroxyethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-5-yl)-2-methylphenyl)carbamoyl)-6-fluorophenyl)(methyl)carbamate (27**).** N, N-Dimethylformamide (7.0 L, 7 L/kg) was charged into a reactor and followed by the addition of **3** (1 kg, 2528 mmol, 1.0 eq.), 3-fluoro-2-(methyl(propoxycarbonyl)amino)benzoic acid (0.774 kg, 3034 mmol, 1.2 eq.) and 1-methylimidazole (0.267 kg, 3287 mmol, 1.3 eq.). Methanesulfonic acid (0.122kg, 1264 mmol, 0.5 eq.) was charged into the reactor at 20 °C. The reaction mixture was stirred for 30 min for complete dissolution at 20 °C. The batch was cooled to 10 °C and EDAC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.679 kg, 3540 mmol, 1.4 eq) was charged into the reactor. An exotherm of approximately 4 °C was observed. The reaction mixture was stirred at 10 °C for 4 h. The mixture was warmed to 20 °C. Isopropyl acetate (25 L, 25 L/kg), 25 wt% aqueous sodium chloride solution (2.5 L, 2.5 L/kg) and 1.0 M aqueous hydrochloric acid (2.5 L, 2.5 L/kg) were charged to the reactor, and the mixture was stirred for 30 min. The agitation was stopped, and the aqueous layer was separated. Water (5 L, 5 L/kg) was charged to the rich organic solution and stirred for 30 min. The agitation was stopped, and the aqueous layer was separated. Next, 2.5% aqueous sodium bicarbonate solution (10 L, 10 L/kg) was charged to the rich organic solution and stirred for 30 min. The agitation was stopped, and the aqueous layer was separated. Water (10 L, 10 L/kg) was charged to the rich organic solution and stirred for 30 min. The agitation was stopped, and the aqueous layer was separated. The rich organic solution was concentrated under reduced pressure (~90 mbar and ~40 °C jacket temperature) to 7 L/kg volume. Dichloromethane (5 L, 5 L/kg) was charged to the product rich

isopropyl acetate solution at 20 °C. Seeds of **23** (10 g, 1%) were charged, and a thin slurry formed. Heptane (7 L, 7 L/kg) was charged to the above slurry slowly over 1 h at 25 °C and stirred for another 1 h before cooling 20 °C over 30 min. The resultant slurry was stirred for 4-6 h at 20 °C. The slurry was filtered. The wet cake was washed with a dichloromethane-heptane mixture (10:7 ratio, 12 vol). The wet cake was dried in a vacuum oven at 25 mm Hg vacuum and 50 °C to provide **23** as a white crystalline solid (1.5 kg, 88% yield). Product is a mixture of four amide rotomers (do not coalesce at elevated temperature). ¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (br s, 1H), 9.96 (m, 1H), 8.07 (br s, 1H), 7.50 (m, 6H), 7.29 (m, 1H), 7.09 (m, 1H), 4.15 (m, 1H), 3.89 (m, 2H), 3.19 (br s, 1H), 3.13 (br s, 2H), 2.90 (m, 1H), 2.44 (m, 1H), 1.97 (m, 3H), 1.82 (m, 3H), 1.50 (m, 3H), 1.09 (m, 7H), 0.85 (m, 1H), 0.70 (m, 2H). ¹³C NMR (100 MHz, DMSO-d₆) δ 168.3, 168.3, 164.9, 164.6, 159.4, 159.2, 156.9, 156.7, 154.9, 154.7, 153.1, 150.9, 139.2, 139.1, 138.0, 137.9, 137.4, 137.2, 135.8, 135.7, 135.6, 134.8, 134.7, 132.6, 132.5, 132.5, 132.4, 131.5, 129.0 (m), 128.3 (m), 127.1, 127.0, 126.0, 125.8, 125.0, 124.8, 124.1, 121.5, 121.4, 121.3, 121.2, 117.9, 117.9, 117.7, 117.7, 115.2, 115.2, 115.1, 115.1, 108.7, 108.7, 106.9, 106.6, 70.4, 66.8, 66.8, 66.7, 45.3, 37.4, 37.2, 31.2, 28.4, 27.1, 26.7, 24.9, 24.6, 22.3, 22.1, 21.8, 21.7, 15.0, 14.9, 14.9, 14.8, 10.1, 9.9. mp 176-181 °C. IR (neat) 3444, 3355, 3243 (br), 2966, 2925, 2878, 2854, 1661, 1467, 1165 cm⁻¹; HRMS (ESI) m/z: calcd for C₃₅H₃₈F₂N₄O₅ [M+H]⁺ 633.2883, found 633.2883.

Chiral HPLC Analysis:

Gradient: Complex

Start % B: 50

25 Min. 81%

26 Min. 100%

30 Min. 100%

Stop Time: 30 min

Flow Rate: 1 ml/min

Wavelength1: 240

Wavelength2: 265

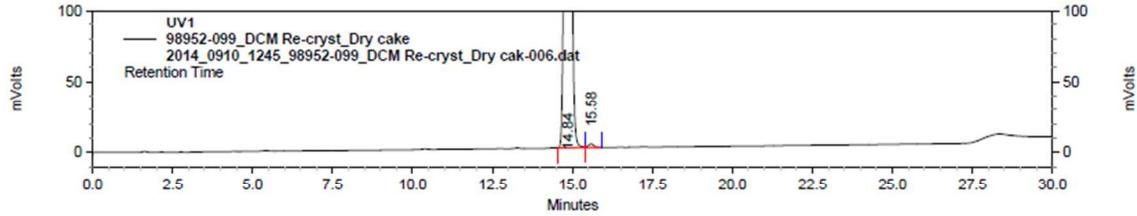
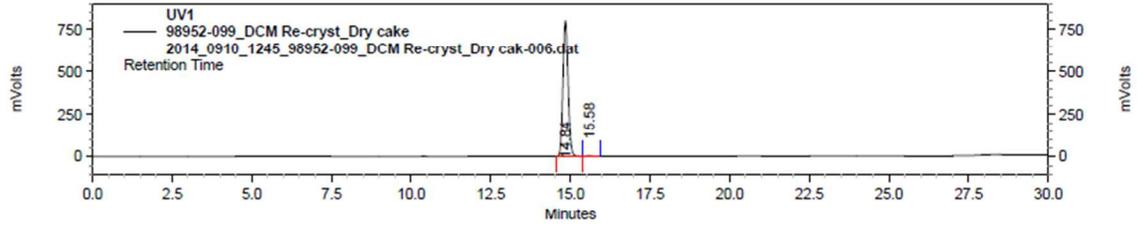
Solvent Pair: 10mM Amm. formate/MeOH/CH₃CN/Water

Solvent A: A2=10mM Amm formate in 90:10 Water/MeOH

Solvent B: B2=70:30 MeOH/CH₃CN

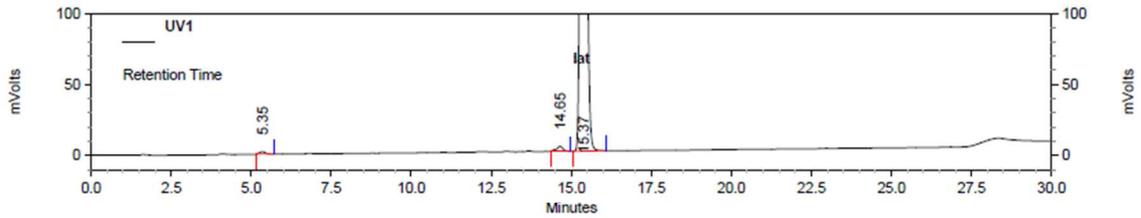
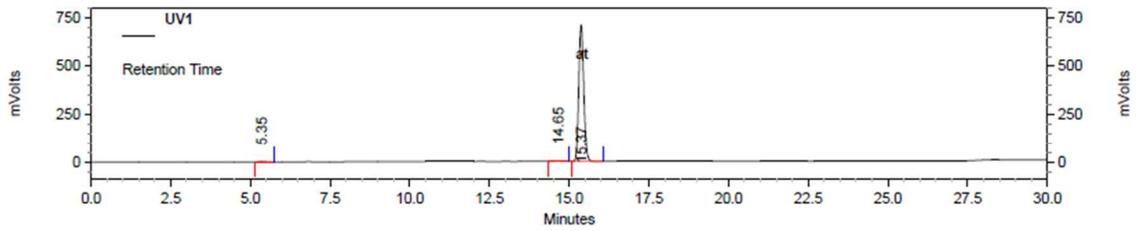
Column 2 : 2: Zorbax Eclipse Plus C18 3.5um 4.6 X 150mm SN:USUXC02881

Standard of 27:



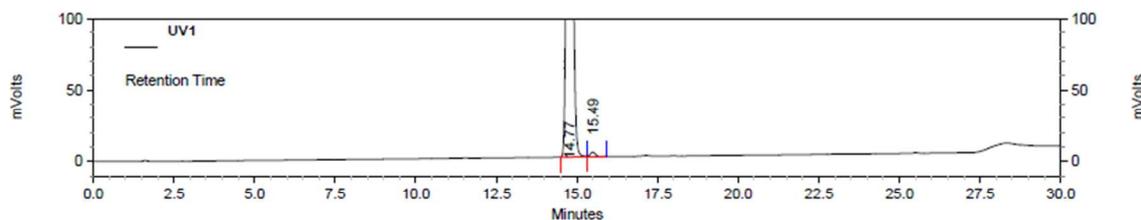
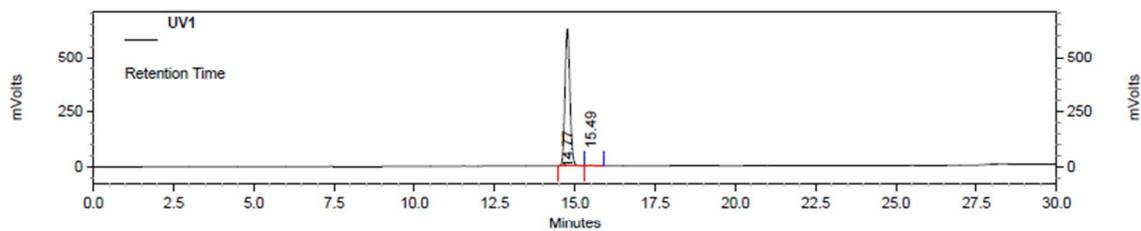
UV1 Results					
PK #	Retention Time	Area	Area Percent	Relative RT	Name
1	14.84	8930962	99.66	0.00	
2	15.58	30417	0.34	0.00	
Totals		8961379	100.00		

Atropisomer of 27:



UV1 Results					
PK #	Retention Time	Area	Area Percent	Relative RT	Name
1	5.35	22153	0.28	0.00	
2	14.65	49067	0.63	0.00	
3	15.37	7745876	99.09	0.00	
Totals		7817096	100.00		

Isolated 27:



UV1 Results					
Pk #	Retention Time	Area	Area Percent	Relative RT	Name
1	14.77	6651769	99.46	0.00	18
2	15.49	36273	0.54	0.00	18-Atropisomer
Totals		6688042	100.00		

Procedure for the preparation of (2S,5R)-6-fluoro-5-(3-(8-fluoro-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (1A). To a 1 L round bottom flask with stir bar was added **27** (100g, 148 mmol, 93.5 mass %) followed by 2-methyltetrahydrofuran (500 mL). The mixture was stirred at rt for 10 min to ensure complete dissolution. MeTHF (150 mL) was added, and an azeotropic distillation was performed at 50 °C and ~70 torr to a total volume of 600 mL. This solution is termed the “**27** solution.” To a 2 L chemglass reactor was charged 2-methyltetrahydrofuran (2000 mL) followed by 1M lithium tert-butoxide in THF (7.9 mL, 7.9 mmol, 0.05 equiv). The **27** solution was added dropwise over 2 h at rt via a simdos pump. After the addition was complete, the reaction aged for 15 min at rt. Methanol (200 mL) was then added to the reactor followed by acetic acid (0.5 mL, 9 mmol). The reaction mixture was distilled to 5 L/kg (60 mbar pressure, T jacket = 40 °C). After the distillation, acetone (150 mL) was added to the thick slurry as the solution warmed to 35 °C. Once at 35 °C, methanol (550 mL) was charged to the reactor, redissolving the batch to provide a yellow solution. The reaction mixture was cooled over 1 h to 20 °C resulting in crystallization of the product. Ten heat cycles were then performed (Starting at 20 °C, the batch was heated to 35 °C over 45 minutes, held at 35 °C for 10 minutes, cooled 20 °C over 60 minutes, and held at 20 °C for 10 minutes). After the heat cycles, the slurry was aged for 1 h at rt. Heptane (1100 mL) was added over 4 h at 20 °C with agitation via a simdos pump. After the addition, the slurry aged at 20 °C overnight. The product was isolated by vacuum filtration and washed with twice with methanol (200 mL). The product was dried with full vacuum for 1.5 h to yield the product as a white crystalline solid (80.52g, 6 wt %

MeOH, 89.4% corrected yield). ¹H NMR (500 MHz, DMSO-d₆) 10.78 (s, 1H), 8.07 (br. s., 1H), 7.95 (d, *J*=7.8 Hz, 1H), 7.72 (dd, *J*=14.2, 8.0 Hz, 1H), 7.56 (d, *J*=10.8 Hz, 1H), 7.45 (br. s., 1H), 7.42 - 7.36 (m, 1H), 7.34 (d, *J*=6.9 Hz, 1H), 7.34 - 7.31 (m, 1H), 7.29 (dd, *J*=7.5, 1.3 Hz, 1H), 4.17 (s, 1H), 3.73 (d, *J*=8.0 Hz, 3H), 2.91 (dd, *J*=16.8, 4.4 Hz, 1H), 2.48 - 2.37 (m, 1H), 1.98 - 1.89 (m, 2H), 1.87 (d, *J*=11.0 Hz, 1H), 1.76 (s, 3H), 1.59 (td, *J*=11.5, 4.1 Hz, 1H), 1.20 - 1.12 (m, 1H), 1.11 (s, 6H). ¹³C NMR (125.8 MHz, DMSO-d₆) 168.2 (d, *J*=1.8 Hz, 1C), 160.1 (d, *J*=3.6 Hz, 1C), 151.9 (d, *J*=228.9 Hz, 1C), 150.5 (d, *J*=41.8 Hz, 1C), 148.7 (d, *J*=205.3 Hz, 1C), 139.2, 135.1, 135.0, 134.8, 131.4, 130.6, 130.0 (d, *J*=7.3 Hz, 1C), 128.5, 127.1 (d, *J*=4.5 Hz, 1C), 125.7, 124.3 (d, *J*=2.7 Hz, 1C), 123.6 (d, *J*=8.2 Hz, 1C), 123.0 (d, *J*=23.6 Hz, 1C), 120.8 (d, *J*=20.0 Hz, 1C), 118.4, 115.3 (d, *J*=7.3 Hz, 1C), 108.8 (d, *J*=5.4 Hz, 1C), 106.7 (d, *J*=28.2 Hz, 1C), 70.4, 45.4, 34.3 (d, *J*=14.5 Hz, 1C), 27.1, 26.8, 24.8, 24.7, 22.1, 14.5. mp 222-225 °C. IR (neat) 3487, 3418, 3375, 2967, 1651, 1394, 756 cm⁻¹; HRMS (ESI) m/z: calcd for C₃₂H₃₀F₂N₄O₄ [M+H]⁺ 573.2308, found 573.2312.

Chiral HPLC Analysis:

Gradient: Complex

Start % B: 0

7 Min. 55%

11 Min. 55%

14 Min. 100%

Stop Time: 17 min

Flow Rate: 1.5 ml/min

Wavelength1: 225

Wavelength2: 256

Solvent Pair: S194/S195 (TFA)

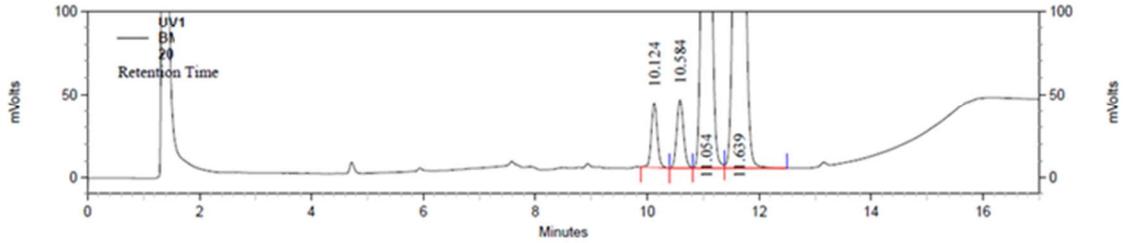
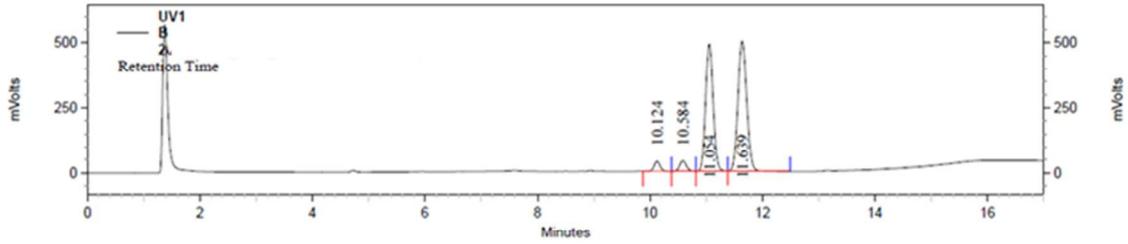
Solvent A: A1=0.05%TFA Water:ACN (95:5) S194

Solvent B: B1=0.05%TFA Water:ACN (5:95) S195

Column 1 : 1: Chiralcel OX-3R 3um 4.6 x 150 mm SN = OX3RCD-TE001

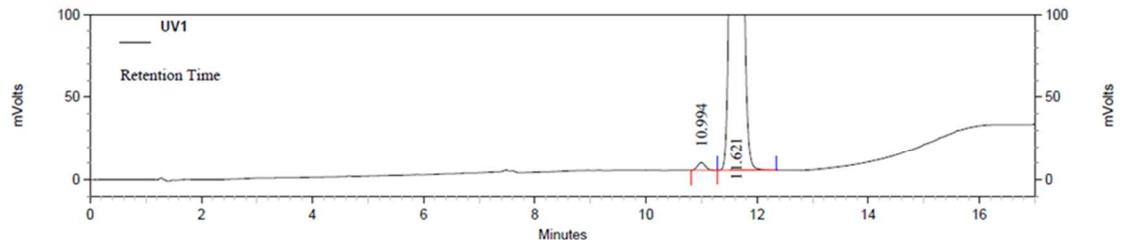
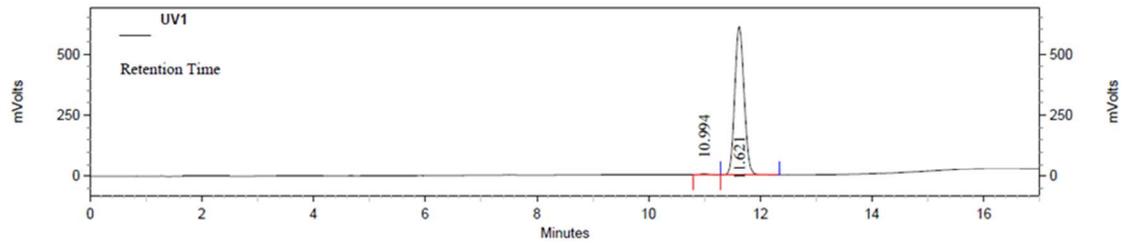
Oven Temperature: 50

Standard Mixture of Atropisomers:



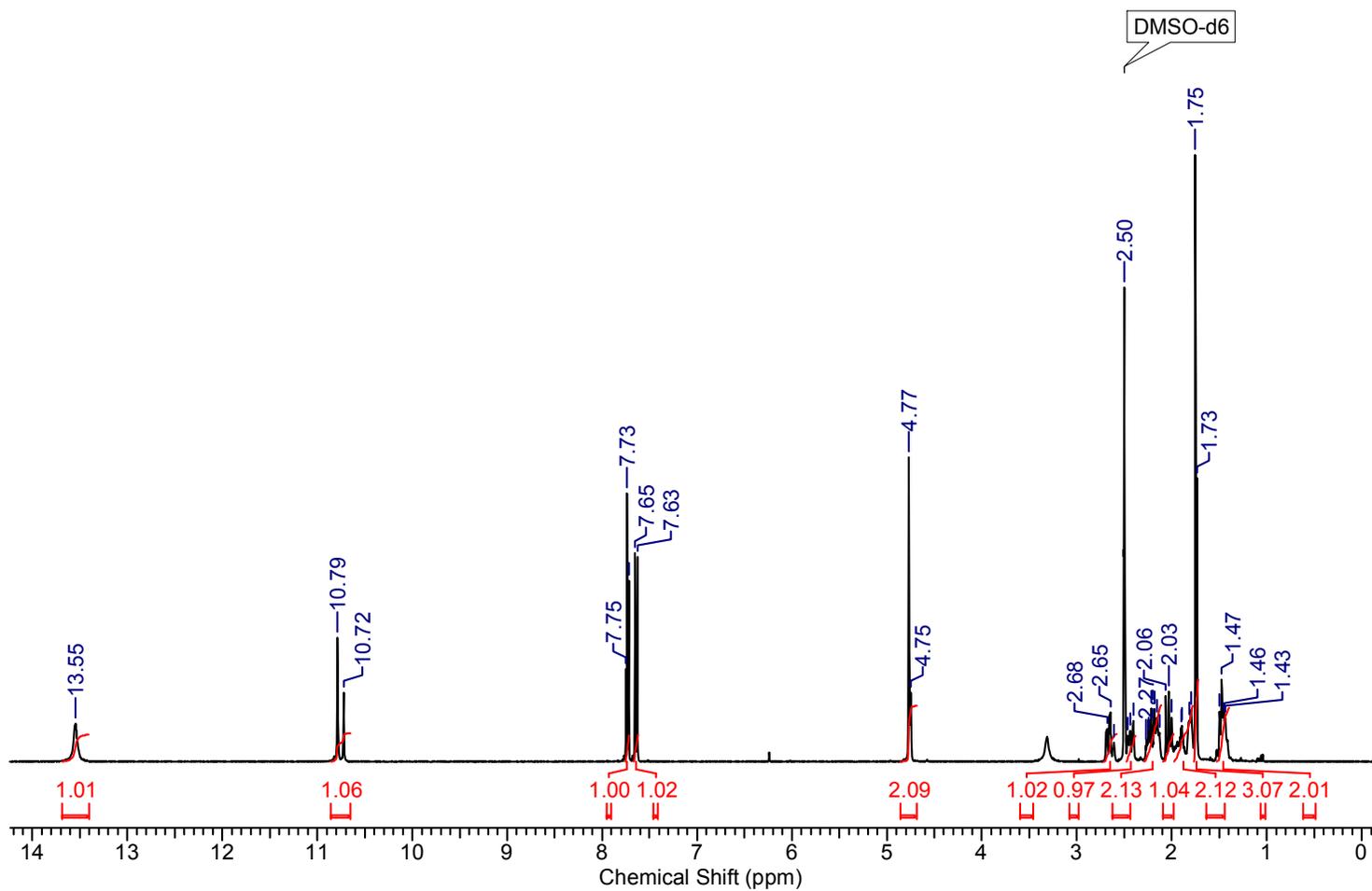
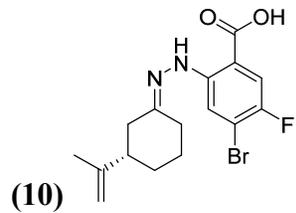
UV1 Results						
Pk #	RT (min)	Area	Area Percent	Relative RT	Name	
1	10.12	286281	2.67	0.00	1C	
2	10.58	342064	3.19	0.00	1D	
3	11.05	4610624	42.96	0.00	1B	
4	11.64	5493775	51.19	0.00	1A	
Totals		10732744	100.00			

Isolated 1A:

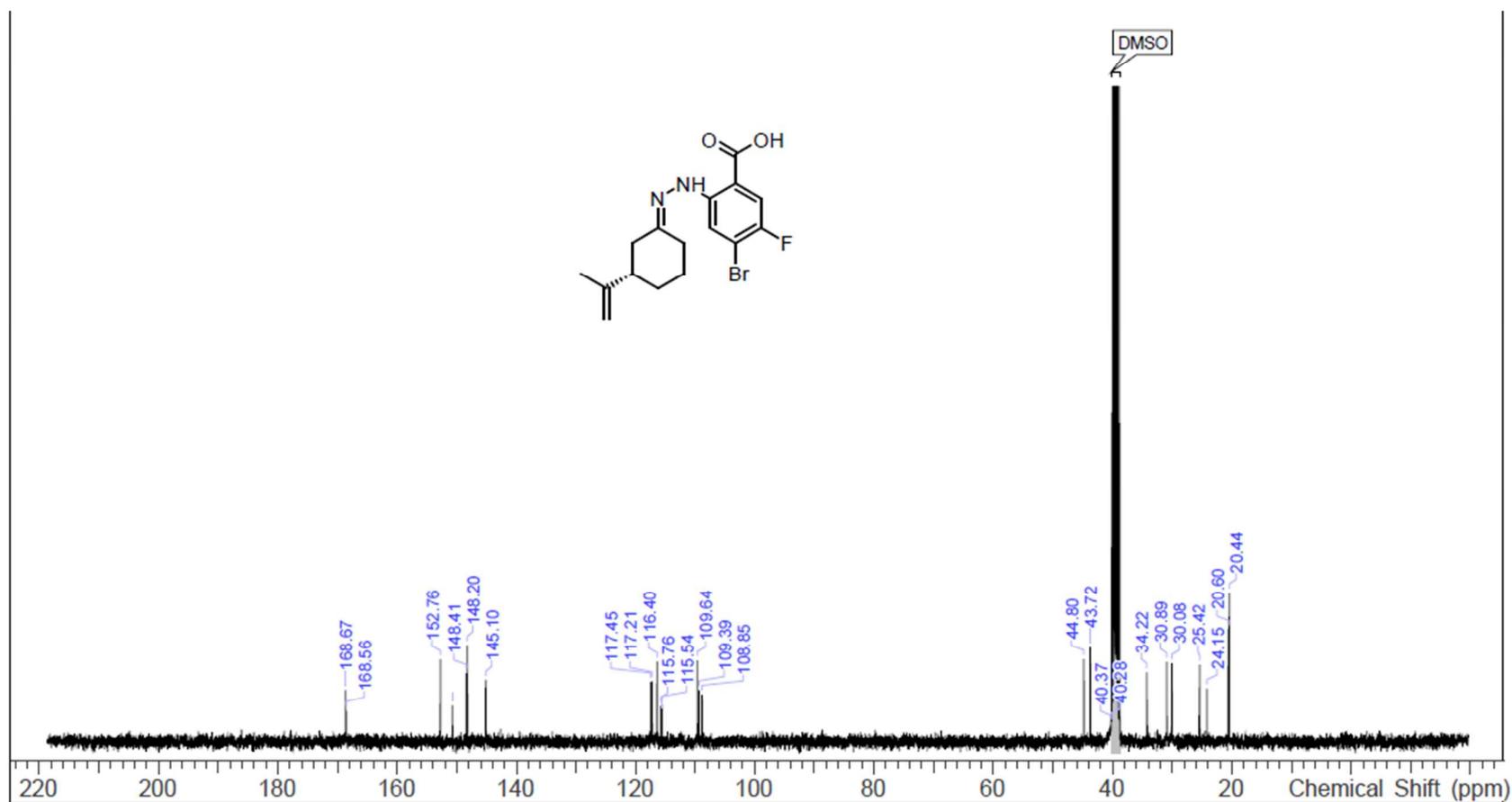
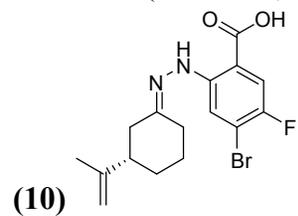


UV1 Results						
Pk #	RT (min)	Area	Area Percent	Relative RT	Name	
					1C	
					1D	
1	10.99	45290	0.64	0.00	1B	
2	11.62	7070016	99.36	0.00	1A	
Totals		7115306	100.00			

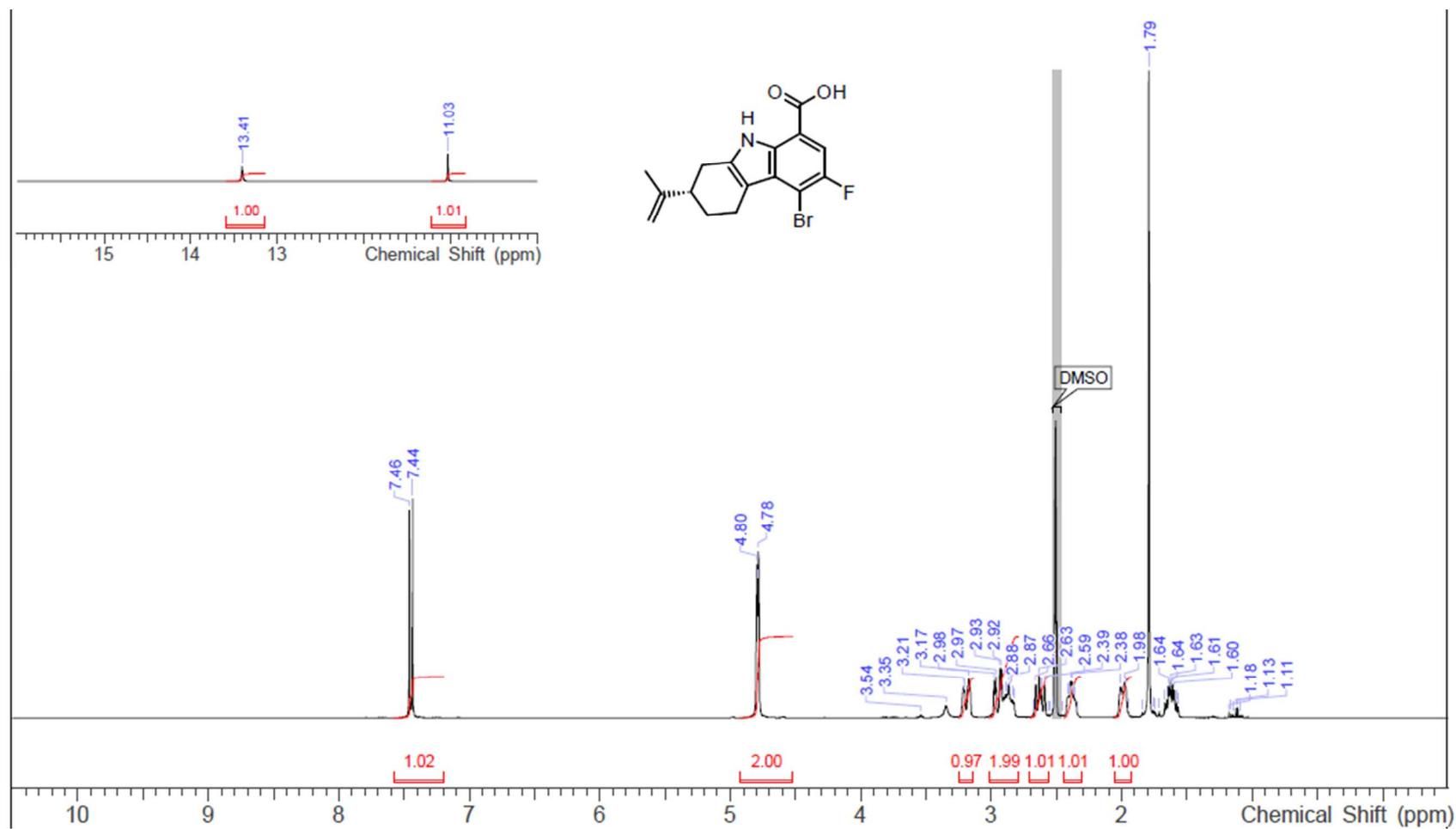
^1H NMR (400 MHz, DMSO- d_6) of (S,E)-4-bromo-5-fluoro-2-(2-(3-(prop-1-en-2-yl)cyclohexylidene)hydrazineyl)benzoic acid



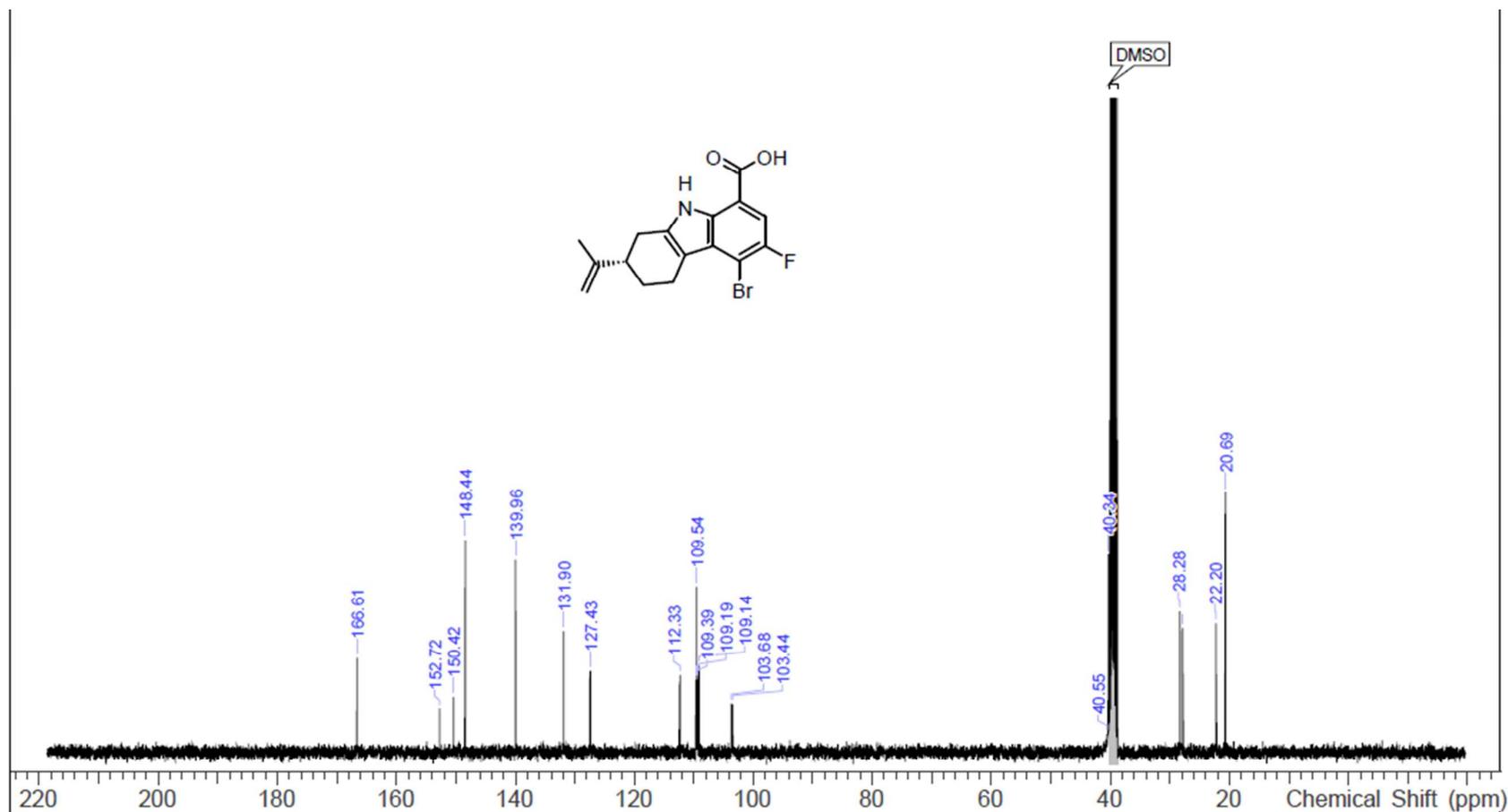
^{13}C NMR (100 MHz, DMSO-d_6) of (S,E)-4-bromo-5-fluoro-2-(2-(3-(prop-1-en-2-yl)cyclohexylidene)hydrazineyl)benzoic acid



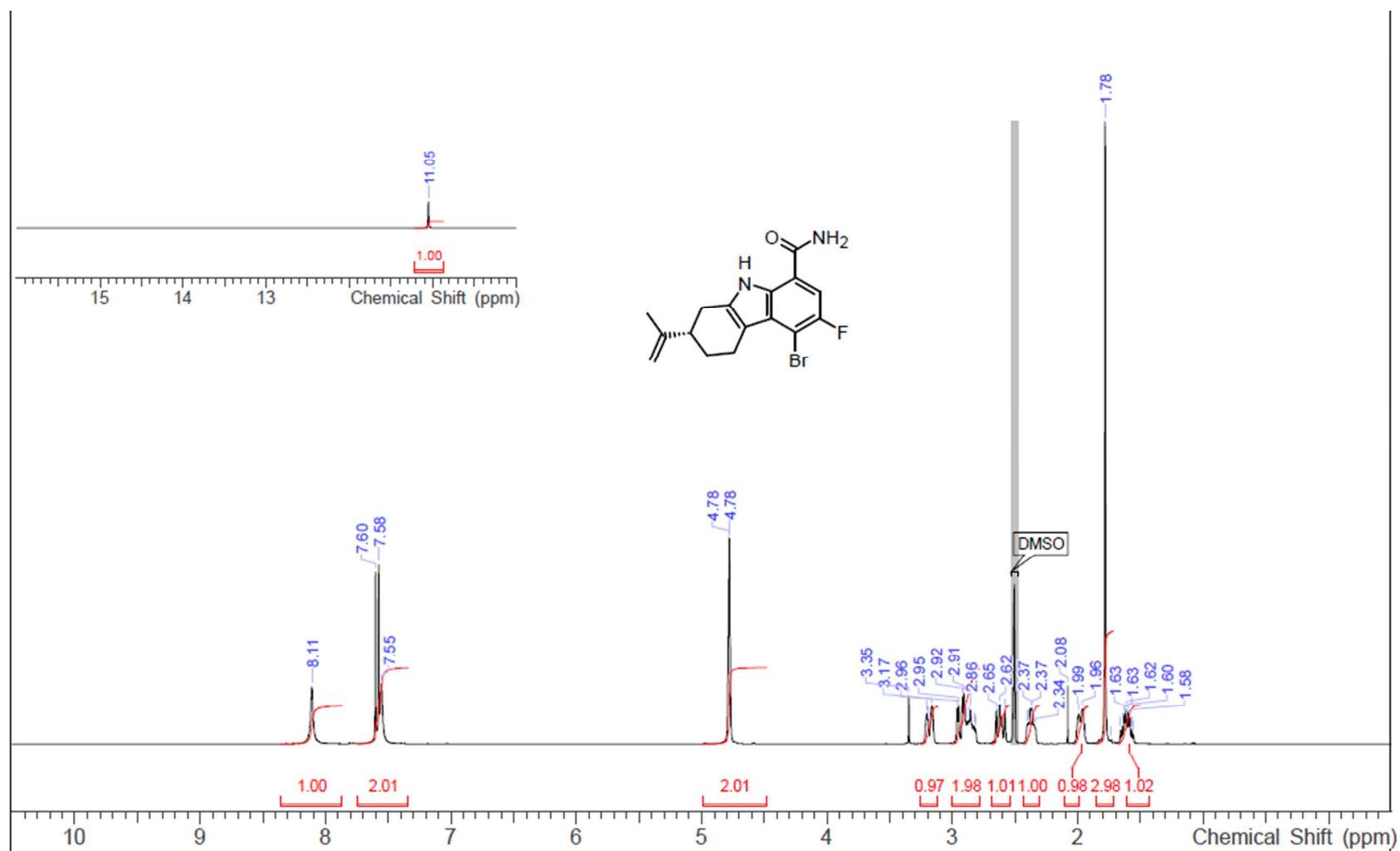
¹H NMR (400 MHz, DMSO-d₆) of (S)-5-bromo-6-fluoro-2-(prop-1-en-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (11)



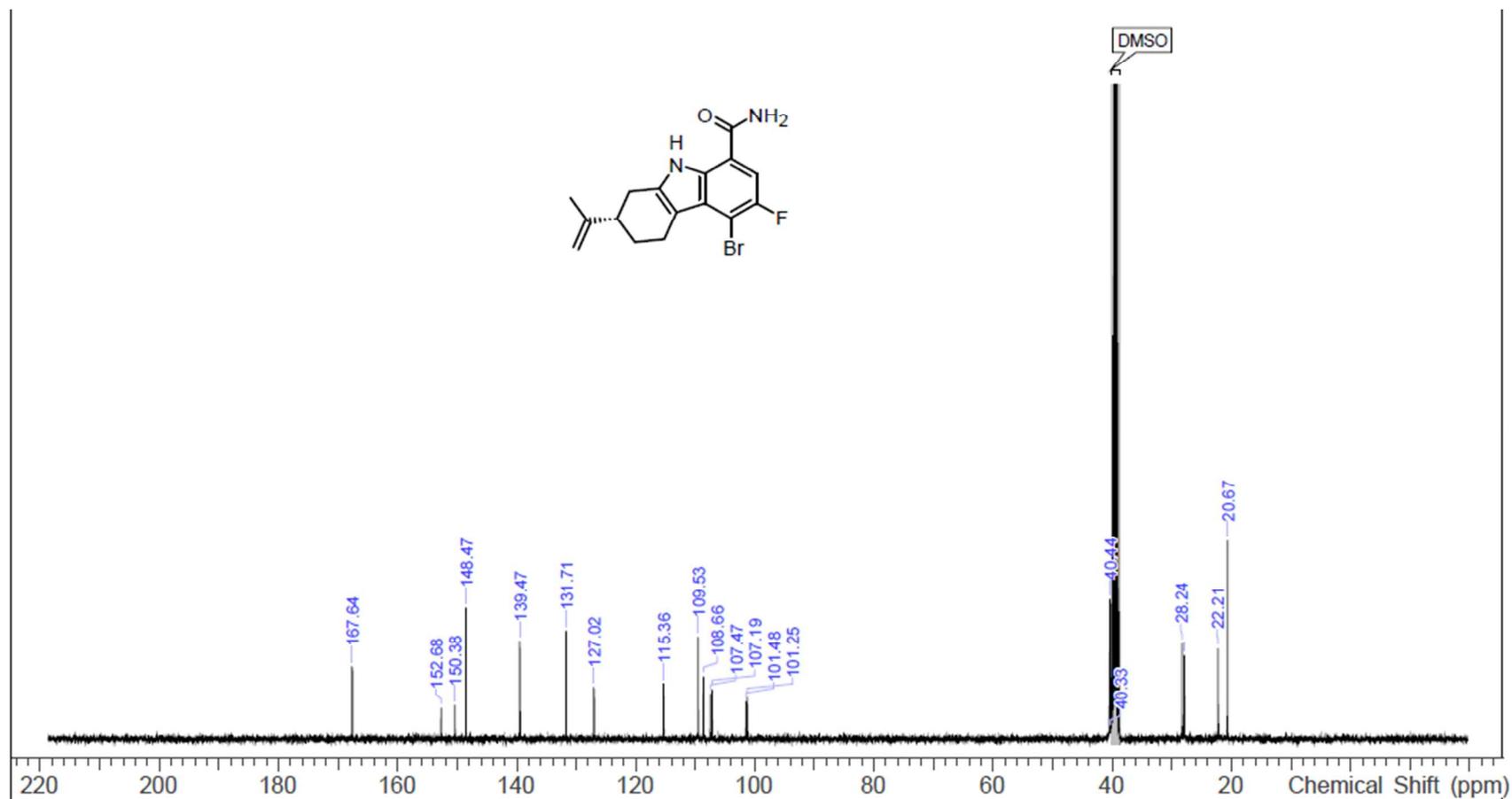
^{13}C NMR (100 MHz, DMSO-d_6) of (S)-5-bromo-6-fluoro-2-(prop-1-en-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid (11)



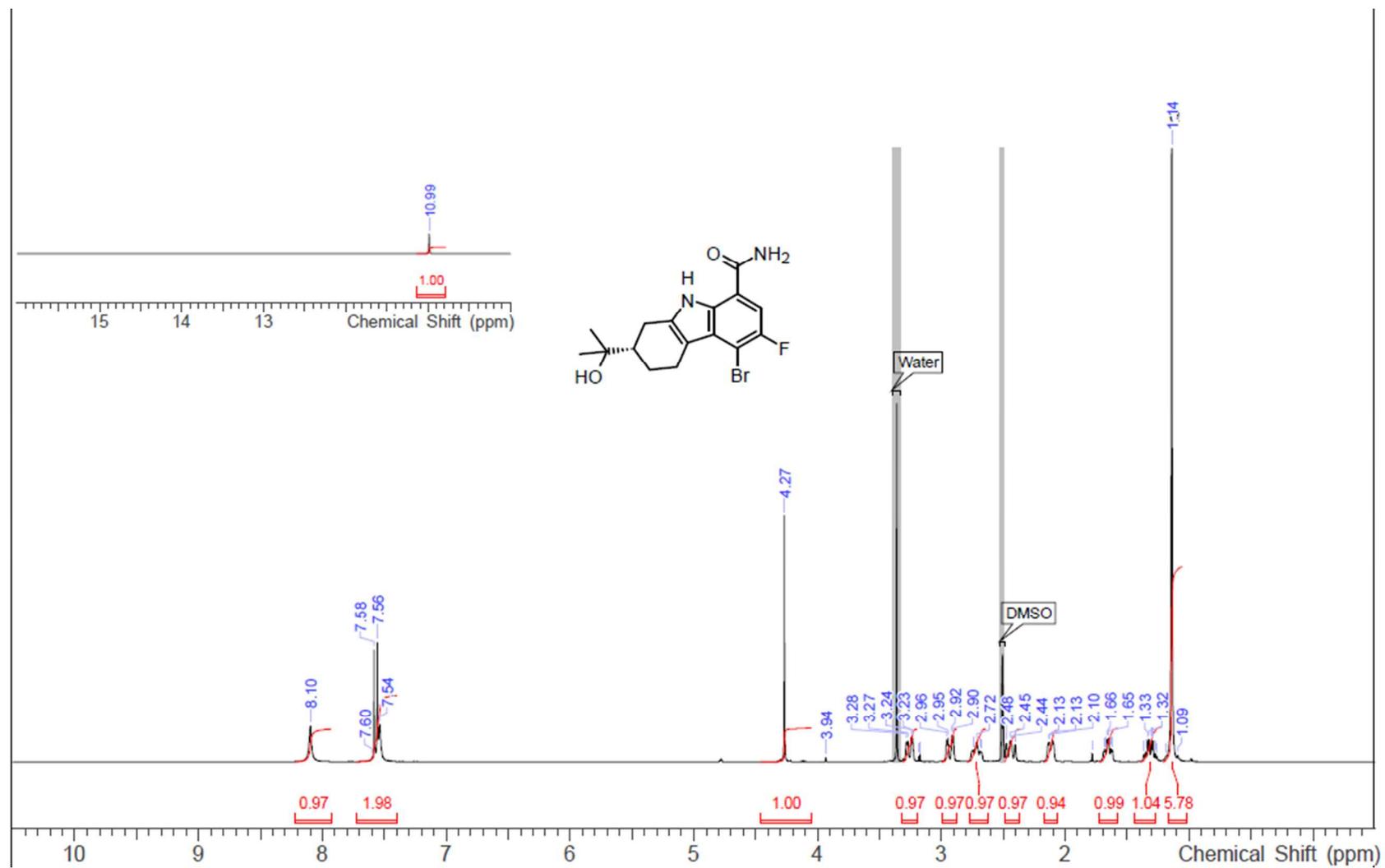
^1H NMR (400 MHz, DMSO-d_6) of (S)-5-bromo-6-fluoro-2-(prop-1-en-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (12)



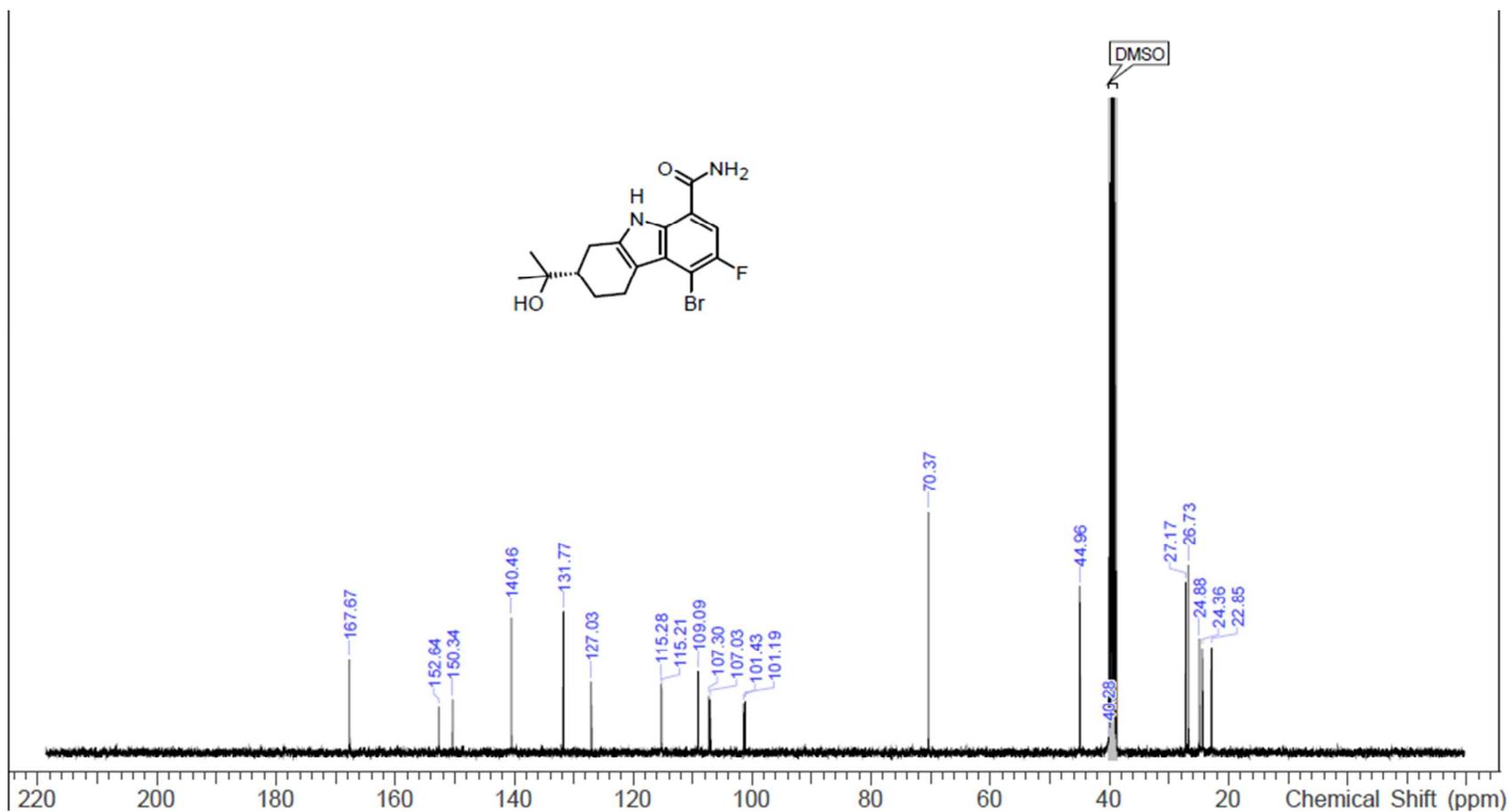
^{13}C NMR (100 MHz, DMSO- d_6) of (S)-5-bromo-6-fluoro-2-(prop-1-en-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (12)

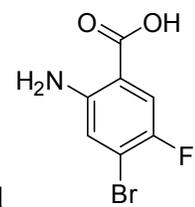


¹H NMR (400 MHz, DMSO-d₆) of (S)-5-bromo-6-fluoro-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (5)

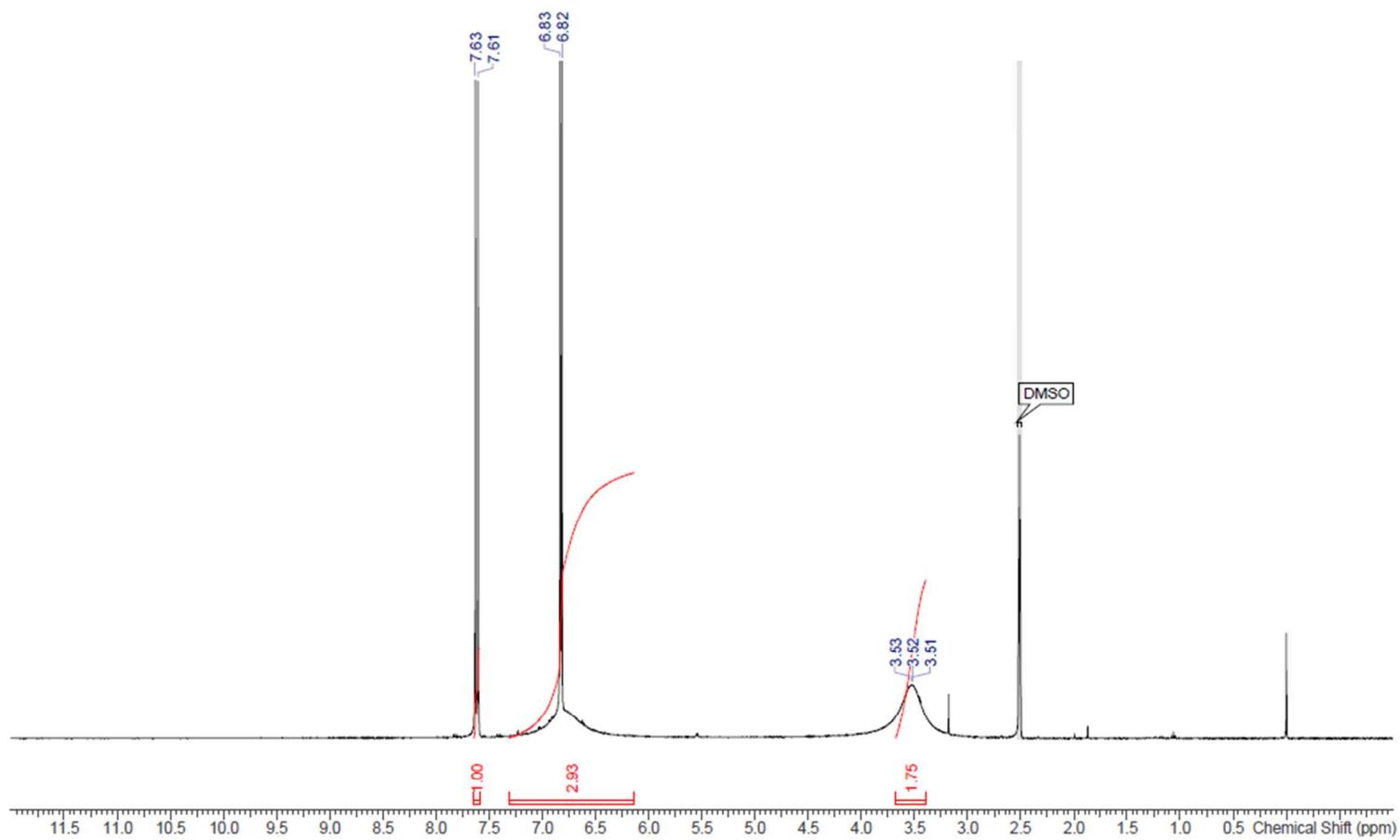


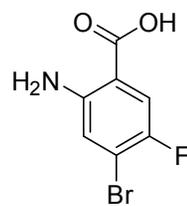
^{13}C NMR (100 MHz, DMSO-d_6) of (S)-5-bromo-6-fluoro-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (5)



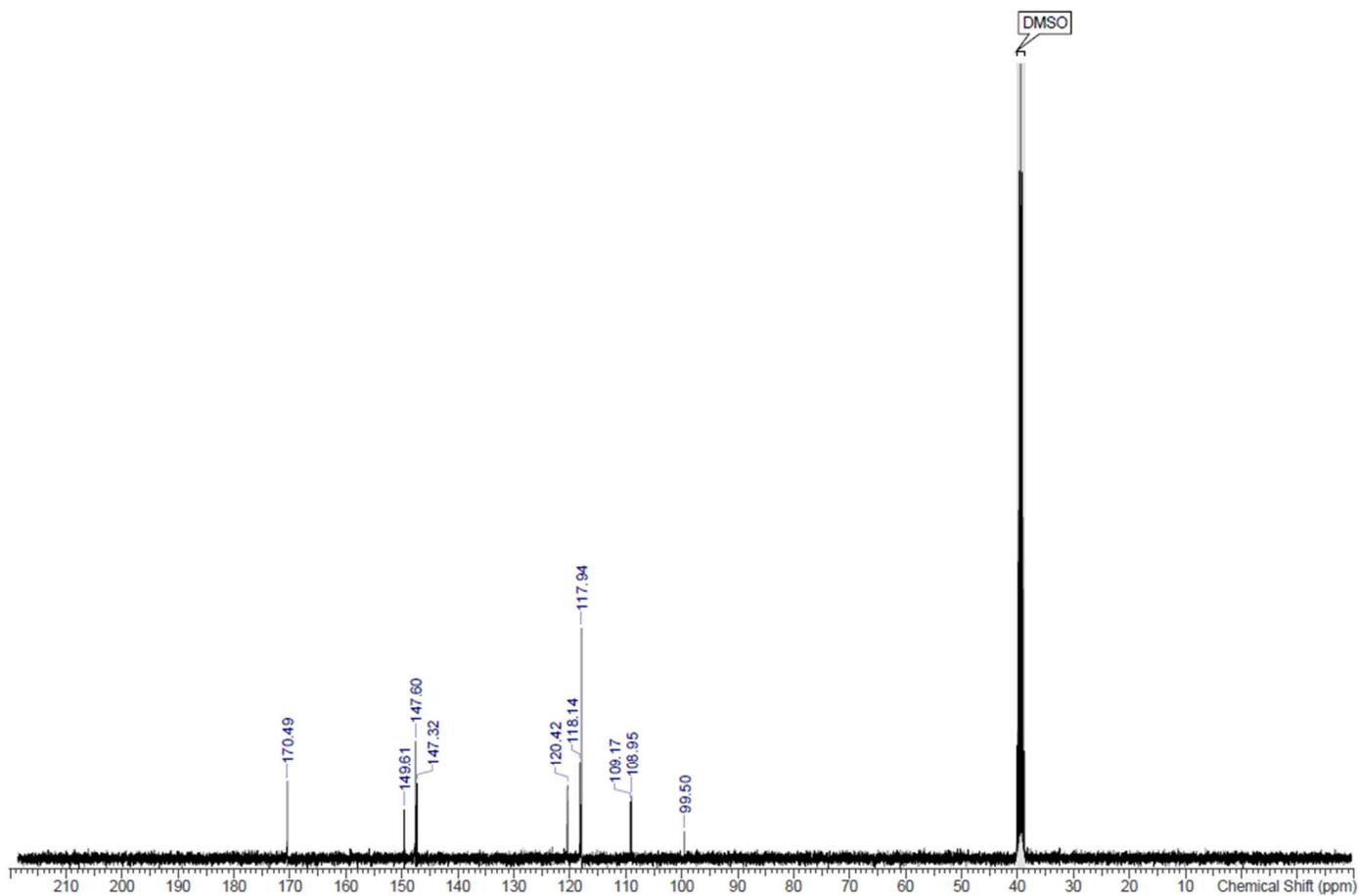


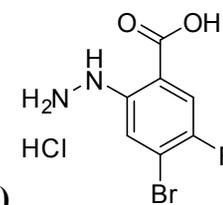
^1H NMR (400 MHz, DMSO- d_6) of **2-amino-4-bromo-5-fluorobenzoic acid**



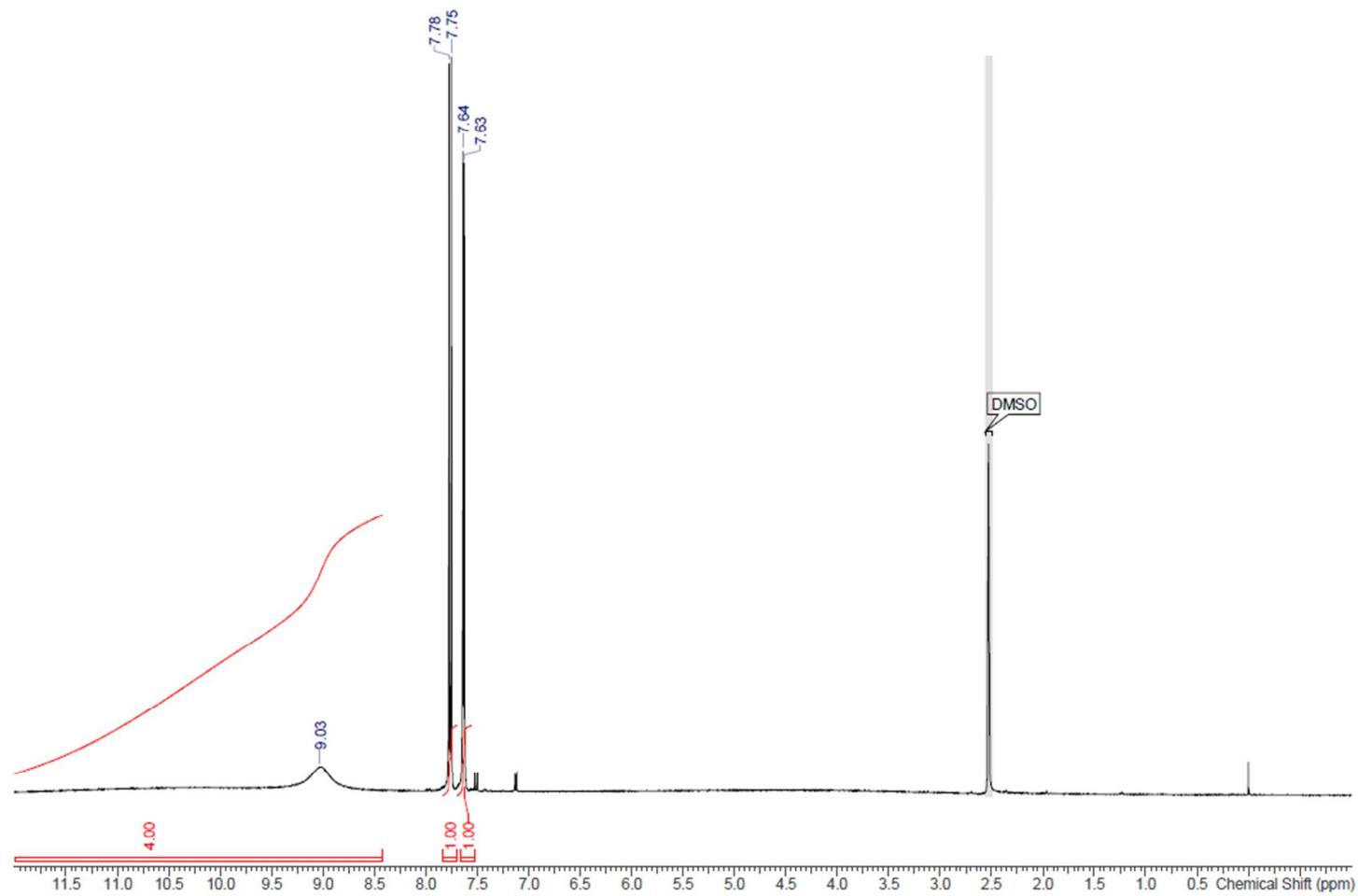


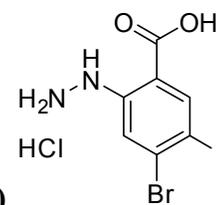
¹³C NMR (100 MHz, DMSO-d₆) of 2-amino-4-bromo-5-fluorobenzoic acid



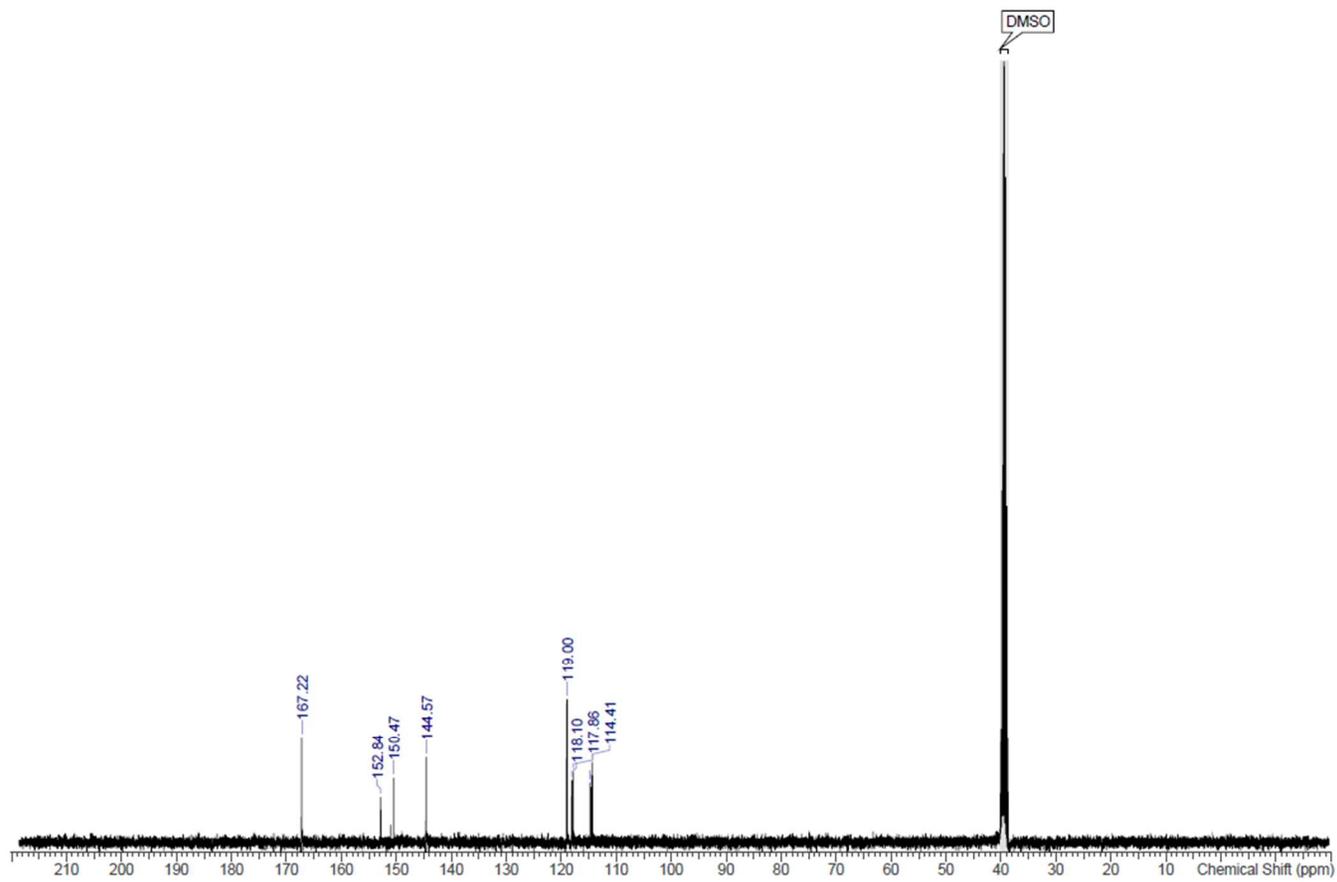


^1H NMR (400 MHz, DMSO-d_6) of 4-bromo-5-fluoro-2-hydrazineylbenzoic acid hydrochloride (6)

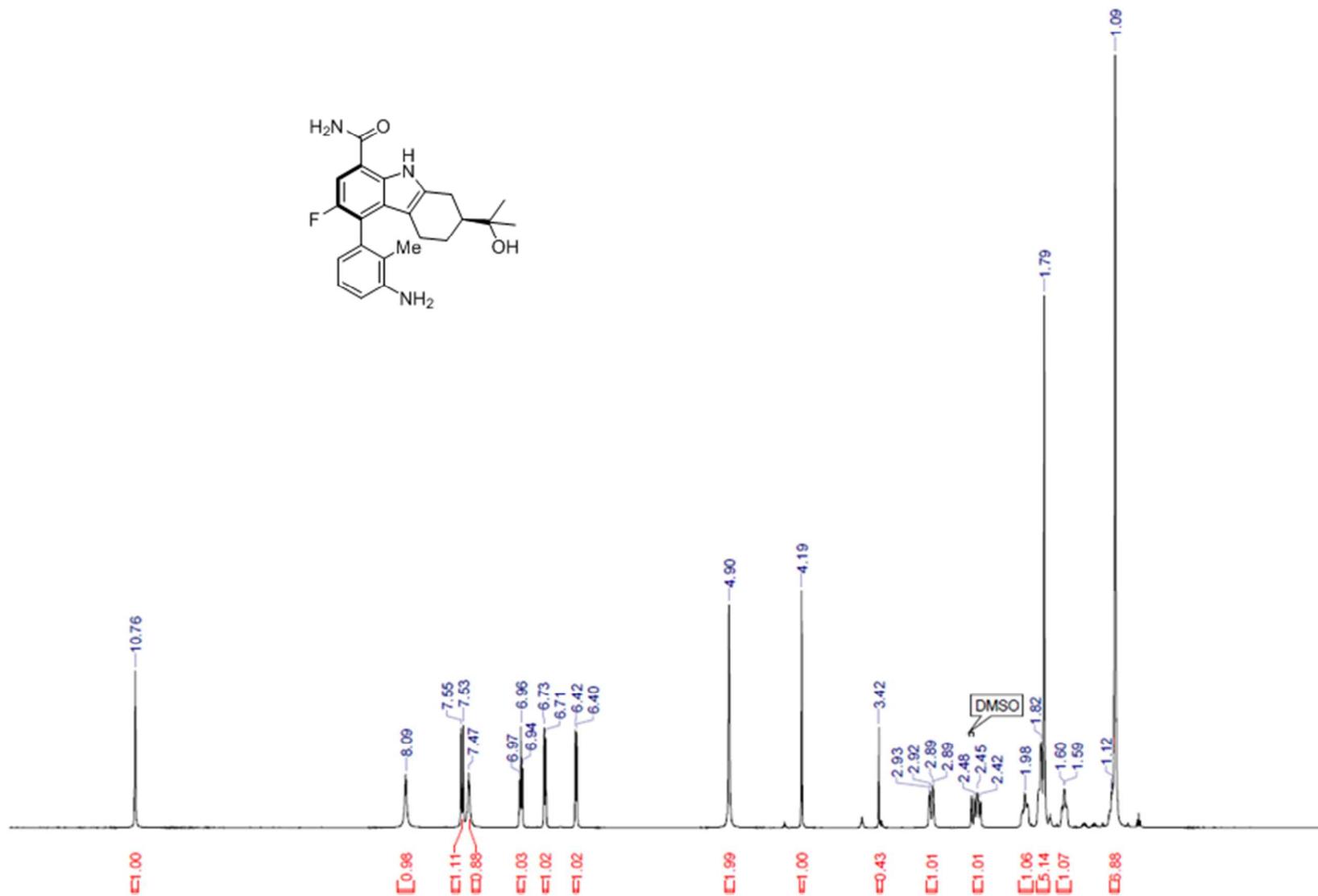




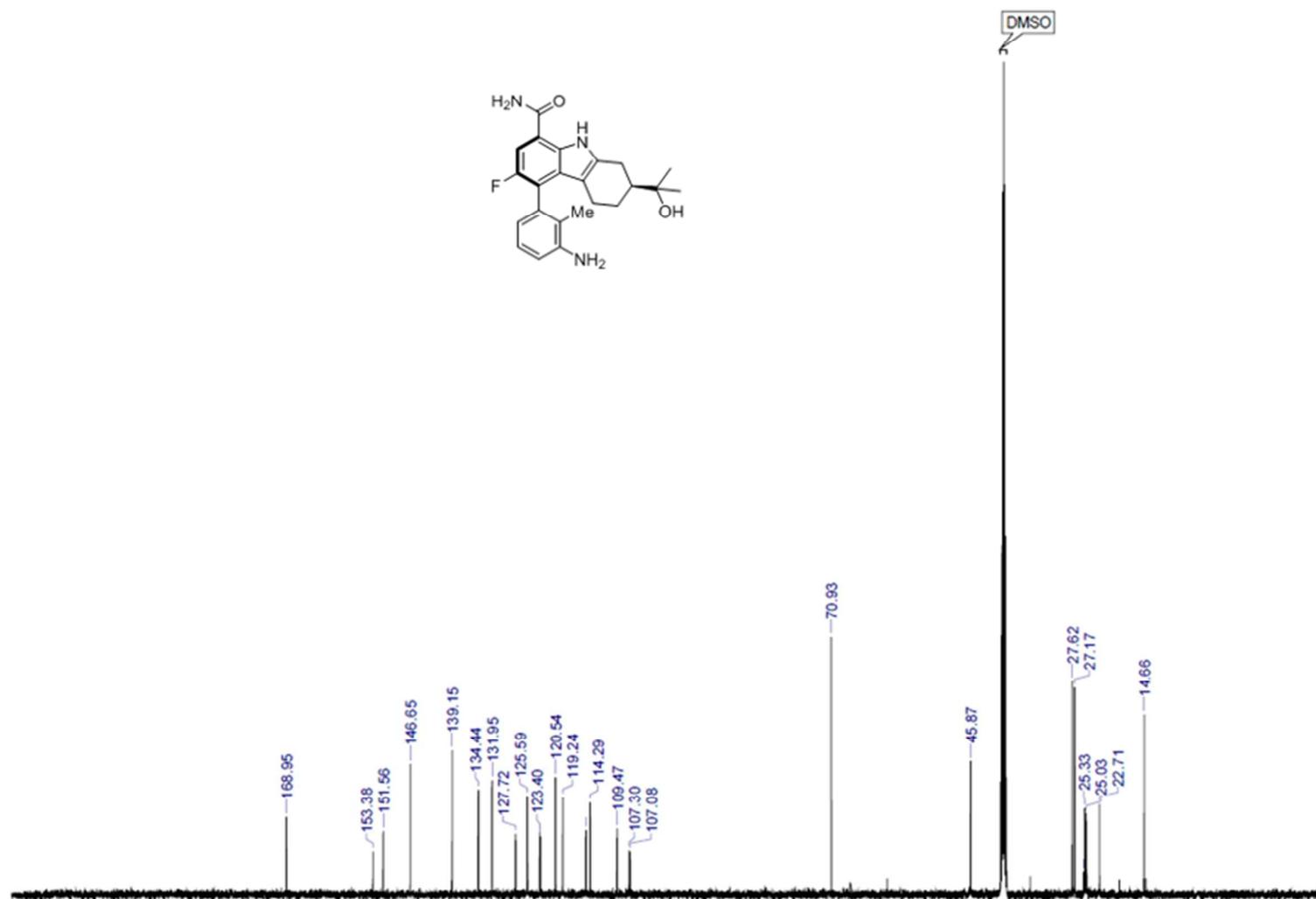
^{13}C NMR (100 MHz, DMSO- d_6) of 4-bromo-5-fluoro-2-hydrazineylbenzoic acid hydrochloride (6)



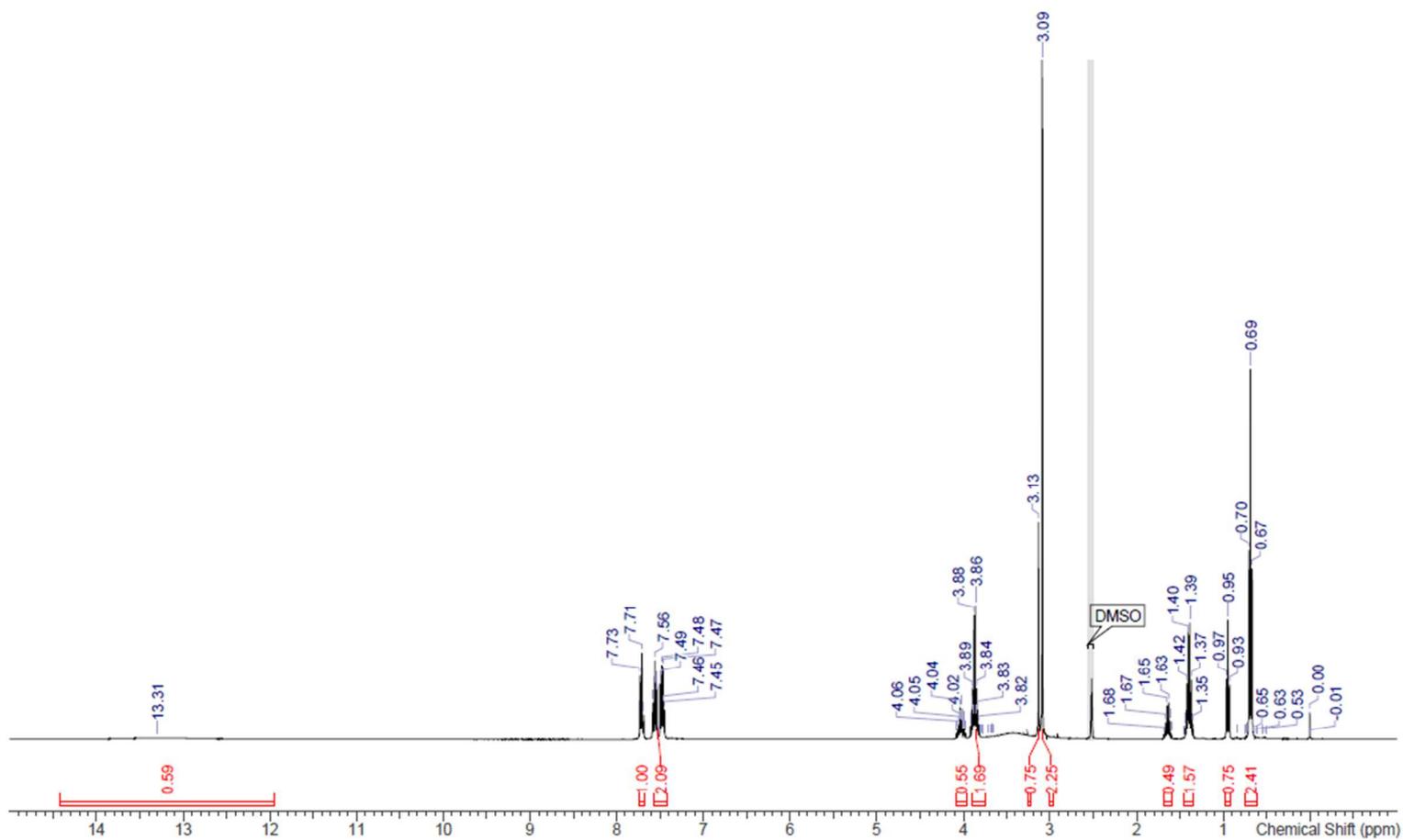
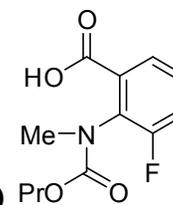
^1H NMR (500 MHz, DMSO-d_6) of (2*S*,5*R*)-5-(3-amino-2-methylphenyl)-6-fluoro-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole-8-carboxamide (3)



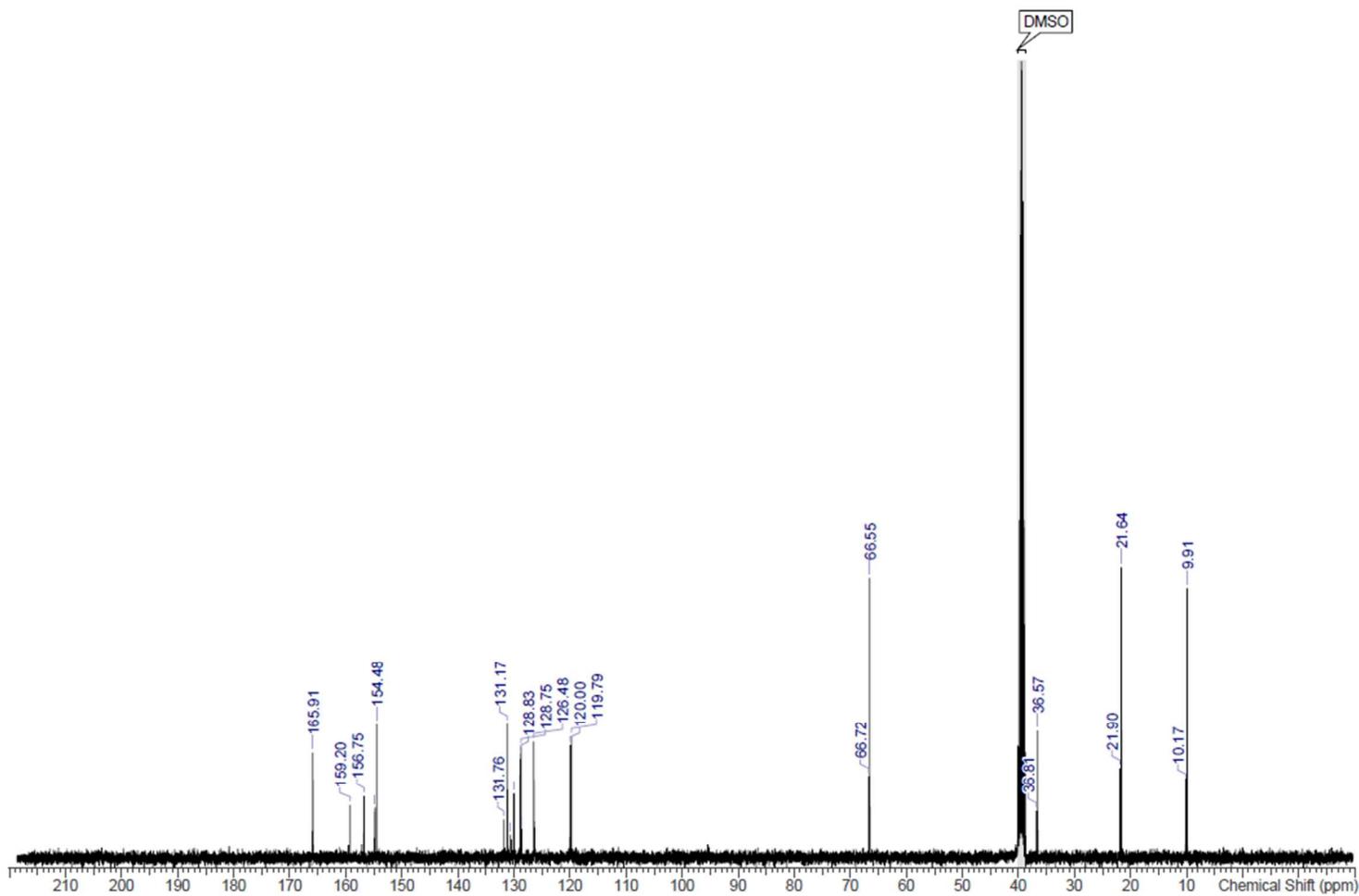
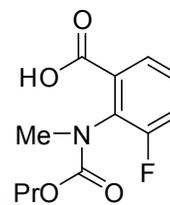
^{13}C NMR (125.8 MHz, DMSO- d_6) of (2S,5R)-5-(3-amino-2-methylphenyl)-6-fluoro-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxamide (3)



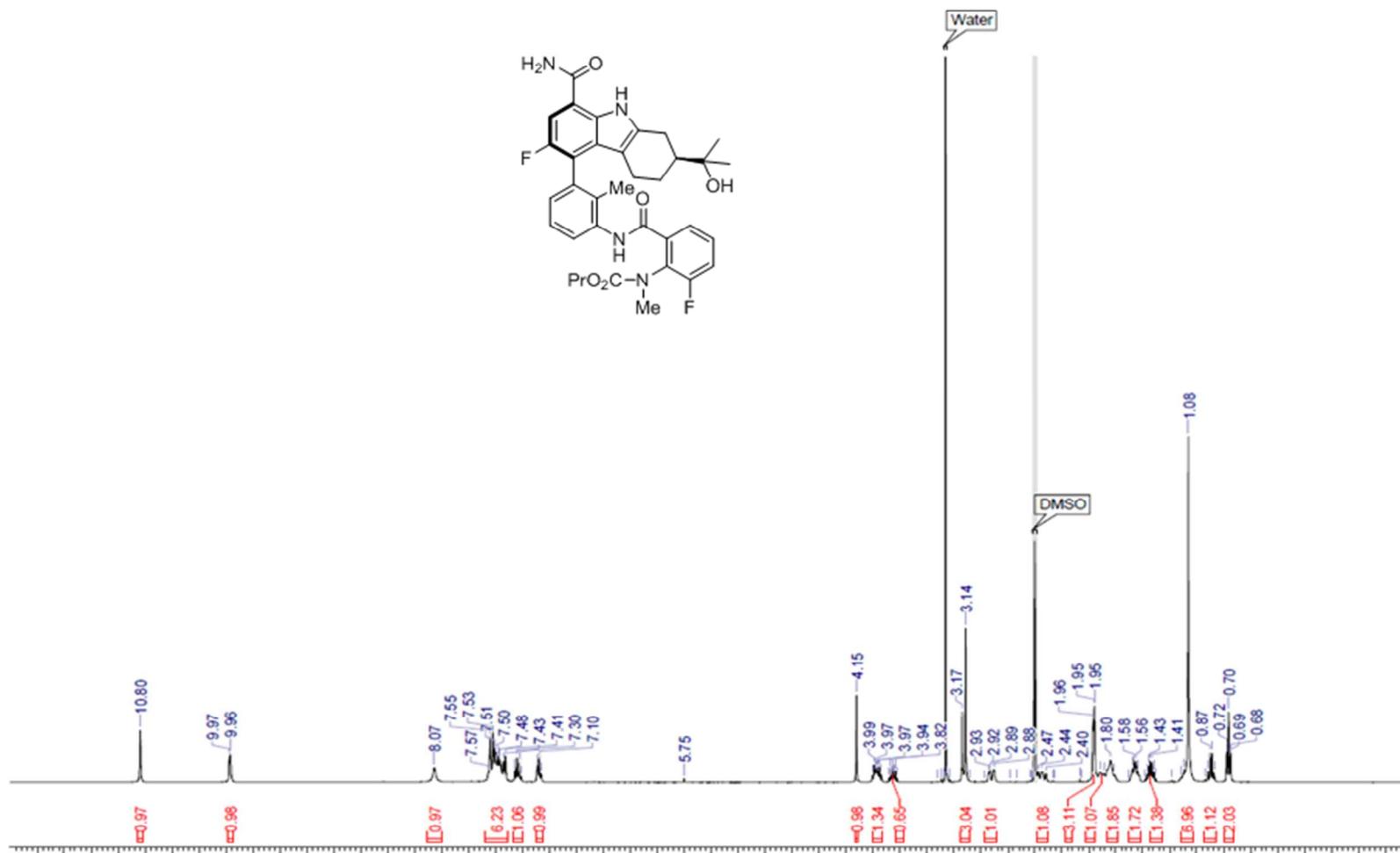
^1H NMR (400 MHz, DMSO- d_6) of 3-fluoro-2-(methyl(propoxycarbonyl)amino)benzoic acid (21)



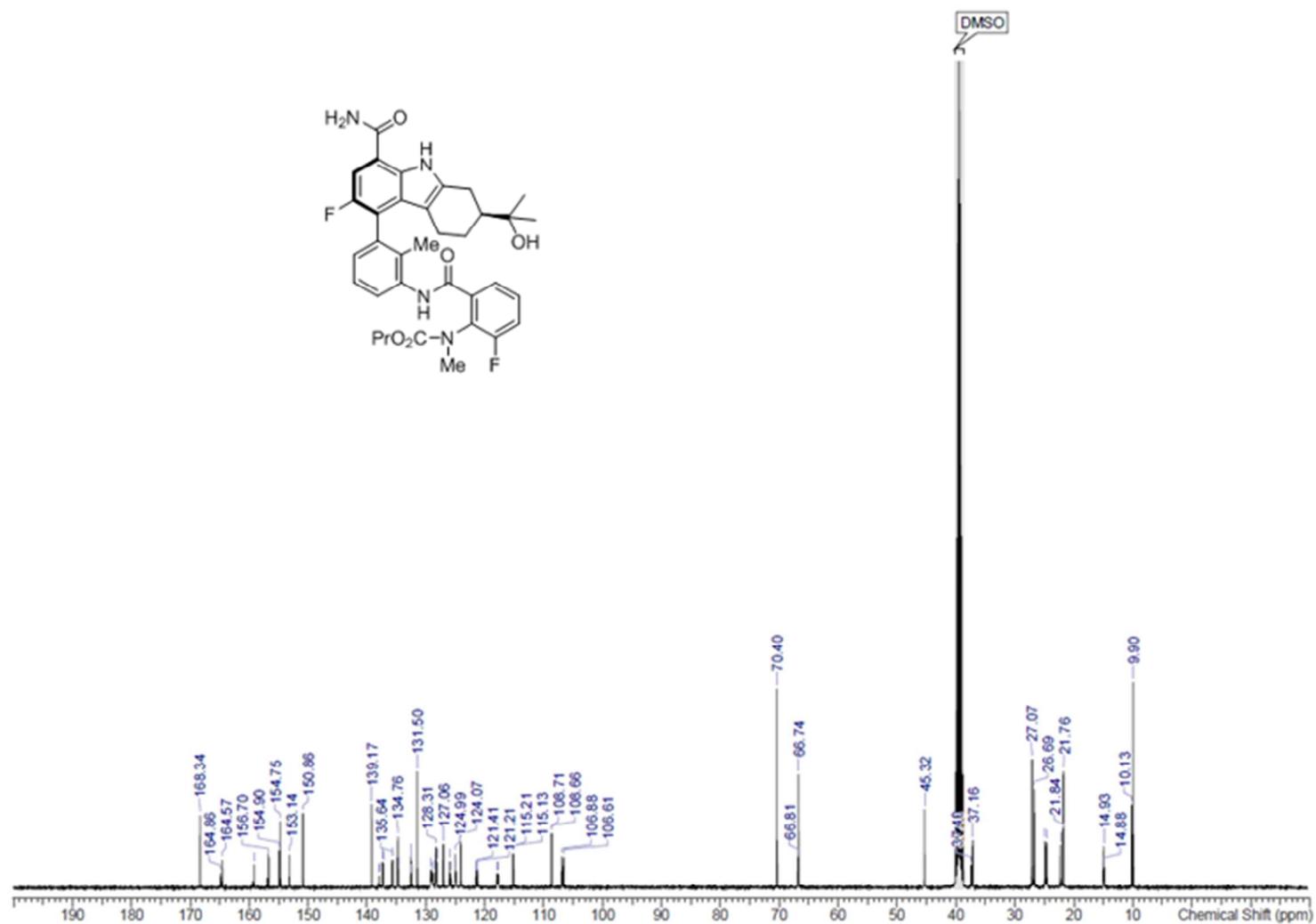
^{13}C NMR (100 MHz, DMSO- d_6) of 3-fluoro-2-(methyl(propoxycarbonyl)amino)benzoic acid (21)



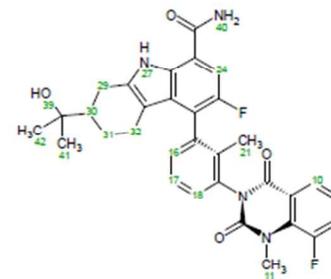
^1H NMR (400 MHz, DMSO-d_6) of (2-((3-((2S,5R)-8-carbamoyl-6-fluoro-2-((S)-1-hydroxyethyl)-2,3,4,9-tetrahydro-1H-carbazol-5-yl)-2-methylphenyl)carbamoyl)-6-fluorophenyl)(methyl)carbamate (27)



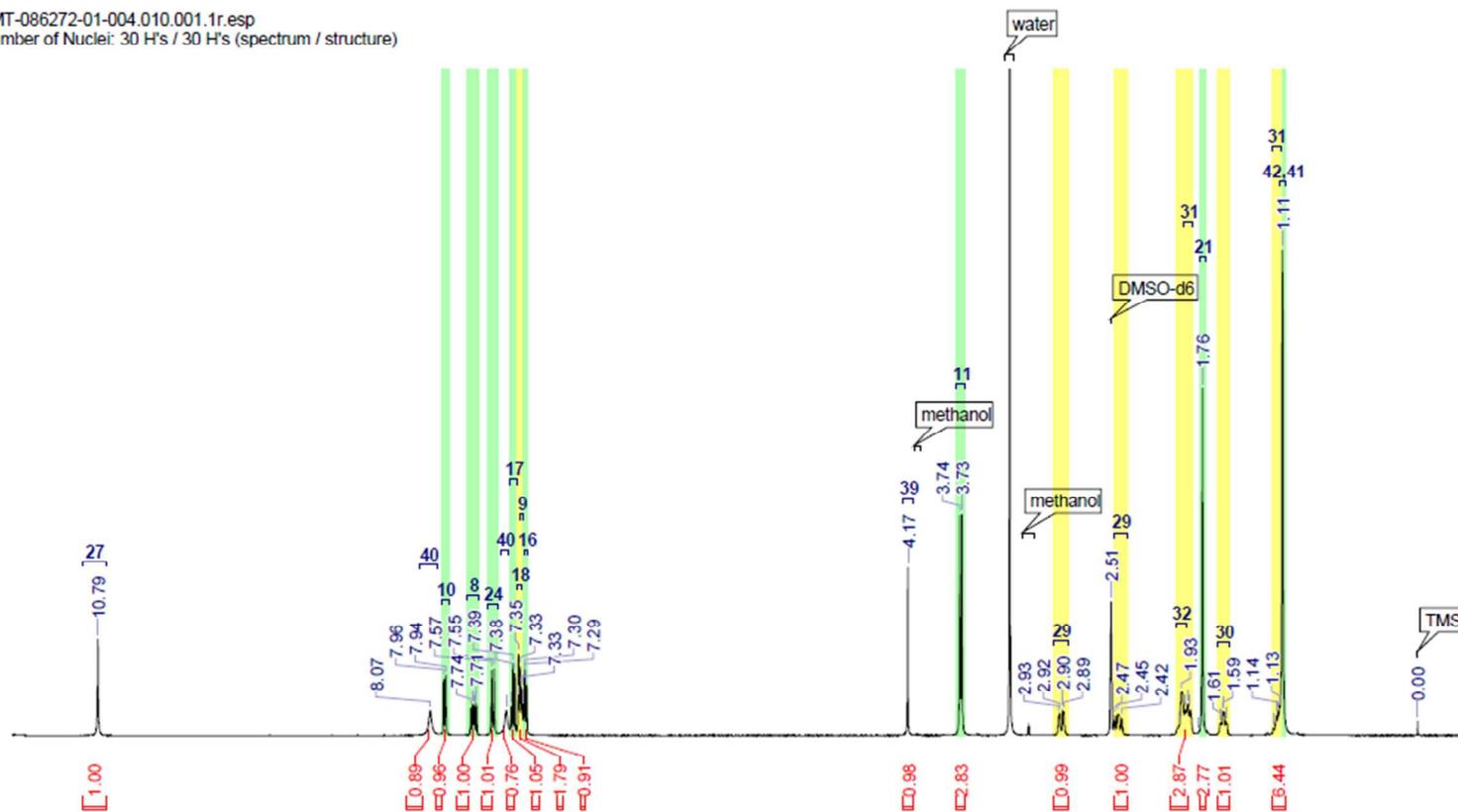
^{13}C NMR (100 MHz, DMSO-d_6) of (2-((3-((2*S*,5*R*)-8-carbamoyl-6-fluoro-2-((*S*)-1-hydroxyethyl)-2,3,4,9-tetrahydro-1*H*-carbazol-5-yl)-2-methylphenyl)carbamoyl-6-fluorophenyl)(methyl)carbamate (27)



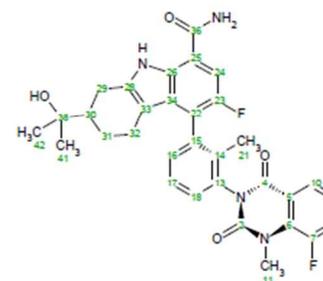
^1H NMR (500 MHz, DMSO- d_6) of (2*S*,5*R*)-6-fluoro-5-(3-(8-fluoro-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole-8-carboxamide (1*A*) – Isolated as methanol solvate



IMT-086272-01-004.010.001.1r.esp
 Number of Nuclei: 30 H's / 30 H's (spectrum / structure)



^{13}C NMR (125.8 MHz, DMSO- d_6) of (2*S*,5*R*)-6-fluoro-5-(3-(8-fluoro-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)-2-methylphenyl)-2-(2-hydroxypropan-2-yl)-2,3,4,9-tetrahydro-1*H*-carbazole-8-carboxamide (1*A*)



BMT-086272-01-004.012.001.1r.esp
Number of Nuclei: 32 C's / 32 C's (spectrum / structure)

