Supporting Information

Gabriel Synthesis of Aminomethyl-Bicyclo[1.1.0]butanes

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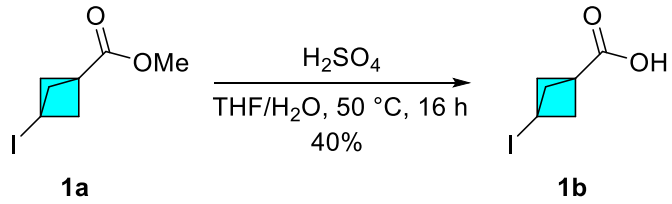
General Experimental. All solvents were purchased from Sigma-Aldrich and used without further purification. All reactions involving heating were performed in aluminum heating blocks. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F254 plates; the developed plate was analyzed by UV lamp (254 nm). Column chromatography was performed with the Teledyne-Isco CombiFlash Rf200 system using pre-packed silica gel column cartridges and hexanes/ethyl acetate or DCM/MeOH as the solvent system. Reverse-phase HPLC was performed with a Teledyne ACCQPrep system. Solvents were UHPLC/MS grade purchased from Sigma-Aldrich. NMR spectra were recorded in $CDCl_3$, DMSO-d_6, on Bruker Avance 500 or 400 MHz spectrometers at 298 K unless otherwise noted. NMR data were processed in ACD/Spectrus Processor (Advanced Chemistry Development, Inc). Chemical shifts are reported in ppm with the TMS or residual solvent signal as the reference and coupling constants (*J*) are given in Hertz (Hz). Liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Shimadzu Nexera UHPLC/LCMS-2020 MS instrument with a Waters Acquity BEH C18 1.7 μm 2.1 x 50 mm column and mobile phase A: 5:95 MeCN:H_2O with 0.05% trifluoroacetic acid; mobile phase B: 95:5 MeCN:H_2O with 0.05% trifluoroacetic acid. Wavelength detection was performed at 220 and 254 nm. High resolution mass spectrometry (HRMS) was performed using a Thermo Fisher QExactive with an orbitrap (ion trap) mass analyzer. X-ray crystallography data collection procedures are described in the relevant section below.

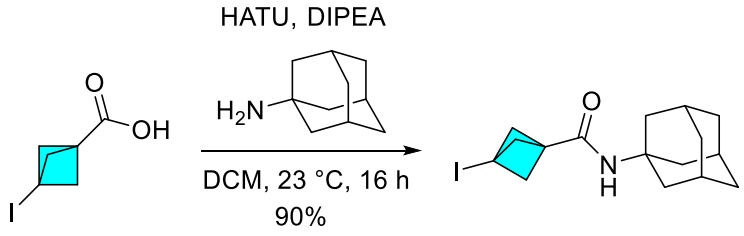
Synthesis of 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid (1b)



1a **1b**

To a cooled solution of methyl 3-iodobicyclo[1.1.1]pentane-1-carboxylate **1a**[1] (16 g, 64 mmol) in H_2O (150 mL) and THF (150 mL) was added concentrated H_2SO_4 dropwise (27 mL, 508 mmol). The reaction was stirred at 50° C for 16 h. Volatiles were removed under vacuum and the aqueous layer was extracted with 2 x equal volume DCM. The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated by rotary evaporation. The residue was triturated with petroleum ether and filtered through a vacuum filter to afford 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (6.0 g, 25 mmol, 40% yield) as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.58 (s, 6H) (COOH proton not observed). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.8, 60.5, 45.8, 5.1. **HRMS** (ESI): Compound **1b** did not ionize as the molecular ion.

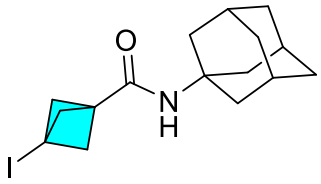
Representative procedure for the synthesis of 3-iodobicyclo[1.1.1]pentane-1-carboxamides (2)



1b **2a**

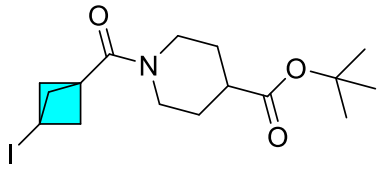
To a 250 mL round bottom flask equipped with magnetic stirbar was added 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol), adamantan-1-amine (1.4 g, 9.2 mmol), and DCM (80 mL). HATU (3.5 g, 9.2 mmol) followed by DIPEA (4.2 ml, 25 mmol) were added and the mixture was stirred at room temperature for 16 h under N_2 atmosphere. After completion, the DCM was removed by rotary evaporation. The solid was resuspended in 100 mL of H_2O and the aqueous layer was extracted with DCM (3 x 100 mL). The organic layers were combined, dried over sodium sulfate, and concentrated by rotary evaporation. The crude material was subjected to flash column chromatography with hexanes/EtOAc as the eluant (120 g Gold column, 20–90% EtOAc over 40 minutes). Desired fractions were combined and concentrated by rotary evaporation to afford **2a** as an off-white solid (2.8 g, 7.5 mmol) in 90% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.06 - 4.91 (m, 1H), 2.50 (s, 6H), 2.11 - 2.05 (m, 3H), 1.99 - 1.94 (m, 6H), 1.70 - 1.65 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5, 60.4, 52.2, 48.6, 41.5, 36.2, 29.4, 6.0. **HRMS** (ESI) calculated for $C_{16}H_{23}INO^+$ $[M+H]^+$: 372.0819, found: 372.0808.

Characterization data for 3-iodobicyclo[1.1.1]pentane-1-carboxamides (2)



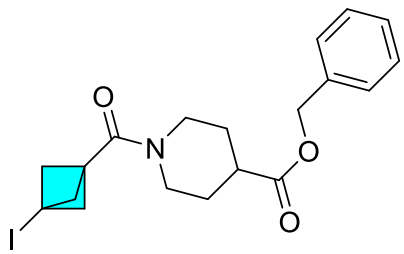
2a

***N*-(adamantan-1-yl)-3-iodobicyclo[1.1.1]pentane-1-carboxamide (2a).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and adamantan-1-amine (1.4 g, 9.2 mmol) gave **2a** as an off-white solid (2.8 g, 7.5 mmol, 90% yield) after purification by flash column chromatography with hexanes/EtOAc (120 g column; 20–90% EtOAc over 40 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.06 - 4.91 (m, 1H), 2.50 (s, 6H), 2.11 - 2.05 (m, 3H), 1.99 - 1.94 (m, 6H), 1.70 - 1.65 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5, 60.4, 52.2, 48.6, 41.5, 36.2, 29.4, 6.0. **HRMS** (ESI) calculated for $C_{16}H_{23}INO^+$ $[M+H]^+$: 372.0819, found: 372.0808.



2b

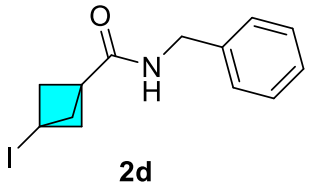
***Tert*-butyl 1-(3-iodobicyclo[1.1.1]pentane-1-carbonyl)piperidine-4-carboxylate (2b).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and *tert*-butyl piperidine-4-carboxylate (1.7 g, 9.2 mmol) gave **2b** (2.2 g, 5.5 mmol, 66% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0–40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.28 (br d, *J*=13.0 Hz, 1H), 3.91 (br d, *J*=13.0 Hz, 1H), 3.13 (br t, *J*=12.3 Hz, 1H), 2.84 (br t, *J*=12.0 Hz, 1H), 2.56 (br s, 6H), 2.49 - 2.39 (m, 1H), 1.89 (br d, *J*=12.5 Hz, 2H), 1.65 - 1.57 (m, 2H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.3, 164.6, 80.8, 61.9, 48.4, 44.7, 41.8, 41.6, 28.0, 7.2. **HRMS** (ESI) calculated for $C_{16}H_{25}INO_3^+$ $[M+H]^+$: 406.0874, found: 406.0866.



2c

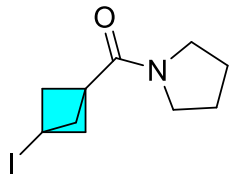
Benzyl 1-(3-iodobicyclo[1.1.1]pentane-1-carbonyl)piperidine-4-carboxylate (2c). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and benzyl piperidine-4-carboxylate TFA salt (3.1 g, 9.2 mmol; an extra equivalent of DIPEA was

used) gave **2c** (2.7 g, 6.1 mmol, 72% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 - 7.32 (m, 5H), 5.14 (s, 2H), 4.34 - 4.25 (m, 1H), 4.00 - 3.90 (m, 1H), 3.18 - 3.09 (m, 1H), 2.85 - 2.78 (m, 1H), 2.69 - 2.53 (m, 7H), 1.99 - 1.91 (m, 2H), 1.71 - 1.62 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.7, 164.6, 135.7, 128.6, 128.3, 128.1, 66.5, 61.8, 48.3, 44.7, 41.7, 40.8, 7.1. **HRMS** (ESI) calculated for $C_{19}H_{23}INO_3^+$ $[M+H]^+$: 440.0717, found: 440.0710.



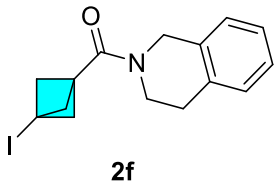
2d

***N*-benzyl-3-iodobicyclo[1.1.1]pentane-1-carboxamide (2d).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and benzylamine (1.0 g, 9.2 mmol) gave **2d** (1.5 g, 4.7 mmol, 56% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 - 7.23 (m, 5H), 5.70 (br s, 1H), 4.40 (d, *J*=6.0 Hz, 2H), 2.54 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 137.6, 128.8, 127.9, 127.8, 60.3, 47.8, 43.6, 5.5. **HRMS** (ESI) calculated for $C_{13}H_{15}INO^+$ $[M+H]^+$: 328.0193, found: 328.0191.



2e

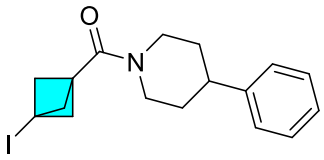
(3-iodobicyclo[1.1.1]pentan-1-yl)(pyrrolidin-1-yl)methanone (2e). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and pyrrolidine (0.66 g, 9.2 mmol) gave **2e** as a light yellow solid (2.0 g, 6.9 mmol, 82% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.45 (dt, *J*=10.1, 7.0 Hz, 4H), 2.64 (s, 6H), 1.96 (quin, *J*=6.9 Hz, 2H), 1.88 - 1.78 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.7, 61.1, 48.6, 46.6, 46.5, 26.5, 23.7, 7.5. **HRMS** (ESI) calculated for $C_{10}H_{15}INO^+$ $[M+H]^+$: 292.0193, found: 292.0186.



2f

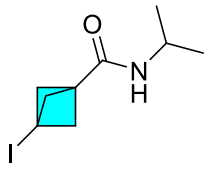
(3,4-dihydroisoquinolin-2(1H)-yl)(3-iodobicyclo[1.1.1]pentan-1-yl)methanone (2f). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and 1,2,3,4-tetrahydroisoquinoline (1.1 g, 9.2 mmol) gave **2f** (2.4 g, 6.7 mmol, 80% yield) as a white solid after purification by flash column chromatography with hexanes/EtOAc (80g column; 0 – 40% EtOAc over 30 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 - 7.06 (m, 4H), 4.73 - 4.63 (m, 2H), 3.76 (q, *J*=6.0 Hz, 2H), 2.92 - 2.82 (m, 2H), 2.71 - 2.66 (m, 6H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 165.2, 165.1, 134.8, 133.7, 133.0, 132.1, 129.0, 128.3, 127.1, 126.7, 126.7, 126.7, 126.5, 125.9, 61.8, 61.7, 48.5, 47.3, 44.8, 43.2, 40.5, 29.4, 28.2, 7.2 (rotamers observed). **HRMS** (ESI) calculated for $C_{15}H_{17}INO^+$ $[M+H]^+$: 354.0349, found: 354.0337.



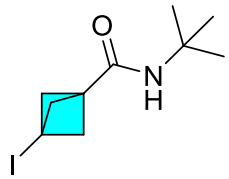
2g

(3-iodobicyclo[1.1.1]pentan-1-yl)(4-phenylpiperidin-1-yl)methanone (2g). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and 4-phenylpiperidine (1.5 g, 9.2 mmol) gave **2g** (2.5 g, 6.6 mmol, 79% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 - 7.28 (m, 2H), 7.24 (d, *J*=7.0 Hz, 1H), 7.21 - 7.15 (m, 2H), 4.67 (br d, *J*=13.0 Hz, 1H), 4.14 (br d, *J*=13.0 Hz, 1H), 3.22 - 3.03 (m, 1H), 2.81 - 2.60 (m, 8H), 1.90 (br t, *J*=12.0 Hz, 2H), 1.69 - 1.58 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7, 144.8, 128.6, 126.7, 126.6, 61.9, 48.5, 46.2, 43.2, 42.6, 33.9, 32.6, 7.4. **HRMS** (ESI) calculated for $C_{17}H_{21}INO^+$ $[M+H]^+$: 382.0662, found: 382.0656.



2h

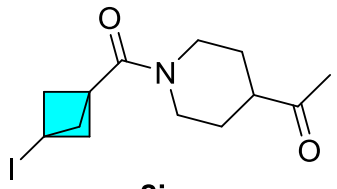
3-iodo-*N*-isopropylbicyclo[1.1.1]pentane-1-carboxamide (2h). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and propan-2-amine (0.55 g, 9.2 mmol) gave **2h** (1.7 g, 6.1 mmol, 73% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.21 (br s, 1H), 4.09 - 3.94 (m, 1H), 2.52 (s, 6H), 1.14 (d, *J*=6.5 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.5, 60.3, 48.0, 41.5, 22.7, 5.7. **HRMS** (ESI) calculated for $C_9H_{15}INO^+$ $[M+H]^+$: 280.0193, found: 280.0191.



2i

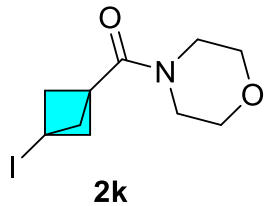
***N*-(*tert*-butyl)-3-iodobicyclo[1.1.1]pentane-1-carboxamide (2i).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and 2-methylpropan-2-amine (0.68 g, 9.2 mmol) gave **2i** (1.9 g, 6.5 mmol, 77% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.14 (br s, 1H), 2.50 (s, 6H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 60.3, 51.5, 48.6, 28.7, 5.8. **HRMS** (ESI) calculated for $C_{10}H_{17}INO^+$ $[M+H]^+$: 294.0349, found: 294.0348.



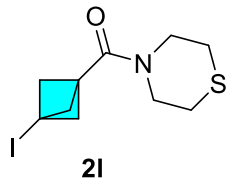
2j

1-(1-(3-iodobicyclo[1.1.1]pentane-1-carbonyl)piperidin-4-yl)ethan-1-one (2j). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and 1-(piperidin-4-yl)ethan-1-one HCl (2.2 g, 9.2 mmol) gave **2j** (2.2 g, 6.5 mmol, 79% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.48 - 4.35 (m, 1H), 4.07 - 3.95 (m, 1H), 3.15 - 3.03 (m, 1H), 2.82 - 2.70 (m, 1H), 2.68 - 2.59 (m, 6H), 2.58 - 2.51 (m, 1H), 2.17 (s, 3H), 1.96 - 1.80 (m, 2H), 1.61 - 1.45 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.3, 164.7, 61.8, 48.6, 48.3, 44.8, 41.9, 27.9, 27.6, 27.3, 7.1. **HRMS** (ESI) calculated for $C_{13}H_{19}INO_2^+$ $[M+H]^+$: 348.0455, found: 348.0437.



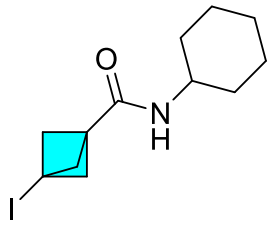
2k

(3-iodobicyclo[1.1.1]pentan-1-yl)(morpholino)methanone (2k). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and morpholine (0.80 g, 9.2 mmol) gave **2k** (2.2 g, 7.2 mmol, 85% yield) as a white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.71 - 3.62 (m, 4H), 3.61 - 3.52 (m, 4H), 2.64 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.9, 66.7, 66.5, 61.7, 48.1, 46.0, 42.5, 6.9. **HRMS** (ESI) calculated for $C_{10}H_{15}INO_2^+$ $[M+H]^+$: 308.0142, found: 308.0132.



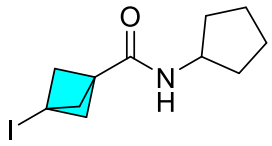
2l

(3-iodobicyclo[1.1.1]pentan-1-yl)(thiomorpholino)methanone (2l). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and thiomorpholine (0.95 g, 9.2 mmol) gave **2l** (2.2 g, 6.7 mmol, 80% yield) as a white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.82 (br dd, *J*=4.6, 2.9 Hz, 4H), 2.64 (s, 6H), 2.62 - 2.56 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.8, 61.8, 48.3, 48.2, 44.9, 27.9, 27.1, 6.9. **HRMS** (ESI) calculated for $C_{10}H_{15}INOS^+$ $[M+H]^+$: 323.9914, found: 323.9911.



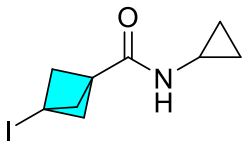
2m

***N*-cyclohexyl-3-iodobicyclo[1.1.1]pentane-1-carboxamide (2m).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and cyclohexanamine (0.92 g, 9.2 mmol) gave **2m** (2.2 g, 7.0 mmol, 83% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.20 (br d, *J*=6.0 Hz, 1H), 3.79 - 3.61 (m, 1H), 2.52 (s, 6H), 1.96 - 1.83 (m, 2H), 1.71 - 1.58 (m, 3H), 1.47 - 1.26 (m, 2H), 1.21 - 1.01 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5, 60.3, 48.3, 48.0, 33.1, 25.4, 24.8, 5.8. **HRMS** (ESI) calculated for $C_{12}H_{19}INO^+$ $[M+H]^+$: 320.0506, found: 320.0497.



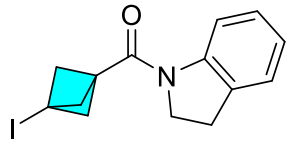
2n

***N*-cyclopentyl-3-iodobicyclo[1.1.1]pentane-1-carboxamide (2n).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and cyclopentanamine (0.79 g, 9.2 mmol) gave **2n** (1.8 g, 6.1 mmol, 72% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.28 (br s, 1H), 4.13 (sxt, *J*=7.1 Hz, 1H), 2.52 (s, 6H), 2.05 - 1.92 (m, 2H), 1.73 - 1.62 (m, 3H), 1.60 - 1.54 (m, 1H), 1.39 - 1.28 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.0, 77.2, 60.3, 51.2, 33.1, 23.7, 5.8. **HRMS** (ESI) calculated for $C_{11}H_{17}INO^+$ $[M+H]^+$: 306.0349, found: 306.0349.



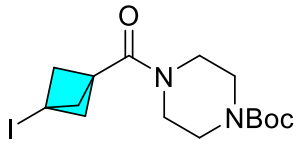
2o

***N*-cyclopropyl-3-iodobicyclo[1.1.1]pentane-1-carboxamide (2o).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and cyclopropanamine (0.53 g, 9.2 mmol) gave **2o** (1.8 g, 6.5 mmol, 77% yield) as a light yellow solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.56 (br s, 1H), 2.72 - 2.63 (m, 1H), 2.51 (s, 6H), 0.81 - 0.74 (m, 2H), 0.54 - 0.47 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 60.3, 47.8, 22.6, 6.6, 5.6. **HRMS** (ESI) calculated for $C_9H_{13}INO^+$ $[M+H]^+$: 278.0036, found: 278.0033.



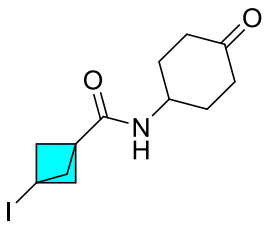
2p

Indolin-1-yl(3-iodobicyclo[1.1.1]pentan-1-yl)methanone (2p). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and indoline (1.1 g, 9.2 mmol) gave **2p** (1.9 g, 5.6 mmol, 67% yield) as a white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J*=8.5 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.07 - 6.99 (m, 1H), 4.11 (t, *J*=8.3 Hz, 2H), 3.21 (t, *J*=8.3 Hz, 2H), 2.72 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.1, 142.8, 130.7, 127.7, 124.5, 124.3, 117.3, 61.2, 49.5, 47.9, 28.4, 7.1. **HRMS** (ESI) calculated for $C_{14}H_{15}INO^+$ $[M+H]^+$: 340.0193, found: 340.0188.



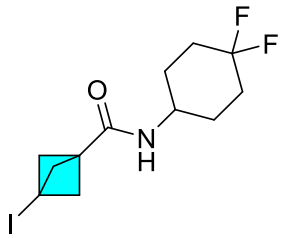
2q

***Tert*-butyl 4-(3-iodobicyclo[1.1.1]pentane-1-carbonyl)piperazine-1-carboxylate (2q).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and *tert*-butylpiperazine-1-carboxylate (1.7 g, 9.2 mmol) gave **2q** (2.9 g, 7.1 mmol, 85% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.58 - 3.49 (m, 4H), 3.47 - 3.34 (m, 4H), 2.65 (s, 6H), 1.47 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.0, 154.4, 80.5, 61.8, 48.2, 45.3, 42.1, 28.3, 6.8. **HRMS** (ESI) calculated for $C_{15}H_{24}IN_2O_3^+$ $[M+H\text{-}tBu]^+$: 351.0200, found: 351.0196.



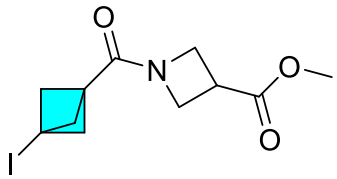
2r

3-Iodo-*N*-(4-oxocyclohexyl)bicyclo[1.1.1]pentane-1-carboxamide (2r). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and 4-aminocyclohexan-1-one (1.0 g, 9.2 mmol) gave **2r** (2.4 g, 7.2 mmol, 86% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.32 (br d, *J*=6.9 Hz, 1H), 4.24 - 4.11 (m, 1H), 2.54 (s, 6H), 2.50 - 2.35 (m, 4H), 2.24 (ddd, *J*=12.8, 6.3, 2.9 Hz, 2H), 1.72 - 1.55 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.1, 166.0, 60.2, 47.8, 46.6, 39.1, 31.9, 5.2. **HRMS** (ESI) calculated for $C_{12}H_{17}INO_2^+$ $[M+H]^+$: 334.0298, found: 334.0294.



2s

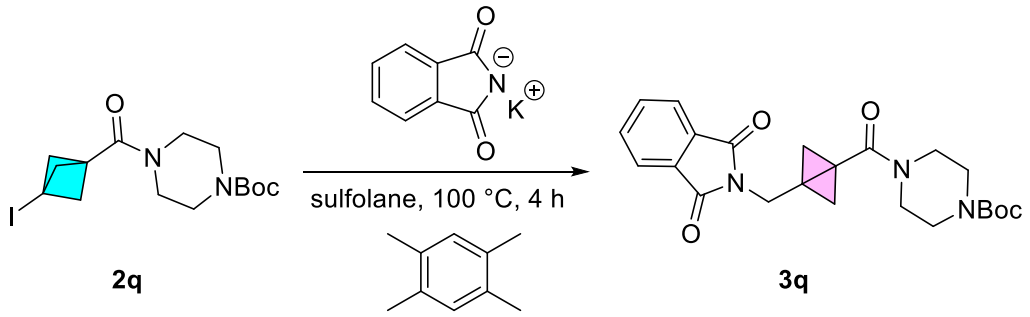
***N*-(4,4-difluorocyclohexyl)-3-iodobicyclo[1.1.1]pentane-1-carboxamide (2s).** The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and 4,4-difluorocyclohexan-1-amine (1.2 g, 9.2 mmol) gave **2s** (2.5 g, 6.9 mmol, 82% yield) as an off-white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.20 (br d, *J*=5.0 Hz, 1H), 3.94 - 3.71 (m, 1H), 2.52 (s, 6H), 2.20 - 2.04 (m, 2H), 2.02 - 1.93 (m, 2H), 1.93 - 1.72 (m, 2H), 1.54 - 1.43 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.9, 122.2 (dd, *J*=243.4, 239.8 Hz), 58.7, 47.8, 46.4 (d, *J*=1.8 Hz), 32.72 - 31.48, 28.6 (d, *J*=10.0 Hz), 5.3. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -215.50 (br d, *J*=237.2 Hz), -222.57 (br d, *J*=238.6 Hz). **HRMS** (ESI) calculated for $C_{12}H_{17}F_2INO^+$ $[M+H]^+$: 356.0317, found: 356.0313.



2t

Methyl 1-(3-iodobicyclo[1.1.1]pentane-1-carbonyl)azetidine-3-carboxylate (2t). The reaction between 3-iodobicyclo[1.1.1]pentane-1-carboxylic acid **1b** (2.0 g, 8.4 mmol) and methyl azetidine-3-carboxylate (1.1 g, 9.2 mmol) gave **2t** (2.2 g, 6.5 mmol, 77% yield) as a white solid after purification by flash column chromatography with hexanes/EtOAc (80 g column; 0 – 40% EtOAc over 30 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.46 - 4.31 (m, 2H), 4.25 - 4.09 (m, 2H), 3.77 (s, 3H), 3.51 - 3.38 (m, 1H), 2.58 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.3, 165.8, 60.8, 53.0, 52.5, 51.3, 46.3, 32.4, 6.4. **HRMS** (ESI) calculated for $C_{11}H_{15}INO_3^+$ $[M+H]^+$: 336.0091, found: 336.0079.

NMR optimization experiments



2q **3q**

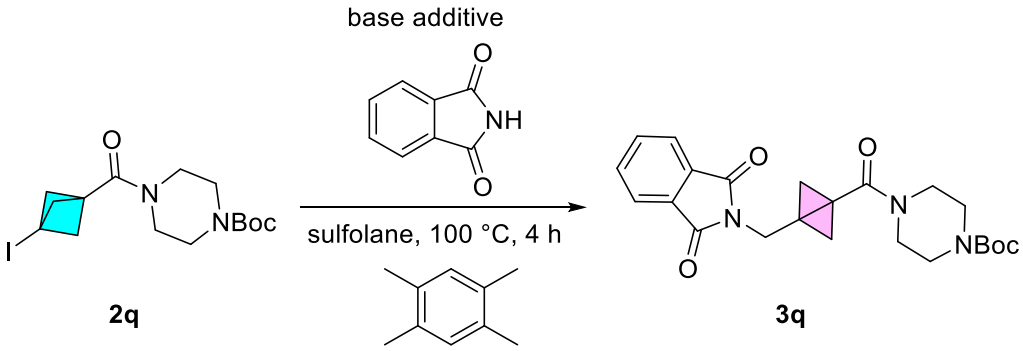
durene (NMR internal standard)

To a 4 mL vial was added **2q** (20 mg, 0.049 mmol, 1.0 equiv), potassium phthalimide (11 mg, 0.059 mmol, 1.2 equiv) in the corresponding solvent system (0.4 mL) and heated to 100 °C for 4 h. 1,2,4,5-tetramethylbenzene (durene, 1.0 equiv, 0.0049 mmol) was added and sample was dissolved in 600 μL $CDCl_3$. A 1D ^1H NMR spectrum was acquired at 298 K (NS = 16, D1 = 3 s). The singlet corresponding **3q** at 2.3 ppm (s, 2H) was integrated relative to the singlet from the internal standard at 6.9 ppm (s, 2H).

Table S1. Solvent Optimization for BCP-I **2q** to BCB-Phthalimide **3q** Transformation

Entry	Solvent	NMR Yield (%)[a,b]
1	Sulfolane	30[c]
2	DMSO	21[c]
3	Ethanol	<5[c]
4	n-Butanol	<5[c]
5	HFIP	0[c]
6	THF	0[c]
7	NMP	9[c]
8	DMF	7[c]
9	AcOH	0
10	Cyrene	0

[a]**2q** (1.0 equiv), phthalimide (1.2 equiv), and additive (1.2 equiv) were heated to 100 °C for 4 h unless otherwise noted. [b]NMR yields using 1,2,4,5-tetramethylbenzene as an internal standard. [c]16 h reaction time.



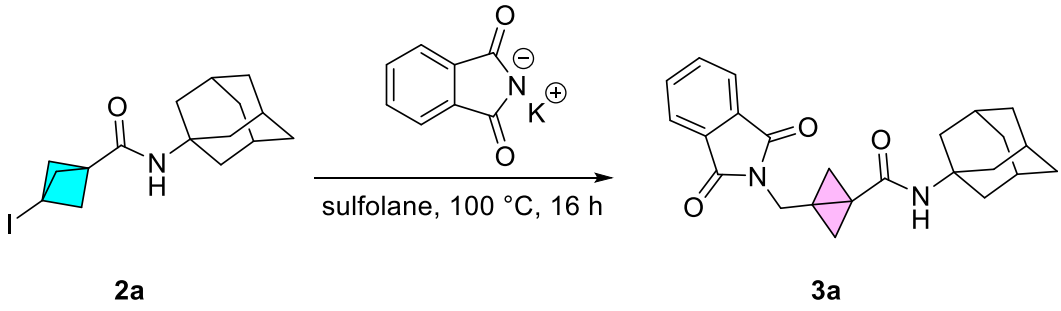
To a 4 mL vial was added **2q** (20 mg, 0.049 mmol, 1.0 equiv), phthalimide (8.7 mg, 0.059 mmol, 1.2 equiv) in the corresponding solvent system (0.4 mL) and heated to 100 °C for 4 h. 1,2,4,5-tetramethylbenzene (durene, 1.0 equiv, 0.049 mmol) was added and sample was dissolved in 600 μL $CDCl_3$. A 1D ^1H NMR spectrum was acquired at 298 K (NS = 16, D1 = 3 s). The singlet corresponding **3q** at 2.3 ppm (s, 2H) was integrated relative to the singlet from the internal standard at 6.9 ppm (s, 2H).

Table S2. Base Optimization for BCP-I **2q** to BCB-Phthalimide **3q** Transformation

Entry	Base	T (°C)	NMR Yield (%)[a,b]
1	-	100	30[c]
2	Pyridine	100	0
3	DIPEA	100	< 5
4	DBU	100	20
5	Cs_2CO_3	100	16
6	K_2CO_3	100	0
7	K_3PO_4	100	< 5

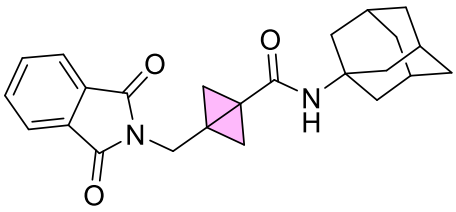
[a]**2q** (1.0 equiv), phthalimide (1.2 equiv), and additive (1.2 equiv) were heated to 100 °C for 4 h unless otherwise noted. [b]NMR yields using 1,2,4,5-tetramethylbenzene as an internal standard. [c]Potassium phthalimide used as control.

Representative procedure for the synthesis of bicyclo[1.1.0]butane-1-carboxamides (3)



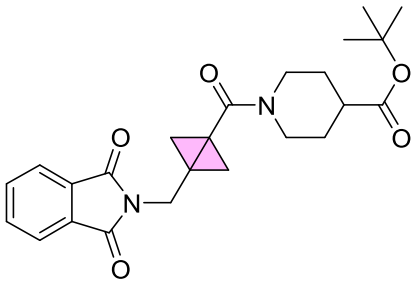
To a 100 mL round bottom flask equipped with magnetic stirbar was added *N*-(adamantan-1-yl)-3-iodobicyclo[1.1.1]pentane-1-carboxamide **2a** (2.5 g, 6.7 mmol), potassium phthalimide (1.5 g, 8.1 mmol), and sulfolane (50 mL). The mixture was stirred at 100 ^{o}C for 16 h. After completion, reaction was resuspended in 100 mL of H_2O and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried over sodium sulfate, and concentrated by rotary evaporation. The crude material was subjected to flash column chromatography with hexanes/EtOAc as the eluant (120g Gold column, 50-90% EtOAc over 40 minutes). Desired fractions were combined and concentrated by rotary evaporation to afford an off-white solid (0.78 g, 2.0 mmol) in 30% yield. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.93 - 7.80 (m, 4H), 7.04 (s, 1H), 3.91 (s, 2H), 2.25 (s, 2H), 1.97 (br s, 3H), 1.91 (br s, 6H), 1.59 (br s, 6H), 1.00 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.4, 166.9, 134.4, 131.6, 123.1, 51.3, 41.0, 36.6, 36.5, 36.0, 28.8, 21.5, 15.4. **HRMS** (ESI) calculated $C_{24}H_{27}N_2O_3^+$ $[M+H]^+$: 391.2016, found: 391.2003.

Characterization data for bicyclo[1.1.0]butane-1-carboxamides (3)



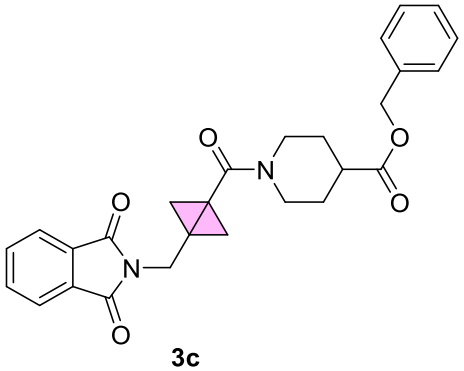
3a

***N*-(adamantan-1-yl)-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide (3a).** The reaction between **2a** (2.5 g, 6.7 mmol) and potassium phthalimide (1.5 g, 8.1 mmol) gave **3a** as an off-white solid (0.78 g, 2.0 mmol, 30% yield) after purification by flash column chromatography with hexanes/EtOAc (120 g Gold column; 50 – 90% EtOAc over 40 min). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.93 - 7.80 (m, 4H), 7.04 (s, 1H), 3.91 (s, 2H), 2.25 (s, 2H), 1.97 (br s, 3H), 1.91 (br s, 6H), 1.59 (br s, 6H), 1.00 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.4, 166.9, 134.4, 131.6, 123.1, 51.3, 41.0, 36.6, 36.5, 36.0, 28.8, 21.5, 15.4. **HRMS** (ESI) calculated $C_{24}H_{27}N_2O_3^+$ $[M+H]^+$: 391.2016, found: 391.2003.



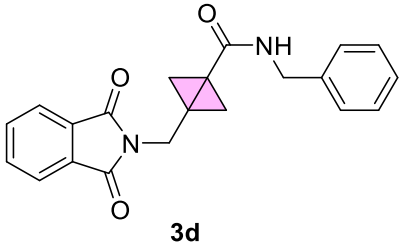
3b

Tert-butyl 1-(3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carbonyl)piperidine-4-carboxylate (3b). The reaction between **2b** (2.0 g, 4.9 mmol) and potassium phthalimide (1.1 g, 5.9 mmol) gave **3b** as an off-white solid (0.63 g, 1.1 mmol, 23% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.81 (m, 2H), 7.72 (br dd, *J*=5.5, 3.0 Hz, 2H), 4.32 (dt, *J*=13.4, 3.6 Hz, 2H), 4.19 (s, 2H), 3.25 (br t, *J*=11.0 Hz, 1H), 2.94 - 2.79 (m, 1H), 2.54 - 2.38 (m, 1H), 2.30 (s, 2H), 1.92 (br dd, *J*=13.5, 3.5 Hz, 2H), 1.72 - 1.61 (m, 2H), 1.47 (s, 9H), 1.27 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.5, 168.0, 167.8, 133.9, 132.3, 123.2, 80.6, 46.1, 42.0, 41.5, 39.1, 37.1, 28.7, 28.1, 27.9, 22.5, 12.4. **HRMS** (ESI) calculated for $C_{24}H_{29}N_2O_5^+$ $[M+H]^+$: 425.2071, found: 425.2062.



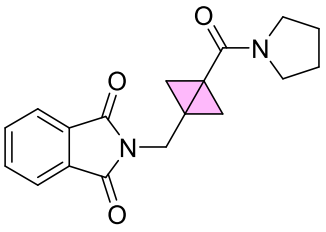
3c

Benzyl 1-(3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carbonyl)piperidine-4-carboxylate (3c). The reaction between **2c** (2.0 g, 4.6 mmol) and potassium phthalimide (1.0 g, 5.5 mmol) gave **3c** as a light yellow solid (0.54 g, 1.2 mmol, 26% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 - 7.81 (m, 2H), 7.76 - 7.66 (m, 2H), 7.41 - 7.31 (m, 5H), 5.16 (s, 2H), 4.35 (br d, *J*=13.5 Hz, 2H), 4.19 (s, 2H), 3.25 (br t, *J*=11.4 Hz, 1H), 2.87 (br t, *J*=11.1 Hz, 1H), 2.71 - 2.52 (m, 1H), 2.30 (s, 2H), 2.03 - 1.94 (m, 2H), 1.82 - 1.67 (m, 2H), 1.27 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.9, 168.0, 167.8, 135.9, 133.9, 132.3, 128.6, 128.3, 128.1, 123.2, 66.4, 46.0, 41.5, 41.2, 39.1, 37.0, 28.6, 27.7, 22.6, 12.4. **HRMS** (ESI) calculated for $C_{27}H_{27}N_2O_5^+$ $[M+H]^+$: 459.1914, found: 459.1908.



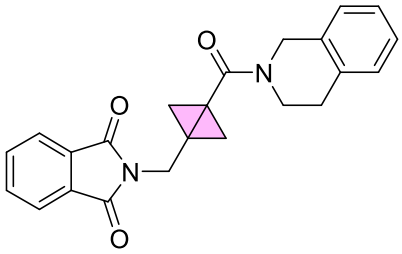
3d

***N*-Benzyl-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide (3d).** The reaction between **2d** (2.0 g, 6.1 mmol) and potassium phthalimide (1.4 g, 7.3 mmol) gave **3d** as an off-white solid (0.47 g, 1.3 mmol, 22% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 - 7.82 (m, 2H), 7.78 - 7.70 (m, 2H), 7.39 - 7.28 (m, 5H), 5.98 - 5.83 (m, 1H), 4.46 (d, *J*=6.0 Hz, 2H), 4.16 (s, 2H), 2.36 (s, 2H), 1.19 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6, 167.9, 138.3, 134.0, 132.1, 128.7, 127.9, 127.6, 123.3, 44.0, 36.8, 36.4, 23.6, 15.8. **HRMS** (ESI) calculated for $C_{21}H_{19}N_2O_3^+$ $[M+H]^+$: 347.1390, found: 347.1381.



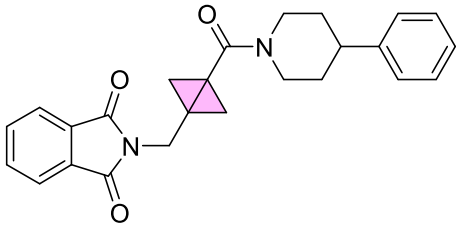
3e

2-((3-(pyrrolidine-1-carbonyl)bicyclo[1.1.0]butan-1-yl)methyl)isoindoline-1,3-dione (3e). The reaction between **2e** (2.0 g, 6.9 mmol) and potassium phthalimide (1.5 g, 8.2 mmol) gave **3e** as an off-white solid (0.62 g, 2.0 mmol, 29% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 - 7.79 (m, 2H), 7.77 - 7.63 (m, 2H), 4.20 (s, 2H), 3.74 - 3.56 (m, 2H), 3.51 - 3.38 (m, 2H), 2.38 (s, 2H), 1.90 (br dd, *J*=11.4, 6.6 Hz, 4H), 1.24 (br s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.0, 167.3, 133.9, 132.3, 123.2, 48.4, 46.1, 38.7, 37.3, 26.2, 24.3, 22.8, 14.0. **HRMS** (ESI) calculated for $C_{18}H_{19}N_2O_3^+$ $[M+H]^+$: 311.1390, found: 311.1377.



3f

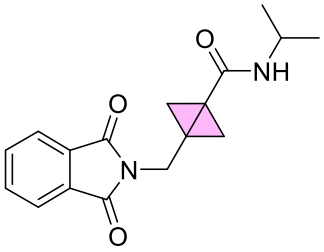
2-((3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)bicyclo[1.1.0]butan-1-yl)methyl)isoindoline-1,3-dione (3f). The reaction between **2f** (2.0 g, 5.7 mmol) and potassium phthalimide (1.3 g, 6.8 mmol) gave **3f** as an off-white solid (0.63 g, 1.7 mmol, 30% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 - 7.78 (m, 2H), 7.76 - 7.67 (m, 2H), 7.25 - 7.08 (m, 4H), 4.94 (br s, 1H), 4.71 (s, 1H), 4.21 (br s, 2H), 4.01 (br t, *J*=5.5 Hz, 1H), 3.90 - 3.79 (m, 1H), 2.90 (t, *J*=6.0 Hz, 2H), 2.39 (s, 2H), 1.33 (s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6, T = 353 K) δ 167.0, 166.8, 134.2, 133.8, 133.0, 131.3, 128.0, 125.9, 125.8, 125.6, 122.5, 37.8, 35.8, 28.5, 28.1, 22.1, 12.0. **HRMS** (ESI) calculated for $C_{23}H_{21}N_2O_3^+$ $[M+H]^+$: 373.1547, found: 373.1541.



3g

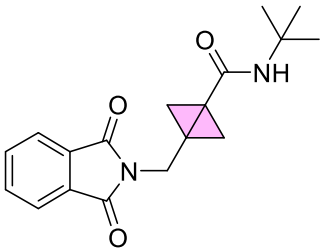
2-((3-(4-phenylpiperidine-1-carbonyl)bicyclo[1.1.0]butan-1-yl)methyl)isoindoline-1,3-dione (3g). The reaction between **2g** (2.0 g, 5.3 mmol) and potassium phthalimide (1.6 g, 8.6

mmol) gave **3g** as an off-white solid (0.59 g, 1.5 mmol, 28% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 - 7.82 (m, 2H), 7.78 - 7.69 (m, 2H), 7.38 - 7.31 (m, 2H), 7.26 - 7.20 (m, 3H), 4.76 - 4.56 (m, 2H), 4.23 (s, 2H), 3.28 - 3.13 (m, 1H), 2.85 - 2.67 (m, 2H), 2.35 (s, 2H), 1.92 (br d, *J*=12.5 Hz, 2H), 1.76 - 1.64 (m, 2H), 1.30 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 167.7, 145.3, 133.9, 132.3, 128.6, 126.8, 126.5, 123.3, 47.5, 43.0, 39.1, 39.1, 37.1, 34.1, 32.9, 22.4, 12.5. **HRMS** (ESI) calculated for $C_{25}H_{25}N_2O_3^+$ $[M+H]^+$: 401.1860, found: 401.1853.



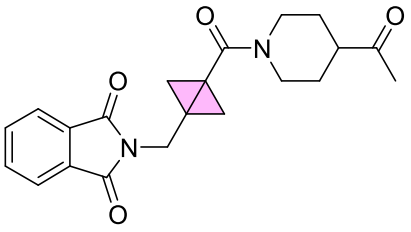
3h

3-((1,3-dioxoisoindolin-2-yl)methyl)-*N*-isopropylbicyclo[1.1.0]butane-1-carboxamide (3h). The reaction between **2h** (2.0 g, 7.2 mmol) and potassium phthalimide (1.6 g, 8.6 mmol) gave **3h** as a light yellow solid (0.36 g, 1.2 mmol, 17% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 - 7.82 (m, 2H), 7.78 - 7.67 (m, 2H), 5.45 (br d, *J*=7.3 Hz, 1H), 4.17 - 4.01 (m, 3H), 2.32 (s, 2H), 1.20 - 1.13 (m, 8H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 167.7, 134.0, 132.1, 123.3, 41.8, 36.8, 36.2, 23.0, 22.9, 15.8. **HRMS** (ESI) calculated for $C_{17}H_{19}N_2O_3^+$ $[M+H]^+$: 299.1390, found: 299.1383.



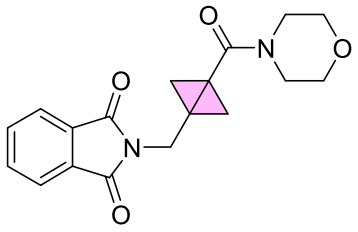
3i

***N*-(*tert*-butyl)-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide (3i).** The reaction between **2i** (2.0 g, 6.8 mmol) and potassium phthalimide (1.5 g, 8.2 mmol) gave **3i** as a light yellow solid (0.43 g, 1.4 mmol, 20% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 - 7.83 (m, 2H), 7.73 (dd, *J*=5.4, 3.1 Hz, 2H), 5.47 (br s, 1H), 4.12 (s, 2H), 2.30 (s, 2H), 1.37 (s, 9H), 1.12 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 167.9, 133.9, 132.2, 123.3, 51.7, 37.0, 36.3, 29.0, 22.6, 16.4. **HRMS** (ESI) calculated for $C_{18}H_{21}N_2O_3^+$ $[M+H]^+$: 313.1547, found: 313.1530.



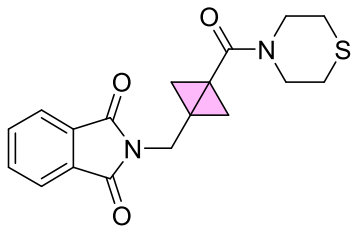
3j

2-((3-(4-acetylpiperidine-1-carbonyl)bicyclo[1.1.0]butan-1-yl)methyl)isoindoline-1,3-dione (3j). The reaction between **2j** (2.0 g, 5.8 mmol) and potassium phthalimide (1.3 g, 6.9 mmol) gave **3j** as an off-white solid (0.51 g, 1.4 mmol, 24% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 - 7.80 (m, 2H), 7.77 - 7.67 (m, 2H), 4.53 - 4.36 (m, 2H), 4.18 (s, 2H), 3.19 (br t, *J*=11.0 Hz, 1H), 2.79 (br t, *J*=11.3 Hz, 1H), 2.58 (tt, *J*=11.1, 3.6 Hz, 1H), 2.30 (s, 2H), 2.19 (s, 3H), 2.00 - 1.83 (m, 2H), 1.66 - 1.51 (m, 2H), 1.27 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.6, 168.0, 167.9, 133.9, 132.2, 123.2, 49.2, 46.2, 41.7, 39.0, 37.0, 28.0, 27.8, 27.4, 22.7, 12.4. **HRMS** (ESI) calculated for $C_{21}H_{23}N_2O_4^+$ $[M+H]^+$: 367.1652, found: 367.1633.



3k

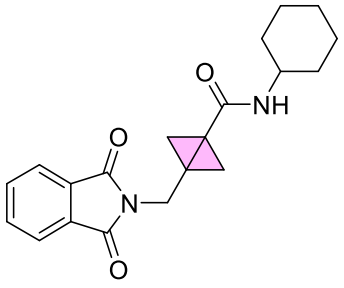
2-((3-(morpholine-4-carbonyl)bicyclo[1.1.0]butan-1-yl)methyl)isoindoline-1,3-dione (3k). The reaction between **2k** (2.0 g, 6.5 mmol) and potassium phthalimide (1.5 g, 7.8 mmol) gave **3k** as a white solid (0.68 g, 2.1 mmol, 32% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 - 7.81 (m, 2H), 7.78 - 7.68 (m, 2H), 4.20 (s, 2H), 3.85 - 3.76 (m, 2H), 3.74 - 3.67 (m, 4H), 3.66 - 3.58 (m, 2H), 2.31 (s, 2H), 1.30 (s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6, T = 353 K) δ 167.0, 166.6, 133.9, 131.4, 122.6, 65.8, 50.2, 44.2, 37.9, 35.7, 22.1, 21.6, 11.5. **HRMS** (ESI) calculated for $C_{18}H_{19}N_2O_4^+$ $[M+H]^+$: 327.1339, found: 327.1336.



3l

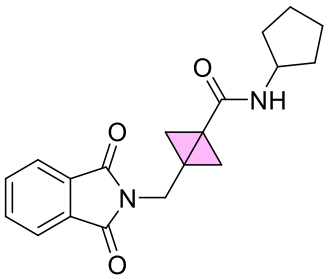
2-((3-(thiomorpholine-4-carbonyl)bicyclo[1.1.0]butan-1-yl)methyl)isoindoline-1,3-dione (3l). The reaction between **2l** (2.0 g, 6.2 mmol) and potassium phthalimide (1.4 g, 7.4 mmol)

gave **3l** as a white solid (0.64 g, 1.9 mmol, 30% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 - 7.84 (m, 2H), 7.76 - 7.68 (m, 2H), 4.20 (s, 2H), 4.12 - 3.80 (m, 4H), 2.70 - 2.62 (m, 4H), 2.30 (s, 2H), 1.28 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.1, 168.0, 133.9, 132.2, 123.3, 49.3, 44.7, 39.0, 36.8, 28.2, 27.3, 22.9, 12.4. **HRMS** (ESI) calculated for $C_{18}H_{19}N_2O_3S^+$ $[M+H]^+$: 343.1111, found: 343.1107.



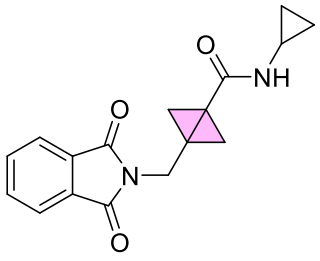
3m

***N*-cyclohexyl-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide (3m).** The reaction between **2m** (2.0 g, 6.3 mmol) and potassium phthalimide (1.4 g, 7.5 mmol) gave **3m** as a light yellow solid (0.53 g, 1.6 mmol, 25% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 - 7.83 (m, 2H), 7.73 (br dd, *J*=5.5, 3.0 Hz, 2H), 5.47 (br d, *J*=8.5 Hz, 1H), 4.11 (s, 2H), 3.85 - 3.71 (m, 1H), 2.33 (s, 2H), 1.99 - 1.86 (m, 2H), 1.77 - 1.67 (m, 2H), 1.66 - 1.55 (m, 1H), 1.44 - 1.31 (m, 2H), 1.28 - 1.00 (m, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 167.7, 134.0, 132.2, 123.3, 48.6, 36.9, 36.4, 33.4, 25.6, 24.9, 22.9, 15.8. **HRMS** (ESI) calculated for $C_{20}H_{23}N_2O_3^+$ $[M+H]^+$: 339.1703, found: 339.1700.



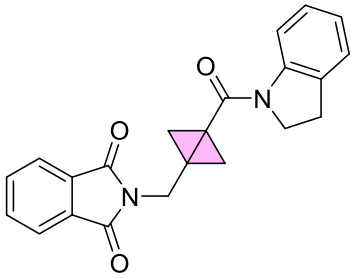
3n

***N*-cyclopentyl-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide (3n).** The reaction between **2n** (2.0 g, 6.6 mmol) and potassium phthalimide (1.5 g, 7.9 mmol) gave **3n** as a light yellow solid (0.51 g, 1.6 mmol, 24% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 - 7.80 (m, 2H), 7.72 (dd, *J*=5.4, 3.1 Hz, 2H), 5.58 (br d, *J*=6.9 Hz, 1H), 4.26 - 4.15 (m, 1H), 4.12 (s, 2H), 2.32 (s, 2H), 2.05 - 1.92 (m, 2H), 1.74 - 1.52 (m, 4H), 1.38 (dq, *J*=12.6, 6.4 Hz, 2H), 1.15 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.1, 167.9, 133.9, 132.1, 123.3, 51.6, 36.8, 36.3, 33.3, 23.7, 22.9, 15.8. **HRMS** (ESI) calculated for $C_{19}H_{21}N_2O_3^+$ $[M+H]^+$: 325.1547, found: 325.1538.



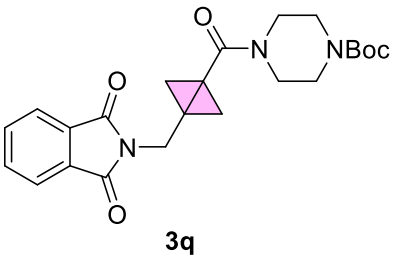
3o

***N*-cyclopropyl-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide (3o).** The reaction between **2o** (2.0 g, 7.2 mmol) and potassium phthalimide (1.6 g, 8.6 mmol) gave **3o** as a light yellow solid (0.51 g, 1.7 mmol, 24% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 - 7.83 (m, 2H), 7.78 - 7.68 (m, 2H), 5.75 (br s, 1H), 4.13 (s, 2H), 2.71 (tq, *J*=7.0, 3.5 Hz, 1H), 2.30 (s, 2H), 1.15 (s, 2H), 0.82 - 0.72 (m, 2H), 0.58 - 0.48 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.9, 167.9, 134.0, 132.1, 123.3, 36.7, 36.2, 23.5, 22.8, 15.6, 6.7. **HRMS** (ESI) calculated for $C_{17}H_{17}N_2O_3^+$ $[M+H]^+$: 297.1234, found: 297.1227.



3p

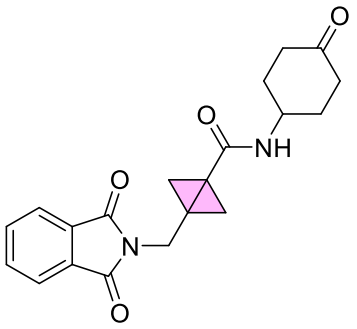
2-((3-(indoline-1-carbonyl)bicyclo[1.1.0]butan-1-yl)methyl)isoindoline-1,3-dione (3p). The reaction between **2p** (2.0 g, 5.9 mmol) and potassium phthalimide (1.3 g, 7.1 mmol) gave **3p** as a white solid (0.69 g, 1.9 mmol, 33% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.91 - 7.81 (m, 4H), 7.82 - 7.74 (m, 1H), 7.23 (d, *J*=7.0 Hz, 1H), 7.11 (t, *J*=7.5 Hz, 1H), 7.03 - 6.94 (m, 1H), 4.35 - 4.20 (m, 2H), 4.16 (s, 2H), 3.19 - 3.05 (m, 2H), 2.42 - 2.31 (m, 2H), 1.32 (br s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.9, 165.7, 142.5, 133.8, 131.5, 131.3, 126.1, 124.1, 122.6, 122.5, 115.9, 48.8, 38.0, 35.6, 27.2, 24.6, 13.9. **HRMS** (ESI) calculated for $C_{22}H_{19}N_2O_3^+$ $[M+H]^+$: 359.1390, found: 359.1381.



3q

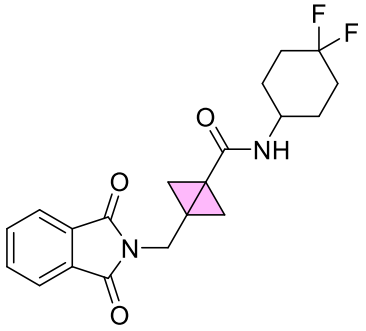
***tert*-Butyl 4-(3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carbonyl)piperazine-1-carboxylate (3q).** The reaction between **2q** (2.0 g, 4.9 mmol) and potassium phthalimide (1.1 g, 5.9 mmol) gave **3q** as an off-white solid (0.58 g, 1.4 mmol, 28%

yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 - 7.83 (m, 2H), 7.77 - 7.68 (m, 2H), 4.20 (s, 2H), 3.84 - 3.71 (m, 2H), 3.64 - 3.53 (m, 2H), 3.51 - 3.40 (m, 4H), 2.31 (s, 2H), 1.49 (s, 9H), 1.30 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.2, 168.0, 154.6, 133.9, 132.2, 123.3, 80.2, 46.7, 42.1, 39.1, 36.8, 28.4, 23.1, 12.4 (two carbons broadened). **HRMS** (ESI) calculated for $C_{23}H_{28}N_3O_5^+$ $[M+H]^+$: 426.2023, found: 426.2012.



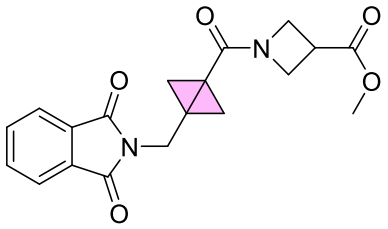
3r

3-((1,3-dioxoisoindolin-2-yl)methyl)-N-(4-oxocyclohexyl)bicyclo[1.1.0]butane-1-carboxamide (3r). The reaction between **2r** (2.0 g, 6.0 mmol) and potassium phthalimide (1.3 g, 7.2 mmol) gave **3r** as a light yellow solid (0.38 g, 1.1 mmol, 18% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 - 7.83 (m, 2H), 7.81 - 7.70 (m, 2H), 5.57 (br d, *J*=7.3 Hz, 1H), 4.31 - 4.20 (m, 1H), 4.16 (s, 2H), 2.55 - 2.38 (m, 4H), 2.34 - 2.22 (m, 4H), 1.70 - 1.62 (m, 2H), 1.20 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.5, 168.4, 167.9, 134.1, 132.1, 123.4, 46.9, 39.2, 36.4, 36.1, 32.2, 24.0, 15.9. **HRMS** (ESI) calculated for $C_{20}H_{21}N_2O_4^+$ $[M+H]^+$: 353.1496, found: 353.1491.



3s

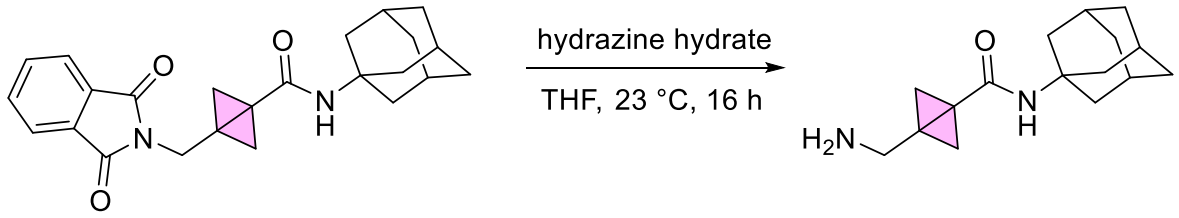
***N*-(4,4-difluorocyclohexyl)-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide (3s).** The reaction between **2s** (2.0 g, 5.6 mmol) and potassium phthalimide (1.3 g, 7.2 mmol) gave **3s** as a light yellow solid (0.40 g, 1.1 mmol, 19% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 80% EtOAc over 60 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 - 7.81 (m, 2H), 7.79 - 7.67 (m, 2H), 5.52 (br d, *J*=8.0 Hz, 1H), 4.13 (s, 2H), 4.00 - 3.74 (m, 1H), 2.31 (s, 2H), 2.17 - 1.98 (m, 4H), 1.95 - 1.77 (m, 2H), 1.59 - 1.45 (m, 2H), 1.18 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.2, 167.8, 134.0, 132.1, 123.3, 124.92 - 120.11, 46.7, 36.4, 36.2, 32.3 (t, *J*=24.5 Hz), 28.8 (d, *J*=10.0 Hz), 23.7, 15.8. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -275.77 (br d, *J*=239.3 Hz), -282.48 (br d, *J*=239.3 Hz). **HRMS** (ESI) calculated for $C_{20}H_{21}F_2N_2O_3^+$ $[M+H]^+$: 375.1515, found: 375.1505.



3t

Methyl 1-(3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carbonyl)azetidine-3-carboxylate (3t). The reaction between **2t** (2.0 g, 6.0 mmol) and potassium phthalimide (1.3 g, 7.2 mmol) gave **3t** as a light yellow solid (0.44 g, 1.3 mmol, 22% yield) after purification by flash column chromatography with hexanes/EtOAc (80 g Gold column; 40 – 48% EtOAc over 60 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 - 7.82 (m, 2H), 7.77 - 7.68 (m, 2H), 4.49 - 4.34 (m, 2H), 4.25 - 4.08 (m, 4H), 3.77 (s, 3H), 3.49 - 3.37 (m, 1H), 2.34 (s, 2H), 1.24 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.6, 170.1, 167.9, 133.9, 132.1, 123.3, 54.1, 52.4, 51.4, 38.0, 36.9, 32.5, 24.0, 12.7. **HRMS** (ESI) calculated for $C_{19}H_{19}N_2O_5^+$ $[M+H]^+$: 355.1288, found: 355.1276.

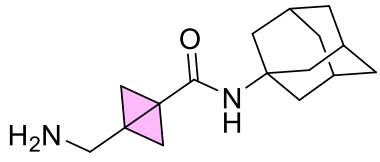
Representative procedure for the synthesis of aminomethyl-bicyclo[1.1.0]butanes (4)



3a **4a**

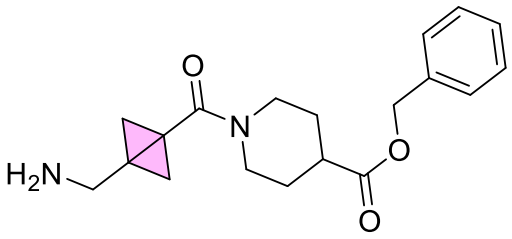
To a 8 mL vial equipped with magnetic stirbar was added *N*-(adamantan-1-yl)-3-((1,3-dioxoisoindolin-2-yl)methyl)bicyclo[1.1.0]butane-1-carboxamide **3a** (0.1 g, 0.26 mmol), and THF (4 mL). Hydrazine monohydrate (64 mg, 1.3 mmol) was added and the mixture was stirred at 23 °C for 16 h. After completion, the clear THF supernatant was decanted and the precipitate was triturated with THF. The THF solution was evaporated and subjected to reverse-phase prep HPLC purification using NH_4OAc/MeCN as the eluant, and desired fractions was concentrated by rotary evaporation followed by lyophilisation to afford the acetate salt of **4a** as a white solid (56 mg, 0.21 mmol) in 80% yield.

Characterization data for aminomethyl-bicyclo[1.1.0]butanes (4)



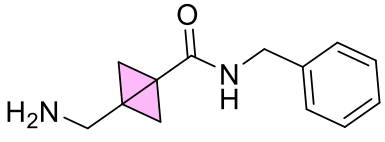
4a

N-(adamantan-1-yl)-3-(aminomethyl)bicyclo[1.1.0]butane-1-carboxamide (4a). The reaction between **3a** (100 mg, 0.26 mmol) and hydrazine hydrate (64 mg, 1.3 mmol) gave **4a** as a white solid (56 mg, 0.21 mmol, 80% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.37 (br s, 1H), 3.24 (br s, 2H), 2.61 (br s, 2H), 2.19 (s, 2H), 2.10 - 2.02 (m, 3H), 1.98 (d, *J*=3.0 Hz, 6H), 1.66 (t, *J*=2.8 Hz, 6H), 1.05 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4, 52.1, 41.7, 39.8, 36.3, 34.2, 29.4, 14.9, 1.0. **HRMS** (ESI) calculated $C_{16}H_{25}N_2O^+$ $[M+H]^+$: 261.1961, found: 261.1947.



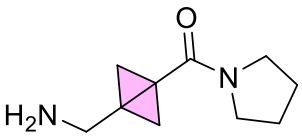
4c

Benzyl 1-(3-(aminomethyl)bicyclo[1.1.0]butane-1-carbonyl)piperidine-4-carboxylate (4c). The reaction between **3c** (100 mg, 0.22 mmol) and hydrazine hydrate (55 mg, 1.1 mmol) gave **4c** as a white solid (55 mg, 0.16 mmol, 76% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, METHANOL-d_4) δ 7.40 - 7.27 (m, 5H), 5.15 (s, 2H), 4.43 - 4.24 (m, 2H), 3.40 (s, 2H), 2.94 (br t, *J*=11.4 Hz, 1H), 2.81 - 2.67 (m, 1H), 2.21 (br d, *J*=2.3 Hz, 2H), 2.06 - 1.86 (m, 5H), 1.77 - 1.52 (m, 2H), 1.38 (s, 2H). **^{13}C NMR** (126 MHz, METHANOL-d_4) δ 175.7, 169.9, 137.7, 129.7, 129.4, 129.3, 67.6, 47.5, 42.8, 42.1, 40.2, 38.8, 38.7, 30.0, 29.1, 21.5, 13.9. **HRMS** (ESI) calculated $C_{19}H_{25}N_2O_3^+$ $[M+H]^+$: 329.1860, found: 329.1847.



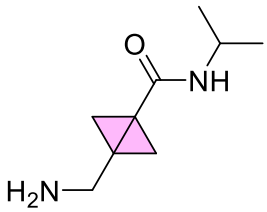
4d

3-(aminomethyl)-N-benzylbicyclo[1.1.0]butane-1-carboxamide (4d). The reaction between **3d** (100 mg, 0.29 mmol) and hydrazine hydrate (72 mg, 1.4 mmol) gave **4d** as a light-yellow solid (60 mg, 0.20 mmol, 70% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.30 (br t, *J*=5.7 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.26 - 7.18 (m, 3H), 4.29 (d, *J*=6.0 Hz, 2H), 2.98 (s, 2H), 2.28 (s, 2H), 1.01 (s, 2H) (two exchangeable protons obscured). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 169.2, 140.0, 128.2, 127.0, 126.6, 42.3, 35.0, 26.2, 14.0 (one carbon obscured). **HRMS** (ESI) calculated $C_{13}H_{17}N_2O^+$ $[M+H]^+$: 217.1335, found: 217.1322.



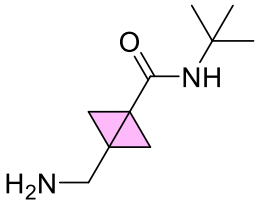
4e

(3-(aminomethyl)bicyclo[1.1.0]butan-1-yl)(pyrrolidin-1-yl)methanone (4e). The reaction between **3e** (100 mg, 0.32 mmol) and hydrazine hydrate (80 mg, 1.6 mmol) gave **4e** as a light-yellow solid (45 mg, 0.24 mmol, 77% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 3.59 (t, *J*=6.5 Hz, 2H), 3.30 (t, *J*=6.8 Hz, 2H), 3.09 (br s, 2H), 2.21 (s, 2H), 1.84 - 1.73 (m, 6H), 1.08 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 167.5, 47.8, 45.8, 36.4, 26.3, 25.7, 23.8, 22.2, 12.2. **HRMS** (ESI) calculated $C_{10}H_{17}N_2O^+$ $[M+H]^+$: 181.1335, found: 181.1325.



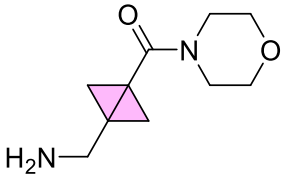
4h

3-(aminomethyl)-N-isopropylbicyclo[1.1.0]butane-1-carboxamide (4h). The reaction between **3h** (100 mg, 0.33 mmol) and hydrazine hydrate (84 mg, 1.7 mmol) gave **4h** as an off-white solid (36 mg, 0.21 mmol, 64% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.48 (br d, *J*=7.6 Hz, 1H), 3.93 - 3.83 (m, 1H), 2.95 (s, 2H), 2.24 (s, 2H), 1.03 (d, *J*=6.5 Hz, 6H), 0.95 (s, 2H) (two exchangeable protons obscured). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.2, 40.5, 34.8, 25.8, 22.5, 13.7 (one carbon obscured). **HRMS** (ESI) calculated $C_9H_{17}N_2O^+$ $[M+H]^+$: 169.1335, found: 169.1325.



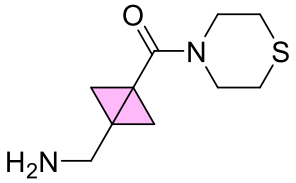
4i

3-(aminomethyl)-N-(tert-butyl)bicyclo[1.1.0]butane-1-carboxamide (4i). The reaction between **3i** (100 mg, 0.32 mmol) and hydrazine hydrate (80 mg, 1.6 mmol) gave **4i** as a colorless viscous oil (38 mg, 0.21 mmol, 65% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 2.98 (br s, 2H), 2.21 (s, 2H), 1.22 (s, 9H), 1.03 (s, 2H) (three exchangeable protons obscured). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.6, 50.4, 35.2, 28.6, 14.3 (two carbons obscured). **HRMS** (ESI) calculated $C_{10}H_{19}N_2O^+$ $[M+H]^+$: 183.1492, found: 183.1480.



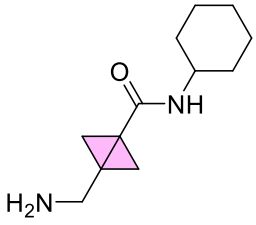
4k

(3-(aminomethyl)bicyclo[1.1.0]butan-1-yl)(morpholino)methanone (4k). The reaction between **3k** (100 mg, 0.30 mmol) and hydrazine hydrate (70 mg, 1.5 mmol) gave **4k** as an off-white solid (40 mg, 0.20 mmol, 67% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 3.78 - 3.54 (m, 10H), 3.06 (s, 2H), 2.17 (s, 2H), 1.13 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 66.9, 66.7, 47.4, 42.6, 38.4, 37.0, 23.8, 11.7. **HRMS** (ESI) calculated $C_{10}H_{17}N_2O_2^+$ $[M+H]^+$: 197.1285, found: 197.1274.



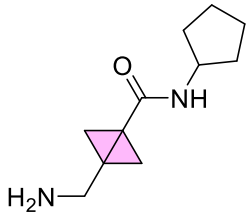
4l

(3-(aminomethyl)bicyclo[1.1.0]butan-1-yl)(thiomorpholino)methanonecarboxamide (4l). The reaction between **3l** (100 mg, 0.29 mmol) and hydrazine hydrate (73 mg, 1.5 mmol) gave **4l** as an off-white solid (50 mg, 0.24 mmol, 82% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (500 MHz, DMSO-d_6, 353 K) δ 4.03 - 3.89 (m, 6H), 3.10 (s, 2H), 2.63 - 2.58 (m, 4H), 2.16 (s, 2H), 1.12 (s, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6, 353 K) δ 168.3, 46.0, 38.2, 35.9, 27.3, 26.5, 10.1 (two carbons obscured). **HRMS** (ESI) calculated $C_{10}H_{17}N_2OS^+$ $[M+H]^+$: 213.1056, found: 213.1045.



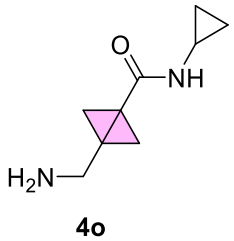
4m

3-(aminomethyl)-N-cyclohexylbicyclo[1.1.0]butane-1-carboxamide (4m). The reaction between **3m** (100 mg, 0.30 mmol) and hydrazine hydrate (74 mg, 1.5 mmol) gave **4m** as an off-white solid (50 mg, 0.24 mmol, 80% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, METHANOL-d_4) δ 3.73 - 3.63 (m, 1H), 3.15 (s, 2H), 2.31 (s, 2H), 1.90 (s, 2H), 1.87 - 1.72 (m, 4H), 1.68 - 1.58 (m, 1H), 1.42 - 1.25 (m, 3H), 1.25 - 1.10 (m, 4H) (one proton obscured). **^{13}C NMR** (101 MHz, METHANOL-d_4) δ 171.2, 50.6, 41.3, 36.9, 34.1, 26.7, 26.5, 23.5, 16.3. **HRMS** (ESI) calculated $C_{12}H_{21}N_2O^+$ $[M+H]^+$: 209.1648, found: 209.1644.



4n

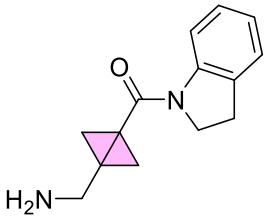
3-(aminomethyl)-N-cyclopentylbicyclo[1.1.0]butane-1-carboxamide (4n). The reaction between **3n** (100 mg, 0.30 mmol) and hydrazine hydrate (77 mg, 1.5 mmol) gave **4n** as a colorless viscous oil (40 mg, 0.22 mmol, 73% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.65 (br d, *J*=5.3 Hz, 1H), 4.22 (sxt, *J*=7.0 Hz, 1H), 3.28 (s, 2H), 2.24 (s, 2H), 2.03 - 1.94 (m, 2H), 1.71 - 1.55 (m, 4H), 1.41 - 1.29 (m, 2H), 1.11 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.8, 51.6, 39.6, 34.5, 33.3, 26.1, 23.7, 14.7. **HRMS** (ESI) calculated $C_{11}H_{19}N_2O^+$ $[M+H]^+$: 195.1492, found: 195.1485.



4o

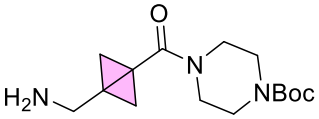
3-(aminomethyl)-N-cyclopropylbicyclo[1.1.0]butane-1-carboxamide (4o). The reaction between **3o** (100 mg, 0.33 mmol) and hydrazine hydrate (84 mg, 1.7 mmol) gave **4o** as a colorless viscous oil (45 mg, 0.27 mmol, 80% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.72 (br d, *J*=2.4 Hz, 1H), 2.95 (s, 2H), 2.61 (tq, *J*=7.3, 3.8 Hz, 1H), 2.21 (s, 2H), 0.94 (s, 2H), 0.62 - 0.53 (m, 2H), 0.43 - 0.36 (m, 2H) (two

protons obscured). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 172.5, 34.8, 26.3, 22.6, 13.6, 5.7 (one carbon obscured). **HRMS** (ESI) calculated $C_9H_{15}N_2O^+$ $[M+H]^+$: 167.1179, found: 167.1177.



4p

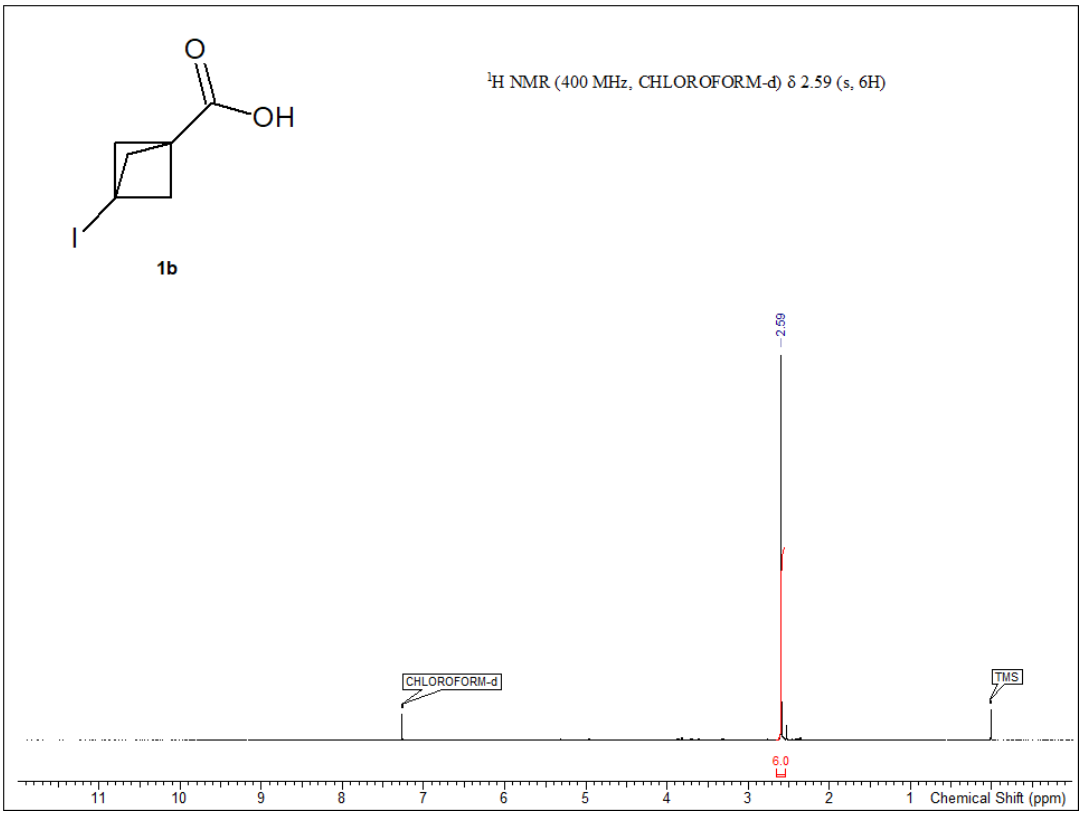
(3-(aminomethyl)bicyclo[1.1.0]butan-1-yl)(indolin-1-yl)methanone (4p). The reaction between **3p** (100 mg, 0.28 mmol) and hydrazine hydrate (70 mg, 1.4 mmol) gave **4p** as a white solid (50 mg, 0.21 mmol, 75% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.01 - 7.73 (m, 1H), 7.23 (d, *J*=7.0 Hz, 1H), 7.13 (t, *J*=7.8 Hz, 1H), 7.02 - 6.94 (m, 1H), 4.24 (br s, 2H), 3.16 (s, 2H), 3.10 (br t, *J*=8.3 Hz, 2H), 2.35 (br s, 2H), 1.25 (s, 2H) (two protons obscured). **^{13}C NMR** (126 MHz, DMSO-d_6, 353 K) δ 167.6, 142.8, 131.6, 126.4, 126.2, 124.3, 122.5, 115.7, 48.9, 38.4, 36.5, 27.2, 12.4. **HRMS** (ESI) calculated $C_{14}H_{17}N_2O^+$ $[M+H]^+$: 229.1335, found: 229.1324.

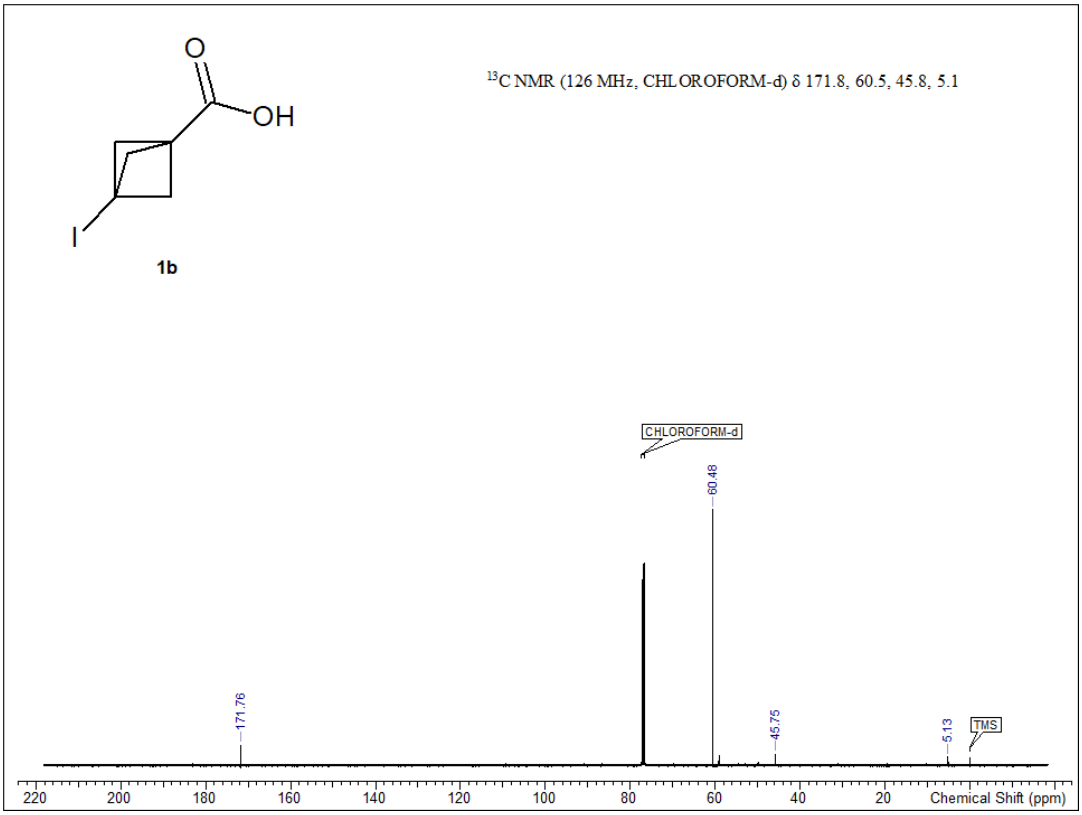


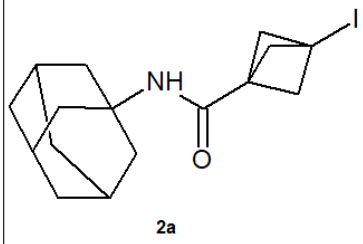
4q

tert-butyl 4-(3-(aminomethyl)bicyclo[1.1.0]butane-1-carbonyl)piperazine-1-carboxylate (4q). The reaction between **3q** (100 mg, 0.23 mmol) and hydrazine hydrate (60 mg, 1.2 mmol) gave **4q** as an off-white solid (53 mg, 0.27 mmol, 77% yield) after purification by preparative reverse-phase HPLC with NH_4OAc buffer/MeCN as the eluant and XSelectC18 (250 x 20 mm, 5 µm) column. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 3.83 - 3.36 (m, 10H), 3.15 (s, 2H), 2.18 (s, 2H), 1.41 (s, 9H), 1.22 (s, 2H) (piperazine protons overlapping). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.7, 153.8, 79.2, 46.0, 44.2, 41.5, 40.1, 38.6, 37.7, 28.0, 23.7, 11.1. **HRMS** (ESI) calculated $C_{15}H_{26}N_3O_3^+$ $[M+H]^+$: 296.1969, found: 296.1960.

NMR Spectra

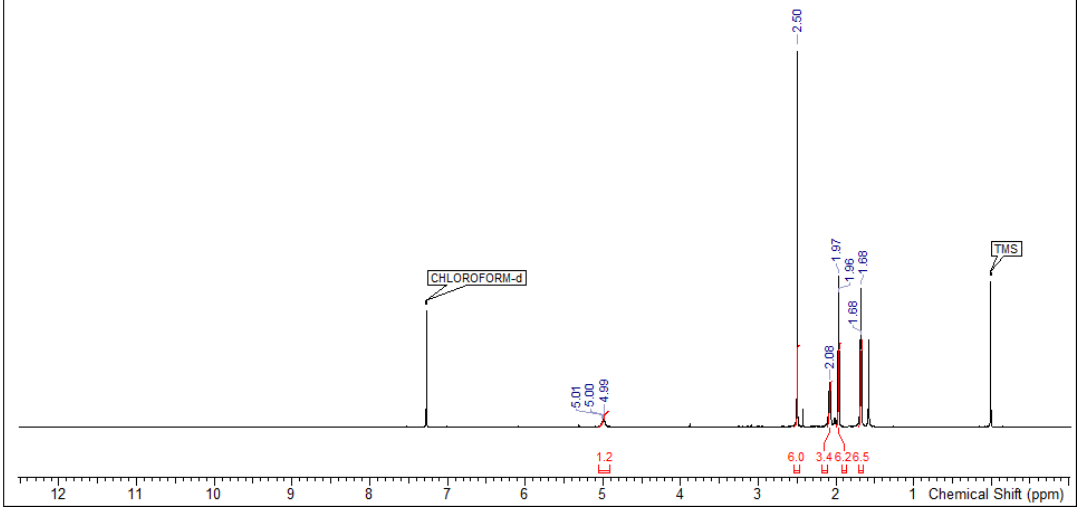

O
OH
I
1b
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 2.59 (s, 6H)
2.59
CHLOROFORM-d
TMS
6.0
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

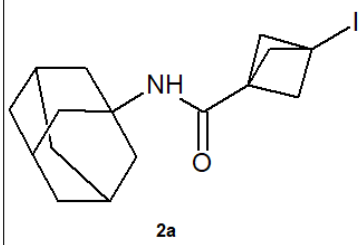

O
OH
I
1b
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 171.8, 60.5, 45.8, 5.1
CHLOROFORM-d
60.48
171.76
45.75
5.13
TMS
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)



2a

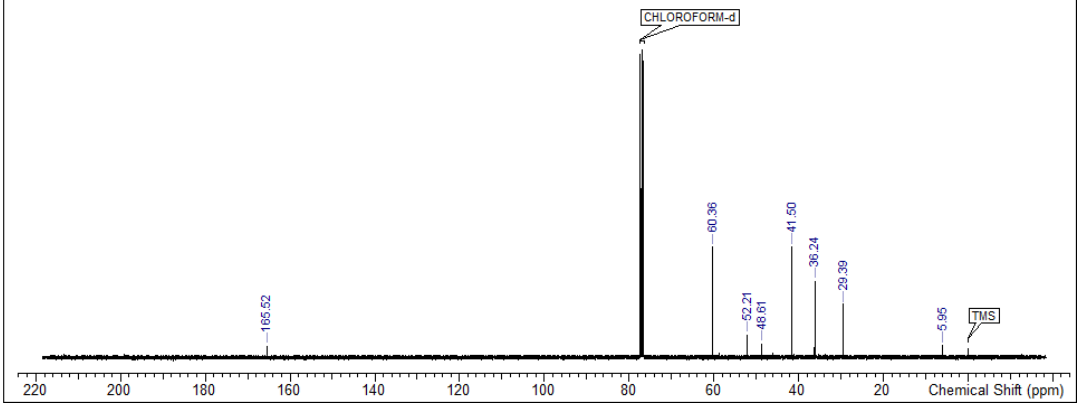
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.06 - 4.91 (m, 1H), 2.50 (s, 6H), 2.11 - 2.05 (m, 3H), 1.99 - 1.94 (m, 6H), 1.70 - 1.65 (m, 6H)

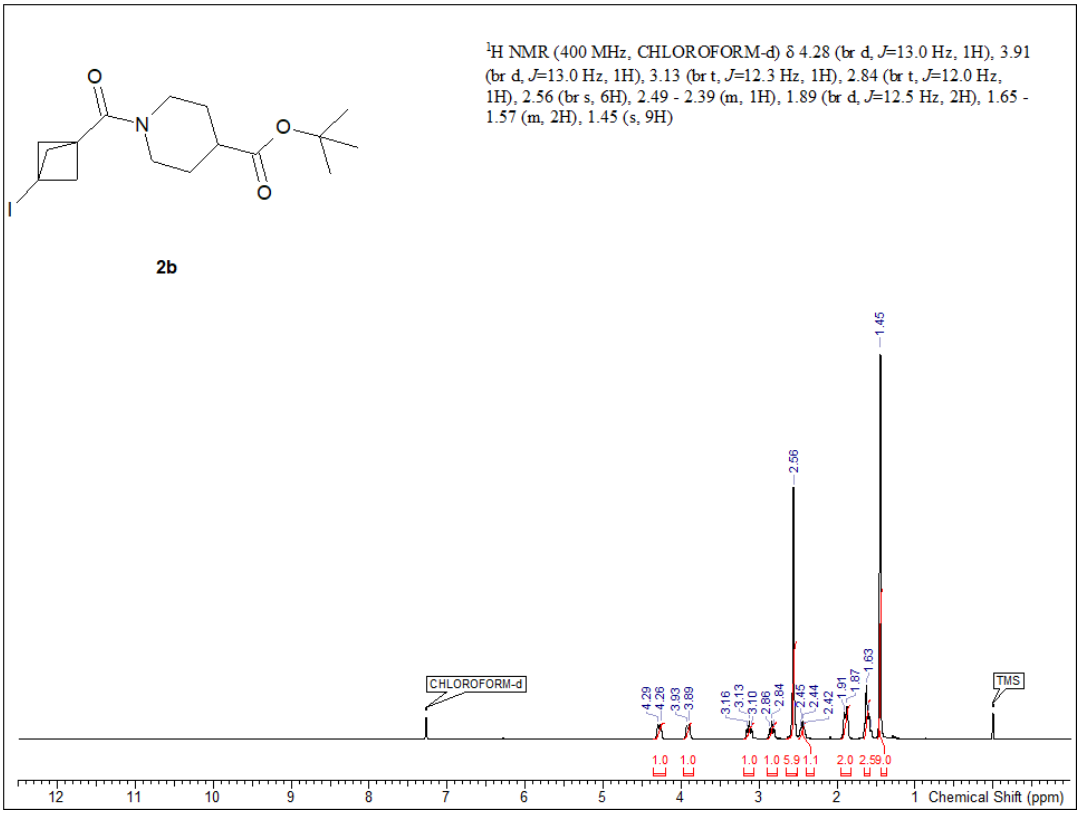




2a

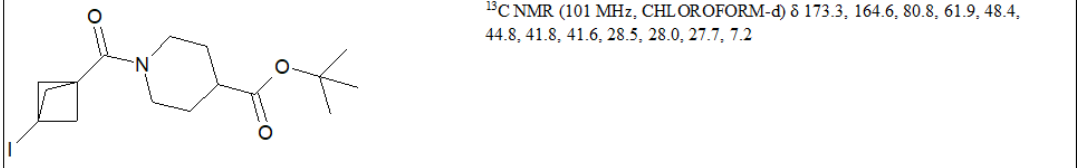
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.5, 60.4, 52.2, 48.6, 41.5, 36.2, 29.4, 6.0





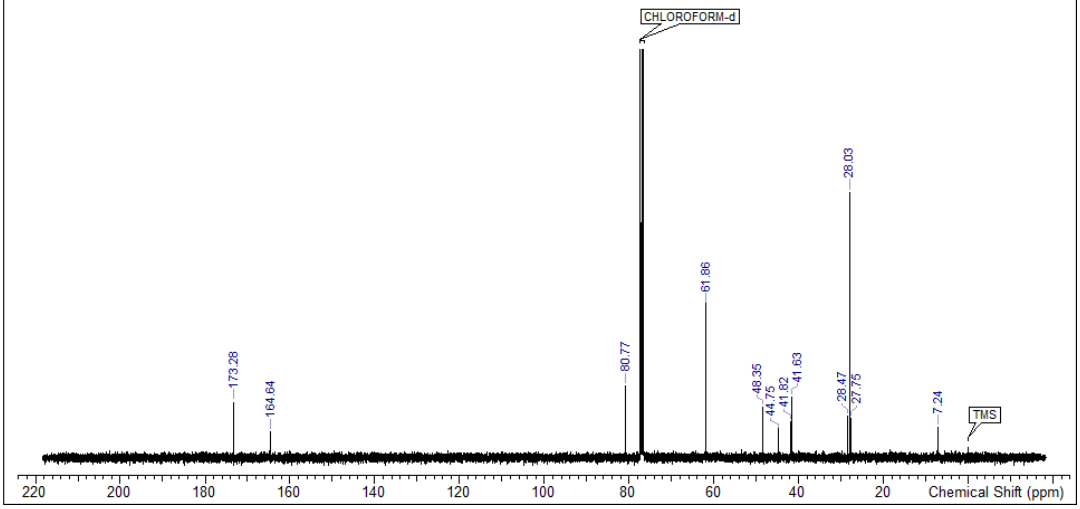
2b

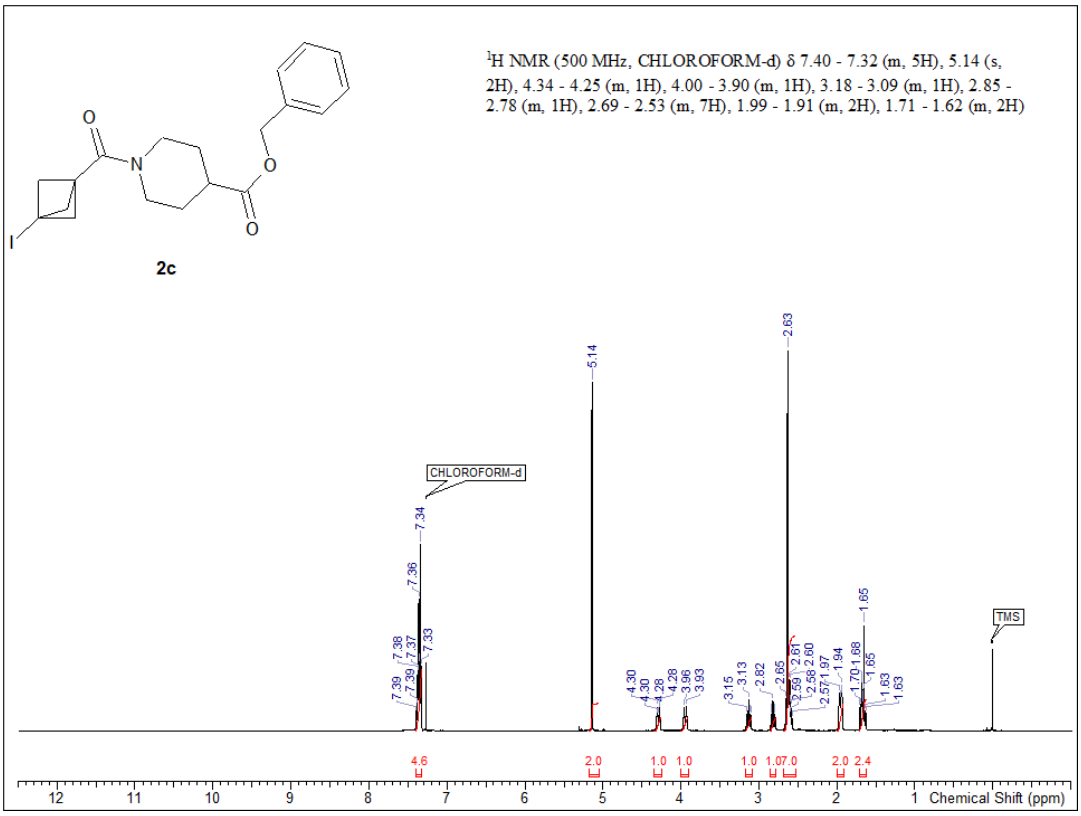
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 4.28 (br d, *J*=13.0 Hz, 1H), 3.91 (br d, *J*=13.0 Hz, 1H), 3.13 (br t, *J*=12.3 Hz, 1H), 2.84 (br t, *J*=12.0 Hz, 1H), 2.56 (br s, 6H), 2.49 - 2.39 (m, 1H), 1.89 (br d, *J*=12.5 Hz, 2H), 1.65 - 1.57 (m, 2H), 1.45 (s, 9H)

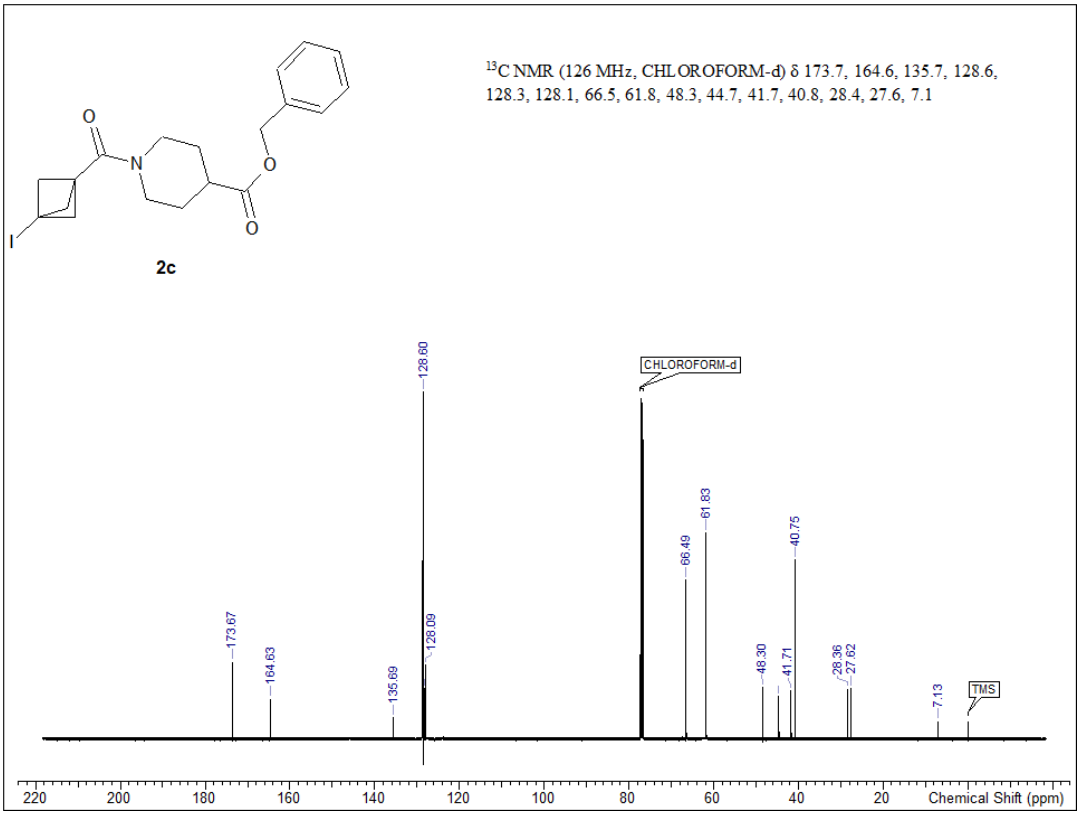


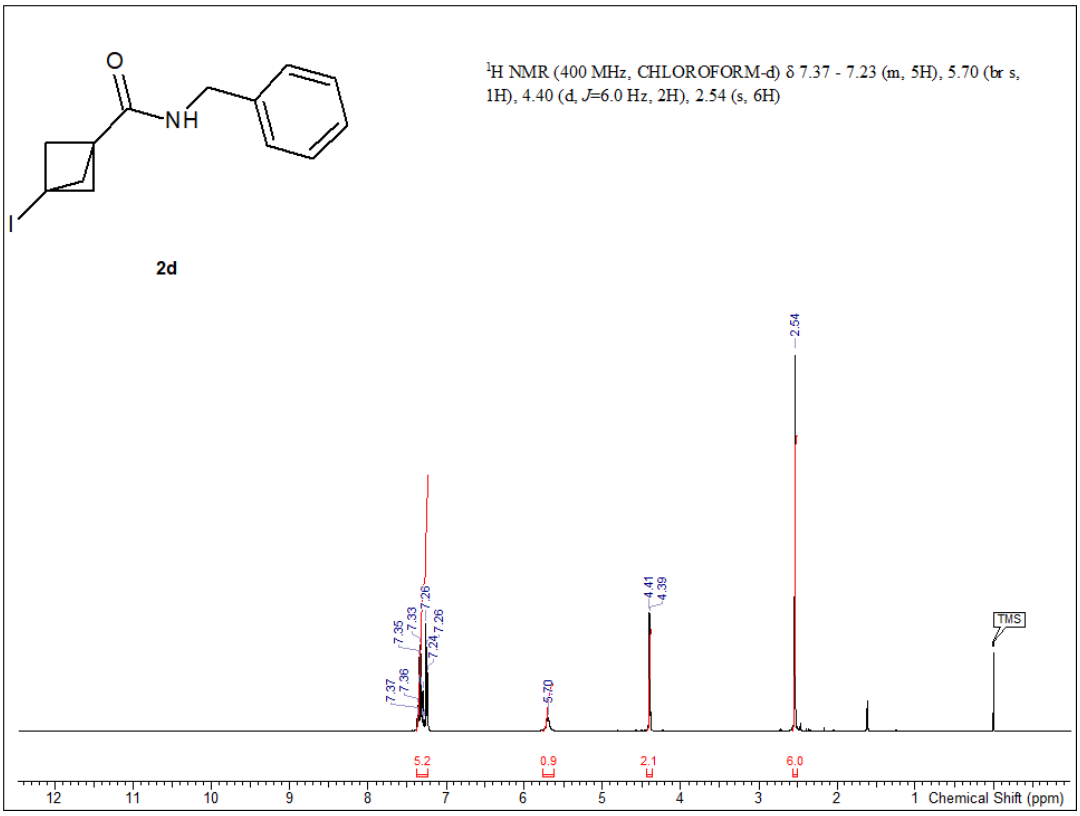
2b

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 173.3, 164.6, 80.8, 61.9, 48.4, 44.8, 41.8, 41.6, 28.5, 28.0, 27.7, 7.2

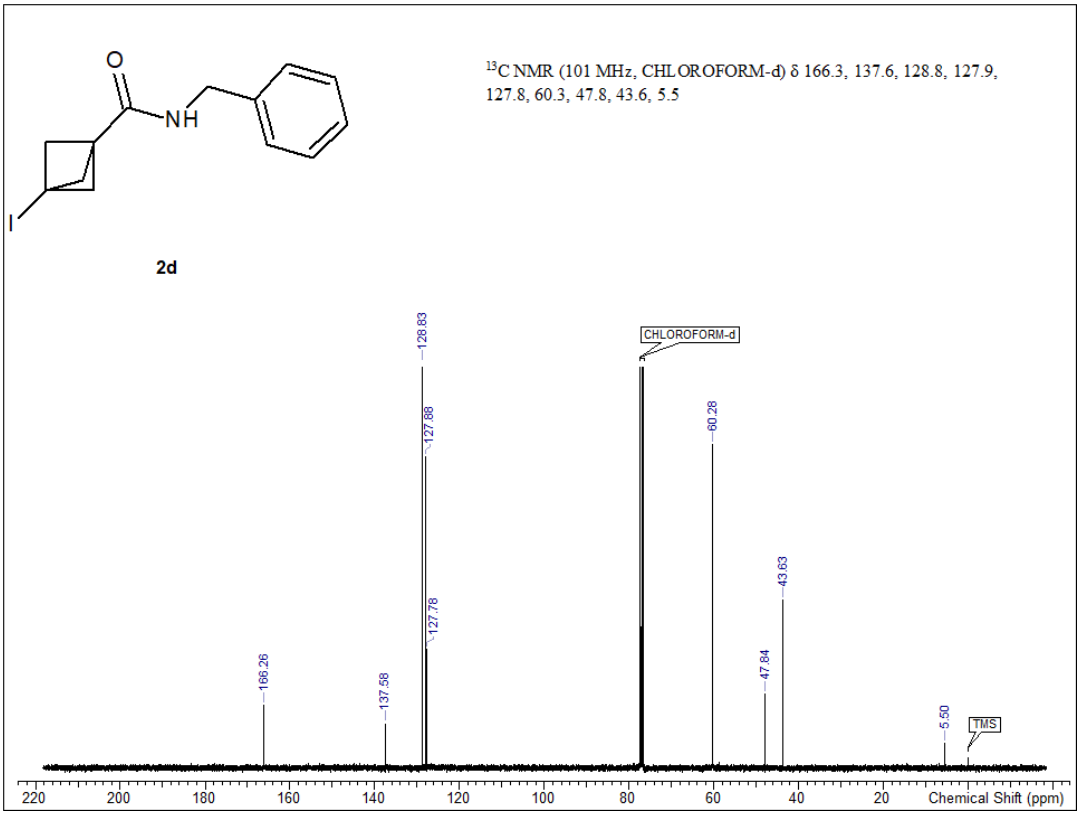



O
N
O
O
I
2c
^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.40 - 7.32 (m, 5H), 5.14 (s, 2H), 4.34 - 4.25 (m, 1H), 4.00 - 3.90 (m, 1H), 3.18 - 3.09 (m, 1H), 2.85 - 2.78 (m, 1H), 2.69 - 2.53 (m, 7H), 1.99 - 1.91 (m, 2H), 1.71 - 1.62 (m, 2H)
CHLOROFORM-d
TMS
Chemical Shift (ppm)

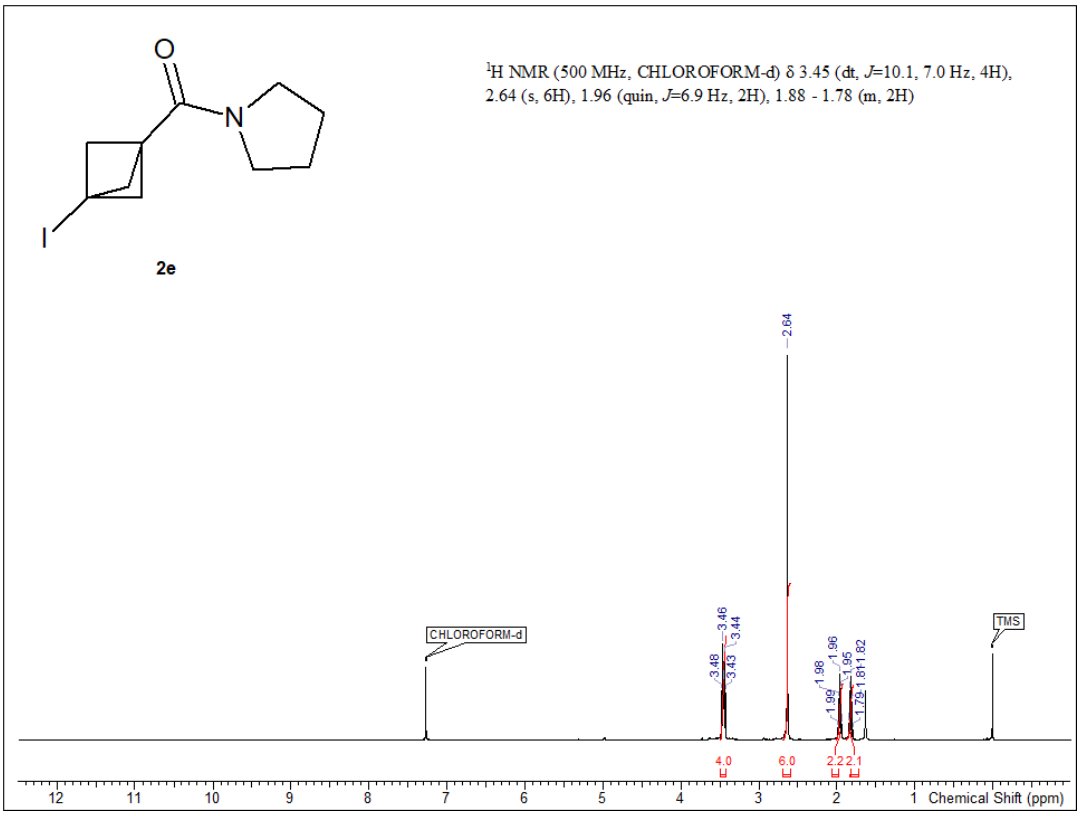

O
N
O
O
I
2c
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 173.7, 164.6, 135.7, 128.6, 128.3, 128.1, 66.5, 61.8, 48.3, 44.7, 41.7, 40.8, 28.4, 27.6, 7.1
CHLOROFORM-d
TMS
Chemical Shift (ppm)

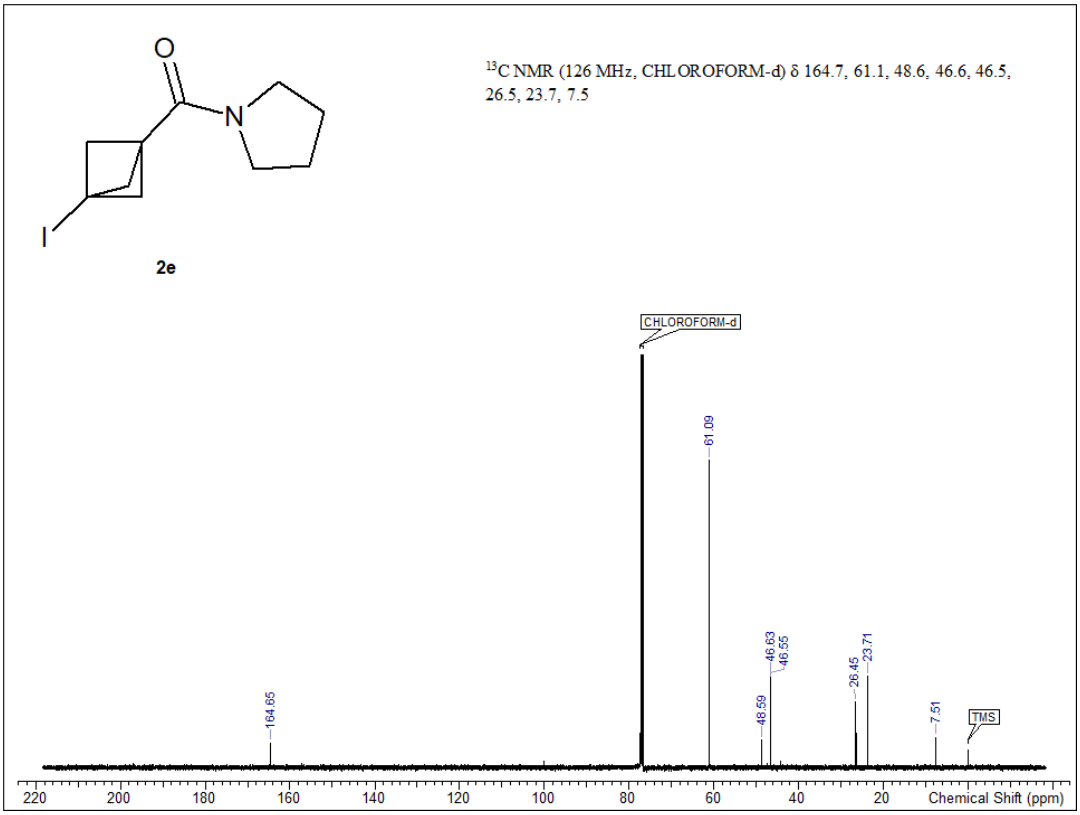


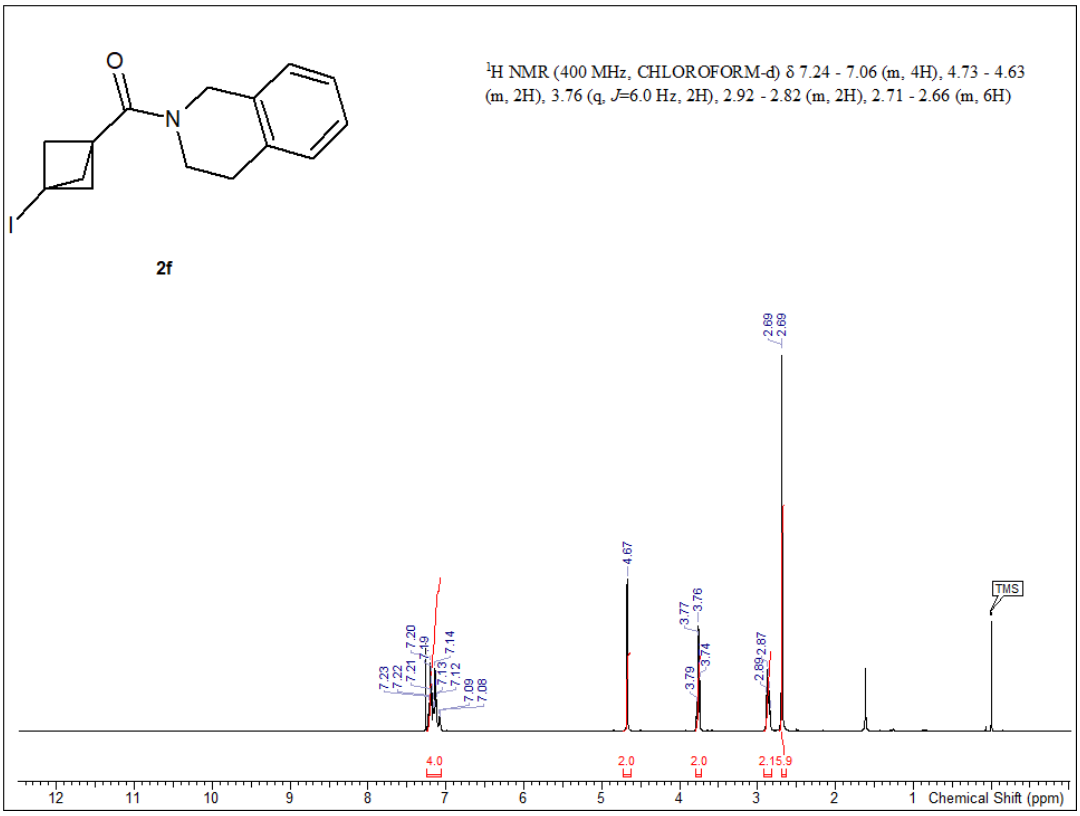
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.37 - 7.23 (m, 5H), 5.70 (br s, 1H), 4.40 (d, *J*=6.0 Hz, 2H), 2.54 (s, 6H)



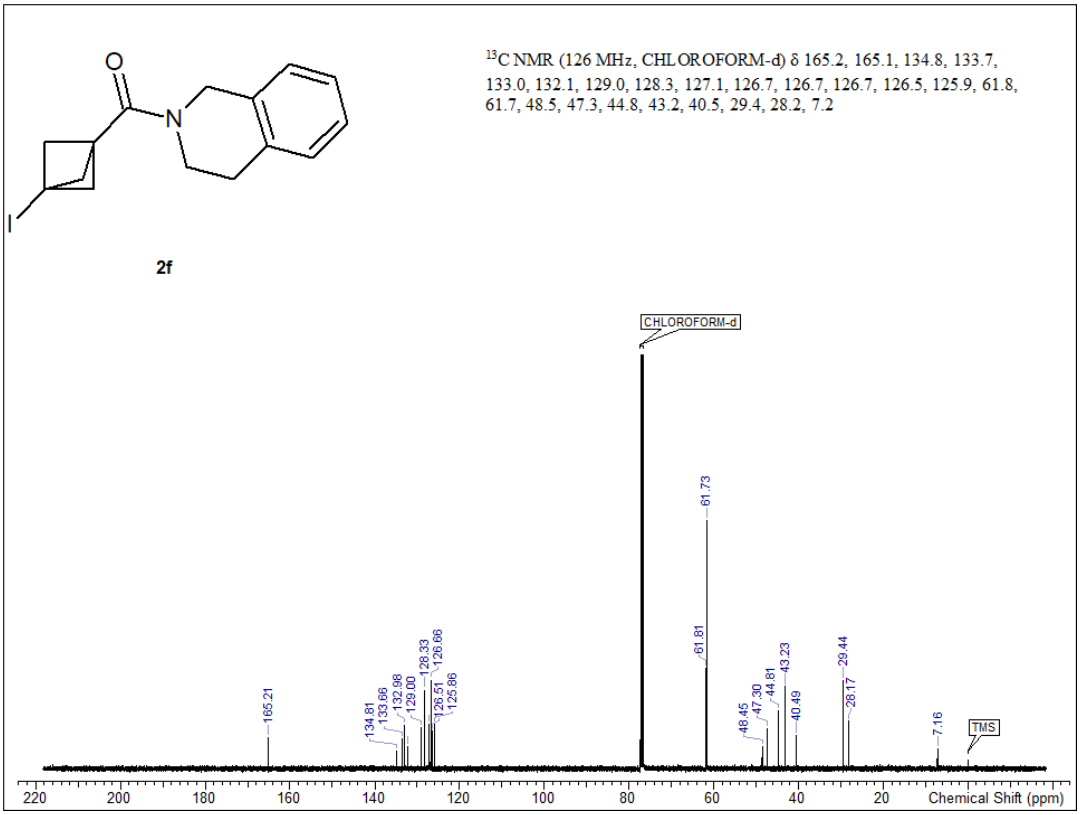
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 166.3, 137.6, 128.8, 127.9, 127.8, 60.3, 47.8, 43.6, 5.5


O
N
I
2e
^{1}H NMR (500 MHz, CHLOROFORM-d) δ 3.45 (dt, *J*=10.1, 7.0 Hz, 4H), 2.64 (s, 6H), 1.96 (quin, *J*=6.9 Hz, 2H), 1.88 - 1.78 (m, 2H)
2.64
CHLOROFORM-d
3.46
3.44
3.48
3.43
1.98
1.96
1.99
1.95
1.79
1.81
1.82
TMS
4.0
6.0
2.2
2.2
2.1
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

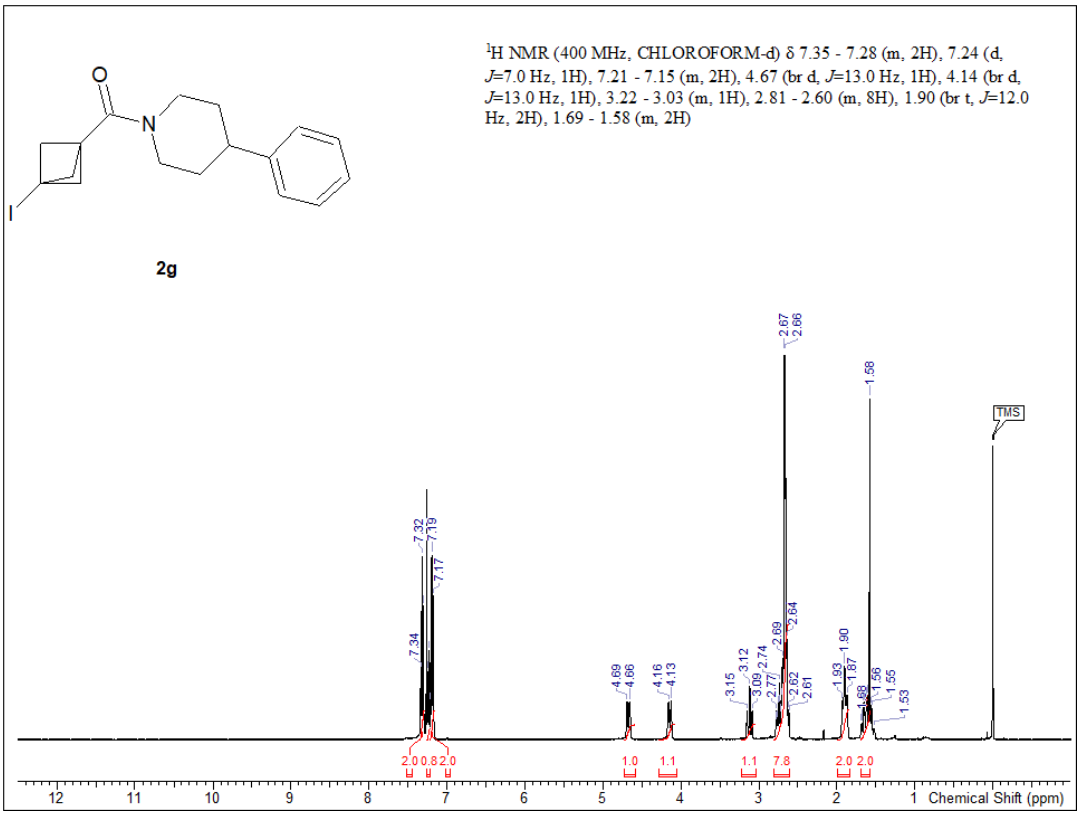

O
N
I
2e
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 164.7, 61.1, 48.6, 46.6, 46.5, 26.5, 23.7, 7.5
CHLOROFORM-d
61.09
164.65
46.63
46.55
48.59
26.45
23.71
7.51
TMS
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

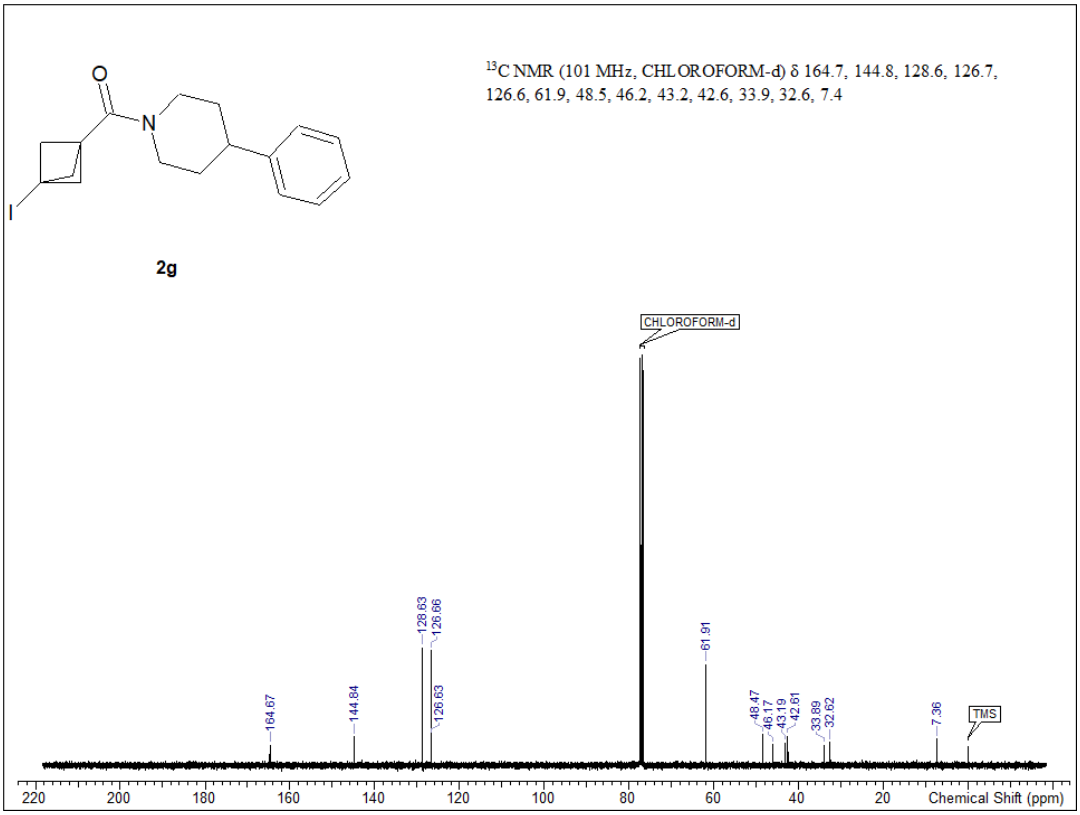


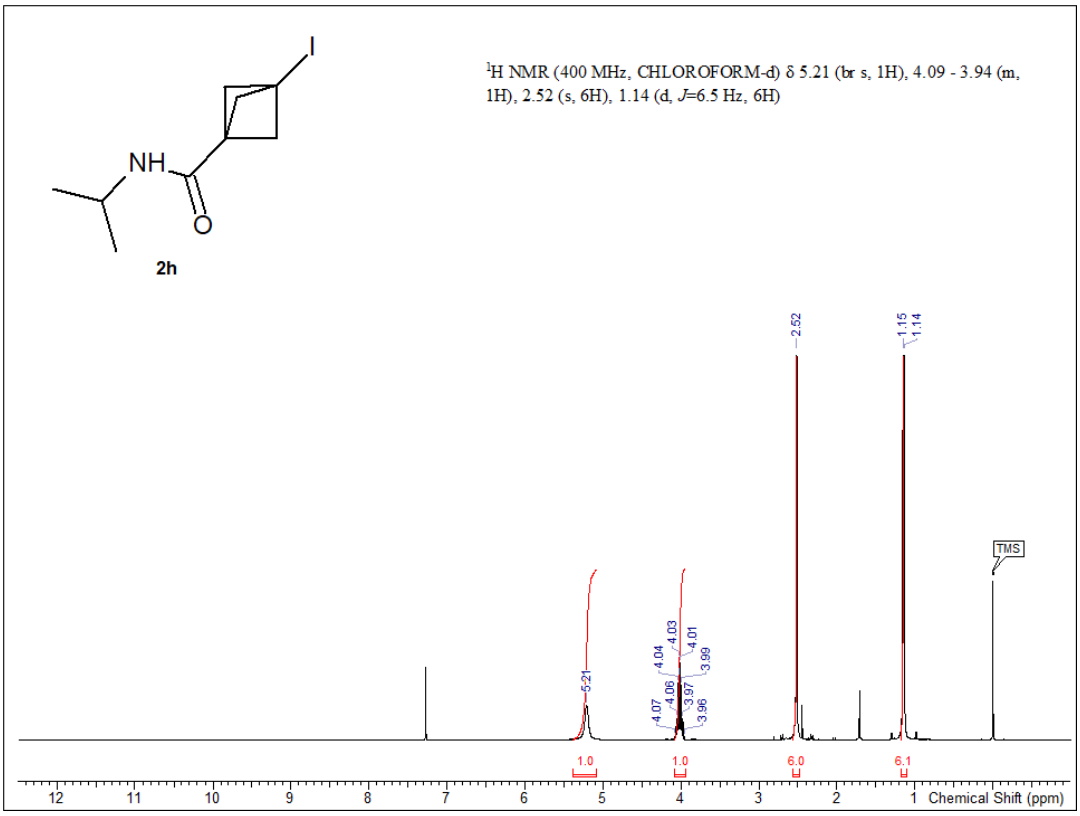
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.24 - 7.06 (m, 4H), 4.73 - 4.63 (m, 2H), 3.76 (q, *J*=6.0 Hz, 2H), 2.92 - 2.82 (m, 2H), 2.71 - 2.66 (m, 6H)

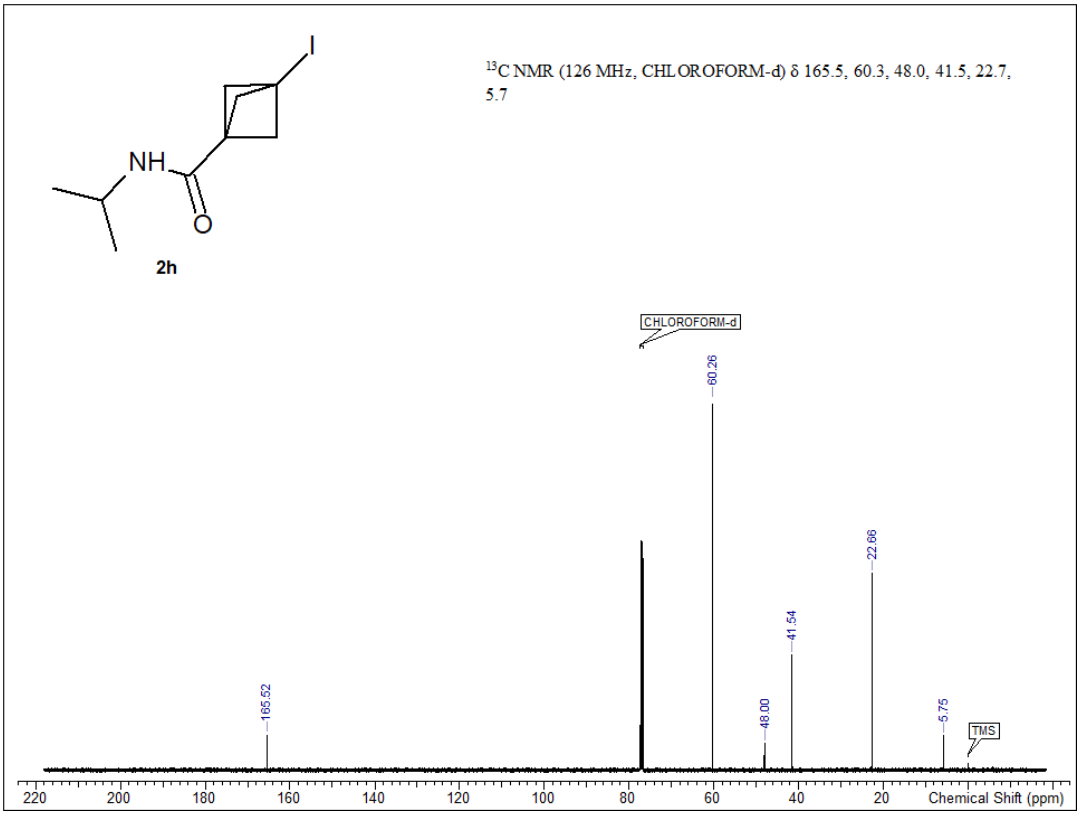


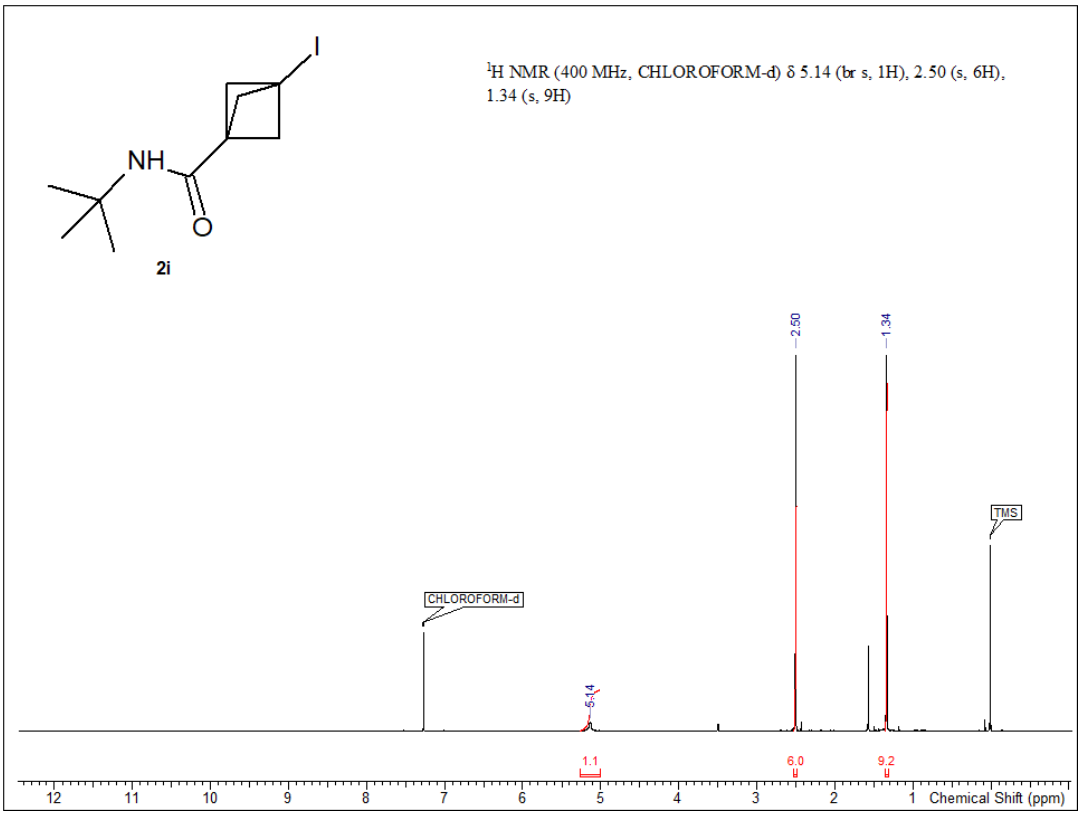
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 165.2, 165.1, 134.8, 133.7, 133.0, 132.1, 129.0, 128.3, 127.1, 126.7, 126.7, 126.7, 126.5, 125.9, 61.8, 61.7, 48.5, 47.3, 44.8, 43.2, 40.5, 29.4, 28.2, 7.2

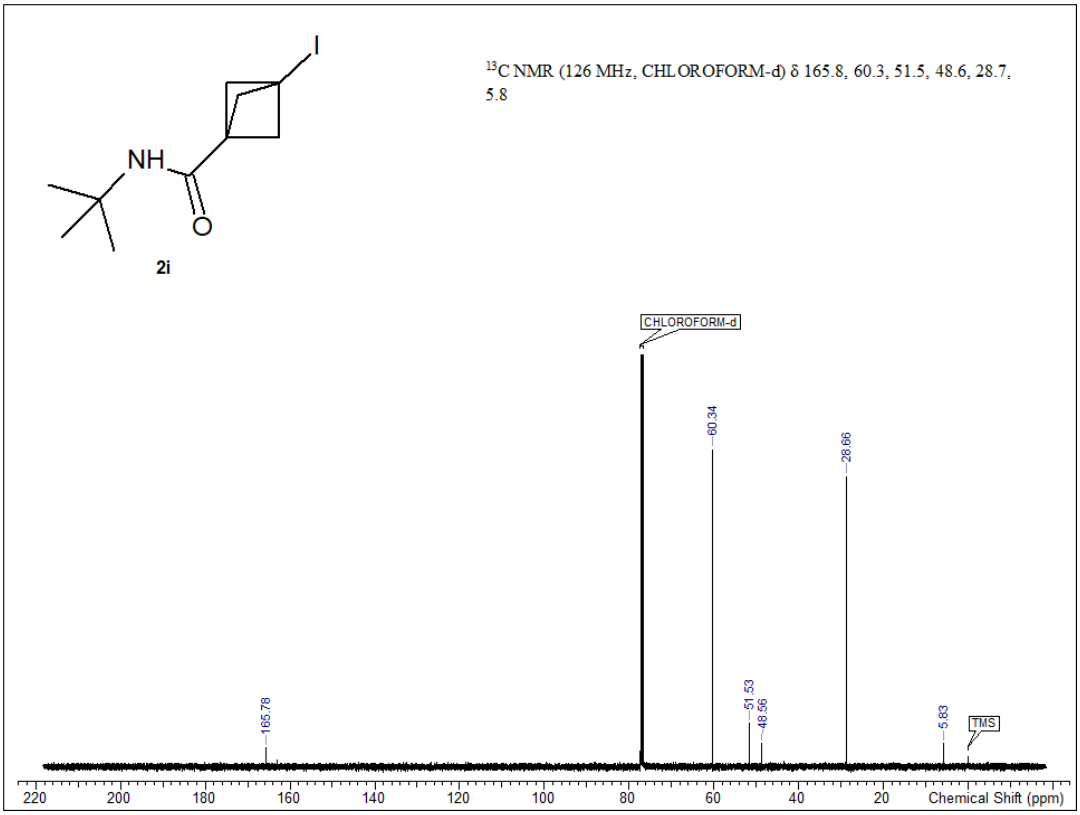

O
N
I
2g
[1]H NMR (400 MHz, CHLOROFORM-d) δ 7.35 - 7.28 (m, 2H), 7.24 (d, J=7.0 Hz, 1H), 7.21 - 7.15 (m, 2H), 4.67 (br d, J=13.0 Hz, 1H), 4.14 (br d, J=13.0 Hz, 1H), 3.22 - 3.03 (m, 1H), 2.81 - 2.60 (m, 8H), 1.90 (br t, J=12.0 Hz, 2H), 1.69 - 1.58 (m, 2H)
TMS
Chemical Shift (ppm)

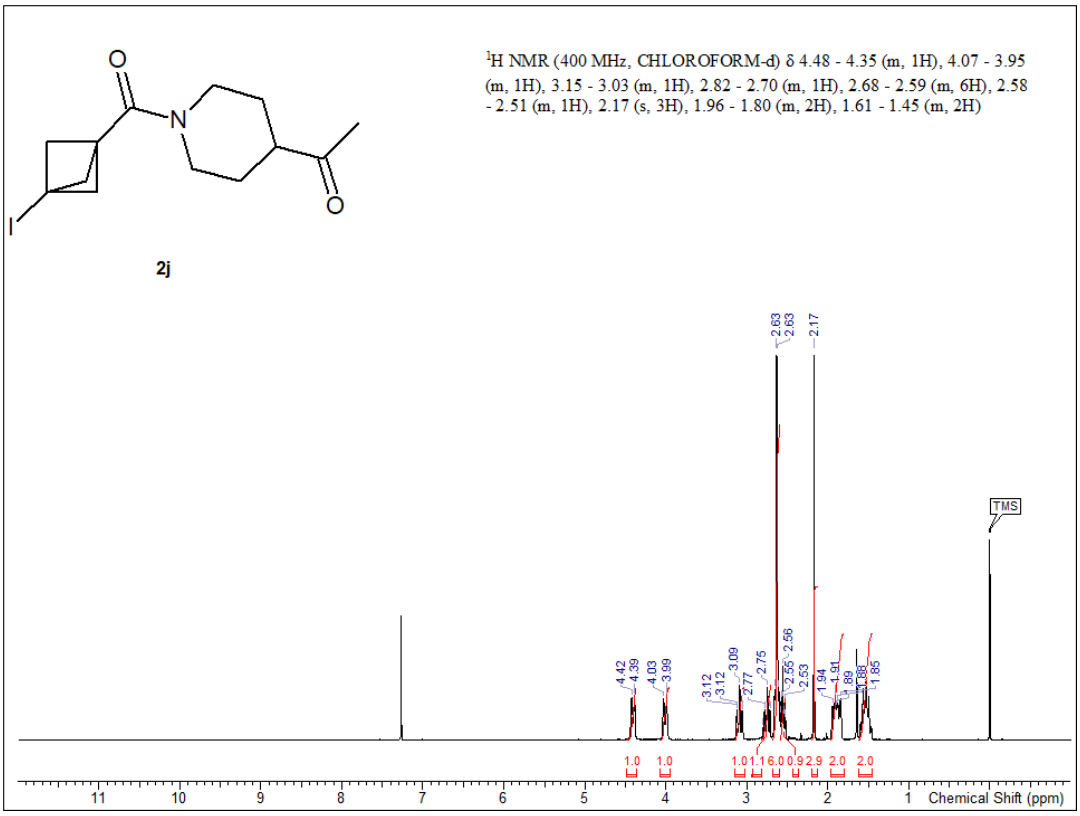

O
N
I
2g
[13]C NMR (101 MHz, CHLOROFORM-d) δ 164.7, 144.8, 128.6, 126.7, 126.6, 61.9, 48.5, 46.2, 43.2, 42.6, 33.9, 32.6, 7.4
CHLOROFORM-d
TMS
Chemical Shift (ppm)


NH
O
I
2h
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.21 (br s, 1H), 4.09 - 3.94 (m, 1H), 2.52 (s, 6H), 1.14 (d, J=6.5 Hz, 6H)
2.52
1.15
1.14
TMS
5.21
4.04
4.03
4.01
3.99
4.07
4.06
3.97
3.96
1.0
1.0
6.0
6.1
12 11 10 9 8 7 6 5 4 3 2 1 Chemical Shift (ppm)


NH
O
I
2h
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 165.5, 60.3, 48.0, 41.5, 22.7, 5.7
CHLOROFORM-d
60.26
22.66
41.54
165.52
48.00
5.75
TMS
220 200 180 160 140 120 100 80 60 40 20 Chemical Shift (ppm)

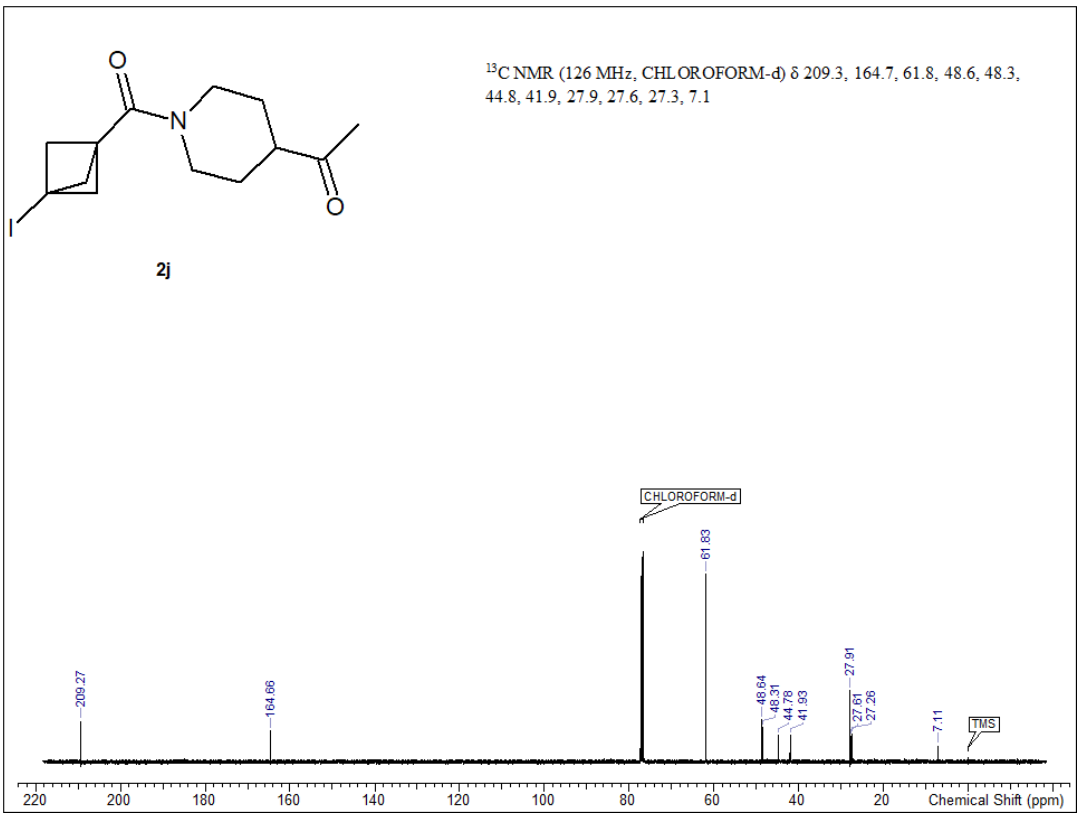

I
NH
O
2i
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.14 (br s, 1H), 2.50 (s, 6H), 1.34 (s, 9H)
2.50
1.34
TMS
CHLOROFORM-d
5.14
1.1
6.0
9.2
12 11 10 9 8 7 6 5 4 3 2 1 Chemical Shift (ppm)


I
NH
O
2i
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 165.8, 60.3, 51.5, 48.6, 28.7, 5.8
CHLOROFORM-d
60.34
28.66
165.78
51.53
48.56
5.83
TMS
220 200 180 160 140 120 100 80 60 40 20 Chemical Shift (ppm)



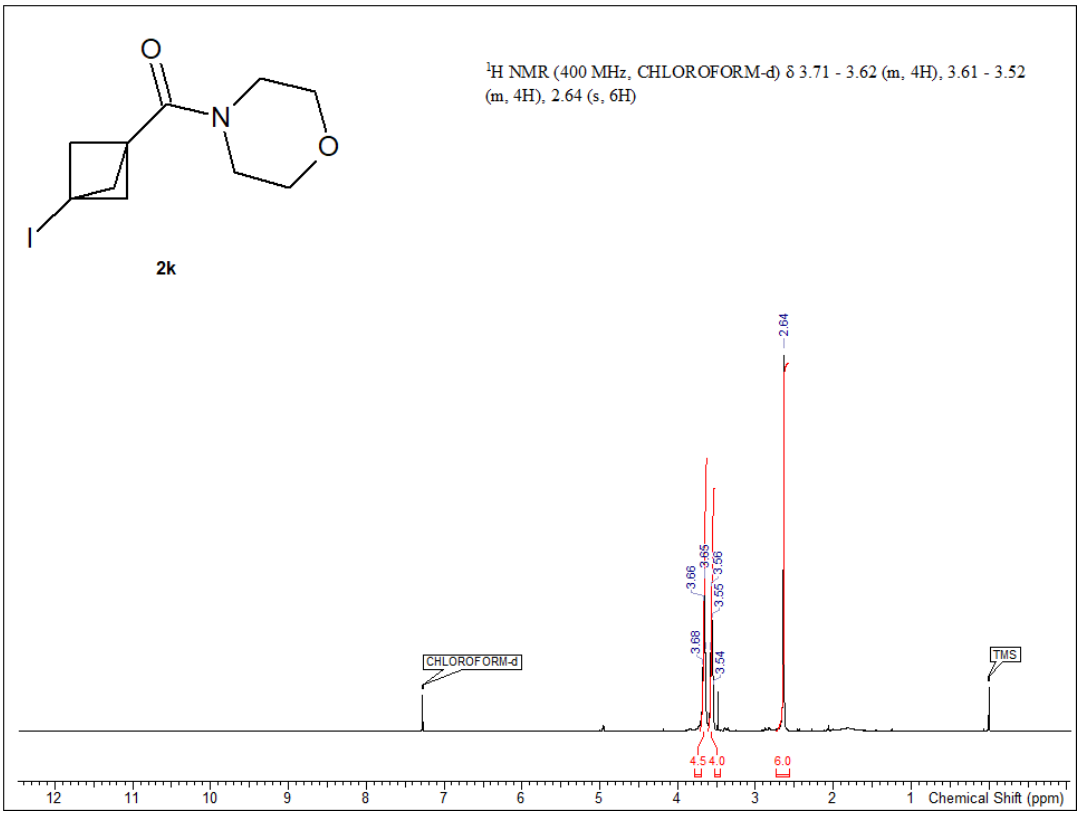
2j

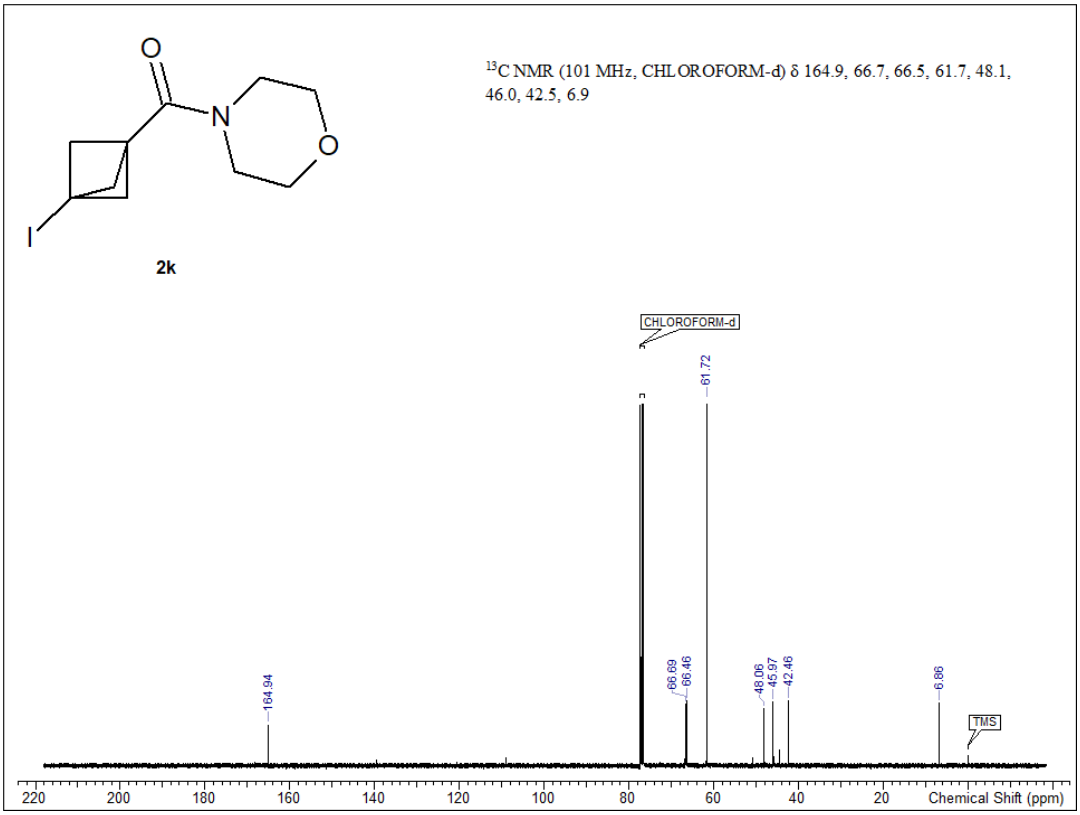
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 4.48 - 4.35 (m, 1H), 4.07 - 3.95 (m, 1H), 3.15 - 3.03 (m, 1H), 2.82 - 2.70 (m, 1H), 2.68 - 2.59 (m, 6H), 2.58 - 2.51 (m, 1H), 2.17 (s, 3H), 1.96 - 1.80 (m, 2H), 1.61 - 1.45 (m, 2H)

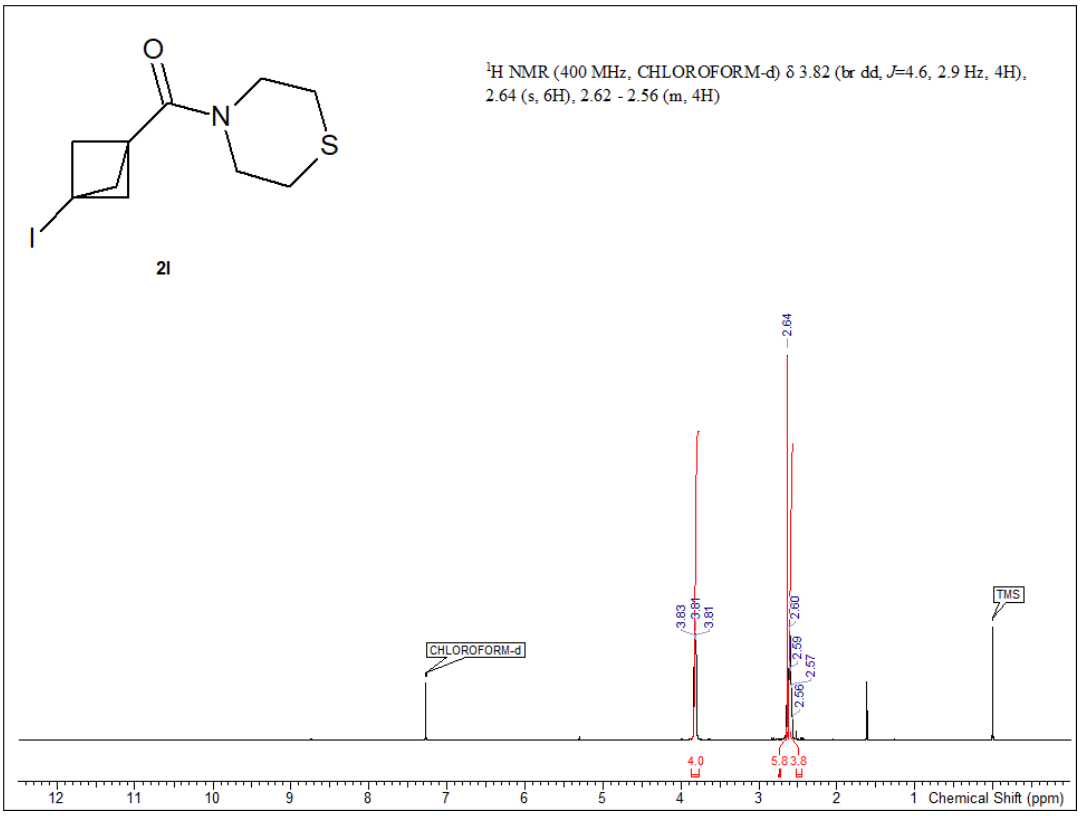


2j

^{13}C NMR (126 MHz, CHLOROFORM-d) δ 209.3, 164.7, 61.8, 48.6, 48.3, 44.8, 41.9, 27.9, 27.6, 27.3, 7.1

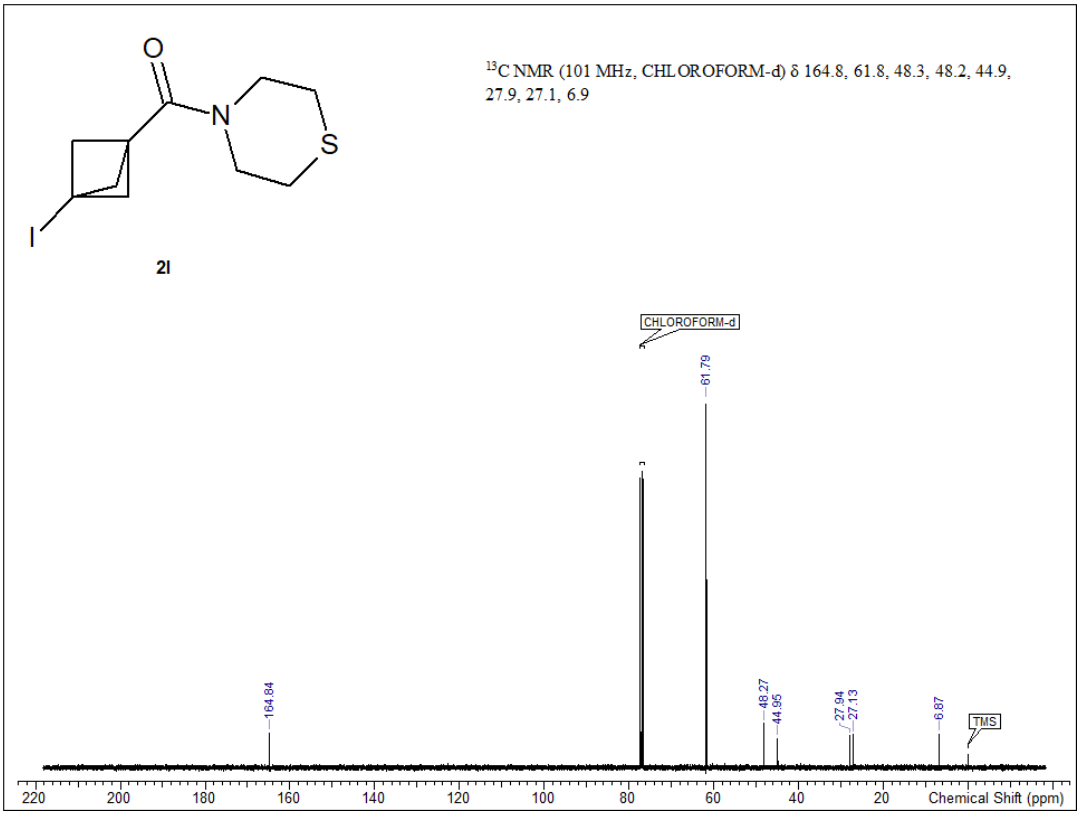

O
N
O
I
2k
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 3.71 - 3.62 (m, 4H), 3.61 - 3.52 (m, 4H), 2.64 (s, 6H)
2.64
3.66
3.65
3.66
3.65
3.68
3.64
CHLOROFORM-d
TMS
4.5
4.0
6.0
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


O
N
O
I
2k
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 164.9, 66.7, 66.5, 61.7, 48.1, 46.0, 42.5, 6.9
CHLOROFORM-d
61.72
164.94
66.69
66.46
48.06
45.97
42.46
6.86
TMS
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)



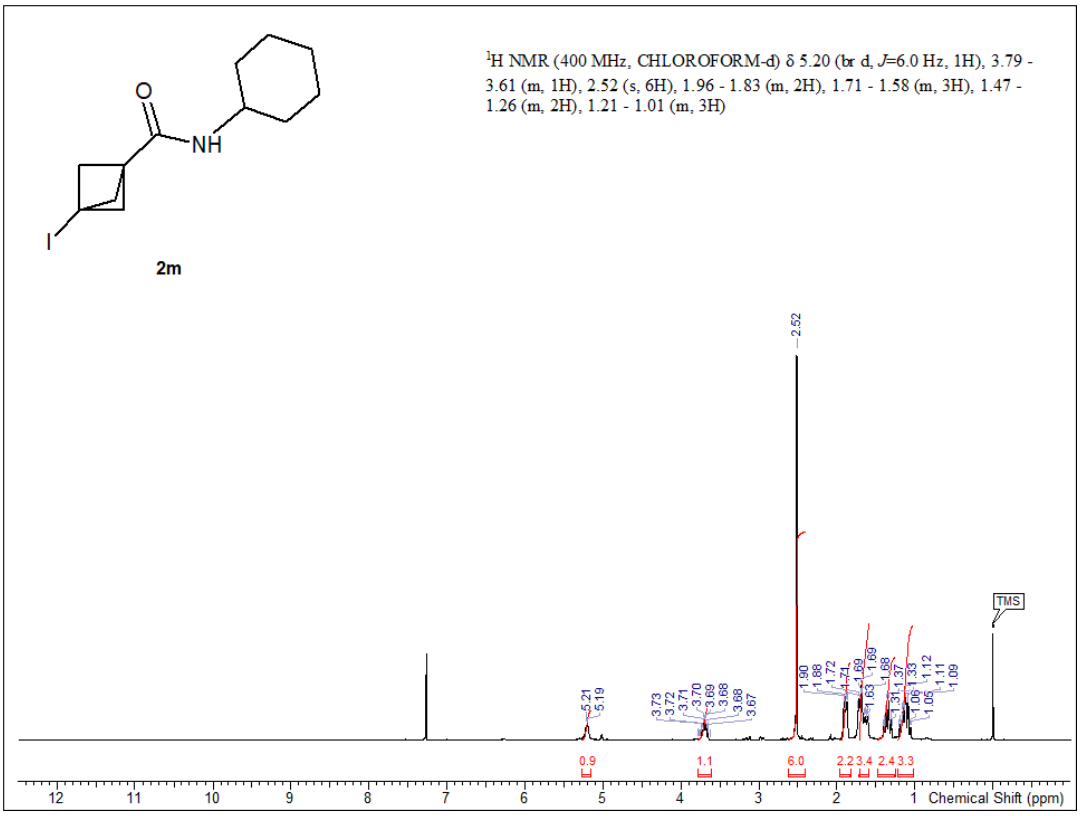
2l

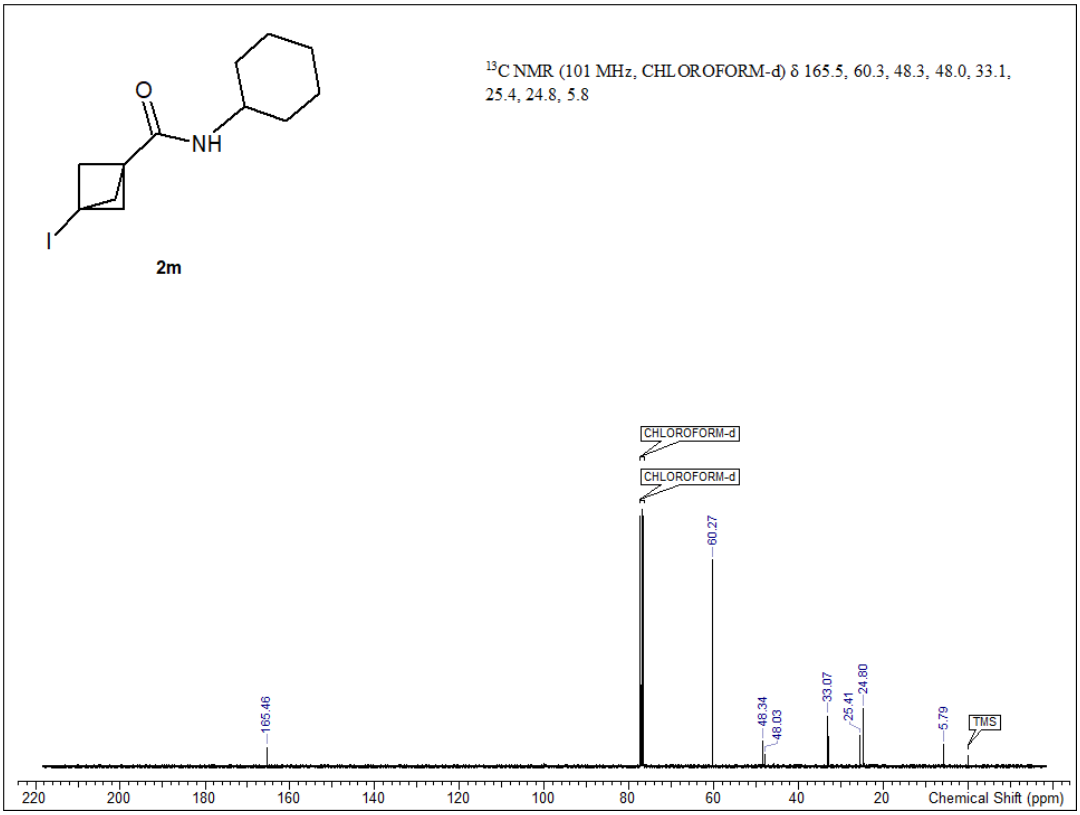
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 3.82 (br dd, *J*=4.6, 2.9 Hz, 4H), 2.64 (s, 6H), 2.62 - 2.56 (m, 4H)

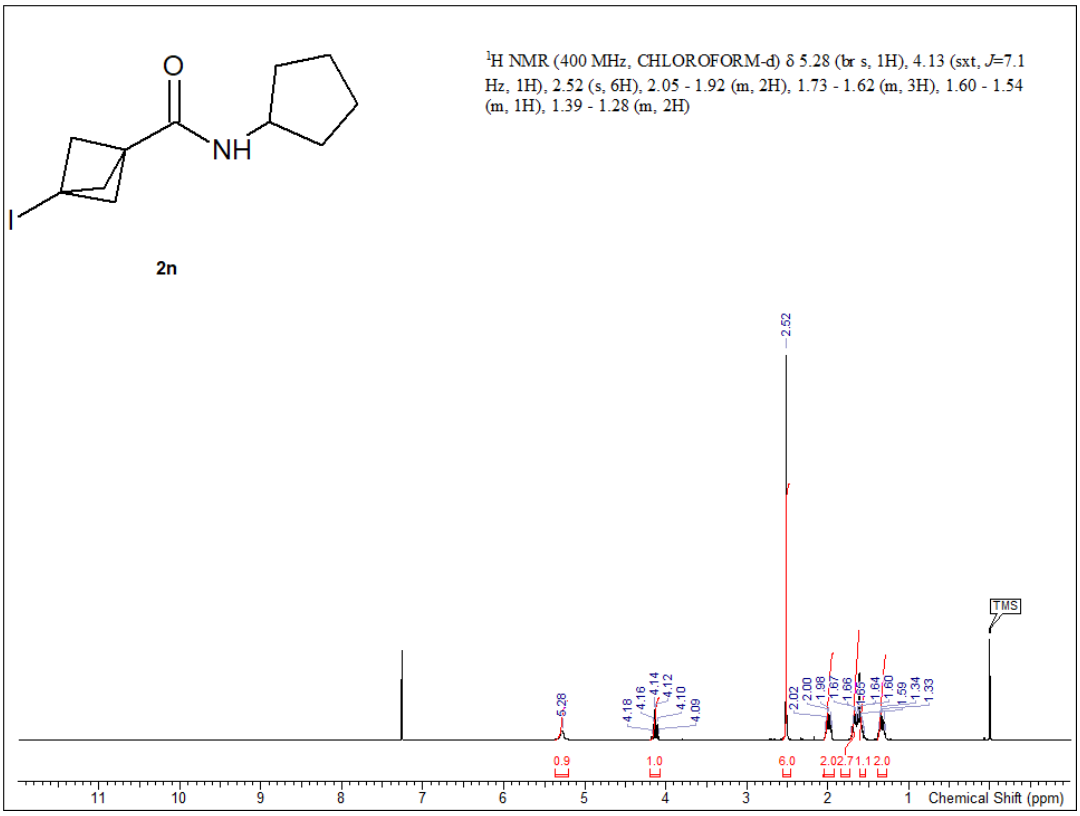


2l

^{13}C NMR (101 MHz, CHLOROFORM-d) δ 164.8, 61.8, 48.3, 48.2, 44.9, 27.9, 27.1, 6.9

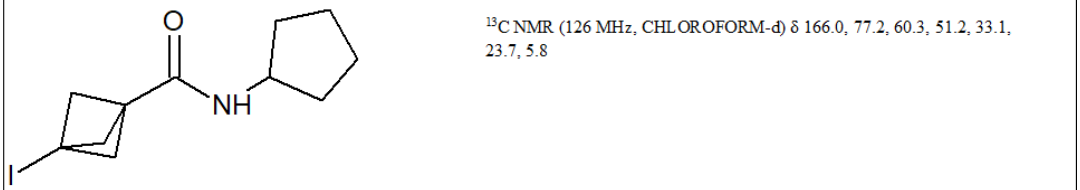

O
NH
I
2m
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.20 (br d, J=6.0 Hz, 1H), 3.79 - 3.61 (m, 1H), 2.52 (s, 6H), 1.96 - 1.83 (m, 2H), 1.71 - 1.58 (m, 3H), 1.47 - 1.26 (m, 2H), 1.21 - 1.01 (m, 3H)
2.52
TMS
5.21
5.19
3.73
3.72
3.71
3.70
3.69
3.68
3.68
3.67
1.90
1.88
1.72
1.71
1.69
1.63
1.69
1.68
1.37
1.31
1.33
1.12
1.11
1.09
1.06
0.9
1.1
6.0
2.2
3.4
2.4
3.3
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


O
NH
I
2m
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.5, 60.3, 48.3, 48.0, 33.1, 25.4, 24.8, 5.8
CHLOROFORM-d
CHLOROFORM-d
60.27
165.46
48.34
48.03
33.07
25.41
24.80
5.79
TMS
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)



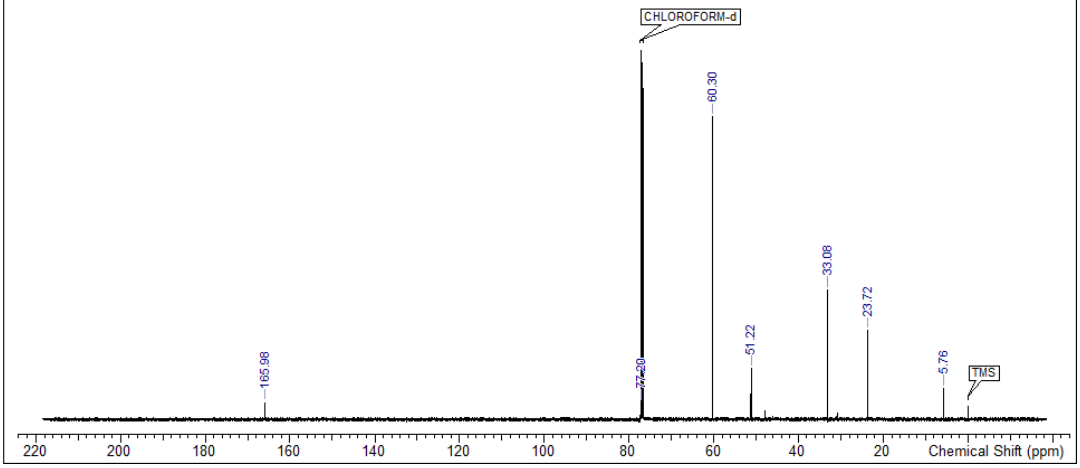
2n

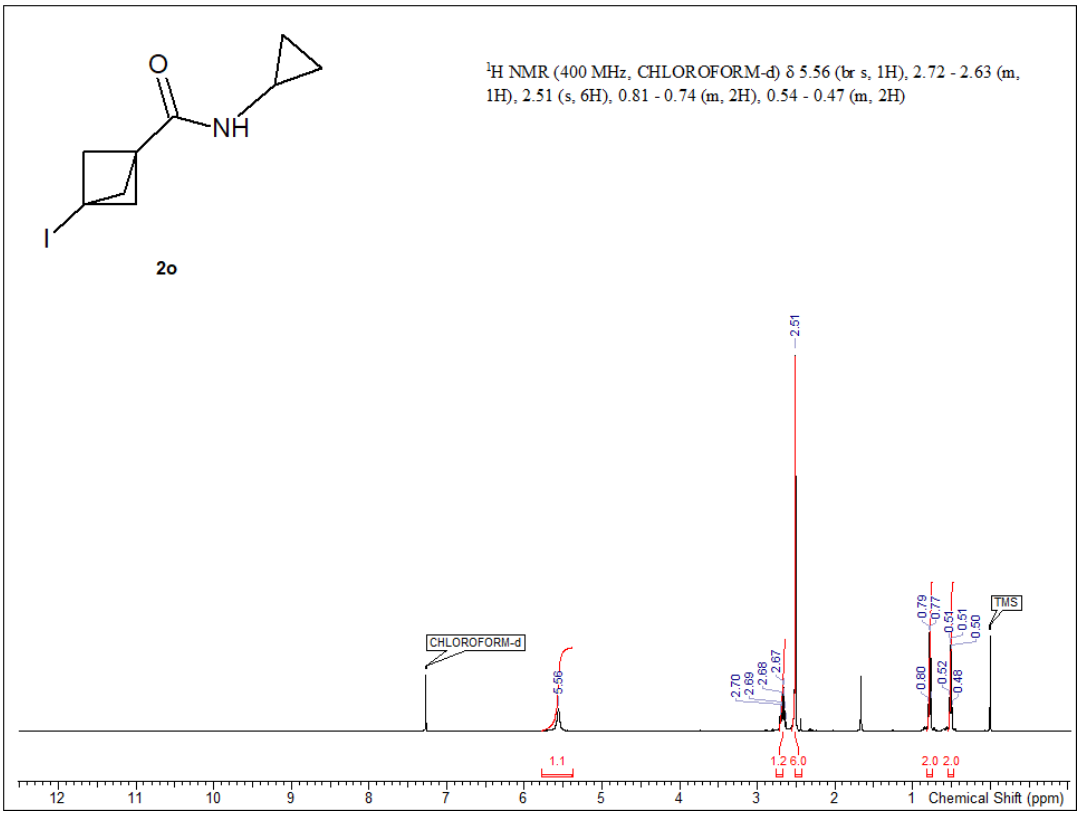
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.28 (br s, 1H), 4.13 (sxt, *J*=7.1 Hz, 1H), 2.52 (s, 6H), 2.05 - 1.92 (m, 2H), 1.73 - 1.62 (m, 3H), 1.60 - 1.54 (m, 1H), 1.39 - 1.28 (m, 2H)



2n

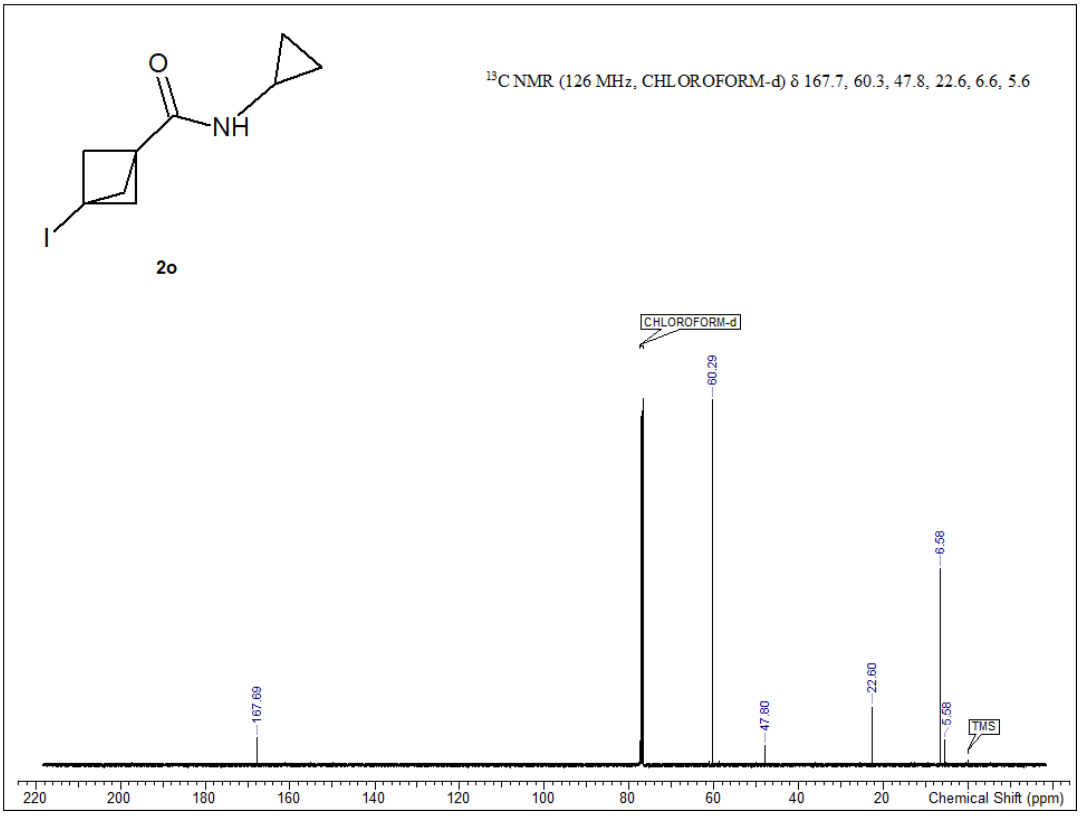
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 166.0, 77.2, 60.3, 51.2, 33.1, 23.7, 5.8





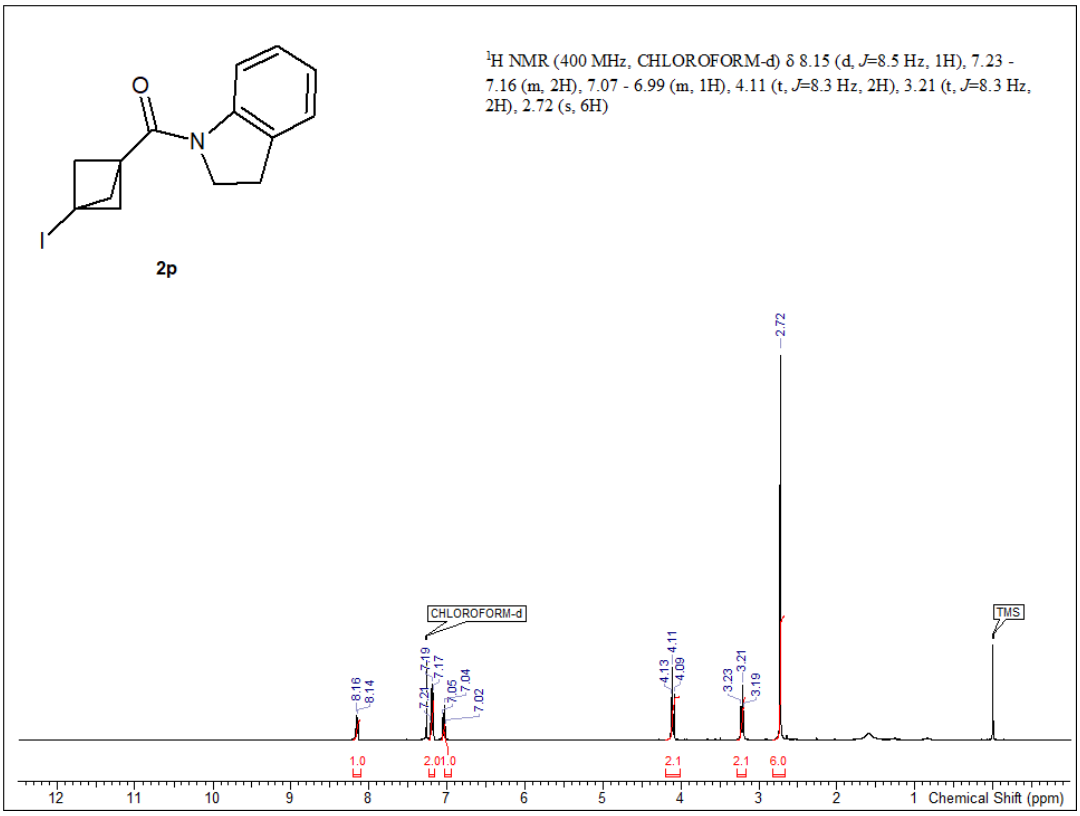
2o

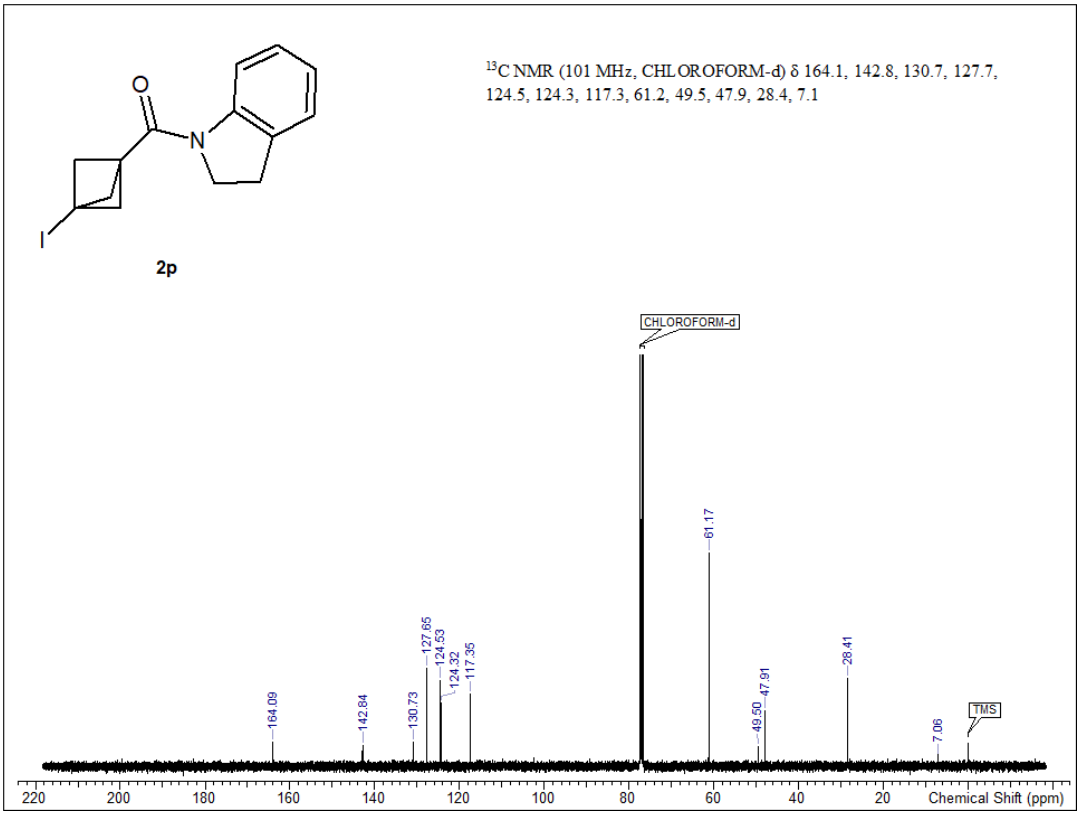
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.56 (br s, 1H), 2.72 - 2.63 (m, 1H), 2.51 (s, 6H), 0.81 - 0.74 (m, 2H), 0.54 - 0.47 (m, 2H)

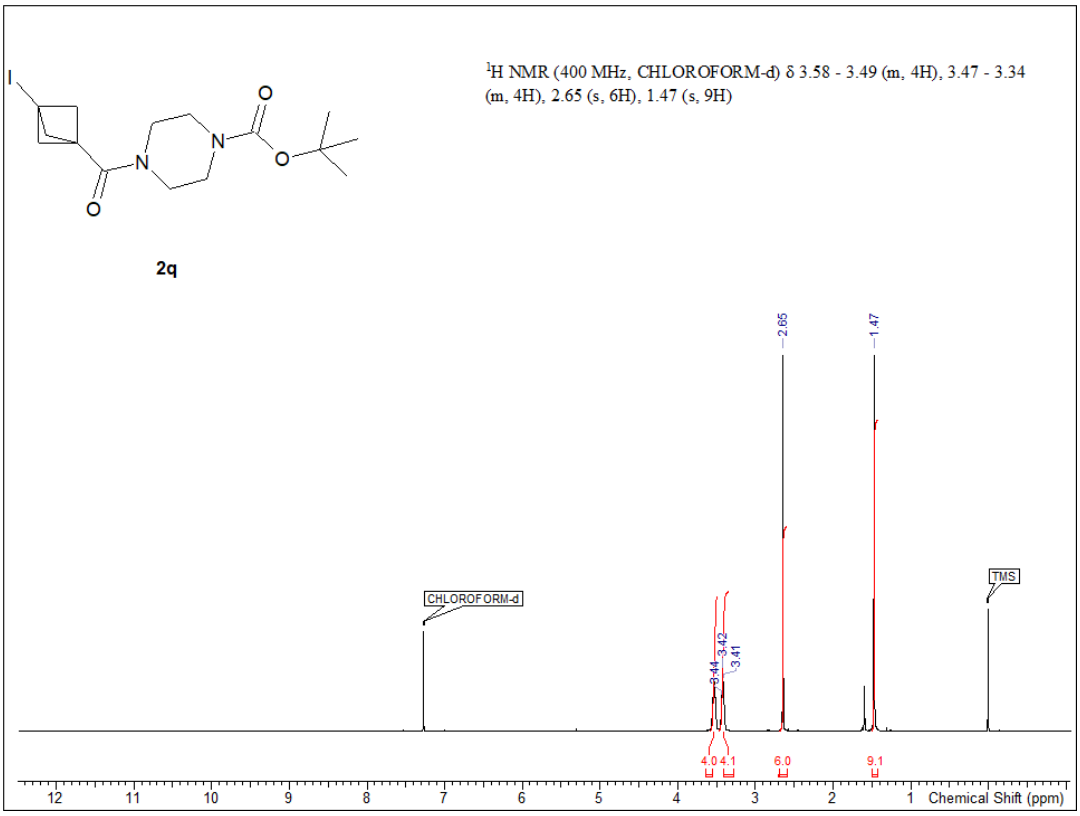


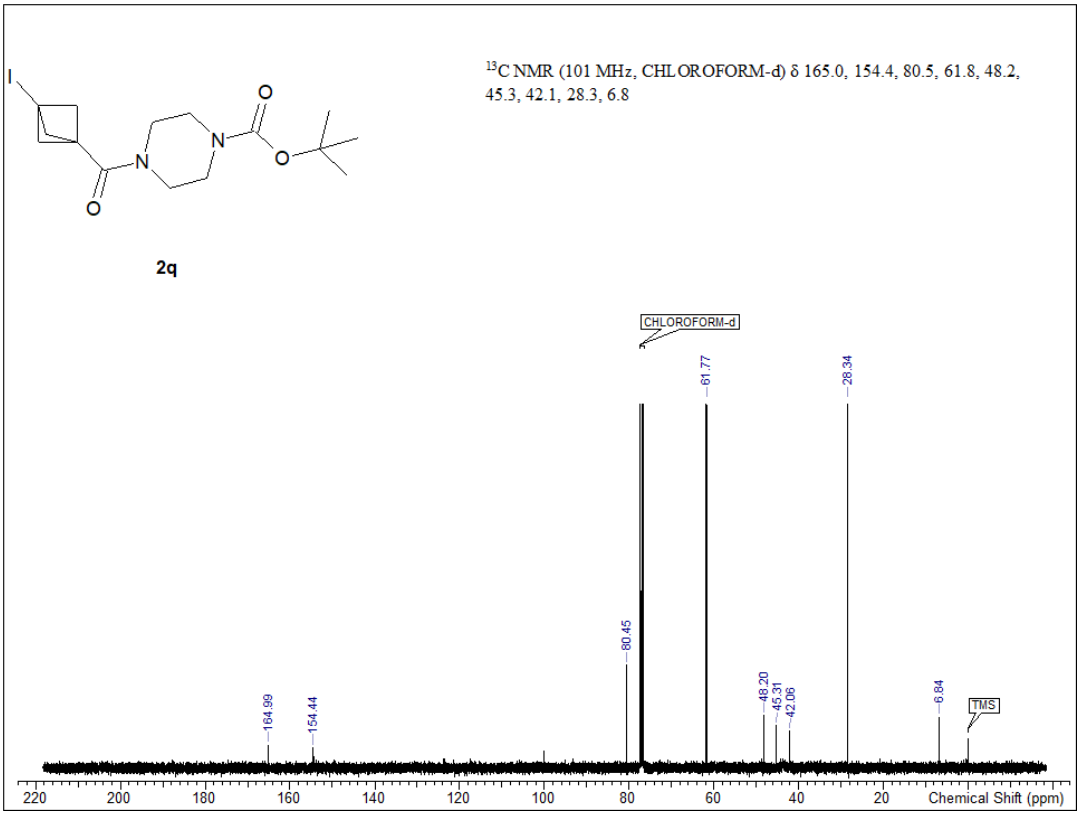
2o

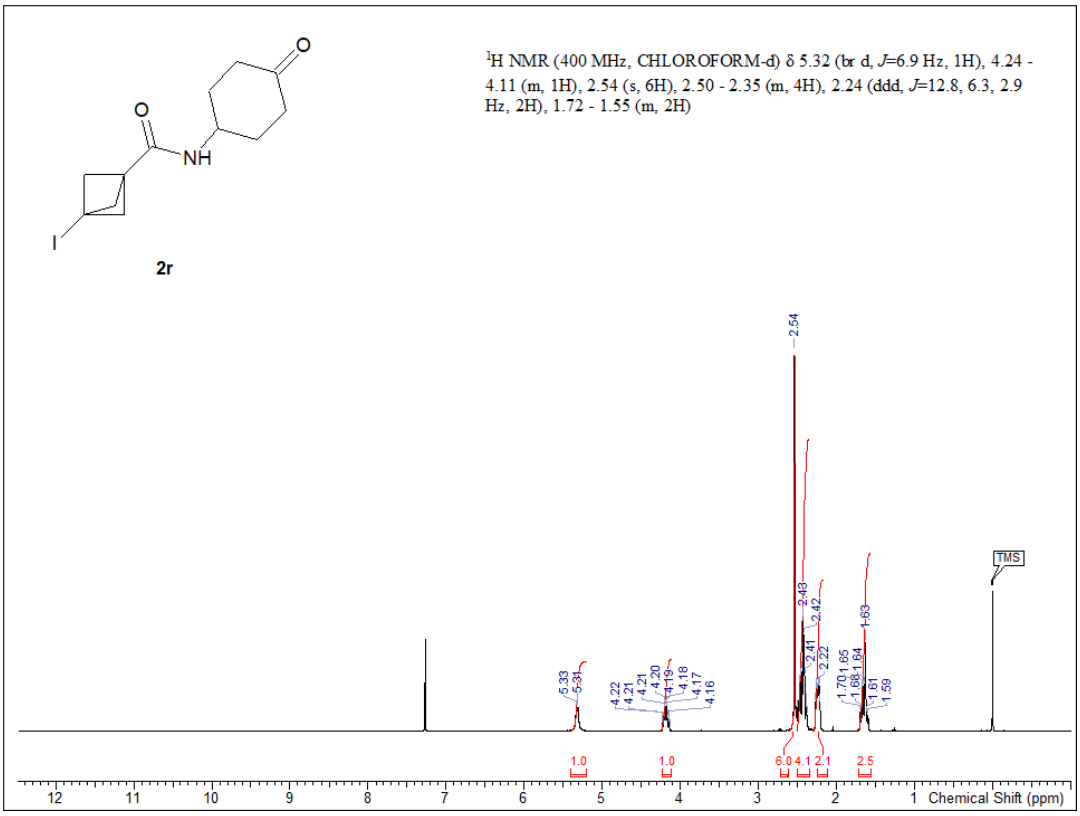
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 167.7, 60.3, 47.8, 22.6, 6.6, 5.6


O
N
I
2p
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.15 (d, *J*=8.5 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.07 - 6.99 (m, 1H), 4.11 (t, *J*=8.3 Hz, 2H), 3.21 (t, *J*=8.3 Hz, 2H), 2.72 (s, 6H)
2.72
CHLOROFORM-d
TMS
8.16
8.14
7.21
7.19
7.17
7.05
7.04
7.02
4.13
4.11
4.09
3.23
3.21
3.19
1.0
2.01
1.0
2.1
2.1
6.0
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

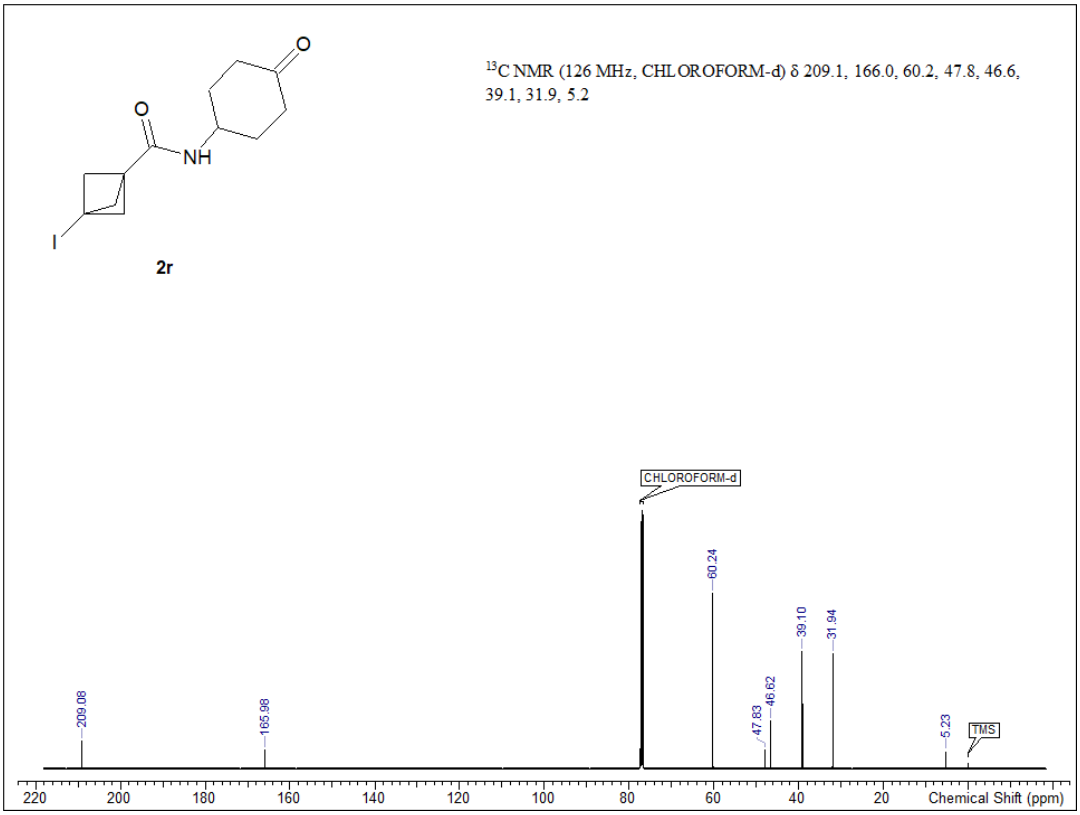

O
N
I
2p
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 164.1, 142.8, 130.7, 127.7, 124.5, 124.3, 117.3, 61.2, 49.5, 47.9, 28.4, 7.1
CHLOROFORM-d
61.17
164.09
142.84
130.73
127.65
124.53
124.32
117.35
49.50
47.91
28.41
7.06
TMS
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)


I
O
N
N
O
O
2q
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 3.58 - 3.49 (m, 4H), 3.47 - 3.34 (m, 4H), 2.65 (s, 6H), 1.47 (s, 9H)
2.65
1.47
CHLOROFORM-d
TMS
3.44
3.42
3.41
4.0
4.1
6.0
9.1
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

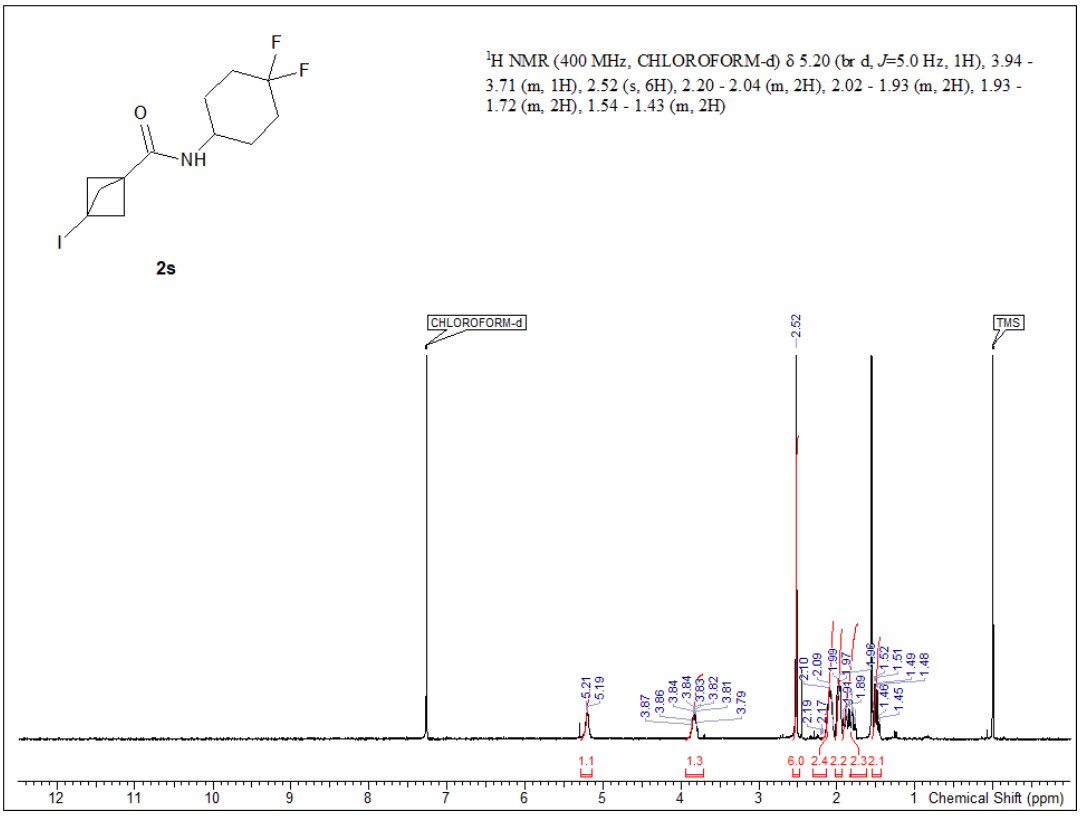

I
O
N
N
O
O
2q
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 165.0, 154.4, 80.5, 61.8, 48.2, 45.3, 42.1, 28.3, 6.8
CHLOROFORM-d
61.77
28.34
80.45
48.20
45.31
42.06
6.84
164.99
154.44
TMS
220
200
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)



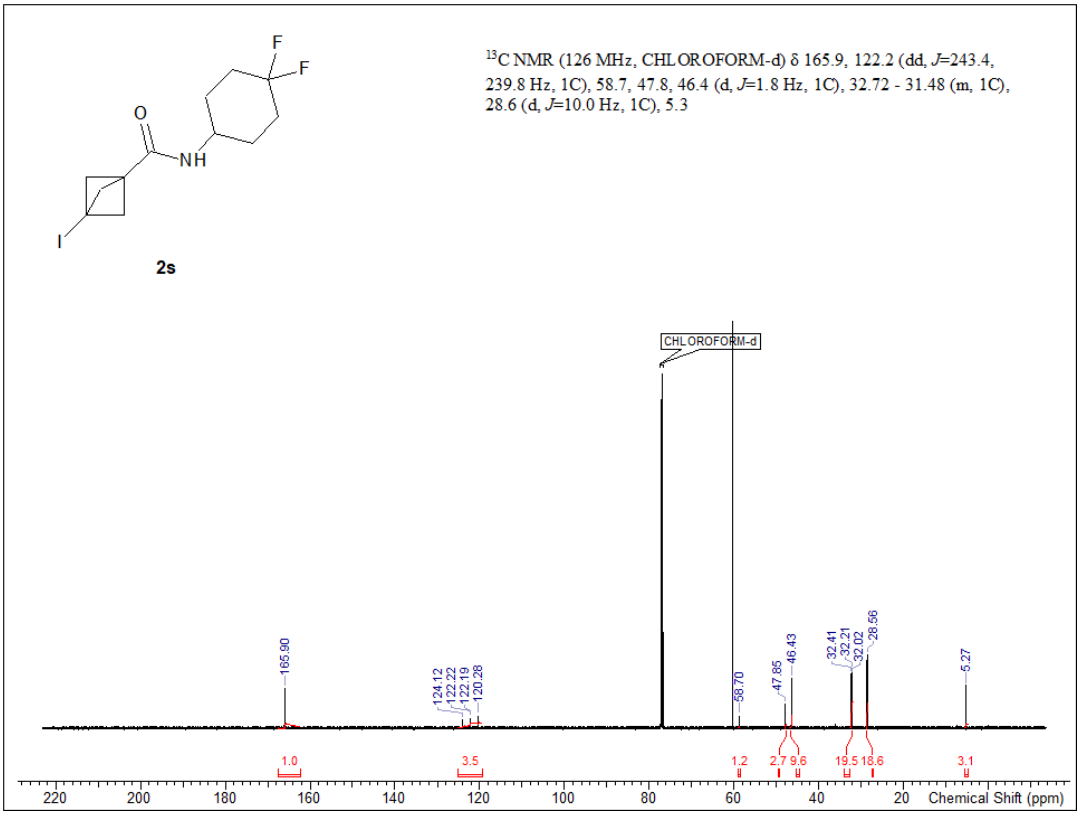
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.32 (br d, *J*=6.9 Hz, 1H), 4.24 - 4.11 (m, 1H), 2.54 (s, 6H), 2.50 - 2.35 (m, 4H), 2.24 (ddd, *J*=12.8, 6.3, 2.9 Hz, 2H), 1.72 - 1.55 (m, 2H)



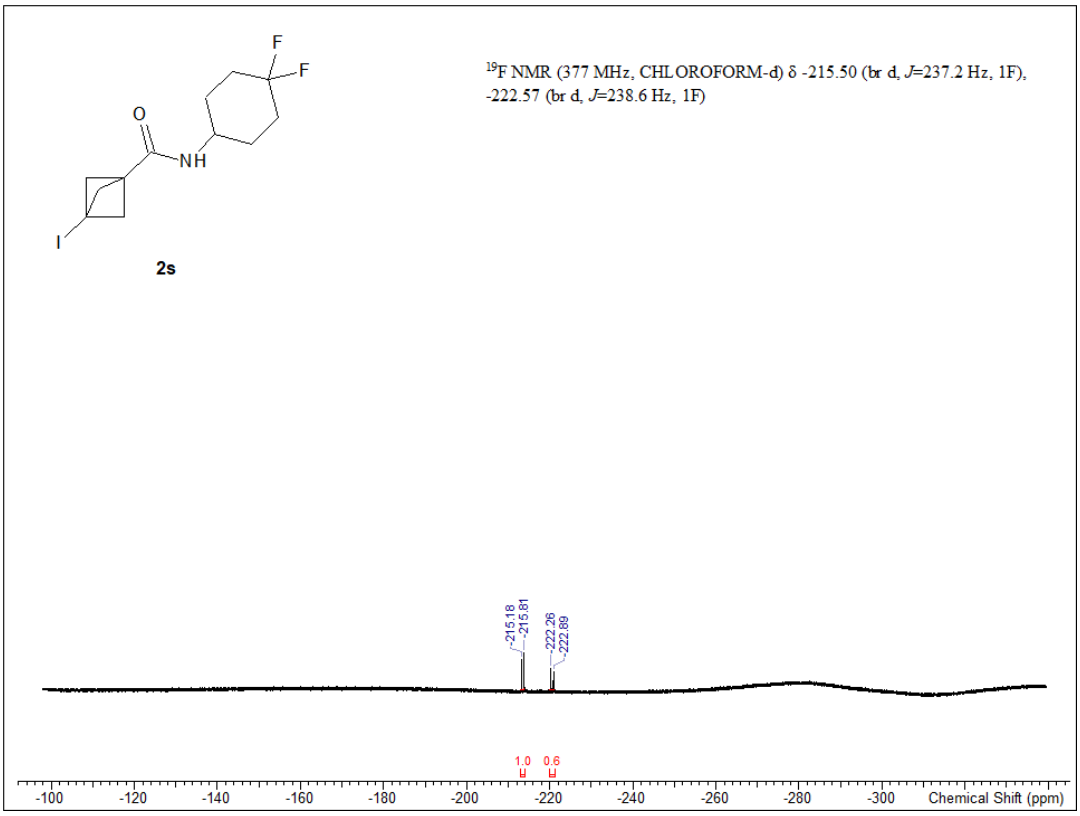
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 209.1, 166.0, 60.2, 47.8, 46.6, 39.1, 31.9, 5.2



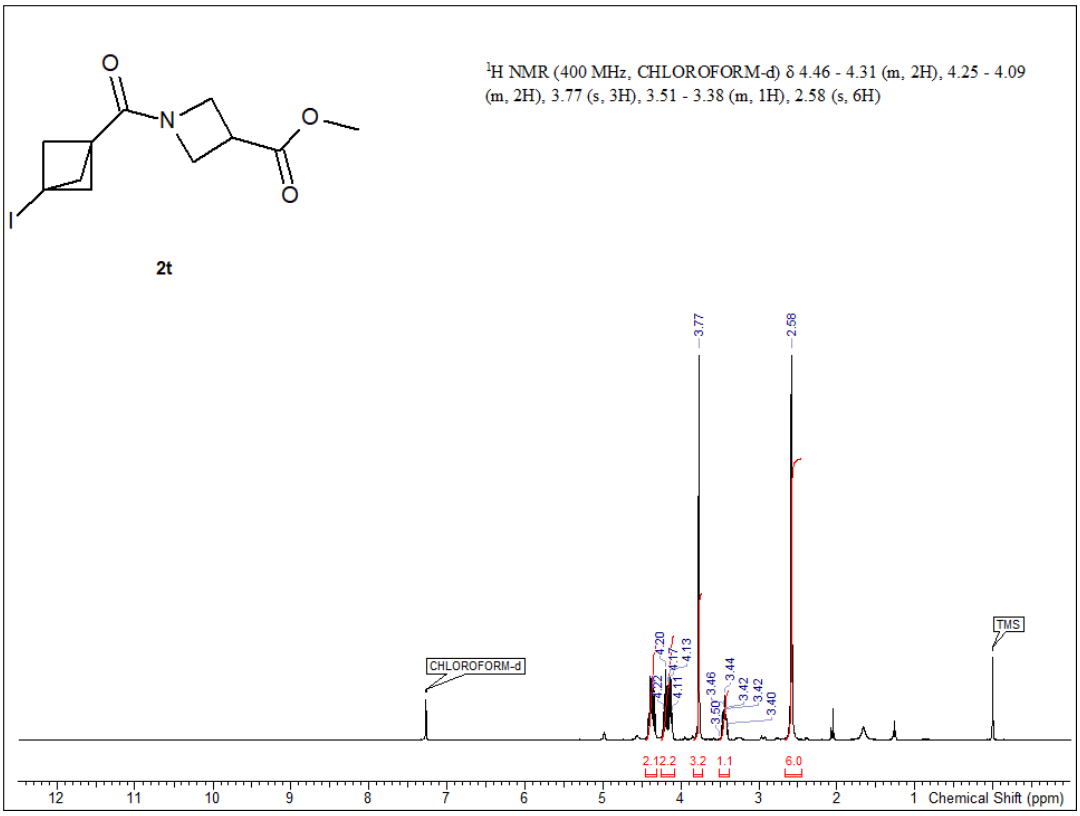
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.20 (br d, *J*=5.0 Hz, 1H), 3.94 - 3.71 (m, 1H), 2.52 (s, 6H), 2.20 - 2.04 (m, 2H), 2.02 - 1.93 (m, 2H), 1.93 - 1.72 (m, 2H), 1.54 - 1.43 (m, 2H)

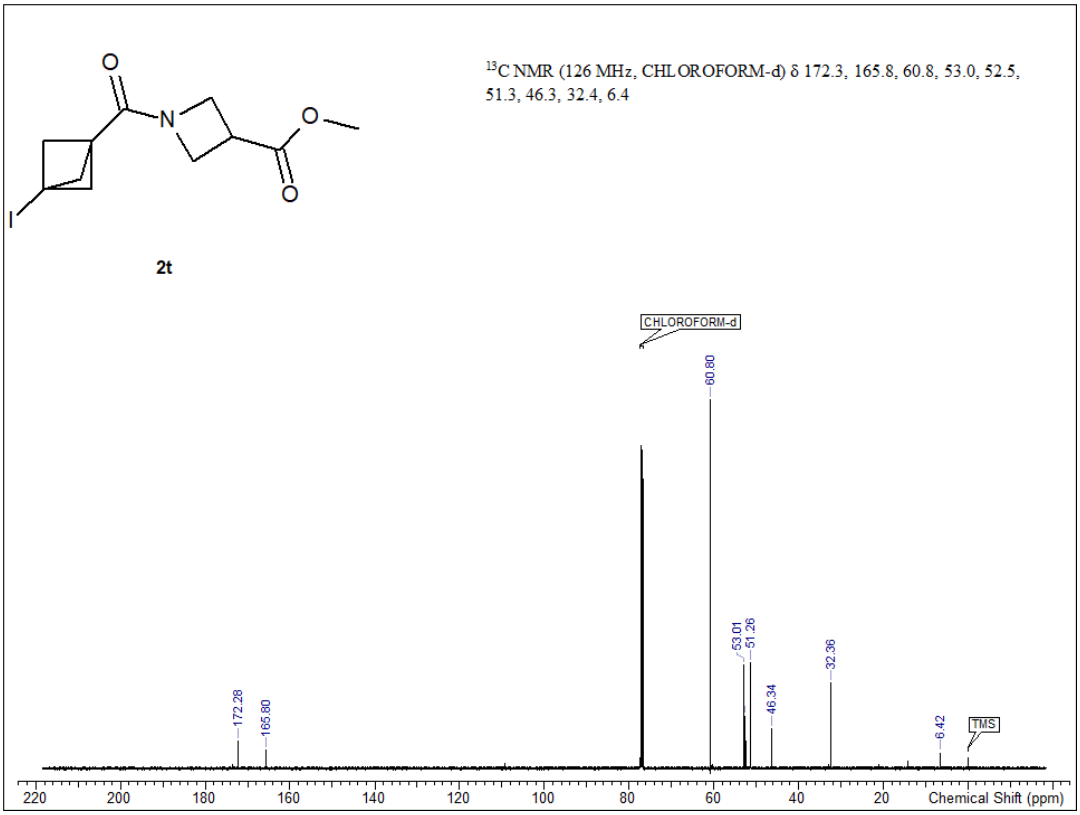


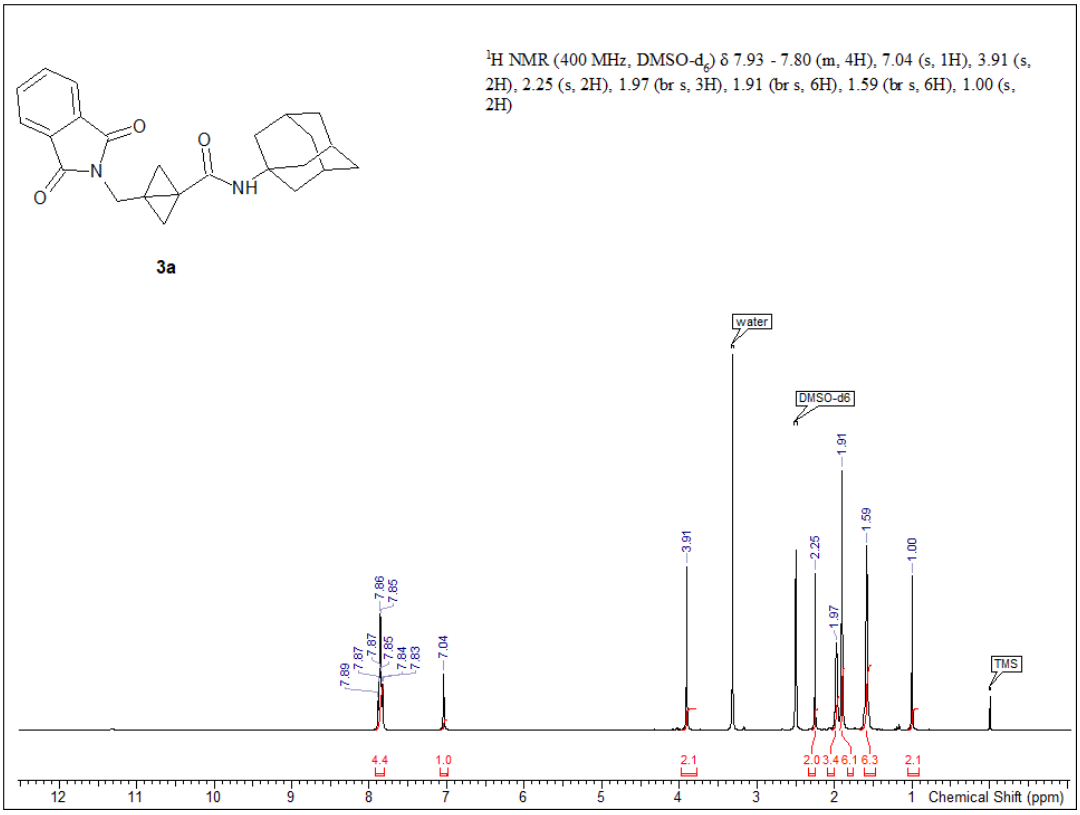
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 165.9, 122.2 (dd, *J*=243.4, 239.8 Hz, 1C), 58.7, 47.8, 46.4 (d, *J*=1.8 Hz, 1C), 32.72 - 31.48 (m, 1C), 28.6 (d, *J*=10.0 Hz, 1C), 5.3



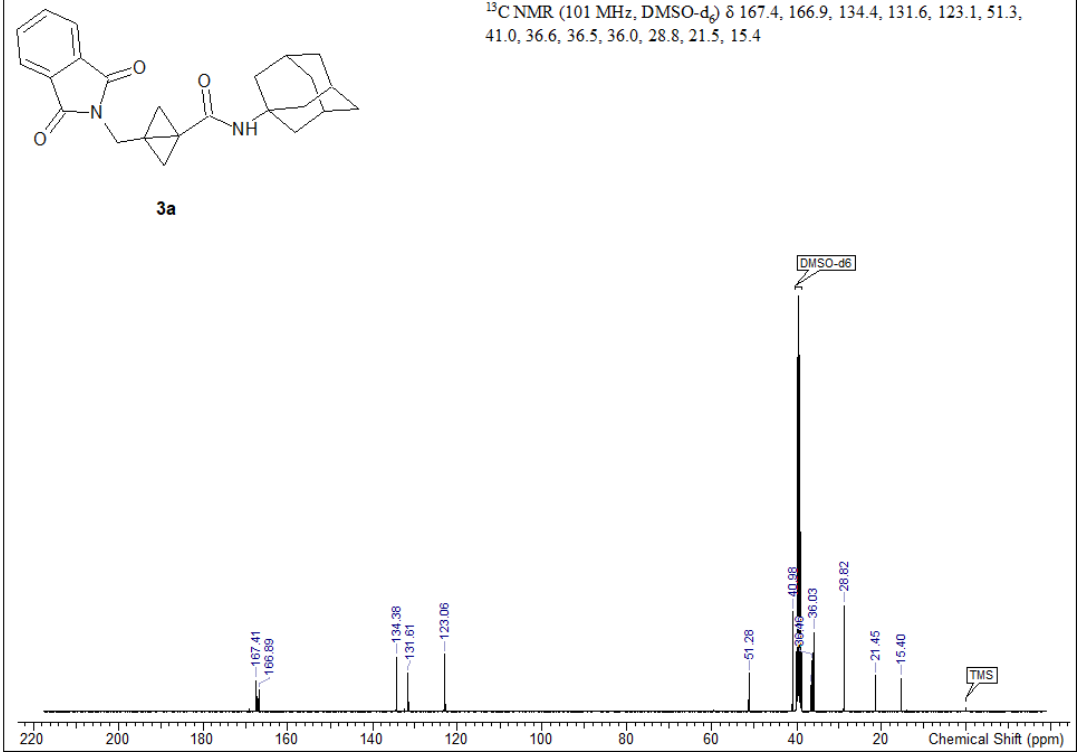
^{19}F NMR (377 MHz, CHLOROFORM-d) δ -215.50 (br d, *J*=237.2 Hz, 1F), -222.57 (br d, *J*=238.6 Hz, 1F)


O
N
O
O
I
2t
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 4.46 - 4.31 (m, 2H), 4.25 - 4.09 (m, 2H), 3.77 (s, 3H), 3.51 - 3.38 (m, 1H), 2.58 (s, 6H)
3.77
2.58
CHLOROFORM-d
TMS
4.20
4.17
4.13
4.11
3.46
3.44
3.42
3.42
3.40
2.1 2.2 3.2 1.1 6.0
12 11 10 9 8 7 6 5 4 3 2 1 Chemical Shift (ppm)

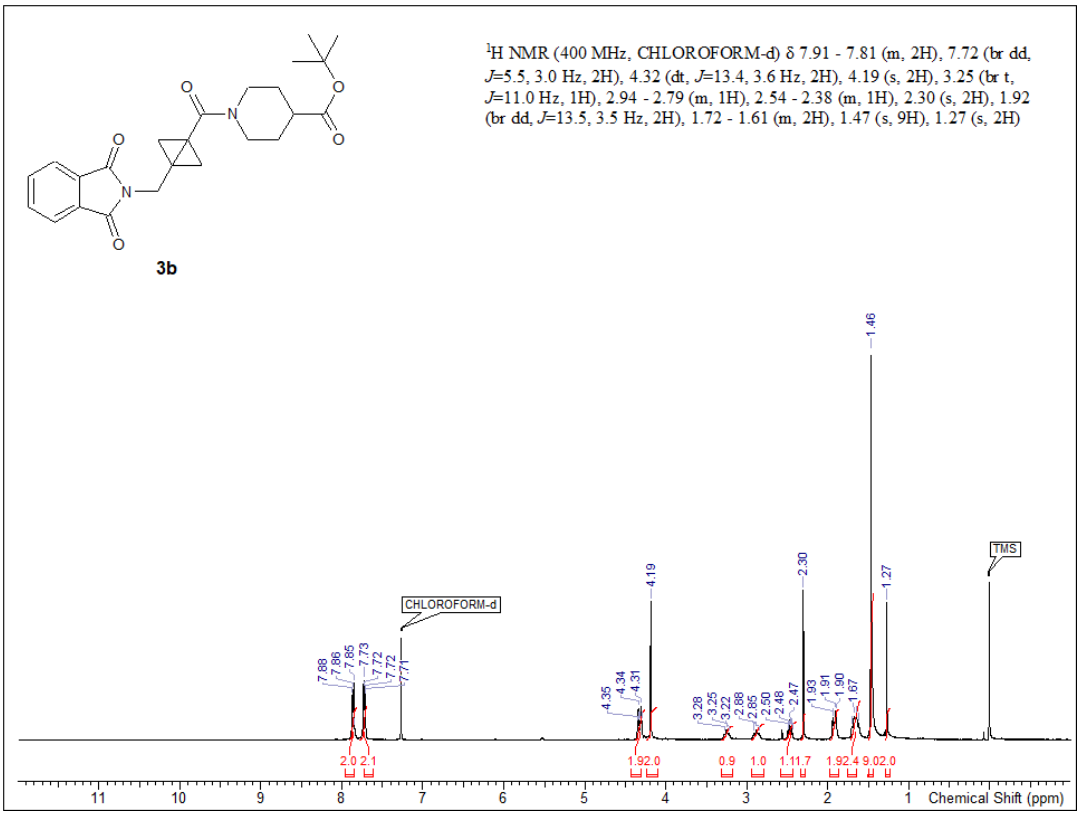

O
N
O
O
I
2t
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 172.3, 165.8, 60.8, 53.0, 52.5, 51.3, 46.3, 32.4, 6.4
CHLOROFORM-d
60.80
53.01
51.26
46.34
32.36
172.28
165.80
6.42
TMS
220 200 180 160 140 120 100 80 60 40 20 Chemical Shift (ppm)



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 - 7.80 (m, 4H), 7.04 (s, 1H), 3.91 (s, 2H), 2.25 (s, 2H), 1.97 (br s, 3H), 1.91 (br s, 6H), 1.59 (br s, 6H), 1.00 (s, 2H)

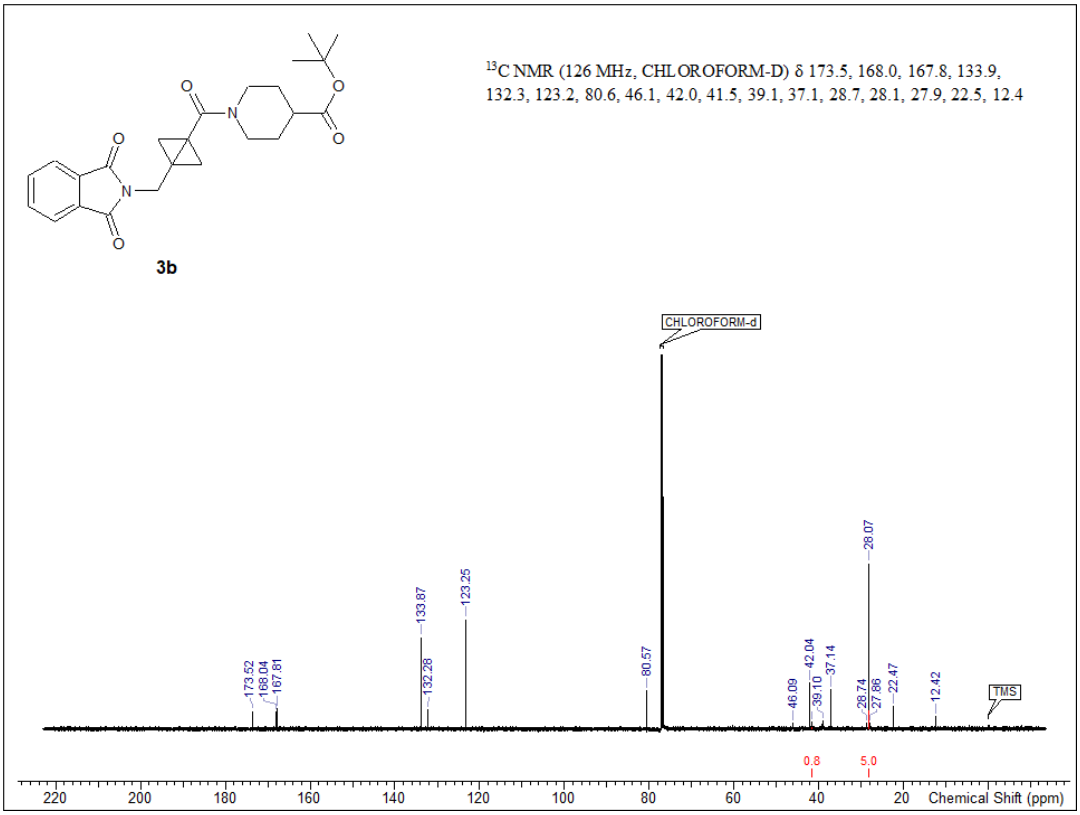


^{13}C NMR (101 MHz, DMSO-d_6) δ 167.4, 166.9, 134.4, 131.6, 123.1, 51.3, 41.0, 36.6, 36.5, 36.0, 28.8, 21.5, 15.4



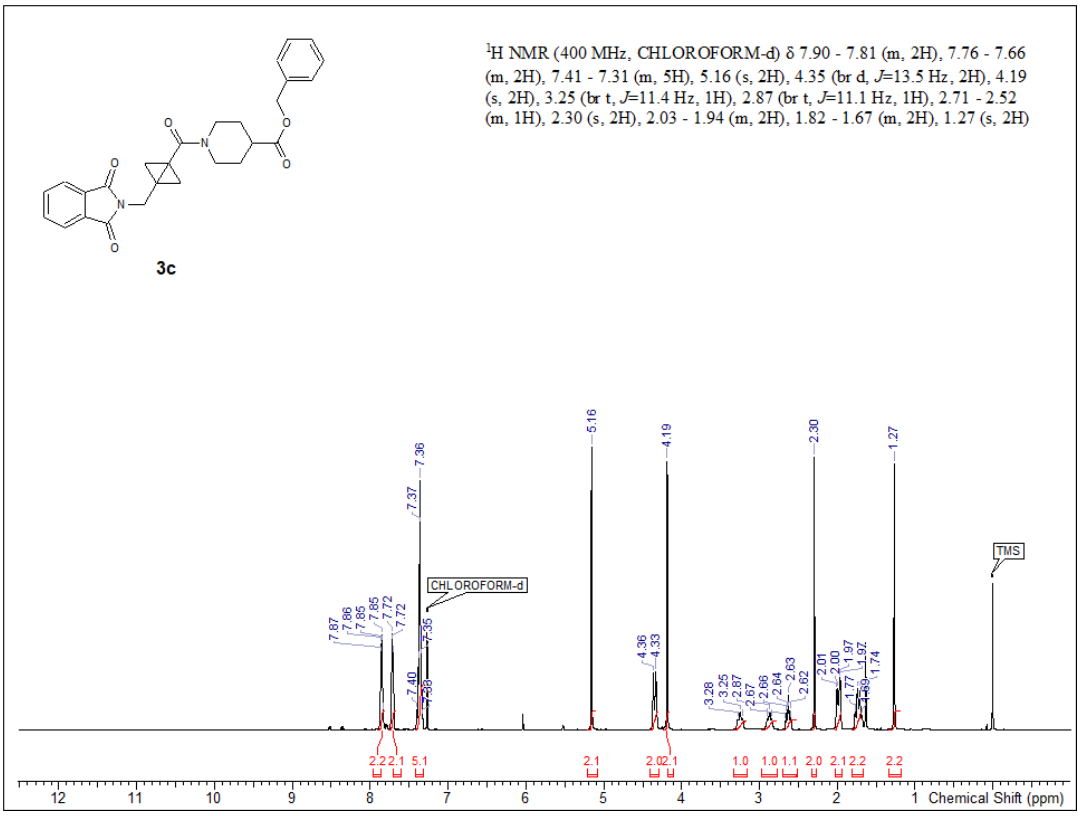
3b

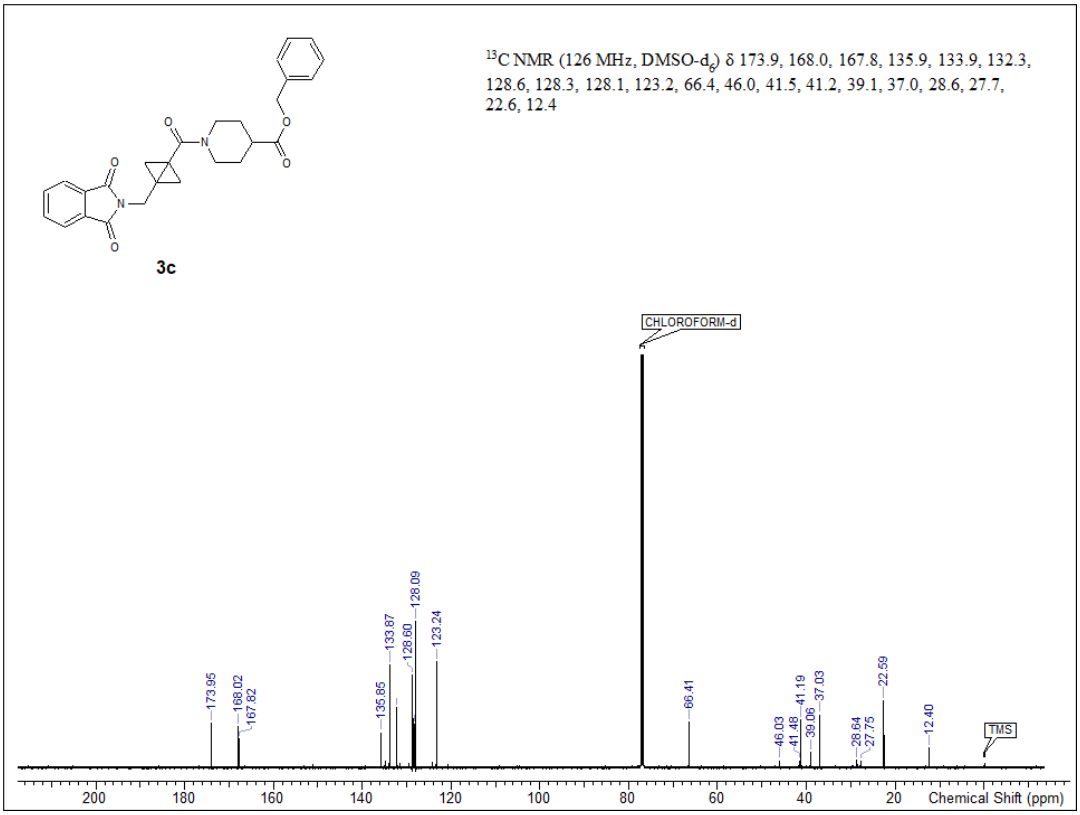
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.91 - 7.81 (m, 2H), 7.72 (br dd, *J*=5.5, 3.0 Hz, 2H), 4.32 (dt, *J*=13.4, 3.6 Hz, 2H), 4.19 (s, 2H), 3.25 (br t, *J*=11.0 Hz, 1H), 2.94 - 2.79 (m, 1H), 2.54 - 2.38 (m, 1H), 2.30 (s, 2H), 1.92 (br dd, *J*=13.5, 3.5 Hz, 2H), 1.72 - 1.61 (m, 2H), 1.47 (s, 9H), 1.27 (s, 2H)

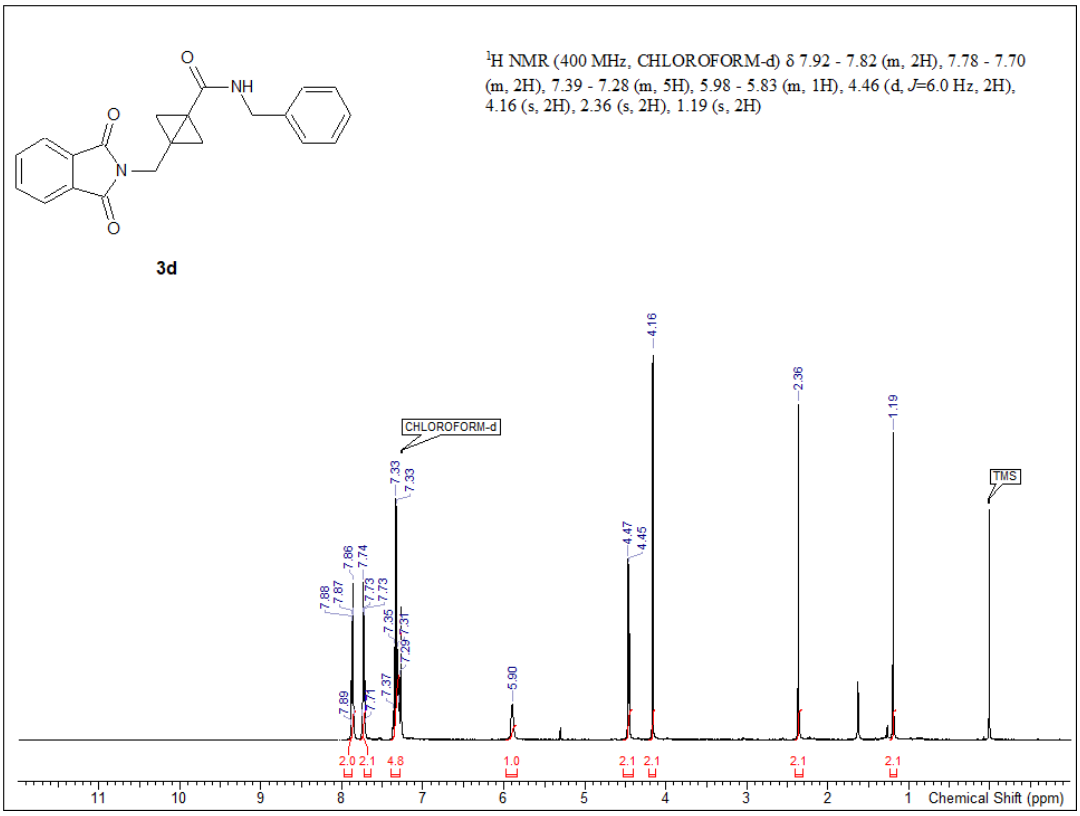


3b

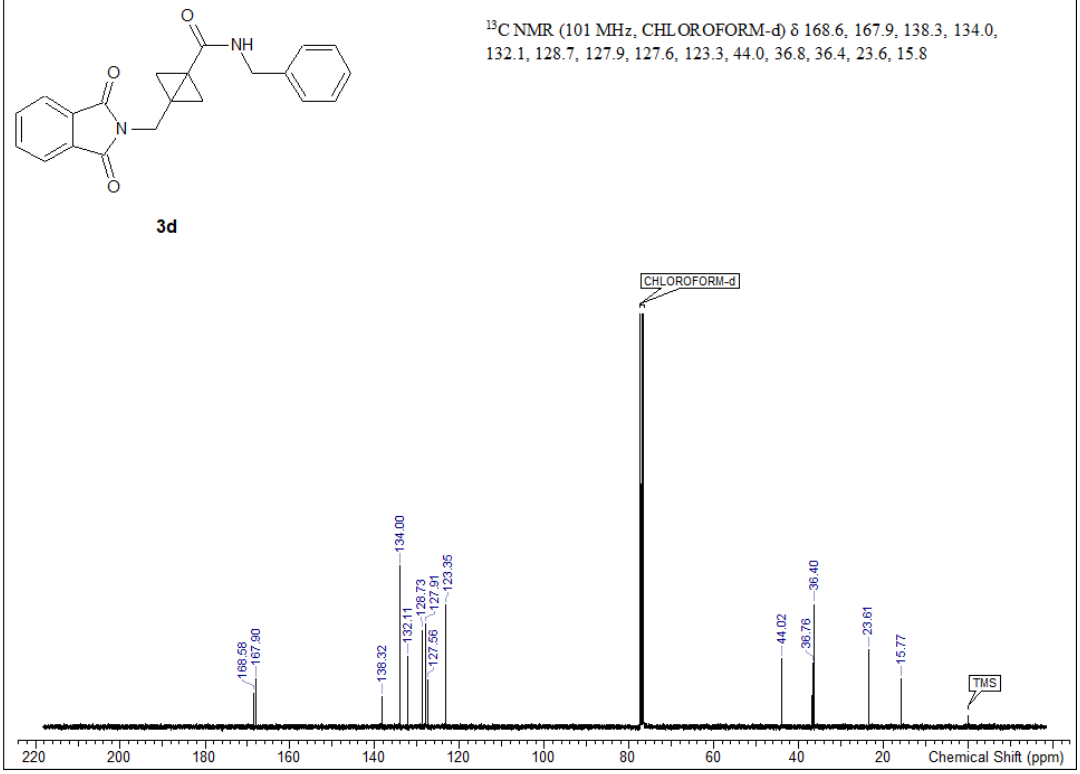
^{13}C NMR (126 MHz, CHLOROFORM-D) δ 173.5, 168.0, 167.8, 133.9, 132.3, 123.2, 80.6, 46.1, 42.0, 41.5, 39.1, 37.1, 28.7, 28.1, 27.9, 22.5, 12.4


3c
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.90 - 7.81 (m, 2H), 7.76 - 7.66 (m, 2H), 7.41 - 7.31 (m, 5H), 5.16 (s, 2H), 4.35 (br d, J=13.5 Hz, 2H), 4.19 (s, 2H), 3.25 (br t, J=11.4 Hz, 1H), 2.87 (br t, J=11.1 Hz, 1H), 2.71 - 2.52 (m, 1H), 2.30 (s, 2H), 2.03 - 1.94 (m, 2H), 1.82 - 1.67 (m, 2H), 1.27 (s, 2H)
CHLOROFORM-d
TMS
Chemical Shift (ppm)

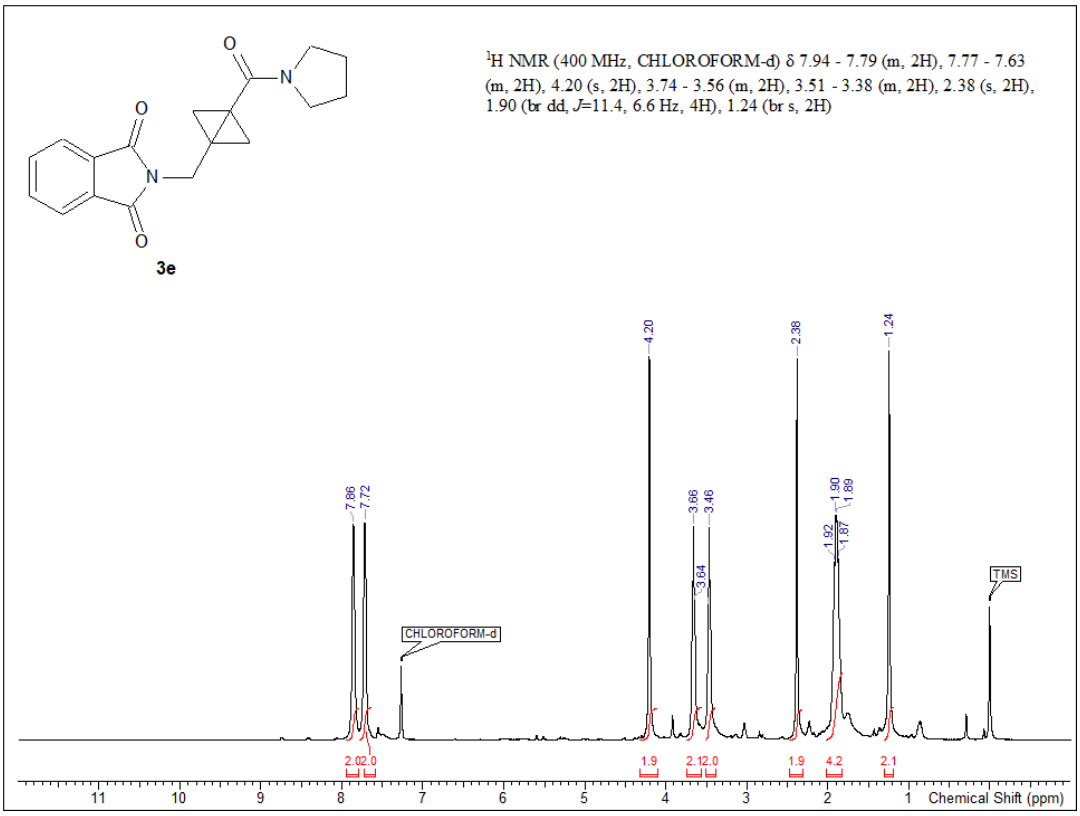

3c
^{13}C NMR (126 MHz, DMSO-d$_6$) δ 173.9, 168.0, 167.8, 135.9, 133.9, 132.3, 128.6, 128.3, 128.1, 123.2, 66.4, 46.0, 41.5, 41.2, 39.1, 37.0, 28.6, 27.7, 22.6, 12.4
CHLOROFORM-d
TMS
Chemical Shift (ppm)

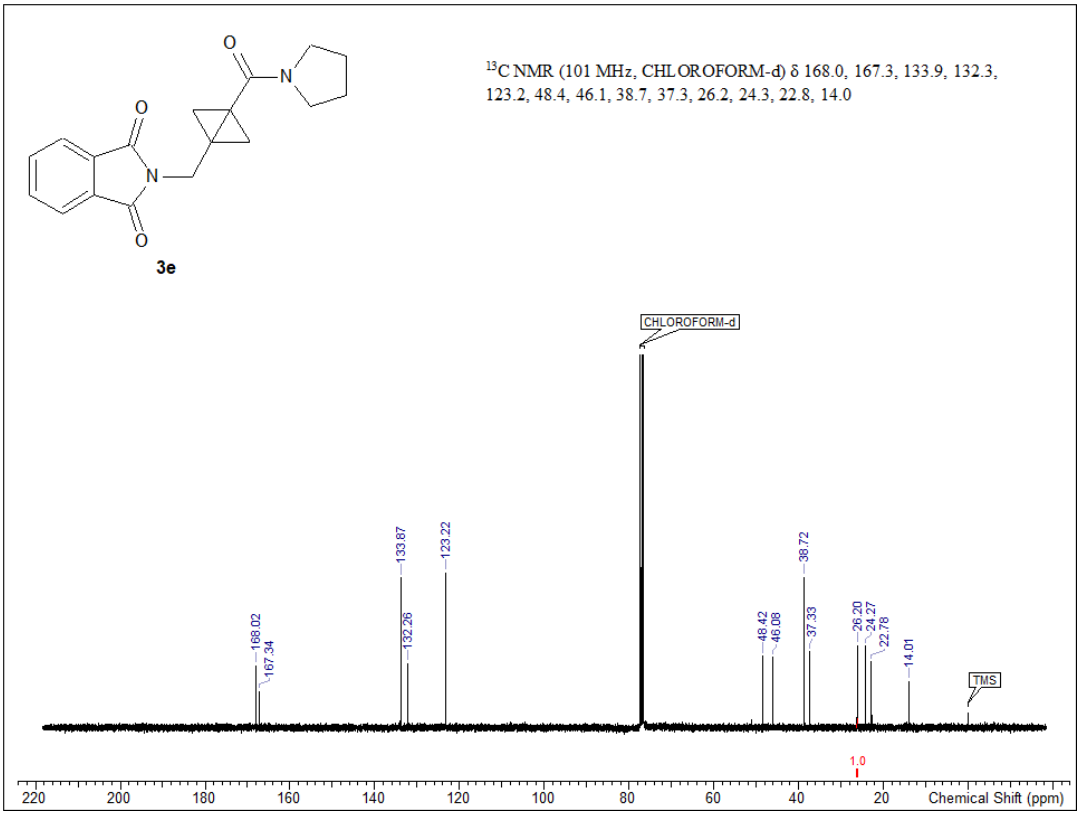


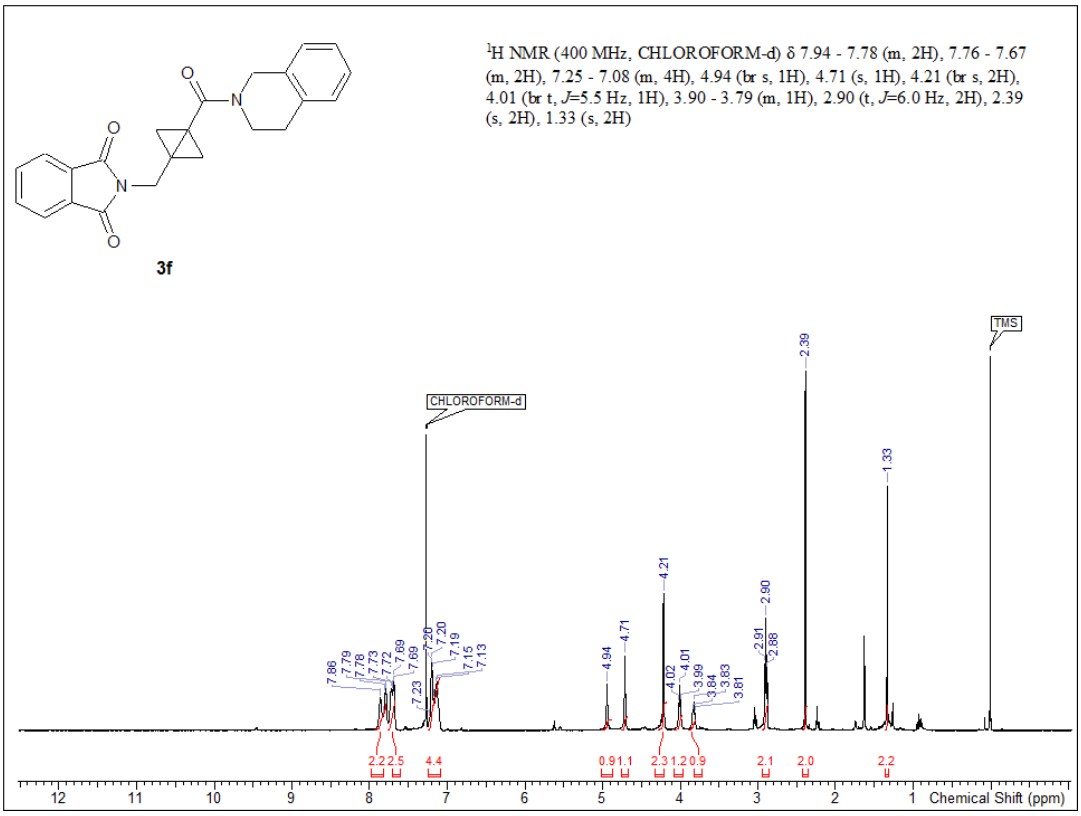
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.92 - 7.82 (m, 2H), 7.78 - 7.70 (m, 2H), 7.39 - 7.28 (m, 5H), 5.98 - 5.83 (m, 1H), 4.46 (d, *J*=6.0 Hz, 2H), 4.16 (s, 2H), 2.36 (s, 2H), 1.19 (s, 2H)



^{13}C NMR (101 MHz, CHLOROFORM-d) δ 168.6, 167.9, 138.3, 134.0, 132.1, 128.7, 127.9, 127.6, 123.3, 44.0, 36.8, 36.4, 23.6, 15.8

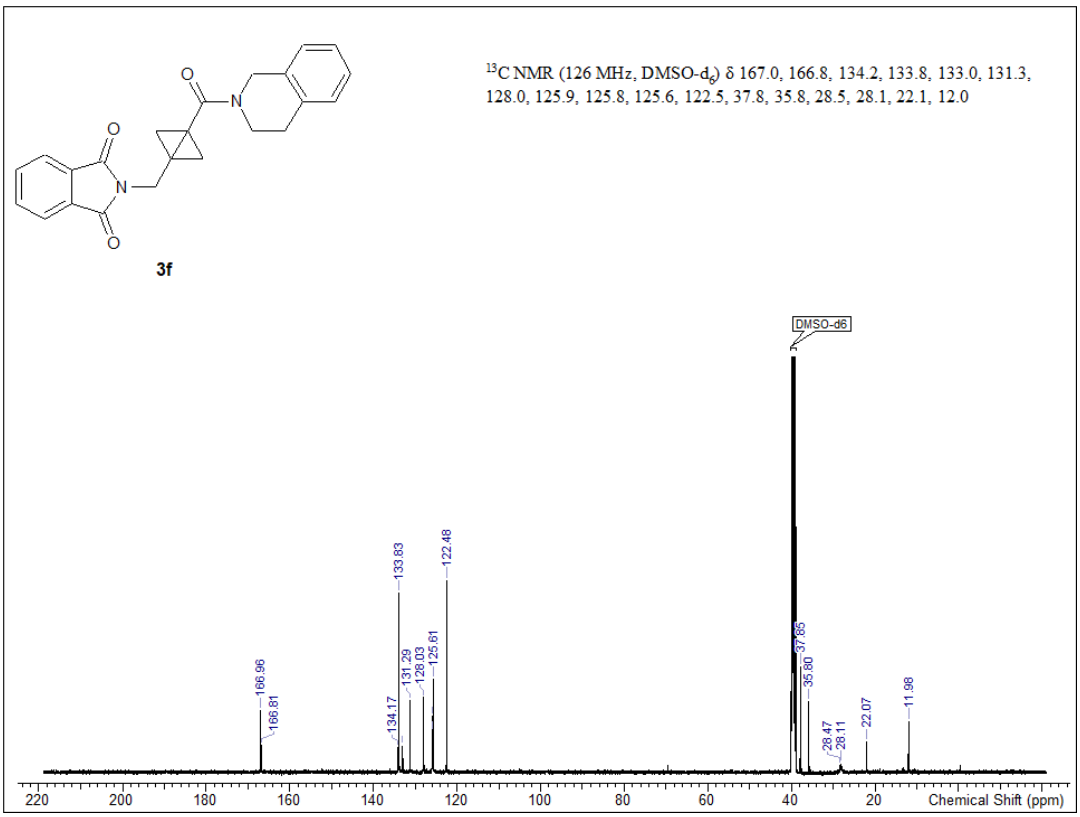

3e
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.94 - 7.79 (m, 2H), 7.77 - 7.63 (m, 2H), 4.20 (s, 2H), 3.74 - 3.56 (m, 2H), 3.51 - 3.38 (m, 2H), 2.38 (s, 2H), 1.90 (br dd, J=11.4, 6.6 Hz, 4H), 1.24 (br s, 2H)
7.86
7.72
4.20
3.66
3.46
3.64
2.38
1.90
1.89
1.92
1.87
1.24
CHLOROFORM-d
TMS
2.0
2.0
1.9
2.1
2.0
1.9
4.2
2.1
Chemical Shift (ppm)


3e
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 168.0, 167.3, 133.9, 132.3, 123.2, 48.4, 46.1, 38.7, 37.3, 26.2, 24.3, 22.8, 14.0
CHLOROFORM-d
168.02
167.34
133.87
132.26
123.22
48.42
46.08
38.72
37.33
26.20
24.27
22.78
14.01
TMS
1.0
Chemical Shift (ppm)



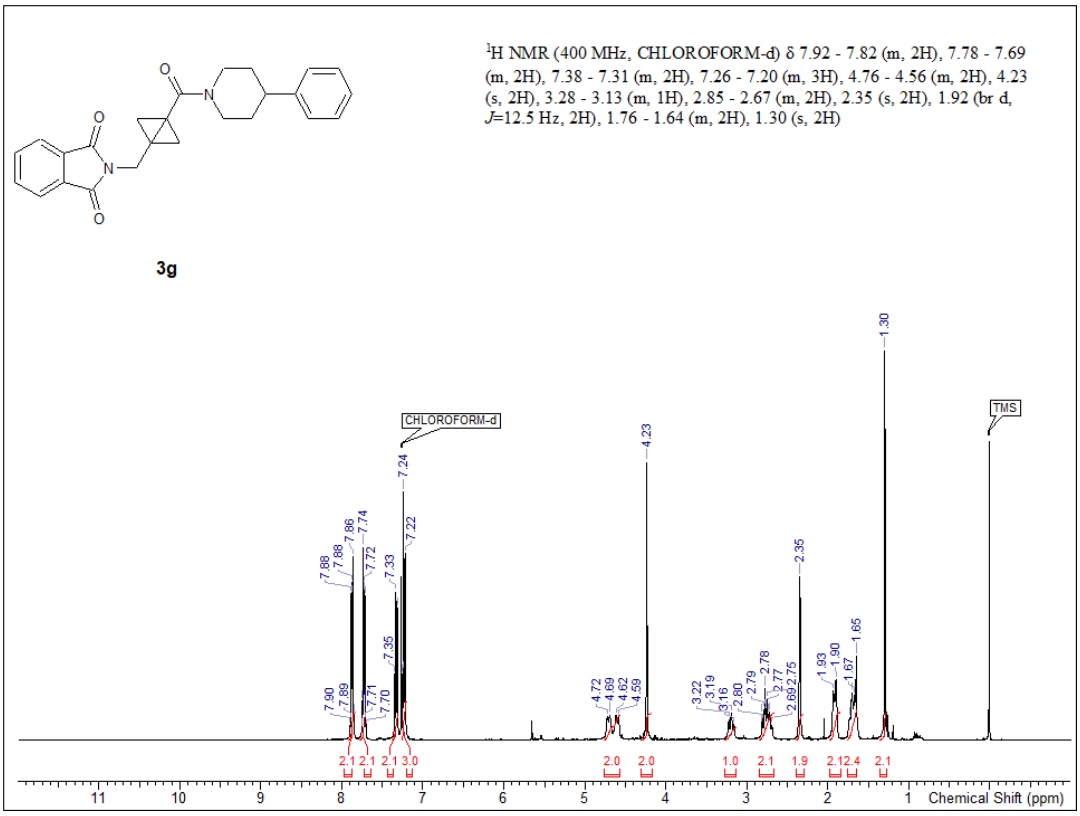
3f

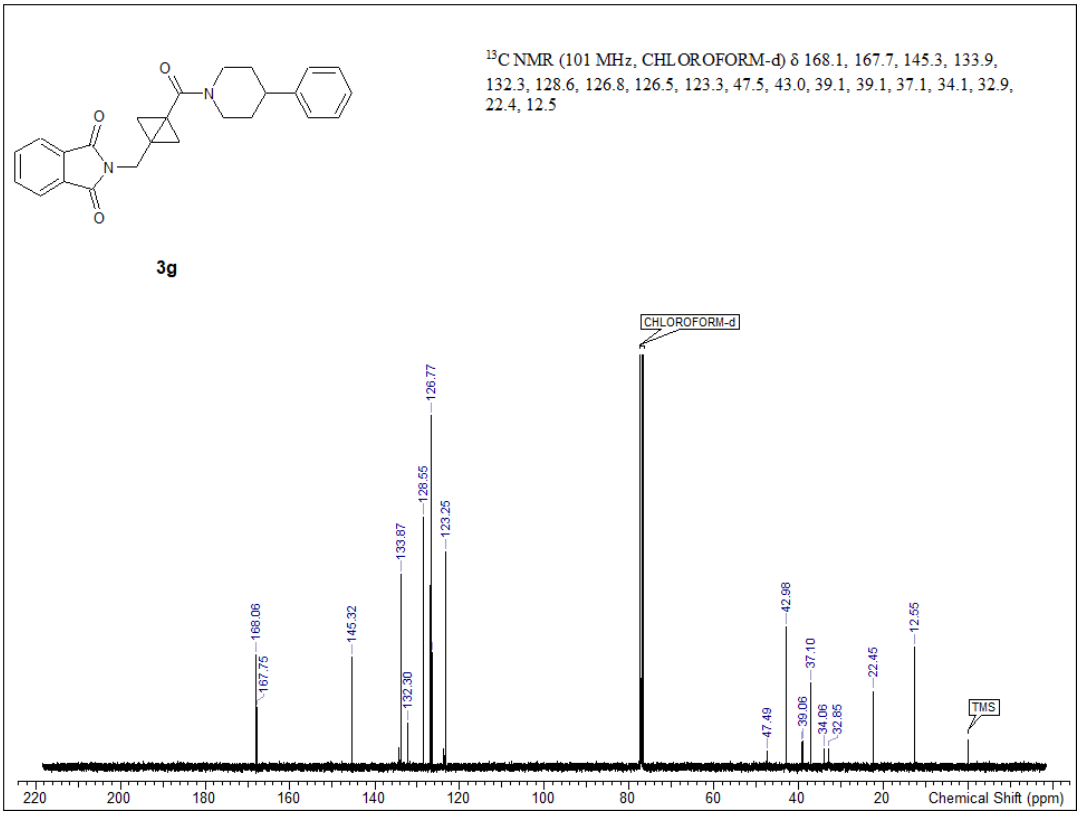
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.94 - 7.78 (m, 2H), 7.76 - 7.67 (m, 2H), 7.25 - 7.08 (m, 4H), 4.94 (br s, 1H), 4.71 (s, 1H), 4.21 (br s, 2H), 4.01 (br t, *J*=5.5 Hz, 1H), 3.90 - 3.79 (m, 1H), 2.90 (t, *J*=6.0 Hz, 2H), 2.39 (s, 2H), 1.33 (s, 2H)

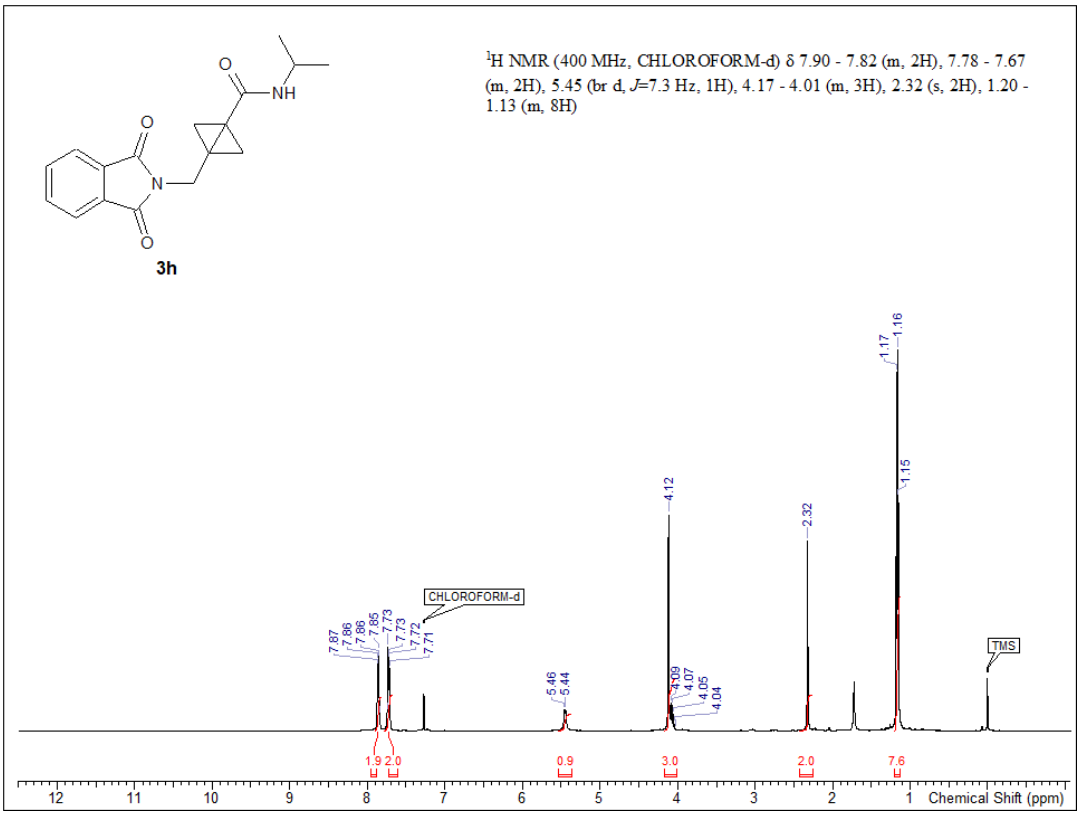


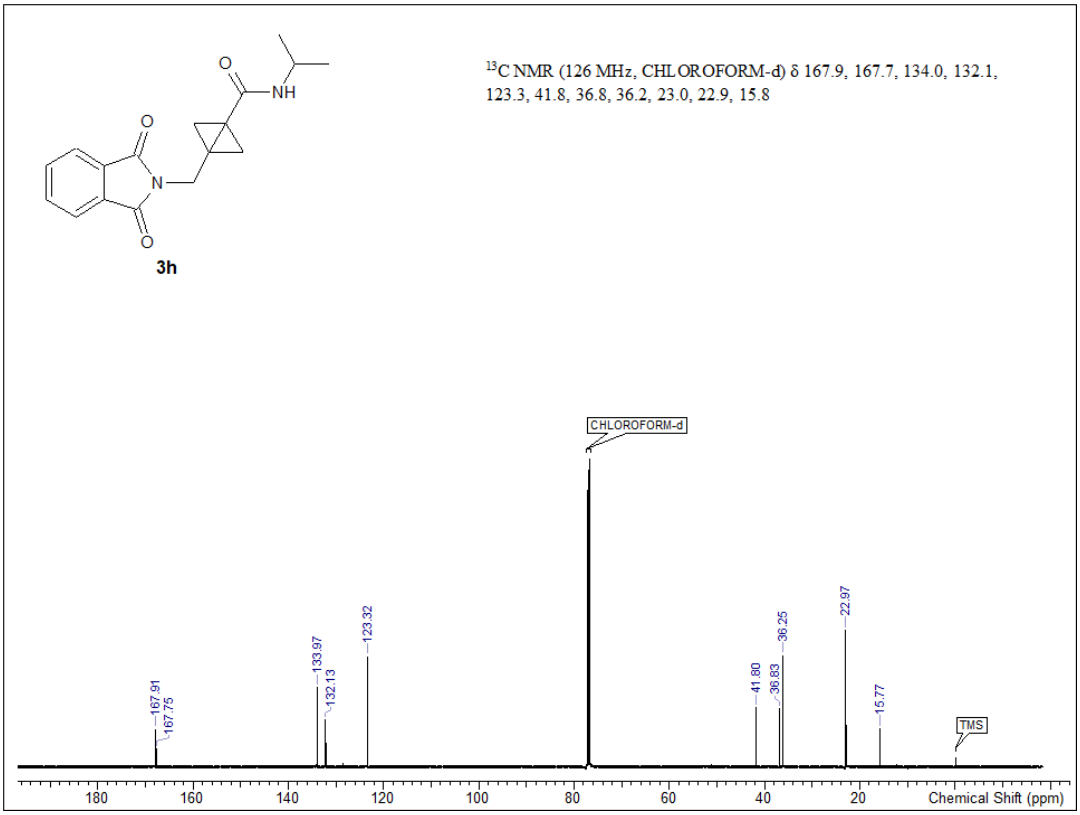
3f

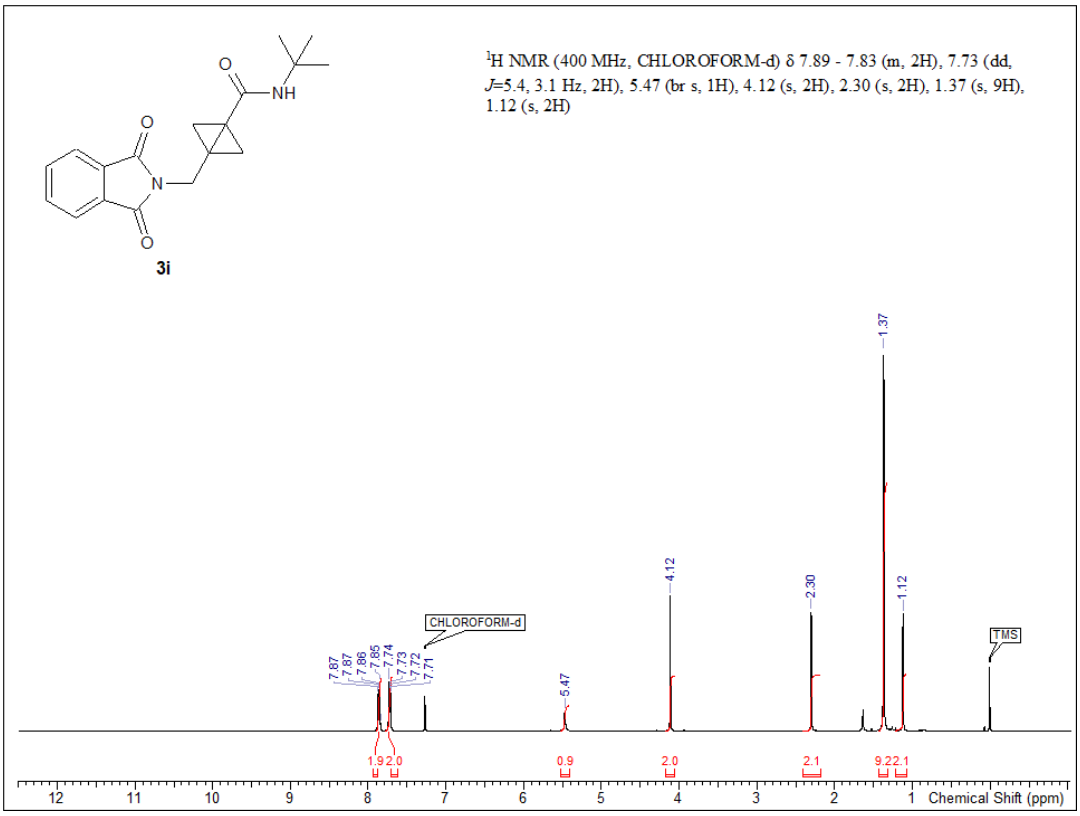
^{13}C NMR (126 MHz, DMSO-d_6) δ 167.0, 166.8, 134.2, 133.8, 133.0, 131.3, 128.0, 125.9, 125.8, 125.6, 122.5, 37.8, 35.8, 28.5, 28.1, 22.1, 12.0

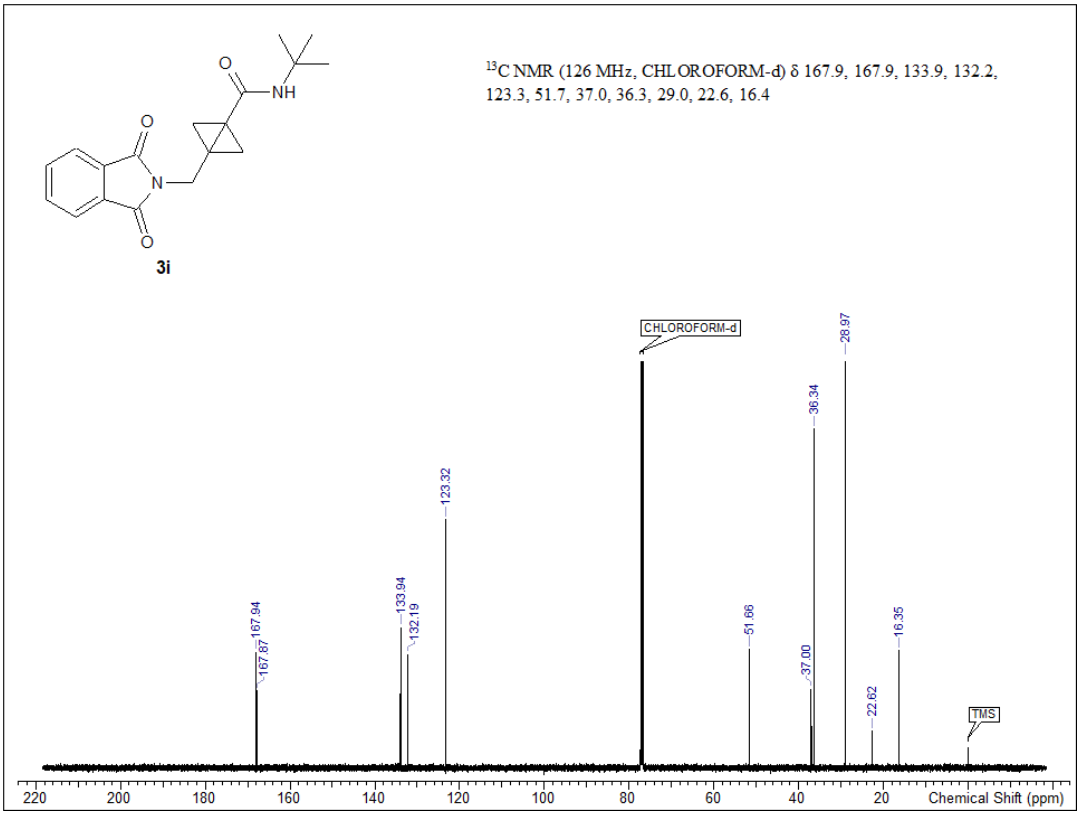

3g
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.92 - 7.82 (m, 2H), 7.78 - 7.69 (m, 2H), 7.38 - 7.31 (m, 2H), 7.26 - 7.20 (m, 3H), 4.76 - 4.56 (m, 2H), 4.23 (s, 2H), 3.28 - 3.13 (m, 1H), 2.85 - 2.67 (m, 2H), 2.35 (s, 2H), 1.92 (br d, J=12.5 Hz, 2H), 1.76 - 1.64 (m, 2H), 1.30 (s, 2H)
CHLOROFORM-d
TMS
Chemical Shift (ppm)

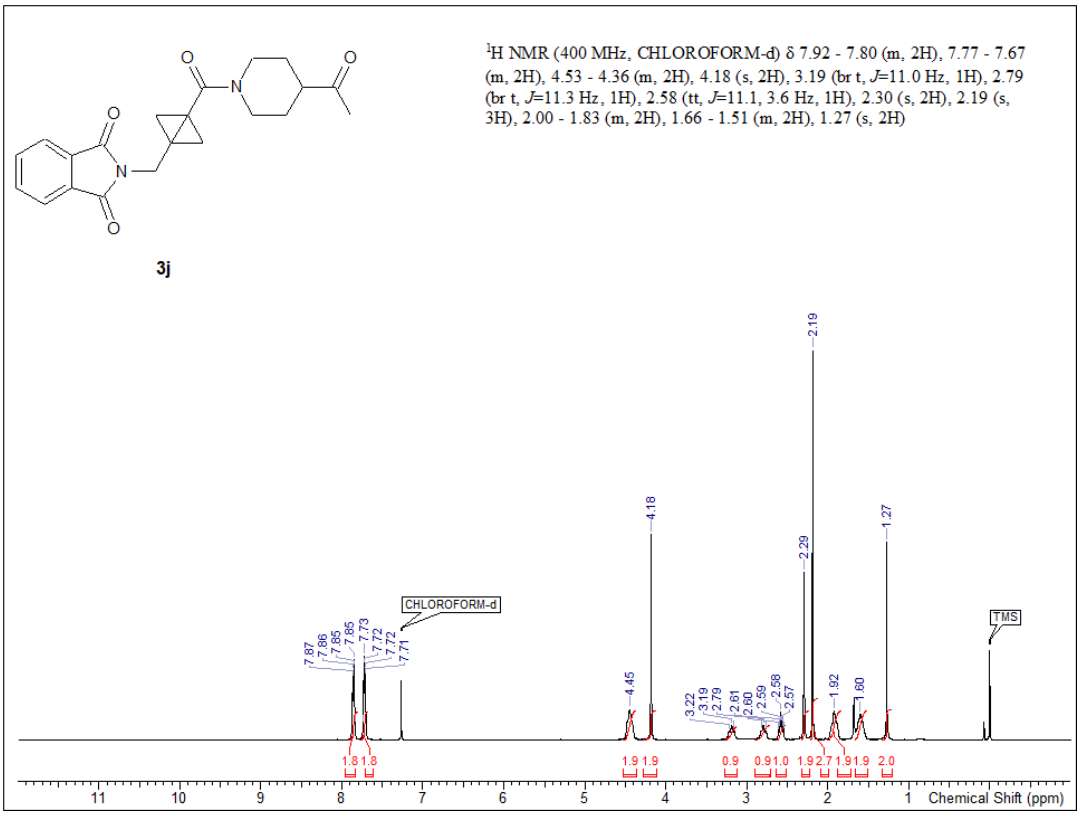

3g
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 168.1, 167.7, 145.3, 133.9, 132.3, 128.6, 126.8, 126.5, 123.3, 47.5, 43.0, 39.1, 39.1, 37.1, 34.1, 32.9, 22.4, 12.5
CHLOROFORM-d
TMS
Chemical Shift (ppm)


O
NH
O
N
O
3h
1H NMR (400 MHz, CHLOROFORM-d) δ 7.90 - 7.82 (m, 2H), 7.78 - 7.67 (m, 2H), 5.45 (br d, J=7.3 Hz, 1H), 4.17 - 4.01 (m, 3H), 2.32 (s, 2H), 1.20 - 1.13 (m, 8H)
7.87
7.86
7.86
7.85
7.73
7.73
7.72
7.71
CHLOROFORM-d
5.46
5.44
4.12
4.09
4.07
4.05
4.04
2.32
1.17
1.16
1.15
TMS
1.9
2.0
0.9
3.0
2.0
7.6
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


O
NH
O
N
O
3h
13C NMR (126 MHz, CHLOROFORM-d) δ 167.9, 167.7, 134.0, 132.1, 123.3, 41.8, 36.8, 36.2, 23.0, 22.9, 15.8
CHLOROFORM-d
167.91
167.75
133.97
132.13
123.32
41.80
36.83
36.25
22.97
15.77
TMS
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

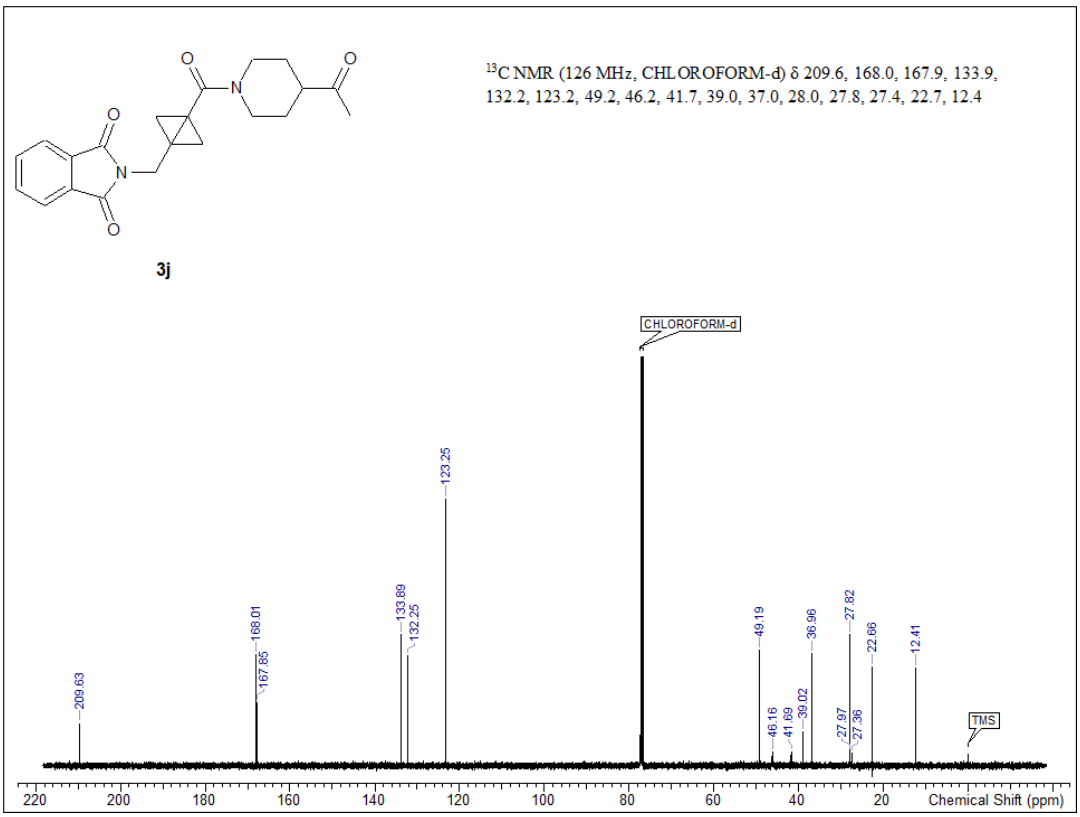

O
NH
O
N
O
3i
1H NMR (400 MHz, CHLOROFORM-d) δ 7.89 - 7.83 (m, 2H), 7.73 (dd, J=5.4, 3.1 Hz, 2H), 5.47 (br s, 1H), 4.12 (s, 2H), 2.30 (s, 2H), 1.37 (s, 9H), 1.12 (s, 2H)
CHLOROFORM-d
TMS
7.87
7.87
7.86
7.85
7.74
7.73
7.72
7.71
5.47
4.12
2.30
1.37
1.12
1.9
2.0
0.9
2.0
2.1
9.2
2.1
Chemical Shift (ppm)


O
NH
O
N
O
3i
13C NMR (126 MHz, CHLOROFORM-d) δ 167.9, 167.9, 133.9, 132.2, 123.3, 51.7, 37.0, 36.3, 29.0, 22.6, 16.4
CHLOROFORM-d
TMS
167.94
167.87
133.94
132.19
123.32
51.66
37.00
36.34
28.97
22.62
16.35
Chemical Shift (ppm)



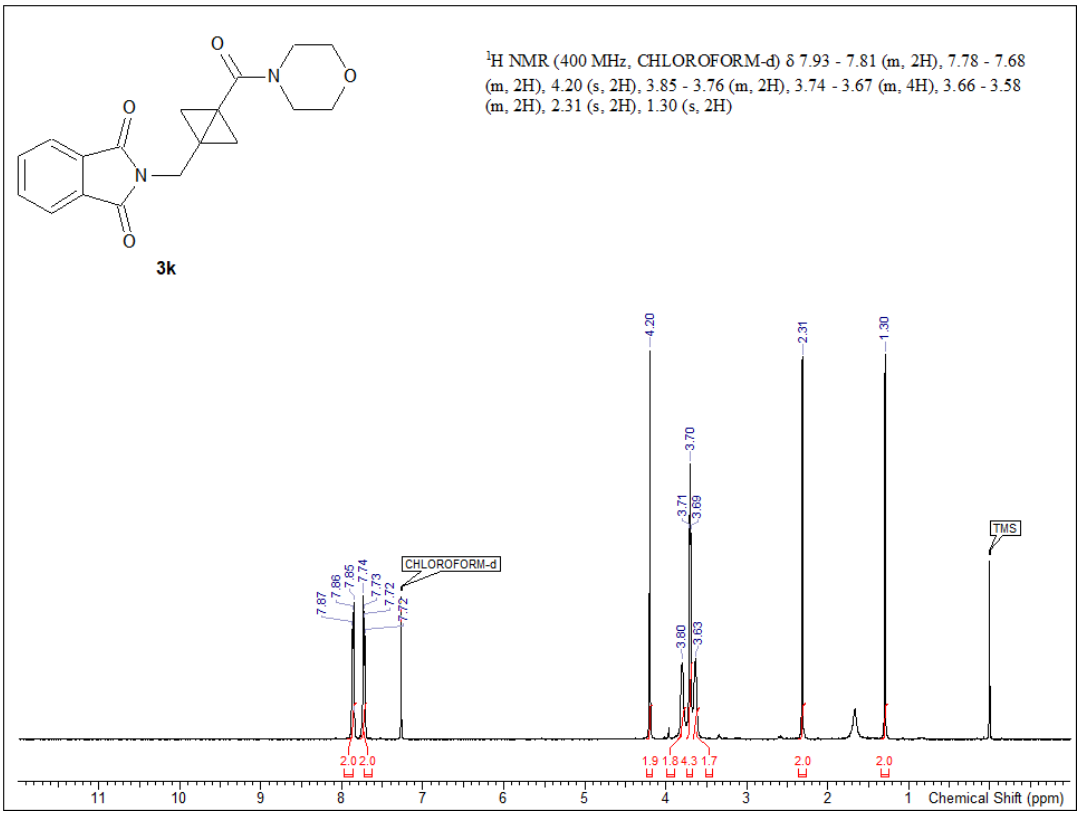
3j

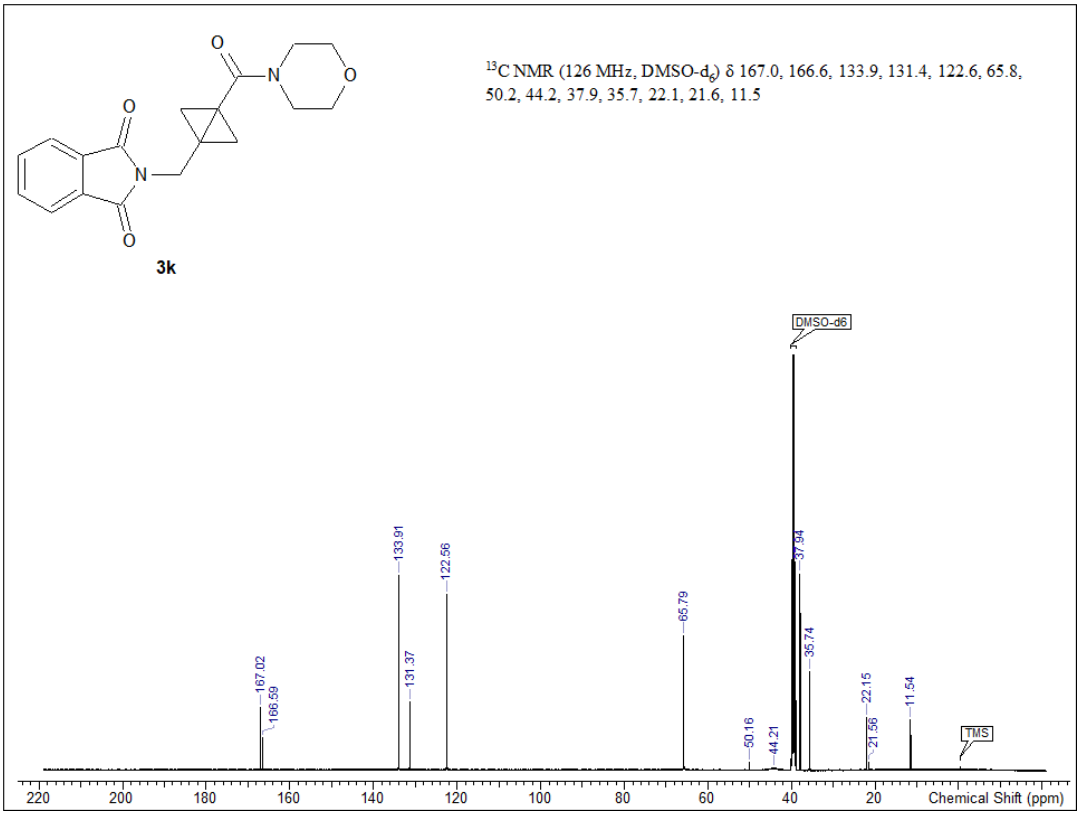
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.92 - 7.80 (m, 2H), 7.77 - 7.67 (m, 2H), 4.53 - 4.36 (m, 2H), 4.18 (s, 2H), 3.19 (br t, *J*=11.0 Hz, 1H), 2.79 (br t, *J*=11.3 Hz, 1H), 2.58 (tt, *J*=11.1, 3.6 Hz, 1H), 2.30 (s, 2H), 2.19 (s, 3H), 2.00 - 1.83 (m, 2H), 1.66 - 1.51 (m, 2H), 1.27 (s, 2H)

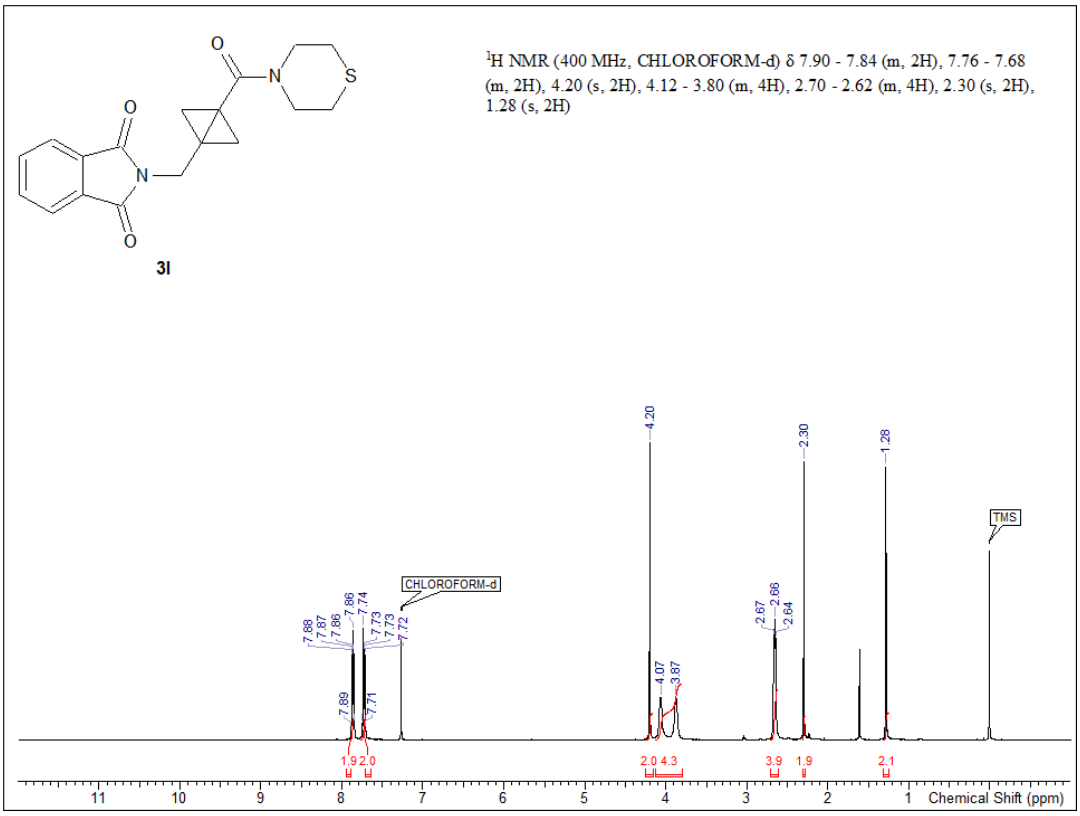


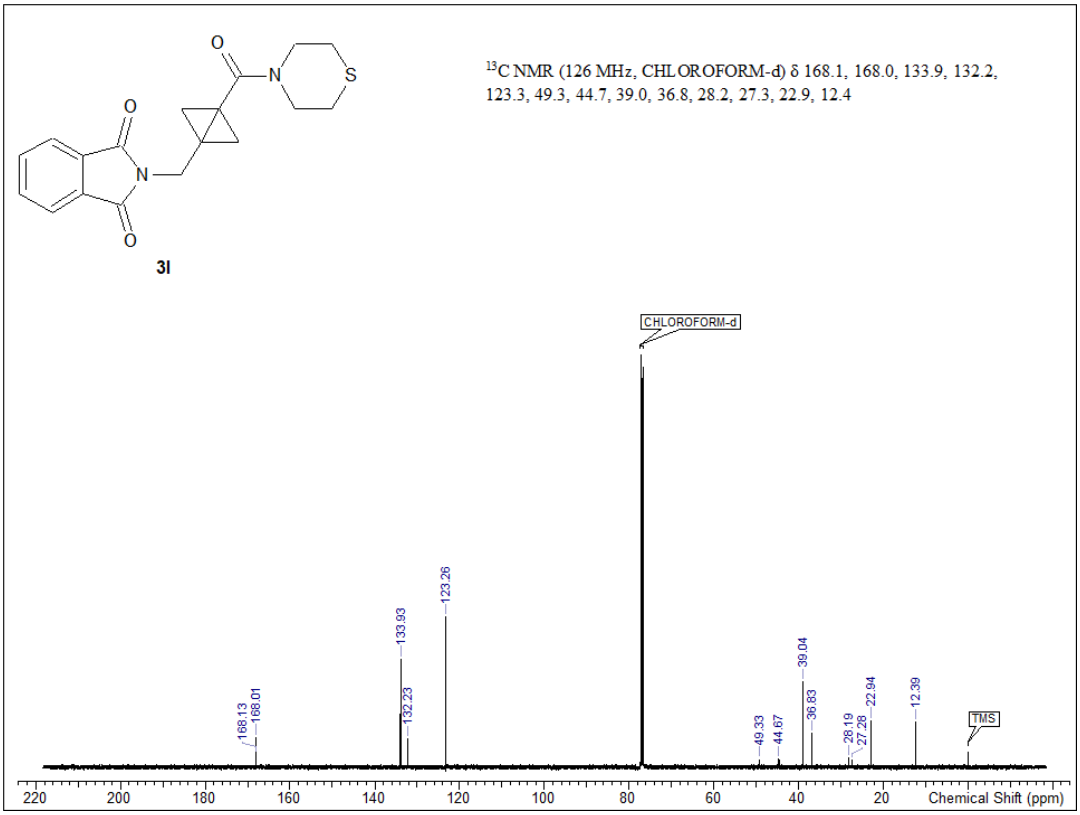
3j

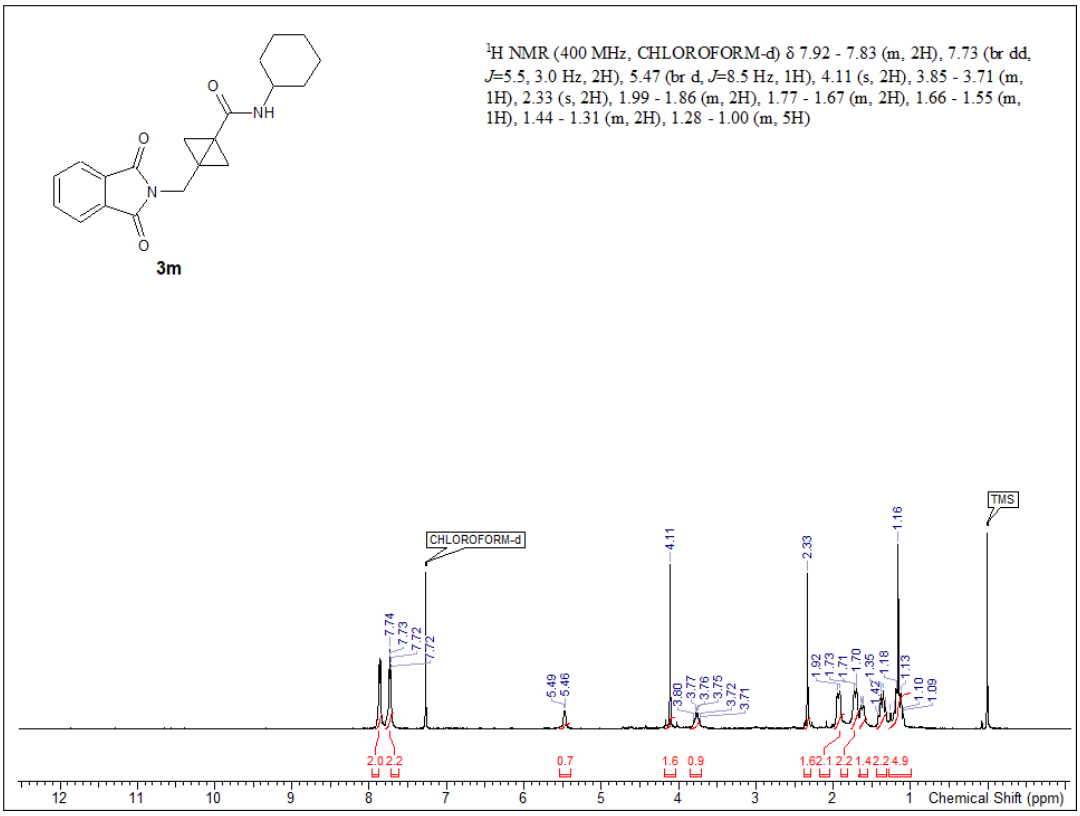
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 209.6, 168.0, 167.9, 133.9, 132.2, 123.2, 49.2, 46.2, 41.7, 39.0, 37.0, 28.0, 27.8, 27.4, 22.7, 12.4

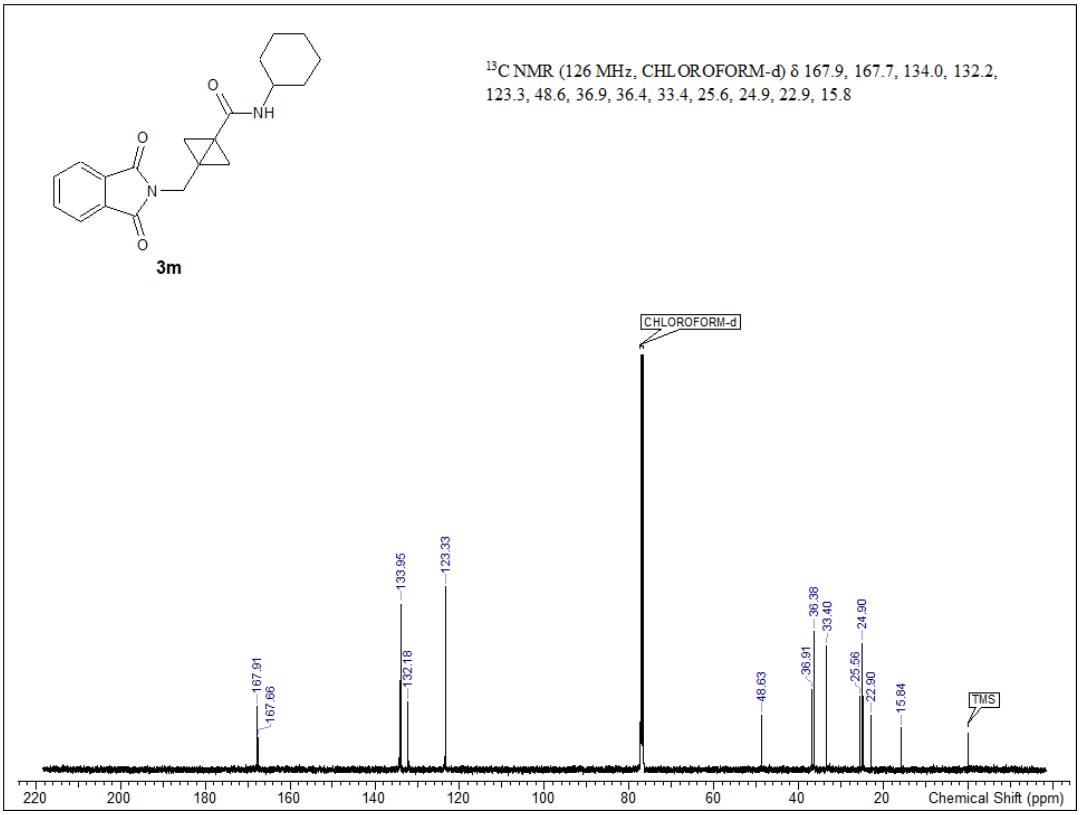

3k
1H NMR (400 MHz, CHLOROFORM-d) δ 7.93 - 7.81 (m, 2H), 7.78 - 7.68 (m, 2H), 4.20 (s, 2H), 3.85 - 3.76 (m, 2H), 3.74 - 3.67 (m, 4H), 3.66 - 3.58 (m, 2H), 2.31 (s, 2H), 1.30 (s, 2H)
CHLOROFORM-d
TMS
Chemical Shift (ppm)

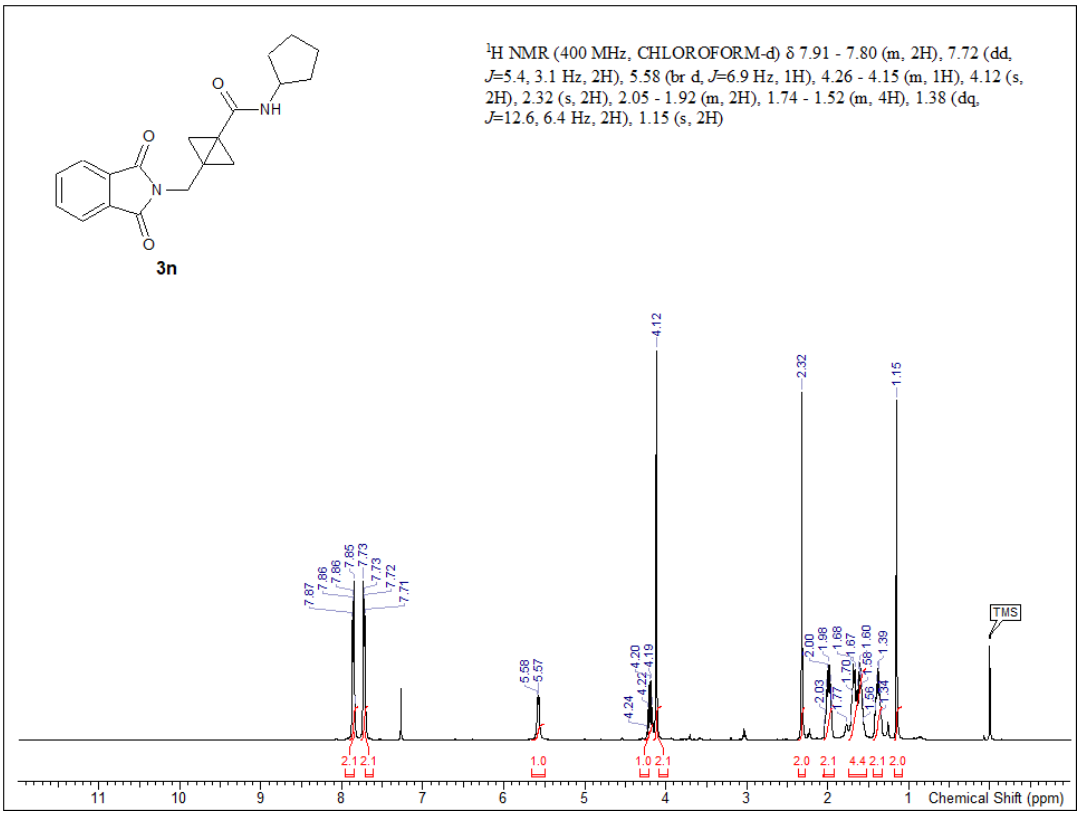

3k
13C NMR (126 MHz, DMSO-d6) δ 167.0, 166.6, 133.9, 131.4, 122.6, 65.8, 50.2, 44.2, 37.9, 35.7, 22.1, 21.6, 11.5
DMSO-d6
TMS
Chemical Shift (ppm)

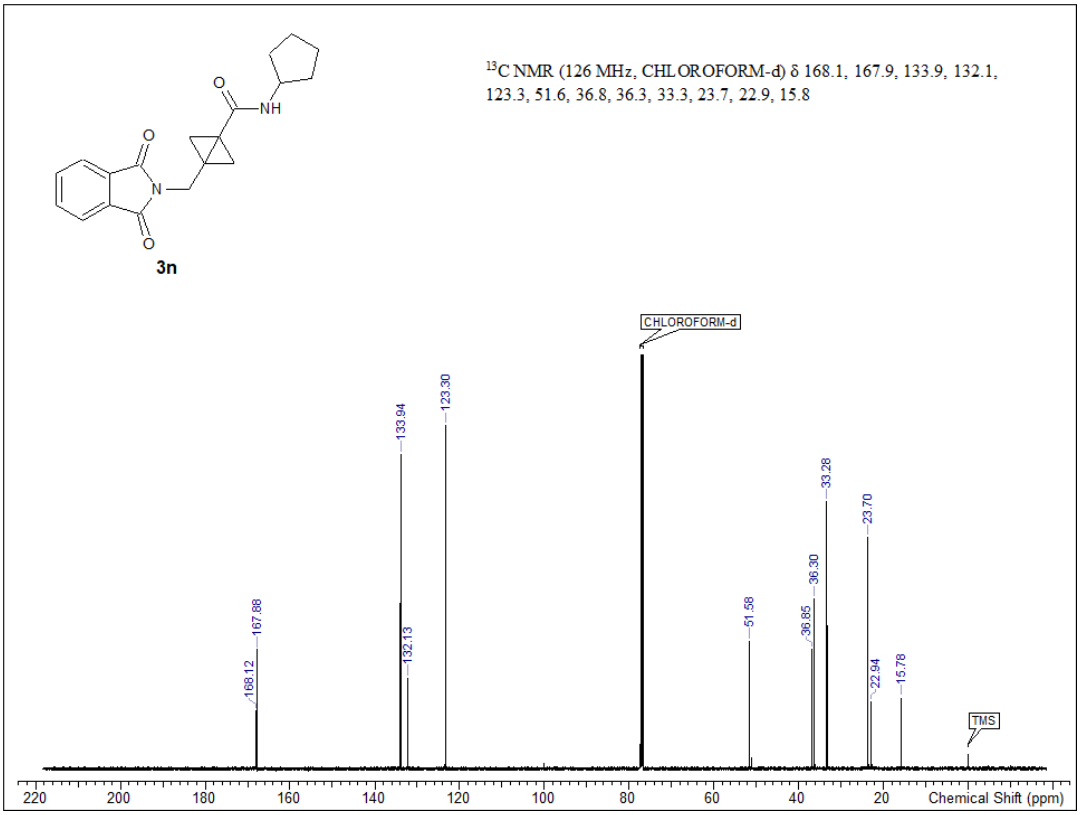

O
N
S
O
N
O
3l
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.90 - 7.84 (m, 2H), 7.76 - 7.68 (m, 2H), 4.20 (s, 2H), 4.12 - 3.80 (m, 4H), 2.70 - 2.62 (m, 4H), 2.30 (s, 2H), 1.28 (s, 2H)
4.20
2.30
1.28
TMS
CHLOROFORM-d
7.88
7.87
7.86
7.86
7.74
7.73
7.73
7.72
7.89
7.71
4.07
3.87
2.67
2.66
2.64
1.9 2.0
2.0 4.3
3.9
1.9
2.1
11 10 9 8 7 6 5 4 3 2 1
Chemical Shift (ppm)

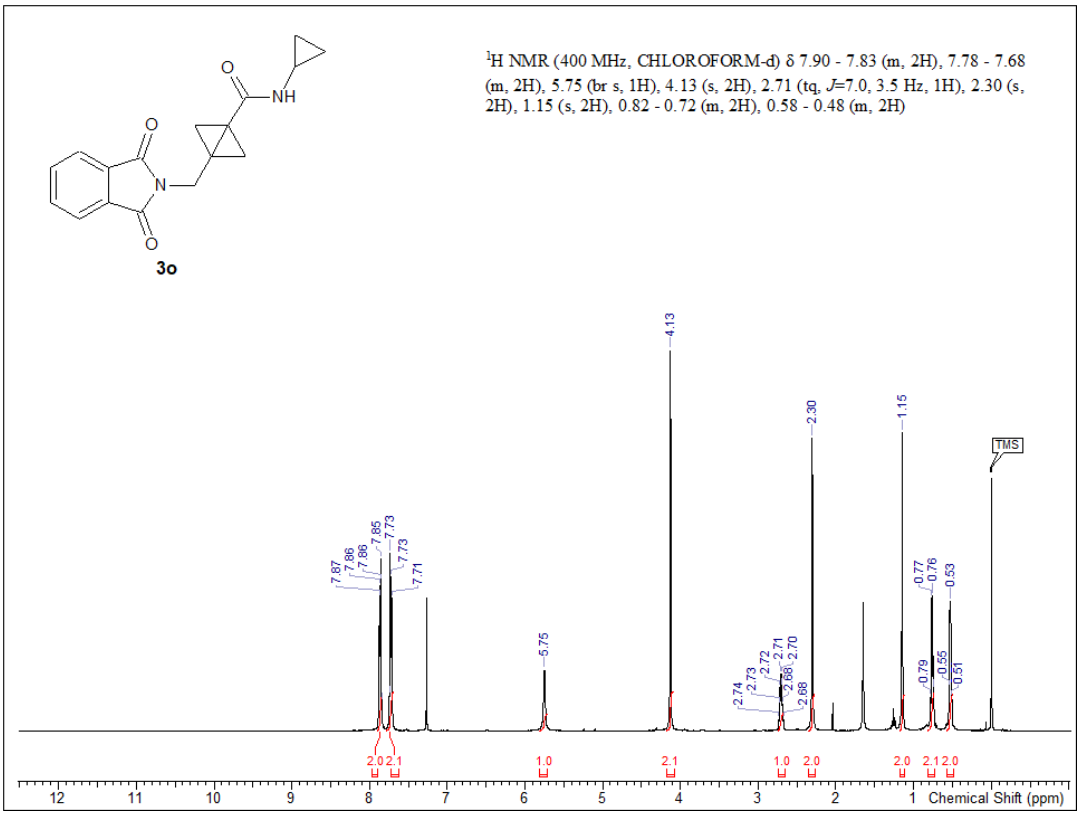

O
N
S
O
N
O
3l
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 168.1, 168.0, 133.9, 132.2, 123.3, 49.3, 44.7, 39.0, 36.8, 28.2, 27.3, 22.9, 12.4
CHLOROFORM-d
168.13
168.01
133.93
132.23
123.26
49.33
44.67
39.04
36.83
28.19
27.28
22.94
12.39
TMS
220 200 180 160 140 120 100 80 60 40 20
Chemical Shift (ppm)

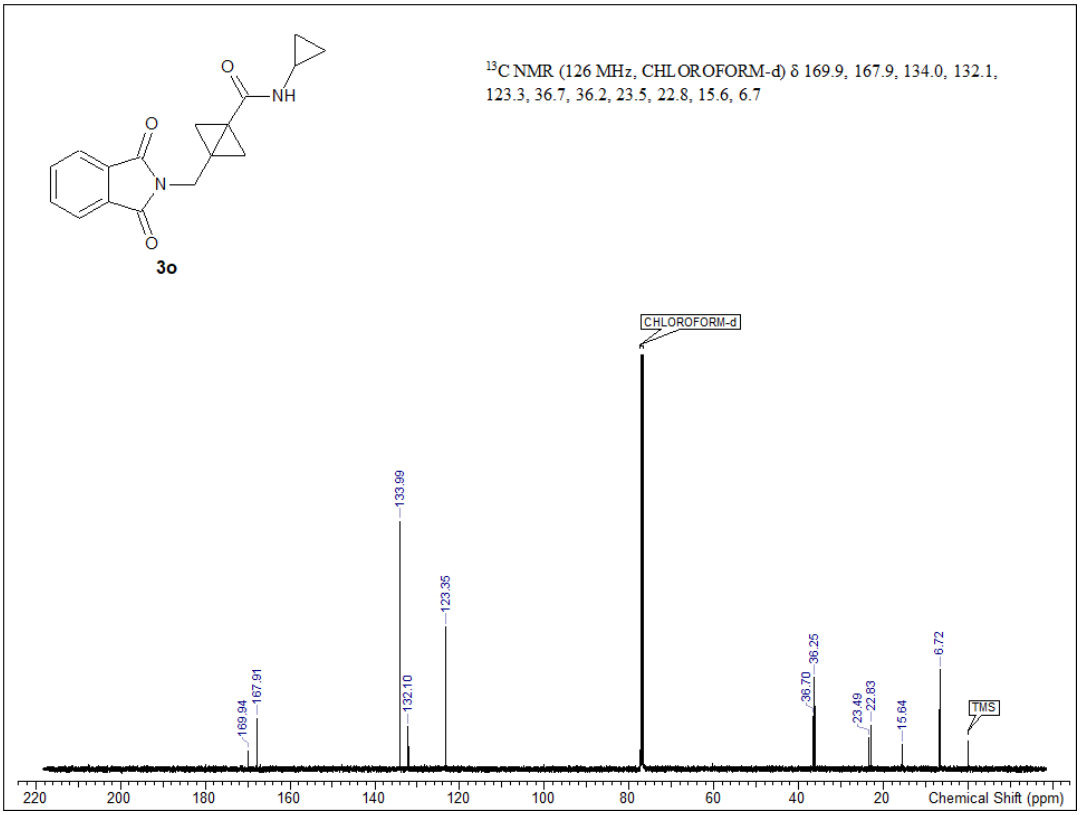

3m
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.92 - 7.83 (m, 2H), 7.73 (br dd, J=5.5, 3.0 Hz, 2H), 5.47 (br d, J=8.5 Hz, 1H), 4.11 (s, 2H), 3.85 - 3.71 (m, 1H), 2.33 (s, 2H), 1.99 - 1.86 (m, 2H), 1.77 - 1.67 (m, 2H), 1.66 - 1.55 (m, 1H), 1.44 - 1.31 (m, 2H), 1.28 - 1.00 (m, 5H)
CHLOROFORM-d
TMS
Chemical Shift (ppm)

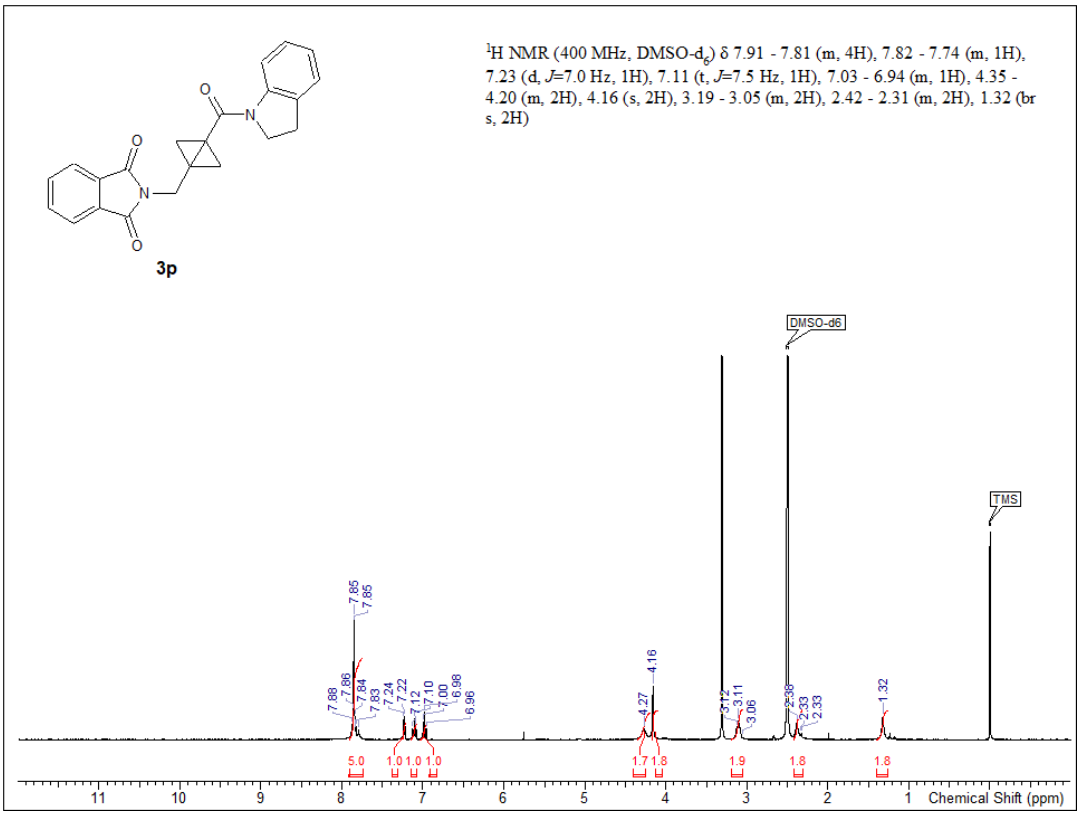

3m
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 167.9, 167.7, 134.0, 132.2, 123.3, 48.6, 36.9, 36.4, 33.4, 25.6, 24.9, 22.9, 15.8
CHLOROFORM-d
TMS
Chemical Shift (ppm)


3n
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.91 - 7.80 (m, 2H), 7.72 (dd, J=5.4, 3.1 Hz, 2H), 5.58 (br d, J=6.9 Hz, 1H), 4.26 - 4.15 (m, 1H), 4.12 (s, 2H), 2.32 (s, 2H), 2.05 - 1.92 (m, 2H), 1.74 - 1.52 (m, 4H), 1.38 (dq, J=12.6, 6.4 Hz, 2H), 1.15 (s, 2H)
TMS
Chemical Shift (ppm)

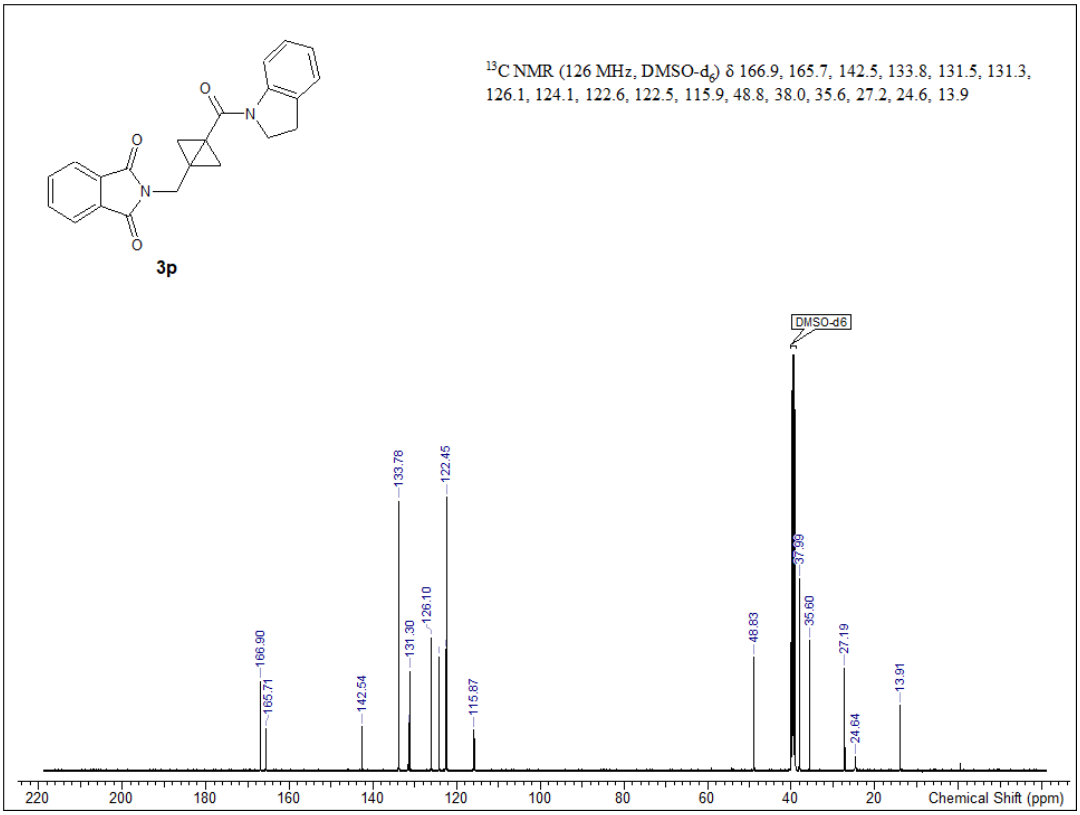

3n
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 168.1, 167.9, 133.9, 132.1, 123.3, 51.6, 36.8, 36.3, 33.3, 23.7, 22.9, 15.8
CHLOROFORM-d
TMS
Chemical Shift (ppm)


O
NH
O
N
O
3o
[1]H NMR (400 MHz, CHLOROFORM-d) δ 7.90 - 7.83 (m, 2H), 7.78 - 7.68 (m, 2H), 5.75 (br s, 1H), 4.13 (s, 2H), 2.71 (tq, J=7.0, 3.5 Hz, 1H), 2.30 (s, 2H), 1.15 (s, 2H), 0.82 - 0.72 (m, 2H), 0.58 - 0.48 (m, 2H)
4.13
2.30
1.15
TMS
7.87
7.86
7.86
7.85
7.73
7.73
7.71
5.75
2.74
2.73
2.72
2.71
2.70
2.68
0.77
0.76
0.79
0.65
0.53
0.51
2.0 2.1
1.0
2.1
1.0 2.0
2.0 2.1 2.0
12 11 10 9 8 7 6 5 4 3 2 1 Chemical Shift (ppm)

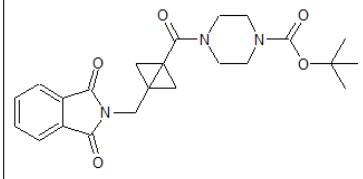

O
NH
O
N
O
3o
[13]C NMR (126 MHz, CHLOROFORM-d) δ 169.9, 167.9, 134.0, 132.1, 123.3, 36.7, 36.2, 23.5, 22.8, 15.6, 6.7
CHLOROFORM-d
133.99
123.35
132.10
169.94
167.91
36.25
36.70
23.49
22.83
15.64
6.72
TMS
220 200 180 160 140 120 100 80 60 40 20 Chemical Shift (ppm)



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 - 7.81 (m, 4H), 7.82 - 7.74 (m, 1H), 7.23 (d, *J*=7.0 Hz, 1H), 7.11 (t, *J*=7.5 Hz, 1H), 7.03 - 6.94 (m, 1H), 4.35 - 4.20 (m, 2H), 4.16 (s, 2H), 3.19 - 3.05 (m, 2H), 2.42 - 2.31 (m, 2H), 1.32 (br s, 2H)

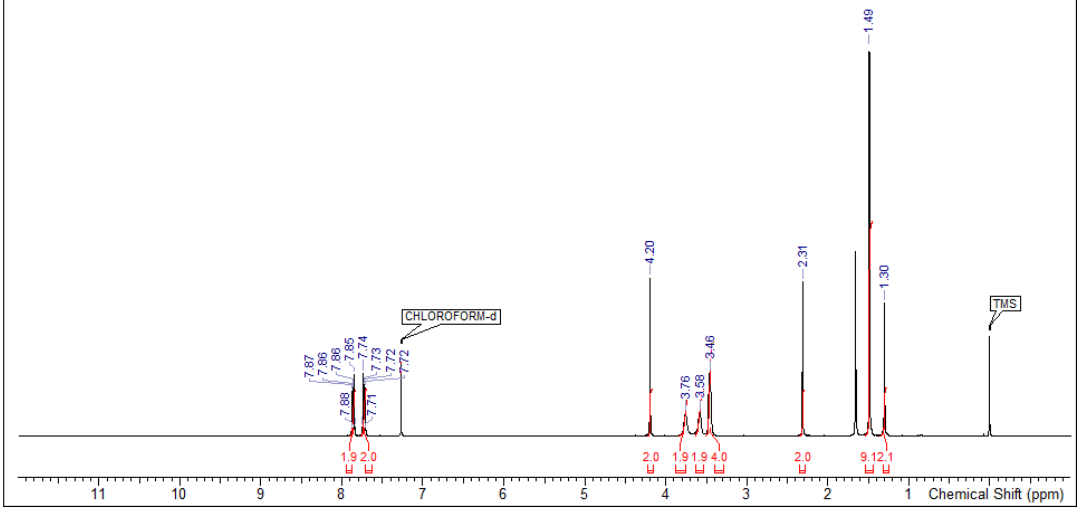


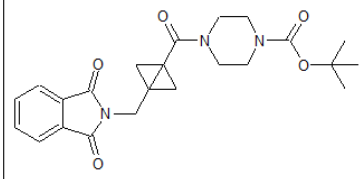
^{13}C NMR (126 MHz, DMSO-d_6) δ 166.9, 165.7, 142.5, 133.8, 131.5, 131.3, 126.1, 124.1, 122.6, 122.5, 115.9, 48.8, 38.0, 35.6, 27.2, 24.6, 13.9



3q

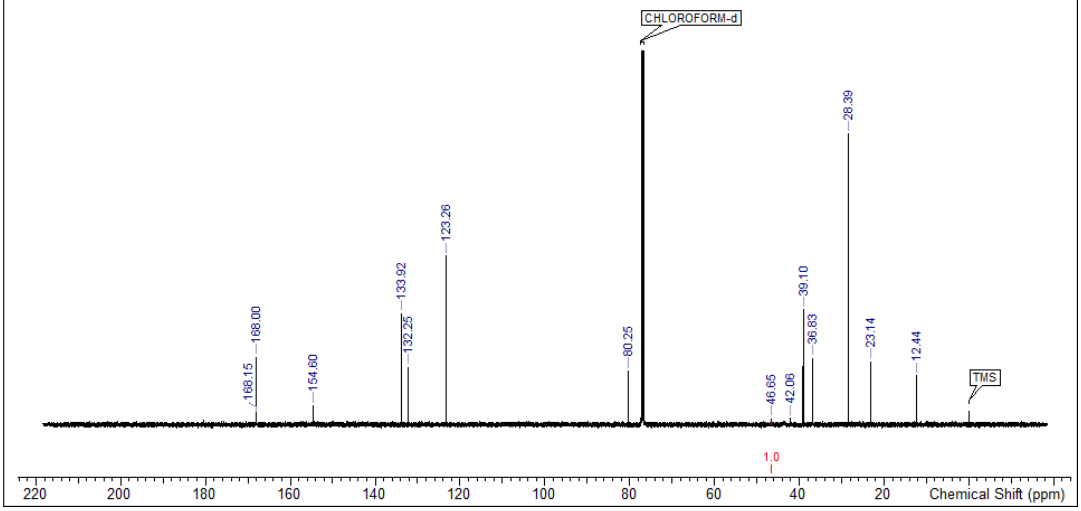
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.90 - 7.83 (m, 2H), 7.77 - 7.68 (m, 2H), 4.20 (s, 2H), 3.84 - 3.71 (m, 2H), 3.64 - 3.53 (m, 2H), 3.51 - 3.40 (m, 4H), 2.31 (s, 2H), 1.49 (s, 9H), 1.30 (s, 2H)

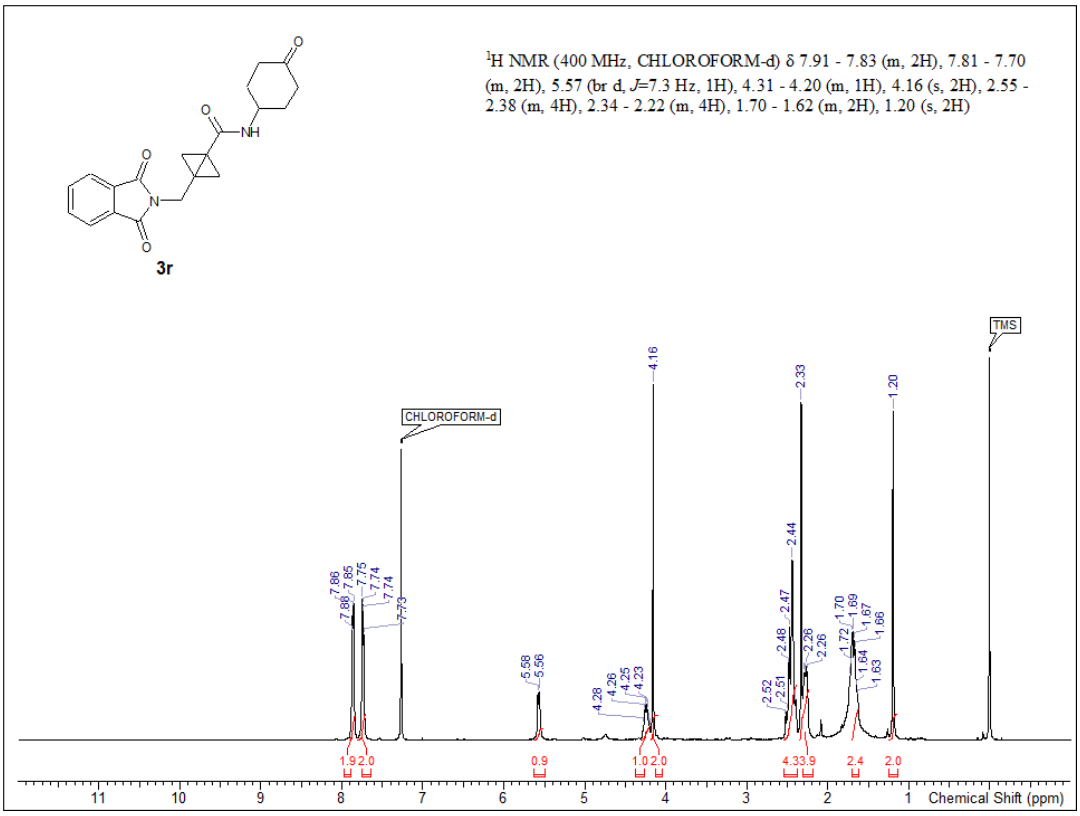


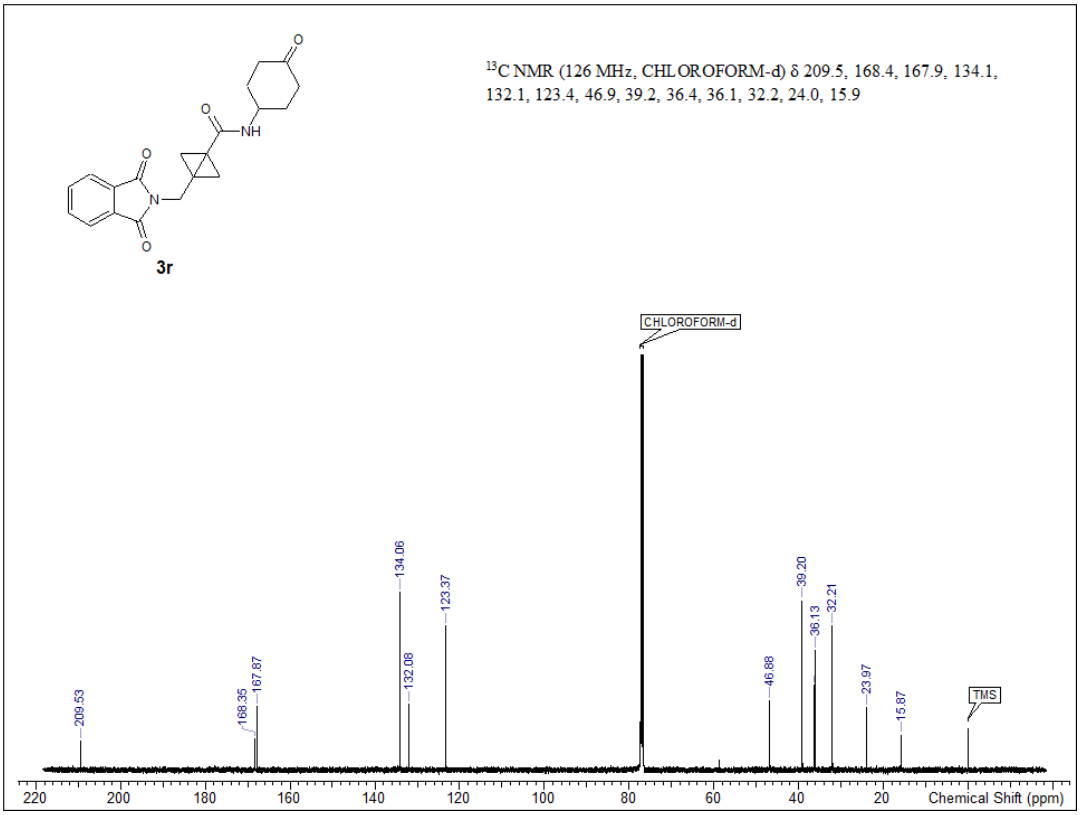


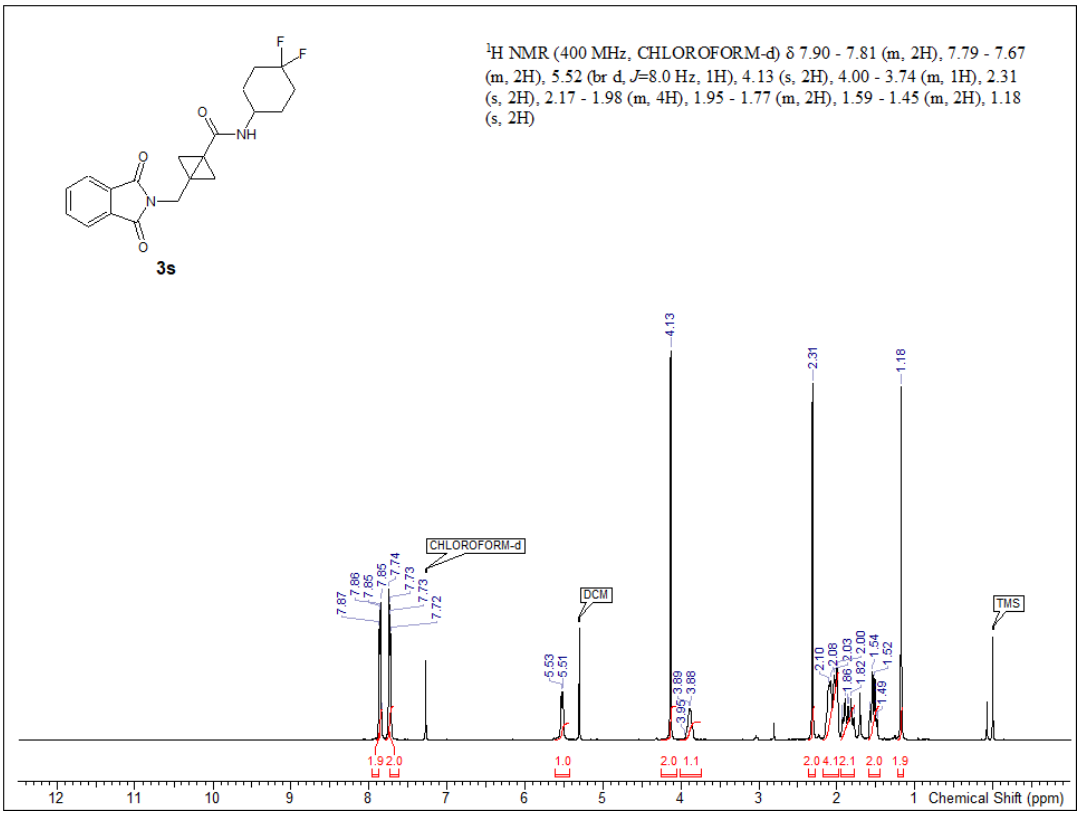
3q

^{13}C NMR (126 MHz, CHLOROFORM-d) δ 168.2, 168.0, 154.6, 133.9, 132.2, 123.3, 80.2, 46.7, 42.1, 39.1, 36.8, 28.4, 23.1, 12.4

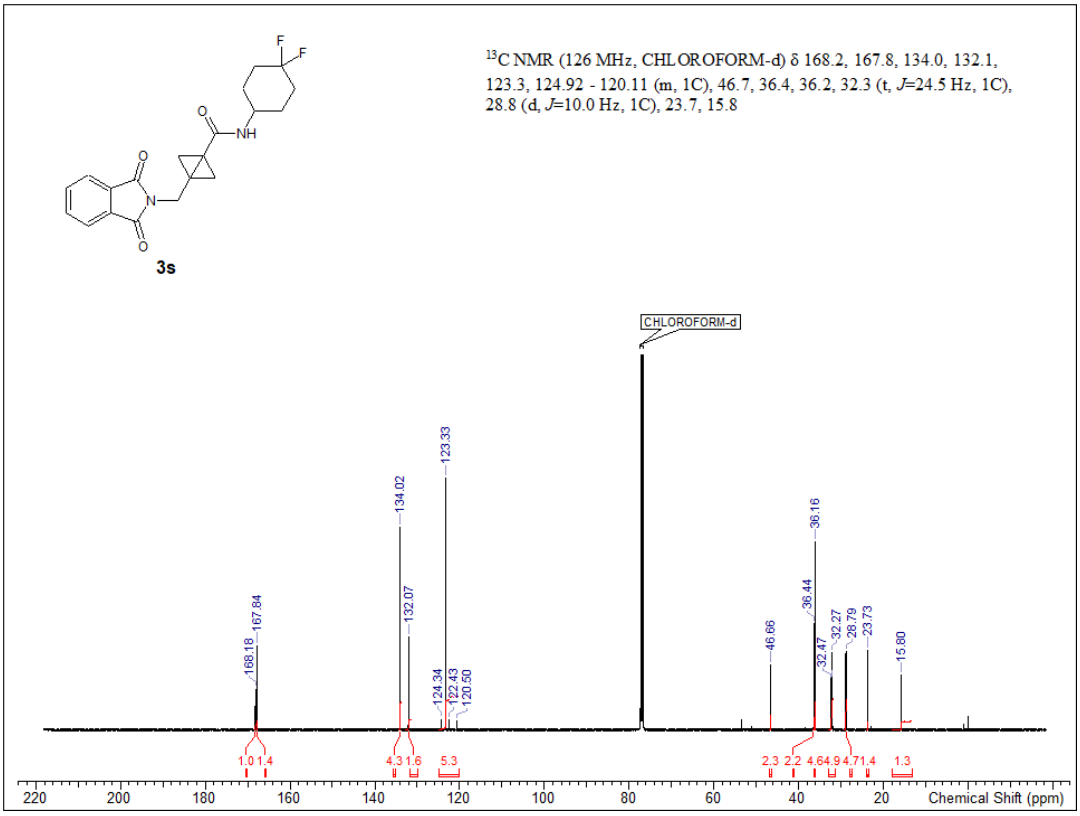



3r
1H NMR (400 MHz, CHLOROFORM-d) δ 7.91 - 7.83 (m, 2H), 7.81 - 7.70 (m, 2H), 5.57 (br d, J=7.3 Hz, 1H), 4.31 - 4.20 (m, 1H), 4.16 (s, 2H), 2.55 - 2.38 (m, 4H), 2.34 - 2.22 (m, 4H), 1.70 - 1.62 (m, 2H), 1.20 (s, 2H)
TMS
CHLOROFORM-d
Chemical Shift (ppm)

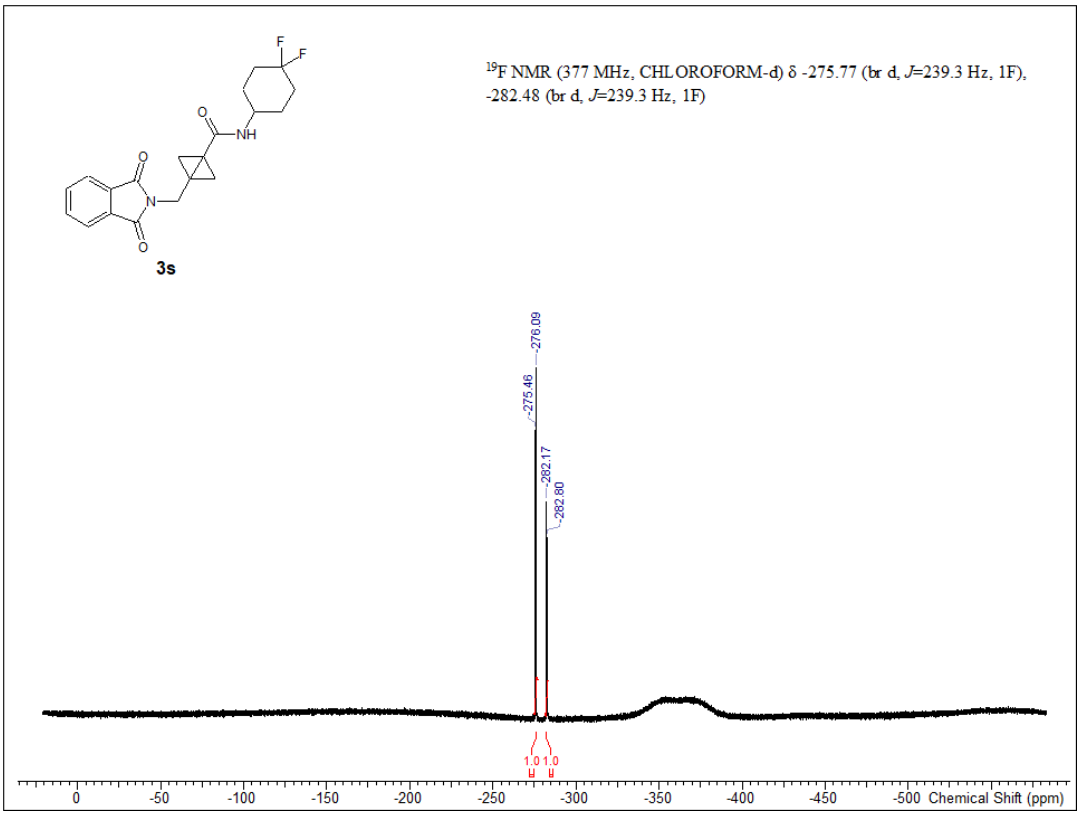

3r
13C NMR (126 MHz, CHLOROFORM-d) δ 209.5, 168.4, 167.9, 134.1, 132.1, 123.4, 46.9, 39.2, 36.4, 36.1, 32.2, 24.0, 15.9
CHLOROFORM-d
TMS
Chemical Shift (ppm)



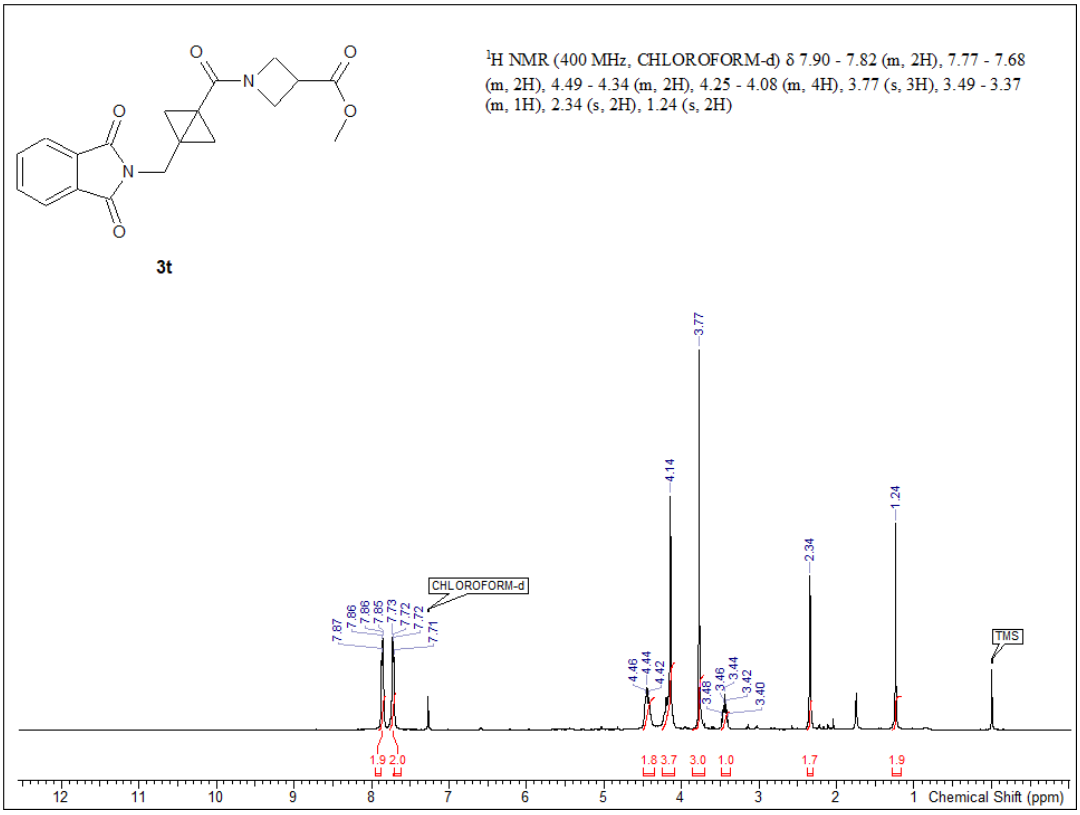
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.90 - 7.81 (m, 2H), 7.79 - 7.67 (m, 2H), 5.52 (br d, *J*=8.0 Hz, 1H), 4.13 (s, 2H), 4.00 - 3.74 (m, 1H), 2.31 (s, 2H), 2.17 - 1.98 (m, 4H), 1.95 - 1.77 (m, 2H), 1.59 - 1.45 (m, 2H), 1.18 (s, 2H)

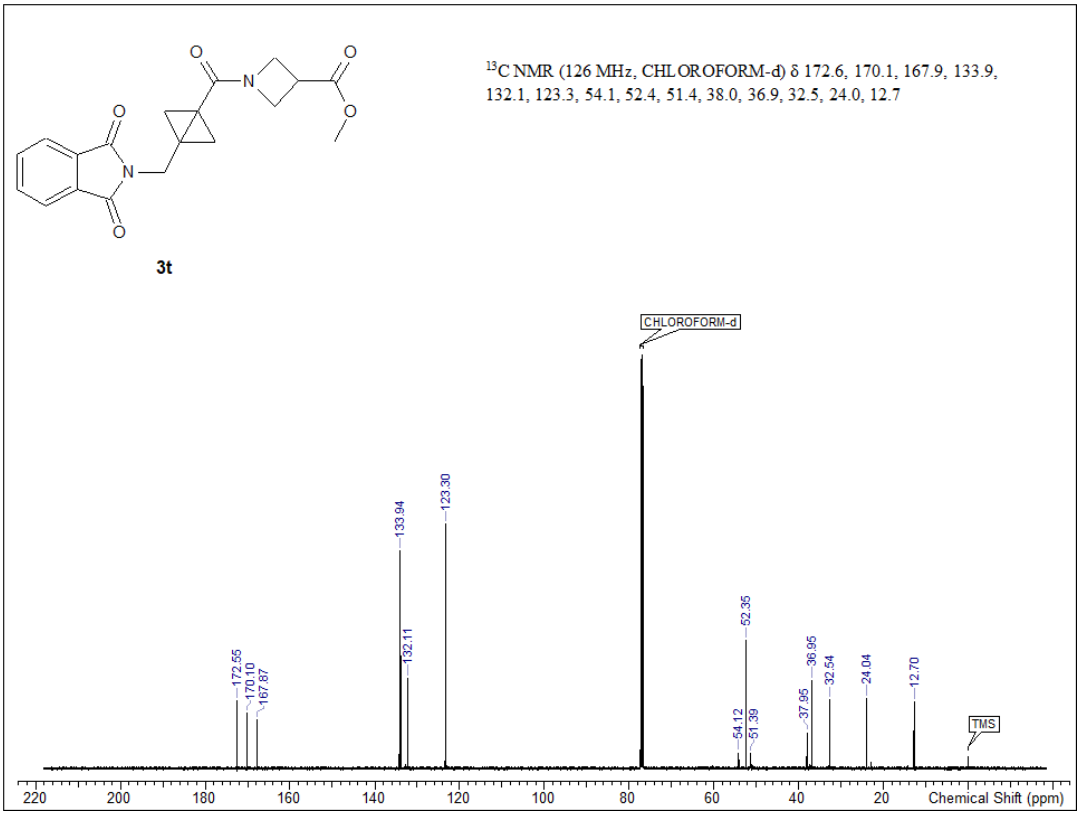


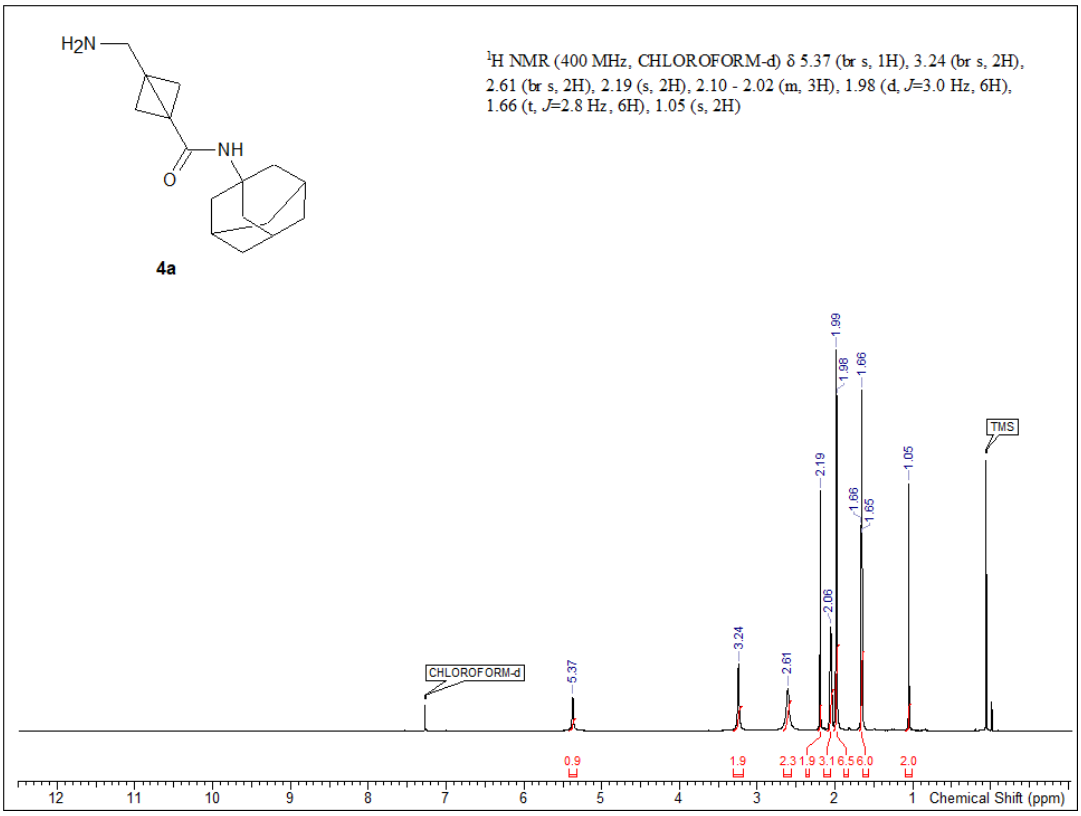
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 168.2, 167.8, 134.0, 132.1, 123.3, 124.92 - 120.11 (m, 1C), 46.7, 36.4, 36.2, 32.3 (t, *J*=24.5 Hz, 1C), 28.8 (d, *J*=10.0 Hz, 1C), 23.7, 15.8

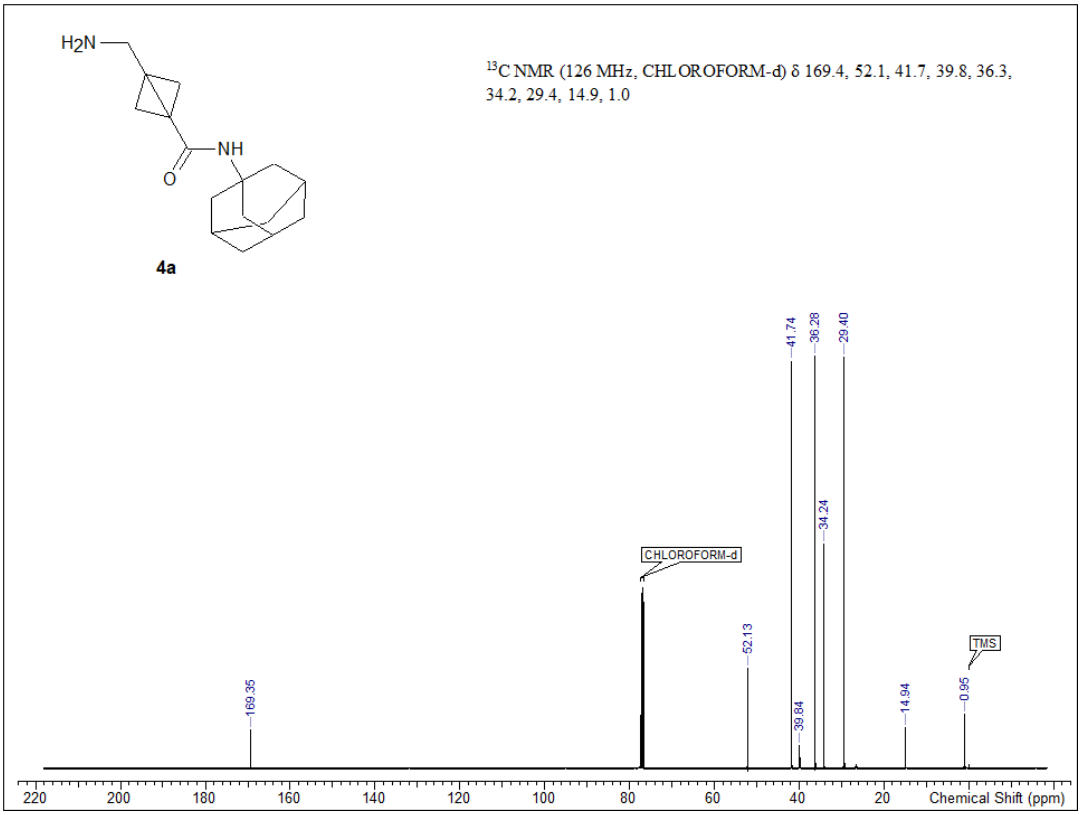


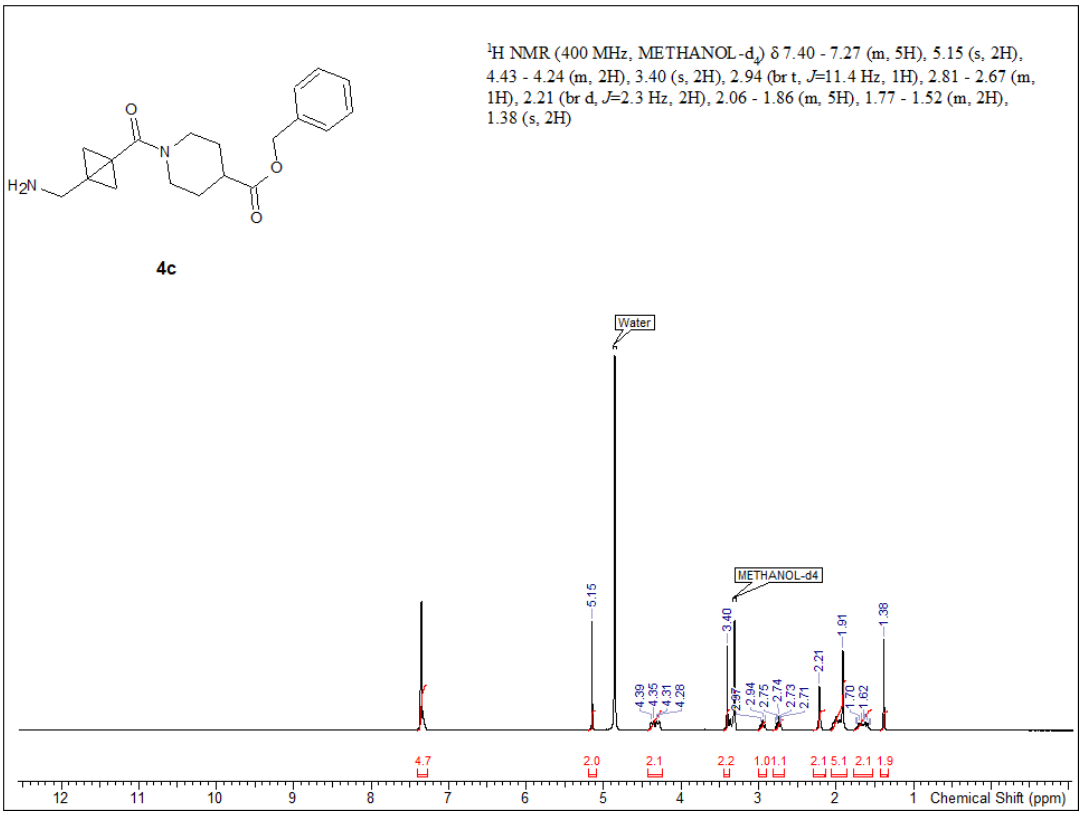
^{19}F NMR (377 MHz, CHLOROFORM-d) δ -275.77 (br d, *J*=239.3 Hz, 1F), -282.48 (br d, *J*=239.3 Hz, 1F)


3t
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.90 - 7.82 (m, 2H), 7.77 - 7.68 (m, 2H), 4.49 - 4.34 (m, 2H), 4.25 - 4.08 (m, 4H), 3.77 (s, 3H), 3.49 - 3.37 (m, 1H), 2.34 (s, 2H), 1.24 (s, 2H)
CHLOROFORM-d
TMS
Chemical Shift (ppm)


3t
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 172.6, 170.1, 167.9, 133.9, 132.1, 123.3, 54.1, 52.4, 51.4, 38.0, 36.9, 32.5, 24.0, 12.7
CHLOROFORM-d
TMS
Chemical Shift (ppm)

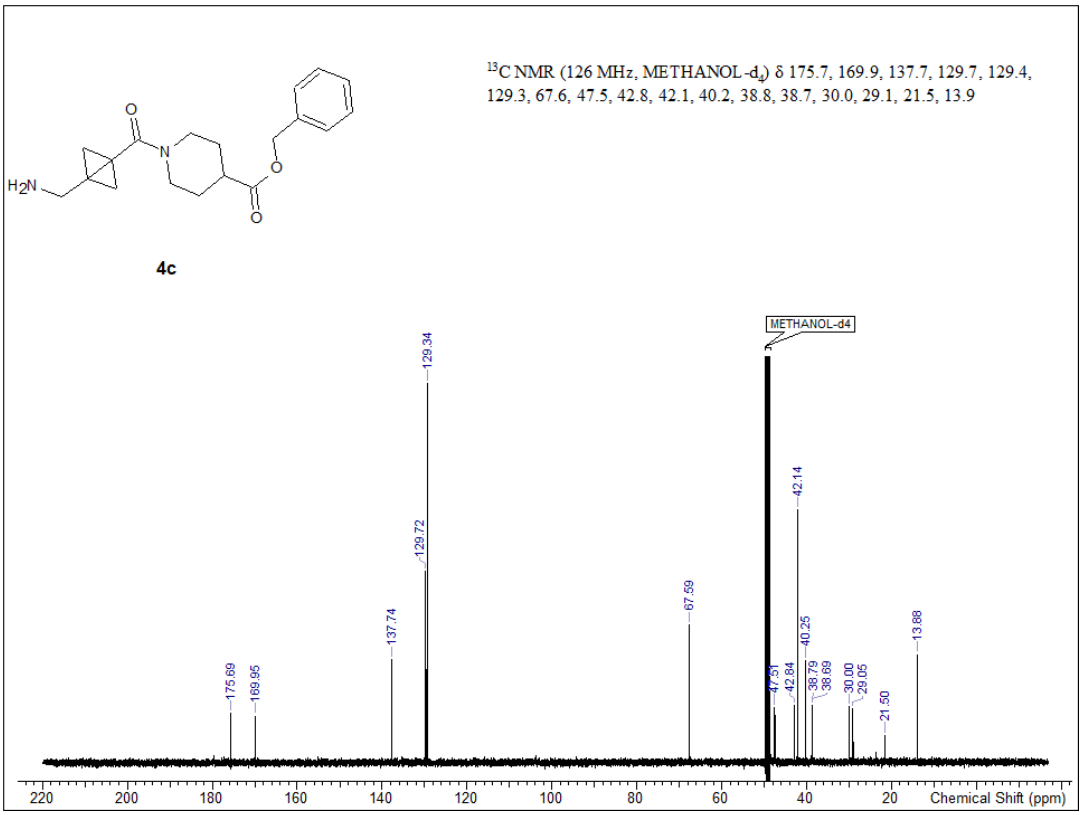

H2N
NH
O
4a
1H NMR (400 MHz, CHLOROFORM-d) δ 5.37 (br s, 1H), 3.24 (br s, 2H), 2.61 (br s, 2H), 2.19 (s, 2H), 2.10 - 2.02 (m, 3H), 1.98 (d, J=3.0 Hz, 6H), 1.66 (t, J=2.8 Hz, 6H), 1.05 (s, 2H)
CHLOROFORM-d
TMS
Chemical Shift (ppm)


H2N
NH
O
4a
13C NMR (126 MHz, CHLOROFORM-d) δ 169.4, 52.1, 41.7, 39.8, 36.3, 34.2, 29.4, 14.9, 1.0
CHLOROFORM-d
TMS
Chemical Shift (ppm)



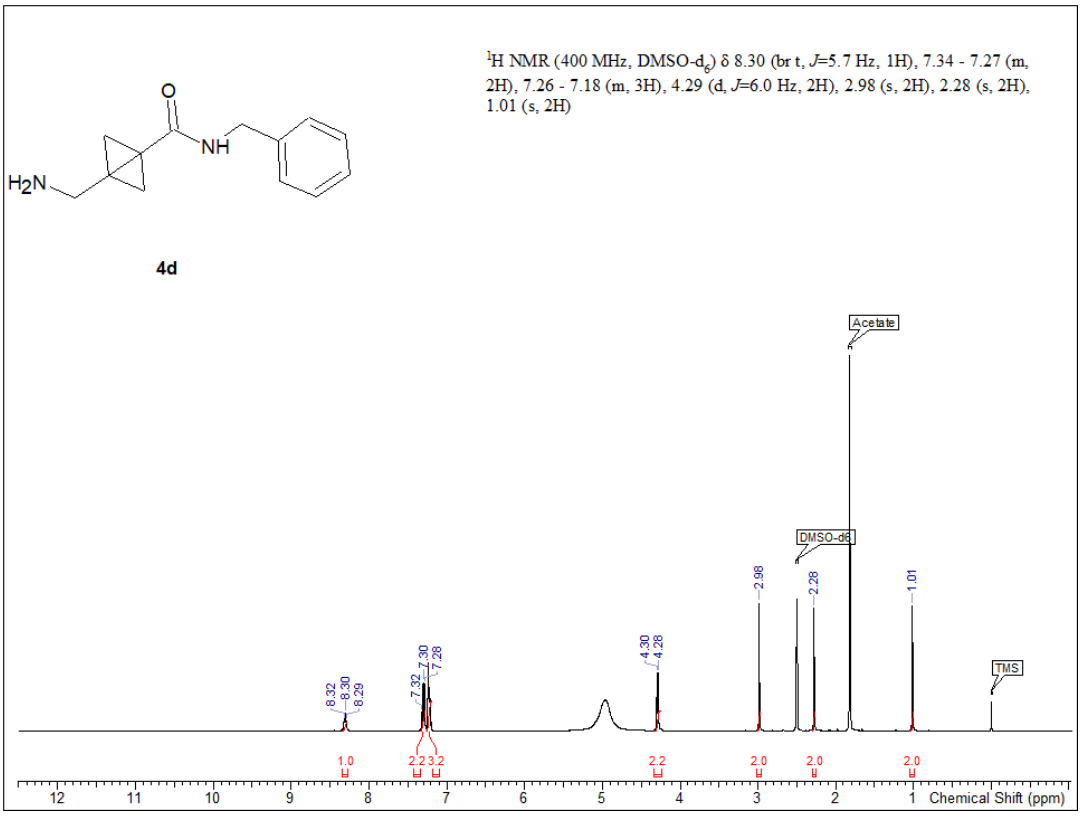
^{1}H NMR (400 MHz, METHANOL-d_4) δ 7.40 - 7.27 (m, 5H), 5.15 (s, 2H), 4.43 - 4.24 (m, 2H), 3.40 (s, 2H), 2.94 (br t, *J*=11.4 Hz, 1H), 2.81 - 2.67 (m, 1H), 2.21 (br d, *J*=2.3 Hz, 2H), 2.06 - 1.86 (m, 5H), 1.77 - 1.52 (m, 2H), 1.38 (s, 2H)

4c



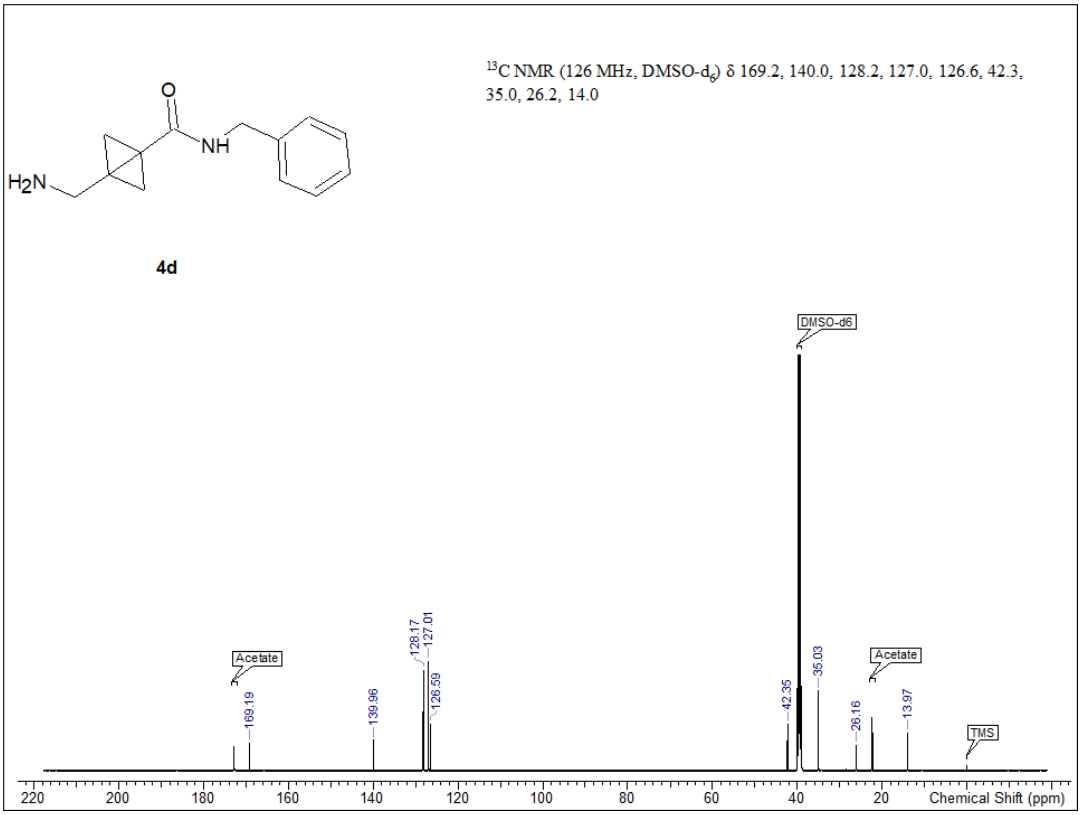
^{13}C NMR (126 MHz, METHANOL-d_4) δ 175.7, 169.9, 137.7, 129.7, 129.4, 129.3, 67.6, 47.5, 42.8, 42.1, 40.2, 38.8, 38.7, 30.0, 29.1, 21.5, 13.9

4c



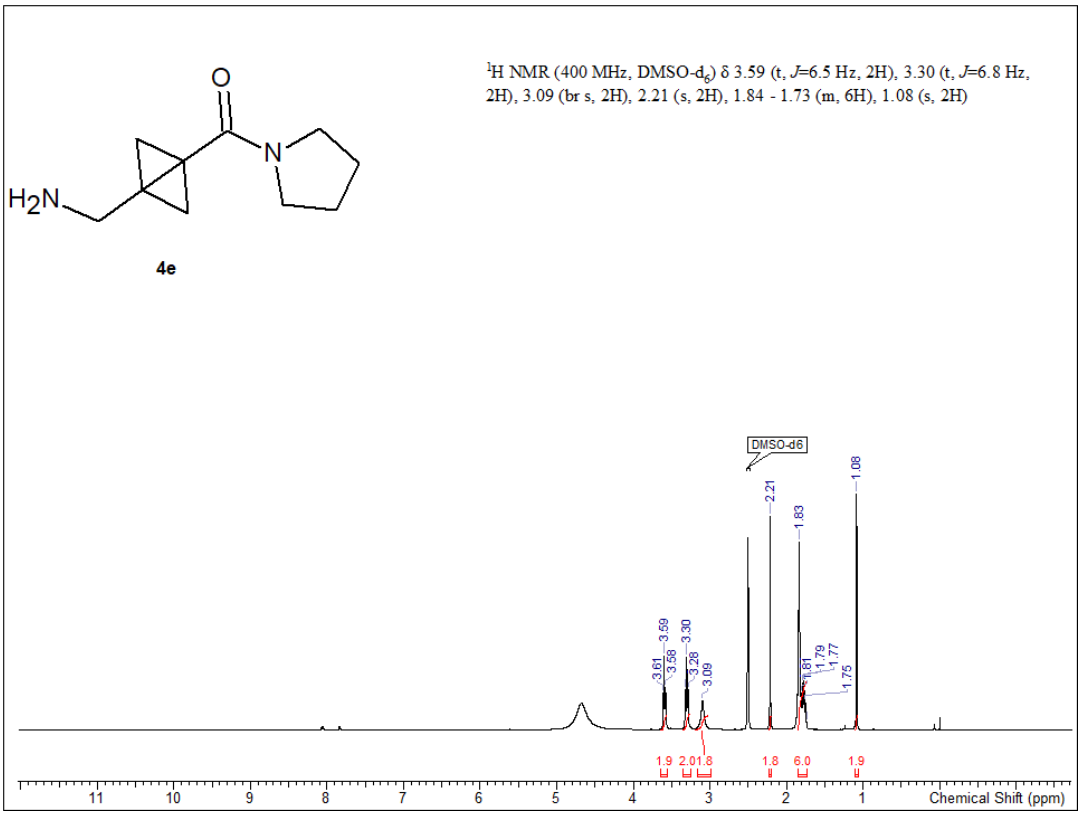
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (br t, *J*=5.7 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.26 - 7.18 (m, 3H), 4.29 (d, *J*=6.0 Hz, 2H), 2.98 (s, 2H), 2.28 (s, 2H), 1.01 (s, 2H)

4d

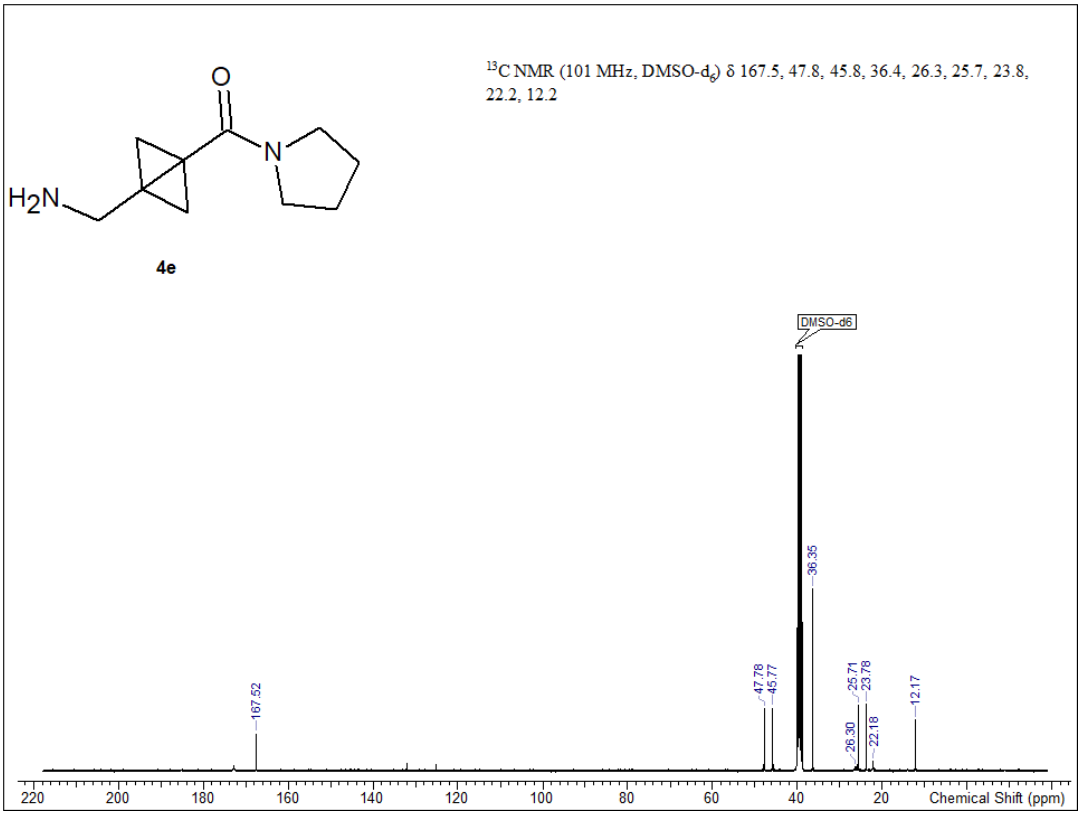


^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2, 140.0, 128.2, 127.0, 126.6, 42.3, 35.0, 26.2, 14.0

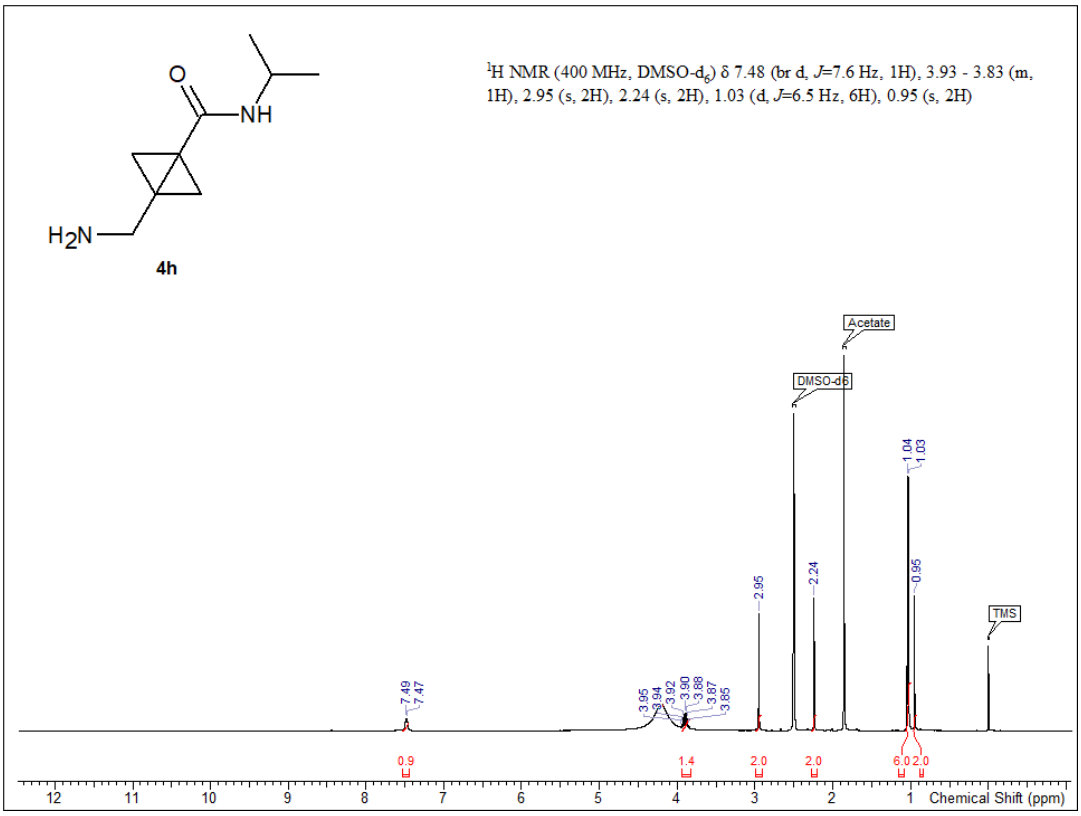
4d



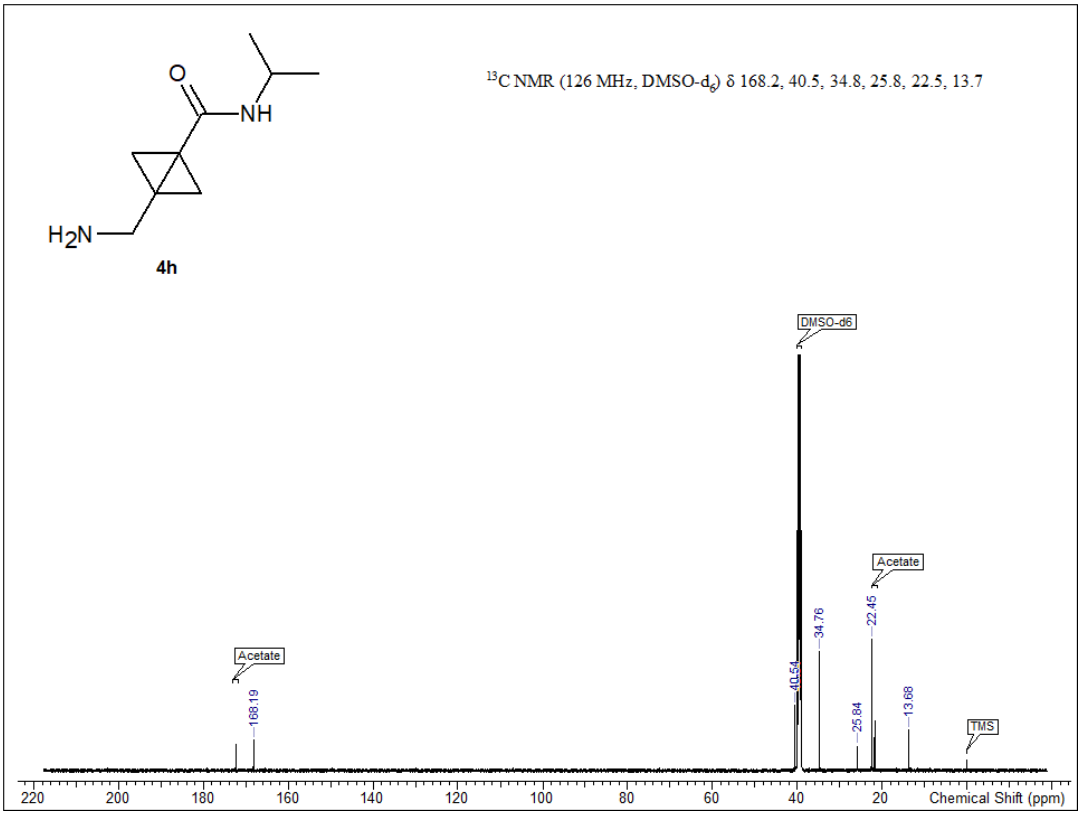
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.59 (t, *J*=6.5 Hz, 2H), 3.30 (t, *J*=6.8 Hz, 2H), 3.09 (br s, 2H), 2.21 (s, 2H), 1.84 - 1.73 (m, 6H), 1.08 (s, 2H)



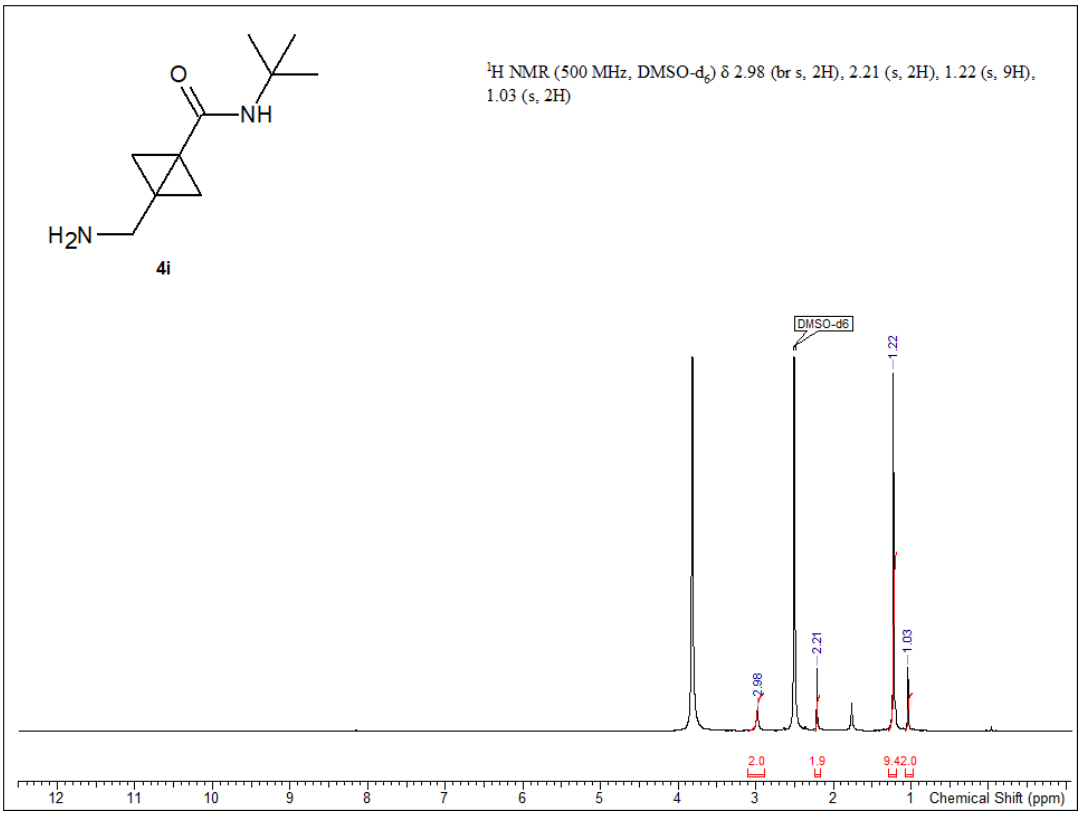
^{13}C NMR (101 MHz, DMSO-d_6) δ 167.5, 47.8, 45.8, 36.4, 26.3, 25.7, 23.8, 22.2, 12.2



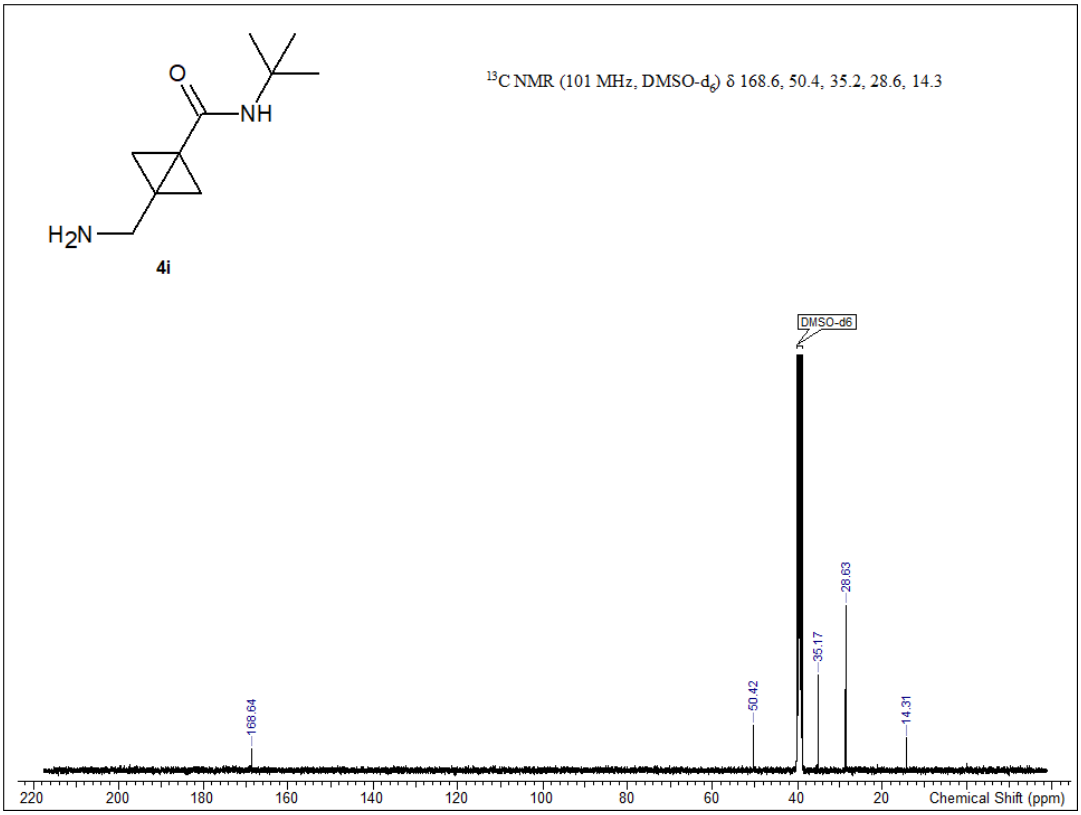
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (br d, *J*=7.6 Hz, 1H), 3.93 - 3.83 (m, 1H), 2.95 (s, 2H), 2.24 (s, 2H), 1.03 (d, *J*=6.5 Hz, 6H), 0.95 (s, 2H)



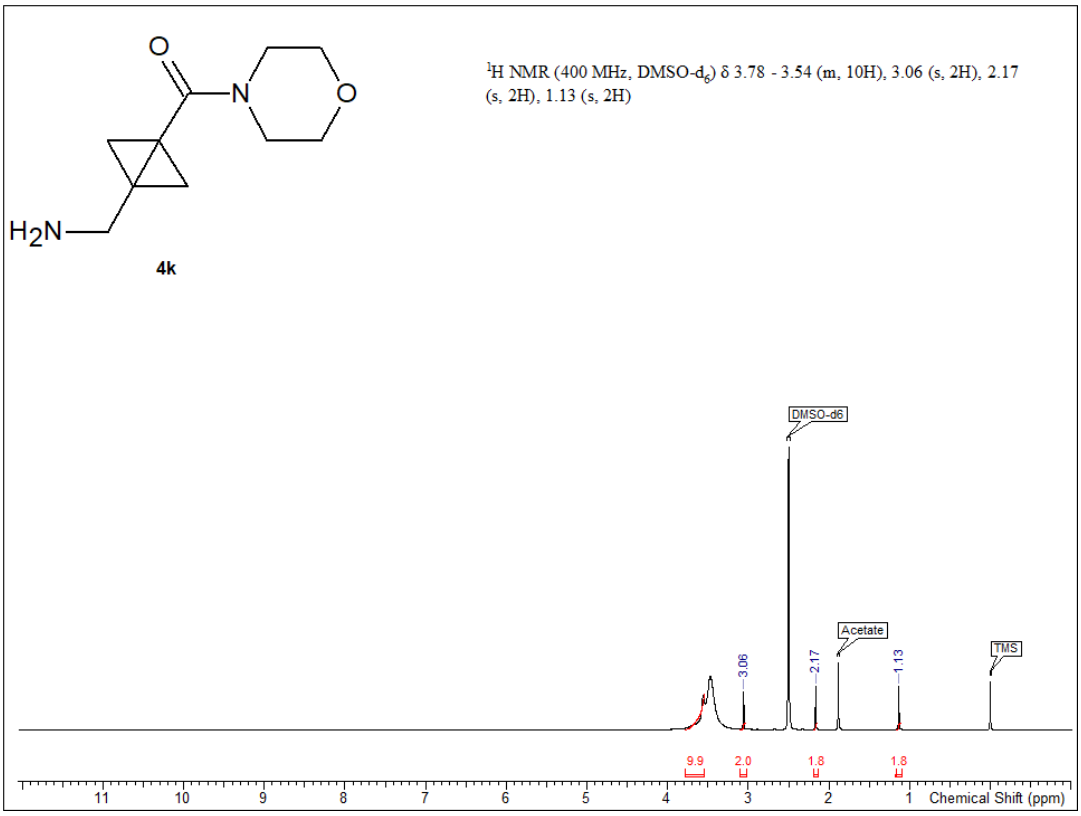
^{13}C NMR (126 MHz, DMSO-d_6) δ 168.2, 40.5, 34.8, 25.8, 22.5, 13.7



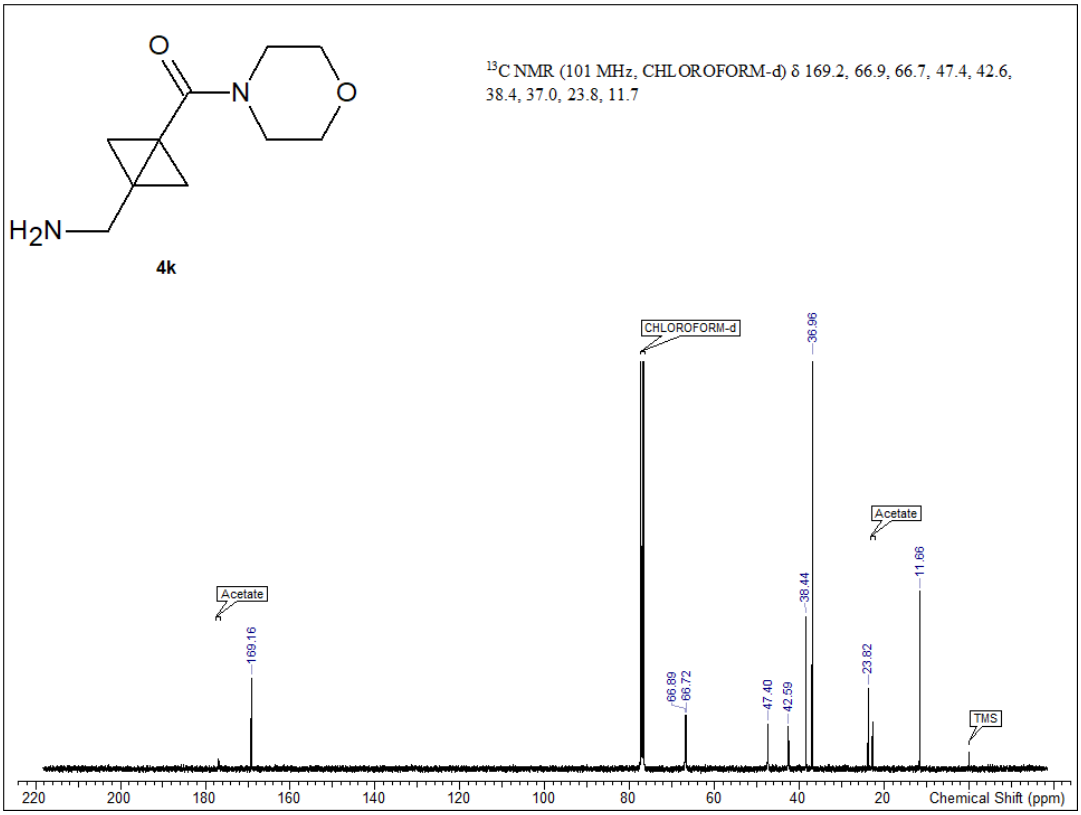
^{1}H NMR (500 MHz, DMSO-d_6) δ 2.98 (br s, 2H), 2.21 (s, 2H), 1.22 (s, 9H), 1.03 (s, 2H)



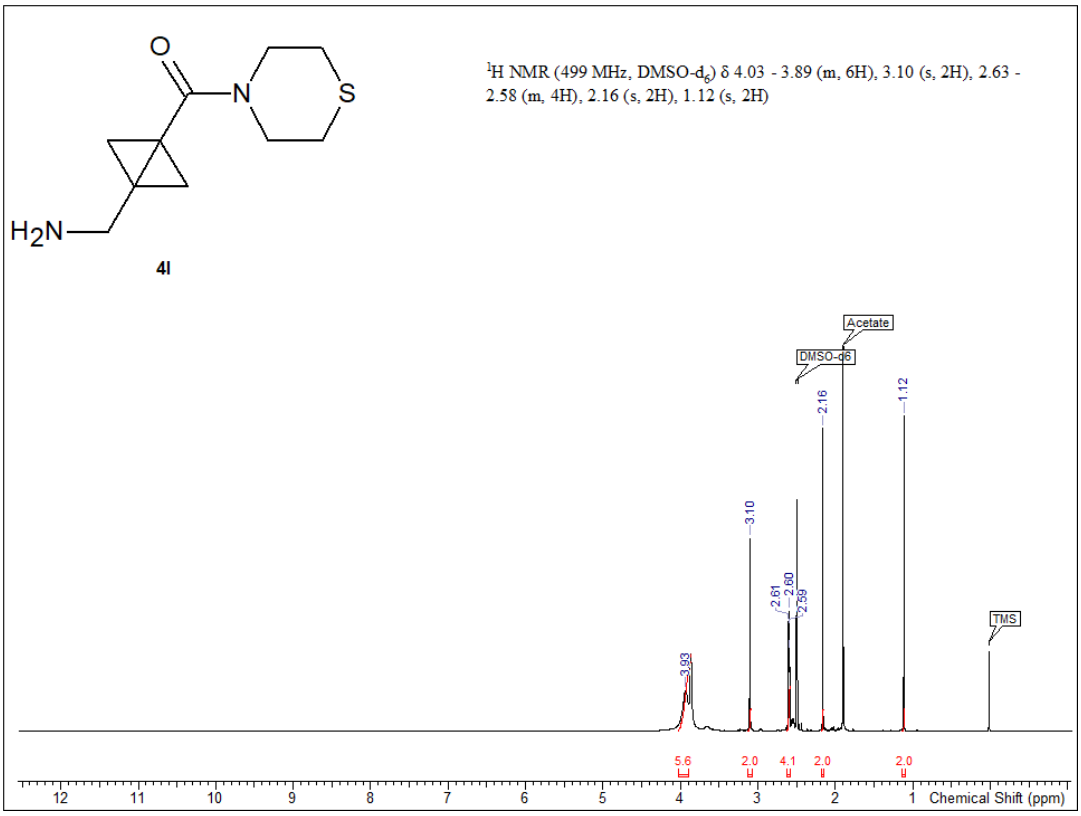
^{13}C NMR (101 MHz, DMSO-d_6) δ 168.6, 50.4, 35.2, 28.6, 14.3



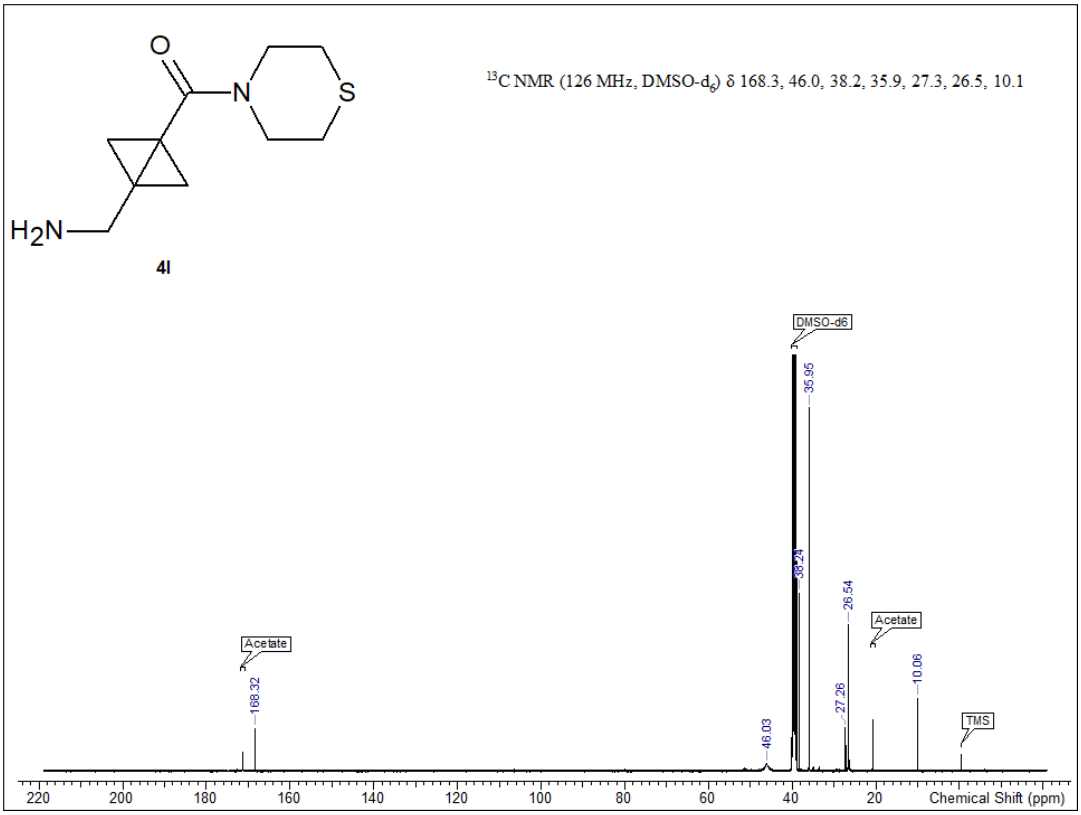
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.78 - 3.54 (m, 10H), 3.06 (s, 2H), 2.17 (s, 2H), 1.13 (s, 2H)



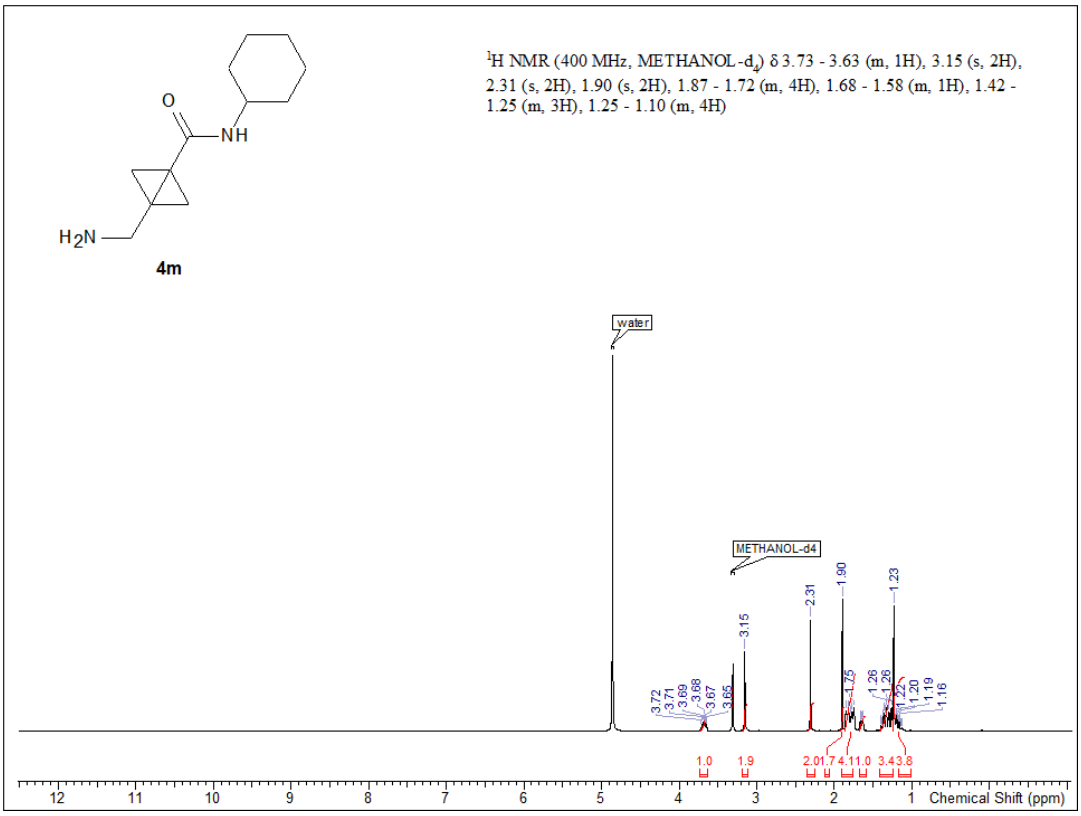
^{13}C NMR (101 MHz, CHLOROFORM-d) δ 169.2, 66.9, 66.7, 47.4, 42.6, 38.4, 37.0, 23.8, 11.7



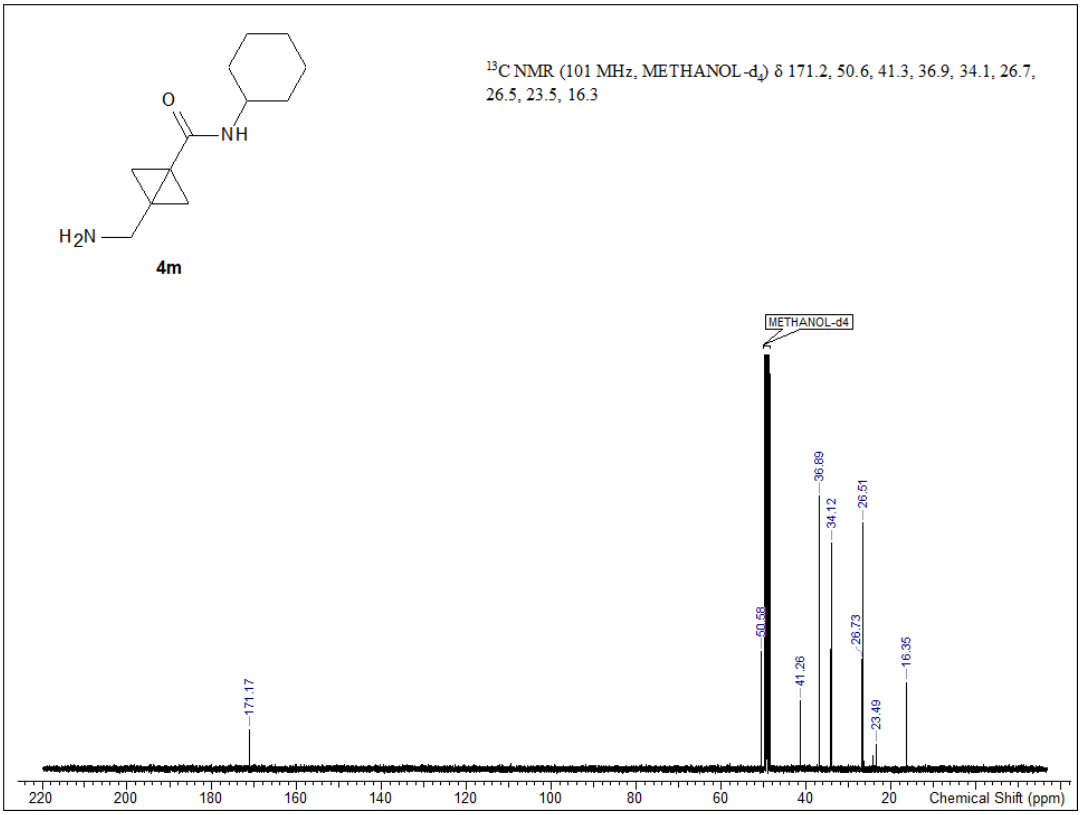
^{1}H NMR (499 MHz, DMSO-d_6) δ 4.03 - 3.89 (m, 6H), 3.10 (s, 2H), 2.63 - 2.58 (m, 4H), 2.16 (s, 2H), 1.12 (s, 2H)



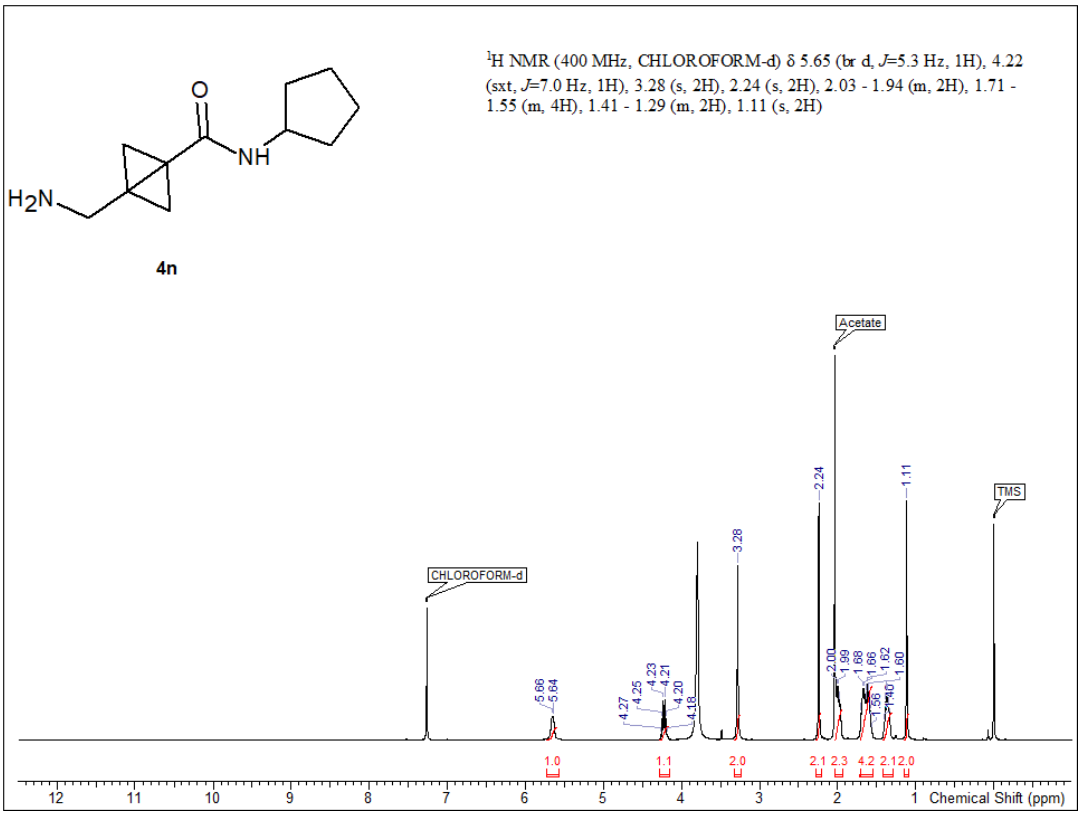
^{13}C NMR (126 MHz, DMSO-d_6) δ 168.3, 46.0, 38.2, 35.9, 27.3, 26.5, 10.1



^{1}H NMR (400 MHz, METHANOL-d_4) δ 3.73 - 3.63 (m, 1H), 3.15 (s, 2H), 2.31 (s, 2H), 1.90 (s, 2H), 1.87 - 1.72 (m, 4H), 1.68 - 1.58 (m, 1H), 1.42 - 1.25 (m, 3H), 1.25 - 1.10 (m, 4H)

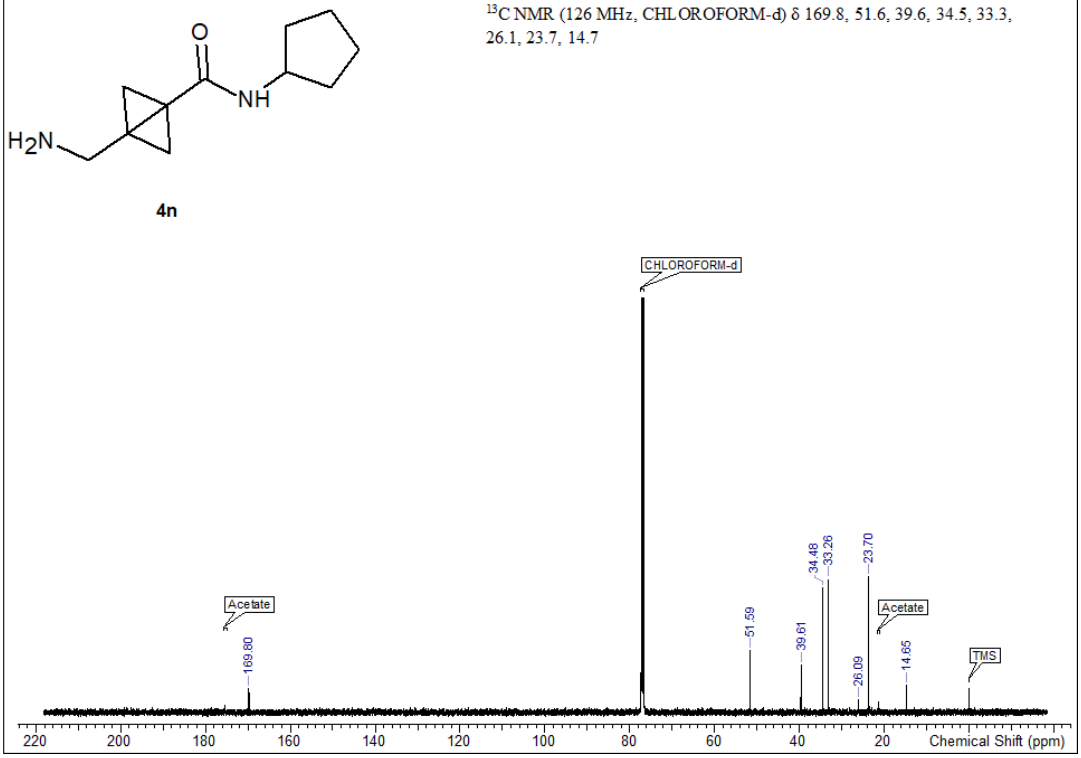


^{13}C NMR (101 MHz, METHANOL-d_4) δ 171.2, 50.6, 41.3, 36.9, 34.1, 26.7, 26.5, 23.5, 16.3



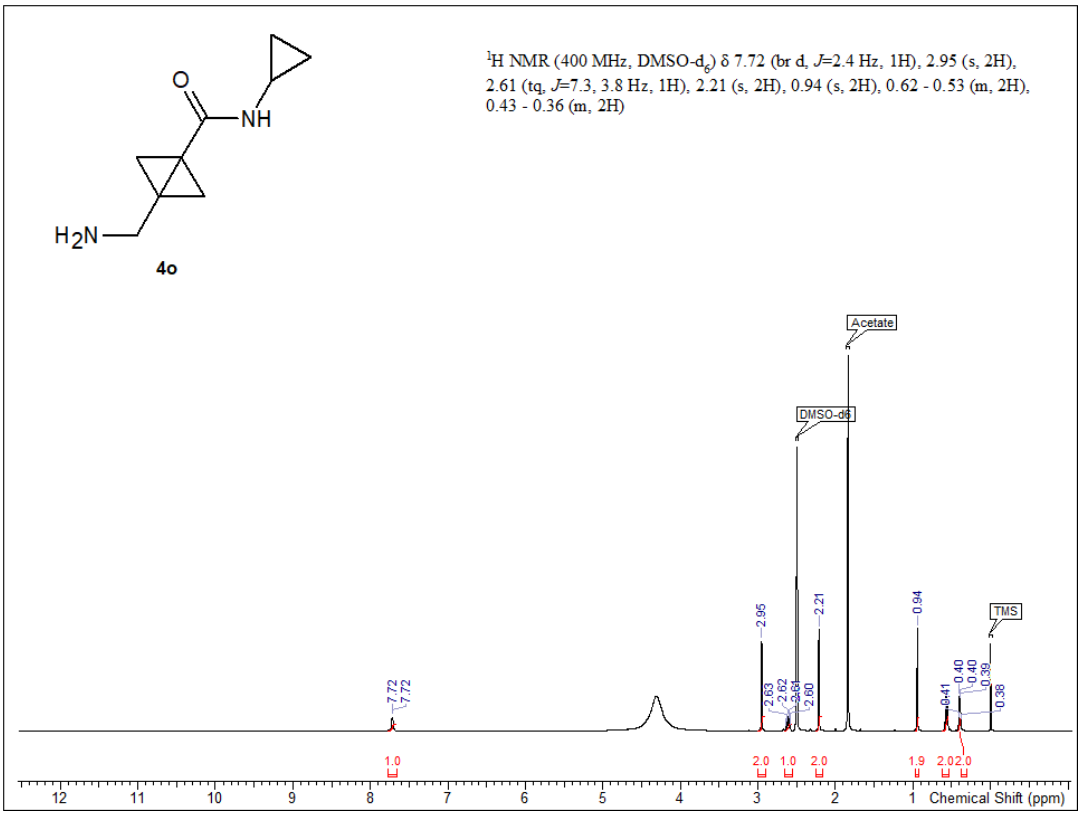
4n

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 5.65 (br d, *J*=5.3 Hz, 1H), 4.22 (sxt, *J*=7.0 Hz, 1H), 3.28 (s, 2H), 2.24 (s, 2H), 2.03 - 1.94 (m, 2H), 1.71 - 1.55 (m, 4H), 1.41 - 1.29 (m, 2H), 1.11 (s, 2H)

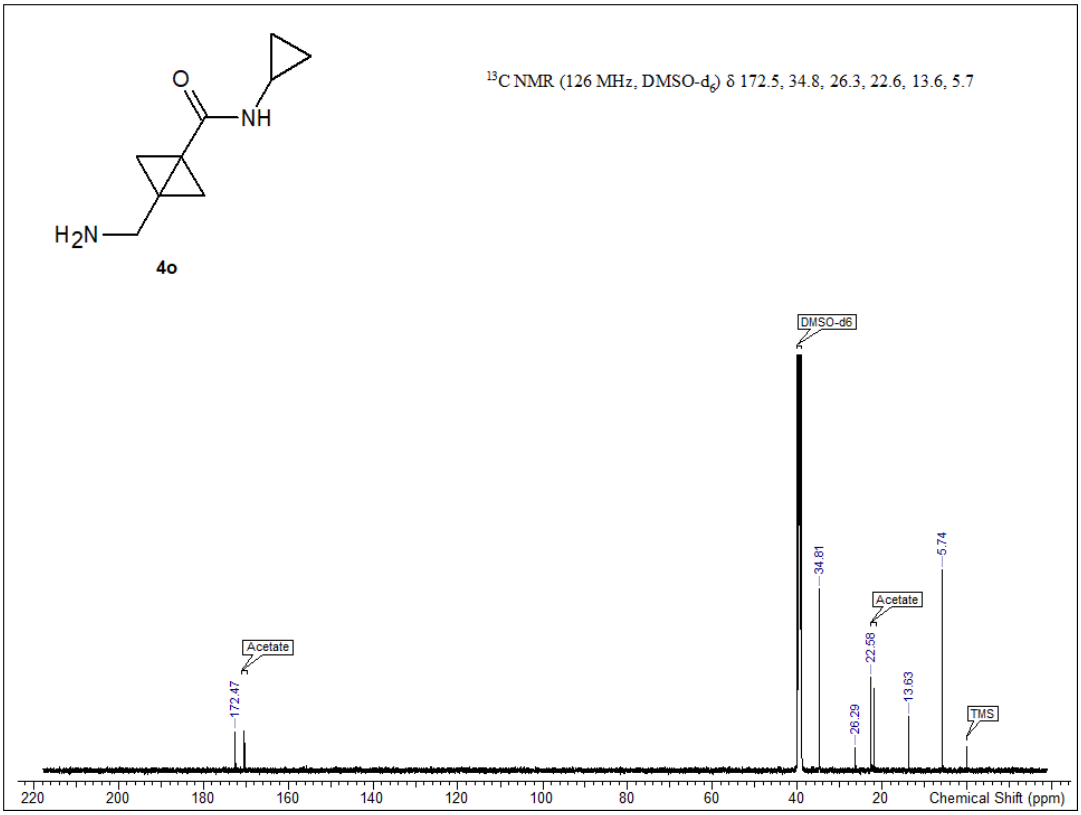


4n

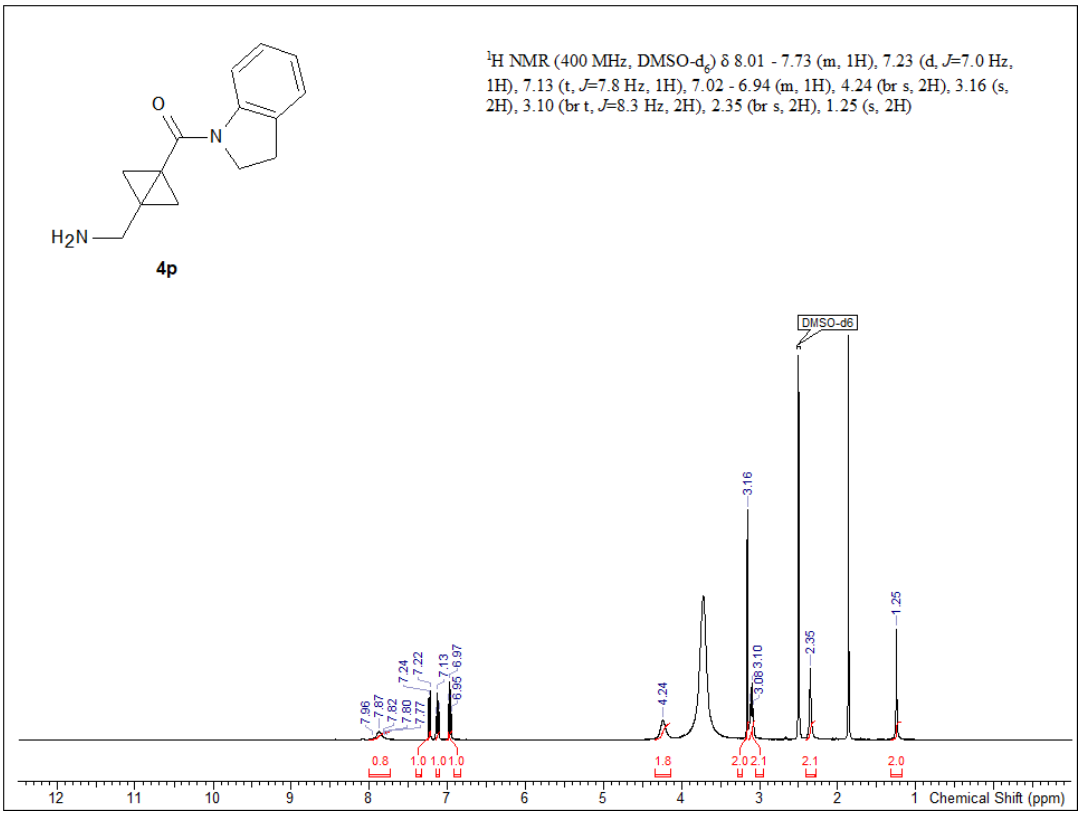
^{13}C NMR (126 MHz, CHLOROFORM-d) δ 169.8, 51.6, 39.6, 34.5, 33.3, 26.1, 23.7, 14.7



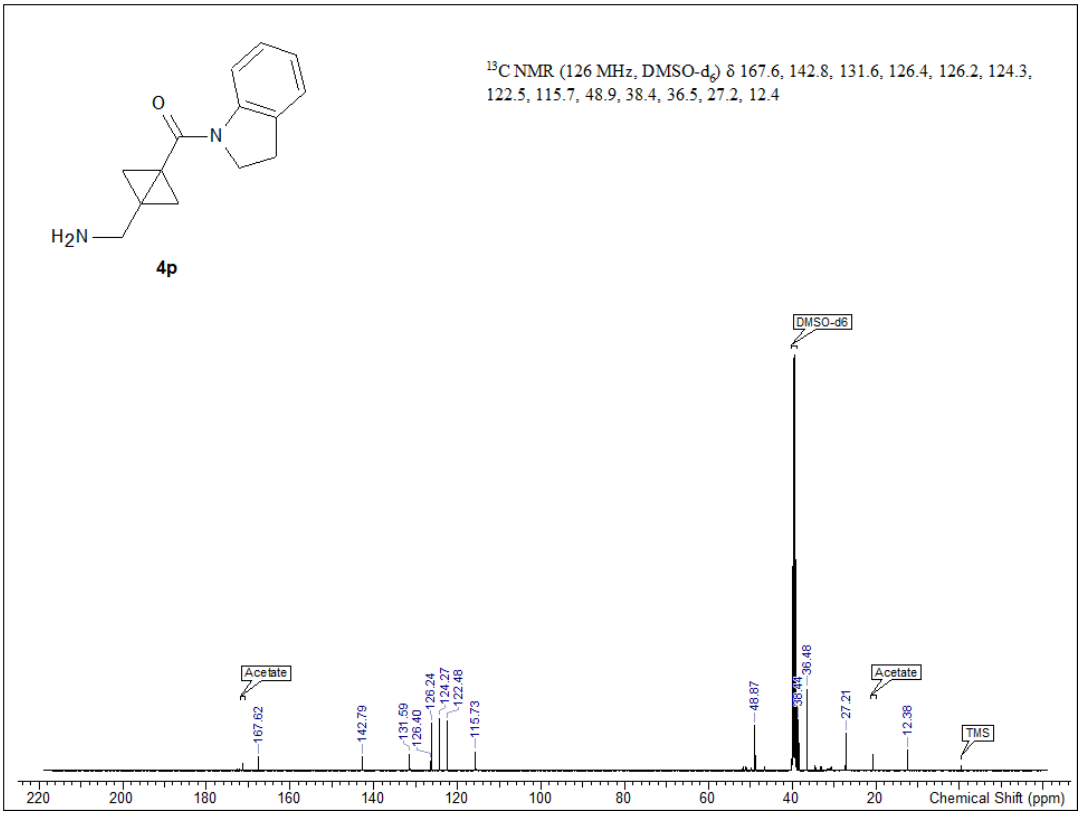
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (br d, *J*=2.4 Hz, 1H), 2.95 (s, 2H), 2.61 (tq, *J*=7.3, 3.8 Hz, 1H), 2.21 (s, 2H), 0.94 (s, 2H), 0.62 - 0.53 (m, 2H), 0.43 - 0.36 (m, 2H)



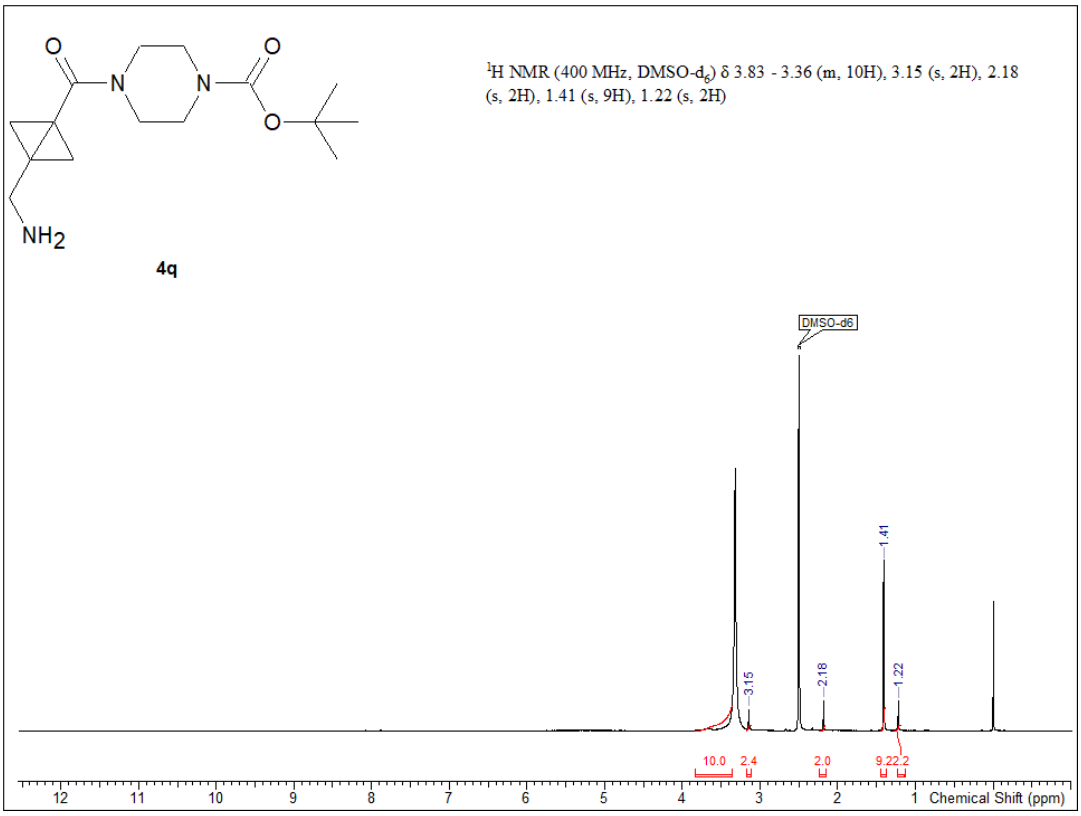
^{13}C NMR (126 MHz, DMSO-d_6) δ 172.5, 34.8, 26.3, 22.6, 13.6, 5.7



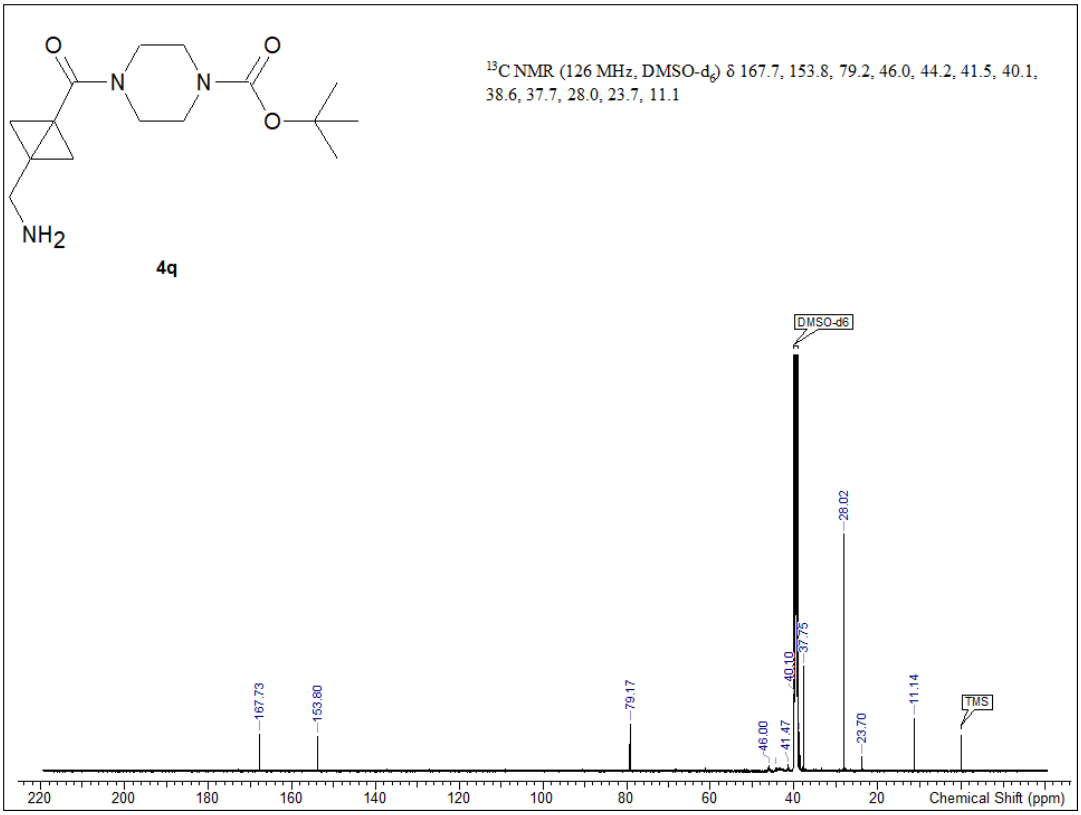
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 - 7.73 (m, 1H), 7.23 (d, *J*=7.0 Hz, 1H), 7.13 (t, *J*=7.8 Hz, 1H), 7.02 - 6.94 (m, 1H), 4.24 (br s, 2H), 3.16 (s, 2H), 3.10 (br t, *J*=8.3 Hz, 2H), 2.35 (br s, 2H), 1.25 (s, 2H)



^{13}C NMR (126 MHz, DMSO-d_6) δ 167.6, 142.8, 131.6, 126.4, 126.2, 124.3, 122.5, 115.7, 48.9, 38.4, 36.5, 27.2, 12.4



^{1}H NMR (400 MHz, DMSO-d_6) δ 3.83 - 3.36 (m, 10H), 3.15 (s, 2H), 2.18 (s, 2H), 1.41 (s, 9H), 1.22 (s, 2H)



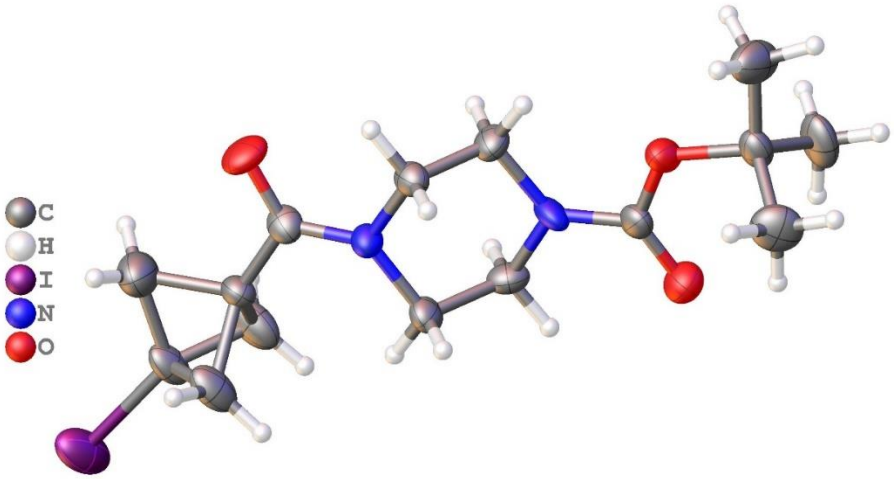
^{13}C NMR (126 MHz, DMSO-d_6) δ 167.7, 153.8, 79.2, 46.0, 44.2, 41.5, 40.1, 38.6, 37.7, 28.0, 23.7, 11.1

X-ray crystallography for 2q, 3q, 4a

Crystal structure determination of compound 2q

Single crystals of compound **2q** [$C_{15}H_{23}IN_2O_3$] were obtained from DCM:n-Heptane (2:1) solvent mixture using slow evaporation method at room temperature. A suitable crystal was mounted on a nylon cryoloop using paratone oil. Data were collected on a Bruker D8 Venture diffractometer equipped with a PHOTON-III area detector, at 150 K. Initial structure solution was achieved with 'Intrinsic Phasing' method in Bruker APEX4 software suite. Using Olex2[2], further structure refinements were performed with the ShelXL[3-5] refinement package using Least Squares minimization.

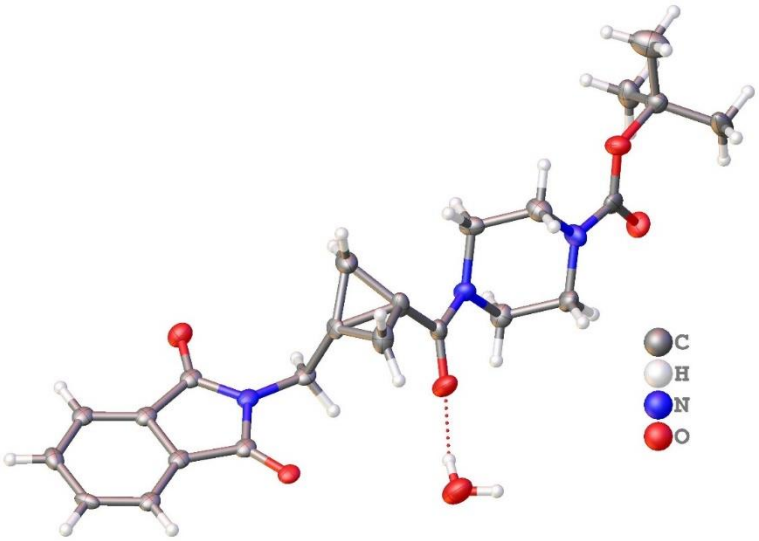
Crystal Data for $C_{15}H_{23}IN_2O_3$ (M =406.25 g/mol): orthorhombic, space group $Pca2_1$ (no. 29), a = 10.2188(3) Å, b = 6.0975(2) Å, c = 28.0255(8) Å, V = 1746.24(9) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 14.505 mm^{-1}, $Dcalc$ = 1.545 g/cm^3, 10600 reflections measured (6.308° ≤ 2Θ ≤ 144.326°), 3003 unique (R_{int} = 0.0742, R_{sigma} = 0.0682) which were used in all calculations. The final R_1 was 0.0745 (I > 2σ(I)) and wR_2 was 0.1999 (all data).



Crystal structure determination of compound 3q

Single crystals of compound **3q** [$C_{23}H_{27}N_3O_5.H_2O$] were obtained from DMF:acetone (1:1) solvent mixture using slow evaporation method at room temperature. A suitable crystal was mounted on a nylon cryoloop using paratone oil. Data were collected on a Bruker D8 Venture diffractometer equipped with a PHOTON-III area detector, at 150 K. Initial structure solution was achieved with 'Intrinsic Phasing' method in Bruker APEX4 software suite. Using Olex2[2], further structure refinements were performed with the ShelXL[3-5] refinement package using Least Squares minimization.

Crystal Data for $C_{23}H_{27}N_3O_5.H_2O$ (M =443.49 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 21.4556(10) Å, b = 6.6688(3) Å, c = 16.0801(8) Å, β = 106.089(2)°, V = 2210.67(18) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 0.802 mm^{-1}, $Dcalc$ = 1.333 g/cm^3, 3853 reflections measured (4.286° ≤ 2Θ ≤ 133.158°), 3853 unique (R_{int} = ?, R_{sigma} = 0.0730) which were used in all calculations. The final R_1 was 0.1382 (I > 2σ(I)) and wR_2 was 0.3797 (all data).



Crystal structure determination of compound 4a

Single crystals of compound **4a** 2[$(C_{16}H_{25}N_2O)^+(CH_3COO)^-$. H_2O] were obtained from a clear solution of chloroform:n-heptane (2:1) solvent mixture by slow evaporation method at room temperature. A suitable crystal was selected and mounted on a nylon cryoloop using paratone oil on a Bruker D8 Venture diffractometer equipped with a PHOTON-III area detector. The crystal was kept at 120(2) K during data collection. Using Olex2[2], the structure was solved with the XT[4] structure solution program using Intrinsic Phasing and refined with the SHELXL[3] refinement package using Least Squares minimization.

Crystal Data for 2[$(C_{16}H_{25}N_2O)^+(CH_3COO)^-$. H_2O] (M =658.86 g/mol): orthorhombic, space group *Pna*2_1 (no. 33), a = 9.9209(3) Å, b = 8.6208(3) Å, c = 41.4159(12) Å, V = 3542.14(19) Å3, Z = 4, T = 120 (2) K, μ(CuKα) = 0.688 mm-1, Dcalc = 1.235 g/cm3, 44391 reflections measured ($4.266° \leq 2\Theta \leq 133.418°$), 6172 unique (Rint = 0.0664, Rsigma = 0.0398) which were used in all calculations. The final R_1 was 0.0577 ($I > 2\sigma(I)$) and wR_2 was 0.1372 (all data).

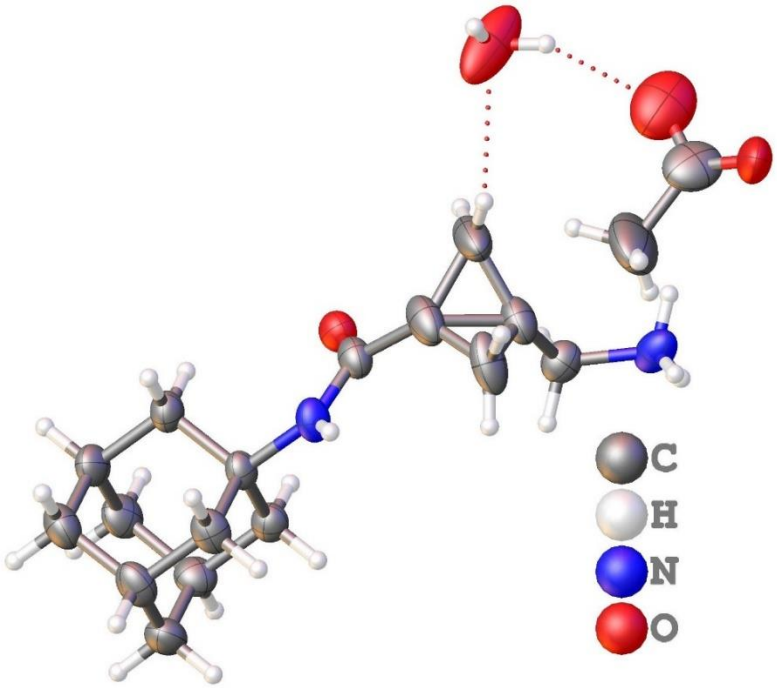


Table S3. X-ray crystallography data table

Identification code	**compound 2q**	**compound 3q**	**compound 4a**
CCDC Number	2315016	2336718	2336719
Empirical formula	$C_{15}H_{23}IN_2O_3$	$C_{23}H_{27}N_3O_5.H_2O$	$2[(C_{16}H_{25}N_2O)^+(CH_3COO)^-.H_2O]$
Formula weight	406.25	443.49	658.86
Temperature/K	150(2)	150(2)	120(2)
Crystal system	orthorhombic	monoclinic	orthorhombic
Space group	$Pca2_1$	$P2_1/c$	$Pna2_1$
a/Å	10.2188(3)	21.4556(10)	9.9209(3)
b/Å	6.0975(2)	6.6688(3)	8.6208(3)
c/Å	28.0255(8)	16.0801(8)	41.4159(12)
α/°	90	90	90
β/°	90	106.089(2)	90
γ/°	90	90	90
Volume/Å^3	1746.24(9)	2210.67(18)	3542.14(19)
Z	4	4	4
ρ_{calc}g/cm^3	1.545	1.333	1.235
μ/mm^{-1}	14.505	0.802	0.688
F(000)	816.0	944.0	1432.0
Crystal size/mm^3	0.199 × 0.101 × 0.081	0.25 × 0.18 × 0.018	0.438 × 0.201 × 0.132
Radiation	CuKα (λ = 1.54178)	CuKα (λ = 1.54178)	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.308 to 144.326	4.286 to 133.158	4.266 to 133.418
Index ranges	$-12 \le h \le 11$, $-7 \le k \le 7$, $-29 \le l \le 34$	$-25 \le h \le 25$, $-7 \le k \le 7$, $-18 \le l \le 18$	$-11 \le h \le 11$, $-10 \le k \le 10$, $-49 \le l \le 49$
Reflections collected	10600	3853	44391
Independent reflections	3003 [R_{int} = 0.0742, R_{sigma} = 0.0682]	3853 [R_{int} = ?, R_{sigma} = 0.0730]	6172 [Rint = 0.0664, Rsigma = 0.0398]
Data/restraints/parameters	3003/1/194	3853/0/248	6172/17/504
Goodness-of-fit on F^2	1.122	1.215	1.052
Final R indexes [I>=2σ (I)]	R_1 = 0.0745, wR_2 = 0.1894	R_1 = 0.1382, wR_2 = 0.3741	R1 = 0.0577, wR2 = 0.1330
Final R indexes [all data]	R_1 = 0.0826, wR_2 = 0.1999	R_1 = 0.1476, wR_2 = 0.3797	R1 = 0.0637, wR2 = 0.1372
Largest diff. peak/hole / e Å^{-3}	0.97/-0.95	0.60/-0.62	0.30/-0.23
Flack parameter	0.026(14)	-	0.46(14)

References

1. Mandler, M. D.; Mignone, J.; Jurica, E. A.; Palkowitz, M. D.; Aulakh, D.; Cauley, A. N.; Farley, C. A.; Zhang, S. S.; Traeger, S. C.; Sarjeant, A.; Paiva, A.; Perez, H. L.; Ellsworth, B. A.; Regueiro-Ren, A., Synthesis of Bicyclo[1.1.0]butanes from Iodo-Bicyclo[1.1.1]pentanes. *Org. Lett.* **2023,** *25*, 7947-7952.
2. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H., OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009,** *42*, 339-341.
3. Sheldrick, G. M., A short history of SHELX. In *Acta Crystallographica Section A: Foundations of Crystallography* International Union of Crystallography2008; Vol. 64, pp 112-122.
4. Sheldrick, G. M., SHELXT - Integrated space-group and crystal-structure determination. *Acta Crystallographica Section A: Foundations of Crystallography* **2015,** *71*, 3-8.
5. Sheldrick, G. M., Crystal structure refinement with SHELXL. *Acta Crystallogr. C* **2015,** *71*, 3-8.