Electronic Supplementary Material (ESI) for Chemical Communications.

-Electronic Supplementary Information-

Ruthenium(II)-Catalyzed C–H Activation and (4+2) Annulation of Aromatic Hydroxamic Acid Esters with Allylic Amides

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General information:

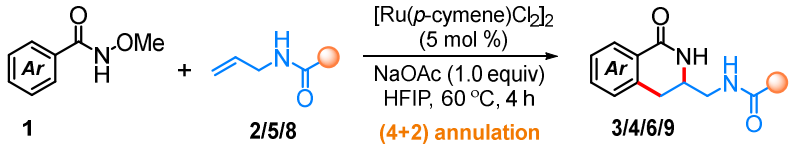
[Ru(*p*-cymene)Cl_2]$_2$ was purchased from Alfa Aesar company. Benzoic acids, carboxylic acids, $MeONH_2$.HCl, allylamine, hexafluoroisopropanol (HFIP), organic solvents, and inorganic bases were purchased from Avra chemicals, Spectrochem and TCI chemicals. All the compounds were utilized without further purification. Commercial grade solvent was directly used for the reaction without drying.

All reactions were monitored by thin layer chromatography (TLC) on Merck 60 F 254 precoated silica plates and visualized using a UV lamp (366 or 254 nm) or by use of potassium permanganate, 5 g K_2CO_3/100 mL water. Products were isolated by column chromatography (Merck silica gel 100-200 μm).

^{13}C and ^{1}H NMR spectra were recorded on a Bruker 400 MHz or Bruker 500 MHz spectrometers. Chemical shift values (δ) are reported in ppm and calibrated to the residual solvent peak- $CDCl_3$ δ = 7.26 ppm for ^{1}H, δ = 77.16 for ^{13}C; DMSO-d_6 δ = 2.51 ppm for ^{1}H, δ = 39.5 ppm for ^{13}C; or calibrated to tetramethylsilane (δ = 0.00). All NMR spectra were recorded at ambient temperature (290 K) unless otherwise noted. ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constant, integration). The following abbreviations are used to indicate multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; dt, doublet of triplet; dq, doublet of quartet; td, triplet of doublet; tt, triplet of triplet; dq, doublet of quartet; br, broad.

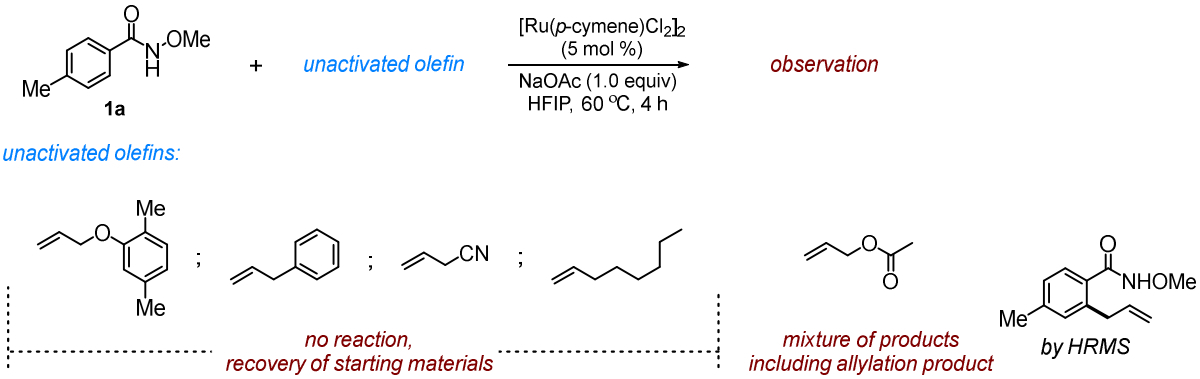
Mass spectra were recorded by electron spray ionization (ESI) method on a Q-TOF Micro with lock spray source.

Typical Ruthenium(II)-Catalyzed (4+2) Annulation Between Hydroxamic Acid Esters (1) and Allylic Amides (2/5/8):

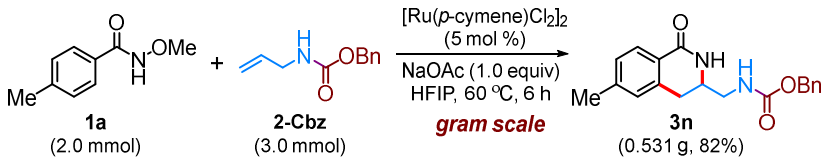


Procedure: To an oven dried screw cap reaction tube (10 × 1.5 cm), corresponding benzamide **1** (0.25 mmol, 1.0 equiv), allylic amide (**2/5/8**, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5.0 mol %), and NaOAc (1.0 equiv) were taken. Next hexafluoroisopropanol (0.5 mL) was added in it and it was capped. The reaction mixture was then stirred at 60 °C for 4 hours under air. After that the solvent was evaporated under reduced pressure. In order to get pure aminomethyl isoquinolinones **3/4/6/9**, the resulting residue was purified by column chromatography on silica gel with a gradient eluent of Hexane/EtOAc or DCM/EtOAc/MeOH mixture.

A summary of Unfruitful Reactions with Different Unactivated Olefins:



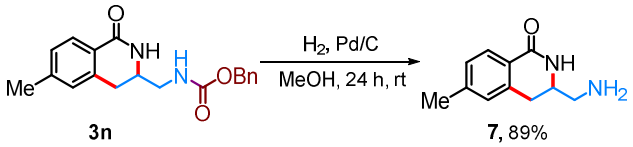
Typical Scaled up Ruthenium(II)-Catalyzed (4+2) Annulation Between Hydroxamic Acid Ester 1a and allylic amide 2-Cbz:



Procedure: To an oven dried round bottom flask (25 mL), corresponding benzamide **1a** (2.0 mmol, 1.0 equiv), allylic amide (1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5.0 mol %), and NaOAc (1.0 equiv) were taken. Next hexafluoroisopropanol (4.0 mL) was added in it and it was

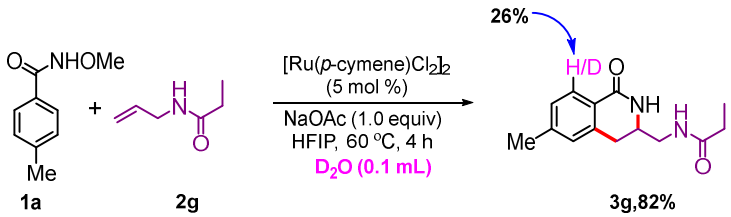
capped with a rubber septum. The reaction mixture was then stirred at 60 °C for 6 h under air. After that the solvent was evaporated under reduced pressure. In order to get pure product **3n**, the resulting residue was purified by column chromatography on silica gel with a gradient eluent of Hexane/EtOAc = (20/80). Product **3n** was obtained in 82% (531 mg) yield.

Hydrogenation of 3n: Cbz-group deprotection:



Procedure: To an oven dried 25 mL round-bottom flask, the product **3n** (0.3 mmol, 1.0 equiv) was taken and it was backfilled with N_2 gas to remove the air. The mouth was capped with a rubber septum. Next the 1.5 mL MeOH was added into it followed by the addition of Pd/C (10 mol %). A balloon of hydrogen was attached to the flask with an adapter that allows the balloon to be closed off from the reaction flask. With the hydrogen balloon closed off, the flask was evacuated until the solvent begins to bubble, and then the balloon was opened to the flask. The reaction mixture was stirred at room temperature for 24 h. After completion (monitored by TLC), the reaction mixture was diluted with ethyl acetate and filtered through a celite pad. In order to get pure product **7**, the resulting residue was purified by column chromatography on silica gel with a gradient eluent of EtOAc: DCM: MeOH (80:15:5) mixture.

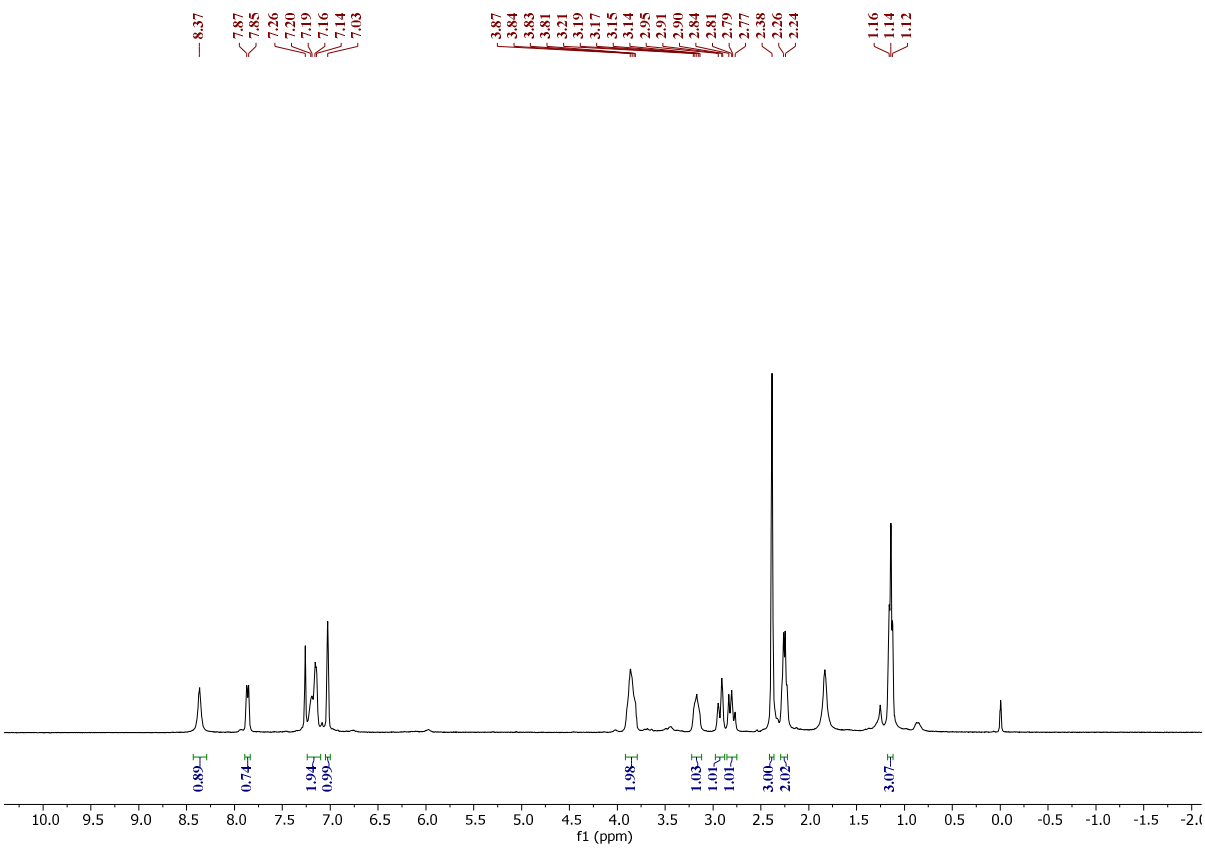
Mechanistic studies:



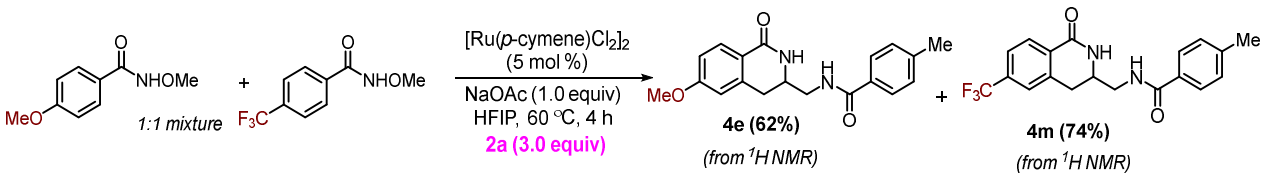
(a) H/D-Scrambling study:

Procedure: To an oven dried screw cap reaction tube (10 × 1.5 cm), corresponding benzamide **1a** (0.25 mmol, 1.0 equiv), allylic amide (**2g**, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5.0 mol %), NaOAc (1.0 equiv), and D_2O (0.1 mL) were taken. Then hexafluoroisopropanol (0.5 mL) was added in it and it was capped. The reaction mixture was stirred at 60 °C for 4 h under air. After that the solvent was evaporated under reduced

pressure. In order to get pure product **3g**, the resulting residue was purified by column chromatography on silica gel with a gradient eluent of Hexane/EtOAc = (15/85). The H/D-scrambling was observed through ^{1}H NMR spectroscopy.

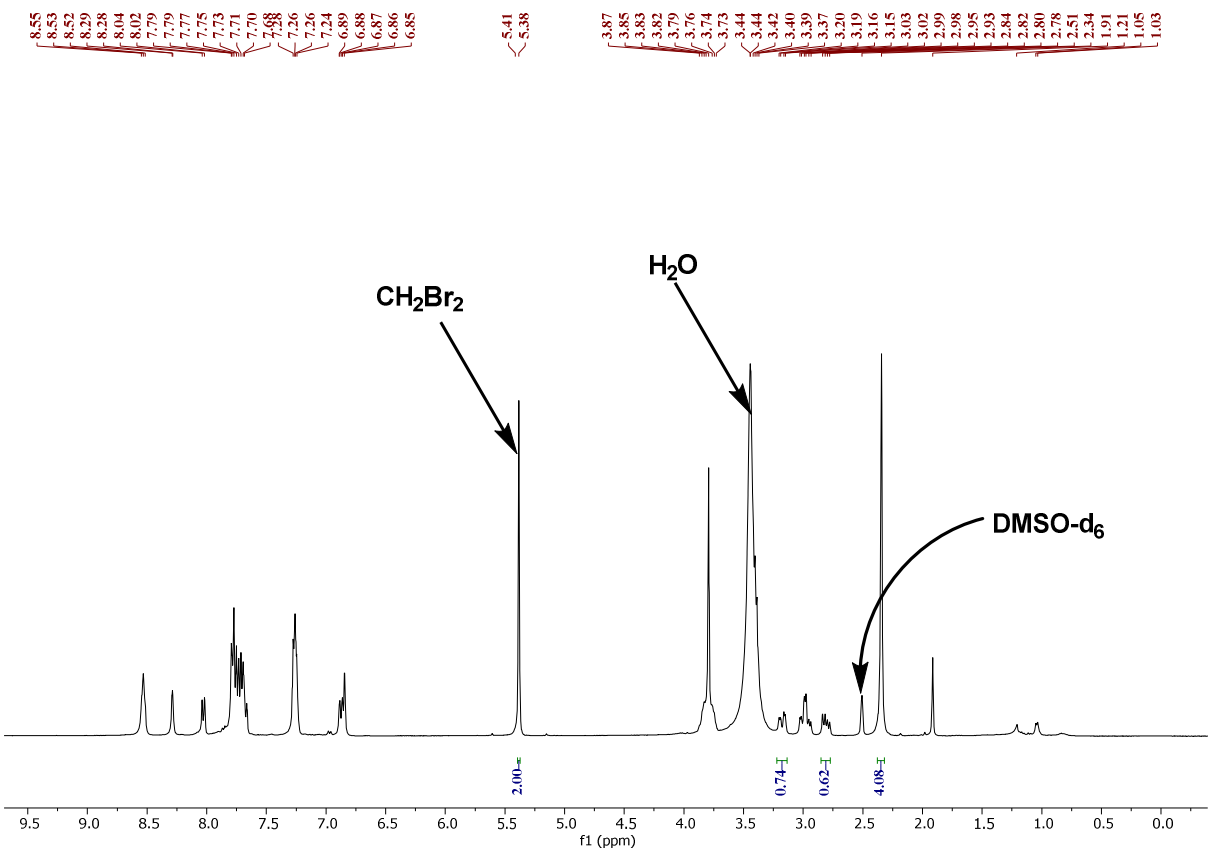


(b) Competition Experiment:

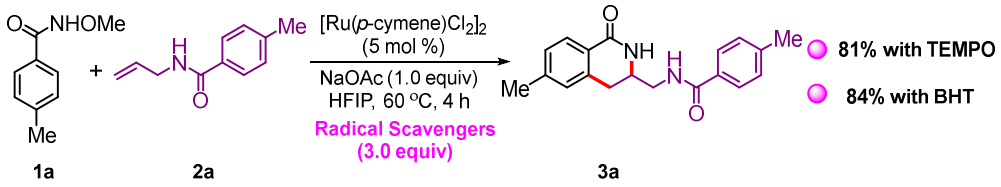


Procedure: To an oven dried screw cap reaction tube (10 × 1.5 cm), corresponding benzamide **1e** and **1m** (1mmol, 1:1 mixture), allylic amide (**2a**, 3.0 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5.0 mol %), NaOAc (1.0 equiv), were taken. Then hexafluoroisopropanol (0.5 mL) was added in it and it was capped. The reaction mixture was stirred at 60 ^{o}C for 4 h under air. After that the solvent was evaporated under reduced pressure. In order to get mixture products **4e** and **4m**, the resulting residue was purified by

column chromatography on silica gel with a gradient eluent of DCM/EtOAc/MeOH = (10/85/5). The ratio of yield for **4e** and **4m** was calculated through ^{1}H NMR spectroscopy using dibromomethane (CH_2Br_2) as the internal standard.

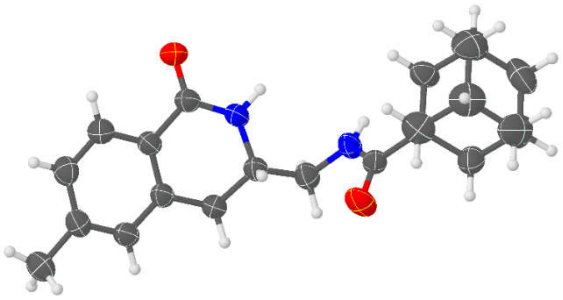


(c) Radical scavenger study:



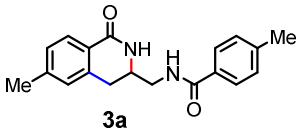
Procedure: To an oven dried screw cap reaction tube (10 × 1.5 cm), corresponding benzamide **1a** (0.25 mmol, 1.0 equiv), allylic amide (**2a**, 1.5 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (5.0 mol %), NaOAc (1.0 equiv), and radical scavenger (3.0 equiv) were taken. Then hexafluoroisopropanol (0.5 mL) was added in it and it was capped. The reaction mixture was then stirred at 60 ^{0}C for 4 hours under air. After that the solvent was evaporated under reduced pressure. In order to get pure product **3a**, the resulting residue was purified by column chromatography on silica gel with a gradient eluent of Hexane/EtOAc = (30/70).

X-ray crystal data of compound 3k: (CCDC 2080961)



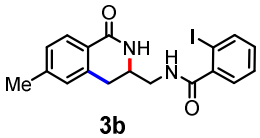
Identification code	Compound **3k**	
Empirical formula	C22 H28 N2 O2	
Formula weight	352.46	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 15.9840(9) Å	a= 90°.
	b = 12.2827(7) Å	b= 94.870(2)°.
	c = 10.0356(5) Å	g = 90°.
Volume	1963.14(19) $Å^3$	
Z	4	
Density (calculated)	1.193 Mg/m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	760	
Crystal size	0.200 x 0.150 x 0.150 mm^3	
Theta range for data collection	3.838 to 25.999°.	
Index ranges	-19<=h<=19, -15<=k<=15, -11<=l<=12	
Reflections collected	57370	
Independent reflections	3822 [R(int) = 0.0668]	
Completeness to theta = 25.242°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7471 and 0.6400	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3822 / 2 / 243	
Goodness-of-fit on F^2	1.109	
Final R indices [I>2sigma(I)]	R1 = 0.0592, wR2 = 0.1564	
R indices (all data)	R1 = 0.0776, wR2 = 0.1841	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.343 and -0.264 $e.Å^{-3}$	

NMR spectroscopic data of synthesized compounds:



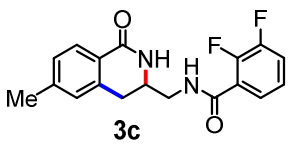
3a

4-methyl-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (3a): Eluent:(Hexane/ EtOAc = 30/70): Melting point = 168–170 °C; white solid; yield = 67.0 mg (87%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.04 (s, 1H), 7.88 – 7.84 (m, 3H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.11 – 7.05 (m, 3H), 4.16 – 4.10 (m, 1H), 4.01 – 3.96 (m, 1H), 3.41 – 3.35 (m, 1H), 2.99 – 2.94 (m, 1H), 2.90 – 2.83 (m, 1H), 2.41 (s, 3H), 2.33 (s, 3H) ppm ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9 (2C), 143.5, 142.0, 138.2, 131.3, 129.2, 128.5, 128.1, 127.9, 127.5, 125.6, 52.1, 43.7, 32.0, 21.8, 21.6 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{19}H_{20}N_2O_2Na$ 331.1417 Found 331.1429.



3b

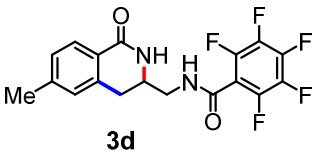
(R)-2-iodo-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (3b): Eluent:(Hexane/ EtOAc = 25/75): Melting point = 214–216 °C; white solid; yield = 90.0 mg (86%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.62 – 8.47 (m, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.83 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.39 (m, 1H), 7.37 – 7.31 (m, 1H), 7.23 – 7.13 (m, 2H), 7.12 (s, 1H), 3.84 – 3.70 (m, 1H), 3.40 – 3.35 (m, 1H), 3.34 – 3.25 (m, 1H), 3.14 – 2.97 (m, 1H), 2.96 – 2.83 (m, 1H), 2.34 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 169.5, 164.5, 142.9, 142.1, 139.1, 137.7, 130.9, 128.7, 128.1 (2×C), 127.6, 127.1, 126.2, 93.5, 50.0, 42.7, 30.8, 21.2 ppm ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{17}IN_2O_2Na$ 443.0227 Found 443.0235.



3c

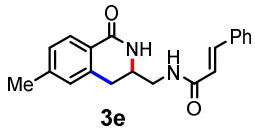
(R)-2,3-difluoro-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (3c): Eluent:(Hexane/ EtOAc = 30/70): Melting point = 215–217 °C; white solid; yield = 77.0 mg (93%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.68 – 7.64 (m, 1H), 7.23 – 7.19 (m,1H), 7.13 – 7.07 (m, 2H), 7.02 (s, 1H), 4.04 – 3.92 (m, 2H), 3.52 – 3.45 (m, 1H), 2.98 (dd, *J* = 15.7, 4.6 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.37 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 163.7, 148.9 (dd, J = 250, 13 Hz), 148.7 (dd, J = 250, 14 Hz), 143.4, 137.6, 128.4, 128.1, 127.8, 126.0 (d, *J* = 3.6 Hz), 125.6, 124.6 – 124.5 (m), 124.2 (d, *J* = 9.4 Hz), 120.1 (d, *J*

= 17.2 Hz), 51.5, 44.1, 31.8, 21.8. ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -137.6 (d, *J* = 21.8 Hz), -139.2 (d, *J* = 21.7 Hz) ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{16}F_2N_2O_2Na$ 353.1072 Found 353.1081.



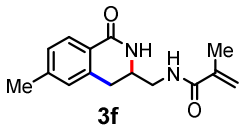
3d

(R)-2,3,4,5,6-pentafluoro-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (3d): Eluent:(Hexane/ EtOAc = 35/65): Melting point = 165–167 °C; white solid; yield = 82.0 mg (85%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.44 – 8.20 (m, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.05 (s, 1H), 7.00 (d, *J* = 7.9, 1H), 4.01 – 3.95 (m, 2H), 3.52 – 3.46 (m, 1H), 2.95 – 2.91 (m, 1H), 2.89 – 2.83 (m, 1H), 2.39 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 158.1, 143.9 (m), 144.2, 142.1 (m), 137.9, 137.5 (m), 128.7, 127.8, 126.8, 124.8, 112.0 (t, J= 20 Hz), 51.8, 43.3, 31.6, 21.7 ppm; **^{19}F NMR** (471 MHz, $CDCl_3$) δ (-139.2) – (-142.5) (m), -151.64 (t, *J* = 20.7 Hz), (-156.5) – (-169.7) (m) ppm; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{18}H_{14}F_5N_2O_2$ 385.0970 Found 385.0956.



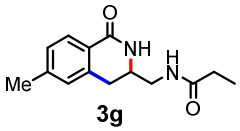
3e

(R)-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)cinnamamide (3e): Eluent:(Hexane/ EtOAc = 30/70): Melting point = 208–210 °C; white solid; yield = 66.0 mg (83%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.85 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.50 – 7.38 (m, 4H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.11 (s, 1H), 6.65 (d, J= 15.8Hz, 1H), 3.71 – 3.62 (m, 1H), 3.30 – 3.20 (m, 1H), 3.06 – 2.88 (m, 1H), 2.86 – 2.72 (m, 1H), 2.33 (s, 3H) ppm (one C-H proton is merged with water peak); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.5, 164.4, 141.9, 139.0, 137.6, 134.8, 129.5, 129.0, 128.5, 127.6, 127.4, 127.0, 126.2, 121.9, 50.1, 42.5, 30.6, 21.1 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{20}H_{20}N_2O_2Na$ 343.1417 Found 343.1425.



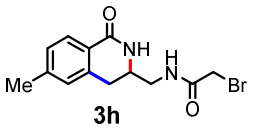
3f

N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)methacrylamide (3f): Eluent:(Hexane/ EtOAc = 35/65): Melting point = 165–167 °C; white solid; yield = 58.0 mg (90%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.71 – 7.68 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.02 (s, 1H), 5.85 (s, 1H), 5.30 (s, 1H), 3.98 – 3.88 (m, 2H), 3.28 – 3.22 (m, 1H), 2.98 – 2.87 (m, 1H), 2.84 – 2.77 (m, 1H), 2.37 (s, 3H), 1.96 (s, 3H) ppm ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 167.7, 143.4, 139.7, 138.1, 128.4, 128.0, 127.6, 125.5, 120.3, 51.9, 43.5, 31.9, 21.7, 18.8 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{15}H_{18}N_2O_2Na$ 281.1260 Found 281.1274.



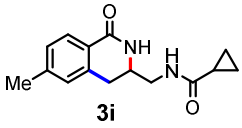
3g

(R)-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)propionamide (3g): Eluent:(Hexane/ EtOAc = 15/85): Melting point = 198–200 °C; Grey solid; yield = 54.0 mg (87%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.03 (s, 1H), 3.90 – 3.84 (m, 2H), 3.19 – 3.12 (m, 1H), 2.95 – 2.90 (m, 1H), 2.83 – 2.77 (m, 1H), 2.38 (s, 3H), 2.26 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8, 167.6, 143.6, 138.0, 128.5, 128.1, 127.6, 125.5, 51.8, 43.4, 31.8, 29.8, 21.8, 10.0 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{14}H_{18}N_2O_2Na$ 269.1260 Found 269.1274.



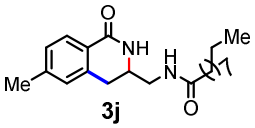
3h

(R)-2-bromo-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)acetamide (3h): Eluent:(DCM/ EtOAc/MeOH = 10/85/5): Melting point = 194 –196 °C; Grey solid; yield = 58.0 mg (75 %); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.45 – 8.42 (m, 1H), 7.81 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.08 (s, 1H), 3.88 (s, 2H), 3.66 – 3.61 (m, 1H), 3.31 – 3.24 (m, 1H), 3.18 – 3.13 (m, 1H), 2.97– 2.92 (m, 1H), 2.78 – 2.72 (m, 1H), 2.33 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.5, 164.4, 142.0, 137.5, 128.4, 127.5, 127.0, 126.1, 49.8, 42.6,30.4, 29.5, 21.1 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{13}H_{15}BrN_2O_2Na$ 333.0209 Found 333.0222.



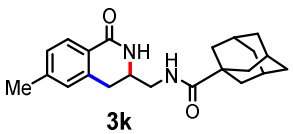
3i

(R)-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)cyclopropanecarboxamide (3i): Eluent:(Hexane/ EtOAc = 15/85): Melting point = 215–217 °C; white solid; yield = 59.0 mg (92%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.02 (s, 1H), 3.89 – 3.85 (m, 2H), 3.25 – 3.12 (m, 1H), 2.96 – 2.87 (m, 1H), 2.86 – 2.72 (m, 1H), 2.38 (s, 3H), 1.53 – 1.40 (m, 1H), 1.04 – 0.85 (m, 2H), 0.72 – 0.69 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.5, 167.5, 143.5, 138.0, 128.5, 128.1, 127.7, 125.6, 51.9, 43.5, 31.7, 21.8, 14.8, 7.4(2C) ppm ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{15}H_{18}N_2O_2Na$ 281.1260 Found 281.1270.



3j

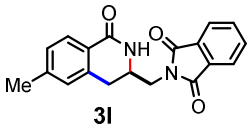
N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)decanamide (3j): Eluent:(DCM/ EtOAc/MeOH = 10/85/5): Melting point = 158 –160 °C; white solid; yield = 65.0 mg (76%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.44-7.41 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.02 (s, 1H), 3.93 – 3.83 (m, 2H), 3.16 – 3.09 (m, 1H), 2.93– 2.88 (m, 1H), 2.82 – 2.75 (m, 1H), 2.38 (s, 3H), 2.22 (t, *J* = 7.7 Hz, 2H), 1.65 – 1.57 (m, 2H), 1.28 – 1.09 (m, 12H), 0.84 (t, *J* = 6.8 Hz, 3H)ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.1, 167.6, 143.5, 138.0, 128.5, 128.0, 127.6, 125.5, 51.9, 43.3, 36.9, 32.0, 31.8, 29.6, 29.5, 29.4,(2C), 25.9, 22.8, 21.7, 14.2 ppm. HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{21}H_{33}N_2O_2$ 345.2537 Found 345.2526.



3k

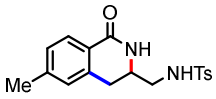
(3R,5R,7R)-N-(((R)-6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)adamantane-1-carboxamide(3k): Eluent:(DCM/ EtOAc/MeOH = 10/85/5): Melting point = 168–170 °C; white solid; yield = 80.0 mg (91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.00 (s, 1H), 3.85 – 3.74 (m, 2H), 3.35 – 3.28 (m,1H), 2.87 – 2.82 (m,1H), 2.79 –2.72(m, 1H), 2.36 (s, 3H), 1.86 (s, 3H), 1.81 (s, 6H), 1.62 –1.59 (m,3H), 1.52-149 (m, 3H)ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.0, 167.9, 143.3, 138.3, 128.4, 127.9, 127.6, 125.6, 52.1, 42.9, 40.8, 39.2, 36.5,

31.9, 28.2, 21.7 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{22}H_{28}N_2O_2Na$ 375.2043 Found 375.2050.



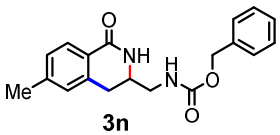
3l

(R)-2-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)isoindoline-1,3-dione (3l): Eluent:(Hexane/ EtOAc = 30/70): Melting point = 200 –202 °C Grey solid; Yield = 60.0 mg (85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 3H), 7.70 – 7.67 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 6.81 – 6.78 (m, 1H), 4.06 – 4.04 (m, 1H), 3.91-3.83 (m, 2H), 3.06 – 3.00 (m, 1H), 2.80 – 2.81 (m, 1H), 2.33 (s, 3H) ppm ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6, 166.1, 143.0, 136.9, 134.3, 131.9, 128.4, 128.1(2C), 125.7, 123.6, 50.8, 41.5, 31.8, 21.7 ppm ; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{19}H_{17}N_2O_3$ 321.1234 Found 321.1229.



3m

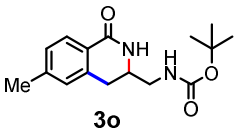
(R)-4-methyl-N-((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzenesulfonamide (3m): Eluent:(Hexane/ EtOAc = 35/65): Melting point = 170 –172 °C, white solid; yield = 48.0 mg (56%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.91 (m, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.98 (s, 1H), 6.54-6.51 (m, 1H), 3.96 – 3.73 (m, 1H), 3.42 – 3.13 (m, 1H), 3.10 – 2.96 (m, 1H), 2.93 – 2.78 (m, 2H), 2.40 (s, 3H), 2.37 (s, 3H) ppm ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.2, 143.7, 143.6, 137.4, 137.3, 129.9, 128.4, (2C) 128.2, 127.1, 125.3, 51.4, 47.1, 31.3, 21.8, 21.7 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{20}N_2O_3SNa$ 367.1087 Found 367.1098.



3n

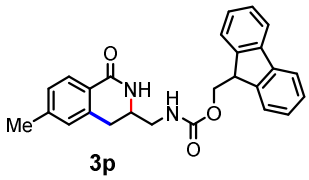
Benzyl((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)carbamate (3n): Eluent: (Hexane/ EtOAc = 20/80): Melting point = 130 –132 °C, white solid ; yield = 71.0 mg (88%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.26 (m, 5H), 6.99 – 6.97 (m, 2H), 6.38 (s, 1H), 5.14-5.05 (m, 2H), 3.87 – 3.83 (m, 1H), 3.65 – 3.61 (m, 1H), 3.26 – 3.19 (m, 1H), 2.91 – 2.86 (m, 1H), 2.83 – 2.77 (m, 1H), 2.36 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 157.0, 143.2, 137.7, 136.6, 128.6, 128.3, 128.2 (2C), 128.1(2C), 125.6, 67.0, 51.9, 45.2, 31.6,

21.7 ppm. ; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{19}H_{21}N_2O_3$ 325.1547 Found 325.1545.



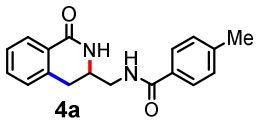
3o

tert-butyl((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)carbamate (3l): Eluent:(Hexane/ EtOAc = 40/60): Melting point = 163–165 °C, Grey solid; yield = 73.0 mg (87%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 6.18 (s, 1H), 3.95 – 3.73 (m, 1H), 3.65 – 3.53 (m, 1H), 3.21 – 3.10 (m, 1H), 2.87 – 2.76 (m, 2H), 2.36 (s, 3H), 1.43 (s, 9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 156.5, 143.2, 137.8, 128.3, 128.0, 127.9, 125.7, 79.5, 52.1, 44.7, 31.6, 28.5, 21.7 ppm. HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{16}H_{22}N_2O_3Na$ 313.1523 Found 313.1540.



3p

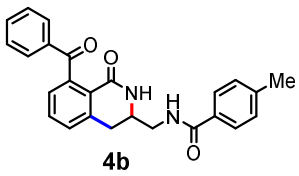
(9H-fluoren-9-yl)methyl((6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)carbamate (3p): Eluent:(Hexane/ EtOAc = 25/75): Melting point = 163–165 °C, white solid; yield = 95.0 mg (92%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.74-7.72 (m, 2H), 7.61 – 7.58 (m, 2H), 7.38 – 7.33 (m, 2H), 7.26 – 7.20 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.40 (s, 1H), 4.38 (d, *J* = 7.3 Hz, 2H), 4.18 (t, *J* = 7.2 Hz, 1H), 3.92 – 3.87 (m, 1H), 3.70 – 3.63 (m, 1H), 3.29 – 3.22 (m, 1H), 2.93– 2.89 (m, 1H), 2.86– 2.82 (m, 1H), 2.35 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 157.0, 144.0, 143.4, 141.4, 137.7, 128.4, 128.2, 128.1, 127.8, 127.2, 125.7, 125.3, 120.1, 67.1, 51.9, 47.4, 45.2, 31.6, 21.8 ppm ; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{26}H_{25}N_2O_3$ 413.1860 Found 413.1851.



4a

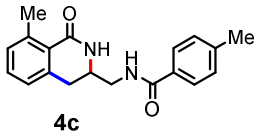
(R)-4-methyl-N-((1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (4a): Eluent:(Hexane/ EtOAc = 18/82): Melting point = 203–205 °C, white solid; yield = 70.0 mg (95%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.12 – 8.08 (m, 1H), 7.99 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.37 – 7.33 (m, 1H), 7.26 (d, J= 7.7 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 2H), 4.18 – 4.12 (m, 1H), 4.05 – 4.00 (m, 1H), 3.44 – 3.37 (m, 1H), 3.04 – 2.99 (m, 1H), 2.95 – 2.88 (m, 1H), 2.32 (s, 3H)

ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 167.8, 142.0, 138.3, 132.9, 131.2, 129.2, 128.2, 127.9, 127.8, 127.5, 127.2, 52.1, 43.7, 32.0, 21.5 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{18}N_2O_2Na$ 317.1260 Found 317.1280.



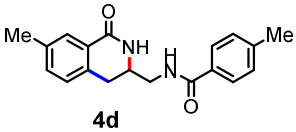
4b

(R)-N-((8-benzoyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4b): Eluent:(Hexane/ EtOAc = 20/80): Sticky liquid; yield = 79.0 mg (79 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.63-7.60 (m, 4H), 7.53-7.49 (m, 1H), 7.42-7.38 (m,1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.27-7.23 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.13-7.11 (m, 3H), 3.90 – 3.85 (m, 1H), 3.43 – 3.37 (m, 1H), 3.17 – 3.10 (m, 1H), 2.98 – 2.92 (m, 1H), 2.86 – 2.79 (m, 1H), 2.33 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.7, 167.8, 166.2, 142.0, 141.4, 139.5, 137.1, 133.0, 132.3, 130.7, 129.2, (2C) 128.8, 128.5, 127.4, 126.7, 126.0, 51.5, 42.4, 32.2, 21.5 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{25}H_{22}N_2O_3Na$ 421.1523 Found 421.1545.



4c

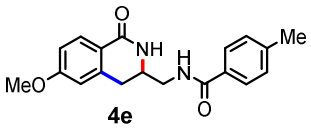
(R)-4-methyl-N-((8-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide(4c): Eluent:(Hexane/ EtOAc = 30/70): Melting point = 182–184 °C, white solid; yield = 64.0 mg (83 %); **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 8.56 – 8.53 (m, 1H), 7.87 – 7.85 (m, 1H), 7.77 (d, *J* = 7.9 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 2H), 3.69 – 3.65 (m, 1H), 3.46 – 3.41 (m, 1H), 3.35 – 3.30 (m, 1H), 2.99 – 2.94 (m, 1H), 2.81 – 2.75 (m, 1H), 2.58 (s, 3H), 2.36 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 166.7, 165.3, 141.2, 139.3, 138.9, 131.4, 130.9, 130.4, 128.8, 127.3, 127.0, 126.0, 50.1, 42.8, 32.6, 21.8, 21.0 ppm ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{19}H_{20}N_2O_2Na$ 331.1417 Found 331.1437.



4d

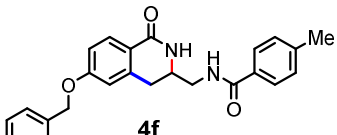
4-methyl-N-((7-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (4d): Eluent:(Hexane/ EtOAc = 30/70): Melting point =167–169 °C, white solid; yield = 70.0 mg (91 %) ; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.54 – 8.50 (m, 1H), 7.95 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.67 (s, 1H), 7.29 – 7.26 (m, 3H), 7.20 – 7.17 (m, 1H), 3.77 – 3.74 (m, 1H), 3.39 (2H signal merged with DMSO water peak), 3.02 – 2.96 (m, 1H), 2.82 – 2.75

(m, 1H), 2.36 (s, 3 H), 2.33 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 166.6, 164.4, 141.2, 135.9, 134.7, 132.5, 131.5, 128.8, 128.6, 127.9, 127.3, (2C) 50.3, 43.1, 30.5, 20.9, 20.7 ppm; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{19}H_{21}N_2O_2$ 309.1598 Found 309.1594.



4e

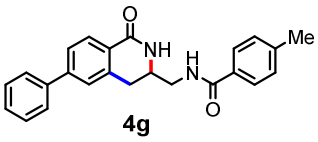
(R)-N-((6-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4e): Eluent:(DCM/ EtOAc/MeOH = 10/85/5): white solid; yield = 73.0 mg (90%); **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 8.54 – 8.51 (m, 1H), 7.80 – 7.75 (m, 4H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.90 – 6.86 (m, 2H), 3.80 (s, 3H), 3.78 – 3.74 (m, 1H), 3.01 (dd, *J* = 16.0, 5.0 Hz, 1H), 2.81 (dd, *J* = 16.0, 8.3 Hz, 1H), 2.36 (s, 3H) (2 C-H proton signals merged with water peak) ppm; **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 166.6, 164.3, 162.0, 141.2, 139.9, 131.5, 129.0, 128.8, 127.3, 121.5, 112.7, 112.6, 55.4, 50.2, 43.1, 31.2, 21.0 ppm ; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{19}H_{21}N_2O_3$ 325.1547 Found 325.1544.



4f

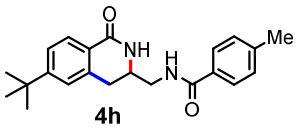
N-((6-(benzyloxy)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4f): Eluent:(DCM/ EtOAc/MeOH = 10/85/5) Melting point = 208–210 °C, white solid; yield = 82.0 mg (82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.07 – 8.04 (m, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.34 (m, 5H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.83 (s, 1H), 5.13 (s, 2H), 4.14 – 3.99 (m, 2H), 3.42 – 3.35 (m, 1H), 2.98 – 2.84 (m, 2H), 2.33 (s, 3H) ppm ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 167.6, 162.4, 142.0, 140.5, 136.3, 131.3, 129.9, 129.2, 128.9, 128.4, 127.6, 127.5, 121.2, 113.8, 113.6, 70.3, 52.1, 43.7, 32.4, 21.6 ppm; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{25}H_{25}N_2O_3$ 401.1860 Found 401.1854.

R)-4-methyl-N-((1-oxo-6-phenyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (4g): Eluent:(DCM/ EtOAc/MeOH = 12/85/3) Melting point = 220–222 °C, White solid; yield = 81.0 mg (87 %); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.56-8.53 (m, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.0 Hz,



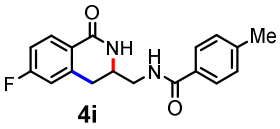
4g

1H), 7.74 (d, J= 7.9 Hz, 2H), 7.72 (d, J= 8.4 Hz, 2H), 7.65 – 7.62 (m, 2H), 7.51 – 7.47 (m, 2H), 7.43 – 7.39 (m, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 3.84 – 3.81 (m, 1H), 3.44 – 3.40 (m, 2H), 3.16 – 3.11 (m, 1H), 2.95 – 2.85 (m, 1H), 2.36 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 166.6, 164.1, 143.4, 141.1, 139.3, 138.4, 131.5, 129.0, 128.8, 128.1, 127.8, 127.6, 127.3, 126.9, 126.3, 125.0, 50.2, 43.1, 30.9, 20.9 ppm; ; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{24}H_{23}N_2O_2$ 371.1754 Found 371.1741.



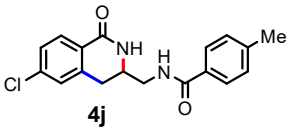
4h

(R)-N-((6-(tert-butyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4h): Eluent:(Hexane/ EtOAc = 35/65): Melting point = 210–212 °C, Grey solid; yield = 73.0 mg (83%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.18-8.15 (m, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.26 (s, 1H), 7.04 (d, *J* = 7.7 Hz, 2H), 4.15-4.09 (m, 1H), 4.03-3.98 (m, 1H), 3.45 – 3.39 (m, 1H), 3.01-2.96 (m, 1H), 2.93-2.86 (m, 1H), 2.31 (s, 3H), 1.36 (s, 9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 167.8, 156.5, 141.8, 138.1, 131.3, 129.1, 127.6, 127.5, 125.5, 124.8, 124.3, 52.2, 43.6, 35.2, 32.3, 31.3, 21.5 ppm; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{22}H_{27}N_2O_2$ 351.2067 Found 351.2067.



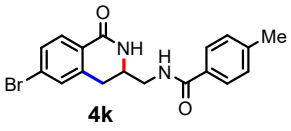
4i

(R)-N-((6-fluoro-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4i): Eluent:(Hexane/ EtOAc = 35/65): Melting point = 187–189 °C, White solid; yield = 66.0 mg (85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.02 – 7.95 (m, 2H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.08 (d, J= 7.8 Hz, 2H), 7.03 – 6.98 (m, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 4.13 – 4.07 (m, 1H), 4.04 – 3.99 (m, 1H), 3.43 – 3.37 (m, 1H), 3.02 – 2.97 (m, 1H), 2.93 – 2.86 (m, 1H), 2.33 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 166.9, 165.4 (d, J = 253.9 Hz), 142.1, 141.2 (d, J = 9.1 Hz), 130.5 (d, J = 9.6 Hz), 131.2, 129.2, 127.4, 124.5 (d, J = 2.1 Hz), 114.7 (d, *J* = 22.0 Hz), 114.4 (d, *J* = 21.9 Hz), 52.0, 43.6, 32.0, 21.5 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{17}FN_2O_2Na$ 335.1166 Found 335.1186.



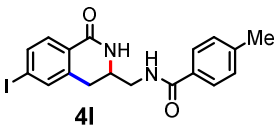
4j

(R)-N-((6-chloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4j): Eluent:(Hexane/ EtOAc = 30/70): Melting point = 210–212 °C, White solid; yield = 68.00 mg (83 %); **^{1}H NMR** (400 MHz, DMSO-*d*6) δ 8.55-8.52 (m,1H), 8.13-8.12 (m, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 3.80 – 3.75 (m, 1H), 3.10 – 3.05 (m, 1H), 2.89 – 2.84 (m, 1H), 2.36 (s, 3H), (2C-H peaks merged with water peak) ppm; **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 166.6, 163.3, 141.2, 140.0, 136.5, 131.4, 128.9, 128.8, 127.9, 127.7, 127.3, 126.9, 49.9, 42.9, 30.3, 21.0 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{17}ClN_2O_2Na$ 351.0871 Found 351.0885.



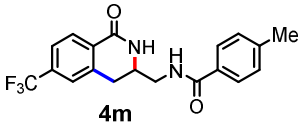
4k

(R)-N-((6-bromo-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4k): Eluent:(Hexane/ EtOAc = 30/70): Melting point = 228–230 °C, White solid; yield = 84.0 mg (80 %); **^{1}H NMR** (400 MHz, DMSO-*d*6) δ 8.54 – 8.51(m, 1H), 8.12 (s, 1H), 7.77 – 7.73 (m, 3H), 7.56 – 7.53 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 3.80 – 3.76 (m, 1H), 3.10 – 3.05 (m, 1H), 2.90 – 2.84 (m, 1H), 2.36 (s, 3H), (2C-H peaks merged with water peak) ppm; **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 166.6, 163.4, 141.1, 140.2, 131.4, 130.8, 129.8, 129.0, 128.8, 128.0, 127.3, 125.5, 49.9, 42.9, 30.2, 20.9 ppm ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{17}BrN_2O_2Na$ 395.0366 Found 395.0371.



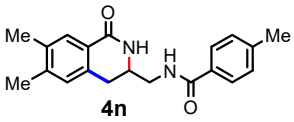
4l

(R)-N-((6-iodo-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4l): Eluent:(Hexane/ EtOAc = 25/75): Melting point = 256–258 °C, White solid; yield = 86.0 mg (82 %); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.53 – 8.50 (m, 1H), 8.10 (s, 1H), 7.75 – 7.72 (m, 4H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 2H), 3.78 – 3.75 (m, 1H), 3.08 – 3.02 (m, 1H), 2.87 – 2.81 (m, 1H), 2.36 (s, 3H), (2 C-H peaks merged with water peak) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 163.6, 141.1, 139.9, 136.6, 135.7, 131.4, 128.7 (2C), 128.3, 127.3, 99.7, 49.8, 42.9, 30.0, 20.9 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{17}IN_2O_2Na$ 443.0227 Found 443.0238.



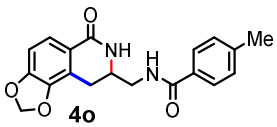
4m

(R)-4-methyl-N-((1-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (4m): Eluent:(Hexane/ EtOAc = 20/80): Melting point = 226–228 °C, White solid; yield = 77.0 mg (85 %); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.55 – 8.52 (m, 1H), 8.30 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.74 – 7.68 (m, 4H), 7.27 (d, J = 7.8 Hz, 2H), 3.85 – 3.81 (m, 1H), 3.21 – 3.16 (m, 1H), 3.00 – 2.94 (m, 1H), 2.35 (s, 3H), (2C-H signal peaks merged with water peak) ppm; **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.7, 162.9, 141.2, 139.0, 132.4, 131.6 (q, J = 31.6 Hz), 131.4 , 128.8, 127.8, 127.3,125.02 (q, J = 5 Hz),123.9 (q, J= 270 Hz),123.47 (q, J=3.75 Hz) 49.8, 43.0, 30.3, 21.0. ppm; **^{19}F NMR** (471 MHz, DMSO-d_6) δ -61.0. HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{19}H_{17}F_3N_2O_2Na$ 385.1144 Found 385.1134.



4n

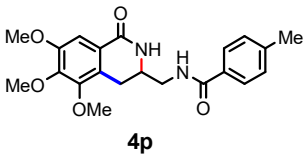
N-((6,7-dimethyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4n): Eluent:(DCM/ EtOAc/MeOH = 15/80/5); Melting point = 215–217 °C; White solid; yield = 78.0 mg (97%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.25 – 8.21 (m, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.73 (s, 1H), 7.07 (d, J = 7.9 Hz, 2H), 7.01 (s, 1H), 4.19 – 4.13 (m, 1H), 3.99 – 3.92 (m, 1H), 3.39 – 3.32 (m, 1H), 2.94 – 2.89 (m, 1H), 2.85 – 2.78 (m, 1H), 2.31 (s, 6H), 2.24 (s, 3H) ppm ; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 167.8, 142.1, 141.8, 135.6, 135.5, 131.3, 129.1, 129.0, 128.6, 127.5, 125.6, 52.3, 43.7, 31.4, 21.5, 20.0, 19.4 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{20}H_{22}N_2O_2Na$ 345.1573 Found 345.1593.



4o

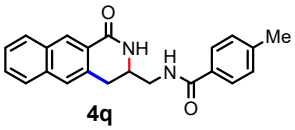
4-methyl-N-((5-oxo-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-7-yl)methyl)benzamide (4o): Eluent:(DCM/ EtOAc/MeOH = 13/80/7); White solid; yield = 78.0 mg (92%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.57 – 8.54 (m, 1H), 7.85 (s, 1H), 7.76 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 6.89 (d, J = 8.1 Hz, 1H), 6.11 (d, J = 5.2 Hz, 2H), 3.79 – 3.76 (m, 1H), 3.42 – 3.39 (m, 2H), 2.96 – 2.91 (m, 1H), 2.73 – 2.67 (m, 1H), 2.36 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 163.8, 149.9, 144.0, 141.2, 131.4, 128.8, 127.3, 123.1, 122.2, 118.4, 106.5,

101.9, 49.9, 43.1, 24.6, 21.0 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{19}H_{18}N_2O_4Na$ 361.1159 Found 361.1173.



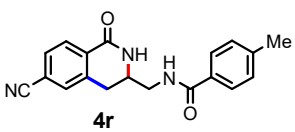
4p

4-methyl-N-((6,7,8-trimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[g]isoquinolin-3-yl)methyl)benzamide (4p): Eluent:(DCM/ EtOAc/MeOH = 10/80/10); Melting point = 168–170 °C; Grey solid; yield = 87.0 mg (91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.01 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.31 (s, 1H), 7.06 (d, *J* = 7.9 Hz, 2H), 4.18 – 4.11 (m, 1H), 3.94 (s, 4H), 3.88 (s, 3H), 3.72 (s, 3H), 3.40 – 3.34 (m, 1H), 3.18 – 3.13 (m, 1H), 2.65 – 2.58 (m, 1H), 2.31 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7, 167.4, 152.5, 150.2, 146.2, 141.9, 131.3, 129.1, 127.4, 125.0, 123.3, 106.6, 61.1, 61.0, 56.1, 52.0, 43.7, 25.2, 21.5 ppm ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{21}H_{24}N_2O_5Na$ 407.1577 Found 407.1598.



4q

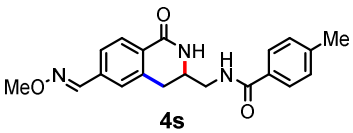
4-methyl-N-((1-oxo-1,2,3,4-tetrahydrobenzo[g]isoquinolin-3-yl)methyl)benzamide (4q): Eluent:(Hexane/ EtOAc = 20/80); Melting point = 208–210 °C; White solid**;** yield = 75.0 mg (87%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.54 (s, 1H), 8.14 – 8.10 (m, 1H), 7.90 (d, *J* = 7.9 Hz, 2H), 7.86 – 7.83 (m, 2H), 7.70 (s, 1H), 7.61 – 7.57 (m, 1H), 7.52 – 7.49 (m, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 4.26 – 4.20 (m, 1H), 4.13 – 4.07 (m, 1H), 3.50 – 3.43 (m, 1H), 3.26 – 3.21 (m, 1H), 3.12 – 3.05 (m, 1H), 2.24 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.0, 167.9, 142.0, 135.6, 133.7, 132.2, 131.4, 129.4, 129.2 (2C), 128.5, 127.5, (2C), 126.4, 126.3, 126.2, 52.4, 44.0, 32.4, 21.5 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{22}H_{20}N_2O_2Na$ 367.1417 Found 367.1426.



4r

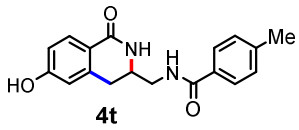
(R)-N-((6-cyano-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4r): Eluent:(DCM/ EtOAc/ MeOH = 17/80/3); Melting point = 234–236 °C; white solid; yield = 48.0 mg (60%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.34 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.82 – 7.78 (m, 2H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 3.83 – 3.80

(m, 1H), 3.16 – 3.10 (m, 1H), 2.95 – 2.89 (m, 1H), 2.35 (s, 3H), (2C-H peaks merged with water peak) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 162.7, 141.2, 139.0, 132.7, 132.1, 131.4, 130.5, 128.8, 127.6, 127.3, 118.4, 114.0, 49.7, 42.9, 30.1, 21.0 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{19}H_{17}N_3O_2Na$ 342.1213 Found 342.1221.



4s

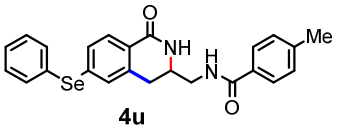
(R,E)-N-((6-((methoxyimino)methyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4s): Eluent:(DCM/ EtOAc/MeOH = 15/80/5); white solid; yield = 50.0 mg (57%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.55 – 8.52 (m, 1H), 8.26 (s, 1H), 8.11 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.9 Hz, 2H), 7.58 – 7.56 (m, 2H), 7.27 (d, J = 7.7 Hz, 2H), 3.92 (s, 3H), 3.78 (s, 1H), 3.17 – 3.02 (m, 1H), 2.95 – 2.78 (m, 1H), 2.36 (s, 3H). (2H signal merged with DMSO water peak); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 163.6, 148.1, 141.1, 138.2, 135.0, 131.5, 129.8, 128.8, 127.4, 127.3, 126.2, 125.2, 61.8, 49.9, 43.0, 30.5, 20.9 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{20}H_{21}N_3O_3Na$ 374.1475 Found 374.1484.



4t

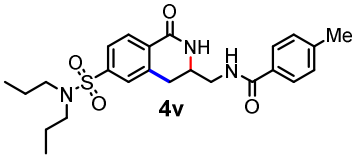
(R)-N-((6-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4t): Eluent:(DCM/ EtOAc/MeOH = 16/80/4); Melting point = 231–233 °C; Grey solid; yield = 43.0 mg (55 %); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.52 (s, 1H), 7.77 (d, J = 7.9 Hz, 2H), 7.71 – 7.65 (m, 2H), 7.28 (d, J = 7.8 Hz, 2H), 6.71 (d, J = 8.7 Hz, 1H), 6.64 (s, 1H), 3.76 – 3.69 (m, 1H), 2.96 – 2.91 (m, 1H), 2.77 – 2.71 (m, 1H), 2.36 (s, 3H), (2 CH signal peaks merged with water peak) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 164.5, 160.7, 141.2, 139.9, 131.5, 129.2, 128.8, 127.3, 120.1, 114.1, 113.8, 50.2, 43.1, 31.1, 21.0 ppm; ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{18}H_{18}N_2O_3Na$ 333.1210 Found 333.1214

4-methyl-N-((1-oxo-6-(phenylselanyl)-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)benzamide (4u): Eluent:(Hexane/ EtOAc= 20/80); Melting point = 196–198 °C; Grey solid; yield = 99.0 mg (88%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.93 (s, 1H), 7.80-7.77 (m, 3H), 7.60 (d, J = 6.1 Hz,



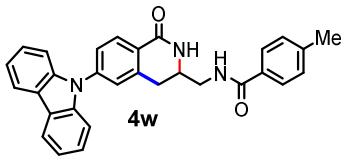
4u

2H), 7.42-7.37 (m, 3H), 7.27 – 7.25 (m, 1H), 7.17 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 4.08 – 4.03 (m, 1H), 3.99 – 3.93 (m, 1H), 3.40 – 3.33 (m, 1H), 2.91 – 2.77 (m, 2H), 2.31 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 167.5, 142.0, 139.7, 139.0, 135.2, 131.2, 129.9, 129.3, 129.2, 129.1 128.8, 128.6, 128.4, 127.4, 126.3, 52.0, 43.6, 31.8, 21.6 ppm; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{24}H_{23}N_2O_2Se$ 451.0919 Found 451.0905.



4v

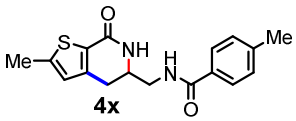
N-((6-(N,N-dipropylsulfamoyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4v): Eluent: (DCM/ EtOAc/MeOH = 15/80/5); Melting point = 238–240 °C; Brown solid; yield = 62.0 mg (52%); **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 8.53 – 8.50 (m, 1H), 8.29 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.74 – 7.70 (m, 4H), 7.27 (d, *J* = 7.9 Hz, 2H), 3.83 – 3.79 (m, 1H), 3.39 (d, *J* = 6.3 Hz, 2H), 3.20 (dd, *J* = 16.3, 5.3 Hz, 1H), 3.03 – 2.94 (m, 5H), 2.35 (s, 3H), 1.47 (h, *J* = 7.4 Hz, 4H), 0.81 (t, *J* = 7.3 Hz, 6H) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 162.9, 142.0, 141.1, 139.1, 132.1, 131.5, 128.7, 127.8, 127.2, 126.4, 124.9, 49.9, 49.7, 43.0, 30.4, 21.7, 20.9, 11.0 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{24}H_{31}N_3O_4SNa$ 480.1927 Found 480.1936.



4w

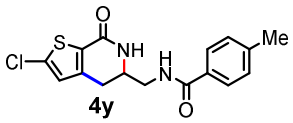
N-((6-(9H-carbazol-9-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-4-methylbenzamide (4w): Eluent:(Hexane/ EtOAc= 15/85); Melting point = 232 –234 °C; Grey solid; yield = 94.0 mg (82%); **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 8.60-8.57 (m,1H), 8.24 (d, *J* = 7.8 Hz, 2H), 8.17 – 8.13 (m, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.60 – 7.57 (m, 2H), 7.53-7.51 (m, 2H), 7.46-7.42 (m, 2H), 7.32-7.29 (m, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 3.92-3.86 (m, 1H), 3.56-3.44 (m, 2H), 3.24-3.19 (m, 1H), 3.02 – 2.96 (m, 1H), 2.34 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 163.7, 141.1, 140.0, 139.8, 139.6, 131.5, 128.8, (2C) 127.6, 127.3, 126.3, 125.6, 124.3, 123.0, 120.5, 120.4, 110.0, 50.2, 43.1, 30.7, 20.9 ppm ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{30}H_{25}N_3O_2Na$ 482.1839 Found 482.1848.

4-methyl-N-((2-methyl-7-oxo-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-5-yl)methyl)benzamide (4x): Eluent:(DCM/ EtOAc/MeOH = 18/80/2);



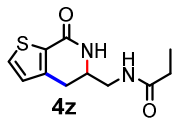
4x

Melting point = 171–173 °C; White solid; yield = 57.0 mg (72%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.55 – 8.52 (m, 1H), 7.77 (d, J = 7.9 Hz, 2H), 7.66 (s, 1H), 7.28 (d, J = 7.8 Hz, 2H), 6.76 (s, 1H), 3.85 – 3.78 (m, 1H), 3.45 – 3.40 (m, 2H), 2.92 – 2.86 (m, 1H), 2.71 – 2.65 (m, 1H), 2.46 (s, 3H), 2.36 (s, 3H) ppm; **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 161.4, 145.4, 144.0, 141.2, 131.5, 128.8, 128.1, 127.3, 126.5, 51.6, 42.8, 27.3, 21.0, 15.4 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{17}H_{18}N_2O_2SNa$ 337.0999 Found 337.0981.



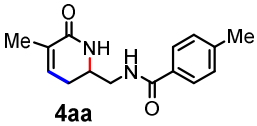
4y

N-((2-chloro-7-oxo-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-5-yl)methyl)-4-methylbenzamide (4y): Eluent:(DCM/ EtOAc/MeOH = 17/80/3); Melting point = 212–214 °C; White solid; yield = 53.0 mg (63 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.80 (d, J = 7.8 Hz, 2H), 7.67 – 7.64 (m, 1H), 7.19 (d, J = 7.8 Hz, 2H), 6.82 (s, 1H), 4.09 – 4.00 (m, 2H), 3.43 – 3.36 (m, 1H), 2.98 – 2.92 (m, 1H), 2.73 – 2.65 (m, 1H), 2.37 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 163.2, 144.2, 142.3, 137.7, 131.0, 129.4, 128.6, 127.4, 126.8, 53.3, 43.5, 28.3, 21.6 ppm ; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{16}H_{15}ClN_2O_2SNa$ 357.0435 Found 357.0452.



4z

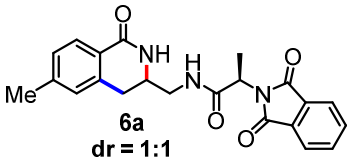
N-((7-oxo-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-5-yl)methyl)propionamide (4z): Eluent:(DCM/ EtOAc/MeOH = 15/80/5); white solid; yield = 55.0 mg (94%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.33 (d, J = 5.2 Hz, 1H), 7.13 – 7.10 (m, 2H), 4.03 – 3.98 (m, 1H), 3.85 – 3.79 (m, 1H), 3.27 – 3.20 (m, 1H), 3.15 – 3.10 (m, 1H), 2.91 – 2.84 (m, 1H), 2.26 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9, 164.6, 145.9, 131.3, 125.4, 123.8, 53.1, 43.1, 29.8, 27.8, 9.9 ppm; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{11}H_{14}N_2O_2SNa$ 261.0677 Found 261.0668.



4aa

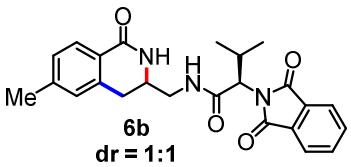
4-methyl-N-((5-methyl-6-oxo-1,2,3,6-tetrahydropyridin-2-yl)methyl)benzamide (4aa): Eluent:(DCM/ EtOAc/MeOH = 15/80/5); Colourless liquid; yield = 43.0 mg (67 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ

8.36 (s, 1H), 7.86 – 7.80 (m, 3H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.37 – 6.35 (m, 1H), 4.00 – 3.94 (m, 1H), 3.85 – 3.77 (m, 1H), 3.25 – 3.18 (m, 1H), 2.36 (s, 3H), 2.22 – 2.13 (m, 1H), 2.05 – 1.93 (m, 1H), 1.86 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.7, 167.9, 142.0, 135.3, 131.3, 130.5, 129.1, 127.5, 51.8, 43.6, 27.8, 21.6, 16.7 ppm; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{15}H_{19}N_2O_2$ 259.1441 Found 259.1436.



6a
dr = 1:1

(R)-2-(1,3-dioxoisoindolin-2-yl)-N-(((R)-6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)propenamide (6a): Eluent: (Hexane/ EtOAc = 15/85); colour less liquid ; yield = 89.0 mg (91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 1H), 7.97 (s, 1H), 7.80 – 7.74 (m, 2H), 7.73 – 7.68 (m, 4H), 7.63 – 7.57 (m, 3H), 7.54 – 7.50 (m, 3H), 7.09 – 7.05 (m, 2H), 6.93 (d, *J* = 11.8 Hz, 2H), 5.01 – 4.91 (m, 2H), 3.89 – 3.86 (m, 1H), 3.72 – 3.60 (m, 3H), 3.33 – 3.26 (m, 1H), 2.90 – 2.74 (m, 3H), 2.70 – 2.67 (m, 1H), 2.62 – 2.56 (m, 1H), 2.35 (d, *J* = 4.8 Hz, 6H), 1.72 – 1.61 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.1(CC*), 168.1(C), 167.9(C*), 167.2(C), 166.7(C*), 143.4(C), 143.3(C*), 137.9(C), 137.3(C*), 133.9(C), 133.7(C*), 132.1(CC*), 128.3(C), 128.2(C*), 127.9(CC*), 127.8(C), 127.7(C*), 125.1(C), 124.7(C*), 123.5(C), 123.4(C*), 51.5(C), 50.7(C*), 49.1(C), 48.6(C*), 44.1(C), 43.2(C*), 31.5(C), 31.2(C*), 21.7(CC*), 15.4(C), 15.3(C*) ppm; [C = First diastereomer, C* = Second diastereomer, CC*= both diastereomer peaks merging]; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{22}H_{22}N_3O_4$ 392.1605 Found 392.1599.

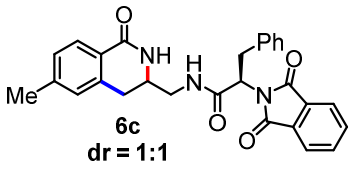


6b
dr = 1:1

(R)-2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(((R)-6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)butanamide (6b): Eluent: (Hexane/ EtOAc = 15/85); colourless liquid; yield = 90.0 mg (86%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 1H), 7.84 – 7.56 (m, 13H), 7.12 – 7.04 (m, 2H), 6.95 (d, *J* = 9.6 Hz, 2H), 4.53 – 4.45 (m, 2H), 3.82–3.75 (m,2H), 3.68 – 3.62 (m,1H), 3.29 – 3.22 (m, 1H), 3.09 – 3.01 (m,1H), 2.90 – 2.79 (m, 3H), 2.73 – 2.65 (m, 2H), 2.36 – 2.34 (m, 6H), 1.27 –1.25 (m, 2H), 1.09 –1.02 (m, 6H), 0.82–0.77 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5(C), 169.4(C*), 168.5(C), 168.3(C*), 166.9(C), 166.8(C*),

143.2(CC*), 137.6(C), 137.4(C*), 134.2(C), 133.9(C*), 131.7(C), 131.6(C*), 128.3(C), 128.2(C*), 128.0(CC*),127.9 (CC*) 125.4(C), 125.2(C*), 123.6(CC*), 61.6(C), 60.3(C*), 51.4(C), 50.9(C*) 43.9(C), 43.3(C*), 31.6(C), 31.5(C*), 28.2(C), 27.6(C*), 21.7(CC*), 20.9(C), 20.5(C*), 19.6(C), 19.4(C*) ppm; [C = First diastereomer, C* = Second diastereomer, CC*= both diastereomer peaks merging]; HRMS (ESI) m/z: [M+Na]+ Calcd. For $C_{24}H_{25}N_3O_4Na$ 442.1737 Found 442.1749.

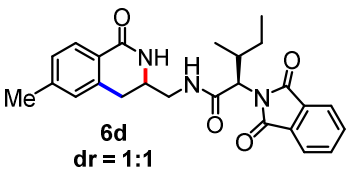
(R)-2-(1,3-dioxoisoindolin-2-yl)-N-(((R)-6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-3-phenylpropanamide (6c):



6c
dr = 1:1

Eluent:(Hexane/ EtOAc = 20/80); colourless liquid ; yield = 96.0 mg (82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 – 8.23 (m, 1H), 7.97– 7.89 (m, 2H), 7.68 (s, 1H), 7.61 – 7.53 (m, 5H), 7.48 – 7.43 (m, 5H), 7.10 – 7.05 (m, 10H), 6.98 – 6.95 (m, 2H), 6.92 – 6.87 (m, 2H), 5.16 – 5.12 (m, 2H), 3.92 – 3.87 (m, 1H), 3.74 – 3.60 (m, 5H), 3.53 – 3.43 (m, 2H), 3.38 – 3.31 (m, 1H), 2.91 – 2.84 (m, 1H), 2.81 – 2.65 (m, 3H), 2.60 – 2.53 (m, 1H), 2.32 – 2.30 (m, 6H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3(CC*), 168.1(C), 167.9(C*), 167.1(C), 166.5(C*), 143.3(C), 143.2(C*), 137.9(C), 137.3(C*), 137.1(CC*), 133.7(C), 133.5(C*), 131.7(C), 131.6(C*), 129.0(C), 128.9(C*), 128.5(CC*), 128.1(CC*), 127.8(2×CC*), 126.7(CC*), 125.0(C), 124.6(C*), 123.4(C), 123.2(C*), 55.3(C), 54.8(C*), 51.6(C), 50.8(C*), 44.0(C), 43.0(C*), 34.8(C), 34.6(C*), 31.5(C), 31.2(C*), 21.6(CC*) ppm; [C = First diastereomer, C* = Second diastereomer, CC*= both diastereomer peaks merging]; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{28}H_{26}N_3O_4$ 468.1918 Found 468.1913.

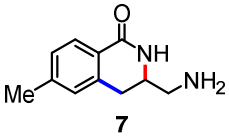
(2R,3S)-2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(((R)-6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)pentanamide (6d):



6d
dr = 1:1

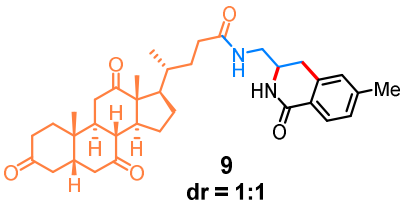
Eluent:(Hexane/ EtOAc = 15/85); colourless liquid ; yield = 92.0 mg (85%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.92 (s, 1H), 7.84 – 7.80 (m, 2H), 7.74 – 7.72 (m, 3H), 7.69 – 7.67 (m, 2H), 7.64 – 7.61 (m, 2H), 7.58 – 7.56 (m, 2H), 7.26 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H),

6.94 (d, J = 10.3 Hz, 2H), 4.58 – 4.52 (m, 2H), 3.79 – 3.74 (m, 3H), 3.68 – 3.62 (m, 1H), 3.29 – 3.21 (m,1H), 3.12 – 3.05 (m, 1H), 2.86 – 2.80 (m, 2H), 2.75 – 2.68 (m, 3H), 2.65 – 2.60 (m, 1H), 2.34 – 2.32 (m, 6H), 1.40 – 1.28 (m, 2H), 1.03 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.95 – 0.90 (m, 2H), 0.79 – 0.72 (m, 6H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.6(C), 169.5(C*), 168.4(C), 168.3(C*), 167.0(C), 166.8(C*), 143.2(CC*), 137.6(C), 137.4(C*), 134.1(C), 133.9(C*), 131.7(C), 131.6(C*), 128.2(CC*), 128.0(C), 127.9(C*CC*), 125.4(C), 125.2(C*), 123.5(CC*), 60.5(C), 59.7(C*), 51.3(C), 50.9(C*), 43.8(C), 43.3(C*), 33.9(C), 33.0(C*), 31.6(C), 31.4(C*), 25.6(CC*), 21.7(C), 21.6(C*), 16.7(C), 16.3(C*), 10.8(C), 10.4(C*) ppm; [C = First diastereomer, C* = Second diastereomer, CC*= both diastereomer peaks merging]; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{25}H_{28}N_3O_4$ 434.2074 Found 434.2069.



7

(R)-3-(aminomethyl)-6-methyl-3,4-dihydroisoquinolin-1(2H)-one (7): colourless liquid; yield = 51.0 mg (89%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 6.98 (s, 1H), 3.79 – 3.64 (m, 1H), 3.03 – 2.69 (m, 4H), 2.51 – 2.45 (m, 2H), 2.35 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.5, 143.0, 137.7, 128.3, 128.1, 128.0, 126.2, 52.8, 46.0, 32.0, 21.7 ppm; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{11}H_{15}N_2O$ 191.1179 Found 191.1177.

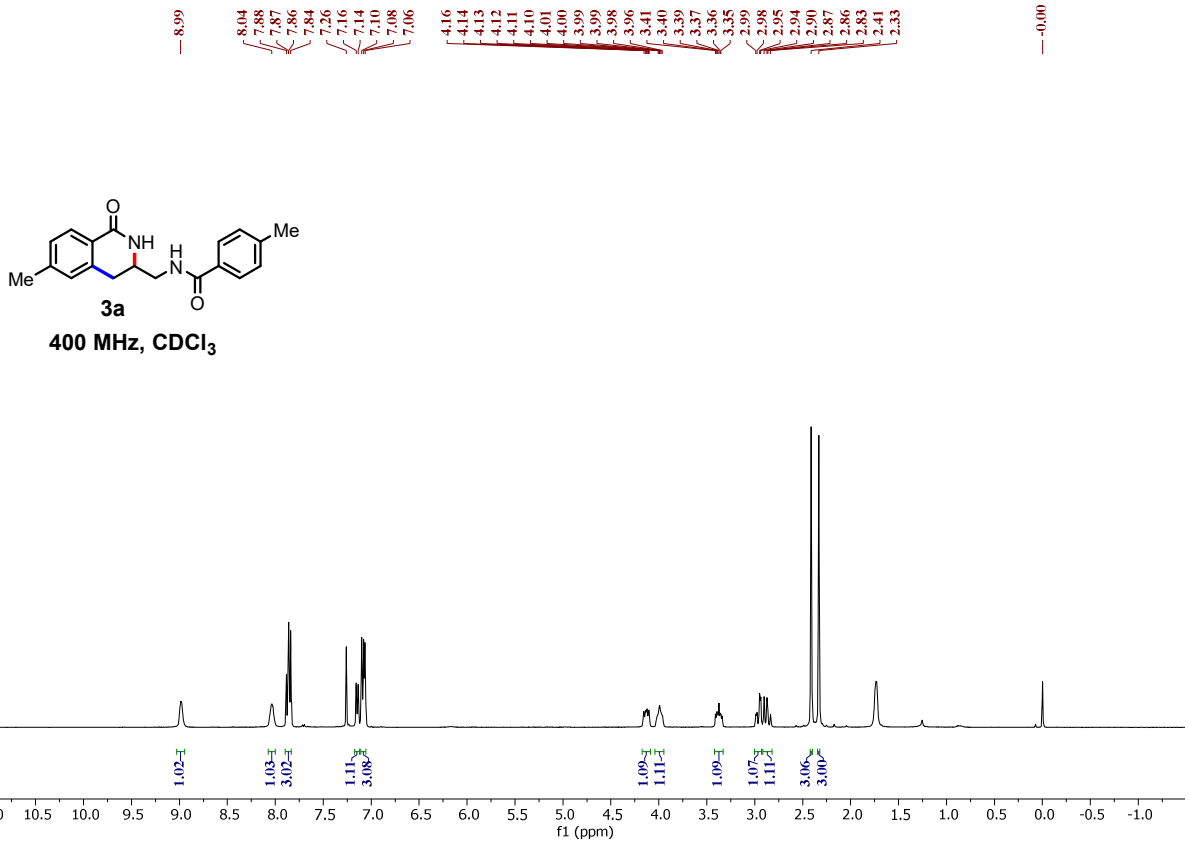


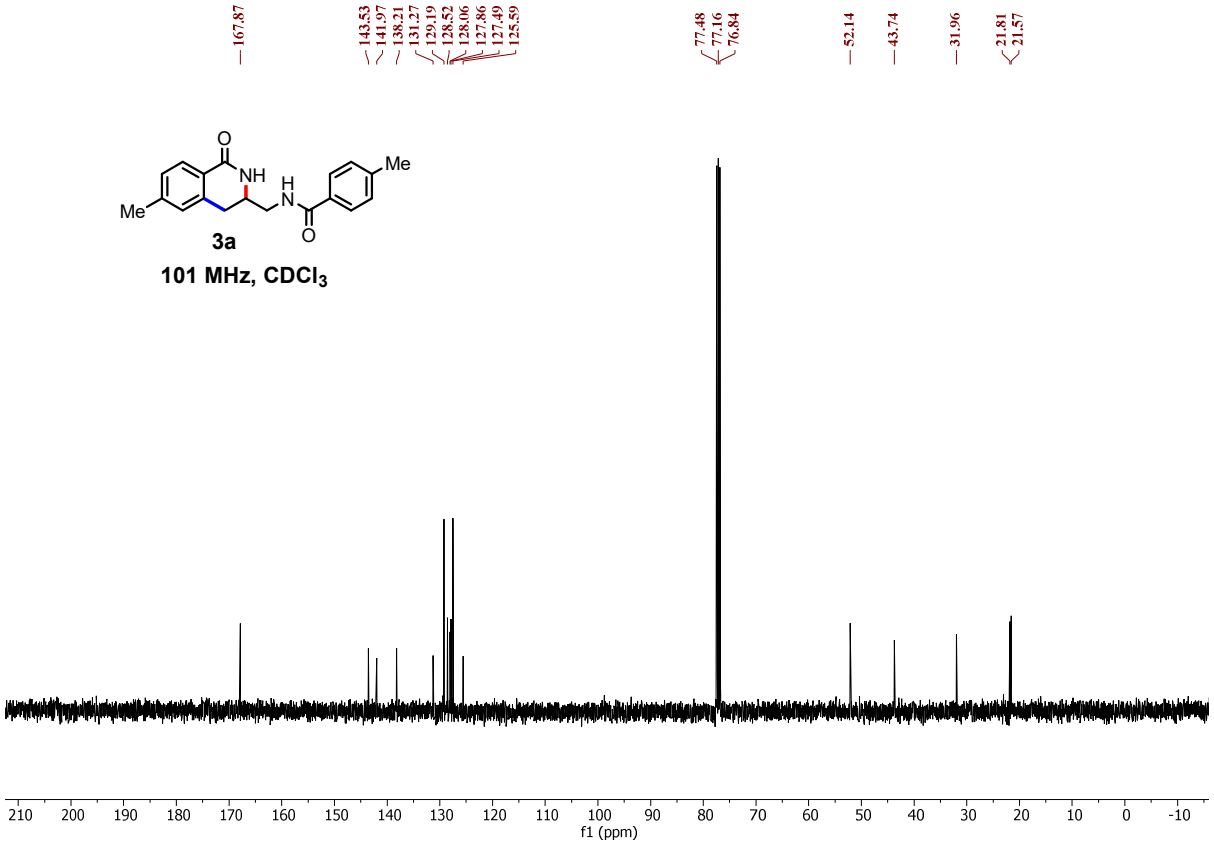
9
dr = 1:1

(R)-4-((5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-N-(((R)-6-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)pentanamide (9): Eluent: (DCM/EtOAc/MeOH = 15/80/5); sticky colourless liquid; yield = 134.0 mg (93%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.39 (s, 2H), 7.85 (d, J = 7.9 Hz, 2H), 7.29 – 7.27 (m, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.00 (s, 2H), 3.87 – 3.79 (m, 4H), 3.17 – 3.12 (m, 2H), 2.92 – 2.75 (m, 10H), 2.35 (s, 6H), 2.33 – 2.26 (m, 7H), 2.23 – 2.113 (m, 10H), 2.10 – 2.05 (m, 4H), 2.02 – 1.99 (m, 1H), 1.97 – 1.90 (m, 8H), 1.76 – 1.68 (m, 2H), 1.62 – 1.55 (m, 2H), 1.39 – 1.34 (m, 7H), 1.28 – 1.15 (m, 7H), 0.99 (d, J = 6.4 Hz, 6H), 0.79 (d, J = 6.6 Hz, 6H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.1(CC*), 209.2(CC*), 208.8(CC*), 174.4(CC*), 167.6(C), 167.5(C*), 143.5(CC*), 137.9(CC*),

128.5(CC*) 128.1(CC*), 127.7(CC*), 125.4(CC*), 57.0(CC*), 51.8(CC*), 51.7(CC*), 49.0(CC*), 46.9(CC*), 45.7(C), 45.6(C*CC*), 45.0(CC*), 43.4(CC*), 42.9(CC*), 38.7(CC*), 36.5(CC*), 36.1(CC*), 35.7(C), 35.6(C*), 35.3(CC*), 33.8(C), 33.7(C*), 31.7(CC*), 31.3(C), 31.2(C*), 27.7(C), 27.6(C*), 25.2(CC*), 22.0(CC*), 21.7(CC*), 18.8(CC*), 11.9(CC*) ppm; [C= First diastereomer, C* = Second diastereomer, CC*= both diastereomer peaks merging]; HRMS (ESI) m/z: [M+H]+ Calcd. For $C_{35}H_{47}N_2O_5$ 575.3479 Found 575.3478.

NMR Spectra of Synthesized Compounds:

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52.14
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Me
Me
3a
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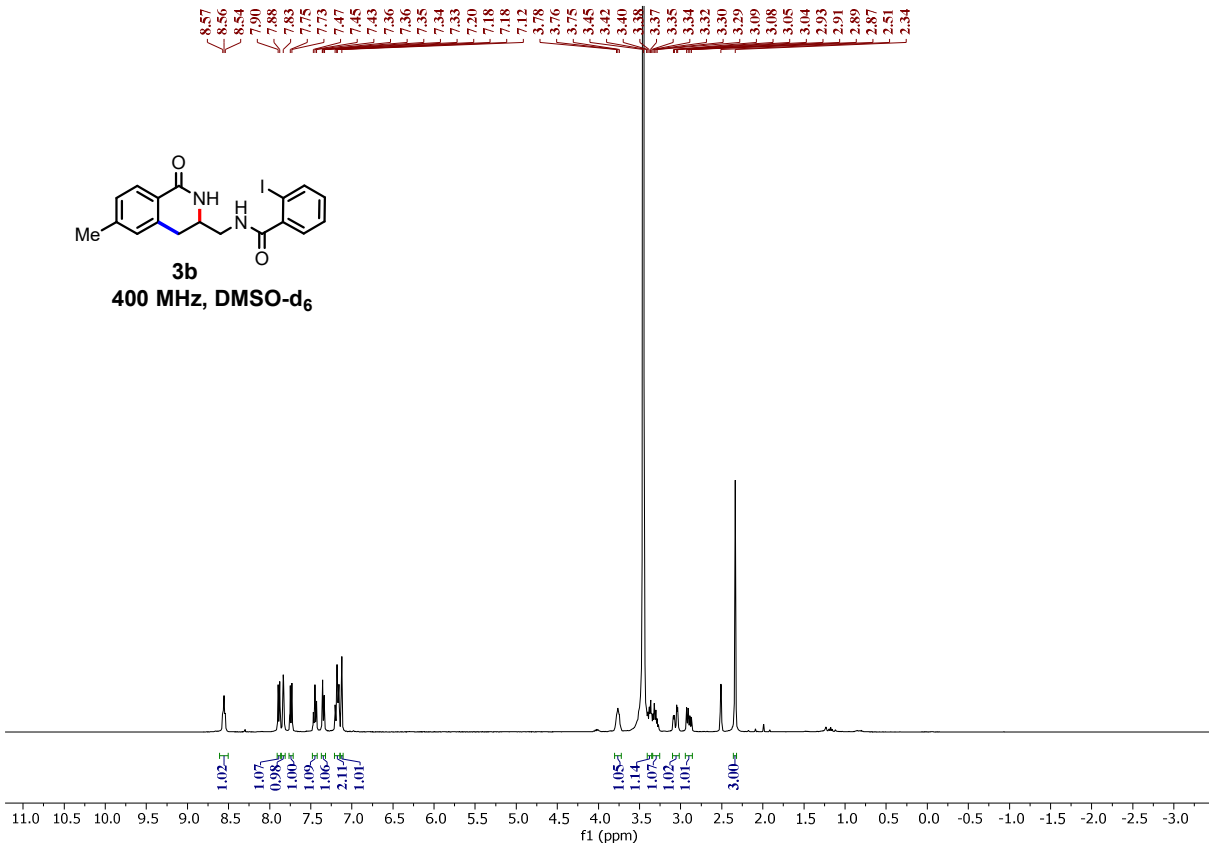
f1 (ppm)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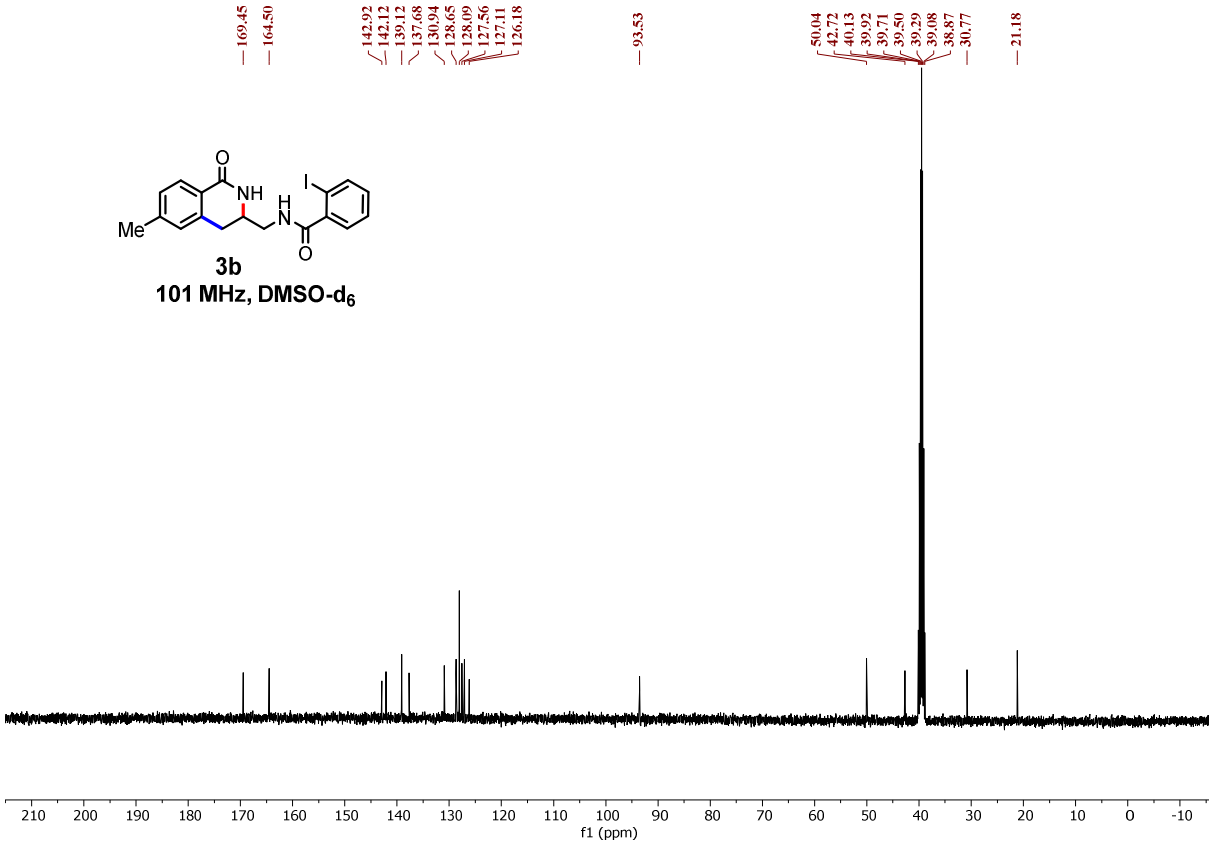
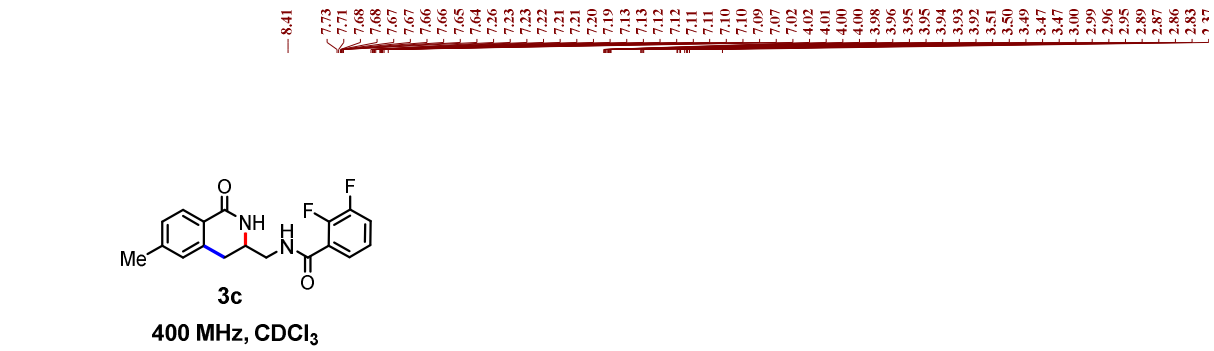
7.45
7.43
7.36
7.36
7.35
7.34
7.33
7.20
7.18
7.18
7.12
3.78
3.76
3.75
3.45
3.42
3.40
3.38
3.37
3.35
3.34
3.32
3.30
3.29
3.09
3.08
3.05
3.04
2.93
2.91
2.89
2.87
2.51
2.34
O
NH
H
N
O
I
Me
3b
400 MHz, DMSO-d6
1.02
1.07
0.98
1.00
1.09
1.06
2.11
1.01
1.05
1.14
1.07
1.02
1.01
3.00
f1 (ppm)



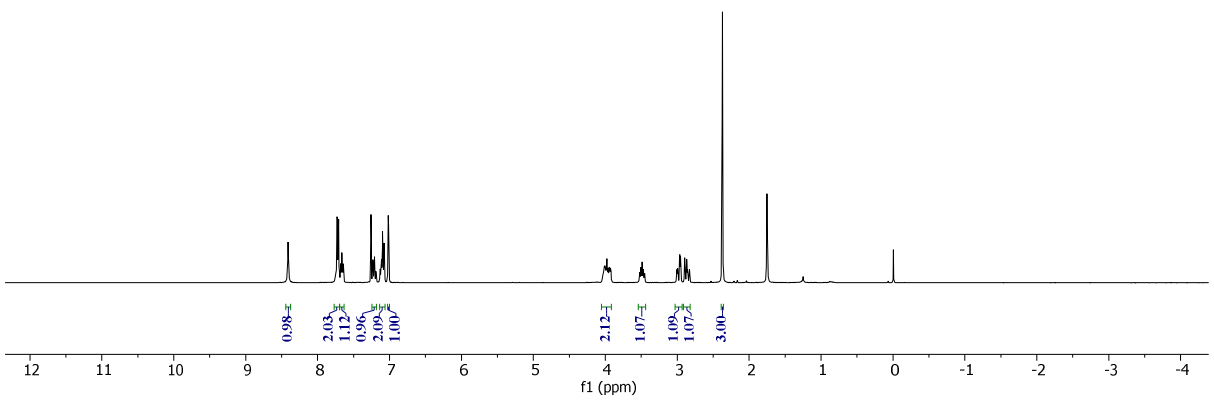
3b

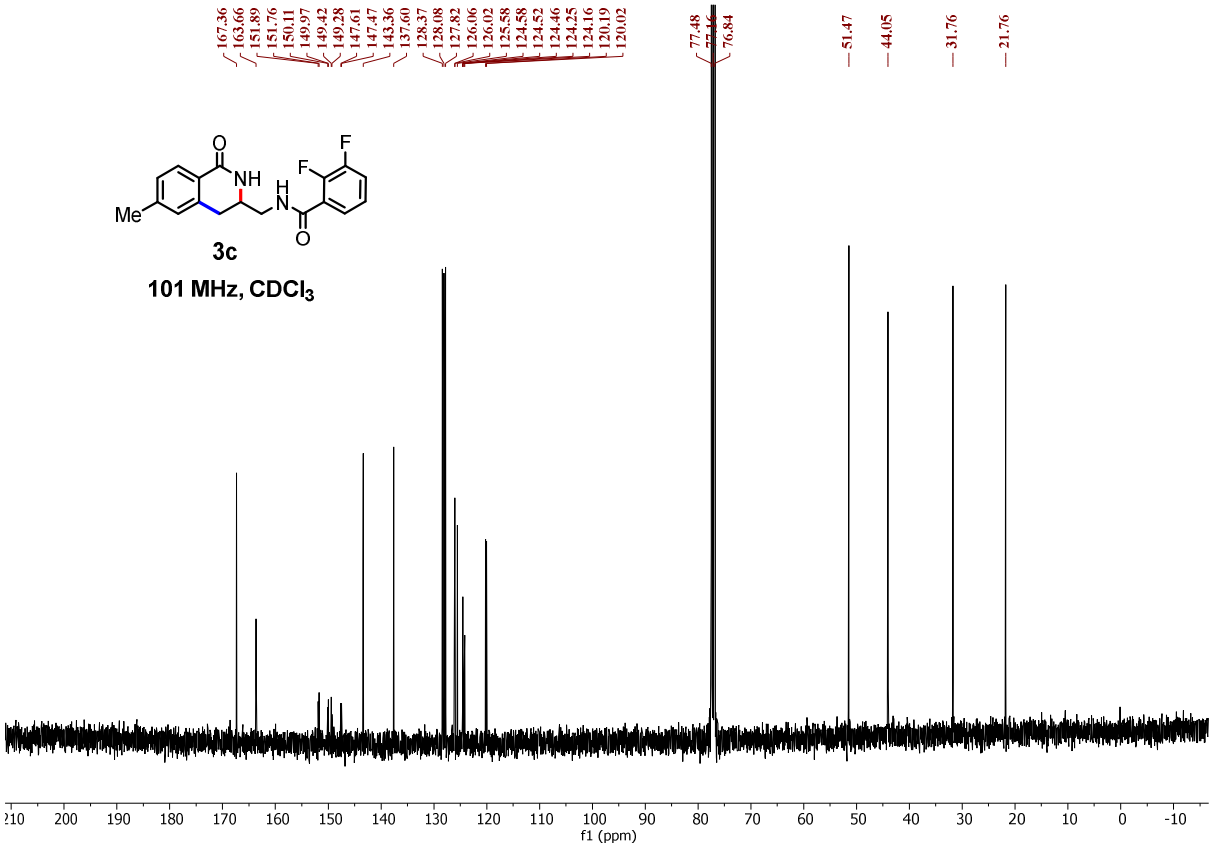
101 MHz, DMSO-d_6



3c

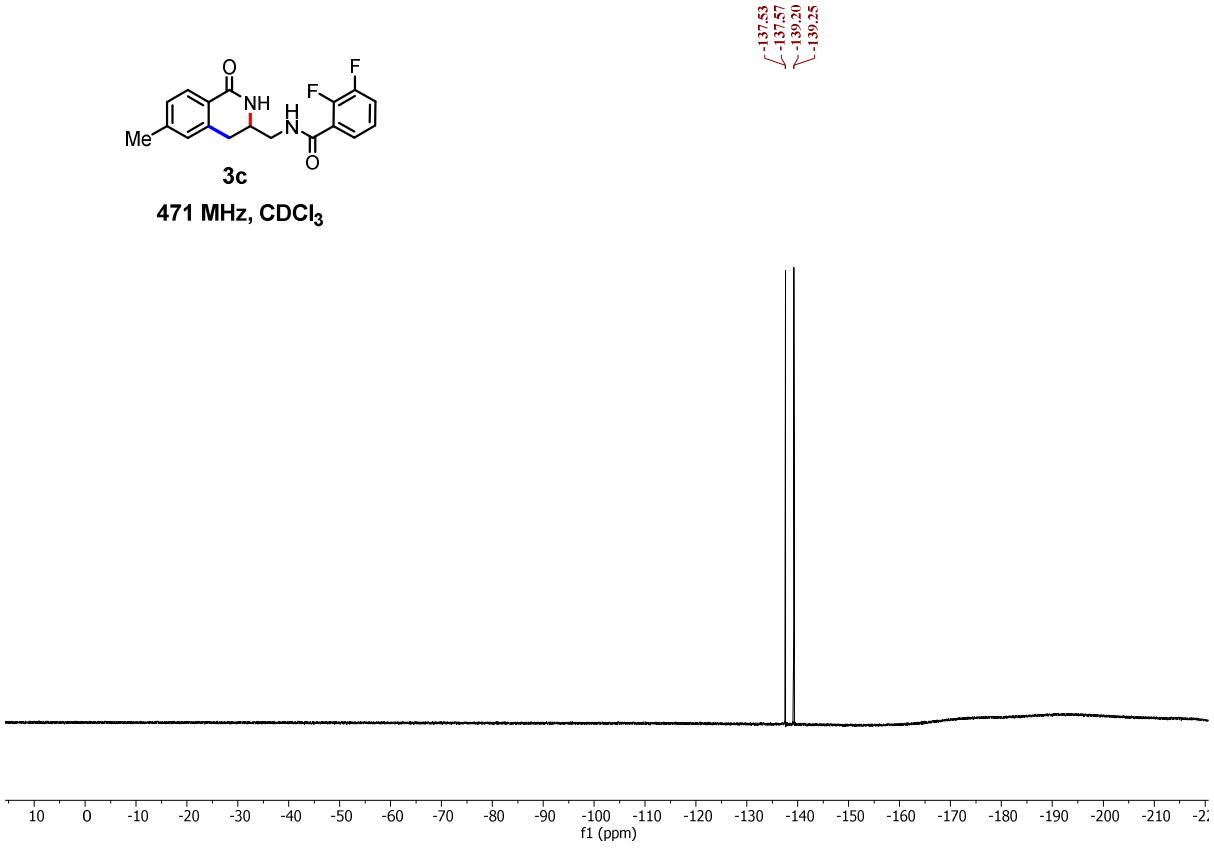
400 MHz, $CDCl_3$





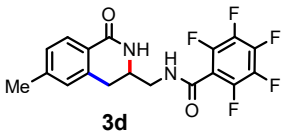
3c

101 MHz, $CDCl_3$



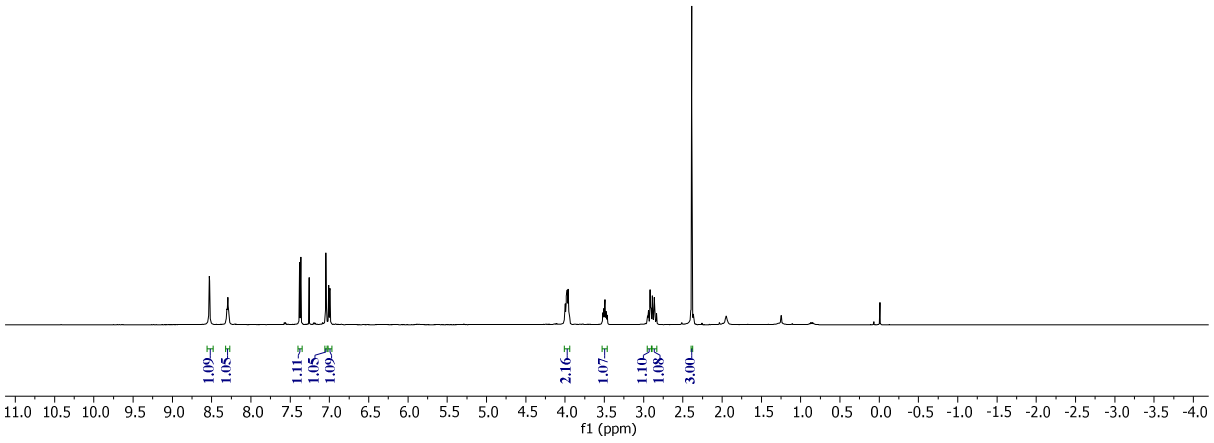
3c

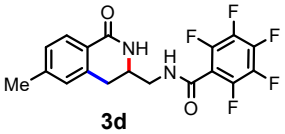
471 MHz, $CDCl_3$



3d

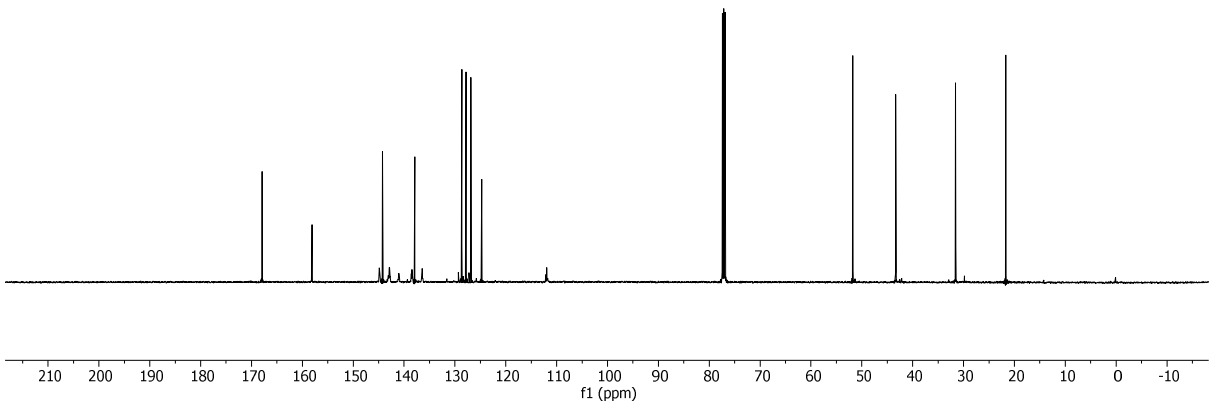
500 MHz, $CDCl_3$



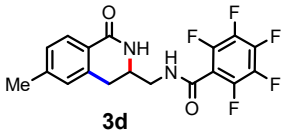


3d

126 MHz, $CDCl_3$

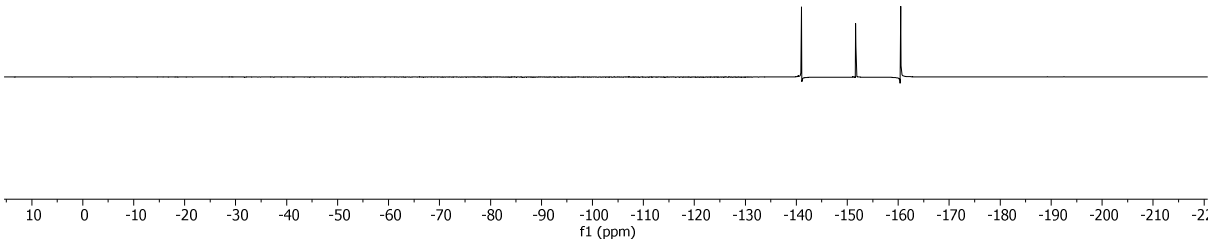


-140.98
-140.99
-141.01
-141.04
-141.05
-141.06
-141.06
-151.60
-151.64
-151.69
-160.35
-160.36
-160.37
-160.40
-160.41
-160.43
-160.44
-160.46
-160.47
-160.48
-160.50
-160.51
-160.52
-160.54
-160.56
-160.58
-160.59



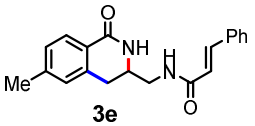
3d

471 MHz, $CDCl_3$



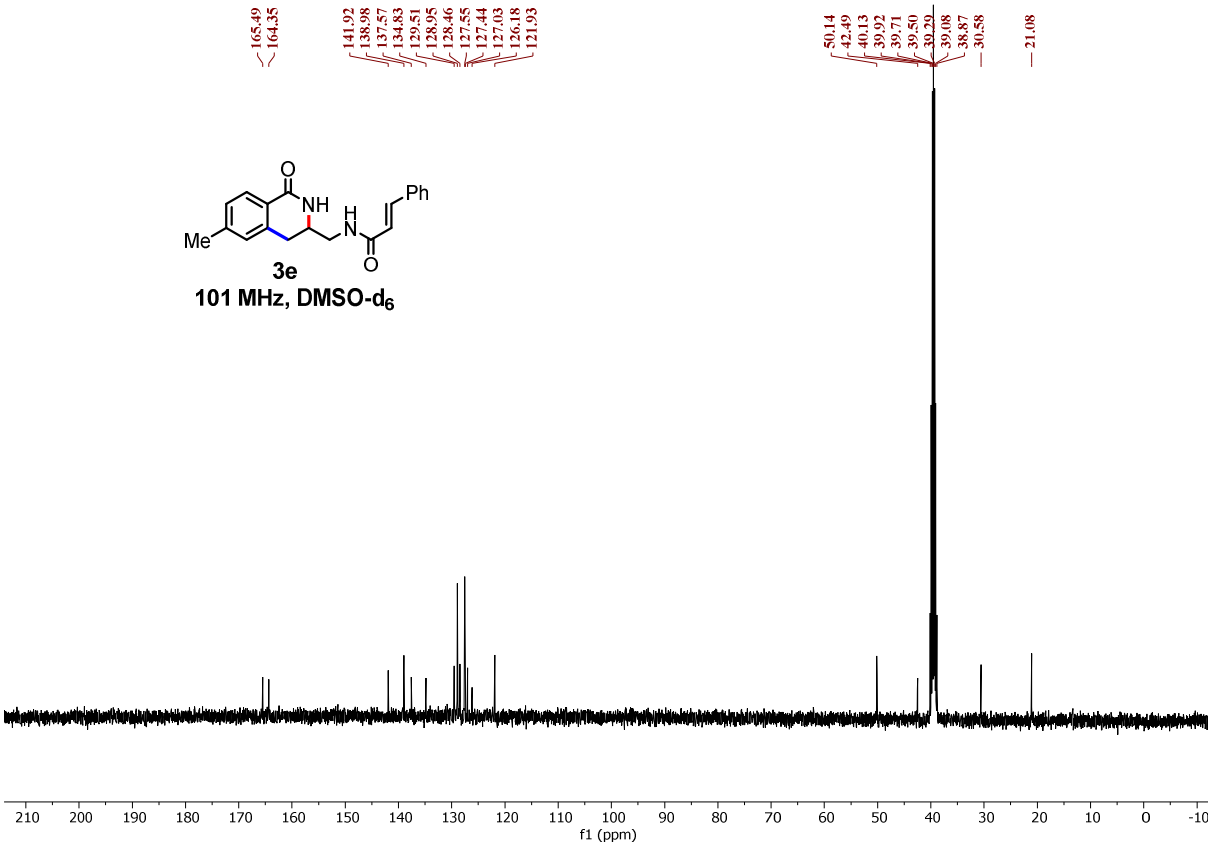
8.31
7.85
7.75
7.73
7.59
7.57
7.48
7.44
7.43
7.41
7.40
7.38
7.16
7.14
7.11
6.67
6.63

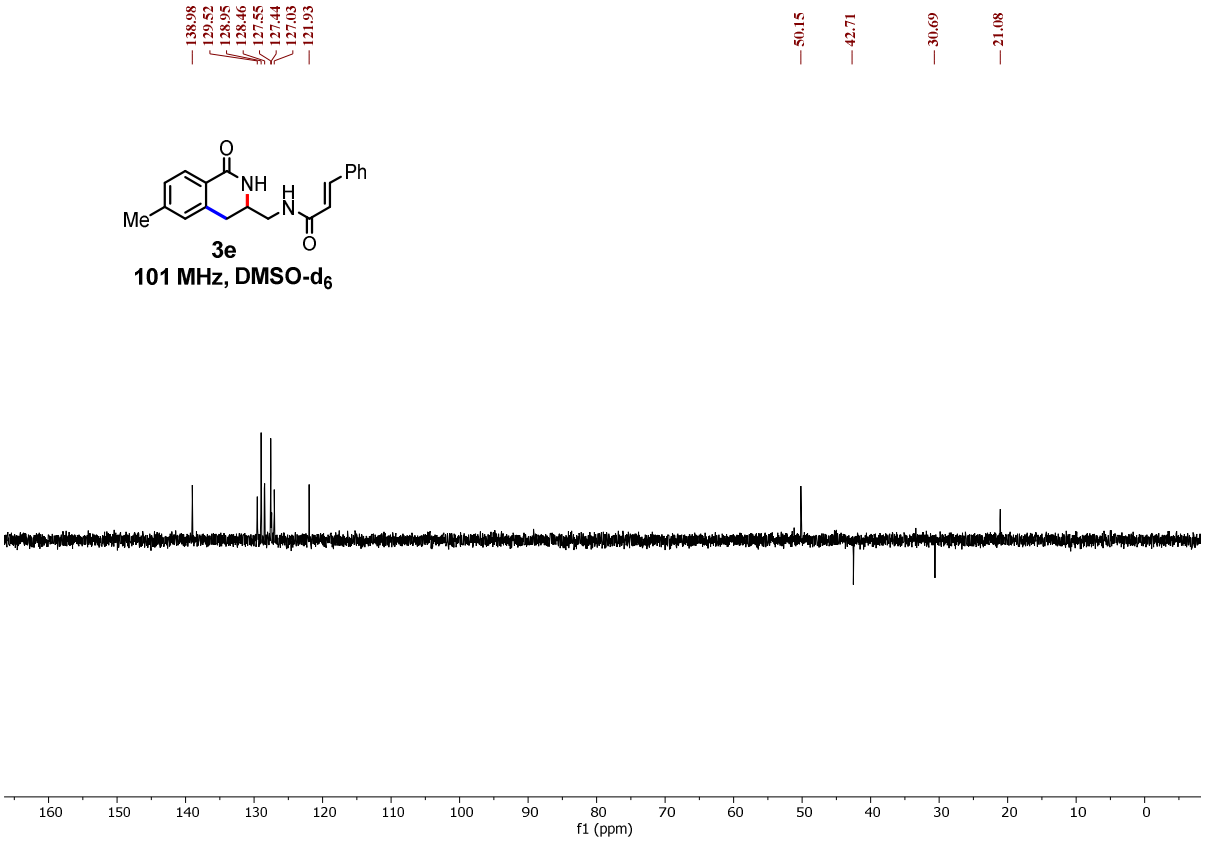
3.71
3.69
3.68
3.37
3.26
3.24
3.01
2.99
2.97
2.95
2.82
2.80
2.78
2.76
2.51
2.33

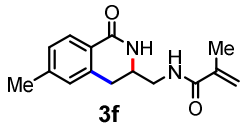


3e

400 MHz, DMSO-d_6

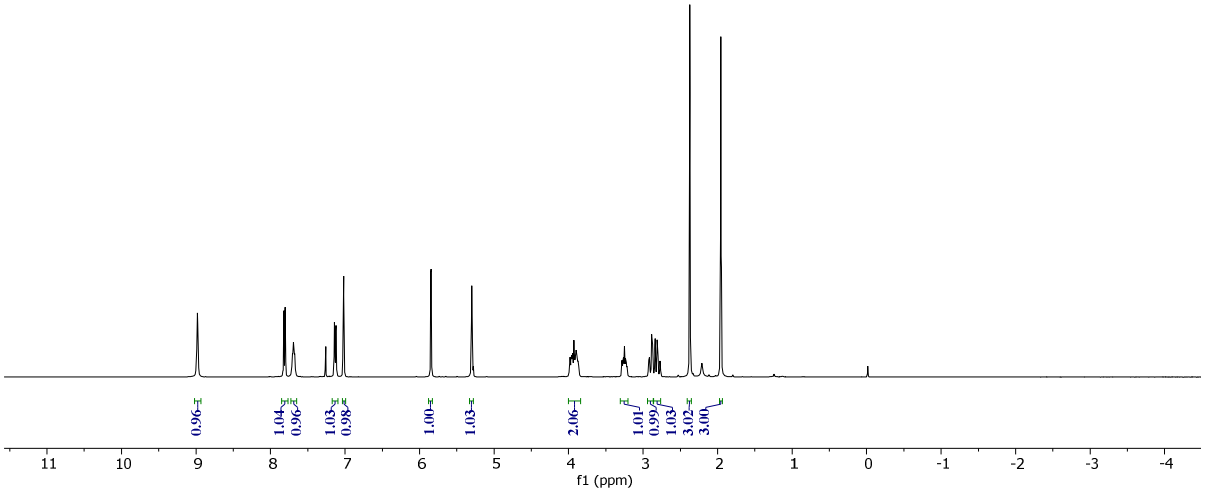

165.49
164.35
141.92
138.98
137.57
134.83
129.51
128.95
128.46
127.55
127.44
127.03
126.18
121.93
50.14
42.49
40.13
39.92
39.71
39.50
39.29
39.08
38.87
30.58
21.08
O
NH
H
N
Ph
Me
O
3e
101 MHz, DMSO-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

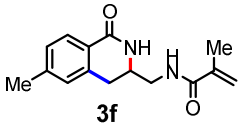

138.98
129.52
128.95
128.46
127.55
127.44
127.03
121.93
50.15
42.71
30.69
21.08
O
NH
H
N
Ph
Me
O
3e
101 MHz, DMSO-d6
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



3f

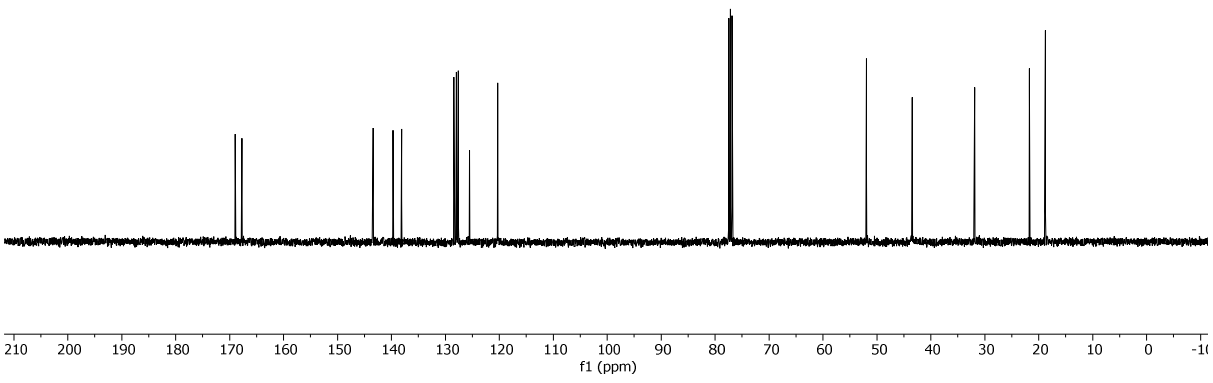
400 MHz, $CDCl_3$

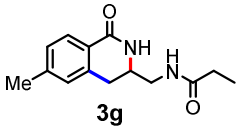




3f

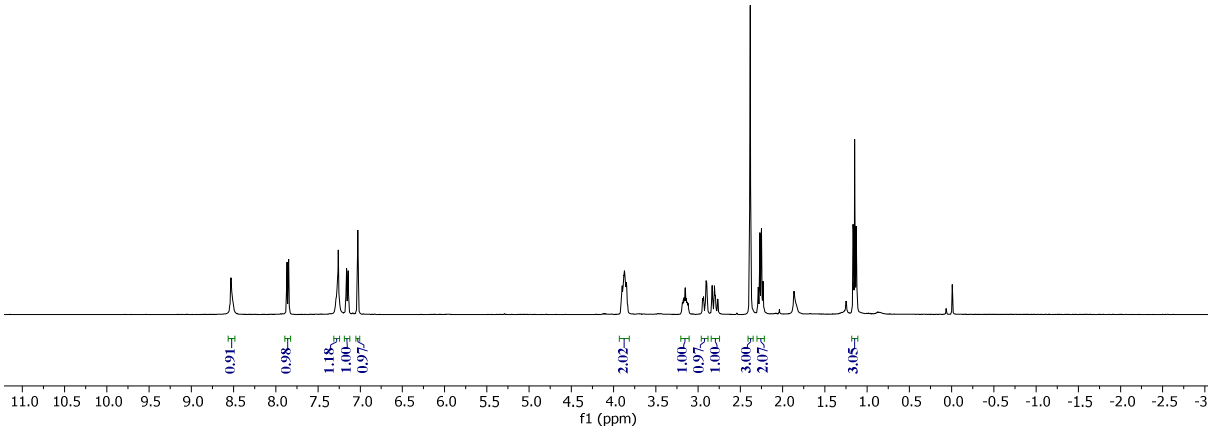
101 MHz, $CDCl_3$

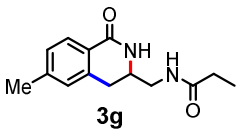




3g

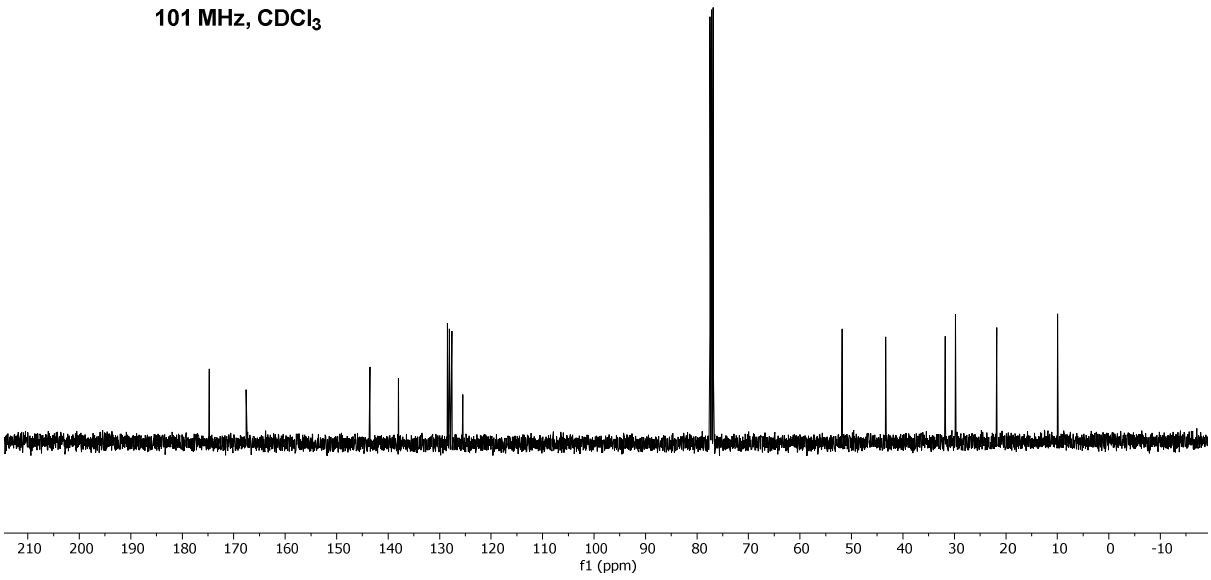
400 MHz, $CDCl_3$

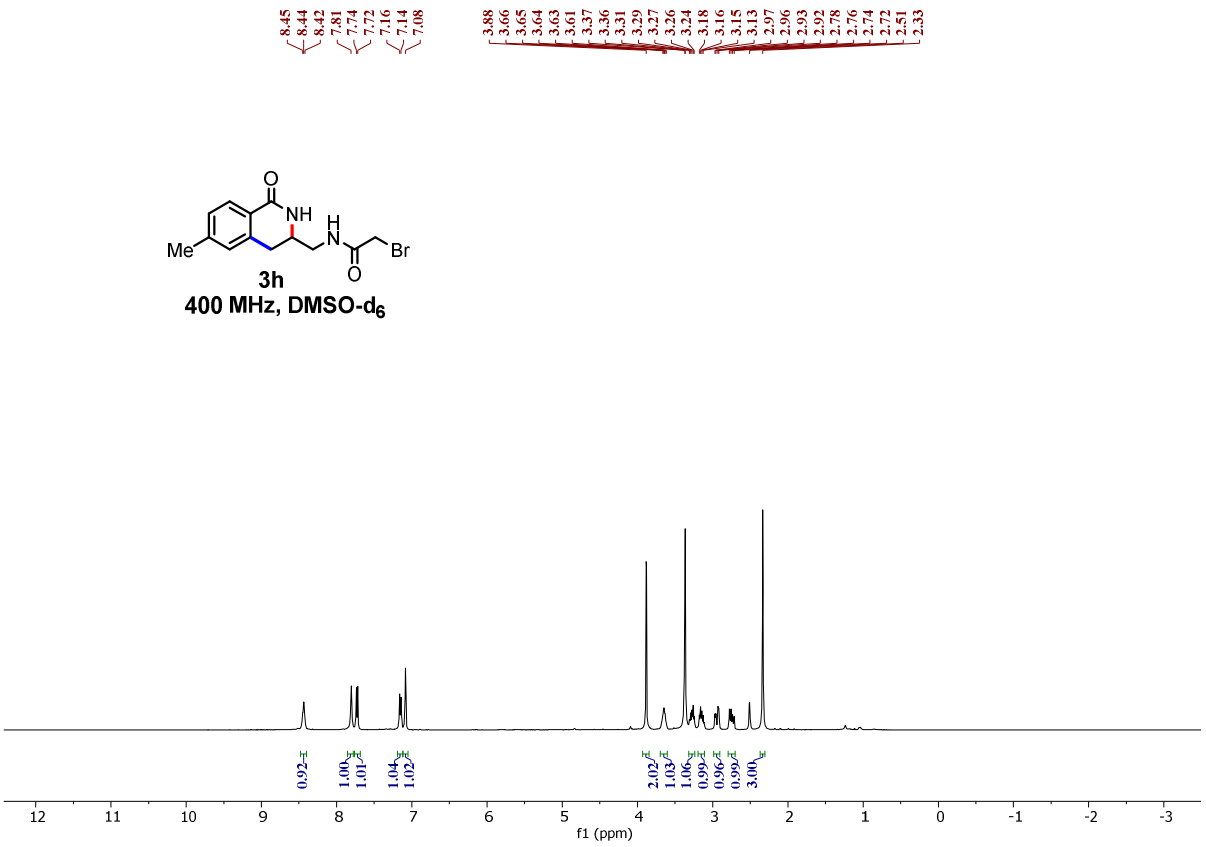


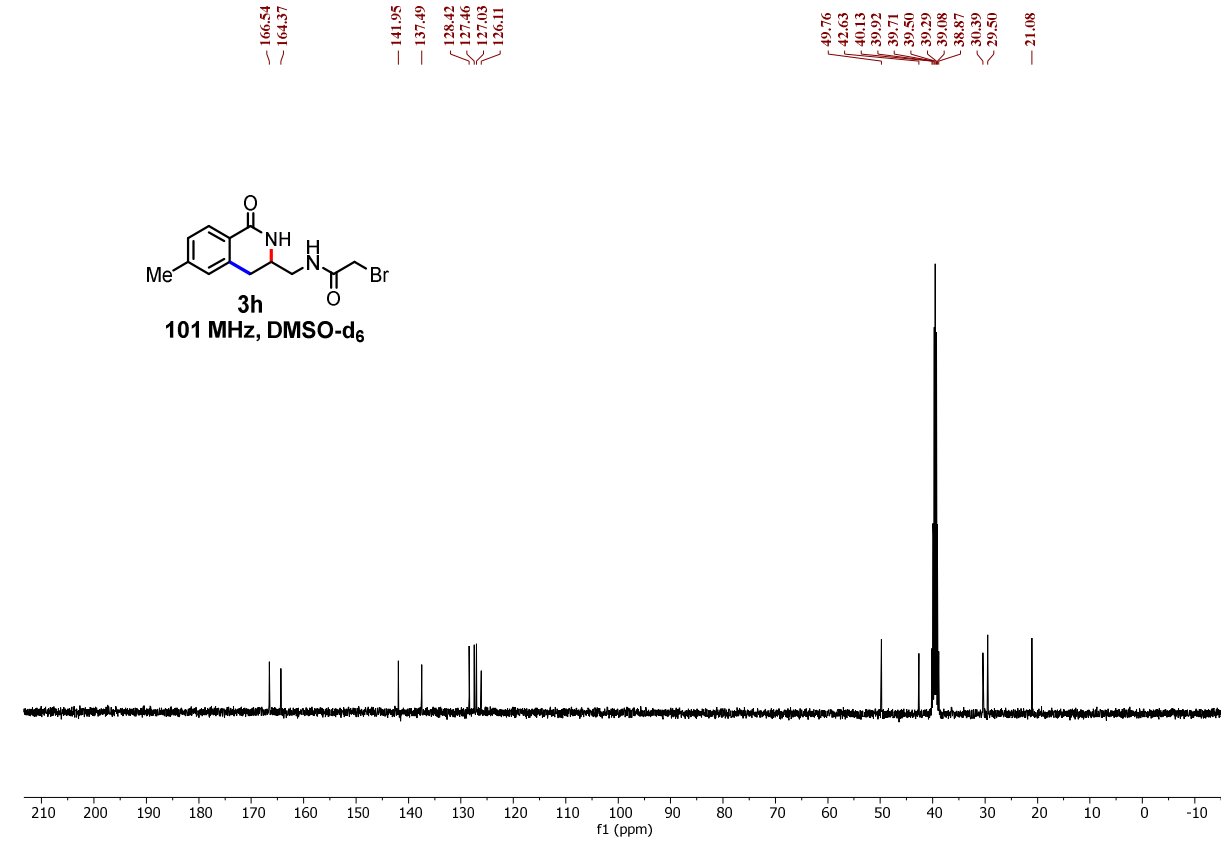


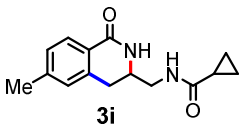
3g

101 MHz, $CDCl_3$



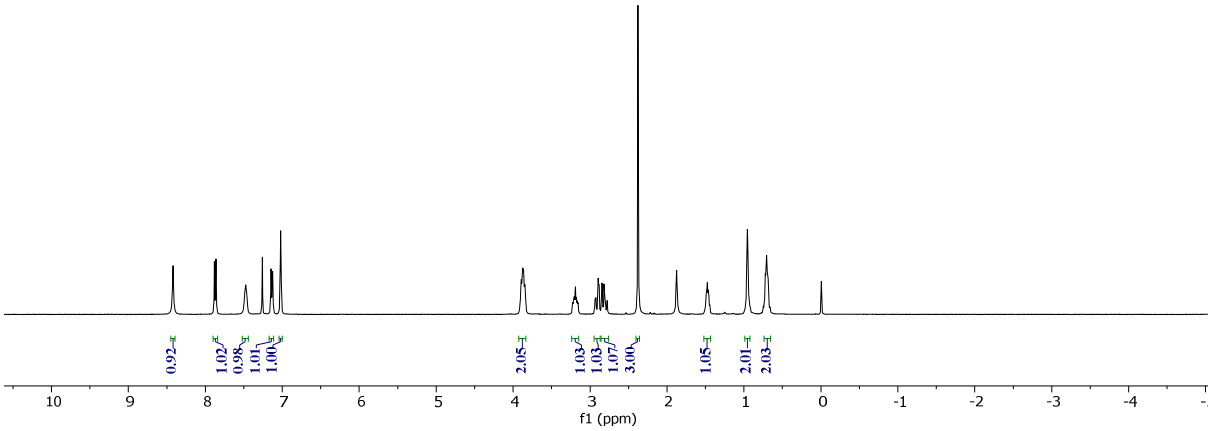

8.45
8.44
8.42
7.81
7.74
7.72
7.16
7.14
7.08
3.88
3.66
3.65
3.64
3.63
3.61
3.37
3.36
3.31
3.29
3.27
3.26
3.24
3.18
3.16
3.15
3.13
2.97
2.96
2.93
2.92
2.78
2.76
2.74
2.72
2.51
2.33
O
NH
H
N
Me
Br
O
3h
400 MHz, DMSO-d6
0.92
1.00
1.01
1.04
1.02
2.02
1.03
1.06
0.99
0.96
0.99
3.00
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)

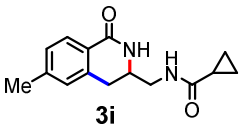

166.54
164.37
141.95
137.49
128.42
127.46
127.03
126.11
49.76
42.63
40.13
39.92
39.71
39.50
39.29
39.08
38.87
30.39
29.50
21.08
O
NH
H
N
Me
Br
O
3h
101 MHz, DMSO-d6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



3i

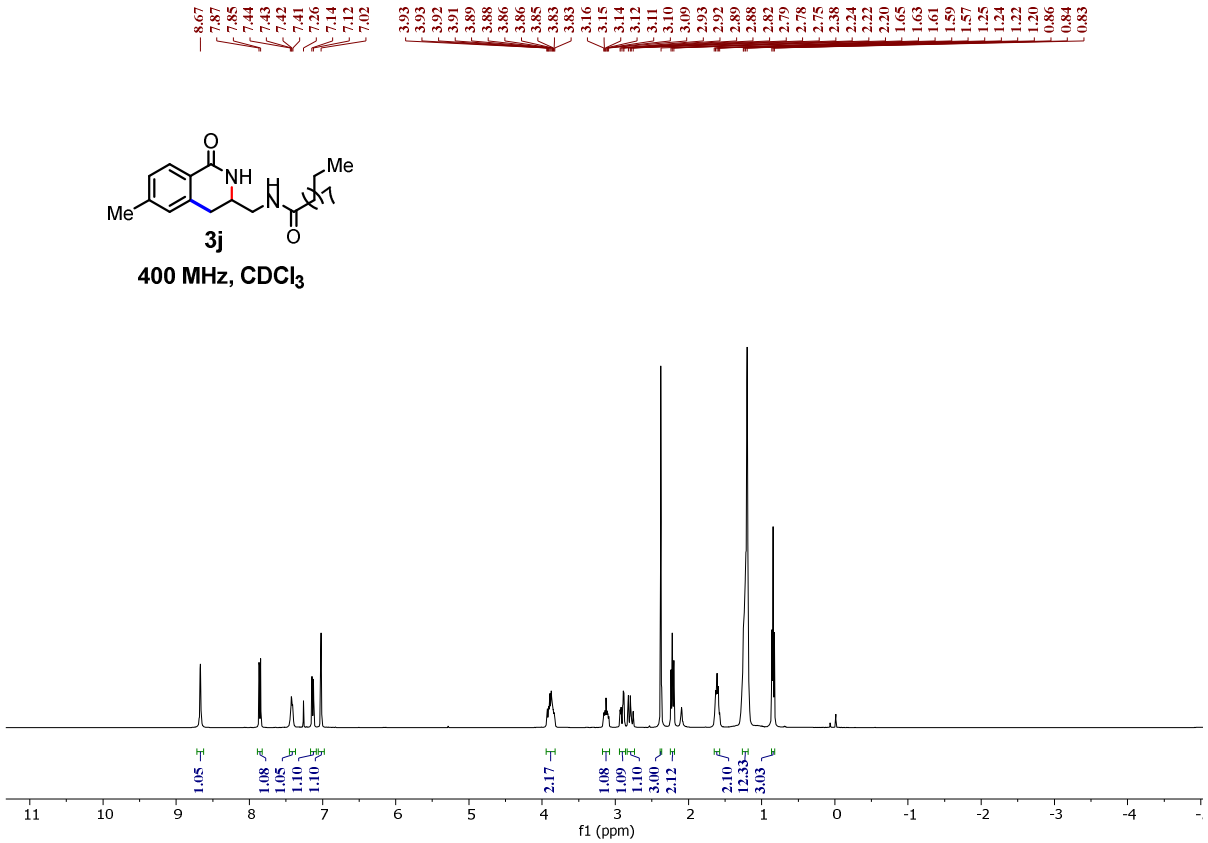
400 MHz, $CDCl_3$

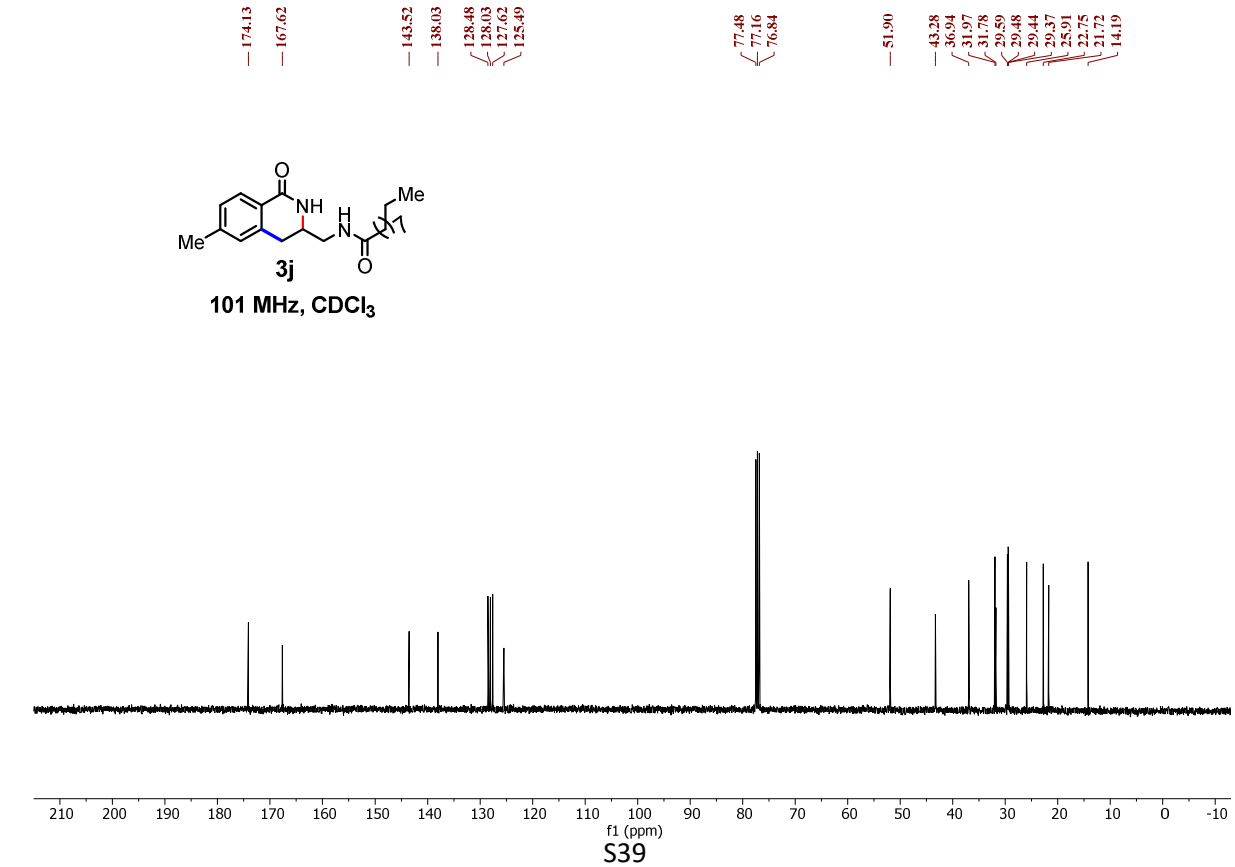


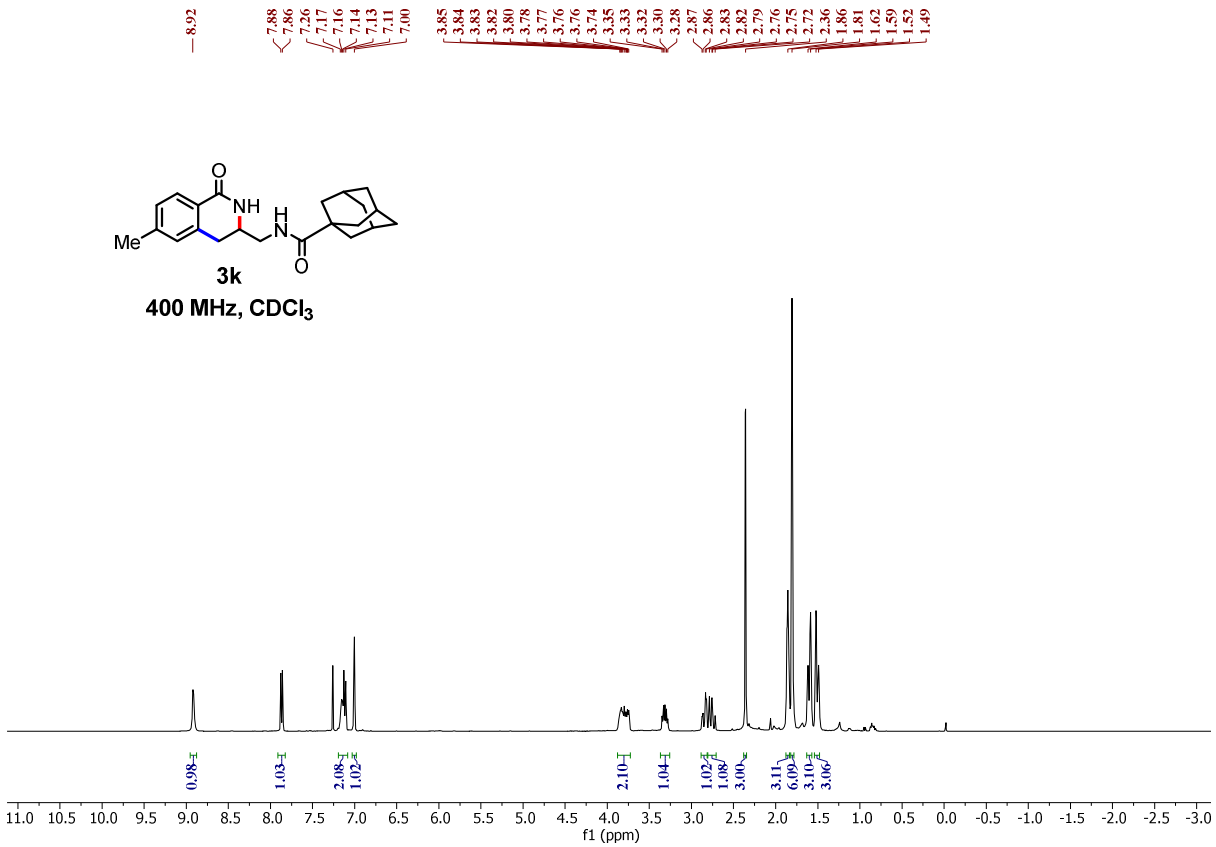


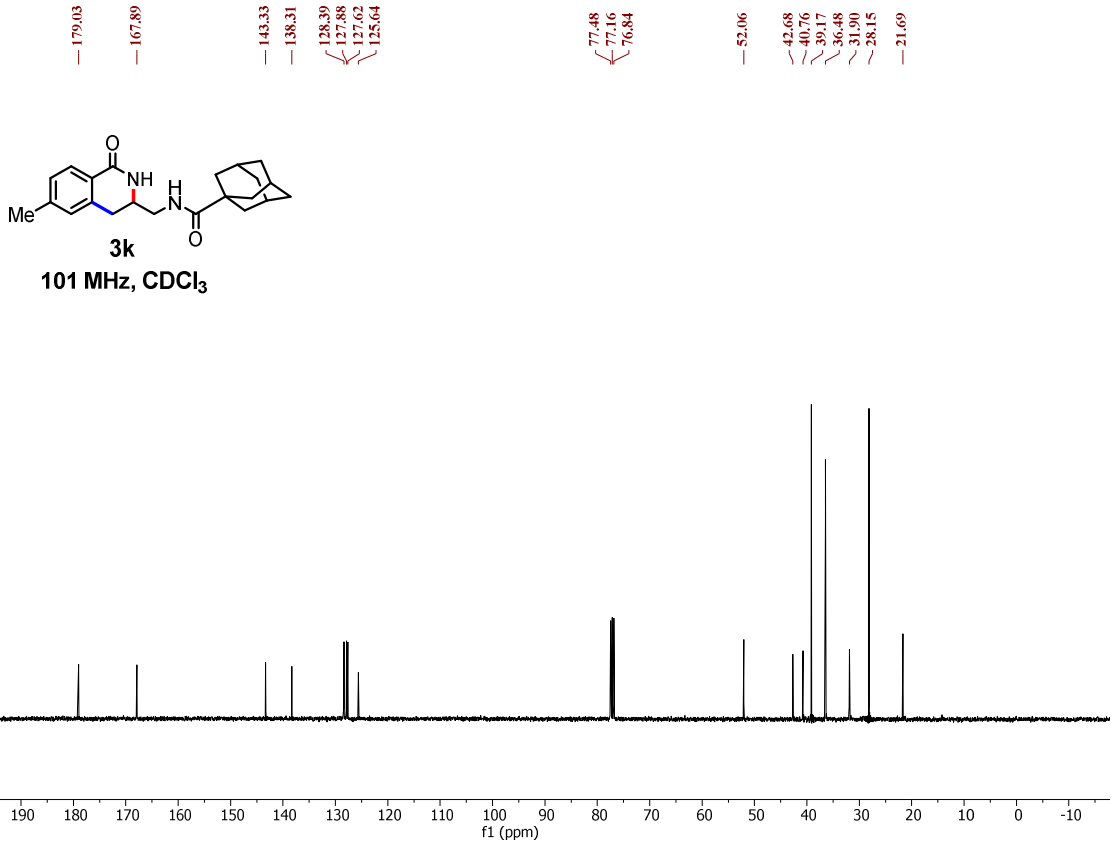
3i

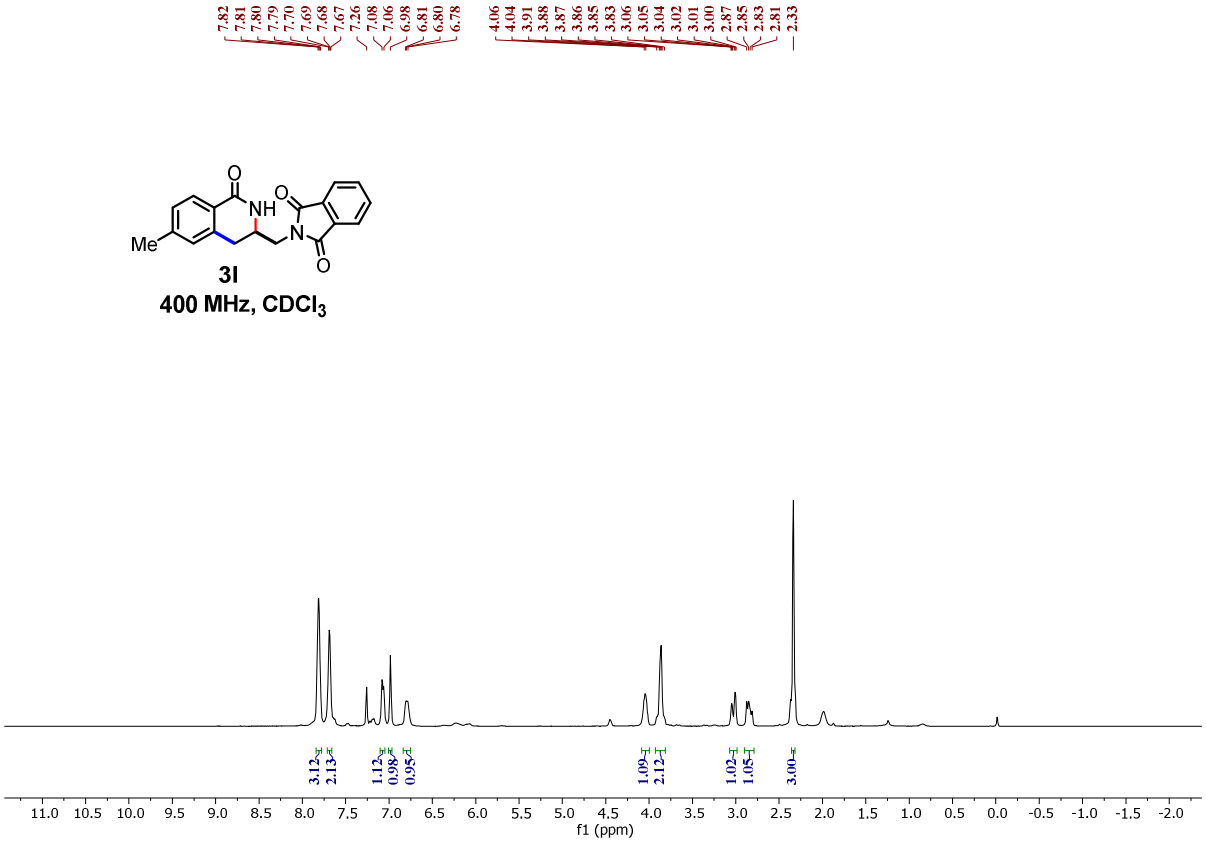
101 MHz, $CDCl_3$

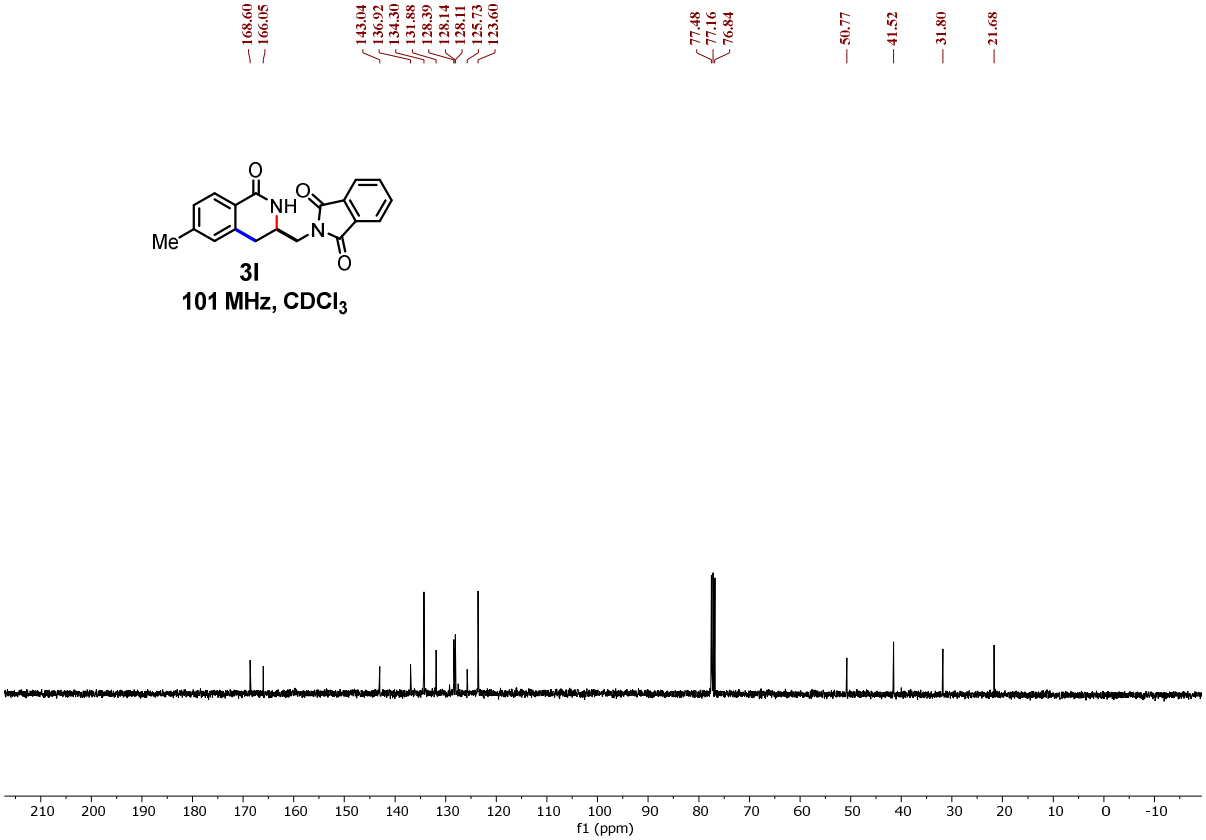

8.67
7.87
7.85
7.44
7.43
7.42
7.41
7.26
7.14
7.12
7.02
3.93
3.93
3.92
3.91
3.89
3.88
3.86
3.86
3.85
3.83
3.83
3.16
3.15
3.14
3.12
3.11
3.10
3.09
2.93
2.92
2.89
2.88
2.82
2.79
2.78
2.75
2.38
2.24
2.22
2.20
1.65
1.63
1.61
1.59
1.57
1.25
1.24
1.22
1.20
0.86
0.84
0.83
O
NH
H
N
Me
Me
O
3j
400 MHz, CDCl3
1.05
1.08
1.05
1.10
1.10
2.17
1.08
1.09
1.10
3.00
2.12
2.10
12.33
3.03
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)


174.13
167.62
143.52
138.03
128.48
128.03
127.62
125.49
77.48
77.16
76.84
51.90
43.28
36.94
31.97
31.78
29.59
29.48
29.44
29.37
25.91
22.75
21.72
14.19
O
NH
H
N
Me
Me
O
3j
101 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.92
7.88
7.86
7.26
7.17
7.16
7.14
7.13
7.11
7.00
3.85
3.84
3.83
3.82
3.80
3.78
3.77
3.76
3.76
3.74
3.35
3.33
3.32
3.30
3.28
2.87
2.86
2.83
2.82
2.79
2.76
2.75
2.72
2.36
1.86
1.81
1.62
1.59
1.52
1.49
O
NH
H
N
O
Me
3k
400 MHz, CDCl3
0.98
1.03
2.08
1.02
2.10
1.04
1.02
1.08
3.00
3.11
6.09
3.10
3.06
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5 -3.0
f1 (ppm)

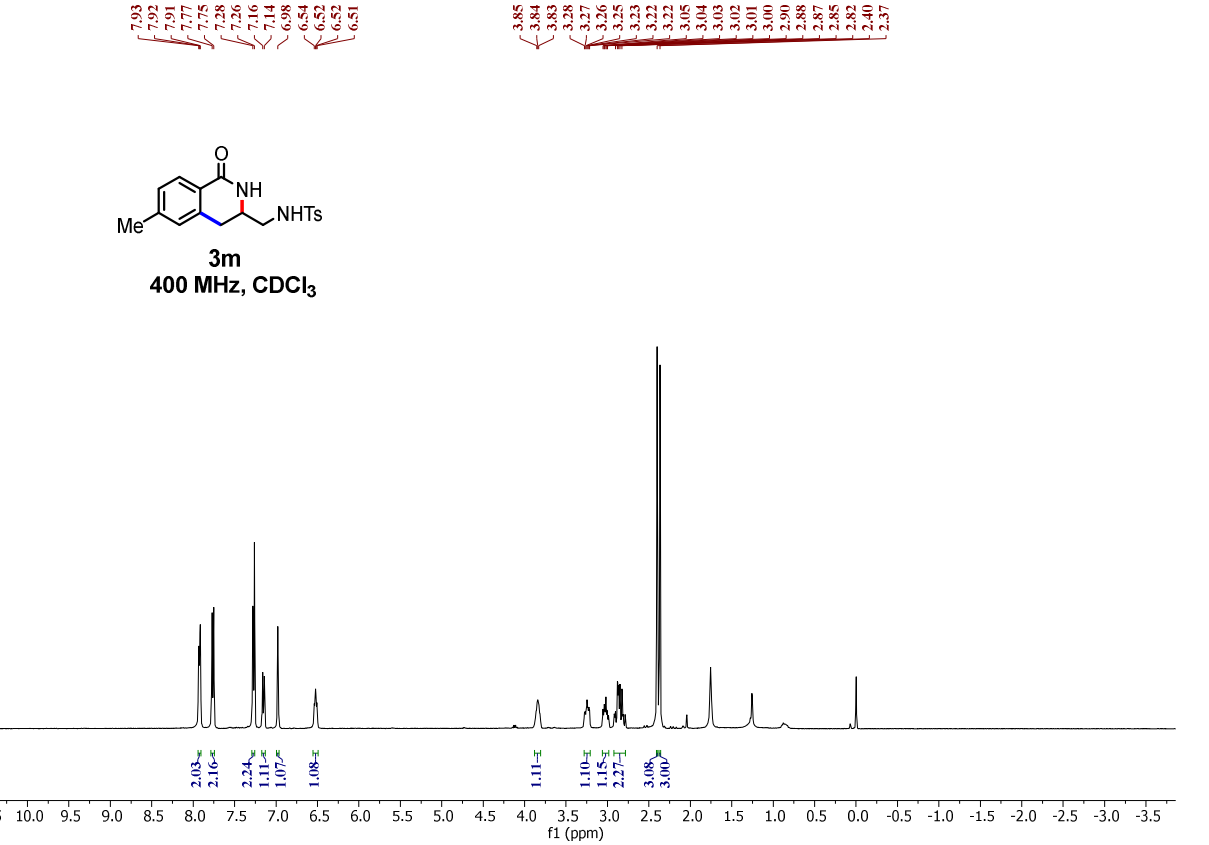

179.03
167.89
143.33
138.31
128.39
127.88
127.62
125.64
77.48
77.16
76.84
52.06
42.68
40.76
39.17
36.48
31.90
28.15
21.69
NH
H
N
Me
O
O
3k
101 MHz, CDCl3
f1 (ppm)


7.82
7.81
7.80
7.79
7.70
7.69
7.68
7.67
7.26
7.08
7.06
6.98
6.81
6.80
6.78
4.06
4.04
3.91
3.88
3.87
3.86
3.85
3.83
3.06
3.05
3.04
3.02
3.01
3.00
2.87
2.85
2.83
2.81
2.33
NH
N
Me
O
O
O
3l
400 MHz, CDCl3
3.12
2.13
1.12
0.98
0.95
1.09
2.12
1.02
1.05
3.00
f1 (ppm)



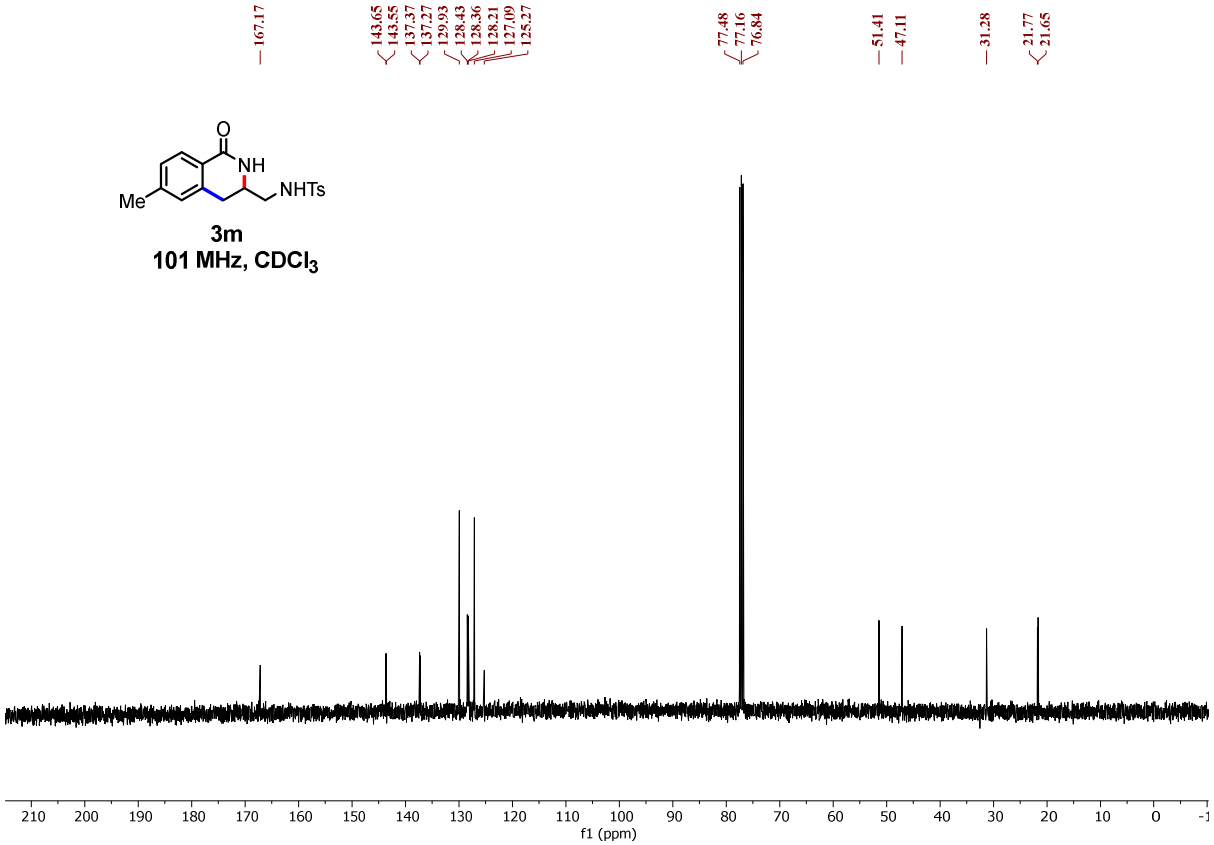
3l

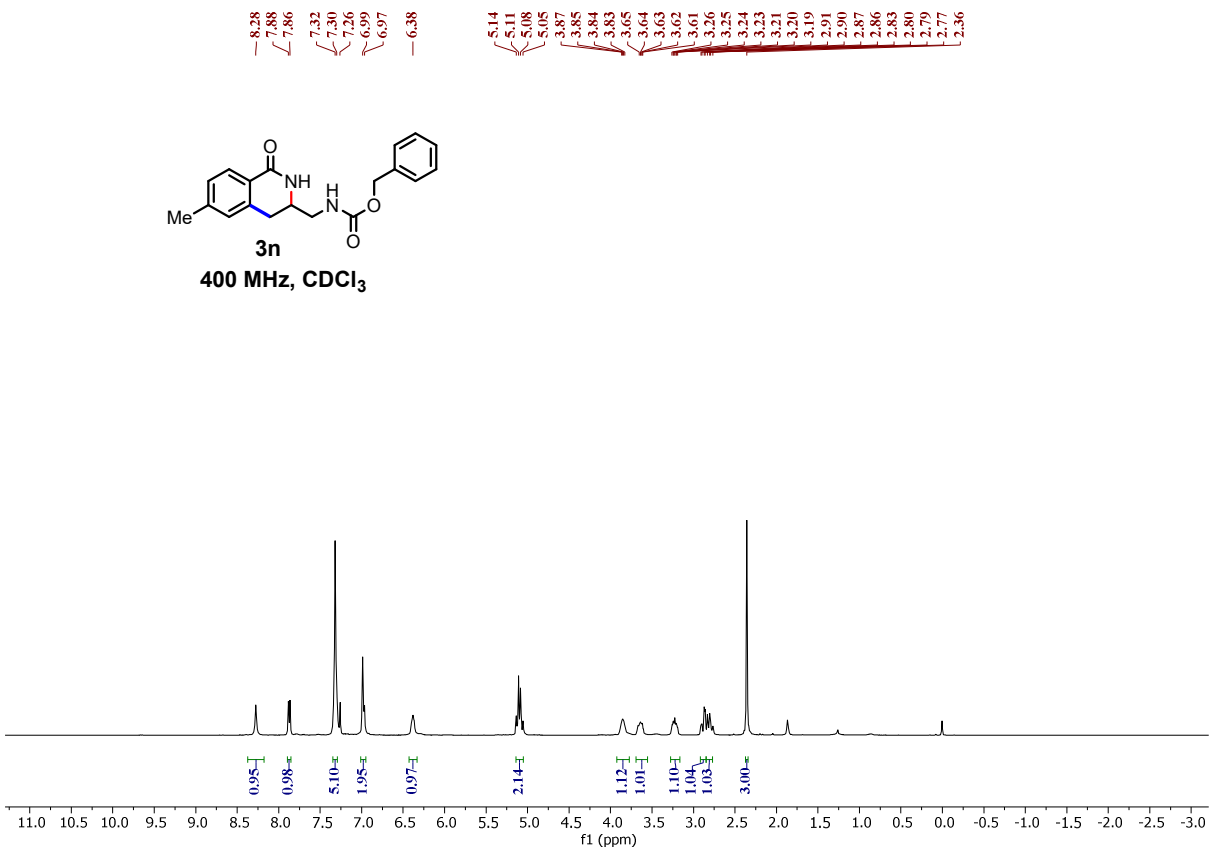
101 MHz, $CDCl_3$

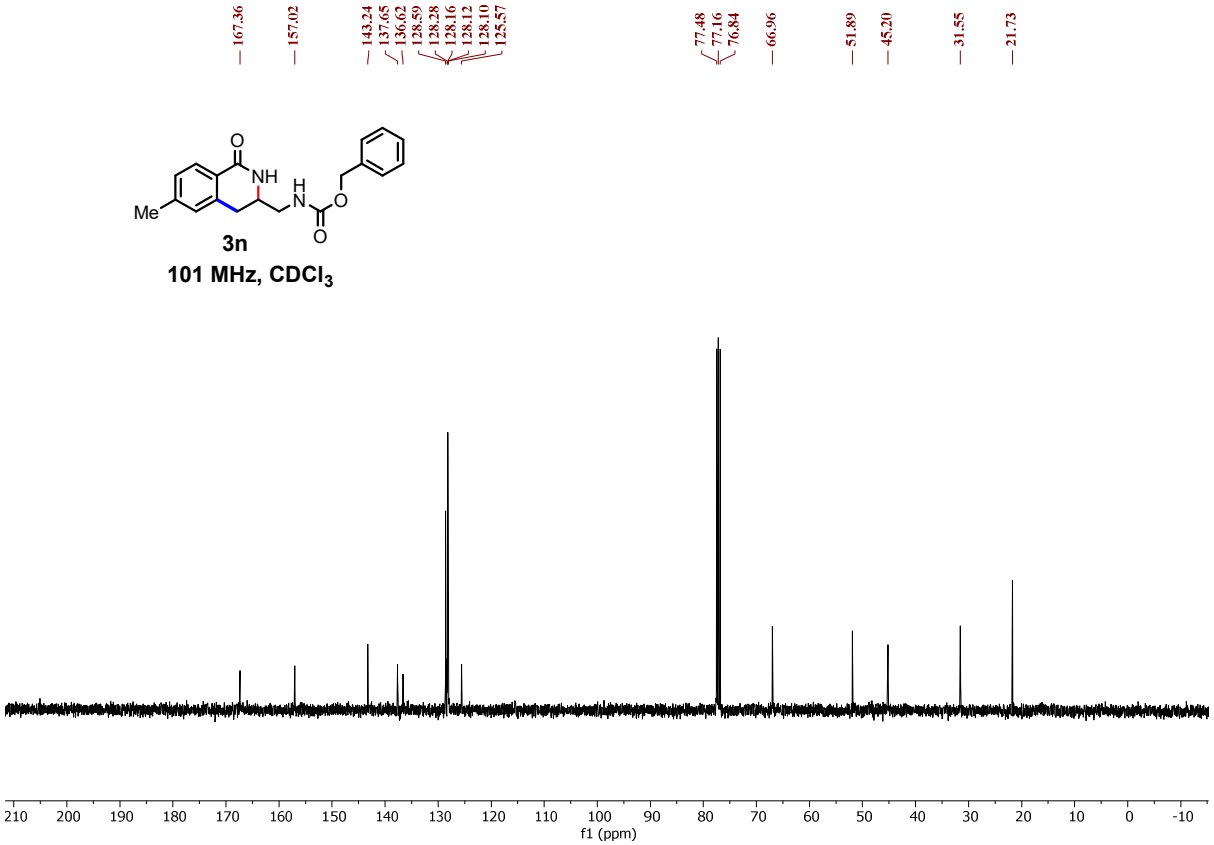


3m

400 MHz, $CDCl_3$


167.17
143.65
143.55
137.37
137.27
129.93
128.43
128.36
128.21
127.09
125.27
77.48
77.16
76.84
51.41
47.11
31.28
21.77
21.65
O
NH
NHTs
Me
3m
101 MHz, CDCl3
f1 (ppm)


8.28
7.88
7.86
7.32
7.30
7.26
6.99
6.97
6.38
5.14
5.11
5.08
5.05
3.87
3.85
3.84
3.83
3.65
3.64
3.63
3.62
3.61
3.26
3.25
3.24
3.23
3.21
3.20
3.19
2.91
2.90
2.87
2.86
2.83
2.80
2.79
2.77
2.36
O
NH
H
N
O
O
Me
3n
400 MHz, CDCl3
0.95
0.98
5.10
1.95
0.97
2.14
1.12
1.01
1.10
1.04
1.03
3.00
f1 (ppm)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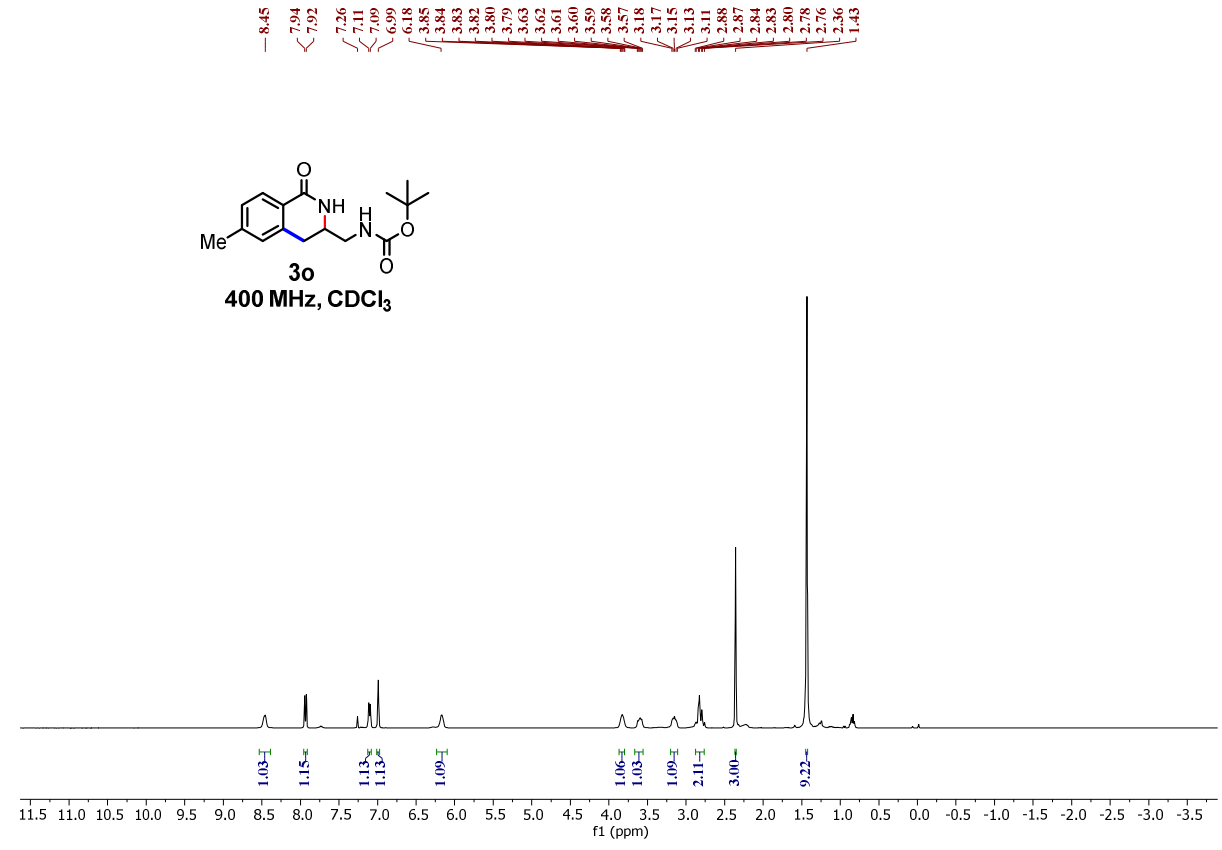
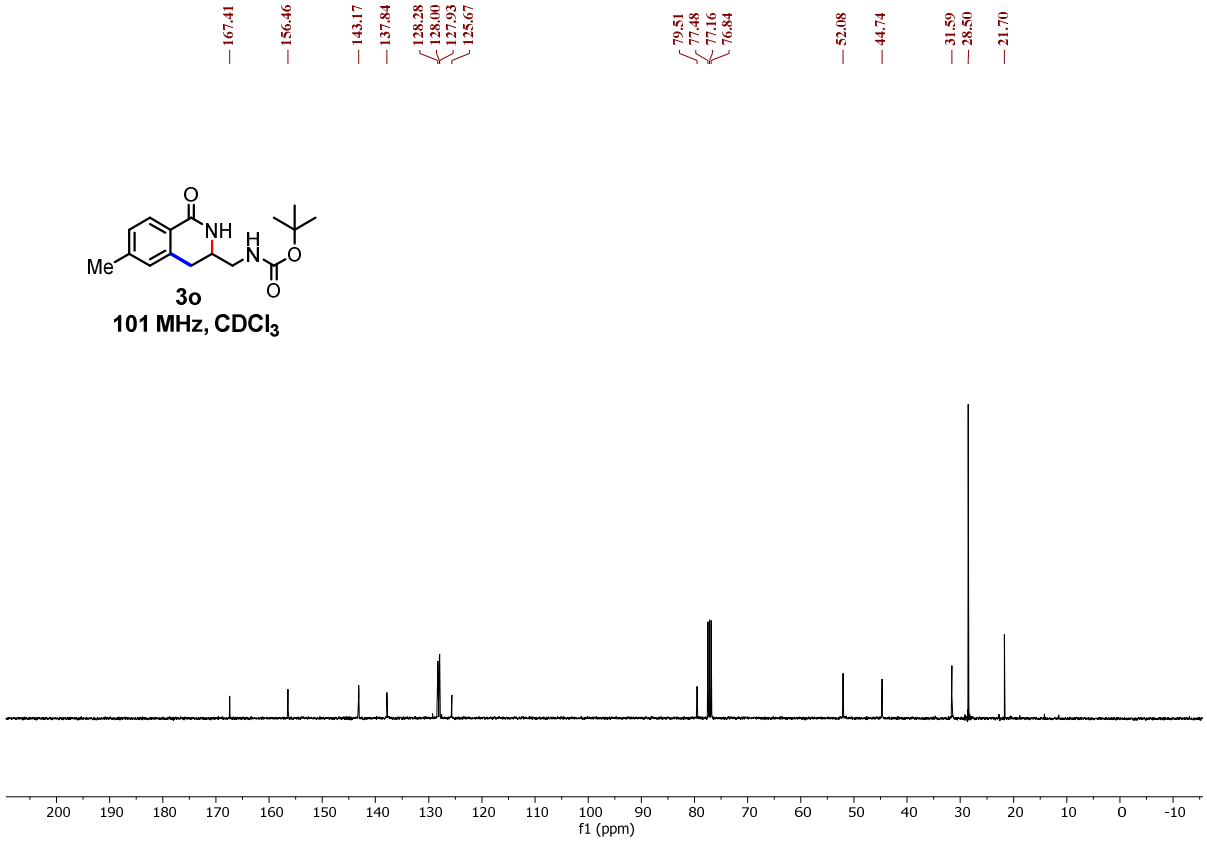
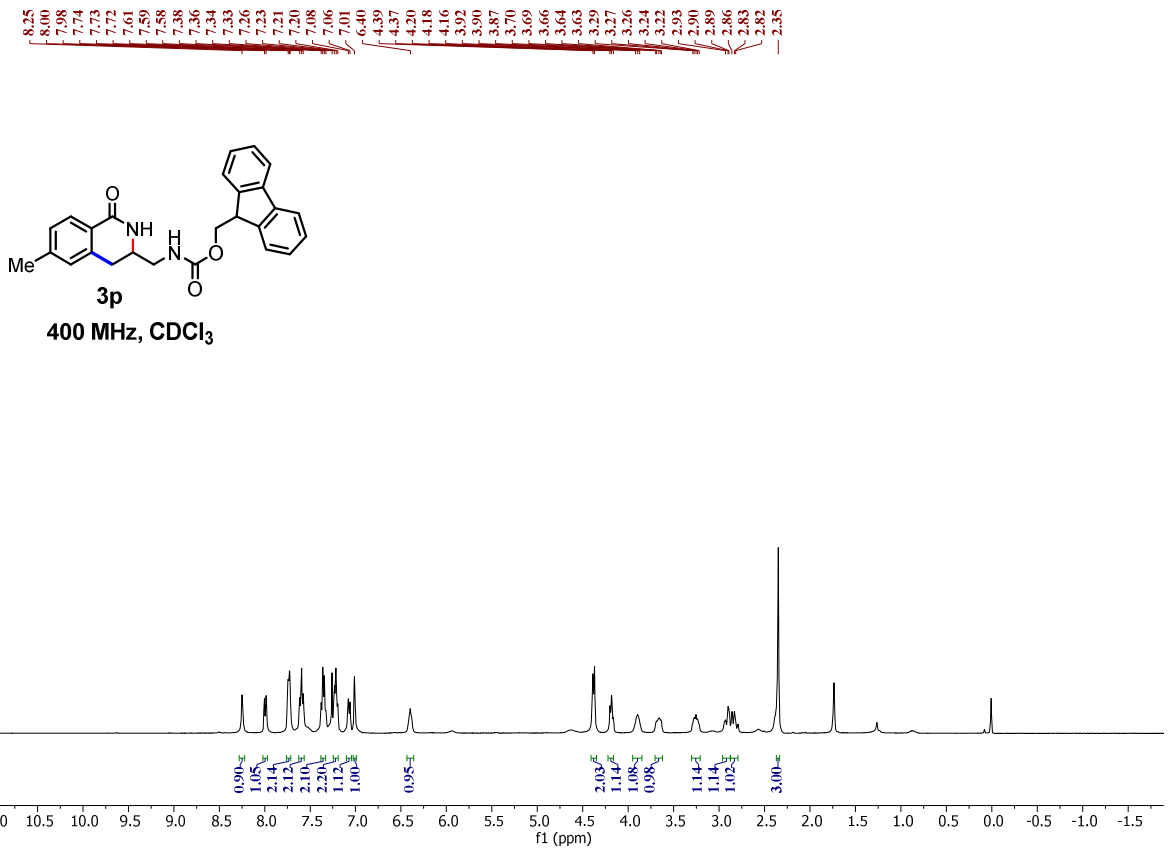
157.02
143.24
137.65
136.62
128.59
128.28
128.16
128.12
128.10
125.57
77.48
77.16
76.84
66.96
51.89
45.20
31.55
21.73
NH
H
N
O
O
Me
O
3n
101 MHz, CDCl3
f1 (ppm)


8.45
7.94
7.92
7.26
7.11
7.09
6.99
6.18
3.85
3.84
3.83
3.82
3.80
3.79
3.63
3.62
3.61
3.60
3.59
3.58
3.57
3.18
3.17
3.15
3.13
3.11
2.88
2.87
2.84
2.83
2.80
2.78
2.76
2.36
1.43
NH
H
N
O
O
Me
O
3o
400 MHz, CDCl3
1.03
1.15
1.13
1.13
1.09
1.06
1.03
1.09
2.11
3.00
9.22
f1 (ppm)


167.41
156.46
143.17
137.84
128.28
128.00
127.93
125.67
79.51
77.48
77.16
76.84
52.08
44.74
31.59
28.50
21.70
O
NH
H
N
O
O
Me
3o
101 MHz, CDCl3
f1 (ppm)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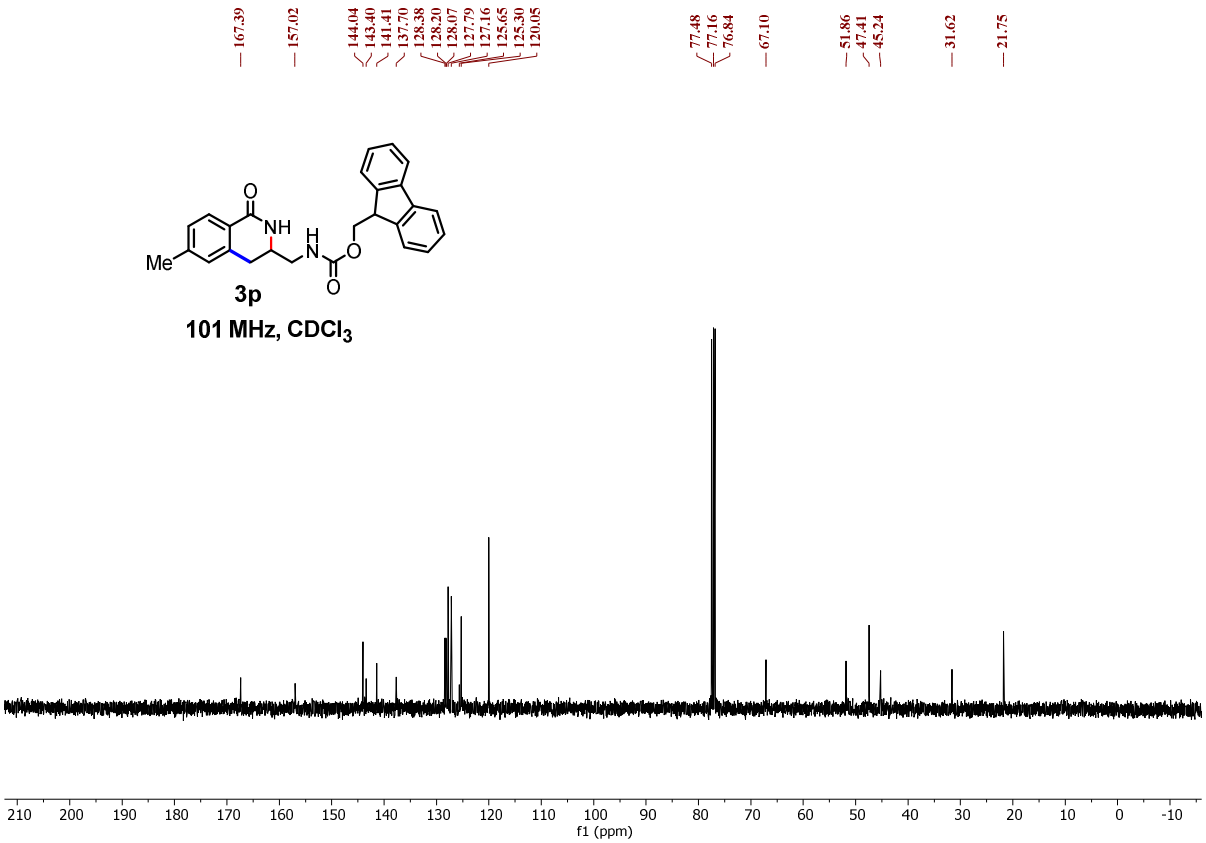
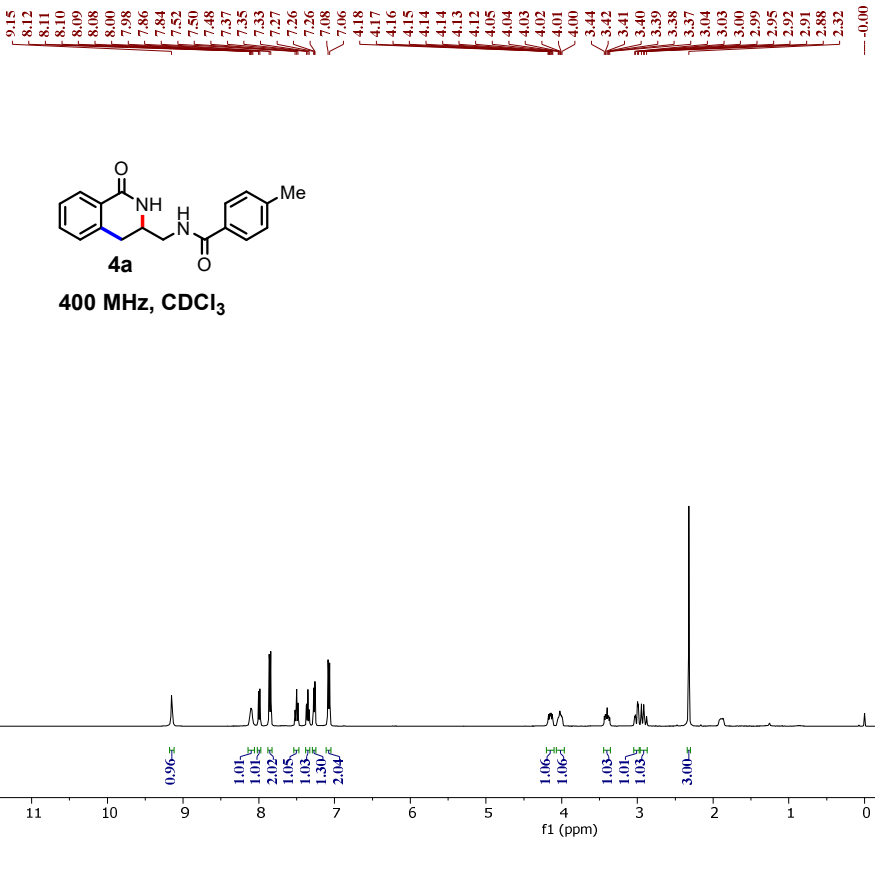
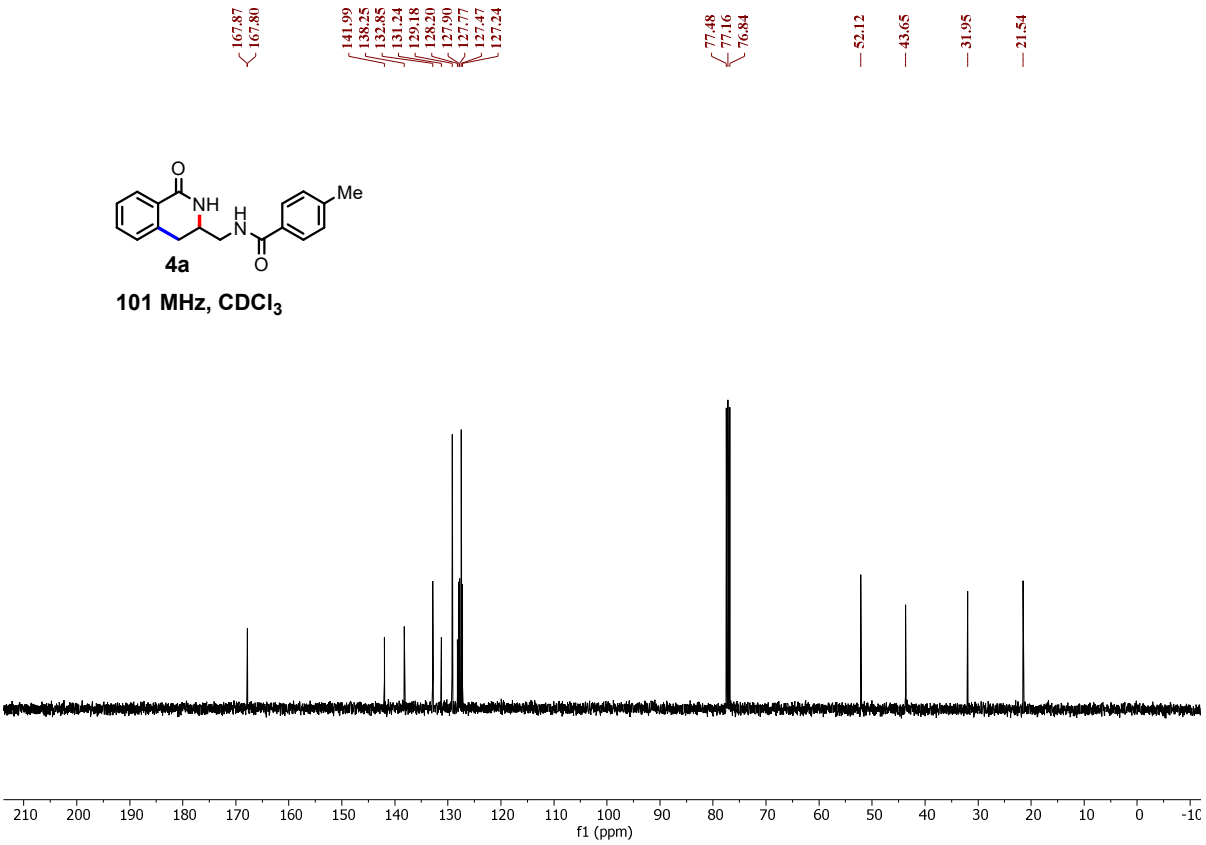
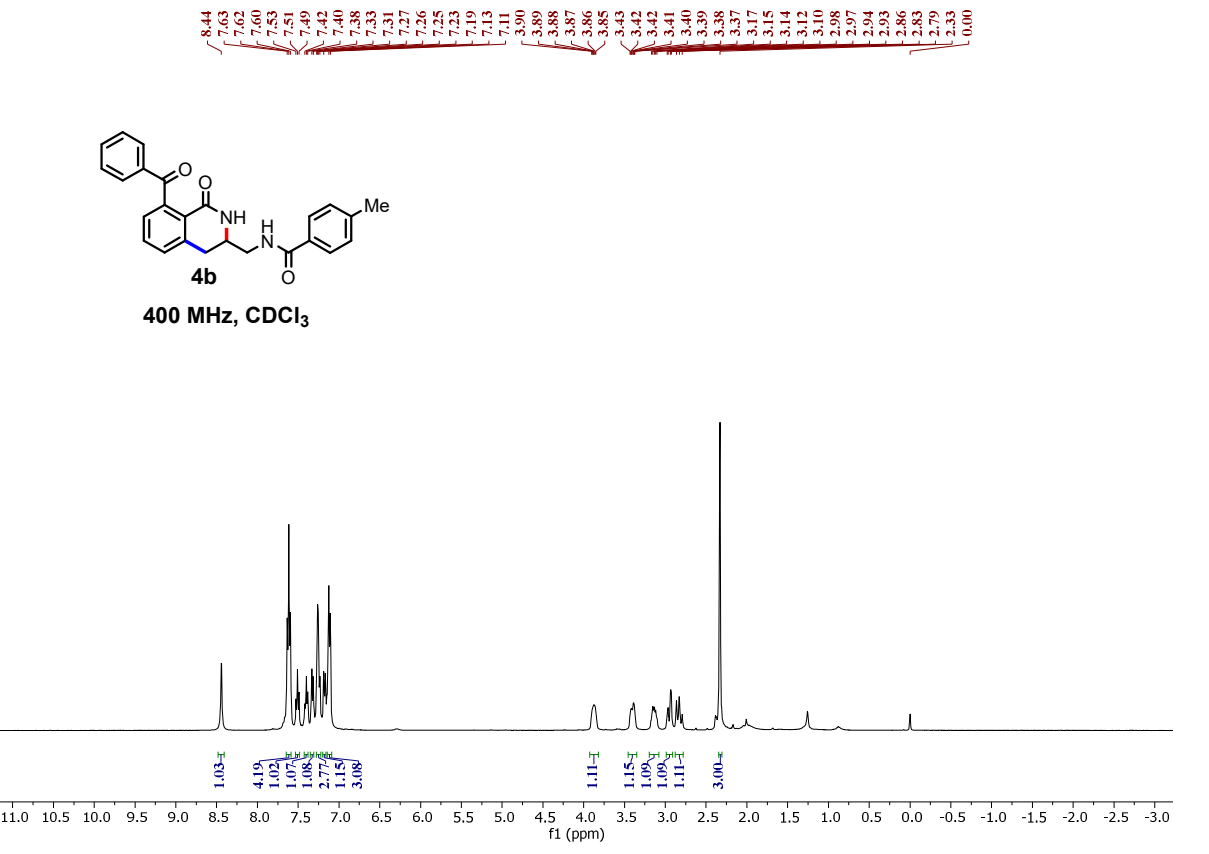
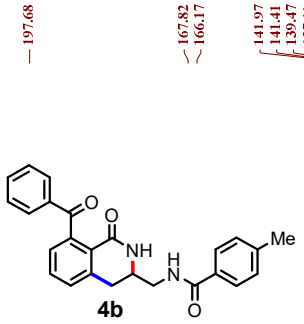
8.00
7.98
7.74
7.73
7.72
7.61
7.59
7.58
7.38
7.36
7.34
7.33
7.26
7.23
7.21
7.20
7.08
7.06
7.01
6.40
4.39
4.37
4.20
4.18
4.16
3.92
3.90
3.87
3.70
3.69
3.66
3.64
3.63
3.29
3.27
3.26
3.24
3.22
2.93
2.90
2.89
2.86
2.83
2.82
2.35
O
NH
H
N
O
O
Me
3p
400 MHz, CDCl3
0.90
1.05
2.14
2.12
2.10
2.20
1.12
1.00
0.95
2.03
1.14
1.08
0.98
1.14
1.14
1.02
3.00
f1 (ppm)


167.39
157.02
144.04
143.40
141.41
137.70
128.38
128.20
128.07
127.79
127.16
125.65
125.30
120.05
77.48
77.16
76.84
67.10
51.86
47.41
45.24
31.62
21.75
O
NH
H
N
O
O
Me
3p
101 MHz, CDCl3
f1 (ppm)


9.15
8.12
8.11
8.10
8.09
8.08
8.00
7.98
7.86
7.84
7.52
7.50
7.48
7.37
7.35
7.33
7.27
7.26
7.08
7.06
4.18
4.17
4.16
4.15
4.14
4.14
4.13
4.12
4.05
4.04
4.03
4.02
4.01
4.00
3.44
3.42
3.41
3.40
3.39
3.38
3.37
3.04
3.03
3.00
2.99
2.95
2.92
2.91
2.88
2.32
-0.00
O
NH
H
N
Me
O
4a
400 MHz, CDCl3
0.96
1.01
1.01
2.02
1.05
1.03
1.30
2.04
1.06
1.06
1.03
1.01
1.03
3.00
f1 (ppm)

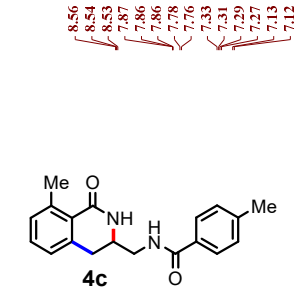

167.87
167.80
141.99
138.25
132.85
131.24
129.18
128.20
127.90
127.77
127.47
127.24
77.48
77.16
76.84
52.12
43.65
31.95
21.54
O
NH
H
N
Me
O
4a
101 MHz, CDCl3
f1 (ppm)


8.44
7.63
7.62
7.60
7.53
7.51
7.49
7.42
7.40
7.38
7.33
7.31
7.27
7.26
7.25
7.23
7.19
7.13
7.11
3.90
3.89
3.88
3.87
3.86
3.85
3.43
3.42
3.42
3.41
3.40
3.39
3.38
3.37
3.17
3.15
3.14
3.12
3.10
2.98
2.97
2.94
2.93
2.86
2.83
2.79
2.33
0.00
O
O
NH
H
N
Me
O
4b
400 MHz, CDCl3
1.03
4.19
1.02
1.07
1.08
2.77
1.15
3.08
1.11
1.15
1.09
1.09
1.11
3.00
f1 (ppm)



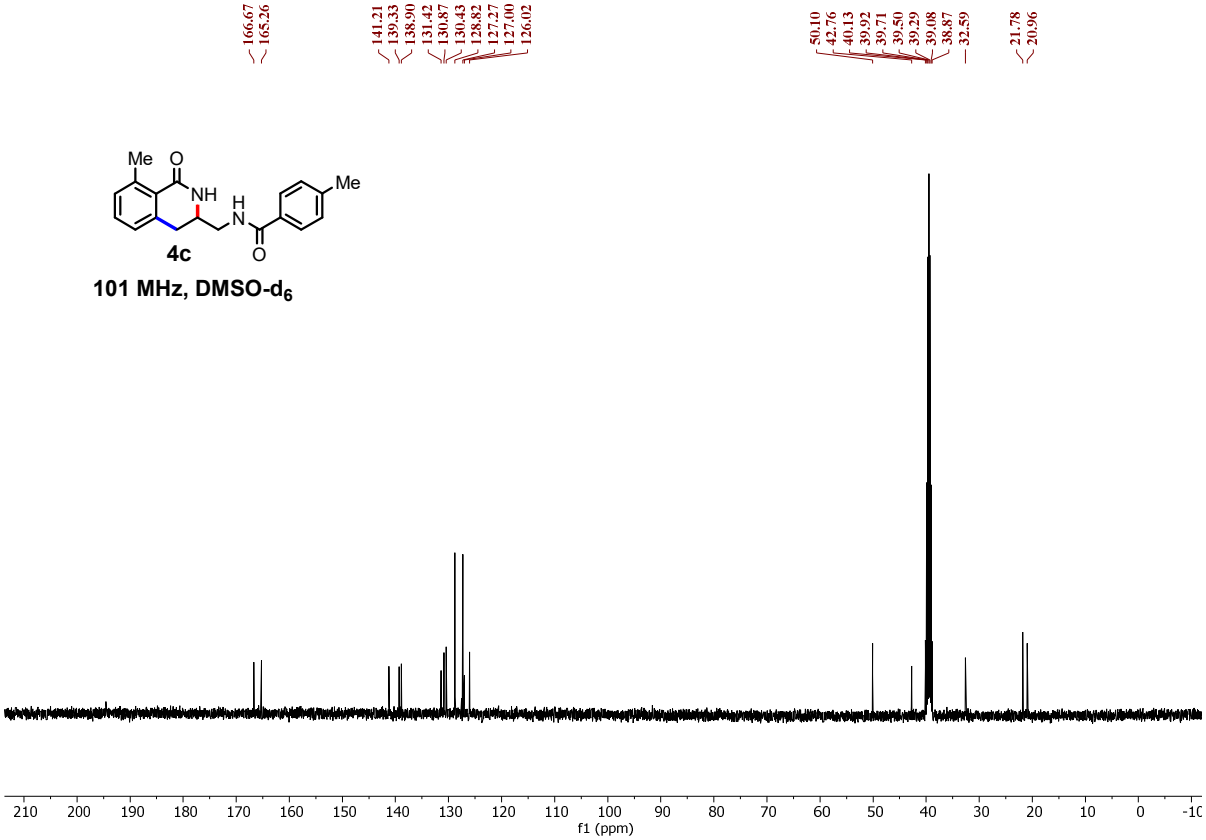
4b

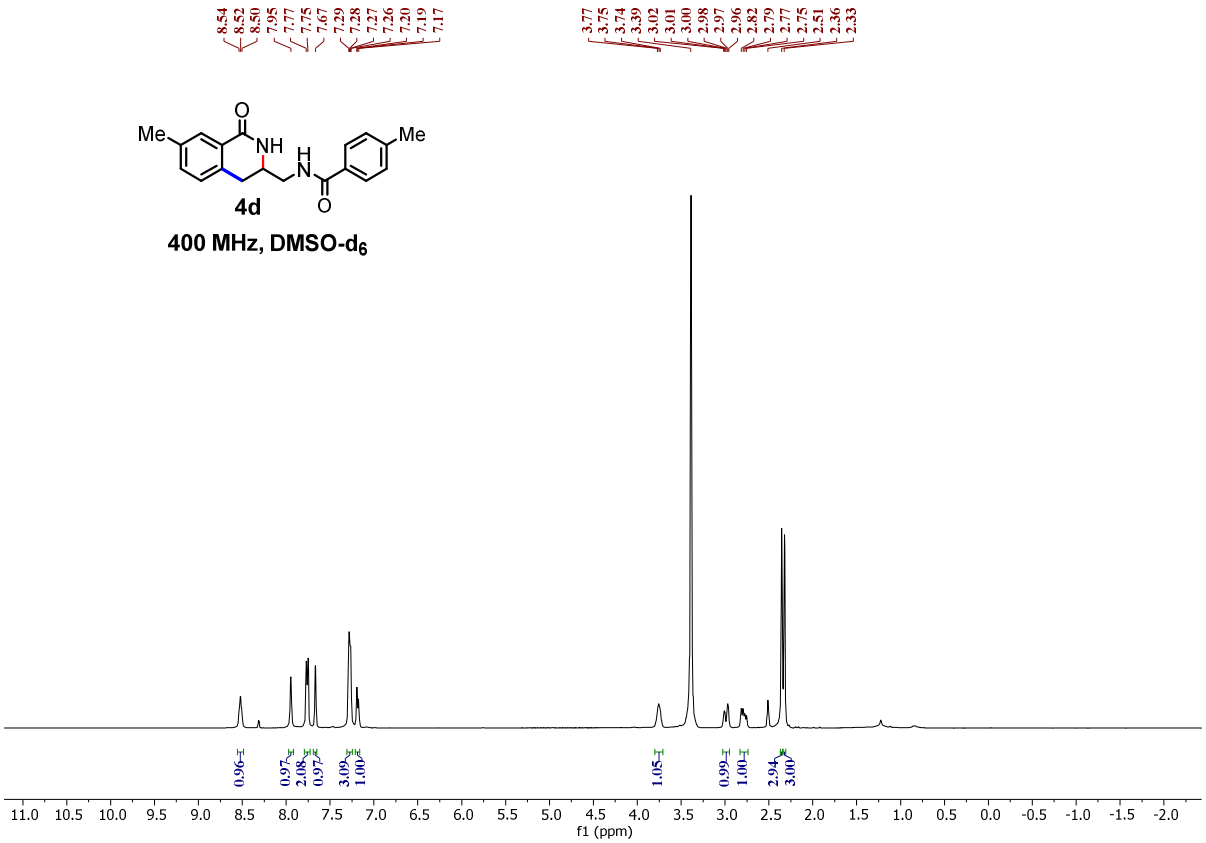
101 MHz, $CDCl_3$

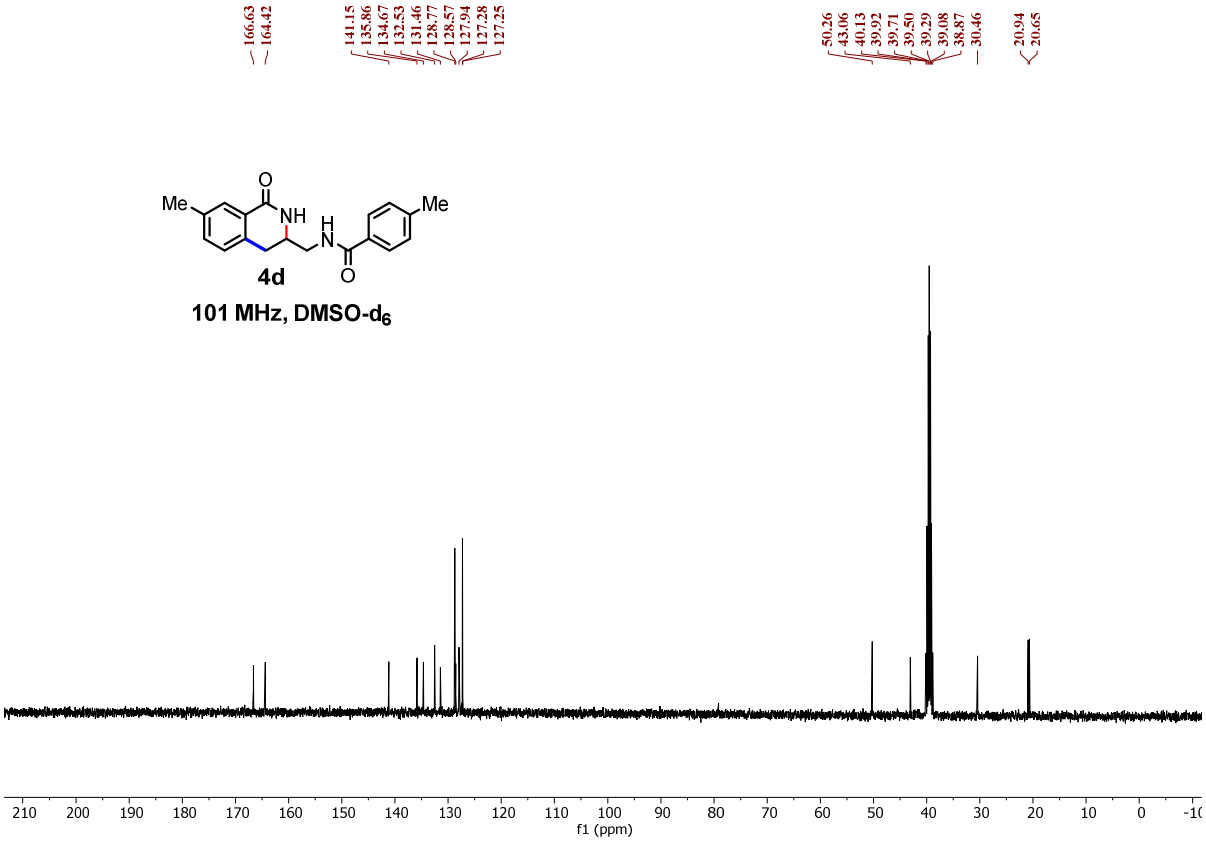


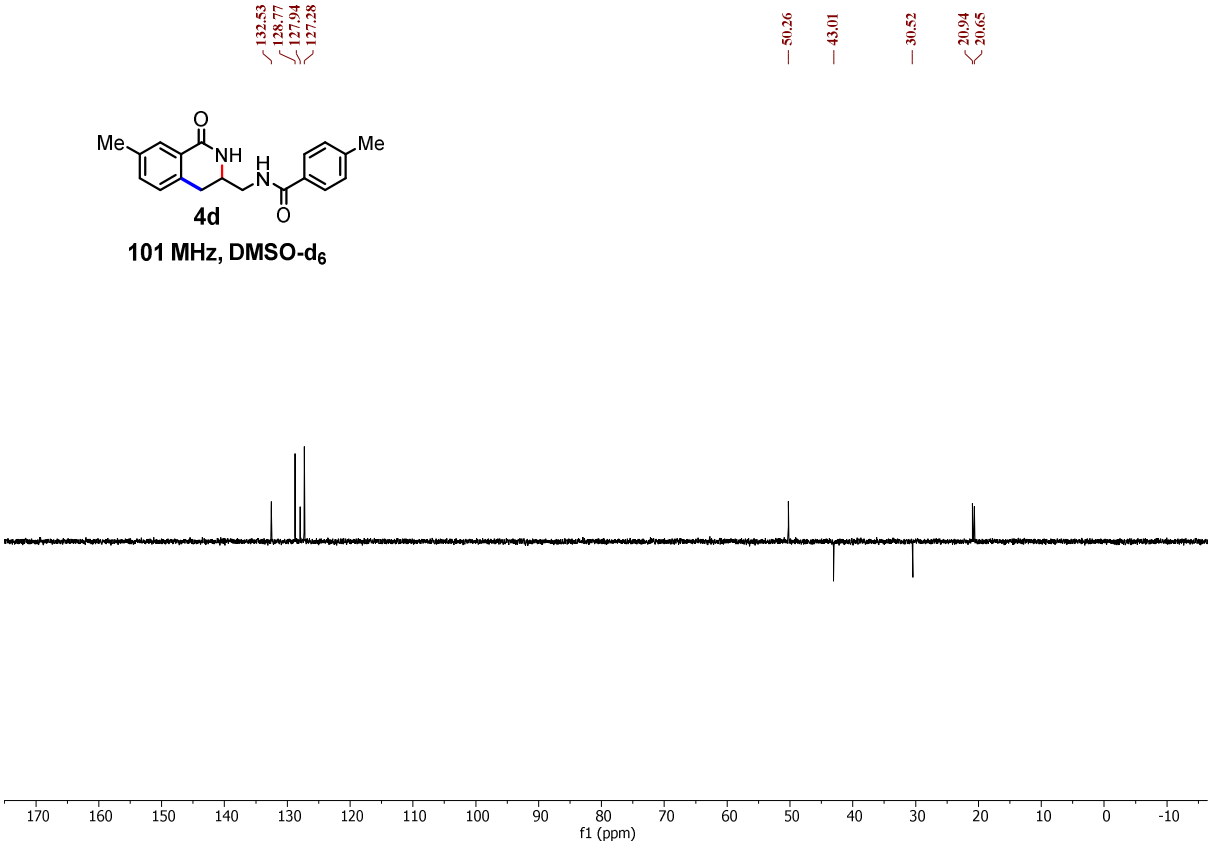
4c

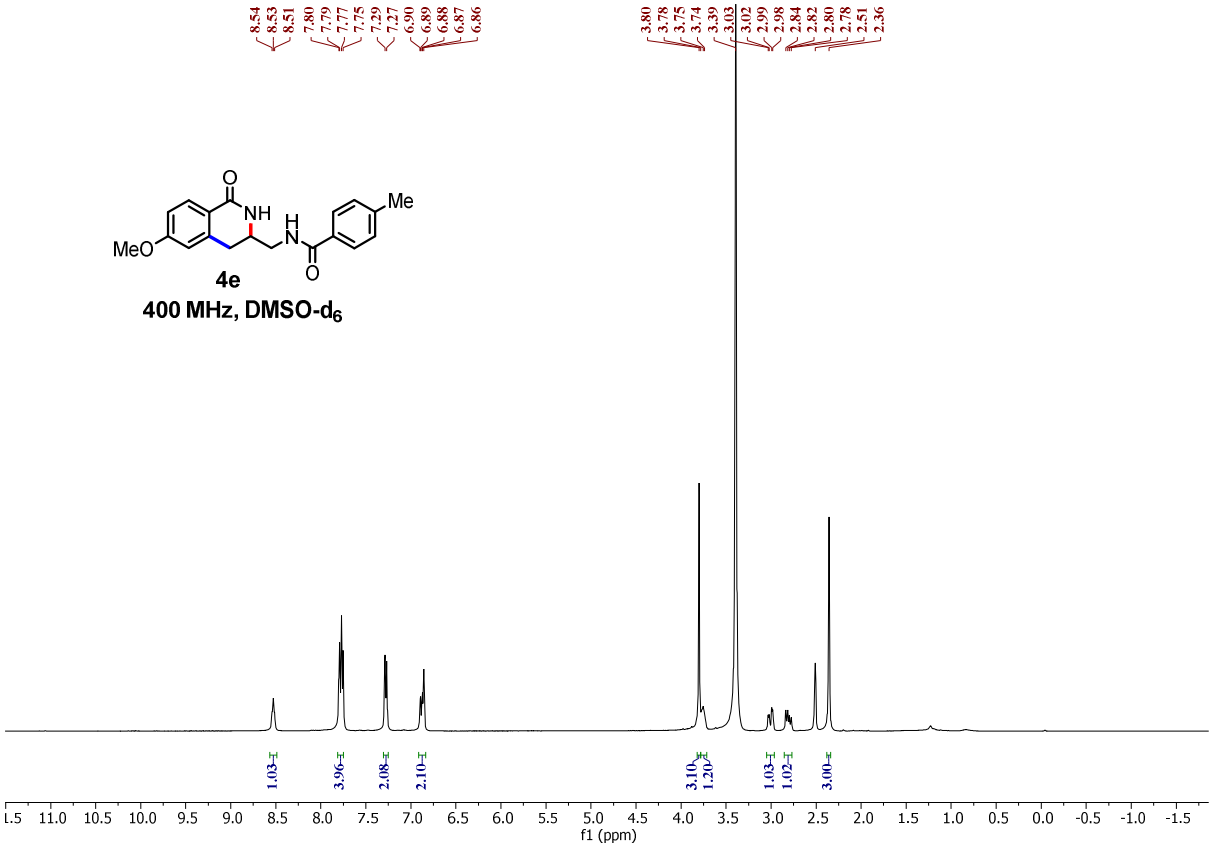
400 MHz, DMSO-d_6

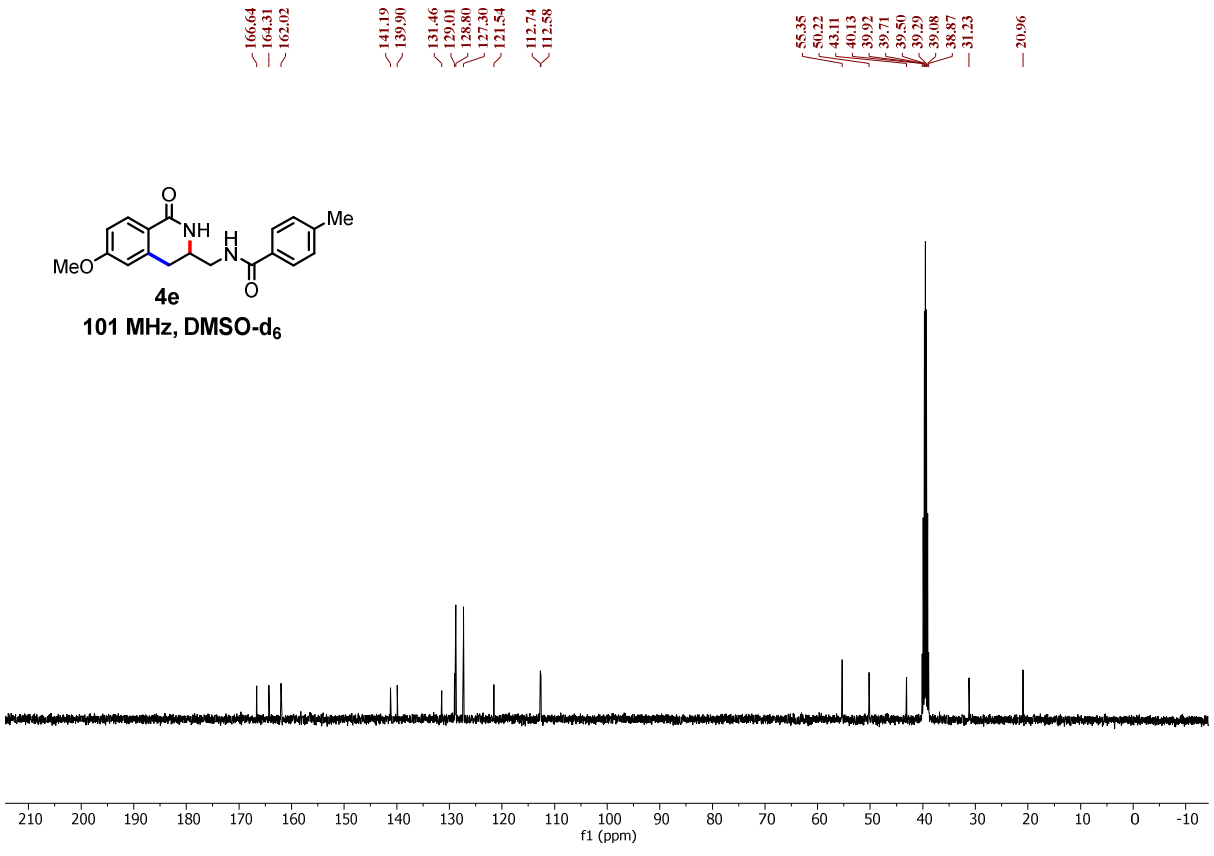

166.67
165.26
141.21
139.33
138.90
131.42
130.87
130.43
128.82
127.27
127.00
126.02
50.10
42.76
40.13
39.92
39.71
39.50
39.29
39.08
38.87
32.59
21.78
20.96
Me
O
NH
H
N
Me
O
4c
101 MHz, DMSO-d6
f1 (ppm)

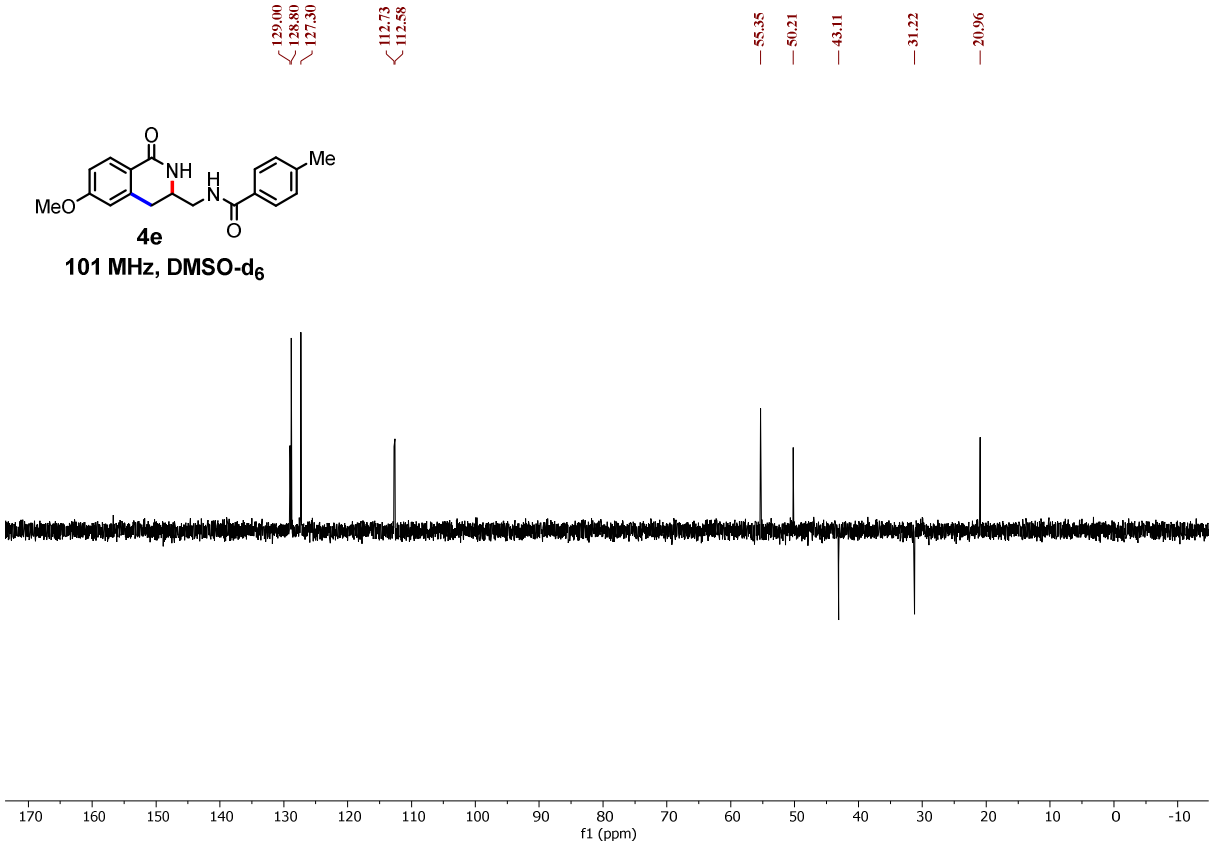

8.54
8.52
8.50
7.95
7.77
7.75
7.67
7.29
7.28
7.27
7.26
7.20
7.19
7.17
3.77
3.75
3.74
3.39
3.02
3.01
3.00
2.98
2.97
2.96
2.82
2.79
2.77
2.75
2.51
2.36
2.33
Me
O
NH
H
N
Me
O
4d
400 MHz, DMSO-d6
0.96
0.97
2.08
0.97
3.09
1.00
1.05
0.99
1.00
2.94
3.00
f1 (ppm)

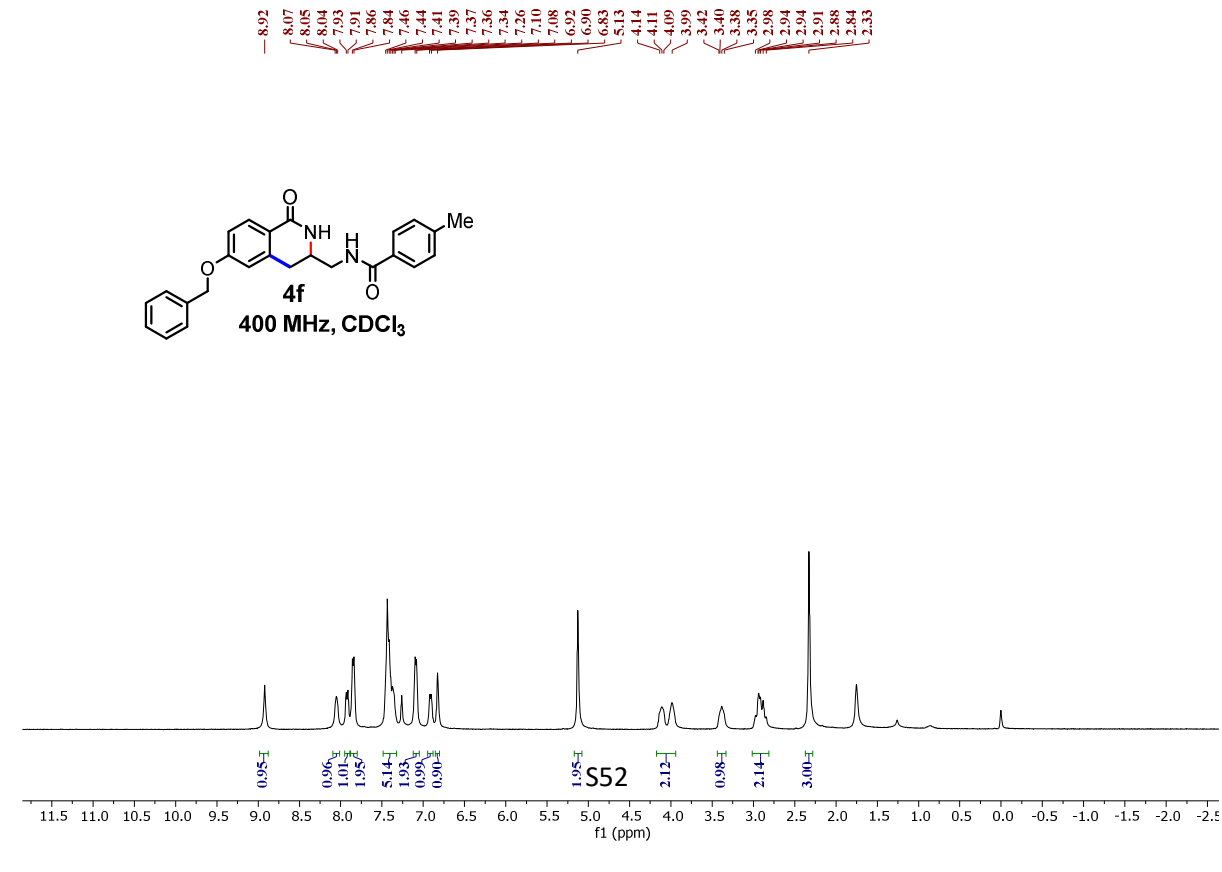

166.63
164.42
141.15
135.86
134.67
132.53
131.46
128.77
128.57
127.94
127.28
127.25
50.26
43.06
40.13
39.92
39.71
39.50
39.29
39.08
38.87
30.46
20.94
20.65
Me
NH
H
N
Me
O
O
4d
101 MHz, DMSO-d6
f1 (ppm)

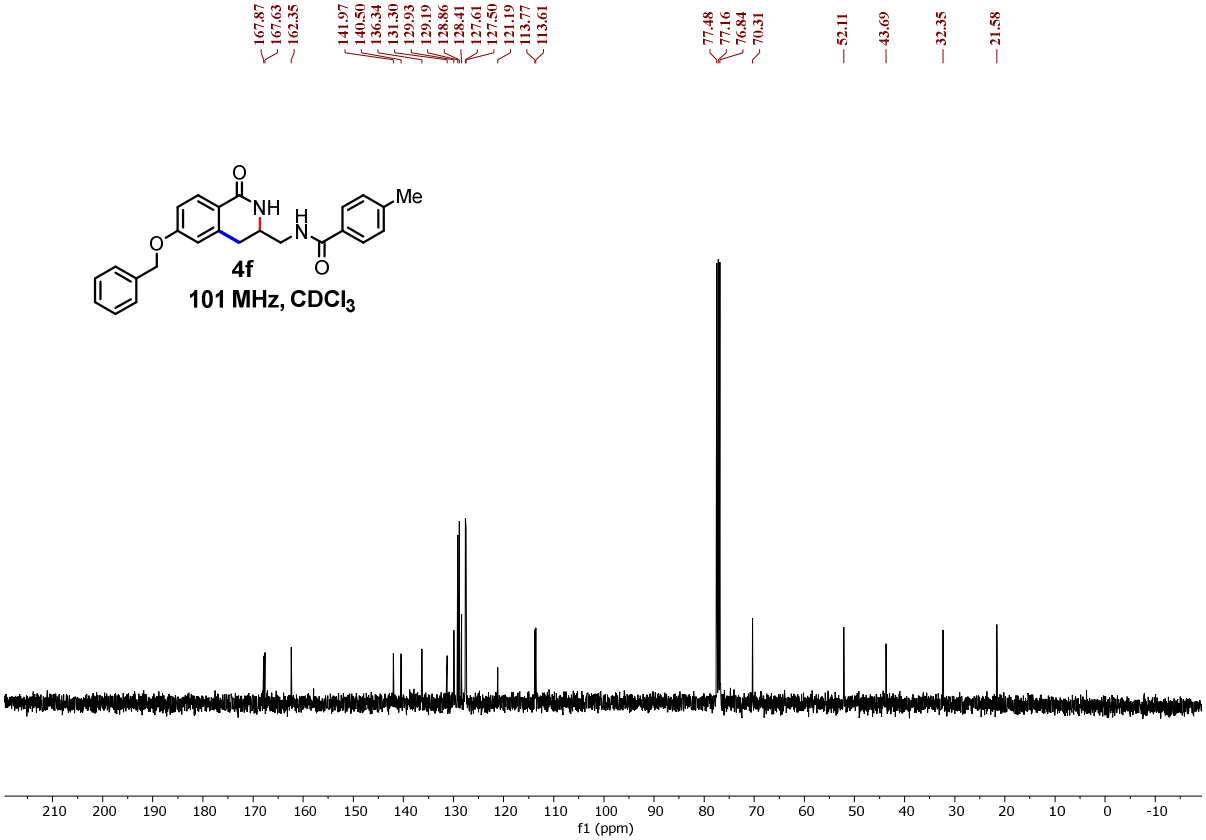

132.53
128.77
127.94
127.28
50.26
43.01
30.52
20.94
20.65
Me
NH
H
N
Me
O
O
4d
101 MHz, DMSO-d6
f1 (ppm)


8.54
8.53
8.51
7.80
7.79
7.77
7.75
7.29
7.27
6.90
6.89
6.88
6.87
6.86
3.80
3.78
3.75
3.74
3.39
3.03
3.02
2.99
2.98
2.84
2.82
2.80
2.78
2.51
2.36
O
NH
H
N
O
MeO
Me
4e
400 MHz, DMSO-d6
1.03
3.96
2.08
2.10
3.10
1.20
1.03
1.02
3.00
f1 (ppm)


166.64
164.31
162.02
141.19
139.90
131.46
129.01
128.80
127.30
121.54
112.74
112.58
55.35
50.22
43.11
40.13
39.92
39.71
39.50
39.29
39.08
38.87
31.23
20.96
O
NH
H
N
O
MeO
Me
4e
101 MHz, DMSO-d6
f1 (ppm)


129.00
128.80
127.30
112.73
112.58
55.35
50.21
43.11
31.22
20.96
O
NH
H
N
Me
MeO
O
4e
101 MHz, DMSO-d6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.92
8.07
8.05
8.04
7.93
7.91
7.86
7.84
7.46
7.44
7.41
7.39
7.37
7.36
7.34
7.26
7.10
7.08
6.92
6.90
6.83
5.13
4.14
4.11
4.09
3.99
3.42
3.40
3.38
3.35
2.98
2.94
2.94
2.91
2.88
2.84
2.33
O
NH
H
N
Me
O
O
4f
400 MHz, CDCl3
0.95
0.96
1.01
1.95
5.14
1.93
0.99
0.90
1.95
2.12
0.98
2.14
3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5
f1 (ppm)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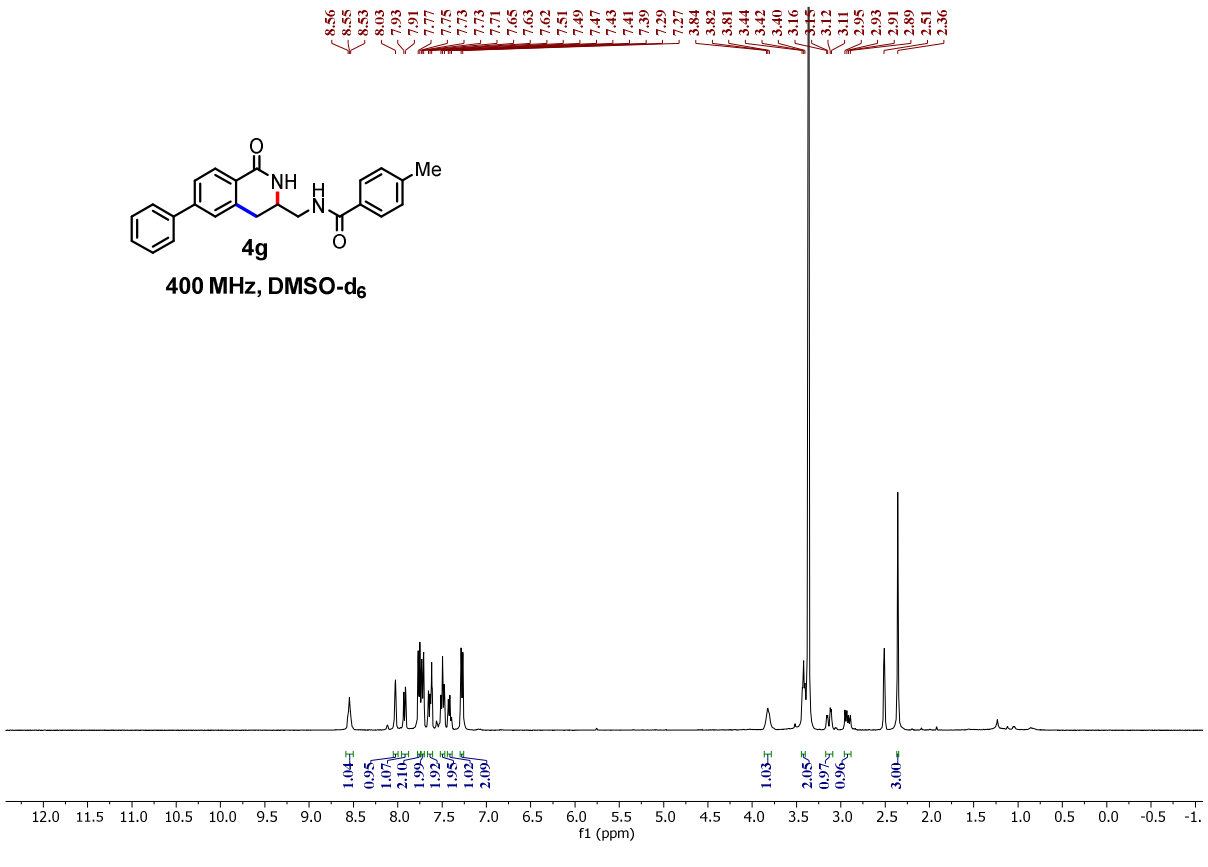
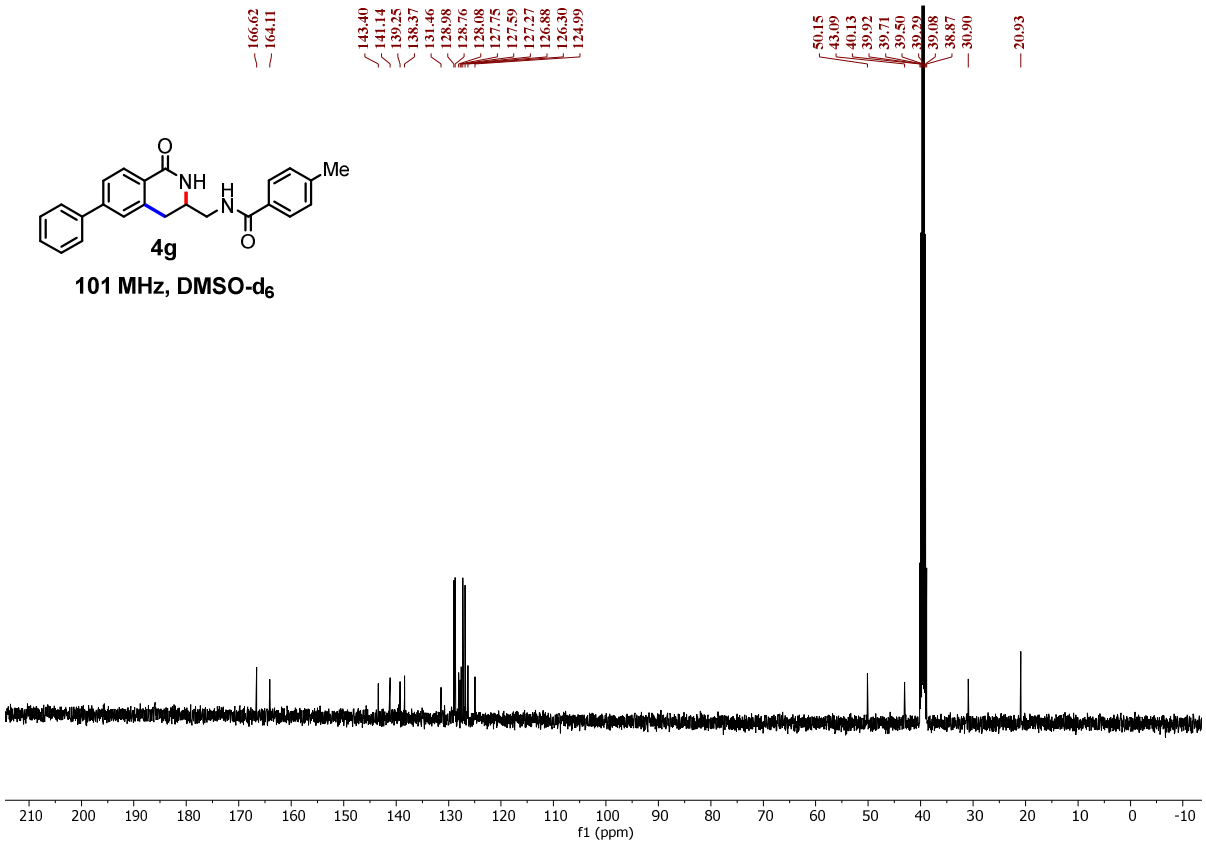
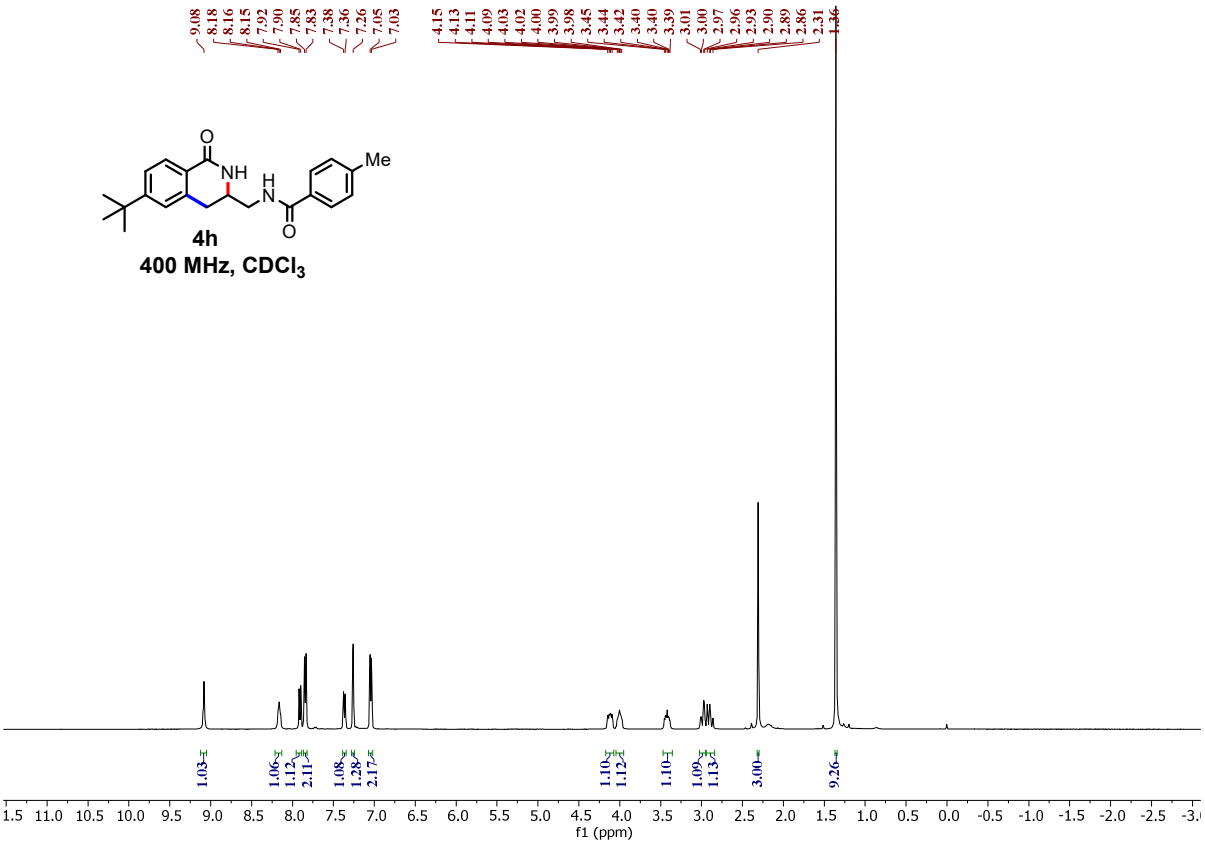
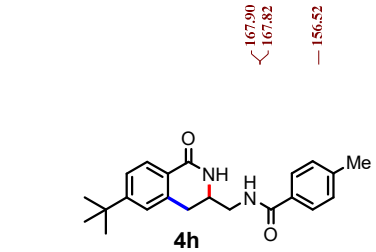
167.63
162.35
141.97
140.50
136.34
131.30
129.93
129.19
128.86
128.41
127.61
127.50
121.19
113.77
113.61
77.48
77.16
76.84
70.31
52.11
43.69
32.35
21.58
O
NH
H
N
O
O
Me
4f
101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.56
8.55
8.53
8.03
7.93
7.91
7.77
7.75
7.73
7.73
7.71
7.65
7.63
7.62
7.51
7.49
7.47
7.43
7.41
7.39
7.29
7.27
3.84
3.82
3.81
3.44
3.42
3.40
3.16
3.15
3.12
3.11
2.95
2.93
2.91
2.89
2.51
2.36
O
NH
H
N
O
Me
4g
400 MHz, DMSO-d6
1.04
0.95
1.07
2.10
1.99
1.92
1.95
1.02
2.09
1.03
2.05
0.97
0.96
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)

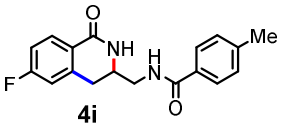

166.62
164.11
143.40
141.14
139.25
138.37
131.46
128.98
128.76
128.08
127.75
127.59
127.27
126.88
126.30
124.99
50.15
43.09
40.13
39.92
39.71
39.50
39.29
39.08
38.87
30.90
20.93
O
NH
H
N
O
Me
4g
101 MHz, DMSO-d6
f1 (ppm)


9.08
8.18
8.16
8.15
7.92
7.90
7.85
7.83
7.38
7.36
7.26
7.05
7.03
4.15
4.13
4.11
4.09
4.03
4.02
4.00
3.99
3.98
3.45
3.44
3.42
3.40
3.40
3.39
3.01
3.00
2.97
2.96
2.93
2.90
2.89
2.86
2.31
1.36
1.03
1.06
1.12
2.11
1.08
1.28
2.17
1.10
1.12
1.10
1.09
1.13
3.00
9.26
O
NH
H
N
O
Me
4h
400 MHz, CDCl3
f1 (ppm)



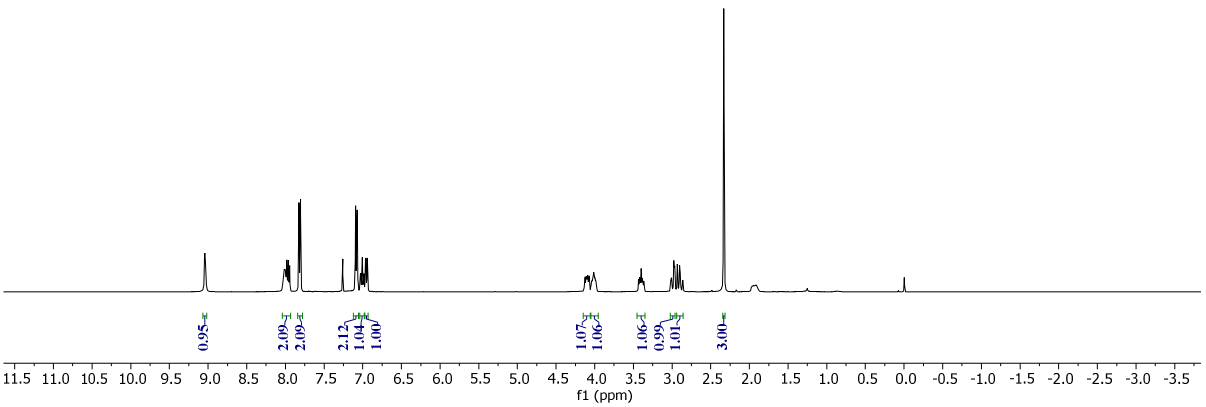
4h

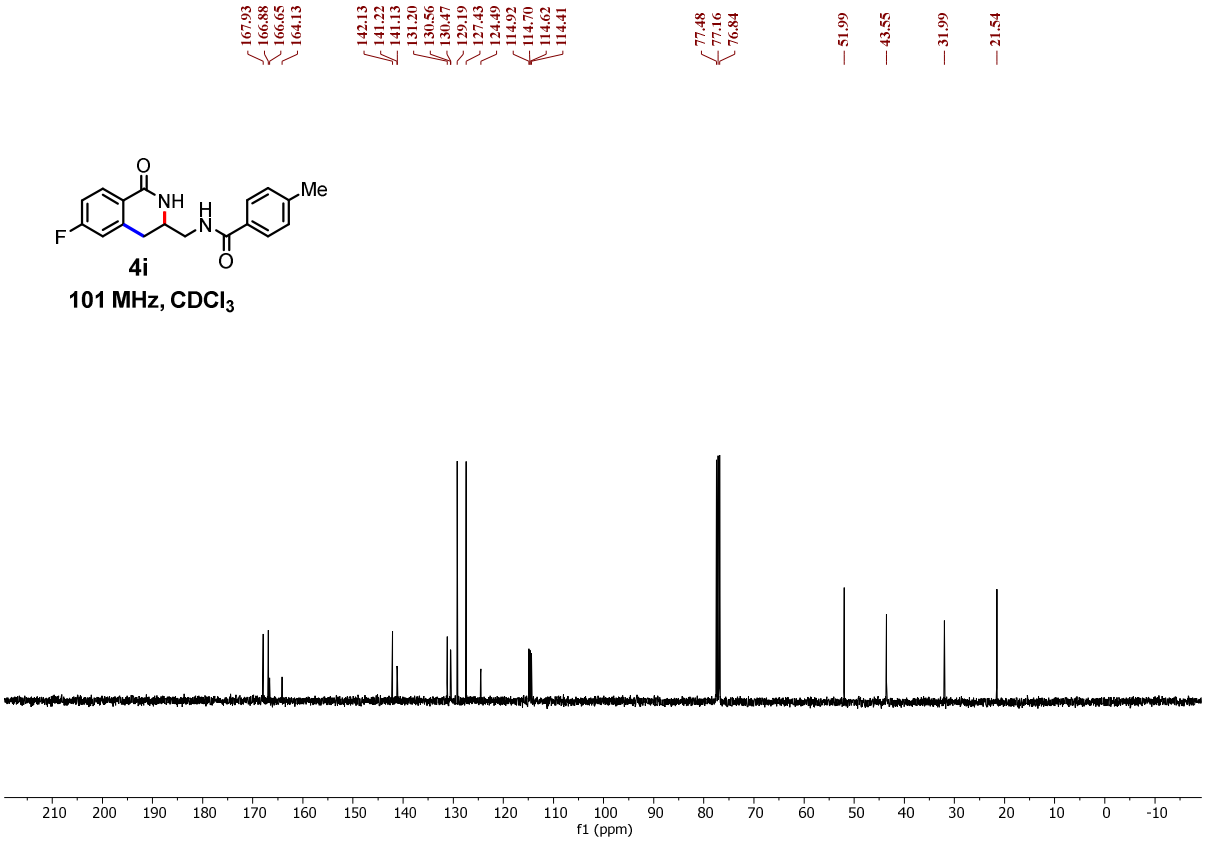
101 MHz, $CDCl_3$

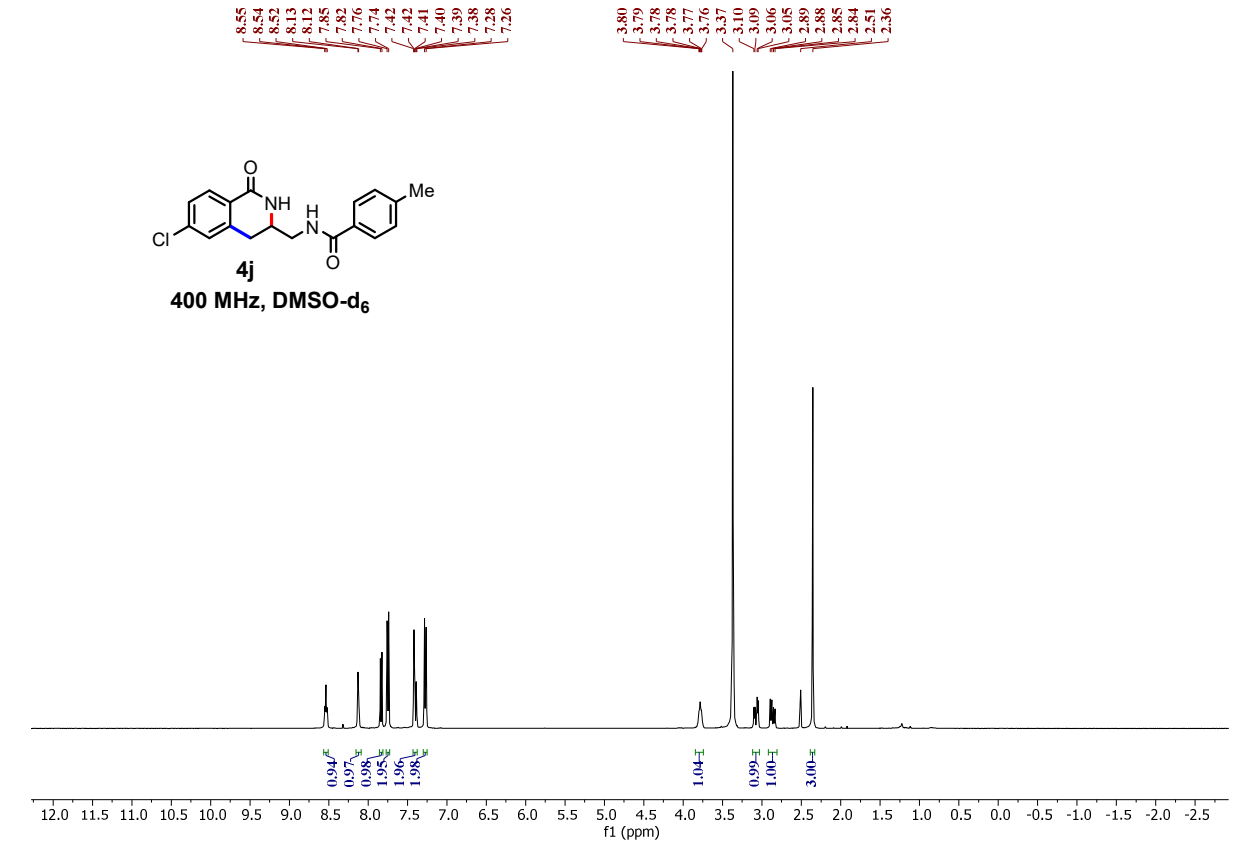


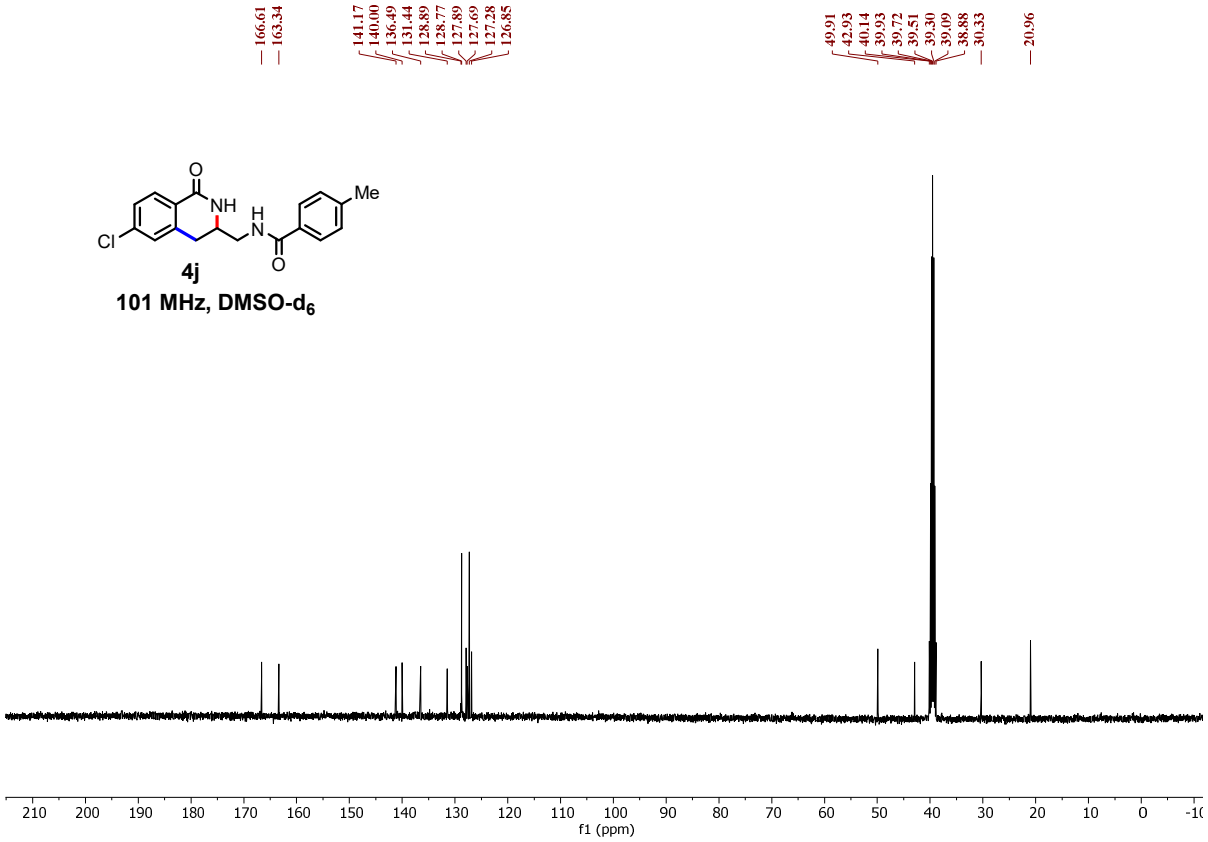
4i

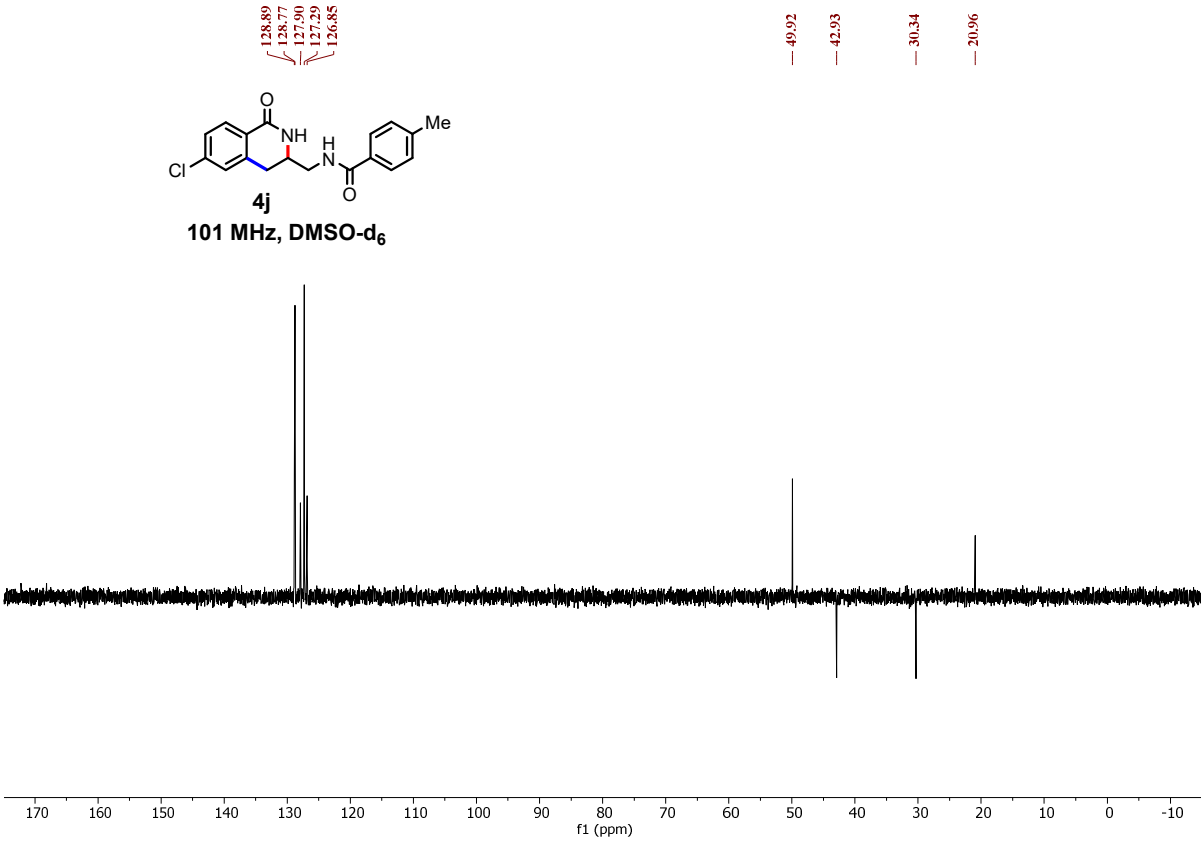
400 MHz, $CDCl_3$

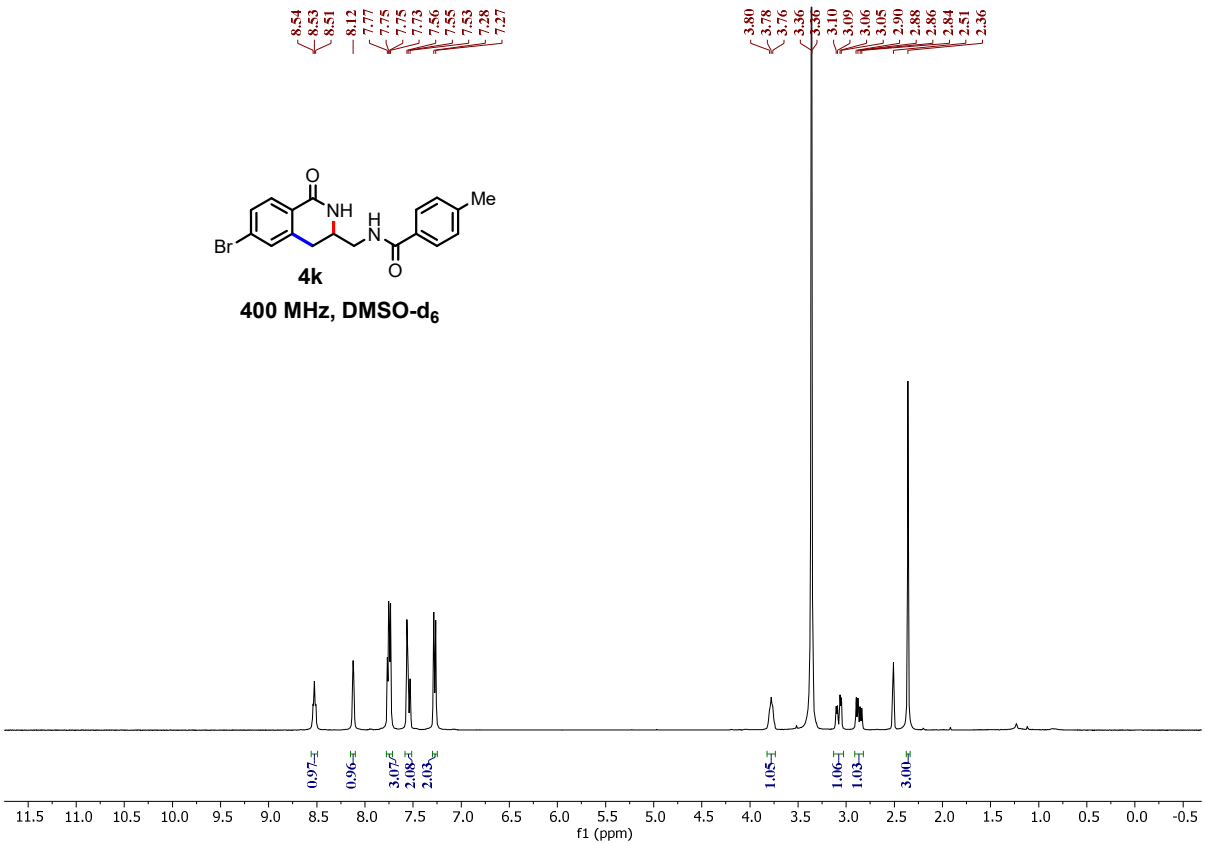



167.93
166.88
166.65
164.13
142.13
141.22
141.13
131.20
130.56
130.47
129.19
127.43
124.49
114.92
114.70
114.62
114.41
77.48
77.16
76.84
51.99
43.55
31.99
21.54
O
NH
H
N
O
F
Me
4i
101 MHz, CDCl3
f1 (ppm)


8.55
8.54
8.52
8.13
8.12
7.85
7.82
7.76
7.74
7.42
7.42
7.41
7.40
7.39
7.38
7.28
7.26
3.80
3.79
3.78
3.78
3.77
3.76
3.37
3.10
3.09
3.06
3.05
2.89
2.88
2.85
2.84
2.51
2.36
O
NH
H
N
O
Cl
Me
4j
400 MHz, DMSO-d6
0.94
0.97
0.98
1.95
1.96
1.98
1.04
0.99
1.00
3.00
f1 (ppm)

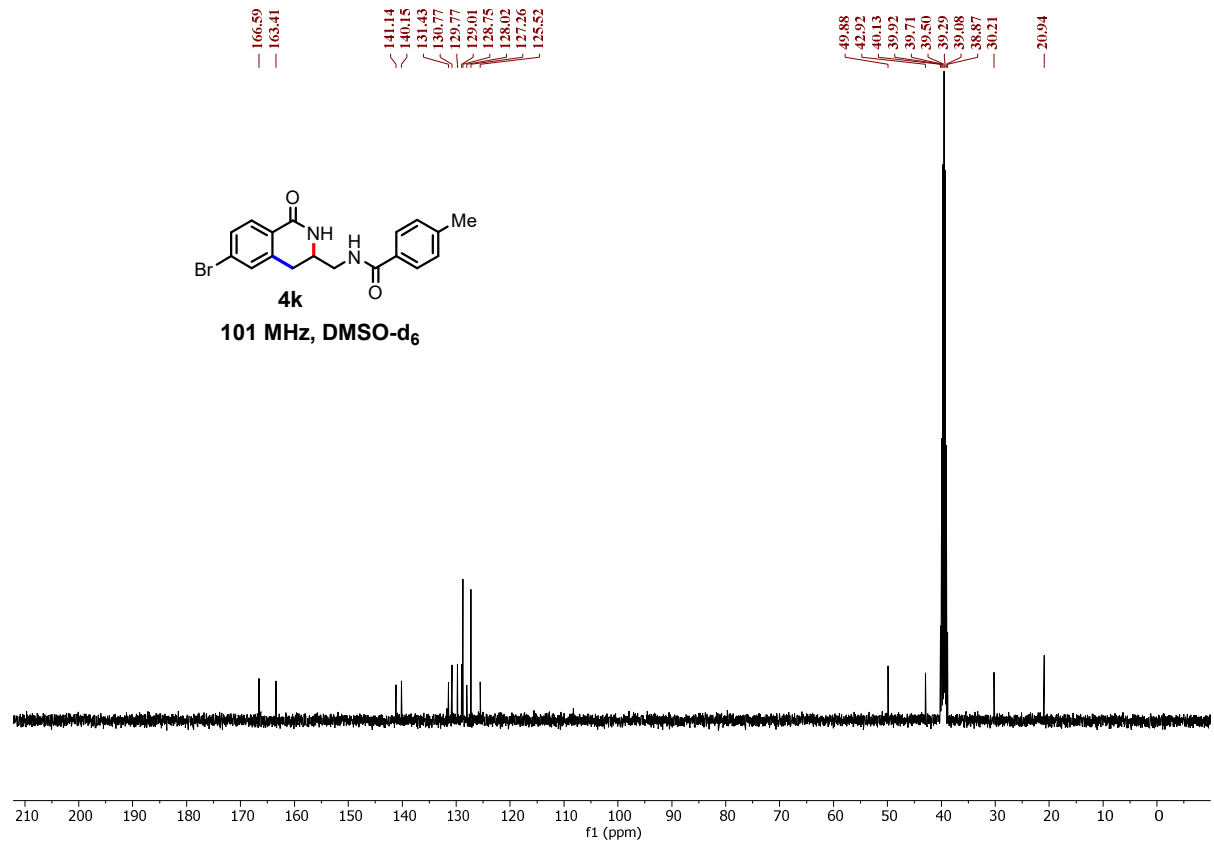

166.61
163.34
141.17
140.00
136.49
131.44
128.89
128.77
127.89
127.69
127.28
126.85
49.91
42.93
40.14
39.93
39.72
39.51
39.30
39.09
38.88
30.33
20.96
O
NH
H
N
O
Cl
Me
4j
101 MHz, DMSO-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


128.89
128.77
127.90
127.29
126.85
49.92
42.93
30.34
20.96
O
NH
H
N
O
Cl
Me
4j
101 MHz, DMSO-d6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



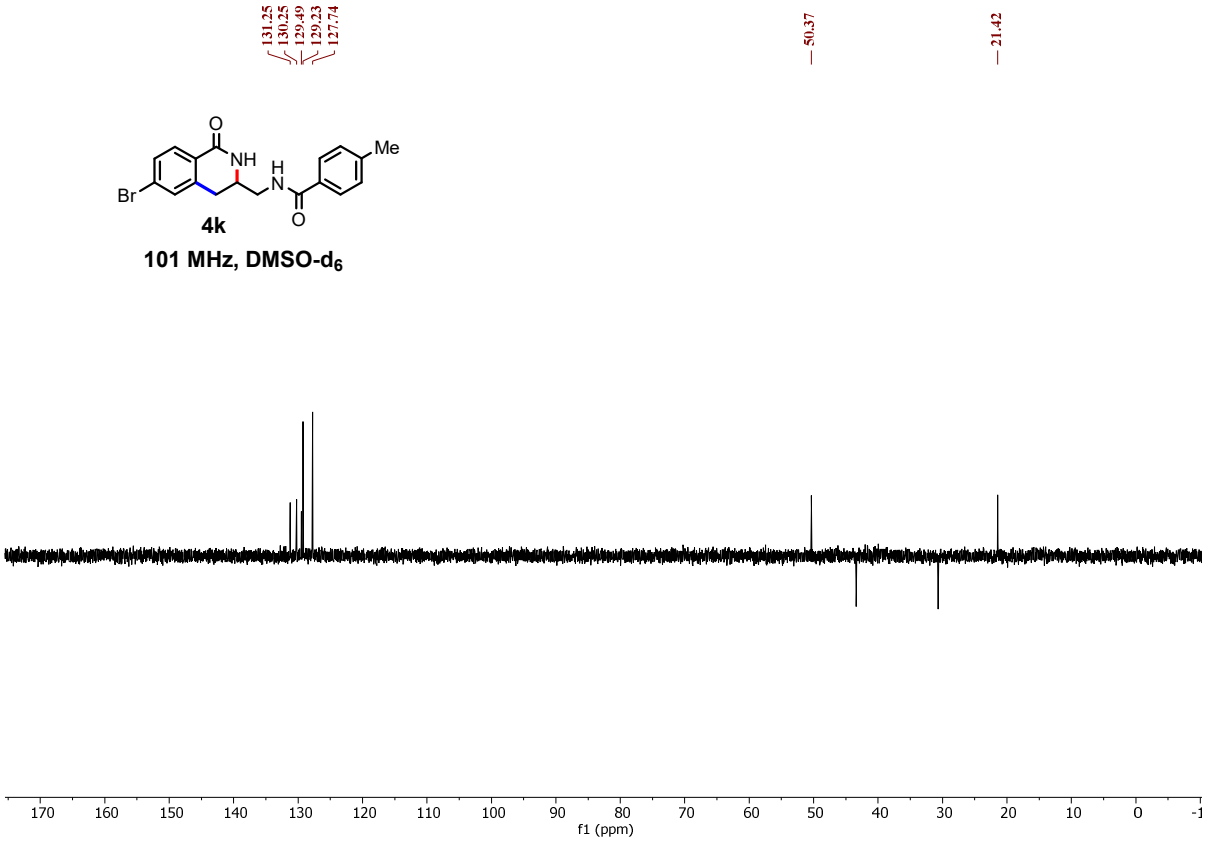
4k

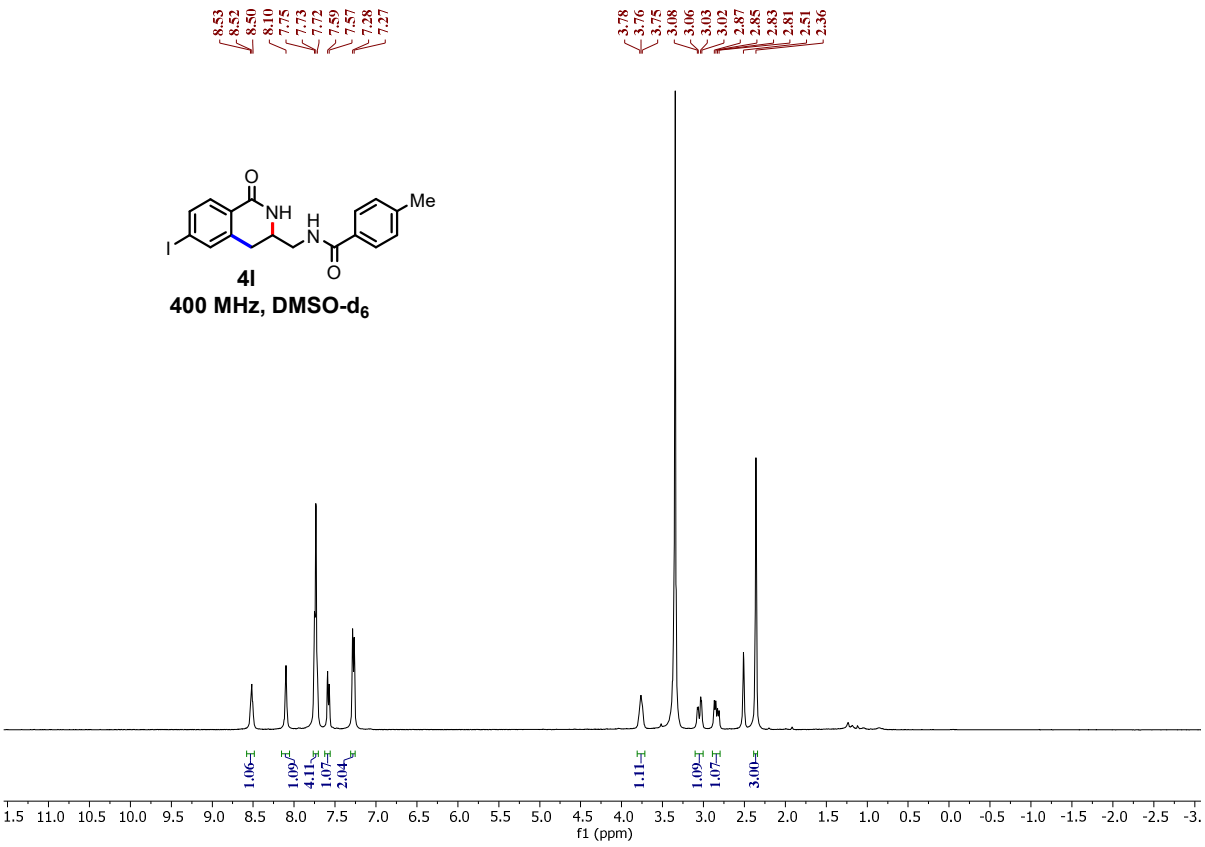
400 MHz, DMSO-d_6

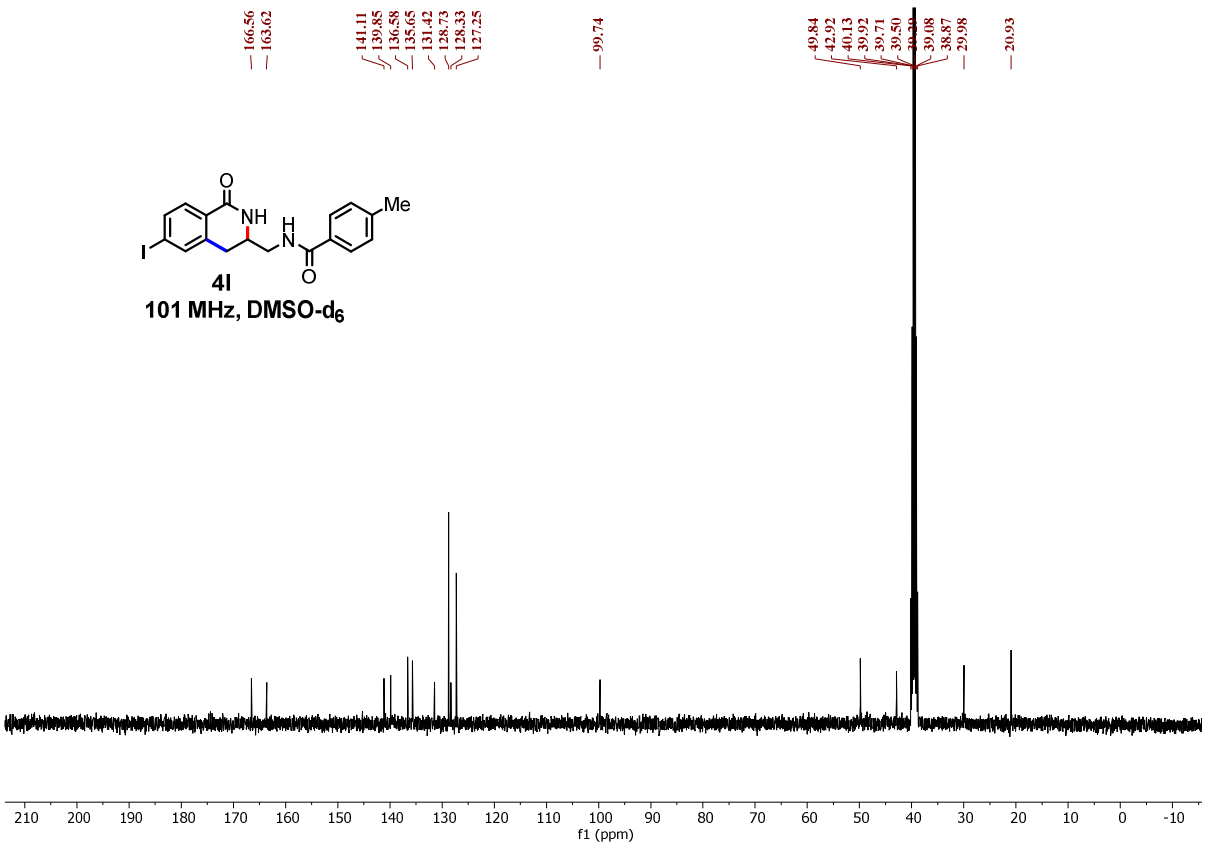


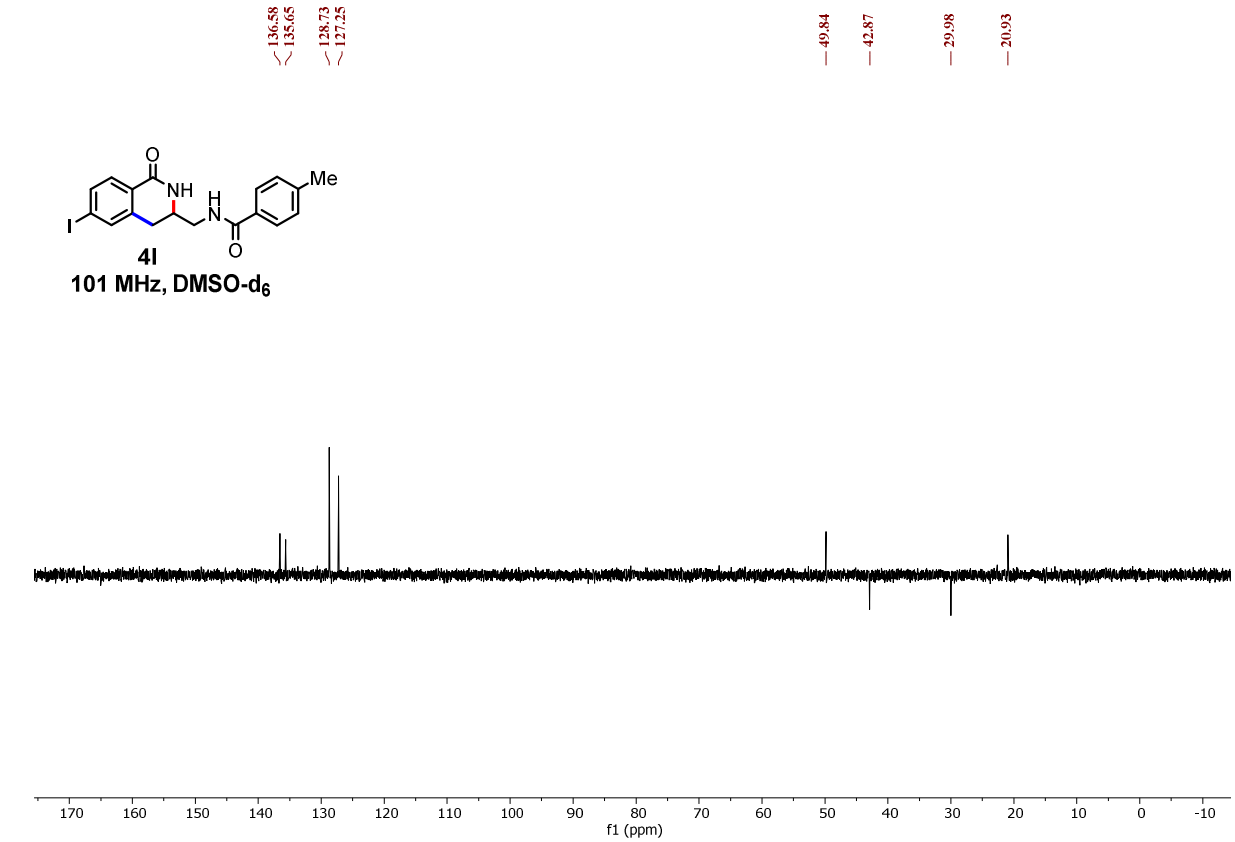
4k

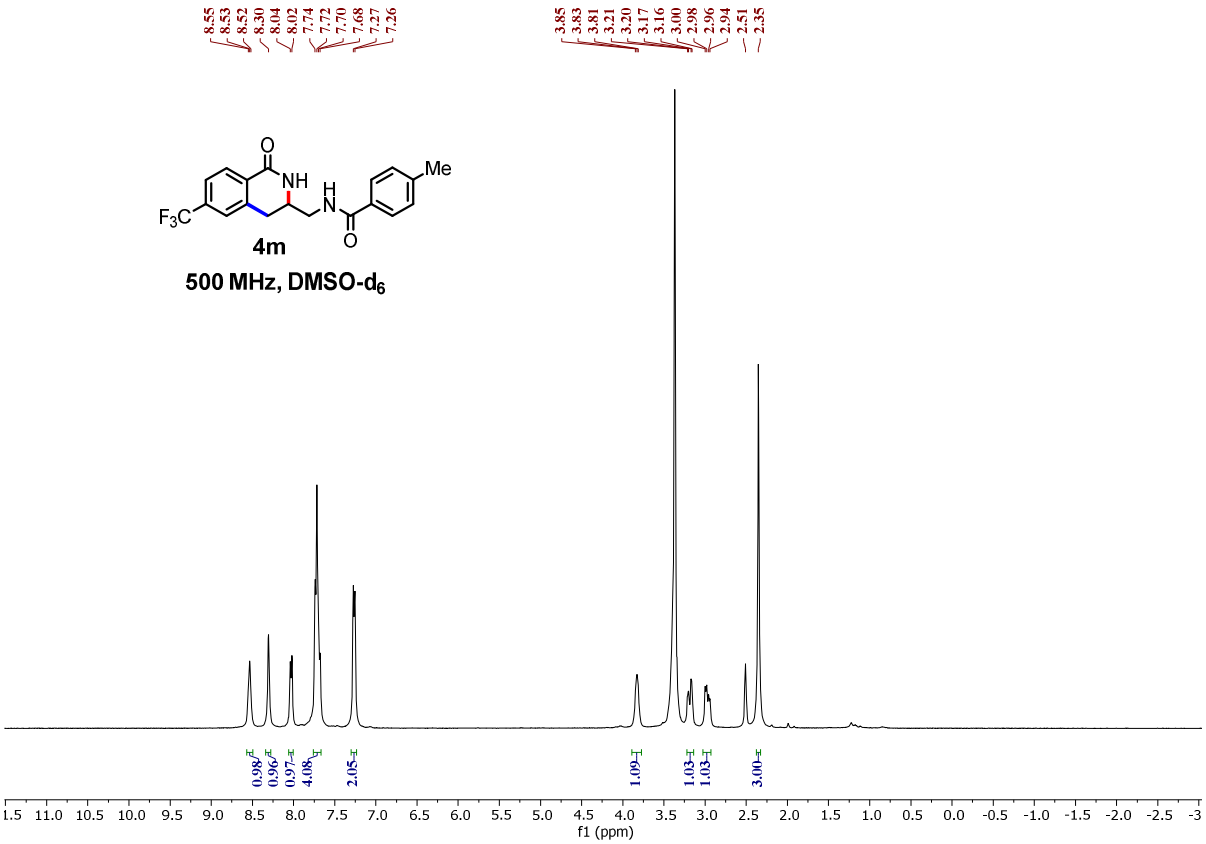
101 MHz, DMSO-d_6

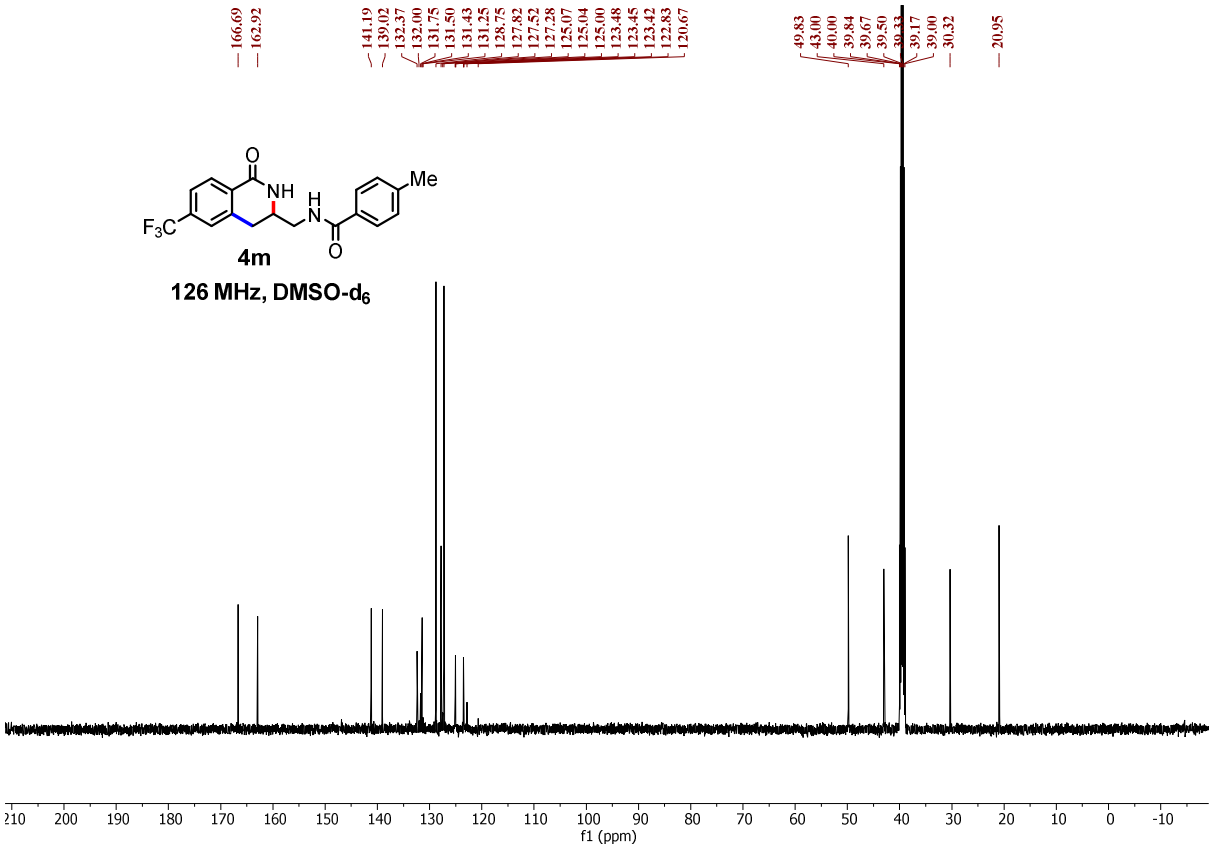

131.25
130.25
129.49
129.23
127.74
50.37
21.42
O
NH
H
N
O
Br
Me
4k
101 MHz, DMSO-d6
f1 (ppm)

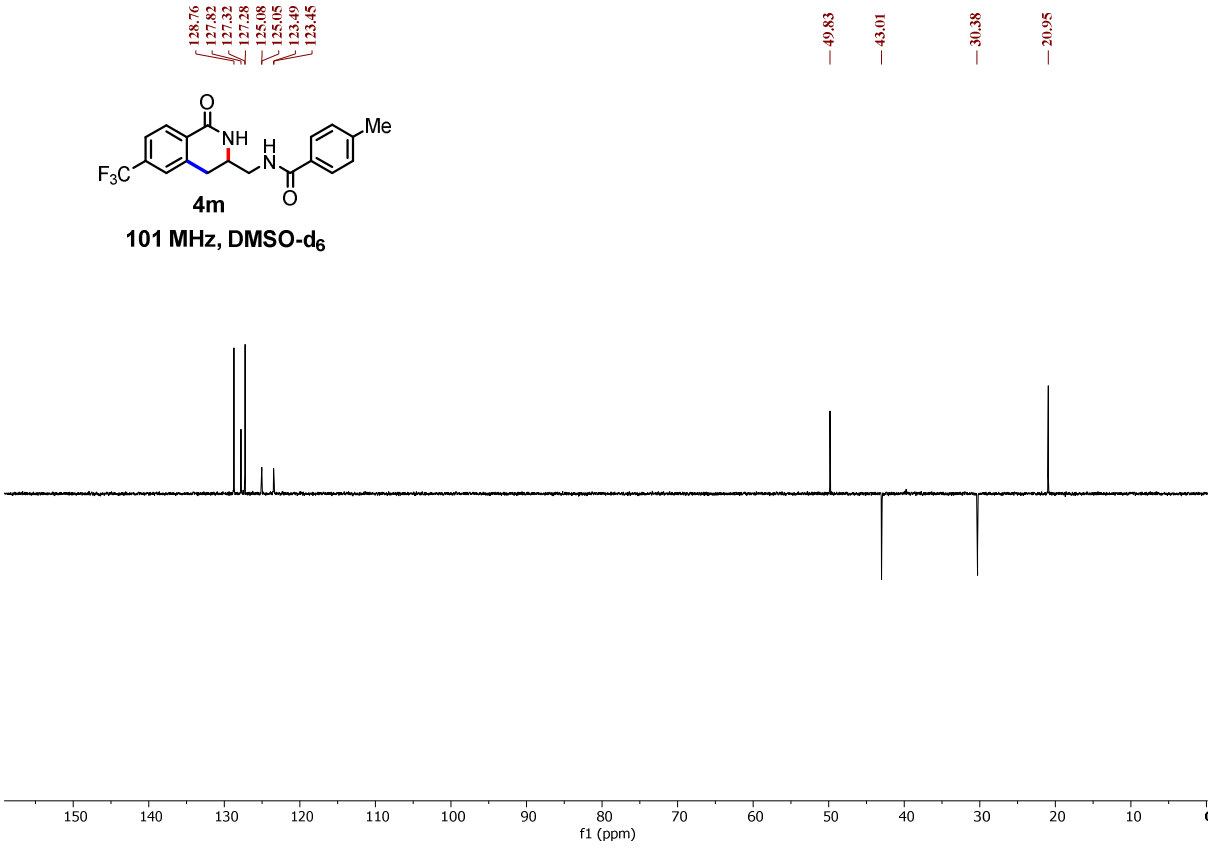

8.53
8.52
8.50
8.10
7.75
7.73
7.72
7.59
7.57
7.28
7.27
3.78
3.76
3.75
3.08
3.06
3.03
3.02
2.87
2.85
2.83
2.81
2.51
2.36
O
NH
H
N
O
I
Me
4l
400 MHz, DMSO-d6
1.06
1.09
4.11
1.07
2.04
1.11
1.09
1.07
3.00
f1 (ppm)

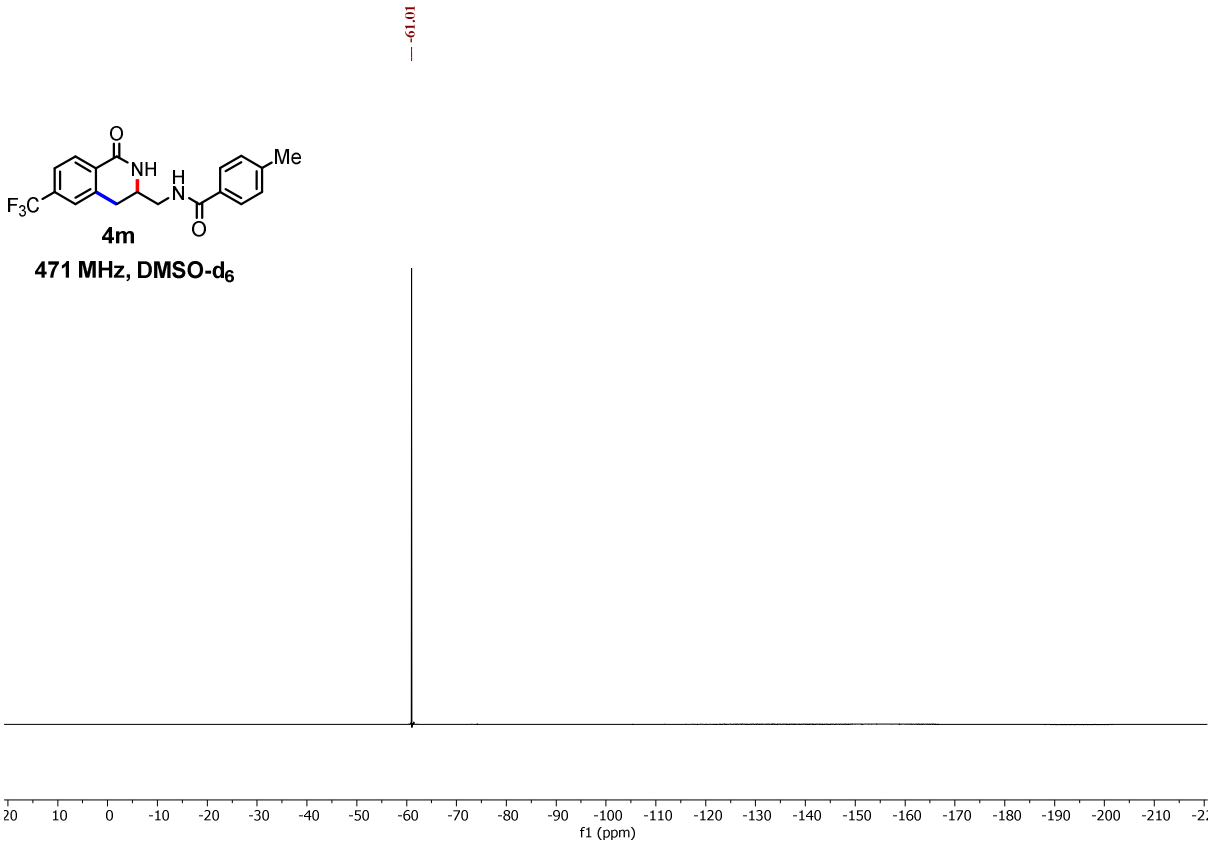

166.56
163.62
141.11
139.85
136.58
135.65
131.42
128.73
128.33
127.25
99.74
49.84
42.92
40.13
39.92
39.71
39.50
39.29
39.08
38.87
29.98
20.93
O
NH
H
N
O
I
Me
4l
101 MHz, DMSO-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

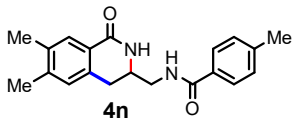

136.58
135.65
128.73
127.25
49.84
42.87
29.98
20.93
O
NH
H
N
O
I
Me
4l
101 MHz, DMSO-d6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.55
8.53
8.52
8.30
8.04
8.02
7.74
7.72
7.70
7.68
7.27
7.26
3.85
3.83
3.81
3.21
3.20
3.17
3.16
3.00
2.98
2.96
2.94
2.51
2.35
O
NH
H
N
O
Me
F3C
4m
500 MHz, DMSO-d6
0.98
0.96
0.97
4.08
2.05
1.09
1.03
1.03
3.00
f1 (ppm)


166.69
162.92
141.19
139.02
132.37
132.00
131.75
131.50
131.43
131.25
128.75
127.82
127.52
127.28
125.07
125.04
125.00
123.48
123.45
123.42
122.83
120.67
49.83
43.00
40.00
39.84
39.67
39.50
39.33
39.17
39.00
30.32
20.95
O
NH
H
N
O
Me
F3C
4m
126 MHz, DMSO-d6
f1 (ppm)

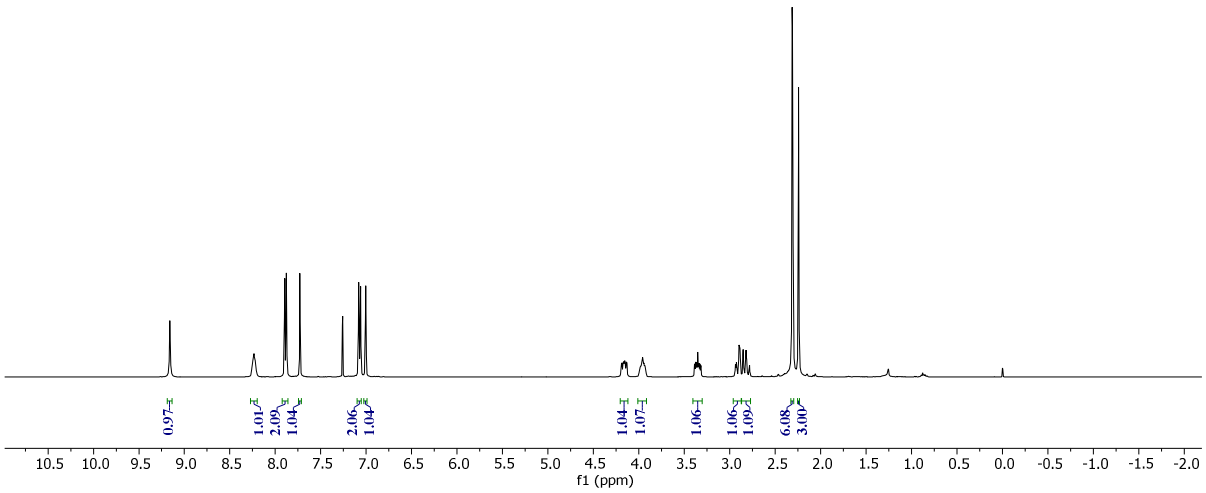

128.76
127.82
127.32
127.28
125.08
125.05
123.49
123.45
49.83
43.01
30.38
20.95
O
NH
H
N
O
Me
F3C
4m
101 MHz, DMSO-d6
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

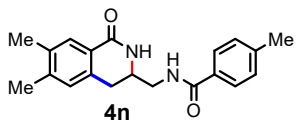

-61.01
O
NH
H
N
O
Me
F3C
4m
471 MHz, DMSO-d6
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)



4n

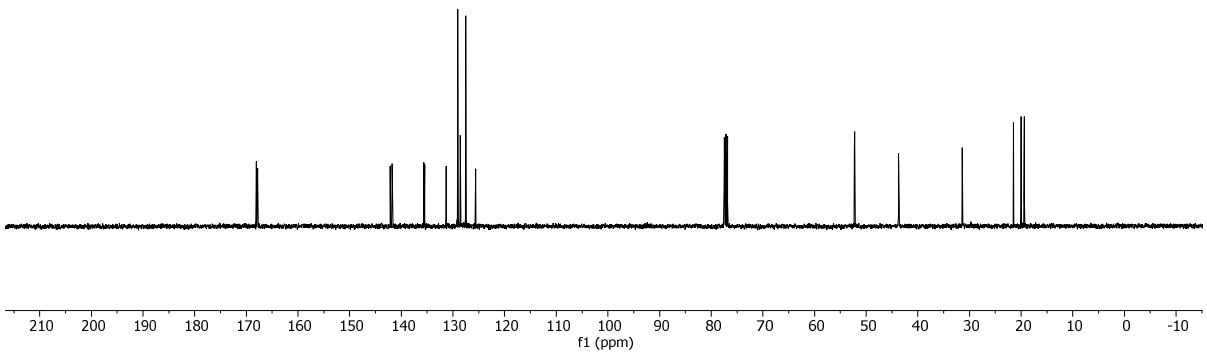
400 MHz, $CDCl_3$

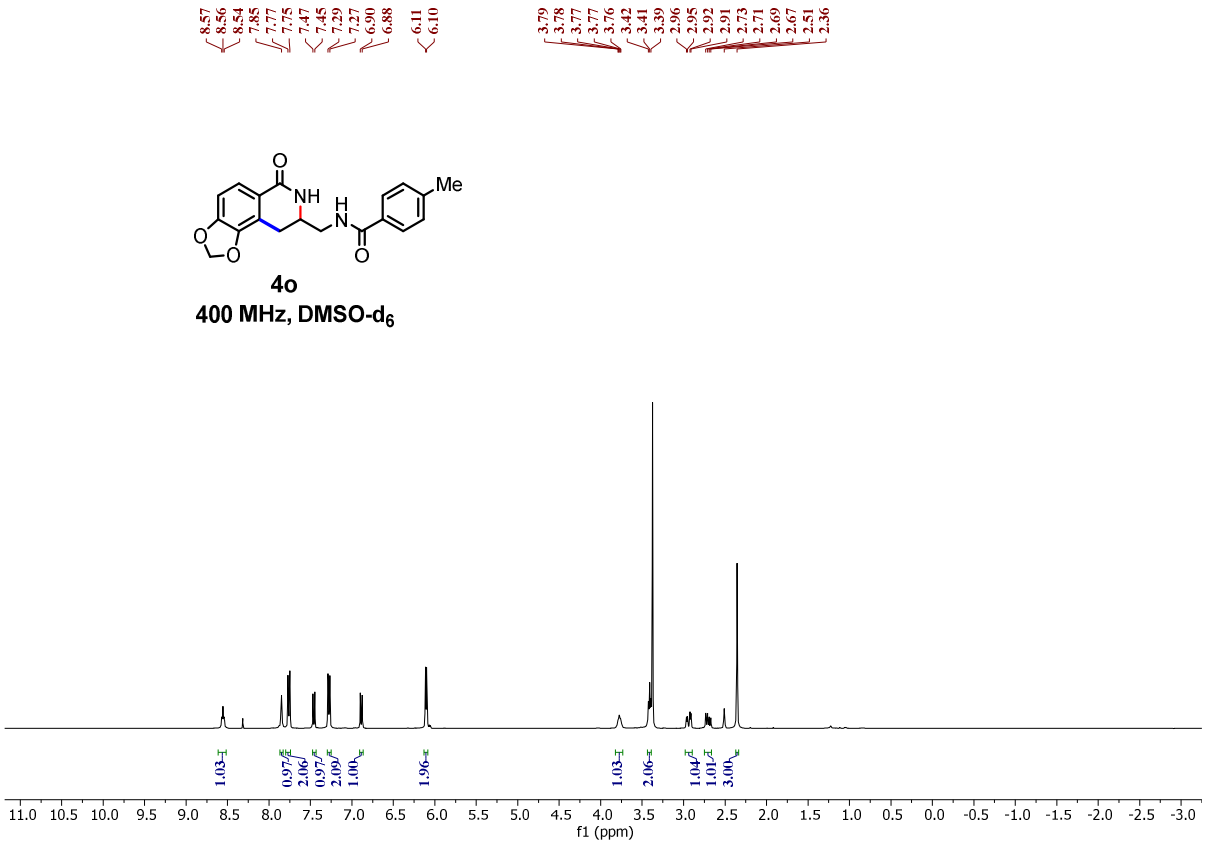




4n

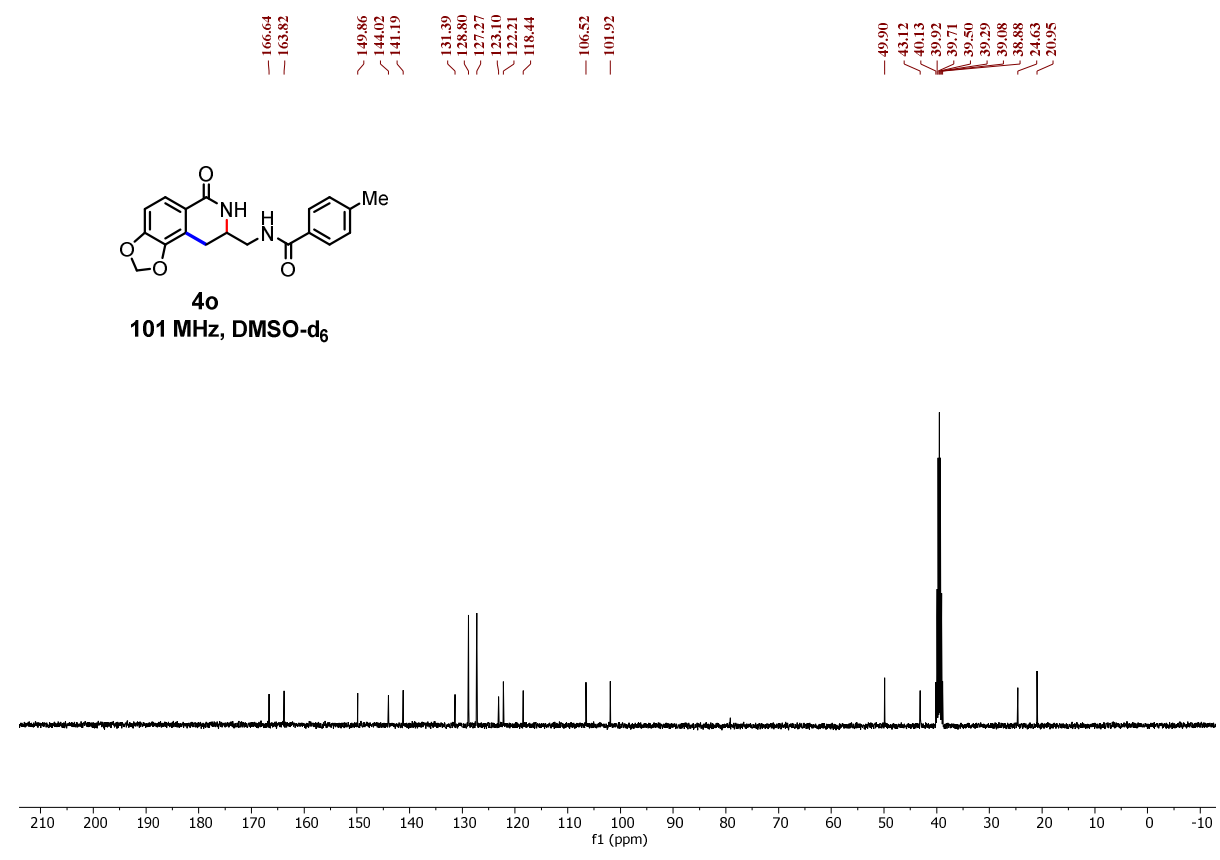
101 MHz, $CDCl_3$





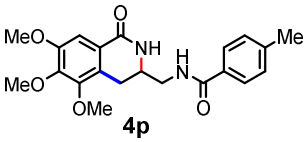
4o

400 MHz, DMSO-d_6



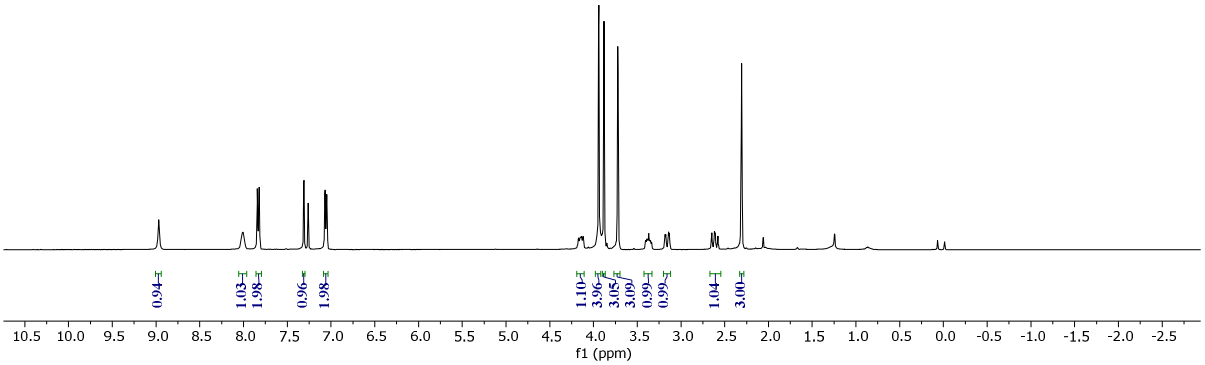
4o

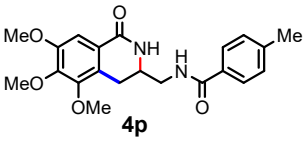
101 MHz, DMSO-d_6



4p

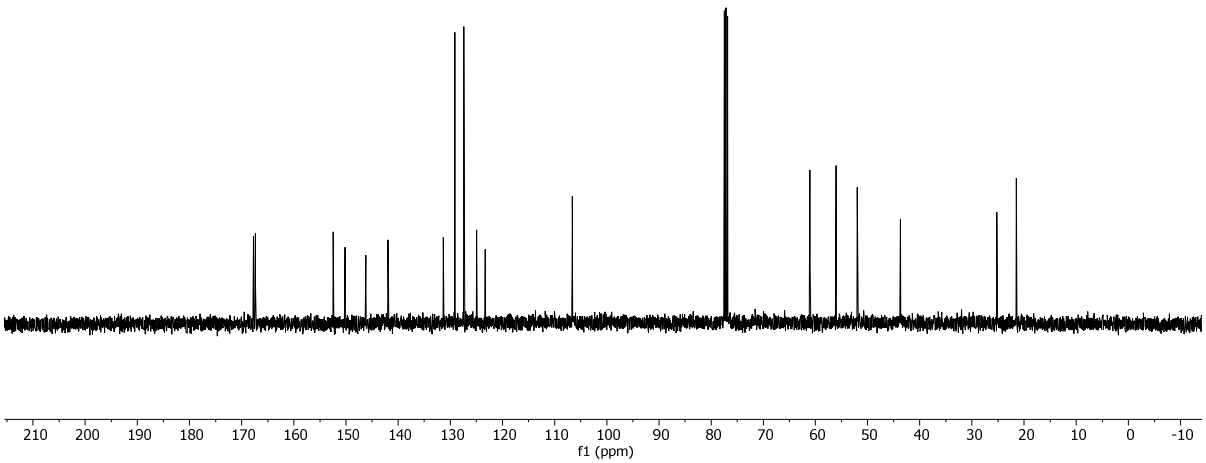
400 MHz, $CDCl_3$

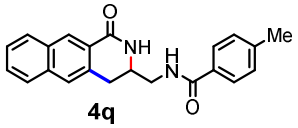




4p

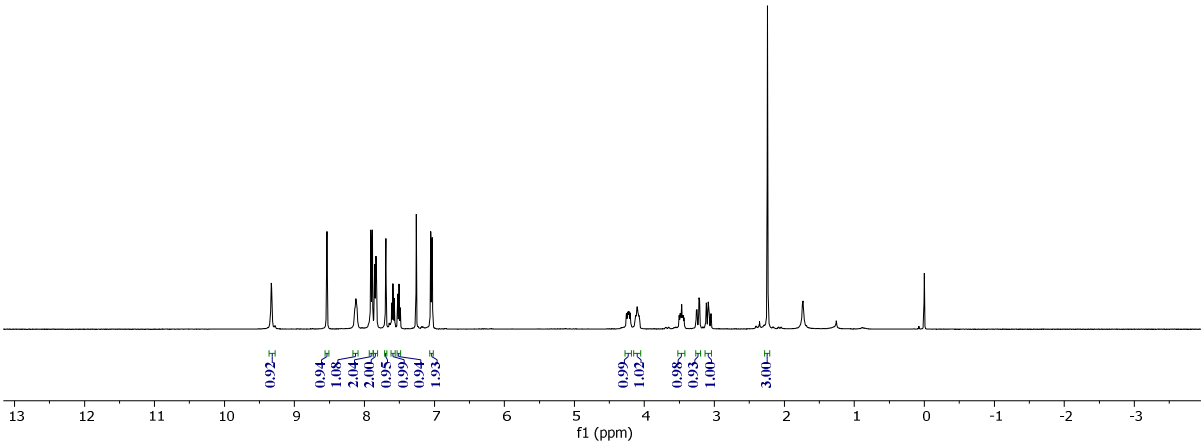
101 MHz, $CDCl_3$

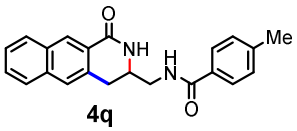




4q

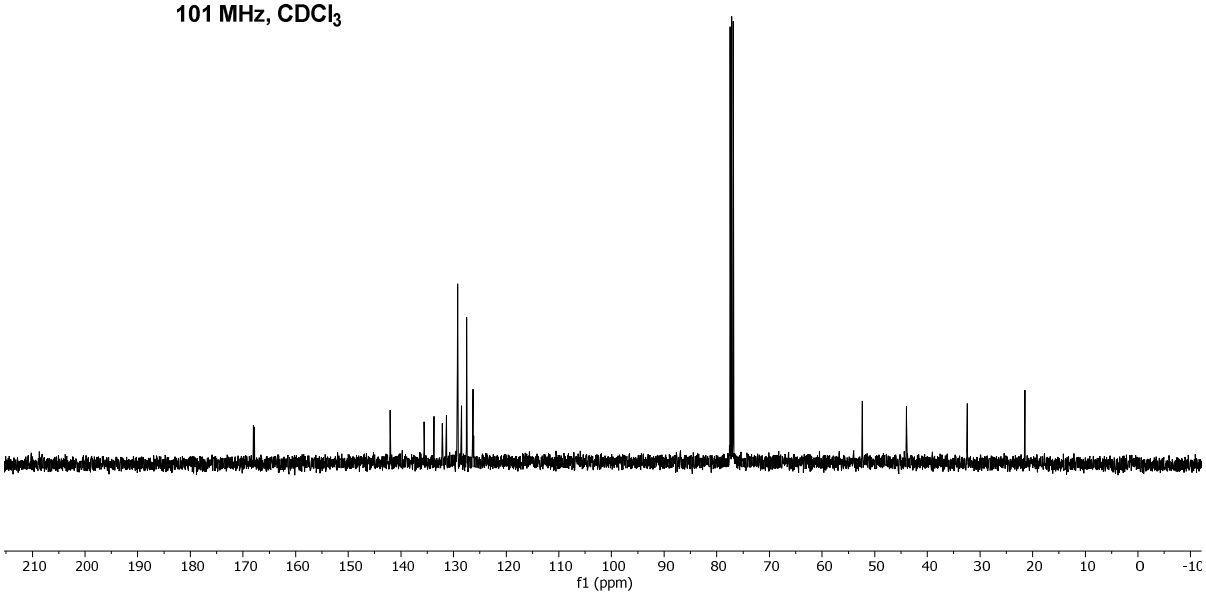
400 MHz, $CDCl_3$

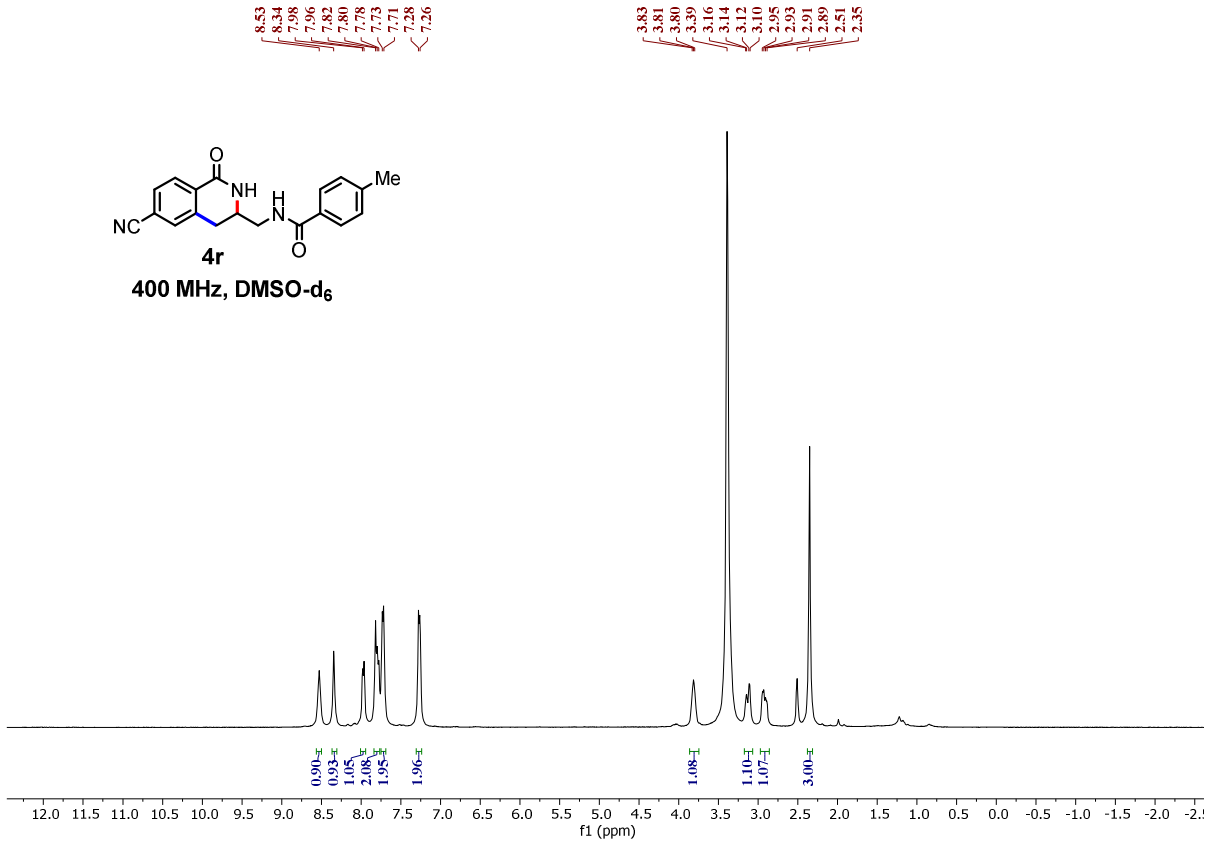


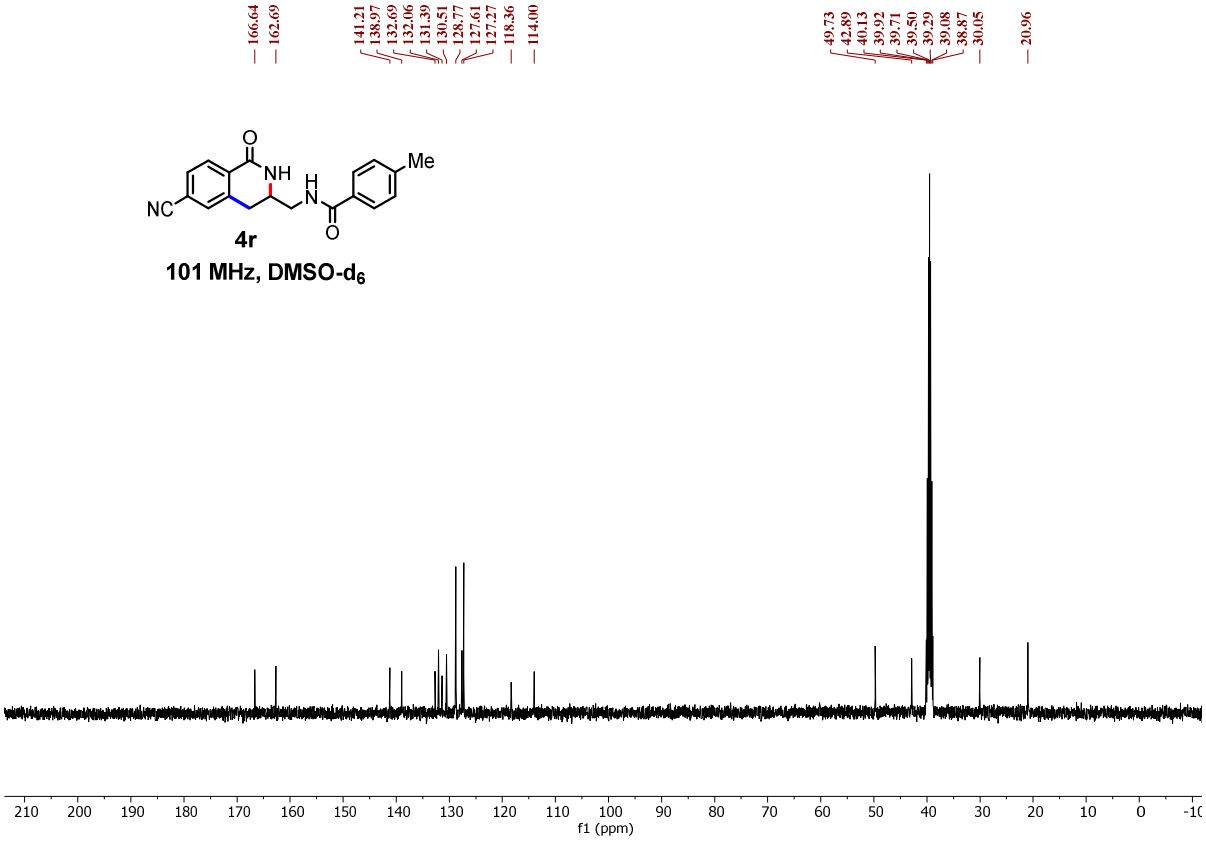


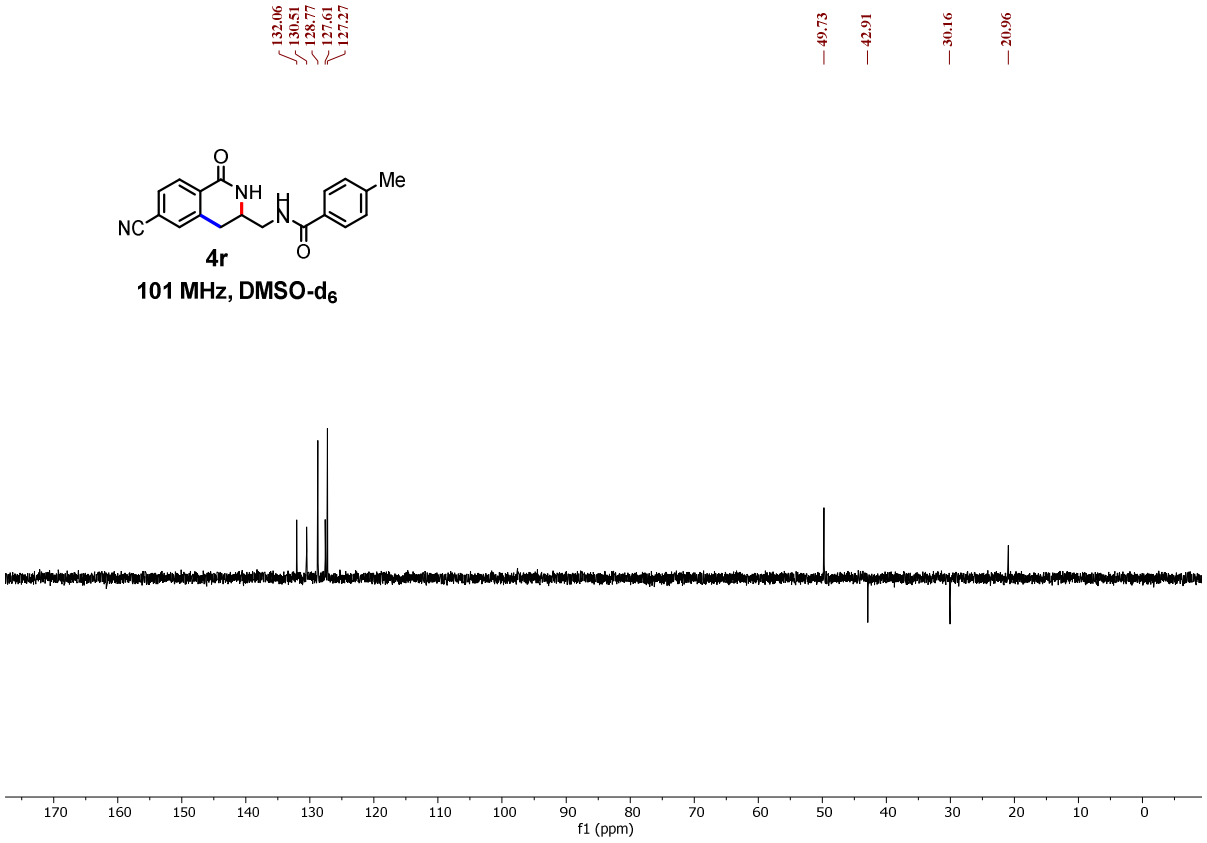
4q

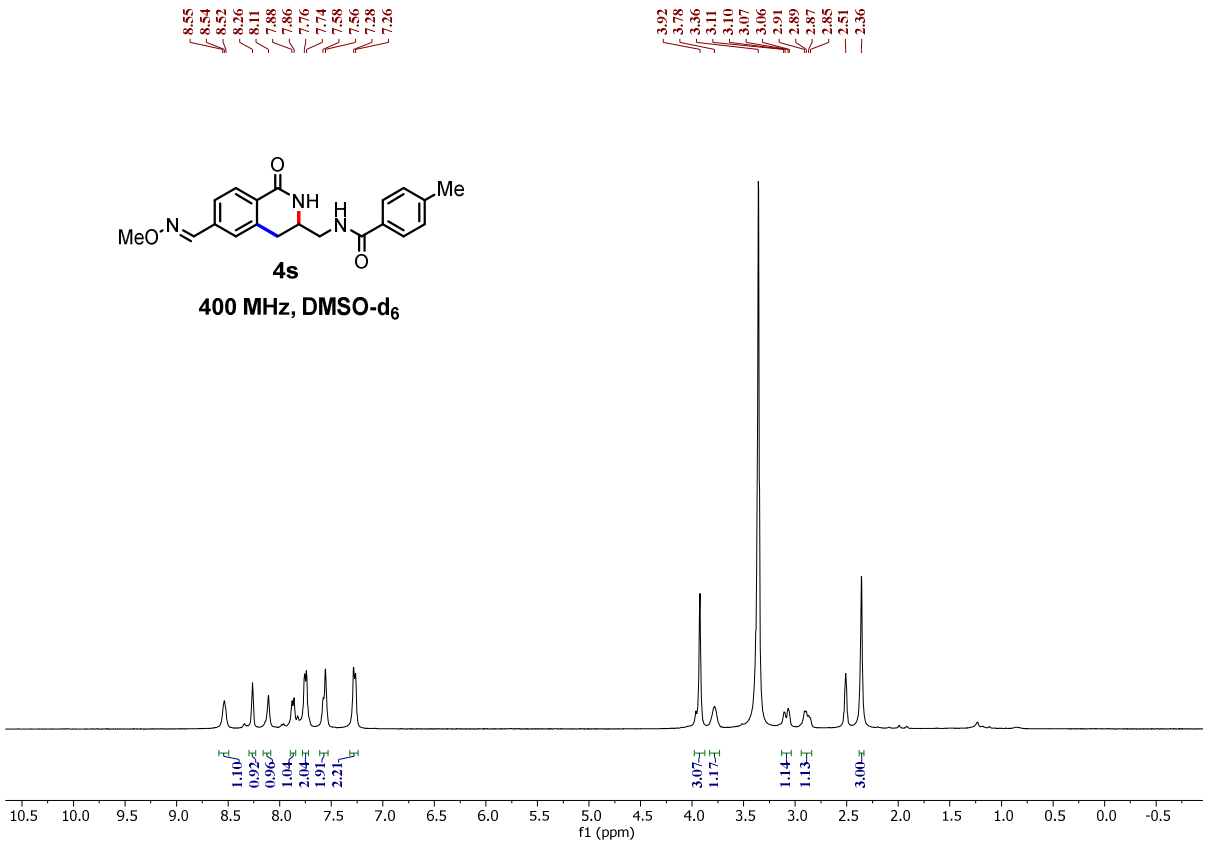
101 MHz, $CDCl_3$

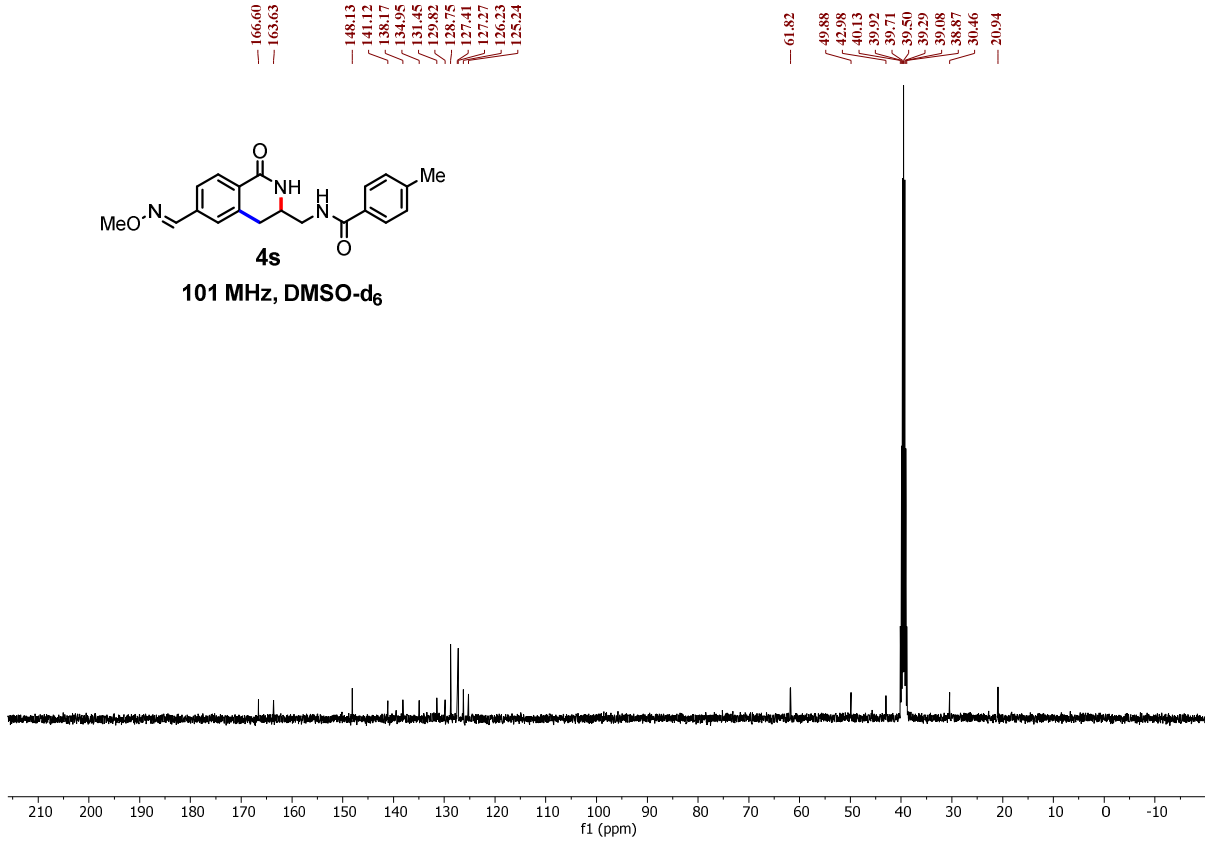


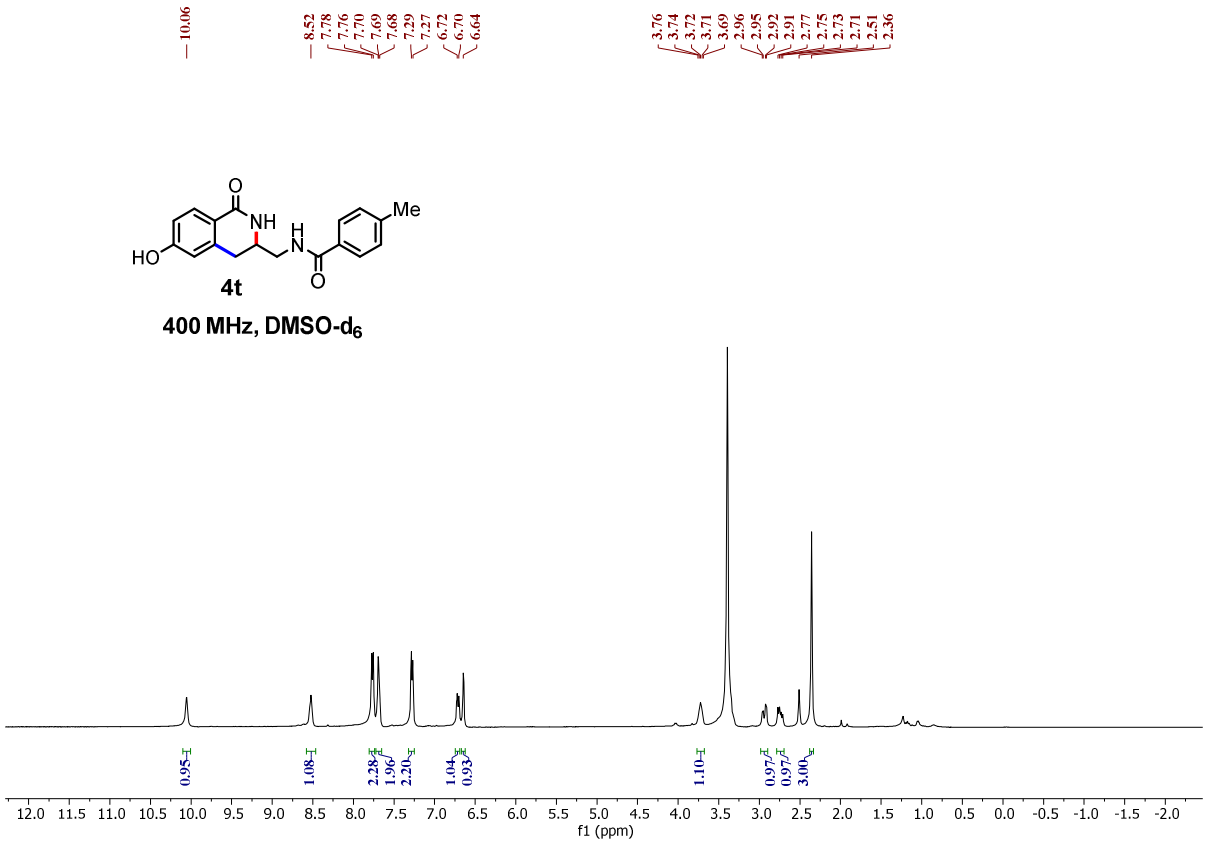

8.53
8.34
7.98
7.96
7.82
7.80
7.78
7.73
7.71
7.28
7.26
3.83
3.81
3.80
3.39
3.16
3.14
3.12
3.10
2.95
2.93
2.91
2.89
2.51
2.35
O
NH
H
N
O
NC
Me
4r
400 MHz, DMSO-d6
0.90
0.93
1.05
2.08
1.95
1.96
1.08
1.10
1.07
3.00
f1 (ppm)

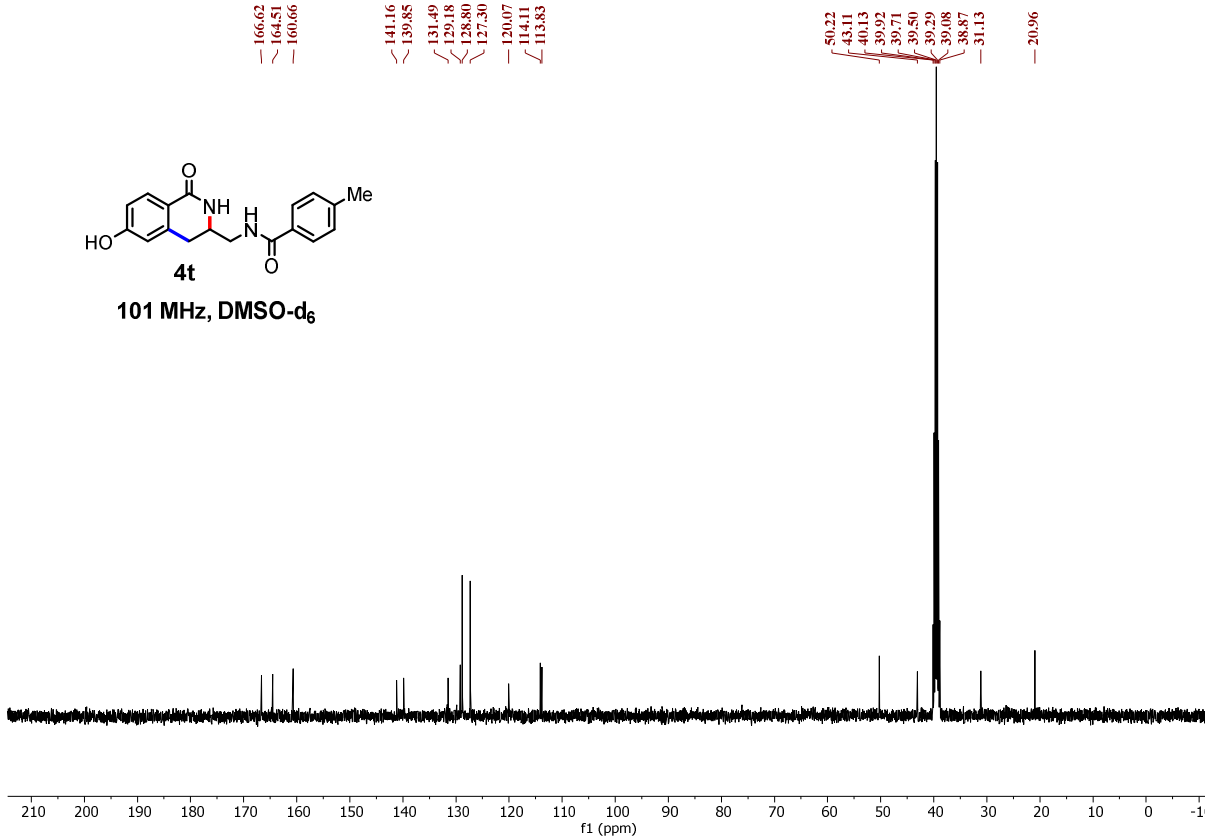

166.64
162.69
141.21
138.97
132.69
132.06
131.39
130.51
128.77
127.61
127.27
118.36
114.00
49.73
42.89
40.13
39.92
39.71
39.50
39.29
39.08
38.87
30.05
20.96
O
NH
H
N
O
NC
Me
4r
101 MHz, DMSO-d6
f1 (ppm)

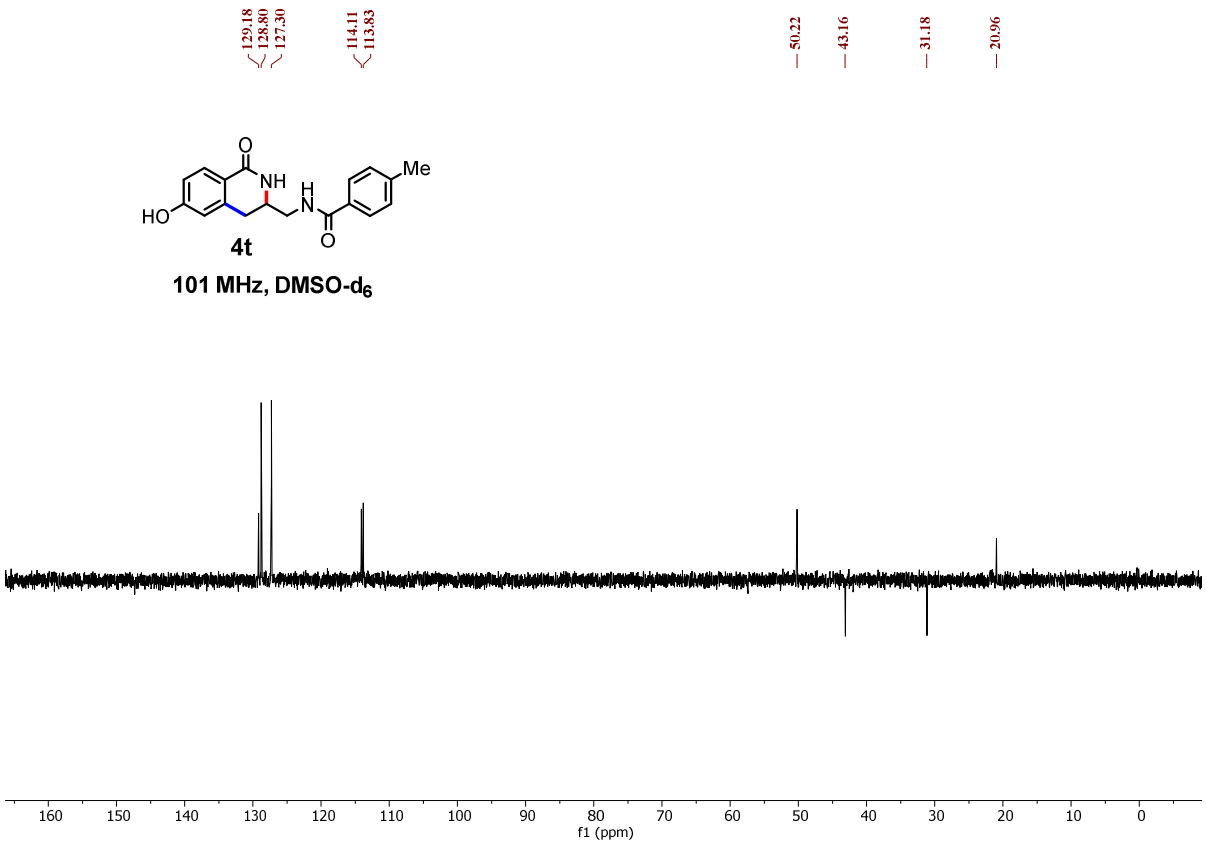

132.06
130.51
128.77
127.61
127.27
49.73
42.91
30.16
20.96
O
NH
H
N
O
NC
Me
4r
101 MHz, DMSO-d6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

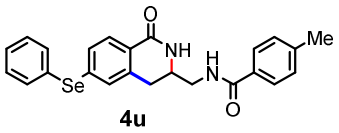

8.55
8.54
8.52
8.26
8.11
7.88
7.86
7.76
7.74
7.58
7.56
7.28
7.26
3.92
3.78
3.36
3.11
3.10
3.07
3.06
2.91
2.89
2.87
2.85
2.51
2.36
O
NH
H
N
O
MeO
N
Me
4s
400 MHz, DMSO-d6
1.10
0.92
0.96
1.04
2.04
1.91
2.21
3.07
1.17
1.14
1.13
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


166.60
163.63
148.13
141.12
138.17
134.95
131.45
129.82
128.75
127.41
127.27
126.23
125.24
61.82
49.88
42.98
40.13
39.92
39.71
39.50
39.29
39.08
38.87
30.46
20.94
O
NH
H
N
Me
MeO
N
O
4s
101 MHz, DMSO-d6
f1 (ppm)


10.06
8.52
7.78
7.76
7.70
7.69
7.68
7.29
7.27
6.72
6.70
6.64
3.76
3.74
3.72
3.71
3.69
2.96
2.95
2.92
2.91
2.77
2.75
2.73
2.71
2.51
2.36
O
NH
H
N
Me
HO
O
4t
400 MHz, DMSO-d6
0.95
1.08
2.28
1.96
2.20
1.04
0.93
1.10
0.97
0.97
3.00
f1 (ppm)

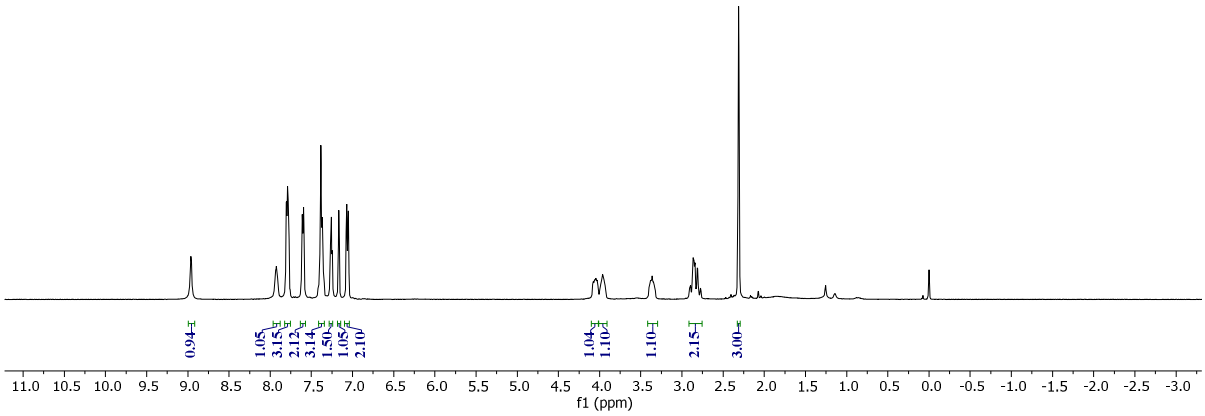

166.62
164.51
160.66
141.16
139.85
131.49
129.18
128.80
127.30
120.07
114.11
113.83
50.22
43.11
40.13
39.92
39.71
39.50
39.29
39.08
38.87
31.13
20.96
O
NH
H
N
HO
Me
O
4t
101 MHz, DMSO-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

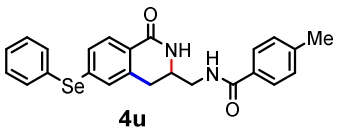

129.18
128.80
127.30
114.11
113.83
50.22
43.16
31.18
20.96
O
NH
H
N
HO
Me
O
4t
101 MHz, DMSO-d6
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



4u

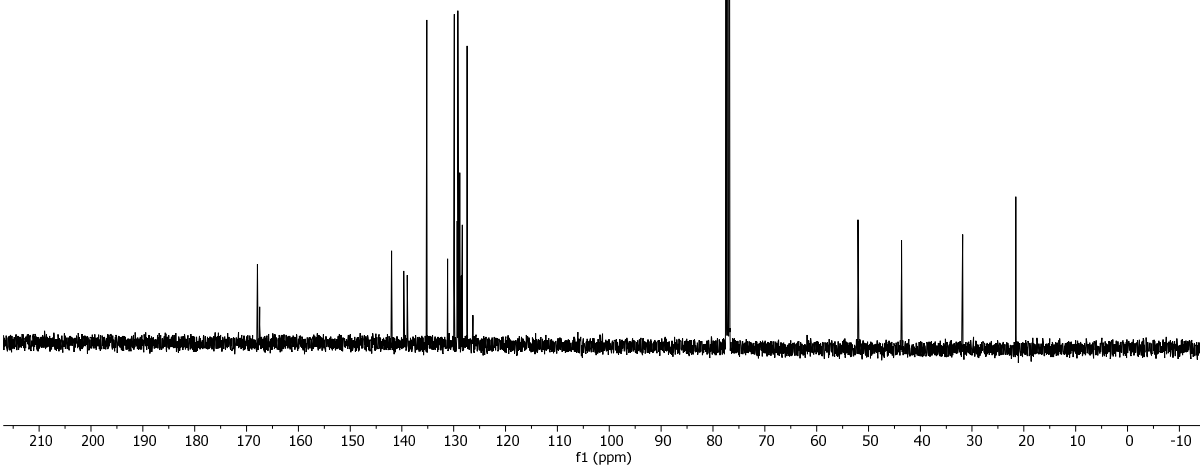
400 MHz, $CDCl_3$

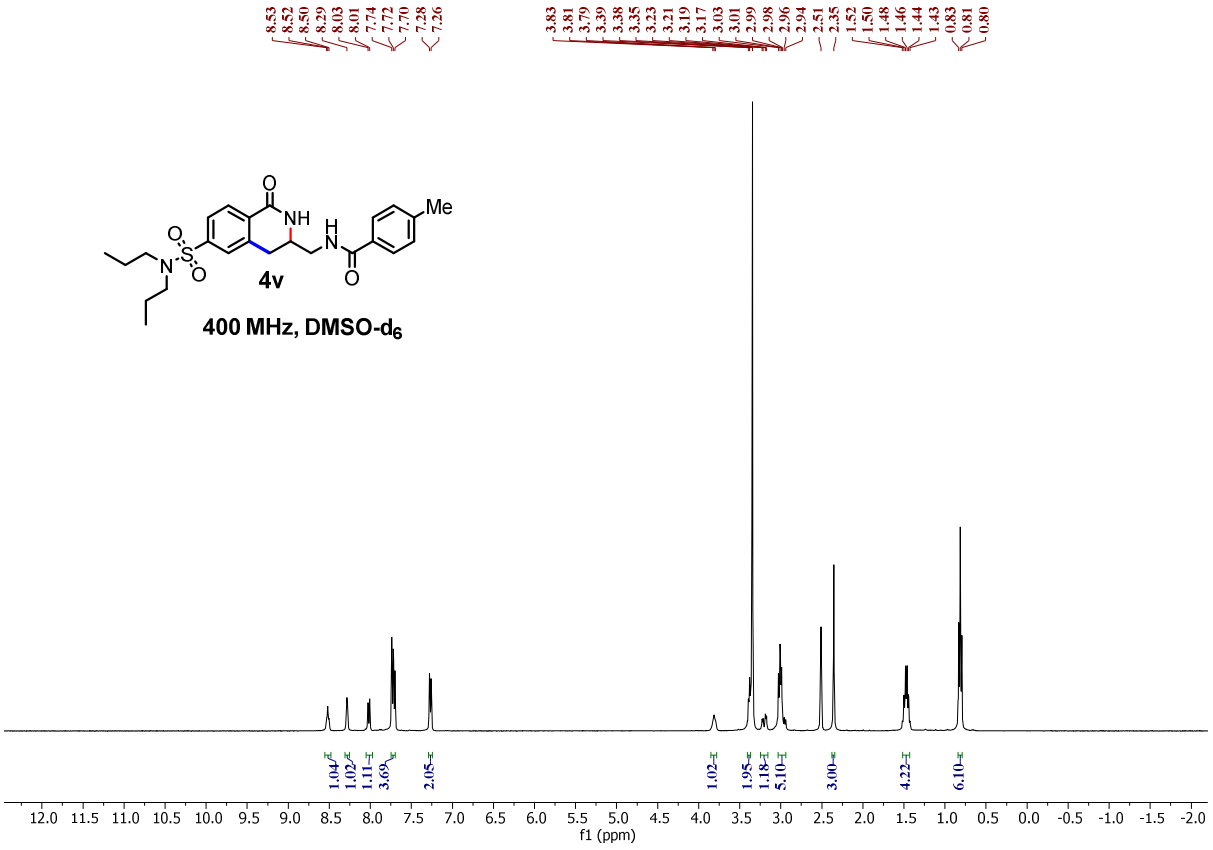


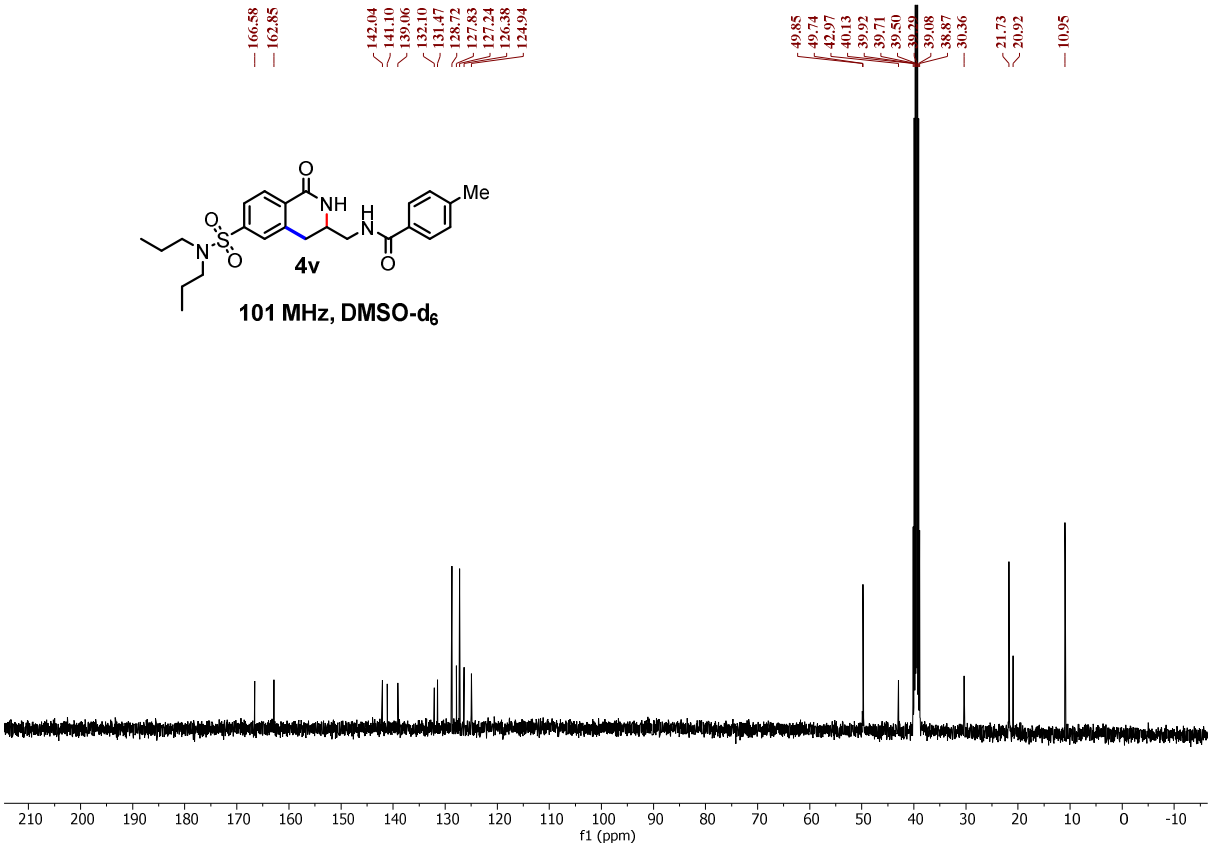


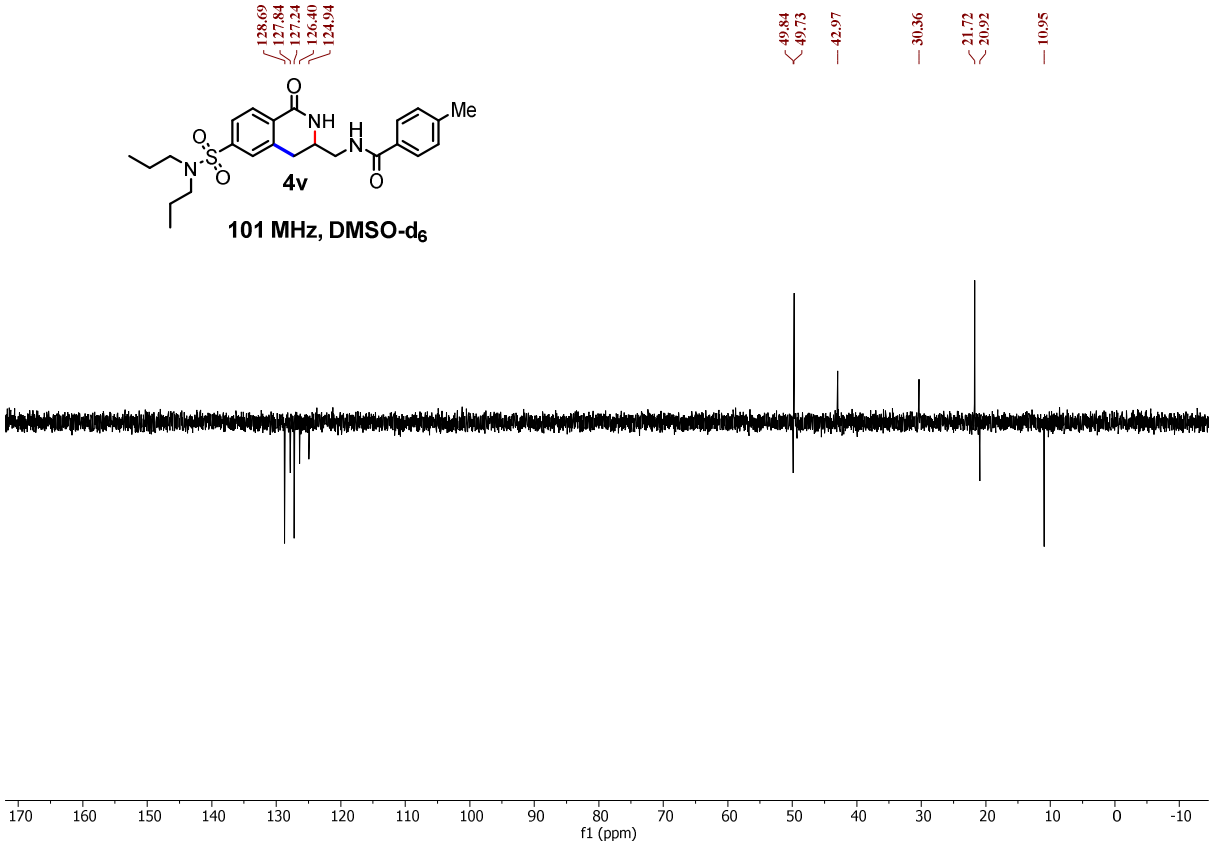
4u

101 MHz, $CDCl_3$

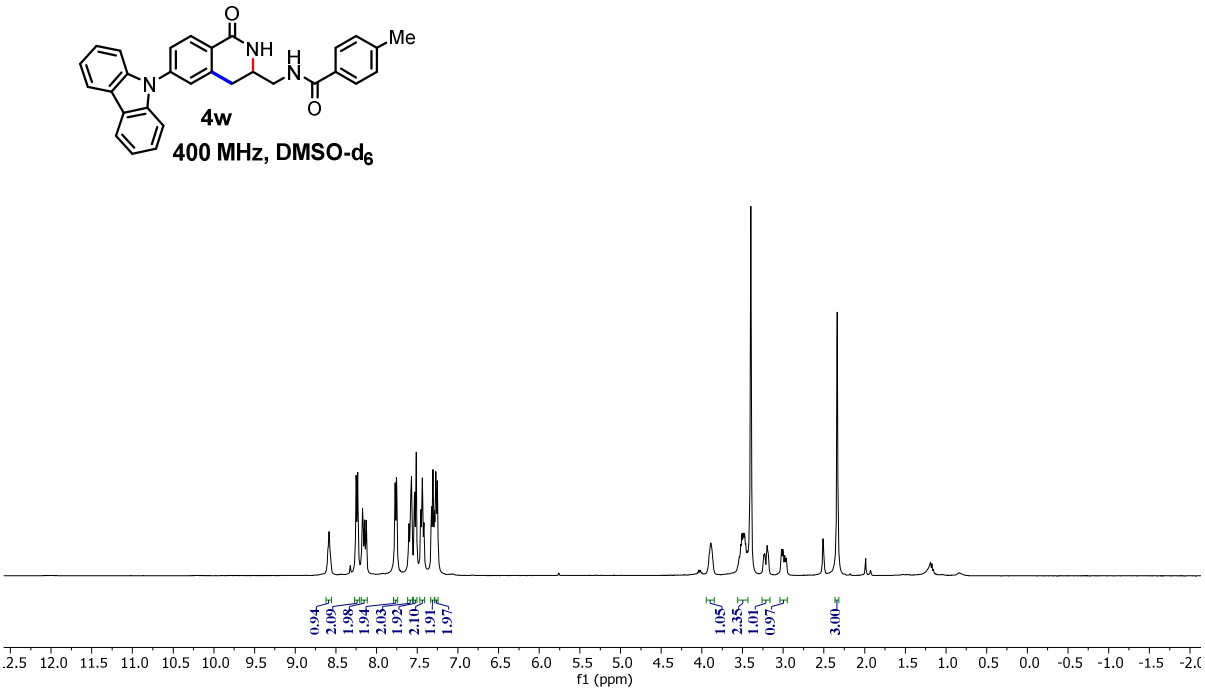


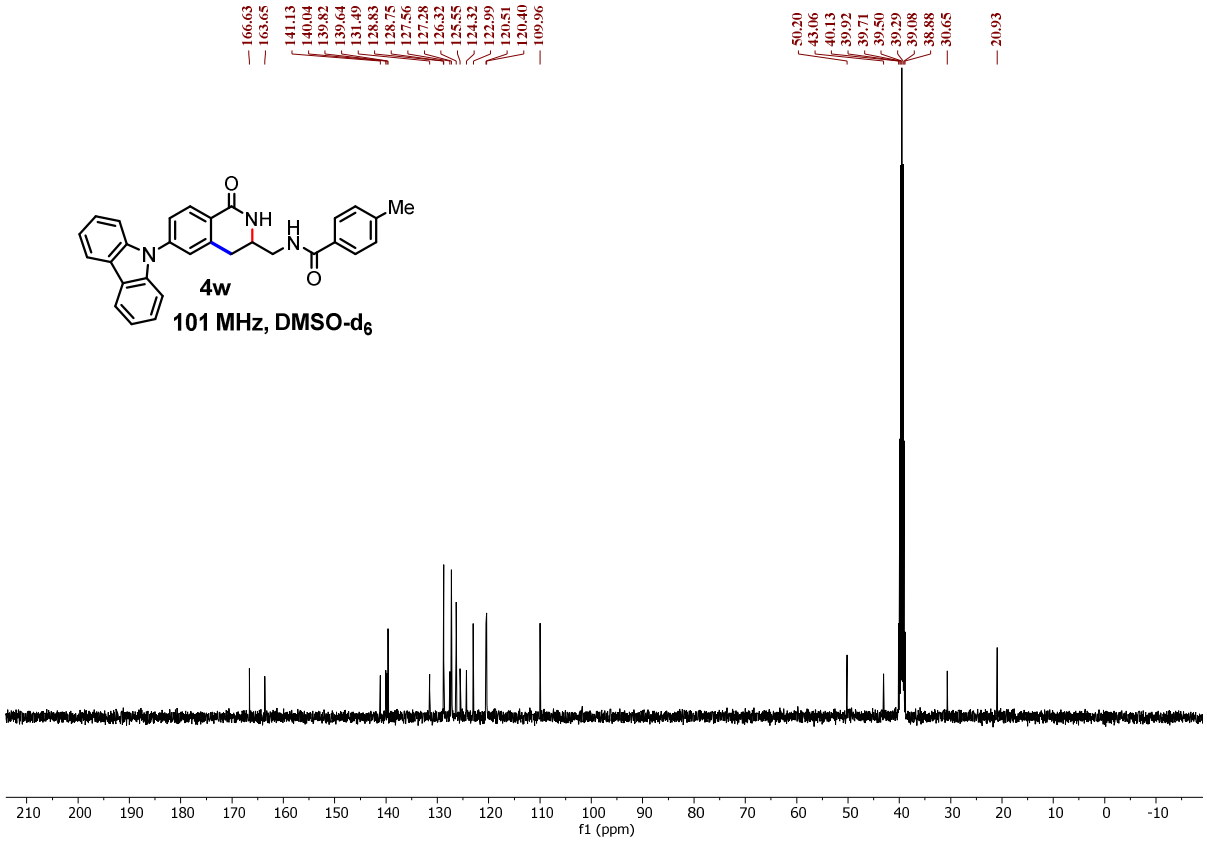

8.53
8.52
8.50
8.29
8.03
8.01
7.74
7.72
7.70
7.28
7.26
3.83
3.81
3.79
3.39
3.38
3.35
3.23
3.21
3.19
3.17
3.03
3.01
2.99
2.98
2.96
2.94
2.51
2.35
1.52
1.50
1.48
1.46
1.44
1.43
0.83
0.81
0.80
O
NH
H
N
Me
O
S
O
N
O
4v
400 MHz, DMSO-d6
1.04
1.02
1.11
3.69
2.05
1.02
1.95
1.18
5.10
3.00
4.22
6.10
f1 (ppm)

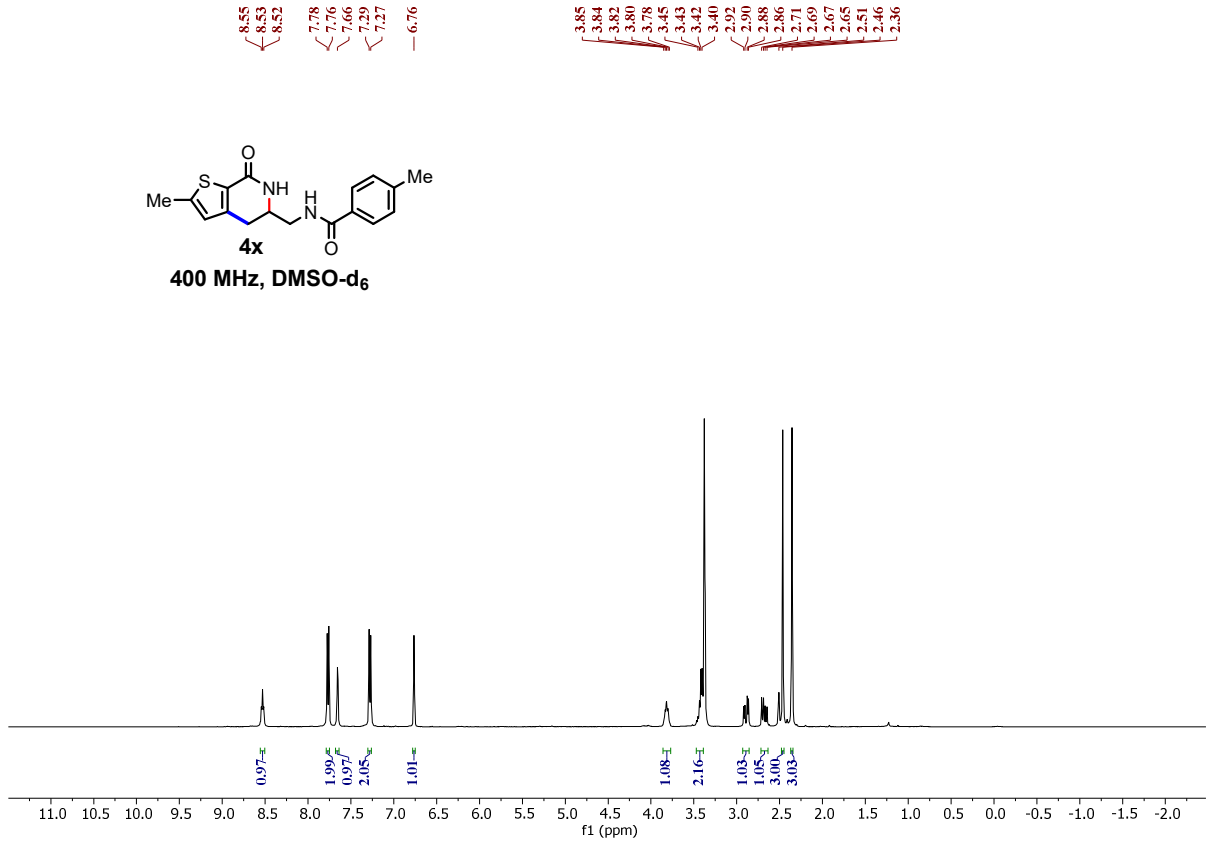

166.58
162.85
142.04
141.10
139.06
132.10
131.47
128.72
127.83
127.24
126.38
124.94
49.85
49.74
42.97
40.13
39.92
39.71
39.50
39.29
39.08
38.87
30.36
21.73
20.92
10.95
O
NH
H
N
Me
O
S
O
N
O
4v
101 MHz, DMSO-d6
f1 (ppm)

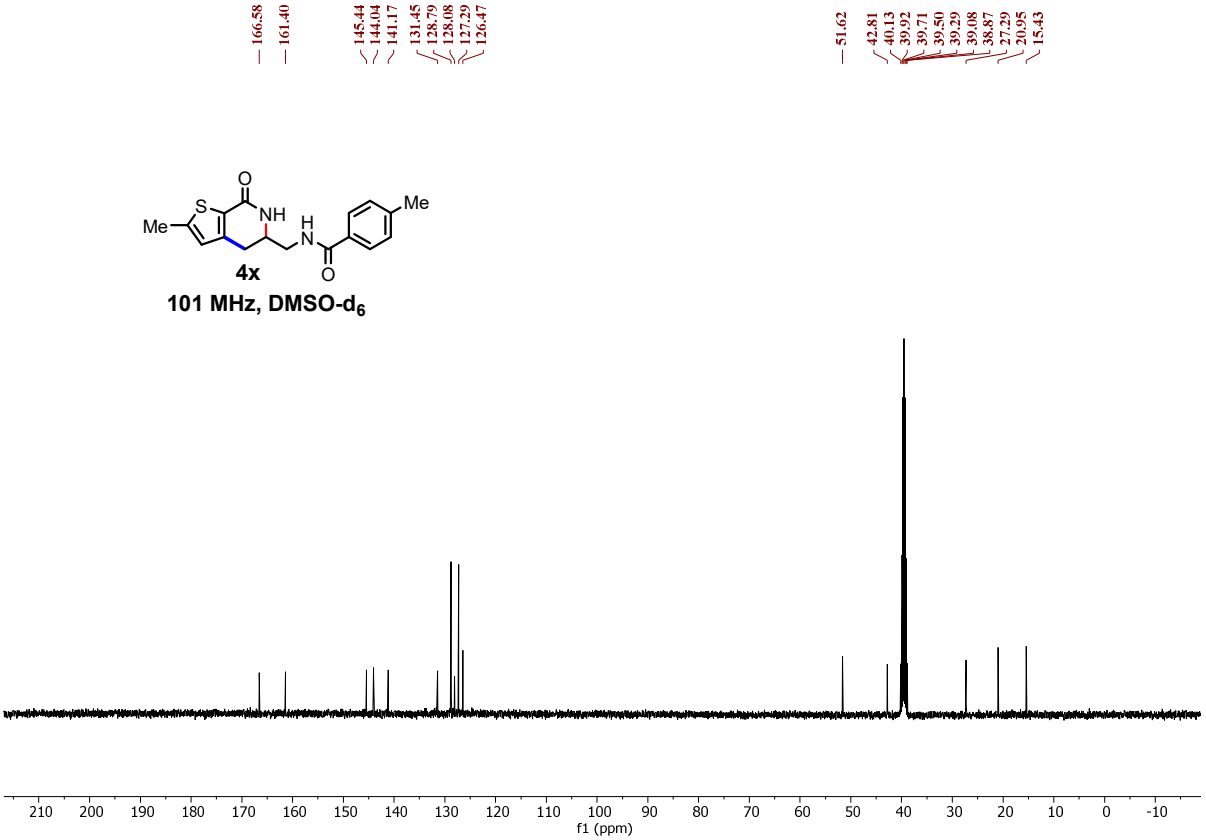

128.69
127.84
127.24
126.40
124.94
49.84
49.73
42.97
30.36
21.72
20.92
10.95
4v
101 MHz, DMSO-d6
f1 (ppm)

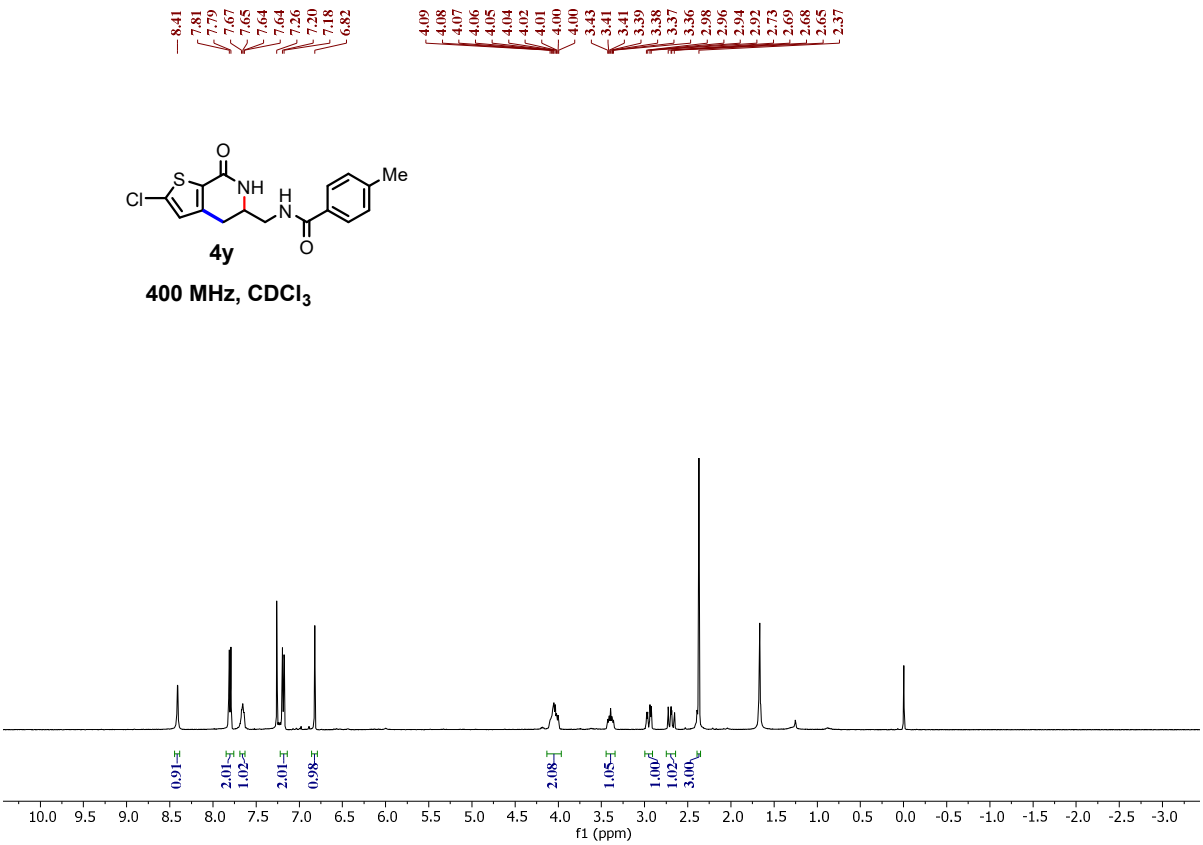

8.60
8.58
8.57
8.25
8.23
8.17
8.15
8.13
7.77
7.75
7.60
7.58
7.57
7.53
7.51
7.46
7.44
7.42
7.32
7.31
7.29
7.27
7.25
3.92
3.91
3.89
3.87
3.86
3.63
3.56
3.54
3.52
3.51
3.49
3.48
3.46
3.44
3.40
3.24
3.23
3.20
3.19
3.02
3.00
2.98
2.96
2.51
2.34

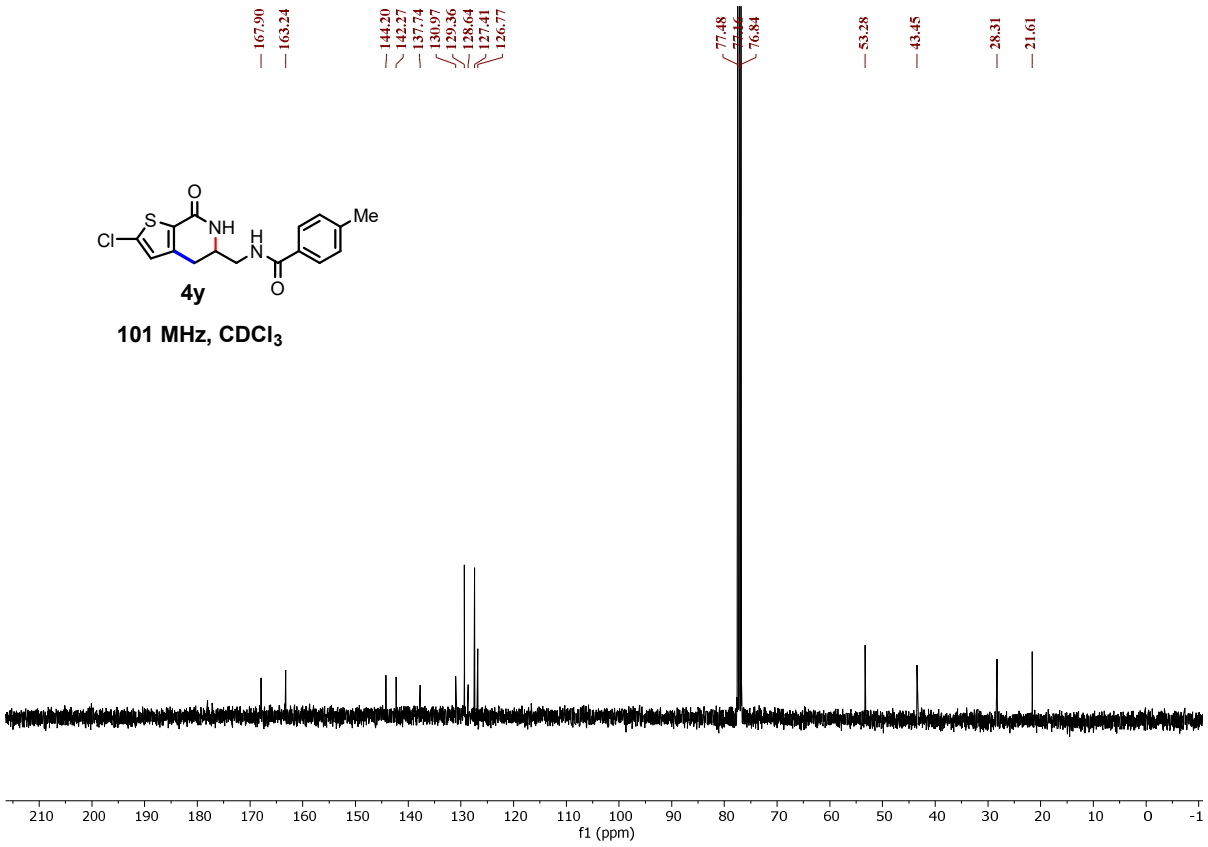

4w
400 MHz, DMSO-d6
0.94
2.09
1.98
1.94
2.03
1.92
2.10
1.91
1.97
1.05
2.35
1.01
0.97
3.00
f1 (ppm)

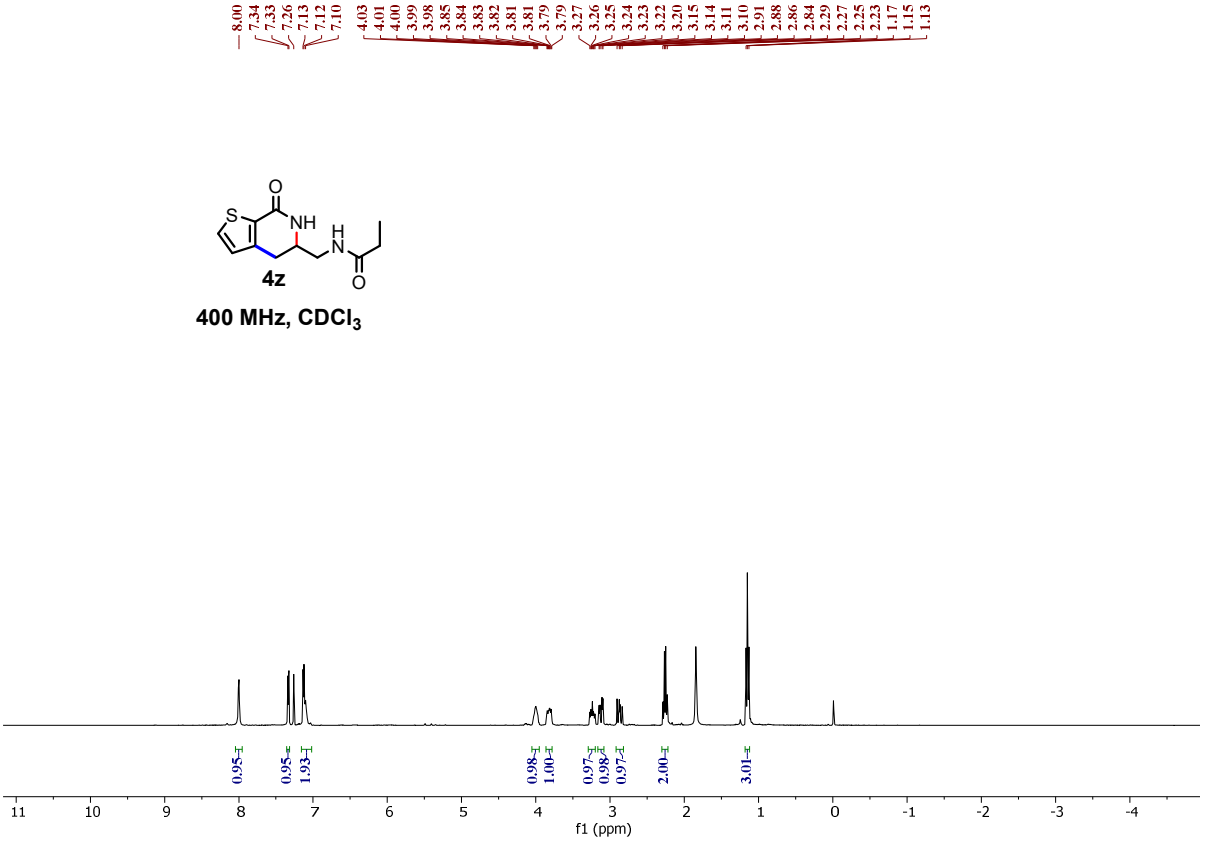

166.63
163.65
141.13
140.04
139.82
139.64
131.49
128.83
128.75
127.56
127.28
126.32
125.55
124.32
122.99
120.51
120.40
109.96
50.20
43.06
40.13
39.92
39.71
39.50
39.29
39.08
38.88
30.65
20.93
O
NH
H
N
O
Me
N
4w
101 MHz, DMSO-d6
f1 (ppm)

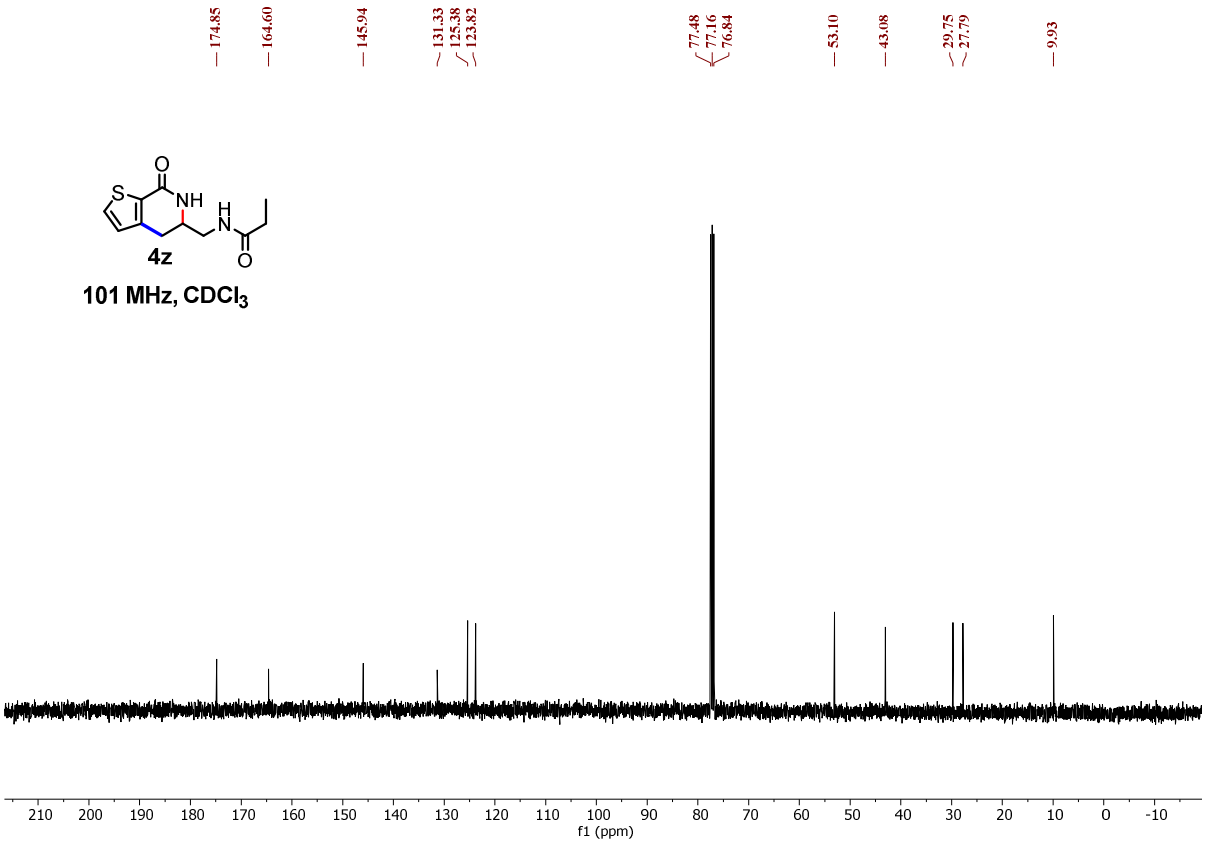

8.55
8.53
8.52
7.78
7.76
7.66
7.29
7.27
6.76
3.85
3.84
3.82
3.80
3.78
3.45
3.43
3.42
3.40
2.92
2.90
2.88
2.86
2.71
2.69
2.67
2.65
2.51
2.46
2.36
O
S
NH
H
N
O
Me
Me
4x
400 MHz, DMSO-d6
0.97
1.99
0.97
2.05
1.01
1.08
2.16
1.03
1.05
3.00
3.03
f1 (ppm)

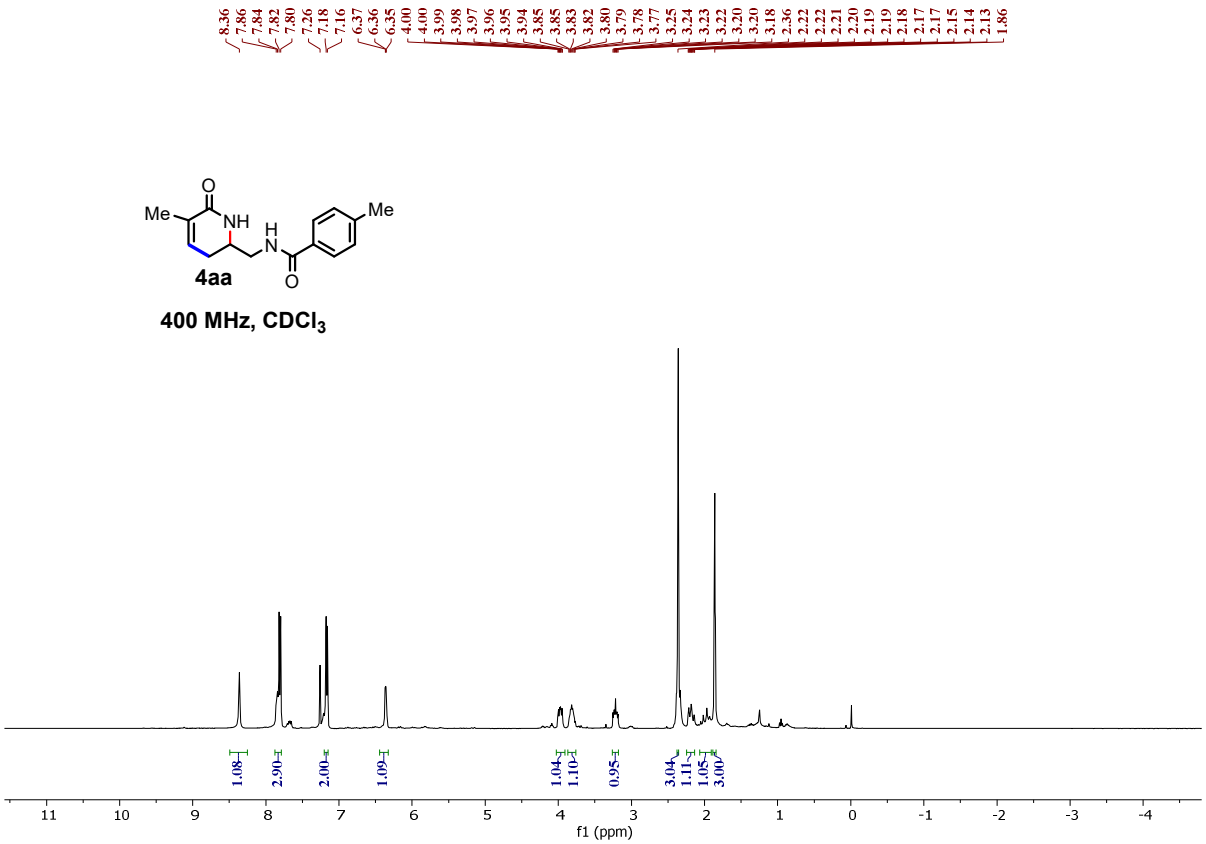

166.58
161.40
145.44
144.04
141.17
131.45
128.79
128.08
127.29
126.47
51.62
42.81
40.13
39.92
39.71
39.50
39.29
39.08
38.87
27.29
20.95
15.43
Me
S
NH
H
N
O
Me
4x
101 MHz, DMSO-d6
f1 (ppm)

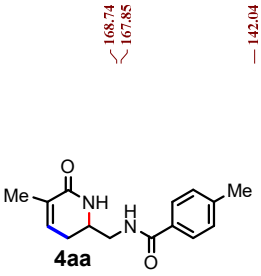

8.41
7.81
7.79
7.67
7.65
7.64
7.64
7.26
7.20
7.18
6.82
4.09
4.08
4.07
4.06
4.05
4.04
4.02
4.01
4.00
4.00
3.43
3.41
3.41
3.39
3.38
3.37
3.36
2.98
2.96
2.94
2.92
2.73
2.69
2.68
2.65
2.37
Cl
S
NH
H
N
O
Me
4y
400 MHz, CDCl3
0.91
2.01
1.02
2.01
0.98
2.08
1.05
1.00
1.02
3.00
f1 (ppm)


167.90
163.24
144.20
142.27
137.74
130.97
129.36
128.64
127.41
126.77
77.48
77.16
76.84
53.28
43.45
28.31
21.61
O
S
NH
Cl
H
N
Me
O
4y
101 MHz, CDCl3
f1 (ppm)


8.00
7.34
7.33
7.26
7.13
7.12
7.10
4.03
4.01
4.00
3.99
3.98
3.85
3.84
3.83
3.82
3.81
3.81
3.79
3.79
3.27
3.26
3.25
3.24
3.23
3.22
3.20
3.15
3.14
3.11
3.10
2.91
2.88
2.86
2.84
2.29
2.27
2.25
2.23
1.17
1.15
1.13
O
S
NH
H
N
O
4z
400 MHz, CDCl3
0.95
0.95
1.93
0.98
1.00
0.97
0.98
0.97
2.00
3.01
f1 (ppm)


174.85
164.60
145.94
131.33
125.38
123.82
77.48
77.16
76.84
53.10
43.08
29.75
27.79
9.93
4z
101 MHz, CDCl3
f1 (ppm)


8.36
7.86
7.84
7.82
7.80
7.26
7.18
7.16
6.37
6.36
6.35
4.00
4.00
3.99
3.98
3.97
3.96
3.95
3.94
3.85
3.85
3.83
3.82
3.80
3.79
3.78
3.77
3.25
3.24
3.23
3.22
3.20
3.20
3.18
2.36
2.22
2.22
2.21
2.20
2.19
2.19
2.18
2.17
2.17
2.15
2.14
2.13
1.86
4aa
400 MHz, CDCl3
1.08
2.90
2.00
1.09
1.04
1.10
0.95
3.04
1.11
1.05
3.00
f1 (ppm)

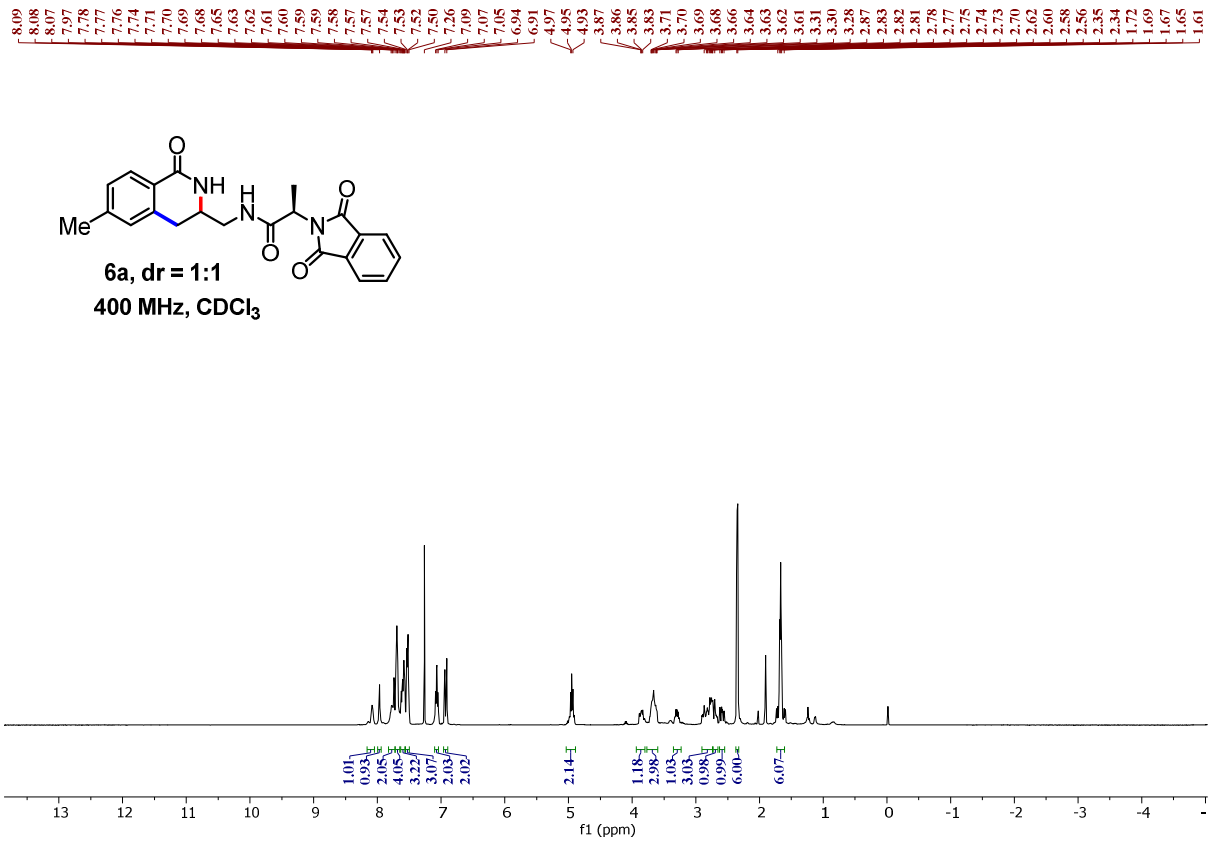


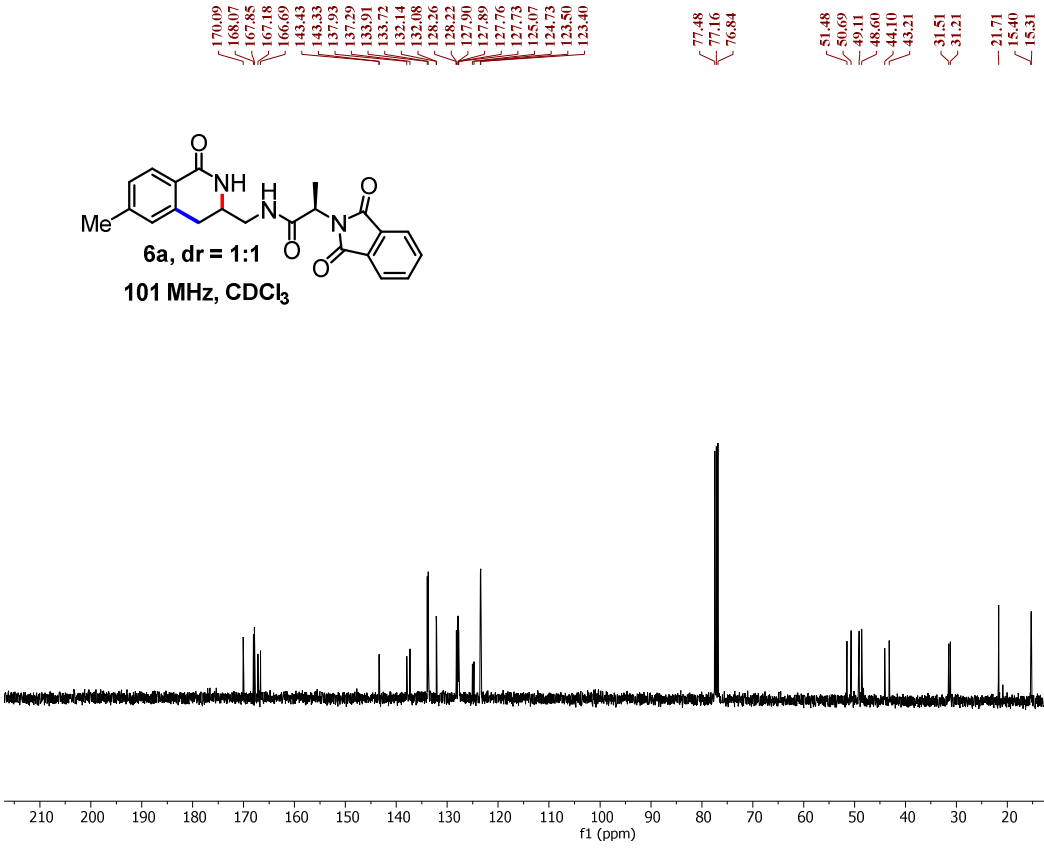
4aa

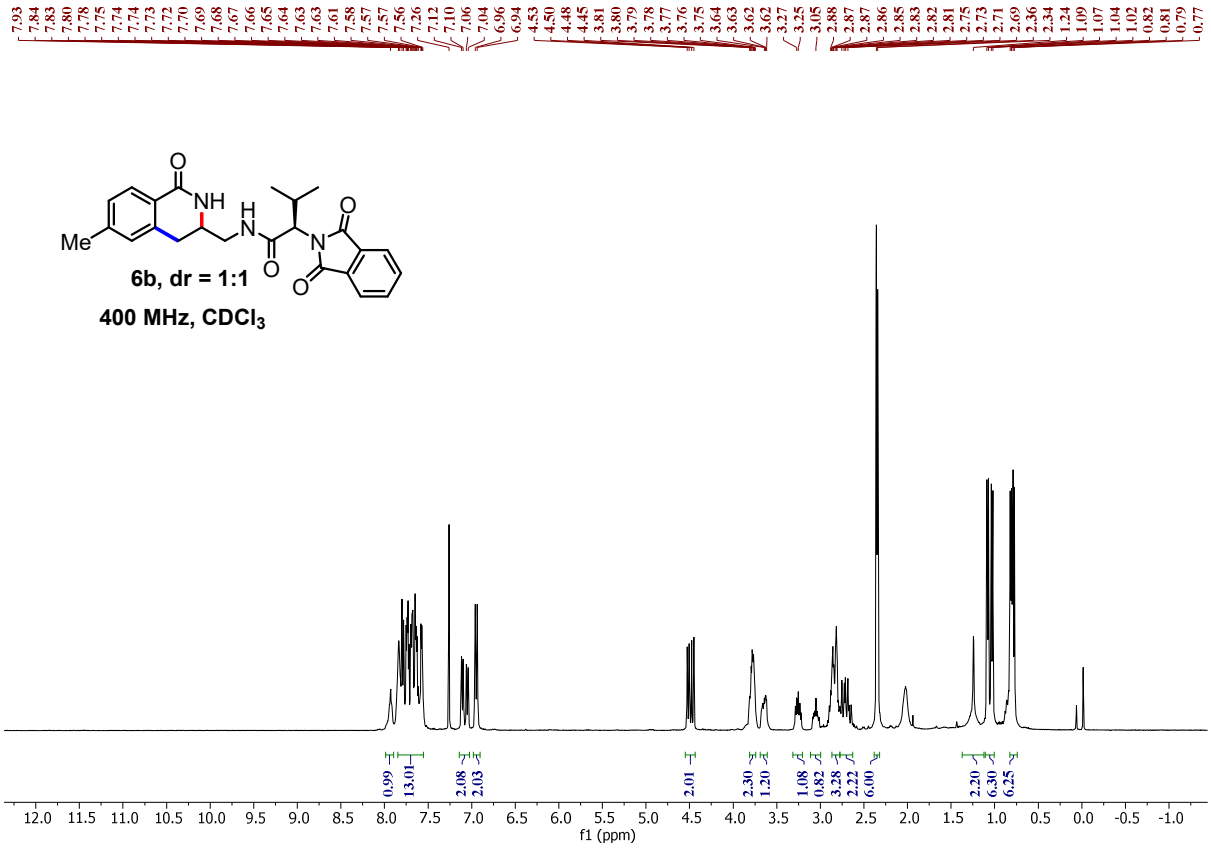
101 MHz, $CDCl_3$

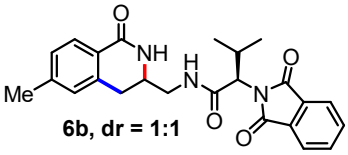
6a, dr = 1:1

400 MHz, $CDCl_3$



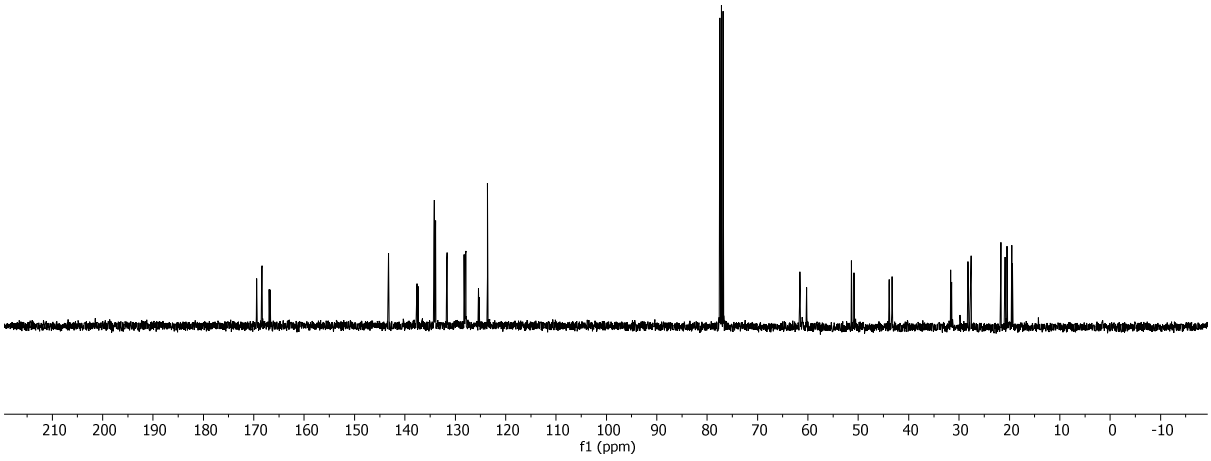

170.09
168.07
167.85
167.18
166.69
143.43
143.33
137.93
137.29
133.91
133.72
132.14
132.08
128.26
128.22
127.90
127.89
127.76
127.73
125.07
124.73
123.50
123.40
77.48
77.16
76.84
51.48
50.69
49.11
48.60
44.10
43.21
31.51
31.21
21.71
15.40
15.31
Me
6a, dr = 1:1
101 MHz, CDCl3
f1 (ppm)

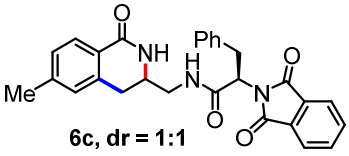

7.93
7.84
7.83
7.80
7.78
7.75
7.74
7.74
7.73
7.72
7.70
7.69
7.68
7.67
7.66
7.65
7.64
7.63
7.63
7.61
7.58
7.57
7.57
7.56
7.26
7.12
7.10
7.06
7.04
6.96
6.94
4.53
4.50
4.48
4.45
3.81
3.80
3.79
3.78
3.77
3.76
3.75
3.64
3.63
3.62
3.62
3.27
3.25
3.05
2.88
2.87
2.87
2.86
2.85
2.83
2.82
2.81
2.75
2.73
2.71
2.69
2.36
2.34
1.24
1.09
1.07
1.04
1.02
0.82
0.81
0.79
0.77
Me
6b, dr = 1:1
400 MHz, CDCl3
0.99
13.01
2.08
2.03
2.01
2.30
1.20
1.08
0.82
3.28
2.22
6.00
2.20
6.30
6.25
f1 (ppm)



6b, dr = 1:1

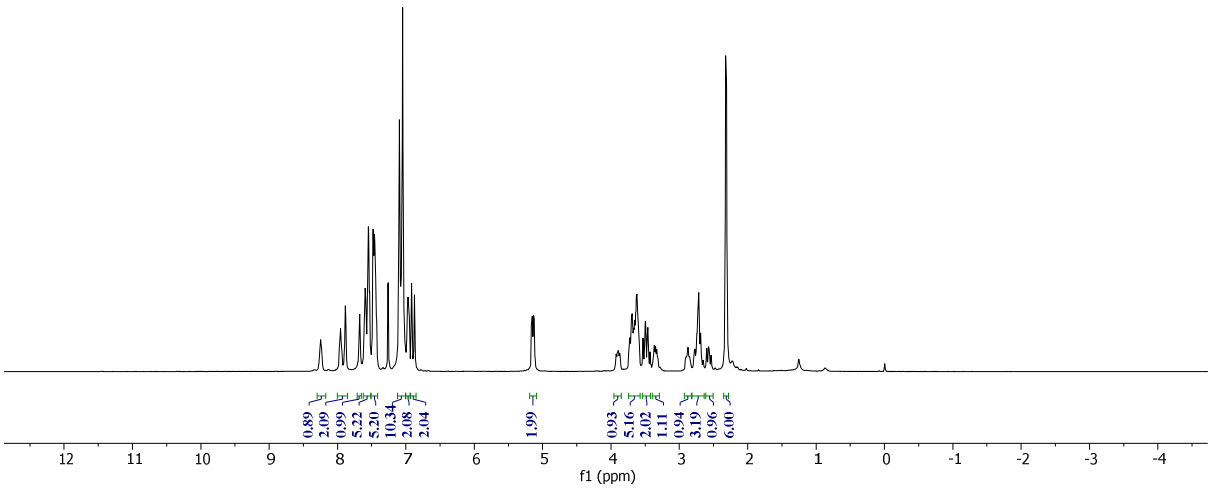
101 MHz, $CDCl_3$

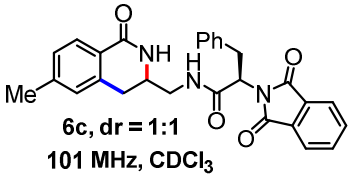




6c, dr = 1:1

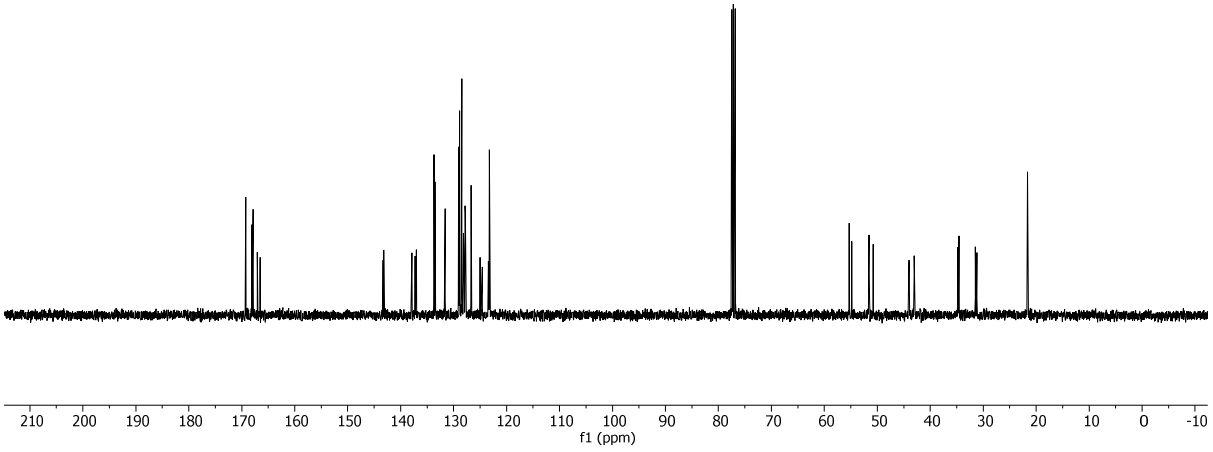
400 MHz, $CDCl_3$

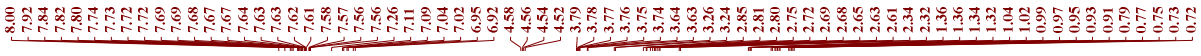


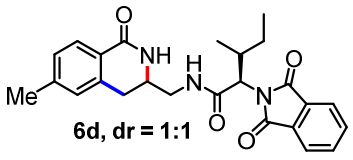


6c, dr = 1:1

101 MHz, $CDCl_3$

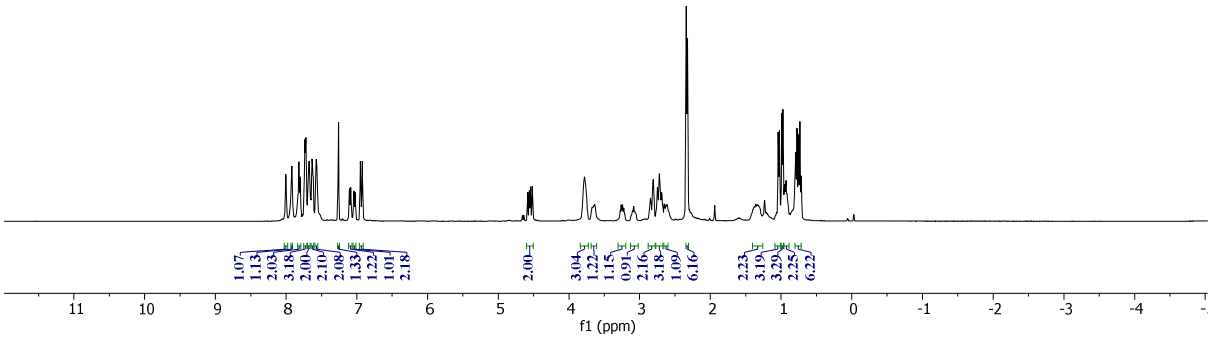


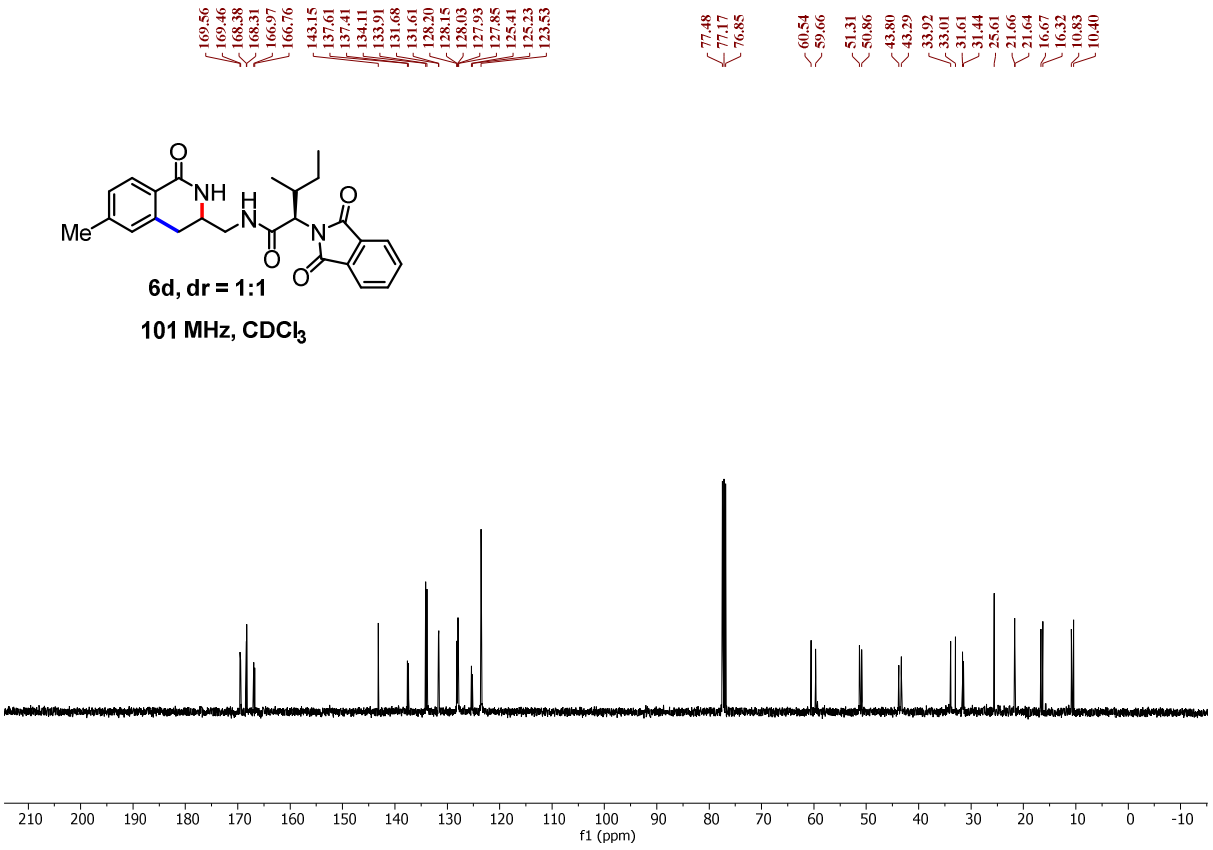


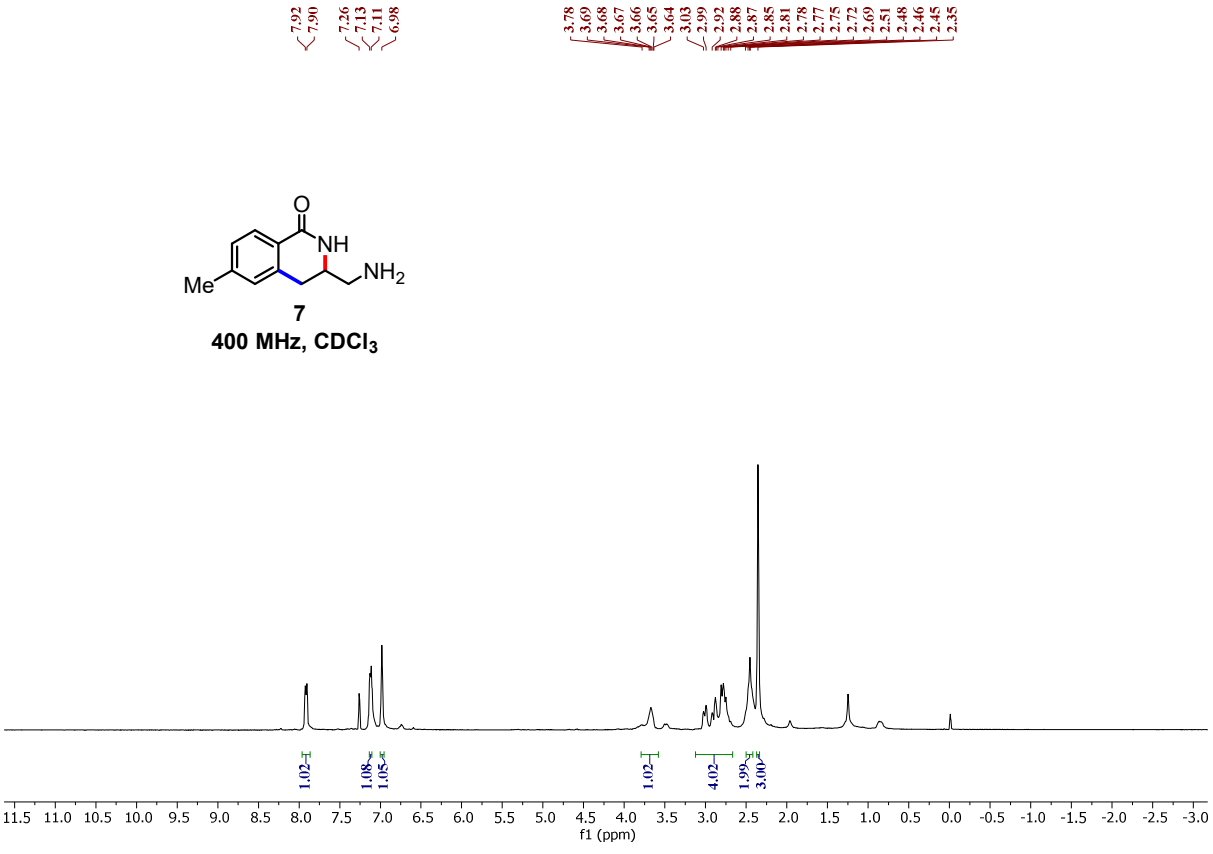


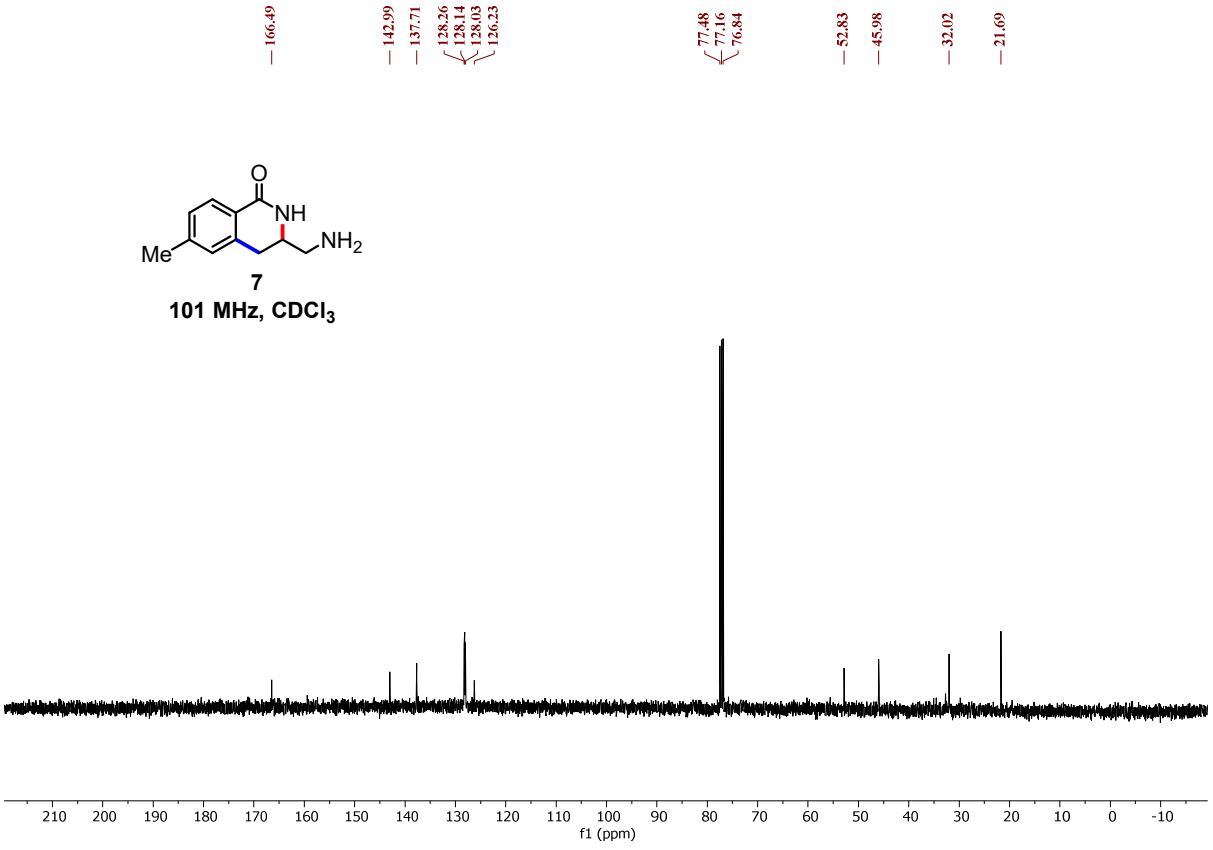
6d, dr = 1:1

400 MHz, $CDCl_3$

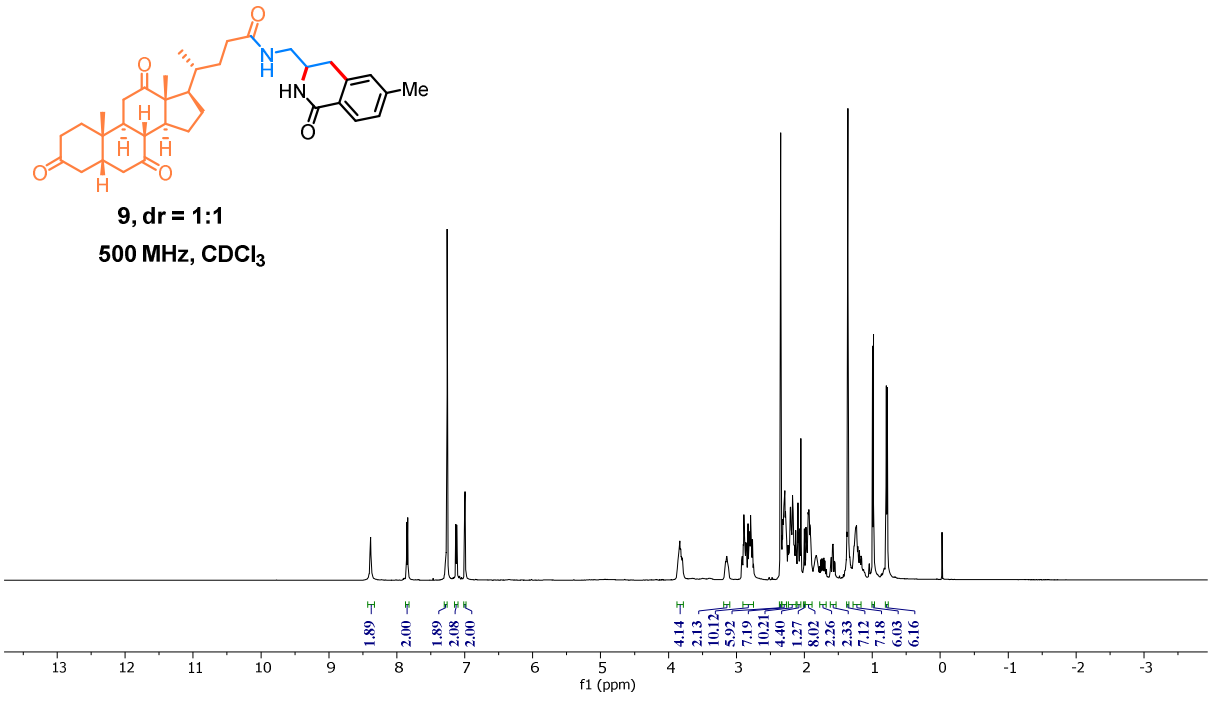


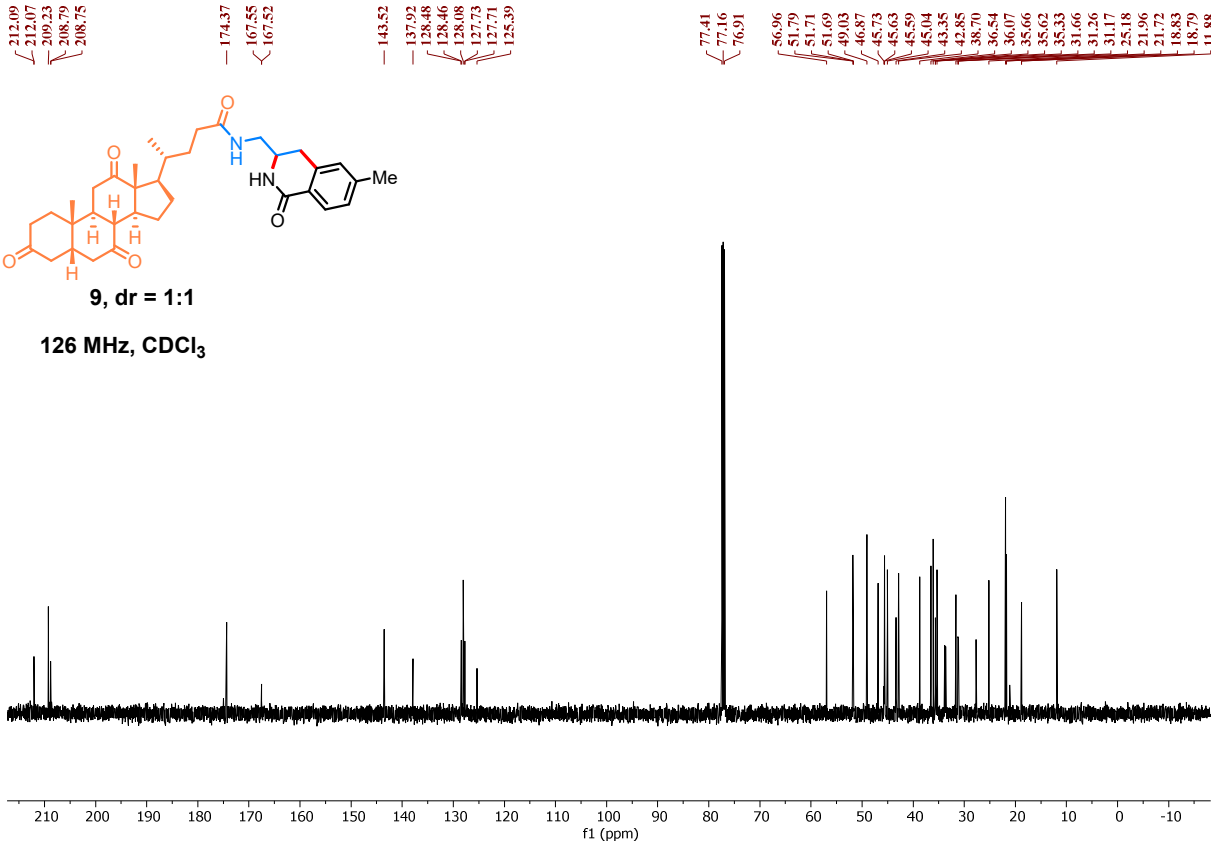

169.56
169.46
168.38
168.31
166.97
166.76
143.15
137.61
137.41
134.11
133.91
131.68
131.61
128.20
128.15
128.03
127.93
127.85
125.41
125.23
123.53
77.48
77.17
76.85
60.54
59.66
51.31
50.86
43.80
43.29
33.92
33.01
31.61
31.44
25.61
21.66
21.64
16.67
16.32
10.83
10.40
O
NH
H
N
Me
O
N
O
O
6d, dr = 1:1
101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.92
7.90
7.26
7.13
7.11
6.98
3.78
3.69
3.68
3.67
3.66
3.65
3.64
3.03
2.99
2.92
2.88
2.87
2.85
2.81
2.78
2.77
2.75
2.72
2.69
2.51
2.48
2.46
2.45
2.35
O
NH
NH2
Me
7
400 MHz, CDCl3
1.02
1.08
1.05
1.02
4.02
1.99
3.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2.5 -3.0
f1 (ppm)


166.49
142.99
137.71
128.26
128.14
128.03
126.23
77.48
77.16
76.84
52.83
45.98
32.02
21.69
O
NH
NH2
Me
7
101 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.39 7.86 7.84 7.26 7.13 7.12 7.00 3.83 2.89 2.87 2.86 2.85 2.83 2.82 2.81 2.81 2.79 2.79 2.77 2.76 2.35 2.33 2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.21 2.21 2.21 2.20 2.20 2.19 2.18 2.17 2.17 2.16 2.16 2.13 2.12 2.10 2.09 2.07 2.06 2.05 2.00 2.00 2.00 1.98 1.97 1.97 1.95 1.94 1.93 1.93 1.92 1.91 1.91 1.37 1.36 1.35 1.26 1.25 1.24 1.23 1.00 0.98 0.80 0.78 -0.02


O
N
H
HN
Me
O
H
H
H
O
O
H
9, dr = 1:1
500 MHz, CDCl3
1.89 2.00 1.89 2.08 2.00 4.14 2.13 10.12 5.92 7.19 10.21 4.40 1.27 8.02 2.26 2.33 7.12 7.18 6.03 6.16
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


212.09
212.07
209.23
208.79
208.75
174.37
167.55
167.52
143.52
137.92
128.48
128.46
128.08
127.73
127.71
125.39
77.41
77.16
76.91
56.96
51.79
51.71
51.69
49.03
46.87
45.73
45.63
45.59
45.04
43.35
42.85
38.70
36.54
36.07
35.66
35.62
35.33
31.66
31.26
31.17
25.18
21.96
21.72
18.83
18.79
O
N
H
HN
O
Me
O
O
H
H
H
H
O
9, dr = 1:1
126 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)