Supporting Information

Multicomponent Reaction for Modular Assembly of Indole-Fused Heterocycles

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1. General Considerations

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-600 spectrometer (College of Life Sciences, Zhejiang University), a Bruker AV-500 spectrometer (College of Pharmaceutical Science, Zhejiang University) or a WNMR-I-400 spectrometer (Department of Chemistry, Zhejiang University) in chloroform-*d* ($CDCl_3$, contain internal TMS) or DMSO-d_6, or CD_3OD. For $CDCl_3$ as solvent, chemical shifts of ^{1}H NMR spectra were reported in ppm with the internal TMS signal at 0 ppm as a standard, and chemical shifts of ^{13}C NMR spectra were reported in ppm with the chloroform signal at 77.16 ppm as a standard. With respect to DMSO-d_6 as solvent, chemical shifts of ^{1}H NMR and ^{13}C NMR spectra were reported in ppm with the DMSO-d_6 signal at 2.50 ppm and 39.52 ppm as the standard respectively. With respect to CD_3OD as solvent, chemical shifts of ^{1}H NMR and ^{13}C NMR spectra were reported in ppm with the CD_3OD signal at 3.31 ppm and 49,00 ppm as the standard respectively.[1] ^{19}F NMR spectra were recorded on a Bruker AV-600 spectrometer. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, dd = double doublet, dt = double of triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration).

HRMS were performed on Agilent Technologies 6546-LC/Q-TOF mass spectrometer (ESI-TOF) (College of Pharmaceutical Sciences, Zhejiang University).

X-Ray crystallographic analyses were performed collected on a 'Bruker D8 Venture' diffractometer (CuK\a radiation, radiation wavelength = 1.54178) or 'Xcalibur, Atlas, Gemini ultra' diffractometer (MoK\a radiation, radiation wavelength = 0.71073), (Department of Chemistry, Zhejiang University).

All reagents and solvents, such as ethyl acetate (EA), petroleum ether (PE), methanol (MeOH), toluene (PhMe), 1,4-dioxane (dioxane), *N*,*N*-Dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (DCM), acetonitrile (MeCN), 1,2-dichloroethane (DCE), triethylamine (TEA) were commercially available and used directly without further purification unless stated otherwise.

Reactions were conducted at Heidolph thermostatic magnetic stirrer and monitored by thin layer chromatography (TLC) using silicycle pre-coated silica gel plates. The products were purified by column chromatography performed over silica gel (200–300 mesh), or recrystallized from suitable solvents.

2. Starting Materials

2.1 Synthesis of starting indoles

The used indoles in this work were listed in Figure S1 and were prepared according to the reported methods or obtained commercially available. Indoles **1a**, **1c**, **1k**, **1p** and **10a** were purchased from Shanghai Bide Pharmatech Ltd. Indoles **1b**, **1d**, **1e**, **1h-1j** and **1q** were prepared according to the **Method A**; Indoles **1f** and **1g** were prepared according to the reported **Method B**; Indole **1n** was synthesized from corresponding acid according to the **Method C**; Indole **1m** was prepared according to the reported **Method D**; Indole **1l** was prepared according to the **Method E**; Indole **1o** was synthesized according to the **Method F**; Indoles **7** was synthesized according to the **Method G**; Substrate **10b** was synthesized according to the **Method H**; Substrate **10c** was synthesized according to the **Method I**; Substrate **10d** was synthesized according to the **Method J**; Substrates **10e** and **10f** were synthesized according to the **Method K**; Substrate **10g** was synthesized according to the **Method L**.

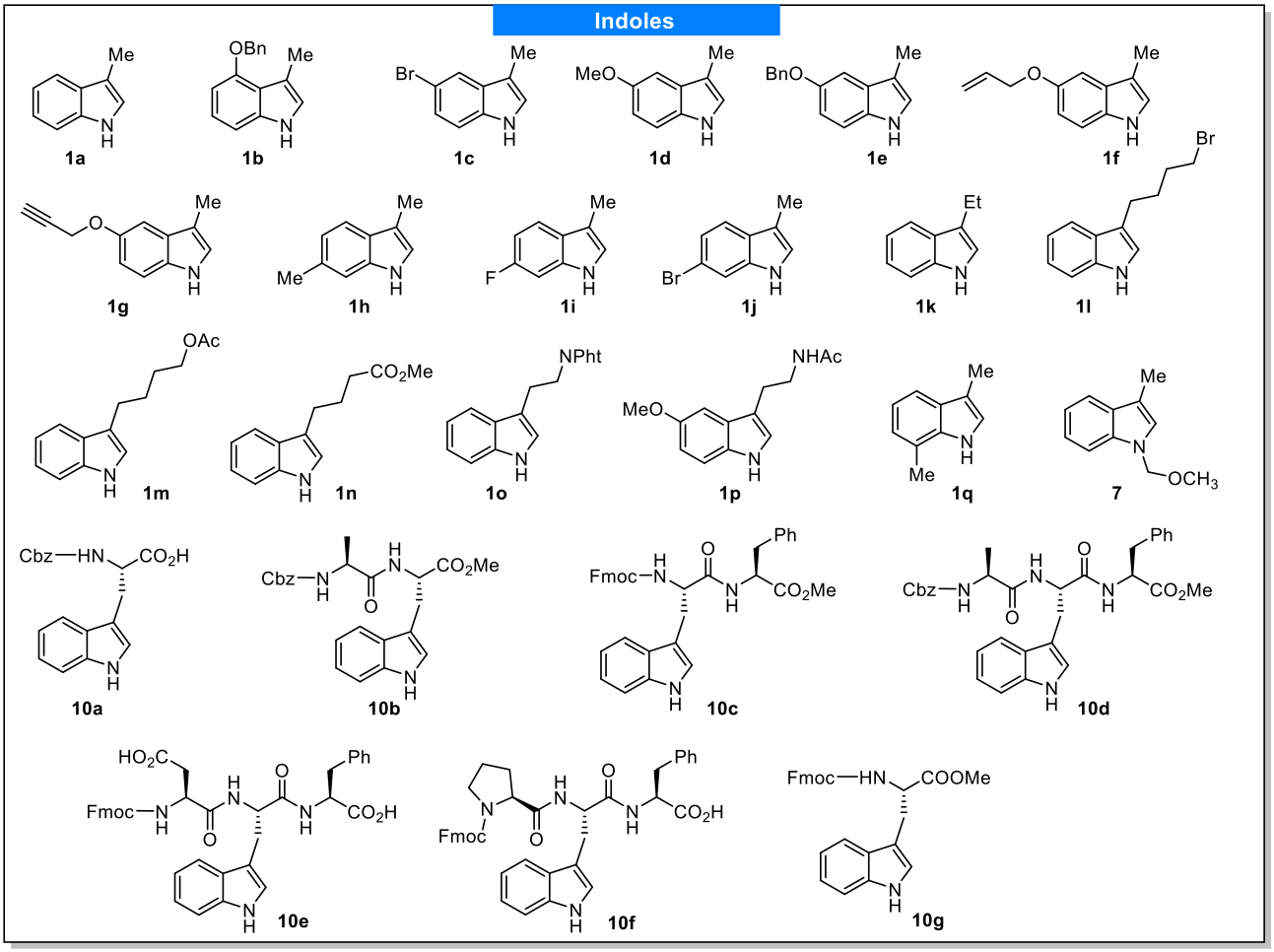
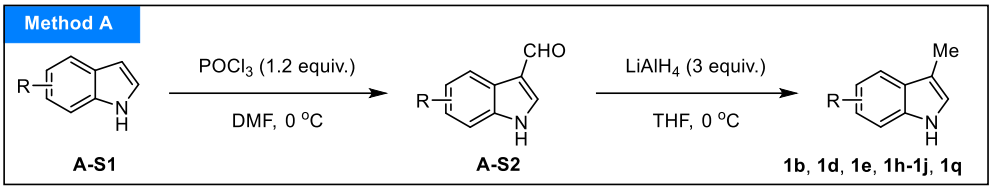


Figure S1. Starting indoles. All used indoles and pyrroles in this protocol are listed.

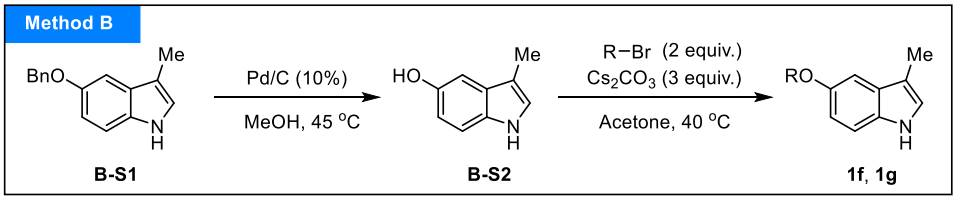
2.1.1 ***Method A*** *for the preparation of indoles*[2]



A flask equipped with a magnetic stir bar was charged with DMF (2 mL) and then purged with argon three times. $POCl_3$ (1.2 mmol, 1.2 equiv.) was added slowly, and the reaction was stirred at 0 °C for 30 minutes. Then the **A-S1** (1.0 mmol) was dissolved in DMF and added dropwise. The mixture was stirred at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding intermediates **A-S2**.

A flask equipped with a magnetic stir bar was charged with intermediates **A-S2** (1.0 mmol). THF (5 mL) was added as solvent. The reaction was stirred at 0 °C for 30 minutes, then $LiAlH_4$ (3.0 mmol, 3 equiv.) was added slowly. The mixture was stirred at 0 °C for 1 h. Water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the corresponding indoles **1b**, **1d**, **1e**, **1h-1j**, **1q**.

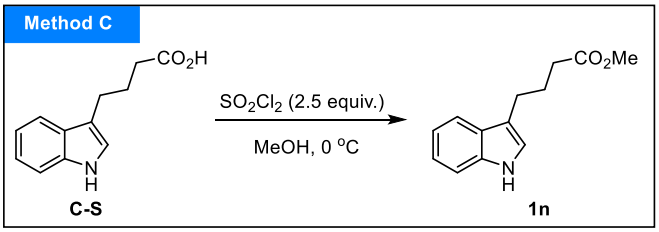
2.1.2 ***Method B*** *for the preparation of indoles*[3]



To a solution of **B-S1** (1.0 mmol) in MeOH (5 mL) was added 10% Pd/C (10% wt.). Then the mixture was purged with hydrogen three times. The resulting reaction mixture was kept at 45 °C for 6 h. After completion, the resulting mixture was concentrated in vacuo; and purified by silica gel column chromatography to afford the **B-S2**.

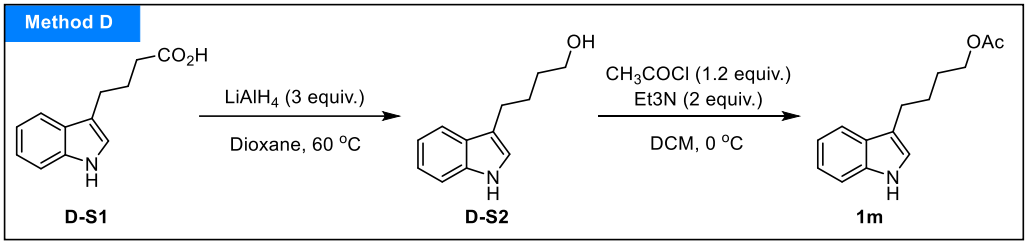
A flask equipped with a magnetic stir bar was charged with indole **B-S2** (1.0 mmol) and Cs_2CO_3 (2.0 mmol). Acetone (5 mL) was added as solvent. The reaction was stirred at room temperature for 15 minutes. Then the corresponding halogenated compounds (1.5 mmol, 1.5 equiv.) was dissolved in acetone and added. The mixture was stirred at 40 °C overnight. Water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding starting indoles **1f** and **1g**.

2.1.3 ***Method C*** *for the preparation of indoles*



A two-neck flask equipped with a magnetic stir bar was charged with indole **C-S** (2.0 mmol) and then purged with argon three times. MeOH (8 mL) was added as solvent. The mixture was stirred at 0 °C for 10 minutes. Thionyl chloride (5.0 mmol, 2.5 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred for 4 h. Saturated aqueous $NaHCO_3$ was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding indole **1n**.

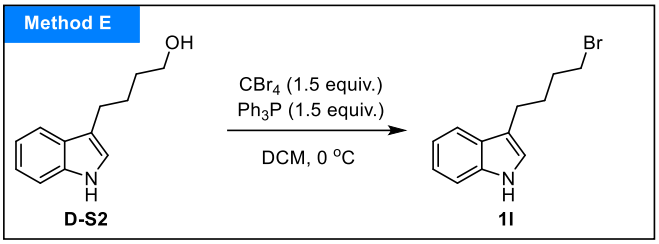
2.1.4 ***Method D*** *for the preparation of indoles*[4]



A flask equipped with a magnetic stir bar was charged with substrate **D-S1** (1.0 mmol). Dioxane (5 mL) was added as solvent. $LiAlH_4$ (3.0 mmol, 3 equiv.) was added slowly, and the reaction was stirred at 60 °C for 12 h. Water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the **D-S2**.

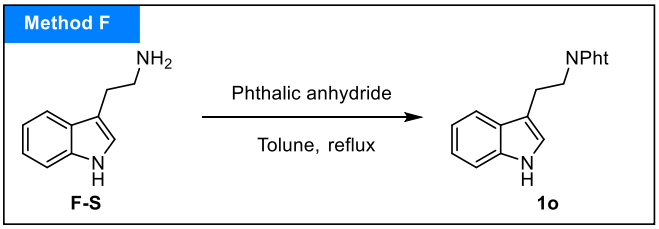
A two-neck flask equipped with a magnetic stir bar was charged with **D-S2** (0.5 mmol) and then purged with argon three times. Triethylamine (1.0 mmol, 2 equiv.) and DCM (3 mL) was added. The reaction was stirred at 0 °C for 10 minutes. Then acetyl chloride (0.6 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred at 0 °C for 1 h. After completion, water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding indole **1m**.

2.1.5 ***Method E*** *for the preparation of indoles*[5]



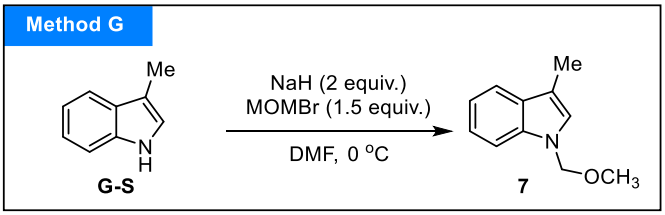
A reaction tube equipped with a magnetic stir bar was charged with intermediate **D-S2** (1.0 mmol). DCM (5 mL) was added as solvent. the mixture was stirred at 0 °C for 10 minutes. Then the triphenylphosphine (1.5 mmol, 1.5 equiv.) and carbon tetrabromide (1.5 mmol, 1.5 equiv.) were added. The reaction was kept at 0 °C and stirred for 1 h. Water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the crude, which was purified by silica gel column chromatography to afford the corresponding indole **1l**.

2.1.6 ***Method F*** *for the preparation of indoles*[6]



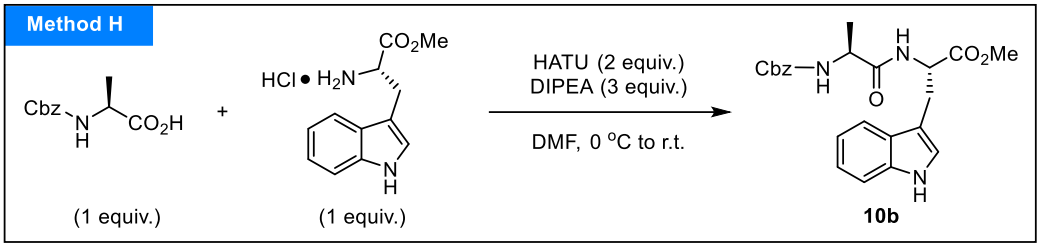
A mixture of tryptamine (1.0 mmol) and phthalic anhydride (1.2 mmol, 1.2 equiv.) in toluene (5 mL) was refluxed overnight. The hot solution was immediately transferred to a beaker and concentrated to give a residue. And the indole **1o** was recrystallized from DCM and hexane to give.

2.1.7 ***Method G*** *for the preparation of indoles*



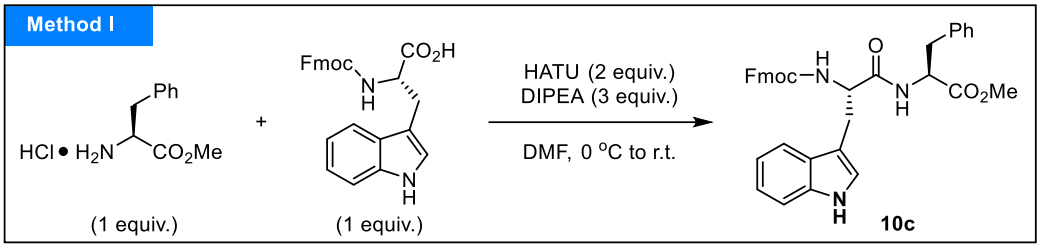
A flask equipped with a magnetic stir bar was charged with indoles **G-S** (1.0 mmol). DMF (5 mL) was added as solvent. NaH (2.0 mmol, 2 equiv.) was added slowly and the reaction was stirred at 0 °C for 30 minutes. Then the corresponding halogenated compounds (1.5 mmol, 1.5 equiv.) was dissolved in DMF and added dropwise. Then the mixture was warmed to room temperature and stirred for 1 h. Water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding starting indole **7**.

2.1.8 ***Method H*** *for the preparation of indoles*[7]



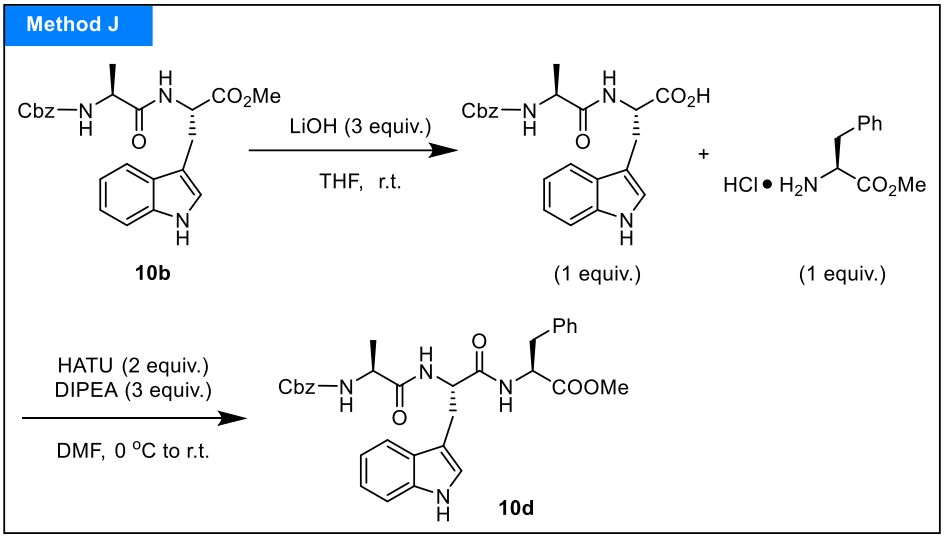
A two-neck flask equipped with a magnetic stir bar was charged with methyl L-tryptophanate hydrochloride (0.5 mmol), Cbz-Ala-OH (0.5 mmol), HATU (1.0 mmol) and then purged with argon three times. DMF (3 mL) was added and the reaction was stirred at 0 °C for 10 minutes. Then DIPEA (1.5 mmol, 3 equiv.) was added dropwise. The mixture was stirred at room temperature for 2 h. After completion, water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with 1 M aqueous HCl (2 x 20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL). Then the organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding indole **10b**.

2.1.9 ***Method I*** *for the preparation of indoles*[7]



A two-neck flask equipped with a magnetic stir bar was charged with Fmoc-Trp-OH (0.5 mmol), methyl L-phenylalaninate hydrochloride (0.5 mmol), HATU (1.0 mmol) and then purged with argon three times. DMF (3 mL) was added, and the reaction was stirred at 0 °C for 10 minutes. Then DIPEA (1.5 mmol, 3 equiv.) was added dropwise. The mixture was stirred at room temperature for 2 h. After completion, water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with 1 M aqueous HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL). Then the organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding indole **10c**.

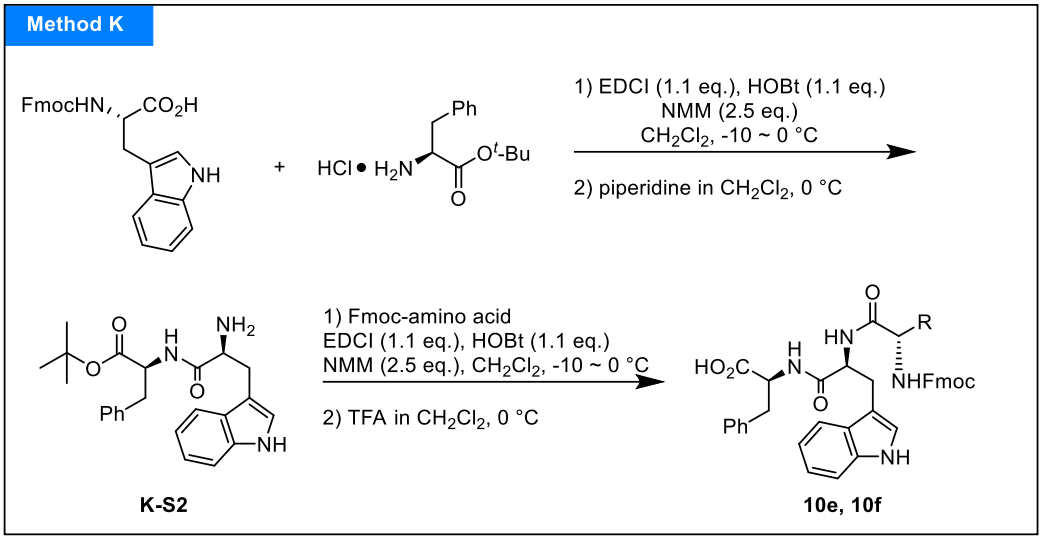
2.1.10 ***Method J*** *for the preparation of indoles*[7]



A flask equipped with a magnetic stir bar was charged with **10b** (1.0 mmol). THF (10 mL) was added as solvent. 2 M aqueous LiOH (3 mmol in 1.5 mL water, 3 equiv.) was added slowly, and the reaction was stirred at room temperature for 2 h. 1 M aqueous HCl was added to quench the reaction and adjust pH value to 4. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the intermediate Cbz-Ala-Trp-OH.

A two-neck flask equipped with a magnetic stir bar was charged with Cbz-Ala-Trp-OH (0.5 mmol), methyl L-phenylalaninate hydrochloride (0.5 mmol), HATU (1.0 mmol) and then purged with argon three times. DMF (3 mL) was added, and the reaction was stirred at 0 °C for 10 minutes. Then DIPEA (1.5 mmol, 3 equiv.) was added dropwise. The mixture was stirred at room temperature for 2 h. After completion, water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with 1 M aqueous HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL). Then the organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding indole **10d**.

2.1.11 ***Method K*** *for the preparation of indoles*[7]



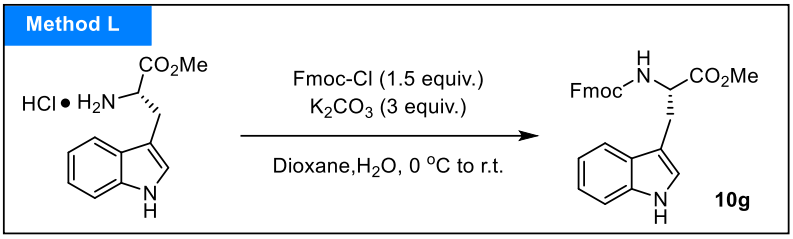
A solution of Fmoc-Trp-OH (1 mmol), tert-Butyl 3-phenyl-*L*-alaninate hydrochloride (1.0 mmol), HOBT (1.1 mmol), and NMM (2.5 mmol) in DCM (10 mL) was cooled in an ice bath and subsequently treated with EDCI (1.1 mmol). After 0.5 h at 0 °C, the mixture was warmed to room temperature, and stirred for 2 h. Then H_2O (30 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The organic phase was washed sequentially with 1 M aqueous HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was used for next step without further purification.

A flask equipped with a magnetic stir bar was charged with the crude. DCM (3 mL) was added and the mixture was cooled to 0 °C. Pyridine (1 mL) was added dropwise. The reaction was stirred at 0 °C for 3 h. Adjusted the mixture to pH = 7 by adding 1 M HCl and extracted with EtOAc. The organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The resulting residue was purified by column chromatography yielding the dipeptide **K-S2.**

A solution of Fmoc amino acid (1 mmol), **K-S2** (1.0 mmol), HOBt (1.1 mmol), and NMM (2.5 mmol) in DCM (10 mL) was cooled in an ice bath and subsequently treated with EDCI (1.1 mmol). After 0.5 h at 0 °C, the mixture was warmed to room temperature, and stirred for 2 h. Then H_2O (30 mL) was added, and the mixture was extracted with EtOAc (3 × 30 mL). The organic phase was washed sequentially with 1 M aqueous HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was used for next step without further purification.

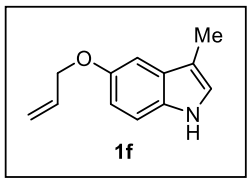
A flask equipped with a magnetic stir bar was charged with the crude. DCM (3 mL) was added and the mixture was cooled to 0 °C. TFA (1 mL) was added and the reaction was stirred at 0 °C for 2 h. Adjusted the mixture to pH = 5-6 by adding saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuum. The resulting residue was purified by column chromatography yielding the tripeptides **10e** and **10f.**

2.1.12 ***Method L*** *for the preparation of indoles*[8]

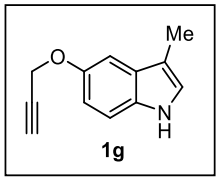


A two-neck flask equipped with a magnetic stir bar was charged with methyl L-tryptophanate hydrochloride (1.0 mmol) and K_2CO_3 (3.0 mmol, 3 equiv.). Dioxane (3 mL) and H_2O (3 mL) were added and the reaction was stirred at 0 °C for 10 minutes. Then 1-(9-fluorenyl)methylchloroformate (1.5 mmol in 3 mL dioxane, 1.5 equiv.) was added dropwise. The mixture was warmed to the room temperature and stirred for 2 h. After completion, water was added to quench the reaction and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to obtain the residue, which was purified by silica gel column chromatography to afford the corresponding indole **10g**.

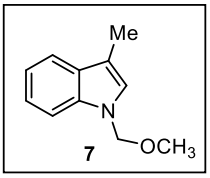
2.2 Characterization of new starting materials



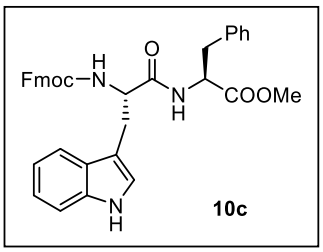
5-(allyloxy)-3-methyl-1*H*-indole (1f): White solid, m.p. 67-70 °C, 72% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (s, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 2H), 6.19 (m, 1H), 5.51 (dq, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H), 5.35 (dd, J_1 = 10.4 Hz, J_2 = 1.6 Hz, 1H), 4.66 (dt, J_1 = 5.2 Hz, J_2 = 1.6 Hz, 2H), 2.35 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 152.9, 134.1, 131.7, 128.7, 122.7, 117.4, 112.7, 111.8, 111.4, 102.4, 70.0, 9.8. **HRMS (ESI)** calcd for $C_{12}H_{14}NO$ ($M+H^+$): 188.1070; Found: 188.1072.



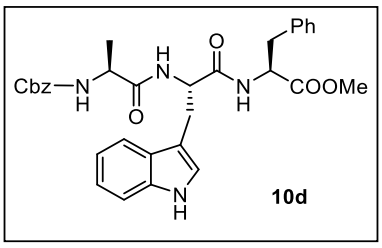
3-methyl-5-(prop-2-yn-1-yloxy)-1*H*-indole (1g): White solid, m.p. 63-66 °C, 75% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.06 – 6.84 (m, 2H), 4.80 (d, *J* = 2.4 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 151.9, 132.1, 128.6, 122.9, 112.8, 111.9, 111.5, 103.1, 79.5, 75.3, 57.2, 9.8. **HRMS (ESI)** calcd for $C_{12}H_{12}NO$ ($M+H^+$): 186.0913; Found: 186.0913.



1-(methoxymethyl)-3-methyl-1*H*-indole (7): Colorless oil, 85% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 5.42 (s, 2H), 3.26 (s, 3H), 2.37 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.8, 129.6, 125.7, 122.2, 119.7, 119.2, 111.9, 109.7, 77.2, 55.9, 9.7. **HRMS (ESI)** calcd for $C_{11}H_{14}NO$ ($M+H^+$): 176.1070; Found: 176.1068.



methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-tryptophyl-*L*-phenylalaninate (10c): White solid, m.p. 184-186 °C, 75% yield. **^{1}H NMR (400 MHz, DMSO)** δ 10.84 (s, 1H), 8.50 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.71 – 6.89 (m, 17H), 4.71 – 4.27 (m, 2H), 4.25 – 3.84 (m, 3H), 3.58 (s, 3H), 3.20 – 2.77 (m, 4H). **^{13}C NMR (101 MHz, DMSO)** δ 172.6, 172.3, 156.2, 144.3, 144.2, 141.1, 137.6, 136.5, 129.6, 128.7, 128.1, 127.7, 127.6, 127.0, 125.9, 125.8, 124.3, 121.3, 120.6, 119.0, 118.7, 111.8, 110.6, 66.1, 55.7, 54.2, 52.3, 47.0, 37.1, 28.2. **HRMS (ESI)** calcd for $C_{36}H_{34}N_3O_5$ ($M+H^+$): 588.2493; Found: 588.2497.

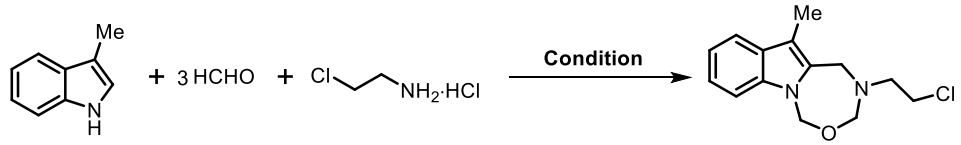


methyl ((benzyloxy)carbonyl)-*L*-alanyl-*L*-tryptophyl-*L*-phenylalaninate (10d): White solid, m.p.=147-150 ºC, 60% yield. **^{1}H NMR (400 MHz, DMSO)** δ 10.86 (s, 1H), 8.44 (d, *J* = 7.2 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.49 – 6.90 (m, 15H), 5.03 (q, *J* = 12.4 Hz, 2H), 4.69 – 4.33 (m, 2H), 4.19 – 3.93 (m, 1H), 3.57 (s, 3H), 3.19 – 2.84 (m, 4H), 1.14 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, DMSO)** δ 172.6, 172.2, 171.9, 156.1, 137.5, 137.4, 136.5, 129.5, 128.8, 128.7, 128.3, 128.3, 127.9, 127.0, 124.0, 121.3, 118.9, 118.7, 111.7, 110.2, 65.9, 54.1, 53.4, 52.3, 50.5, 37.1, 28.2, 18.7. **HRMS (ESI)** calcd for $C_{32}H_{35}N_4O_6$ ($M+H^+$): 571.2551; Found: 571.2556.

3. Optimization of the Reaction Conditions

3.1 Reaction optimization for the multicomponent synthesis of 1,3,6-oxadiazepino [3,4-*a*] Indoles

Table S1. Reaction Optimization for the multicomponent synthesis of 1,3,6-oxadiazepino [3,4-*a*] Indole[a]



1a **2** **3a** **4a**

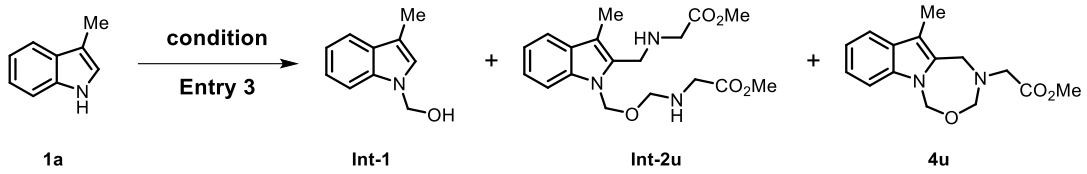
Entry	2 (eq.)	3a (eq.)	Solvent	Temp.	Yield (%)[b]
1	5	2	AcOH	45 ºC	37
2	5	2	DMF	45 ºC	32
3	5	2	THF	45 ºC	75
4	5	2	MeCN	45 ºC	63
5	5	2	DMSO	45 ºC	15
6	5	2	DCM	45 ºC	70
7	5	2	MeOH	45 ºC	Trace
8	5	2	DMF/MeCN (1:1)	45 ºC	65
9	5	2	THF	60 ºC	73
10	5	2	THF	70 ºC	54
11	5	4	THF	45 ºC	71
12	10	2	THF	45 ºC	74

[a] Reaction condition: The reaction was conducted with **1a** (0.2 mmol, 1 equiv.), formaldehyde **2** (37% in water, 5 or 10 equiv.), **3a** (2 or 4 equiv.), solvent (2 mL). [b] Yield refers to isolated product.

3.2 Real-time monitoring test of 1,3,6-oxadiazepino [3,4-*a*] Indoles

To detect the content change of reaction components, a mixture of **1** (0.2 mmol), formaldehyde **2** (37% in water, 0.08 mL, 5 equiv.) and glycine methyl ester hydrochloride **3u** (0.4 mmol, 2 equiv.) in THF (2 mL) was stirred at room temperature for 15 minutes. Then the reaction was heated to 45 ºC until the reaction was completed. The content of intermediates and product was detected at 15 min, 30 min, 45 min, 60 min, 90 min, 120 min, 150 min and 180 min.

Table S2. Real-time monitoring test for the multicomponent synthesis of **4u**

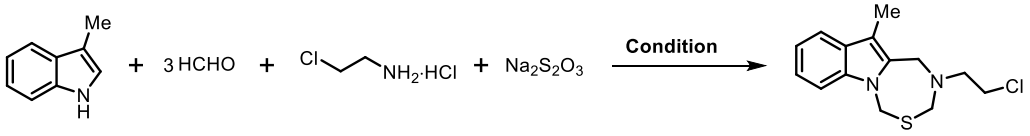


1a Int-1 Int-2u 4u

Time (min)	Temp.	Int-1 (yield, %)	Int-2u (yield, %)	4u (yield, %)
15	r. t.	54	-	-
30	45 °C	22	10	trace
45	45 °C	13	30	trace
60	45 °C	trace	33	35
90	45 °C	-	16	55
120	45 °C	-	trace	65
150	45 °C	-	-	71
180	45 °C	-	-	73

3.3 Reaction optimization for the multicomponent synthesis of 1,3,6-thiadiazepino [3,4-*a*] Indoles

Table S3. Reaction Optimization for the multicomponent synthesis of 1,3,6-thiadiazepino [3,4-*a*] Indole[a]



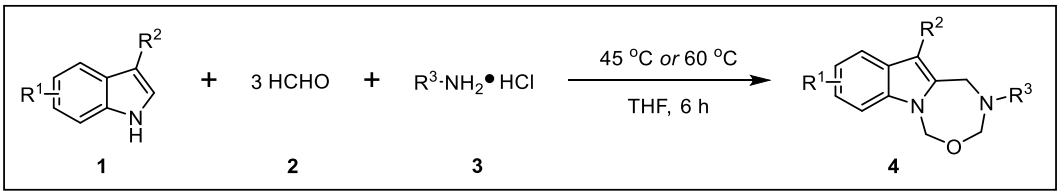
1a 2 3a 5 6a

Entry	2 (eq.)	3a (eq.)	$Na_2S_2O_3$ (eq.)	12N HCl aqueous (eq.)	Solvent	Temp.	Yield (%)[b]
1	5	2	2	2	AcOH	45 °C	Trace
2	5	2	2	2	DMF	45 °C	45
3	5	2	2	2	THF	45 °C	78
4	5	2	2	2	MeCN	45 °C	74
5	5	2	1	1	THF	45 °C	63
6	5	2	1.5	1.5	THF	45 °C	74
7	5	2	2	2	THF	r.t.	72
8	5	2	2	2	THF	50 °C	81
9	5	2	2	2	THF	60 °C	80

[a] Reaction condition: The reaction was conducted with **1a** (0.2 mmol, 1 equiv.), formaldehyde **2** (37% in water, 5 equiv.), **3a** (2 equiv.), $Na_2S_2O_3$ **5** (1, 1.5 or 2 equiv.), 12N HCl aqueous (1, 1.5, 2 equiv.), solvent (2 mL). [b] Yield refers to isolated product.

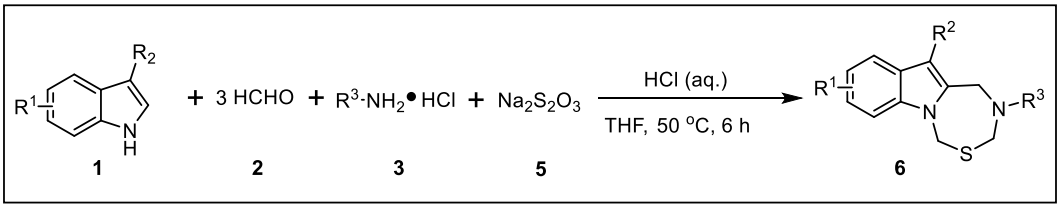
4. Procedures of the oxa(thia)diazepino Indoles Synthesis and Characterization

4.1 General procedure for the synthesis of 1,3,6-oxadiazepino [3,4-*a*] Indoles (4)



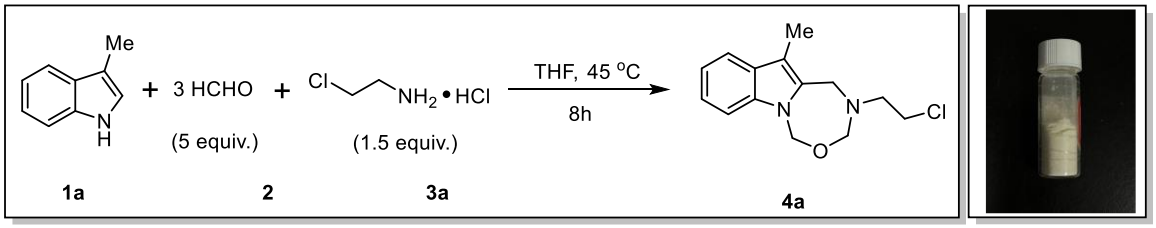
A mixture of **1** (0.2 mmol), formaldehyde **2** (37% in water, 0.08 mL, 5 equiv.) and corresponding primary amine hydrochloride **3** (0.4 mmol, 2 equiv.) in THF (2 mL) was stirred at 45 °C or 60 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding indole products **4**.

4.2 General procedure for the synthesis of 1,3,6-thiadiazepino [3,4-*a*] Indoles (6)



A mixture of **1** (0.2 mmol), formaldehyde **2** (37% in water, 0.08 mL, 5 equiv.), corresponding primary amine hydrochloride **3** (0.4 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.4 mmol) and 12N HCl (0.4 mmol) in THF (2 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding indole products **6**.

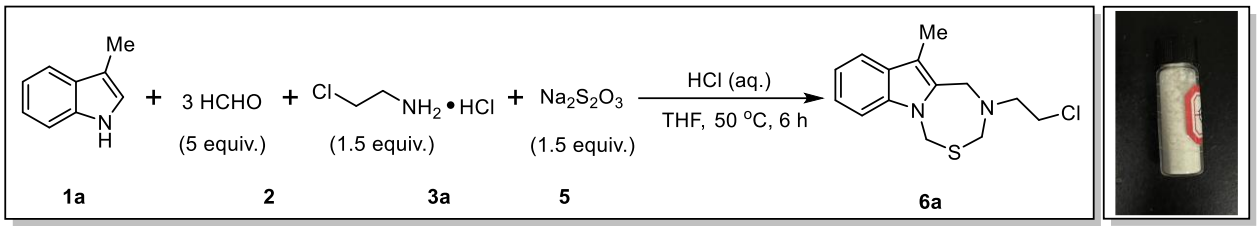
4.3 Gram scale experiment for synthesis of 4a



A mixture of **1a** (1.31 g, 10 mmol), formaldehyde **2** (37% in water, 4 mL, 5 equiv.) and chloroethylamine hydrochloride **3a** (1.74 g, 15 mmol) in THF (40 mL) was stirred at 45 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three

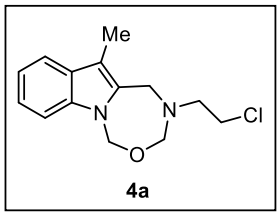
times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give **4a** (1.85 g, 70.0% yield).

4.4 Gram scale experiment for synthesis of 6a

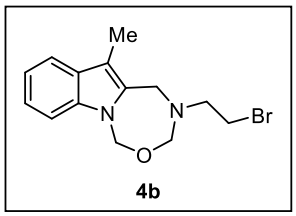


A mixture of **1a** (1.31 g, 10 mmol), formaldehyde **2** (37% in water, 4 mL, 5 equiv.), chloroethylamine hydrochloride **3a** (1.74 g, 15 mmol), $Na_2S_2O_3$ **5** (2.37 g,15 mmol) and 12N HCl (1.25 mL,15 mmol) in THF (40 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give **6a** (2.40 g, 85.7% yield).

4.5 Characterization of products 4 and 6

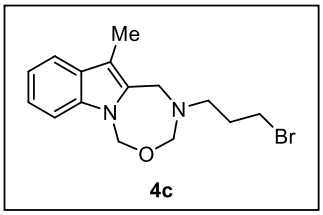


2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4a): White solid, m.p. 120-122 °C (37.5 mg, 71% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, J_1 = 11.5 Hz, J_2 = 4.5 Hz, 1H), 7.14 – 7.04 (m, 1H), 5.60 (s, 2H), 4.75 (s, 2H), 4.23 (s, 2H), 3.49 (t, *J* = 6.5 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.9, 133.9, 128.0, 122.4, 119.4, 119.0, 111.1, 108.6, 90.8, 75.7, 50.7, 47.2, 42.0, 8.8. **HRMS (ESI)** calcd for $C_{14}H_{18}N_2OCl$ ($M+H^+$): 265.1102; Found: 265.1103.



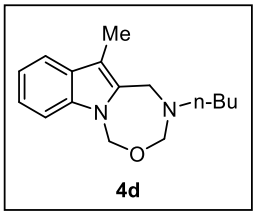
2-(2-bromoethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4b): Off-white solid, m.p. 102-104 °C (30.8 mg, 50% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 5.68 (s, 2H), 4.82 (s, 2H), 4.30 (s, 2H), 3.41 (t, *J* = 6.4 Hz, 2H),

2.88 (t, *J* = 6.4 Hz, 2H), 2.35 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.0, 133.9, 128.0, 122.4, 119.4, 119.0, 111.1, 108.6, 90.7, 75.7, 50.8, 47.1, 30.4, 8.8. **HRMS (ESI)** calcd for $C_{14}H_{18}N_2OBr$ ($M+H^+$): 309.0597; Found: 309.0591.



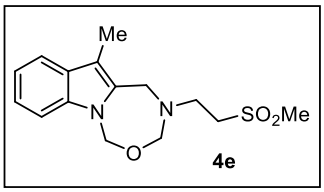
4c

2-(3-bromopropyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4c): Off-white solid, m.p. 69-71 °C (43.8 mg, 68% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.16 – 7.10 (m, 1H), 5.64 (s, 2H), 4.76 (s, 2H), 4.21 (s, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 6.5 Hz, 2H), 2.31 (s, 3H), 1.96 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.9, 134.2, 128.1, 122.2, 119.2, 118.9, 111.0, 108.6, 91.0, 75.6, 46.9, 46.6, 31.4, 30.3, 8.8. **HRMS (ESI)** calcd for $C_{15}H_{20}N_2OBr$ ($M+H^+$): 323.0754; Found: 323.0752.



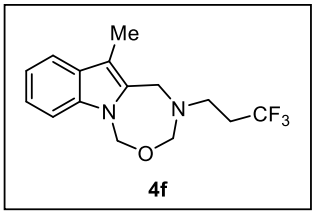
4d

2-butyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4d): Off-white solid, m.p. 106-107 °C (38.7 mg, 75% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.16 – 7.10 (m, 1H), 5.64 (s, 2H), 4.79 (s, 2H), 4.24 (s, 2H), 2.44 – 2.36 (m, 2H), 2.32 (s, 3H), 1.46 (dt, J_1 = 15.0 Hz, J_2 = 7.5 Hz, 2H), 1.33 – 1.25 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.8, 134.6, 128.1, 122.0, 119.1, 118.8, 110.8, 108.5, 91.0, 75.6, 48.5, 46.9, 29.7, 20.4, 14.0, 8.8. **HRMS (ESI)** calcd for $C_{16}H_{23}N_2O$ ($M+H^+$): 259.1805; Found: 259.1804.



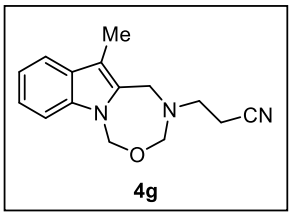
4e

11-methyl-2-(2-(methylsulfonyl)ethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4e): Light yellow solid, m.p. 135-137 °C (47 mg, 76% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.23 (ddd, J_1 = 15.0 Hz, J_2 = 9.0 Hz, J_3 = 4.5 Hz, 2H), 7.15 – 7.07 (m, 1H), 5.62 (s, 2H), 4.75 (s, 2H), 4.23 (s, 2H), 3.03 (t, *J* = 6.5 Hz, 2H), 2.95 – 2.84 (m, 5H), 2.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.0, 133.1, 128.0, 122.6, 119.5, 119.1, 111.6, 108.6, 90.3, 75.7, 52.7, 47.1, 43.2, 42.2, 8.8. **HRMS (ESI)** calcd for $C_{15}H_{21}N_2O_3S$ ($M+H^+$): 309.1267; Found: 309.1264.



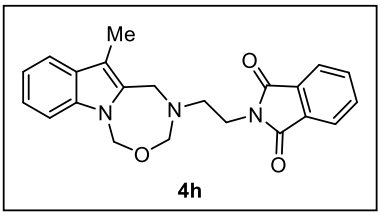
4f

11-methyl-2-(3,3,3-trifluoropropyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4f): Off-white solid, m.p. 65-67 °C (48.9 mg, 82% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.14 – 7.08 (m, 1H), 5.62 (s, 2H), 4.73 (s, 2H), 4.20 (s, 2H), 2.72 – 2.59 (m, 2H), 2.31 – 2.26 (m, 3H), 2.25 – 2.15 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.9, 133.5, 128.0, 126.4 (q, *J* = 276.9 Hz), 122.4, 119.3, 119.0, 111.3, 108.6, 90.7, 75.7, 46.9, 42.1 (q, *J* = 3.4 Hz), 32.5 (q, *J* = 27.6 Hz), 8.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -65.76. **HRMS (ESI)** calcd for $C_{15}H_{18}N_2OF_3$ ($M+H^+$): 299.1366; Found: 299.1369.



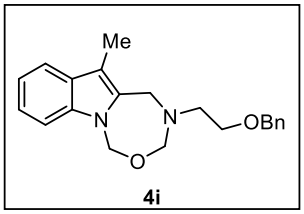
4g

3-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)propanenitrile (4g): Light yellow solid, m.p. 137-139 °C (31.1 mg, 61% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 – 7.05 (m, 1H), 5.58 (s, 2H), 4.73 (s, 2H), 4.22 (s, 2H), 2.65 (t, *J* = 6.5 Hz, 2H), 2.36 (t, *J* = 6.5 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 134.9, 132.4, 126.9, 121.4, 118.4, 117.9, 117.6, 110.2, 107.5, 89.3, 74.6, 46.0, 43.8, 15.8, 7.7. **HRMS (ESI)** calcd for $C_{15}H_{18}N_3O$ ($M+H^+$): 256.1444; Found: 256.1441.



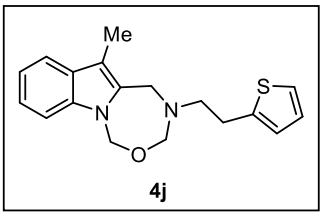
4h

2-(2-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)ethyl)isoindoline-1,3-dione (4h): Light yellow solid, m.p. 170-172 °C (60.8 mg, 81% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.85 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.71 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.15 – 7.06 (m, 1H), 5.61 (s, 2H), 4.71 (s, 2H), 4.30 (s, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.73 (s, 2H), 2.40 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 168.5, 135.9, 134.0, 133.9, 132.2, 128.1, 123.2, 122.2, 119.2, 118.9, 111.4, 108.5, 91.4, 75.6, 46.8, 46.4, 35.5, 8.8. **HRMS (ESI)** calcd for $C_{22}H_{22}N_3O_3$ ($M+H^+$): 376.1656; Found: 376.1655.



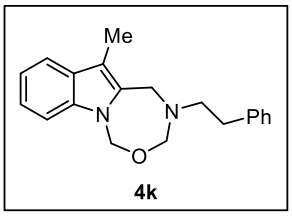
4i

2-(2-(benzyloxy)ethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4i): Colorless gel, (36 mg, 53% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.30 (m, 4H), 7.30 – 7.23 (m, 2H), 7.18 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 7.08 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 =1.0 Hz, 1H), 5.61 (s, 2H), 4.79 (s, 2H), 4.54 (s, 2H), 4.22 (s, 2H), 3.45 (t, *J* = 5.5 Hz, 2H), 2.62 (t, *J* = 5.5 Hz, 2H), 2.14 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 138.2, 135.9, 134.3, 128.5, 128.1, 128.0, 127.8, 122.1, 119.2, 118.8, 111.0, 108.5, 91.2, 75.7, 73.3, 67.3, 48.5, 47.3, 8.6. **HRMS (ESI)** calcd for $C_{21}H_{25}N_2O_2$ ($M+H^+$): 337.1911; Found: 337.1908.



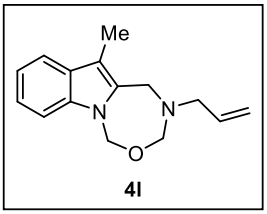
4j

11-methyl-2-(2-(thiophen-2-yl)ethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4j): Yellow solid, m.p. 95-98 °C (43.1 mg, 69% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.16 – 7.07 (m, 2H), 6.91 (dd, J_1 = 5.2 Hz, J_2 = 3.6 Hz, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 5.66 (s, 2H), 4.80 (s, 2H), 4.28 (s, 2H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.5, 135.9, 134.2, 128.1, 126.6, 124.8, 123.6, 122.2, 119.2, 118.9, 111.0, 108.5, 91.0, 75.6, 50.3, 46.9, 28.3, 8.8. **HRMS (ESI)** calcd for $C_{18}H_{21}N_2OS$ ($M+H^+$): 313.1369; Found: 313.1368.



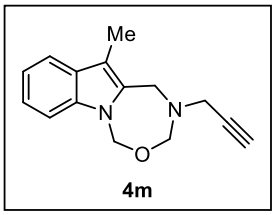
4k

11-methyl-2-phenethyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4k): Off-white solid, m.p. 102-104 °C (42 mg, 68% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.06 (m, 8H), 5.61 (s, 2H), 4.77 (s, 2H), 4.24 (s, 2H), 2.79 – 2.71 (m, 2H), 2.68 – 2.60 (m, 2H), 2.31 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 140.0, 135.9, 134.4, 128.7, 128.4, 128.1, 126.2, 122.1, 119.2, 118.9, 110.8, 108.6, 91.0, 75.7, 50.5, 47.0, 34.3, 8.9. **HRMS (ESI)** calcd for $C_{20}H_{23}N_2O$ ($M+H^+$): 307.1805; Found: 307.1805.



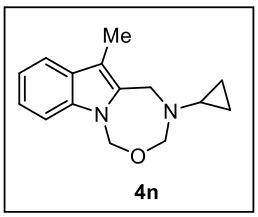
4l

2-allyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4l): Off-white solid, m.p. 90-92 °C (31 mg, 64% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.20 (ddd, J_1 = 8.0 Hz, J_2 = 5.0 Hz, J_3 = 1.0 Hz, 1H), 7.13 – 7.05 (m, 1H), 5.85 – 5.73 (m, 1H), 5.61 (s, 2H), 5.14 (ddd, J_1 = 10.0 Hz, J_2 = 3.0 Hz, J_3 = 1.0 Hz, 1H), 5.07 (ddd, J_1 = 17.0 Hz, J_2 = 3.0 Hz, J_3 = 1.5 Hz, 1H), 4.75 (s, 2H), 4.19 (s, 2H), 3.01 (d, *J* = 6.5 Hz, 2H), 2.22 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 135.9, 135.9, 134.6, 128.8, 122.1, 119.2, 118.9, 118.2, 111.0, 108.5, 90.6, 75.7, 52.4, 46.8, 8.9. **HRMS (ESI)** calcd for $C_{15}H_{19}N_2O$ ($M+H^+$): 243.1492; Found: 243.1490.



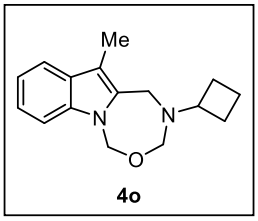
4m

11-methyl-2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4m): yellow solid, m.p. 100-102 °C (39.4 mg, 82% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.16 – 7.11 (m, 1H), 5.63 (s, 2H), 4.83 (s, 2H), 4.38 (s, 2H), 3.19 (d, *J* = 2.5 Hz, 2H), 2.34 (s, 3H), 2.31 (t, *J* = 2.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.0, 132.9, 128.1, 122.3, 119.3, 119.0, 112.1, 108.5, 90.0, 80.1, 75.6, 72.7, 46.5, 38.8, 8.7. **HRMS (ESI)** calcd for $C_{15}H_{17}N_2O$ ($M+H^+$): 241.1335; Found: 241.1336.



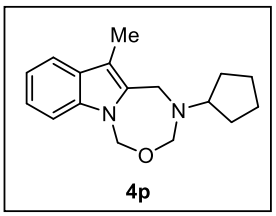
4n

2-cyclopropyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4n): Off-white solid, m.p. 101-103 °C (37.3 mg, 77% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.22 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 7.16 – 7.08 (m, 1H), 5.69 (s, 2H), 4.78 (s, 2H), 4.23 (s, 2H), 2.33 (s, 3H), 1.94 – 1.76 (m, 1H), 0.46 (d, *J* = 5.0 Hz, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.0, 134.7, 128.2, 122.0, 119.2, 118.8, 110.9, 108.5, 90.5, 75.5, 47.5, 30.1, 8.6, 6.8. **HRMS (ESI)** calcd for $C_{15}H_{19}N_2O$ ($M+H^+$): 243.1492; Found: 243.1493.



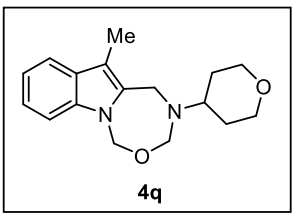
4o

2-cyclobutyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4o): white solid, m.p. 117-119 °C (38.4 mg, 75% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.13 – 7.06 (m, 1H), 5.59 (s, 2H), 4.68 (s, 2H), 4.16 (s, 2H), 3.07 – 2.92 (m, 1H), 2.24 (s, 3H), 2.01 – 1.90 (m, 2H), 1.86 – 1.74 (m, 2H), 1.62 (dd, J_1 = 19.0 Hz, J_2 = 9.5 Hz, 1H), 1.55 – 1.44 (m, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 135.7, 134.5, 128.1, 122.0, 119.2, 118.8, 110.5, 108.5, 86.4, 75.5, 51.4, 44.3, 27.5, 13.8, 8.7. **HRMS (ESI)** calcd for $C_{16}H_{21}N_2O$ ($M+H^+$): 257.1648; Found: 257.1649.



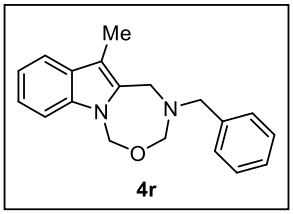
4p

2-cyclopentyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4p): Yellow solid, m.p. 104-106 °C (44.3 mg, 82% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.19 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 7.12 – 7.06 (m, 1H), 5.59 (s, 2H), 4.80 (s, 2H), 4.24 (s, 2H), 2.69 (tt, J_1 = 9.5 Hz, J_2 = 6.5 Hz, 1H), 2.29 (s, 3H), 1.89 – 1.76 (m, 2H), 1.71 – 1.59 (m, 2H), 1.49 – 1.30 (m, 4H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 135.6, 134.8, 128.2, 122.0, 119.1, 118.8, 110.3, 108.6, 89.7, 76.0, 57.8, 47.7, 31.3, 23.6, 9.0. **HRMS (ESI)** calcd for $C_{17}H_{23}N_2O$ ($M+H^+$): 271.1805; Found: 271.1807.

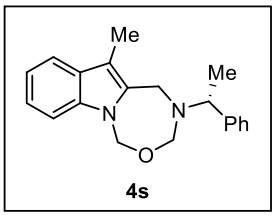


4q

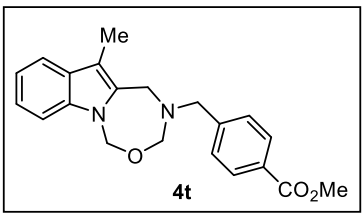
11-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4q): Light yellow solid, m.p. 109-111 °C (44 mg, 77% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.49 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.20 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 7.12 – 7.06 (m, 1H), 5.60 (d, J = 2.5 Hz, 2H), 4.82 (d, J = 7.0 Hz, 2H), 4.26 (s, 2H), 3.88 (dd, J_1 = 12.5 Hz, J_2 = 2.0 Hz, 2H), 3.19 (td, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 2H), 2.49 (ddd, J_1 = 11.0 Hz, J_2 = 7.0 Hz, J_3 = 4.0 Hz, 1H), 2.27 (s, 3H), 1.77 (dd, J_1 = 12.5 Hz, J_2 = 1.0 Hz, 2H), 1.45 (ddd, J_1 = 24.0 Hz, J_2 = 12.0 Hz, J_3 = 4.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.8, 134.9, 128.2, 122.1, 119.2, 118.9, 110.1, 108.6, 87.3, 76.0, 66.8, 52.5, 45.7, 31.5, 9.0. **HRMS (ESI)** calcd for $C_{17}H_{23}N_2O_2$ ($M+H^+$): 287.1754; Found: 287.1757.



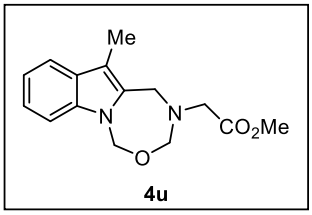
2-benzyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4r): White solid, m.p. 108-110 °C (55.5 mg, 95% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.28 – 7.18 (m, 4H), 7.15 – 7.08 (m, 1H), 5.67 (s, 2H), 4.81 (s, 2H), 4.14 (s, 2H), 3.55 (s, 2H), 2.00 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 138.2, 135.9, 134.2, 129.0, 128.3, 128.2, 127.2, 122.1, 119.1, 118.9, 111.1, 108.6, 91.0, 75.7, 53.5, 46.5, 8.7. **HRMS (ESI)** calcd for $C_{19}H_{21}N_2O$ ($M+H^+$): 293.1648; Found: 293.1644.



(*S*)-11-methyl-2-(1-phenylethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4s): White solid, m.p. 148-150 °C (56.3 mg, 92% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.27 – 7.18 (m, 4H), 7.14 – 7.07 (m, 1H), 5.66 (d, *J* = 113.0 Hz, 2H), 5.10 (s, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.29 – 3.99 (m, 2H), 3.64 – 3.47 (m, 1H), 1.89 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 144.8, 135.7, 134.8, 128.5, 128.3, 127.4, 127.1, 122.0, 119.1, 118.9, 110.6, 108.6, 88.4, 76.1, 56.2, 46.7, 22.0, 8.8. **HRMS (ESI)** calcd for $C_{20}H_{23}N_2O$ ($M+H^+$): 307.1805; Found: 307.1804.

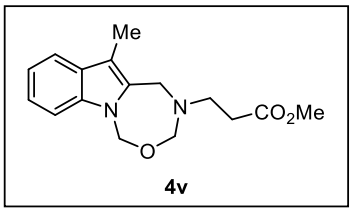


methyl 4-((11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)methyl)benzoate (4t): Off-white solid, m.p. 139-141 °C (52.5mg, 75% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 3H), 7.18 – 7.11 (m, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 5.60 (s, 2H), 4.74 (s, 2H), 4.04 (s, 2H), 3.84 (s, 3H), 3.52 (s, 2H), 1.88 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.1, 143.7, 136.0, 133.8, 129.7, 129.2, 128.8, 128.1, 122.2, 119.2, 119.0, 111.3, 108.6, 91.2, 75.7, 53.2, 52.1, 46.4, 8.7. **HRMS (ESI)** calcd for $C_{21}H_{23}N_2O_3$ ($M+H^+$): 351.1703; Found: 351.1702.



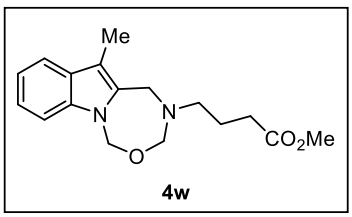
4u

methyl 2-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)acetate (4u): Off-white solid, m.p. 90-92 °C (40 mg, 73% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.15 – 7.09 (m, 1H), 5.65 (s, 2H), 4.79 (s, 2H), 4.36 (s, 2H), 3.71 (s, 3H), 3.20 (s, 2H), 2.22 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.2, 136.1, 132.9, 128.1, 122.4, 119.4, 119.0, 112.1, 108.6, 91.4, 75.6, 51.9, 50.3, 47.2, 8.4. **HRMS (ESI)** calcd for $C_{25}H_{19}N_2O_3$ ($M+H^+$): 275.1390; Found: 275.1391.



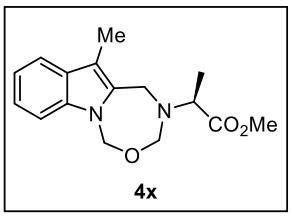
4v

methyl 3-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)propanoate (4v): white solid, m.p. 170-172 °C (39 mg, 67% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.13 – 7.04 (m, 1H), 5.61 (s, 2H), 4.74 (s, 2H), 4.22 (s, 2H), 3.67 (s, 3H), 2.70 (t, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 2.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.8, 135.9, 134.1, 128.1, 122.2, 119.2, 118.9, 111.1, 108.5, 90.7, 75.6, 51.7, 47.0, 44.6, 32.9, 8.7. **HRMS (ESI)** calcd for $C_{16}H_{21}N_2O_3$ ($M+H^+$): 289.1547; Found: 289.1545.



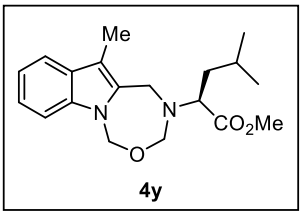
4w

methyl 4-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)butanoate (4w): Off-white solid, m.p. 125-128 °C (42.9 mg, 71% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.18 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 7.08 (td, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 5.58 (s, 2H), 4.71 (s, 2H), 4.16 (s, 2H), 3.63 (s, 3H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.33 – 2.25 (m, 5H), 1.80 – 1.70 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.0, 135.9, 134.3, 128.1, 122.1, 119.2, 118.8, 111.0, 108.5, 91.0, 75.6, 51.5, 48.0, 46.6, 31.7, 22.6, 8.7. **HRMS (ESI)** calcd for $C_{17}H_{23}N_2O_3$($M+H^+$): 303.1703; Found: 303.1700.



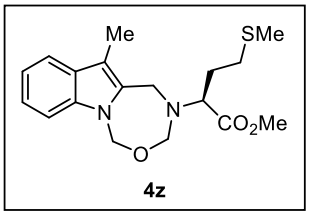
4x

methyl (*S*)-2-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)propanoate (4x): White solid, m.p. 94-96 °C (40.3 mg, 70% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.22 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 7.14 – 7.09 (m, 1H), 5.78 (d, *J* = 12.0 Hz, 1H), 5.53 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.41 – 4.23 (m, 2H), 3.71 (s, 3H), 3.27 (q, *J* = 7.0 Hz, 1H), 2.21 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.7, 135.8, 133.5, 128.0, 122.3, 119.2, 119.0, 111.3, 108.5, 87.7, 75.8, 55.5, 52.0, 47.1, 16.5, 8.5. **HRMS (ESI)** calcd for $C_{16}H_{21}N_2O_3$ ($M+H^+$): 289.1547; Found: 289.1546.



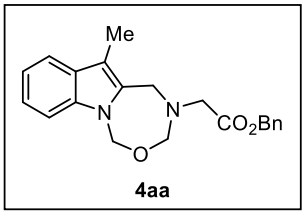
4y

methyl (*S*)-4-methyl-2-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)pentanoate (4y): Colorless oil, (58.7 mg, 89% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 5.2 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 5.57 (dd, J_1 = 47.6 Hz, J_2 = 12.0 Hz, 2H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.26 – 4.13 (m, 2H), 3.45 (s, 3H), 3.24 (dd, J_1 = 9.6 Hz, J_2 = 5.4 Hz, 1H), 2.17 (s, 3H), 1.52 (ddd, J_1 = 14.0 Hz, J_2 = 9.6 Hz, J_3 = 4.8 Hz, 1H), 1.43 – 1.34 (m, 2H), 0.74 (d, *J* = 6.4 Hz, 3H), 0.64 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.1, 135.8, 134.1, 128.2, 122.1, 119.1, 118.9, 110.7, 108.5, 87.9, 75.7, 60.1, 51.8, 47.4, 39.5, 25.1, 23.5, 21.9, 8.8. **HRMS (ESI)** calcd for $C_{19}H_{27}N_2O_3$ ($M+H^+$): 331.2016; Found: 331.2018.



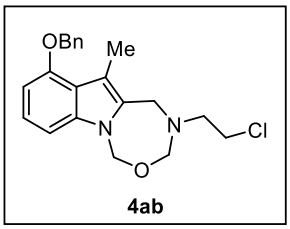
4z

methyl (*S*)-2-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)-4-(methylthio)butanoate (4z): Yellow solid, m.p. 62-64 °C (35.5 mg, 51% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.13 – 7.08 (m, 1H), 5.77 – 5.52 (m, 2H), 4.86 (dd, J_1 = 98.0 Hz, J_2 = 12.0 Hz, 2H), 4.29 (s, 2H), 3.54 (s, 3H), 3.46 – 3.37 (m, 1H), 2.41 – 2.28 (m, 2H), 2.26 (s, 3H), 2.00 – 1.83 (m, 5H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 173.2, 135.9, 134.1, 128.1, 122.3, 119.3, 119.0, 110.9, 108.5, 87.9, 75.7, 60.5, 52.0, 47.4, 30.0, 29.5, 15.2, 8.7. **HRMS (ESI)** calcd for $C_{18}H_{25}N_2O_3S$ ($M+H^+$): 349.1580; Found: 349.1575.



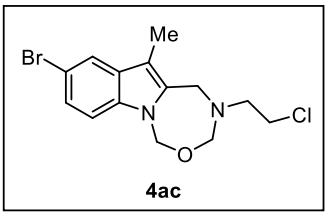
4aa

benzyl 2-(11-methyl-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-2(3*H*)-yl)acetate (4aa): white solid, m.p. 88-90 °C (40.0 mg, 57% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.27 (m, 5H), 7.27 – 7.17 (m, 2H), 7.12 – 7.06 (m, 1H), 5.59 (s, 2H), 5.14 (s, 2H), 4.77 (s, 2H), 4.32 (s, 2H), 3.22 (s, 2H), 2.10 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 170.6, 136.1, 135.5, 132.9, 128.6, 128.5, 128.4, 128.0, 122.4, 119.4, 119.0, 112.2, 108.6, 91.4, 75.6, 66.6, 50.4, 47.2, 8.3. **HRMS (ESI)** calcd for $C_{21}H_{23}N_2O_3$ ($M+H^+$): 351.1703; Found: 351.1701.



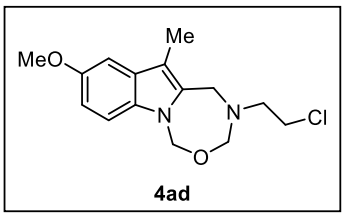
4ab

10-(benzyloxy)-2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ab): Off-white solid, m.p. 156-158 °C (30.3 mg, 41% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.51 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 5.62 (s, 2H), 5.18 (s, 2H), 4.78 (s, 2H), 4.23 (s, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.46 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 154.0, 137.6, 137.5, 132.3, 128.5, 127.7, 127.2, 123.0, 117.6, 111.6, 102.3, 100.8, 90.9, 75.9, 69.9, 50.6, 46.8, 42.0, 11.3. **HRMS (ESI)** calcd for $C_{21}H_{24}N_2O_2Cl$ ($M+H^+$): 371.1521; Found: 371.1520.



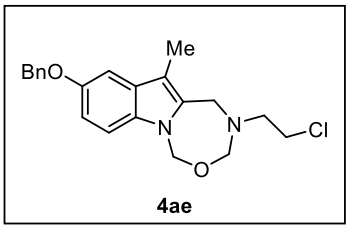
4ac

9-bromo-2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ac): Off-white solid, m.p. 148-150 °C (45.8 mg, 67% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.61 (d, *J* = 2.0 Hz, 1H), 7.28 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 5.60 (s, 2H), 4.78 (s, 2H), 4.25 (s, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.75 (t, *J* = 6.5 Hz, 2H), 2.24 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 135.3, 134.6, 129.7, 125.0, 121.6, 112.5, 110.7, 110.1, 90.8, 75.8, 50.7, 47.2, 41.9, 8.6. **HRMS (ESI)** calcd for $C_{14}H_{17}N_2OBrCl$ ($M+H^+$): 343.0207; Found: 343.0204.



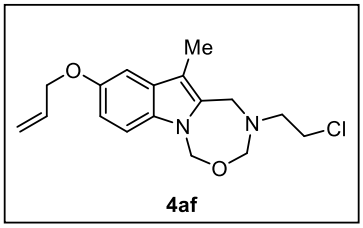
4ad

2-(2-chloroethyl)-9-methoxy-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ad): White solid, m.p. 109-111 °C (48.8 mg, 83% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.17 (d, *J* = 9.0 Hz, 1H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1H), 5.60 (s, 2H), 4.78 (s, 2H), 4.24 (s, 2H), 3.88 (s, 3H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.77 (t, *J* = 6.5 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 154.0, 134.6, 131.1, 128.3, 112.1, 110.7, 109.3, 101.0, 90.8, 75.9, 56.0, 50.7, 47.3, 42.0, 8.8. **HRMS (ESI)** calcd for $C_{15}H_{20}N_2O_2Cl$ ($M+H^+$): 295.1208; Found: 295.1212.



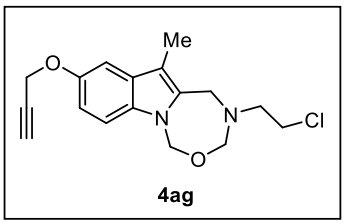
4ae

9-(benzyloxy)-2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ae): Light yellow solid, m.p. 98-100 °C (57.0 mg, 77% yield). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 5.57 (s, 2H), 5.10 (s, 2H), 4.75 (s, 2H), 4.21 (s, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.75 (t, *J* = 6.6 Hz, 2H), 2.23 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 153.2, 137.7, 134.7, 131.3, 128.6, 128.3, 127.9, 127.6, 112.8, 110.7, 109.3, 102.7, 90.8, 75.9, 71.0, 50.7, 47.3, 42.1, 8.8. **HRMS (ESI)** calcd for $C_{21}H_{24}N_2O_2Cl$ ($M+H^+$): 371.1521; Found: 371.1520.



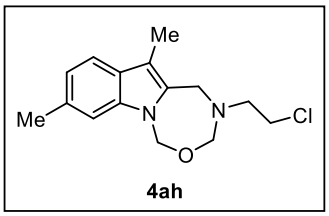
4af

9-(allyloxy)-2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4af): Yellow solid, m.p. 65-67 °C (50.6 mg, 79% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.17 (d, *J* = 9.0 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1H), 6.22 – 6.02 (m, 1H), 5.60 (s, 2H), 5.49 – 5.25 (m, 2H), 4.77 (s, 2H), 4.59 (dt, J_1 = 5.5 Hz, J_2 = 1.5 Hz, 2H), 4.24 (s, 2H), 3.51 (t, *J* = 6.5 Hz, 2H), 2.77 (t, *J* = 6.5 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 152.9, 134.7, 134.0, 131.3, 128.3, 117.4, 112.8, 110.7, 109.2, 102.6, 90.8, 75.9, 69.9, 50.7, 47.3, 42.0, 8.8. **HRMS (ESI)** calcd for $C_{17}H_{22}N_2O_2Cl$ ($M+H^+$): 321.1364; Found: 321.1367.



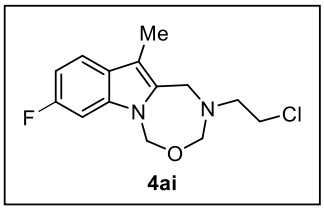
4ag

2-(2-chloroethyl)-11-methyl-9-(prop-2-yn-1-yloxy)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ag): White solid, m.p. 66-68 °C (51.5 mg, 81% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.18 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.94 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1H), 5.60 (s, 2H), 4.84 – 4.68 (m, 4H), 4.24 (s, 2H), 3.51 (t, J = 6.5 Hz, 2H), 2.77 (t, J = 6.5 Hz, 2H), 2.52 (t, J = 2.5 Hz, 1H), 2.26 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 151.9, 134.9, 131.7, 128.2, 112.8, 110.8, 109.3, 103.3, 90.8, 79.3, 75.9, 75.1, 57.0, 50.7, 47.3, 42.0, 8.8. **HRMS (ESI)** calcd for $C_{17}H_{20}N_2O_2Cl$ ($M+H^+$): 319.1208; Found: 319.1208.



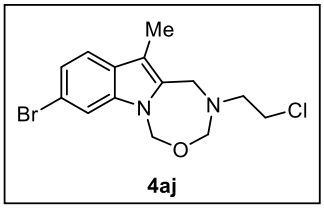
4ah

2-(2-chloroethyl)-8,11-dimethyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ah): Yellow solid, m.p. 165-168 °C (36.7 mg, 66% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.39 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 5.62 (s, 2H), 4.77 (s, 2H), 4.24 (s, 2H), 3.51 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.5 Hz, 2H), 2.48 (s, 3H), 2.27 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.3, 133.1, 132.2, 125.9, 121.0, 118.6, 111.0, 108.7, 90.8, 75.6, 50.6, 47.2, 42.0, 21.9, 8.8. **HRMS (ESI)** calcd for $C_{15}H_{20}N_2OCl$ ($M+H^+$): 279.1259; Found: 279.1260.



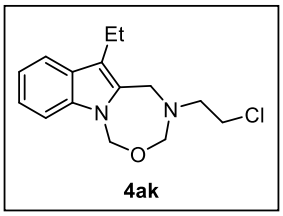
4ai

2-(2-chloroethyl)-8-fluoro-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ai): Off-white solid, m.p. 121-123 °C (35.5 mg, 63% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.38 (dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz, 1H), 6.94 (dd, J_1 = 10.0 Hz, J_2 = 2.0 Hz, 1H), 6.86 (ddd, J_1 = 9.5 Hz, J_2 = 9.0 Hz, J_3 = 2.0 Hz, 1H), 5.55 (s, 2H), 4.76 (s, 2H), 4.22 (s, 2H), 3.50 (t, J = 6.5 Hz, 2H), 2.76 (t, J = 6.5 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 161.3, 159.4, 136.0, 135.9, 134.2, 134.2, 124.5, 119.7, 119.6, 111.2, 108.0, 107.8, 95.5, 95.3, 90.8, 75.8, 50.6, 47.3, 42.0, 8.7. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -120.75. **HRMS (ESI)** calcd for $C_{14}H_{17}N_2OFCl$ ($M+H^+$): 283.1008; Found: 283.1007.



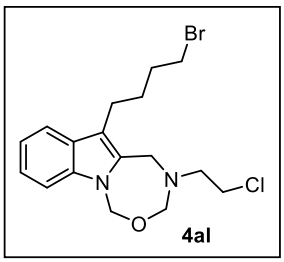
4aj

8-bromo-2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4aj): White solid, m.p. 138-140 °C (57.5 mg, 84% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.42 (d, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.19 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 5.56 (s, 2H), 4.76 (s, 2H), 4.22 (s, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.7, 134.6, 126.9, 122.6, 120.2, 116.0, 111.7, 111.3, 90.8, 75.7, 50.7, 47.3, 42.0, 8.7. **HRMS (ESI)** calcd for $C_{14}H_{17}N_2OBrCl$ ($M+H^+$): 343.0207; Found: 343.0202.



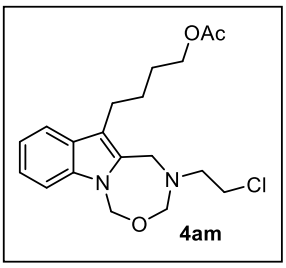
4ak

2-(2-chloroethyl)-11-ethyl-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4ak): Off-white solid, m.p. 79-80 °C (41.1 mg, 74% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.65 (s, 2H), 4.80 (s, 2H), 4.28 (s, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.92 – 2.65 (m, 4H), 1.28 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 136.1, 133.3, 127.1, 122.3, 119.3, 119.1, 118.0, 108.7, 90.8, 75.7, 50.8, 47.3, 42.1, 17.6, 16.2. **HRMS (ESI)** calcd for $C_{15}H_{20}N_2O$ ($M+H^+$): 279.1259; Found: 279.1257.

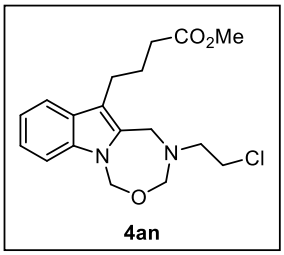


4al

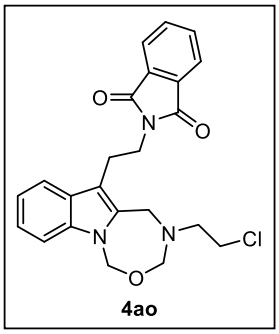
11-(4-bromobutyl)-2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indole (4al): Light yellow oil, (72.2 mg, 94% yield). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.15 – 7.07 (m, 1H), 5.66 (s, 2H), 4.79 (s, 2H), 4.27 (s, 2H), 3.51 (t, *J* = 6.6 Hz, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 1.94 (dt, J_1 = 15.0 Hz, J_2 = 6.6 Hz, 2H), 1.79 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 136.0, 134.1, 127.2, 122.4, 119.5, 119.0, 115.5, 108.8, 90.7, 75.8, 50.8, 47.5, 42.2, 33.7, 32.5, 29.8, 23.5. **HRMS (ESI)** calcd for $C_{17}H_{23}N_2OBrCl$ ($M+H^+$): 385.0677; Found: 385.0672.



4-(2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-11-yl)butyl acetate (4am): Colorless gel, (66.2 mg, 91% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.22 (ddd, J_1 = 8.0 Hz, J_2 = 7.0 Hz, J_3 = 1.0 Hz, 1H), 7.15 – 7.07 (m, 1H), 5.66 (s, 2H), 4.78 (s, 2H), 4.26 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.78 (dd, J_1 = 13.5 Hz, J_2 = 7.0 Hz, 4H), 2.04 (d, *J* = 2.5 Hz, 3H), 1.70 (dt, J_1 = 7.0 Hz, J_2 = 3.5 Hz, 4H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.2, 136.0, 134.1, 127.3, 122.3, 119.4, 119.0, 115.7, 108.7, 90.7, 75.8, 64.3, 50.8, 47.5, 42.1, 28.6, 27.7, 24.0, 21.0. **HRMS (ESI)** calcd for $C_{19}H_{26}N_2O_3Cl$ ($M+H^+$): 365.1626; Found: 365.1621.

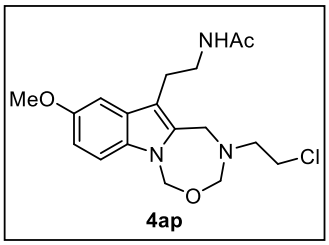


methyl 4-(2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-11-yl)butanoate (4an): Light yellow gel, (56.0 mg, 80% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.15 – 7.08 (m, 1H), 5.66 (s, 2H), 4.79 (s, 2H), 4.26 (s, 2H), 3.68 (s, 3H), 3.51 (t, *J* = 6.5 Hz, 2H), 2.78 (dd, J_1 = 12.5 Hz, J_2 = 6.5 Hz, 4H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.97 (p, *J* = 7.0 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.9, 136.0, 134.4, 127.3, 122.4, 119.5, 119.1, 115.1, 108.7, 90.7, 75.8, 51.6, 50.8, 47.4, 42.1, 33.5, 26.3, 23.6. **HRMS (ESI)** calcd for $C_{18}H_{24}N_2O_3Cl$ ($M+H^+$): 351.1470; Found: 351.1470.



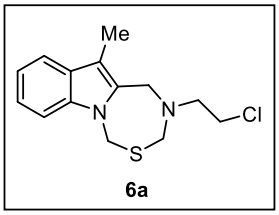
2-(2-(2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-11-yl)ethyl)isoindoline-1,3-dione (4ao): White solid, m.p. 161-163 °C (59.8 mg, 68% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.85 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H), 7.72 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 3H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.66 (s, 2H), 4.79 (s, 2H), 4.31 (s, 2H), 3.94 – 3.80 (m, 2H), 3.57 (t, *J* = 6.5 Hz, 2H), 3.15 – 3.00 (m, 2H), 2.82 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.2, 136.0, 135.1, 134.0, 132.2, 127.1, 123.3,

122.6, 119.8, 119.0, 111.9, 108.8, 91.0, 75.8, 50.9, 47.3, 42.0, 38.7, 23.7. **HRMS (ESI)** calcd for $C_{23}H_{22}N_3O_3ClNa$ ($M+Na^+$): 446.1232; Found: 446.1242.



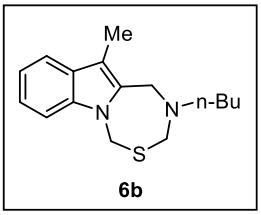
4ap

***N*-(2-(2-(2-chloroethyl)-9-methoxy-2,3-dihydro-1*H*,5*H*-[1,3,6]oxadiazepino[3,4-*a*]indol-11-yl)ethyl)acetamide (4ap):** White solid, m.p. 125-127 °C (29.9 mg, 41% yield). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.20 (d, *J* = 8.4 Hz, 1H), 7.02 (s, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 5.63 (s, 3H), 4.78 (s, 2H), 4.24 (s, 2H), 3.87 (s, 3H), 3.59 – 3.37 (m, 4H), 2.92 (s, 2H), 2.79 (s, 2H), 1.95 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 170.1, 154.2, 135.9, 131.2, 127.6, 112.4, 112.2, 109.6, 100.8, 90.7, 76.0, 56.0, 50.8, 47.5, 42.0, 40.6, 24.5, 23.4. **HRMS (ESI)** calcd for $C_{18}H_{25}N_3O_3Cl$ ($M+H^+$): 366.1579; Found: 366.1578.



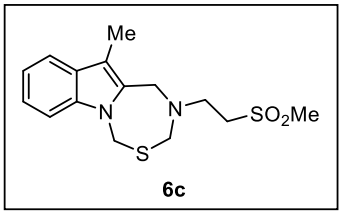
6a

2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6a): Yellow solid, m.p. 124-126 °C (45.4 mg, 81% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 4.0 Hz, 2H), 7.18 – 7.08 (m, 1H), 5.30 (dd, J_1 = 68.8 Hz, J_2 = 12.8 Hz, 2H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.53 – 4.24 (m, 2H), 4.08 (d, *J* = 15.2 Hz, 1H), 3.56 (t, *J* = 6.4 Hz, 2H), 2.72 (t, *J* = 6.4 Hz, 2H), 2.32 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.9, 132.5, 128.0, 122.5, 119.4, 119.1, 112.6, 108.7, 63.8, 50.4, 48.2, 47.3, 41.8, 9.0. **HRMS (ESI)** calcd for $C_{17}H_{15}N_2SCl$ ($M+H^+$):281.0874; Found: 281.0874.



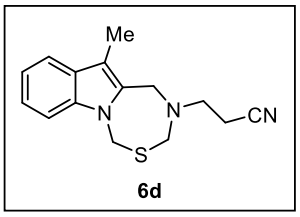
6b

2-butyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6b): Colorless gel, (30.7 mg, 56% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.12 (ddd, J_1 = 8.0 Hz, J_2 = 5.6 Hz, J_3 = 2.4 Hz, 1H), 5.53 – 5.05 (m, 2H), 4.79 – 4.37 (m, 2H), 4.24 (m, 2H), 2.43 – 2.21 (m, 5H), 1.48 – 1.38 (m, 2H), 1.31 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.8, 133.2, 128.2, 122.2, 119.2, 118.9, 112.4, 108.6, 64.0, 48.4, 48.1, 47.4, 29.4, 20.5, 14.0, 9.0. **HRMS (ESI)** calcd for $C_{16}H_{23}N_2S$ ($M+H^+$): 275.1576; Found: 275.1581.



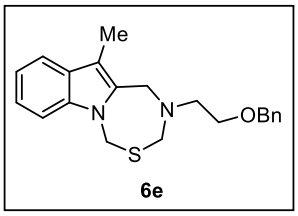
6c

11-methyl-2-(2-(methylsulfonyl)ethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6c): Light yellow solid, m.p. 146-148 °C (49.9 mg, 77% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.53 (d, J = 7.6 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.13 (m, 1H), 5.29 (dd, J_1 = 72.0 Hz, J_2 = 13.6 Hz, 2H), 4.74 – 4.53 (m, 1H), 4.35 (dd, J_1 = 26.4 Hz, J_2 = 8.8 Hz, 2H), 4.05 (d, J = 15.6 Hz, 1H), 3.09 (t, J = 6.0 Hz, 2H), 2.97 (s, 3H), 2.93 – 2.83 (m, 2H), 2.33 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.9, 131.8, 128.0, 122.7, 119.6, 119.2, 113.1, 108.7, 63.4, 52.5, 47.8, 47.3, 43.1, 42.4, 9.1. **HRMS (ESI)** calcd for $C_{15}H_{20}N_2O_2S_2Na$ ($M+Na^+$): 347.0858; Found: 347.0861.



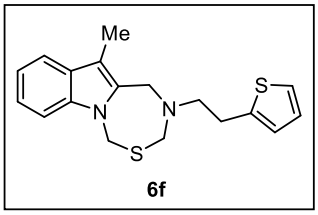
6d

3-(11-methyl-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-2(3*H*)-yl)propanenitrile (6d): Light yellow solid, m.p. 146-148 °C (40.1 mg, 74% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56 (d, J = 7.6 Hz, 1H), 7.29 (dd, J_1 = 6.4 Hz, J_2 = 3.6 Hz, 2H), 7.17 (m, 1H), 5.34 (dd, J_1 = 68.4 Hz, J_2 = 14.2 Hz, 2H), 4.80 – 4.65 (m, 1H), 4.39 (d, J = 18.4 Hz, 2H), 4.12 (d, J = 15.6 Hz, 1H), 2.68 (t, J = 6.4 Hz, 2H), 2.48 (t, J = 6.4 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.9, 132.1, 128.0, 122.6, 119.5, 119.1, 118.6, 112.7, 108.7, 63.3, 48.1, 47.3, 44.5, 16.6, 9.1. **HRMS (ESI)** calcd for $C_{15}H_{17}N_3SNa$ ($M+Na^+$): 294.1035; Found: 294.1036.

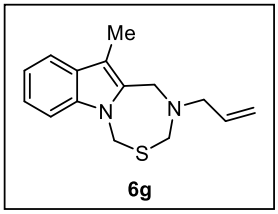


6e

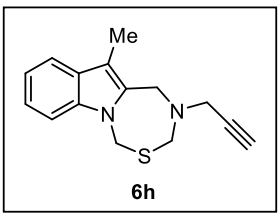
2-ethyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6e): Yellow solid, m.p. 86-88 °C (50.0 mg, 71% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (d, J = 7.6 Hz, 1H), 7.40 – 7.25 (m, 5H), 7.24 – 7.17 (m, 2H), 7.13 – 7.03 (m, 1H), 5.25 (dd, J_1 = 70.8 Hz, J_2 = 14.0 Hz, 2H), 4.75 – 4.40 (m, 4H), 4.18 (dd, J_1 = 113.2 Hz, J_2 = 15.2 Hz, 2H), 3.63 – 3.31 (m, 2H), 2.59 (t, J = 5.6 Hz, 2H), 2.21 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 138.2, 135.8, 132.9, 128.5, 128.1, 127.9, 127.8, 122.3, 119.3, 119.0, 112.5, 108.7, 73.3, 67.2, 64.1, 48.5, 48.3, 47.4, 9.0. **HRMS (ESI)** calcd for $C_{21}H_{25}N_2OS$ ($M+H^+$): 353.1682; Found:353.1688.



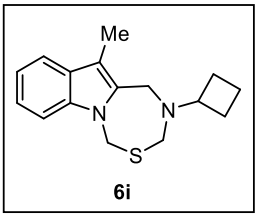
11-methyl-2-(2-(thiophen-2-yl)ethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6f): Light yellow solid, m.p. 86-88 °C (47.2 mg, 72% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, J = 7.6 Hz, 1H), 7.30 (m, 2H), 7.23 – 7.10 (m, 2H), 6.97 (dd, J_1 = 5.2 Hz, J_2 = 3.6 Hz, 1H), 6.91 – 6.79 (m, 1H), 5.35 (dd, J_1 = 71.6 Hz, J_2 = 14.4 Hz, 2H), 4.62 (dd, J_1 = 94.4 Hz, J_2 = 12.0 Hz, 2H), 4.26 (dd, J_1 = 121.6 Hz, J_2 = 16.0 Hz, 2H), 3.03 (t, J = 7.2 Hz, 2H), 2.71 (t, J = 7.2 Hz, 2H), 2.38 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.6, 135.8, 132.9, 128.1, 126.7, 124.8, 123.7, 122.3, 119.3, 119.1, 112.5, 108.7, 64.0, 50.0, 47.9, 47.4, 27.9, 9.2. **HRMS (ESI)** calcd for $C_{18}H_{21}N_2S_2$ ($M+H^+$): 329.1141; Found: 329.1145.



2-allyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6g): Light yellow solid, m.p. 120-122 °C (48.0 mg, 93% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, J = 7.6 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.13 (m, 1H), 5.81 (m, 1H), 5.46 – 5.11 (m, 4H), 4.54 (dd, J_1 = 72.8 Hz, J_2 = 12.0 Hz, 2H), 4.20 (dd, J_1 = 104.0 Hz, J_2 = 14.8 Hz, 2H), 3.15 – 2.90 (m, 2H), 2.29 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.9, 134.9, 132.8, 128.2, 122.3, 119.3, 119.0, 118.6, 112.6, 108.7, 63.3, 51.9, 48.0, 47.3, 9.2. **HRMS (ESI)** calcd for $C_{15}H_{19}N_2S$ ($M+H^+$): 259.1263; Found: 259.1263.

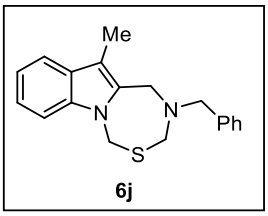


11-methyl-2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6h): White solid, m.p. 117-119 °C (50.2 mg, 98% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, J = 7.6 Hz, 1H), 7.33 – 7.21 (m, 2H), 7.13 (m, 1H), 5.27 (dd, J_1 = 76.4 Hz, J_2 = 14.8 Hz, 2H), 4.75 – 4.55 (m, 2H), 4.29 (dd, J_1 = 161.2 Hz, J_2 = 15.6 Hz, 2H), 3.26 – 3.03 (m, 2H), 2.35 (s, 3H), 2.31 (t, J = 2.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.0, 131.5, 128.1, 122.5, 119.4, 119.2, 113.6, 108.7, 80.0, 73.1, 63.1, 47.3, 47.3, 38.6, 9.0. **HRMS (ESI)** calcd for $C_{15}H_{17}N_2S$ ($M+H^+$): 257.1107; Found: 257.1106.



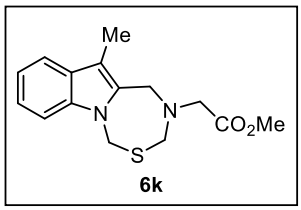
6i

2-cyclobutyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6i): Off-white solid, m.p. 124-126 °C (45.2 mg, 83% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.52 (d, J = 7.6 Hz, 1H), 7.28 – 7.20 (m, 2H), 7.16 – 7.06 (m, 1H), 5.28 (dd, J_1 = 83.2 Hz, J_2 = 14.4 Hz, 2H), 4.48 (dd, J_1 = 55.2 Hz, J_2 = 12.4 Hz, 2H), 4.15 (dd, J_1 = 150.4 Hz, J_2 = 15.6 Hz, 2H), 3.19 – 2.88 (m, 1H), 2.29 (s, 3H), 2.14 – 1.72 (m, 4H), 1.72 – 1.47 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.6, 132.9, 128.1, 122.2, 119.2, 119.0, 112.1, 108.5, 60.2, 51.3, 47.4, 44.6, 27.4, 13.9, 9.2. **HRMS (ESI)** calcd for $C_{16}H_{21}N_2S$ ($M+H^+$): 273.1420; Found: 273.1424.



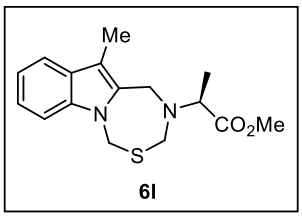
6j

2-benzyl-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6j): Off-white solid, m.p. 118-120 °C (54.8 mg, 89% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.51 (d, J = 7.6 Hz, 1H), 7.35 – 7.20 (m, 8H), 7.11 (m, 1H), 5.27 (dd, J_1 = 75.6 Hz, J_2 = 14.8 Hz, 2H), 4.63 (d, J = 14.8 Hz, 1H), 4.31 (dd, J_1 = 30.0 Hz, J_2 = 14.4 Hz, 2H), 4.07 (dd, J_1 = 17.2 Hz, J_2 = 10.0 Hz, 1H), 3.64 – 3.40 (m, 2H), 2.07 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 137.9, 135.9, 132.9, 129.1, 128.5, 128.2, 127.3, 122.3, 119.3, 119.1, 112.7, 108.7, 63.6, 53.2, 47.9, 47.3, 9.0. **HRMS (ESI)** calcd for $C_{19}H_{21}N_2S$ ($M+H^+$): 309.1420; Found: 309.1422.



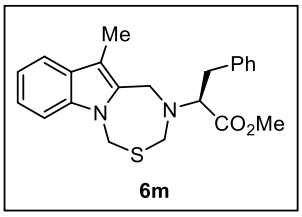
6k

methyl 2-(11-methyl-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-2(3*H*)-yl)acetate (6k): Yellow solid, m.p. 146-148 °C (45.2 mg, 78% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.56 (d, J = 8.0 Hz, 1H), 7.34 – 7.23 (m, 2H), 7.20 – 7.11 (m, 1H), 5.31 (dd, J_1 = 66.0 Hz, J_2 = 14.4 Hz, 2H), 4.75 (t, J = 14.0 Hz, 1H), 4.50 (t, J = 17.2 Hz, 2H), 4.11 (d, J = 15.6 Hz, 1H), 3.76 (s, 3H), 3.22 (s, 2H), 2.27 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.1, 136.0, 131.7, 128.1, 122.6, 119.5, 119.2, 113.4, 108.7, 64.6, 51.9, 50.3, 47.7, 47.2, 8.7. **HRMS (ESI)** calcd for $C_{15}H_{19}N_2O_2S$ ($M+H^+$): 291.1162; Found: 291.1160.



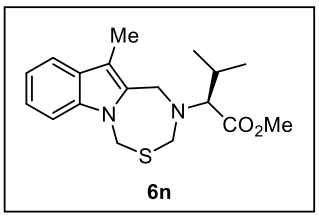
6l

methyl (*S*)-2-(11-methyl-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-2(3*H*)-yl)propanoate (6l): Light yellow gel, (42.5 mg, 70% yield). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 3.6 Hz, 2H), 7.18 – 7.07 (m, 1H), 5.31 (dd, J_1 = 66.0 Hz, J_2 = 14.8 Hz, 2H), 4.71 – 4.36 (m, 3H), 4.07 (d, *J* = 16.0 Hz, 1H), 3.76 (d, *J* = 12.4 Hz, 3H), 3.27 (d, *J* = 5.6 Hz, 1H), 2.15 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 174.7, 135.8, 131.8, 128.0, 122.5, 119.3, 119.2, 113.4, 108.6, 60.9, 54.8, 52.2, 47.3, 17.1, 8.7. **HRMS (ESI)** calcd for $C_{16}H_{21}N_2O_2S$ (M+H$^+$): 305.1318; Found: 305.1318.



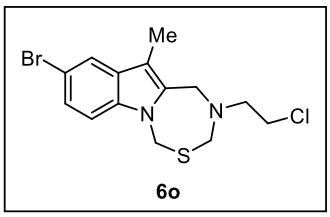
6m

methyl (*S*)-2-(11-methyl-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-2(3*H*)-yl)-3-phenylpropanoate (6m): Yellow solid, m.p. 124-126 °C (54.7 mg, 72% yield). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (d, *J* = 7.2 Hz, 1H), 7.31 – 6.99 (m, 8H), 5.63 – 5.08 (m, 2H), 4.98 – 3.87 (m, 4H), 3.74 – 2.63 (m, 6H), 2.24 (m, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 173.0, 136.7, 135.9, 132.1, 129.2, 128.4, 128.1, 126.8, 122.5, 119.3, 119.2, 113.0, 108.7, 62.6, 61.0, 51.6, 48.1, 47.4, 37.3, 9.1. **HRMS (ESI)** calcd for $C_{22}H_{24}N_2O_2SNa$ (M+Na$^+$): 403.1451; Found: 403.1453.



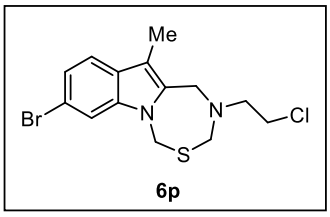
6n

methyl (*S*)-3-methyl-2-(11-methyl-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-2(3*H*)-yl)butanoate (6n): Off-white solid, m.p. 129-131 °C (35.2 mg, 53% yield). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.16 – 7.02 (m, 1H), 5.30 (d, *J* = 29.6 Hz, 2H), 4.79 – 3.99 (m, 4H), 3.93 – 2.92 (m, 4H), 2.15 (d, *J* = 35.6 Hz, 4H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 171.9, 135.7, 132.4, 128.0, 122.4, 119.2, 119.1, 113.1, 108.6, 61.1, 51.5, 47.6, 47.2, 27.4, 20.1, 16.5, 9.0. **HRMS (ESI)** calcd for $C_{18}H_{25}N_2O_2S$ (M+H$^+$): 333.1631; Found: 333.1630.



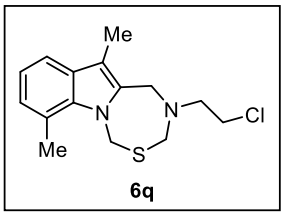
6o

9-bromo-2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6o): Yellow solid, m.p. 169-171 °C (68 mg, 95% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 1.6 Hz, 1H), 7.30 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 5.49 – 5.06 (m, 2H), 4.69 (d, *J* = 13.6 Hz, 1H), 4.35 (dd, J_1 = 29.2 Hz, J_2 =14.8 Hz, 2H), 4.07 (d, *J* = 15.6 Hz, 1H), 3.54 (t, *J* = 6.4 Hz, 2H), 2.70 (t, *J* = 5.6 Hz, 2H), 2.26 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 134.5, 133.8, 129.8, 125.2, 121.7, 112.6, 112.2, 110.2, 63.7, 50.4, 48.2, 47.5, 41.7, 8.9. **HRMS (ESI)** calcd for $C_{14}H_{17}N_2SBrCl$ ($M+H^+$): 358.9979; Found: 358.9974.



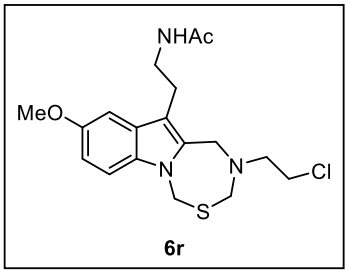
6p

8-bromo-2-(2-chloroethyl)-11-methyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6p): Yellow solid, m.p. 184-186 °C (58.0 mg, 81% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.32 (m, 2H), 7.20 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 5.38 – 5.08 (m, 2H), 4.68 (d, *J* = 13.6 Hz, 1H), 4.35 (dd, J_1 = 30.0 Hz, J_2 = 14.8 Hz, 2H), 4.06 (d, *J* = 16.0 Hz, 1H), 3.54 (t, *J* = 6.4 Hz, 2H), 2.70 (m, 2H), 2.28 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.6, 133.2, 126.9, 122.6, 120.4, 116.1, 112.9, 111.8, 63.7, 50.4, 48.2, 47.4, 41.7, 8.9. **HRMS (ESI)** calcd for $C_{14}H_{17}N_2SBrCl$ ($M+H^+$): 358.9979; Found: 358.9979.



6q

2-(2-chloroethyl)-7,11-dimethyl-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indole (6q): Light yellow solid, m.p. 132-135 °C (45.9 mg, 78% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.06 (d, *J* = 15.2 Hz, 1H), 5.31 (d, *J* = 15.2 Hz, 1H), 4.72 (d, *J* = 13.6 Hz, 1H), 4.34 (d, *J* = 17.6 Hz, 2H), 4.10 (d, *J* = 16.0 Hz, 1H), 3.55 (t, *J* = 6.0 Hz, 2H), 2.84 – 2.59 (m, 5H), 2.29 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 134.6, 132.8, 128.6, 126.1, 120.1, 119.5, 117.3, 113.1, 63.6, 50.4, 49.6, 48.0, 41.8, 20.9, 9.1. **HRMS (ESI)** calcd for $C_{15}H_{20}N_2SCl$ ($M+H^+$): 295.1030; Found: 295.1026.

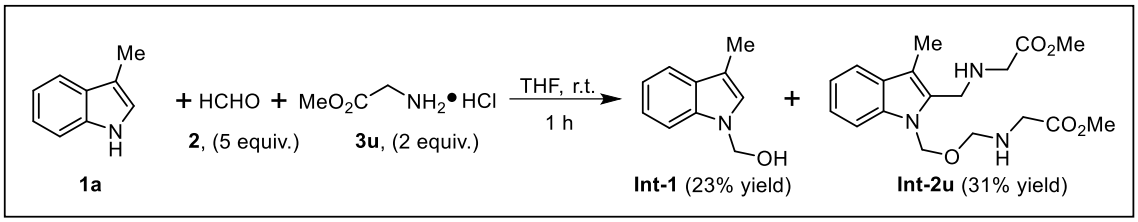


6r

***N*-(2-(2-(2-chloroethyl)-9-methoxy-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-11-yl)ethyl)acetamide (6r):** Light yellow solid, m.p. 144-146 °C (54.1 mg, 71% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.16 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.90 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 5.59 (s, 1H), 5.28 (m, 2H), 4.53 (dd, J_1 = 106.0 Hz, J_2 =12.4 Hz, 2H), 4.19 (dd, J_1 = 91.2 Hz, J_2 = 16.0 Hz, 2H), 3.86 (s, 3H), 3.60 – 3.32 (m, 4H), 2.93 (d, J = 41.6 Hz, 2H), 2.72 (s, 2H), 1.94 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.2, 154.3, 134.2, 131.2, 127.5, 113.5, 112.7, 109.8, 100.8, 63.7, 56.0, 50.4, 48.2, 47.6, 41.8, 40.5, 24.7, 23.5. **HRMS (ESI)** calcd for $C_{18}H_{24}N_3O_2SClNa$ ($M+Na^+$): 404.1170; Found: 404.1176.

5. Mechanistic Investigation

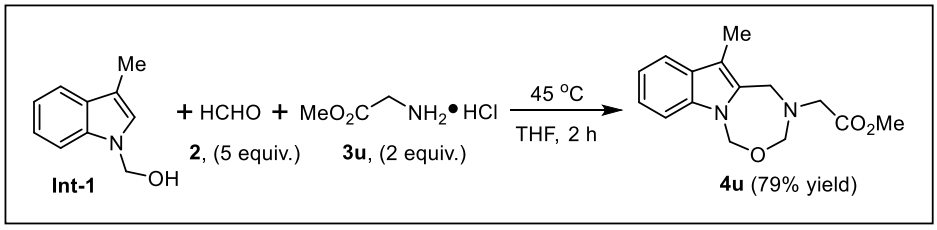
5.1 Procedure for the synthesis of Int-1 and Int-2u



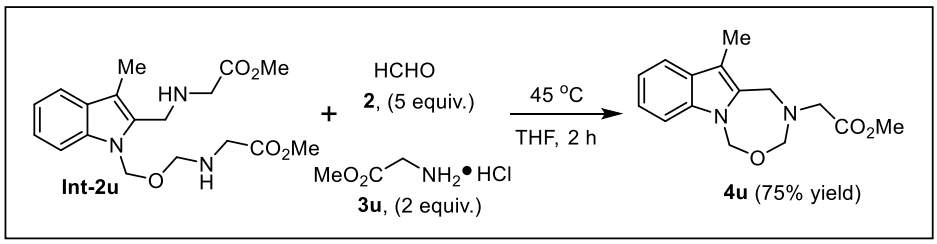
A mixture of **1a** (1 mmol), formaldehyde **2** (37% in water, 0.4 mL, 5 equiv.) and glycine methyl ester hydrochloride **3u** (2 mmol, 2 equiv.) in THF (10 mL) was stirred at room temperature for 1 h. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding products **Int-1** and **Int-2u**.

5.2 stepwise and crossover control reactions

We subjected the compounds **Int-1** and **Int-2u** to the stepwise control reactions respectively. As a result, formation of **4u** was observed in both reactions, which indicated that the **Int-1** and **Int-2u** were involved as intermediates for the formation of the desired product.



A mixture of **Int-1** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.) and glycine methyl ester hydrochloride **3u** (0.2 mmol, 2 equiv.) in THF (1.5 mL) was stirred at 45 °C for 2 h. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding indole product **4u** (21.6 mg, 79%).



A mixture of **Int-2u** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.) and glycine methyl ester hydrochloride **3u** (0.2 mmol, 2 equiv.) in THF (1.5 mL) was stirred at 45 °C for 2 h. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding indole product **4u** (20.5 mg, 75%).

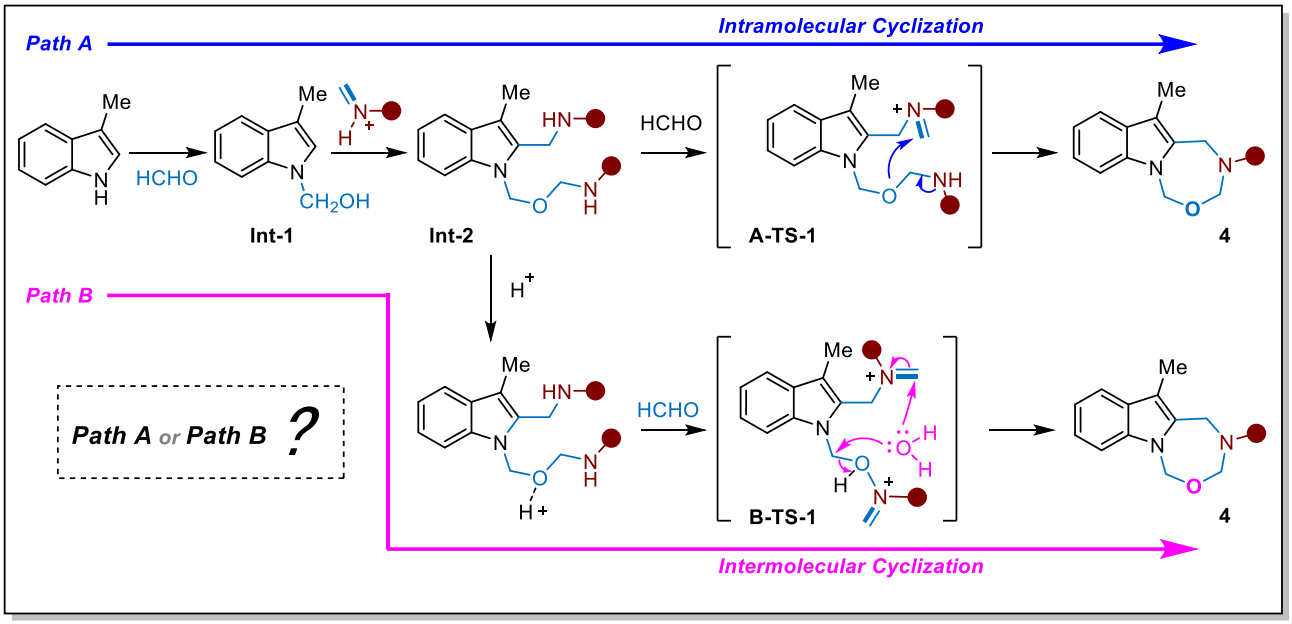
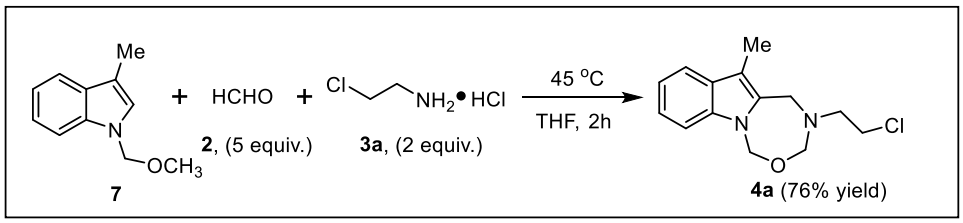


Figure S2. Proposed reaction pathways of 1,3,6-oxadiazepino [3,4-*a*] indoles.

Based on these observations, a plausible reaction mechanism is proposed (Figure S2). Intermediates **Int-1** and **Int-2** were subsequently formed via the Mannich alkylamination. At this stage, there are two possible reaction pathways to the final compound. ***Path A*** involves intramolecular cyclization: **A-TS-1** undergoes the retro-Mannich reaction and cyclization to furnish the **4**. In contrast, as described in ***Path B***: after forming **Int-2,** a hydrogen bonding induced the iminium formation at N position of indole. The subsequent iminium formation of **B-TS-1** engages in intermolecular cyclization with one molecule water to deliver the desired product **4**.

To gain a deeper understanding of the reaction mechanism, a series of control experiments were carried out to detect reaction process. We subjected the substare **7** to the cross-over reaction conditions respectively.

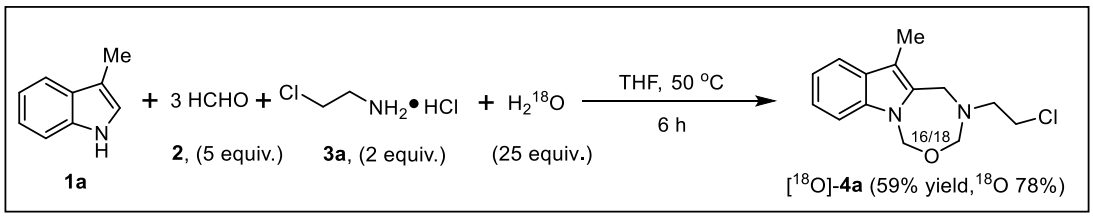


A mixture of **7** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.) and **3a** (0.2 mmol, 2 equiv.) in THF (1.5 mL) was stirred at 45 °C for 2 h. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **4a** (20.1 mg, 76%).

The result suggests that O-substituted indoles can be transformed into desired compounds as well, like that the presence of a methoxymethyl group (**7**) can promote the cyclization process. However, due to the difficulty in cleaving the C-O bond of methoxy group, the mechanism involved intramolecular cyclization (***Path A***) may not be applicable in this case, and an alternative mechanism ***Path B*** could complete the cyclization involving another molecule water is proposed as a better explanation.

5.3 Isotope-labeling reaction

To further gain insights into the mechanism, **1a** was also subjected to react with paraformaldehyde **2** and **3u** with an addition of O^{18}-labelled H_2O.



A mixture of **1a** (0.1 mmol), paraformaldehyde **2** (0.5 mmol, 5 equiv.), corresponding primary amine hydrochloride **3** (0.2 mmol, 2 equiv.) and $H_2{}^{18}O$ (97%, 2.5 mmol, 25 equiv.) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding indole product [^{18}O]-**4a** (15.7 mg,59%).

Subsequently, we conducted high-resolution mass spectrometry analysis on the products **4a** and [^{18}O]-**4a**. The results (Figure S3 and S4, Table S4 and S5) showed that the compound [^{18}O]-**4a** contains a significant amount of oxygen-18 isotopes (detected by abundance). Based on these observations, a plausible reaction mechanism is proposed (Figure S5).

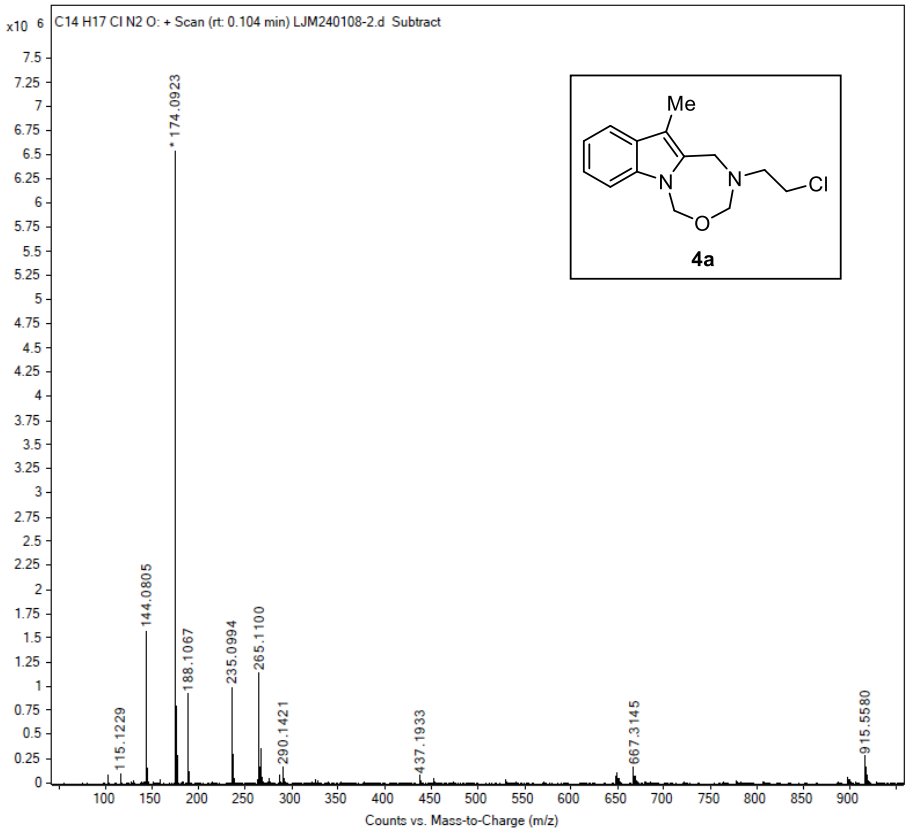


Figure S3. Full Mass-to-Charge spectra of **4a**

Table S4. Formula calculator results of **4a**

m/z	Formula	Measured Mass	Diff(ppm)	Abund	Abund%
265.1100	C14 H18 Cl N2 O	256.1102	0.17	1134957	100
Total				1134957	100

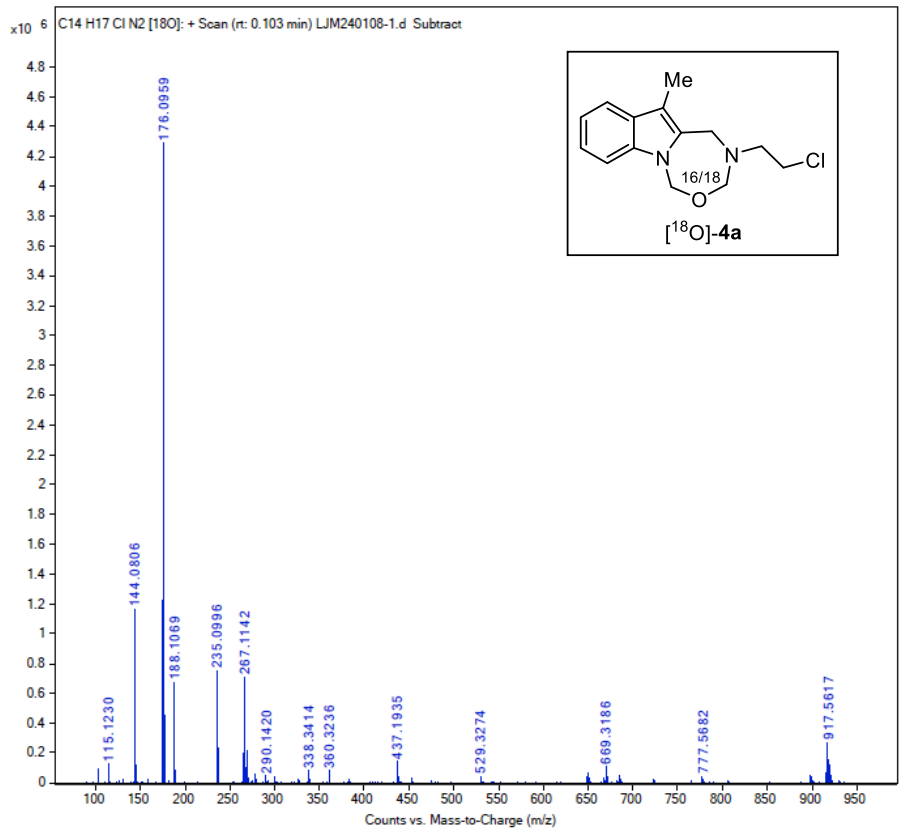


Figure S4. Full Mass-to-Charge spectra of [^{18}O]-**4a**

Table S5. Formula calculator results of [^{18}O]-**4a**

m/z	Formula	Measured Mass	Diff(ppm)	Abund	Abund%
265.1100	C14 H18 Cl N2 O	256.1102	0.17	196617.25	21.8
267.1142	C14 H18 Cl N2 [18O]	267.1145	0.52	705156.75	78.2
Total				9017774	100

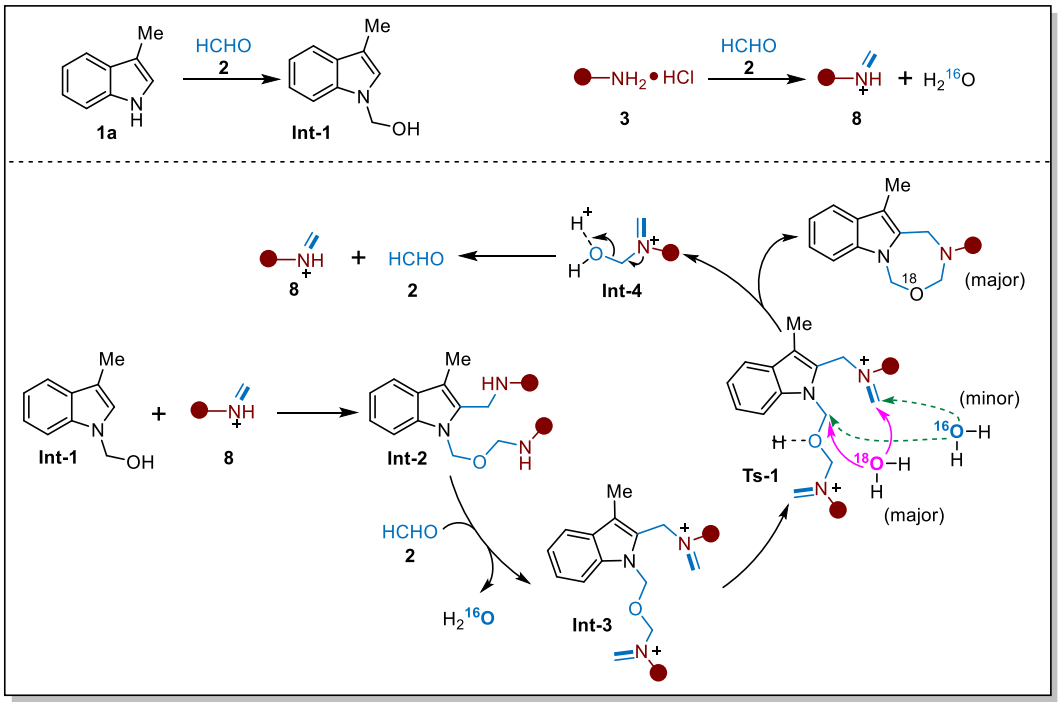
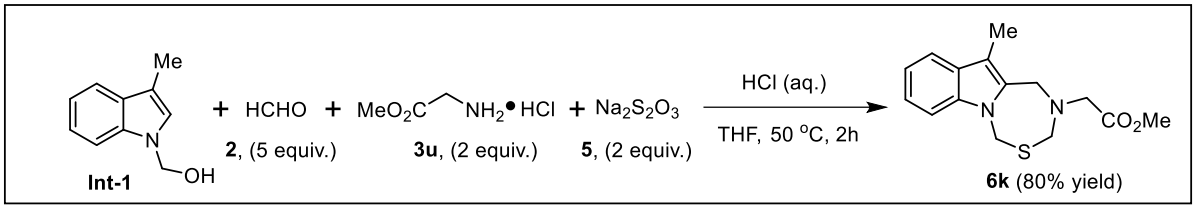
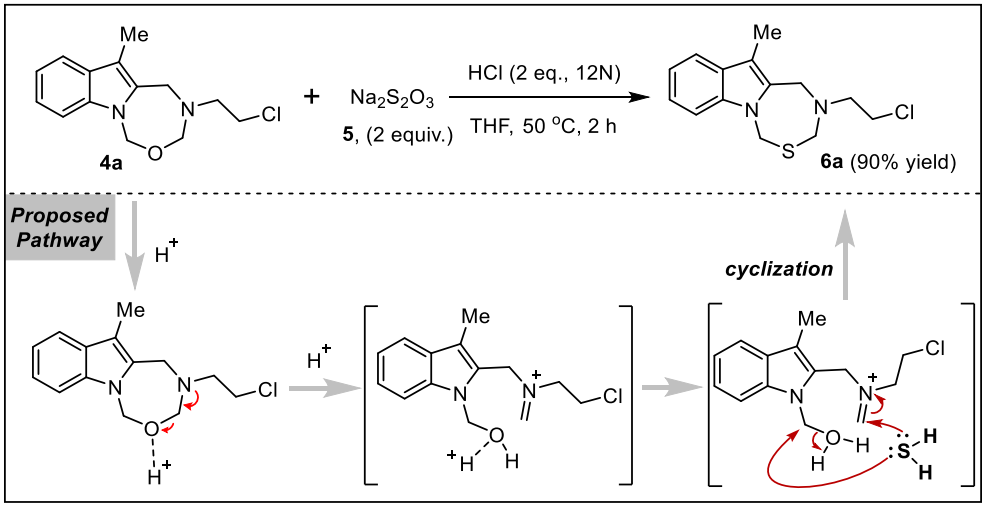


Figure S5. plausible reaction mechanism of Isotope-labeling reaction

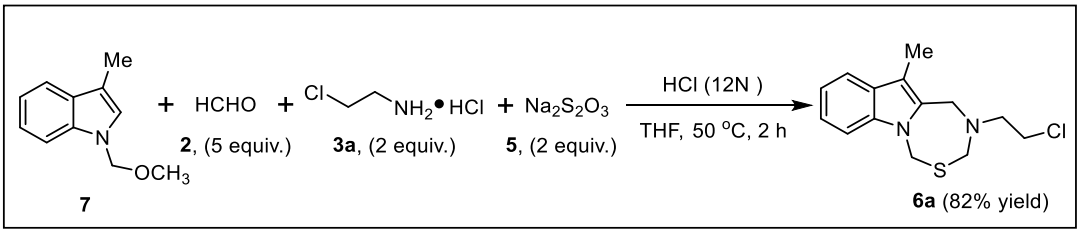
5.4 stepwise and crossover control reactions for 1,3,6-thiadiazepino [3,4-*a*] Indoles



A mixture of **Int-1** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), corresponding primary amine hydrochloride **3** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding indole product **6k** (23.2 mg, 80%).

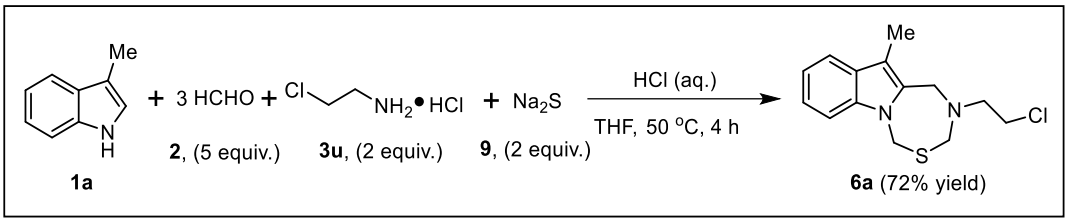


A mixture of **4a** (0.1 mmol), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding indole product **6a** (90% yield).



A mixture of **7** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), **3a** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1.5 mL) was stirred at 45 °C for 2 h. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined

organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **6a** (23.0 mg, 82%).



A mixture of **1a** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), **3a** (0.2 mmol, 2 equiv.), Na_2S **9** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1.5 mL) was stirred at 50 °C for 4 h. The reaction was quenched by saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **6a** (20.1 mg, 72%).

When $Na_2S_2O_3$ was replaced with Na_2S, the MCRs would deliver the same products, thus indicating H_2S was the real nucleophilic reagent.

In conclusion, our research team has carried out a series of experiments to uncover the underlying mechanism of 1,3,6-thiadiazepino [3,4-*a*] indoles. Our findings suggest that the reaction mechanism is strikingly similar to that of 1,3,6-oxadiazepino [3,4-*a*] indoles. Based on these results, we have developed a compelling reaction mechanism (Figure S6).

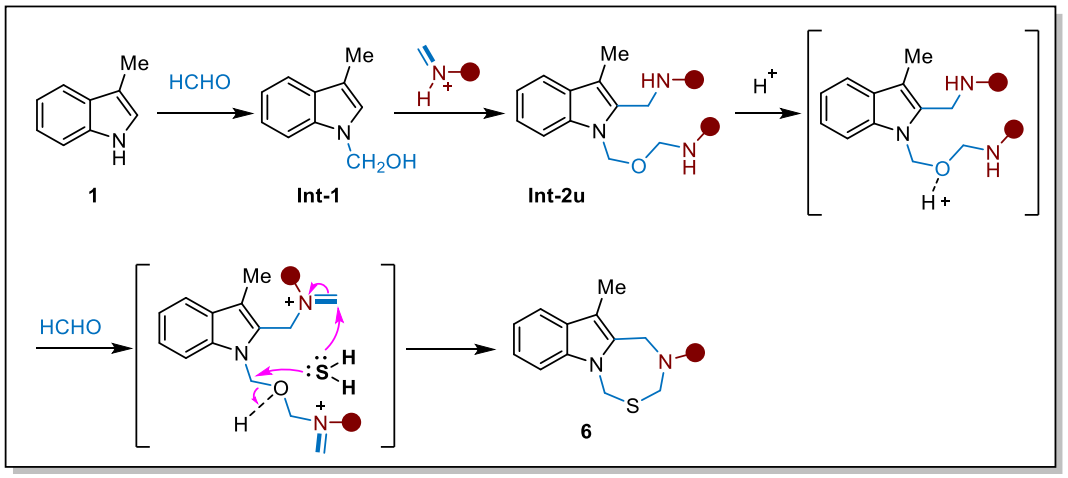
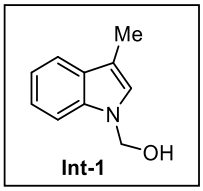


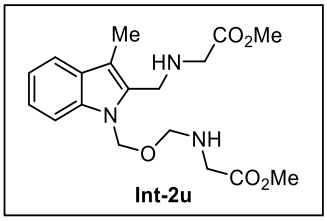
Figure S6. Proposed reaction pathway of 1,3,6-thiadiazepino [3,4-*a*] indoles.

5.5 Characterization of Corresponding Compounds



Int-1

(3-methyl-1*H*-indol-1-yl)methanol (Int-1): Colorless gel. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.21 – 7.14 (m, 1H), 6.90 (s, 1H), 5.49 (s, 2H), 2.78 (s, 1H), 2.33 (d, *J* = 1.2 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.0, 129.7, 124.9, 122.2, 119.8, 119.3, 112.3, 109.3, 69.5, 9.6. **HRMS (ESI)** calcd for $C_{10}H_{12}NO$ ($M+H^+$): 162.0913; Found: 162.0910.



Int-2u

methyl ((1-((((2-methoxy-2-oxoethyl)amino)methoxy)methyl)-3-methyl-1*H*-indol-2-yl)methyl)glycinate (Int-2u): Colorless gel. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.21 (q, *J* = 8.0 Hz, 2H), 7.15 – 7.08 (m, 1H), 5.34 (s, 2H), 4.24 (s, 2H), 4.21 (s, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.41 (s, 2H), 3.22 (s, 2H), 2.28 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.2, 137.2, 133.2, 127.8, 122.1, 119.1, 119.0, 110.3, 108.1, 78.8, 61.9, 54.6, 51.9, 50.4, 47.9, 8.6.

6. Late-stage functionalization

6.1 antitumor activities evaluation

6.1.1 Cell Lines and Cell Culture

Bel-7402, MDA-MB-231, A549, HCT116, Ges-1 and 3T3 cell lines were originally obtained from FuHeng Biology (Shanghai, China). Bel-7402 was cultured in RPMI-1640 medium (Sigma-Aldrich). MDA-MB-231, A549, HCT116, Ges-1 and 3T3 cells were cultured in DMEM medium (Sigma-Aldrich). All media were supplemented with 10% fetal bovine serum (FBS, Every Green). All growth media were supplemented with 1% penicillin−streptomycin−glutamine (Gibco). All cells were propagated at 1:3 dilutions at 37 °C in 5% CO_2 humid atmosphere. Authentication of cell lines was confirmed by short tandem repeating (STR) profiling.

6.1.2 Cell Viability and Cell Proliferation Assays

The 3-(4,5-Dimethy-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) colorimetric assay was utilized to evaluate cell proliferation. Bel-7402, MDA-MB-231, A549, HCT116, Ges-1 and 3T3 cells were seeded in 96-well plates at 5000 cells per well. After incubation at 37 ℃ for 24 h, cells were treated with vehicle (dimethyl sulfoxide, DMSO) or indicated compounds for 72 h. Afterward, 10 μL of 5 mg/mL MTT solution was added into each well and further incubated at 37 ℃ for another 4 h. Then 100 μL of triplex 10% SDS-0.1% HCl-PBS solutions was added to dissolve the formazan deposited on the bottom of the plates, and the plates were further incubated at 37 °C overnight. The absorbance at 570 nm was measured with the reference wavelength at 650 nm using a Spectrophotometer (Multiskan go, Thermo). IC_{50} values were calculated using log (inhibitor) vs. normalized response function of GraphPad Prism 8 software.

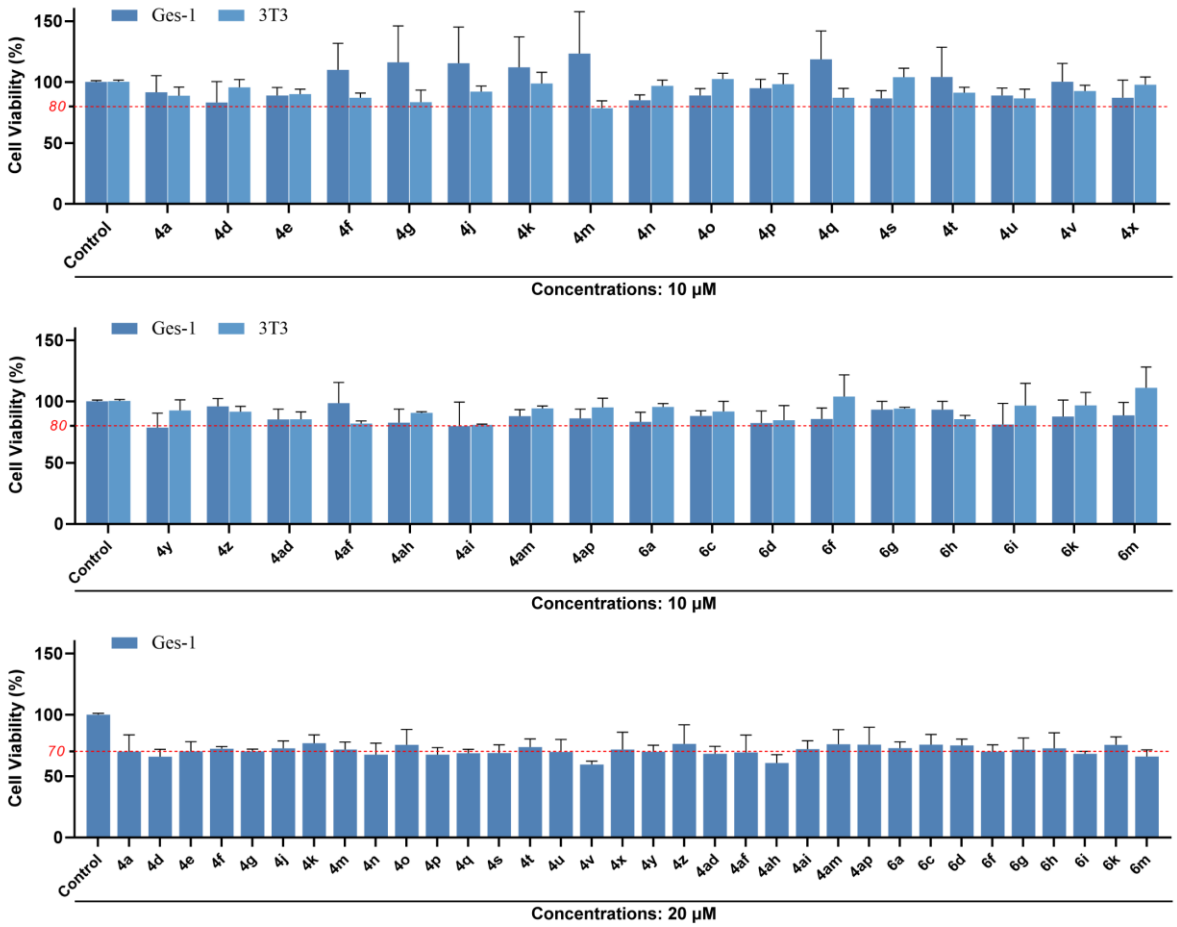


Figure S7. Cytotoxicity evaluation of selected compounds in Ges-1 and 3T3 cell.

A

Concentrations: 10 μM

	BEL7402	MDA-MB-231	A549	HCT116
4a	32	22	31	15
4d	37	23	20	41
4e	35	16	7	26
4f	29	20	32	28
4g	28	19	27	21
4j	39	18	24	46
4k	36	14	40	29
4m	28	14	17	22
4n	32	1	24	11
4o	38	19	17	29
4p	36	30	27	32
4q	25	20	26	26
4s	45	36	13	24
4t	30	12	16	25
4u	36	20	31	15
4v	51	28	21	9
4x	29	19	21	19
4y	49	20	21	19
4z	38	14	16	18
4ad	34	21	20	11
4af	38	27	23	18
4ah	54	28	8	19
4ai	35	9	3	12
4am	27	25	18	18
4ap	33	18	28	29
6a	57	36	16	24
6c	55	18	17	20
6d	59	18	14	19
6f	45	23	15	24
6g	51	47	79	16
6h	43	29	71	19
6i	60	30	45	26
6k	65	14	14	24
6m	42	14	13	24

Inhibiton Rate (%) 0 20 40 60 80 100

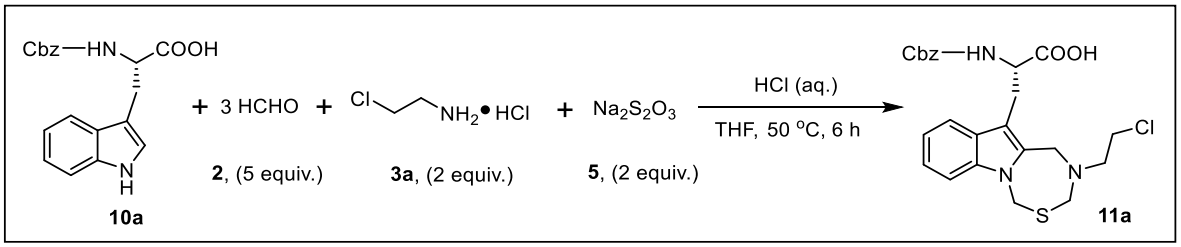
B

Compound	BEL7402 cell inhition IC_{50} (μM)
4ah	16.5 ± 0.20
4v	23.9 ± 2.75
6k	12.6 ± 3.84
6d	16.1± 2.28
6i	13.5 ±0.24
6g	13.2 ± 0.82

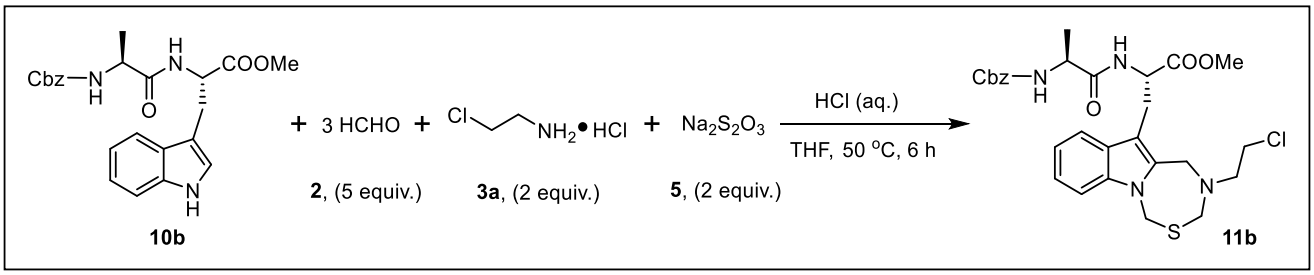
Compound	A549 cell inhition IC_{50} (μM)
6g	9.6± 0.48
6h	11.7 ± 0.13

Figure S8. Anticancer profiling of the corresponding compounds.

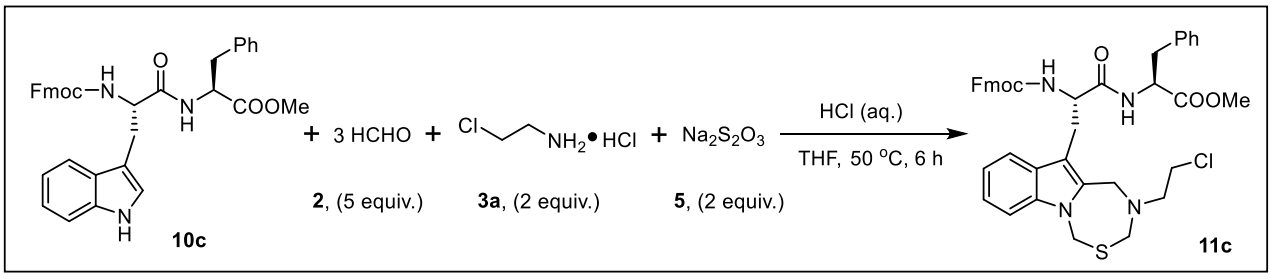
6.2 late-stage modifications of tryptophan-containing peptides



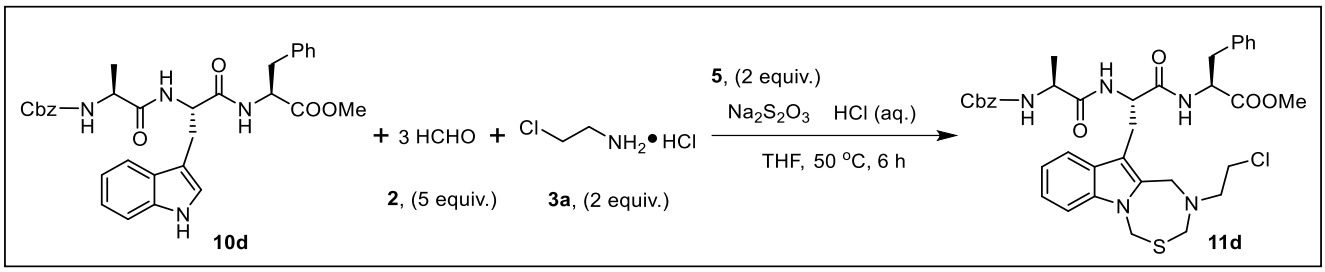
A mixture of Cbz-Trp-OH **10a** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), **3a** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$ to neutral. The aqueous layer was extracted with DCM (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **11a**.



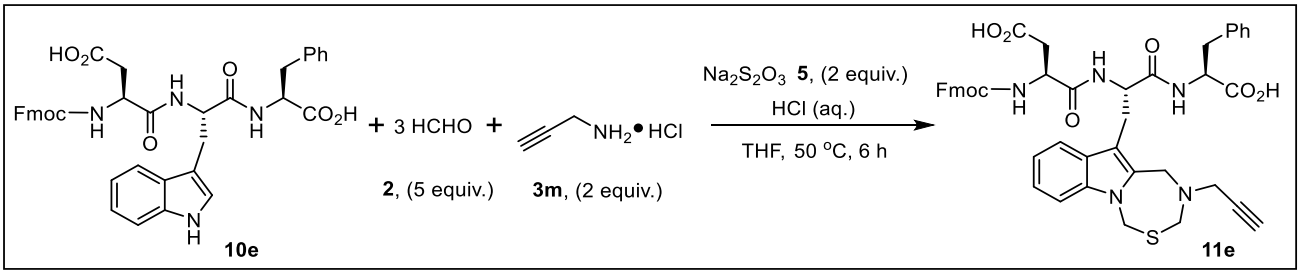
A mixture of Cbz-Ala-Trp-OMe **10b** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), **3a** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$ to neutral. The aqueous layer was extracted with DCM (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **11b**.



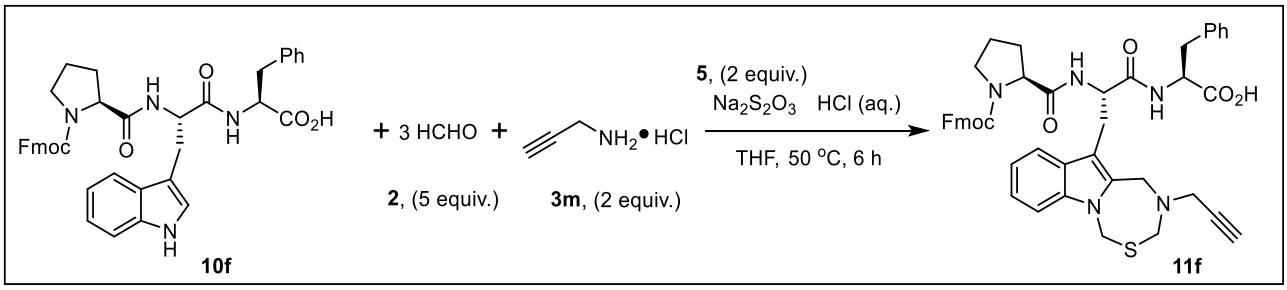
A mixture of Fmoc-Trp-Phe-OMe **10c** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), **3a** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$ to neutral. The aqueous layer was extracted with DCM (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **11c**.



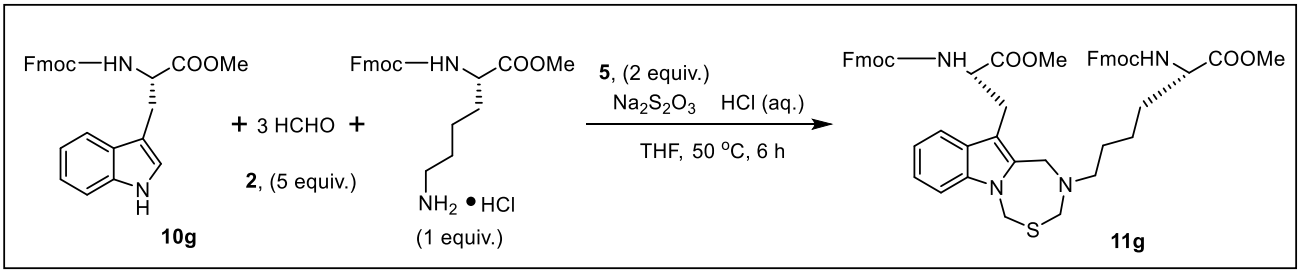
A mixture of Cbz-Ala-Trp-Phe-OMe **10d** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), **3a** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$ to neutral. The aqueous layer was extracted with DCM (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **11d**.



A mixture of Fmoc-Asn-Trp-Phe-OH **10e** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), propargylamine hydrochloride **3m** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$ to neutral. The aqueous layer was extracted with DCM (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by HPLC to give corresponding product **11e**.

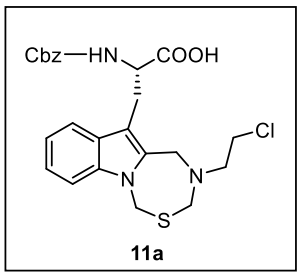


A mixture of Fmoc-Pro-Trp-Phe-OH **10f** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), propargylamine hydrochloride **3m** (0.2 mmol, 2 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$ to neutral. The aqueous layer was extracted with DCM (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by HPLC to give corresponding indole product **11f**.

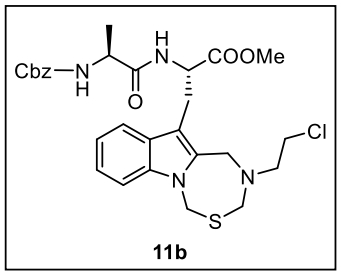


A mixture of Fmoc-Trp-OMe **10g** (0.1 mmol), formaldehyde **2** (37% in water, 0.04 mL, 5 equiv.), Fmoc-Lys-OMe hydrochloride (0.1 mmol, 1 equiv.), $Na_2S_2O_3$ **5** (0.2 mmol) and 12N HCl (0.2 mmol) in THF (1 mL) was stirred at 50 °C until the reaction was completed. The reaction was quenched by saturated aqueous $NaHCO_3$ to neutral. The aqueous layer was extracted with DCM (three times), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography to give corresponding product **11g**.

6.3 Characterization of Corresponding Compounds

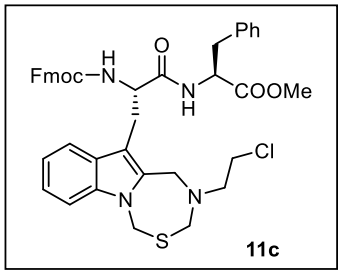


(*S*)-2-(((benzyloxy)carbonyl)amino)-3-(2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-11-yl)propanoic acid (11a): White solid, m.p. 104-106 °C (32.1 mg, 66% yield). **^{1}H NMR (400 MHz, DMSO)** δ 12.79 (s, 1H), 7.85 – 6.61 (m, 10H), 5.55 (m, 2H), 5.05 – 4.65 (m, 3H), 4.22 (m, 4H), 3.72 – 3.21 (m, 4H), 2.55 (s, 2H). **^{13}C NMR (101 MHz, DMSO)** δ 174.1, 156.6, 137.4, 136.4, 135.4, 128.8, 128.3, 128.1, 127.1, 122.3, 119.6, 118.7, 113.0, 110.2, 65.9, 63.0, 55.6, 50.8, 47.5, 46.7, 42.4, 26.7. **HRMS (ESI)** calcd for $C_{24}H_{27}N_3O_4ClS$ ($M+H^+$): 488.1405; Found: 488.1397.

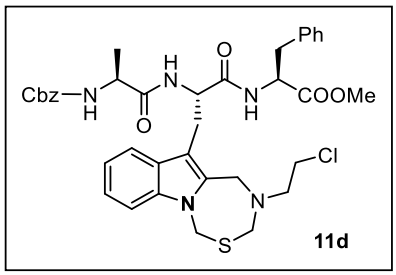


methyl (*S*)-2-((*S*)-2-(((benzyloxy)carbonyl)amino)propanamido)-3-(2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6] thiadiazepino [3,4-*a*]indol-11-yl)propanoate (11b): White solid, m.p. 162-164 °C (33.1 mg, 58% yield). **^{1}H NMR (400 MHz, DMSO)** δ 8.32 (d, *J* = 16.4 Hz, 1H), 7.71 – 6.86 (m, 10H), 5.84 – 5.26 (m, 2H), 5.19 – 4.66 (m, 3H), 4.59 – 3.97 (m, 5H), 3.89 – 2.90 (m, 8H), 2.54 (s, 1H), 1.19 (s, 3H). **^{13}C NMR (101 MHz, DMSO)** δ

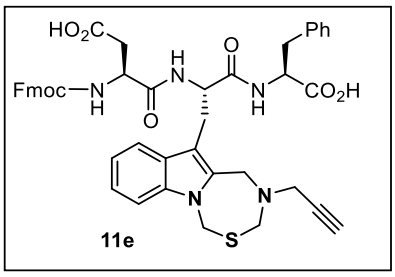
173.1, 172.6, 172.4, 156.1, 137.5, 136.2, 135.5, 128.8, 128.3, 127.1, 122.3, 119.6, 118.9, 118.6, 112.1, 111.2, 110.2, 65.9, 62.9, 62.4, 53.8, 53.5, 52.5, 52.3, 50.7, 50.5, 50.3, 47.4, 47.1, 46.8, 42.5, 27.3, 26.8, 18.6. **HRMS (ESI)** calcd for $C_{28}H_{34}N_4O_5ClS$ ($M+H^+$): 573.1933; Found: 573.1926.



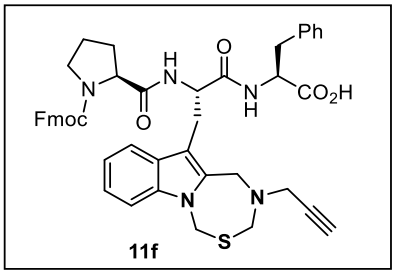
methyl ((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-11-yl)propanoyl)-L-phenylalaninate (11c): White solid, m.p. 152-154 ℃ (46.3 mg, 63% yield). **^{1}H NMR (400 MHz, DMSO)** δ 8.38 (d, *J* = 6.8 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.75 – 7.58 (m, 3H), 7.56 – 7.08 (m, 12H), 7.04 (d, *J* = 7.2 Hz, 1H), 5.52 (m, 2H), 4.94 – 4.64 (m, 1H), 4.63 – 3.94 (m, 8H), 3.83 – 3.47 (m, 5H), 3.22 – 2.66 (m, 4H), 2.53 (s, 2H). **^{13}C NMR (101 MHz, DMSO)** δ 172.2, 172.1, 156.1, 144.3, 141.2, 137.5, 136.3, 135.5, 129.6, 129.6, 128.7, 128.1, 127.6, 127.2, 127.0, 125.8, 125.7, 122.2, 120.6, 119.5, 112.5, 110.0, 66.1, 62.8, 56.1, 54.0, 52.4, 50.7, 47.1, 46.7, 42.5, 37.1, 27.7. **HRMS (ESI)** calcd for $C_{41}H_{42}N_4O_5ClS$ ($M+H^+$): 737.2559; Found: 737.2552.



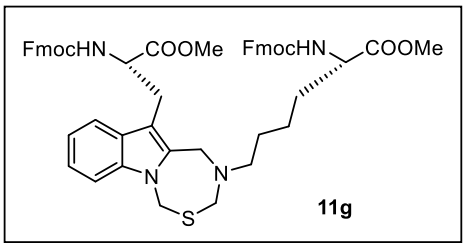
methyl ((*S*)-2-((*S*)-2-(((benzyloxy)carbonyl)amino)propanamido)-3-(2-(2-chloroethyl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino [3,4-*a*]indol-11-yl)propanoyl)-L-phenylalaninate (11d): White solid, m.p. 155-157 ℃ (38.1 mg, 53% yield). **^{1}H NMR (400 MHz, DMSO)** δ 8.45 – 8.23 (m, 1H), 7.96 (d, *J* = 6.0 Hz, 1H), 7.77 – 6.94 (m, 15H), 5.74 – 5.24 (m, 2H), 5.10 – 4.68 (m, 3H), 4.59 – 3.91 (m, 6H), 3.66 (s, 2H), 3.53 (s, 3H), 3.21 – 2.90 (m, 3H), 2.88 – 2.74 (m, 1H), 2.54 (d, *J* = 6.4 Hz, 2H), 1.13 (m, 3H). **^{13}C NMR (101 MHz, DMSO)** δ 172.5, 172.0, 156.1, 137.5, 136.3, 135.6, 135.2, 129.6, 129.5, 128.8, 128.7, 128.3, 127.3, 127.0, 122.1, 119.4, 112.3, 112.0, 109.9, 65.9, 63.0, 62.5, 54.0, 52.3, 50.7, 50.6, 47.2, 46.7, 42.5, 37.1, 27.7, 18.7. **HRMS (ESI)** calcd for $C_{37}H_{43}N_5O_6ClS$ ($M+H^+$): 720.2617; Found: 720.2619.



(5*S*,8*S*,11*S*)-11-benzyl-5-(carboxymethyl)-1-(9*H*-fluoren-9-yl)-3,6,9-trioxo-8-((2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-a]indol-11-yl)methyl)-2-oxa-4,7,10-triazadodecan-12-oic acid (11e): Colorless gel (33.4 mg, 41% yield). **^{1}H NMR (500 MHz, DMSO)** δ 8.62 – 6.93 (m, 20H), 6.93 – 5.72 (m, 3H), 5.49 (m, 2H), 5.27 – 3.68 (m, 10H), 3.36 – 2.85 (m, 6H), 2.84 – 2.53 (m, 1H), 2.44 (t, *J* = 10.0 Hz, 1H). **^{13}C NMR (126 MHz, DMSO)** δ 173.0, 172.3, 171.6, 171.0, 156.3, 144.3, 144.2, 141.2, 137.8, 136.3, 129.7, 129.5, 128.6, 128.1, 127.6, 126.9, 125.8, 122.2, 120.6, 119.5, 116.9, 114.6, 109.9, 80.4, 76.3, 66.3, 61.9, 56.5, 54.3, 53.9, 51.9, 47.1, 46.5, 37.2, 36.7, 27.6. **HRMS (ESI)** calcd for $C_{45}H_{44}N_5O_8S$ ($M+H^+$): 814.2905; Found: 814.2917.



((*S*)-2-((*S*)-1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)pyrrolidine-2-carboxamido)-3-(2-(prop-2-yn-1-yl)-2,3-dihydro-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-a]indol-11-yl)propanoyl)-L-phenylalanine (11f): Colorless gel (57.2 mg, 72% yield). **^{1}H NMR (500 MHz, DMSO)** δ 8.35 – 6.72 (m, 19H), 6.66 (s, 2H), 5.88 – 4.92 (m, 2H), 4.86 – 3.84 (m, 9H), 3.82 – 2.57 (m, 9H), 2.19 – 1.84 (m, 1H), 1.78 – 1.41 (m, 3H). **^{13}C NMR (126 MHz, DMSO)** δ 173.0, 173.0, 171.0, 158.9, 158.6, 154.7, 154.4, 144.4, 144.2, 141.2, 141.0, 137.9, 136.1, 133.8, 129.5, 128.6, 128.5, 128.2, 127.6, 126.8, 125.6, 122.2, 120.6, 120.5, 119.4, 116.9, 109.7, 80.4, 76.0, 74.5, 67.4, 67.1, 62.0, 59.8, 54.3, 54.0, 53.8, 47.7, 47.1, 47.0, 46.6, 37.1, 31.8, 27.9, 24.2, 23.3. **HRMS (ESI)** calcd for $C_{46}H_{46}N_5O_6S$ ($M+H^+$): 796.3163; Found: 796.3164.



methyl (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-6-(11-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl)-1*H*,5*H*-[1,3,6]thiadiazepino[3,4-*a*]indol-2(3*H*)-yl)hexanoate (11g): White solid, m.p. 128-130 °C (36.5 mg, 41% yield). **^{1}H NMR (400 MHz, DMSO)** δ 8.09 – 7.21 (m, 20H), 7.18 – 6.98 (m, 2H), 5.71 – 5.25 (m, 2H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.54 – 3.81 (m, 11H), 3.74 – 3.41 (m, 6H), 3.31 – 2.91 (m, 2H), 2.18 (s, 2H), 1.79 – 1.48 (m, 2H), 1.46 – 1.19 (m, 4H). **^{13}C NMR (101 MHz,**

DMSO) δ 172.9, 172.5, 156.1, 156.0, 143.8, 143.7, 140.7, 135.7, 135.1, 127.6, 127.0, 125.2, 124.8, 121.6, 120.1, 119.0, 118.5, 118.1, 111.8, 111.1, 109.6, 65.8, 65.6, 62.4, 62.1, 55.4, 55.2, 53.8, 52.1, 51.8, 47.8, 46.6, 46.6, 46.4, 30.5, 26.1, 23.3. **HRMS (ESI)** calcd for $C_{52}H_{53}N_4O_8S$ ($M+H^+$): 893.3579; Found: 893.3583.

7. X-ray Crystallographic Data

7.1 X-Ray crystal structure of 4a

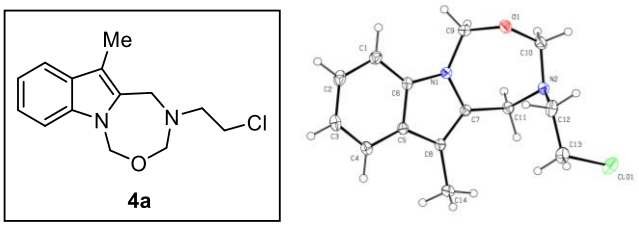


Figure S9. X-Ray Crystallography of **4a**.

A single crystal of **4a** was obtained through slow evaporation from its solution in EtOAc. The structure and absolute configuration of **4a** was then determined by x-ray crystallographic analysis (CCDC No: 2243493).

Table S6. Crystal data and structure refinement for **4a**.

Compound	4a
CCDC code	2243493
Empirical formula	$C_{14}H_{17}ClN_2O$
Formula weight	264.74
Temperature/K	170.0
Crystal system	triclinic
Space group	P-1
a/Å	4.9523(2)
b/Å	9.0139(4)
c/Å	14.5673(7)
α/°	100.404(2)
β/°	92.408(2)
γ/°	94.706(2)
Volume/Å^3	636.36(5)
Z	2
ρ_{calc}g/cm^3	1.382
μ/mm^{-1}	0.290
F(000)	280.0
Crystal size/mm^3	0.48 × 0.1 × 0.06
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.614 to 54.248

Index ranges	$-6 \le h \le 6, -11 \le k \le 11, -18 \le l \le 18$
Reflections collected	8009
Independent reflections	2817 [R_{int} = 0.0240, R_{sigma} = 0.0352]
Data/restraints/parameters	2817/0/164
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0341, wR_2 = 0.0874
Final R indexes [all data]	R_1 = 0.0368, wR_2 = 0.0900
Largest diff. peak/hole / e $Å^{-3}$	0.23/-0.30

7.2 X-Ray crystal structure of 4s

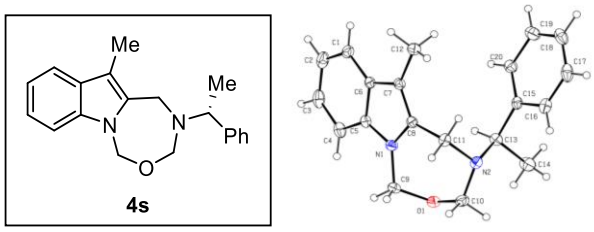


Figure S10. X-Ray Crystallography of **4s**.

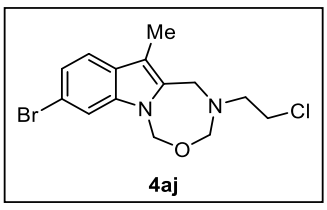
A single crystal of **4s** was obtained through slow evaporation from its solution in EtOAc. The structure and absolute configuration of **4s** was then determined by x-ray crystallographic analysis (CCDC No: 2243494).

Table S7. Crystal data and structure refinement for **4s**.

Compound	4s
CCDC code	2243494
Empirical formula	$C_{20}H_{22}N_2O$
Formula weight	306.39
Temperature/K	170.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.3944(8)
b/Å	9.3978(8)

c/Å	20.419(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1610.8(3)
Z	4
ρ_{calc}g/cm^3	1.263
μ/mm^{-1}	0.611
F(000)	656.0
Crystal size/mm^3	0.45 × 0.36 × 0.3
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.66 to 136.354
Index ranges	-9 ≤ h ≤ 10, -11 ≤ k ≤ 11, -24 ≤ l ≤ 24
Reflections collected	18171
Independent reflections	2945 [R_{int} = 0.0255, R_{sigma} = 0.0174]
Data/restraints/parameters	2945/0/210
Goodness-of-fit on F^2	1.187
Final R indexes [I>=2σ (I)]	R_1 = 0.0431, wR_2 = 0.1051
Final R indexes [all data]	R_1 = 0.0432, wR_2 = 0.1052
Largest diff. peak/hole / e Å^{-3}	0.27/-0.54
Flack parameter	0.03(4)

7.3 X-Ray crystal structure of 4aj



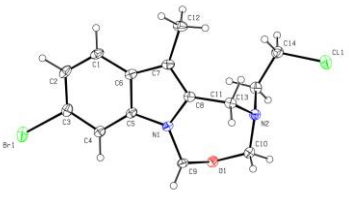


Figure S11. X-Ray Crystallography of **4aj**.

A single crystal of **4aj** was obtained through slow evaporation from its solution in EtOAc. The structure and absolute configuration of **4aj** was then determined by x-ray crystallographic analysis (CCDC No: 2243505).

Table S8. Crystal data and structure refinement for **4aj**.

Compound	4aj
CCDC code	2243505
Empirical formula	$C_{14}H_{15}BrClN_2O$
Formula weight	342.64
Temperature/K	170.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.4362(6)
b/Å	11.6969(6)
c/Å	10.4292(6)
α/°	90
β/°	96.360(2)
γ/°	90
Volume/Å^3	1386.51(13)
Z	4
ρ_{calc}g/cm^3	1.641
μ/mm^{-1}	3.150
F(000)	692.0
Crystal size/mm^3	0.38 × 0.26 × 0.19
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.998 to 50.682
Index ranges	-13 ≤ h ≤ 13, -14 ≤ k ≤ 14, -12 ≤ l ≤ 12
Reflections collected	28315
Independent reflections	2541 [R_{int} = 0.0434, R_{sigma} = 0.0226]
Data/restraints/parameters	2541/0/173
Goodness-of-fit on F^2	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0281, wR_2 = 0.0707
Final R indexes [all	R_1 = 0.0302, wR_2 = 0.0722

data]	
Largest diff. peak/hole / e Å^{-3}	0.82/-0.65

7.4 X-Ray crystal structure of 6a

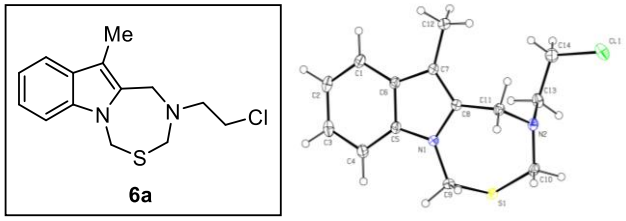


Figure S12. X-Ray Crystallography of **6a**.

A single crystal of **6a** was obtained through slow evaporation from its solution in EtOAc. The structure and absolute configuration of **5f** was then determined by x-ray crystallographic analysis (CCDC No: 2249556).

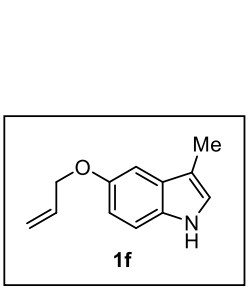
Table S9. Crystal data and structure refinement for **5f**.

Compound	6a
CCDC code	2249556
Empirical formula	$C_{14}H_{17}ClN_2S$
Formula weight	280.80
Temperature/K	170.00
Crystal system	triclinic
Space group	P-1
a/Å	5.0074(4)
b/Å	9.0205(7)
c/Å	15.1568(13)
α/°	80.365(3)
β/°	89.851(3)
γ/°	84.042(3)
Volume/Å^3	671.24(9)
Z	2
ρ_{calc}g/cm^3	1.389
μ/mm^{-1}	2.528
F(000)	296.0
Crystal size/mm^3	0.2 × 0.05 × 0.03
Radiation	GaKα (λ = 1.34139)

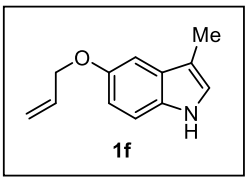
2Θ range for data collection/°	5.146 to 121.152
Index ranges	$-6 \leq h \leq 6$, $-11 \leq k \leq 11$, $-19 \leq l \leq 19$
Reflections collected	11083
Independent reflections	3025 [R_{int} = 0.0483, R_{sigma} = 0.0545]
Data/restraints/parameters	3025/0/164
Goodness-of-fit on F^2	1.140
Final R indexes [I>=2σ (I)]	R_1 = 0.0491, wR_2 = 0.1250
Final R indexes [all data]	R_1 = 0.0539, wR_2 = 0.1273
Largest diff. peak/hole / e $Å^{-3}$	0.47/-0.31

8. Copies of NMR Spectra

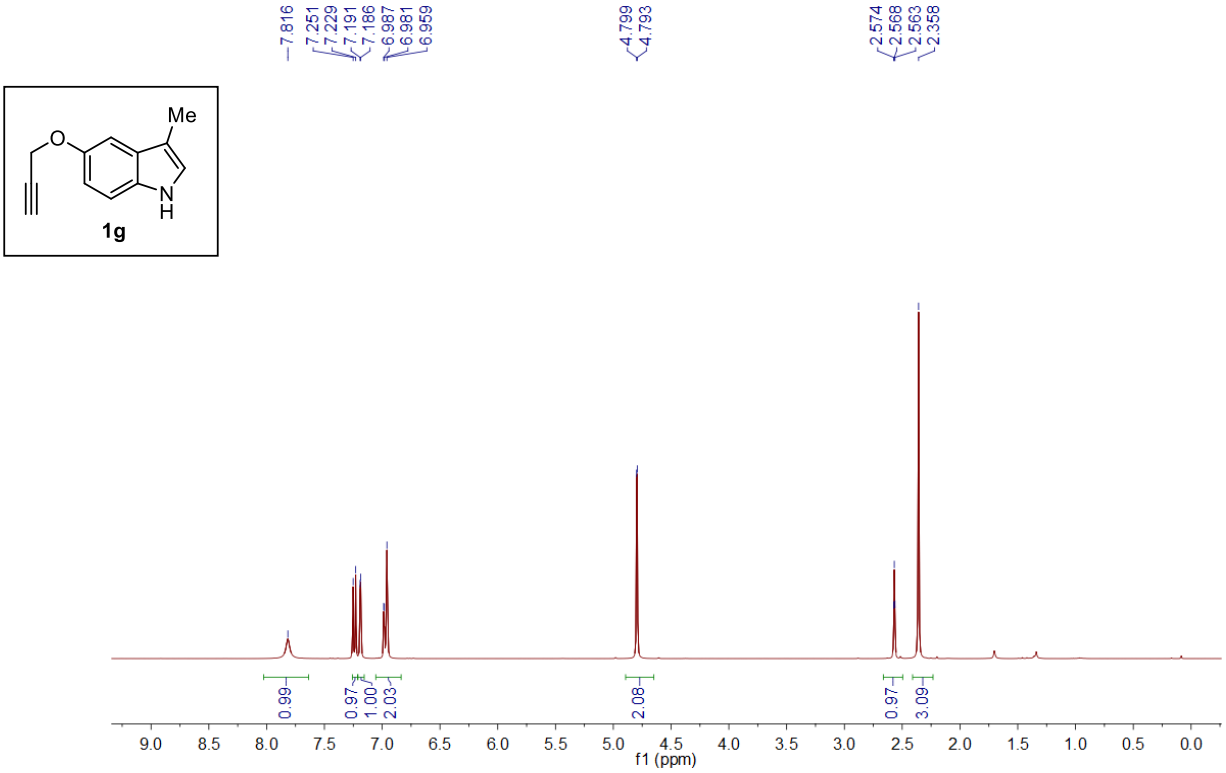
^{1}H-NMR spectrum of compound **1f** (400 MHz, $CDCl_3$)



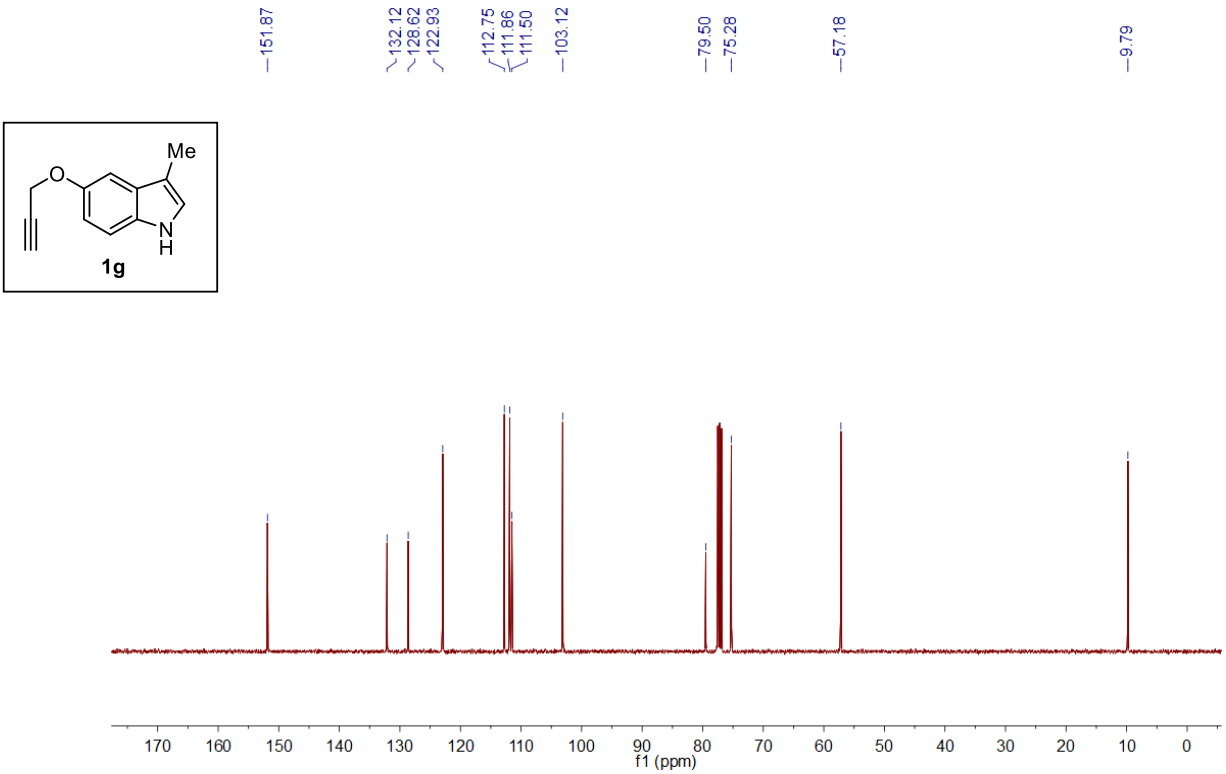
^{13}C-NMR spectrum of compound **1f** (101 MHz, $CDCl_3$)



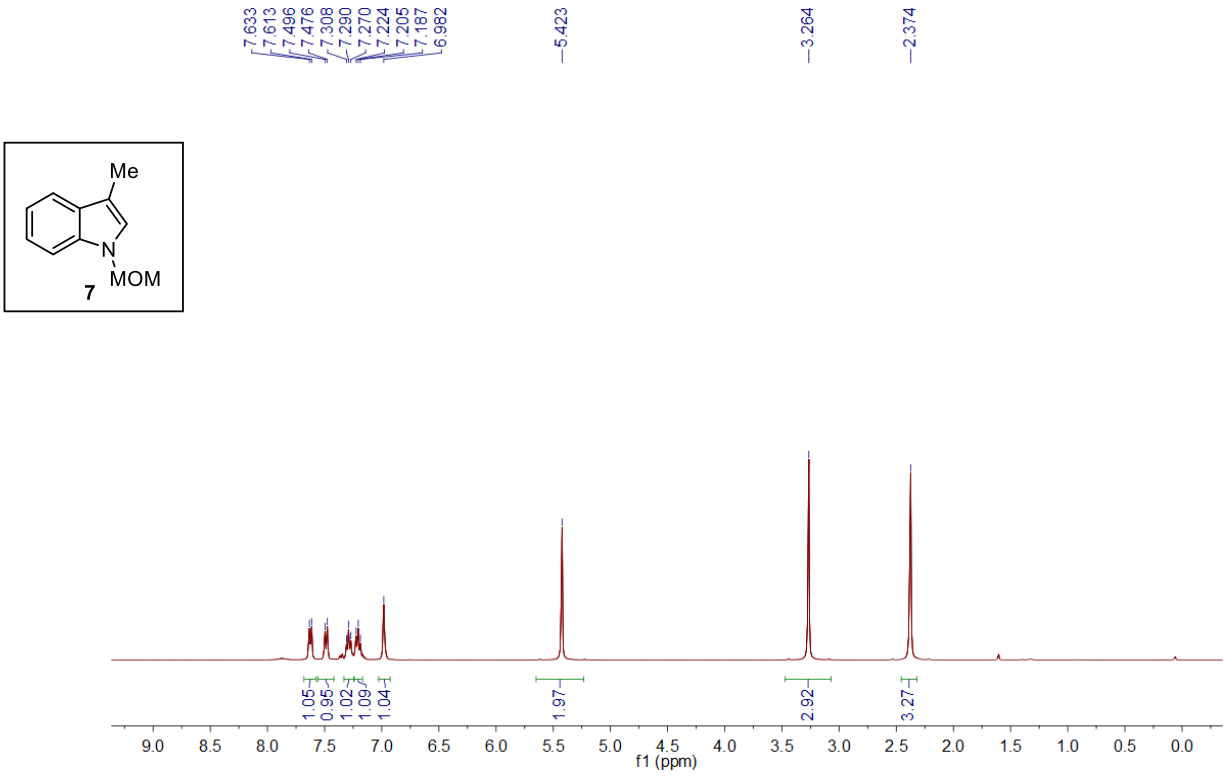
^{1}H-NMR spectrum of compound **1g** (400 MHz, $CDCl_3$)



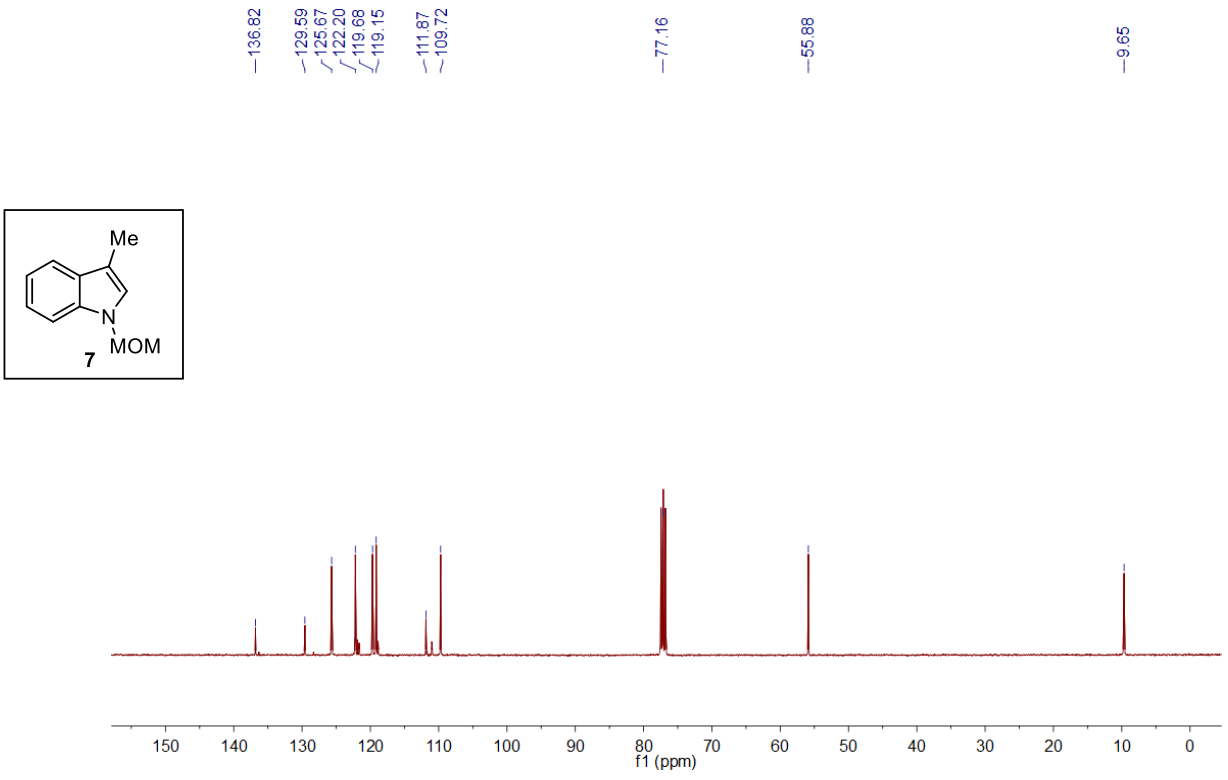
^{13}C-NMR spectrum of compound **1g** (101 MHz, $CDCl_3$)



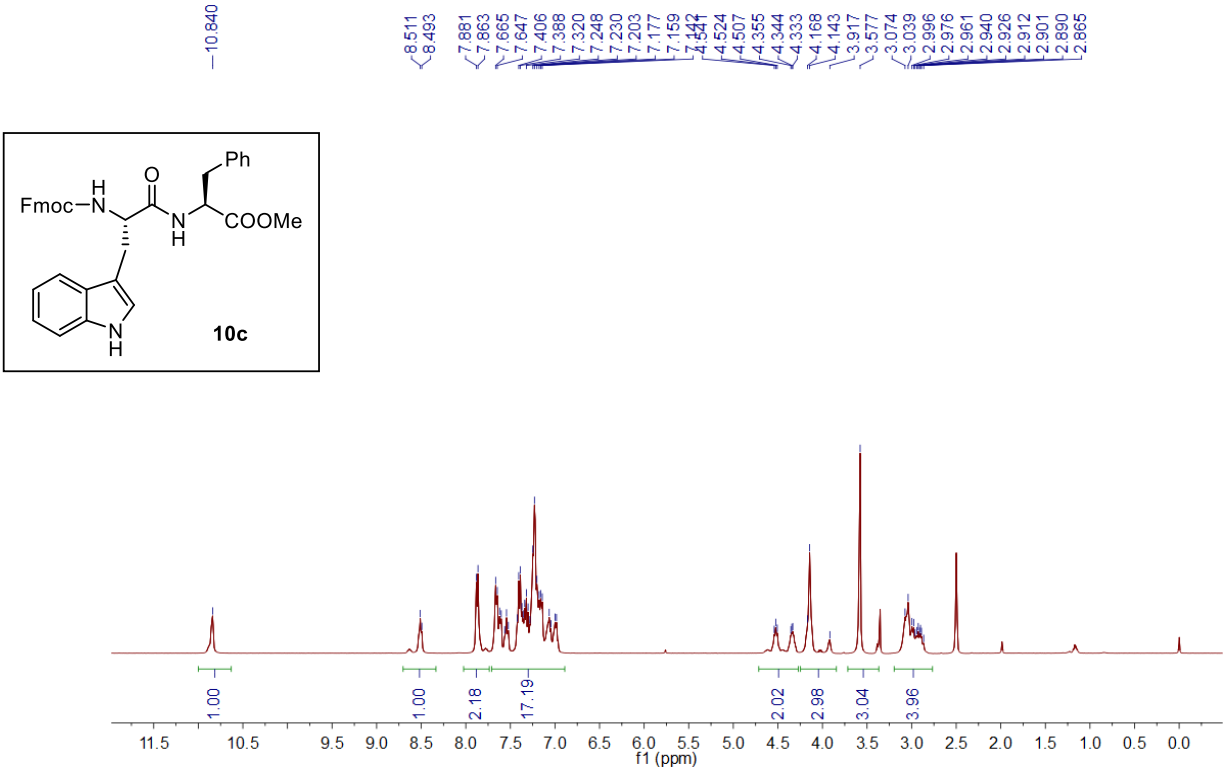
^{1}H-NMR spectrum of compound **7** (400 MHz, $CDCl_3$)



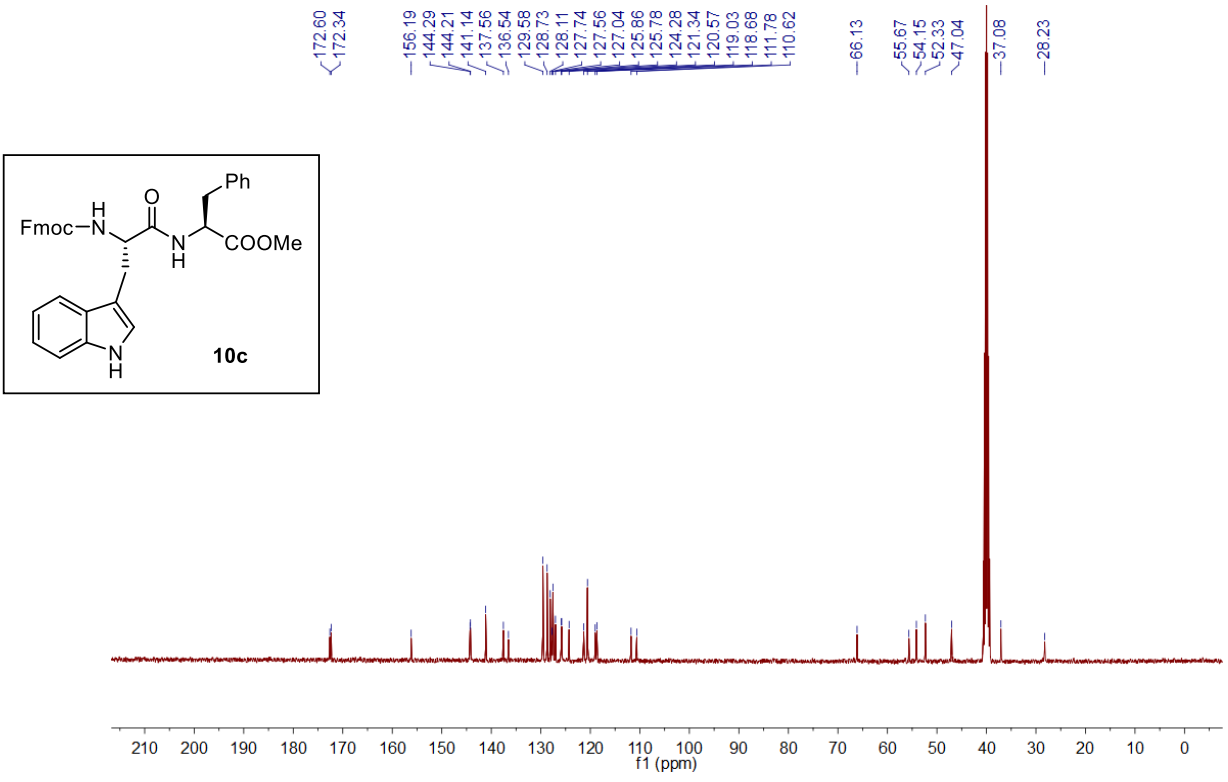
^{13}C-NMR spectrum of compound **7** (101 MHz, $CDCl_3$)



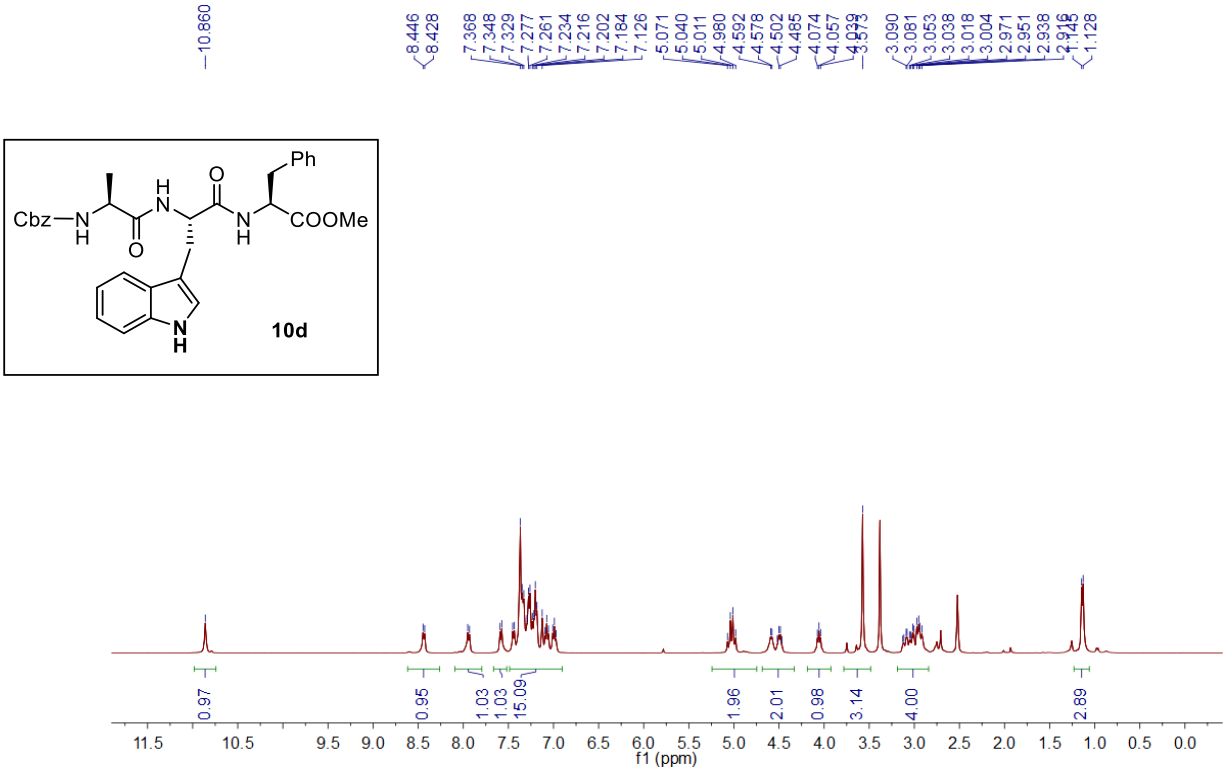
^{1}H-NMR spectrum of compound **10c** (400 MHz, DMSO)



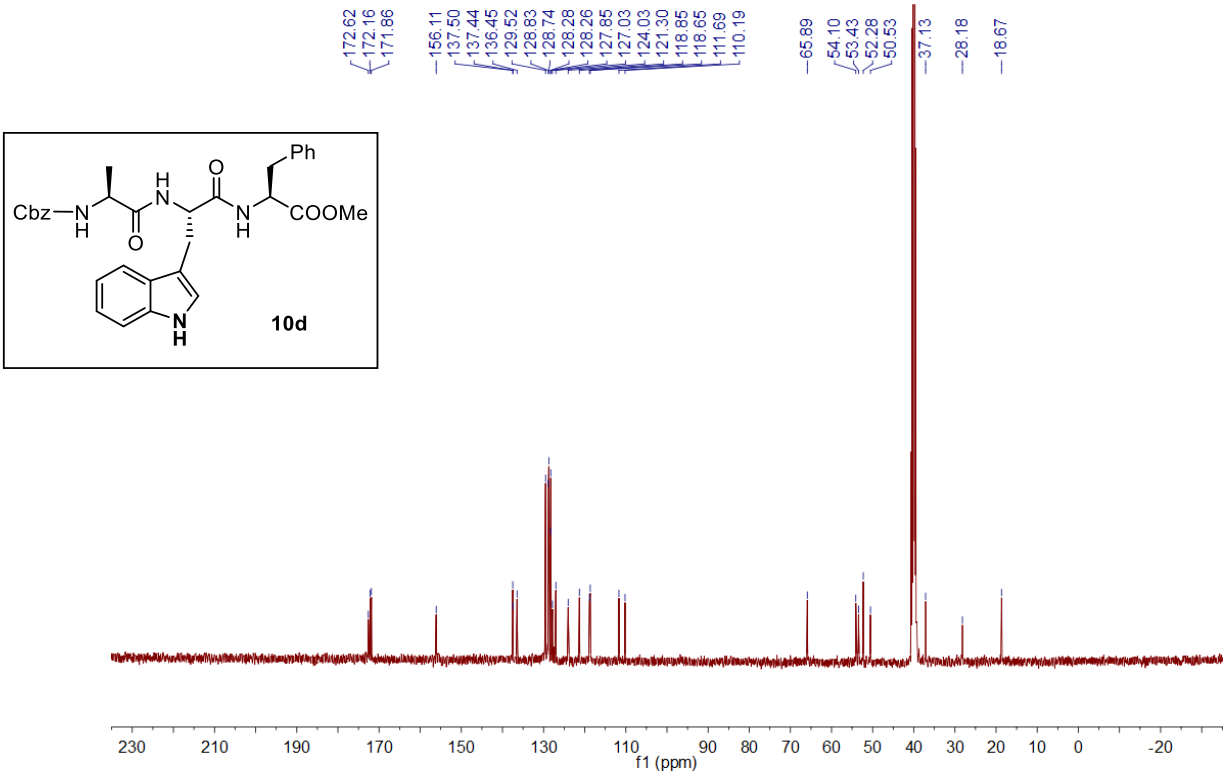
^{13}C-NMR spectrum of compound **10c** (101 MHz, DMSO)



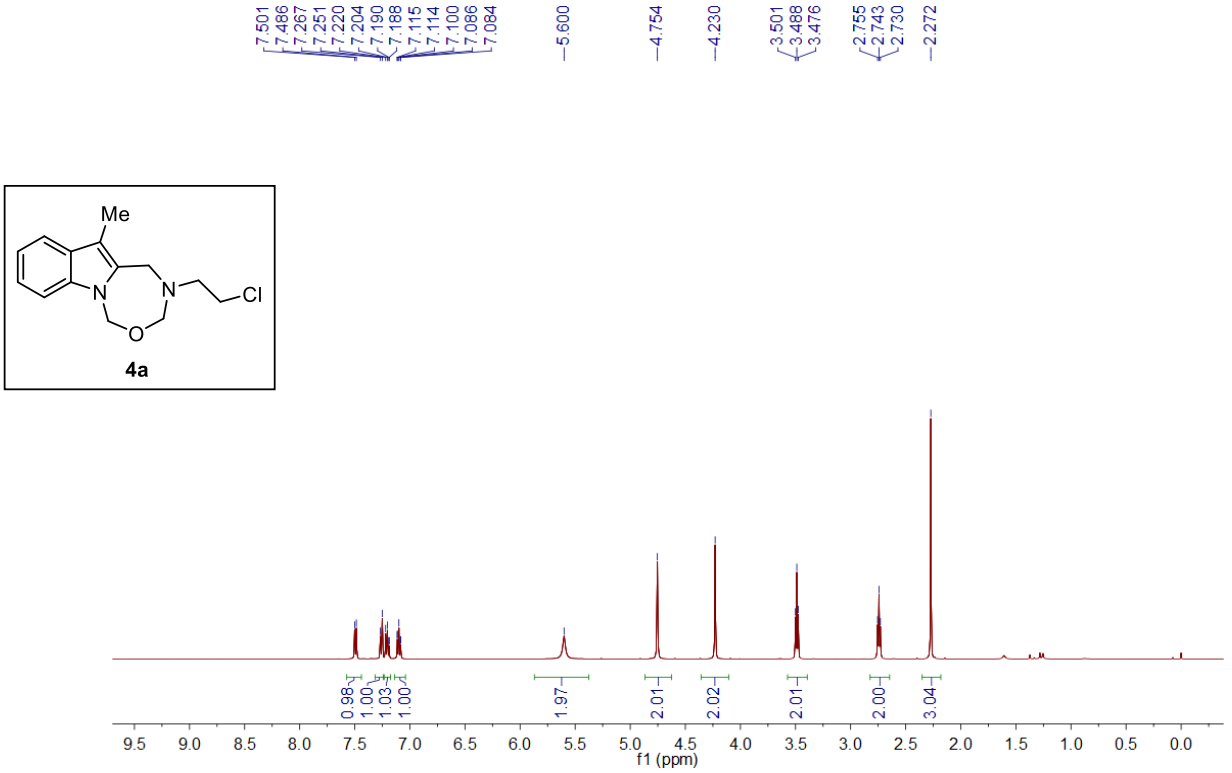
^{1}H-NMR spectrum of compound **10d** (400 MHz, DMSO)



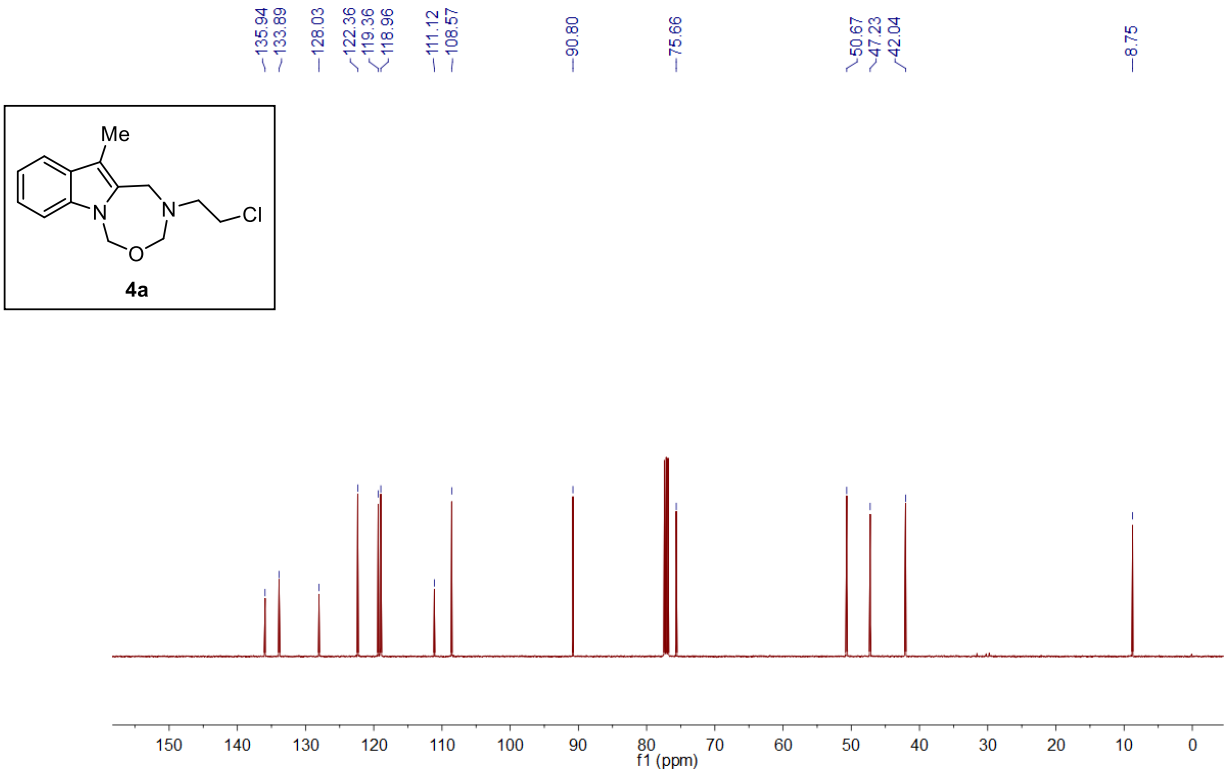
^{13}C-NMR spectrum of compound **10d** (101 MHz, DMSO)



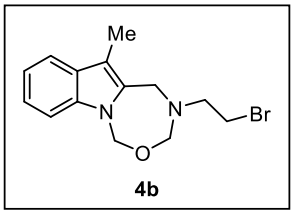
^{1}H-NMR spectrum of compound **4a** (500 MHz, $CDCl_3$)

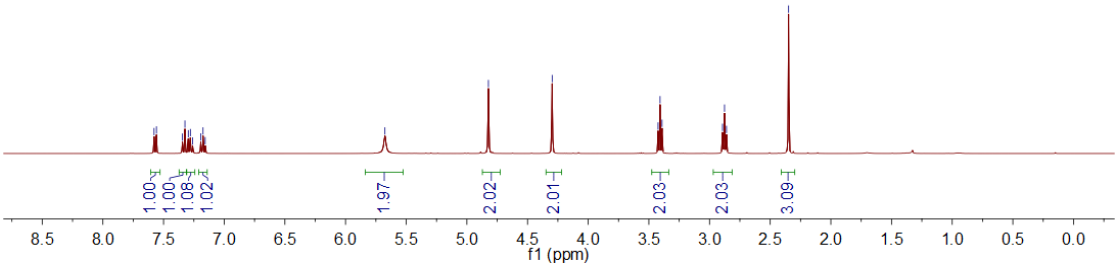


^{13}C-NMR spectrum of compound **4a** (126 MHz, $CDCl_3$)

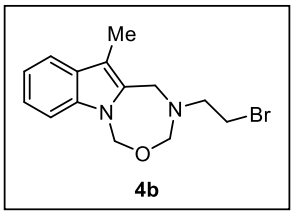


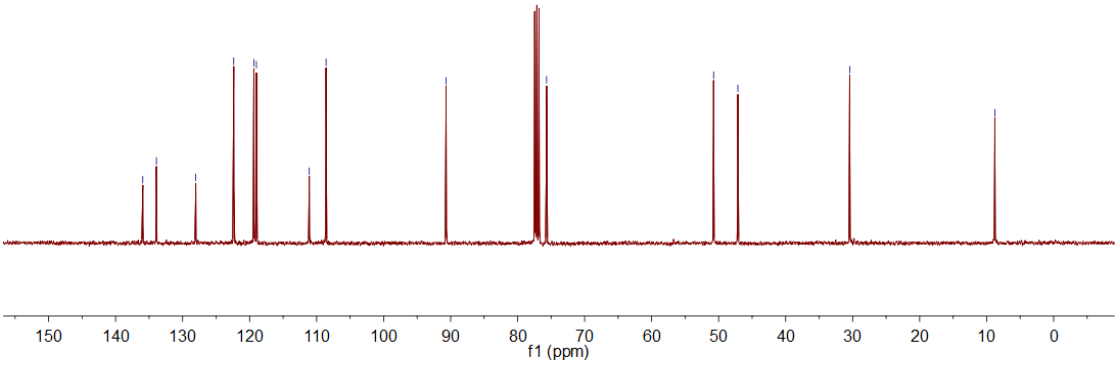
^{1}H-NMR spectrum of compound **4b** (400 MHz, $CDCl_3$)



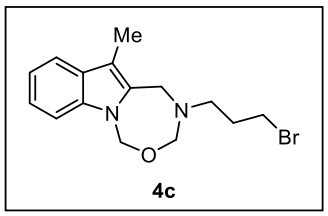


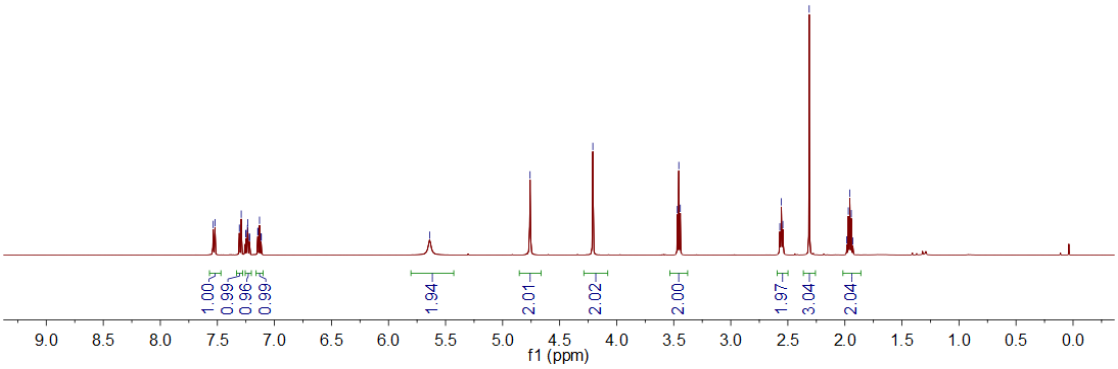
^{13}C-NMR spectrum of compound **4b** (101 MHz, $CDCl_3$)



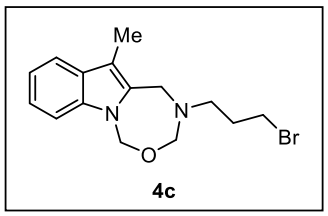


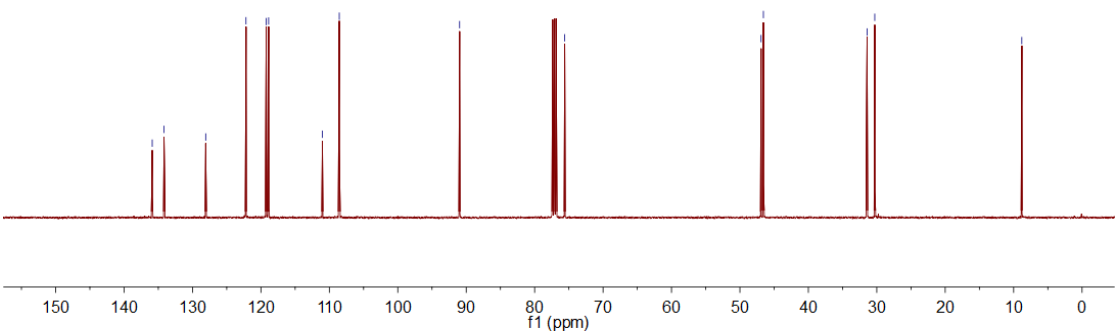
^{1}H-NMR spectrum of compound **4c** (500 MHz, $CDCl_3$)



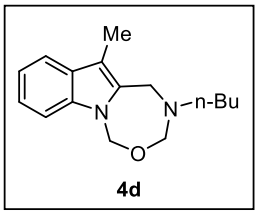


^{13}C-NMR spectrum of compound **4c** (126 MHz, $CDCl_3$)

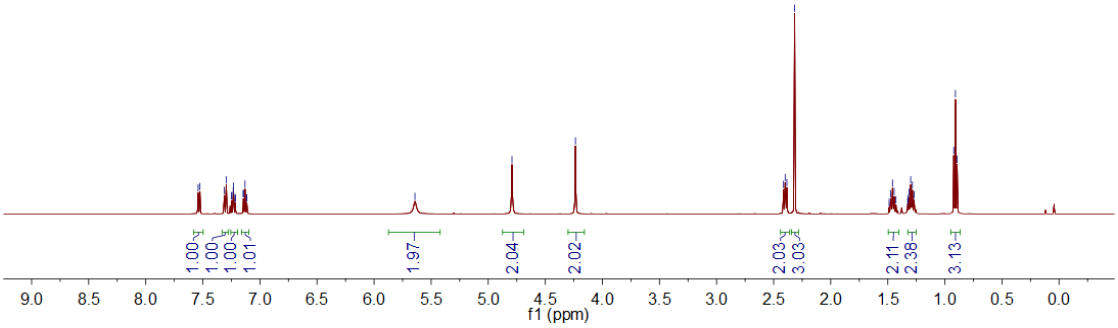




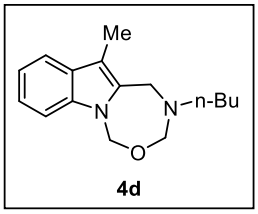
^{1}H-NMR spectrum of compound **4d** (500 MHz, $CDCl_3$)



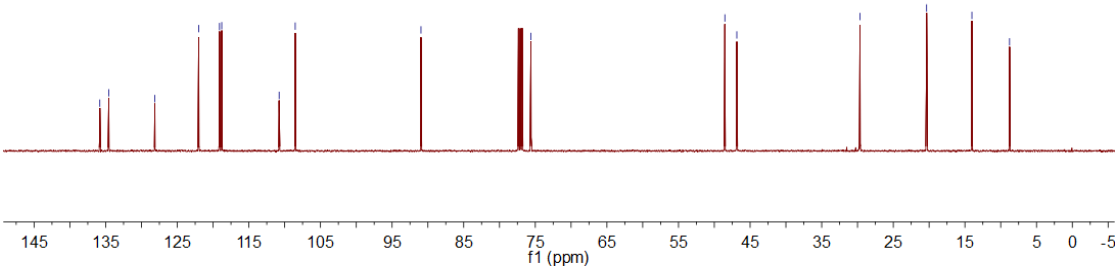
4d



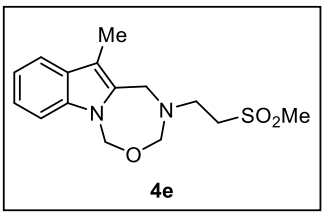
^{13}C-NMR spectrum of compound **4d** (126 MHz, $CDCl_3$)

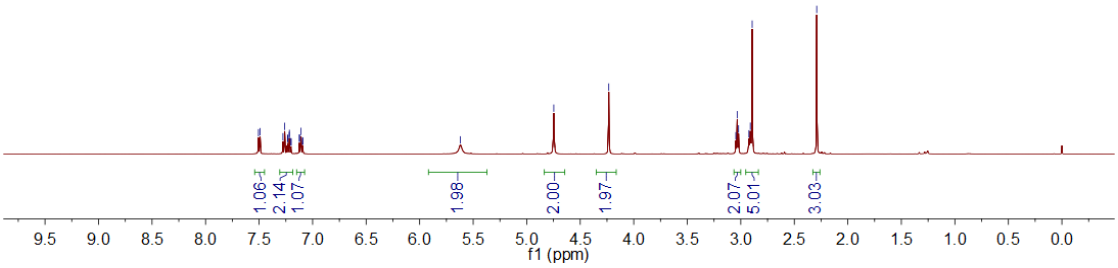


4d

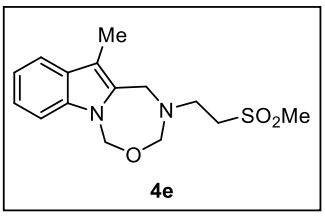


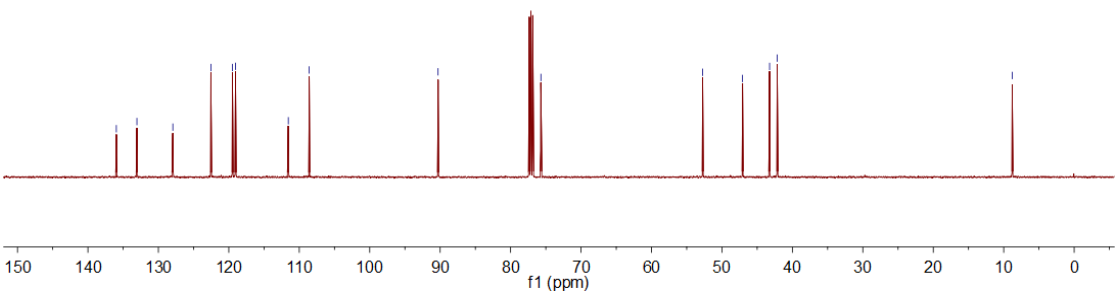
^{1}H-NMR spectrum of compound **4e** (500 MHz, $CDCl_3$)



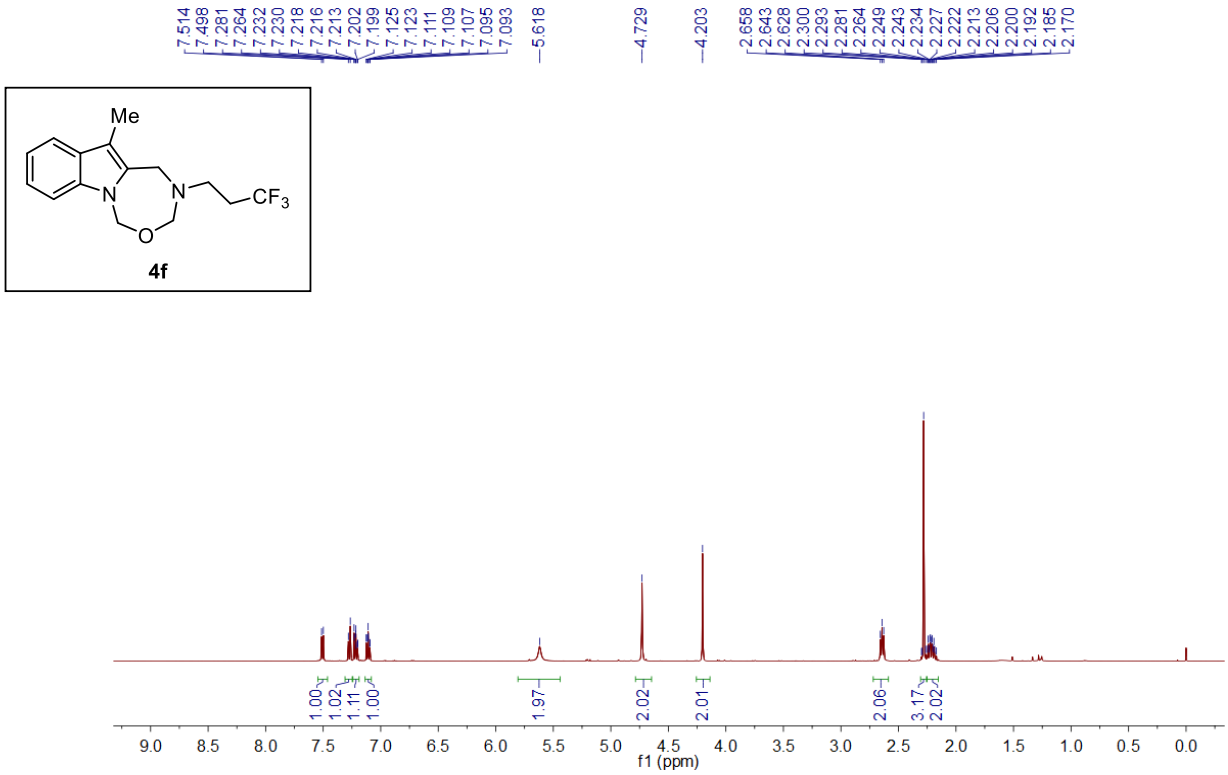


^{13}C-NMR spectrum of compound **4e** (126 MHz, $CDCl_3$)

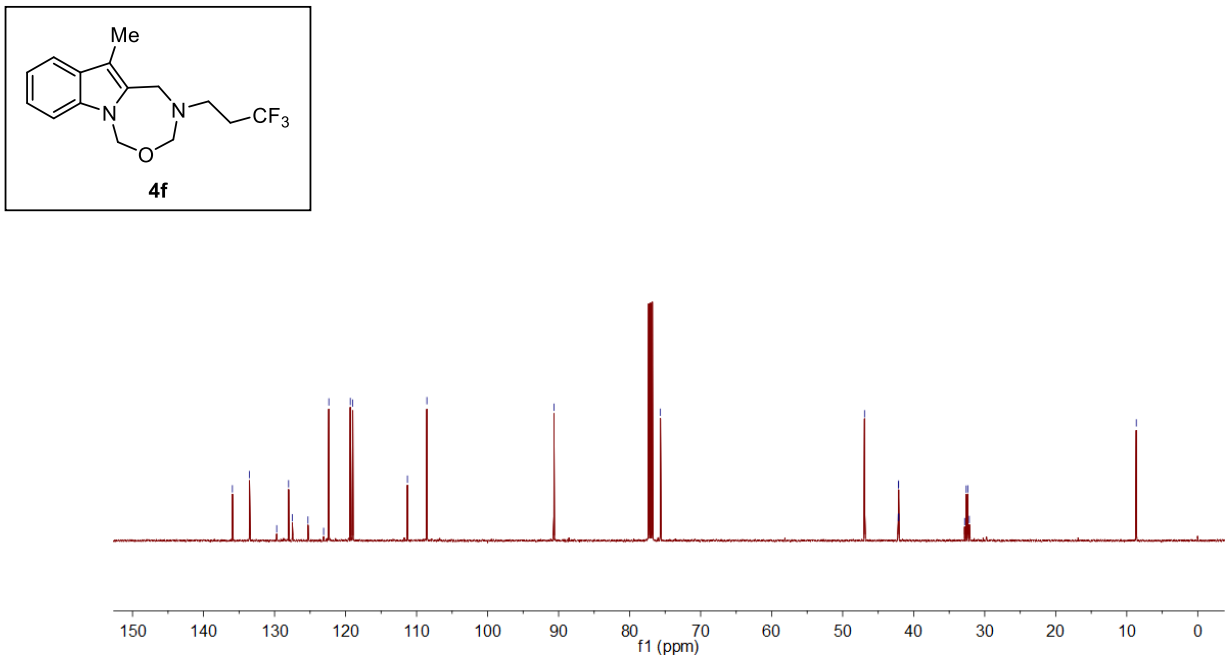




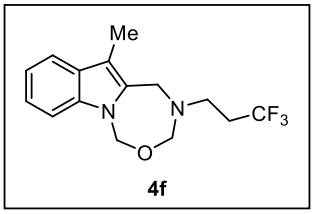
^{1}H-NMR spectrum of compound **4f** (500 MHz, $CDCl_3$)



^{13}C-NMR spectrum of compound **4f** (126 MHz, $CDCl_3$)

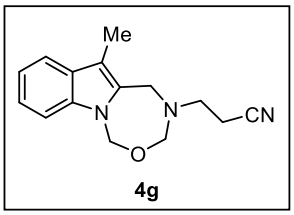


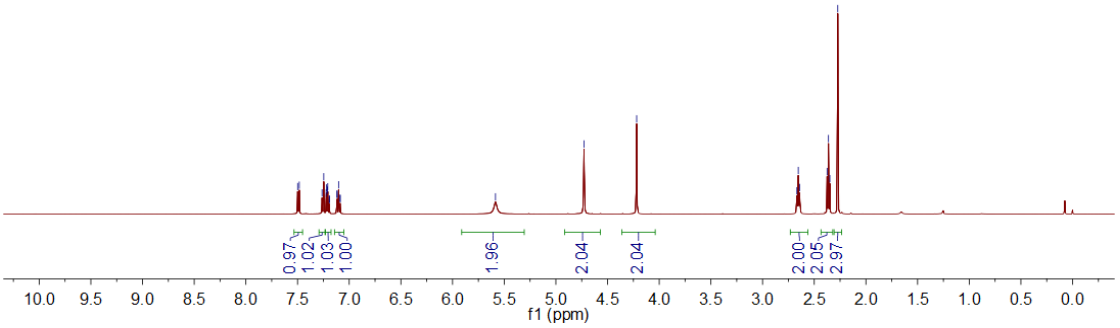
^{19}F-NMR spectrum of compound **4f** (376 MHz, $CDCl_3$)



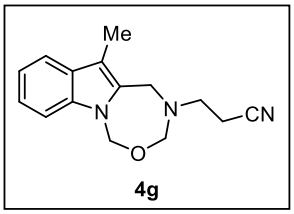
4f

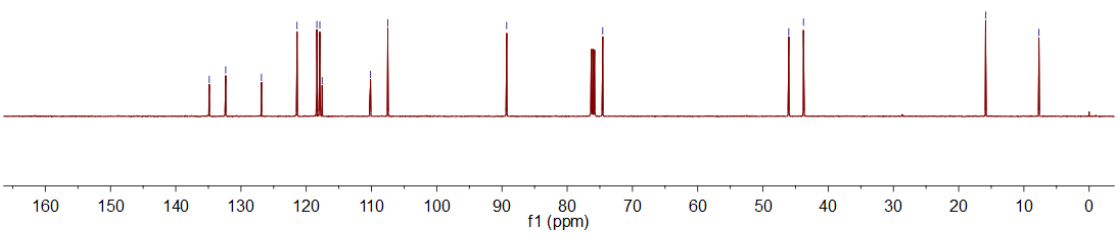
^{1}H-NMR spectrum of compound **4g** (500 MHz, $CDCl_3$)



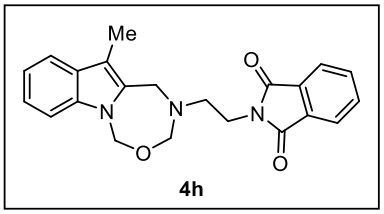


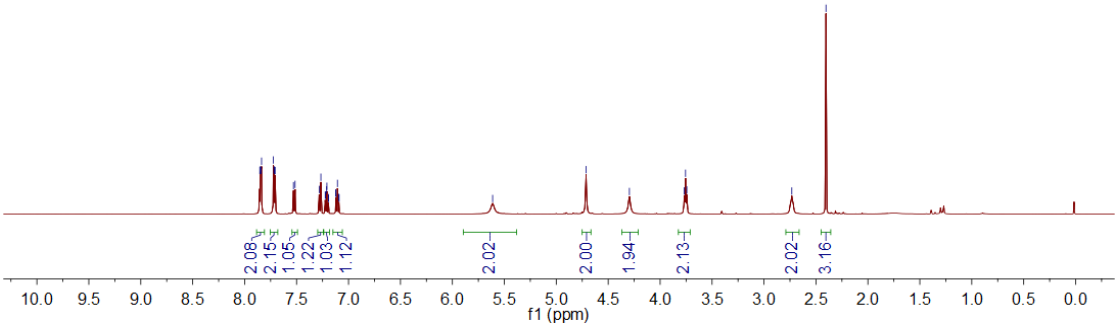
^{13}C-NMR spectrum of compound **4g** (126 MHz, $CDCl_3$)



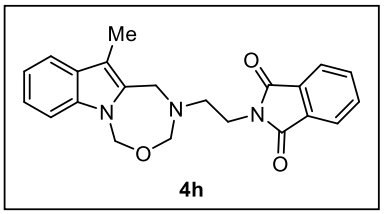


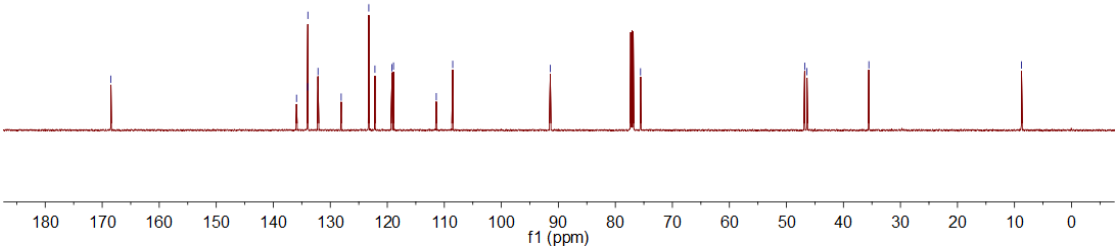
^{1}H-NMR spectrum of compound **4h** (500 MHz, $CDCl_3$)



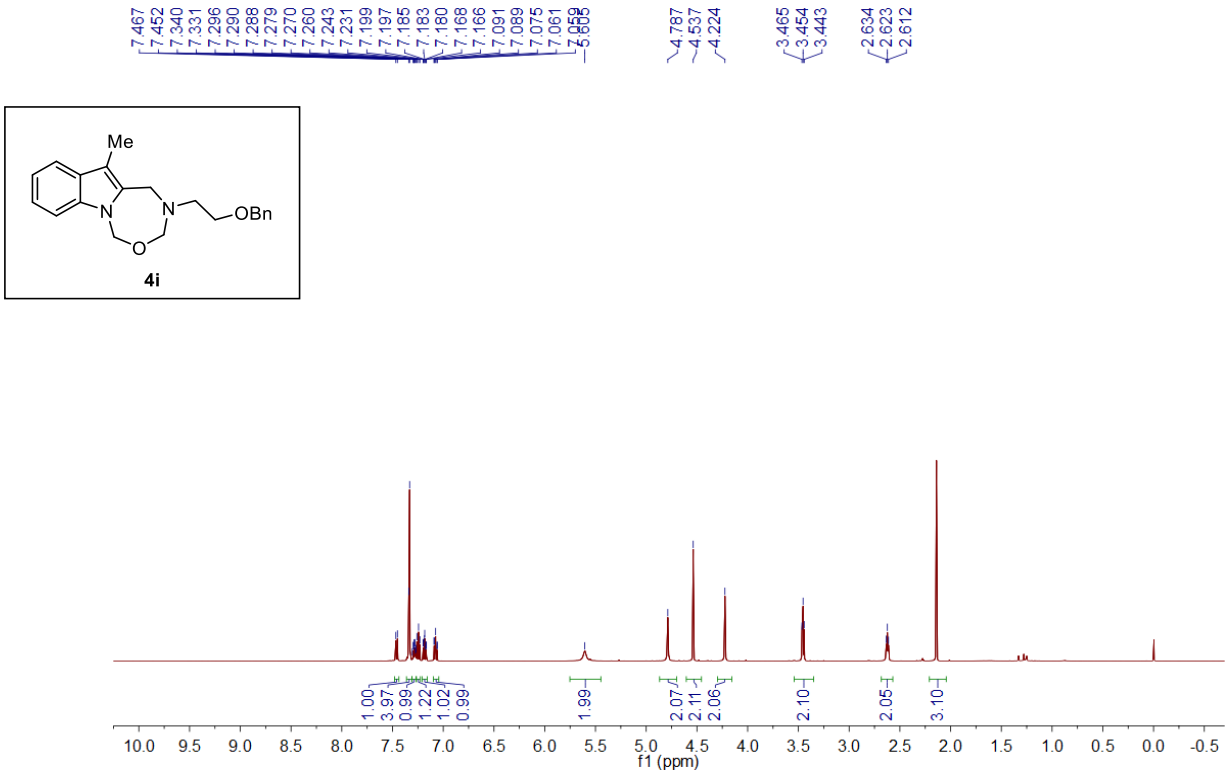


^{13}C-NMR spectrum of compound **4h** (150 MHz, $CDCl_3$)

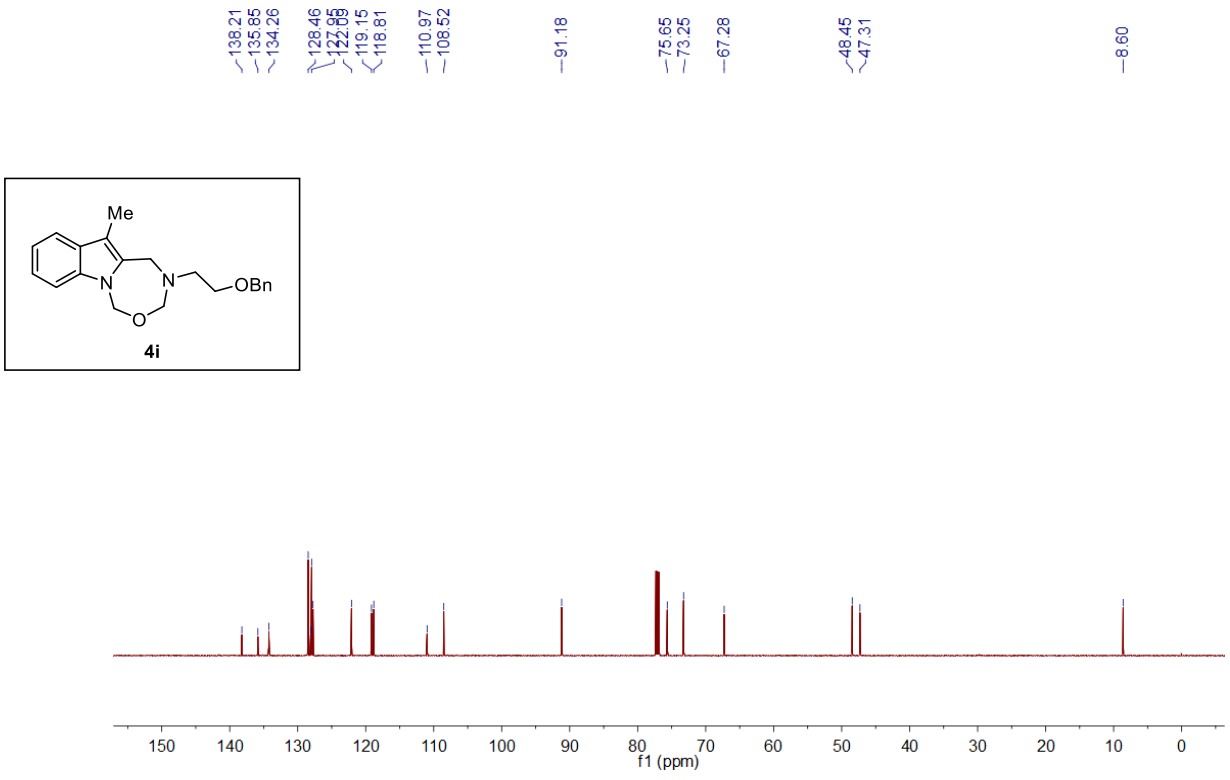




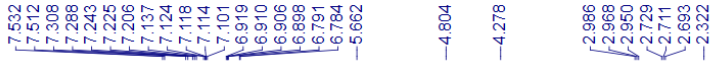
^{1}H-NMR spectrum of compound **4i** (500 MHz, $CDCl_3$)

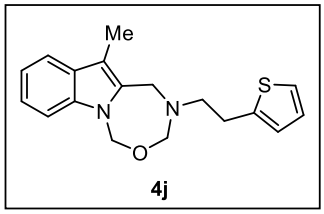


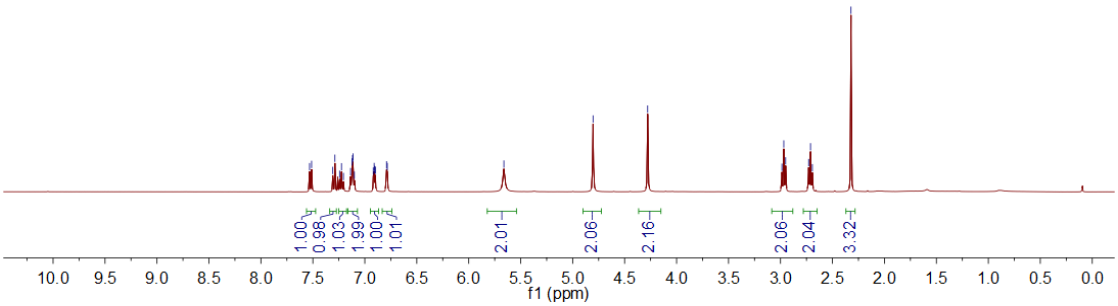
^{13}C-NMR spectrum of compound **4i** (150 MHz, $CDCl_3$)



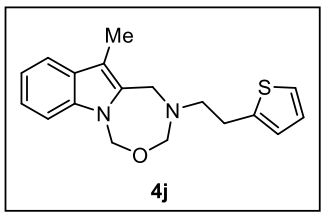
^{1}H-NMR spectrum of compound **4j** (400 MHz, $CDCl_3$)

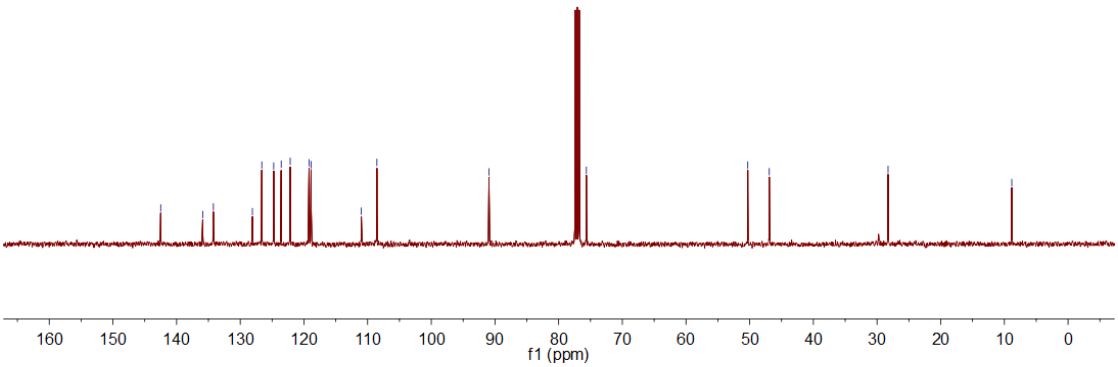




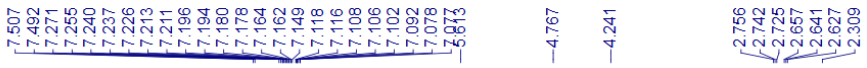


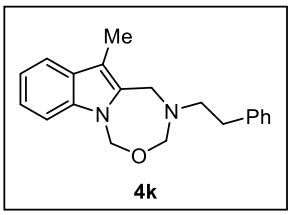
^{13}C-NMR spectrum of compound **4j** (101 MHz, $CDCl_3$)

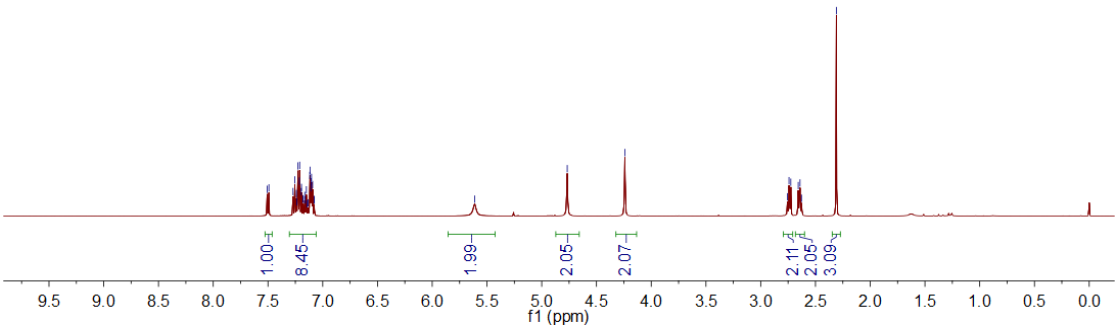




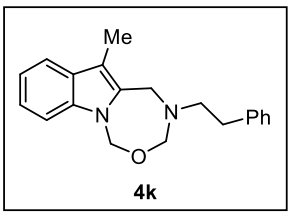
^{1}H-NMR spectrum of compound **4k** (500 MHz, $CDCl_3$)

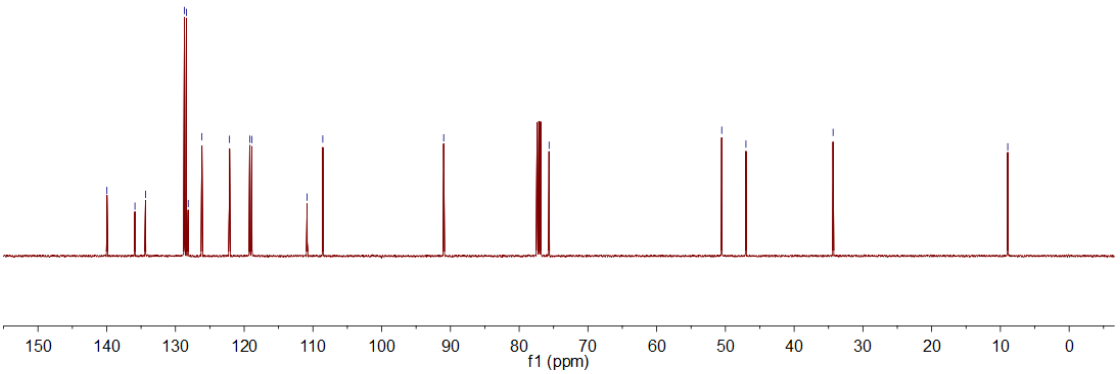




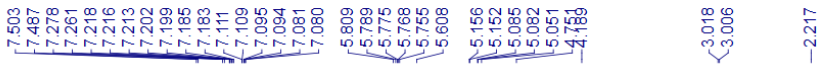


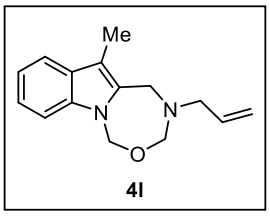
^{13}C-NMR spectrum of compound **4k** (126 MHz, $CDCl_3$)

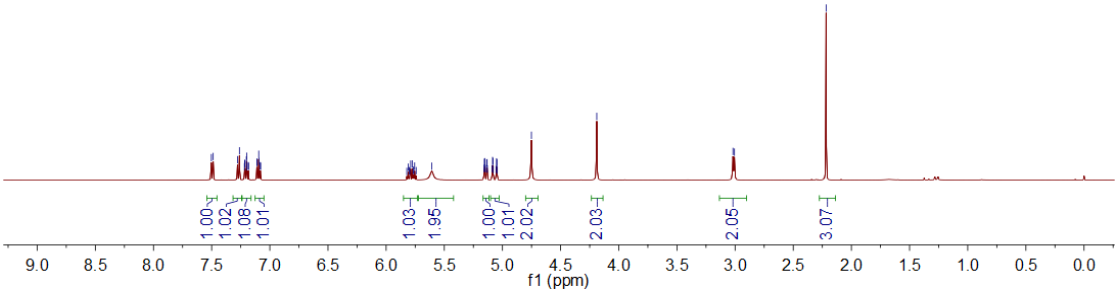




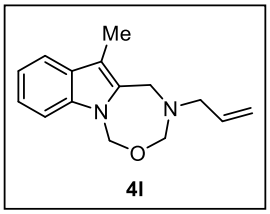
^{1}H-NMR spectrum of compound **4l** (500 MHz, $CDCl_3$)

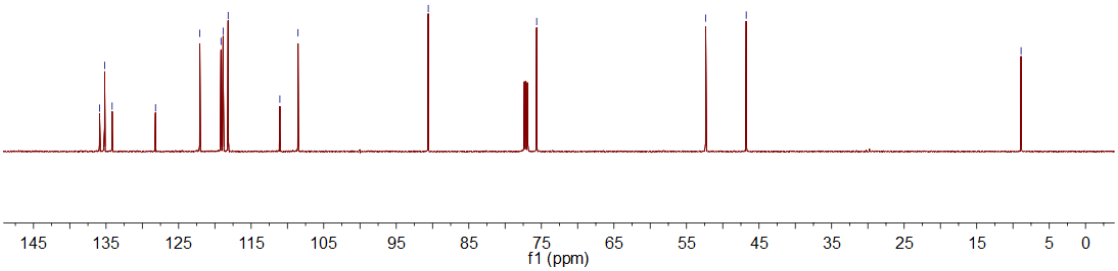




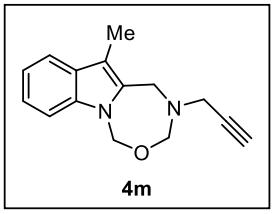


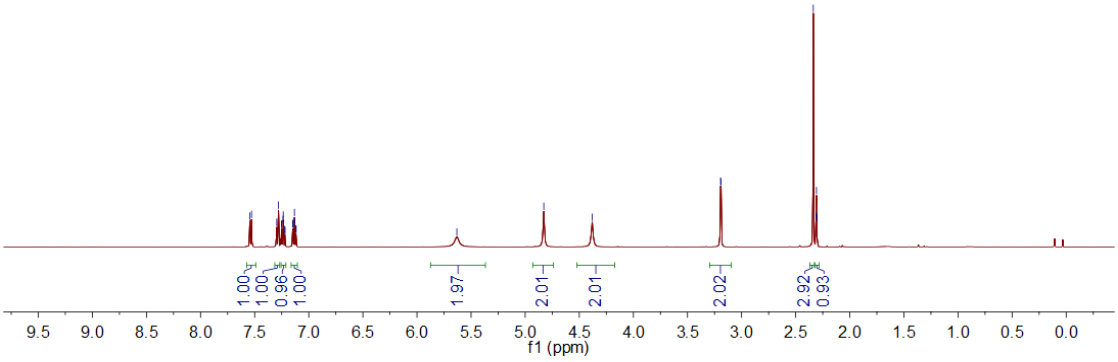
^{13}C-NMR spectrum of compound **4l** (150 MHz, $CDCl_3$)



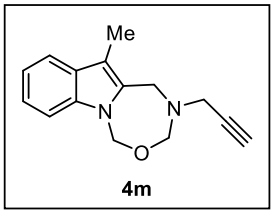


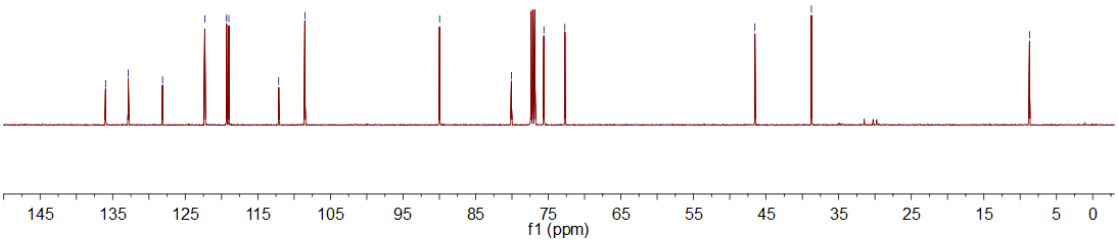
^{1}H-NMR spectrum of compound **4m** (500 MHz, $CDCl_3$)



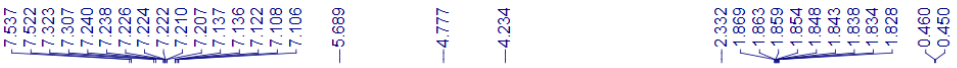


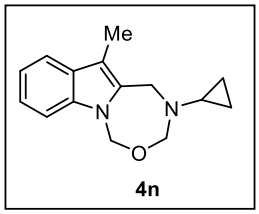
^{13}C-NMR spectrum of compound **4m** (126 MHz, $CDCl_3$)

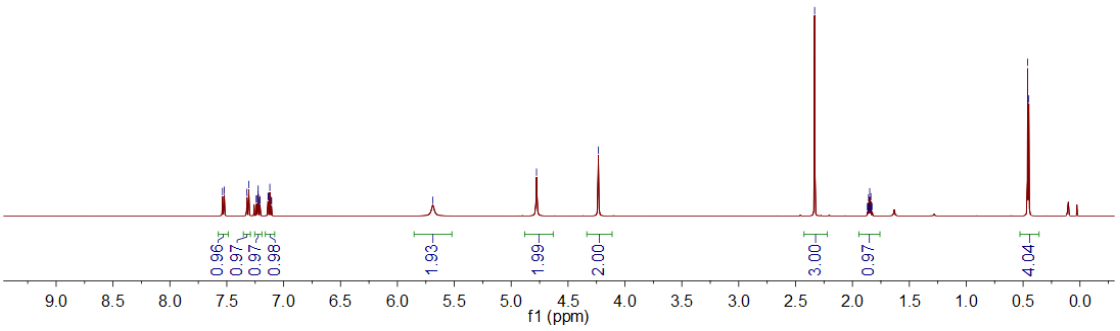




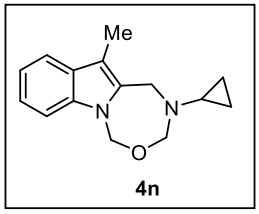
^{1}H-NMR spectrum of compound **4n** (500 MHz, $CDCl_3$)

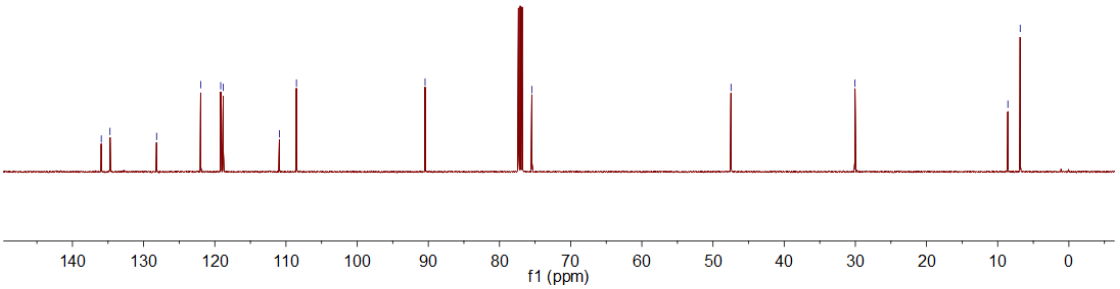




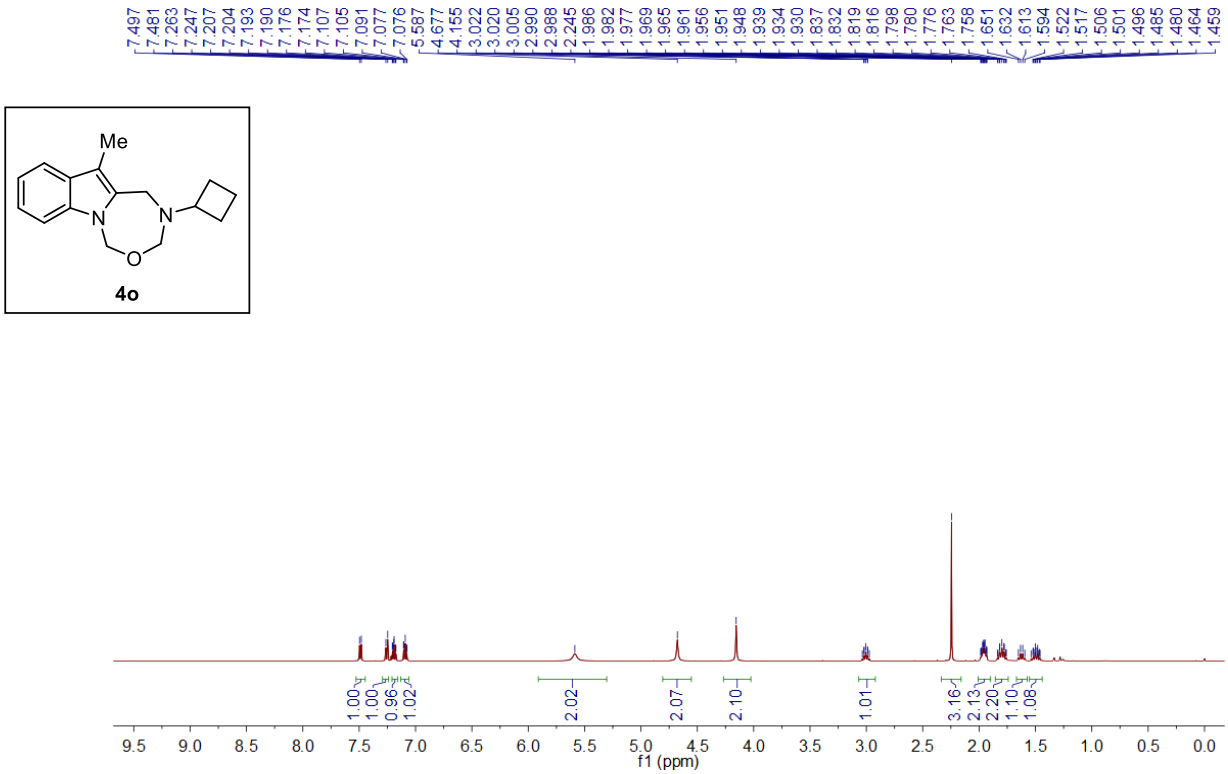


^{13}C-NMR spectrum of compound **4n** (126 MHz, $CDCl_3$)

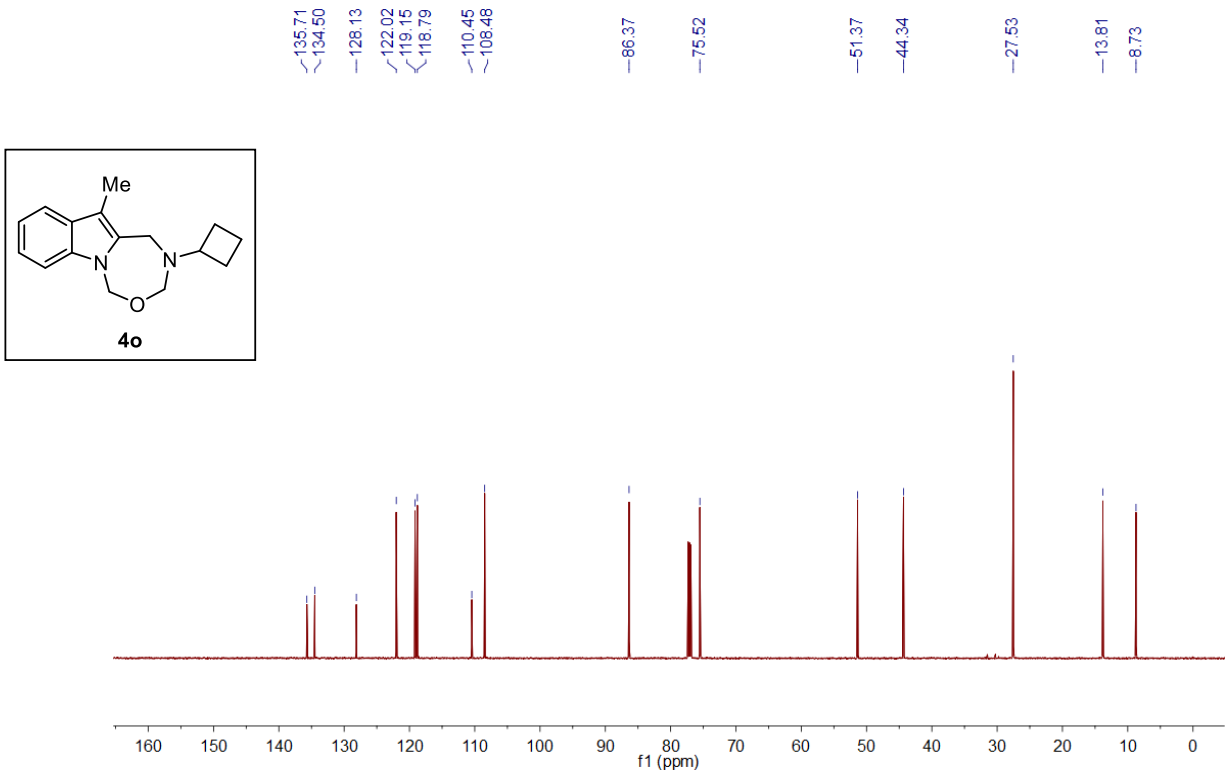




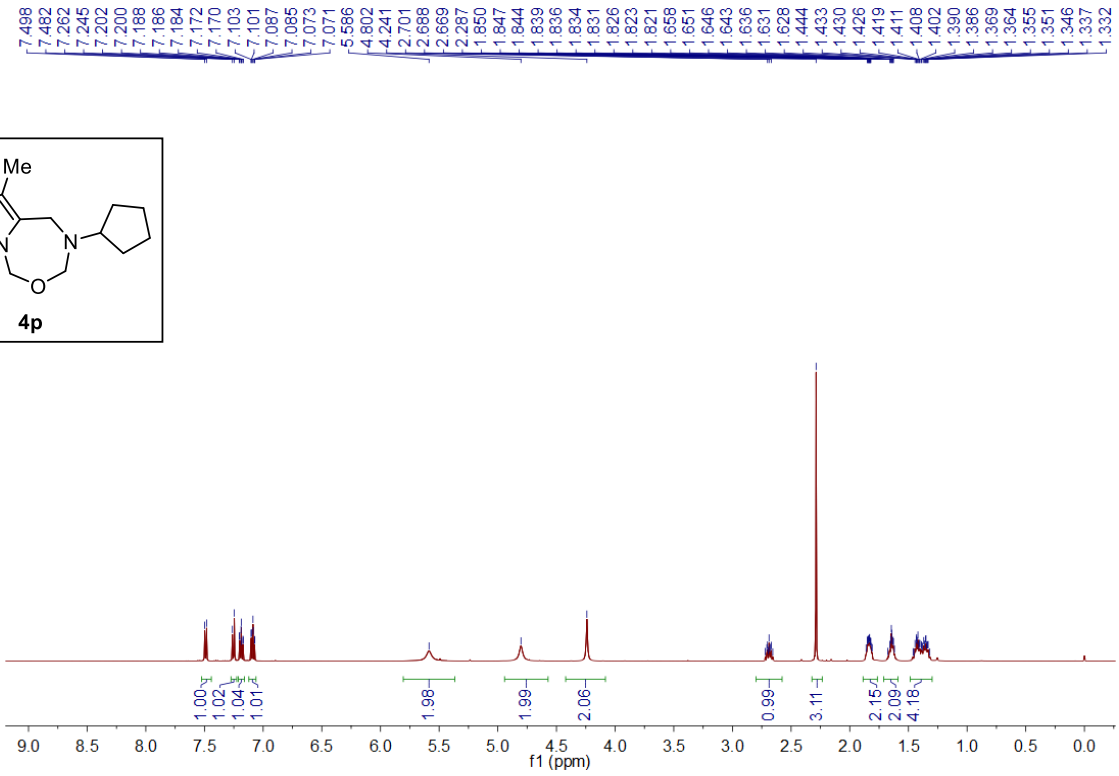
^{1}H-NMR spectrum of compound **4o** (500 MHz, $CDCl_3$)



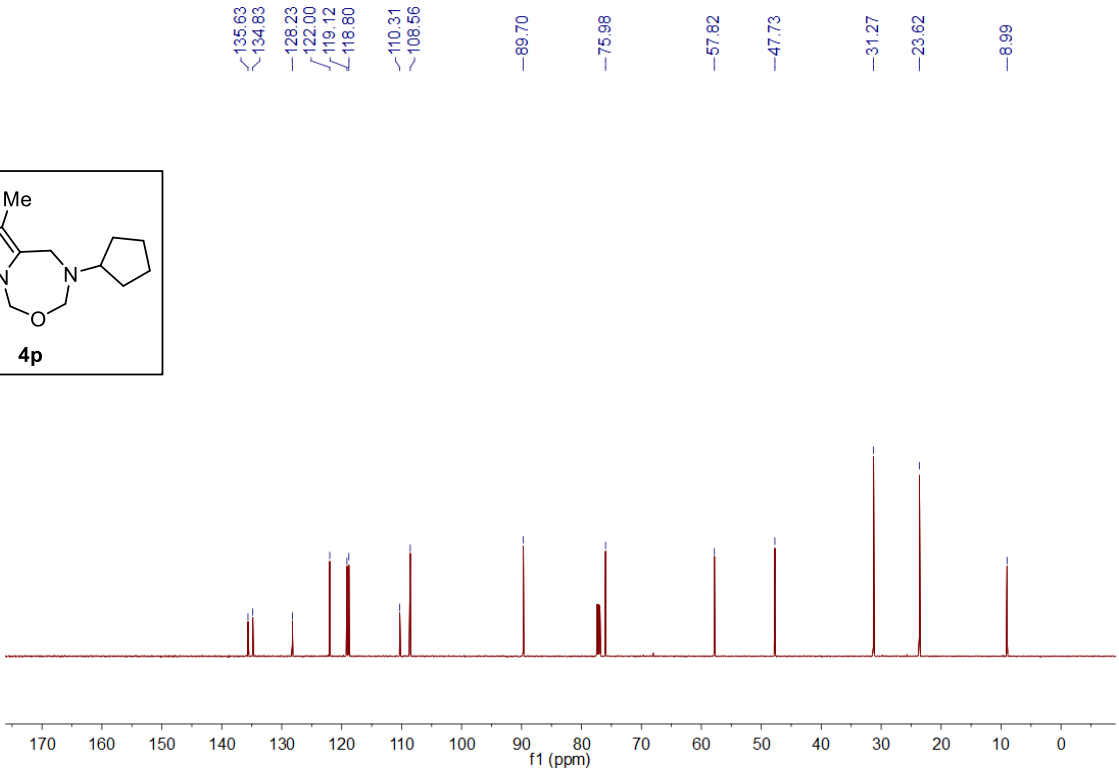
^{13}C-NMR spectrum of compound **4o** (150 MHz, $CDCl_3$)



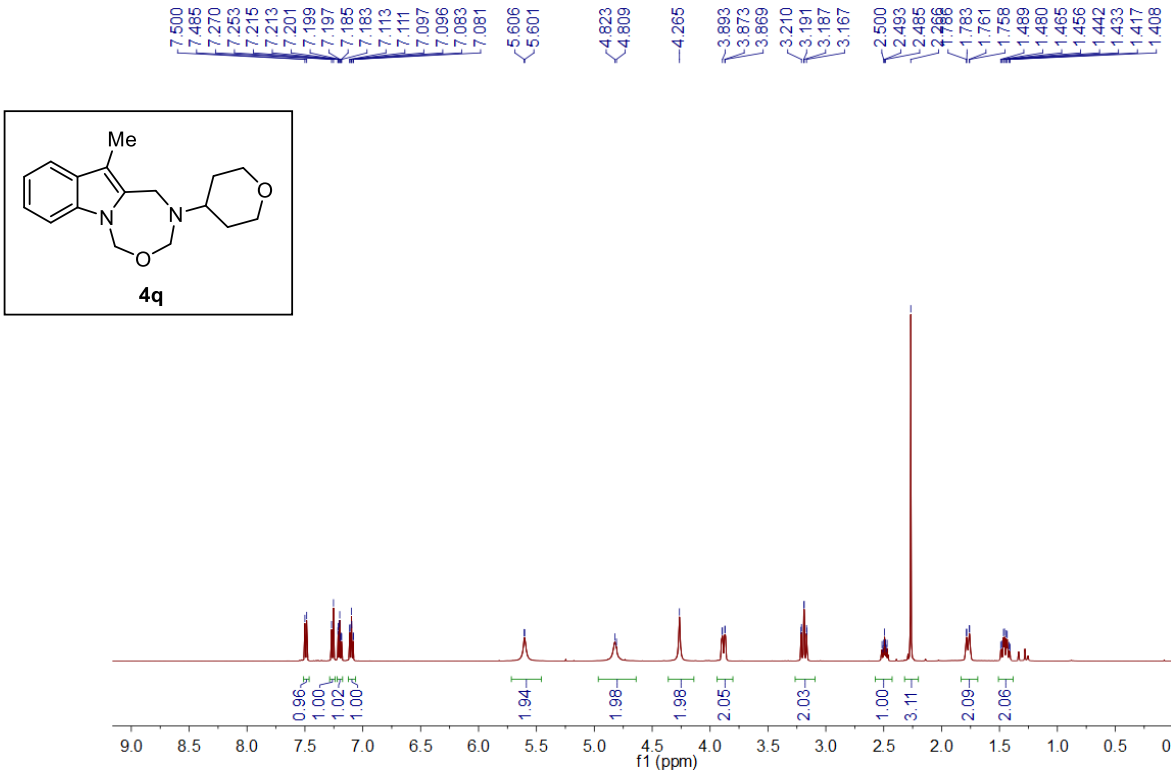
^{1}H-NMR spectrum of compound **4p** (500 MHz, $CDCl_3$)



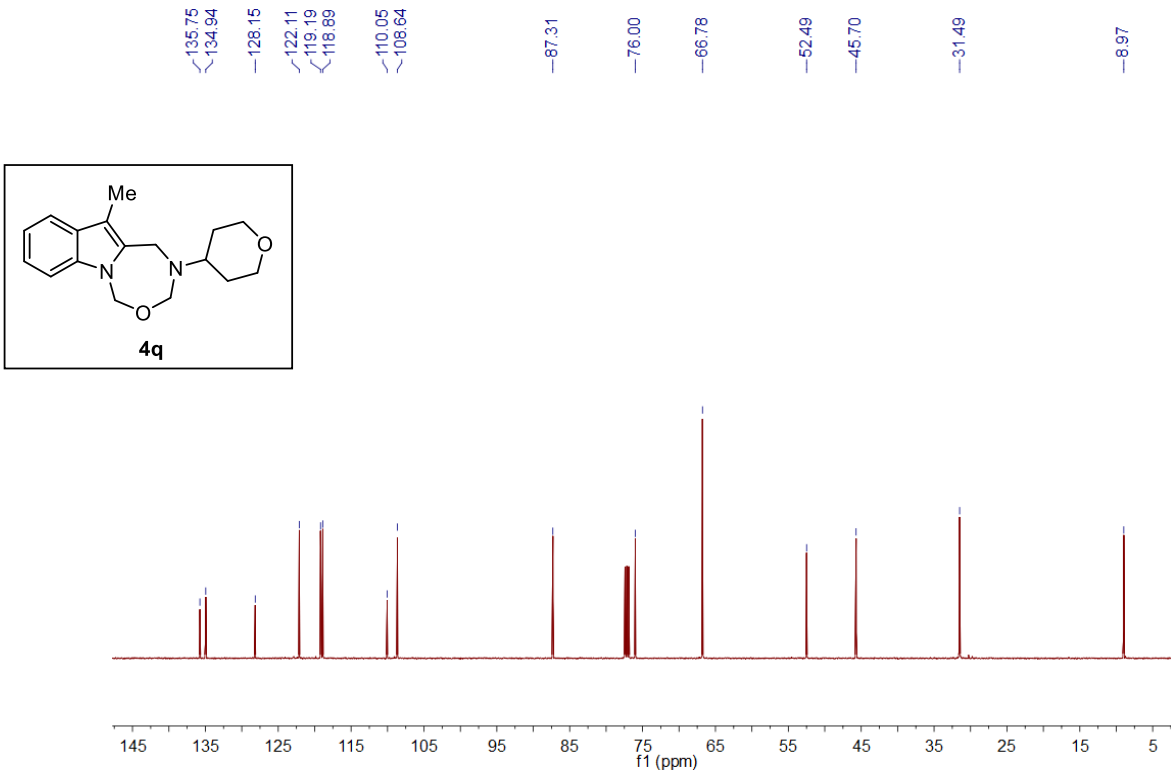
^{13}C-NMR spectrum of compound **4p** (150 MHz, $CDCl_3$)



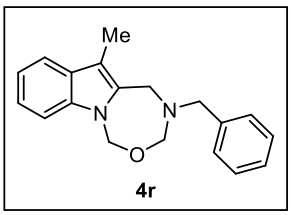
^{1}H-NMR spectrum of compound **4q** (500 MHz, $CDCl_3$)

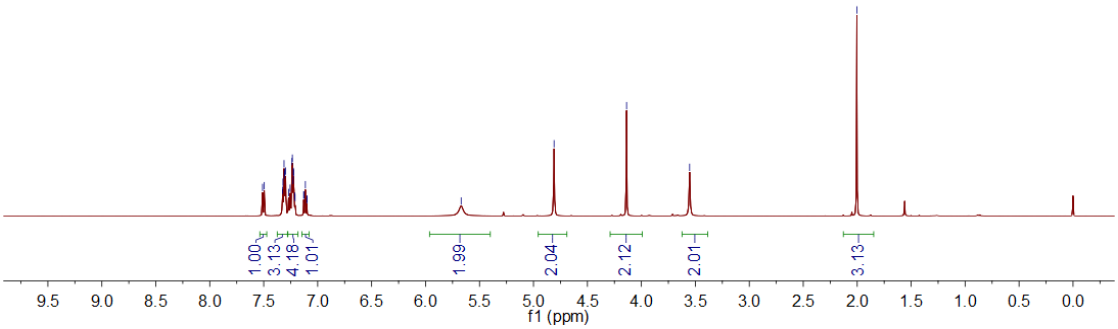


^{13}C-NMR spectrum of compound **4q** (126 MHz, $CDCl_3$)

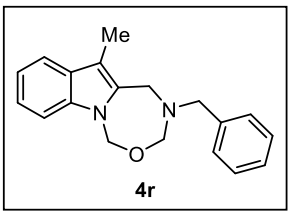


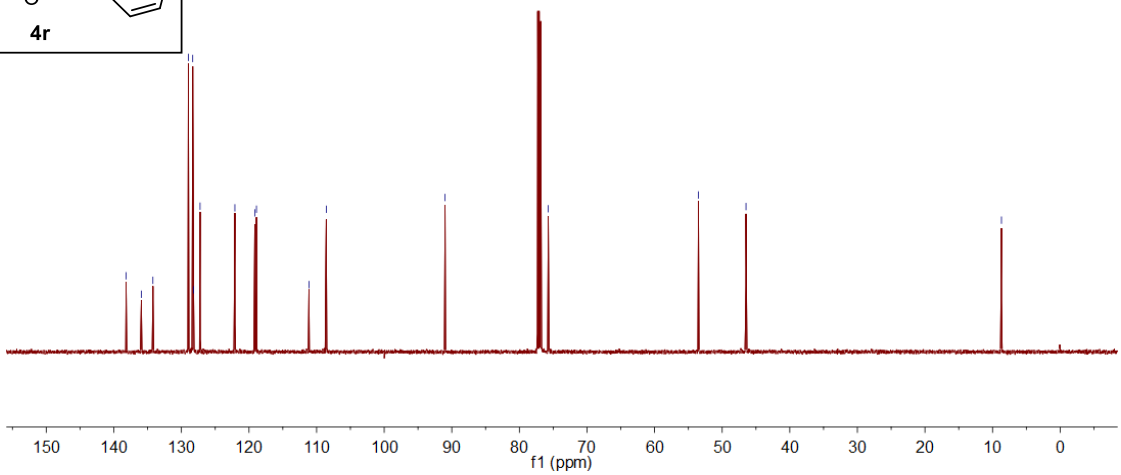
^{1}H-NMR spectrum of compound **4r** (500 MHz, $CDCl_3$)



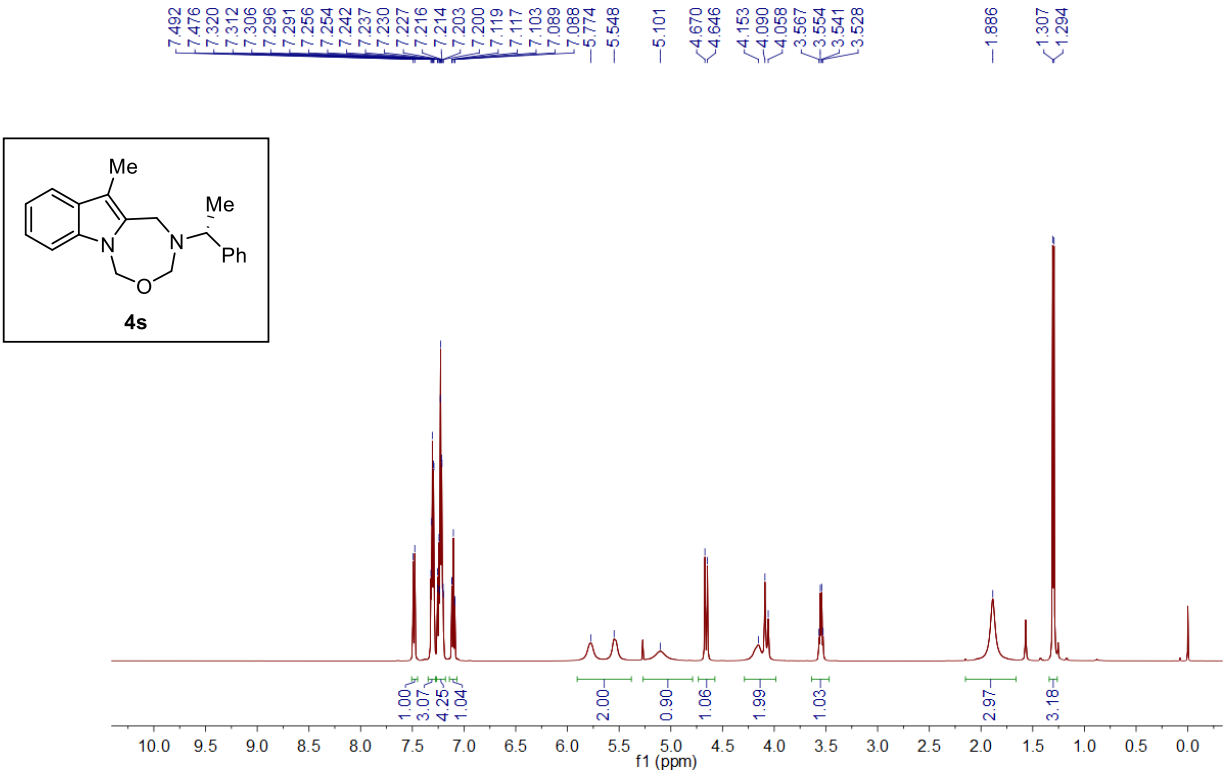


^{13}C-NMR spectrum of compound **4r** (150 MHz, $CDCl_3$)

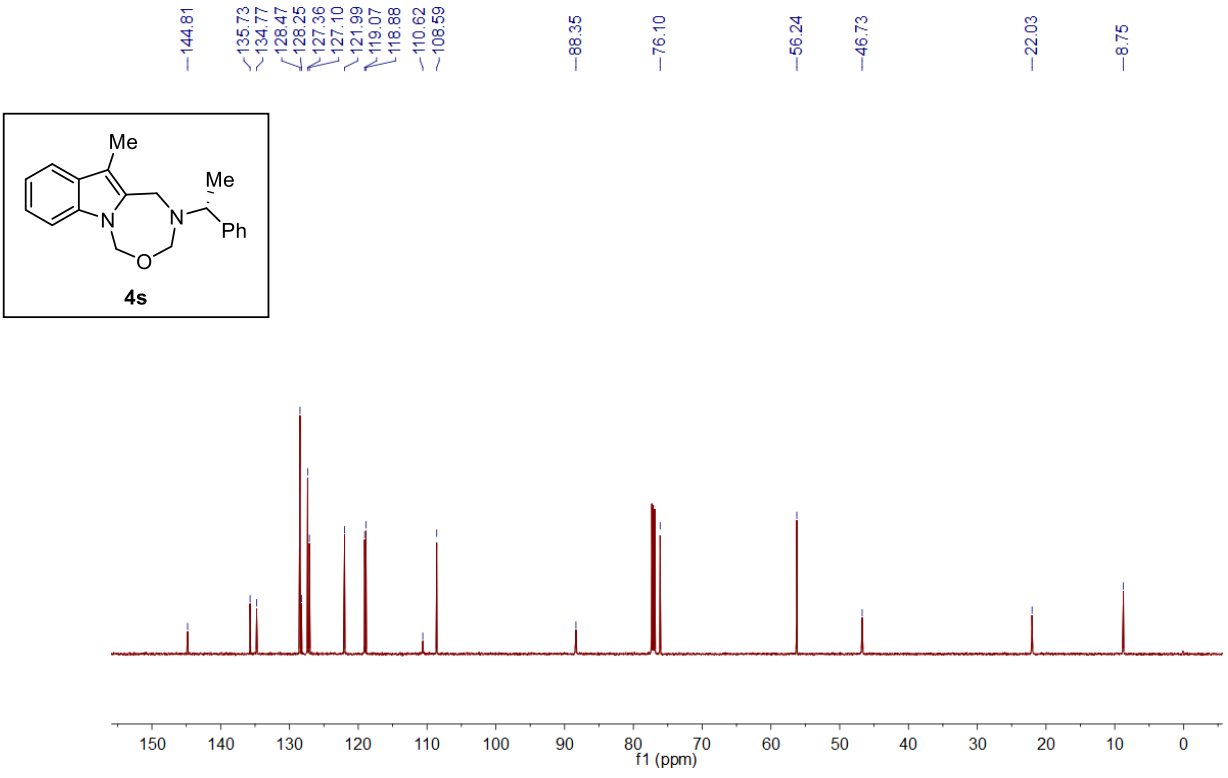




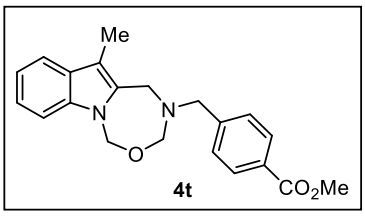
^{1}H-NMR spectrum of compound **4s** (500 MHz, $CDCl_3$)

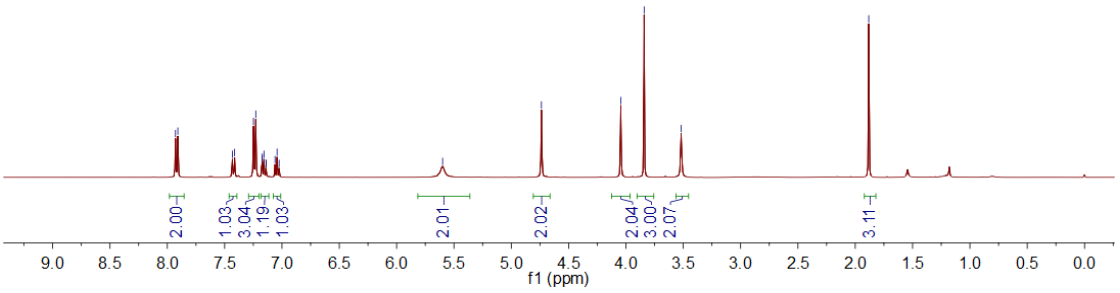


^{13}C-NMR spectrum of compound **4s** (150 MHz, $CDCl_3$)

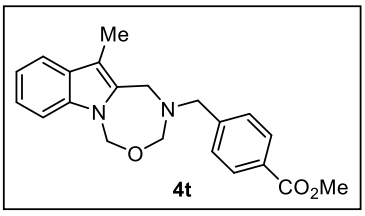


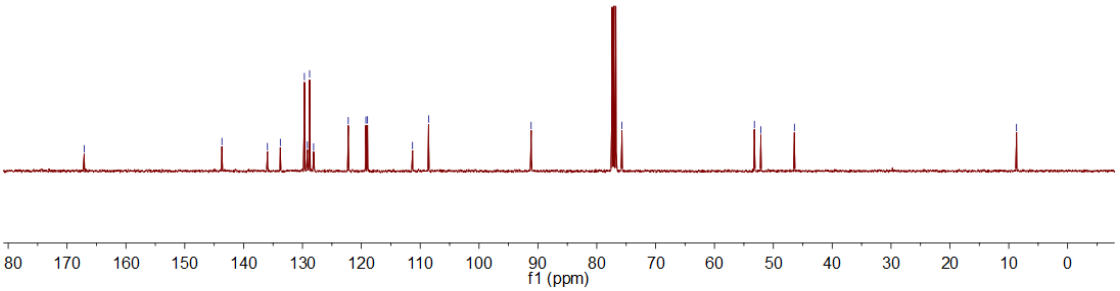
^{1}H-NMR spectrum of compound **4t** (400 MHz, $CDCl_3$)



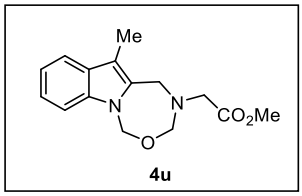


^{13}C-NMR spectrum of compound **4t** (101 MHz, $CDCl_3$)

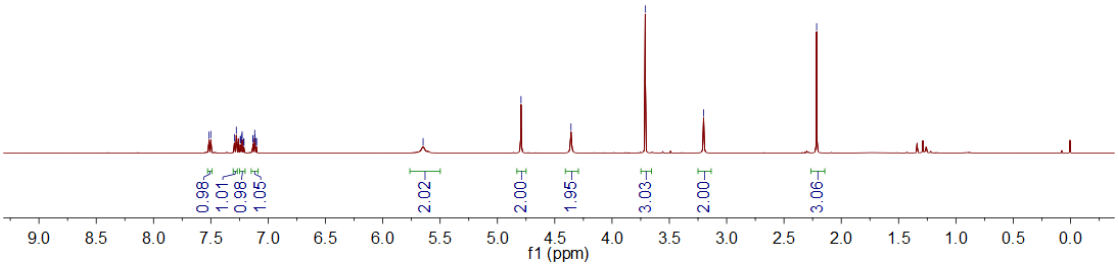




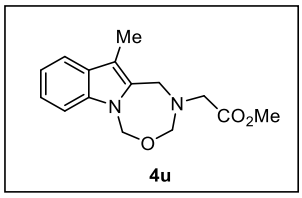
^{1}H-NMR spectrum of compound **4u** (500 MHz, $CDCl_3$)



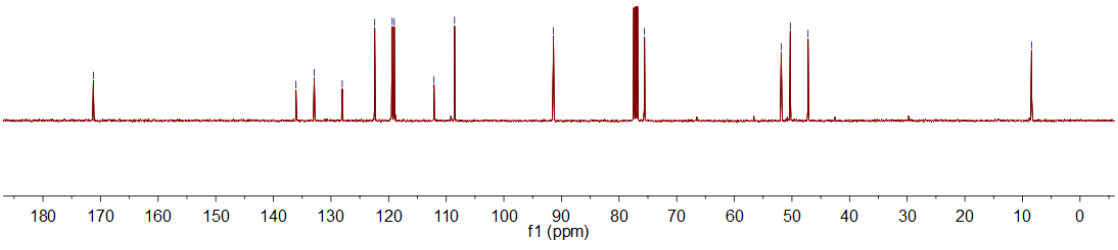
4u



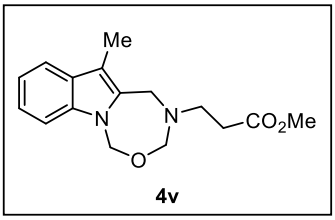
^{13}C-NMR spectrum of compound **4u** (101 MHz, $CDCl_3$)

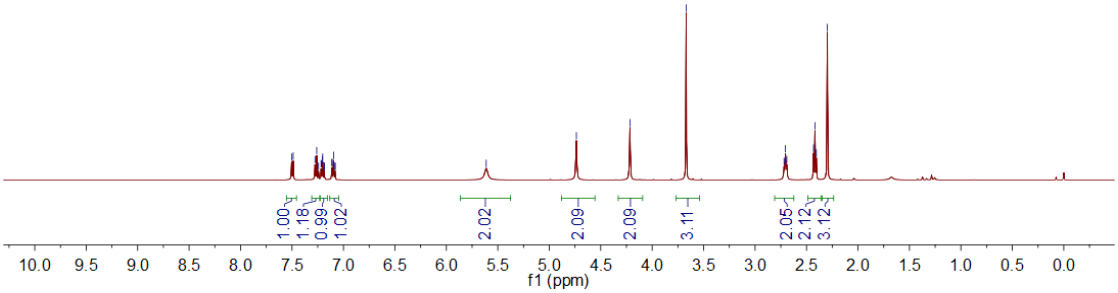


4u

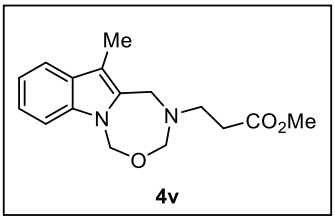


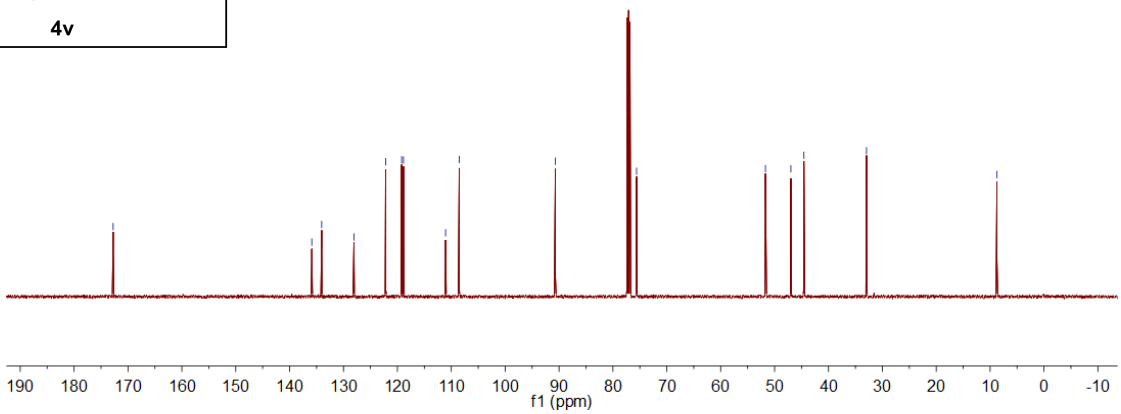
^{1}H-NMR spectrum of compound **4v** (500 MHz, $CDCl_3$)



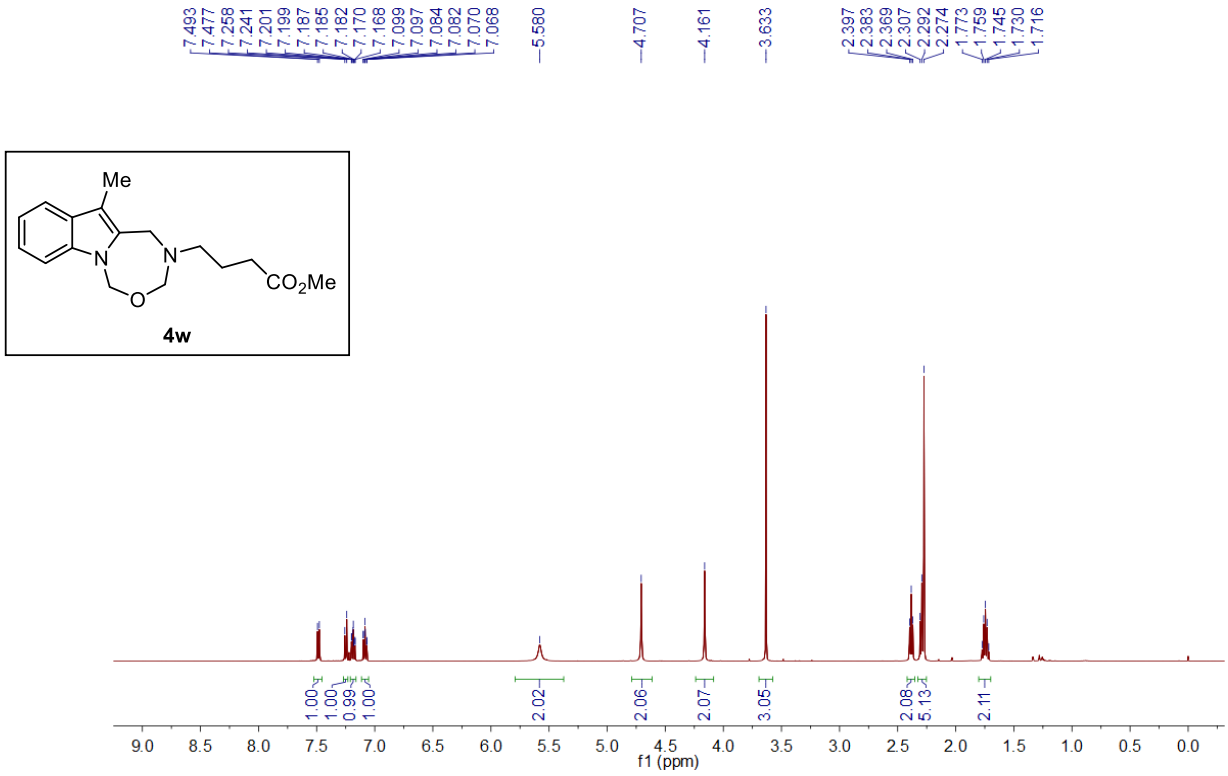


^{13}C-NMR spectrum of compound **4v** (126 MHz, $CDCl_3$)

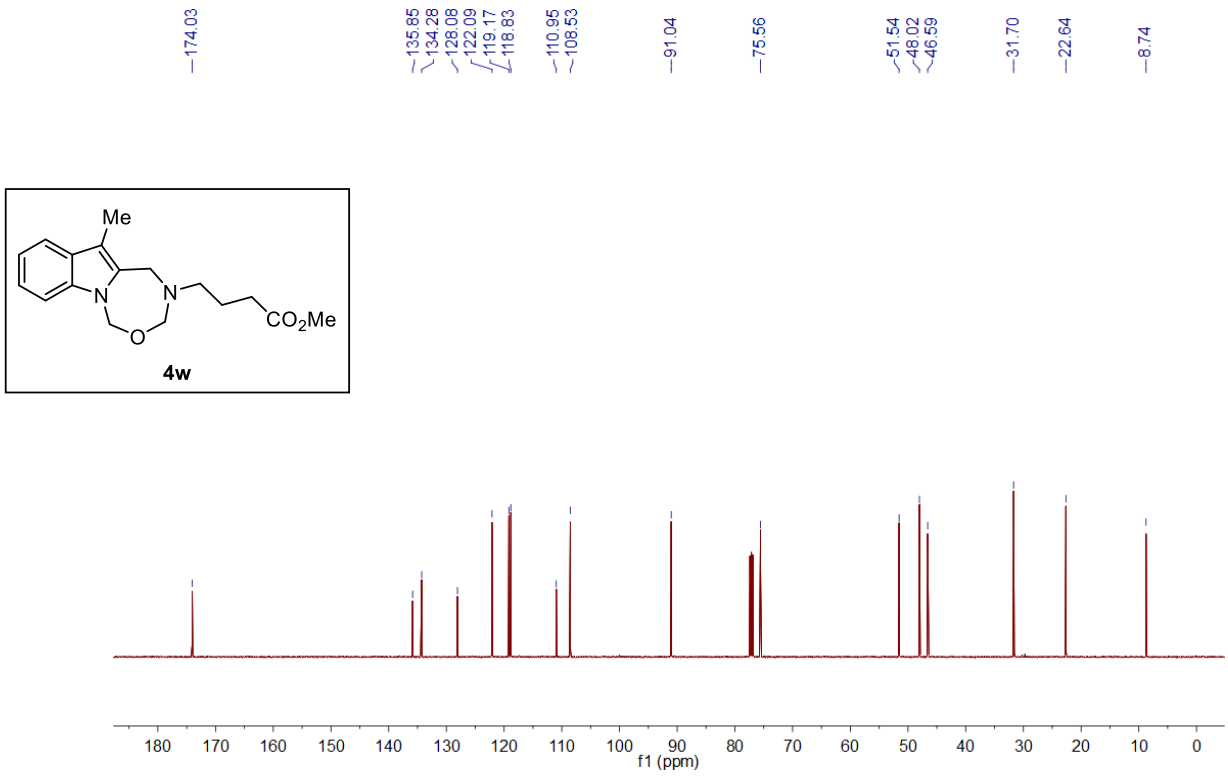




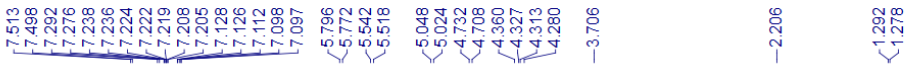
^{1}H-NMR spectrum of compound **4w** (500 MHz, $CDCl_3$)

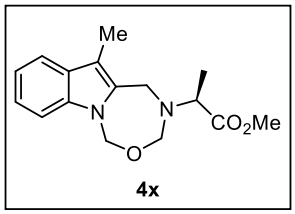


^{13}C-NMR spectrum of compound **4w** (126 MHz, $CDCl_3$)

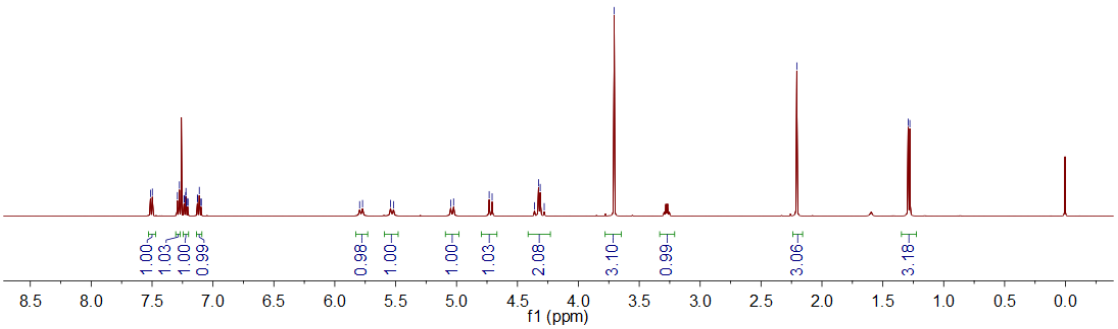


^{1}H-NMR spectrum of compound **4x** (500 MHz, $CDCl_3$)

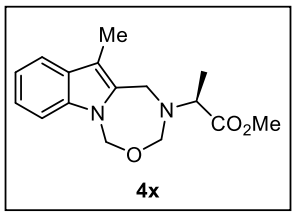




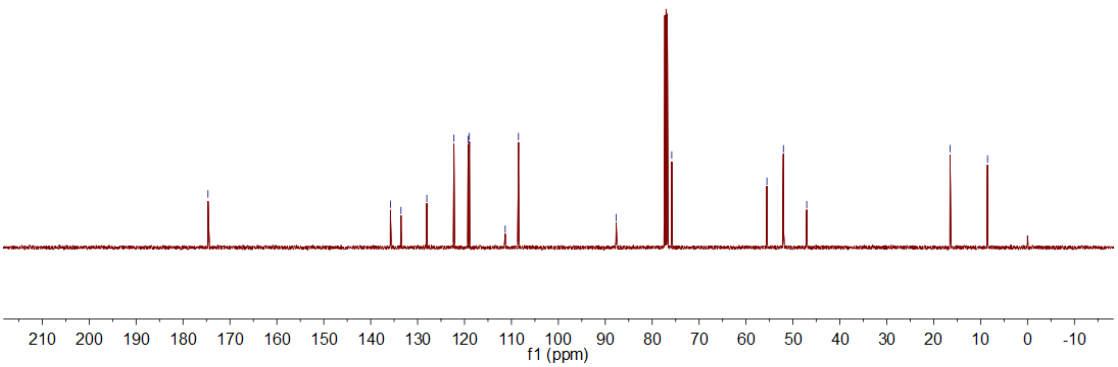
4x



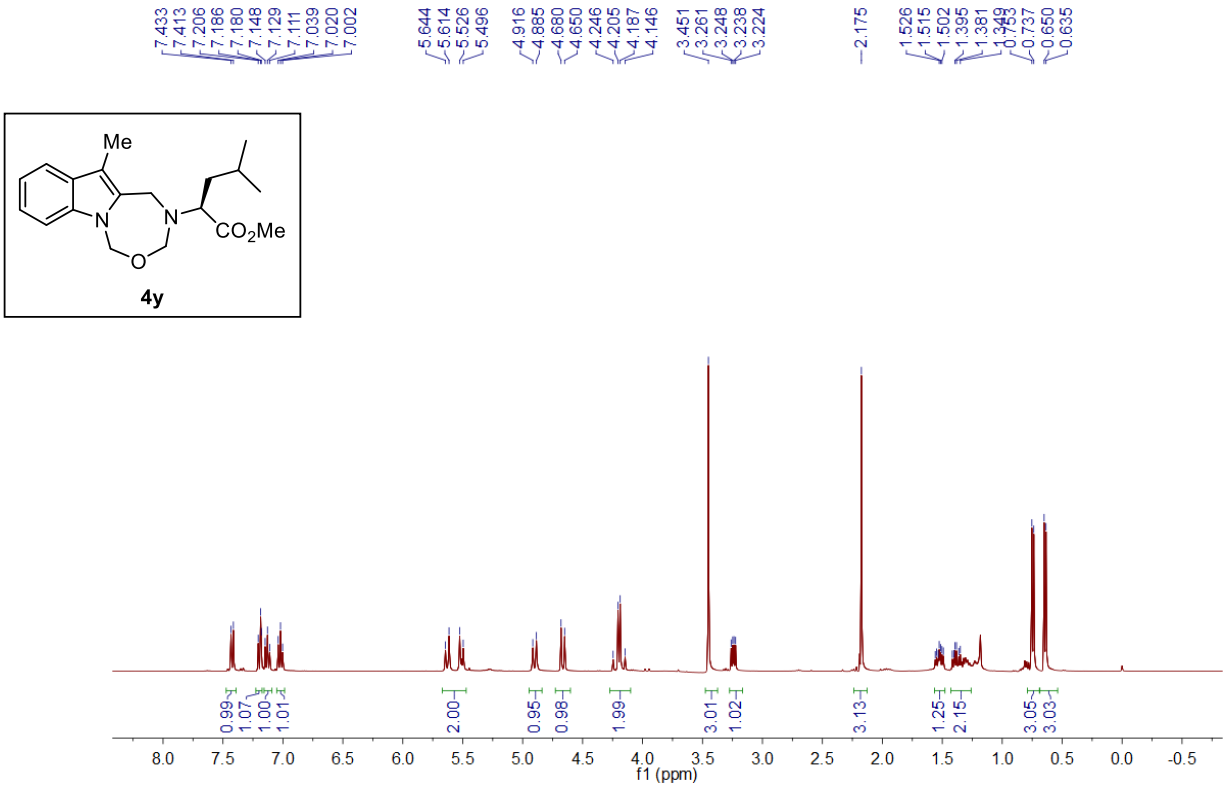
^{13}C-NMR spectrum of compound **4x** (126 MHz, $CDCl_3$)



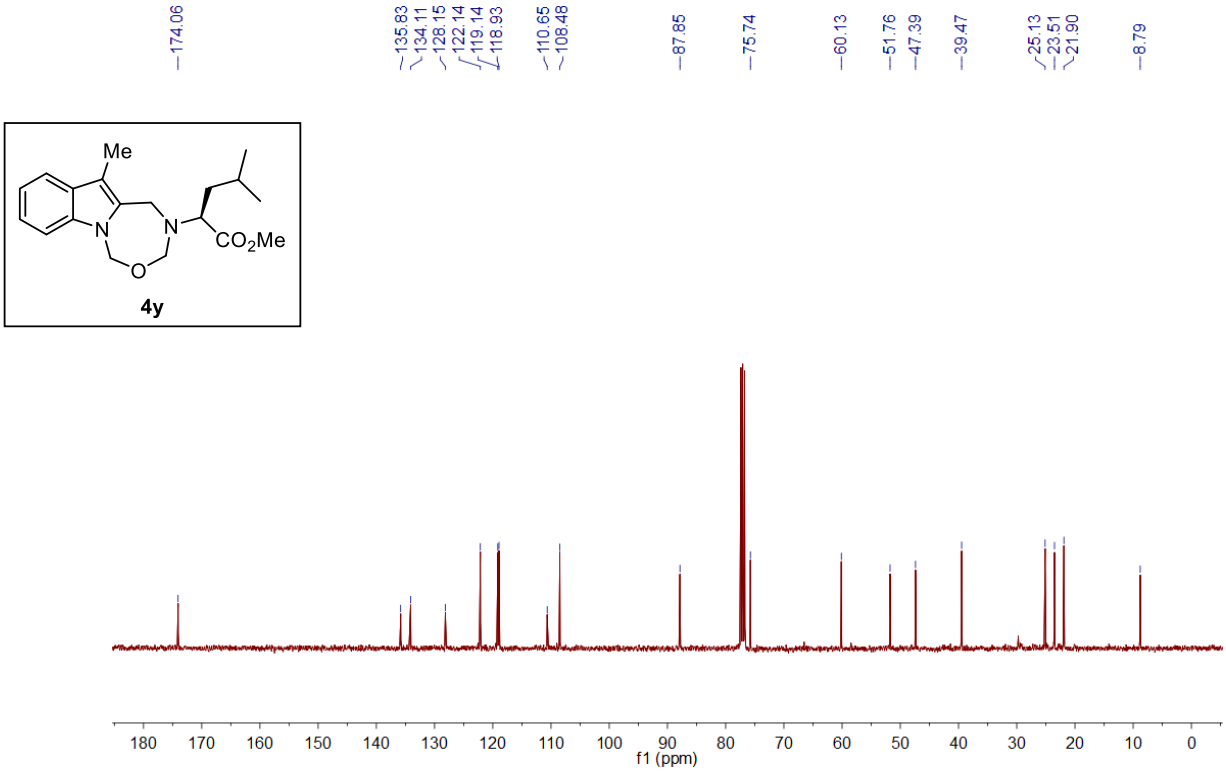
4x



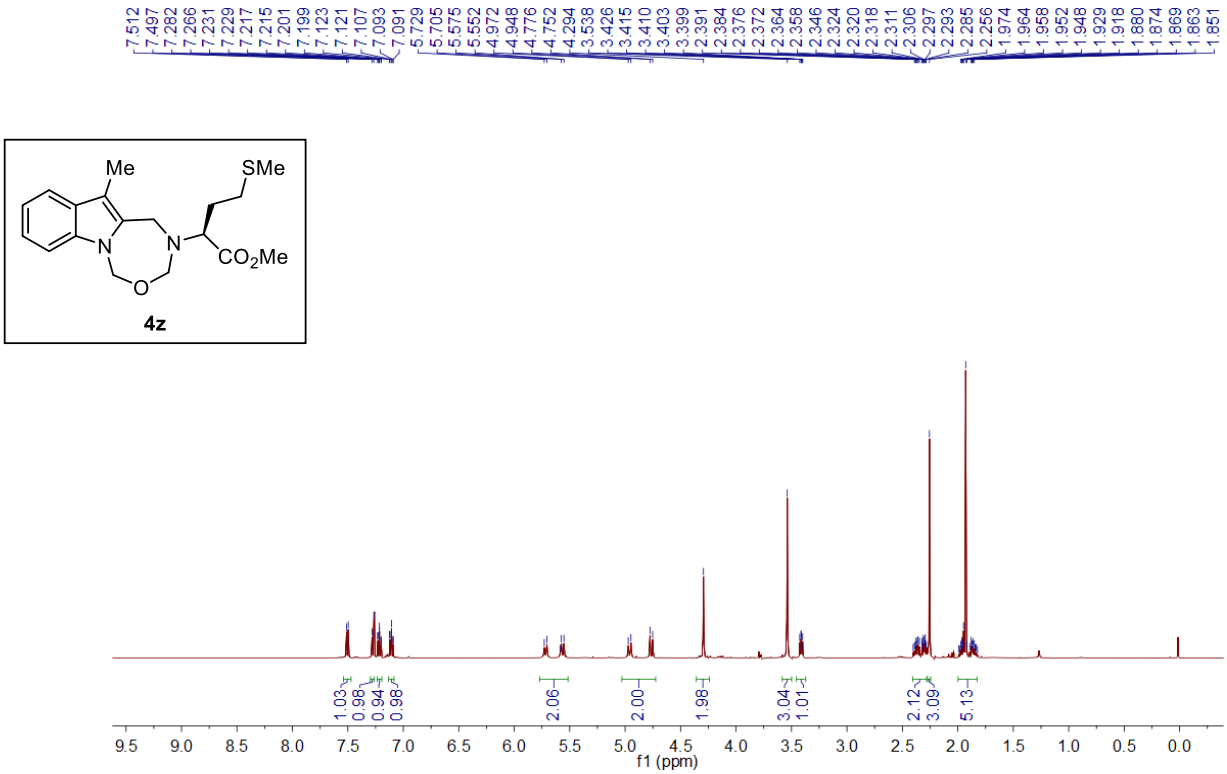
^{1}H-NMR spectrum of compound **4y** (400 MHz, $CDCl_3$)



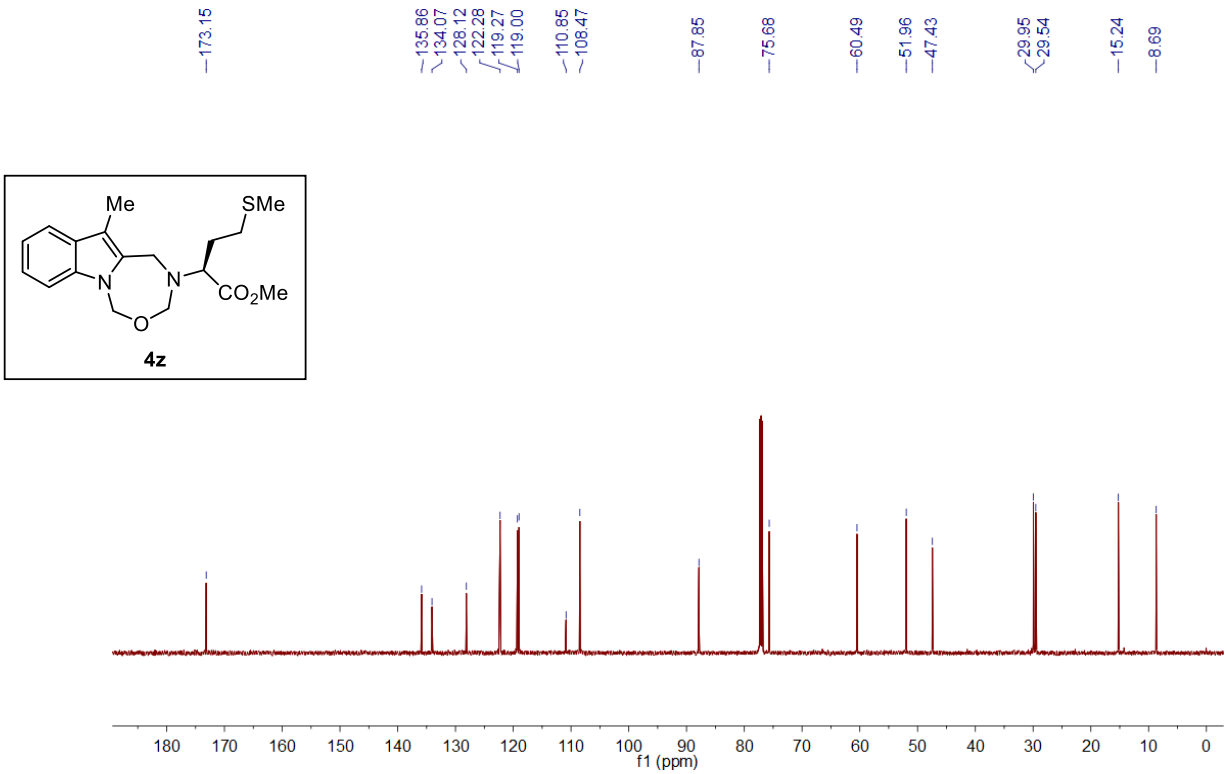
^{13}C-NMR spectrum of compound **4y** (101 MHz, $CDCl_3$)



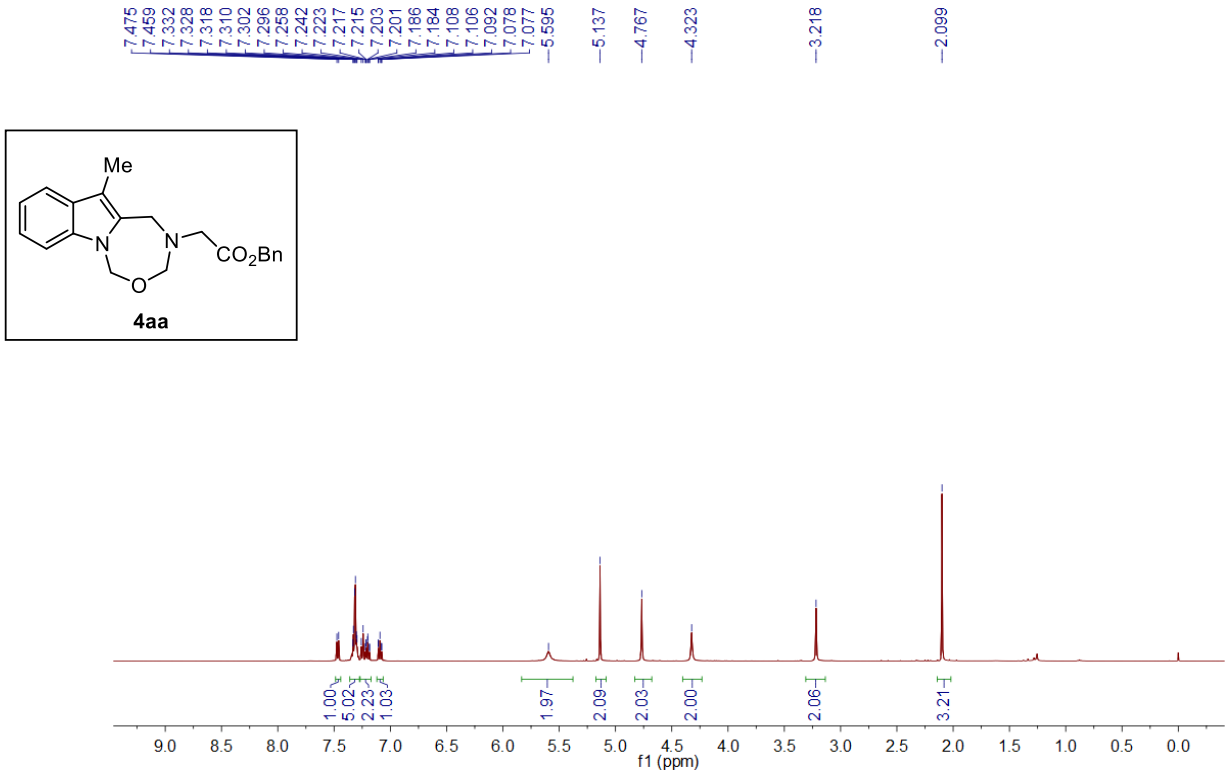
^{1}H-NMR spectrum of compound **4z** (500 MHz, $CDCl_3$)



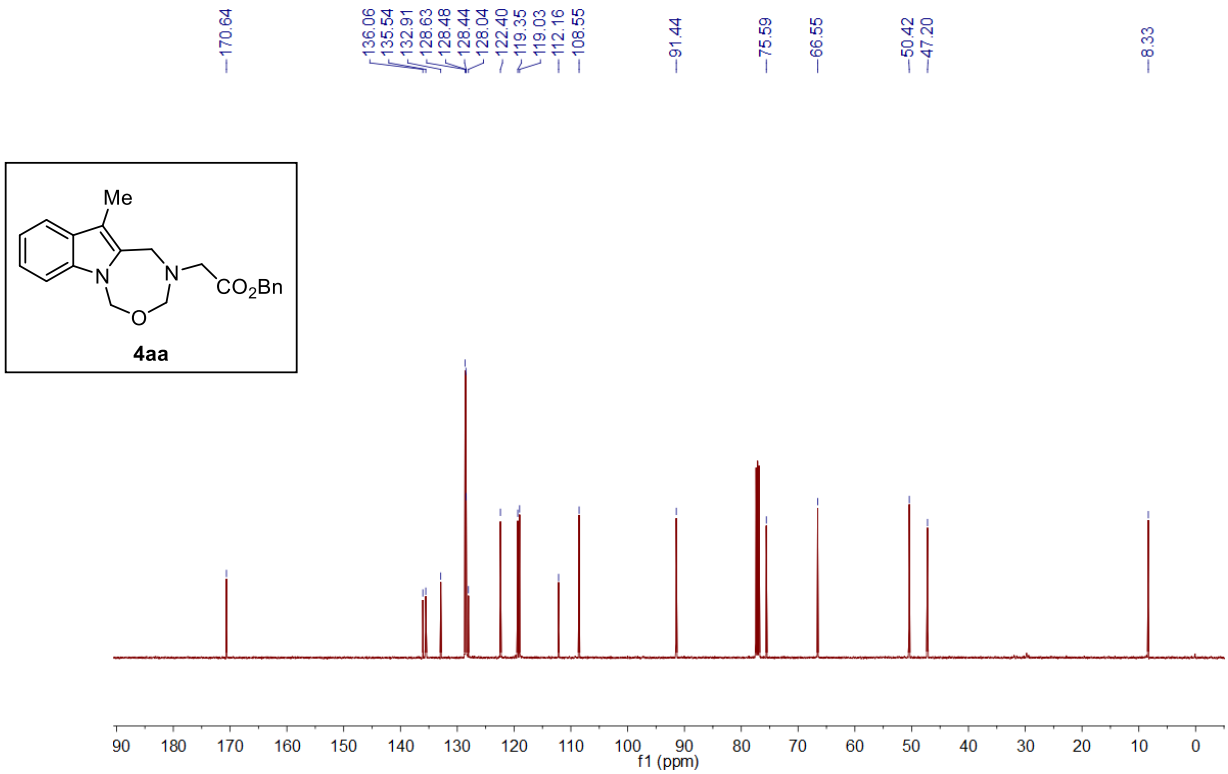
^{13}C-NMR spectrum of compound **4z** (150 MHz, $CDCl_3$)



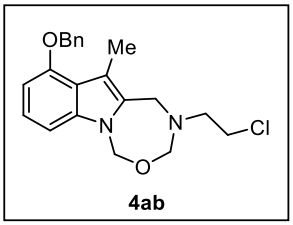
^{1}H-NMR spectrum of compound **4aa** (500 MHz, $CDCl_3$)

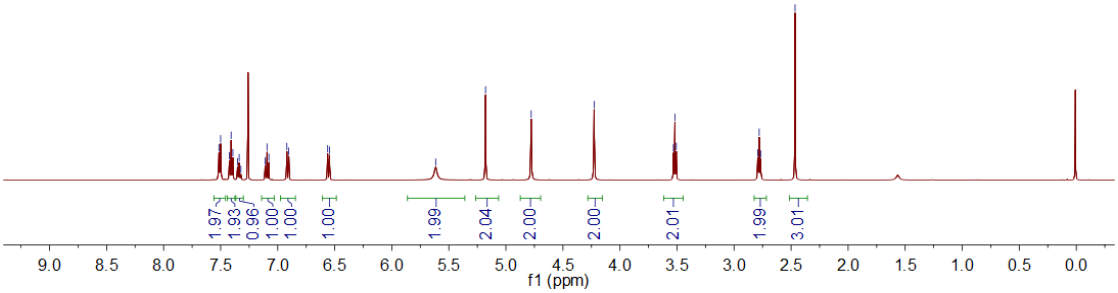


^{13}C-NMR spectrum of compound **4aa** (126 MHz, $CDCl_3$)

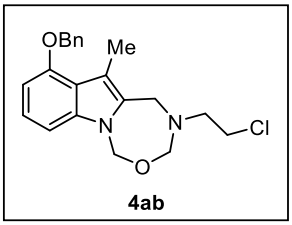


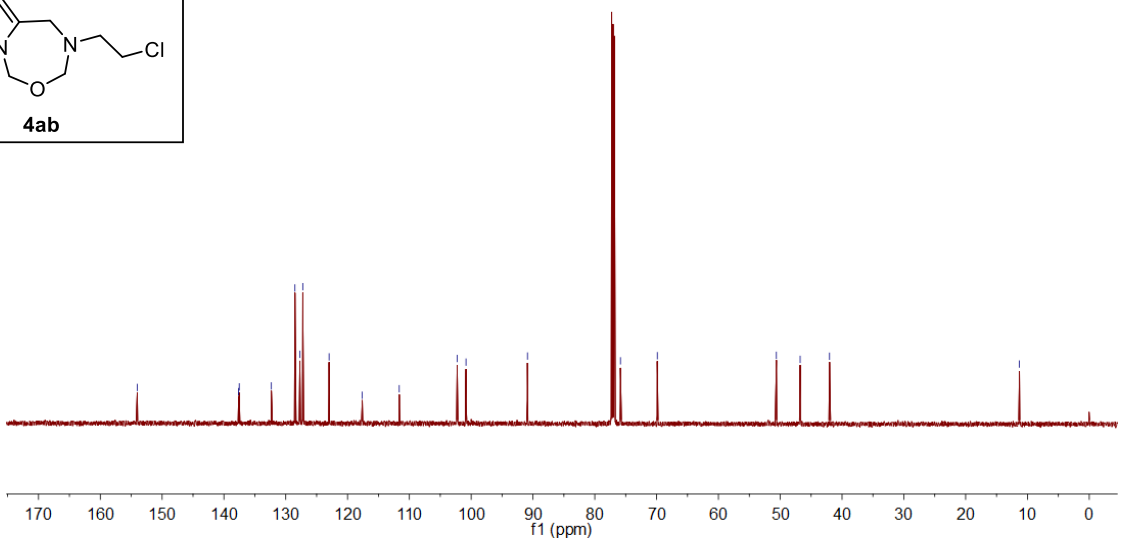
^{1}H-NMR spectrum of compound **4ab** (500 MHz, $CDCl_3$)



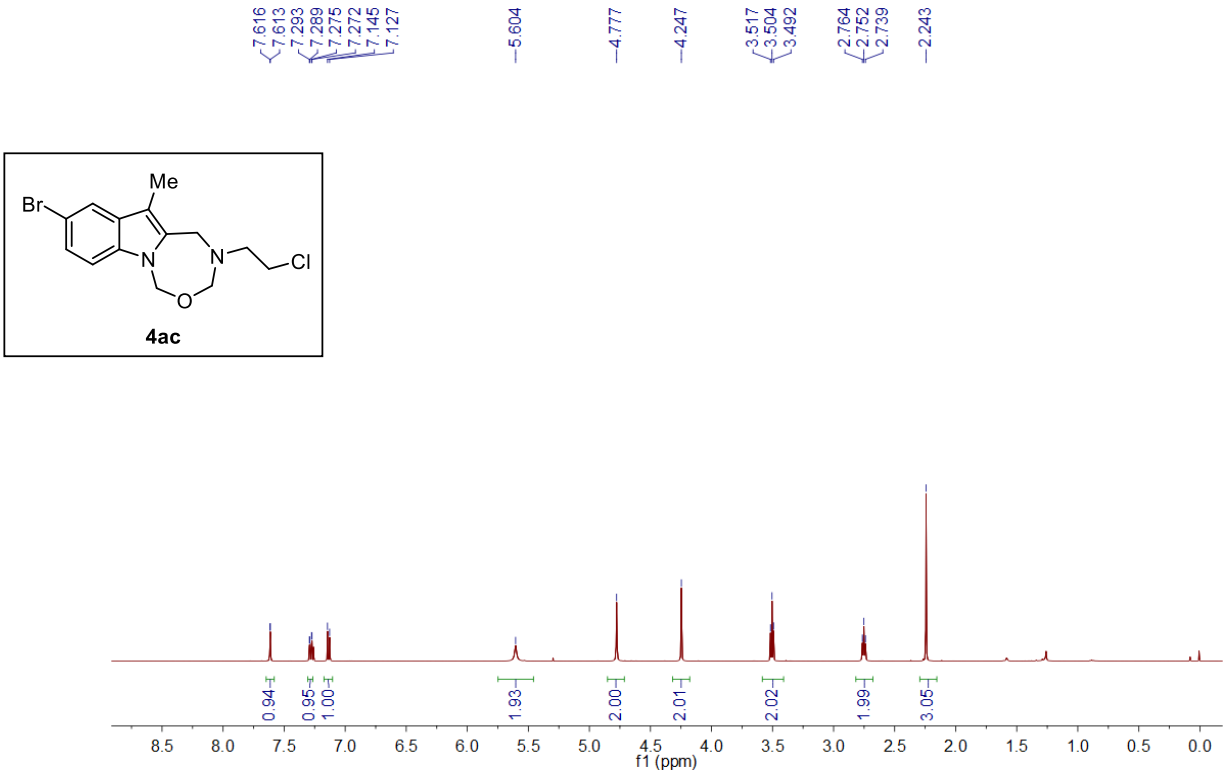


^{13}C-NMR spectrum of compound **4ab** (150 MHz, $CDCl_3$)

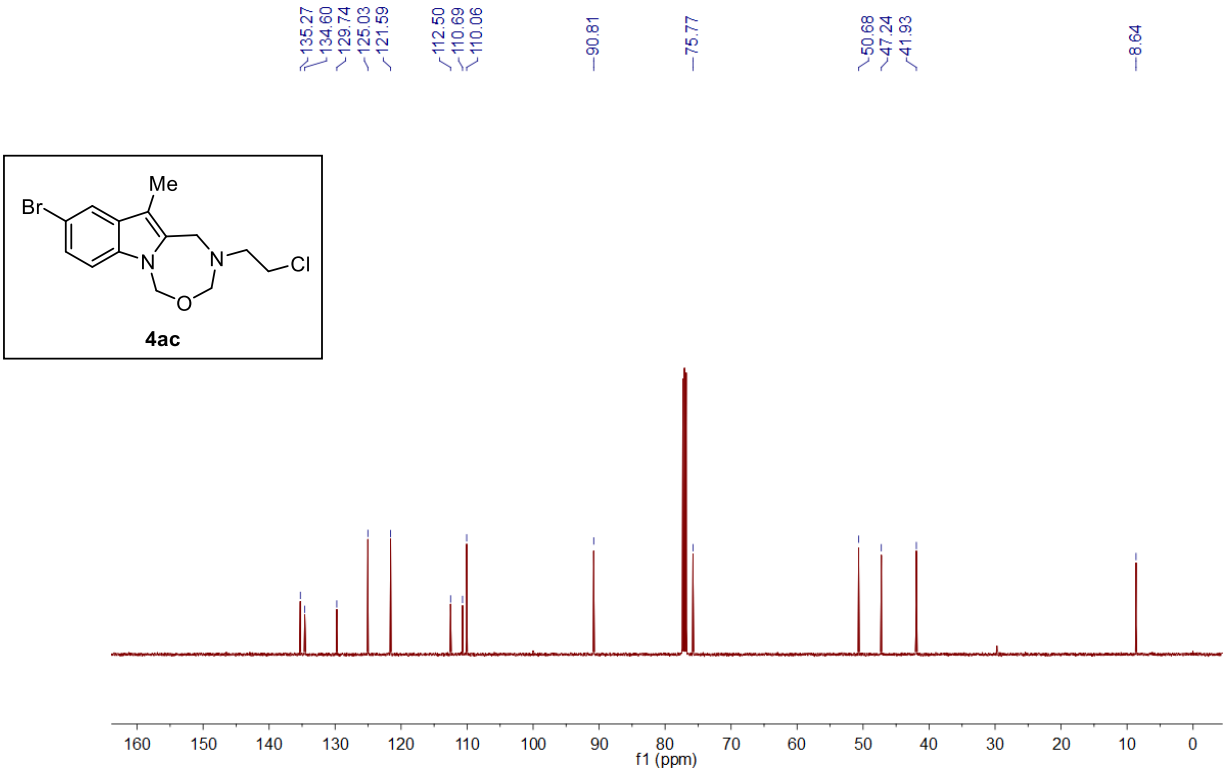




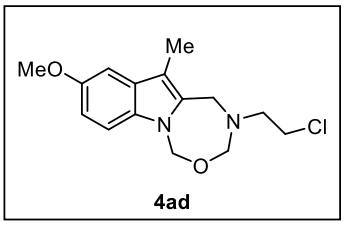
^{1}H-NMR spectrum of compound **4ac** (500 MHz, $CDCl_3$)



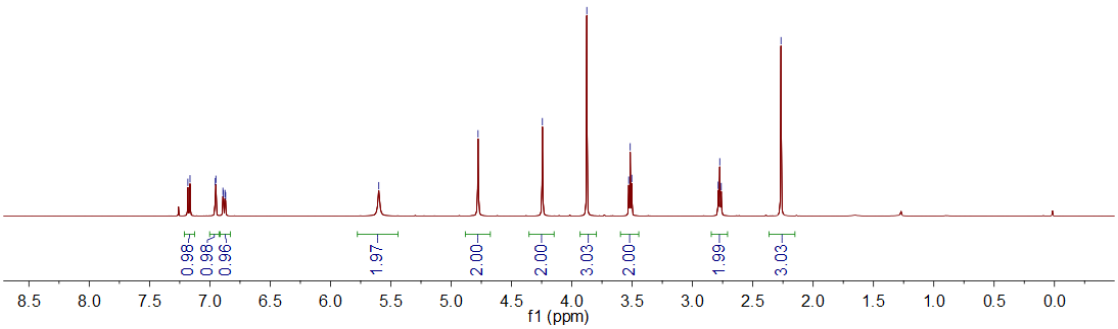
^{13}C-NMR spectrum of compound **4ac** (126 MHz, $CDCl_3$)



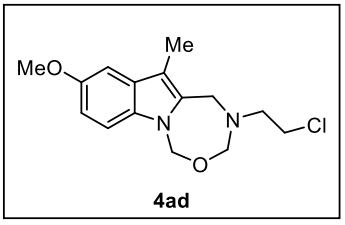
^{1}H-NMR spectrum of compound **4ad** (500 MHz, $CDCl_3$)



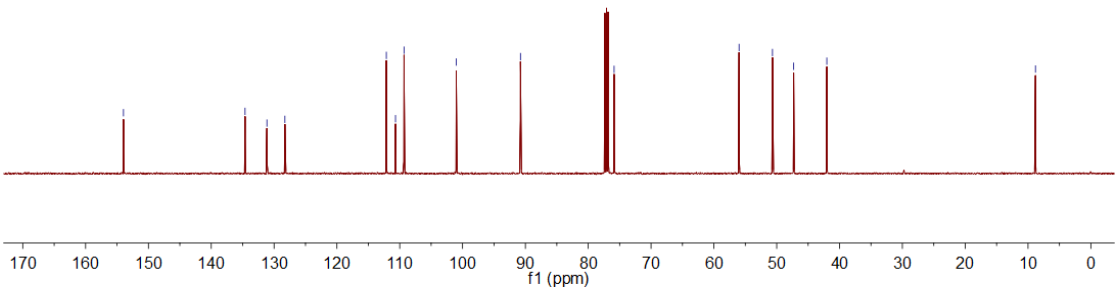
4ad



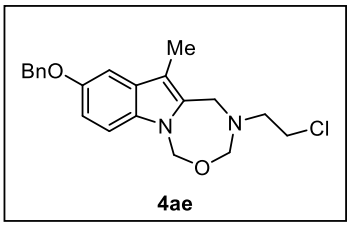
^{13}C-NMR spectrum of compound **4ad** (126 MHz, $CDCl_3$)



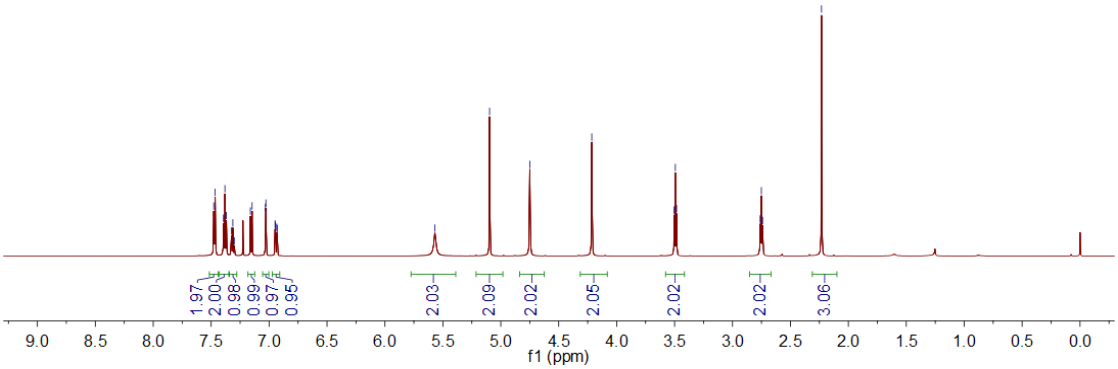
4ad



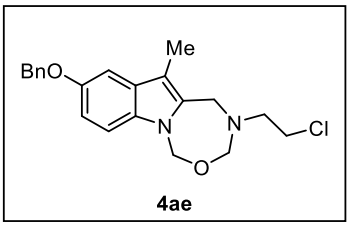
^{1}H-NMR spectrum of compound **4ae** (600 MHz, $CDCl_3$)



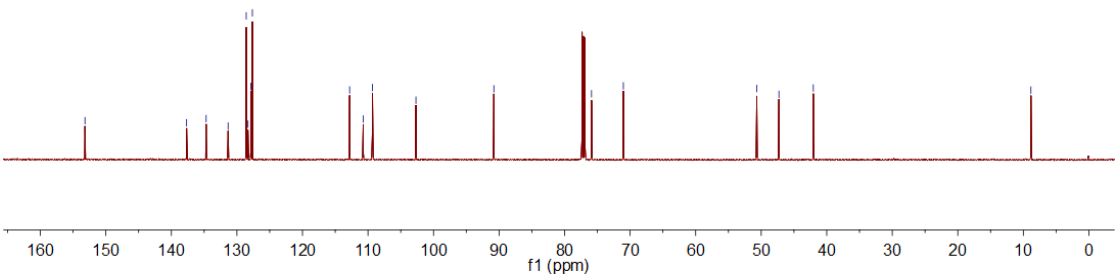
4ae



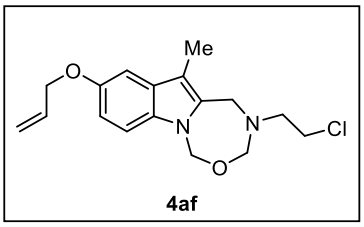
^{13}C-NMR spectrum of compound **4ae** (150 MHz, $CDCl_3$)

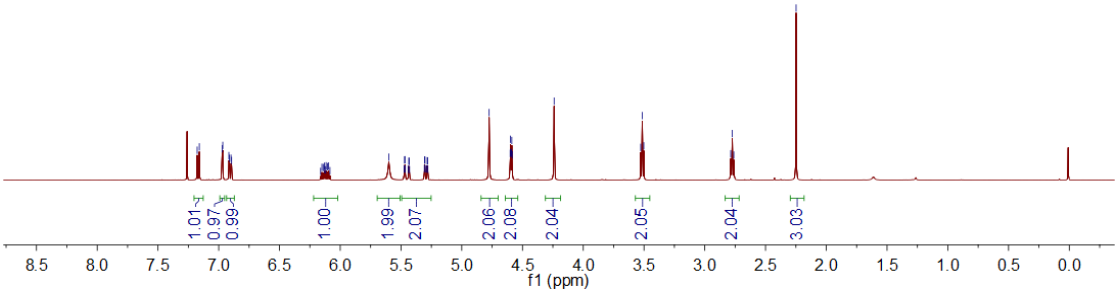


4ae

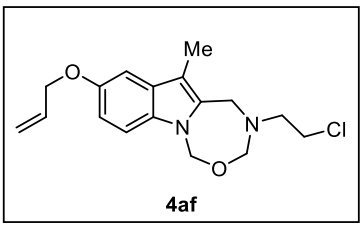


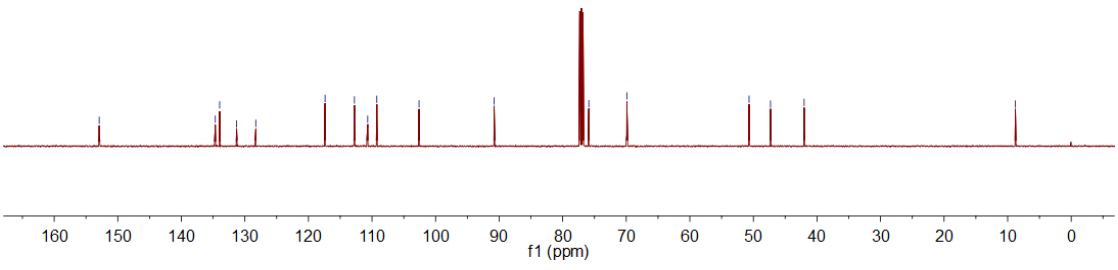
^{1}H-NMR spectrum of compound **4af** (500 MHz, $CDCl_3$)



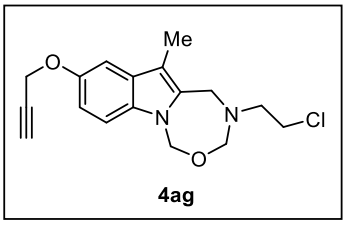


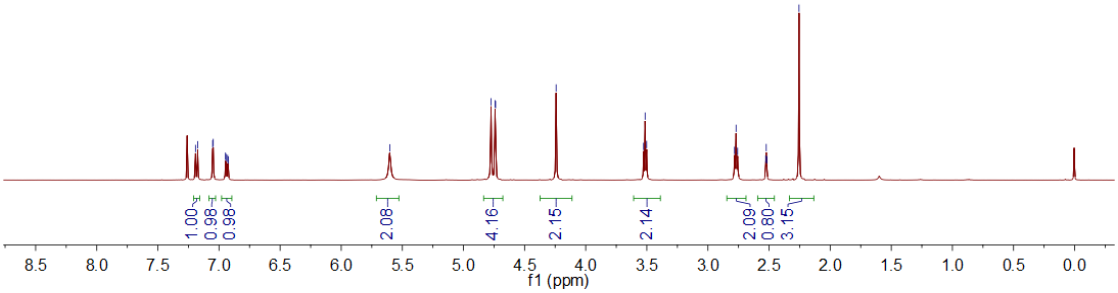
^{13}C-NMR spectrum of compound **4af** (126 MHz, $CDCl_3$)



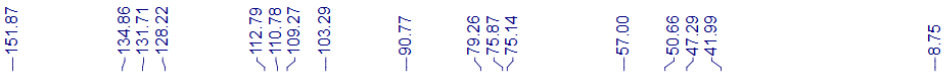


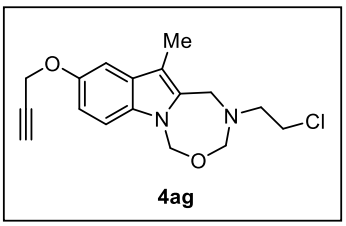
^{1}H-NMR spectrum of compound **4ag** (500 MHz, $CDCl_3$)

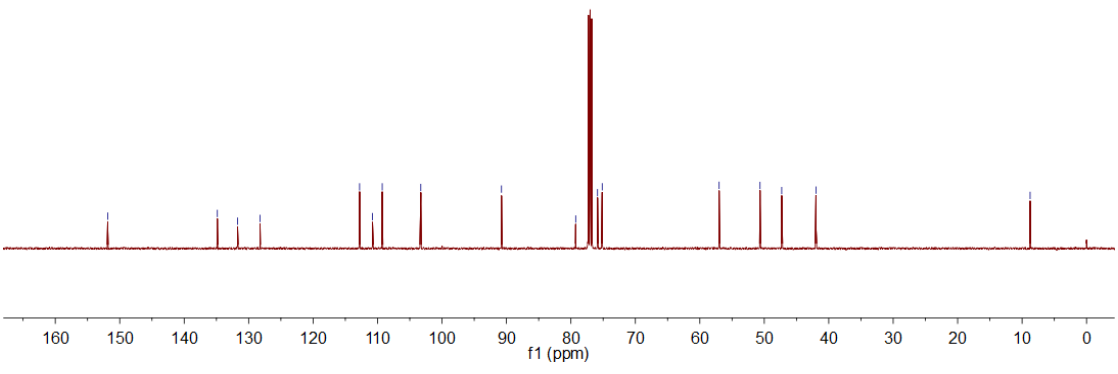




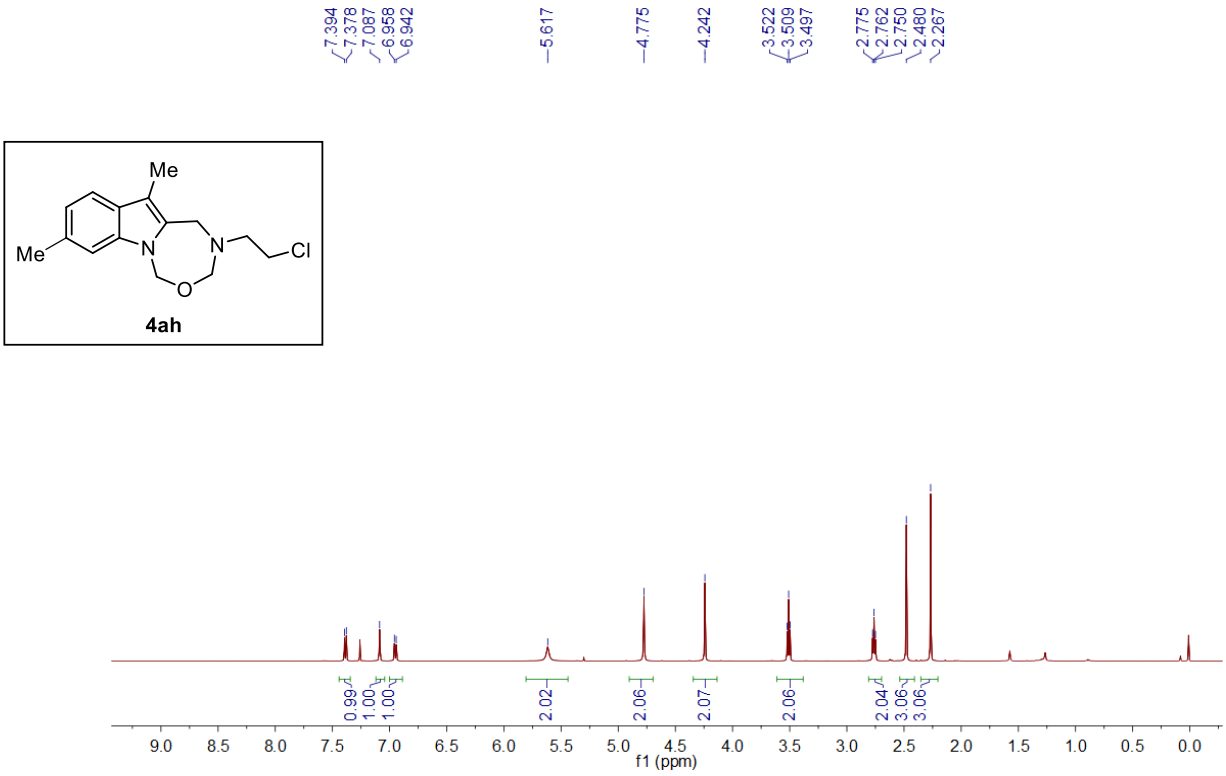
^{13}C-NMR spectrum of compound **4ag** (126 MHz, $CDCl_3$)



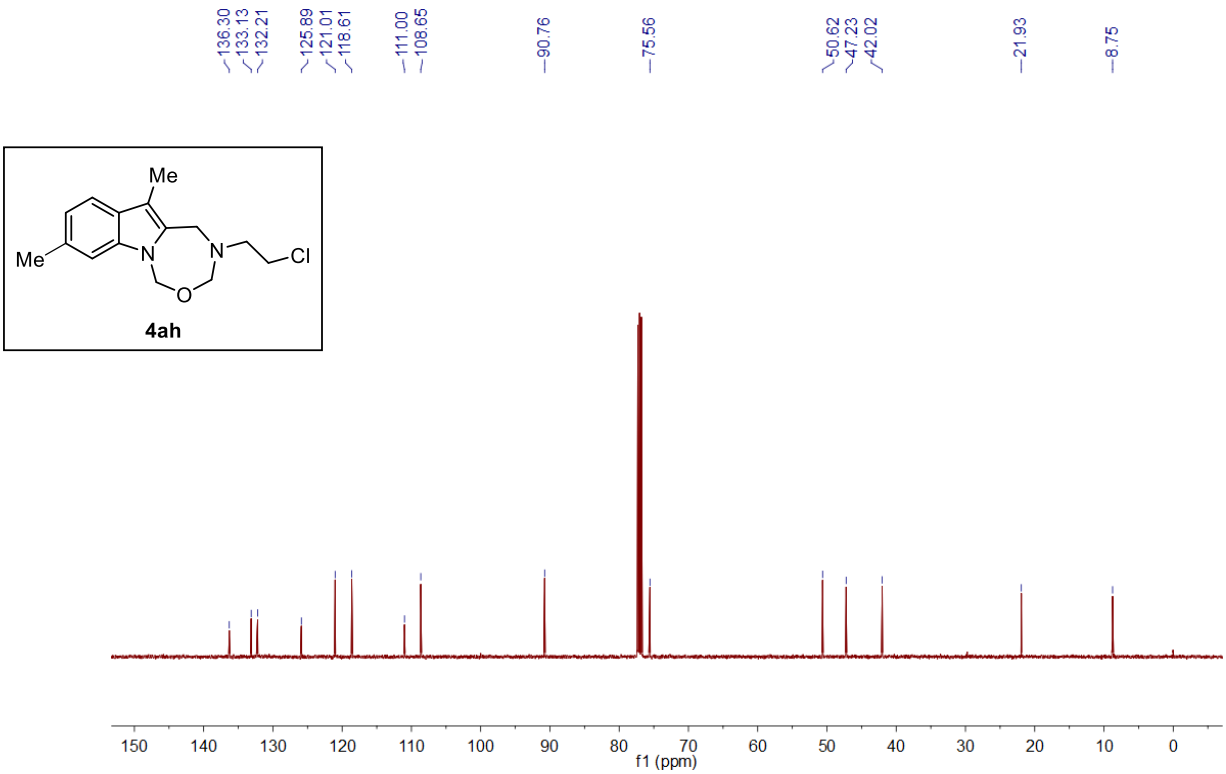




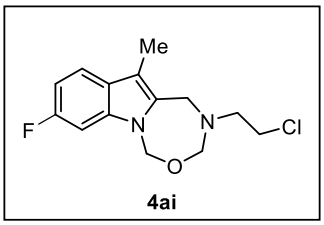
^{1}H-NMR spectrum of compound **4ah** (500 MHz, $CDCl_3$)



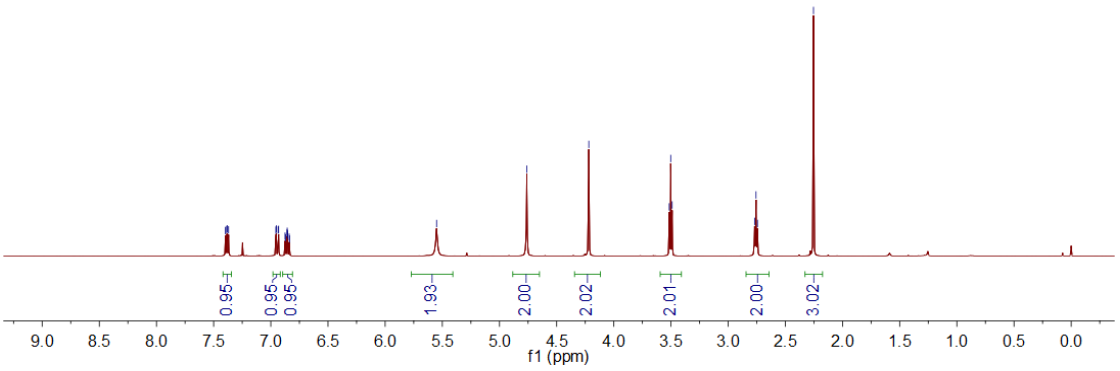
^{13}C-NMR spectrum of compound **4ah** (126 MHz, $CDCl_3$)



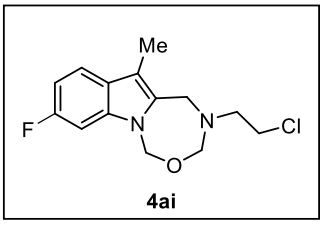
^{1}H-NMR spectrum of compound **4ai** (500 MHz, $CDCl_3$)



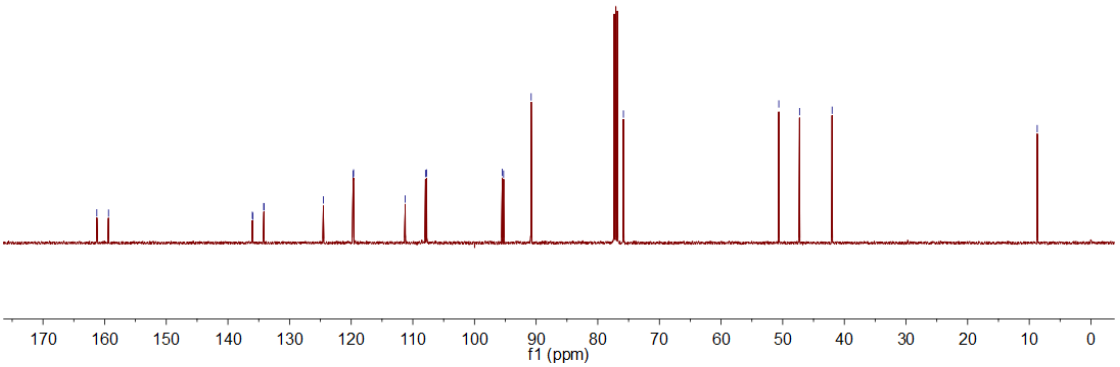
4ai



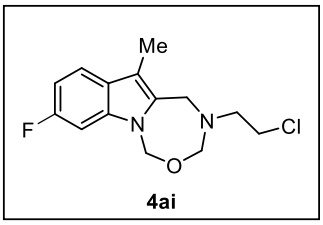
^{13}C-NMR spectrum of compound **4ai** (126 MHz, $CDCl_3$)



4ai

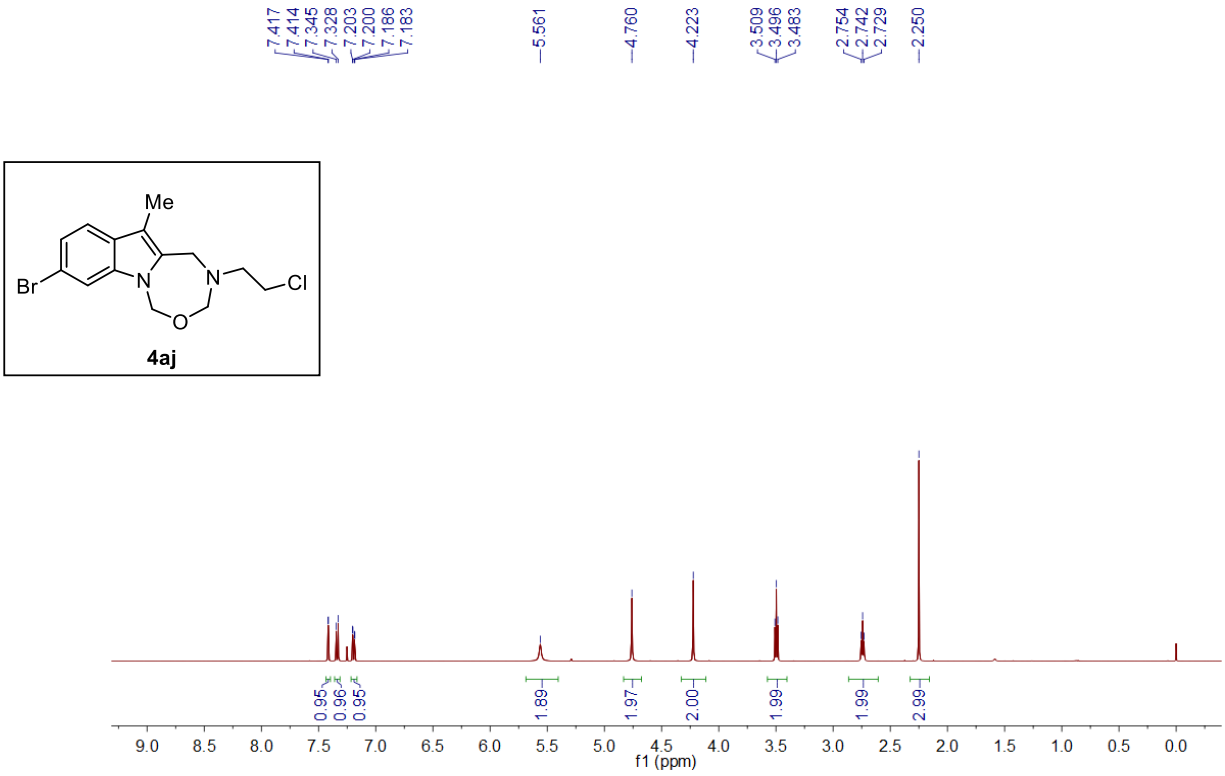


^{19}F-NMR spectrum of compound **4ai** (376 MHz, $CDCl_3$)

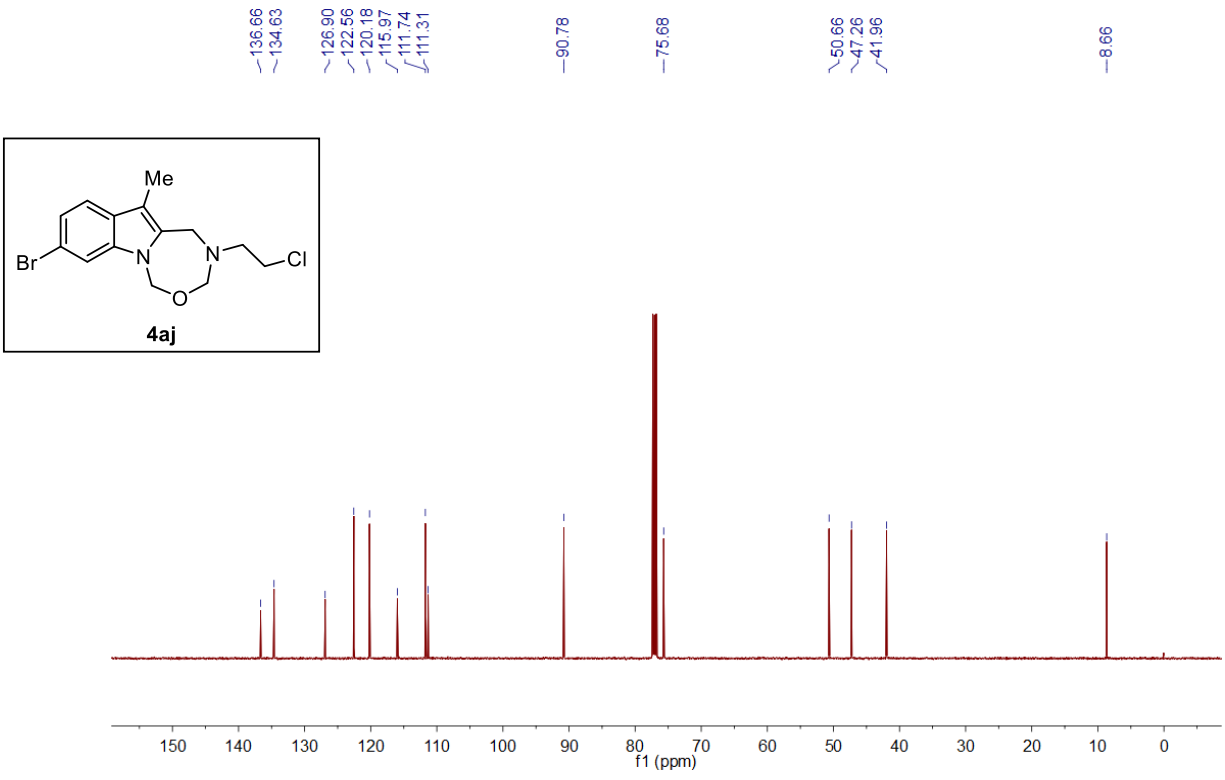


4ai

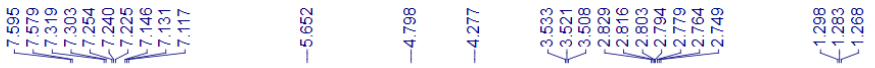
^{1}H-NMR spectrum of compound **4aj** (500 MHz, $CDCl_3$)

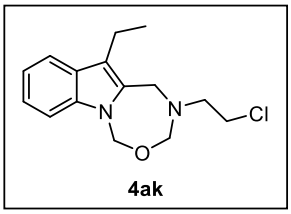


^{13}C-NMR spectrum of compound **4aj** (126 MHz, $CDCl_3$)

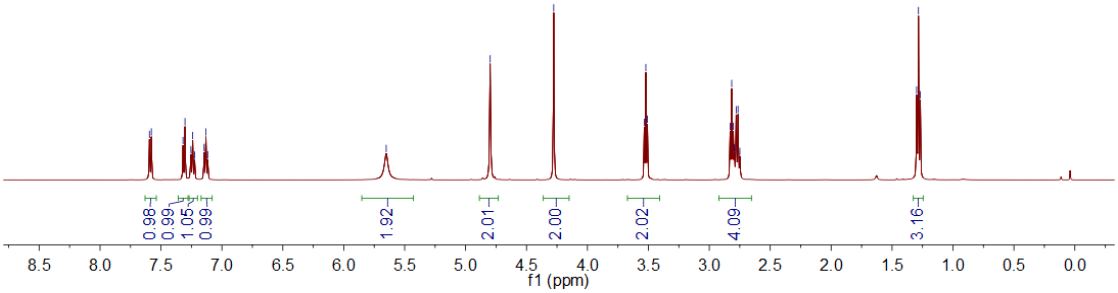


^{1}H-NMR spectrum of compound **4ak** (500 MHz, $CDCl_3$)

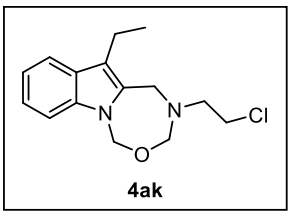




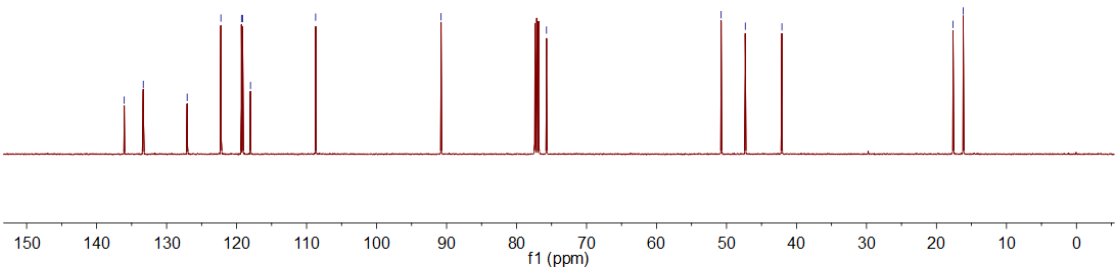
4ak



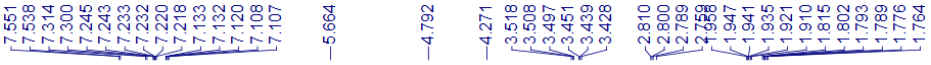
^{13}C-NMR spectrum of compound **4ak** (126 MHz, $CDCl_3$)

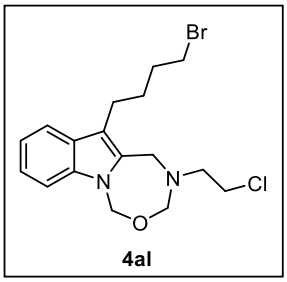


4ak

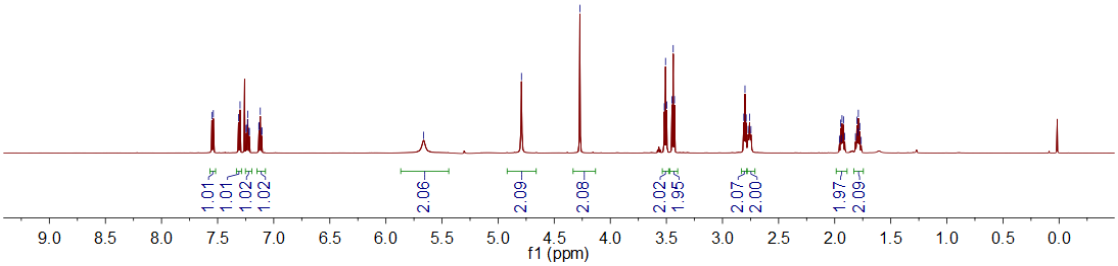


^{1}H-NMR spectrum of compound **4al** (600 MHz, $CDCl_3$)

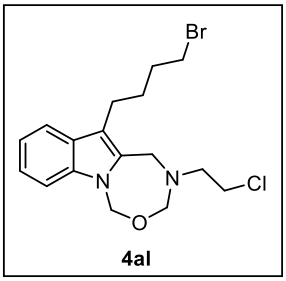




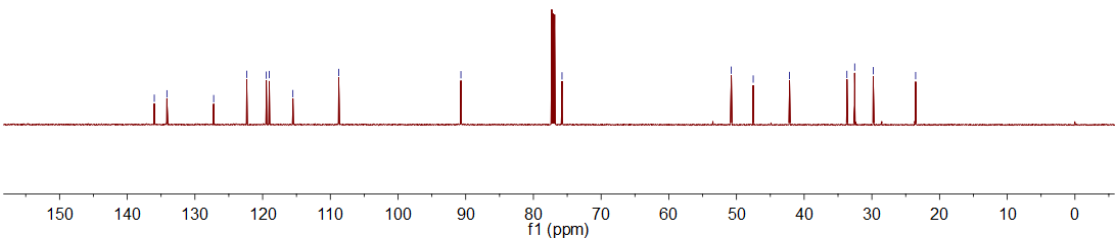
4al



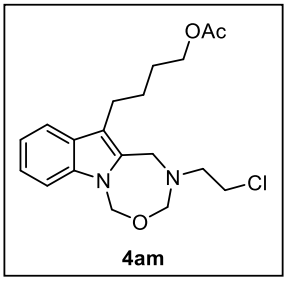
^{13}C-NMR spectrum of compound **4al** (150 MHz, $CDCl_3$)



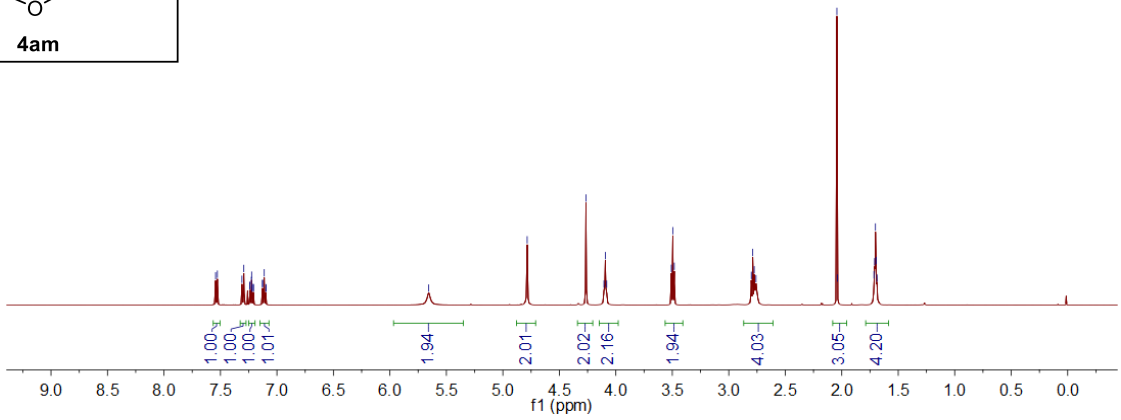
4al



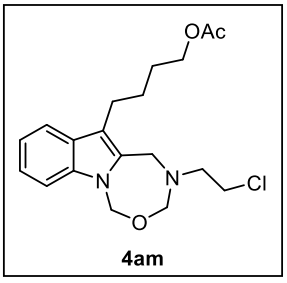
^{1}H-NMR spectrum of compound **4am** (500 MHz, $CDCl_3$)



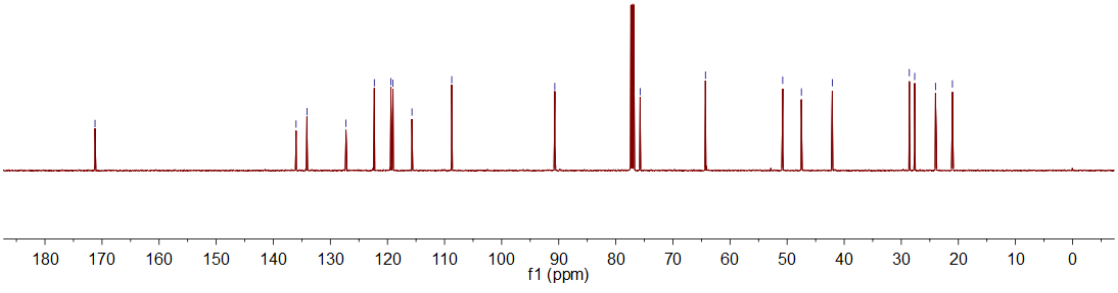
4am



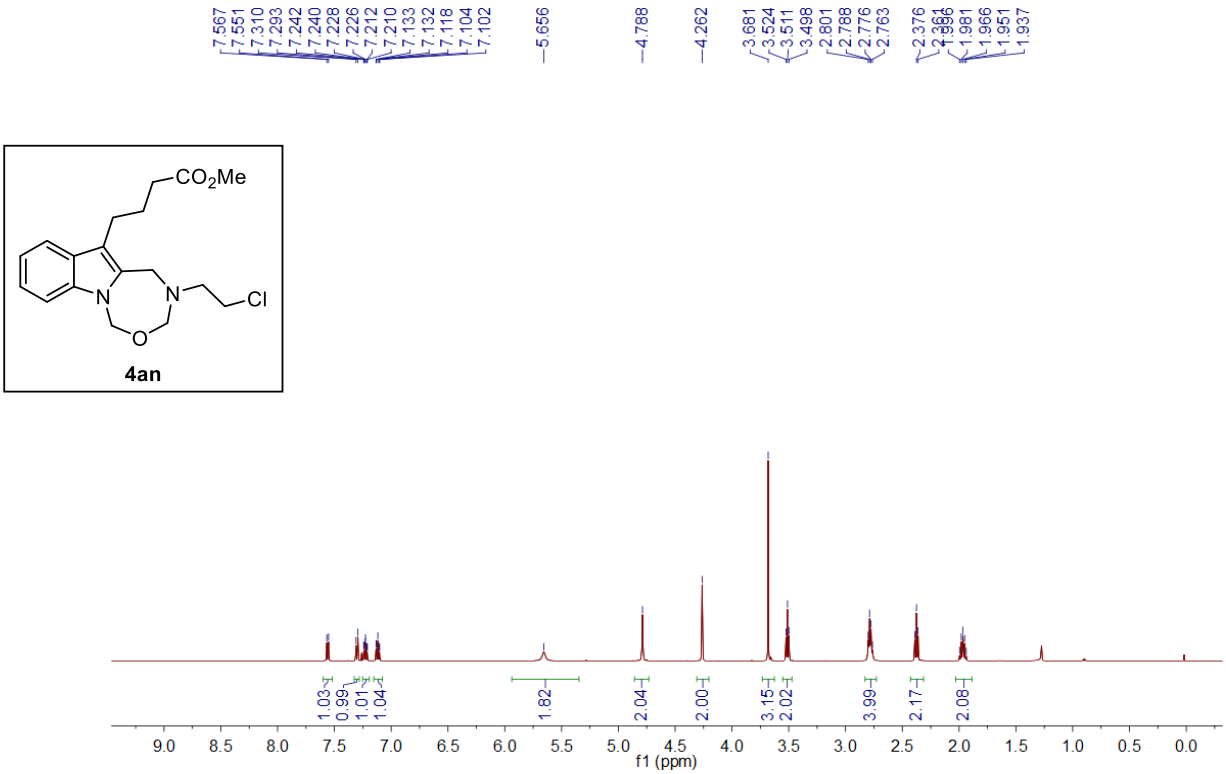
^{13}C-NMR spectrum of compound **4am** (126 MHz, $CDCl_3$)



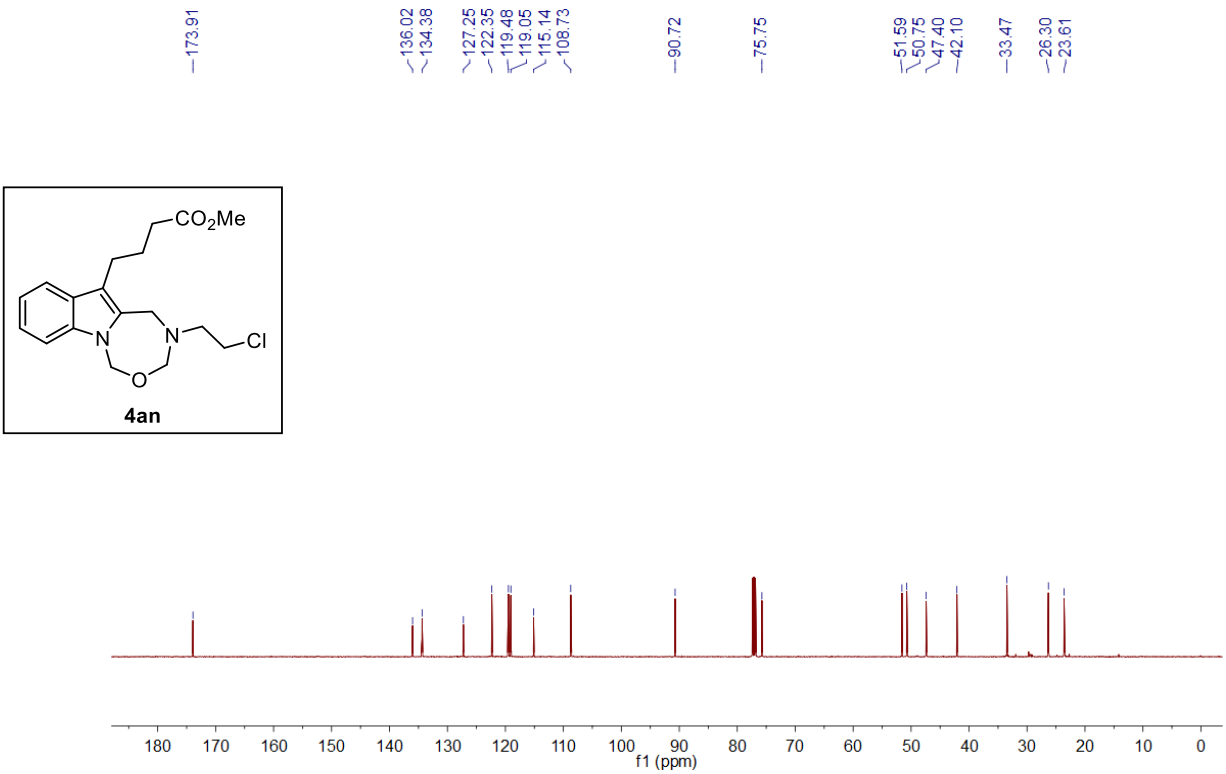
4am



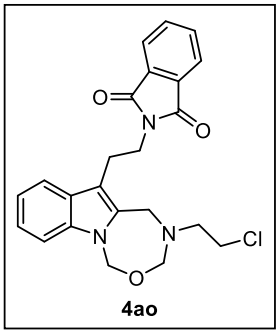
^{1}H-NMR spectrum of compound **4an** (500 MHz, $CDCl_3$)

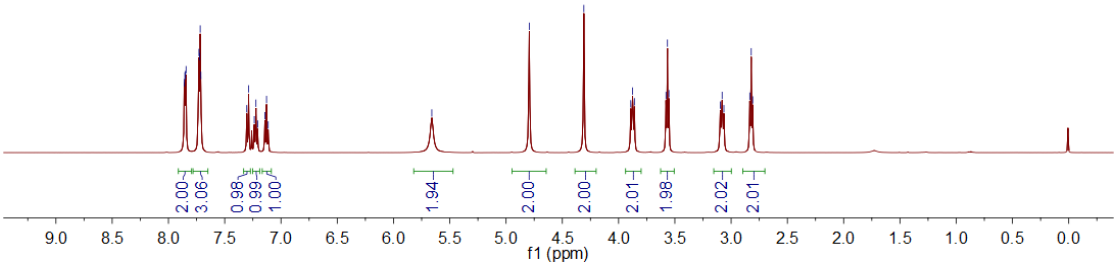


^{13}C-NMR spectrum of compound **4an** (126 MHz, $CDCl_3$)

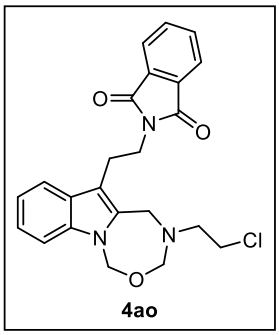


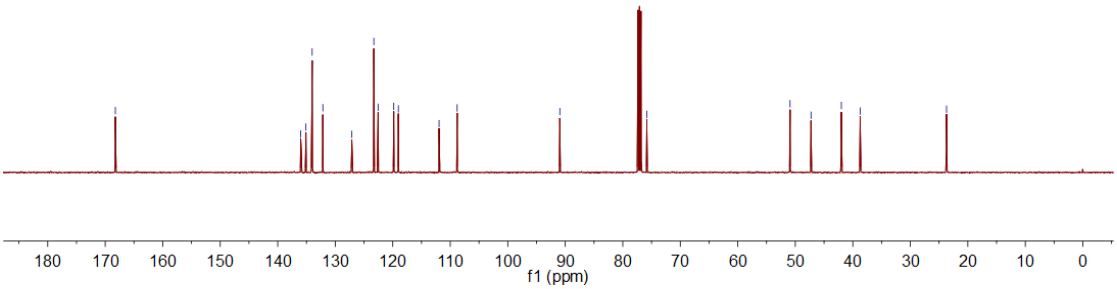
^{1}H-NMR spectrum of compound **4ao** (500 MHz, $CDCl_3$)



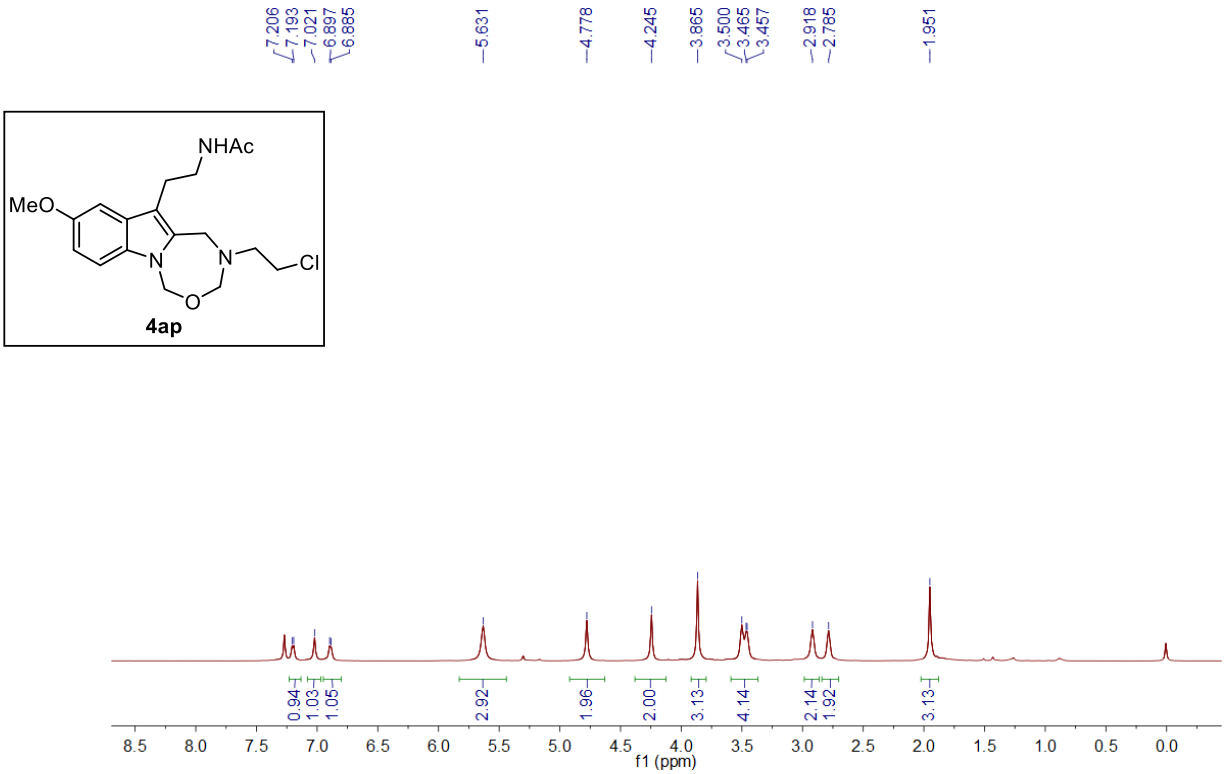


^{13}C-NMR spectrum of compound **4ao** (126 MHz, $CDCl_3$)

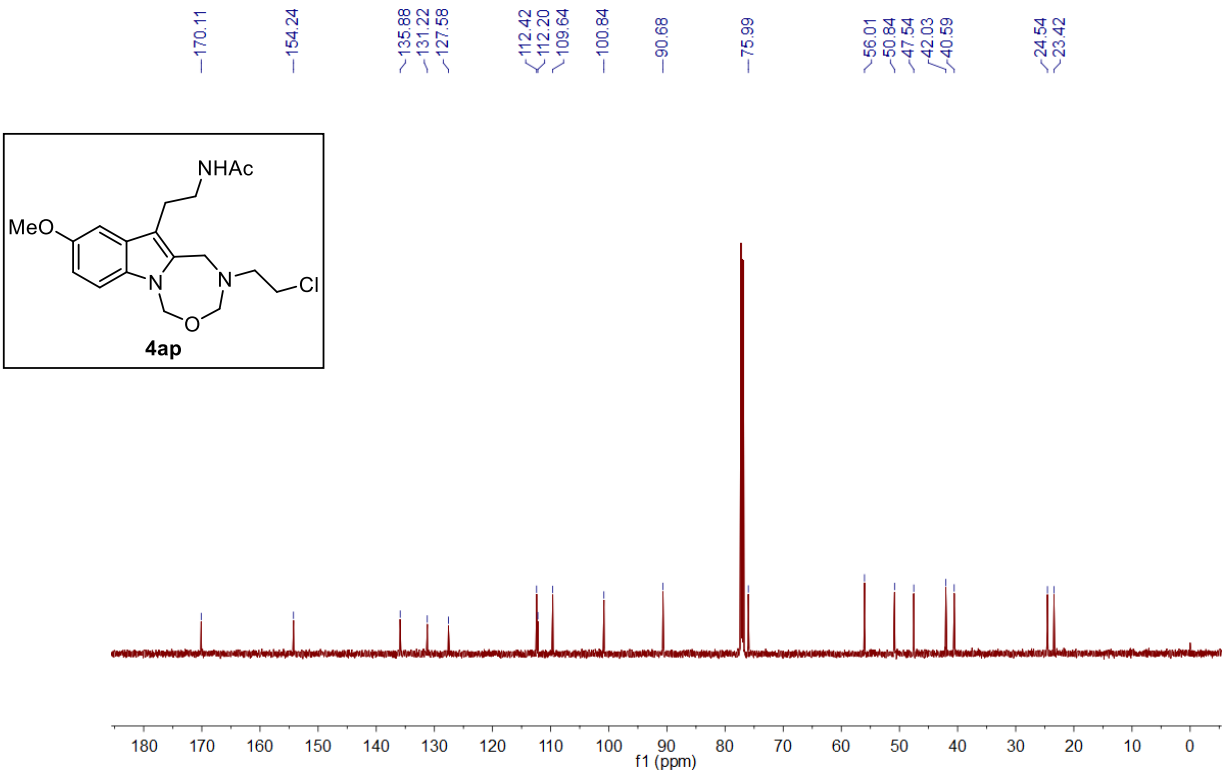




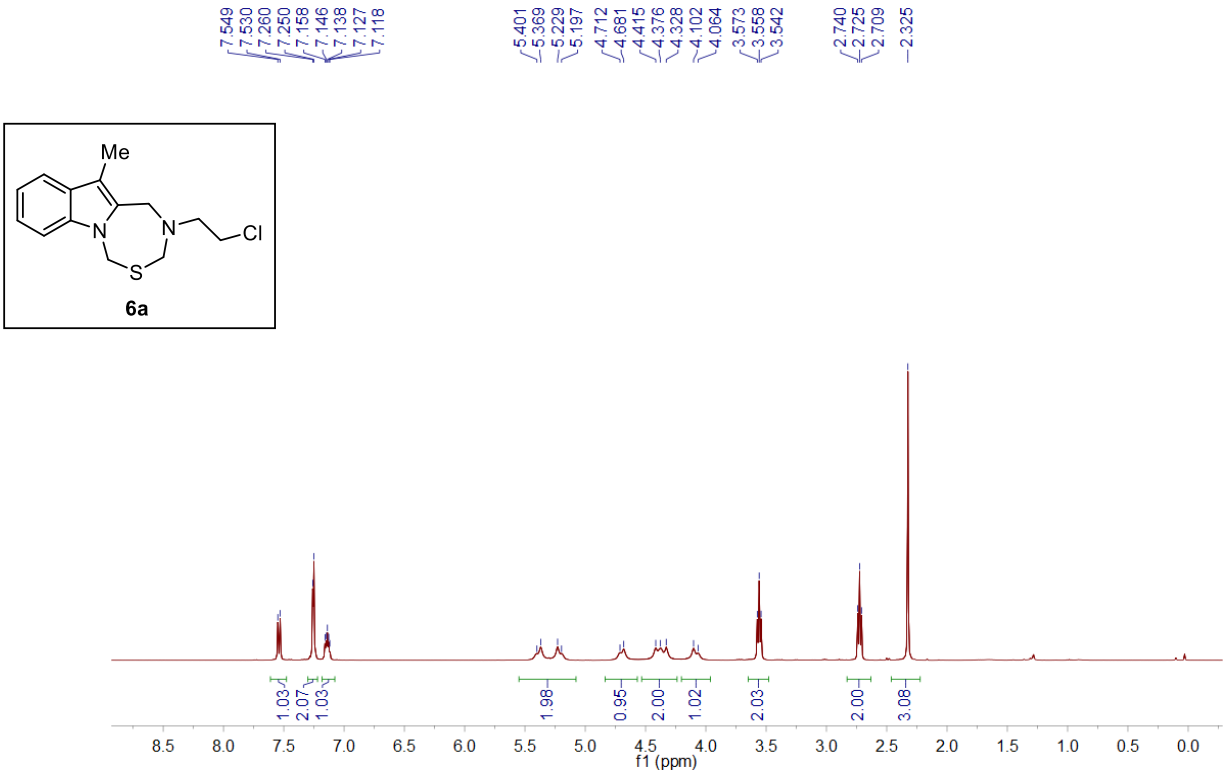
^{1}H-NMR spectrum of compound **4ap** (600 MHz, $CDCl_3$)



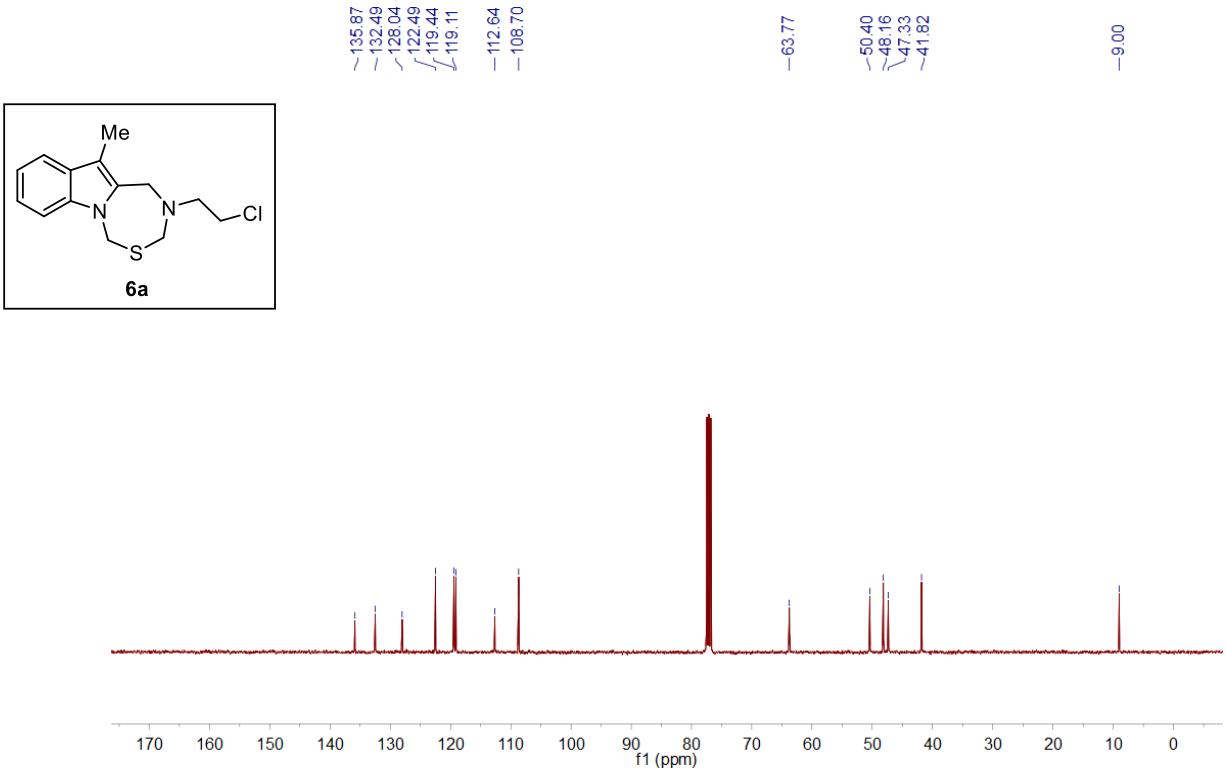
^{13}C-NMR spectrum of compound **4ap** (150 MHz, $CDCl_3$)



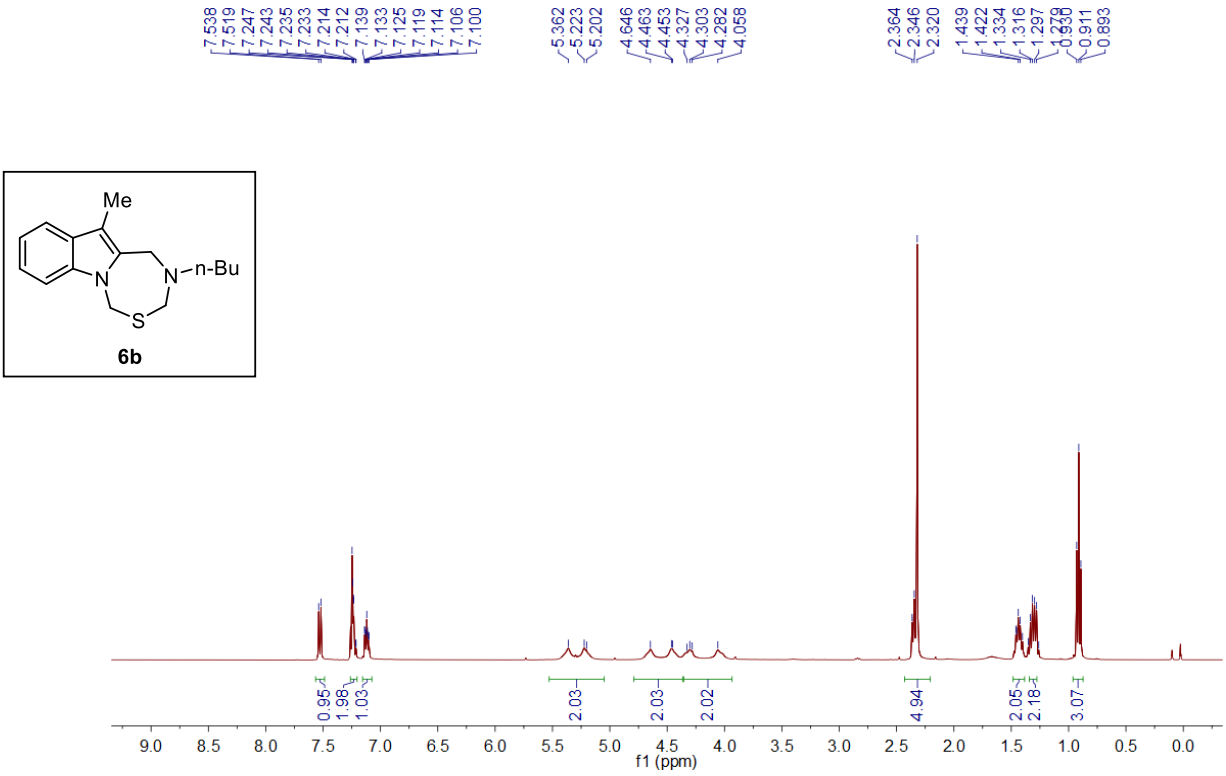
^{1}H-NMR spectrum of compound **6a** (400 MHz, $CDCl_3$)



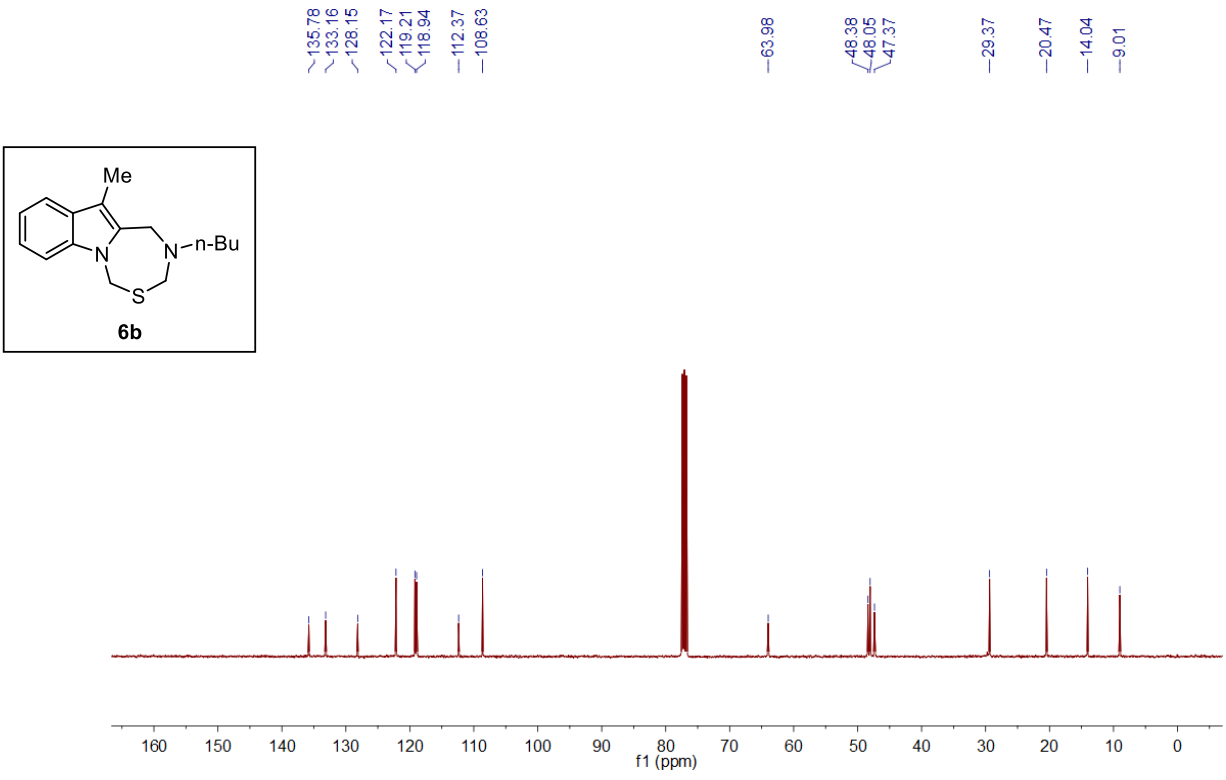
^{13}C-NMR spectrum of compound **6a** (101 MHz, $CDCl_3$)



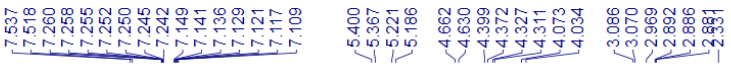
^{1}H-NMR spectrum of compound **6b** (400 MHz, $CDCl_3$)

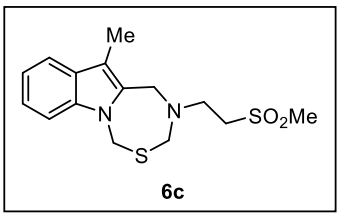


^{13}C-NMR spectrum of compound **6b** (101 MHz, $CDCl_3$)

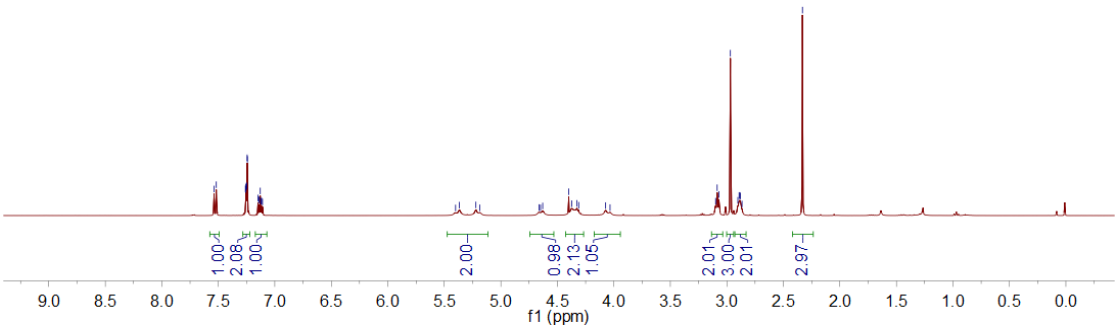


^{1}H-NMR spectrum of compound **6c** (400 MHz, $CDCl_3$)

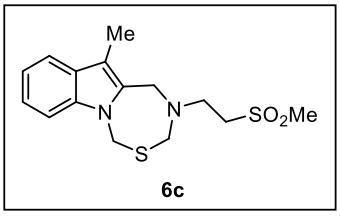




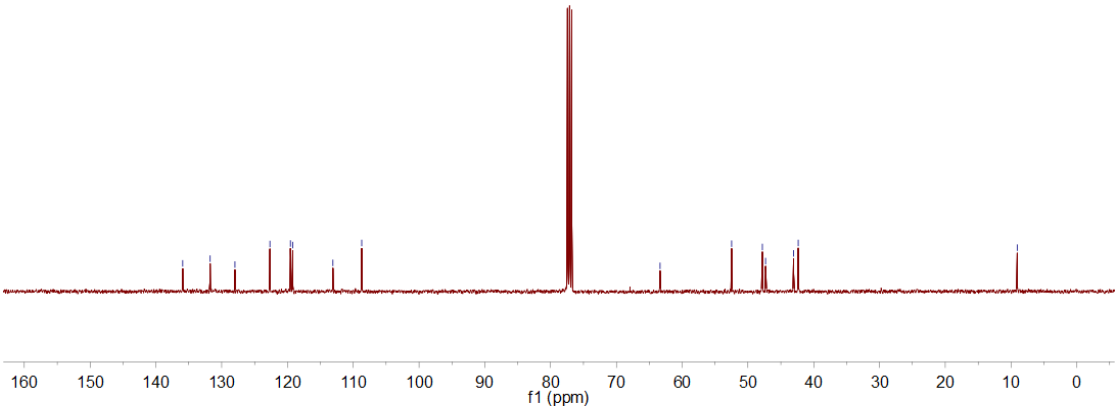
6c



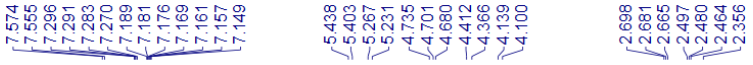
^{13}C-NMR spectrum of compound **6c** (101 MHz, $CDCl_3$)

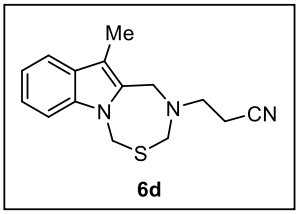


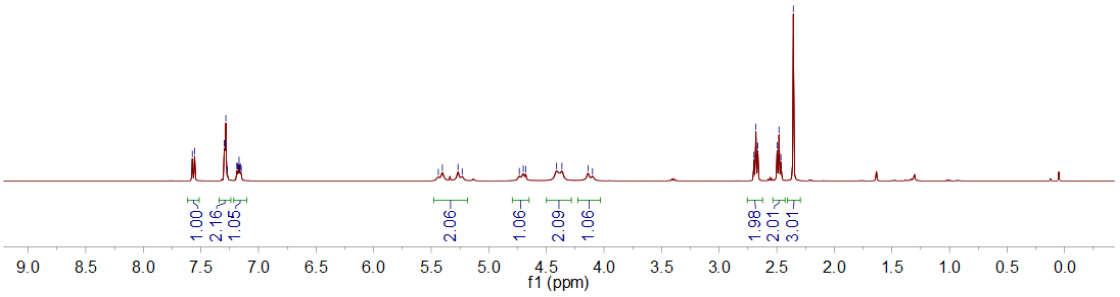
6c



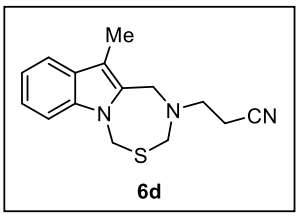
^{1}H-NMR spectrum of compound **6d** (400 MHz, $CDCl_3$)

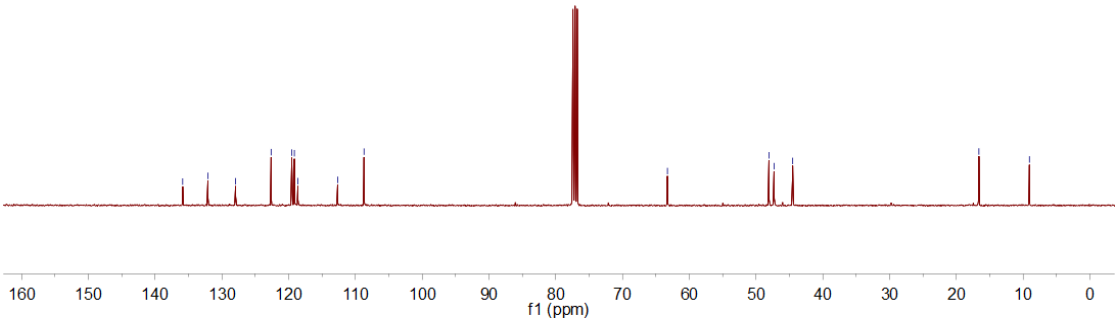




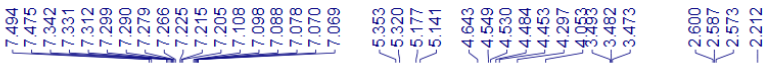


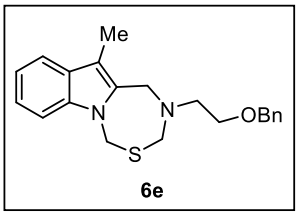
^{13}C-NMR spectrum of compound **6d** (101 MHz, $CDCl_3$)

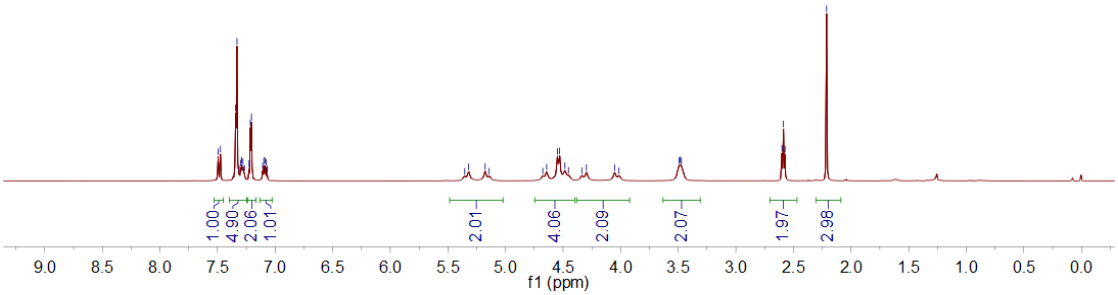




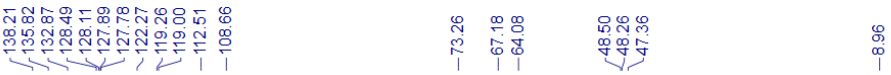
^{1}H-NMR spectrum of compound **6e** (400 MHz, $CDCl_3$)

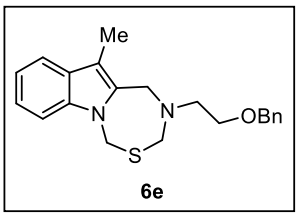


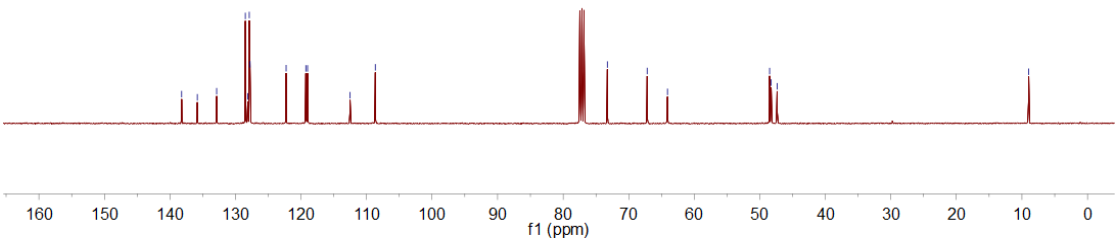




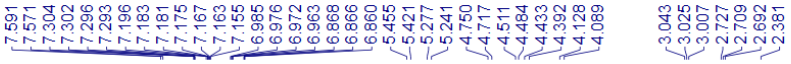
^{13}C-NMR spectrum of compound **6e** (101 MHz, $CDCl_3$)

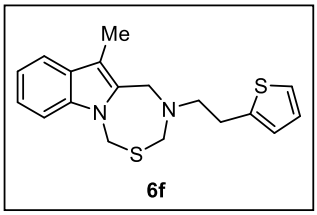


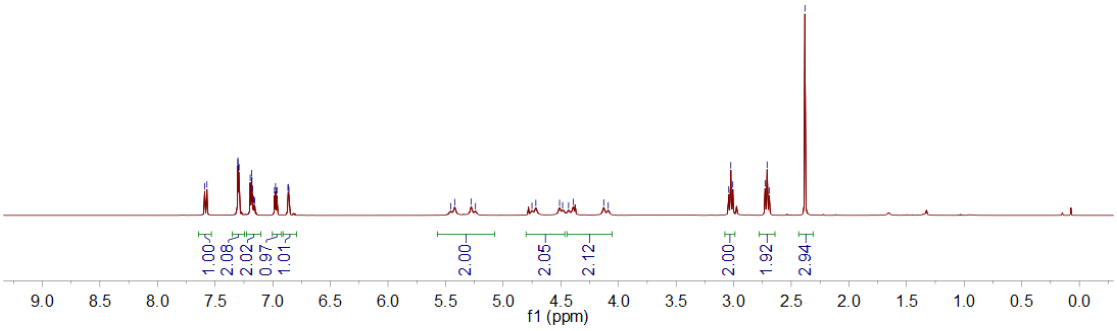




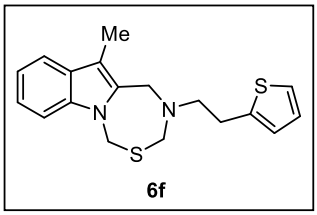
^{1}H-NMR spectrum of compound **6f** (400 MHz, $CDCl_3$)

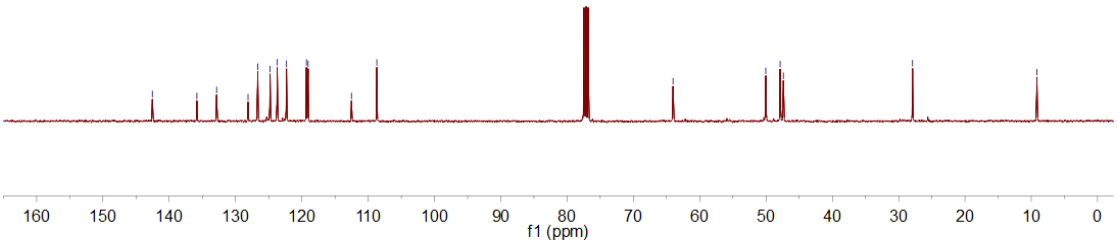




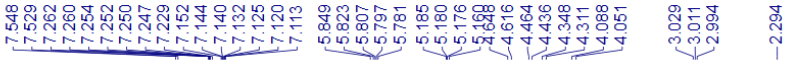


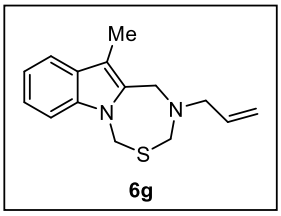
^{13}C-NMR spectrum of compound **6f** (101 MHz, $CDCl_3$)

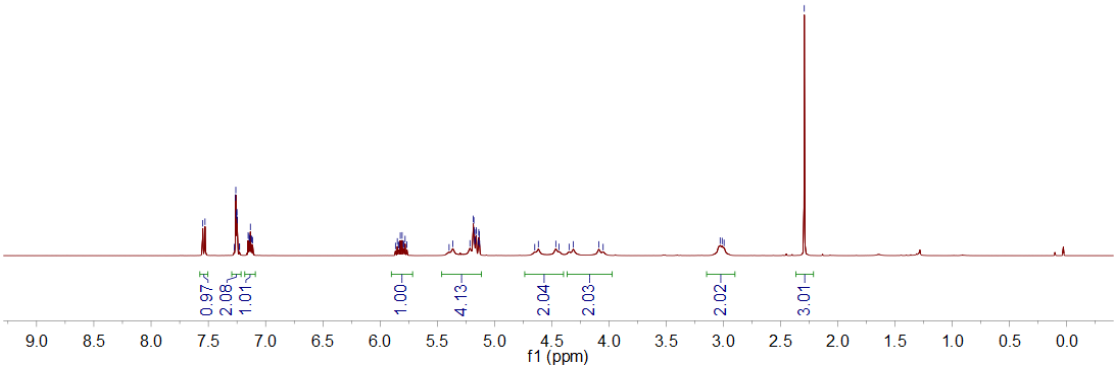




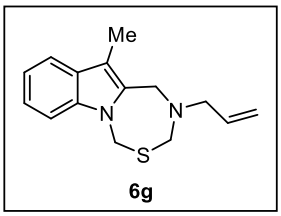
^{1}H-NMR spectrum of compound **6g** (400 MHz, $CDCl_3$)

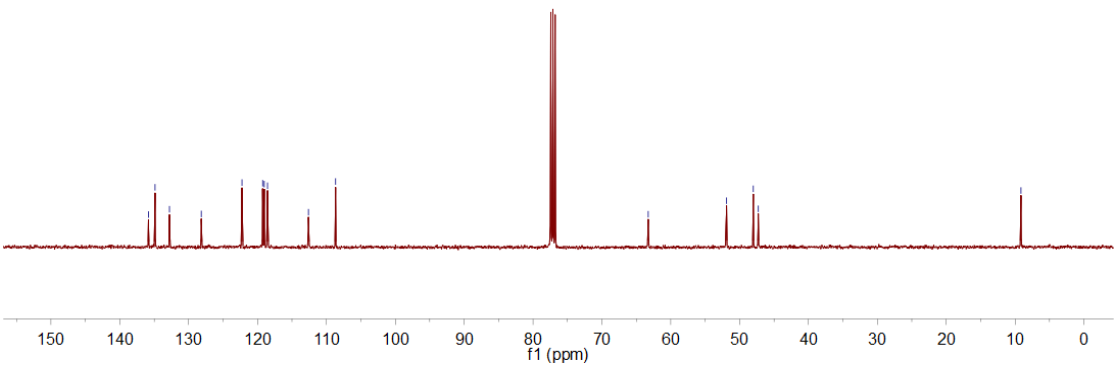




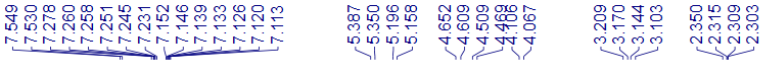


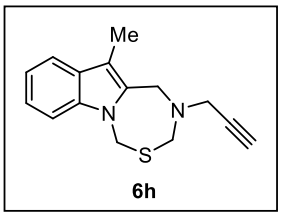
^{13}C-NMR spectrum of compound **6g** (101 MHz, $CDCl_3$)

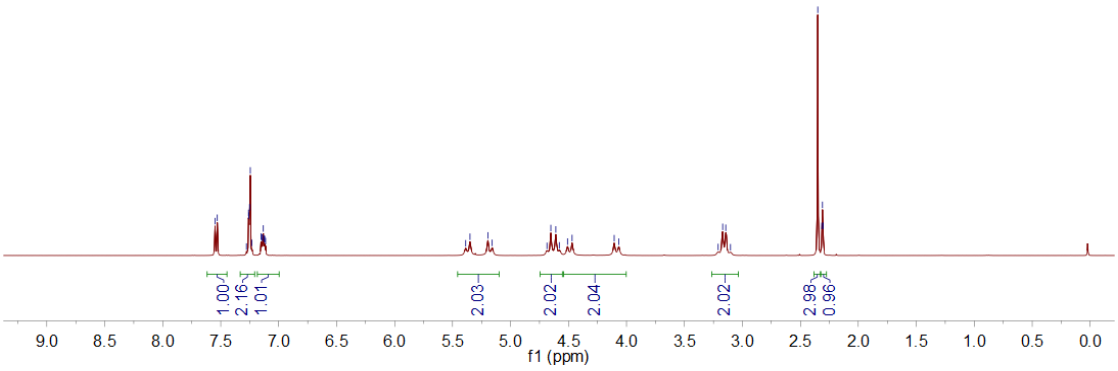




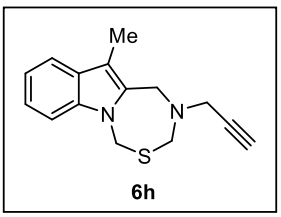
^{1}H-NMR spectrum of compound **6h** (400 MHz, $CDCl_3$)

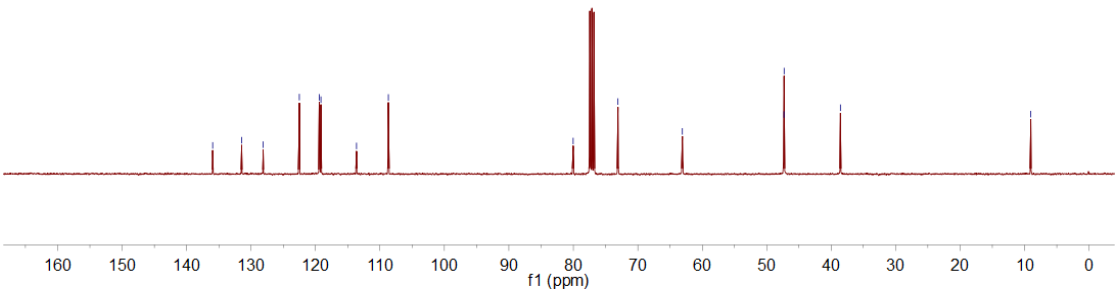




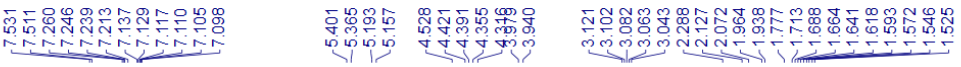


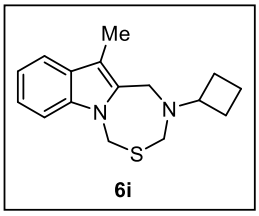
^{13}C-NMR spectrum of compound **6h** (101 MHz, $CDCl_3$)

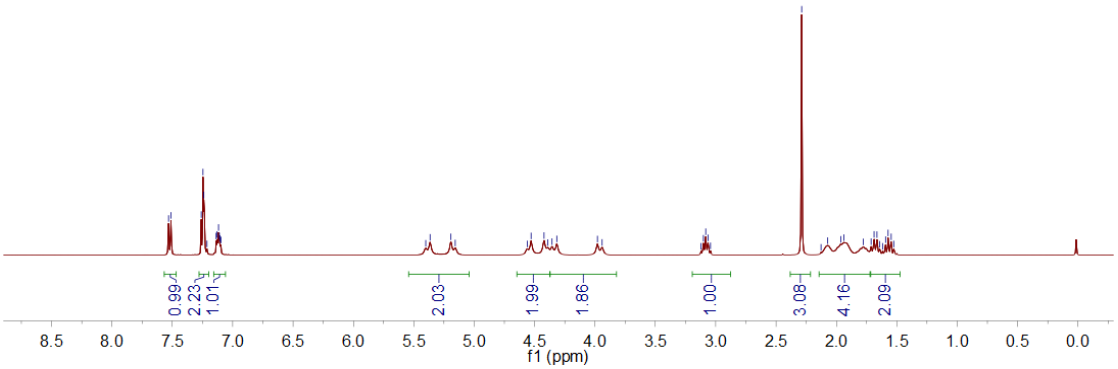




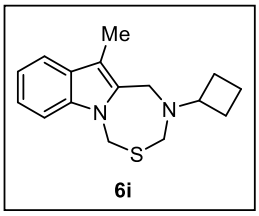
^{1}H-NMR spectrum of compound **6i** (400 MHz, $CDCl_3$)

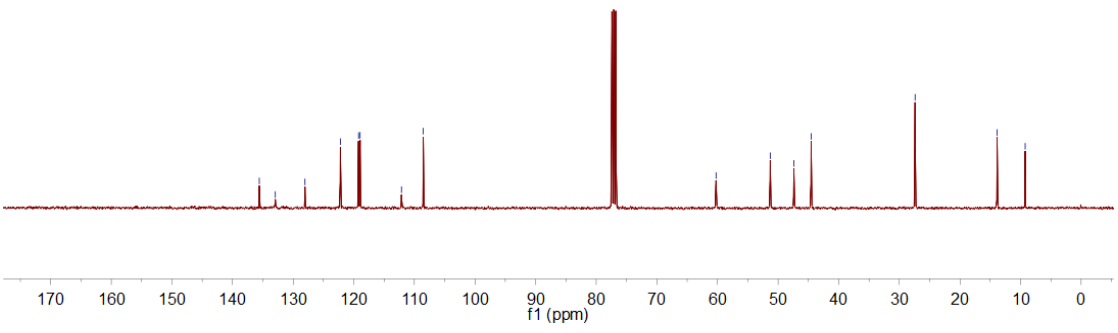




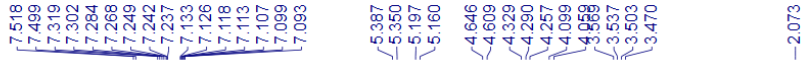


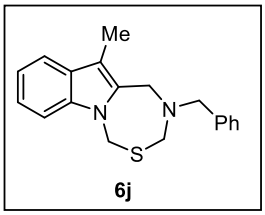
^{13}C-NMR spectrum of compound **6i** (101 MHz, $CDCl_3$)

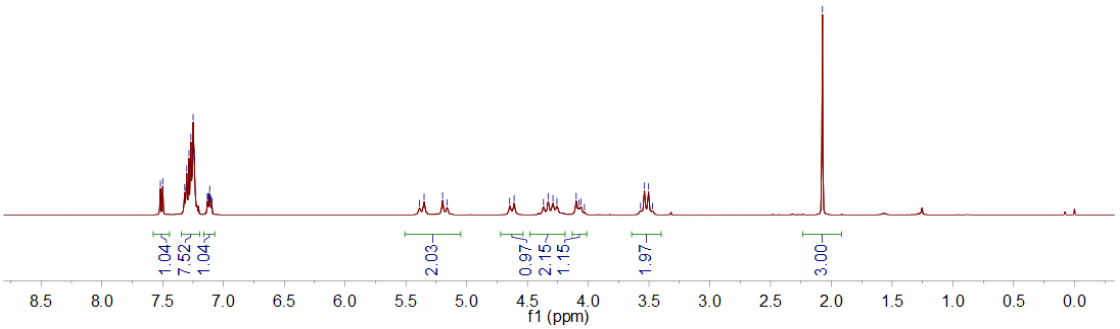




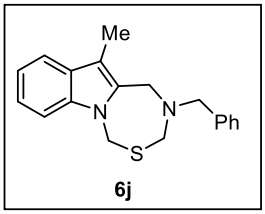
^{1}H-NMR spectrum of compound **6j** (400 MHz, $CDCl_3$)

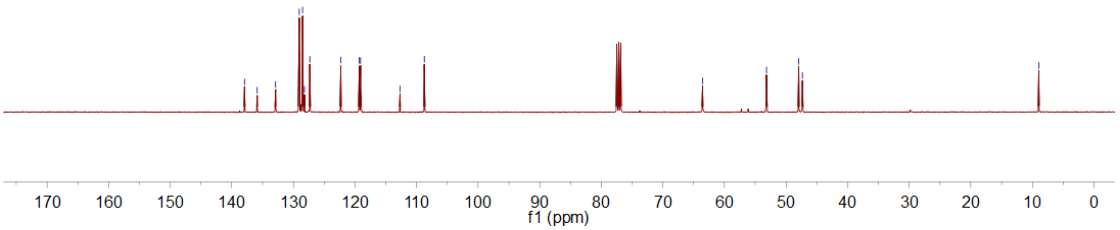




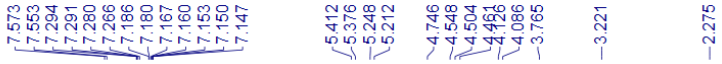


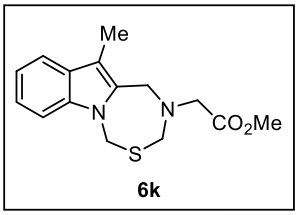
^{13}C-NMR spectrum of compound **6j** (101 MHz, $CDCl_3$)

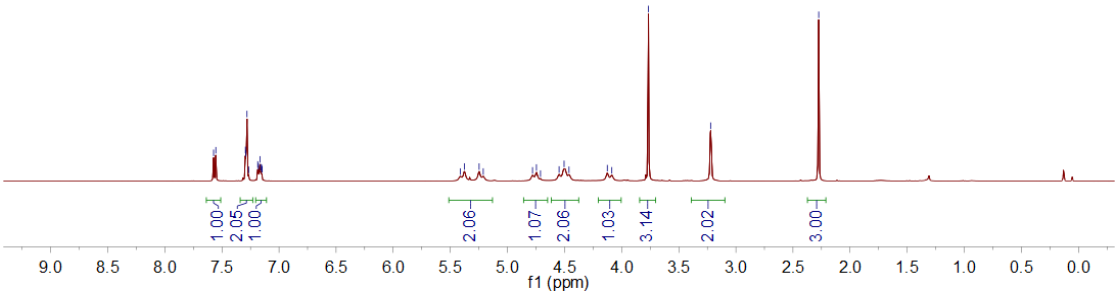




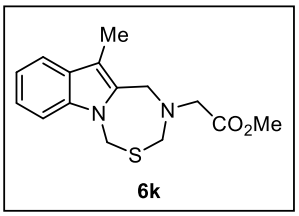
^{1}H-NMR spectrum of compound **6k** (400 MHz, $CDCl_3$)

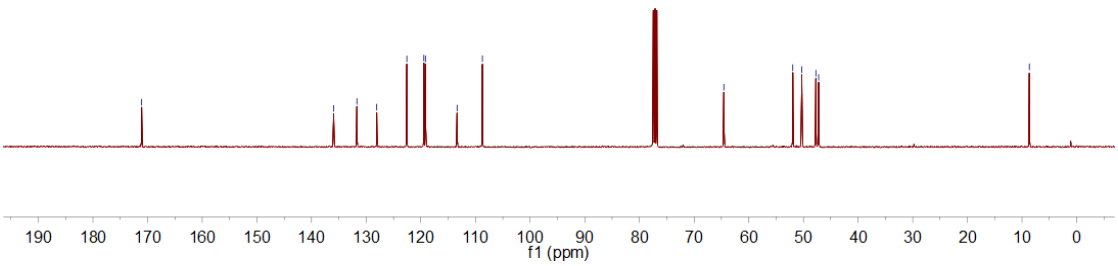




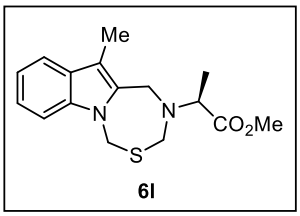


^{13}C-NMR spectrum of compound **6k** (101 MHz, $CDCl_3$)

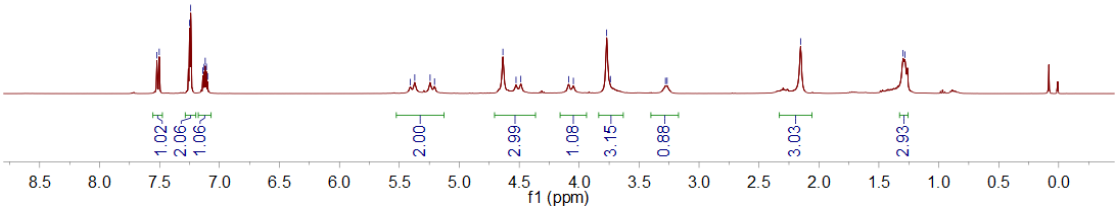




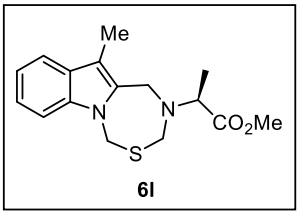
^{1}H-NMR spectrum of compound **6l** (400 MHz, $CDCl_3$)



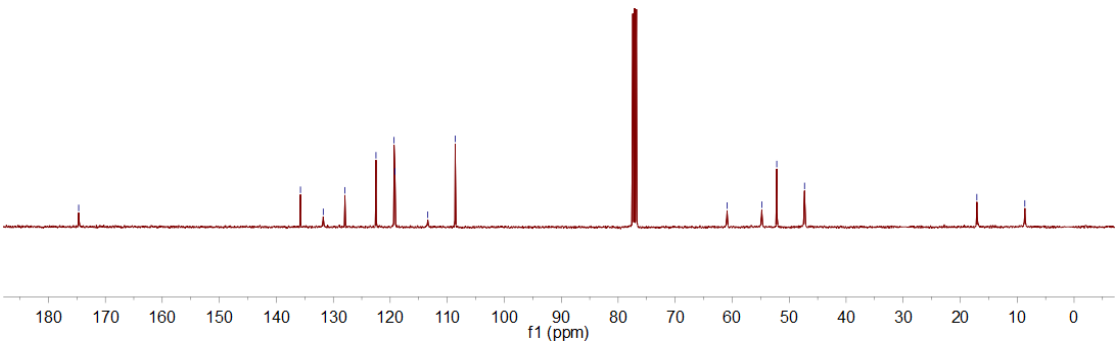
6l



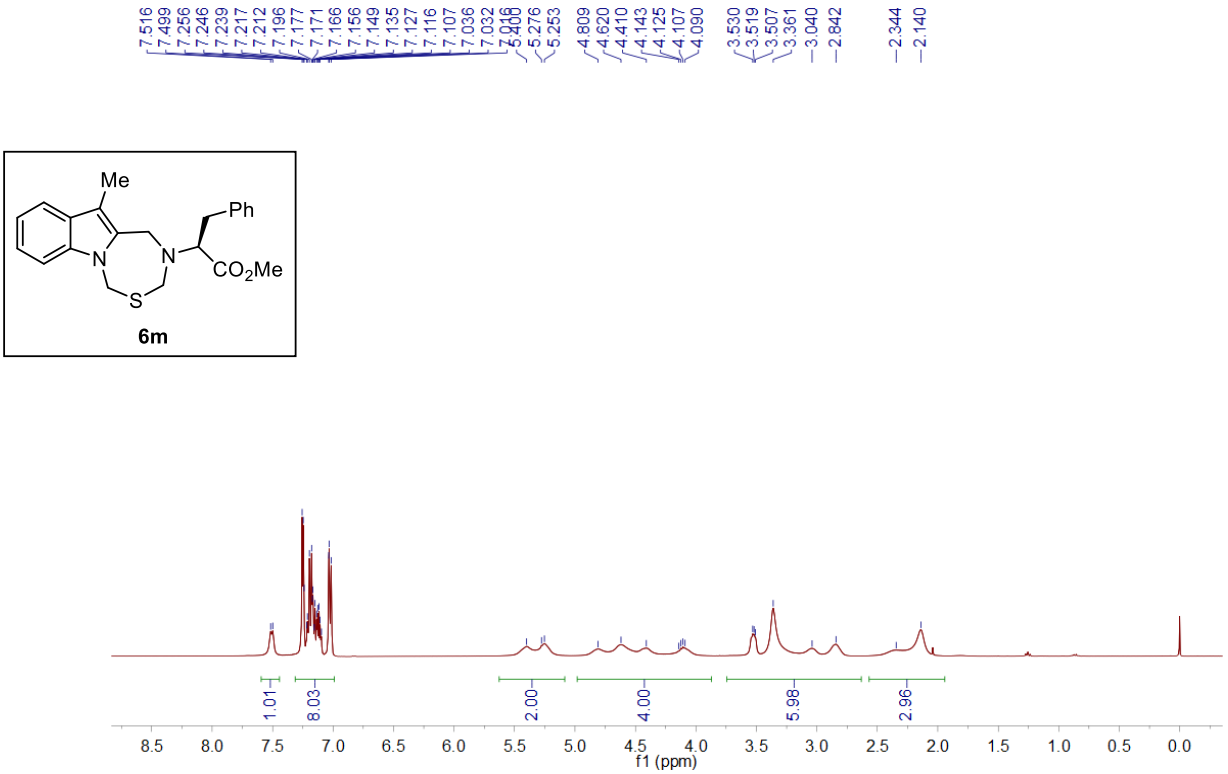
^{13}C-NMR spectrum of compound **6l** (101 MHz, $CDCl_3$)



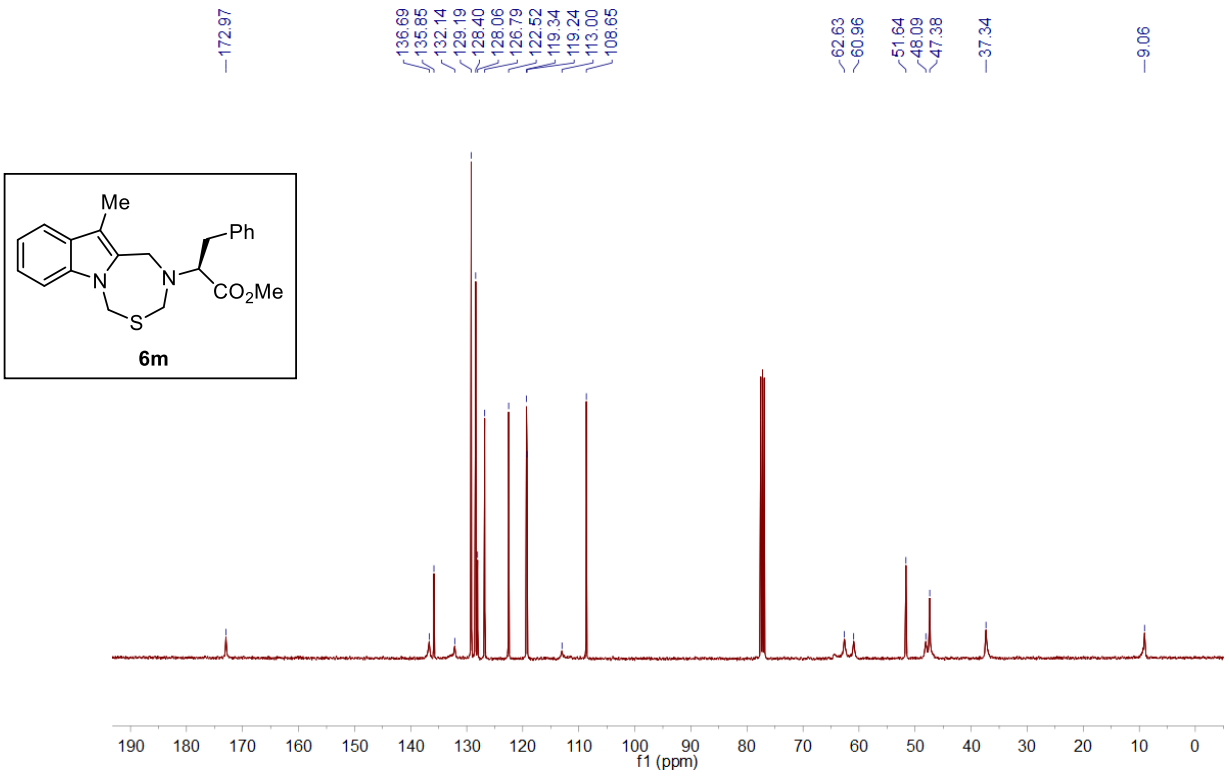
6l



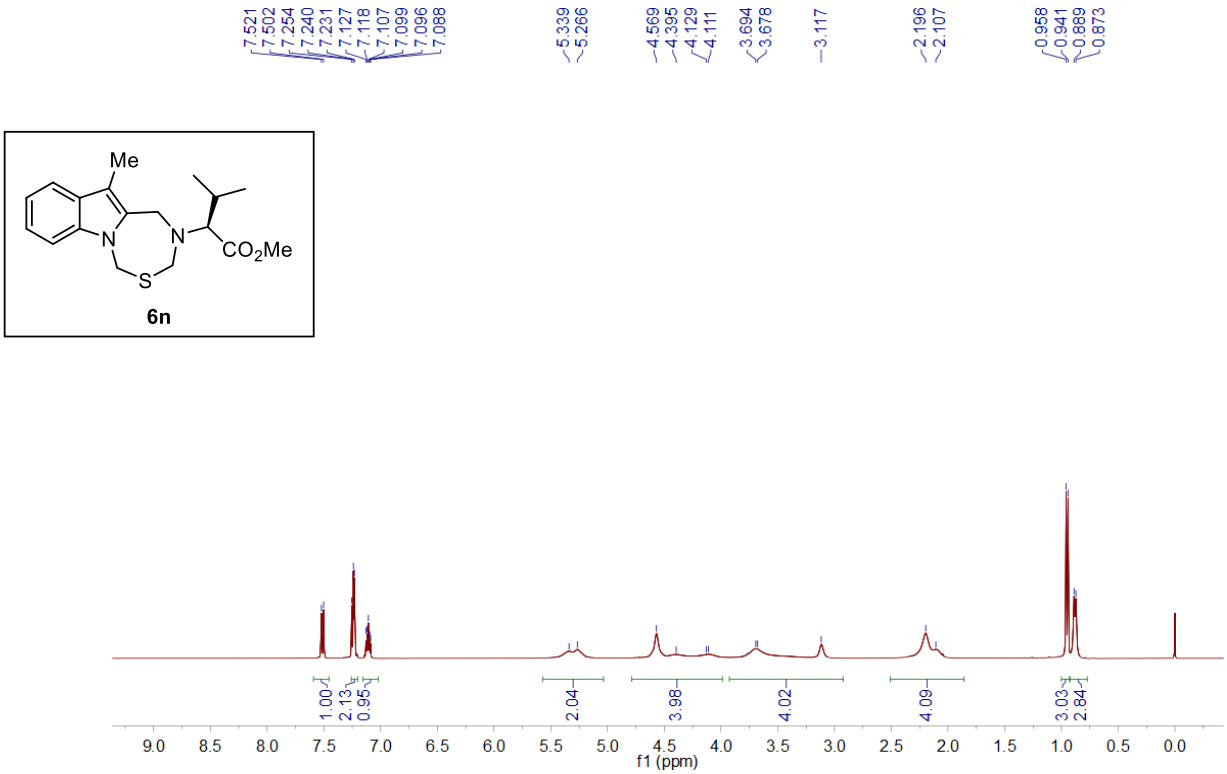
^{1}H-NMR spectrum of compound **6m** (400 MHz, $CDCl_3$)



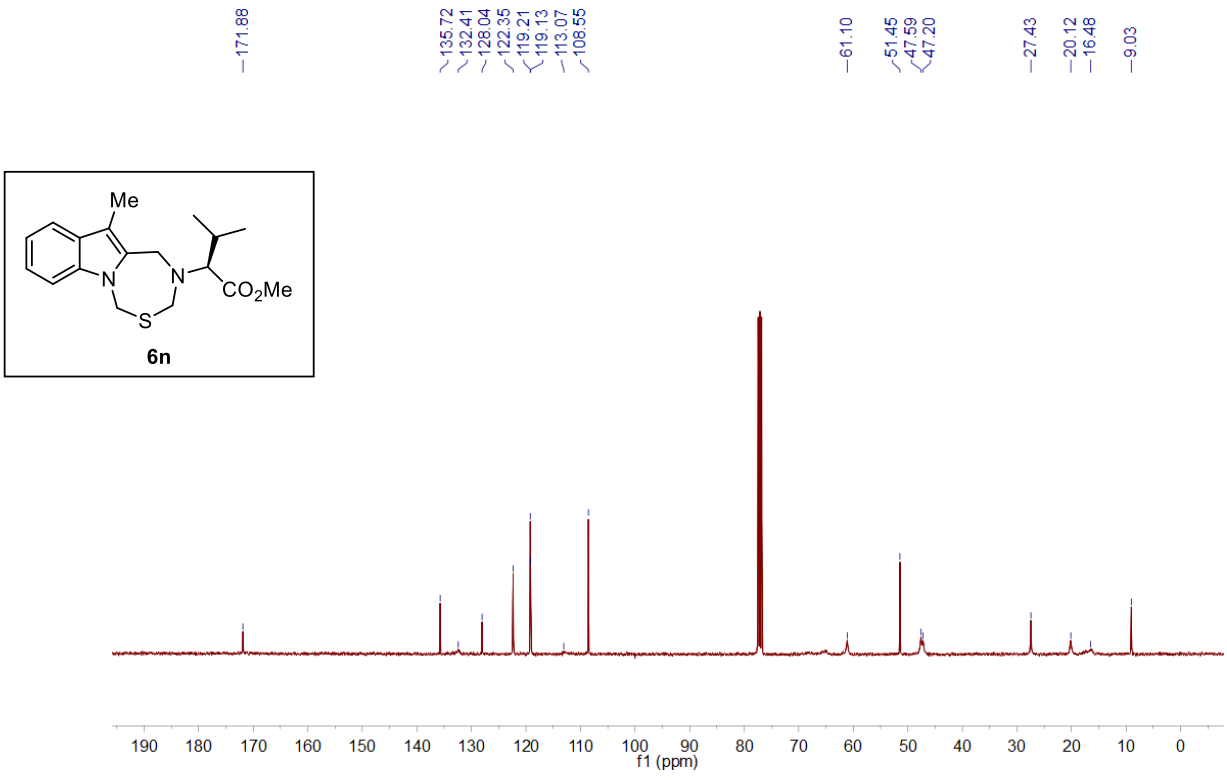
^{13}C-NMR spectrum of compound **6m** (101 MHz, $CDCl_3$)



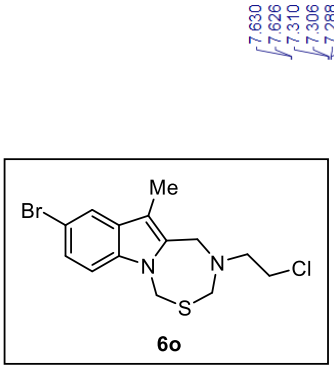
^{1}H-NMR spectrum of compound **6n** (400 MHz, $CDCl_3$)



^{13}C-NMR spectrum of compound **6n** (101 MHz, $CDCl_3$)

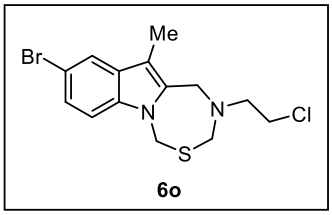


^{1}H-NMR spectrum of compound **6o** (400 MHz, $CDCl_3$)



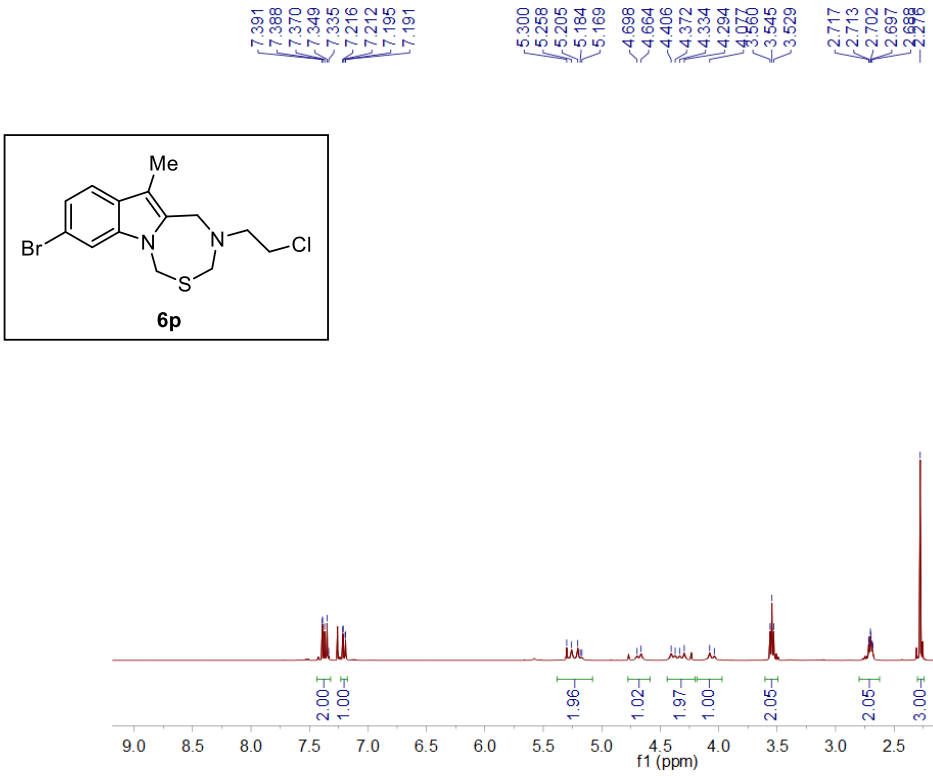
6o

^{13}C-NMR spectrum of compound **6o** (101 MHz, $CDCl_3$)

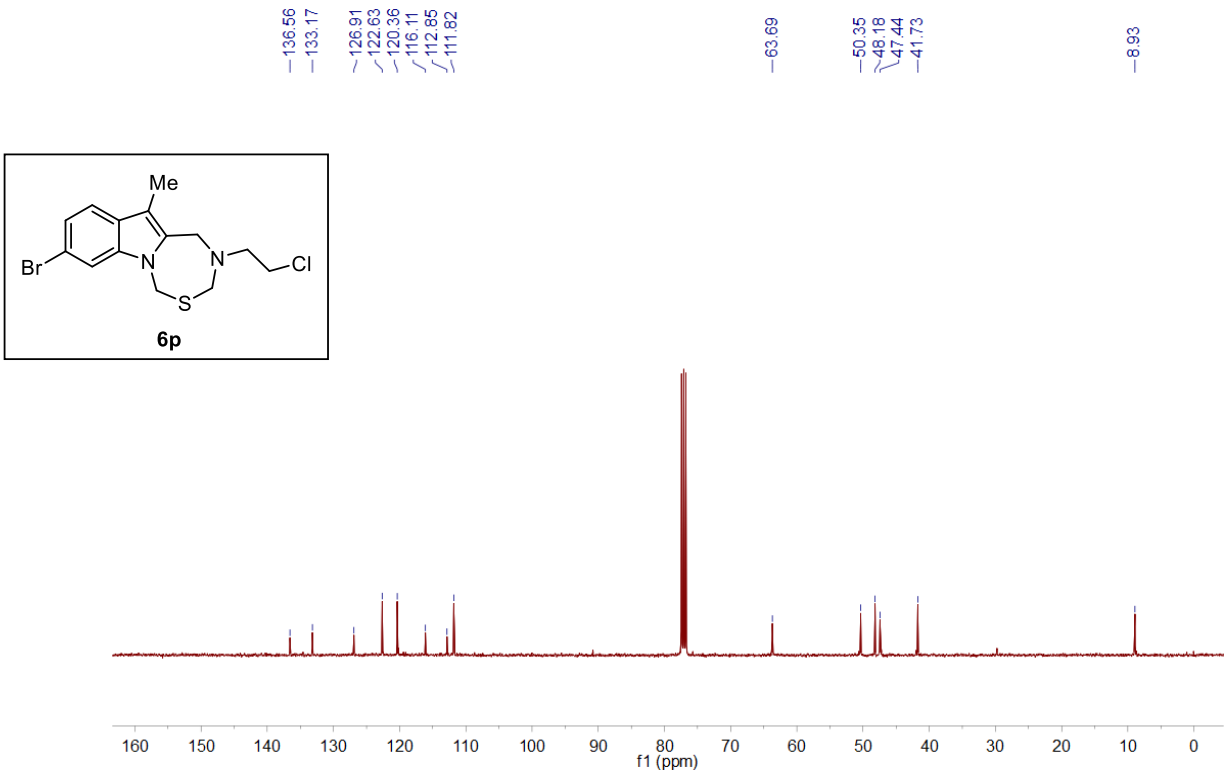


6o

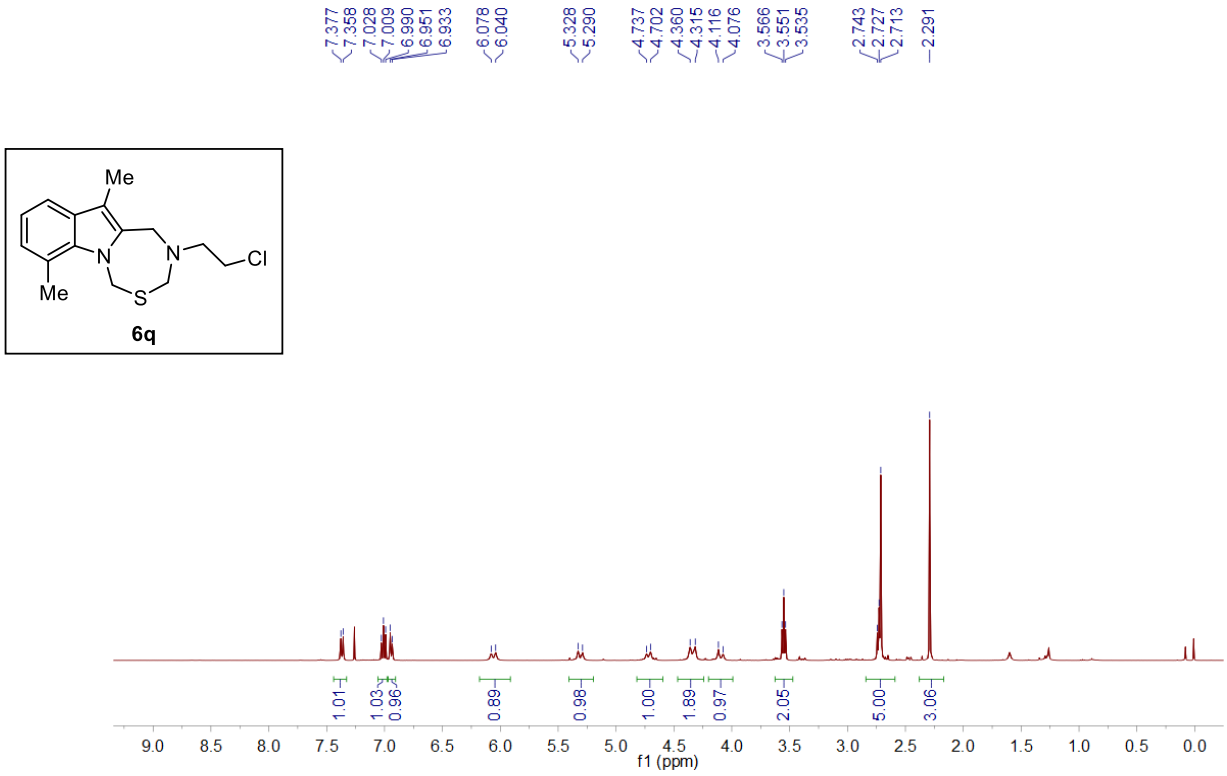
^{1}H-NMR spectrum of compound **6p** (400 MHz, $CDCl_3$)



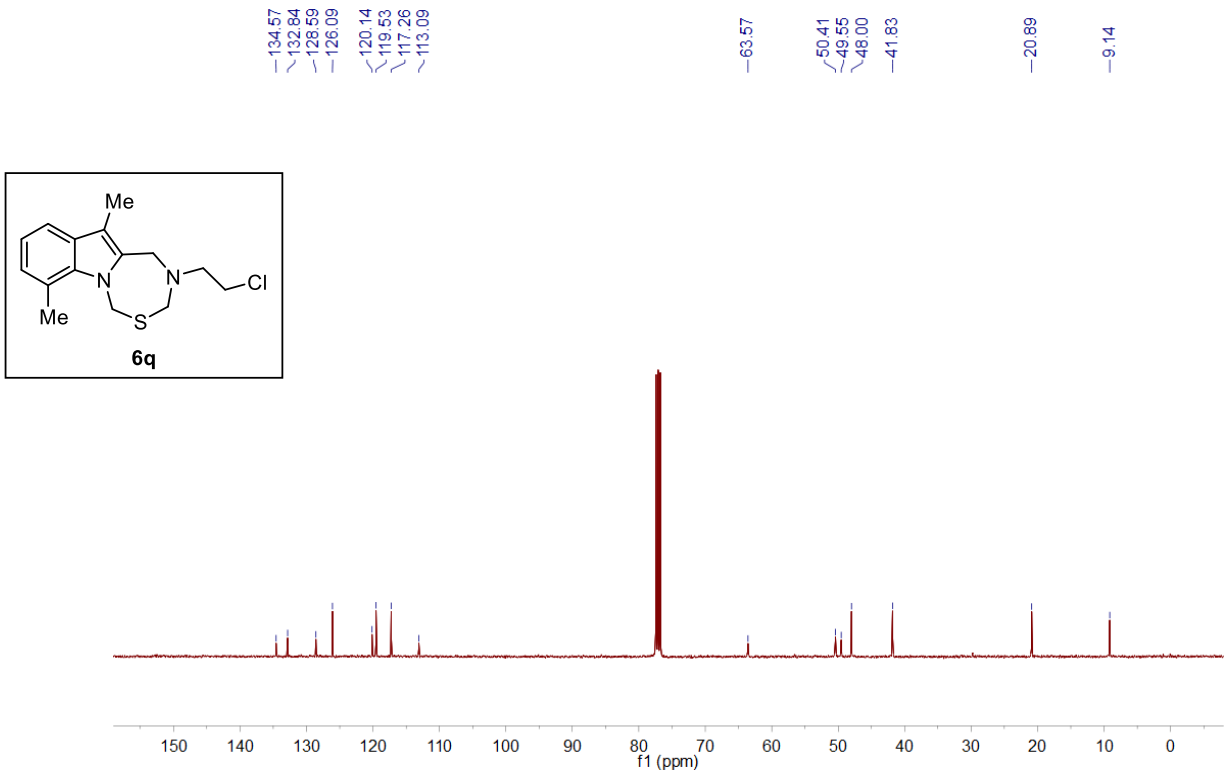
^{13}C-NMR spectrum of compound **6p** (101 MHz, $CDCl_3$)



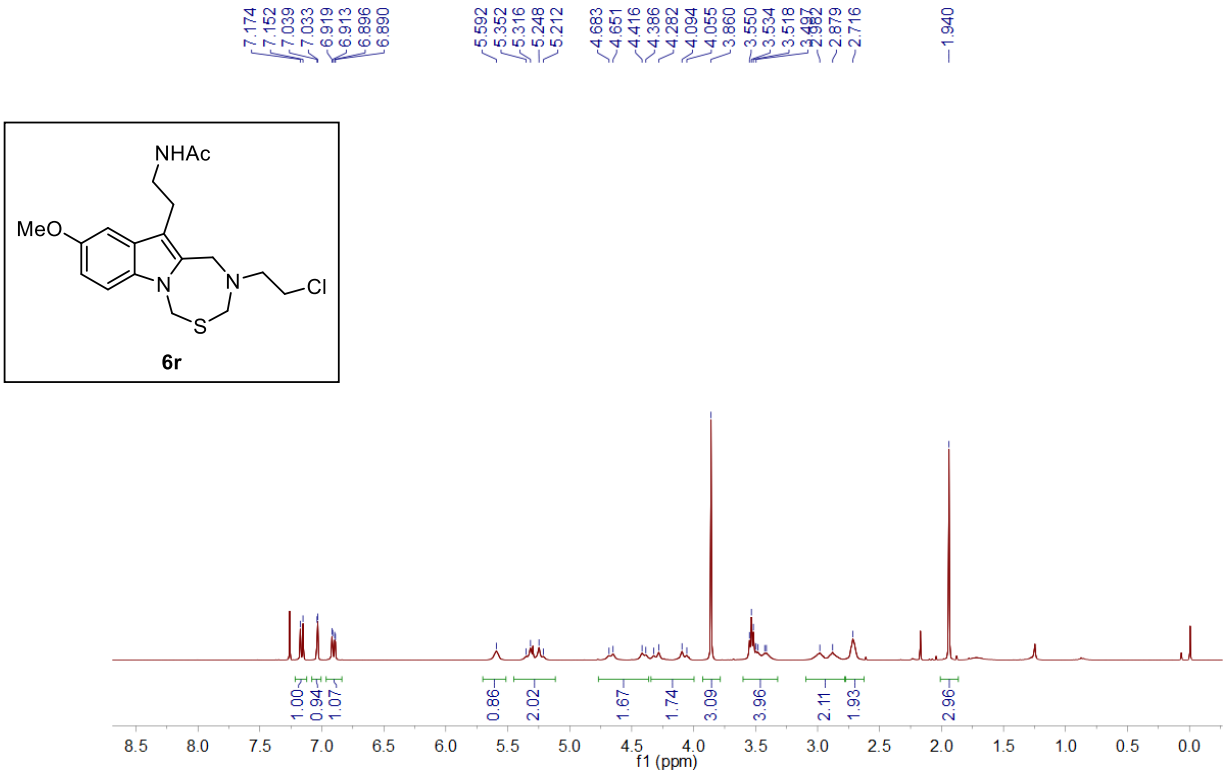
^{1}H-NMR spectrum of compound **6q** (400 MHz, $CDCl_3$)



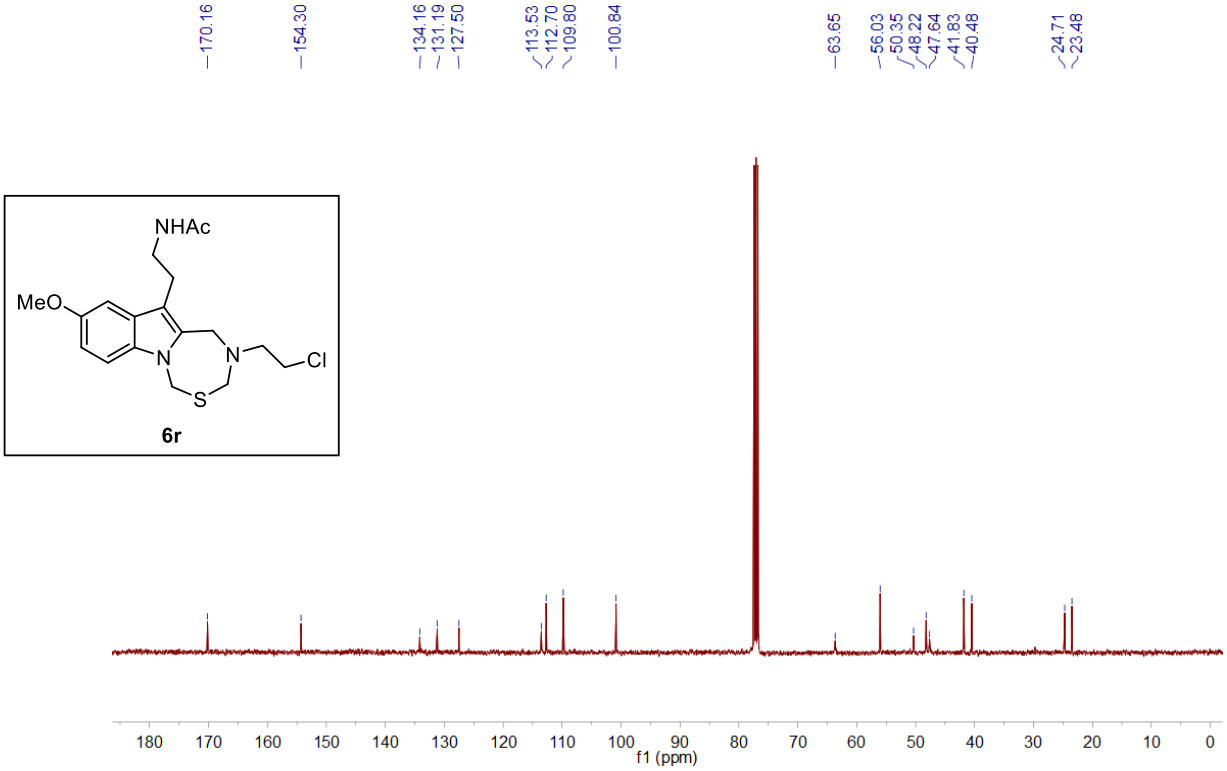
^{13}C-NMR spectrum of compound **6q** (101 MHz, $CDCl_3$)



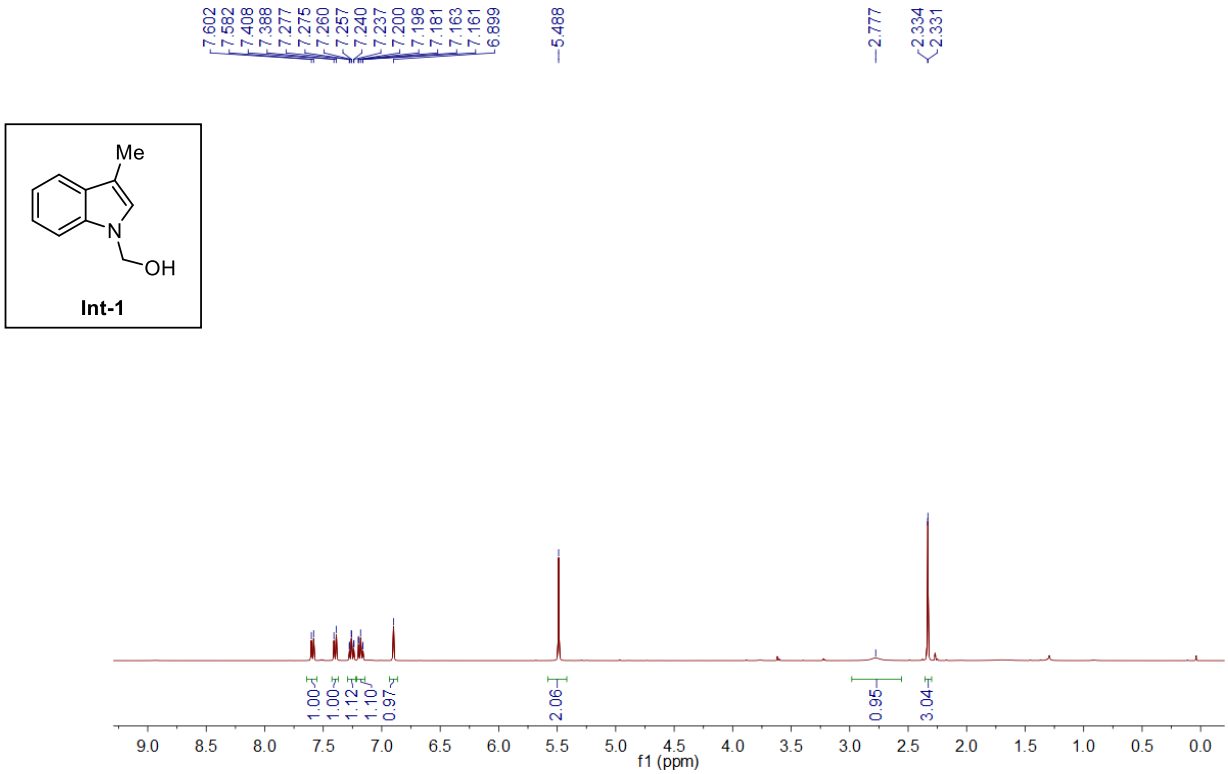
^{1}H-NMR spectrum of compound **6r** (400 MHz, $CDCl_3$)



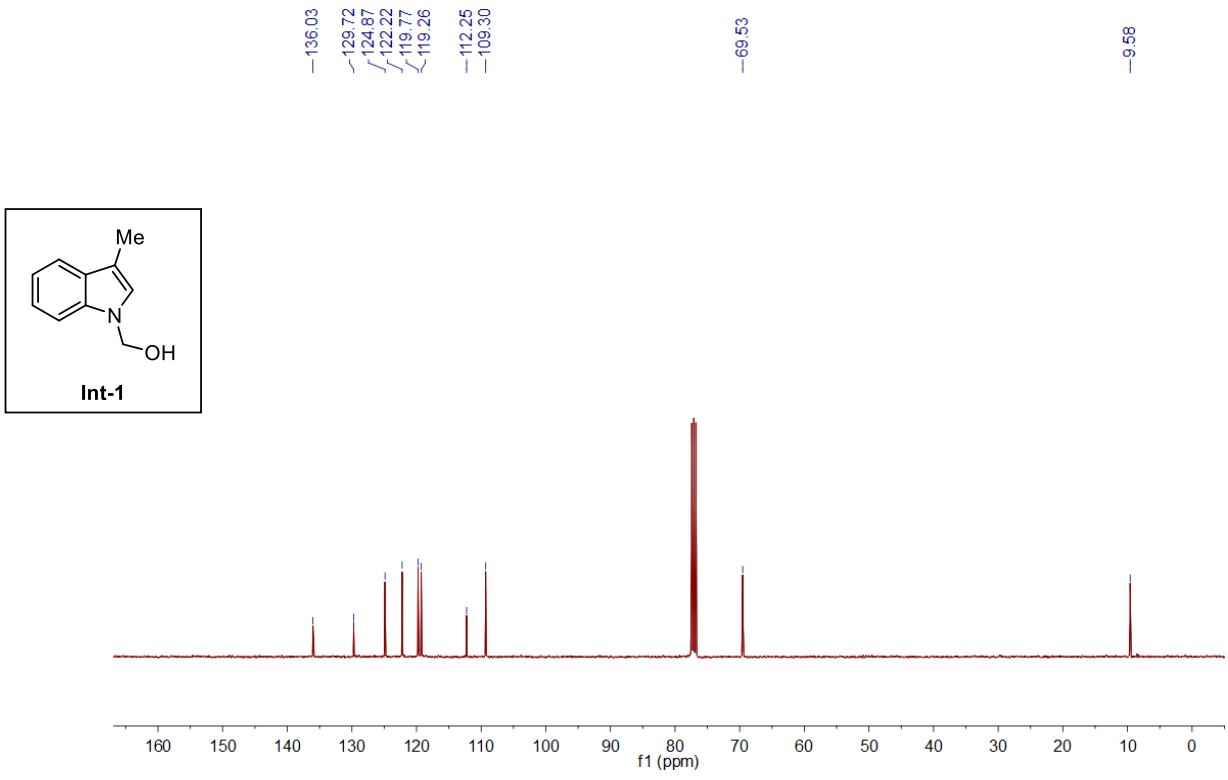
^{13}C-NMR spectrum of compound **6r** (101 MHz, $CDCl_3$)



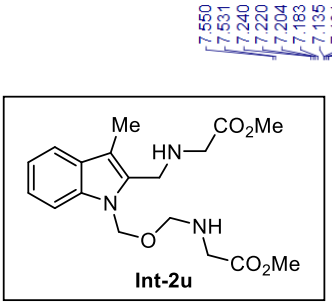
^{1}H-NMR spectrum of compound **Int-1** (400 MHz, $CDCl_3$)



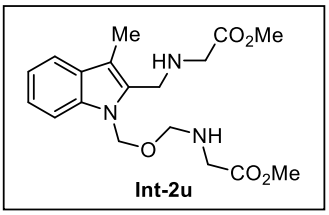
^{13}C-NMR spectrum of compound **Int-1** (101 MHz, $CDCl_3$)



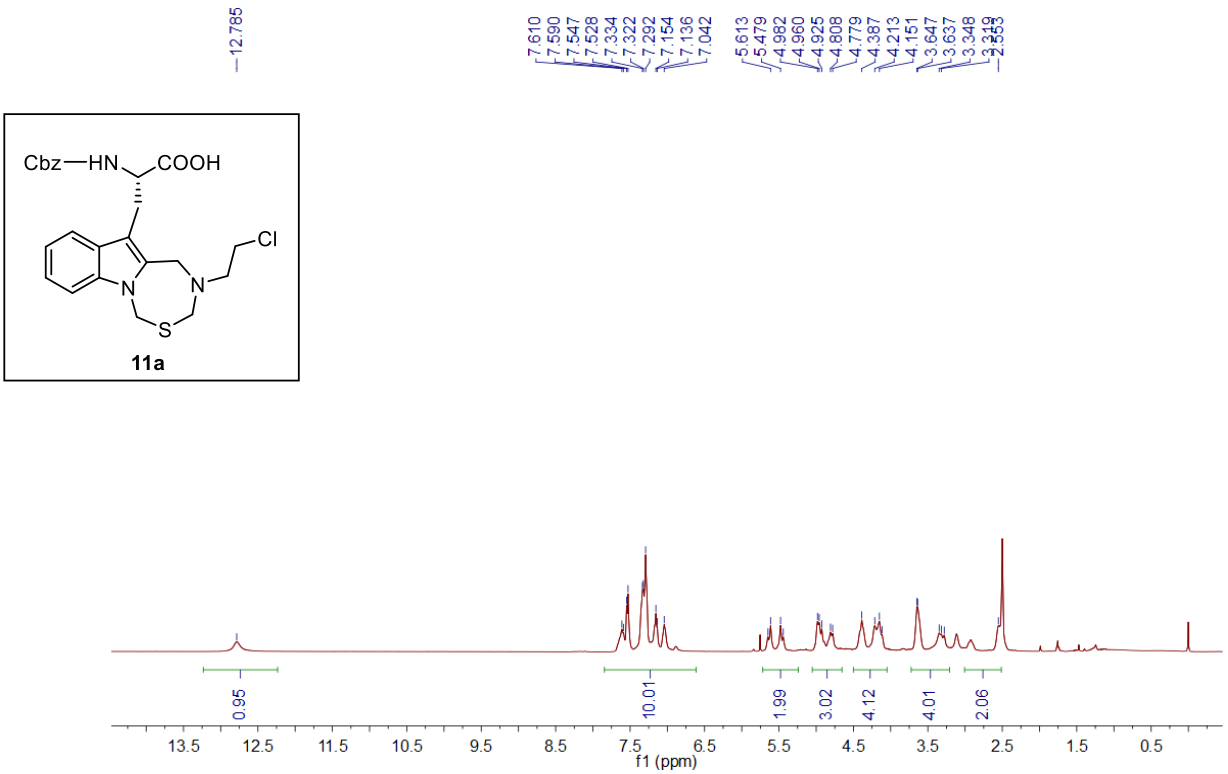
^{1}H-NMR spectrum of compound **Int-2u** (400 MHz, $CDCl_3$)



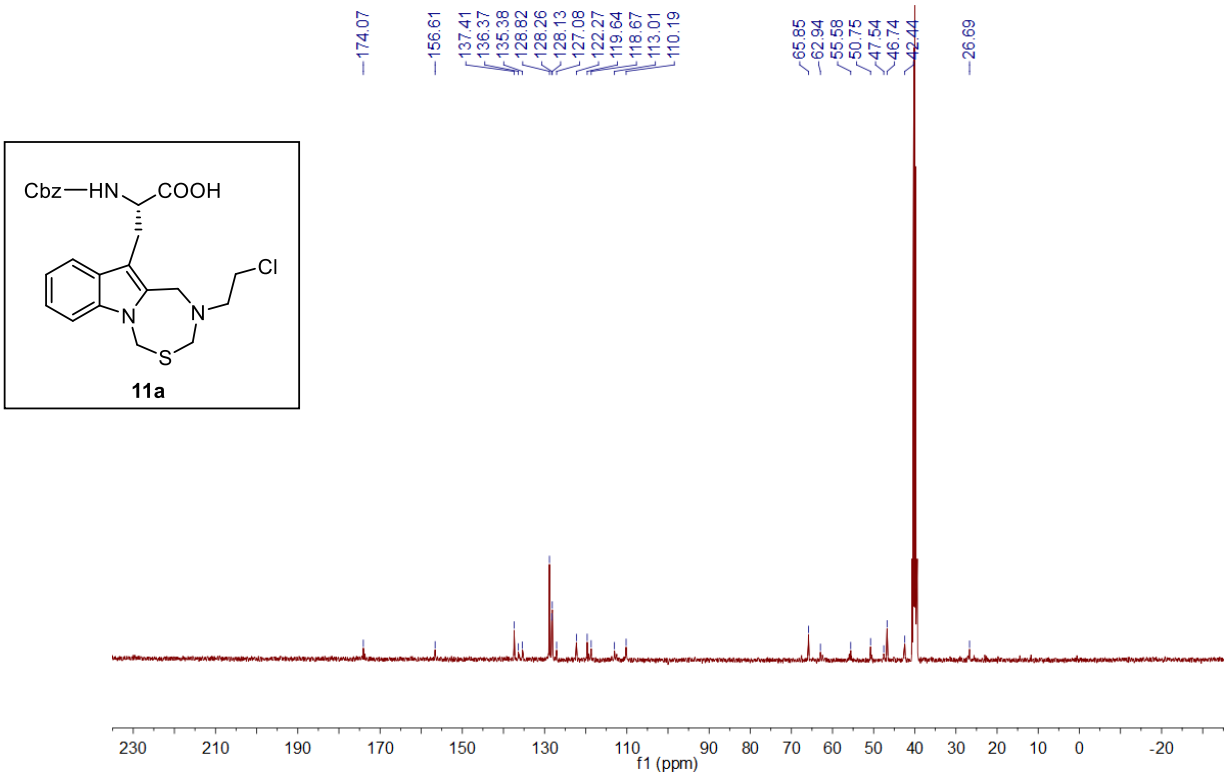
^{13}C-NMR spectrum of compound **Int-2u** (101 MHz, $CDCl_3$)



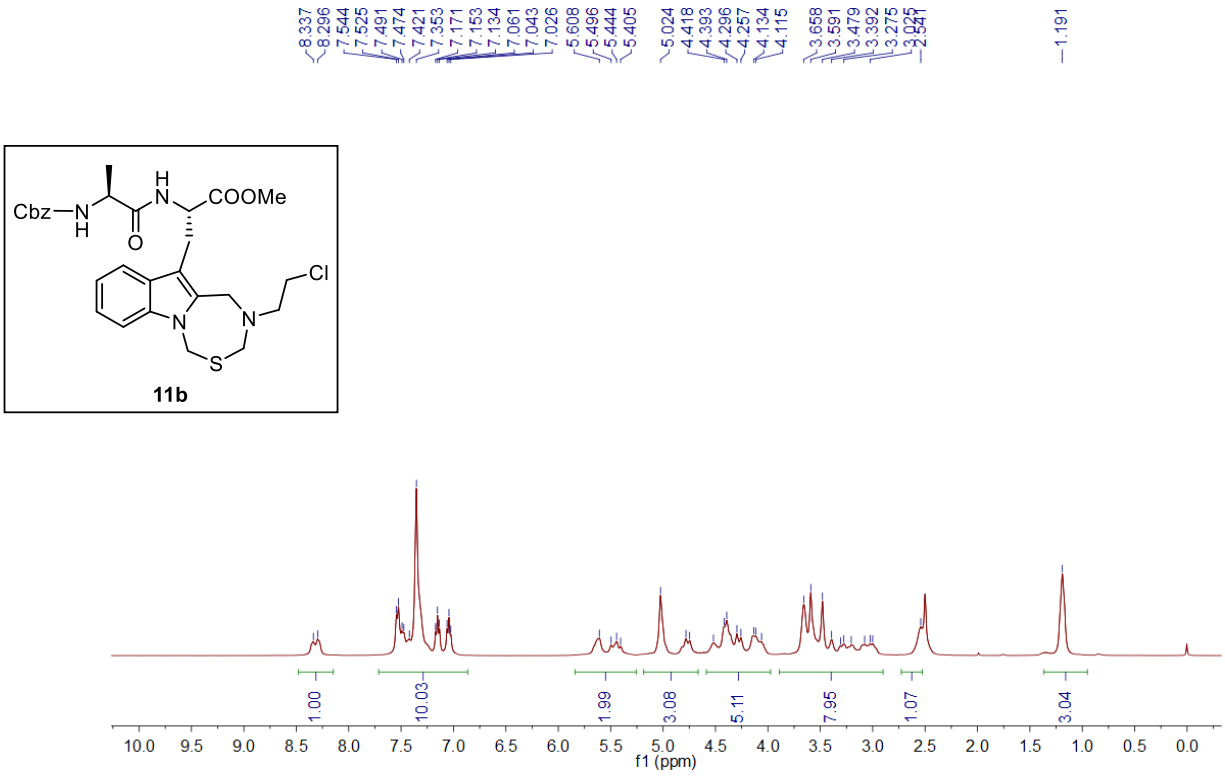
^{1}H-NMR spectrum of compound **11a** (400 MHz, DMSO)



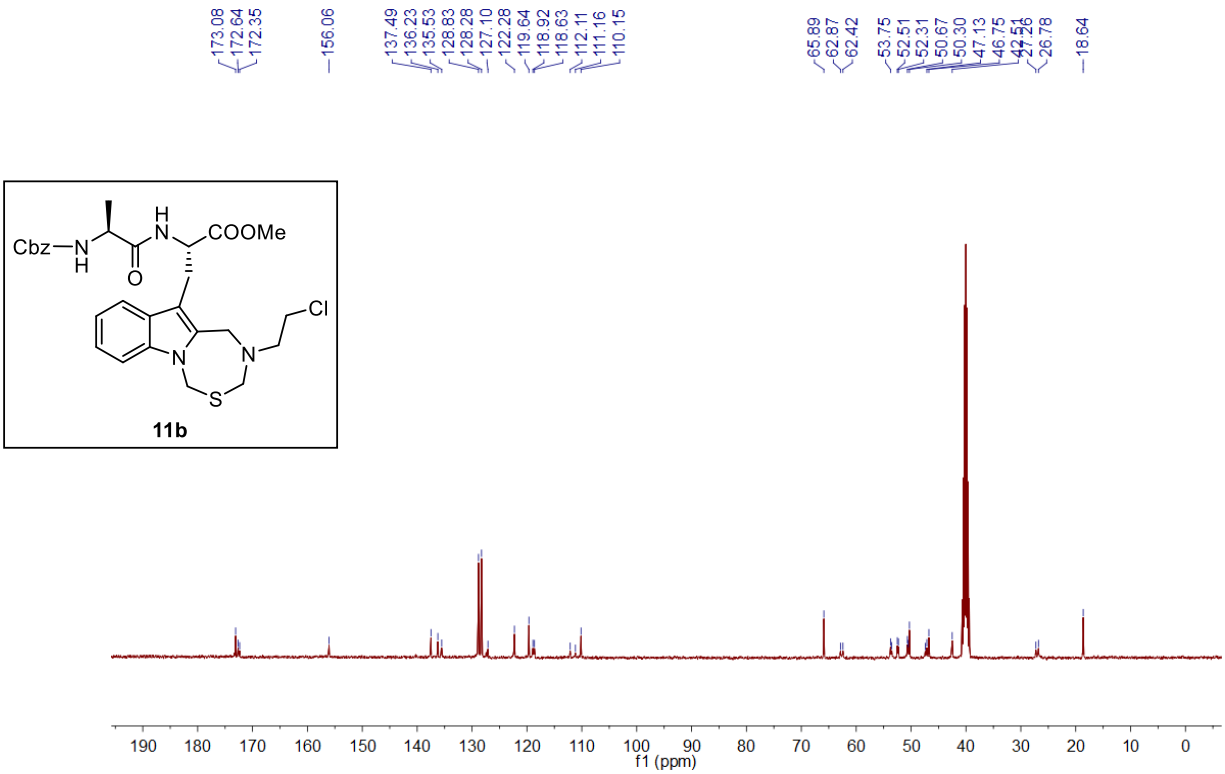
^{13}C-NMR spectrum of compound **11a** (101 MHz, DMSO)



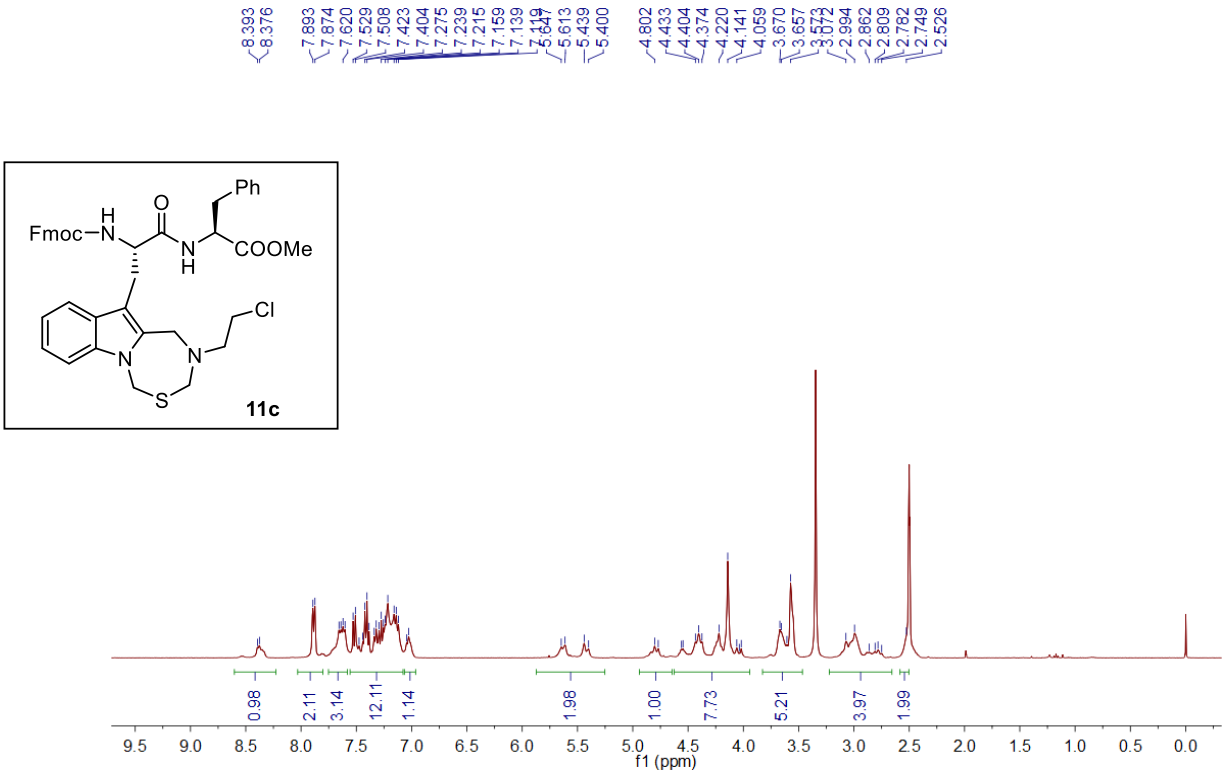
[1]H-NMR spectrum of compound **11b** (400 MHz, DMSO)



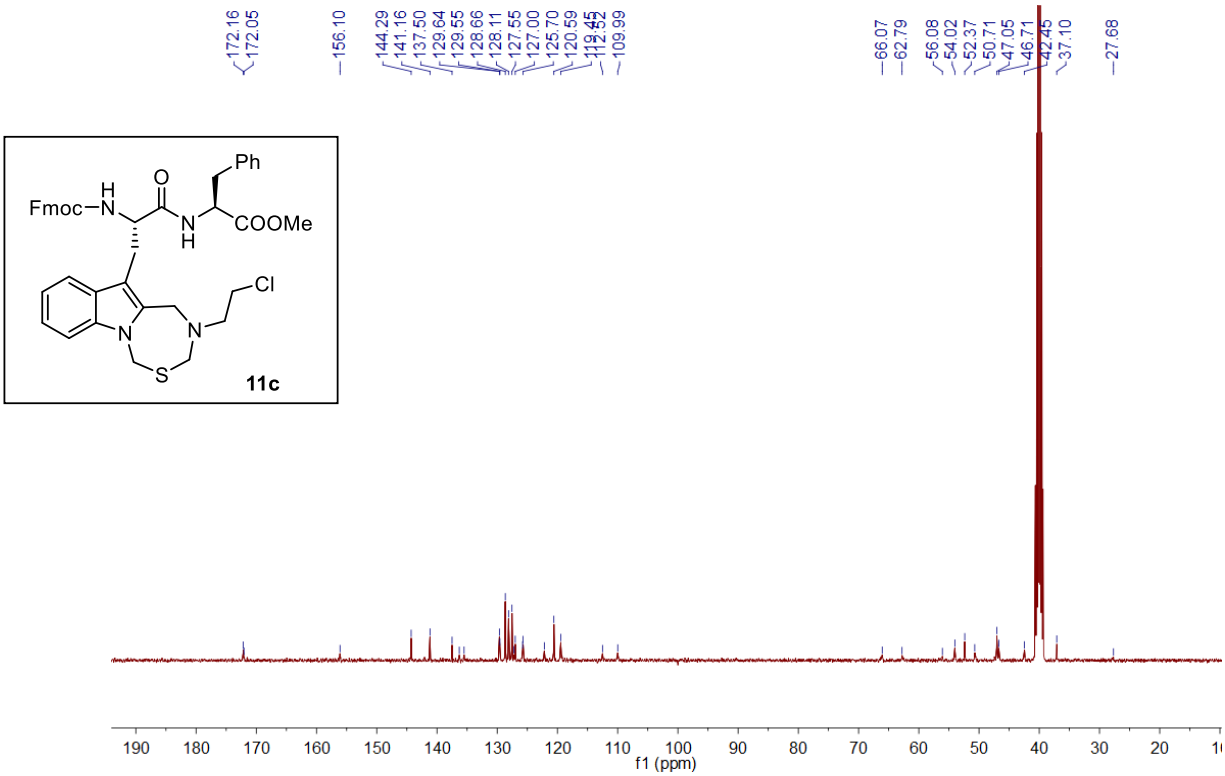
[13]C-NMR spectrum of compound **11b** (101 MHz, DMSO)



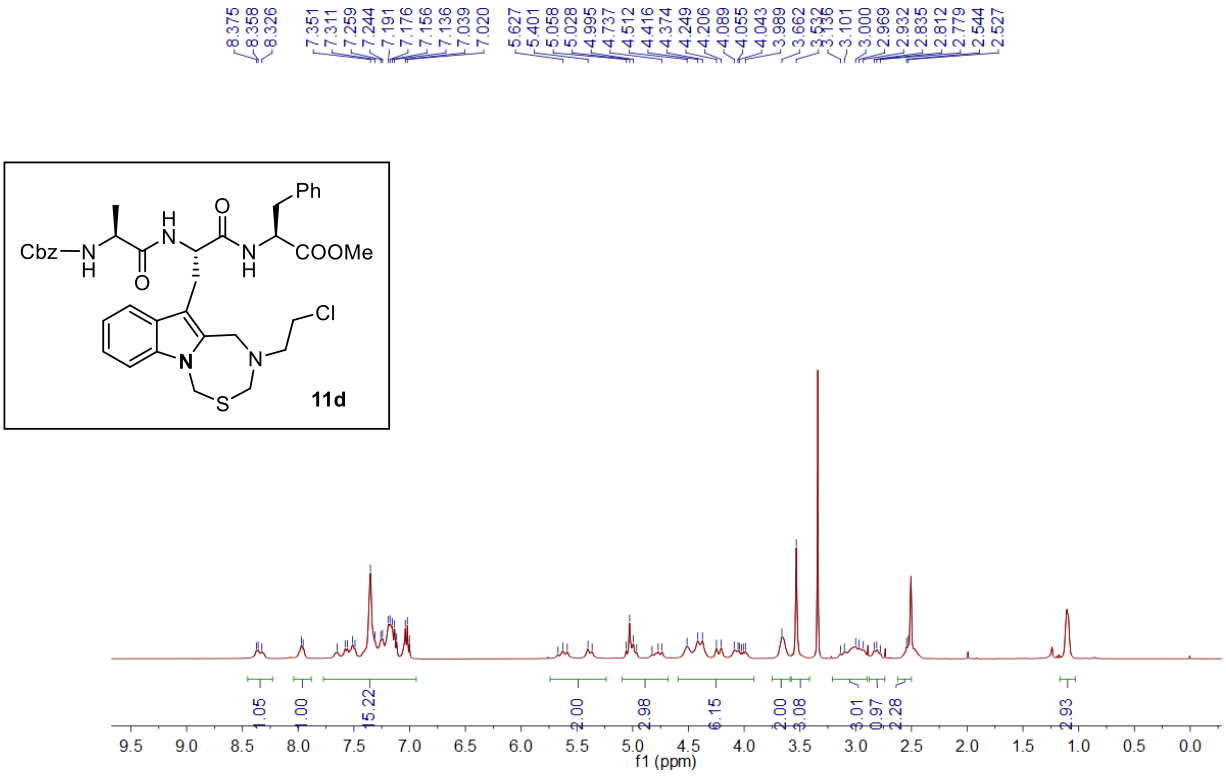
^{1}H-NMR spectrum of compound **11c** (400 MHz, DMSO)



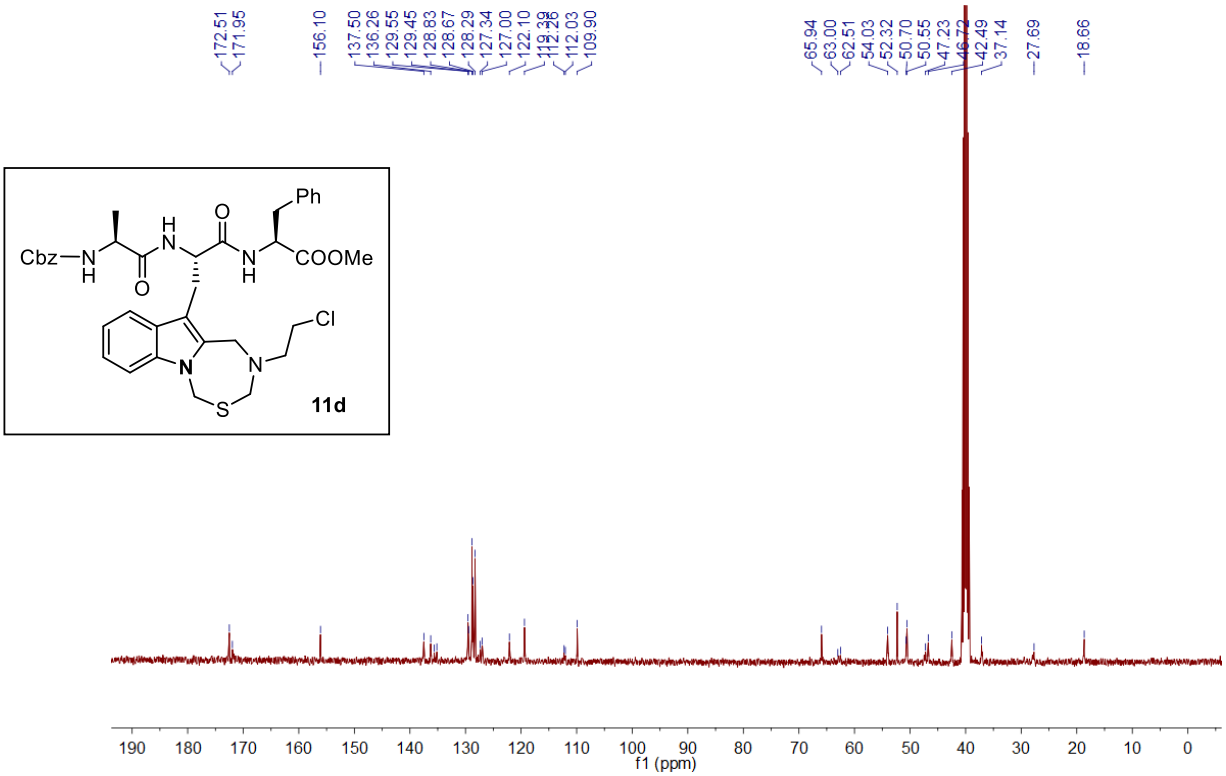
^{13}C-NMR spectrum of compound **11c** (101 MHz, DMSO)



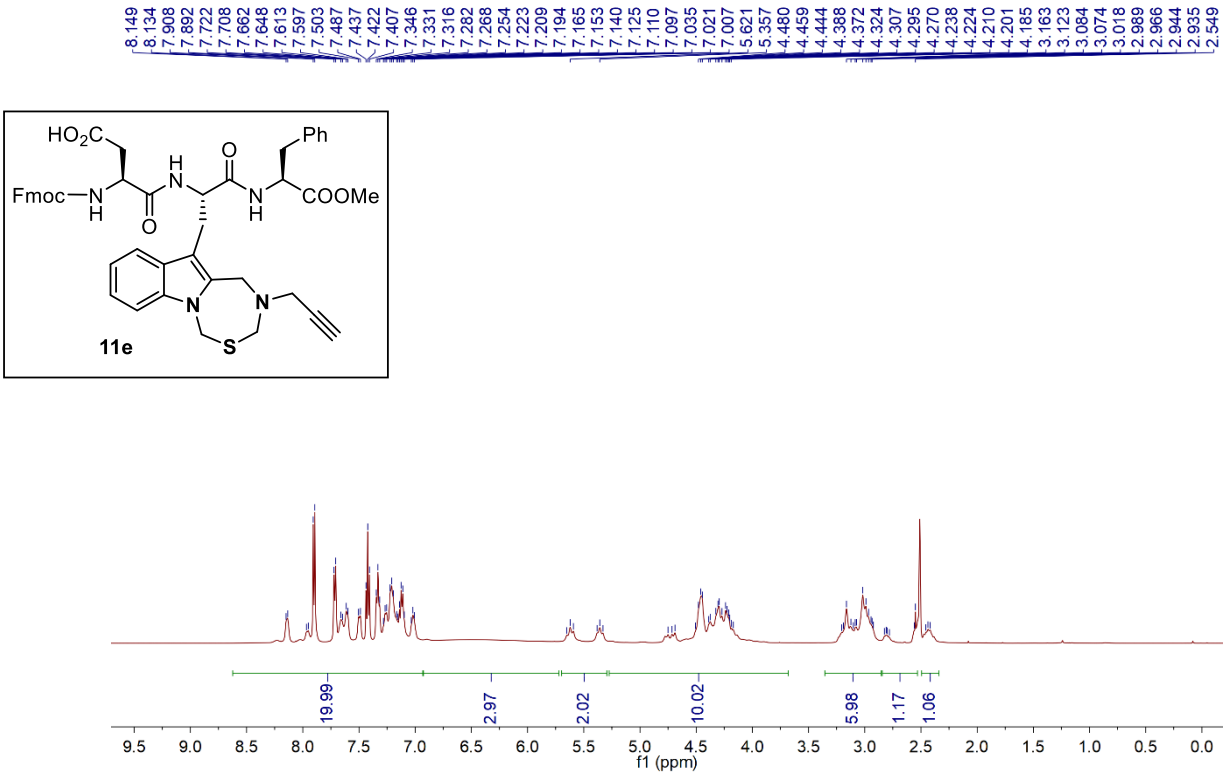
[1]H-NMR spectrum of compound **11d** (400 MHz, DMSO)



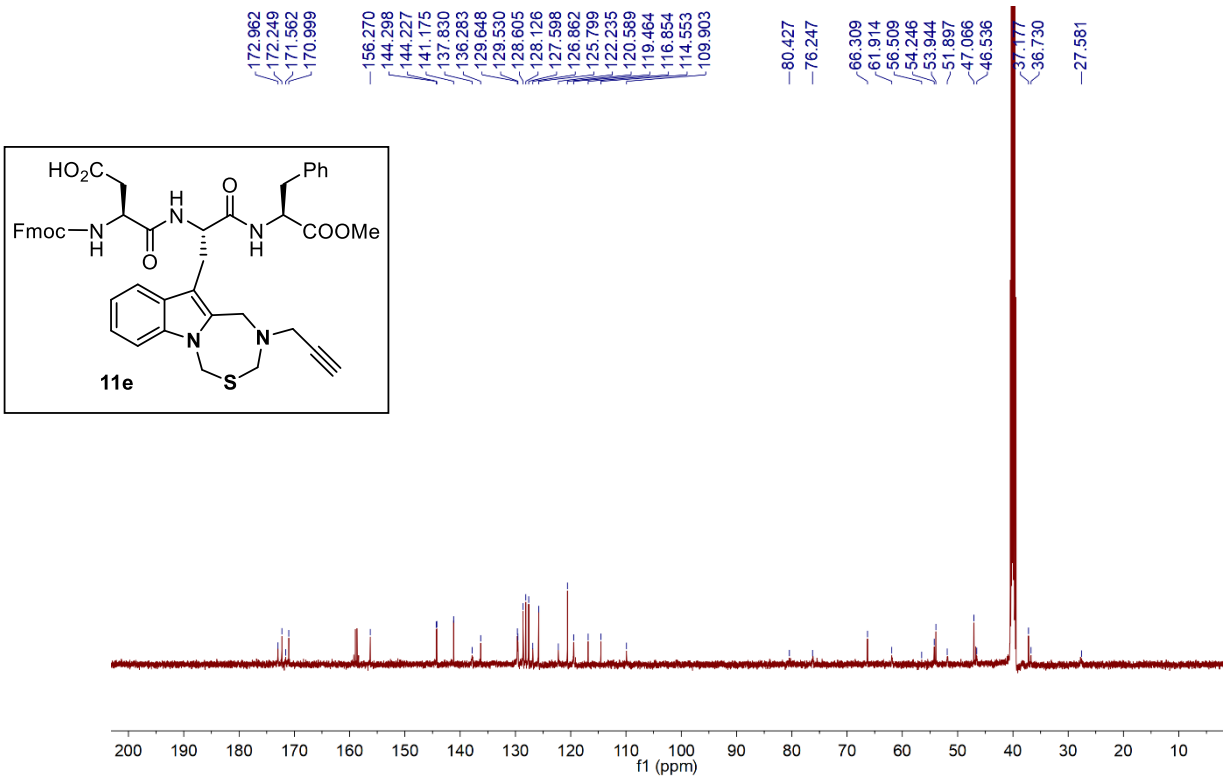
[13]C-NMR spectrum of compound **11d** (101 MHz, DMSO)



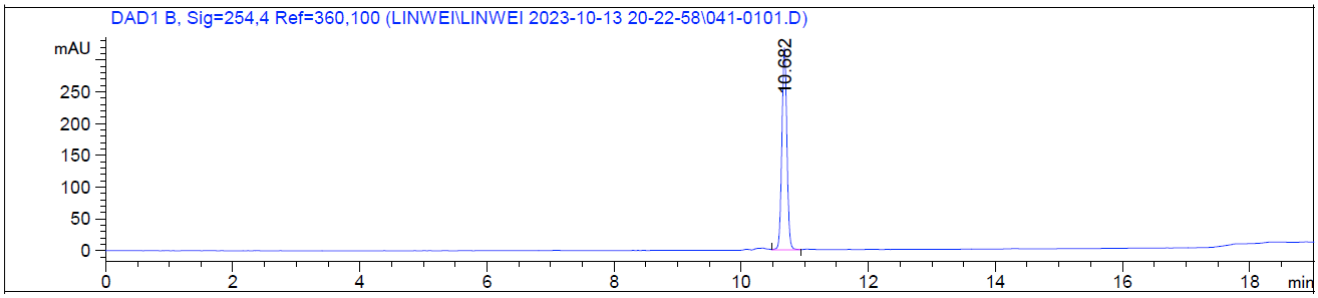
[1]H-NMR spectrum of compound **11e** (500 MHz, DMSO)



[13]C-NMR spectrum of compound **11e** (126 MHz, DMSO)

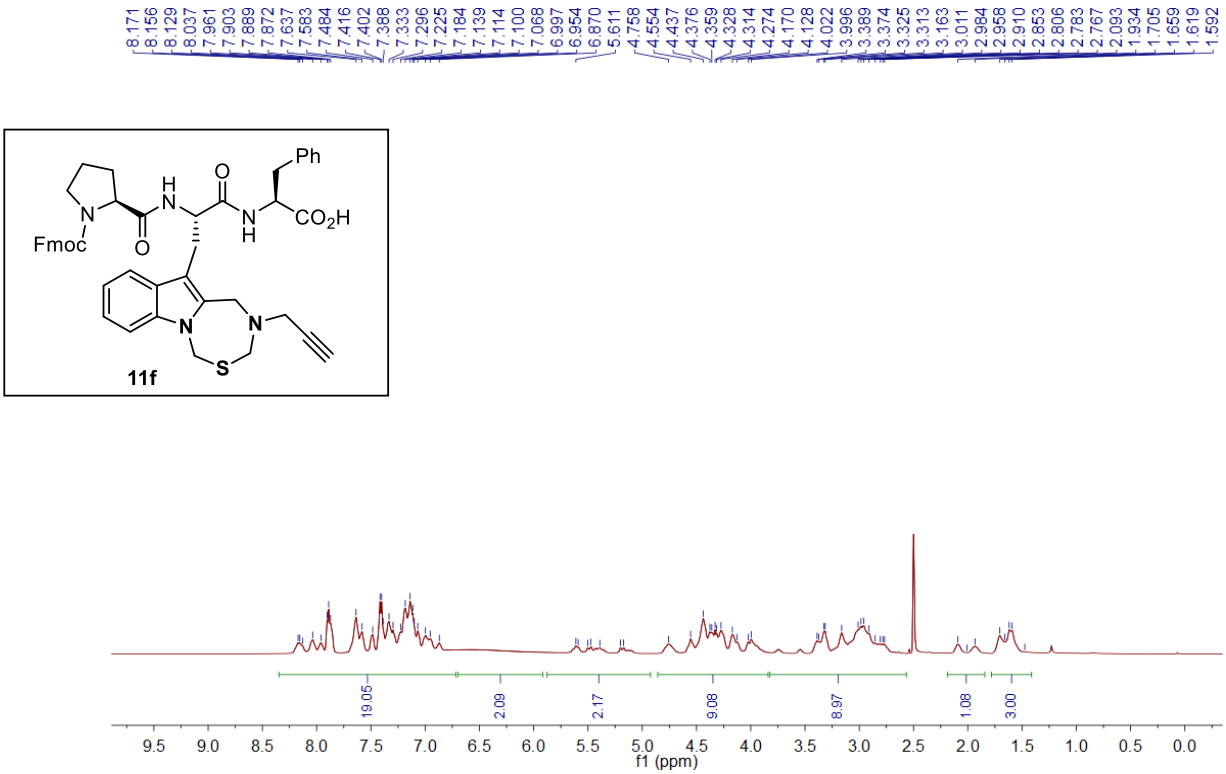


HPLC Traces of compound **11e**

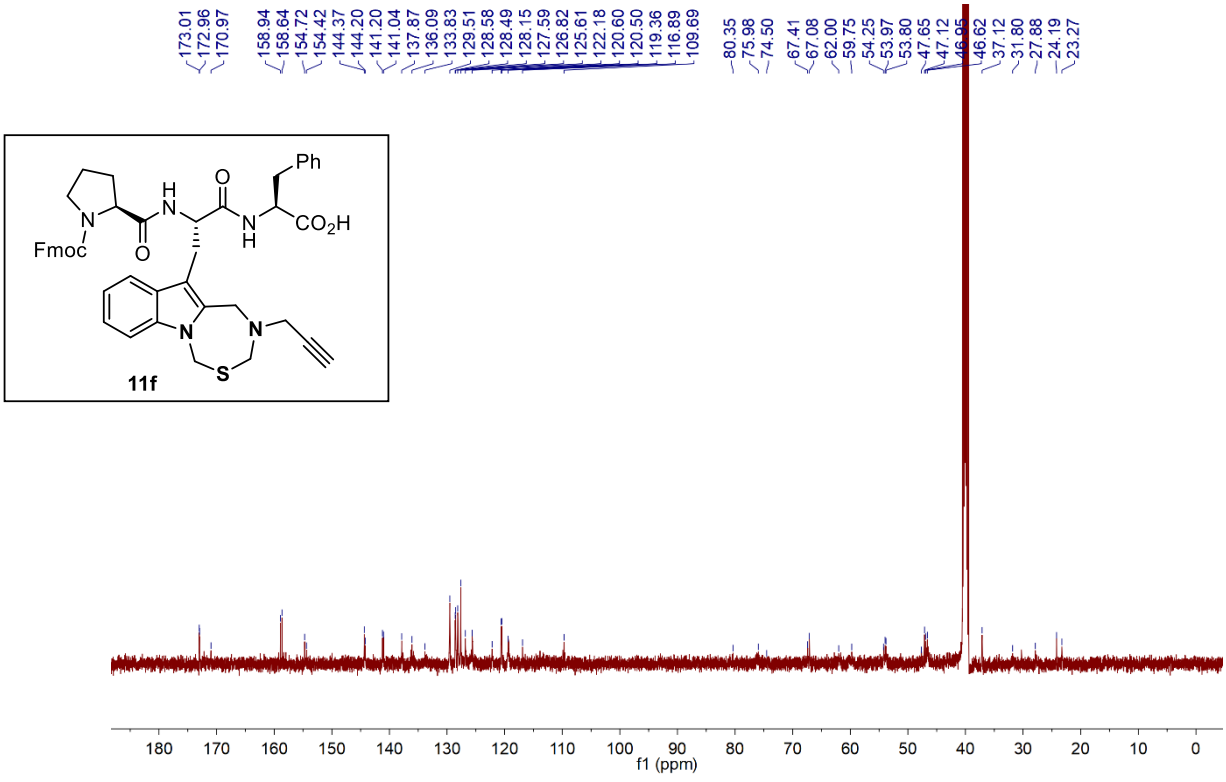


Peak	RT (min)	Area (mAU*s)	Height (mAU)	Area (%)
1	10.682	4740.34277	859.01117	100.000
Total		4740.34277	859.01117	100.000

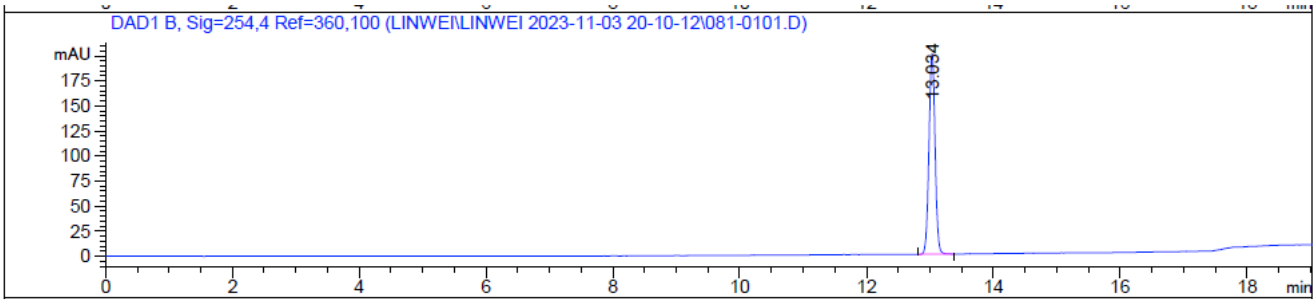
^{1}H-NMR spectrum of compound **11f** (500 MHz, DMSO)



^{13}C-NMR spectrum of compound **11f** (126 MHz, DMSO)

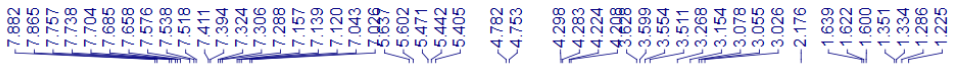


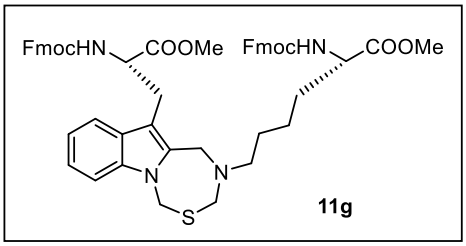
HPLC Traces of compound **11f**

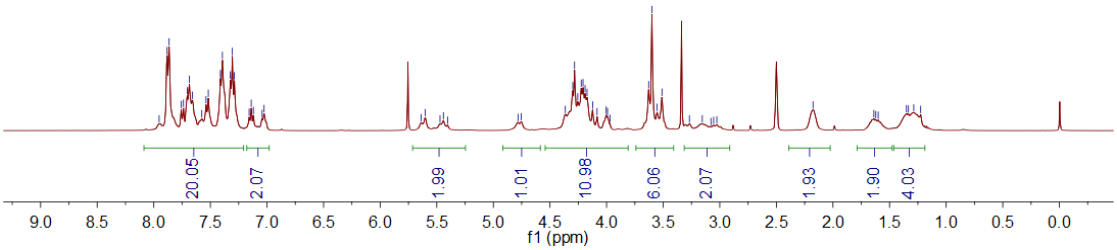


Peak	RT (min)	Area (mAU*s)	Height (mAU)	Area (%)
1	13.034	3734.58301	559.70966	100.000
Total		3734.58301	559.70966	100.000

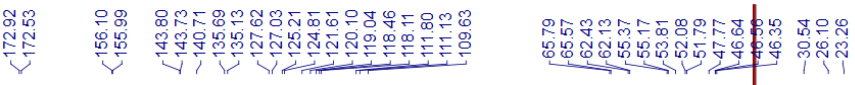
[1]H-NMR spectrum of compound **11g** (400 MHz, DMSO)

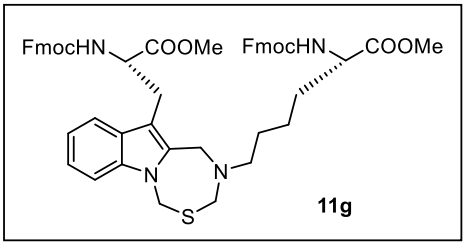


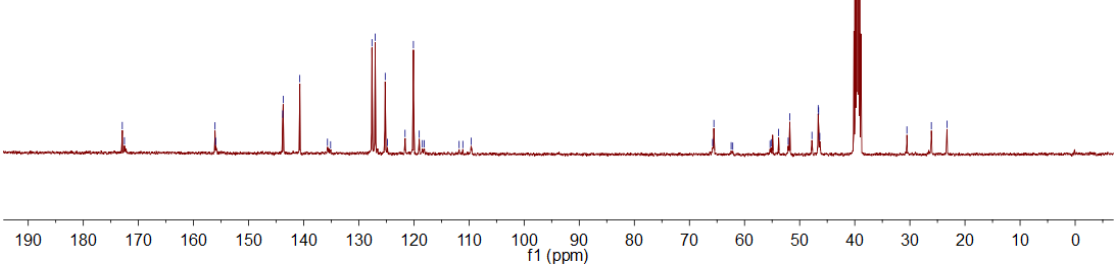




[13]C-NMR spectrum of compound **11g** (101 MHz, DMSO)







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