Electronic Supplementary Information

Simplified Hybrids of Ecteinascidin 743 and Cribrostatin 4 and Inhibitory Activity against Proliferation of Cancer Cells

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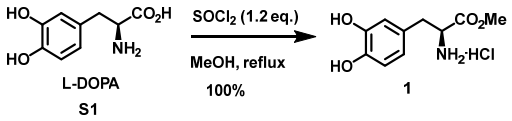
1. General methods

Unless otherwise noted, all reactions were carried out under nitrogen atmosphere with dry solvents. Tetrahydrofuran (THF) was distilled immediately from sodium-benzophenoneketyl prior to use. Dichloromethane (DCM) was distilled immediately before use from calcium hydride. External bath temperatures were used to record all reaction temperatures. Other solvents were purified according to the reference Purification of Laboratory Chemicals (Seventh Edition). Silica gel (300~400 mesh) and petroleum ether, ethyl acetate (EtOAc), dichloromethane (DCM), methanol (MeOH) and acetone were used for product purification by flash column chromatography. Analytical thin-layer chromatography (TLC) was performed with glass TLC plates, and visualization was accomplished with UV light, phosphomolybdic acid or ammonium molybdate staining and subsequent heating. ^{1}H NMR, ^{13}C NMR and 2D NMR spectra were recorded on either 400 MHz/500 MHz NMR instruments. IR spectra were recorded on Fourier transform infrared spectrometer and listed in cm^{-1}. High resolution mass spectral analyses (HRMS) were determined on a Q-TOF-MS spectrometer. Optical rotations were measured with a polarimeter with a sodium lamp.

2. Experimental procedures and characterization of compounds

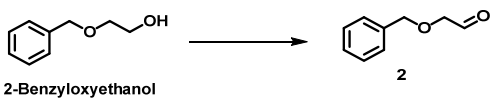
2.1 Compound 1



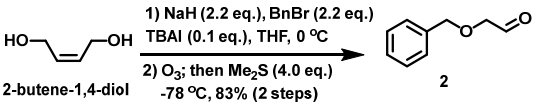
To a suspension of L-DOPA (39.0 g, 200.0 mmol, 1.0 equiv.) in MeOH (500 mL) was added $SOCl_2$ (17.0 mL, 240.0 mmol, 1.2 equiv.) dropwise at 0 °C over 30 mins. The reaction mixture was then heated to reflux overnight. The volatiles were removed under reduced pressure. Toluene was added a few times to the mixture and evaporated to remove residual MeOH. The product was collected as a white solid without further purification.

Spectral data of **1** is consistent with the literature.[1] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.95 (s, 1H), 8.63 (s, 3H), 6.68 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.0, 2.0 Hz, 1H), 4.08 (t, J = 6.4 Hz, 1H), 3.67 (s, 3H), 3.01 (dd, J = 14.0, 5.6 Hz, 1H), 2.92 (dd, J = 14.0, 6.8 Hz, 1H).

2.2 Compound 2



Entry	Condition	Yield
1	DMP (1.2 eq.), DCM, r. t.	64%
2	PCC (1.2 eq.), DCM, r. t.	trace
3	$(COCl)_2$ (1.2 eq.), DMSO (2.4 eq.), Et_3N (6.0 eq.), DCM, -78 °C	81%
4	TEMPO (0.01 eq.), KBr (1.0 eq.), $NaHCO_3$ (1.0 eq.), NaClO (1.1 eq.), DCM/H_2O, 0 °C	40%

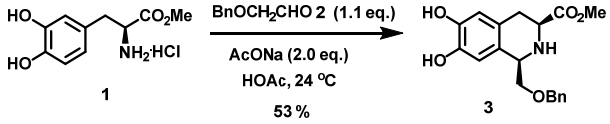


To a stirred solution of 2-*cis*-butene-1,4-diol (20.5 mL, 250.0 mmol, 1.0 equiv.) in THF (500 mL) was added sodium hydride (60% in mineral oil, 22.0 g, 550.0 mmol, 2.2 equiv.) with caution at 0 °C. After stirring for 1 h at 0 °C, benzyl bromide (65.0 mL, 550.0 mmol, 2.2 equiv.) was added dropwise followed by adding TBAI (9.2 g, 25.0 mmol, 0.1 equiv.). The resulting mixture was stirred overnight. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl solution and the mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo.

The resulting crude product was dissolved in DCM/MeOH (3:1, 700 mL) and cooled down to -78 °C. Ozone was bubbled through the reaction until the solution turned blue. The excess ozone was removed by nitrogen stream. Dimethyl sulfide (73.0 mL, 1000.0 mmol, 4.0 equiv.) was then added. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 10:1) to afford **2** (62.2 g, 83%) as a yellow oil.

Spectral data of **2** is consistent with the literature.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.40-7.27 (m, 5H), 4.63 (s, 2H), 4.10 (s, 2H).

2.3 Compound 3



To a suspension of **1** (44.0 g, 178.0 mmol, 1.0 equiv.), NaOAc (29.0 g, 356.0 mmol, 2.0 equiv.) in HOAc (800 mL) was added **2** (29.0 g, 196.0 mmol, 1.1 equiv.) in HOAc (200 mL) dropwise at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight. HOAc was removed under reduced pressure, and the solid residue was dissolved with EtOAc. The insolubles were removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 150:1) to afford **3** (32.6 g, 53%) as a yellowish solid.

$[\alpha]_D^{20} = -93.60$ (c = 1.00 in MeOH); mp: 129-132 °C

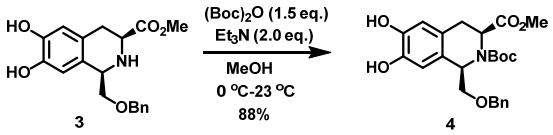
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 6.49 (s, 1H), 6.47 (s, 1H), 4.47-4.40 (m, 2H), 4.12 (dd, *J* = 8.4, 3.6 Hz, 1H), 3.83 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.74 (s, 3H), 3.63 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.47-3.40 (m, 1H), 2.87-2.74 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 143.5, 143.3, 137.7, 128.5, 127.8, 125.6, 115.8, 111.7, 73.5, 73.2, 55.7, 55.3, 52.4, 31.6.

IR (film) ν =3320, 2946, 2832, 1637, 1525, 1452, 1260, 1023, 799 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{19}H_{22}NO_5^+$ 344.1492, found 344.1491.

2.4 Compound 4



To a solution of **3** (31.8 g, 92.7 mmol, 1.0 equiv.) in MeOH (650 mL) was successively added Et_3N (25.7 mL, 185.4 mmol, 2.0 equiv.) and $(Boc)_2O$ (30.3 g, 139.1 mmol,1.5 equiv.) at 0 °C. The reaction mixture was stirred overnight. Most of MeOH was removed under reduced pressure. The concentrated residue was treated with 1 N aq. HCl to pH<2, and the mixture was extracted with DCM. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 100:1) to afford **4** (36.2 g, 88%) as a white solid.

$[\alpha]_D^{20} = -20.20$ (c = 2.00 in MeOH), mp: 55-57 °C

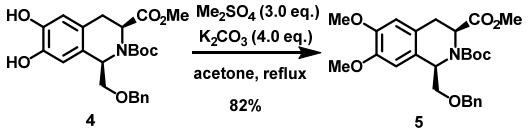
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.15 (m, 5H), 6.75 (s, 0.2H), 6.71 (s, 0.8H), 6.67 (s, 0.8H), 6.64 (s, 0.2H), 5.22 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.99 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.52-4.43 (m, 2H), 4.43-4.37 (m, 0.2H), 4.24 (t, *J* = 9.2 Hz, 0.8H), 3.77 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.75-3.66 (m, 3H), 3.59 (dd, *J* = 9.6, 8.0 Hz, 1H), 2.93 (s, 1H), 2.90 (s, 1H), 1.46-1.41 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 & 173.7, 155.2 & 155.1, 144.0 & 143.5, 142.8 & 142.6, 138.1 & 138.0, 128.4 & 128.3, 128.2 & 127.6, 127.5 & 127.4, 124.2 (overlap), 114.8 & 114.8, 114.6 & 114.2, 81.7 & 81.2, 73.3 & 73.1, 73.1 & 72.7, 56.1 (overlap), 55.3 & 55.0, 52.4 & 52.2, 30.3 & 30.1, 28.4 & 28.3.

IR (film) ν =3356, 2977, 2952, 1750, 1667, 1455, 1394, 1270, 1160 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{24}H_{30}NO_7^+$ 444.2017, found 444.2012.

2.5 Compound 5



To a solution of **4** (36.0 g, 81.2 mmol, 1.0 equiv.) in acetone (600 mL) was successively added K_2CO_3 (44.8 g, 324 mmol, 4.0 equiv.) and Me_2SO_4 (23 mL, 243 mmol, 3.0 equiv.) at room temperature. The reaction mixture was then heated to reflux overnight. After removal of the insolubles by filtration, the filtrate was concentrated in vacuo. The mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 50:1) to afford **5** (31.4 g, 82%) as a white solid.

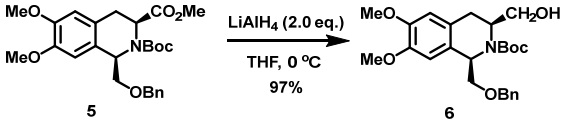
$[\alpha]_D^{20} = -9.70$ (c = 2.00 in MeOH), mp: 30-33 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 6.87 (s, 0.4H), 6.80 (s, 0.6H), 6.68-6.66 (m, 1H), 5.28 (dd, *J* = 8.4, 4.8 Hz, 0.6H), 5.06 (dd, *J* = 8.4, 4.4 Hz, 0.4H), 4.61-4.54 (m, 1H), 4.52-4.45 (m, 1.4H), 4.33-4.28 (m, 0.6H), 3.88-3.83 (m, 1H), 3.87 (s, 3H), 3.82-3.79 (m, 3H), 3.75-3.71 (m, 3H), 3.64-3.55 (m, 1H), 3.06-2.97 (m, 2H), 1.48 (s, 3.6H), 1.42 (s, 5.4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 & 173.2, 154.9 & 154.6, 148.3 & 147.6, 138.6 & 138.3, 128.6 & 128.3, 128.1 & 127.4, 127.8 & 127.5, 127.2 & 127.2, 124.2 & 124.0, 111.5 & 111.1, 110.7 &

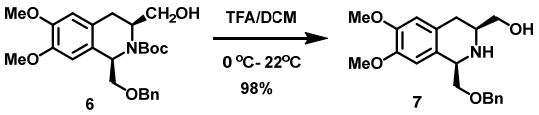
110.6, 80.9 & 80.9, 73.7 & 72.8, 73.1 & 72.7, 56.1 (overlap), 56.0 (overlap), 55.7 & 55.2, 54.8 & 54.3, 52.2 & 52.1, 30.6 & 30.3, 28.4 & 28.2.
IR (film) ν =2952, 2864, 1749, 1693, 1513, 1386, 1258, 1161 cm^{-1}.
HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{26}H_{33}NNaO_7^+$ 494.2149, found 494.2151.

2.6 Compound 6



To a suspension of $LiAlH_4$ (5.1 g, 133.2 mmol, 2.0 equiv.) in dry THF (500 mL) was added **5** (31.4 g, 66.6 mmol, 1.0 equiv.) in dry THF (100 mL) dropwise under N_2 atmosphere at 0 °C. The mixture was then warmed to room temperature and stirred for 3 h. The reaction was quenched by adding H_2O (5.0 mL) dropwise, followed by aqueous 15% NaOH (5.0 mL) and H_2O (15.0 mL). The mixture was warmed to room temperature and stirred overnight. After removal of the insolubles by filtration, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 60:1) to afford **6** (28.7 g, 97%) as a yellow solid.
$[\alpha]_D^{20} = +49.60$ (c = 1.00 in MeOH), mp: 26-28 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 6.71 (s, 1H), 6.65 (s, 1H), 5.49 (s, 0.5H), 5.21 (s, 0.5H), 4.82-4.20 (m, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.73-3.64 (m, 2H), 3.49 (s, 1H), 3.18-3.09 (m, 1H), 3.03-2.74 (m, 2H), 1.47 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 148.2, 147.4, 137.6, 128.4, 127.8, 127.7, 126.4, 126.1, 125.4, 111.5, 109.9, 80.5, 73.3, 73.0, 72.8, 71.9, 65.4, 64.4, 56.0, 55.9, 54.1, 53.1, 52.8, 51.9, 29.2, 28.4.
IR (film) ν =3468, 2934, 2864, 1683, 1514, 1454, 1391, 1254, 1164, 729 cm^{-1}.
HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{25}H_{33}NNaO_6^+$ 466.2200, found 466.2200.

2.7 Compound 7



To a solution of **6** (28.7 g, 64.7 mmol, 1.0 equiv.) in DCM (400 mL) was added TFA (40 mL) dropwise at 0 °C. The reaction was warmed to room temperature and stirred overnight. The solvents and violates were removed under reduced pressure. The resulting mixture was neutralized by adding saturated aqueous $NaHCO_3$ solution, and then extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 50:1) to afford **7** (21.7 g, 98%) as a yellowish solid.
$[\alpha]_D^{20} = -52.00$ (c = 0.50 in MeOH), mp: 118-121 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 6.65 (s, 1H), 6.58 (s, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.23-4.18 (m, 1H), 3.93 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.79 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.71 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.56 (dd, *J* = 11.2, 7.6 Hz, 1H), 3.11-3.03 (m, 1H), 2.83 (s, 3H), 2.64 (dd, *J* = 15.6, 10.4 Hz, 1H), 2.54 (dd, *J* = 15.6, 4.0 Hz,

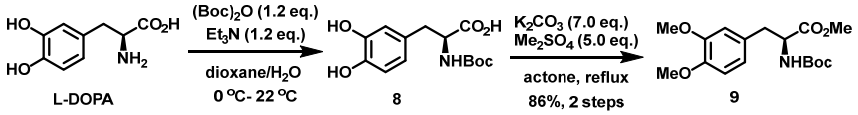
1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 147.4, 138.0, 128.4, 127.9, 127.8, 127.3, 127.3, 112.0, 108.2, 73.9, 73.4, 65.9, 56.0, 56.0, 55.8, 54.6, 31.5.

IR (film) ν =3319, 2930, 2857, 1515, 1453, 1218, 1094 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ calcd for $C_{20}H_{26}NO_4^+$ 344.1856, found 344.1864.

2.8 Compound 9

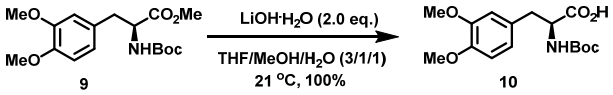


To a solution of L-DOPA (50.0 g, 253.0 mmol, 1.0 equiv.) in dioxane/H_2O (1:1, 1200 mL) was successively added Et_3N (42.0 mL, 303.6 mmol, 1.2 equiv.) and $(Boc)_2O$ (66.3 g, 303.6mmol, 1.2 equiv.) at 0 °C. The reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure, and H_2O (50 mL) and EtOAc (200 mL) were added. The aqueous phase was acidified with 1 N aq. HCl to pH<2, and then extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resulting crude **8** was used for the next step without further purification.

To a solution of above crude **8** (36.0 g, 120.0 mmol, 1.0 equiv.) in acetone (700 mL) was successively added K_2CO_3 (116.1 g, 840.0 mmol, 7.0 equiv.) and Me_2SO_4 (56.9 mL, 600.0 mmol, 5.0 equiv.) at room temperature. The reaction was then heated to reflux overnight. After removal of the insolubles by filtration, the filtrate was concentrated in vacuo. The residue was treated with H_2O and extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 15:1) to afford **9** (35 g, 86%) as a white solid.

Spectral data is consistent with the literature.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.0 Hz, 1H), 6.65-6.60 (m, 2H), 4.98 (d, *J* = 8.4 Hz, 1H), 4.56-4.70 (m, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.06-2.93 (m, 2H), 1.39 (s, 9H).

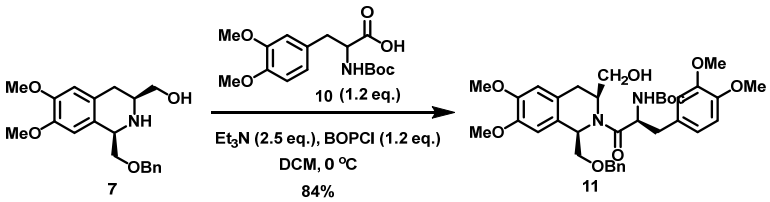
2.9 Compound 10



To a solution of **9** (34.0 g, 100.3 mmol, 1.0 equiv.) in THF/MeOH/H_2O (3:1:1, 500 mL) was added $LiOH{\cdot}H_2O$ (8.4 g, 200.6 mmol, 2.0 equiv.) at 0 °C. The reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was distributed between H_2O and DCM. The aqueous phase was acidified with 1 N aq. HCl to pH<2, and extracted with DCM. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to afford **10** (29.5 g, 100%) as a white solid.

Spectral data is consistent with the literature.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.0 Hz, 1H), 6.74-6.68 (m, 2H), 6.16 (s, 0.3H), 5.01 (s, 0.7H), 4.53 (s, 0.7H), 4.34 (s, 0.3H), 3.84 (s, 6H), 3.17-3.06 (m, 1H), 3.05-2.94 (m, 1H), 1.44-1.24 (m, 9H).

2.10 Compound 11



To a mixture of **7** (18.5 g, 54.0 mmol, 1.0 equiv.), **10** (21.1 g, 64.8 mmol, 1.2 equiv.) and BOPCl (16.5 g, 64.8 mmol, 1.2 equiv.) in DCM (500 mL) was added Et_3N (18.7 mL, 135.0 mmol, 2.5 equiv.) dropwise at 0 °C. The reaction was stirred at 0 °C overnight, until it was quenched with saturated aqueous NH_4Cl solution. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 100:1) to afford **11** (29.4 g, 84%) as a white solid.

$[\alpha]_D^{20} = +34.20$ (c = 2.00 in MeOH), mp: 62-64 °C

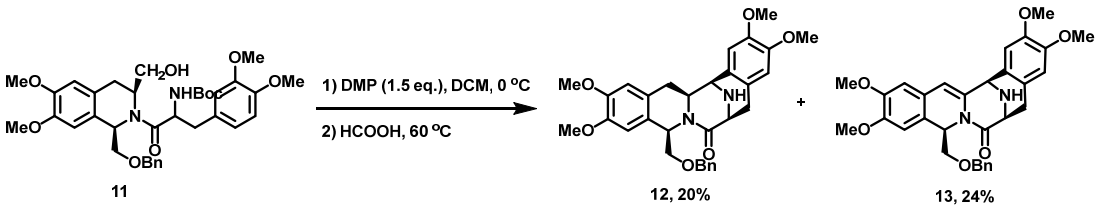
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 6.88 (s, 0.7H), 6.75-6.70 (m, 1.3H), 6.69-6.63 (m, 1.6H), 6.60 (d, *J* = 8.0 Hz, 0.7H), 6.40 (s, 0.7H), 5.60-5.53 (m, 1H), 5.42 (d, *J* = 8.4 Hz, 0.7H), 5.20-5.12 (m, 0.3H), 5.07-4.96 (m, 1H), 4.60 (s, 1.3H), 4.53-4.43 (m, 0.3H), 4.42 (s, 0.7H), 4.12-4.04 (m, 0.7H), 3.87-3.74 (m, 9H), 3.72 (s, 3H), 3.57-3.33 (m, 3H), 3.13-2.88 (m, 3H), 2.83 (dd, *J* = 16.0, 7.2 Hz, 0.3H), 2.32 (d, *J* = 16.2 Hz, 0.7H), 1.99 (dd, *J* = 16.4, 6.4 Hz, 0.7H), 1.81-1.72 (m, 0.3H), 1.46-1.32 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 & 172.7, 155.9 & 154.9, 149.0 & 148.8, 148.7 & 148.0, 147.9 & 147.8, 147.6 & 147.6, 138.0 & 137.1, 129.7 & 128.5, 128.3 (overlap), 128.0 & 127.9, 127.7 & 127.6, 126.2 & 125.3, 126.1 & 123.0, 121.6 & 121.5, 112.9 & 112.4, 111.4 & 111.2, 111.1 & 110.9, 110.3 & 109.5, 80.4 & 79.8, 73.3 & 73.3, 73.0 & 71.9, 65.1 & 64.2, 56.6 & 54.0, 56.0 (overlap), 55.9 (overlap), 55.8 (overlap), 55.8 (overlap), 53.1 & 52.1, 52.0 & 51.7, 39.3 & 39.0, 29.3 & 29.1, 28.3 & 28.3.

IR (film) ν =3429, 2934, 1701, 1631, 1515, 1441, 1264, 1160, 733 cm^{-1}.

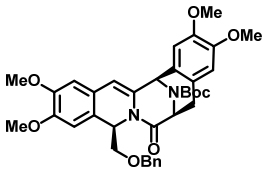
HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{36}H_{46}N_2NaO_9^+$ 673.3096, found 673.3099.

2.11 Compounds 14, 12 and 13



To a solution of compound **11** (5.72 g, 8.8 mmol, 1.0 equiv.) in DCM (80 mL) was added Dess-Martin periodinane (5.6 g, 13.2 mmol, 1.5 equiv.) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h. The whole mixture was filtered through a short pad of silica gel and washed with DCM. The combined filtrate and washings were concentrated in vacuo. The residue (containing crude **14**) was used directly in the next step without further purification.

- **The intermediate 14 involved in this two-step transformation was also isolated and characterized.**



14

14: $[\alpha]_D^{20} = +82.80$ (c = 1.00 in MeOH), mp: 90-94 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (m, 2H), 7.21-7.16 (m, 1H), 7.06-7.02 (m, 2H), 6.70 (s, 1H), 6.67 (s, 1H), 6.65 (s, 1H), 6.36-6.28 (m, 1H), 5.99 (s, 0.7H), 5.90 (s, 0.3H), 5.80 (t, *J* = 7.2 Hz, 1H), 5.65 (s, 0.7H), 5.44 (s, 0.3H), 5.17 (s, 0.3H), 5.08-5.02 (m, 0.7H), 3.94-3.88 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.82-3.77 (m, 1H), 3.60 (s, 3H), 3.29-3.19 (m,1 H), 3.13-2.97 (m, 3H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 152.3, 148.8, 148.3, 147.8, 138.4, 133.7, 128.0, 128.0, 127.0, 126.6, 125.7, 124.3, 123.1, 122.0, 111.5, 110.6, 109.3, 108.6, 105.0, 104.2, 81.2, 72.5, 70.8, 56.1, 56.0, 55.7, 54.7, 53.3, 52.7, 52.1, 32.8, 28.4.

IR (film) ν =2933, 2854, 1697, 1515, 1453, 1367, 1250, 1163 cm^{-1}.

HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{36}H_{40}N_2NaO_8^+$ 651.2677, found 651.2663.

The above residue was dissolved in HCOOH (40 mL) and stirred at 60 ºC for 30 mins. Most of HCOOH was removed under reduced pressure, and the resulting residue was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 100:1) to afford **12** (0.9 g, 20%) as a yellow solid, along with **13** (1.1 g, 24%) as a yellow solid.

Characterizations of **12**:

$[\alpha]_D^{20} = -65.50$ (c = 0.40 in MeOH), mp: 86-90 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.14 (m, 3H), 6.94-6.90 (m, 2H), 6.70 (s, 1H), 6.68 (s, 1H), 6.63 (s, 1H), 6.54 (s, 1H), 5.29 (dd, *J* = 6.0, 3.2 Hz, 1H), 4.11-4.07 (m, 2H), 4.04-3.98 (m, 2H), 3.95 (td, *J* = 7.2, 3.2 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.45 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.23-3.15 (m, 2H), 3.05 (d, *J* = 16.8 Hz, 1H), 2.73 (d, *J* = 7.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 148.8, 148.0, 147.6, 146.9, 138.5, 128.0, 127.9, 127.1, 126.9, 126.6, 126.4, 124.5, 111.7, 111.4, 111.3, 110.6, 72.8, 72.8, 61.2, 56.1, 56.0, 56.0, 55.9, 55.1, 54.6, 54.3, 34.2, 33.1.

IR (film) ν =3303, 2935, 2834, 1638, 1515, 1453, 1264, 1125 cm^{-1}.

HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{31}H_{34}N_2NaO_6^+$ 553.2309, found 553.2309.

Characterizations of **13**:

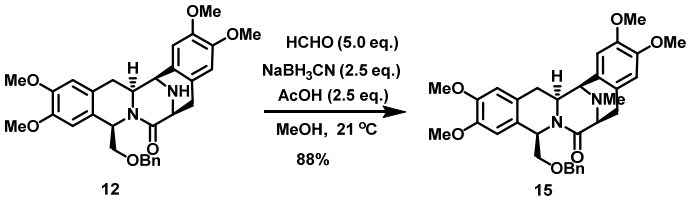
$[\alpha]_D^{20} = -25.50$ (c = 0.40 in MeOH), mp: 86-90 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.21 (m, 2H), 7.21-7.16 (m, 1H), 7.06-7.03 (m, 2H), 6.66 (s, 2H), 6.64 (s, 1H), 6.36 (s, 1H), 5.86-5.80 (m, 2H), 4.53 (s, 1H), 4.11-4.08 (m, 1H), 3.92 (d, *J* = 12.0 Hz, 1H), 3.88 (s, 3H), 3.88-3.84 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.26 (dd, *J* = 16.4, 6.0 Hz, 1H), 3.10 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.07-3.04 (m, 1H), 3.03-2.99 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 148.7, 148.6, 148.0, 147.6, 138.5, 137.1, 128.0, 127.0, 126.6, 126.5, 124.9, 123.3, 122.2, 111.6, 110.7, 109.6, 108.3, 102.9, 72.6, 70.8, 56.1, 56.0, 55.6, 54.8, 54.7, 51.6, 33.8.

IR (film) ν =3306, 2936, 2834, 1639, 1513, 1464, 1358, 1263, 1123 cm^{-1}.
HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{31}H_{32}N_2NaO_6^+$ 551.2153, found 551.2153.

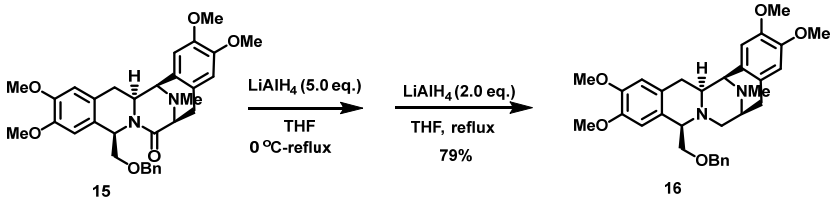
2.12 Compound 15



12 15

To a solution of compound **12** (440 mg, 0.8 mmol, 1.0 equiv.) in MeOH (5 mL) was added HCHO (37% in H_2O, 329 mg, 4.0 mmol, 5.0 equiv.), $NaBH_3CN$ (126 mg, 2.0 mmol, 2.5 equiv.), and acetic acid (114 μL, 2.0 mmol, 2.5 equiv.). The reaction was stirred at room temperature for 1 h, until it was quenched with H_2O. The whole mixture was concentrated under reduced pressure. The residue was distributed with DCM and washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 50:1) to afford **15** (385 mg, 88%) as a yellow solid.
$[\alpha]_D^{20} = -68.00$ (c = 1.00 in MeOH), mp: 77-79 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.13 (m, 3H), 6.93-6.88 (m, 2H), 6.68 (s, 1H), 6.68 (s, 1H), 6.62 (s, 1H), 6.54 (s, 1H), 5.27 (dd, *J* = 6.4, 3.2 Hz, 1H), 4.10 (d, *J* = 12.4 Hz, 1H), 4.01 (d, *J* = 11.6 Hz, 1H), 4.04-3.98 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76-3.73 (m, 1H), 3.70 (dt, *J* = 6.4, 1.2 Hz, 1H), 3.45 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.26 (dd, *J* = 17.2, 6.8 Hz, 1H), 3.21 (dd, *J* = 9.6, 6.4 Hz, 1H), 2.84 (d, *J* = 17.2 Hz, 1H), 2.73-2.61 (m, 2H), 2.47 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 148.7, 147.9, 147.6, 147.0, 138.5, 128.2, 128.0, 127.1, 126.8, 126.6, 125.7, 122.5, 112.1, 111.4, 111.3, 110.6, 72.8, 72.8, 60.9, 60.3, 57.7, 56.1, 56.0, 55.9, 55.8, 55.1, 40.0, 32.9, 28.4.
IR (film) ν = 2934, 2834, 1640, 1514, 1464, 1359, 1256, 1113, 731 cm^{-1}.
HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{32}H_{36}N_2NaO_6^+$ 567.2466, found 567.2468.

2.13 Compound 16



15 16

To a stirred suspension of $LiAlH_4$ (114 mg, 3.0 mmol, 5.0 equiv.) in anhydrous THF (10 mL) was added **15** (326 mg, 0.6 mmol, 1.0 equiv.) in anhydrous THF (5 mL) dropwise at 0 °C under N_2. The reaction was then heated to reflux for 1 h, until it was quenched with H_2O (0.1 mL) dropwise, followed by adding aqueous 15% NaOH (0.1 mL) and H_2O (0.3 mL). After filtration, the filtrate was concentrated in vacuo to give the crude intermediate (the semi-*N*,*O*-aminal).
To a stirred suspension of $LiAlH_4$ (46 mg, 1.2 mmol, 2.0 equiv.) in anhydrous THF (10 mL) was added the above crude intermediate in anhydrous THF (5 mL) dropwise at 0 °C under N_2. The reaction mixture was heated to reflux overnight, until it was quenched with H_2O (0.05 mL) dropwise,

followed by adding aqueous 15% NaOH (0.05 mL) and H_2O (0.15 mL). The mixture was warmed to room temperature and stirred overnight. After removal of the insolubles by filtration, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1) to afford **16** (221 mg, 79%) as a yellow solid.

$[\alpha]_D^{20} = +26.80$ (c = 1.00 in MeOH), mp: 61-64 ℃

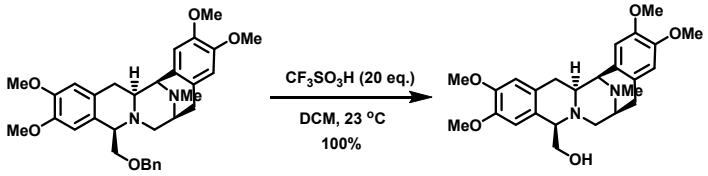
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.22 (m, 3H), 7.21-7.17 (m, 2H), 6.68 (s, 1H), 6.58 (s, 1H), 6.56 (s, 1H), 6.50 (s, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 6H), 3.74 (s, 3H), 3.58-3.52 (m, 2H), 3.37 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.24 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.21-3.14 (m, 2H), 3.05 (dd, *J* = 17.2, 7.6 Hz, 1H), 3.01-2.92 (m, 2H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.48 (dd, *J* = 14.8, 2.8 Hz, 1H), 2.36 (dd, *J* = 14.4, 11.6 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 147.3, 147.1, 146.1, 138.7, 128.3, 128.2, 127.4, 127.3, 127.3, 124.4, 112.6, 110.6, 110.5, 77.1, 76.7, 73.3, 64.0, 63.3, 61.6, 60.1, 56.2, 55.9, 55.8, 53.8, 41.2, 33.3, 27.3.

IR (film) ν = 2931, 2832, 1514, 1464, 1247, 1115, 1002 cm^{-1}.

HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{32}H_{39}N_2O_5^+$ 531.2853, found 531.2857.

2.14 Compound 17



To a solution of **16** (35.4 mg, 0.067 mmol, 1.0 equiv.) in DCM (5 mL) was added CF_3SO_3H (118 μL, 1.3 mmol, 20.0 equiv.) dropwise at room temperature. The mixture was stirred for 1 h, until the solvent was removed under reduced pressure. The residual mixture was neutralized with saturated aqueous $NaHCO_3$ solution, and then extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 50:1) to afford **17** (29.5 mg, 100%) as a white solid.

$[\alpha]_D^{20} = +42.40$ (c = 0.50 in MeOH), mp: 92-96 ℃

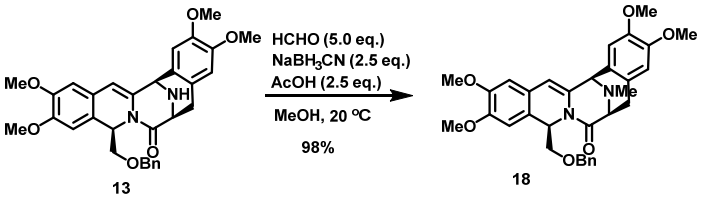
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.55 (s, 1H), 6.51 (s, 1H), 6.50 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.82-3.78 (m, 1H), 3.57 (dd, *J* = 2.8, 1.2 Hz, 1H), 3.52 (t, *J* = 2.8 Hz, 1H), 3.36 (d, *J* = 10.4 Hz, 1H), 3.20-3.12 (m, 2H), 3.12-3.00 (m, 2H), 2.97 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.56 (d, *J* = 16.8 Hz, 1H), 2.49 (dd, *J* = 14.8, 3.2 Hz, 1H), 2.42 (dd, *J* = 15.2, 11.2 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 147.7, 147.6, 146.4, 127.6, 127.6, 126.8, 124.4, 112.8, 110.7, 110.6, 109.5, 65.2, 63.8, 63.8, 60.5, 59.4, 56.2, 56.0, 55.9, 55.9, 53.4, 41.5, 32.9, 27.1.

IR (film) ν = 3365, 2928, 2835, 1516, 1464, 1257, 1115, 1041 cm^{-1}.

HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{25}H_{33}N_2O_5^+$ 441.2384, found 441.2389.

2.15 Compound 18



13 18

To a solution of **13** (4.7 g, 8.9 mmol, 1.0 equiv.) in MeOH (100 mL) was added HCHO (3.6 g, 44.5 mmol, 5.0 equiv.), $NaBH_3CN$ (1.4 g, 22.3 mmol, 2.5 equiv.), and acetic acid (1.3 mL, 22.3 mmol, 2.5 equiv.) at room temperature. The reaction was stirred at room temperature for 1 h, until it was quenched with H_2O. The whole mixture was concentrated under reduced pressure. The resulting mixture was diluted with DCM, and washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1) to afford **18** (4.73 g, 98%) as a white solid.

$[\alpha]_D^{20} = -31.60$ (c = 0.50 in MeOH), mp: 81-85 °C

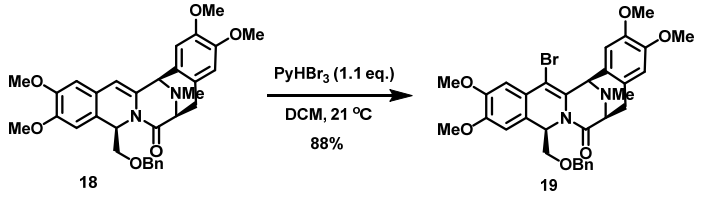
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.22 (m, 2H), 7.22-7.16 (m, 1H), 7.07-7.03 (m, 2H), 6.66 (s, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 6.34 (s, 1H), 5.90 (s, 1H), 5.87 (dd, *J* = 8.0, 5.6 Hz, 1H), 4.18 (s, 1H), 3.91 (d, *J* = 12.4 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.83-3.79 (m, 1H), 3.69 (dt, *J* = 6.4, 1.6 Hz, 1H), 3.61 (s, 3H), 3.33 (dd, *J* = 16.4, 6.4 Hz, 1H), 3.10 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.04-2.98 (m, 2H), 2.54 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 148.7, 148.6, 148.0, 147.5, 138.5, 133.8, 128.0, 127.0, 126.7, 126.6, 124.5, 122.9, 122.3, 111.2, 110.7, 109.6, 108.3, 105.9, 72.6, 71.0, 61.8, 61.4, 56.1, 56.0, 56.0, 55.6, 51.4, 41.8, 33.5.

IR (film) ν = 2936, 2835, 1640, 1513, 1464, 1358, 1252, 1192, 1005 cm^{-1}.

HRMS (ESI, m/z): $[M + Na]^+$ $C_{32}H_{34}N_2NaO_6^+$ 565.2309, found 565.2311.

2.16 Compound 19



18 19

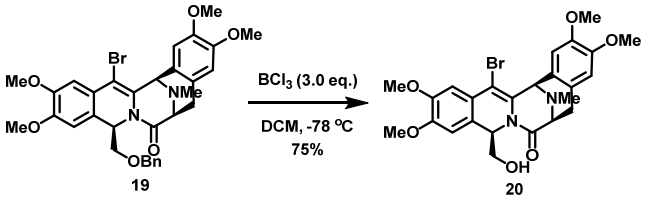
To a solution of **18** (3.3 g, 6.0 mmol, 1.0 equiv.) in DCM (50 mL) was added pyridinium tribromide (2.1 g, 6.6 mmol, 1.1 equiv.) at room temperature. The reaction was stirred at room temperature for 1 h, until it was quenched with H_2O. The whole mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 100:1) to afford **19** (3.3 g, 88%) as a yellowish solid.

$[\alpha]_D^{20} = +98.20$ (c = 1.00 in MeOH), mp: 72-74 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.23 (m, 2H), 7.22-7.17 (m, 1H), 7.14 (s, 1H), 7.06-7.03 (m, 2H), 7.02 (s, 1H), 6.65 (s, 1H), 6.33 (s, 1H), 5.91 (dd, *J* = 7.6, 5.2 Hz, 1H), 5.22 (s, 1H), 3.95 (s, 3H), 3.89 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77-3.81 (m, 1H), 3.66 (dt, *J* = 6.0, 1.2 Hz, 1H), 3.59 (s, 3H), 3.31 (dd, *J* = 16.4, 6.4 Hz, 1H), 3.08 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.01-2.95 (m, 2H), 2.55 (s, 3H).

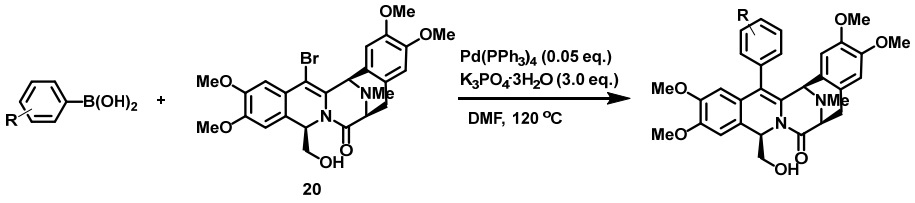
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 148.9, 148.8, 148.6, 147.7, 138.3, 132.4, 128.0, 127.1, 126.6, 126.5, 124.4, 122.8, 122.6, 111.3, 110.1, 109.4, 108.9, 103.3, 72.5, 70.9, 60.6, 59.6, 56.1, 56.0, 55.6, 51.1, 41.7, 33.2.
IR (film) ν = 2936, 2855, 1670, 1511, 1464, 1377, 1264, 1131, 1006 cm^{-1}.
HRMS (ESI, m/z): $[M + Na]^+$ $C_{32}H_{33}BrN_2NaO_6^+$ 643.1414, found 643.1409.

2.17 Compound 20

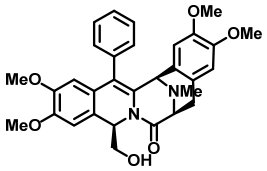


To a solution of **19** (3.2 g, 5.2 mmol, 1.0 equiv.) in DCM (50 mL) was added BCl_3 (1.0 M in toluene, 15.6 mL, 15.6 mmol, 3.0 equiv.) dropwise at -78 °C under N_2. The reaction was stirred at -78 °C for 3 h, until it was quenched by adding saturated aqueous $NaHCO_3$ solution. The whole mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1) to afford **20** (2.1 g, 75%) as a white solid.
$[\alpha]_D^{20} = +167.00$ (c = 0.40 in MeOH), mp: 101-105 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.04 (s, 1H), 6.66 (s, 1H), 6.64 (s, 1H), 5.72 (dd, *J* = 7.6, 5.2 Hz, 1H), 5.24 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.67 (dt, *J* = 6.0, 1.6 Hz, 1H), 3.35 (dd, *J* = 16.4, 6.0 Hz, 1H), 3.22-3.14 (m, 1H), 3.10-3.04 (m, 1H), 3.04-2.97 (m, 2H), 2.55 (s, 3H), 0.82 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 149.1, 149.0, 148.9, 148.1, 132.1, 126.5, 124.2, 122.6, 122.4, 111.2, 109.9, 109.7, 108.8, 103.5, 64.0, 60.7, 59.6, 56.2, 56.1, 56.0, 55.8, 53.0, 41.7, 33.6.
IR (film) ν =3521, 2937, 2834, 1667, 1611, 1512, 1464, 1379, 1250, 1132 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{25}H_{28}BrN_2O_6^+$ 531.1125, found 531.1119.

2.18 General procedure for the synthesis of 21a~21l



A mixture of vinyl bromide **20** (37.1 mg, 0.07 mmol, 1.0 equiv.), the corresponding arylboronic acid (0.168 mmol, 2.4 equiv.), $Pd(PPh_3)_4$ (4.0 mg, 0.0035 mmol, 0.05 equiv.), $K_3PO_4{\cdot}3H_2O$ (56.0 mg, 0.21 mmol, 3.0 equiv.) in DMF (2 mL) was stirred at 120 °C under N_2 overnight. The reaction was quenched with H_2O. The whole mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford **21a~21l.**



21a

21a: white solid, 99% yield. Flash column chromatography (petroleum ether/acetone = 1:1).

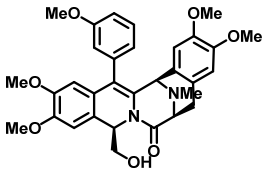
$[\alpha]_D^{20} = +93.00$ (c = 0.40 in MeOH), mp: 119-121 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 1H), 7.55-7.47 (m, 2H), 7.47-7.43 (m, 1H), 7.37-7.33 (m, 1H), 6.72 (s, 1H), 6.59 (s, 1H), 6.29 (s, 1H), 6.11 (s, 1H), 5.81 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.47 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 3.71-3.67 (m, 1H), 3.58 (s, 3H), 3.35-3.27 (m, 2H), 3.26-3.18 (m, 1H), 3.02 (d, *J* = 15.6 Hz, 1H), 2.65 (s, 3H), 1.01 (t, *J* = 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 148.6, 148.5, 147.7, 136.4, 131.3, 130.7, 130.0, 129.4, 128.7, 128.3, 126.9, 125.3, 124.0, 122.3, 119.8, 111.0, 110.1, 109.1, 109.0, 64.8, 61.1, 56.9, 56.1, 55.9, 55.8, 53.0, 41.8, 33.8.

IR (film) ν =3523, 2936, 2833, 1663, 1623, 1513, 1463, 1379, 1221, 731 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ $C_{31}H_{33}N_2O_6^+$ 529.2333, found 529.2335.



21b

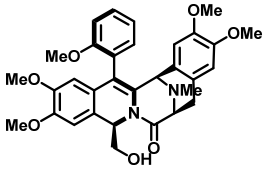
21b: (*d.r.*=1:0.9, two atropisomers), white solid, 75% yield. Flash column chromatography (DCM/MeOH = 80:1)

$[\alpha]_D^{20} = +108.50$ (c = 0.40 in MeOH), mp: 115-118 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.47 (m, 0.9H, one isomer), 7.46-7.41 (m, 1H, one isomer), 7.04-6.98 (m, 3.8H, two isomers), 6.93 (dt, *J*=7.6, 1.2 Hz, 1H, one isomer), 6.91-6.88 (m, 0.9H, one isomer), 6.72 (s, 1H, one isomer), 6.71 (s, 0.9H, one isomer), 6.59 (s, 1.9H, two isomers), 6.41 (s, 0.9H, one isomer), 6.33 (s, 1H, one isomer), 6.18 (s, 0.9H, one isomer), 6.16 (s, 1H, one isomer), 5.83-5.77 (m, 1.9H, two isomers), 4.53 (s, 1H, one isomer), 4.46 (s, 0.9H, one isomer), 3.90 (s, 3H, one isomer), 3.86 (s, 5.4H, one isomer), 3.84 (s, 2.7H, one isomer), 3.82 (s, 3H, one isomer), 3.82 (s, 3H, one isomer), 3.74 (s, 2.7H, one isomer), 3.71 (s, 3H, one isomer), 3.70-3.65 (m, 1.9H, two isomers), 3.61 (s, 2.7H, one isomer), 3.61 (s, 3H, one isomer), 3.35-3.25 (m, 3.8H, two isomers), 3.24-3.17 (m, 1.9H, two isomers), 3.03 (s, 1H, one isomer), 2.99 (s, 0.9H, one isomer), 2.65 (s, 3H, one isomer), 2.61 (s, 2.7H, one isomer), 1.03-0.95 (m, 1.9H, two isomers).

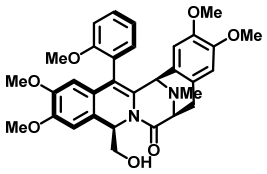
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (overlap, two isomers), 160.2 & 160.2 (two isomers), 148.6 & 148.6 (two isomers), 148.5 (overlap, two isomers), 147.7 & 147.6 (two isomers), 137.8 &137.8 (two isomers), 130.4 (overlap, two isomers), 129.9 & 129.9 (two isomers), 129.8 (overlap, two isomers), 127.0 (overlap, two isomers), 125.2 (overlap, two isomers), 124.1 (overlap, two isomers), 123.5 & 122.9 (two isomers), 122.2 (overlap, two isomers), 119.5 (overlap, two isomers), 118.0 & 116.6 (two isomers), 113.3 & 112.5 (two isomers), 111.0 (overlap, two isomers), 110.0 (overlap, two isomers), 109.2 (overlap, two isomers), 109.1 (overlap, two isomers), 64.8 & 64.7 (two isomers), 61.1 (overlap, two isomers), 57.0 & 56.9 (two isomers), 56.1 (overlap, two isomers), 56.0 (overlap,

two isomers), 55.8 (overlap, two isomers), 55.8 (overlap, two isomers), 55.4 & 55.3 (two isomers), 53.0 & 53.0 (two isomers), 41.9 & 41.8 (two isomers), 33.9 & 33.8 (two isomers).
IR (film) ν =3521, 2936, 2834, 1664, 1624, 1513, 1464, 1380, 1246, 733 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{32}H_{35}N_2O_7^+$ 559.2439, found 559.2436.



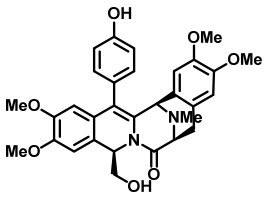
21c

21c: white solid, 28% yield. Flash column chromatography (petroleum ether/acetone = 2:1)
$[\alpha]_D^{20} = +76.00$ (c = 0.20 in MeOH), mp: 118-122 ℃
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (td, *J* = 8.4, 1.6 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 6.24 (s, 1H), 6.04 (s, 1H), 5.80 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.49 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.69-3.67 (m, 1 H), 3.67 (s, 3H), 3.57 (s, 3H), 3.38-3.25 (m, 3H), 3.03 (dd, *J* = 16.4, 1.6 Hz, 1H), 2.65 (s, 3H), 0.92 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 158.6, 148.8, 148.6, 148.3, 147.6, 132.1, 130.1, 129.8, 127.0, 125.6, 125.0, 124.4, 122.2, 121.4, 117.2, 111.8, 111.0, 110.4, 109.8, 108.0, 64.5, 61.3, 57.1, 56.1, 56.0, 55.9, 55.9, 55.8, 52.9, 41.9, 34.0.
IR (film) ν =3454, 2936, 2835, 1664, 1513, 1463, 1381, 1263, 779 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{32}H_{35}N_2O_7^+$ 559.2439, found 559.2436.



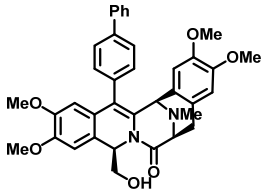
21d

21d: white solid, 31% yield. Flash column chromatography (petroleum ether/acetone = 2:1)
$[\alpha]_D^{20} = +120.00$ (c = 0.20 in MeOH), mp: 120-123 ℃
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H), 7.26-7.23 (m, 1H), 7.13 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.09 (td, *J* = 7.2, 0.8 Hz, 1H), 6.71 (s, 1H), 6.58 (s, 1H), 6.36 (s, 1H), 6.07 (s, 1H), 5.83 (dd, *J* = 7.6, 5.6 Hz, 1H), 4.24 (s, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.71-3.66 (m, 1H), 3.59 (s, 3H), 3.37-3.23 (m, 3H), 3.02 (d, *J* = 16.4 Hz, 1H), 2.59 (s, 3H), 1.13 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 157.5, 148.7, 148.5, 148.3, 147.5, 133.4, 130.8, 130.1, 127.1, 125.3, 124.8, 124.1, 122.3, 120.5, 115.3, 111.3, 111.0, 110.0, 109.3, 108.7, 64.9, 61.2, 57.6, 56.1, 55.9, 55.9, 55.8, 55.2, 53.2, 42.1, 33.7.
IR (film) ν =3449, 2936, 2834, 1664, 1513, 1463, 1381, 1257, 780 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{32}H_{35}N_2O_7^+$ 559.2439, found 559.2441.



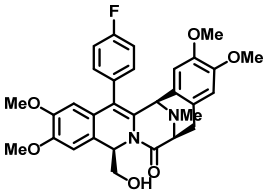
21e

21e: white solid, 59% yield. Flash column chromatography (DCM/MeOH = 50:1)
$[\alpha]_D^{20} = +112.00$ (c = 0.40 in MeOH), mp: 147-151 ℃
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.00 (dd, *J* = 8.0, 2.8 Hz, 1H), 6.96 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 6.47 (s, 1H), 6.33 (s, 1H), 6.16 (s, 1H), 5.80 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.51 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.72-3.69 (m, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.33 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.29 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.24 -3.16 (m, 1H), 3.03 (d, *J* = 12.0 Hz, 1H), 2.63 (s, 3H), 1.09 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 155.9, 148.6, 148.6, 148.4, 147.7, 132.5, 131.9, 129.9, 128.0, 126.9, 125.6, 124.0, 122.2, 119.6, 116.2, 116.0, 111.0, 110.0, 109.2, 109.1, 64.7, 61.1, 56.9, 56.1, 55.9, 55.8, 55.8, 53.1, 41.8, 33.8.
IR (film) ν =3313, 2937, 2834, 1664, 1514, 1464, 1382, 1264, 731 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{31}H_{33}N_2O_7^+$ 545.2282, found 545.2280.



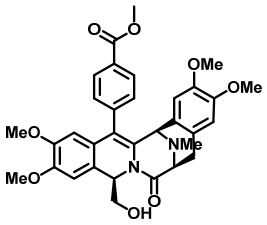
21f

21f: white solid, 60% yield. Flash column chromatography (DCM/acetone = 5:1)
$[\alpha]_D^{20} = +124.00$ (c = 0.20 in MeOH), mp: 131-133 ℃
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.0 2.0 Hz, 1H), 7.77 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.72-7.68 (m, 2H), 7.54-7.48 (m, 3H), 7.45-7.38 (m, 2H), 6.73 (s, 1H), 6.59 (s, 1H), 6.36 (s, 1H), 6.19 (s, 1H), 5.82 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.53 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 3.70 (d, *J* = 5.6 Hz, 1H), 3.60 (s, 3H), 3.36-3.26 (m, 2H), 3.26-3.20 (m, 1H), 3.02 (d, *J* = 15.2 Hz, 1H), 2.66 (s, 3H), 1.01 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 148.7, 148.6, 148.5, 147.7, 141.0, 140.1, 135.4, 131.7, 131.2, 130.2, 129.0, 127.9, 127.8, 127.2, 127.0, 127.0, 125.3, 124.1, 122.3, 119.3, 111.1, 110.1, 109.1, 109.1, 64.8, 61.2, 57.0, 56.2, 56.0, 55.8, 55.8, 53.1, 41.9, 33.8.
IR (film) ν =3454, 2935, 2855, 1665, 1513, 1463, 1380, 1259, 1127, 754 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{37}H_{37}N_2O_6^+$ 605.2646, found 605.2644.



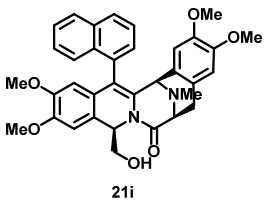
21g

21g: white solid, 63% yield. Flash column chromatography (petroleum ether/acetone = 2:1)
$[\alpha]_D^{20} = +78.50$ (c = 0.40 in MeOH), mp: 123-125 ℃
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (ddd, *J* = 8.0, 5.6, 2.4 Hz, 1H), 7.33 (ddd, *J* = 8.0, 5.2, 2.0 Hz, 1H), 7.28 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.23 (td, *J* = 8.4, 2.8 Hz, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 6.26 (s, 1H), 6.06 (s, 1H), 5.79 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.42 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.68 (dt, *J* = 5.6, 1.6 Hz, 1H), 3.59 (s, 3H), 3.33-3.25 (m, 2H), 3.22-3.15 (m, 1H), 3.00 (dd, *J* = 16.4, 1.6 Hz, 1H), 2.62 (s, 3H), 1.09-1.00 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 162.5 (d, J_{C-F} = 249.4 Hz), 148.7, 148.6, 148.5, 147.7, 132.9 (d, J_{C-F} = 7.9 Hz), 132.5 (d, J_{C-F} = 7.9 Hz), 132.4 (d, J_{C-F} = 3.6 Hz), 130.5, 126.7, 125.2, 124.2, 122.3, 118.6, 116.4 (d, J_{C-F} = 21.3 Hz), 116.0 (d, *J* = 21.4 Hz), 111.1, 110.1, 108.9, 108.8, 64.7, 61.1, 57.0, 56.2, 55.9, 55.8, 53.0, 41.8, 33.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ -112.9 (s).
IR (film) ν =3520, 2937, 2834, 1664, 1511, 1464, 1380, 1222, 1127, 779 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{31}H_{32}FN_2O_6^+$ 547.2239, found 547.2236.



21h

21h: white solid, 42% yield. Flash column chromatography (petroleum ether/acetone = 2:1)
$[\alpha]_D^{20} = +96.20$ (c = 0.20 in MeOH), mp: 130-134 ℃
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.21 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.46 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.72 (s, 1H), 6.59 (s, 1H), 6.22 (s, 1H), 6.01 (s, 1H), 5.81 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.39 (s, 1H), 3.99 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.70-3.67 (m, 1H), 3.56 (s, 3H), 3.34-3.26 (m, 2H), 3.25-3.17 (m, 1H), 3.01 (dd, *J* = 16.4, 1.6 Hz, 1H), 2.64 (s, 3H), 0.98 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 166.6, 148.7, 148.7, 148.6, 147.7, 141.7, 131.5, 131.0, 130.7, 130.4, 130.2, 129.9, 126.6, 124.7, 124.2, 122.3, 118.7, 111.1, 110.2, 108.8, 108.7, 64.8, 61.2, 57.1, 56.2, 55.9, 55.9, 55.8, 53.0, 52.4, 41.8, 33.7.
IR (film) ν =3518, 2938, 2834, 1721, 1665, 1513, 1463, 1380, 1267, 1120, 741 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{33}H_{35}N_2O_8^+$ 587.2388, found 587.2387.



21i

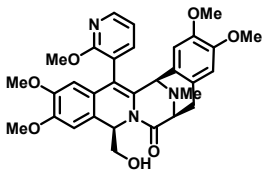
21i: *d.r.*=1:0.3 (two atropisomers), white solid, 80% yield. Flash column chromatography (DCM/MeOH = 80:1)
$[\alpha]_D^{20} = +128.50$ (c = 0.40 in MeOH), mp: 130-133 ℃
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-7.98 (m, 3H, one isomer), 7.96-7.93 (m, 0.3H, one isomer),

7.69-7.46 (m, 5.5H, two isomers), 7.41-7.36 (m, 0.3H, one isomer), 6.77 (s, 0.3H, one isomer), 6.76 (s, 1H, one isomer), 6.57 (s, 1H, one isomer), 6.54 (s, 0.3H, one isomer), 6.47 (s, 1H, one isomer), 5.94-5.89 (m, 2.3H, two isomers), 5.86 (s, 0.3H, one isomer), 5.47 (s, 0.3H, one isomer), 4.55 (s, 0.3H, one isomer), 3.97 (s, 1H, one isomer), 3.87 (s, 3.9H, two isomers), 3.82 (s, 3H, one isomer), 3.81 (s, 3H, one isomer), 3.77 (s, 0.9H, one isomer), 3.76-3.70 (m, 1.3H, two isomers), 3.58-3.34 (m, 2.6H, two isomers), 3.34-3.30 (m, 0.3H, one isomer), 3.33 (s, 3.9H, two isomers), 3.25 (dd, *J*= 16.4, 6.0 Hz, 1H, one isomer), 3.06-2.95 (m, 1.3H, two isomers), 2.94 (s, 0.9H, one isomer), 2.73 (s, 0.9H, one isomer), 2.43 (s, 3H, one isomer), 1.22-1.16 (m, 1.3H, two isomers).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 & 169.4 (two isomers), 148.70 (overlap, two isomers), 148.6 & 148.5 (two isomers), 148.5 & 148.4 (two isomers), 147.5 & 147.5 (two isomers), 134.0 & 133.9 (two isomers), 133.3 & 133.1(two isomers), 131.9 (overlap, two isomers), 129.8 (overlap, two isomers), 129.0 & 128.9 (two isomers), 128.8 & 128.6 (two isomers), 127.0 & 126.8 (two isomers), 126.7 & 126.5 (two isomers), 126.3 (overlap, two isomers), 126.1 & 126.1 (two isomers), 125.8 (overlap, two isomers), 125.7 (overlap, two isomers), 125.4 & 125.0 (two isomers), 124.1 & 123.8 (two isomers), 122.1 & 121.9 (two isomers), 117.1 & 116.5 (two isomers), 111.1 & 110.8 (two isomers), 110.0 (overlap, two isomers), 109.6 & 109.3 (two isomers), 109.1 & 109.0 (two isomers), 65.5 & 64.9 (two isomers), 61.2 & 61.0 (two isomers), 57.3 & 57.0 (two isomers), 56.1 & 56.1 (two isomers), 55.9 & 55.8 (two isomers), 55.8 & 55.7 (two isomers), 55.0 (two isomers), 53.3 (two isomers), 42.1 & 42.0 (two isomers), 33.7 & 32.1 (two isomers).

IR (film) ν =3523, 2935, 2833, 1664, 1512, 1463, 1378, 1255, 1131, 782 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ $C_{35}H_{35}N_2O_6^+$ 579.2490, found 579.2487.



21j

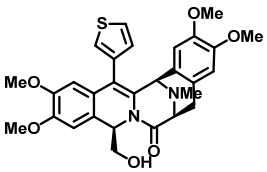
21j: *d.r.*=1:0.7 (two atropisomers), white solid, 46% yield. Flash column chromatography (petroleum ether/acetone = 4:1)

$[\alpha]_D^{20} = +0.21$ (c = 0.40 in MeOH), mp: 118-120 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (ddd, *J* = 7.2, 4.8, 1.6 Hz, 1.7H, two isomers), 7.68 (dd, *J* = 7.2, 2.0 Hz, 1H, one isomer), 7.59 (dd, *J* = 7.2, 2.0 Hz, 0.7H, one isomer), 7.13 (dd, *J* = 7.2, 5.2 Hz, 1H, one isomer), 7.07 (dd, *J* = 7.2, 4.8 Hz, 0.7H, one isomer), 6.72 (s, 1H, one isomer), 6.72 (s, 0.7H, one isomer), 6.60 (s, 1H, one isomer), 6.59 (s, 0.7H, one isomer), 6.25 (s, 0.7H, one isomer), 6.13 (s, 1H, one isomer), 6.01 (s, 0.7H, one isomer), 5.97 (s, 1H, one isomer), 5.84-5.77 (m, 1.7H, two isomers), 4.42 (s, 1H, one isomer), 4.20 (s, 0.7H, one isomer), 4.01 (s, 2.1H, one isomer), 3.87 (s, 3H, one isomer), 3.86 (s, 2.1H, one isomer), 3.84 (s, 3H, one isomer), 3.82 (s, 2.1H, one isomer), 3.81 (s, 3H, one isomer), 3.72-3.67 (m, 1.7H, two isomers), 3.70 (s, 2.1H, one isomer), 3.69 (s, 3H, one isomer), 3.60 (s, 2.1H, one isomer), 3.59 (s, 3H, one isomer), 3.36-3.20 (m, 5.1H, two isomers), 3.05-3.02 (m, 1H, one isomer), 3.01-2.97 (m, 0.7H, one isomer), 2.64 (s, 3H, one isomer), 2.60 (s, 2.1H, one isomer), 0.94-0.83 (m, 1.7H, two isomers).

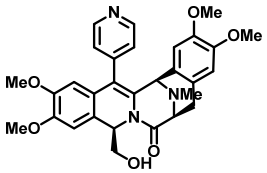
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 & 169.0 (two isomers), 162.9 & 162.2 (two isomers), 148.9 & 148.8 (two isomers), 148.7 & 148.6 (two isomers), 148.5 & 148.5 (two isomers), 147.7 & 147.7 (two isomers), 147.5 (overlap, two isomers), 142.1 & 140.8 (two isomers), 131.8 & 130.6 (two

isomers), 126.7 & 126.5 (two isomers), 124.7 & 124.7 (two isomers), 124.4 & 124.3 (two isomers), 122.4 & 122.3 (two isomers), 119.3 & 118.9 (two isomers), 117.1 & 116.5 (two isomers), 115.3 & 113.4 (two isomers), 111.2 & 111.1 (two isomers), 110.2 & 110.0 (two isomers), 109.8 & 108.9 (two isomers), 108.3 & 107.6 (two isomers), 64.8 & 64.3 (two isomers), 61.2 & 61.1 (two isomers), 57.6 & 57.2 (two isomers), 56.1 & 56.1 (two isomers), 56.02 (overlap, two isomers), 55.9 & 55.8 (two isomers), 55.8 (overlap, two isomers), 54.0 & 53.6 (two isomers), 53.1 & 52.9 (two isomers), 42.0 & 41.9 (two isomers), 33.8 & 33.6 (two isomers).
IR (film) ν =3511, 2940, 2835, 1667, 1513, 1462, 1380, 1246, 1127, 782 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{31}H_{34}N_3O_7^+$ 560.2391, found 560.2390.



21k

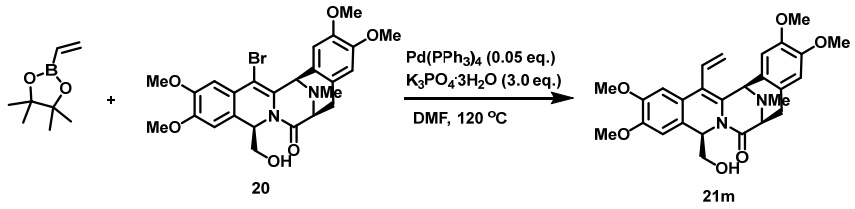
21k: white solid, 87% yield. Flash column chromatography (DCM/MeOH = 80:1)
$[\alpha]_D^{20} = +181.50$ (c = 0.40 in MeOH), mp: 118-122 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 5.2, 3.2 Hz, 1H), 7.35-7.32 (m, 1H), 7.13 (s, 1H), 6.70 (s, 1H), 6.59 (s, 1H), 6.31 (s, 1H), 6.19 (s, 1H), 5.78 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.58 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 3.68 (dt, *J* = 5.6, 1.6 Hz, 1H), 3.63 (s, 3H), 3.31 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.27 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.22-3.14 (m, 1H), 3.01 (dd, *J* = 16.4, 1.6 Hz, 1H), 2.62 (s, 3H), 1.01 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 148.7, 148.5, 148.5, 147.7, 131.0, 129.8, 127.0, 126.8, 125.1, 124.1, 122.1, 111.0, 110.0, 109.1, 108.7, 64.8, 61.1, 57.1, 56.1, 55.9, 55.9, 55.8, 53.0, 41.7, 33.8.
IR (film) ν =3527, 2935, 2854, 1664, 1513, 1463, 1379, 1223, 1127, 731 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{29}H_{31}N_2O_6S^+$ 535.1897, found 535.1895.



21l

21l: white solid, 66% yield. Flash column chromatography (DCM/MeOH = 80:1)
$[\alpha]_D^{20} = +88.50$ (c = 0.40 in MeOH), mp: 98-102 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 4.8 Hz, 1H), 8.81 (d, *J* = 5.2 Hz, 1H), 7.43 (d, *J* = 4.8 Hz, 1H), 7.34 (d, *J* = 4.8 Hz, 1H), 6.73 (s, 1H), 6.60 (s, 1H), 6.18 (s, 1H), 6.01 (s, 1H), 5.80 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.38 (s, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.73-3.69 (m, 1H), 3.70 (s, 3H), 3.59 (s, 3H), 3.35-3.26 (m, 2H), 3.20 (dt, *J* = 11.6, 7.2 Hz, 1H), 3.00 (dd, *J* = 16.4, 1.6 Hz, 1H), 2.64 (s, 3H), 0.96 (t, *J* = 6.8 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 151.2, 150.2, 148.8, 148.8, 148.8, 147.7, 145.5, 130.8, 126.4, 126.3, 125.9, 124.3, 123.9, 122.4, 117.1, 111.2, 110.3, 108.7, 108.5, 64.7, 61.1, 57.1, 56.2, 56.0, 55.8, 53.0, 41.8, 33.6.
IR (film) ν =3269, 2937, 2834, 1667, 1513, 1463, 1379, 1223, 731 cm^{-1}.
HRMS (ESI, m/z): $[M + H]^+$ $C_{30}H_{32}N_3O_6^+$ 530.2286, found 530.2283.

2.19 Compound 21m



A mixture of **20** (37.1 mg, 0.07 mmol, 1.0 equiv.), pimacol vinylboronate (28.5 μL, 0.168 mmol, 2.4 equiv.), $Pd(PPh_3)_4$ (4.0 mg, 0.0035 mmol, 0.05 equiv.), $K_3PO_4{\cdot}3H_2O$ (56.0 mg, 0.21 mmol, 3.0 equiv.) in DMF (2 mL) was stirred at 120 °C under N_2 overnight. The reaction was quenched with H_2O, and the whole mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1) to afford **21m** (86%) as a white solid.

$[\alpha]_D^{20} = +88.00$ (c = 0.20 in MeOH), mp: 102-105 °C

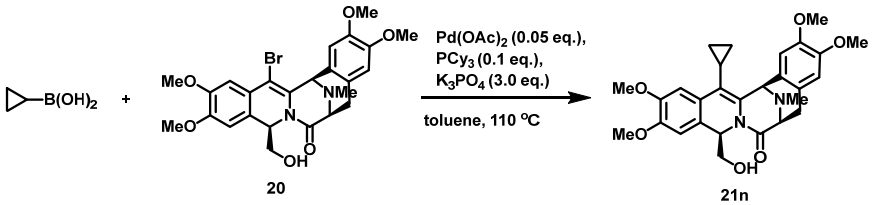
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.85 (dd, *J* = 18.0, 11.2 Hz, 1H), 6.71 (s, 1H), 6.69 (s, 1H), 6.63 (s, 1H), 5.77 (dd, *J* = 11.2, 1.6 Hz, 1H), 5.70 (dd, *J* = 7.6, 5.2 Hz, 1H), 5.60 (dd, *J* = 18.0, 2.0 Hz, 1H), 4.95 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.67 (dt, *J* = 5.2, 1.6 Hz, 1H), 3.35 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.21-3.13 (m, 1H), 3.07-2.99 (m, 2H), 2.56 (s, 3H), 0.82 (t, *J* = 6.8 Hz, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 148.8, 148.5, 148.4, 147.9, 131.6, 130.2, 127.2, 124.4, 123.1, 123.0, 121.4, 116.8, 111.2, 110.3, 108.9, 108.7, 64.2, 61.0, 56.4, 56.1, 56.1, 55.9, 55.8, 52.8, 41.7, 33.9.

IR (film) ν =3525, 2935, 2855, 1662, 1512, 1464, 1377, 1359, 1258, 780 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ $C_{27}H_{31}N_2O_6^+$ 479.2177, found 479.2174.

2.20 Compound 21n



A mixture of **20** (37.1 mg, 0.07 mmol, 1.0 equiv.), cyclopropyl boronic acid (14.4 mg, 0.168 mmol, 2.4 equiv.), $Pd(OAc)_2$ (0.8 mg, 0.0035 mmol, 0.05 equiv.), PCy_3 (1.96 mg, 0.007 mmol, 0.1 equiv.), K_3PO_4 (44.6 mg, 0.21 mmol, 3.0 equiv.) in toluene (2 mL) was stirred at 110 °C under N_2 overnight. The reaction was quenched with H_2O, and the whole mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1) to afford **21n** (54%) as a white solid.

$[\alpha]_D^{20} = +156.00$ (c = 0.20 in MeOH), mp: 104-106 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.90 (s, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 5.68 (dd, *J* = 8.4, 5.2 Hz, 1H), 5.29 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.62 (dt, *J* = 5.2, 1.6 Hz, 1H), 3.32 (dd, *J* = 16.0, 5.6 Hz, 1H), 3.15 (ddd, *J* = 11.6, 8.0, 5.2 Hz, 1H), 3.07-2.96 (m,

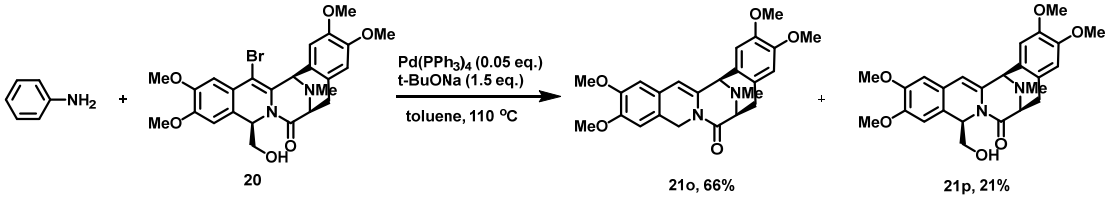
2H), 2.51 (s, 3H), 1.82-1.74 (m, 1H), 1.40-1.32 (m, 1H), 1.23-1.15 (m, 1H), 0.89-0.81 (m, 1H), 0.77-0.70 (m, 1H), 0.66 (dd, *J* = 8.0, 5.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 148.7, 148.3, 148.2, 147.8, 132.1, 127.0, 125.2, 124.7, 123.1, 117.6, 111.6, 109.9, 109.7, 108.4, 63.5, 61.2, 56.6, 56.1, 55.8, 52.4, 41.6, 34.1, 10.2, 9.2, 7.4.

IR (film) ν =3519, 2936, 2833, 1657, 1511, 1464, 1343, 1264, 732 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ $C_{28}H_{33}N_2O_6^+$ 493.2333, found 493.2332.

2.21 Compounds 21o and 21p



To a solution of **20** (37.1 mg, 0.07 mmol,1.0 equiv.), $Pd(PPh_3)_4$ (4.0 mg, 0.0035 mmol, 0.05 equiv.), *t*-BuONa (10.1 mg, 0.105 mmol, 1.5 equiv.) in toluene (2 mL) was added aniline (9.6 μL, 0.105 mmol, 1.0 equiv.) under N_2. The reaction was stirred at 110 °C overnight, until it was quenched with H_2O. The whole mixture was extracted with DCM. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1) to afford **21o** (66%, yellow solid) and **21p** (21%, yellow solid).

Characterizations of **21o**:

$[\alpha]_D^{20} = -30.00$ (c = 0.20 in MeOH), mp: 118-123 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.61 (s, 1H), 6.60 (s, 1H), 6.58 (s, 1H), 5.78 (s, 1H), 5.30 (d, *J* = 16.8 Hz, 1H), 4.35 (d, *J* = 16.8 Hz, 1H), 4.17 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 6H), 3.70 (dt, *J* = 6.4, 1.6 Hz, 1H), 3.32 (dd, *J* = 16.4, 6.4 Hz, 1H), 3.00 (dd, *J* = 16.4, 1.6 Hz, 1H), 2.54 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 148.8, 148.3, 148.2, 147.6, 134.9, 126.9, 124.2, 122.6, 121.1, 111.3, 110.1, 109.4, 108.5, 105.3, 61.5, 61.1, 56.1, 56.1, 55.9, 43.7, 41.5, 32.8.

IR (film) ν =2937, 2833, 1640, 1514, 1464, 1359, 1254, 1126, 1002 cm^{-1}.

HRMS (ESI, m/z): $[M + H]^+$ $C_{24}H_{27}N_2O_5^+$ 423.1914, found 423.1913.

Characterizations of **21p**:

$[\alpha]_D^{20} = +23.00$ (c = 0.40 in MeOH), mp: 117-120 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.66 (s, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 5.90 (s, 1H), 5.70 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.20 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (dt, *J* = 6.0, 1.2 Hz, 1H), 3.36 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.26-3.19 (m, 1H), 3.17-3.09 (m, 1H), 3.03 (dd, *J* = 16.4, 1.6 Hz, 1H), 2.54 (s, 3H), 1.16 (t, *J* = 6.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 149.0, 148.8, 148.3, 147.9, 133.6, 126.5, 124.2, 122.8, 122.0, 111.1, 110.3, 109.5, 108.5, 106.2, 65.0, 61.7, 61.4, 56.1, 56.1, 56.0, 55.8, 53.8, 41.8, 33.9.

IR (film) ν =3518, 2936, 2835, 1637, 1513, 1464, 1359, 1265, 1128, 732.

HRMS (ESI, m/z): $[M + Na]^+$ $C_{32}H_{28}N_2NaO_6^+$ 475.1840, found 475.1841.

3. The cytotoxicity test

Cell Lines and Culture Methods. A549 and HepG2 cell lines were cultured in RPMI-1640 (KeyGen BioTECH, KGM31800H-500) medium supplemented with 10% (v/v) fetal bovine serum (FBS, CELLMAX, SA311.02) and 1% (v/v) penicillin−streptomycin. MDA-MB-231 cell line was cultured in DMEM (KeyGen BioTECH, KGM12800-500) supplemented with 10% (v/v) FBS and 1% (v/v) penicillin−streptomycin. All cells were grown in a humidified incubator at 37 °C and 5% CO_2.

Cell Growth Inhibition Assays. Cells were grown at 37 °C, under 95% air and 5% CO_2 until about reaching 70% confluency, and subcultured at least twice before the experiment. Cells were seeded in 96-well plates at the individual density in 100 μL of culture medium for 24 h. The cell seeding numbers for individual cell lines were as follows: A549 (2500/well), HepG2 (1500/well), MDA-MB-231 (2800/well) and L-02 (800/well). Compounds were prepared as a 10 mM stock solution in 100% DMSO, and each compound of final gradient concentrations from 1 μM to 84 μM was added to each well. After 72 h, cell viability was assessed by 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Briefly, 40 μL MTT (2.5 mg/mL in PBS, KeyGen BioTECH) was added to each well and incubated for 3~4 h, then the medium was discarded and replaced with 150 μL dimethyl sulfoxide (DMSO, Sigma–Aldrich). The plates were shaken for 10 mins for mixing and the absorbance was read at 490 nm via the microplate reader (ALLSHENG). The readings were normalized to the DMSO-treated cells, and the IC_{50} was calculated by nonlinear regression analysis using GraphPad Prism 8 software.

Table S1. Preliminary examination of inhibitory activities against the proliferation of A549 cells at 60 μM.

Compound	Inhibition %	Compound	Inhibition %	Compound	Inhibition %
12	0	**21a**	18.7	**21i**	24.2
13	24.1	**21b**	5.8	**21j**	9.9
15	7.9	**21c**	9.8	**21k**	14.3
16	21.8	**21d**	22.2	**21l**	7.6
17	14.4	**21e**	28.9	**21m**	0
18	21.7	**21f**	**83.6**	**21n**	0
19	0	**21g**	33.3	**21o**	8.0
20	13.9	**21h**	15.5	**21p**	0
				Cisplatin	73.9

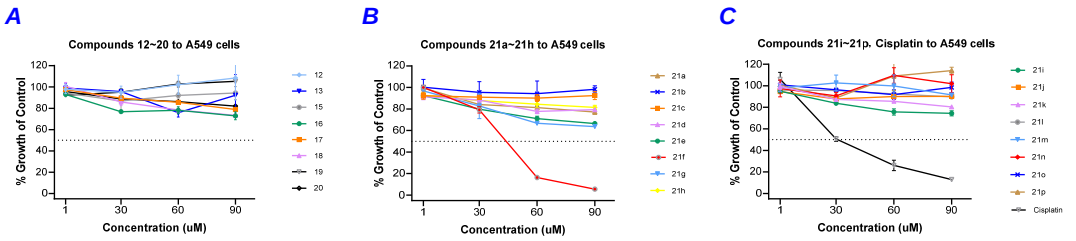


Figure S1. Cytotoxicity assessment of simplified ecteinascidin-cribrostatin analogs 12~20 (*A*), 21a~21h (*B*), 21i~21p and Cisplatin (*C*). A549 cells were treated with indicated doses for 3 days. Cell viability was determined by the MTT assay.

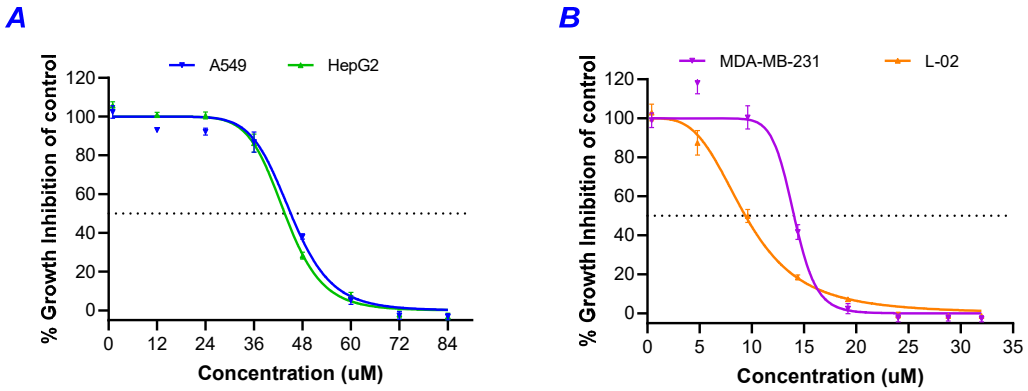
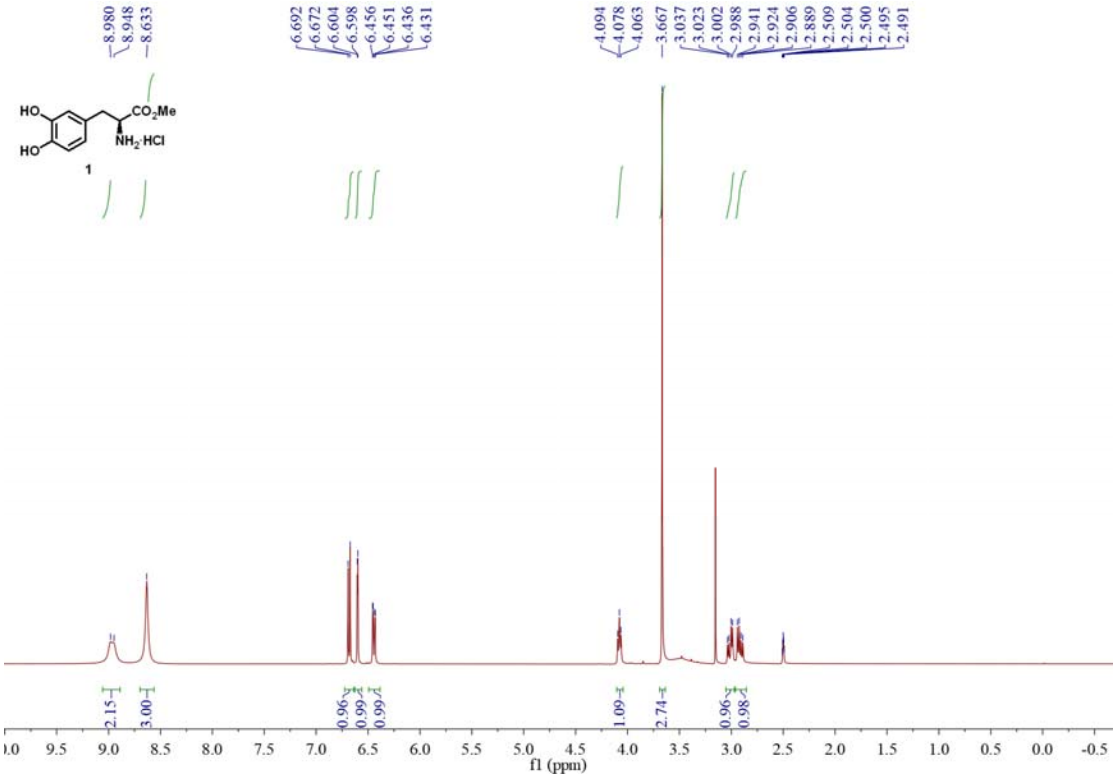


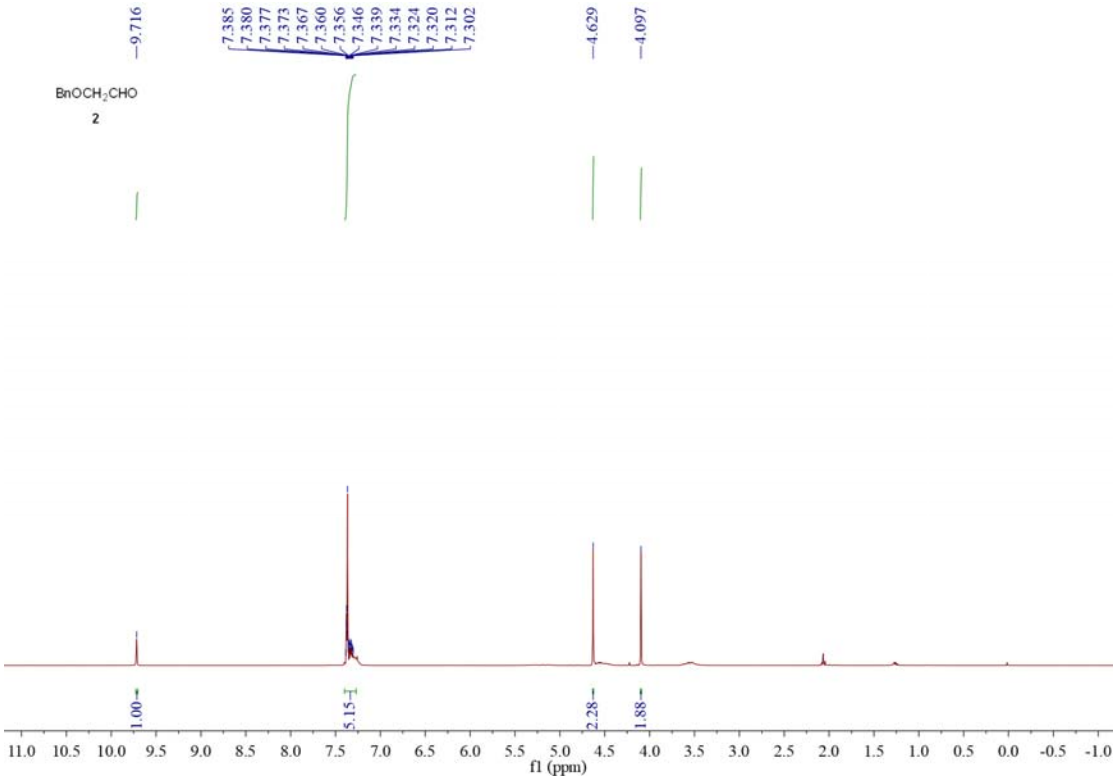
Figure S2. A549 and HepG2 (*A*), MDA-MB-231 cancer cells and L-02 normal cells (*B*) were incubated with increasing concentrations of compound **21f** and growth over 72 h was assessed by the MTT assay.

4. Copies of ^{1}H, ^{13}C, ^{19}F and 2D NMR spectra

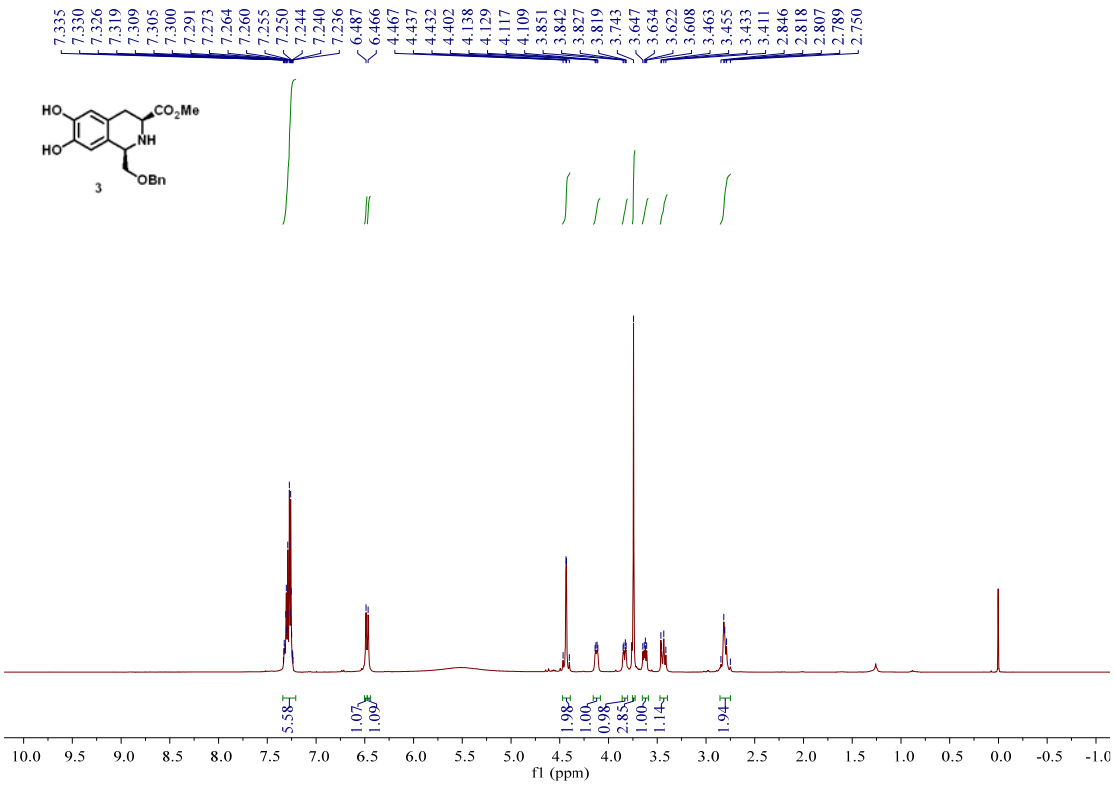
^{1}H NMR Spectrum of 1 (400 MHz, DMSO-d_6)



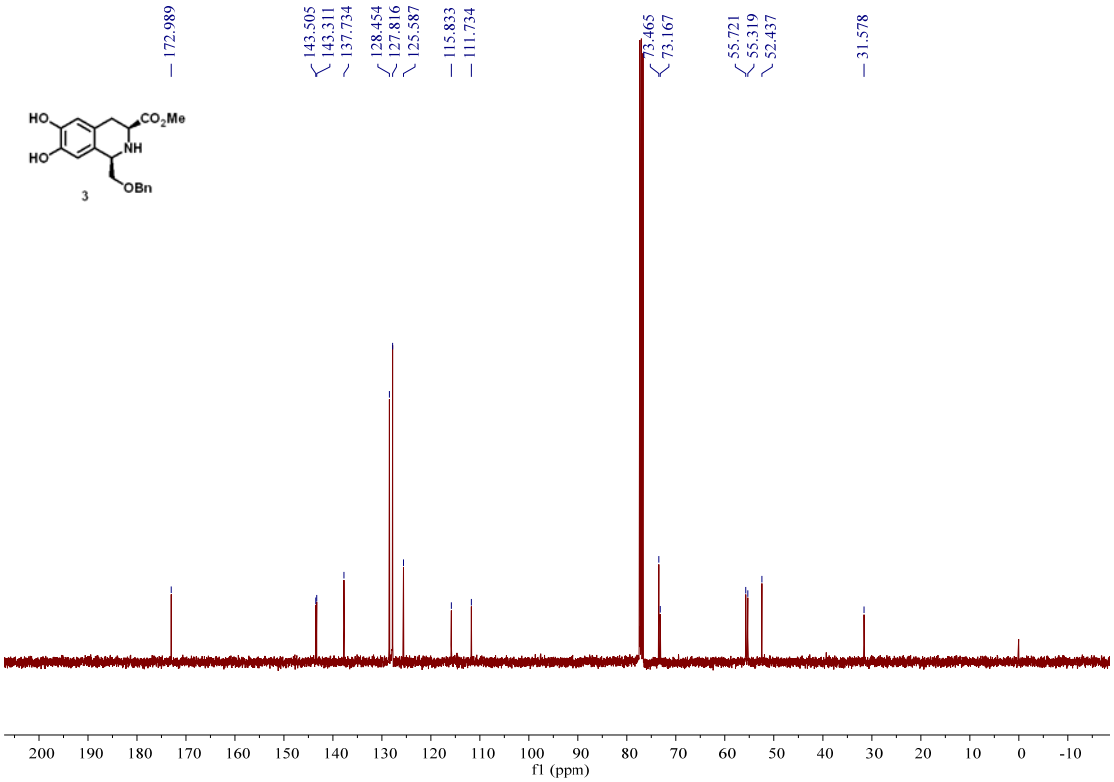
^{1}H NMR Spectrum of 2 (400 MHz, $CDCl_3$)



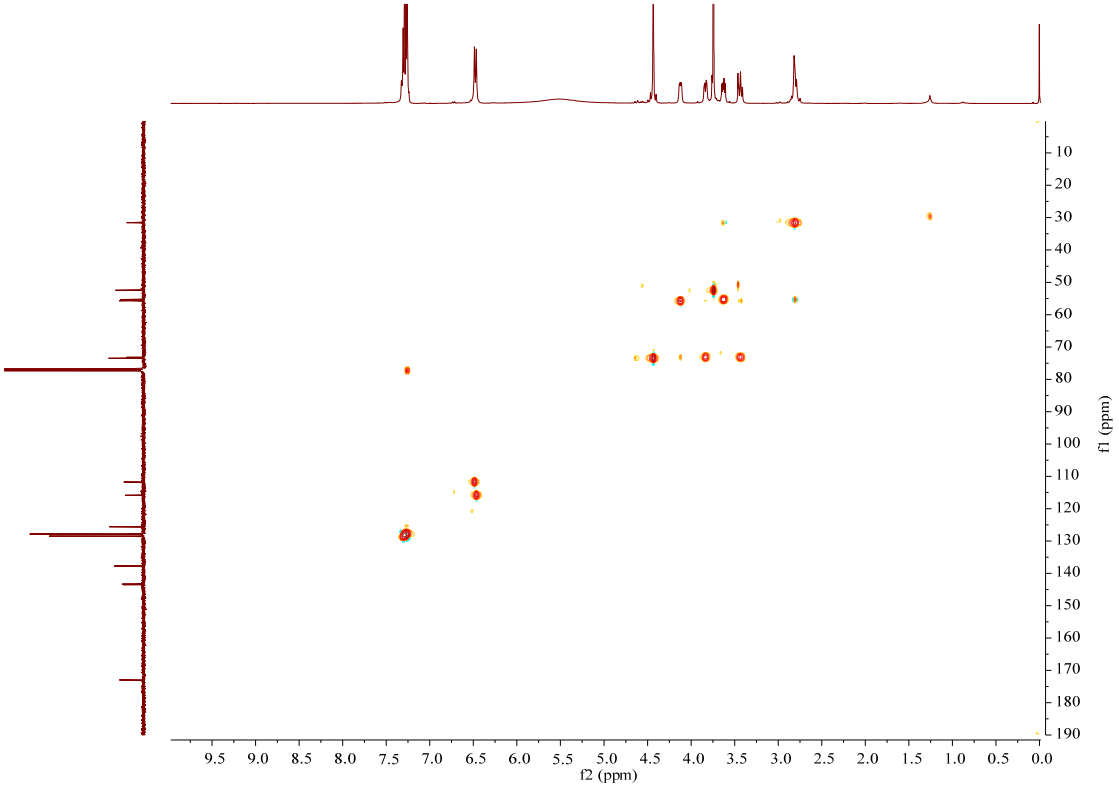
^{1}H NMR Spectrum of 3 (400 MHz, $CDCl_3$)



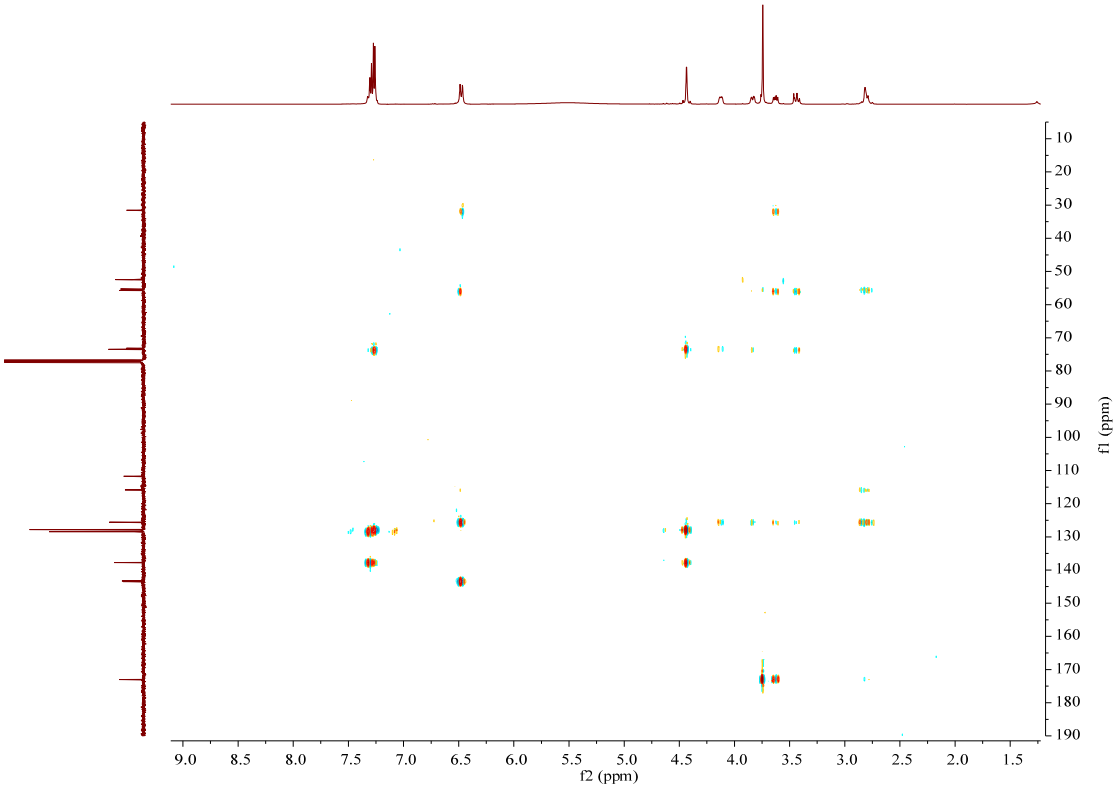
^{13}C NMR Spectrum of 3 (101 MHz, $CDCl_3$)



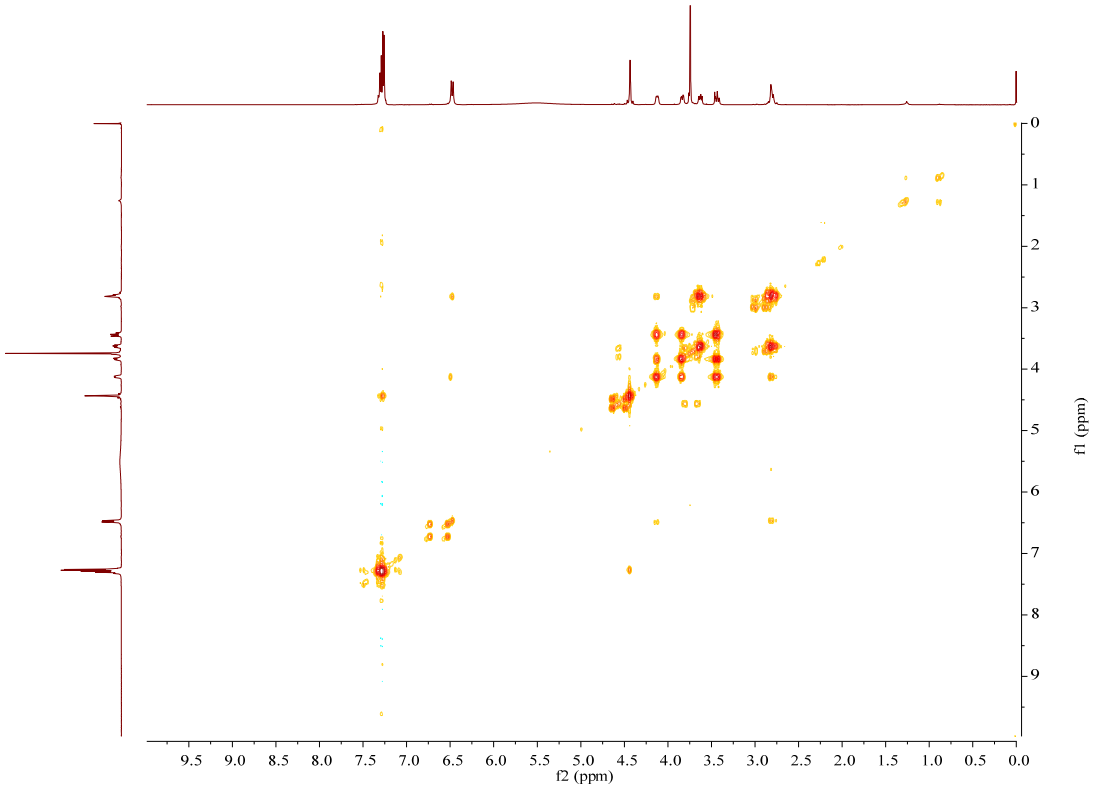
HSQC of 3



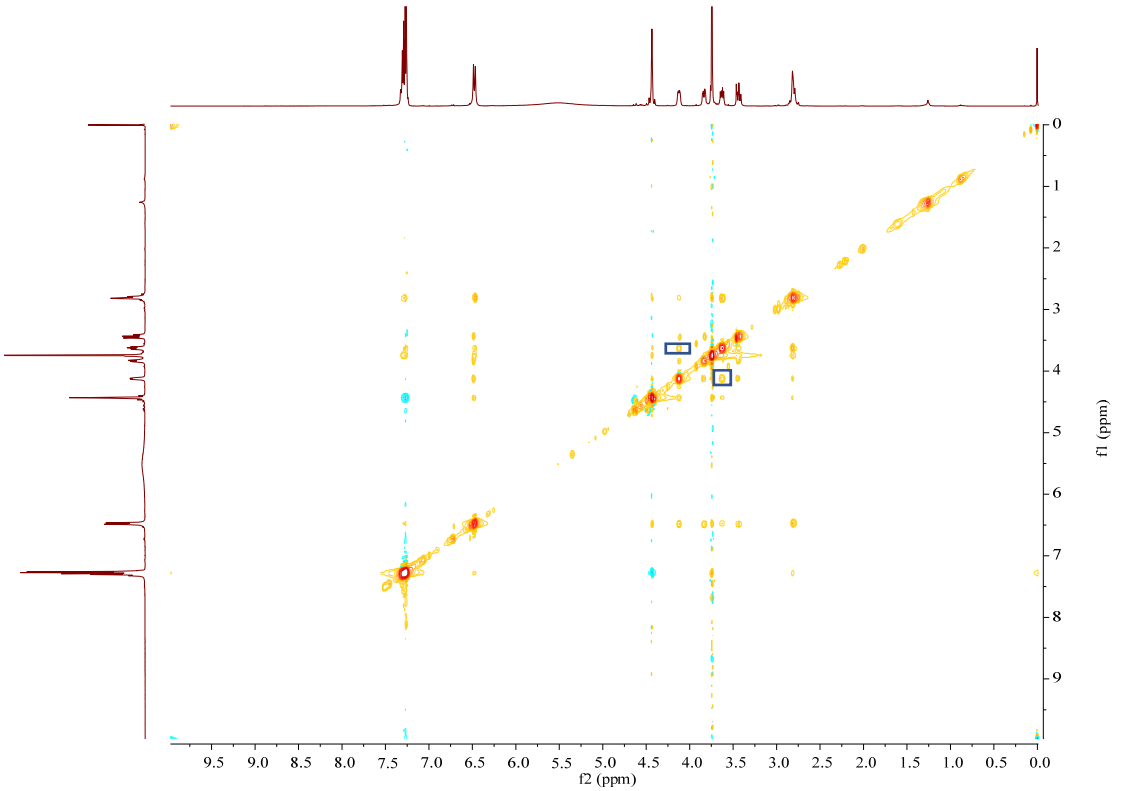
HMBC of 3



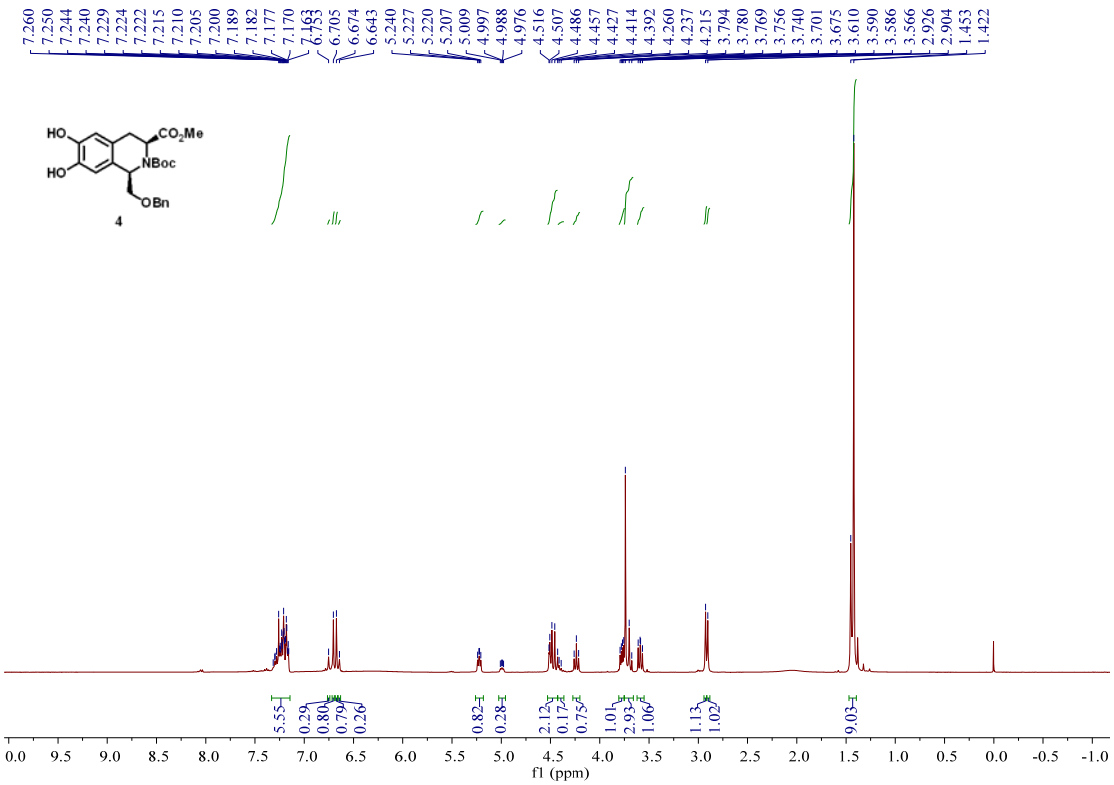
COSY of 3



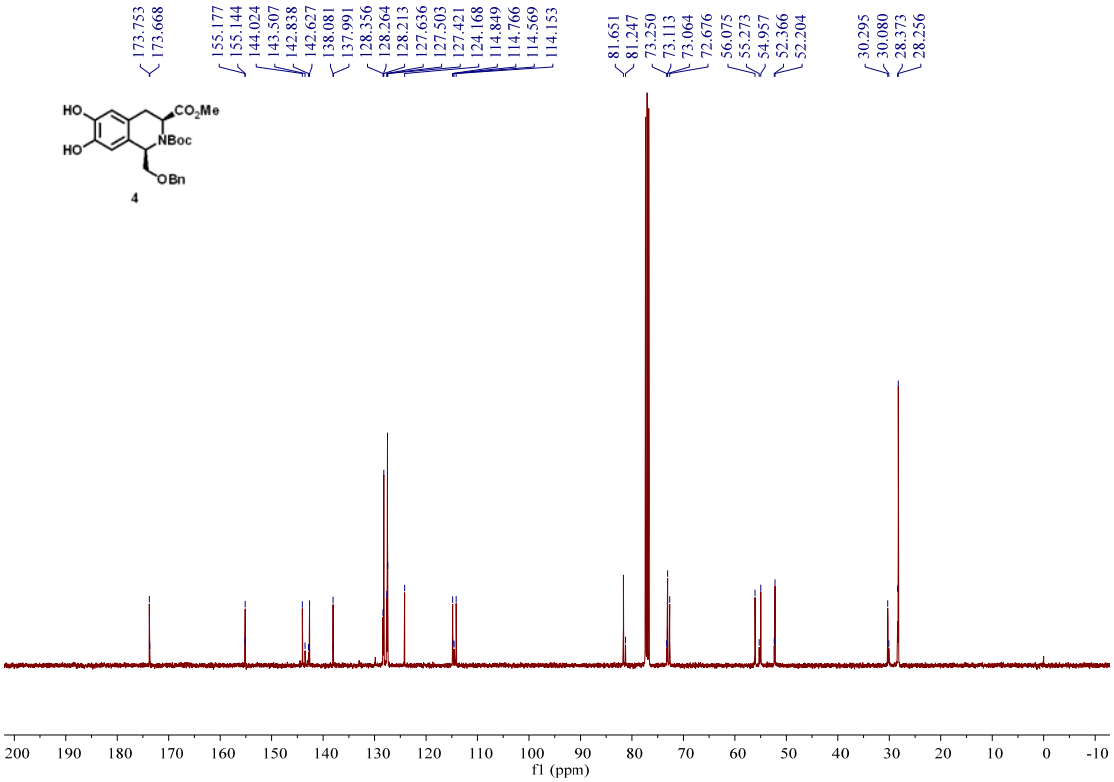
NOE of 3



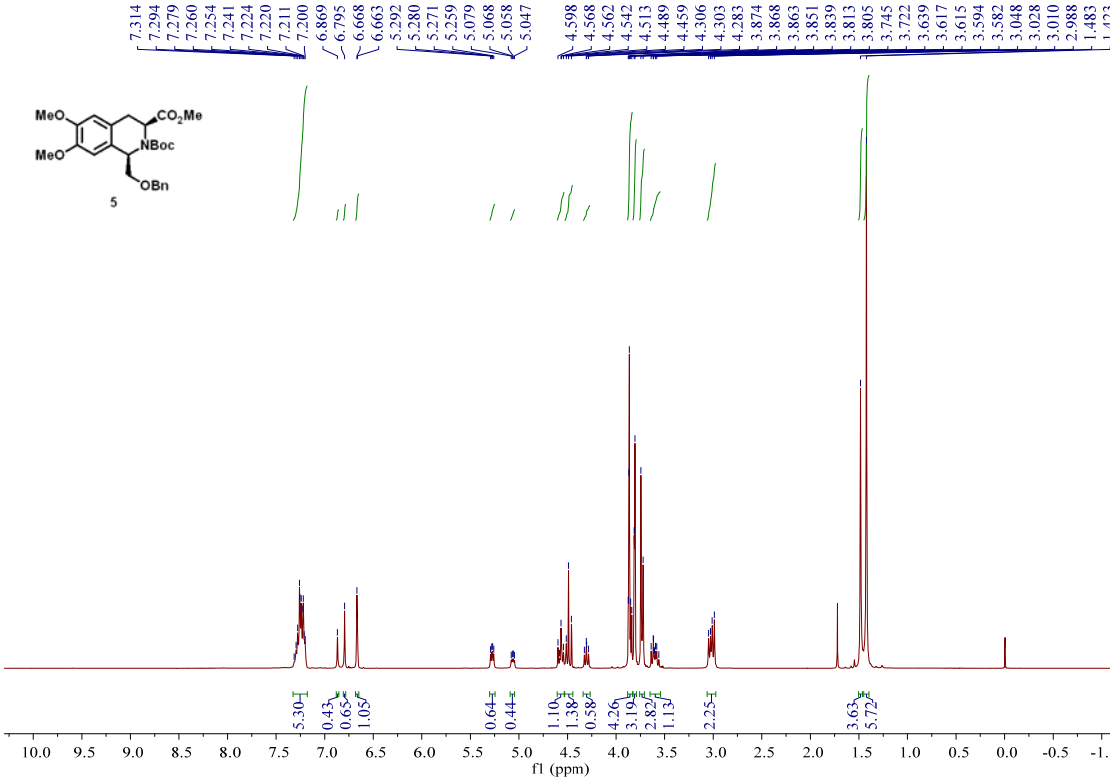
^{1}H NMR Spectrum of 4 (400 MHz, $CDCl_3$)



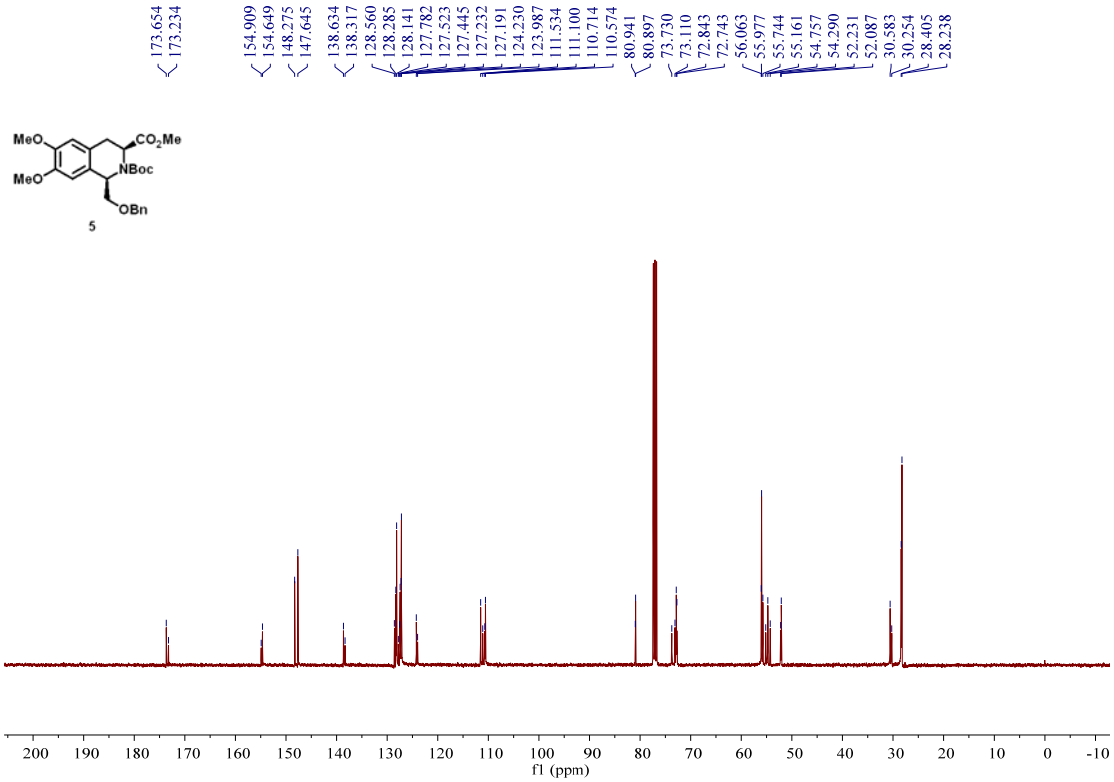
^{13}C NMR Spectrum of 4 (101 MHz, $CDCl_3$)



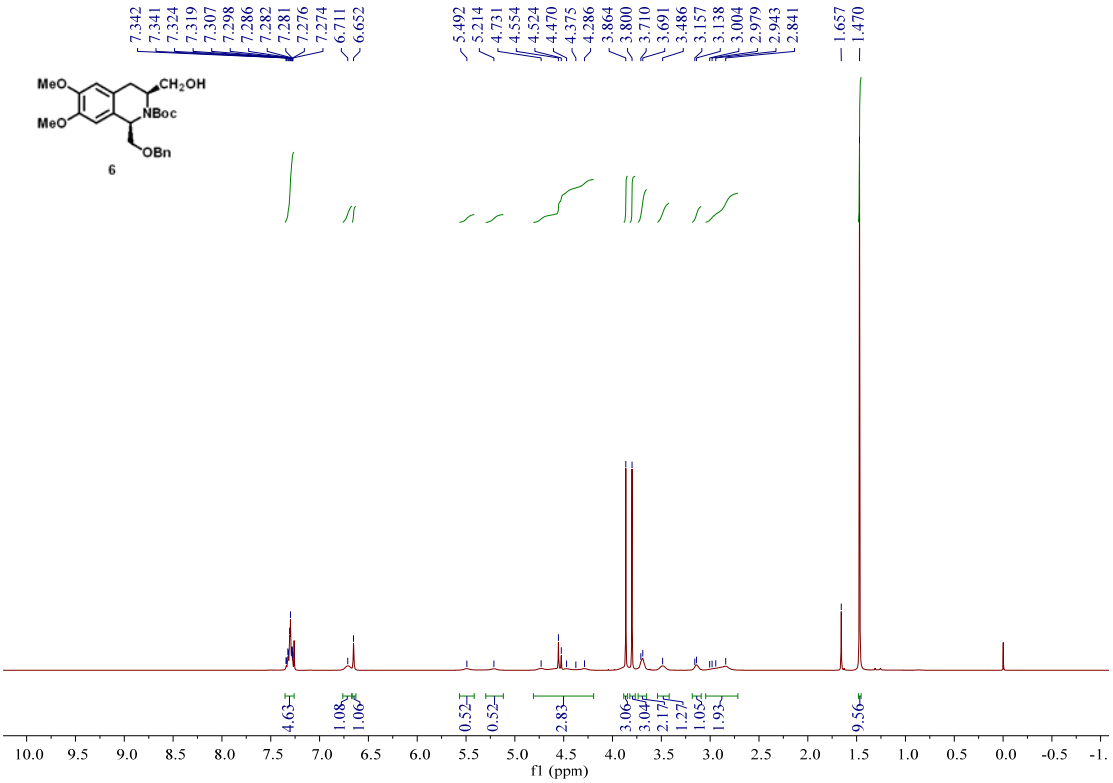
^{1}H NMR Spectrum of 5 (400 MHz, $CDCl_3$)



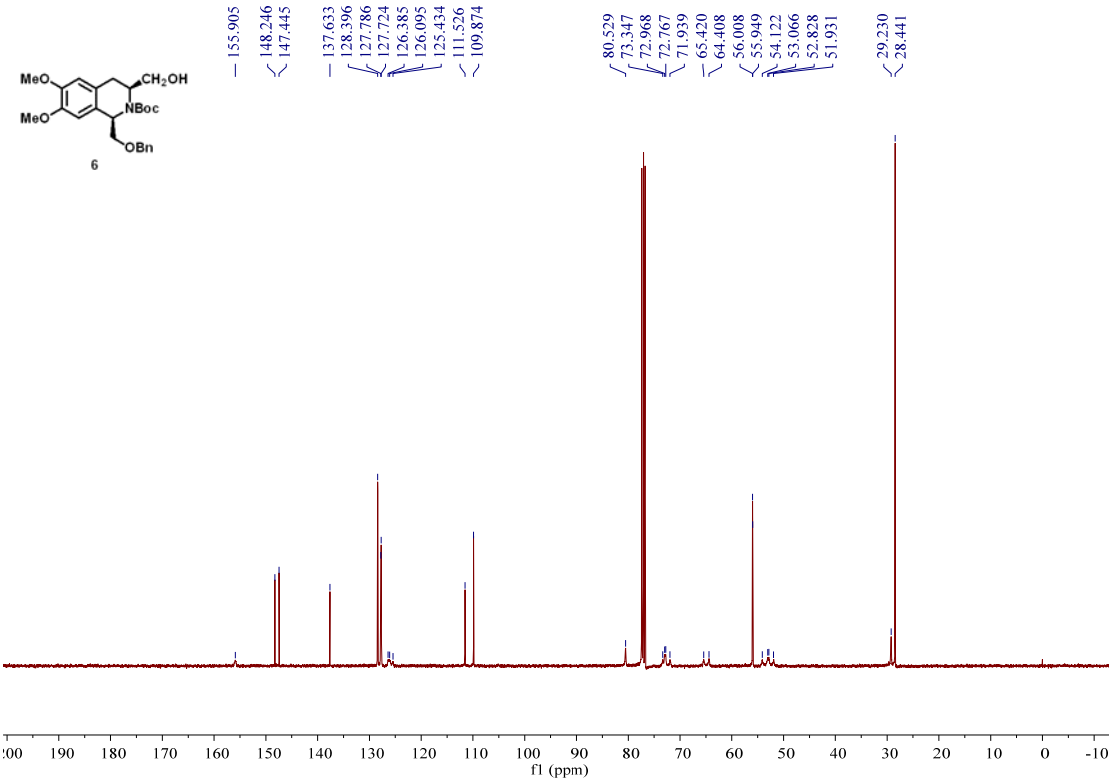
^{13}C NMR Spectrum of 5 (101 MHz, $CDCl_3$)



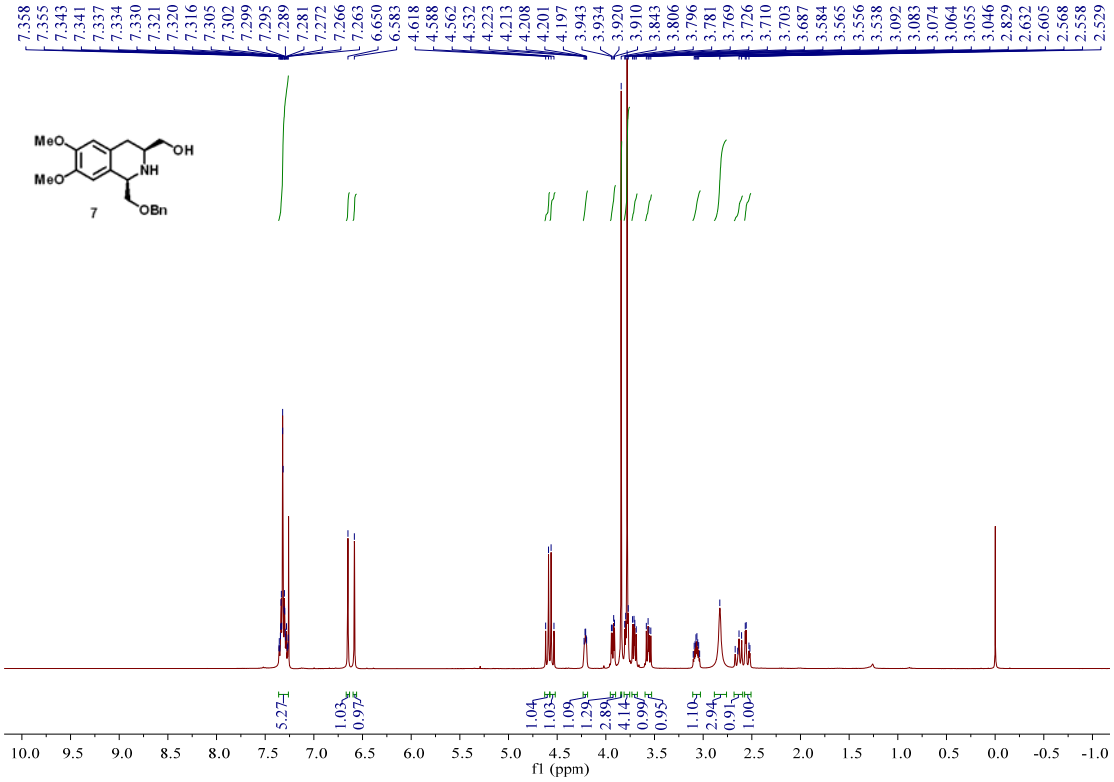
^{1}H NMR Spectrum of 6 (400 MHz, $CDCl_3$)



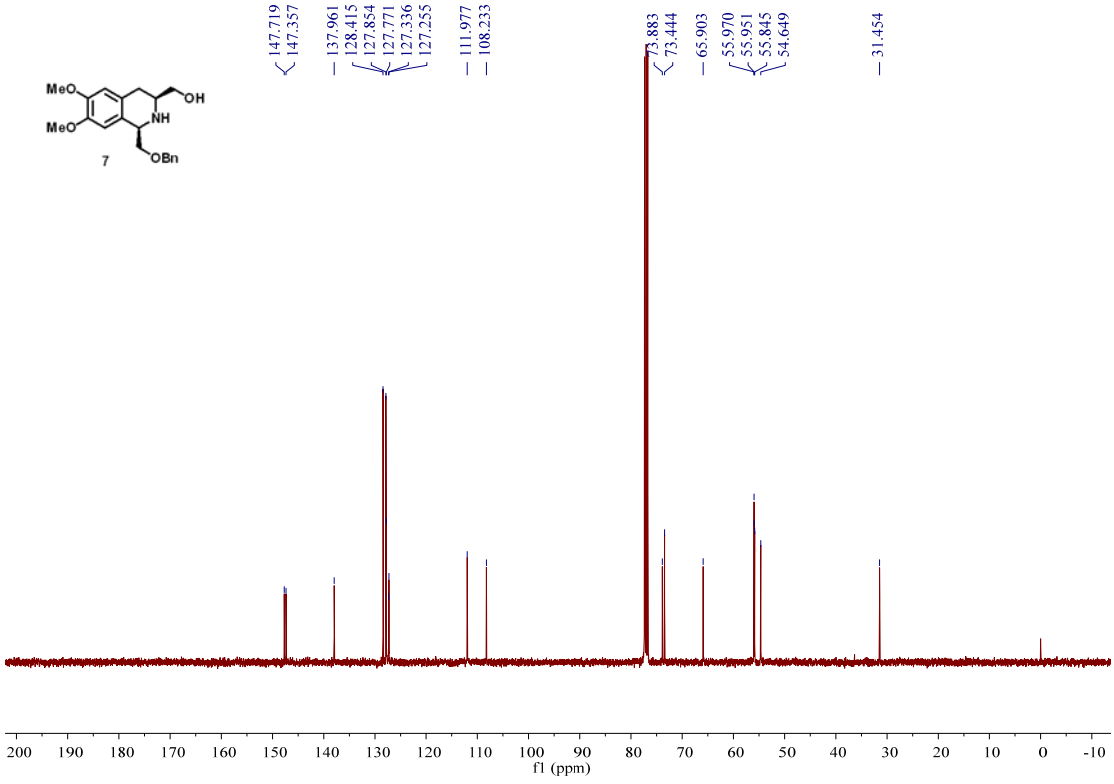
^{13}C NMR Spectrum of 6 (101 MHz, $CDCl_3$)



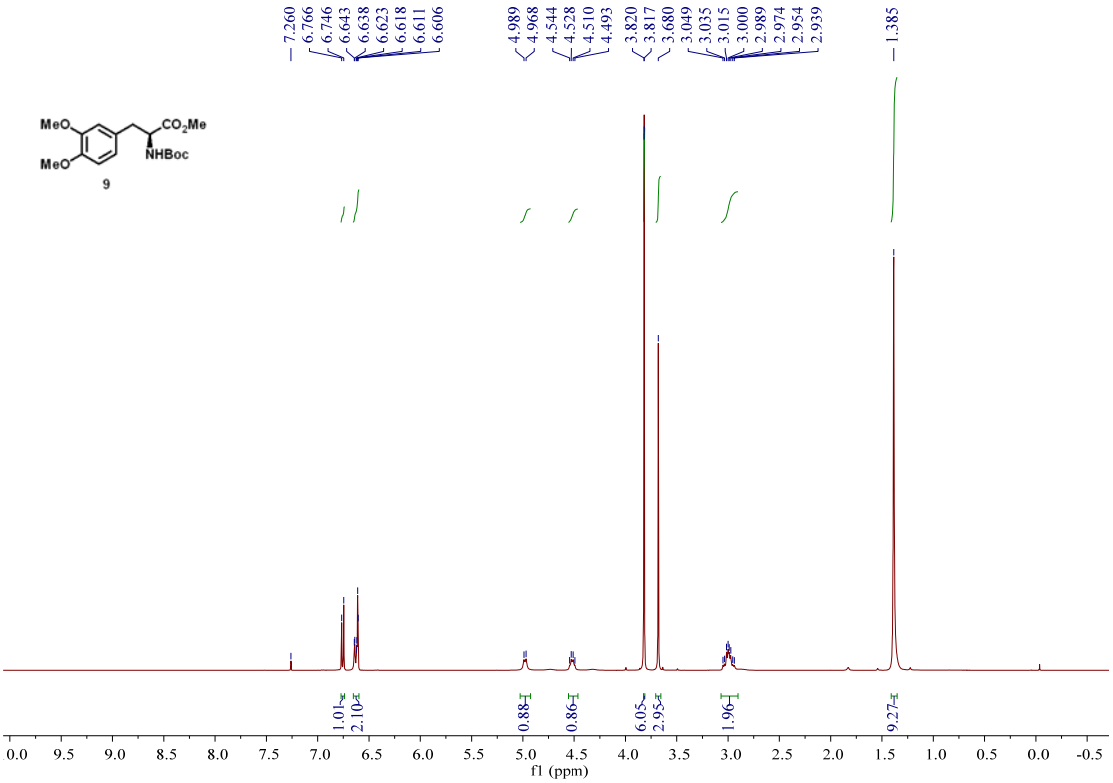
^{1}H NMR Spectrum of 7 (400 MHz, $CDCl_3$)



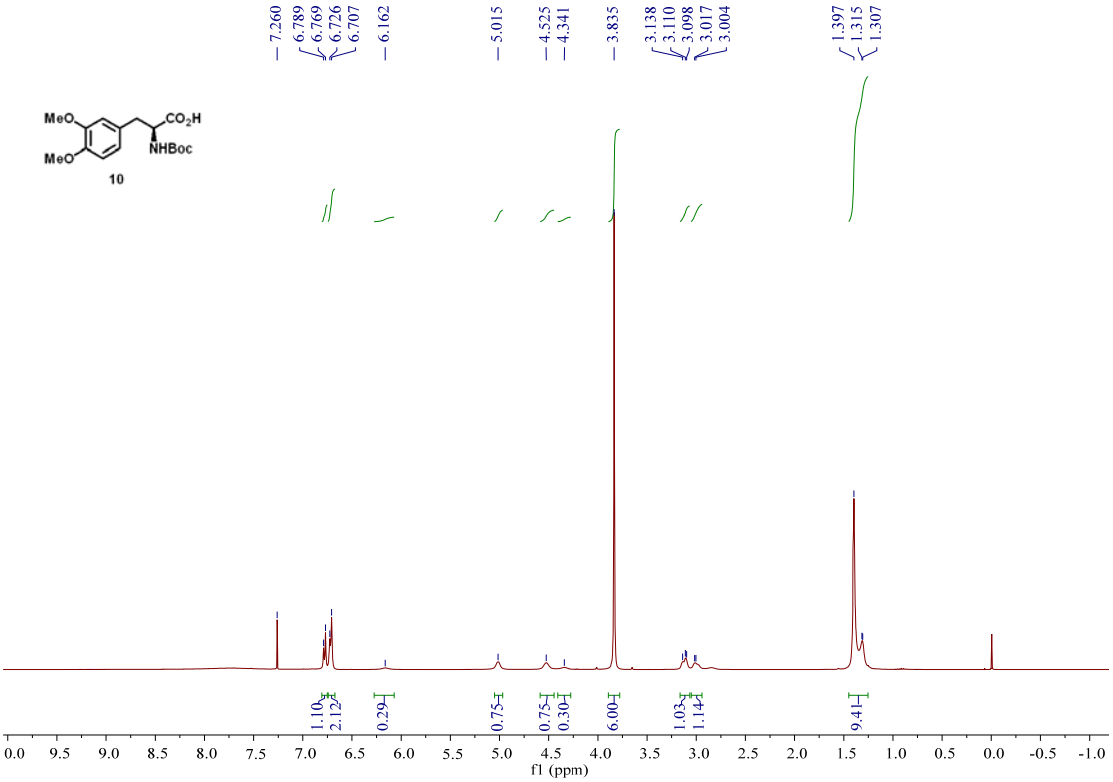
^{13}C NMR Spectrum of 7 (101 MHz, $CDCl_3$)



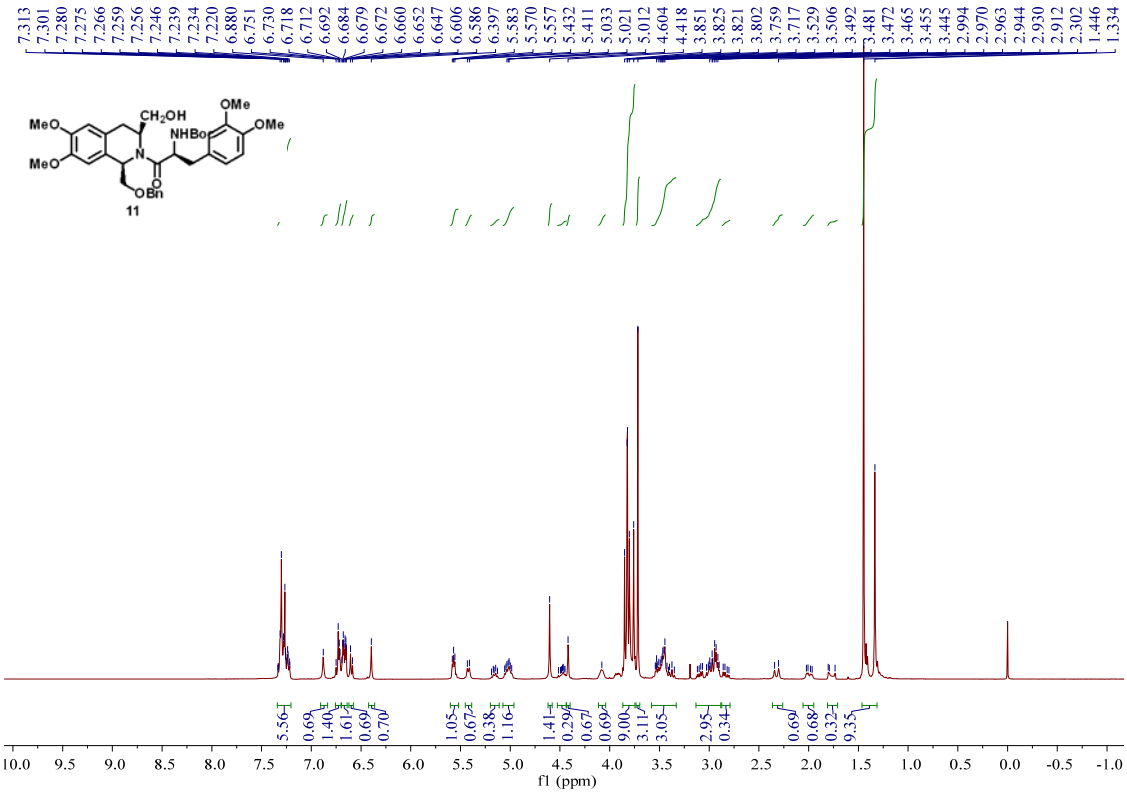
^{1}H NMR Spectrum of 9 (400 MHz, $CDCl_3$)



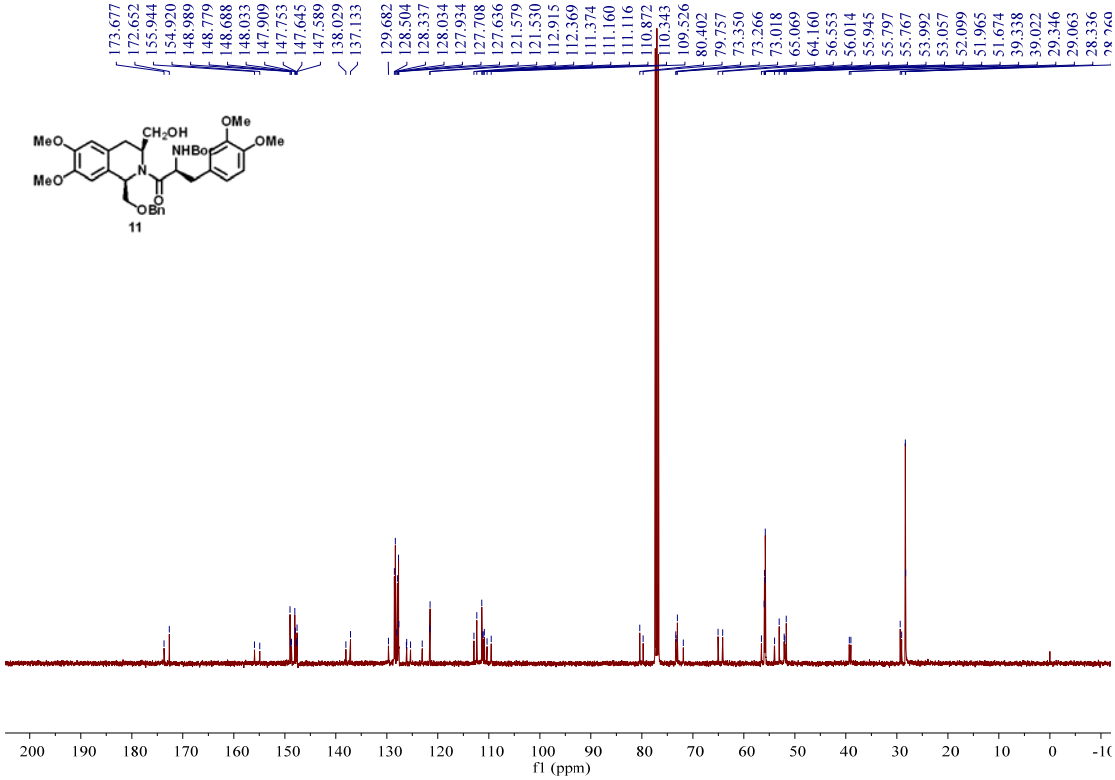
^{1}H NMR Spectrum of 10 (400 MHz, $CDCl_3$)



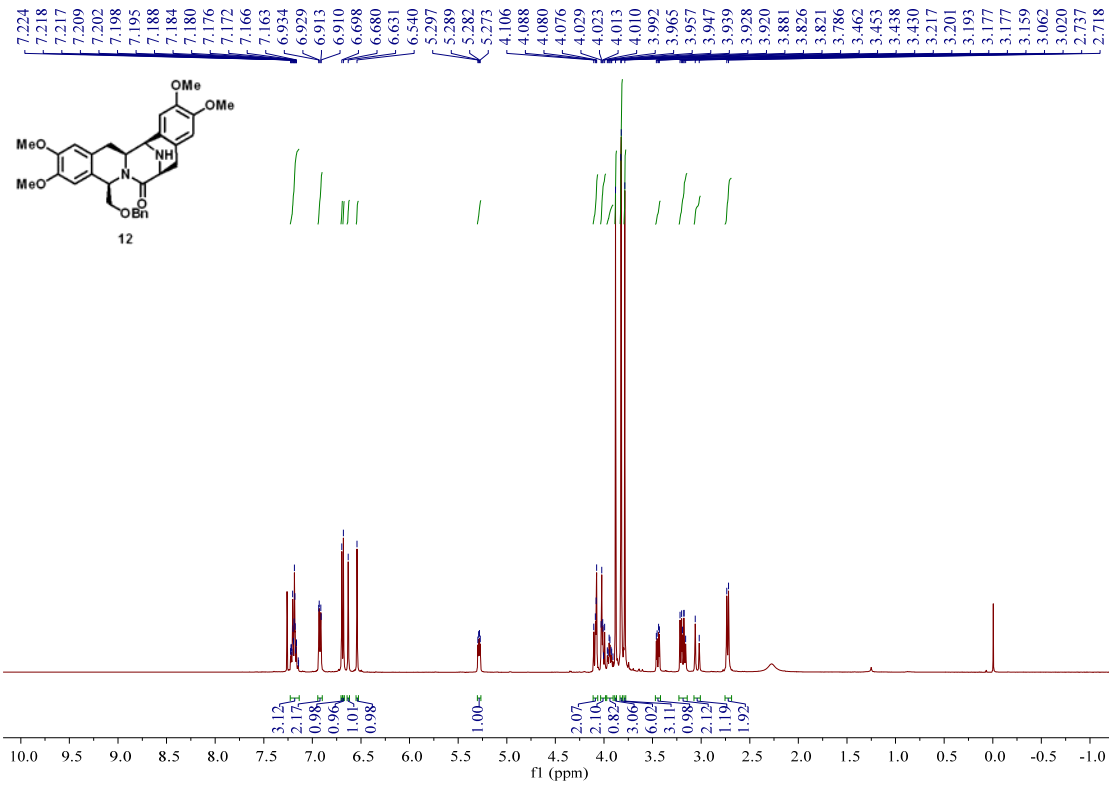
^{1}H NMR Spectrum of 11 (400 MHz, $CDCl_3$)



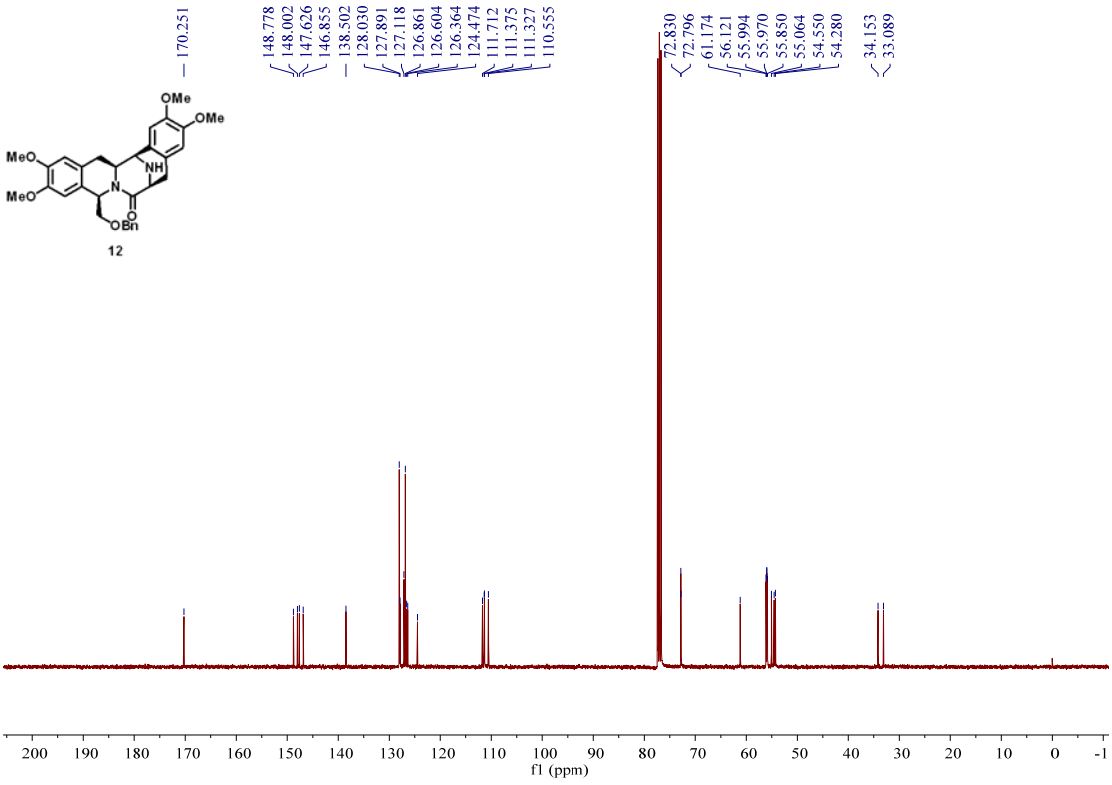
^{13}C NMR Spectrum of 11 (101 MHz, $CDCl_3$)



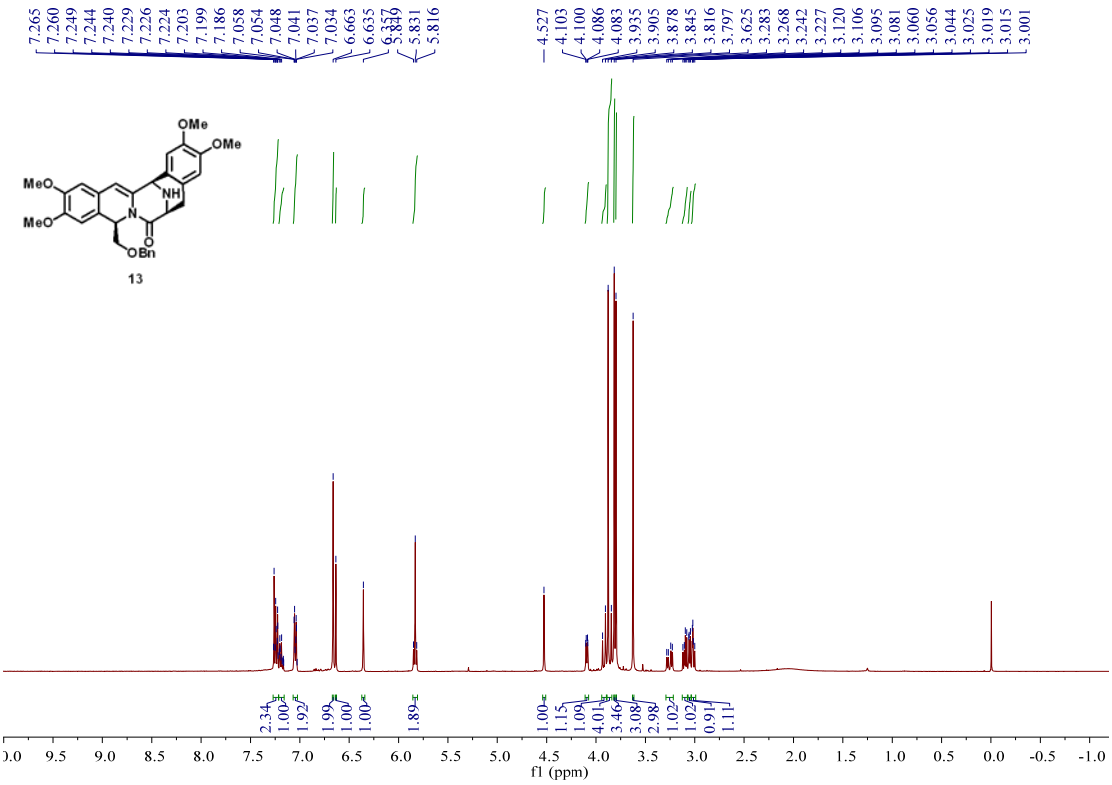
^{1}H NMR Spectrum of 12 (400 MHz, $CDCl_3$)



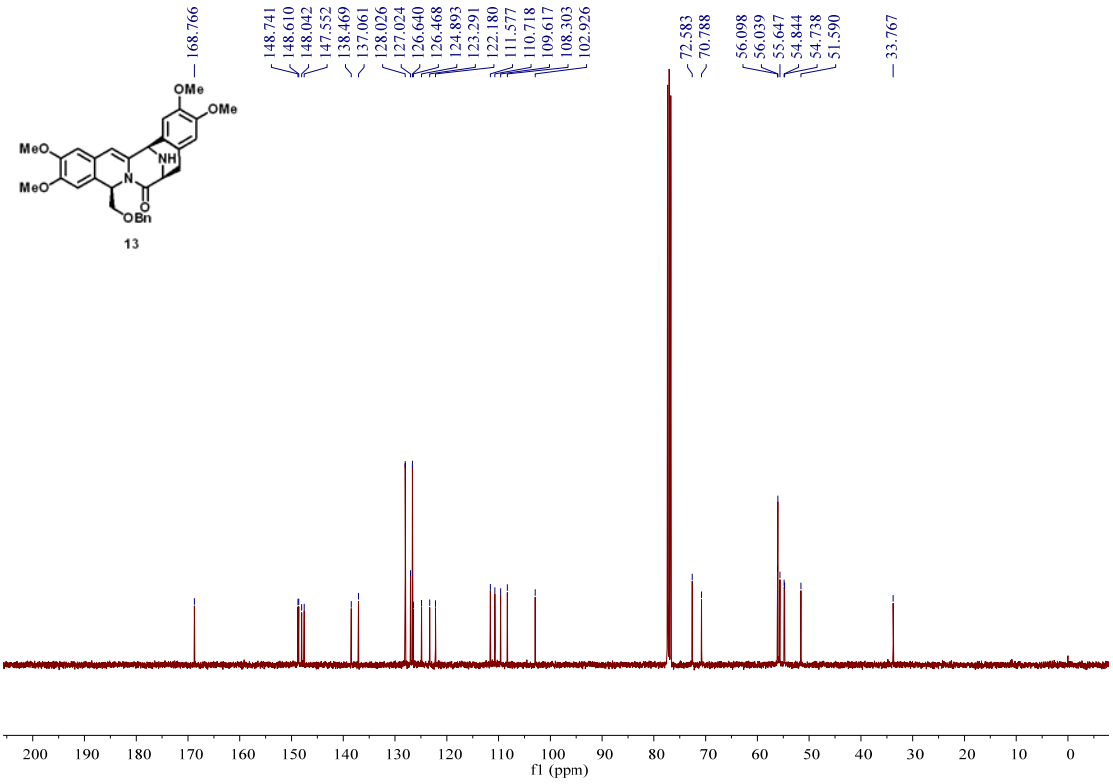
^{13}C NMR Spectrum of 12 (101 MHz, $CDCl_3$)



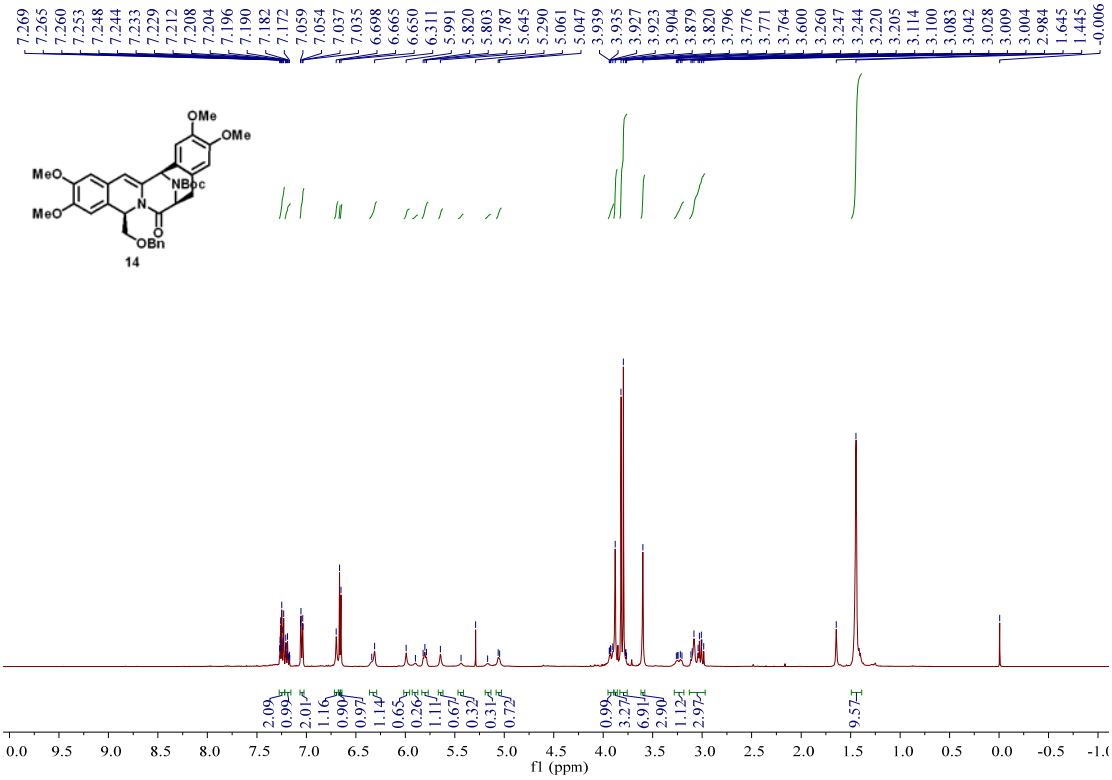
^{1}H NMR Spectrum of 13 (400 MHz, $CDCl_3$)



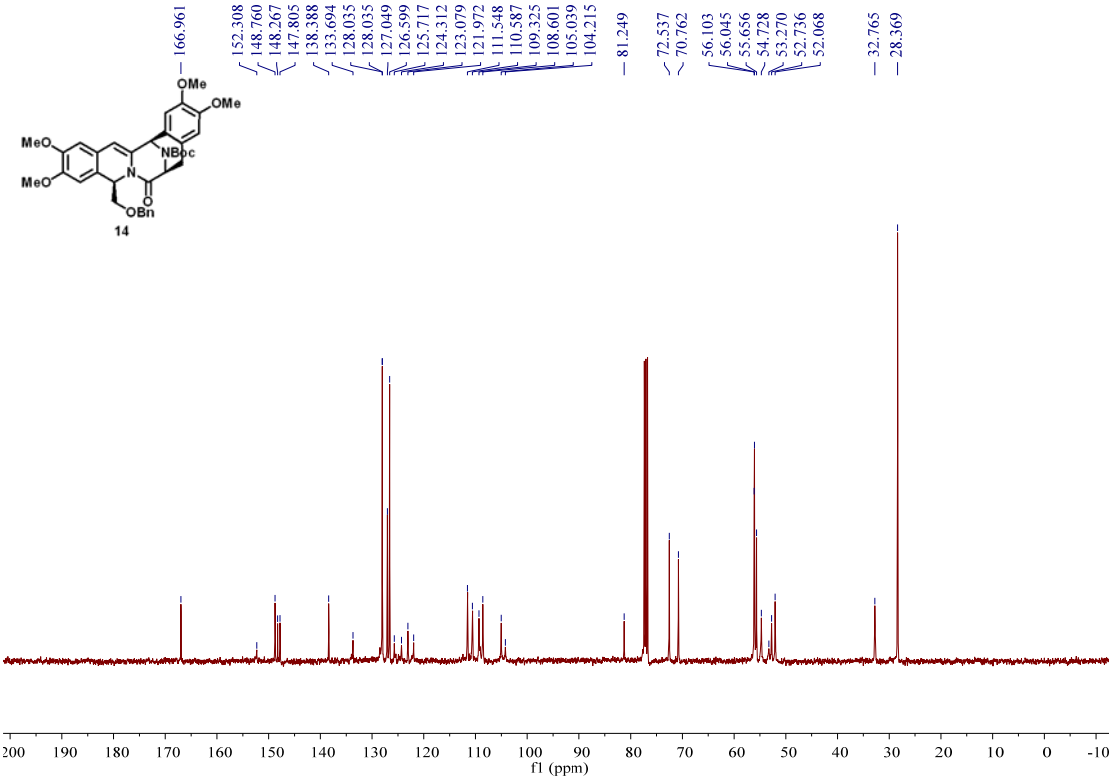
^{13}C NMR Spectrum of 13 (101 MHz, $CDCl_3$)



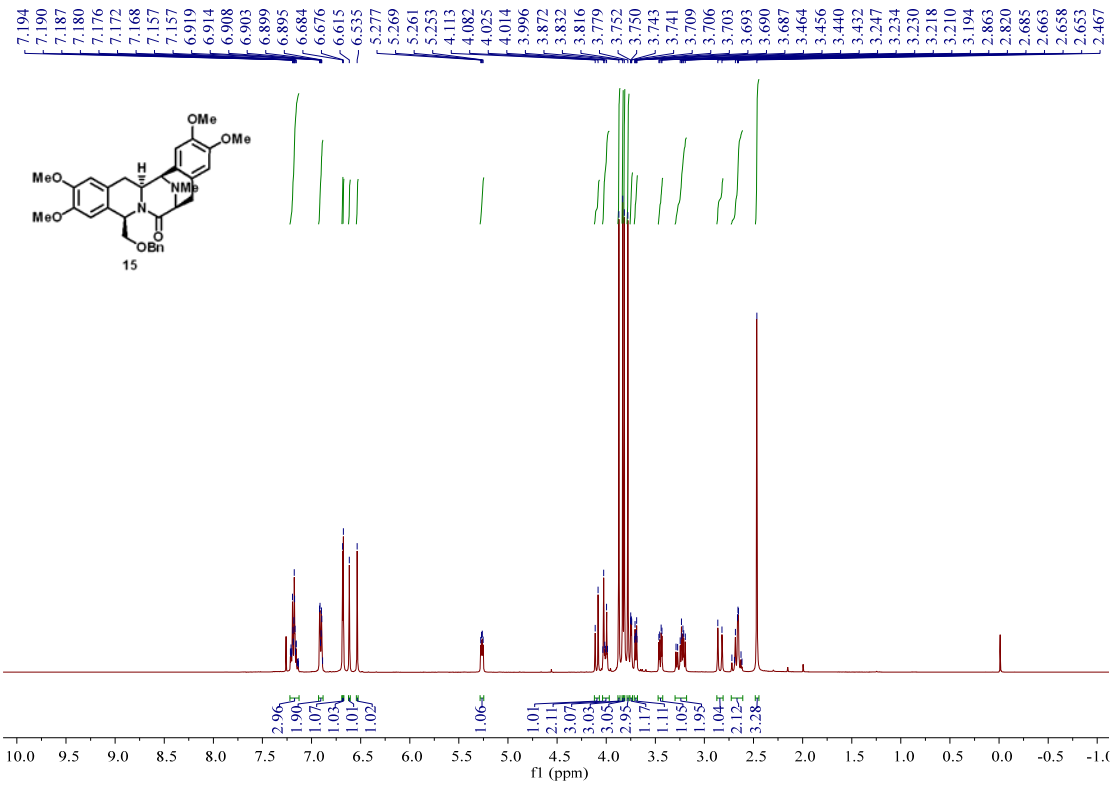
^{1}H NMR Spectrum of 14 (400 MHz, $CDCl_3$)



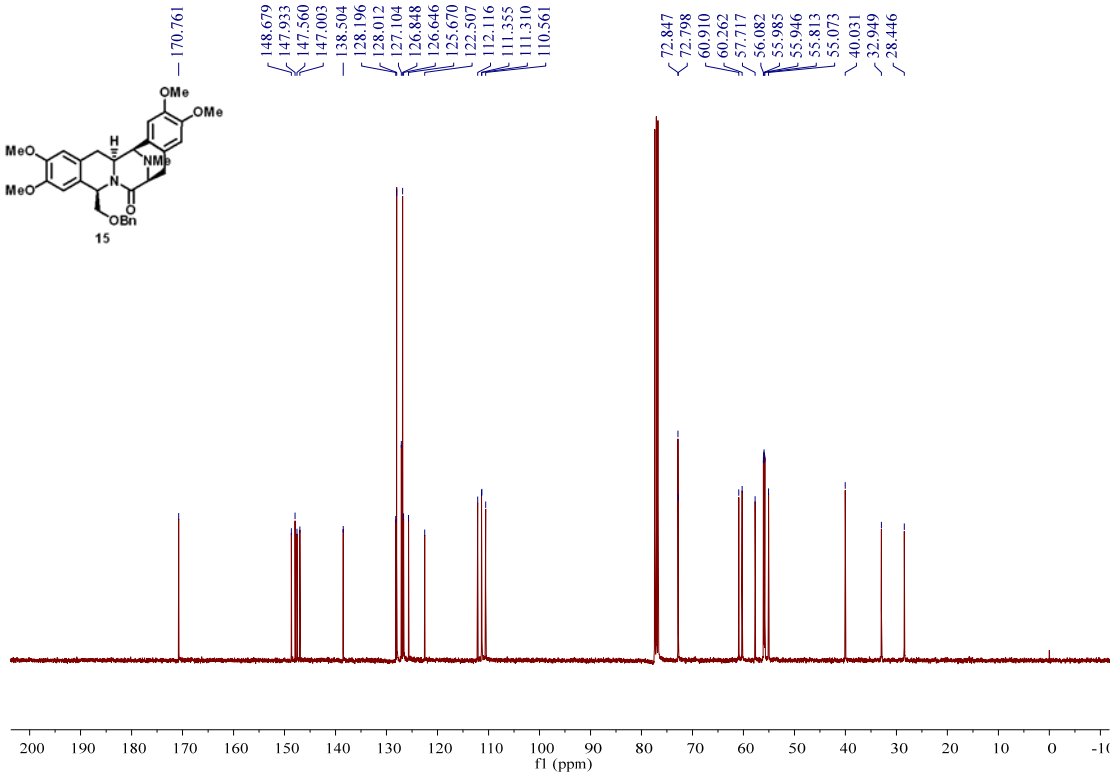
^{13}C NMR Spectrum of 14 (101 MHz, $CDCl_3$)



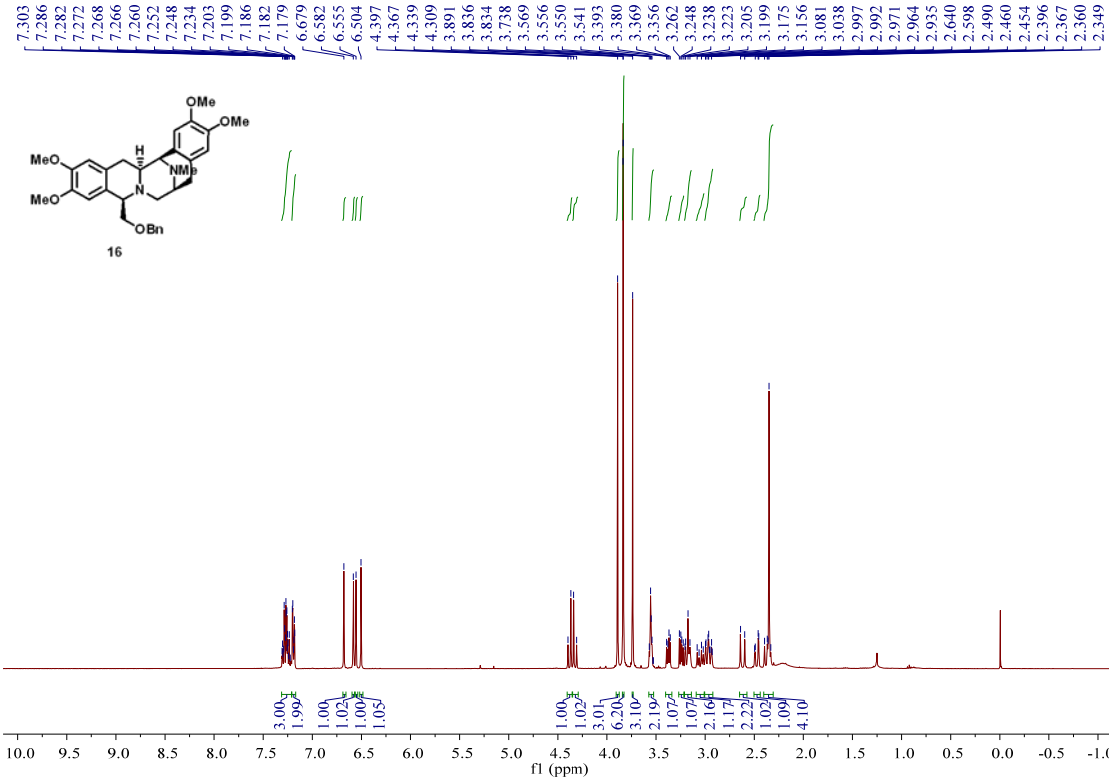
^{1}H NMR Spectrum of 15 (400 MHz, $CDCl_3$)



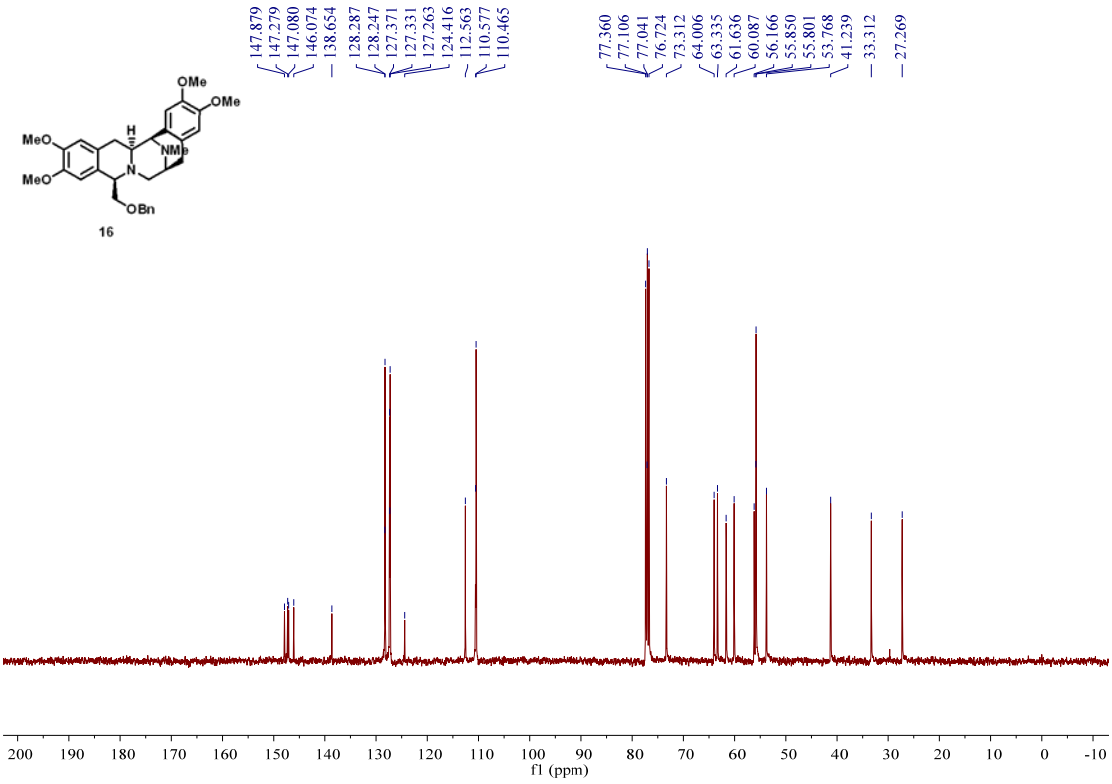
^{13}C NMR Spectrum of 15 (101 MHz, $CDCl_3$)



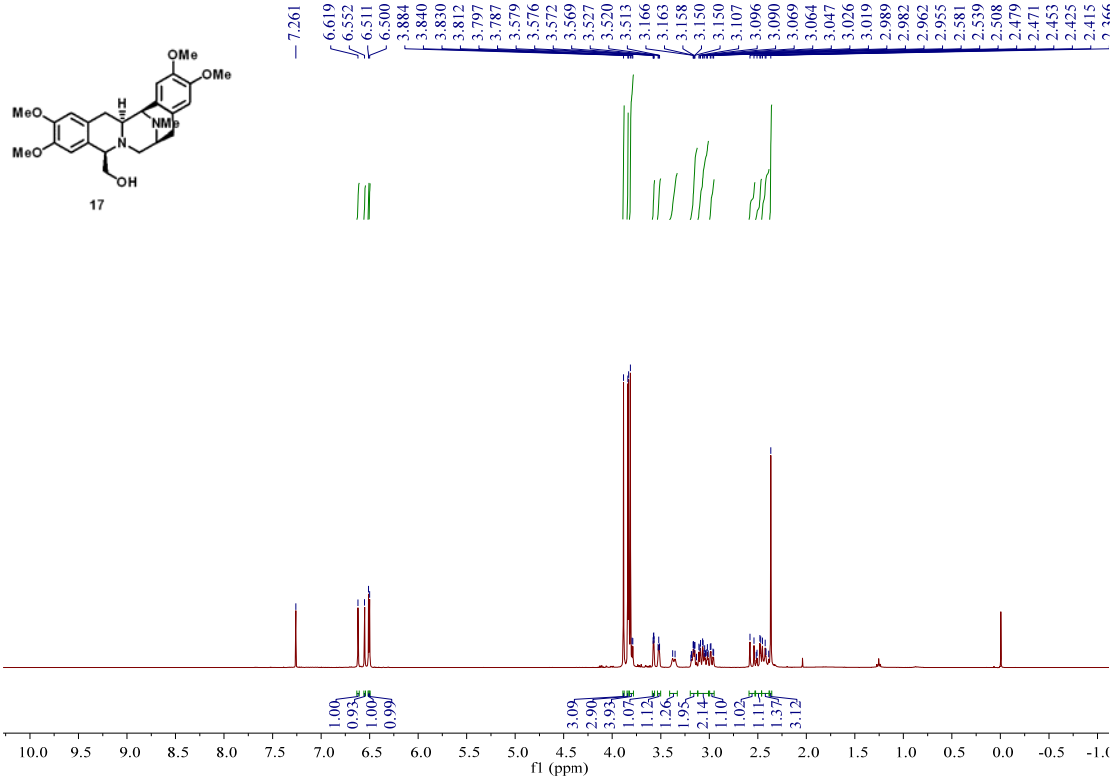
^{1}H NMR Spectrum of 16 (400 MHz, $CDCl_3$)



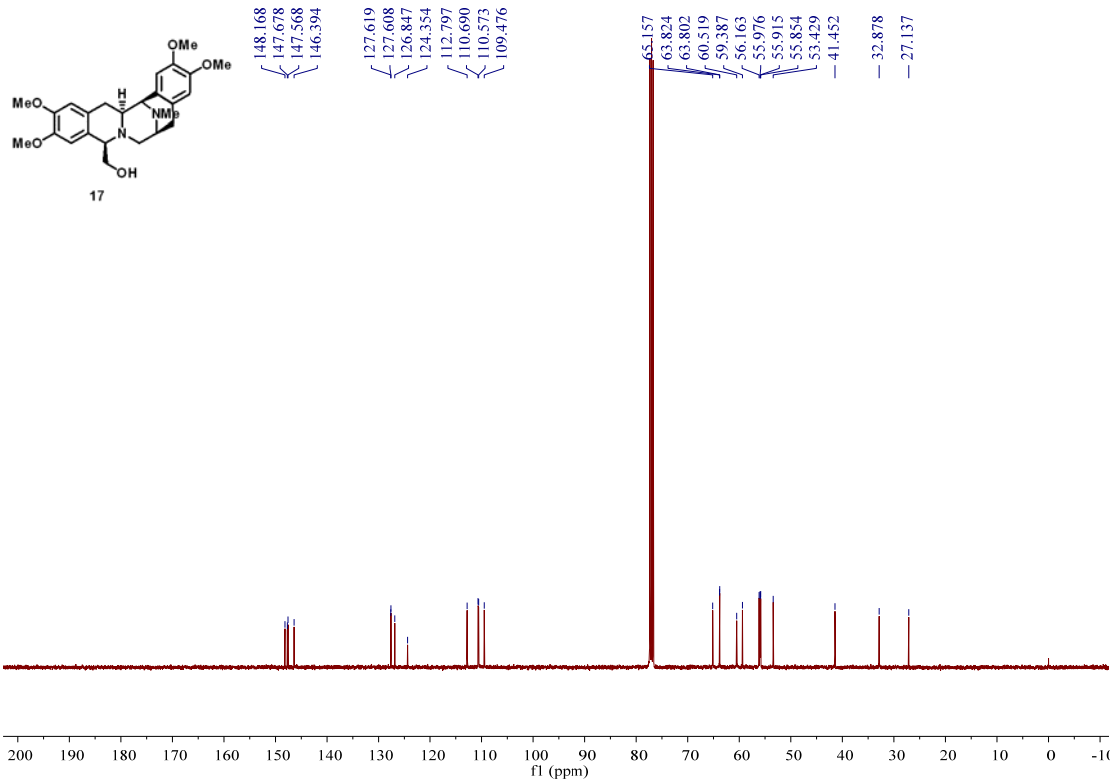
^{13}C NMR Spectrum of 16 (101 MHz, $CDCl_3$)



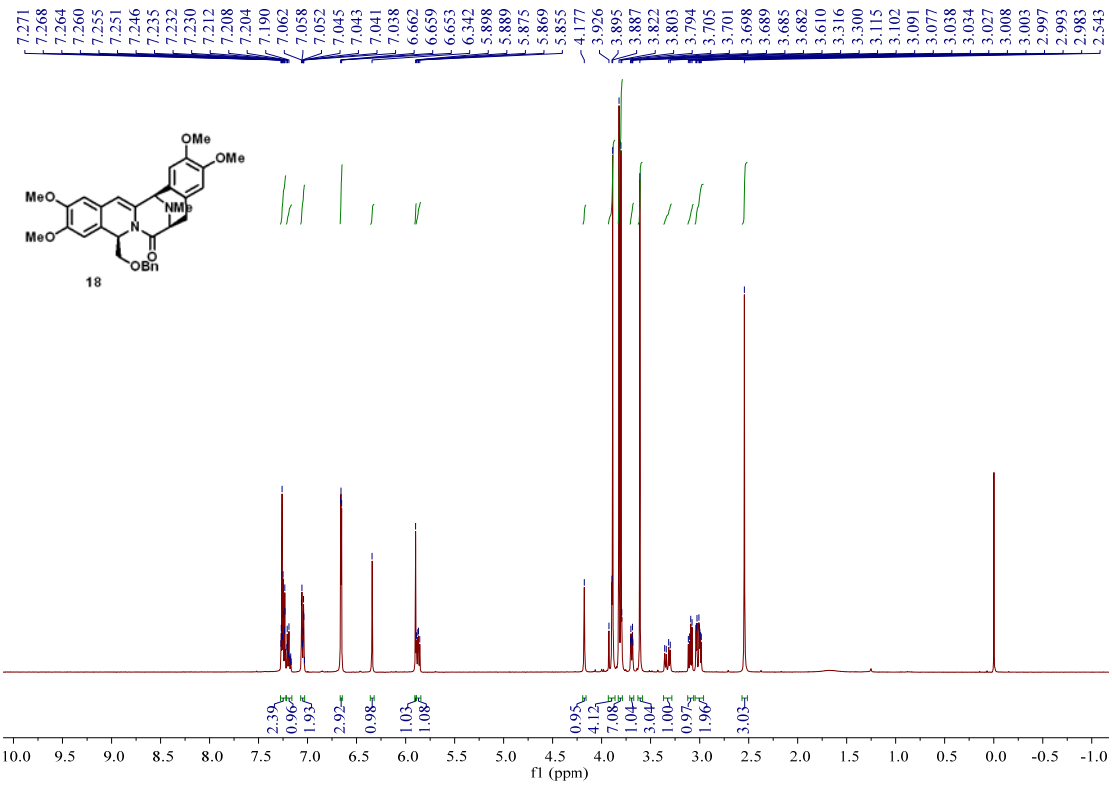
^{1}H NMR Spectrum of 17 (400 MHz, $CDCl_3$)



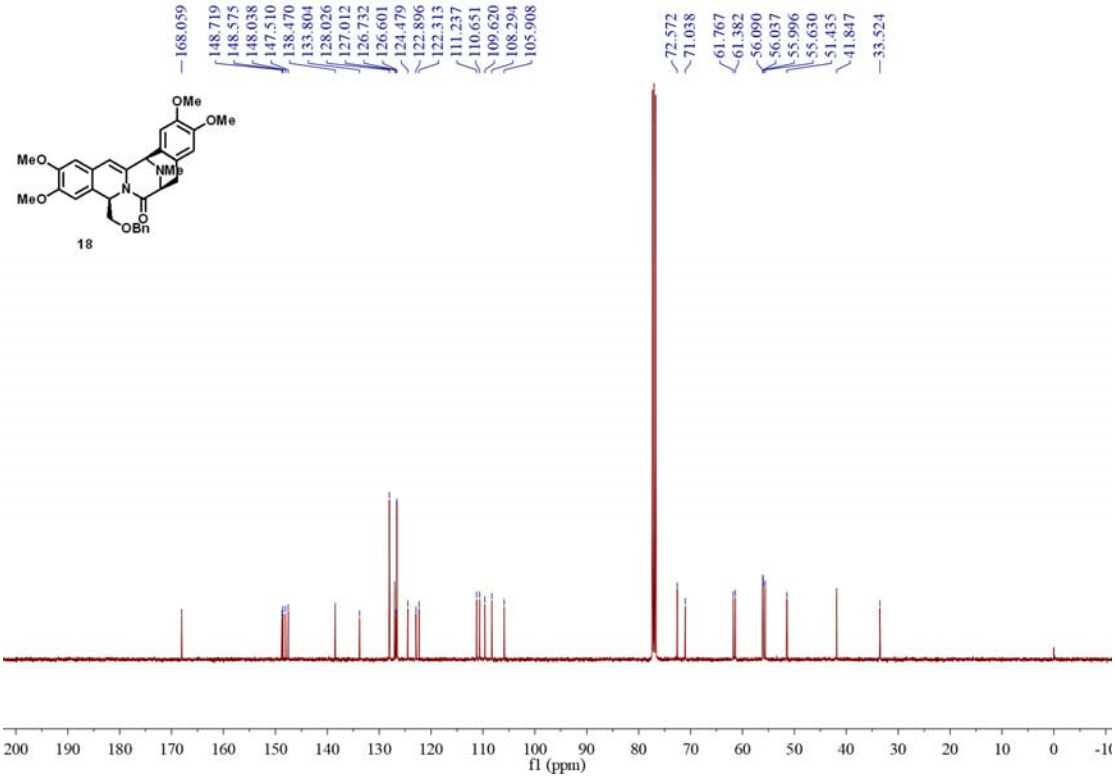
^{13}C NMR Spectrum of 17 (101 MHz, $CDCl_3$)



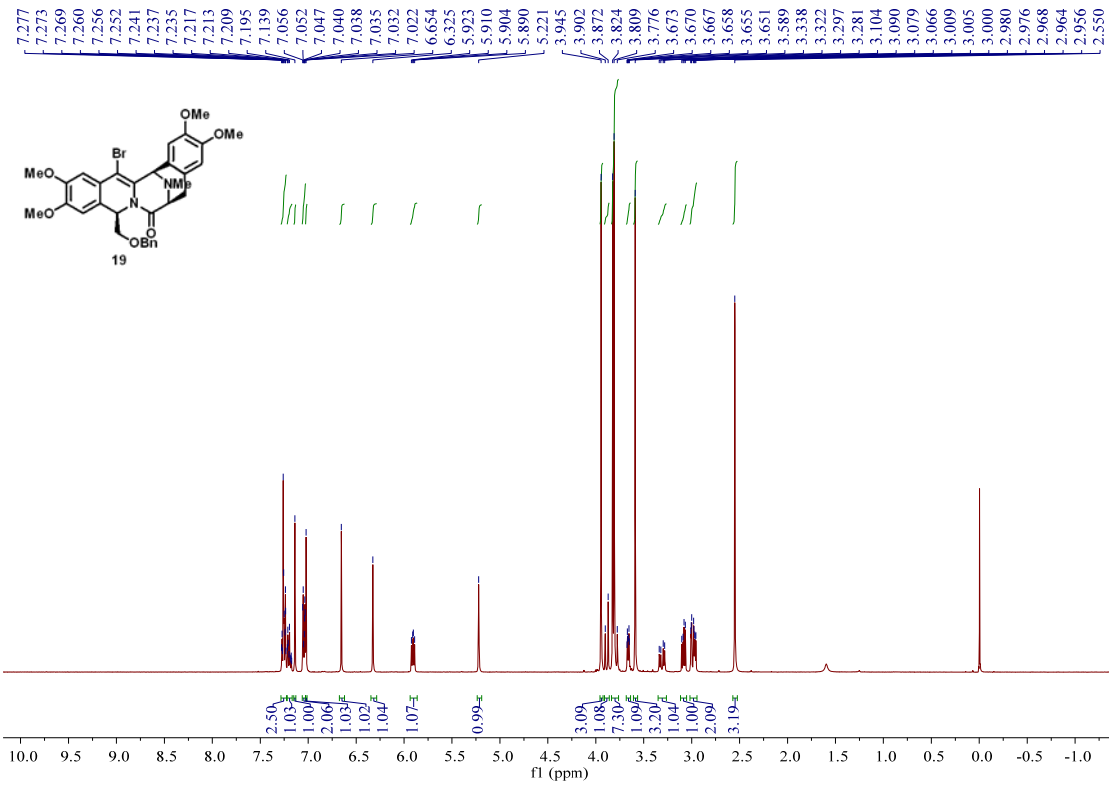
^{1}H NMR Spectrum of 18 (400 MHz, $CDCl_3$)



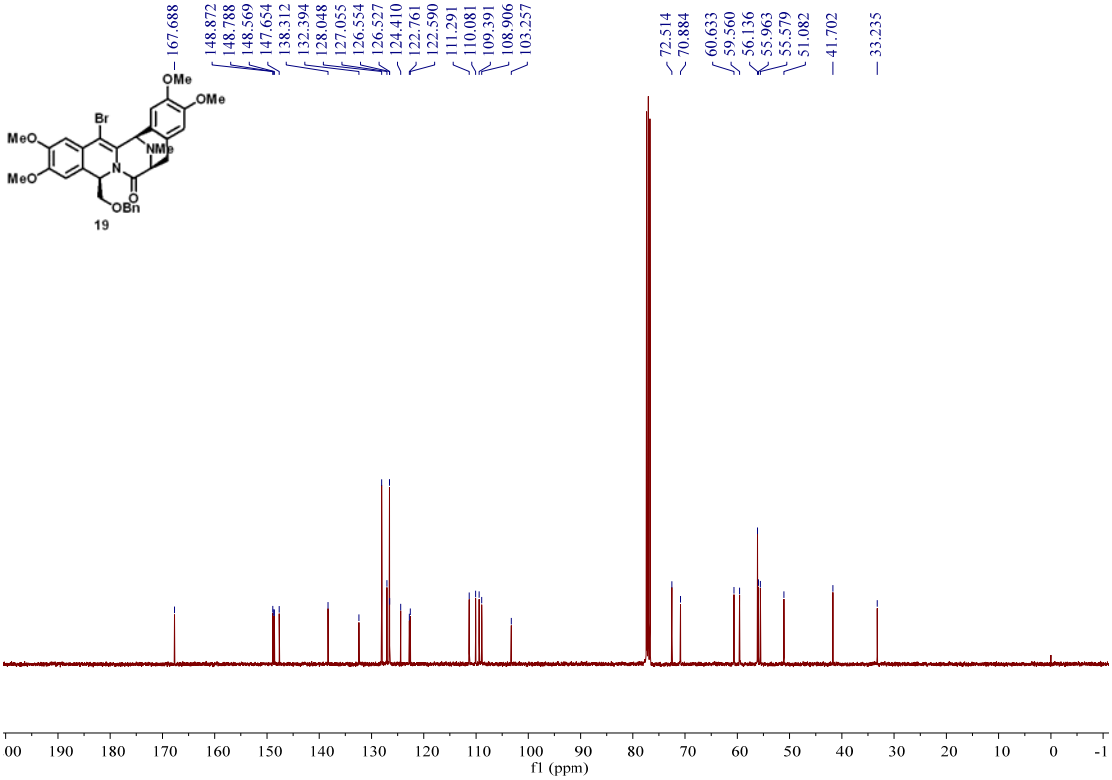
^{13}C NMR Spectrum of 18 (101 MHz, $CDCl_3$)



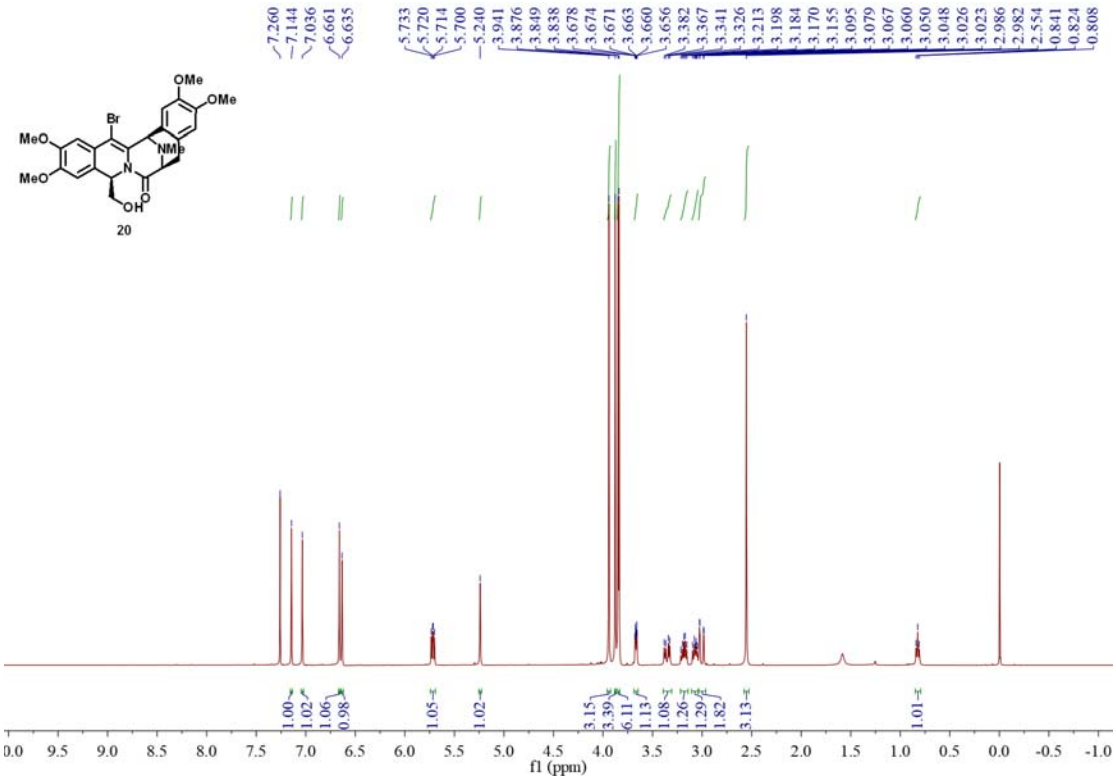
^{1}H NMR Spectrum of 19 (400 MHz, $CDCl_3$)



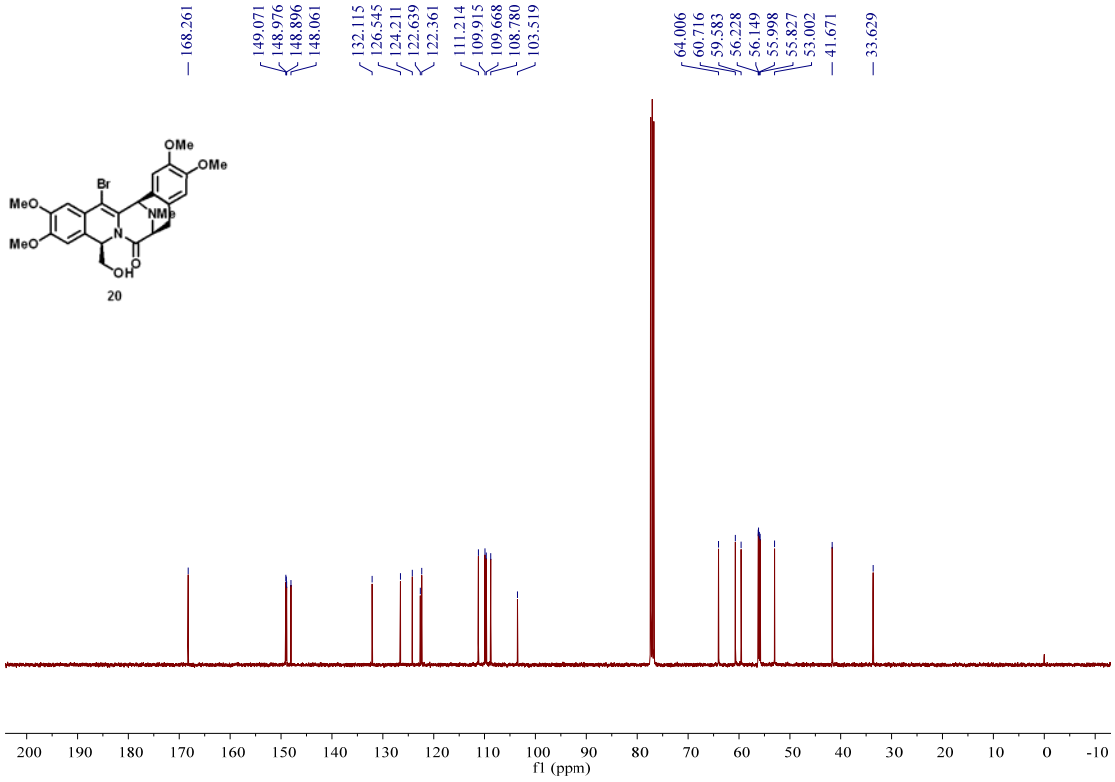
^{13}C NMR Spectrum of 19 (101 MHz, $CDCl_3$)



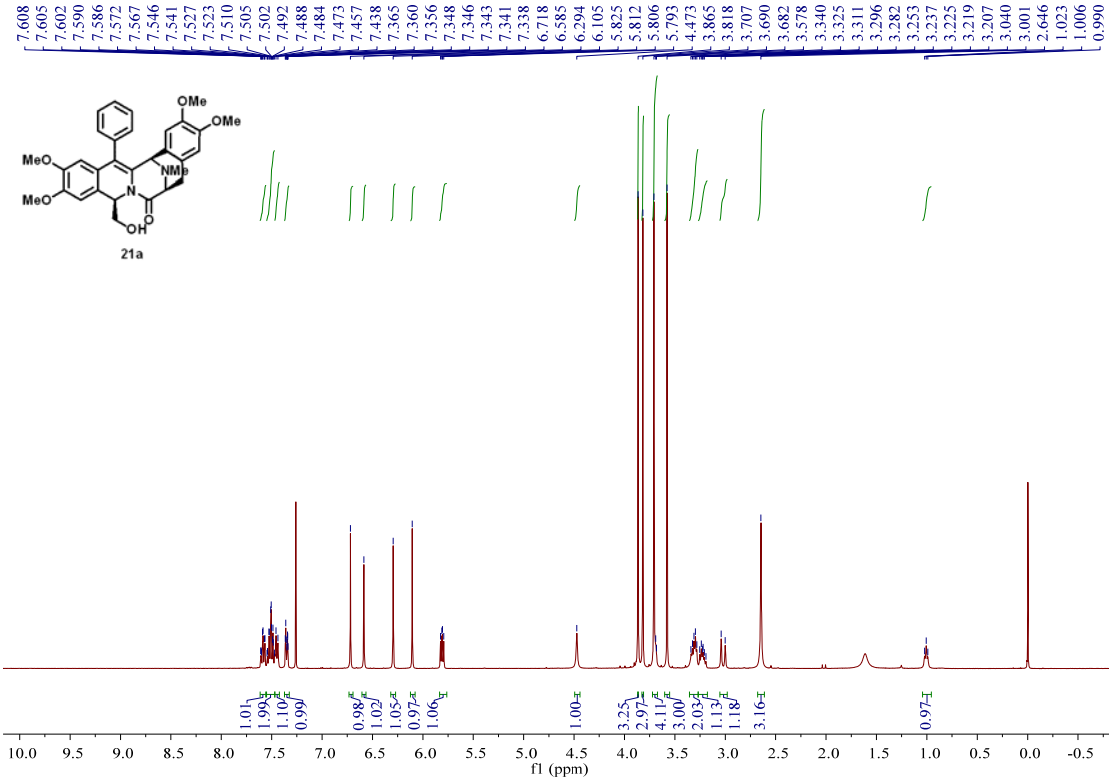
^{1}H NMR Spectrum of 20 (400 MHz, $CDCl_3$)



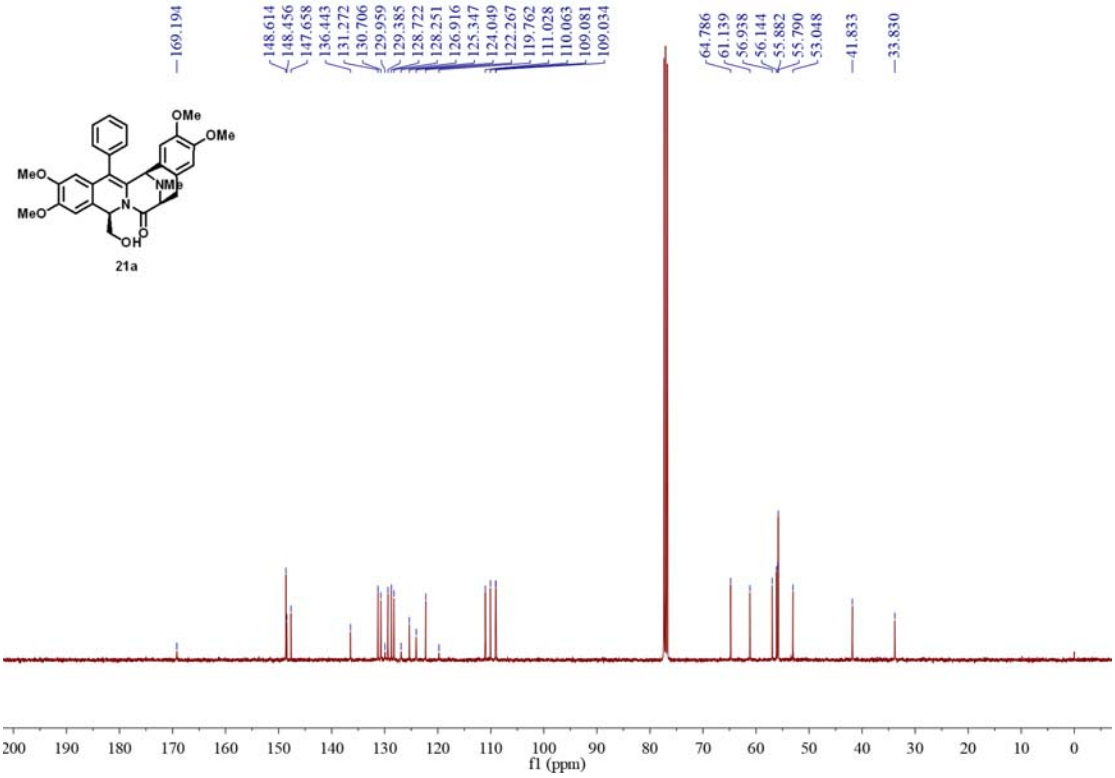
^{13}C NMR Spectrum of 20 (101 MHz, $CDCl_3$)



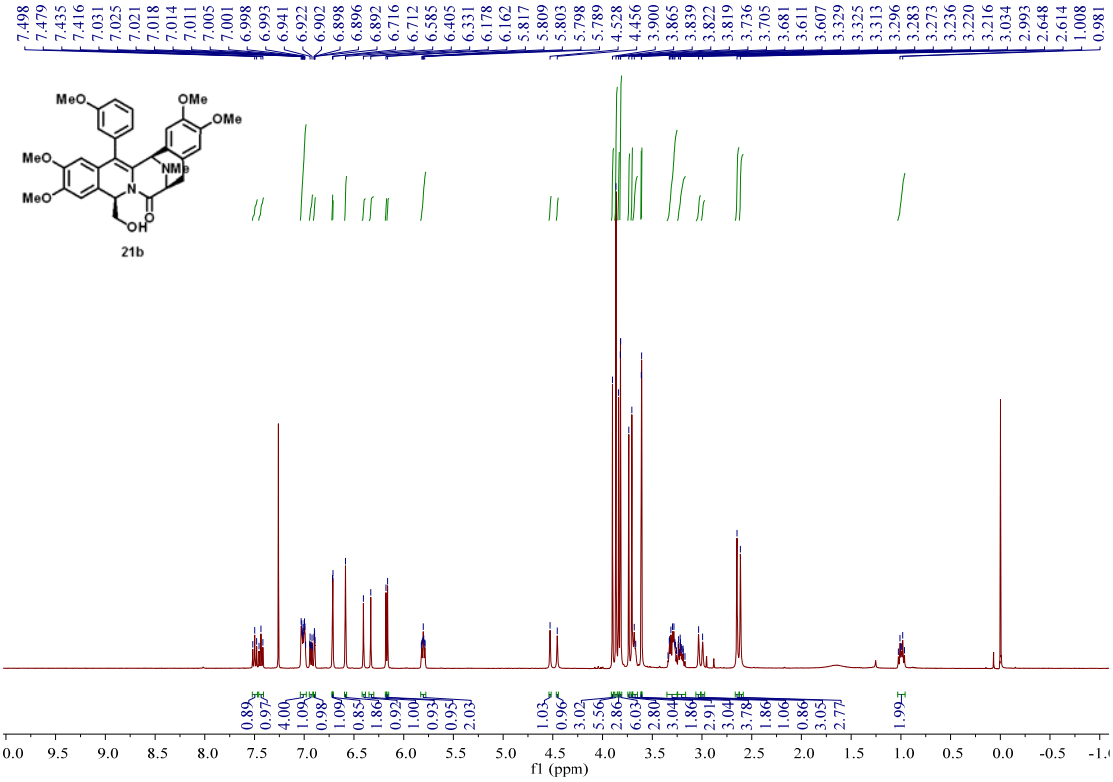
^{1}H NMR Spectrum of 21a (400 MHz, $CDCl_3$)



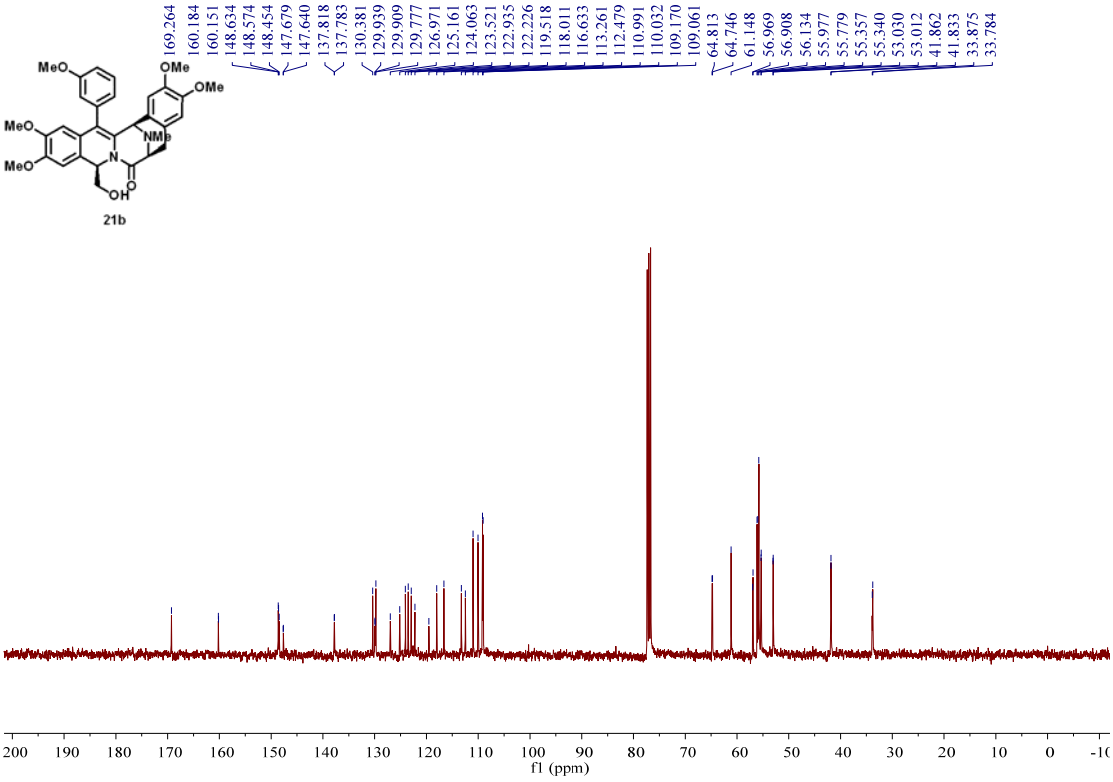
^{13}C NMR Spectrum of 21a (101 MHz, $CDCl_3$)



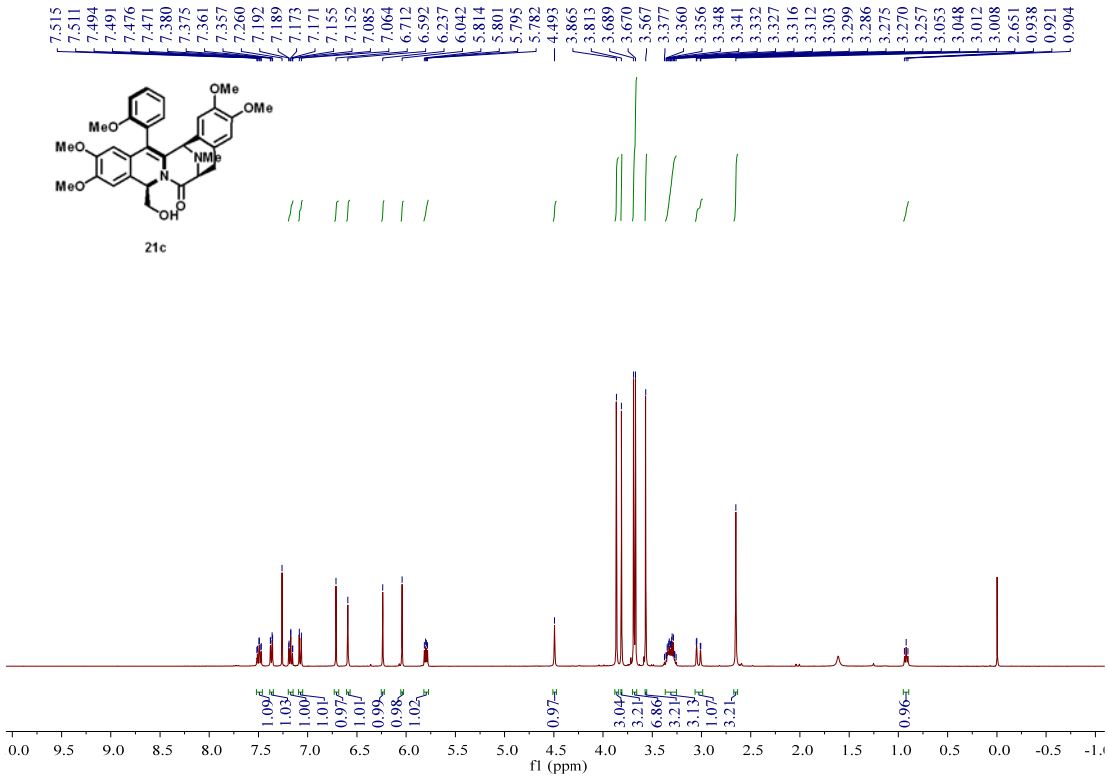
^{1}H NMR Spectrum of 21b (400 MHz, $CDCl_3$)



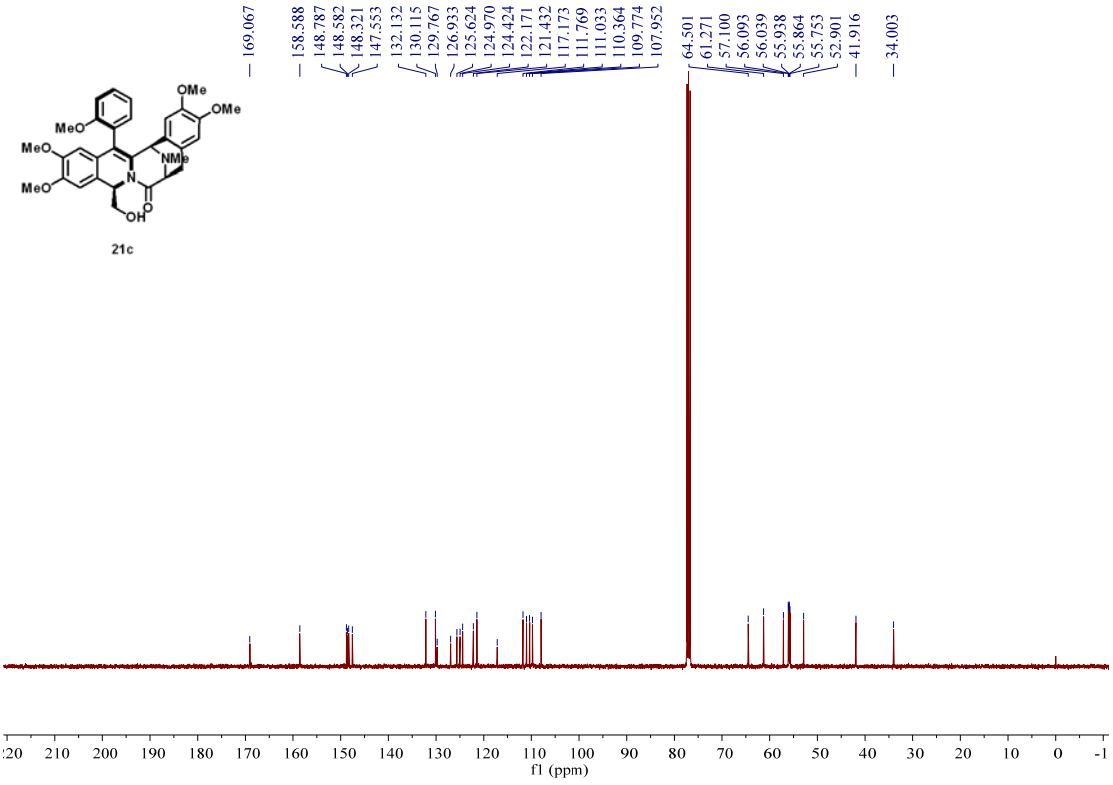
^{13}C NMR Spectrum of 21b (101 MHz, $CDCl_3$)



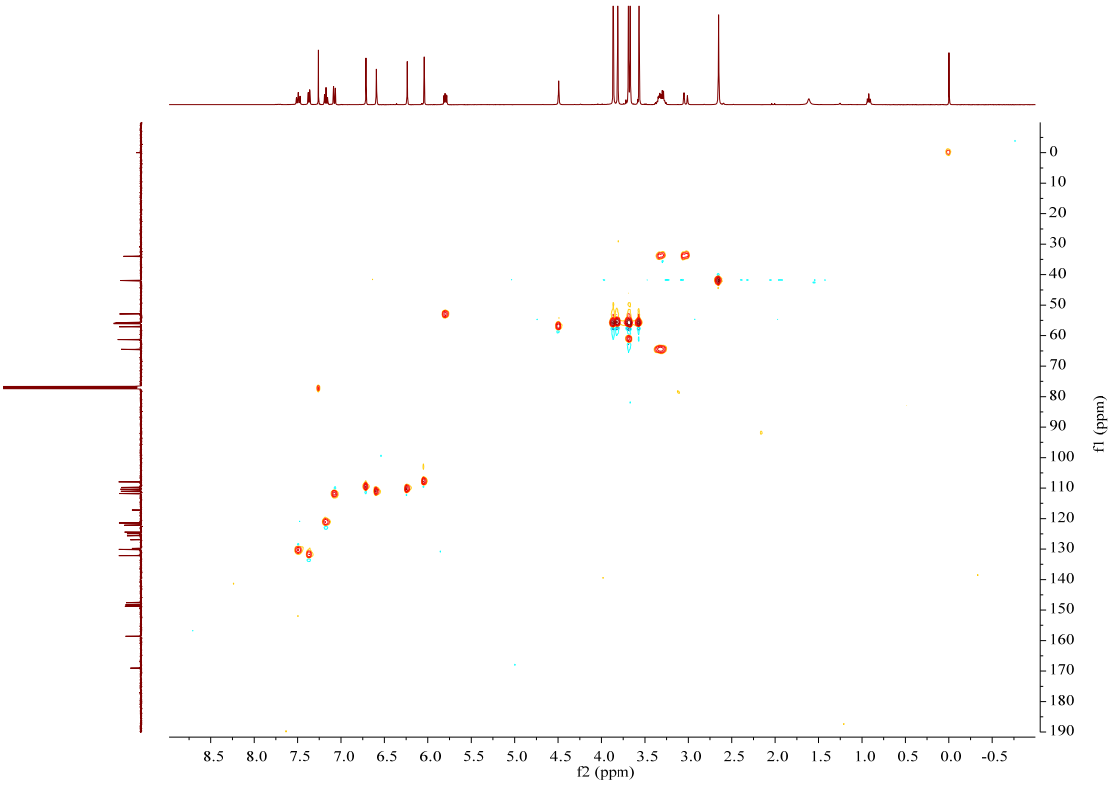
^{1}H NMR Spectrum of 21c (400 MHz, $CDCl_3$)



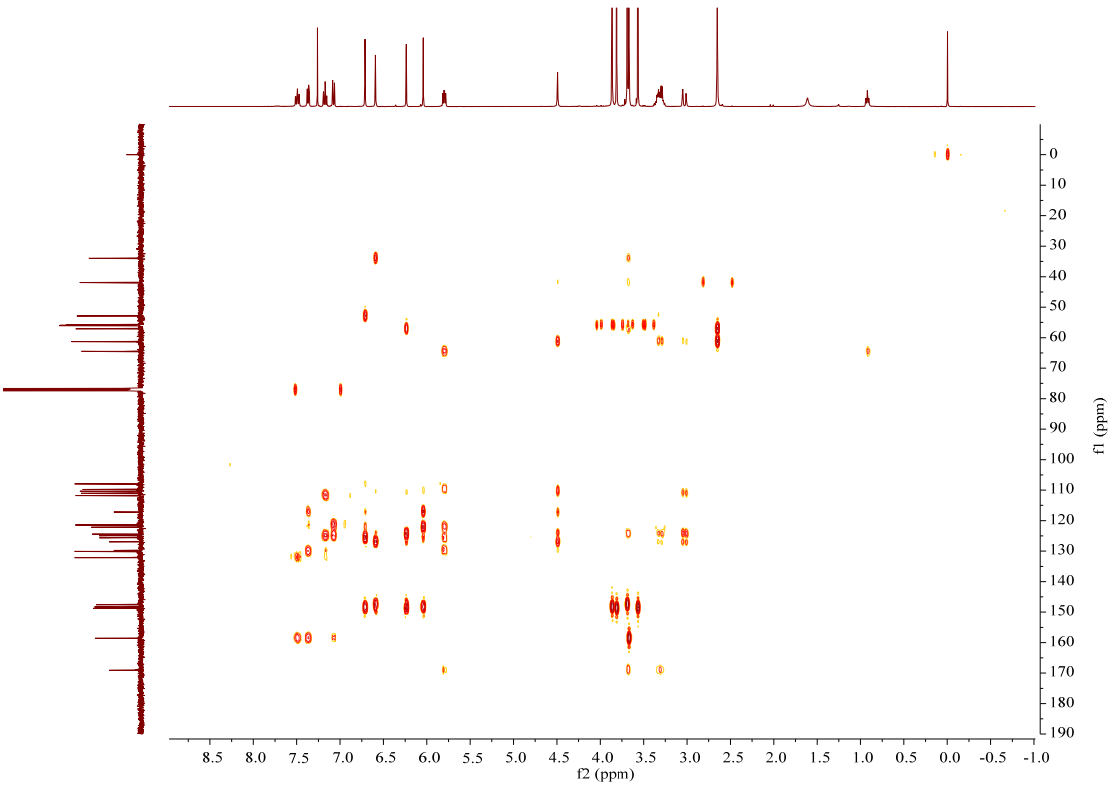
^{13}C NMR Spectrum of 21c (101 MHz, $CDCl_3$)



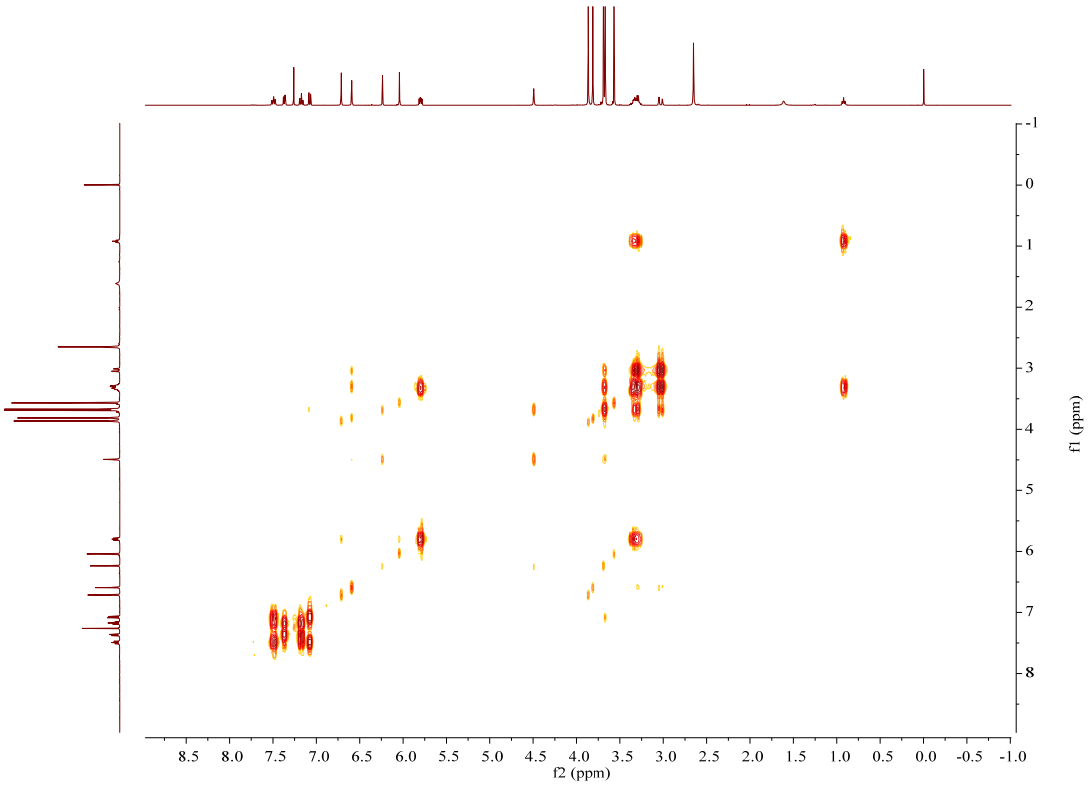
HSQC of 21c



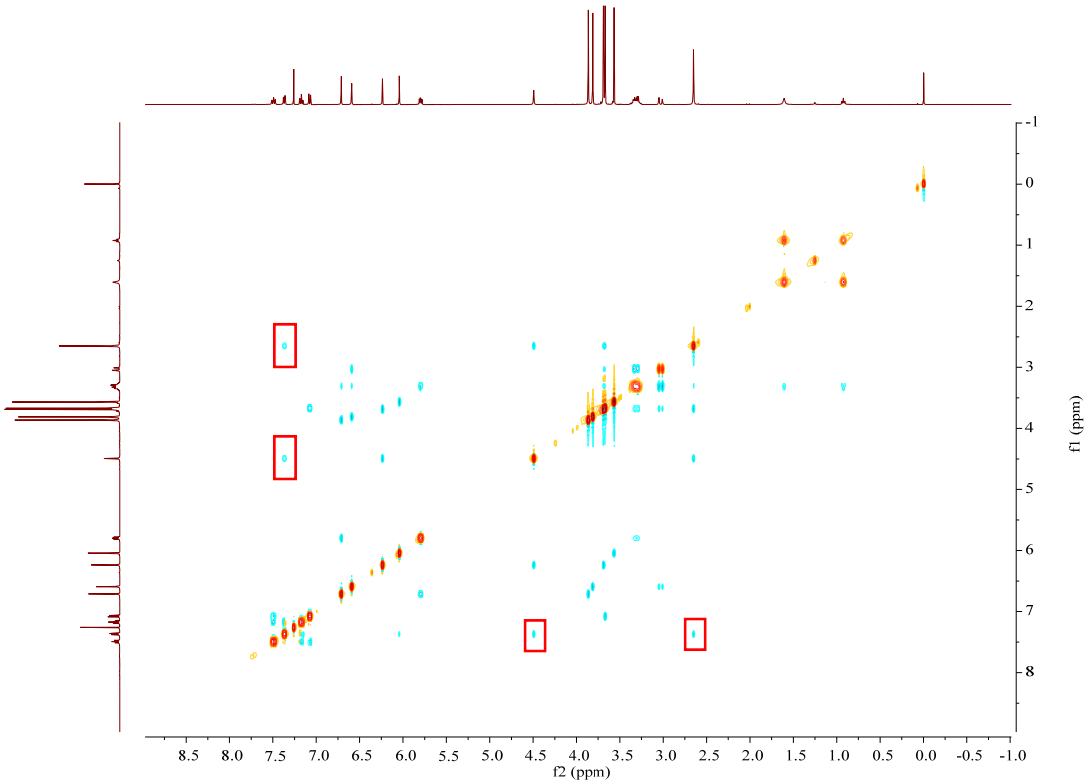
HMBC of 21c



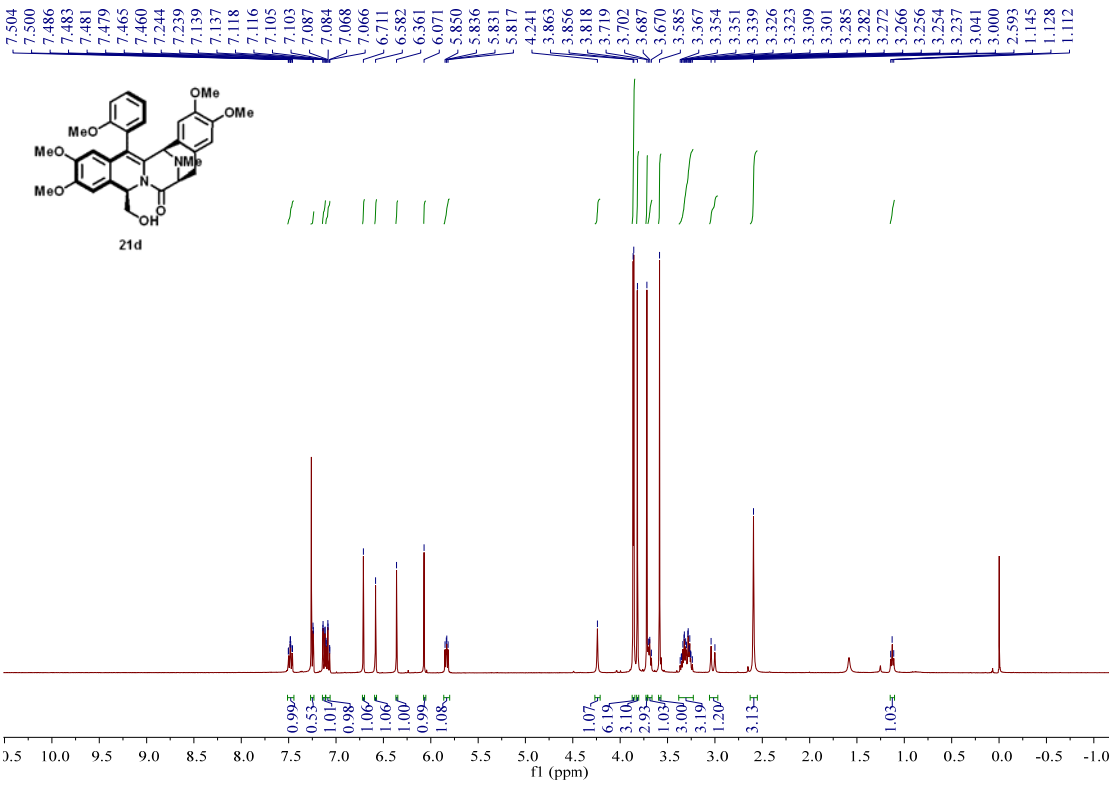
COSY of 21c



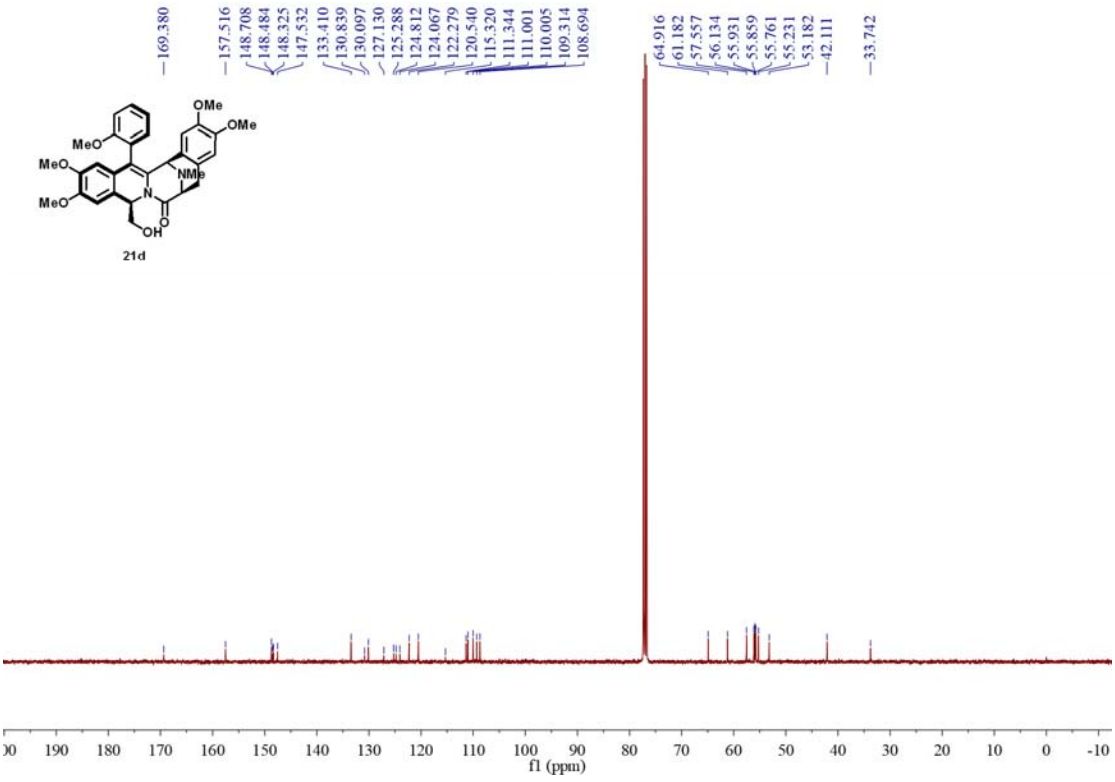
NOE of 21c



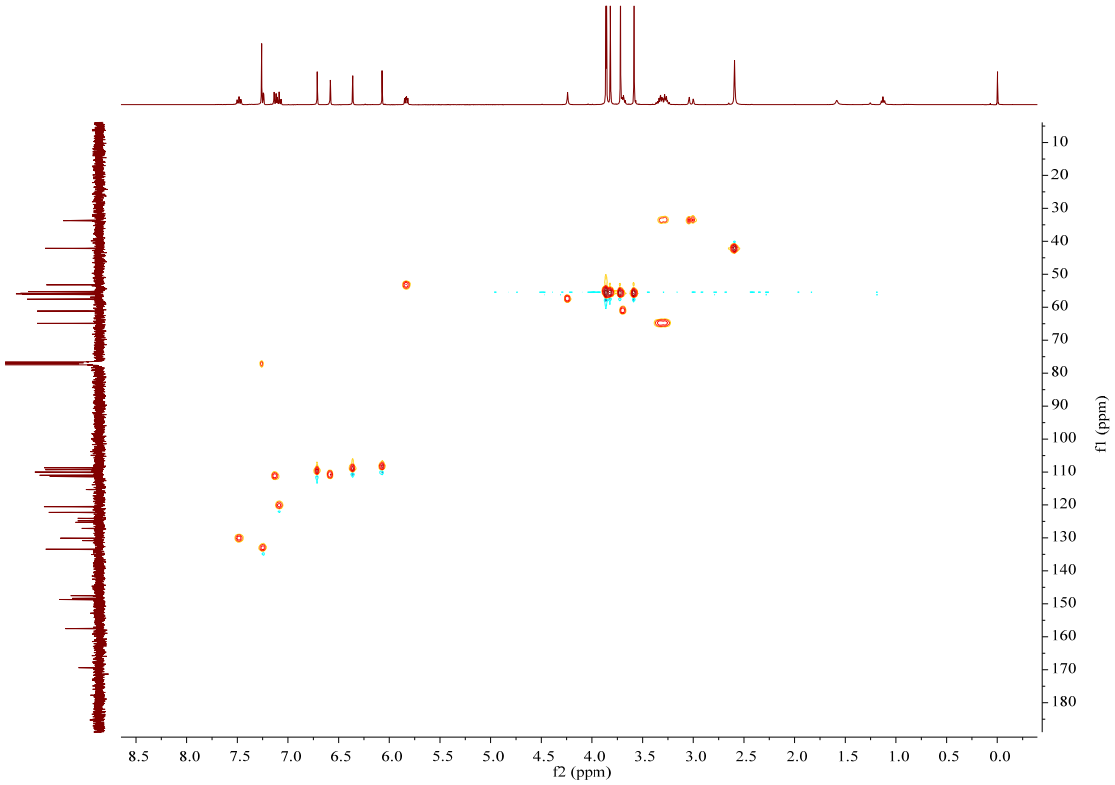
^{1}H NMR Spectrum of 21d (400 MHz, $CDCl_3$)



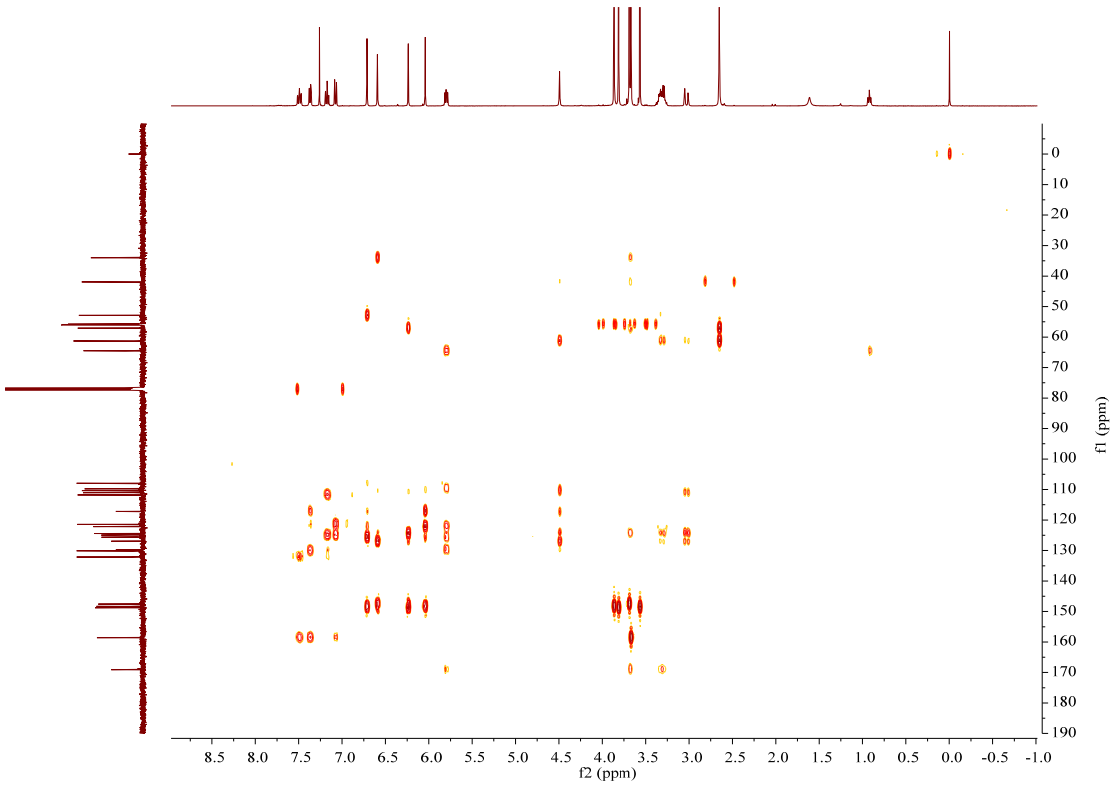
^{13}C NMR Spectrum of 21d (101 MHz, $CDCl_3$)



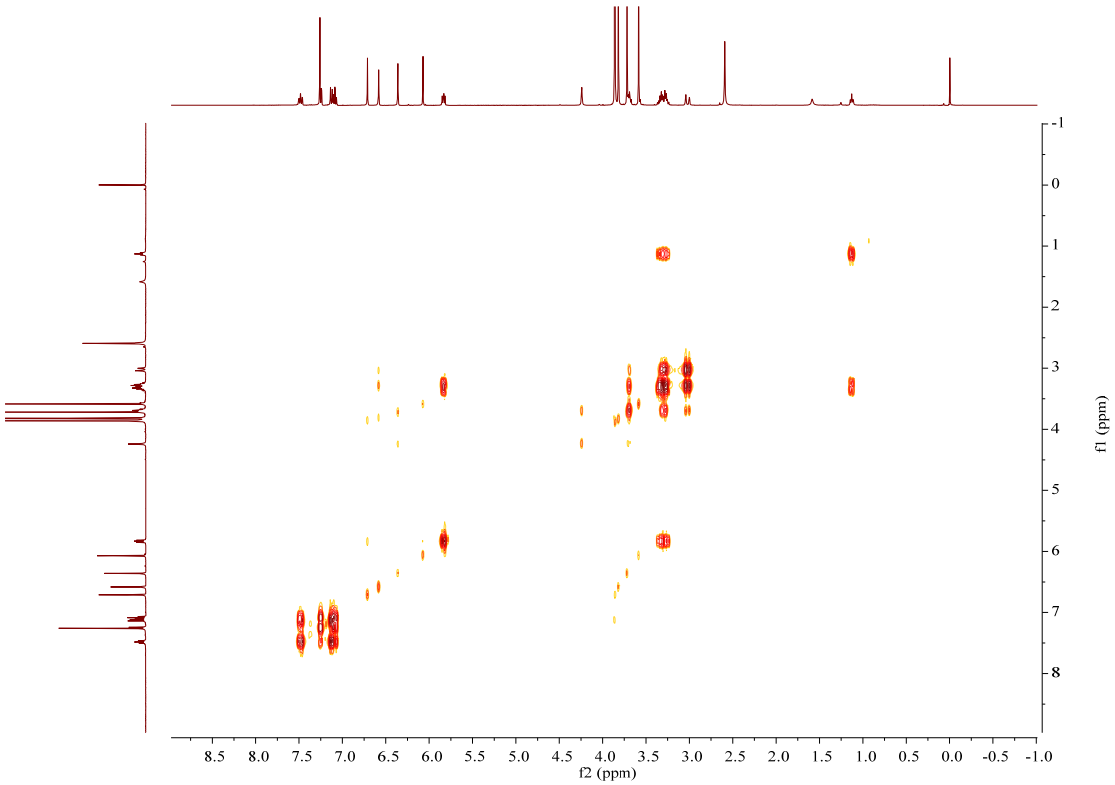
HSQC of 21d



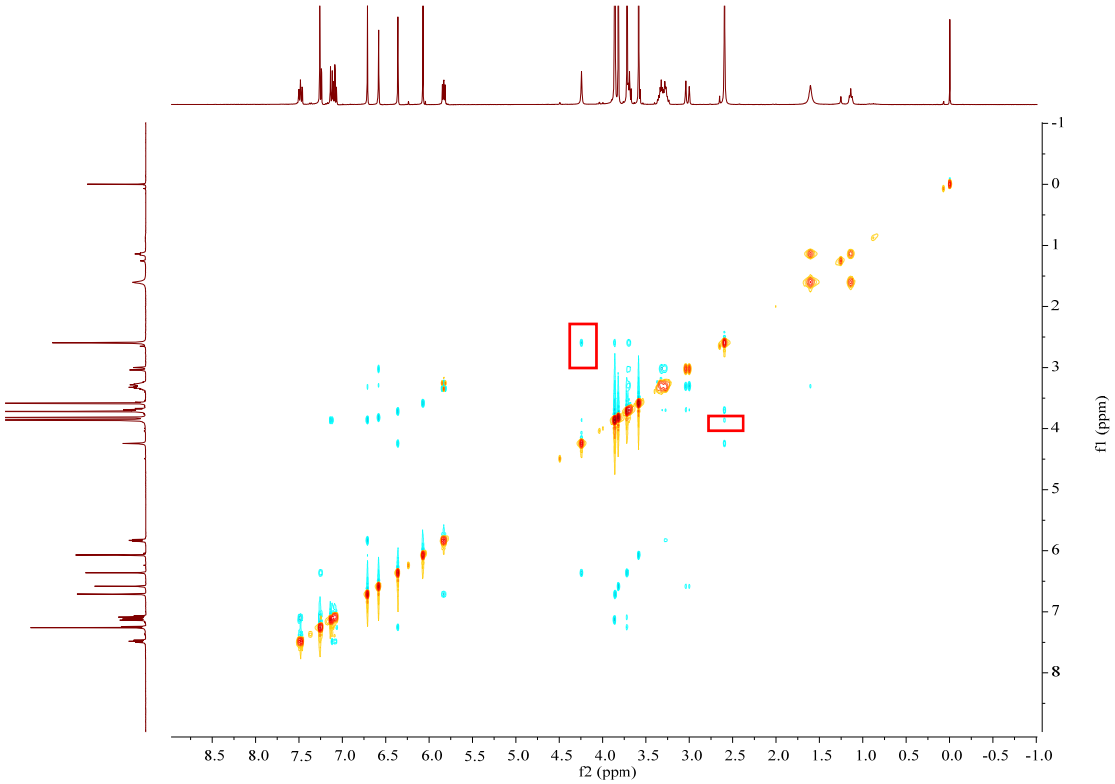
HMBC of 21d



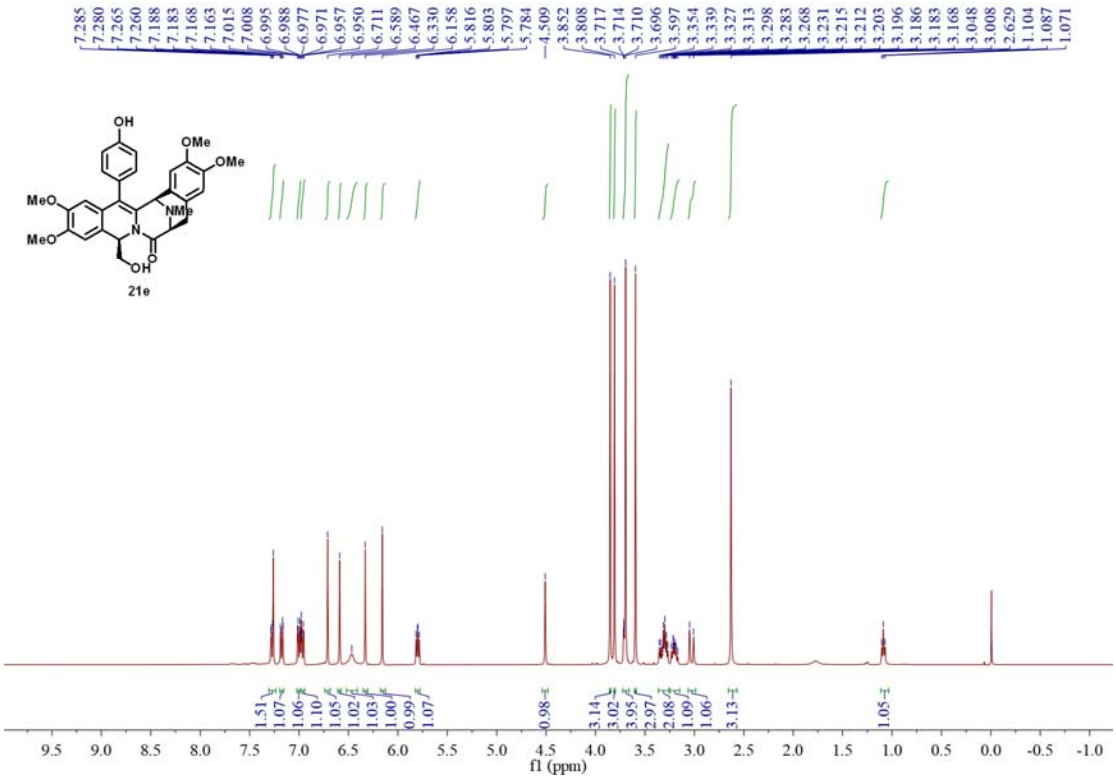
COSY of 21d



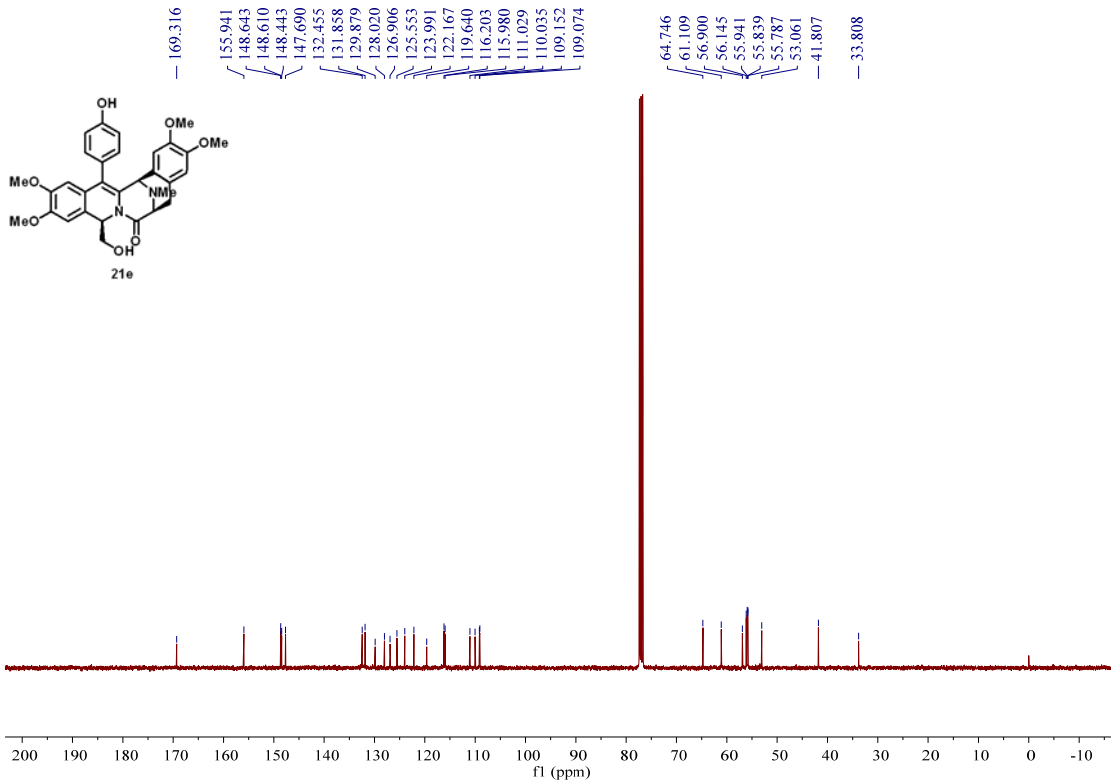
NOE of 21d



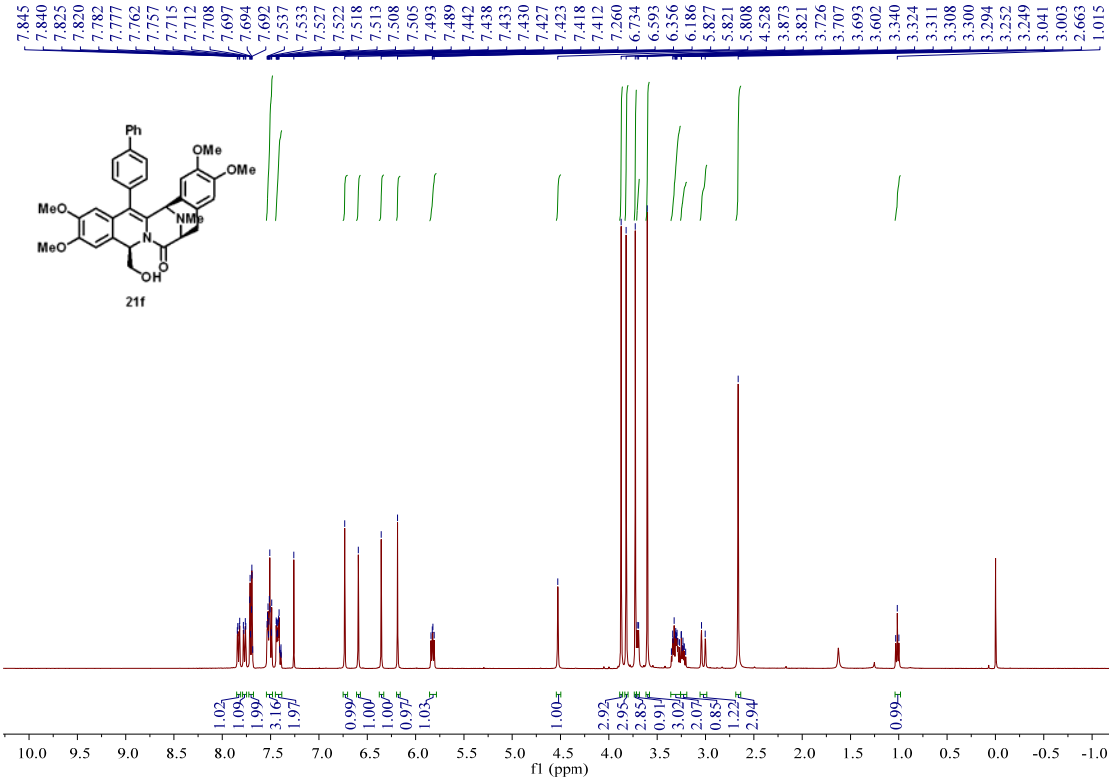
^{1}H NMR Spectrum of 21e (400 MHz, $CDCl_3$)



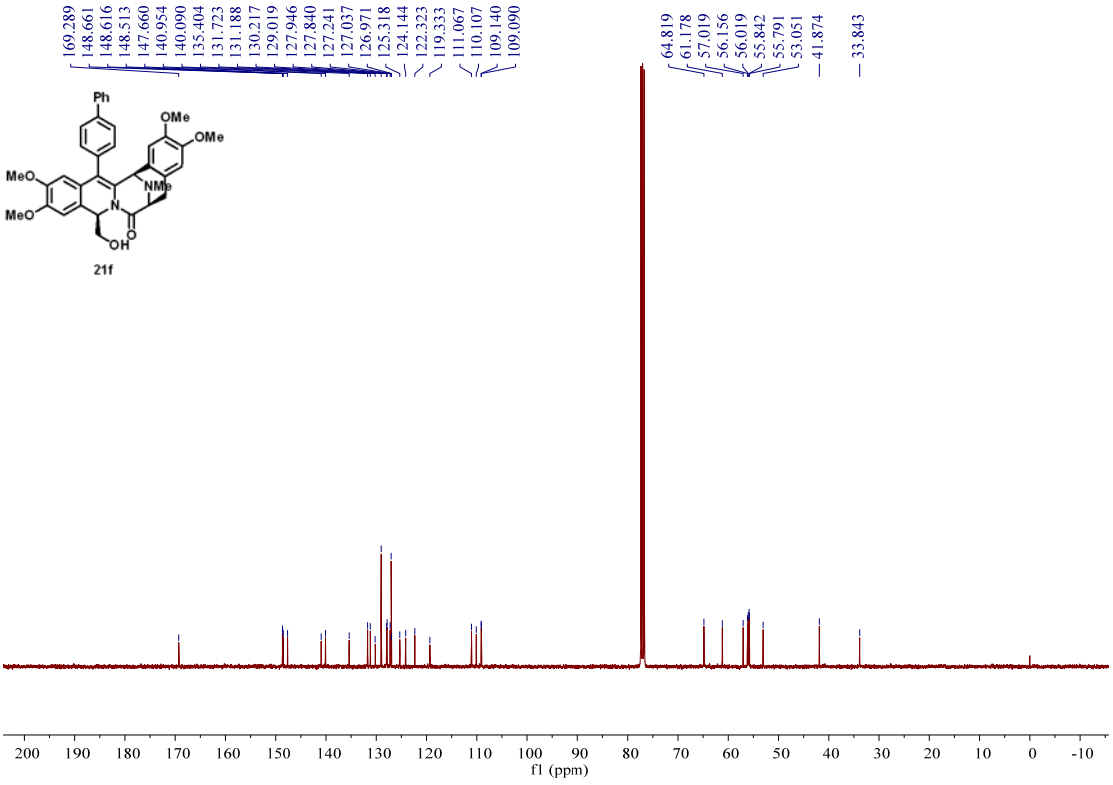
^{13}C NMR Spectrum of 21e (101 MHz, $CDCl_3$)



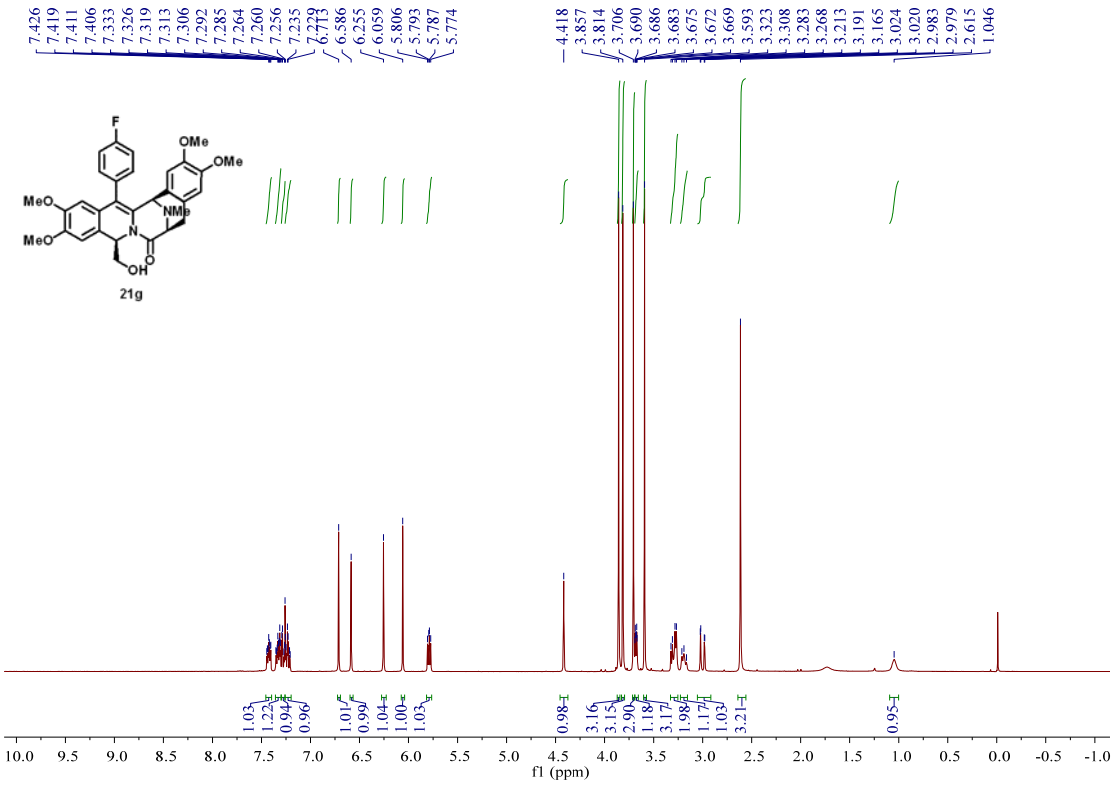
^{1}H NMR Spectrum of 21f (400 MHz, $CDCl_3$)



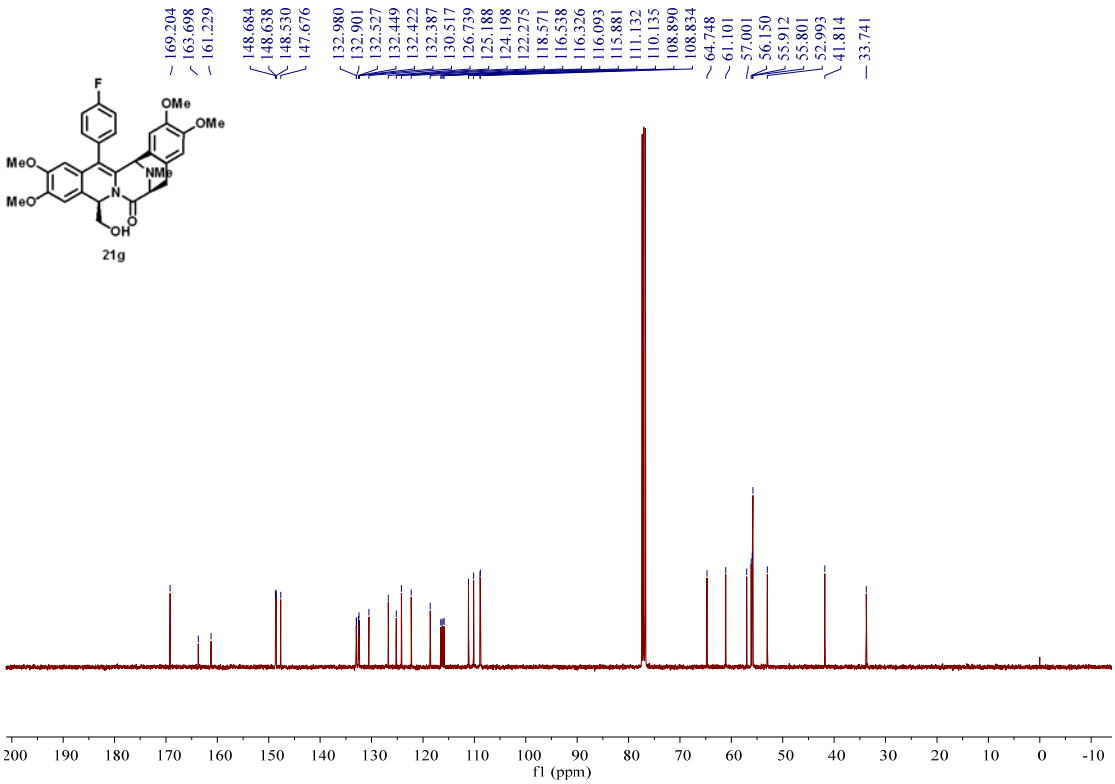
^{13}C NMR Spectrum of 21f (101 MHz, $CDCl_3$)



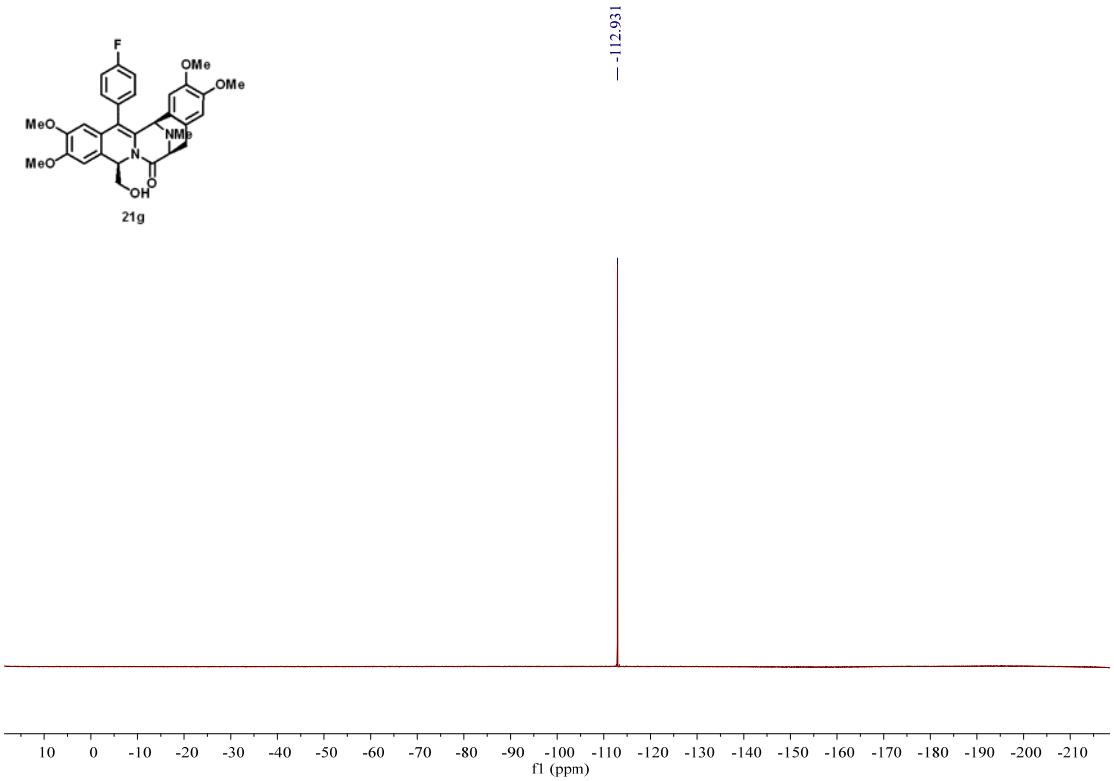
^{1}H NMR Spectrum of 21g (400 MHz, $CDCl_3$)



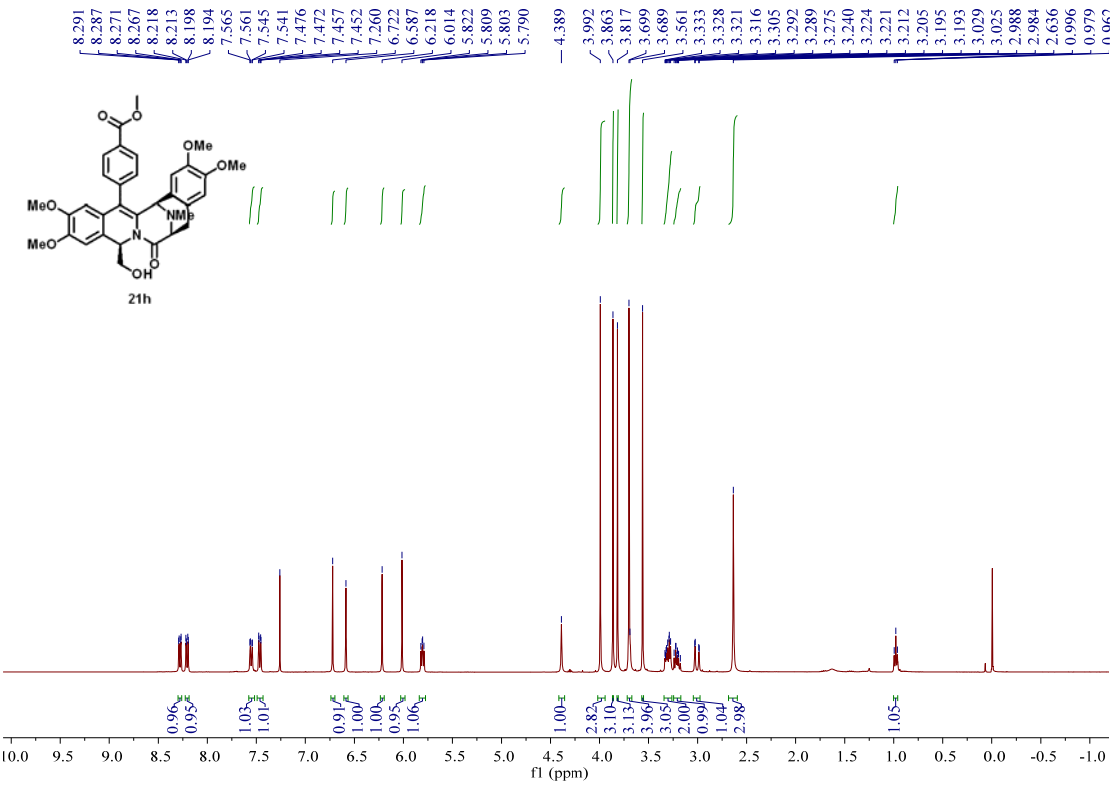
^{13}C NMR Spectrum of 21g (101 MHz, $CDCl_3$)



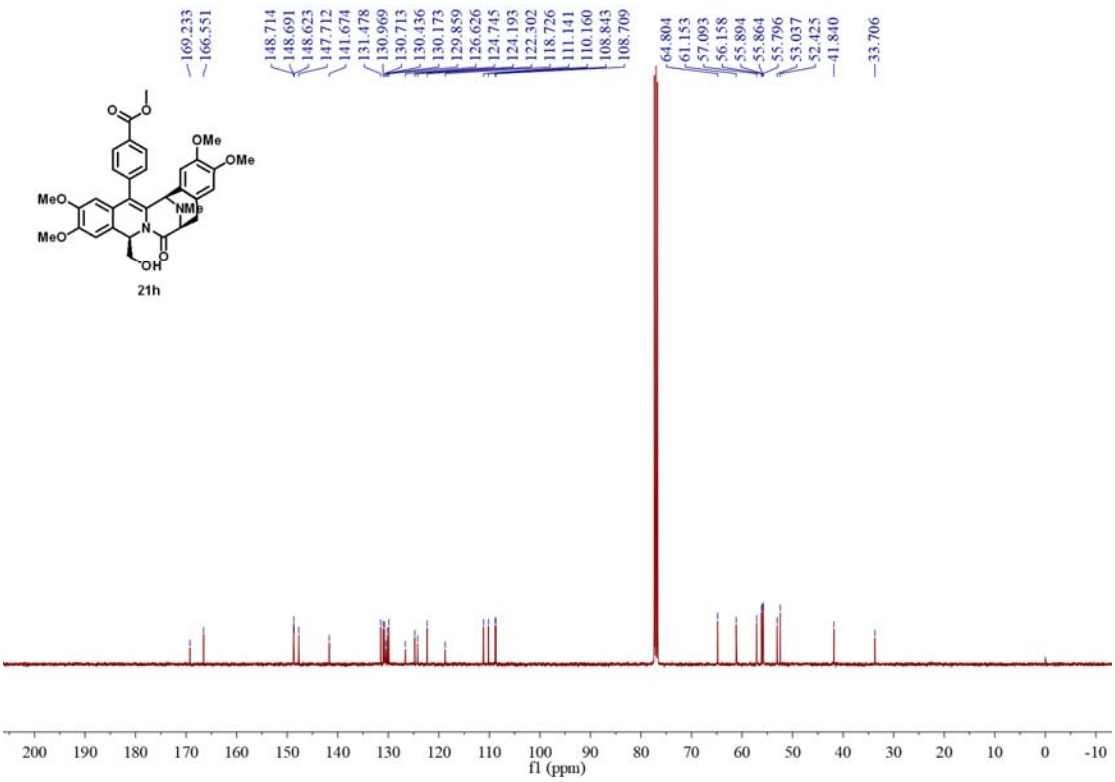
^{19}F NMR Spectrum of 21g (400 MHz, $CDCl_3$)



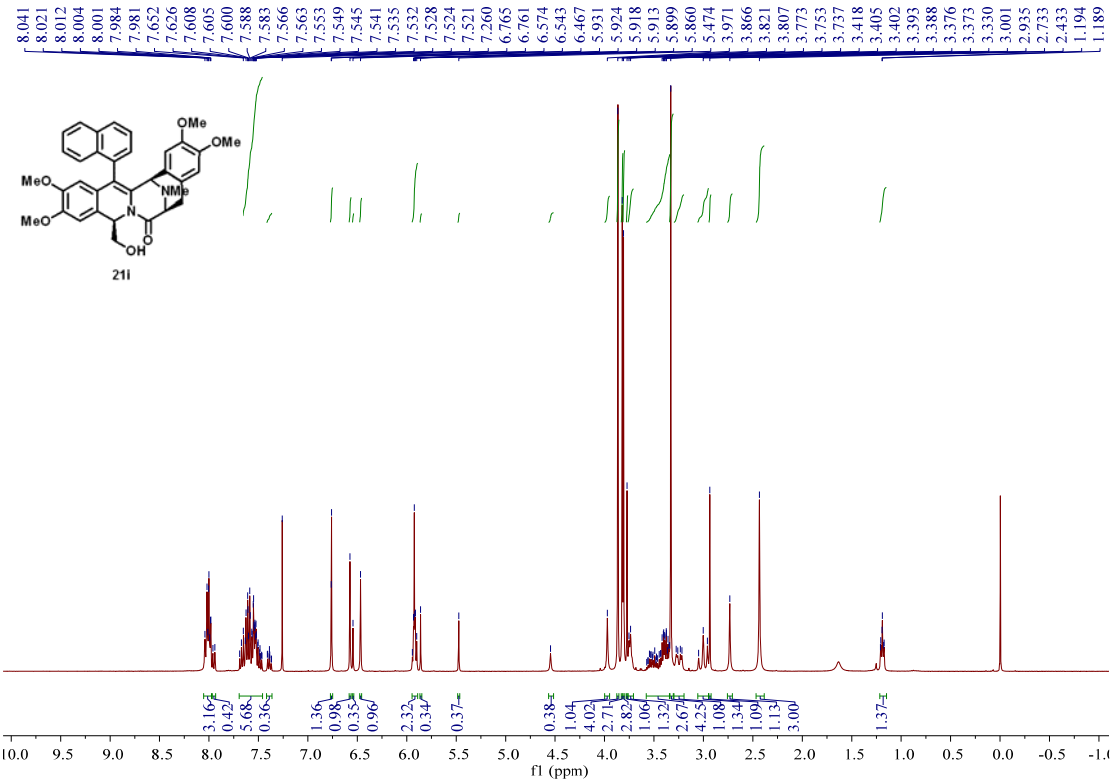
^{1}H NMR Spectrum of 21h (400 MHz, $CDCl_3$)



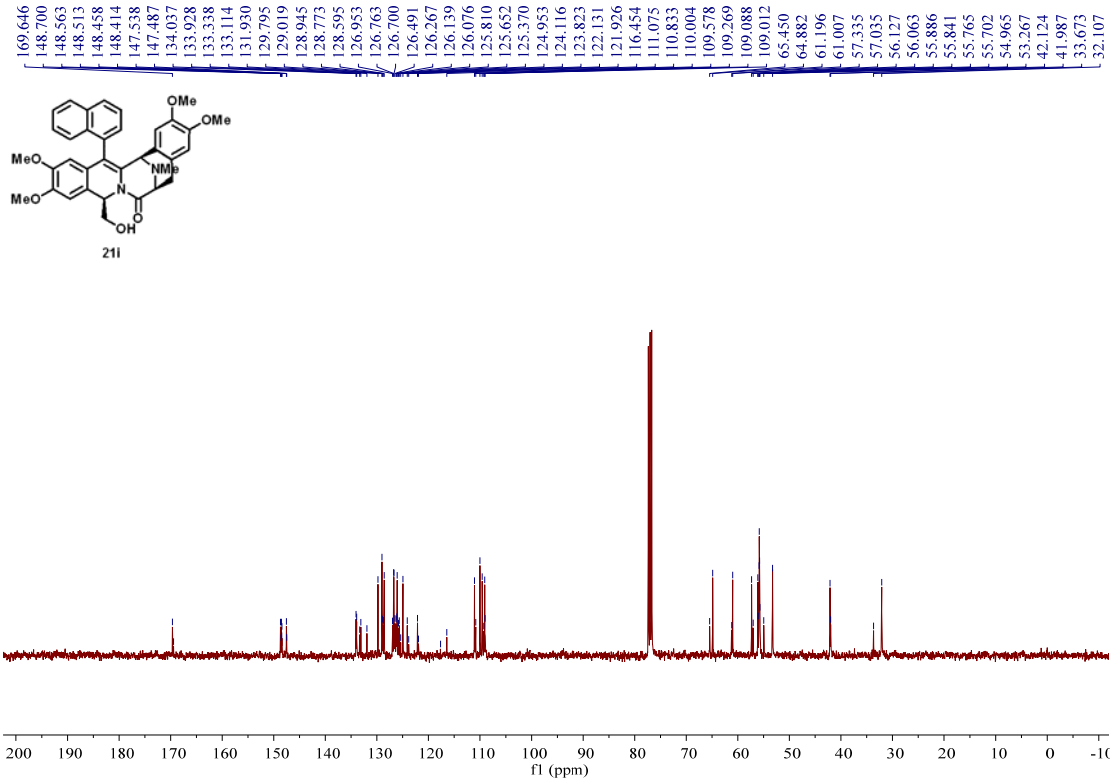
^{13}C NMR Spectrum of 21h (101 MHz, $CDCl_3$)



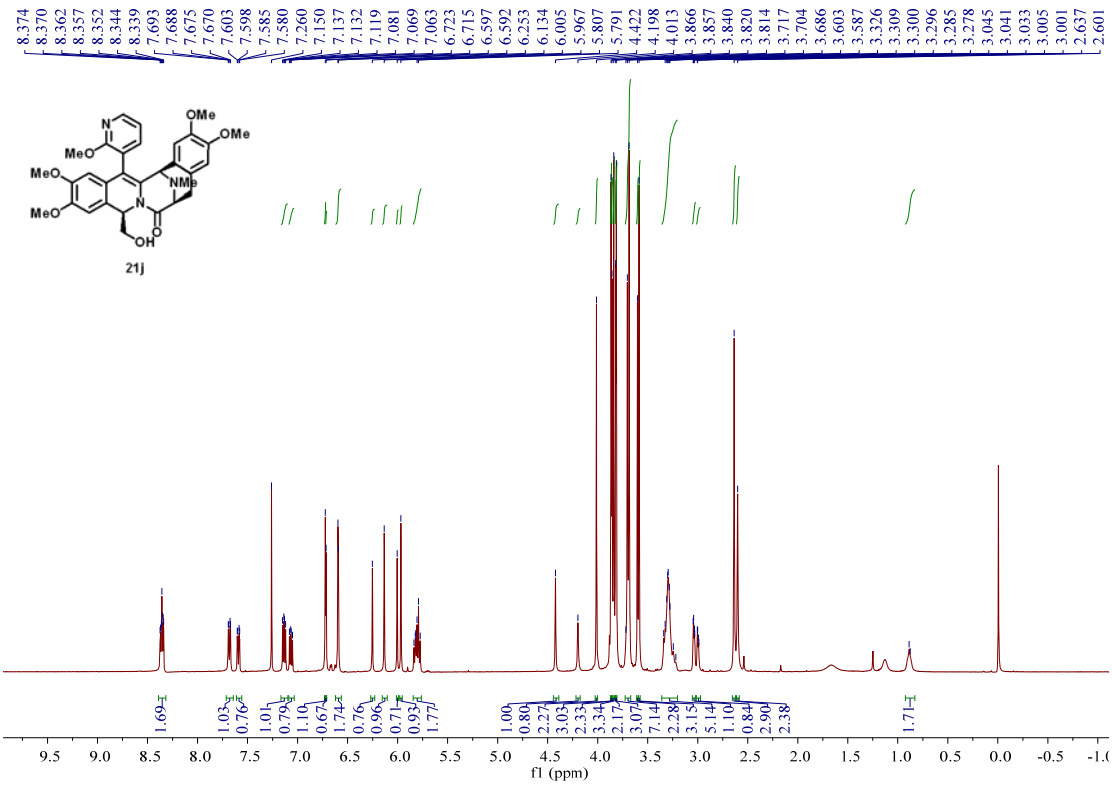
^{1}H NMR Spectrum of 21i (400 MHz, $CDCl_3$)



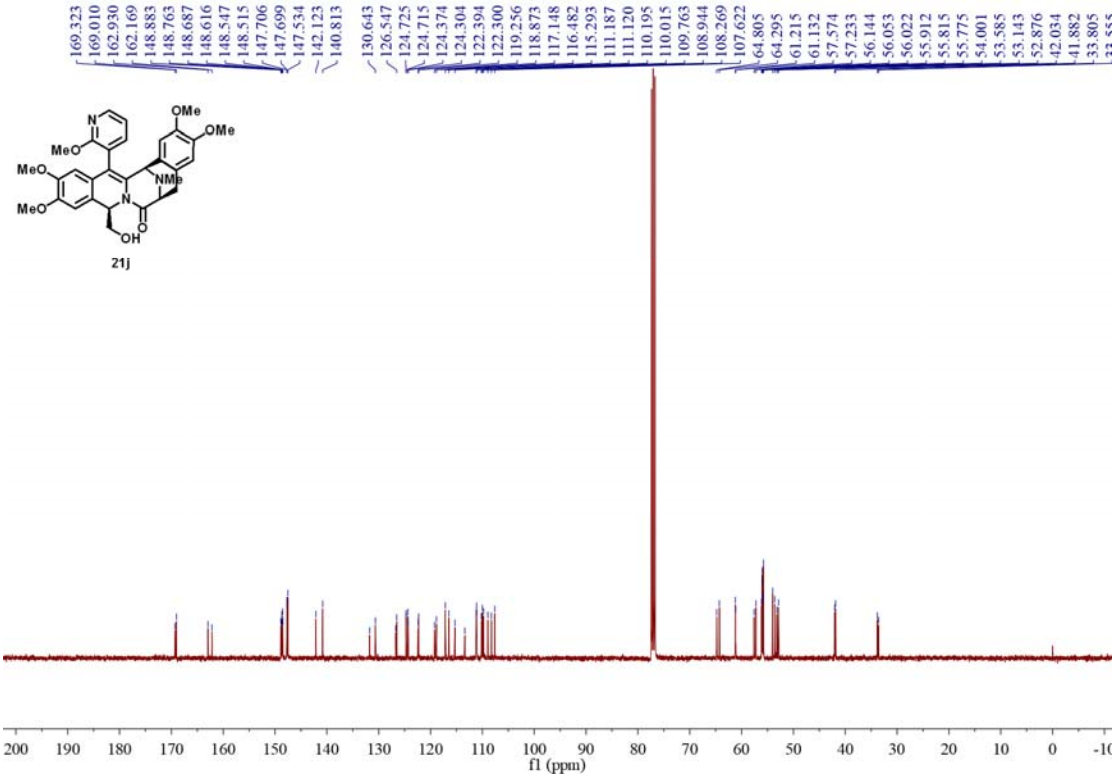
^{13}C NMR Spectrum of 21i (101 MHz, $CDCl_3$)



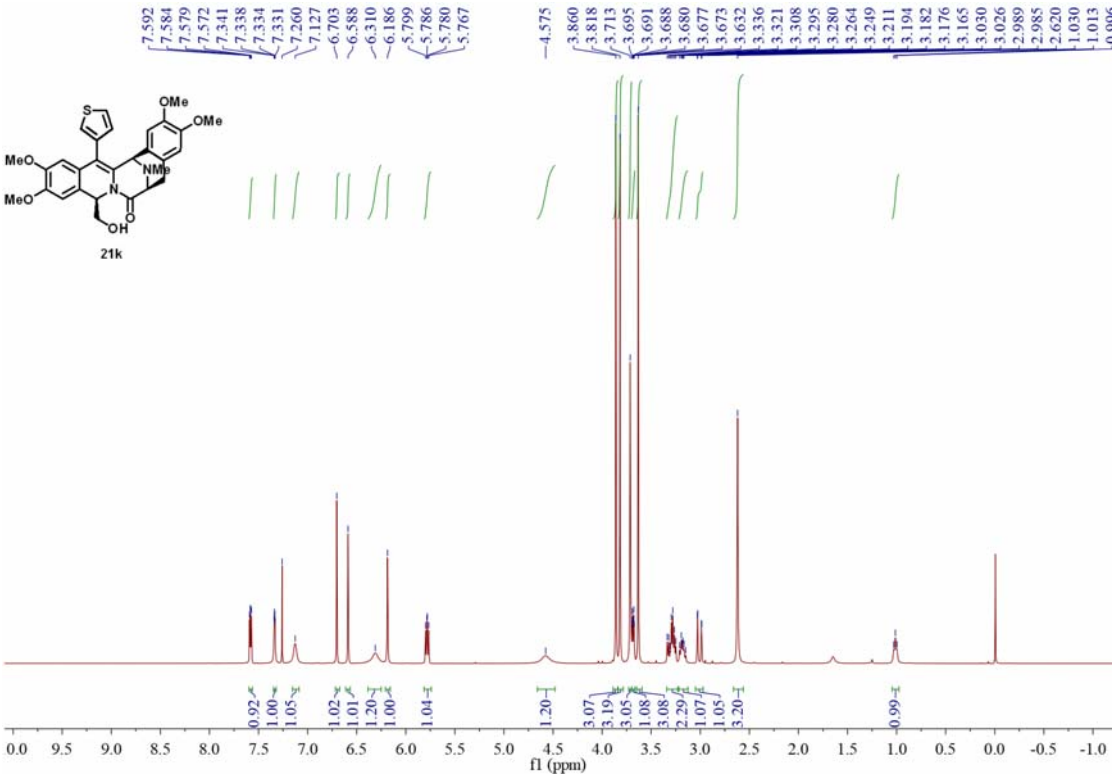
^{1}H NMR Spectrum of 21j (400 MHz, $CDCl_3$)



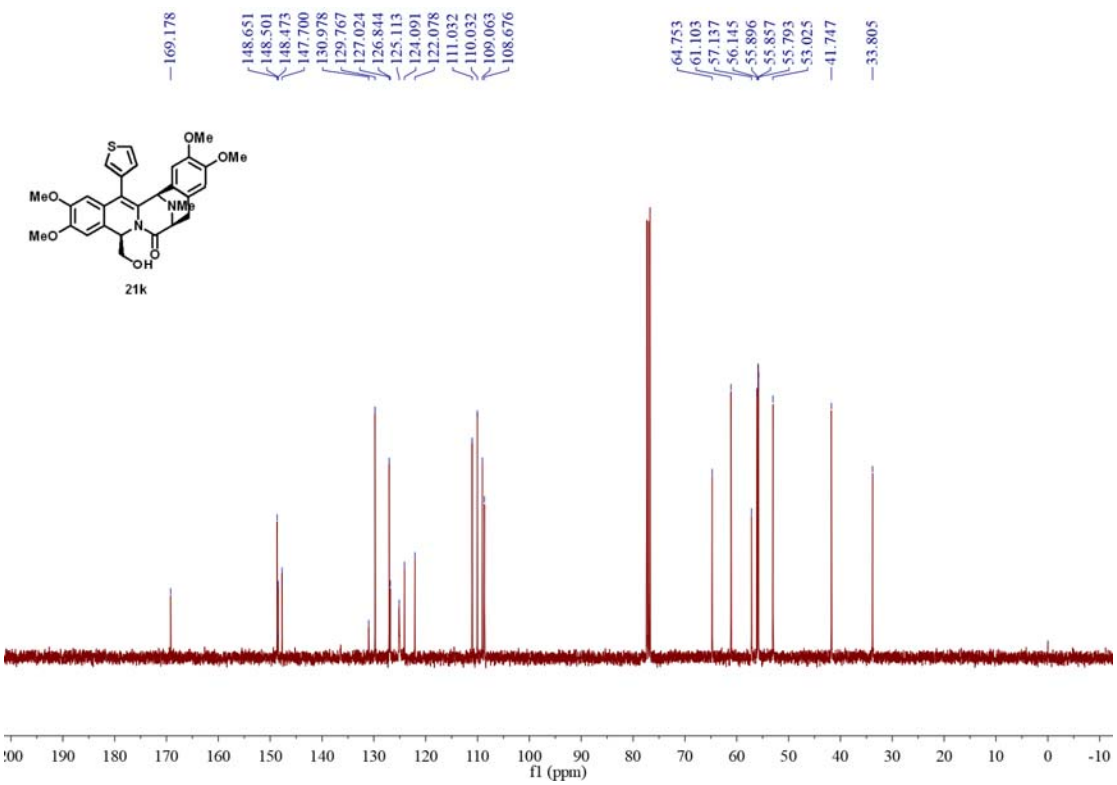
^{13}C NMR Spectrum of 21j (101 MHz, $CDCl_3$)



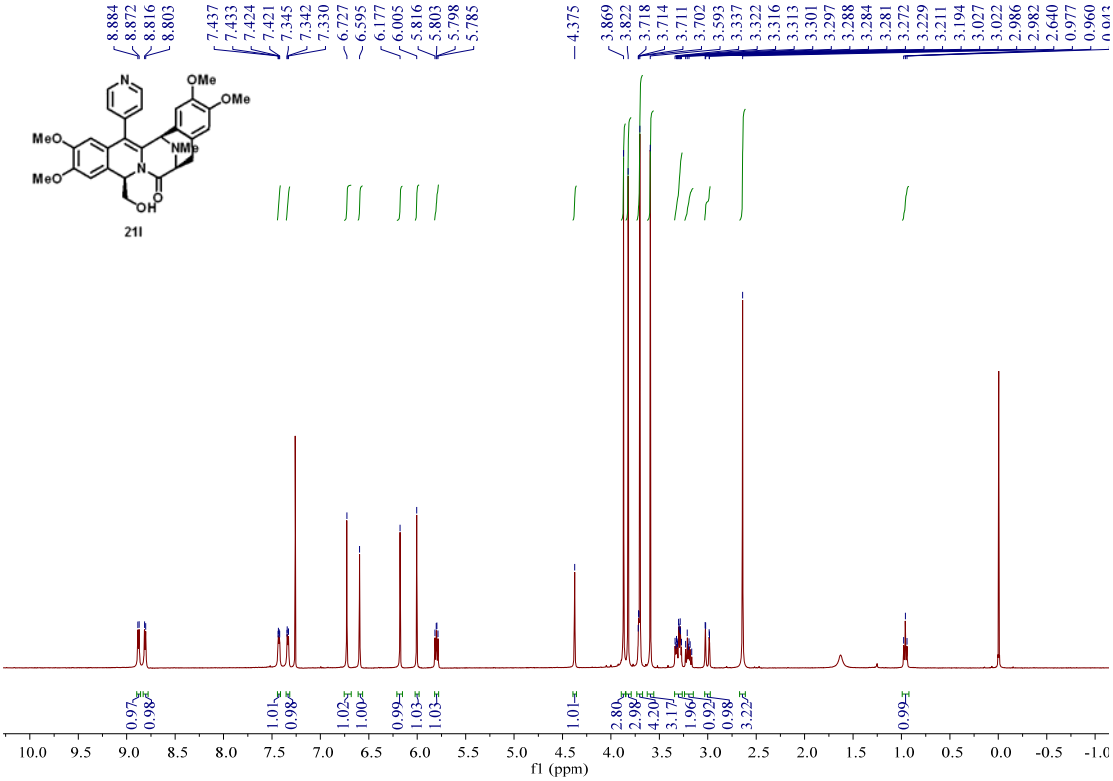
^{1}H NMR Spectrum of 21k (400 MHz, $CDCl_3$)



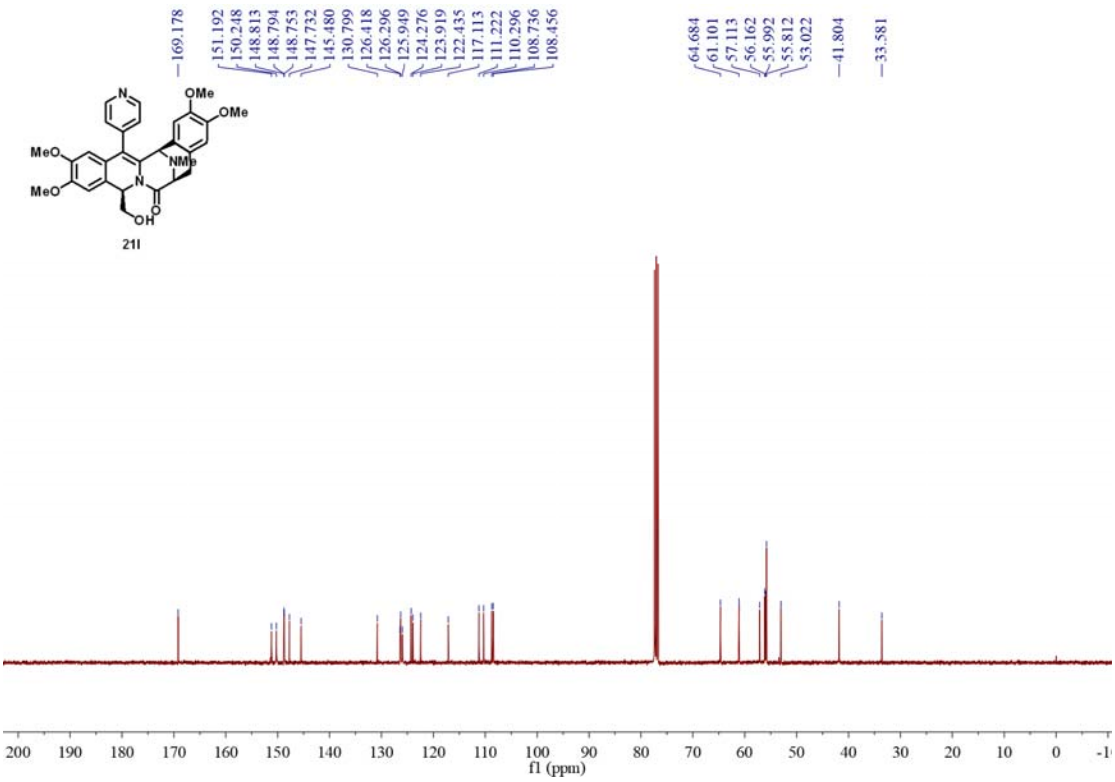
^{13}C NMR Spectrum of 21k (101 MHz, $CDCl_3$)



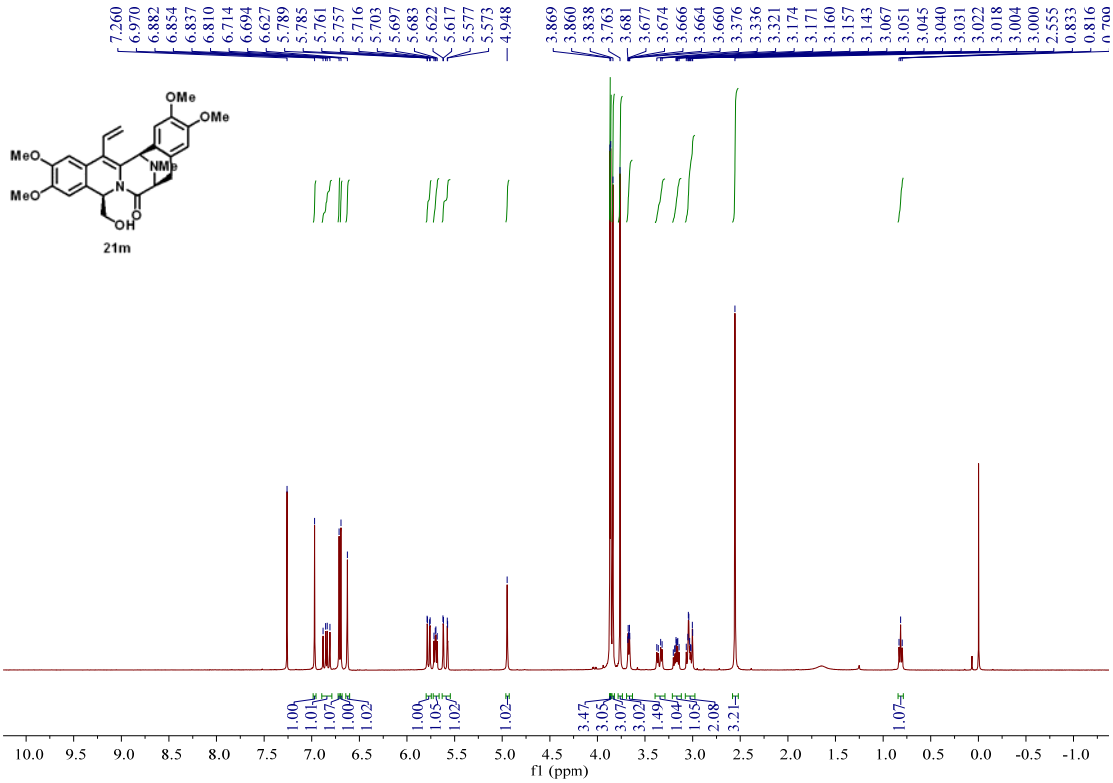
^{1}H NMR Spectrum of 21*l* (400 MHz, $CDCl_3$)



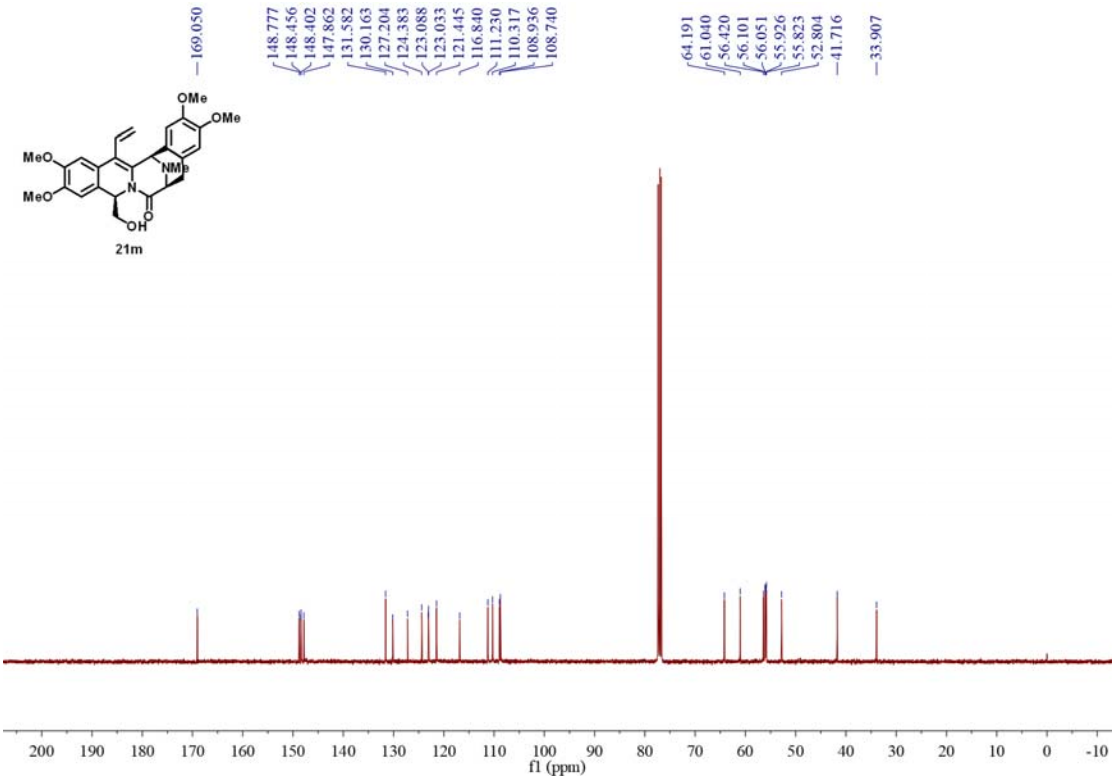
^{13}C NMR Spectrum of 21*l* (101 MHz, $CDCl_3$)



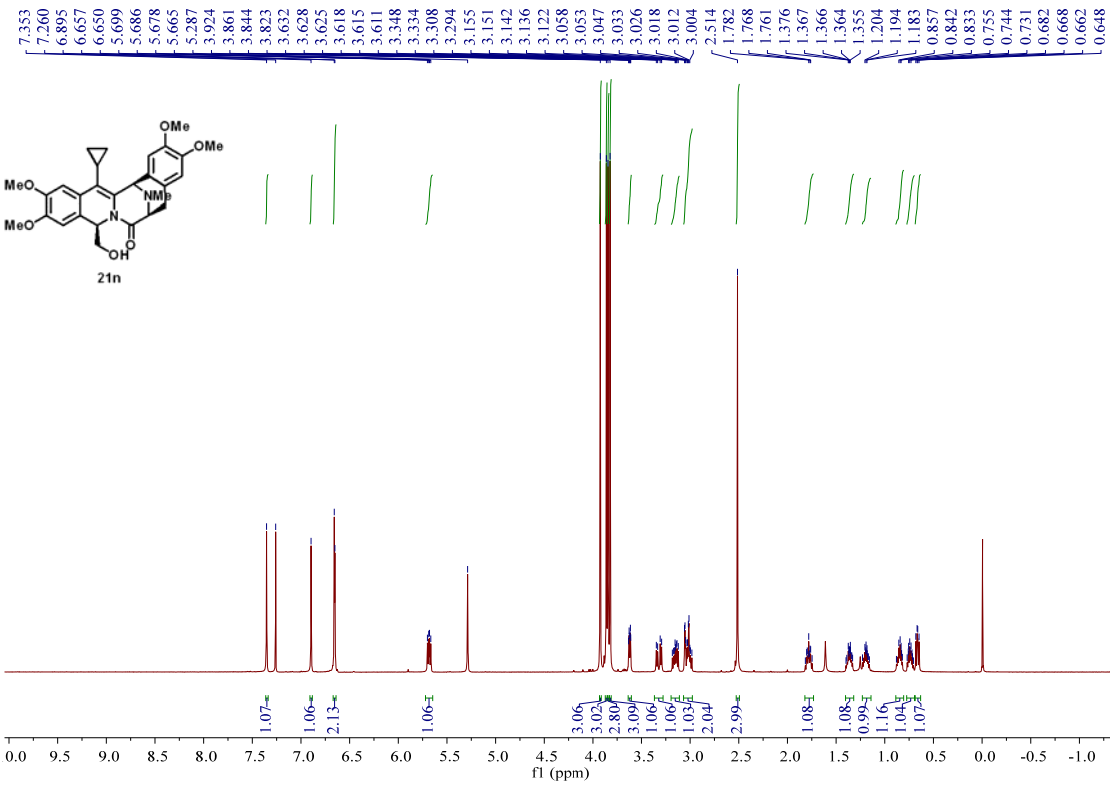
^{1}H NMR Spectrum of 21m (400 MHz, $CDCl_3$)



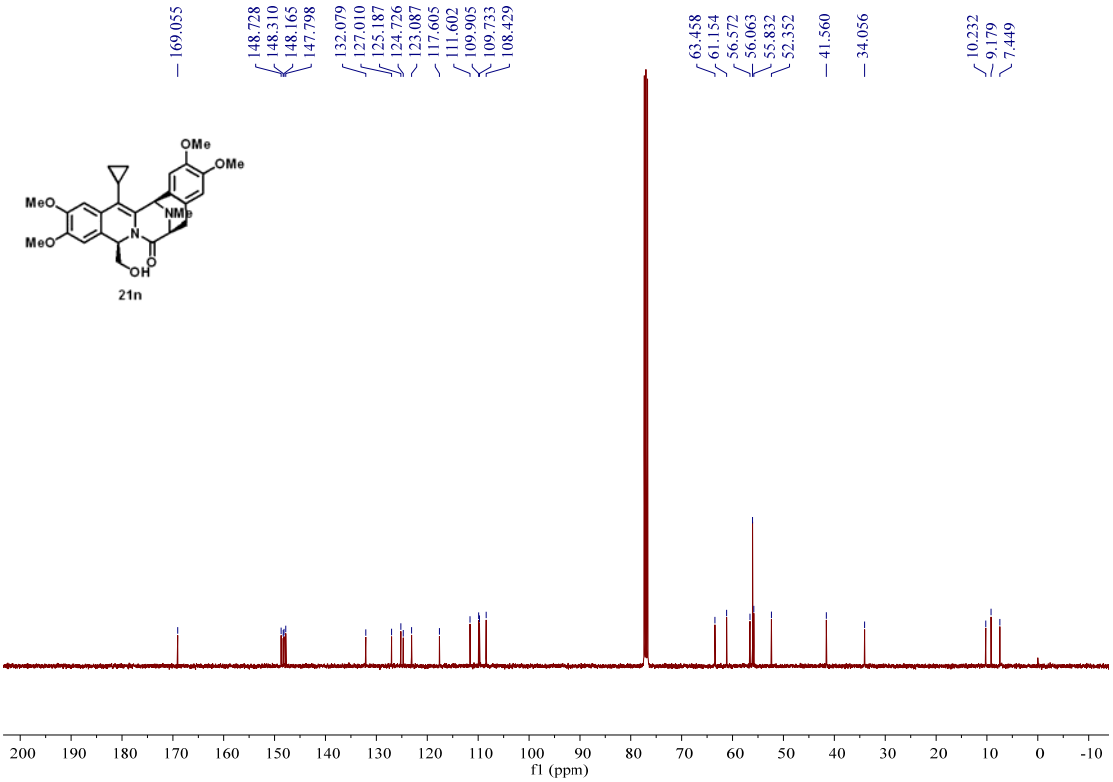
^{13}C NMR Spectrum of 21m (101 MHz, $CDCl_3$)



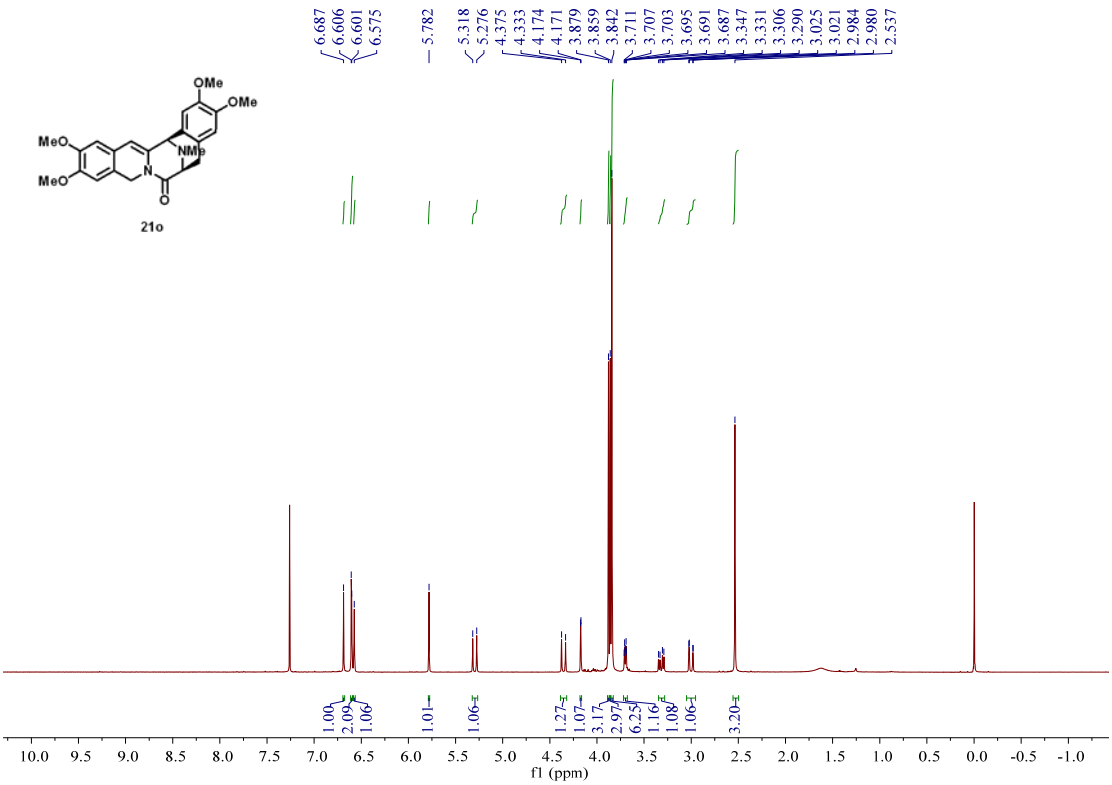
^{1}H NMR Spectrum of 21n (400 MHz, $CDCl_3$)



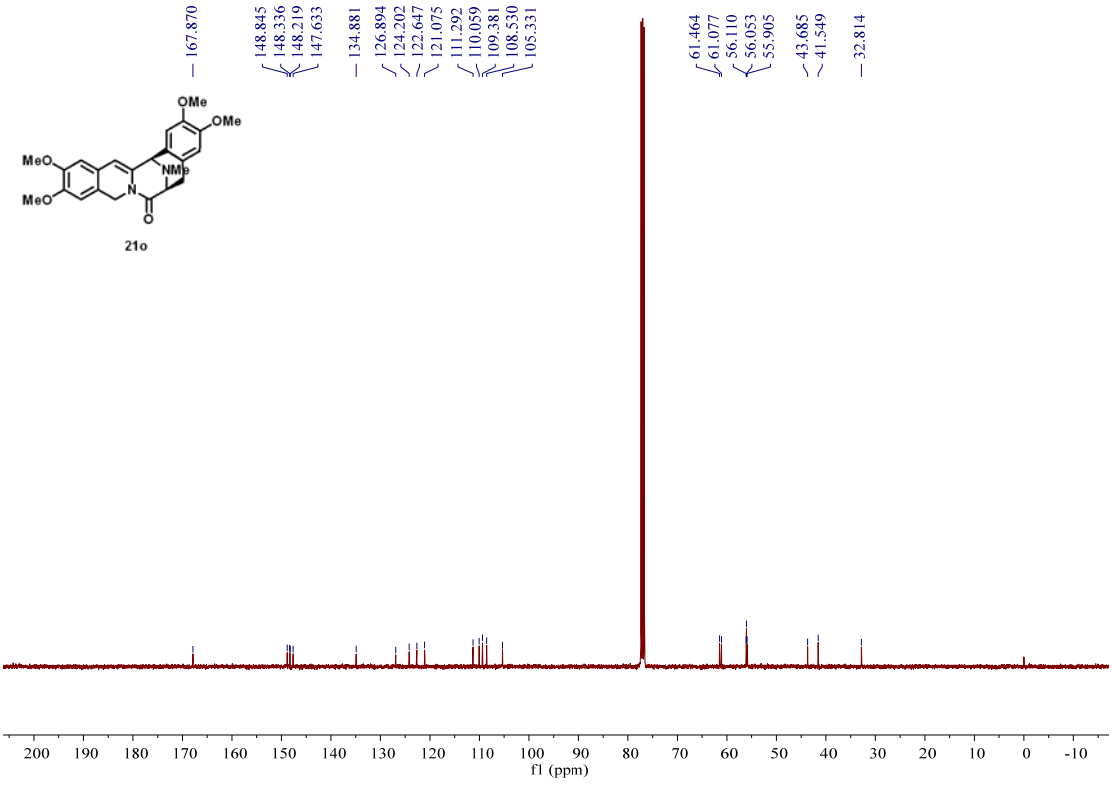
^{13}C NMR Spectrum of 21n (101 MHz, $CDCl_3$)



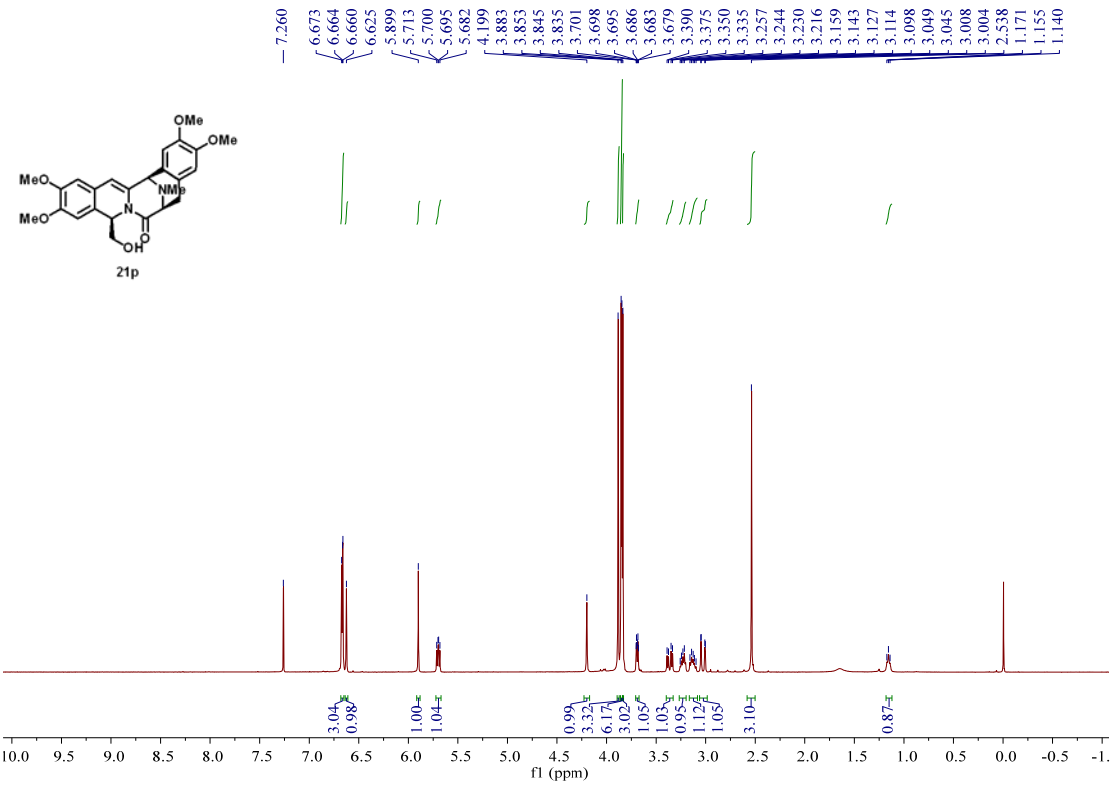
^{1}H NMR Spectrum of 21o (400 MHz, $CDCl_3$)



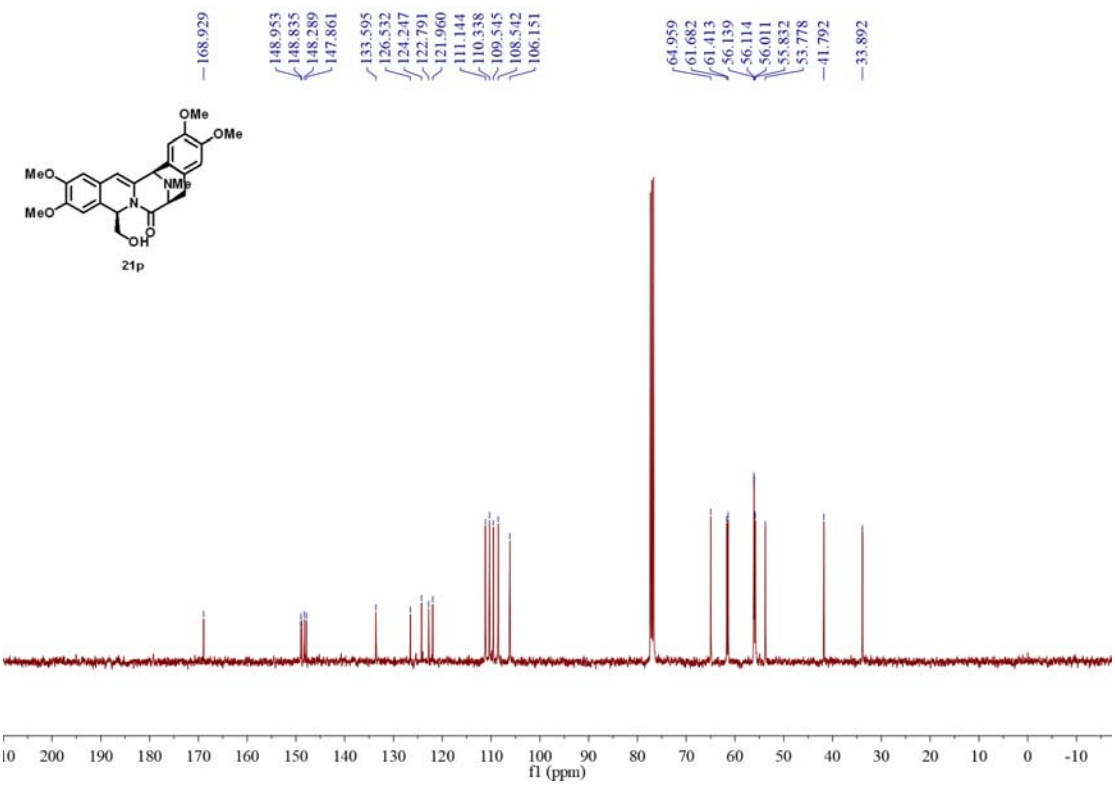
^{13}C NMR Spectrum of 21o (101 MHz, $CDCl_3$)



^{1}H NMR Spectrum of 21p (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of 21p (101 MHz, $CDCl_3$)



5. References

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