Supporting Information

Semisynthesis of Bersavine and Berbamine Derivatives that Target the CaMKIIγ:cMyc Axis for Lymphoma Therapy

Berkley Lujan,[a] Mingfeng Zhang,[†b] Yujie Cao,[†a] Arnav Kacker,[a] Lina Mai,[a] Shunqian Wu,[b] Taylor Alexander,[ac] Wendong Huang,*[b] and Kevin G. M. Kou*[a]

[a] Department of Chemistry, University of California, Riverside, California 92507, United States

[b] Department of Diabetes Complications & Metabolism Research, City of Hope National Medical Center, Duarte, California 91010, United States

[c] Kyowa Kirin, Inc., 9420 Athena Cir, La Jolla, CA 92037.

[†] Denotes equal contributions.

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1. General Information

i) Solvents and reagents

Commercial reagents were purchased from MilliporeSigma, Acros Organics, Chem-Impex, TCI, Oakwood, and Alfa Aesar, and used without additional purification. Solvents were purchased from Fisher Scientific, Acros Organics, Alfa Aesar, and MilliporeSigma., dichloromethane (CH_2Cl_2), and Ethanol (EtOH) were sparged with argon or nitrogen and dried by passing through alumina columns using argon in a Glass Contour (Pure Process Technology) solvent purification system. Dimethylformamide (DMF) was purchased in Sure/Seal or AcroSeal bottling and dispensed under N_2. Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc.

ii) Reaction setup, progress monitoring, and product purification

All reagents, including the solvent, were added outside the glovebox for the aminoalkylation reactions. As for the phenolic derivative reactions all the reagents and solvents were added inside the glovebox. Reaction progresses were monitored using thin-layer chromatography (TLC) on EMD Silica Gel 60 F254 or Macherey–Nagel SIL HD (60 Å mean pore size, 0.75 mL/g specific pore volume, 5–17 μm particle size, with fluorescent indicator) silica gel plates. Visualization of the developed plates was performed under UV light (254 nm). Purification and isolation of products were performed via silica gel or basic alumina chromatography. Organic solutions were concentrated under reduced pressure on IKA® temperature-controlled rotary evaporator equipped with an ethylene glycol/water condenser.

iii) Analytical instrumentation

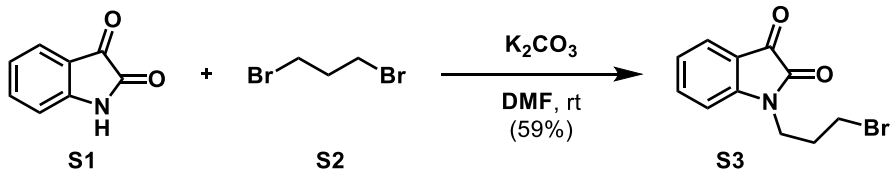
Melting points were measured with the MEL-TEMP melting point apparatus.

Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker Avance NEO 400 (not ^{1}H decoupled) or Bruker Avance 600 MHz spectrometers (^{1}H decoupled). Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR in $CDCl_3$).[1] Data for ^{1}H NMR spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublets of doublets), coupling constant (Hz), integration. Data for ^{13}C spectroscopy are reported in terms of chemical shift (δ ppm).

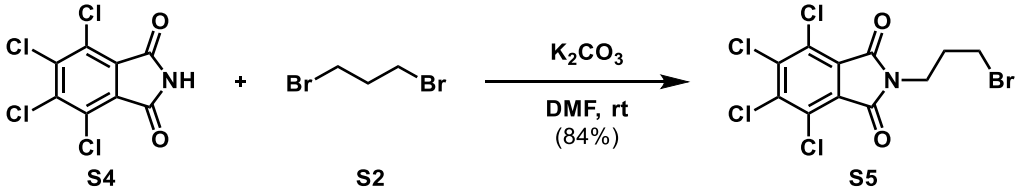
IR spectroscopic data were recorded on a NICOLET 6700 FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory. Samples are loaded onto the diamond surface either neat or as a solution in organic solvent and the data acquired after the solvent had evaporated.

High resolution accurate mass (ESI) spectral data were obtained from the Analytical Chemistry Instrumentation Facility at the University of California, Riverside, on an Agilent 6545 Q-TOF LC/MS instrument (supported by NSF grant CHE-1828782).

2. Synthesis of Alkylating Agents

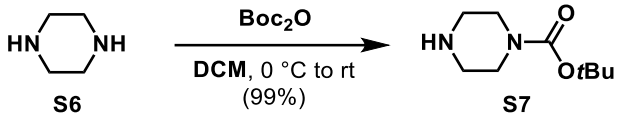


1-(3-Bromopropyl)indoline-2,3-dione (S3). A suspension of isatin (**S1**, 2.50 g, 17 mmol, 1 equiv), anhydrous K_2CO_3 (7.04 g, 51 mmol, 3 equiv) and 1,3-dibromoethane (**S2**, 5.2 mL, 51 mmol, 3 equiv) in DMF (57 mL) was stirred at rt for 24 h and then filtered to remove the solids. The filtrate was concentrated under reduced pressure. The residue was poured into H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (eluting with 0–40% EtOAc/hex) yielded the product (**S3)** as an orange solid (2.7 g, 59%). R_f = 0.41 (33% EtOAc/hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 3.88 (t, *J* = 7.0 Hz, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 2.27 (q, *J* = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.2, 158.4, 150.8, 138.6, 125.7, 124.0, 117.7, 110.2, 38.9, 30.4, 30.2. IR: 3057, 3022, 2956, 2927, 1730, 1610, 1597, 1467, 1454, 1365, 1352, 1295 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{11}H_{10}{}^{79}BrNO_2$: 267.9968; found: 267.9974; *m/z* $[M+2+H]^+$ calculated for $C_{11}H_{10}{}^{81}BrNO_2$: 269.9948; found: 269.9953. mp: 86.8–88.1 °C.

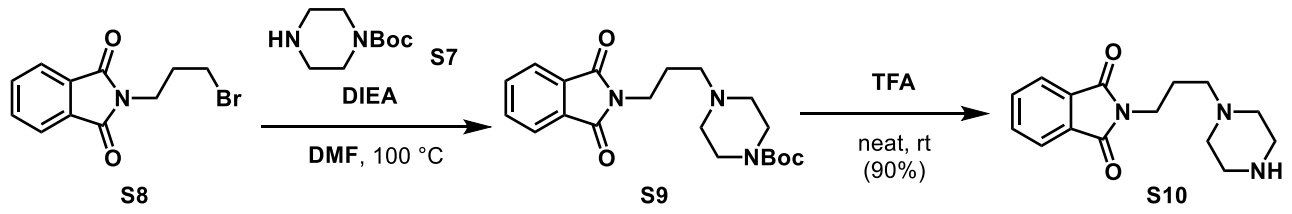


2-(3-Bromopropyl)-4,5,6,7-tetrachloroisoindoline-1,3-dione (S5). To a stirred solution of tetrachloroisoindoline-1,3-dione (1.00 g, 3.5 mmol, 1 equiv) in DMF (11.7 mL) were added 1,3-dibromopropane (**S2**, 1.1 mL, 10.5 mmol, 3 equiv), anhydrous K_2CO_3 (1.40 g, 10.5 mmol, 3 equiv) at rt. The reaction mixture was stirred at rt for 3 h. After completion of the reaction as indicated by TLC analysis, the resulting solution was poured into ice cold H_2O (60 mL), which was then extracted with

EtOAc (3 × 20 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford **S5** as a white solid (1.2 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.27 (q, *J* = 6.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 140.4, 129.9, 127.7, 37.7, 31.3, 29.6. IR: 2964, 2947, 2930, 2868, 1772, 1703, 1438, 1399, 1369, 1317, 1297, 1269 cm^{-1}. HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{11}H_6BrCl_4NO_2$: 405.8380; found: 405.8380. mp: 160.0–163.0 °C.



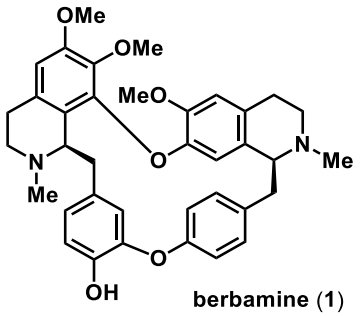
***tert*-Butyl piperazine-1-carboxylate (S7).** To a solution of piperazine (**S6**, 1.00 g, 11.6 mmol, 1 equiv) dissolved in CH_2Cl_2 (39 mL) at 0 ºC was added a solution of di-*tert*-butyl dicarbonate (1.27 g, 5.8 mmol, 0.5 equiv, dissolved in 6 mL of CH_2Cl_2) dropwise. The mixture was allowed to react overnight (18 h). The resulting white precipitate was removed by gravity filtration and washed with ice cold CH_2Cl_2 (40 mL). The filtrate was concentrated under reduced pressure. The residue obtained in this manner was suspended in dH_2O (100 mL), resulting in the formation of more white precipitate. The precipitate was again removed by gravity filtration and washed with dH_2O (100 mL). The collected dH_2O was saturated with K_2CO_3 and extracted with Et_2O (3 × 70 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield the title compound (**S7**) as a white solid (1.07 g, 99%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.40 (t, *J* = 5.2 Hz, 4H), 2.78 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.4, 81.3, 46.1, 44.8, 28.6. IR: 3322, 2976, 2869, 1683, 1540, 1474, 1455, 1416, 1391, 1364, 1285, 1235 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_9H_{18}N_2O_2$: 187.1441; found: 187.1453. mp: 46.4–48.3 °C.



2-(3-(Piperazin-1-yl)propyl)isoindoline-1,3-dione (S10). A round-bottomed flask charged with DMF (33 mL), *N*-bromopropylphthalimide (1.42 g, 5.3 mmol, 1 equiv), *tert*-butyl piperazine-1-carboxylate (**S7**, 0.98 g, 5.3 mmol), and DIEA (1.1 mL, 6.3 mmol, 1.2 equiv) was heated at 100 ºC for 24 h. The reaction

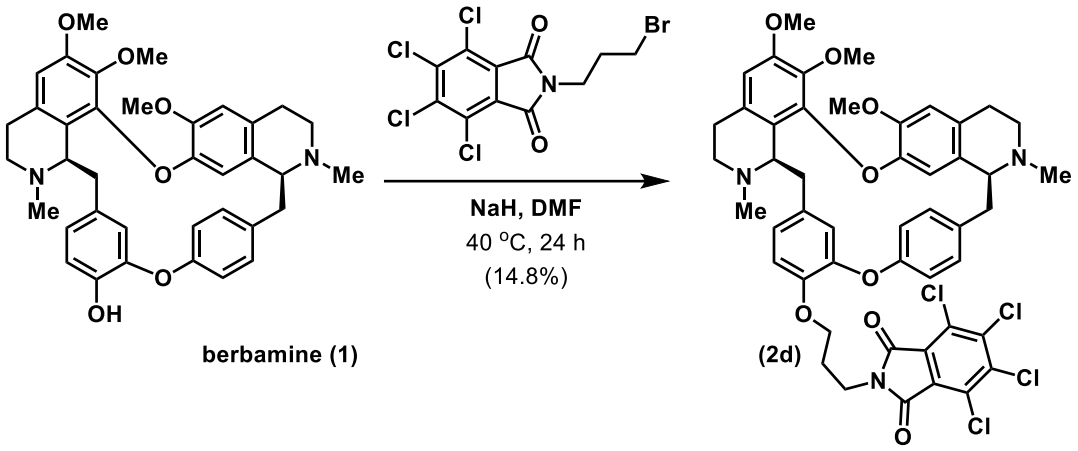
mixture was concentrated *in vacuo* to yield the **S9** as a white solid (1.96 g, quantitative yield), which was used directly in the next step without purification.

The crude *N*-Boc,*N'*-alkylpiperazine **S9** (2.0 g, ~5.3 mmol) was subjected to neat TFA (3.7 mL) for 5 min at rt. The TFA was removed*in vacuo*, and the resulting residue azeotropically distilled with MeOH (40 mL) to afford *N*-alkylpiperazine **S10** as a white solid (1.30 g, 90%).[1]H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.0 Hz, 1H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 1H), 3.79 (t, *J* = 6.7 Hz, 1H), 3.13 (s, 2H), 2.85 (s, 2H), 2.62 (t, *J* = 6.7 Hz, 1H), 1.91 (t, *J* = 6.7 Hz, 1H); [13]C NMR (101 MHz, $CDCl_3$) δ 168.6, 134.3, 132.3, 123.4, 55.6, 49.6, 43.3, 36.3, 24.8. IR: 3007, 2963, 2892, 2788, 2702, 2452, 1772, 1703, 1670, 1465, 1380, 1296 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{15}H_{19}N_3O_2$: 274.1550; found: 274.1575. mp: 186.0–187.1 °C.



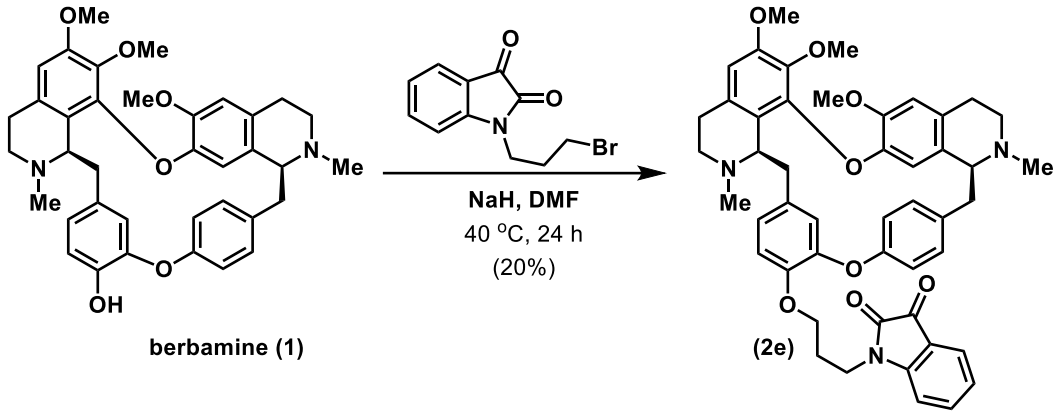
berbamine (**1**)

Berbamine (1). Berbamine hydrochloride (500 mg) was neutralized with a solution of sat. $NaHCO_{3(aq)}$ (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide neutral berbamine (**1**) as light brown solid (450 mg, 90%), which was directly used without further purification. [1]H NMR (400 MHz, CD_3OD) δ 7.37 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.11 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.77–6.69 (m, 2H), 6.68 (d, *J* = 7.1 Hz, 1H), 6.53 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.40 (s, 2H), 5.99 (s, 1H), 4.05–3.84 (m, 2H), 3.74 (s, 3H), 3.57 (s, 3H), 3.52–3.40 (m, 1H), 3.30–3.17 (m, 2H), 3.10 (s, 3H), 3.06–2.94 (m, 3H), 2.93–2.84 (m, 4H), 2.78–2.68 (m, 1H), 2.65 (dd, 1H), 2.56 (s, 3H), 2.54–2.47 (m, 1H), 2.18 (s, 3H); [13]C NMR (101 MHz, CD_3OD) δ 156.2, 153.5, 151.3, 149.5, 149.3, 145.9, 144.9, 138.3, 136.2, 135.3, 133.5, 131.4, 130.5, 129.9, 128.8, 124.8, 122.4, 122.3, 121.6, 121.1, 117.4, 116.5, 112.5, 106.9, 64.4, 63.5, 61.0, 56.3, 55.9, 46.0, 45.4, 43.2, 42.6, 38.6, 37.2, 26.1, 25.1. IR: 3047, 2929, 2866, 2852, 2796, 1713, 1604, 1504, 1467, 1410, 1356, 1315 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{37}H_{41}N_2O_6$: 609.2959; found: 609.2992. mp: 193.7–195.0 °C. All spectroscopic data are consistent with previously published literature.[1]

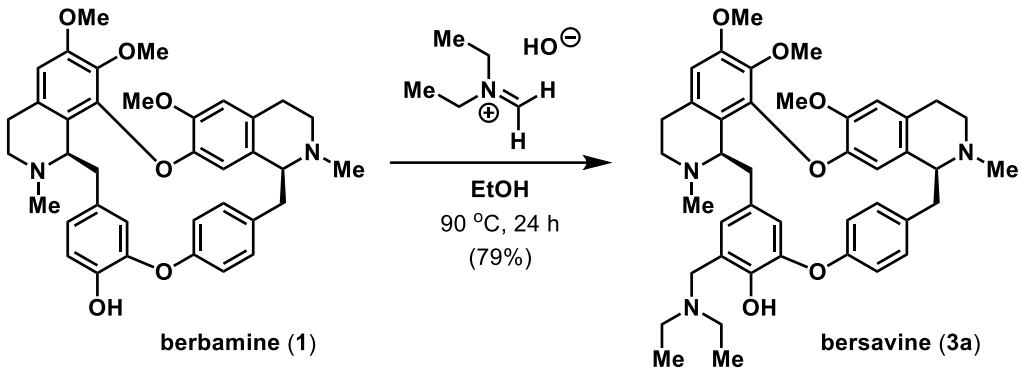


4,5,6,7-Tetrachloro-2-(3-(((1^{1}S,3^1*R*)-1^6,3^6,3^7-Trimethoxy-1^2,3^2-dimethyl-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphane-5^4-yl)oxy)propyl)isoindoline-1,3-dione (2d). In a dram vial, berbamine **(1)** (50.0 mg, 0.082 mmol, 1.0 equiv) was dissolved in DMF (1.5 mL, 0.052 M) and the solution cooled to 0^{o}C. NaH (washed with hexanes, 1.9 mg, 0.082 mmol, 1.0 equiv) was added and the resulting solution was stirred at 0 ^{o}C for 30 min. A solution of 3-(3-bromopropyl)-4,5,6,7-tetrachloroisoindoline-1,3-dione (33.0 mg, 0.082 mmol, 1.0 equiv) was dissolved in DMF (1.5 mL, 0.052 M) and added to the solution of berbamine at 0 ^{o}C. The reaction mixture was allowed to stir in an ice bath at 0 ^{o}C for 40 min. The ice bath was removed, and the reaction mixture heated at 40 ^{o}C for 24 h. The reaction was quenched H_2O (5mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography using basic alumina (eluting with 89:10:1 CH_2Cl_2/MeOH/NH_4OH) to afford **(2d)** a light yellow solid (11.3 mg, 14.8%). R_f = 0.76 (89:10:1CH_2Cl_2/MeOH/NH_4OH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (d, *J* = 8.2 Hz, 1H), 7.09 (dd, *J* = 15.1, 8.8 Hz, 1H), 6.76 (dd, *J* = 17.9, 8.3 Hz, 1H), 6.68 (s, 1H), 6.62 (t, *J* = 9.0 Hz, 2H), 6.46 (dd, *J* = 50.2, 2.7 Hz, 3H), 5.99 (s, 1H), 4.05–3.89 (m, 2H), 3.81 (t, *J* = 6.8 Hz, 2H), 3.73 (s, 4H), 3.66–3.59 (m, 2H), 3.57 (s, 4H), 3.55–3.51 (m, 1H), 3.49–3.40 (m, 1H), 3.29–3.22 (m, 1H), 3.11 (s, 3H), 3.08–2.95 (m, 2H), 2.94–2.84 (m, 2H), 2.76–2.63 (m, 3H), 2.57 (s, 2H), 2.48 (s, 3H), 2.19 (s, 1H), 2.15–2.09 (m, 2H), 2.07–1.99 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 165.6, 165.3, 164.5, 155.7, 153.5, 151.2, 150.7, 150.4, 144.9, 140.7, 138.3, 136.0, 135.8, 133.6, 131.7, 131.6, 130.5, 130.0, 129.9, 128.7, 127.4, 126.0, 124.9, 124.7, 122.1, 121.1, 118.7, 116.8, 112.5, 106.9, 71.6, 61.0, 56.3, 55.9, 54.8, 46.0, 43.3, 43.0, 42.6, 38.9, 37.2, 37.1, 32.3, 26.1. IR: 2929, 2867, 2836, 2791, 1774, 1716, 1592, 1502, 1445, 1431, 1397, 1354 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{48}H_{45}{}^{35}Cl_4N_3O_8$: 932.2034; found:

932.2068; *m/z* $[M+2+H]^+$ calculated for $C_{48}H_{45}{}^{35}Cl_3{}^{37}ClN_3O_8$: 934.2005; found: 934.2057. mp: decomposed at 260 °C.

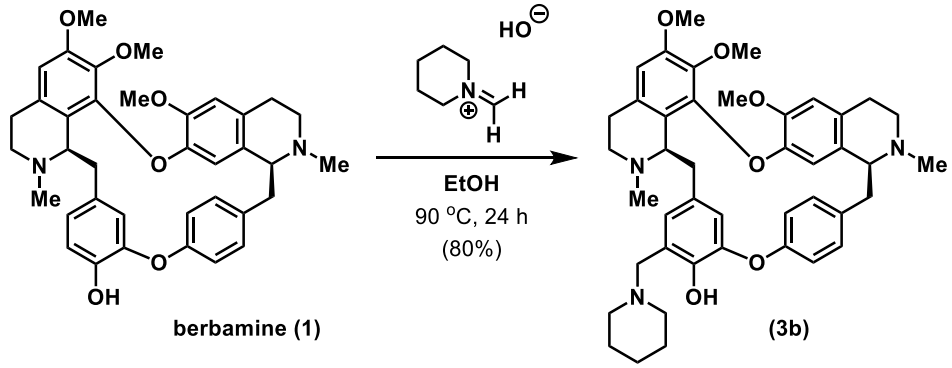


1-(3-(((1^{1}S,3^1*R*)-1^6,3^6,3^7-Trimethoxy-1^2,3^2-dimethyl-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphane-5^4-yl)oxy)propyl)indoline-2,3-dione (2e). In a dram vial, berbamine **(1)** (50.0 mg, 0.082 mmol, 1.0 equiv) was dissolved in DMF (1.5 mL, 0.052 M) and the solution cooled to 0°C. NaH (washed with hexanes, 1.9 mg, 0.082 mmol, 1.0 equiv) was added and the resulting solution was stirred at 0 °C for 30 min. A solution of N-(3-bromopropyl)phthalimide (22.0 mg, 0.082 mmol, 1.0 equiv) was dissolved in DMF (1.5 mL, 0.052 M) and added to the solution of berbamine at 0 °C. The reaction mixture was allowed to stir in an ice bath at 0 °C for 40 min. The ice bath was removed, and the reaction mixture heated at 40 °C for 24 h. The reaction was quenched H_2O (5mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography using basic alumina (eluting with 89:10:1 CH_2Cl_2/MeOH/NH_4OH) to afford **(2e)** an orange solid (13.3 mg, 20%). R_f = 0.66 (89:10:1 CH_2Cl_2/MeOH/NH_4OH).^{1}H NMR (400 MHz, CD_3OD) δ 7.41–7.26 (m, 2H), 7.12 (ddd, *J* = 12.8, 7.4, 2.6 Hz, 2H), 6.90–6.74 (m, 2H), 6.74–6.61 (m, 3H), 6.52 (dd, *J* = 8.3, 2.6 Hz, 2H), 6.40 (s, 2H), 6.11–5.95 (m, 1H), 4.21–4.08 (m, 1H), 4.02–3.86 (m, 3H), 3.73 (s, 3H), 3.63 (s, 2H), 3.56 (s, 2H), 3.53–3.37 (m, 2H), 3.29–3.17 (m, 3H), 3.10 (s, 3H), 3.07–2.95 (m, 3H), 2.96–2.83 (m, 5H), 2.68 (ddd, *J* = 34.1, 13.9, 7.9 Hz, 3H), 2.56 (d, *J* = 1.9 Hz, 5H); ^{13}C NMR (101 MHz, CD_3OD) δ 184.8, 174.5, 160.4, 156.3, 154.0, 152.4, 151.7, 151.3, 149.0, 148.4, 145.0, 143.6, 139.3, 138.5, 135.2, 133.6, 131.6, 129.5, 129.3, 126.8, 125.7, 124.6, 124.6, 122.4, 121.1, 119.5, 119.2, 117.5, 114.7, 112.5, 111.9, 110.5, 107.1, 71.4, 67.9, 67.5, 61.0, 56.4, 56.0, 42.9, 42.3, 38.6, 37.6, 30.8, 28.5, 28.2, 25.5. IR: 2928, 2848, 2795, 1736, 1608, 1583, 1504, 1448, 1411, 1355, 1314, 1264 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{48}H_{50}N_3O_8$: 796.3592; found: 796.3647. mp: 132.8–135.0 °C.



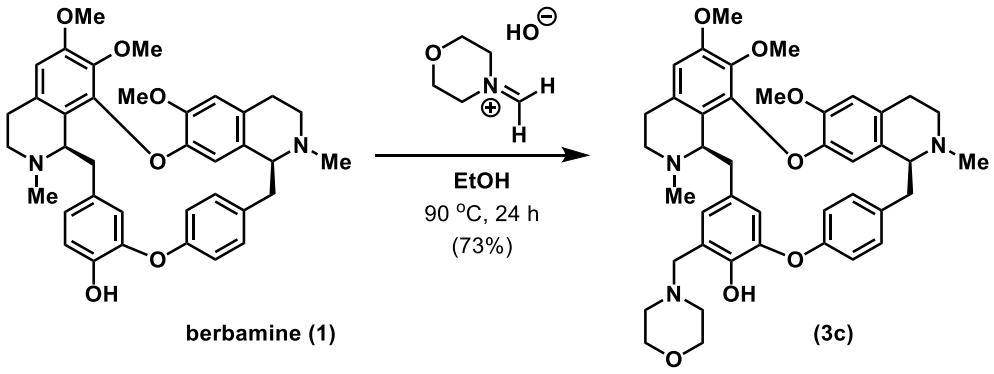
Preparation of a 1 M solution of the iminium ion: To a flame-dried round-bottomed flask under nitrogen was added paraformaldehyde (150 mg, 4.99 mmol, 1.05 equiv) and dissolved in anhydrous EtOH (5.0 mL, 1.0 M). Diethylamine (0.50 mL, 4.8 mmol, 1 equiv) was added via syringe and the reaction mixture was heated to 55 °C for 30 min.

Bersavine (3a). A solution of diethyliminium in anhydrous EtOH (1 M, 0.2 mL, 0.2 mmol, 1.2 equiv) was added to a solution of neutralized berbamine **(1)** (100 mg, 0.165 mmol, 1.0 equiv) dissolved in anhydrous EtOH (1.0 mL) and the reaction mixture was refluxed at 90 °C for 24 h. The reaction mixture was then cooled to rt, quenched with a solution of sat. $NaHCO_{3(aq)}$ (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography using basic alumina (eluting with 1.5:98.5 MeOH/CH_2Cl_2) afforded bersavine (**3a)** as a pale yellow solid (90.5 mg, 79%). R_f = 0.33 (1.5:98.5 MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 6.1 Hz, 1H), 6.66 (s, 1H), 6.57 (s, 1H), 6.52 (d, *J* = 5.9 Hz, 1H), 6.39 (s, 3H), 5.98 (s, 1H), 4.02–3.93 (m, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.84 (d, *J* = 5.2 Hz, 2H), 3.73 (s, 3H), 3.56 (s, 3H), 3.44 (s, 1H), 3.29–3.20 (m, 2H), 3.10 (s, 3H), 3.05–2.92 (m, 3H), 2.92–2.83 (m, 4H), 2.72 (q, *J* = 7.2 Hz, 4H), 2.63–2.57 (m, 1H), 2.55 (s, 3H), 2.48 (d, *J* = 16.6 Hz, 1H), 2.18 (s, 3H), 1.16 (t, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.2, 153.4, 151.3, 149.6, 149.3, 146.8, 144.9, 138.3, 136.2, 134.0, 133.4, 131.4, 130.4, 129.9, 128.8, 124.5, 123.1, 122.5, 122.3, 121.5, 121.1, 116.5, 112.4, 106.9, 64.3, 63.4, 61.0, 57.1, 56.3, 54.8, 47.6, 46.0, 45.2, 43.1, 42.6, 38.9, 37.1, 26.1, 24.7, 11.5. IR: 2959, 2930, 2834, 2795, 1595, 1581, 1504, 1462, 1408, 1355, 1312, 1240 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{42}H_{52}N_3O_6$: 694.3851; found: 694.3865. mp: 164.8–166.7 °C.



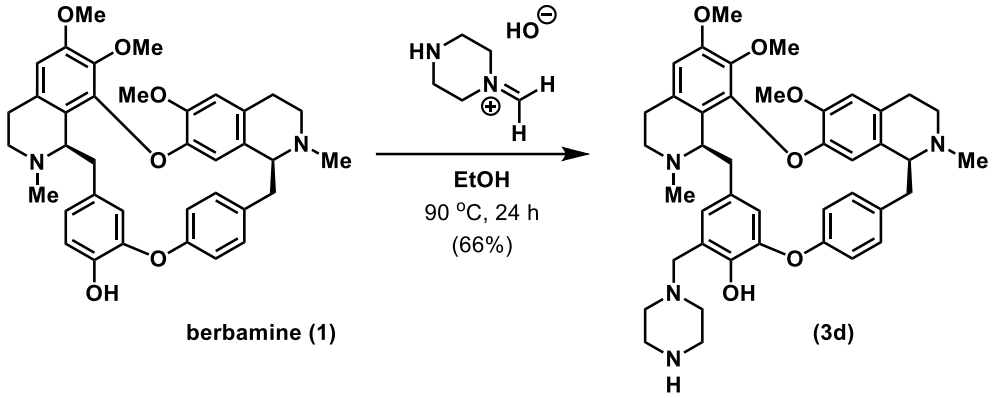
Preparation of a 1 M solution of the iminium ion: To a flame-dried round-bottomed flask under nitrogen was added paraformaldehyde (150 mg, 4.99 mmol, 1 equiv) and anhydrous EtOH (5.0 mL, 1.0 M). Piperidine (0.49 mL, 4.98 mmol, 1 equiv) was added via syringe and the reaction mixture was heated to 55 °C for 30 min.

(1^1S,3^1R)-1^6,3^6,3^7-Trimethoxy-1^2,3^2-dimethyl-5^5-(piperidin-1-ylmethyl)-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphan-5^4-ol (3b). A solution of the iminium in anhydrous EtOH (1 M, 0.2 mL, 0.2 mmol, 1.2 equiv) was added to a solution of neutralized berbamine **(1)** (100 mg, 0.165 mmol, 1.0 equiv) in anhydrous EtOH (1.0 mL, 0.165 M) and the reaction was refluxed at 90 °C for 24 h. The mixture was then cooled to rt, quenched with sat. $NaHCO_{3(aq)}$ (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography using basic alumina (eluting with 1.5:98.5 MeOH/CH_2Cl_2) to afford **(3b)** a beige solid (93 mg, 80%). R_f = 0.58 (1.5:98.5 MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.08 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.66 (s, 1H), 6.60–6.50 (m, 2H), 6.39 (s, 3H), 5.98 (s, 1H), 4.05–3.91 (m, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.73–3.65 (m, 6H) 3.56 (s, 3H), 3.50–3.38 (m, 1H), 3.25 (dd, *J* = 12.8, 6.8 Hz, 2H), 3.10 (s, 3H), 3.03–2.93 (m, 3H), 2.92–2.79 (m, 4H), 2.79–2.66 (m, 1H), 2.62–2.46 (m, 9H), 2.17 (s, 3H), 1.66 (t, *J* = 5.6 Hz, 4H), 1.57–1.49 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.1, 153.5, 151.3, 149.5, 149.3, 146.4, 145.0, 138.3, 136.2, 134.1, 133.5, 131.4, 130.4, 129.9, 128.8, 124.7, 122.9, 122.5, 122.3, 121.6, 121.1, 116.4, 112.5, 106.9, 64.4, 63.4, 62.2, 61.0, 56.3, 55.9, 54.8, 46.1, 45.4, 43.1, 42.6, 38.9, 37.2, 26.9, 26.2, 25.0. IR: 2928, 2832, 2794, 2164, 1603, 1580, 1503, 1444, 1406, 1353, 1307, 1264 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{43}H_{52}N_3O_6$: 706.3851; found: 706.3870. mp: 137.6–139.2 °C.



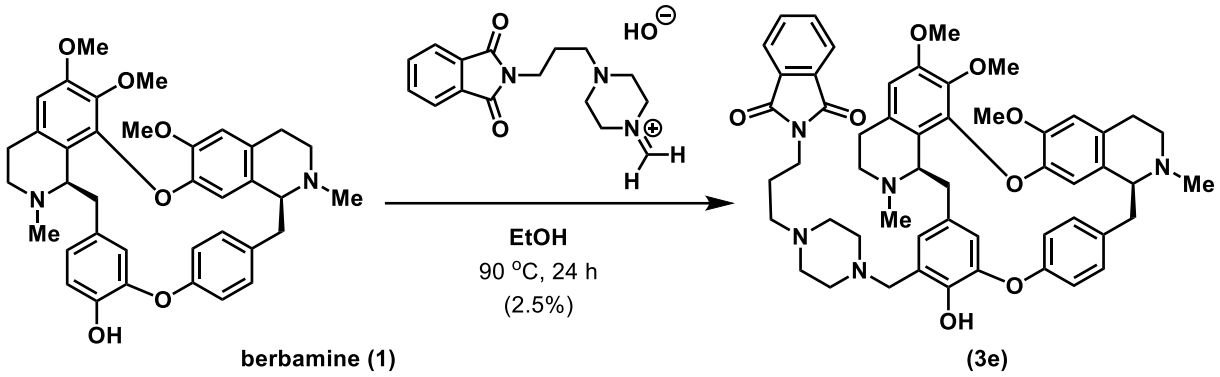
Preparation of a 1 M solution of the iminium ion: To a flame-dried round-bottomed flask under nitrogen was added paraformaldehyde (150 mg, 4.95 mmol, 1 equiv) and dissolved in anhydrous EtOH (5.0 mL, 1.0 M). Morpholine (0.43 mL, 4.95 mmol, 1 equiv) was added via syringe and the reaction mixture was heated to 55 °C for 30 min.

(1^1S,3^1R)-1^6,3^6,3^7-Trimethoxy-1^2,3^2-dimethyl-5^5-(morpholinomethyl)-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphan-5^4-ol (3c). A solution of the iminium in anhydrous EtOH (1 M, 0.2 mL, 0.2 mmol, 1.2 equiv) was added to a solution of neutralized berbamine **(1)** (100 mg, 0.165 mmol, 1.0 equiv) in anhydrous EtOH (1.0 mL, 0.165 M) and the reaction was refluxed at 90 °C for 24 h. The mixture was then cooled to rt, quenched with a solution of sat. $NaHCO_{3(aq)}$ (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography using basic alumina (eluting with 1.5:98.5 MeOH/CH_2Cl_2) to afford **(3c)** a white solid (85 mg, 73%). R_f = 0.46 (1.5:98.5 MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 2H), 6.53 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.39 (s, 3H), 5.98 (s, 1H), 3.98 (d, *J* = 9.3 Hz, 1H), 3.90 (d, *J* = 9.2 Hz, 1H), 3.73 (s, 6H), 3.67 (q, 2H), 3.55 (s, 3H), 3.48–3.39 (m, 1H), 3.28–3.20 (m, 2H), 3.10 (s, 3H), 3.05–2.92 (m, 3H), 2.92–2.79 (m, 4H), 2.71 (s, 1H), 2.65 (dd, *J* = 10.0, 5.3 Hz, 1H), 2.57–2.55 (m, 7H), 2.49 (d, *J* = 18.6 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.1, 153.5, 151.3, 149.5, 149.3, 145.6, 144.9, 138.3, 136.3, 134.5, 133.5, 131.5, 130.4, 129.9, 128.8, 125.2, 122.7, 122.5, 122.3, 121.5, 121.1, 116.6, 112.4, 106.9, 67.8, 64.3, 63.4, 61.2, 61.0, 56.3, 55.9, 54.1, 53.2, 50.8, 46.1, 45.4, 43.2, 42.6, 38.9, 37.2, 26.1, 24.8. IR: 2930, 2918, 2896, 2832, 2792, 2748, 2224, 2165, 1600, 1578, 1492, 1446 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{42}H_{50}N_3O_7$: 708.3643; found: 708.3667. mp: 156.5–158.5 °C.



Preparation of a 1 M solution of the iminium ion: To a flame-dried round-bottomed flask under nitrogen was added paraformaldehyde (149.5 mg, 4.98 mmol, 1 equiv) and dissolved in anhydrous EtOH (5.0 mL, 1.0 M). Piperazine (427.3 mg, 4.96 mmol, 1 equiv) was added via syringe and the reaction mixture was heated to 55 °C for 30 min.

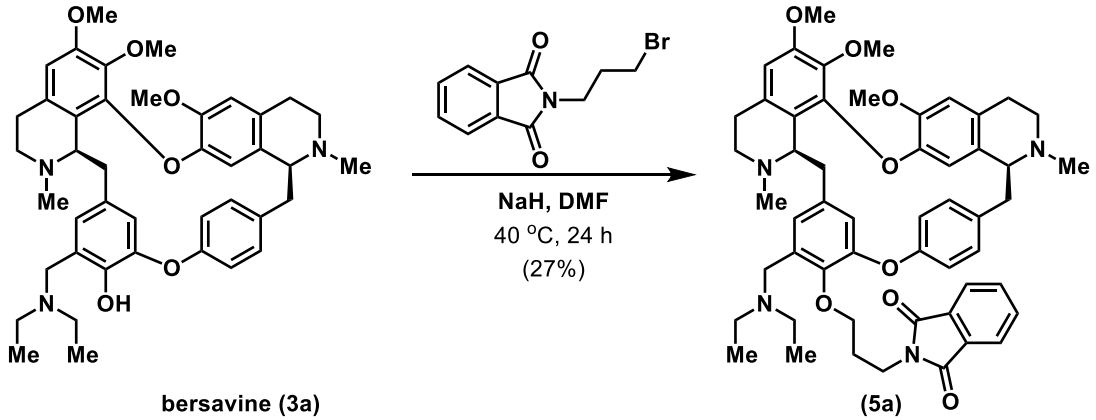
(1^1S,3^1*R*)-1^6,3^6,3^7-Trimethoxy-1^2,3^2-dimethyl-5^5-(piperazin-1-ylmethyl)-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphan-5^4-ol (3d). A solution of the iminium in anhydrous EtOH (1 M, 0.2 mL, 0.2 mmol, 1.2 equiv) was added to a solution of neutralized berbamine **(1)** (100 mg, 0.165 mmol, 1.0 equiv) in anhydrous EtOH (1.0 mL, 0.165 M) and the reaction was refluxed at 90 °C for 24 h. The mixture was then cooled to rt, quenched with a solution of sat. $NaHCO_{3(aq)}$ (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography using basic alumina (eluting with 1:1 MeOH/EtOAc) to afford **(3d)** a light-yellow oil (76.3 mg, 66%). R_f = 0.33 (1:1 MeOH/EtOAc). ^{1}H NMR (600 MHz, CD_3OD) δ 7.37 (d, *J* = 8.0 Hz, 1H), 7.16 (d, 1H), 6.67 (s, 1H), 6.62 (s, 1H), 6.53 (d, *J* = 6.2 Hz, 2H), 6.40 (s, 2H), 5.99 (s, 1H), 4.06–3.95 (m, 1H), 3.91 (d, *J* = 9.2 Hz, 1H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.74 (s, 3H), 3.72–3.70 (m, 1H), 3.67 (d, *J* = 13.9 Hz, 1H), 3.63 (d, *J* = 10.4 Hz, 2H), 3.28–2.25 (m, 3H), 3.17 (d, *J* = 20.8 Hz, 1H), 3.10 (s, 3H), 3.04–2.96 (m, 2H), 2.95–2.85 (m, 9H), 2.78 (s, 1H), 2.74 (s, 2H), 2.64–2.58 (m, 4H), 2.56 (s, 3H), 2.51 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 156.2, 153.5, 151.3, 149.4, 149.3, 145.7, 144.9, 138.3, 136.3, 136.2, 133.5, 131.4, 129.9, 128.7, 125.2, 125.0, 122.8, 122.4, 122.2, 121.5, 121.1, 116.6, 112.4, 106.9, 61.3, 61.0, 56.3, 55.9, 53.9, 53.5, 46.2, 46.0, 43.1, 42.6, 38.8, 26.1. IR: 2929, 2869, 2850, 1605, 1583, 1505, 1494, 1448, 1410, 1358, 1312, 1263 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{42}H_{51}N_4O_6$: 707.3804; found: 707.3834.



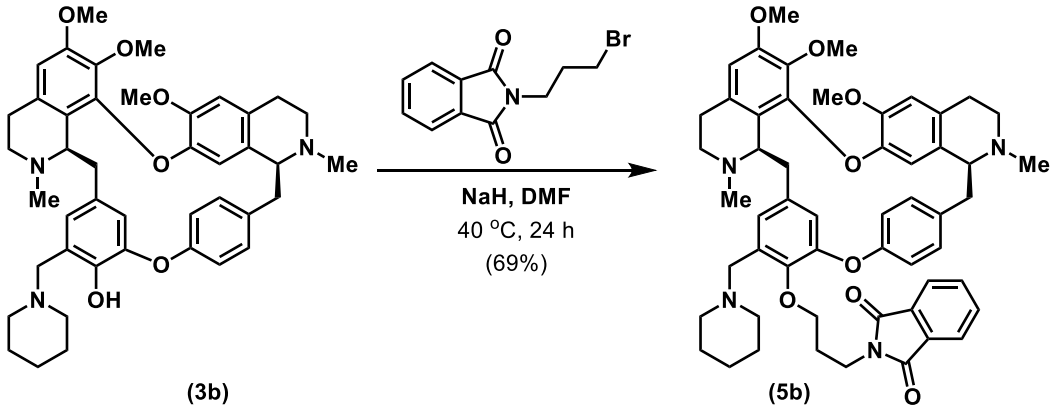
berbamine (1) (3e)

Preparation of a 1 M solution of the iminium ion: To a flame-dried round-bottomed flask under nitrogen was added paraformaldehyde (5.0 mg, 0.2 mmol, 1.05 equiv) and 2-(3-(piperazin-1-yl)propyl)isoindoline-1,3-dione **S10** (54.5 mg, 0.19 mmol, 1 equiv) and anhydrous EtOH (0.2 mL, 1.0 M). Then 0.1 mL of DMSO was added via syringe and the reaction mixture was heated to 55 °C for 30 min.

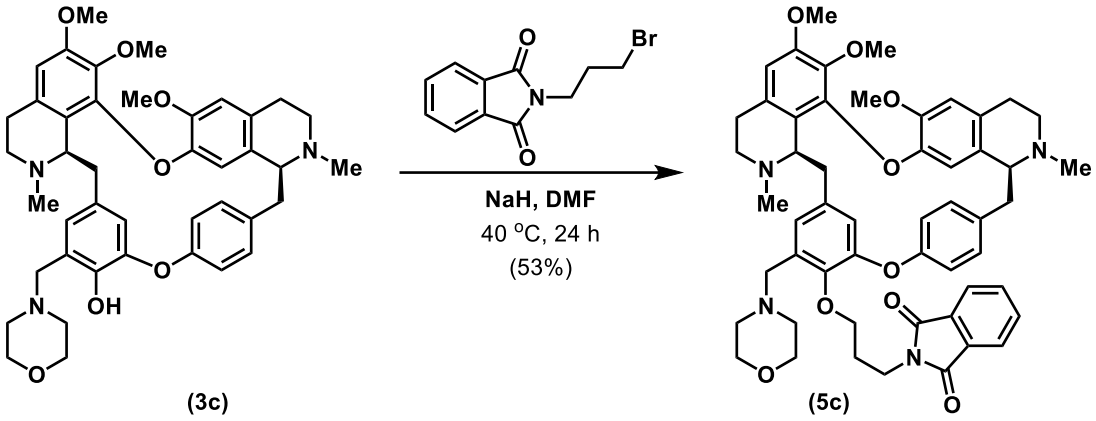
2-(3-(4-(((1^{1}S,3^{1}R)-5^4-Hydroxy-1^6,3^6,3^7-trimethoxy-1^2,3^2-dimethyl-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphane-5^5-yl)methyl)piperazin-1-yl)propyl)isoindoline-1,3-dione (3e). A solution of the iminium in anhydrous EtOH (1 M, 0.2 mL, 0.2 mmol, 1.2 equiv) was added to a solution of neutralized berbamine **(1)** (80.0 mg, 0.13 mmol, 1.0 equiv) in anhydrous EtOH (0.8 mL, 0.165 M), and the reaction mixture was refluxed at 90 °C for 24 h. The mixture was then cooled to rt, quenched with sat. $NaHCO_{3(aq)}$ (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography using basic alumina (eluting with 1:9 MeOH/CH_2Cl_2) to afford **(3e)** a beige solid (2.5 mg, 2.5%). R_f = 0.65 (1:9 MeOH/CH_2Cl_2). ^{1}H NMR (700 MHz, CD_3OD) δ 7.9–7.73 (m, 4H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.67 (s,1H), 6.56 (s, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 6.40 (s, 3H), 6.00 (s, 1H), 4.00 (s, 1H), 3.92 (d, *J* = 9.3 Hz, 1H), 3.76 (t, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 3.68–3.62 (m, 3H), 3.56 (d, *J* = 16.9 Hz, 3H), 3.50–3.44 (m, 1H), 3.35 (s, 3H), 3.27 (dd, *J* = 12.9, 6.5 Hz, 2H), 3.11 (s, 3H), 3.08–3.01 (m, 1H), 3.01–2.97 (m, 2H), 2.95–2.86 (m, 3H), 2.75 (s, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.52 (s, 3H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.22–2.18 (m, 3H), 2.06–2.03 (m, 2H), 1.88 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (176 MHz, CD_3OD) δ 210.1, 170.0, 153.6, 151.4, 149.8, 149.4, 145.0, 135.3, 133.6, 131.5, 130.9, 130.8, 129.9, 127.5, 125.0, 124.7, 124.1, 122.8, 121.2, 112.5, 71.6, 61.0, 60.7, 57.1, 56.3, 55.9, 54.0, 53.2, 49.8, 43.1, 42.6, 37.6, 36.5, 33.1, 33.1, 32.7, 30.8, 30.7, 30.4, 30.3, 30.2, 28.1, 26.9, 25.9, 23.7, 23.7, 23.7, 14.4. IR: 2973, 2926, 2888, 1653, 1452, 1418, 1380, 1328, 1273, 1087, 1045, 879 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{53}H_{60}N_5O_8$: 894.4436; found: 894.4464. mp: 110.0–112.2 °C.



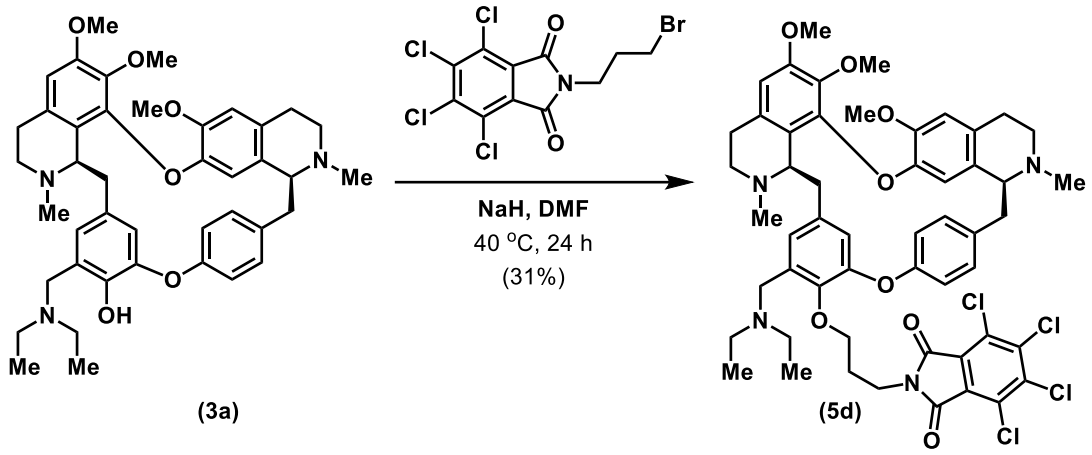
2-(3-(((1^{1}S,3^1*R*)-5^5-((Diethylamino)methyl)-1^6,3^6,3^7-trimethoxy-1^2,3^2-dimethyl-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphane-5^4-yl)oxy)propyl)isoindoline-1,3-dione (5a). In a dram vial, bersavine **(3a)** (90.5 mg, 0.13 mmol, 1.0 equiv) was dissolved in DMF (2.5 mL, 0.052 M) and the solution cooled to 0 °C. NaH (washed with hexanes, 3.1 mg, 0.13 mmol, 1.0 equiv) was added and the resulting solution was stirred at 0 °C for 30 min. A solution of *N*-(3-bromopropyl)phthalimide (35 mg, 0.13 mmol, 1.0 equiv) dissolved in DMF (2.5 mL, 0.052 M) was added to the bersavine solution at 0 °C. The reaction mixture was allowed to stir in an ice bath at 0 °C for 40 min. The ice bath was removed, and the reaction mixture heated at 40 °C for 24 h. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography using silica (eluting with 93:6:1 CH_2Cl_2/MeOH/NH_4OH) to afford **(5a)** a beige solid (31.2 mg, 27%). R_f = 0.48 (93:6:1 CH_2Cl_2/MeOH/NH_4OH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (s, 4H), 7.29 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.97 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.66 (s, 1H), 6.43–6.36 (m, 3H), 5.95 (s, 1H), 4.17–4.14 (m, 2H), 3.95 (d, *J* = 8.2 Hz, 1H), 3.88 (t, *J* = 6.9 Hz, 3H), 3.78 (d, *J* = 7.1 Hz, 1H), 3.73 (s, 3H), 3.55 (s, 3H), 3.50–3.38 (m, 1H), 3.23 (dd, *J* = 12.8, 6.9 Hz, 2H), 3.10 (s, 3H), 3.04–2.94 (m, 3H), 2.92–2.83 (m, 4H), 2.71 (m, 4H), 2.68–2.62 (m, 1H), 2.55 (s, 3H), 2.53–2.44 (m, 1H), 2.22–2.13 (m, 5H), 1.19–1.11 (m, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ 169.8, 155.7, 154.0, 153.5, 151.2, 149.2, 146.7, 144.9, 141.5, 139.7, 139.4, 138.3, 136.4, 136.2, 135.2, 133.5, 133.3, 131.5, 131.4, 130.9, 130.4, 129.9, 128.8, 126.9, 124.1, 122.1, 121.4, 121.1, 117.8, 113.7, 112.5, 107.0, 72.2, 64.3, 63.3, 61.0, 56.3, 55.9, 52.3, 47.9, 47.6, 46.0, 45.4, 43.1, 42.6, 38.9, 37.2, 36.3, 30.3, 26.1, 24.8, 11.4, 11.2. IR: 2931, 2836, 2792, 1770, 1710, 1607, 1581, 1504, 1492, 1465, 1445, 1408 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{53}H_{61}N_4O_8$: 881.4484; found: 881.4531. mp: 210.0–213.2 °C.



2-(3-(((1^{1}S,3^1*R*)-1^6,3^6,3^7-Trimethoxy-1^2,3^2-dimethyl-5^5-(piperidin-1-ylmethyl)-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphane-5^4-yl)oxy)propyl)isoindoline-1,3-dione (5b). In a dram vial, **(3b)** (40.0 mg, 0.056 mmol, 1.0 equiv) was dissolved in DMF (1.0 mL, 0.052 M) and the solution cooled to 0°C. NaH (washed with hexanes, 1.4 mg, 0.056 mmol, 1.0 equiv) was added and the resulting solution was stirred at 0 °C for 30 min. A solution of *N*-(3-bromopropyl)phthalimide (15.0 mg, 0.056 mmol, 1.0 equiv) was dissolved in DMF (1.0 mL, 0.052 M) and added to the **(3b)** solution at 0 °C. The reaction mixture was allowed to stir in an ice bath at 0 °C for 40 min. The ice bath was removed, and the reaction mixture heated at 40 °C for 24 h. The reaction was quenched H_2O (5mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography using silica (eluting with 89:10:1 CH_2Cl_2/MeOH/NH_4OH) to afford **(5b)** a light brown solid (34.4 mg, 69%). R_f = 0.54 (89:10:1 CH_2Cl_2/MeOH/NH_4OH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.75–7.72 (m, 4H), 7.31 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.99 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.85 (s, 1H), 6.66 (s, 1H), 6.48–6.37 (m, 3H), 6.35 (s, 1H), 5.97 (s, 1H), 4.15 (qt, *J* = 9.5, 6.2 Hz, 2H), 3.96 (s, 1H), 3.90 (t, *J* = 8.6, 4.5 Hz, 3H), 3.73 (s, 3H), 3.70 (m, 2H), 3.63 (s, 2H), 3.56 (s, 3H), 3.44 (s, 1H), 3.28–3.20 (m, 2H), 3.10 (s, 3H), 3.00 (t, *J* = 11.3 Hz, 2H), 2.94–2.82 (m, 4H), 2.67–2.58 (m, 5H), 2.56 (s, 3H), 2.18–2.17 (m, 4H), 1.62–1.61 (m, 4H), 1.51–1.41 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 169.8, 155.8, 154.0, 153.5, 151.3, 149.2, 146.9, 144.9, 139.3, 138.4, 136.4, 135.2, 133.5, 133.4, 131.6, 129.9, 128.7, 127.2, 124.1, 122.1, 121.4, 121.1, 118.0, 112.5, 107.0, 72.2, 71.5, 64.3, 63.3, 61.0, 57.9, 56.3, 55.9, 55.2, 54.8, 46.1, 45.2, 43.1, 42.6, 38.9, 37.2, 36.3, 30.8, 30.3, 26.7, 26.2, 24.8. IR: 2929, 2848, 2794, 2005, 1770, 1711, 1605, 1581, 1503, 1443, 1395, 1353 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{54}H_{61}N_4O_8$: 893.4484; found: 893.4531. mp: 106.1–106.9 °C.



2-(3-(((1^{1}S,3^1*R*)-1^6,3^6,3^7-Trimethoxy-1^2,3^2-dimethyl-5^5-(morpholinomethyl)-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphane-5^4-yl)oxy)propyl)isoindoline-1,3-dione (5c). In a dram vial, **(3c)** (89.0 mg, 0.126 mmol, 1.0 equiv) was dissolved in DMF (2.4 mL, 0.052 M) and the solution cooled to 0°C. NaH (washed with hexanes, 3.0 mg, 0.126 mmol, 1.0 equiv) was added and the resulting solution was stirred at 0 °C for 30 min. A solution of *N*-(3-bromopropyl)phthalimide (34.0 mg, 0.126 mmol, 1.0 equiv) was dissolved in DMF (2.4 mL, 0.052 M) and added to the **(3c)** solution at 0 °C. The reaction mixture was allowed to stir in an ice bath at 0 °C for 40 min. The ice bath was removed, and the reaction mixture heated at 40 °C for 24 h. The reaction was quenched H_2O (5mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography using basic alumina (eluting with 0.5:99.5 MeOH/CH_2Cl_2) to afford **(5c)** a light brown solid (59.2 mg, 53%). R_f = 0.5 (0.5:99.5 MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 7.78–7.74 (m, 4H), 7.33 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.84 (s, 1H), 6.67 (s, 1H), 6.43–6.33 (m, 4H), 5.97 (m, 1H), 4.21–4.10 (m, 2H), 4.00–3.96 (m, 1H), 3.90 (t, *J* = 6.9 Hz, 3H), 3.73 (s, 3H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.64–3.60 (m, 2H), 3.56 (s, 3H), 3.55–3.50 (m, 1H), 3.10 (s, 3H), 3.03–2.96 (m, 3H), 2.93–2.88 (m, 4H), 2.70–2.63 (m, 1H), 2.58 (s, 3H), 2.51 (s, 5H), 2.21–2.17 (m, 6H); ^{13}C NMR (151 MHz, CD_3OD) δ 169.8, 156.0, 154.2, 153.5, 151.5, 151.3, 144.9, 138.3, 135.2, 133.5, 133.4, 131.5, 129.8, 128.6, 127.0, 124.1, 122.1, 121.1, 117.6, 112.4, 107.0, 72.3, 71.6, 67.9, 61.0, 58.2, 56.3, 55.9, 54.7, 54.1, 43.2, 42.6, 38.8, 36.4, 35.7, 32.8, 30.3, 26.2, 26.0, 23.7, 14.4. IR: 2931, 2859, 2799, 2161, 2052, 1981, 1770, 1709, 1604, 1581, 1504, 1443 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{53}H_{59}N_4O_9$: 895.4277; found: 895.4312. mp: 165.5–167.2 °C.



4,5,6,7-Tetrachloro-2-(3-(((1^{1}S,3^1*R*)-5^5-((diethylamino)methyl)-1^6,3^6,3^7-trimethoxy-1^2,3^2-dimethyl-1^1,1^2,1^3,1^4,3^1,3^2,3^3,3^4-octahydro-2,6-dioxa-1(7,1),3(8,1)-diisoquinolina-5(1,3),7(1,4)-dibenzenacyclooctaphane-5^4-yl)oxy)propyl)isoindoline-1,3-dione (5d). In a dram vial, **(3a)** (125.9 mg, 0.181 mmol, 1.0 equiv) was dissolved in DMF (1.8 mL, 0.01 M) and the solution cooled to 0°C. NaH (washed with hexanes, 3.34 mg, 0.181 mmol, 1.0 equiv) was added and the resulting solution was stirred at 0 °C for 30 min. A solution 3-(3-bromopropyl)-4,5,6,7-tetrachloroisoindoline-1,3-dione (73.5 mg, 0.181 mmol, 1 equiv) was dissolved in DMF (0.5 mL, 0.36 M) and added to the **(3a)** solution at 0 °C. The reaction mixture was allowed to stir in an ice bath at 0 °C for 40 min. The ice bath was removed, and the reaction mixture heated at 40 °C for 24 h. The reaction was quenched H_2O (5mL) and extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography using basic alumina (eluting with 5:95 MeOH/CH_2Cl_2) to afford **(5d)** a light yellow solid (56.9 mg, 31%). R_f = 0.5 (5:95 MeOH/CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.5 Hz, 1H), 7.06 (s, 1H), 6.86 (d, *J* = 31.0 Hz, 1H), 6.50 (s, 1H), 6.44–6.30 (m, 2H), 6.26 (s, 2H), 5.89 (s, 1H), 4.17–3.97 (m, 1H), 3.98–3.89 (m, 1H), 3.87–3.77 (m, 2H), 3.74 (s, 3H), 3.71–3.67 (m, 1H), 3.58 (s, 3H), 3.56–3.48 (m, 2H), 3.38 (d, *J* = 30.9 Hz, 2H), 3.17 (s, 2H), 3.08 (s, 3H), 2.99–2.86 (m, 3H), 2.84–2.73 (m, 4H), 2.68–2.58 (m, 2H), 2.56 (s, 1H), 2.54 (s, 3H), 2.42 (s, 1H), 2.28 (t, 2H), 2.20 (s, 2H), 2.15–2.07 (m, 1H), 1.99 (s, 2H), 1.25 (s, 1H), 1.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 153.9, 152.6, 151.9, 150.0, 149.9, 149.1, 149.0, 148.4, 144.8, 143.6, 143.6, 139.7, 137.1, 132.4, 132.0, 130.3, 130.1, 129.4, 129.0, 127.7, 125.1, 121.4, 119.9, 115.2, 111.2, 105.6, 70.2, 63.8, 61.9, 60.6, 55.9, 55.6, 52.1, 51.9, 51.7, 47.1, 47.0, 46.9, 46.1, 43.0, 43.0, 42.0, 38.6, 36.3, 31.2, 29.8, 28.3, 25.8. IR: 2924, 2854, 1716, 1654, 1583, 1506, 1446, 1401, 1373, 1355, 1299, 1263 cm^{-1}. HRMS (ESI+): *m/z* $[M+H]^+$ calculated for $C_{53}H_{56}{}^{35}Cl_4N_4O_8$: 1017.2926;

found: 1017.2961; *m/z* $[M+2+H]^+$ calculated for $C_{53}H_{56}{}^{35}Cl_3{}^{37}ClN_4O_8$: 1019.2896; found: 1019.2952. mp: 166.3–198.7 °C.

3. Bioassays

a. Preparation of compound solutions

A stock solution of most compounds was prepared in 5% dimethyl sulfoxide (DMSO) in H_2O at a concentration of 20 mM and kept at –20 °C before use. For compound **5a**, a stock solution was prepared in 55% DMSO/H_2O at 30 mM concentration. Stock solutions were diluted to 150 μM concentrations with complete cell culture medium, and further diluted through 1:3 serial dilutions to obtain 7 doses.

b. Cell culture and cell viability

Human T cell lymphoma cells H9 were purchased from American Tissue Type Culture Collection (ATCC; HTB-176). Cells were cultured at a density between 10^5 and 2×10^6 cells/ml, in RPMI 1640 (Corning) supplemented with 10% Fetal Bovine Serum (FBS; Omega scientific), 1% glutamine, and 1% of penicillin-streptomycin (Corning) and maintained at 37 °C under 5% CO_2 in a humidified atmosphere.

To test the cell viability, cells were adjusted with the complete culture medium to obtain a final density of 1.4×10^5 cells/ml and 50 μl of cell suspension were seeded in each well of the 96-well culture plate (final $7x10^3$ cells in 50ul culture medium per well). The diluted compound solutions were directly added into each well to treat the cells with serial concentrations. H9 cells were incubated in the presence of compounds or solvent control (0.2% DMSO) for 24 h or 72 h at 37 °C in a humidified 5% CO_2 atmosphere.

The CellTiter-Glo Luminescent Cell Viability Assay (Promega, Cat# G7571) was used to perform the viability of H9 cells by following the manufacturer's instructions. Briefly, after 24 h and 72 h of incubation, cells were allowed to equilibrate at room temperature for approximately 30 min, and then added the CellTiter-Glo reagent. The plates were further incubated for additional 10 min at room temperature for the stabilization of the luminescent signal, then read the luminescence on Cytation 5. The cell viability (%) was calculated using the following formula:

Viability (%) = [RLU (treated cells)/ RLU (control cells)] × 100

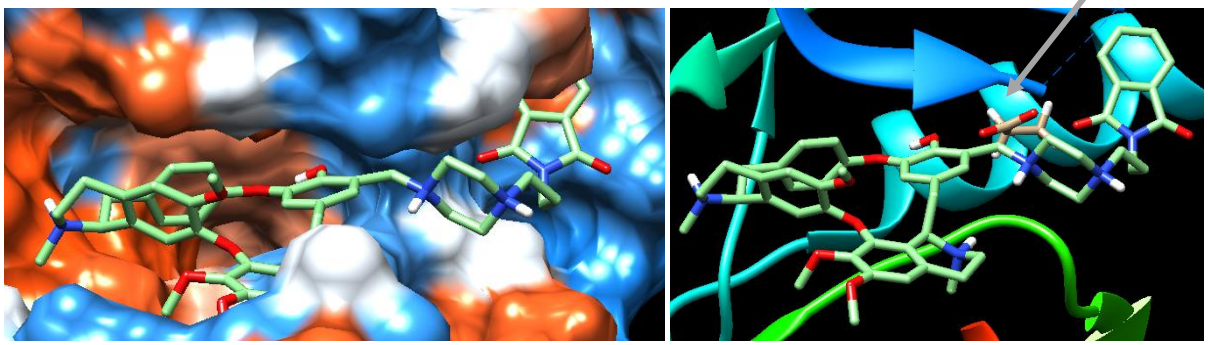
4. Computational Studies

i) Molecular Docking

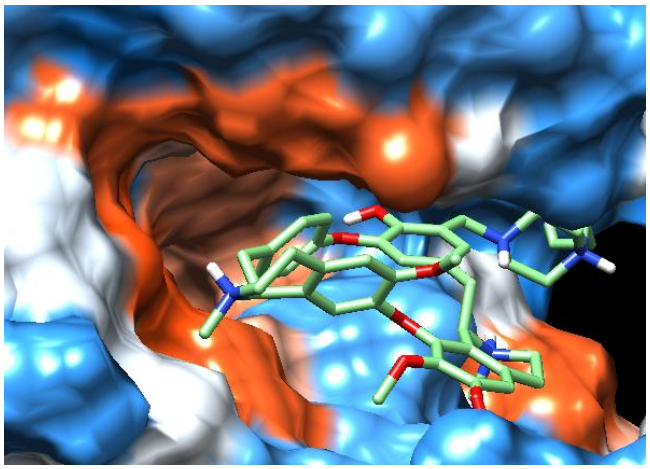
Docking studies were conducted on CaMKIIγ from PDB structure 2V7O[2] as the receptor using AutoDock Vina,[3,4] visualizing with UCSF Chimera 1.14.[5] The receptor was prepared by deleting the original ligand and water molecules, as well as a peripheral molecule of H_2O_2. The search volume was set as follows to consistently capture the ATP binding site for all docking analyses:

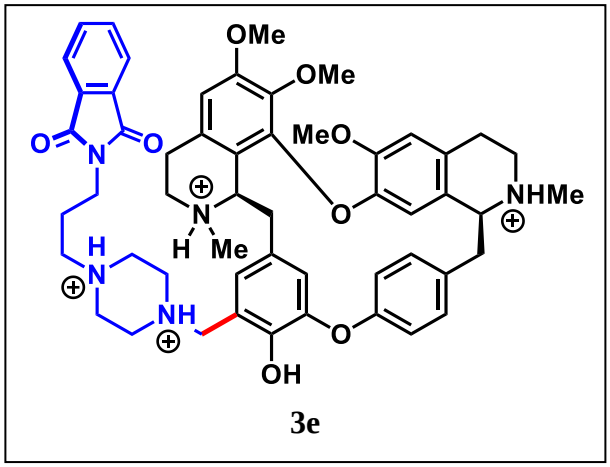
Center:	-17.9945	-29.8844	-5.05699
Size:	34.0661	22.4371	38.0551

For bersavine derivatives **3a–3e,** exemplified using **3e** below, the added tertiary amino group, when protonated, potentially forms an interaction with glutamate-61 at the edge of the hydrophilic pocket, reinforced by a hydrogen bonding interaction with the phenolic group. This interaction prevents the macrocyclic scaffolds from settling deep into the hydrophobic pocket, reducing their effectiveness as inhibitors.

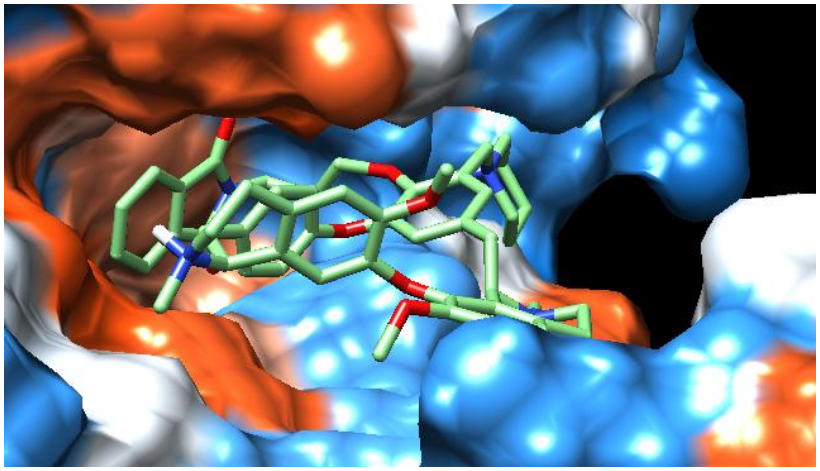


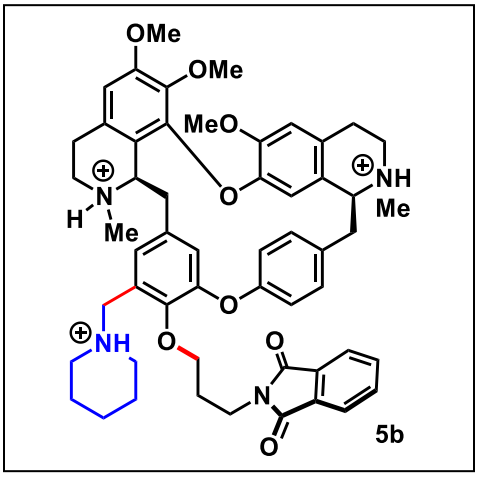
The top images represent the front view (analogous to the orientation in the manuscript) where the inhibitor spans the hydrophobic and hydrophilic pockets of the ATP-binding site. When viewed from the left (the image below), it is clear that the macrocycle does not extend deeply into the hydrophilic cavity:





This contrasts with compound **5b** (below) where the alkylphthalimide appendage extends deep into the hydrophobic cavity of the ATP-binding site:



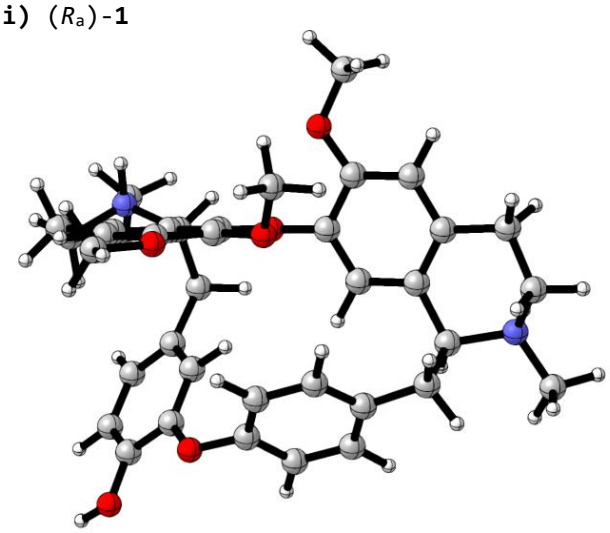


Of note, the protonated piperidinium in this pose is anchored to Glu-61 like that shown with compound **3e**.

ii) Density Functional Theory (DFT)

DFT calculations were performed using Gaussian16.[6] The computed structures were visualized using CYLview.[7] Structures were minimized using the B3LYP/6-31G(d) level of theory in the gas phase at 298.15 K. Frequency calculations were performed to verify the nature of the stationary points and obtain free energies.

i) (R_a)-**1**



B3LYP SCF Energy: -1995.51920791
B3LYP Free Energy: -1995.5192079

Cartesian coordinates

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C	2.03158000	1.72644500	-0.57588400
C	4.38853200	3.07225800	-1.13738200
C	4.02808400	1.94883700	-1.88969500
C	2.85335700	1.24608000	-1.60674600
C	2.39758300	0.04348300	-2.41192600
C	2.55085900	-1.38766400	-1.80511800
C	2.23374700	-1.52295100	-0.32659000
C	0.87605900	-1.50958900	0.07551000
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C	-1.39767900	-1.32402800	-0.82753600
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C	-5.70425200	-1.18316800	-0.65199000
C	-6.28539000	0.19913100	-0.38090500
N	-5.54738700	1.22860200	-1.21253000
C	-6.30057900	2.52574400	-1.31417500
C	-4.07720700	1.36518100	-0.76647700
C	-3.94568700	2.11889400	0.58777500
C	-2.50354700	2.52090400	0.83953200
C	-1.72227300	1.85543600	1.78967100
C	-0.36241700	2.14269200	1.92676100
C	0.22188200	3.09618000	1.09590900
C	-0.55310200	3.81708600	0.18256800
C	-1.90981600	3.53009700	0.06491300
C	-3.52993200	-2.43834900	-0.70181000
C	-2.13882100	-2.52410400	-0.76262600
O	-1.41893600	-3.66665900	-0.74580600
C	-2.11722100	-4.91640000	-0.75812700
C	0.52160200	-1.57282900	1.42662900
O	-0.79184100	-1.49830500	1.79746500
C	-1.32347100	-2.62060800	2.52987700
C	1.55194200	-1.61728200	2.40116100
O	1.13018500	-1.58526800	3.68497800
C	2.10277200	-1.62393800	4.73487300
C	2.88569800	-1.67413300	2.00625600
C	3.22889100	-1.62511500	0.65125600
C	4.69830800	-1.74653700	0.29081300
C	5.00146200	-1.39858400	-1.15847200
N	3.94035200	-2.01023700	-2.04992100
C	4.36321600	-2.05065100	-3.48979000
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H	5.30138900	3.61291700	-1.37672000
H	4.66521400	1.65212700	-2.72048700
H	1.31962300	0.12796900	-2.58108400
H	2.84534800	0.06214400	-3.41146100
H	1.88268000	-2.03819700	-2.37810500
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H	-6.07501800	-1.86178600	0.12445800
H	-6.10953800	-1.56760600	-1.59924200
H	-7.34266600	0.25605400	-0.64995800
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H	-4.30163800	1.48565900	1.40602200
H	-2.15832600	1.07397200	2.40439900
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H	-0.96615000	-2.61848600	3.56054000
H	2.77918500	-0.76408200	4.67511800
H	2.67795900	-2.55617900	4.70551900
H	1.53259400	-1.57586900	5.66237600
H	3.67347300	-1.73606700	2.74772000
H	5.04259600	-2.76947400	0.50178300
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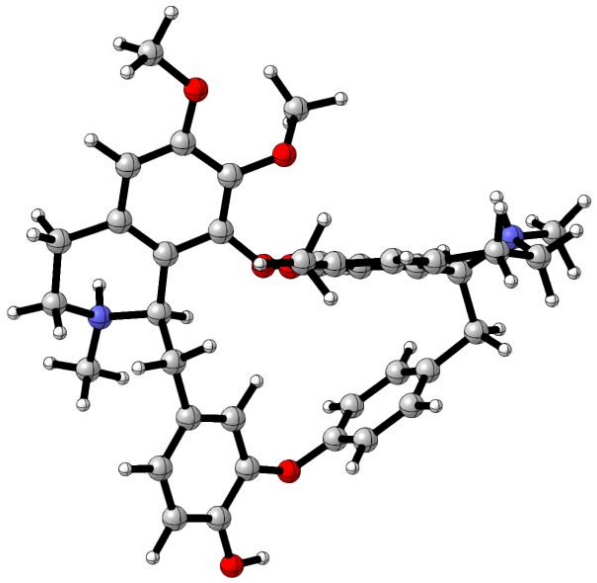
H	5.96789500	-1.79451700	-1.47992800
H	3.83707300	-2.98600500	-1.74839900
H	4.67371800	-1.05589600	-3.80537900
H	3.52811900	-2.39768500	-4.10041000
H	5.20403100	-2.74073500	-3.57923700

ii) (S_a)-**1**



B3LYP SCF Energy: -1995.52870716
B3LYP Free Energy: -1995.5287072

Cartesian coordinates

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C	0.84440300	3.01053000	0.12013300
C	2.10738500	5.15153800	1.38655400
C	2.64666200	3.86672300	1.46585900
C	2.03302700	2.78172500	0.82693800
C	2.60300300	1.37649800	0.89533700
C	2.87825700	0.70379400	-0.47476400
C	2.93376100	-0.81298300	-0.42975800
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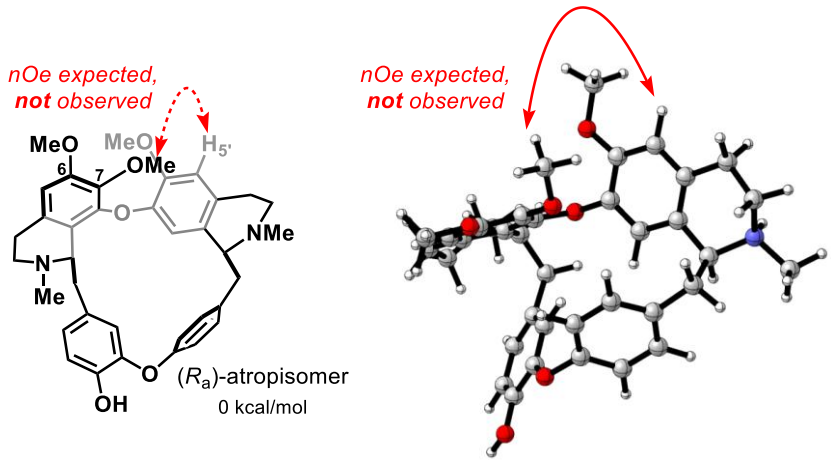
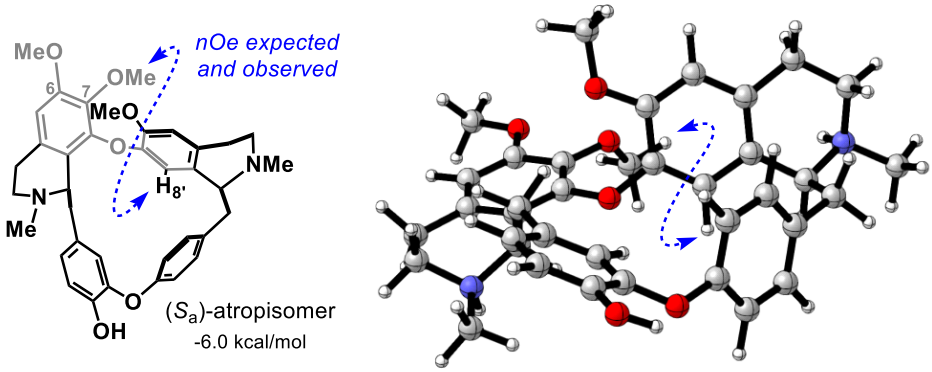
O	0.56854600	-0.74113800	-0.41747000
C	-0.64181500	-1.12183000	0.13862500
C	-1.78749100	-0.88048600	-0.59754400
C	-3.06005200	-1.19471100	-0.08458900
C	-3.15894200	-1.80681200	1.16857000
C	-4.46902700	-2.37850200	1.68360700
C	-5.69649800	-2.03571200	0.83648900
N	-5.34408900	-1.94568200	-0.63738100
C	-6.57071800	-1.84685300	-1.50052400
C	-4.28630000	-0.85213400	-0.90584500
C	-4.89941800	0.56377500	-0.68983800
C	-3.86470300	1.66977000	-0.69229900
C	-3.33444500	2.12359900	0.52326800
C	-2.34519200	3.09865000	0.55550400
C	-1.86815000	3.62467100	-0.64727500
C	-2.40972100	3.22399300	-1.86724700
C	-3.41120800	2.25068100	-1.88234600
C	-1.99719300	-2.00270100	1.93224500
C	-0.74134200	-1.62687700	1.45734500
O	0.41498200	-1.72091200	2.14587500
C	0.40223600	-2.33222500	3.44062500
C	1.68526300	-2.91888900	-0.40172000
O	0.48760800	-3.57504200	-0.35697000
C	0.14653300	-4.34692700	-1.52210000
C	2.91211900	-3.63009200	-0.37392900
O	2.79632100	-4.97405100	-0.31880500
C	3.98475000	-5.77045600	-0.27541400
C	4.11789700	-2.93244200	-0.41250100
C	4.13301500	-1.53251900	-0.45118600
C	5.47714700	-0.83846900	-0.58609900
C	5.40370000	0.67665300	-0.44072900
N	4.17300200	1.19383900	-1.15370200
C	4.24514100	2.67284800	-1.41798100
H	-0.40663100	6.59749700	0.08088200
H	0.31827100	2.18869900	-0.35651900
H	2.57995600	5.99194800	1.88429500
H	3.55335500	3.71348400	2.04715500
H	3.49939500	1.35322800	1.52484000
H	1.88950900	0.70813500	1.39043900
H	2.09114800	1.01210700	-1.16734600
H	-1.67997300	-0.44238500	-1.58487300
H	-4.67100000	-2.04312600	2.70762300
H	-4.37175700	-3.47075200	1.74583800
H	-6.47262300	-2.79887300	0.93058700
H	-6.13758200	-1.07632200	1.10560400
H	-4.87478200	-2.82584800	-0.87892900
H	-7.16381700	-0.98892600	-1.18625100
H	-6.26474800	-1.73331900	-2.54185400
H	-7.15356200	-2.76166000	-1.38038300
H	-4.05097200	-0.96276300	-1.96966300
H	-5.64045300	0.74791900	-1.47554300
H	-5.42743600	0.59797400	0.26766100
H	-3.69791600	1.70998500	1.46030100
H	-1.93703300	3.44474400	1.49928800
H	-2.04616900	3.67211100	-2.78620400
H	-3.83529700	1.94538600	-2.83635800
H	-2.08527700	-2.46189000	2.91075900
H	0.05347200	-3.36853400	3.37731800
H	-0.22441400	-1.76422700	4.13725800
H	1.43660800	-2.31431800	3.78301100
H	0.09416600	-3.70401400	-2.40914800
H	0.86563000	-5.15207500	-1.68503800
H	-0.83746000	-4.77169200	-1.31572900
H	4.58443800	-5.63505500	-1.18270200
H	3.64169900	-6.80305300	-0.21514500
H	4.58490600	-5.53111000	0.60951500
H	5.05933800	-3.46958500	-0.41519200
H	5.91885700	-1.08673300	-1.56157700
H	6.18243400	-1.21738600	0.16224400
H	5.32105400	0.99843400	0.59800400
H	6.27179500	1.16939500	-0.88430300
H	4.16413700	0.73481300	-2.07161700
H	5.08808200	2.85250700	-2.08802800
H	4.38605600	3.20242600	-0.47857700
H	3.31312500	2.99794100	-1.88023400

iii) Atropisomerism of the diarylether linkage

The (R_a)-atropisomer places the 7-methoxy group in proximity with $H_{5'}$. The consequential nOe interaction in the NOESY spectrum was not observed.[1]



The (S_a)-atropisomer places the 7-methoxy group in proximity with $H_{8'}$. The consequential nOe interaction in the NOESY spectrum was observed. The DFT calculations suggesting the (S_a)-atropisomeric linkage of bisBIAs in consistent with the reported experimental NOESY data.[1]



5. References

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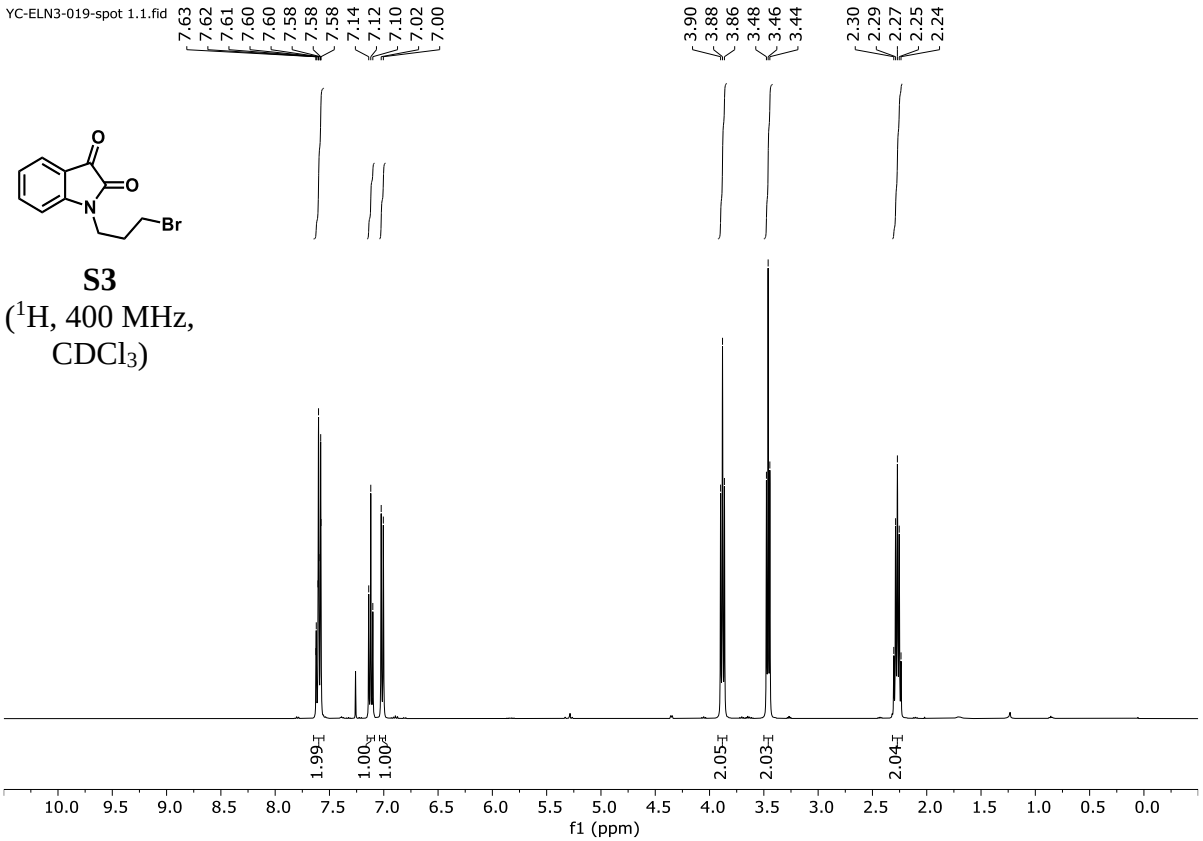
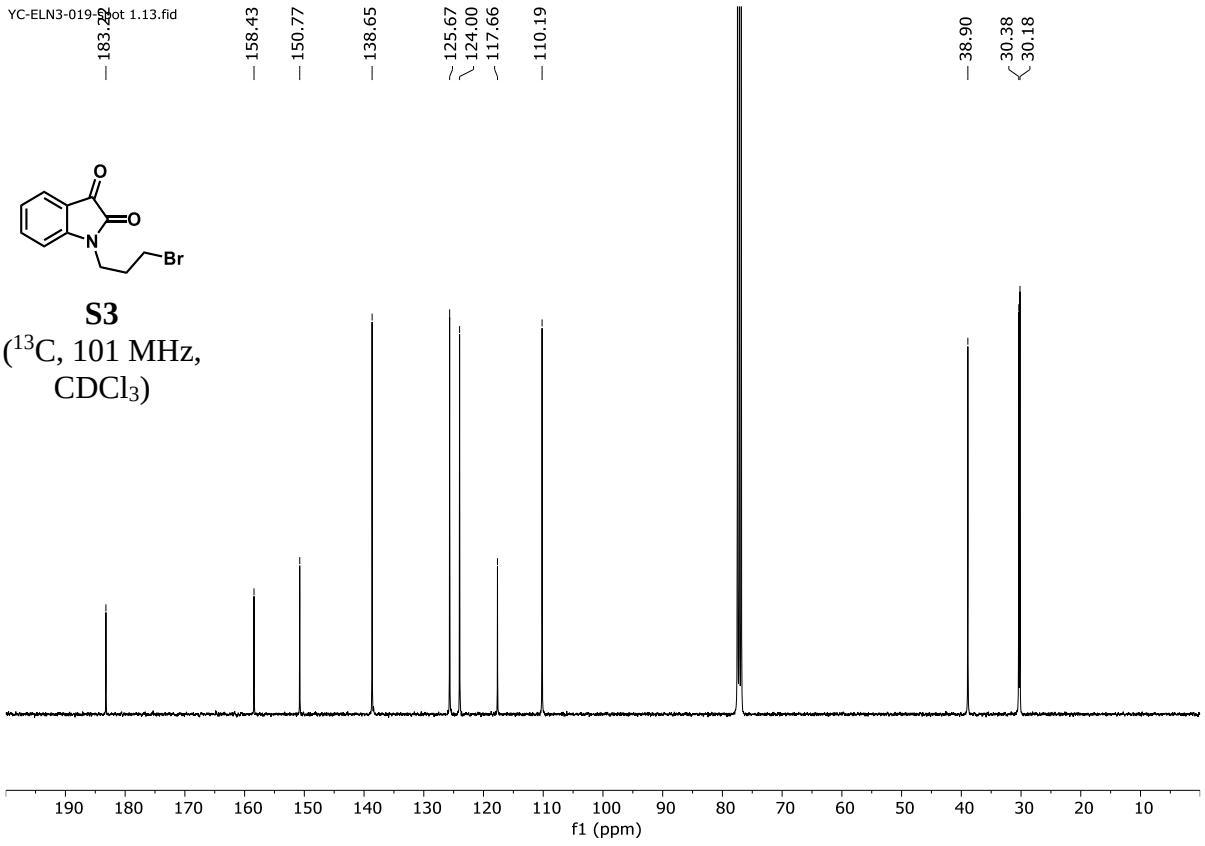
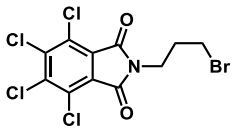
6. NMR Spectra



S3
(^{1}H, 400 MHz, $CDCl_3$)



S3
(^{13}C, 101 MHz, $CDCl_3$)



S5
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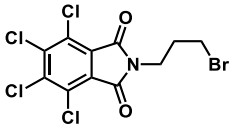
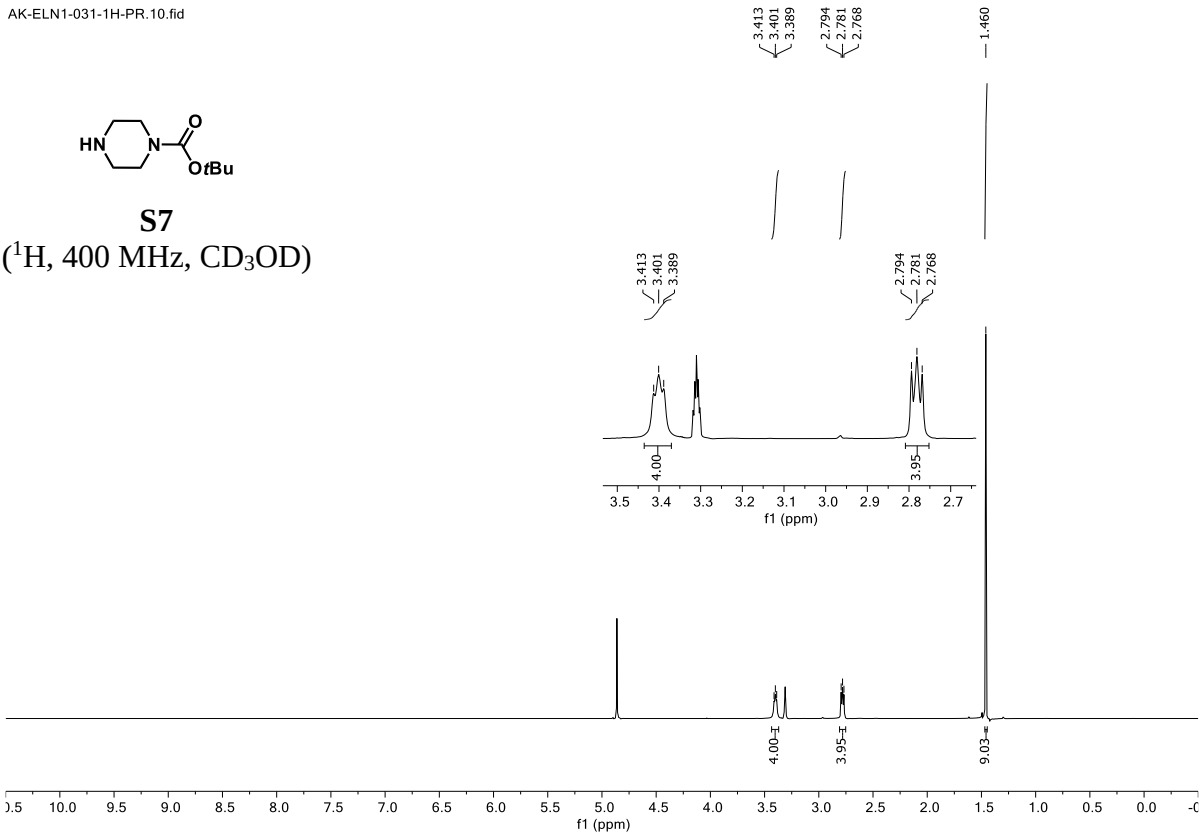
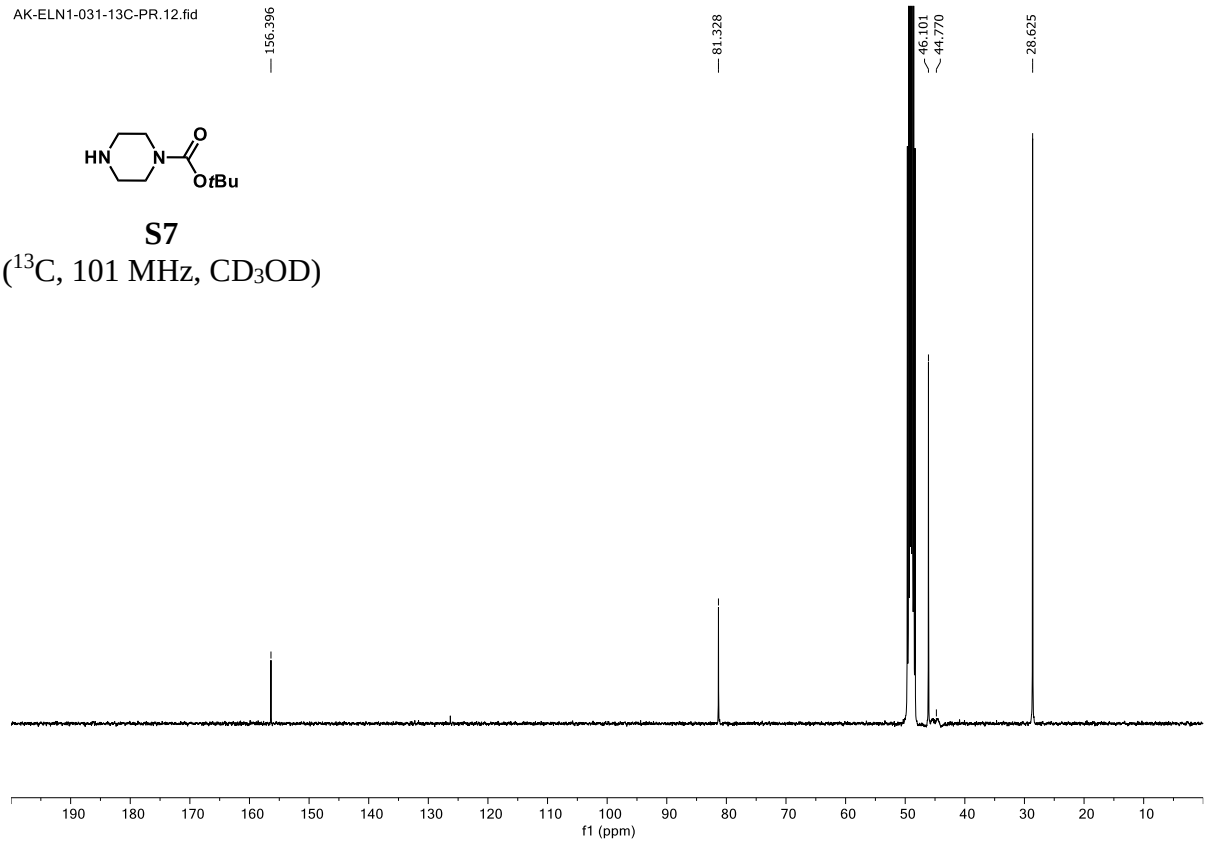


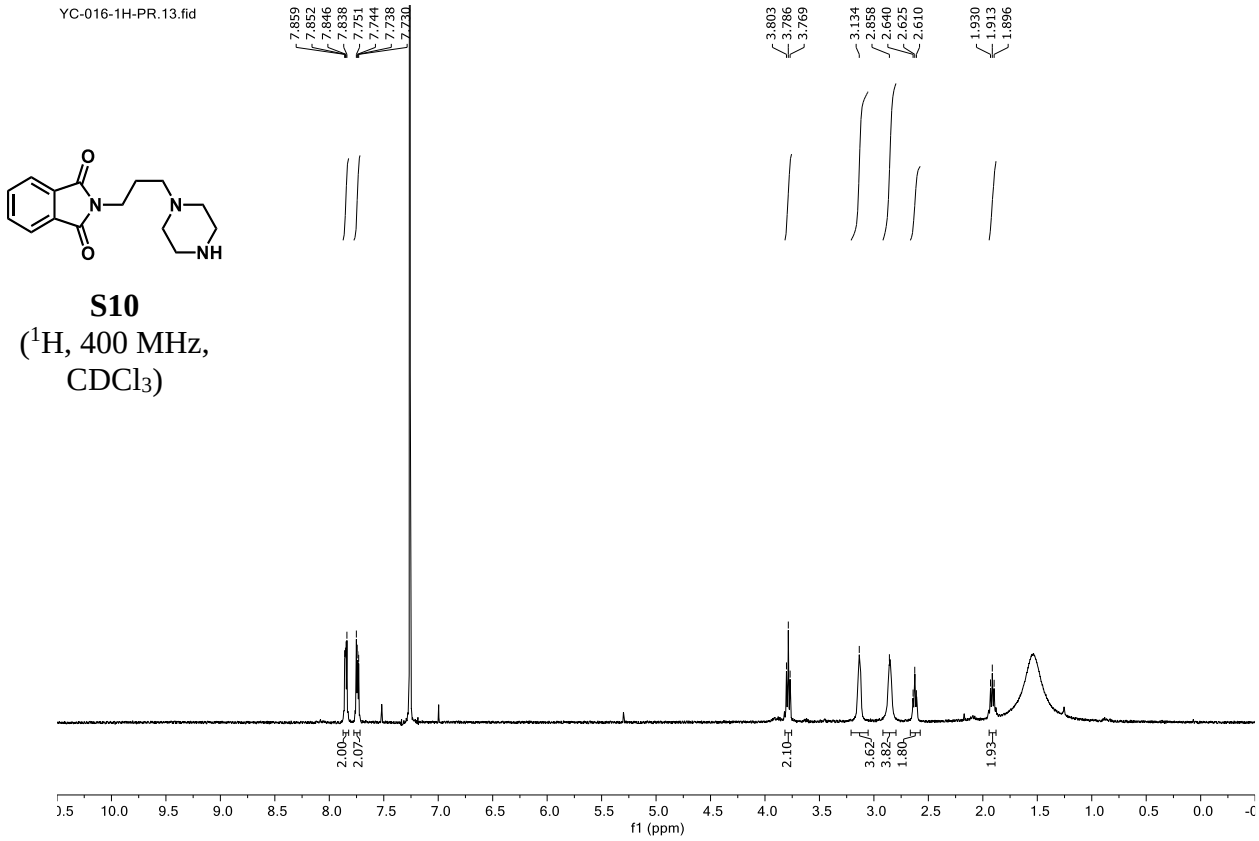
S5
(^{13}C, 101 MHz, $CDCl_3$)



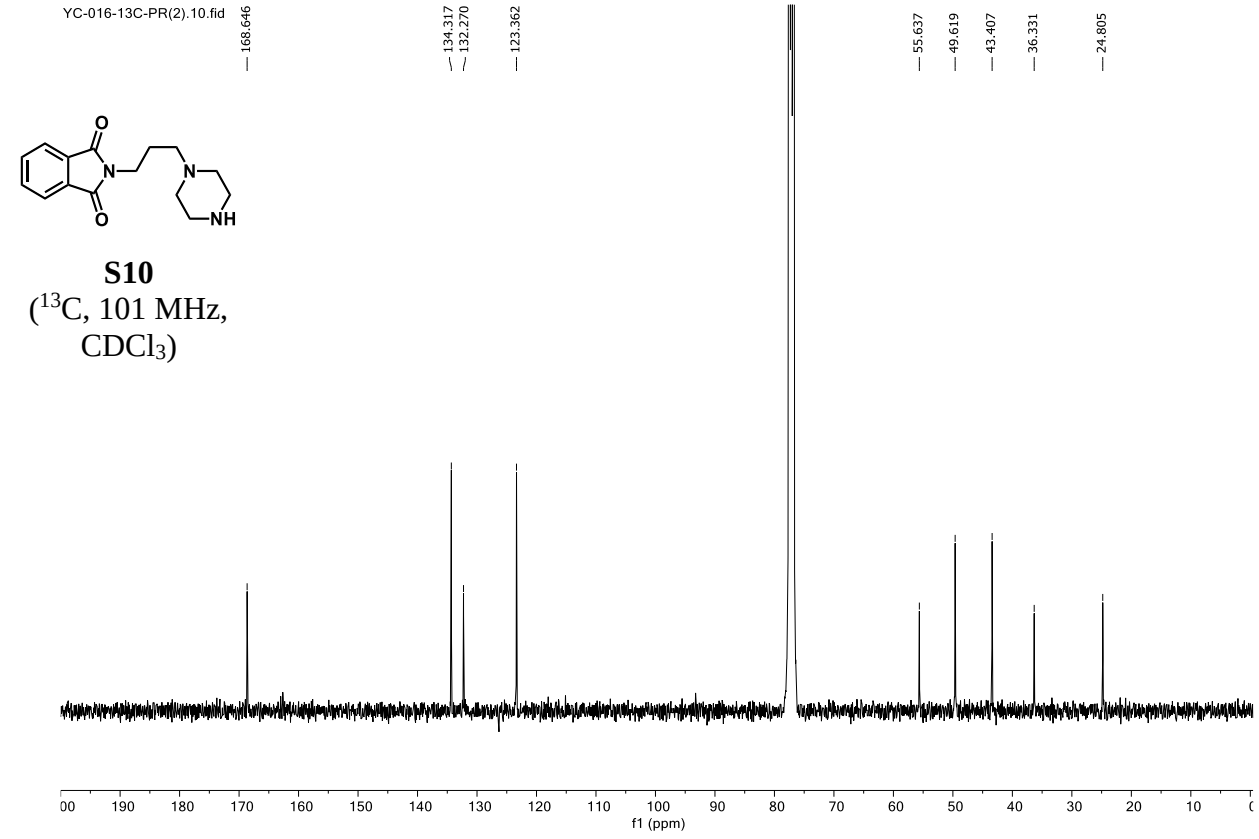
S7
(^{1}H, 400 MHz, CD_3OD)



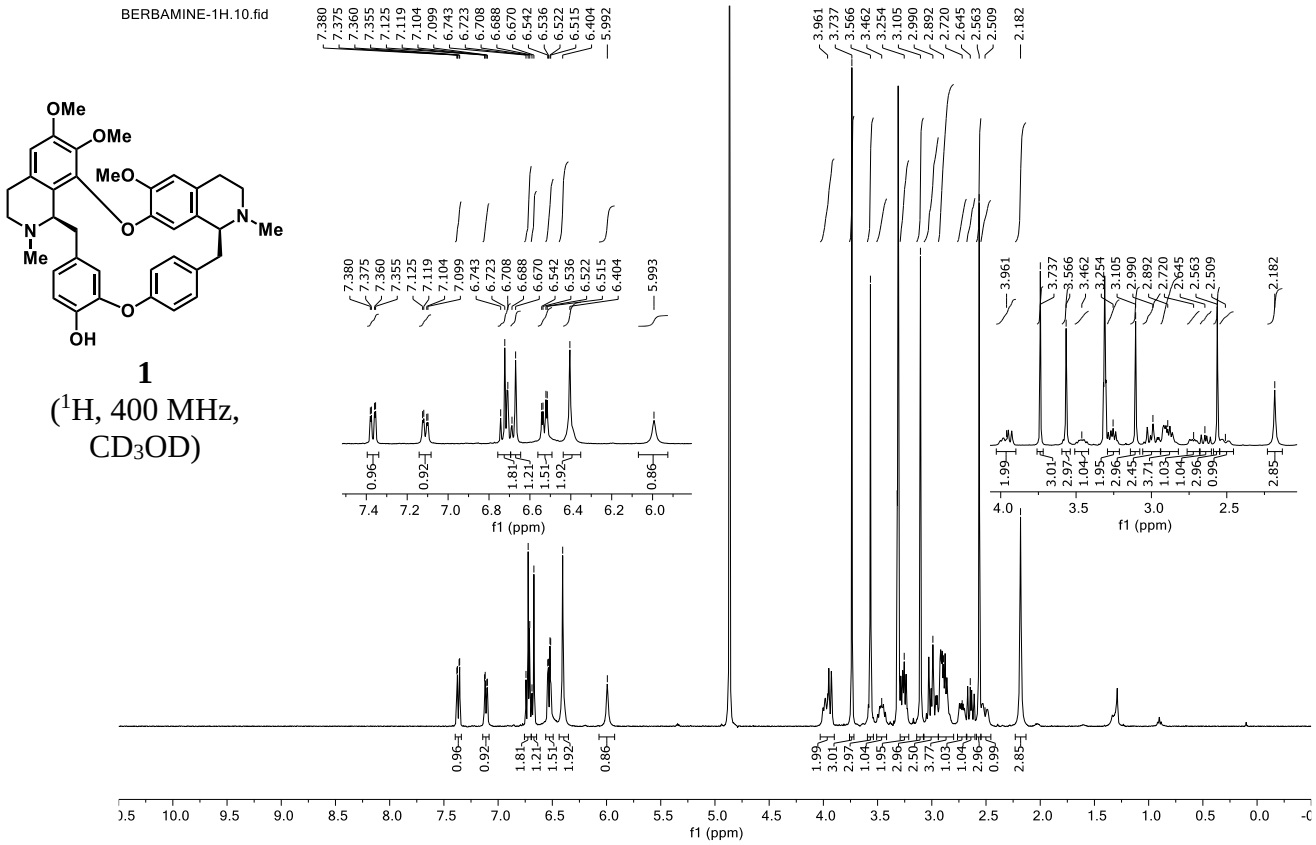
S7
(^{13}C, 101 MHz, CD_3OD)



S10
(^{1}H, 400 MHz,
$CDCl_3$)



S10
(^{13}C, 101 MHz,
$CDCl_3$)



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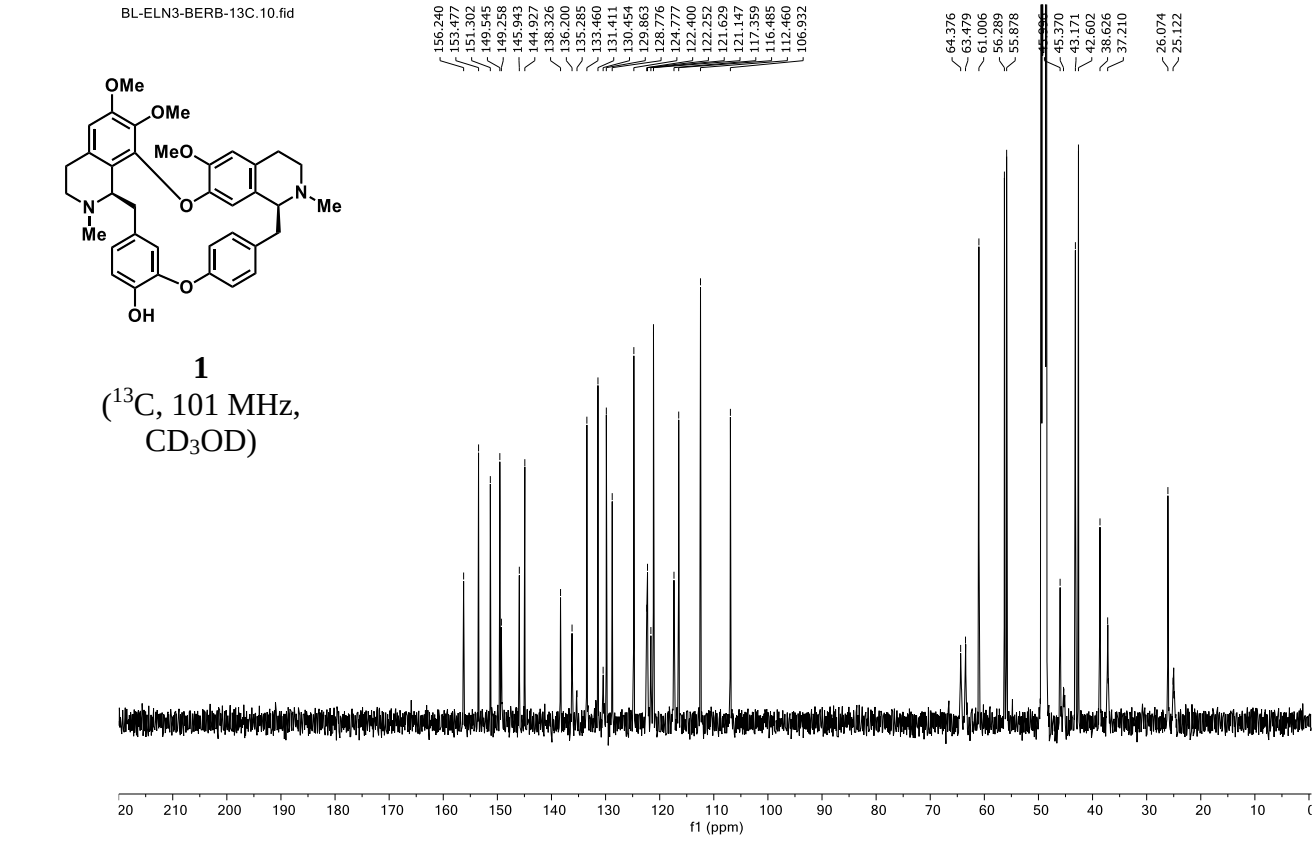

1
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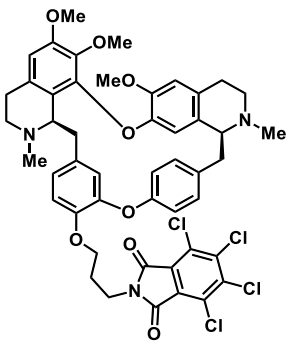
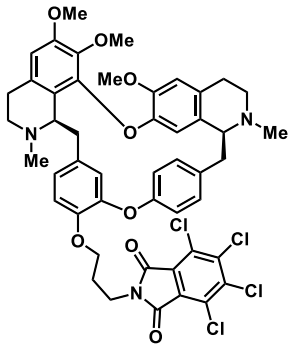


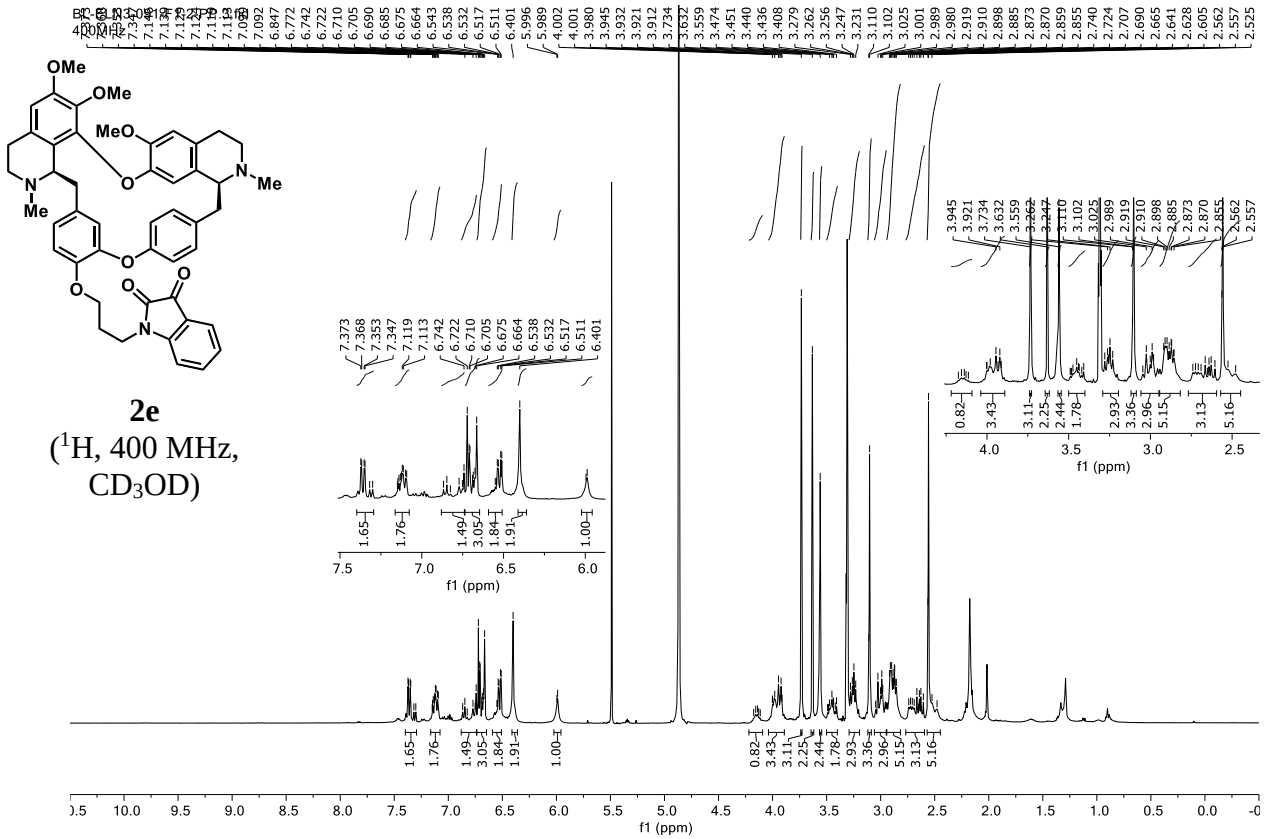
2d

(^{1}H, 400 MHz, CD_3OD)

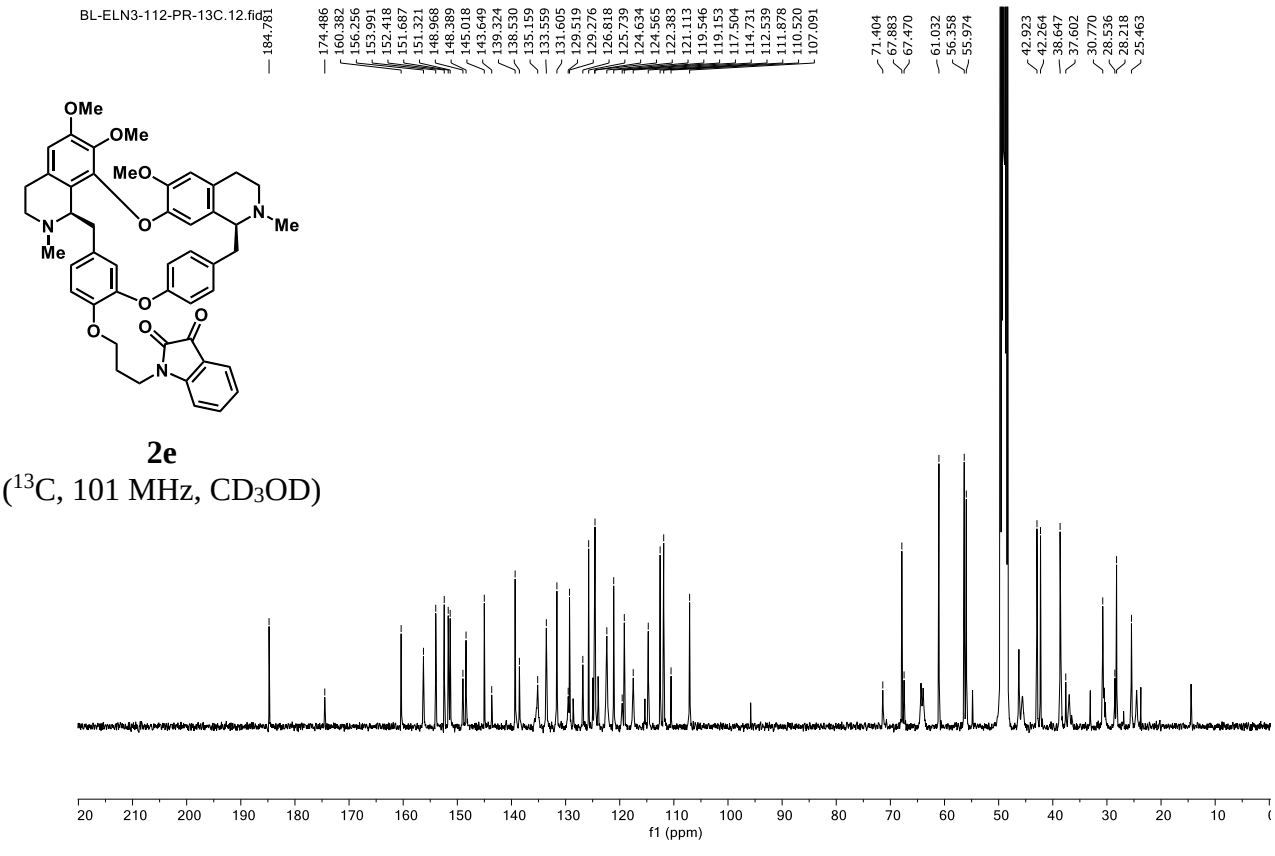


2d

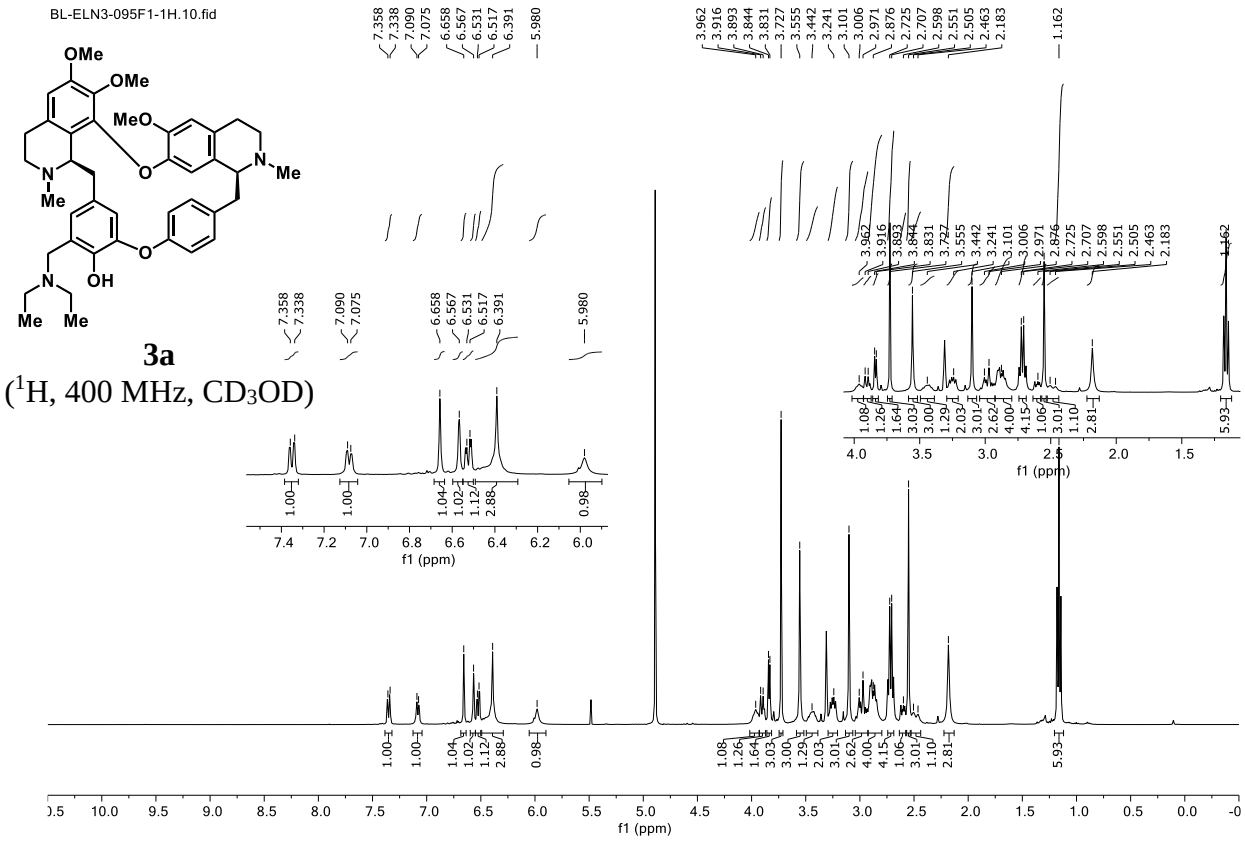
(^{13}C, 101 MHz, CD_3OD)



2e
(^{1}H, 400 MHz, CD_3OD)

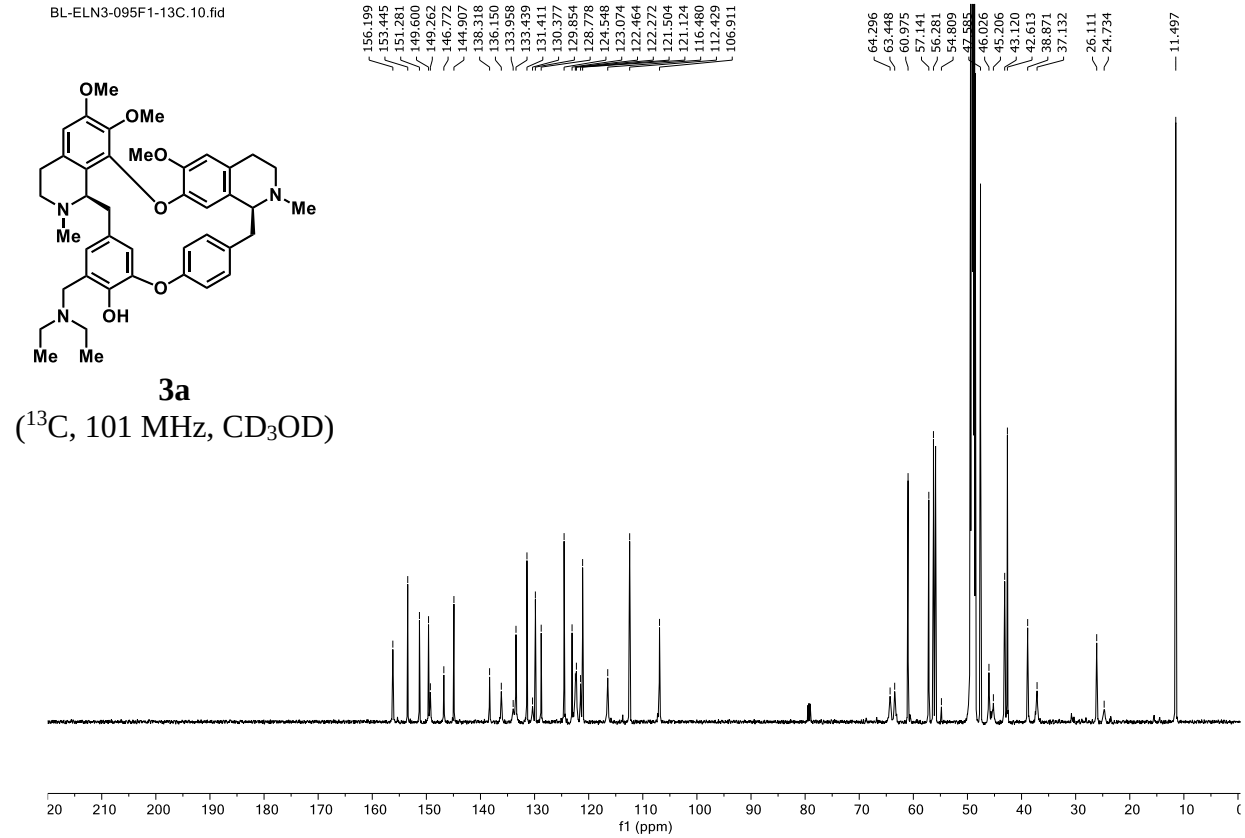


2e
(^{13}C, 101 MHz, CD_3OD)



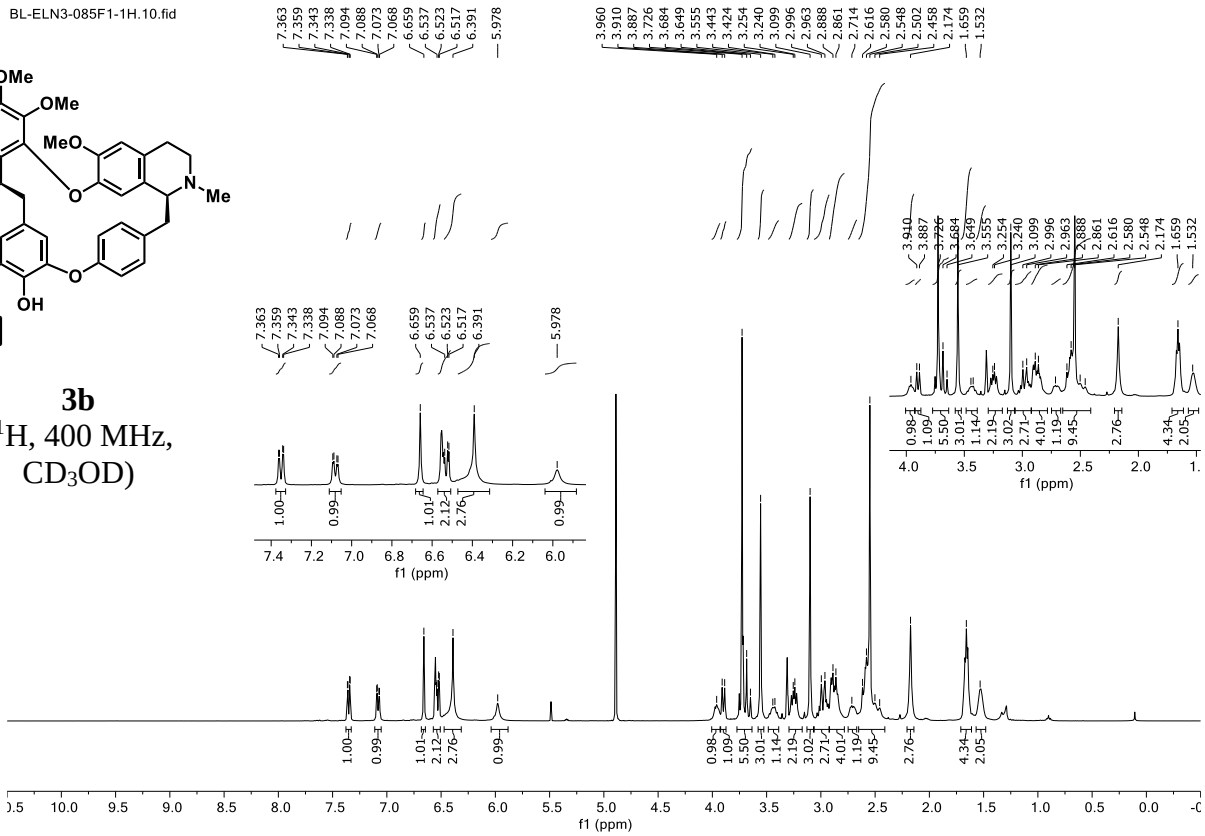
3a

(^{1}H, 400 MHz, CD_3OD)

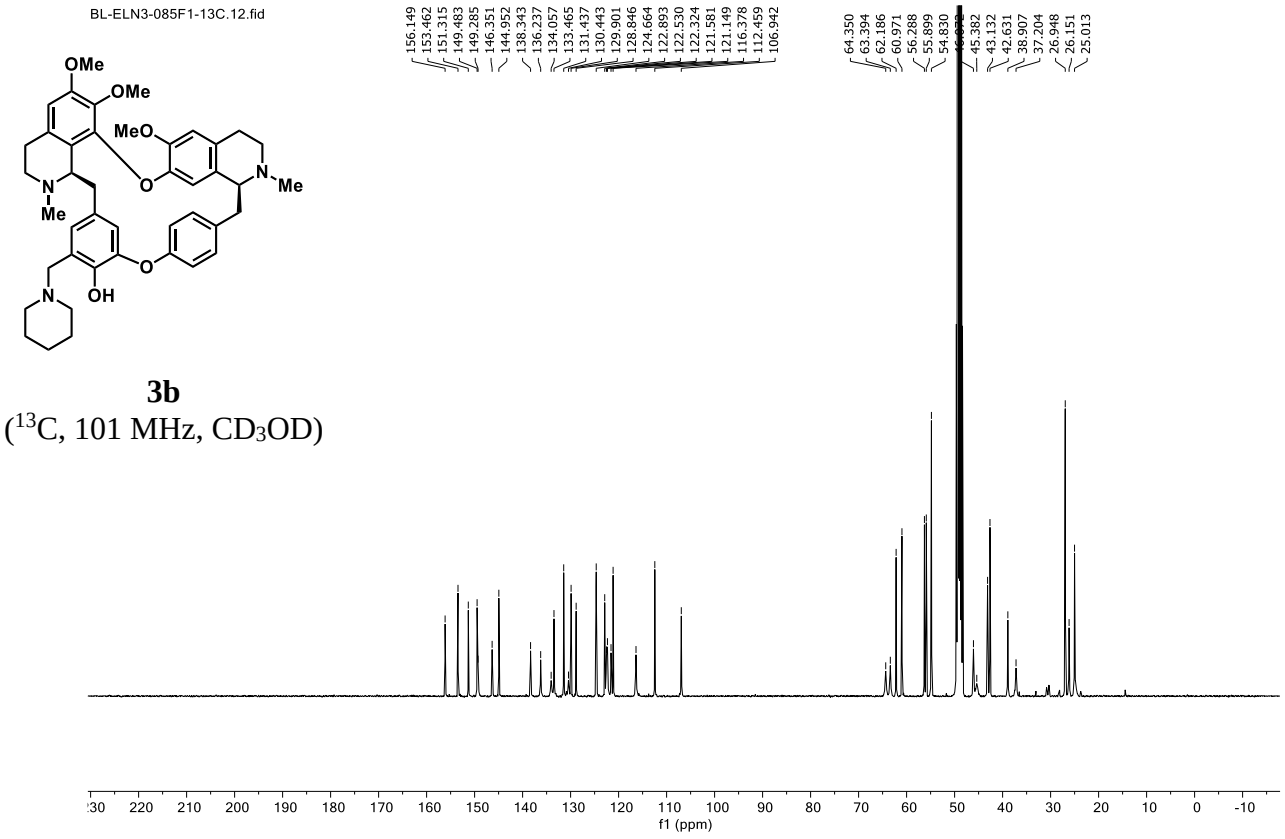


3a

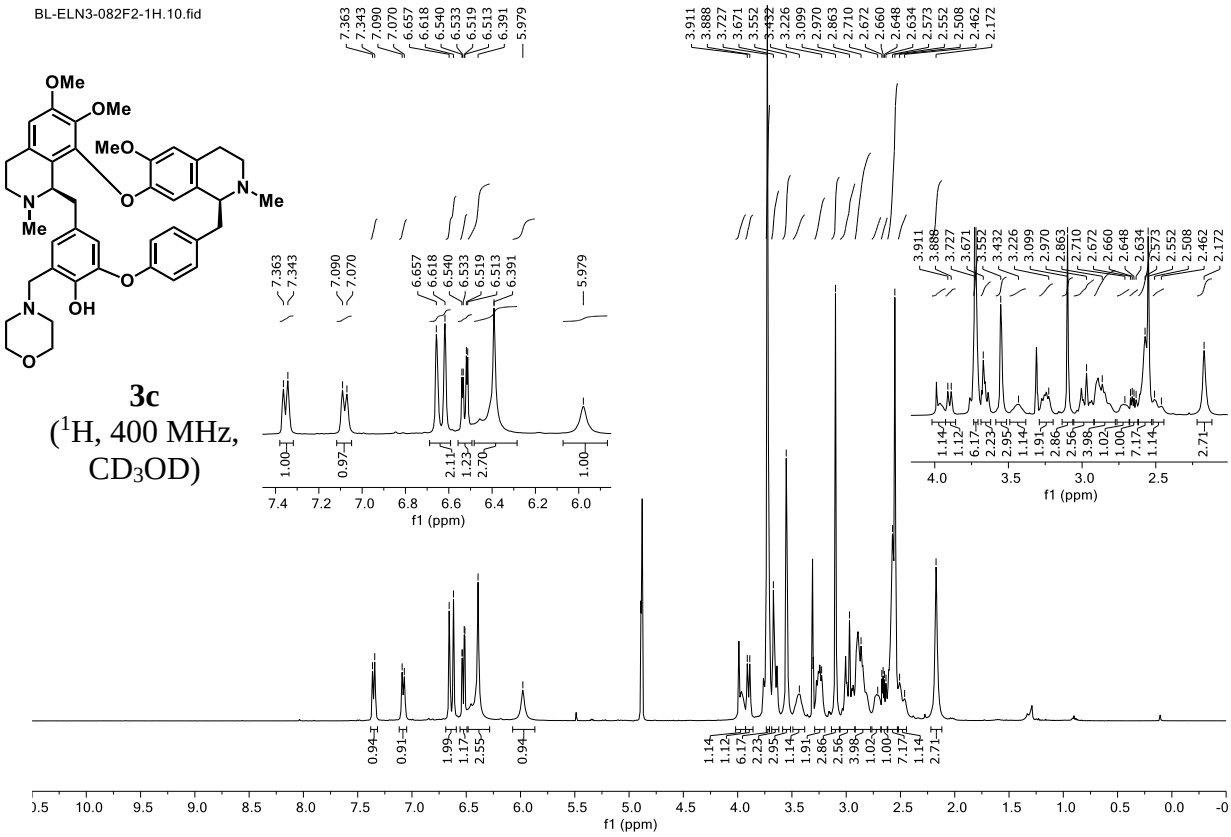
(^{13}C, 101 MHz, CD_3OD)



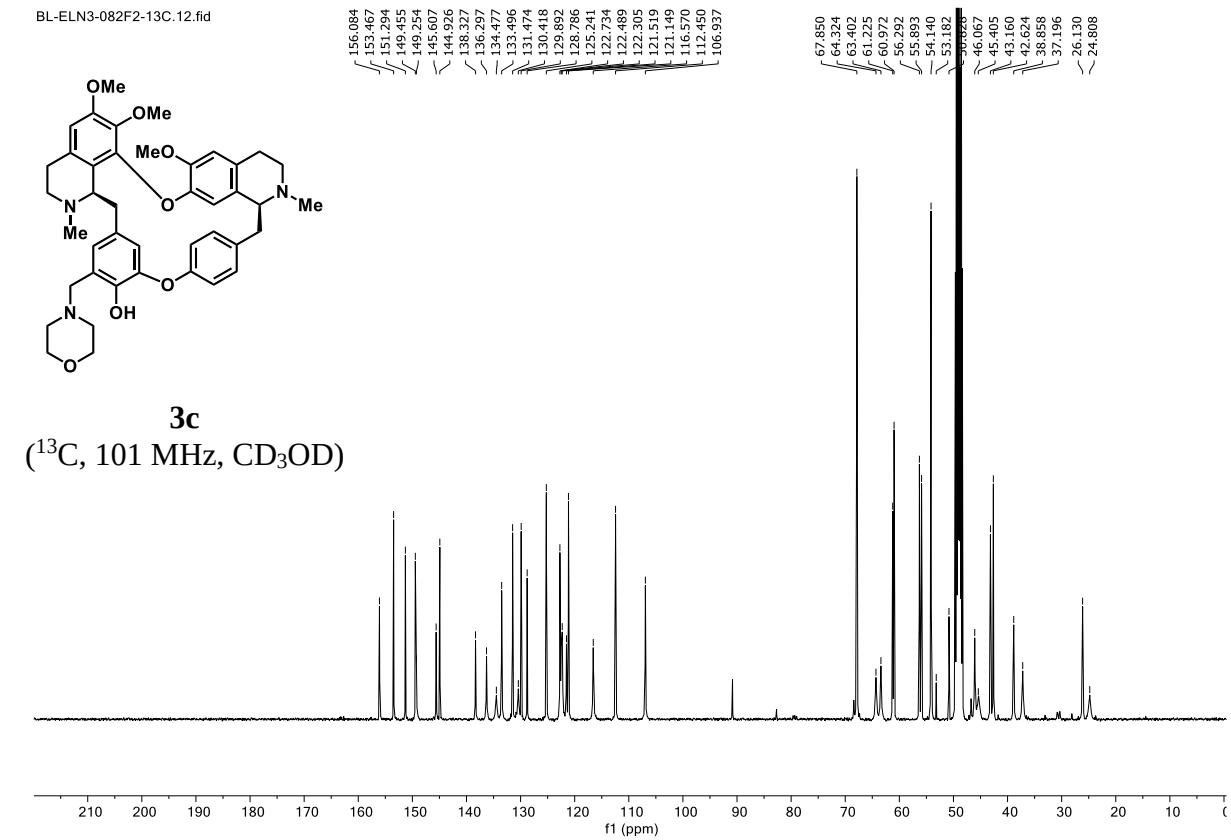
3b
(^{1}H, 400 MHz, CD_3OD)



3b
(^{13}C, 101 MHz, CD_3OD)



3c
(^{1}H, 400 MHz, CD_3OD)



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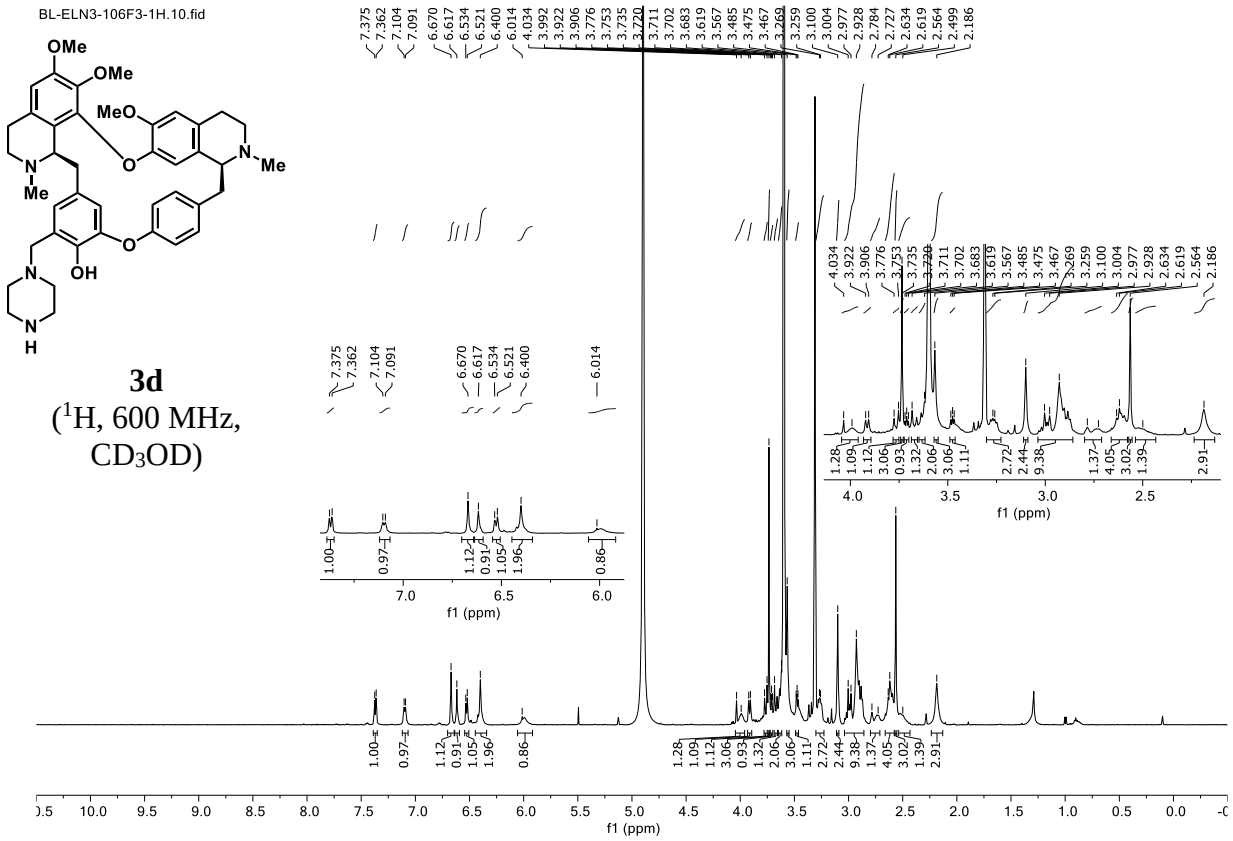
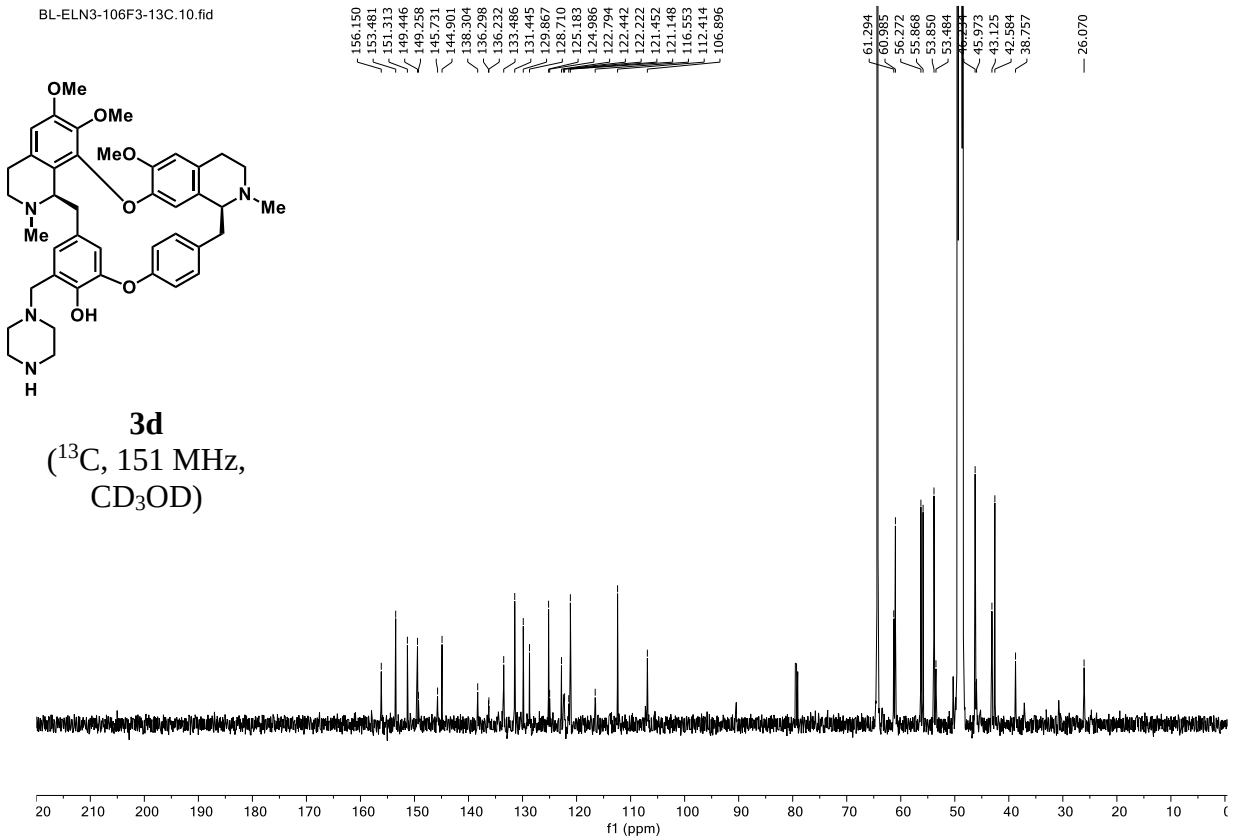


3d
(^{1}H, 600 MHz,
CD_3OD)



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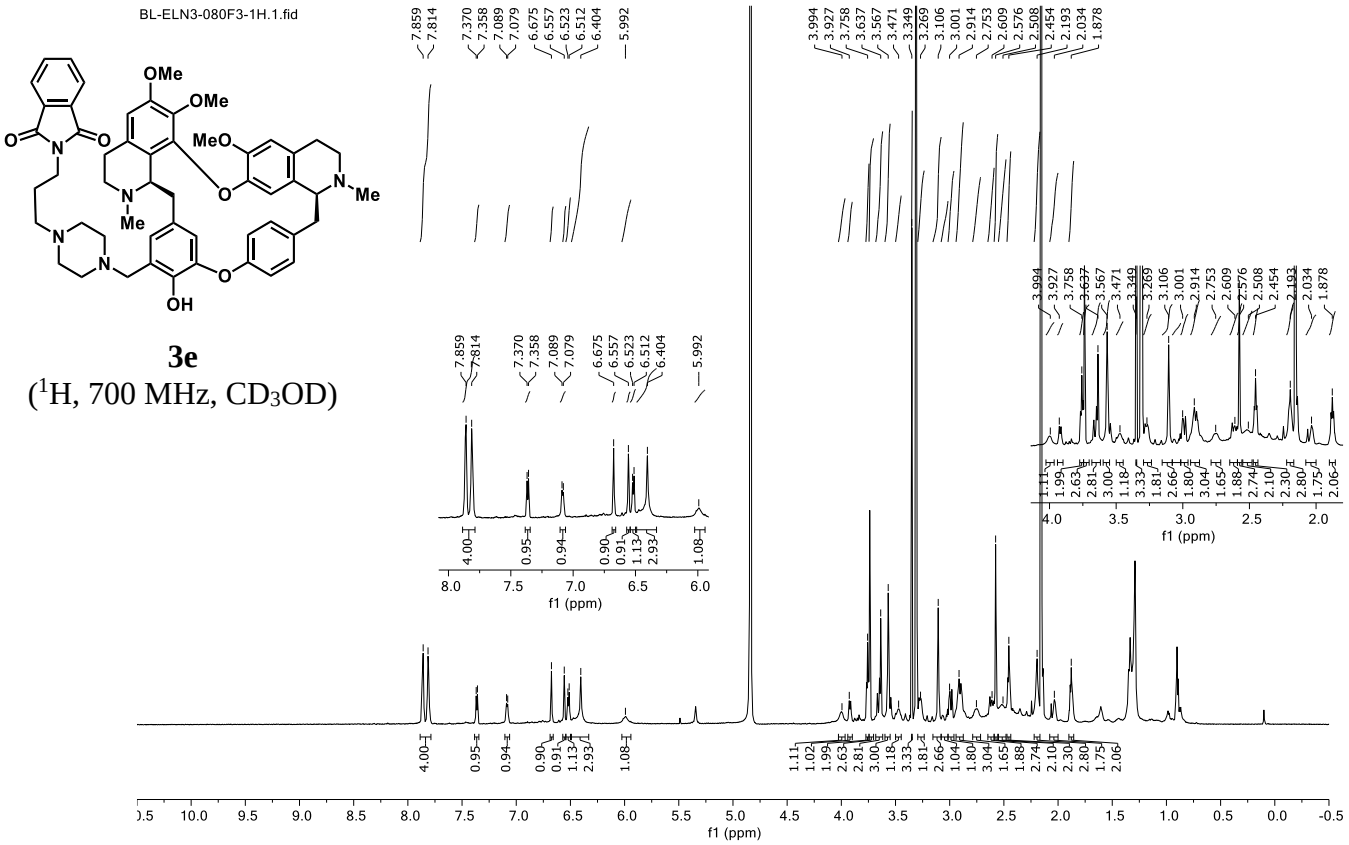
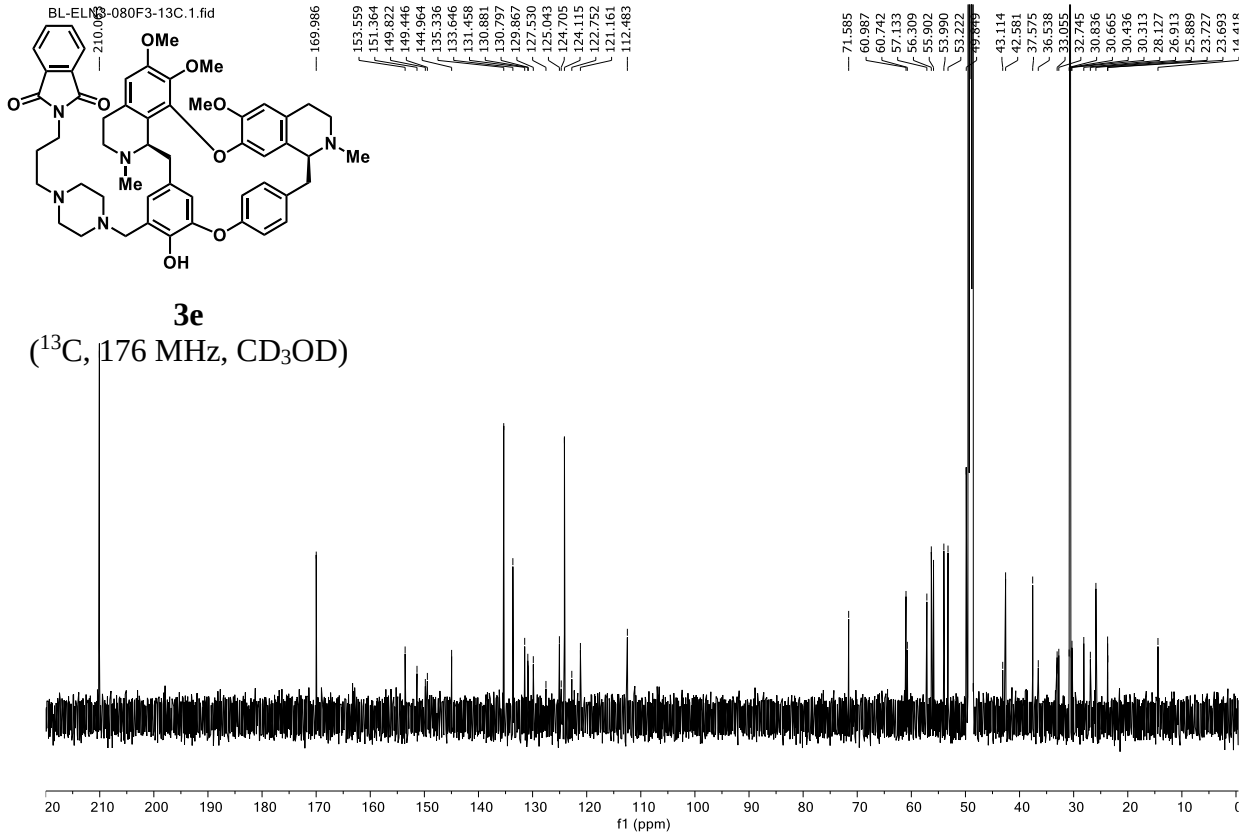
(^{13}C, 151 MHz,
CD_3OD)



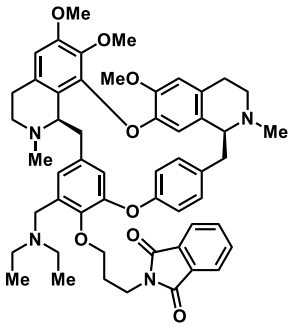
3e

(^{1}H, 700 MHz, CD_3OD)

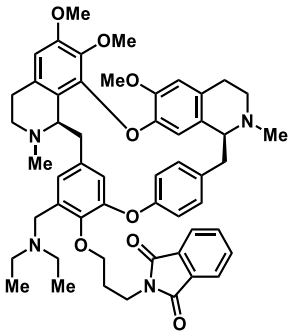


3e

(^{13}C, 176 MHz, CD_3OD)



5a
(^{1}H, 400 MHz, CD_3OD)



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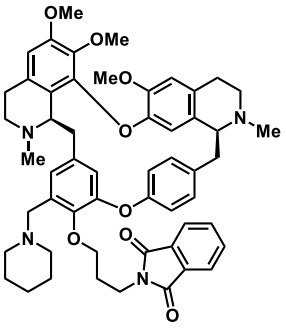
(^{13}C, 101 MHz, CD_3OD)



5b
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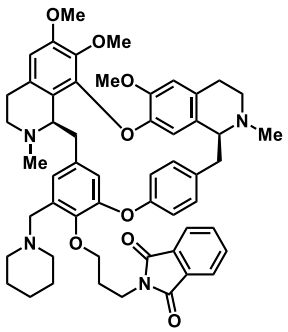

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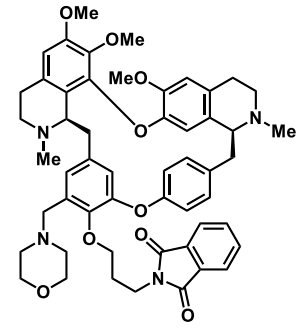
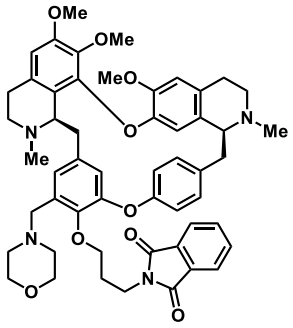


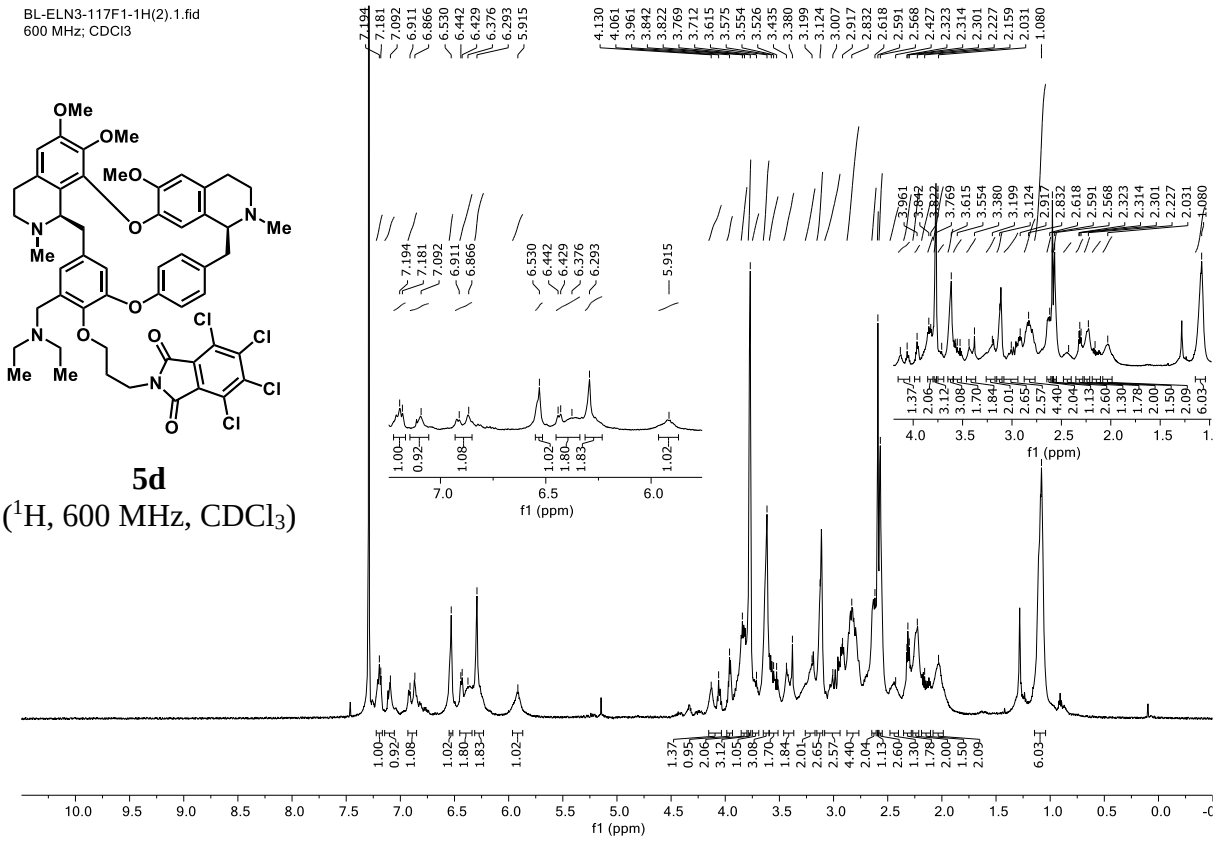
5c

(^{1}H, 400 MHz, CD_3OD)



5c

(^{13}C, 151 MHz, CD_3OD)



5d
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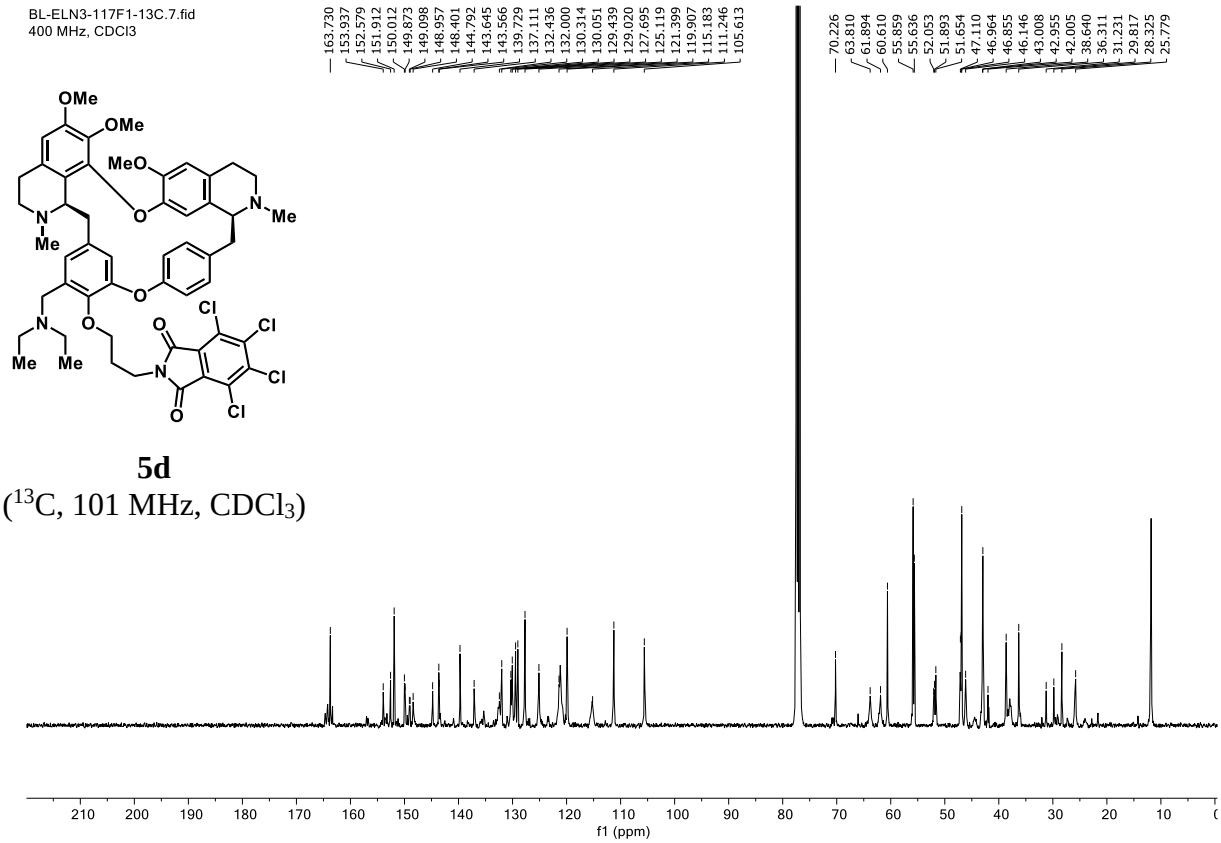

5d
(^{13}C, 101 MHz, $CDCl_3$)