Supporting information

Facile access to versatile aza-macrolides through iridium-catalysed cascade allyl-amination/macrocyclisation

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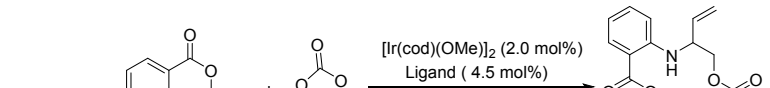
Table of Contents

1. General information

All general catalytic reactions were assembled in an N_2-filled glovebox using oven-dried glassware. Unless otherwise stated, all commercial materials and solvents were used directly without further purification. Melting points were determined in open glass capillaries and were uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were measured on a 400 MHz Bruker spectrometer (^{1}H NMR 400 MHz, ^{13}C NMR 101 MHz, ^{19}F NMR 376 MHz), and all spectra were referenced to the solvent peaks (^{1}H NMR: residual $CDCl_3$ = 7.26 ppm, CD_2Cl_2 = 5.32 ppm, ^{13}C NMR: $CDCl_3$ = 77.00 ppm, CD_2Cl_2 = 53.84 ppm). Solid-state NMR measurement was performed on a Bruker 400 MHz Avance III SS-NMR spectrometer. High-resolution mass spectra (HRMS) were recorded using Agilent 6545 spectrometer. HPLC analysis performed on Agilent Technologies HPLC-1260 Series with multi-wavelength detector (MWD). Column chromatography was performed on silica gel (70−230 mesh ASTM) using the reported eluents. Thin-layer chromatography (TLC) was carried out on 4×15 cm plates with a layer thickness of 0.2 mm (silica gel 60 F254). Isatoic anhydrides[1] and substituted vinylethylene carbonates[2] were synthesized according to the previously reported procedure.

2. Optimization of Reaction Conditions

Table S1. Ligand screening



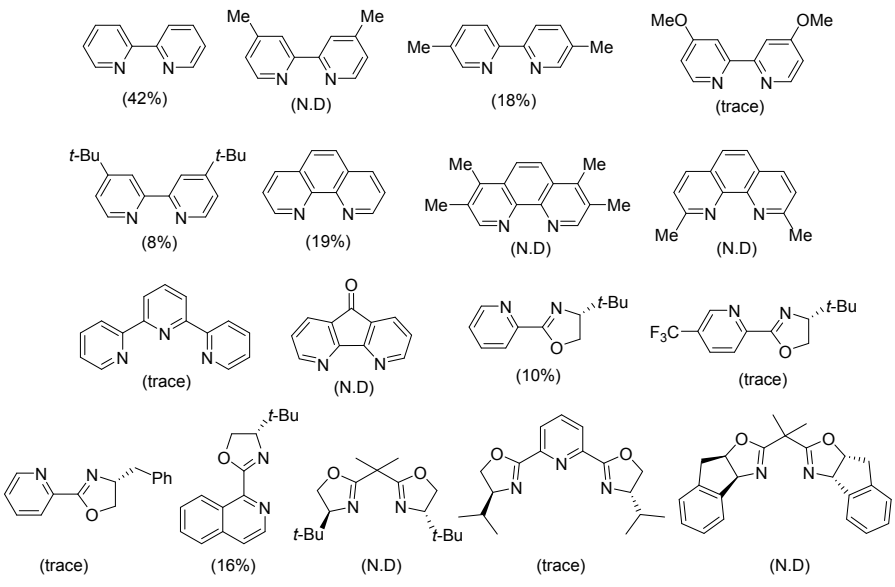
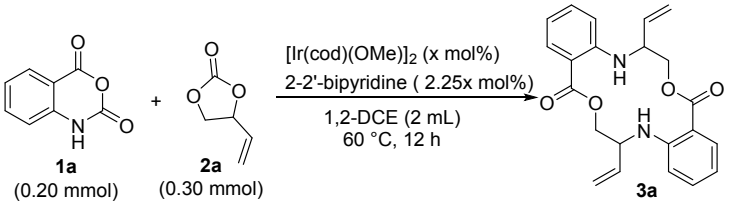


Table S2. Loading of Ir-catalyst

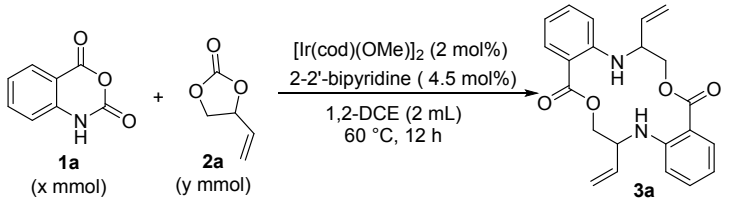


1a (0.20 mmol) + **2a** (0.30 mmol) → **3a**

Entry	$[Ir(cod(OMe)]_2$ (x mol%)	**3a**[a]
1	1.0	N.D
2	**2.0**	**42%**
3	3.0	42%
4	5.0	43%
5	10	41%

[a]Isolated yields.

Table S3. Ratio of the reaction partner

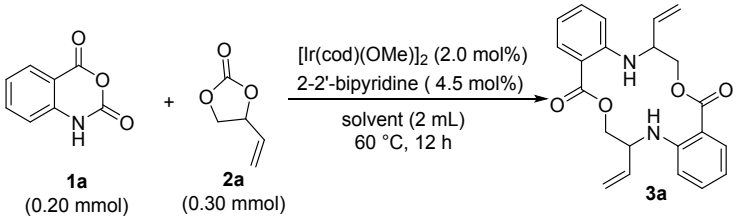


1a (x mmol) + **2a** (y mmol) → **3a**

Entry	x : y	**3a**[a]
1	0.2 : 0.24	<20%
2	**0.2 : 0.3**	**42%**
3	0.2 : 0.6	41%
4	0.3 : 0.2	N.R

[a]Isolated yields.

Table S4. Solvent screening

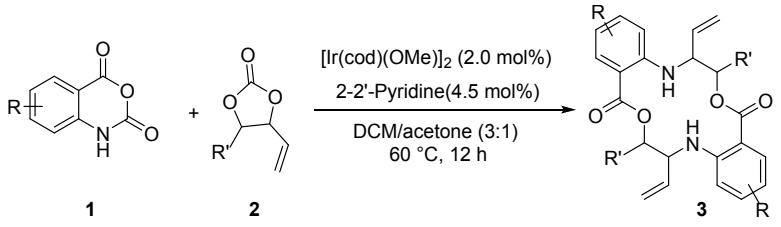


1a (0.20 mmol) + **2a** (0.30 mmol) → **3a**

Entry	Solvent	**3a**[a]
1	DCM/acetone = 1:1	45%
2	DCM/ trichloethane = 1:1	35%
3	acetone/ trichloethane = 1:1	32%
4	DCM/acetone = 2:1	44%
3	**DCM/acetone = 3:1**	**62%**
4	DCM/acetone = 5:1	49%
5	DCM/acetone = 7:1	55%
6	DCM/acetone = 9:1	54%
7	DCM/acetone = 1:9	57%
8	DCM/acetone = 1:7	44%
9	DCM/acetone = 1:5	46%
10	DCM/acetone = 1:3	60%
11	DCM/acetone = 1:2	42%
12[b]	DCM/acetone = 3:1	46%
13[c]	DCM/acetone = 3:1	50%

[a] Isolated yields; [b] Solvent (1 mL); [c] Solvent (4 mL).

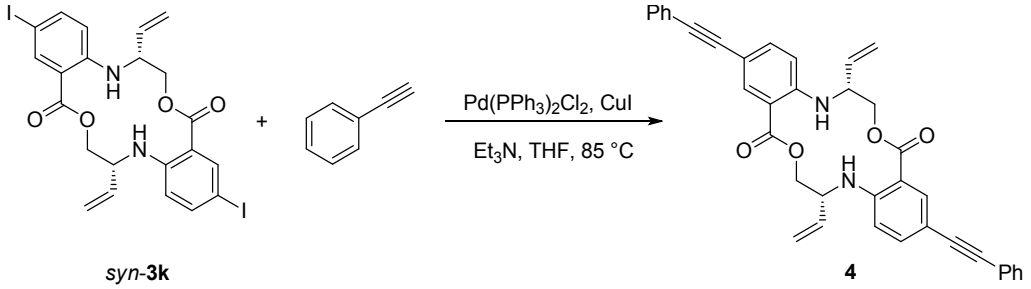
3. General Catalytic Procedure



1 **2** **3**

To a tube, isatoic anhydride **1** (0.20 mmol, 1 equiv), VEC **2** (0.30 mmol, 1.5 equiv), $[Ir(cod)(OMe)]_2$ (0.004 mmol, 2.0 mol%), 2-2'-bipyridine (0.009 mmol, 4.5 mol%) were added sequentially and dissolved in DCM (1.5 mL) and acetone (0.5 mL) in an N_2-filled glovebox. The sealed tube was then removed from the glovebox, heated at 60 °C and stirred for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified column chromatography on silica gel (EtOAc/PE) yielded the target products **3**.

4. Late-stage functionalization[3]



syn-**3k** **4**

A sealed tube was charged with *syn*-**3i** (32 mg, 0.05 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.7 mg, 2.0 mol %), CuI (0.4 mg, 4.0 mol %), phenylacetylene (21 mg, 0.20 mmol, 4.0 equiv), Et_3N (2 mL) and THF (2 mL). The reaction mixture was then stirred at 85 ºC for 12 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL) and filtered through a plug of celite. The mixture was concentrated *in vacuo* and purified by column chromatography on silica gel (EtOAc/PE: 1: 20→1:10, v/v) afford the desired product **4** (29 mg, 99%) as a yellow solid.

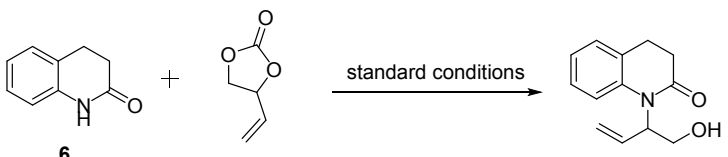
5. Experiments with mechanistic studies (Scheme 4)

(a)

5 **2a**

To a tube *N*-methyl substituted isatoic anhydride **5** (36 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv), $[Ir(cod)(OMe)]_2$ (3 mg, 2.0 mol%), 2-2'-bipyridine (1.4 mg, 4.5 mol%) were added sequentially and dissolved in DCM (1.5 mL) and acetone (0.5 mL) in an N_2-filled glovebox. The sealed tube was then removed from the glovebox, heated at 60 °C and stirred for 12 h. No product was detected by TLC analysis.

(b)

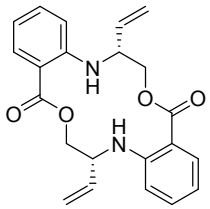


6 **2a** **7**: 32%

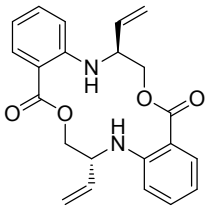
To a tube 3,4-dihydro-2(*H*)-quinoline (**6**; 30 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv), $[Ir(cod)(OMe)]_2$ (3 mg, 2.0 mol%), 2-2'-bipyridine (1.4 mg, 4.5 mol%) were

added sequentially and dissolved in DCM (1.5 mL) and acetone (0.5 mL) in an N_2-filled glovebox. The sealed tube was then removed from the glovebox, heated at 60 °C and stirred for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/PE: 1: 10→1: 2, v/v) afford the desired product (14 mg, 32%) as an unstable colorless oil.

6. Characterization of compounds 3



syn-**3a**



anti-**3a**

The general procedure was followed using isatoic anhydride **1a** (33 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3a** (12 mg, 31%) as a white solid and *anti*-**3a** (12 mg, 31%) as a white solid (total yields of **3a**: 62%).

***Syn*-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3a):**

M. p. 200−201 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 7.9, 1.5 Hz, 2H), 7.34–7.27 (m, 2H), 7.07 (d, J = 6.9 Hz, 2H), 6.64 (t, J = 7.5 Hz, 2H), 6.59 (d, J = 8.4 Hz, 2H), 5.88 (ddd, J = 17.0, 10.3, 4.5 Hz, 2H), 5.46 (d, J = 17.1 Hz, 2H), 5.31 (d, J = 10.4 Hz, 2H), 5.10 (dd, J = 12.2, 8.5 Hz, 2H), 4.29–4.14 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (C_q), 148.6 (C_q), 134.4 (CH), 134.1 (CH), 131.4 (CH), 117.8 (CH_2), 115.9 (CH), 113.3 (C_q), 112.3 (CH), 65.2 (CH_2), 56.7 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{23}N_2O_4^+$ $[M+H]^+$: 379.1652, Found 379.1656.

***Anti*-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3a):**

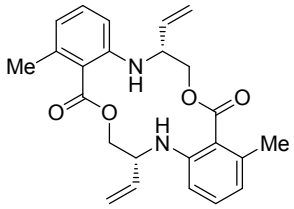
M. p. 195−195 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.0, 1.6 Hz, 2H), 7.42–7.32 (m, 2H), 7.19 (d, J = 9.5 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.77–6.69 (m, 2H), 5.98 (ddd, J = 17.2, 10.5, 5.0 Hz, 2H), 5.40

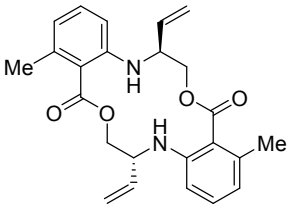
(d, J = 17.3 Hz, 2H), 5.27 (d, J = 10.5 Hz, 2H), 4.97 (dd, J = 11.1, 3.1 Hz, 2H), 4.54–4.42 (m, 2H), 4.30 (dd, J = 11.1, 2.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C_q), 149.4 (C_q), 135.7 (CH), 134.3 (CH), 132.3 (CH), 117.1 (CH_2), 116.7 (CH), 113.7 (CH), 113.7 (C_q), 64.3 (CH_2), 55.1 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{23}N_2O_4^+$ $[M+H]^+$: 379.1652, Found 379.1655.



syn-**3b**



anti-**3b**

The general procedure was followed using isatoic anhydride **1b** (36 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3b** (13 mg, 32%) as a white solid and *anti*-**3b** (11 mg, 27%) as a white solid (total yields of **3b**: 59%).

***Syn*-1,10-dimethyl-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3b):**

M. p. 176−180 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 7.9 Hz, 2H), 6.52 (d, J = 6.9 Hz, 2H), 6.47 (d, J = 7.4 Hz, 2H), 6.38 (d, J = 8.4 Hz, 2H), 5.83 (ddd, J = 17.1, 10.3, 5.1 Hz, 2H), 5.48 (d, J = 17.3, 1.2 Hz, 2H), 5.33 (d, J = 10.5, 2H), 5.18 – 5.09 (m, 2H), 4.13–4.03 (m, 2H), 3.99 (dd, J = 11.5, 3.7 Hz, 2H), 2.36 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (C_q), 147.8 (C_q), 138.8 (C_q), 134.5 (CH), 131.9 (CH), 119.1 (CH), 118.2 (CH_2), 115.3 (C_q), 109.7 (CH), 64.1 (CH_2), 57.1 (CH), 22.0 (CH_3).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_4^+$ $[M+H]^+$: 407.1965, Found 407.1969.

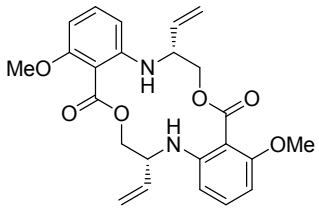
***Anti*-1,10-dimethyl-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3b):**

M. p. 145−148 °C.

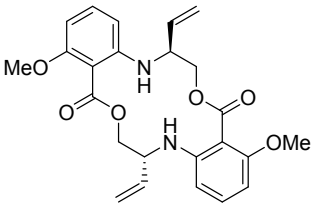
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, J = 7.9 Hz, 2H), 6.58–6.49 (m, 4H), 6.02 (d, J = 6.2 Hz, 2H), 5.82 (ddd, J = 17.2, 10.4, 5.9 Hz, 2H), 5.38 (d, J = 17.3 Hz, 2H), 5.28 (d, J = 10.4 Hz, 2H), 4.74 (dd, J = 11.3, 3.0 Hz, 2H), 4.44 (dd, J = 11.3, 5.3 Hz, 2H), 4.26 (dd, J = 6.9, 4.0 Hz, 2H), 2.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C_q), 146.5 (C_q), 139.3 (C_q), 136.2 (CH), 131.5 (CH), 119.8 (CH), 117.9 (CH_2), 116.7 (C_q), 110.8 (CH), 66.3 (CH_2), 55.5 (CH), 21.7 (CH_3).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_4^+$ $[M+H]^+$: 407.1965, Found 407.1965.



syn-**3c**



anti-**3c**

The general procedure was followed using isatoic anhydride **1c** (39 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:20→1:10, v/v) yielded *syn*-**3c** (9 mg, 20%) as a white solid and *anti*-**3c** (14 mg, 31%) as a white solid (total yields of **3c**: 51%).

***Syn*-1,10-dimethoxy-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3c):**

M. p. 224−232 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, J = 8.3 Hz, 2H), 6.50 (d, J = 6.8 Hz, 2H), 6.21 (d, J = 8.2 Hz, 2H), 6.15 (d, J = 8.4 Hz, 2H), 5.86–5.75 (m, 2H), 5.45 (d, J = 17.2 Hz, 2H), 5.31 (d, J = 10.4 Hz, 2H), 5.15 (t, J = 11.3 Hz, 2H), 4.12 (d, J = 5.3 Hz, 2H), 3.97 (dd, J = 11.7, 3.7 Hz, 2H), 3.78 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C_q), 159.5 (C_q), 148.8 (C_q), 134.6 (CH), 132.8 (CH), 118.1 (CH_2), 105.2 (C_q), 105.0 (CH), 99.7 (CH), 64.1 (CH_2), 57.2 (CH), 56.0 (CH_3).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_6^+$ $[M+H]^+$: 439.1864, Found 439.1869.

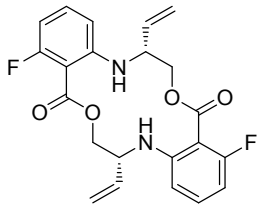
***Anti*-1,10-dimethoxy-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3c):**

M. p. 214−218 °C.

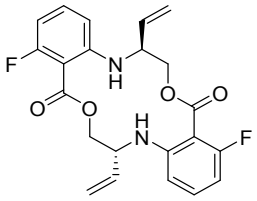
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.3 Hz, 2H), 6.32–6.26 (m, 4H), 5.82 (ddd, J = 16.7, 8.2, 4.8 Hz, 4H), 5.36 (d, J = 17.3 Hz, 2H), 5.26 (d, J = 10.4 Hz, 2H), 4.70 (dd, J = 11.4, 3.0 Hz, 2H), 4.45 (dd, J = 11.4, 5.5 Hz, 2H), 4.22 (d, J = 2.4 Hz, 2H), 3.80 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C_q), 159.4 (C_q), 147.2 (C_q), 136.3 (CH), 132.4 (CH), 117.9 (CH_2), 106.9 (C_q), 105.9 (CH), 100.5 (CH), 66.5 (CH_2), 56.1 (CH), 55.6 (CH_3).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_6^+$ $[M+H]^+$: 439.1864, Found 439.1866.



syn-**3d**



anti-**3d**

The general procedure was followed using isatoic anhydride **1d** (37 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3d** (14 mg, 33%) as a white solid and *anti*-**3d** (12 mg, 28%) as a white solid (total yields of **3d**: 61%).

***Syn*-1,10-difluoro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3d):**

M. p. 235−237 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (td, J = 8.3, 6.4 Hz, 2H), 6.96 (d, J = 6.9 Hz, 2H), 6.37 – 6.23 (m, 4H), 5.83 (ddd, J = 17.0, 10.3, 5.0 Hz, 2H), 5.48 (d, J = 17.2 Hz, 2H), 5.35 (d, J = 10.3 Hz, 2H), 5.23 (t, J = 11.4 Hz, 2H), 4.14–4.04 (m, 2H), 3.98 (dd, J = 11.7, 3.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C_q), 162.1 (d, $^1J_{C–F}$ = 253.5 Hz, C_q), 149.7 (d, $^3J_{C–F}$ = 4.9 Hz, C_q), 133.9 (d, $^3J_{C–F}$ = 11.7 Hz, CH), 133.7 (CH), 118.5 (CH_2), 107.5 (d, $^4J_{C–F}$ = 2.7 Hz, CH), 103.6 (d, $^2J_{C–F}$ = 16.4 Hz, C_q), 103.3 (d, $^2J_{C–F}$ = 23.1 Hz, CH), 64.2 (CH_2), 58.1 (CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ –108.8.

HRMS (ESI) m/z calcd for $C_{22}H_{21}F_2N_2O_4^+$ $[M+H]^+$: 415.1464, Found 415.1469.

***Anti*-1,10-difluoro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3d):**

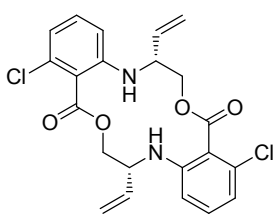
M. p. 195−195 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (td, J = 8.3, 6.4 Hz, 2H), 6.85 (d, J = 6.6 Hz, 2H), 6.49 (d, J = 8.5 Hz, 2H), 6.38 (dd, J = 10.3, 8.4 Hz, 2H), 5.93–5.82 (m, 2H), 5.42 (d, J = 17.3 Hz, 2H), 5.31 (d, J = 10.4 Hz, 2H), 4.98 (dd, J = 11.1, 2.6 Hz, 2H), 4.35 (dd, J = 11.1, 4.3 Hz, 2H), 4.31 (s, 2H).

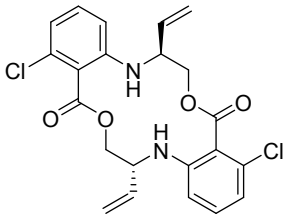
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C_q), 162.6 (d, $^1J_{C–F}$ = 254.7 Hz, C_q), 149.3 (d, $^3J_{C–F}$ = 4.5 Hz, CH), 135.6 (CH_2), 133.7 (d, $^3J_{C–F}$ = 11.8 Hz, C_q), 118.0 (CH), 108.5 (d, $^4J_{C–F}$ = 2.9 Hz, CH), 104.4 (d, $^2J_{C–F}$ = 15.3 Hz, CH), 104.0 (d, $^2J_{C–F}$ = 23.2 Hz, C_q), 65.2 (CH), 56.1 (CH_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ –108.1.

HRMS (ESI) m/z calcd for $C_{22}H_{21}F_2N_2O_4^+$ $[M+H]^+$: 415.1464, Found 415.1468.



syn-**3e**



anti-**3e**

The general procedure was followed using isatoic anhydride **1e** (40 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:10, v/v) yielded *syn*-**3e** (14 mg, 31%) as a white solid and *anti*-**3e** (16 mg, 35%) as a white solid (total yields of **3e**: 66%).

***Syn*-1,10-dichloro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3e):**

M. p. 205−210 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 8.2 Hz, 2H), 6.67 (d, J = 7.8 Hz, 2H), 6.42 (t, J = 10.3 Hz, 2H), 6.36 (d, J = 7.0 Hz, 2H), 5.80 (ddd, J = 17.1, 10.3, 5.1 Hz, 2H), 5.46 (d, J = 17.1 Hz, 2H), 5.36 (d, J = 10.3 Hz, 2H), 5.15 (t, J = 11.3 Hz, 2H), 4.11 (dt, J = 6.8, 5.4 Hz, 2H), 4.02 (dd, J = 11.6, 3.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C_q), 148.5 (C_q), 133.6 (CH), 133.5 (C_q), 132.4 (CH), 118.7 (CH_2), 118.3 (CH), 114.8 (C_q), 110.6 (CH), 64.2 (CH_2), 57.1 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{21}Cl_2N_2O_4^+$ $[M+H]^+$: 447.0873, Found 447.0874.

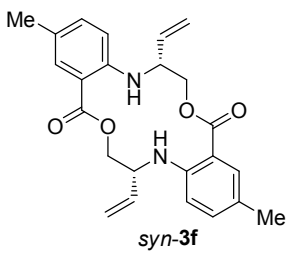
***Anti*-1,10-dichloro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3e):**

M. p. 186−187 °C.

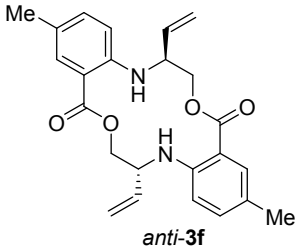
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, J = 8.2 Hz, 2H), 6.72 (d, J = 7.9 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 5.87 (d, J = 5.4 Hz, 2H), 5.84–5.74 (m, 2H), 5.40 (d, J = 17.3 Hz, 2H), 5.32 (d, J = 10.4 Hz, 2H), 4.81 (dd, J = 11.5, 3.1 Hz, 2H), 4.47 (dd, J = 11.5, 5.8 Hz, 2H), 4.20 (dd, J = 5.5, 3.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8 (C_q), 147.1 (C_q), 135.5 (CH), 133.1 (C_q), 131.9 (CH), 118.6 (CH), 118.6 (CH_2), 116.8 (C_q), 111.4 (CH), 66.3 (CH_2), 56.1 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{21}Cl_2N_2O_4^+$ $[M+H]^+$: 447.0874, Found 447.0875.



syn-**3f**



anti-**3f**

The general procedure was followed using isatoic anhydride **1f** (36 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3f** (14 mg, 34%) as a white solid and *anti*-**3f** (12 mg, 29%) as a white solid (total yields of **3f**: 63%).

***Syn*-2,11-dimethyl-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3f):**

M. p. 135−136 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 1.8 Hz, 2H), 7.13 (dd, J = 8.5, 2.1 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 6.53 (d, J = 8.5 Hz, 2H), 5.88 (ddd, J = 17.0, 10.3, 4.5 Hz, 2H), 5.43 (d, J = 17.2 Hz, 2H), 5.28 (d, J = 10.3 Hz, 2H), 5.06 (dd, J = 12.1, 7.8 Hz, 2H), 4.23 (dd, J = 8.6, 3.6 Hz, 4H), 2.22 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C_q), 146.4 (C_q), 135.1 (CH), 134.6 (CH), 131.6 (CH), 125.0 (C_q), 117.7 (CH_2), 113.0 (C_q), 112.5 (CH), 65.5 (CH_2), 56.3 (CH), 19.9 (CH_3).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_4^+$ $[M+H]^+$: 407.1965, Found 407.1967.

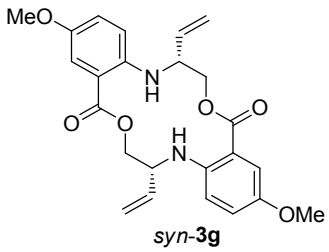
***Anti*-2,11-dimethyl-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3f):**

M. p. 205−206 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 1.5 Hz, 2H), 7.19 (dd, J = 8.5, 1.9 Hz, 2H), 7.01 (d, J = 9.6 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 6.04–5.89 (m, 2H), 5.38 (d, J = 17.3 Hz, 2H), 5.26 (d, J = 10.5 Hz, 2H), 4.91 (dd, J = 11.1, 3.1 Hz, 2H), 4.48–4.39 (m, 2H), 4.32 (dd, J = 11.1, 2.4 Hz, 2H), 2.26 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C_q), 147.2 (C_q), 135.9 (CH), 135.3 (CH), 132.2 (CH), 125.9 (C_q), 117.0 (CH_2), 114.0 (CH), 113.6 (C_q), 64.3 (CH_2), 55.4 (CH), 20.2 (CH_3).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_4^+$ $[M+H]^+$: 407.1965, Found 407.1966.



syn-**3g**

The general procedure was followed using isatoic anhydride **1g** (39 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:20→1:10, v/v) yielded *syn*-**3g** (20 mg, 45%) as a yellow solid.

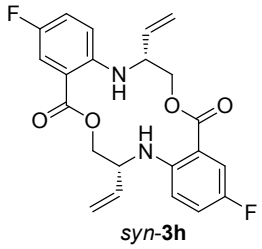
***Syn*-2,11-dimethoxy-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3g):**

M. p. 186−188 °C.

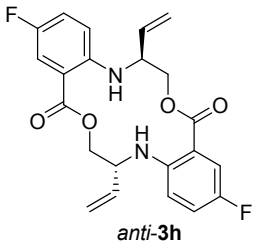
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 3.1 Hz, 2H), 6.96 (dd, J = 9.1, 3.1 Hz, 2H), 6.67 (d, J = 6.6 Hz, 2H), 6.58 (d, J = 9.1 Hz, 2H), 5.93–5.81 (m, 2H), 5.41 (dt, J = 17.1, 1.3 Hz, 2H), 5.30–5.25 (m, 2H), 4.98 (dd, J = 11.3, 6.6 Hz, 2H), 4.29 (dd, J = 11.3, 3.4 Hz, 2H), 4.21 (s, 2H), 3.73 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C_q), 150.4 (C_q), 143.4 (C_q), 135.0 (CH), 122.7 (CH), 117.9 (CH_2), 114.8 (CH), 114.3 (CH), 113.3 (C_q), 65.9 (CH_2), 56.4 (CH), 55.8 (CH_3).

HRMS (ESI) m/z calcd for $C_{24}H_{27}N_2O_6^+$ $[M+H]^+$: 439.1864, Found 439.1863.



syn-**3h**



anti-**3h**

The general procedure was followed using isatoic anhydride **1h** (37 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3h** (13 mg, 31%) as a white solid and *anti*-**3h** (13 mg, 31%) as a white solid (total yields of **3h**: 62%).

***Syn*-2,11-difluoro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3h):**

M. p. 185−187 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 9.2, 3.1 Hz, 2H), 7.03 (ddd, J = 9.2, 7.9, 3.1 Hz, 2H), 6.87 (d, J = 7.0 Hz, 2H), 6.51 (dd, J = 9.2, 4.4 Hz, 2H), 5.87 (ddd, J = 17.0, 10.3, 4.6 Hz, 2H), 5.45 (d, J = 17.2 Hz, 2H), 5.32 (d, J = 10.4 Hz, 2H), 5.06 (dd, J = 11.2, 8.0 Hz, 2H), 4.23–4.07 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5 (d, $^4J_{C–F}$ = 2.7 Hz, C_q), 153.8 (d, $^1J_{C–F}$ = 235.5 Hz, C_q), 145.5 (d, $^4J_{C–F}$ = 1.3 Hz, C_q), 134.2 (CH), 121.6 (d, $^2J_{C–F}$ = 22.8 Hz, CH), 118.1 (CH_2), 116.8 (d, $^2J_{C–F}$ = 23.6 Hz, CH), 113.6 (d, $^3J_{C–F}$ = 7.0 Hz, CH), 113.4 (d, $^3J_{C–F}$ = 6.7 Hz, C_q), 65.4 (CH_2), 57.4 (CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ –128.8.

HRMS (ESI) m/z calcd for $C_{22}H_{21}F_2N_2O_4^+$ $[M+H]^+$:415.1464, Found 415.1465.

***Anti*-2,11-difluoro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3h):**

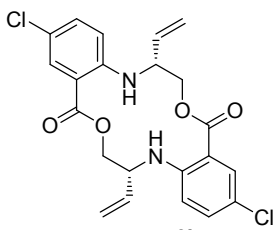
M. p. 227−228 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 8.8, 6.7 Hz, 2H), 7.29–7.19 (m, 2H), 6.37 – 6.27 (m, 2H), 6.22 (dd, J = 11.9, 2.4 Hz, 2H), 5.85 (ddd, J = 17.0, 10.3, 4.6 Hz, 2H), 5.45 (d, J = 17.2 Hz, 2H), 5.33 (d, J = 10.4 Hz, 2H), 5.09 (dd, J = 11.2, 8.0 Hz, 2H), 4.11 (dt, J = 17.7, 6.0 Hz, 4H).

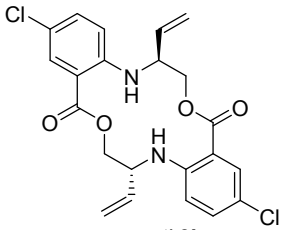
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C_q), 166.9 (d, $^1J_{C–F}$ = 251.3 Hz, C_q), 151.0 (d, $^3J_{C–F}$ = 12.6 Hz, C_q), 133.8 (d, $^3J_{C–F}$ = 11.6 Hz, CH), 133.6 (CH), 118.3 (CH_2), 109.7 (d, $^4J_{C–F}$ = 1.9 Hz, C_q), 103.5 (d, $^2J_{C–F}$ = 22.8 Hz, CH), 98.8 (d, $^2J_{C–F}$ = 26.2 Hz, CH), 64.9 (CH_2), 57.3 (CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ –103.7.

HRMS (ESI) m/z calcd for $C_{22}H_{21}F_2N_2O_4^+$ $[M+H]^+$:415.1464, Found 415.1467.



syn-**3i**



anti-**3i**

The general procedure was followed using isatoic anhydride **1i** (40 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3i** (15 mg, 33%) as a white solid and *anti*-**3i** (14 mg, 31%) as a white solid (total yields of **3i**: 64%).

***Syn*-2,11-dichloro-6,15-divinyl-6,7,15,16-**

tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3i):

M. p. 215−218 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 2.6 Hz, 2H), 7.20 (dd, J = 9.0, 2.6 Hz, 2H), 7.04 (d, J = 7.0 Hz, 2H), 6.49 (d, J = 9.0 Hz, 2H), 5.85 (ddd, J = 17.1, 10.3, 4.6 Hz, 2H), 5.45 (d, J = 17.2 Hz, 2H), 5.32 (d, J = 10.3 Hz, 2H), 5.10 (dd, J = 12.3, 9.6 Hz, 2H), 4.11 (dd, J = 12.3, 3.4 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C_q), 147.5 (C_q), 134.1 (CH), 133.7 (CH), 130.4 (CH), 120.6 (C_q), 118.2 (CH_2), 114.2 (C_q), 113.8 (CH), 65.1 (CH_2), 57.5 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{21}Cl_2N_2O_4^+$ $[M+H]^+$: 447.0873, Found 447.0875.

***Anti*-2,11-dichloro-6,15-divinyl-6,7,15,16-**

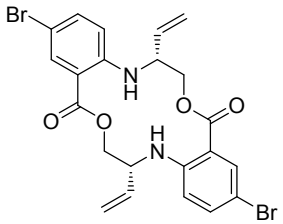
tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3i):

M. p. 214−216 °C.

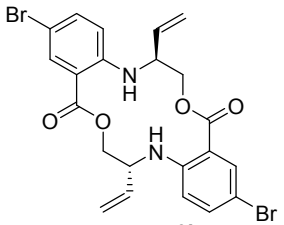
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 2.6 Hz, 2H), 7.31 (dd, J = 9.0, 2.6 Hz, 2H), 7.21 (d, J = 9.9 Hz, 2H), 6.80 (d, J = 9.1 Hz, 2H), 5.98 (ddd, J = 17.2, 10.5, 4.9 Hz, 2H), 5.41 (d, J = 17.5 Hz, 2H), 5.32 (d, J = 10.8 Hz, 2H), 5.03 (dd, J = 11.1, 3.0 Hz, 2H), 4.50–4.41 (m, 2H), 4.13 (dd, J = 11.1, 2.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 (C_q), 148.3 (C_q), 135.3 (CH), 134.2 (CH), 131.2 (CH), 121.5 (C_q), 117.4 (CH_2), 115.3 (CH), 114.6 (C_q), 64.2 (CH_2), 55.4 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{21}Cl_2N_2O_4^+$ $[M+H]^+$: 447.0873, Found 447.0876.



syn-**3j**



anti-**3j**

The general procedure was followed using isatoic anhydride **1j** (49 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3j** (16 mg, 30%) as a white solid and *anti*-**3j** (15 mg, 28%) as a white solid (total yields of **3j**: 58%).

***Syn*-2,11-dibromo-6,15-divinyl-6,7,15,16-**

tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3j):

M. p. 210−212 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 2.4 Hz, 2H), 7.32 (dd, J = 8.9, 2.4 Hz, 2H), 7.06 (d, J = 7.0 Hz, 2H), 6.43 (d, J = 9.0 Hz, 2H), 5.85 (ddd, J = 17.0, 10.3, 4.5 Hz, 2H), 5.44 (d, J = 17.2 Hz, 2H), 5.32 (d, J = 10.4 Hz, 2H), 5.11 (dd, J = 12.3, 9.7 Hz, 2H), 4.17–4.04 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C_q), 147.9 (C_q), 136.8 (CH), 133.6 (CH), 133.2 (CH), 118.3 (CH_2), 114.8 (C_q), 114.2 (CH), 107.4 (C_q), 65.1 (CH_2), 57.6 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{21}Br_2N_2O_4^+$ $[M+H]^+$: 534.9863, Found 534.9862.

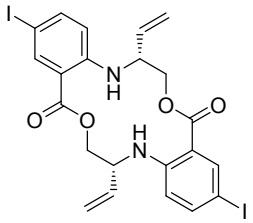
***Anti*-2,11-dibromo-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3j):**

M. p. 215−216 °C.

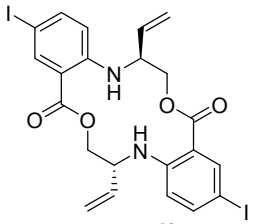
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 2.5 Hz, 2H), 7.43 (dd, J = 9.0, 2.5 Hz, 2H), 7.21 (d, J = 9.8 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 5.98 (ddd, J = 17.2, 10.5, 4.9 Hz, 2H), 5.40 (dd, J = 17.2, 0.7 Hz, 2H), 5.32 (d, J = 10.5 Hz, 2H), 5.02 (dd, J = 11.1, 3.0 Hz, 2H), 4.50–4.38 (m, 2H), 4.15 (dd, J = 11.1, 2.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C_q), 148.6 (C_q), 137.0 (CH), 135.2 (CH), 134.2 (CH), 117.4 (CH_2), 115.6 (CH), 115.1 (C_q), 108.3 (C_q), 64.2 (CH_2), 55.3 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{21}Br_2N_2O_4^+$ $[M+H]^+$: 534.9863, Found 534.9861.



syn-**3k**



anti-**3k**

The general procedure was followed using isatoic anhydride **1k** (58 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:10, v/v) yielded *syn*-**3k** (16 mg, 25%) as a white solid and *anti*-**3k** (13 mg, 20%) as a yellow solid (total yields of **3k**: 45%).

***Syn*-2,11-diiodo-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3k):**

M. p. 200−201 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 2.2 Hz, 2H), 7.48 (dd, J = 8.9, 2.1 Hz, 2H), 7.07 (d, J =

7.0 Hz, 2H), 6.33 (d, J = 8.9 Hz, 2H), 5.84 (ddd, J = 17.0, 10.3, 4.5 Hz, 2H), 5.44 (d, J = 17.1 Hz, 2H), 5.32 (d, J = 10.3 Hz, 2H), 5.10 (dd, J = 11.1, 8.6 Hz, 2H), 4.08 (dd, J = 14.9, 4.3 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (C_q), 148.3 (C_q), 142.4 (CH), 139.1 (CH), 133.5 (CH), 118.2 (CH_2), 115.4 (C_q), 114.6 (CH), 75.9 (C_q), 65.0 (CH_2), 57.5 (CH).

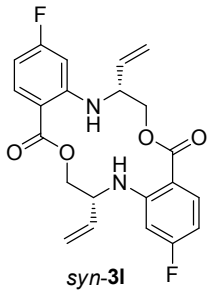
HRMS (ESI) m/z calcd for $C_{22}H_{21}I_2N_2O_4^+$ $[M+H]^+$:630.9585, Found 630.9582.

***Anti*-2,11-diiodo-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3k):**

M. p. = 204−205°C.

Solid-state ^{13}C NMR (100.6 MHz) δ 170.0 (C_q), 152.9 (C_q), 143.4 (CH), 138.5 (CH), 134.0 (CH), 119.1 (CH_2), 116.4 (C_q), 79.6 (CH), 66.5 (C_q), 56.6 (CH_2), 52.6 (CH).

HRMS (ESI) m/z calcd for $C_{22}H_{21}I_2N_2O_4^+$ $[M+H]^+$:630.9585, Found 630.9583.



syn-**3l**

The general procedure was followed using isatoic anhydride **1l** (37 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:50→1:20, v/v) yielded *syn*-**3l** (15 mg, 36%) as a white solid.

***Syn*-3,12-difluoro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3l):**

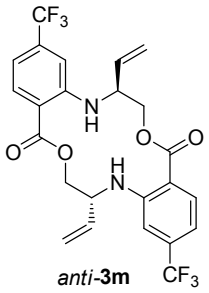
M. p. 153−156 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 8.7, 6.8 Hz, 2H), 7.23 (d, J = 6.3 Hz, 2H), 6.31 (td, J = 8.5, 2.3 Hz, 2H), 6.22 (dd, J = 11.9, 2.3 Hz, 2H), 5.85 (ddd, J = 17.0, 10.3, 4.6 Hz, 2H), 5.45 (d, J = 17.2 Hz, 2H), 5.33 (d, J = 10.4 Hz, 2H), 5.09 (dd, J = 11.2, 8.1 Hz, 2H), 4.13 (dd, J = 16.5, 5.4 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8 (C_q), 166.9 (d, $^1J_{C–F}$ = 251.3 Hz, C_q), 151.1 (d, $^3J_{C–F}$ = 12.4 Hz, C_q), 133.8 (d, $^3J_{C–F}$ = 11.6 Hz, CH), 133.6 (CH), 118.3 (CH_2), 109.7 (d, $^4J_{C–F}$ = 1.9 Hz, C_q), 103.6 (d, $^2J_{C–F}$ = 22.8 Hz, CH), 98.9 (d, $^2J_{C–F}$ = 26.2 Hz, CH), 64.9 (CH_2), 57.3 (CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ –103.7.

HRMS (ESI) m/z calcd for $C_{22}H_{21}F_2N_2O_4^+$ $[M+H]^+$:415.1464, Found 415.1466.



anti-**3m**

The general procedure was followed using isatoic anhydride **1m** (47 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:20→1:10, v/v) yielded *anti*-**3m** (27 mg, 52%) as a white solid.

***Anti*-3,12-bis(trifluoromethyl)-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*anti*-3m):**

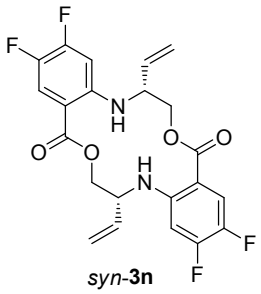
M. p. 245−246 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.03 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 9.9 Hz, 2H), 7.14 (s, 2H), 6.98 (d, J = 8.3 Hz, 2H), 6.04 (tt, J = 23.6, 8.9 Hz, 2H), 5.44 (d, J = 17.3 Hz, 2H), 5.35 (d, J = 5.1 Hz, 2H), 5.10 (dd, J = 11.2, 3.0 Hz, 2H), 4.66–4.50 (m, 2H), 4.19 (dd, J = 11.2, 1.7 Hz, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 167.0 (C_q), 150.2 (C_q), 135.6 (q, $^2J_{C–F}$ = 32.0 Hz, C_q), 135.6 (CH), 133.1 (CH), 124.2 (q, $^1J_{C–F}$ = 273.0 Hz, C_q), 117.5 (CH_2), 116.6 (C_q), 113.1 (q, $^3J_{C–F}$ = 3.6 Hz, CH), 111.0 (q, $^3J_{C–F}$ = 4.0 Hz, CH), 64.7 (CH_2), 55.5 (CH).

^{19}F NMR (376 MHz, CD_2Cl_2) δ –64.0.

HRMS (ESI) m/z calcd for $C_{24}H_{21}F_6N_2O_4^+$ $[M+H]^+$:515.1400, Found 515.1404.



syn-**3n**

The general procedure was followed using isatoic anhydride **1n** (40 mg, 0.20 mmol, 1.0 equiv), VEC **2a** (35 mg, 0.30 mmol, 1.5 equiv). After 12 h, purification by column chromatography on silica gel (EtOAc/PE = 1:20→1:10, v/v) yielded *syn*-**3n** (19 mg, 42%) as a white solid.

***Syn*-2,3,11,12-tetrafluoro-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (*syn*-3n):**

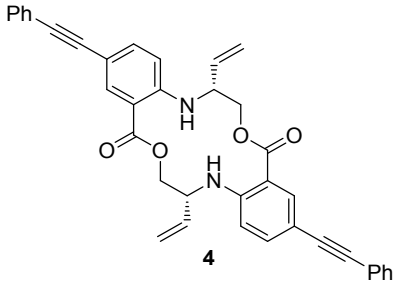
M. p. 200−203 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 10.8, 9.1 Hz, 2H), 7.06 (d, J = 6.8 Hz, 2H), 6.32 (dd, J = 13.0, 6.6 Hz, 2H), 5.84 (ddd, J = 17.0, 10.3, 4.7 Hz, 2H), 5.45 (d, J = 17.1 Hz, 2H), 5.34 (d, J = 10.3 Hz, 2H), 5.06 (dd, J = 11.6, 8.6 Hz, 2H), 4.14 (dd, J = 11.6, 3.5 Hz, 2H), 4.09–4.00 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (d, $^4J_{C–F}$ = 1.8 Hz, C_q), 154.6 (d, $^1J_{C–F}$ = 253.8 Hz; d, $^2J_{C–F}$ = 13.8 Hz, C_q), 146.9 (d, $^3J_{C–F}$ = 10.2 Hz, C_q), 141.6 (d, $^1J_{C–F}$ = 238.2 Hz; d, $^2J_{C–F}$ =13.5 Hz, C_q), 133.4 (CH), 119.4 (d, $^2J_{C–F}$ = 19.0 Hz; d, $^3J_{C–F}$ = 3.1 Hz, CH), 118.4 (CH_2), 108.4 (d, $^3J_{C–F}$ = 4.6 Hz; d, $^4J_{C–F}$ = 2.5 Hz, C_q), 100.9 (d, $^2J_{C–F}$ = 21.7 Hz, CH), 65.1 (CH_2), 57.8 (CH).

^{19}F NMR (376 MHz, $CDCl_3$) δ –127.4, –152.6.

HRMS (ESI) m/z calcd for $C_{22}H_{19}F_4N_2O_4^+$ $[M+H]^+$:451.1275, Found 451.1274.



4

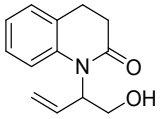
***Syn*-2,11-bis(phenylethynyl)-6,15-divinyl-6,7,15,16-tetrahydrodibenzo[*e*,*l*][1,8,4,11]dioxadiazacyclotetradecine-9,18(5*H*,14*H*)-dione (4):**

M. p. 205−207 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 1.9 Hz, 2H), 7.46 (dd, J = 11.1, 5.0 Hz, 4H), 7.42 (dd, J = 8.7, 1.7 Hz, 2H), 7.35–7.26 (m, 8H), 6.54 (t, J = 11.9 Hz, 2H), 5.88 (ddd, J = 16.9, 10.3, 4.6 Hz, 2H), 5.47 (d, J = 17.1 Hz, 2H), 5.34 (d, J = 10.3 Hz, 2H), 5.17 (dd, J = 11.4, 9.0 Hz, 2H), 4.19 (s, 2H), 4.11 (dd, J = 11.5, 3.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C_q), 148.5 (C_q), 137.1 (CH), 134.6 (CH), 133.7 (CH), 131.3 (CH), 128.2 (CH), 127.8 (CH), 123.6 (C_q), 118.2 (CH_2), 113.3 (C_q), 112.3 (CH), 110.4 (C_q), 89.0 (C_q), 87.6 (C_q), 65.0 (CH_2), 57.5 (CH).

HRMS (ESI) m/z calcd for $C_{38}H_{31}N_2O_4^+$ $[M+H]^+$: 579.2278, Found 579.2277.



7

1-(1-Hydroxybut-3-en-2-yl)-3,4-dihydroquinolin-2(1*H*)-one (7):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.11 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 7.00 (td, J = 7.4, 0.9 Hz, 1H), 6.15 (ddd, J = 17.4, 10.6, 5.1 Hz, 1H), 5.29–5.23 (m, 1H), 5.16 (ddd, J = 17.4, 1.7, 0.9 Hz, 1H), 4.87 (dt, J = 6.9, 4.9 Hz, 1H), 4.10 (s, 1H), 4.02 (dd, J = 11.7, 3.9 Hz, 1H), 3.53 (d, J = 31.6 Hz, 1H), 2.95–2.76 (m, 2H), 2.70–2.53 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C_q), 140.6 (C_q), 133.3 (CH), 128.0 (C_q), 127.6 (CH), 127.3 (CH), 123.5 (CH), 117.0 (CH_2), 116.5 (CH), 63.9 (CH_2), 62.2 (CH), 33.1 (CH_2), 25.5 (CH_2).

HRMS (ESI) m/z calcd for $C_{13}H_{16}NO_2^+$ $[M+H]^+$: 218.1176, Found 218.1177.

7. Photophysical data of compounds 3

Table S5. Maximum excitation, maximum emission and fluorescence quantum yields of 3

Compounds	λ_{ex} (nm)[a] in DCM	λ_{em} (nm)[a] in DCM	(Φ_f)[c] in DCM
syn-**3a**	320	397	26.15%
syn-**3c**	330	414	8.70%
syn-**3h**	330	419	11.14%
syn-**3j**	350	424	6.26%
syn-**3k**	330	-[d]	-[d]
syn-**3f**	330	415	16.26%
syn-**3n**	330	401	30.62%
anti-**3m**	330	417	36.19%
syn-**3i**	330	418	12.17%

[a]Excitation maximum in DCM. [b]Exmission maximum in DCM. [c]Absolute quantum yield determined in DCM with an integrating sphere system. [d]Quenched by the heavy atom effect of iodine.

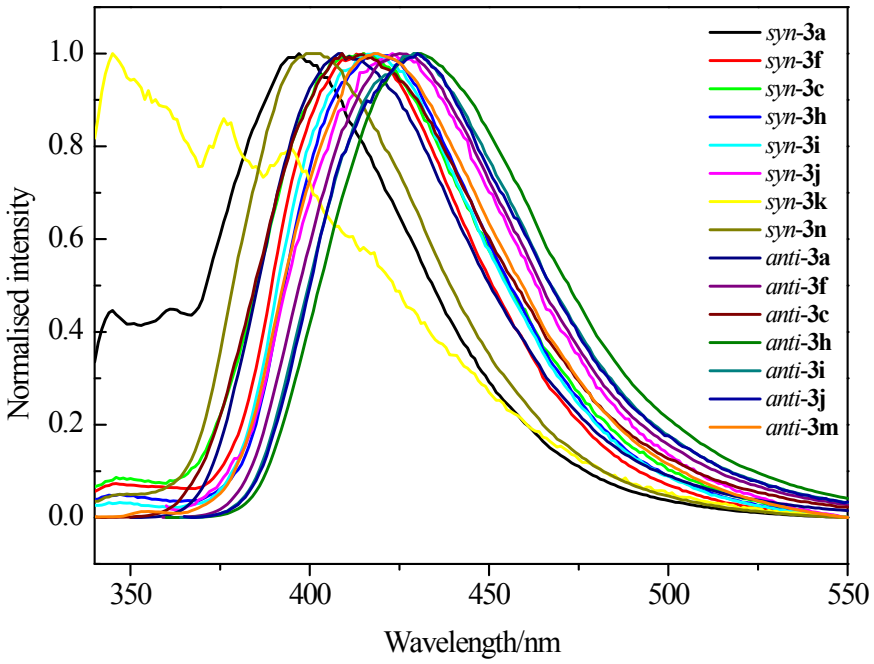


Figure S1. Normalized fluorescence spectra of aza-macrolides **3** in DCM.

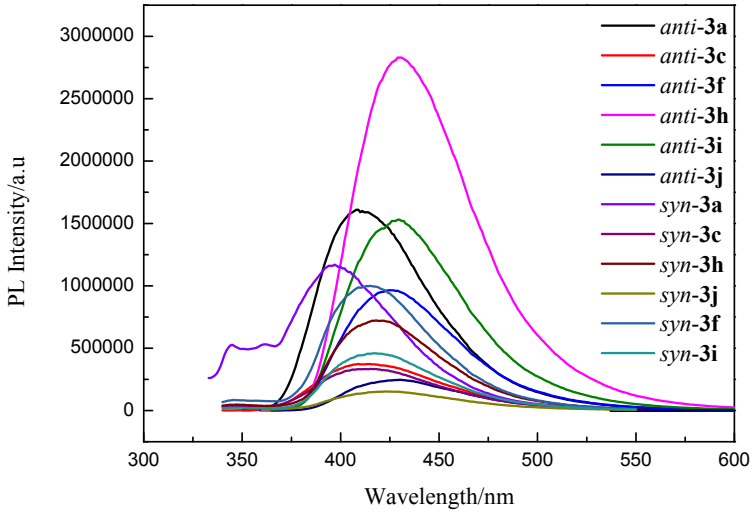


Figure S2. Fluorescence spectra of aza-macrolides **3** in DCM

.

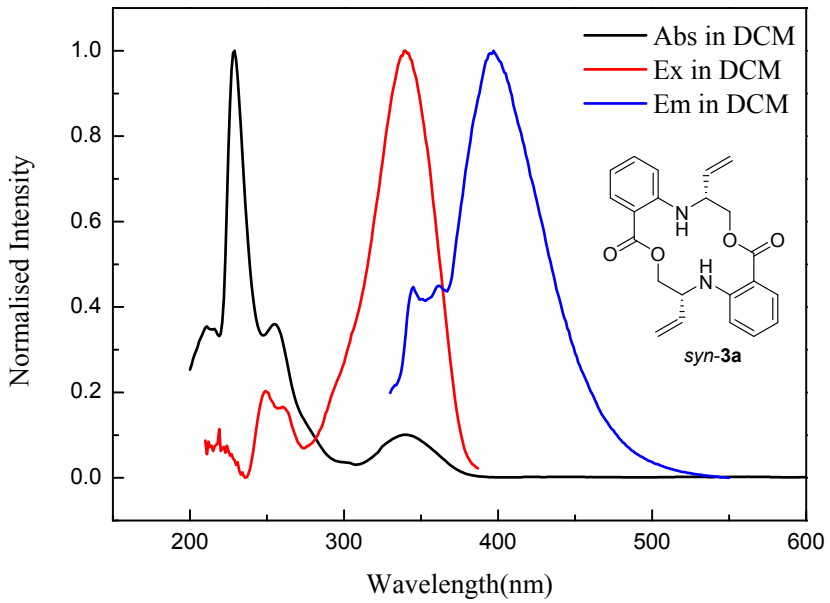


Figure S3. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3a** in DCM.

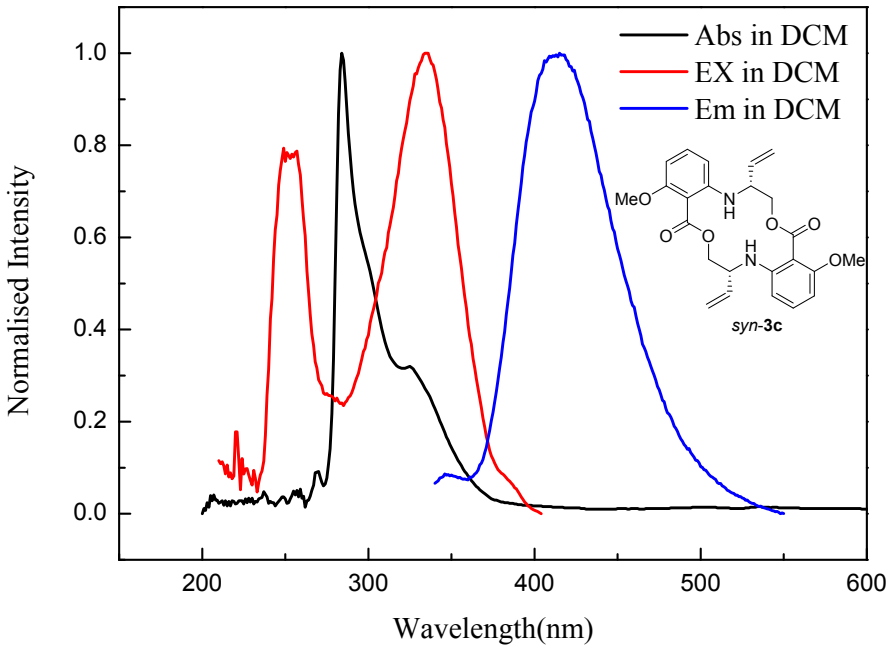


Figure S4. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3c** in DCM.

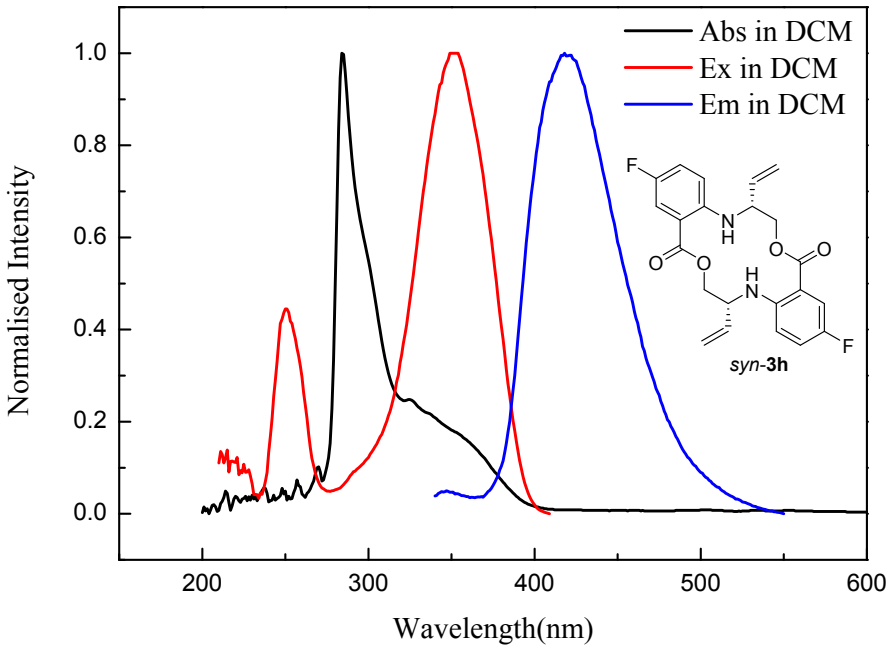


Figure S5. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3h** in DCM.

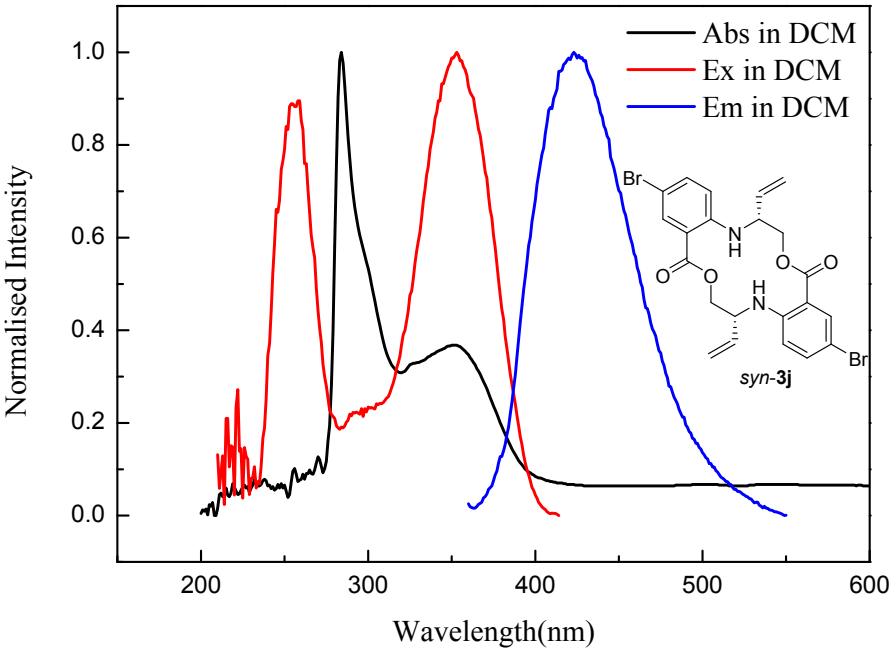


Figure S6. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3j** in DCM.

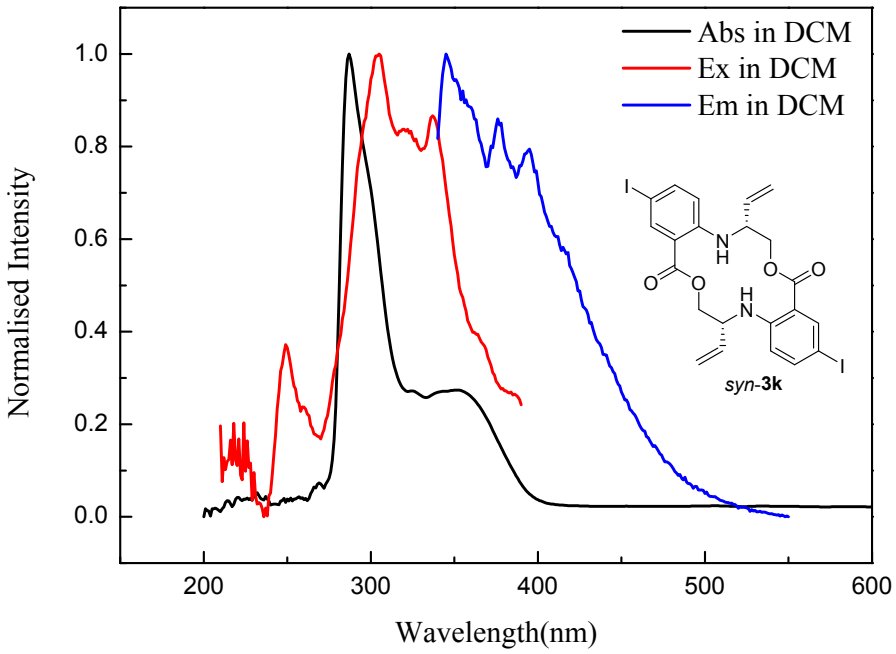


Figure S7. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3k** in DCM.

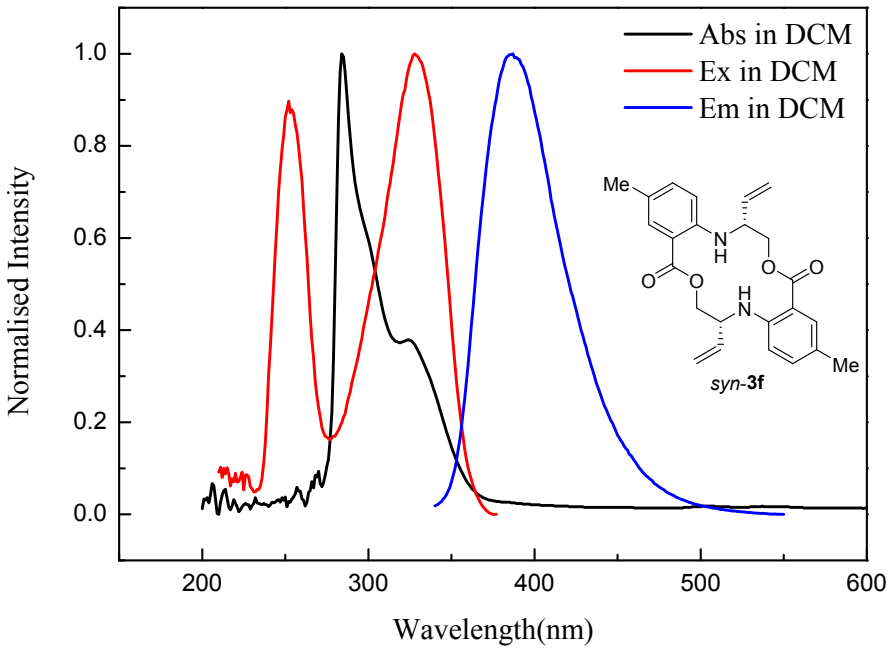


Figure S8. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3f** in DCM.

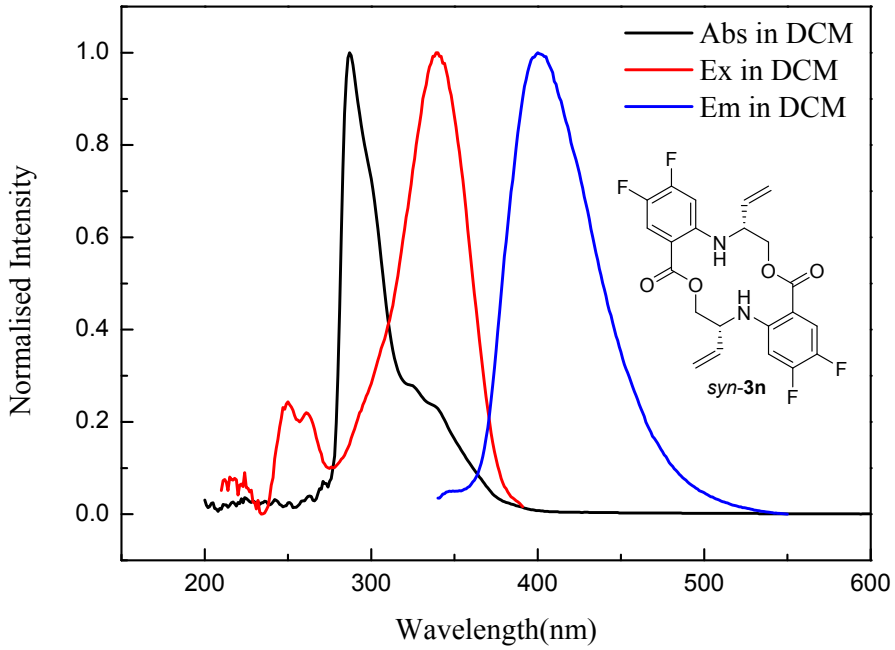


Figure S9. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3n** in DCM.

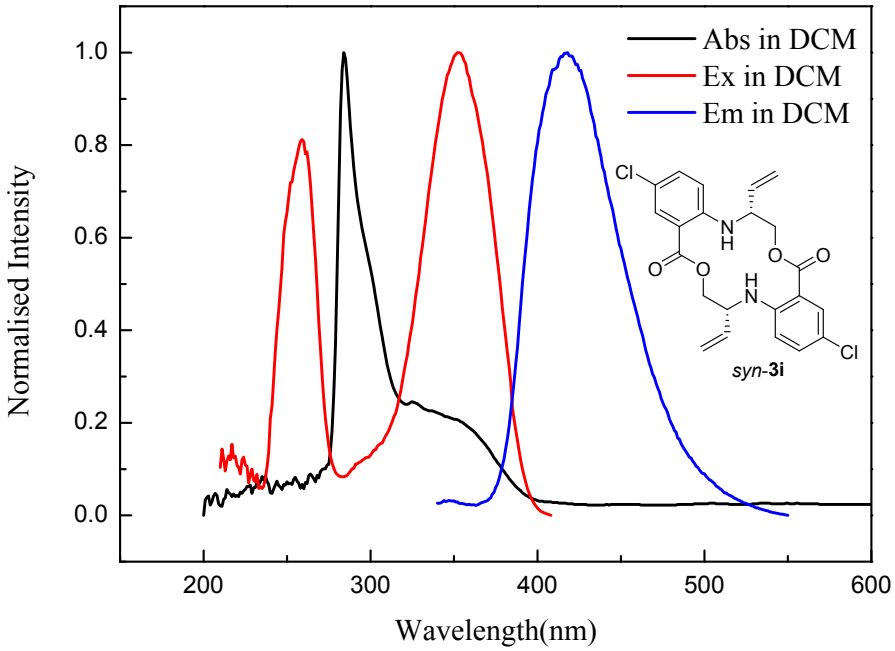


Figure S10. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *syn*-**3i** in DCM.

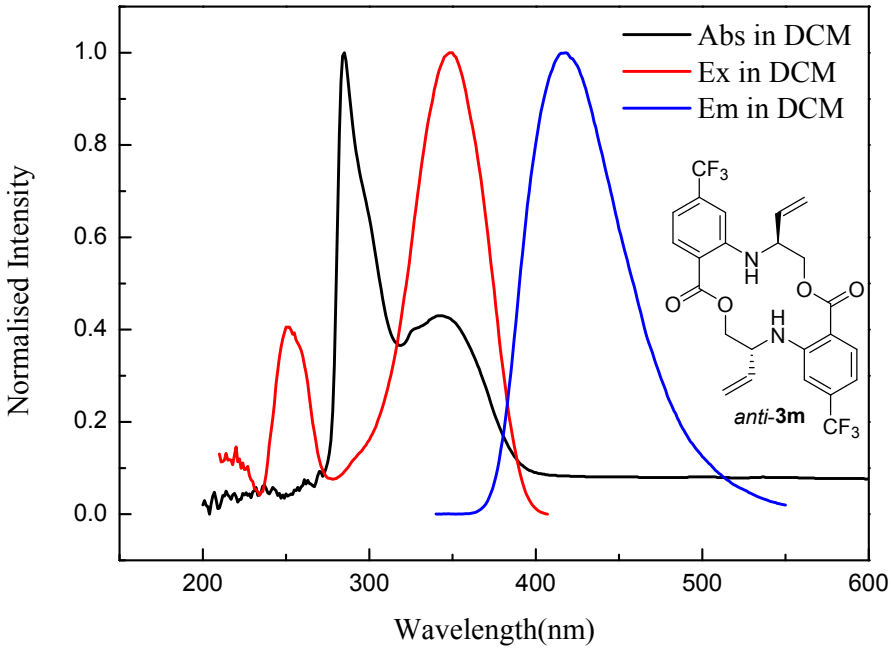


Figure S11. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *anti*-**3m** in DCM.

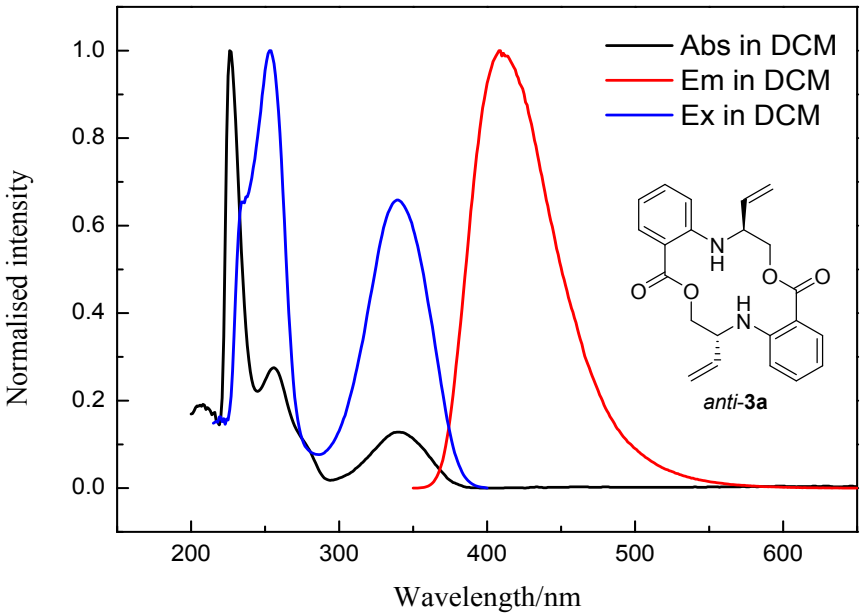


Figure S12. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *anti*-**3a** in DCM.

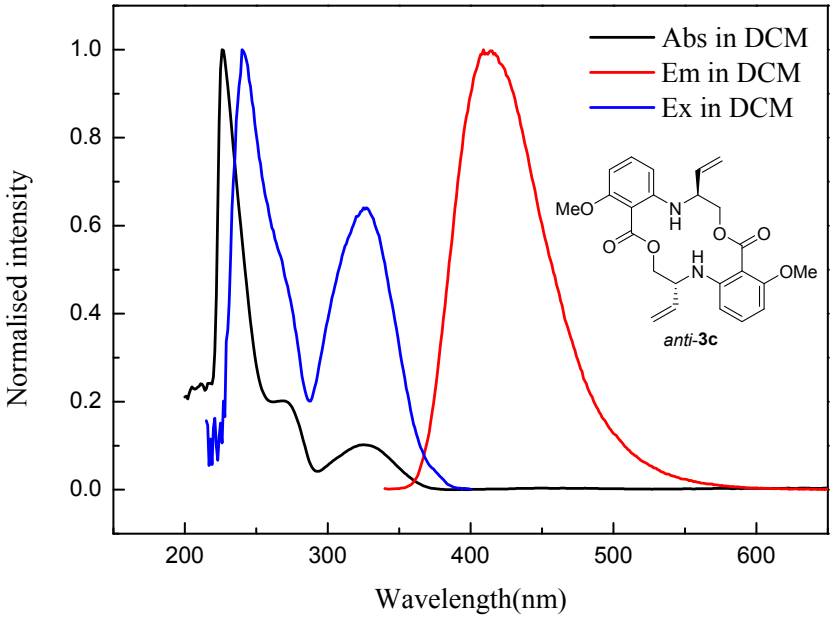


Figure S13. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *anti*-**3c** in DCM.

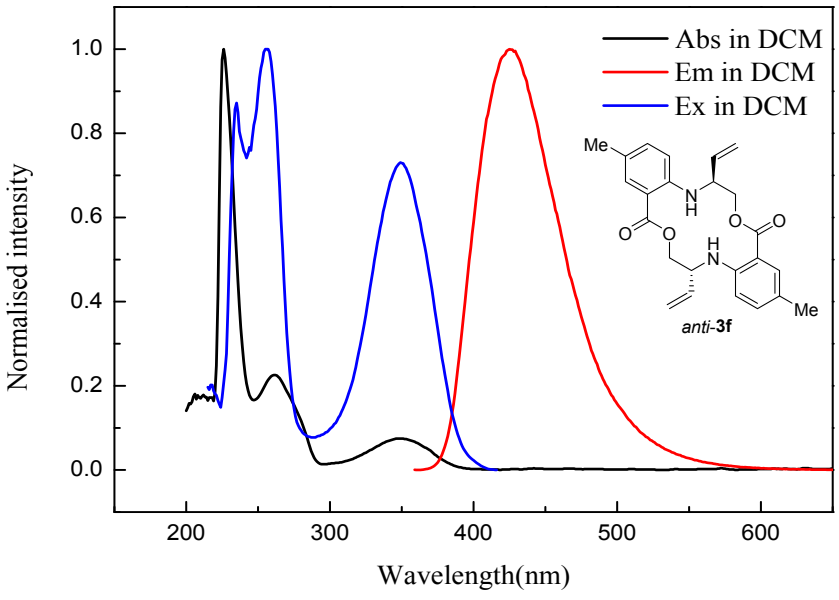


Figure S14. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *anti*-**3f** in DCM.

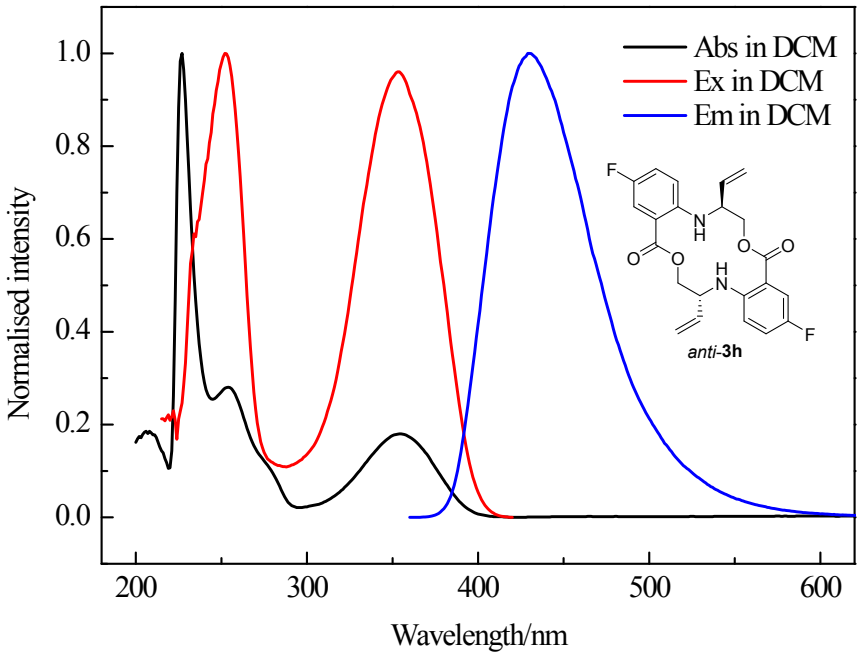


Figure S15. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *anti*-**3h** in DCM.

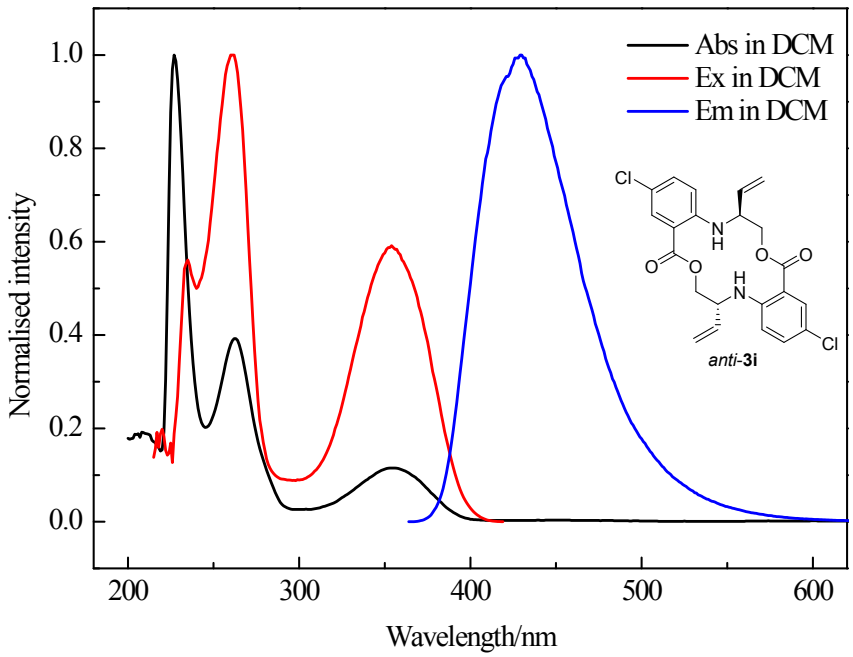


Figure S16. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *anti*-**3i** in DCM.

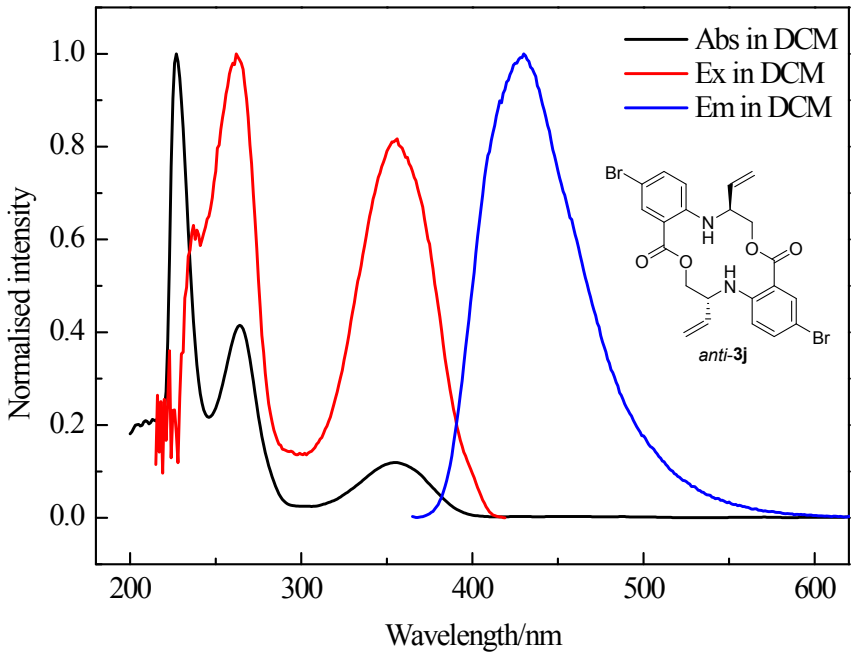
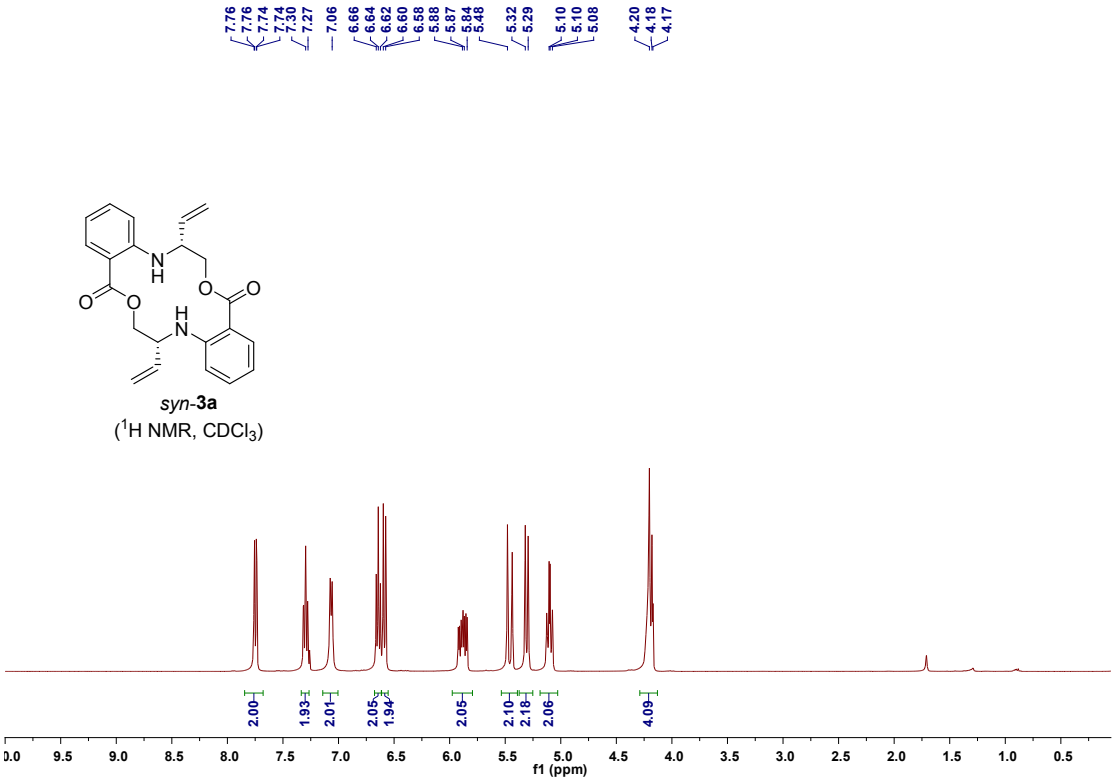
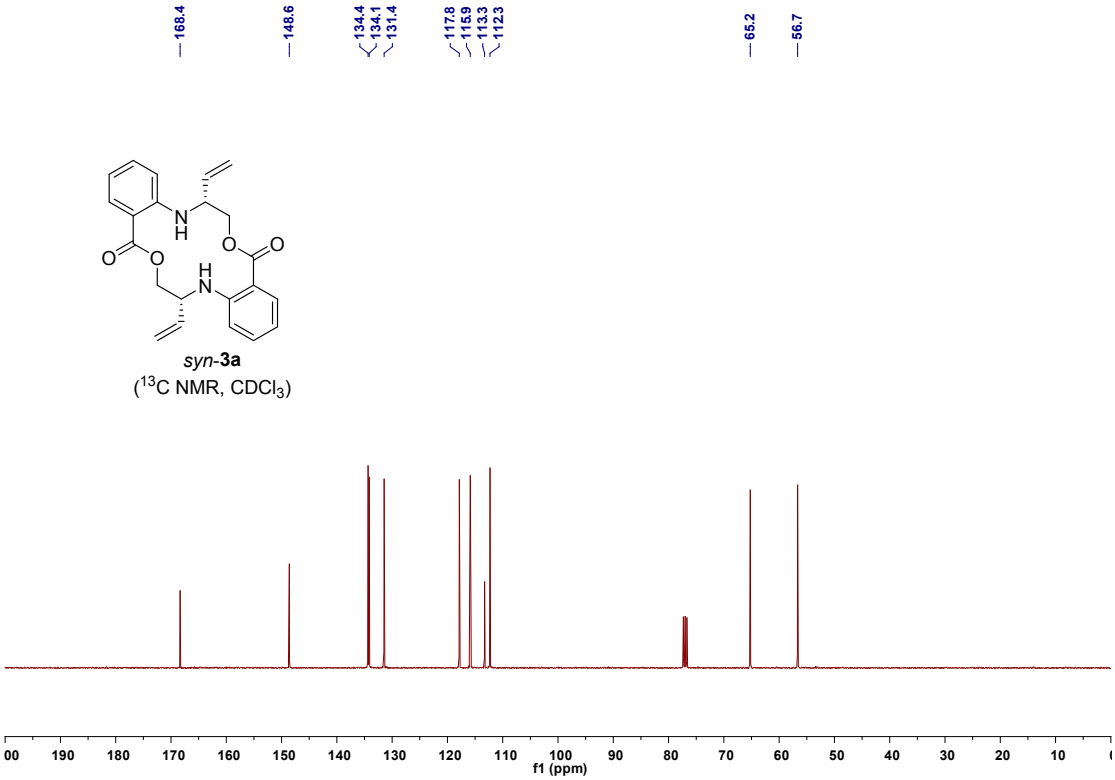


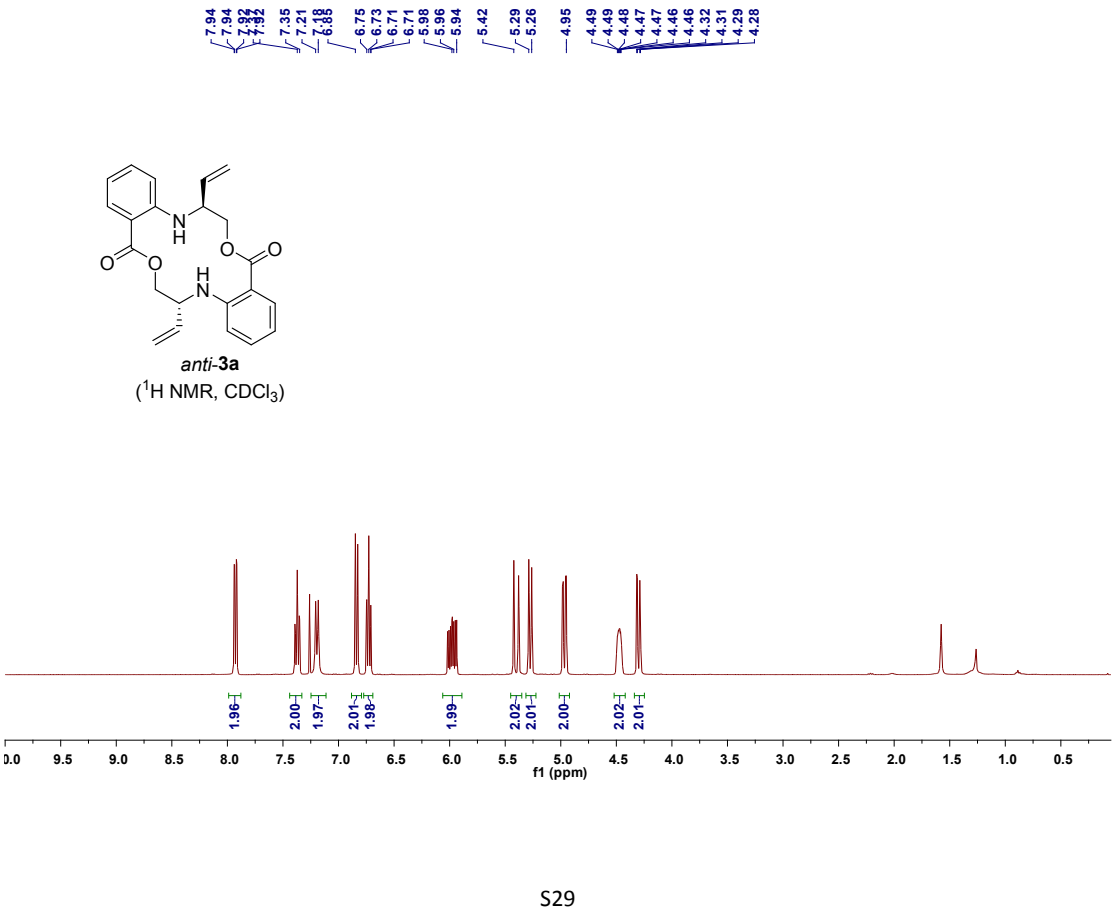
Figure S17. Normalized UV absorption spectra, fluorescence excitation spectra and fluorescence emission spectra of *anti*-**3j** in DCM.

8. NMR spectra of compounds 3

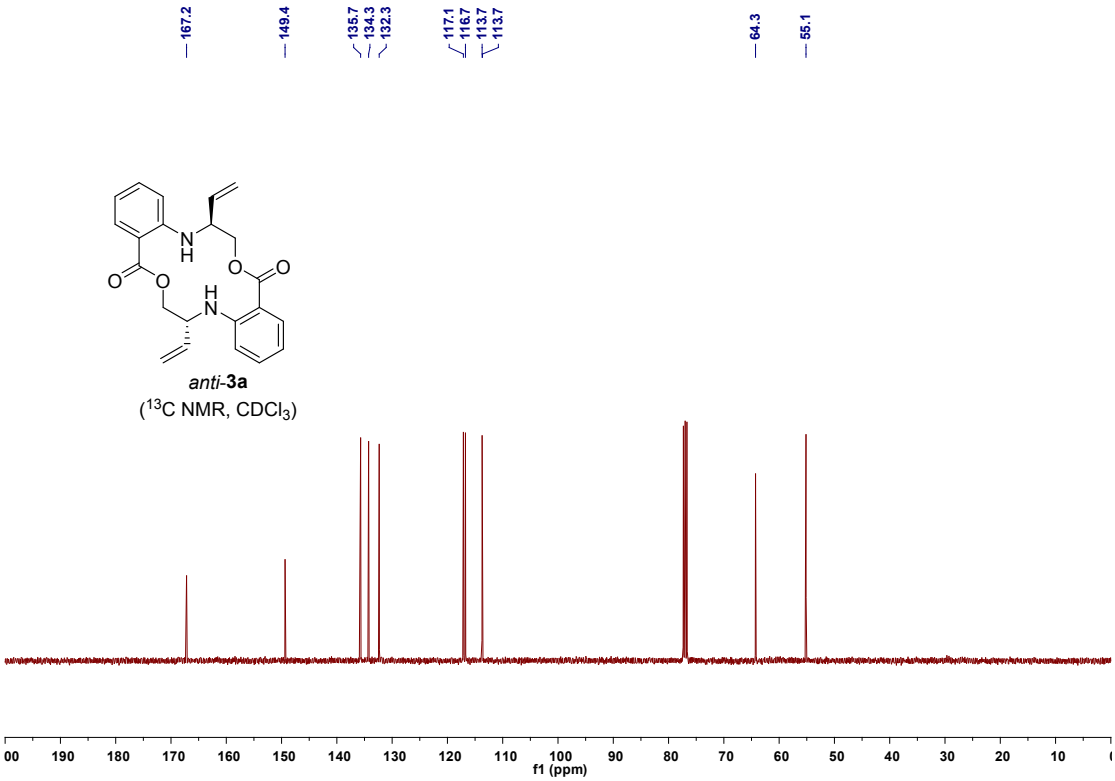




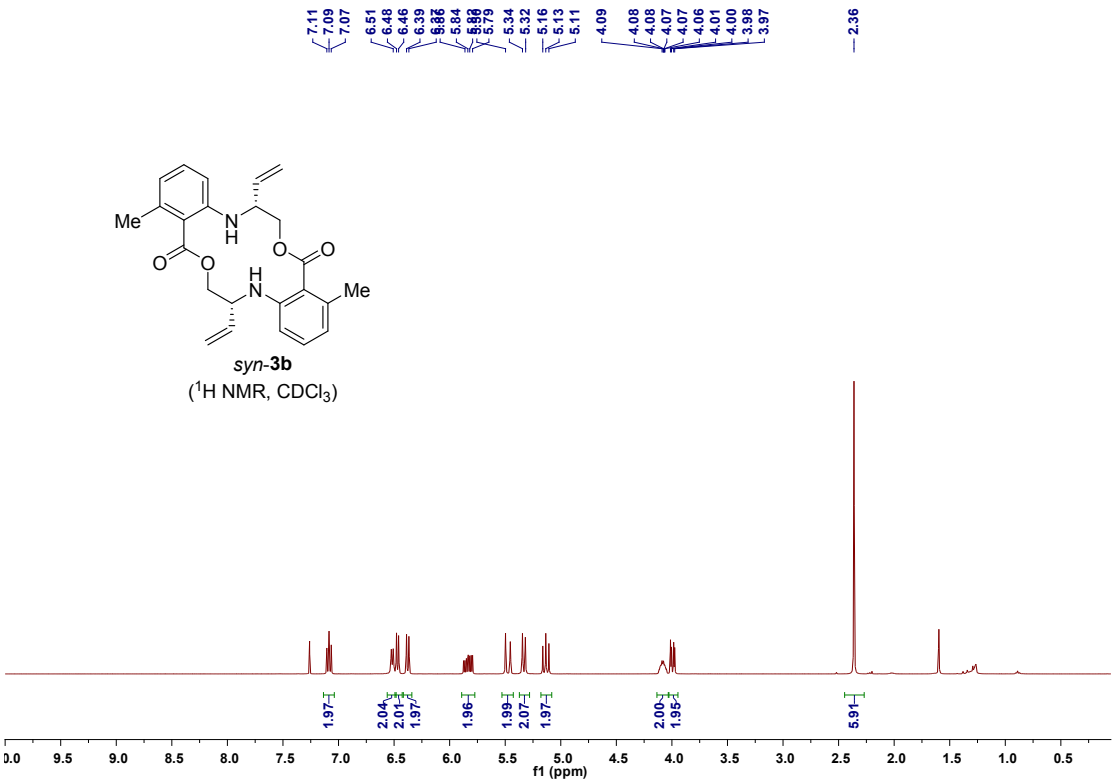
syn-**3a**
(^{13}C NMR, $CDCl_3$)



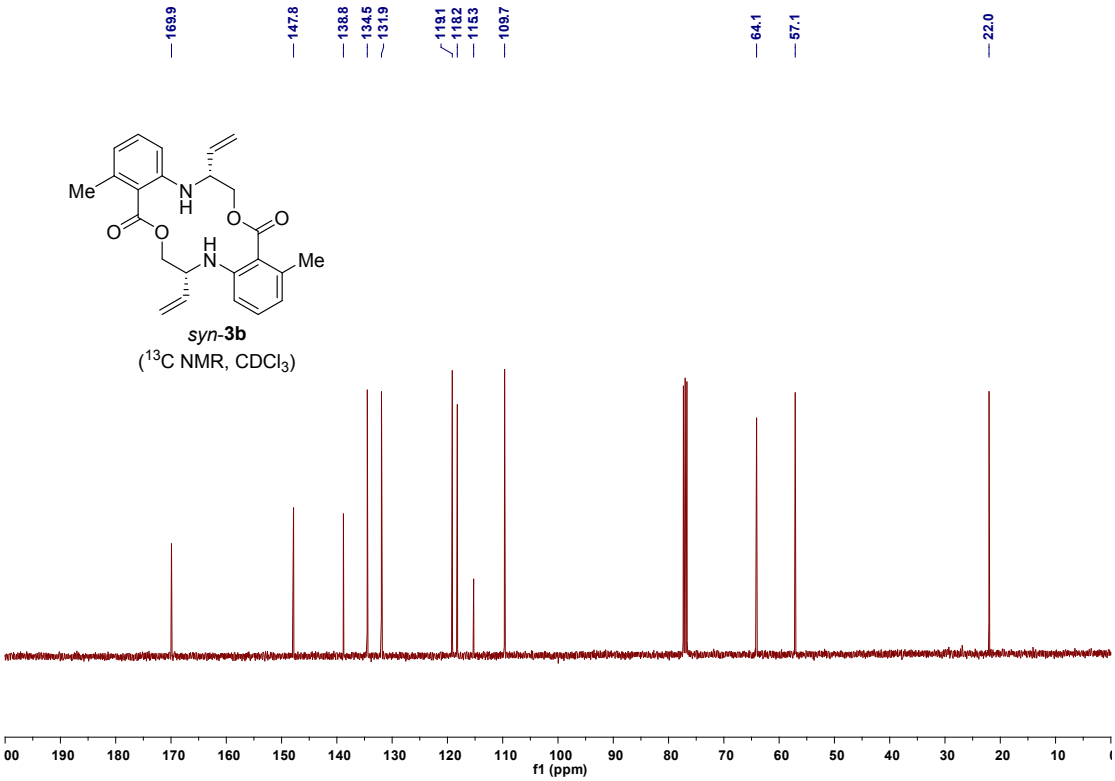
anti-**3a**
(^{1}H NMR, $CDCl_3$)



anti-**3a**
(^{13}C NMR, $CDCl_3$)

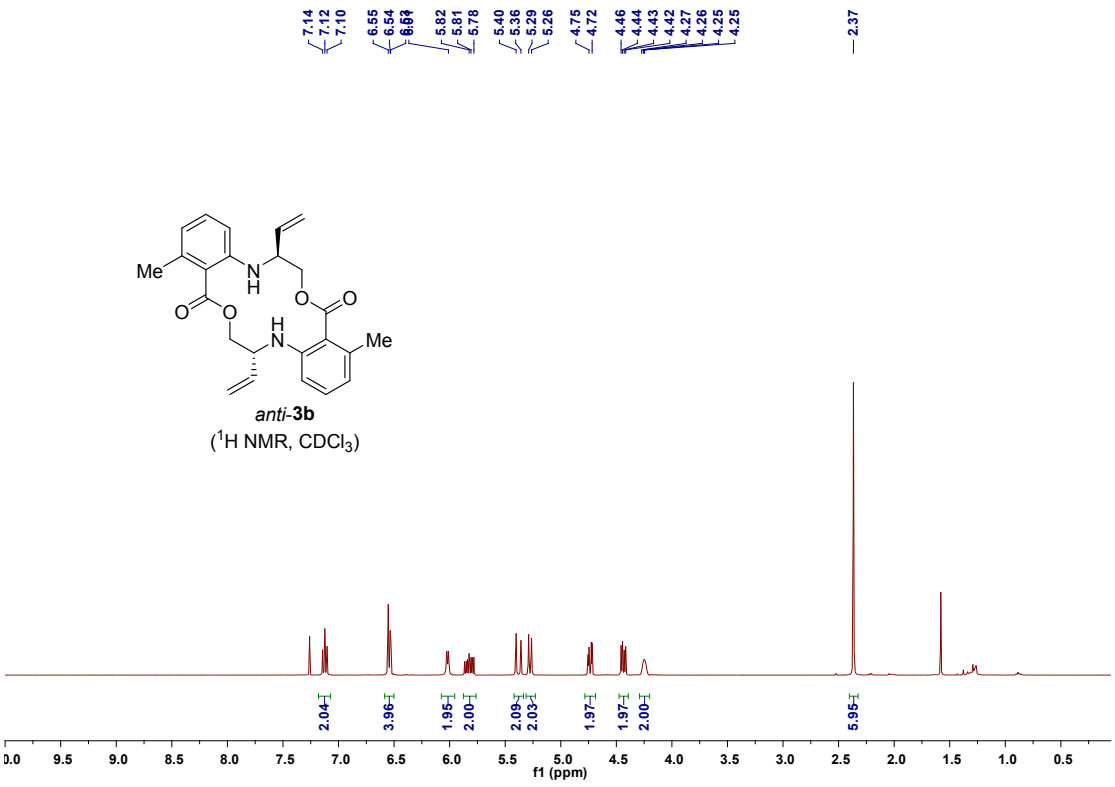


syn-**3b**
(^{1}H NMR, $CDCl_3$)



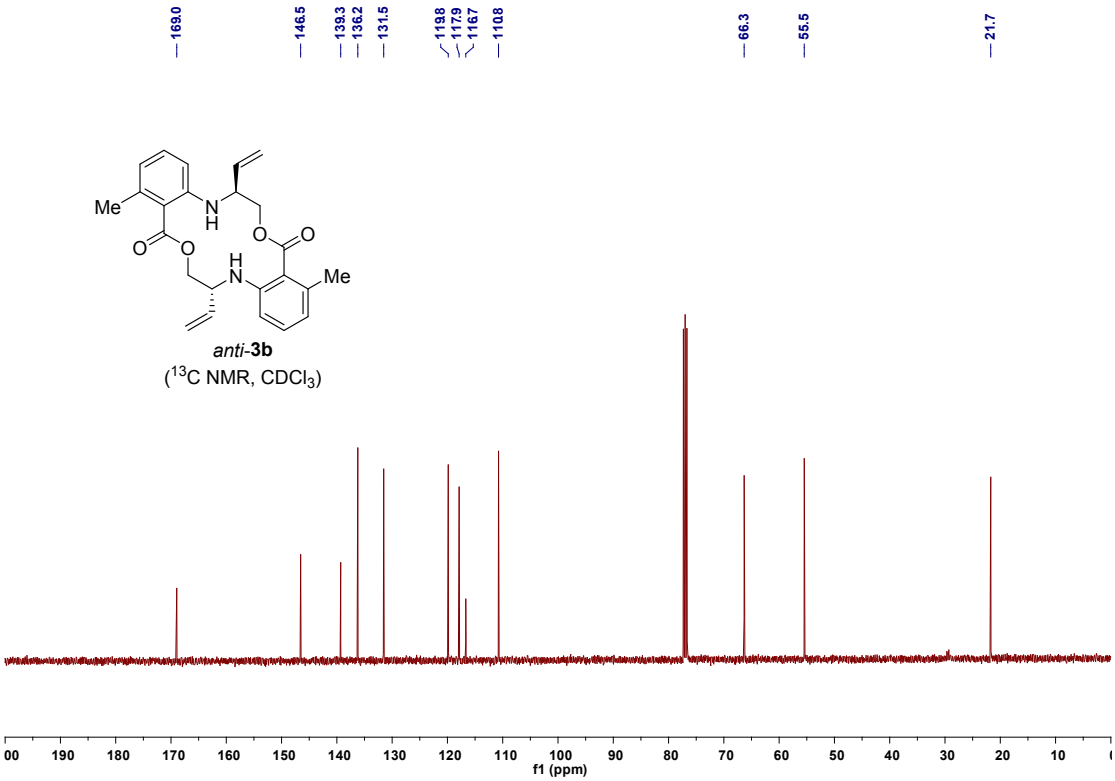
syn-**3b**

(^{13}C NMR, $CDCl_3$)



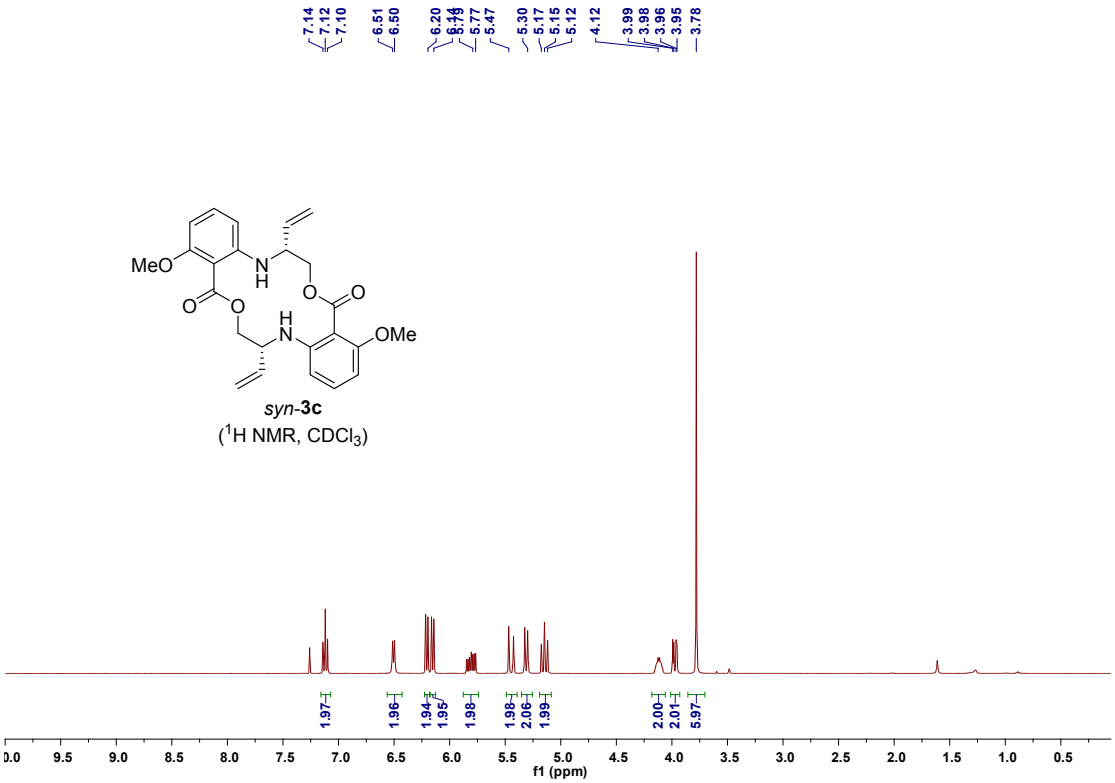
anti-**3b**

(^{1}H NMR, $CDCl_3$)



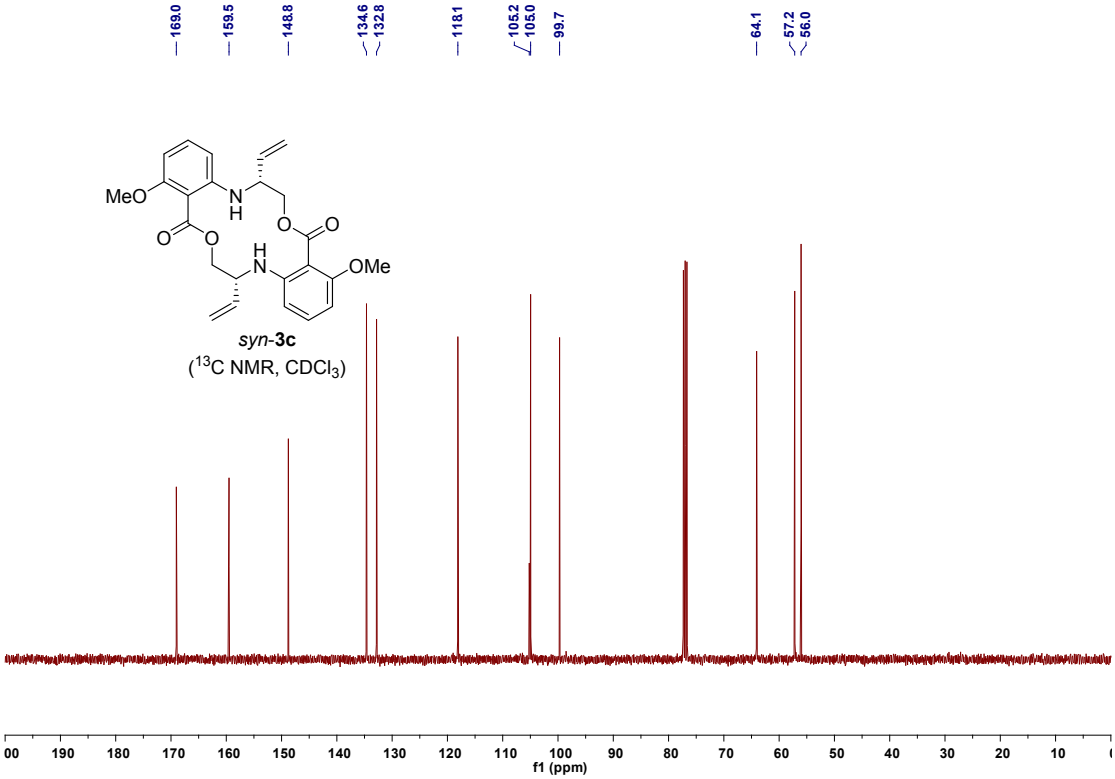
anti-**3b**

(^{13}C NMR, $CDCl_3$)



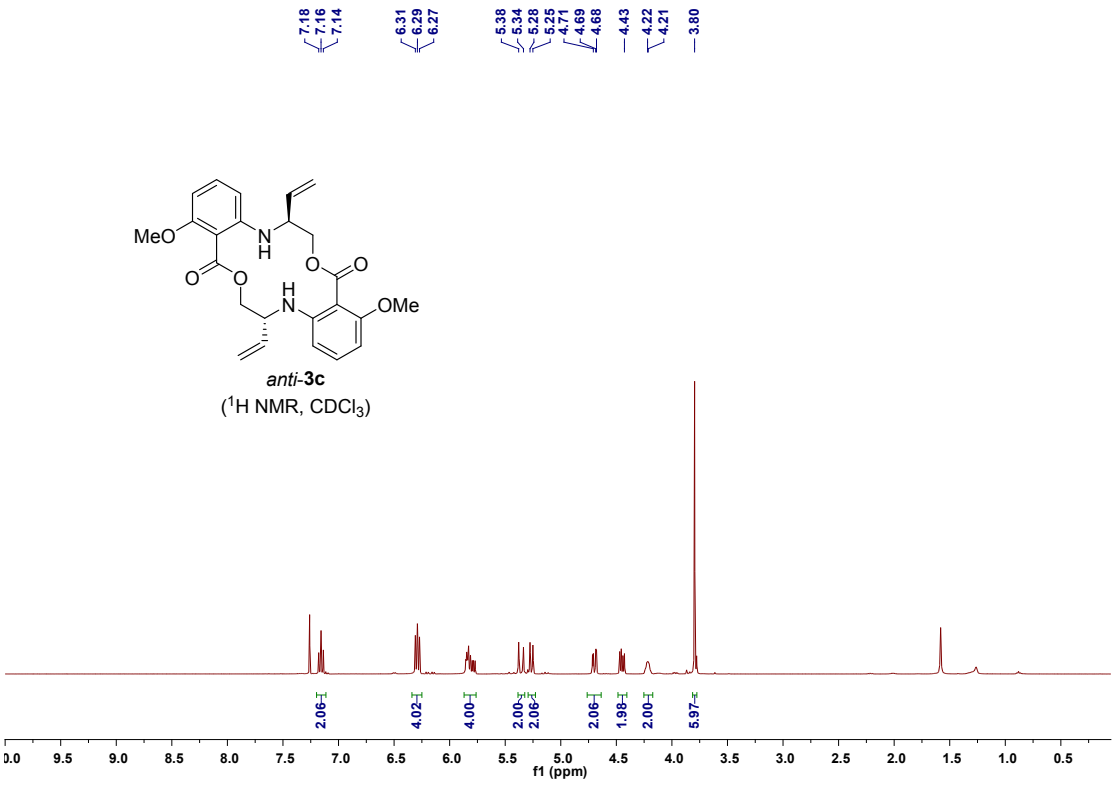
syn-**3c**

(^{1}H NMR, $CDCl_3$)



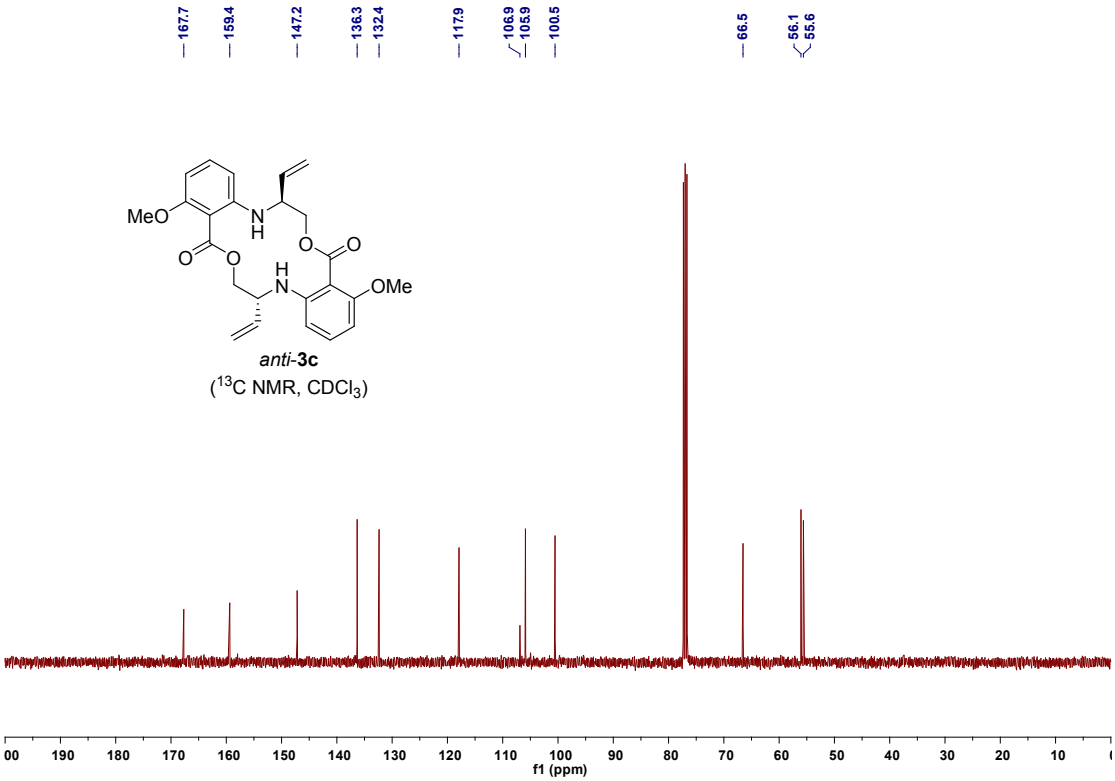
syn-**3c**

(^{13}C NMR, $CDCl_3$)

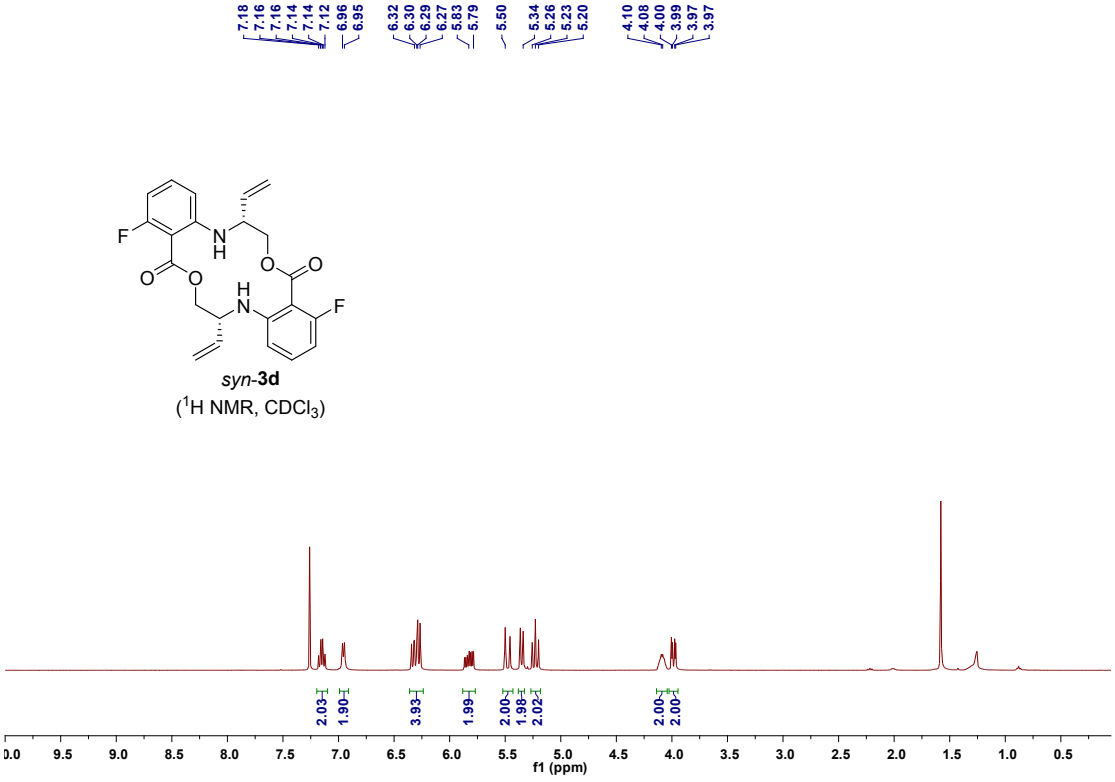


anti-**3c**

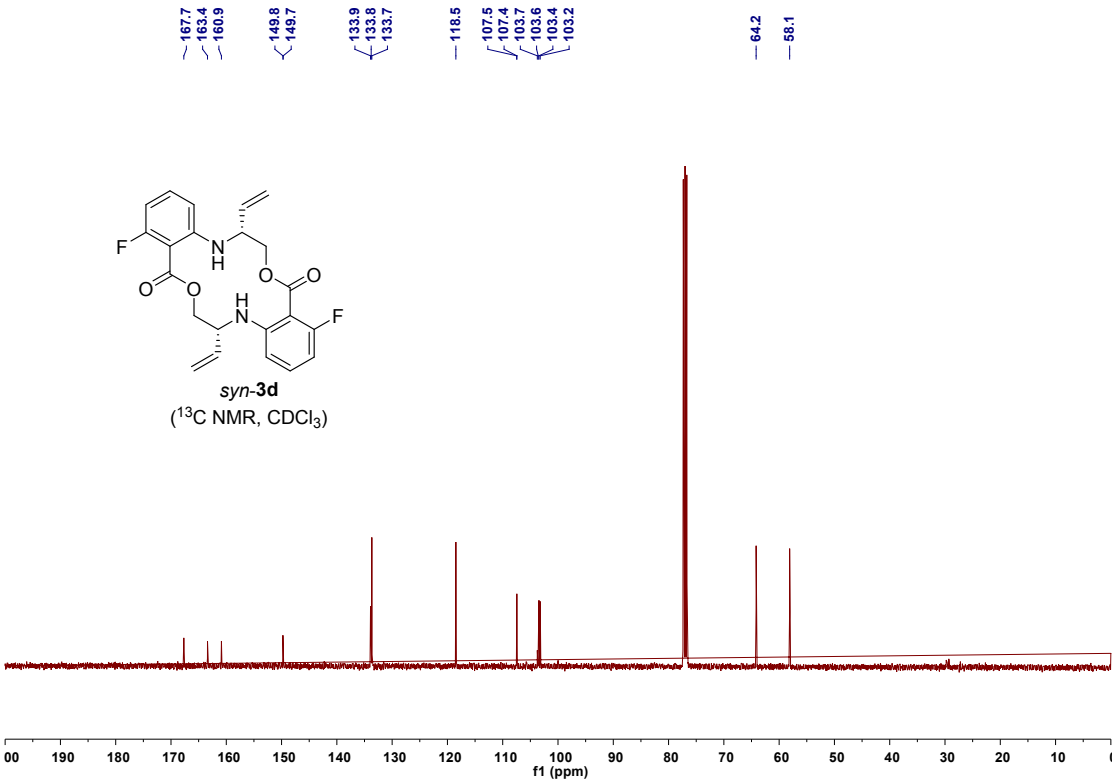
(^{1}H NMR, $CDCl_3$)



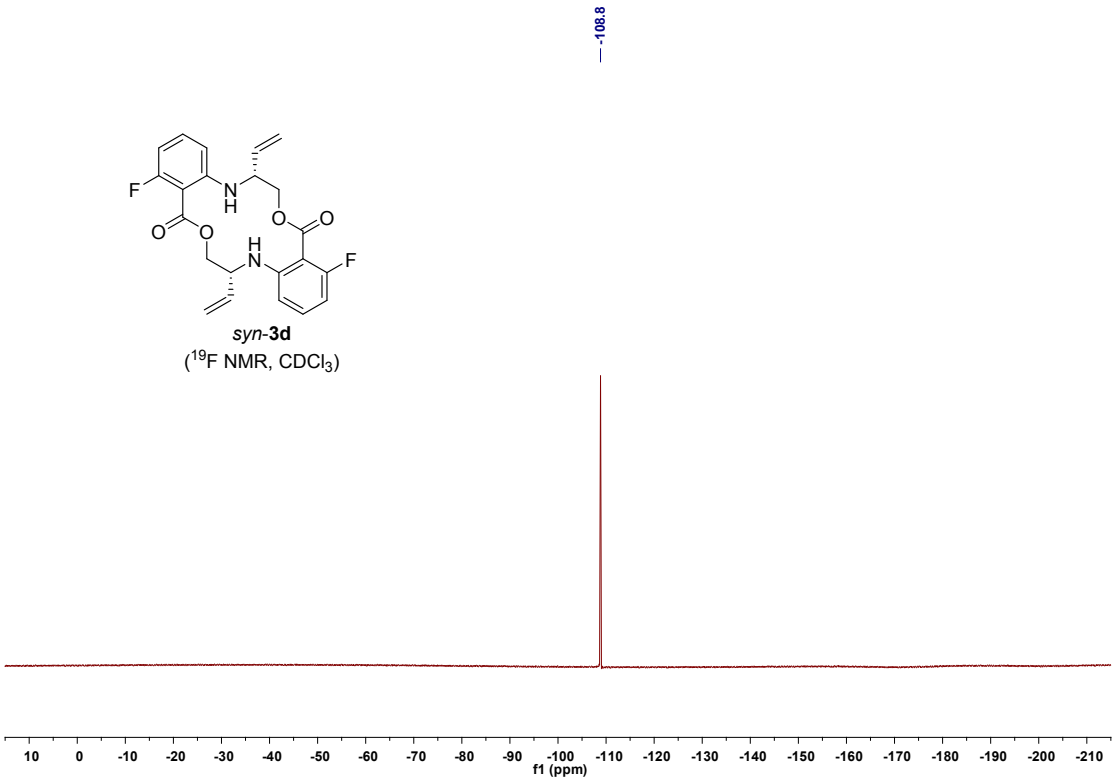
anti-**3c**
(^{13}C NMR, $CDCl_3$)



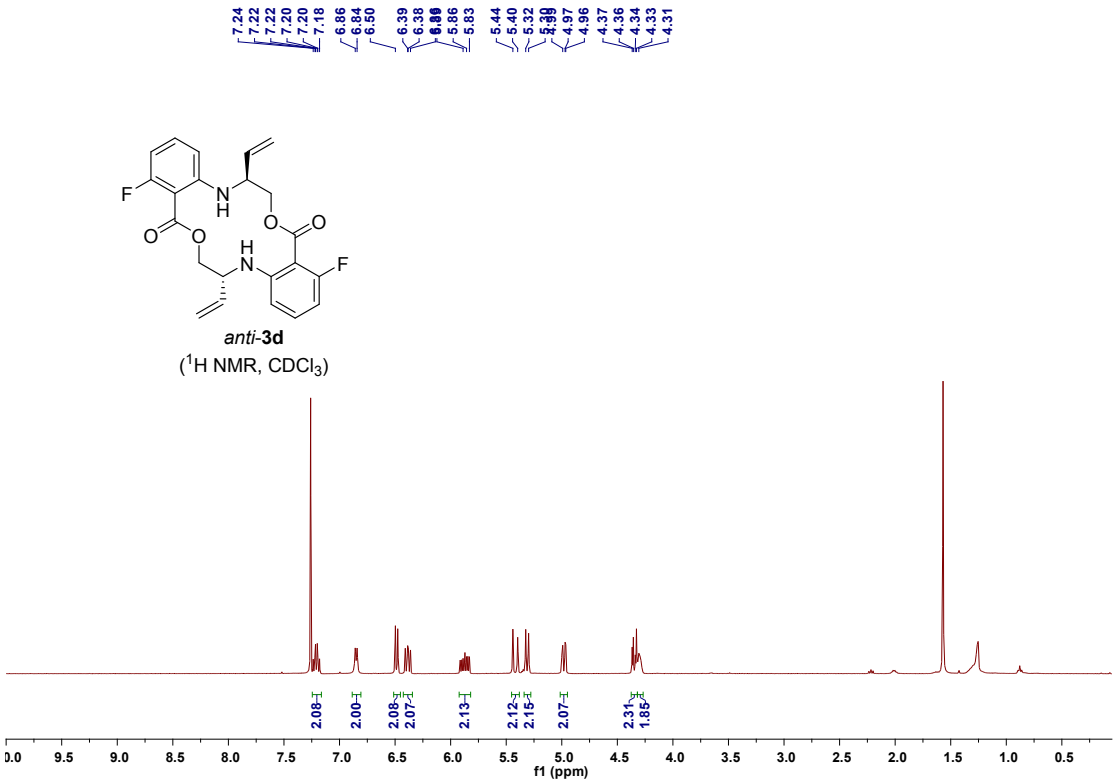
syn-**3d**
(^{1}H NMR, $CDCl_3$)



syn-**3d**
(^{13}C NMR, $CDCl_3$)

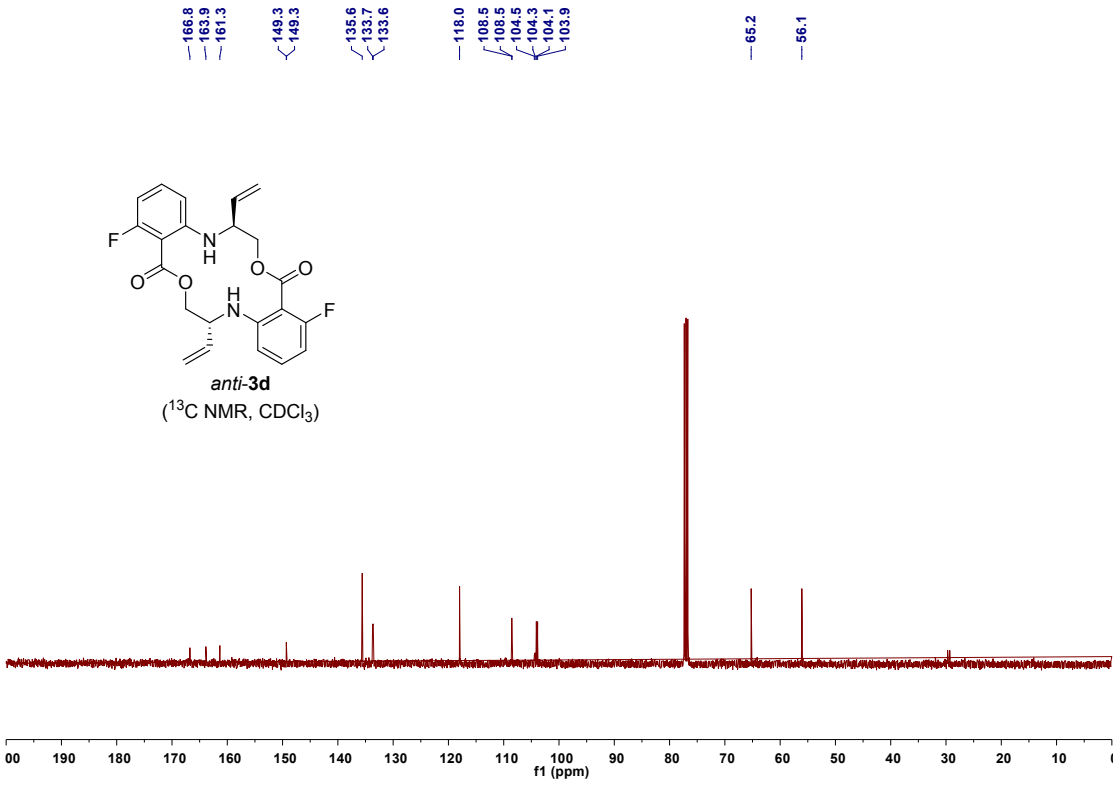


syn-**3d**
(^{19}F NMR, $CDCl_3$)



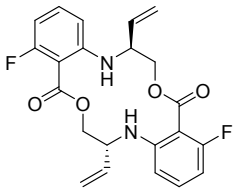
anti-**3d**

(^{1}H NMR, $CDCl_3$)



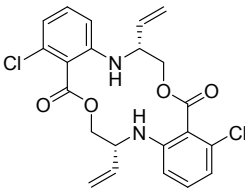
anti-**3d**

(^{13}C NMR, $CDCl_3$)



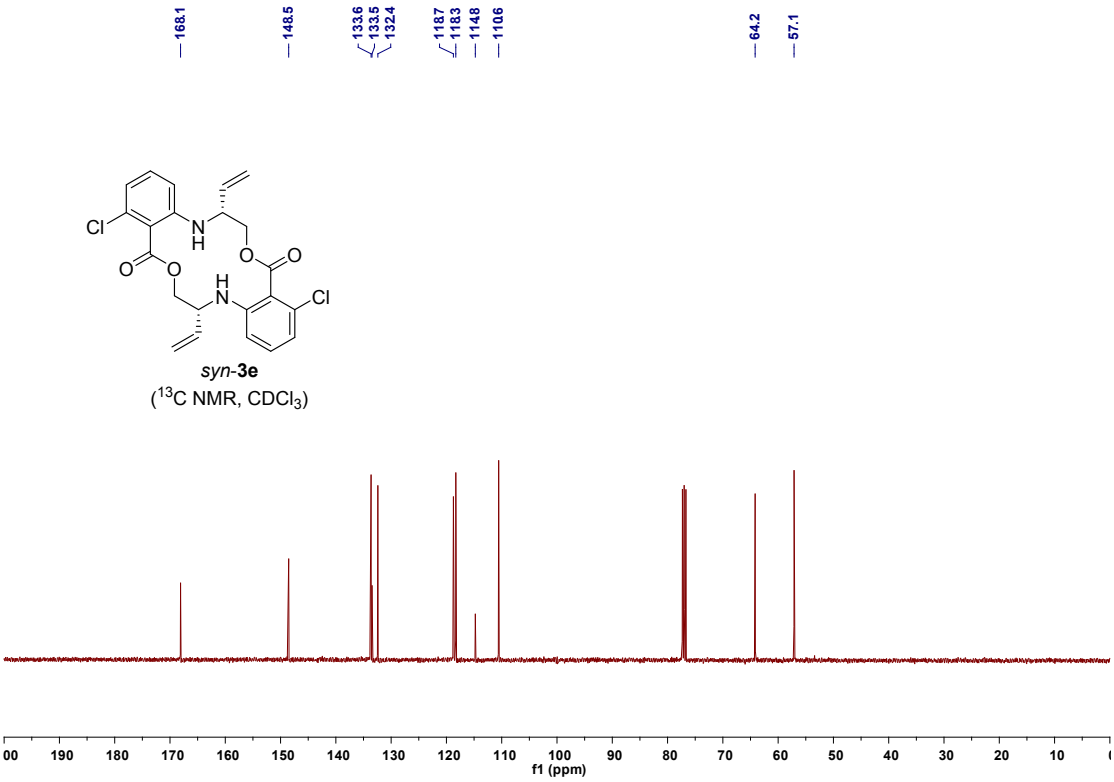
anti-**3d**

(^{19}F NMR, $CDCl_3$)



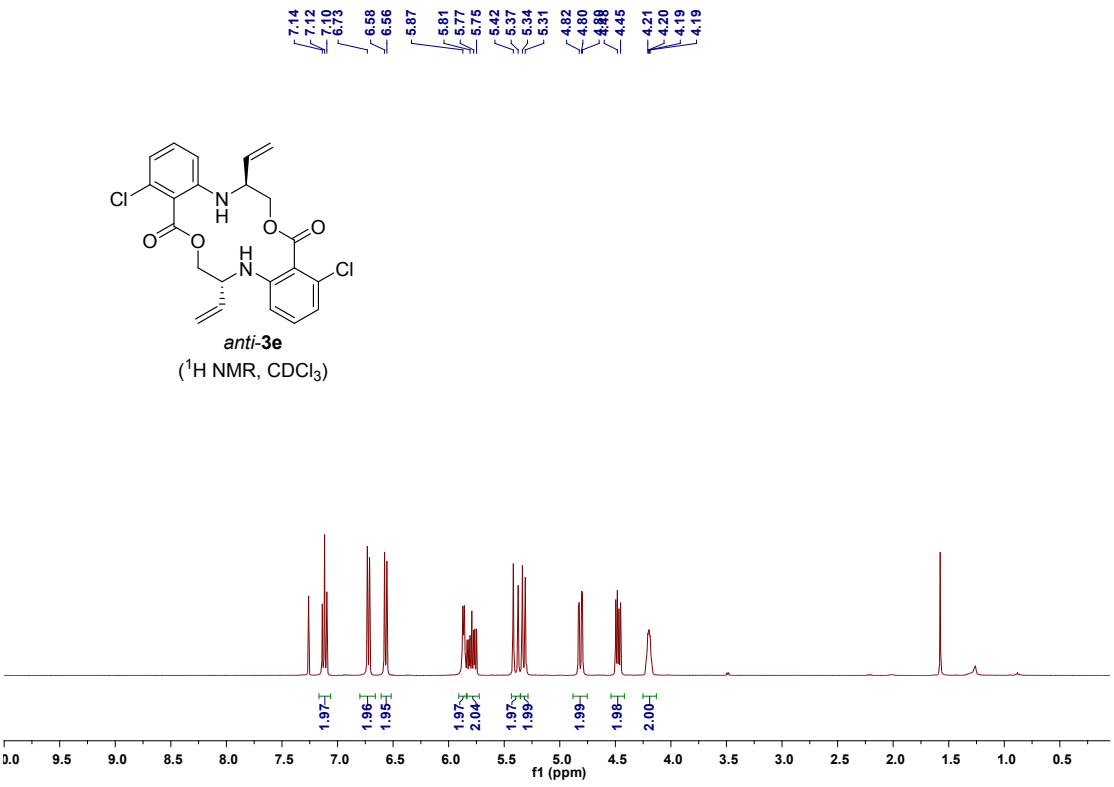
syn-**3e**

(^{1}H NMR, $CDCl_3$)



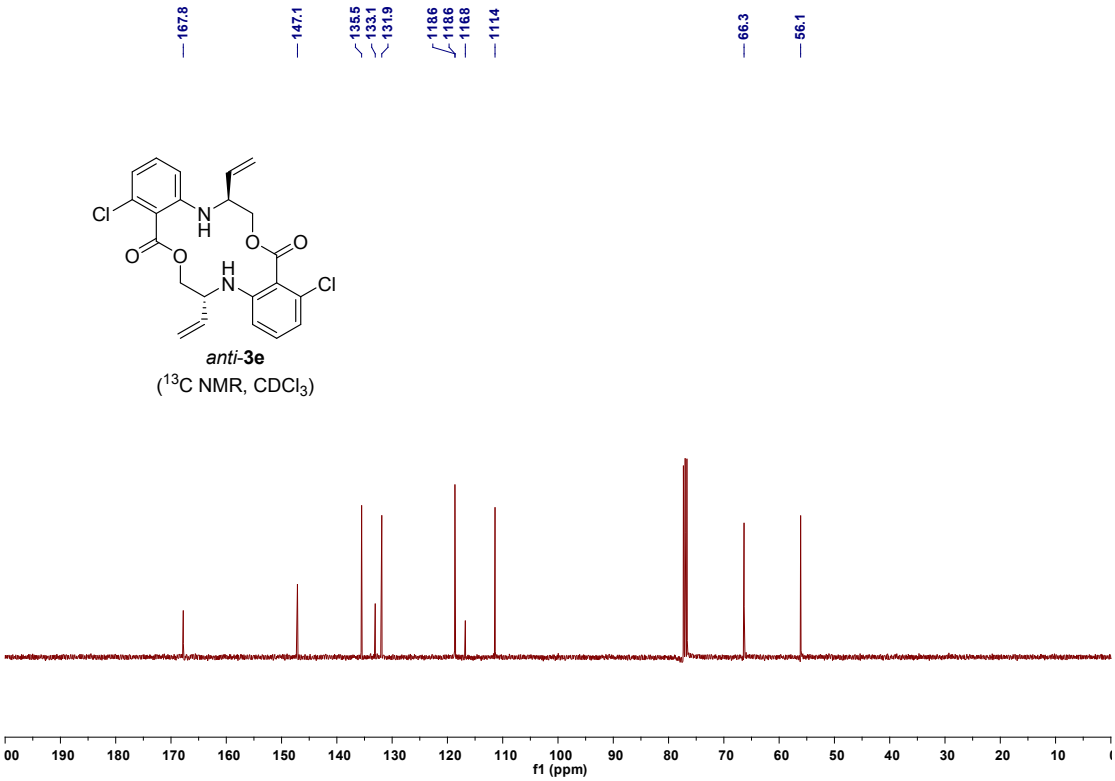
syn-**3e**

(^{13}C NMR, $CDCl_3$)

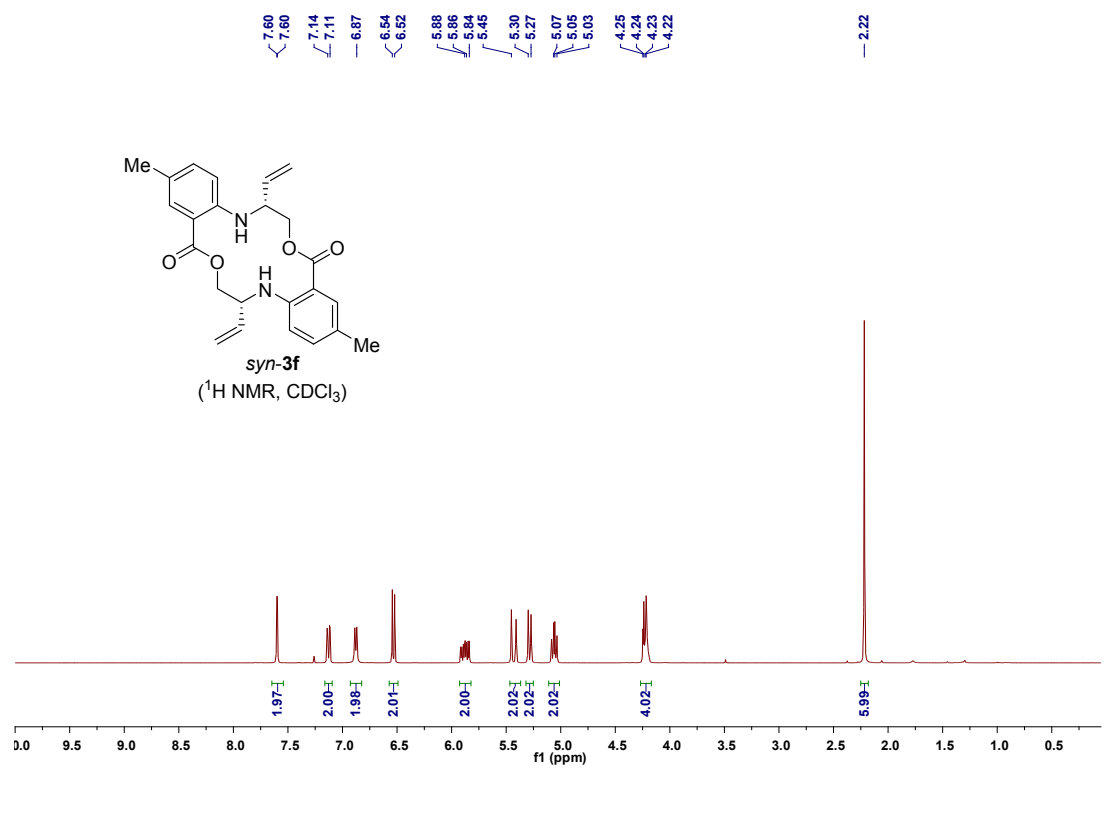


anti-**3e**

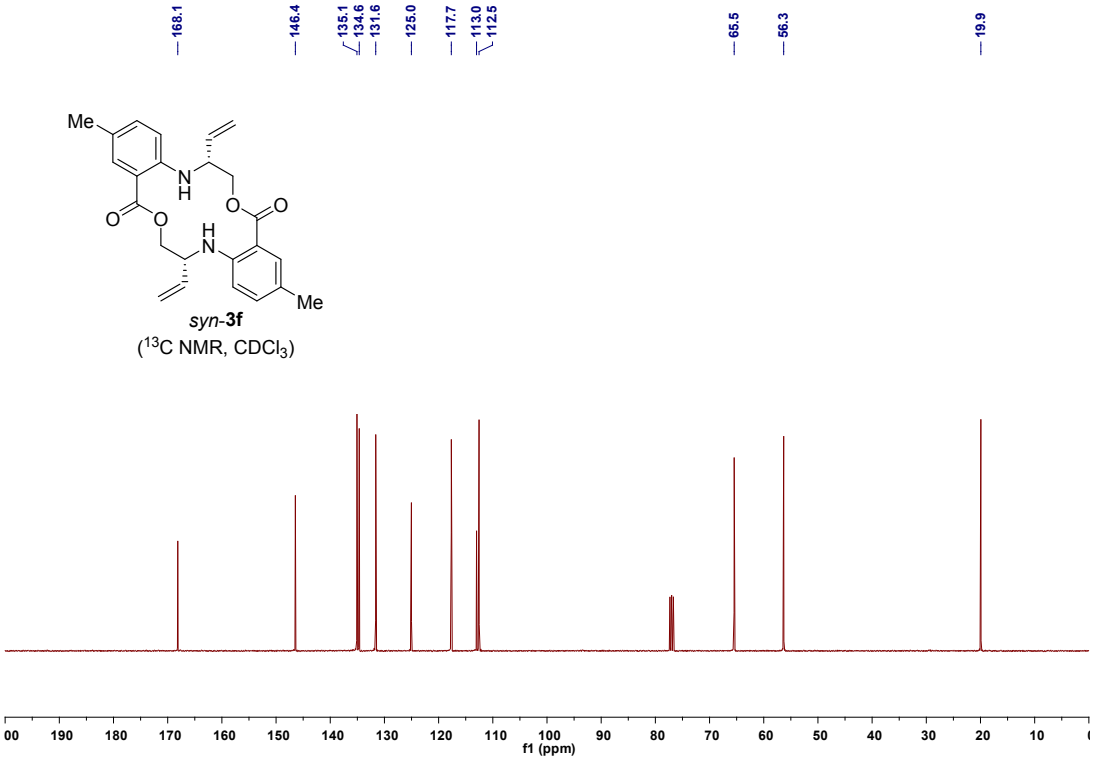
(^{1}H NMR, $CDCl_3$)



anti-**3e**
(^{13}C NMR, $CDCl_3$)

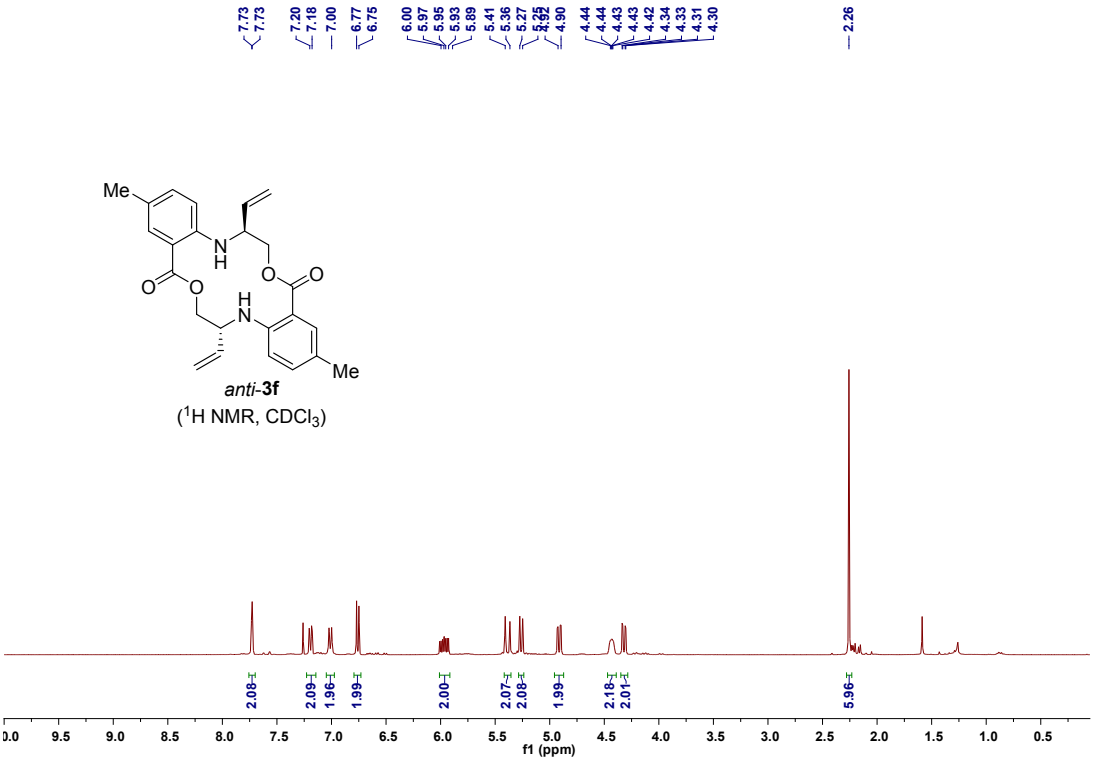


syn-**3f**
(^{1}H NMR, $CDCl_3$)



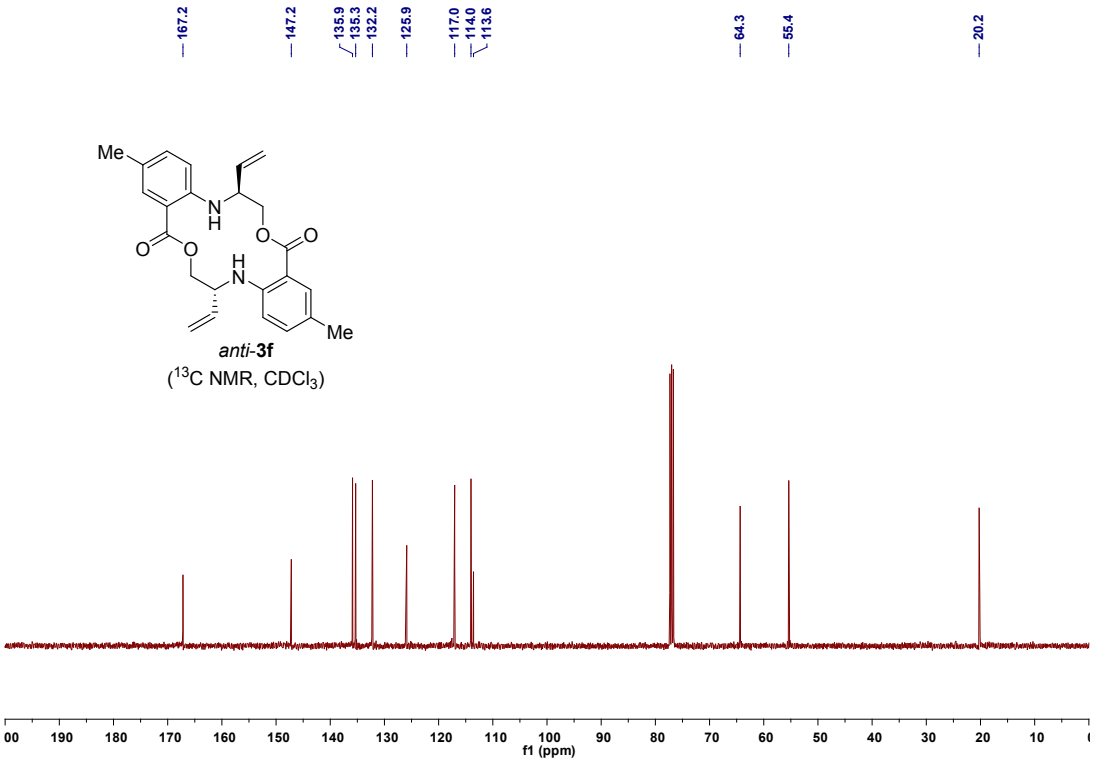
syn-**3f**

(^{13}C NMR, $CDCl_3$)



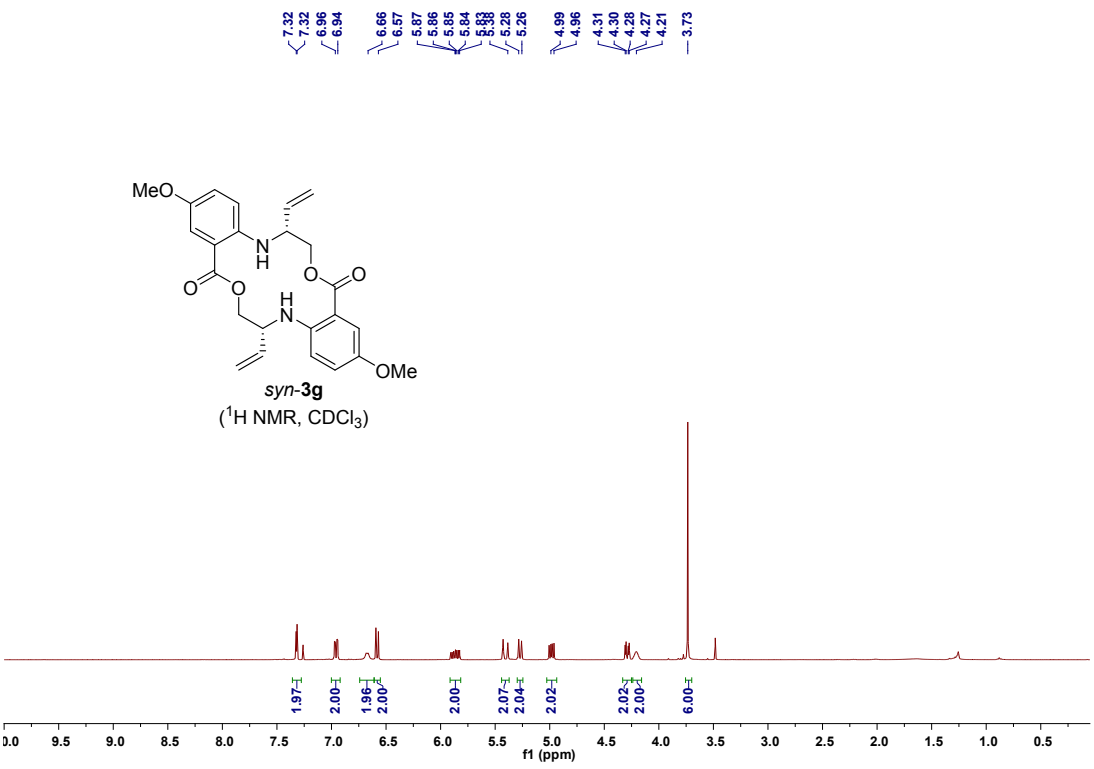
anti-**3f**

(^{1}H NMR, $CDCl_3$)



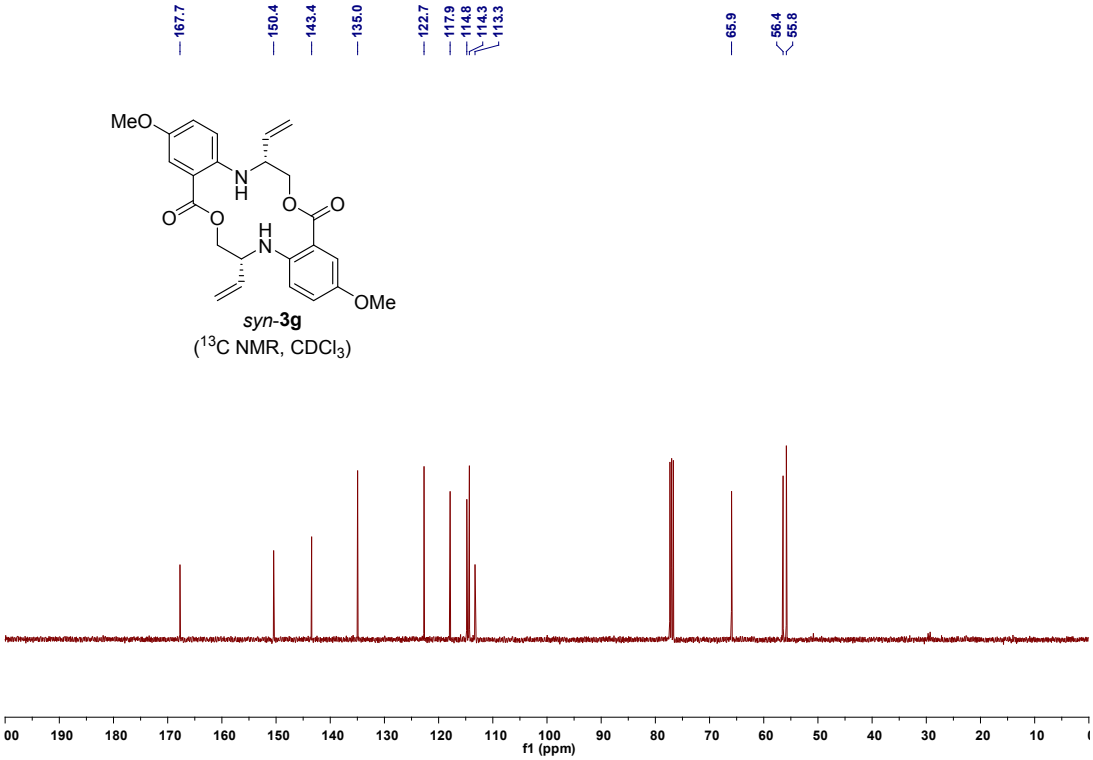
anti-**3f**

(^{13}C NMR, $CDCl_3$)

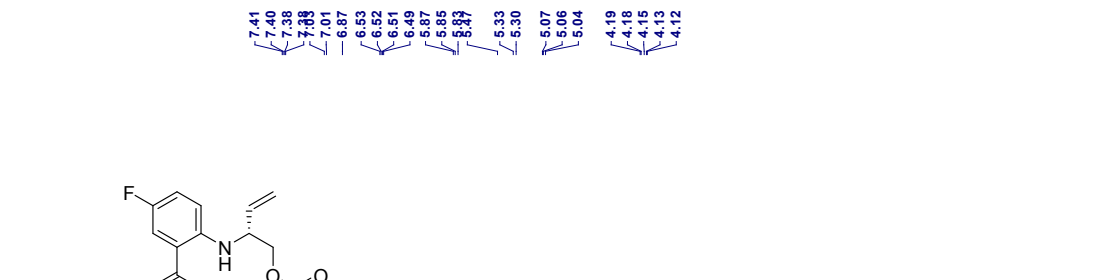


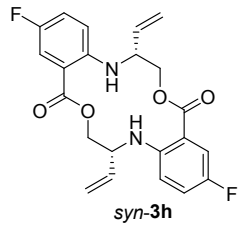
syn-**3g**

(^{1}H NMR, $CDCl_3$)

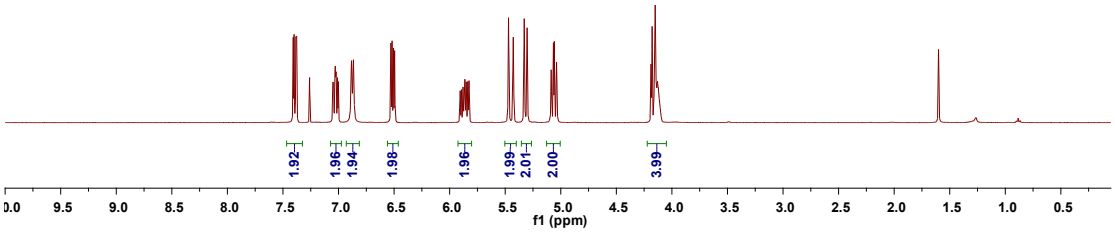


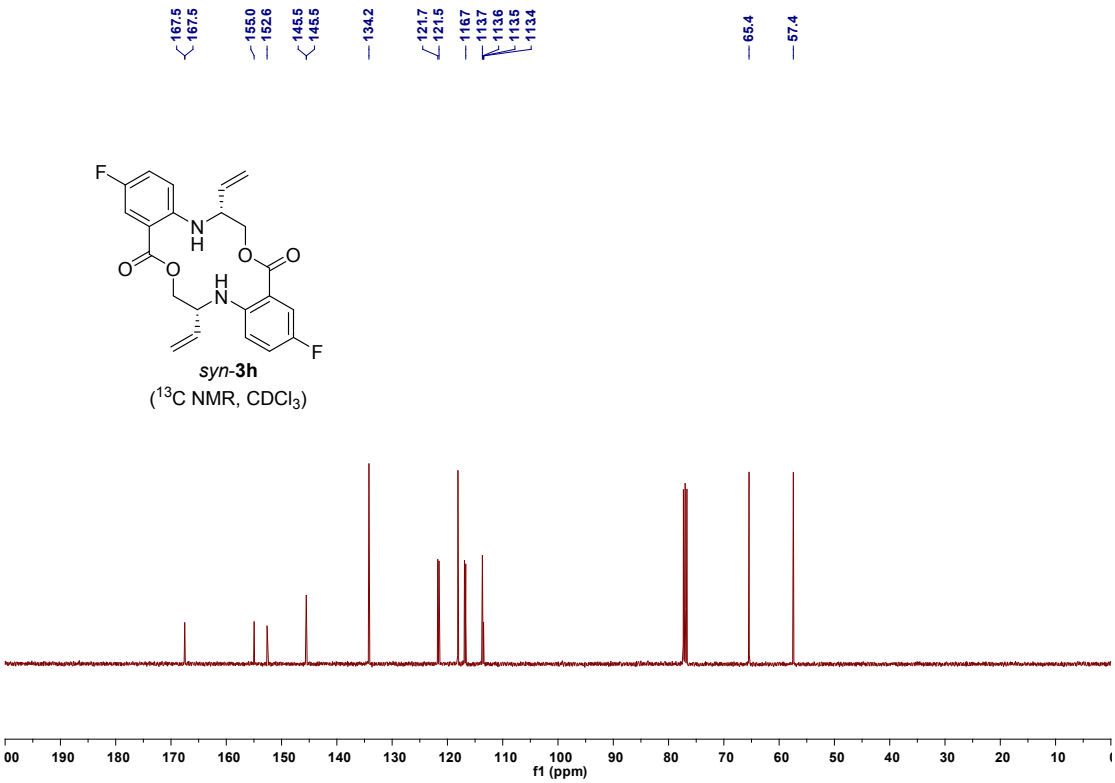
syn-**3g**
(^{13}C NMR, $CDCl_3$)





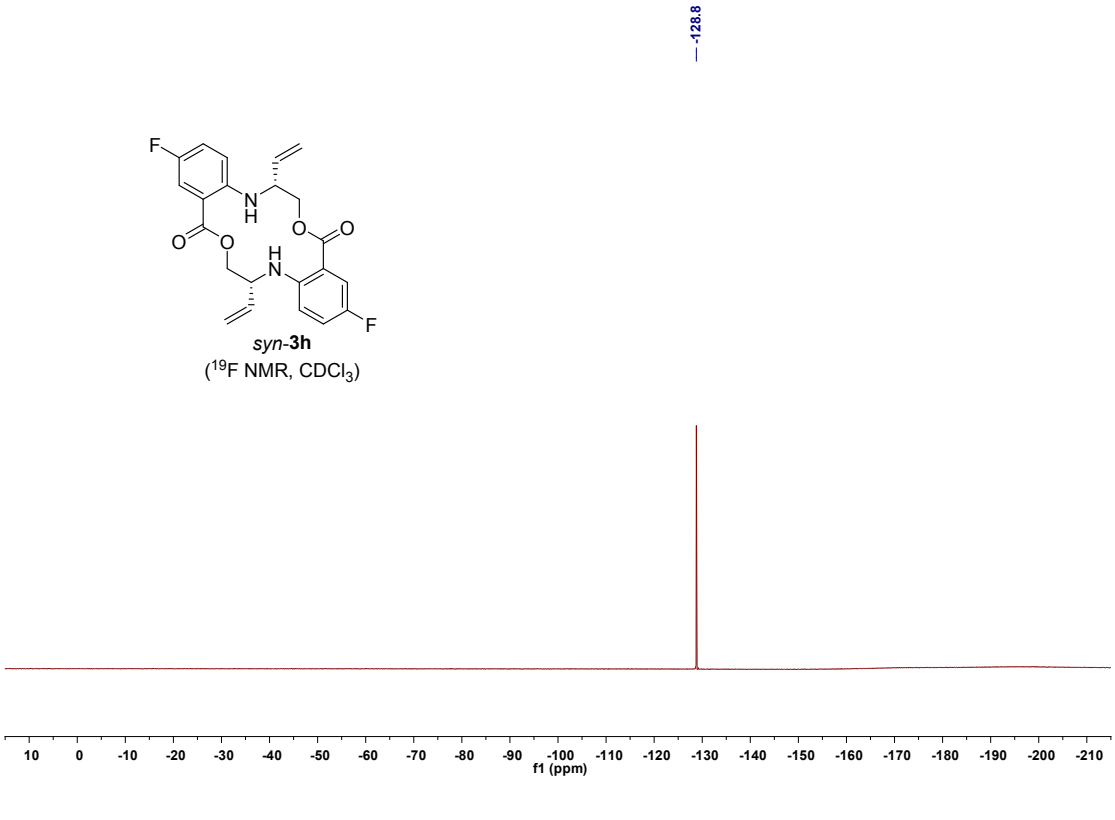
syn-**3h**
(^{1}H NMR, $CDCl_3$)





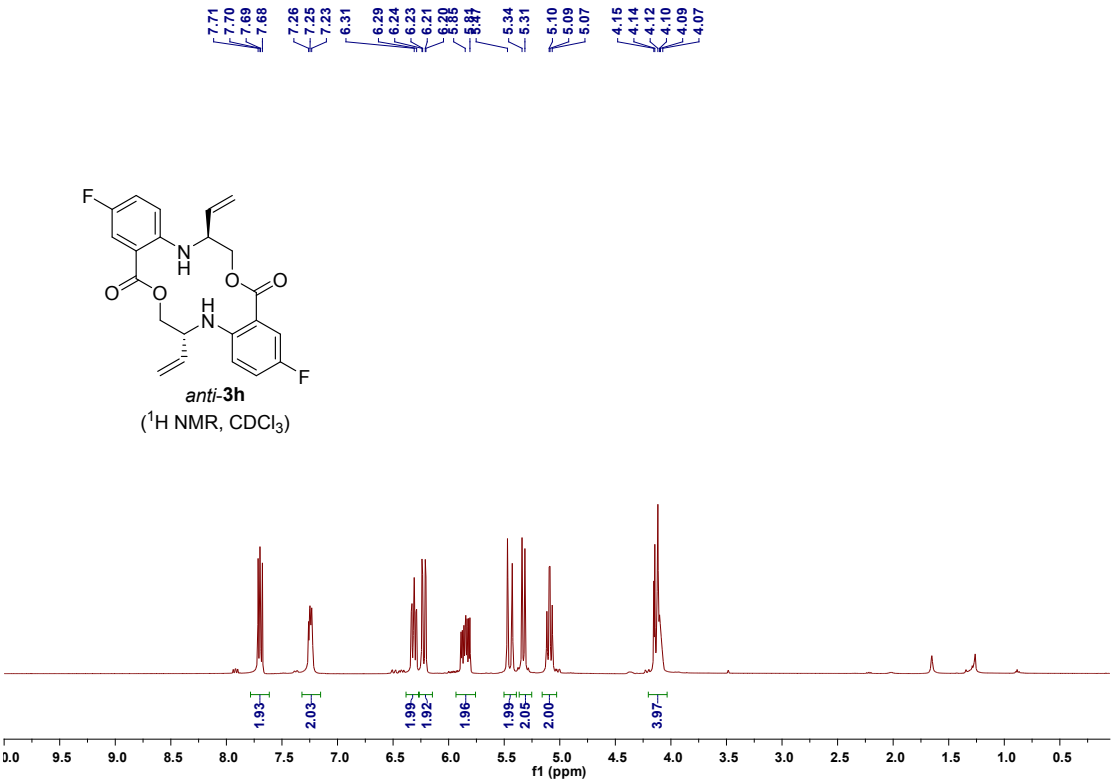
syn-**3h**

(^{13}C NMR, $CDCl_3$)



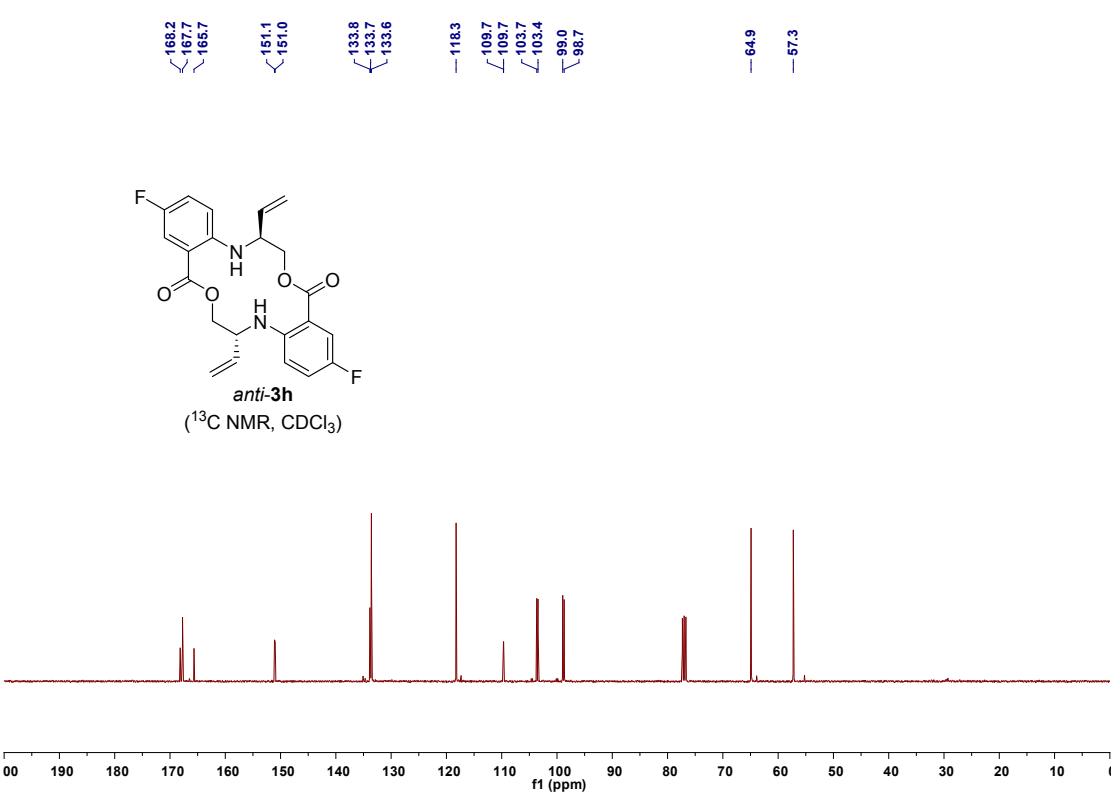
syn-**3h**

(^{19}F NMR, $CDCl_3$)



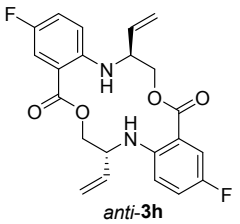
anti-**3h**

(^{1}H NMR, $CDCl_3$)



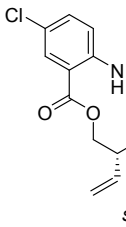
anti-**3h**

(^{13}C NMR, $CDCl_3$)



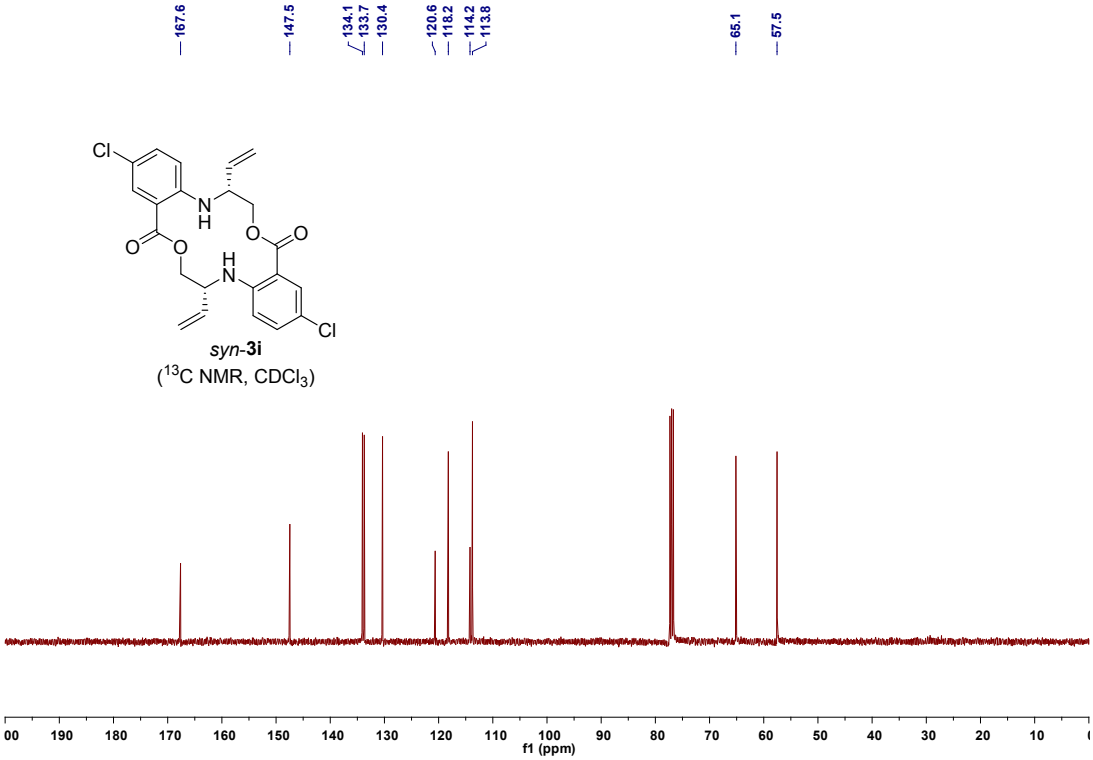
anti-**3h**

(^{19}F NMR, $CDCl_3$)



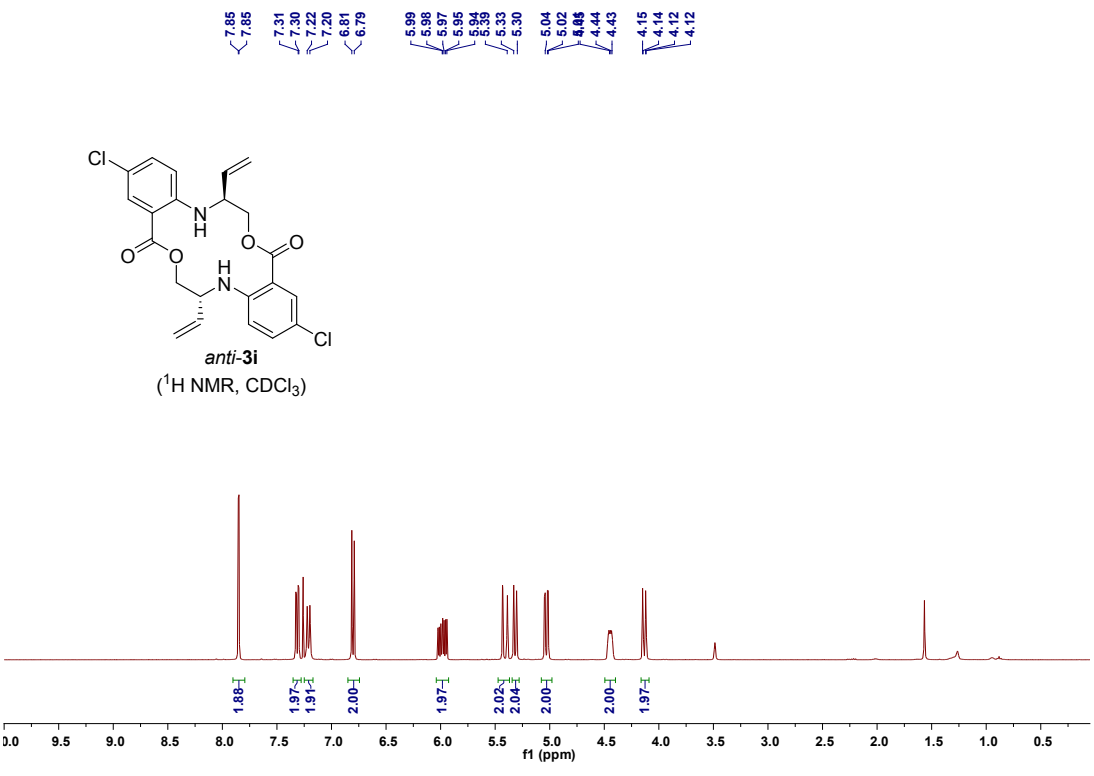
syn-**3i**

(^{1}H NMR, $CDCl_3$)



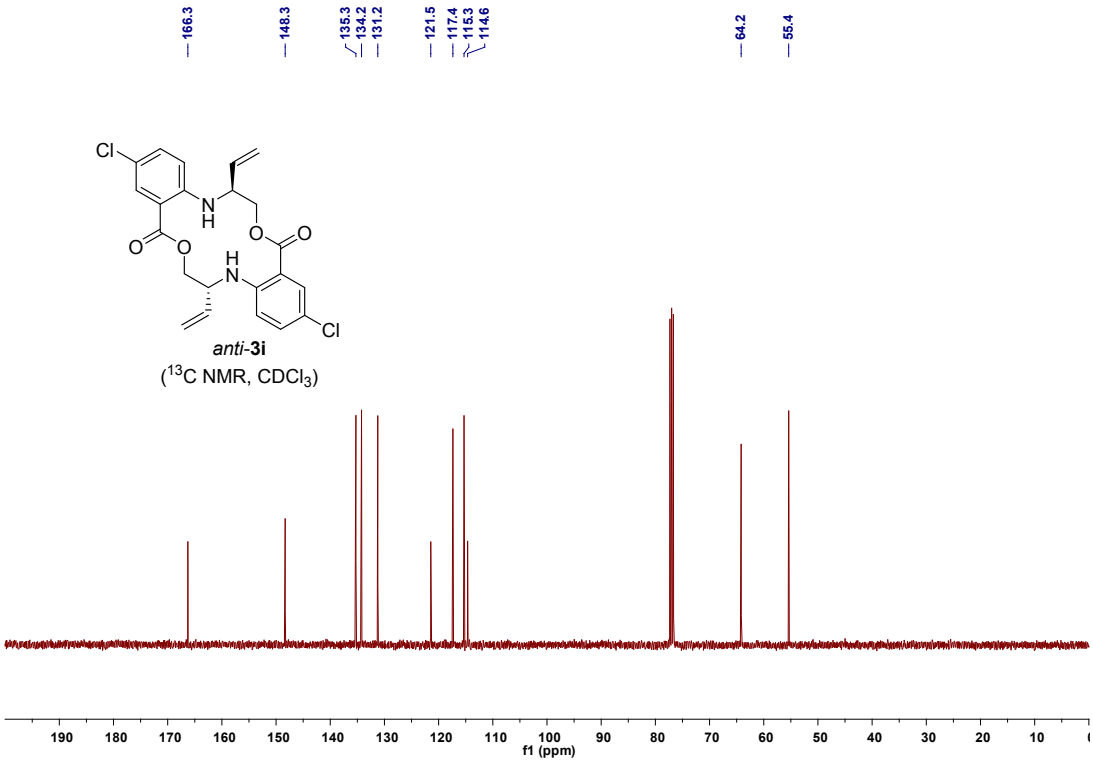
syn-**3i**

(^{13}C NMR, $CDCl_3$)



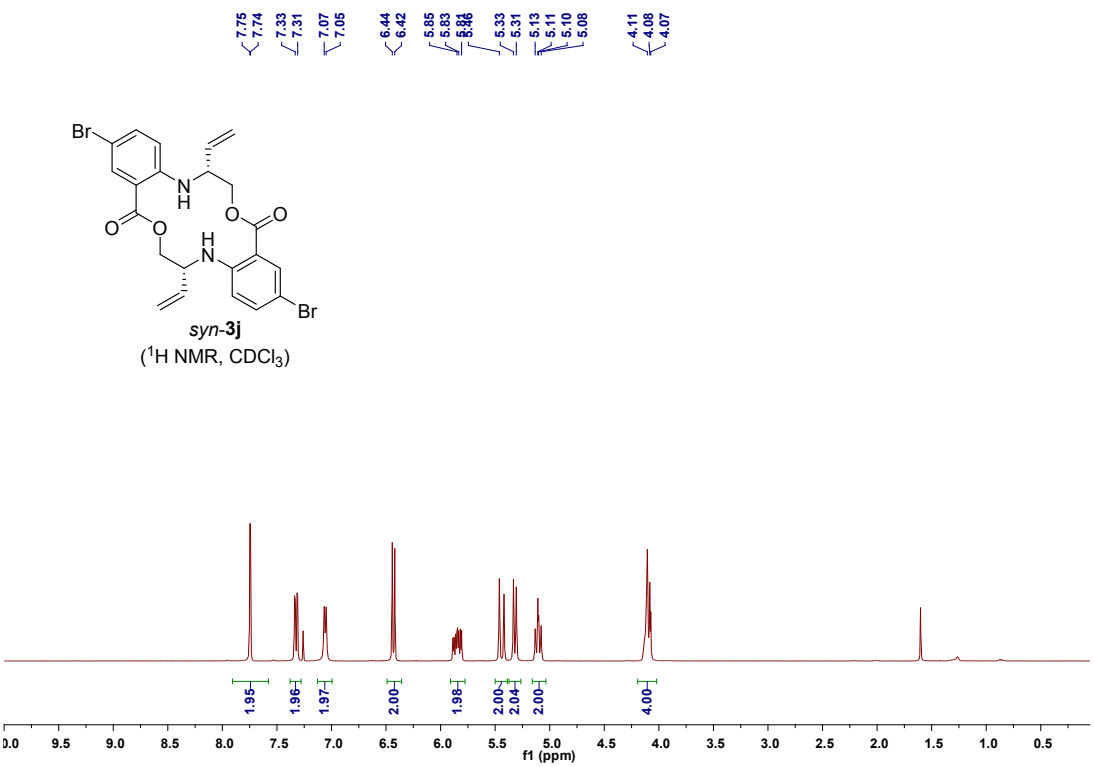
anti-**3i**

(^{1}H NMR, $CDCl_3$)



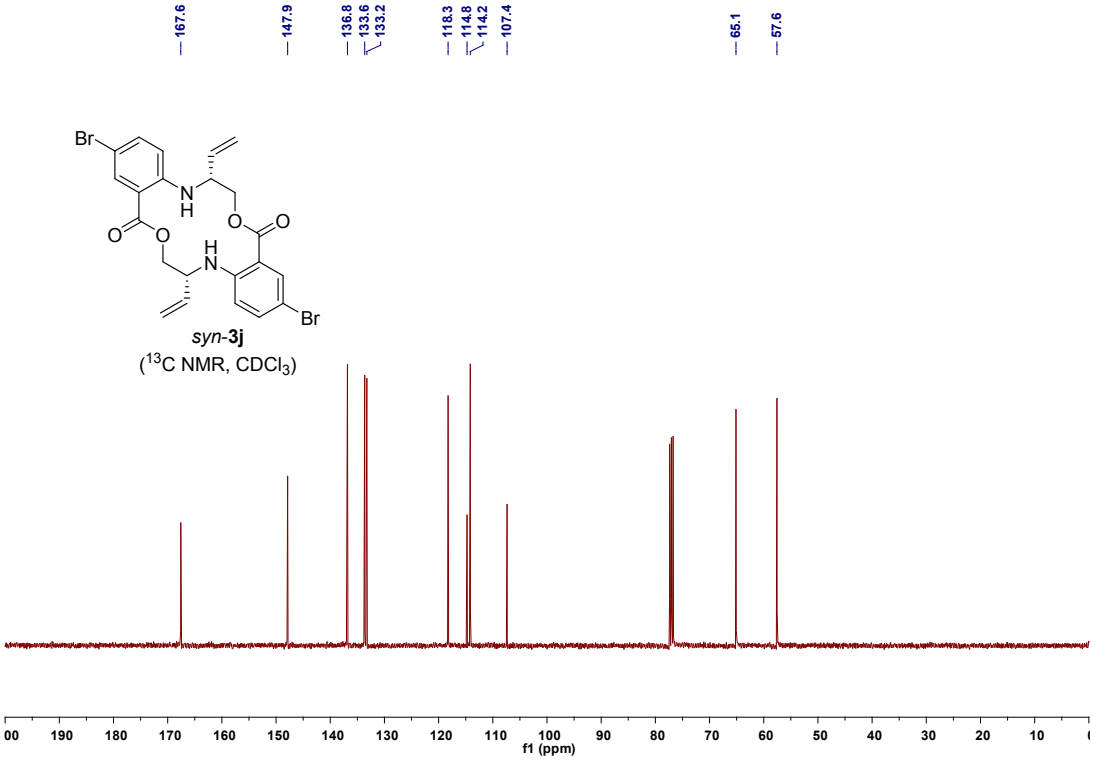
anti-**3i**

(^{13}C NMR, $CDCl_3$)



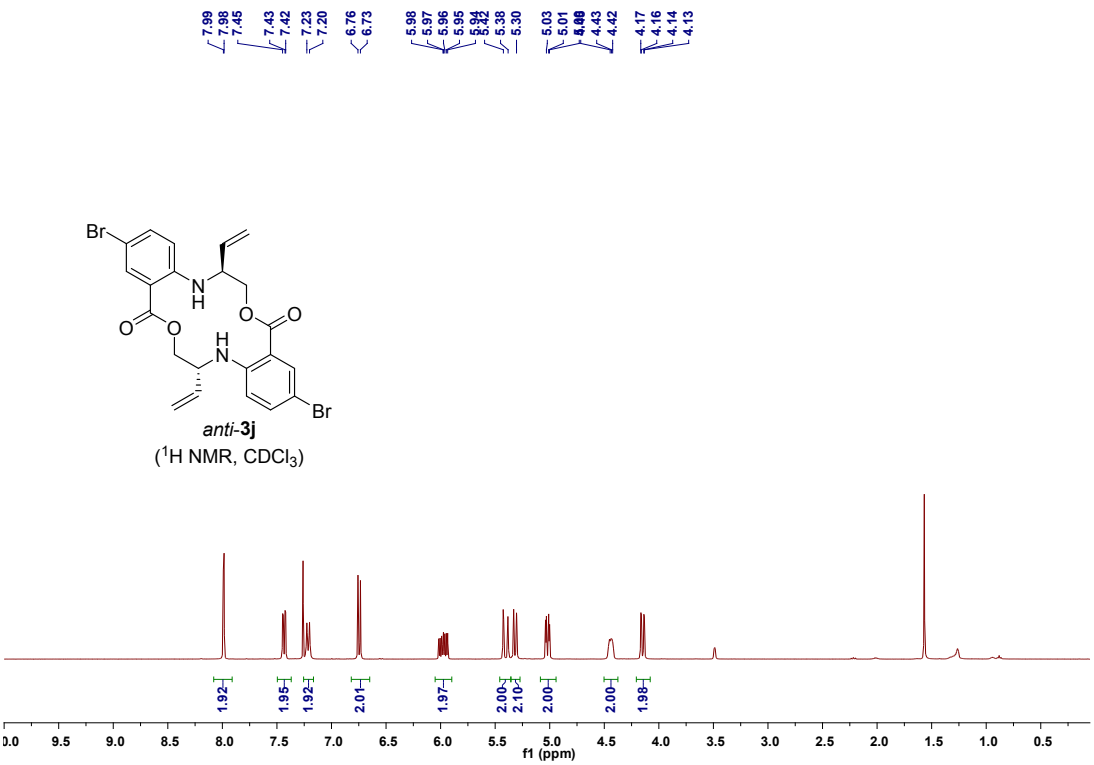
syn-**3j**

(^{1}H NMR, $CDCl_3$)



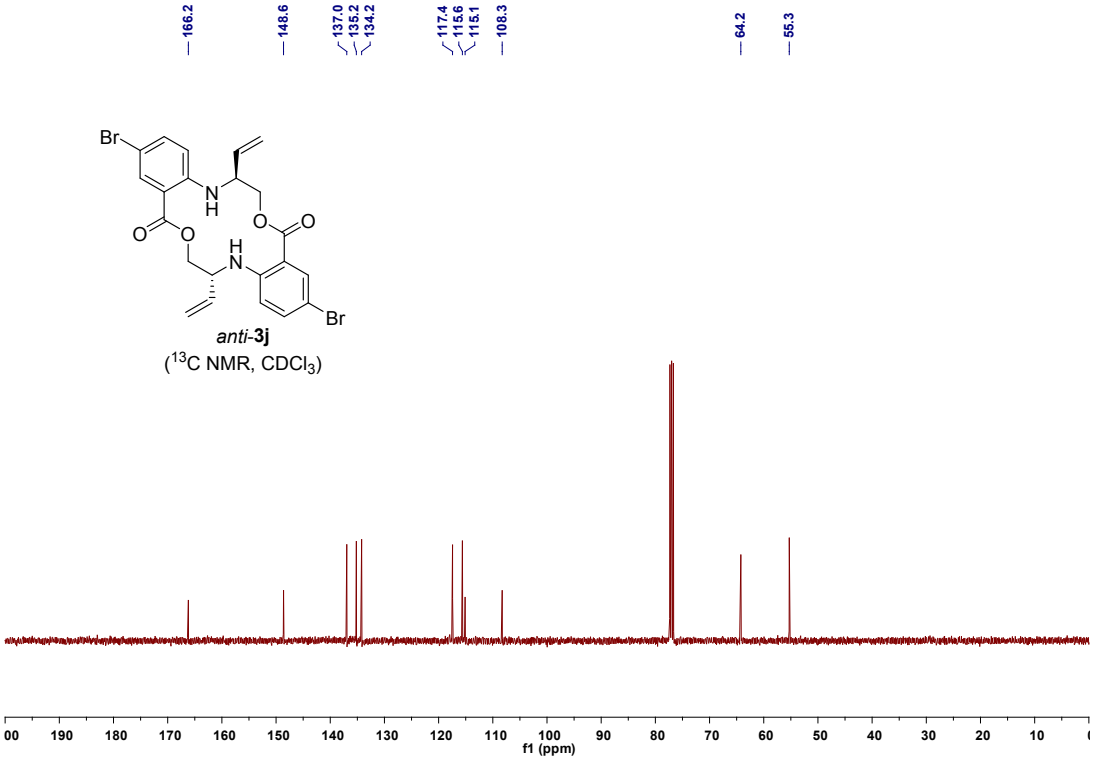
syn-**3j**

(^{13}C NMR, $CDCl_3$)



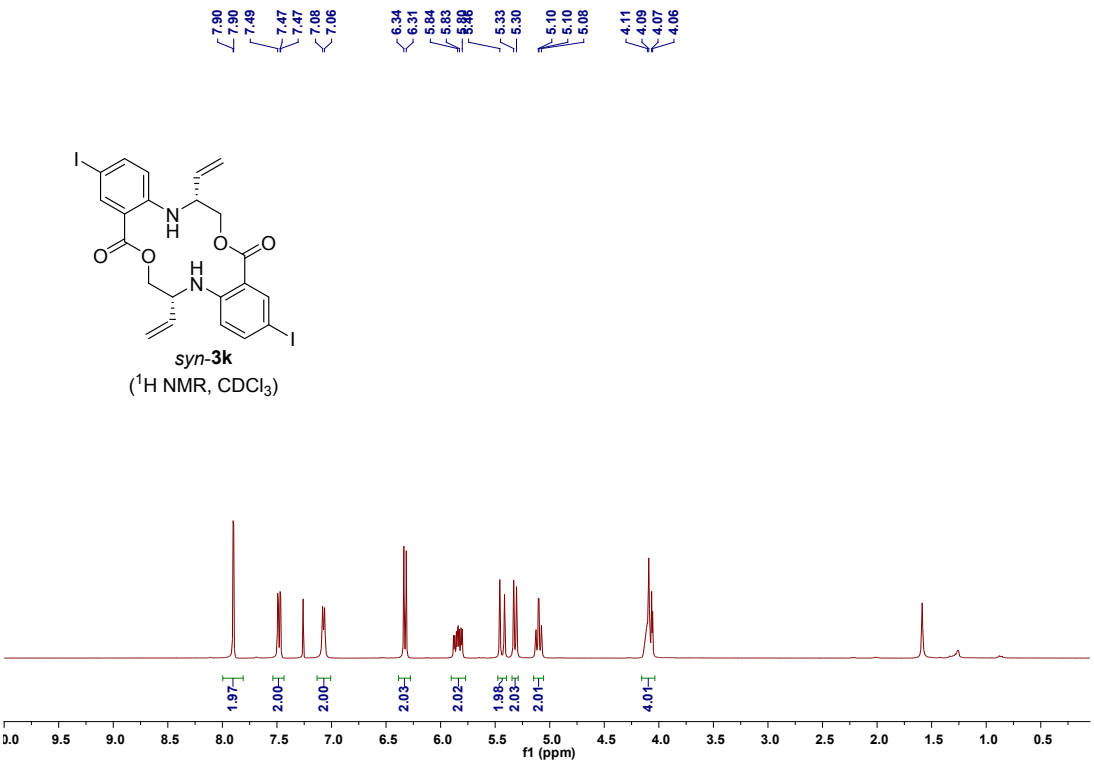
anti-**3j**

(^{1}H NMR, $CDCl_3$)



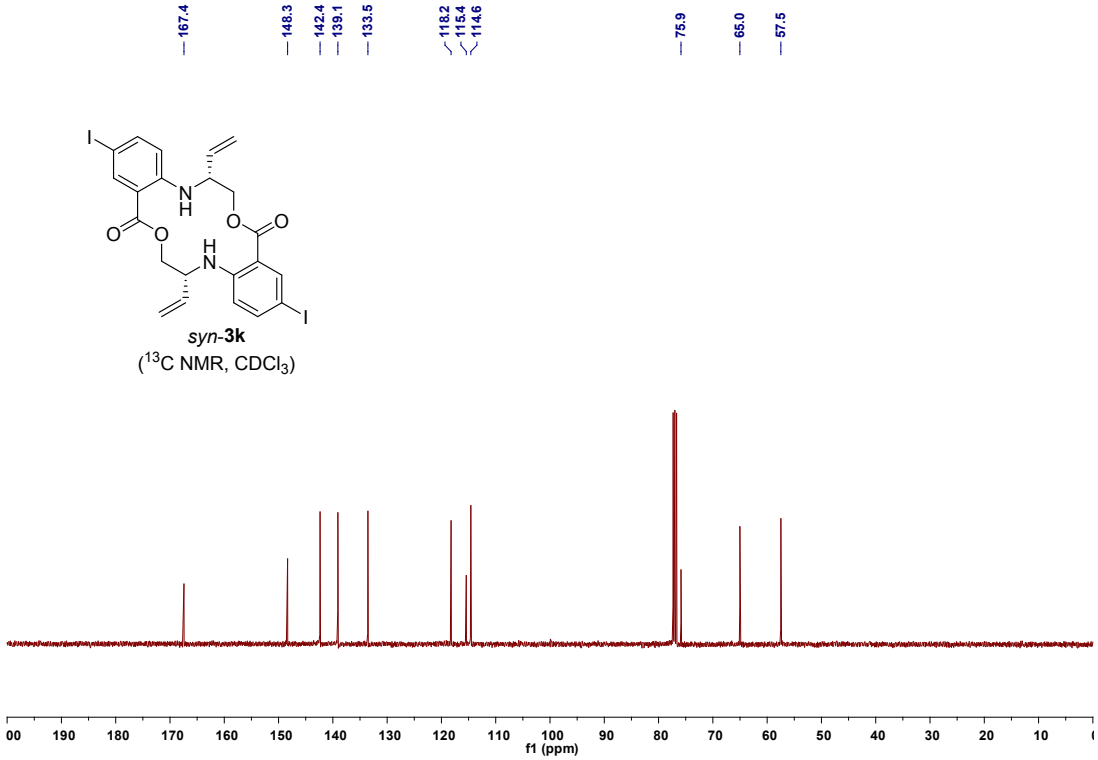
anti-**3j**

(^{13}C NMR, $CDCl_3$)



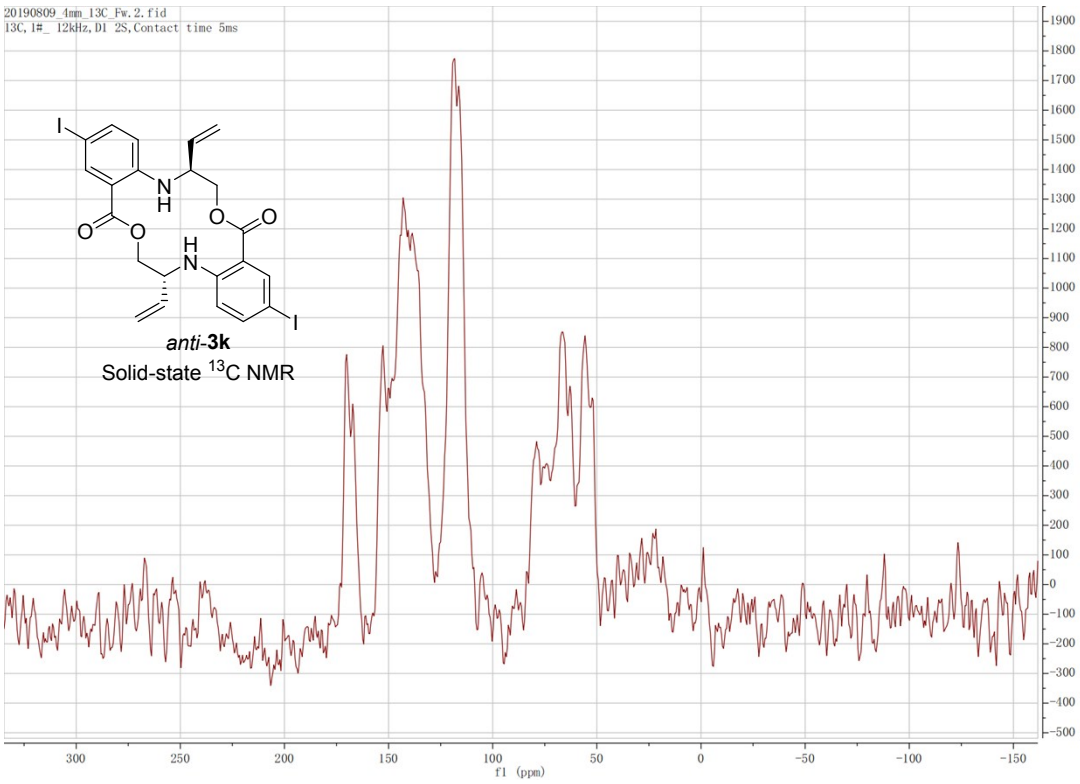
syn-**3k**

(^{1}H NMR, $CDCl_3$)



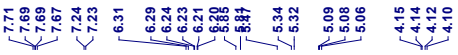
syn-**3k**

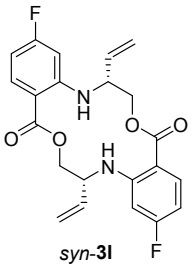
(^{13}C NMR, $CDCl_3$)



anti-**3k**

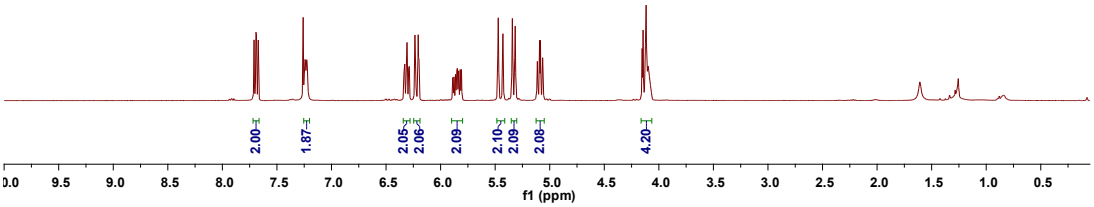
Solid-state ^{13}C NMR

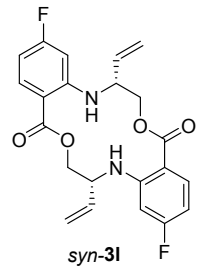




syn-**3l**

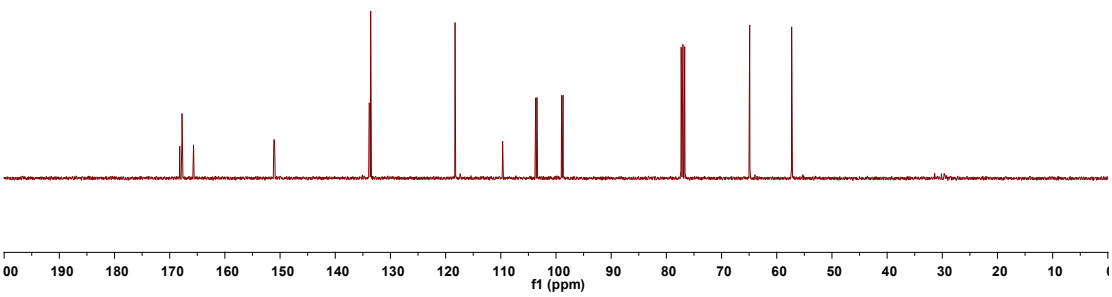
(^{1}H NMR, $CDCl_3$)

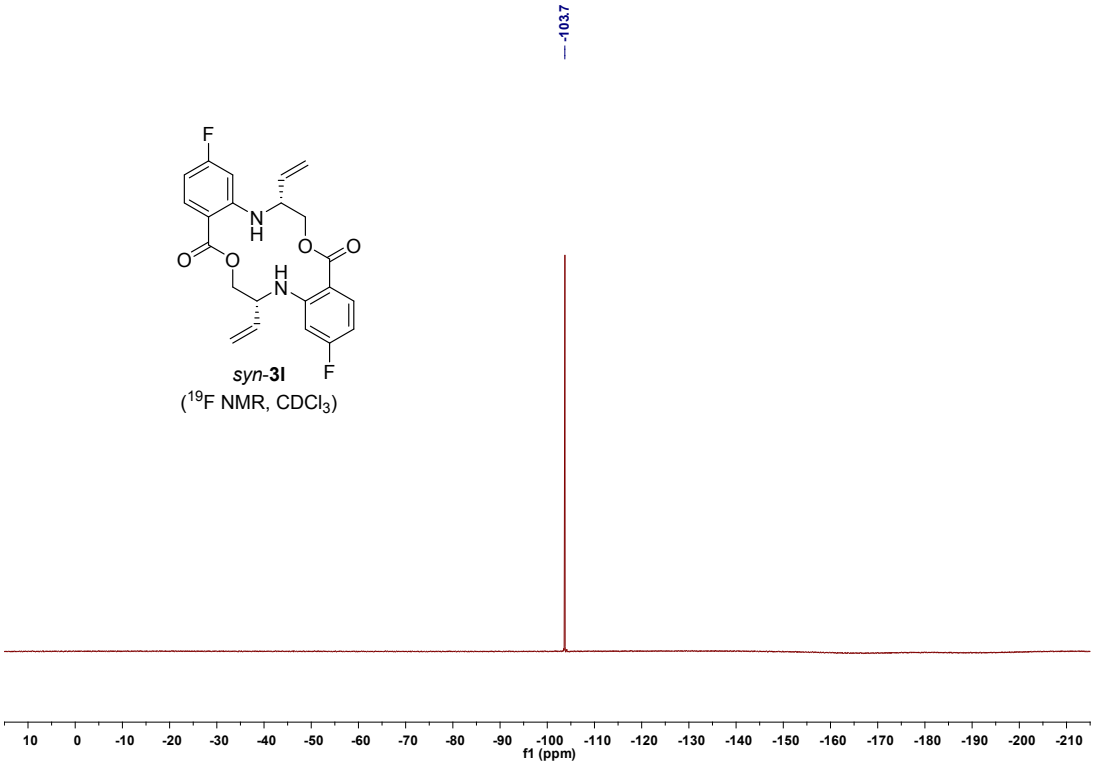




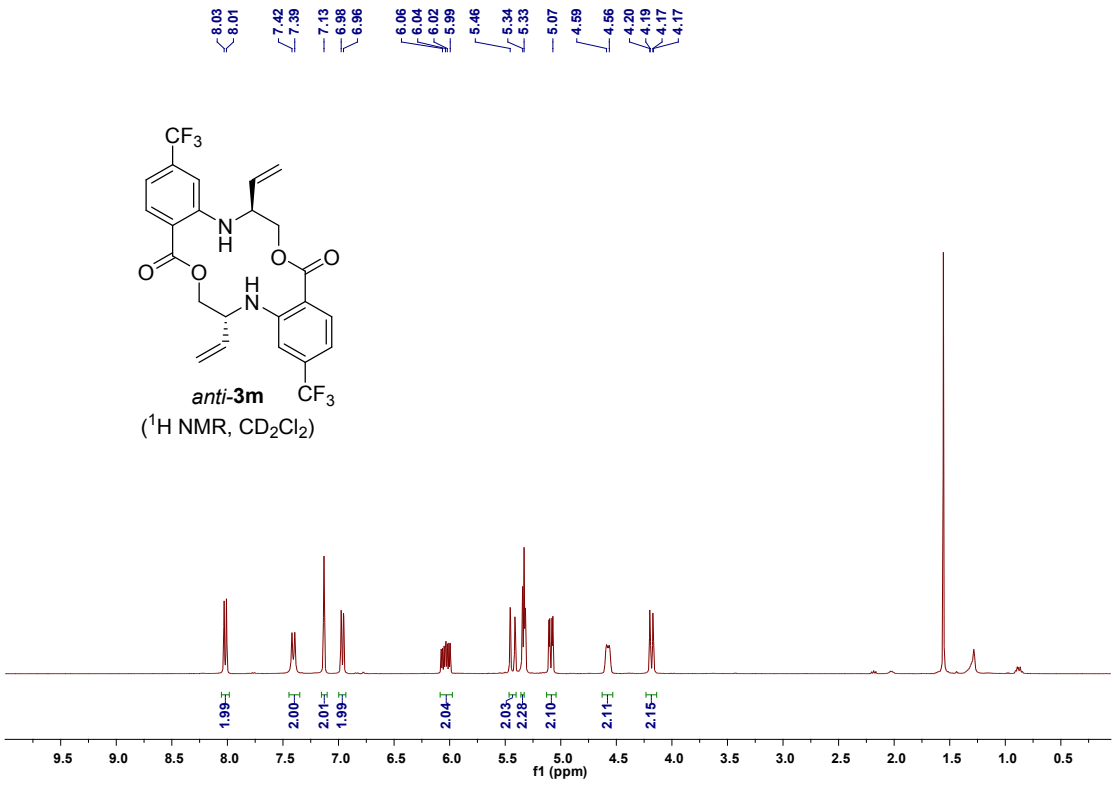
syn-**3l**

(^{13}C NMR, $CDCl_3$)

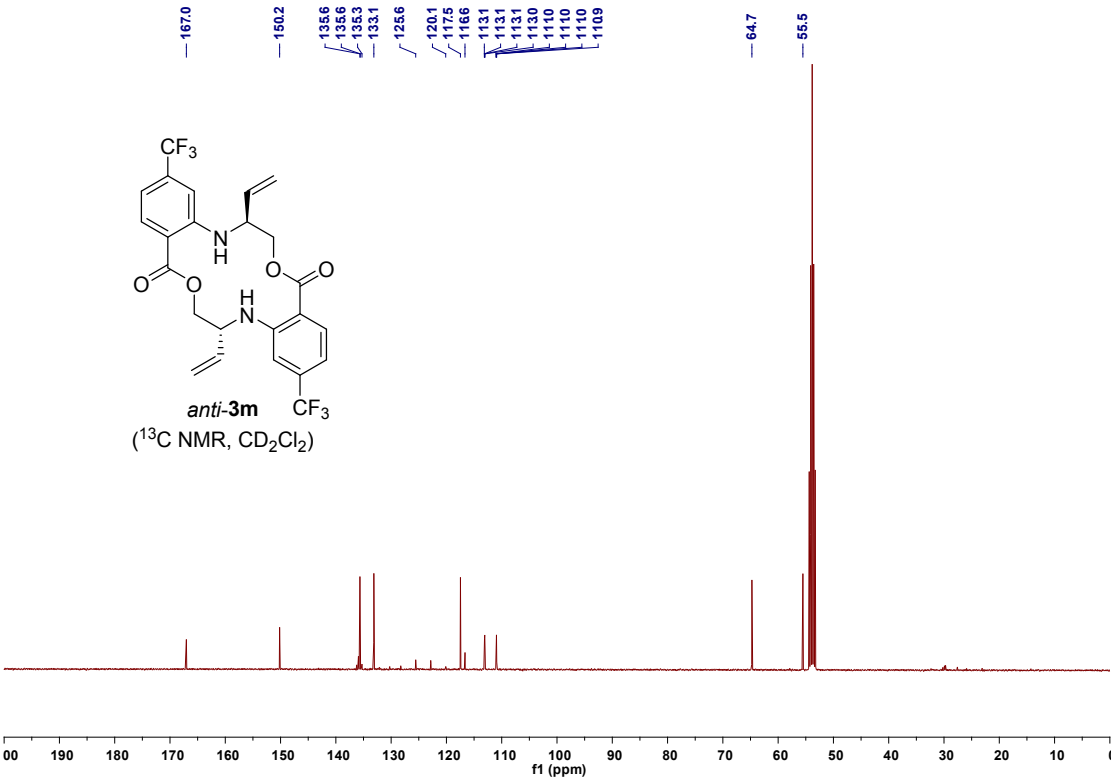




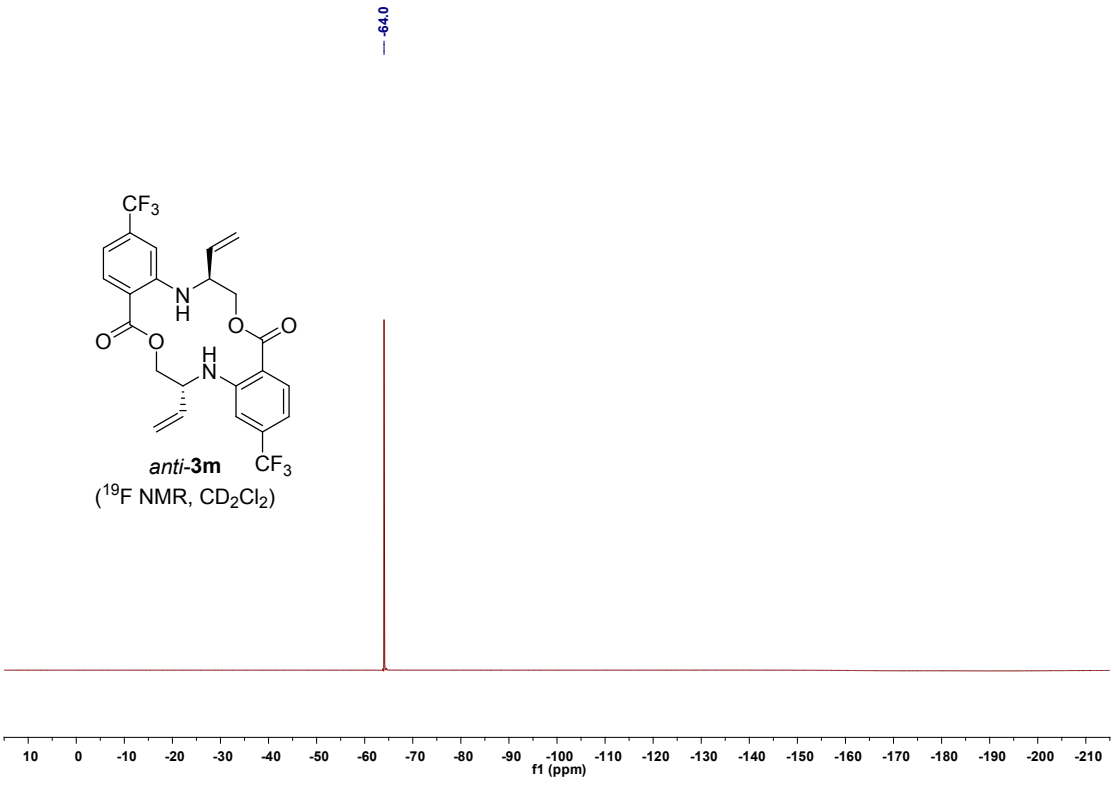
syn-**3l**
(^{19}F NMR, $CDCl_3$)



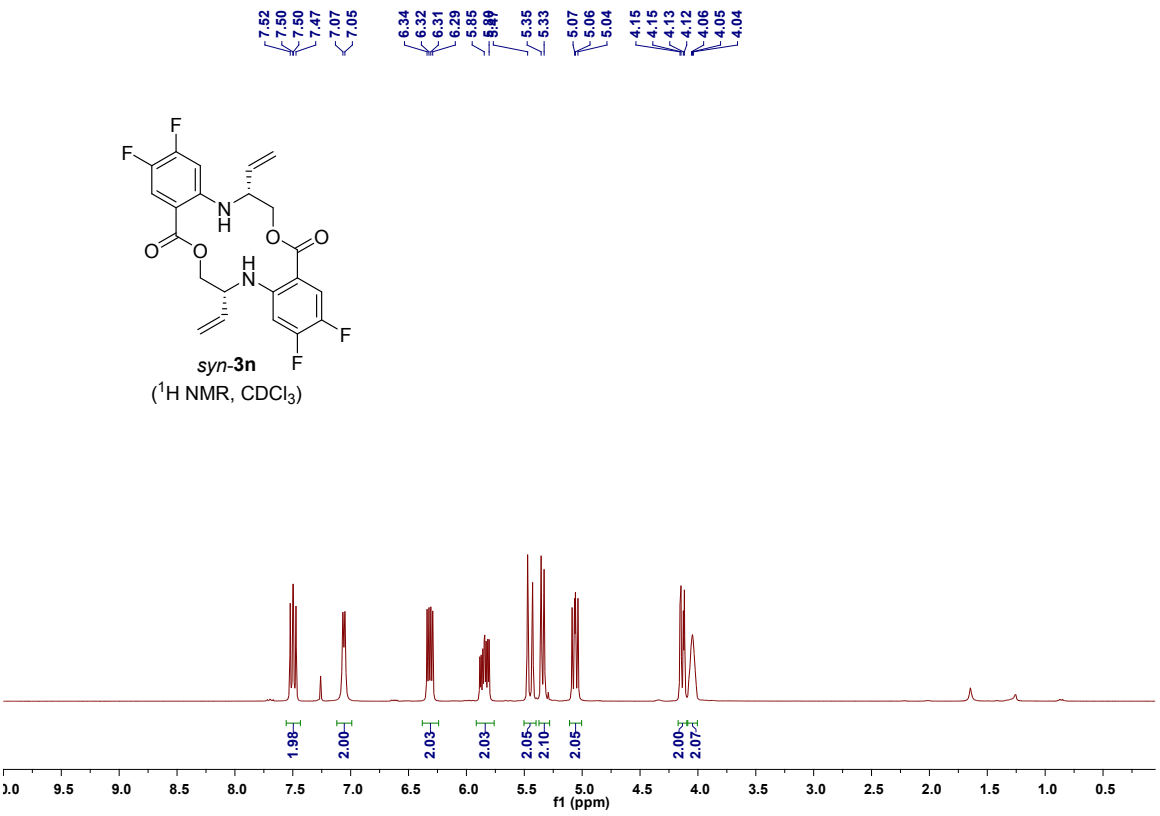
anti-**3m**
(^{1}H NMR, CD_2Cl_2)



anti-**3m**
(^{13}C NMR, CD_2Cl_2)

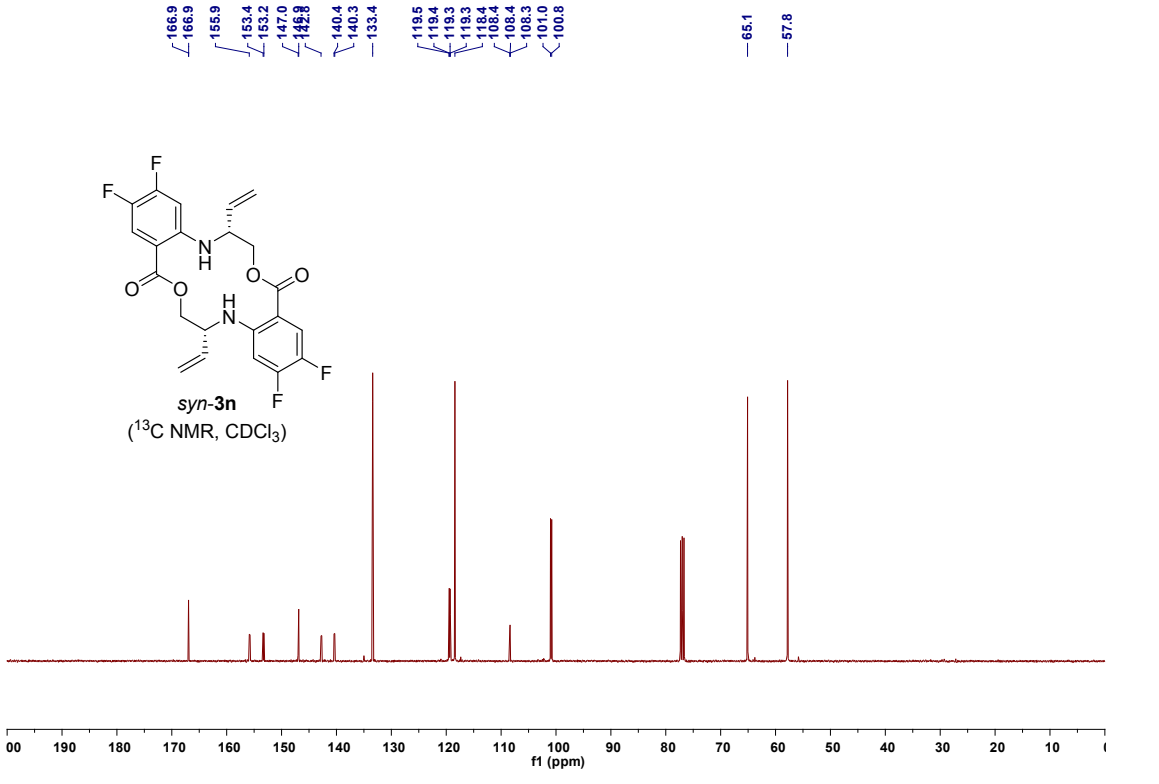


anti-**3m**
(^{19}F NMR, CD_2Cl_2)



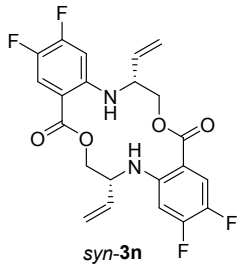
syn-**3n**

(^{1}H NMR, $CDCl_3$)



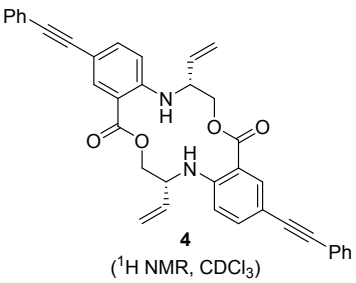
syn-**3n**

(^{13}C NMR, $CDCl_3$)



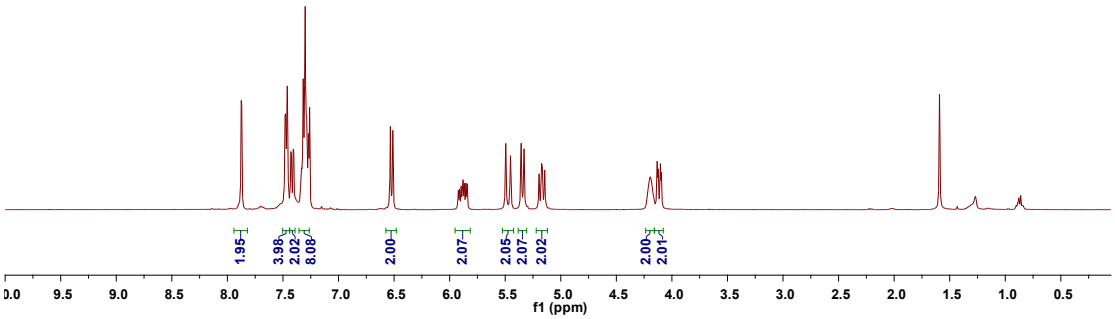
syn-**3n**

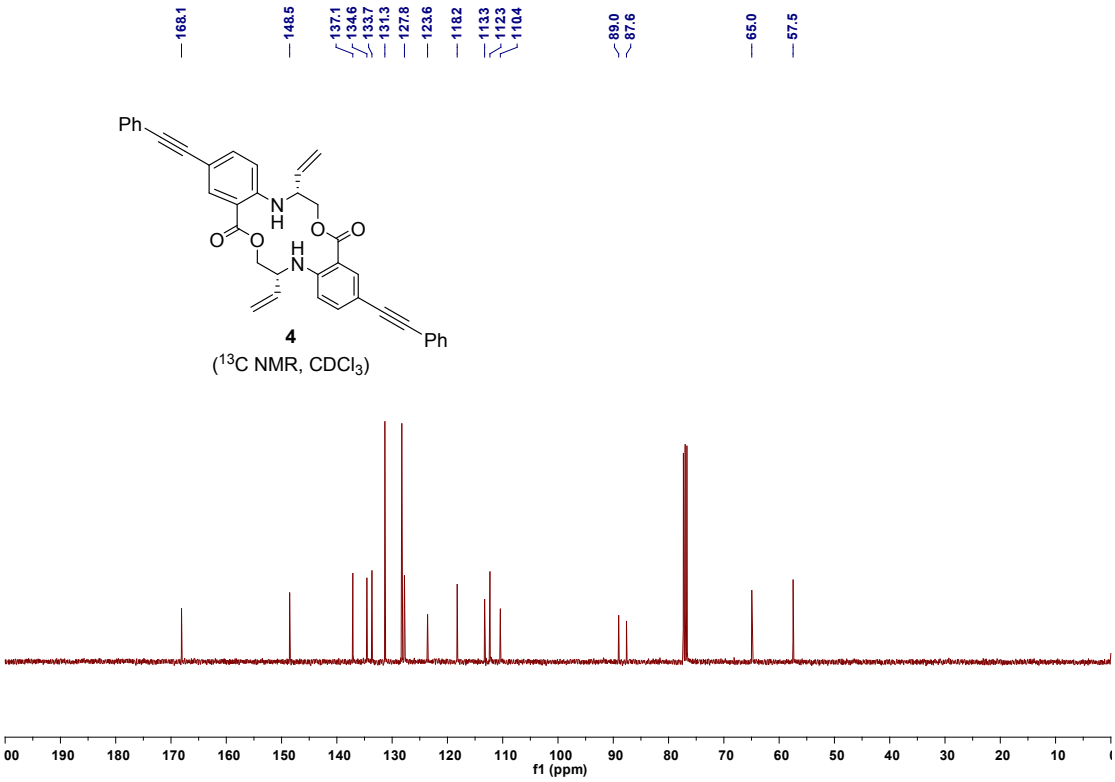
(^{19}F NMR, $CDCl_3$)

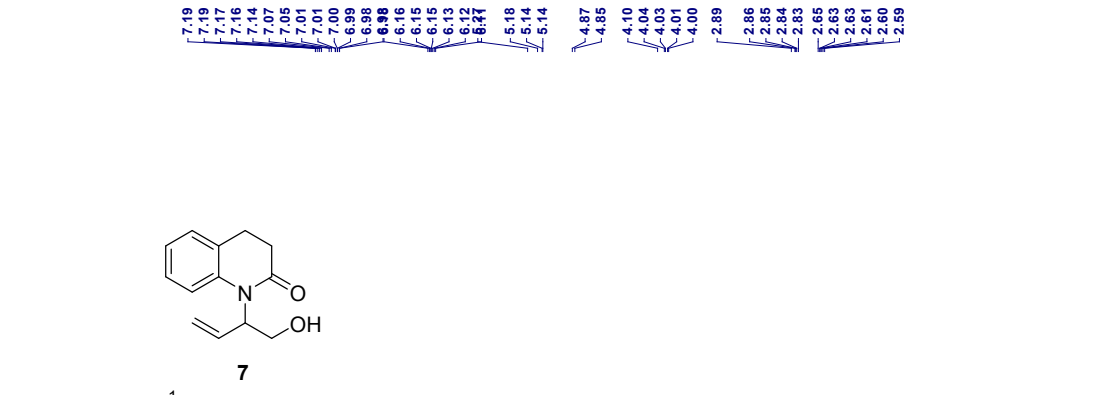


4

(^{1}H NMR, $CDCl_3$)

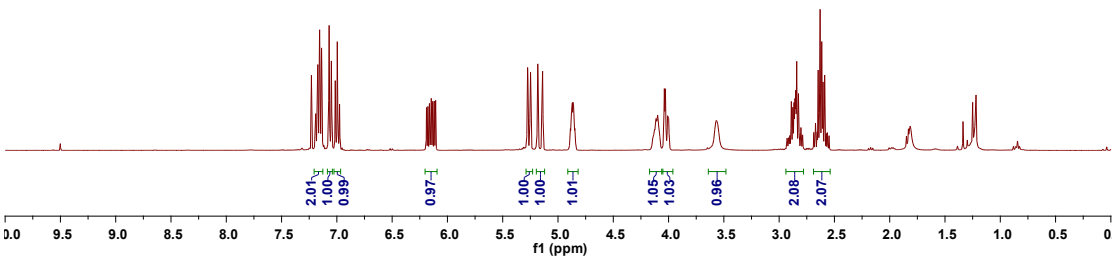


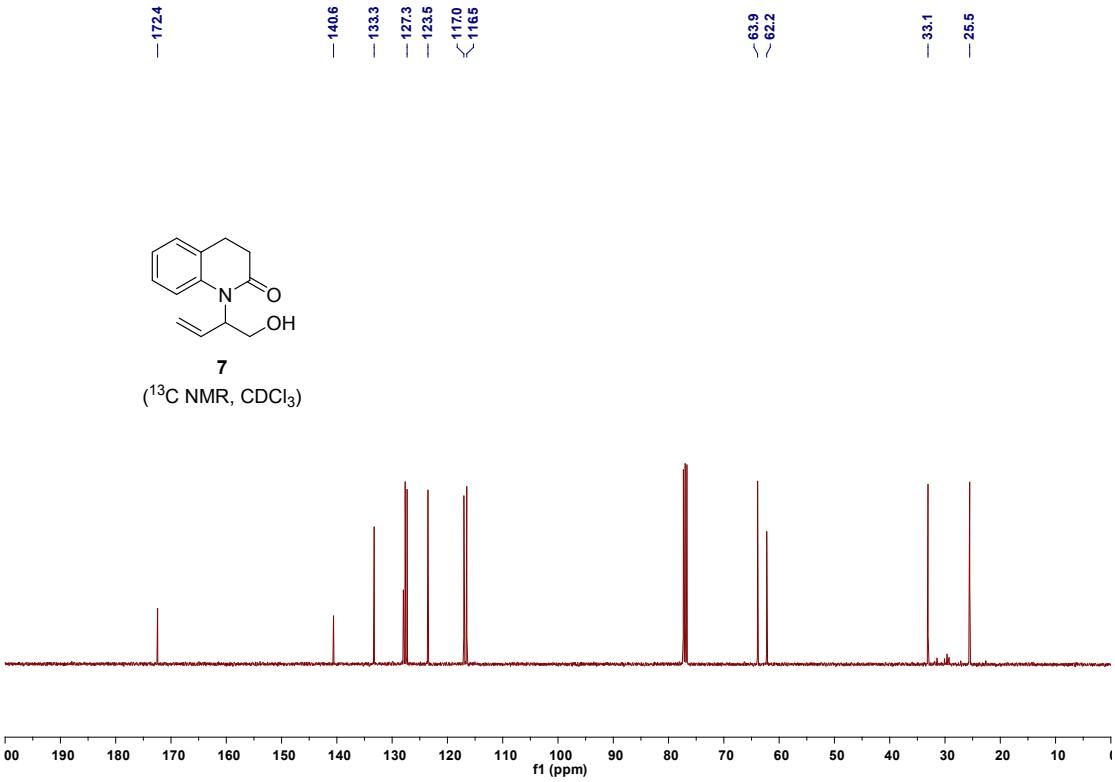




7

(^{1}H NMR, $CDCl_3$)





9. X-ray Crystallographic Analysis

Single crystals suitable for X-ray diffraction experiment were obtained by slow evaporation of DCM/*n*-hexane (1:10, V/V) solution containing the corresponding compounds. All the data were collected at 293.1(2) K with an Xcalibur Eos Gemini diffractometer using graphite-monochromatized enhance X-ray source Mo-*K*α (λ=0.71073 Å) radiation for *syn*-**3a**, *anti*-**3a**, *syn*-**3g** and *syn*-**3l**, and Cu-*K*α (λ=1.54184 Å) radiation for *anti*-**3m**. *CrysAlisPro*[4] was used for both data collection and processing. The intensities were corrected for absorption using empirical model implemented in SCALE3 ABSPACK scaling algorithm.[4] The structures were solved by Intrinsic Phasing method with *SHELXT*[5] and refined by full-matrix least-squares methods using the *OLEX2*,[6] which utilizes the *SHELXL-2015* module.[7] All non-hydrogen atoms in the structures were refined with anisotropic models. All the H atoms except the H(N) were introduced at ideal positions with riding mode. The H(N) atoms were assigned from difference Fourier maps and their positions and isotropic thermal displacement parameters were refined with freely. One of the vinyl groups in the structure of *anti*-**3a**, one vinyl group in *syn*-**3l** and one trifluoromethyl group in *anti*-**3m** were disordered. Each relevant C atoms or F atoms were split over two positions and refined with free occupancies and restrained "C-C" or "C-F" bond lengths with "SADI 0.01" commands.

Details of the experiment and refinement results as follows:

Syn-**3a**: $C_{22}H_{22}N_2O_4$, M_r = 378.41 gmol^{-1}, Crystal dimensions: 0.182 x 0.35 x 0.36 mm, monoclinic, space group *P21/n*, *a* = 13.7113(9) Å, *b* = 9.7397(5), *c* = 14.7226(8) Å, β = 102.505(6), *V* = 1919.5(2) Å^3, *Z* = 4, D_c = 1.309 Mg/m^3, μ = 0.091 mm^{-1}, F000 = 800, *T* = 293.1(2) K, θ range for cell measurement: 3.52-29.33°, R_{int} = 0.0279, R_1 = 0.0629 (0.1199), *wR2* = 0.1194 (0.1471), 8543 reflections are measured with 4391 independent reflections of which 2512 are I_o>2σ(I_o), 261 parameters, 0 restraints, *GooF* = 1.026, -0.224<Δρ<0.211 e/Å^3.

Anti-**3a**: $C_{22}H_{22}N_2O_4$, M_r = 378.41 gmol^{-1}, Crystal dimensions: 0.32 x 0.33 x 0.35 mm, monoclinic, space group *P21/n*, *a* = 14.5996(10) Å, *b* = 8.1161(5), *c* = 16.4481(14) Å, β = 99.915(7), *V* = 1919.9(2) Å^3, *Z* = 4, D_c = 1.309 Mg/m^3, μ = 0.091 mm^{-1}, F000 = 800, *T* = 293.1(2) K, θ range for cell measurement: 3.45-29.33°, R_{int} = 0.0370, R_1 = 0.0564 (0.1374), *wR* = 0.1107 (0.1421), 10170 reflections are measured with 4506 independent reflections of which 2192 are I_o>2σ(I_o), 280 parameters, 2 restraints, *GooF* = 0.992, -0.158<Δρ<0.207 e/Å^3.

Syn-**3g**: $C_{24}H_{26}N_2O_6$, M_r = 438.47 gmol^{-1}, Crystal dimensions: 0.20 x 0.21 x 0.38 mm, orthorhombic, space group *Pbca*, *a* = 11.5668(5) Å, *b* = 17.1785(9), *c* = 23.0513(10) Å, *V* = 4580.3(4) Å^3, *Z* = 8, D_c = 1.272 Mg/m^3, μ = 0.092 mm^{-1}, F000 = 1856, *T* = 293.1(2) K, θ range for cell measurement: 3.44-29.49°, R_{int} = 0.0485, R_1 = 0.0608 (0.1159), *wR* = 0.1341 (0.1672), 25391 reflections are measured with 5572 independent reflections of which 3156 are I_o>2σ(I_o), 299 parameters, 6 restraints, *GooF* = 1.069, -0.304<Δρ<0.290 e/Å^3.

Syn-**3l**: $C_{22}H_{20}N_2O_4F_2$, M_r=414.40 gmol^{-1}, Crystal dimensions: 0.11 x 0.32 x 0.33 mm, monoclinic, space group *P21/c*, *a* = 16.6617(5) Å, *b* = 9.8335(5), *c* = 12.6100(9) Å, β = 105.347(7), *V* = 1992.4(3) Å^3, *Z* = 4, D_c = 1.382 Mg/m^3, μ = 0.108 mm^{-1}, F000 = 864, *T* = 293.1(2) K, θ range for cell measurement: 3.63-29.26°, R_{int} = 0.0354, R_1 = 0.0609 (0.1145), *wR* = 0.1262 (0.1623), 9755 reflections are measured with 4601 independent reflections of which 2577 are I_o>2σ(I_o), 298 parameters, 20 restraints, *GooF* = 1.050, -0.409<Δρ<0.314 e/Å^3.

Anti-**3m**: $C_{24}H_{20}N_2O_4F_6$, M_r=514.42 gmol^{-1}, Crystal dimensions: 0.10 x 0.13 x 0.16 mm, monoclinic, space group *P21/c*, *a* = 10.1630(3) Å, *b* = 10.7505(3), *c* = 10.3964(3) Å, β =

91.940(3), V = 1135.22(6) Å^3, Z = 2, D_c = 1.505 Mg/m^3, μ = 1.184 mm^{-1}, F000 = 528, T = 293.1(2) K, θ range for cell measurement: 4.35-67.07°, R_{int} = 0.0275, R_1 = 0.0481 (0.0596), wR = 0.1290 (0.1455), 4348 reflections are measured with 2029 independent reflections of which 1663 are I_o>2σ(I_o), 195 parameters, 38 restraints, $GooF$ = 1.088, -0.171<Δρ<0.221 e/Å^3.

Crystal structures of *syn*-3a, *anti*-3a, *syn*-3g , *syn*-3l, and *anti*-3m [8]

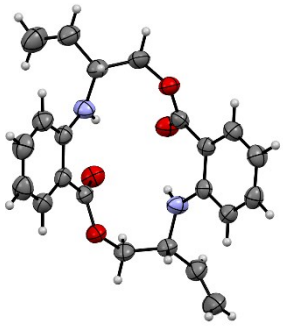


Fig. 2A ORTEP plots for molecular structures of *syn*-**3a** with the probability at 50% level.

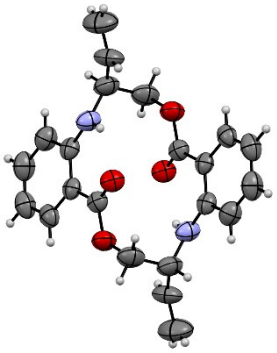


Fig. 2B ORTEP plots for molecular structures of *anti*-**3a** with the probability at 50% level. For the crystal structure of *anti*-**3a**, two half molecules were in the asymmetric unit cell, each lying about an inversion centre.

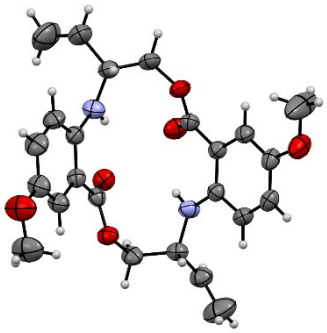


Figure S18. ORTEP plots for X-ray structures of *syn*-**3g** with the probability at 50% level.

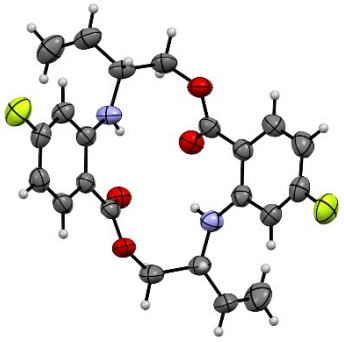


Figure S19. ORTEP plots for X-ray structures of *syn*-**3l** with the probability at 50% level. The molecule lied on an invention centre.

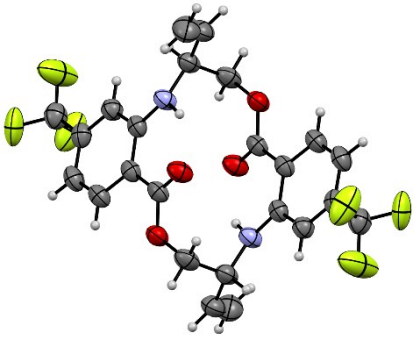


Figure S20. ORTEP plots for molecular structures of *anti*-**3m** with the probability at 50% level. For the crystal structure of *anti*-**3m**, only a half molecule was in the asymmetric unit cell, which lied about an invention centre.

11. References

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7. G. M. Sheldrick, *Acta Cryst. C*, 2015, **71**, 3.

8. CCDC 1942738 (*syn*-**3a**), 1942739 (*anti*-**3a**), 1942740 (*syn*-**3g**), 1942741 (*syn*-**3l**) and 1942742 (*anti*-**3m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.