

# Supporting Information

## TEMPO-Catalyzed Electrochemical Dehydrogenative Cyclocondensation of *o*-Aminophenols: Synthesis of Aminophenoxazinones as Antiproliferative Agents

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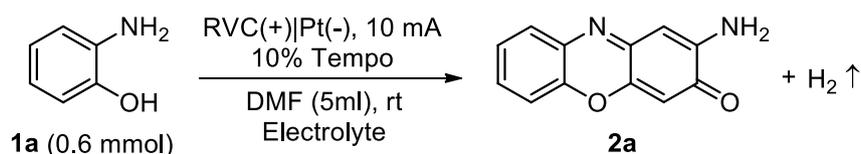
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## 1. General information

Unless otherwise stated, chemicals were obtained from commercial sources and were used without further purification. Column chromatography purifications were performed using 200-300 mesh silica gel. NMR spectra were recorded on Bruker AV-400 and Bruker AV-500 instruments. The spectra data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant ( $J$ ) in Hertz. HRMS were obtained using Agilent 1290 HPLC-6224 TOF Spectrometer. Cyclic voltammograms were obtained on a CHI 760E potentiostat. 3-(4,5-dimethyl thiazol-2-yl) -2,5-diphenyltetrazolium bromide (MTT) was purchased from Sigma (Shanghai, China). DMEM, fetal bovine serum (FBS), N-2 supplement were purchased from Gibco. The human hepatic cells HepG2 were purchased from the Chinese Academy of Sciences Cell Cultures Library (Wuhan, China), and cultured in DMEM with addition of 10% FBS and 1% penicillin/streptomycin.

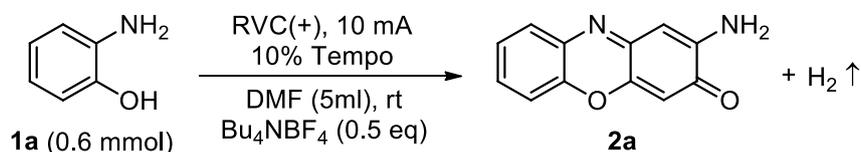
## 2. Additional optimization of the electrolysis

a) Electrolyte



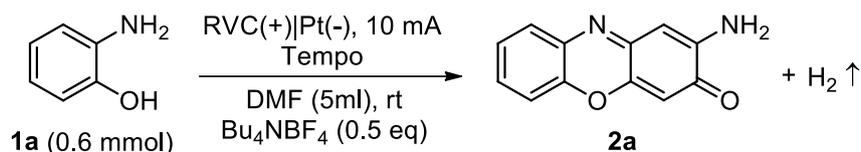
Entry	Electrolyte	Yield
1	<i>n</i> Bu <sub>4</sub> NBF <sub>4</sub> (1 eq)	82
2	<i>n</i> Bu <sub>4</sub> NPF <sub>6</sub> (1 eq)	57
3	NaBF <sub>4</sub> (1 eq)	63
4	LiSO <sub>3</sub> CF <sub>3</sub> (1 eq)	55
5	LiN(SO <sub>2</sub> F) <sub>2</sub> (1 eq)	51
6	<i>n</i> Bu <sub>4</sub> NBF <sub>4</sub> (0.5 eq)	79
7	none	47

b) Cathode



Entry	Cathode	Yield
1	Pt	82
2	C	77
3	Ni	73
4	RVC	80

c) Amount of catalyst



Entry	The amount of catalyst (%)	Yield
1	5	79
2	10	86
3	15	85
4	20	85

### 3. Cyclic voltammometry

The cyclic voltammograms were recorded in an electrolyte of *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.1 M) in DMF using a glassy carbon disk working electrode (diameter, 3 mm), a Pt wire auxiliary electrode and a SCE reference electrode. The scan rate is 100 mV/s.

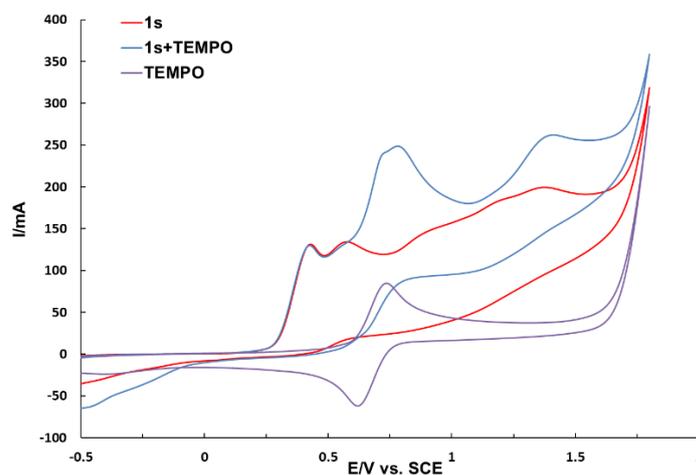


Figure S1. Cyclic voltammometry towards oxidation potentials for 15 mM of **1s**, 3 mM of TEMPO, and 3 mM of TEMPO with 15 mM of **1s**.

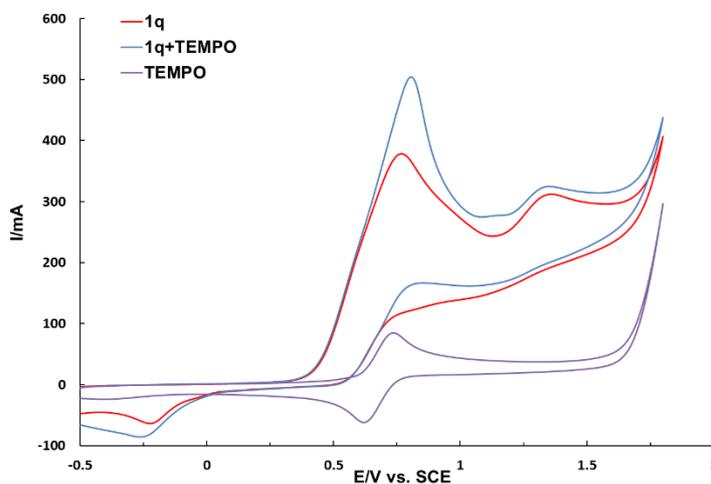


Figure S2. Cyclic voltammometry towards oxidation potentials for 15 mM of **1q**, 3 mM of TEMPO, and 3 mM of TEMPO with 15 mM of **1q**.

2-Aminobenzenethiol (**1r**) exhibited low electroactivities in the range of potentials examined.

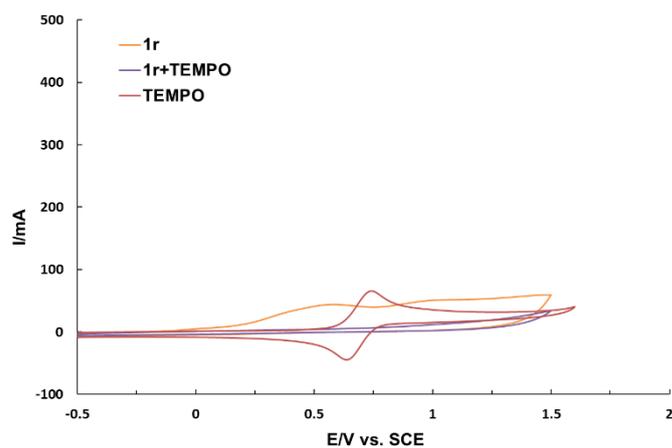


Figure S3. Cyclic voltammety towards oxidation potentials for 15 mM of **1r**, 3 mM of TEMPO, and 3 mM of TEMPO with 15 mM of **1r**.

2-Aminopyridin-3-ol (**1s**) exhibited low electroactivities in the range of potentials examined as well.

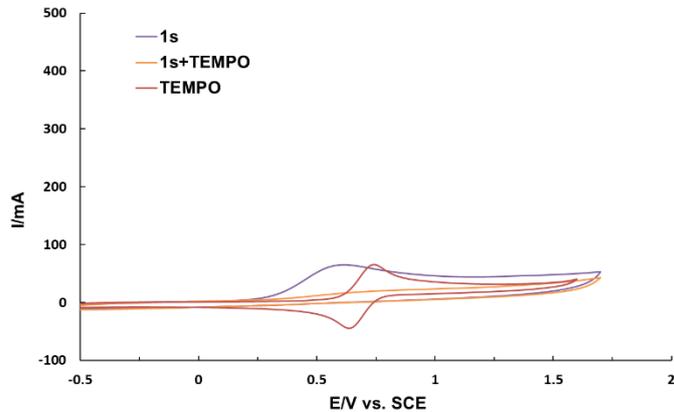


Figure S4. Cyclic voltammety towards oxidation potentials for 15 mM of **1s**, 3 mM of TEMPO, and 3 mM of TEMPO with 15 mM of **1s**.

The strong electron-withdrawing effect of nitro group resulted in the much higher oxidation potential of **1t** (+1.22 V vs. SCE) compared to that of **1a** (+0.34 V vs. SCE), and TEMPO could not mediate the oxidation of **1t** under the reaction condition.

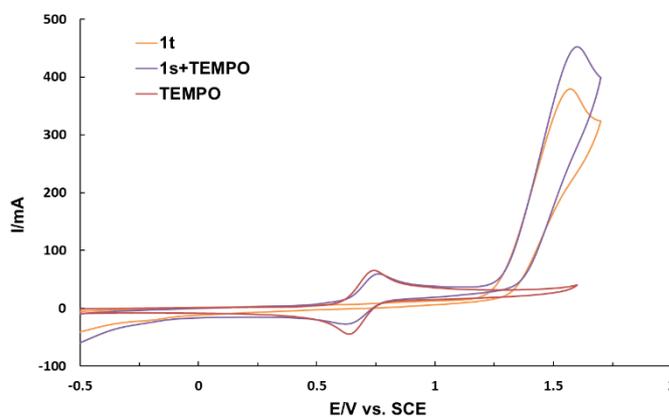


Figure S5. Cyclic voltammetry towards oxidation potentials for 15 mM of **1t**, 3 mM of TEMPO, and 3 mM of TEMPO with 15 mM of **1t**.

Surprisingly, the secondary amine, 2-(methylamino)phenol (**1u**), proved to be electroactive under the electrochemical condition (+0.32 V vs. SCE), so the unstable intermediates or steric hindrance might lead to unsuccessful dimerization.

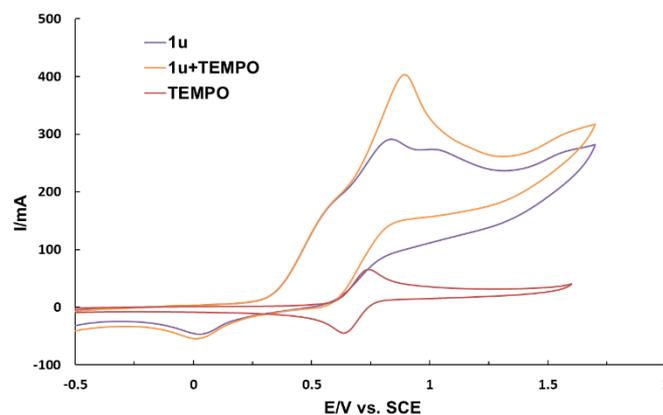


Figure S6. Cyclic voltammetry towards oxidation potentials for 15 mM of **1u**, 3 mM of TEMPO, and 3 mM of TEMPO with 15 mM of **1u**.

#### 4. General experimental procedures

The substrate (0.6 mmol, 1.0 equiv), TEMPO (0.06 mmol, 0.1 equiv),  $n\text{Bu}_4\text{NBF}_4$  (0.6 mmol, 1.0 equiv) were placed in a 10 mL three-necked round-bottomed flask. The flask was equipped with a stopper, a RVC (100 PPI, 10 mm  $\times$  10 mm  $\times$  5 mm) anode and a platinum plate (10 mm  $\times$  10 mm  $\times$  0.1 mm) cathode. The electrolysis was carried out at r.t. in DMF (5.0 mL) using a constant current of 10 mA until complete consumption of the substrate (monitored by TLC). The reaction mixture was extracted with EtOAc (15 mL  $\times$  3). The collected organic layers were dried, evaporated and chromatographed through silica gel eluting with ethyl acetate/hexanes to give the desired products.

#### Large-Scale General Procedure:

The gram-scale electrolysis of **1a** was conducted in a 1-L beaker using a reticulated vitreous carbon (100 PPI, 30 mm  $\times$  30 mm  $\times$  10 mm) as the anode, a platinum plate (30 mm  $\times$  30 mm  $\times$  0.1 mm) as the cathode. Compound **1a** (5.3 g, 50.0 mmol), TEMPO (5 mmol, 10 mol %),  $n\text{Bu}_4\text{NBF}_4$  (50 mmol, 1.0 equiv), DMF (420 mL) were added. The reaction mixture is electrolyzed at a current of 100 mA/mmol at r.t. for 41 h, and the reaction is complete as judged by TLC analysis. The solvent was evaporated in vacuum, and the residue was extracted with EtOAc (200 mL  $\times$  3). The collected organic layers were dried, evaporated and chromatographed through silica gel eluting with ethyl acetate/hexanes to give the desired products.

#### 9-V battery instrument

The substrate (0.6 mmol, 1.0 equiv), TEMPO (0.06 mmol, 0.1 equiv),  $n\text{Bu}_4\text{NBF}_4$  (0.6 mmol, 1 equiv), DMF (5 mL) were placed in a 10 mL beaker-type cell. The flask was equipped with a stopper, a RVC (100 PPI, 10 mm  $\times$  10 mm  $\times$  5 mm) anode and a platinum plate (100 PPI, 10 mm  $\times$  10 mm  $\times$  0.1 mm) cathode. The electrolysis was carried out at r.t. in DMF using 9-V commercially available battery as power source until complete consumption of the substrate (monitored by TLC). The reaction mixture was extracted with EtOAc (15 mL  $\times$  3). The collected organic layers were dried, evaporated and chromatographed through silica gel eluting with ethyl acetate/hexanes to give the desired products.

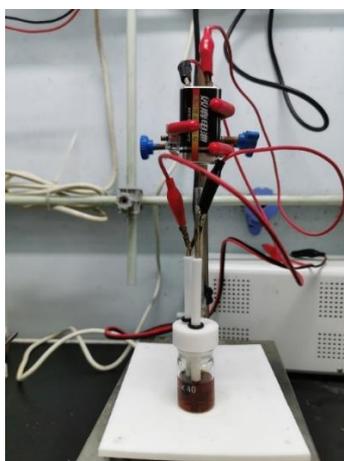
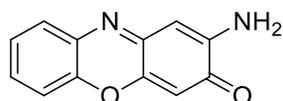
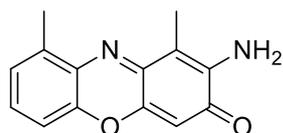


Figure S7. The use of 9-V battery as a commercially available power source for electrochemical synthesis of **2a**.

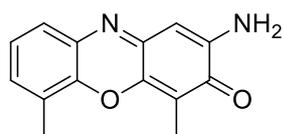
## 5. Experimental details and characterization of compounds



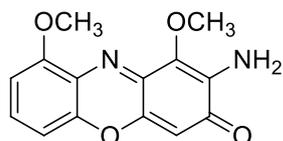
2-Amino-3*H*-phenoxazin-3-one (**2a**).<sup>[1]</sup> Dark red solid, yield = 82%; **<sup>1</sup>H NMR (500 MHz, DMSO)**:  $\delta$  7.68–7.37 (4H, m), 6.81 (2H, s), 6.34 (2H, s); **<sup>13</sup>C NMR (125 MHz, DMSO)**:  $\delta$  180.1, 148.8, 148.1, 147.3, 141.8, 133.6, 128.7, 127.9, 125.2, 115.8, 103.3, 98.2; **HRMS (ESI)**: Calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>  $m/z$  213.0659, Found  $m/z$  213.0661.



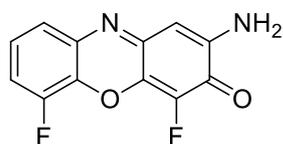
2-Amino-1,9-dimethyl-3*H*-phenoxazin-3-one (**2b**). Dark red solid, yield = 80%; **<sup>1</sup>H NMR (500 MHz, DMSO)**:  $\delta$  7.34–7.20 (3H, m), 6.37 (2H, s), 6.23 (1H, s), 2.59 (3H, s), 2.22 (3H, m); **<sup>13</sup>C NMR (125 MHz, DMSO)**:  $\delta$  179.5, 148.7, 145.8, 143.6, 141.8, 136.6, 131.6, 128.3, 125.8, 113.2, 105.6, 102.0, 16.3, 9.6; **HRMS (ESI)**: Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>  $m/z$  241.0972, Found  $m/z$  241.0971.



2-Amino-4,6-dimethyl-3*H*-phenoxazin-3-one (**2c**).<sup>[1]</sup> Dark red solid, yield = 79%; **<sup>1</sup>H NMR (500 MHz, DMSO)**:  $\delta$  7.46 (1H, d,  $J = 7.5$  Hz), 7.26 (1H, d,  $J = 7.5$  Hz), 7.21 (1H, t,  $J = 7.5$  Hz), 6.68 (2H, s), 6.26 (1H, s), 2.40 (3H, s), 2.04 (3H, m); **<sup>13</sup>C NMR (125 MHz, DMSO)**:  $\delta$  180.3, 148.2, 147.1, 145.1, 140.9, 133.7, 130.1, 126.0, 125.3, 124.7, 111.6, 98.0, 14.8, 8.0; **HRMS (ESI)**: Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>  $m/z$  241.0972, Found  $m/z$  241.0976.

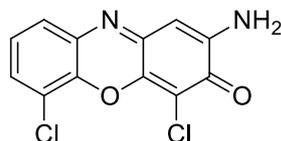


2-Amino-1,9-dimethoxy-3*H*-phenoxazin-3-one (**2d**). Dark red solid, yield = 68%; **<sup>1</sup>H NMR (400 MHz, DMSO)**:  $\delta$  7.45 (1H, t,  $J = 8.4$  Hz), 7.08 (1H, d,  $J = 8.4$  Hz), 7.03 (1H, d,  $J = 8.4$  Hz), 6.30 (2H, s), 6.25 (1H, s), 3.98 (3H, s), 3.87 (3H, s); **<sup>13</sup>C NMR (100 MHz, DMSO)**:  $\delta$  179.9, 155.4, 147.0, 142.6, 140.7, 137.6, 132.1, 129.5, 123.9, 107.7, 107.3, 101.4, 59.9, 56.4; **HRMS (ESI)**: Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>  $m/z$  273.0870, Found  $m/z$  273.0877.

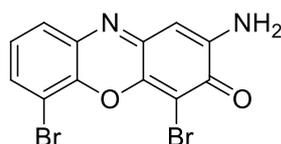


2-Amino-4,6-difluoro-3*H*-phenoxazin-3-one (**2e**).<sup>[1]</sup> Black solid, yield = 62%; **<sup>1</sup>H NMR**

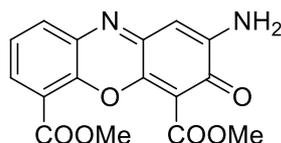
**(500 MHz, DMSO):**  $\delta$  7.55 (1H, d,  $J$  = 8.0 Hz), 7.47–7.44 (1H, m), 7.40–7.23 (1H, m), 7.09 (2H, s), 6.32 (1H, s);  **$^{13}\text{C}$  NMR (125 MHz, DMSO):**  $\delta$  172.2 (d,  $^2J_{\text{C-F}}$  = 16 Hz), 149.2 (d,  $^1J_{\text{C-F}}$  = 248 Hz), 147.3, 146.6 (d,  $^4J_{\text{C-F}}$  = 2 Hz), 138.7 (d,  $^1J_{\text{C-F}}$  = 252 Hz), 135.2, 132.5 (d,  $^3J_{\text{C-F}}$  = 6 Hz), 129.5 (d,  $^3J_{\text{C-F}}$  = 11 Hz), 124.5 (d,  $^3J_{\text{C-F}}$  = 7 Hz), 123.7 (d,  $^4J_{\text{C-F}}$  = 2 Hz), 115.2 (d,  $^2J_{\text{C-F}}$  = 17 Hz), 96.4;  **$^{19}\text{F}$  NMR (376 MHz, DMSO):**  $\delta$  -137.5, -161.3; **HRMS (ESI):** Calcd. for  $\text{C}_{12}\text{H}_7\text{F}_2\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$   $m/z$  249.0471, Found  $m/z$  249.0477.



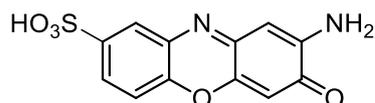
2-Amino-4,6-dichloro-3H-phenoxazin-3-one (**2f**).<sup>[1]</sup> Black solid, yield = 69%;  **$^1\text{H}$  NMR (500 MHz, DMSO):**  $\delta$  7.67 (1H, d,  $J$  = 8.0 Hz), 7.61 (1H, d,  $J$  = 8.0 Hz), 7.40 (1H, t,  $J$  = 8.0 Hz), 7.10 (2H, s), 6.38 (1H, s);  **$^{13}\text{C}$  NMR (125 MHz, DMSO):**  $\delta$  174.2, 147.3, 147.1, 143.8, 137.6, 134.8, 128.8, 126.8, 125.6, 119.8, 109.6, 97.5; **HRMS (ESI):** Calcd. for  $\text{C}_{12}\text{H}_7\text{Cl}_2\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$   $m/z$  280.9879, Found  $m/z$  280.9877.



2-Amino-4,6-dibromo-3H-phenoxazin-3-one (**2g**).<sup>[1]</sup> Dark red solid, yield = 71%;  **$^1\text{H}$  NMR (500 MHz, DMSO):**  $\delta$  7.78 (1H, d,  $J$  = 8.0 Hz), 7.73 (1H, d,  $J$  = 8.0 Hz), 7.37 (1H, t,  $J$  = 8.0 Hz), 7.13 (2H, s), 6.40 (1H, s);  **$^{13}\text{C}$  NMR (125 MHz, DMSO):**  $\delta$  174.4, 147.6, 147.1, 146.0, 139.0, 135.0, 131.8, 127.3, 126.3, 108.7, 101.1, 97.6; **HRMS (ESI):** Calcd. for  $\text{C}_{12}\text{H}_7\text{Br}_2\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$   $m/z$  368.8869, Found  $m/z$  368.8867.

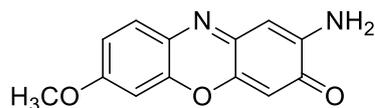


Dimethyl 2-amino-3-oxo-3H-phenoxazine-4,6-dicarboxylate (**2h**). Dark red solid, yield = 64%;  **$^1\text{H}$  NMR (400 MHz, DMSO):**  $\delta$  7.96 (2H, t,  $J$  = 8.0 Hz), 7.53 (1H, t,  $J$  = 8.0 Hz), 7.07 (2H, s), 6.44 (1H, s), 3.91 (6H, s);  **$^{13}\text{C}$  NMR (100 MHz, DMSO):**  $\delta$  176.6, 164.1, 163.3, 147.0, 146.3, 144.9, 140.0, 134.3, 132.5, 130.5, 125.1, 118.7, 110.2, 98.4, 52.3, 52.2; **HRMS (ESI):** Calcd. for  $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_6$   $[\text{M}+\text{H}]^+$   $m/z$  329.0769, Found  $m/z$  329.0773.

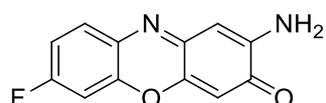


2-Amino-3-oxo-3H-phenoxazine-8-sulfonic acid (**2i**).<sup>[4]</sup> Red solid, eluted with  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ , yield = 42%;  **$^1\text{H}$  NMR (400 MHz, DMSO):**  $\delta$  7.84 (1H, s), 7.66 (1H, d,  $J$  = 8.8 Hz), 7.44 (1H, d,  $J$  = 8.8 Hz), 6.84 (2H, s), 6.38 (1H, s), 6.36 (1H, s);  **$^{13}\text{C}$  NMR (100 MHz, DMSO):**  $\delta$  180.7, 149.3, 149.0, 147.9, 145.7, 142.3, 133.2, 126.7, 125.1, 115.8, 104.0,

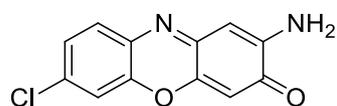
98.8; **HRMS (ESI)**: Calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup> *m/z* 293.0227, Found *m/z* 293.0222.



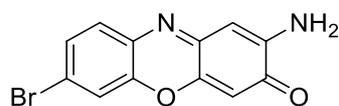
2-Amino-7-methoxy-3*H*-phenoxazin-3-one (**2j**).<sup>[3]</sup> Dark red solid, yield = 53%; **<sup>1</sup>H NMR (500 MHz, DMSO)**: δ 7.65 (1H, d, *J* = 9.0 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 7.56 (1H, d, *J* = 8.0 Hz), 6.97 (2H, s), 6.36 (1H, s), 6.33 (1H, s), 3.86 (3H, s); **<sup>13</sup>C NMR (125 MHz, DMSO)**: δ 179.7, 160.0, 148.5, 146.5, 145.6, 143.2, 128.9, 128.3, 113.3, 103.2, 100.0, 98.8, 56.0; **HRMS (ESI)**: Calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> *m/z* 243.0765, Found *m/z* 243.0762.



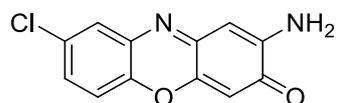
2-Amino-7-fluoro-3*H*-phenoxazin-3-one (**2k**).<sup>[2]</sup> Black solid, yield = 62%; **<sup>1</sup>H NMR (500 MHz, DMSO)**: δ 7.74 (1H, dd, *J* = 9.0, 6.0 Hz), 7.47 (1H, d, *J* = 9.0, 2.5 Hz), 7.26 (1H, td, *J* = 9.0, 2.5 Hz), 6.77 (2H, s), 6.36 (1H, s), 6.34 (1H, s); **<sup>13</sup>C NMR (125 MHz, DMSO)**: δ 180.1, 160.5 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.7 Hz), 148.3, 147.5 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.8 Hz), 147.1, 142.4 (d, <sup>3</sup>*J*<sub>C-F</sub> = 13.4 Hz), 130.7 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.5 Hz), 129.3 (d, <sup>3</sup>*J*<sub>C-F</sub> = 10.0 Hz), 112.9 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.3 Hz), 103.7, 103.3 (d, <sup>2</sup>*J*<sub>C-F</sub> = 27.4 Hz), 98.4; **<sup>19</sup>F NMR (376 MHz, DMSO)**: δ -109.4; **HRMS (ESI)**: Calcd. for C<sub>12</sub>H<sub>8</sub>FN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> *m/z* 231.0559, Found *m/z* 231.0553.



2-Amino-7-chloro-3*H*-phenoxazin-3-one (**2l**).<sup>[2]</sup> Black solid, yield = 61%; **<sup>1</sup>H NMR (400 MHz, DMSO)**: δ 7.70 (1H, d, *J* = 8.8 Hz), 7.66 (1H, d, *J* = 2.0 Hz), 7.43 (1H, dd, *J* = 8.8, 2.0 Hz), 6.92 (2H, s), 6.63 (1H, s), 6.35 (1H, s); **<sup>13</sup>C NMR (100 MHz, DMSO)**: δ 185.4, 153.6, 153.5, 152.7, 147.4, 137.9, 137.1, 134.2, 130.6, 121.1, 108.9, 103.5; **HRMS (ESI)**: Calcd. for C<sub>12</sub>H<sub>8</sub>ClN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> *m/z* 247.0269, Found *m/z* 247.0270.

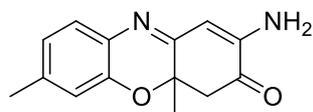


2-Amino-7-bromo-3*H*-phenoxazin-3-one (**2m**). Dark red solid, yield = 68%; **<sup>1</sup>H NMR (500 MHz, DMSO)**: δ 7.79–7.55 (3H, m), 6.94 (2H, s), 6.35 (2H, s); **<sup>13</sup>C NMR (125 MHz, DMSO)**: δ 180.2, 148.4, 148.4, 147.5, 142.3, 133.0, 129.2, 128.2, 120.1, 118.7, 103.7, 98.4; **HRMS (ESI)**: Calcd. for C<sub>12</sub>H<sub>8</sub>BrN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> *m/z* 290.9764, Found *m/z* 290.9759.

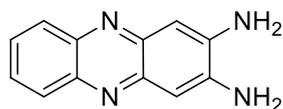


2-Amino-8-chloro-3*H*-phenoxazin-3-one (**2n**). Black solid, yield = 63%; **<sup>1</sup>H NMR (400 MHz, DMSO)**: δ 7.75 (1H, d, *J* = 2.4 Hz), 7.53 (1H, d, *J* = 8.8 Hz), 7.48 (1H, dd, *J* = 8.8,

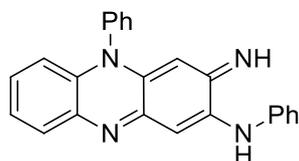
1.2 Hz), 7.00 (2H, s), 6.39 (1H, s), 6.36 (1H, s); **<sup>13</sup>C NMR (125 MHz, DMSO)**:  $\delta$  180.1, 149.0, 148.7, 147.8, 140.7, 134.6, 128.6, 127.9, 126.6, 117.5, 103.6, 97.9; **HRMS (ESI)**: Calcd. for C<sub>12</sub>H<sub>8</sub>ClN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>  $m/z$  247.0269, Found  $m/z$  247.0263.



2-Amino-4a,7-dimethyl-4,4a-dihydro-3H-phenoxazin-3-one (**2o**).<sup>[2]</sup> Yellow solid, yield = 83%; **<sup>1</sup>H NMR (500 MHz, DMSO)**:  $\delta$  7.09 (1H, d,  $J = 8.0$  Hz), 6.79 (1H, d,  $J = 8.0$  Hz), 6.71 (1H, s), 6.39 (2H, s), 6.04 (1H, s), 3.19 (1H, d,  $J = 16.0$  Hz), 2.98 (1H, d,  $J = 16.0$  Hz), 2.26 (3H, s), 1.09 (3H, m); **<sup>13</sup>C NMR (125 MHz, DMSO)**:  $\delta$  191.5, 160.8, 146.4, 143.7, 136.5, 132.6, 125.4, 123.0, 116.5, 105.8, 70.9, 49.1, 21.9, 20.8; **HRMS (ESI)**: Calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>  $m/z$  243.1129, Found  $m/z$  243.1133.



Phenazine-2,3-diamine (**2p**).<sup>[1]</sup> Red solid, yield = 79%; **<sup>1</sup>H NMR (400 MHz, DMSO)**:  $\delta$  7.90 (1H, dd,  $J = 6.4, 3.2$  Hz), 7.56 (1H, dd,  $J = 6.4, 3.2$  Hz), 6.92 (2H, s), 6.27 (4H, s); **<sup>13</sup>C NMR (100 MHz, DMSO)**:  $\delta$  144.5, 142.5, 140.7, 128.3, 126.9, 102.6; **HRMS (ESI)**: Calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>4</sub> [M+H]<sup>+</sup>  $m/z$  211.0978, Found  $m/z$  211.0972.



3-Imino-N,5-diphenyl-3,5-dihydrophenazin-2-amine (**2q**).<sup>[1]</sup> Dark red solid, yield = 85%; **<sup>1</sup>H NMR (400 MHz, DMSO)**:  $\delta$  7.68 (1H, dd,  $J = 7.6, 1.6$  Hz), 7.62 (1H, t,  $J = 7.6$  Hz), 7.54 (1H, d,  $J = 7.6$  Hz), 7.37 (2H, d,  $J = 7.2$  Hz), 7.25–7.13 (4H, m), 6.90 (1H, t,  $J = 7.6$  Hz), 6.70 (2H, d,  $J = 7.2$  Hz), 6.60 (2H, s), 6.48–6.44 (2H, m), 5.24 (1H, s); **<sup>13</sup>C NMR (100 MHz, DMSO)**:  $\delta$  152.8, 151.4, 150.3, 149.9, 137.3, 136.0, 134.7, 131.3, 131.0, 129.9, 129.0, 128.9, 128.0, 127.6, 123.2, 123.1, 121.2, 114.6, 99.4, 90.6; **HRMS (ESI)**: Calcd. for C<sub>24</sub>H<sub>19</sub>N<sub>4</sub> [M+H]<sup>+</sup>  $m/z$  363.1604, Found  $m/z$  363.1609.

## 6. Cell viability assay

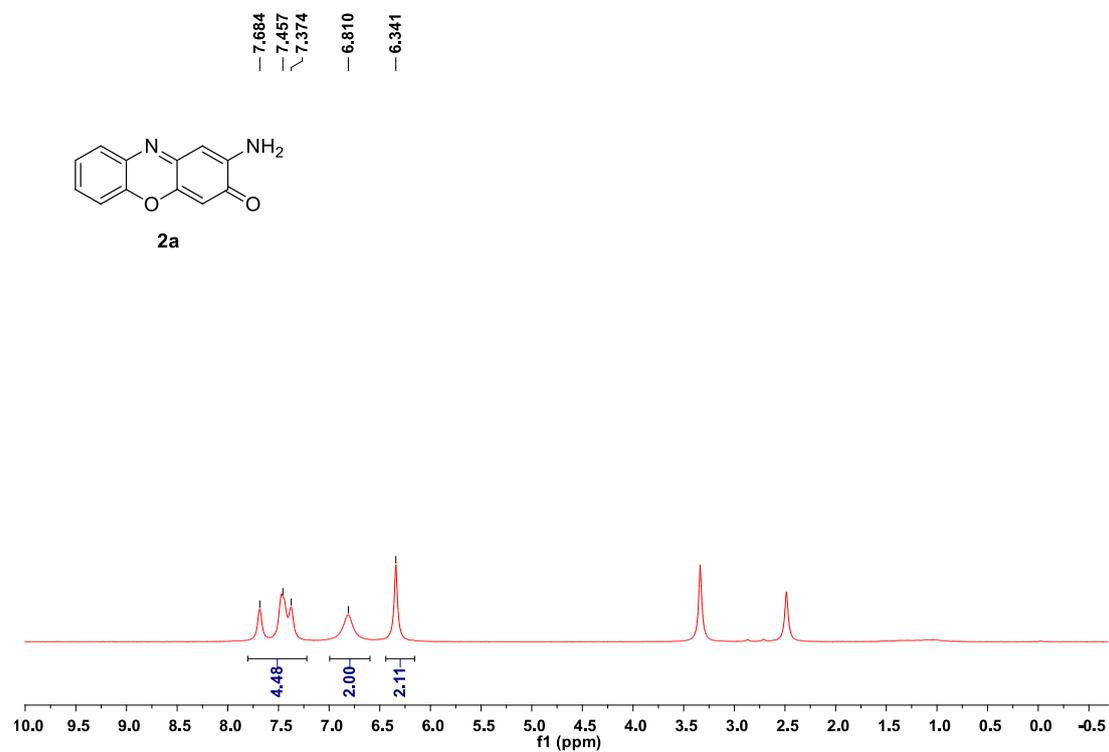
Cell Counting Kit-8 (CCK-8, Biosharp, Hefei, China) assay was performed to determine the cell proliferation. Cells were seeded in 96-well plates with  $1 \times 10^4$ /well for 24h. Then cells were treated with 10  $\mu$ g/mL of sample for 24 h. Supernatant was then removed, and CCK-8 solutions were added followed by incubating for 1 h at 37 °C according to the manufacturer's protocol. A Biotek Epoch™ Microplate Spectrophotometer ( San Jose, CA, USA) was used to measure the absorbance at 450 nm. Cell viability was calculated comparing to control group which treating with corresponding vehicle. Assays were performed on three independent experiments.

## 7. Reference:

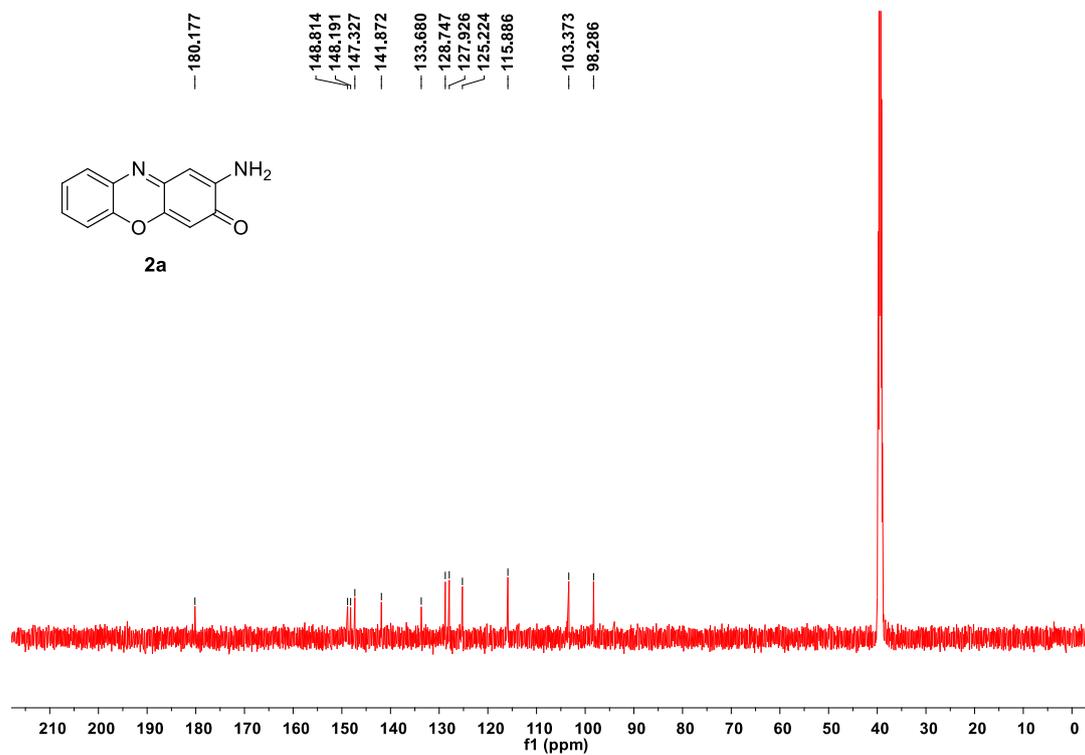
- [1] F. Ferlin, P. M. L. Navarro, Y. Gu, D. Lanari and L. Vaccaro, *Green Chem.*, 2020, **22**, 397;
- [2] J. M. Granda, K. Piekielska, M. Wasinska, N. Kawecka and M. Giurg, *Synthesis*, 2015, **47**, 3321.
- [3] F. A. Macías, D. Marín, A. Oliveros-Bastidas, D. Chinchilla, A. M. Simonet and J. M. Molinillo, *J. Agric. Food. Chem.*, 2006, **54**, 991.
- [4] S. Forte, J. Polak, D. Valensin, M. Taddei, R. Basosi, S. Vanhulle, A. Jarosz-Wilkolazka, R. Pognia, *J. Mol. Catal., B Enzym.*, 2010, **63**, 116.

## 8. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra

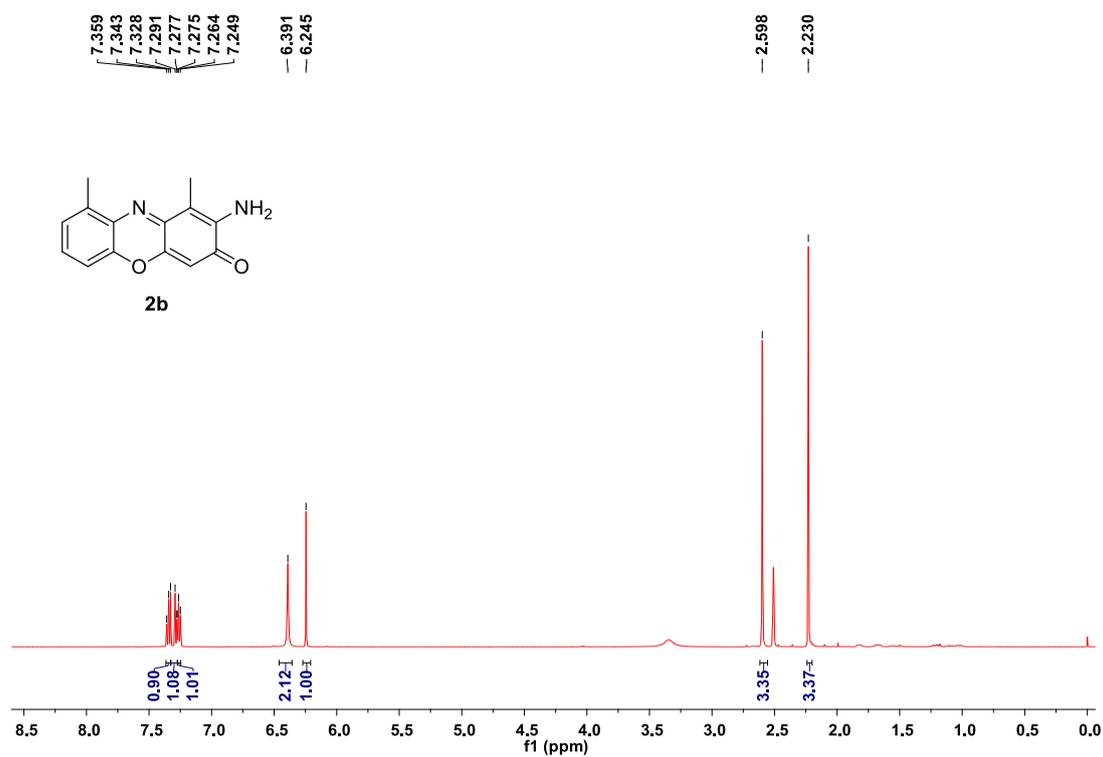
$^1\text{H}$  NMR spectrum of compound **2a**



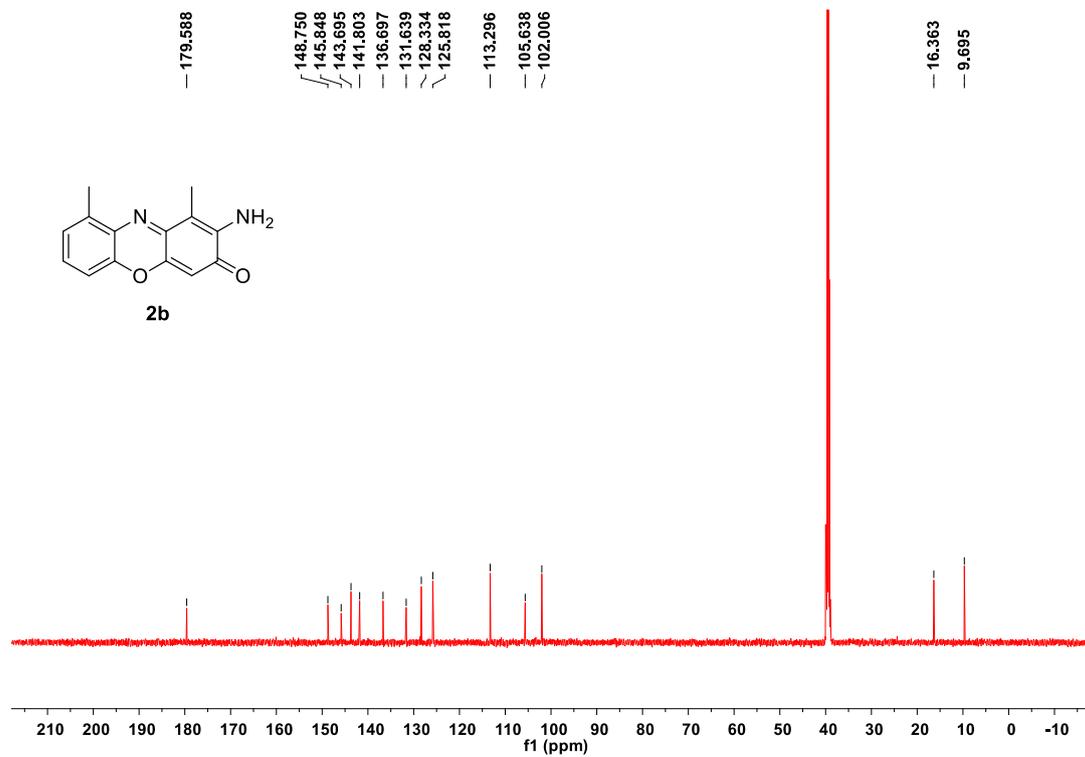
$^{13}\text{C}$  NMR spectrum of compound **2a**



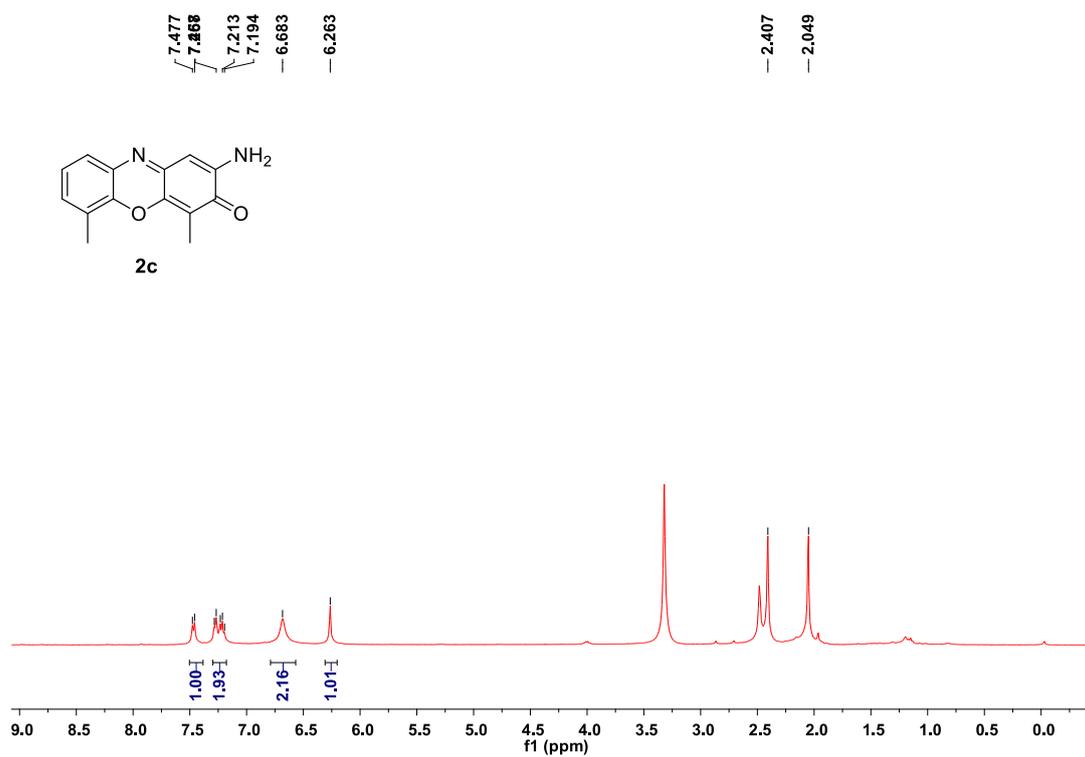
<sup>1</sup>H NMR spectrum of compound **2b**



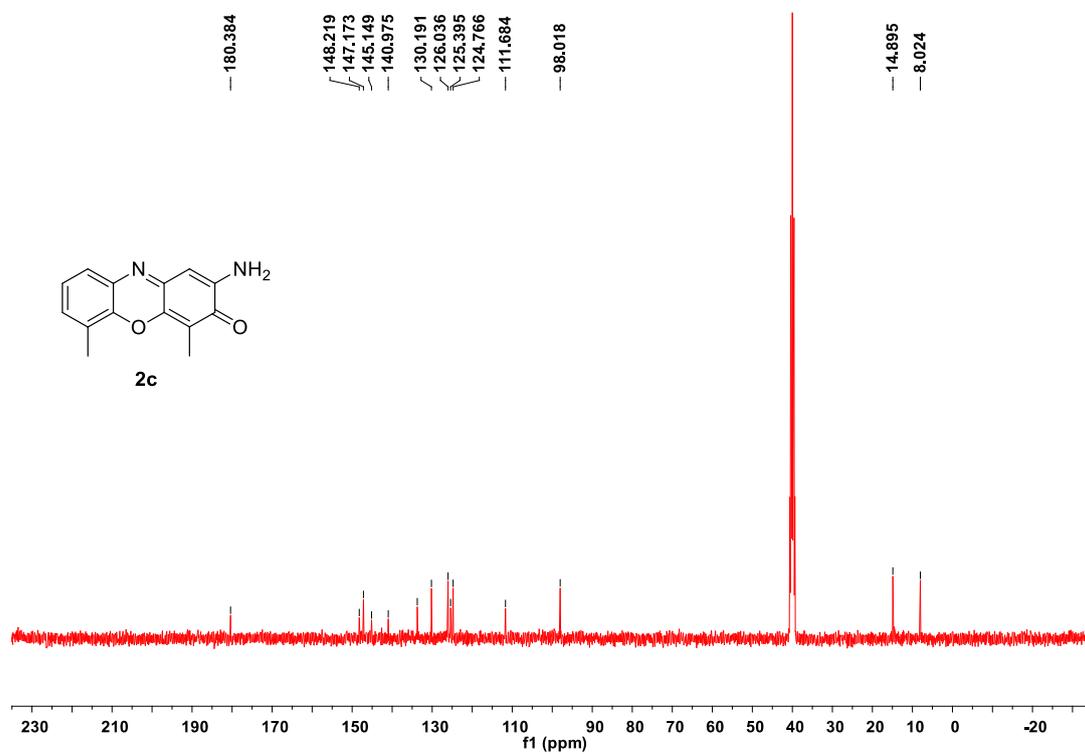
<sup>13</sup>C NMR spectrum of compound **2b**



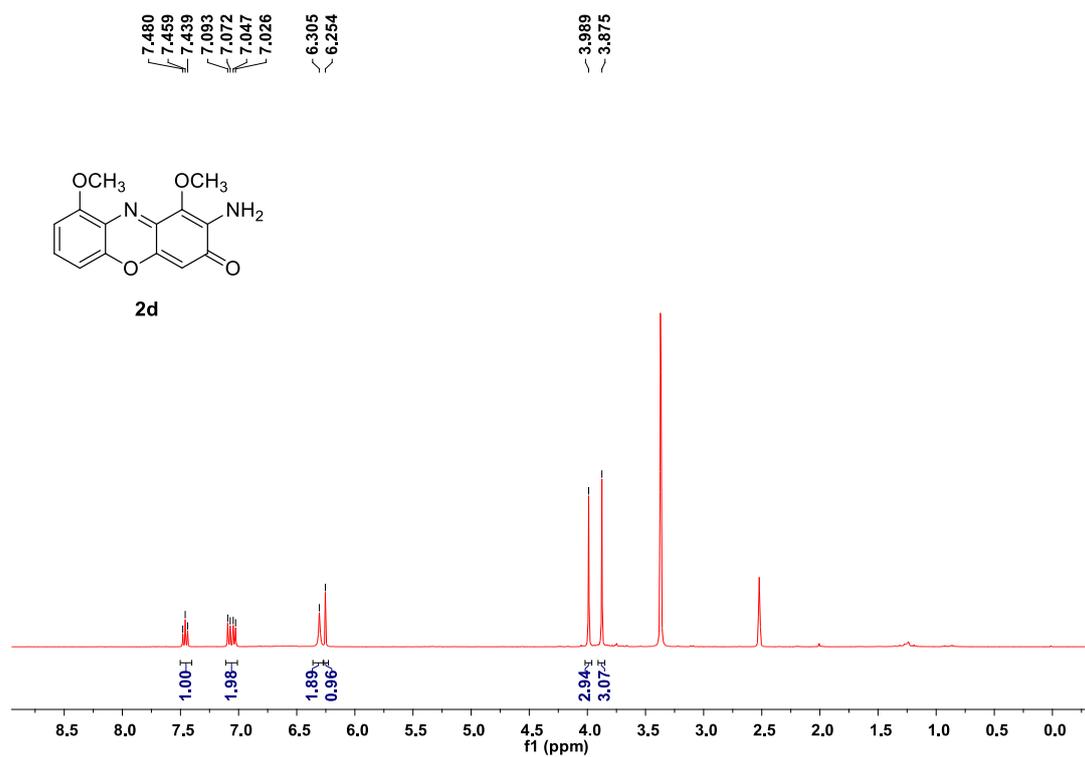
<sup>1</sup>H NMR spectrum of compound **2c**



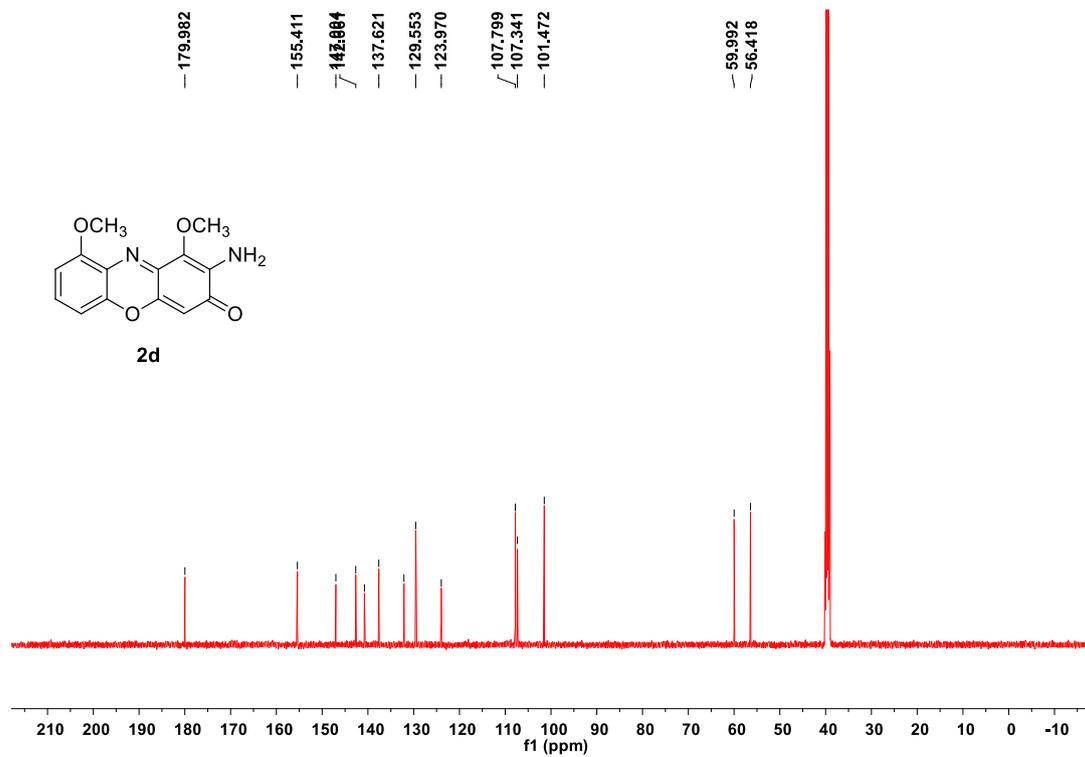
<sup>13</sup>C NMR spectrum of compound **2c**



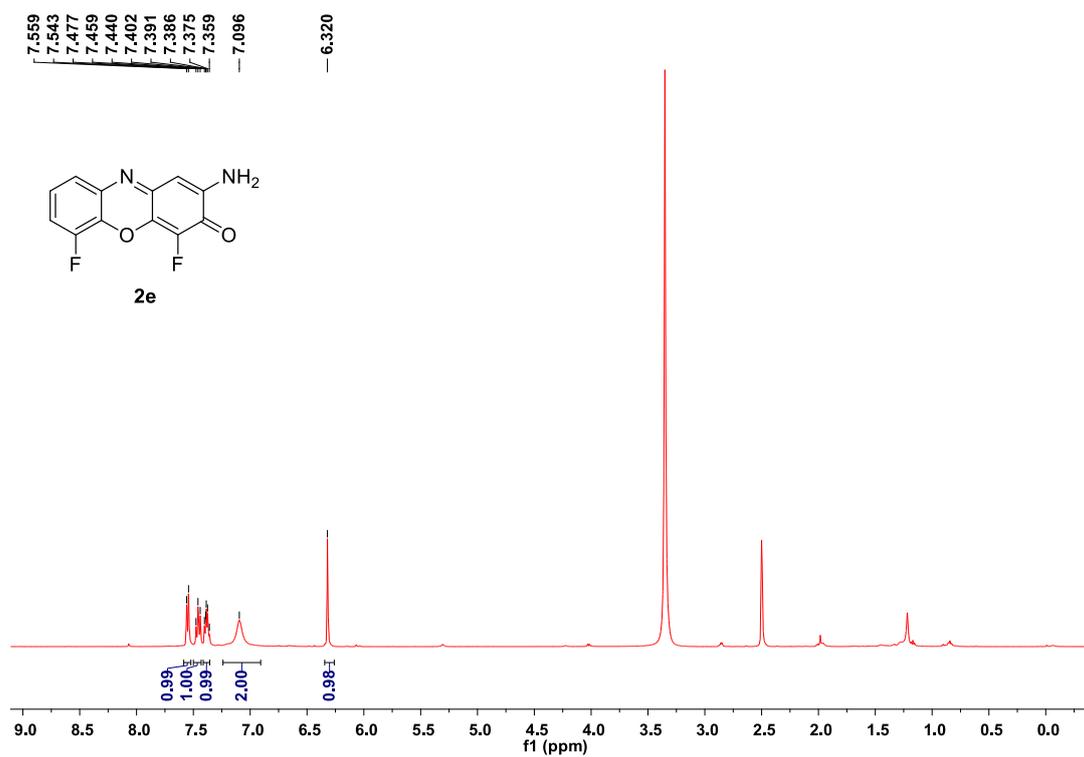
<sup>1</sup>H NMR spectrum of compound **2d**



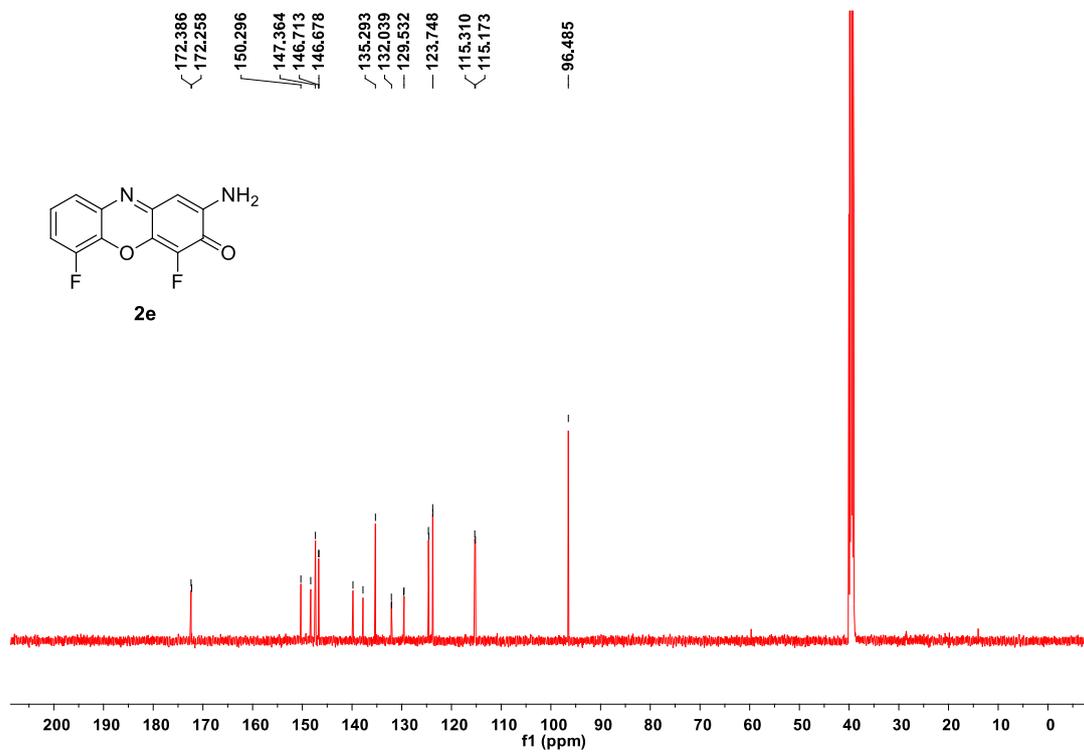
<sup>13</sup>C NMR spectrum of compound **2d**



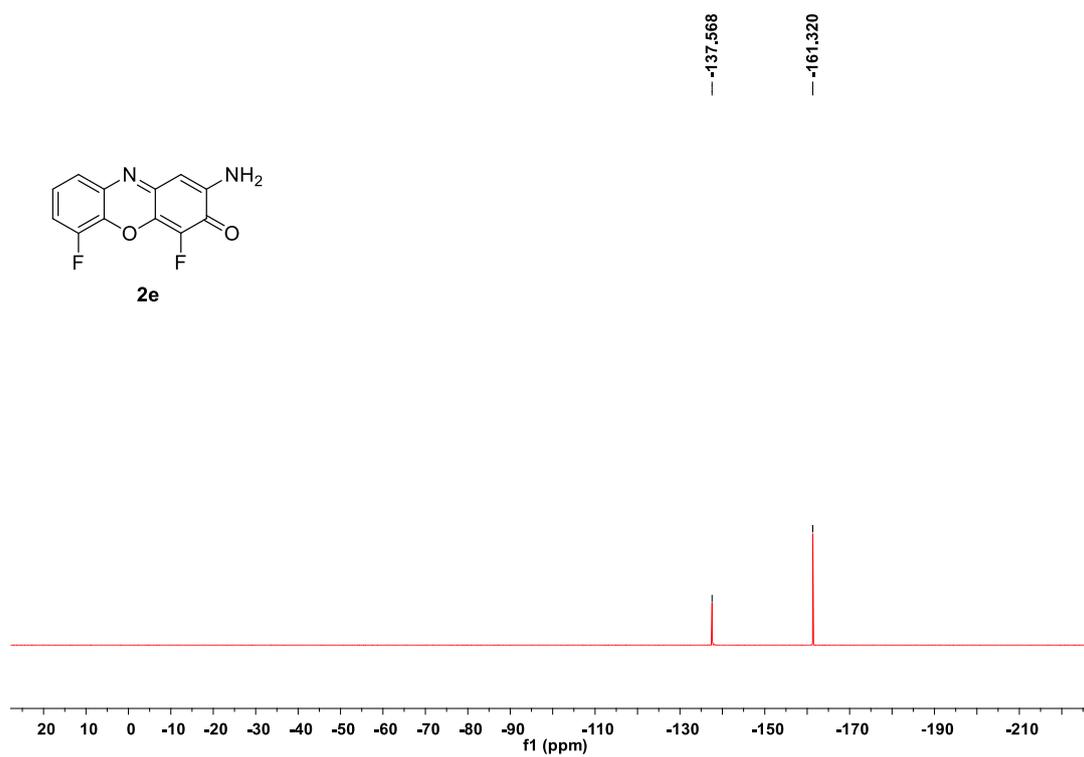
<sup>1</sup>H NMR spectrum of compound **2e**



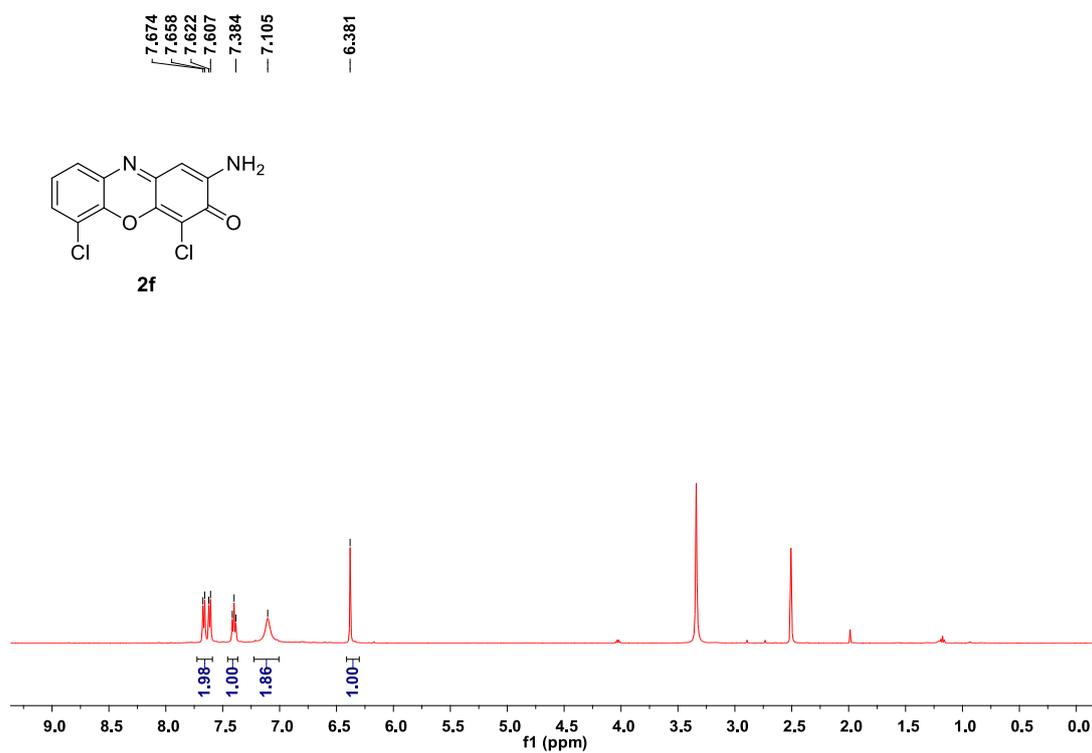
<sup>13</sup>C NMR spectrum of compound **2e**



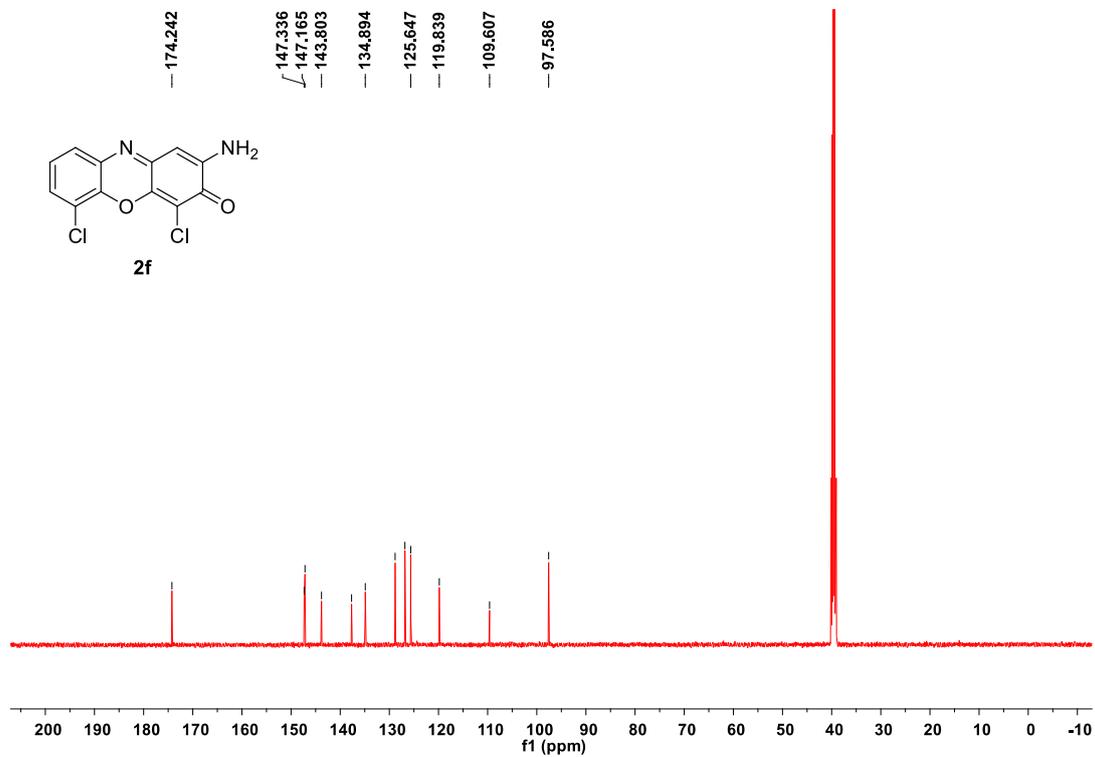
$^{19}\text{F}$  NMR spectrum of compound **2e**



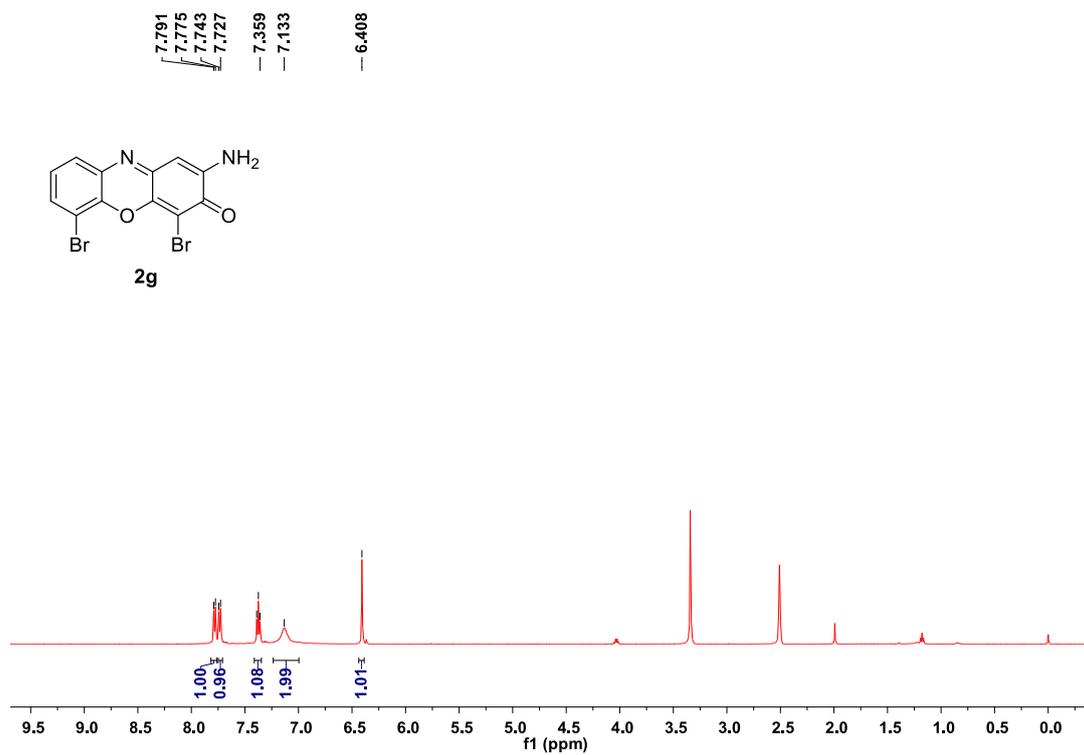
<sup>1</sup>H NMR spectrum of compound **2f**



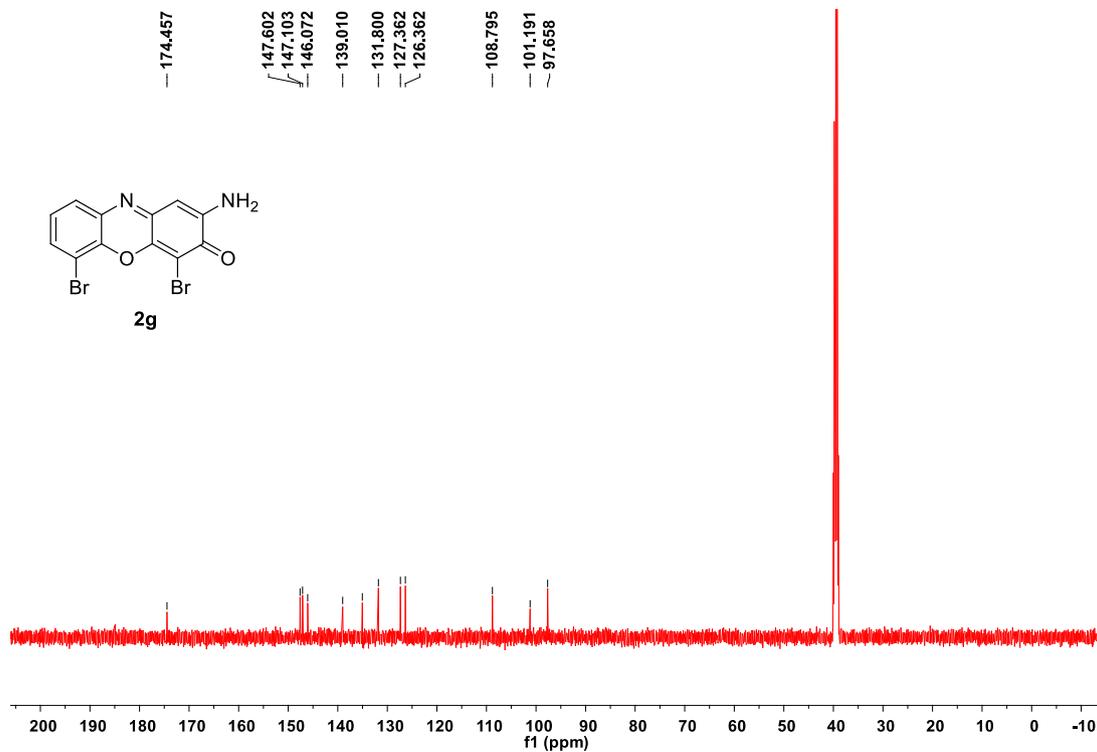
<sup>13</sup>C NMR spectrum of compound **2f**



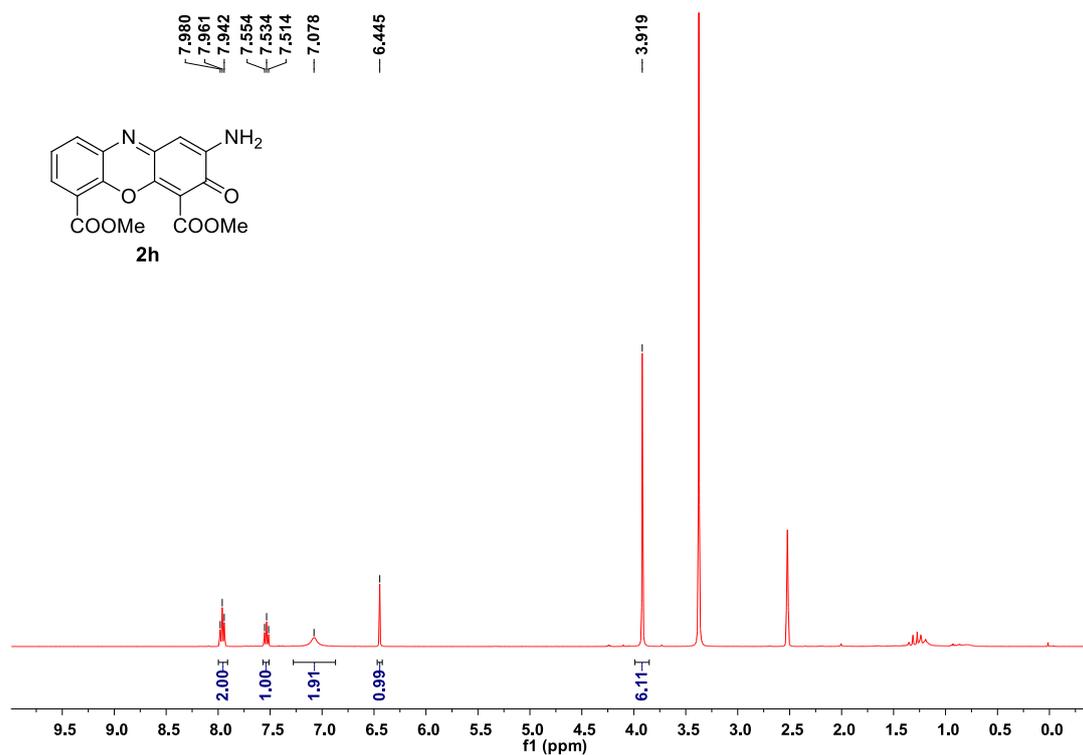
<sup>1</sup>H NMR spectrum of compound **2g**



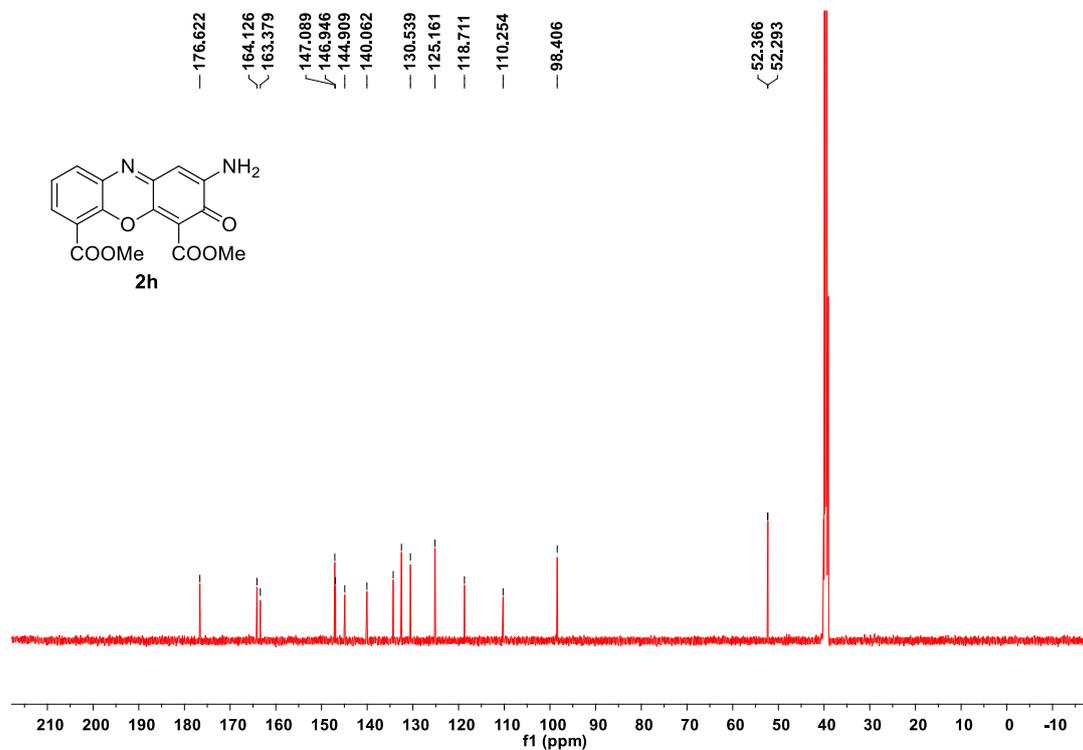
<sup>13</sup>C NMR spectrum of compound **2g**



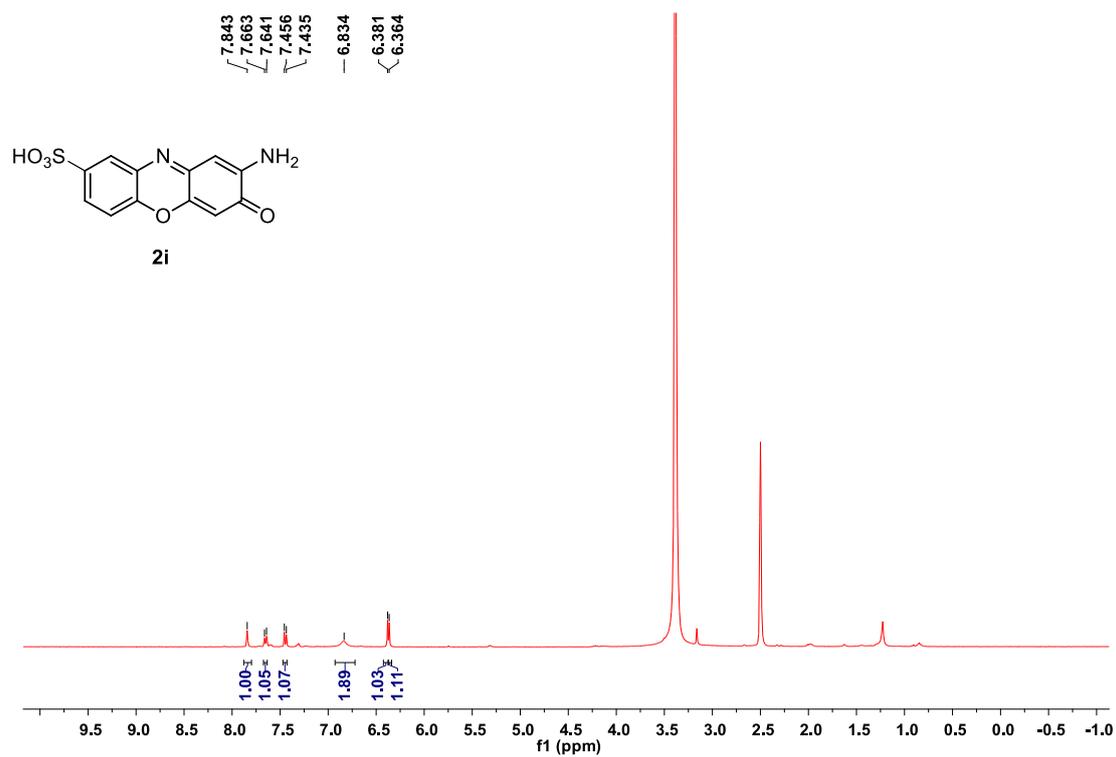
<sup>1</sup>H NMR spectrum of compound **2h**



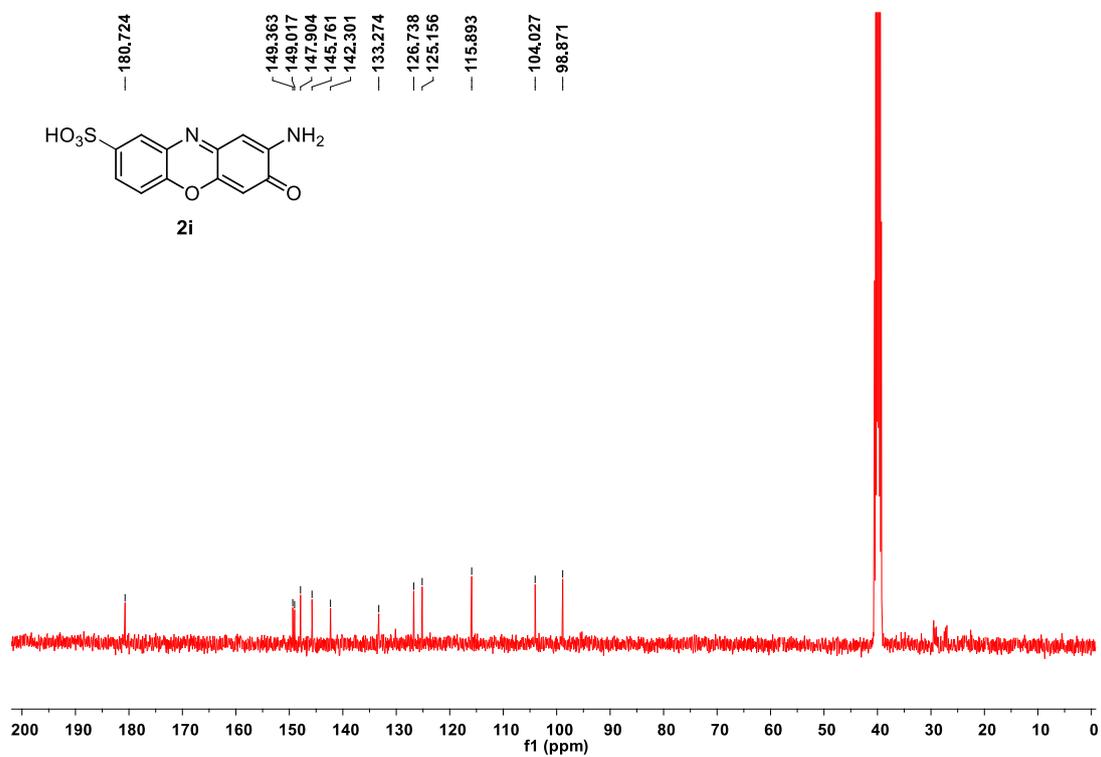
<sup>13</sup>C NMR spectrum of compound **2h**



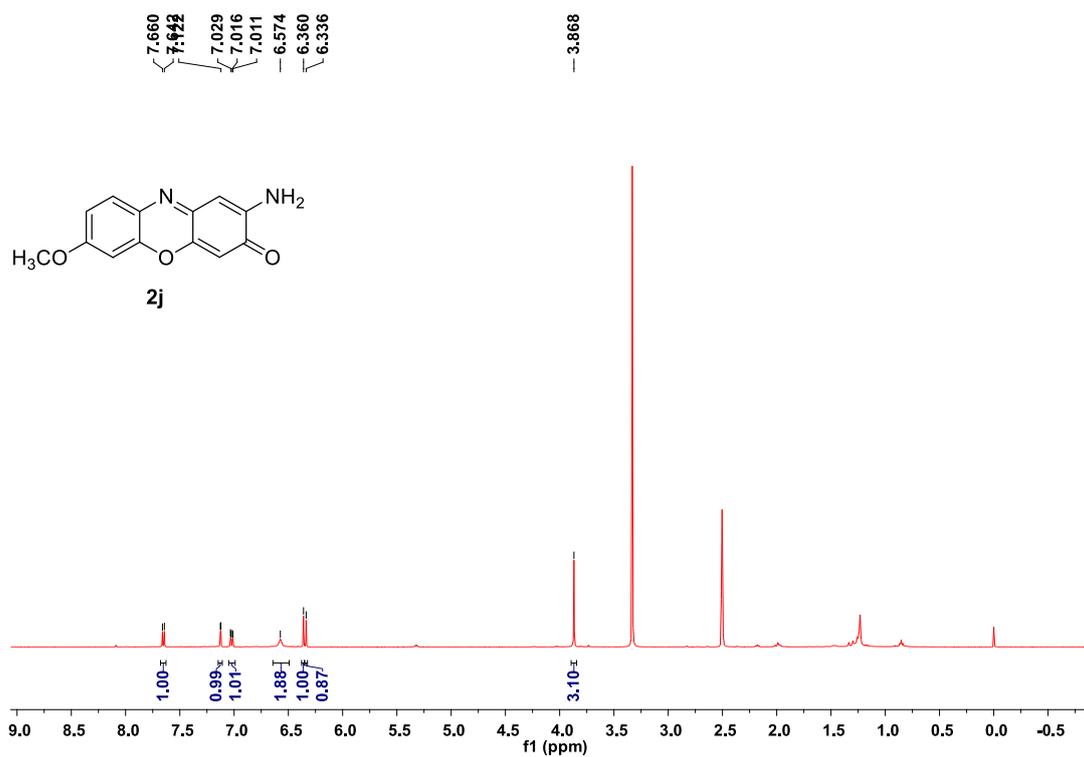
<sup>1</sup>H NMR spectrum of compound **2i**



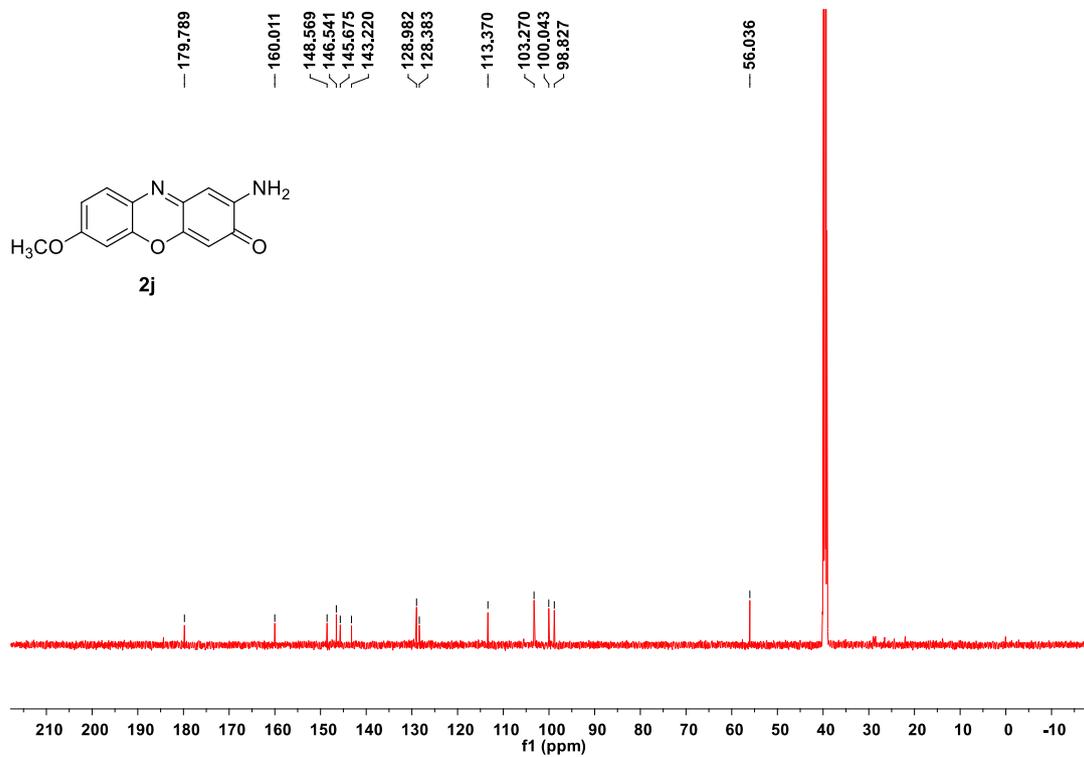
<sup>13</sup>C NMR spectrum of compound **2i**



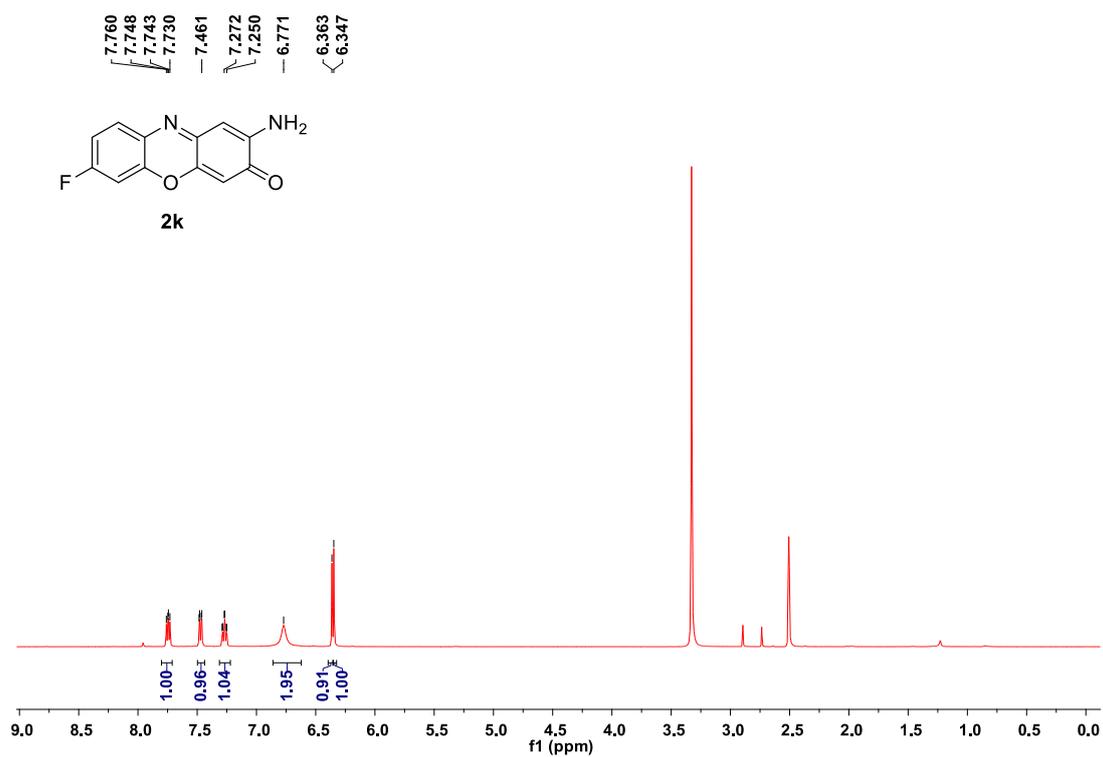
<sup>1</sup>H NMR spectrum of compound **2j**



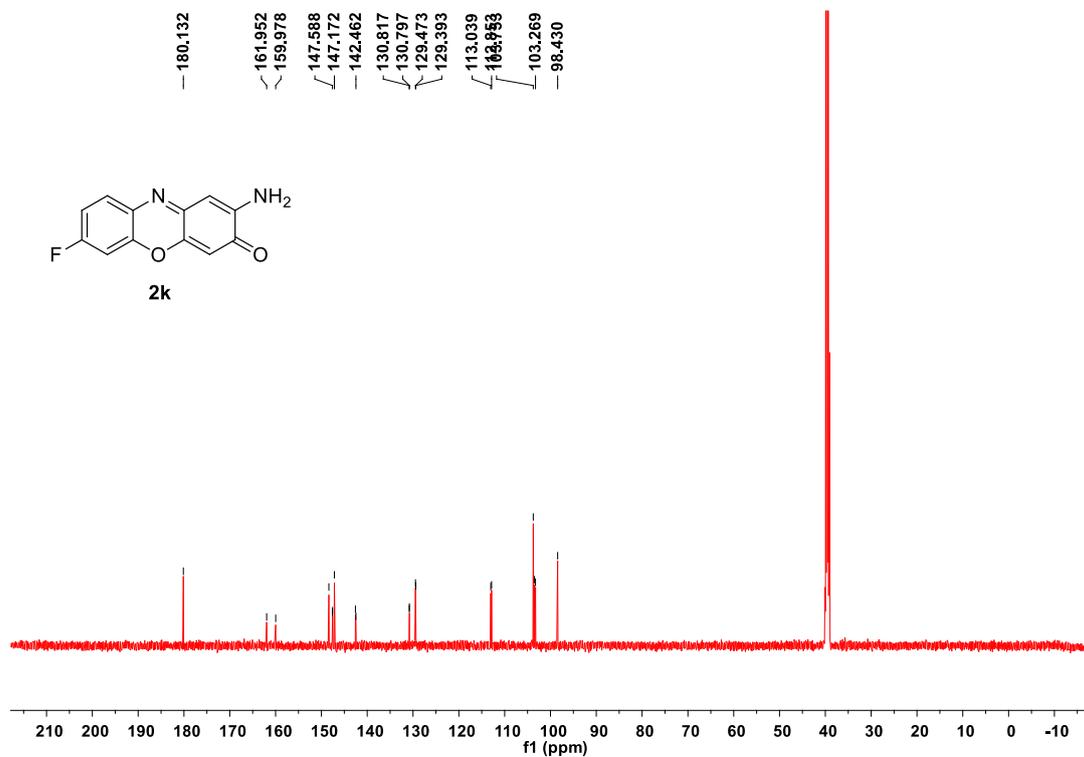
<sup>13</sup>C NMR spectrum of compound **2j**



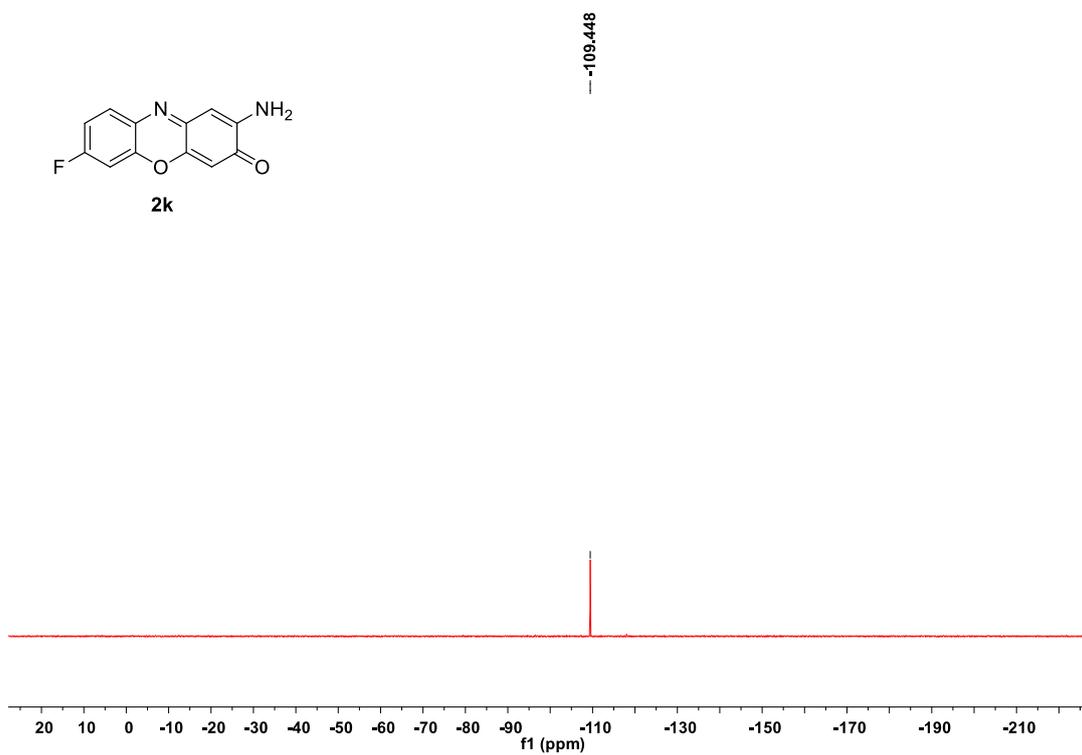
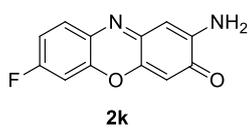
<sup>1</sup>H NMR spectrum of compound **2k**



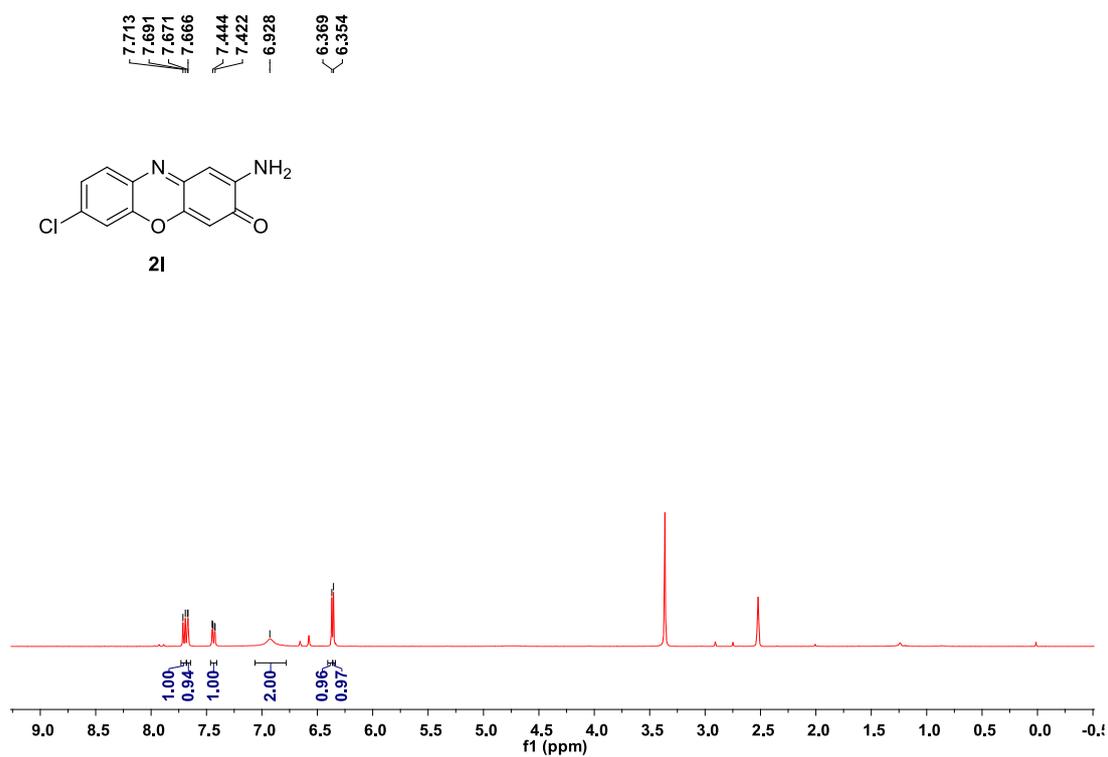
<sup>13</sup>C NMR spectrum of compound **2k**



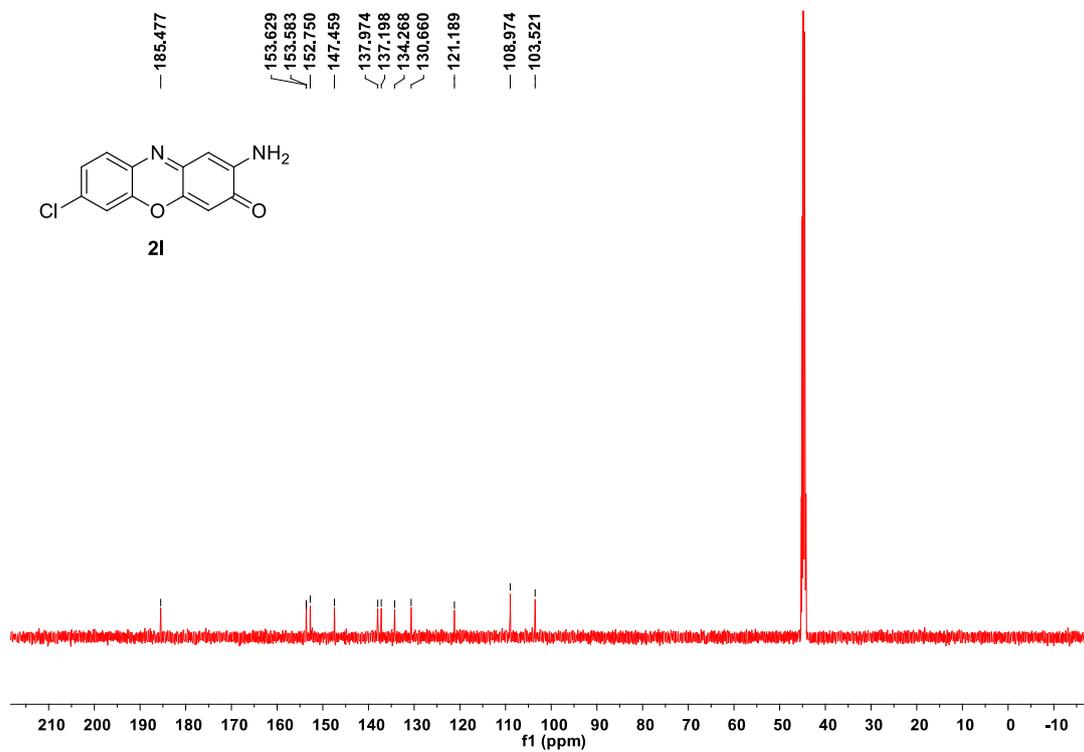
$^{19}\text{F}$  NMR spectrum of compound **2k**



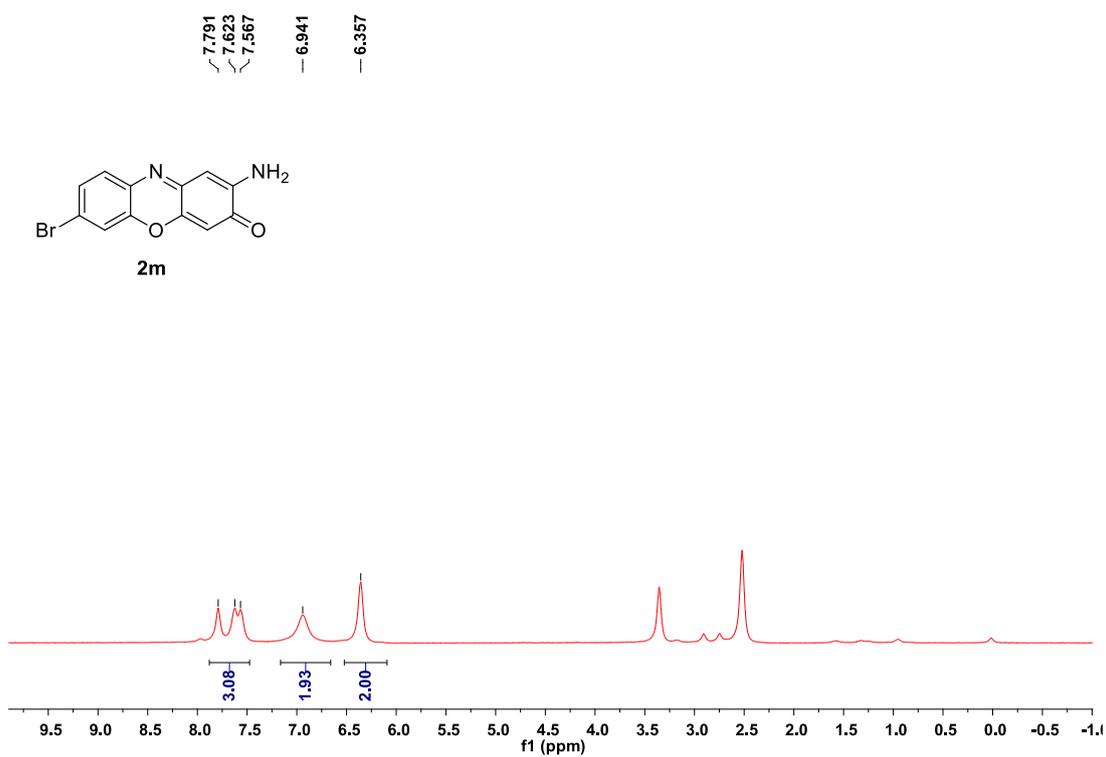
<sup>1</sup>H NMR spectrum of compound **2I**



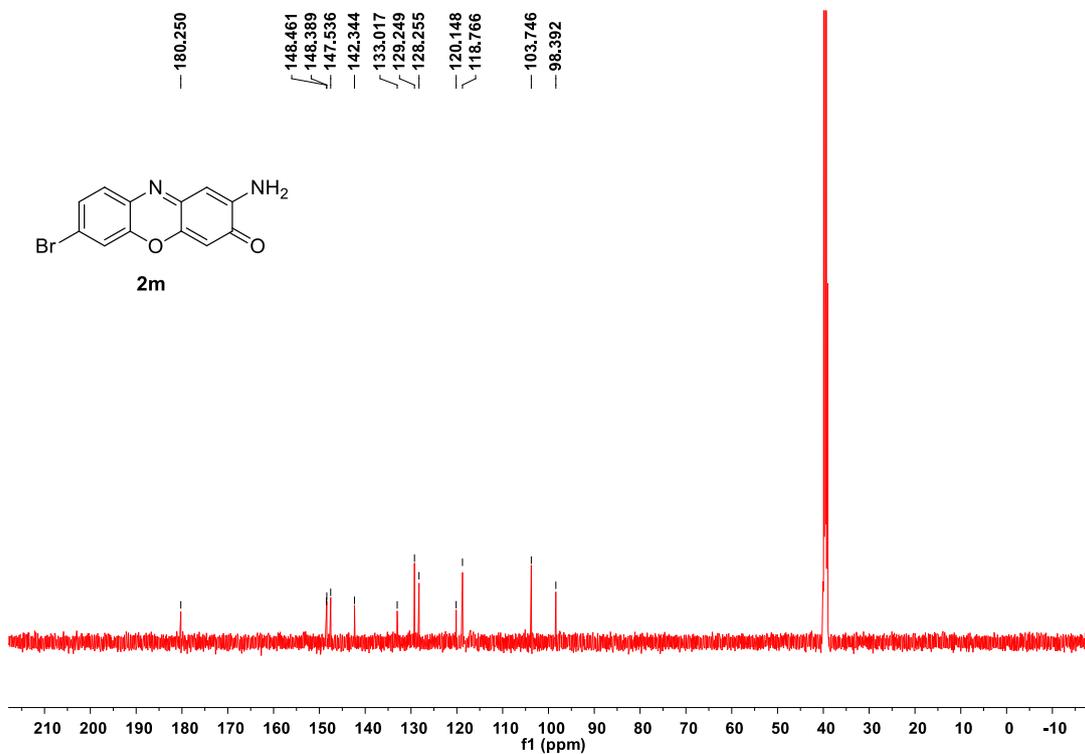
<sup>13</sup>C NMR spectrum of compound **2I**



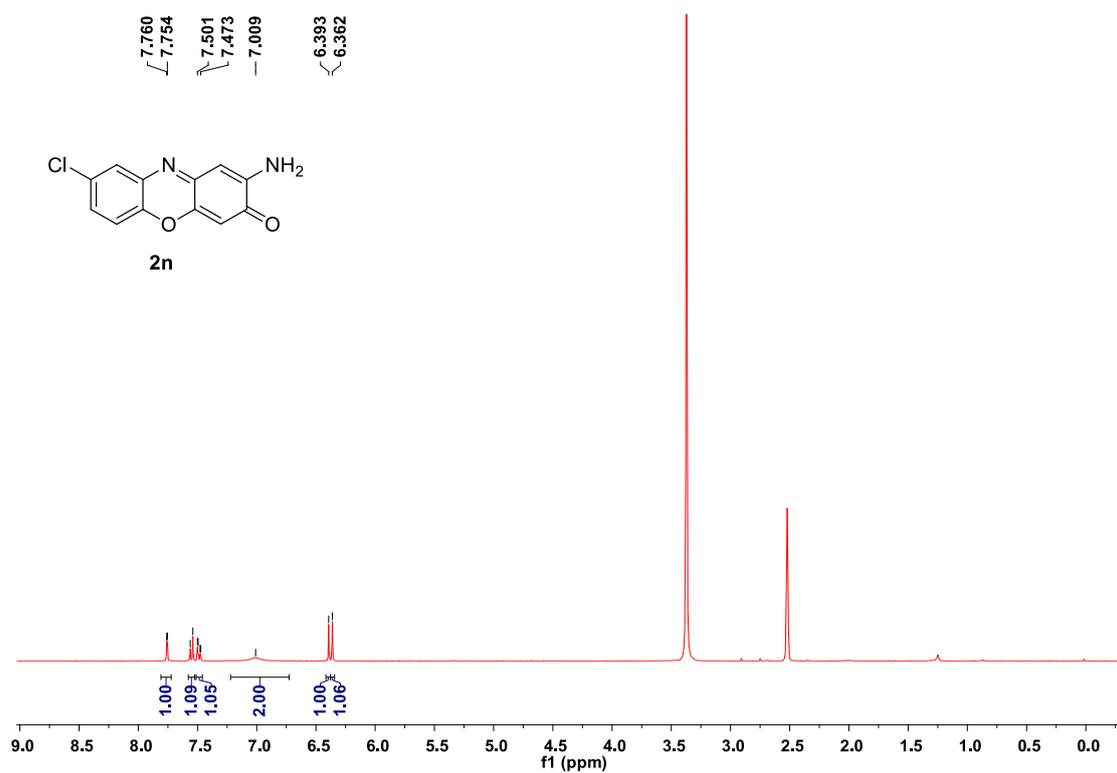
<sup>1</sup>H NMR spectrum of compound **2m**



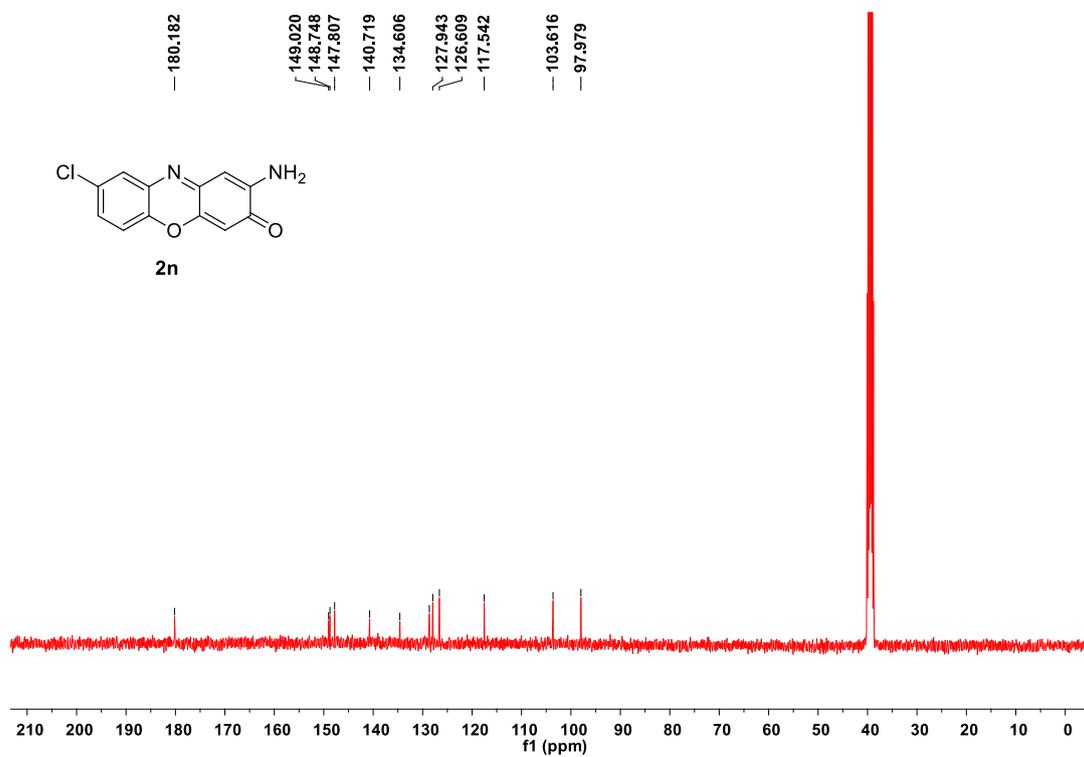
<sup>13</sup>C NMR spectrum of compound **2m**



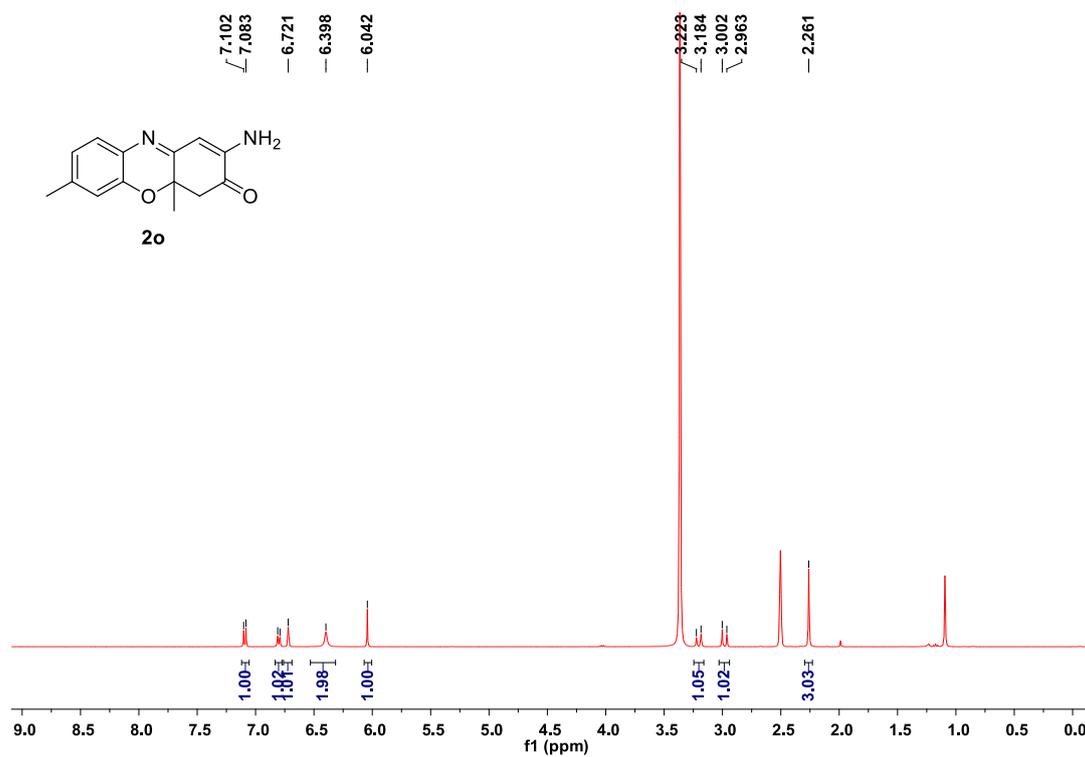
<sup>1</sup>H NMR spectrum of compound **2n**



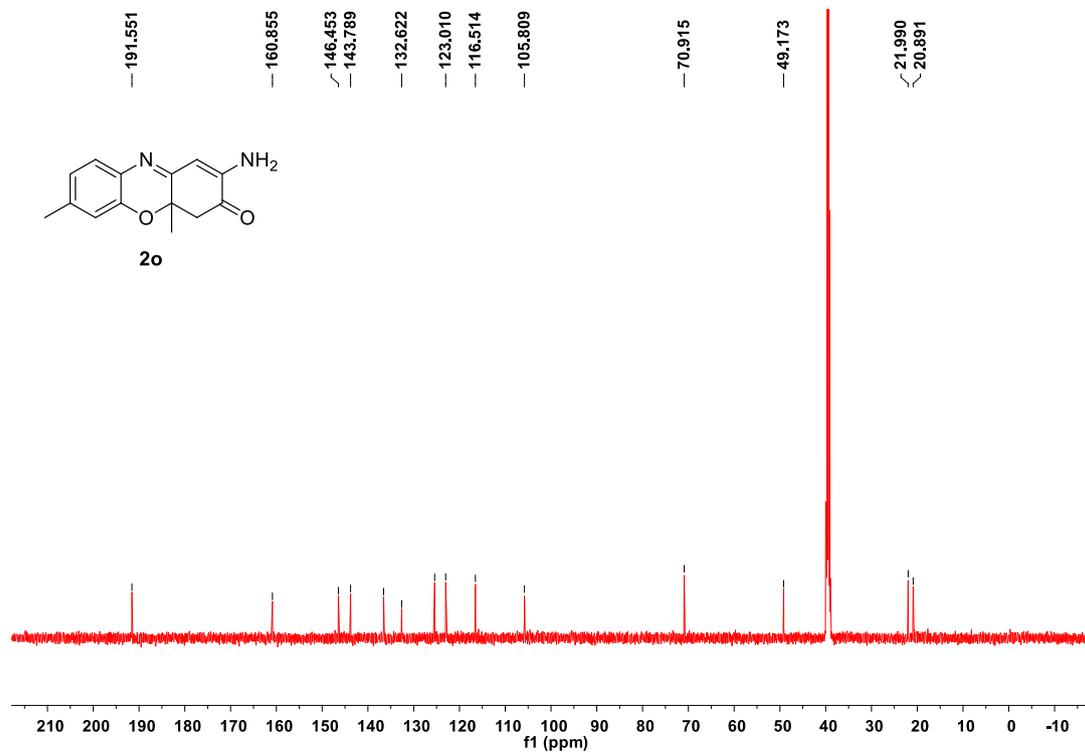
<sup>13</sup>C NMR spectrum of compound **2n**



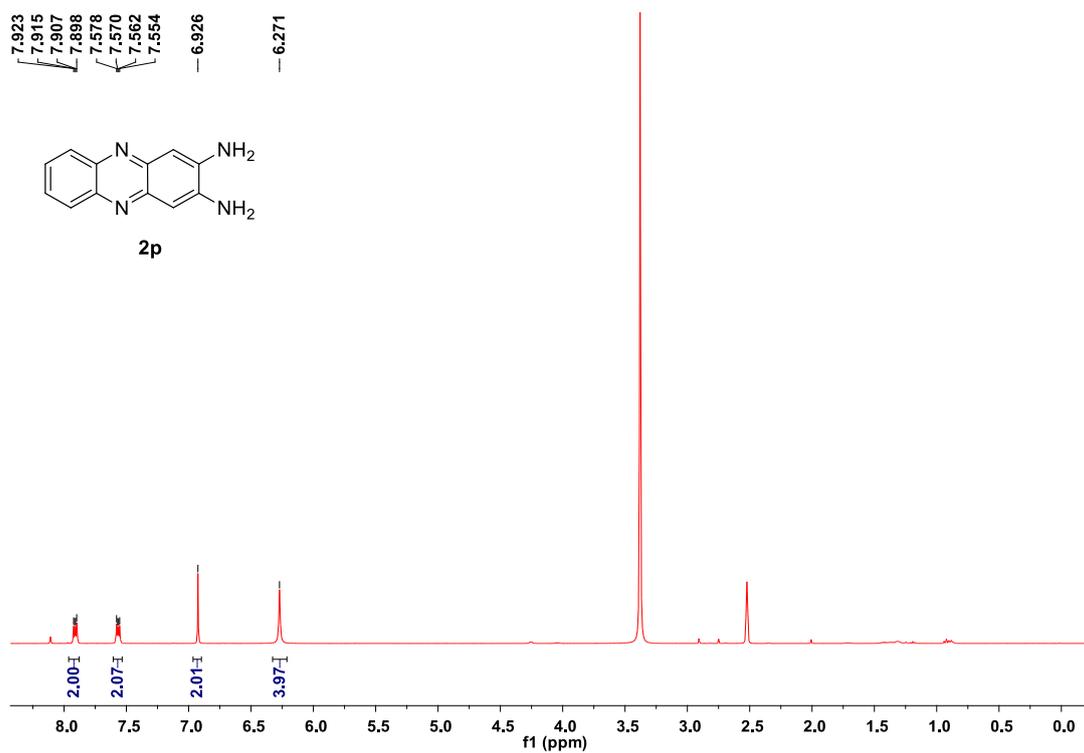
<sup>1</sup>H NMR spectrum of compound **2o**



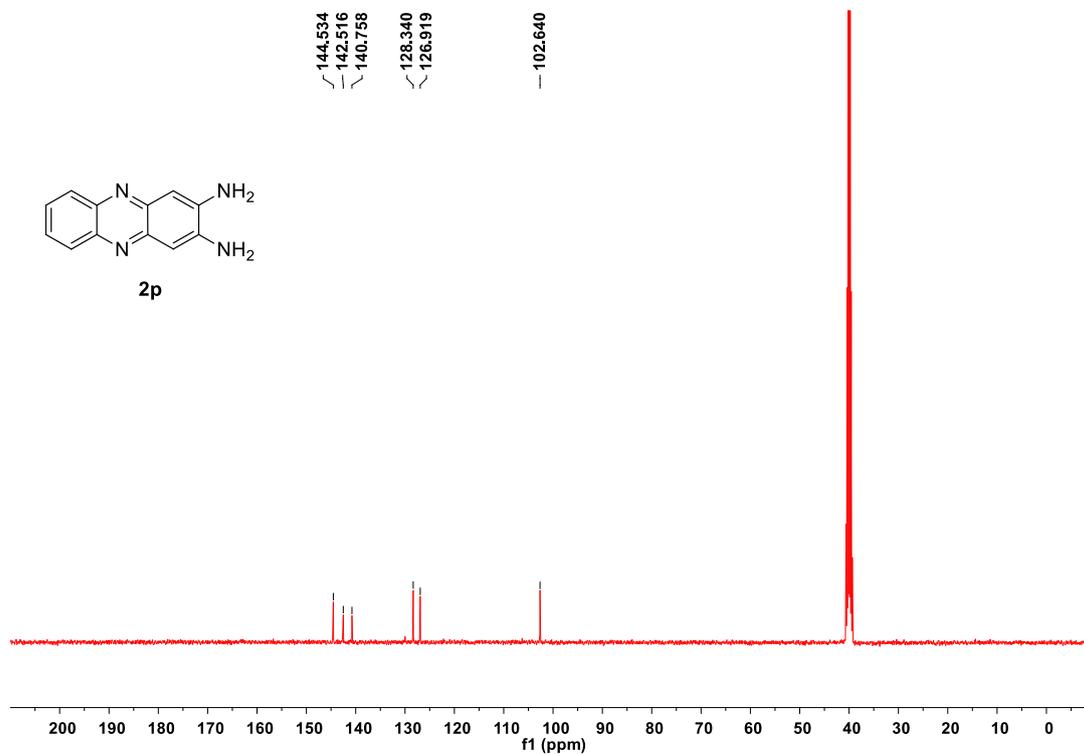
<sup>13</sup>C NMR spectrum of compound **2o**



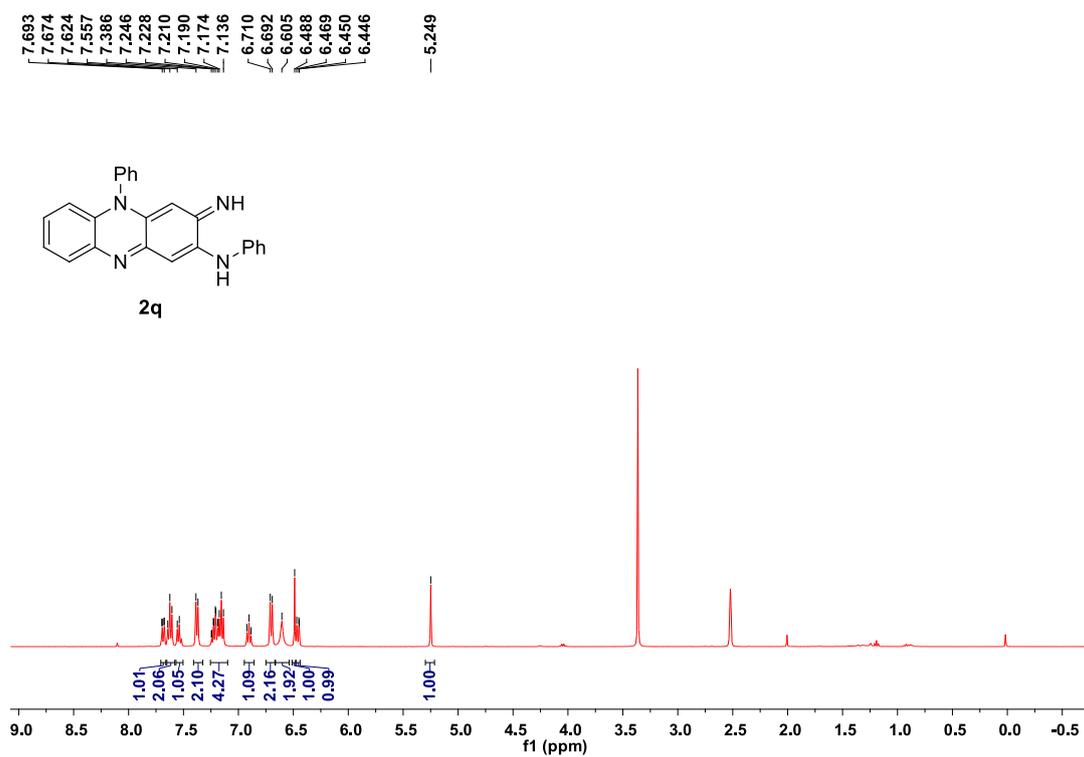
<sup>1</sup>H NMR spectrum of compound **2p**



<sup>13</sup>C NMR spectrum of compound **2p**



<sup>1</sup>H NMR spectrum of compound **2q**



<sup>13</sup>C NMR spectrum of compound **2q**

