Supporting Information for

Influence of B-Ring Modifications on Proton Affinity, Transmembrane Anion Transport and Anti-Cancer Properties of Synthetic Prodigiosenes

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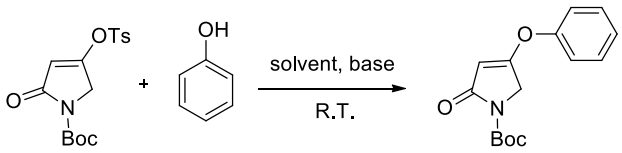
1. Synthesis

General Information

All chemicals were purchased and used as received unless otherwise indicated. Moisture-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Solutions of air- and moisture-sensitive compounds were introduced via syringe or cannula through a septum. Flash chromatography was performed using Silicycle ultra pure silica (230-400 mm) or 150 mesh Brockmann III activated neutral or basic alumina oxide as indicated. The NMR spectra were recorded using a Bruker 500 MHz or 300 MHz spectrometer using $CDCl_3$ or DMSO-d^6 as solvent and are reported in parts per million (δ) using the solvent signals at 7.26 ppm for ^1H and at 71.16 ppm for ^{13}C while $CDCl_3$ was used, and at 2.50 ppm for ^1H and at 39.50 ppm for ^{13}C while DMSO-d6 was used, as an internal reference with *J* values given in Hz. Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in ESI+ mode. Melting points were determined using a Fisher-Johns melting point apparatus, and are uncorrected. Compounds **7**,[1] **8a**,[2] **9**[3] and **11**[4] were prepared according to literature procedures.

Optimization conditions for the phenolic substitution of 9 to 10b.



9 **10b**

Entry	Base (eq.)	Solvent (conc. of **9**)	Time	Conv. (**9**)	Yield (**10b**)[a]
1	DABCO (3 eq.)	DCM (0.07 M)	4 h	100%	13%
2	Proton sponge (2.2 eq.)	DCM (0.07 M)	16 h	0%	0%
3	DIPEA (2.2 eq.)[b]	DCM (0.07 M)	16 h	0%	0%
4	NaH (1.1 eq.)	DMF (0.1 M)	1 h	100%	0%
5	DBU (3 eq.)	DCM (0.07 M)	1 h	100%	0%
6	Cs_2CO_3 (2.2 eq.)	MeCN (0.07 M)	16 h	100%	0%
7	NaOH/TBAB (2.2eq.)	DCM/H2O (0.07 M)	1 h	100%	0%
8	DABCO (4.4 eq)[c]	DCM (0.06 M)	2 h	100%	26%
9	DABCO (4.4 eq)[d]	‘’	5 h	100%	9%
10	DABCO (1.1 eq.)	DCM (0.07 M)	16 h	not complete	n.d.[e]
11	DABCO (2.2 eq.)	‘’	16 h	100%	30%
12	DABCO (2.2 eq.)	dioxane (0.07 M)	5 h	100%	0%

13	DABCO (2.2 eq.)	THF (0.07 M)	4 h	100%	0%
14	DABCO (2.2 eq.)	MeCN (0.07 M)	7 h	100%	22%
15	DABCO (2.2 eq.)	toluene (0.07 M)	4 h	100%	0%
16	DABCO (2.2 eq.) [f]	DCM (0.07 M)	5 h	100%	26%
18	DABCO (2.2 eq.)	DCM (0.3 M)	5 h	100%	32%
19	DABCO (2.2 eq.)	DCM (0.01 M)	48 h	not complete	n.d.[e]
17	DABCO (2.2 eq.)	DCM (0.02 M)	16 h	not complete	60%[g]
20	DABCO (3.2 eq.)	DCM (0.02 M)	16 h	100%	60%

[a] isolated yield, [b] 50 °C, [c] 45 °C, [d] 0 °C, [e] Inextricable mixture of **9** and **10b**, [f] molecular sieves, [g] contained traces of starting material

Table S1

Experimental

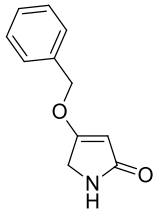
General procedure 1 (GP1) for the synthesis of pyrrolinone 10: To a solution of compound **9** (5.6 mmol, 1 eq.) in CH_2Cl_2 (310 mL), was added the corresponding phenol (11.3 mmol, 2.0 eq.) and DABCO (12.3 mmol, 2.2 eq.). The reaction was stirred for 16 h at room temperature and then quenched with HCl 1 M (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with a 10% NaOH solution (100 mL) and brine (100 mL), and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude product was purified using flash chromatography (SiO_2, EtOAc/hexane 4/6).

General procedure 2 (GP2) for Boc deprotection: To a cold (0 °C) solution of compound **10** (1.8 mmol) in CH_2Cl_2 (3 mL) was added TFA (3 mL). After 30 min stirring at room temperature the reaction was quenched through the slow addition of a solution of sat. aqueous $NaHCO_3$ until pH 7, then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), and then dried (Na_2SO_4). After evaporation of the solvent under vacuum, the pure pyrrolinone **8** was obtained and used without further purification.

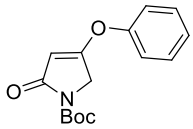
General procedure 3 (GP3) for the synthesis of dipyrrinones 12:[4] To a solution of pyrrolinone **8** (3.02 mmol, 2.2 eq.) in dry CH_2Cl_2 (45 mL) was added triethylamine (1.14 mL, 8.22 mmol, 6.0 eq.) at 0 °C. TMSOTf (750 μL, 4.11 mmol, 3.0 eq.) was then added drop-wise. After 20 min a solution of the aldehyde (1 eq.) was added in dry CH_2Cl_2 (45 mL). The reaction was stirred at this temperature for three hours, and then TMSOTf (150 μL, 4.11 mmol, 0.6 eq.) was added. After stirring for one hour at 0 °C, the reaction was quenched through the addition of phosphate buffer (pH = 7, 100 mL). The solution was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were washed with brine, and then dried (Na_2SO_4). After evaporation of the solvent the resulting brown oil was dissolved in THF (90 mL) and concentrated aqueous HCl (300 μL) was added. After a few minutes the reaction was quenched via the addition of saturated aqueous $NaHCO_3$ (200 mL), then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were washed with water (2 x 100 mL). After concentration of the combined organic fractions under vacuum, the resulting solid **12** was triturated in hot methanol then isolated via filtration and washed with methanol to give the desired product as a yellow solid.

General procedure 4 (GP4) for the synthesis of bromodipyrrinone 13:[5] To a stirred solution of dipyrrinone **12** (0.23 mmol, 1 eq.) in dry CH_2Cl_2 (10 mL) was added $POBr_3$ (270 mg, 0.93 mmol, 2.0 eq.). The resulting solution was heated at reflux temperature under nitrogen for 17 h then more $POBr_3$ (270 mg, 0.93 mmol, 2.0 eq.) was added. The resulting solution was heated at reflux temperature under nitrogen for 24 h, then $POBr_3$ (135 mg, 0.46 mmol, 1.0 eq.) was again added. After heating at reflux temperature for a further 17 h, the reaction mixture was cooled to room temperature. Saturated aqueous $NaHCO_3$ (30 mL) was added at 0 °C. The organic layer was separated, washed with brine and water, then dried (Na_2SO_4) and the solvent evaporated under vacuum. The crude product was purified using flash chromatography (Al_2O_3, type III, basic, CH_2Cl_2 100%).

General procedure 5 (GP5) for the Suzuki-Miyaura coupling to give 3:[6] Compound **13** (0.48 mmol, 1 eq.) was dissolved in DME (9 mL). Then LiCl (60 mg, 1.44 mmol, 3 eq) and boronic acid **14** (121 mg, 0.57 mmol, 1.2 eq) were added. The solution was degassed by bubbling with N_2 for 5 min, and then palladium tetrakis (56 mg, 10 mol/%) was added. A degassed 2 M solution of Na_2CO_3 was added (1.0 mL, 1.92 mmol, 4 eq.) and the suspension was stirred at 85 °C for 18 h. The solution was allowed to cool to room temperature then poured into water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL), and then dried (Na_2SO_4). Purification using chromatography (Al_2O_3 basic type III, EtOAc/hexane 1/9 then 2/8) gave a red film. Formation of the HCl salt: the compound was dissolved in a mixture of MeOH/$CHCl_3$ (20:1), then a 0.1 M solution of HCl in MeOH (1.5 eq.) was added. After 15 min stirring the solvents were partially removed under reduced pressure. The obtained precipitate was isolated via filtration and then washed with water and hexane, to give the desired product as a dark red solid.

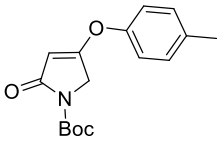


4-(Benzyloxy)-1*H*-pyrrol-2(5*H*)-one 8a:[7] To a solution of pyrrolinone **7** (3 g, 26 mmol) in benzyl alcohol (5.5 mL, 53 mmol) was added methylensulfonic acid (134 μl, 2.08 mmol). The solution was heated at 80 °C under *vacuum* (40 mmHg) for 6 h. The *vacuum* was removed and the reaction was stirred at 80 °C overnight. The mixture was poured into a mixture of ice and water (25 mL) and CH_2Cl_2 (50 mL). A saturated solution of $NaHCO_3$ was added until pH 7 and the mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the benzyl alcohol then co-evaporated with water. The resulting solid was recrystallized from toluene (30 mL). Isolation viahot filtration gave the title compound as a white solid (1 g, 24%). ^{1}H NMR (DMSO, 500 MHz) 3.88 (s, 2H), 5.05 (s, 2H), 5.17 (s, 1H), 7.37-7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) 47.1, 73.3, 95.4, 128.0, 128.8, 134.7, 174.7, 175.8 (1 C non accounted for). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{11}N_1Na_1O_2$, 212.0682; found, 212.0675.

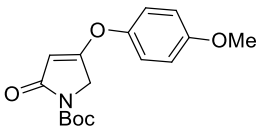


***Tert*-butyl 2-oxo-4-phenoxy-2,5-dihydro-1*H*-pyrrole-1-carboxylate 10b**: Obtained following the GP1 to give a white solid (60%, 46 mg). Mp 95 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.55 (s, 9H), 4.39 (s, 2H), 4.94 (s, 1H), 7.12-7.13 (m, 2H), 7.28-7.30 (m, 1H), 7.40-7.44 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 28.2, 49.4,

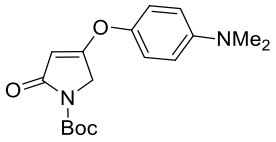
82.9, 98.4, 120.2, 126.7, 130.3, 149.5, 154.0, 168.8, 173.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{17}N_1Na_1O_4$, 298.1050; found, 298.1038.



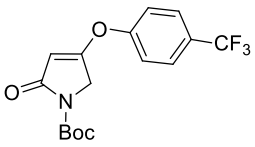
***Tert*-butyl 2-oxo-4-(*p*-tolyloxy)-2,5-dihydro-1*H*-pyrrole-1-carboxylate 10c**: Obtained following the GP1 to give a white solid (54%, 900 mg). Mp 93 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.55 (s, 9H), 2.36 (s, 3H), 4.38 (d, *J* = 1.0 Hz, 2H), 4.92 (t, *J* = 1.0 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 21.0, 28.3, 49.4, 82.9, 98.2, 119.9, 130.7, 136.5, 149.5, 151.9, 168.8, 173.5. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{19}N_1Na_1O_4$, 312.1206; found, 312.1195.



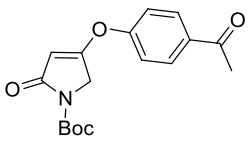
***Tert*-butyl 4-(4-methoxyphenoxy)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 10d**: Obtained following the GP1 to give a white solid (66%, 56 mg). Mp 79 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.54 (s, 9H), 3.80 (s, 3H), 4.36 (s, 2H), 4.89 (s, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 28.2, 49.3, 55.8, 82.8, 98.1, 115.1, 121.1, 147.6, 149.5, 157.8, 168.8, 173.9. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{19}N_1Na_1O_5$, 328.1155; found, 328.1141.



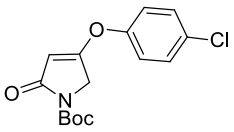
***Tert*-butyl 4-(4-(dimethylamino)phenoxy)-2-oxo-2, 5-dihydro-1*H*-pyrrole-1-carboxylate 10e**: Obtained following the GP1 to give a creamy white solid (47%, 600 mg). Mp 105 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.55 (s, 9H), 2.96 (s, 6H), 4.36 (d, *J* = 1.0 Hz, 2H), 4.92 (t, *J* = 1.0 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 28.3, 40.9, 49.3, 82.7, 97.8, 113.2, 120.6, 144.9, 149.1, 149.6, 169.1, 174.4. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{22}N_2Na_1O_4$, 341.1472; found, 341.1460.



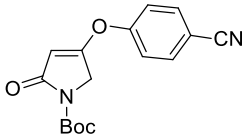
***Tert*-butyl 2-oxo-4-(4-(trifluoromethyl)phenoxy)-2,5-dihydro-1*H*-pyrrole-1-carboxylate 10f**: Obtained following the GP1 to give a creamy white solid (62%, 1.19 g). Mp 167 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.55 (s, 9H), 4.43 (s, 2H), 5.00 (s, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 28.2, 49.4, 83.2, 99.1, 120.8, 123.7 (q, $J^1_{F\text{-}C}$ = 270 Hz), 127.8, 129.1 (q, $J^2_{F\text{-}C}$ = 33 Hz), 149.4, 156.3, 168.1, 172.0. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{16}F_3N_1Na_1O_4$, 366.0924; found, 366.0931.



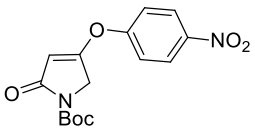
***Tert*-butyl 4-(4-acetylphenoxy)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 10g**: Obtained following the GP1 to give a creamy white solid (59%, 520 mg). Mp 160 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.56 (s, 9H), 2.62 (s, 3H), 4.43 (d, *J* = 1.0 Hz, 2H), 5.03 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 26.8, 28.2, 49.4, 83.1, 99.1, 120.3, 130.9, 135.5, 149.4, 157.4, 168.3, 171.9, 196.5. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{19}N_1Na_1O_5$, 340.1155; found, 340.1141.



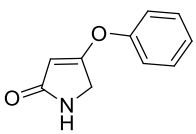
***Tert*-butyl 4-(4-chlorophenoxy)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 10h**: Obtained following the GP1 to give a white solid (67%, 1.1 g). Mp 129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.56 (s, 9H), 4.39 (s, 2H), 4.96 (s, 1H), 7.09 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 28.2, 49.3, 83.1, 98.6, 121.7, 130.5, 132.2, 149.4, 152.5, 168.4, 172.7. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{16}Cl_1N_1Na_1O_4$, 332.0660; found, 332.0663.



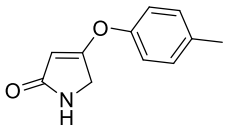
***Tert*-butyl 4-(4-cyanophenoxy)-2-oxo-2, 5-dihydro-1*H*-pyrrole-1-carboxylate 10i**: Obtained following the GP1 to give a white solid (48%, 600 mg). Mp 164 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.55 (s, 9H), 4.42 (d, *J* = 1.0 Hz, 2H), 5.03 (t, *J* = 1.0 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 28.2, 49.3, 83.3, 99.5, 110.8, 117.8, 121.3, 134.7, 149.3, 156.9, 167.9, 171.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{16}N_2Na_1O_4$, 323.1002; found, 323.0993.



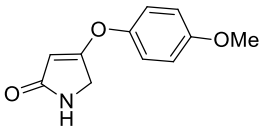
***Tert*-butyl 4-(4-nitrophenoxy)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 10j**: Obtained following the GP1 to give a white solid (47%, 40 mg). Mp 153 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.55 (s, 9H), 4.45 (d, *J* = 0.5 Hz, 2H), 5.08 (s, 1H), 7.34 (d, *J* = 9.0 Hz, 2H), 8.34 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 28.2, 49.3, 83.4, 99.8, 121.0, 126.3, 145.8, 149.3, 158.3, 167.8, 171.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{16}N_1Na_1O_6$, 343.0901; found, 343.0890.



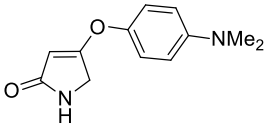
4-Phenoxy-1H-pyrrol-2(5*H*)-one 8b: Obtained following the GP2 to give a white solid (91%, 287 mg). Mp 116 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 4.12 (d, *J* = 1.0 Hz, 2H), 4.93 (t, *J* = 1.0 Hz, 1H), 6.91 (br s, 1H), 7.14 - 7.16 (m, 2H), 7.24-7.28 (m, 1H), 7.39-7.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 47.0, 97.9, 120.2, 126.3, 130.2, 154.6, 174.3, 175.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_9N_1Na_1O_2$, 198.0525; found, 198.0521.



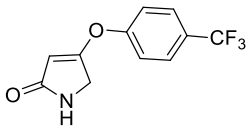
4-(*p*-Tolyloxy)-1*H*-pyrrol-2(5*H*)-one 8c: Obtained following the GP2 to give a white solid (94%, 190 mg). Mp 126 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 2.36 (s, 3H), 4.10 (t, *J* = 1.0 Hz, 2H), 4.91-4.92 (m, 1H), 6.49 (br s, 1H), 7.06 (d, *J* = 9.0 Hz, 2H), 7.19 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 21.0, 46.9, 97.6, 119.9, 130.6, 136.0, 152.4, 174.6, 175.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{11}N_1Na_1O_2$, 212.0682; found, 212.0674.



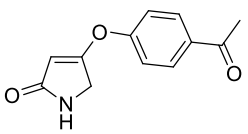
4-(4-Methoxyphenoxy)-1*H*-pyrrol-2(5*H*)-one 8d: Obtained following the GP2 to give a white solid (99%, 435 mg). Mp 149 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 3.81 (s, 3H), 4.09 (s, 2H), 4.89 (s, 1H), 6.48 (br s, 1H), 6.88-6.93 (m, 2H), 7.04-7.09 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 46.9, 55.8, 97.5, 115.0, 121.2, 148.2, 157.5, 175.0, 175.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{11}N_1Na_1O_3$, 228.0631; found, 228.0639.



4-(4-(Dimethylamino)phenoxy)-1*H*-pyrrol-2(5H)-one 8e: Obtained following the GP2 to give a creamy white solid (quant., 410 mg). Mp 163 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 2.94 (s, 6H), 4.07-4.08 (m, 2H), 4.89-4.89 (m, 1H), 6.47 (br s, 1H), 6.68 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 41.0, 46.8, 97.2, 113.3, 120.7, 145.5 148.9, 175.5 (1 C non accounted for). HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{15}N_2O_2$, 219.1128; found, 219.1120.

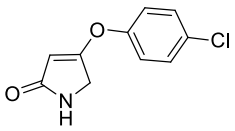


4-(4-(Trifluoromethyl)phenoxy)-1*H*-pyrrol-2(5*H*)-one 8f: Obtained following the GP2 to give a white solid (95%, 800 mg). Mp 198 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 4.16 (s, 2H), 5.02 (s, 1H), 6.67 (br s, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 47.0, 98.8, 120.7, 123.7 (q, $J^1_{C\text{-}F}$ = 271 Hz), 127.7 (q, $J^3_{C\text{-}F}$ = 4 Hz), 128.6 (q, $J^2_{C\text{-}F}$ = 32 Hz), 156.9, 173.0, 174.5. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_8F_3N_1NaO_2$, 266.0399; found, 266.0398.

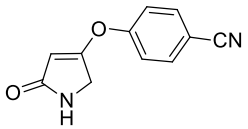


4-(4-Acetylphenoxy)-1*H*-pyrrol-2(5*H*)-one 8g: Obtained following the GP2 to give a white solid (94%, 322 mg). Mp 143 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 2.61 (s, 3H), 4.15 (s, 2H), 5.03 (s, 1H), 6.78 (br s, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 26.7, 47.0, 98.9, 120.2,

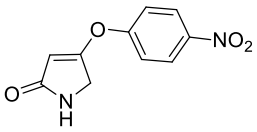
130.8, 135.0, 158.0, 172.8, 174.6, 196.6. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{11}N_1Na_1O_3$, 240.0631; found, 240.0619.



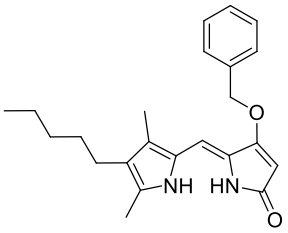
4-(4-Chlorophenoxy)-1*H*-pyrrol-2(5*H*)-one 8h: Obtained following the GP2 to give a white solid (quant, 745 mg). Mp 187 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 4.11-4.12 (m, 2 H), 4.94-4.95 (m, 1 H), 6.67 (br s, 1H), 7.10 (d, *J* = 9.0 Hz, 2 H), 7.38 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) 46.9, 98.2, 121.7, 130.3, 131.7, 153.0, 173.8, 174.8. ESI (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_8Cl_1N_1Na_1O_2$, 232.0136; found, 232.0139.



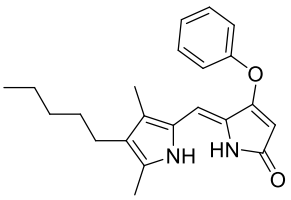
4-((5-Oxo-2, 5-dihydro-1*H*-pyrrol-3-yl)oxy)benzonitrile 8i: Obtained following the GP2 to give a white solid (quant., 400 mg). Mp 170 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 4.15-4.16 (m, 2H), 5.05-5.06 (m, 1H), 6.84 (br s, 1H), 7.30 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 46.9, 99.4, 110.2, 118.0, 121.1, 134.6, 157.6, 172.2, 174.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_8N_2Na_1O_2$, 223.0478; found, 223.0468.



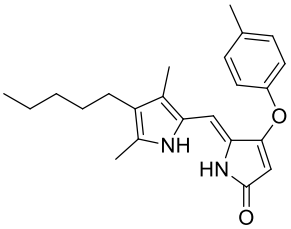
4-(4-Nitrophenoxy)-1*H*-pyrrol-2(5*H*)-one 8j: Obtained following the GP2 to give a white solid (90%, 420 mg). Dec. > 195 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 4.19 (s, 2H), 5.12 (s, 1H), 6.22 (br s, 1H), 7.35 (d, *J* = 9.0 Hz, 2H), 8.33 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 46.8, 99.7, 120.8, 126.2, 145.5, 159.0, 171.9, 173.7. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_8N_2Na_1O_4$, 243.0376; found, 243.0370.



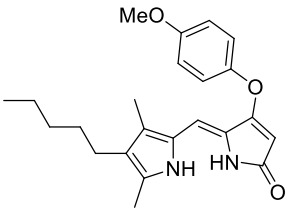
(*Z*)-4-(Benzyloxy)-5-((3,5-dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-1*H*-pyrrol-2(5*H*)-one12a:
Obtained following GP3. After concentration under *vacuum*, the resulting suspension was washed with water and hexane. Isolation viafiltration gavea yellow solid that was purified using flash chromatography (SiO_2, CH_2Cl_2/MeOH 99/1 then 98/2) to give 334 mg (38 %) of yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.90 (t, *J* = 7.0 Hz, 3H), 1.28-1.36 (m, 4H), 1.43 (quint., *J* = 7.5 Hz, 2H), 2.10 (s, 3H), 2.34 (s, 3H), 2.36 (t, *J* = 7.0 Hz, 2H), 5.10 (s, 2H), 5.15 (d, *J* = 1.5 Hz, 1H), 6.45 (s, 1H), 7.38-7.45 (m, 5H), 10.24 (br s, 1H), 11.00 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.6, 14.3, 22.8, 24.3, 30.7, 31.8, 72.9, 90.7, 101.1, 121.5, 121.7 (2 C), 126.1, 127.8, 128.6, 128.8, 132.5, 135.6, 166.6, 173.1. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{29}N_2O_2$, 365.2224; found, 365.2225.



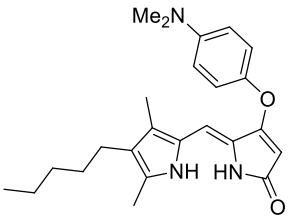
(*Z*)-5-((3,5-Dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-4-phenoxy-1*H*-pyrrol-2(5*H*)-one **12b**: Obtained following the GP3 to give a yellow solid (53%, 240 mg). Mp 213 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.88 (t, *J* = 7.5 Hz, 3H), 1.26-1.33 (m, 4H), 1.42 (quint., *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 2.27 (s, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 4.93 (d, *J* = 1.5 Hz, 1H), 6.60 (s, 1H), 7.24-7.29 (m, 3H), 7.43-7.46 (m, 2H), 10.30 (s, 1H), 11.13 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.7, 14.3, 22.8, 24.3, 30.6, 31.8, 93.1, 102.0, 120.4, 121.1, 121.8, 122.1, 125.7, 127.0, 130.1, 133.4, 155.4, 165.9, 172.5. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_2$, 351.2067; found, 351.2059.



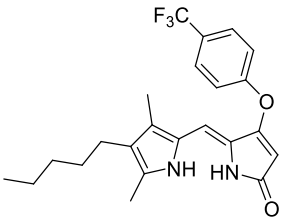
(*Z*)-5-((3,5-Dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-4-(p-tolyloxy)-1*H*-pyrrol-2(5*H*)-one **12c**: Obtained following the GP3 to give a yellow solid (70%, 140 mg). Dec. > 195 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.88 (t, *J* = 7.5 Hz, 3H), 1.26-1.34 (m, 4H), 1.42 (quint., *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 2.26 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 4.89 (s, 1H), 6.59 (s, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 10.28 (br s, 1H), 11.09 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.7, 14.3, 21.0, 22.8, 24.3, 30.6, 31.8, 92.8, 101.8, 120.2, 121.2, 121.8, 122.0, 126.9, 130.5, 133.2, 135.4, 153.2, 166.3, 172.6. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{28}N_2Na_1O_2$: 387.2043, found, 387.2045.



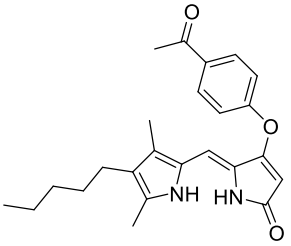
(*Z*)-5-((3,5-Dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-4-(4-methoxyphenoxy)-1*H*-pyrrol-2(5*H*)-one **12d**: Obtained following the GP3 to give a yellow solid (76%, 271 mg). Dec. > 200 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.88 (t, *J* = 7.5 Hz, 3H), 1.27-1.33 (m, 4H), 1.42 (quint., *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 2.26 (s, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 4.84 (d, *J* = 2.0 Hz, 1H), 6.58 (s, 1H), 6.93-6.96 (m, 2H), 7.15-7.18 (m, 2H), 10.27 (s, 1H), 10.07 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.7, 14.3, 22.8, 24.3, 30.7, 31.8, 55.8, 92.6, 101.8, 115.0, 121.1, 121.5, 121.7, 122.0, 126.8, 133.2, 148.9, 157.2, 166.8, 172.6. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{28}N_2Na_1O_3$, 403.1992; found, 403.1972.



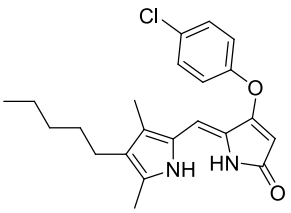
(*Z*)-5-((3,5-Dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-4-(4-(dimethylamino)phenoxy)-1*H*-pyrrol-2(5*H*)-one 12e: Obtained following the GP3 to give a yellow solid (53%, 237 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.89 (t, *J* = 7.0 Hz, 3H), 1.26-1.34 (m, 4H), 1.42 (quint., *J* = 7.0 Hz, 2H), 2.14 (s, 3H), 2.26 (s, 3H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.98 (s, 6H), 4.85 (s, 1H), 6.58 (s, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 10.28 (s, 1H), 11.04 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.7, 14.3, 22.8, 24.3, 30.7, 31.8, 41.1, 92.4, 101.4, 113.4, 120.7, 121.1, 121.4, 121.8 (2 C), 126.4, 132.9, 146.2, 148.6, 167.3, 172.8. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{32}N_3O_2$, 394.2489; found, 394.2501.



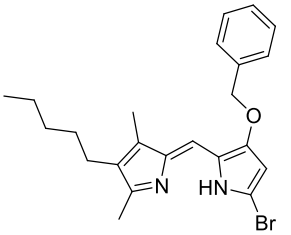
(*Z*)-5-((3,5-Dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-4-(4-(trifluoromethyl)phenoxy)-1H-pyrrol-2(5*H*)-one 12f: Obtained following the GP3 to give a yellow solid (40%, 245 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.88 (t, *J* = 7.3 Hz, 3H), 1.27-1.34 (m, 4H), 1.42 (quint., *J* = 7.3 Hz, 2H), 2.14 (s, 3H), 2.29 (s, 3H), 2.35 (t, *J* = 7.3 Hz, 2H), 5.03 (s, 1H), 6.58 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 10.32 (s, 1H), 11.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.8, 14.2, 22.8, 24.3, 30.6, 31.8, 94.1, 102.6, 120.4, 120.6, 121.8, 122.5, 124.0 (q, $J^1_{C\text{-}F}$ = 270 Hz), 127.3 (q, $J^2_{C\text{-}F}$ = 17 Hz), 127.5 (q, $J^3_{C\text{-}F}$ = 4 Hz), 127.9, 134.2, 158.0, 164.4, 172.0. (HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{25}F_3N_2Na_1O_2$, 441.1760; found, 441.1752.



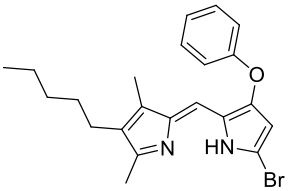
(*Z*)-4-(4-Acetylphenoxy)-5-((3,5-dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-1*H*-pyrrol-2(5*H*)-one 12g: Obtained following the GP3 to give a yellow solid (61%, 153 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) 0.88 (t, *J* = 7.0 Hz, 3H), 1.26-1.32 (m, 4H), 1.39-1.44 (m, 2H), 2.13 (s, 3H), 2.27 (s, 3H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.63 (s, 3H), 5.05 (s, 1H), 6.57 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 10.26 (br s, 1H), 11.16 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.8, 14.2, 22.7, 24.3, 26.8, 30.6, 31.7, 94.3, 102.6, 120.0, 120.7, 121.8, 122.4, 127.8, 130.7, 134.1, 134.4, 159.2, 164.2, 172.0, 196.8. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{28}N_2Na_1O_3$, 415.1992; found, 415.1975.



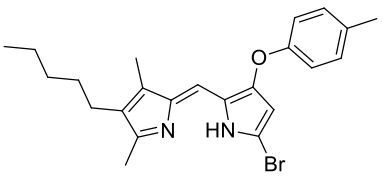
(*Z*)-4-(4-Chlorophenoxy)-5-((3,5-dimethyl-4-pentyl-1*H*-pyrrol-2-yl)methylene)-1*H*-pyrrol-2(5*H*)-one 12h: Obtained following the GP3 to give a yellow solid (83%, 540 mg). Dec. > 210 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.88 (t, *J* = 6.7 Hz, 3H), 1.28-1.34 (m, 4H), 1.38-1.45 (m, 2H), 2.13 (s, 3H), 2.28 (s, 3H), 2.33-2.36 (m, 2H), 4.91 (s, 1H), 6.57 (s, 1H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 10.28 (br s, 1H), 11.13 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 11.7, 14.3, 22.8, 24.3, 30.6, 31.8, 93.2, 102.2, 120.7, 121.7, 121.8, 122.3, 127.4, 130.2, 131.0, 133.7, 153.9, 165.5, 172.2. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{26}Cl_1N_2O_2$, 385.1677; found, 385.1659.



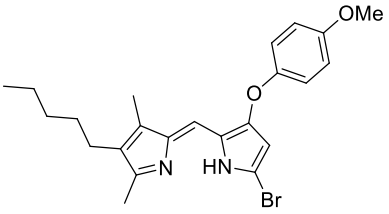
(*Z*)-3-(Benzyloxy)-5-bromo-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole 13a: Obtained following the GP4 to give a yellow glass (41%, 144 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.90 (t, *J* = 7.0 Hz, 3H), 1.26-1.36 (m, 4H), 1.43 (quint., *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 2.28 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 5.02 (s, 2H), 5.64 (s, 1H), 6.95 (s, 1H), 7.36-7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 12.5, 14.2, 22.7, 24.1, 30.4, 31.7, 73.3, 100.0, 116.7, 124.2, 126.5, 127.9, 128.5, 128.7, 132.0, 136.0, 136.5, 138.1, 143.0, 165.4. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{28}Br_1N_2O$, 427.138; found, 427.1363.



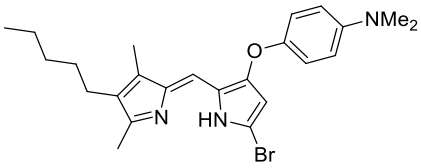
(*Z*)-5-Bromo-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-3-phenoxy-1*H*-pyrrole 13b: Obtained following the GP4 to give a yellow glass (50%, 70 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.89 (t, *J* = 7.5 Hz, 3H), 1.26-1.36 (m, 4H), 1.43 (quint., *J* = 7.5 Hz, 2H), 2.16 (s, 3H), 2.31 (s, 3H), 2.36 (t, *J* = 7.5 Hz, 2H), 5.51 (s, 3H), 7.07 (s, 1H), 7.18-7.22 (m, 3H), 7.37-7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 12.6, 14.2, 22.7, 24.2, 30.3, 31.7, 103.3, 117.8, 119.6, 124.9 (2C), 127.0, 129.9, 133.3, 136.3, 139.7, 141.8, 156.6, 163.2. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{26}Br_1N_2O_1$, 413.1223; found, 413.1204.



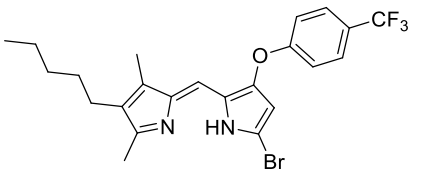
(*Z*)-5-Bromo-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-3-(p-tolyloxy)-1*H*-pyrrole 13c: Obtained following the GP4 to give a yellow glass (58%, 90 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.90 (t, *J* = 7.0 Hz, 3H), 1.27-1.36 (m, 4H), 1.44 (quint., *J* = 7.5 Hz, 2H), 2.17 (s, 3H), 2.31 (s, 3H), 2.35-2.38 (m, 5H), 5.46 (s, 1H), 7.07 (s, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 12.6, 14.2, 20.9, 22.7, 24.1, 30.3, 31.7, 102.9, 117.6, 119.5, 124.7, 126.9, 130.4, 133.0, 134.6, 136.4, 139.3, 142.0, 154.3, 163.8. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{28}Br_1N_2O_1$, 427.138; found, 427.1375.



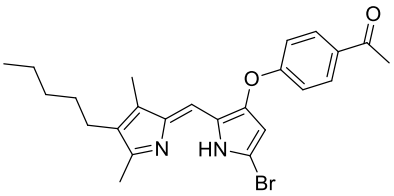
(*Z*)-5-Bromo-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-3-(4-methoxyphenoxy)-1*H*-pyrrole 13d: Obtained following the GP4 to give an orange solid (46%, 53 mg). Mp 128 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.89 (t, *J* = 7.0 Hz, 3 H), 1.26-1.35 (m, 4 H), 1.43 (quint., *J* = 7.0 Hz, 2 H), 2.16 (s, 3 H), 2.31 (s, 3 H), 2.36 (t, *J* = 7.0 Hz, 2 H), 3.82 (s, 3 H), 5.39 (s, 1 H), 6.88-6.92 (m, 2 H), 7.07 (s, 1 H), 7.11-7.15 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 12.6, 14.2, 22.7, 24.2, 30.3, 31.7, 55.8, 102.5, 114.9, 117.6, 120.9, 124.7, 126.8, 133.0, 136.2, 139.2, 142.1, 150.0, 156.8, 164.5. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{28}Br_1N_2O_2$, 443.1329; found, 443.1345.



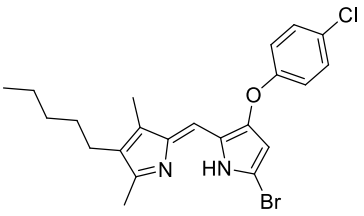
(*Z*)-4-((5-Bromo-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrol-3-yl)oxy)-*N*,*N*-dimethylaniline 13e: Obtained following the GP4 to give a yellow glass (15%, 68 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) 0.90 (t, *J* = 7.2 Hz, 3H), 1.26-1.37 (m, 4H), 1.44 (quint., *J* = 7.2 Hz, 2H), 2.16 (s, 3H), 2.30 (s, 3H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.95 (s, 6H), 5.38 (s, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 7.07 (s, 1H), 7.08 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) 9.8, 12.6, 14.2, 22.7, 24.2, 30.4, 31.7, 41.1, 102.2, 113.6, 117.4, 120.6, 124.5, 126.8, 132.6, 136.5, 138.7, 142.6, 147.5, 148.4, 165.3. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{31}BrN_3O$, 456.1645; found, 456.1624.



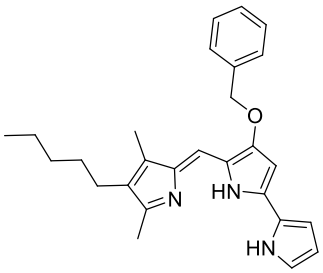
(*Z*)-5-Bromo-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-3-(4-(trifluoromethyl)phenoxy)-1*H*-pyrrole 13f: Obtained following the GP4 to give a yellow glass (60%, 150 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.90 (t, *J* = 7.2 Hz, 3H), 1.26-1.36 (m, 4H), 1.43 (quint., *J* = 7.2 Hz, 2H), 2.15 (s, 3H), 2.33 (s, 3H), 2.36 (t, *J* = 7.2 Hz, 2H), 5.66 (s, 1H), 7.01 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 12.7, 14.2, 22.7, 24.1, 30.3, 31.7, 104.7, 118.3, 119.1, 124.1 (q, $J^1_{C\text{-}F}$ = 270 Hz), 125.4, 126.6 (q, $J^2_{C\text{-}F}$ = 32 Hz), 127.3 (q, $J^3_{C\text{-}F}$ = 4 Hz), 134.3, 135.9, 140.6, 141.0, 159.5, 160.9 (1 C non accounted for). HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{25}Br_1F_3N_2O_1$, 481.1097; found, 481.1075.



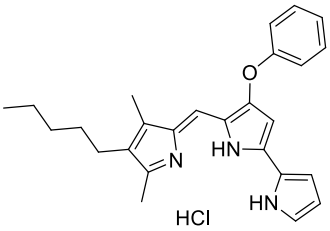
(*Z*)-1-(4-((5-Bromo-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrol-3-yl)oxy)phenyl)ethanone 13g: Obtained following the GP4 to give a yellow glass (63%, 110 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.89 (t, *J* = 7.5 Hz, 3H), 1.25-1.35 (m, 4H), 1.42 (quint., *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 2.32 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.60 (s, 3H), 5.69 (s, 1H), 7.00 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 12.7, 14.2, 22.7, 24.1, 26.7, 30.2, 31.7, 105.1, 118.4, 118.5, 125.4, 127.3, 130.7, 133.4, 134.4, 135.9, 140.6, 141.1, 160.5, 160.8, 196.8. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{28}Br_1N_2O_2$, 455.1329; found, 455.1346.



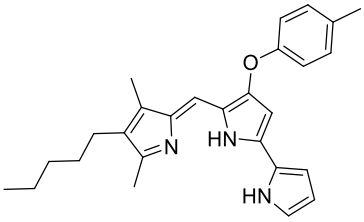
(*Z*)-5-Bromo-3-(4-chlorophenoxy)-2-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole 13h: Obtained following the GP4 to give an orange solid (34%, 80 mg). Mp 98 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.85 (t, *J* = 7.3 Hz, 3H), 1.22-1.31 (m, 4H), 1.39 (quint., *J* = 7.3 Hz, 2H), 2.11 (s, 3H), 2.27 (s, 3H), 2.32 (t, *J* = 7.3 Hz, 2H), 5.48 (s, 1H), 6.99 (s, 1H), 7.10 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 12.7, 14.2, 22.7, 24.1, 30.3, 31.7, 103.5, 118.0, 120.8, 125.1, 127.1, 129.9, 133.7, 136.0, 140.2, 141.2, 155.2, 162.5 (1 C non accounted for). HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{25}Br_1Cl_1N_2O_1$, 447.0833; found, 447.0845.



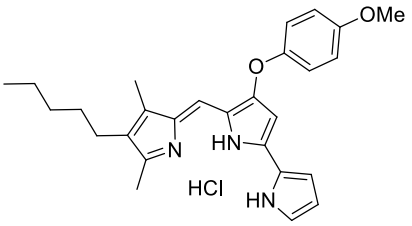
(Z)-4-(Benzyloxy)-5-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*,1'*H*-2,2'-bipyrrole 3a: Obtained following the GP5. After evaporation of the solvent under reduced pressure, the crude material was purified using flash chromatography (Al_2O_3 neutral type III CH_2Cl_2/hexane 5/5 then EtOAc/hexane 1/9 then 2/8) to give a dark brown solid (47%, 45 mg). Rf = 0.55 (EtOAc/hexane 5/5). ^{1}H NMR ($CDCl_3$, 300 MHz) 0.85 (t, *J* = 7.0 Hz, 3H), 1.21-1.32 (m, 6H), 1.78 (s, 3H), 2.10 (s, 3H), 2.21 (t, *J* = 7.0 Hz, 2H), 5.18 (s, 2H), 6.10 (s, 1H), 6.13-6.14 (m, 1H), 6.61-6.62 (m, 1H), 6.65 (s, 1H), 6.95 (s, 1H), 7.38-7.52 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 10.7, 14.2, 22.7, 24.3, 30.5, 31.9, 73.1, 96.2, 109.8, 111.6, 113.8, 122.2, 123.2, 125.9, 127.8, 127.8, 128.4, 128.7, 129.9, 136.5, 167.1 (3 carbon non accounted for). HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{32}N_3O_1$, 414.2540; found, 414.2521.



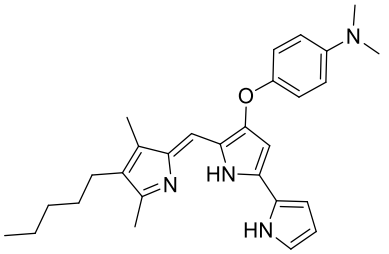
(*Z*)-5-((3,5-Dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-4-phenoxy-1*H*,1'*H*-2,2'-bipyrrole hydrochloride 3b: Obtained following the GP5 to give a red solid (25%, 25 mg). Mp 125 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.89 (t, *J* = 7.2 Hz, 3H), 1.26-1.35 (m, 4H), 1.44 (quint., *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.58 (s, 3H), 5.89 (s, 1H), 6.28 (s, 1H), 6.71 (s, 1H), 7.17 (s, 1H), 7.22-7.26 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 12.43 (br s, 1H), 12.72 (br s, 1H), 12.77 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.3, 12.9, 14.2, 22.7, 24.1, 29.9, 31.7, 96.2, 111.5, 114.0, 116.1, 119.8, 120.0, 122.6, 125.2, 125.9, 126.2, 128.0, 130.3, 139.3, 145.5, 149.9, 155.5, 162.6 (1 carbon non accounted for). HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{30}N_3O_1$, 400.2383; found, 400.22367.



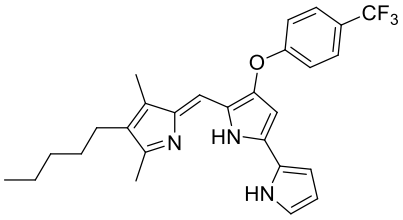
(*Z*)-5-((3,5-Dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-4-(*p*-tolyloxy)-1*H*,1'*H*-2,2'-bipyrrole 3c: Obtained following the GP5 to give a red glass (30%, 26 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.86 (t, *J* = 7.2 Hz, 3H), 1.24-1.36 (m, 6H), 1.83 (s, 3H), 2.14 (s, 3H), 2.23 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 5.97 (s, 1H), 6.09 (t, *J* = 2.7 Hz, 1H), 6.51 (d, *J* = 2.7 Hz, 1H), 6.64 (s, 1H), 7.08 (s, 1H), 7.19 (d, *J* = 9.0 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.9, 10.5, 14.2, 21.0, 22.7, 24.3, 30.5, 31.9, 99.5, 109.8, 111.9, 114.7, 119.6, 122.4, 123.8, 126.1, 128.9, 130.4, 131.0, 134.4, 136.9, 138.3, 154.8, 157.7, 165.9. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{32}N_3O_1$, 414.2540; found, 414.2537.



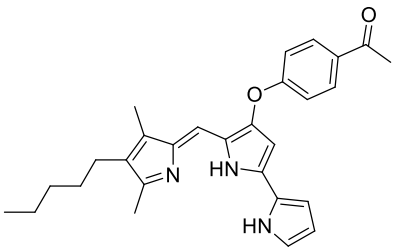
(*Z*)-5-((3,5-Dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-4-(4-methoxyphenoxy)-1*H*,1'*H*-2,2'-bipyrrole 3d: Obtained following the GP5 to give a red solid (28%, 23 mg). Mp 78 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.90 (t, *J* = 7.4 Hz, 3H), 1.26-1.36 (m, 4H), 1.45 (quint., *J* = 7.4 Hz, 2H), 2.26 (s, 3H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.58 (s, 3H), 3.85 (s, 3H), 5.80 (s, 1H), 6.27-6.28 (m, 1H), 6.71 (s, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 7.15-7.17 (m, 3H), 7.23 (s, 1H), 12.42 (br s, 1H), 12.65 (br s, 1H), 12.70 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.3, 12.8, 14.2, 22.7, 24.1, 30.0, 31.7, 55.8, 95.7, 111.5, 113.8, 115.2, 116.1, 119.7, 121.3, 122.6, 125.0, 126.2, 127.8, 139.0, 145.7, 148.9, 149.5, 157.5, 163.7. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{32}N_3O_2$, 430.2489; found, 430.2472.



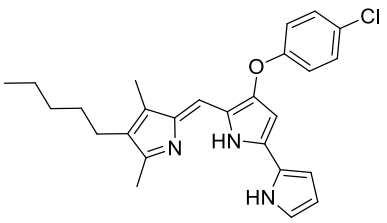
(*Z*)-4-((5-((3,5-Dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*,1'*H*-[2,2'-bipyrrol]-4-yl)oxy)-*N*,*N*-dimethylaniline 3e: Obtained following the GP5 to give a red glass (48%, 32 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.87 (t, *J* = 7.5 Hz, 3H), 1.23-1.37 (m, 6H), 1.80 (s, 3H), 2.15 (s, 3H), 2.23 (t, *J* = 7.5 Hz, 2H), 3.00 (s, 6H), 5.91 (s, 1H), 6.08 (t, *J* = 2.7 Hz, 1H), 6.50 (d, *J* = 2.7 Hz, 1H), 6.62 (s, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 7.11 (s, 1H), 7.20 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.8, 10.3, 14.2, 22.7, 24.3, 30.5, 32.0, 41.2, 98.8, 109.7, 111.9, 113.7, 114.4, 120.8, 122.4, 123.5, 125.9, 128.9, 130.6, 136.9, 137.9, 147.9, 148.2, 158.0, 167.3. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{35}N_4O$, 443.2805; found, 443.2790.



(*Z*)-5-((3,5-Dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-4-(4-(trifluoromethyl)phenoxy)-1*H*,1'H-2,2'-bipyrrole 3f: Obtained following the GP5 to give a red glass (28%, 40 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.86 (t, *J* = 7.5 Hz, 3H), 1.23-1.37 (m, 6H), 1.96 (s, 3H), 2.14 (s, 3H), 2.26 (t, *J* = 7.5 Hz, 2H), 6.13 (s, 1H), 6.17 (t, *J* = 2.6 Hz, 1H), 6.56 (d, *J* = 2.6, 1H), 6.73 (s, 1H), 7.01 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.9, 10.8, 14.2, 22.7, 24.3, 30.4, 31.9, 101.4, 110.2, 112.1, 115.2, 119.2, 122.4, 124.2 (q, $J^1_{C\text{-}F}$ = 270 Hz), 124.5, 126.4, 126.5 (q, $J^2_{C\text{-}F}$ = 32 Hz), 127.4, 128.7, 132.3, 136.3, 139.5, 156.7, 159.8, 163.1. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{29}F_3N_3O_1$, 468.2257; found, 468.2276.



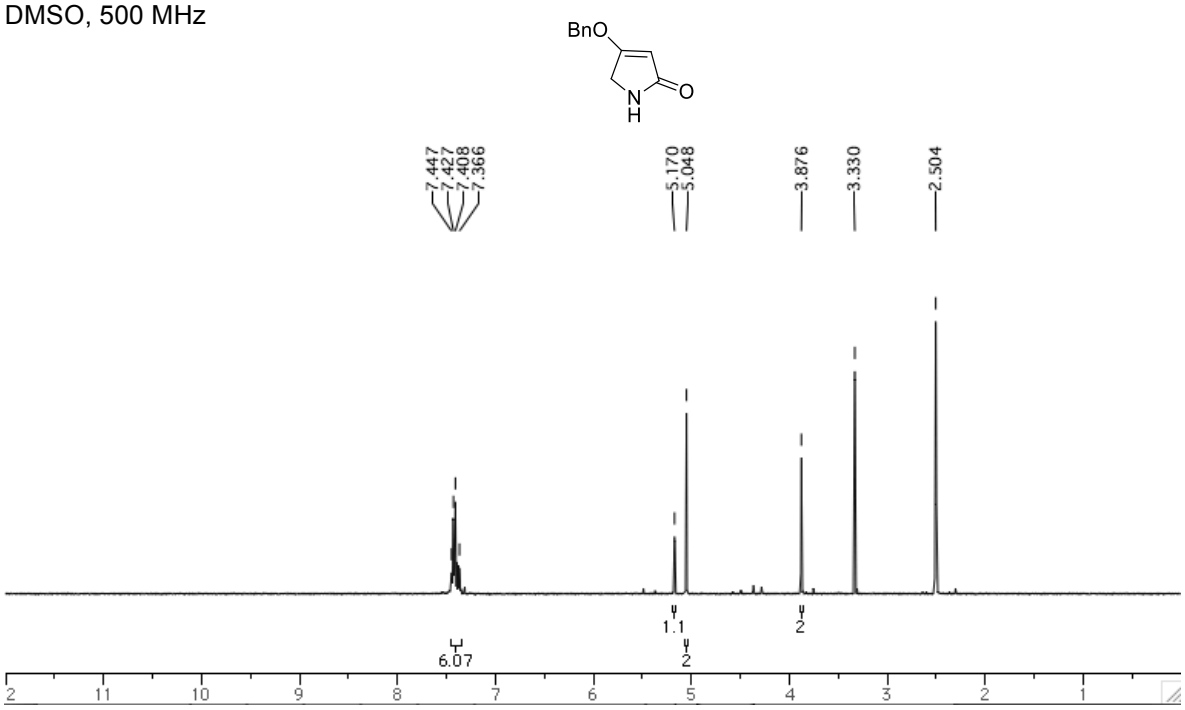
(*Z*)-1-(4-((5-((3,5-Dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*,1'*H*-[2,2'-bipyrrol]-4-yl)oxy)phenyl)ethanone 3g: Obtained following GP5 to give a red glass (16%, 16 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.86 (t, *J* = 7.5 Hz, 3H), 1.22-1.36 (m, 8H), 1.92 (s, 3H), 2.13 (s, 3H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.64 (s, 3H), 6.15 (t, *J* = 3.0 Hz, 1H), 6.20 (s, 1H), 6.56 (d, *J* = 3.0 Hz, 1H), 6.70 (s, 1H), 7.01 (s, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 8.06 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.9, 11.0, 14.2, 22.7, 24.3, 26.7, 30.4, 31.9, 101.7, 110.2, 112.0, 115.3, 116.6, 118.6, 122.3, 124.5, 126.6, 128.7, 130.8, 132.2, 133.3, 139.5, 156.4, 161.2, 162.6, 196.9. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{32}N_3O_2$, 442.2489; found, 442.2502.



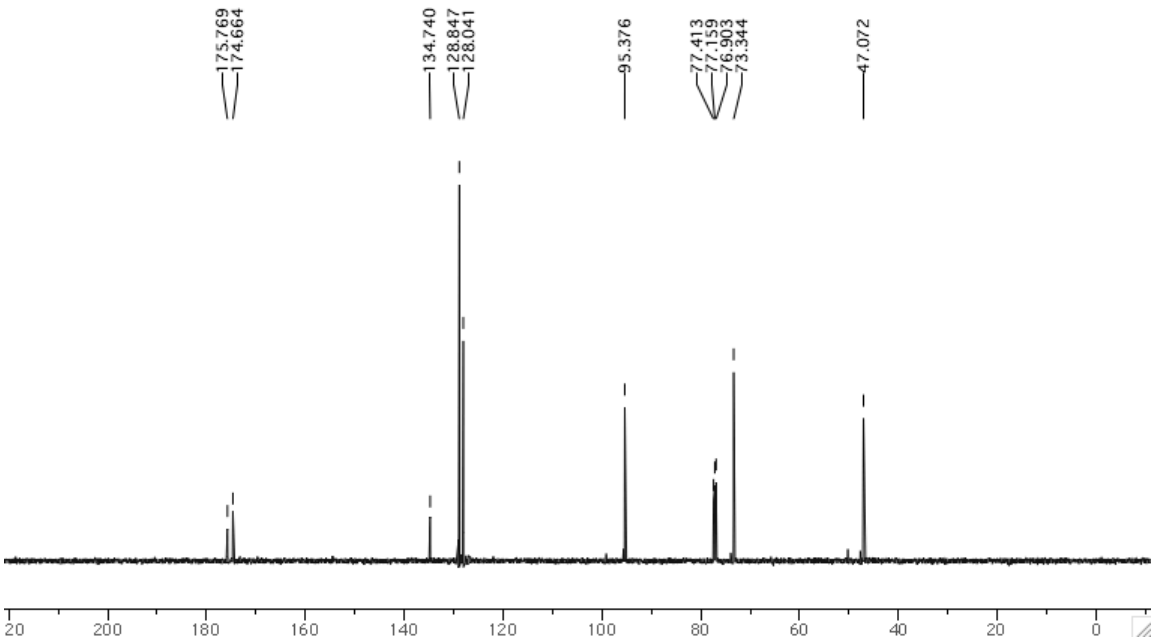
(*Z*)-4-(4-Chlorophenoxy)-5-((3,5-dimethyl-4-pentyl-2*H*-pyrrol-2-ylidene)methyl)-1*H*,1'*H*-2,2'-bipyrrole 3h: Obtained following the GP5 to give a red solid (36%, 28 mg). Mp 55 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.86 (t, *J* = 7.5 Hz, 3 H), 1.22-1.36 (m, 6 H), 1.85 (s, 3 H), 2.14 (s, 3 H), 2.24 (t, *J* = 7.5 Hz, 2 H), 6.01 (s, 1 H), 6.12 (dd, *J* = 3.5, 3.0 Hz, 1 H), 6.53 (dd, *J* = 3.5, 1.5 Hz, 1 H), 6.66 (br s, 1 H), 7.04 (s, 1H), 7.24 (d, *J* = 8.7 Hz, 2 H), 7.41 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.9, 10.7, 14.2, 22.7, 24.3, 30.5, 31.9, 100.1, 110.0, 112.0, 114.9, 121.0, 122.4, 124.2, 126.2, 128.7, 129.8, 130.0, 130.0, 131.7, 138.8, 155.6, 157.0, 164.6. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{29}Cl_1N_3O_1$, 434.1994; found, 434.1973.

2. ^{1}H and ^{13}C NMR spectra

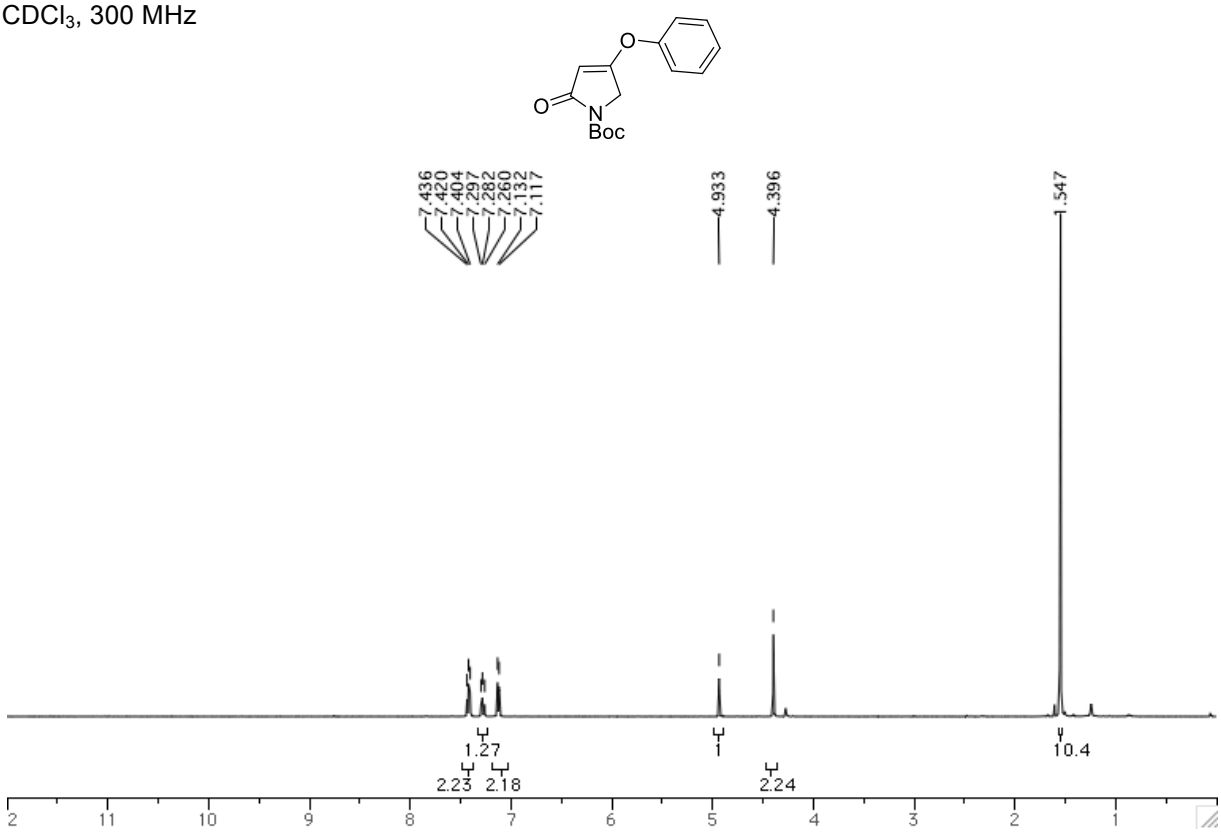
^{1}H NMR for **8a**
DMSO, 500 MHz



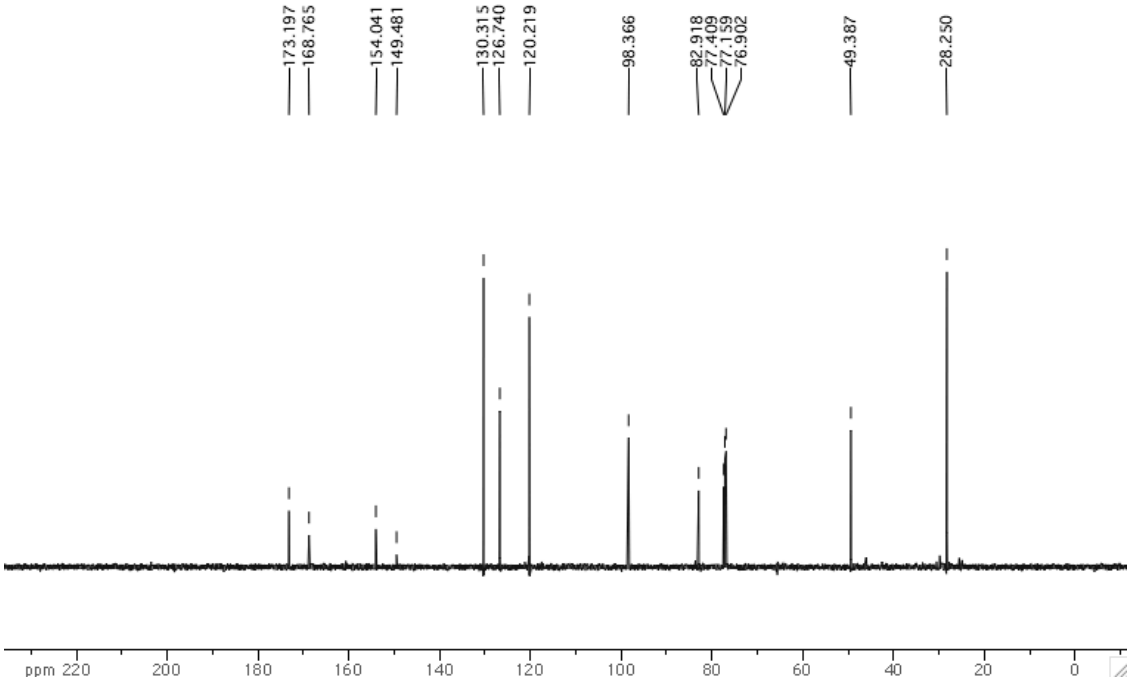
^{13}C NMR for **8a**
$CDCl_3$, 125 MHz



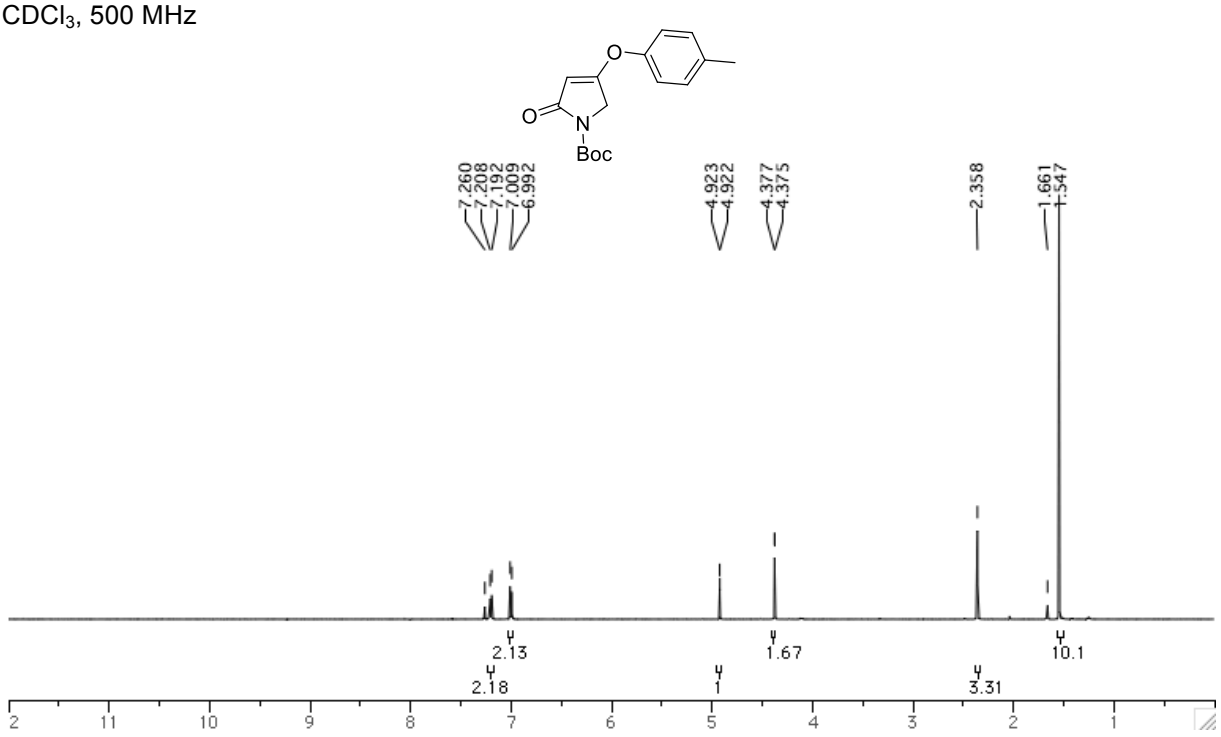
^{1}H NMR for **10b**
$CDCl_3$, 300 MHz



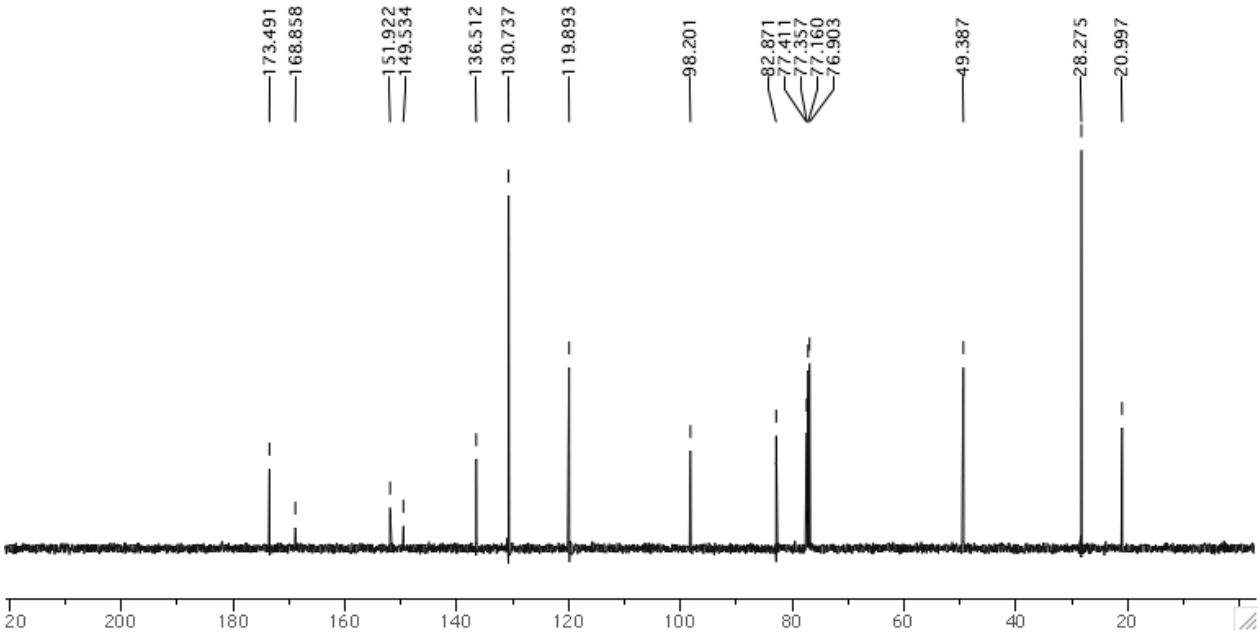
^{13}C NMR for **10b**
$CDCl_3$, 125 MHz



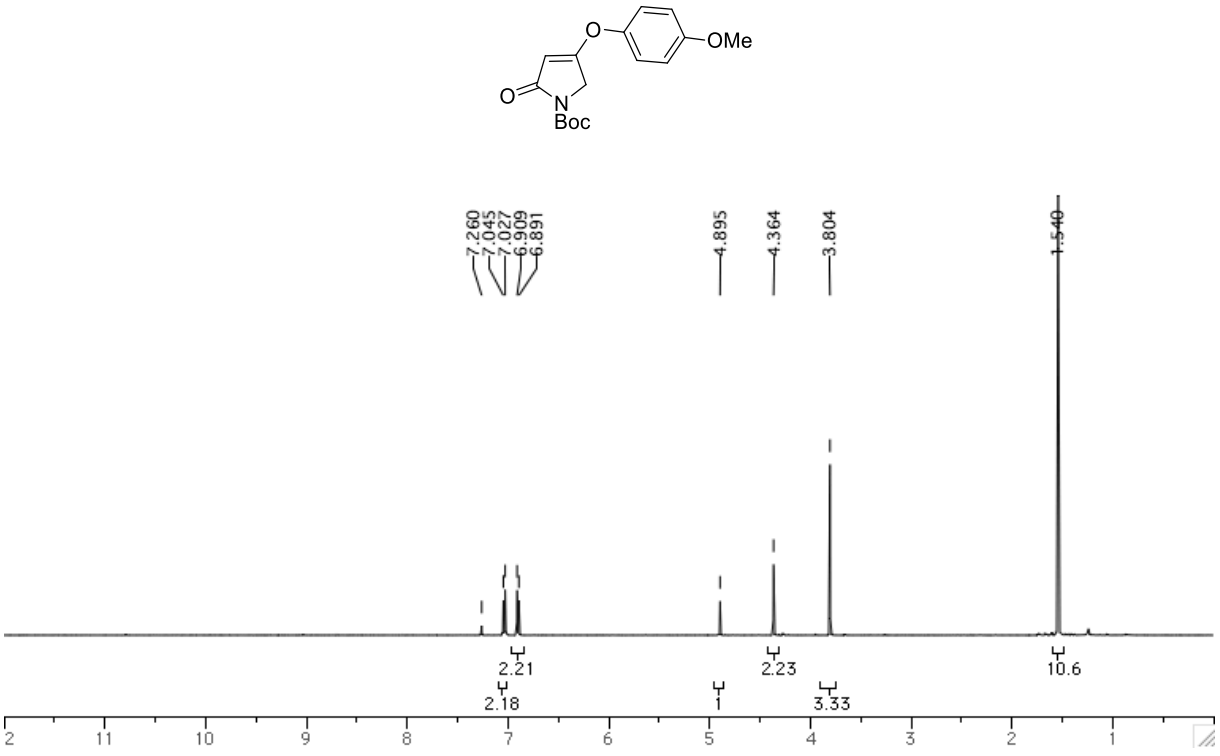
^{1}H NMR for **10c**
$CDCl_3$, 500 MHz



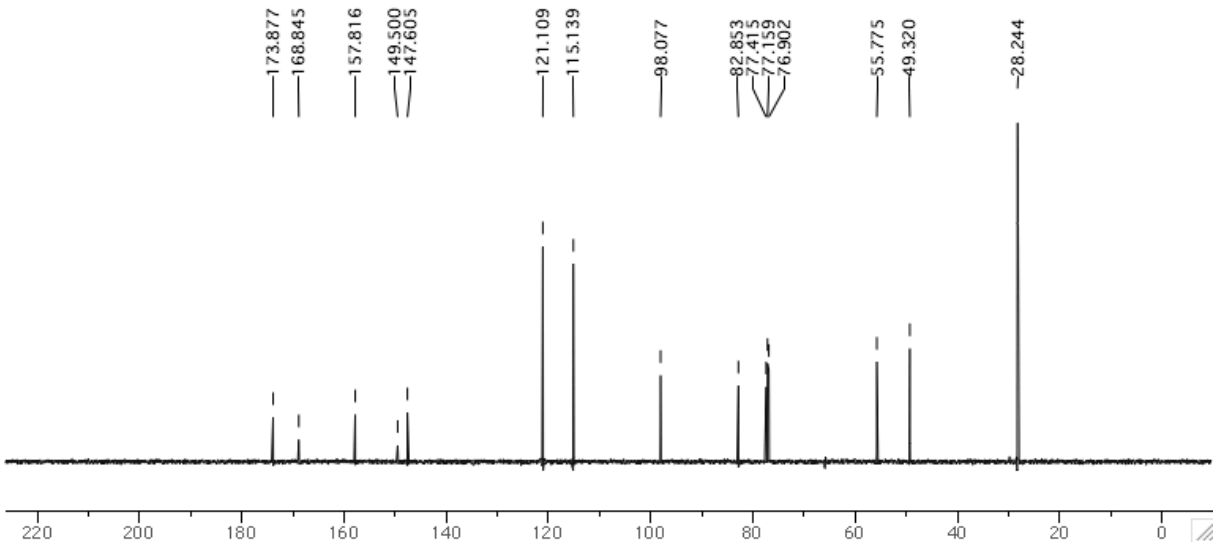
^{13}C NMR for **10c**
$CDCl_3$, 125 MHz



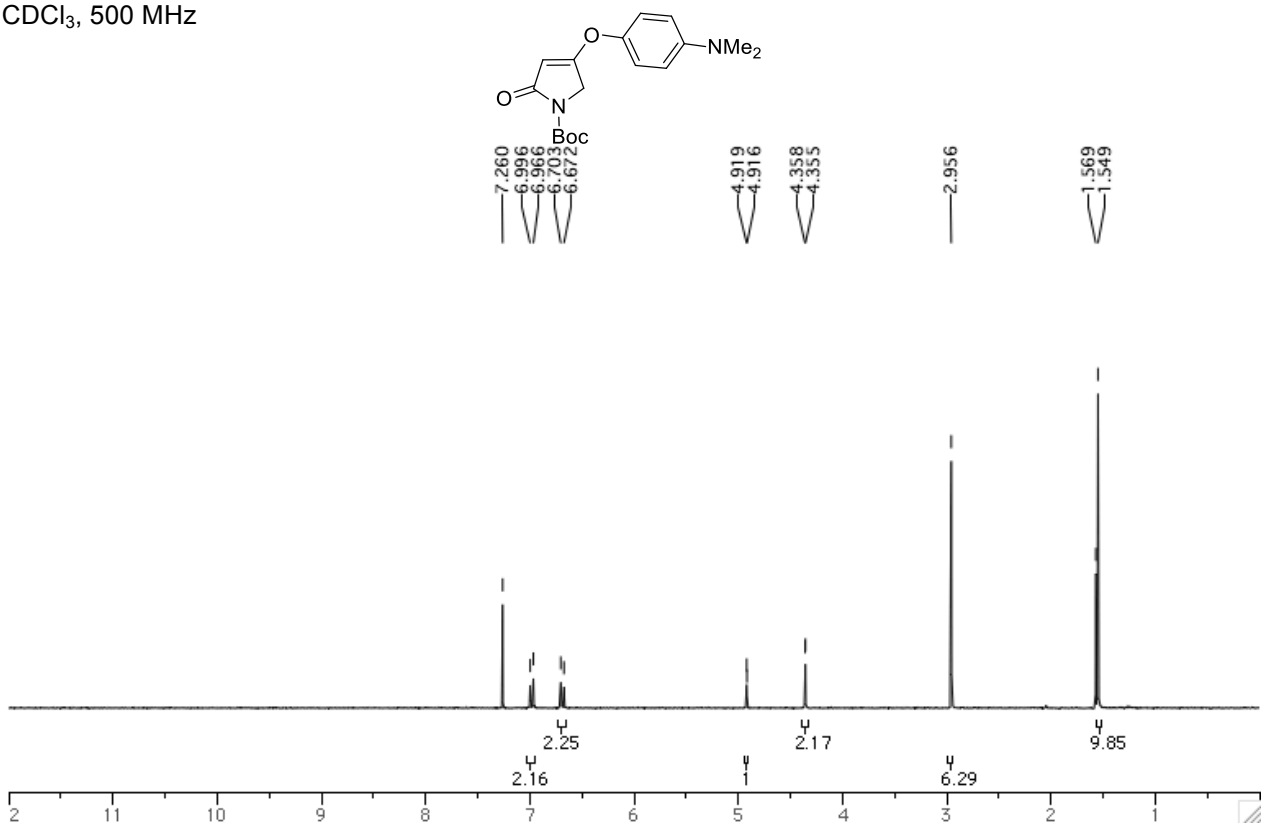
^{1}H NMR for **10d**
$CDCl_3$, 500 MHz



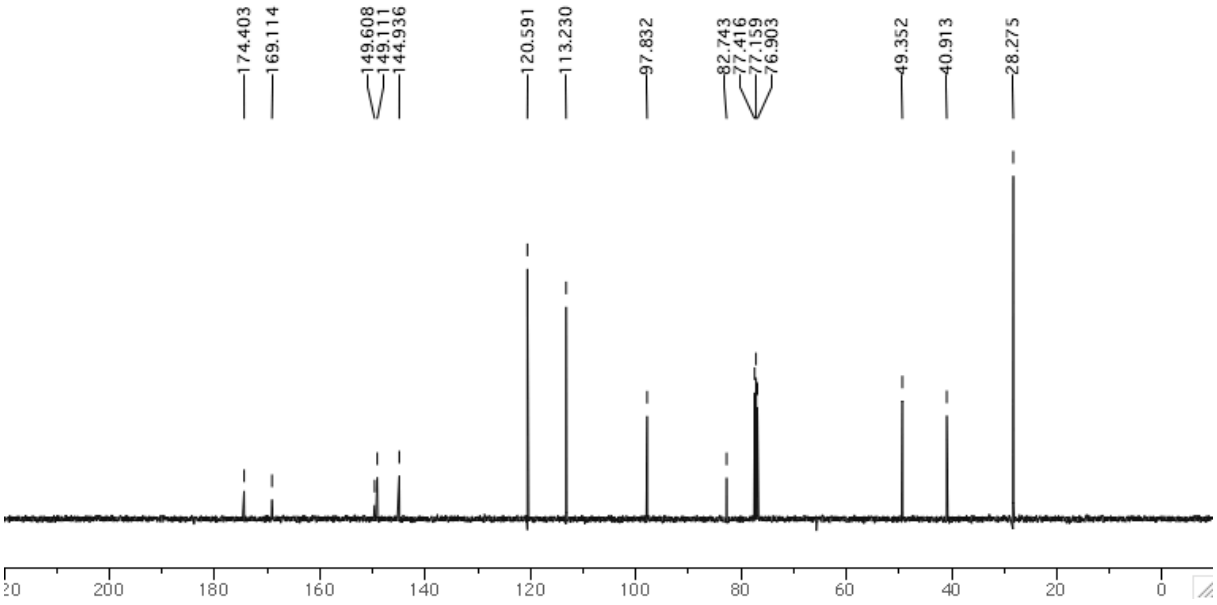
^{13}C NMR for **10d**
$CDCl_3$, 125 MHz



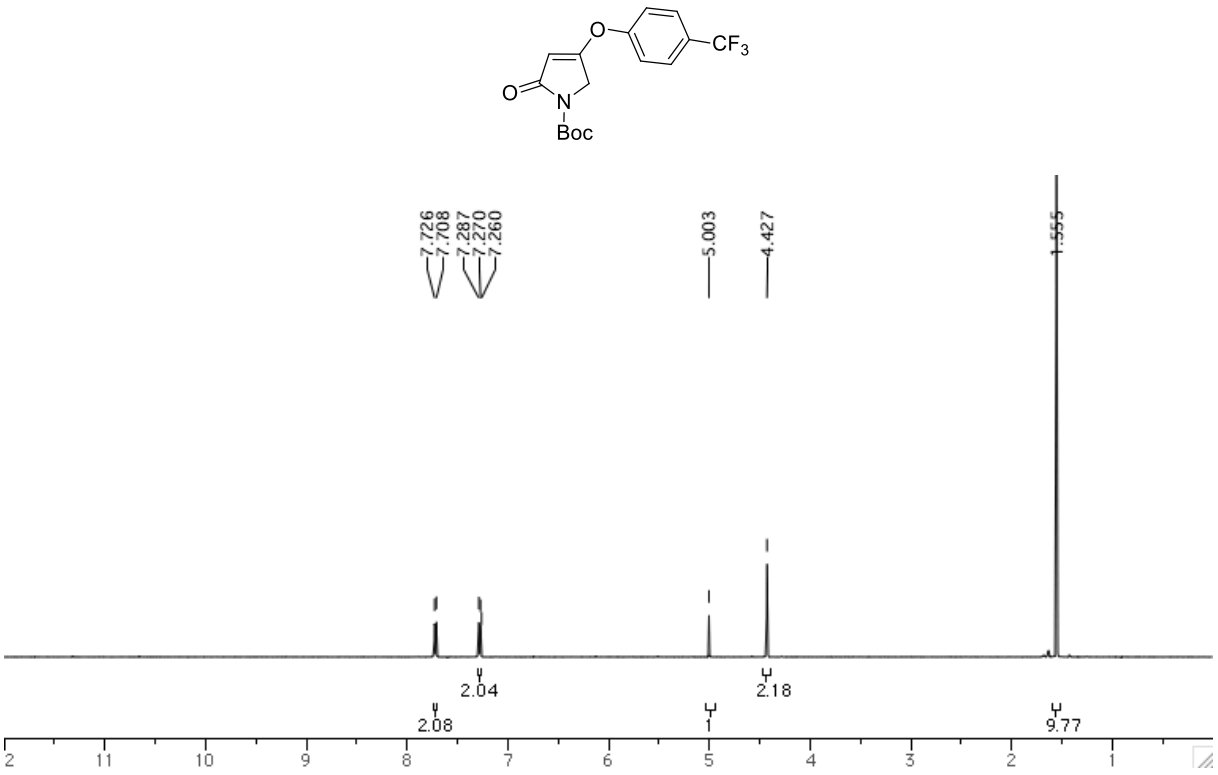
^{1}H NMR for **10e**
$CDCl_3$, 500 MHz



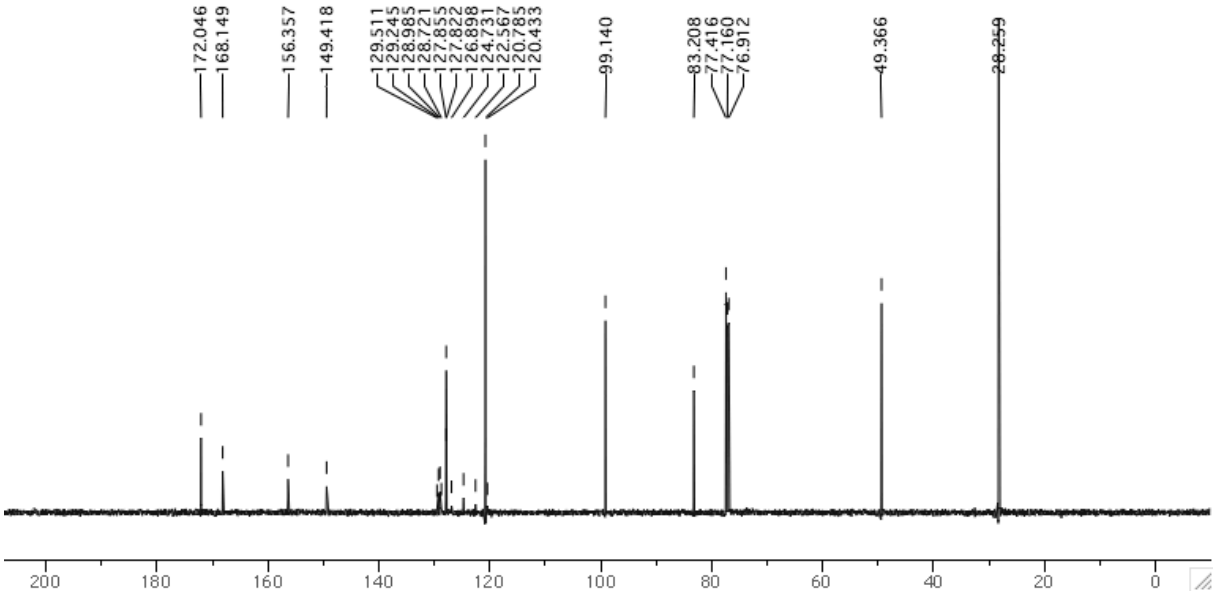
^{13}C NMR for **10e**
$CDCl_3$, 125 MHz



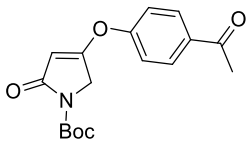
^{1}H NMR for **10f**
$CDCl_3$, 500 MHz

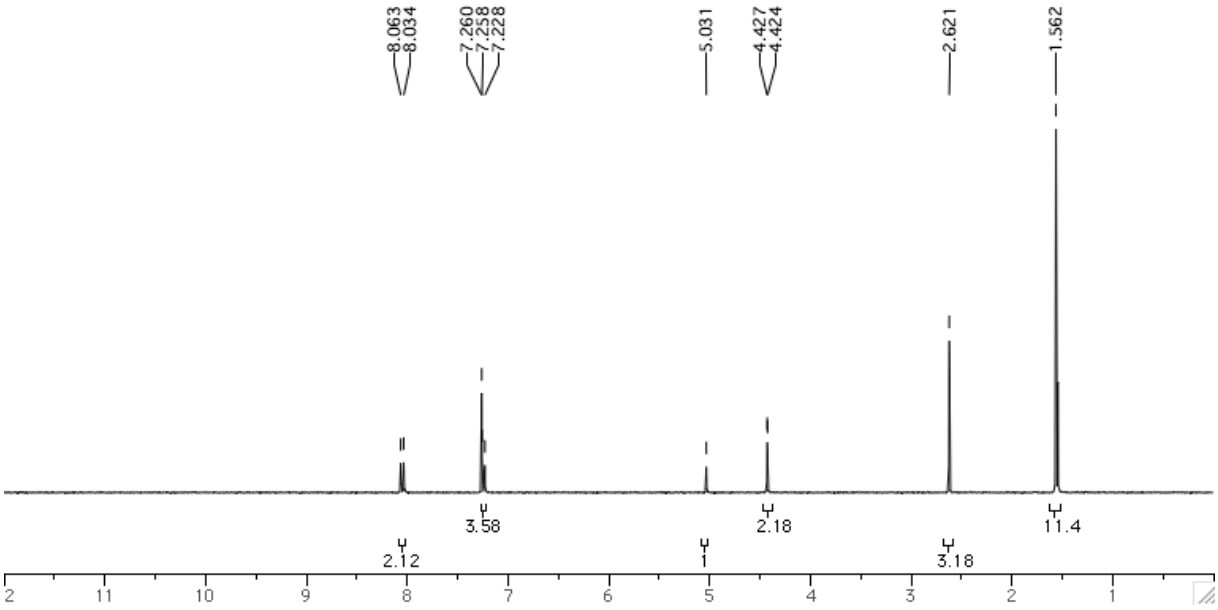


^{13}C NMR for **10f**
$CDCl_3$, 125 MHz

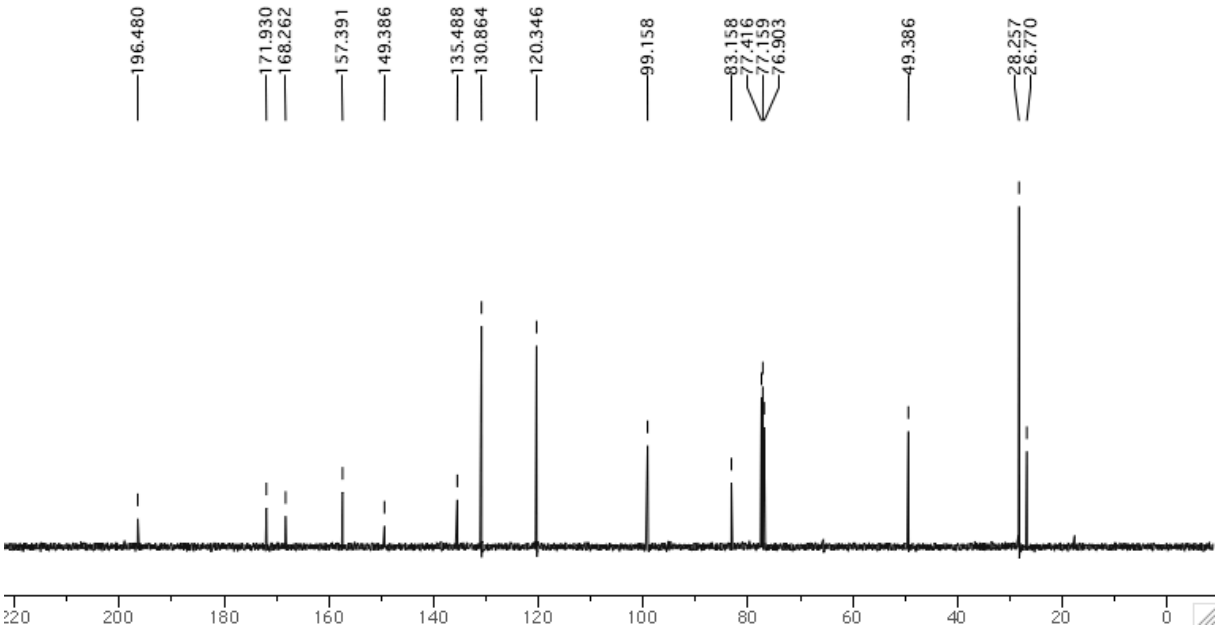


^{1}H NMR for **10g**
$CDCl_3$, 500 MHz

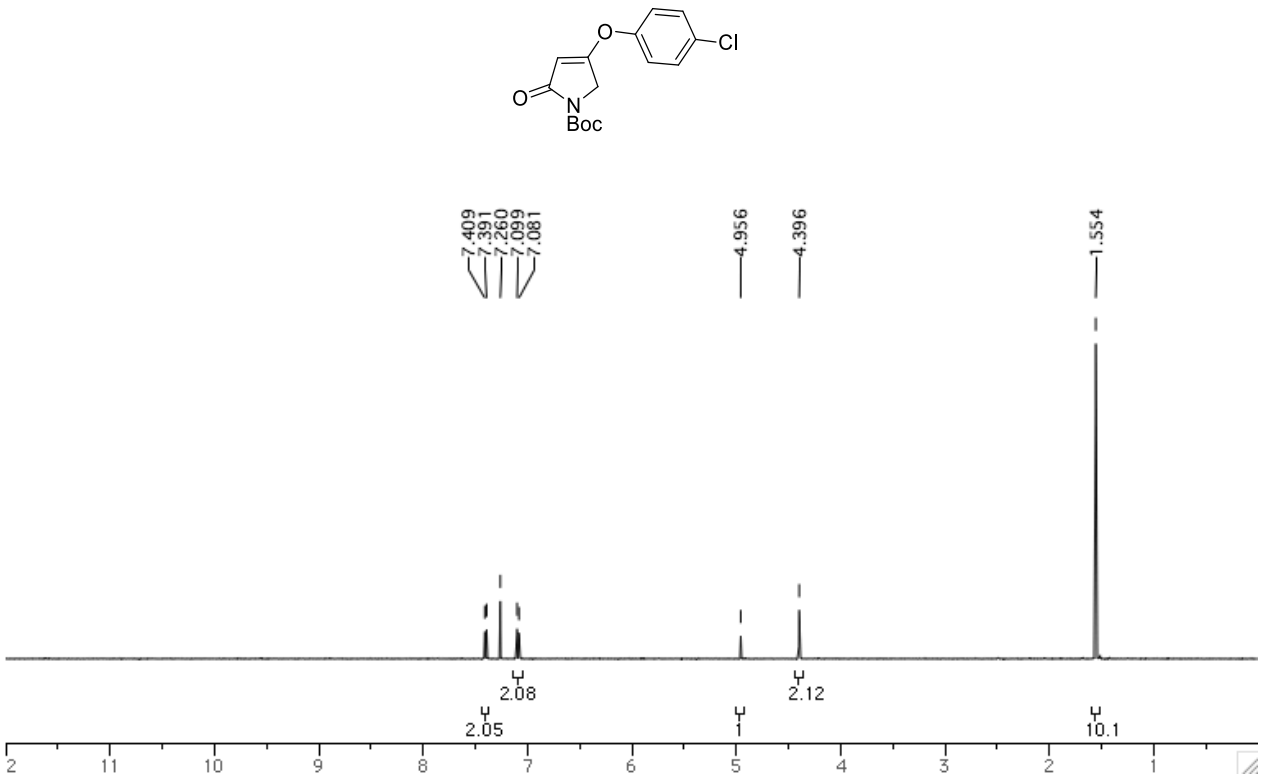




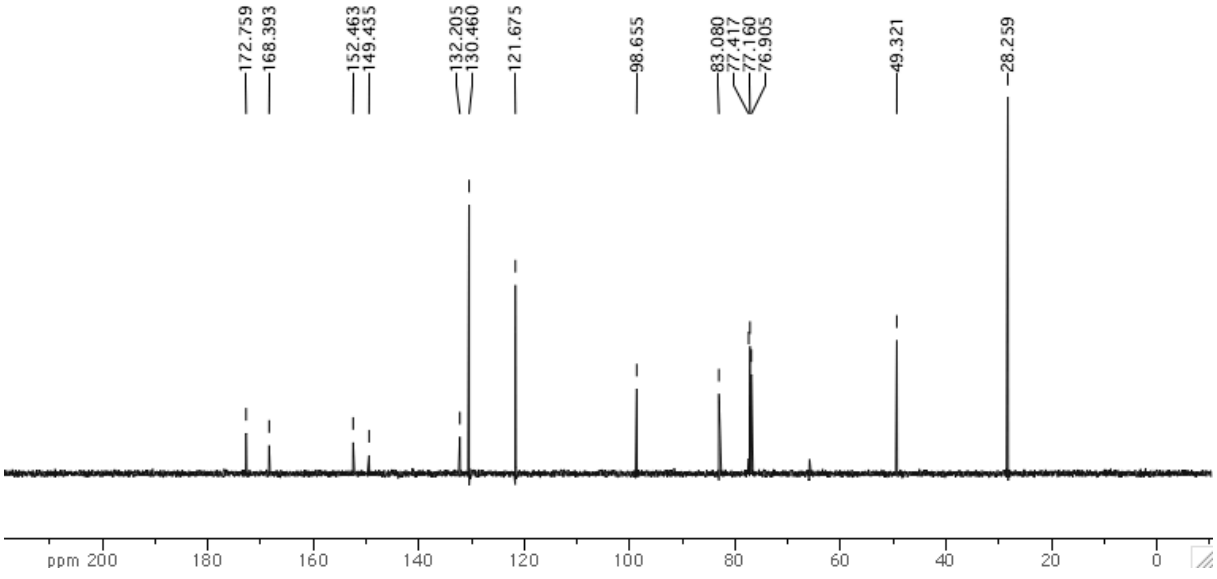
^{13}C NMR for **10g**
$CDCl_3$, 125 MHz



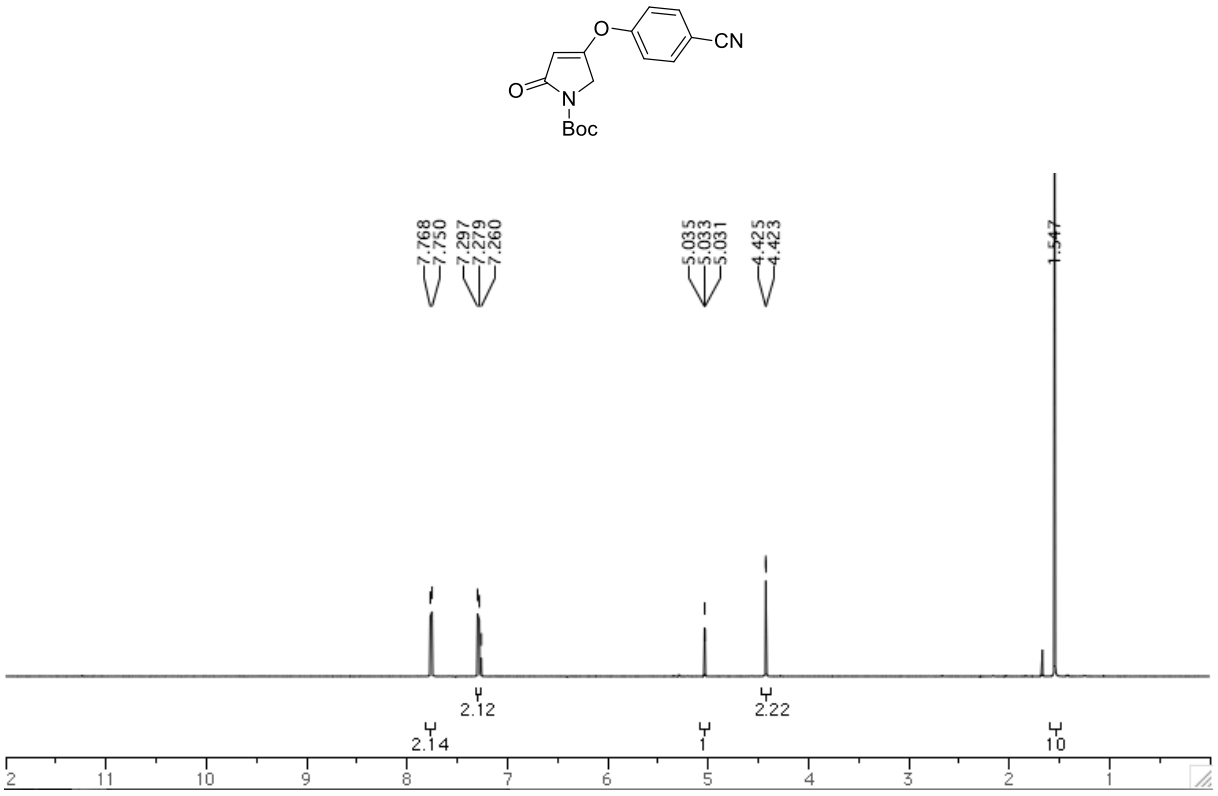
^{1}H NMR for **10h**
$CDCl_3$, 500 MHz



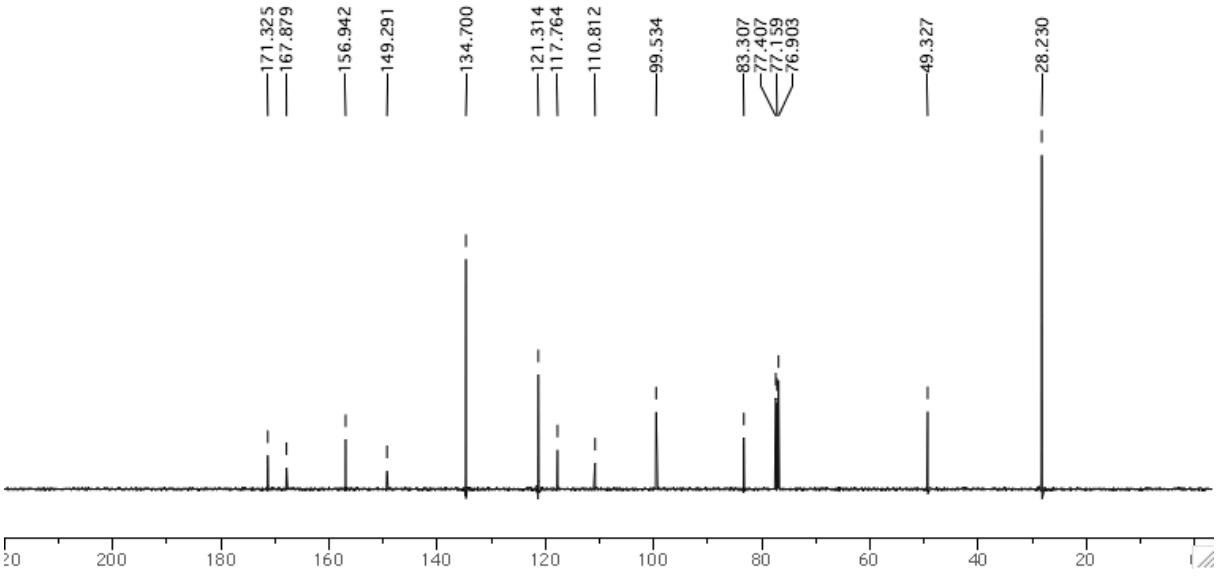
^{13}C NMR for **10h**
$CDCl_3$, 125 MHz



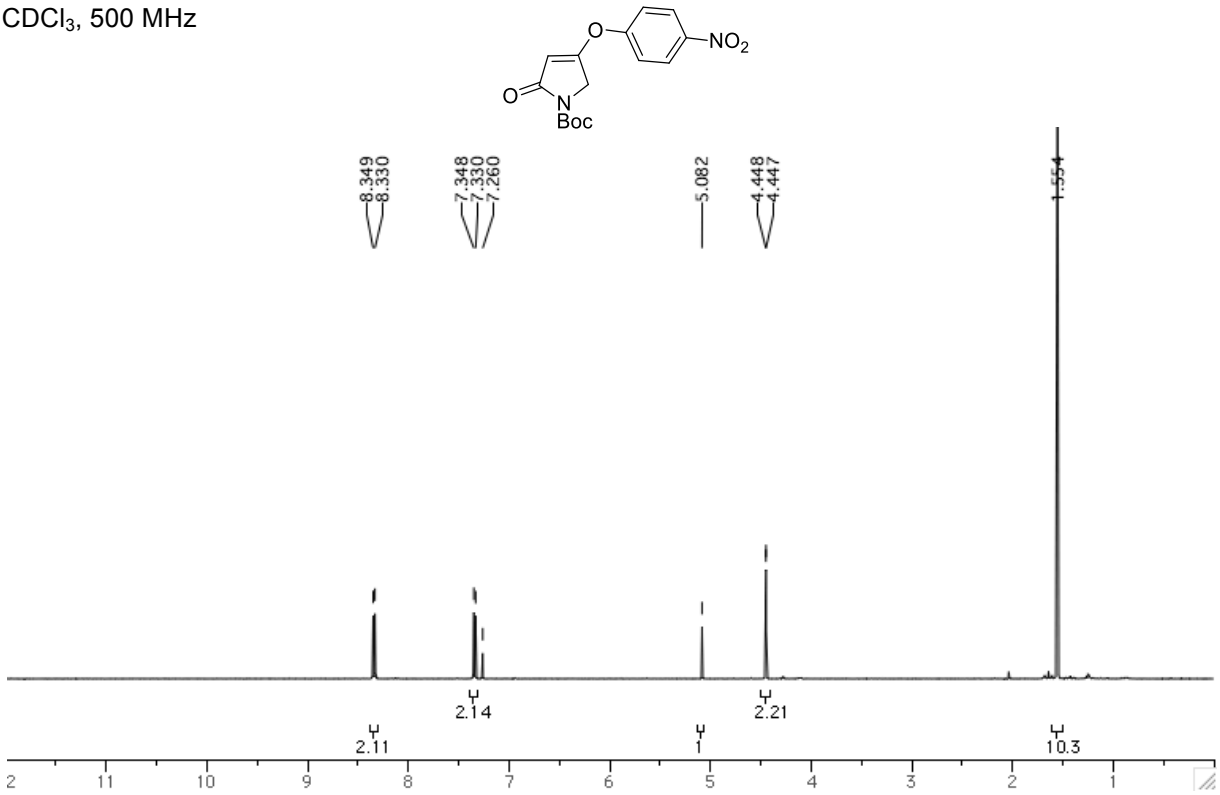
^{1}H NMR for **10i**
$CDCl_3$, 500 MHz



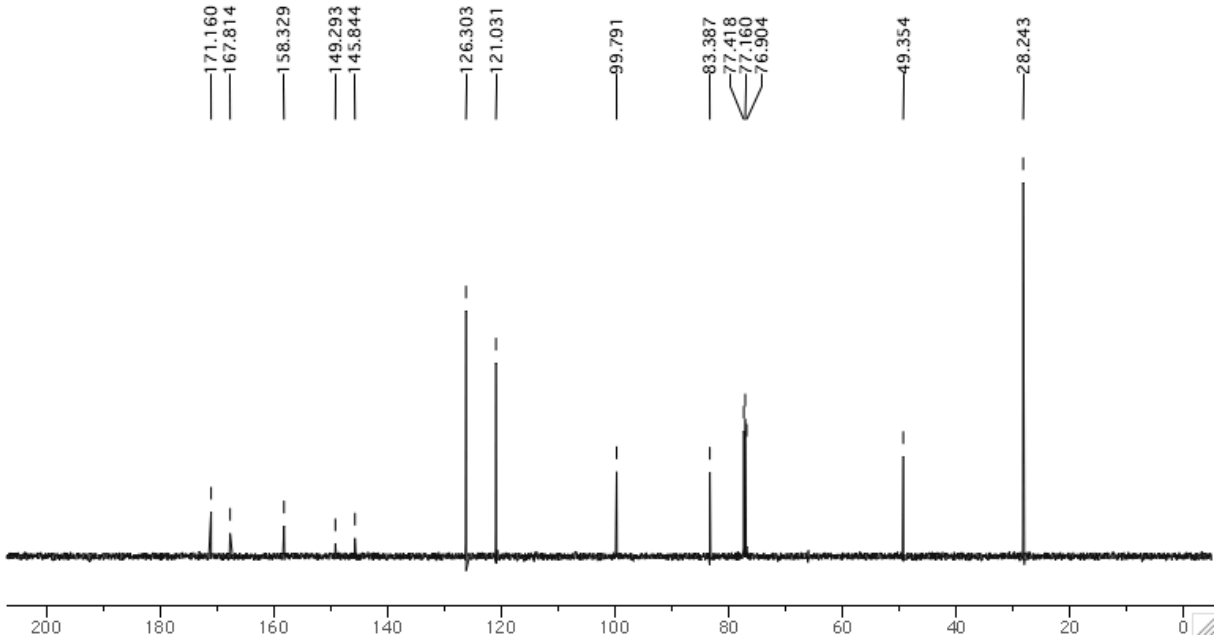
^{13}C NMR for **10i**
$CDCl_3$, 125 MHz



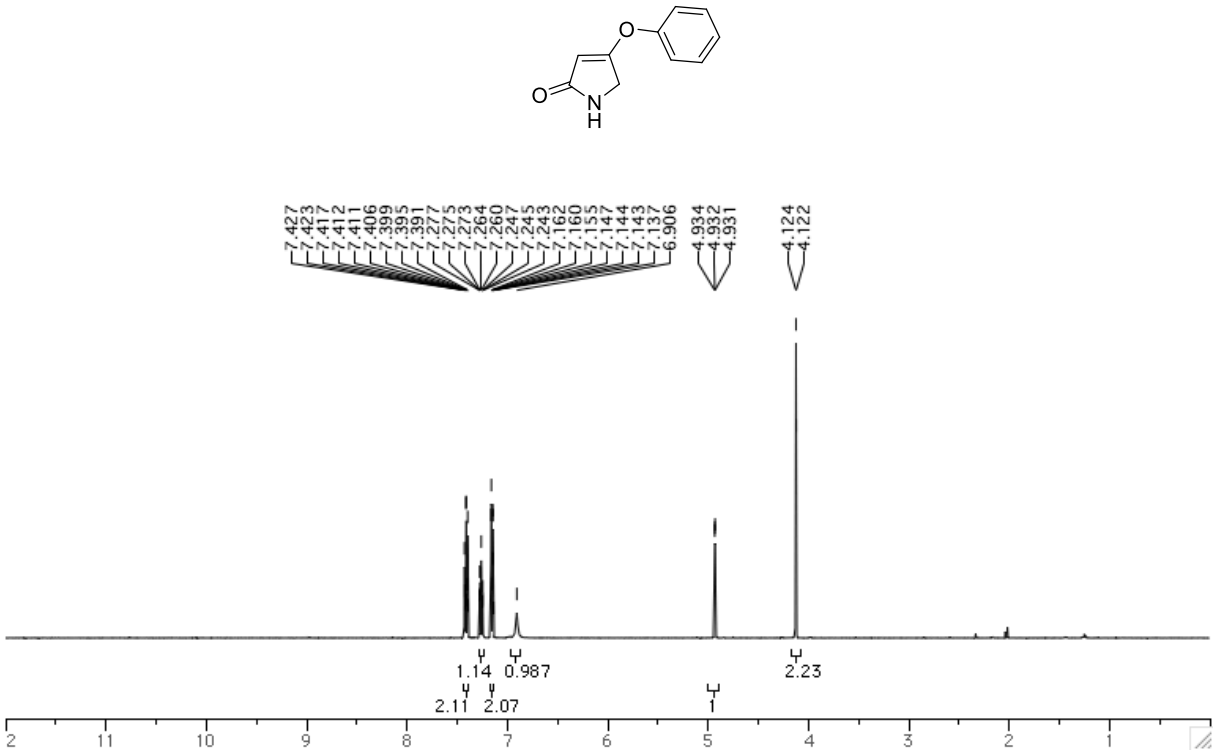
^{1}H NMR for **10j**
$CDCl_3$, 500 MHz



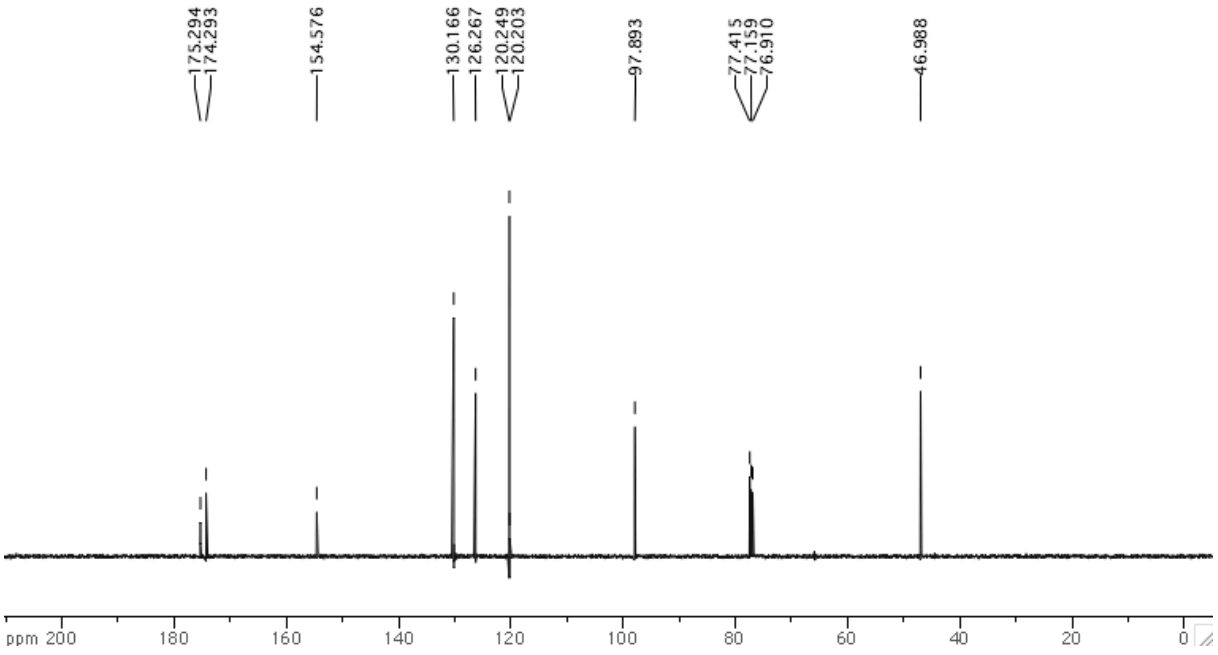
^{13}C NMR for **10j**
$CDCl_3$, 125 MHz



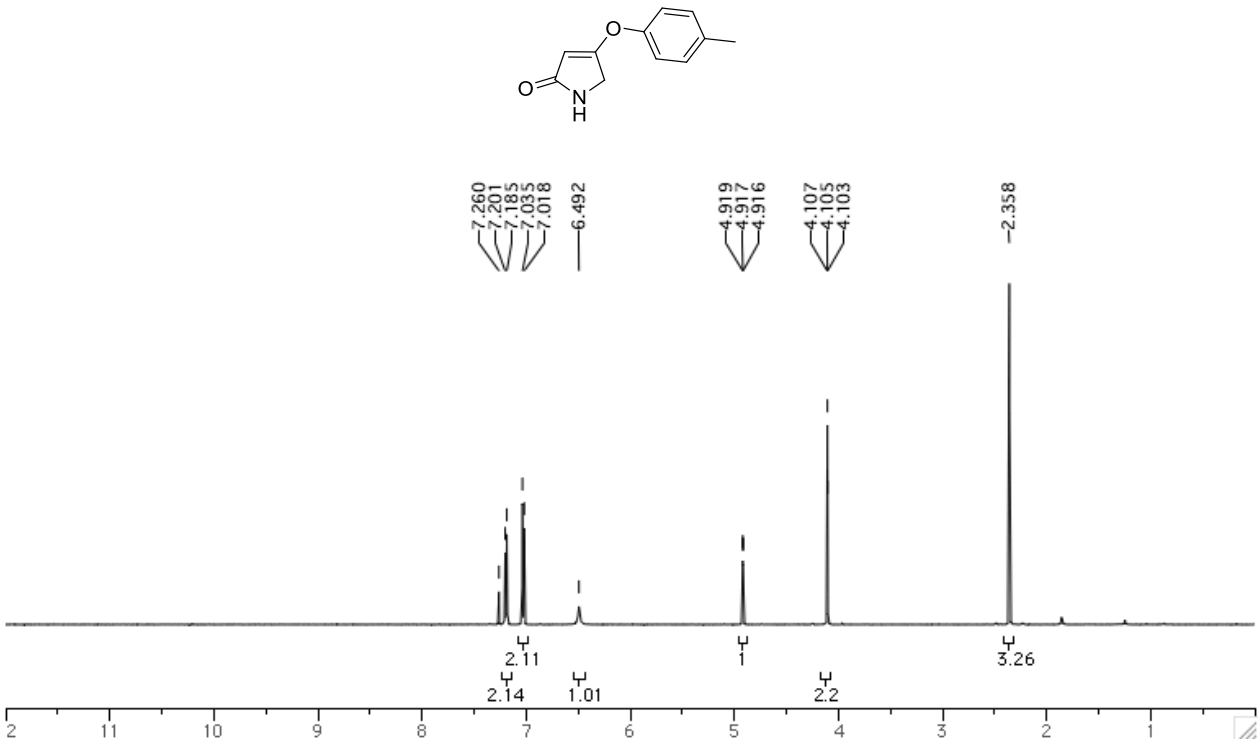
^{1}H NMR for **8b**
$CDCl_3$, 500 MHz



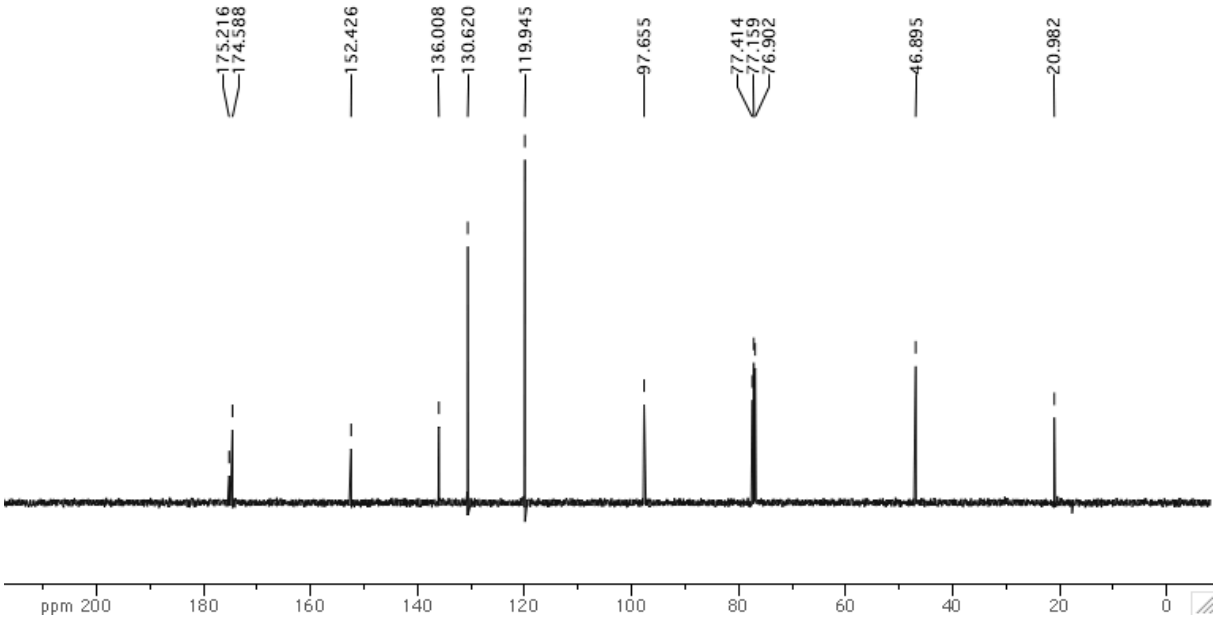
^{13}C NMR for **8b**
$CDCl_3$, 125 MHz



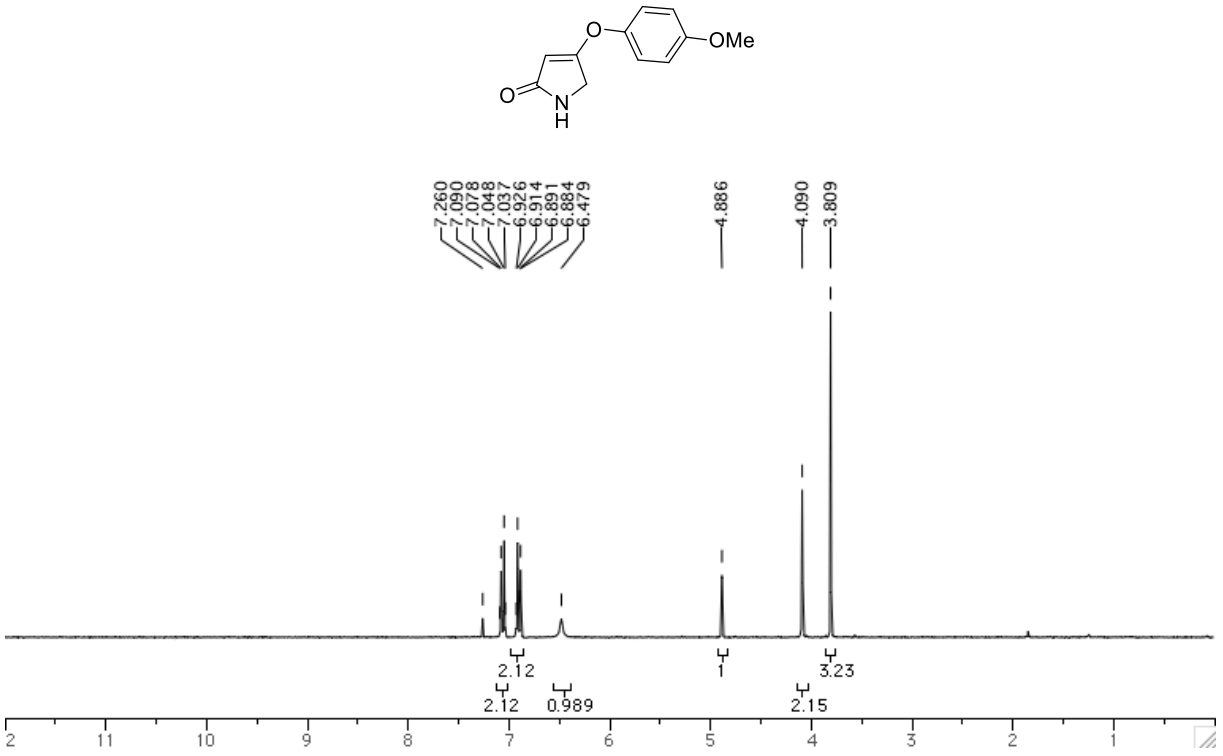
^{1}H NMR for **8c**
$CDCl_3$, 500 MHz



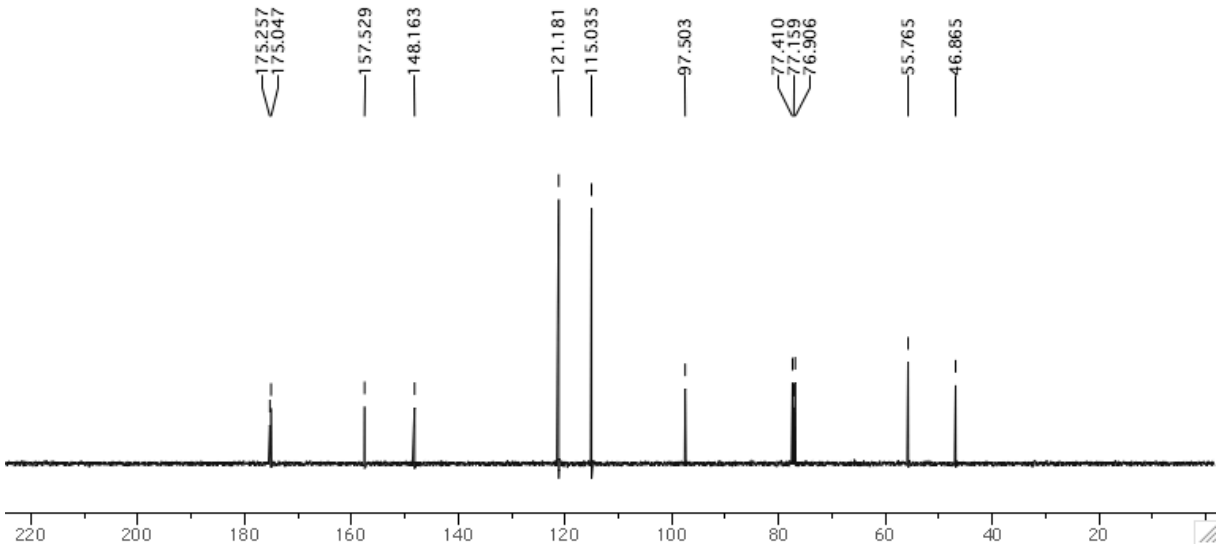
^{13}C NMR for **8c**
$CDCl_3$, 125 MHz



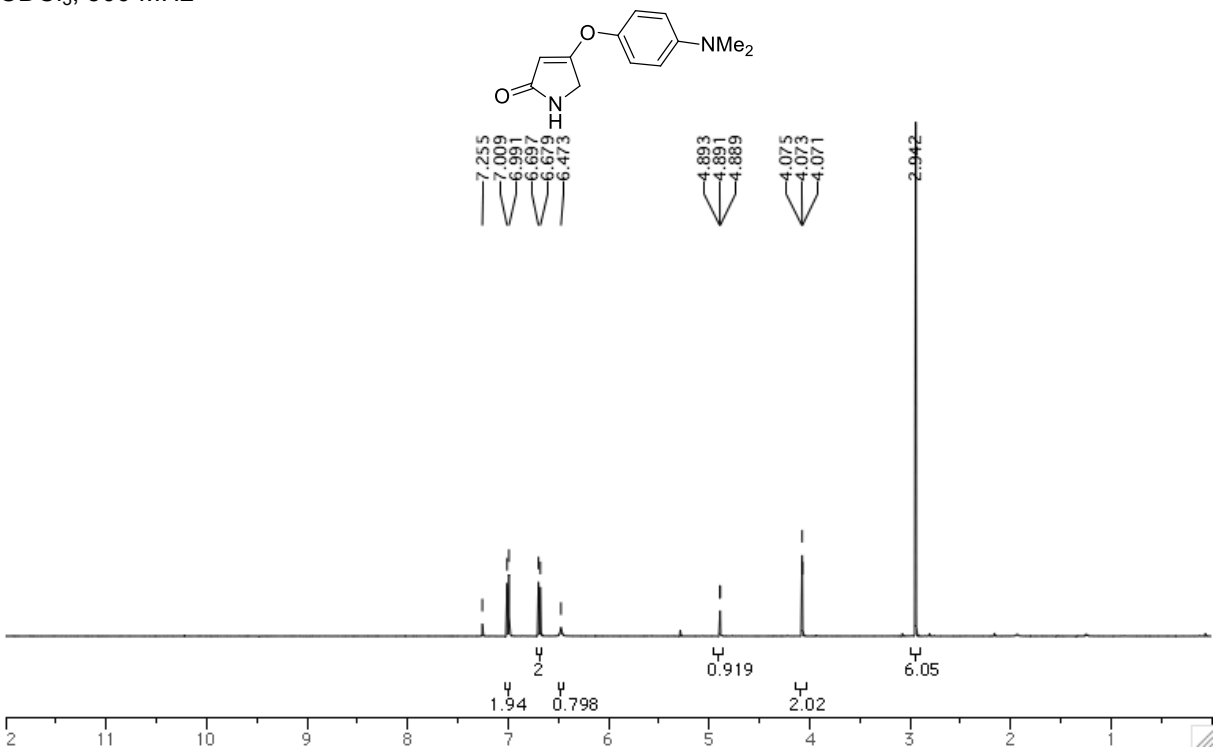
^{1}H NMR for **8d**
$CDCl_3$, 500 MHz



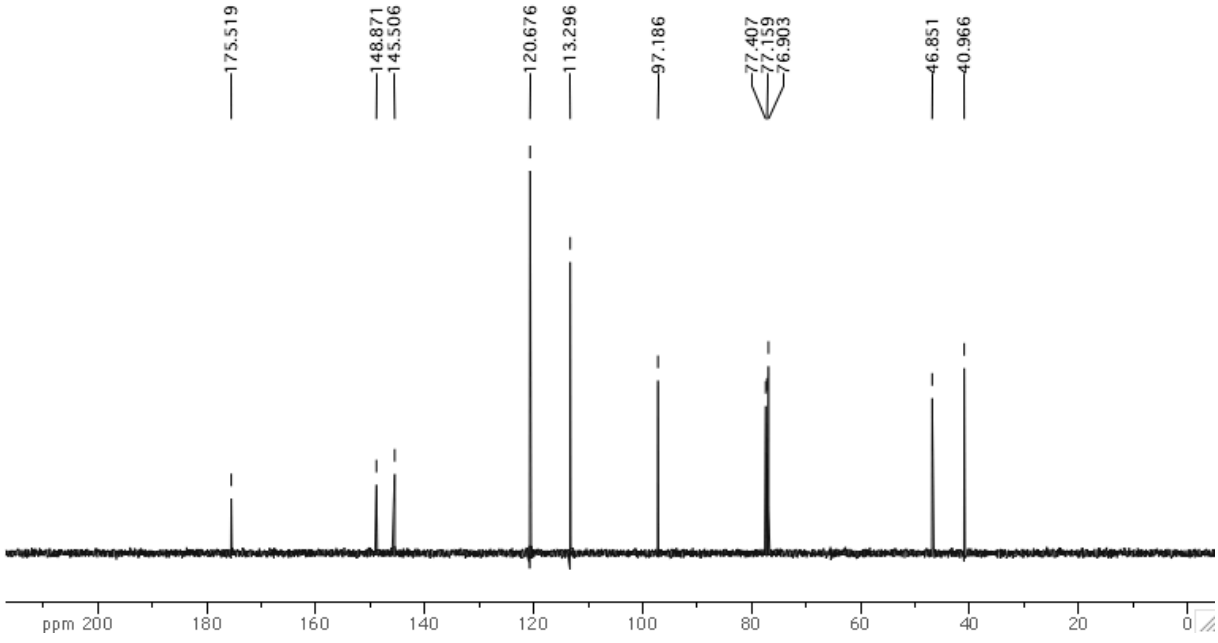
^{13}C NMR for **8d**
$CDCl_3$, 125 MHz



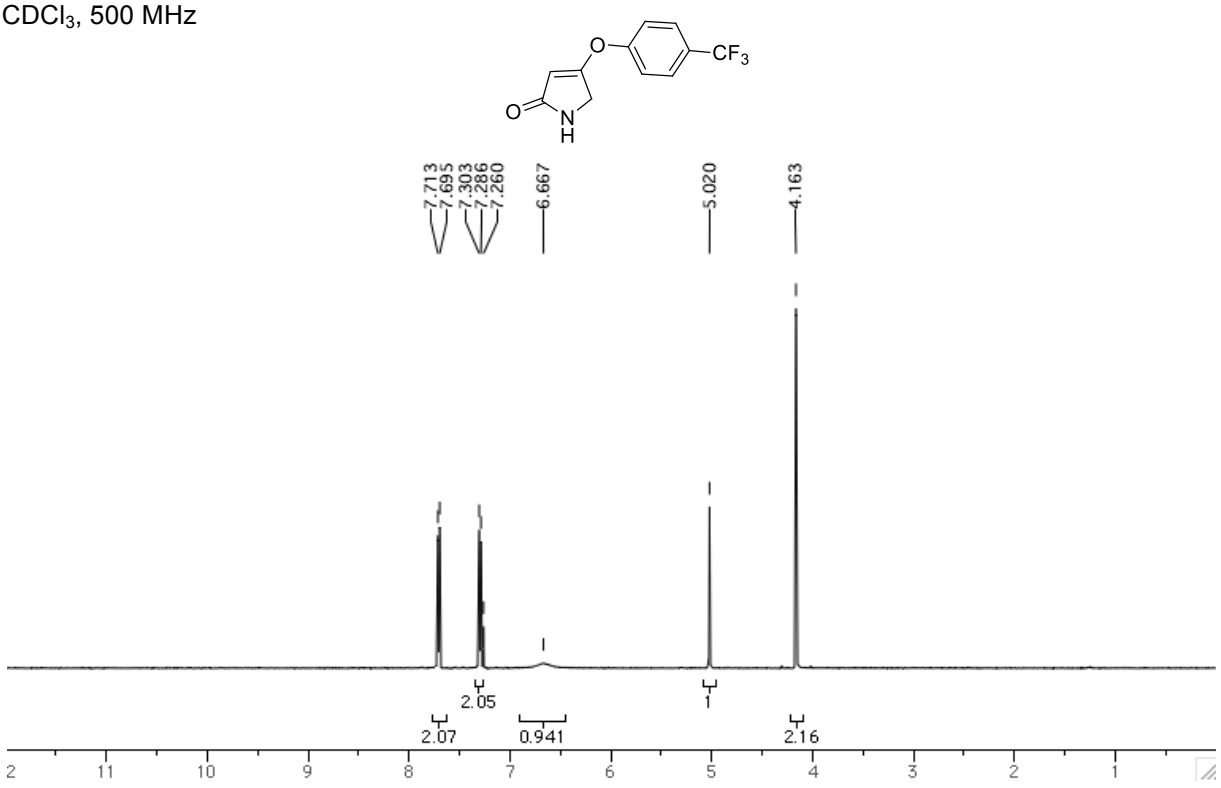
^{1}H NMR for **8e**
$CDCl_3$, 500 MHz



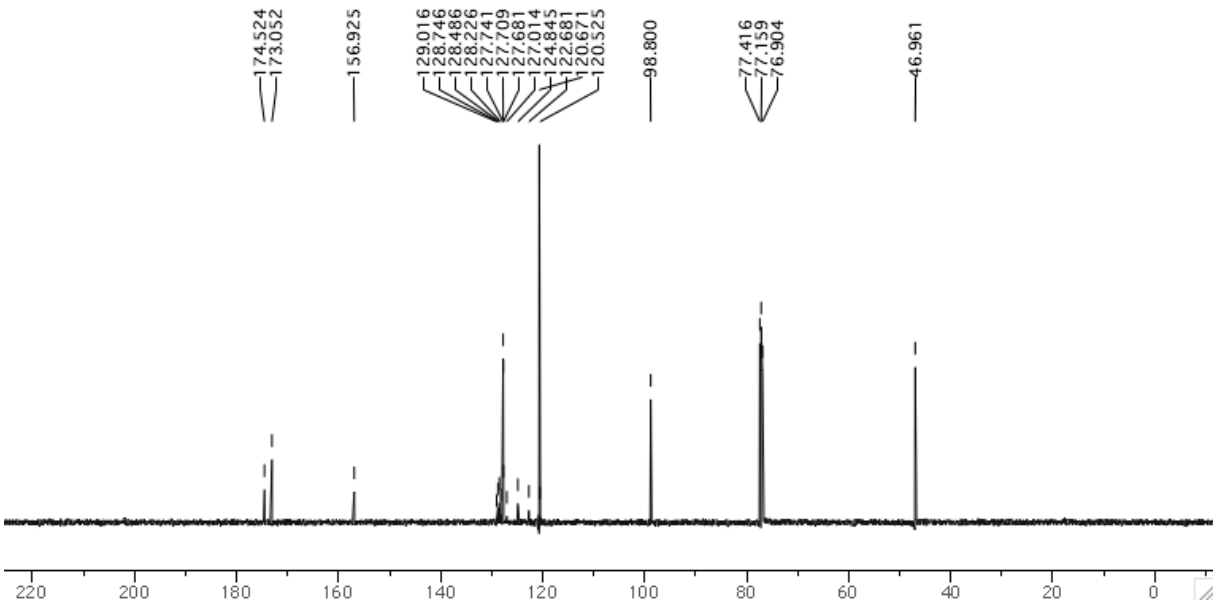
^{13}C NMR for **8e**
$CDCl_3$, 125 MHz



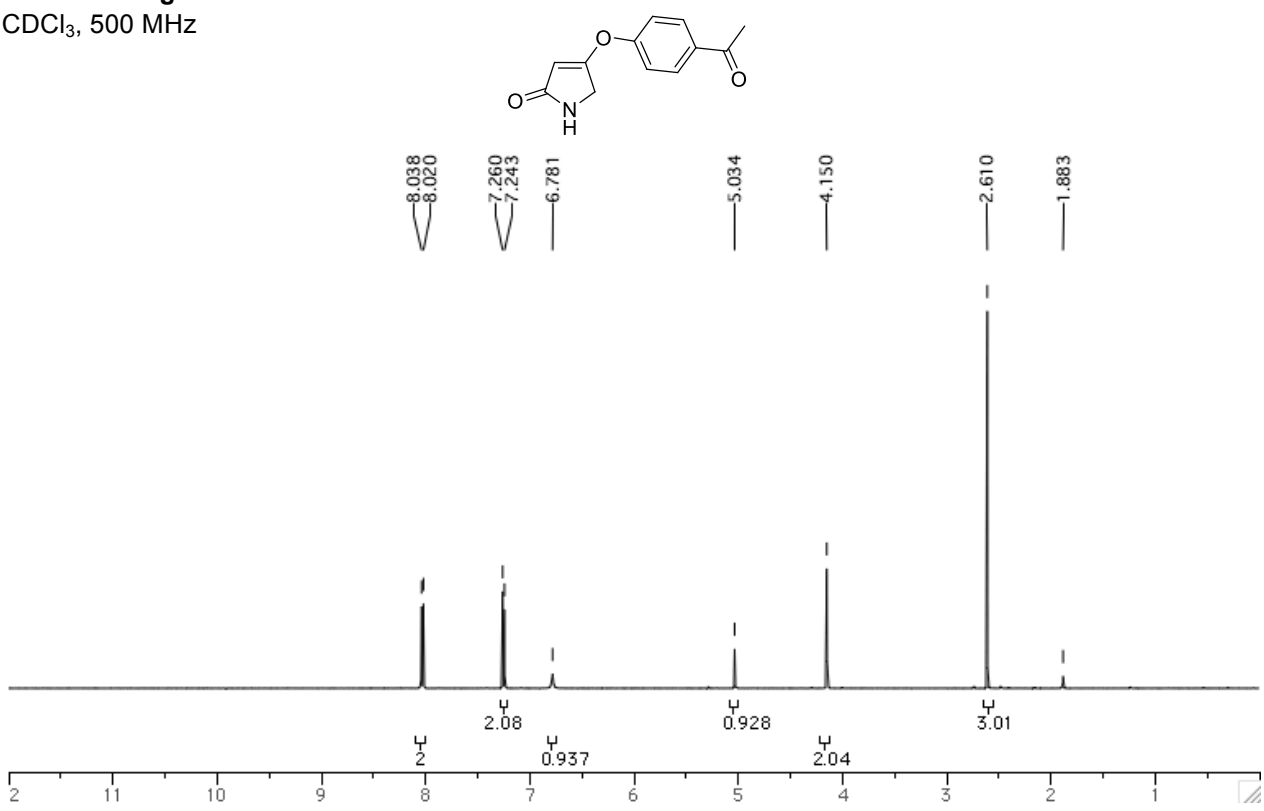
^{1}H NMR for **8f**
$CDCl_3$, 500 MHz



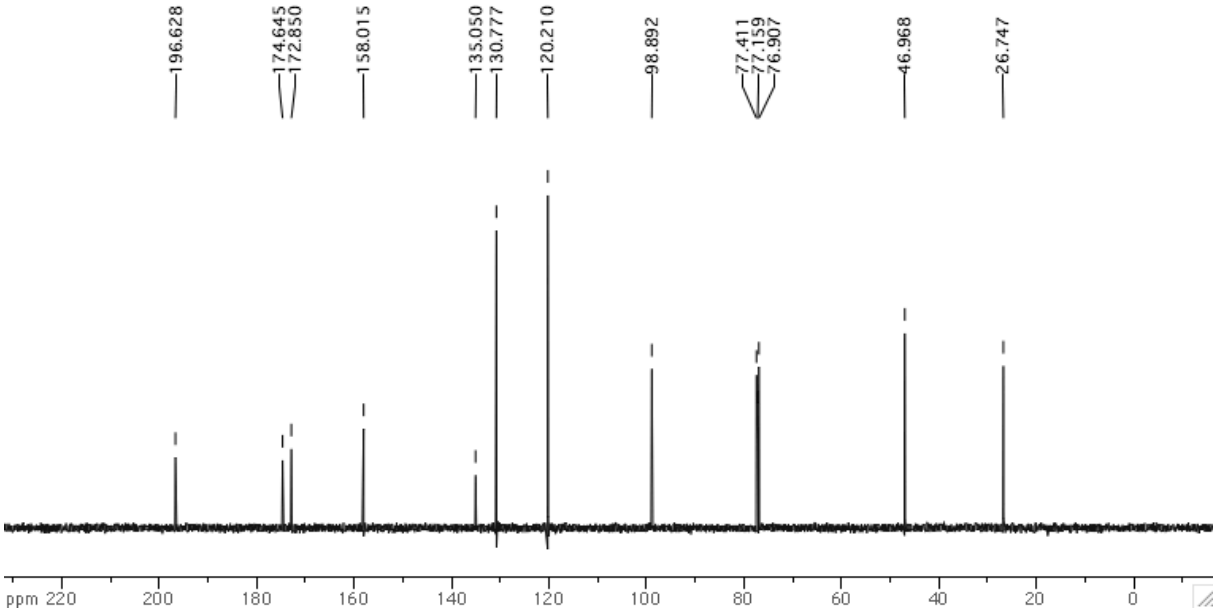
^{13}C NMR for **8f**
$CDCl_3$, 125 MHz



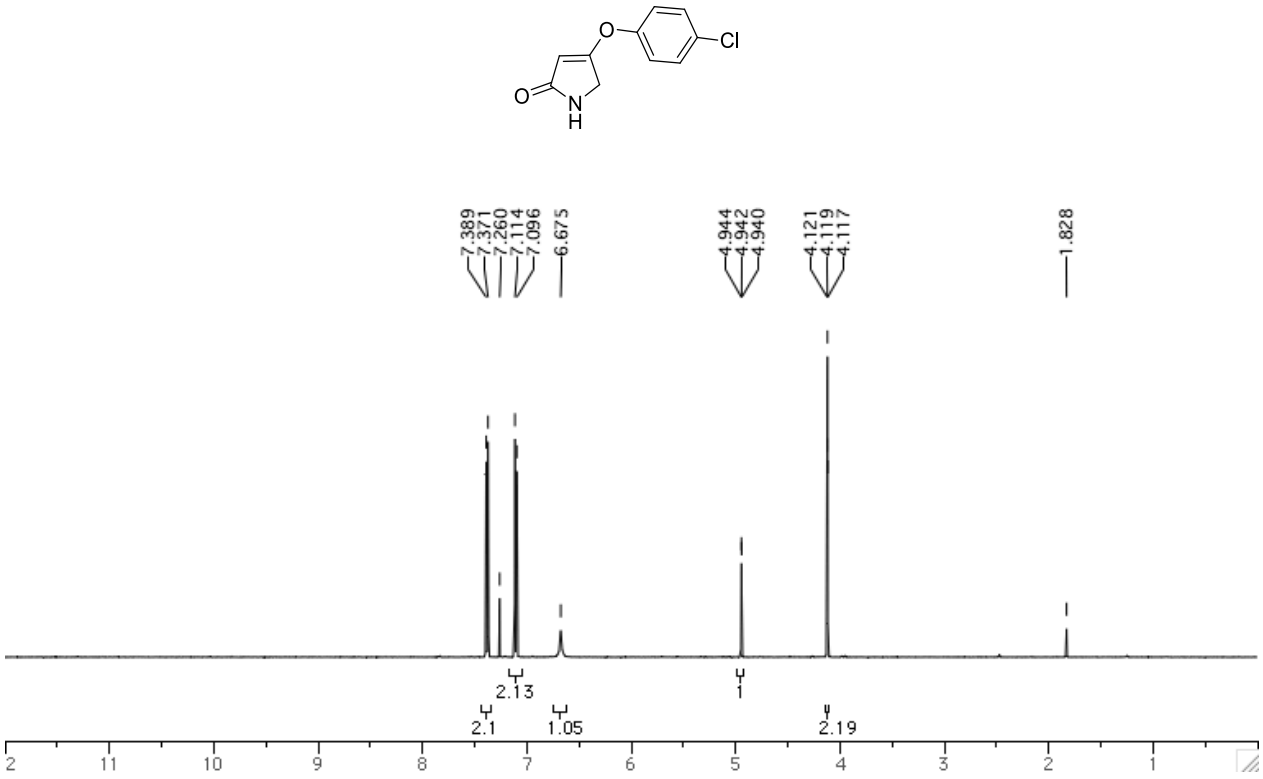
^{1}H NMR for **8g**
$CDCl_3$, 500 MHz



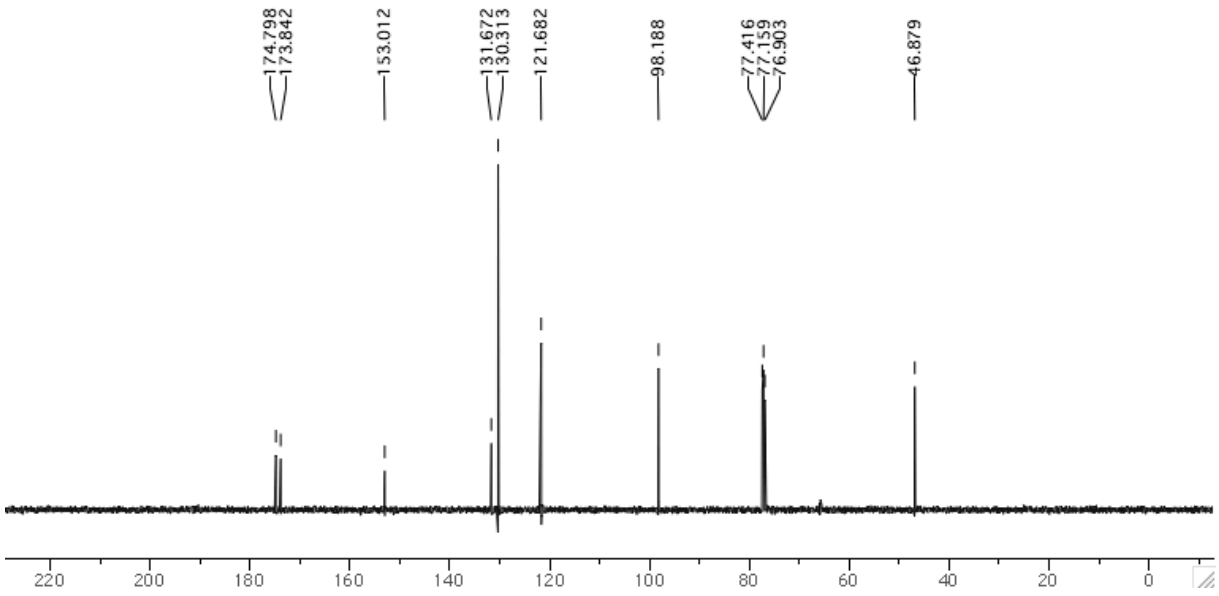
^{13}C NMR for **8g**
$CDCl_3$, 125 MHz



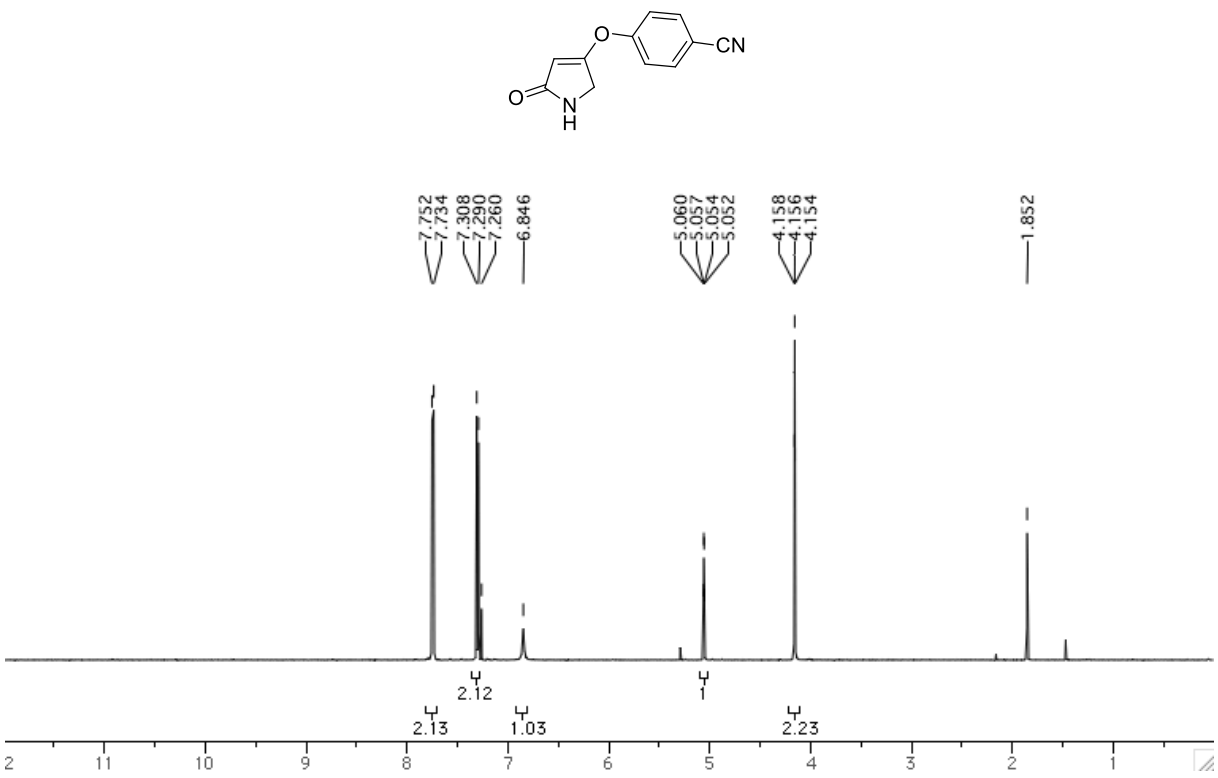
^{1}H NMR for **8h**
$CDCl_3$, 500 MHz



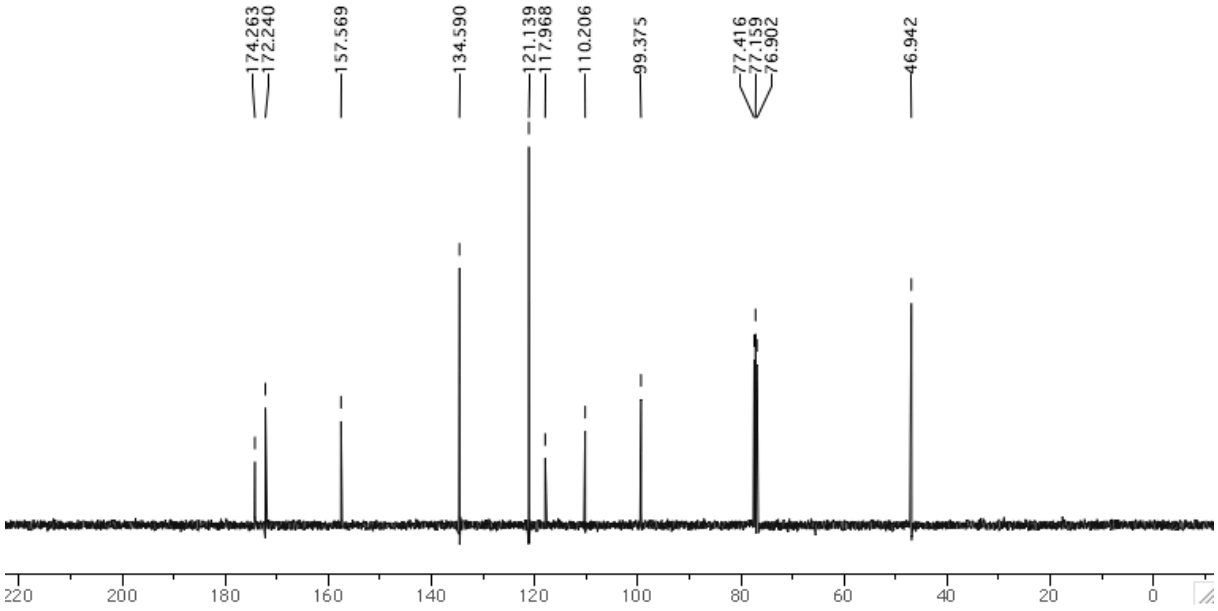
^{13}C NMR for **8h**
$CDCl_3$, 125 MHz



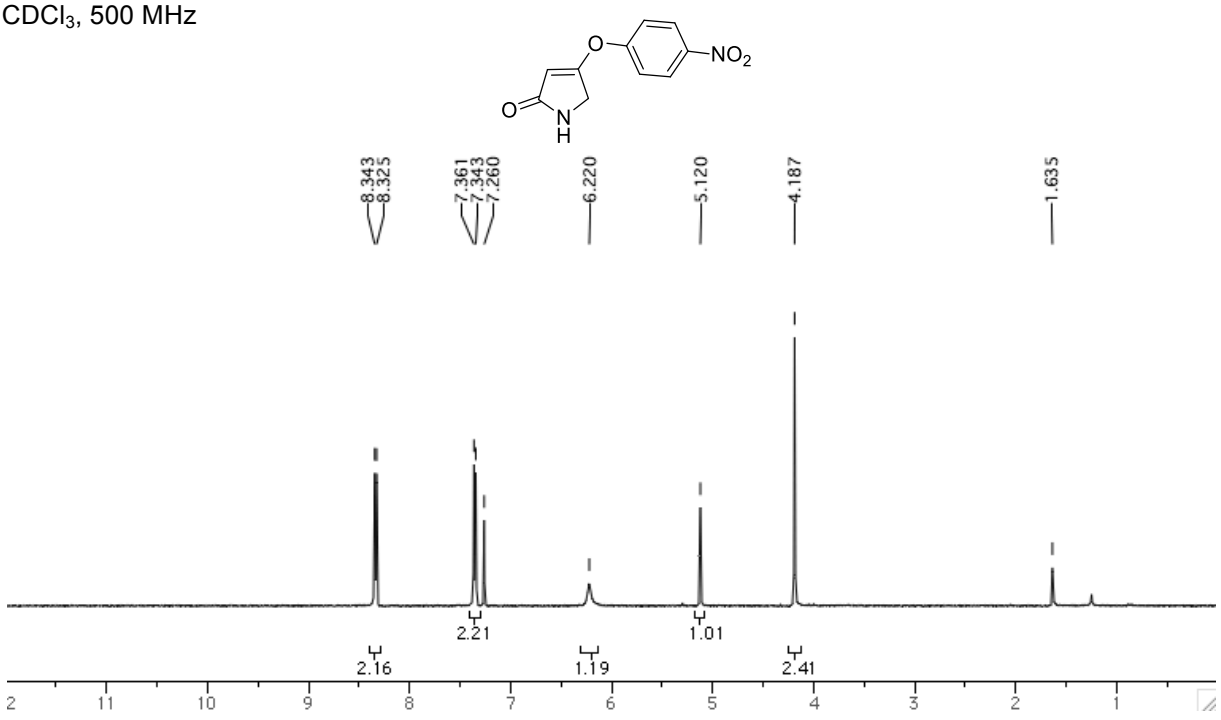
^{1}H NMR for **8i**
$CDCl_3$, 500 MHz



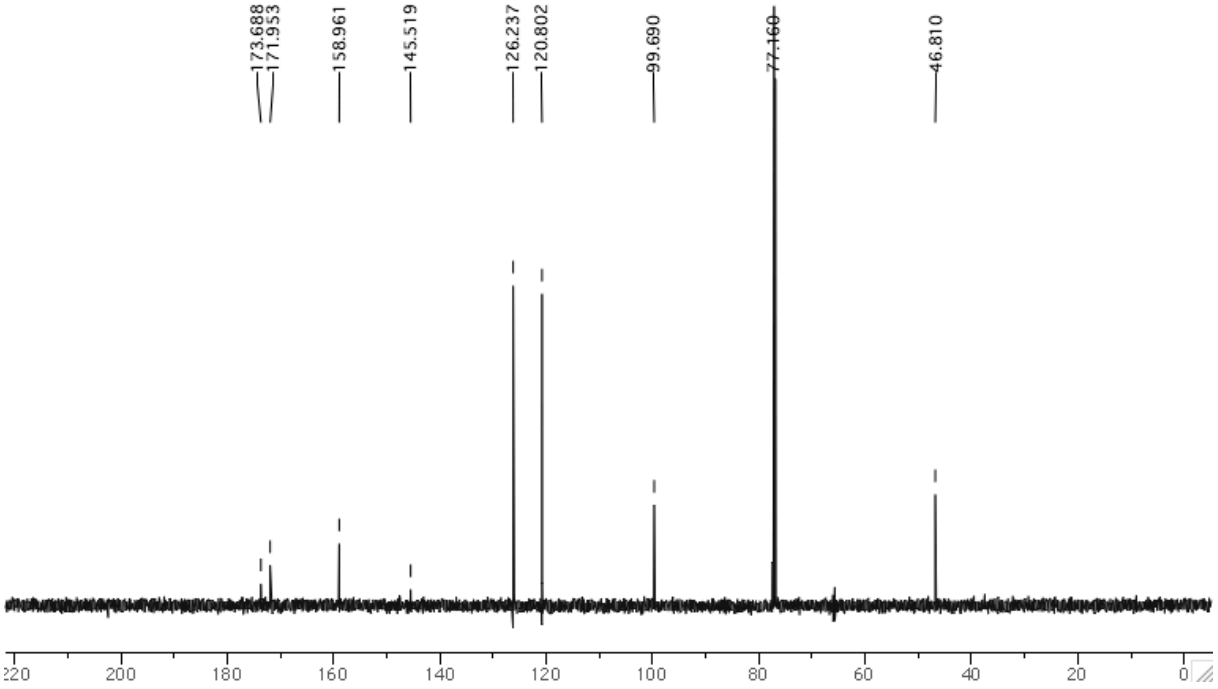
^{13}C NMR for **8i**
$CDCl_3$, 125 MHz



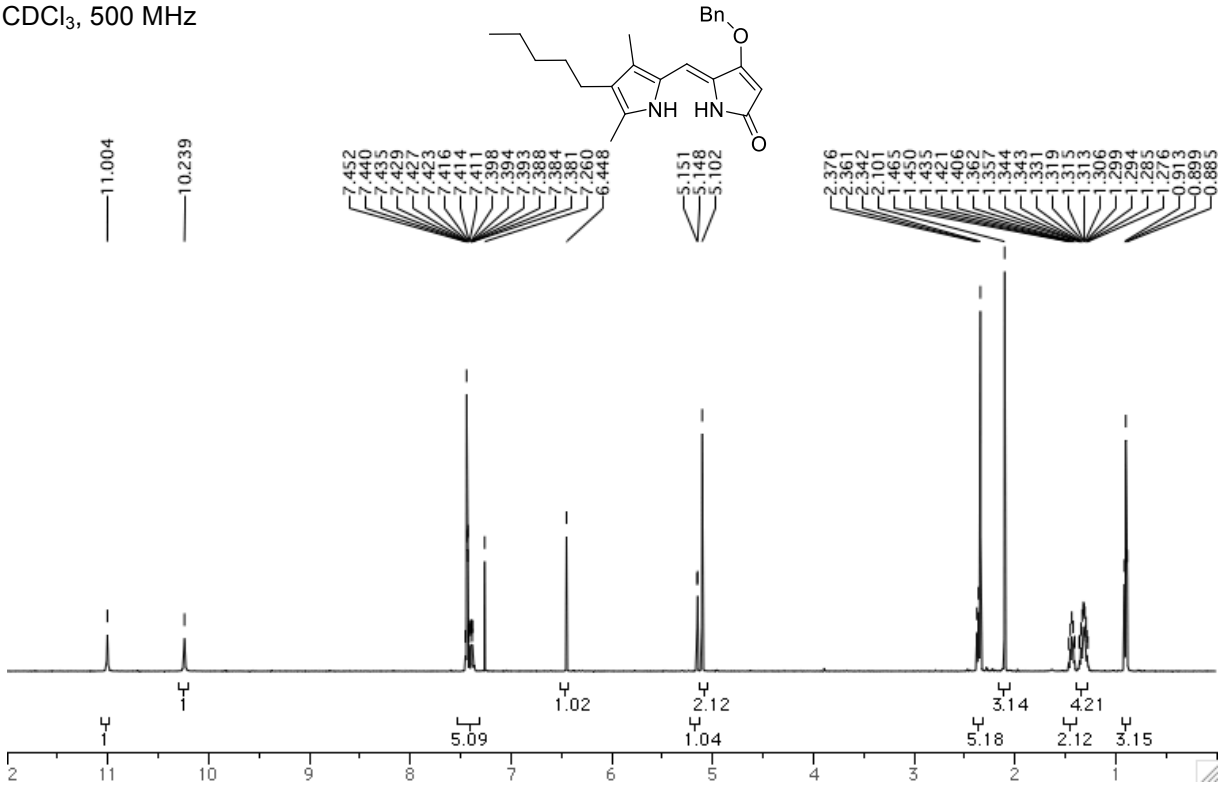
^{1}H NMR for **8j**
$CDCl_3$, 500 MHz



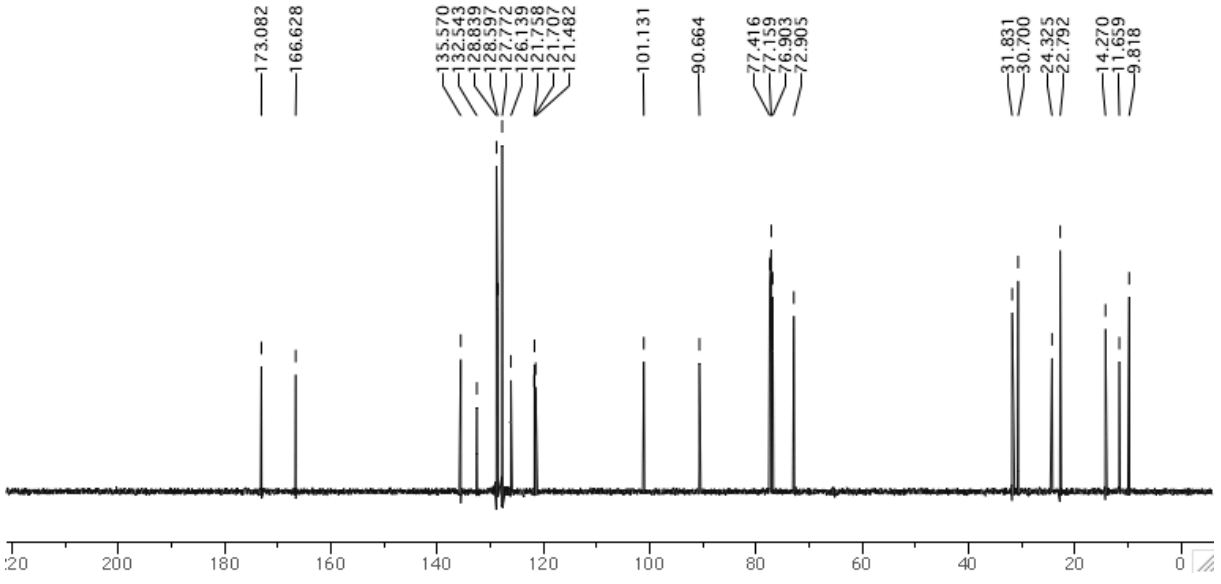
^{13}C NMR for **8j**
$CDCl_3$, 125 MHz



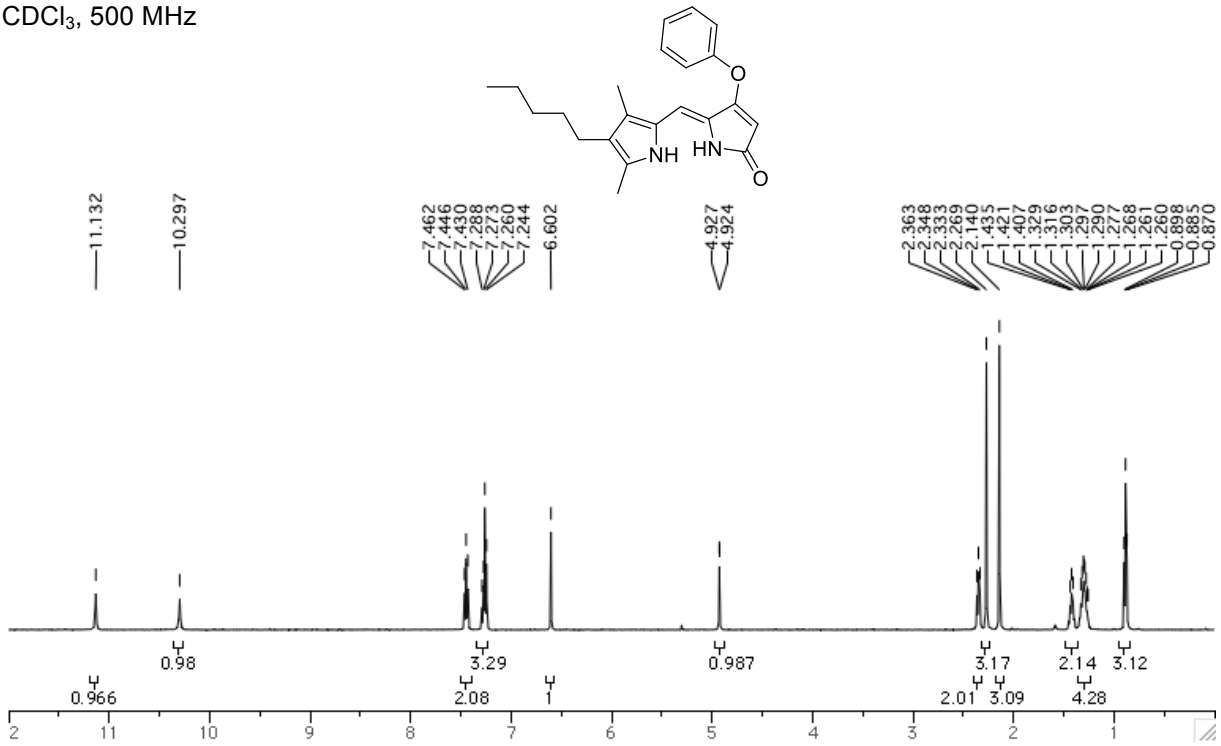
^{1}H NMR for **12a**
$CDCl_3$, 500 MHz



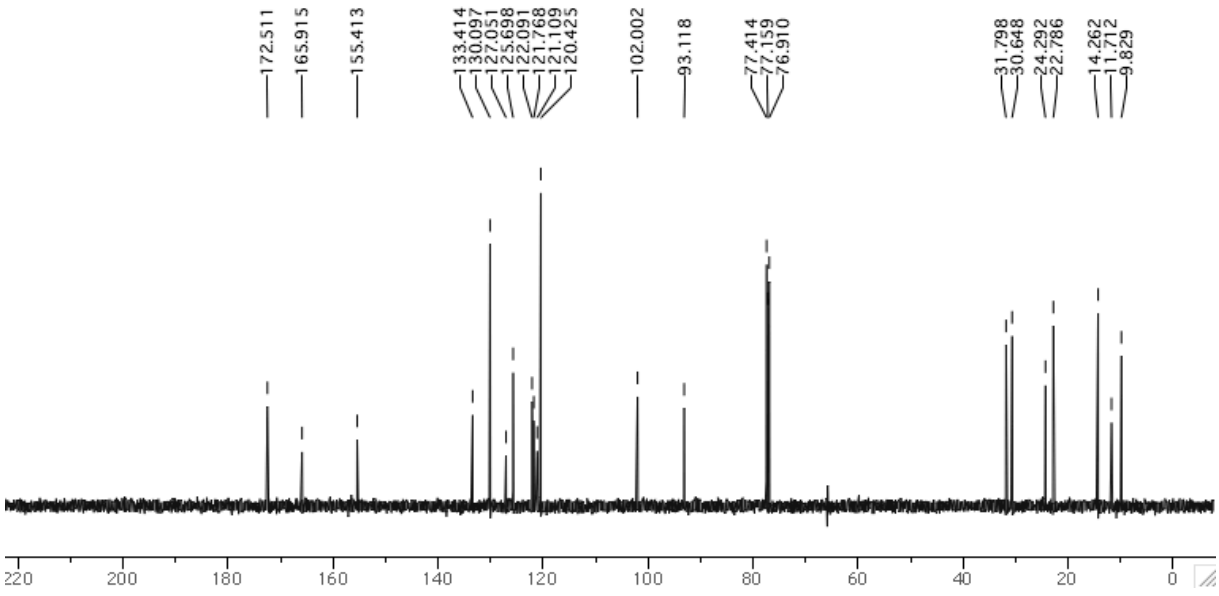
^{13}C NMR for **12a**
$CDCl_3$, 125 MHz



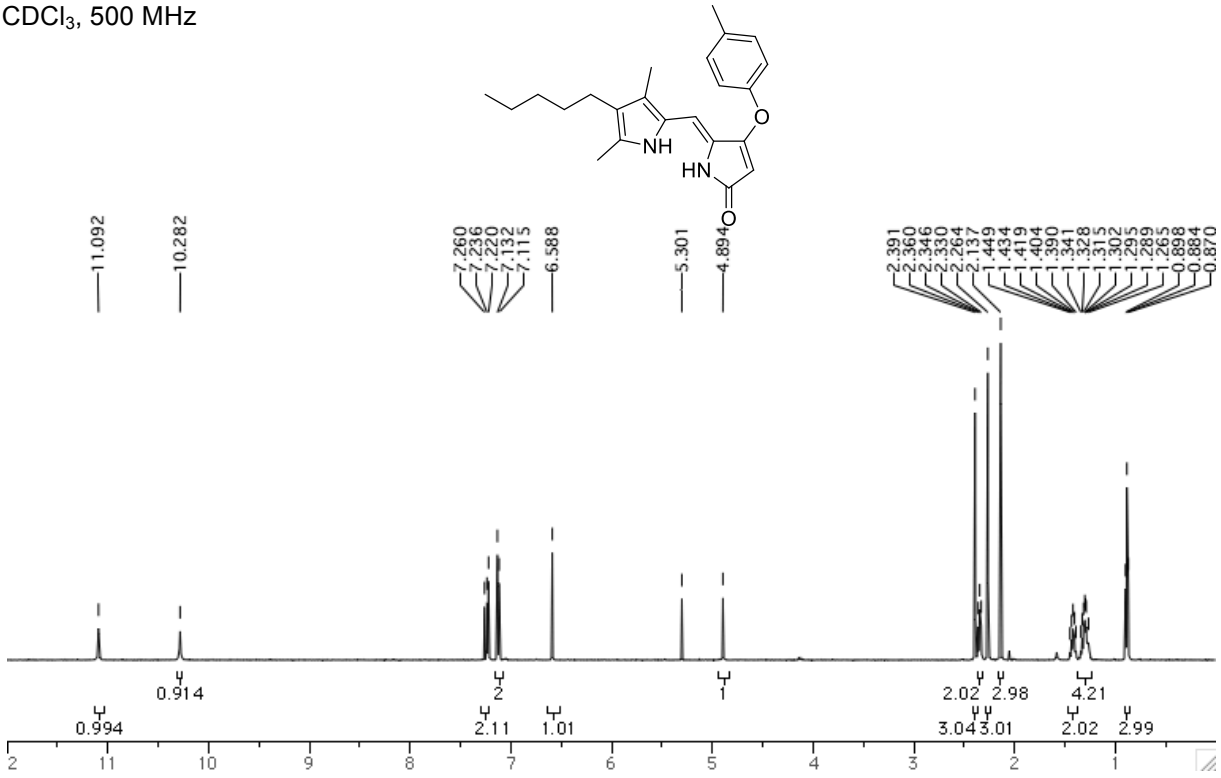
^{1}H NMR for **12b**
$CDCl_3$, 500 MHz



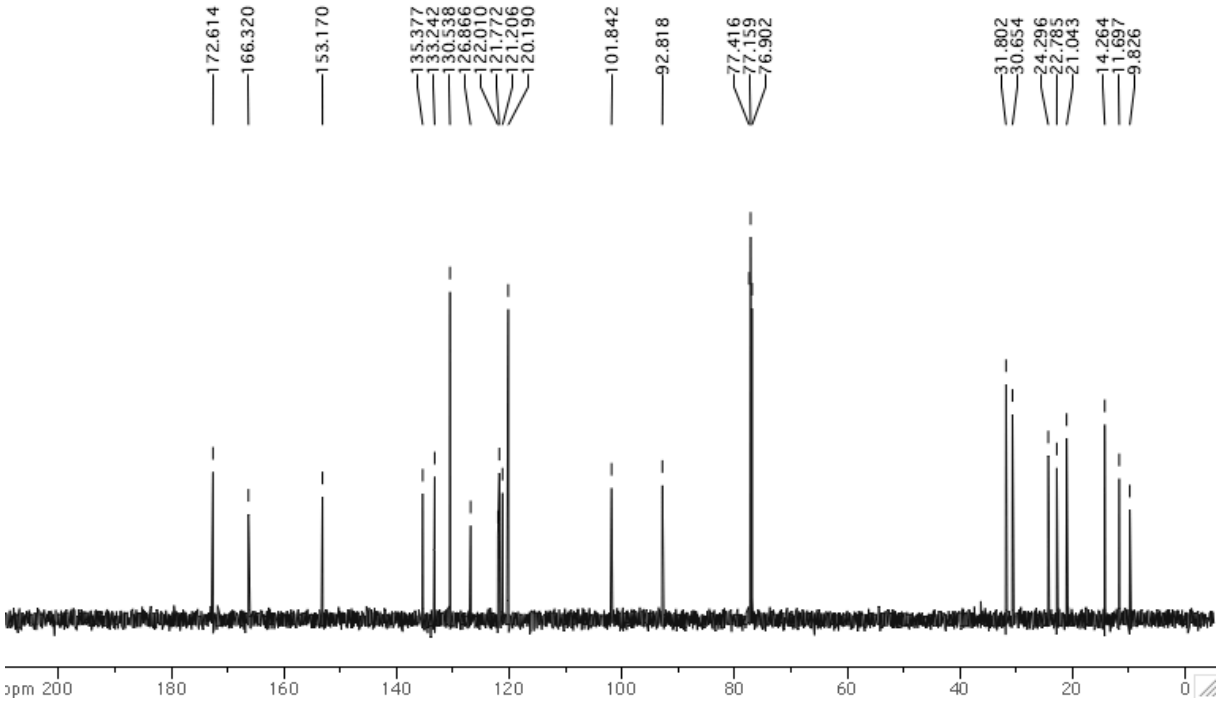
^{13}C NMR for **12b**
$CDCl_3$, 125 MHz



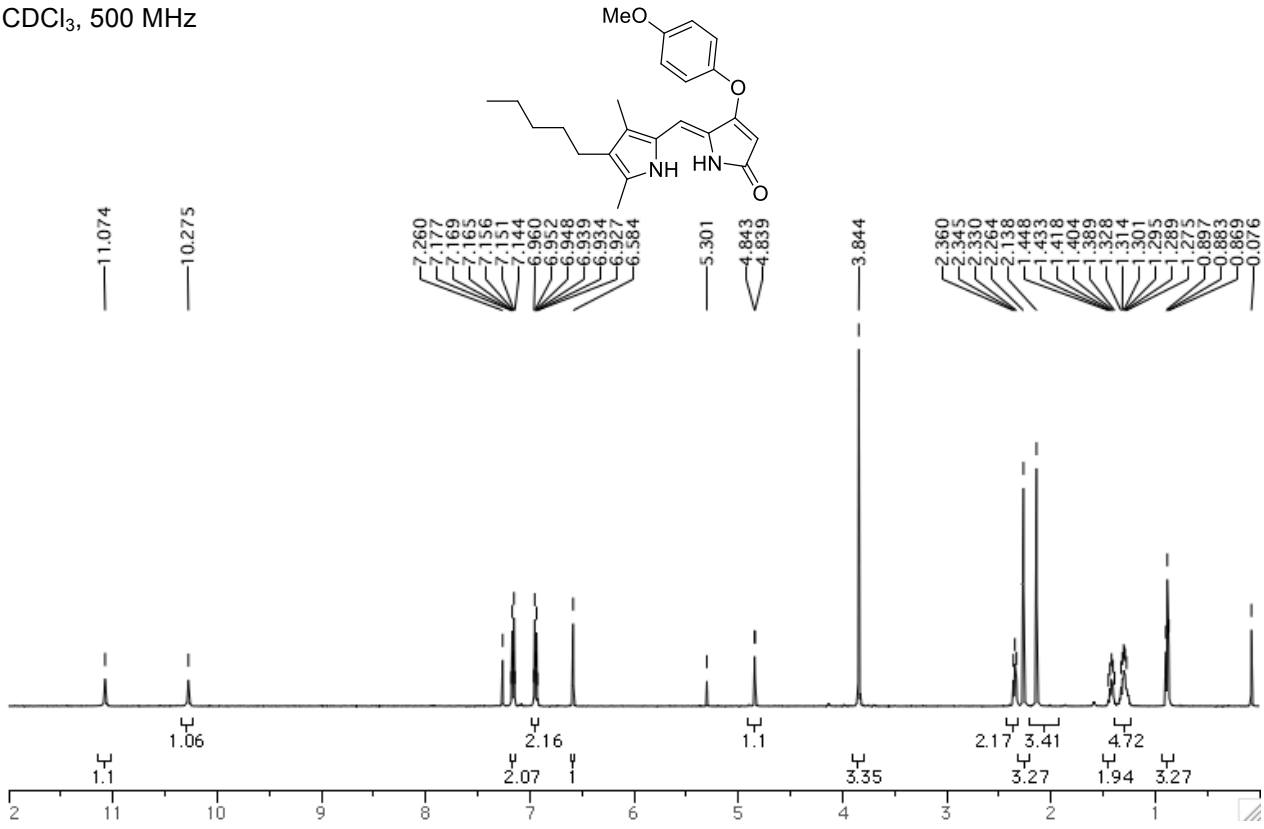
^{1}H NMR for **12c**
$CDCl_3$, 500 MHz



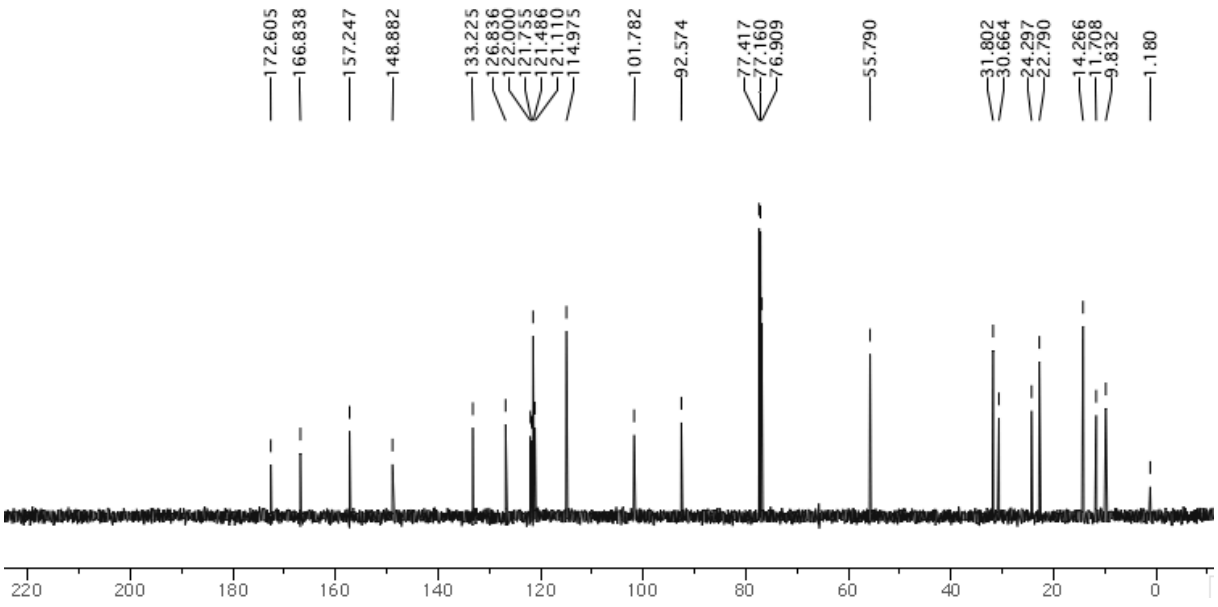
^{13}C NMR for **12c**
$CDCl_3$, 125 MHz



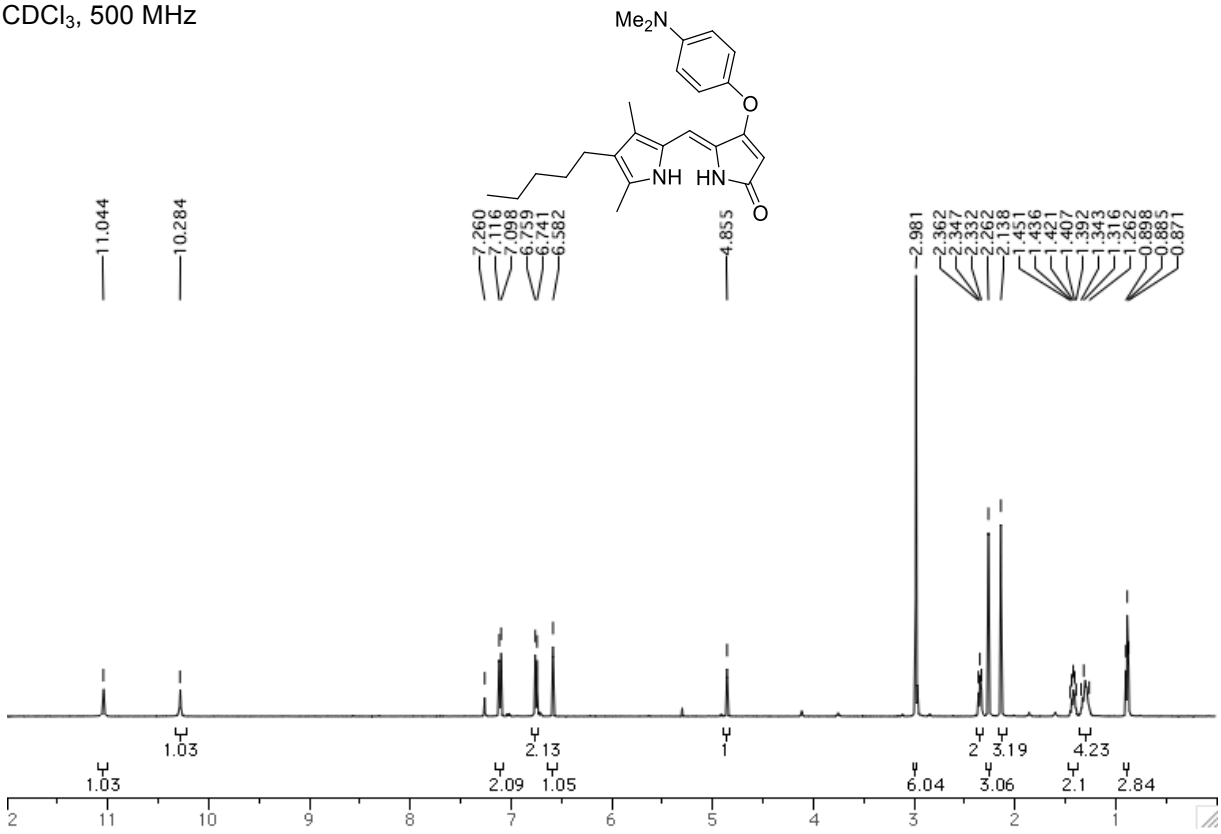
^{1}H NMR for **12d**
$CDCl_3$, 500 MHz



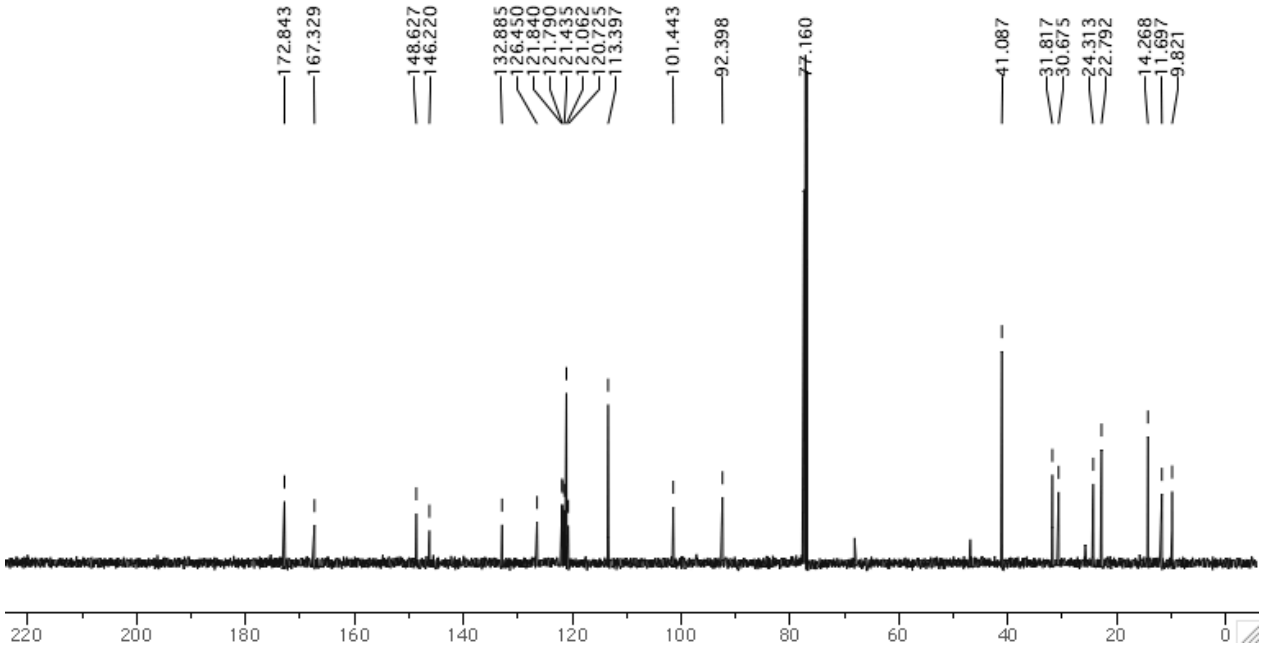
^{13}C NMR for **12d**
$CDCl_3$, 125 MHz



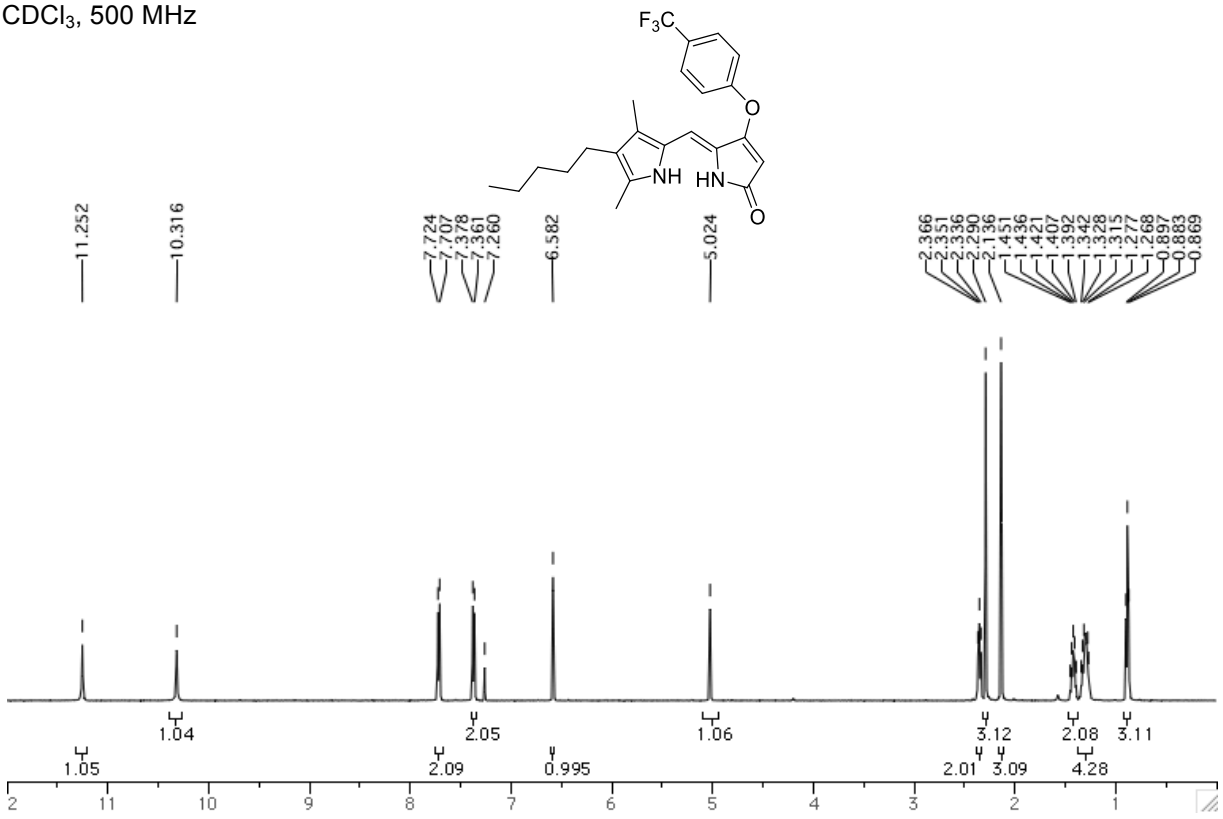
^{1}H NMR for **12e**
$CDCl_3$, 500 MHz



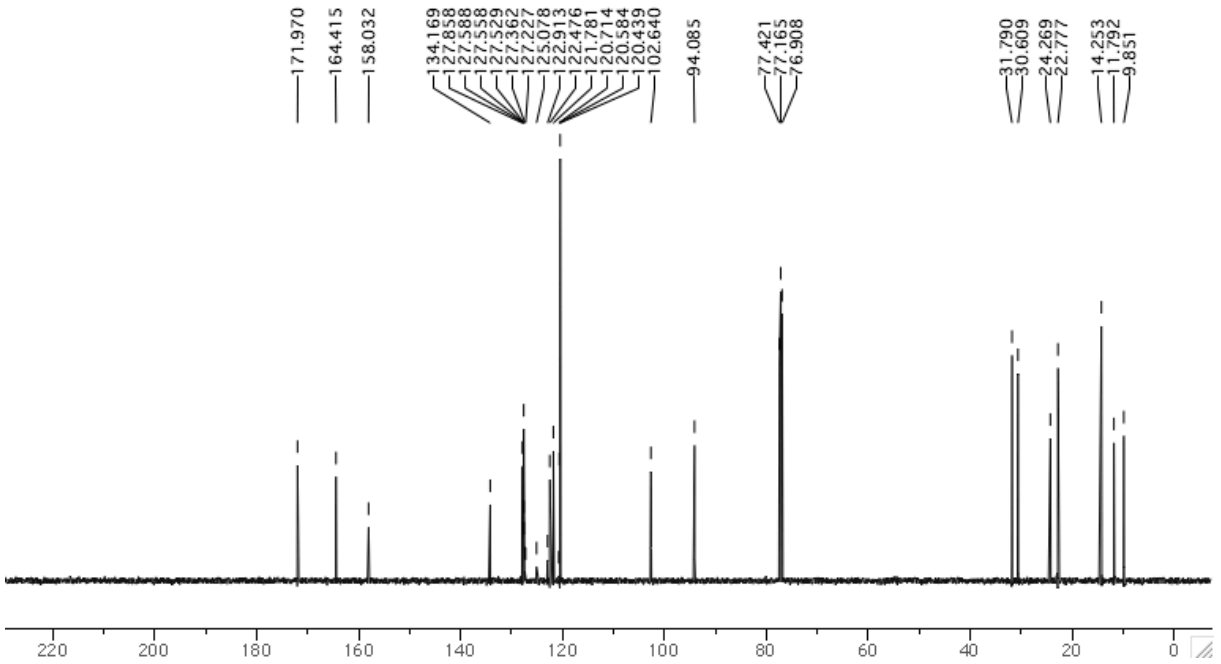
^{13}C NMR for **12e**
$CDCl_3$, 125 MHz



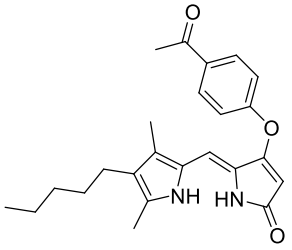
^{1}H NMR for **12f**
$CDCl_3$, 500 MHz

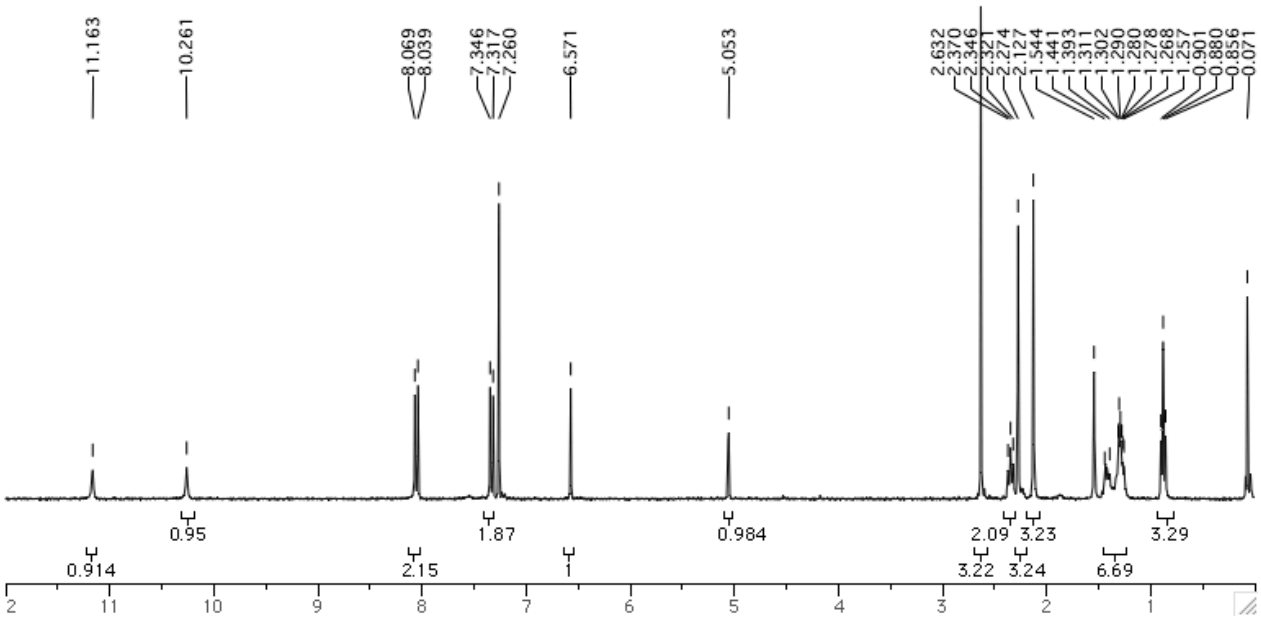


^{13}C NMR for **12f**
$CDCl_3$, 125 MHz

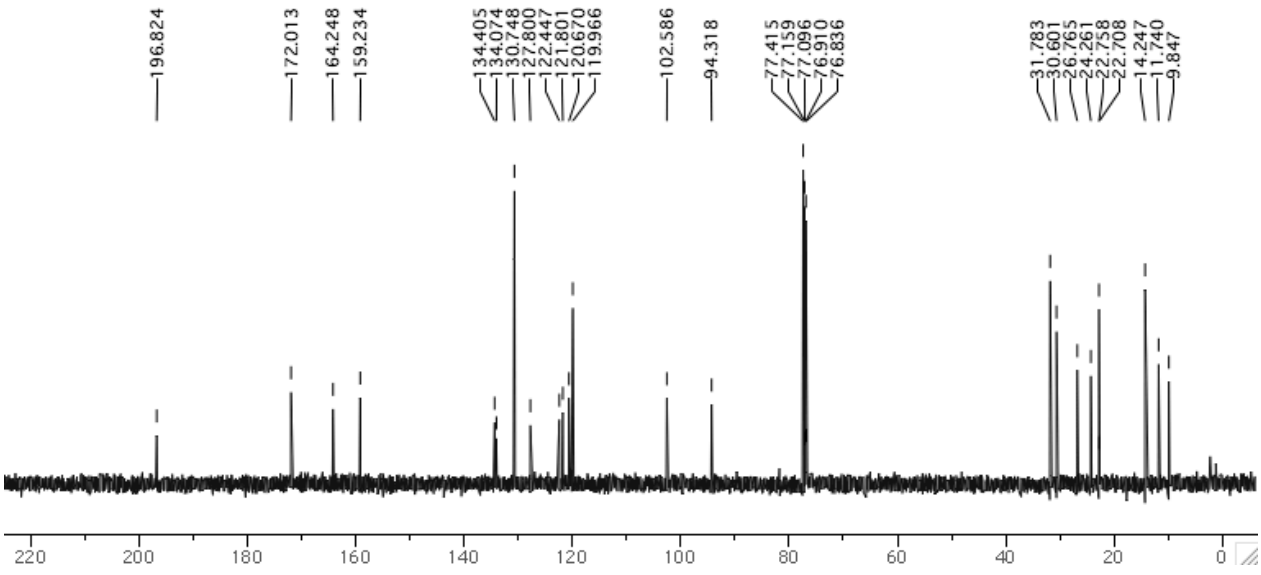


^{1}H NMR for **12g**
$CDCl_3$, 500 MHz

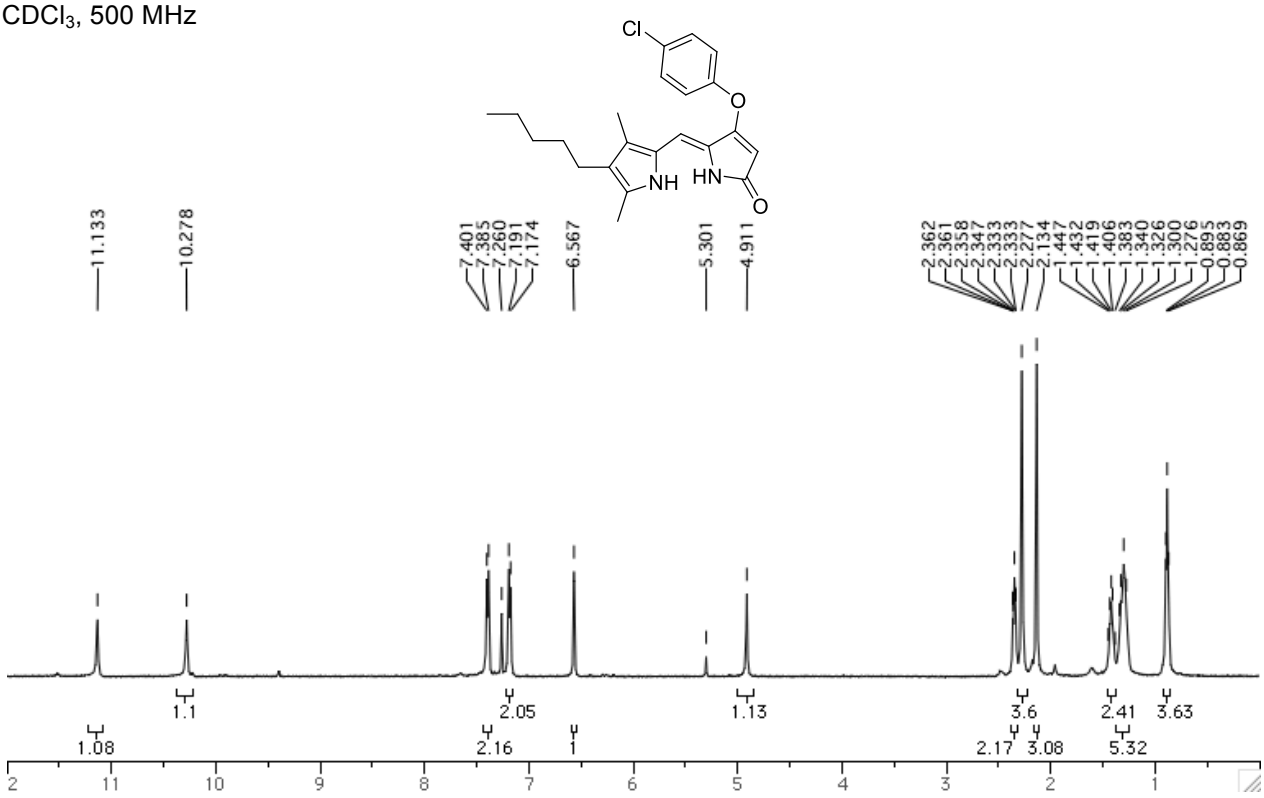




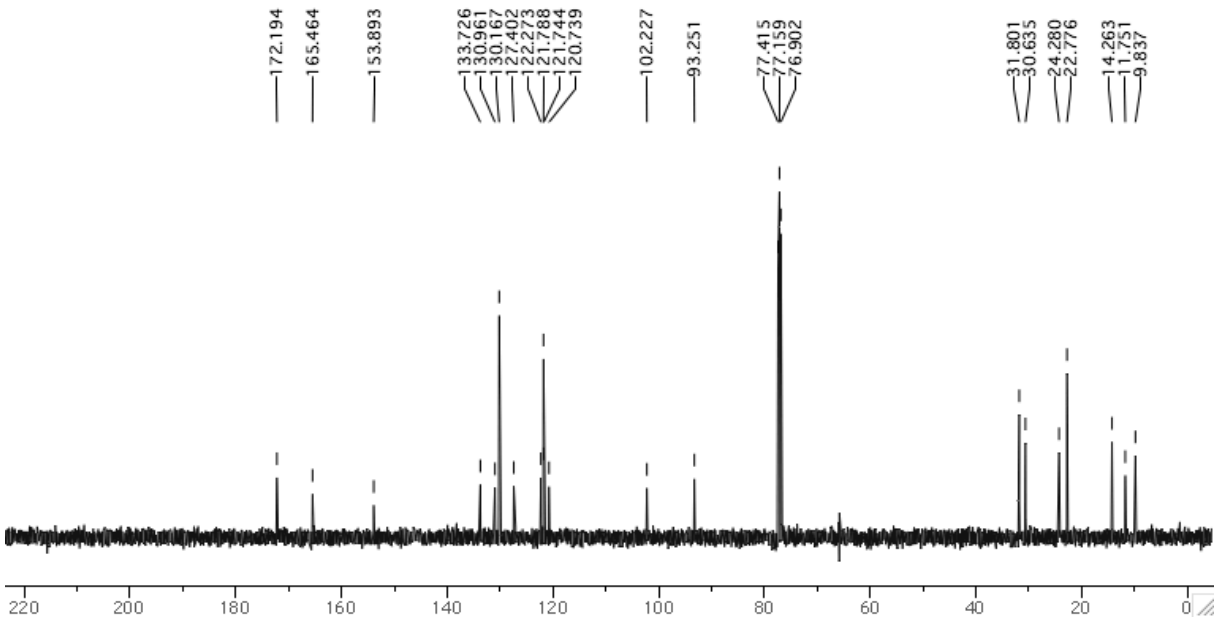
^{13}C NMR for **12g**
$CDCl_3$, 125 MHz



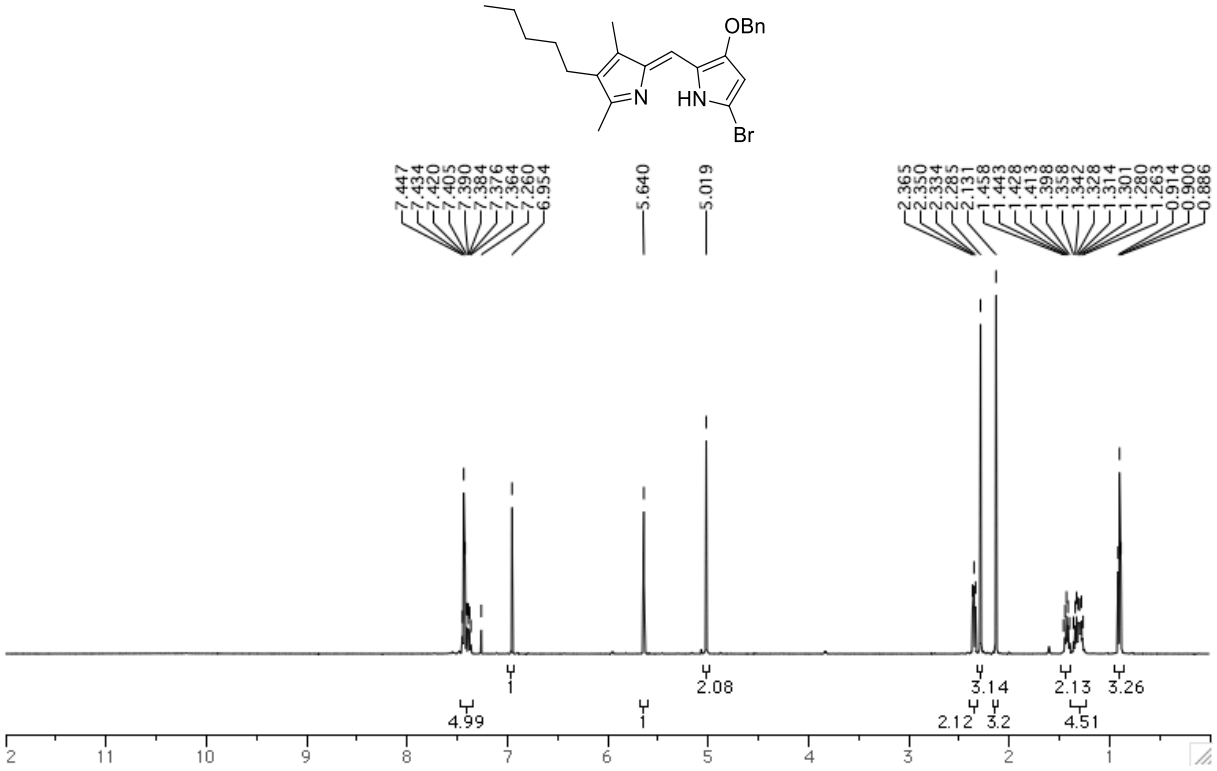
^{1}H NMR for **12h**
$CDCl_3$, 500 MHz



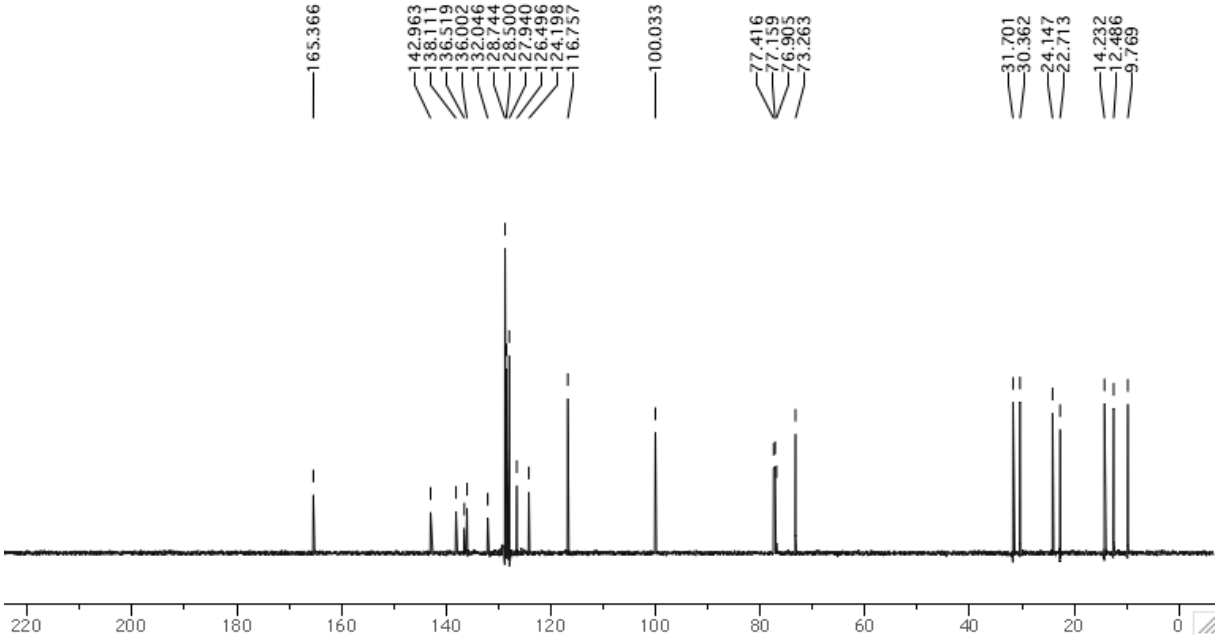
^{13}C NMR for **12h**
$CDCl_3$, 125 MHz



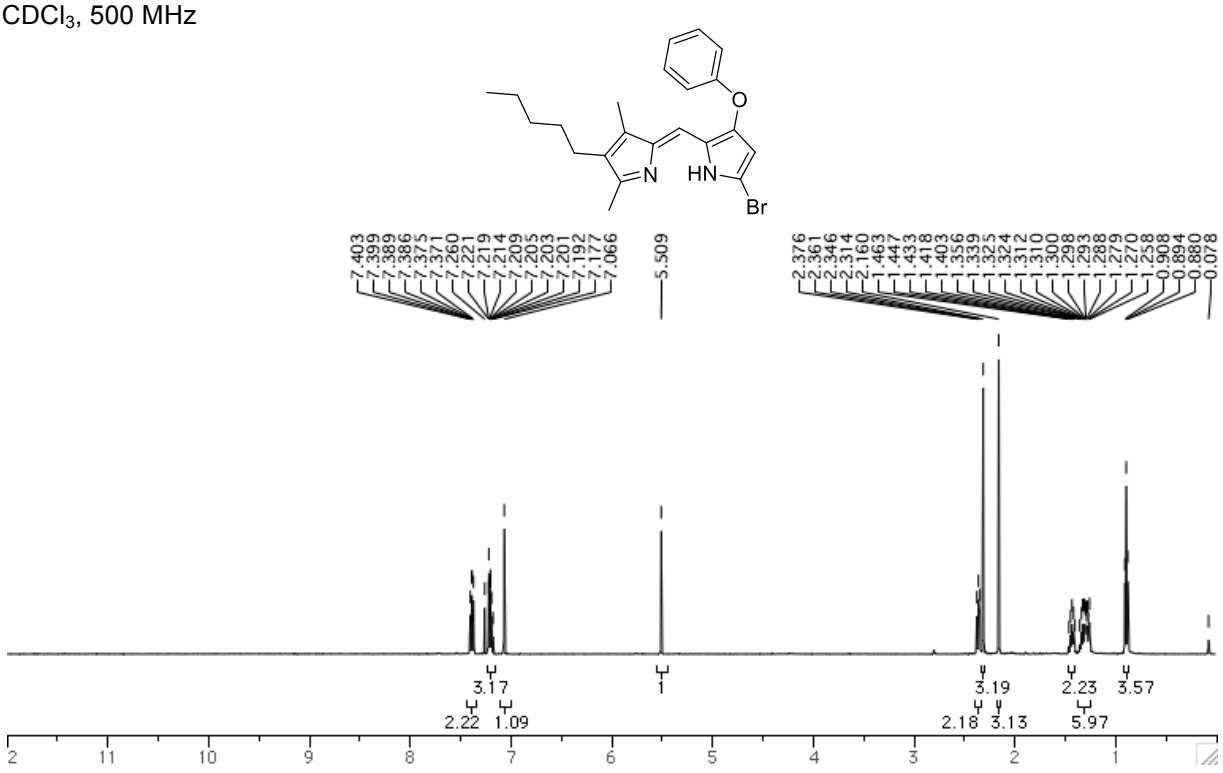
^{1}H NMR for **13a**
$CDCl_3$, 500 MHz



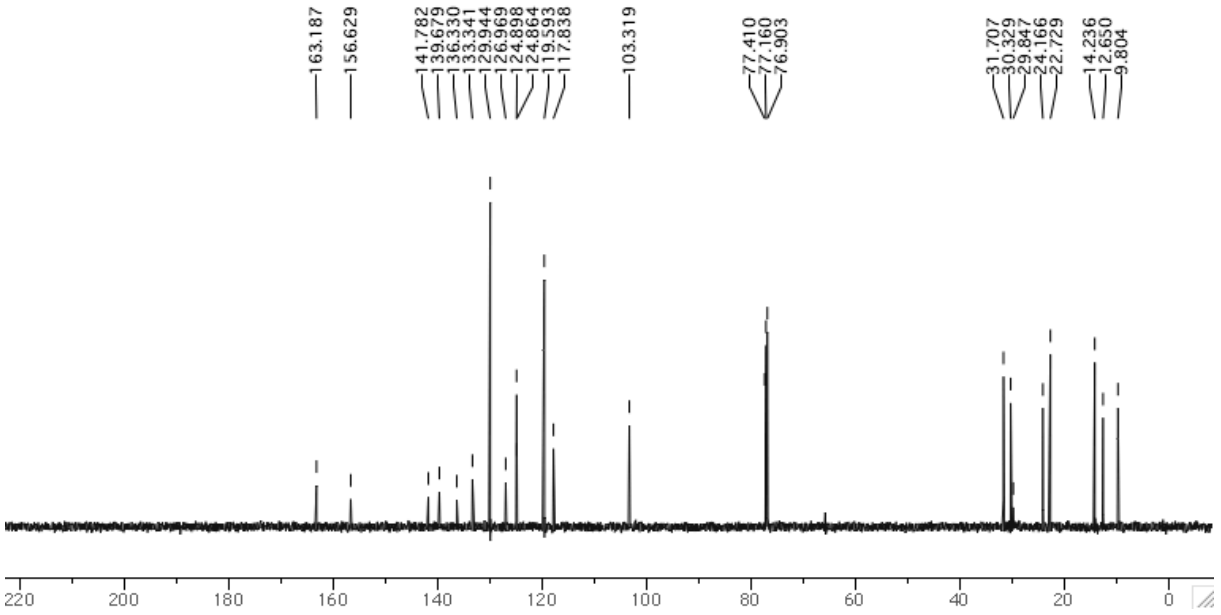
^{13}C NMR for **13a**
$CDCl_3$, 125 MHz



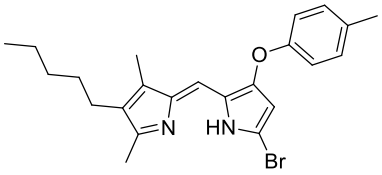
^{1}H NMR for **13b**
$CDCl_3$, 500 MHz

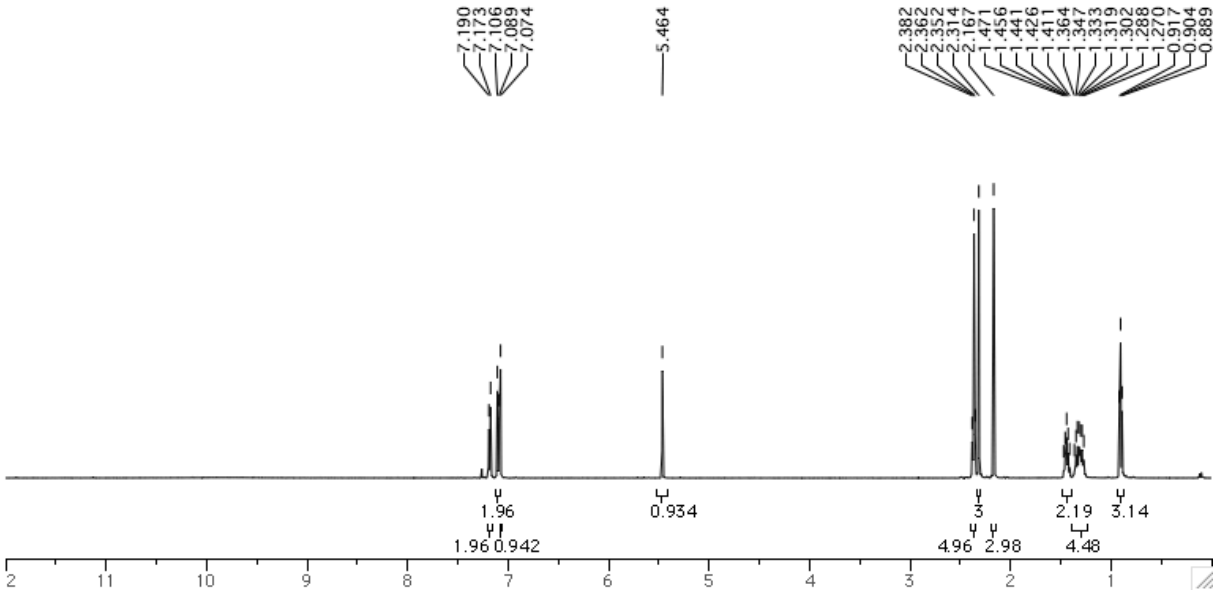


^{13}C NMR for **13b**
$CDCl_3$, 125 MHz

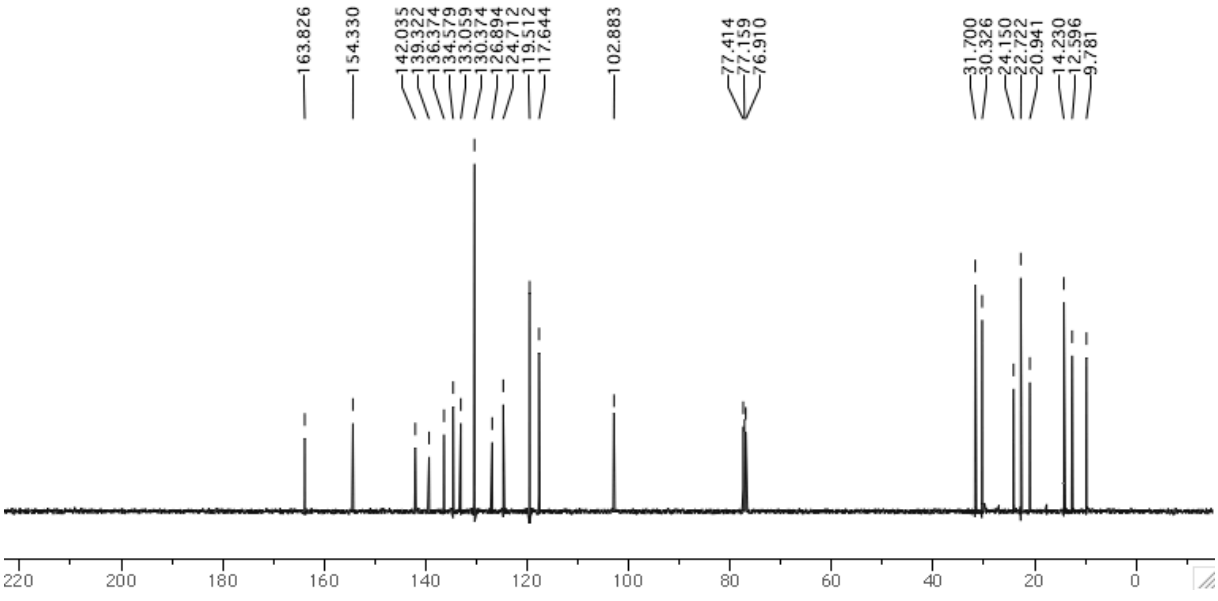


^{1}H NMR for **13c**
$CDCl_3$, 500 MHz

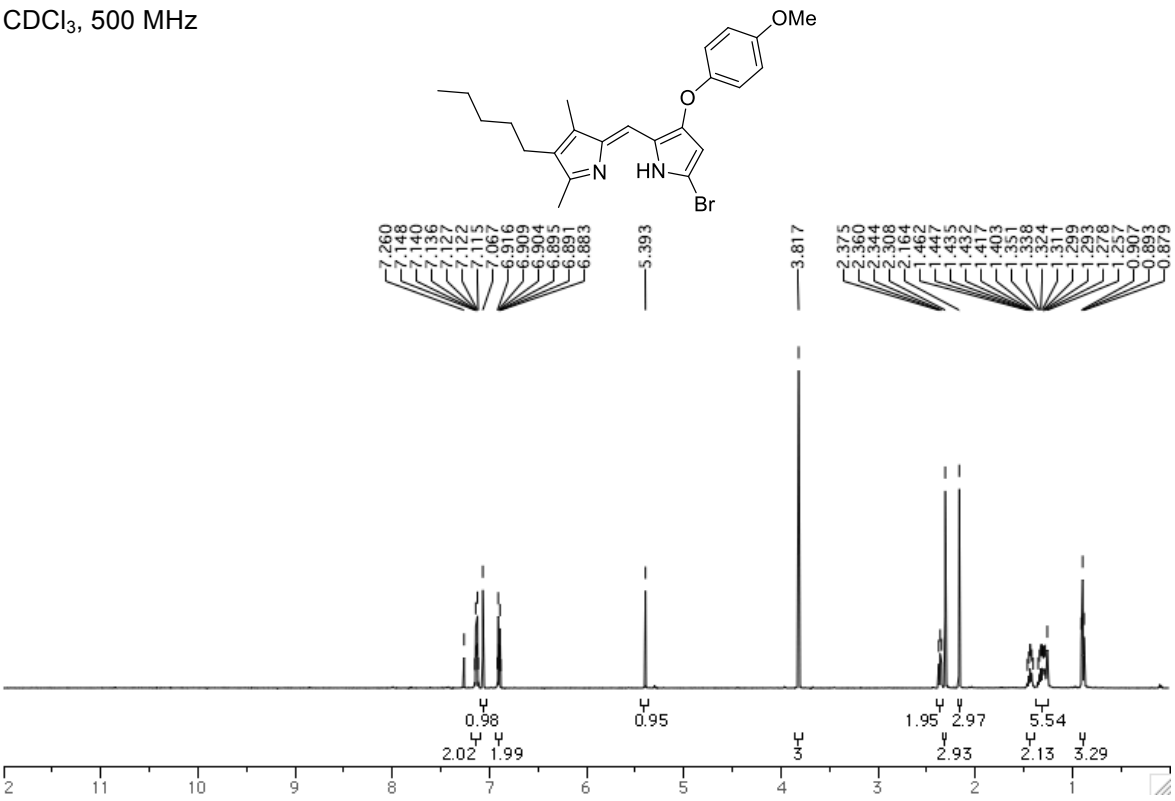




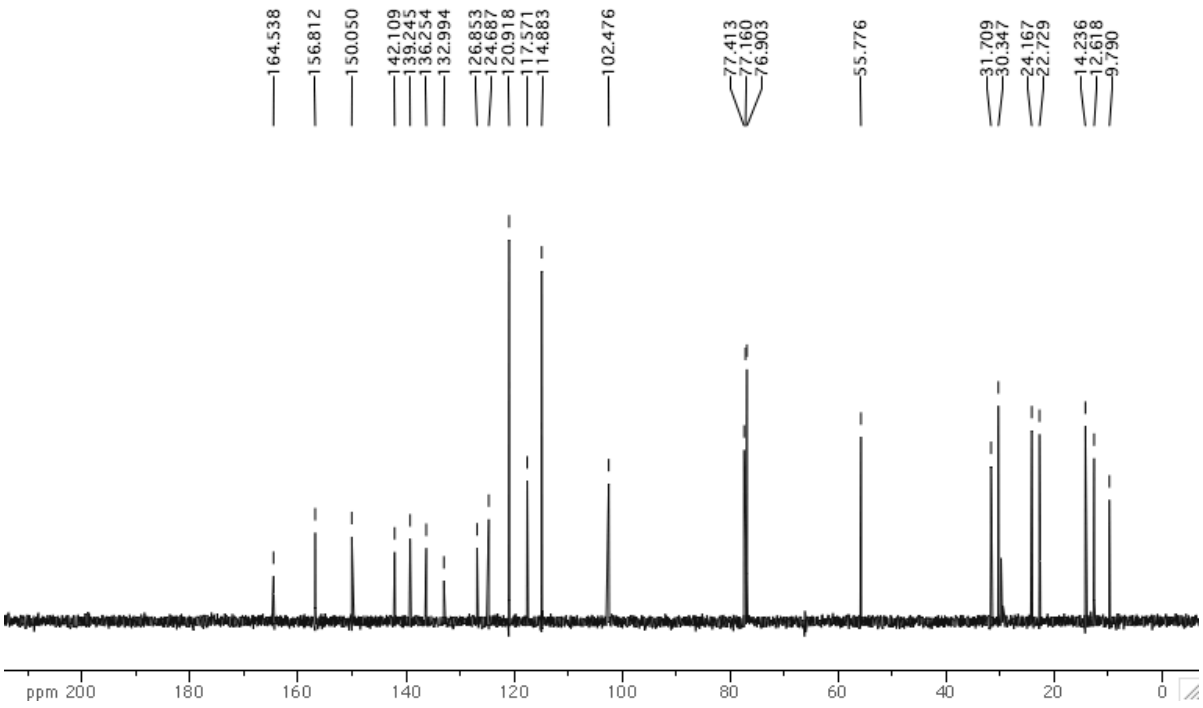
^{13}C NMR for **13c**
$CDCl_3$, 125 MHz



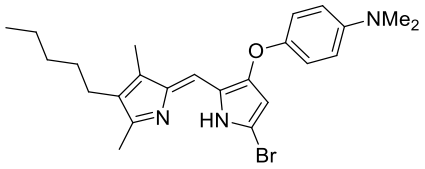
^{1}H NMR for **13d**
$CDCl_3$, 500 MHz

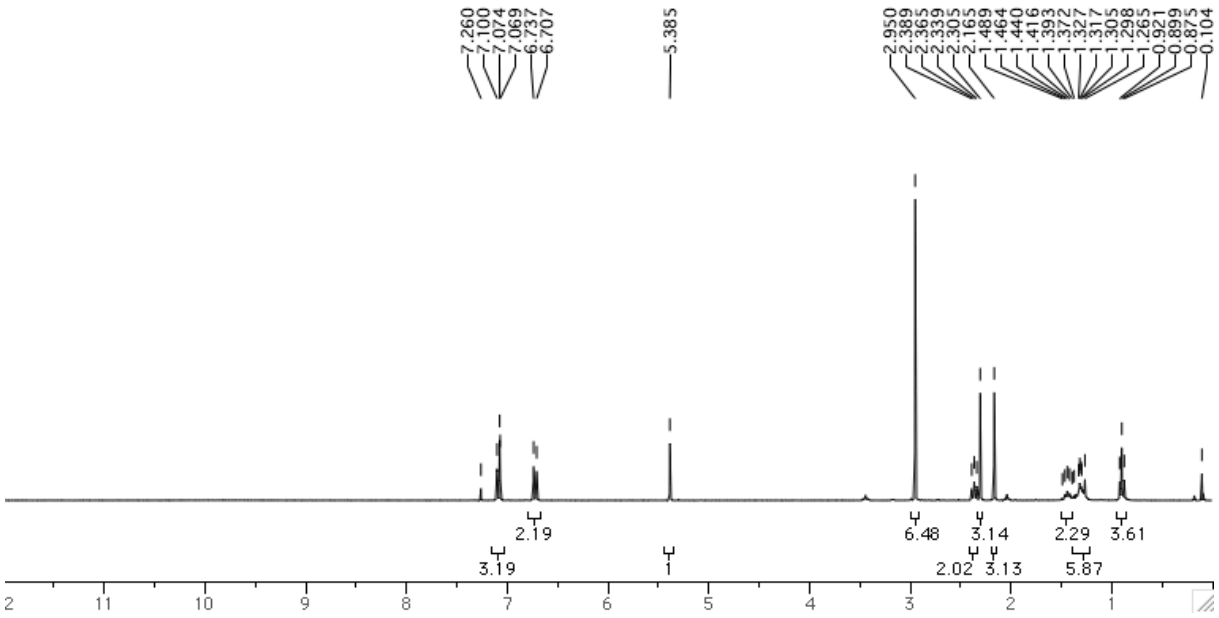


^{13}C NMR for **13d**
$CDCl_3$, 125 MHz

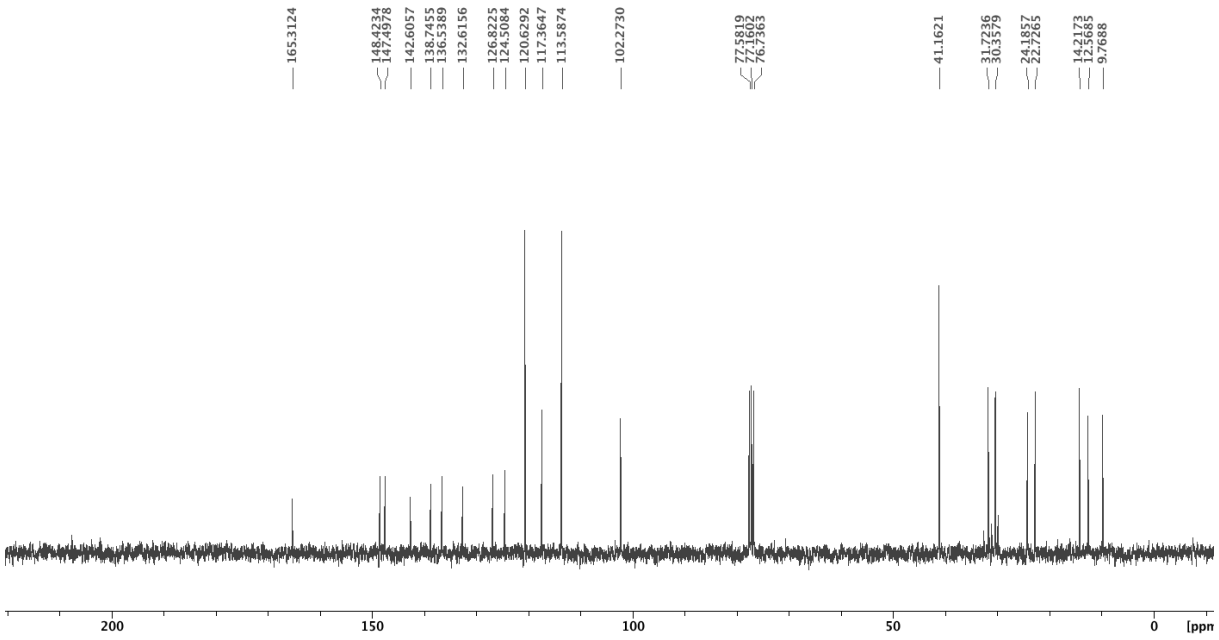


^{1}H NMR for **13e**
$CDCl_3$, 300 MHz

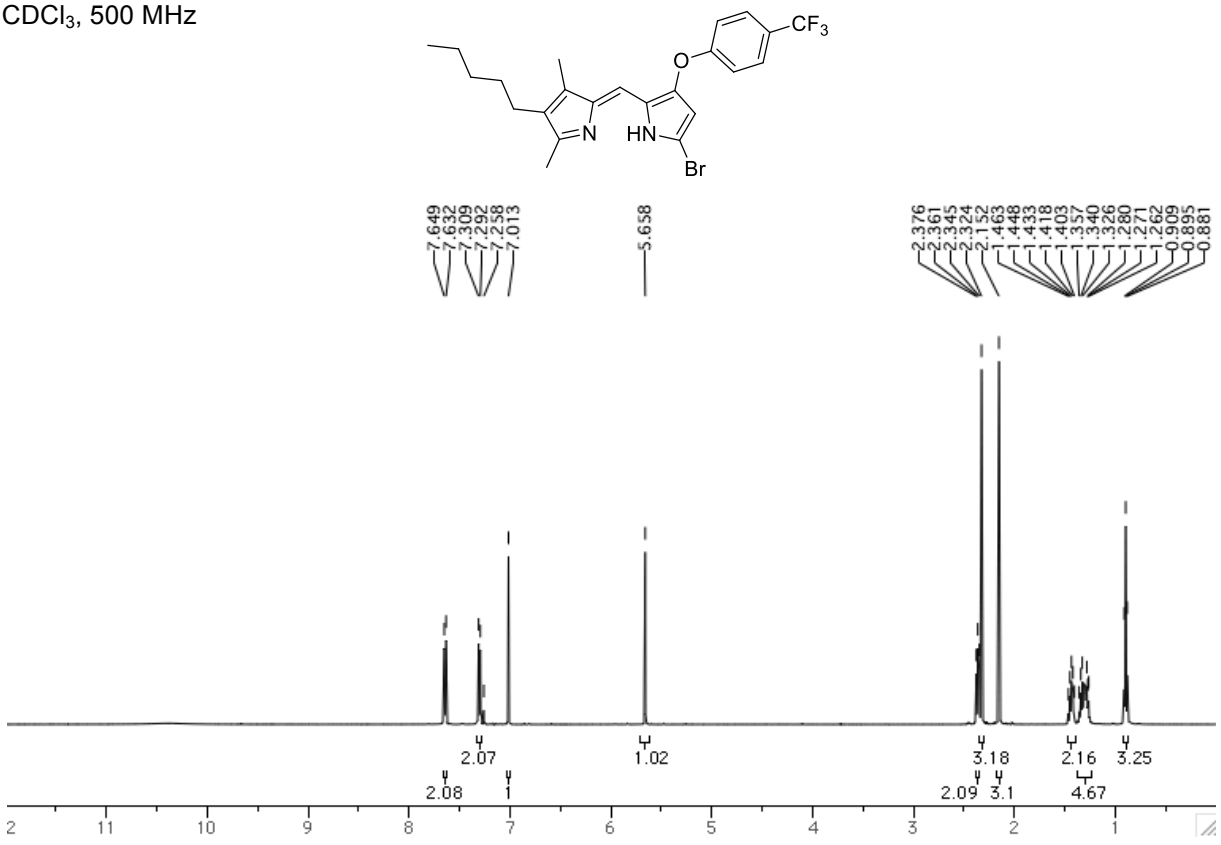




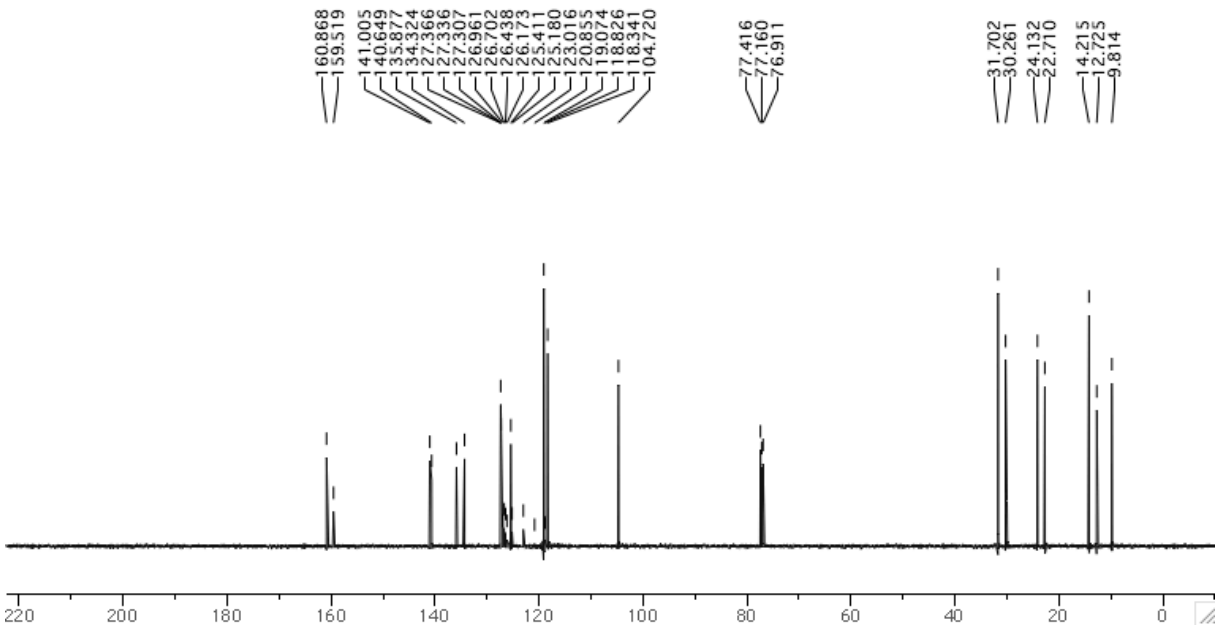
^{13}C NMR for **13e**
$CDCl_3$, 100 MHz



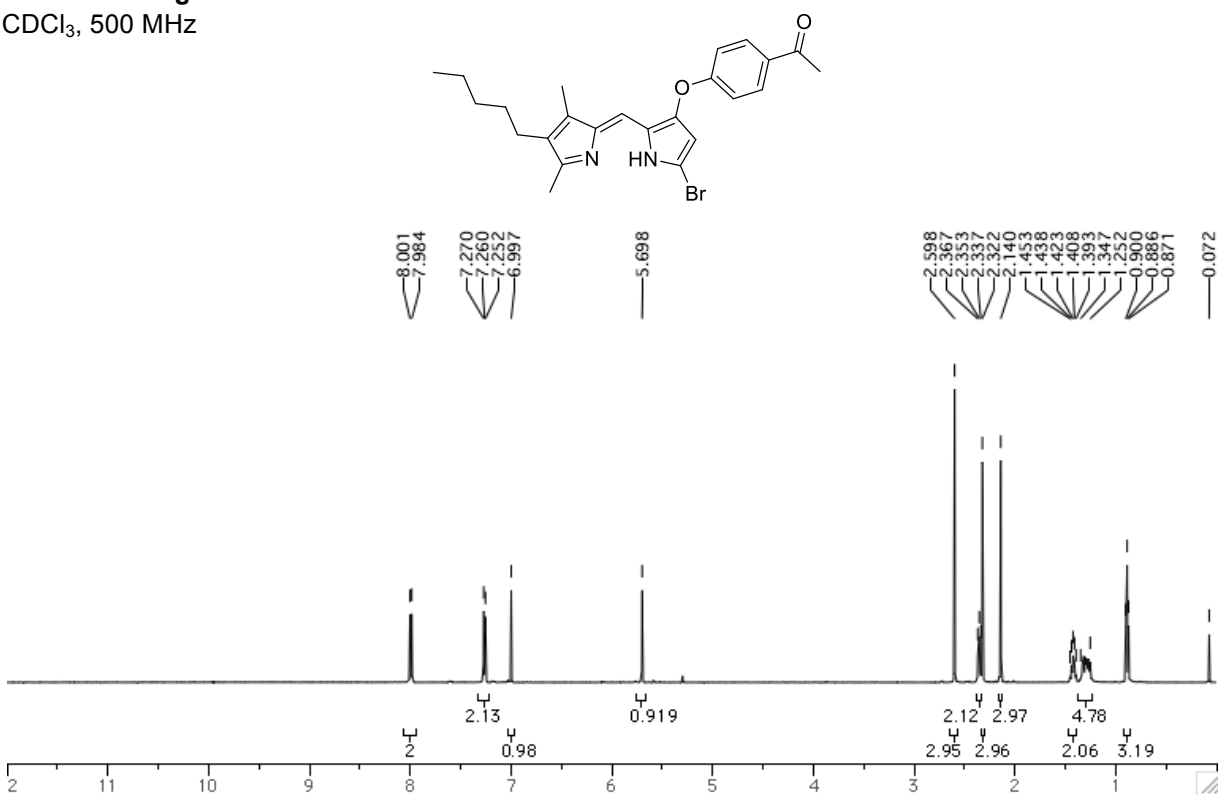
^{1}H NMR for **13f**
$CDCl_3$, 500 MHz



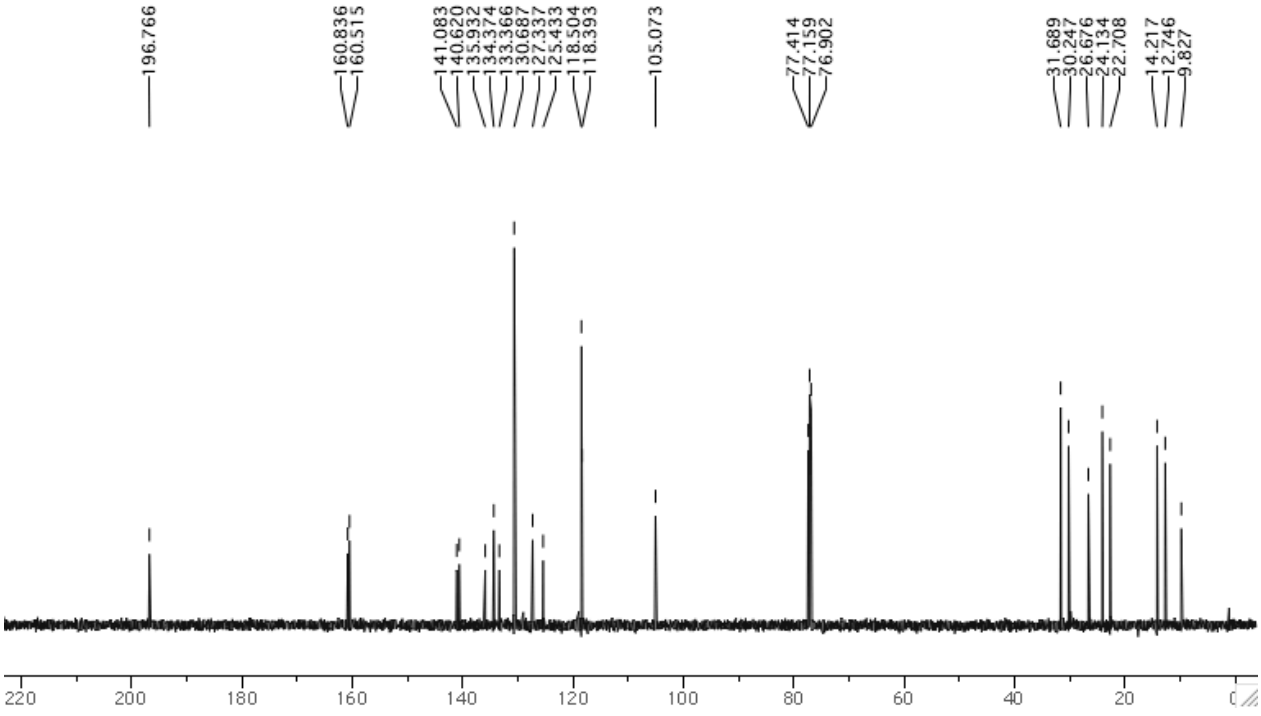
^{13}C NMR for **13f**
$CDCl_3$, 125 MHz



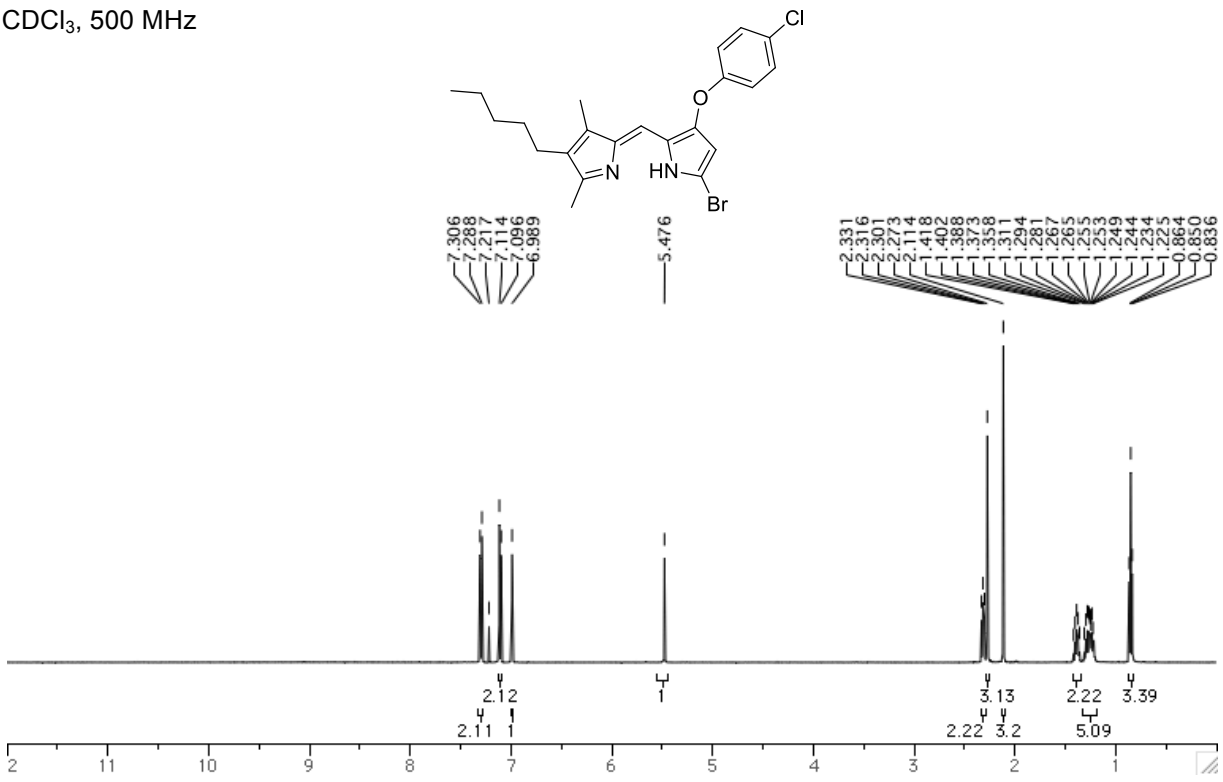
^{1}H NMR for **13g**
$CDCl_3$, 500 MHz



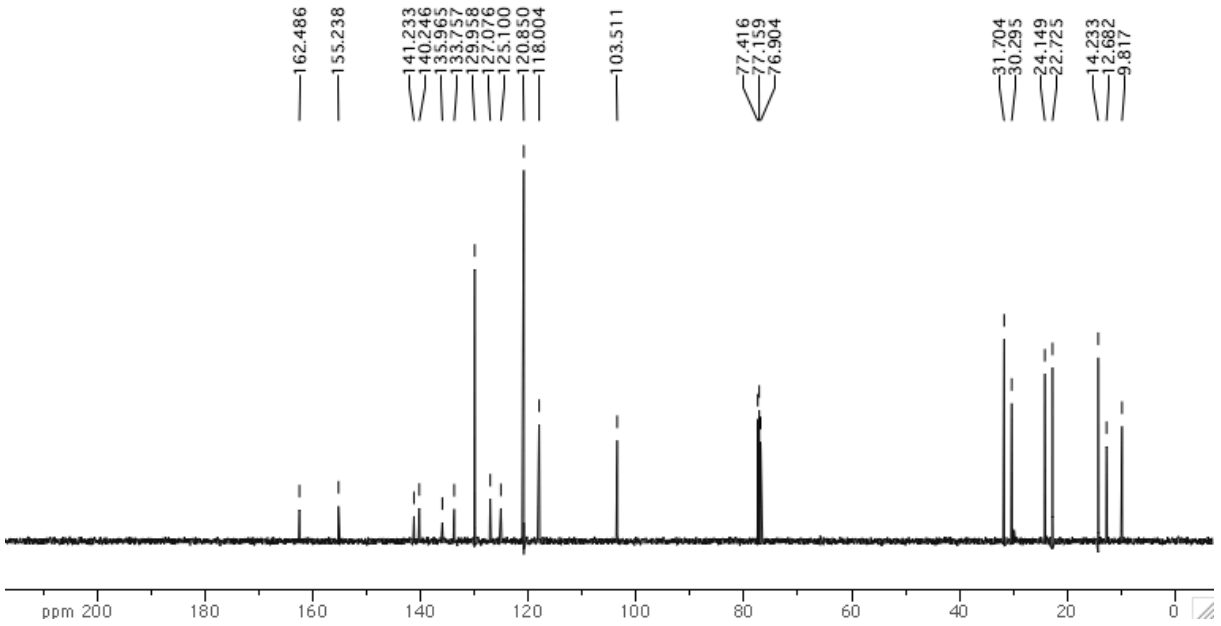
^{13}C NMR for **13g**
$CDCl_3$, 125 MHz



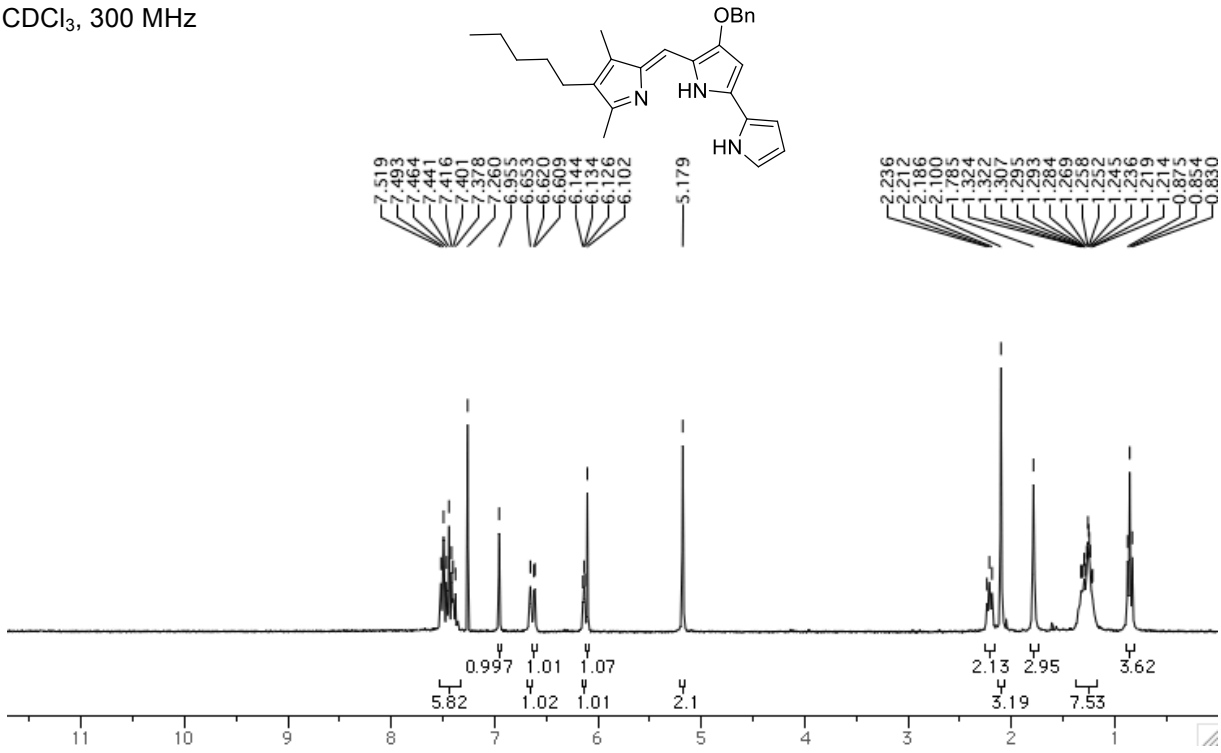
^{1}H NMR for **13h**
$CDCl_3$, 500 MHz



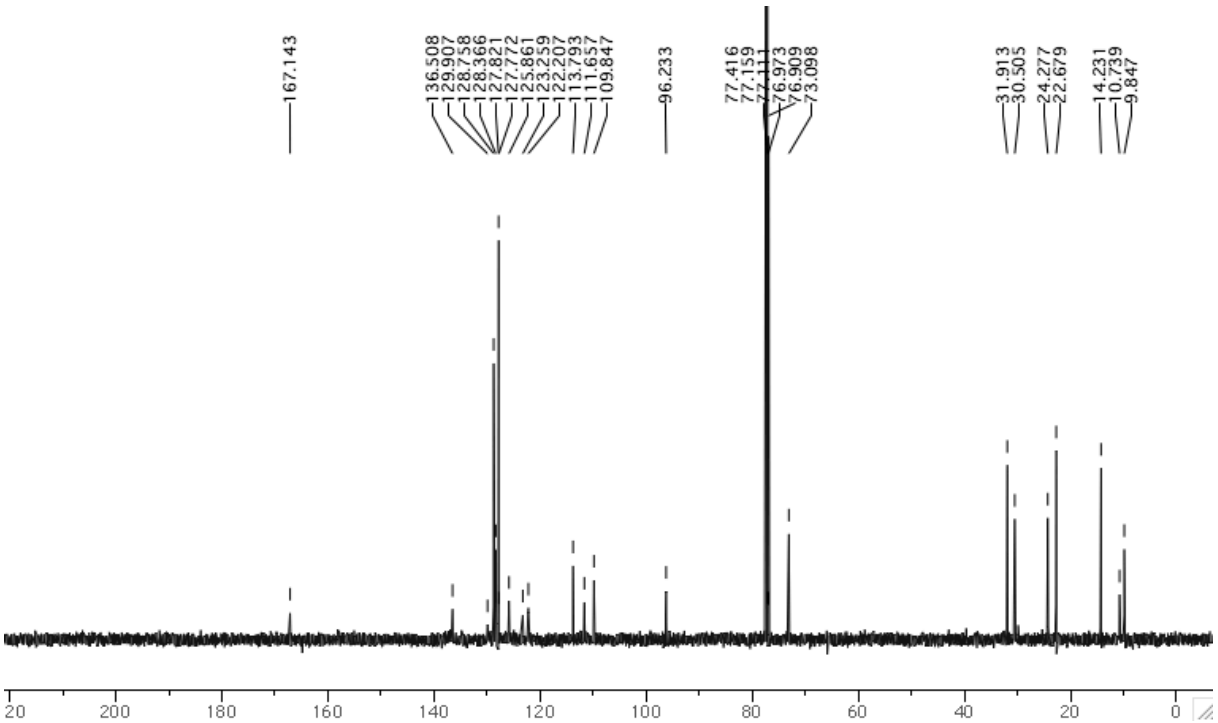
^{13}C NMR for **13h**
$CDCl_3$, 125 MHz



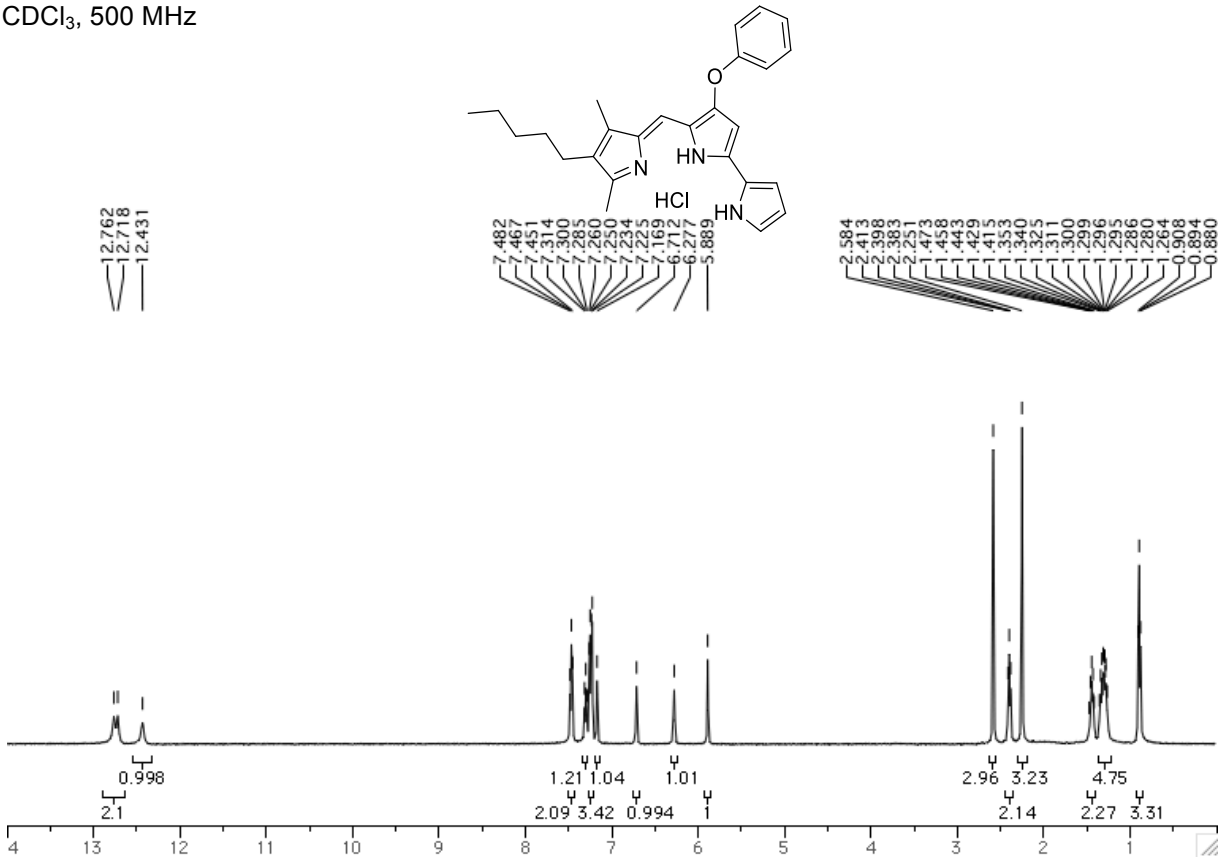
^{1}H NMR for **3a**
$CDCl_3$, 300 MHz



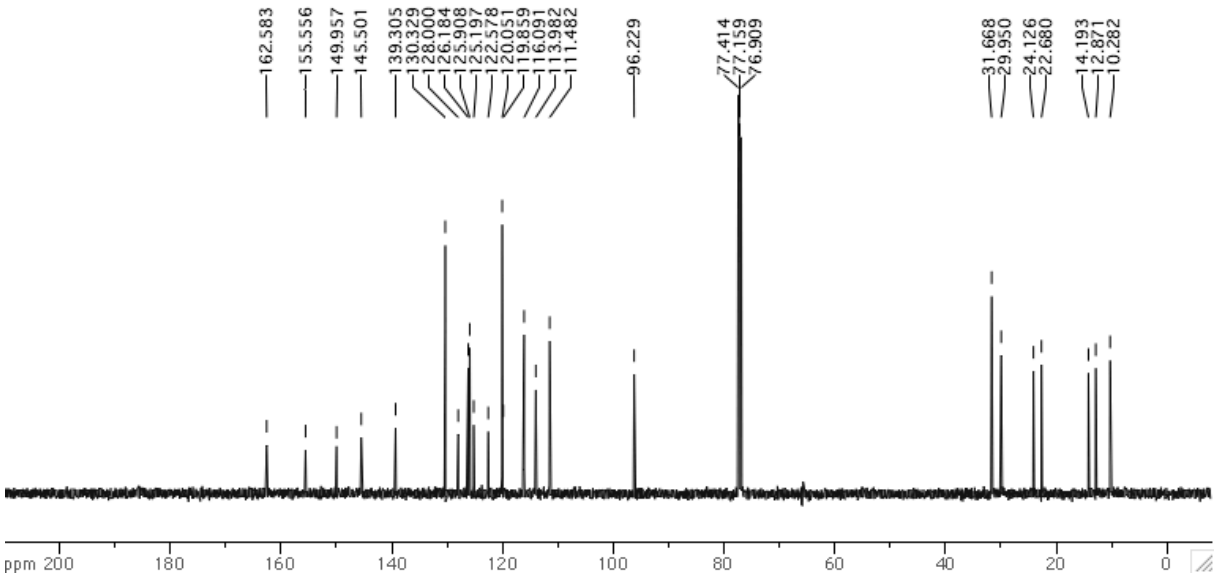
^{13}C NMR for **3a**
$CDCl_3$, 125 MHz



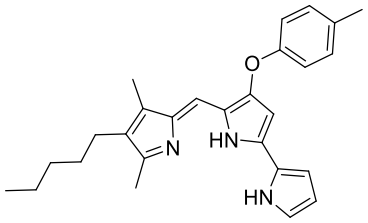
^{1}H NMR for **3b**
$CDCl_3$, 500 MHz

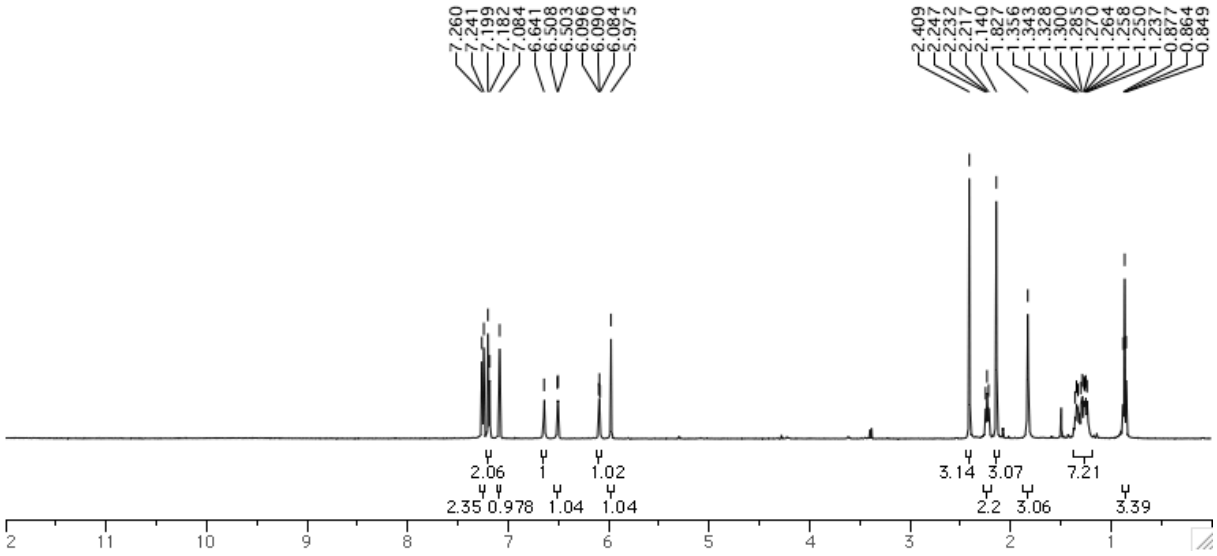


^{13}C NMR for **3b**
$CDCl_3$, 125 MHz

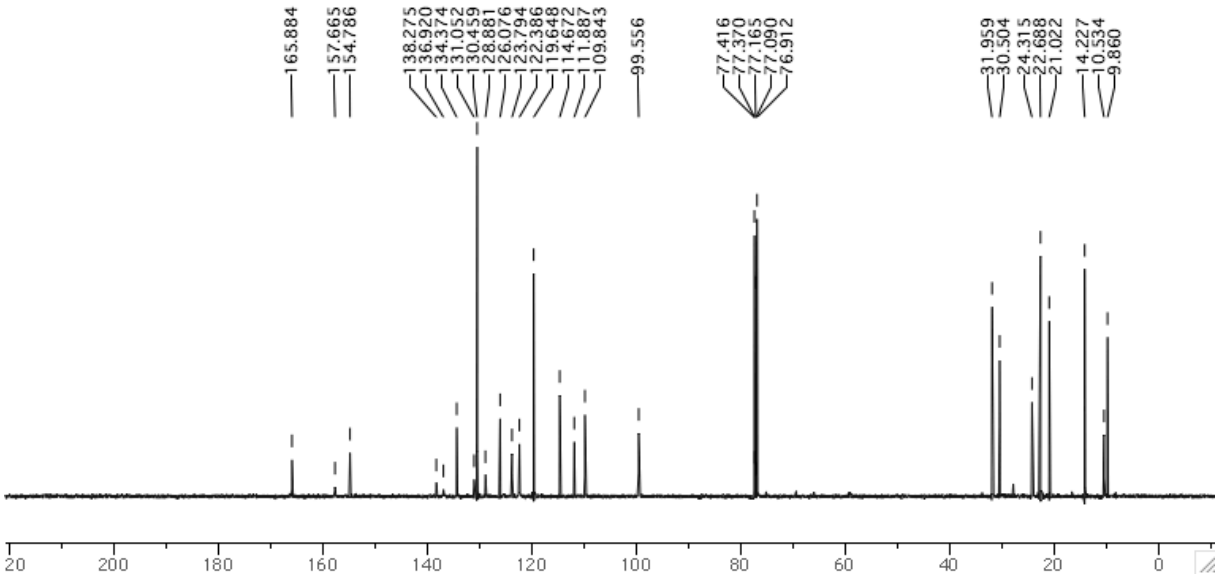


^{1}H NMR for **3c**
$CDCl_3$, 500 MHz

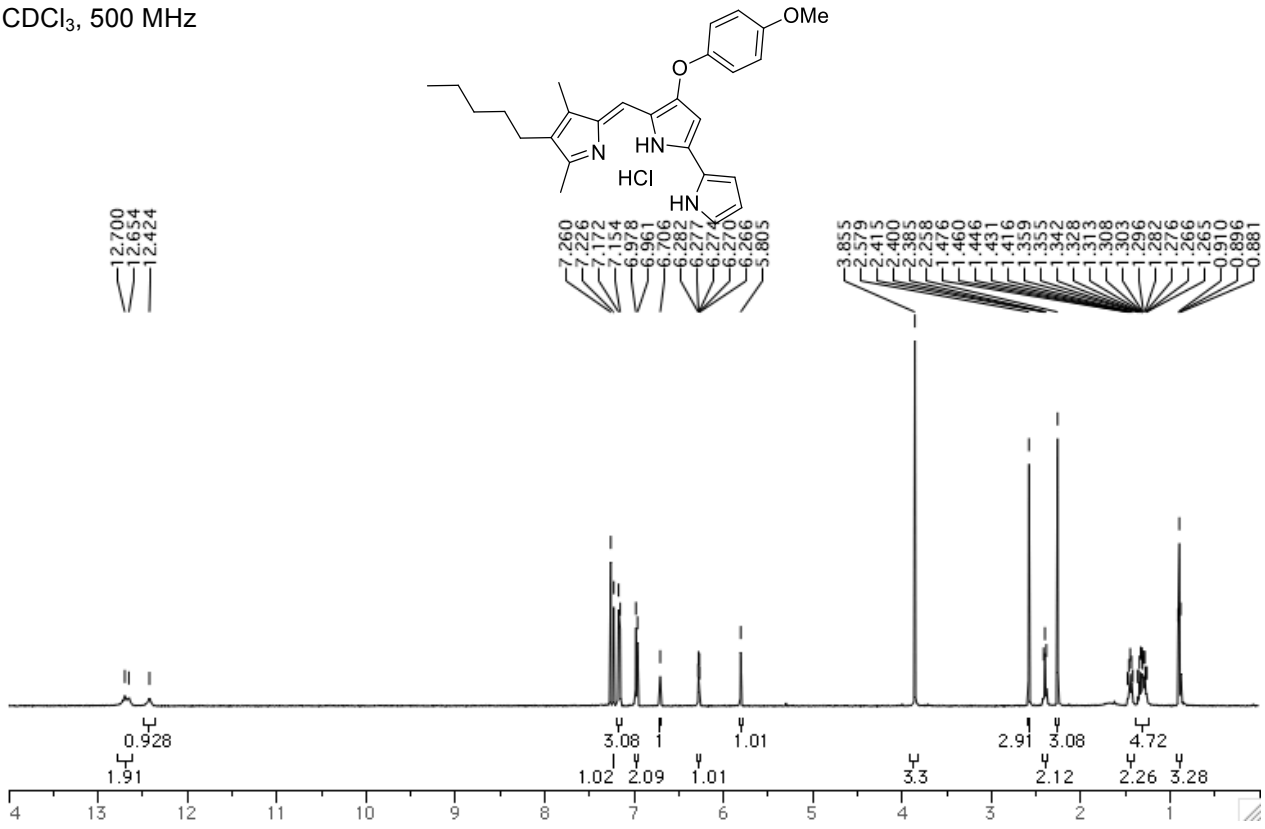




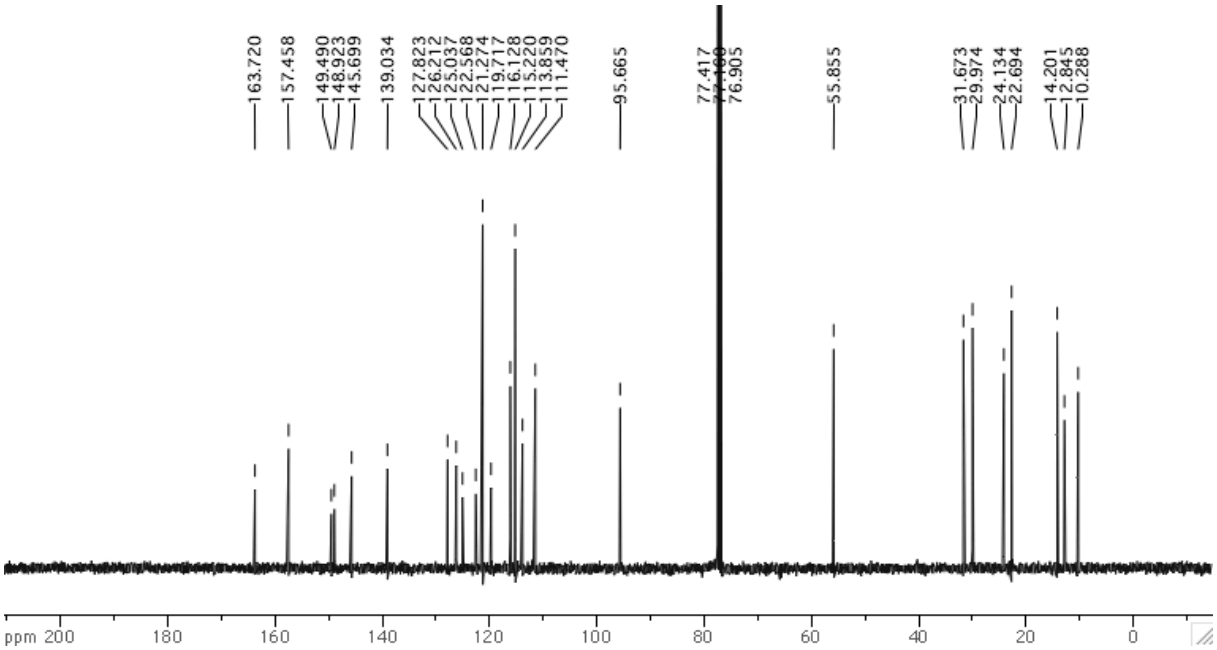
^{13}C NMR for **3c**
$CDCl_3$, 125 MHz



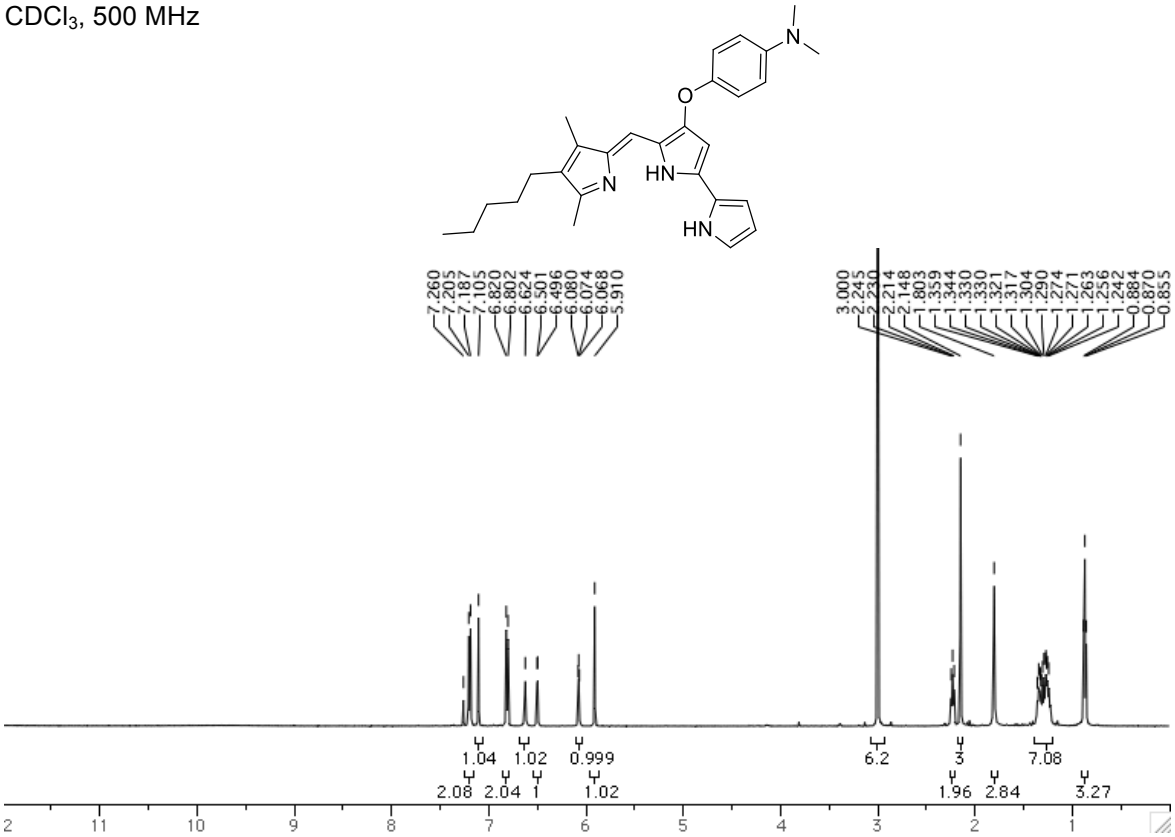
^{1}H NMR for **3d**
$CDCl_3$, 500 MHz



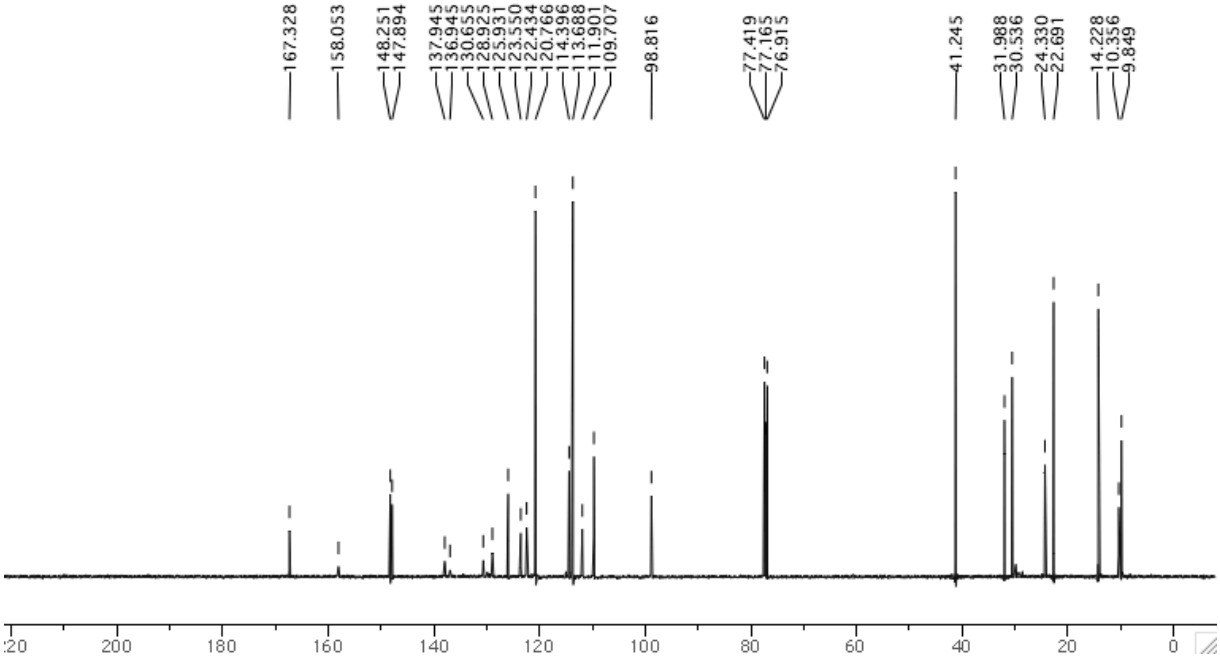
^{13}C NMR for **3d**
$CDCl_3$, 125 MHz



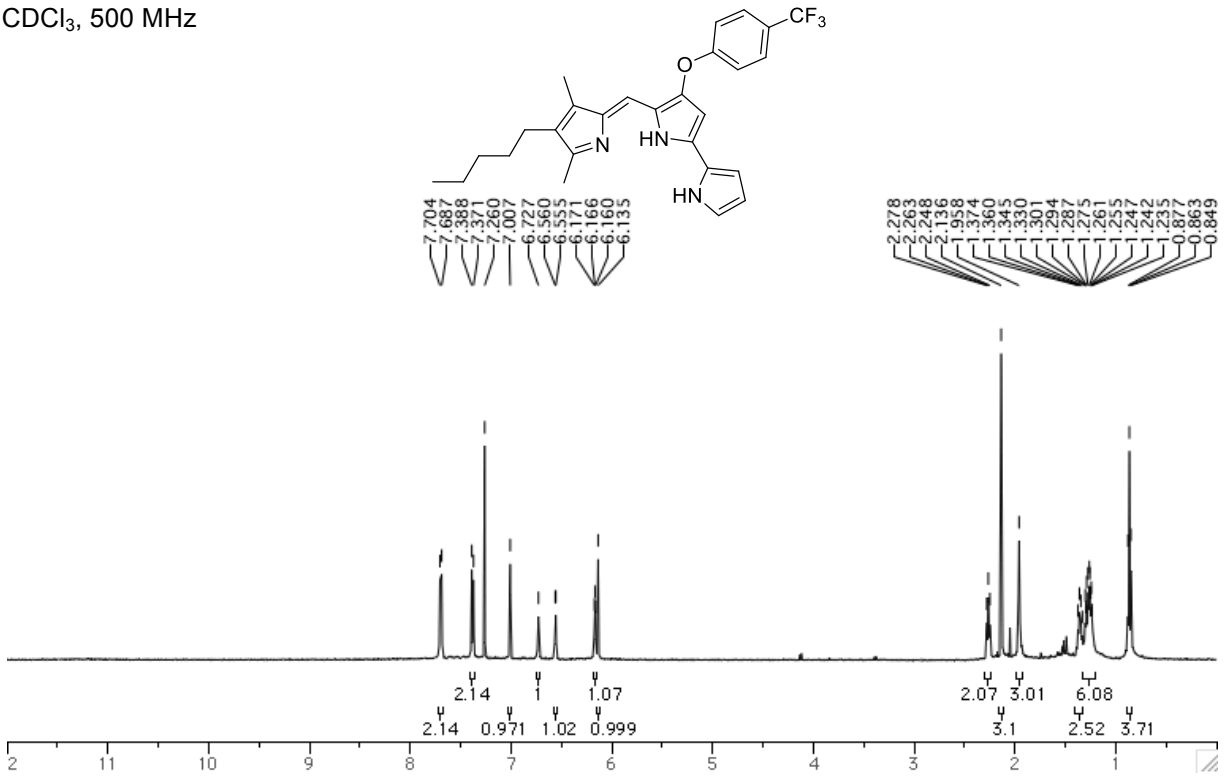
^{1}H NMR for **3e**
$CDCl_3$, 500 MHz



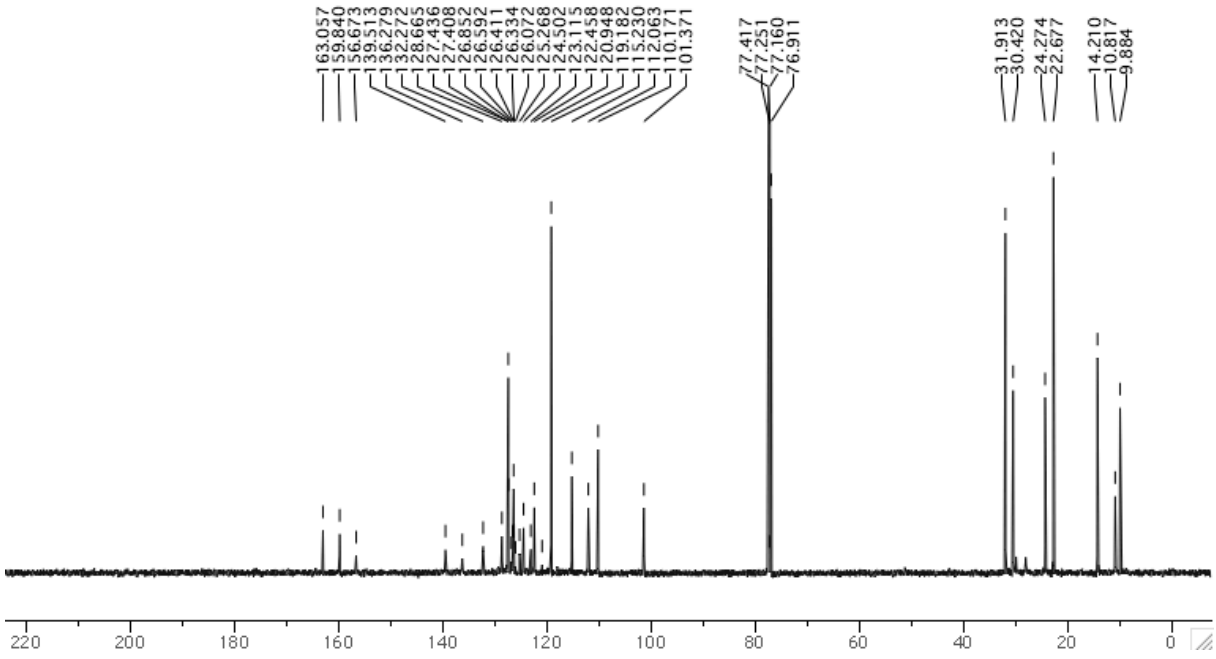
^{13}C NMR for **3e**
$CDCl_3$, 125 MHz



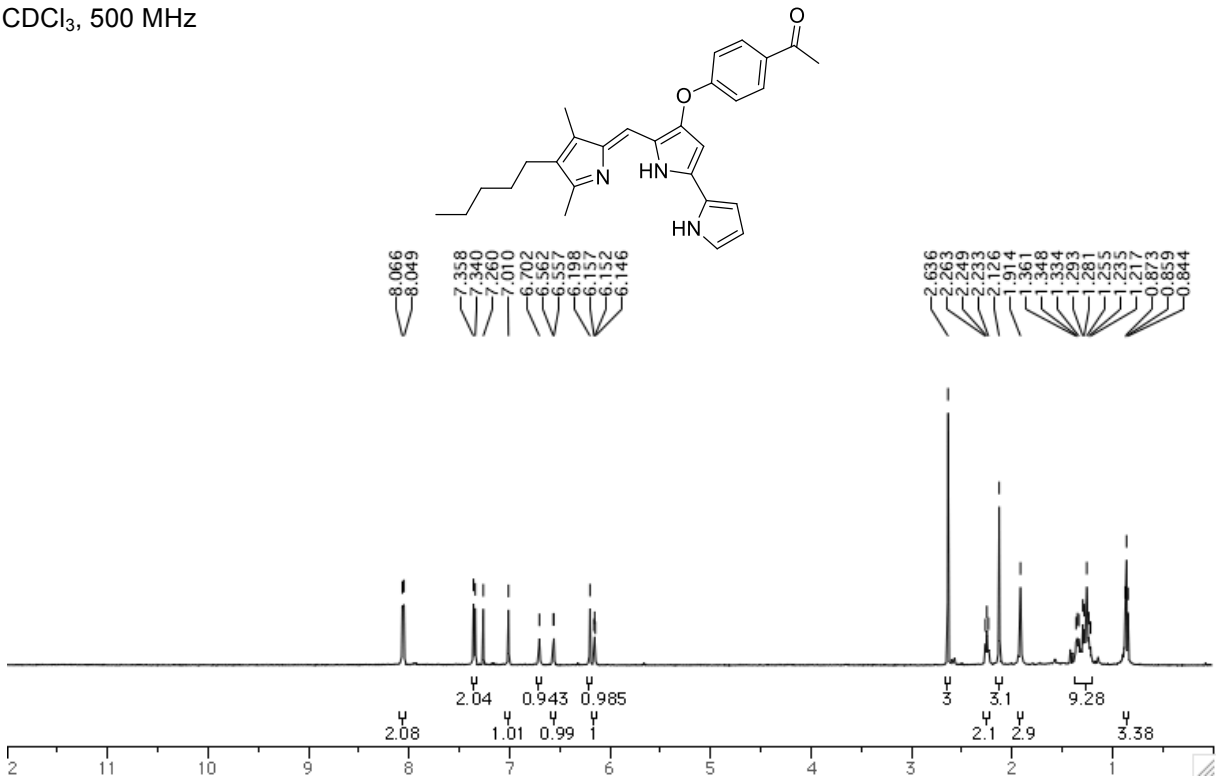
^{1}H NMR for **3f**
$CDCl_3$, 500 MHz



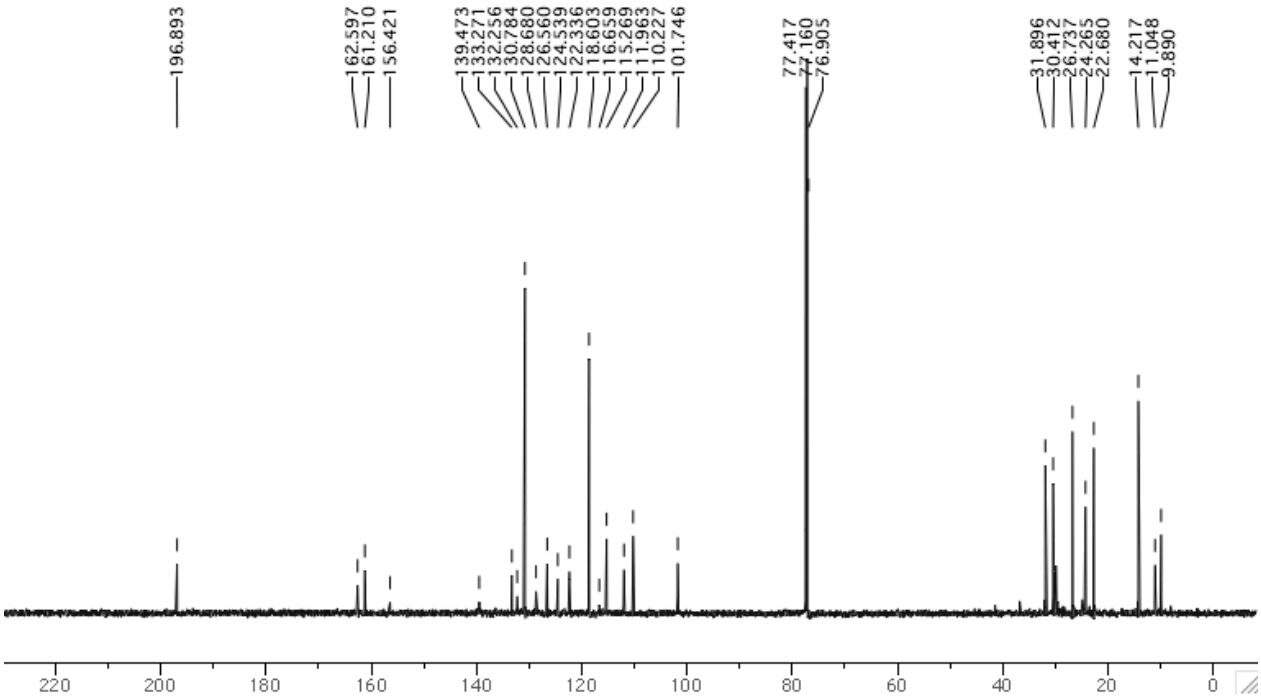
^{13}C NMR for **3f**
$CDCl_3$, 125 MHz



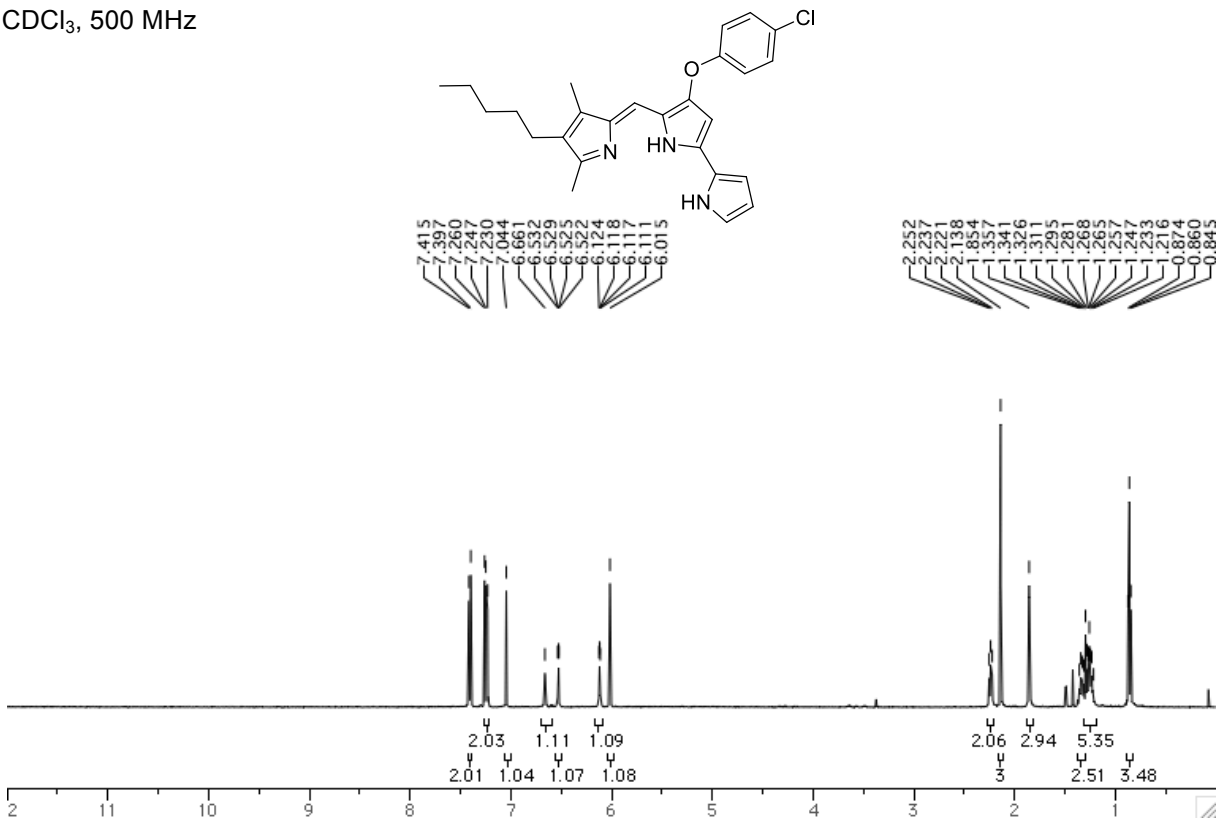
^{1}H NMR for **3g**
$CDCl_3$, 500 MHz



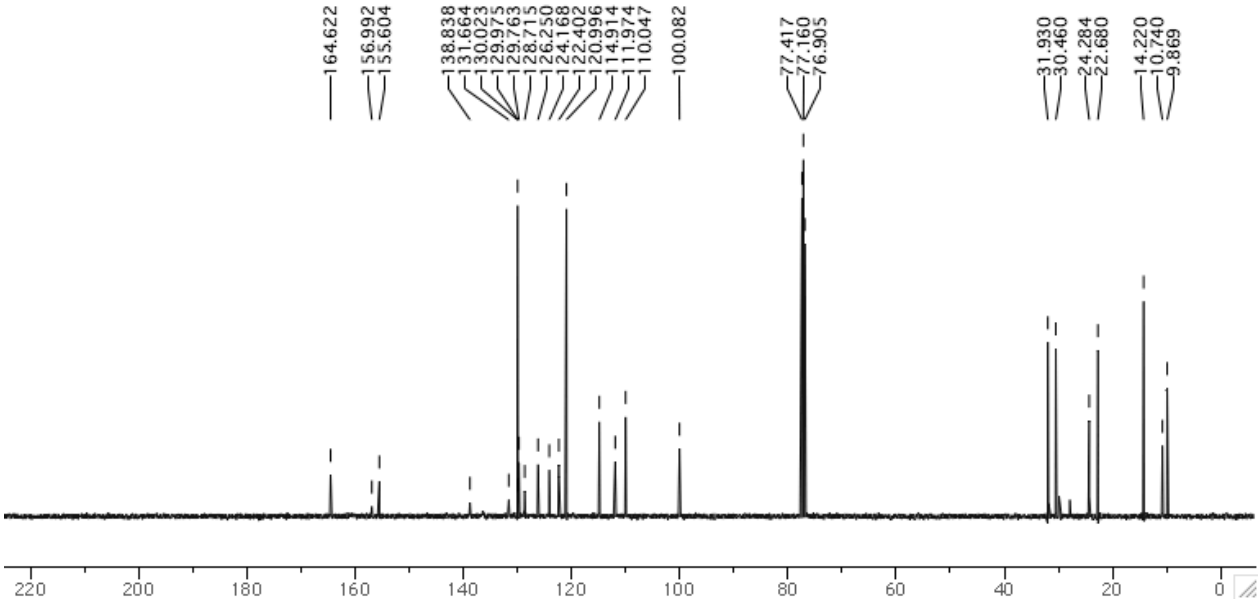
^{13}C NMR for **3g**
$CDCl_3$, 125 MHz



^{1}H NMR for **3h**
$CDCl_3$, 500 MHz



^{13}C NMR for **3h**
$CDCl_3$, 125 MHz



3. NCI data

Table S2: Half Growth Inhibition in nM for prodigiosenes **3h**, **3b**, **3d**, **3a**. Values are a mean of two experiments (provided by the NCI, http://dtp.cancer.gov).

	GI_{50} (nM)			
	3h	**3b**	**3d**	**3a**
CCRF-CEM	20	5< GI_{50}<10	26	26
HL-60(TB)	138	27	209	63
K-562	42	14< GI_{50}<18	58	41
MOLT-4	50	19	78	38
RPMI-8226	38	12< GI_{50}<16	60	32
SR	19	6-11	31	24
A549/ATCC	51	17	34	31
HOP-62	167	30	117	130
HOP-92	30	7< GI_{50}<12	80	13
NCI-H226	440	47	128	137
NCI-H23	116	23	169	86
NCI-H322M	122	27	210	67
NCI-H460	39	12< GI_{50}<16	62	37
NCI-H522	38	18	13	37
COLO205	79	16< GI_{50}<20	77	35
HCC-2998	34	9< GI_{50}<13	66	40
HCT-116	27	12< GI_{50}<16	32	27
HCT-15	53	10< GI_{50}<15	73	31
HT29	34	12< GI_{50}<16	44	26
KM12	26	6< GI_{50}<11	43	30
SW-620	31	13< GI_{50}<17	42	33
SF-268	55	12< GI_{50}<17	104	44
SF-295	127	23	130	56
SF-539	83	18	99	58
SNB-19	221	48	267	161
SNB-75	75	21	119	50
U251	43	10< GI_{50}<15	54	26
LOXIMVI	11	8< GI_{50}<12	30	16
MALME-3M	234	36	169	87
M14	50	16	95	27
MDA-MB-435	47	17	91	34
SK-MEL-2	44	16	73	25
SK-MEL-28	122	30	140	75
SK-MEL-5	25	14	52	27
UACC-257	176	38	126	133
UACC-62	36	14	70	23
IGROV1	166	32	169	111
OVCAR-3	71	16	98	35
OVCAR-4	38	6< GI_{50}<11	87	31
OVCAR-5	90	19	94	59
OVCAR-8	94	21	110	44
NCI/ADR-RES	385	38	288	167
SK-OV-3	292	44	265	211
786-0	61	15	91	44
A498	84	14	113	35
ACHN	117	21	113	42
CAKI-1	91	12< GI_{50}<17	86	39
RXF393	95	15	75	59
SN12C	84	27	124	58
TK-10	235	34	191	45
UO-31	101	18	111	67
PC-3	69	16< GI_{50}<20	67	30
DU-145	52	9< GI_{50}<14	102	47
MCF7	41	17< GI_{50}<21	51	38

MDA-MB-231/ATCC	14	3< GI_{50}<8	47	17
HS578T	76	16	87	62
BT-549	289	34	300	177
T-47D	52	18	110	38
MDA-MB-468	24	10	46	61

Table S3: Total Growth Inhibition in μM for prodigiosenes **3h**, **3b**, **3d**, **3a**. Values are a mean of two experiments (provided by the NCI, http://dtp.cancer.gov).

	TGI (μM)			
	3h	**3b**	**3d**	**3a**
CCRF-CEM	> 100	1.7	> 100	> 100
HL-60(TB)	1.2	0.2	0.9	0.4
K-562	> 100	> 10	> 100	> 100
MOLT-4	1.9	0.2	1.4	4.2
RPMI-8226	1.4	0.2	0.7	0.3
SR	> 100	> 10	> 100	>100
A549/ATCC	0.3	0.05	0.2	0.2
HOP-62	14.4	1.5	15.9	1.6
HOP-92	0.3	0.05	0.3	0.06
NCI-H226	> 100	1.7	3.8	1.8
NCI-H23	2.9	0.5	2.2	1.4
NCI-H322M	74	3.1	10.9	3.1
NCI-H460	12	1.1	> 10	1.3
NCI-H522	1.1	0.1	0.2	0.5
COLO205	1.5	0.1	0.3	0.4
HCC-2998	5.0	0.6	4.2	1.5
HCT-116	1.2	0.1	0.6	1.6
HCT-15	1.2	0.06	0.4	0.2
HT29	18	1.3	1.6	1.2
KM12	1.1	0.03	0.4	0.6
SW-620	1.9	0.5	1.0	0.8
SF-268	> 10	1.1	1.7	1.4
SF-295	0.8	0.1	0.6	0.3
SF-539	0.7	0.06	0.4	0.7
SNB-19	> 10	1.5	6.0	> 10
SNB-75	0.5	0.06	0.4	0.3
U251	0.5	0.07	0.7	0.1
LOXIMVI	0.05	0.02	0.2	0.04
MALME-3M	1.6	0.1	0.8	0.3
M14	0.6	0.04	0.3	0.08
MDA-MB-435	0.3	0.05	0.3	0.2
SK-MEL-2	0.1	0.04	0.2	0.07
SK-MEL-28	1.2	0.1	0.6	0.6
SK-MEL-5	0.08	0.03	0.1	0.09
UACC-257	2.9	0.3	0.5	1.1
UACC-62	0.1	0.03	0.2	0.05
IGROV1	> 10	1.3	2.3	1.6
OVCAR-3	0.5	0.05	0.4	0.3
OVCAR-4	> 100	0.7	6.0	1.2
OVCAR-5	> 10	0.7	3.3	1.9
OVCAR-8	> 10	0.1	0.6	0.7
NCI/ADR-RES	14	0.2	1.6	1.1
SK-OV-3	17	0.6	1.8	1.7
786-0	0.4	0.04	0.3	0.1
A498	1.9	0.06	0.7	0.5
ACHN	1.7	0.1	5.5	0.8
CAKI-1	0.4	0.05	0.4	0.7
RXF393	0.7	0.1	0.4	0.6

SN12C	> 10	0.2	1.0	0.8
TK-10	3.2	0.3	1.0	0.7
UO-31	0.3	0.07	0.3	0.2
PC-3	> 10	0.7	> 10	1.6
DU-145	2.9	0.1	2.9	1.3
MCF7	2.8	0.7	1.2	0.9
MDA-MB-231/ATCC	0.1	0.02	0.6	0.2
HS578T	0.5	0.07	0.4	0.5
BT-549	> 10	0.8	2.5	1.5
T-47D	4.0	0.6	1.1	0.9
MDA-MB-468	2.2	0.3	1.2	0.5

Table S4: Half lethal concentration in μM for prodigiosenes **3h**, **3b**, **3d**, **3a**. Values are a mean of two experiments (provided by the NCI, http://dtp.cancer.gov).

	LC_{50} (μM)			
	3h	**3b**	**3d**	**3a**
CCRF-CEM	> 100	> 100	> 100	> 100
HL-60(TB)	> 100	> 100	> 10	4.7
K-562	> 100	> 100	> 100	> 100
MOLT-4	> 100	> 100	> 100	> 100
RPMI-8226	> 100	> 100	> 100	> 100
SR	> 100	> 100	> 100	> 100
A549/ATCC	29	2.1	4.3	5.3
HOP-62	> 100	> 10	12	7.2
HOP-92	> 100	7.9	> 100	> 10
NCI-H226	> 100	> 100	> 100	> 100
NCI-H23	42	5.1	20	8.0
NCI-H322M	> 100	24	> 100	29
NCI-H460	> 100	5.6	> 10	6.6
NCI-H522	50	3.0	11	4.0
COLO205	9.5	1.9	2.7	3.8
HCC-2998	> 100	3.7	31	5.7
HCT-116	6.7	0.6	2.9	1.6
HCT-15	63	0.6	9.5	> 100
HT29	> 100	11	> 100	> 100
KM12	24	0.2	32.	3.1
SW-620	12	3.0	> 10	5.2
SF-268	39	4.1	7.3	5.0
SF-295	17	0.8	51	2.4
SF-539	7.1	0.3	1.7	2.9
SNB-19	36	4.4	> 10	10.2
SNB-75	> 100	5.4	37	>10
U251	3.2	0.5	3.0	1.1
LOXIMVI	> 100	0.03	5.2	1.1
MALME-3M	6.4	0.7	3.2	1.7
M14	> 10	0.2	1.6	1.5
MDA-MB-435	4.0	0.3	0.9	2.4
SK-MEL-2	0.8	0.08	0.6	0.4
SK-MEL-28	> 10	0.9	3.1	3.1
SK-MEL-5	0.3	0.06	0.3	0.3
UACC-257	> 100	5.2	> 100	> 10
UACC-62	0.6	0.06	0.5	0.7
IGROV1	> 100	7.3	> 100	7.3
OVCAR-3	3.5	0.3	2.1	1.6
OVCAR-4	> 100	3.8	23	4.4
OVCAR-5	60	7.7	26	8.6
OVCAR-8	48	0.4	2.4	2.8

NCI/ADR-RES	> 100	1.2	> 10	4.8
SK-OV-3	> 100	5.7	14	> 10
786-0	> 100	0.3	1.7	2.7
A498	25	0.3	3.3	2.6
ACHN	> 100	72	60	> 10
CAKI-1	> 100	> 100	> 100	> 10
RXF393	14	1.9	3.3	3.1
SN12C	10	0.8	3.9	3.3
TK-10	76	6.9	16	3.5
UO-31	0.6	0.3	0.6	0.7
PC-3	> 100	> 10	> 100	> 10
DU-145	> 100	> 10	63	> 10
MCF7	> 100	4.9	5.8	6.3
MDA-MB-231/ATCC	> 10	0.9	> 10	5.5
HS578T	31	5.3	> 10	> 100
BT-549	> 100	6.9	26	4.2
T-47D	> 100	31	> 100	> 10
MDA-MB-468	27	2.4	0.5	3.0

4. NMR titrations

As shown in **Fig. 3** of the paper, ^{1}H NMR experiments were performed at 25 °C on **3b**. Methanesulfonic acid (MsOH) was used as the acid. In a typical NMR experiment, a 1 mM solution of **3b** was prepared. Then, MsOH in $CDCl_3$ solution was added and a ^{1}H NMR spectrum was recorded using a Bruker AVIII-600 MHz instrument. After adding 6 eq of MsOH, a solution of TBACl in $CDCl_3$ was consecutively added to the NMR tube. After each addition of TBACl, a ^{1}H-NMR spectrum was recorded using Bruker AVIII-600 MHz instrument.

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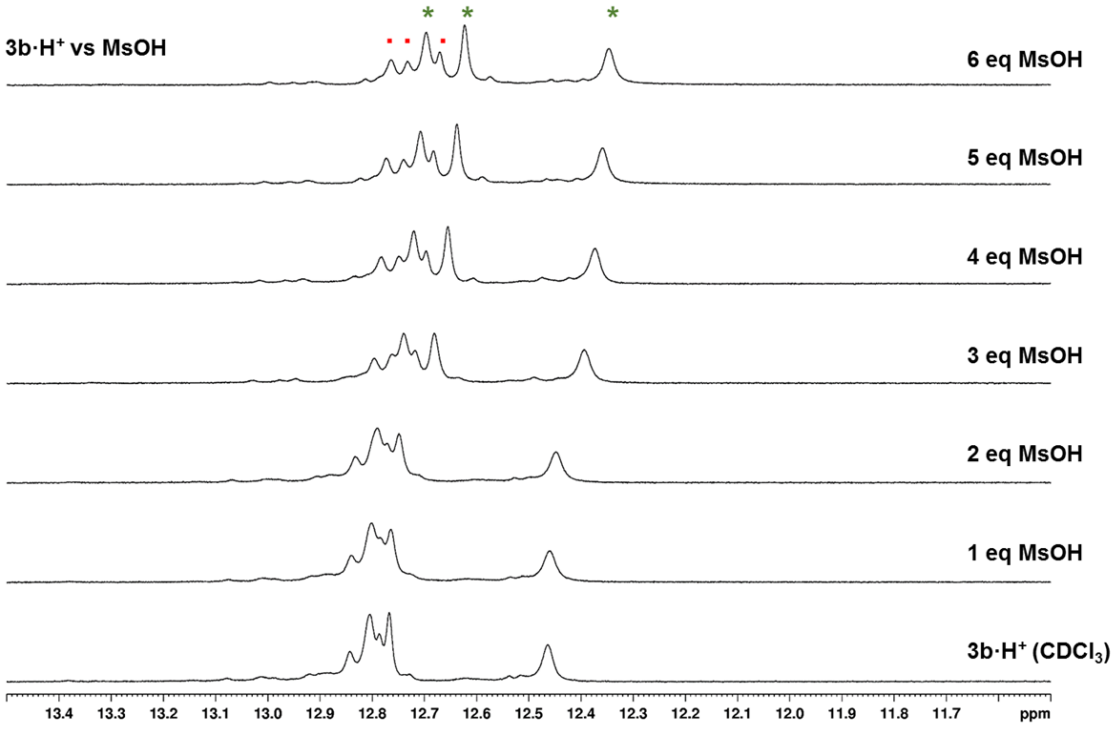


Figure S1. 1H NMR spectra of the NH pyrrole region of 3b·H+ during a titration with equivalents of MsOH in CDCl3 at 25 °C. As increasing equivalents of acid are added, 6 signals can be observed separating from each other. Three minor signals correspond to the 3 NH protons of the α isomer (•) and the 3 major signals correspond to the NH protons of the β isomer (*) (see Scheme 4 in the paper).

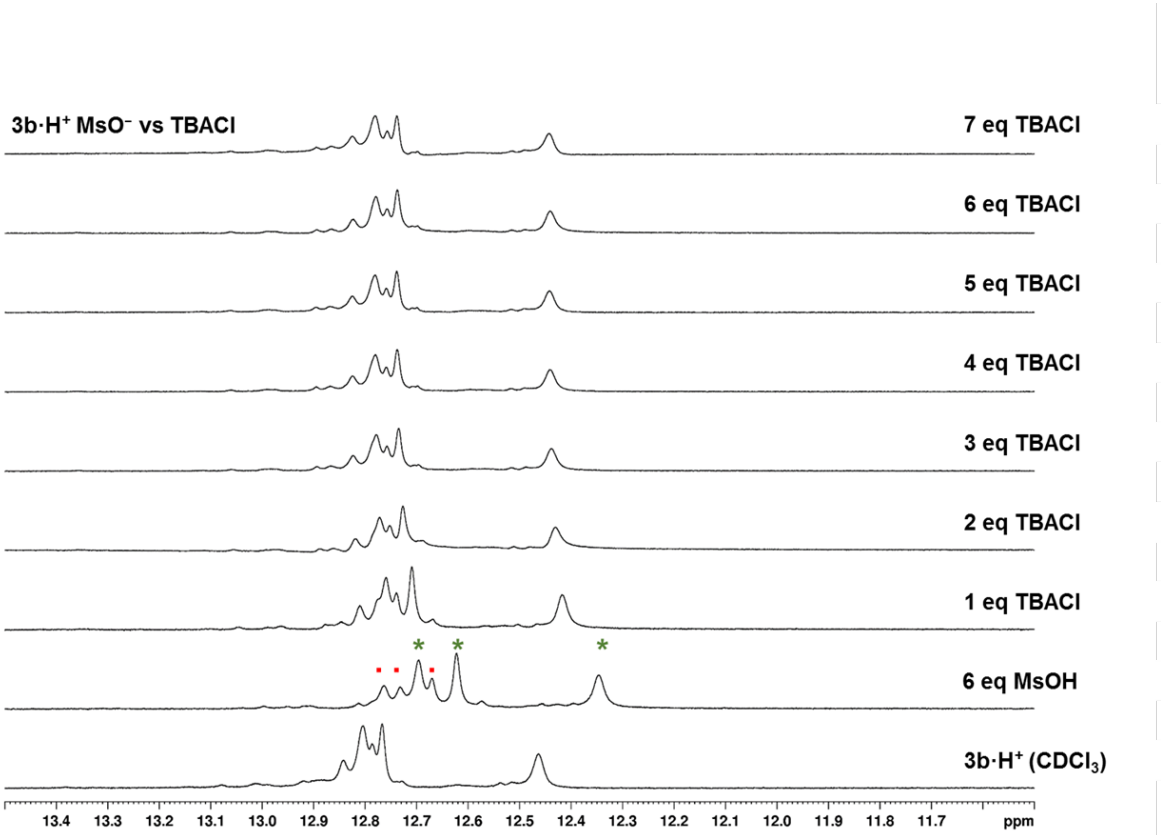
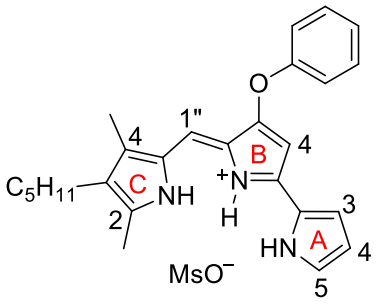
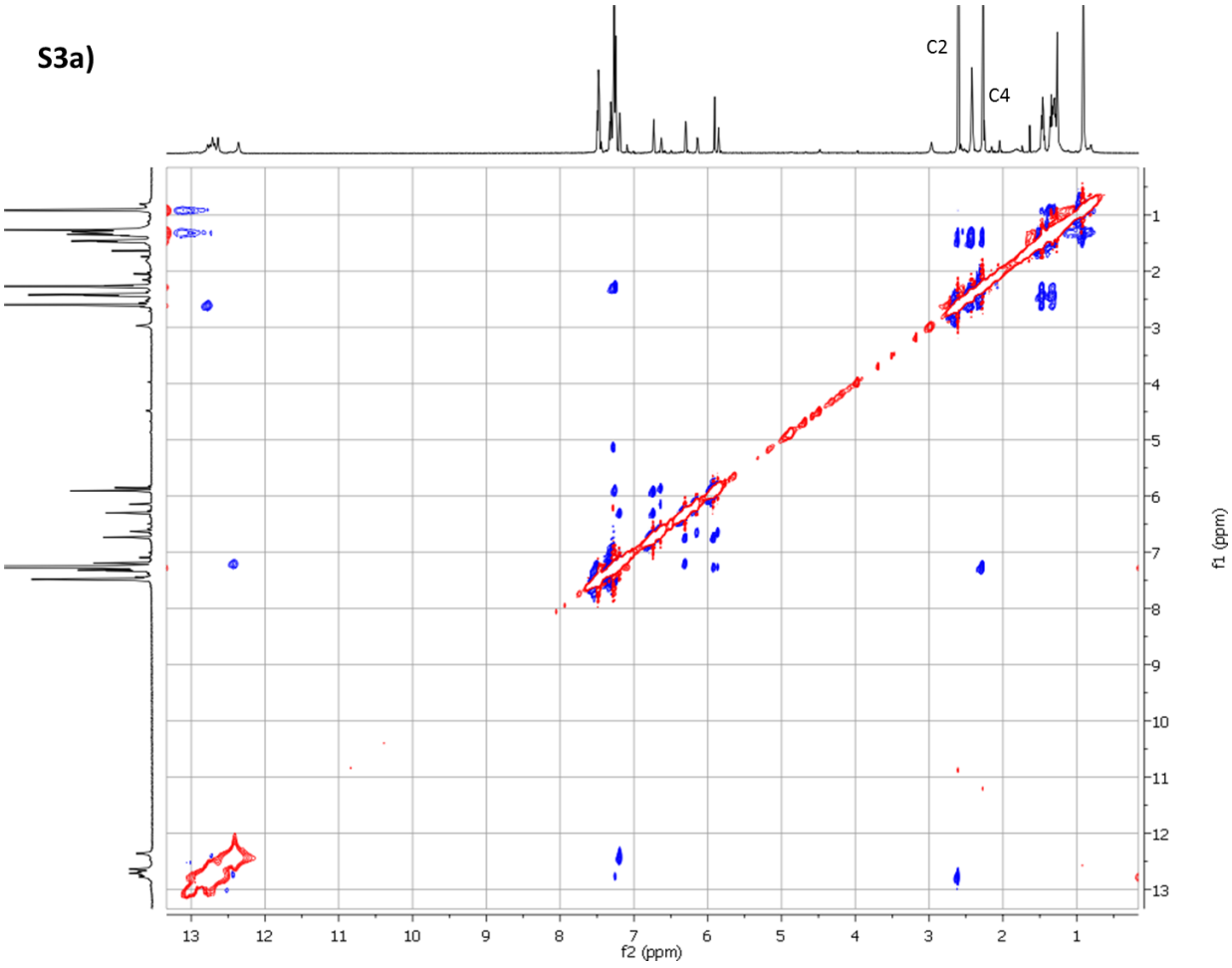


Figure S2. NMR spectra showing a titration of compound **3b** containing 6 eq of MsOH with TBACl. After the addition of 6 eq of MsOH, 6 signals can be observed corresponding to the 3 NH protons of the α conformer (•) and 3 NH protons of the β conformer (*). As equivalents of TBACl are added to the sample, the signals for the α conformer merge with the signals of the β conformer.

5. 3b•HOMs NOESY



S3a)



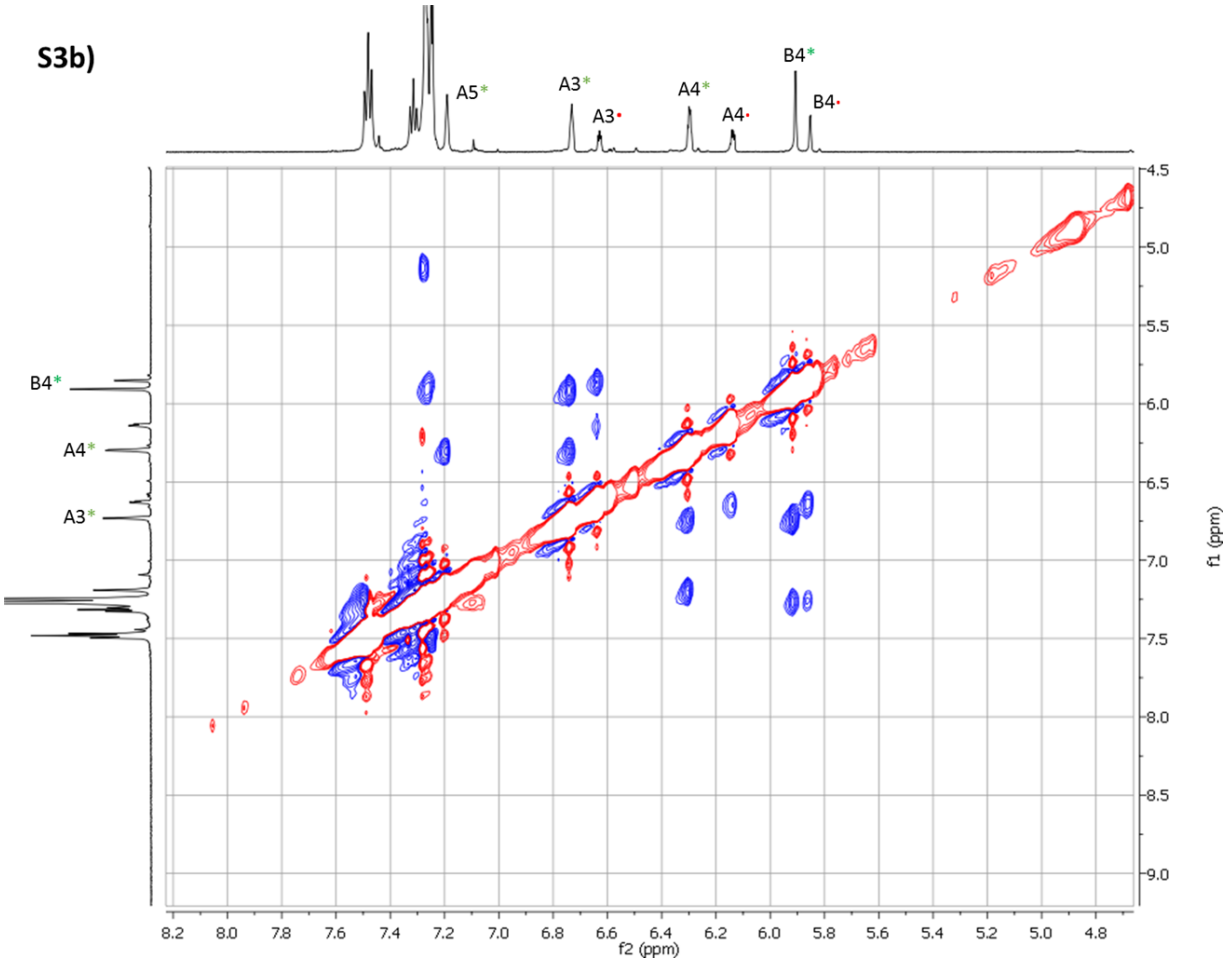
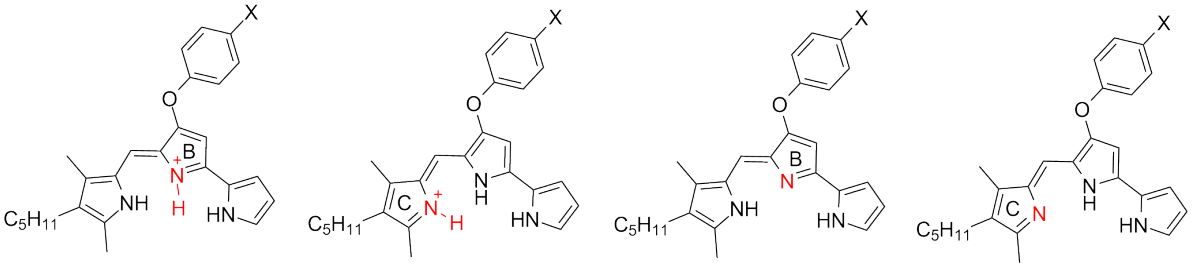


Figure S3. a) Full NOESY spectrum of **3b·HOMs** in $CDCl_3$. b) Expanded region.

6. LogP Values.

Log P is most commonly used for estimating the lipophilicity of a compound and is defined as the logarithm of the partition coefficient in an octanol/water mixture. Log P values were calculated for two tautomers of the protonated and non-protonated form (I, II, III and IV) of compounds **1**, **3b**, **3d**-**f** and **3h** using the VCCLab software.[8, 9] Each tautomer consist of the mixture of the α and β isomer



I II III IV

X	Log*P* (Protonated)		Log*P* (Free Base)	
	Ring **B (I)**	Ring **C (II)**	Ring **B (III)**	Ring **C (IV)**
3d (OCH_3)	4.90 ± 1.41	4.82 ± 1.41	6.18 ± 1.68	6.15 ±1.66
3e (NMe_2)	5.06 ± 1.44	4.98 ± 1.45	6.37 ± 1.65	6.31 ± 1.63
3b (H)	5.01 ± 1.35	4.93 ± 1.37	6.28 ± 1.49	6.26 ± 1.47
3h (Cl)	5.52 ± 1.52	5.43 ± 1.55	6.83 ± 1.61	6.79 ± 1.60
3f (CF_3)	5.81 ± 1.48	5.69 ± 1.55	7.08 ± 1.63	7.01 ± 1.62
Prodigiosin **1**	3.28 ± 1.15	3.42 ± 1.0	4.44 ± 1.11	4.62 ± 1.36

Table S4. Calculated LogP values for compounds **1**, **3b**, **3d**-**f** and **3h**.

7. Determination of pKa Values for Prodigiosenes 1, 3b, 3d-f and 3h

We used a spectrophotometric procedure described by Manderville and colleagues to determine the apparent pK_a values for prodigiosenes **1**, **3b**, **3d-f** and **3h**.[10] The UV-vis spectra were recorded on a Shimadzu UV-1800 UV-Visible spectrophotometer. Standard 10 mm quartz glass cells from Starna Cells Inc. were used. All UV-Vis spectra were recorded at 25 °C with baseline correction. The pH measurements were made using an Accumet AR25A dual channel pH/ion meter equipped with an Accumet pH microelectrode. Calibration was achieved using commercial buffers (Thermo Scientific, pH 4.00, 7.00 and 10.00, all ±0.01). Stock solutions (2 mM) of prodigiosenes **1**, **3b**, **3d-f** and **3h** were prepared in CH_3CN. Then, 15 µL of the stock solution was added to a quartz cuvette containing 2 mL total volume of 1:1 CH_3CN/H_2O (v/v). The ionic strength was kept constant by using 0.1 M NaCl. Acidity constants were determined spectrophotometrically by monitoring absorbance changes in the UV-Vis spectra after additions of dilute HCl or NaOH solutions under constant temperature conditions (25 °C). The pKa values were determined from a plot of log (ionization ratio) vs. pH.

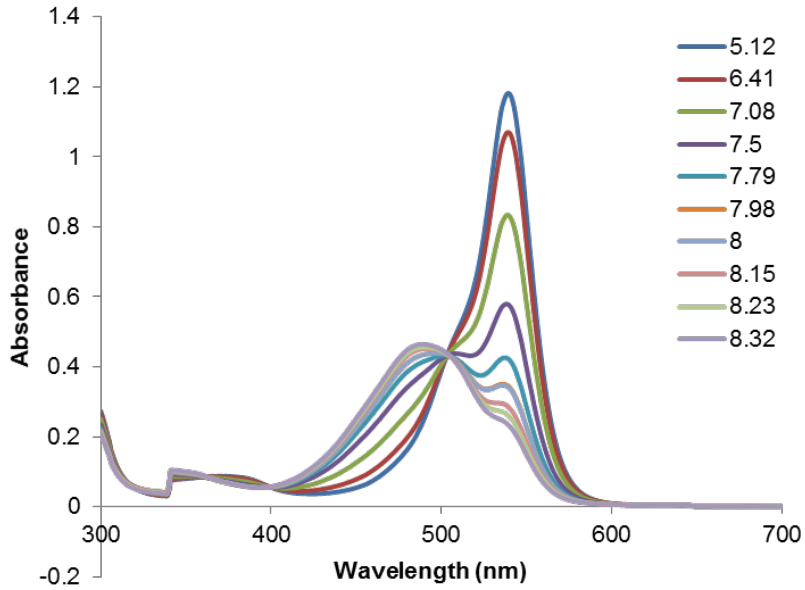


Figure S4. UV-vis absorbance spectra for **3e** as a function of pH in 1:1 CH_3CN–H_2O (v/v) at 25 °C (0.1 M NaCl). Each titration was performed in triplicate.

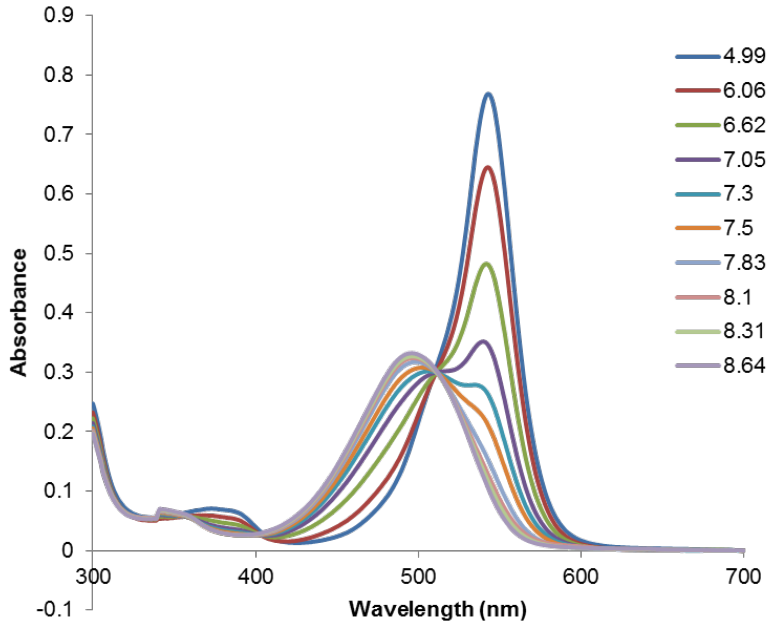


Figure S5. UV-vis absorbance spectra for **3f** as a function of pH in 1:1 CH_3CN–H_2O (v/v) at 25 °C (0.1 M NaCl). Each titration was performed in triplicate.

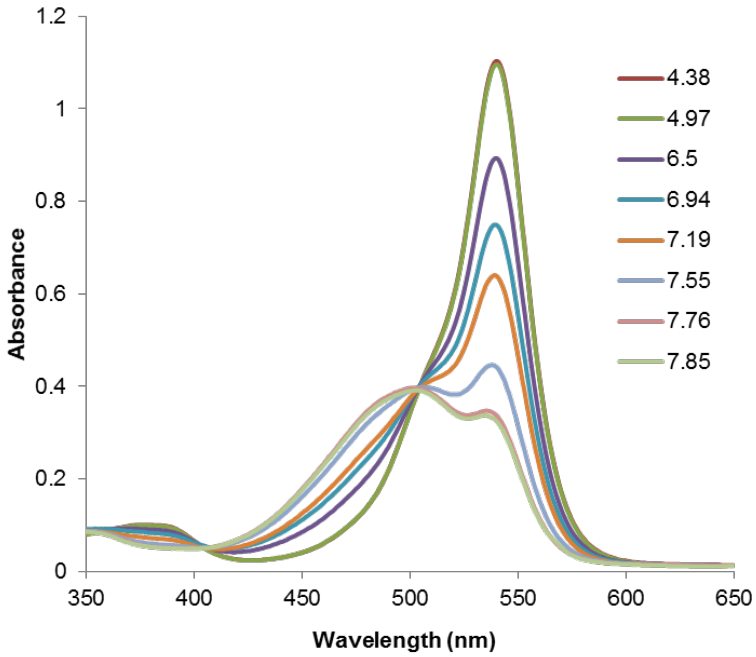


Figure S6. UV-vis absorbance spectra for **3b** as a function of pH in 1:1 CH_3CN–H_2O (v/v) at 25 °C (0.1 M NaCl). Each titration was performed in triplicate.

8. Anion exchange transport assays

Materials. Egg-yolk phosphatidylcholine (EYPC) lipid was purchased from Avanti Polar Lipids. Polycarbonate membranes and the extrusion apparatus used for making the liposomes was also from Avanti Polar Lipids. Salts (> 99% purity) were purchased from Sigma-Aldrich and used as received. The fluorescent dye lucigenin was purchased from Sigma-Aldrich. Prodigiosin **1** was provided by the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, NCI. Buffer solutions were made using ultra-pure water (distilled and then passed through a Millipore filtering system). The pH adjustments were made using concentrated NaOH solution. Fluorescence experiments were completed using a Hitachi model F-4500 fluorescence spectrophotometer.

Preparation of EYPC liposomes. EYPC lipid solution (~60 mg of lipid) was evaporated under reduced pressure to produce a thin film that was then dried *in vacuo* overnight. The resulting lipid film was hydrated with 1 mL of a solution containing 20 mM HEPES (pH = 7.4), 100 mM NaCl and 1 mM of the lucigenin dye.[11] After 9 freeze/thaw cycles (thawing and then warming to 45°C) the liposomes were extruded through a 200 nm polycarbonate membrane 31 times at room temperature to convert any large multi-lamellar vesicles (LMVs) into small unilamellar vesicles (SUV). The liposome solution was then passed through a Sephadex (G-25) column to remove any excess lucigenin dye. The isolated liposomes were diluted in 20 mM HEPES (pH 7.4, 75 mM Na_2SO_4) to give a final concentration of 13 mM in EYPC lipid, assuming complete retention of lipid during the gel filtration process. The size of the liposomes was confirmed using dynamic light scattering experiments.

Chloride-Nitrate Anion Exchange Transport Assay in EYPC Liposomes. In a typical experiment, 0.04 mL of the stock EYPC liposome solution was diluted into 2 mL of a solution of 20 mM HEPES (pH 7.4, 100 mM $NaNO_3$) to give a solution that was 0.2 mM in lipid. The lucigenin's fluorescence was monitored for 720 s with an excitation wavelength of 372 nm and an emission at 504 nm. At t = 30 s we added 1 μL of a 4 μM DMSO solution of the prodigiosene transporter to the cuvette containing the EYPC solution, giving a 1:125,000 ligand to lipid ratio (or 0.0008 mol % wrt lipid concentration). The efflux of Cl- from within the liposomes due to the transporter's catalysis of chloride-nitrate exchange was observed by an increase in the lucigenin's fluorescence. At t = 660 s, we added 0.05 mL of a solution of 10 % Triton-X detergent in order to destroy the liposomes and allow for determination of the maximal fluorescence quenching of lucigenin by Cl-. Experiments were repeated in triplicate and all traces reported in figures 7 in the main text and Fig S7 are the average of three trials.

Initial rates and Half-life

For comparative purposes, the relative transport activity for various ionophores was expressed as the initial rate of lucigenin fluorescence as chloride and nitrate were exchanged across the membrane. Addition of a transporter leads to movement of internal chloride across the membrane, which results in increase in fluorescence of lucigenin. Rates are obtained by linear fitting of initial slopes of fluorescence traces. Half-life were manually calculated for each prodigiosene from fluorescence plots in figure 6.

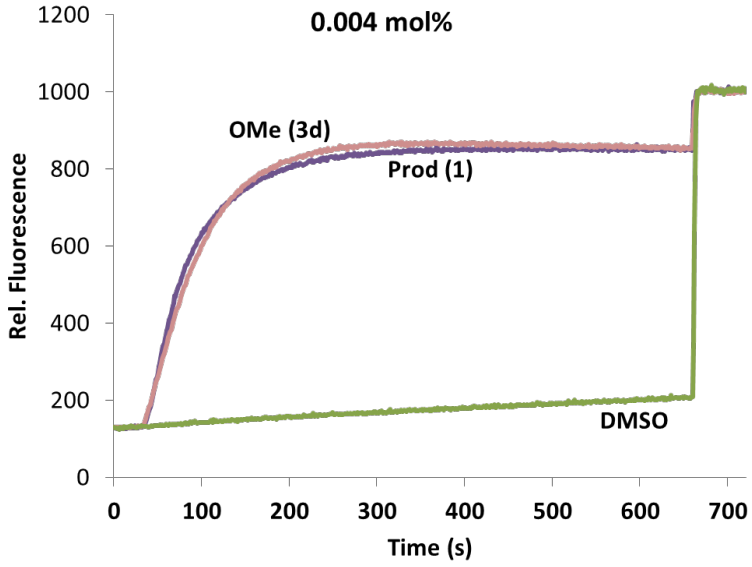


Figure S7. Anion exchange assay for prodigiosin **1** and analog **3d**. Change in fluorescence of lucigenin observed in EYPC liposomes at 25°C. The data was collected using 0.004 mol% of prodigiosene transporter relative to EYPC lipid. Liposomes containing 1 mM lucigenin, 20 mM HEPES buffer and 100 mM NaCl (pH 7.43) were suspend in 20 mM HEPES and 100 mM $NaNO_3$ solution (pH 7.43); at t = 30 s, prodigiosene transporter was added and the fluorescence monitored (λ_{ex} = 372 nm, λ_{em} = 504 nm); at t = 660 s, addition of triton-X; traces shown are an average of three trials.

9. References

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