Electronic Supplementary Information

Silver-catalyzed synthesis of pyrrolopiperazine fused with oxazine/imidazole via domino approach: their evaluation of anti-cancer activity

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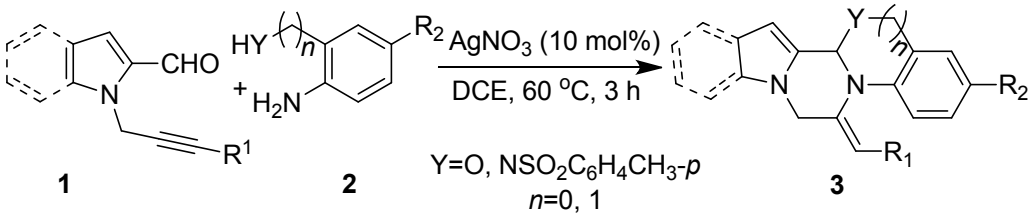
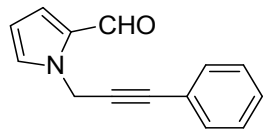
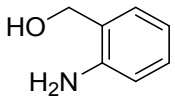
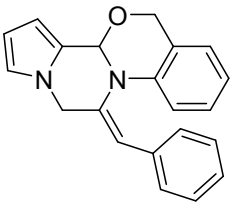
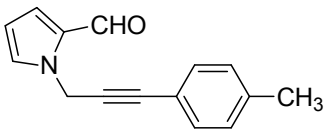
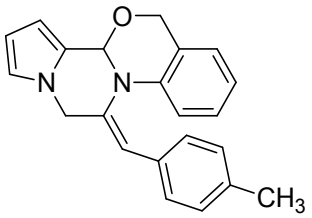
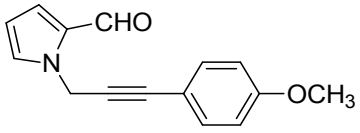
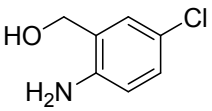
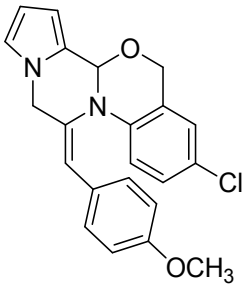
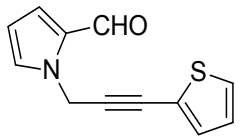
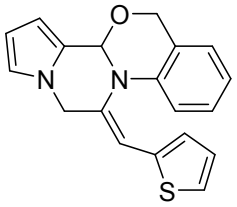
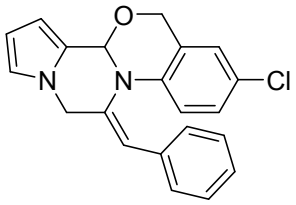
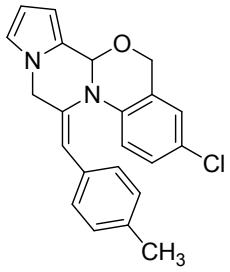
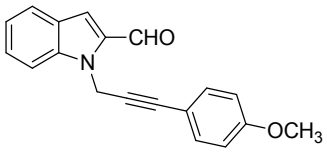
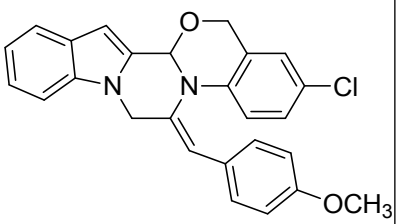
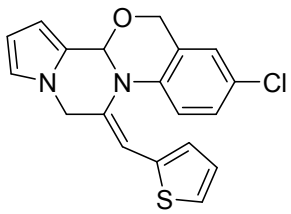
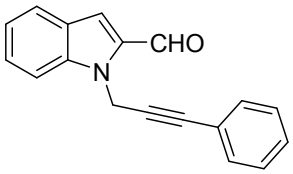
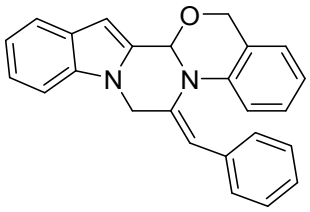
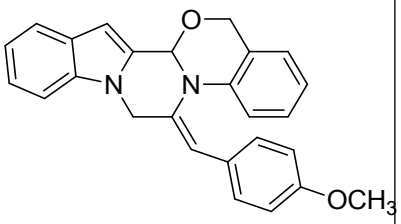
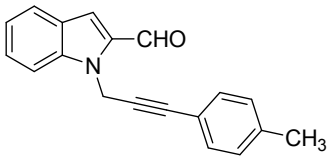
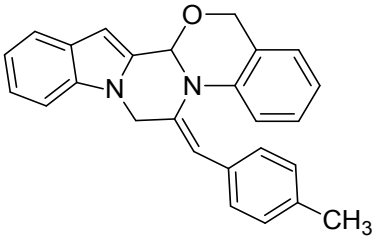
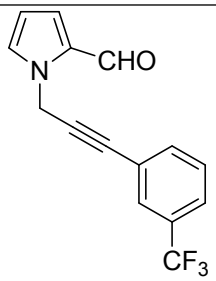
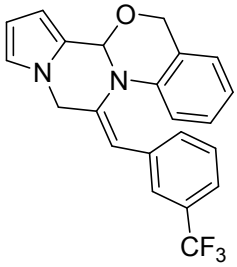
Table S-1: $AgNO_3$ mediated synthesis of compound **3**[a].

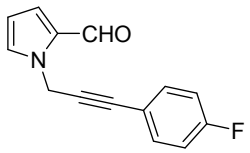
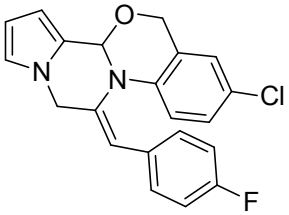
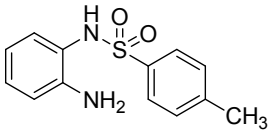
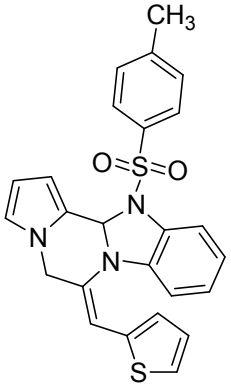
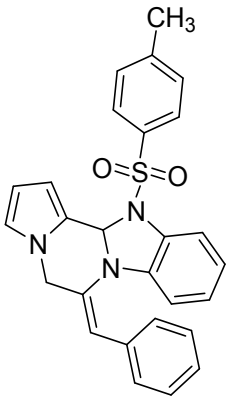
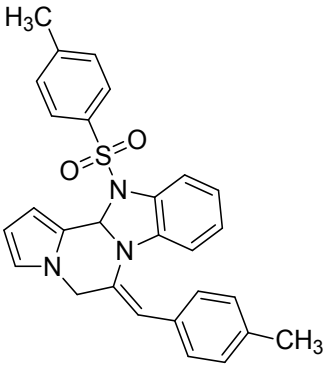


1 **2** **3**

Entry	δ-Alkynyl aldehydes (1)	Nucleophilic amine (2)	Pyrrolopiperazine fused with oxazine/imidazole (3)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	82
2	 **1b**	**2a**	 **3b**	82
3	 **1c**	 **2b**	 **3c**	80

4	 **1d**	**2a**	 **3d**	80
5	**1a**	**2b**	 **3e**	80
6	**1b**	**2b**	 **3f**	75
7	 **1e**	**2b**	 **3g**	76
8	**1d**	**2b**		

			 **3h**	78
9	 **1f**	**2a**	 **3i**	82
10	**1e**	**2a**	 **3j**	80
11	 **1g**	**2a**	 **3k**	78
12	 **1h**	**2a**	 **3l**	82

13	 **1i**	**2b**	 **3m**	84
14	**1d**	 **2c**	 **3n**	78
15	**1a**	**2c**	 **3o**	78
16	**1b**	**2c**	 **3p**	80

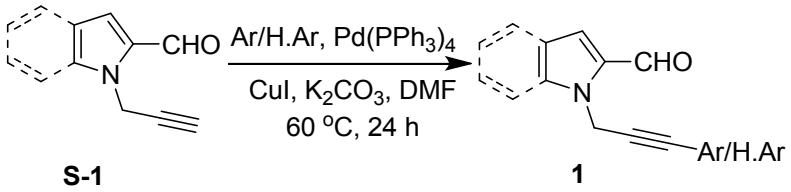
[a]All reactions were carried out by using **1** (1.0 equiv.), **2** (1.3 equiv.) and $AgNO_3$ (10 mol%), in a DCE (5 mL) at 60 ºC for 3 h. [b]Isolated yields after column chromatography.

Chemistry

General methods: Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using hexane and ethyl acetate. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ and DMSO-d_6 solutions by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using a melting point apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer. HRMS data were recorded by electrospray ionization with a Q-TOF mass analyzer.

All starting materials δ-Alkynyl aldehydes (**1a-i**) were prepared according to the known procedure.[1a]

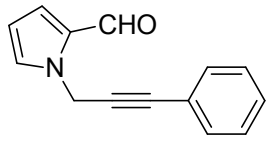
Genereal procedure for the synthesis of δ-Alkynyl aldehydes (1a-i)



S-1 **1**

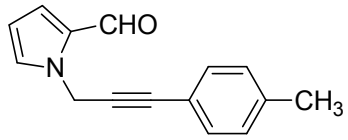
A mixture of S-1[1] (2.72 mmol), the appropriate aryl halide (2.75 mmol), potassium carbonate (0.69 g, 13.64 mmol), CuI (7.6 mg, 0.109 mmol), and $Pd(PPh_3)_4$ (23.1 mg, 0.05 mmol) in dry DMF (5 mL) was stirred at 60 °C for 24 h. After completion of the reaction, the mixture was cooled to room temperature. Then, the reaction mixture was diluted with HCl 0.1 M solution (200 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers and dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel using hexane/ethyl acetate to give the desired product.

1-(3-Phenylprop-2-yn-1-yl)-1*H*-indole-2-carbaldehyde (1a):



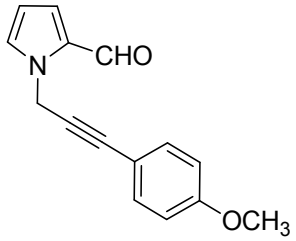
Brown crystals; Yield: 72%; mp: 58-59 °C (lit[2] 58-60 °C); R_f = 0.4 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (d, J = 1.2 Hz, 1H), 7.45-7.43 (m,2H), 7.36 (s, 1H), 7.33-7.29 (m, 3H), 6.98 (dd, J_1,J_2= 1.6 &1.6 Hz, 1H), 6.29 (q, J = 2.4 & 1.2 & 2.8 Hz, 1H), 5.43 (s, 2H).

1-(3-(p-Tolyl)prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde (1b):



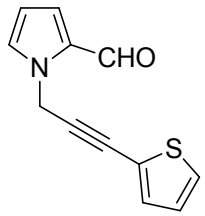
Off white crystals; Yield: 75%; mp: 45-46 °C (lit[3] 44.7-45.6 °C) ; R_f = 0.5 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (d, J = 1.2 Hz, 1H), 7.35 (t, J = 9.2 & 8.0 Hz, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.98 (dd, J_1,J_2= 1.6 & 1.6 Hz, 1H), 6.29 (q, J = 2.8 & 1.2 & 2.8 Hz, 1H), 5.41 (s, 2H), 2.35 (s, 3H).

1-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde (1c):



Pale yellow crystals; Yield: 73%; mp: 69-70 °C (lit[2] 69-71°C); R_f = 0.3 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (d, J = 1.2 Hz, 1H), 7.38 (t, J = 2.4 & 6.4 Hz, 3H), 6.98 (d, J = 1.6 Hz, 1H), 6.85 (dd, J_1,J_2= 2.8 & 4.8 Hz, 2H), 6.29-6.27(m, 1H), 5.40 (s, 2H), 3.80 (s, 3H).

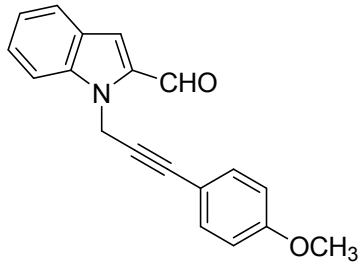
1-(3-(Thiophen-2-yl)prop-2-yn-1-yl)-1*H*-pyrrole-2-carbaldehyde (1d):



Brown liquid; Yield: 62%; R_f = 0.5 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.32 (s, 1H), 7.28-7.26 (m, 1H), 7.23 (d, J = 3.6 Hz, 1H),6.98-6.96 (m, 2H), 6.29 (q, J = 2.8 & 1.2 & 2.8 Hz, 1H), 5.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6,

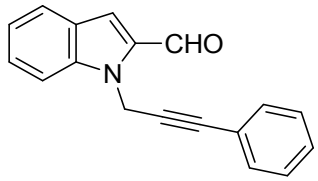
132.8, 131.0, 130.5, 127.7, 127.0, 125.0, 122.0, 110.2, 86.7, 79.4, 39.1; Mass: m/z (CI) 216 (M+1, 100).

1-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)-1H-indole-2-carbaldehyde (1e):



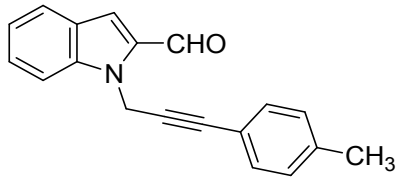
Yellow crystals; Yield: 70%; mp: 72-74 °C (lit[2] 73-74 °C) ; R_f = 0.3 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 8.0 & 8.4 Hz, 1H), 7.30-7.28 (m, 3H), 7.22 (t, J = 7.2 & 7.2 Hz, 1H), 6.77 (d, J = 9.2 Hz, 2H), 5.67 (s, 2H), 3.77 (s, 3H).

1-(3-Phenylprop-2-yn-1-yl)-1*H*-indole-2-carbaldehyde (1f):



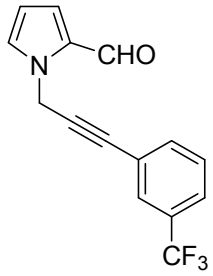
Pale yellow liquid; Yield: 78%; mp: 76-77 °C (lit[2] 77-78 °C); R_f = 0.8 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.48 (dtd, J_d = 1.2, J_t = 0.4 &1.2, J_d = 1.2 Hz, 1H), 7.36-7.34 (m, 2H), 7.30 (d, J = 1.2 Hz,1H), 7.27-7.26 (m, 2H), 7.24-7.20 (m, 2H), 5.68 (s, 2H)**.**

1-(3-(*p*-Tolyl)prop-2-yn-1-yl)-1*H*-indole-2-carbaldehyde (1g):



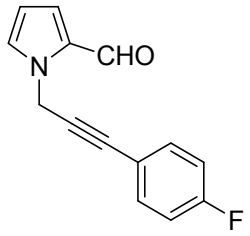
Off white crystals; Yield: 62%; mp: 90-95 °C; R_f= 0.5 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 8.0 & 7.2 Hz, 1H), 7.30 (s, 1H), 7.23-7.20 (m, 3H), 7.05 (d, J = 7.6 Hz, 2H), 5.67 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.7, 140.3, 138.5, 134.6, 131.7 (2C), 128.9 (2C), 127.2, 126.7, 123.5, 121.4, 119.4, 118.5, 111.1, 84.3, 82.9, 34.8, 21.4; Mass: m/z (CI) 274 (M+1, 100).

1-(3-(3-(Trifluoromethyl)phenyl)prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (1h):



Brown crystals; Yield: 56.4%; mp: 55-58 °C; R_f = 0.3 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (d, J = 0.8 Hz, 1H), 7.72 (s, 1H), 7.61 (t, J = 9.8 Hz, 2H), 7.45 (t, J = 7.6 & 8.0 Hz, 1H), 7.32-7.30 (s, 1H), 7.01 (dd, J_1,J_2 = 1.6 & 1.6 Hz, 1H), 6.32-6.34 (m, 1H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 134.9, 131.1, 130.5, 128.9, 128.7, 128.6 (2) (C-F J = 251.4 Hz), 125.3, 125.3, 125.2 (C-F J = 7.5 Hz), 125.0, 123.1, 110.3, 84.5, 84.3, 38.8; Mass: m/z (CI) 278 (M+1, 100).

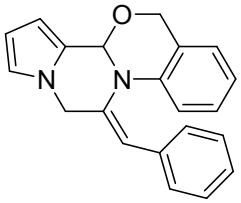
1-(3-(4-Fluorophenyl)prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (1i):



White needles; Yield: 70.5%; mp: 63-65 °C (lit[3] 62.4–64.1°C) ; R_f = 0.5 (5% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (d, J = 0.8 Hz, 1H), 7.44-7.41 (m, 2H), 7.34-7.32 (m, 1H), 7.03-6.97 (m, 3H), 6.30-6.28 (m, 1H), 5.41 (s, 2H).

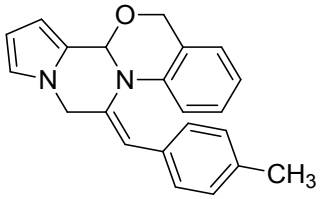
General Procedure for the preparation of compound (3a-p): To a stirred solution of **1** (1.0 equiv.), **2** (1.3 equiv.) and $AgNO_3$ (10 mol%) in dichloroethane (5 mL) was stirred at 60 ºC for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (20 mL)and extracted with DCM (2×20 mL). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography using EtOAc / hexane to give the desired product.

(*Z*)-11-Benzylidene-11,12-dihydro-3bH,5*H*-benzo[*d*]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine (3a)



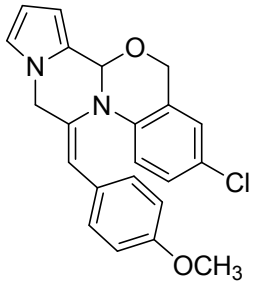
Yellow crystals; Yield: 82%; mp: 135-140 °C; R_f= 0.6 (5% EtOAc/ *n*-hexane);IR :3398, 2924, 2852, 1634, 1301 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 7.2 Hz, 3H), 6.87 (t, *J* = 5.2 & 3.6 Hz, 1H), 6.69-6.66 (m, 3H),6.57 (t, *J* = 4.4 & 5.2 Hz, 1H), 6.36 (d, *J* = 3.6 Hz, 1H), 6.26 (t, *J*= 3.6 & 2.8 Hz, 1H), 6.19 (s, 1H), 5.85 (s, 1H), 5.17 (d, *J* = 14.8 Hz, 1H), 5.07 (d, *J* = 14.8 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 135.0, 130.9, 128.4, 128.3 (2C), 127.4 (2C), 126.5, 126.4, 125.2, 124.4, 123.7, 120.7, 119.0, 118.9, 108.9, 106.2, 81.9, 66.7, 51.5; Mass: m/z (CI) 315 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{21}H_{18}N_2O]^+$ = $[M + H]^+$ 315.1480, found 315.1492.

(*Z*)-11-(4-Methylbenzylidene)-11,12-dihydro-3*bH*,5*H*-benzo[d]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine (3b)



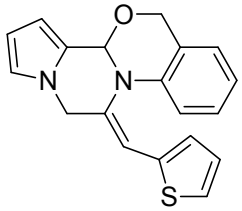
Dark red crystals; Yield: 82%; mp: 100-104 °C; R_f= 0.6 (5% EtOAc/ *n*-hexane); IR: 3365, 2923, 1648, 1489, 714, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 7.6 Hz, 2H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 2H), 6.76-6.64 (m, 3H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.34 (d, *J* = 3.2 Hz, 1H), 6.25-6.22 (m, 2H), 5.87 (s, 1H), 5.13 (d, *J* = 15.2 Hz, 1H), 5.06 (d, *J* = 14.4 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 136.5, 131.9, 130.2, 129.1, 128.3 (2C), 126.8, 126.6 (2C), 125.4, 124.4, 123.3, 120.4, 119.0, 118.3, 108.8, 105.9, 81.9, 66.2, 51.0, 21.2; Mass: m/z (CI) 329 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{22}H_{20}N_2O]^+$ = $[M + H]^+$ 329.1644, found 329.1648.

(*Z*)-7-Chloro-11-(4-methoxybenzylidene)-11,12-dihydro-3*bH*,5*H*benzo[*d*]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine(3c)



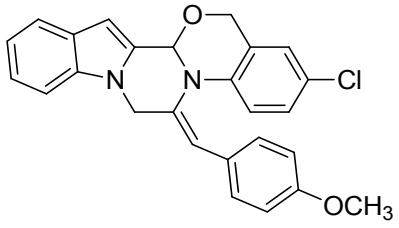
Yellow needles; Yield: 80%; mp: 92-95 °C; R_f = 0.6 (5% EtOAc/ *n*-hexane); IR: 3298, 2940, 1688, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 2.4 Hz, 1H), 6.72-6.67 (m, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.50 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H), 6.24 (t, J = 2.8 & 5.6 Hz, 2H), 5.85 (s, 1H), 5.06 (d, J = 15.2 Hz, 1H), 5.01 (d, J = 15.2 Hz, 1H), 4.67 (d, J = 12.4 Hz, 1H), 4.59 (d, J = 12.4 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 137.9, 129.7 (2C), 129.1, 127.2, 126.7, 125.3, 125.0, 124.7, 124.3, 119.4, 119.2, 113.9, 113.3 (2C), 108.9, 106.1, 81.9, 65.7, 55.2, 50.8; Mass: m/z (CI) 379 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{22}H_{19}ClN_2O_2]^+ = [M + H]^+$ 379.1213, found 379.1208.

(*Z*)-11-(Thiophen-2-ylmethylene)-11,12-dihydro-3*bH*,5*H*-benzo[*d*]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine (3d)



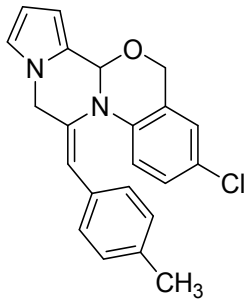
Light yellow crystals; Yield: 80%; mp: 106-110 °C; R_f = 0.6 (5% EtOAc/ *n*-hexane); IR: 3410, 2899, 1588, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 4.4 Hz, 1H), 7.0-6.90 (m, 4H), 6.82-6.73 (m, 3H), 6.61 (s, 1H), 6.29 (s, 1H), 6.20 (s, 1H), 5.97 (s, 1H), 5.08 (d, J = 14.4 Hz, 1H), 4.90 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 12.8 Hz, 1H), 4.51 (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 136.6, 130.3, 128.6, 127.7, 127.5, 126.1 (2C), 124.8, 122.6, 120.4, 120.1, 119.1, 115.5, 108.8, 105.4, 81.4, 63.6, 47.5; Mass: m/z (CI) 321 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{19}H_{16}N_2OS]^+ = [M + H]^+$ 321.1064, found 321.1062.

(*Z*)-11-Benzylidene-7-chloro-11,12-dihydro-3*bH*,5*H*-benzo[d]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine (3e)



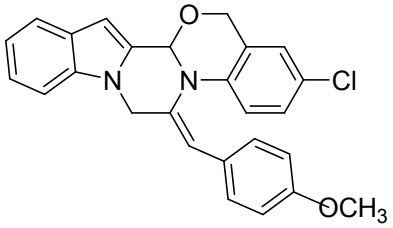
Light yellow crystals; Yield: 80%; mp: 100-104 °C; R_f = 0.6 (5% EtOAc/*n*-hexane); IR: 3400, 2850, 1633, 1489, 720, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 3.6 Hz, 2H), 7.02 (d, *J* = 4.0 Hz, 3H), 6.86 (s, 1H), 6.69 (s, 1H), 6.62 (d, *J* = 10.0 Hz, 1H), 6.48 (d, *J* = 8.8 Hz, 1H), 6.34-6-36 (m, 1H), 6.26 (t, *J* = 2.4 & 3.2 Hz, 1H), 6.21 (s, 1H), 5.81 (s, 1H), 5.11 (d, *J* = 15.2 Hz, 1H), 5.02 (d, *J* = 14.8 Hz, 1H), 4.76 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.2, 135.3, 131.1, 128.4 (2C), 128.0 (2C), 127.0, 126.4, 125.8, 125.0, 124.9, 124.3 (2C), 119.8 (2C), 108.6, 106.4, 81.9, 66.3, 51.0; Mass: m/z (CI) 349 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{21}H_{17}ClN_2O]^+$ = $[M + H]^+$ 349.1098, found 349.1102.

(*Z*)-7-Chloro-11-(4-methylbenzylidene)-11,12-dihydro-3*bH*,5*H*-benzo[*d*]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine(3f)



Colorless needles; Yield: 75%; mp: 155-160°C; R_f = 0.7 (5% EtOAc/ *n*-hexane); IR : 3124, 2851, 1638, 1488, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.0 Hz, 2H), 6.86 (m, *J* = 7.6 Hz, 3H), 6.67-6.64 (m, 2H), 6.49 (d, *J* = 8.8 Hz, 1H), 6.33 (d, *J* = 3.2, 1H), 6.24 (q, *J* = 2.8 & 3.6 & 4.4 Hz, 2H), 5.83 (s, 1H), 5.07 (d, *J* = 14.8 Hz, 1H), 5.00 (d, *J* = 14.8 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.9, 131.8, 129.9, 129.2, 128.4 (2C), 128.3 (2C), 126.7, 125.4, 124.9, 124.8, 124.3, 119.7, 119.2, 108.9, 106.3, 81.9, 65.9, 51.0, 21.1; Mass: m/z (CI) 363 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{22}H_{19}ClN_2O]^+$ = $[M + H]^+$: 363.1284, found 363.1259.

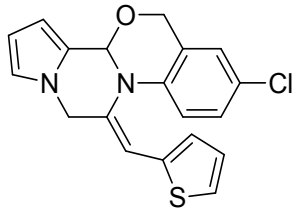
(*Z*)-4-Chloro-8-(4-methoxybenzylidene)-8,9-dihydro-2*H*,15*bH*-benzo[4',5'][1,3]oxazino[2',3':3,4]pyrazino[1,2-*a*]indole (3g)



Brown crystals; Yield: 76%; mp: 86-90 °C; R_f = 0.6 (5% EtOAc/ *n*-hexane); IR: 3356, 2800 1785, 1456, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.8

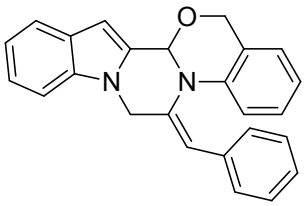
Hz, 1H), 7.28 (s, 1H), 7.15 (t, *J* = 6.4 & 7.6 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 6.68 (t, *J* = 7.2 & 8.4 Hz, 3H), 6.61 (s, 1H), 5.88 (s, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.47 (d, *J* = 15.6 Hz, 1H), 3.74 (s, 3H), 3.65 (d, *J* = 16.8 Hz, 1H), 3.57 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 139.4, 132.4, 131.5, 130.1, 129.4 (2C), 129.0, 128.2, 127.8, 126.5, 126.3, 126.0, 124.7, 122.3, 121.4, 120.6, 113.4 (2C), 109.2, 103.6, 99.7, 80.5, 66.7, 55.3, 36.2; Mass: m/z (CI) 429 (M+1, 100).

(*Z*)-7-Chloro-11-(thiophen-2-ylmethylene)-11,12-dihydro-3*bH*,5*H*-benzo[*d*]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine (3h)



Dark red needles; Yield: 78%; mp: 75-80 °C; R_f = 0.7 (5% EtOAc/ *n*-hexane); IR: 3255, 2700, 1658, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 4.8 Hz, 1H), 7.01 (d, *J* = 3.2 Hz, 1H), 6.94-6.92 (m, 3H), 6.82 (s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H), 6.28 (d, *J* = 3.6 Hz, 1H), 6.20 (t, *J* = 2.8 & 3.2 Hz, 1H), 5.95 (s, 1H), 5.03 (d, *J* = 14.4 Hz, 1H), 4.85 (d, *J* = 14.8 Hz, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 4.50 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 136.3, 129.8, 128.9, 128.0, 127.6, 126.3, 125.7, 125.0, 124.8, 124.1, 119.3, 116.8, 108.9, 105.7, 81.5, 63.2, 47.4, 29.7; Mass: m/z (CI) 355 (M+1, 100), HR-MS (ESI+) m/z calculated for $[C_{19}H_{15}ClN_2OS]^+ = [M + H]^+$ 355.0678, found 355.0672.

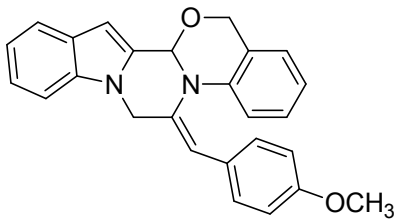
(*Z*)-8-Benzylidene-8,9-dihydro-2*H*,15*bH*-benzo[4',5'][1,3]oxazino[2',3':3,4]pyrazino[1,2-*a*]indole (3i)



Brown crystals; Yield: 82%; mp: 80-84 °C; R_f = 0.5 (5% EtOAc/ *n*-hexane); IR : 3412, 2965, 1598, 1485, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.28-7.24 (m, 1H), 7.20-7.14 (m, 2H), 7.12-7.03 (m, 5H), 6.99 (t, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.71 (s, 1H), 6.22 (s, 1H), 5.95 (s, 1H), 4.98 (d, *J* = 15.2 Hz, 1H), 4.48 (d, *J* = 15.2 Hz, 1H), 3.78 (d, *J* = 16.0 Hz, 1H), 3.65 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 137.2, 132.3, 130.0, 128.4 (3C), 128.1, 127.8 (2C), 127.7,

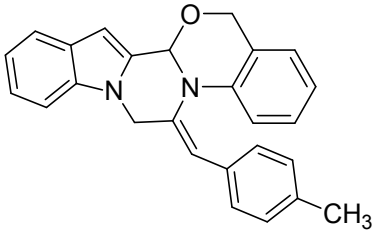
126.6, 126.1, 126.0, 125.0, 124.7, 122.1, 121.3, 120.4, 109.2, 103.3, 99.5, 80.3, 67.05, 37.05: Mass: m/z (CI) 365 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{25}H_{20}N_2O]^+ = [M + H]^+$ 365.1656, found 365.1648.

(*Z*)-8-(4-Methoxybenzylidene)-8,9-dihydro-2*H*,15*bH*-benzo[4',5'][1,3]oxazino[2',3':3,4]pyrazino[1,2-*a*]indole (3j)



Dark brown crystals; Yield: 80%; mp: 100-105 °C; R_f = 0.6 (10% EtOAc/ *n*-hexane); IR : 3392, 3053, 2923, 1607, 1509, 1461, 1243, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.23-7.10 (m, 4H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 3.6 Hz, 2H), 6.63 (s, 1H), 6.61 (s, 1H), 5.94 (s, 1H), 4.98 (d, *J* = 15.2 Hz, 1H), 4.52 (d, *J* = 14.8 Hz, 1H), 3.72 (s, 3H), 3.69 (d, *J* = 15.6 Hz, 1H), 3.58 (d, *J* = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 140.8, 132.4, 130.0, 129.5 (2C), 129.2, 128.5, 127.8, 127.0, 126.0, 125.0, 124.8, 124.7, 122.1, 121.3, 120.4, 113.3 (2C), 109.2, 103.0, 99.4, 80.4, 67.1, 55.2, 36.2; Mass: m/z (CI) 395 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{26}H_{22}N_2O_2]^+ = [M + H]^+$ 395.1752, found 395.1754.

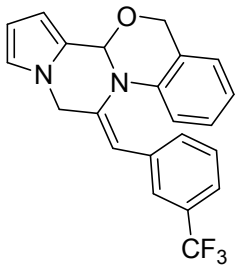
(*Z*)-8-(4-Methylbenzylidene)-8,9-dihydro-2*H*,15*bH*-benzo[4',5'][1,3]oxazino[2',3':3,4]pyrazino[1,2-*a*]indole(3k)



Colorless needles; Yield: 78%; mp: 92-95 °C; R_f=0.5 (5% EtOAc/ *n*-hexane); IR: 3356, 2956, 1685, 1067, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.22-7.03 (m, 5H), 6.92-6.79 (m, 4H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 17.6 Hz, 2H), 5.95 (s, 1H), 5.0 (d, *J* = 15.2 Hz, 1H), 4.55 (d, *J* = 15.2 Hz, 1H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.61 (d, *J* = 16.0 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 135.5, 134.1, 132.3, 130.0, 128.6 (2C), 128.5, 128.4 (2C), 127.8, 126.8, 126.0, 125.0, 124.8, 124.7, 122.1, 121.3, 120.4, 109.2, 103.2, 99.4, 80.4, 67.1, 36.6, 29.7; Mass: m/z (CI) 379

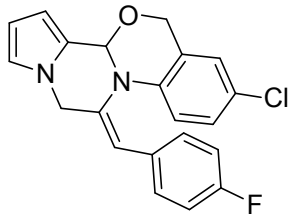
(M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{26}H_{22}N_2O]^+$ = $[M + H]^+$379.1799, found 379.1805.

(Z)-11-(3-(Trifluoromethyl)benzylidene)-3*b*,5,11,12-tetrahydrobenzo[*d*]pyrrolo[2',1':3,4]pyrazino[2,1-*b*][1,3]oxazine (3l):



Light yellow crystals; Yield: 82 %; mp: 135-140 °C; R_f = 0.4 (5% EtOAc/ *n*-hexane); IR: 3122, 1653, 1485, 1025, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.22-7.17 (m, 2H), 7.11 (t, *J* = 6.0 & 6.0 Hz, 1H), 6.90 (d, *J* = 6.4 Hz, 1H), 6.75 (t, *J* = 1.6 & 1.6 Hz, 1H), 6.69 (t, *J* = 6.0 & 6.0 Hz, 1H), 6.63 (t, *J* = 5.6 & 5.6 Hz, 1H), 6.53 (d, *J* = 6.4 Hz, 1H), 6.44-6.42 (m, 1H), 6.34-6.33 (m, 1H), 6.11 (s, 1H), 5.85 (s, 1H), 5.26 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 4.62 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 136.1, 132.4, 130.9, 129.5, 129.2, 127.6, 126.1, 125.1 (C-F *J* = 246 Hz), 124.8, 124.7, 124.6 (C-F *J* = 10.2 Hz), 122.9, 122.7 (2C), 121.7, 120.2, 119.0, 111.6, 109.1, 106.6, 81.9, 67.4, 52.1; Mass: m/z (CI) 383 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{22}H_{18}ON_2F_3]^+$ = $[M + H]^+$ 383.1365, found 383.1357.

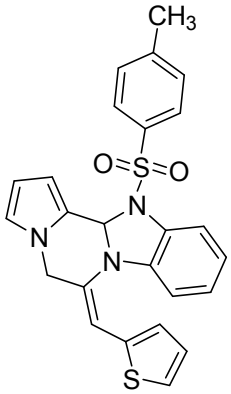
(Z)-7-Chloro-11-(4-fluorobenzylidene)-3*b*,5,11,12-tetrahydrobenzo[d]pyrrolo[2',1':3,4]pyrazino[2,1-b][1,3]oxazine (3m):



Brown needles; Yield: 84%; mp: 190-192 °C; R_f = 0.6 (5% EtOAc/ *n*-hexane); IR: 2986, 1658, 1458, 12541, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.09 (t, *J* = 5.4 Hz, 2H), 6.91 (s, 1H), 6.77-6.69 (m, 4H), 6.51 (d, *J* = 6.8 Hz, 1H), 6.39-6.37 (m, 1H), 6.29 (t, *J* = 2.4 & 2.8 Hz, 1H), 6.17 (s, 1H), 5.82 (s, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 9.6 Hz, 1H), 4.59 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 160.6 (C-F *J* = 196.4 Hz), 137.8, 130.8, 130.5 (C-F *J* = 27 Hz), 129.9, 129.8, 126.6, 126.0, 125.1,

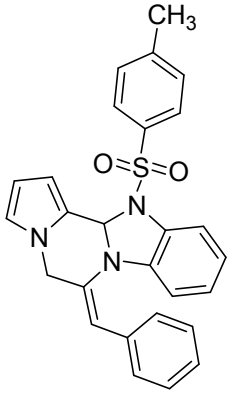
124.6, 124.4, 120.3, 115.6, 115.5, 119.2, 114.6, 114.5, 109.0, 106.4, 82.0, 66.3, 51.3; Mass: m/z (CI) 367 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{21}H_{17}ON_2ClF]^+$ = $[M + H]^+$ 367.1008, found 367.1002.

(*Z*)-6-(Thiophen-2-ylmethylene)-12-tosyl-5,6,12,12*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (3n)



Off white crystals; Yield: 78%; mp: 170-175 °C; R_f = 0.4 (10% EtOAc/*n*-hexane); IR: 3430, 2956, 1588, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 7.6 Hz, 3H), 7.11-6.86 (m, 7H), 6.78 (s, 1H), 6.52 (t, J = 12.4 & 8.8 Hz, 3H), 6.24 (t, J = 6.8 & 10.0 Hz, 2H), 4.68 (d, J = 14.4 Hz, 1H), 4.45 (d, J = 14.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.7, 139.6, 136.5, 133.7, 131.2, 130.2 (2C), 128.3, 127.9, 127.5 (2C), 127.1, 126.5, 126.3, 125.1, 120.8, 119.7, 118.0, 117.9, 110.5, 108.3, 105.6, 74.4, 44.4, 21.1; Mass: m/z (CI) 460 (M+1, 100), HR-MS (ESI+) m/z calculated for $[C_{25}H_{21}N_3O_2S_2]^+$ = $[M + H]^+$ 460.1151, found 460.1153.

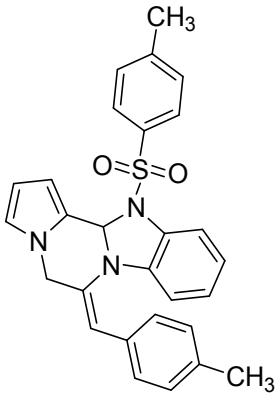
(*Z*)-6-Benzylidene-12-tosyl-5,6,12,12*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (3o)



Pale yellow crystals; Yield: 78%; mp: 175-180 °C; R_f = 0.4 (10% EtOAc/ *n*-hexane);IR : 3421, 3023, 2917, 1644, 1167, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 3H), 7.24 (s, 2H), 7.11 (t, J = 7.6 & 7.2 Hz, 1H), 6.98 (t, J = 7.6 & 7.6 Hz, 2H), 6.82-6.77 (m,

4H), 6.56 (s, 2H), 6.47 (d, *J* = 3.6 Hz, 1H), 6.20 (s, 1H), 6.17 (t, *J* = 2.8 & 3.2 Hz, 1H), 5.94-5.92 (m, 1H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.58 (d, *J* = 15.6 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 139.6, 134.5, 134.3, 131.4, 130.4, 129.8 (2C), 128.6 (2C), 128.2 (2C), 127.7 (2C), 127.2, 126.2, 125.6, 120.8, 120.2, 119.2, 119.1, 111.0, 108.9, 106.6, 75.2, 46.5, 21.7; Mass: m/z (CI) 454 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{27}H_{23}N_3O_2S]^+ = [M + H]^+$ 454.1584, found 454.1584.

(*Z*)-6-(4-Methylbenzylidene)-12-tosyl-5,6,12,12*a*-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (3p):



Pale yellow crystals; Yield: 80%; mp: 175-180 °C; R_f = 0.4 (10% EtOAc/*n*-hexane); IR: 3358, 2875, 1588, 712 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.4 Hz, 3H), 7.26 (d, *J* = 3.2 Hz, 2H), 6.81-6.77 (m, 4H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.56 (s, 2H), 6.48 (d, *J* = 3.6 Hz, 1H), 6.20 (s, 1H), 6.17 (t, *J* = 3.2 & 2.8 Hz, 1H), 5.98 (q, *J* = 3.6 & 2.4 & 3.2 Hz, 1H), 4.74 (d, *J* = 16.4 Hz, 1H), 4.55 (d, *J* = 15.6 Hz, 1H), 2.45 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.0, 139.3, 136.1, 133.8, 132.7, 131.3, 130.7, 130.4 (2C), 129.1 (2C), 128.5 (2C), 127.9 (2C), 126.9, 126.7, 120.7, 120.1, 119.3, 115.0, 111.9, 107.8, 105.1, 74.9, 46.5, 21.6, 21.3; Mass: m/z (CI) 468 (M+1, 100); HR-MS (ESI+) m/z calculated for $[C_{28}H_{25}N_3O_2S]^+ = [M + H]^+$ 468.1767, found 468.1740.

Single crystal X-ray data:

The X-ray data collection was monitored by SMART program (Bruker, 2003). All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2003). SHELX-97 was used for structure solution and full matrix leastsquares refinement on F2. Molecular and packing diagrams were generated using ORTEP-3 and Mercury-3.0. Geometrical calculations were performed using SHELXTL (Bruker, 2003) and PLATON.

Crystal data of (3p): CCDC 1555220, Single crystals suitable for X-ray diffraction of **3p** were grown from DCM: EtOAc (1:1). Molecular formula = C_{28} H_{25} N_3 O_2 S, Formula weight = 467.57, Crystal system = Triclinic, space group = P -1, a = 9.0323(6) Å, b = 10.9047(7) Å, c = 12.9519(9) Å, V = 1185.55(14) Å3, T = 296(2) K, Z = 2, Dc = 1.310 Mg/m^3, 18387 Reflections collected, 3324 [R(int) = 0.1105] independent reflections, Goodness of fit = 1.01.

Pharmacology Cell proliferation Assay

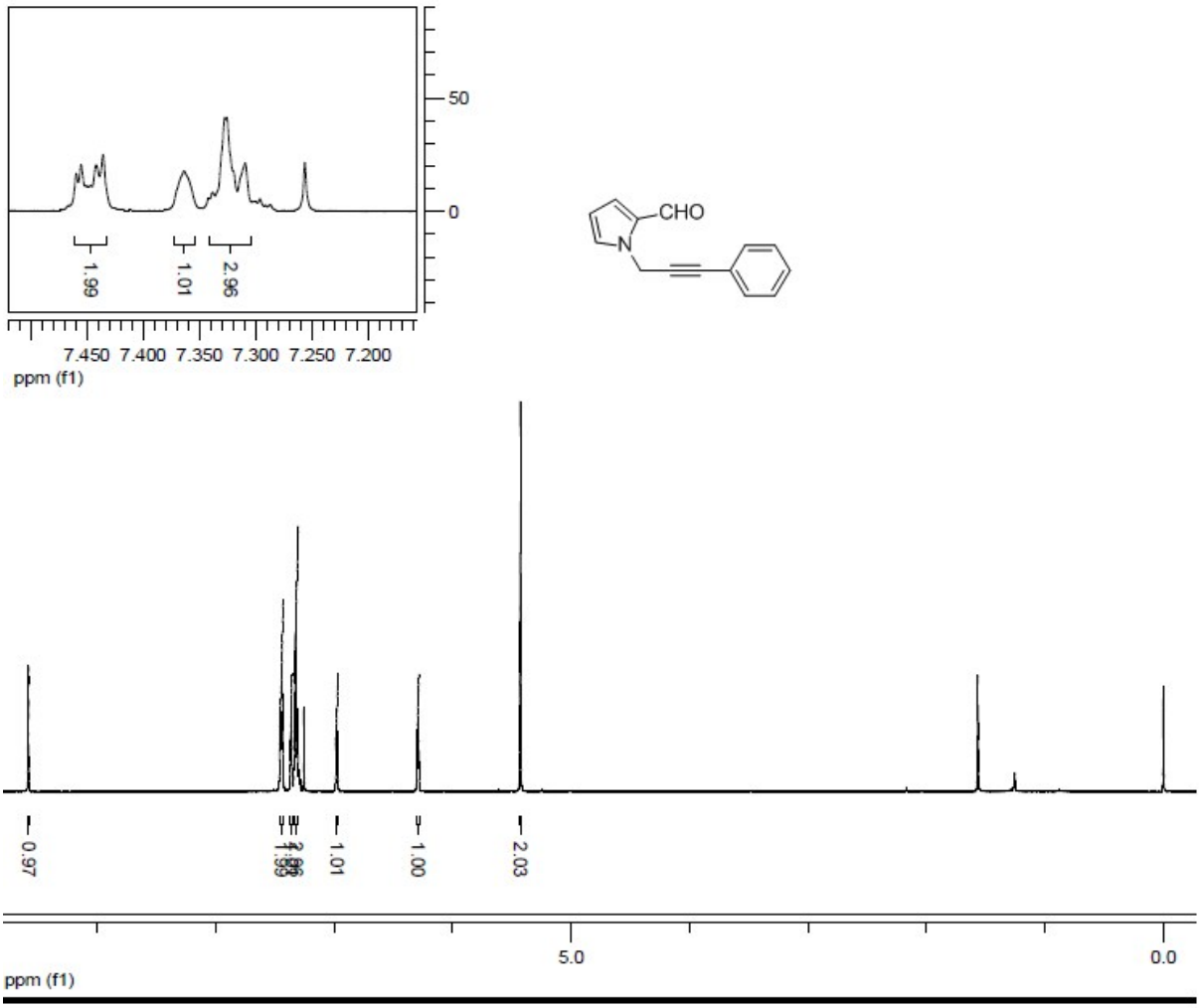
Chronic myeloid leukemia cell line K562 was cultured in RPMI1640 medium supplemented with 10 % fetal bovine serum, 1 % glutamine and antibiotics. Breast cancer cell lines BT474 and MCF7 were cultured in DMEM medium supplemented with 10 % fetal bovine serum, 1 % glutamine and antibiotics. Cytotoxicity measurements were performed by culturing $3x10^3$ cells per well in a 96-well plate in the presence of indicated drugs for 48 hours followed by three-hour incubation with deep blue reagent before measuring absorbance at 570 nm. Cellular IC_{50} values for each compound against three cell lines were calculated as percentage inhibition of cellular activity when compared to that of untreated control cells.

References

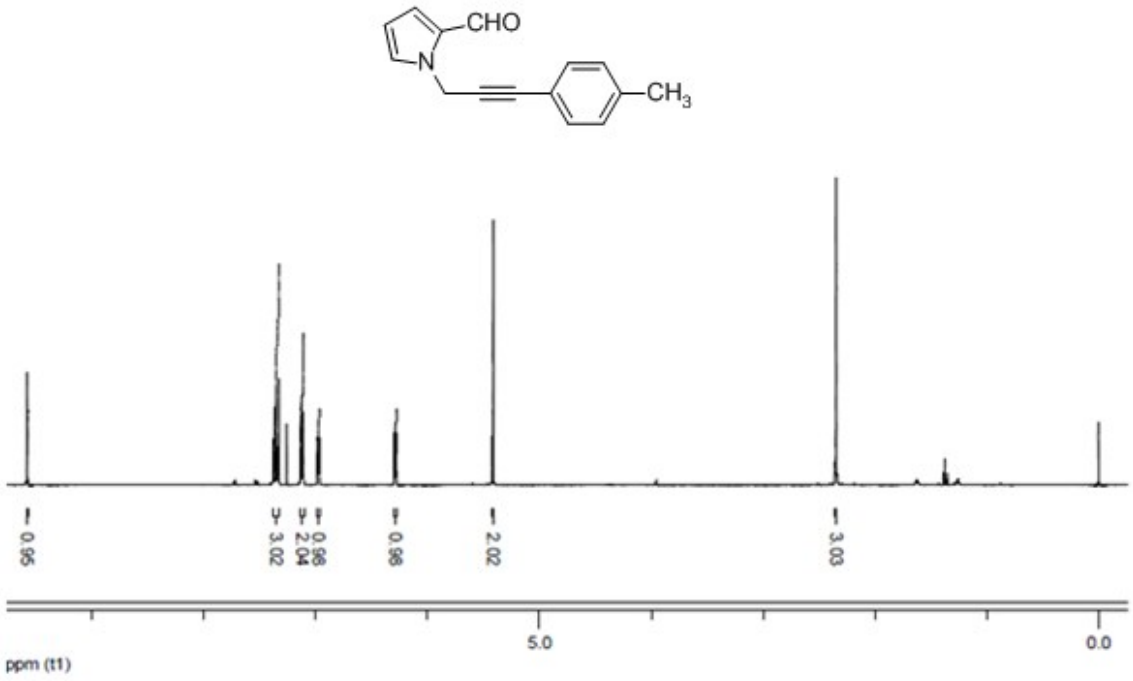
1. (a) G. Abbiati, A. Arcadi, A. Bellinazzi, E. Beccalli, E.Rossi, S. Zanzola, C. Organica and A. Marchesini, *J. Org. Chem.,* 2005, **70***,* 4088-4095. (b) G. Bashiardes, I. Safir and F. Barbot, *Synlett,* 2007, **11**, 1707-1710.
2. S. Guven, M. S. Ozer, S. Kaya, N. Menges and M. Balci, *Org. Lett.*, 2015, **17**, 2660-2663.
3. Masahiro Yoshida and S. Yodokawa, *Heterocycles*, 2012, **86**, 599-609.

Copies of ^{1}H and ^{13}C NMR spectra

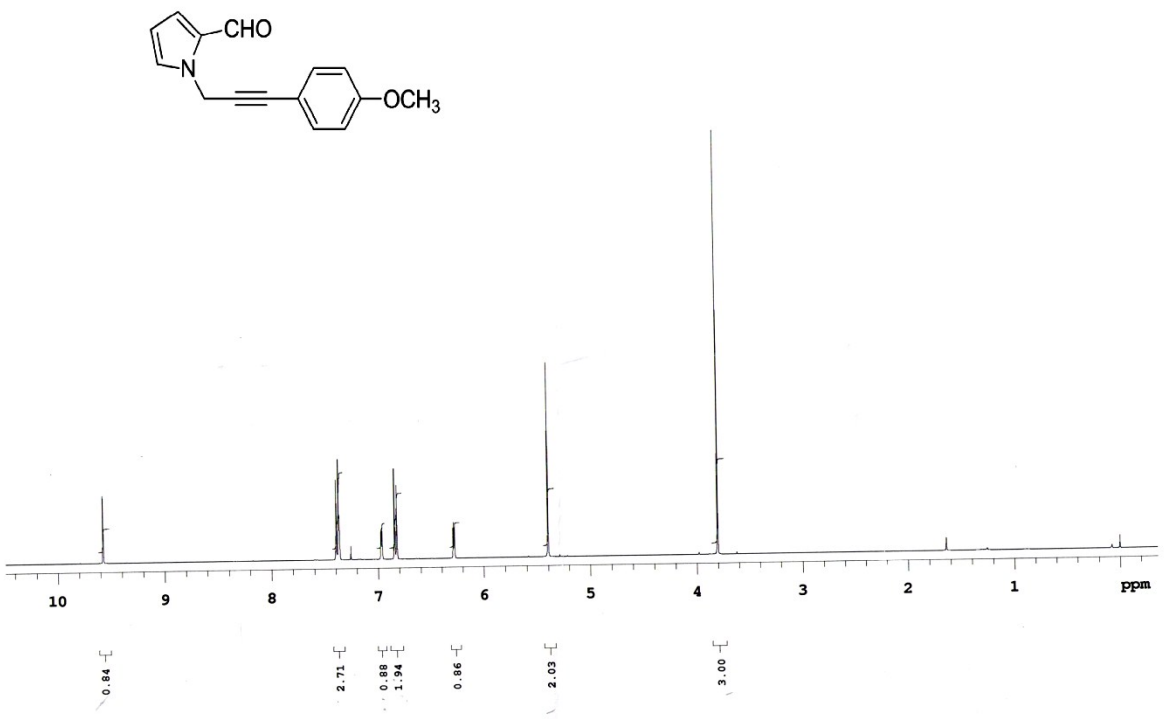
^{1}H NMR (400 MHz, $CDCl_3$) (1a):



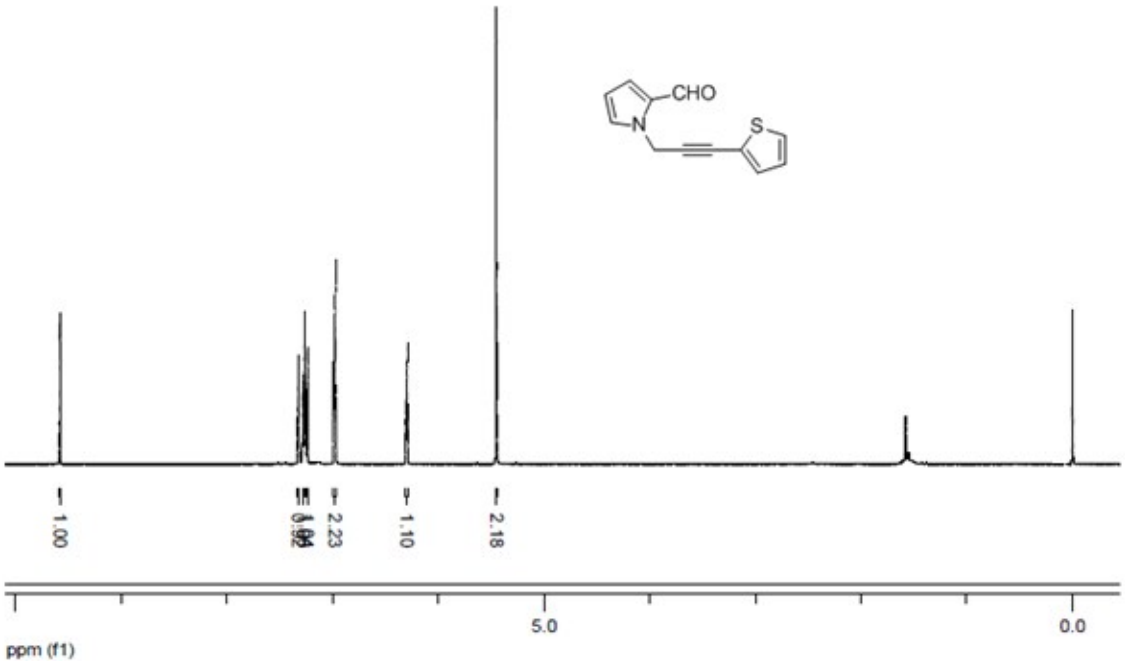
^{1}H NMR (400 MHz, $CDCl_3$) (1b):



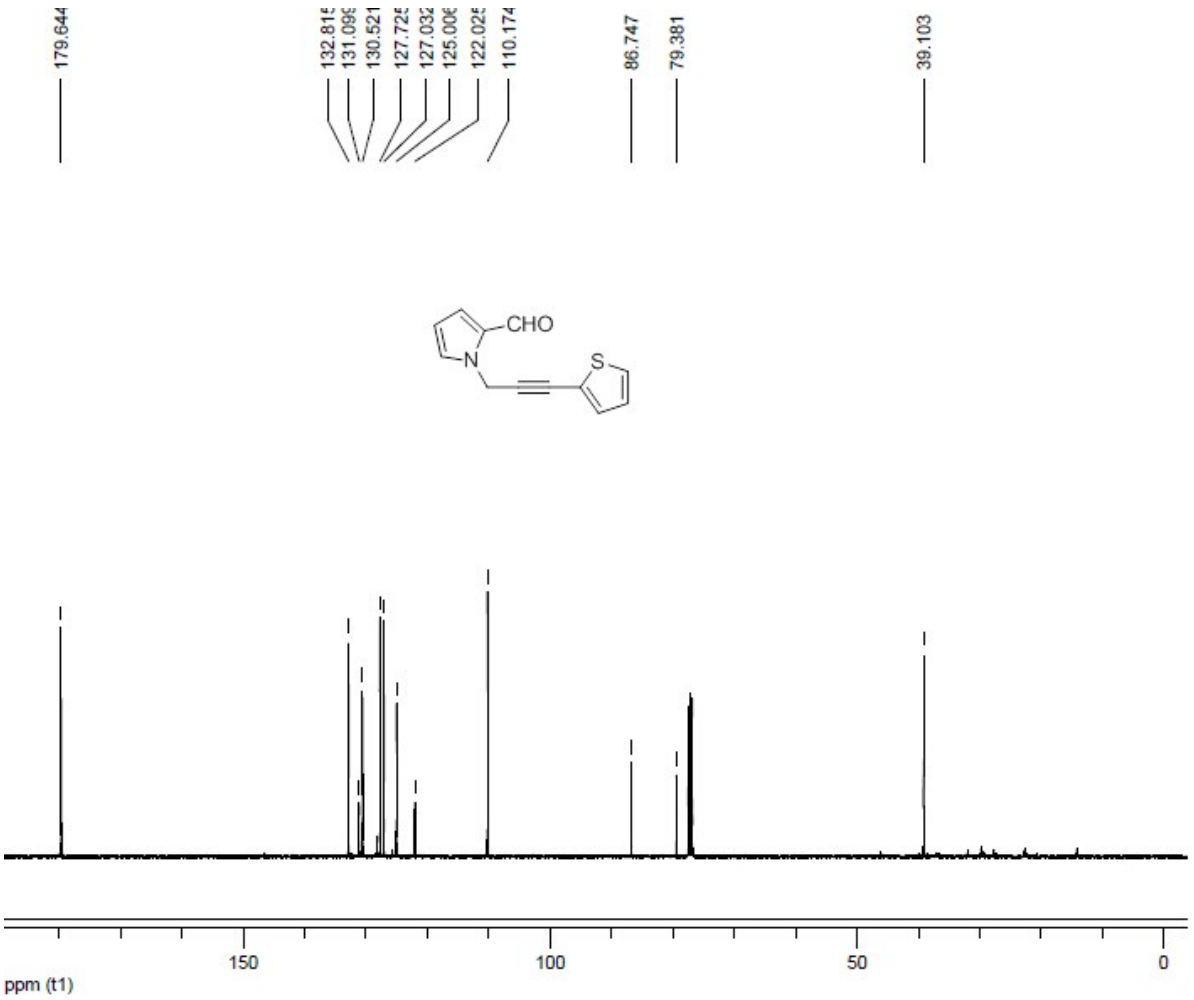
^{1}H NMR (400 MHz, $CDCl_3$) (1c):



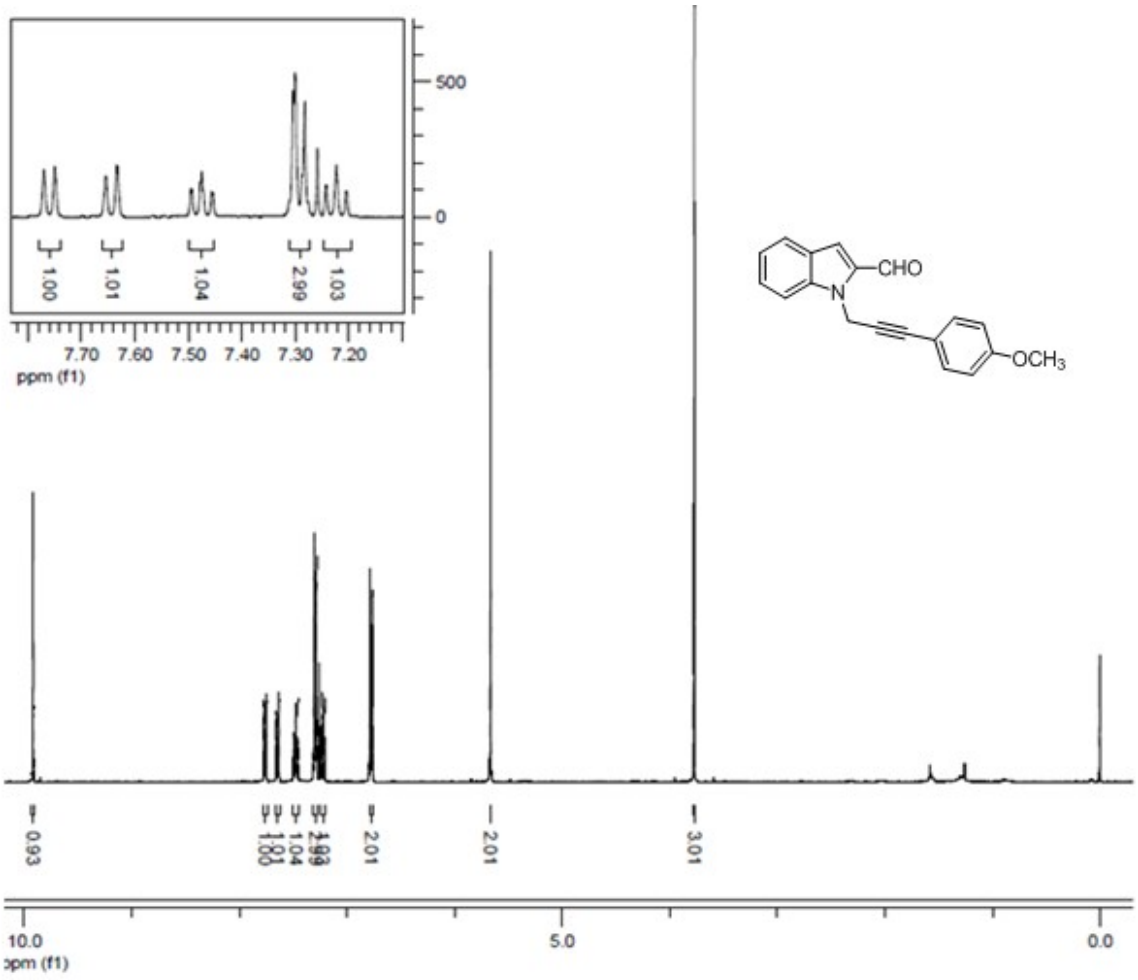
^{1}H NMR (400 MHz, $CDCl_3$) (1d):



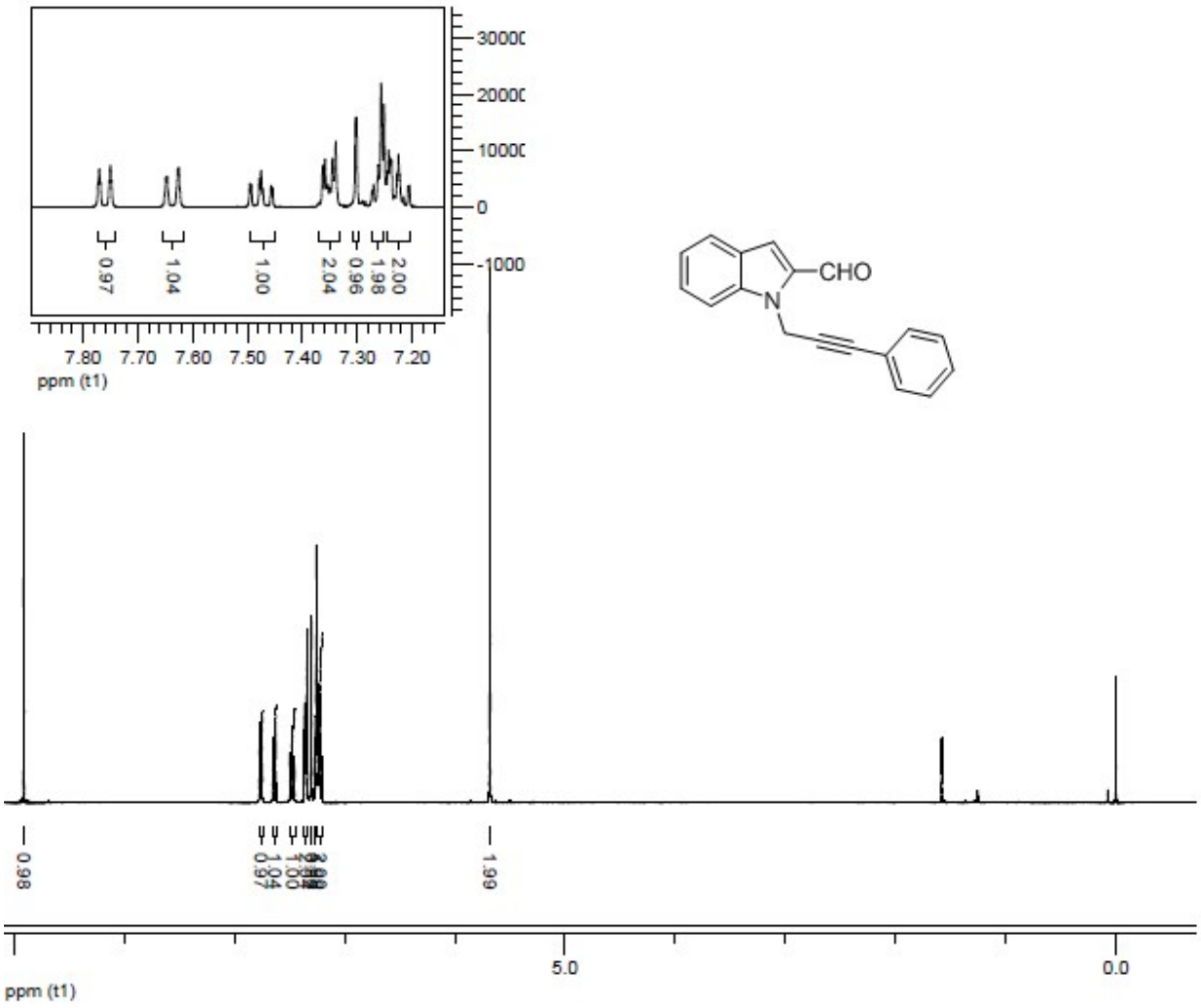
^{13}C NMR (100 MHz, $CDCl_3$), (1d):



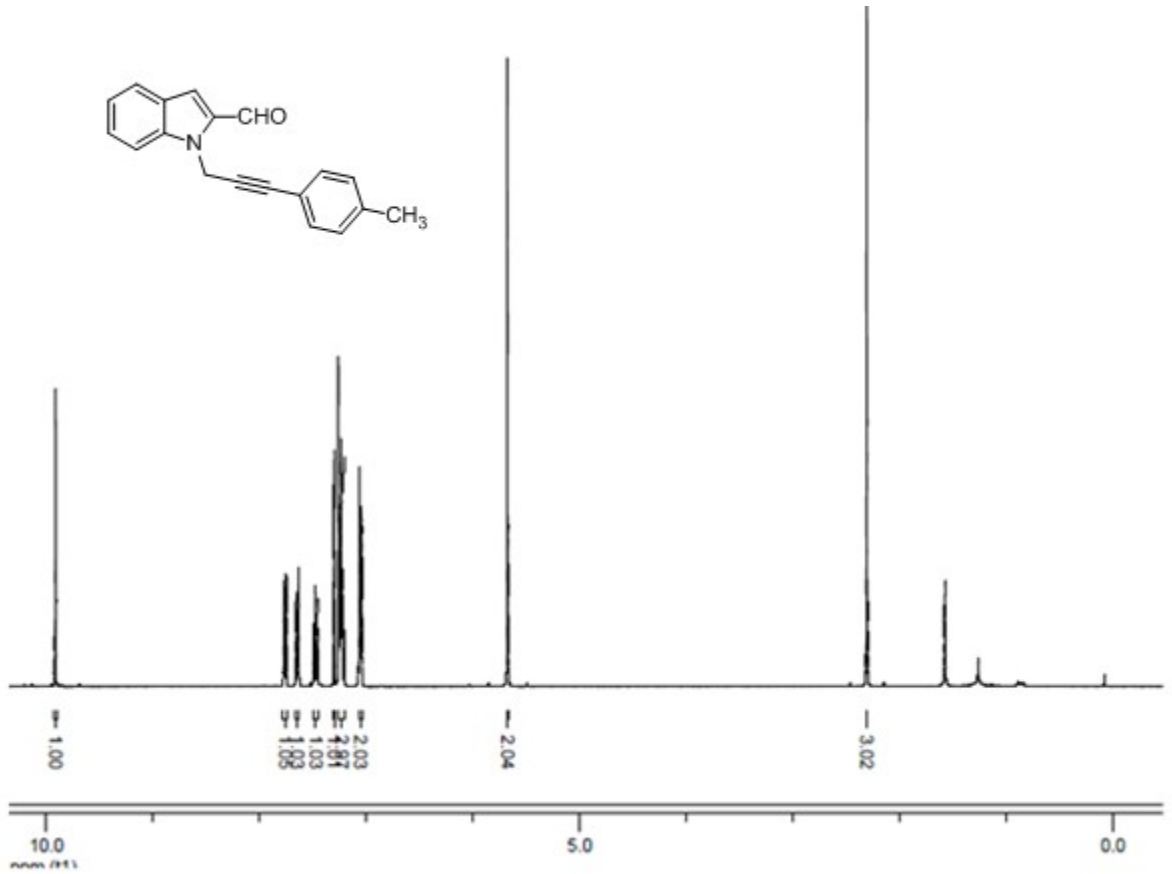
^{1}H NMR (400 MHz, $CDCl_3$) (1e):



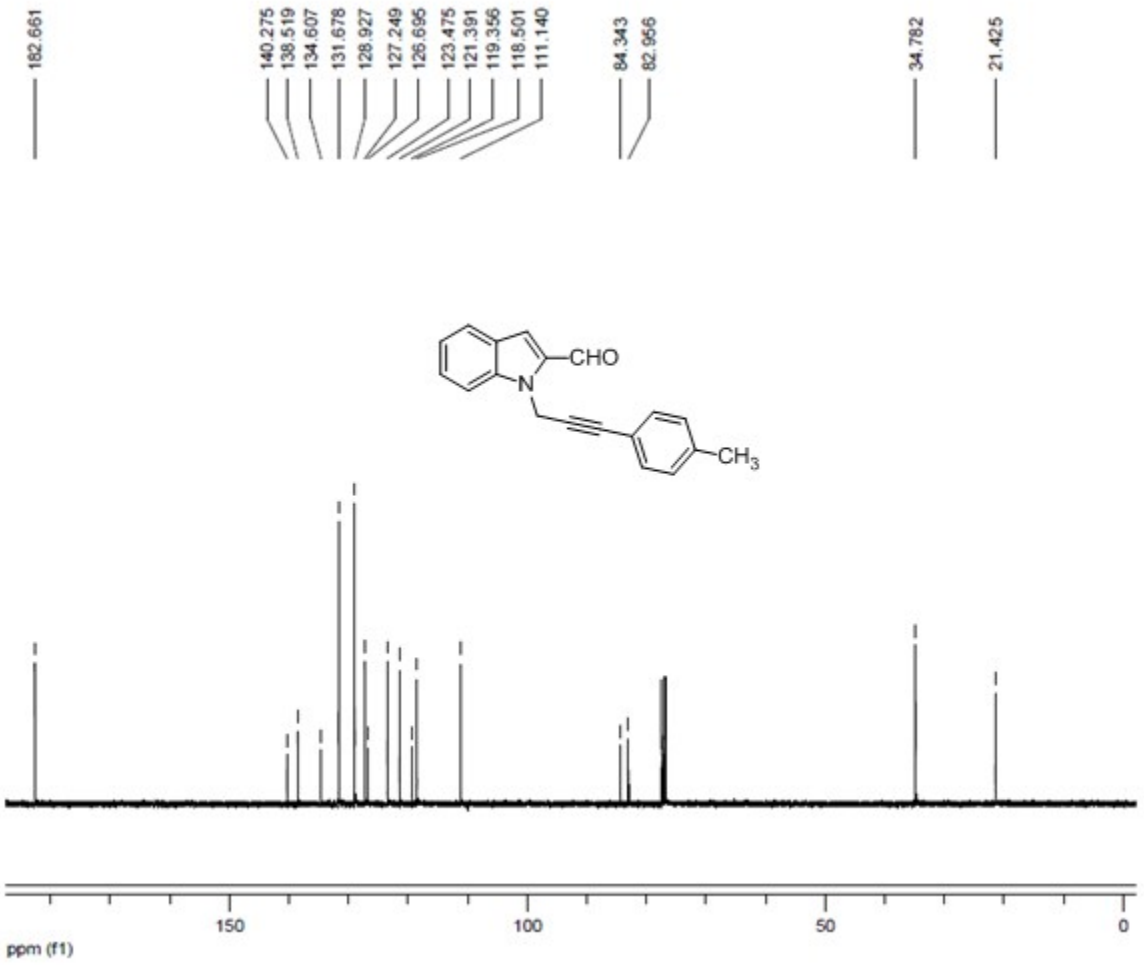
^{1}H NMR (400 MHz, $CDCl_3$) (1f):



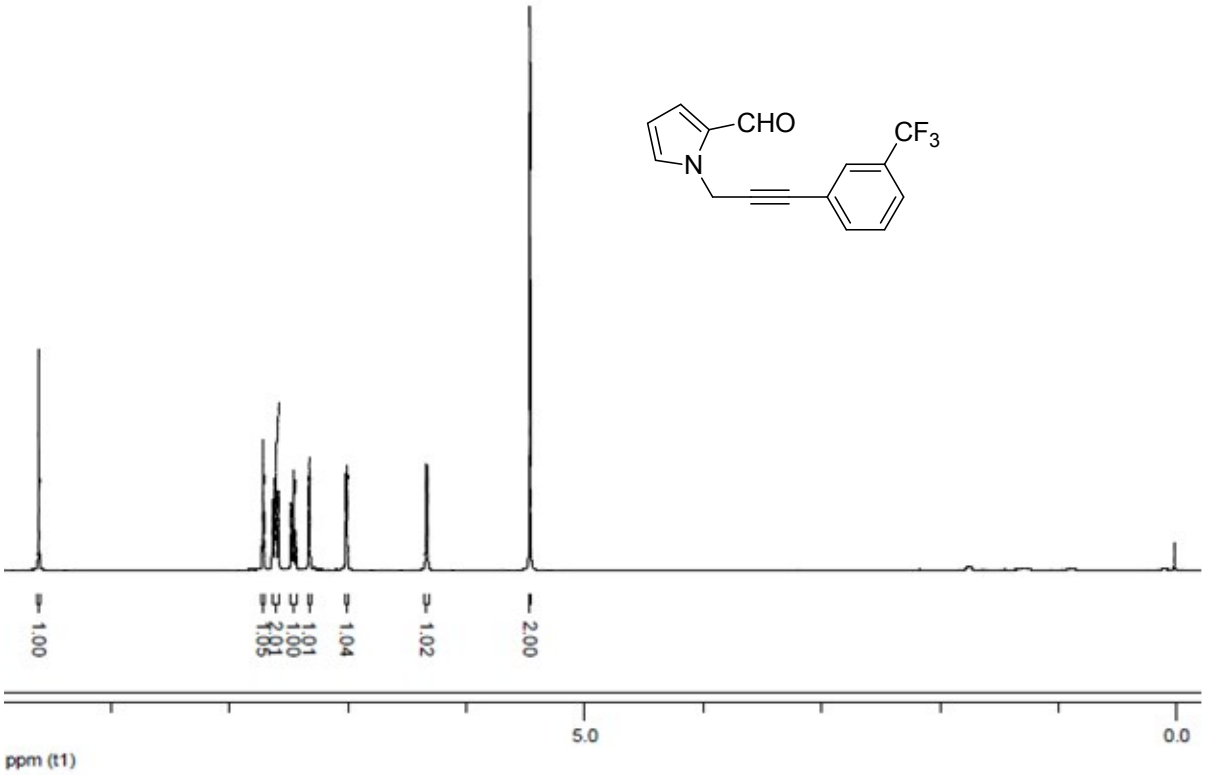
^{1}H NMR (400 MHz, $CDCl_3$), (1g):



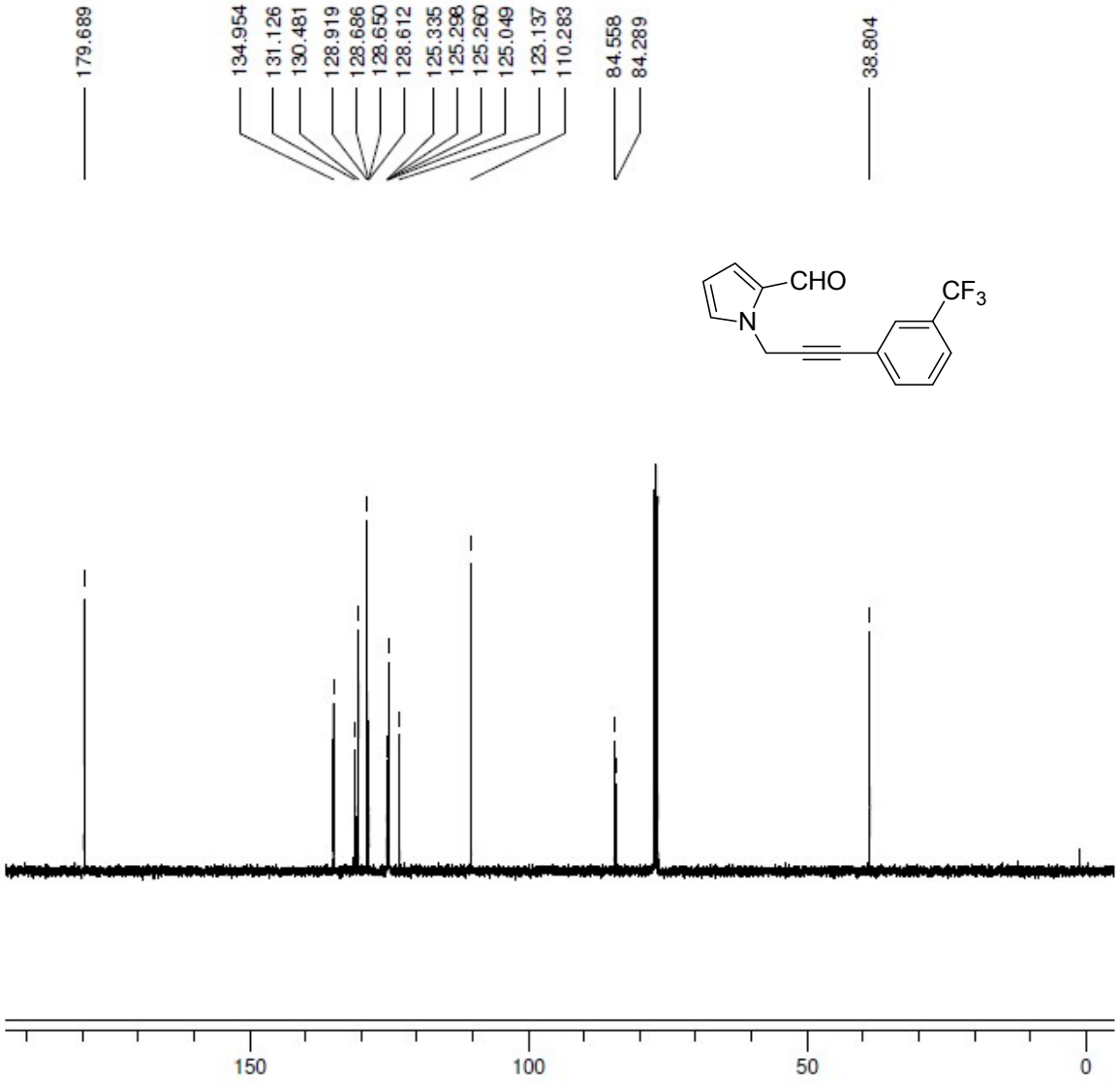
^{13}C NMR (100 MHz, $CDCl_3$) (1g):



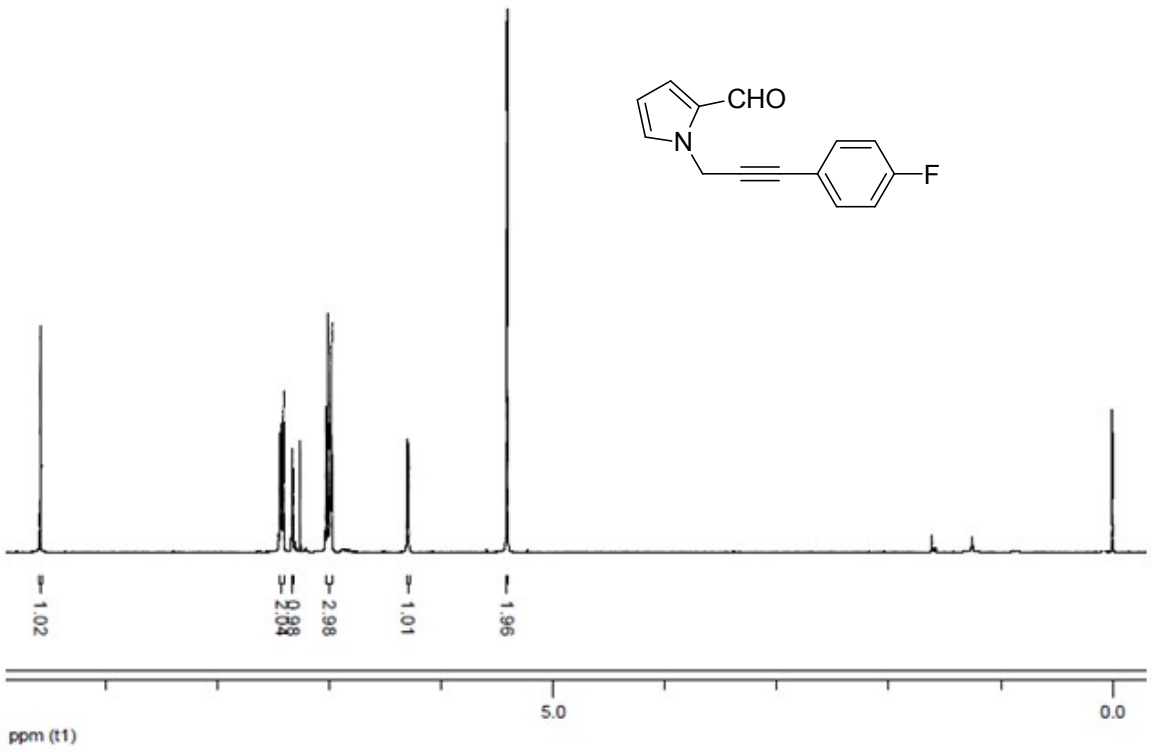
^{1}H NMR (400 MHz, $CDCl_3$) (1h):



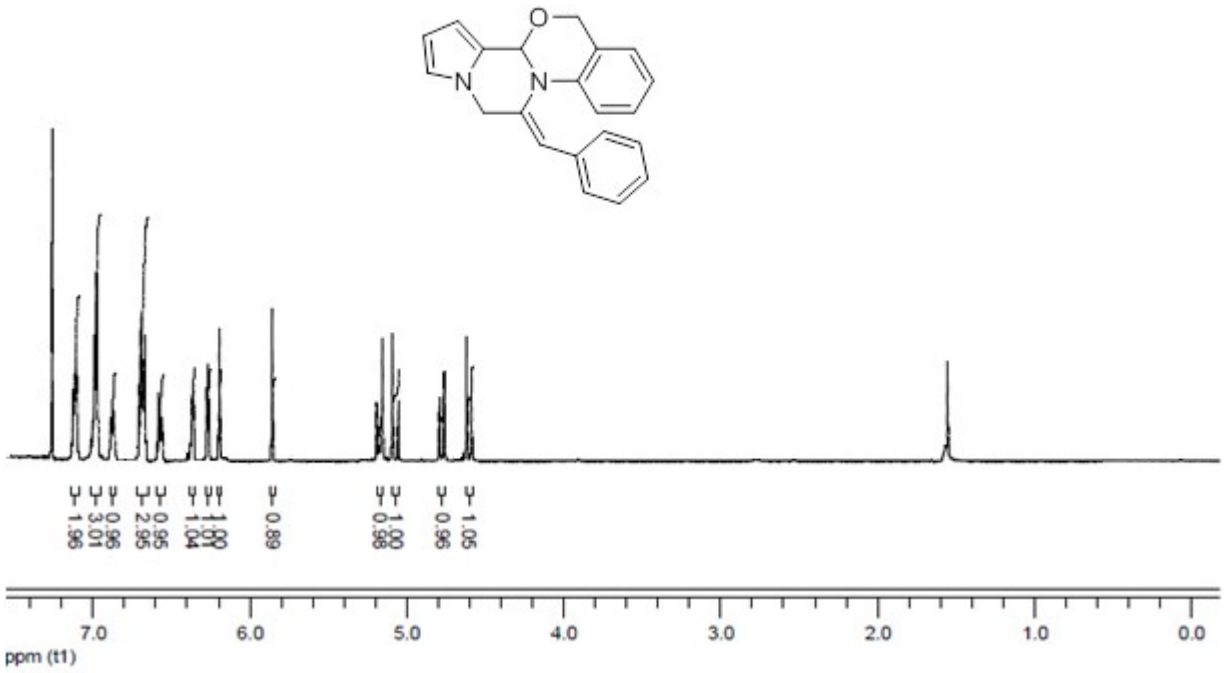
^{13}C NMR (100 MHz, $CDCl_3$) (1h):



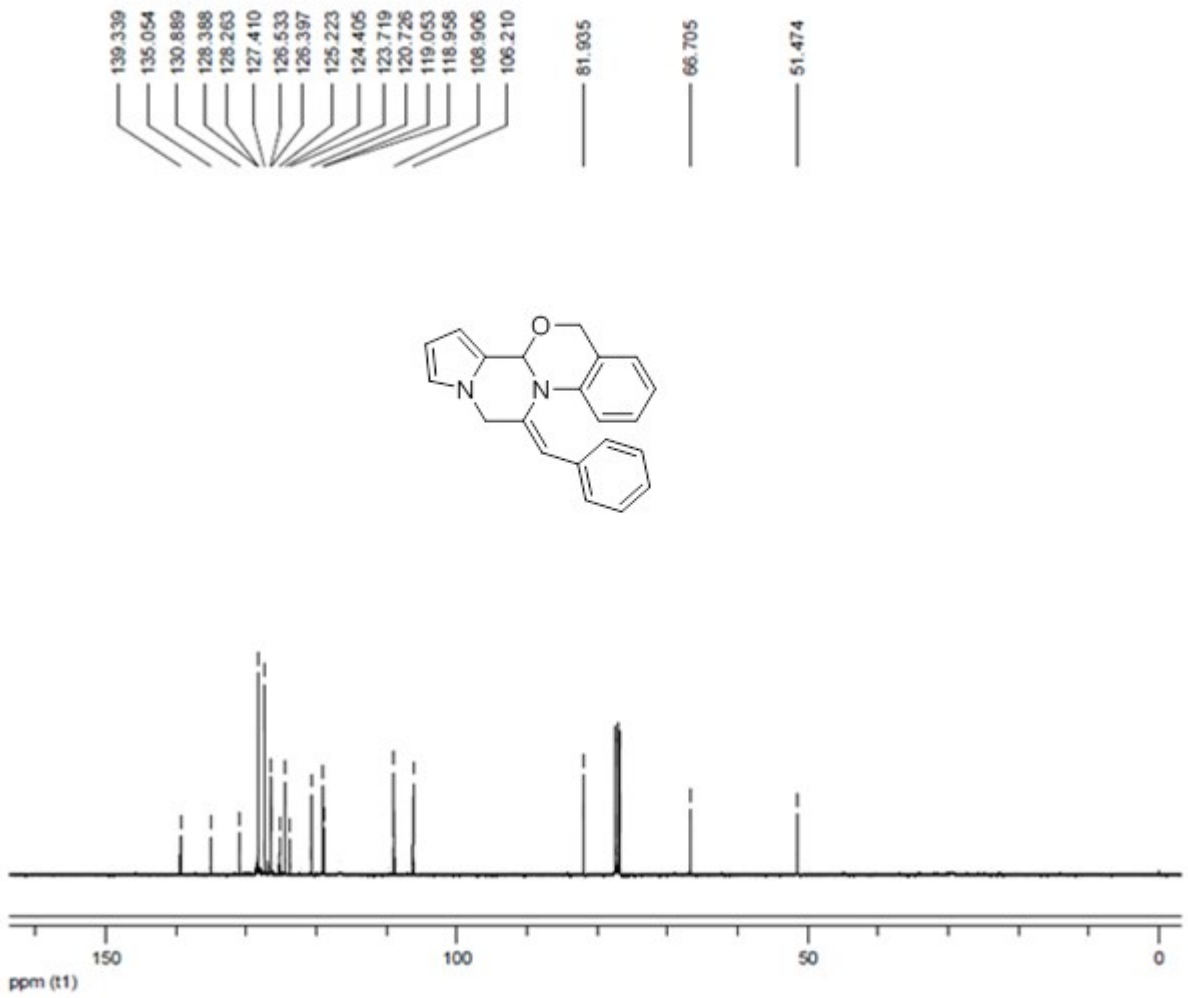
^{1}H NMR (400 MHz, $CDCl_3$) (1i):



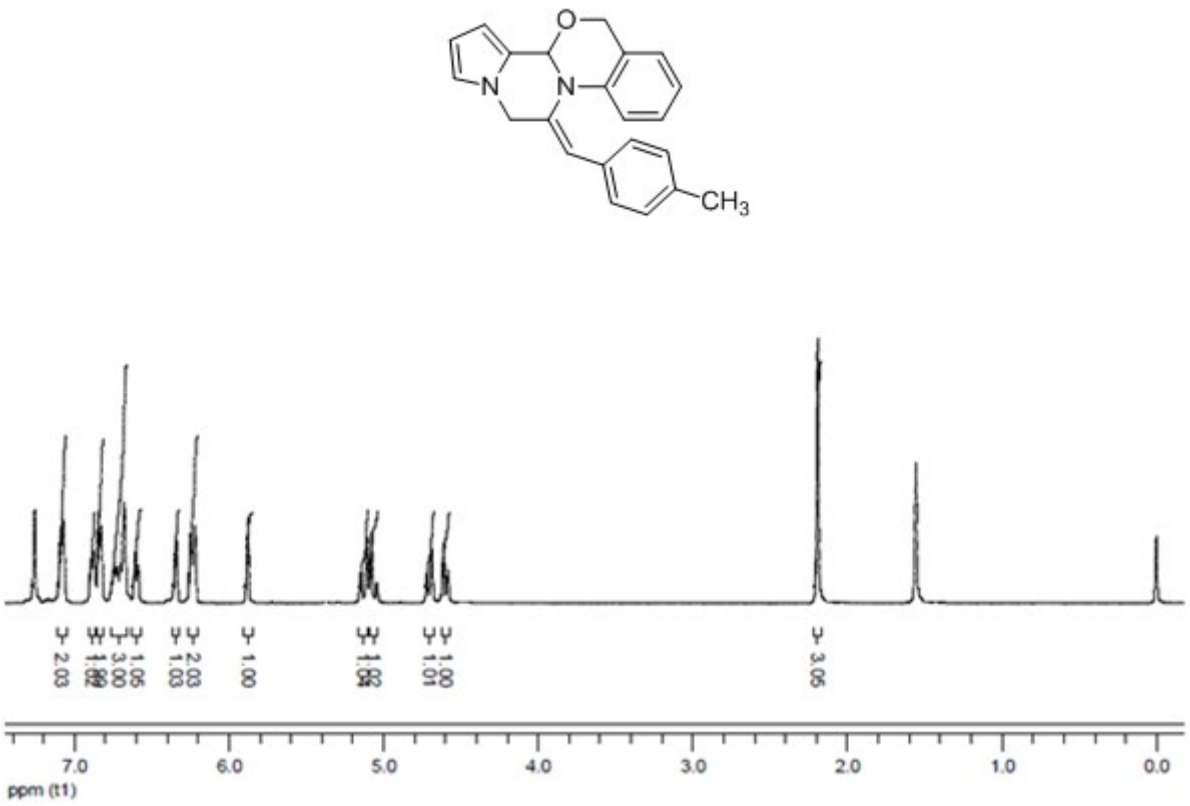
^{1}H NMR (400 MHz, $CDCl_3$), (3a):



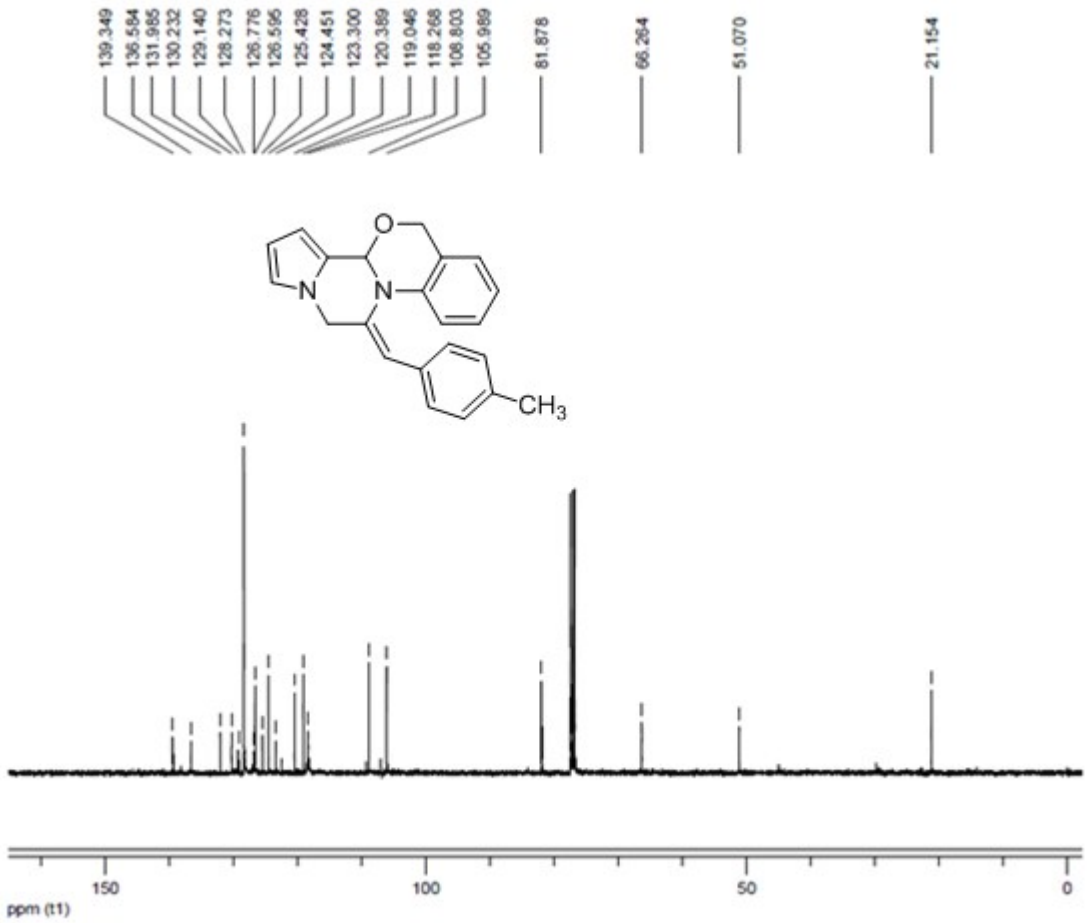
^{13}C NMR (100 MHz, $CDCl_3$) (3a):



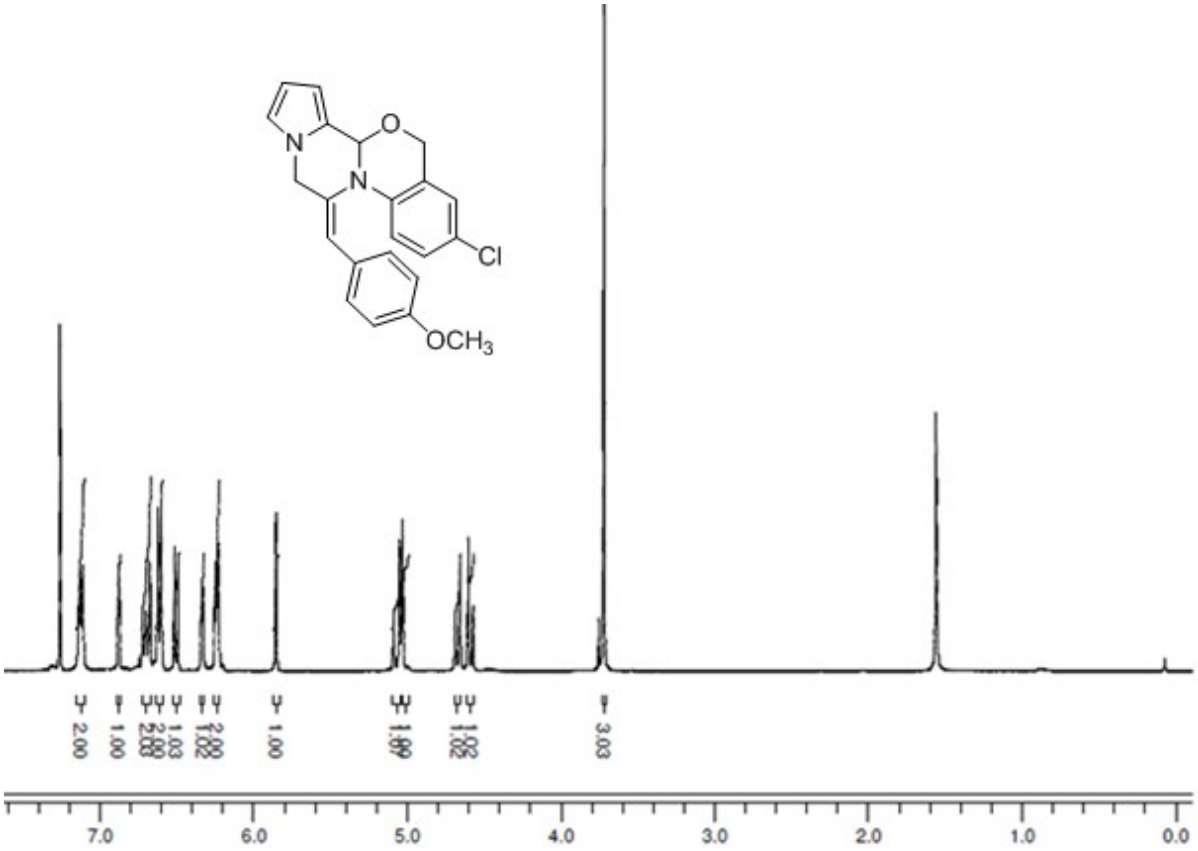
^{1}H NMR (400 MHz, $CDCl_3$) (3b):



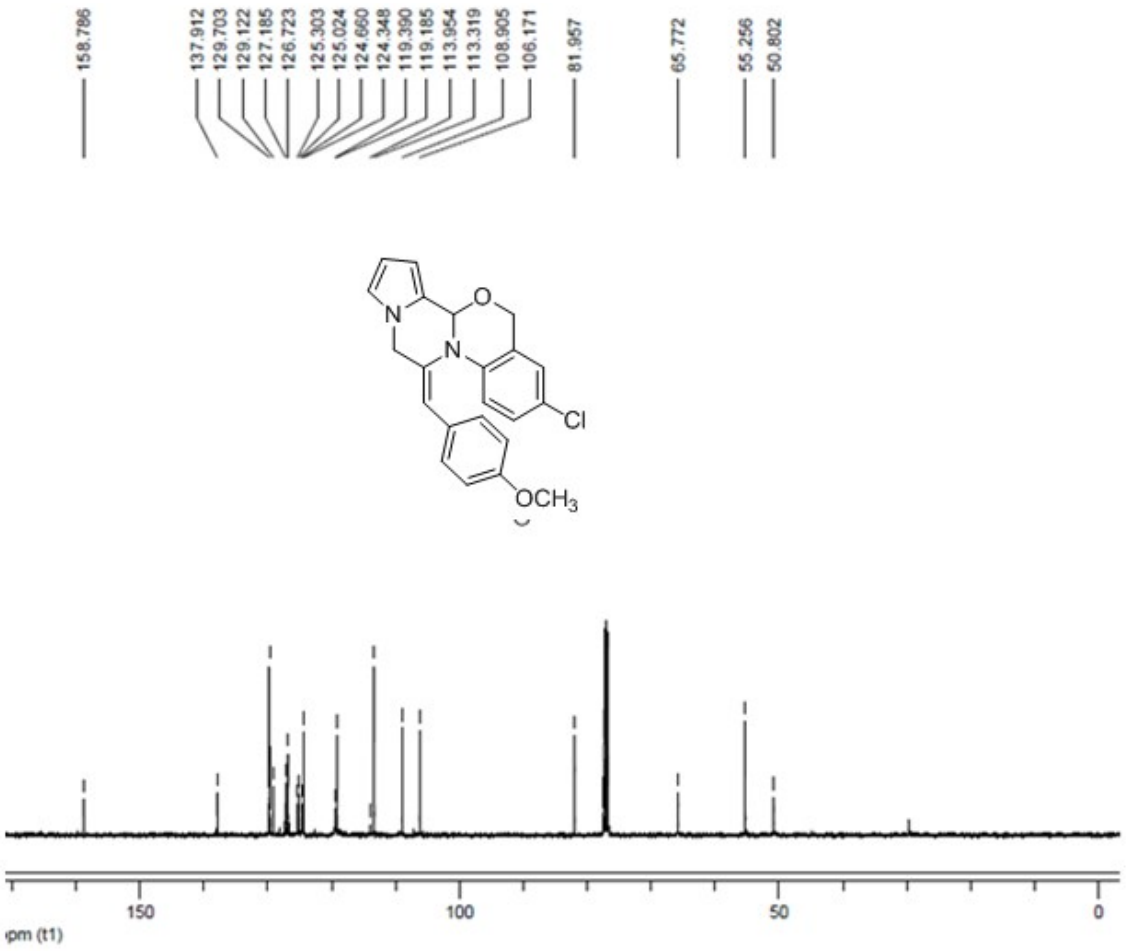
^{13}C NMR (100 MHz, $CDCl_3$) (3b):



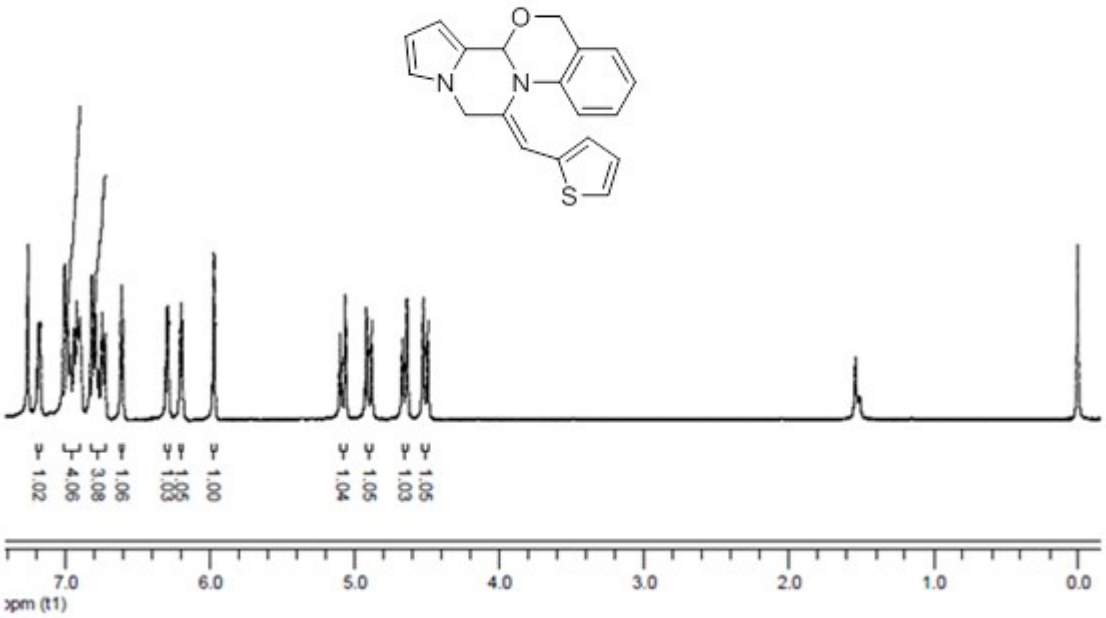
^{1}H NMR (400 MHz, $CDCl_3$) (3c):



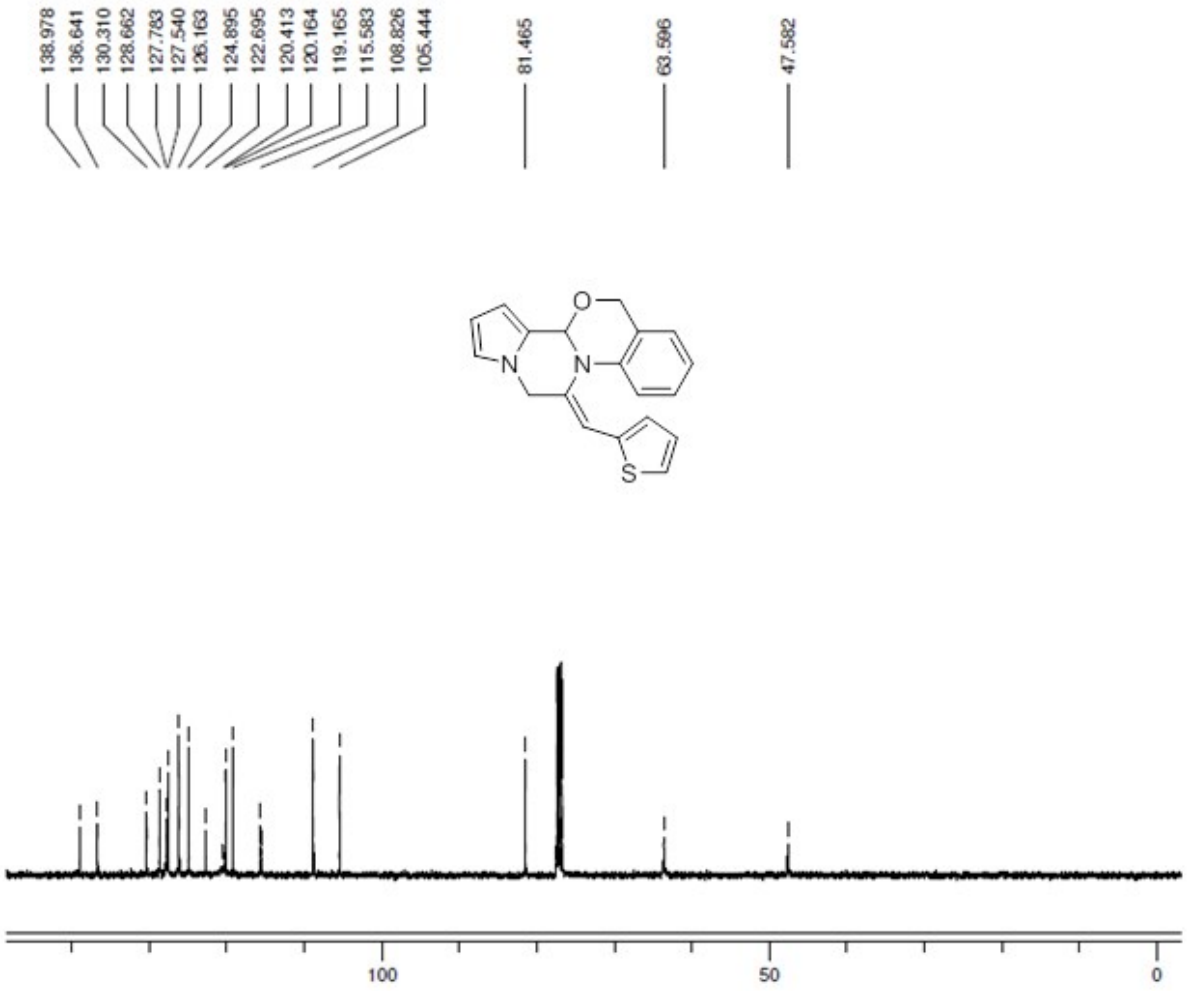
^{13}C NMR (100 MHz, $CDCl_3$) (3c):



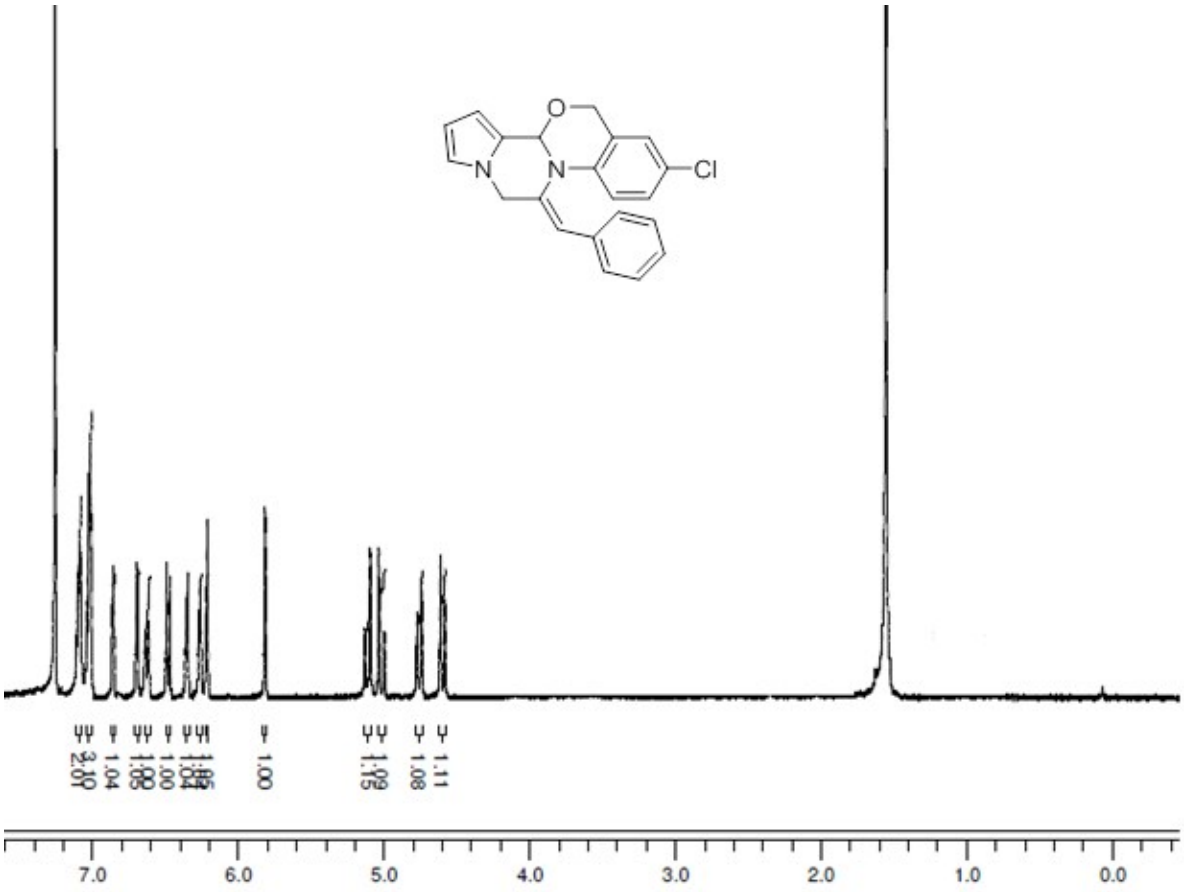
^{1}H NMR (400 MHz, $CDCl_3$) (3d):



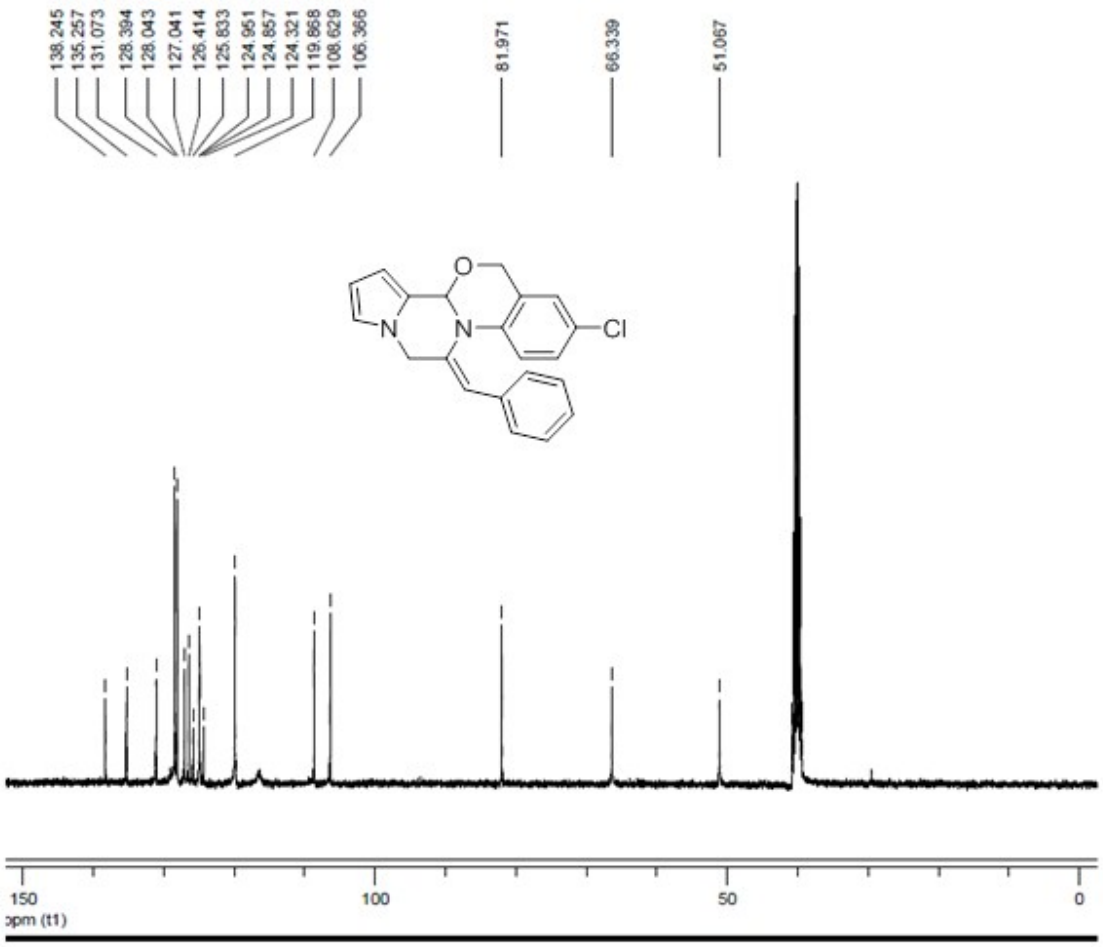
^{13}C NMR (100 MHz, $CDCl_3$) (3d):



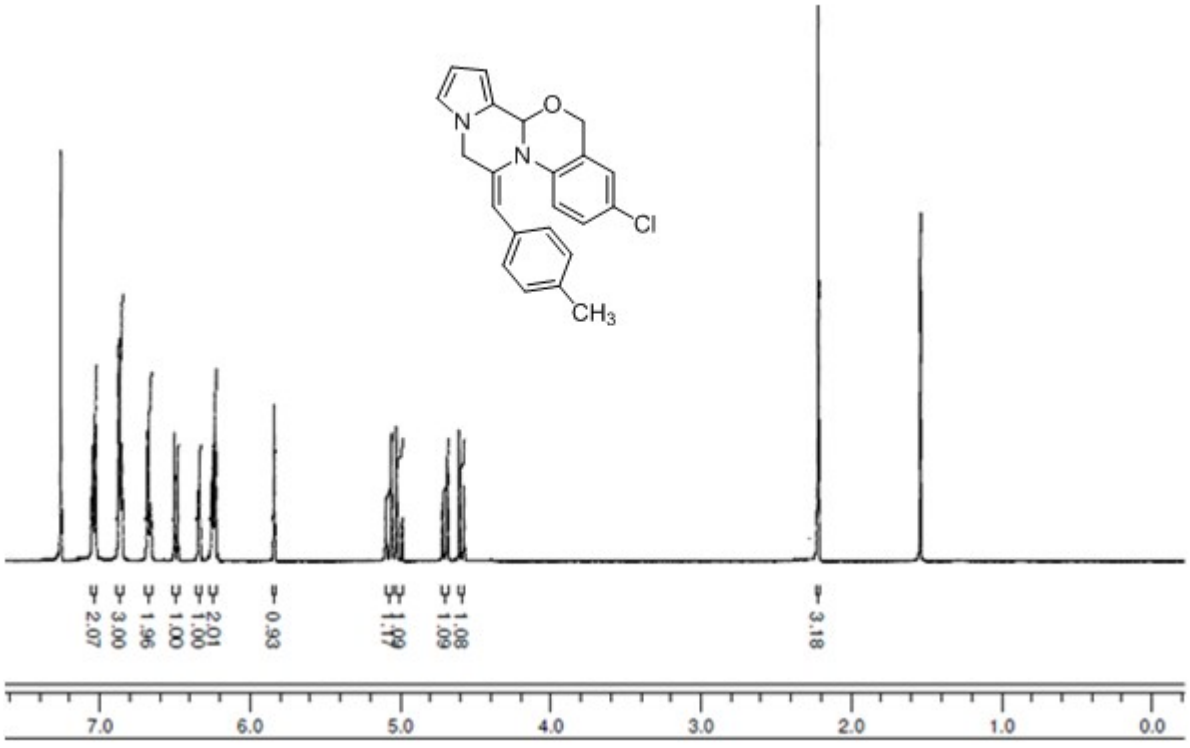
^{1}H NMR (400 MHz, $CDCl_3$) (3e):



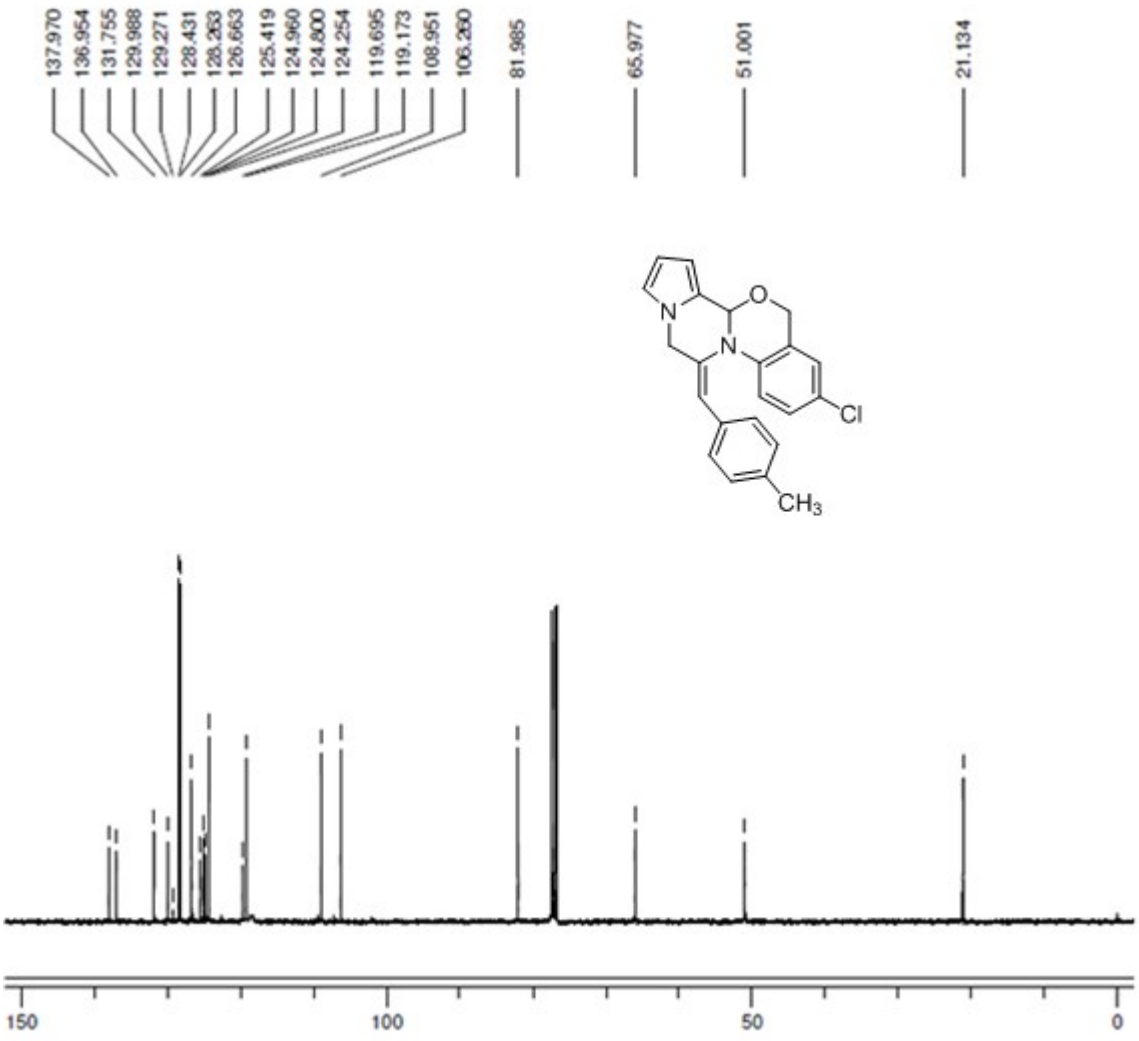
^{13}C NMR (100 MHz, DMSO-d_6) (3e):



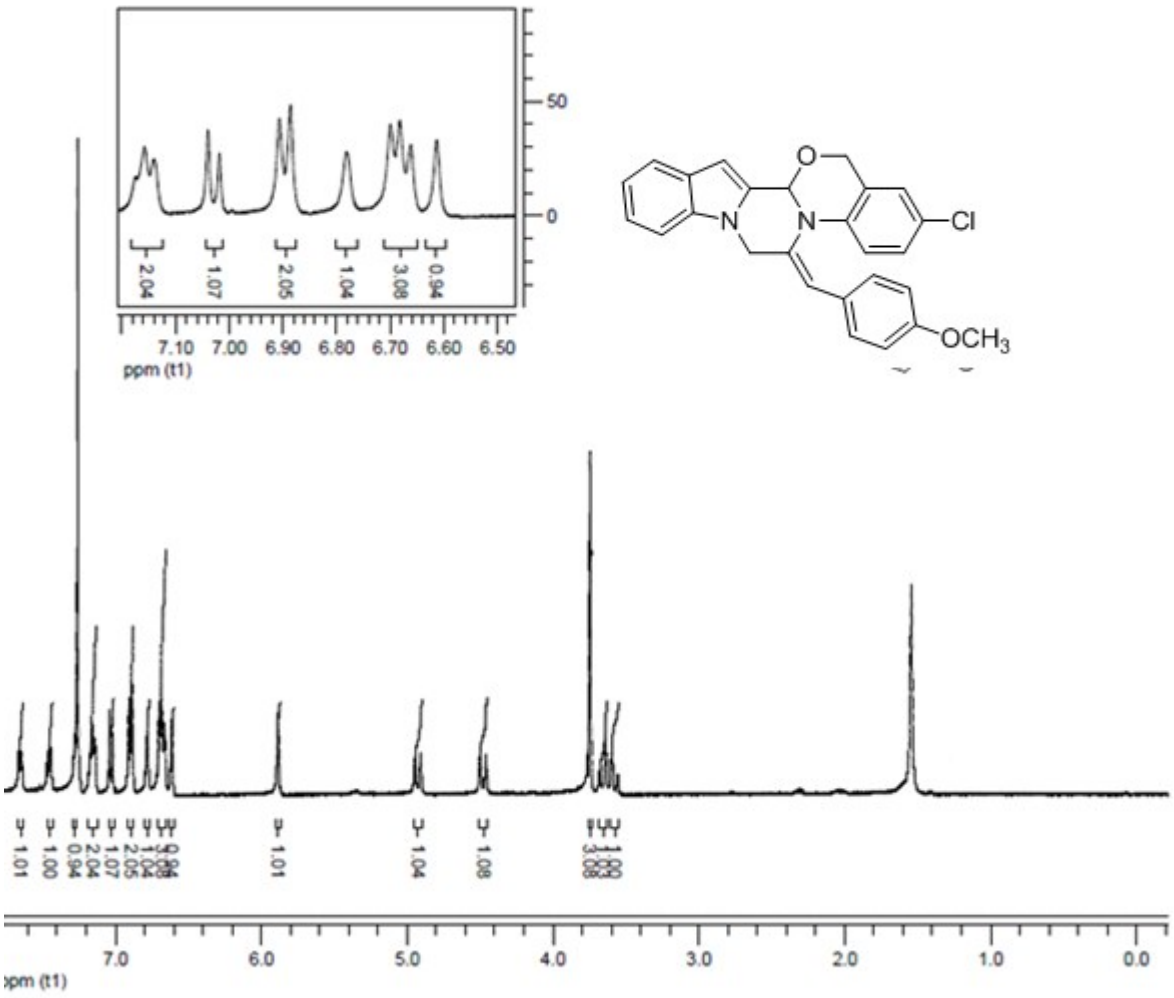
^{1}H NMR (400 MHz, $CDCl_3$), (3f):



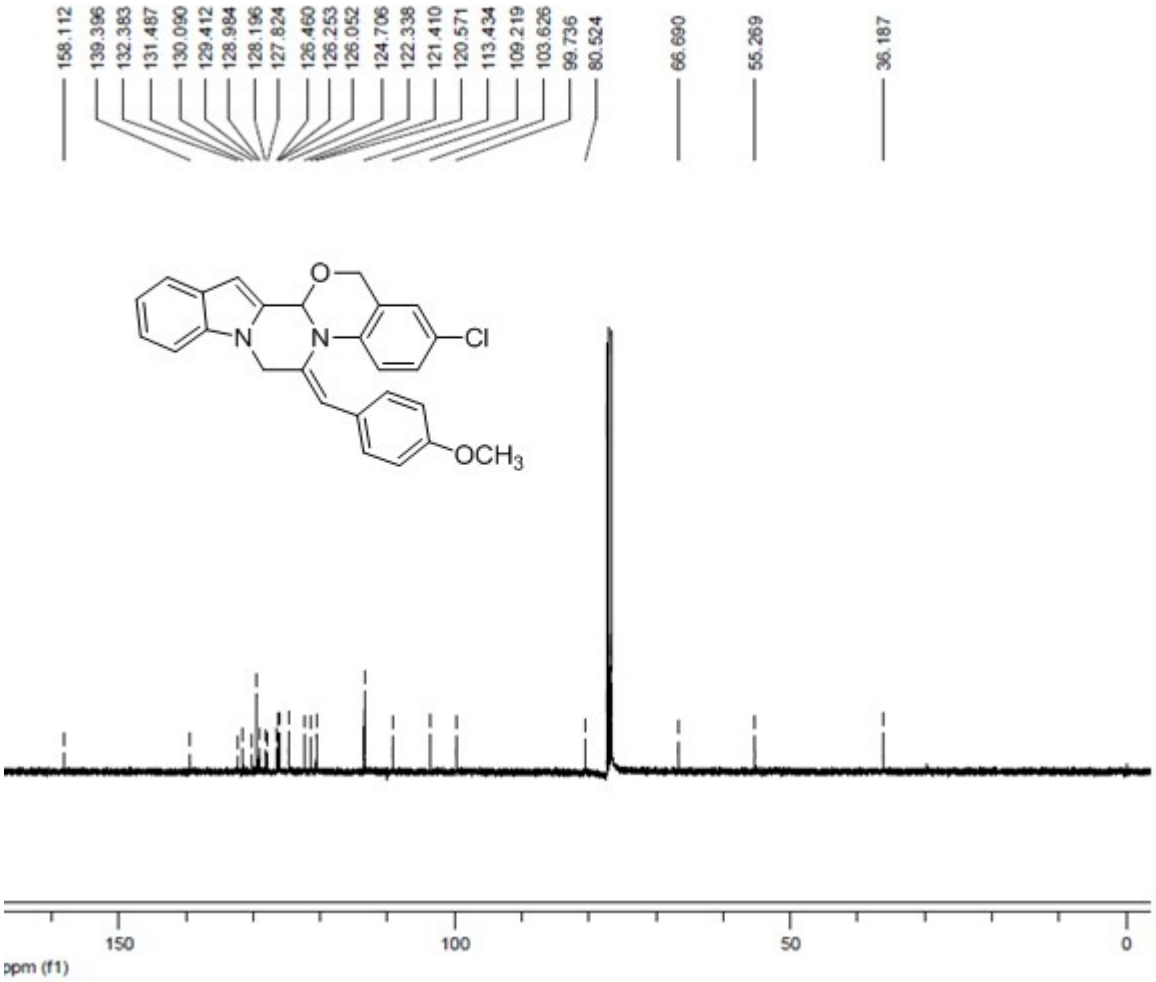
^{13}C NMR (100 MHz, $CDCl_3$) (3f):



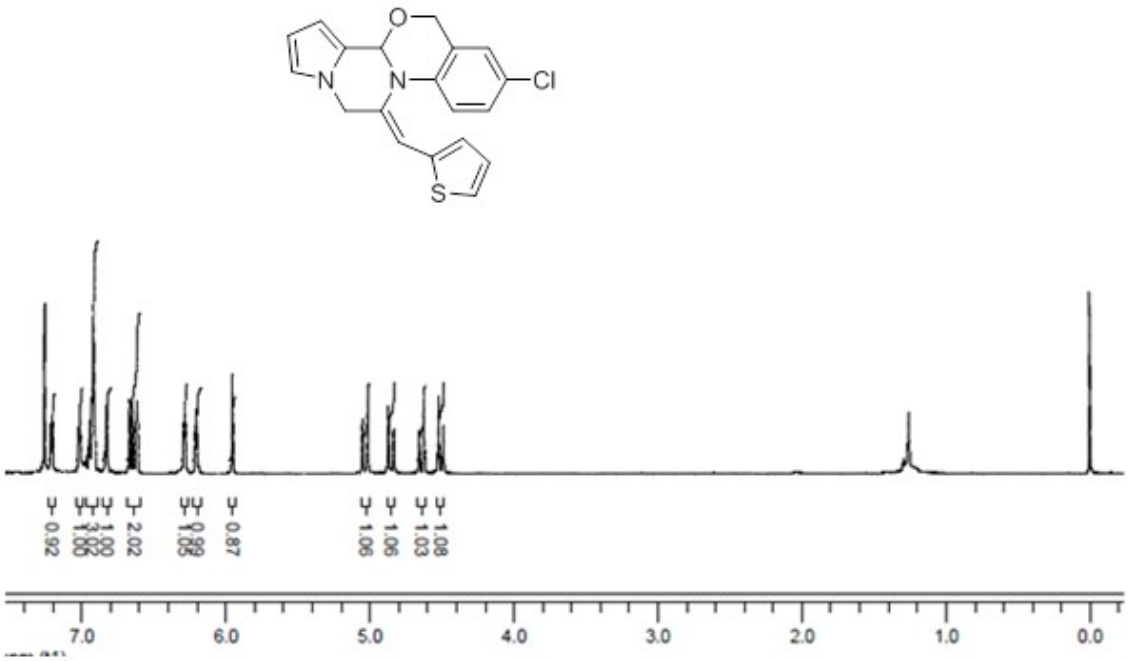
^{1}H NMR (400 MHz, $CDCl_3$) (3g):



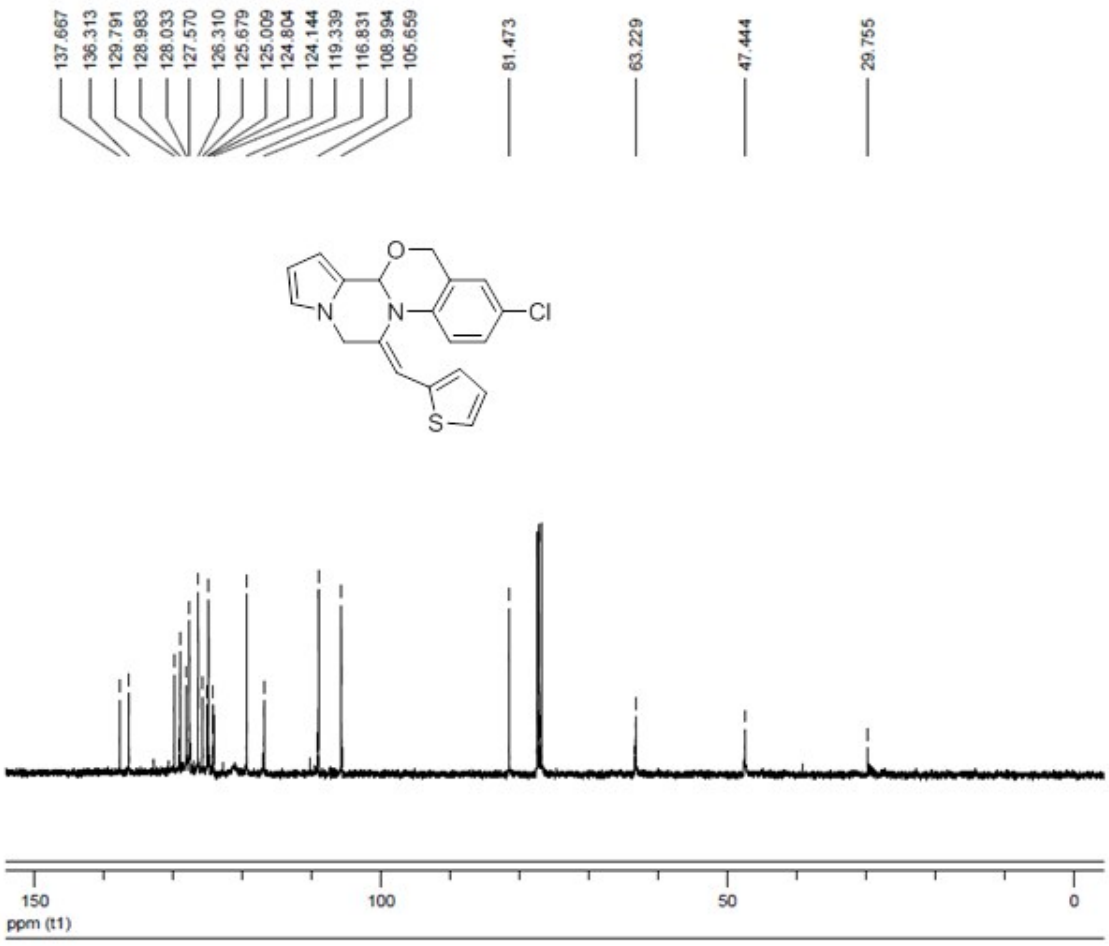
^{13}C NMR (100 MHz, $CDCl_3$) (3g):



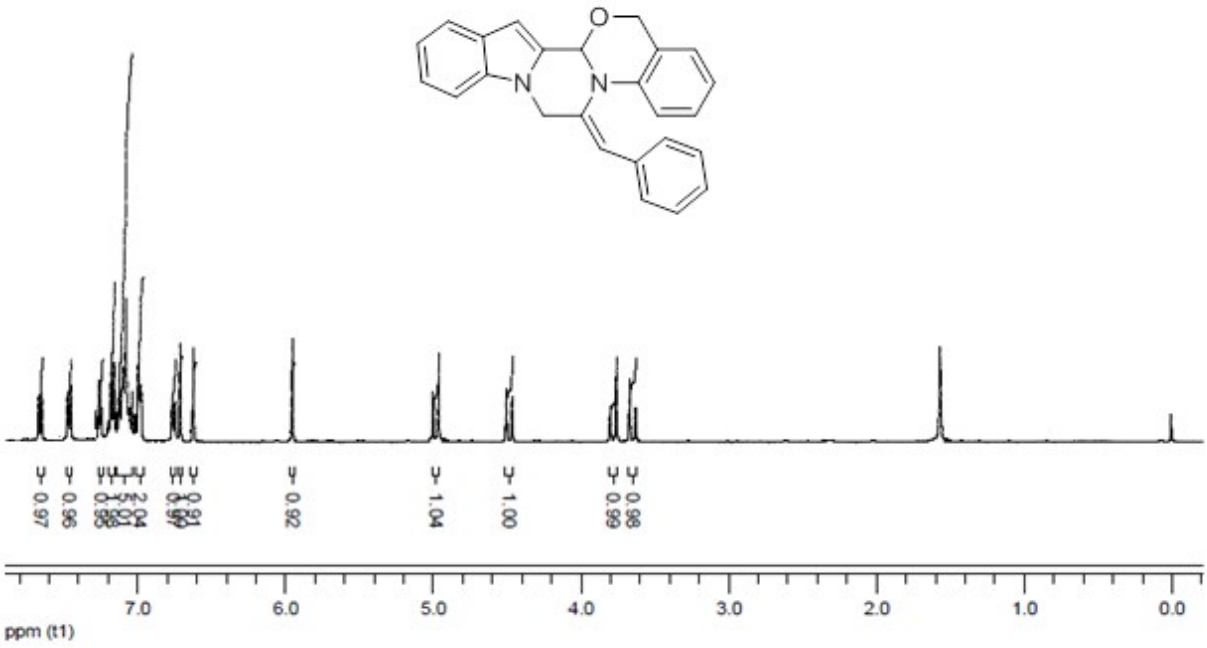
^{1}H NMR (400 MHz, $CDCl_3$) (3h):



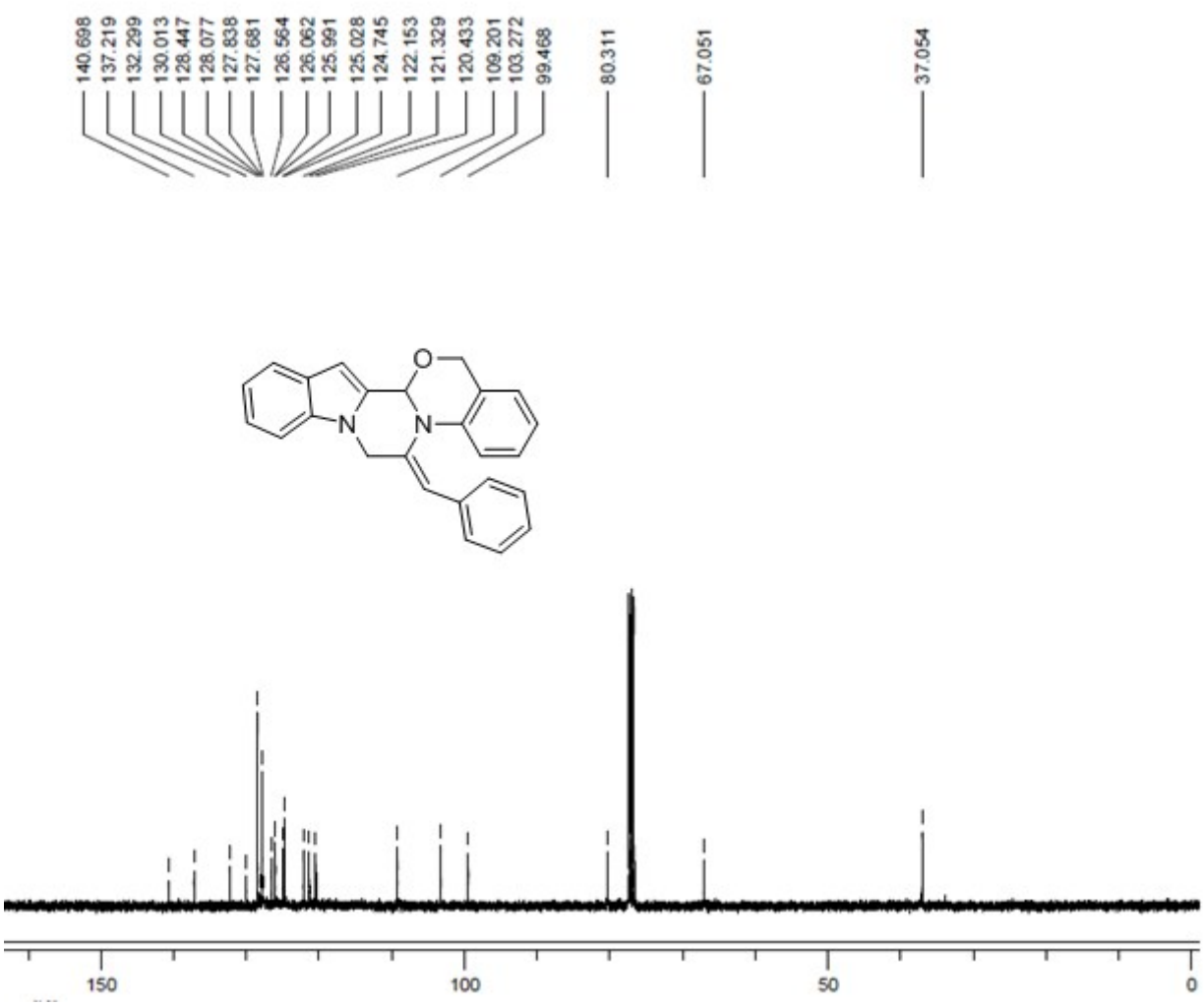
^{13}C NMR (100 MHz, $CDCl_3$) (3h):



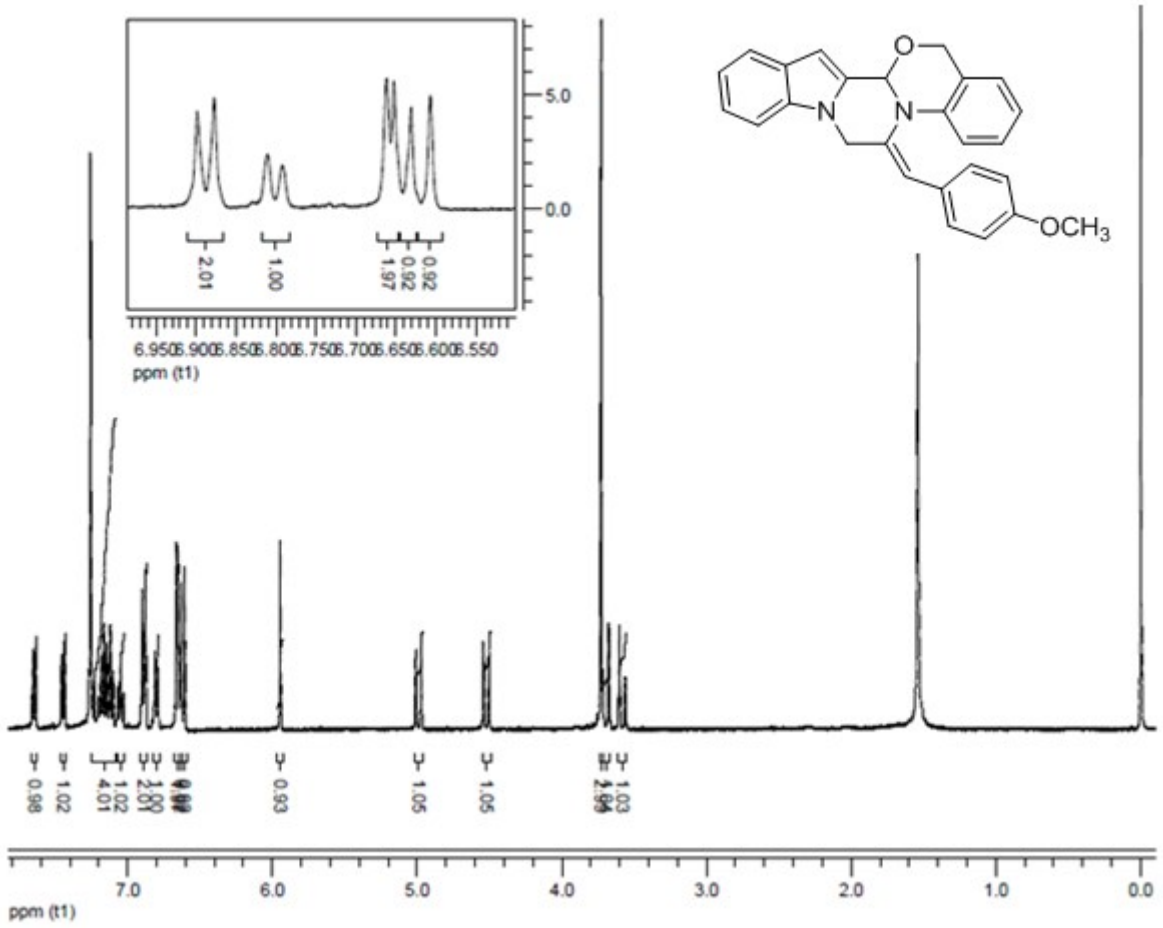
^{1}H NMR (400 MHz, $CDCl_3$) (3i):



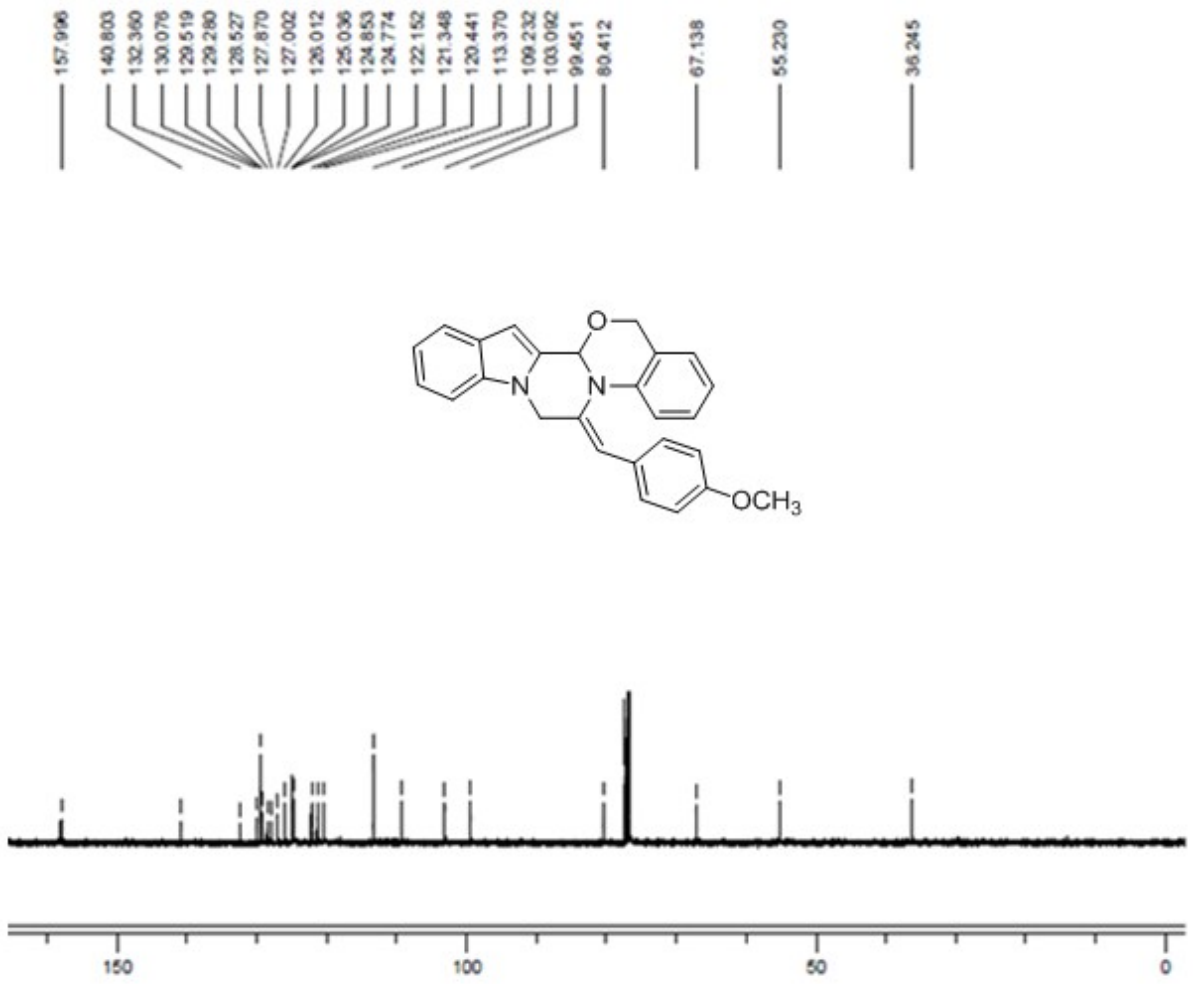
^{13}C NMR (100 MHz, $CDCl_3$) (3i):



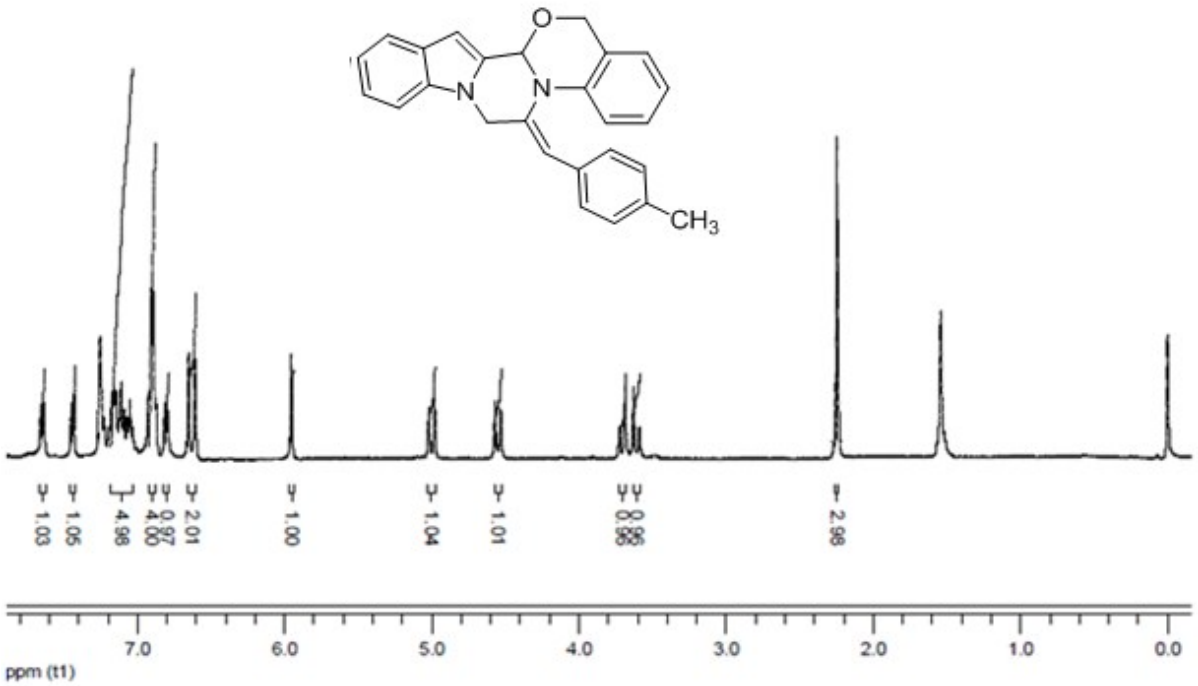
^{1}H NMR (400 MHz, $CDCl_3$) (3j):



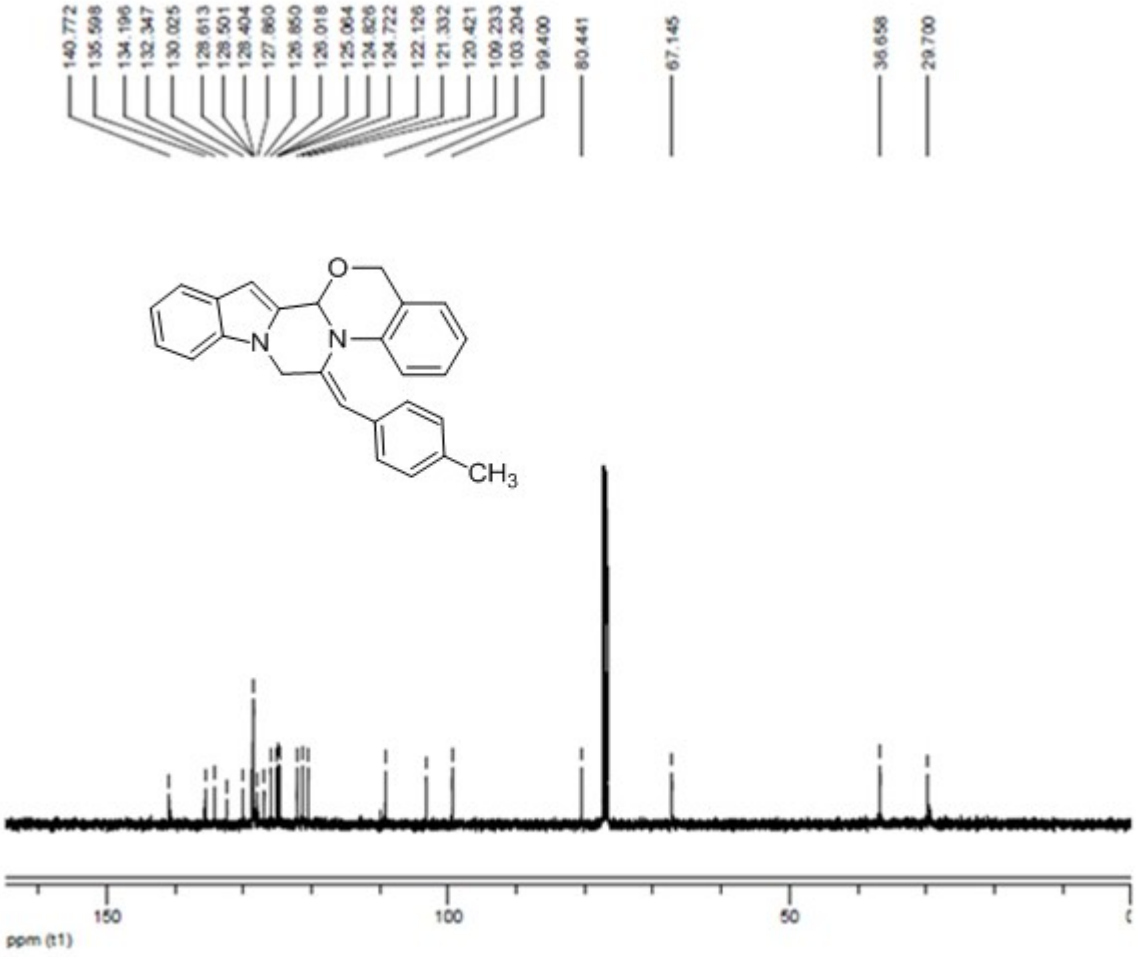
^{13}C NMR (100 MHz, $CDCl_3$) (3j):



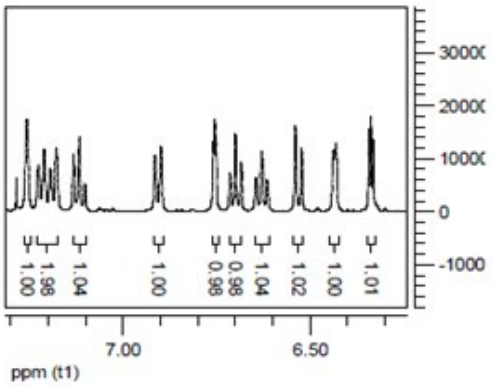
^{1}H NMR (400 MHz, $CDCl_3$) (3k):

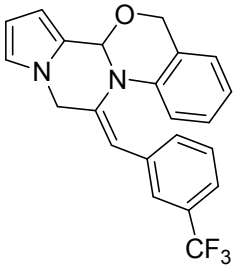


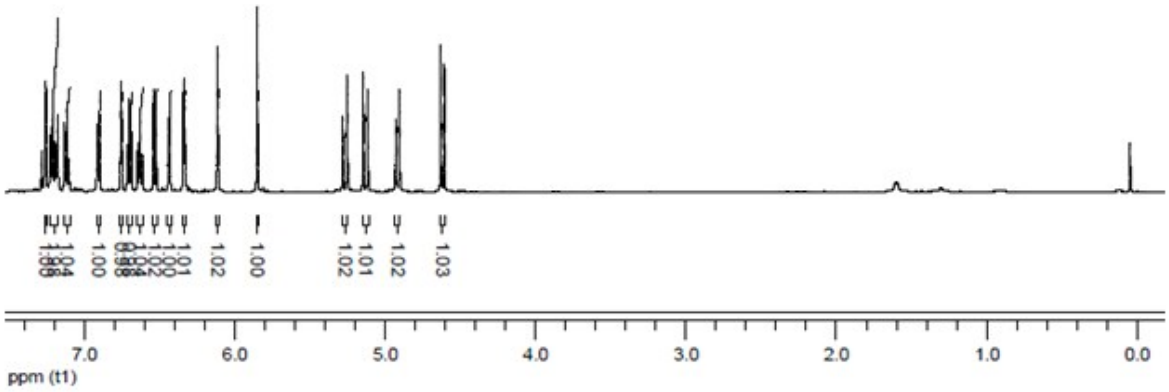
^{13}C NMR (100 MHz, $CDCl_3$), (3k):



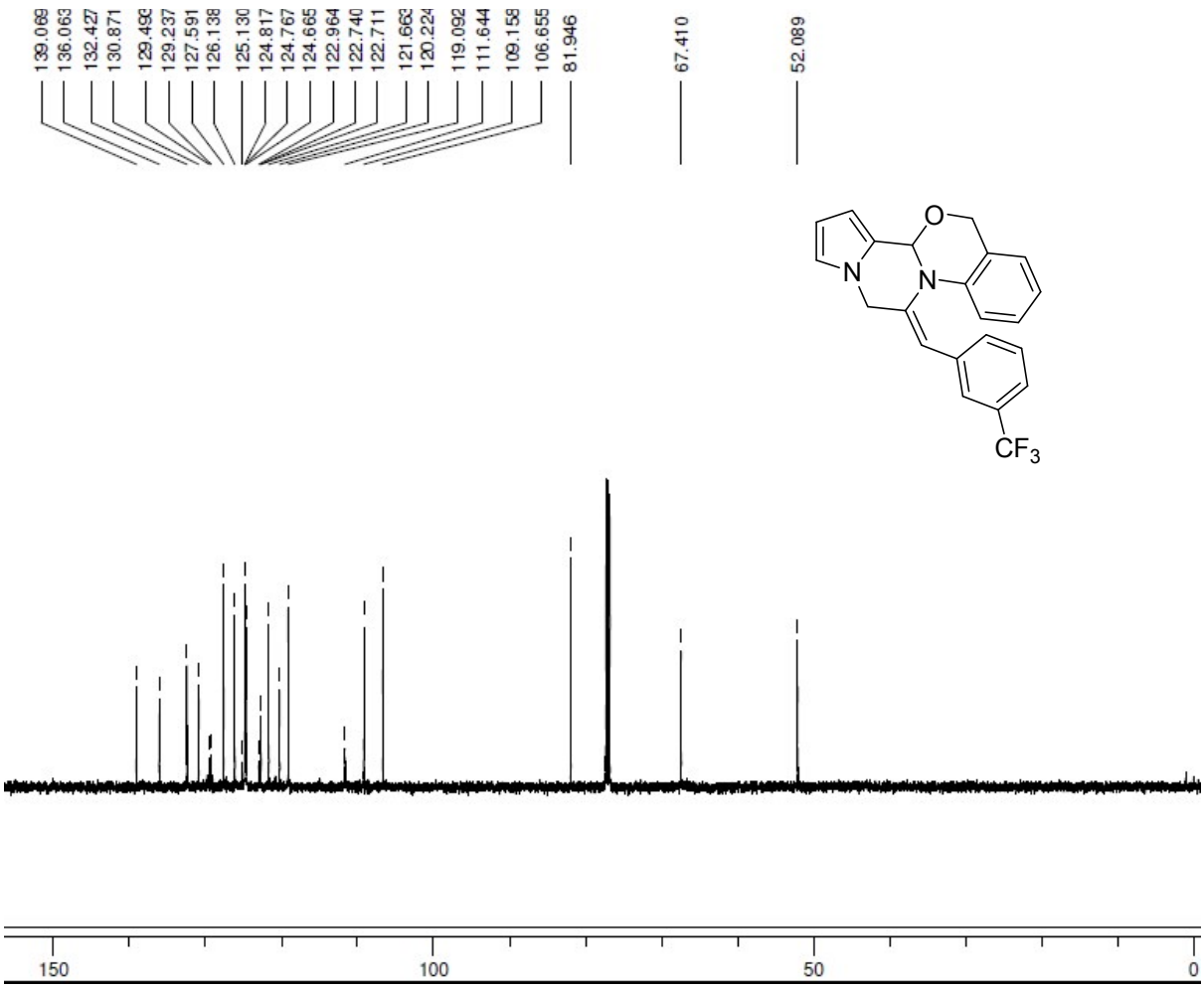
^{1}H NMR (400 MHz, $CDCl_3$) (3l):



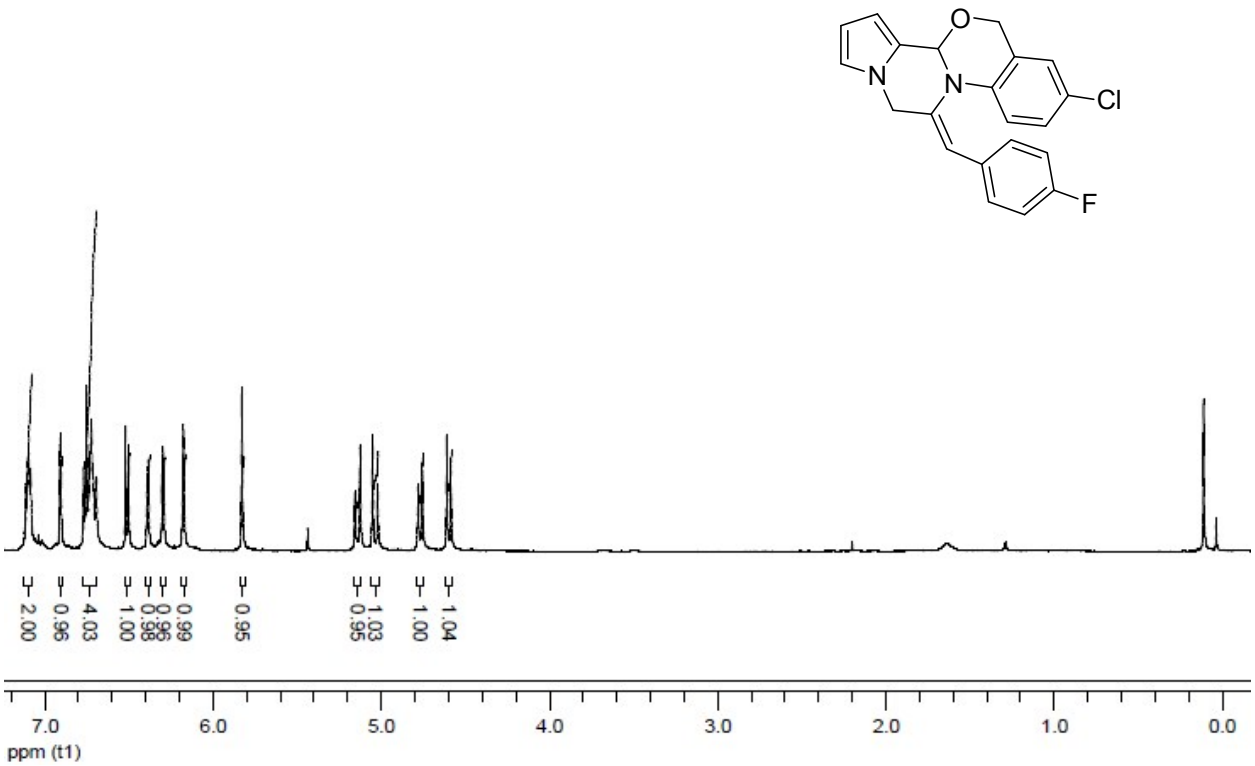




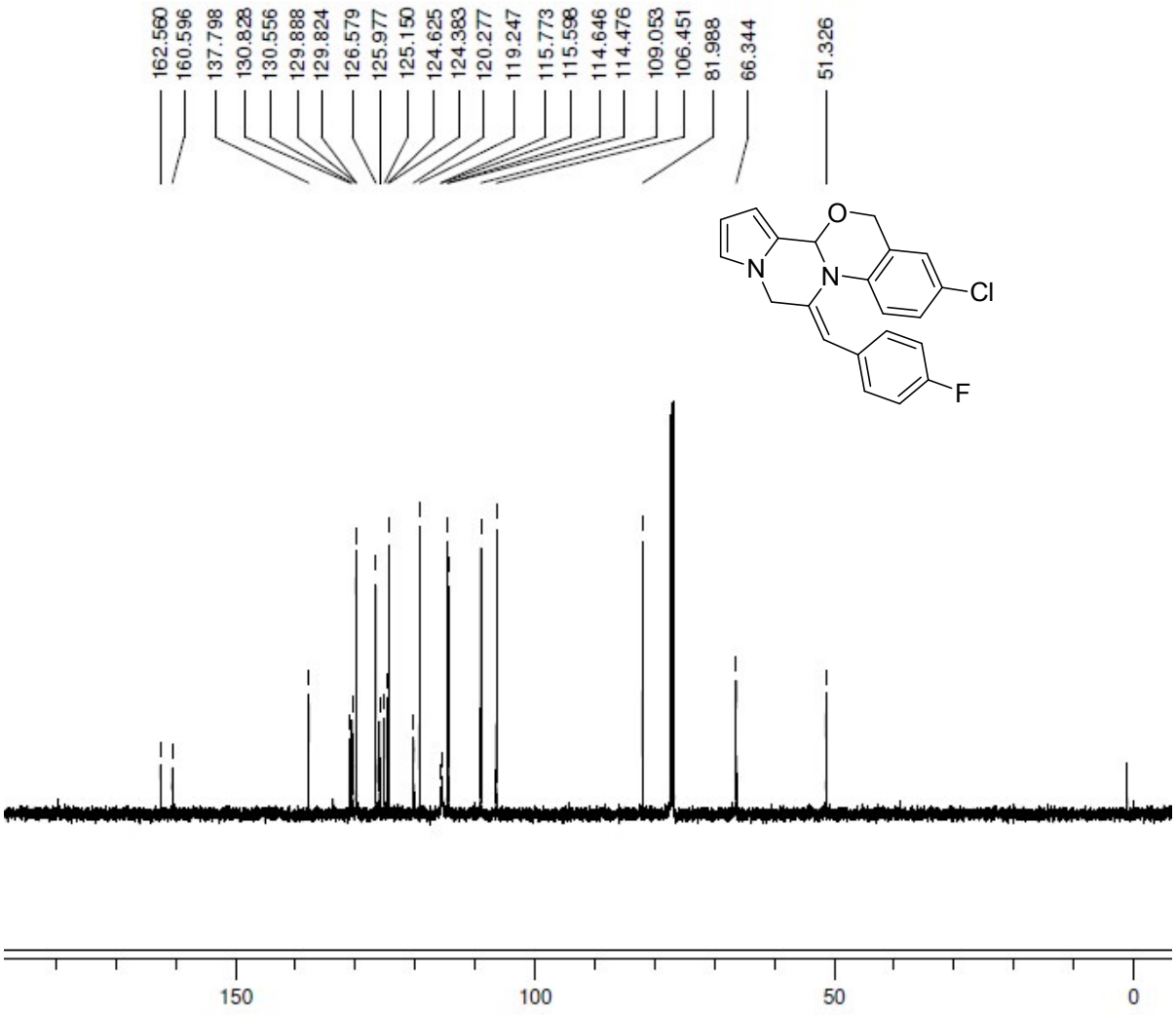
^{13}C NMR (100 MHz, $CDCl_3$) (3l):



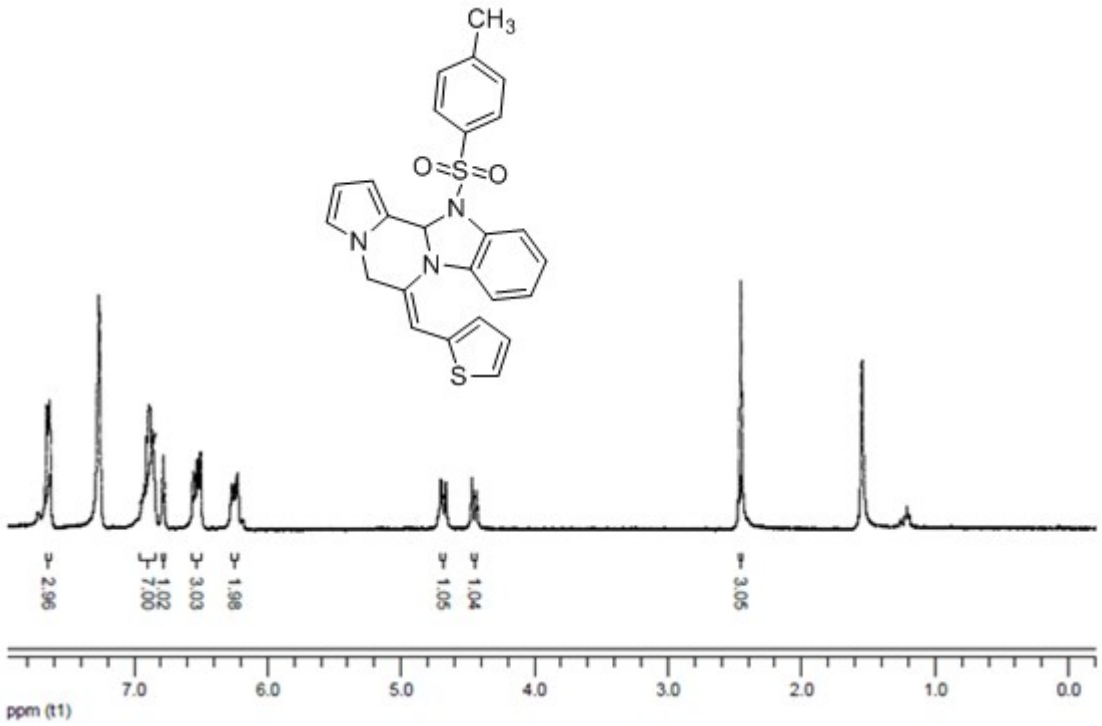
^{1}H NMR (400 MHz, $CDCl_3$) (3m):



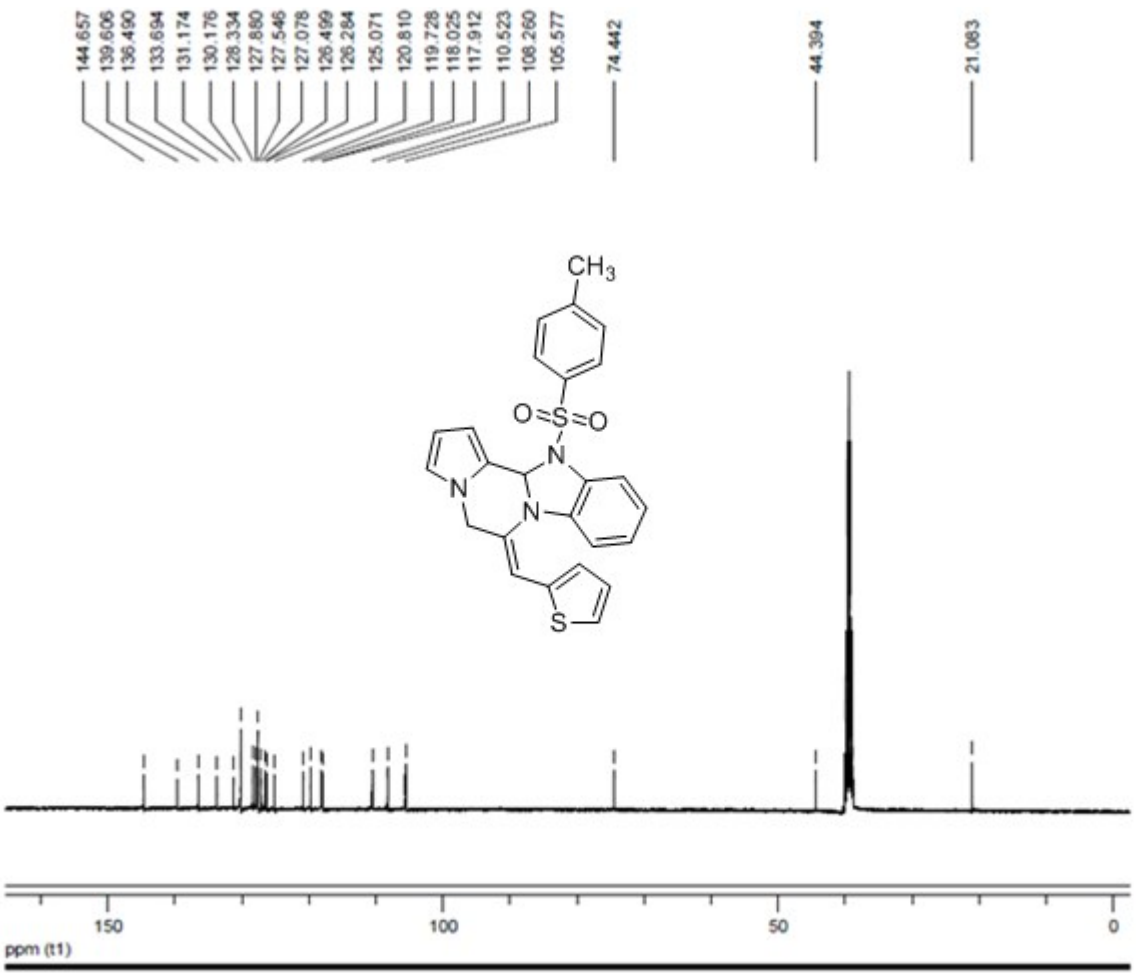
^{13}C NMR (100 MHz, $CDCl_3$) (3m):



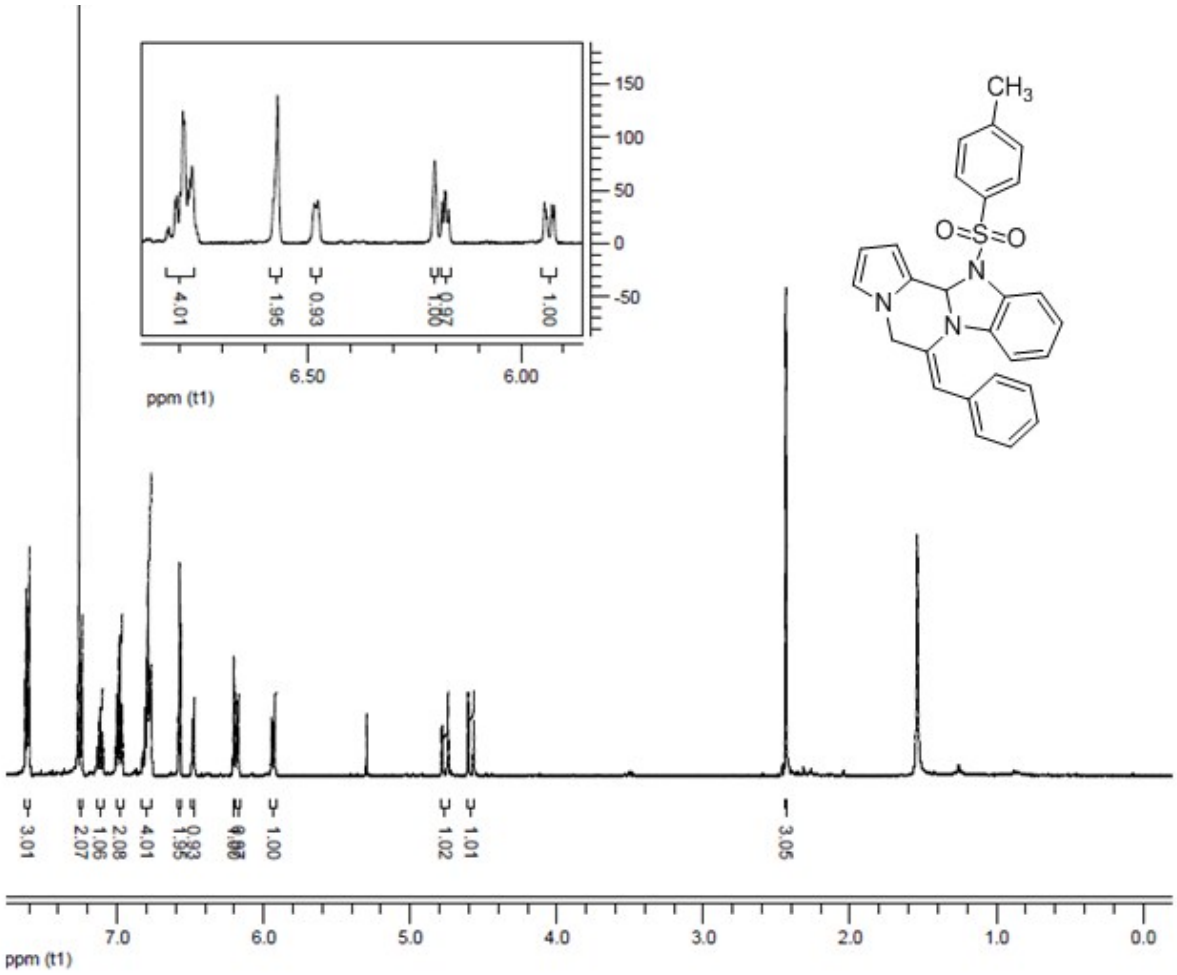
^{1}H NMR (400 MHz, $CDCl_3$) (3n)



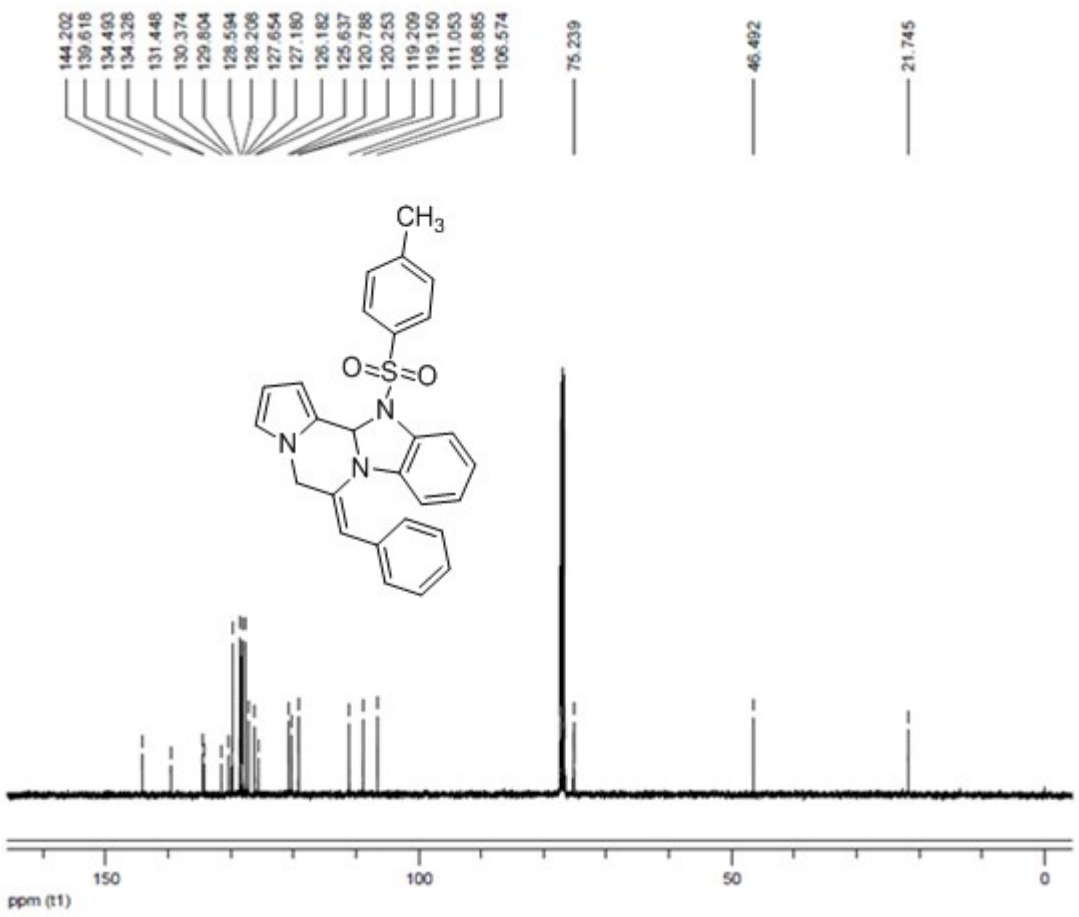
^{13}C NMR (100 MHz, DMSO-d_6) (3n):



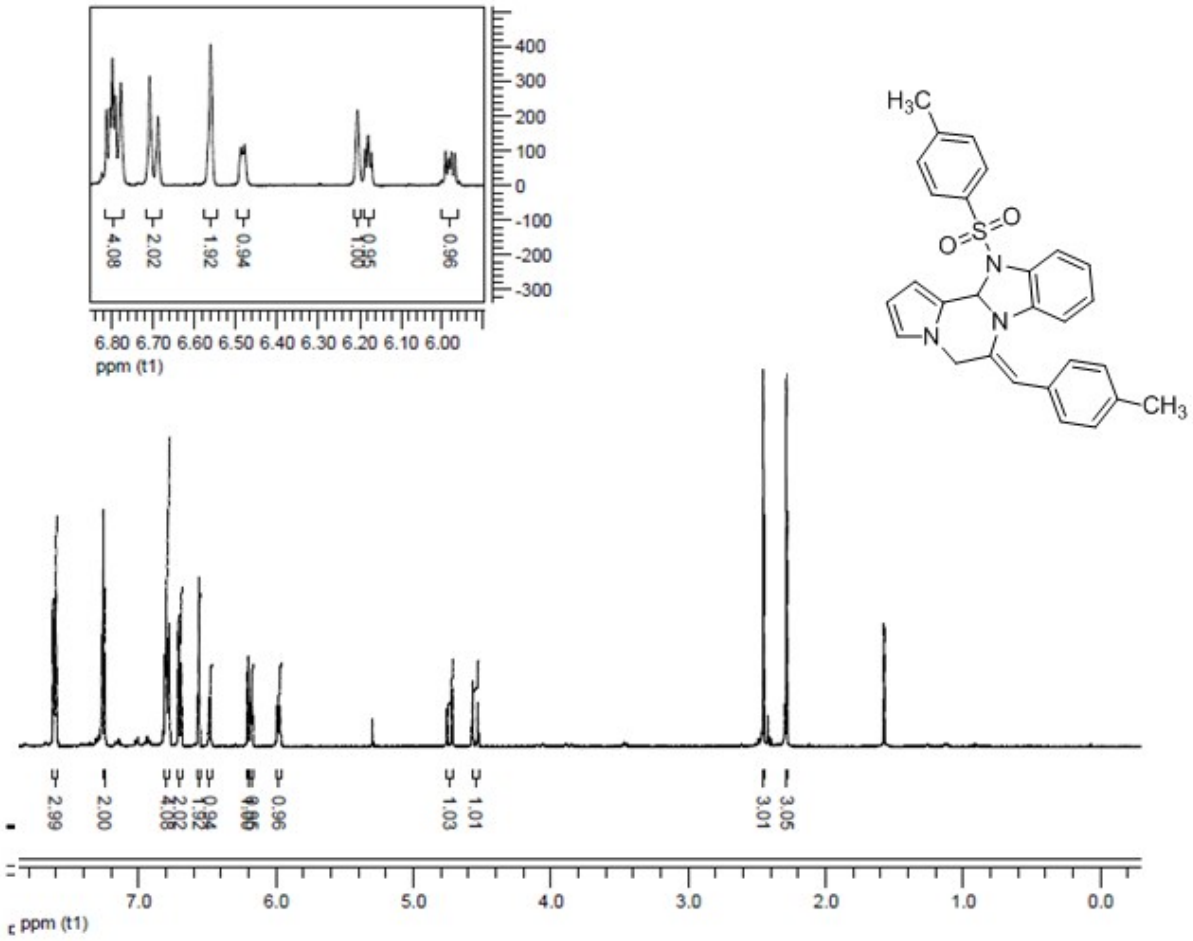
^{1}H NMR (400 MHz, $CDCl_3$) (3o):



^{13}C NMR (100 MHz, $CDCl_3$) (3o):



^{1}H NMR (400 MHz, $CDCl_3$) (3p):



^{13}C NMR (100 MHz, DMSO-d_6) (3p):