Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

One-Pot Chemoselective Domino Condensation to Form Fused Pyrrolo-Pyrazino-Indolizines Framework: Discovery of Novel AIE Molecules

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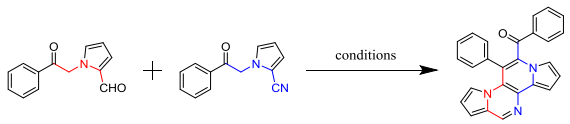
1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254}. Visualization on TLC was achieved by the use of UV light (254 nm). Solvents mixtures were understood as volume/volume. Purifications of reaction products were carried out by chromatography using silica gel (200–300 mesh). Melting points were determined with a SGW X-4 digital melting point apparatus, and the thermometer was uncorrected. NMR spectra were mostly recorded for ^{1}H NMR at 500 MHz and for ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ). The spectra data presented here are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (s) in Hertz. For ^{13}C NMR TMS (δ = 0), $CDCl_3$ (δ = 77.05) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS were obtained using ESI ionization. UV-Visible absorption spectra were measured using Shimadzu UV-1800 spectrophotometer. Fluorescence spectra were measured on a Shimadzu RF-5301PC spectrometer with a slit width 5 nm for emission. The water/DMSO mixtures with different water fractions were prepared by slowly adding distilled water into the DMSO solution of samples under ultrasound at room temperature. Fluorescence quantum yields of compounds in solution and in powders were measured on Absolutely Photoluminescence Quantum Yield Measurement System (HAMAMARSU, C11347-11Quantaurus-QY). The transmission electron microscopy (TEM) images were measured on JEOL JEM-1230, Japan.

2. Optimization of reaction conditions

Table S1. Optimization of intermolecular aldol cyclization conditions[a]



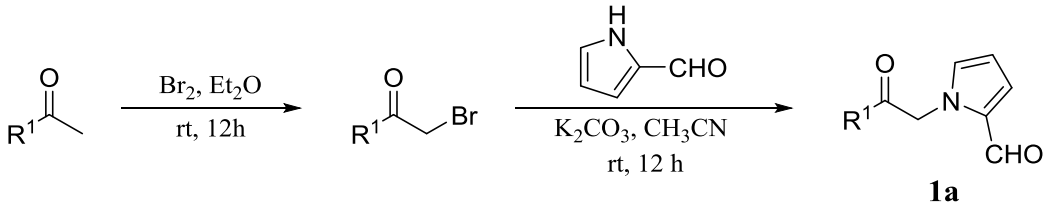
1a-1 **1b-1** **2a**

entry	base	solvent	temp (°C)	yield (%)[b]
1	DABCO	DMF	80	0
2	Et_3N	DMF	80	0
3	DBU	DMF	80	47
4	$NaHCO_3$	DMF	80	0
5	K_2CO_3	DMF	80	42
6	*t*-BuOK	DMF	80	52
7	*t*-BuOK	CH_3CN	80	18
8	*t*-BuOK	EtOH	80	22
9	*t*-BuOK	THF	80	14
10	*t*-BuOK	DMF:THF = 1:1	80	45
11	*t*-BuOK	DMF:CH_3CN = 1:1	80	53
12	*t*-BuOK	DMF:EtOH = 1:1	80	54
13	*t*-BuOK	DMF:toluene = 1:1	80	65
14	*t*-BuOK	DMF:toluene = 1:1	40	43
15 [c]	***t*-BuOK**	**DMF:toluene = 1:1**	**120**	**72**

[a] Reaction Conditions: **1a-1** (0.2 mmol, 1.0 equiv.), **1b-1** (0.2 mmol, 1.0 equiv.), base (0.24 mmol, 1.2 equiv.), 4.0 ml of solvent, 12 h. [b] Isolated yield. [c] Further changes in the ratios cannot improve the reaction yield.

3. General procedure for the synthesis

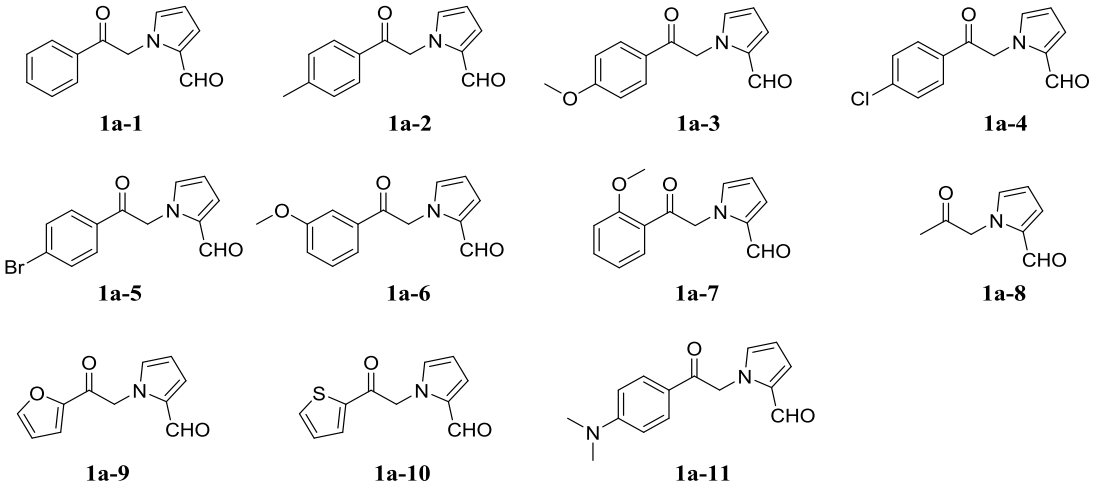
3.1. General procedure for the synthesis of 1a



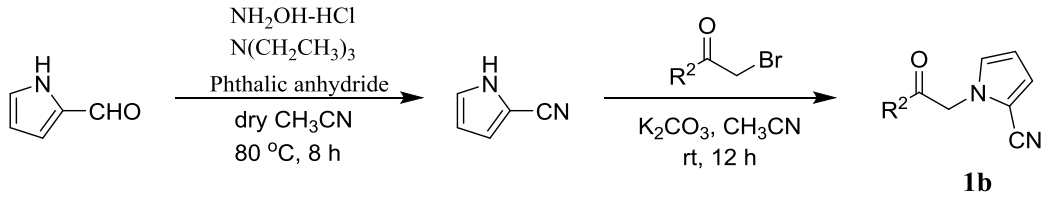
1a

Bromine (20.0 mmol, 1.0 eq) was added dropwise to a solution of ketone (20.0 mmol, 1.0 equiv.) in Et_2O (30 mL). The reaction mixture was stirred at room temperature for 12 h. A saturated sodium thiosulfate solution (70 mL) was added and stirred for 30 min. The organic layer was washed by saturated $NaHCO_3$ solution (30 mL × 3) and dried over with anhydrous Na_2SO_4. After evaporation, the resulting residue was subjected to column chromatography (hexane:EtOAc = 15:1) to get the substituted methyl bromide.[1]

A mixture of 1*H*-pyrrole-2-carboxaldehyde (5.0 mmol, 1.0 equiv.), substituted methyl bromide (5.5 mmol, 1.1 equiv.) and K_2CO_3 (6.0 mmol, 1.2 equiv.) was stirred in CH_3CN (40 mL) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (30 mL), and washed with H_2O (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL) one more time. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane:EtOAc = 10:1) to afford **1a** as white solid. These compounds have been described in the literature earlier,[2–4] except for **1a-11**. **1-(2-(4-(Dimethylamino)phenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde (1a-11):** ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.51 (1H, d, J = 1.0 Hz), 7.90 (2H, dt, J = 9.5, 2.0 Hz), 7.00 (1H, dd, J = 4.0 1.5 Hz), 7.48 (1H, tt, J = 7.5, 1.0 Hz), 6.88 (2H, d, J = 9.0 Hz), 6.33 (1H, dd, J = 4.0, 2.5 Hz), 5.67 (2H, s), 3.07 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.5, 179.8, 153.8, 132.8, 131.7, 130.3, 124.7, 122.7, 110.9, 110.1, 53.8, 40.1; HRMS Calcd. for $C_{15}H_{16}N_2O_2 + H^+$: 257.1294, found: 257.1290.

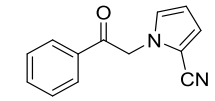


3.2. General procedure for the synthesis of 1b

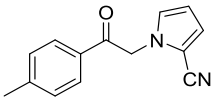


To a cold solution of hydroxylamine hydrochloride (0.38g, 5.5 mmol, 1.1 equiv.) in anhydrous acetonitrile (50 mL), triethylamine (0.77 mL, 5.5 mmol, 1.1 equiv.) and 1*H*-pyrrole-2-carboxaldehyde (5.0 mmol, 1.0 equiv.) were added and stirred for around 30 mins. Then phthalic anhydride (0.75g, 5.05 mmol, 1.01 equiv.) was slowly added under nitrogen protection. The resulting mixture was stirred at 80 °C for about 8 h. After concentration, the resulting residue was added cold CH_2Cl_2 (30 ml × 3) and stirred. The combined filtrates were washed with 5% ammonia water to remove phthalic acid completely. The separated organic layer was dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. Finally the residue was purified by passing it through a short silica gel column using $CHCl_3$ as eluent to give pure 1*H*-pyrrole-2-carbonitrile as

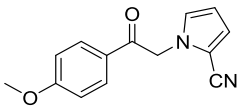
yellow oil (80%).[5] A mixture of 1*H*-pyrrole-2-carbonitrile (3.0 mmol, 1.0 equiv.), substituted methyl bromide (3.3 mmol, 1.1 equiv.) and K_2CO_3 (3.6 mmol, 1.2 equiv.) was stirred in CH_3CN (20 mL) at room temperature. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (30 mL), and washed with H_2O (30 mL). The water layer was extracted with EtOAc (30 mL) one more time. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane: EtOAc = 10:1) to afford **1b** as white solid. These compounds have been described in the literature earlier,[6] except for **1b-13**. **1-(2-oxo-2-(4-(Trifluoromethyl)phenyl)ethyl)-1*H*-pyrrole-2-carbonitrile (1b-13):** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (2H, d, J = 8.0 Hz), 7.81 (2H, d, J = 8.5 Hz), 6.90 (1H, dd, J = 4.0 1.5 Hz), 6.88 (1H, dd, J = 2.5, 1.5 Hz), 6.30 (1H, dd, J = 4.0, 2.5 Hz), 5.50 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.8, 136.7, 135.6 ($^2J_{C\text{-}F}$=38.8 Hz), 128.5, 128.0, 126.2 ($^3J_{C\text{-}F}$=3.8Hz), 123.3 ($^1J_{C\text{-}F}$=271.3 Hz), 120.7, 113.4, 110.4, 105.0, 54.3; HRMS Calcd. for $C_{14}H_9F_3N_2O + H^+$: 279.0745, found: 279.0749.



1b-1



1b-2



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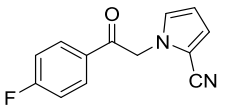

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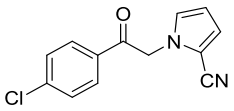

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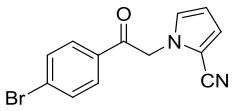

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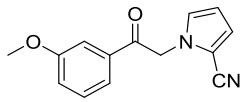

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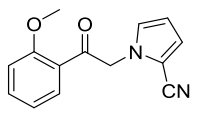

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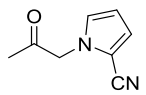

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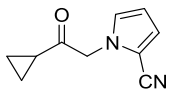

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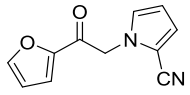

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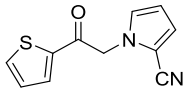
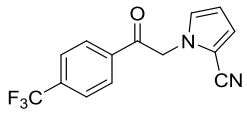


1b-12



1b-13

3.3. Experimental section and characterization data of 2

General procedure for products **3**: A mixture of *N*-substituted pyrrole-2-carbaldehyde **1a** (0.2 mmol, 1.0 equiv.), *N*-substituted pyrrole-2-carbonitrile **1b** (0.2 mmol, 1.0 equiv.) and *t*-BuOK (0.24 mmol, 1.2 equiv.) were stirred in mixed solvent (DMF:toluene = 1:1, 4.0 mL) at 120 °C under N_2. After being stirred for 12 h, the reaction was quenched by 8.0 mL water and the mixture was extracted with EtOAc (3 × 8.0 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 15:1) to provide the desired product **2**.

Phenyl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2a): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2a** as yellow

solid (27.7 mg, 72% yield). Mp: 116−118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (2H, dt, J = 7.0, 1.0 Hz), 7.67 (1H, s), 7.46 (1H, tt, J = 7.5, 1.5 Hz), 7.30 (2H, tt, J = 7.5, 1.0 Hz), 7.24 (1H, m) , 7.00 (5H, m), 6.90 (1H, dd, J = 4.0, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 1.0 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.61 (1H, dd, J = 3.0, 1.5 Hz), 6.03 (1H, dd, J = 4.0, 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.6, 135.6, 134.4, 132.3, 132.0, 131.3, 130.0, 129.4, 128.9, 128.8, 128.1, 128.0, 127.1, 122.1, 120.6, 119.0, 116.3, 113.9, 113.8, 109.0, 106.1, 103.1; HRMS Calcd. for $C_{26}H_{17}N_3O + H^+$: 388.1450, found: 388.1453.

(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(m-tolyl)methanone (2b): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-(p-tolyl)ethyl)-1*H*-pyrrole-2-carbonitrile **1b-2** (22.4 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2b** as yellow solid (20.9 mg, 52% yield). Mp: 124−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (2H, dt, J = 7.0, 1.5 Hz), 7.65 (1H, s), 7.48 (1H, tt, J = 7.5, 1.0 Hz), 7.31 (2H, tt, J = 7.5, 1.0 Hz), , 7.20 (1H, d, J = 7.5, 2.5 Hz), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.87 (2H, d, J = 7.5 Hz), 6.81 (2H, d, J = 7.5 Hz), 6.74 (2H, m), 6.62 (1H, dd, J = 2.5, 1.5 Hz), 6.04 (1H, dd, J = 4.0, 3.0 Hz), 2.13 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.7, 137.9, 135.6, 134.3, 132.0, 131.2, 129.8, 129.4, 129.2, 128.9, 128.8, 128.7, 127.3, 122.1, 120.6, 118.9, 116.2, 113.8, 113.7, 109.9, 106.1, 102.9, 21.1; HRMS Calcd. for $C_{27}H_{19}N_3O + H^+$: 402.1606, found: 402.1602.

(4-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2c): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-(4-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-3** (24.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2c** as yellow solid (23.4 mg, 56% yield). Mp: 143−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (2H, dt, J = 8.0, 1.0 Hz), 7.64 (1H, s), 7.48 (1H, dt, J = 7.0, 1.5 Hz), 7.31 (2H, t, J = 7.5 Hz), 7.22 (1H, d, J = 8.0 Hz) , 6.89 (3H, m), 6.75 (1H, dd, J = 4.0, 1.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.63 (1H, dd, J = 2.5, 1.5 Hz), 6.53 (2H, d, J = 9.0 Hz), 6.05 (1H, dd, J = 4.0, 2.5 Hz), 3.64 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.8, 165.8, 159.2, 135.6, 134.4, 131.9, 131.2, 129.4, 128.8, 127.3, 124.4, 121.8, 120.6, 118.9, 116.1, 113.8, 113.7, 113.5, 109.9, 1106.0, 103.0, 55.0; HRMS Calcd. for $C_{27}H_{19}N_3O_2 + H^+$: 418.1556, found: 418.1562.

(4-Fluorophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2d): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-(4-fluorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-4** (22.8 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2d** as yellow solid (25.9 mg, 64% yield). Mp: 125−127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (2H, dd, J = 8.0, 1.0 Hz), 7.66 (1H, s), 7.50 (1H, t, J = 7.5 Hz), 7.33 (2H, t, J = 8.0 Hz), 7.23 (1H, d, J = 1.5 Hz), 6.98 (2H, m) , 6.91 (1H, dd, J = 4.0, 2.0 Hz), 6.76 (1H, dd, J = 4.0, 1.0 Hz), 6.73 (1H, dd, J = 4.0, 1.5 Hz), 6.71 (2H, t, J = 8.5 Hz), 6.64 (1H, dd, J = 2.5, 1.5 Hz), 6.06 (1H, dd, J = 4.0, 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.5, 162.3 (d, J = 309.0 Hz), 135.5, 134.6, 132.1, 131.8 (d, J = 10.5 Hz), 131.2, 129.4, 129.0, 128.8, 128.3, 127.0, 121.1, 120.7, 119.1, 116.4, 115.2 (d, J = 27.1 Hz), 114.0, 113.7, 110.1, 106.2, 103.3; HRMS Calcd. for $C_{26}H_{16}FN_3O + H^+$: 406.1356, found: 406.1352.

(4-Chlorophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2e):

Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-(4-chlorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-5** (24.4 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2e** as yellow solid (24.0 mg, 57% yield). Mp: 115−117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ7.70 (2H, dt, J = 7.5, 1.5 Hz), 7.66 (1H, s), 7.52 (1H, tt, J = 7.0, 1.5 Hz), 7.35 (2H, tt, J = 7.5, 1.5 Hz), 7.20 (1H, m), 7.00 (2H, d, J = 8.5 Hz) , 6.93 (2H, d, J = 8.5 Hz), 6.91 (1H, dd, J = 3.5, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 0.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.65 (1H, J = 3.5, 2.0 Hz), 6.07(1H, dd, J = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.3, 135.4, 134.7, 134.4, 132.2, 131.3, 131.2, 130.8, 129.4, 129.0, 128.7, 128.3, 126.8, 120.9, 120.8, 119.1, 116.5, 114.0, 113.6, 110.2, 106.2, 103.3; HRMS Calcd. for $C_{26}H_{16}ClN_3O + H^+$: 422.1060, found: 422.1063.

(4-Bromophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2f): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-(4-bromophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-6** (28.8 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2f** as yellow solid (27.9 mg, 60% yield). Mp: 132−134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (2H, dt, J = 8.0, 1.5 Hz), 7.66 (1H, s), 7.53 (1H, tt, J = 7.5, 1.5 Hz), 7.35 (2H, tt, J = 8.0, 1.5 Hz), 7.20 (1H, m), 7.15 (2H, d, J = 7.5 Hz) , 6.91 (1H, dd, J = 4.0, 3.0 Hz), 6.87 (2H, d, J = 8.5 Hz), 6.76 (1H, dd, J = 4.0, 1.0 Hz), 6.75 (1H, dd, J = 4.0, 1.5 Hz), 6.65 (1H, dd, J = 3.0, 1.5 Hz), 6.08 (1H, J = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 135.4, 134.7, 132.1, 131.6, 131.3, 131.2, 131.1, 129.4, 129.0, 128.7, 126.7, 122.7, 120.9, 120.8, 119.2, 116.5, 114.0, 113.7, 110.2, 106.2, 103.3; HRMS Calcd. for $C_{26}H_{16}BrN_3O + H^+$: 466.0555, found: 466.0552.

(3-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2g): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-(3-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-7** (24.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2g** as yellow solid (22.2 mg, 51% yield). Mp: 138−140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (2H, d, J = 8.0 Hz), 7.66 (1H, s), 7.49 (1H, tt, J = 7.5, 1.0 Hz), 7.32 (2H, t, J = 7.5 Hz), 7.24 (1H, d, J = 2.5 Hz), 6.91 (2H, m), 6.76 (2H, m), 6.63 (1H, dd, J = 3.0, 2.0 Hz), 6.58 (2H, m), 6.50 (1H, t, J = 1.5 Hz), 6.05 (1H, dd, J = 4.0, 2.5 Hz), 3.55 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.6, 159.0, 135.6, 134.4, 133.5, 131.9, 131.2, 129.4, 129.1, 128.9, 128.8, 127.0, 122.6, 121.9, 120.6, 119.0, 116.3, 114.8, 114.7, 113.9, 113.8, 110.0, 106.1, 103.1, 55.1; HRMS Calcd. for $C_{27}H_{19}N_3O_2 + H^+$: 418.1556, found: 418.1551.

(2-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2h): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-(2-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-8** (24.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2h** as yellow solid (17.9 mg, 43% yield). Mp: 142−144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (2H, dt, J = 8.5, 1.5 Hz), 7.61 (1H, s), 7.43 (1H, tt, J = 7.5, 1.5 Hz), 7.30 (1H, m), 7.24 (2H, tt, J = 7.5, 2.0 Hz), 7.12 (1H, dd, J = 7.5, 1.5 Hz), 7.01 (1H, ddd J = 8.0, 3.5, 1.5 Hz), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.73 (3H, m), 6.48 (1H, s), 6.35 (1H, d, J = 8.0 Hz), 5.93 (1H, dd, J = 4.0, 2.5 Hz), 3.49 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.8, 156.7, 135.9, 134.0, 132.6, 132.1, 131.5, 130.4, 129.2, 128.8, 128.3, 128.2, 121.4, 120.1, 120.0, 119.5, 118.30, 115.8, 113.9, 113.7, 109.6, 108.9, 105.8, 102.8, 54.5; HRMS Calcd. for $C_{27}H_{19}N_3O_2 + H^+$: 418.1556, found: 418.1553.

1-(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)ethanone (2i): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-oxopropyl)-1*H*-pyrrole-2-carbonitrile **1b-9** (14.8 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2i** as yellow solid (18.5 mg, 57% yield). Mp: 138−140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (2H, dt, J = 8.5, 1.5 Hz), 7.66 (1H, tt, J = 7.5, 1.5 Hz), 7.52 (1H, s), 7.52 (2H, t, J = 7.5 Hz), 7.08 (1H, d, J = 2.5 Hz), 6.96 (1H, dd J = 3.5, 1.5 Hz) , 6.95 (1H, dd, J = 2.5, 1.5 Hz), 6.80 (1H, dd, J = 4.0, 3.0 Hz), 6.65 (1H, dd, J = 4.0, 1.0 Hz), 6.36 (1H, dd, J = 4.0, 3.0 Hz), 1.80 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9, 135.2, 135.1, 131.1, 131.0, 129.7, 129.6, 128.4, 120.8, 119.1, 115.9, 115.6, 113.5, 110.4, 106.2, 102.6, 13.0; HRMS Calcd. for $C_{21}H_{15}N_3O + H^+$: 326.1293, found: 326.1295.

Cyclopropyl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2j): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-cyclopropyl-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-10** (17.4 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2j** as yellow solid (18.2 mg, 52% yield). Mp: 127−129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (2H, d, J = 7.0 Hz), 7.65 (1H, tt, J = 7.0, 1.0 Hz), 7.52 (2H, t, J = 7.0 Hz), 7.53 (1H, s), 7.28 (1H, d, J = 2.5 Hz), 6.97 (2H, m) , 6.85 (1H, dd, J = 4.0, 3.0 Hz), 6.66 (1H, dd, J = 4.0, 1.0 Hz), 6.34 (1H, dd, J = 4.0, 3.0 Hz), 1.51 (1H, m), 0.25 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ ^{13}C NMR (126 MHz, $CDCl_3$) δ = 192.25, 136.5, 134.6, 132.9, 131.2, 129.6, 129.4, 129.3, 128.6, 120.9, 120.7, 118.8, 115.8, 114.1, 113.4, 110.1, 106.4, 102.7, 10.7, 6.6; HRMS Calcd. for $C_{23}H_{17}N_3O + H^+$: 352.1450, found: 352.1446.

Furan-2-yl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2k): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-(furan-2-yl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-11** (20.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2k** as yellow solid (18.1 mg, 48% yield). Mp: 124−126 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (2H, dt, J = 8.0, 1.5 Hz), 7.46 (1H, s), 7.52 (1H, tt, J = 7.5, 1.0 Hz), 7.38 (2H, t, J = 8.0 Hz), 7.34 (1H, m), 7.03 (1H, d, J = 1.0 Hz), 6.91 (1H, dd, J = 4.0, 3.0 Hz), 6.89 (1H, dd, J = 4.0, 2.0 Hz), 6.80 (1H, dd, J = 2.5, 1.0 Hz), 6.74 (1H, dd, J = 4.0, 1.0 Hz), 6.22 (1H, dd, J = 4.0, 3.0 Hz), 6.04 (1H, J = 3.0, 1.5 Hz), 5.76 (1H, J = 3.5, 0.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 144.8, 143.3, 135.5, 134.4, 131.9, 131.1, 129.2, 128.9, 128.4, 125.6, 120.7, 119.6, 116.7, 114.4, 113.4, 112.6, 112.0, 111.3, 110.2, 106.3, 103.7; HRMS Calcd. for $C_{24}H_{15}N_3O_2 + H^+$: 378.1243, found: 378.1238.

(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(thiophen-2-yl)methanone (2l): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-(thiophen-2-yl)ethyl)-1*H*-pyrrole-2-carbonitrile **1b-12** (21.6 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2l** as yellow solid (20.4 mg, 52% yield). Mp: 148−150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (2H, dt, J = 7.0, 1.0 Hz), 7.65 (1H, s), 7.51 (1H, tt, J = 7.5, 1.5 Hz), 7.35 (2H, t, J = 7.5 Hz), 7.26 (1H, m), 7.06 (1H, dd, J = 5.0, 1.0 Hz), 6.90 (1H, dd, J = 4.0, 2.5 Hz) , 6.81 (2H, m), 6.75 (1H, dd, J = 3.5, 0.5 Hz), 6.72 (1H, dd, J = 3.0, 1.0 Hz), 6.68 (1H, dd, J = 5.0, 3.5 Hz), 6.14 (1H, J = 3.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.4, 135.2, 134.5, 132.8, 132.7, 131.2, 130.8, 129.4, 128.9, 128.6, 126.9, 126.7, 120.8, 119.0, 116.6, 115.1, 114.1, 113.6, 110.2, 106.5, 103.5; HRMS

Calcd. for $C_{24}H_{15}N_3OS + H^+$: 394.1014, found: 394.1016.

Phenyl(5-(p-tolyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2m): Following the general procedure, 1-(2-oxo-2-(p-tolyl)ethyl)-1*H*-pyrrole-2-carbaldehyde **1a-2** (22.7 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2m** as yellow solid (22.5 mg, 56% yield). Mp: 130−132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (1H, s), 7.62 (2H, d, J = 8.0 Hz), 7.18 (1H, d, J = 2.5 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.02 (5H, m), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.74 (2H, m), 6.61 (1H, dd, J = 2.5, 1.5 Hz), 6.02 (1H, dd, J = 4.0, 3.0 Hz), 2.33 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.0, 145.8, 132.9, 132.4, 132.3, 131.2, 130.0, 129.7, 129.7, 128.9, 128.0, 127.2, 121.6, 120.6, 118.7, 116.2, 113.8, 113.8, 109.9, 106.1, 102.9, 21.9; HRMS Calcd. for $C_{27}H_{19}N_3O + H^+$: 402.1606, found: 402.1610.

(5-(4-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2n): Following the general procedure, 1-(2-(4-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-3** (24.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2n** as yellow solid (24.2 mg, 58% yield). Mp: 137−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (2H, d, J = 9.0 Hz), 7.64 (1H, s), 7.18 (1H, d, J = 2.5 Hz), 7.03 (5H, m), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.79 (2H, d, J = 9.0 Hz), 6.73 (2H, m), 6.60 (1H, dd, J = 3.0, 1.5 Hz), 6.02 (1H, dd, J = 4.0, 3.0 Hz), 3.80 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.7, 164.7, 132.5, 132.4, 131.2, 130.0, 128.9, 128.3, 128.0, 127.2, 121.3, 120.6, 118.6, 116.2, 114.2, 113.9, 113.7, 109.9, 106.0, 102.8, 55.6; HRMS Calcd. for $C_{27}H_{19}N_3O_2 + H^+$: 418.1556, found: 418.1558.

(5-(4-Chlorophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2o): Following the general procedure, 1-(2-(4-chlorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-4** (24.7 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2o** as yellow solid (18.9 mg, 45% yield). Mp: 139−141 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, s), 7.61 (2H, dt, J = 8.5, 1.5 Hz), 7.27 (2H, dt, J = 7.0, 2.0 Hz), 7.24 (1H, d, J = 2.5 Hz), 7.07 (1H, tt, J = 7.5, 1.0 Hz), 7.03 (2H, tt, J = 8.0, 1.5 Hz), 6.97 (2H, d, J = 7.0 Hz) , 6.92 (1H, dd, J = 4.0, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 0.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5 Hz), 6.60 (1H, dd, J = 2.5, 1.5 Hz), 6.03 (1H, J = 4.0, 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.5, 140.9, 134.0, 132.2, 131.4, 131.3, 130.7, 130.0, 129.2, 128.8, 128.3, 128.2, 126.9, 122.4, 120.6, 119.3, 116.4, 113.8, 113.7, 109.9, 106.1, 103.3; HRMS Calcd. for $C_{26}H_{16}ClN_3O + H^+$: 422.1060, found: 422.1067.

(5-(4-Bromophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2p): Following the general procedure, 1-(2-(4-bromophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-5** (29.1 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2p** as yellow solid (26.5 mg, 57% yield). Mp: 142−144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, s), 7.53 (2H, dt, J = 9.0, 2.0 Hz), 7.43 (2H, dt, J = 8.5, 2.0 Hz), 7.24 (1H, m), 7.05 (1H, tt, J = 8.5, 1.5 Hz), 7.03 (2H, td, J = 7.5, 1.5 Hz) , 6.96 (2H, dt, J = 7.0, 1.5 Hz), 6.92 (1H, dd, J = 4.0, 3.0 Hz), 6.76 (1H, dd, J = 4.0, 0.5 Hz), 6.74 (1H, dd, J = 4.0, 1.5), 6.60 (1H, dd, J = 2.5, 1.5 Hz), 6.03 (1H, J = 4.0, 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.7, 134.4, 132.2, 131.3, 131.2, 130.7, 130.0, 129.8, 128.8, 128.3, 128.2, 126.9, 122.4, 120.7, 119.3, 116.4, 113.8, 113.7, 110.0,

106.1, 103.4; HRMS Calcd. for $C_{26}H_{16}BrN_3O + H^+$: 466.0555, found: 466.0557.

(5-(3-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2q): Following the general procedure, 1-(2-(3-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-6** (24.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2q** as yellow solid (22.1 mg, 53% yield). Mp: 126−128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (1H, s), 7.26 (1H, dt, J = 7.5, 1.5 Hz), 7.20 (2H, m), 7.03 (6H, m), 6.90 (1H, dd, J = 4.0, 2.5 Hz), 6.75 (1H, dd, J = 4.0, 1.0 Hz), 6.72 (1H, dd, J = 4.0, 1.5 Hz), 6.61 (1H, dd, J = 3.0, 1.5 Hz), 6.03 (1H, dd, J = 4.0, 3.0 Hz), 3.76 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.4, 159.8, 136.8, 132.3, 132.0, 131.2, 130.0, 129.9, 128.8, 128.1, 128.1, 127.1, 122.6, 122.1, 121.5, 120.6, 119.0, 116.3, 113.9, 113.8, 112.6, 109.9, 106.2, 103.1, 55.5; HRMS Calcd. for $C_{27}H_{19}N_3O_2 + H^+$: 418.1556, found: 418.1548.

(5-(2-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2r): Following the general procedure, 1-(2-(2-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-7** (24.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2r** as yellow solid (19.6 mg, 47% yield). Mp: 123−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (1H, s), 7.43 (1H, dd, J = 8.0, 2.0 Hz), 7.38 (1H, d, J = 2.5 Hz), 7.33 (1H, ddd, J = 7.0, 2.0, 1.0 Hz), 7.02 (1H, tt, J = 7.0, 1.5 Hz), 6.97 (2H, t, J = 8.0 Hz), 6.93 (2H, d, J = 7.0 Hz), 6.91 (1H, dd, J = 4.0, 2.5 Hz), 6.79 (1H, td, J = 8.0, 0.5 Hz), 6.71 (3H, m), 6.56 (1H, dd, J = 2.5, 1.5 Hz), 5.98 (1H, dd, J = 4.0, 3.0 Hz), 3.51 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.5, 159.3, 135.0, 134.9, 132.8, 131.2, 129.8, 128.9, 127.7, 127.3, 126.8, 120.9, 120.7, 120.3, 118.4, 115.8, 113.9, 113.6, 111.5, 109.7, 106.2, 102.6, 55.9; HRMS Calcd. for $C_{27}H_{19}N_3O_2 + H^+$: 418.1556, found: 418.1551.

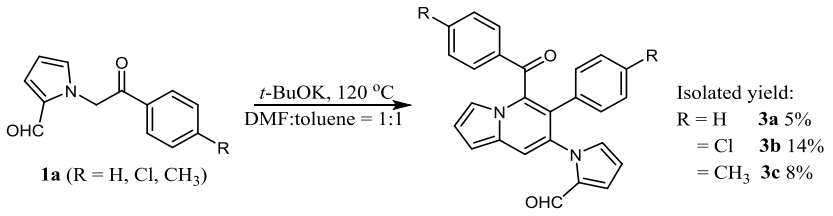
(5-(Furan-2-yl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2s): Following the general procedure, 1-(2-(furan-2-yl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-8** (20.3 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2t** as yellow solid (20.0 mg, 53% yield). Mp: 153−155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (2H, dd, J = 7.0, 1.5 Hz), 7.64 (1H, s), 7.53 (1H, tt, J = 7.5, 1.5 Hz), 7.38 (2H, t, J = 8.0 Hz), 7.34 (1H, m), 7.03 (1H, dd, J = 2.0, 1.0 Hz), 6.91 (1H, dd, J = 4.0, 3.0 Hz), 6.90 (1H, dd, J = 4.0, 1.5 Hz), 6.80 (1H, dd, J = 3.0, 1.5 Hz), 6.74 (1H, dd, J = 4.0, 1.0 Hz), 6.22 (1H, dd, J = 4.0, 2.5 Hz), 6.04 (1H, dd, J = 3.5, 2.0 Hz), 5.76 (1H, dd, J = 3.0, 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 144.8, 143.3, 135.5, 134.4, 131.9, 131.1, 129.2, 128.9, 128.4, 125.6, 120.7, 119.6, 116.7, 114.4, 113.4, 112.6, 112.0, 111.3, 110.2, 106.3, 103.7; HRMS Calcd. for $C_{24}H_{15}N_3O_2 + H^+$: 378.1243, found: 378.1247.

Phenyl(5-(thiophen-2-yl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2t): Following the general procedure, 1-(2-oxo-2-(thiophen-2-yl)ethyl)-1*H*-pyrrole-2-carbaldehyde **1a-9** (21.9 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (21.0 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2u** as yellow solid (18.1 mg, 46% yield). Mp: 148−150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (1H, s), 7.62 (1H, dd, J = 4.0, 1.0 Hz), 7.41 (1H, dd, J = 4.0, 1.0 Hz), 7.33 (1H, m), 7.07 (5H, m), 6.92 (2H, m), 6.75 (2H, m), 6.58 (1H, dd, J = 2.0, 1.5 Hz), 6.03 (1H, dd, J = 3.5, 2.0 Hz); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 183.3, 142.6, 136.7, 135.9, 132.5, 131.8, 131.2, 129.9, 128.9, 128.4, 128.2, 128.1, 127.0, 121.7, 120.6, 119.2, 116.3, 113.9, 113.8, 109.9, 106.1, 103.2; HRMS Calcd. for $C_{24}H_{15}N_3OS + H^+$: 393.0936, found: 393.0942.

(5-(4-(dimethylamino)phenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(4-(trifluoromethyl)phenyl)methanone (2u): Following the general procedure, 1-(2-oxo-2-(thiophen-2-yl)ethyl)-1*H*-pyrrole-2-carbaldehyde **1a-10** (25.6 mg, 0.1 mmol) and 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile **1b-13** (27.8 mg, 0.1 mmol) were used. Purification *via* column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2u** as yellow solid (28.4 mg, 57% yield). Mp: 158−160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (3H, m), 7.31 (2H, d, J = 8.5 Hz), 7.20 (3H, m), 6.88 (1H, dd, J = 4.0, 3.0 Hz), 6.73 (2H, m), 6.63 (1H, m), 6.53 (2H, d, J = 9.5 Hz), 6.05 (1H, dd, J = 4.0, 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 187.7, 154.5, 136.8, 133.8, 132.2, 131.1, 130.3, 129.7 (q, $^2J_{C\text{-}F}$ = 32.1 HZ), 126.8, 124.8 (q, $^3J_{C\text{-}F}$ = 3.8 HZ), 123.8 (q, $^1J_{C\text{-}F}$ = 270.8 HZ), 122.7, 120.8, 119.3, 118.2, 116.3, 114.1, 113.7, 111.1, 110.1, 106.1, 102.8, 40.0; HRMS Calcd. for $C_{29}H_{21}F_3N_4O + H^+$: 499.1746, found: 499.1751.

4. Mechanistic investigations



A mixture of *N*-substituted pyrrole-2-carbaldehyde **1a** (0.1 mmol, 1.0 equiv.) and *t*-BuOK (0.12 mmol, 1.2 equiv.) were stirred in mixed solvent (DMF:toluene = 1:1, 2.0 mL) at 120 °C under N_2. After being stirred for 12 h, the reaction was quenched by 4.0 mL water and the mixture was extracted with EtOAc (3 × 4.0 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. By using 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde (**1a-1**), 1-(2-(4-chlorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde (**1a-4**) and 1-(2-oxo-2-(p-tolyl)ethyl)-1*H*-pyrrole-2-carbaldehyde (**1a-2**) as starting materials, small amount of desired product **3a** (1.0 mg), **3b** (3.3 mg) and **3c** (1.7 mg) was obtained from the residue after column chromatography (hexane:EtOAc = 15:1). The structures of **3a**, **3b** and **3c** were confirmed by TLC and NMR, which was consistent with our previous report (*Tetrahedron* **2018**, *74*, 6088–6094).

5. References

(1) J. Chen, D. Liu, N. Butt, C. Li, D. Fan, Y. Liu and W. Zhang, Palladium Catalyzed Asymmetric Hydrogenation of α-Acyloxy-1-arylethanones, *Angew. Chem. Int. Ed.,* 2013, **52**, 11632.

(2) M. Kim, Y. Jung and I. Kim, Domino Knoevenagel condensation/intramolecular aldol cyclization route to diverse indolizines with densely functionalized pyridine units, *J. Org. Chem.*, 2013, **78**, 10395.

(3) S. B. Hu, Z. P. Chen, B. Song, J. Wang and Y. G. Zhou, Enantioselective Hydrogenation of Pyrrolo[1,2-*a*]pyrazines, Heteroaromatics Containing Two Nitrogen Atoms, *Adv. Synth. Catal.,* 2017, **359**,2762.

(4) M. Kim, Y. Jung and I. Kim, Domino Knoevenagel Condensation/Intramolecular Aldol Cyclization Route to Diverse Indolizines with Densely Functionalized Pyridine Units, *J. Org. Chem.,* 2013, **78**, 10395.

(5) E. Wang and G. Lin, A new one pot method for the conversion of aldehydes into nitriles using hydroxyamine and phthalic anhydride, *Tetrahedron Lett.,* 1998, **39**, 4047.

(6) N. Shao, J. Li, H. Zhu, S. Zhang and H. Zou, Functionalized N-containing heterocyclic scaffolds derived from N-substituted pyrroles *via* inter- and intramolecular annulations, *Tetrahedron*, 2018, 74, 6088.

6. Photophysical properties of compounds 2

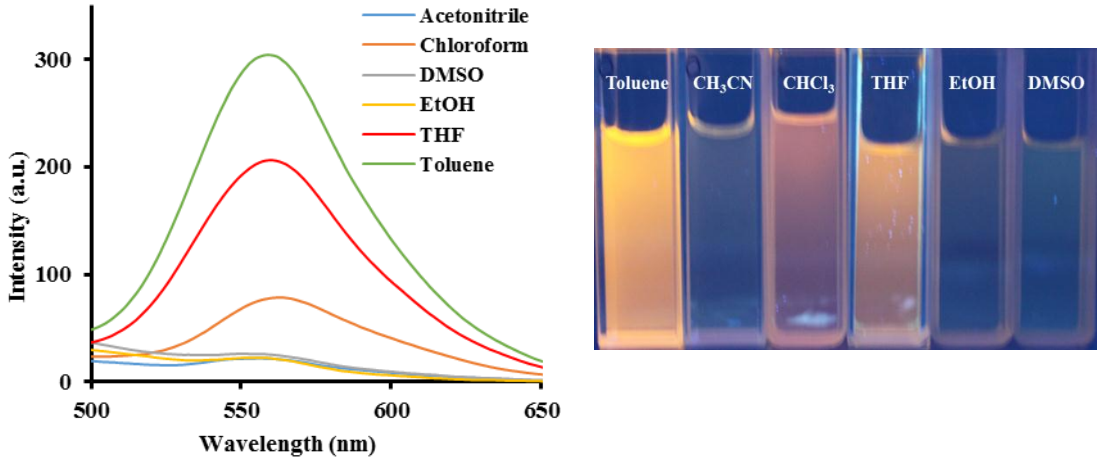


Figure S1. Emission spectra (left) of **2a** (λ_{ex}= 378 nm) and fluorescence photographs (right) of **2a** (under 365 nm) in different solvents. (concentration: 30 μM)

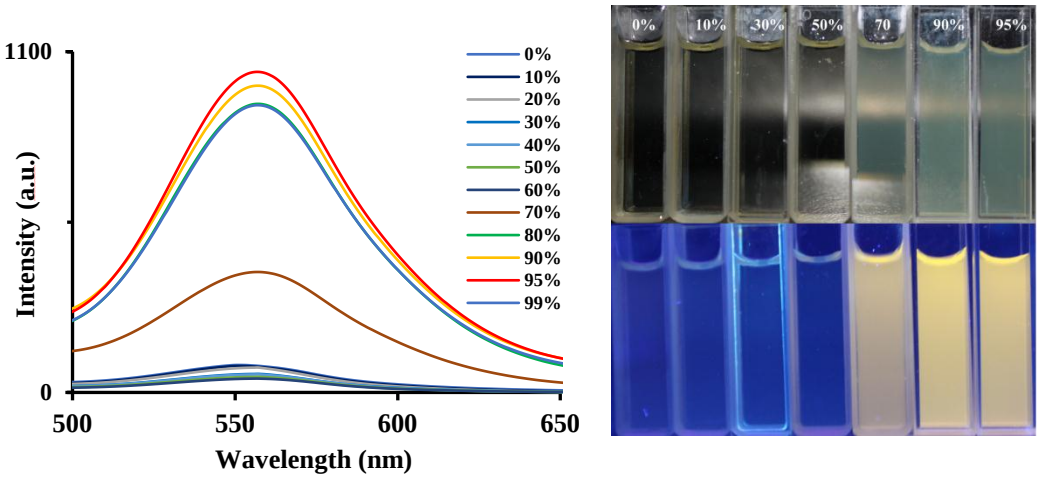


Figure S2. Emission spectra (left) of **2a** (λ_{ex}= 378 nm) and fluorescence photographs (right) of **2a** (under normal light and 365 nm) in different water fraction. (concentration: 10 μM)

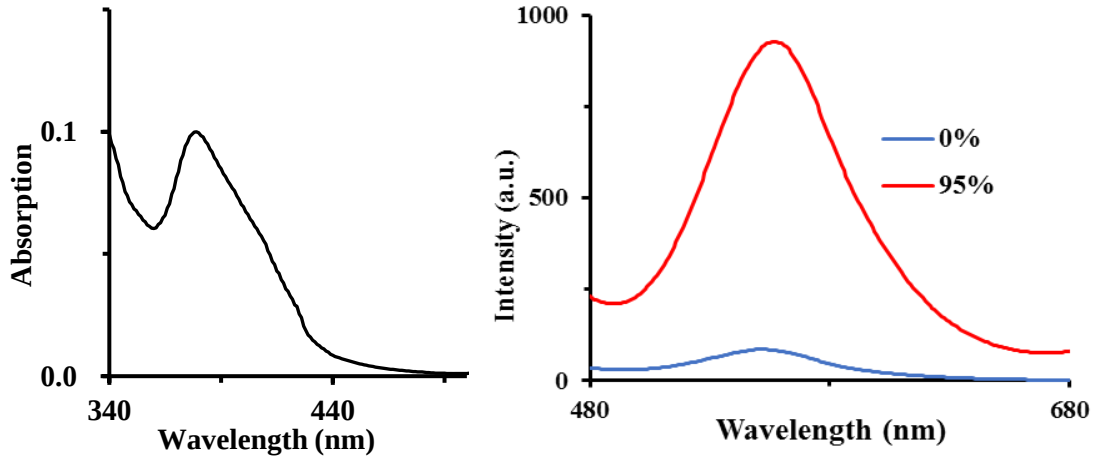


Figure S3. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2a** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

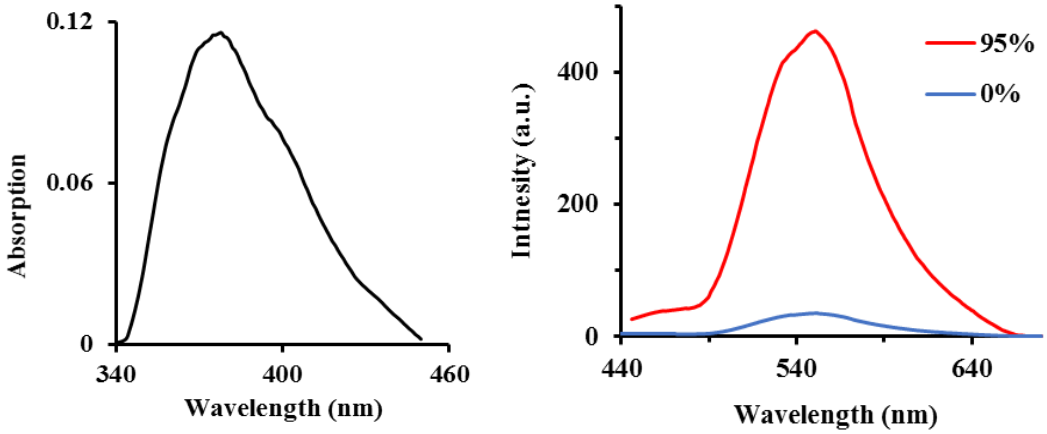


Figure S4. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2b** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

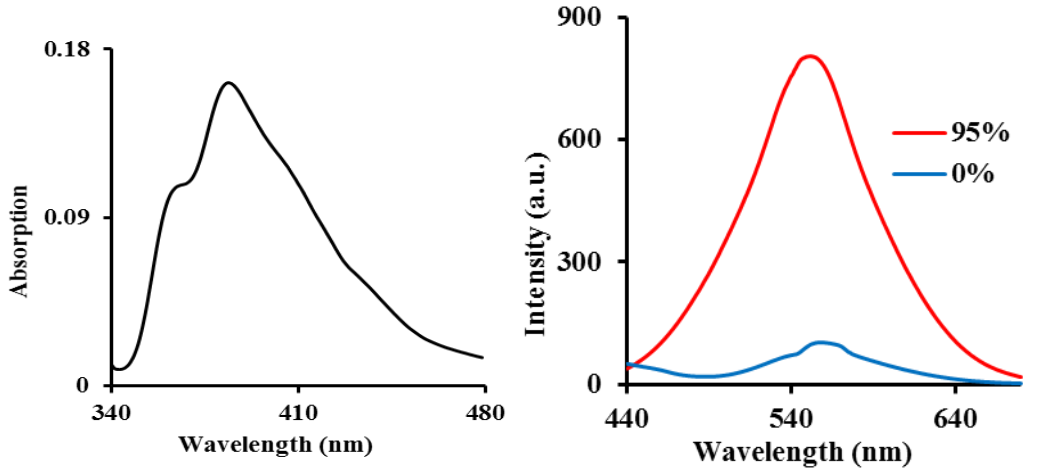


Figure S5. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2c** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

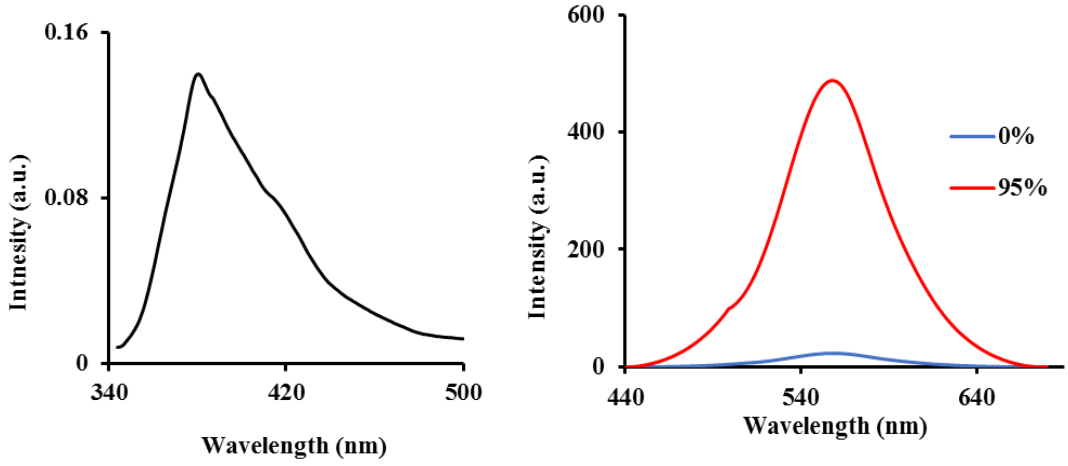


Figure S6. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2d** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

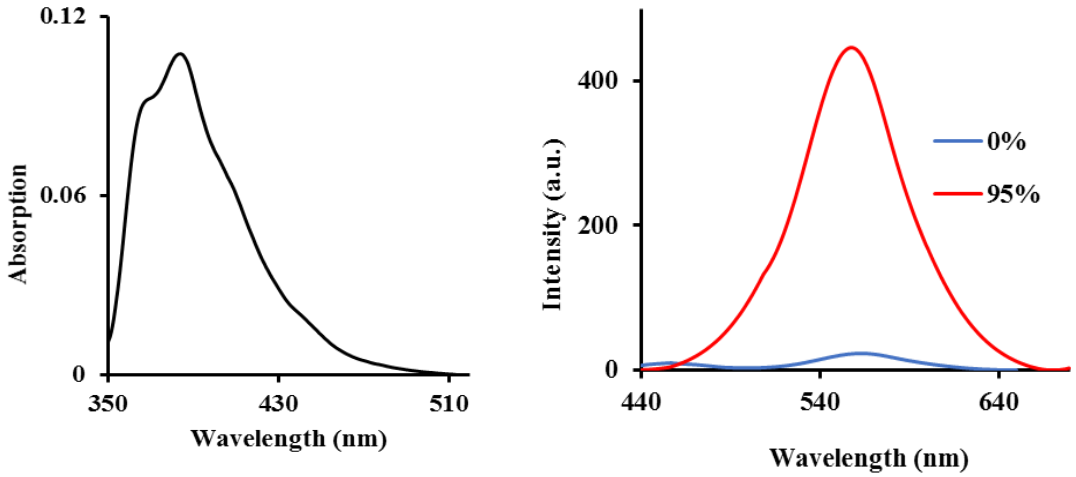


Figure S7. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2e** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

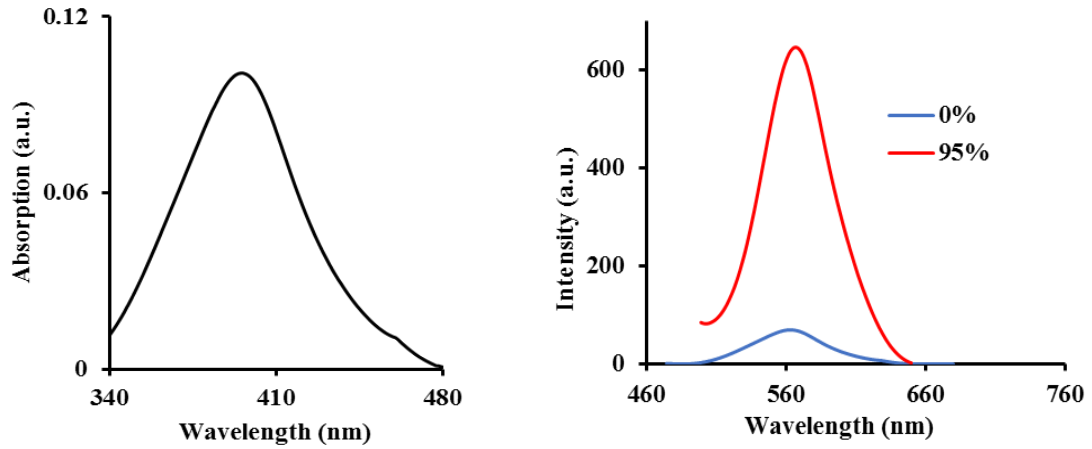


Figure S8. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2f** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

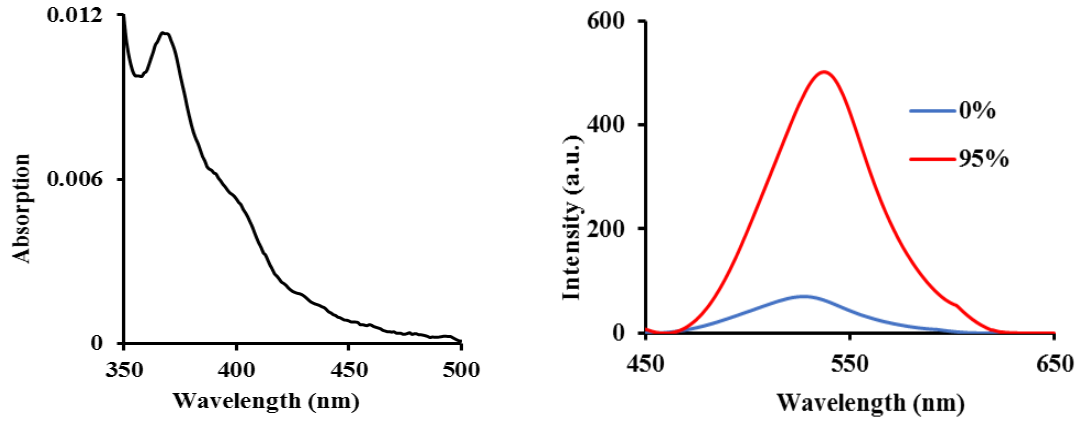


Figure S9. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2g** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

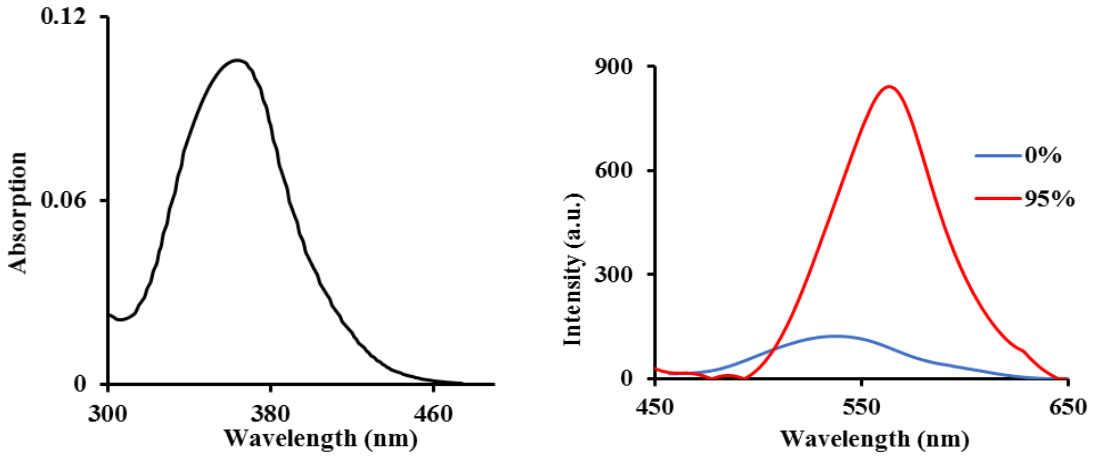


Figure S10. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2h** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

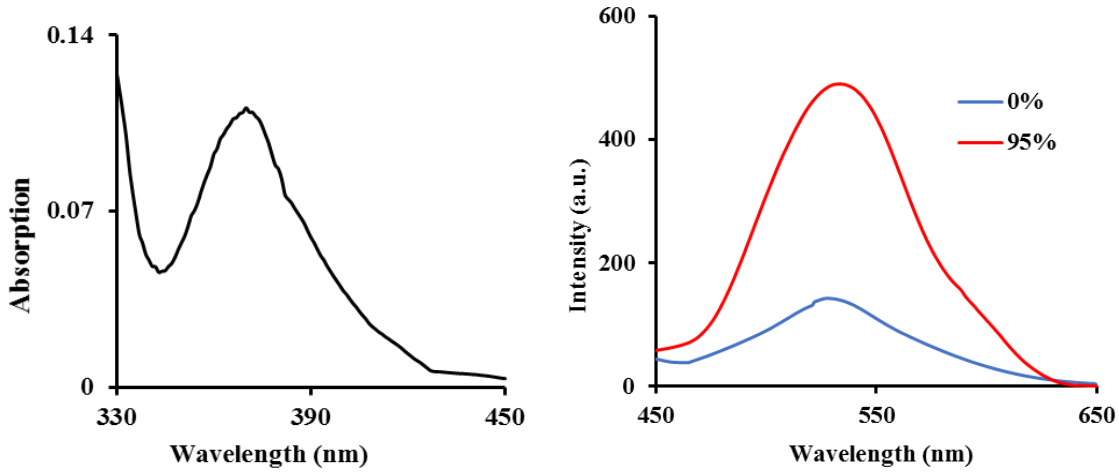


Figure S11. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2i** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

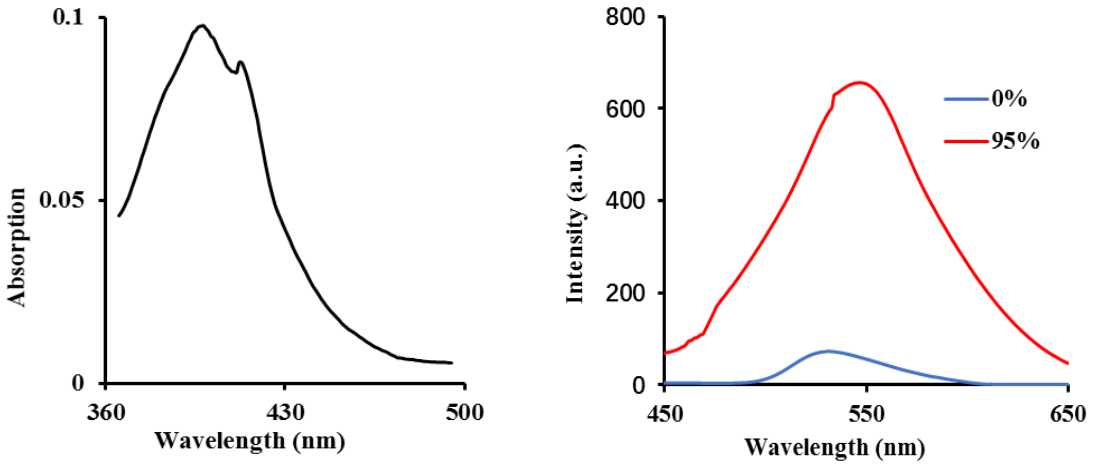


Figure S12. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2j** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

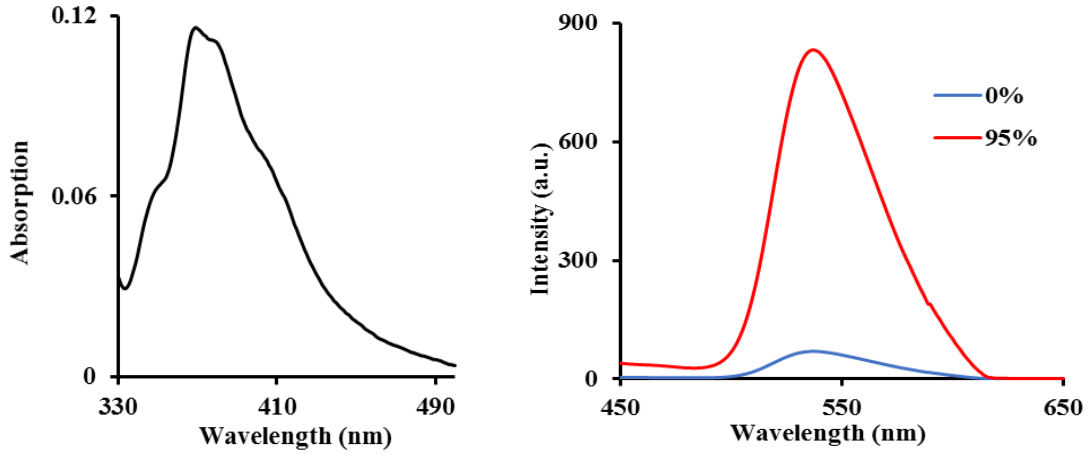


Figure S13. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2k** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

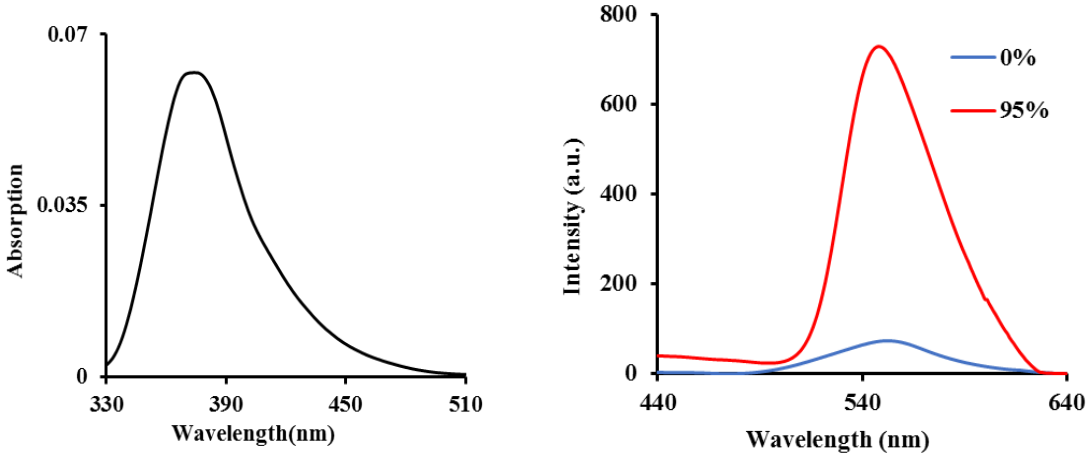


Figure S14. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2l** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

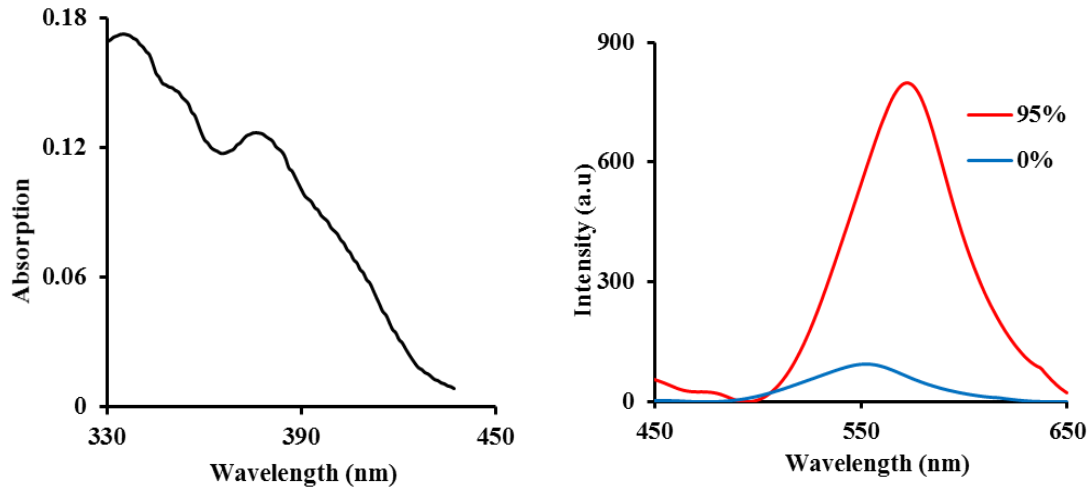


Figure S15. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2m** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

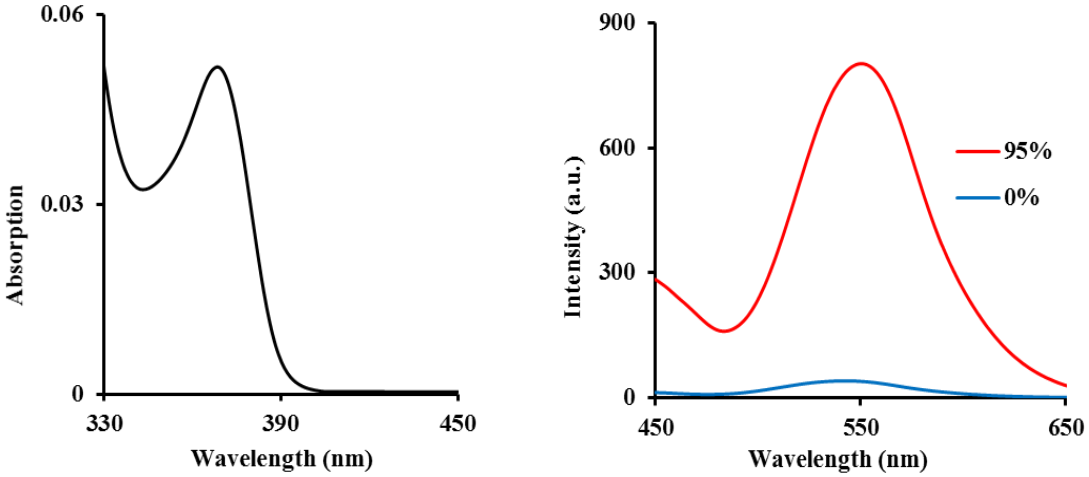


Figure S16. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2n** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

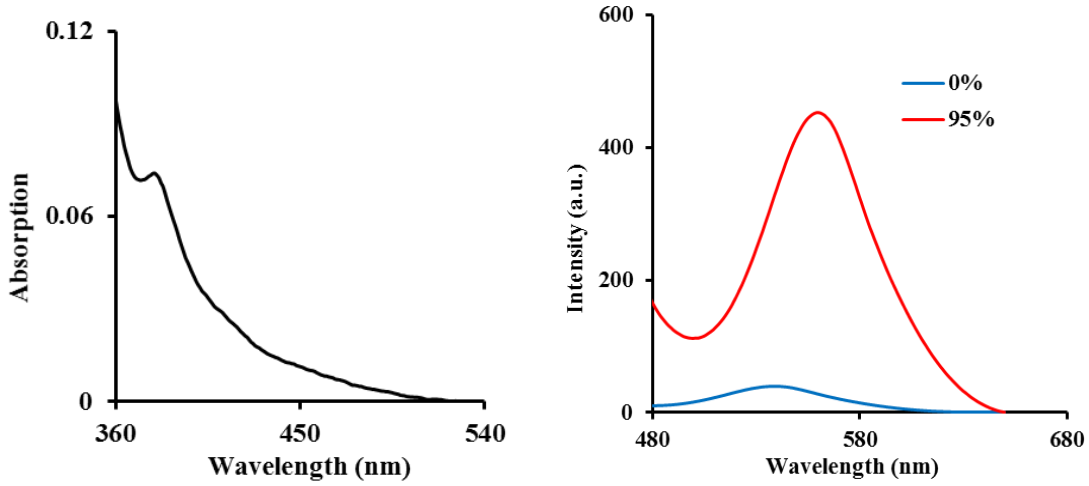


Figure S17. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2o** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

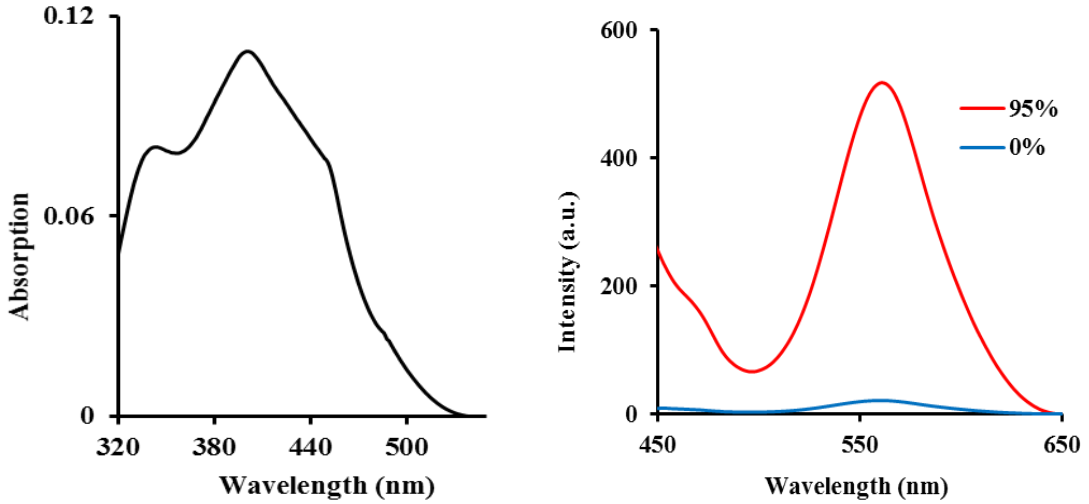


Figure S18. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2p** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

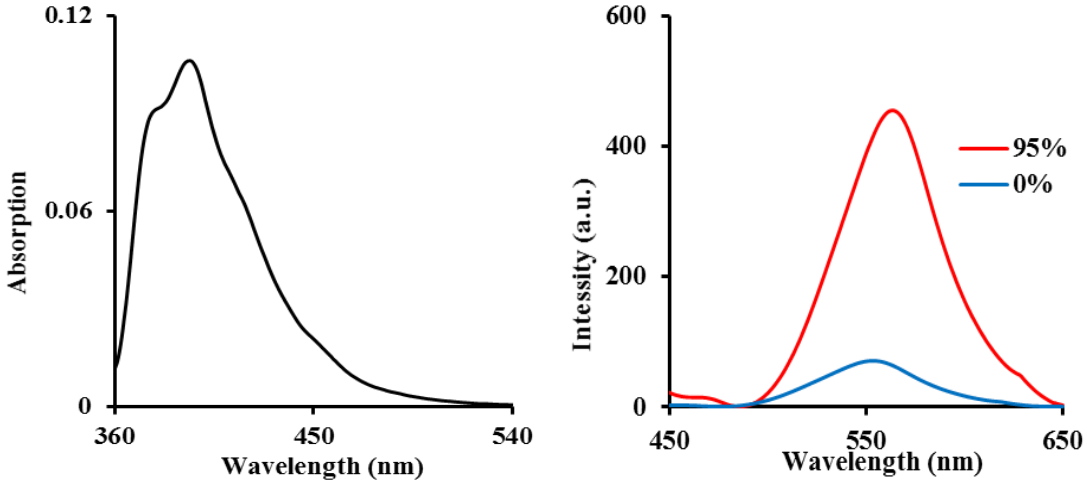


Figure S19. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2q** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

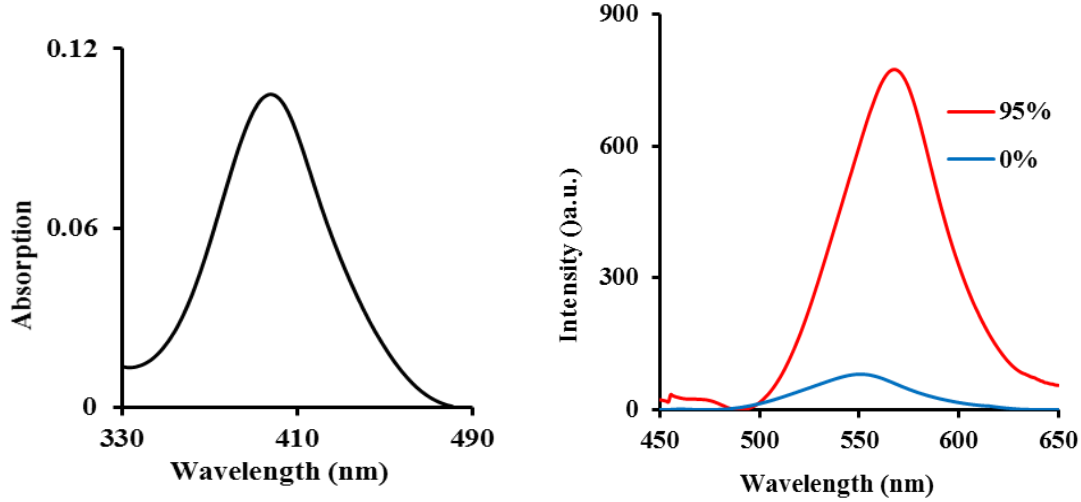


Figure S20. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2r** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

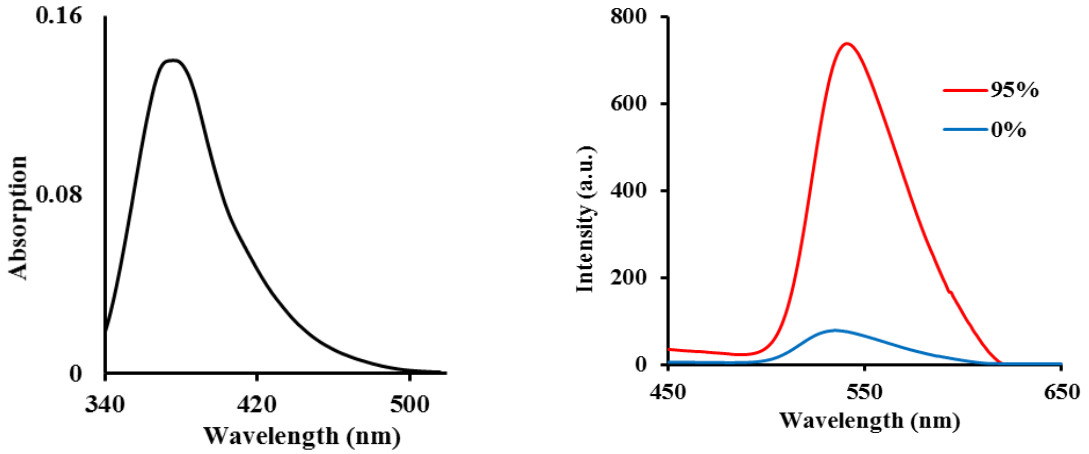


Figure S21. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2s** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

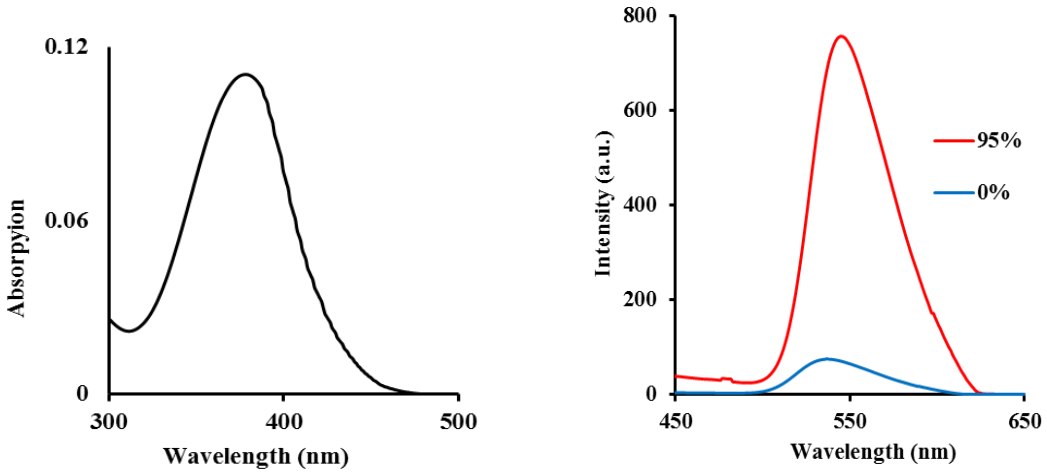


Figure S22. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2t** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

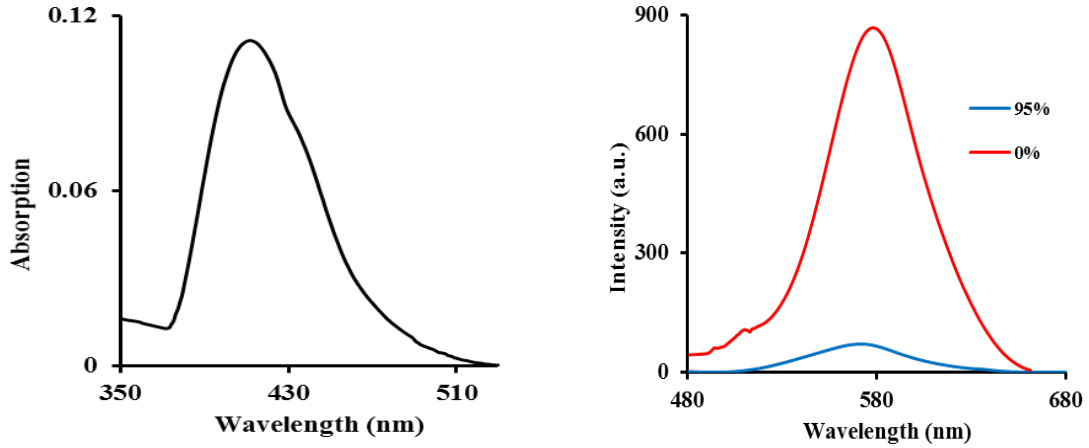


Figure S23. UV absorption (left, DMSO, 10 μM) and emission spectra (right) of **2u** in DMSO (blue line, 10 μM) and in 95% water/DMSO mixture (red line, 10 μM).

7. Cell culture and cytotoxicity

7.1 Cell culture and cytotoxicity

CT26 cells were cultured in RPMI-1640 medium (Sigma) while HUVEC cells in DMEM medium (Sigma) containing 10% fetal bovine serum (FBS) and a mixture of 0.1 mg/mL streptomycin and 100 units/mL penicillin at 37 °C in a humidified 5% CO_2 atmosphere. The cytotoxicity of **2a** was determined by MTT assay. Firstly, cells were seeded in 96-well plate at a density of 1×10^4 cells per well and allowed to attach overnight. Then the cells were exposed to **2a** at a series of concentrations for 24 hours. Subsequently, MTT solution (5 $mg \cdot mL^{-1}$) was added to each well for an additional 4 hours incubation at 37 °C. After that, the medium was replaced with 100μL of DMSO to dissolve the insoluble and purple formazan crystals in the bottom of the well. The plate was shaken for 30 min, and the absorbance of the solution in each well was measured by microplate reader at 570 nm. Cell viability was calculated in reference to negative cells without exposure to test agents. All of experiments were repeated thrice.

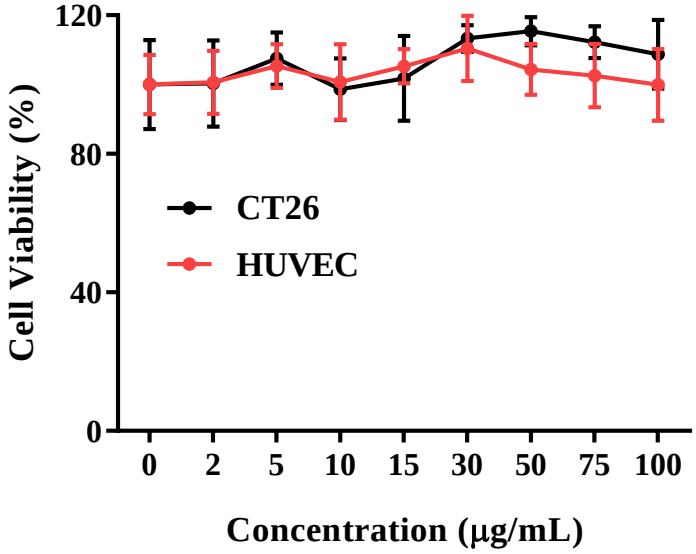


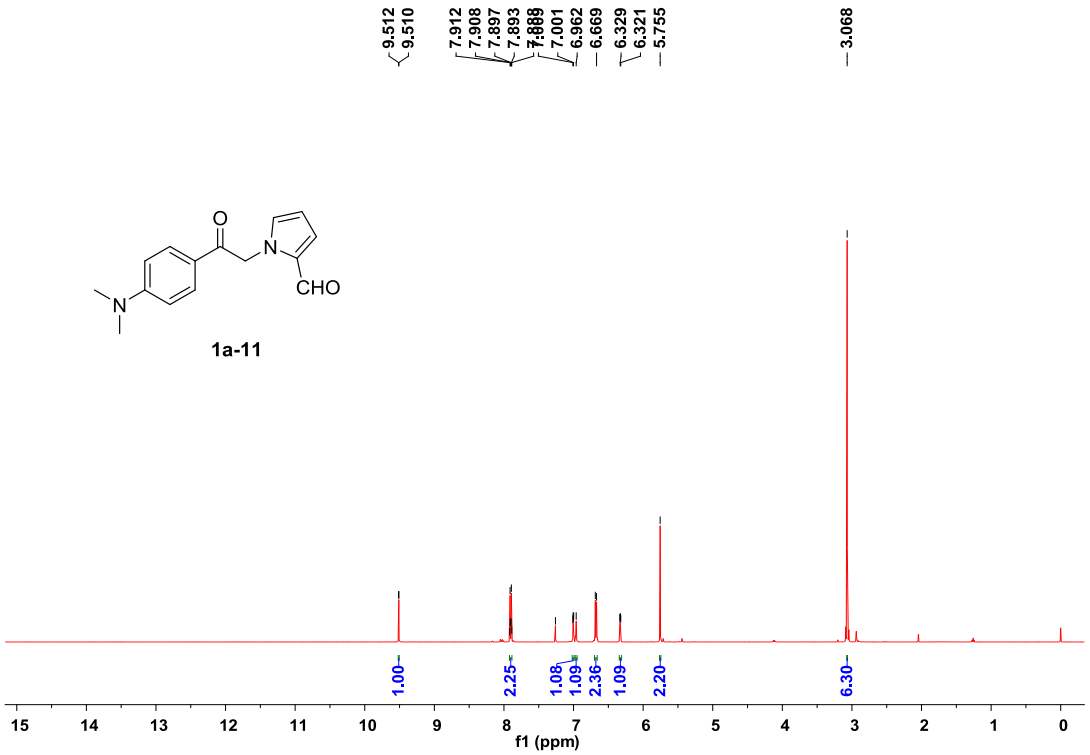
Figure S24. MTT assay of CT26 cells and HUVECs incubation (24h) with **2a** at different concentrations

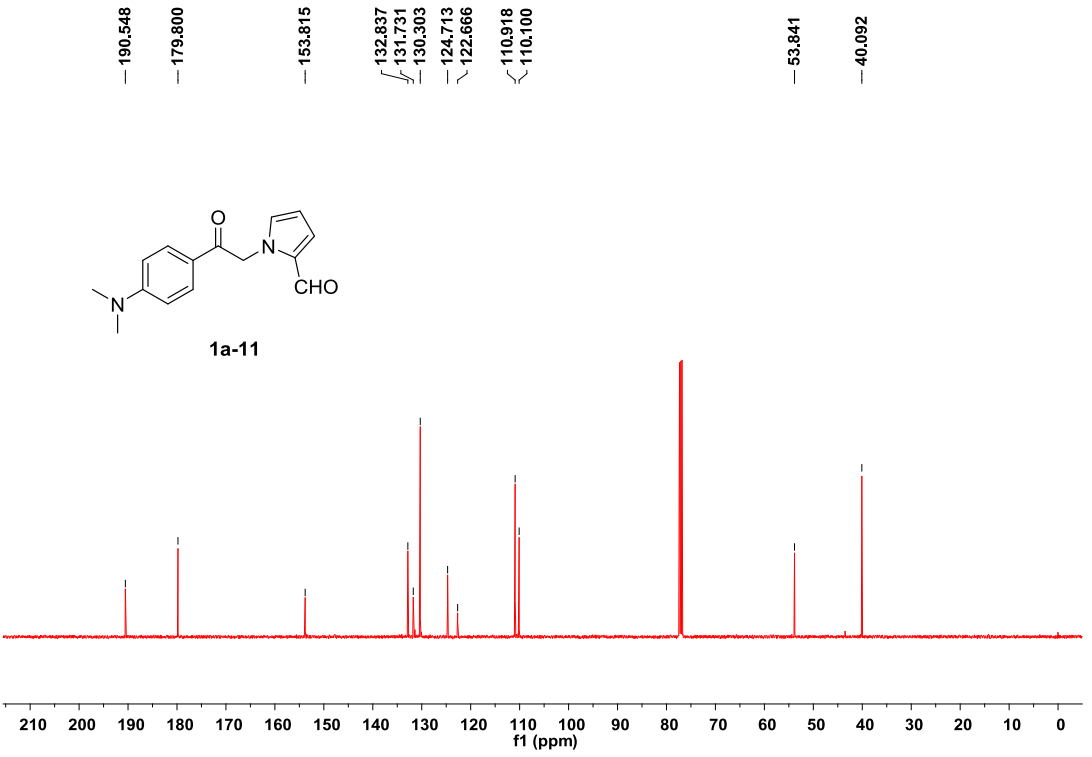
7.2 Cellular uptake

CT26 cells were seeded in 24-well plate at a density of 5×10^4 cells per well and allowed to attach overnight. Subsequently, the cells were treated with **2a** at a final concentration of 30 $\mu g \cdot mL^{-1}$ for 2, 6 and 10 hours. After washing trice with PBS and fixed, the cells were observed using confocal laser scanning microscope (Olympus BX61, Japan, FITC channel).

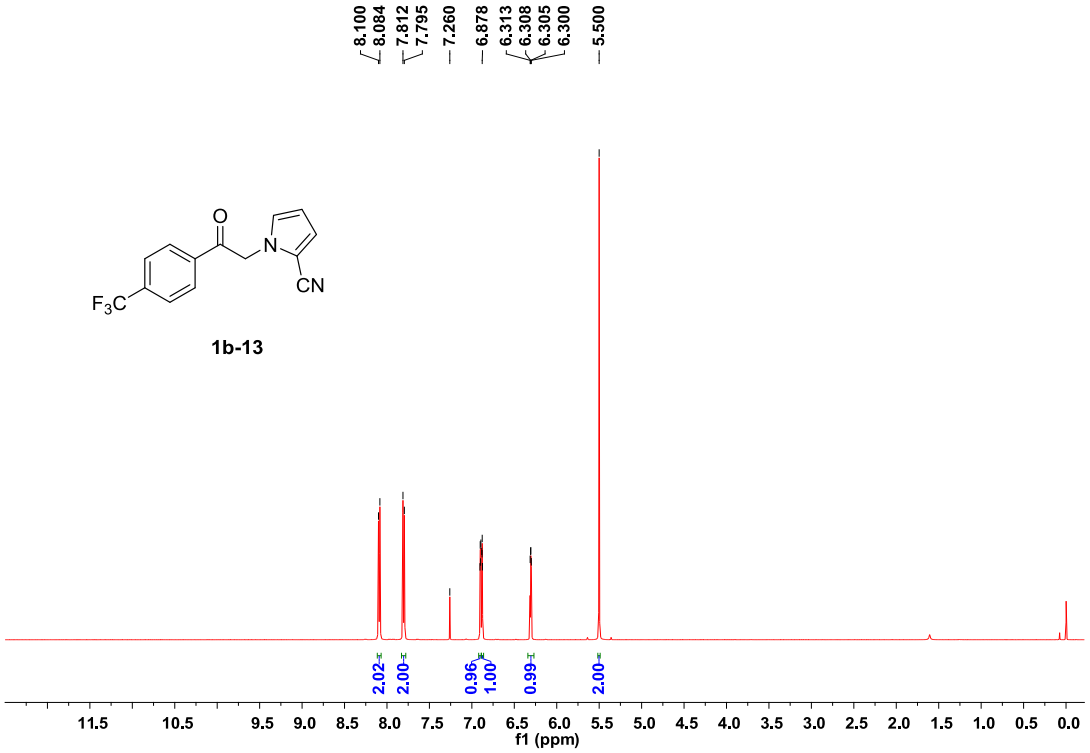
8. NMR spectroscopic data

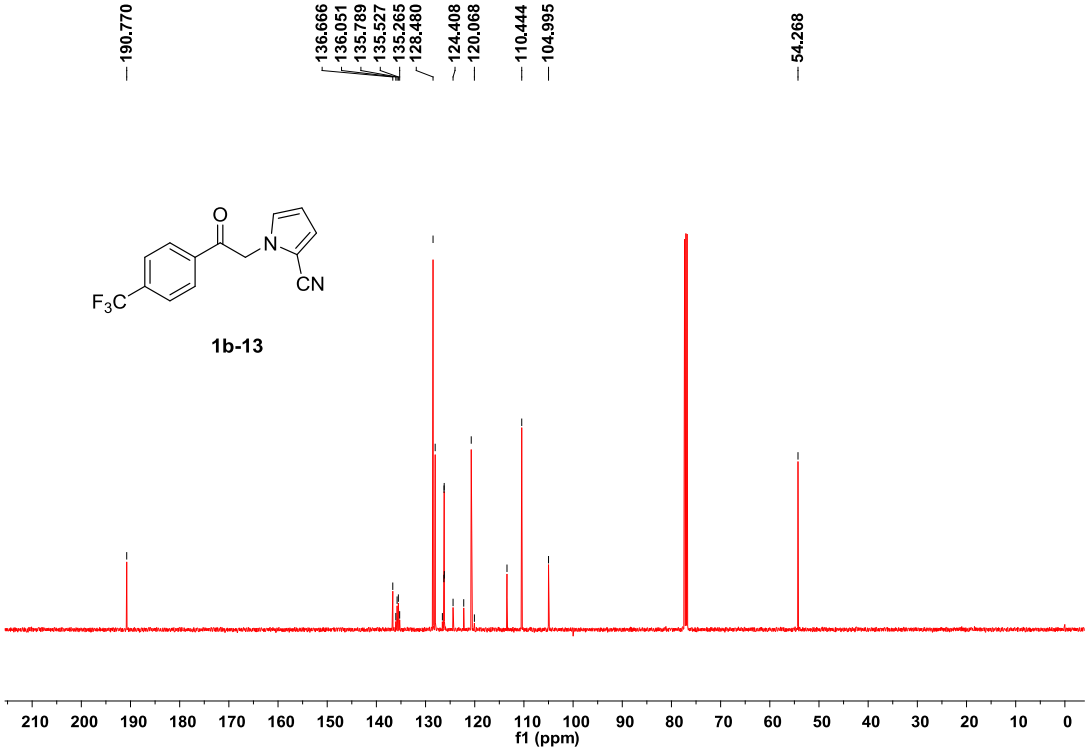
1-(2-(4-(Dimethylamino)phenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde (1a-11)



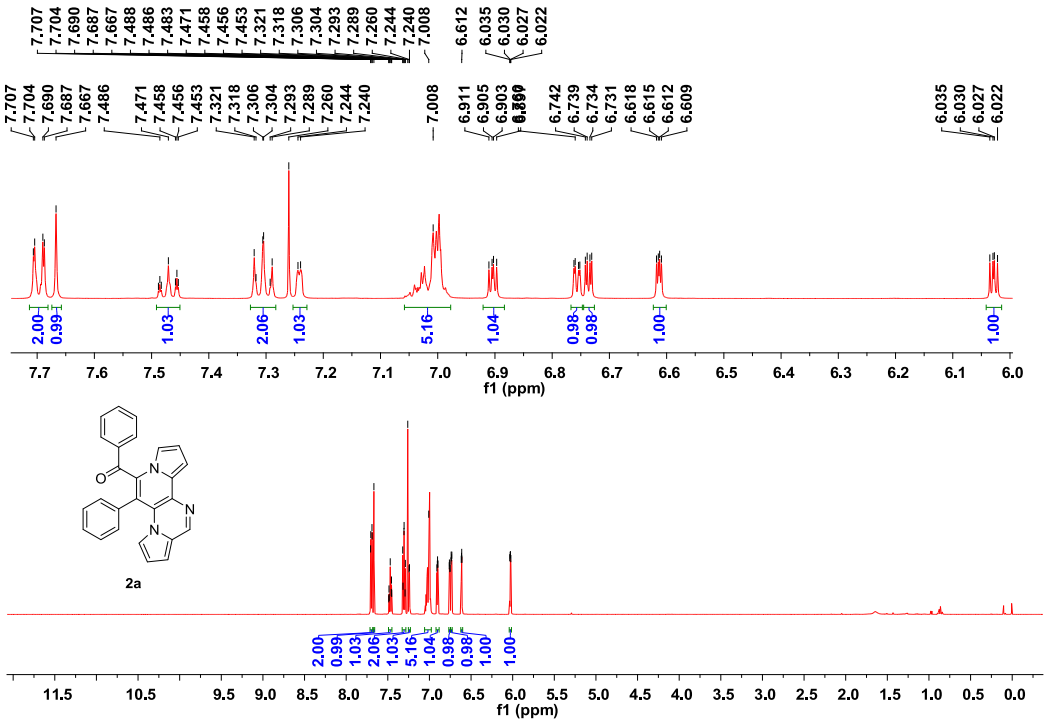


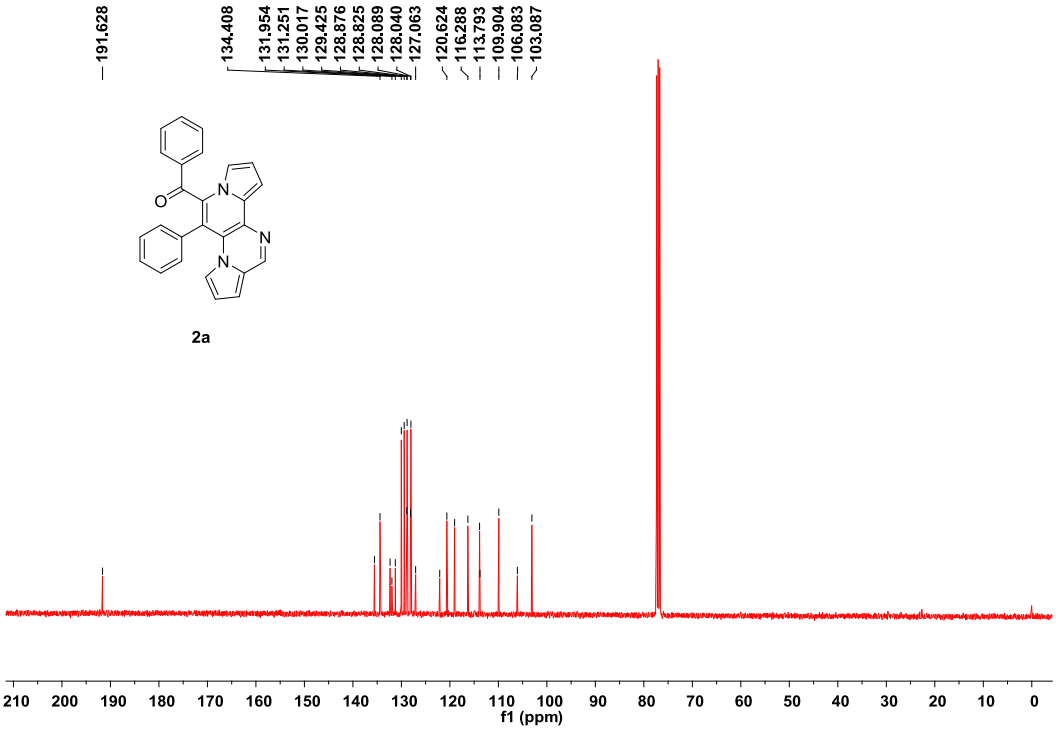
1-(2-oxo-2-(4-(Trifluoromethyl)phenyl)ethyl)-1*H*-pyrrole-2-carbonitrile (1b-13)



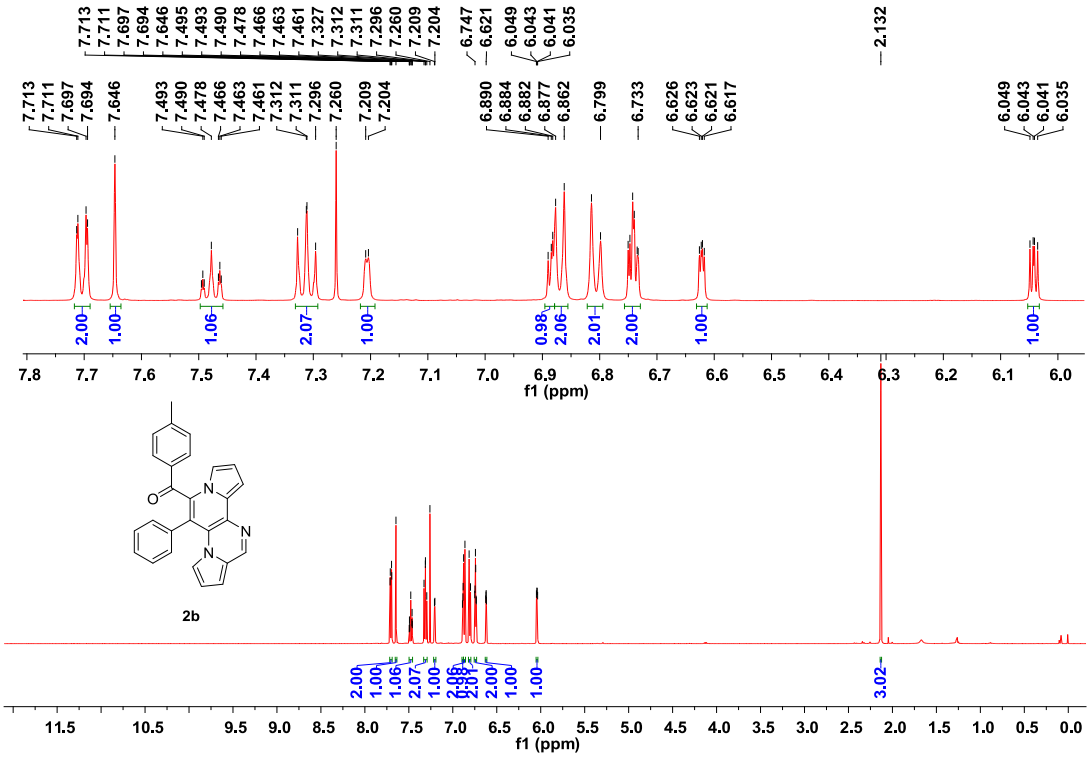


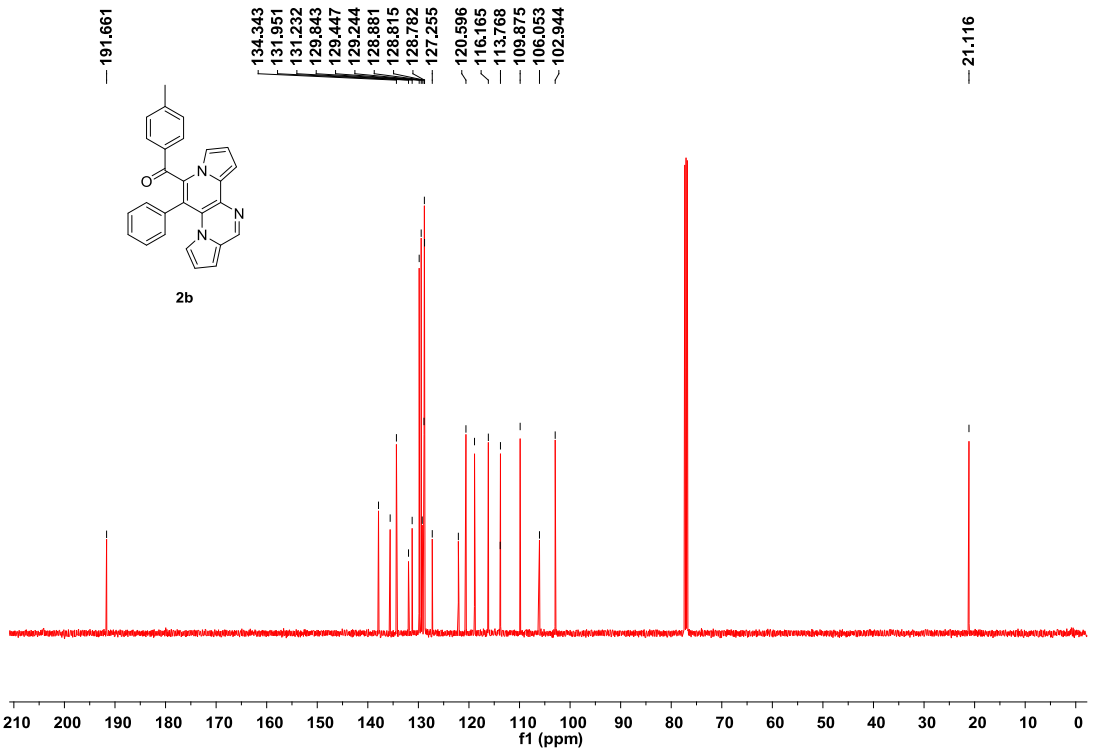
Phenyl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2a)



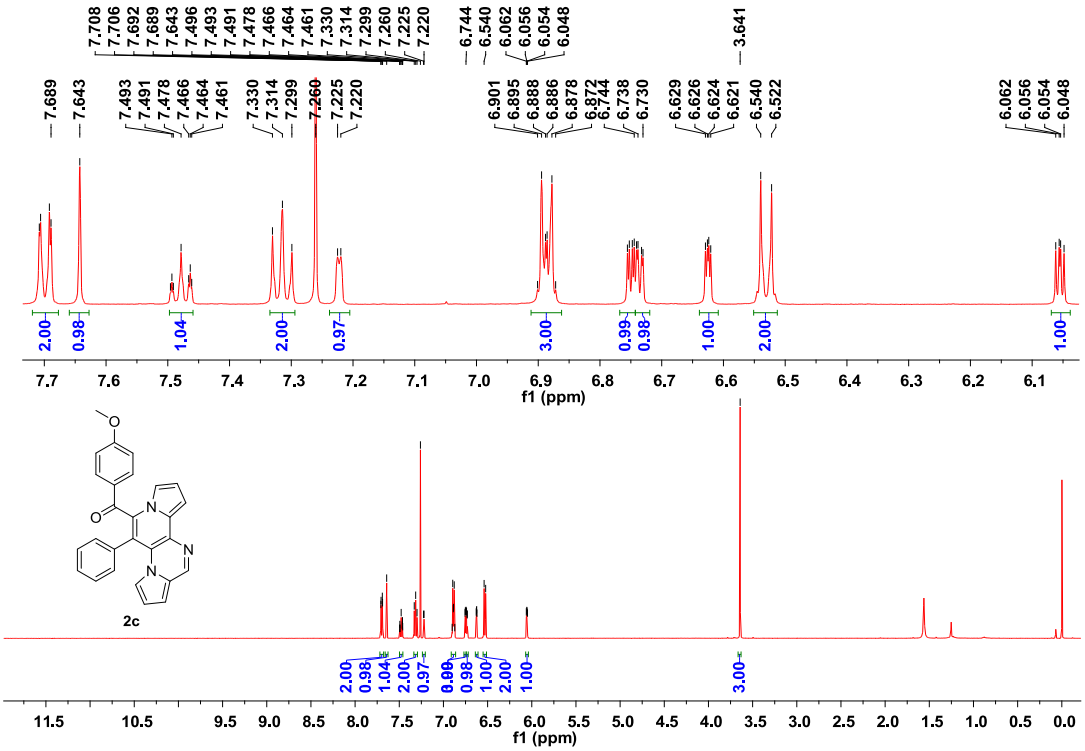


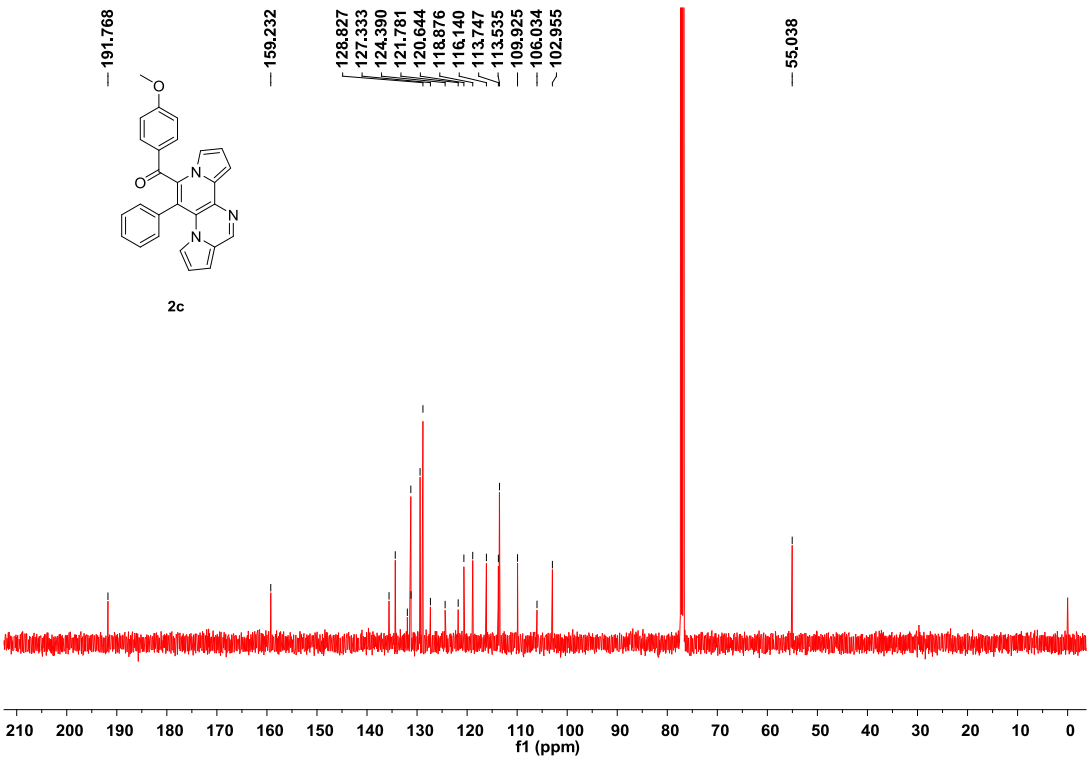
(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(m-tolyl)methanone (2b)



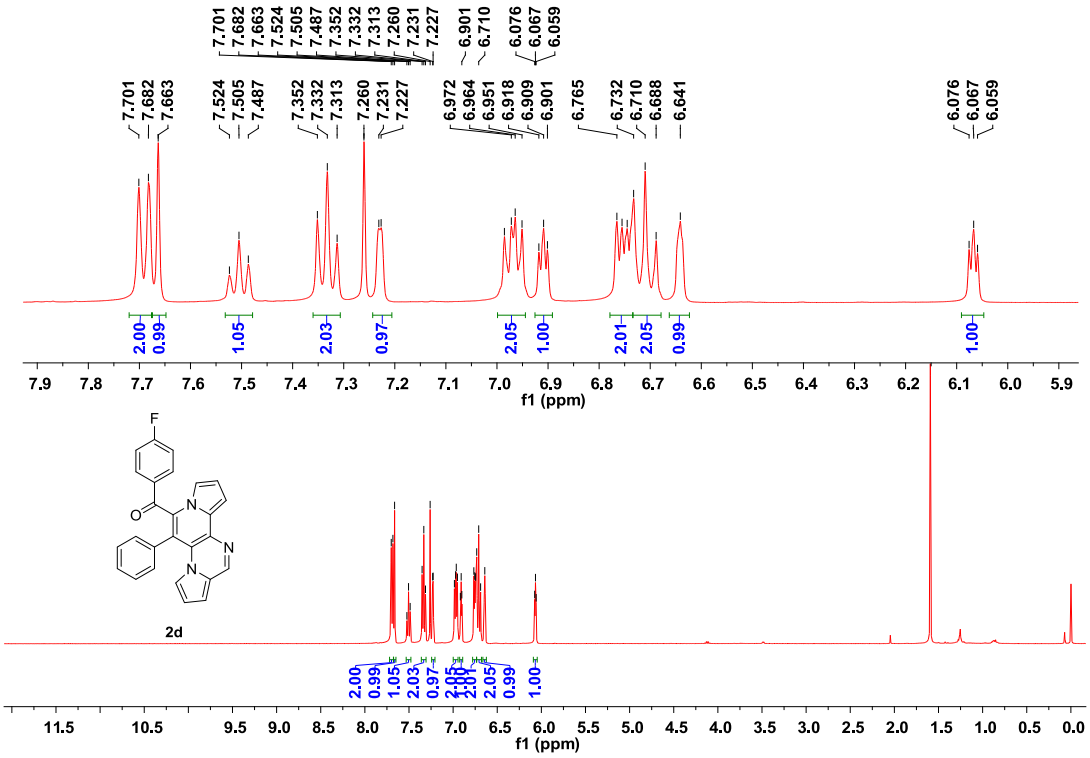


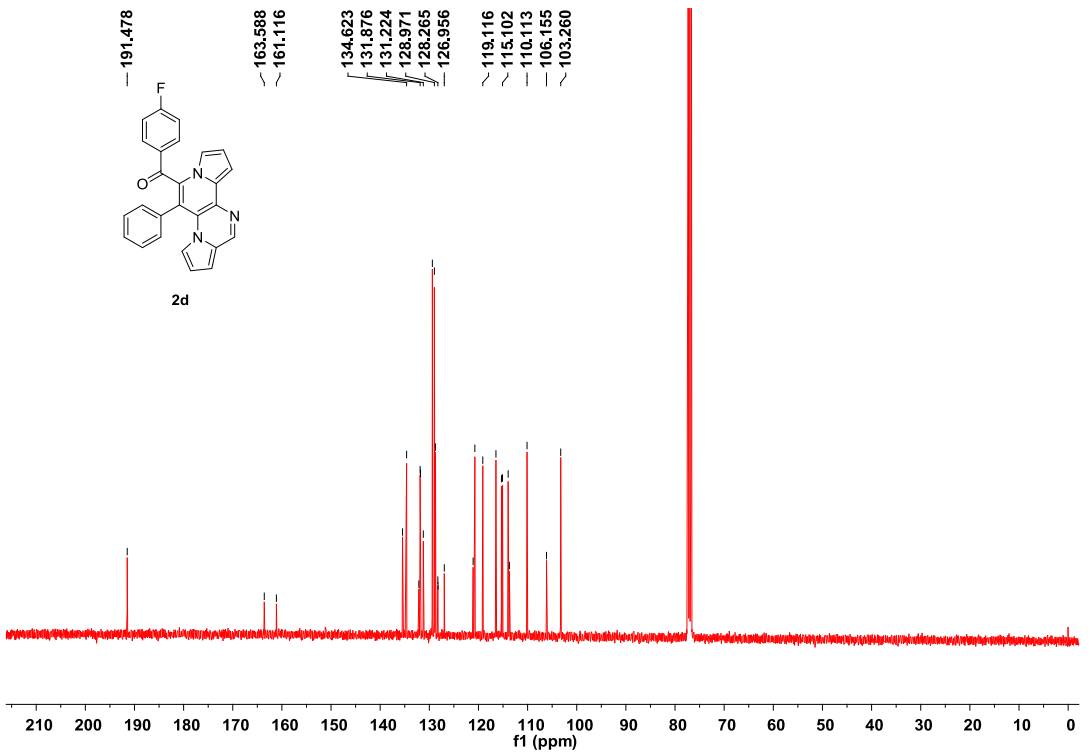
(4-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2c)



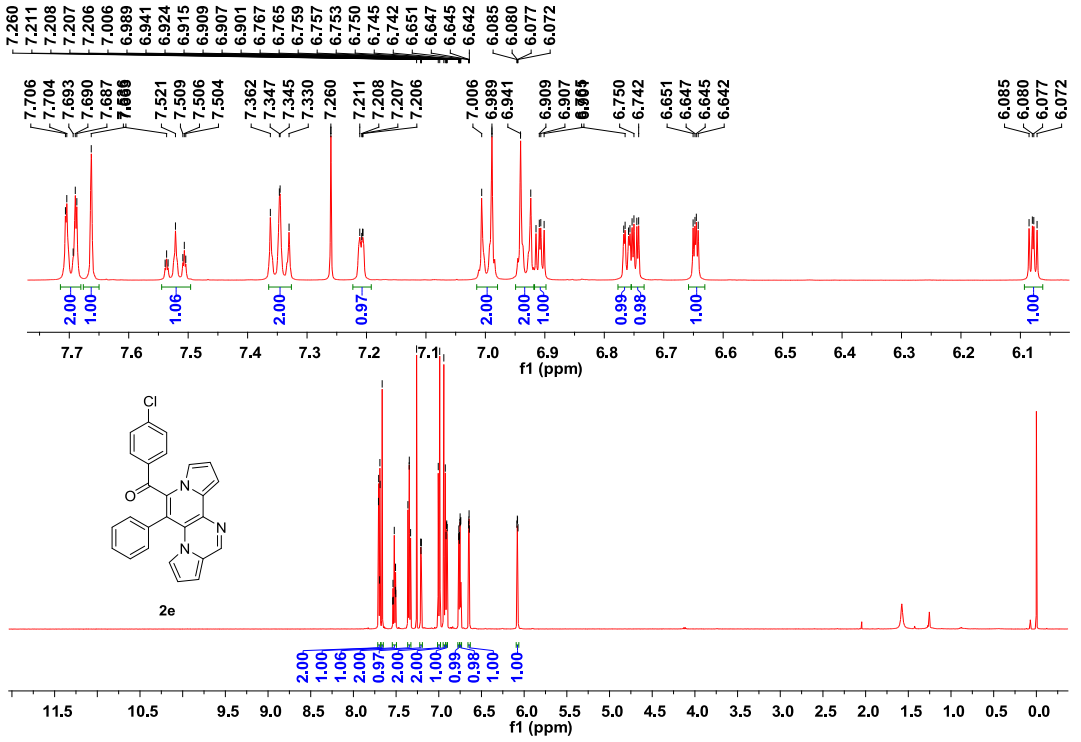


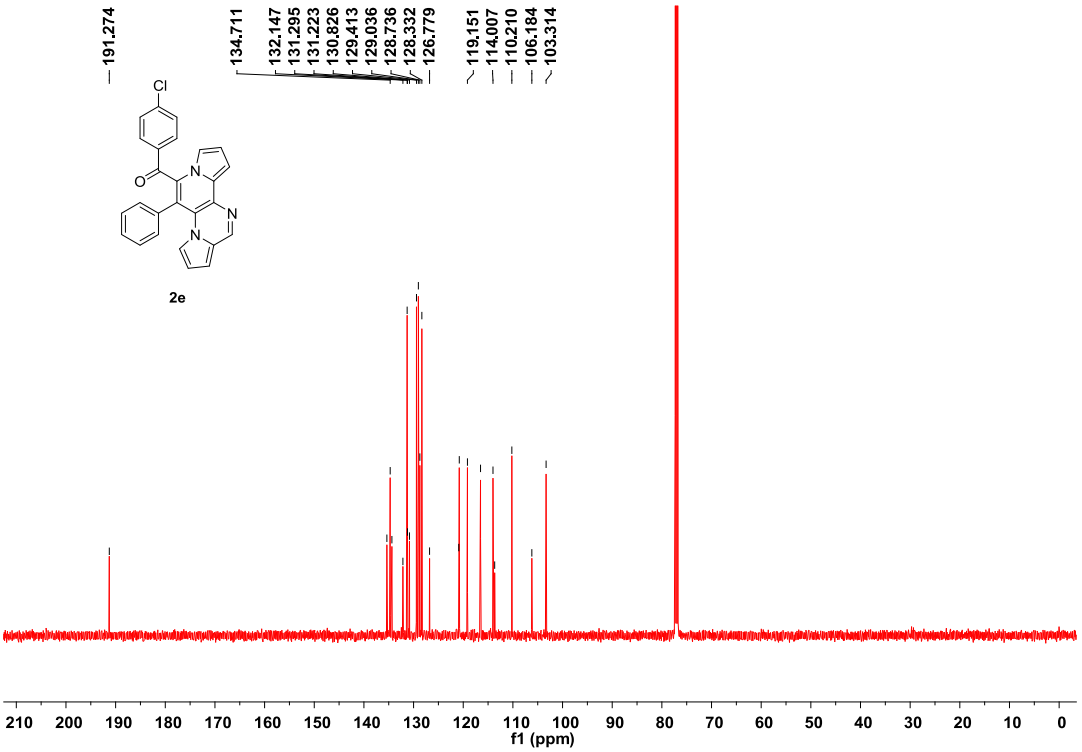
(4-Fluorophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2d)



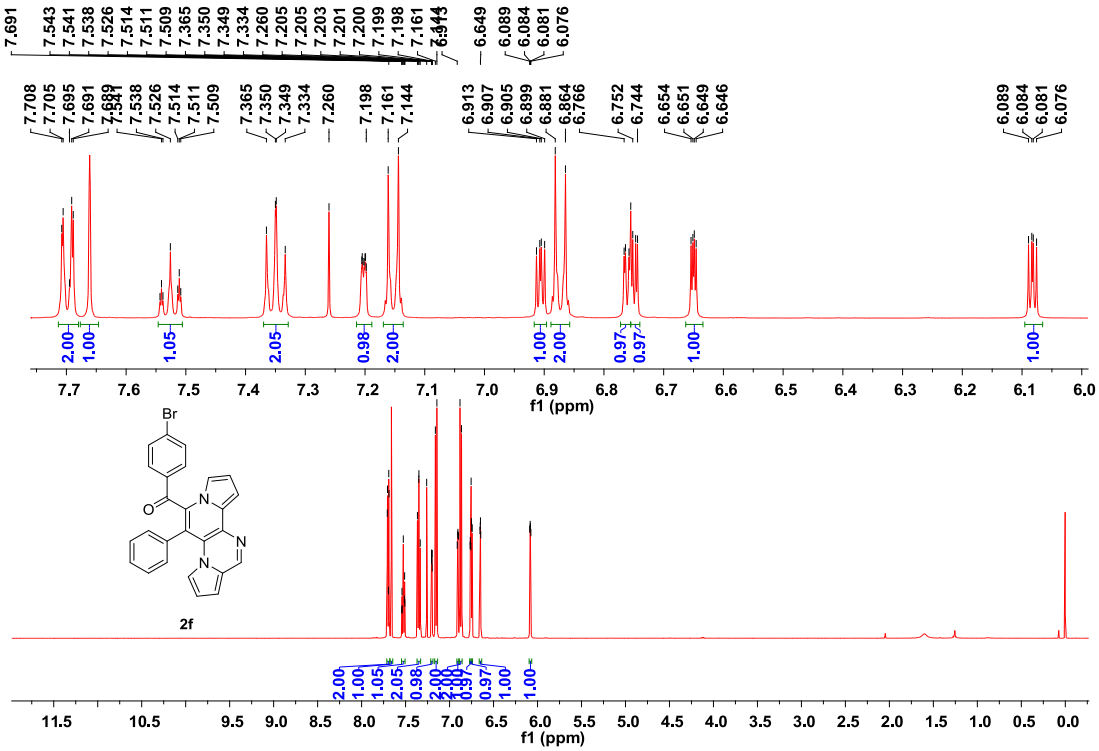


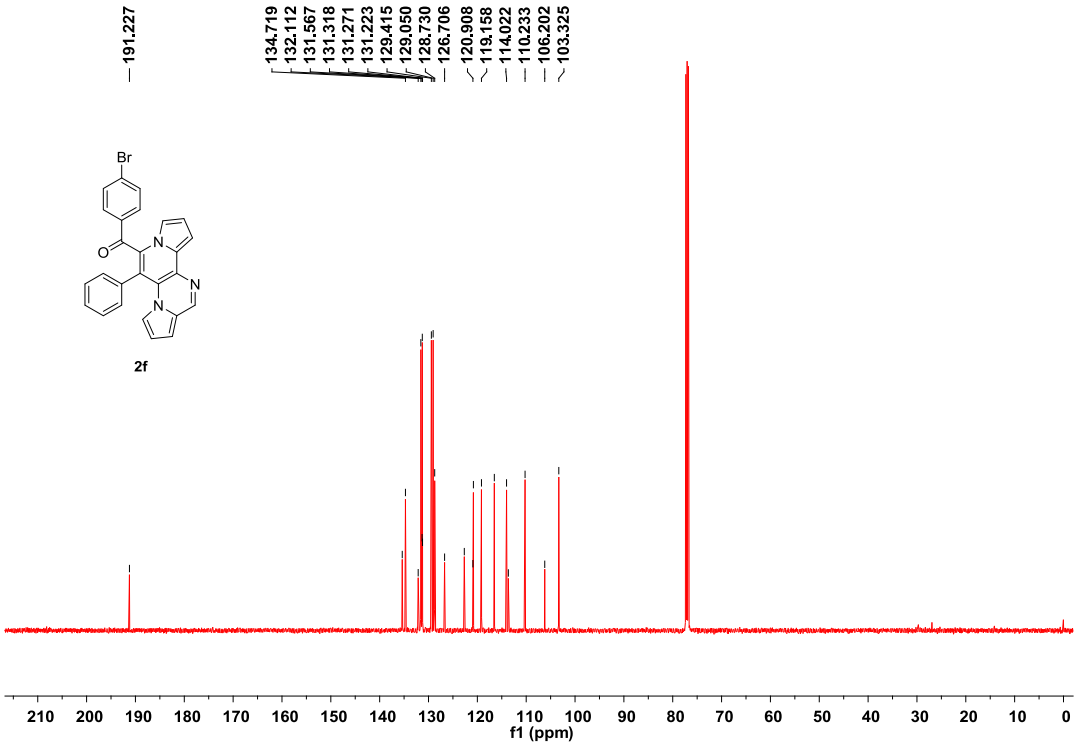
(4-Chlorophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2e)



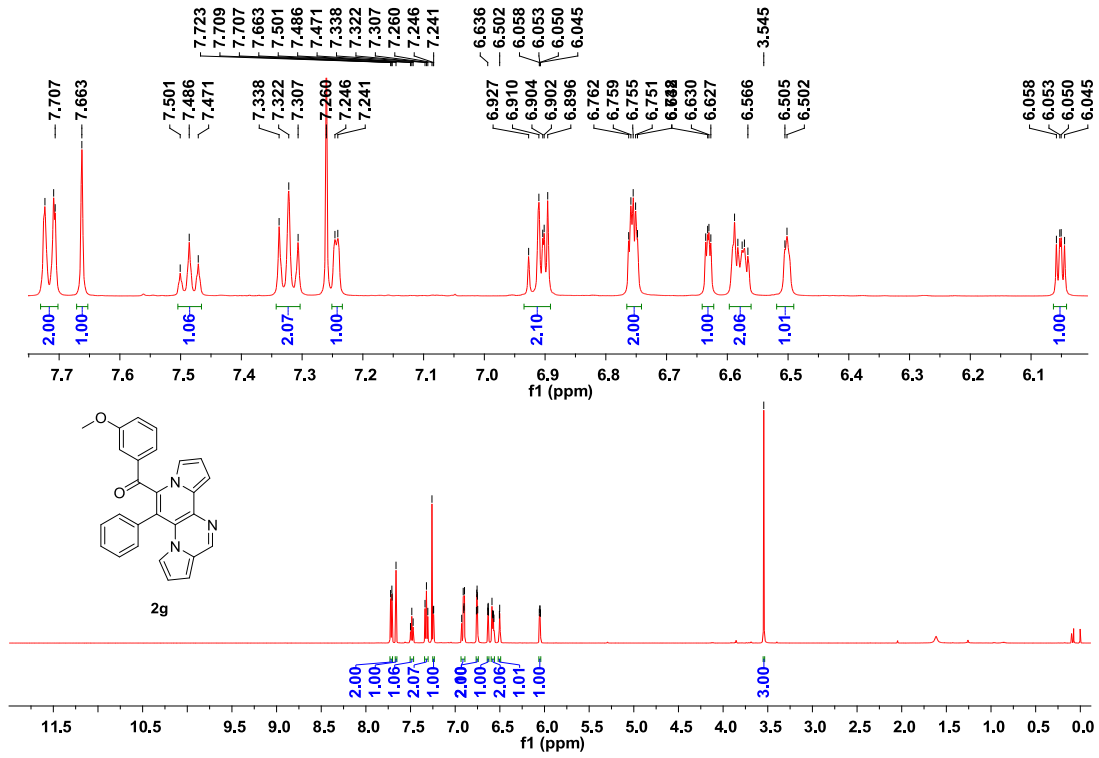


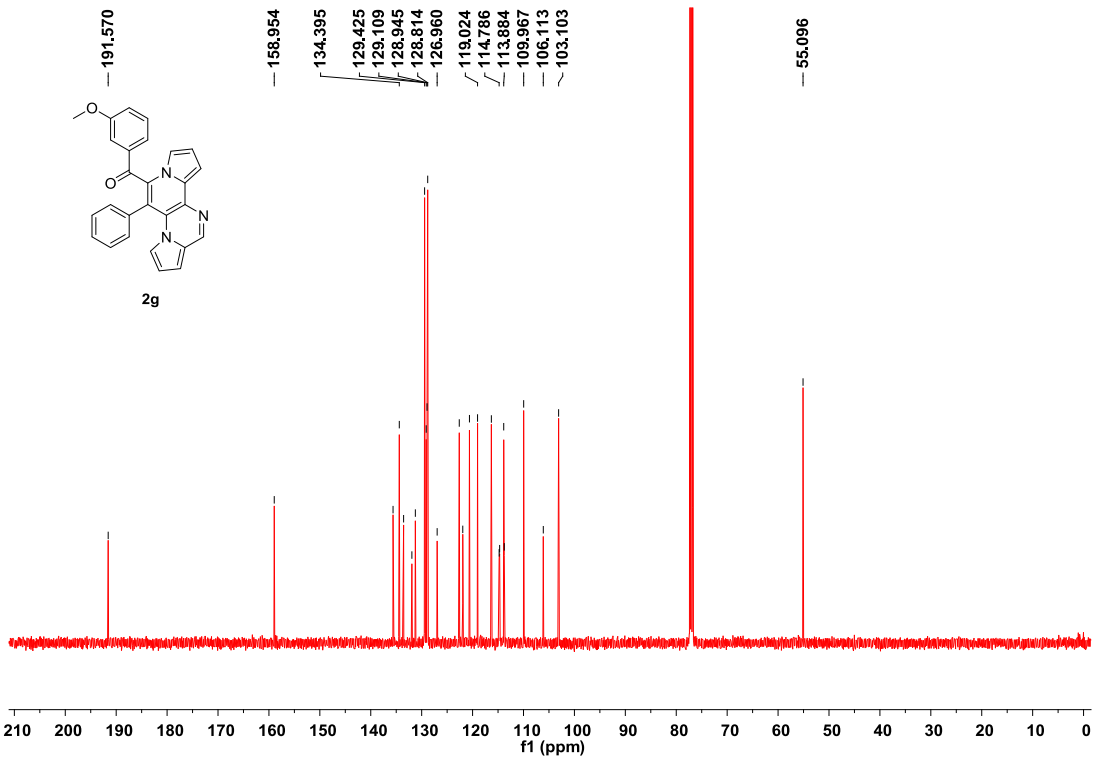
(4-Bromophenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2f)



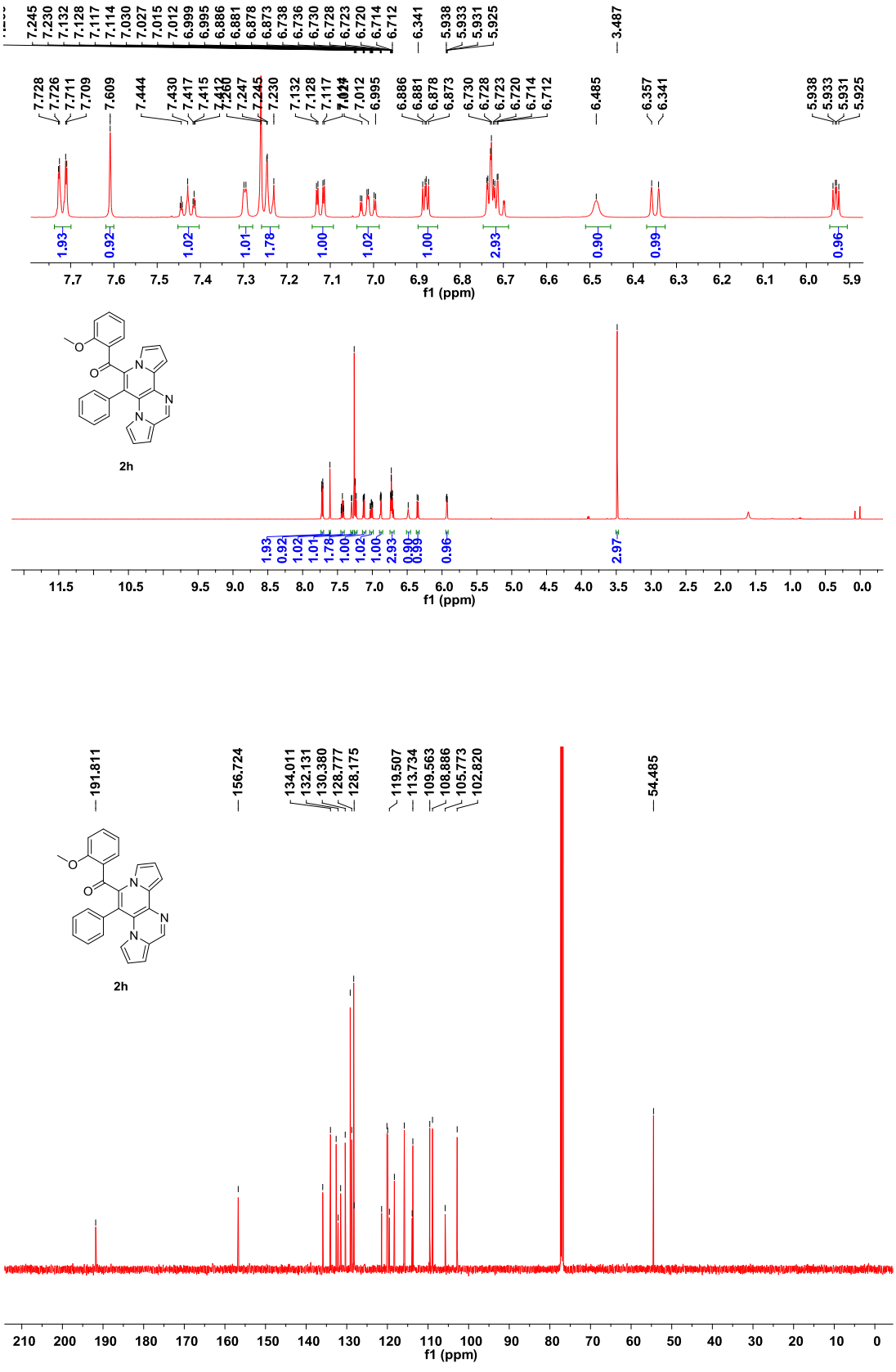


(3-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2g)

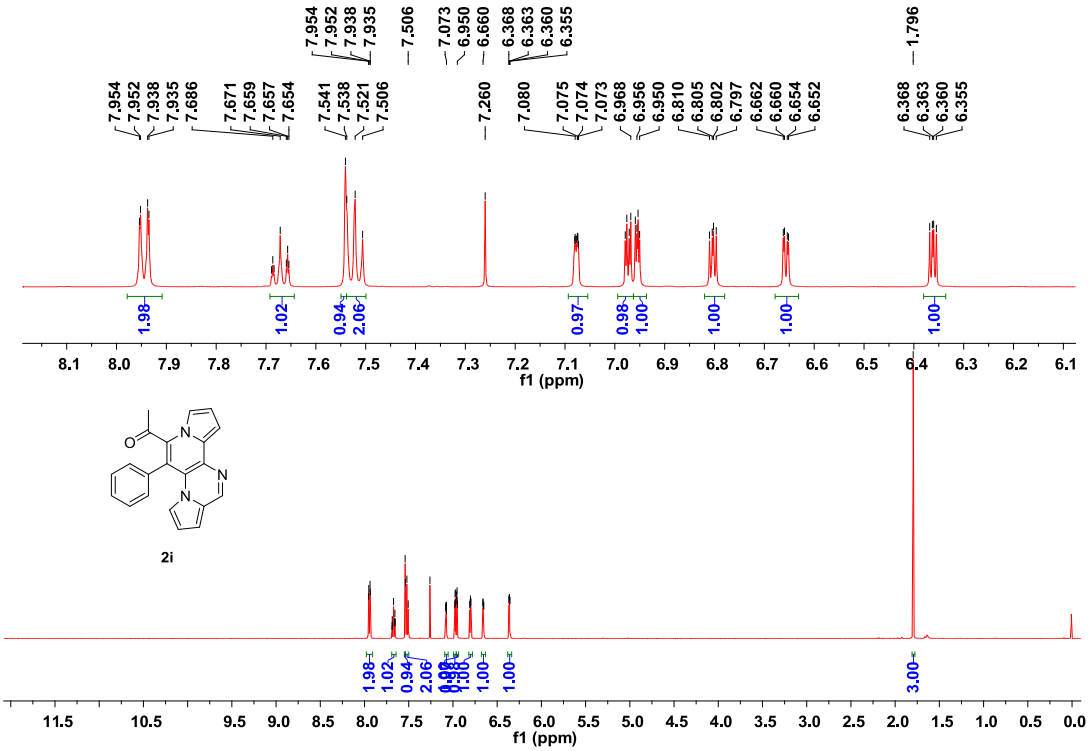


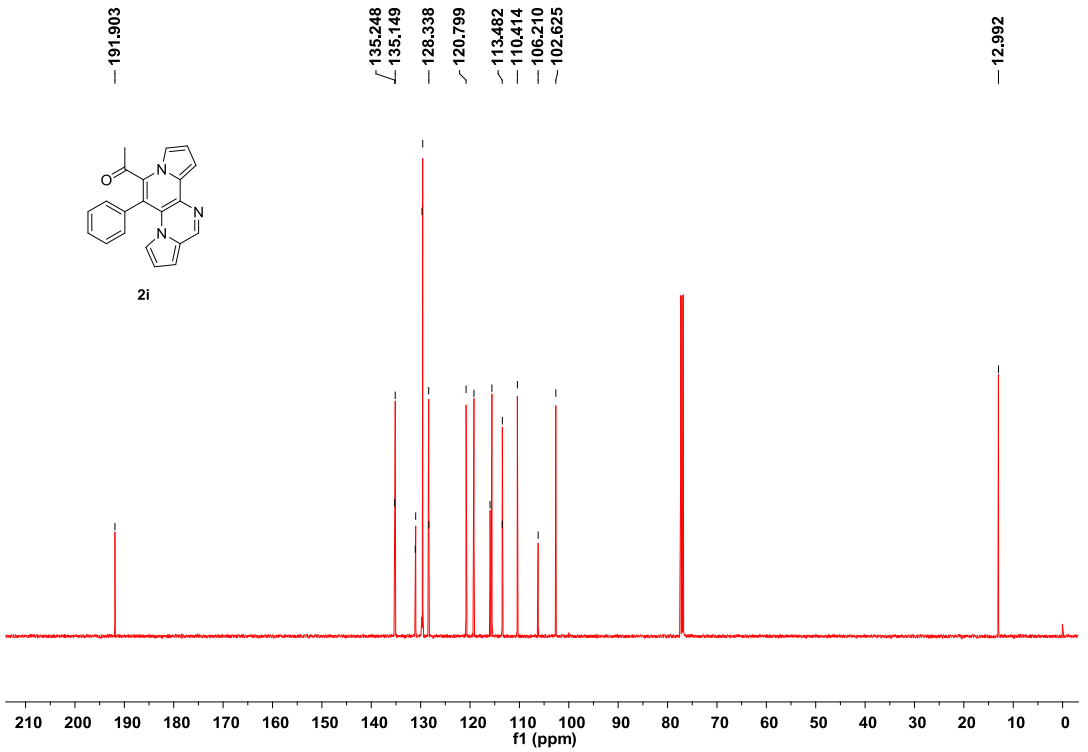


(2-Methoxyphenyl)(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2h)

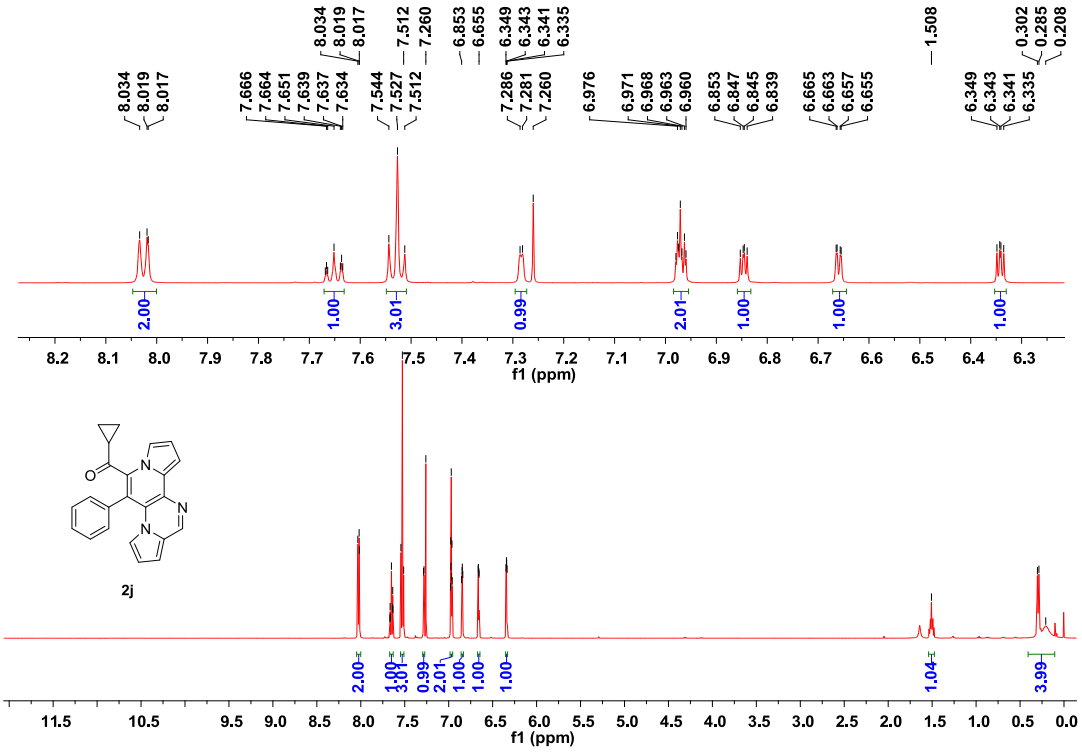


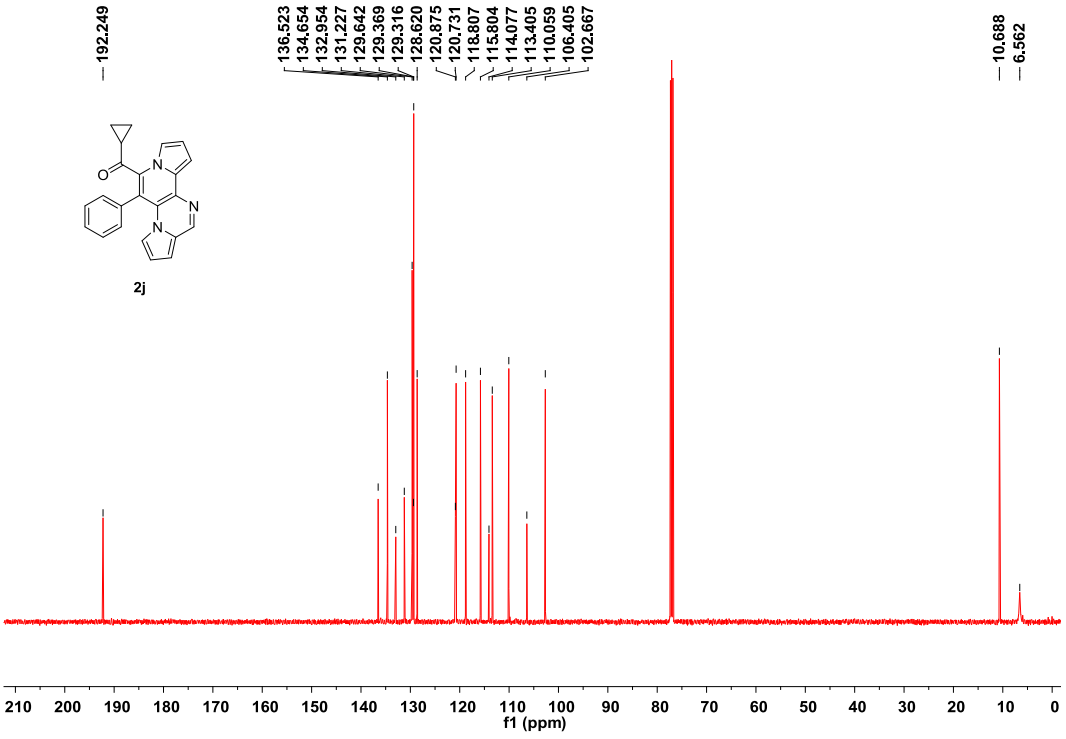
1-(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)ethanone (2i)



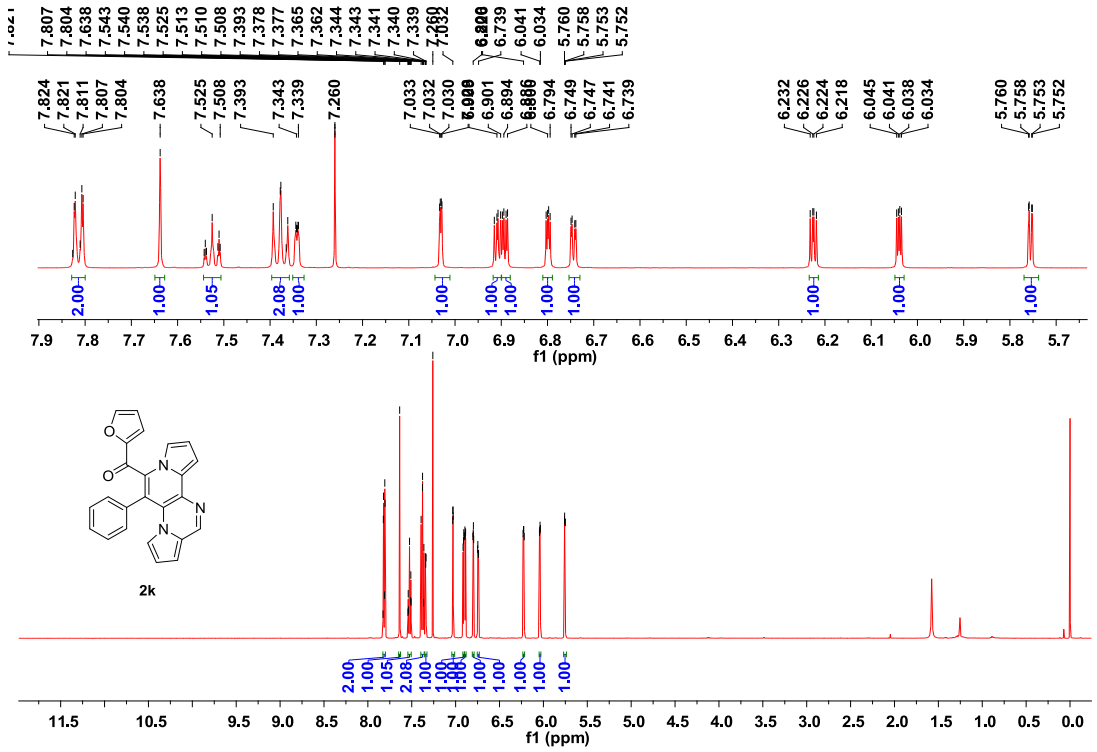


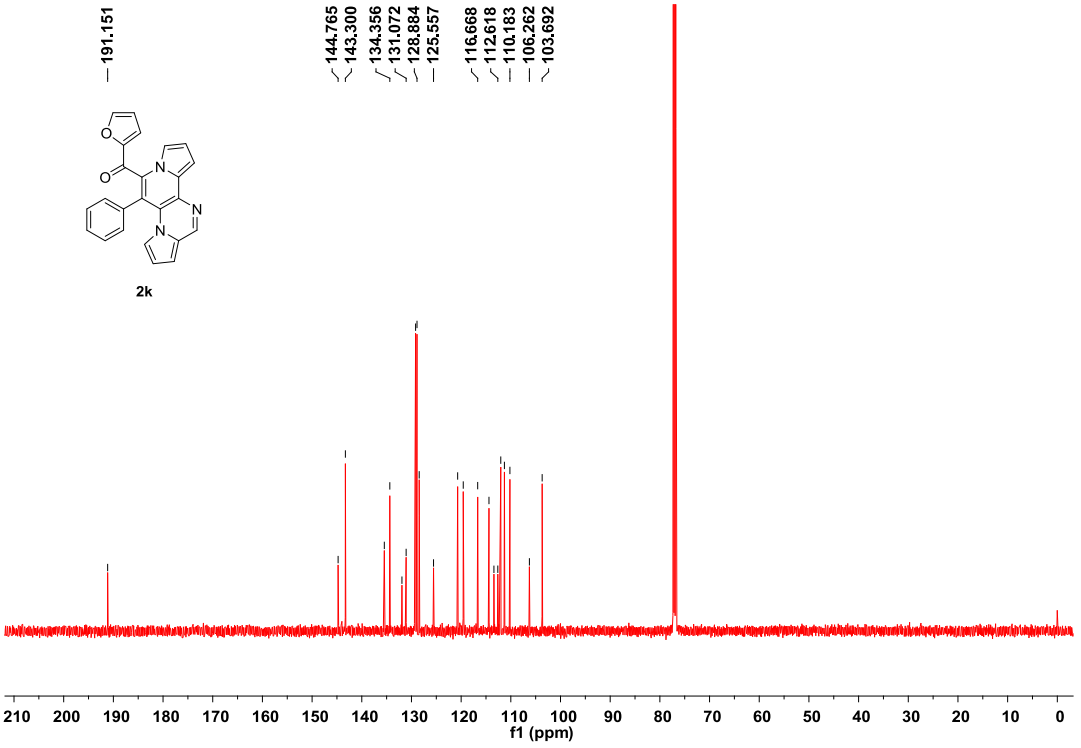
Cyclopropyl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2j)



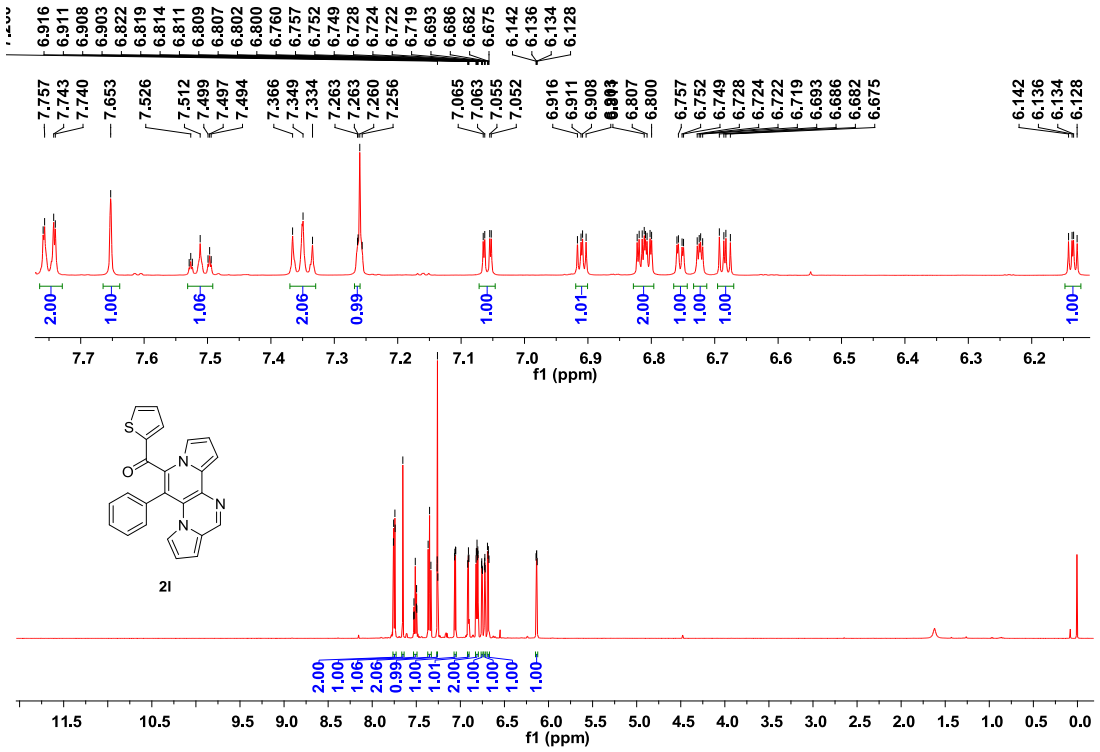


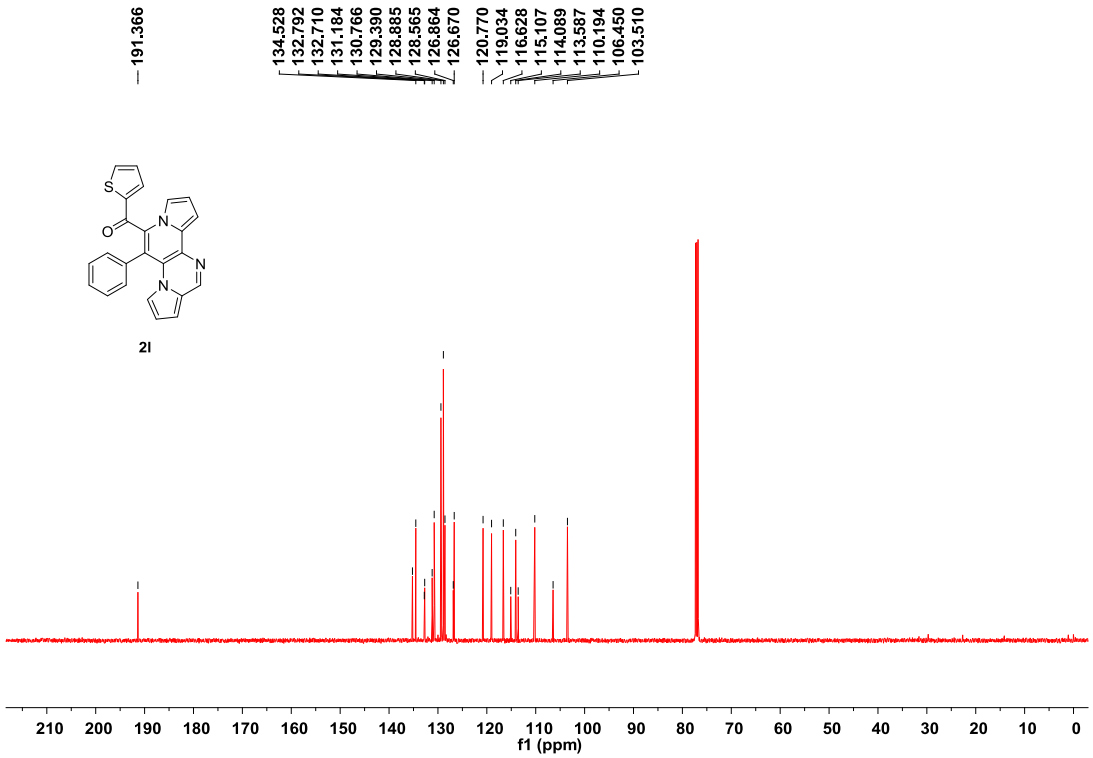
Furan-2-yl(5-phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2k)



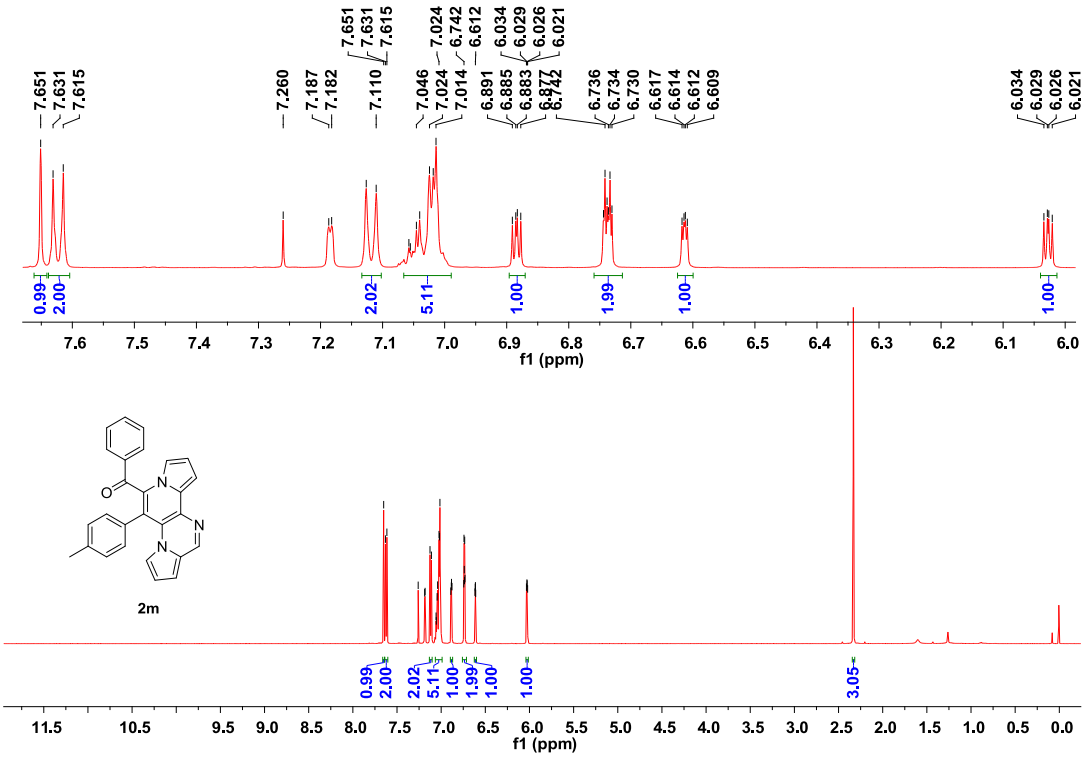


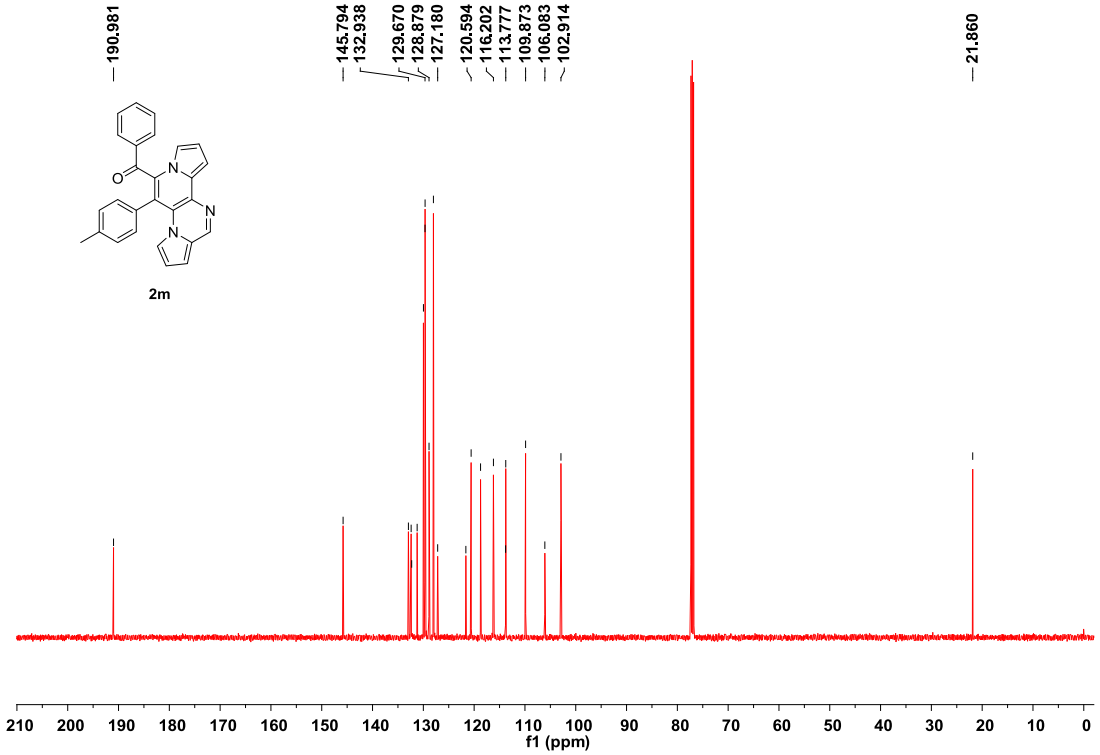
(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(thiophen-2-yl)methanone (2l)



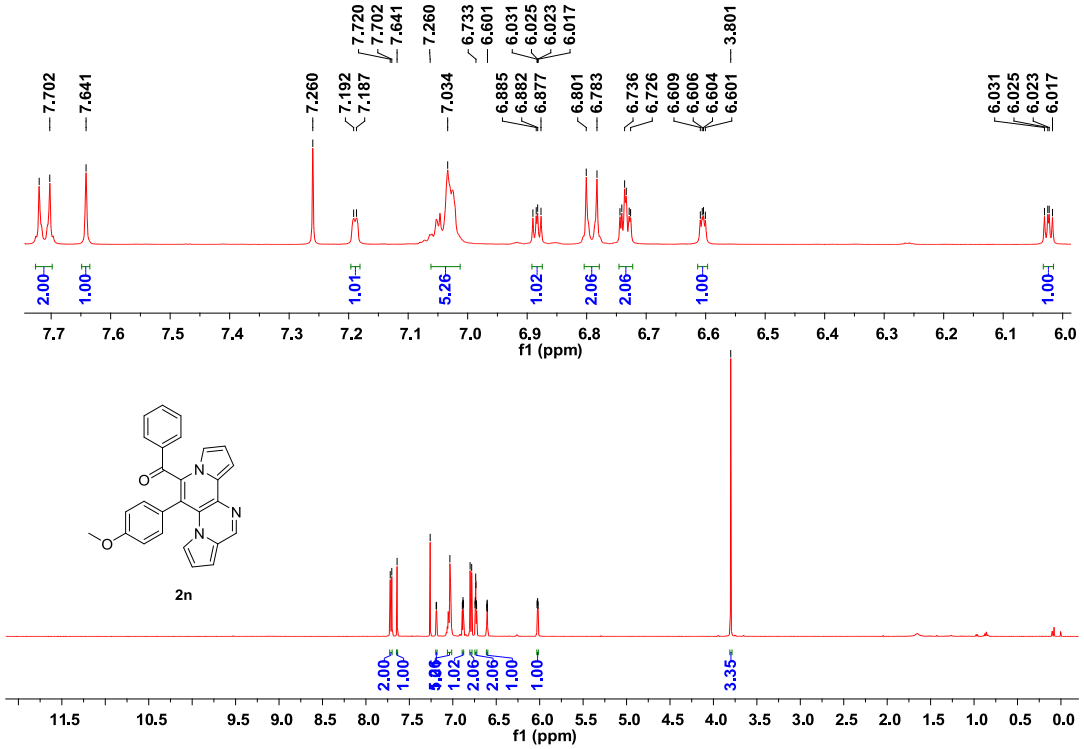


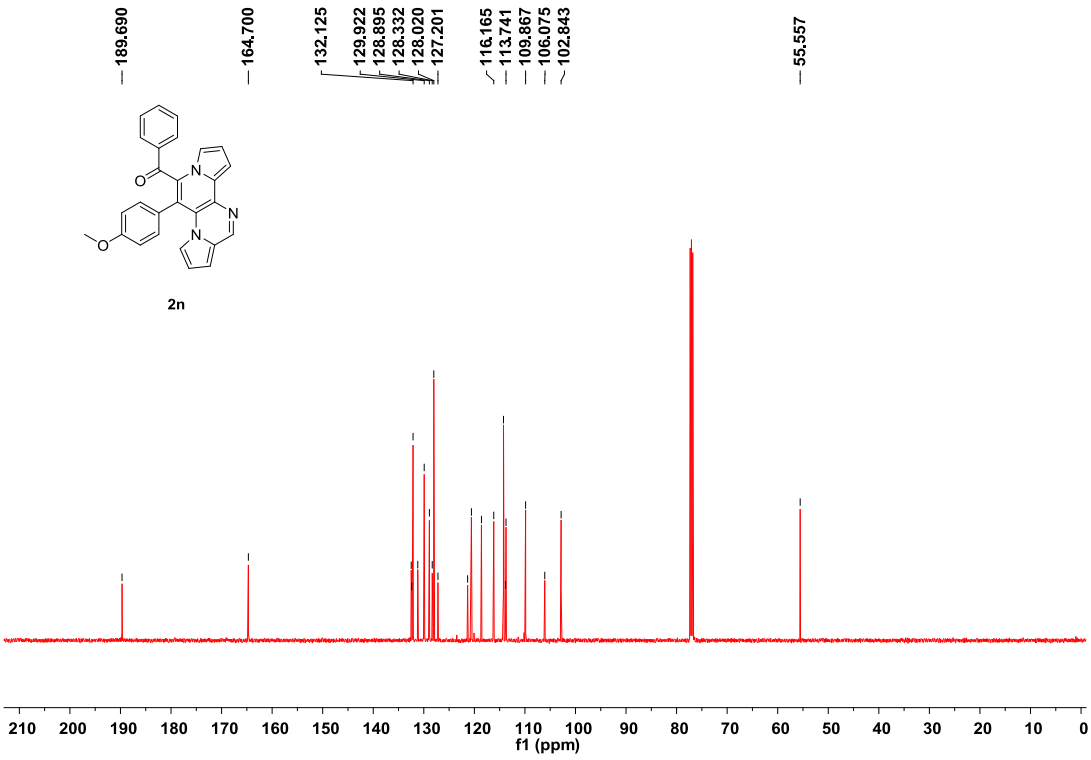
Phenyl(5-(p-tolyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)methanone (2m)



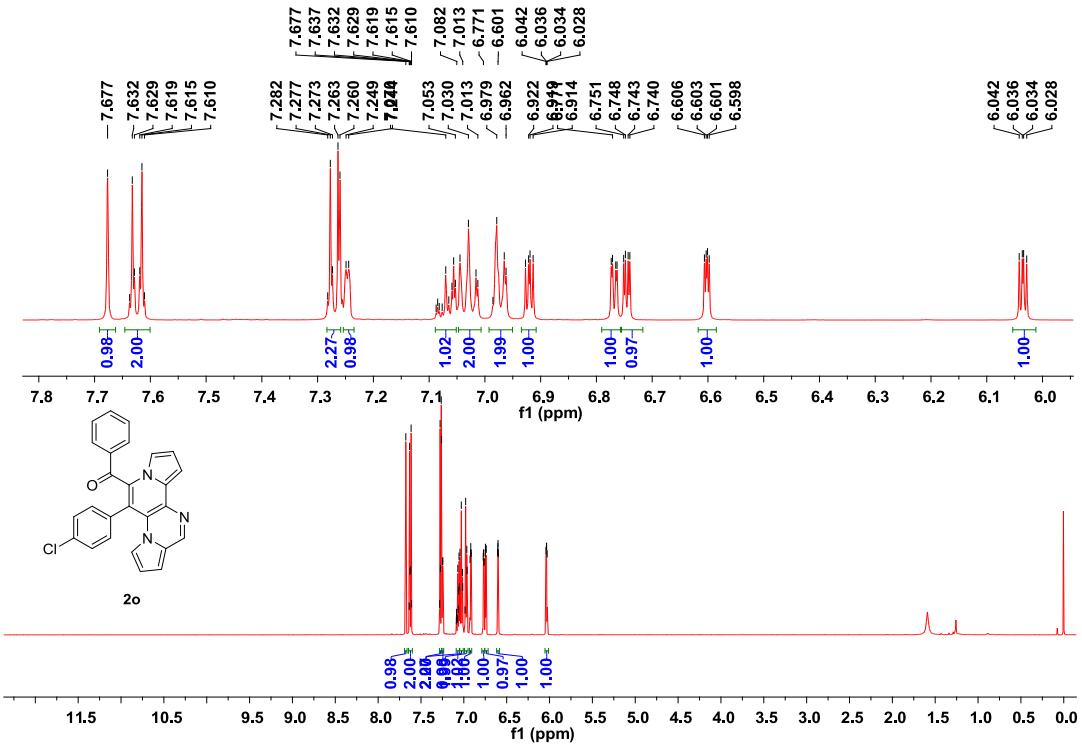


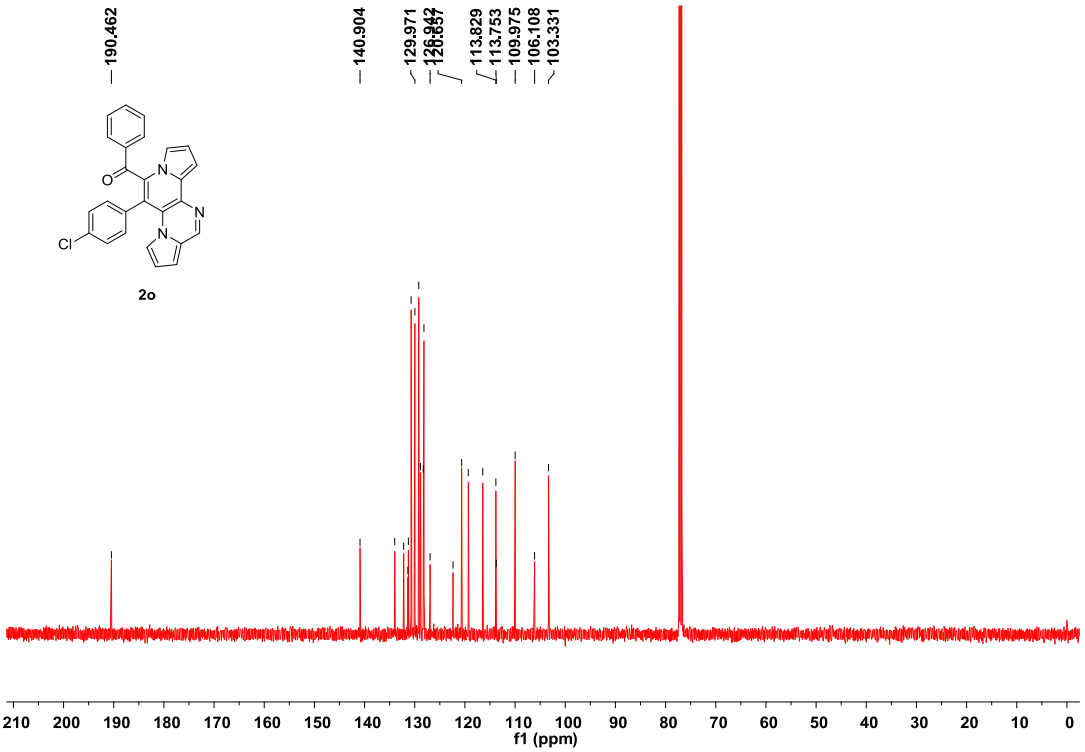
(5-(4-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2n)



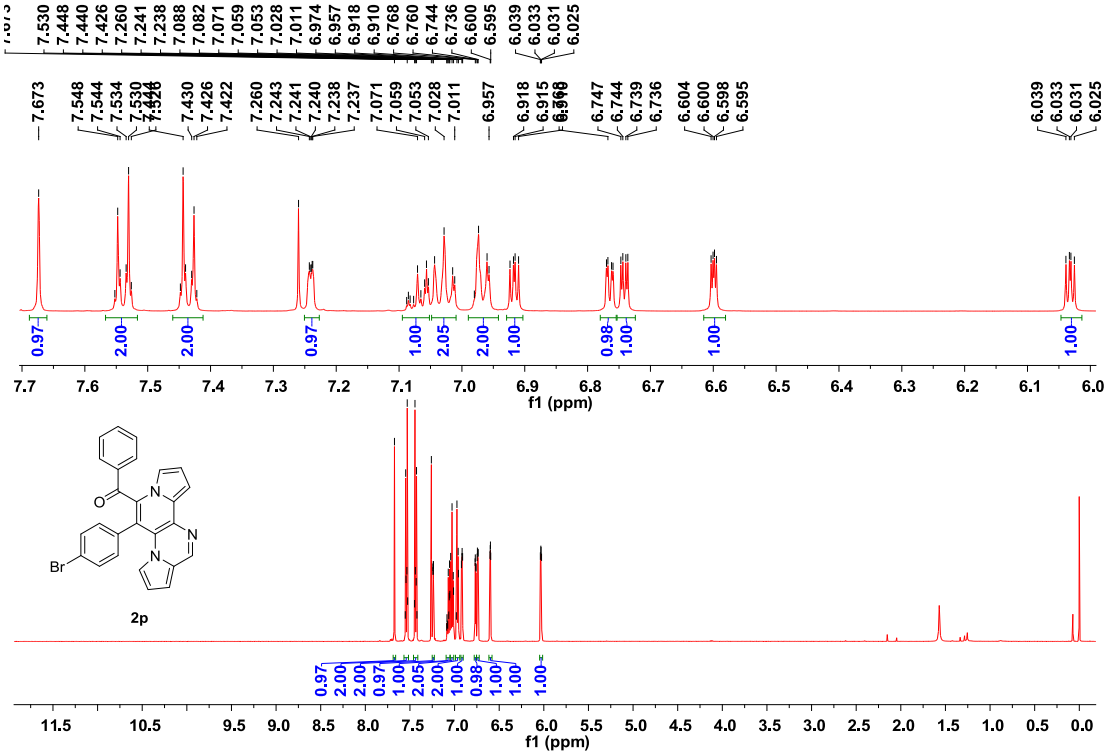


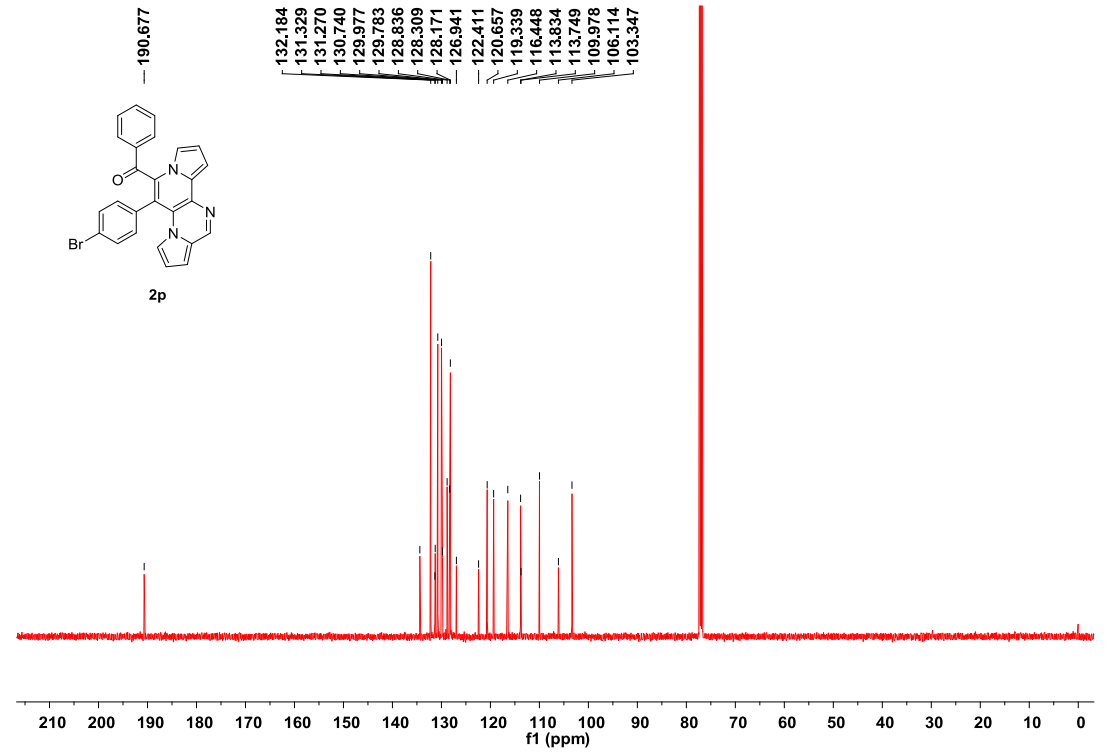
(5-(4-Chlorophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2o)



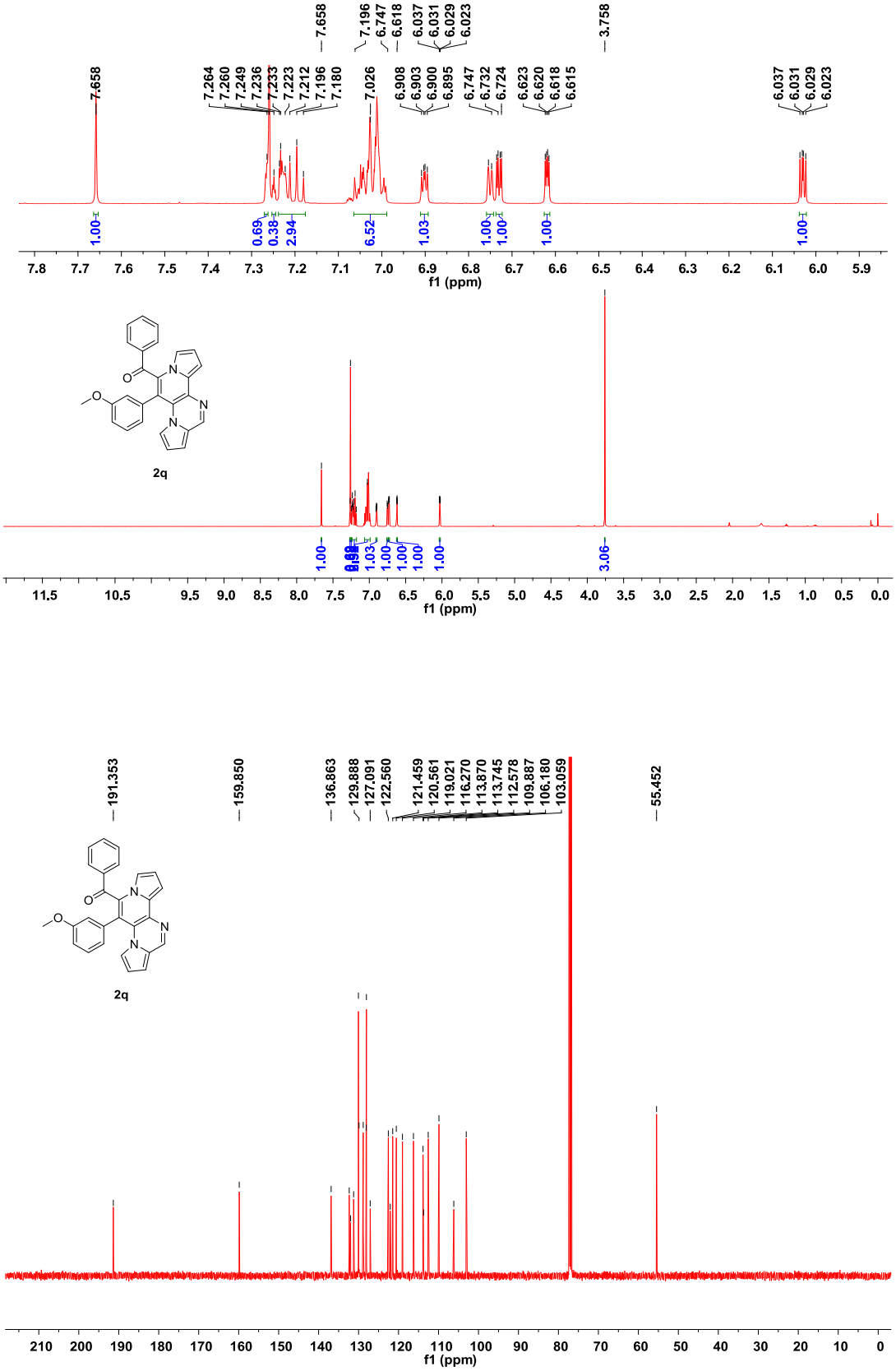


(5-(4-Bromophenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2p)

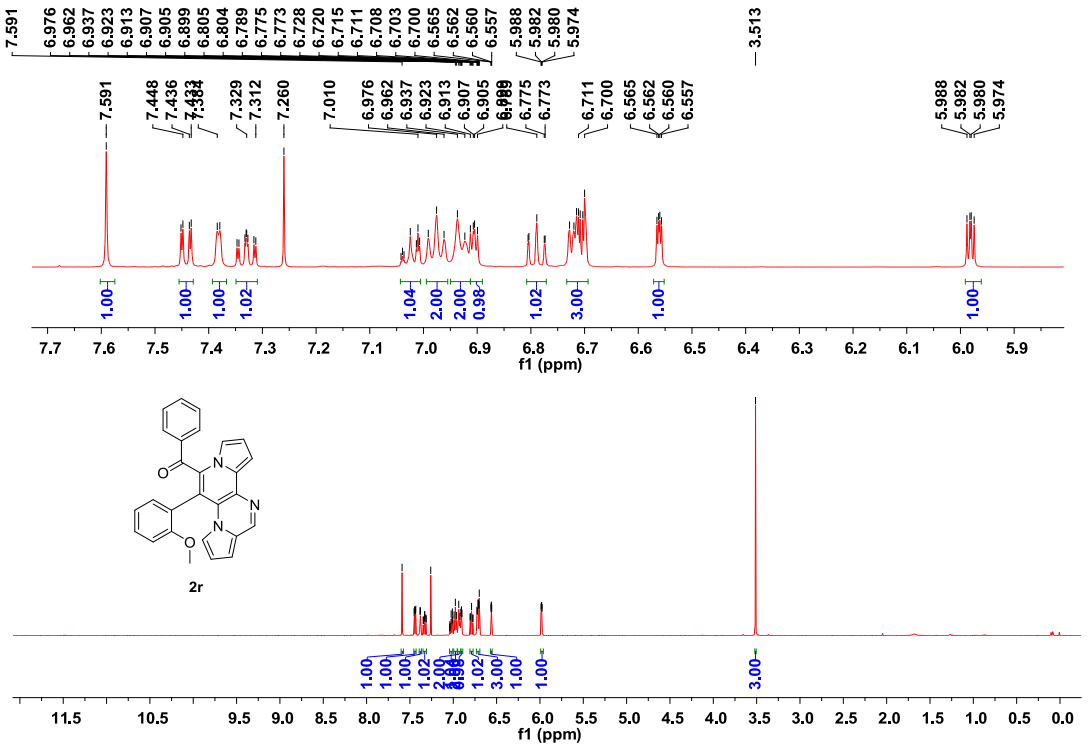


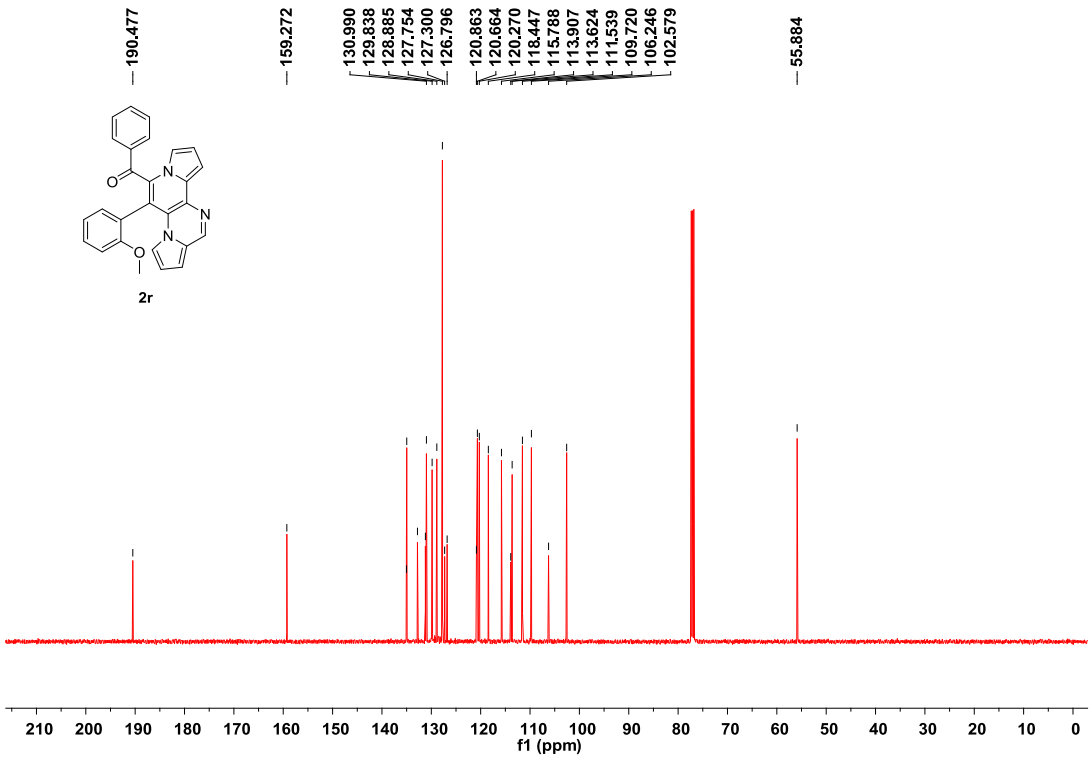


5-(3-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2q)

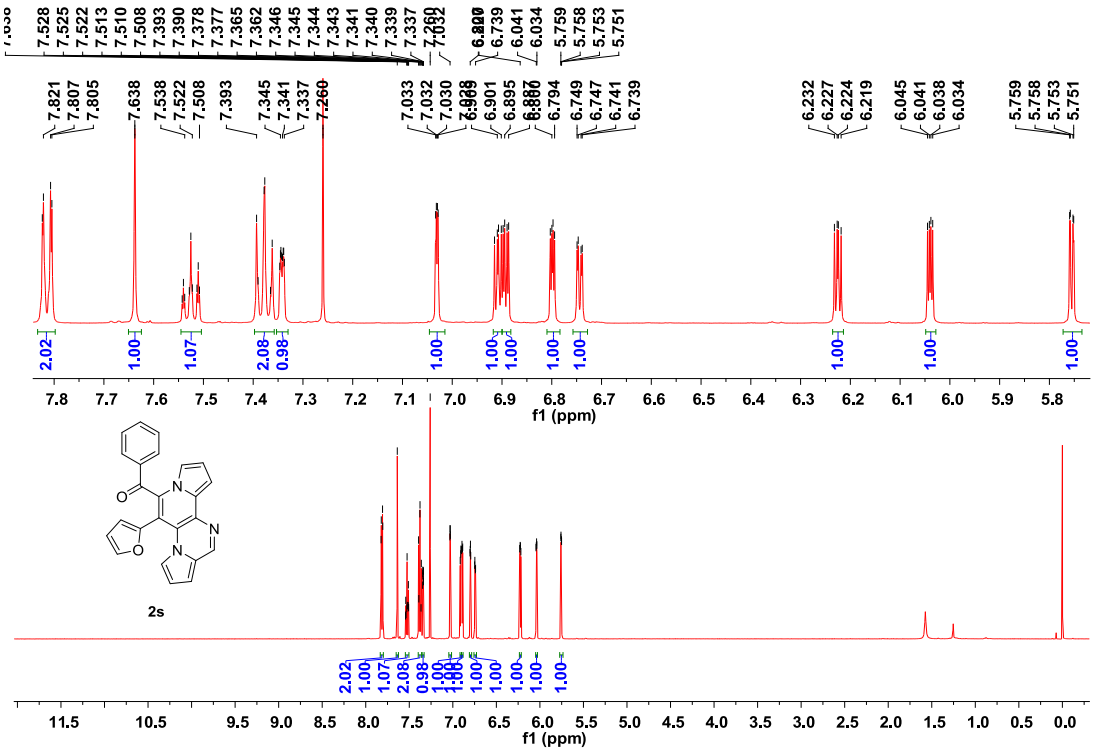


(5-(2-Methoxyphenyl)pyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(phenyl)methanone (2r)





(5-(Furan-2-yl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(phenyl)methanone (2s)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1.07
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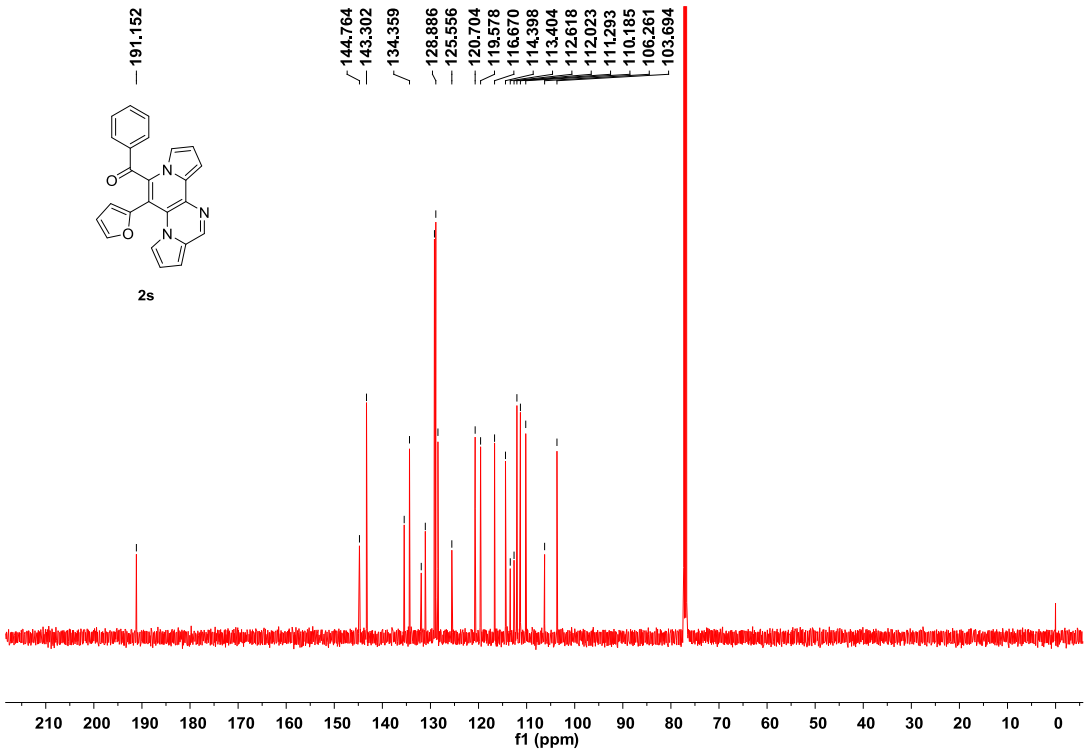
1.00
1.00
f1 (ppm)
2s
f1 (ppm)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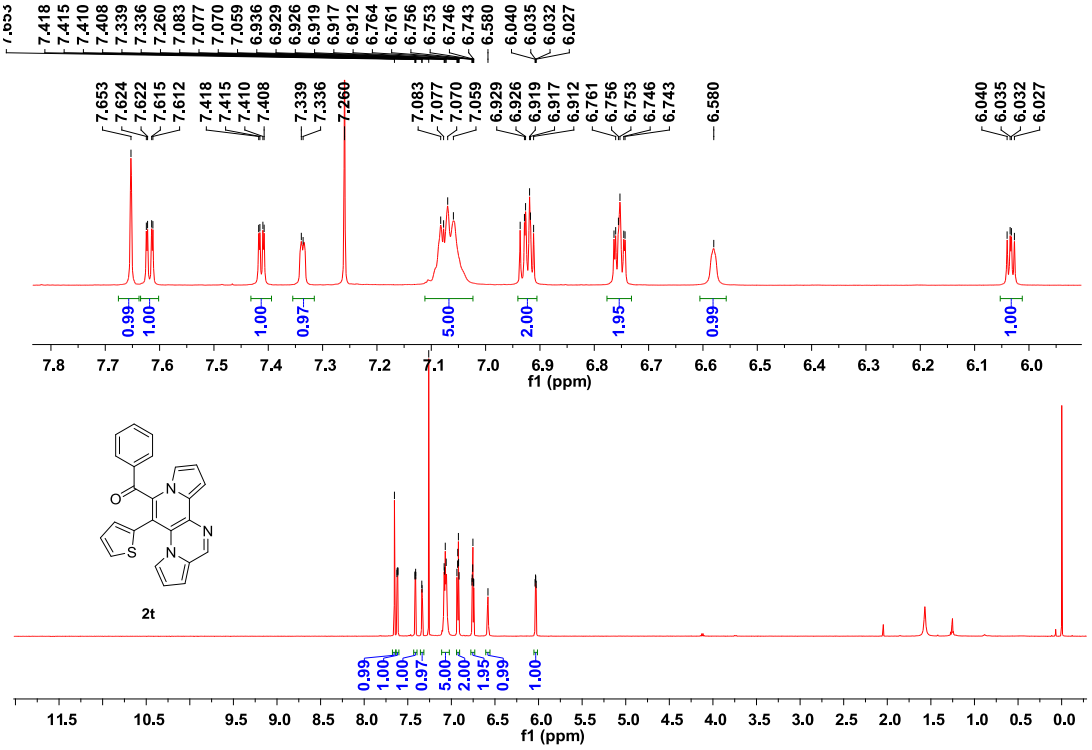
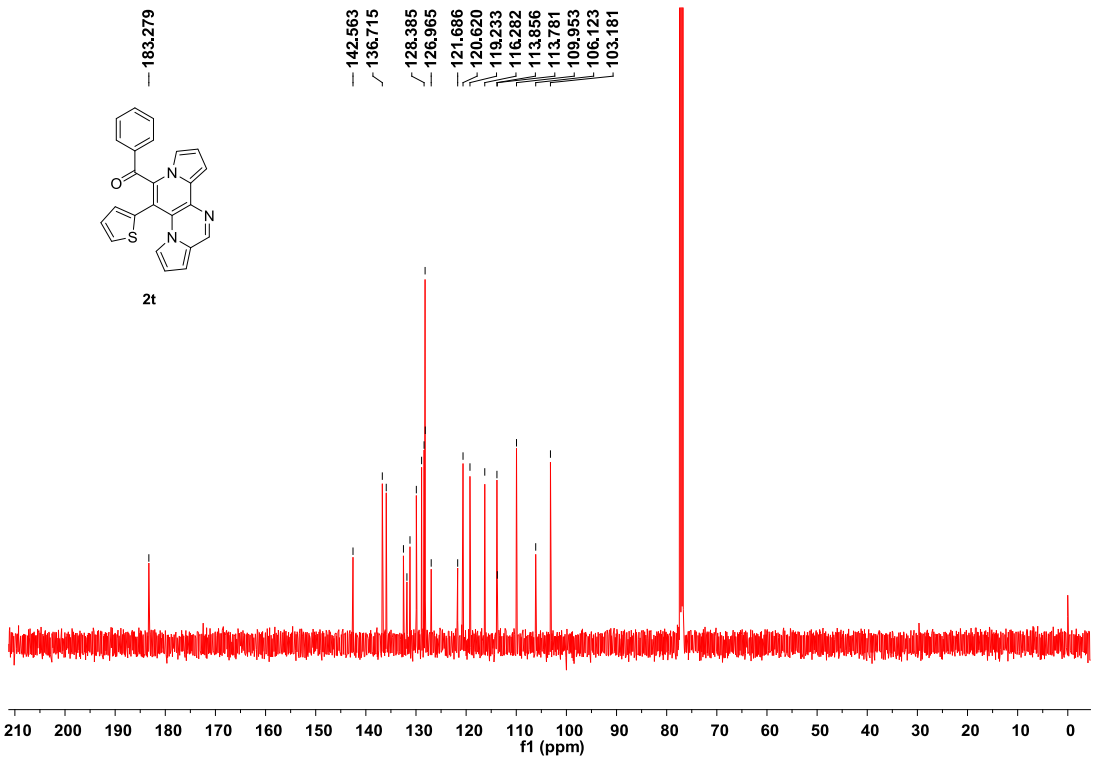
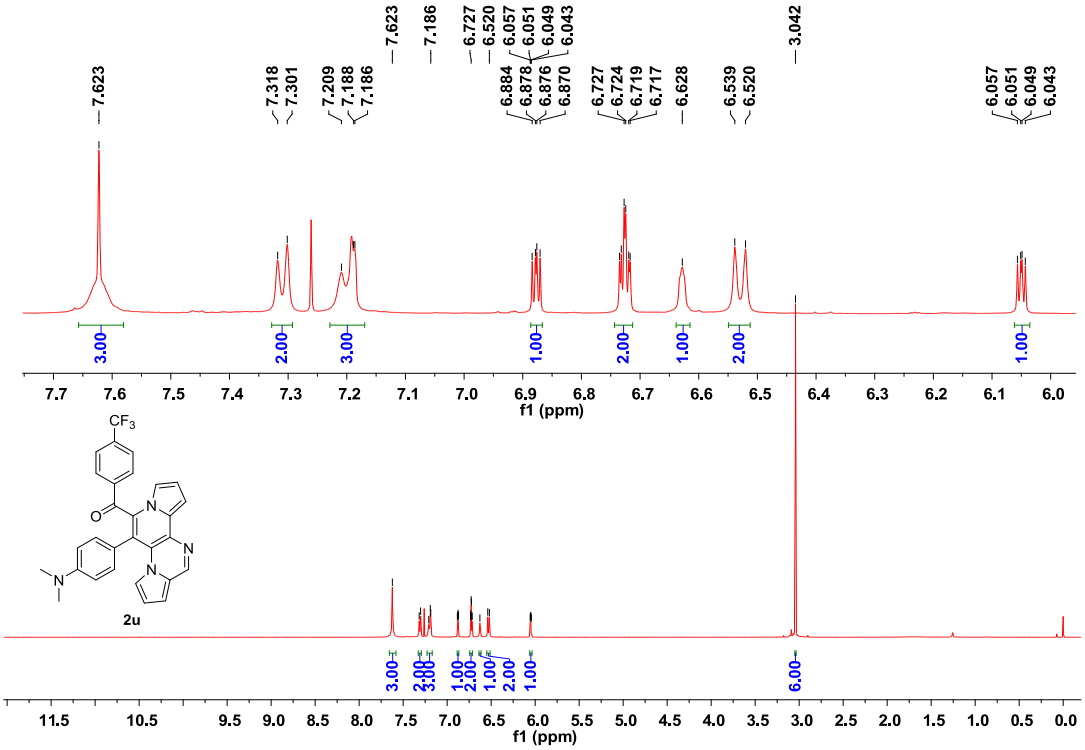
111.293
110.185
106.261
103.694
2s
f1 (ppm)

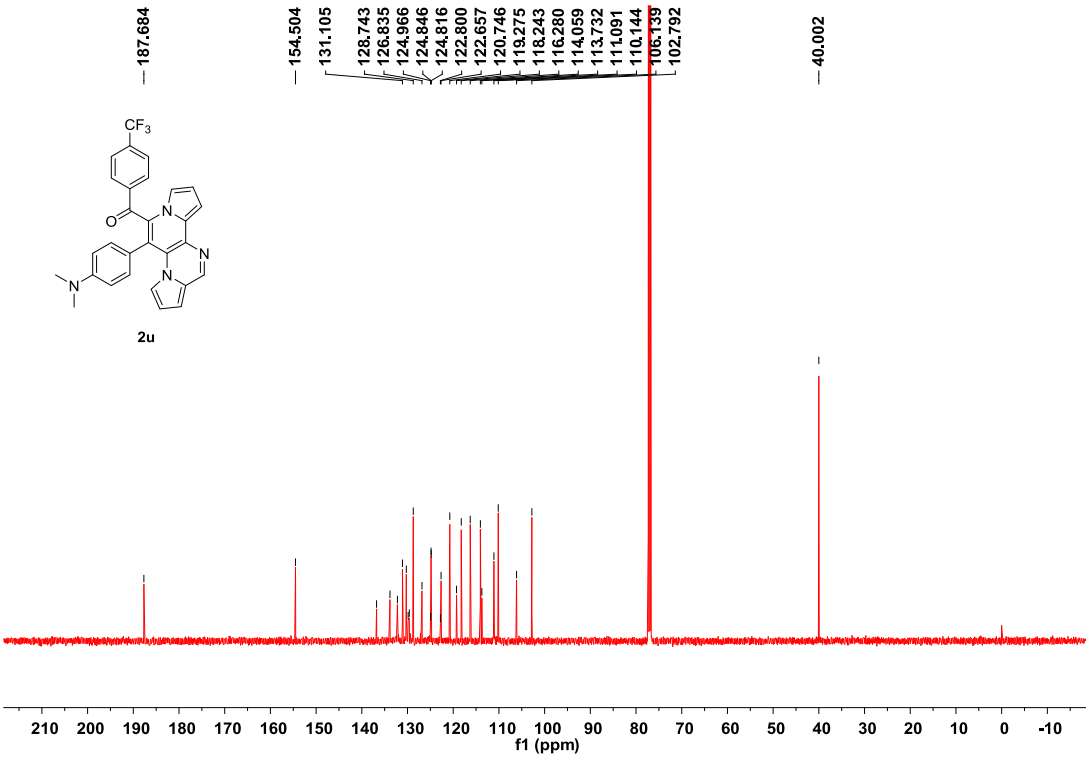
Phenyl(5-(thiophen-2-yl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)methanone (2t)





(5-(4-(dimethylamino)phenyl)pyrrolo[1',2':1,6]pyrazino[2,3-g]indolizin-6-yl)(4-(trifluoromethyl)phenyl)methanone (2u)

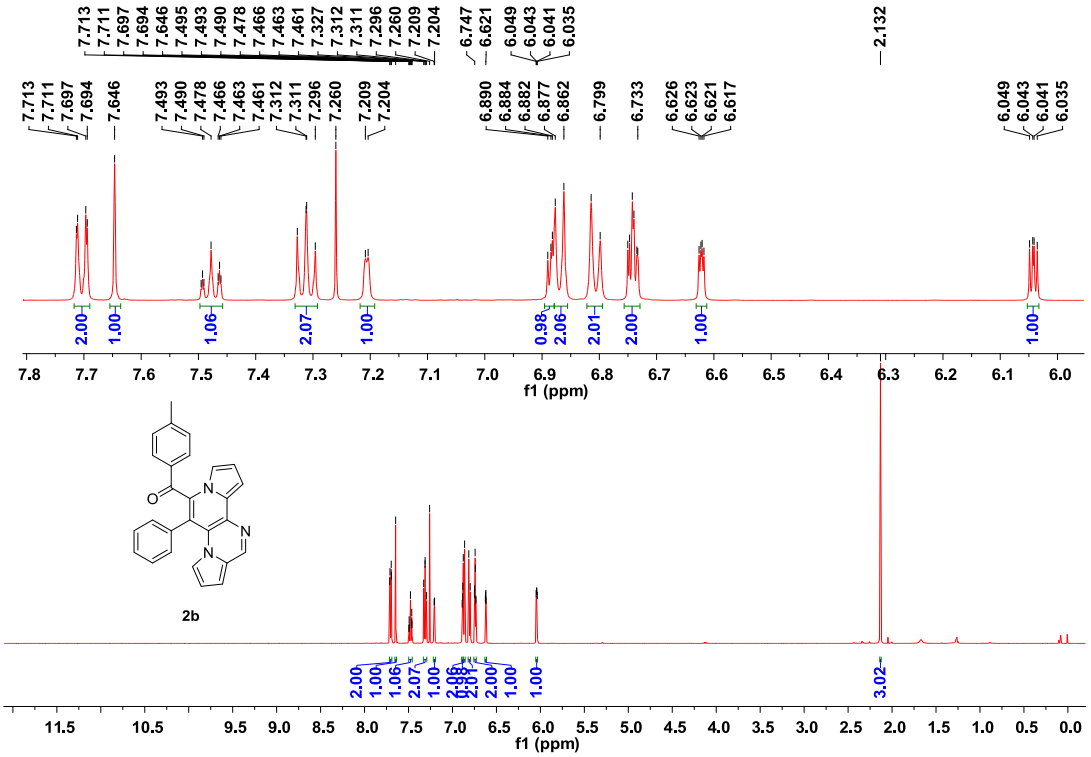




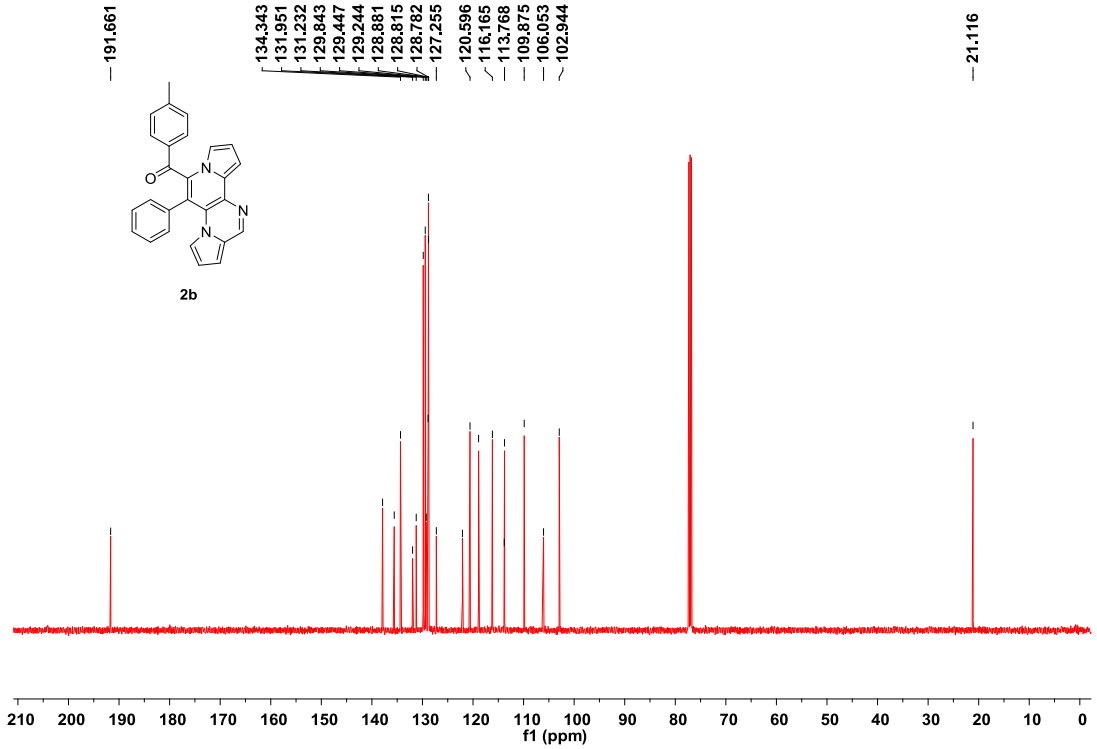
9. Characterization data for 2b

(5-Phenylpyrrolo[1',2':1,6]pyrazino[2,3-*g*]indolizin-6-yl)(m-tolyl)methanone (2b): Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (21.3 mg, 0.1 mmol) and 1-(2-oxo-2-(p-tolyl)ethyl)-1*H*-pyrrole-2-carbonitrile **1b-2** (22.4 mg, 0.1 mmol) were used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1) afforded **2b** as yellow solid (20.9 mg, 52% yield). Mp: 124−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (2H, dt, J = 7.0, 1.5 Hz), 7.65 (1H, s), 7.48 (1H, tt, J = 7.5, 1.0 Hz), 7.31 (2H, tt, J = 7.5, 1.0 Hz), , 7.20 (1H, d, J = 7.5, 2.5 Hz), 6.88 (1H, dd, J = 4.0, 2.5 Hz), 6.87 (2H, d, J = 7.5 Hz), 6.81 (2H, d, J = 7.5 Hz), 6.74 (2H, m), 6.62 (1H, dd, J = 2.5, 1.5 Hz), 6.04 (1H, dd, J = 4.0, 3.0 Hz), 2.13 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.7, 137.9, 135.6, 134.3, 132.0, 131.2, 129.8, 129.4, 129.2, 128.9, 128.8, 128.7, 127.3, 122.1, 120.6, 118.9, 116.2, 113.8, 113.7, 109.9, 106.1, 102.9, 21.1; HRMS Calcd. for $C_{27}H_{19}N_3O + H^+$: 402.1606, found: 402.1602.

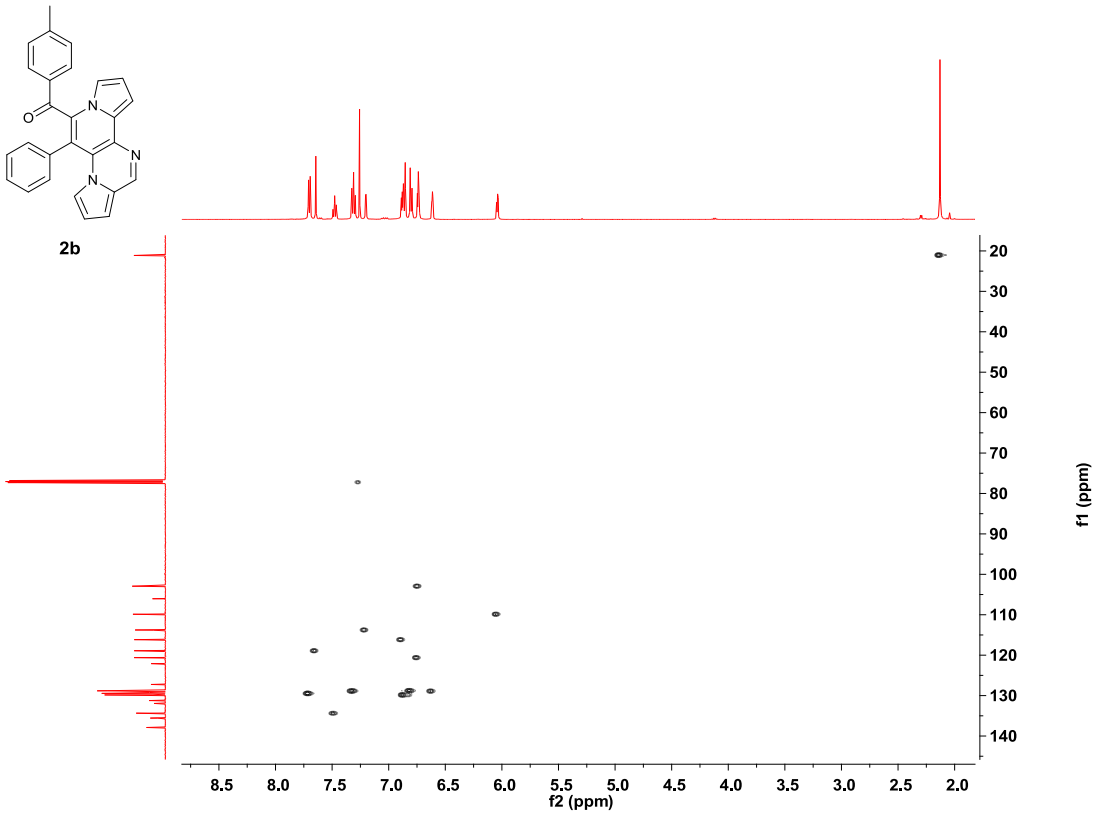
^{1}H NMR of 2b



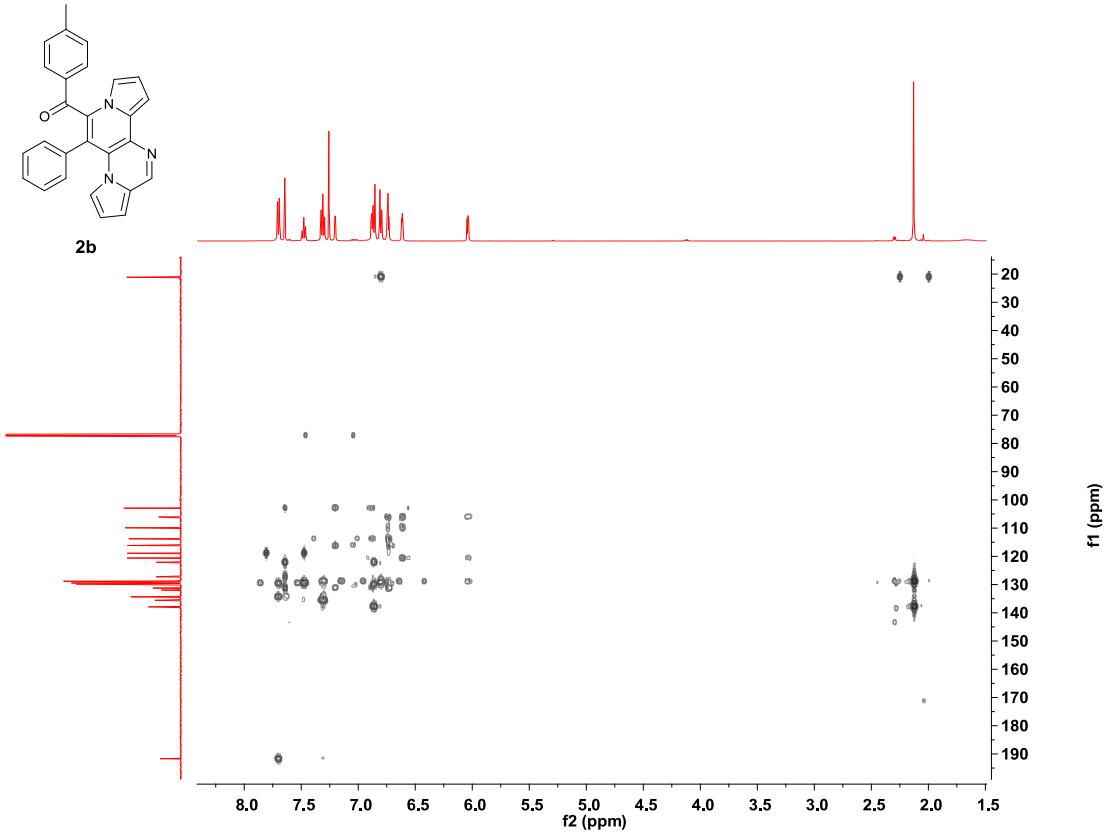
^{13}C NMR of 2b



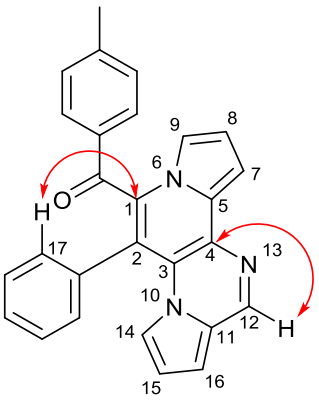
HSQC of 2b



HMBC of 2b



All carbon and hydrogen atoms can be confirmed by the NMR data, and the correlation from HMBC showed the structure of **2b**. C-1 (δ 113.8) and H-17 (δ 6.86), C-4 (δ 132.0) and H-12 (δ 7.65) of **2b** were determined by ^{1}H NMR, ^{13}C NMR, HSQC and HMBC. The correlation of C-1 and H-17 from HMBC showed the first step of aldol condensation. The second step of aldol condensation and further aldimine condensation can be showed by the correlation of C-4 and H-12 from HMBC.



2b