Electronic Supplementary Information

Aza-Dicyclopenta[*a*,*g*]naphthalenes: Controllable Seesaw-like Emissive Behavior and Narrowband AIEgens

Jinbiao Li, Jiaxin Lao, Hongbin Zou*

College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, 310058, PR China

* Corresponding author. Tel: +8657188208451; email: zouhb@zju.edu.cn

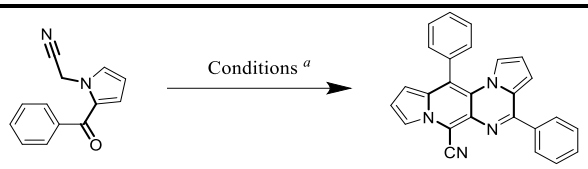
List of Contents

I. 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). 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) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS was 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. Size distribution was determined on a DLS using a Mastersizer 3000. Morphology was observed on a S4 JEM-F200 transmission electron microscope. Powder X-ray diffraction was observed on a Bruker D8 ADVANCE. Laser confocal scanning microscope images were collected on a confocal laser scanning microscope (CLSM, ZEISS-LSM880). 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 aggregation state were measured on Absolutely Photoluminescence Quantum Yield Measurement System (HAMAMARSU, C11347-11Quantaurus-QY).

II. Reaction conditions optimization

Table S1: Details for the optimization of the reaction condition.



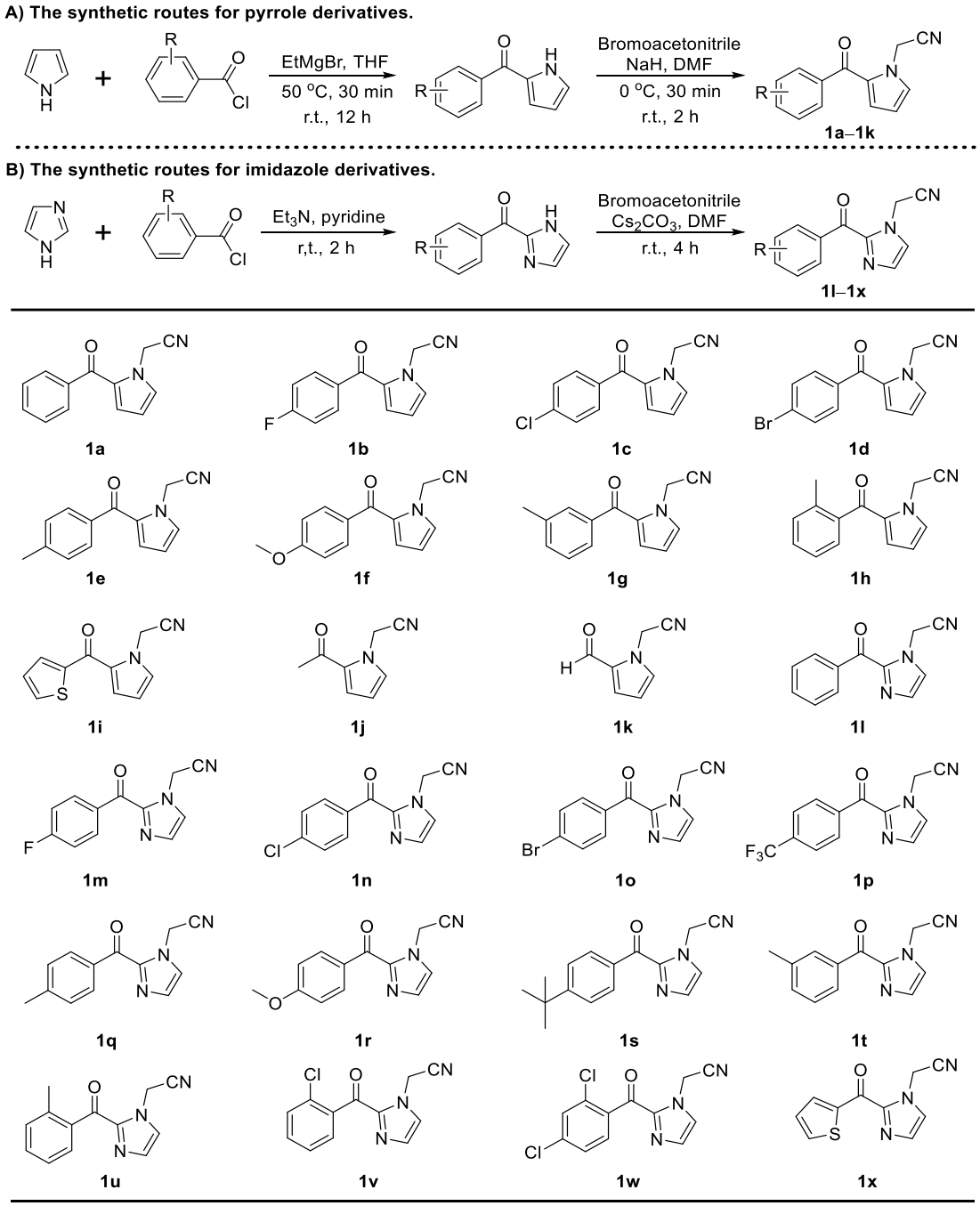
1a **2a**

Entry	Base	Solvent	Temp. (°C)	Time	Yield [b]
1	DABCO	DMF	r.t.[c]	2 h	0
2	Et_3N	DMF	r.t.	2 h	0
3	DBU	DMF	r.t.	2 h	< 5%
4	K_2CO_3	DMF	r.t.	2 h	0
5	CH_3ONa	DMF	r.t.	2 h	12%
6	^{t}BuOLi	DMF	r.t.	2 h	0
7	^{t}BuONa	DMF	r.t.	2 h	< 5%
8	^{t}BuOK	DMF	r.t.	2 h	23%
9	^{t}BuOK	CH_3CN	r.t.	2 h	35%
10	^{t}BuOK	EtOH	r.t.	2 h	< 5%
11	^{t}BuOK	THF	r.t.	2 h	57%
12	^{t}BuOK	DMSO	r.t.	2 h	22%
13	^{t}BuOK	DCM	r.t.	2 h	< 5%
14	^{t}BuOK	Toluene	r.t.	2 h	0
15	^{t}BuOK	THF	40	2 h	29%
16	^{t}BuOK	THF	-5	2 h	48%
17	^{t}BuOK	THF	r.t.	1 h	64%
18	^{t}BuOK	THF	r.t.	5 min	41%
19	**^{t}BuOK**	**THF**	**r.t.**	**30 min**	**76%**

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), base (2.0 equiv.), solvent (2 mL), under N_2; [b] Isolated yield; [c] Room temperature.

Details of the investigated reaction condition optimization were presented here. We embarked upon the optimization of intermolecular cascade condensation by using 2-(2-benzoyl-1*H*-pyrrol-1-yl)acetonitrile as the model substrate. The base and the solvent were found to play a key role in the reaction. After screening a range of bases, we centered on ^{t}BuOK which produced the best overall yield of **2a** in the presence of DMF at room temperature (Table S1, entries 1–8). Various solvents were then examined and THF turned out to be the most favorable one (Table S1, entries 8–14). The reaction temperature was gradually increased from -5 to 40 °C and the results showed that it was also a key role in the reaction yield (Table S1, entries 11, 15 and 16). Different reaction time, from 5 minutes to 2 hours, was also tested, and the results indicated that longer or shorter reaction time than 30 minutes would diminish the reaction yields (Table S1, entries 11 and 17–19). Therefore, the reaction was found to produce the desired product **2a** most efficiently under the catalysis of ^{t}BuOK in THF at room temperature for 30 minutes (Table S1, entry 19).

III. General procedures for the synthesis of starting materials



Scheme S1. The synthetic routes for starting materials.

General procedures A: the synthetic routes for pyrrole derivatives. To a freshly prepared solution of ethyl magnesium in diethyl ether (3.0 M, 4 mL) was added dropwise a solution of pyrrole (0.603 g, 9.0 mmol) in diethyl ether (4 mL) under 50 °C. The mixture was refluxed for a further 30 minutes. Then the reaction mixture was cooled to room temperature, and corresponding acid chloride (10.8 mmol, 1.2 equiv) dissolved in tetrahydrofuran (10 mL) was added dropwise over a period of 20 minutes. The solution was stirred overnight. The reaction mixture was then poured into a concentrated aqueous ammonium chloride solution (20 mL), and extracted with dichloromethane

(20 mL × 3). The organic layer was washed with water (10 mL × 3), dried with Na_2SO_4, filtered and evaporated. The crude material was purified by flash chromatography (hexane: EtOAc = 10:1) to give the desired product 2-ketopyrrole.[1] The substrate 2-ketopyrrole (4.0 mmol 1.0 equiv.) was dissolve in anhydrous DMF (20 mL), and NaH (60% in mineral oil, 230 mg, 4.8 mmol, 1.2 equiv.) was added under 0 ºC. The solution was stired under 0 ºC for a further 30 minutes. Then bromoacetonitrile (571 mg, 4.8 mmol, 1.2 eq) dissolved in DMF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature and stired for 2 hours. Then it was added dropwise to ice water (150 mL) and the desired product precipitated from the mixture. It was then filtered and the residue was recrystallized from ethanol to give the desired products (Scheme S1A).

General procedures B: the synthetic routes for imidazole derivatives. Imidazole (6.80 g, 0.1 mol) was dissolved in pyridine (14 mL), and triethylamine (41.8 mL, 0.3 mol) was added. The reaction mixture was cooled with an ice bath. The corresponding aroyl chloride (0.30 mol) was added dropwise under cooling, then the mixture was stirred at room temperature for 2 hours. Aqueous NaOH solution (40 w/w%, 20 mL) was carefully added, and the mixture was refluxed for 1 hours. The reaction mixture was poured into cold water (200 mL), and the precipitated solid was filtered, washed with water and dried at 70 °C. These compounds have been described in the literature earlier.[2] The 2-aroylimidazoles (4.0 mmol 1.0 equiv.) were dissolve in CH_3CN (10 mL) and CH_2Cl_2 (20 mL), and Cs_2CO_3 (1.56 g, 4.8 mmol, 1.2 equiv.) was added under room temperature. Then bromo acetonitrile (571 mg, 4.8 mmol, 1.2 eq) was added dropwise. The reaction mixture was stired for further 4 hours. Then it was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethanol to give the desired products (Scheme S1B).

Unless otherwise noted, all reagents and solvents purchased from commercial sources were used without further purification. The compounds **1a**–**1f**, **1j**, **1k** have been described in the literature earlier[3] and our previous research.

2-(2-(3-Methylbenzoyl)-1H-pyrrol-1-yl)acetonitrile (**1g**)

Following the general procedures A, **1g** was obtained as white solid (797 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.79 (1H, d, J = 7.5 Hz), 7.67 (1H, dd, J = 7.5, 2.5 Hz), 7.41 (2H, m), 7.23 (1H, dd, J = 3.0, 0.5 Hz), 6.89 (1H, dd, J = 4.0, 0.5 Hz), 6.47 (1H, dd, J = 4.0, 2.5 Hz), 5.39 (2H, s), 2.29 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.23, 140.59, 134.71, 133.49, 131.52, 129.37, 127.35, 125.49, 124.57, 122.78, 116.63, 111.17, 38.45, 22.14; HRMS (ESI) *m/z* calcd. for $C_{14}H_{12}N_2O$ $[M+H]^+$ 225.1028, found 225.1032.

2-(2-(2-Methylbenzoyl)-1H-pyrrol-1-yl)acetonitrile (**1h**)

Following the general procedures A, **1h** was obtained as white solid (771 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.82 (1H, dd, J = 8.0, 1.0 Hz), 7.54 (1H, dd, J = 8.5, 6.5 Hz), 7.34 (2H, m), 7.21 (1H, dd, J = 3.0, 1.0 Hz), 6.92 (1H, dd, J = 4.0, 1.0 Hz), 6.44 (1H, dd, J = 4.0, 3.0 Hz), 5.37 (2H, s), 2.31 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.81, 141.76, 137.97, 136.54, 131.68, 131.24, 130.85, 130.62, 126.08, 123.15, 115.36, 112.64, 36.57, 22.37; HRMS (ESI) *m/z* calcd. for $C_{14}H_{12}N_2O$ $[M+H]^+$ 225.1028, found 225.1032.

2-(2-(Thiophene-2-carbonyl)-1H-pyrrol-1-yl)acetonitrile (**1i**)

Following the general procedures A, **1i** was obtained as white solid (778 mg, 90% yield). ^{1}H NMR

(500 MHz, $CDCl_3$): δ 7.78 (1H, dd, J = 4.0, 1.0 Hz), 7.56 (1H, dd, J = 5.0, 1.0 Hz), 7.34 (1H, dd, J = 3.5, 0.5 Hz), 7.21 (1H, dd, J = 5.0, 4.0 Hz), 6.91 (1H, dd, J = 4.0, 1.0 Hz), 6.47 (1H, dd, J = 4.0, 3.0 Hz), 5.53 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.16, 141.46, 140.70, 137.10, 136.43, 130.49, 128.24, 125.25, 113.88, 111.43, 36.36; HRMS (ESI) *m/z* calcd. for $C_{11}H_8N_2OS$ $[M+H]^+$ 217.0436, found 217.0439.

2-(2-Benzoyl-1H-imidazol-1-yl)acetonitrile (**1l**)

Following the general procedures B, **1l** was obtained as white solid (768 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (2H, d, J = 7.5 Hz), 7.60 (1H, t, J = 8.0 Hz), 7.49 (2H, t, J = 8.0 Hz), 7.32 (1H, d, J = 1.0 Hz), 7.30 (1H, d, J = 1.0 Hz), 5.45 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.93, 142.14, 136.25, 133.47, 131.01, 130.46, 128.31, 125.32, 114.10, 36.56.; HRMS (ESI) *m/z* calcd. for $C_{12}H_9N_3O$ $[M+H]^+$ 212.0824, found 212.0826.

2-(2-(4-Fluorobenzoyl)-1H-imidazol-1-yl)acetonitrile (**1m**)

Following the general procedures B, **1m** was obtained as white solid (797 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (2H, dd, J = 9.0, 5.5 Hz), 7.35 (1H, d, J = 1.0 Hz), 7.34 (1H, d, J = 1.0 Hz), 7.18 (2H, dd, J = 9.0, 8.0 Hz), 5.49 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.13, 166.11 ($^1J_{C\text{-}F}$ = 254 Hz), 141.98, 133.84 ($^3J_{C\text{-}F}$ = 9 Hz), 132.47 ($^4J_{C\text{-}F}$ = 3 Hz), 130.50, 125.29, 115.52 ($^2J_{C\text{-}F}$ = 22 Hz), 113.90, 36.63; HRMS (ESI) *m/z* calcd. for $C_{12}H_8FN_3O$ $[M+H]^+$ 230.0730, found 230.0736.

2-(2-(4-Chlorobenzoyl)-1H-imidazol-1-yl)acetonitrile (**1n**)

Following the general procedures B, **1n** was obtained as white solid (823 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (2H, d, J = 8.5 Hz), 7.48 (2H, d, J = 8.5 Hz), 7.34 (2H, s), 5.48(2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 184.73, 142.45, 132.64, 131.96, 130.32, 129.17, 128.05, 124.37, 113.15, 36.09; HRMS (ESI) *m/z* calcd. for $C_{12}H_8ClN_3O$ $[M+H]^+$ 246.0434, found 246.0436.

2-(2-(4-Bromobenzoyl)-1H-imidazol-1-yl)acetonitrile (**1o**)

Following the general procedures B, **1o** was obtained as white solid (1017 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz), 7.34 (2H, s), 5.47 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): 181.61, 140.84, 133.86, 131.56, 130.60, 129.58, 127.93, 124.42, 112.81, 35.60; HRMS (ESI) *m/z* calcd. for $C_{12}H_8BrN_3O$ $[M+H]^+$ 289.9929, found 289.9931.

2-(2-(4-(Trifluoromethyl)benzoyl)-1H-imidazol-1-yl)acetonitrile (**1p**)

Following the general procedures B, **1p** was obtained as white solid (949 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (2H, d, J = 8.0 Hz), 7.77 (2H, d, J = 8.0 Hz), 7.38 (2H, m), 5.51 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.80, 141.74, 139.08, 134.50 ($^2J_{C\text{-}F}$ = 33 Hz), 131.31, 130.92, 125.29, 125.25 ($^3J_{C\text{-}F}$ = 4 Hz), 123.67 125.25 ($^1J_{C\text{-}F}$ = 275 Hz), 113.71, 36.67; HRMS (ESI) *m/z* calcd. for $C_{13}H_8F_3N_3O$ $[M+H]^+$ 280.0698, found 280.0701

2-(2-(4-Methylbenzoyl)-1H-imidazol-1-yl)acetonitrile (**1q**)

Following the general procedures B, **1q** was obtained as white solid (846 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (2H, d, J = 9.0 Hz), 7.35 (2H, d, J = 9.0 Hz), 7.33 (1H, d, J = 1.0 Hz),

7.31 (1H, d, J = 1.0 Hz), 5.52 (2H, s), 2.41 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.25, 151.28, 141.32, 135.57, 130.09, 128.73, 123.67, 114.21, 113.57, 37.36, 21.47; HRMS (ESI) *m/z* calcd. for $C_{13}H_{11}N_3O$ $[M+H]^+$ 226.0980, found 226.0984.

2-(2-(4-Methoxybenzoyl)-1H-imidazol-1-yl)acetonitrile (**1r**)

Following the general procedures B, **1r** was obtained as white solid (877 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (2H, d, J = 9.0 Hz), 7.33 (1H, d, J = 1.0 Hz), 7.31 (1H, d, J = 1.0 Hz), 6.99 (2H, d, J = 9.0 Hz), 5.48 (2H, s), 3.90 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.19, 164.05, 142.41, 133.61, 130.14, 129.01, 124.77, 114.13, 113.66, 55.55, 36.48; HRMS (ESI) *m/z* calcd. for $C_{13}H_{11}N_3O_2$ $[M+H]^+$ 242.0930, found 242.0933.

2-(2-(4-(Tert-butyl)benzoyl)-1H-imidazol-1-yl)acetonitrile (**1s**)

Following the general procedures B, **1s** was obtained as white solid (961 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (2H, d, J = 7.0 Hz), 7.53 (2H, d, J = 7.0 Hz), 7.33 (1H, d, J = 0.5 Hz), 7.32 (1H, d, J = 0.5 Hz), 5.49 (2H, s), 1.35 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.74, 157.32, 142.31, 133.61, 130.95, 130.39, 125.37, 124.99, 114.04, 36.48, 35.20, 31.06; HRMS (ESI) *m/z* calcd. for $C_{16}H_{17}N_3O$ $[M+H]^+$ 268.1450, found 268.1455.

2-(2-(3-Methylbenzoyl)-1H-imidazol-1-yl)acetonitrile (**1t)**

Following the general procedures B, **1t** was obtained as white solid (801 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (1H, dd, J = 8.0, 1.5 Hz), 7.43 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 7.33 (1H, d, J = 1.0 Hz), 7.31 (1H, d, J = 1.0 Hz), 7.30 (1H, m), 7.29 (1H, m), 5.54 (2H, s), 2.44 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.92, 142.65, 138.07, 136.47, 131.55, 131.36, 130.93, 130.56, 125.28, 125.18, 113.87, 36.41, 20.33; HRMS (ESI) *m/z* calcd. for $C_{13}H_{11}N_3O$ $[M+H]^+$ 226.0980, found 226.0984.

2-(2-(2-Methylbenzoyl)-1H-imidazol-1-yl)acetonitrile (**1u**)

Following the general procedures B, **1u** was obtained as white solid (774 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (1H, td, J = 8.5, 1.0 Hz), 7.27 (1H, d, J = 7.0 Hz), 7.22 (2H, m), 7.18 (2H,m), 5.56 (2H, s), 2.27 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.92, 143.10, 135.73, 132.93, 130.90, 130.40, 129.22, 126.88, 125.92, 119.48, 114.32, 113.82, 34.26. HRMS (ESI) *m/z* calcd. for $C_{13}H_{11}N_3O$ $[M+H]^+$ 226.0980, found 226.0983.

2-(2-(2-Chlorobenzoyl)-1H-imidazol-1-yl)acetonitrile (**1v**)

Following the general procedures B, **1v** was obtained as white solid (862 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (1H, ddd, J = 7.5, 1.5, 0.5 Hz), 7.46 (2H, m), 7.38 (2H, m), 7.30 (1H, d, J = 1.0 Hz), 5.53 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.39, 142.00, 136.81, 132.07, 131.98, 131.50, 130.36, 130.18, 126.48, 125.79, 113.66, 36.27; HRMS (ESI) *m/z* calcd. for $C_{12}H_8ClN_3O$ $[M+H]^+$ 246.0434, found 246.0440.

2-(2-(2,4-Dichlorobenzoyl)-1H-imidazol-1-yl)acetonitrile (**1w**)

Following the general procedures B, **1w** was obtained as white solid (915 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (1H, d, J = 8.5 Hz), 7.49 (1H, d, J = 2.0 Hz), 7.37 (2H, m), 7.32 (1H, d,

J = 1.0 Hz), 5.53 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.18, 141.77, 137.78, 135.03, 133.18, 131.59, 131.34, 130.36, 126.88, 125.97, 113.51, 36.29; HRMS (ESI) *m/z* calcd. for $C_{12}H_7Cl_2N_3O$ $[M+H]^+$ 280.0044, found 280.0048.

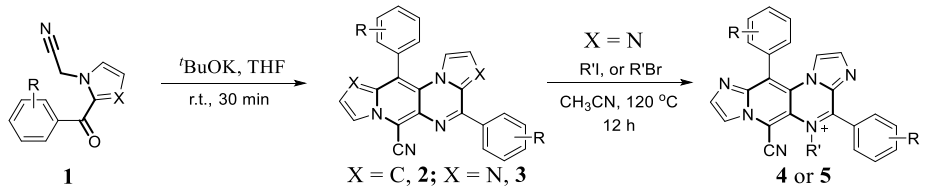
2-(2-(Thiophene-2-carbonyl)-1H-imidazol-1-yl)acetonitrile (**1x**)

Following the general procedures B, **1x** was obtained as white solid (729 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (1H, dd, J = 4.0, 1.0 Hz), 7.78 (1H, dd, J = 5.0, 1.0 Hz), 7.34 (1H, d, J = 0.5 Hz), 7.32 (1H, d, J = 0.5 Hz), 7.21 (1H, dd, J = 5.0, 4.0 Hz), 5.53 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.16, 141.46, 140.70, 137.10, 136.43, 130.49, 128.24, 125.25, 113.88, 36.36; HRMS (ESI) *m/z* calcd. for $C_{10}H_7N_3OS$ $[M+H]^+$ 218.0388, found 218.0384.

IV. General procedure for the synthesis of the products 2, 3, 4 and 5

The general procedure for the products 2 and 3: ^{t}BuOK (45 mg, 0.4 mmol, 2.0 equiv.) was added to the solution of **1** (0.2 mmol, 1.0 equiv.) in THF (2 mL) under N_2. The mixture was stirred under room temperature for 30 minutes. Then the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to obtain the desired product **2** or **3** (Scheme S2).

The general procedure for the products 4 and 5: Iodine or bromo substitutes (0.2 mmol, 2.0 equiv.) was added to the solution of **3** (0.1 mmol, 1.0 equiv.) in CH_3CN (2 mL) in sealed tube. The mixture was stirred under 120 °C for 12 hours. Then the reaction mixture was concentrated under reduced pressure. The residue was washed by ethyl acetate for three times, it was then filtered and obtain the the residue as desired product **4** or **5** (Scheme S2).

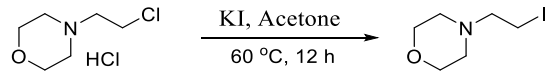


Scheme S2. The synthetic routes for the products **2**, **3**, **4** and **5**.

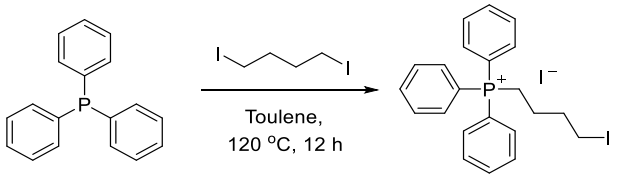
The synthetic routes for 4-(2-iodoethyl)morpholine: 4-(2-Chloroethyl)morpholine hydrochloride (5 g, 0.0269 mol) and sodium iodide (20 g, 0.1334 mol) were placed in acetone (50 mL) and refluxed for 16 h. Chloroform (50 mL) and brine solution (50 mL) were then added and the mixture stirred for 10 min. The solid was removed by filtration and added to a mixture of chloroform (50 mL) and saturated sodium bicarbonate solution (50 mL). The mixture was stirred for 5 min and the organic layer was removed. The aqueous layer was then extracted with additional chloroform (2 × 25 mL). The organic layers were combined, washed with brine, and dried over sodium sulfate. The solvent was removed under reduced pressure to give the title product as a yellow oil, which was used without futher purification (Scheme S3).[4]

The synthetic routes for (4-iodobutyl)triphenylphosphonium iodide: 1,4-Diiodobutane (1.0 mmol) and triphenylphosphine (0.9 mmol) were dissolved in dry hexane (20 mL). The reaction mixture was flushed with argon and stirred at room temperature for 24 h. The white precipitate was suction filtered and dried in a vacuum desiccator. The target compounds were highly hygroscopic and were used without further purification (Scheme S3).[5]

a) The synthetic routes for 4-(2-iodoethyl)morpholine.



b) The synthetic routes for (4-iodobutyl)triphenylphosphonium iodide.



Scheme S3. The synthetic routes for the iodine substitutes.

Unless otherwise noted, all iodine and bromo substitutes purchased from commercial sources were used without further purification. The compounds 4-(2-iodoethyl)morpholine and (4-iodobutyl)triphenylphosphonium iodid have been described in the literature earlier (Scheme S3).

4,11-Diphenylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2a**)

Following the general procedures, **1a** was used as the starting material and **2a** was obtained as red solid, yield 76%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (2H, m), 7.89 (1H, dd, J = 2.5, 1.5 Hz), 7.64 (3H, m), 7.56 (3H, m), 7.50 (2H, m), 7.03 (1H, dd, J = 4.0, 2.5 Hz), 6.95 (1H, dd, J = 4.0, 1.5 Hz), 6.67 (1H, dd, J = 3.0, 1.5 Hz), 6.38 (1H, dd, J = 4.0, 2.5 Hz), 6.25 (1H, dd, J = 4.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.10, 137.20, 135.44, 135.18, 132.68, 130.73, 129.92, 129.50, 129.24, 129.07, 128.59, 125.06, 122.67, 121.77, 117.50, 116.85, 113.84, 113.64, 112.79, 112.71, 106.31, 103.76; HRMS (ESI) *m/z* calcd. for $C_{26}H_{16}N_4$ $[M+H]^+$ 385.1453, found 385.1457.

4,11-Bis(4-fluorophenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2b**)

Following the general procedures, **1b** was used as the starting material and **2b** was obtained as red solid, yield 61%.^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (2H, m), 7.89 (1H, dd, J = 2.5, 1.5 Hz), 7.50 (2H, m), 7.35 (2H, tt, J = 9.0, 2.0 Hz), 7.24 (2H, tt, J = 9.0, 2.0 Hz), 7.04 (1H, dd, J = 4.0, 2.5 Hz), 6.93 (1H, dd, J = 4.0, 2.5 Hz), 6.70 (1H, dd, J = 2.5, 1.5 Hz), 6.43 (1H, dd, J = 4.0, 3.0 Hz), 6.24 (1H, dd, J = 4.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.91 ($^1J_{C\text{-}F}$ = 137 Hz), 155.92, 135.16, 133.26, 133.24, 132.61, 131.33 ($^3J_{C\text{-}F}$ = 8 Hz), 131.08 ($^3J_{C\text{-}F}$ = 8 Hz), 130.96, 124.93, 122.58, 120.62, 117.18 ($^2J_{C\text{-}F}$ = 33 Hz), 117.14, 115.73 ($^2J_{C\text{-}F}$ = 22 Hz), 113.85, 113.66, 113.07, 112.64, 103.72; HRMS (ESI) *m/z* calcd. for $C_{26}H_{14}F_2N_4$ $[M+H]^+$421.1265, found 421.1268.

4,11-Bis(4-chlorophenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2c**)

Following the general procedures, **1c** was used as the starting material and **2c** was obtained as red solid, yield 79%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (2H, tt, J = 8.5, 2.0 Hz), 7.80 (1H, dd, J = 2.5, 1.5 Hz), 7.55 (2H, tt, J = 8.5, 2.0 Hz), 7.44 (2H, tt, J = 8.5, 2.0 Hz), 7.38 (2H, tt, J = 8.5, 2.0 Hz), 6.96 (1H, dd, J = 4.0, 2.5 Hz), 6.84 (1H, dd, J = 4.0, 1.5 Hz), 6.66 (1H, dd, J = 3.0, 3.0 Hz), 6.36 (1H, dd, J = 4.0, 3.0 Hz), 6.16 (1H, dd, J = 4.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.80, 136.98, 135.77, 135.47, 135.00, 133.50, 132.33, 130.77, 130.31, 128.89, 124.79, 122.68, 120.35, 117.46, 117.16, 113.89, 113.54, 113.21, 112.60, 106.65, 103.77.; HRMS (ESI) *m/z* calcd. for $C_{26}H_{14}Cl_2N_4$ $[M+H]^+$ 453.0674, found 453.0676.

4,11-Bis(4-bromophenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2d**)

Following the general procedures, **1d** was used as the starting material and **2d** was obtained as red solid, yield 54%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (2H, tt, J = 8.0, 1.5 Hz), 7.87 (1H, dd, J = 2.5, 1.5 Hz), 7.79 (2H, tt, J = 8.0, 2.0 Hz), 7.67 (2H, tt, J = 8.0, 2.0 Hz), 7.39 (2H, tt, J = 8.0, 2.0 Hz), 7.04 (1H, dd, J = 4.0, 2.5 Hz), 6.90 (1H, dd, J = 4.0, 1.5 Hz), 6.74 (1H, dd, J = 3.0, 3.0 Hz), 6.45 (1H, dd, J = 4.0, 3.0 Hz), 6.24 (1H, dd, J = 4.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.88, 135.92, 134.99, 134.00, 133.26, 132.23, 131.86, 131.03, 130.52, 125.39, 124.74, 123.92, 122.70, 120.33, 117.39, 117.18, 113.91, 113.53, 113.24, 112.60, 106.69, 103.79; HRMS (ESI) *m/z* calcd. for $C_{26}H_{14}Br_2N_4$ $[M+H]^+$ 540.9663, found 540.9665.

4,11-Di-p-tolylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2e**)

Following the general procedures, **1e** was used as the starting material and **2e** was obtained as red solid, yield 81%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (2H, d, J = 8.0 Hz), 7.87 (1H, dd, J = 3.0, 1.5 Hz), 7.44 (2H, d, J = 8.0 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.35 (2H, d, J = 7.5 Hz), 7.01 (1H, dd, J = 4.0, 3.0 Hz), 6.95 (1H, dd, J = 4.0, 1.0 Hz), 6.73 (1H, dd, J = 3.0, 1.5 Hz), 6.38 (1H, dd, J = 4.0, 3.0 Hz), 6.25 (1H, dd, J = 4.0, 1.5 Hz), 2.54 (3H, s), 2.47 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.97, 141.08, 139.44, 135.57, 134.48, 132.83, 132.13, 130.58, 129.28, 129.05, 129.03, 125.08, 122.66, 121.92, 117.58, 116.65, 113.95, 113.53, 112.62, 112.54, 106.00, 103.67, 21.57; HRMS (ESI) *m/z* calcd. for $C_{28}H_{20}N_4$ $[M+H]^+$ 413.1766, found 413.1770.

4,11-Bis(4-methoxyphenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2f**)

Following the general procedures, **1f** was used as the starting material and **2f** was obtained as red solid, yield 87%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (2H, d, J = 9.0 Hz), 7.84 (1H, dd, J = 3.0, 1.5 Hz), 7.40 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.05 (2H, d, J = 8.0 Hz), 7.00 (1H, dd, J = 4.5, 2.5 Hz), 6.94 (1H, dd, J = 4.0, 1.0 Hz), 6.76 (1H, dd, J = 3.0, 1.5 Hz), 6.39 (1H, dd, J = 4.0, 3.0 Hz), 6.28 (1H, dd, J = 4.0, 1.5 Hz), 3.96 (3H, s), 3.91 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.78, 159.33, 155.27, 134.57, 131.89, 129.63, 129.44, 128.72, 126.02, 123.95, 121.58, 120.58, 116.66, 115.53, 114.25, 112.97, 112.92, 112.47, 111.59, 111.39, 104.65, 102.57, 54.43, 54.42; HRMS (ESI) *m/z* calcd. for $C_{28}H_{20}N_4O_2$ $[M+H]^+$ 445.1665, found 445.1669.

4,11-Di-m-tolylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2g**)

Following the general procedures, **1g** was used as the starting material and **2g** was obtained as red solid, yield 86%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (2H, m), 7.85 (1H, d, J = 7.5 Hz), 7.53 (1H, t, J = 7.5 Hz), 7.43 (2H, m), 7.37 (1H, d, J = 7.5 Hz), 7.31 (2H, m), 7.02 (1H, dd, J = 4.0, 3.0 Hz), 6.94 (1H, dd, J = 4.0, 1.5 Hz), 6.71 (1H, dd, J = 3.0, 1.0 Hz), 6.39 (1H, dd, J = 4.0, 3.0 Hz), 6.28 (1H, dd, J = 4.0, 1.5 Hz), 2.49 (3H, s), 2.48 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.30, 139.81, 138.36, 137.20, 135.49, 135.07, 132.73, 131.51, 130.22, 129.80, 129.64, 129.58, 128.41, 126.26, 126.20, 125.12, 122.75, 122.00, 117.43, 116.73, 113.91, 113.56, 112.73, 112.71, 106.11, 103.76, 21.62, 21.60; HRMS (ESI) *m/z* calcd. for $C_{28}H_{20}N_4$ $[M+H]^+$ 413.1766, found 413.1768.

4,11-Di-o-tolylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2h**)

Following the general procedures, **1h** was used as the starting material and trace amount of **2h** was detected by HRMS (ESI) *m/z* calcd. for $C_{28}H_{20}N_4$ $[M+H]^+$ 413.1766, found 413.1769.

4,11-Di(thiophen-2-yl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2i**)

Following the general procedures, **1i** was used as the starting material and **2i** was obtained as red solid, yield 84%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (1H, dd, J = 3.5, 1.5 Hz), 7.85 (1H, dd, J = 2.5, 1.5 Hz), 7.69 (1H, dd, J = 5.0, 1.5 Hz), 7.60 (1H, dd, J = 5.0, 1.0 Hz), 7.33 (1H, dd, J = 5.5, 3.0 Hz), 7.27 (1H, dd, J = 3.5, 1.0 Hz), 7.25 (1H, dd, J = 4.5, 1.5 Hz), 7.21 (1H, dd, J = 5.0, 4.0 Hz), 7.03 (1H, dd, J = 4.0, 2.5 Hz), 6.79 (1H, dd, J = 3.0, 1.0 Hz), 6.50 (1H, dd, J = 4.0, 3.0 Hz), 6.43 (1H, dd, J = 4.0, 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.92, 141.25, 134.66, 134.64, 132.90, 130.49, 129.70, 129.01, 128.63, 128.44, 127.97, 123.84, 122.66, 119.06, 117.01, 114.14, 113.61, 113.55, 113.30, 111.79, 106.42, 103.68; HRMS (ESI) *m/z* calcd. for $C_{22}H_{12}N_4S_2$ $[M+H]^+$ 397.0582, found 397.0584.

4,11-Dimethylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2j**)

Following the general procedures, **1j** was used as the starting material and **2j** was obtained as red solid, yield 42%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (1H, dd, J = 2.5, 1.0 Hz), 7.81 (1H, dd, J = 2.5, 1.5 Hz), 7.08 (1H, dd, J = 4.0, 2.5 Hz), 6.92 (1H, dd, J = 4.0, 1.0 Hz), 6.82 (1H, dd, J = 4.0, 1.0 Hz), 6.74 (1H, dd, J = 3.5, 3.0 Hz), 2.95 (3H, s), 2.68 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.28, 135.33, 132.29, 126.49, 122.36, 117.63, 116.29, 114.11, 113.81, 112.86, 109.93, 101.85, 22.11, 17.55; HRMS (ESI) *m/z* calcd. for $C_{16}H_{12}N_4$ $[M+H]^+$ 261.1140, found 261.1144.

Pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (**2k**)

Following the general procedures, **1k** was used as the starting material and **2k** was obtained as red solid, yield 85%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.77 (1H, s), 8.62 (1H, s), 8.40 (1H, d, J = 2.0 Hz), 7.87 (1H, d, J = 2.5 Hz), 7.20 (1H, dd, J = 3.5, 2.5 Hz) , 7.04 (1H, d, J = 4.0 Hz), 6.87 (1H, d, J = 4.0 Hz), 6.83 (1H, dd, J = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, d_6-DMSO): δ 149.8, 139.9, 131.0, 125.1, 120.6, 119.6, 118.2, 114.4, 113.9, 113.6, 112.6, 107.0, 105.7, 103.1; HRMS (ESI) *m/z* calcd. for $C_{14}H_8N_4$ $[M+H]^+$ 233.0827, found 233.0825.

4,11-Diphenylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3a**)

Following the general procedures, **1l** was used as the starting material and **3a** was obtained as orange solid, yield 55%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (2H, dd, J = 2.5, 1.5 Hz), 8.21 (1H, d, J = 1.0 Hz), 8.00 (1H, d, J = 1.0 Hz), 7.71 (3H, m), 7.57 (5H, m), 7.47 (1H, d, J =1.5 Hz), 6.88 (1H, d, J = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.71, 143.51, 138.14, 137.66, 134.52, 133.55, 133.12, 132.26, 132.08, 130.59, 130.36, 130.13, 129.36, 128.55, 122.48, 121.22, 118.37, 113.31, 112.21, 107.89; HRMS (ESI) *m/z* calcd. for $C_{24}H_{14}N_6$ $[M+H]^+$ 387.1358, found 387.1361.

4,11-Bis(4-fluorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3b**)

Following the general procedures, **1m** was used as the starting material and **3b** was obtained as orange solid, yield 47%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00─8.96 (2H, m), 8.23 (1H, d, J = 1.5 Hz), 8.01 (1H, d, J = 1.0 Hz), 7.57─7.54 (2H, m), 7.53 (1H, d, J = 1.5 Hz), 7.41 (2H, tt, J = 8.5, 2.0 Hz), 7.28 (2H, tt, J = 8.0, 2.0 Hz), 6.98 (1H, d, J = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.40, 143.47, 138.18, 137.57, 133.38, 133.26, 133.13, 133.06, 131.59, 131.52, 129.33 ($^1J_{C\text{-}F}$ = 325 Hz), 129.30 ($^1J_{C\text{-}F}$ = 325 Hz), 122.59, 120.09, 118.20, 117.46 ($^2J_{C\text{-}F}$ = 21 Hz), 115.73 ($^2J_{C\text{-}F}$ = 23 Hz) , 113.47, 112.08, 108.02; HRMS (ESI) *m/z* calcd. for $C_{24}H_{12}F_2N_6$ $[M+H]^+$ 423.1170, found 423.1177.

4,11-Bis(4-chlorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3c**)

Following the general procedures, **1n** was used as the starting material and **3c** was obtained as orange solid, yield 42%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (2H, d, J = 8.5 Hz), 8.19 (1H, s), 8.00 (1H, s), 7.69 (2H, d, J = 7.0 Hz), 7.50 (5H, m), 7.00 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.10, 143.21, 138.71, 138.21, 137.37, 136.85, 133.34, 133.17, 132.65, 131.89, 130.97, 130.50, 130.43, 128.82, 122.38, 119.81, 118.30, 113.54, 111.97, 108.15; HRMS (ESI) *m/z* calcd. for $C_{24}H_{12}Cl_2N_6$ $[M+H]^+$ 455.0579, found 455.0582.

4,11-Bis(4-bromophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3d**)

Following the general procedures, **1o** was used as the starting material and **3d** was obtained as orange solid, yield 53%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (2H, dt, J = 9.0, 2.0 Hz), 8.23 (1H, d, J = 1.0 Hz), 8.01 (1H, d, J = 1.0 Hz), 7.84 (2H, tt, J = 8.5, 2.0 Hz), 7.72 (2H, tt, J = 9.0, 2.5 Hz), 7.54 (1H, d, J = 1.5 Hz), 7.45 (2H, tt, J = 9.0, 2.0 Hz), 7.04 (1H, d, J = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.53, 143.20, 138.32, 137.46, 133.43, 133.26, 133.23, 132.13, 131.87, 131.16, 131.02, 127.46, 125.07, 122.34, 119.85, 118.31, 113.54, 112.02, 108.24, 100.00; HRMS (ESI) *m/z* calcd. for $C_{24}H_{12}Br_2N_6$ $[M+H]^+$ 542.9568, found 542.9574.

4,11-Bis(4-(trifluoromethyl)phenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3e**)

Following the general procedures, **1p** was used as the starting material and **3e** was obtained as orange solid, yield 21%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (2H, d, J = 8.0 Hz), 8.26 (1H, d, J = 1.5 Hz), 8.03 (1H, d, J = 1.0 Hz), 7.99 (2H, d, J = 8.0 Hz), 7.85 (2H, d, J = 8.5 Hz), 7.73 (2H, d, J = 8.0 Hz), 7.56 (1H, d, J = 1.0 Hz), 6.93 (1H, d, J = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.42, 143.07, 138.53, 137.48, 135.90, 135.89, 133.80, 133.48 ($^2J_{C\text{-}F}$ = 33 Hz), 132.98, 132.68 ($^2J_{C\text{-}F}$ = 33 Hz), 130.95, 130.24, 127.11 ($^3J_{C\text{-}F}$ = 4 Hz), 125.47 ($^3J_{C\text{-}F}$ = 4 Hz), 123.87 ($^1J_{C\text{-}F}$ = 270 Hz), 123.67 ($^1J_{C\text{-}F}$ = 271 Hz), 122.43, 119.43, 118.24, 113.67, 111.74, 108.95; HRMS (ESI) *m/z* calcd. for $C_{26}H_{12}F_6N_6$ $[M+H]^+$ 523.1106, found 523.1109.

4,11-Di-p-tolylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3f**)

Following the general procedures, **1q** was used as the starting material and **3f** was obtained as orange solid, yield 57%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (2H, d, J = 8.5 Hz), 8.17 (1H, d, J = 1.5 Hz), 7.96 (1H, d, J = 1.0 Hz), 7.50 (2H, d, J = 7.5 Hz), 7.46 (1H, d, J = 1.5 Hz), 7.41 (2H, d, J = 7.5 Hz), 7.36 (2H, d, J = 8.0 Hz), 6.98 (1H, d, J = 1.5 Hz); 2.54 (3H, s), 2.46 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.09, 143.45, 142.77, 140.48, 137.63, 137.52, 133.61, 132.81, 131.68, 130.78, 130.49, 129.20, 129.09, 122.49, 121.21, 118.32, 113.13, 112.21, 107.38, 21.73, 21.65; HRMS (ESI) *m/z* calcd. for $C_{26}H_{18}N_6$ $[M+H]^+$ 415.1671, found 415.1675.

4,11-Bis(4-methoxyphenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3g**)

Following the general procedures, **1r** was used as the starting material and **3g** was obtained as orange solid, yield 63%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94 (2H, d, J = 9.0 Hz), 8.16 (1H, d, J = 1.0 Hz), 7.97 (1H, s), 7.45─7.47 (3H, m), 7.20 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 7.03 (1H, d, J = 1.0 Hz), 3.95 (3H, s), 3.92 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.04, 161.06,

152.69, 143.52, 137.70, 137.44, 133.97, 133.45, 132.81, 132.65, 130.79, 127.14, 123.87, 122.80, 121.00, 118.30, 115.60, 113.97, 113.76, 113.21, 112.39, 107.04, 55.53, 55.51; HRMS (ESI) *m/z* calcd. for $C_{26}H_{18}N_6O_2$ $[M+H]^+$ 447.1569, found 447.1573.

4,11-Bis(4-(tert-butyl)phenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3h**)

Following the general procedures, **1s** was used as the starting material and **3h** was obtained as orange solid, yield 74%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (2H, dt, J = 8.5, 2.0 Hz), 8.20 (1H, d, J = 0.5 Hz), 8.00 (1H, d, J = 1.0 Hz), 7.71 (2H, d, J = 8.5 Hz), 7.61 (2H, dt, J = 7.0, 1.5 Hz), 7.48─7.46 (2H, m), 6.87 (1H, d, J = 1.0 Hz), 1.46 (3H, s), 1.40 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.70, 153.89, 153.61, 143.54, 137.86, 137.78, 133.86, 133.07, 131.87, 130.41, 129.07, 128.97, 127.09, 125.63, 122.75, 121.45, 118.34, 113.22, 112.29, 107.55, 35.10, 35.07, 31.39, 31.18; HRMS (ESI) *m/z* calcd. for $C_{32}H_{30}N_6$ $[M+H]^+$ 499.2610, found 499.2615. When 3 mmol **1r** was used as starting materials and **3h** was obtained in the yield of 71%.

4,11-Di-m-tolylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3i**)

Following the general procedures, **1t** was used as the starting material and **3i** was obtained as orange solid, yield 52%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63─8.62 (2H, m), 8.20 (1H, s), 8.00 (1H, s), 7.59 (1H, t, J = 8.0 Hz), 7.50─7.44 (3H, m), 7.40 (1H, d, J = 7.0 Hz), 7.34─7.32 (2H, m), 6.88 (1H, s), 2.51 (3H, s), 2.49 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.99, 143.47, 140.11, 138.21, 137.92, 137.69, 134.54, 133.62, 133.08, 132.93, 132.11, 131.18, 130.95, 130.06, 129.67, 128.42, 127.90, 126.29, 122.57, 121.40, 118.42, 113.25, 112.21, 107.72, 21.70, 21.68; HRMS (ESI) *m/z* calcd. for $C_{26}H_{18}N_6$ $[M+H]^+$ 415.1671, found 415.1676.

4,11-Di-o-tolylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3j**)

Following the general procedures, **1u** was used as the starting material. We tried different methylation reagents and reaction conditions and could not produce **3j**.

4,11-Bis(2-chlorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3k**)

Following the general procedures, **1v** was used as starting materials and **3k** was obtained as orange solid, yield 37%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (1H, d, J = 1.0 Hz), δ 8.03 (1H, d, J = 1.5 Hz), 7.79 (1H, dd, J = 7.0, 1.5 Hz), 7.75 (1H, dd, J = 7.0, 1.0 Hz), 7.68 (1H, td, J = 7.5, 1.5 Hz), 7.62 (1H, td, J = 7.5, 1.5 Hz), 7.59 (1H, dd, J = 8.0, 1.5 Hz), 7.57 (1H, dd, J = 7.5, 1.5 Hz), 7.53─7.46 (3H, m), 6.89 (1H, d, J = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.50, 142.72, 138.48, 137.85, 134.46, 134.15, 133.96, 133.50, 132.97, 132.06, 131.54, 131.51, 131.32, 131.25, 130.86, 130.56, 128.42, 126.81, 123.25, 118.24, 117.51, 113.54, 111.85, 109.31; HRMS (ESI) m/z calcd. for $C_{24}H_{12}Cl_2N_6$ $[M+H]^+$ 455.0579, found 455.0586.

4,11-Bis(2,4-dichlorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3l**)

Following the general procedures, **1w** was used as the starting material and **3l** was obtained as orange solid, yield 24%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (1H, d, J = 2.0 Hz), 8.04 (1H, d, J = 1.0 Hz), 7.79─7.77 (2H, m), 7.63 (1H, d, J = 2.0 Hz), 7.62 (2H, dd, J = 8.5, 2.0 Hz), 7.56 (1H, d, J

= 1.5 Hz), 7.52 (1H, d, *J* = 8.0 Hz), 7.47 (1H, dd, *J* = 8.5, 2.0 Hz), 7.02 (1H, d, *J* = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.44, 142.52, 138.56, 137.80, 137.66, 137.25, 135.10, 134.71, 134.55, 132.69, 132.51, 132.24, 132.20, 130.89, 130.60, 129.62, 128.92, 127.24, 123.26, 117.48, 116.99, 113.71, 111.61, 109.66; HRMS (ESI) *m/z* calcd. for $C_{24}H_{10}Cl_4N_6$ $[M+H]^+$ 522.9799, found 522.9805.

4,11-Di(thiophen-2-yl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (**3m**)

Following the general procedures, **1x** was used as the starting material and **3m** was obtained as orange solid, yield 41%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (1H, dd, *J* = 4.0, 1.0 Hz), 8.18 (1H, d, *J* = 1.0 Hz), 8.00 (1H, d, *J* = 1.0 Hz), 7.80 (1H, dd, *J* = 4.5, 1.0 Hz), 7.73 (1H, dd, *J* = 5.0, 1.0 Hz), 7.54 (1H, d, *J* = 1.0 Hz), 7.39 (1H, dd, *J* = 5.0, 3.5 Hz), 7.34 (1H, dd, *J* = 3.5, 1.0 Hz), 7.27 (1H, dd, *J* = 5.0, 4.0 Hz), 6.98 (1H, d, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.44, 143.50, 143.31, 138.81, 137.55, 136.60, 135.08, 133.96, 133.49, 133.37, 130.17, 129.98, 128.79, 128.75, 124.26, 118.32, 114.09, 113.38, 111.93, 107.71; HRMS (ESI) *m/z* calcd. for $C_{20}H_{10}S_6$ $[M+H]^+$ 542.9568, found 542.9574.

6-Cyano-5-methyl-4,11-diphenylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizin-5-ium iodide (**2aa**)

Following the general procedures, **2a** was used as the starting material. We tried different methylation reagents and reaction conditions and could not produce **2aa**.

6-Cyano-5-methyl-4,11-diphenylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**4a**)

Following the general procedures, **3a** and iodomethane were used as starting materials and **4a** was obtained as yellow solid, yield 90%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.98 (1H, d, *J* = 2.0 Hz), 8.81 (2H, d, *J* = 7.0 Hz), 8.64 (1H, d, *J* = 2.0 Hz), 7.92 (1H, t, *J* = 7.5 Hz), 7.86 (2H, t, *J* = 7.5 Hz), 7.77─7.68 (6H, m), 6.54 (1H, d, *J* = 1.0 Hz), 3.40 (3H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 155.19, 138.28, 136.16, 135.20, 134.79, 134.21, 133.27, 132.61, 132.37, 130.97, 130.95, 130.91, 129.70, 129.22, 128.80, 119.05, 117.62, 114.86, 111.19, 110.89, 38.52; HRMS (ESI) *m/z* calcd. for $C_{25}H_{17}IN_6$ $[M-I]^+$ 528.0559, found 528.0564.

6-Cyano-4,11-bis(4-fluorophenyl)-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**4b**)

Following the general procedures, **3b** and iodomethane were used as starting materials and **4b** was obtained as yellow solid, yield 94%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.98 (1H, d, *J* = 2.5 Hz), 8.96─8.93 (2H, m), 8.63 (1H, d, *J* = 2.0 Hz), 7.80─7.77 (3H, m), 7.72 (2H, tt, *J* = 9.0, 2.0 Hz), 7.58 (2H, tt, *J* = 8.5, 2.0 Hz), 6.67 (1H, d, *J* = 1.5 Hz), 3.41 (3H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 153.89, 138.18, 136.28, 135.07, 134.95, 133.73, 133.66, 133.56, 133.49, 132.34, 130.69, 129.96, 123.56 ($^1J_{C\text{-}F}$ = 346 Hz), 123.53 ($^1J_{C\text{-}F}$ = 345 Hz), 119.35, 118.26 ($^2J_{C\text{-}F}$ = 23 Hz), 116.67 ($^2J_{C\text{-}F}$ = 26 Hz), 116.39, 114.82, 111.16, 38.70; HRMS (ESI) *m/z* calcd. for $C_{25}H_{15}F_2IN_6$ $[M-I]^+$ 437.1321, found 437.1325.

4,11-Bis(4-chlorophenyl)-6-cyano-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**4c**)

Following the general procedures, **3c** and iodomethane were used as starting materials and **4c** was

obtained as yellow solid, yield 92%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.99 (1H, d, J = 2.0 Hz), 8.74 (2H, tt, J = 9.0, 2.0 Hz), 8.65 (1H, d, J = 2.0 Hz), 7.95 (2H, tt, J = 9.0, 2.0 Hz), 7.81 (3H, m), 7.77 (2H, tt, J = 9.0, 2.0 Hz), 6.70 (1H, d, J = 1.5 Hz), 3.43 (3H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 153.96, 138.44, 138.17, 137.58, 137.56, 136.13, 135.11, 134.99, 132.93, 132.67, 132.42, 132.21, 131.11, 129.80, 129.49, 127.49, 119.42, 116.51, 114.93, 111.08, 38.79; HRMS (ESI) *m/z* calcd. for $C_{25}H_{15}Cl_2IN_6$ $[M-I]^+$ 469.0730, found 469.0733.

4,11-Bis(4-bromophenyl)-6-cyano-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**4d**)

Following the general procedures, **3d** and iodomethane were used as starting materials and **4d** was obtained as yellow solid, yield 95%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.99 (1H, d, J = 2.0 Hz), 8.79 (2H, d, J = 8.0 Hz), 8.65 (1H, d, J = 2.0 Hz), 8.08 (2H, d, J = 8.0 Hz), 7.94 (2H, d, J = 8.5 Hz), 7.82 (1H, s), 7.69 (2H, d, J = 8.0 Hz), 6.70 (1H, d, J = 1.0 Hz), 3.43 (3H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 154.11, 138.14, 136.05, 135.11, 134.99, 134.01, 133.27, 133.09, 132.78, 132.43, 129.72, 127.87, 127.65, 126.38, 119.40, 116.54, 114.93, 111.09, 38.80; HRMS (ESI) *m/z* calcd. for $C_{25}H_{15}Br_2IN_6$ $[M-I]^+$ 556.9719, found 556.9731.

6-Cyano-4,11-bis(4-methoxyphenyl)-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide **4e**

Following the general procedures, **3g** and iodomethane were used as starting materials and **4e** was obtained as yellow solid, yield 85%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.93 (2H, d, J = 9.0 Hz), 8.91 (1H, d, J = 2.0 Hz), 8.60 (1H, d, J = 2.0 Hz), 7.75 (1H, d, J = 1.5 Hz), 7.63 (2H, d, J = 8.5 Hz), 7.40 (2H, d, J = 9.0 Hz), 7.24 (2H, d, J = 9.5 Hz), 6.66 (1H, d, J = 1.0 Hz), 3.97 (3H, s), 3.91 (3H, s), 3.43 (3H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 163.77, 162.16, 153.82, 138.13, 136.30, 135.49, 134.55, 133.14, 132.29, 132.14, 129.95, 126.48, 120.16, 119.02, 117.66, 116.33, 114.82, 114.65, 111.34, 109.88, 56.18, 56.17, 38.62; HRMS (ESI) *m/z* calcd. for $C_{27}H_{21}IN_6O_2$ $[M-I]^+$ 461.1721, found 461.1730.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**4f**)

Following the general procedures, **3h** and iodomethane were used as starting materials and **4f** was obtained as yellow solid, yield 88%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (2H, d, J = 8.5 Hz), 8.57 (1H, d, J = 1.5 Hz), 8.40 (1H, d, J = 2.5 Hz), 7.84 (2H, d, J = 8.5 Hz), 7.74 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 9.0 Hz), 7.49 (1H, d, J = 1.5 Hz), 6.55 (1H, d, J = 1.5 Hz), 3.51 (3H, s), 1.44 (9H, s), 1.38 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.86, 156.36, 156.21, 138.06, 136.39, 135.47, 134.31, 132.38, 131.11, 130.98, 130.52, 129.82, 127.45, 125.79, 125.12, 118.57, 118.12, 113.65, 110.46, 39.29, 35.36, 35.22, 31.36, 31.11; HRMS (ESI) *m/z* calcd. for $C_{33}H_{33}IN_6$ $[M-I]^+$ 513.2761, found 513.2771.

6-Cyano-5-methyl-4,11-di-m-tolylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**4g**)

Following the general procedures, **3i** and iodomethane were used as starting materials and **4g** was obtained as yellow solid, yield 84%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.98 (1H, s), 8.65 (2H, s),

8.60 (1H, d, J = 1.5 Hz), 7.74─7.78 (3H, m), 7.56 (4H, m), 6.62 (1H, s), 3.43 (3H, s), 2.51 (6H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 155.22, 140.71, 138.35, 138.23, 136.09, 135.20, 134.81, 134.24, 133.94, 133.15, 132.33, 131.33, 131.11, 130.78, 129.60, 129.12, 128.68, 128.25, 127.92, 119.13, 117.67, 114.85, 111.20, 110.79, 38.54, 21.74, 21.62; HRMS (ESI) *m/z* calcd. for $C_{27}H_{21}IN_6$ $[M-I]^+$ 429.1822, found 429.1825.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-ethylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5a**)

Following the general procedures, **3h** and iodoethane were used as starting materials and **5a** was obtained as yellow solid, yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (2H, d, J = 8.5 Hz), 8.53 (1H, d, J = 2.0 Hz), 8.41 (1H, d, J = 2.0 Hz), 7.86 (2H, d, J = 8.5 Hz), 7.73 (2H, d, J = 8.0 Hz), 7.58 (2H, d, J = 8.5 Hz), 7.45 (1H, d, J = 1.5 Hz), 6.43 (1H, d, J = 1.5 Hz), 3.81 (2H, q, J = 7.5 Hz), 1.43 (9H, s), 1.37 (9H, s), 1.24 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.73, 156.38, 156.01, 138.09, 136.14, 135.46, 134.23, 131.13, 130.95, 130.18, 130.07, 127.62, 125.75, 125.53, 118.64, 117.98, 114.41, 110.66, 110.59, 46.11, 35.36, 35.20, 31.33, 31.12, 16.19; HRMS (ESI) *m/z* calcd. for $C_{34}H_{35}IN_6$ $[M-I]^+$ 527.2918, found 527.2924.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-propylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5b**)

Following the general procedures, **3h** and 1-iodopropane were used as starting materials and **5b** was obtained as yellow solid, yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (2H, d, J = 8.5 Hz), 8.50 (1H, d, J = 2.0 Hz), 8.40 (1H, d, J = 2.0 Hz), 7.88 (2H, d, J = 8.0 Hz), 7.78 (2H, d, J = 8.5 Hz), 7.61 (2H, d, J = 9.0 Hz), 7.51 (1H, d, J = 1.5 Hz), 6.52 (1H, d, J = 1.5 Hz), 3.70─3.67 (2H, m), 1.73─1.65 (2H, m), 1.46 (9H, s), 1.39 (9H, s), 0.59 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.88, 156.43, 156.24, 138.16, 136.07, 135.50, 134.36, 131.11, 131.01, 130.71, 130.22, 130.06, 127.75, 125.80, 125.45, 118.62, 117.74, 114.22, 110.83, 110.47, 52.14, 35.40, 35.23, 31.34, 31.11, 24.51; HRMS (ESI) *m/z* calcd. for $C_{35}H_{37}IN_6$ $[M-I]^+$ 541.3074, found 541.3082.

5-Allyl-4,11-Bis(4-(tert-butyl)phenyl)-6-cyanoimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5c**)

Following the general procedures, **3h** and 3-iodoprop-1-ene were used as starting materials and **5c** was obtained as yellow solid, yield 90%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 9.04 (1H, d, J = 2.5 Hz), 8.76 (2H, d, J = 8.5 Hz), 8.64 (1H, d, J = 2.0 Hz), 7.86 (2H, d, J = 8.5 Hz), 7.78 (1H, d, J = 1.5 Hz), 7.73 (2H, d, J = 9.0 Hz),7.59 (2H, d, J = 8.5 Hz), 6.45 (1H, d, J = 1.5 Hz), 5.68─5.60 (1H, m), 5.14 (1H, d, J = 10.5 Hz), 4.74 (1H, d, J = 12 Hz), 4.38 (2H, d, J = 4.5 Hz), 1.44 (9H, s), 1.38 (9H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 156.57, 156.02, 155.08, 138.29, 136.06, 135.30, 134.85, 132.56, 131.55, 131.18, 130.93, 130.31, 130.26, 127.81, 126.17, 125.58, 118.94, 118.35, 117.35, 115.92, 111.28, 111.25, 111.23, 51.93, 35.54, 35.43, 31.50, 31.33; HRMS (ESI) *m/z* calcd. for $C_{35}H_{35}IN_6$ $[M-I]^+$ 539.2918, found 539.2920..

5-(But-3-yn-1-yl)-4,11-bis(4-(tert-butyl)phenyl)-6-cyanoimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5d**)

Following the general procedures, **3h** and 4-iodobut-1-yne were used as starting materials and **5d**

was obtained as yellow solid, yield 94%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (2H, d, J = 8.5 Hz), 8.49 (1H, s), 8.40 (1H, s), 7.92 (2H, d, J = 8.0 Hz), 7.81 (2H, d, J = 7.5 Hz), 7.62 (2H, d, J = 8.5 Hz), 7.53 (1H, d, J = 1.5 Hz), 6.52 (1H, d, J = 1.0 Hz), 3.97 (2H, t, J = 7.0 Hz), 2.61─2.58 (2H, m), 1.99 (1H, t, J = 2.0 Hz), 1.47 (9H, s), 1.40 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.04, 156.73, 156.48, 138.19, 137.10, 136.41, 135.60, 134.51, 131.07, 131.04, 130.61, 130.59, 130.56, 130.06, 128.06, 125.85, 125.08, 118.61, 117.71, 114.14, 110.93, 110.33, 72.54, 48.73, 35.44, 35.25, 31.30, 31.11, 20.88; HRMS (ESI) *m/z* calcd. for $C_{36}H_{35}IN_6$ $[M-I]^+$ 551.2918, found 551.2931.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(pent-4-yn-1-yl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5e**)

Following the general procedures, **3h** and 5-iodopent-1-yne were used as starting materials and **5e** was obtained as yellow solid, yield 91%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 9.02 (1H, d, J = 2.0 Hz), 8.75 (2H, d, J = 8.5 Hz), 8.72 (1H, d, J = 2.5 Hz), 7.91 (2H, d, J = 7.5 Hz), 7.77 (1H, d, J = 1.0 Hz), 7.74─7.70 (4H, m), 6.49 (1H, d, J = 1.0 Hz), 3.72 (2H, t, J = 8.0 Hz), 2.83 (1H, t, J = 2.5 Hz), 1.79─1.76 (2H, m), 1.74─1.68 (2H, m), 1.46 (9H, s), 1.38 (9H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 156.55, 155.90, 155.03, 138.28, 136.15, 135.31, 134.84, 131.52, 130.98, 130.92, 130.15, 130.05, 128.08, 126.16, 126.00, 118.95, 117.58, 115.52, 111.21, 110.82, 82.52, 72.69, 49.29, 35.56, 35.43, 31.48, 31.33, 29.19, 15.41; HRMS (ESI) *m/z* calcd. for $C_{37}H_{37}IN_6$ $[M-I]^+$ 565.3074, found 565.3078.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-hydroxyethyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5f**)

Following the general procedures, **3h** and 2-iodoethan-1-ol were used as starting materials and **5f** was obtained as yellow solid, yield 92%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (2H, d, J = 8.5 Hz), 8.40 (1H, d, J = 2.5 Hz), 8.31 (1H, d, J = 2.0 Hz), 7.78 (2H, d, J = 8.0 Hz), 7.74 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.48 (1H, d, J = 1.5 Hz), 6.45 (1H, d, J = 1.5 Hz), 3.79 (2H, t, J = 5.0 Hz), 3.66 (1H, t, J = 6.5 Hz), 3.54─3.51 (2H, m), 1.44 (9H, s), 1.38 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.82, 156.66, 156.23, 138.17, 136.26, 135.33, 134.33, 132.37, 131.12, 130.98, 130.15, 130.09, 127.76, 125.78, 125.25, 118.50, 117.63, 113.69, 111.01, 110.46, 58.86, 53.28, 35.41, 35.22, 31.33, 31.11; HRMS (ESI) *m/z* calcd. for $C_{34}H_{35}IN_6O$ $[M-I]^+$ 543.2867, found 543.2875.

2-(4,11-Bis(4-(tert-butyl)phenyl)-6-cyanoimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium-5-yl)ethane-1-sulfonate (**5g**)

Following the general procedures, **3h** and 1,2-oxathiolane 2,2-dioxide were used as starting materials and **5g** was obtained as yellow solid, yield 88%. ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.79 (1H, d, J = 2.0 Hz), 8.75 (2H, d, J = 9.0 Hz), 8.73 (1H, d, J = 2.0 Hz), 7.88 (2H, d, J = 8.0 Hz), 7.77 (1H, d, J = 1.0 Hz), 7.72 (2H, d, J = 8.5 Hz), 7.65 (2H, d, J = 8.5 Hz), 6.55 (1H, d, J = 1.5 Hz), 3.72 (2H, t, J = 7.5 Hz), 2.02 (2H, t, J = 7.0 Hz), 1.81─1.76 (2H, m), 1.46 (9H, s), 1.38 (9H, s); ^{13}C NMR (125 MHz, d_6-DMSO): δ 156.50, 155.80, 155.03, 138.29, 136.11, 135.25, 134.80, 132.67, 131.58, 131.24, 131.22, 130.91, 129.95, 129.90, 128.09, 126.13, 125.91, 118.98, 117.60, 115.44, 111.24, 110.87, 49.17, 48.01, 35.53, 35.42, 31.50, 31.33, 27.54; HRMS (ESI) *m/z* calcd. for $C_{35}H_{36}N_6O_3S$ $[M+H]^+$ 621.2648, found 621.2649.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-oxopropyl)imidazo[1',2':1,6]pyrido[3,4-

e]imidazo[1,2-a]pyrazin-5-ium bromide (**5h**)

Following the general procedures, **3h** and 1-bromopropan-2-one were used as starting materials and **5h** was obtained as yellow solid, yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.03 (1H, d, J = 2.0 Hz), 8.75 (2H, d, J = 8.5 Hz), 8.53 (1H, d, J = 2.0 Hz), 7.73 (2H, d, J = 8.5 Hz), 7.61 (4H, d, J = 8.5 Hz), 7.48 (1H, d, J = 1.5 Hz), 6.44 (1H, d, J = 1.5 Hz), 5.39 (2H, s), 1.82 (3H, s), 1.45 (9H, s), 1.38 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.01, 156.92, 156.32, 156.24, 138.12, 136.51, 135.44, 134.44, 132.20, 131.07, 130.99, 130.49, 130.02, 127.74, 125.81, 124.88, 118.43, 117.42, 113.97, 110.88, 110.38, 59.75, 35.38, 35.23, 31.31, 31.11, 26.88; HRMS (ESI) *m/z* calcd. for $C_{35}H_{35}BrN_6O$ $[M\text{-}Br]^+$ 555.2867, found 555.2871.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-ethoxy-2-oxoethyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium bromide (**5i**)

Following the general procedures, **3h** and ethyl 2-bromoacetate were used as starting materials and **5i** was obtained as yellow solid, yield 87%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.20 (1H, s), 8.74 (2H, d, J = 8.5 Hz), 8.37 (1H, s), 7.73─7.78 (4H, m), 7.60 (2H, d, J = 8.5 Hz), 7.48 (1H, s), 6.42 (1H, s), 5.04 (2H, s), 4.04 (2H, q, J = 7.0 Hz), 1.46 (9H, s), 1.37 (9H, s), 1.19 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.88, 156.96, 156.45, 156.31, 138.14, 136.60, 135.50, 134.44, 132.76, 131.01, 130.30, 127.60, 125.82, 124.62, 118.46, 117.61, 113.51, 110.89, 110.33, 62.53, 51.57, 35.37, 35.23, 31.30, 31.10, 14.03; HRMS (ESI) *m/z* calcd. for $C_{36}H_{37}BrN_6O_2$ $[M\text{-}Br]^+$ 585.2973, found 585.2980.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-octadecylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5j**)

Following the general procedures, **3h** and 1-iodooctadecane were used as starting materials and **5j** was obtained as yellow solid, yield 86%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (2H, d, J = 8.5 Hz), 8.44 (2H, d, J = 8.0 Hz), 7.88 (2H, d, J = 8.0 Hz), 7.75 (2H, d, J = 8.0 Hz), 7.61 (1H, s), 7.60 (1H, s), 7.48 (1H, s), 6.46 (1H, s), 3.72 (2H, t, J = 8.0 Hz), 1.64─1.60 (2H, m), 1.45 (9H, s), 1.38 (9H, s), 1.25─1.10 (28H, m), 0.88─0.85 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.78, 156.29, 156.10, 138.13, 136.04, 135.45, 134.28, 131.12, 130.98, 130.64, 130.15, 130.12, 127.67, 125.77, 125.53, 118.62, 117.78, 114.38, 110.79, 110.53, 50.88, 35.36, 35.21, 31.94, 31.33, 31.11, 31.01, 29.73, 29.71, 29.68, 29.51, 29.38, 28.94, 26.41, 22.71, 14.15; HRMS (ESI) *m/z* calcd. for $C_{50}H_{67}IN_6$ $[M\text{-}I]^+$ 751.5422, found 751.5431.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(4-(triphenylphosphonio)butyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5k**)

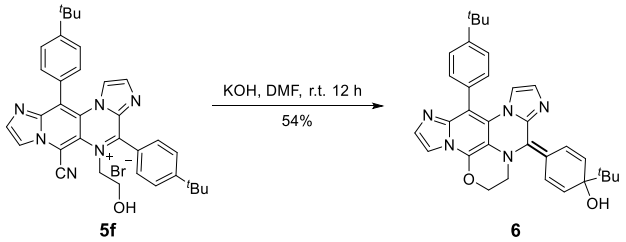
Following the general procedures, **3h** and (4-iodobutyl)triphenylphosphonium iodide were used as starting materials and **5k** was obtained as yellow solid, yield 53%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (2H, d, J = 8.5 Hz), 8.53 (1H, d, J = 2.0 Hz), 8.35 (1H, d, J = 2.0 Hz), 7.90 (2H, d, J = 8.5 Hz), 7.77 (2H, d, J = 8.5 Hz), 7.62 (2H, d, J = 8.5 Hz), 7.50 (1H, d, J = 1.0 Hz), 6.42 (1H, d, J = 1.5 Hz), 3.85 (2H, t, J = 5.5 Hz), 3.62 (4H, t, J = 4.5 Hz), 2.54 (2H, t, J = 5.5 Hz), 2.41─2.39 (4H, m), 1.46 (9H, s), 1.39 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.94, 156.60, 156.26, 138.16, 136.21, 135.46, 134.39, 131.34, 131.06, 131.01, 130.27, 130.12, 127.90, 125.83, 125.58, 118.57, 117.70,

113.47, 110.76, 110.47, 66.86, 57.17, 53.32, 47.26, 35.42, 35.24, 31.35, 31.11; HRMS (ESI) *m/z* calcd. for $C_{38}H_{42}IN_7$ $[M-I]^+$ 612.3445, found 612.3452.

4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-morpholinoethyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (**5l**)

Following the general procedures, **3h** and 4-(2-iodoethyl)morpholine were used as starting materials and **5l** was obtained as yellow solid, yield 61%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.14 (1H, d, J = 1.0 Hz), 8.73 (2H, d, J = 8.5 Hz), 8.00 (1H, d, J = 1.5 Hz), 7.96 (2H, d, J = 8.5 Hz), 7.78─7.67 (17H, m), 7.59 (2H, d, J = 9.0 Hz), 7.48 (1H, d, J = 1.5 Hz), 6.50 (1H, d, J = 1.5 Hz), 4.11 (2H, t, J = 6.0 Hz), 3.41─3.35 (2H, m), 2.06─2.01 (2H, m), 1.82─1.76 (2H, m), 1.36 (9H, s), 1.36 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.68, 156.22, 156.16, 138.17, 136.45, 135.65, 135.14, 135.12, 134.28, 134.05, 133.97, 133.82, 133.74, 131.60, 131.20, 130.98, 130.72, 130.62, 130.51, 130.31, 130.25, 127.63, 125.71, 125.40, 118.58, 117.96, 117.87, 117.19, 112.59, 110.81, 110.53, 49.39, 35.32, 35.19, 31.37, 31.11, 29.69, 19.50, 19.48; HRMS (ESI) *m/z* calcd. for $C_{54}H_{53}I_2N_6P$ $[M-2I]^{2+}$ 408.2029, found 408.2030.

V. The synthesis of the products 6



Scheme S4. Reaction procedure for **6.**

Compound **5f** (124 mg, 0.2 mmol, 1.0 equiv.), KOH (13 mg, 0.24 mmol, 1.2 eq) and 2.0 mL DMF was stirred at room temperature for 36 hours. After the reaction was completed, the reaction mixture was poured into water (10 mL) and extracted with EtOAc (3 × 10 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 ($CHCl_3$: MeOH = 20 : 1) to obtain the desired product **6** (light green solid, 56 mg, yield 54% (Scheme S4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (2H, d, J = 8.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.49 (1H, d, J = 2.0 Hz), 7.26 (4H, s), 7.24 (1H, d, J = 1.5 Hz), 7.06 (1H, d, J = 2.5 Hz), 6.37 (1H, d, J = 1.0 Hz), 3.62 (2H, t, J = 4.0 Hz), 3.28 (2H, t, J = 4.0 Hz), 1.40 (9H, s), 1.32 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.65, 153.32, 152.74, 143.17, 139.15, 136.93, 133.28, 133.03, 132.52, 131.93, 129.38, 128.88, 126.01, 125.14, 125.05, 116.12, 114.50, 107.37, 89.60, 61.08, 51.63, 34.88, 34.85, 31.36, 31.35. HRMS (ESI) *m/z* calcd. for $C_{33}H_{35}N_5O_2$ $[M+H]^+$ 534.2869, found 534.2872.

VI. Photophysical properties

Table S2: Optical properties of PPI (**2**).

Compound	$\lambda_{max, abs}$[a]	$\lambda_{max, em}$		Stokes shift[d]	FWHM[e]	Quantum yield (Φ_f)[f]		α_{AIE}[g]
		Solution[b]	Aggregation[c]			Solution[b]	Aggregation[c]	
2a	371	493	487	122	85	12.5%	0.91%	0.07
2b	373	487	485	114	87	16.3%	1.26%	0.08
2c	378	496	484	118	86	11.4%	0.87%	0.13
2d	375	498	496	123	85	19.8%	2.15%	0.11
2e	387	511	501	124	97	21.6%	1.98%	0.09
2f	393	531	512	138	82	13.4%	1.31%	0.10
2g	381	509	499	128	84	15.6%	1.24%	0.08
2i	379	496	491	117	106	11.7%	0.65%	0.06
2j	376	476	473	100	94	10.9%	1.02%	0.09
2k	358	474	472	116	89	8.5%	0.33%	0.04

[a] UV absorption in dmso solution. [b] Solution of compounds in DMSO and [c] aggregation state of compounds in 95% water/DMSO mixture. [d] Calculated in solution. [e] FWHM, full width at half maxima, calculated in solution. [f] Absolute fuorescence quantum yield measured by calibrated integration. [g] The value was measure by intensity in aggragation/intnesity in solution. (10 μM, nm).

Table S3: Optical properties of IPIP (**3**).

Compound	$\lambda_{max, abs}$[a]	$\lambda_{max, em}$		Stokes shift[d]	FWHM[e]	Quantum yield (Φ_f)[f]		α_{AIE}[g]
		Solution[b]	Aggregation[c]			Solution[b]	Aggregation[c]	
3a	381	549	551, 575	168	70	10.8%	5.4%	0.14
3b	377	552	550	175	74	15.2%	6.8%	0.21
3c	373	550	551, 582	177	73	14.9%	8.3%	0.10
3d	376	552	550, 576	176	75	13.0%	6.9%	0.13
3e	379	550	552	171	71	17.1%	7.1%	0.24
3f	381	550	553	169	77	16.4%	10.3%	0.17
3g	401	553	557	152	76	11.3%	5.7%	0.26
3h	395	551	556	156	70	14.2%	7.5%	0.35
3i	393	547	552	154	73	12.2%	6.1%	0.22
3k	371	541	543, 557	170	68	16.8%	8.2%	0.19
3l	384	540	544, 561	156	69	15.4%	7.3%	0.25
3m	393	561	557	168	75	13.5%	6.9%	0.13

[a]UV absorption in DMSO solution. [b] Solution of compounds in DMSO and [c] aggregation state of compounds in 95% water/DMSO mixture. [d] Calculated in solution. [e] FWHM, full width at half maxima, calculated in solution. [f] Absolute fuorescence quantum yield measured by calibrated integration. [g] The value was measure by intensity in aggragation/intnesity in solution. (10 μM, nm).

Table S4: Optical properties of IPIP-ND (**4** and **5)**.

Compound	$\lambda_{max, abs}$[a]	$\lambda_{max, em}$		Stokes shift[d]	FWHM[e]	Quantum yield (Φ_f)[f]		α_{AIE}[g]
		Solution[b]	Aggregation[c]			Solution[b]	Aggregation[c]	
4a	374	511	510	137	43	0.39%	15.2%	36.56
4b	371	515	511	144	44	0.78%	17.4%	42.35
4c	370	512	524	142	45	0.46%	18.8%	46.17
4d	374	516	513	142	47	0.76%	14.6%	41.52
4e	371	529	518	158	49	0.81%	14.9%	30.58
4f	374	535	532	161	43	0.56%	16.7%	10.49
4g	371	523	521	152	43	1.07%	19.5%	28.96
5a	374	527	525	153	43	1.26%	12.8%	10.77
5b	371	531	528	160	43	0.94%	15.6%	10.65
5c	373	533	532	160	47	0.37%	17.2%	13.44
5d	374	534	531	160	43	0.42%	15.9%	12.48
5e	371	532	525	160	42	0.32%	14.5%	13.58
5f	375	531	523	157	43	0.63%	16.7%	12.49
5g	375	530	522	155	44	0.17%	19.3%	11.49
5h	374	531	530	157	43	0.43%	18.5%	12.53
5i	373	533	528	160	43	0.25%	19.1%	13.82
5j	374	534	526	160	44	0.78%	15.4%	14.37
5k	372	531	529	159	43	0.91%	16.1%	15.36
5l	369	535	525	166	46	0.93%	11.2%	21.29

[a] UV absorption in solution. [b] Solution of compounds in DMSO and [c] aggregation state of compounds in 95% water/DMSO mixture. [d] Calculated in aggregation state. [e] FWHM, full width at half maxima, calculated in aggregation. [f] Absolute fuorescence quantum yield measured by calibrated integration. [g] Intensity in aggragation/intnesity in solution. (10 μM, nm).

Table S5. Optical properties of **2c**, **3c** and **4c** in different state.

Compound	λ_{abs}[a] (nm)	λ_{em} (nm)	Quantum yield (Φ_f)[f]	Lifetimes (τ , ns)
2c	378	496, 484	11.4%[b], 0.87%[c]	4.58[b], 2.31[c],
3c	373	550[b], 551[c], 567[d], 584[e]	14.9%[b], 8.3%[c], 7.2%[d], 6.1%[e]	4.22[b], 5.71[c], 7.33[d], 3.61[e]
4c	370	512[b], 524[c]	0.46%[b], 18.8%[c], 0.58%[d]	5.59[b], 6.02[c], 2.03[e]

[a] UV absorption in DMSO solution. [b] Calculated in DMSO solution, [c] in aggregation, [d] in solid, and [e] in crystal state for **2c**, **3c**, **4c**. [f] Absolute fuorescence quantum yield measured by calibrated integration. (concentration: 10 μM).

Table S6. Optical properties **2c**, **3c**, **3h**, **4c**, **4h**, **5i**, and **6** in different solvents.[a]

Compound		PET	Toluene	THF	$CHCl_3$	Dioxane	Acetone	CH_3CN	MetOH	DMSO
2c	$\lambda_{max, abs,}$	376	378	377	379	375	376	375	375	378
	$\lambda_{max, em}$	583	470	490	471	472	493	493	475	496
	Stokes shift	207	92	113	92	97	117	118	100	118
	FWHM	57	87	89	86	89	86	87	90	86
3c	$\lambda_{max, abs,}$	386	402	396	382	406	391	393	385	373
	$\lambda_{max, em}$	517	527	537	518	532	541	540	538	550
	Stokes shift	131	125	141	136	126	150	147	153	177
	FWHM	68	65	67	65	67	67	68	70	73
3h	$\lambda_{max, abs,}$	386	407	401	391	406	397	391	389	395
	$\lambda_{max, em}$	524	534	539	515	534	541	543	539	551
	Stokes shift	138	127	138	124	128	144	152	150	156
	FWHM	81	73	74	77	73	72	72	75	71
4c	$\lambda_{max, abs,}$	386	397	403	395	399	395	391	386	394
	$\lambda_{max, em}$	498	464	478	458	465	526	524	525	511
	Stokes shift	112	67	75	63	66	131	133	139	117
	FWHM	-	90	72	-	59	47	44	46	-
4h	$\lambda_{max, abs,}$	375	385	396	387	391	374	381	385	374
	$\lambda_{max, em}$	492	469	472	469	470	533	533	533	539
	Stokes shift	117	84	76	82	79	159	152	148	165
	FWHM	-	-	70	-	60	54	50	54	-
5i	$\lambda_{max, abs,}$	376	387	391	382	395	377	376	379	369
	$\lambda_{max, em}$	498	465	473	463	470	535	535	534	537
	Stokes shift	122	78	82	81	75	158	159	155	168
	FWHM	-	87	70	-	61	52	48	44	47
6	$\lambda_{max, abs,}$	366	384	392	381	389	375	373	377	371
	$\lambda_{max, em}$	471	475	485	483	469	493	491	501	496
	Stokes shift	105	91	93	102	80	118	118	124	125
	FWHM	-	60	64	65	59	69	65	70	60

[a] The UV absorption and the emission spectra was measured in solution (10 μM, nm).

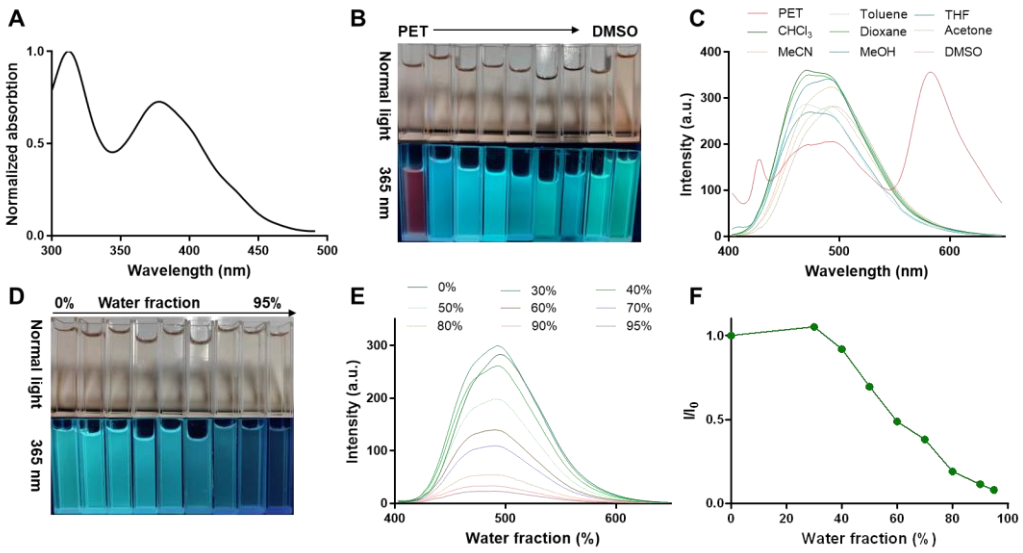


Figure S1. Luminescence properties of **2c**. (A) Absorption of **2c** in DMSO; (B) Photos of **2c** in various solvents under 365 nm UV light (up) and normal light (down), from left to right: PET, toluene, THF, chloroform, dioxane, acetone, acetonitrile, methanol, DMSO; (C) Emission spectra of **2c** in different solvents; (D) Photos of **2c** in different water fractions (DMSO/water) under 365 nm UV light (up) and under normal light (down); (E) Emission spectra of **2c** in different water fractions (DMSO/water mixture; (F) Plots of emission intensity of **2c** (497 nm) in different water fractions. (concentration: 10 μM).

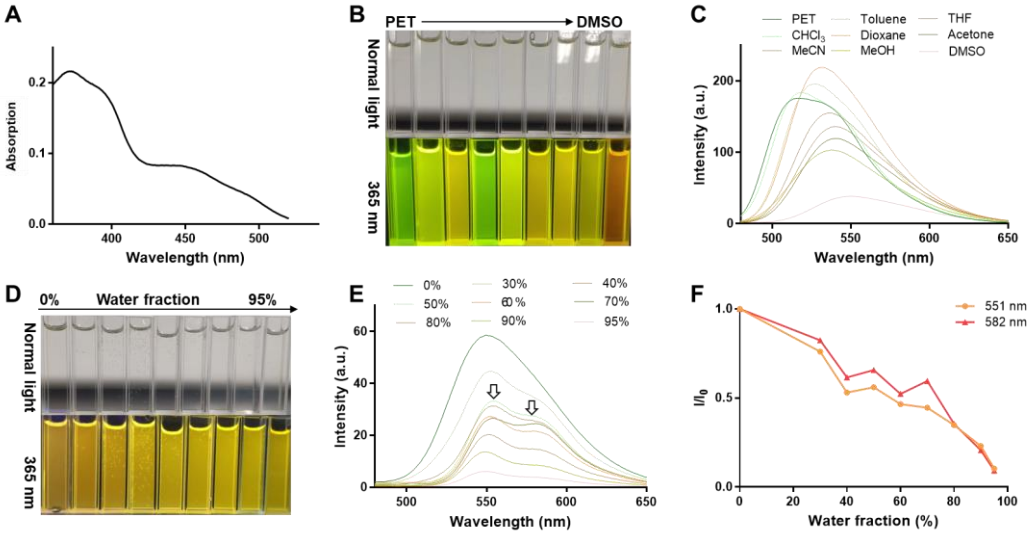


Figure S2. Luminescence properties of **3c**. (A) Absorption of **3c** in DMSO; (B) Photos of **3c** in various solvents under 365 nm UV light (up) and normal light (down), from left to right: PET, toluene, THF, chloroform, dioxane, acetone, acetonitrile, methanol, DMSO; (C) Emission spectra of **3c** in different solvents; (D) Photos of **3c** in different water fractions (DMSO/water) under 365 nm UV light (up) and under normal light (down); (E) Emission spectra of **3c** in different water fractions (DMSO/water mixture; (F) Plots of emission intensity of **3c** (551 and 582 nm) in different water fractions. (concentration: 10 μM).

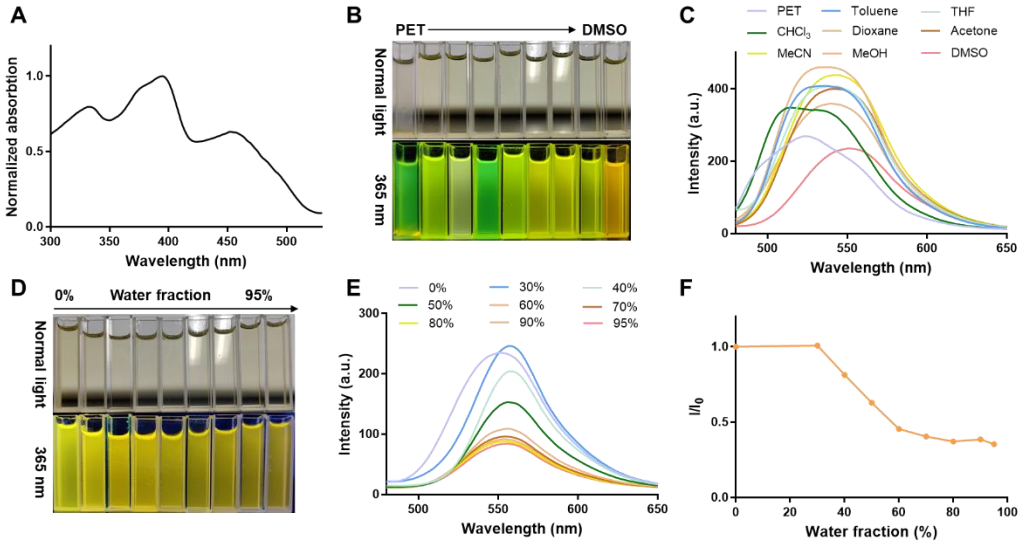


Figure S3. Luminescence properties of **3h**. (A) Absorption of **3h** in DMSO; (B) Photos of **3h** in various solvents under 365 nm UV light (up) and normal light (down), from left to right: PET, toluene, THF, chloroform, dioxane, acetone, acetonitrile, methanol, DMSO; (C) Emission spectra of **3h** in different solvents; (D) Photos of **3h** in different water fractions (DMSO/water) under 365 nm UV light (up) and under normal light (down); (E) Emission spectra of **3h** in different water fractions (DMSO/water mixture; (F) Plots of emission intensity of **3h** (551 nm) in different water fractions. (concentration: 10 μM).

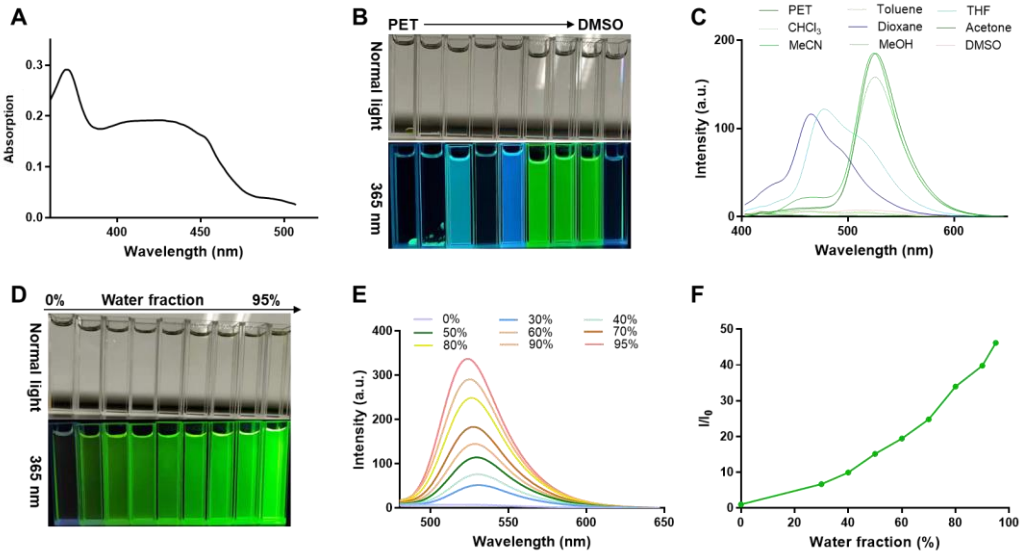


Figure S4. Luminescence properties of **4c**. (A) Absorption of **4c** in DMSO; (B) Photos of **4c** in various solvents under 365 nm UV light (up) and normal light (down), from left to right: PET, toluene, THF, chloroform, dioxane, acetone, acetonitrile, methanol, DMSO; (C) Emission spectra of **4c** in different solvents; (D) Photos of **4c** in different water fractions (DMSO/water) under 365 nm UV light (up) and under normal light (down); (E) Emission spectra of **4c** in different water fractions (DMSO/water mixture; (F) Plots of emission intensity of **4c** (524 nm) in different water fractions. (concentration: 10 μM).

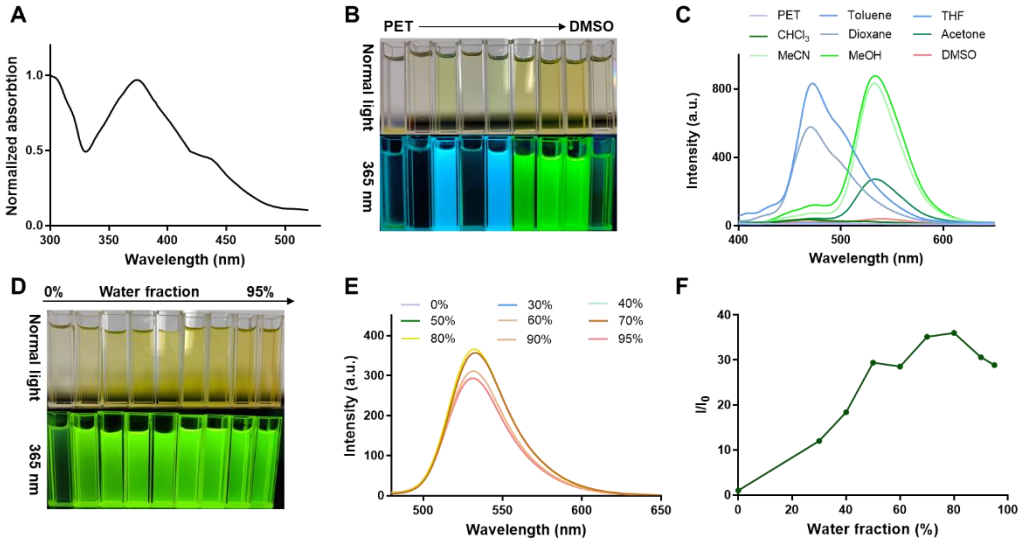


Figure S5. Luminescence properties of **4f**. (A) Absorption of **4f** in DMSO; (B) Photos of **4f** in various solvents under 365 nm UV light (up) and normal light (down), from left to right: PET, toluene, THF, chloroform, dioxane, acetone, acetonitrile, methanol, DMSO; (C) Emission spectra of **4f** in different solvents; (D) Photos of **4f** in different water fractions (DMSO/water) under 365 nm UV light (up) and under normal light (down); (E) Emission spectra of **4f** in different water fractions (DMSO/water mixture; (F) Plots of emission intensity of **4f** (520 nm) in different water fractions. (concentration: 10 μM).

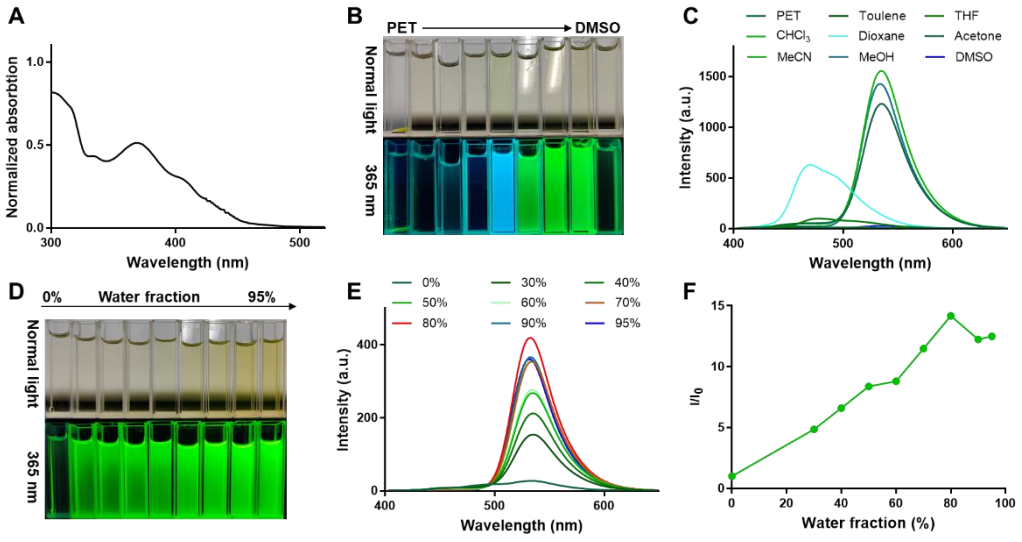


Figure S6. Luminescence properties of **5f**. (A) Absorption of **5f** in DMSO; (B) Photos of **5f** in various solvents under 365 nm UV light (up) and normal light (down), from left to right: PET, toluene, THF, chloroform, dioxane, acetone, acetonitrile, methanol, DMSO; (C) Emission spectra of **5f** in different solvents; (D) Photos of **5f** in different water fractions (DMSO/water) under 365 nm UV light (up) and under normal light (down); (E) Emission spectra of **5f** in different water fractions (DMSO/water mixture; (F) Plots of emission intensity of **5f** (531 nm) in different water fractions. (concentration: 10 μM).

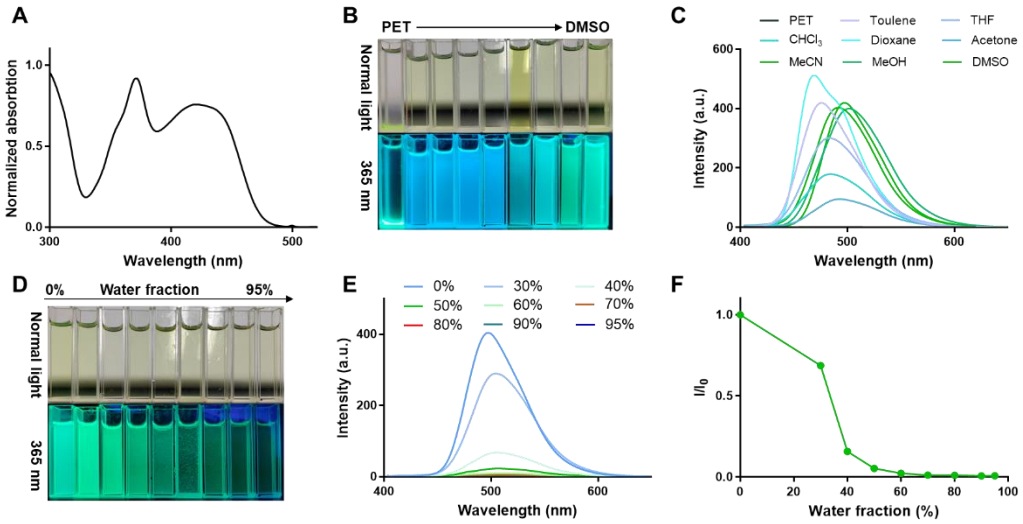


Figure S7. Luminescence properties of **6**. (A) Absorption of **6** in DMSO; (B) Photos of **6** in various solvents under 365 nm UV light (up) and normal light (down), from left to right: PET, toluene, THF, chloroform, dioxane, acetone, acetonitrile, methanol, DMSO; (C) Emission spectra of **6** in different solvents; (D) Photos of **6** in different water fractions (DMSO/water) under 365 nm UV light (up) and under normal light (down); (E) Emission spectra of **6** in different water fractions (DMSO/water mixture; (F) Plots of emission intensity of **6** (497 nm) in different water fractions. (concentration: 10 μM).

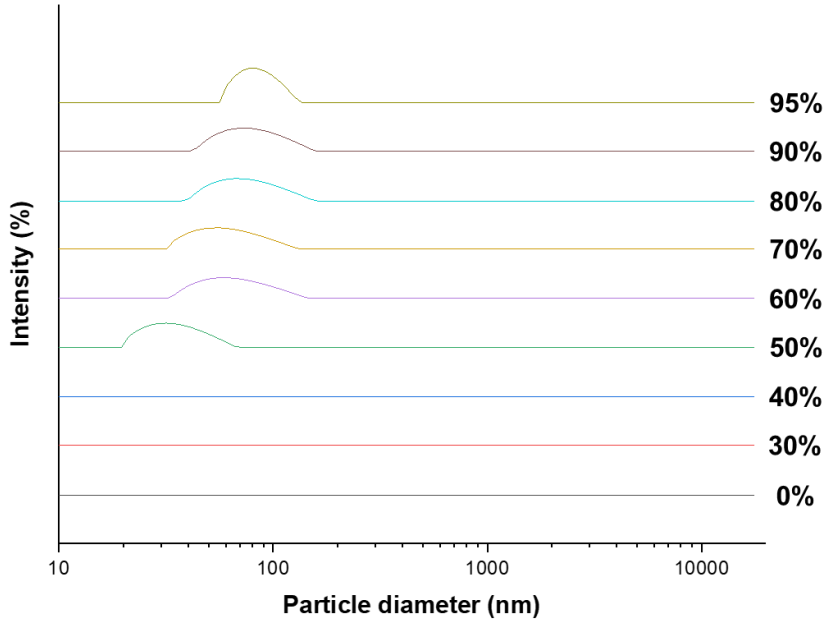


Figure S8. DLS size distribution of **2c** in different water fraction (DMSO/water mixture, concentration: 10 μM).

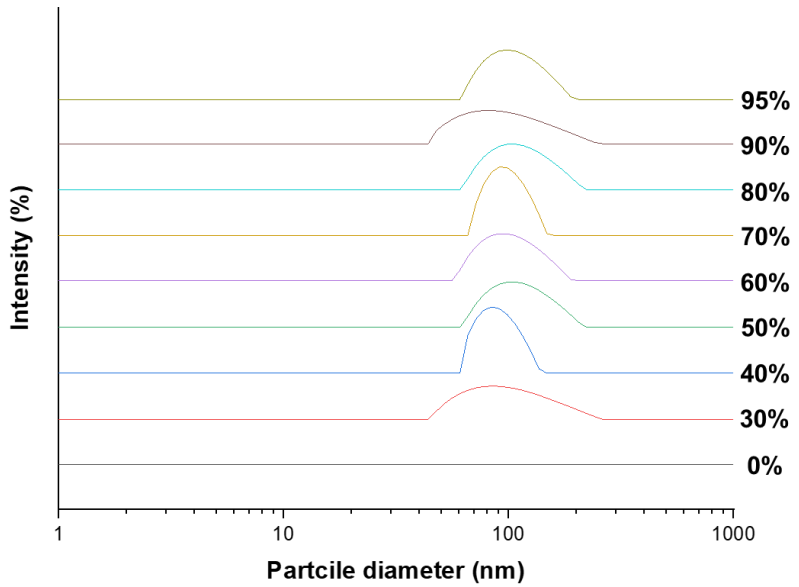


Figure S9. DLS size distribution of **3c** in different water fraction (DMSO/water mixture, concentration: 10 μM).

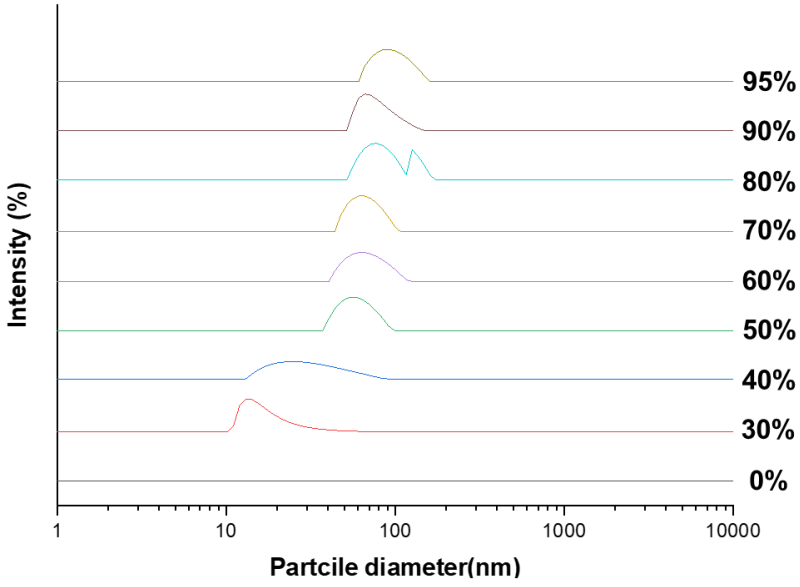


Figure S10. DLS size distribution of **4c** in different water fraction (DMSO/water mixture, concentration: 10 μM).

VII. Cell culture and cytotoxicity

Cell culture: Hela cells were seeded in 96-well plate at the density of 1×10^5 cells per well with Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and a mixture of 0.1 mg/mL streptomycin and 100 units/mL penicillin, and then allowed to attach overnight at 37 °C under 5% CO_2. Hela cells were incubated with **3h**, **5j**, **5k**, and **5l** in different concentrations for 24 h. MTT solution (5 $mg \cdot mL^{-1}$) was added to each well for 4 hours at 37 °C. Then 100 μL DMSO was added to each well in order to dissolve the formazan crystals. The absorbance of 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 S11).

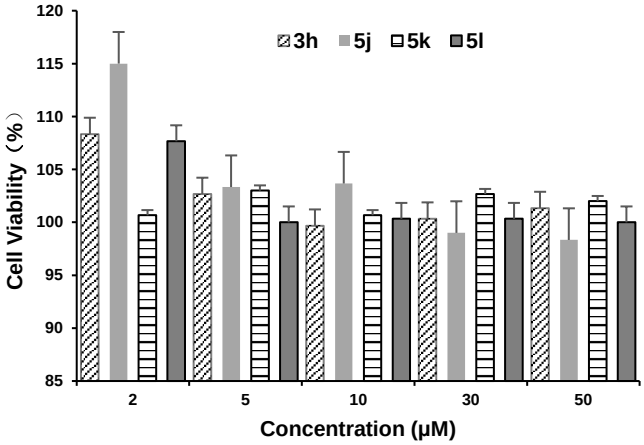


Figure S11. MTT assay of Hela incubation (12 h) with **3h**, **5j**, **5k**, and **5l** at different concentrations

Co-localization tests of 3h and Nile Red in lipid droplets imaging: Hela cells were seeded in glass bottom cell culture dishes at the density of 1×10^5 cells per dish with Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and a mixture of 0.1 mg/mL streptomycin and 100 units/mL penicillin, and then allowed to attach overnight at 37 °C under 5% CO_2. Hela cells were incubated with oleic acid (0.78 mM) for 4 h, and then stained with **3h** (10 μM) and Nile Red (5 μM) for 1 h, which were washed twice with PBS and imaged by a confocal microscope..

Co-localization tests of 5j and DiI in cell membrane imaging: Hela cells were seeded in glass bottom cell culture dishes at the density of 1×10^5 cells per dish with Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and a mixture of 0.1 mg/mL streptomycin and 100 units/mL penicillin, and then allowed to attach overnight at 37 °C under 5% CO_2. Hela cells were incubated with **5j** (10 μM) and DiI (1 μM) for 15 min, which were washed twice with PBS and imaged by a confocal microscope..

Co-localization tests of 5k and Mito-tracker Red in mitochondrion imaging: Hela cells were seeded in glass bottom cell culture dishes at the density of 1×10^5 cells per dish with Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and a mixture of 0.1 mg/mL streptomycin and 100 units/mL penicillin, and then allowed to attach overnight at 37 °C under 5% CO_2. Hela cells were incubated with **5k** (10 μM) and Mito-tracker Red (1 μM) for 2 h, which were washed twice with PBS and imaged by a confocal microscope..

Co-localization tests of 5l and Lyso-tracker Red in lysosome imaging: Hela cells were seeded in glass bottom cell culture dishes at the density of 1×10^5 cells per dish with Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and a mixture of 0.1 mg/mL streptomycin and 100 units/mL penicillin, and then allowed to attach overnight at 37 °C under 5% CO_2. Hela cells were incubated with **5l** (10 μM) and Lyso-tracker Red (1 μM) for 1 h, which were washed twice with PBS and imaged by a confocal microscope..

VIII. References

1. M. Milen, T. Földesi, A. Dancsó, G. Simig, B. Volk, Synthesis of three new tricyclic ring systems: pyrrolotriazepines condensed with an imidazole, a triazole, or a tetrazole ring. *Synlett* **2015**, *26*, 2418–2424.

2. J. Guo, F. Zhao, W. Yin, M. Zhu, C. Hao, Y. Pang, T. Wu, J. Wang, D. Zhao, H. Li, M. Cheng, Design, synthesis, structure-activity relationships study and X-ray crystallography of 3-substituted-indolin-2-one-5-carboxamide derivatives as PAK4 inhibitors, *Eur. J. Med. Chem.* **2018**, *155*, 197–209.

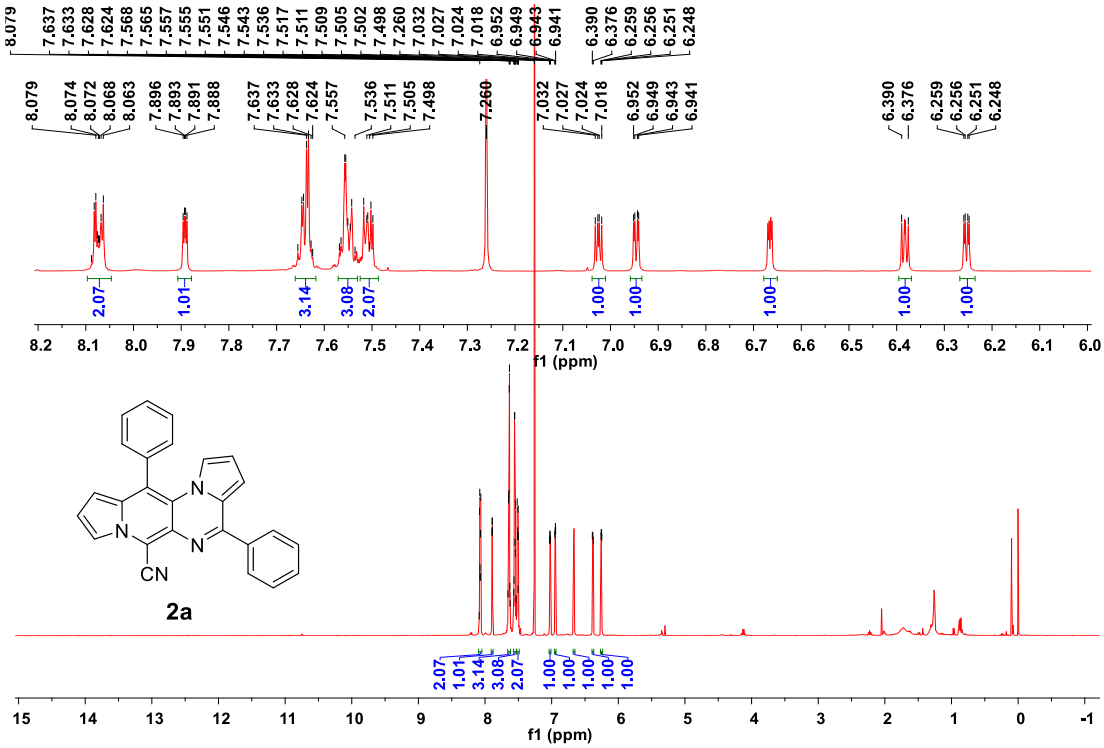
3. C. He, Z. Wang , Y. Chen, G. Zhang, Y. Yu, Palladium(II)-catalyzed C(sp)-C(sp^2) coupling: a direct approach to multi-substituted pyrrolo[1,2-a]pyrazines, *Synthesis* 2021, *53*, 2051–2056.

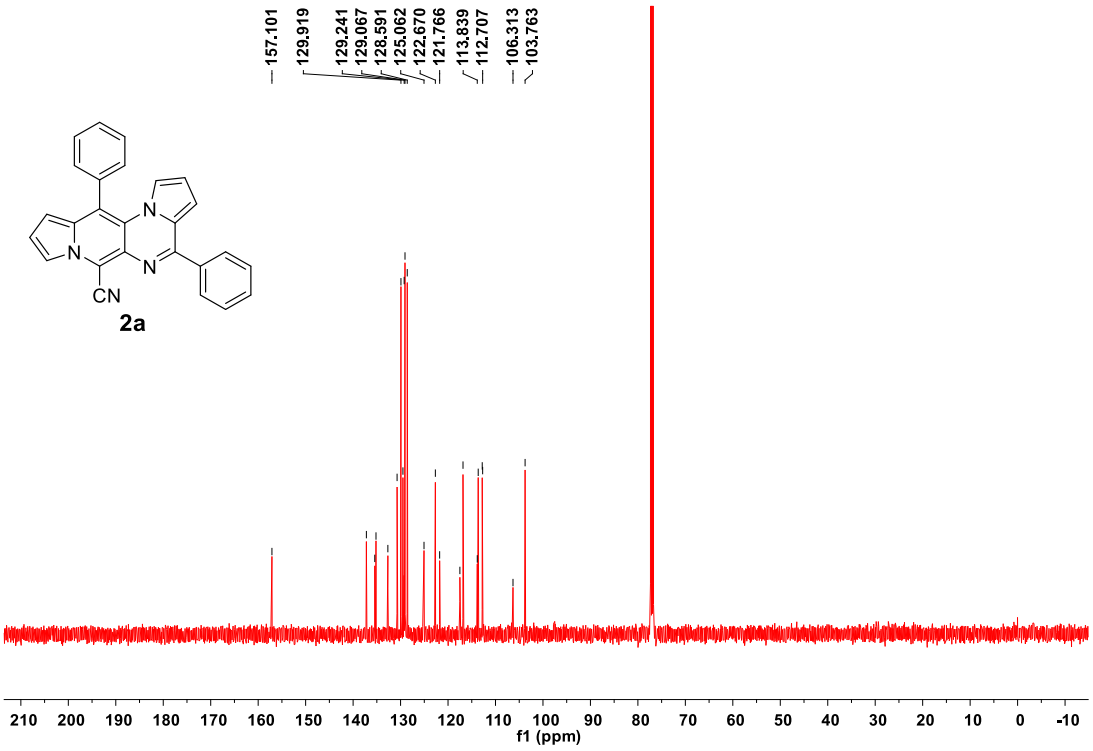
4. H. H. Seltzman, C. Shiner, E. E. Hirt, A. F. Gilliam, B. F. Thomas, R. Maitra, R. Snyder, S. L. Black, P. R. Patel, Y. Mulpuri, I. Spigelman, Peripherally selective cannabinoid 1 receptor (CB1R) agonists for the treatment of neuropathic pain, *J. Med. Chem.* **2016**, *59*, 7525–7543

5. X. C. Chen, G. X. Tang, W. H. Luo, W. Shao, J. Dai, S. T. Zeng, Z. S. Huang, S. B. Chen, J. H. Tan, Monitoring and modulating mtDNA G-quadruplex dynamics reveal its close relationship to cell glycolysis, *J. Am. Chem. Soc.* **2021**, *143*, 20779–20791.

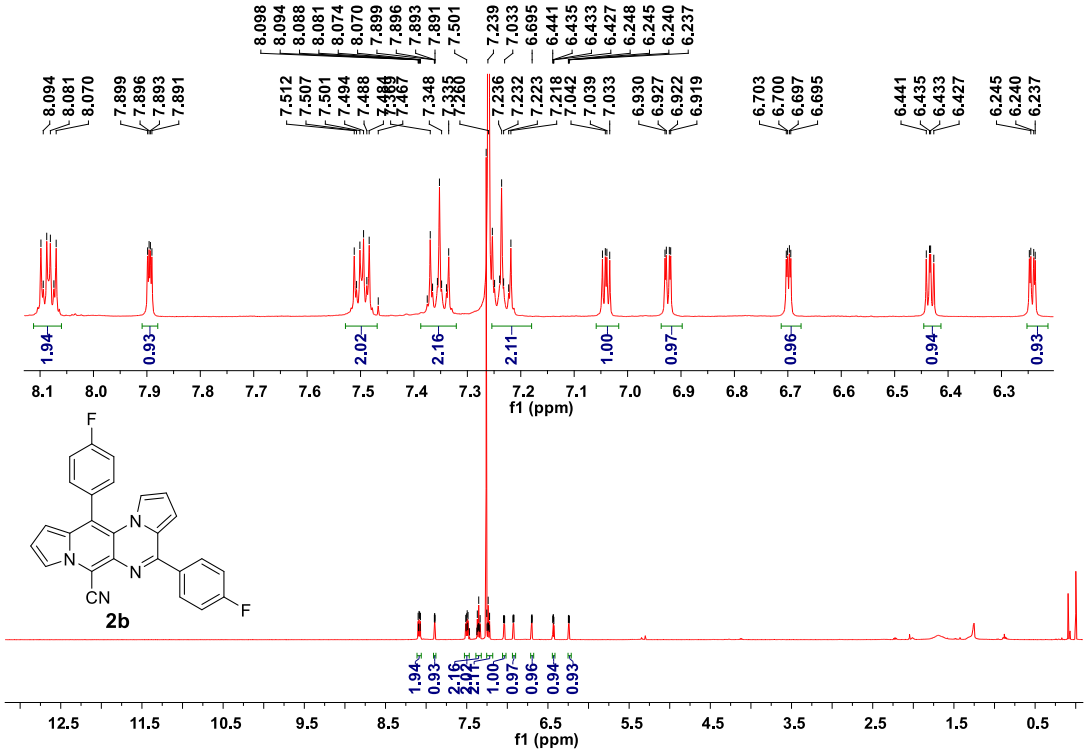
IX. NMR spectroscopic data

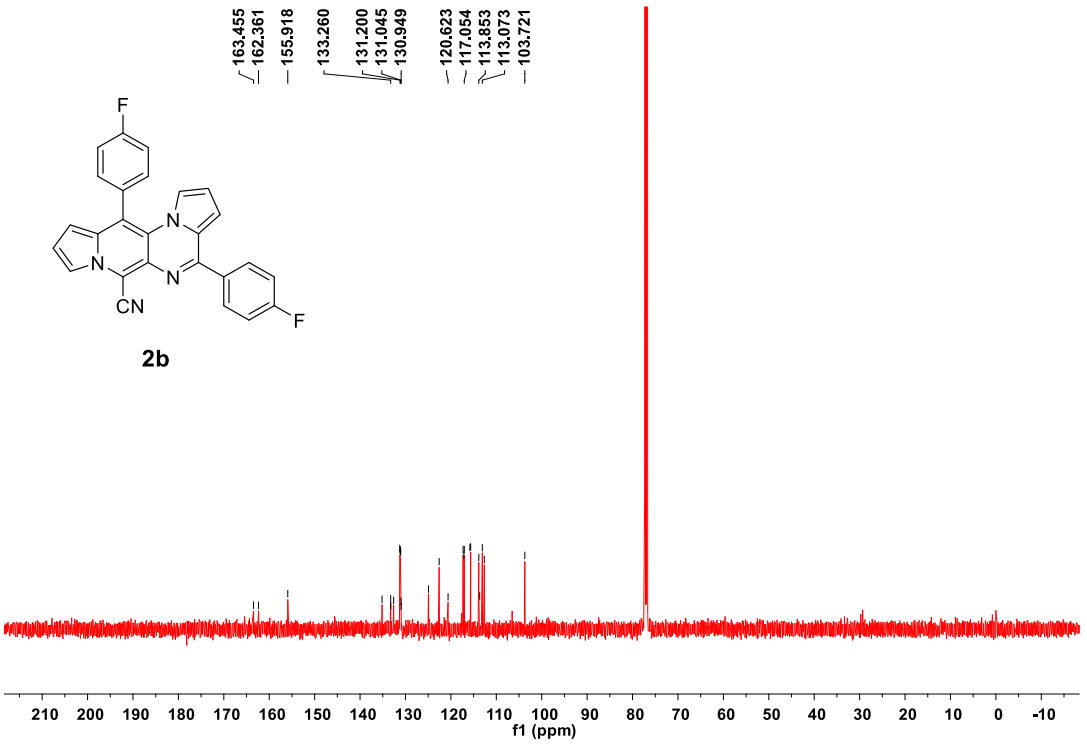
4,11-Diphenylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2a)



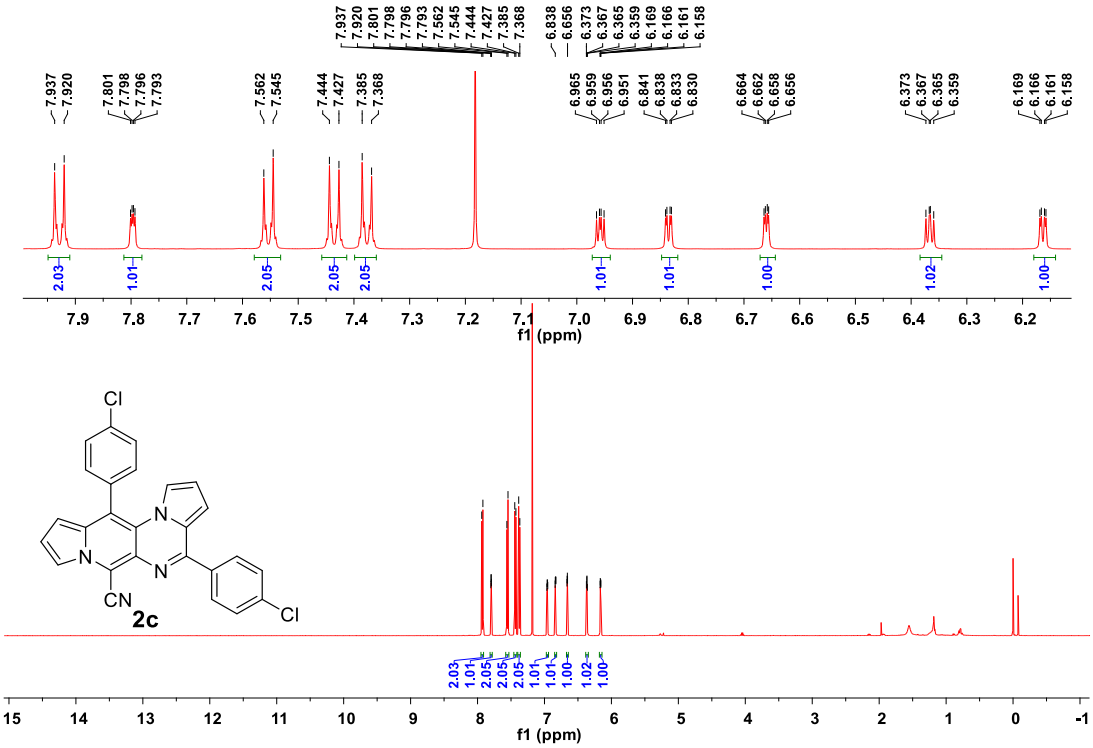


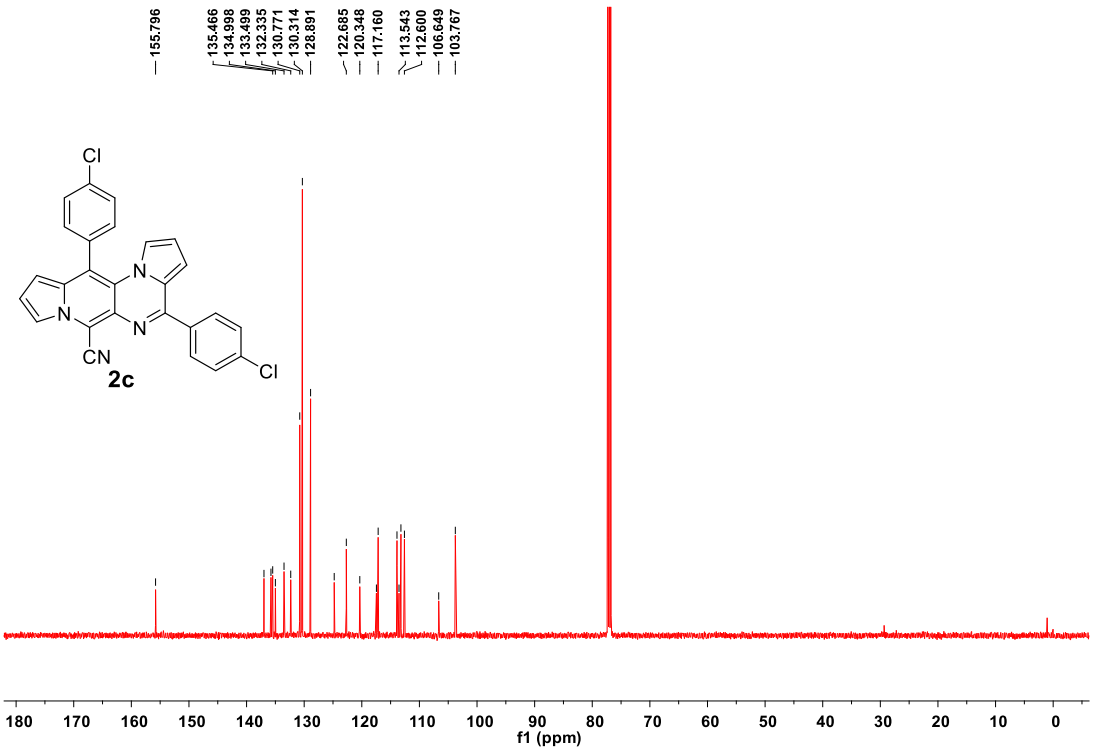
4,11-Bis(4-fluorophenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2b)



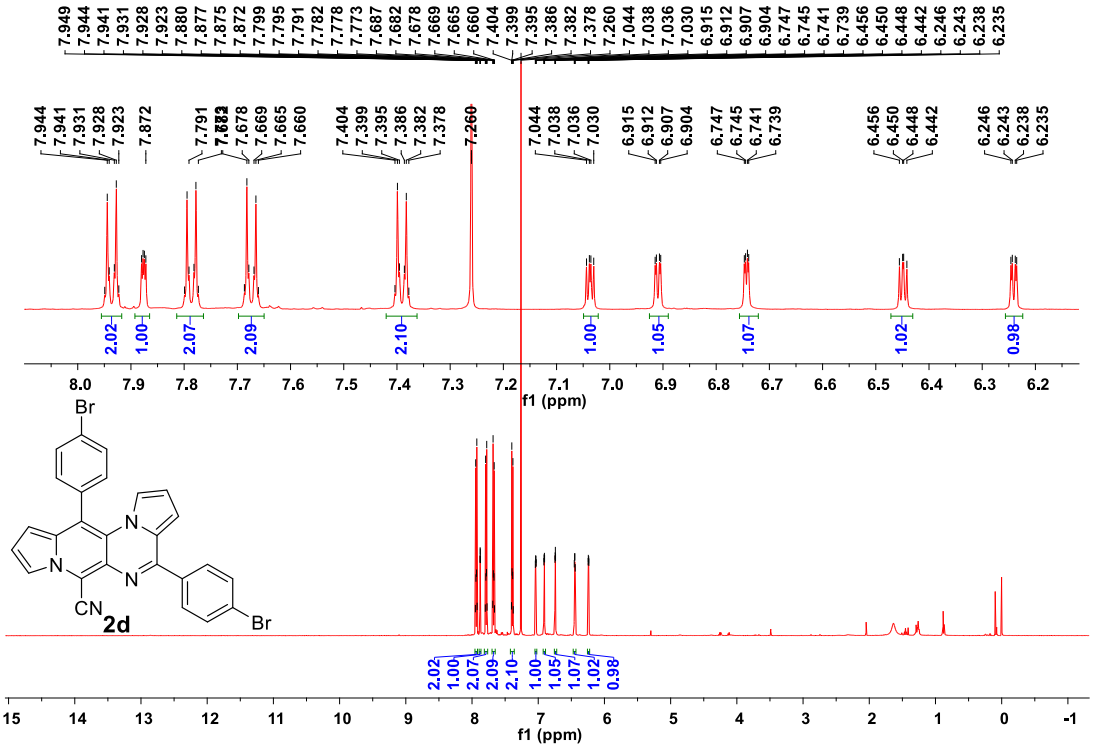


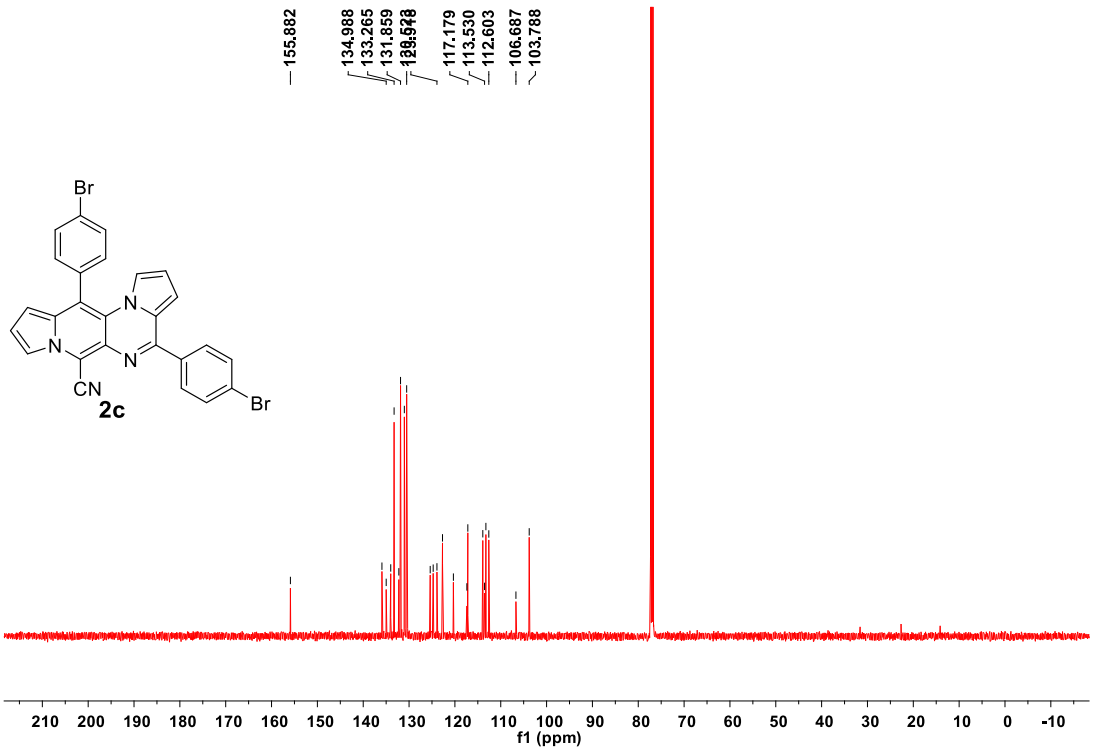
4,11-Bis(4-chlorophenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2c)



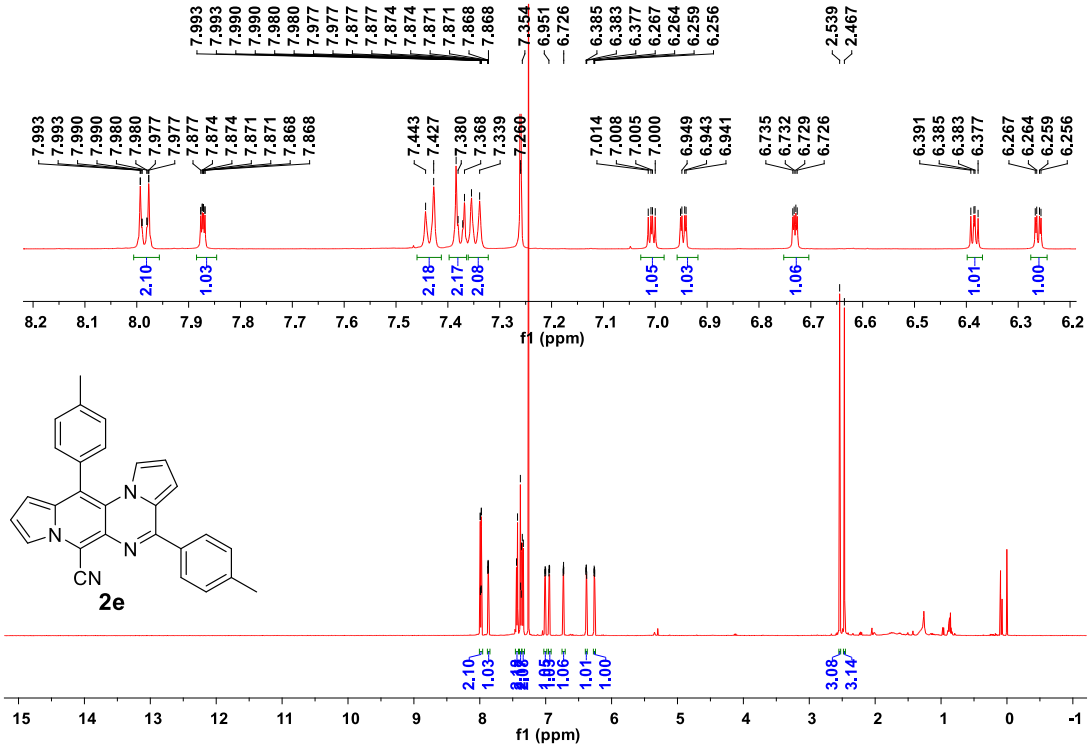


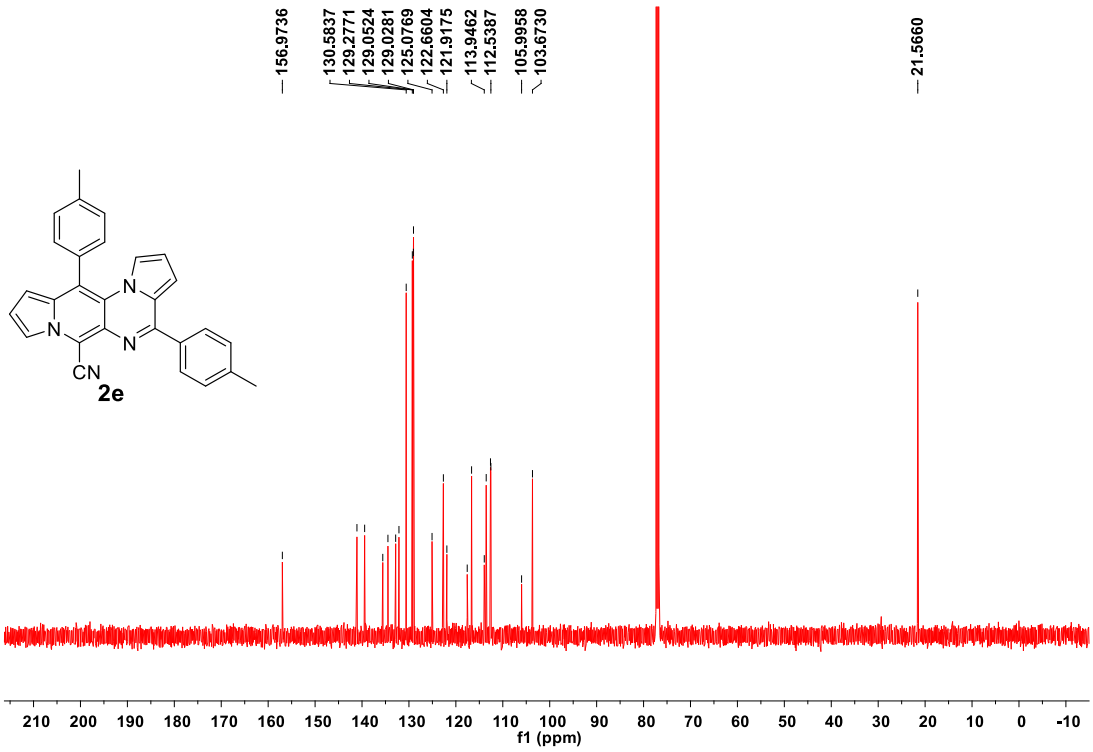
4,11-Bis(4-bromophenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2d)



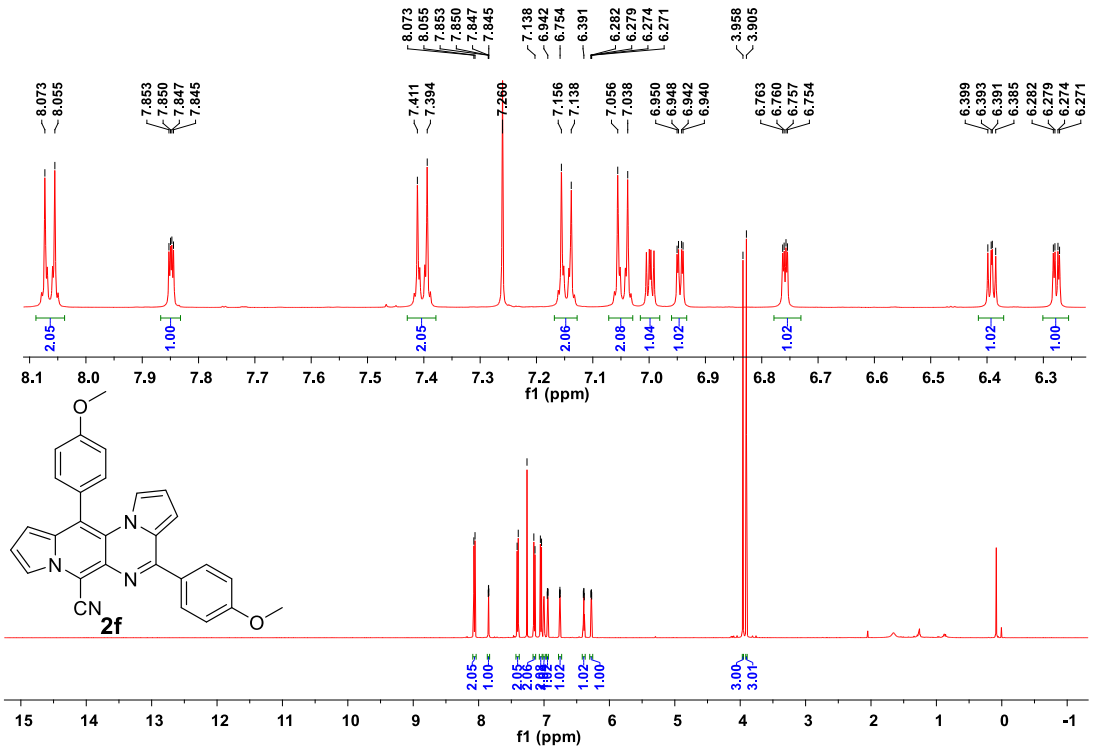


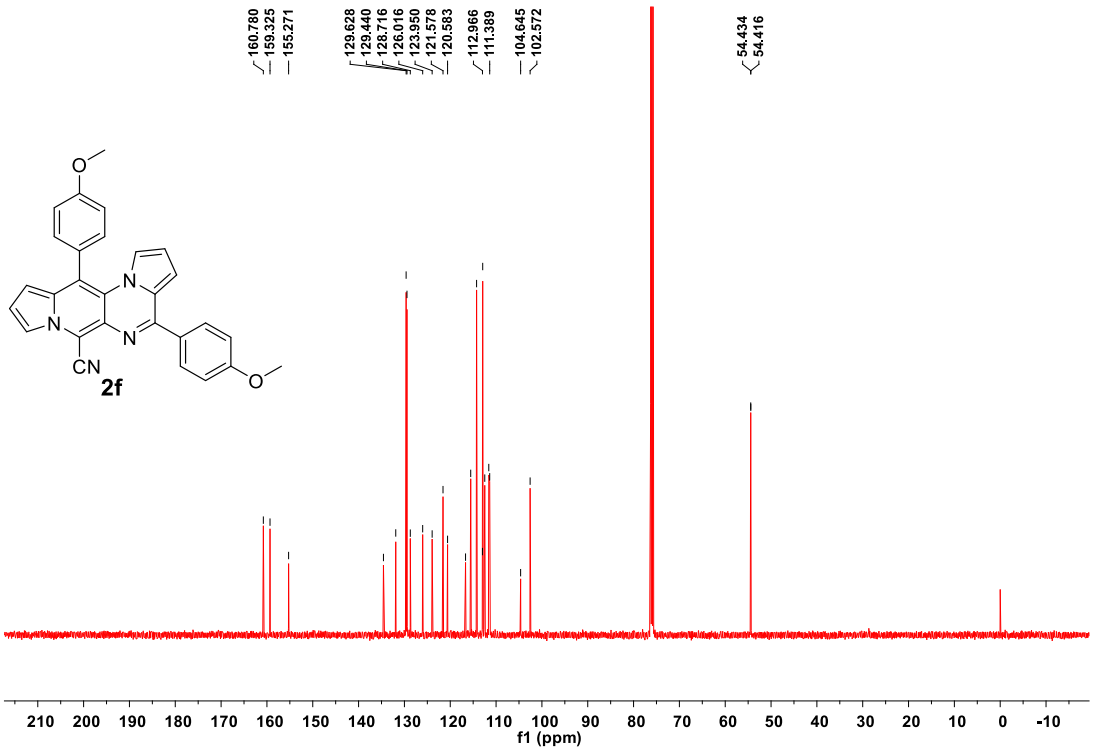
4,11-Di-p-tolylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2e)



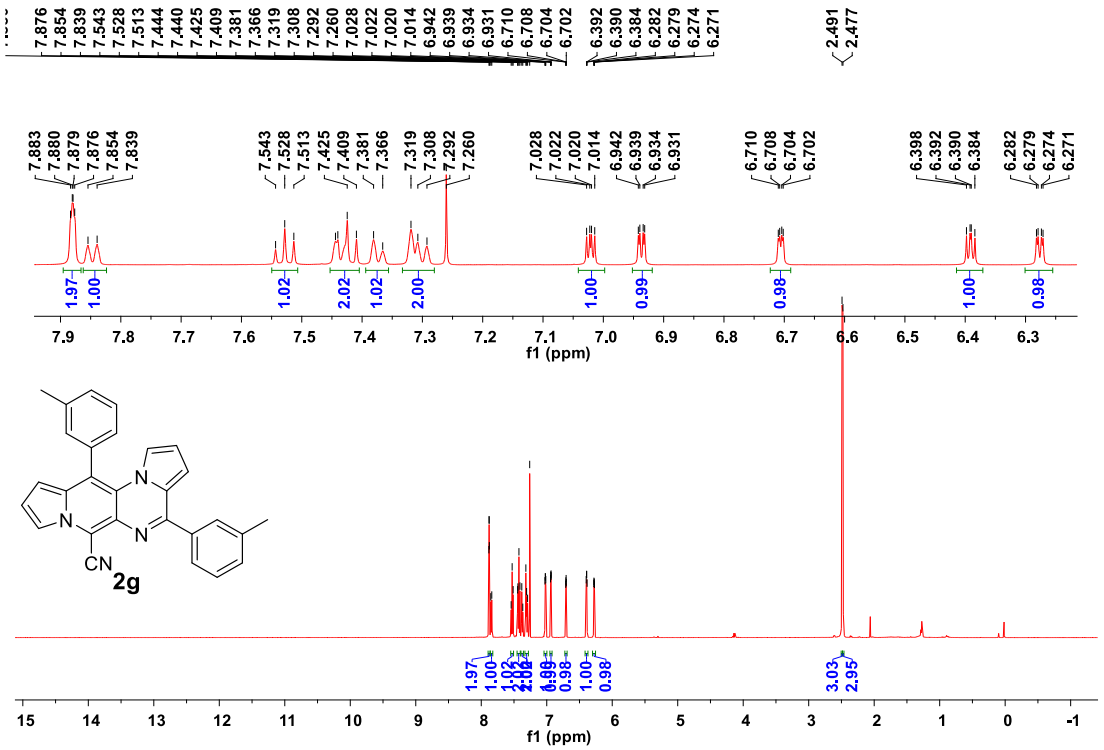


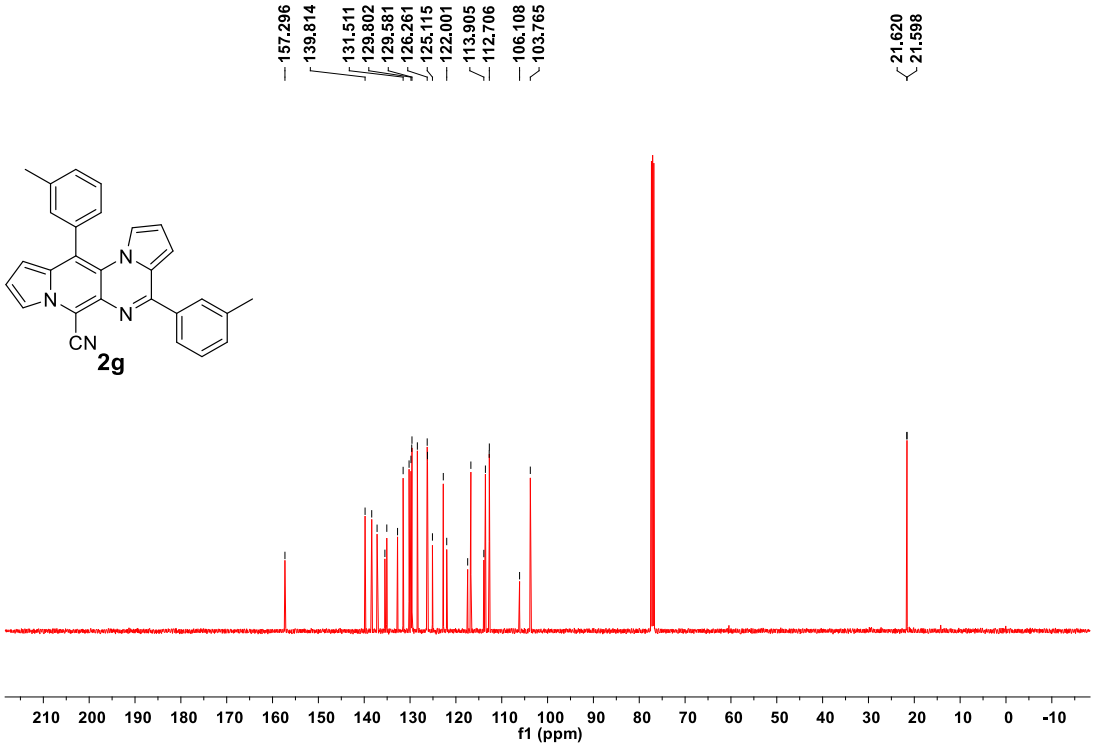
4,11-Bis(4-methoxyphenyl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2f)



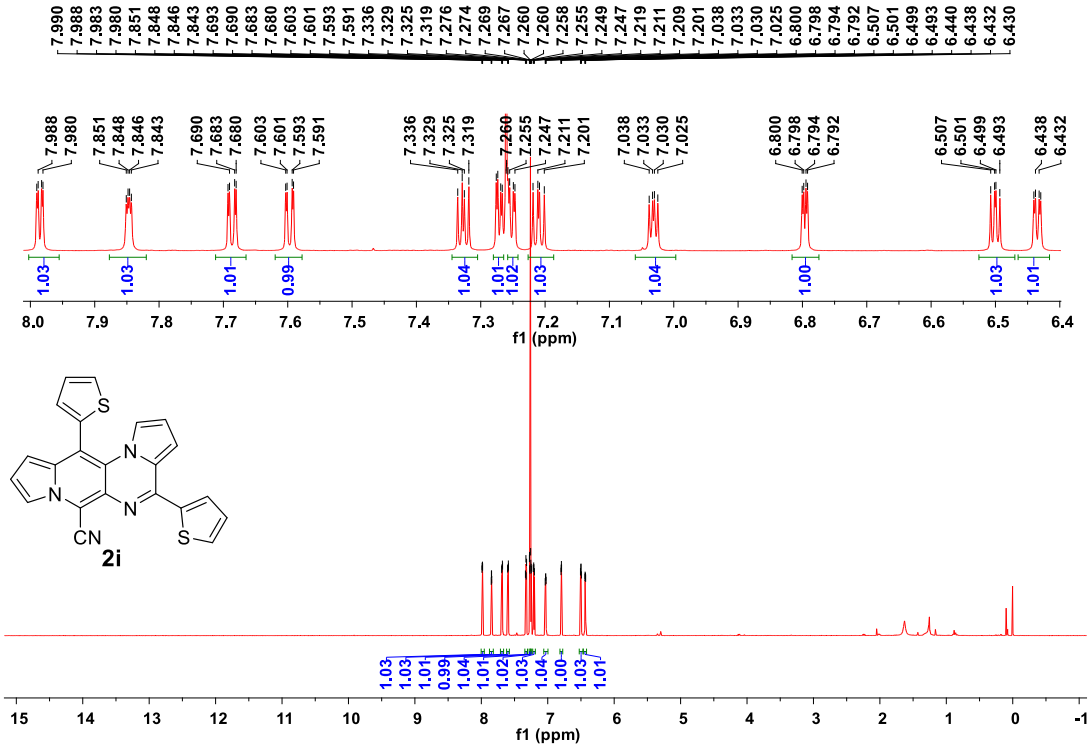


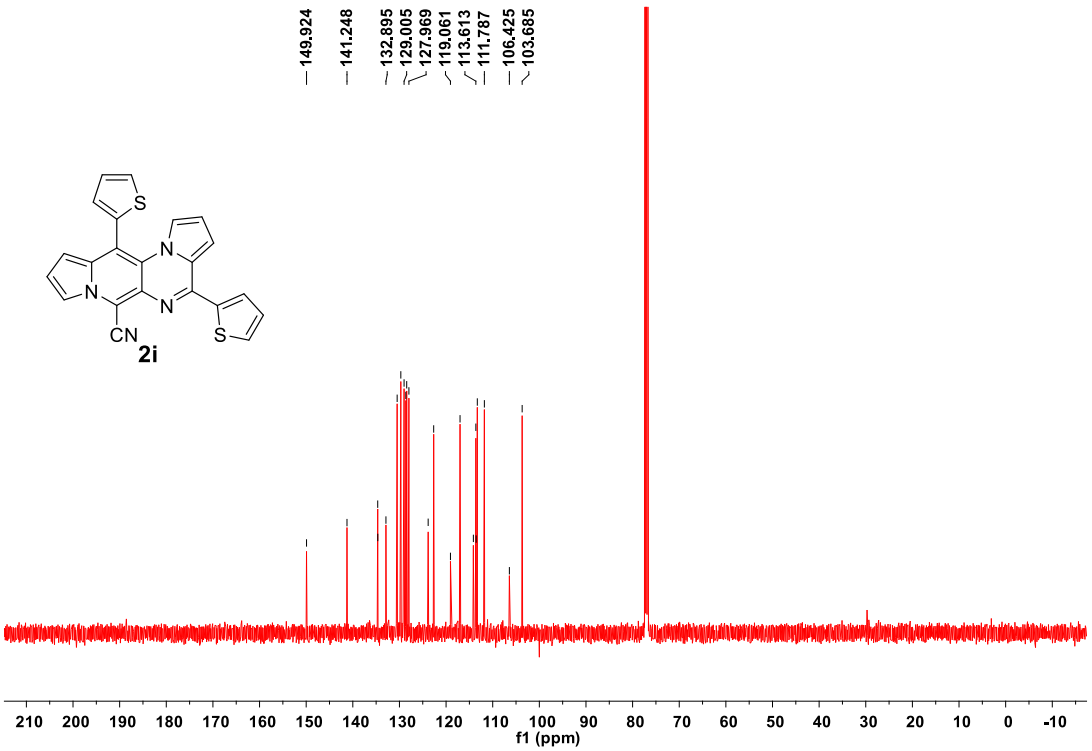
4,11-Di-o-tolylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2g)



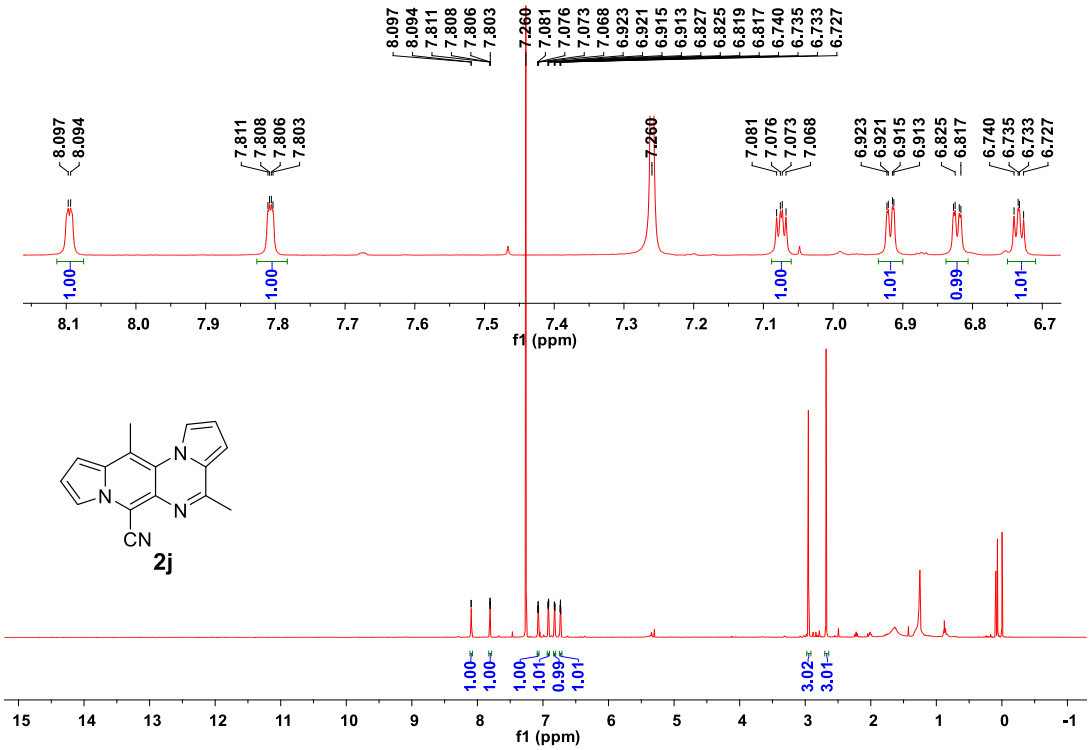


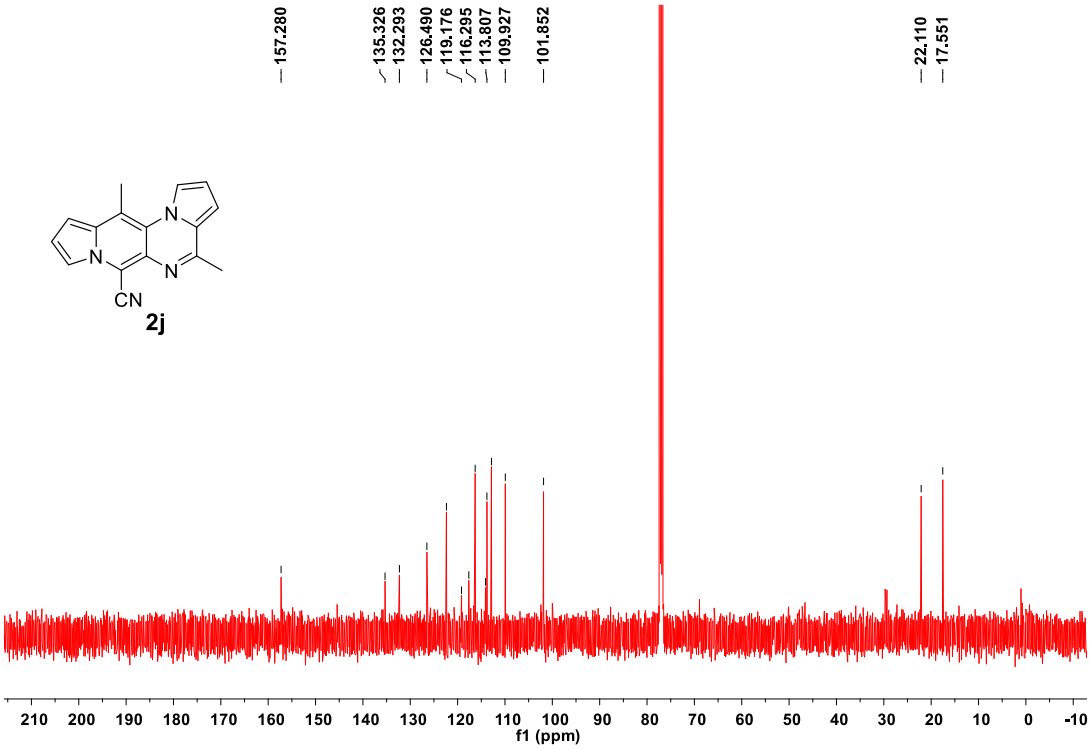
4,11-Di(thiophen-2-yl)pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2i)



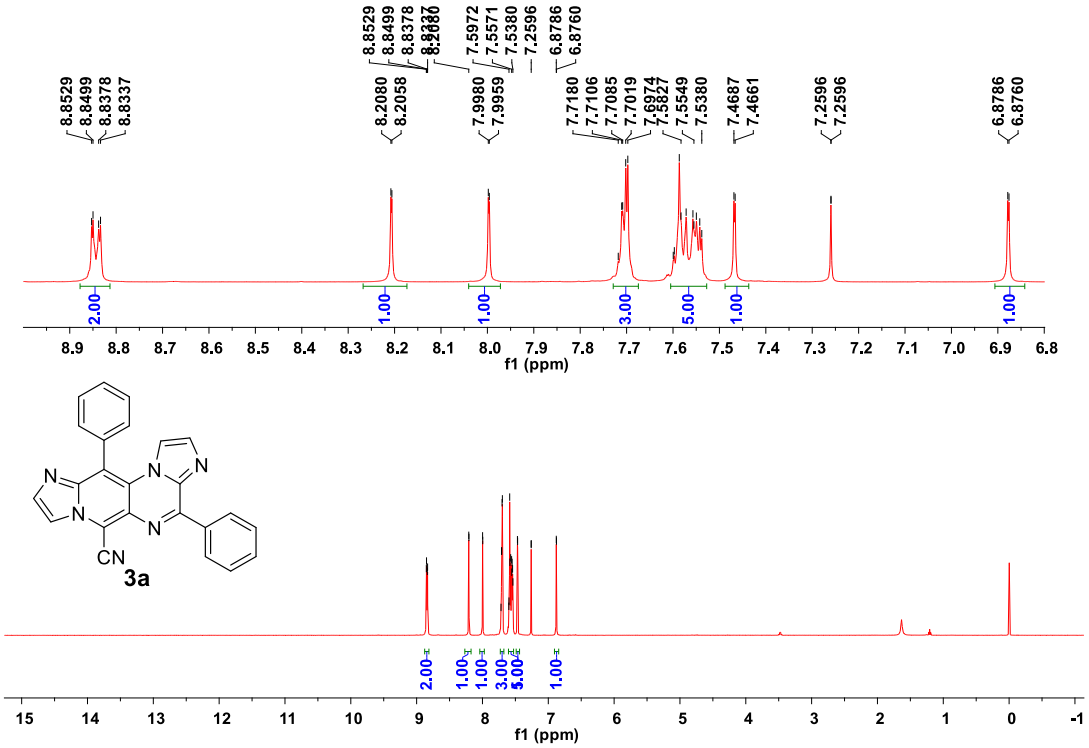


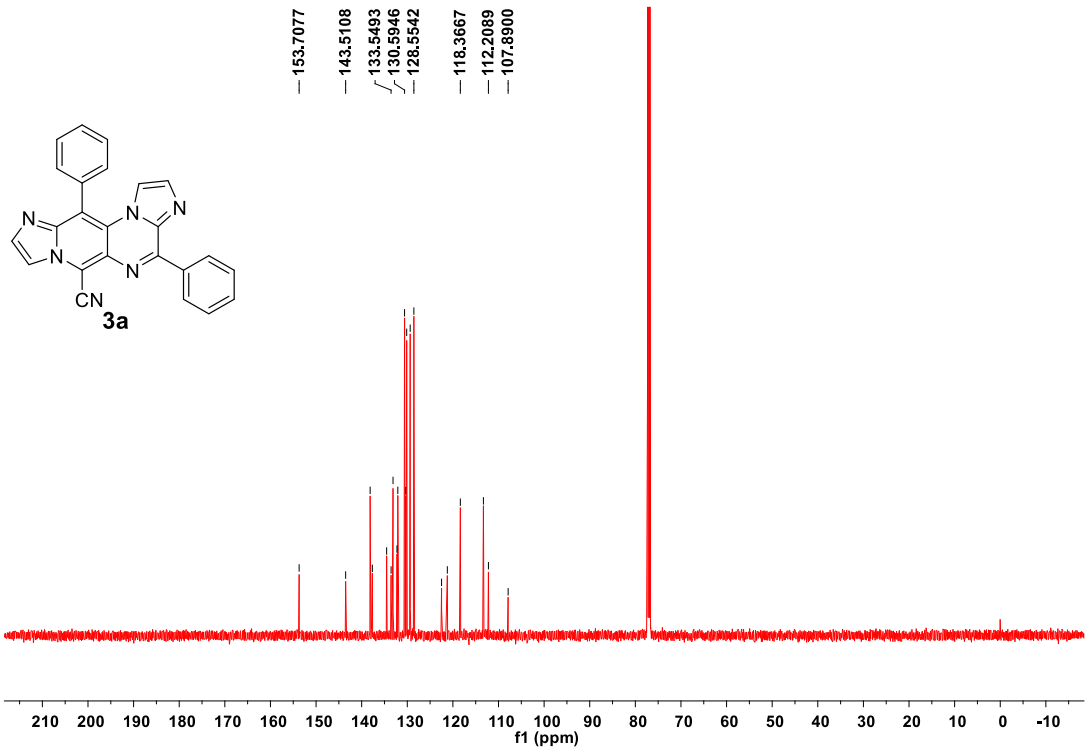
4,11-Dimethylpyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2j)



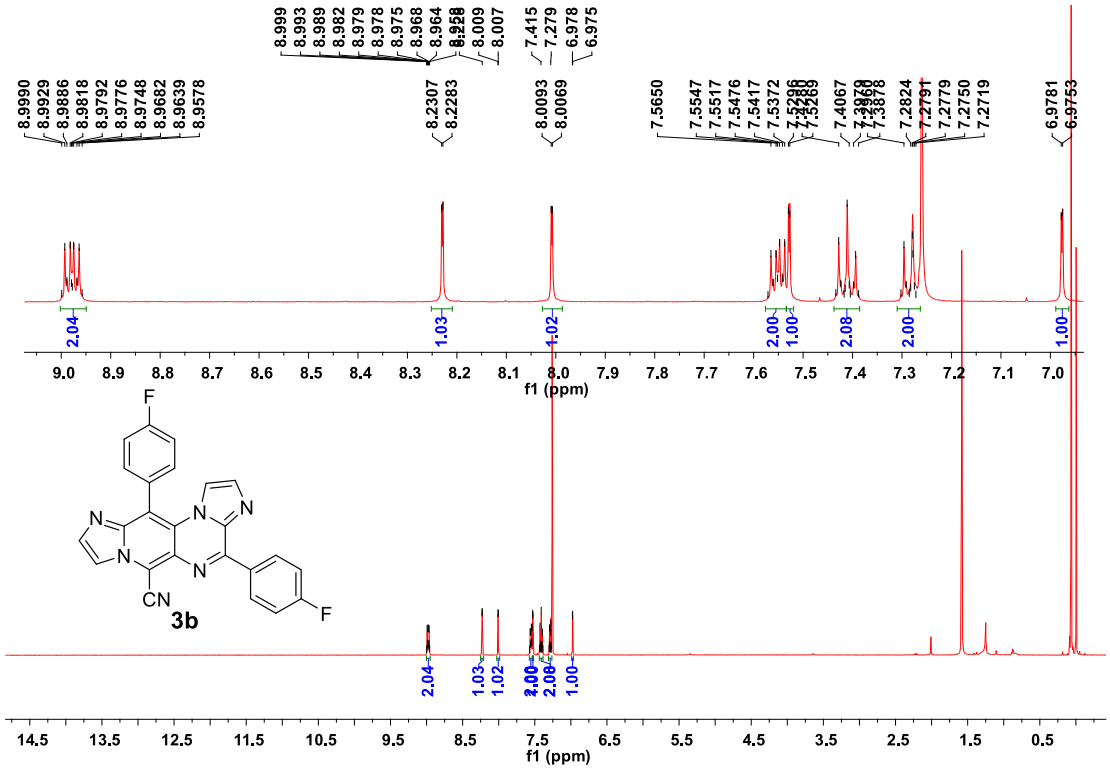


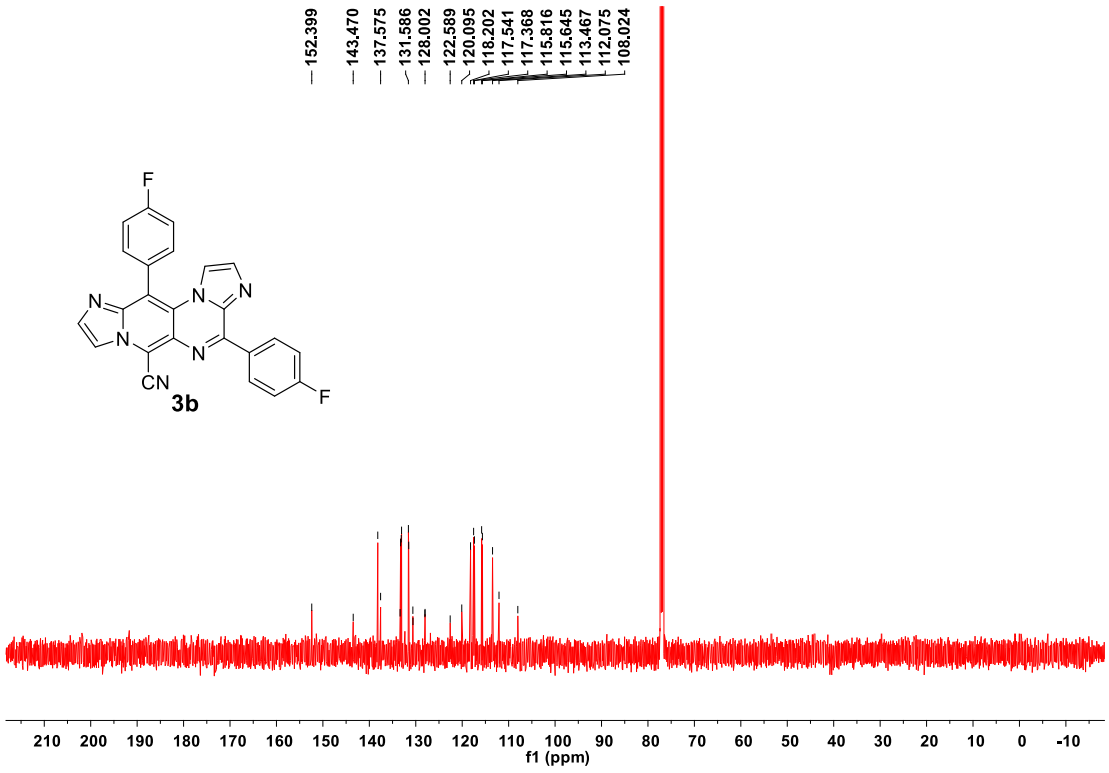
4,11-Diphenylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3a)



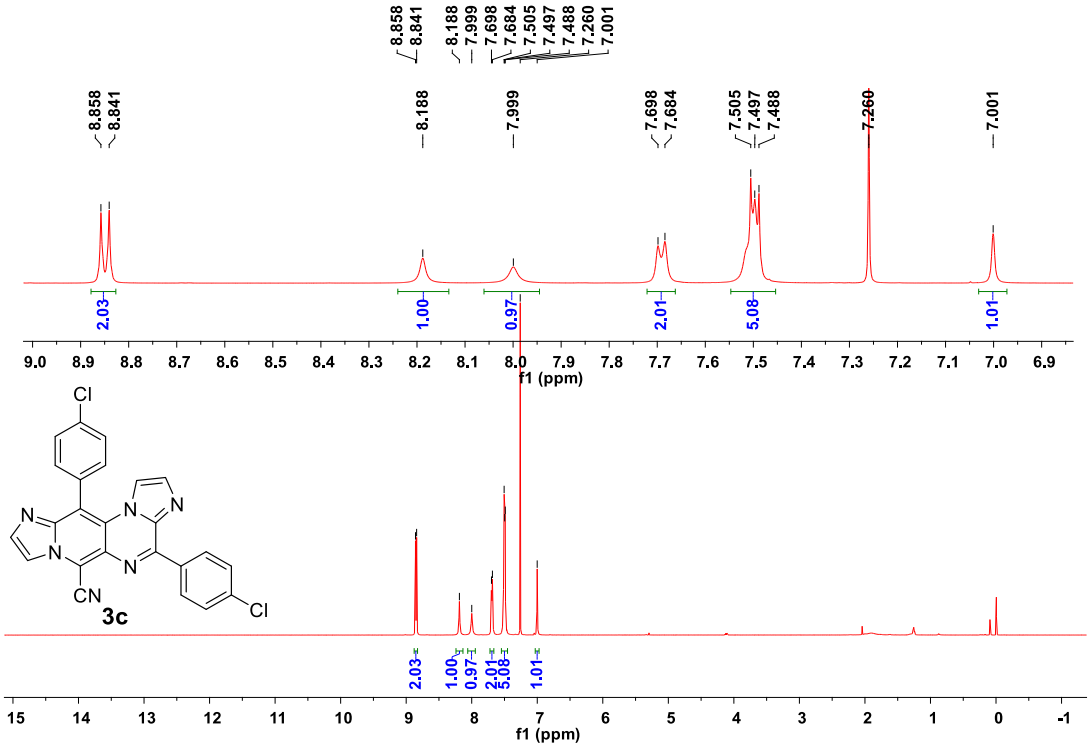


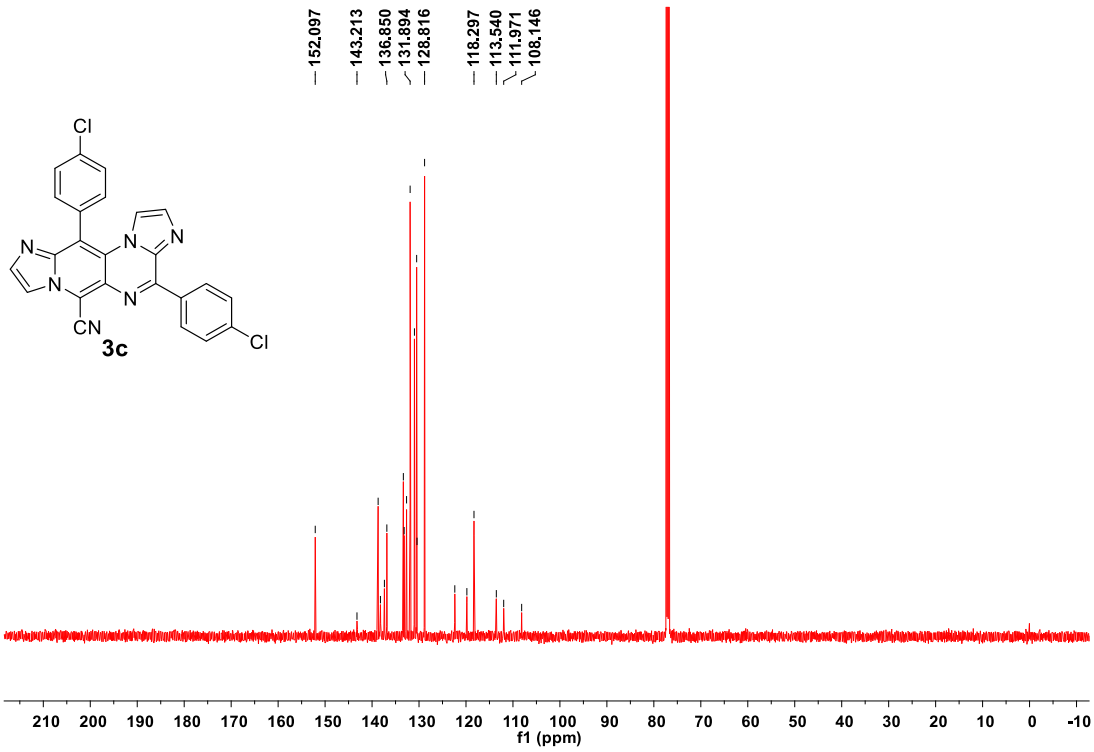
4,11-Bis(4-fluorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3b)



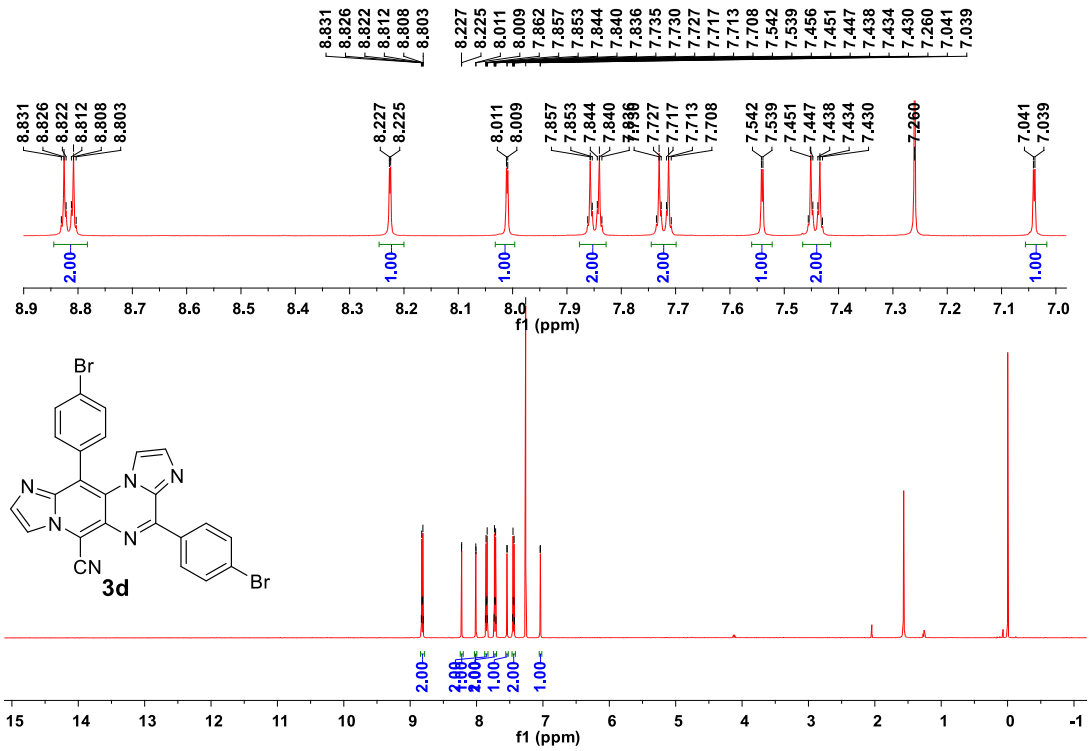


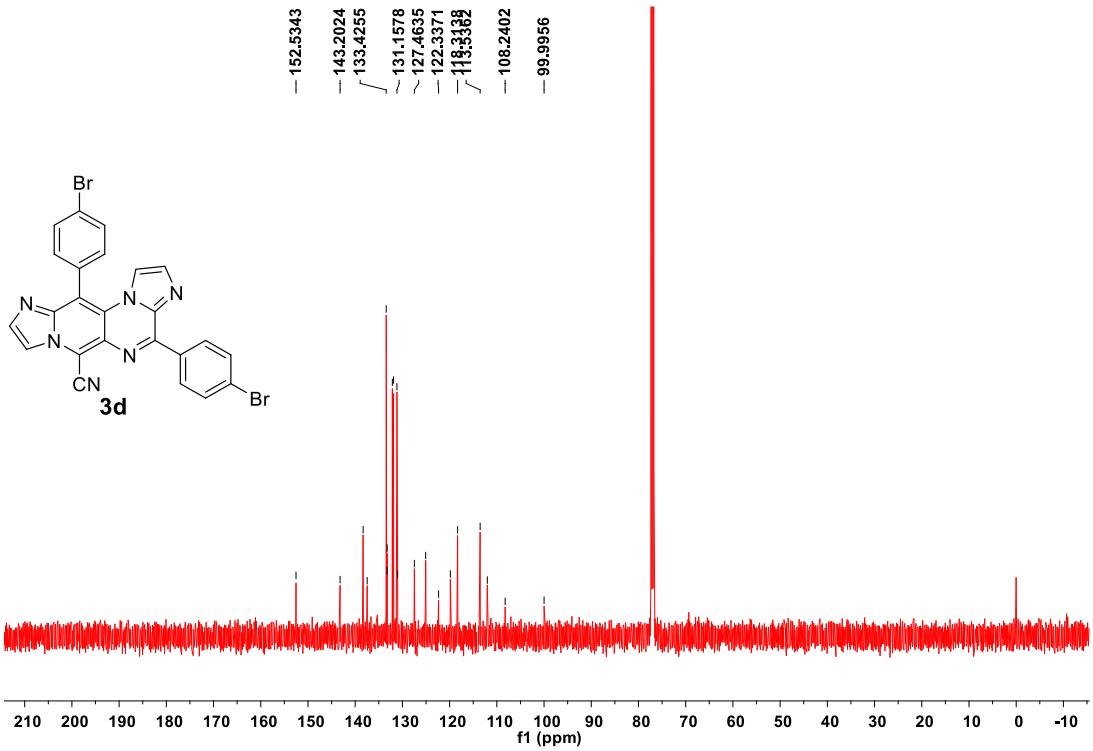
4,11-Bis(4-chlorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3c)



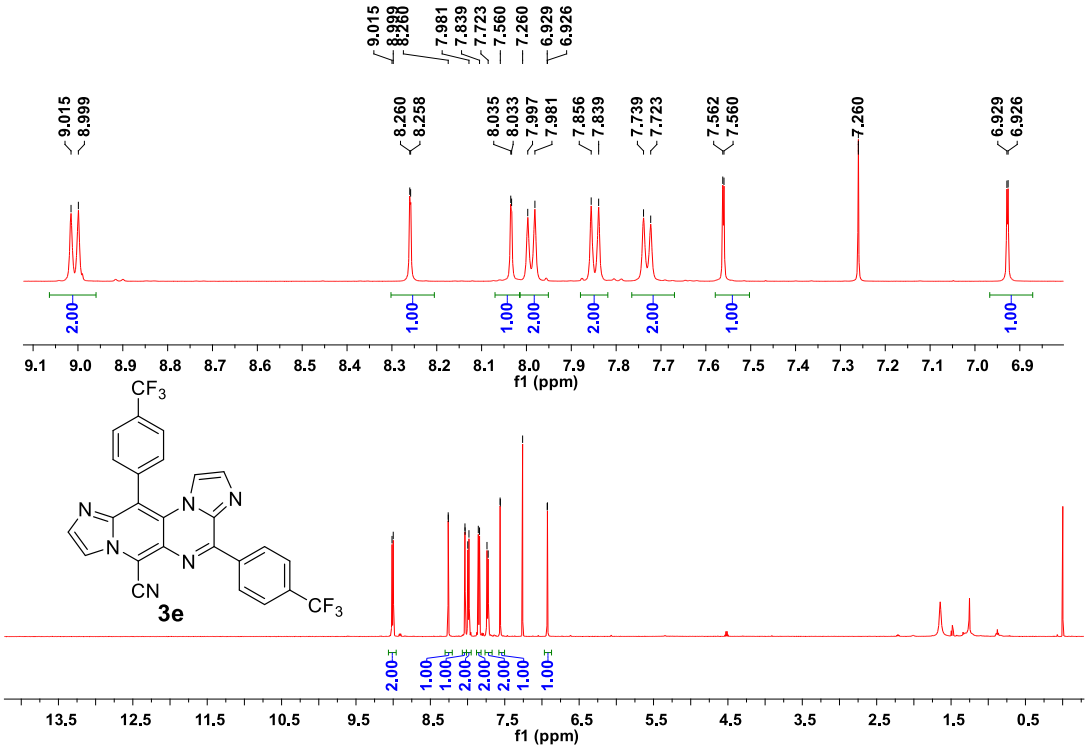


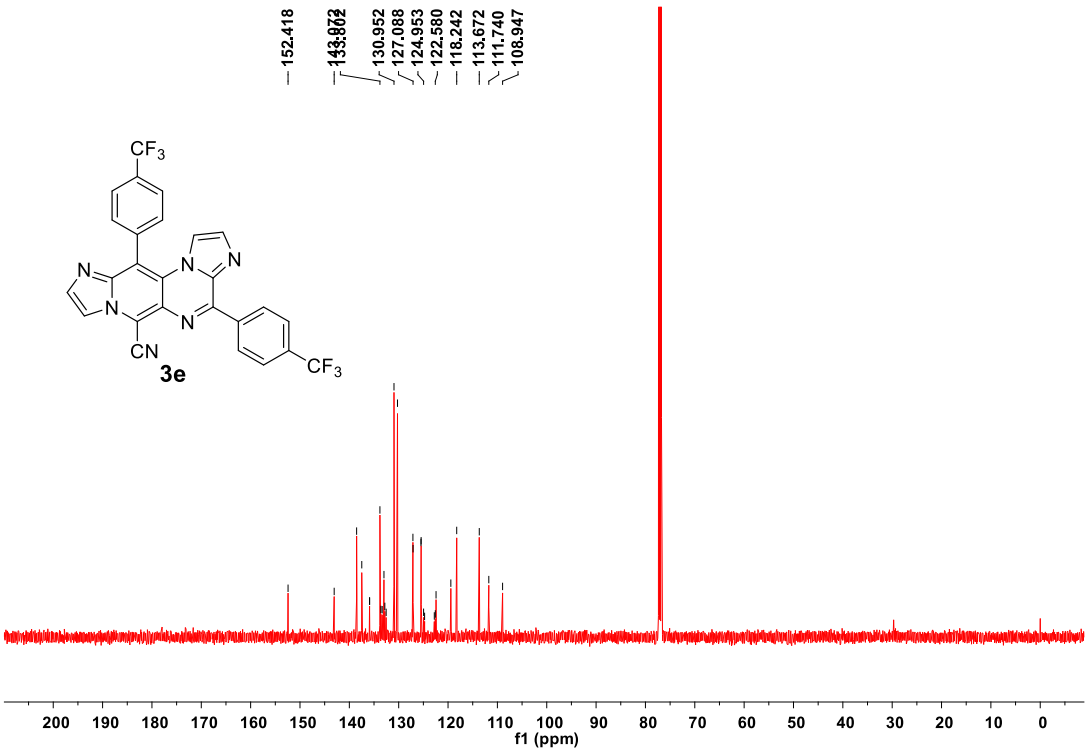
4,11-Bis(4-bromophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3d)



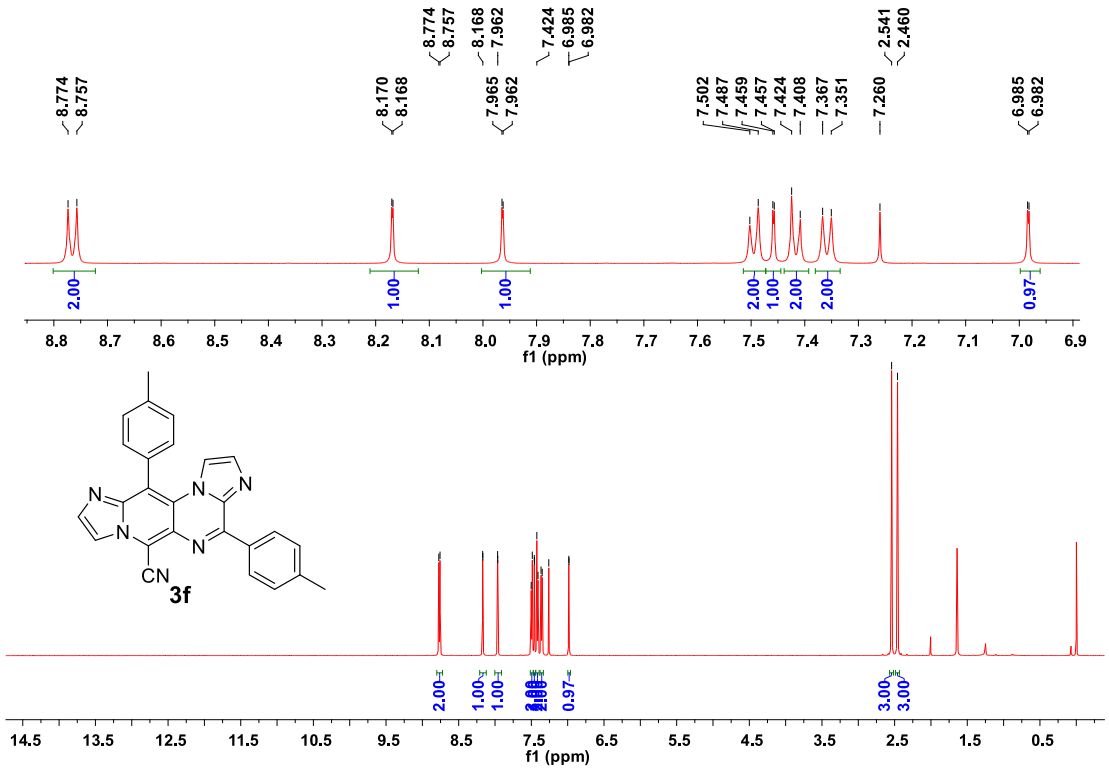


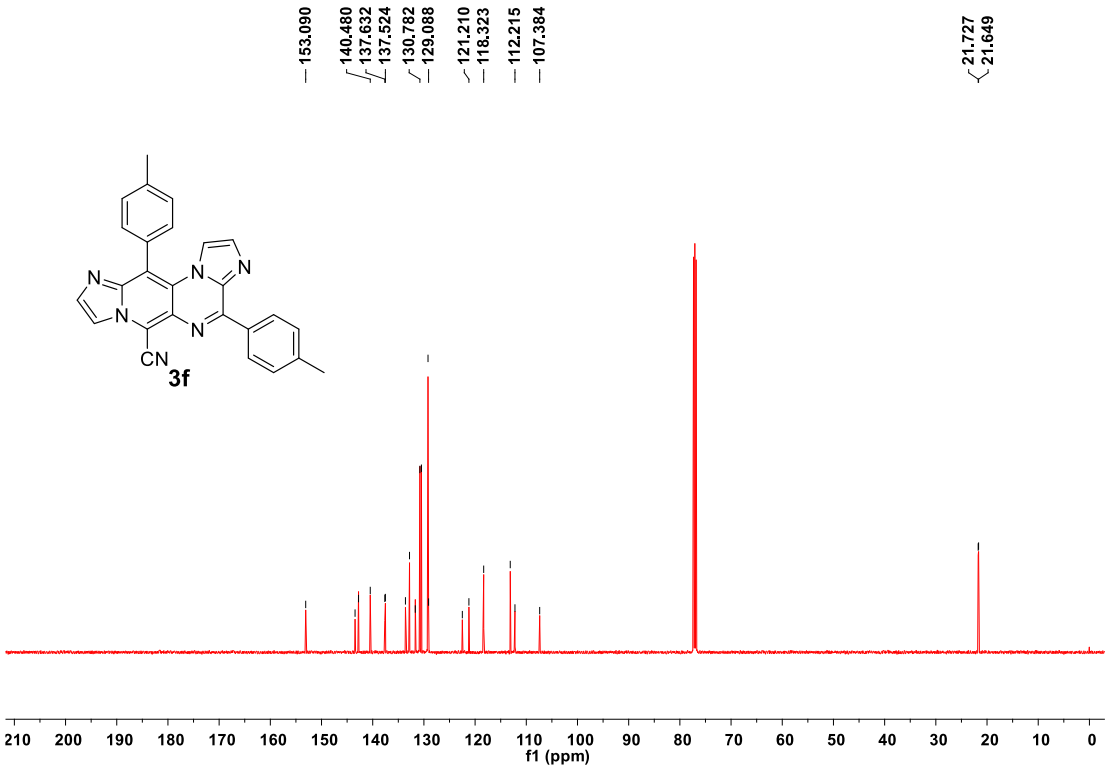
4,11-Bis(4-(trifluoromethyl)phenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3e)



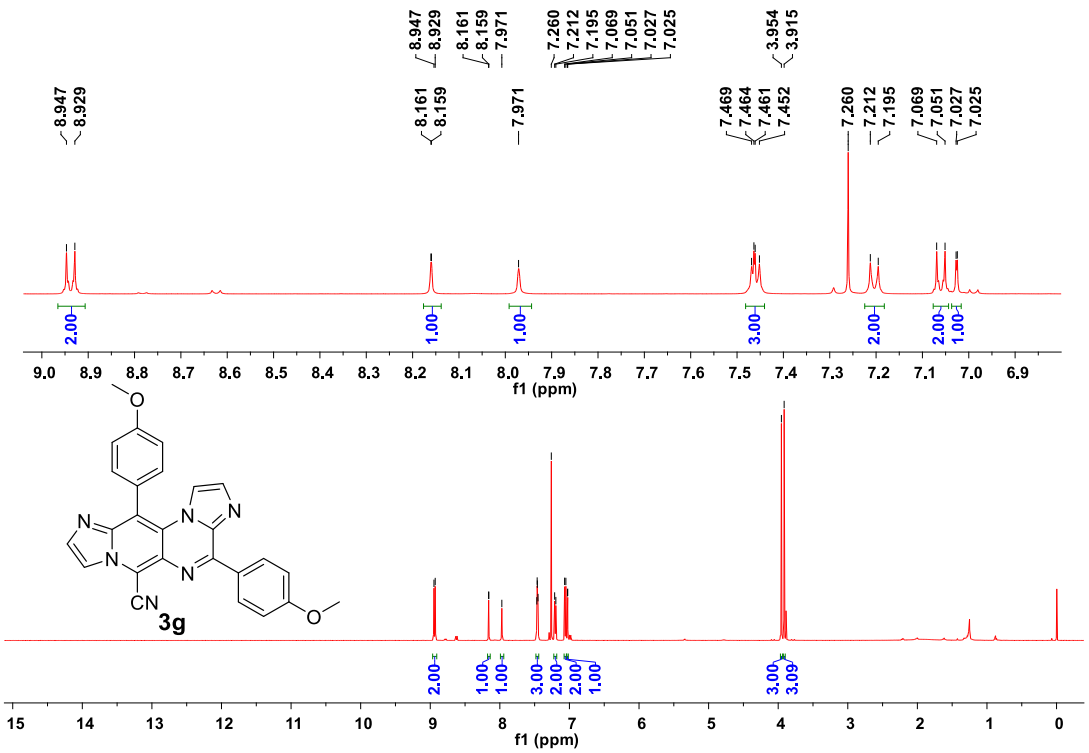


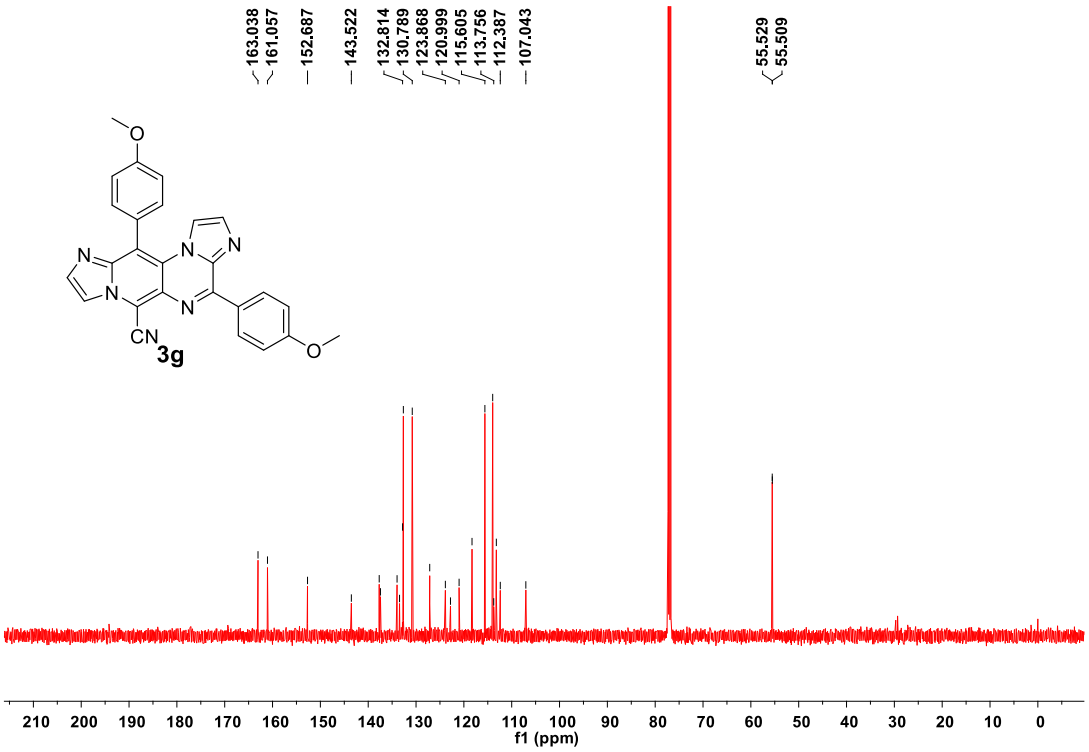
4,11-Di-p-tolylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3f)



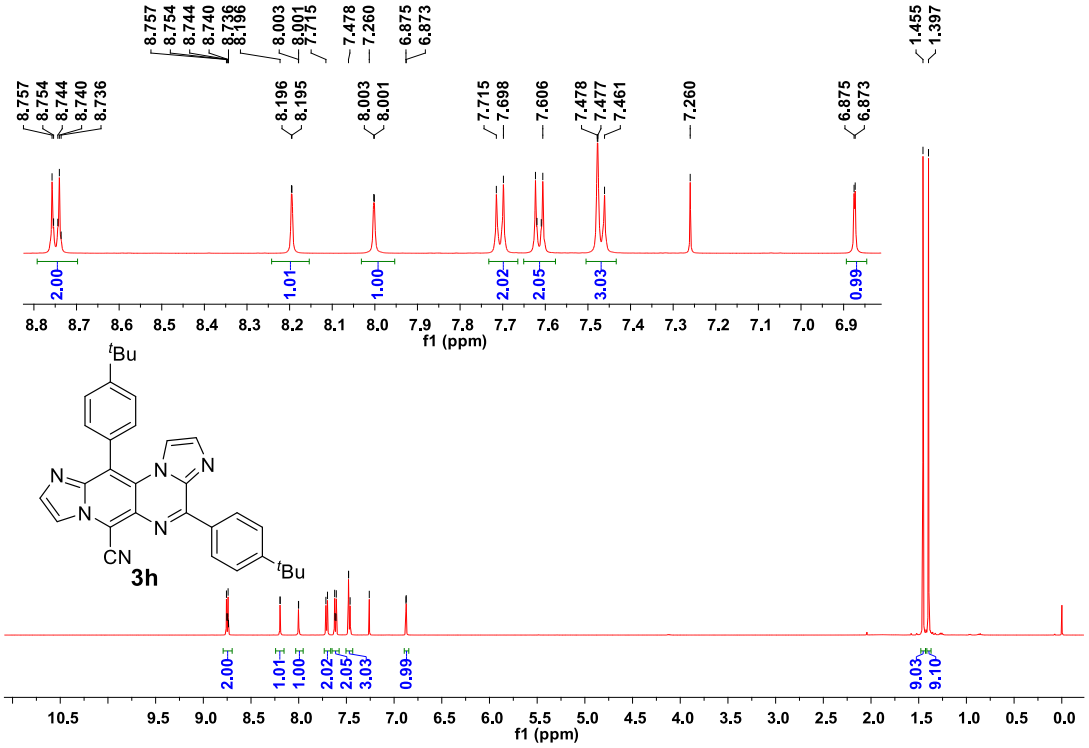


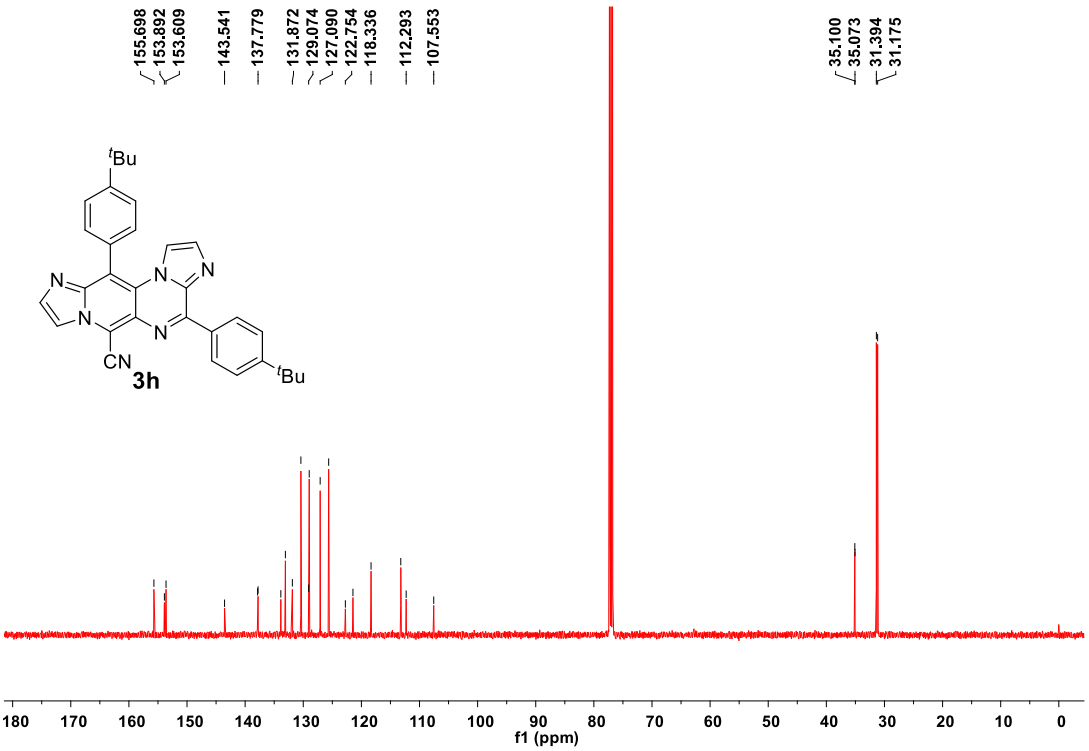
4,11-Bis(4-methoxyphenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3g)



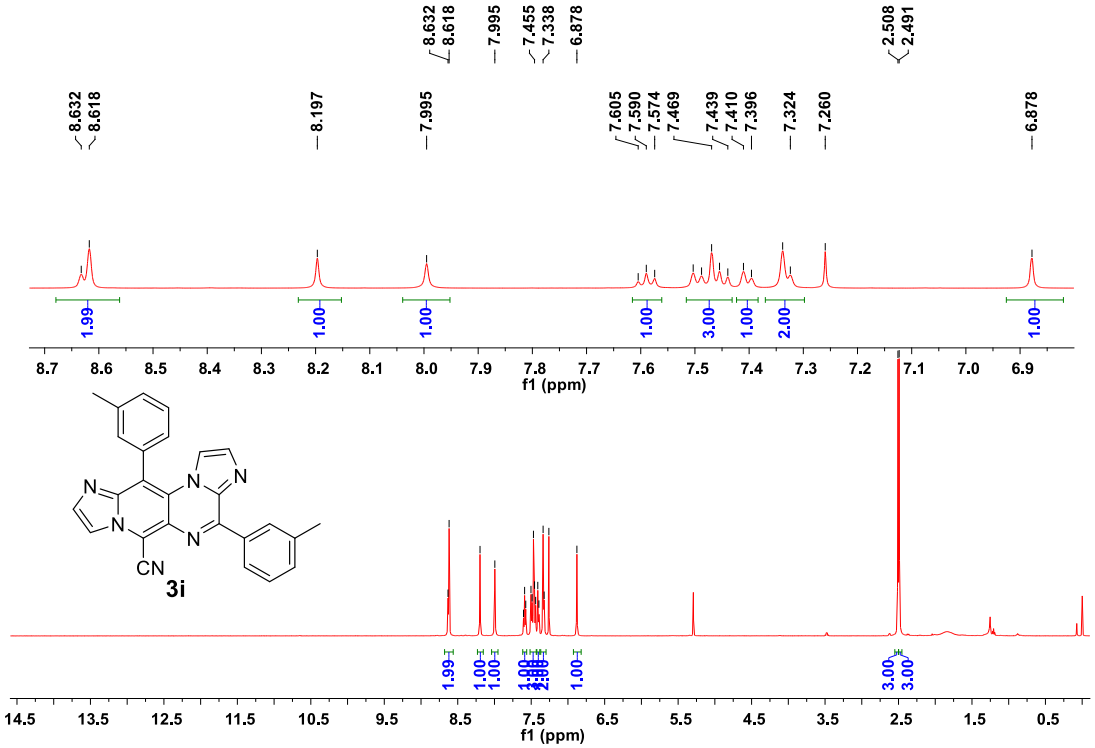


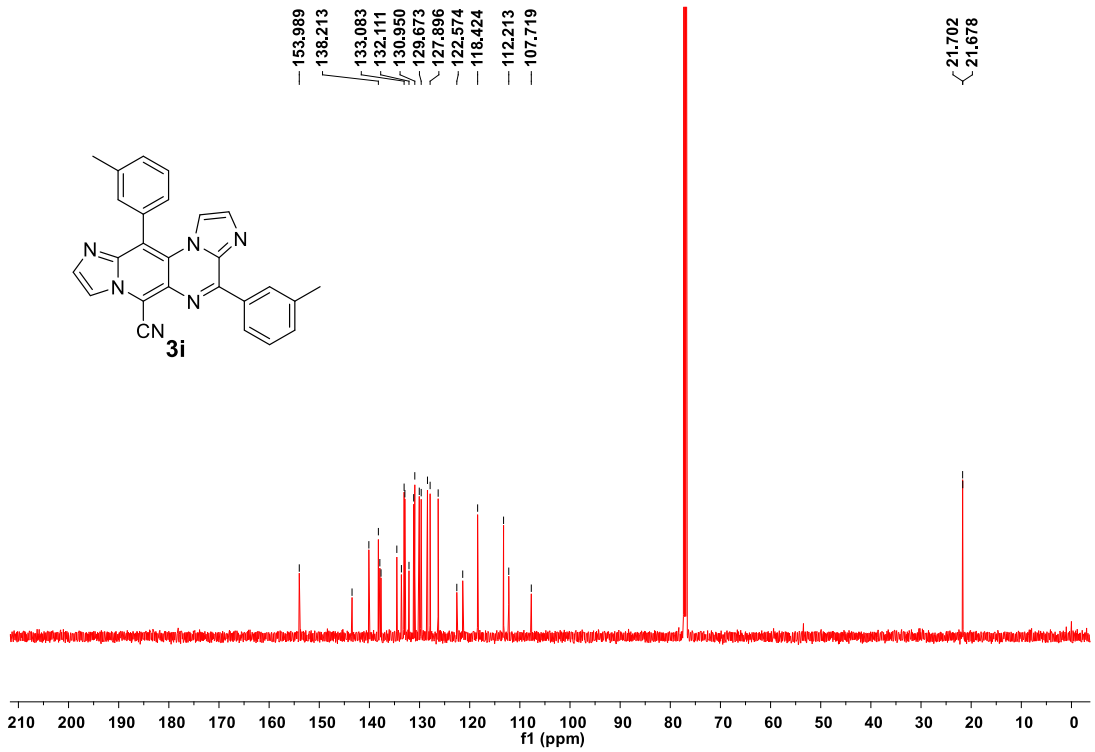
4,11-Bis(4-(tert-butyl)phenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3h)



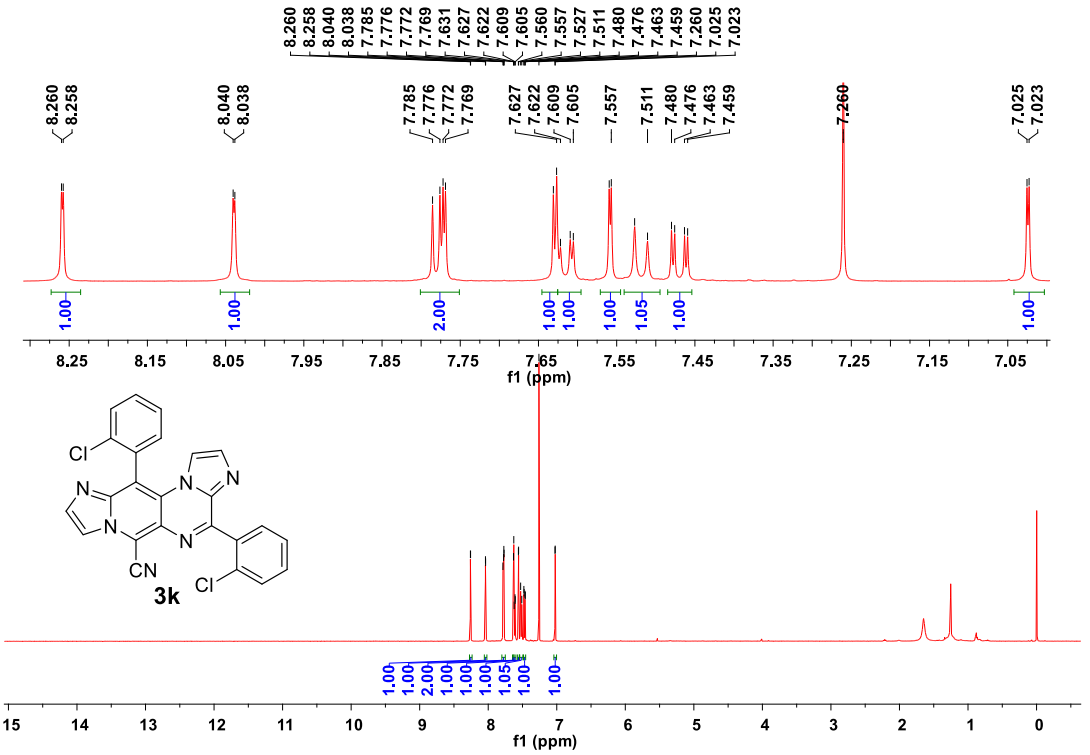


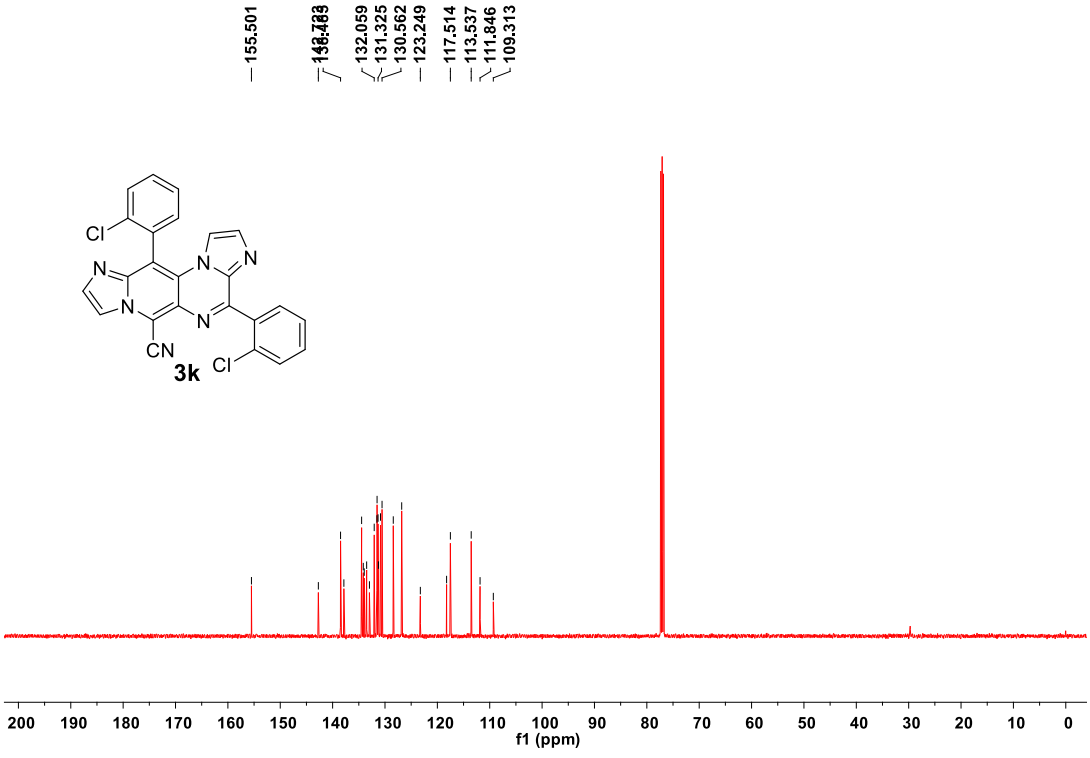
4,11-Di-m-tolylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3i)



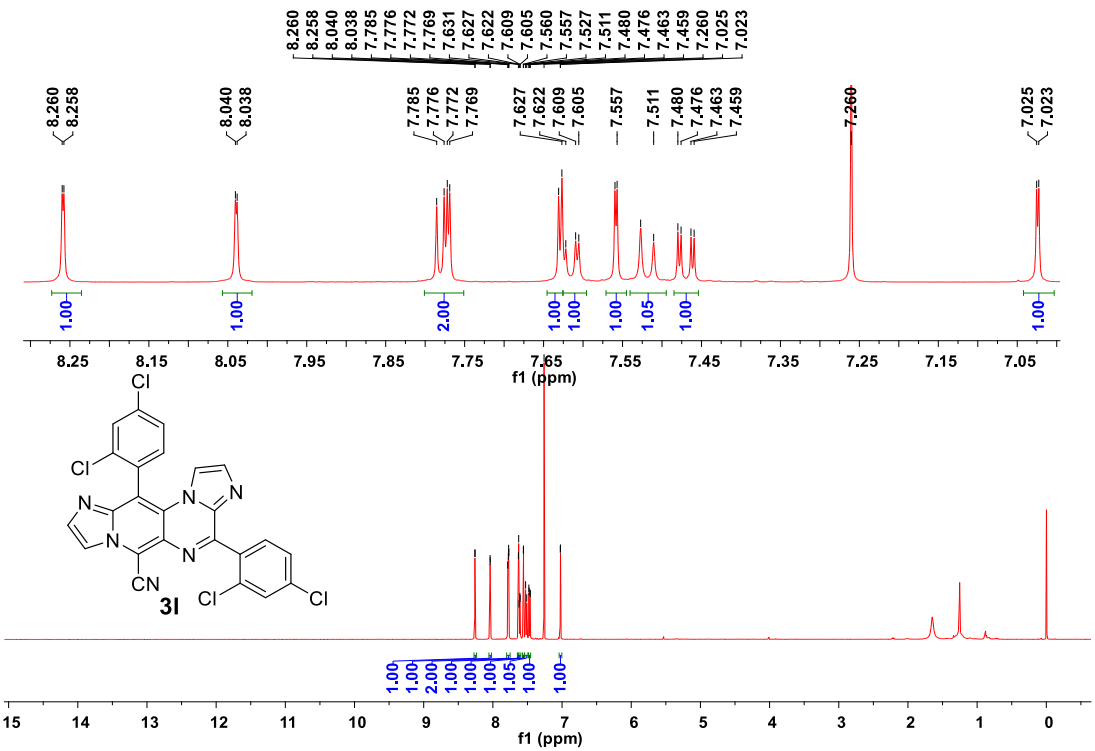


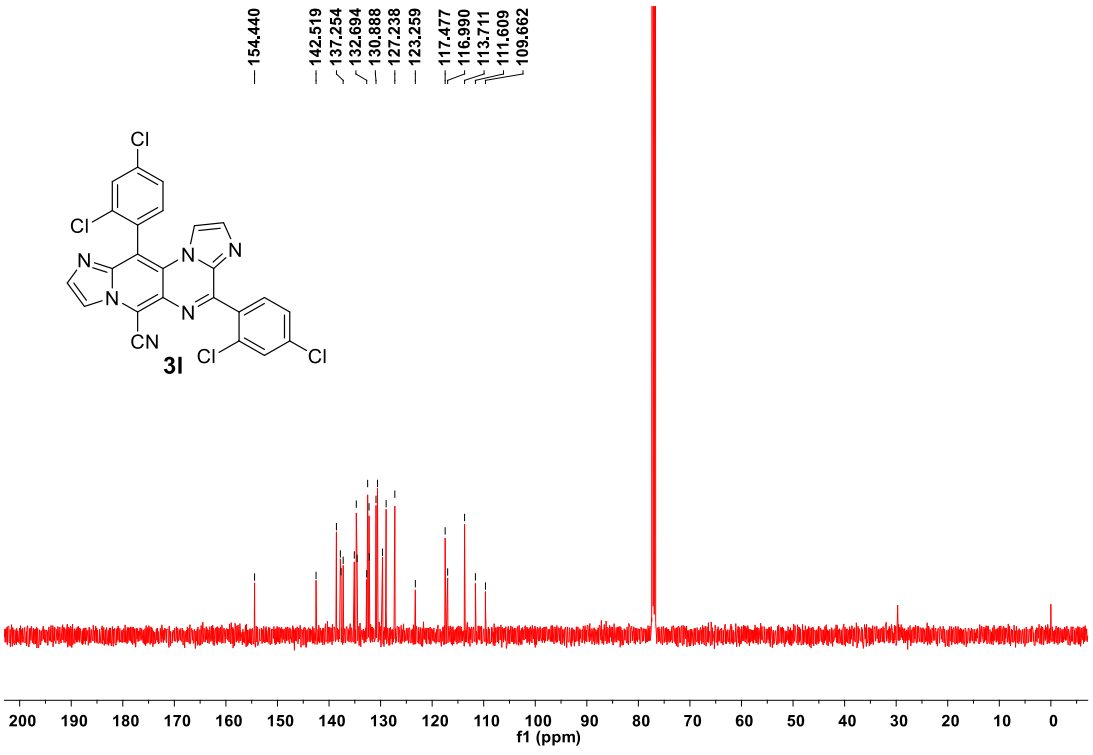
4,11-Bis(2-chlorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3k)



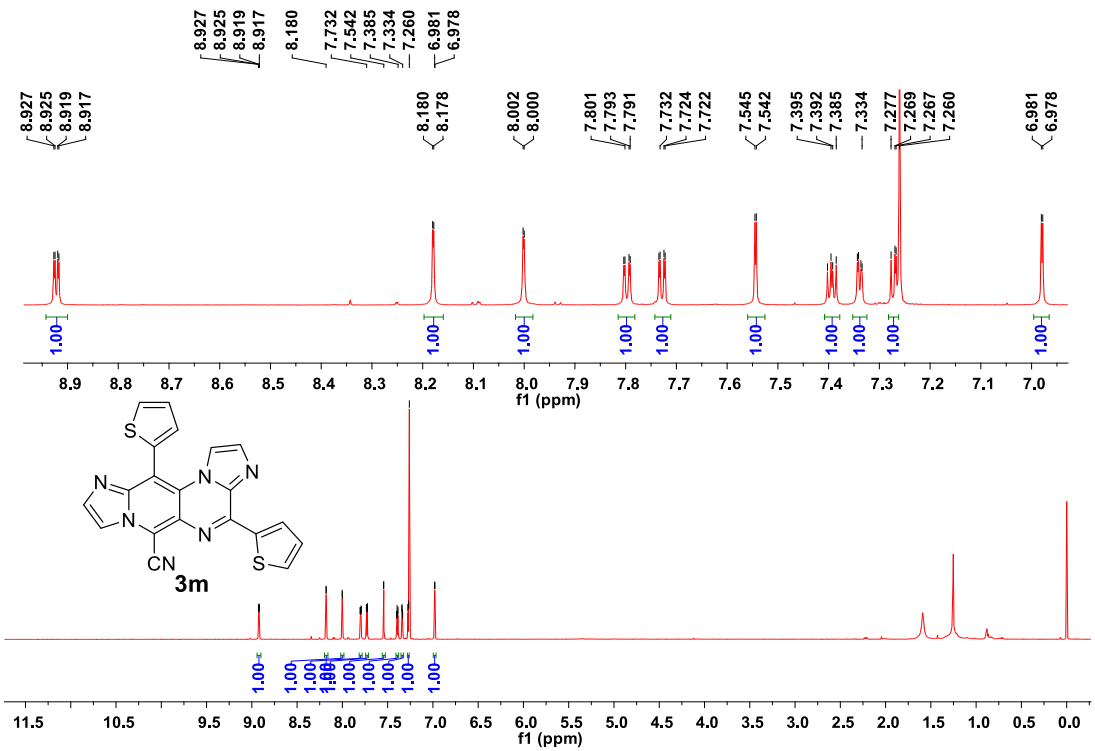


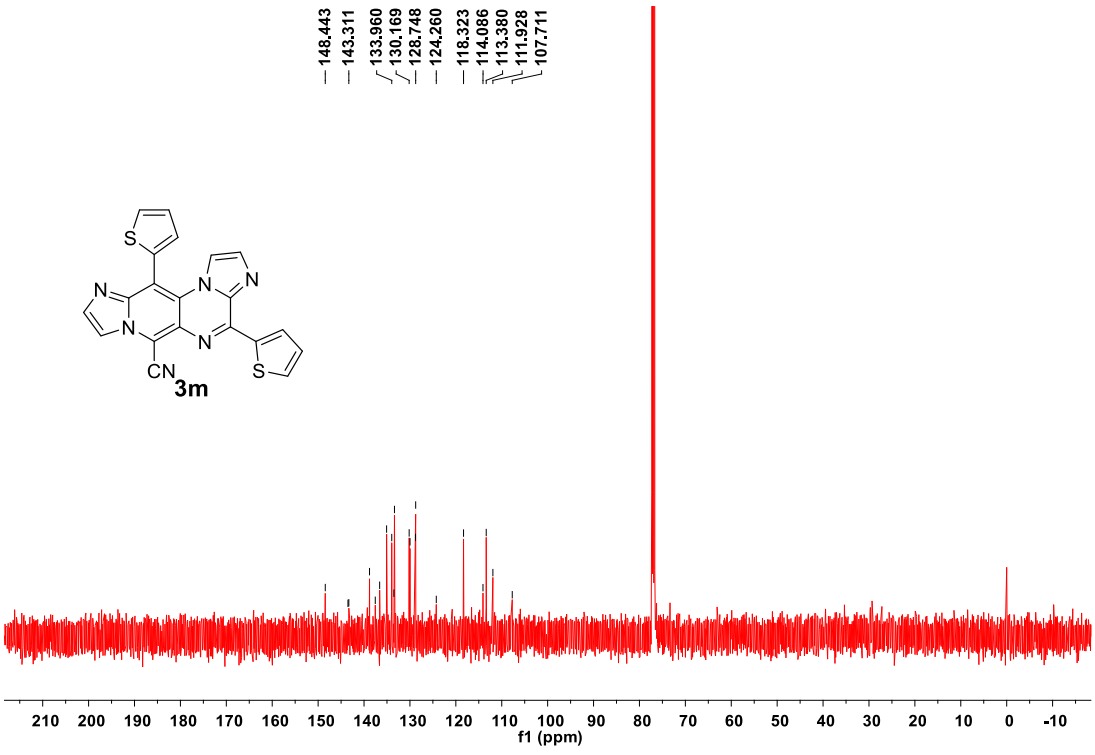
4,11-Bis(2,4-dichlorophenyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3l)



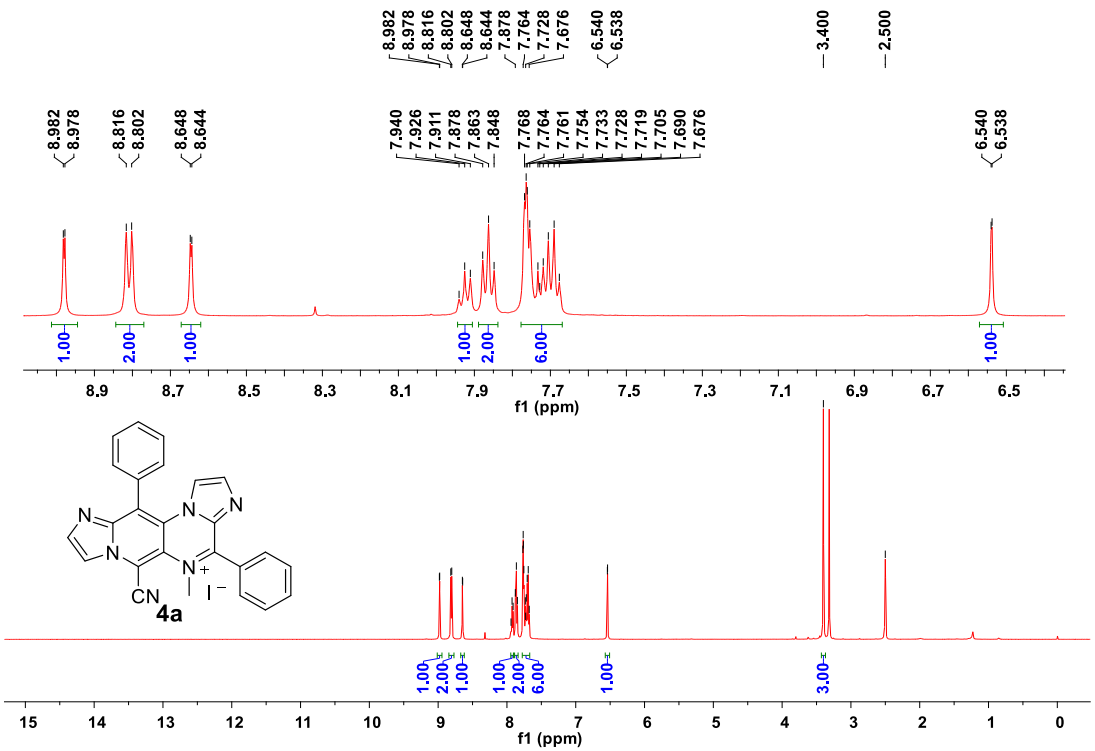


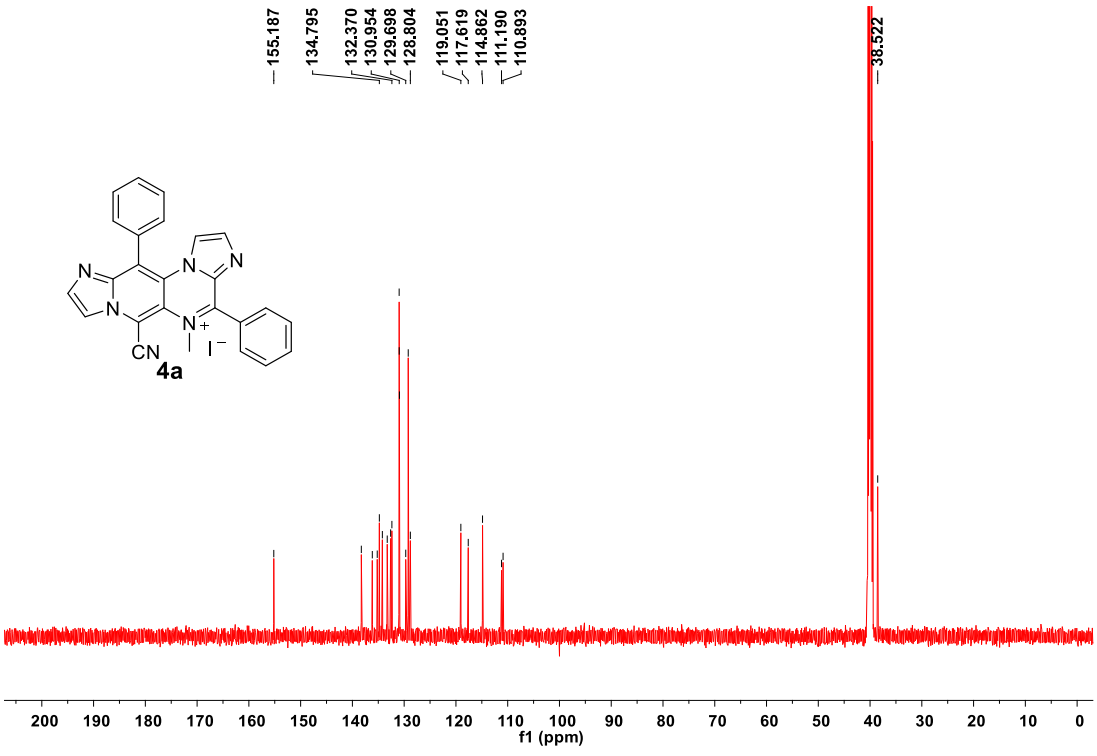
4,11-Di(thiophen-2-yl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazine-6-carbonitrile (3m)



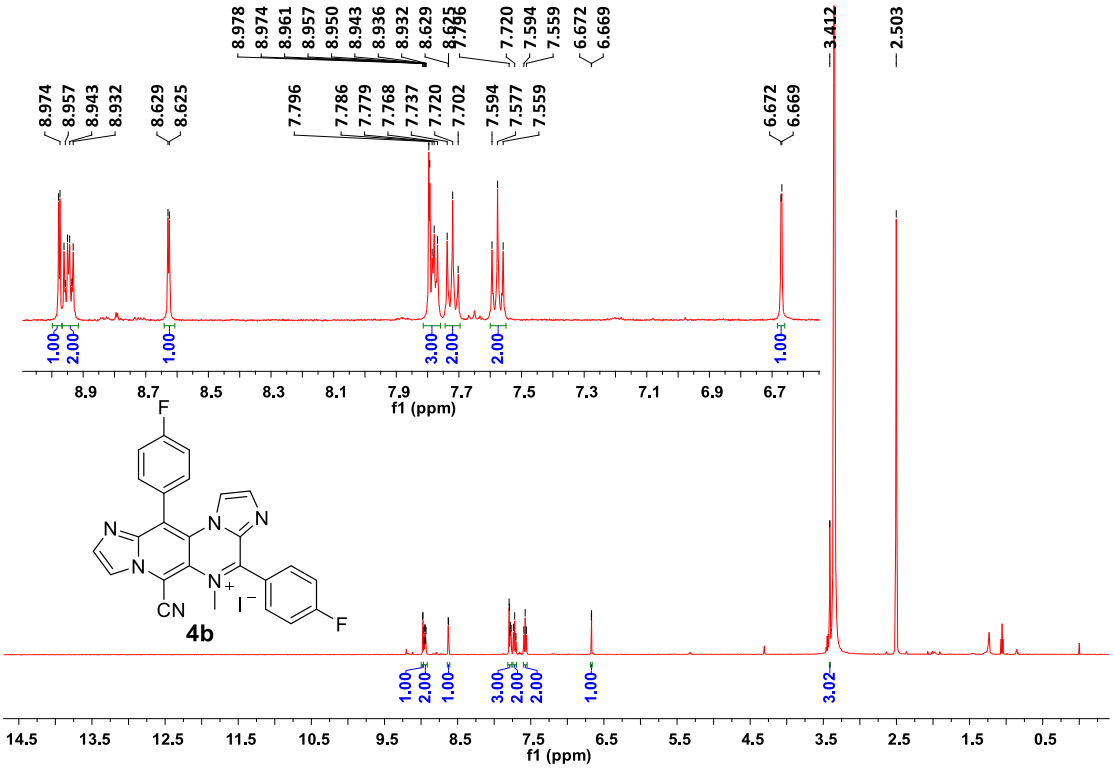


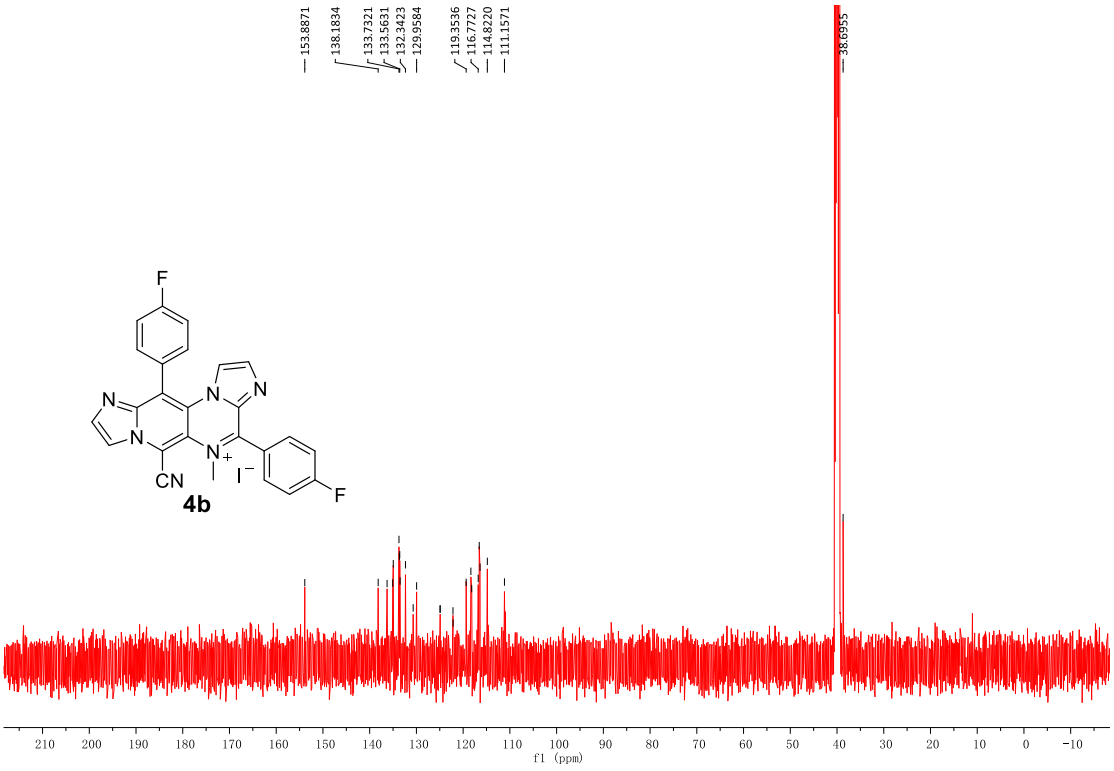
6-Cyano-5-methyl-4,11-diphenylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (4a)



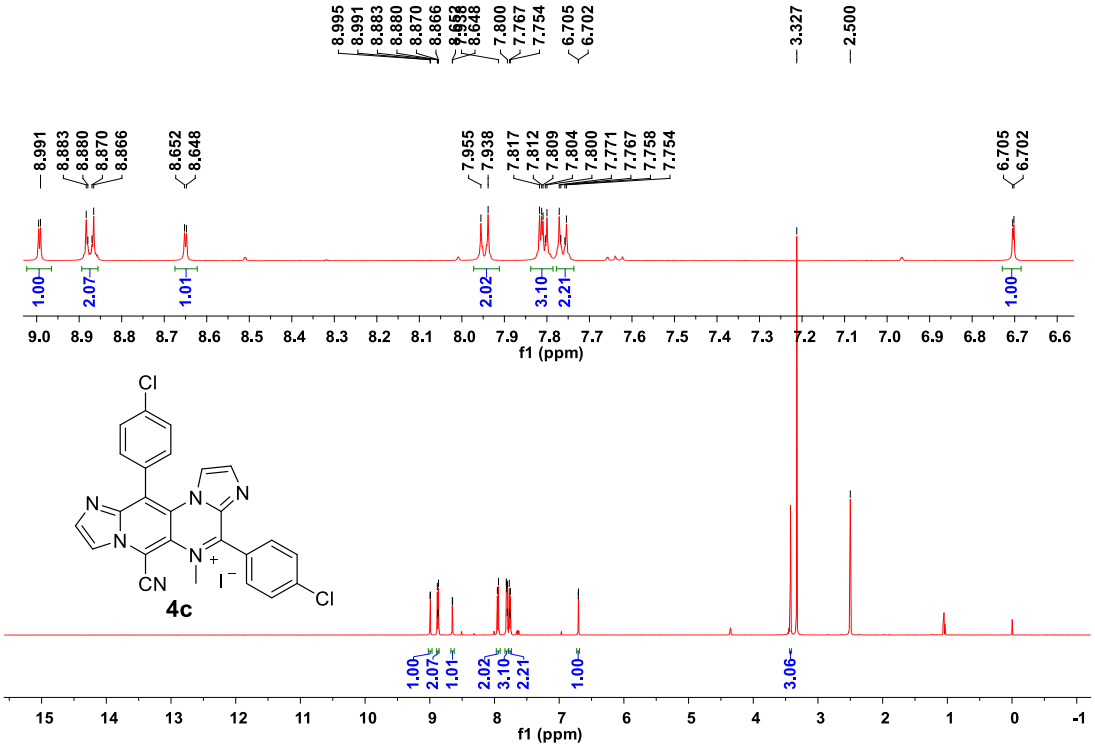


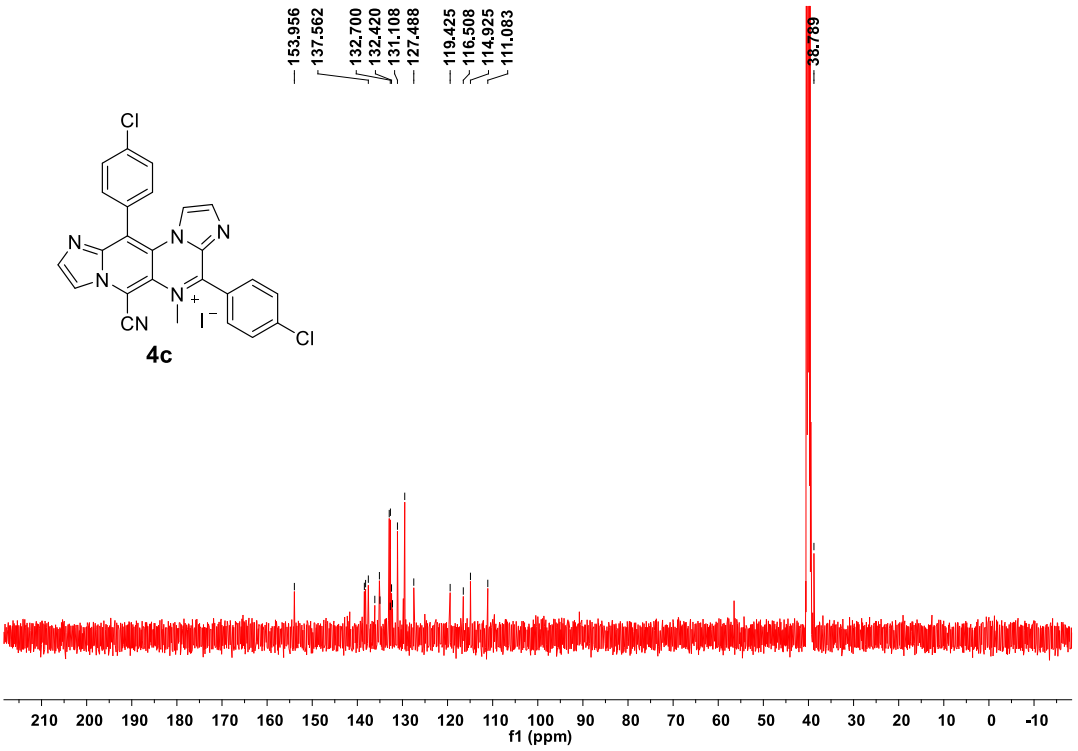
6-Cyano-4,11-bis(4-fluorophenyl)-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (4b)



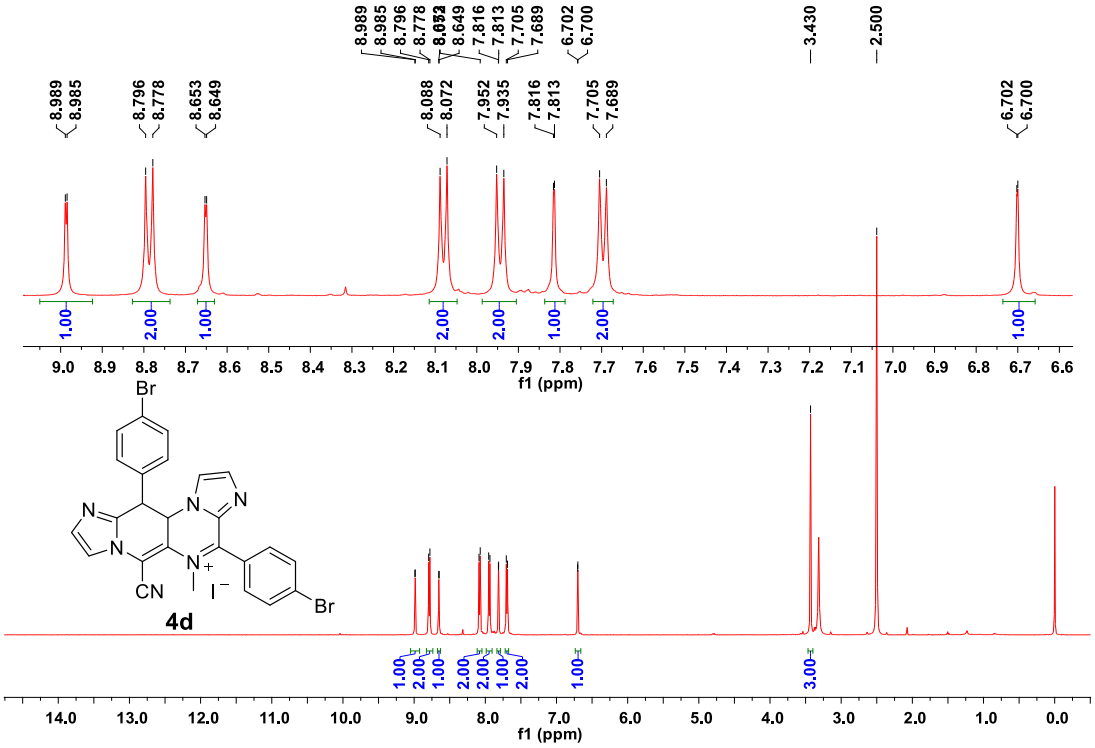


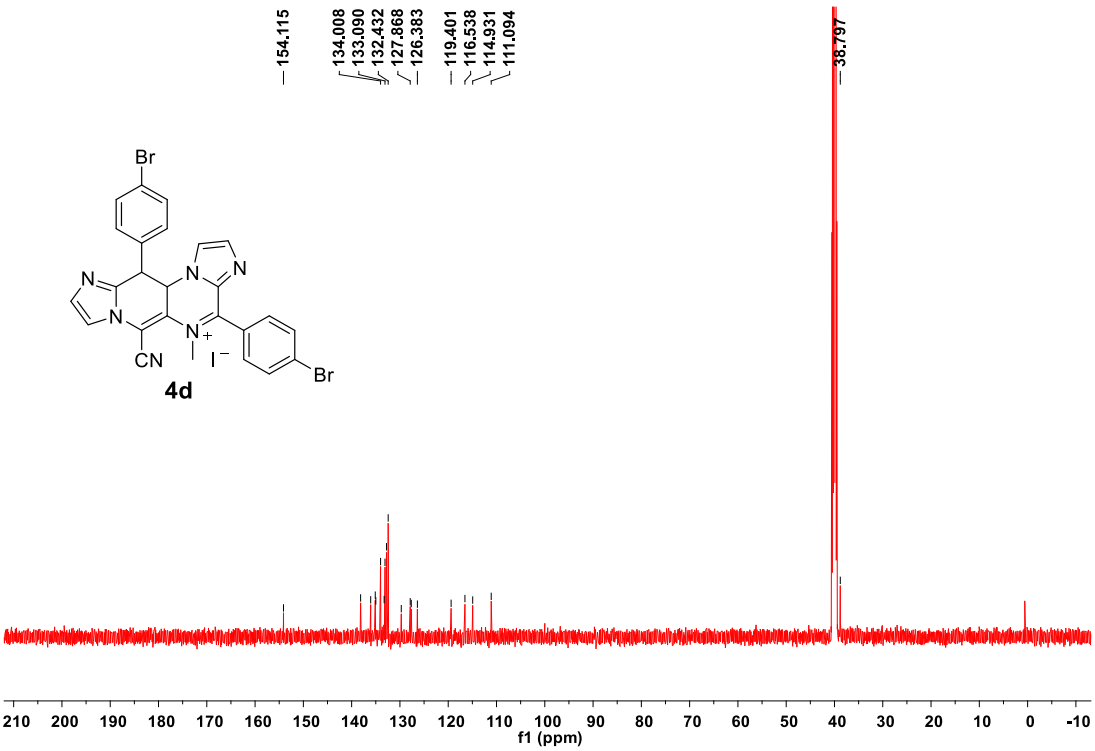
4,11-Bis(4-chlorophenyl)-6-cyano-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (4c)



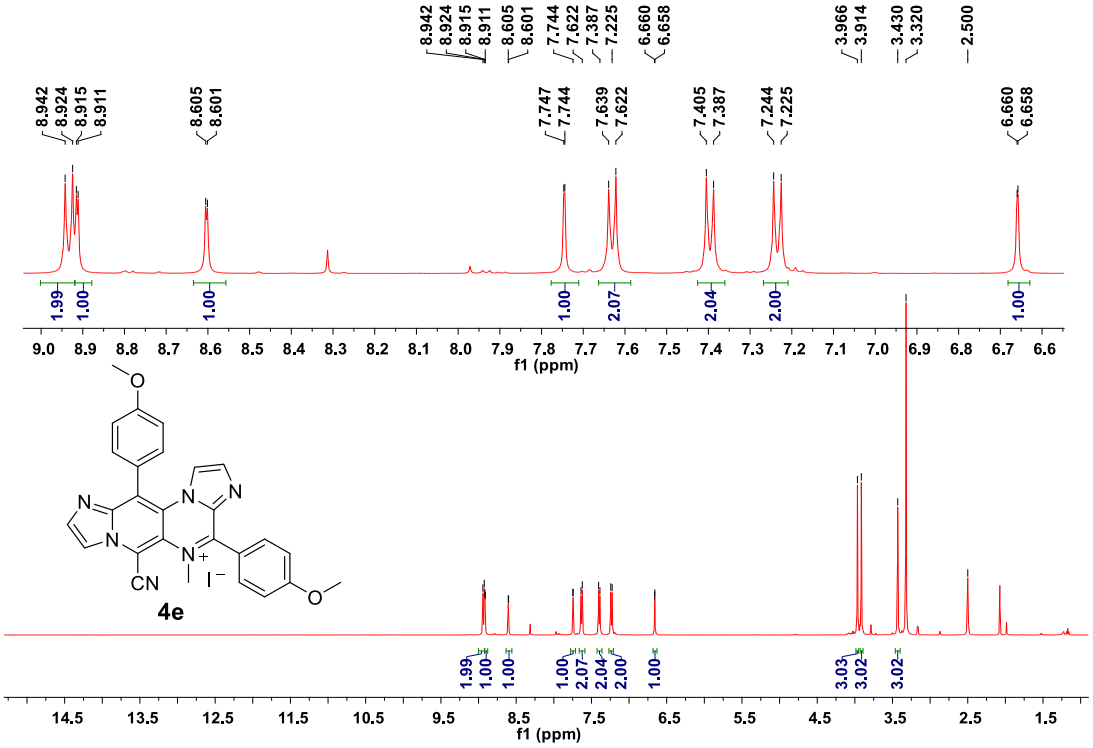


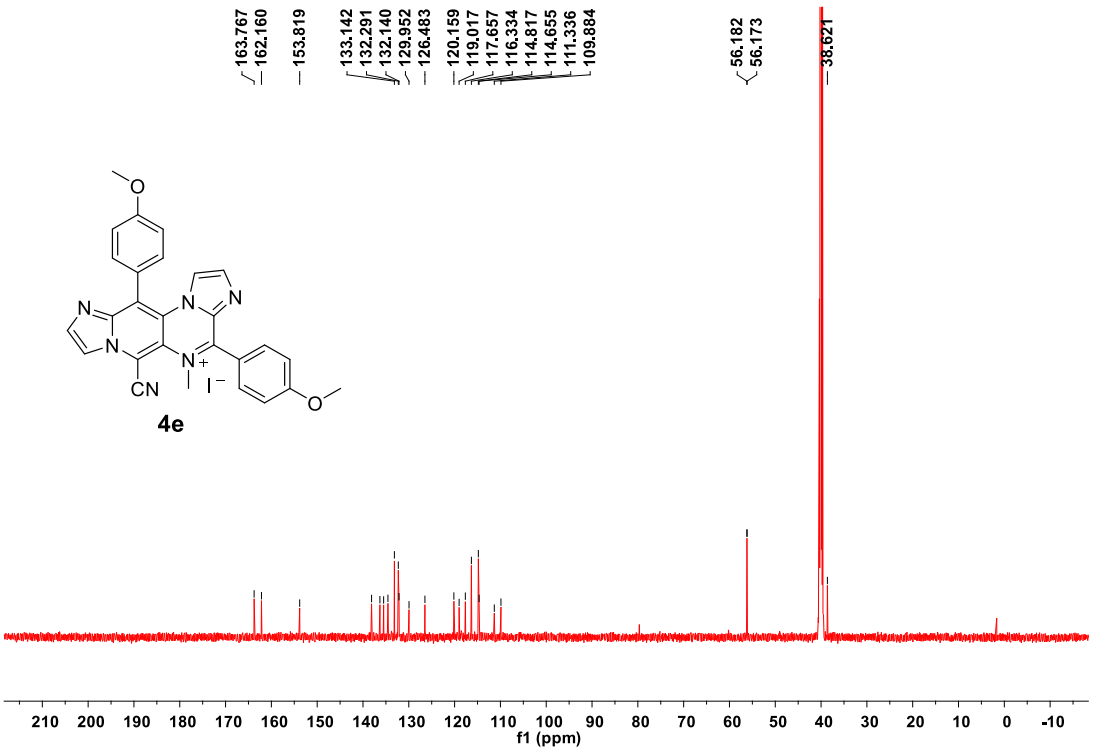
4,11-Bis(4-bromophenyl)-6-cyano-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (4d)



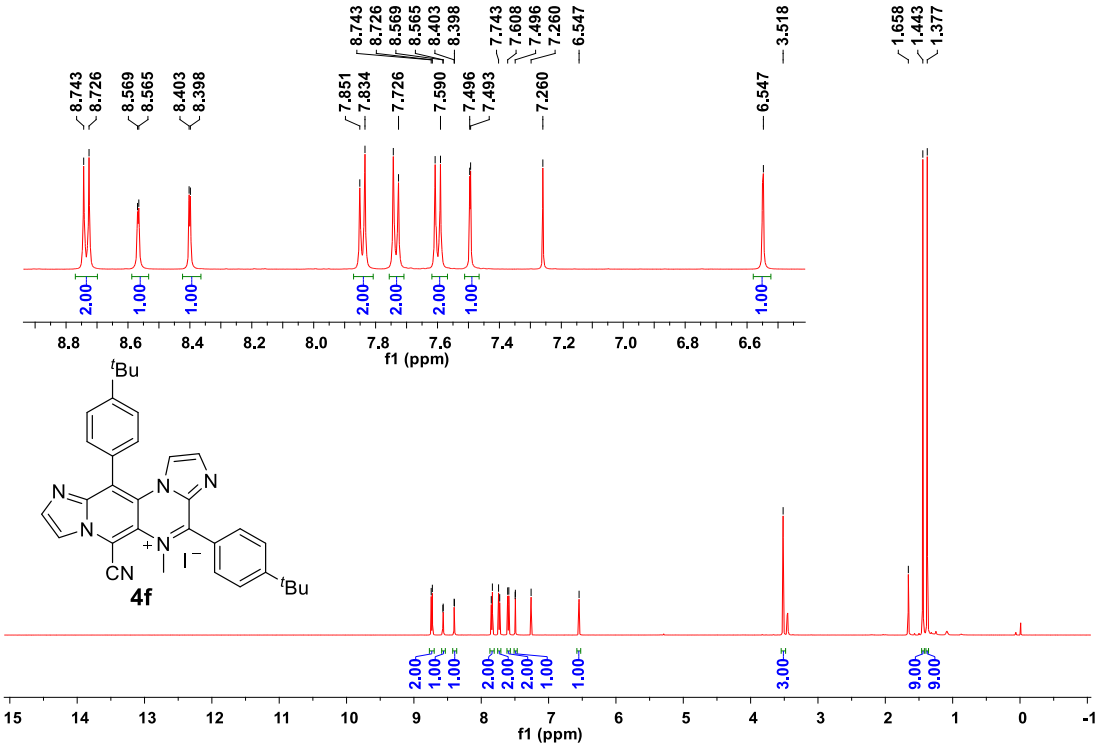


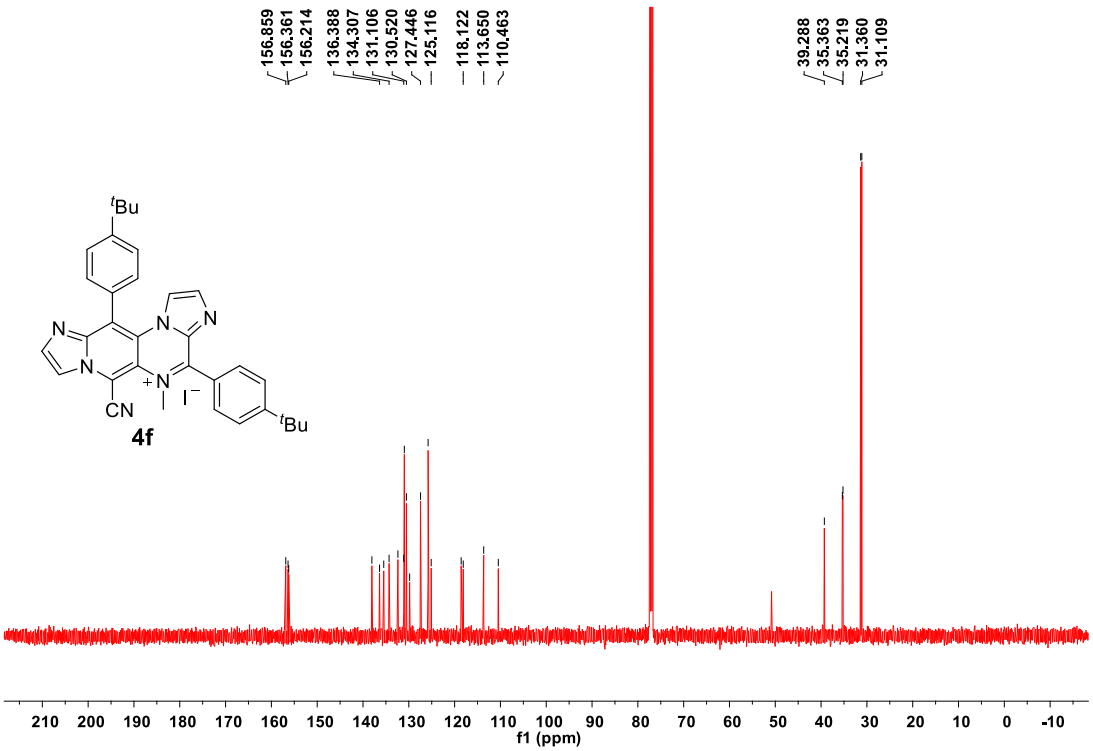
6-Cyano-4,11-bis(4-methoxyphenyl)-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (4e)



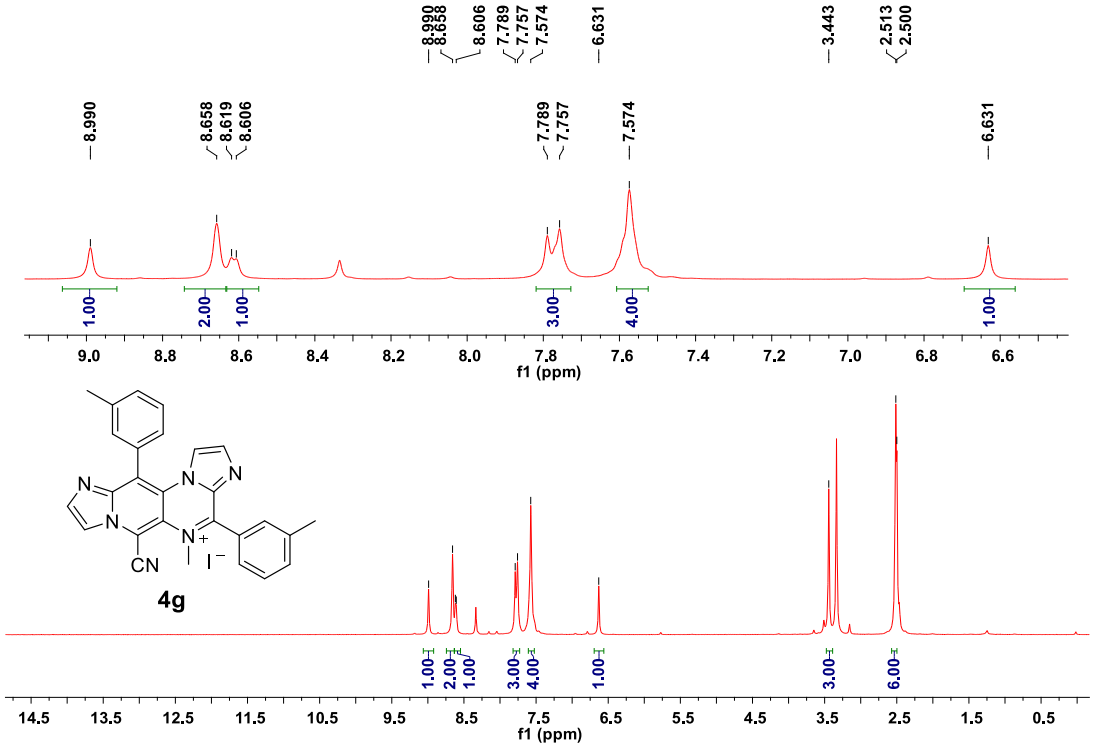


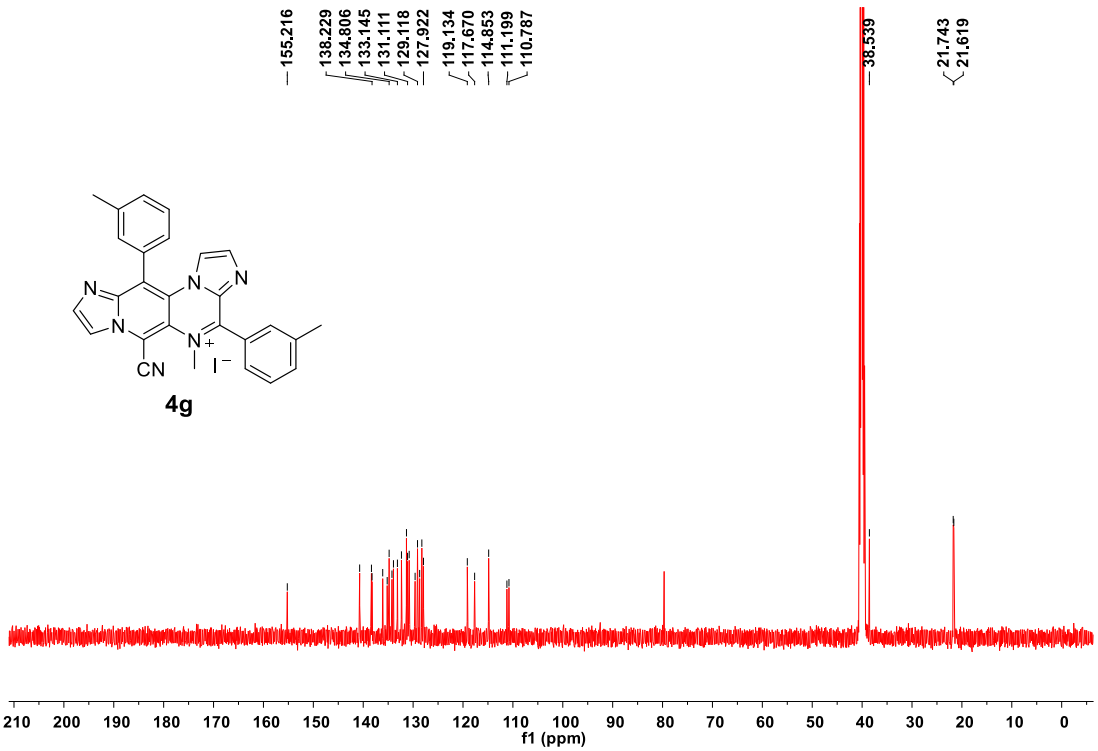
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-methylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (4f)



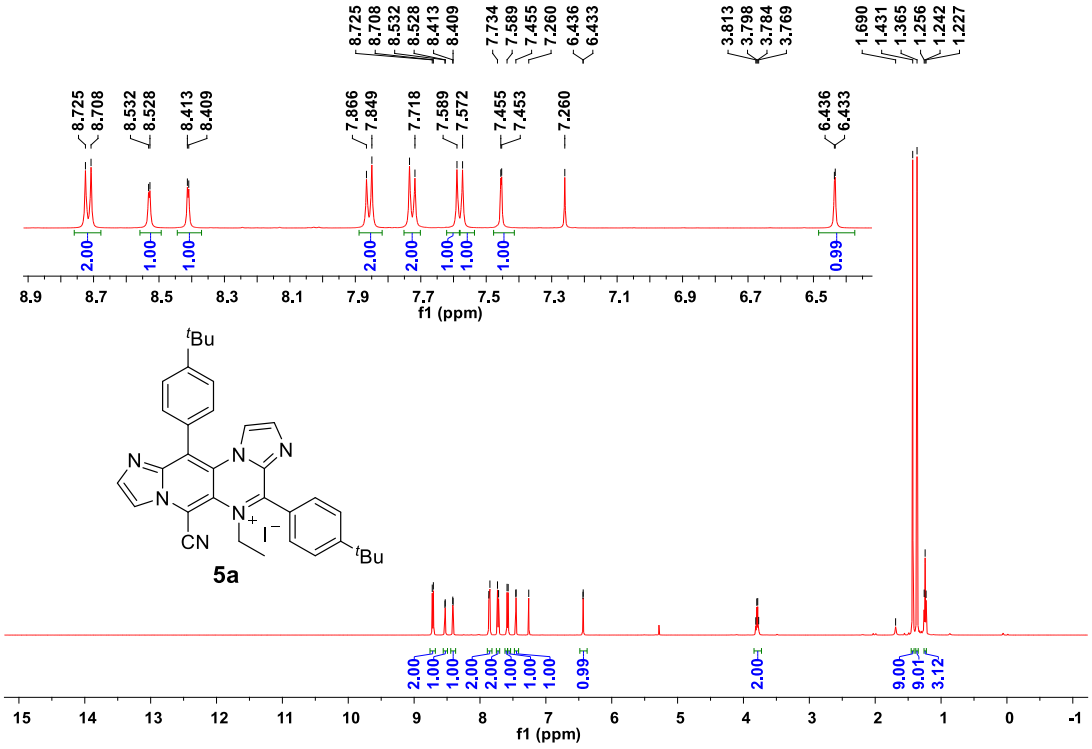


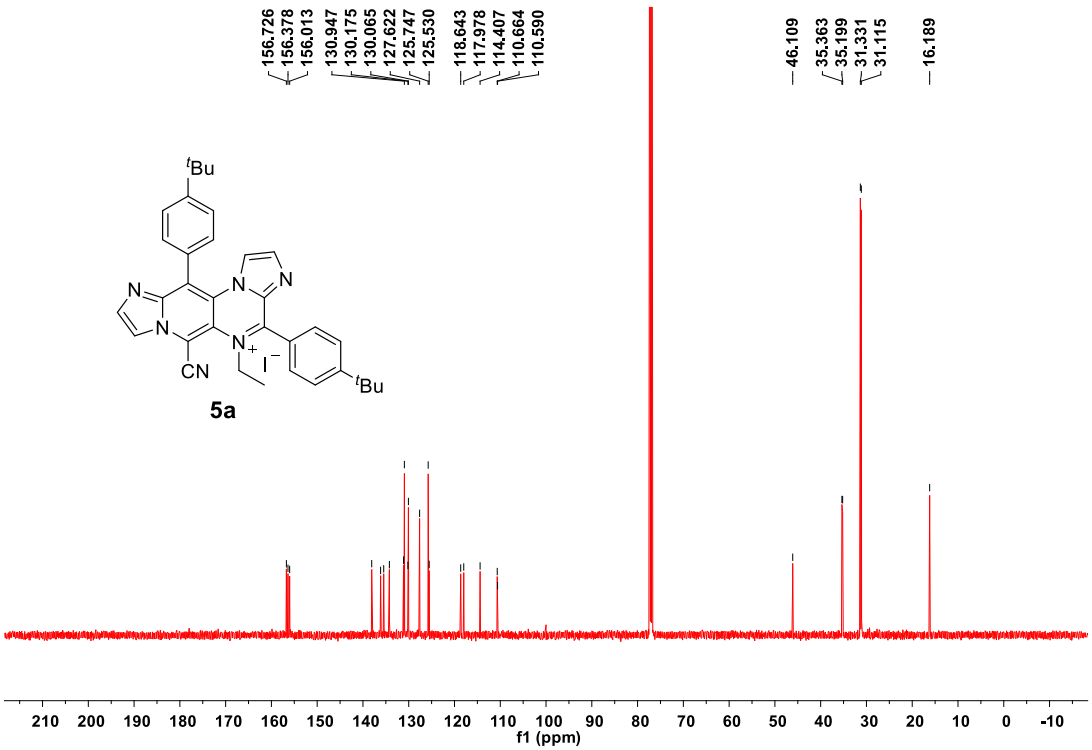
6-Cyano-5-methyl-4,11-di-m-tolylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (4g)



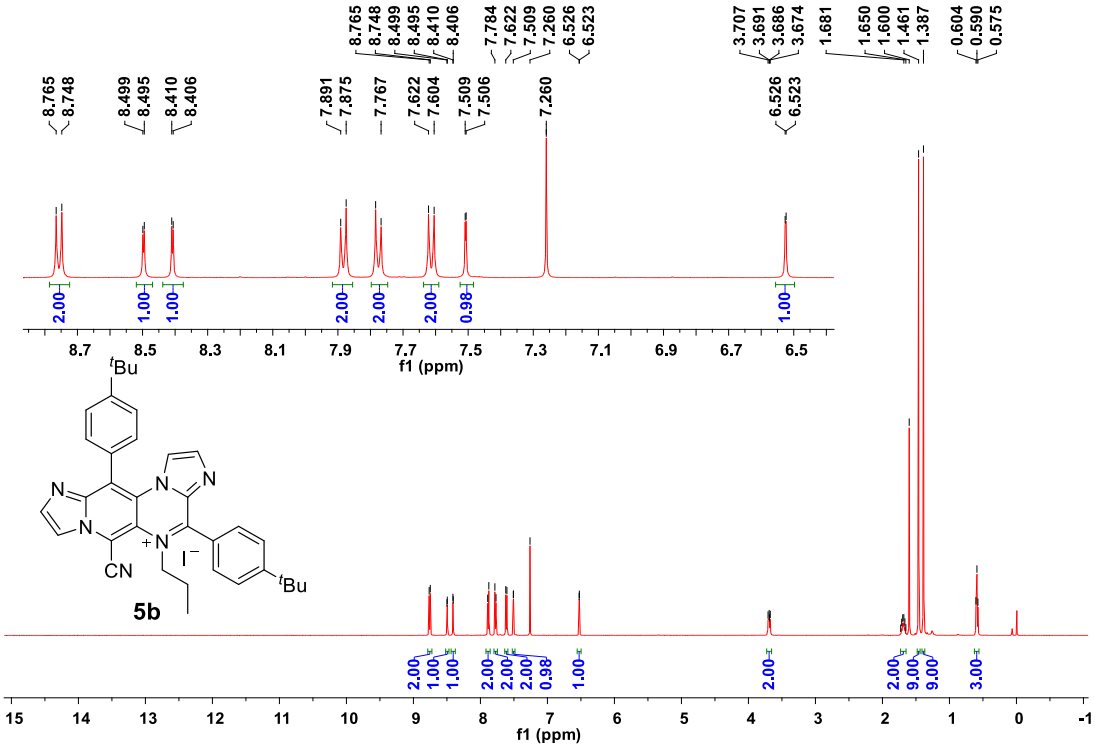


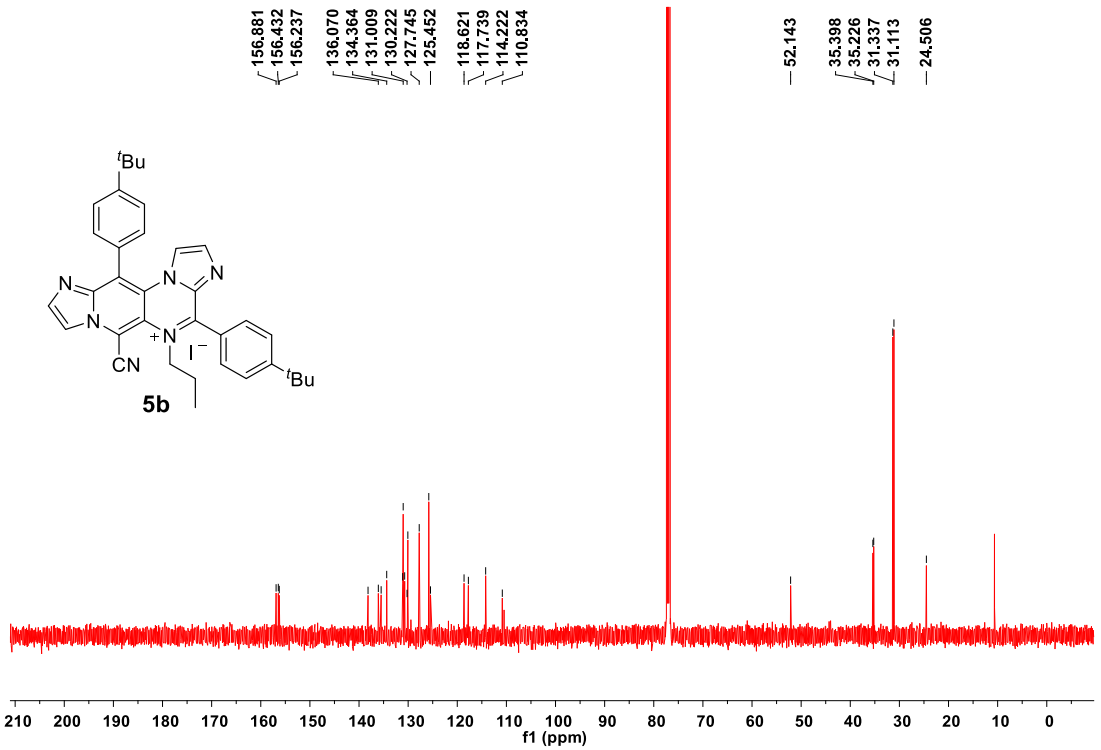
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-ethylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5a)



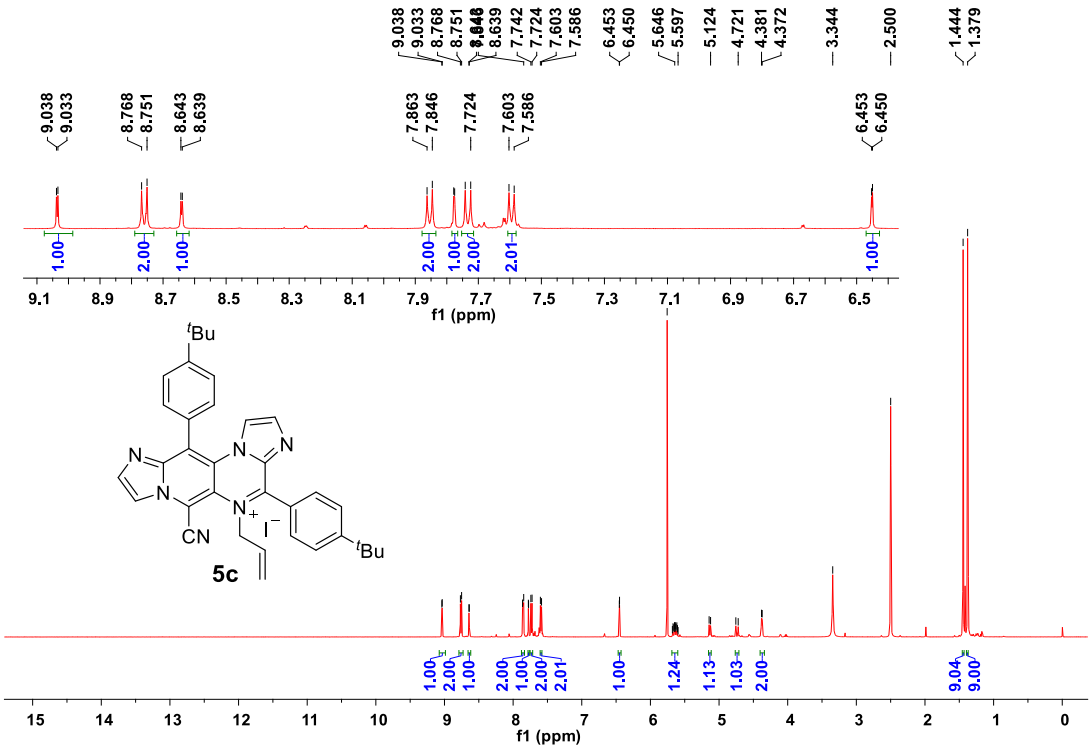


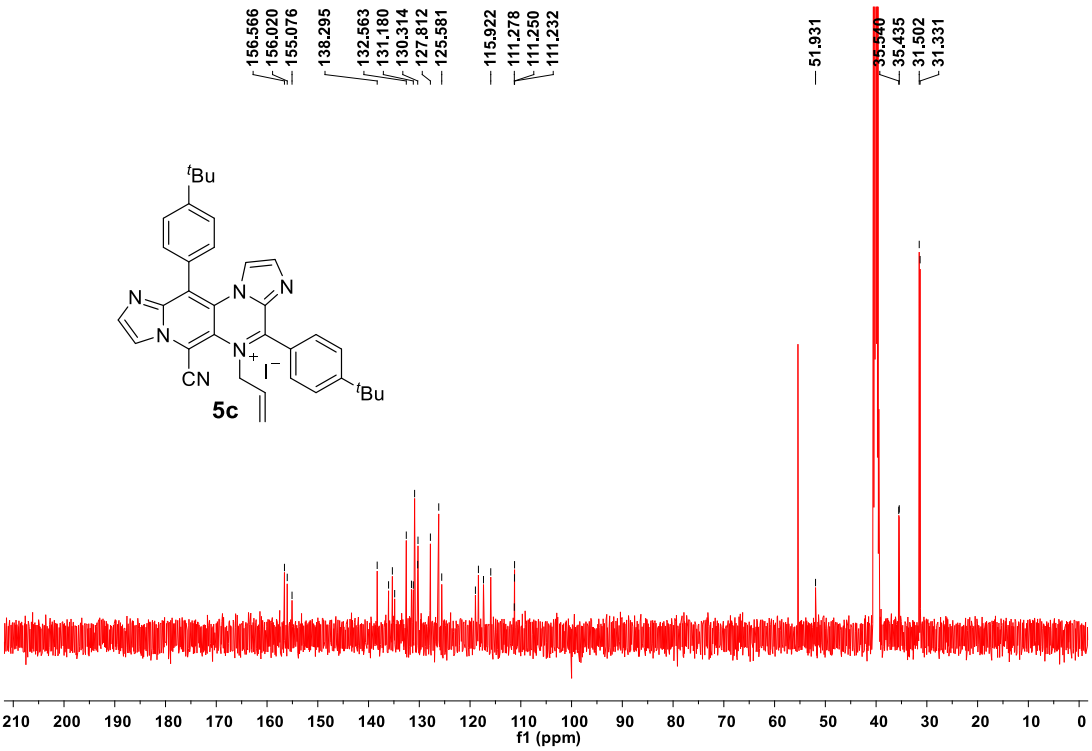
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-propylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5b)



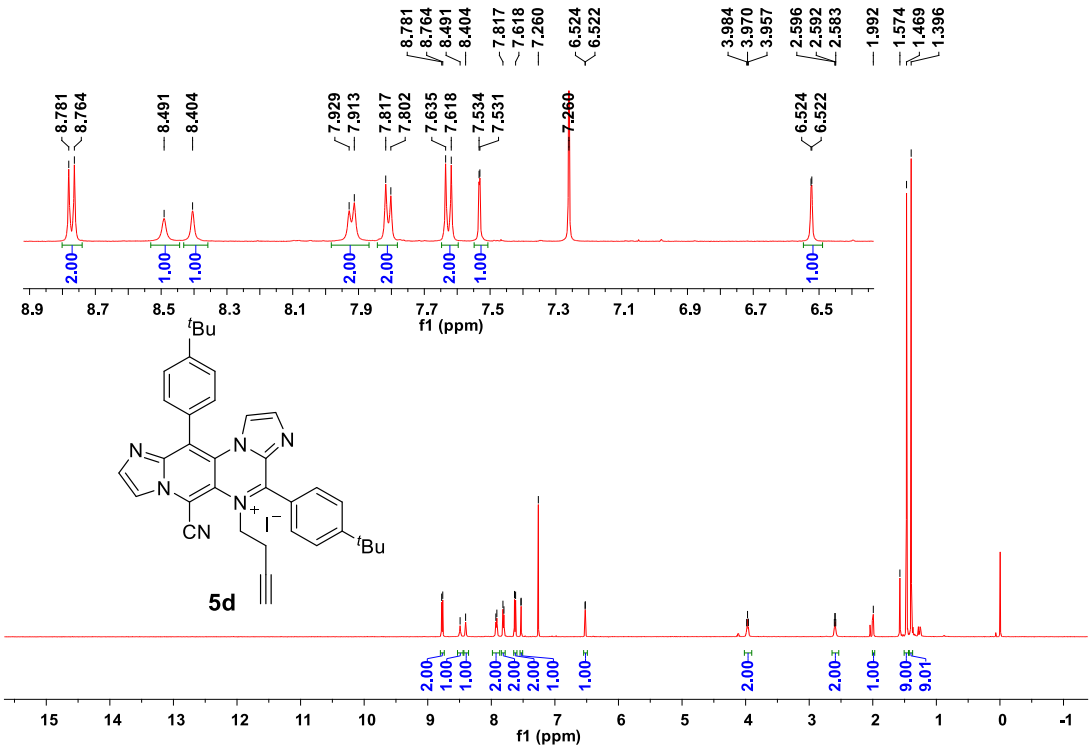


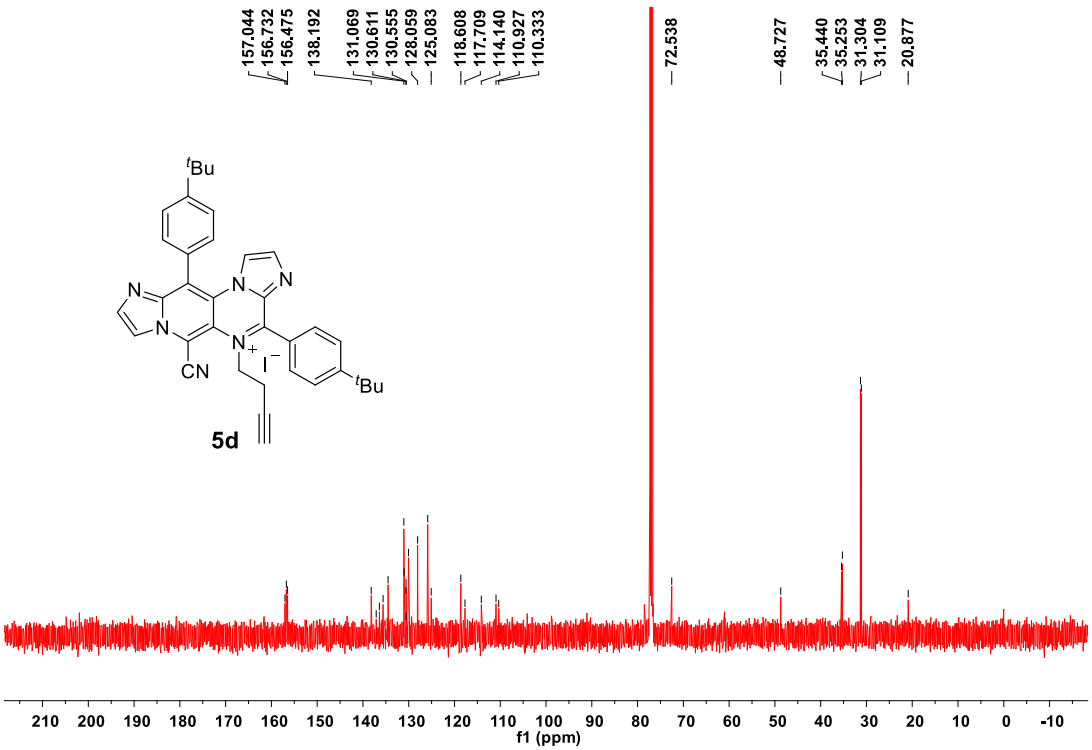
5-Allyl-4,11-bis(4-(tert-butyl)phenyl)-6-cyanoimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5c)



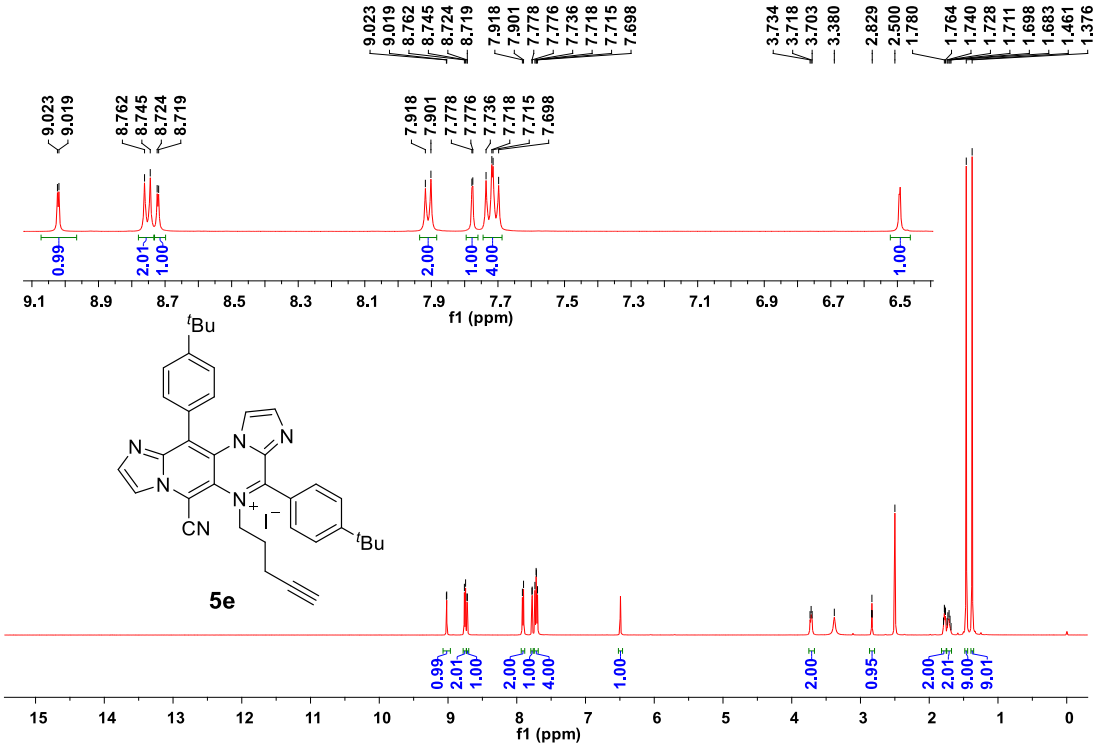


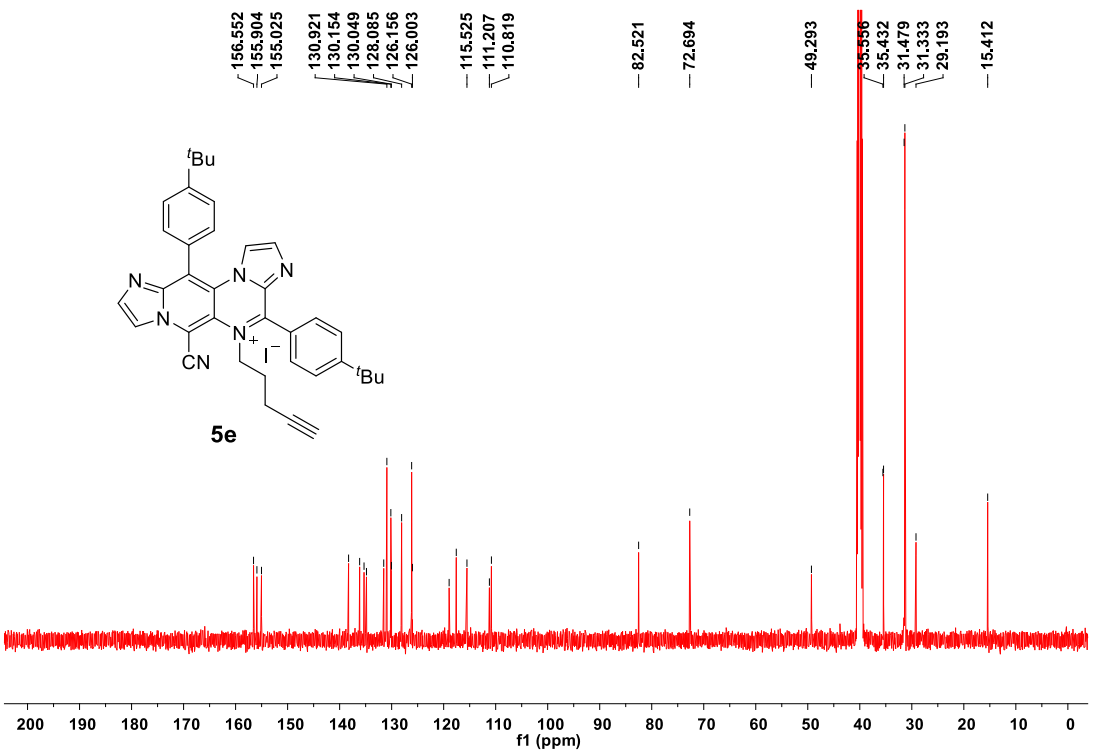
5-(But-3-yn-1-yl)-4,11-bis(4-(tert-butyl)phenyl)-6-cyanoimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium (5d)



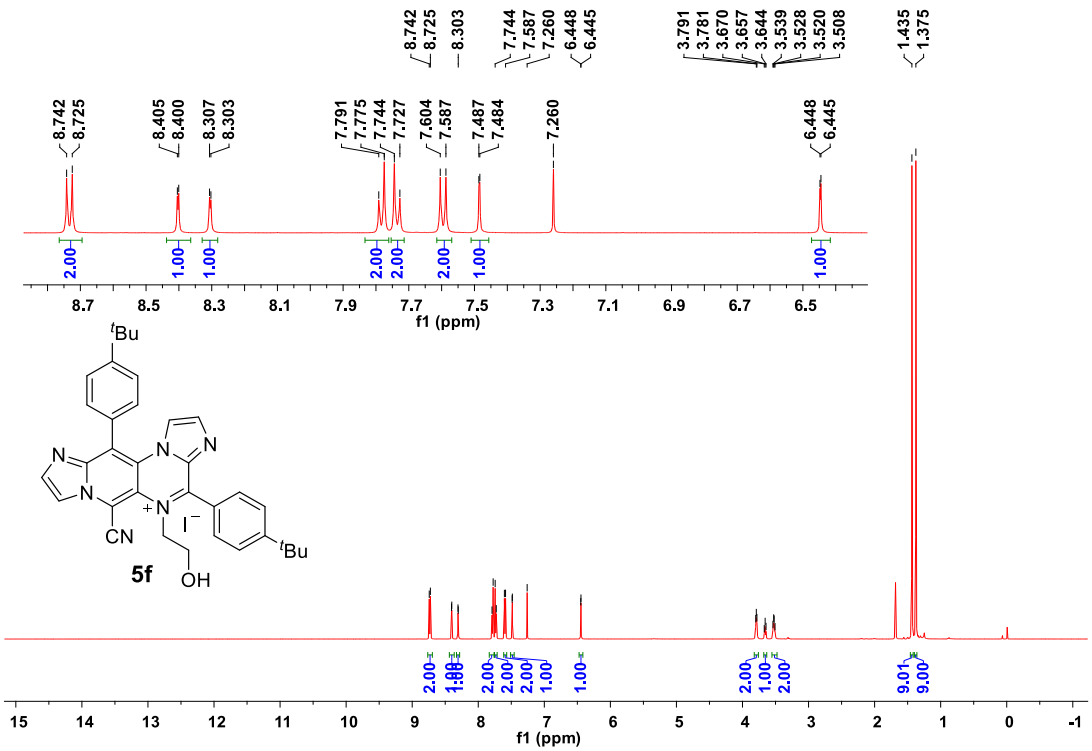


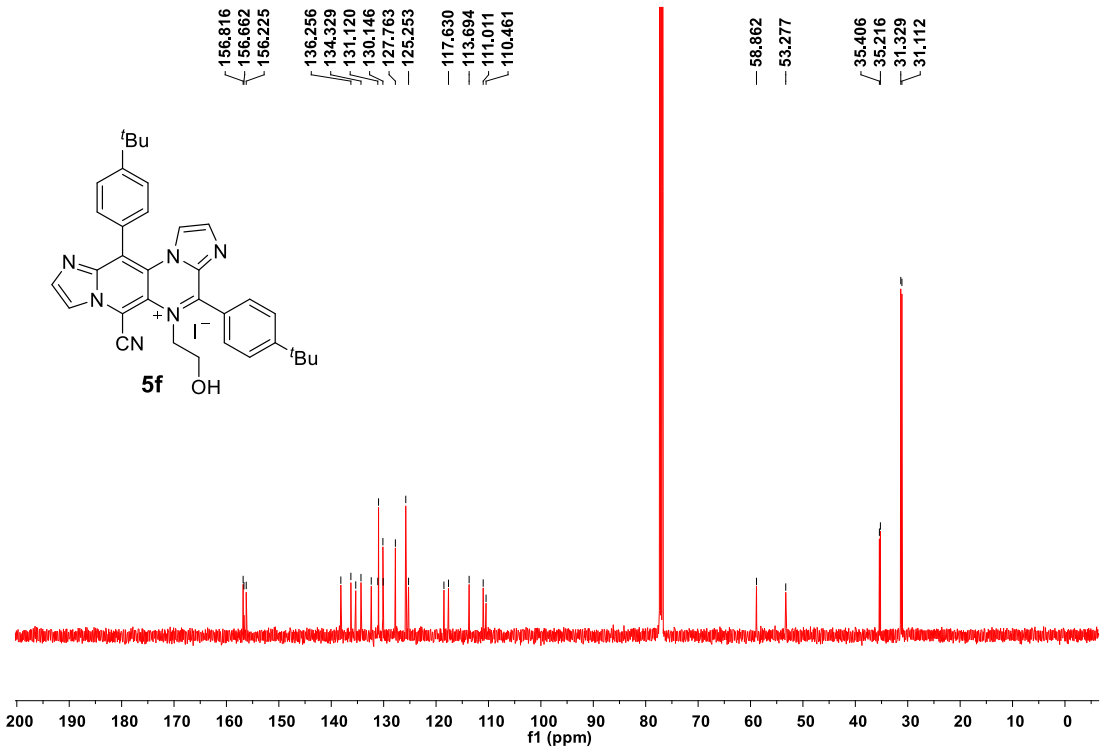
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(pent-4-yn-1-yl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5e)



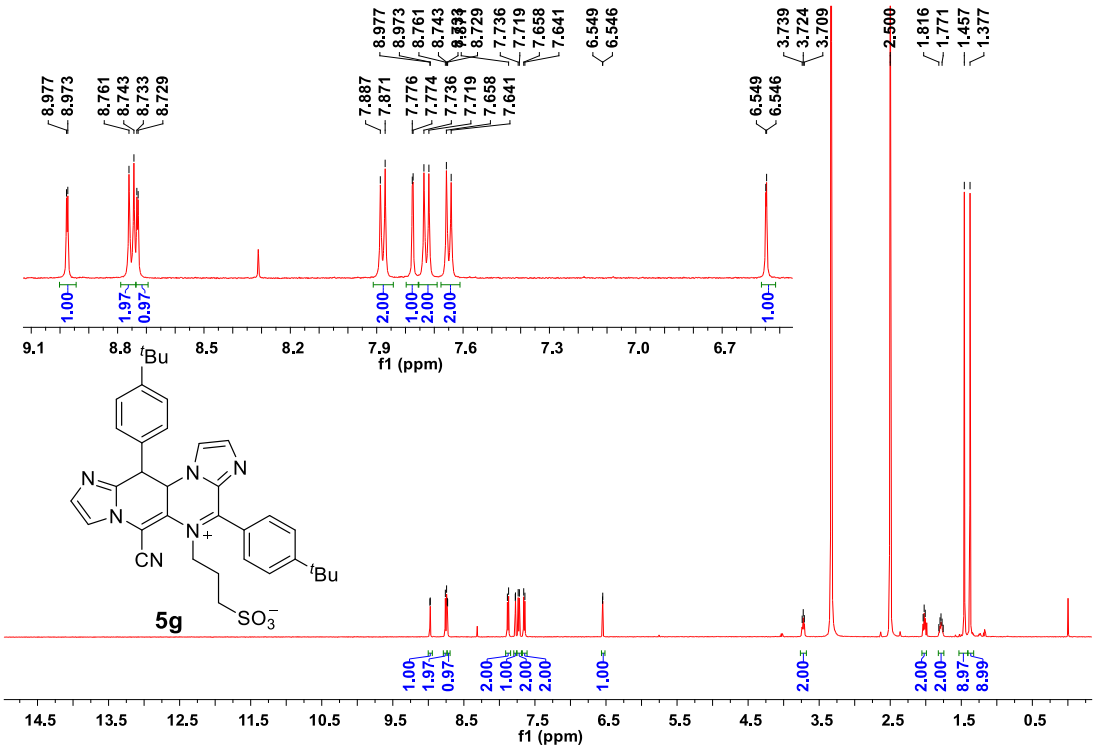


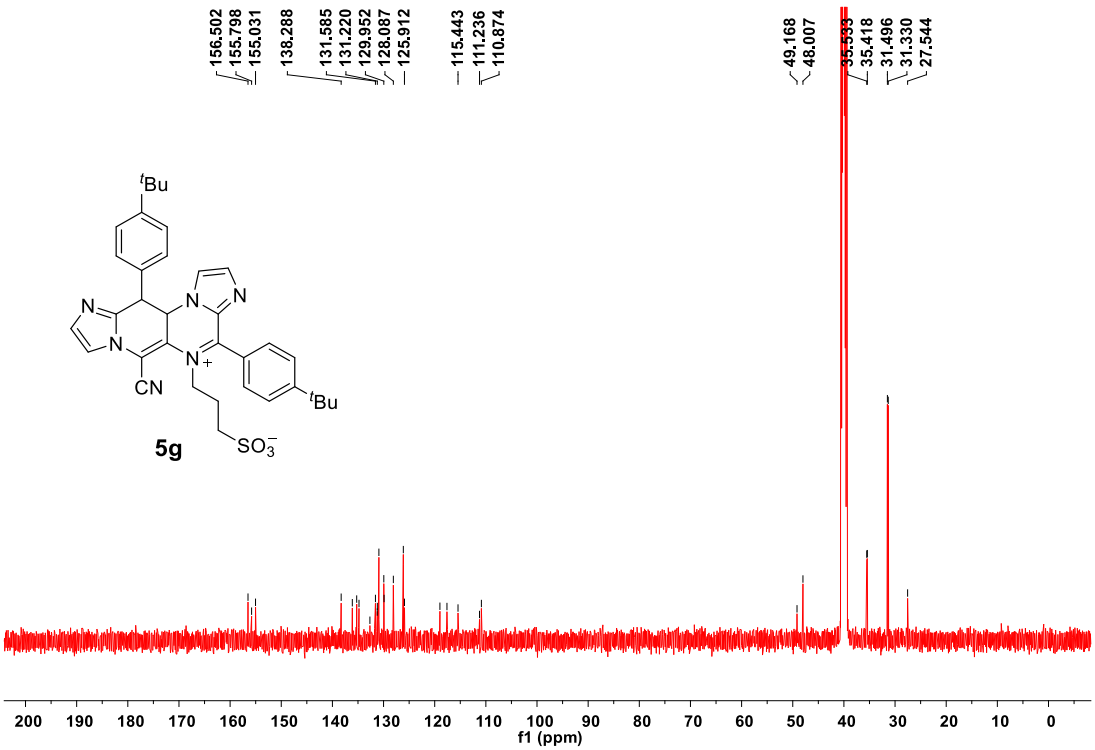
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-hydroxyethyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5f)



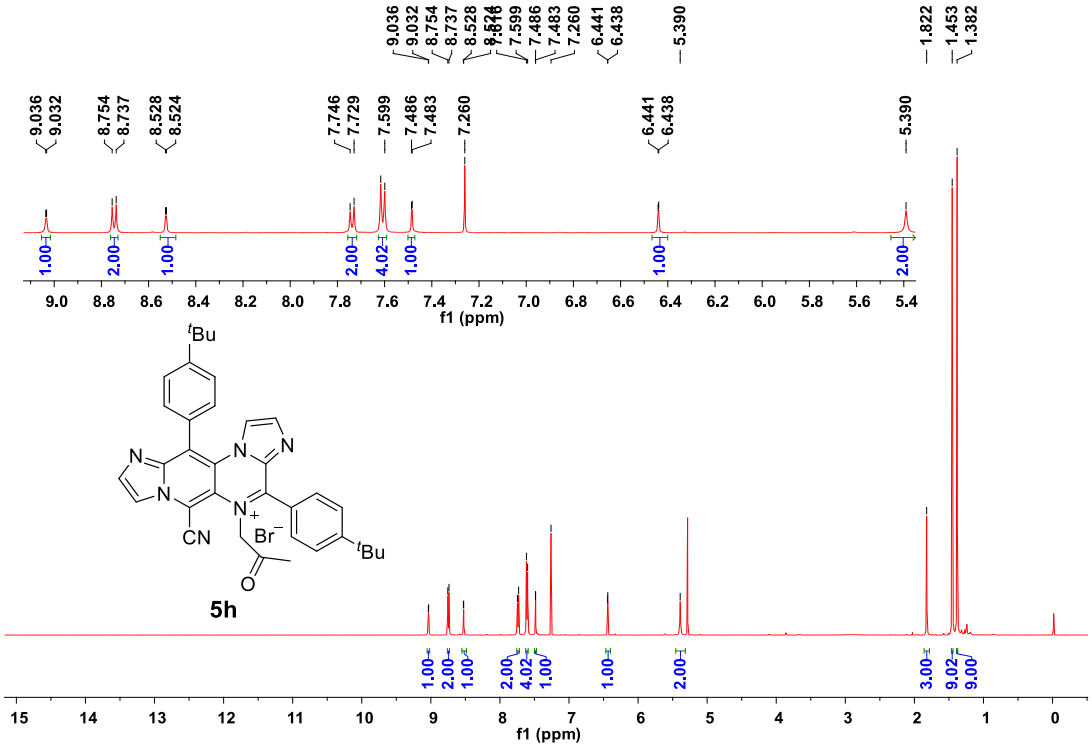


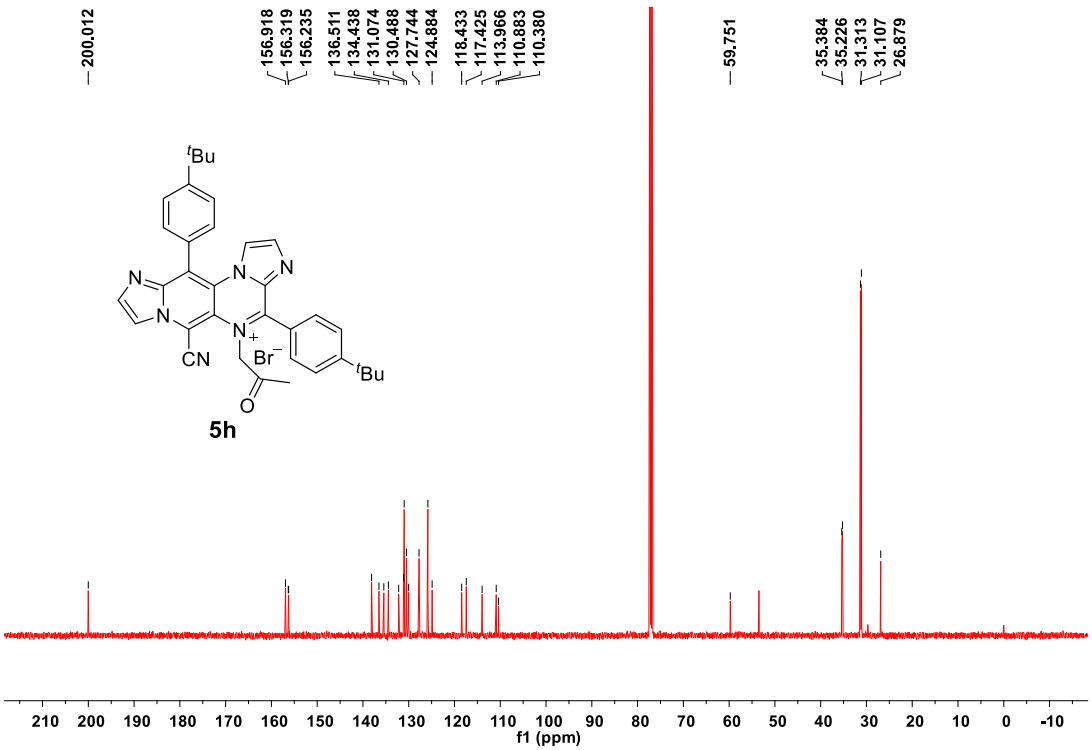
2-(4,11-Bis(4-(tert-butyl)phenyl)-6-cyanoimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium-5-yl)ethane-1-sulfonate (5g)



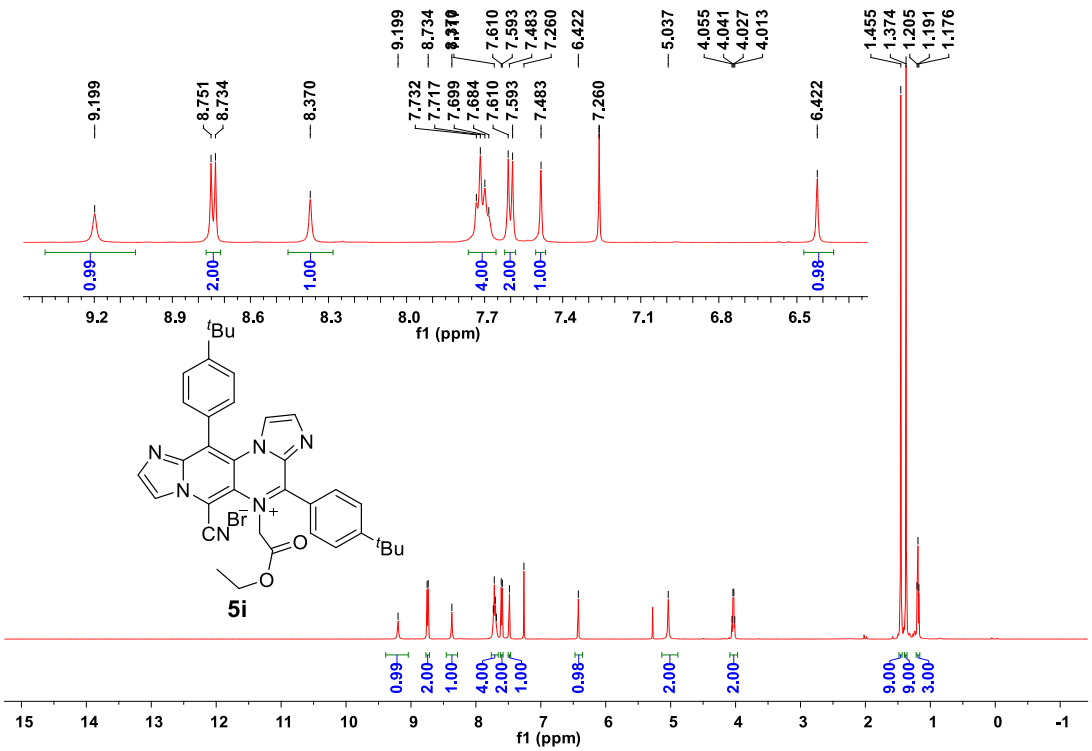


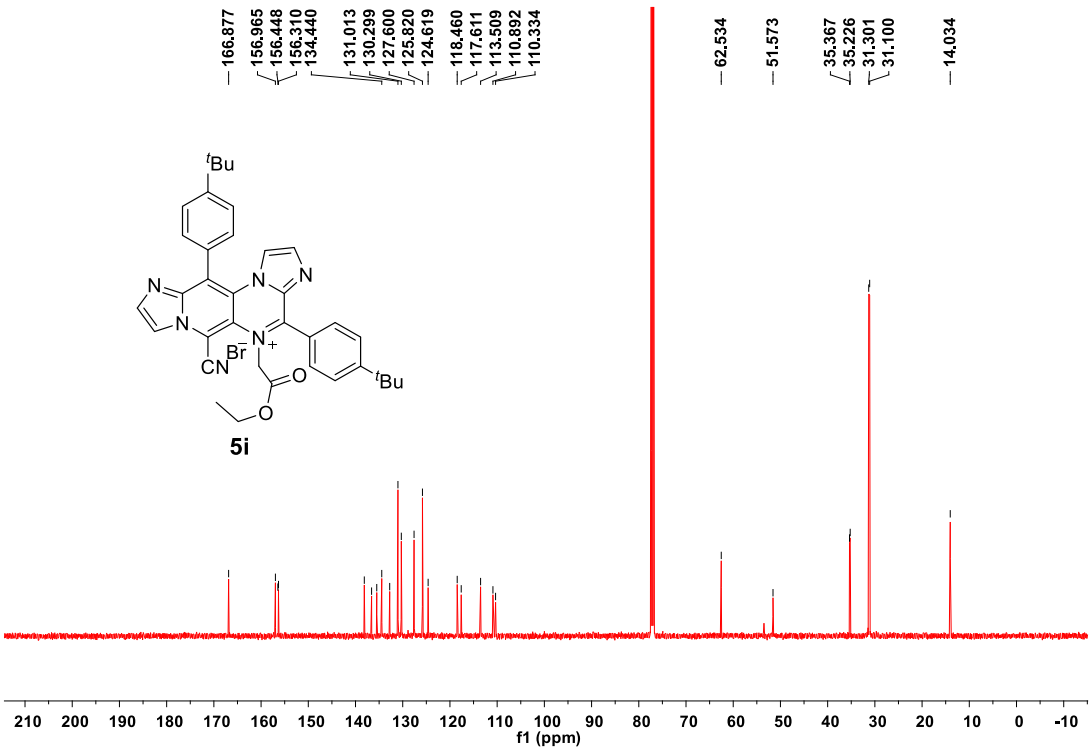
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-oxopropyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium bromide (5h)



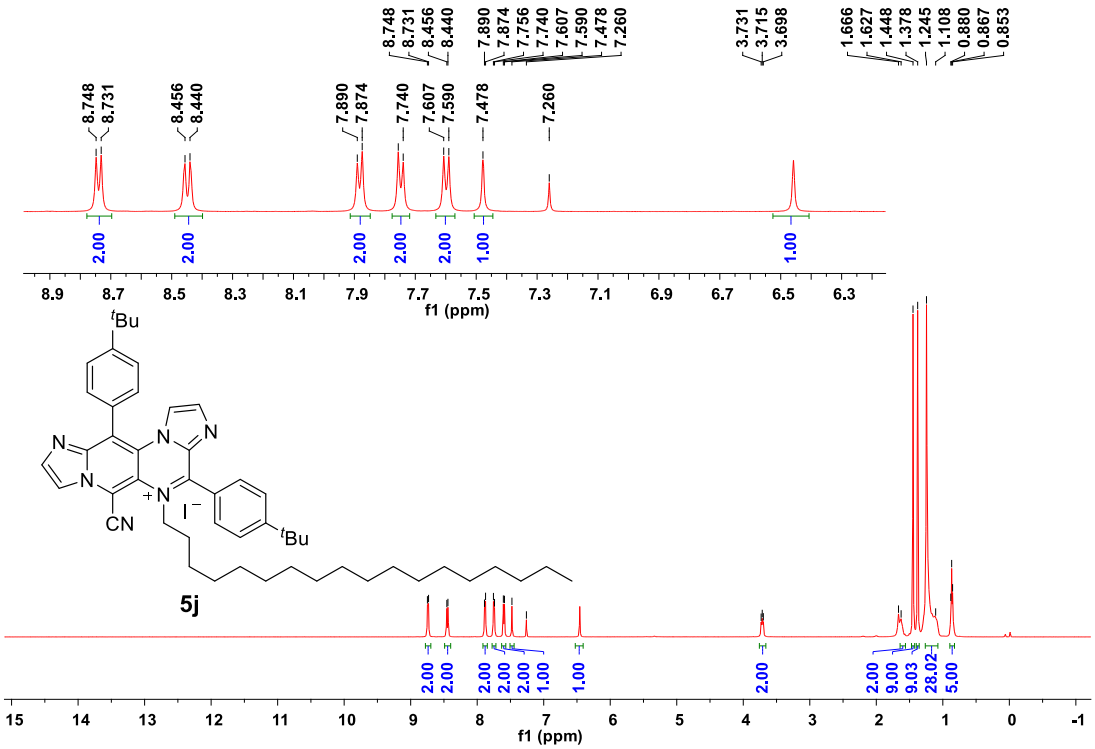


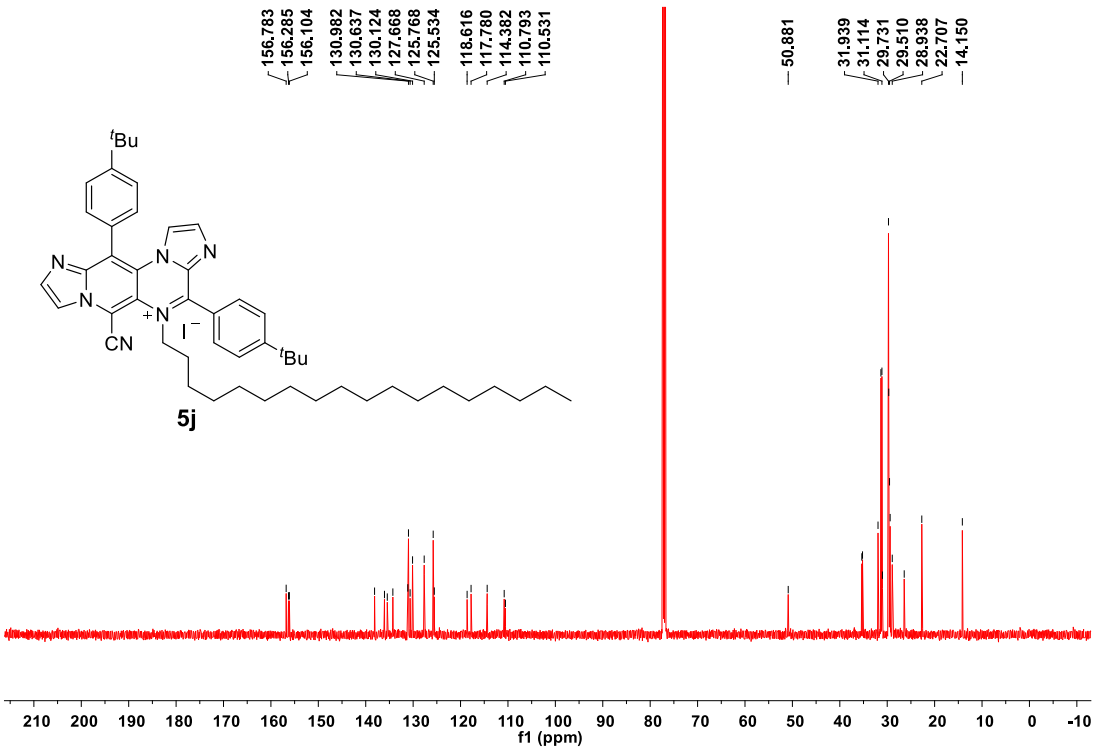
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-ethoxy-2-oxoethyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium bromide (5i)



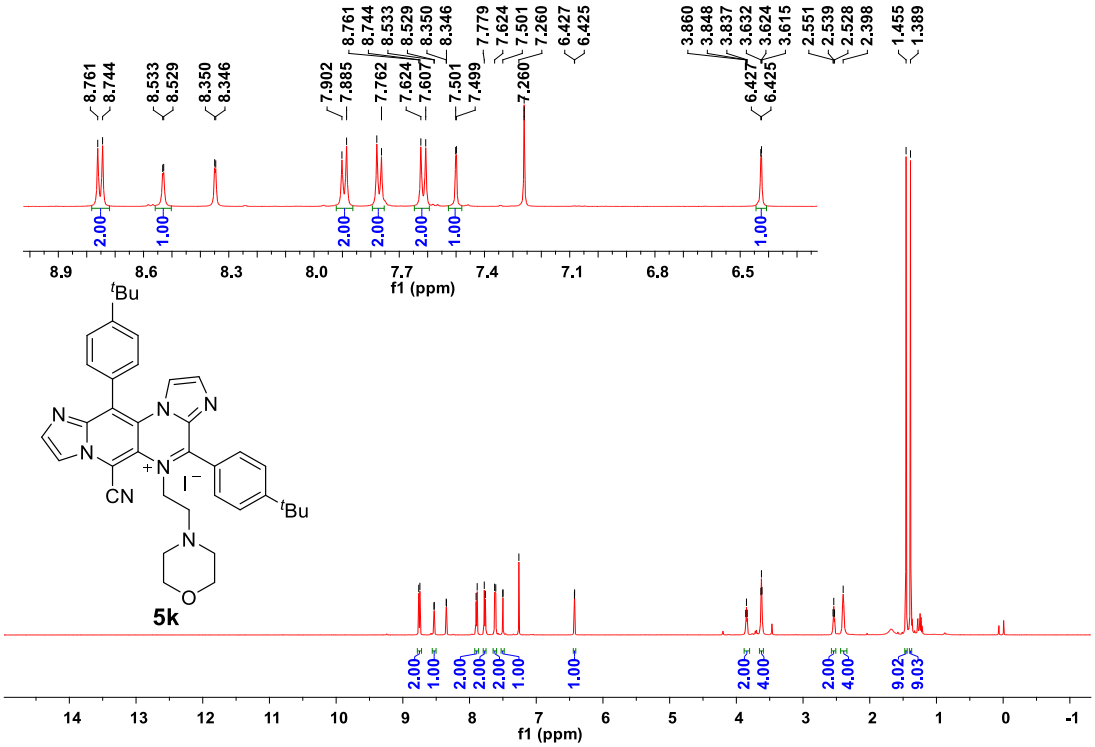


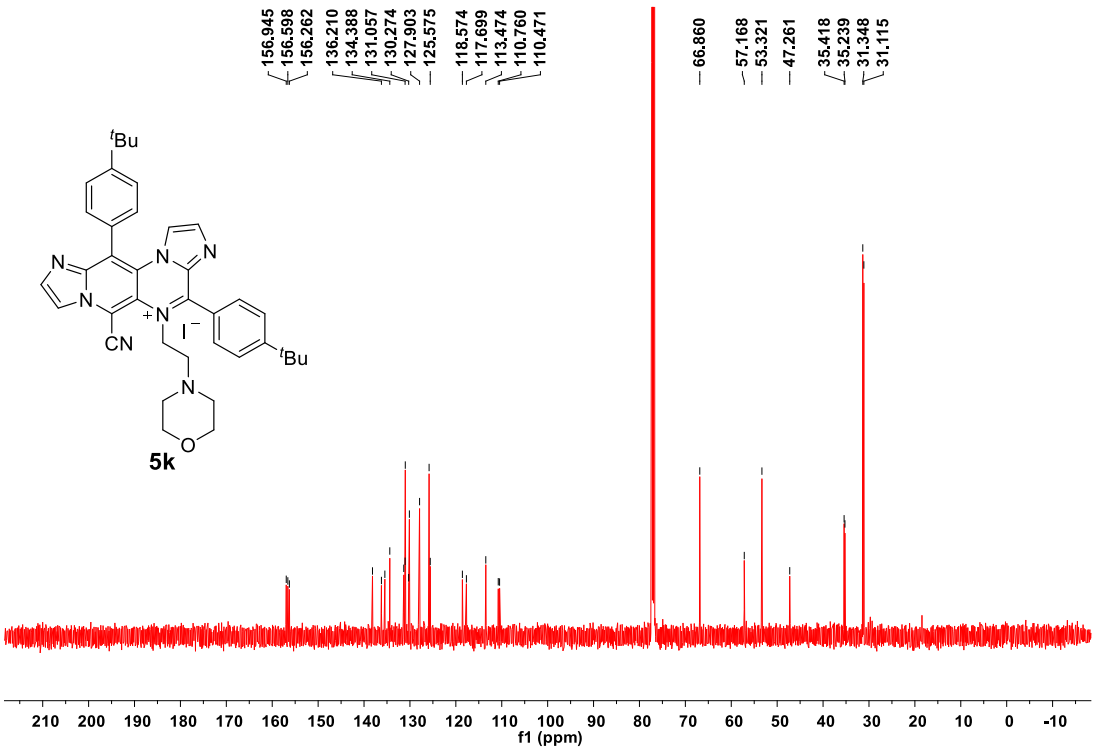
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-octadecylimidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5j)



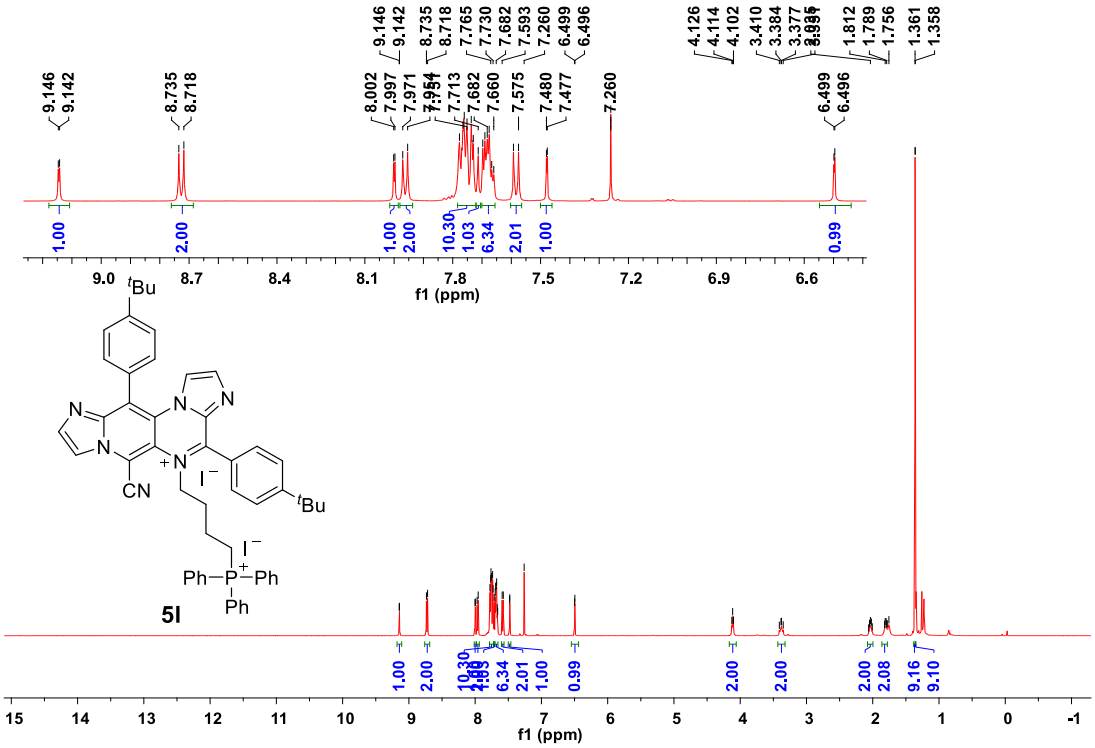


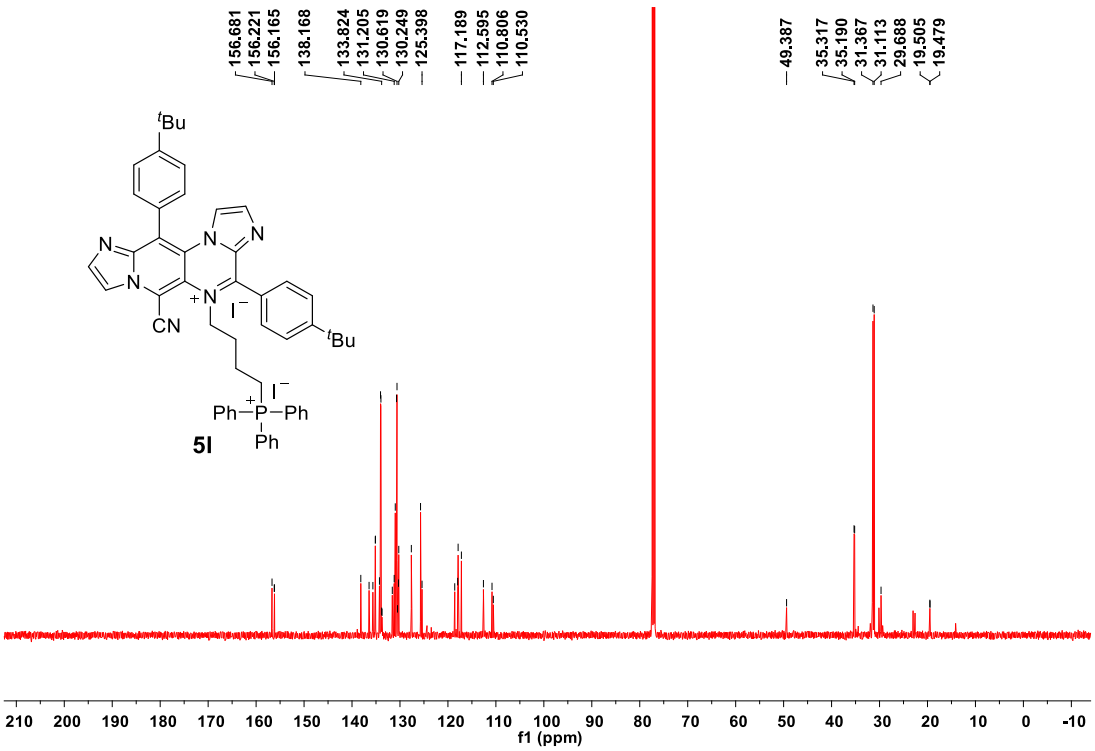
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(2-morpholinoethyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5k)



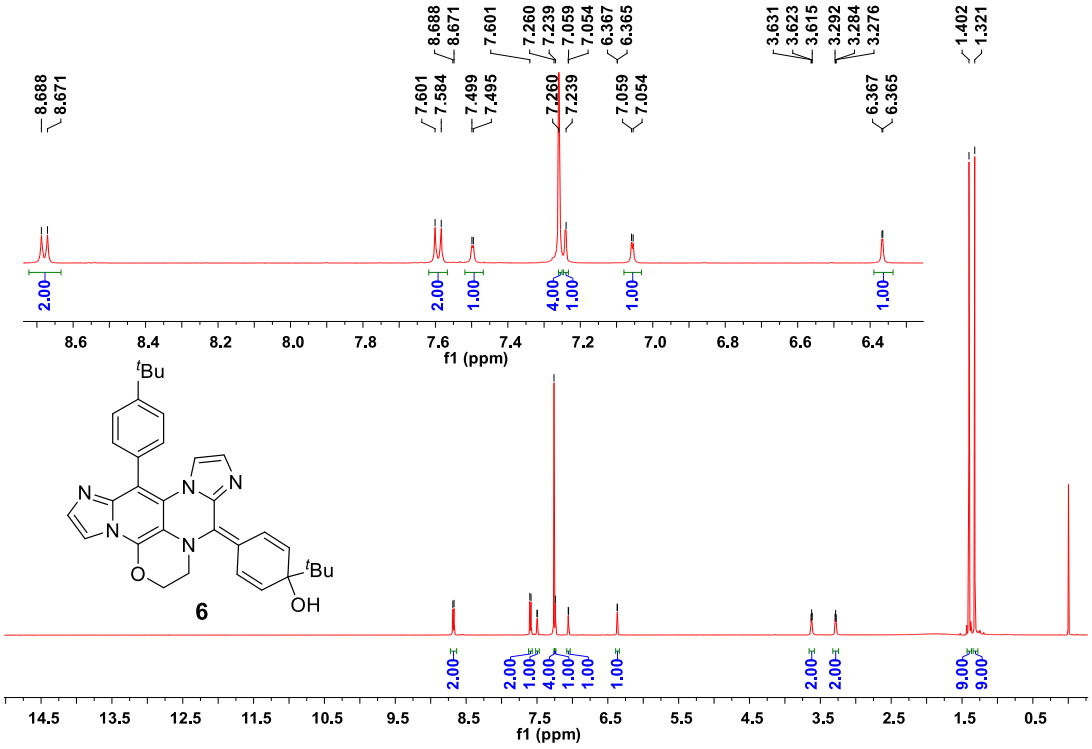


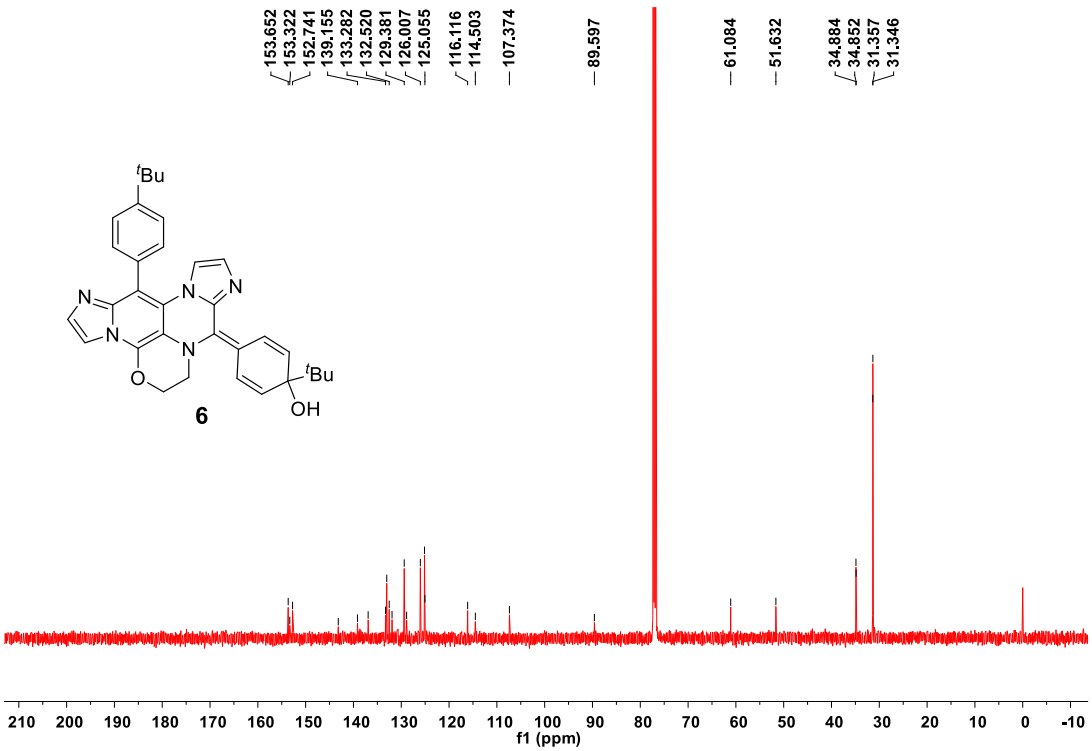
4,11-Bis(4-(tert-butyl)phenyl)-6-cyano-5-(4-(triphenylphosphonio)butyl)imidazo[1',2':1,6]pyrido[3,4-e]imidazo[1,2-a]pyrazin-5-ium iodide (5l)





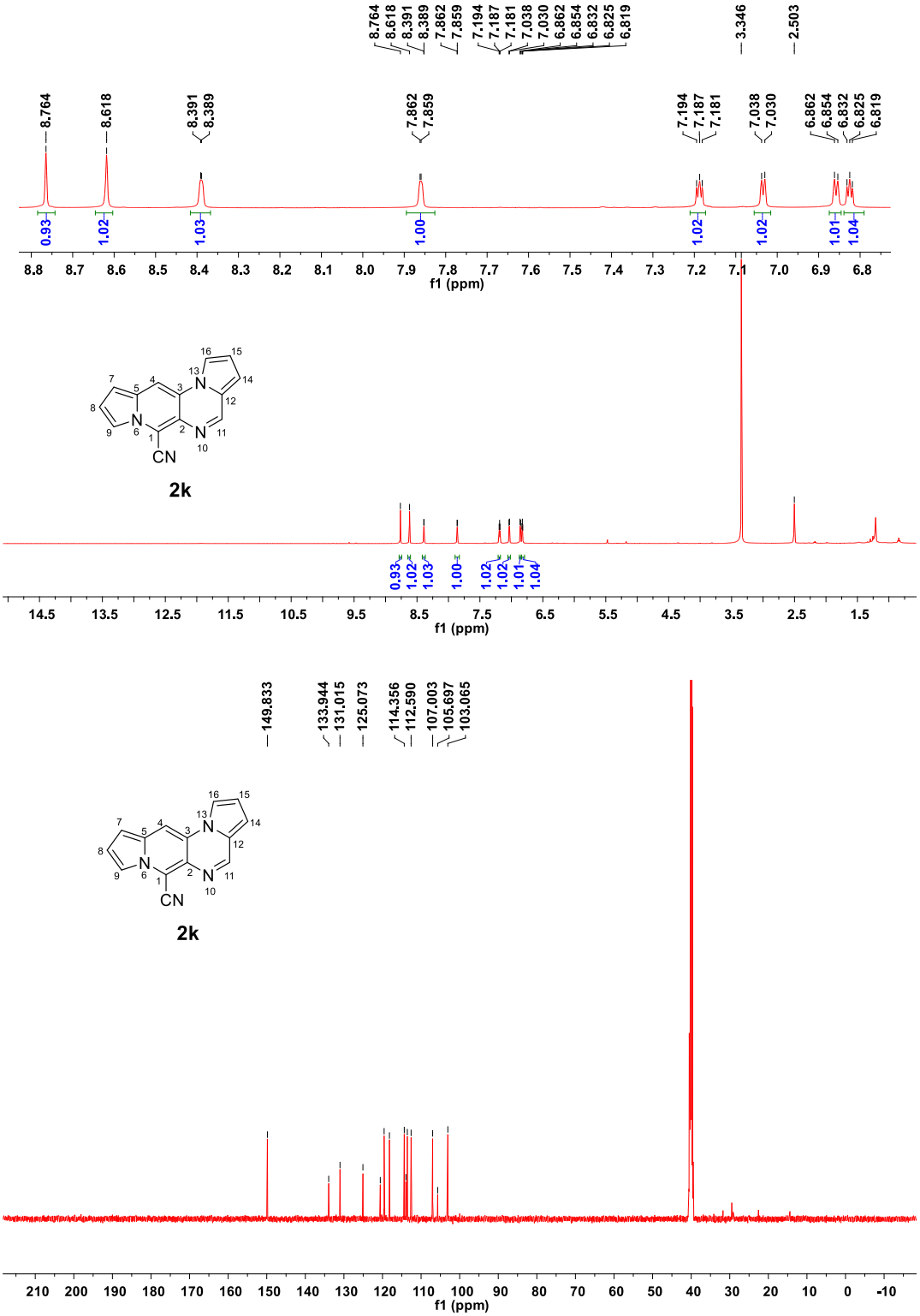
1-(Tert-butyl)-4-(11-(4-(tert-butyl)phenyl)-5,6-dihydro-7H-4-oxa-1,3a,6a,8,10a-pentaazadicyclopenta[a,e]phenalen-7-ylidene)cyclohexa-2,5-dien-1-ol (6)



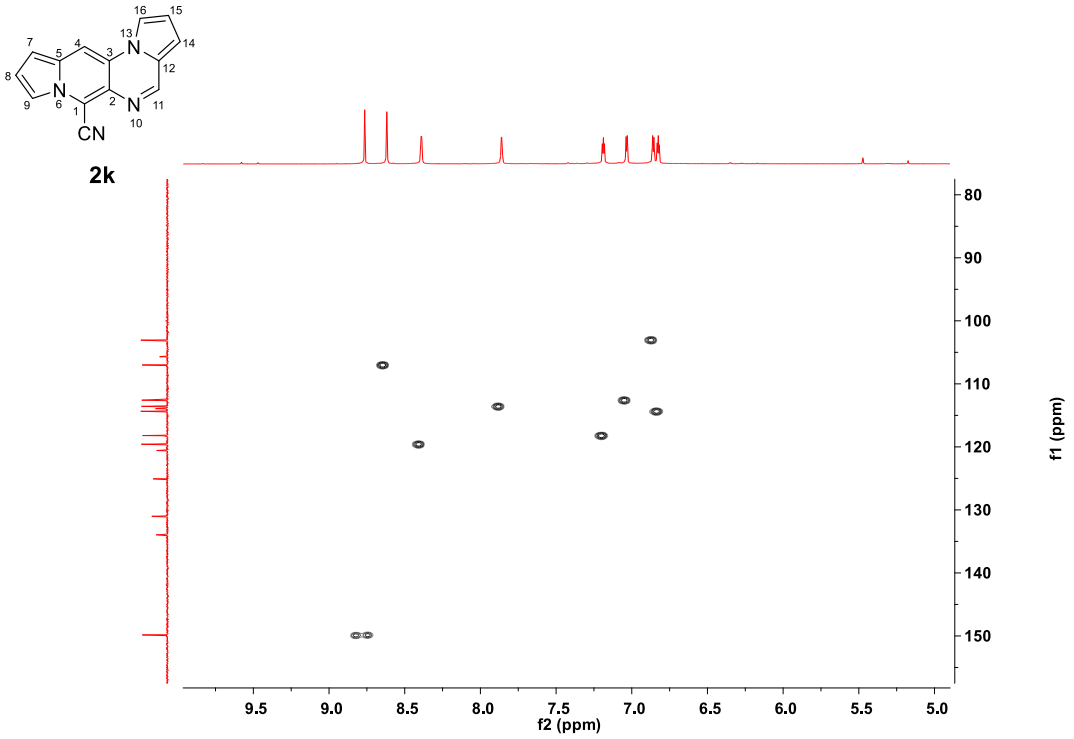


Pyrrolo[1',2':4,5]pyrazino[2,3-f]indolizine-6-carbonitrile (2k)

C-2 (δ 133.9), H-4 (δ 8.62) and H-11 (δ 8.77) of **2k** were determined by ^{1}H NMR, ^{13}C NMR and HSQC. The correlation of C-7 and H-5 from HMBC showed that the intermolecular aldol cyclization of **2k** might be the first step. The correlation of C-7 and H-10 from HMBC showed further aldimine condensation.



HSQC of **2k**



HMBC of **2k**