

Preparation of a Library of Cycloimmonium Salts by Westphal Condensation Through Parallel Synthesis in Solid-Phase

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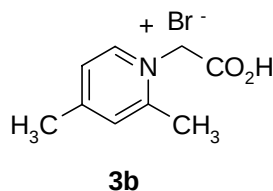
28871- Alcalá de Henares, Madrid, Spain

Supporting Information

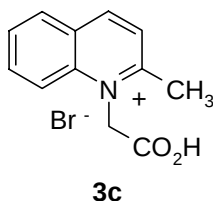
General methods. All reactions were carried out under argon in oven-dried glassware. Toluene, ethyl ether and THF were dried and distilled from sodium. Methylene chloride was dried and distilled from calcium hydride. Acetone and *iso*-propanol were high quality solvents and used as received. Anhydrous DMF was stored under molecular sieves. Commercial reagents were purchased from Aldrich and used without further purification. Resins were purchased from Advanced Chemtech (PS-Wang) and Argonaut Technologies (ArgoGel-Wang).

High Performance Liquid Chromatography (HPLC) analysis was performed using Agilent Technology 1100 series instrument with Atlantis dC-18 (30 x 4.6 mm I. D.) column under the following assay conditions: 0.05% ammonium acetate/H₂O: MeOH: MeCN 100:0:0 mobile phase, then gradient up to 0:50:50 (5.5 min), and final mobile phase 0:0:100 (6.5 min), 1 mL/min flow rate, 210 nm, 40 °C column temperature. Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) were measured on Varian Gemini 200 (50 MHz for ¹³C) or Varian Unity 300 (75 MHz for ¹³C) instruments. High Resolution Mass Spectrometry (HRMS) measurements were performed on LCT Micromass instrument using ES technique.

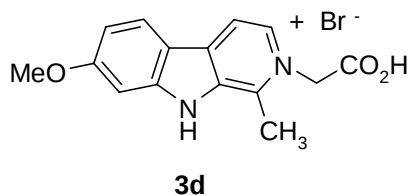
Synthesis of cycloimmonium salts 3b-h. General procedure. To a solution of the corresponding heterocycle (1 equiv) in toluene, ethyl bromoacetate (1 equiv) and nBu₄NI (1.1 equiv) were added and the reaction mixture was refluxed overnight. The reaction was cooled at room temperature and the precipitate filtered, washed with ethyl ether and dried *in vacuo*. The solid was suspended in 48% HBr and refluxed for 1 h. The reaction was cooled at room temperature, concentrated to dryness and the residue triturated with toluene, filtered and dried *in vacuo*.



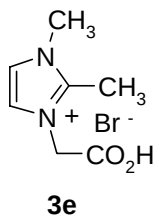
¹H-NMR (300 MHz; CD₃OD): δ 8.75 (d, 1 H, *J* = 6.5 Hz); 7.95 (s, 1 H); 7.84 (d, 1 H, *J* = 6.5 Hz); 5.53 (s, 2 H); 2.79 (s, 3 H); 2.70 (s, 3 H). **¹³C-RMN** (50 MHz, CD₃OD): δ 168.1; 162.1; 156.5; 146.6; 131.3; 127.4; 58.6; 21.9; 19.9. **HRMS** (ES): Calculated for C₉H₁₂NO₂⁺: 166.0868; Found: 166.0855. Yield: 89 %.



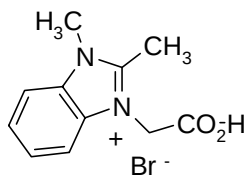
¹H NMR (300 MHz, *d*₆-DMSO): δ 9.25 (d, *J* = 8.5 Hz, 1 H); 8.49-8.45 (m, 2H); 8.28-8.25 (m, 1 H); 8.23 (d, *J* = 8.5 Hz, 1 H); 8.02 (t, *J* = 7.5 Hz, 1 H); 6.00 (s, 2 H); 2.53 (s, 3 H). **¹³C NMR** (75 MHz, *d*₆-DMSO): δ 166.4; 161.1; 146.5; 138.3; 135.1; 130.1; 128.6; 127.7; 124.5; 117.8; 52.6; 22.4. **HRMS** (ES): Calculated for C₁₂H₁₃NO₂⁺: 202.0876; Found: 202.0868. Yield: 60 %.



¹H NMR (300 MHz, CD₃OD): δ 12.38 (s, 1 H); 8.41 (d, *J* = 6.6 Hz, 1 H); 8.34 (d, *J* = 6.6 Hz, 1 H); 8.22 (d, *J* = 8.8 Hz, 1 H); 7.17 (d, *J* = 2.1 Hz, 1 H); 7.08 (dd, *J* = 8.8 and 2.1 Hz, 1 H); 5.63 (s, 2 H); 4.01 (s, 3 H); 3.04 (s, 3 H). **¹³C NMR** (50 MHz, CD₃OD): δ 169.0; 167.8; 165.5; 148.1; 140.38; 136.2; 135.94; 133.9; 125.3; 115.2; 114.8; 95.0; 58.1; 56.4; 15.3. **HRMS**: Calculated for C₁₅H₁₅N₂O₃⁺: 271.1083; Found: 271.1083. Yield: 63 %.

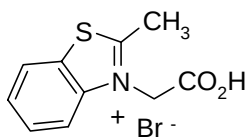


¹H NMR (300 MHz, *d*₆-DMSO): δ 12.38 (s, 1 H); 7.67 (d, *J* = 7.1 Hz, 2H); 5.17 (s, 2H), 3.82 (s, 3H), 3.56 (s, 3H). **¹³C NMR** (75 MHz, *d*₆-DMSO): δ 167.9; 145.6; 123.2; 49.8; 36.0; 10.4. **HRMS**: Calculated for C₇H₁₂N₂O₂⁺ : 155.0793; Found: 155.0821. Yield: 65 %.



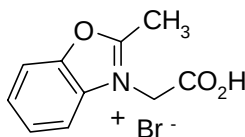
3f

¹H NMR (300 MHz, CD₃OD): δ 8.0-7.9 (m, 2 H); 7.7-7.6 (m, 2 H); 5.46 (s, 2 H); 4.10 (s, 3 H); 2.92 (s, 3 H). **¹³C NMR** (75 MHz, CD₃OD): δ 168.92; 153.9; 133.0; 127.9; 127.7; 127.5; 113.8; 113.4; 60.0; 33.3; 31.9. **HRMS**: Calculated for C₁₁H₁₃N₂O₂⁺ : 209.0977; Found: 209.0987. Yield: 78 %.



3g

¹H NMR (300 MHz, *d*₆-DMSO): δ 8.50 (d, *J* = 7.4 Hz, 1 H); 8.30 (d, *J* = 8.3 Hz, 1 H); 7.90 (t, *J* = 7.2 Hz, 1 H); 7.82 (t, *J* = 7.3 Hz, 1H), 5.79 (s, 2 H); 3.21 (s, 3 H). **¹³C NMR** (75 MHz, *d*₆-DMSO): δ 178.2; 165.8; 140.4; 128.9; 127.9; 127.5; 124.3; 115.9; 49.6; 16.8. **HRMS**: Calculated for C₁₀H₁₁NO₂S⁺ : 208.0405; Found: 208.0432. Yield: 85 %.



3h

¹H NMR (300 MHz, *d*₆-DMSO): δ 7.29 (d, *J* = 7.9 Hz, 1 H); 7.20 (t, *J* = 6.4 Hz, 1 H); 6.97 (d, *J* = 8.1 Hz, 1 H); 6.85 (t, *J* = 7.7 Hz, 1H), 4.52 (s, 2 H); 1.73 (s, 3 H). **¹³C NMR** (75 MHz, *d*₆-DMSO): δ 169.6; 165.6; 146.5; 128.9; 128.3; 127.4; 114.4; 112.4; 47.0; 13.3.

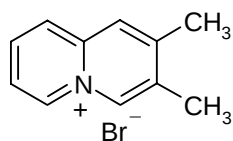
Synthesis of resin-bound cycloimmonium salts **2**.

2a. Into a suspension of Wang resin (1.5 g; 1.2 mmol) in dichloromethane/DMF 1:1 (12 mL) at 0 °C the following reagents were added: bromoacetic acid (0.84 g; 6.01 mmol), DIC (0.76 g; 6.01 mmol), HOBt (0.81 g; 6.01 mmol) and 2-picoline (0.56 g; 6.01 mmol). After 15 min at 0 °C, the mixture was shaken at room temperature for 2h. The resin was filtered and treated again to the above conditions with extra 2-picoline (1.12 g; 12.02 mmol) and shaken at room temperature overnight. The resin suspension was filtered and washed with 2-propanol and dichloromethane (repeated five times) and dried *in vacuo*. A light yellow resin was obtained (1.72 g; 0.68 mmol/g; quant.).

2b,d-g. General procedure. Wang resin (1.5 g, 1.2 mmol) was swollen in dichloromethane and filtered. A solution of the corresponding cycloimmonium salt **3** (1.5-3 equiv) in dichloromethane/DMF 1:1 (12 mL) was added, followed by DIC (3 equiv) and HOBt (3 equiv). The reaction mixture was shaken at room temperature overnight, filtered, washed with DMF, iPrOH, DCM and dried *in vacuo*. A portion of the dried resin (c.a. 100 mg) was treated with a 25% solution of trifluoroacetic acid in dichloromethane (10 mL/g) at room temperature for 1h, filtered and washed with dichloromethane and methanol. The filtrate was collected and evaporated *in vacuo*: **2a** (0.68 mmol/g, quant.); **2b** (0.45 mmol/g; 68%); **2d** (0.20 mmol/g; 32%); **2e** (0.27 mmol/g; 40%); **2f** (0.50 mmol/g; 77%); **2g** (0.66 mmol/g; quant.).

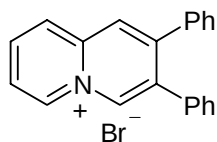
Westphal reaction on solid-phase. General procedure. Resin **2** (c. a. 300 mg) was placed in a reaction vessel and then a solution of the 1,2-diketone compound **4** (3 equiv.) in dry THF (3 mL) was added, followed by triethyl amine (3 equiv) and the mixture was heated at 70 °C for 18 h. Then, the reaction mixture was filtered and the resin rinsed with THF and MeOH. The combined cleavage and rinse solutions were concentrated *in vacuo*. The product

was precipitated by adding diethyl ether and dichloromethane. The precipitate was filtered, washed with diethyl ether and *dried in vacuo*.



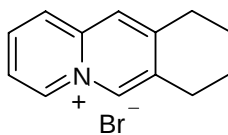
5aa

¹H NMR (300 MHz, CD₃OD): δ 9.1-9.0 (m, 2 H); 8.4-8.3 (m, 2 H); 8.23 (t, *J* = 7.6 Hz, 1 H,); 7.92 (t, *J* = 7.6 Hz, 1 H,); 2.69 (s, 3 H); 2.61 (s, 3 H). **¹³C NMR** (50 MHz; CD₃OD): δ 152.1; 136.9; 136.6; 136.2, 135.2; 127.1; 126.6; 123.8; 20.0; 17.1. **HRMS**: Calculated for C₁₁H₁₂N⁺: 158.0970; Found: 158.0978. Yield: 80 %. Purity: 100 %.



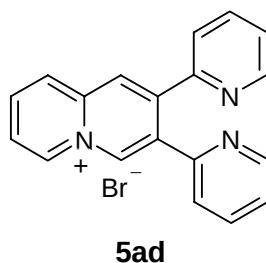
5ab

¹H NMR (300 MHz, CD₃OD): δ 9.36 (s, 1 H); 9.28 (d, *J* = 6.6 Hz, 1 H,); 8.59 (s, 1 H); 8.58 (d, *J* = 8.5 Hz, 1 H,); 8.38 (t, *J* = 8.5 Hz, 1 H,); 8.07 (t, *J* = 7.1 Hz, 1 H,); 7.5-7.4 (m, 10 H). **¹³C NMR** (75 MHz, CD₃OD): δ 151.3; 143.5; 138.8; 137.7; 137.4; 137.2; 135.6; 131.02; 130.7; 130.6; 130.3; 129.9; 129.8; 129.3; 128.1; 124.9. **HRMS**: Calculated for C₂₁H₁₆N⁺: 282.1283; Found: 282.1298. Yield: 64 %. Purity: 97 %.

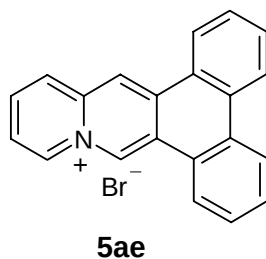


5ac

¹H NMR (300 MHz, CD₃OD): δ 9.02 (s, 1 H); 8.93 (d, *J* = 6.9 Hz, 1 H); 8.31 (d, *J* = 8.6 Hz, 1 H); 8.2-8.1 (m, 2 H); 7.88 (t, *J* = 6.7 Hz, 1 H); 3.2-3.1 (m, 4 H); 2.0-1.9 (m, 4 H). **¹³C NMR** (50 MHz, CD₃OD): δ 148.0; 146.3; 145.5; 132.6; 131.7; 130.58; 126.9; 126.51; 104.91; 47.9; 46.3; 20.5. **HRMS**: Calculated for C₁₃H₁₄N⁺: 184.1126; Found: 184.1128. Yield : 80 %. Purity: 98 %.

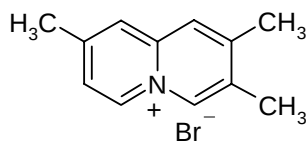


¹H NMR (300 MHz, CD₃OD): δ 9.61 (s, 1 H); 9.40 (d, *J* = 6.6 Hz, 1 H); 8.85 (s, 1 H); 8.68 (d, *J* = 8.6 Hz, 1 H); 8.52 (m, 2 H); 8.48 (t, *J* = 7.8 Hz, 1 H); 8.16 (t, *J* = 7.1 Hz, 1 H); 8.0-7.9 (m, 2 H); 7.59 (t, *J* = 7.5 Hz, 2 H); 7.5-7.4 (m, 2 H). **¹³C NMR** (75 MHz, CD₃OD): δ 154.9; 153.9; 150.8; 150.6; 148.6; 144.0; 138.8; 138.6; 138.5; 136.9; 129.5; 128.8; 128.6; 126.5; 126.2; 125.6; 125.5; 125.1; 123.1. **HRMS**: Calculated for C₁₉H₁₄N₃⁺: 284.1188; Found: 284.1181. Yield: 95 %. Purity: 90 %.



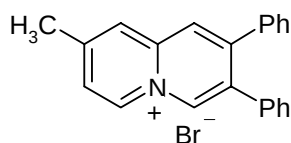
¹H NMR (300 MHz, CD₃OD): δ 10.61 (s, 1 H); 9.61 (s, 1 H); 9.48 (d, *J* = 6.8 Hz, 1 H); 8.89 (d, *J* = 7.7 Hz, 1 H); 8.82 (d, *J* = 7.9 Hz, 1 H); 8.73 (d, *J* = 8.1 Hz, 1 H); 8.60 (d, *J* = 8.8 Hz, 1 H); 8.27 (t, *J* = 8.0 Hz, 1 H); 8.04 (t, *J* = 6.6 Hz, 1 H); 8.0-7.8 (m, 4 H). **¹³C NMR** (75 MHz, CD₃OD): δ 157.1; 141.2; 139.5; 136.0; 135.0; 134.3; 133.6;

132.2; 130.1; 130.0; 128.1; 126.7; 126.5; 126.0; 125.2; 125.1; 124.2; 121.2. **HRMS:** Calculated for $C_{21}H_{14}N^+$: 280.1126; Found: 280.1118. Yield: 69 %. Purity: 100 %.



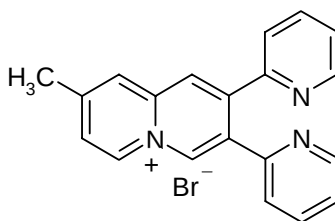
5ba

1H NMR (300 MHz, CD_3OD): δ 8.94-8.91 (m, 2 H); 8.13 (s, 2 H); 7.79 (d, J = 6.2 Hz, 1 H); 2.70 (s, 3 H); 2.66 (s, 3 H); 2.61 (s, 3 H). **^{13}C NMR** (50 MHz, CD_3OD): δ 151.6; 149.9; 135.8; 135.5, 134.5; 125.9; 125.7; 125.6; 21.5; 19.9; 16.9. **HRMS:** Calculated for $C_{12}H_{14}N^+$: 172.1126; Found: 172.1114. Yield: 95 %. Purity: 100 %.



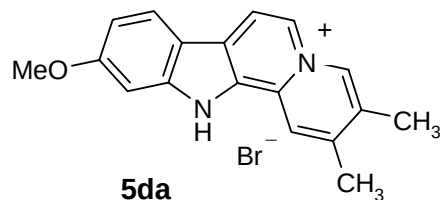
5bb

1H NMR (300 MHz, CD_3OD): δ 9.24 (s, 1 H); 9.15 (t, J = 7.5 Hz, 1 H); 8.43 (s, 1 H); 8.35 (s, 1 H); 7.76 (t, J = 7.4 Hz, 1 H); 7.46-7.34 (m, 10 H); 2.78 (s, 3 H). **^{13}C NMR** (50 MHz, CD_3OD): δ 151.2; 150.8; 143.1; 137.7; 137.2; 136.7; 135.6; 136.1; 134.1; 130.8; 130.6; 130.5; 130.2; 130.0, 129.7; 129.6; 127.2; 126.9; 126.6; 21.8. **HRMS:** Calculated for $C_{22}H_{18}N^+$: 296.1439; Found: 296.1421. Yield: 82 %. Purity: 75 %.

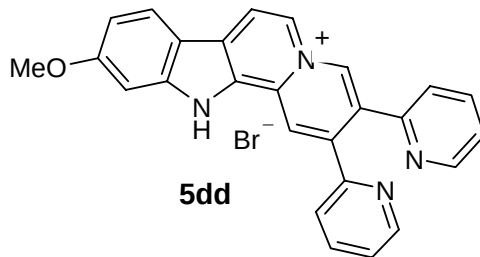


5bd

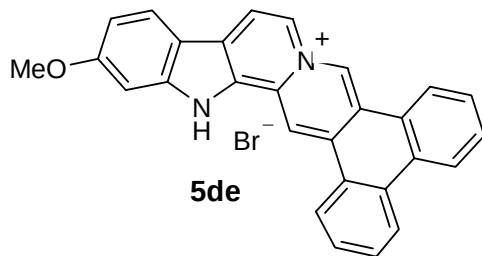
¹H NMR (300 MHz, CD₃OD): δ 9.48 (s, 1 H); 9.24 (d, *J* = 6.9 Hz, 1 H); 8.68 (s, 1 H); 8.57 (bs, 2 H); 8.46 (s, 1 H); 8.03 (d, *J* = 6.6 Hz, 1 H); 7.93-7.88 (m, 2 H); 7.58-7.45 (m, 4 H); 2.81 (s, 3 H). **¹³C NMR** (75 MHz, CD₃OD): δ 115.1; 154.1; 152.6; 150.7; 148.3; 138.6; 138.5; 138.0; 137.2; 136.0; 128.1; 127.7; 127.3; 126.4; 126.2; 125.8; 125.4; 125.1; 21.8. **HRMS**: Calculated for C₂₀H₁₆N₃⁺: 298.1344; Found: 298.1319. Yield: 90 %. Purity: 78 %.



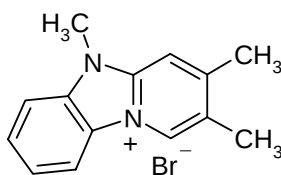
¹H NMR (300 MHz, CD₃OD): δ 8.93 (s, 1 H); 8.65 (d, *J* = 6.7 Hz, 1 H); 8.38-8.34 (m, 2 H); 8.08 (d, *J* = 8.7 Hz, 2 H); 7.15 (s, 1 H); 7.02 (d, *J* = 8.7 Hz, 1 H); 3.99 (s, 3 H); 2.70 (s, 3 H); 3.55 (s, 3 H). **¹³C NMR** (75 MHz, CD₃OD): δ 163.1; 149.8; 144.3; 134.6; 133.6; 131.4; 130.1; 127.1; 124.1; 123.2; 120.3; 116.0; 115.7; 113.8; 95.1; 56.3; 20.2; 16.8. **HRMS**: Calculated for C₁₈H₁₇N₂O⁺: 277.1341; Found: 277.1323. Yield: 98 %. Purity: 90 %.



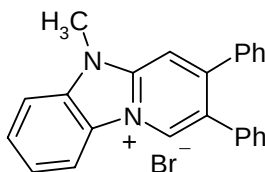
¹H NMR (300 MHz, *d*₆-DMSO): δ 9.70 (s, 1 H); 9.22 (s, 1 H); 9.14 (d, *J* = 6.2 Hz, 1 H); 8.80 (d, *J* = 6.2 Hz, 1 H); 8.63-8.57 (m, 2 H); 8.33 (d, *J* = 8.9 Hz, 1 H); 7.93-7.89 (m, 2 H); 7.53-7.45 (m, 4 H); 7.22 (s, 1 H); 7.11 (d, *J* = 8.6 Hz, 1 H); 4.04 (s, 3 H). **¹³C NMR** (50 MHz, *d*₆-DMSO): δ 161.1; 153.4; 152.5; 149.1; 148.9; 144.1; 142.9; 137.0; 136.5; 136.4; 131.4; 130.1; 129.8; 127.1; 124.0; 123.9; 123.6; 123.4; 123.0; 122.8; 121.5; 115.92; 114.0; 112.3; 94.1; 55.3; **HRMS**: Calculated for C₂₆H₁₉N₄O⁺: 403.1559; Found: 403.1546. Yield: 99 %. Purity: 92 %.



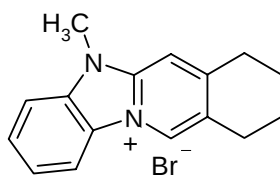
^1H NMR (300 MHz, $\text{CD}_3\text{OD} + d_6\text{-DMSO}$): δ 10.68 (s, 1 H); 9.85 (s, 1 H); 9.10-9.00 (m, 1 H); 8.92-8.55 (m, 5 H); 8.12 (d, $J = 8.4$ Hz, 1H); 8.87-8.81 (m, 4 H); 7.10 (s, 1 H); 6.95 (d, $J = 8.5$ Hz, 1H); 4.37 (s, 3 H). **^{13}C NMR** (75 MHz, $d_6\text{-DMSO}$, 70 $^\circ\text{C}$): δ 160.7; 156.0; 147.0; 138.6; 135.4; 131.5; 129.9; 128.4; 128.2; 128.0; 127.5; 124.8; 124.6; 123.8; 123.6; 123.2; 122.5; 122.1; 117.8; 115.4; 113.5; 111.9; 107.8; 94.6; 49.0. **HRMS**: Calculated for $\text{C}_{28}\text{H}_{19}\text{N}_2\text{O}^+$: 399.1497; Found: 399.1470. Yield: 99 %. Purity: 83 %.



^1H NMR (300 MHz, CD_3OD): δ 9.23 (s, 1 H); 8.47 (d, $J = 8.4$ Hz; 1 H); 8.07 (s, 1 H); 8.04-8.00 (m, 1 H); 7.92-7.87 (m, 1 H); 7.74 (t, $J = 7.3$ Hz, 1 H); 4.18 (s, 3 H); 2.71 (s, 3 H); 2.56 (s, 3 H). **^{13}C NMR** (75 MHz, $d_6\text{-DMSO}$): δ 140.3; 137.2; 129.3; 128.8; 127.9; 127.8; 125.5; 125.4; 123.4; 123.3; 111.5; 101.8; 30.1. **HRMS**: Calculated for $\text{C}_{14}\text{H}_{15}\text{N}_2^+$: 211.1235; Found: 211.1214. Yield: 97 %. Purity: 84 %.

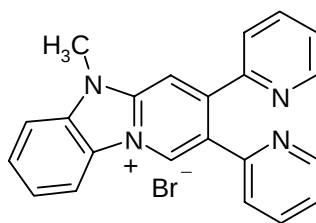


^1H NMR (300 MHz, CD_3OD): δ 9.50 (s, 1 H); 8.63 (d, J = 8.2 Hz, 1 H); 8.30 (s, 1 H); 8.11 (d, J = 8.4 Hz, 1 H); 7.99-7.95 (m, 1 H); 7.80 (t, J = 7.3 Hz, 1 H); 7.44-7.34 (m, 10 H); 4.31 (s, 3 H). **^{13}C NMR** (75 MHz, CD_3OD): δ 154.1; 153.8; 143.9; 138.7; 136.7; 135.2; 133.6; 133.4; 132.8; 131.6; 131.3; 131.0; 130.7; 130.0; 129.9; 128.3; 128.2; 126.6; 115.4; 114.1; 113.6; 111.8; 48.2. **HRMS**: Calculated for $\text{C}_{24}\text{H}_{19}\text{N}_2^+$: 335.1548; Found: 335.1534. Yield: 86 %. Purity: 88 %.



5fc

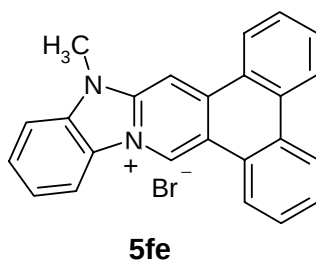
^1H NMR (300 MHz, CD_3OD): δ 9.21 (s, 1 H); 8.46 (d, J = 8.4 Hz, 1 H); 8.01-7.98 (m, 2 H); 8.89 (t, J = 7.8 Hz, 1 H); 7.22 (t, J = 7.7 Hz, 1 H); 4.16 (s, 3 H); 3.29-3.01 (m, 4 H); 2.01 (s, 4 H). **^{13}C NMR** (50 MHz, CD_3OD): δ 154.2; 143.18; 134.4; 130.4; 129.3; 127.5; 125.4; 114.4; 112.1; 109.4; 31.2; 30.7; 27.1; 22.9; 22.8. **HRMS**: Calculated for $\text{C}_{16}\text{H}_{17}\text{N}_2^+$: 237.1392; Found: 237.1381. Yield: 90 %. Purity: 93 %.



5fd

^1H NMR (300 MHz, CD_3OD): δ 9.76 (s, 1 H); 8.67 (d, J = 8.4 Hz, 1 H); 8.58-8.55 (m, 3 H); 8.16 (d, J = 8.4 Hz, 1 H); 8.01 (t, J = 8.3 Hz, 1 H); 7.94-7.82 (m, 3 H); 7.58 (t, J = 6.8 Hz, 1 H); 7.50-7.44 (m, 2 H); 4.36 (s, 3 H). **^{13}C NMR** (75 MHz, CD_3OD): δ 156.2; 155.1; 151.1; 150.9; 150.8; 149.9; 144.1; 138.9; 138.8; 135.4; 131.6; 131.2;

128.8, 128.4, 126.9; 126.7; 125.6; 124.9; 115.5; 113.9; 112.7; 31.8. **HRMS**: Calculated for $C_{22}H_{17}N_4^+$: 337.1453; Found: 337.1420. Yield: 95 %. Purity: 93 %.



¹H NMR (300 MHz, CD₃OD): δ 10.19 (s, 1 H); 8.82-8.71 (m, 3 H); 8.39 (t, J = 6.4 Hz, 2 H); 8.02-7.97 (m, 2 H); 7.82-7.63 (m, 6 H); 4.22 (s, 3 H). **¹³C NMR** (75 MHz, CD₃OD): δ 153.9; 143.5; 134.3; 131.4; 130.5; 130.4; 130.1; 129.0; 127.6; 127.4; 125.8; 125.6; 125.1; 114.4; 114.2; 113.3; 113.0; 110.2, 45.0. **HRMS**: Calculated for $C_{24}H_{17}N_2^+$: 333.1392; Found: 333.1371. Yield: 97 %. Purity: 84 %.