Supplementary Material (ESI) for Chemical Communications

Supporting Information

Discovery of an Imidazo-Phenanthridine Synthon Produced in a 'Five-Step One-Pot Reaction' Leading to a New Family of Heterocycles with Novel Pysical Properties

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1) Instruments and Materials

All reactions were carried out using oven-dried glassware. All starting materials and solvents were commercially available (reagent grade) and used as supplied, from Aldrich Chemical Co., without further purification.

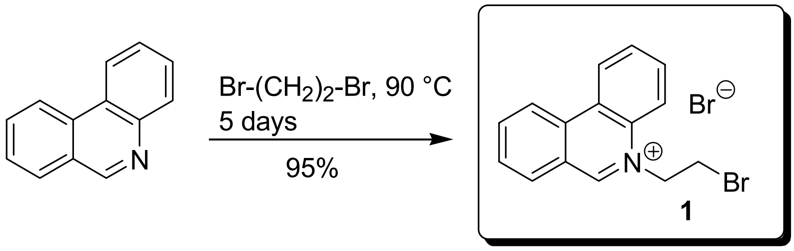
^{1}H NMR and ^{13}C NMR were recorded using a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts (δ) are given in ppm relative to residual solvent peak. Coupling constants (J) are given in Hz. The multiplicities are expressed as follows: s = singlet, d = doublet, t = triplet, q = quartet. Infra-red spectral analyses were performed on a JASCO 410 spectrophotometer, using a KBr disc; peaks are quoted in wavenumbers (cm^{-1}) and their relative intensity are reported as follows: s = strong, m = medium, w = weak. UV-Vis spectroscopy was performed on Shimadzu UV-310PC UV-VIS-NIR scanning spectrophotometer. Mass spectra were obtained using a JEOL JMS 700 spectrometer operating, in FAB, EI or CI mode. Microanalyses were performed on a CE-440 elemental analyzer. Melting points were determined on a digital IA9000 series melting point apparatus, using capillary tubes. ITC data has been collected using a Microcal VP-ITC system.

Definitions of abbreviations: EtOAC = Ethyl acetate; DIP = Dihydro Imidazo-Phenanthridinium bromide; IP = Imidazo-Phenanthridinium bromide; NBS = N-Bromosuccinimide; r.t. = Room temperature; ITC = Isothermal Titration Calorimetry; PIPES buffer = Piperazine-1,4-bis(2-ethanesulfonic acid).

2) Methodology

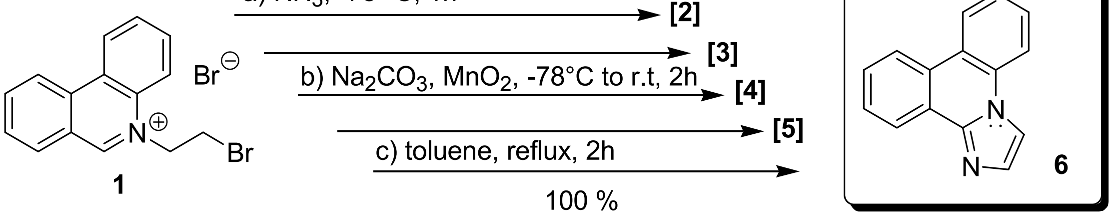
a. Synthetic procedure and analytical data

(I) 2-bromo-ethyl-phenanthridinium bromide, 1



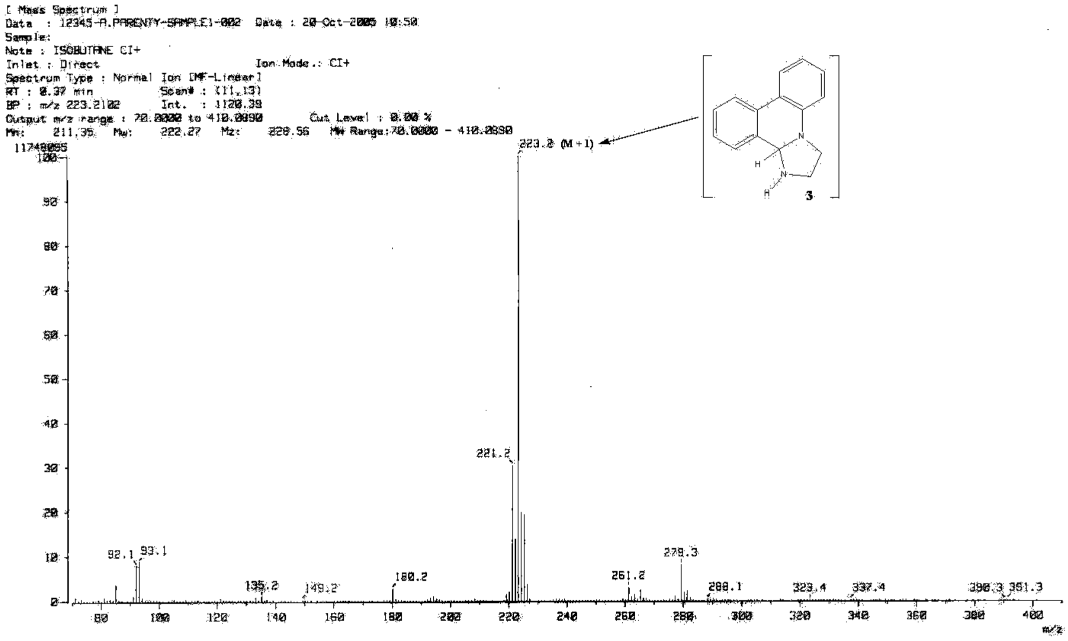
Phenanthridine (5.44 g; 30.3 mmol) was dissolved in 1,2-dibromoethane (114.2 g; 50 mL; 608 mmol) and stirred at 90 ˚C for five days. Any precipitate formed during the reaction was recovered by filtration daily. After each filtration, the precipitate was rinsed with an additional 5 mL of 1,2-dibromoethane and the mother liquor stirred at 90 ˚C until the next filtration. The reaction was complete when no more precipitate formed. The precipitates were combined and washed with acetone to give **1** (10.56 g; 28.8 mmol) as a beige powder in a 95% yield; **mp**: 234-235 ˚C (dec.); **^{1}H NMR** (D_2O, 400 MHz): δ 9.81 (s, 1H), 8.72 (d, 1H, *J*=7.2 Hz), 8.63 (d, 1H, *J*=7.2 Hz), 8.37 (d, 1H, *J*=7.2 Hz), 8.26 (d, 1H, *J*=7.2 Hz), 8.18 (t, 1H, *J*=7.2 Hz), 7.98 (t, 1H, *J*=7.2 Hz), 7.90 (m, 2H), 5.37 (t, 2H, *J*=5.8 Hz), 4.05 (t, 2H, *J*=5.8 Hz); **^{13}C NMR** (D_2O, 100 MHz): δ 155.27 (CH), 139.03 (CH), 135.59 (C), 133.18 (CH), 132.78 (C), 132.58 (CH), 130.85 (CH), 130.72 (CH), 126.57 (C), 125.13 (CH), 123.32 (C), 123.00 (CH), 118.91(CH), 58.87 (CH_2), 29.41(CH_2); **IR** (KBr, cm^{-1}): 2947(w), 1620(m), 763(s), 717(m); MS (EI): 288.1 (M-Br) (100), 206.2 (8); Anal. Calcd for $C_{15}H_{13}NBr_2$: C, 49.32; H, 3.59; N, 3.84. Found: C, 49.15; H, 3.48; N, 3.76.

(II) Imidazo[1,2-f]phenanthridine, 6



2-bromo-ethyl-phenanthridinium (**1**) (700 mg; 1.9 mmol) was added to stirred liquid ammonia (50 ml) at -78 ˚C on a dry ice / acetone bath. The cooling bath was removed to warm the reaction mixture to -30˚C, the boiling point of ammonia, and the reaction stirred for 1 hour to yield intermediate **3** in solution (see following MS). The medium was returned at -78˚C before adding Na_2CO_3 (1g; 9.4 mmol) followed by MnO_2 (1.65g; 19 mmol) and the bath removed to slowly let the ammonia evaporate yielding intermediate **5** along with excess MnO_2 starting material (see following MS). The residual mixture was dried under vacuum for 10 minutes to remove any remaining ammonia vapour. Toluene (20 ml) was added and the reaction mixture refluxed for 3 hours then filtered. The inorganic residue was rinsed with acetone (3 x 5ml) and the filtrate was concentrated to dryness to afford **6** (410 mg; 1.9 mmol), as an off-white powder, in a quantitative yield. **mp**: 77-78 ˚C; **Rf** = 0.3 in ethyl acetate; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.79 (m, 1H), δ 8.51 (dd, 1H, *J*=8.0 and 1.0 Hz), δ 8.42 (m, 1H), δ 8.05 (d, 1H, *J*=1.2 Hz), δ 7.93 (dd, 1H, *J*=8.0 and 1.0 Hz), δ 7.7 (m, 3H), δ 7.68 (d, 1H, *J*=1.2 Hz), δ 7.58 (td, 1H, *J*=8.0 and 1.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 142.08 (C), δ 131.49 (C), δ 130.45 (C), δ 129.19 (CH), δ 129.06 (CH), δ 128.86 (CH), δ 127.68 (C), δ 125.53 (CH), δ 124.59 (CH), δ 124.29 (CH), δ 122.42 (CH), δ 121.91 (C), δ 115.94 (CH), δ 112.15 (CH); **IR** (KBr, cm^{-1}): 3432 (s), 1629 (m), 1532 (m), 1495 (w), 1463 (m), 1439 (m), 1316 (m), 1262 (s), 1104 (s), 803 (m), 719 (s); **MS** (FAB): 219.4 (M+1) (100), 178.7 (3), 164.9 (2), 98.8 (5), 71.2 (7), 57.4 (10); Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84; Found: C, 82.40; H, 4.65; N, 12.90.

a. MS evidence of intermediate 3



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[ Mass Spectrum ]
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Sample:
Note : ISOBUTANE CI+
Inlet : Direct                          Ion Mode : CI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.37 min             Scan# : (11,13)
BP : m/z 223.2102         Int.   : 1120.39
Output m/z range : 70.0000 to 410.0890        Cut Level : 0.00 %
Mn:    211.35   Mw:     222.27   Mz:     228.56   MW Range:70.0000 - 410.0890
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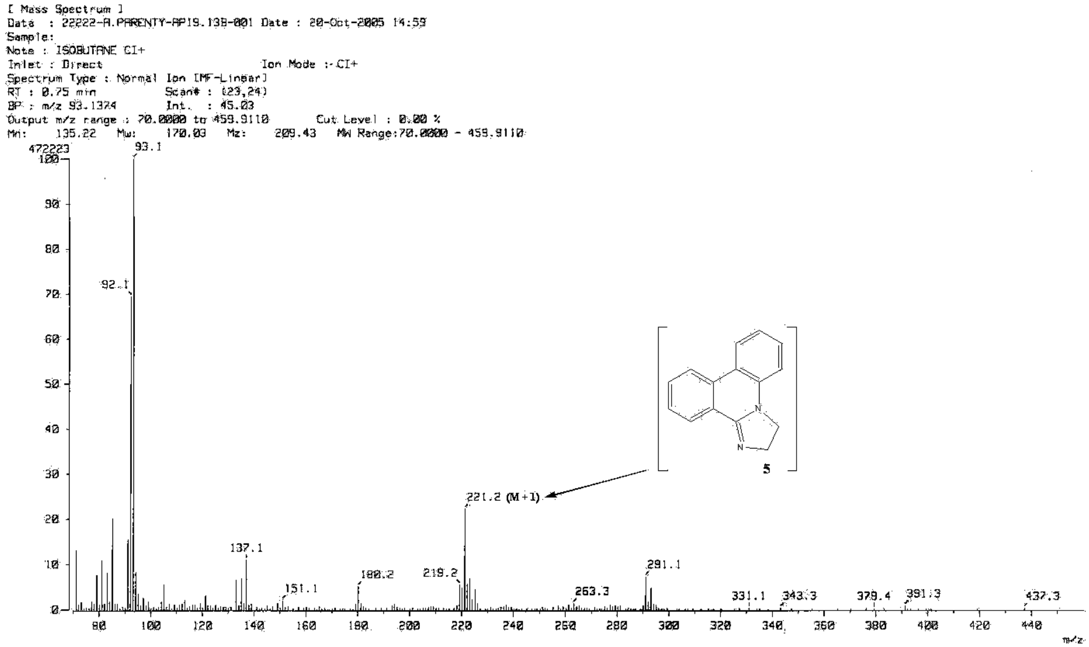
b. **MS evidence of intermediate 4**



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[ Mass Spectrum ]
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Sample:
Note : ISOBUTANE CI+
Inlet : Direct                          Ion Mode : CI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.75 min             Scan# : (23,24)
BP : m/z 93.1374          Int.   : 45.03
Output m/z range : 70.0000 to 459.9110        Cut Level : 0.00 %
Mn:    135.22   Mw:     170.03   Mz:     209.43   MW Range:70.0000 - 459.9110
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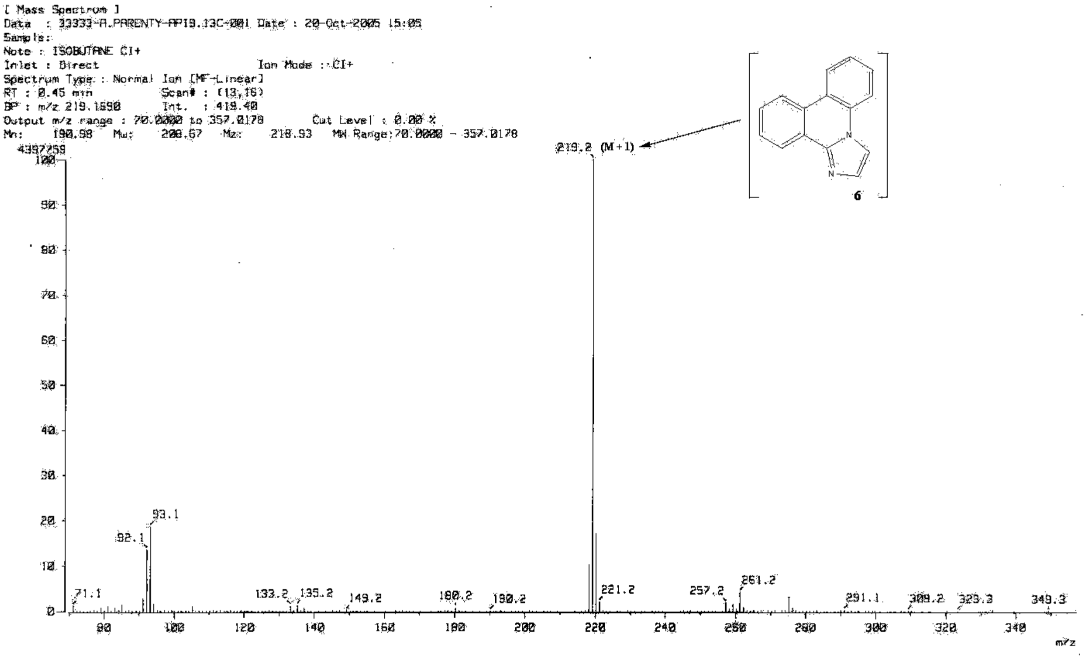
c. MS evidence of intermediate 5



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[ Mass Spectrum ]
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Sample:
Note : ISOBUTANE CI+
Inlet : Direct                          Ion Mode : CI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.45 min           Scan# : (13,16)
BP : m/z 219.1690       Int.   : 419.40
Output m/z range : 70.0000 to 357.0178        Cut Level : 0.00 %
Mn:     190.98   Mw:     200.67   Mz:     210.93   MW Range:70.0000 - 357.0178
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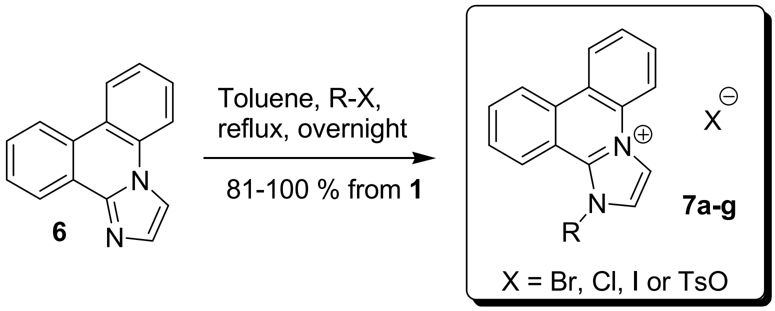
(III) General procedure for the synthesis of IPs 7a-g

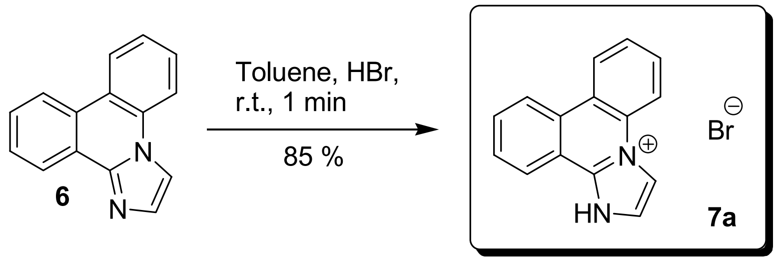


Freshly made imidazo-phenanthridine **6** (410 mg; 1.9 mmol) was dissolved in toluene (20 ml) and the electrophilic agent R-X (2-20 equivalents)[*1] was added. The reaction was stirred overnight under reflux.[*2] The final product precipitates from the solution and is recovered by filtration. The residue was washed extensively with diethyl ether and dried to yield the corresponding Imidazo-phenanthridinium framework **IP** (**7a-g**).

[*1] The quantity of electophilic reactive added in excess depends on the its physical properties: 20 equivalents were used with inexpensive liquid with low boiling point, whereas only 2 equivalents are necessary with solid starting material.

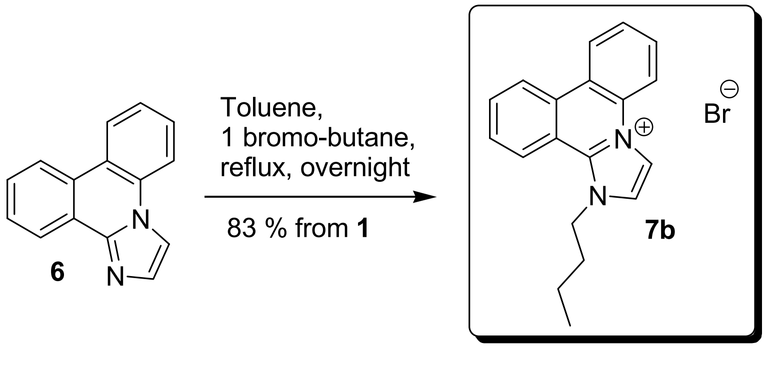
[*2] At the exception of the electrophile HBr, where r.t. conditions and only 1 minute stirring were used on 1 ml of a 48% HBr aqueous solution.

(IV) 1*H*-Imidazo[1,2-f]phenanthridinium bromide, 7a



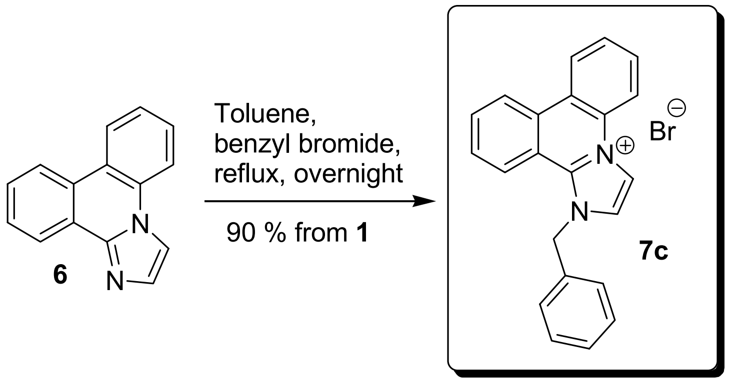
mp: 337-339 ˚C (dec.); **^{1}H NMR** (D_2O, 400 MHz): δ 7.57 (d, 1H, *J*=2.0 Hz), δ 7.33 (d, 1H, *J*=2.0 Hz), δ 7.14 (m, 3H), δ 7.07 (t, 2H, *J*=7.4 Hz), δ 6.97 (d, 2H, *J*=7.4 Hz), δ 6.92 (t, 1H, *J*=7.4 Hz); **^{13}C NMR** (D_2O, 100 MHz): δ 135.63 (C), δ 132.39 (CH), δ 130.34 (CH), δ 129.24 (CH), δ 127.87 (CH), δ 127.09 (C), δ 126.57 (C), δ 122.85 (CH), δ 122.41 (CH), δ 121.94 (CH), δ 120.66 (CH), δ 119.36 (C), δ 115.49 (CH), δ 114.12 (CH), δ 113.21 (C); **IR** (KBr, cm^{-1}): 3030 (s), 2842 (s), 2669 (s), 1660 (w), 1628 (s), 1559 (s), 1533 (m), 1469 (m), 1446 (m), 1395 (m), 915 (w), 757 (s), 716 (s), 691 (m), 611 (w); **MS** (FAB): 219.4 (M-Br) (85), 188.6 (100), 187.6 (90), 95.8 (80), 78.0 (20), 59.3 (10), 48.4 (8); Anal. Calcd for $C_{15}H_{11}BrN_2.2H_2O$: C, 53.75; H, 3.51; N, 8.36; Found: C, 53.60; H, 3.48; N, 8.36.

(V) 1-Butyl-1*H*-imidazo[1,2-f]phenanthridinium bromide, 7b



mp: 245-246 ˚C; **^{1}H NMR** ($(CD_3)_2SO$, 400 MHz): δ 9.25 (d, 1H, *J*=2.4 Hz), δ 9.04 (d, 1H, *J*=8.0 Hz), δ 8.98 (d, 1H, *J*=8.0 Hz), δ 8.66 (d, 2H, *J*=8.0 Hz), δ 8.45 (d, 1H, *J*=2.4 Hz), δ 8.10 (t, 1H, *J*=7.6 Hz), δ 8.01 (t, 1H, *J*=8.0 Hz), δ 7.98 (t, 1H, *J*=8.0 Hz), δ 7.88 (t, 1H, *J*=7.6 Hz), δ 4.91 (t, 2H, *J*=7.0 Hz), δ 1.98 (m, 2H), δ 1.49 (m, 2H), δ 0.97 (t, 3H, *J*=7.6 Hz); **^{13}C NMR** ($(CD_3)_2SO$, 100 MHz): δ 135.84 (C), δ 132.26 (CH), δ 130.82 (CH), δ 129.88 (CH), δ 129.45 (C), δ 128.31 (C), δ 126.77 (CH), δ 125.03 (CH), δ 124.80 (CH), δ 124.33 (CH), δ 121.61 (C), δ 117.28 (CH), δ 116.85 (C), δ 114.58 (CH), δ 50.85 (CH_2), δ 30.49 (CH_2), δ 18.97 (CH_2), δ 13.52 (CH_3); **IR** (KBr, cm^{-1}): 3029 (s), 1557 (s), 1532 (s), 1464 (m), 1356 (s), 1287 (w), 798 (m), 757 (s), 715 (w); **MS** (FAB): 233.3 (M-Br) (100), 154.9 (10), 137.1 (12), 90.8 (6), 79.0 (6); **MS** (FAB): 275.2 (M-Br) (100), 219.4 (12), 218.4 (5), 195.6 (2), 164.9 (1); Anal. Calcd for $C_{19}H_{19}BrN_2$: C, 63.23; H, 5.39; N, 7.89; Found: C, 63.36; H, 4.92; N, 7.90.

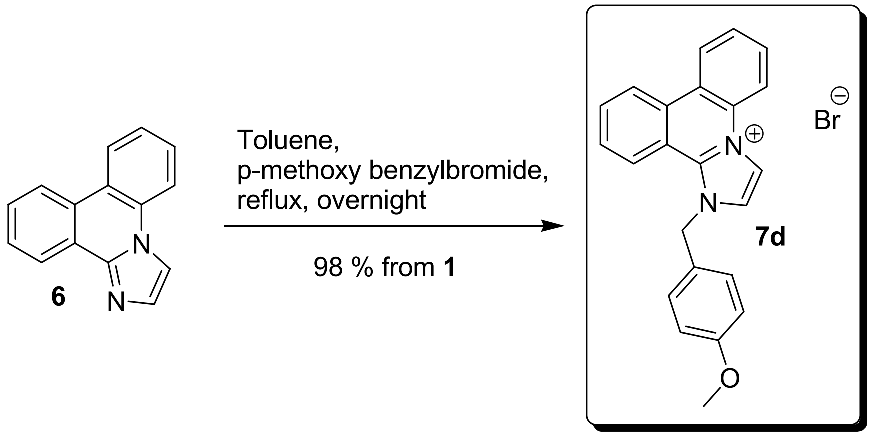
(VI) 1-Benzyl-1*H*-imidazo[1,2-f]phenanthridinium bromide, 7c



mp: 265-266 ˚C; **^{1}H NMR** ($(CD_3)_2SO$, 400 MHz): δ 9.38 (d, 1H, *J*=2.4 Hz), δ 8.99 (t, 2H, *J*=9.2 Hz), δ 8.73 (d, 1H, *J*=8.0 Hz), δ 8.50 (d, 1H, *J*=2.4 Hz), δ 8.44 (d, 1H, *J*=8.4 Hz), δ 8.02 (t, 2H, *J*=8.0 Hz), δ 7.91 (t, 1H, *J*=8.0 Hz), δ 7.81 (t, 1H, *J*=8.0 Hz), δ 7.41 (m, 2H), δ 7.37 (m, 3H); **^{13}C NMR** ($(CD_3)_2SO$, 100 MHz): δ 136.50 (C), δ 133.98 (C), δ 132.40 (CH), δ 130.90 (CH), δ 130.07 (CH), δ 129.60 (C), δ 129.48 (CH), δ 129.10 (CH), δ 128.43 (CH), δ 128.24 (CH), δ 127.24 (CH), δ 126.45 (CH), δ 125.11 (CH), δ 124.81 (CH), δ 124.22 (CH), δ 121.73 (C), δ 117.43 (CH), δ 116.42 (C), δ 115.22 (CH), δ 53.78 (CH_2); **IR** (KBr, cm^{-1}): 3434 (s), 3029 (s), 1613 (m), 1556 (s), 1530 (s), 1466 (s), 1270 (w), 1087 (w), 793 (m), 751 (s), 735 (s), 713 (s); **MS** (FAB): 309.2 (M-Br) (100), 289.1 (2), 219.4 (5), 218.4 (5), 154.9 (15), 92.8 (20), 90.8

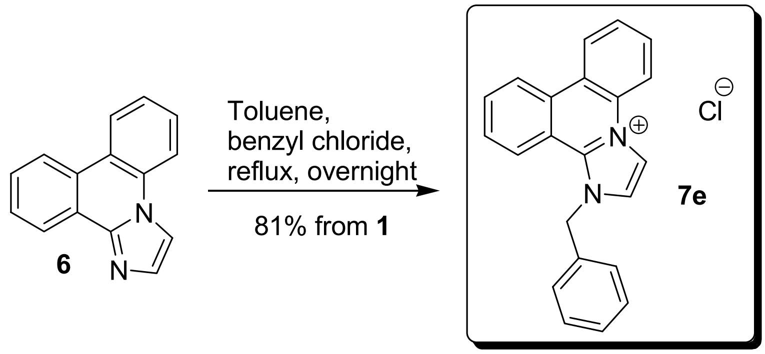
(8), 41.5 (5); Anal. Calcd for $C_{22}H_{17}BrN_2$: C, 67.88; H, 4.40; N, 7.20; Br, 20.31; Found: C, 67.72; H, 4.31; N, 7.20; Br, 20.31.

(VII) 1-(4-Methoxy-benzyl)-1*H*-imidazo[1,2-f]phenanthridinium bromide, 7d



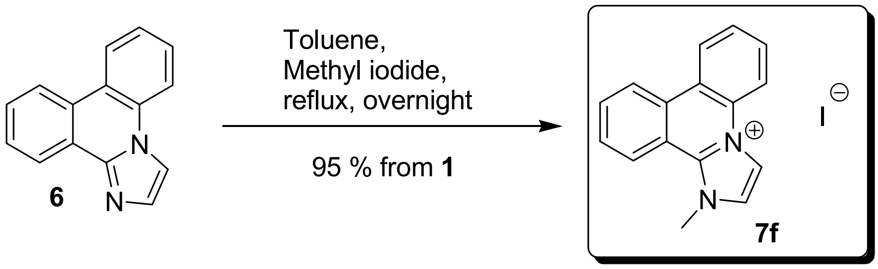
mp: 169-170 ˚C; ^{1}**H NMR** (($(CD_3)_2SO$, 400 MHz): δ 9.33 (d, 1H, *J*=2.4 Hz), δ 9.00 (d, 1H, *J*=8.4 Hz), δ 8.97 (d, 1H, *J*=8.0 Hz), δ 8.71 (d, 1H, *J*=8.0 Hz), δ 8.53 (d, 1H, *J*=8.0 Hz), δ 8.40 (d, 1H, *J*=2.4 Hz), δ 8.01 (m, 2H), δ 7.89 (t, 1H, *J*=7.4 Hz), δ 7.84 (t, 1H, *J*=7.4 Hz), δ 7.32 (d, 2H, *J*=8.0 Hz), δ 7.16 (m, 1H), δ 7.12 (m, 1H), δ 6.97 (d, 2H, *J*=8.8 Hz), δ 6.14 (s, 2H), δ 3.74 (s, 3H); ^{13}**C NMR** ($(CD_3)_2SO$, 100 MHz): δ 159.17 (C), δ 136.38 (C), δ 132.37 (CH), δ 130.88 (CH), δ 130.01 (C), δ 129.55 (C), δ 129.49 (CH), δ 128.40 (CH), δ 128.30 (CH), δ 126.91 (CH), δ 125.53 (C), δ 125.31 (CH), δ 124.80 (CH), δ 124.19 (CH), δ 121.69 (C), δ 117.40 (CH), δ 116.48 (C), δ 115.06 (CH), δ 114.46 (CH), δ 55.14 (CH_3), δ 53.48 (CH_2); **IR** (KBr, cm^{-1}): 3432 (m), 3032 (s), 1613 (s), 1556 (s), 1532 (s), 1516 (s), 1465 (s), 1249 (s), 1179 (s), 1029 (s), 803 (m), 758 (s); **MS** (FAB): 339.3 (M-Br) (100), 231.3 (4), 219.4 (10), 155.0 (18), 122.4 (50), 90.9 (8), 79.0 (8); Anal. Calcd for $C_{23}H_{19}BrN_2O$: C, 65.88; H, 4.57; N, 6.68; 3.82; Found: C, 65.96; H, 4.50; N, 6.53.

(VIII) 1-Benzyl-1H-imidazo[1,2-f]phenanthridinium chloride, 7e



mp: 239-240 ˚C; ^{1}**H NMR** (D_2O, 400 MHz): δ 8.192 (d, 1H, J=2.0 Hz), δ 7.84 (d, 1H, J=2.0 Hz), δ 7.81 (m, 1H), δ 7.50 (d, 1H, J=8.0 Hz), δ 7.39 (m, 5H), δ 7.36 (t, 1H, J=8.0 Hz), δ 7.26 (m, 4H), δ 7.15 (t, 1H, J=8.0 Hz), δ 5.65 (s, 2H); ^{13}**C NMR** (D_2O, 100 MHz): δ 135.42 (C), δ 132.86 (C), δ 132.19 (CH), δ 130.55 (CH), δ 129.56 (CH), δ 129.30 (CH), δ 129.21 (CH), δ 128.84 (CH), δ 128.05 (CH), δ 127.78 (C), δ 127.33 (CH), δ 126.64 (CH), δ 124.25 (CH), δ 123.10 (CH), δ 122.71 (CH), δ 120.35 (C), δ 116.03 (CH), δ 115.05 (C), δ 113.90 (CH); **IR** (KBr, cm^{-1}): 3435 (s), 3024 (s), 1664 (m), 1614 (m), 1556 (s), 1530 (s), 1466 (m), 1360 (w), 751 (s), 737 (s), 714 (m); **MS** (FAB): 309.2 (M-Br) (100), 219.4 (5), 195.6 (8), 137.2 (18), 92.8 (18), 90.8 (10), 53.4 (5); Anal. Calcd for $C_{22}H_{17}ClN_2$: C, 72.63; H, 4.97; N, 8.12; Found: C, 72.36; H, 4.46; N, 8.10.

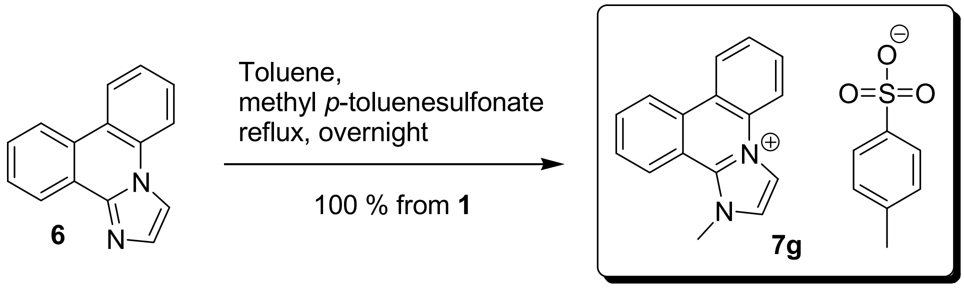
(IX) 1-Methyl-1*H*-imidazo[1,2-f]phenanthridinium iodide, 7f



mp: 332-334 ˚C (dec.); ^{1}**H NMR** ($(CD_3)_2SO$, 400 MHz): δ 9.19 (d, 1H, J=2.0 Hz), δ 9.01 (d, 1H, J=8.0 Hz), δ 8.96 (d, 1H, J=8.0 Hz), δ 8.81 (d, 1H, J=8.0 Hz), δ 8.63 (d, 1H, J=2.0 Hz), δ 8.10 (t, 1H, J=8.0 Hz), δ 7.98 (t, 2H, J=8.0 Hz), δ 7.88 (t, 1H, J=8.0 Hz); ^{13}**C NMR** ($(CD_3)_2SO$, 100 MHz): δ 136.47 (C), δ 132.27 (CH), δ 130.84 (CH), δ

129.66 (C), δ 129.59 (CH), δ 129.26 (C), δ 128.31 (CH), δ 127.48 (CH), δ 125.37 (CH), δ 124.84 (CH), δ 124.13 (CH), δ 121.49 (C), δ 117.19 (CH), δ 114.20 (CH), δ 39.47 (CH_3); **IR** (KBr, cm^{-1}): 3437 (m), 3078 (s), 1612 (w), 1560 (s), 1531 (s), 1469 (m), 1442 (m), 1430 (m), 1276 (s), 1159 (w), 1119 (w), 757 (s), 734 (s), 715 (s), 689 (s), 609 (m); Anal. Calcd for $C_{16}H_{13}IN_2$: C, 53.35; H, 3.64; N, 7.78; Found: C, 53.32; H, 3.53; N, 7.71.

(X) 1-Methyl-1*H*-imidazo[1,2-f]phenanthridinium tosylate, 7g

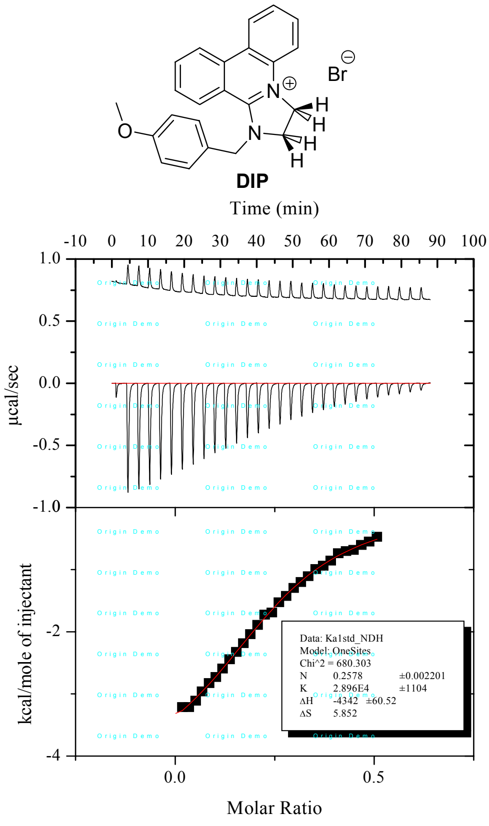


mp: 115-116 °C; ^{1}**H NMR** (D_2O, 400 MHz): δ 7.91 (d, 1H, *J*=2.4 Hz), δ 7.77 (d, 1H, *J*=8.0 Hz), δ 7.67 (d, 1H, *J*=2.4 Hz), δ 7.64 (d, 1H, *J*=8.0 Hz), δ 7.55 (d, 2H, *J*=8.0 Hz), δ 7.45 (m, 3H), δ 7.41 (t, 1H, *J*=8.0 Hz), δ 7.32 (t, 1H, *J*=8.0 Hz), δ 7.29 (t, 1H, *J*=8.0 Hz), δ 7.23 (t, 1H, *J*=8.0 Hz), δ 7.11 (d, 2H, *J*=8.0 Hz), δ 3.90 (s, 3H), δ 2.16 (s, 3H); ^{13}**C NMR** (D_2O, 100 MHz): δ 142.17 (C), δ 139.41 (C), δ 134.57 (C), δ 132.17 (CH), δ 130.59 (CH), δ 129.35 (CH), δ 123.81 (CH), δ 123.01 (CH), δ 122.57 (CH), δ 119.70 (C), δ 115.51 (CH), δ 114.63 (C), δ 113.06 (CH), δ 39.11 (CH_3), δ 20.33 (CH_3); **IR** (KBr, cm^{-1}): 3441 (m), 3113 (m), 3087 (m), 1706 (w), 1615 (w), 1561 (m), 1532 (m), 1472 (w), 1357 (w), 1215 (s), 1198 (s), 1119 (s), 1033 (s), 1010 (s), 817 (w), 755 (s), 680 (s), 567 (s); **MS** (FAB): 233.3 (M-Br) (100), 178.7 (3), 94.8 (1), 77.1 (1); Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 65.55; H, 4.75; N, 6.66; Found: C, 65.58; H, 4.53; N, 6.63.

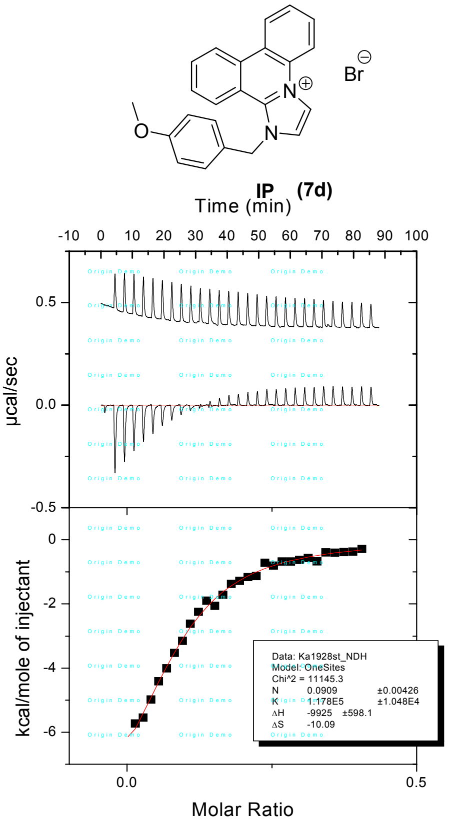
b. DNA affinity measurement

Isothermal Titration Calorimetry, ITC,[i] data has been collected using a Microcal VP-ITC system with six compounds in salmon testes DNA. Similar experiments have been conducted using the intercalator ethidium bromide as a reference. All experiments were carried out in a PIPES buffer with 0.2M NaCl, pH = 7. In a typical experiment, **29 x 10**μl of a 1mM ligand solution were injected every 3 minutes into the sample cell, which contained approximately 0.3 mM DNA (in base pairs). The experiments were performed at 25°C with the syringe rotating at 310 r.p.m. Control experiments of ligands injected into the buffer solution were run separately and were subtracted from the corresponding ligand-DNA titration to account for heats of dilution. Data were collected and analysed with Microcal Origin 5.0 software according to the theory of Wiseman *et al.,* 1989.

An example of thermograms obtained from the **IP 7d** (RHS), along with that of the corresponding **DIP** (LHS).



DIP



IP (7d)

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[i] Cliff, M. J.; Ladbury, J. E., Journal of Molecular Recognition **2003**, 16, 383-391.