Supporting information

An efficient synthesis of novel dibenzoxazepine-fused heterocycles through multicomponent reaction

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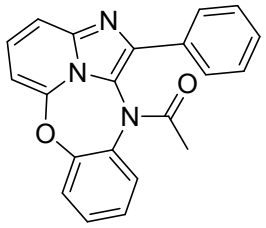
General

^{1}H NMR (400 MHz) spectra were recorded by using high performance digital FT-NMR spectrometer with TMS as an internal standard. ^{13}C NMR (100 MHz & 125 MHz) spectra were recorded by using high performance digital FT-NMR spectrometer. LR-MS and HRMS were obtained in the EI mode on a double-focusing mass analyzer or the ESI (positive ion mode) on a TOF mass analyzer. Purity was recorded on high-performance liquid chromatography (HPLC), conditions were as follows: ACN/H_2O eluent at 2 mLmin^{-1} flow (containing 0.05% TFA) at 40 ^{o}C, 5 min, gradient 5% ACN to 95% ACN, monitored by UV absorption at both 214 and 254 nm. TLC was carried out with glass pre-coated silica gel plates. TLC spots were visualized under UV light. All the solvents and reagents were used directly as obtained commercially unless otherwise noted.

Typical Procedure for the Synthesis of the titled compounds

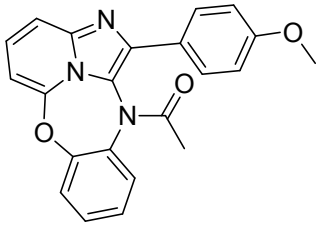
2-Amino-6-bromo-heterocycle (1 mmol), aldehydes (1.05 mmol) and 2-isocyanophenyl acetate (1.05 mmol) were taken in a 5 mL sealed microwave tube and the mixture was stirred for 10 min at 140 ^{o}C in parallel synthesizer (Radleys Discovery Technology, Carousel 12 Place Reaction Station), TLC showed the starting materials were completely consumed. The reaction mixture was dissolved in 3 mL of dioxane / H_2O (4:1), then K_2CO_3 (2 mmol) were added, and the mixture was stirred at 100 ^{o}C for another 2 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by a short column chromatography (SiO_2) to afford the final products.

1-(1-phenyl-11*H*-6-oxa-2,2a^{1},11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5a)



Isolated as white powder; HPLC purity 98%; m.p. 213-217 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.03 (d, J = 7.6 Hz, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.45 (dd, J = 60.8, 18.0 Hz, 7H), 7.25 – 7.12 (m, 1H), 6.60 (d, J = 7.3 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 173.3, 150.7, 146.8, 145.9, 138.7, 138.2, 136.2, 134.0, 131.7, 130.6(2×C), 130.5, 130.3, 128.8, 128.5, 128.3(2×C), 123.5, 119.4, 115.1, 22.8; HRMS (ESI), calcd for $C_{21}H_{16}N_3O_2$ (M+H) 342.1243, found: 342.1240.

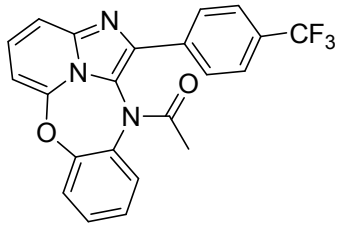
1-(1-(4-methoxyphenyl)-11*H*-6-oxa-2,2a^{1},11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5b)



Isolated as white powder; HPLC purity 100%; m.p. 195-198 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.98 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 7.8 Hz, 1H), 7.49 – 7.30 (m, 4H), 7.23 – 7.16 (m, 1H), 7.05

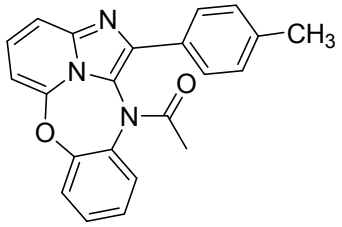
(d, J = 8.6 Hz, 2H), 6.58 (d, J = 7.5 Hz, 1H), 3.89 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 172.8, 160.7, 150.0, 146.0, 145.1, 138.0, 135.6, 130.9, 129.7, 128.9 (2×C), 127.8, 127.7, 125.8, 122.8, 117.9, 115.3 (2×C), 114.2, 99.5, 56.0, 22.1; HRMS (ESI), calcd for $C_{22}H_{18}N_3O_3$ (M+H) 372.1348, found: 372.1347.

1-(1-(4-(trifluoromethyl)phenyl)-11*H*-6-oxa-2,2a1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5c)



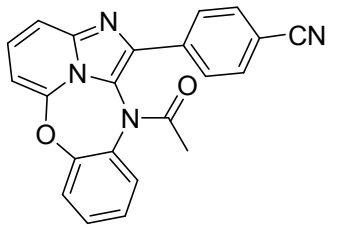
Isolated as white powder; HPLC purity 100%; m.p. 243-247 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70℃) δ_H: 8.24 (d, J = 8.3 Hz, 2H), 7.86 (t, J = 12.8 Hz, 3H), 7.58 (d, J = 3.6 Hz, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.42 – 7.31 (m, 2H), 6.82 (dd, J = 6.9, 1.3 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 172.1, 149.6, 145.7, 144.9, 136.5, 136.1, 134.9, 130.8, 129.3, 128.2, 127.5, 127.3 (2×C), 126.5 (2×C), 125.9, 122.9, 122.5, 119.1, 114.2, 99.6, 21.7; HRMS (ESI), calcd for $C_{22}H_{15}F_3N_3O_2$ (M+H) 410.1116, found: 410.1119.

1-(1-(p-tolyl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5d)



Isolated as white powder; HPLC purity 100%; m.p. 204-207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.93 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 7.48 – 7.29 (m, 6H), 7.23 – 7.17 (m, 1H), 6.59 (d, J = 7.2 Hz, 1H), 2.43 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 172.0, 149.3, 145.3, 144.4, 138.8, 137.5, 134.8, 130.2, 129.9(2×C), 129.8, 129.1, 127.2, 127.0, 126.8(2×C), 122.1, 117.6, 113.6, 98.8, 21.3(2×C); HRMS (ESI), calcd for $C_{22}H_{18}N_3O_2$ (M+H) 356.1399, found: 356.1393.

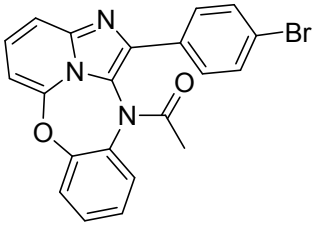
4-(11-acetyl-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-1-yl)benzonitrile (5e)



Isolated as white powder; HPLC purity 100%; m.p. 254-259 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 8.20 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.2 Hz, 3H), 7.58 (d, J = 4.4 Hz, 2H), 7.51 – 7.42 (m, 1H), 7.42 – 7.31 (m, 2H), 6.82 (dd, J = 6.7, 1.4 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.6, 149.2, 145.3, 144.6, 137.2, 134.4, 132.9 (2×C), 132.4, 131.3, 130.5,

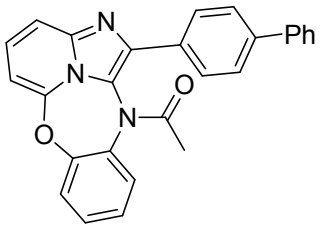
129.0, 128.1, 127.2 (2×C), 122.2, 119.1, 118.6, 113.9, 112.0, 99.5, 21.3; HRMS (ESI), calcd for $C_{22}H_{15}N_4O_2$ (M+H) 367.1195, found: 367.1202.

1-(1-(4-bromophenyl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5f)



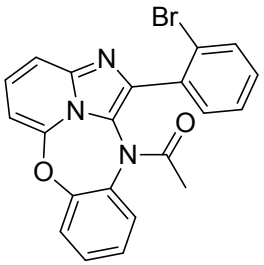
Isolated as white powder; HPLC purity 100%; m.p. 237-240 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 7.98 (d, J = 8.2 Hz, 2H), 7.86 (s, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 3.5 Hz, 2H), 7.47 (dd, J = 8.0, 4.1 Hz, 1H), 7.40 – 7.29 (m, 2H), 6.80 (dd, J = 6.6, 1.5 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.8, 149.2, 145.3, 144.5, 136.2, 134.6, 132.4(2×C), 131.6, 130.4, 129.0, 128.3(2×C), 127.6, 127.1, 122.9, 122.1, 118.0, 113.7, 99.1, 21.3; HRMS (ESI), calcd for $C_{21}H_{15}BrN_3O_2$ (M+H) 420.0348, found: 420.0338.

1-(1-([1,1'-biphenyl]-4-yl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5g)



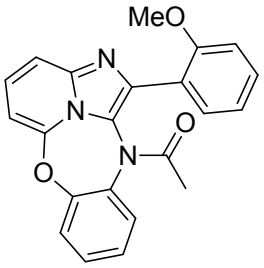
Isolated as pink powder; HPLC purity 100%; m.p. 254-259 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.13 (d, J = 8.1 Hz, 2H), 7.79 – 7.63 (m, 5H), 7.48 (dd, J = 14.5, 7.1 Hz, 3H), 7.44 – 7.33 (m, 4H), 7.25 – 7.12 (m, 1H), 6.61 (d, J = 7.1 Hz, 1H), 2.04 (d, J = 4.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 171.6, 148.8, 144.9, 144.1, 140.9, 139.9, 136.6, 134.3, 131.1, 129.8, 128.6, 128.4(2×C), 127.3(2×C), 127.2, 126.9, 126.8(2×C), 126.6, 126.5(2×C), 121.6, 117.5, 113.3, 98.5, 21.0; HRMS (ESI), calcd for $C_{27}H_{20}N_3O_2$ (M+H) 418.1556, found: 418.1543.

1-(1-(2-bromophenyl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5h)



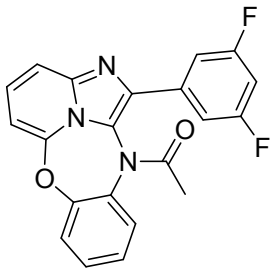
Isolated as white powder; HPLC purity 100%; m.p. 195-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.76 (d, J = 5.7 Hz, 1H), 7.66 (dd, J = 7.8, 1.2 Hz, 1H), 7.40 (ddd, J = 16.7, 11.3, 4.1 Hz, 7H), 7.23 (s, 1H), 6.64 (d, J = 7.4 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 170.9, 148.9, 144.9, 143.7, 137.2, 133.8, 133.6, 133.4, 131.7, 130.0, 129.9, 129.6, 127.4, 126.6, 126.2, 122.8, 121.4, 118.5, 113.6, 98.6, 21.0; HRMS (ESI), calcd for $C_{21}H_{15}BrN_3O_2$ (M+H) 420.0348, found: 420.0338.

1-(1-(2-methoxyphenyl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5i)



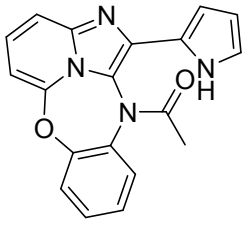
Isolated as white powder; HPLC purity 100%; m.p. 199-202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.63 (t, J = 7.8 Hz, 2H), 7.49 – 7.32 (m, 5H), 7.18 (dt, J = 23.2, 7.6 Hz, 2H), 7.07 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 7.2 Hz, 1H), 3.86 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.1, 156.9, 149.2, 145.1, 144.4, 135.5, 134.6, 131.5, 130.4, 129.9, 129.7, 126.6, 126.3, 122.1, 121.8, 121.4, 119.2, 113.7, 111.6, 98.6, 56.0, 21.30; HRMS (ESI), calcd for $C_{22}H_{18}N_3O_3$ (M+H) 372.1348, found: 372.1350.

1-(1-(3,5-difluorophenyl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5j)



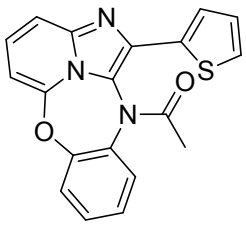
Isolated as white powder; HPLC purity 100%; m.p. 223-228 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 7.81 (s, 1H), 7.65 – 7.54 (m, 4H), 7.46 (ddd, J = 7.8, 5.5, 3.6 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.22 (s, 1H), 6.82 (dd, J = 6.6, 1.7 Hz, 1H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.8, 164.7, 162.2, 149.2, 145.3, 144.3, 135.1, 134.5, 131.3, 130.5, 129.0, 127.9, 127.2, 122.1, 118.6, 113.8, 109.8, 109.5, 104.1, 99.3, 21.3; HRMS (ESI), calcd for $C_{21}H_{14}F_2N_3O_2$ (M+H) 378.1054, found: 378.1052.

1-(1-(1H-pyrrol-2-yl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5k)



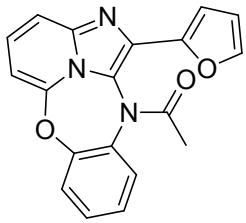
Isolated as beige powder; HPLC Purity 99%; m.p. 138-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.67 (s, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.48 – 7.30 (m, 3H), 7.24 (d, J = 8.7 Hz, 1H), 7.22 – 7.13 (m, 1H), 6.93 (s, 1H), 6.74 (s, 1H), 6.58 (d, J = 7.3 Hz, 1H), 6.37 (d, J = 2.9 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 172.0, 148.7, 144.8, 143.9, 134.4, 131.7, 129.7, 129.0, 126.9,126.8, 123.6, 121.5, 118.9, 115.0, 112.3, 109.8, 106.8, 98.5, 21.0; HRMS (ESI), calcd for $C_{19}H_{15}N_4O_2$ (M+H) 331.1195, found: 331.1194.

1-(1-(thiophen-2-yl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5l)



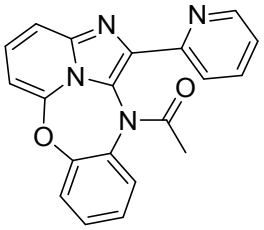
Isolated as pink powder; HPLC Purity 100%; m.p.191-194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.69 (d, J = 3.1 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 4.8 Hz, 2H), 7.35 (dd, J = 16.9, 8.1 Hz, 3H), 7.20 (dd, J = 16.3, 6.7 Hz, 2H), 6.59 (d, J = 7.4 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 171.8, 148.7, 144.8, 144.0, 134.5, 134.3, 133.0, 129.8, 128.9, 127.6, 127.2, 126.6, 126.1, 124.9, 121.5, 116.4, 113.0, 98.6, 20.9; HRMS (ESI), calcd for $C_{19}H_{14}N_3O_2S$ (M+H) 348.0807, found: 348.0797.

1-(1-(furan-2-yl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5m)



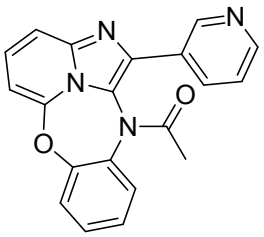
Isolated as light brown powder; HPLC purity 100%; m.p. 136-140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.65 – 7.56 (m, 2H), 7.41 (d, J = 6.5 Hz, 1H), 7.34 (dd, J = 15.7, 8.3 Hz, 3H), 7.24 – 7.17 (m, 1H), 7.00 (d, J = 3.4 Hz, 1H), 6.59 (d, J = 4.5 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.9, 149.1, 147.7, 145.4, 144.7, 143.2, 142.8, 134.5, 130.1, 129.5, 127.7, 126.9, 121.8, 117.1, 113.5, 111.7, 109.1, 99.1, 21.4; HRMS (ESI), calcd for $C_{19}H_{14}N_3O_3$ (M+H) 332.1035, found: 332.1028.

1-(1-(pyridin-2-yl)-11*H*-6-oxa-2,2a1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5n)



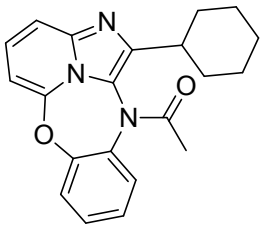
Isolated as light orange powder; HPLC purity 98%; m.p. 212-214 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.74 (d, J = 4.9 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.42 – 7.29 (m, 4H), 7.26 – 7.18 (m, 2H), 6.61 (d, J = 7.4 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 171.8, 152.3, 149.7, 149.0, 145.7, 144.1, 136.6, 135.8, 134.6, 129.8, 129.7, 127.5, 126.8, 122.9, 121.7, 121.5, 120.1, 113.8, 99.1, 21.6; HRMS (ESI), calcd for $C_{20}H_{15}N_4O_2$ (M+H) 343.1195, found: 343.1190.

1-(1-(pyridin-3-yl)-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5o)



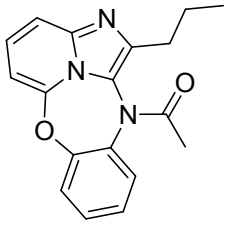
Isolated as grey powder; HPLC 100%; m.p. 196-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 9.25 (s, 1H), 8.67 (s, 1H), 8.35 (d, J = 7.9 Hz, 1H), 7.87 (s, 1H), 7.61 – 7.49 (m, 3H), 7.49 – 7.41 (m, 1H), 7.35 (dt, J = 16.1, 8.7 Hz, 2H), 6.80 (dd, J = 7.1, 1.1 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ_C: 171.2, 170.5, 149.5, 148.8, 147.4, 144.7, 144.2, 143.6, 135.0, 134.6, 134.5, 133.8, 131.6, 130.7, 129.5, 129.0, 128.4, 128.0, 127.6, 127.4, 124.5, 123.9, 122.4, 122.0, 118.2, 116.2, 113.7, 99.5, 99.3, 22.3, 20.8; HRMS (ESI), calcd for $C_{20}H_{15}N_4O_2$ (M+H) 343.1195, found: 343.1182.

1-(1-cyclohexyl-11*H*-6-oxa-2,2a1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5p)



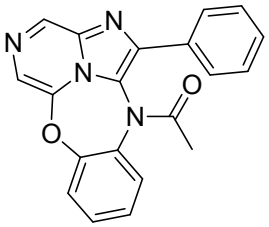
Isolated as white crystal; HPLC purity 100%; m.p. 199-203 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 7.64 (s, 1H), 7.52 (d, J = 3.9 Hz, 2H), 7.46 – 7.36 (m, 1H), 7.28 – 7.15 (m, 2H), 6.69 (dd, J = 6.9, 1.2 Hz, 1H), 2.81 (s, 1H), 2.08 (s, 3H), 2.01 (d, J = 12.0 Hz, 1H), 1.84 (d, J = 13.5 Hz, 1H), 1.73 (s, 4H), 1.59 – 1.33 (m, 3H), 1.34 – 1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 172.4, 170.5, 149.5, 149.3, 145.8, 145.2, 144.4, 144.0, 136.1, 135.3, 130.7, 130.0, 129.0, 128.3, 127.3, 127.0, 126.5, 125.2, 122.5, 121.9, 117.3, 114.8, 113.6, 113.5, 98.5, 98.0, 36.7, 36.4, 33.4, 32.7, 30.9, 30.4, 26.7 (2×C), 26.5 (2×C), 26.1, 25.9, 22.5, 21.2; HRMS (ESI), calcd for $C_{21}H_{22}N_3O_2$ (M+H) 348.1712, found: 348.1703.

1-(1-propyl-11*H*-6-oxa-2,2a^1,11-triazadibenzo[*cd,g*]azulen-11-yl)ethanone (5q)



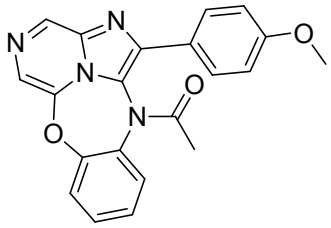
Isolated as brown amorphous solid; HPLC purity 100%; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 7.61 (s, 1H), 7.51 (d, J = 4.3 Hz, 2H), 7.44 – 7.34 (m, 1H), 7.27 – 7.14 (m, 2H), 6.70 (dd, J = 6.4, 1.8 Hz, 1H), 2.66 (s, 2H), 2.07 (s, 3H), 1.79 – 1.64 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 171.7, 169.6, 148.8, 144.7, 143.8, 143.49, 140.9, 139.4, 135.4, 134.6, 130.3, 129.6, 128.7, 126.8, 126.5, 126.2, 124.8, 122.1, 121.5, 118.1, 115.5, 113.0, 112.8, 98.0, 97.6, 29.4, 29.1, 22.0, 20.7, 13.7; HRMS (ESI), calcd for $C_{18}H_{18}N_3O_2$ (M+H) 308.1399, found: 308.1403.

1-(1-phenyl-11*H*-6-oxa-2,2a^1,4,11-tetraazadibenzo[*cd,g*]azulen-11-yl)ethanone (5r)



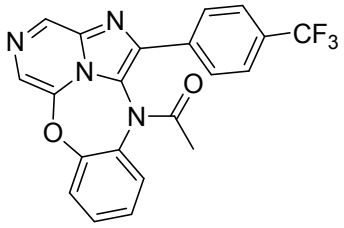
Isolated as pink powder; HPLC purity 97%; m.p. 227-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 8.86 (s, 1H), 8.10 – 8.04 (m, 2H), 7.90 (s, 2H), 7.65 – 7.52 (m, 4H), 7.48 (ddd, J = 7.9, 6.6, 2.5 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 170.7, 148.8, 140.4, 139.2 (2×C), 138.8, 133.7, 131.4, 130.2, 129.1, 128.9, 128.5, 127.3, 126.9, 126.6 (2×C), 121.9, 118.9, 116.1, 21.0; HRMS (ESI), calcd for $C_{20}H_{15}N_4O_2$ (M+H) 343.1195, found: 343.1198.

1-(1-(4-methoxyphenyl)-11*H*-6-oxa-2,2a^1,4,11-tetraazadibenzo[*cd,g*]azulen-11-yl)ethanone (5s)



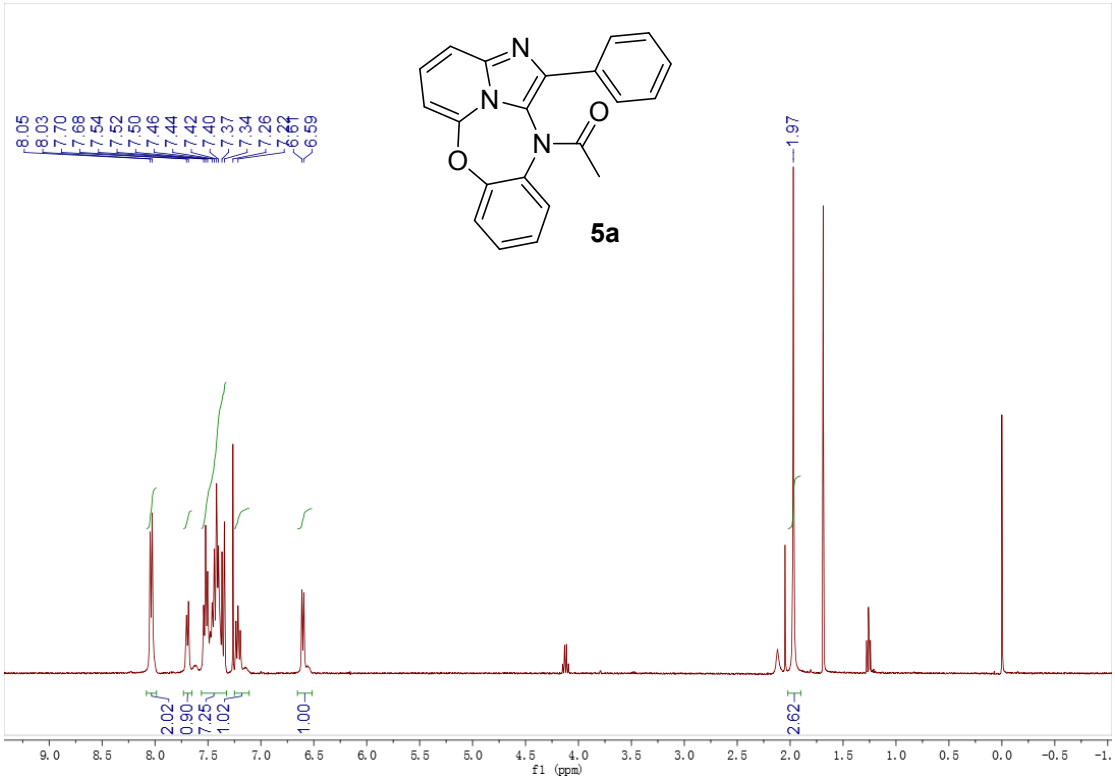
Isolated as light orange powder; HPLC purity 100%; m.p. 234-238 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 8.82 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.88 (s, 2H), 7.60 (s, 2H), 7.52 – 7.44 (m, 1H), 7.12 (d, J = 8.3 Hz, 2H), 3.85 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 170.8, 160.1, 148.7, 140.4, 138.8 (2×C), 133.7, 130.1, 129.0, 128.0 (2×C), 126.8, 123.8, 121.9, 118.0, 116.0, 115.8, 114.3, 113.7, 54.9, 21.0; HRMS (ESI), calcd for $C_{21}H_{16}N_4NaO_3$ (M+Na) 395.1120, found: 395.1111.

1-(1-(4-(trifluoromethyl)phenyl)-11*H*-6-oxa-2,2a^1,4,11-tetraazadibenzo[*cd,g*]azulen-11-yl)ethanone (5t)

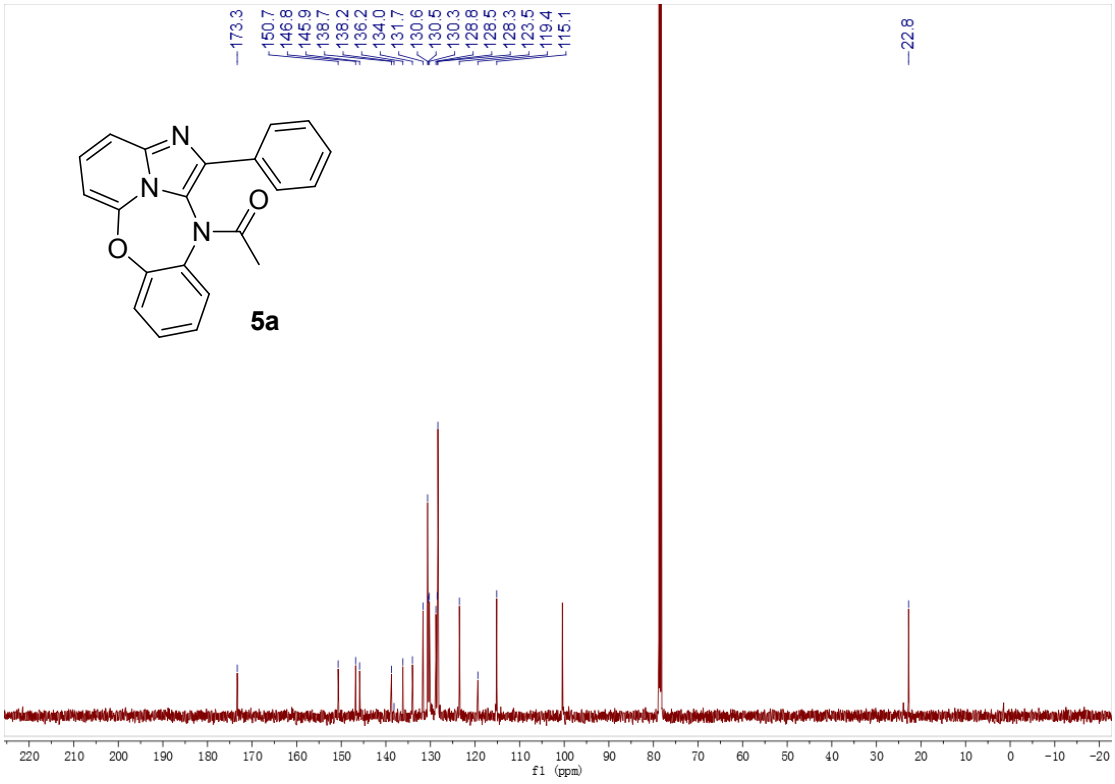


Isolated as light pink powder; HPLC purity 100%; m.p. 251-256 °C; ^{1}H NMR (400 MHz, DMSO-d_6 70 °C) δ_H: 8.89 (s, 1H), 8.28 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 7.1 Hz, 1H), 7.93 (s, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 6.0 Hz, 2H), 7.54 – 7.46 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 171.3, 171.0, 166.4, 149.8, 149.6, 141.1, 140.9, 140.2 (2×C), 139.7, 139.5, 137.8, 136.2, 135.7, 135.3, 134.3, 132.0, 131.2, 129.8, 129.1, 128.2, 127.8,127.6 (2×C), 126.7, 126.0, 123.3, 122.7, 120.4, 118.3, 117.1, 116.8, 22.8, 21.7; HRMS (ESI), calcd for $C_{21}H_{14}F_3N_4O_2$ (M+H) 411.1069, found: 411.1071.

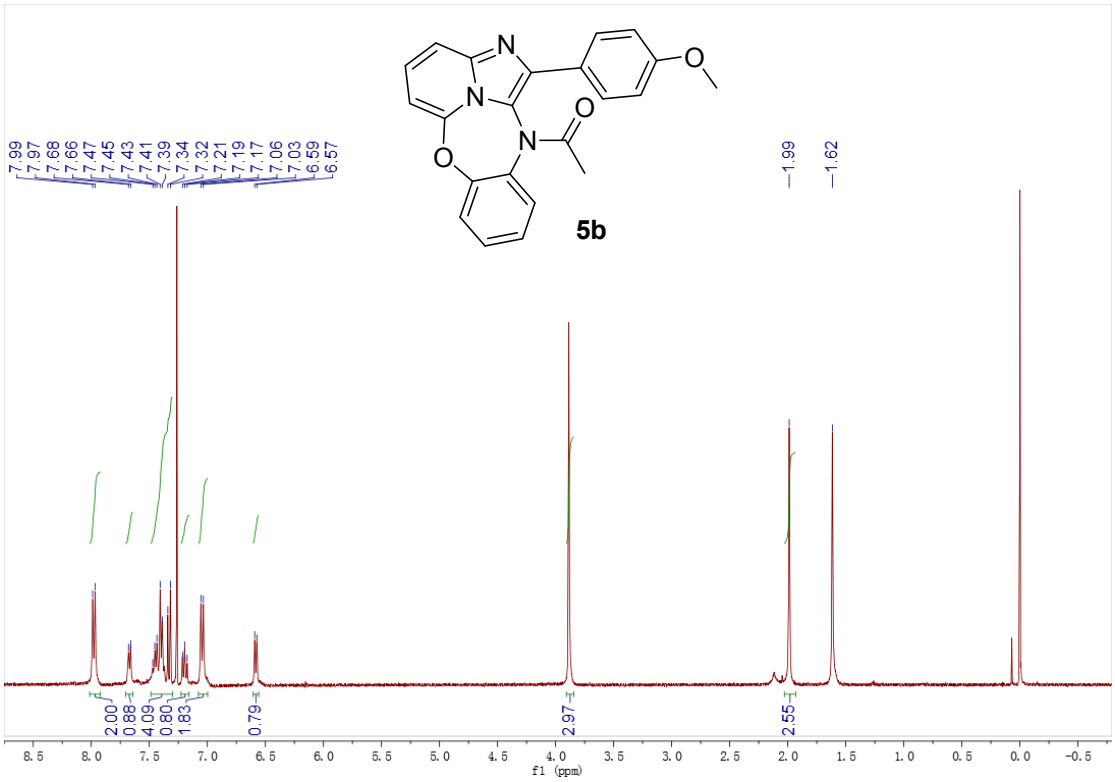
^{1}H NMR spectrum of **5a** in $CDCl_3$



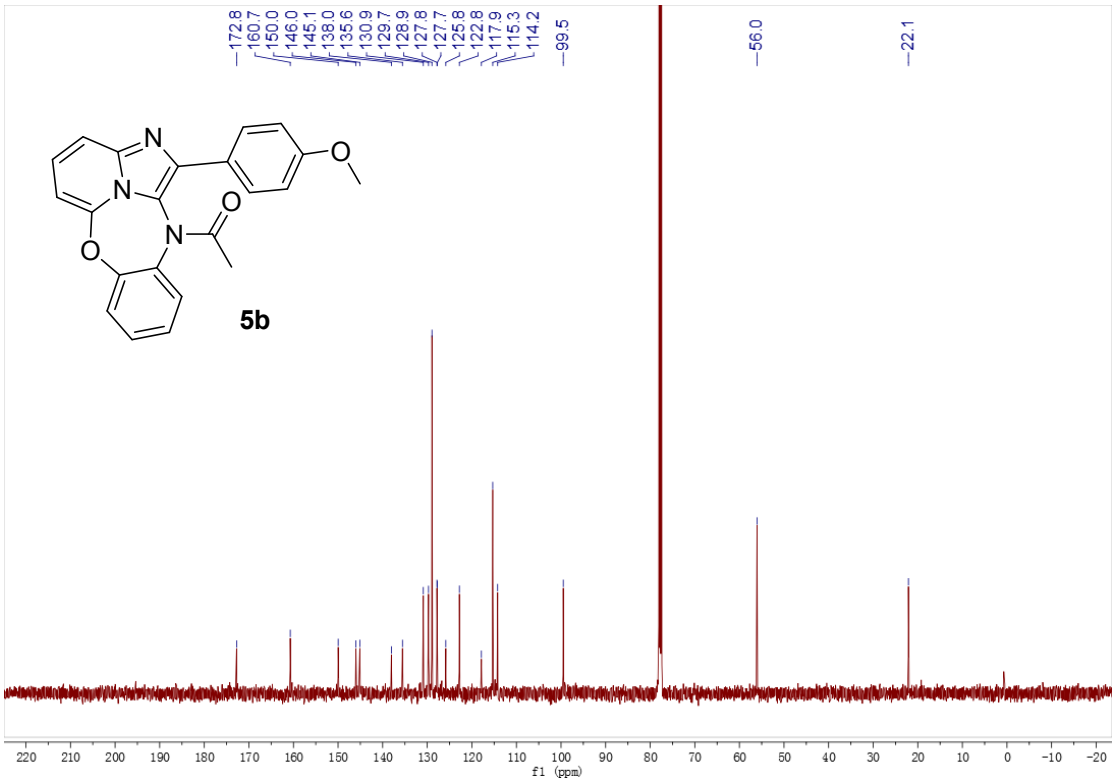
^{13}C NMR spectrum of **5a** in $CDCl_3$



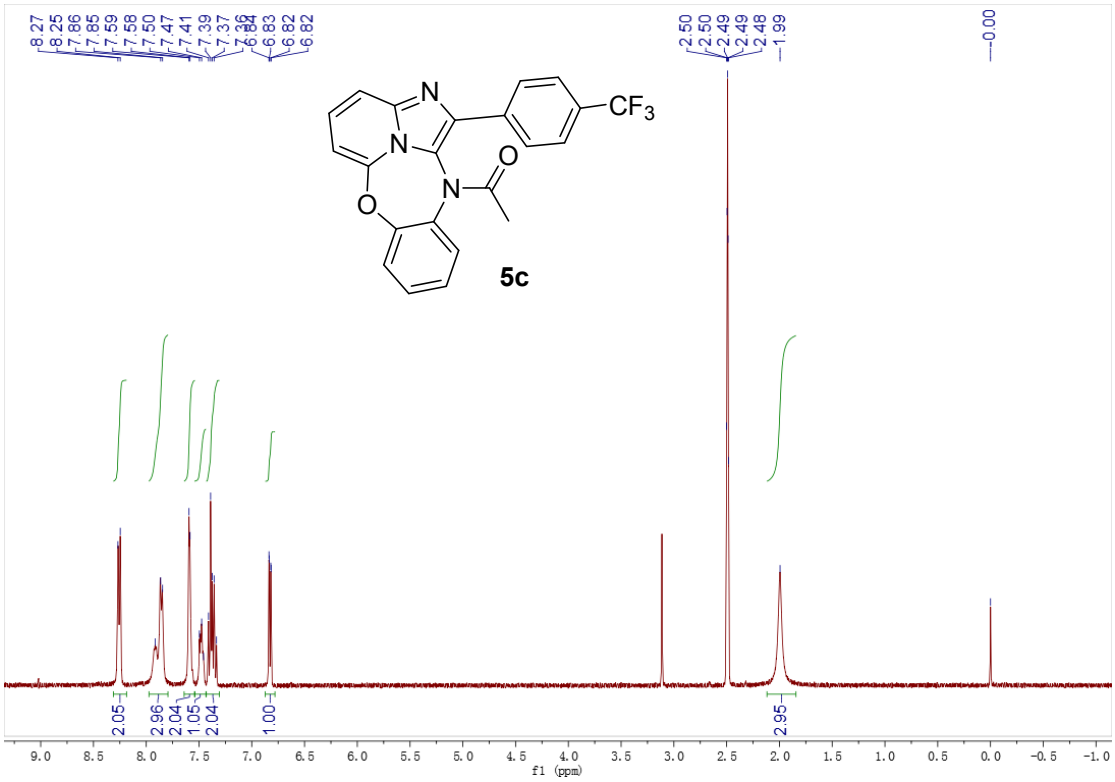
^{1}H NMR spectrum of **5b** in $CDCl_3$



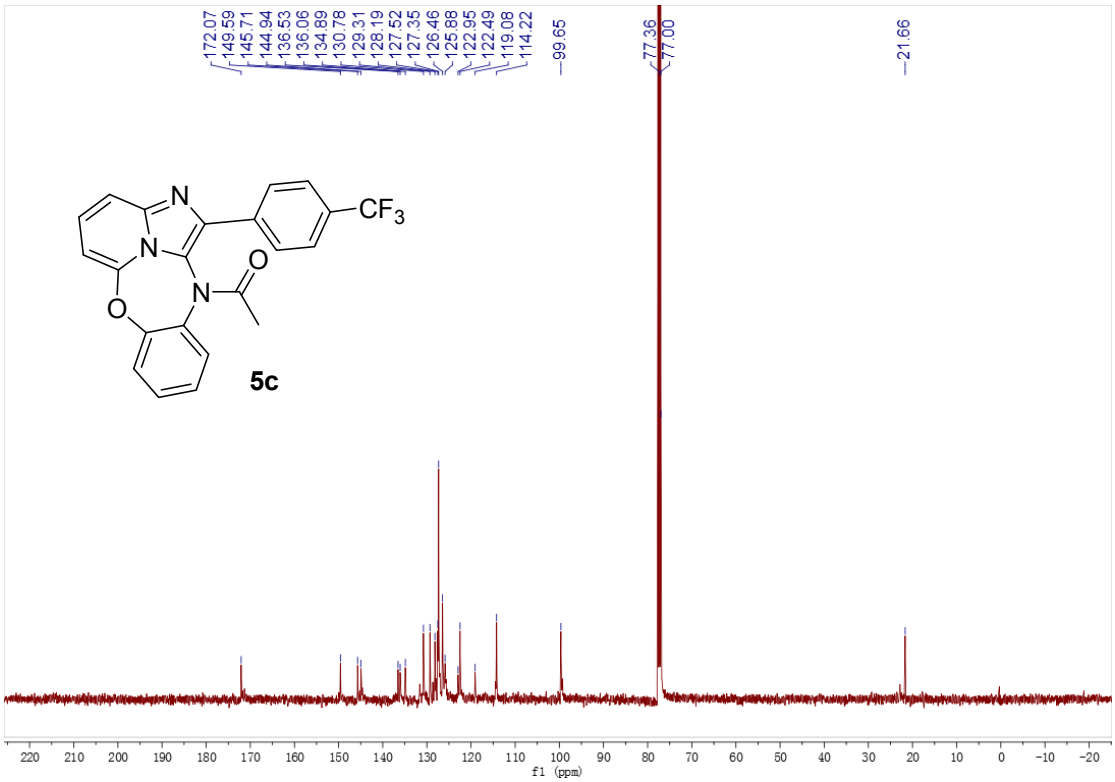
^{13}C NMR spectrum of **5b** in $CDCl_3$



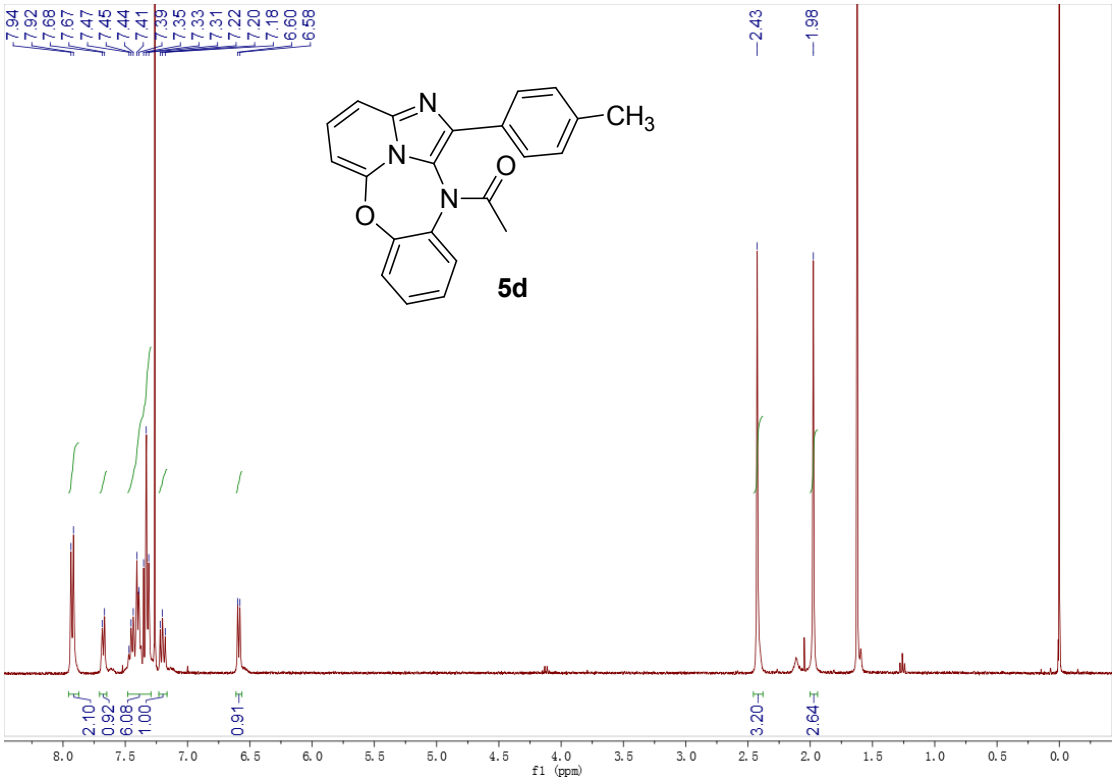
^{1}H NMR spectrum **5c** in DMSO-d_6 70 °C



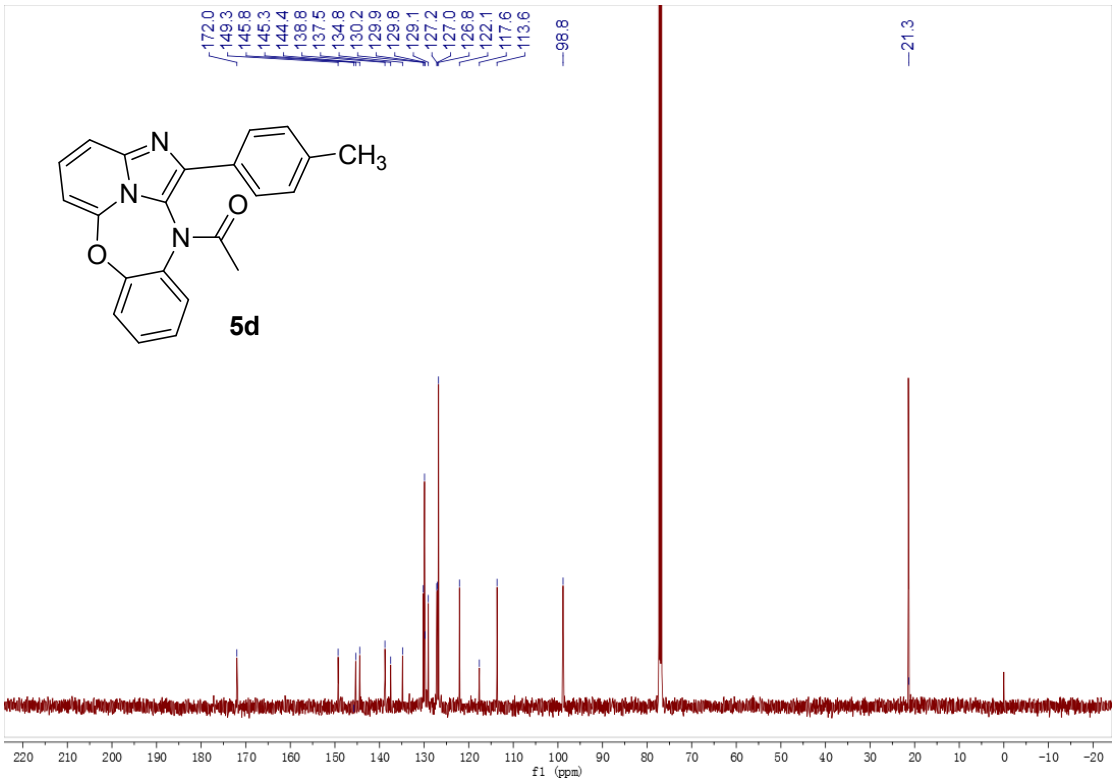
^{13}C NMR spectrum of **5c** in $CDCl_3$



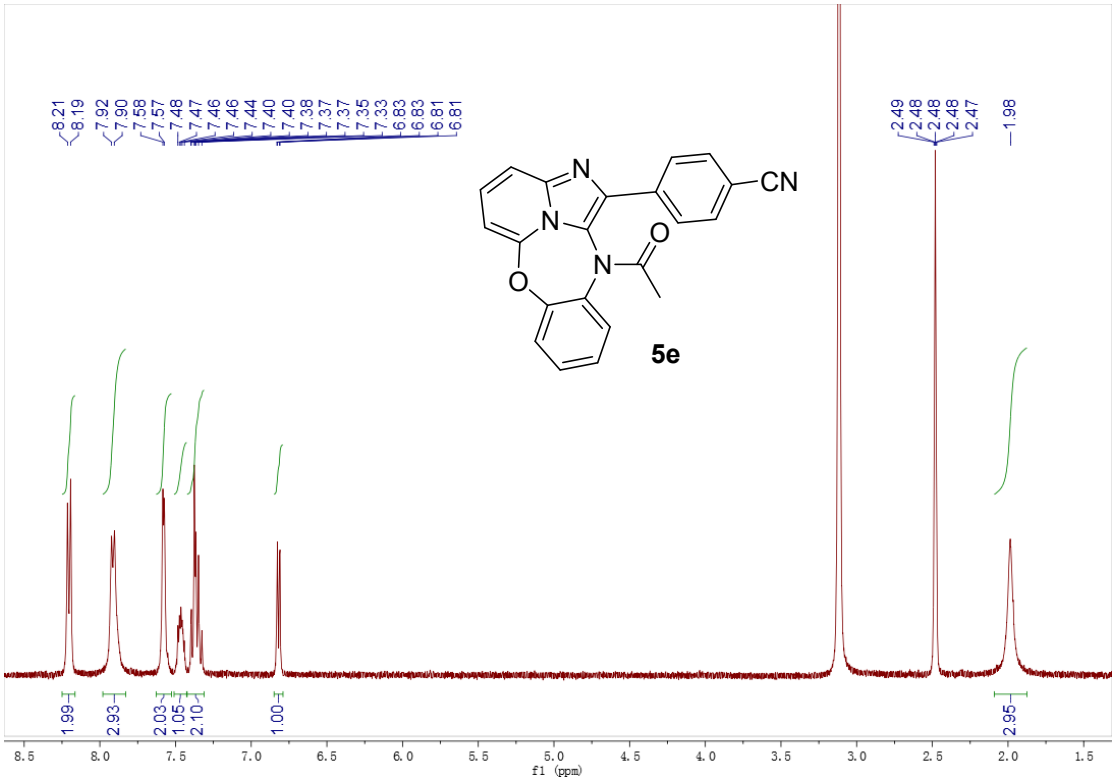
^{1}H NMR spectrum of **5d** in $CDCl_3$



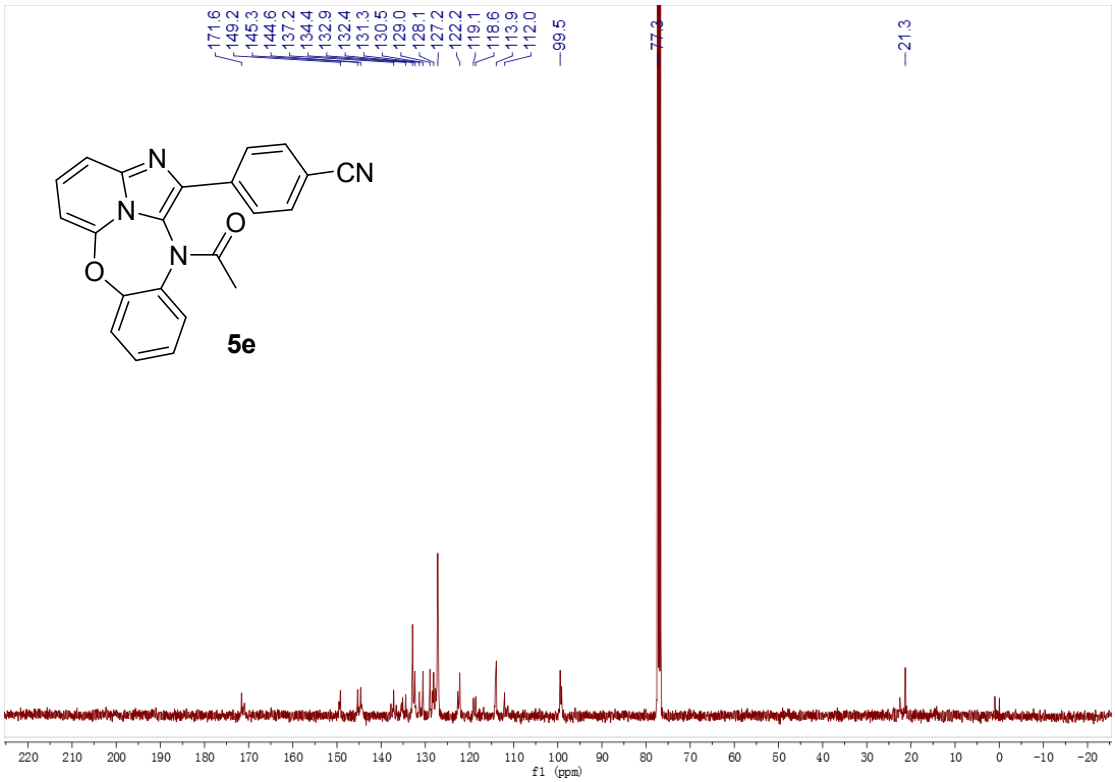
^{13}C NMR spectrum **5d** in $CDCl_3$



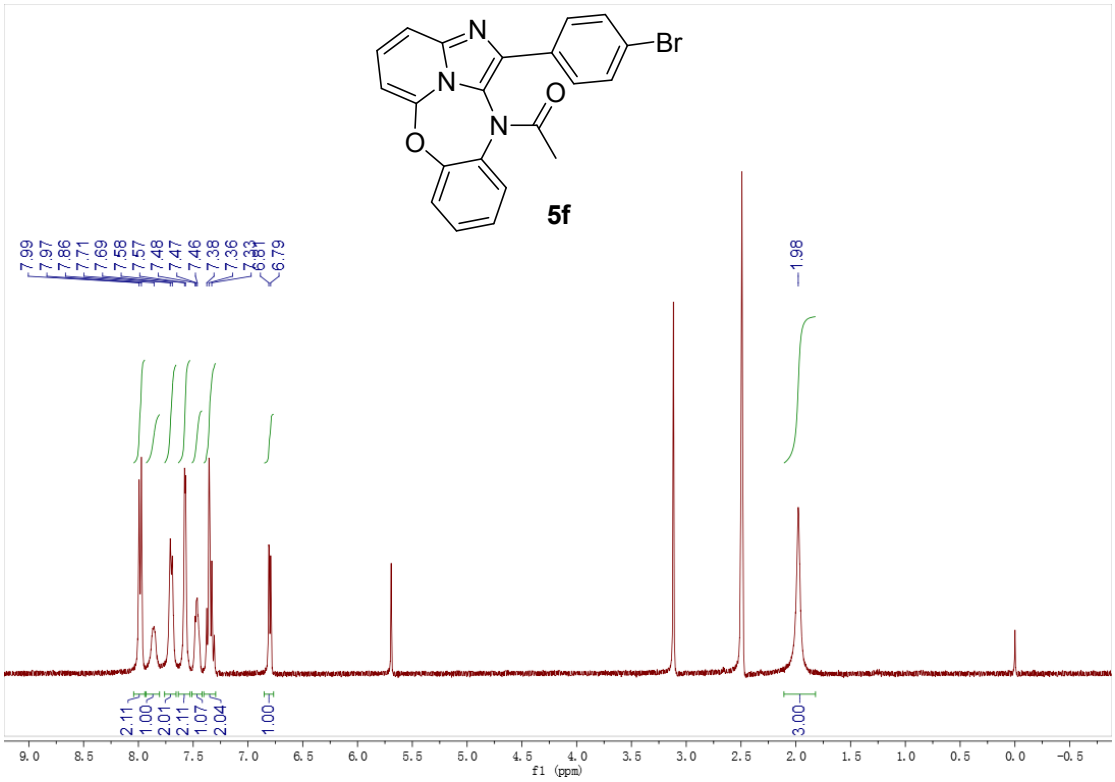
^{1}H NMR spectrum of **5e** in DMSO-d_6 70 °C



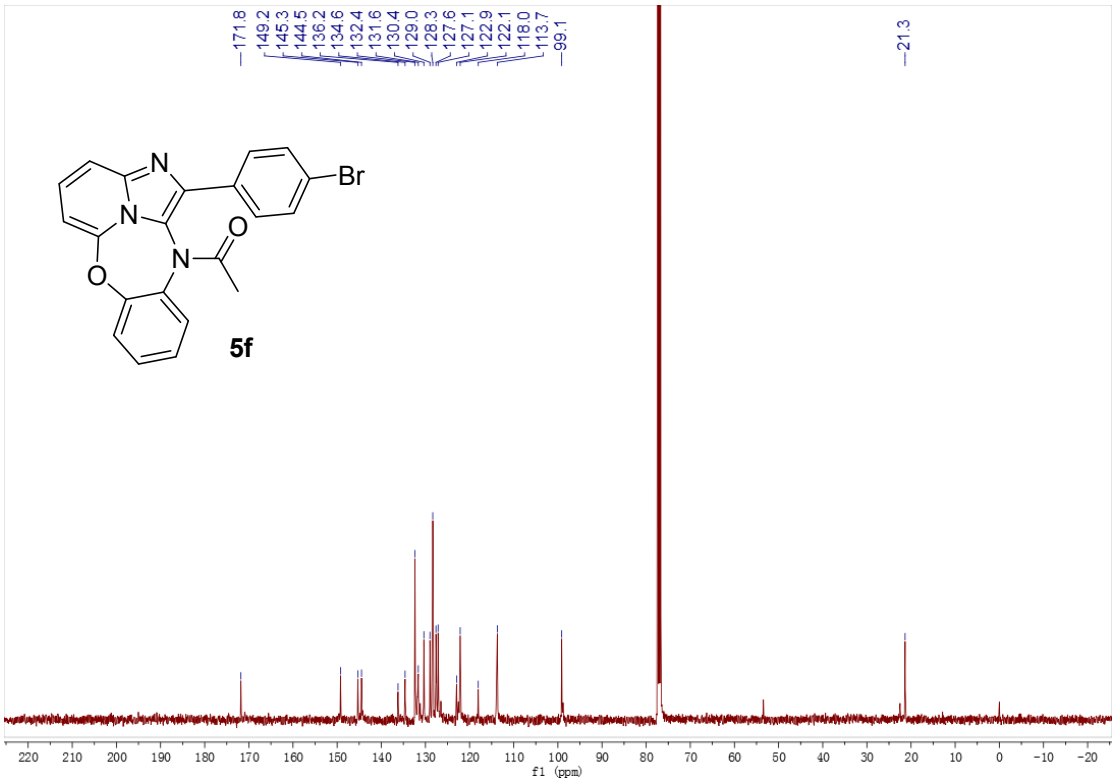
^{13}C NMR spectrum of **5e** in $CDCl_3$



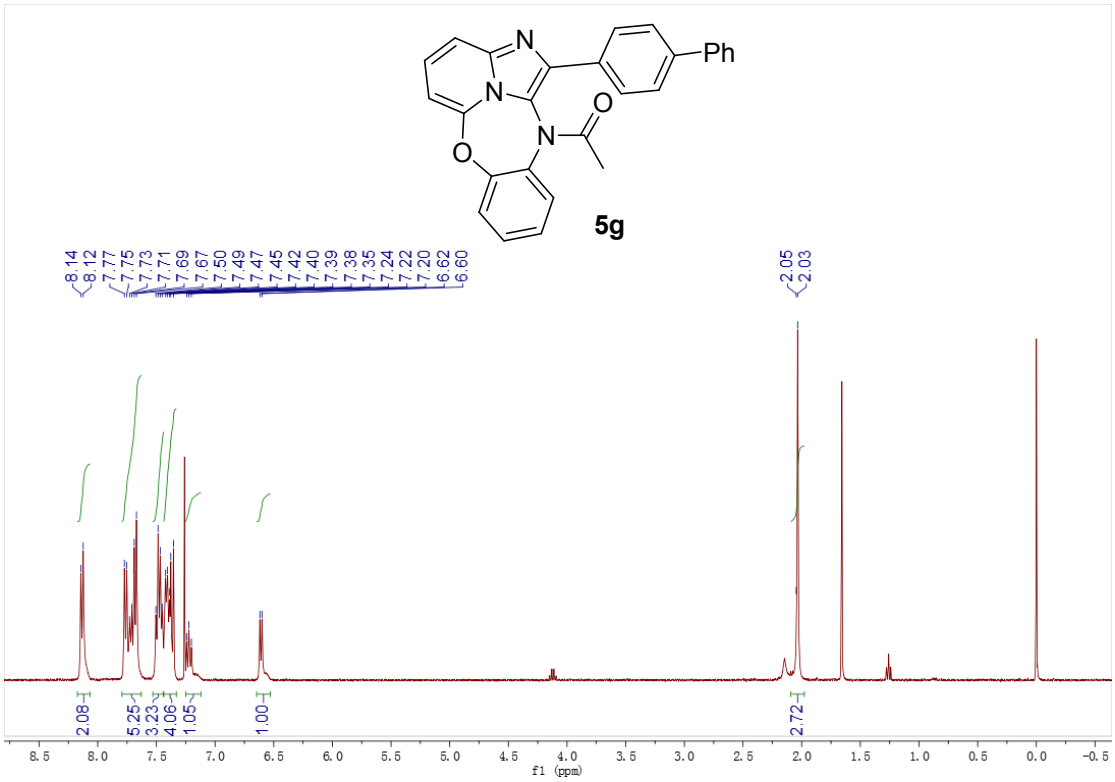
^{1}H NMR spectrum of **5f** in DMSO-d_6 70 °C



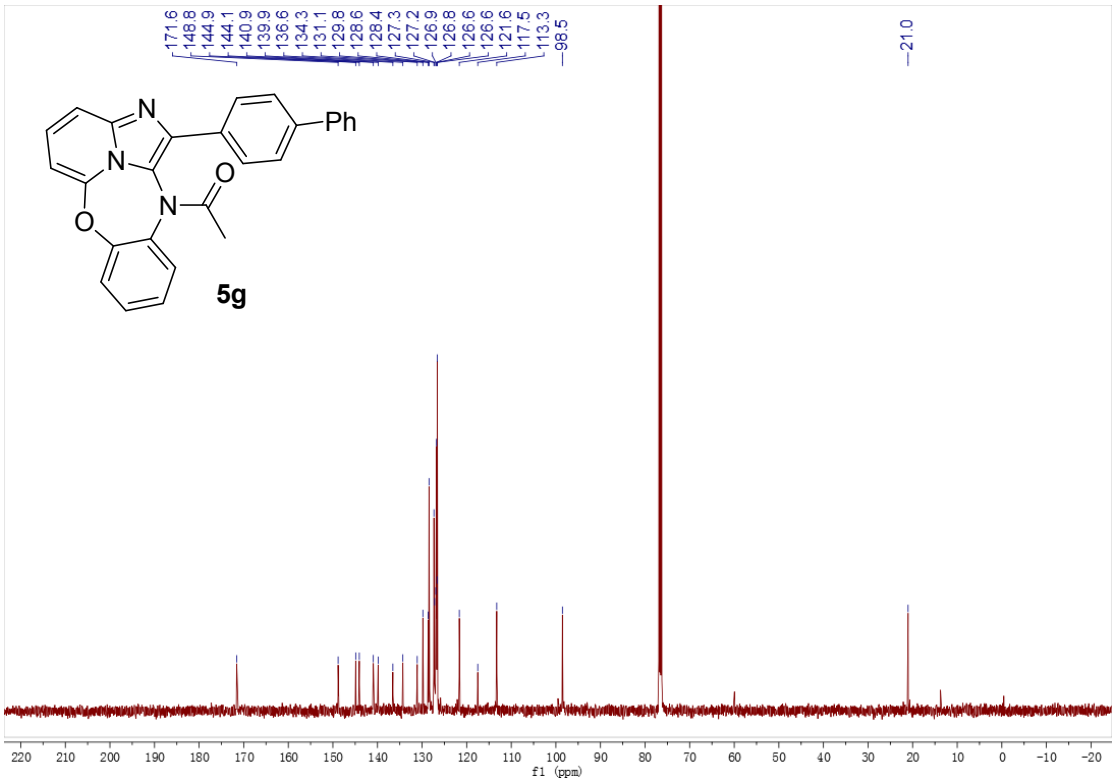
^{13}C NMR spectrum of **5f** in $CDCl_3$



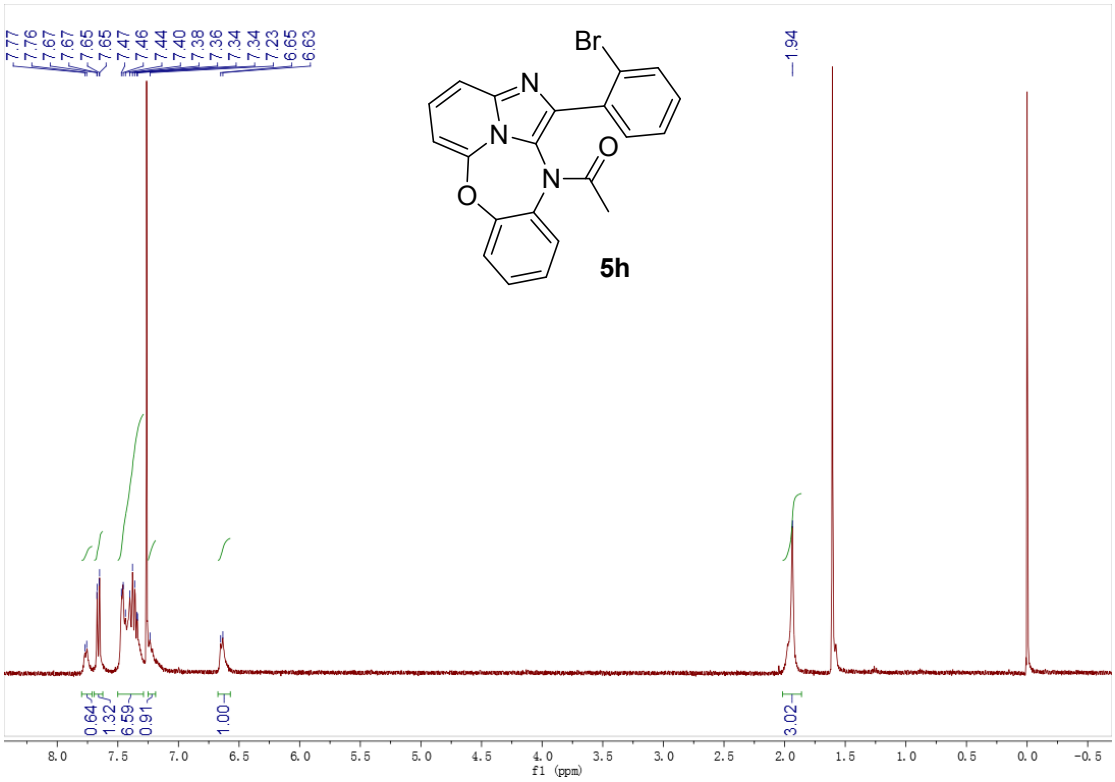
^{1}H NMR spectrum of **5g** in $CDCl_3$



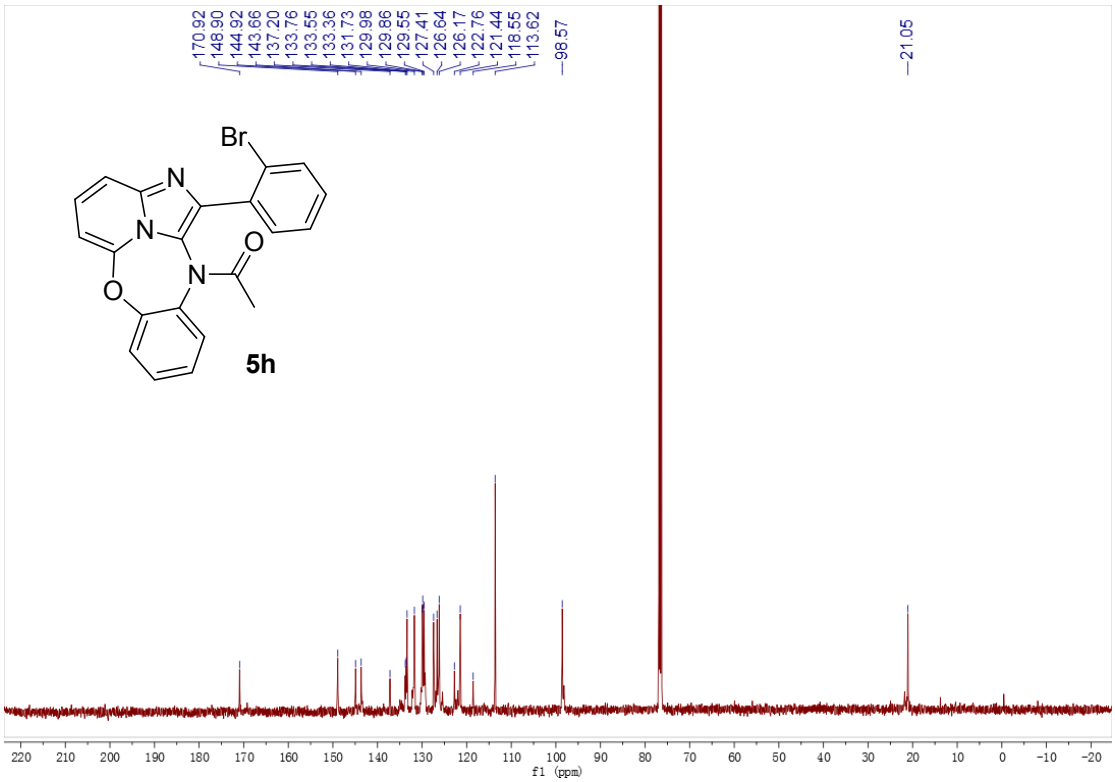
^{13}C NMR spectrum of **5g** in $CDCl_3$



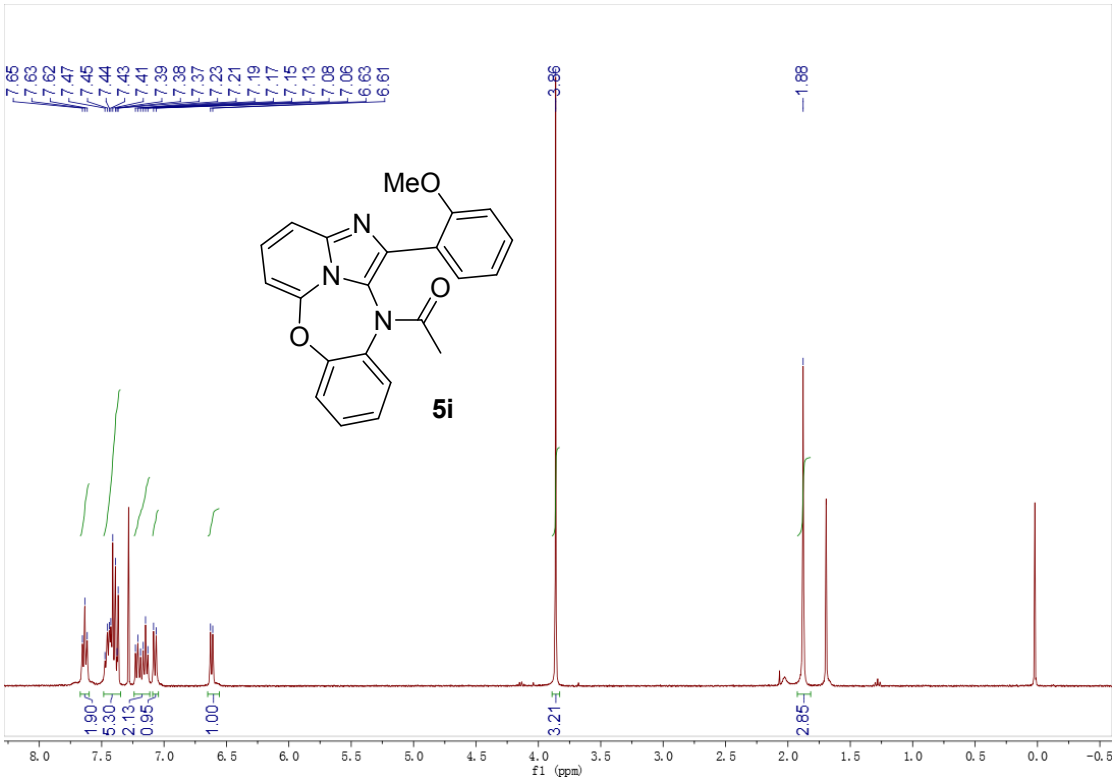
^{1}H NMR spectrum of **5h** in $CDCl_3$



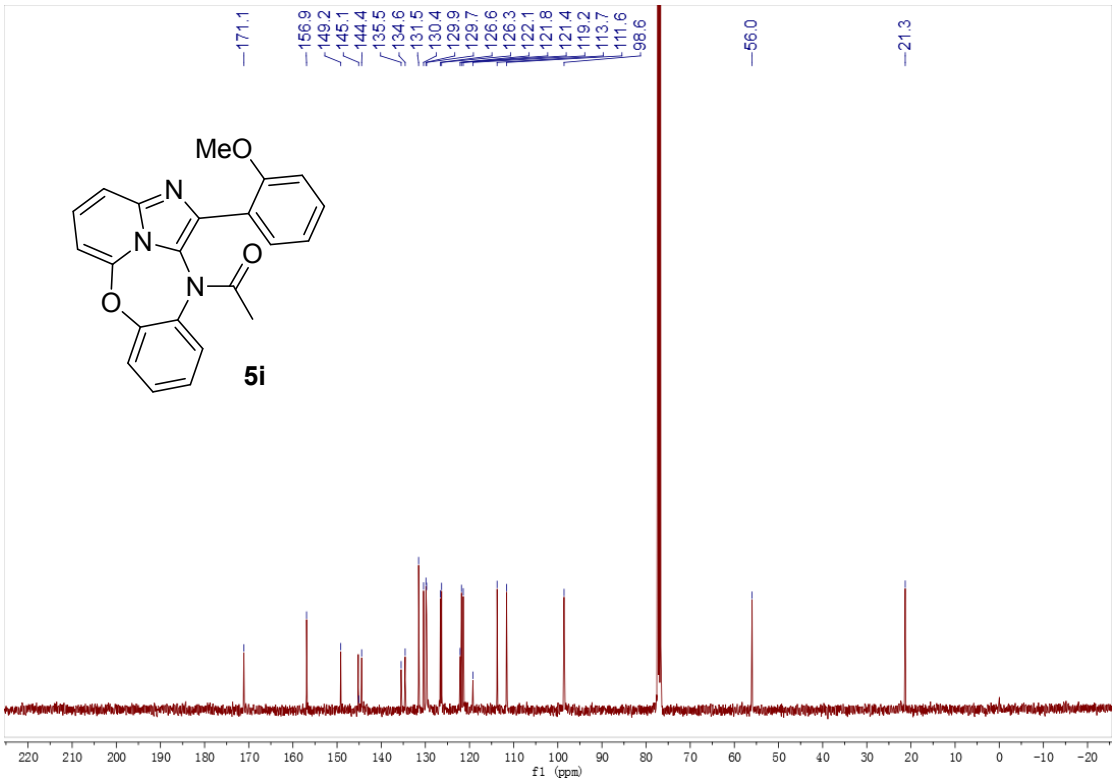
^{13}C NMR spectrum of **5h** in $CDCl_3$



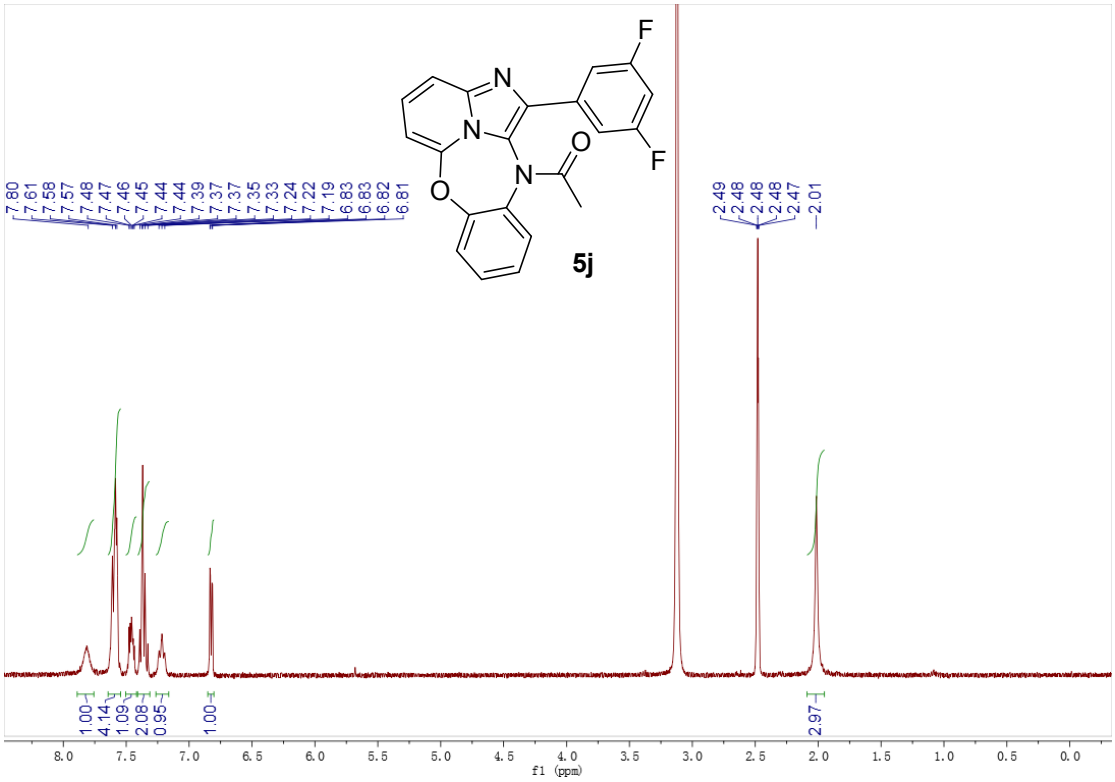
^{1}H NMR spectrum of **5i** in $CDCl_3$



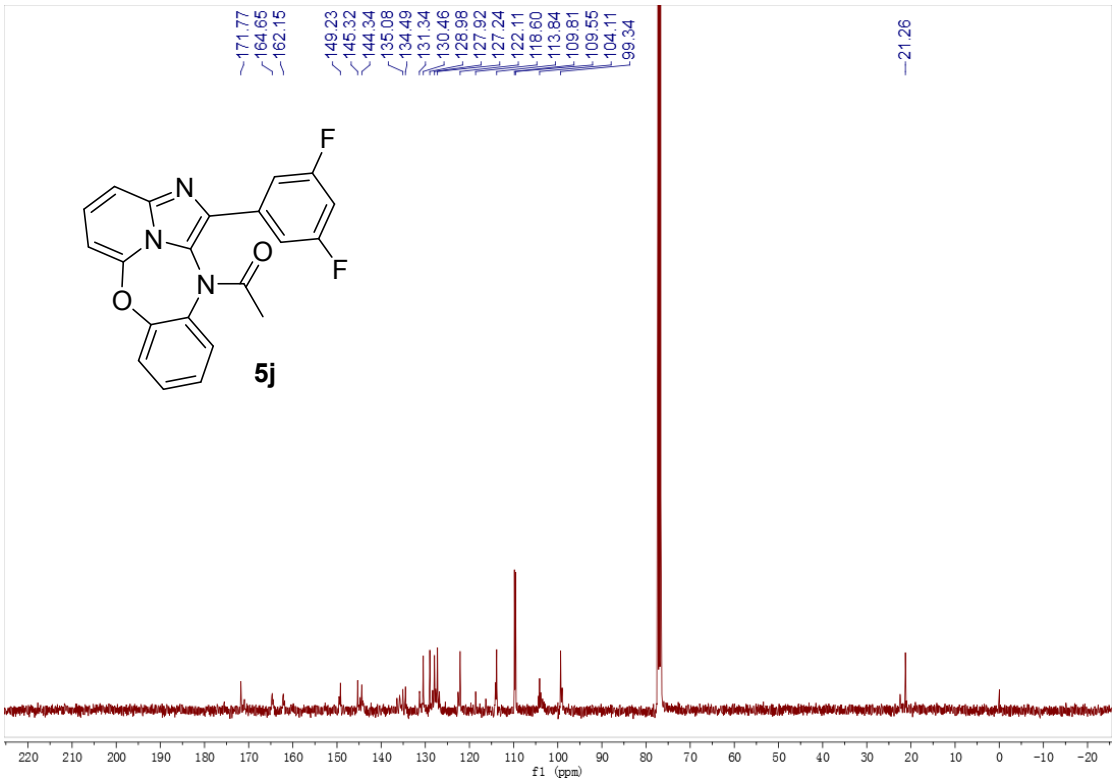
^{13}C NMR spectrum of **5i** in $CDCl_3$



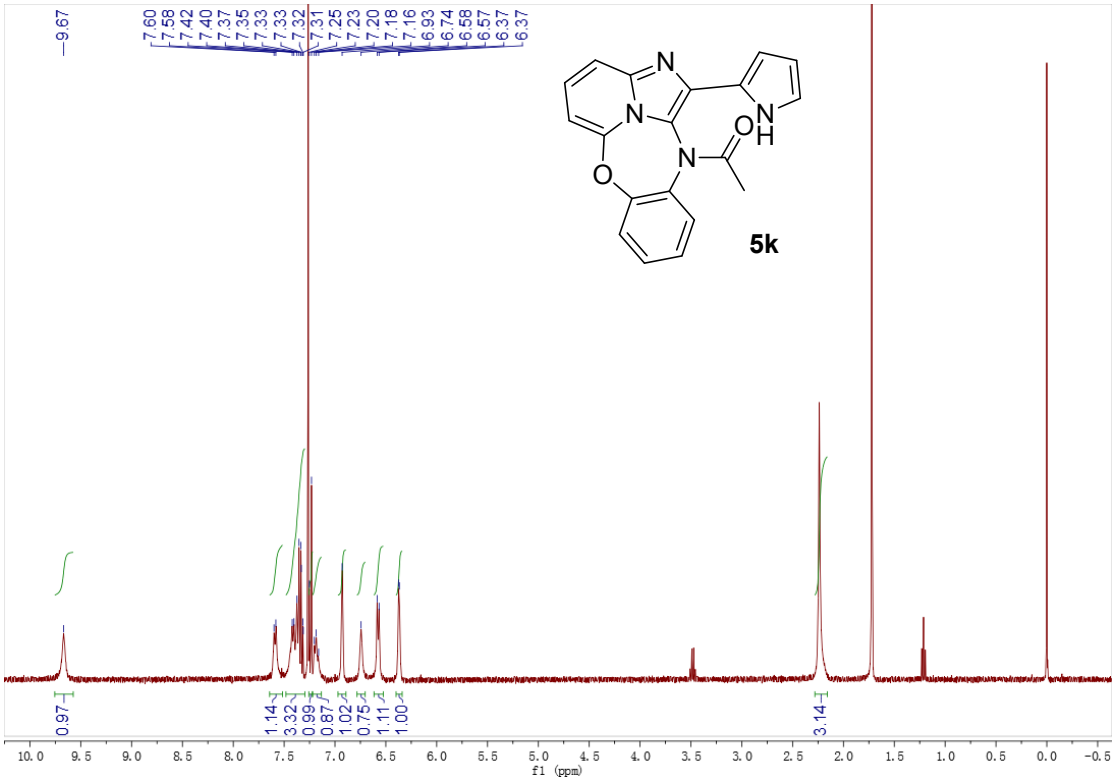
^{1}H NMR spectrum of **5j** in DMSO-d_6 70 °C



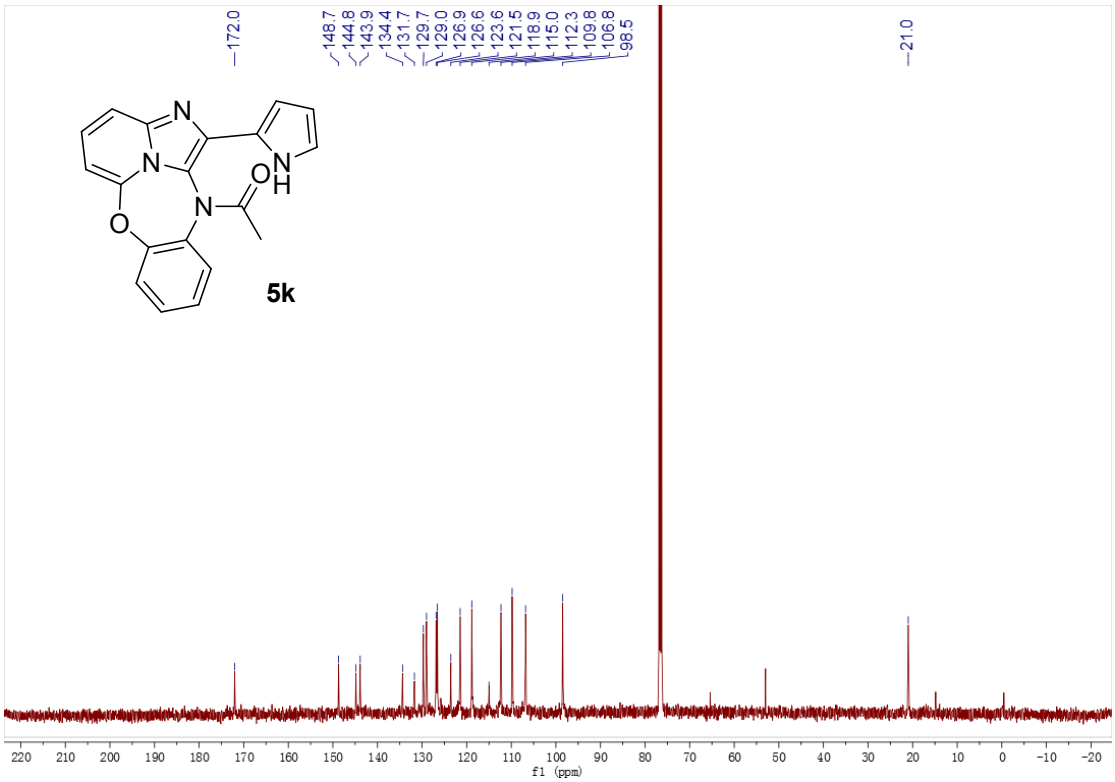
^{13}C NMR spectrum of **5j** in $CDCl_3$



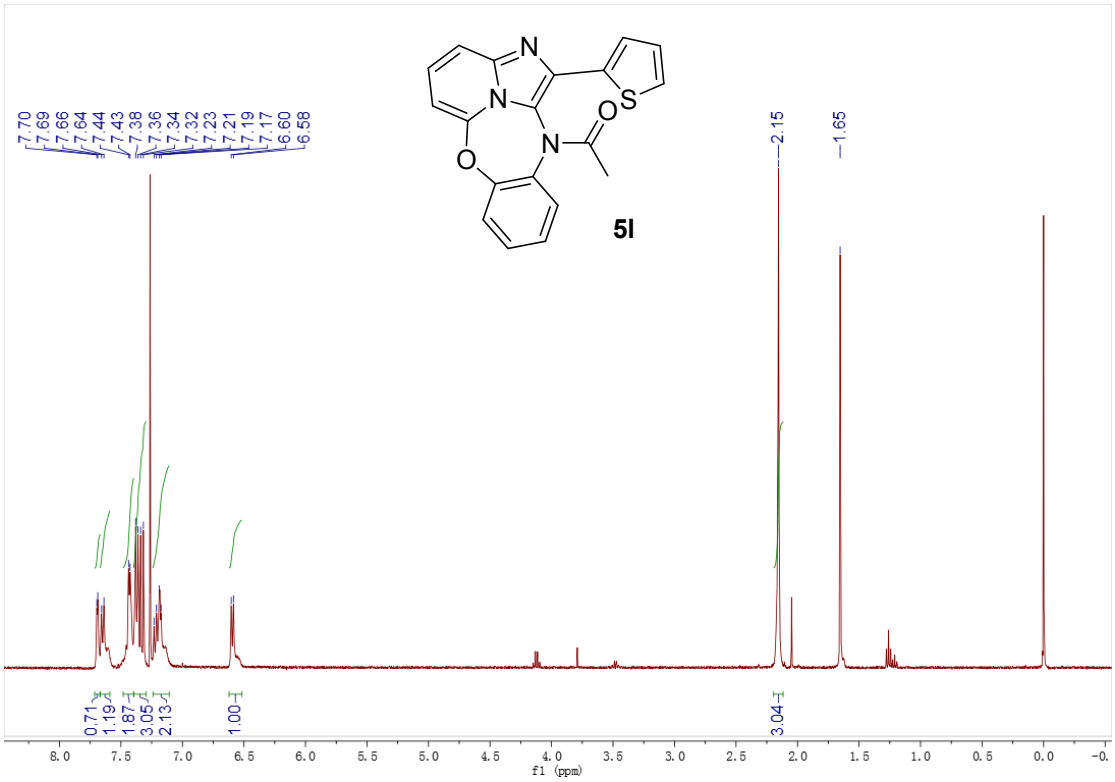
^{1}H NMR spectrum of **5k** in $CDCl_3$



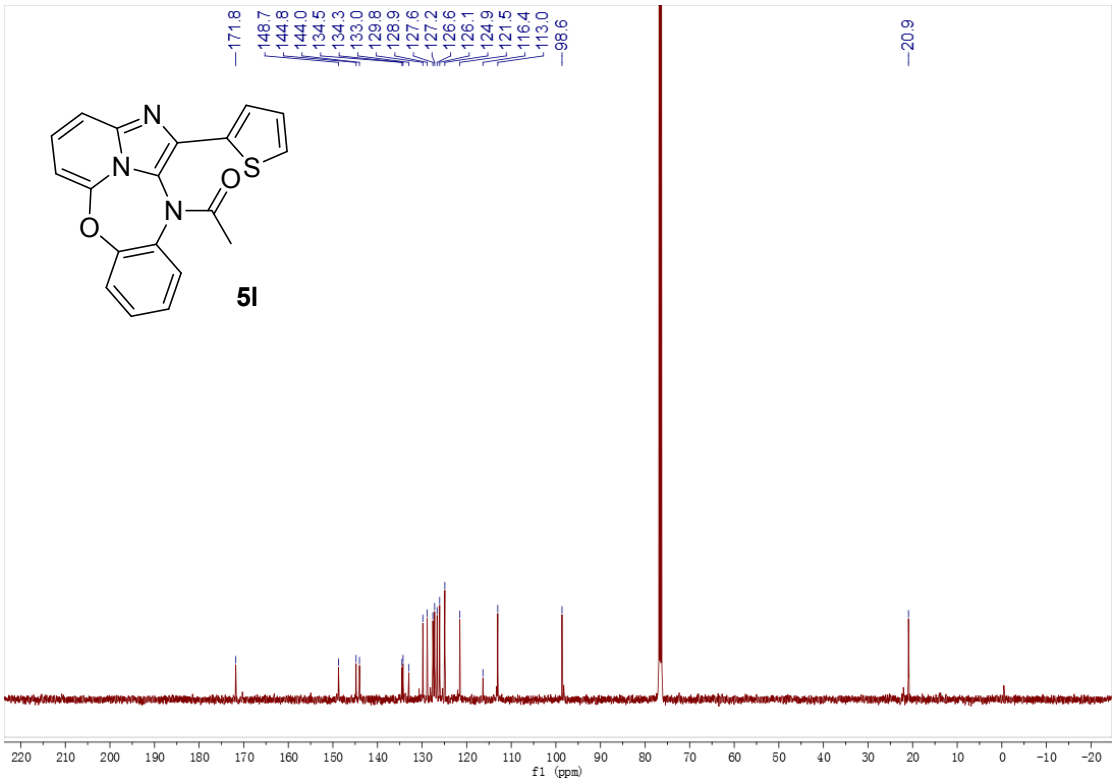
^{13}C NMR spectrum of **5k** in $CDCl_3$



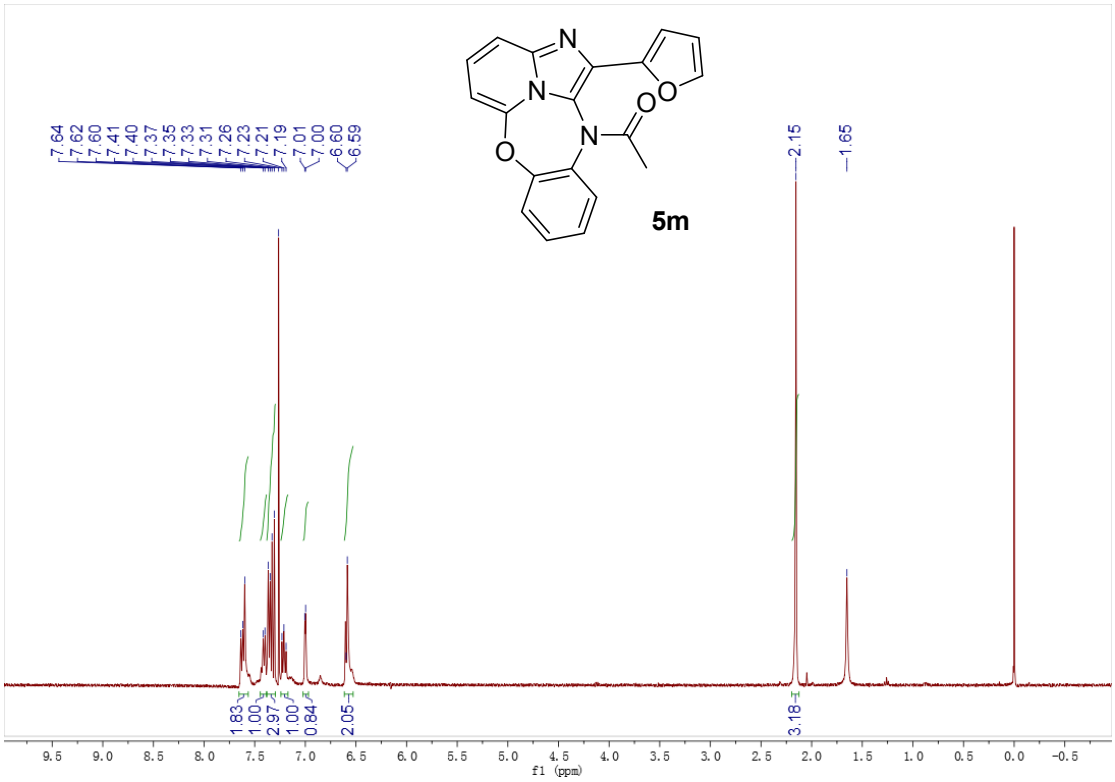
^{1}H NMR spectrum of **5l** in $CDCl_3$



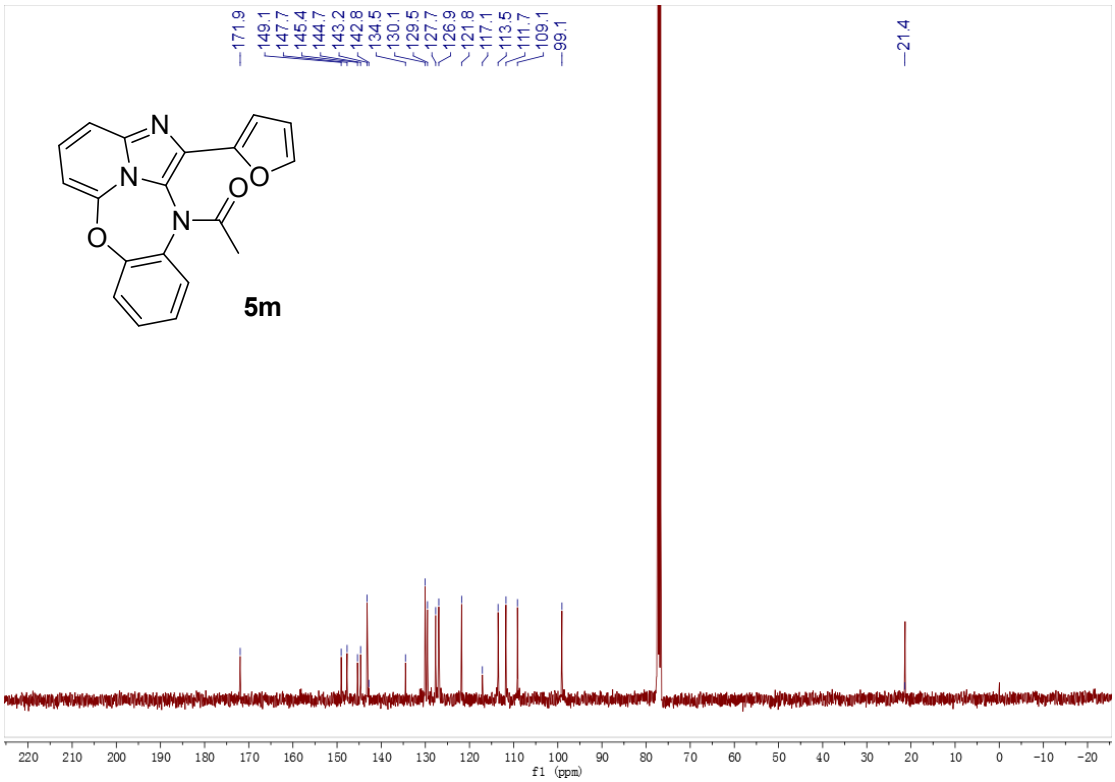
^{13}C NMR spectrum of **5l** in $CDCl_3$



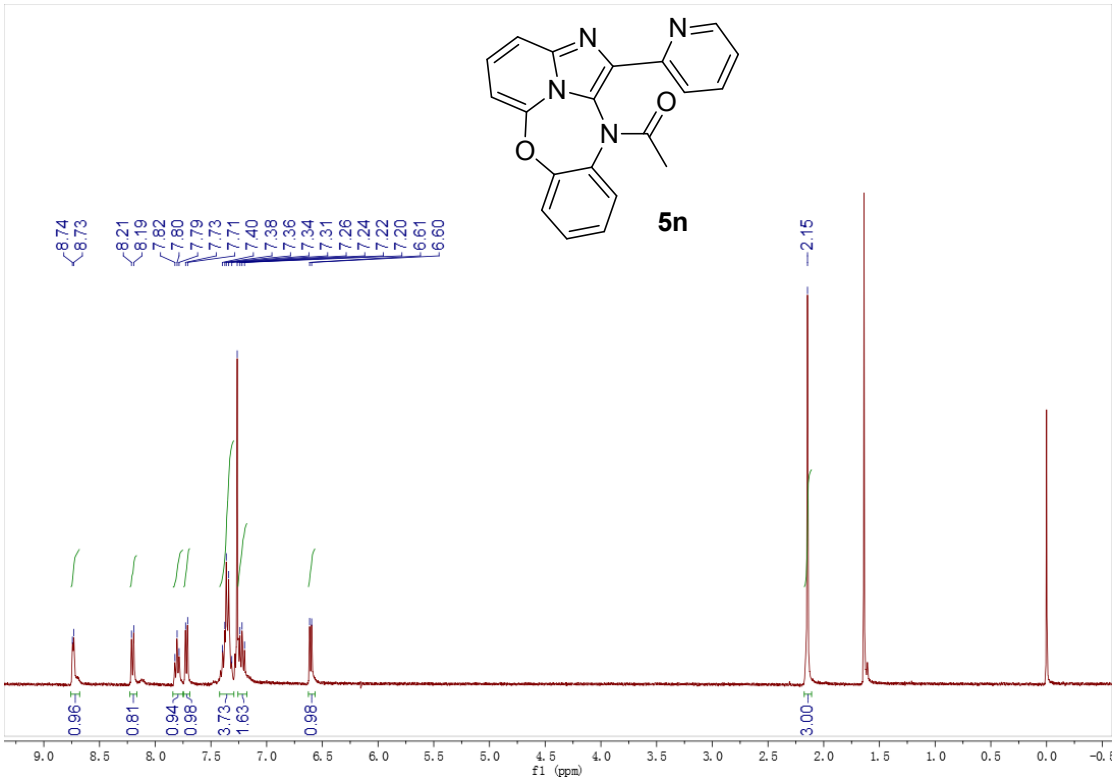
^{1}H NMR spectrum of **5m** in $CDCl_3$



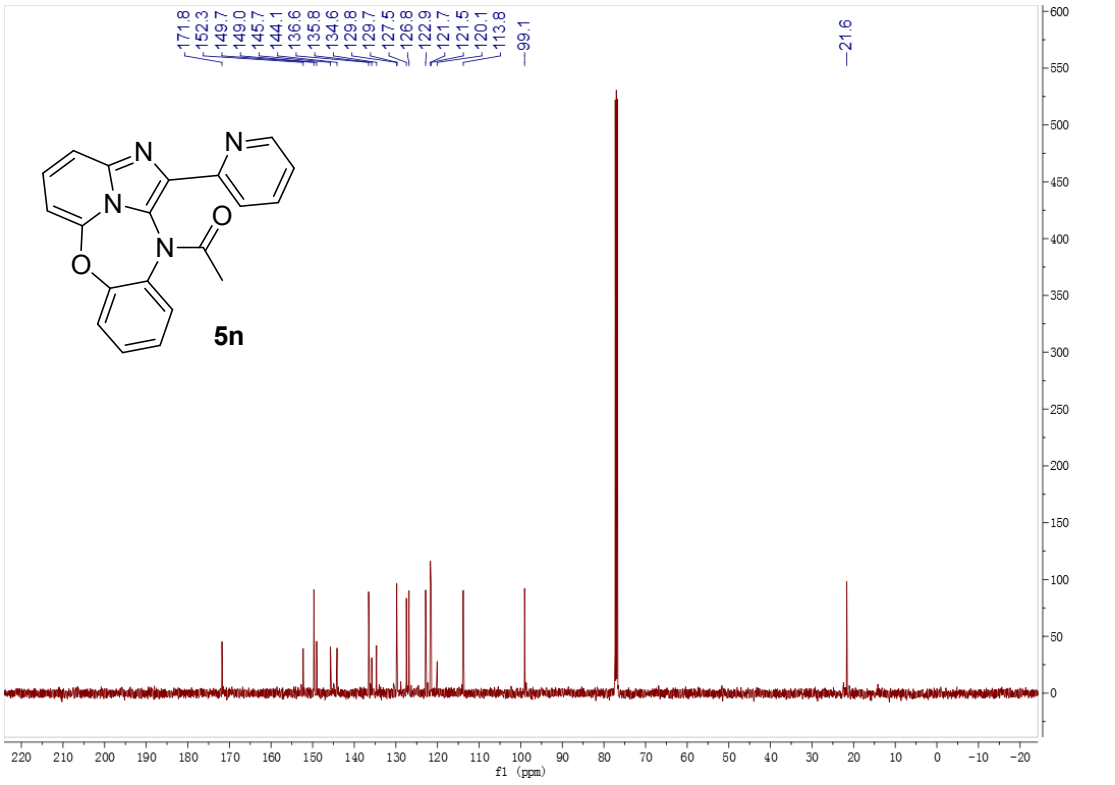
^{13}C NMR spectrum of **5m** in $CDCl_3$



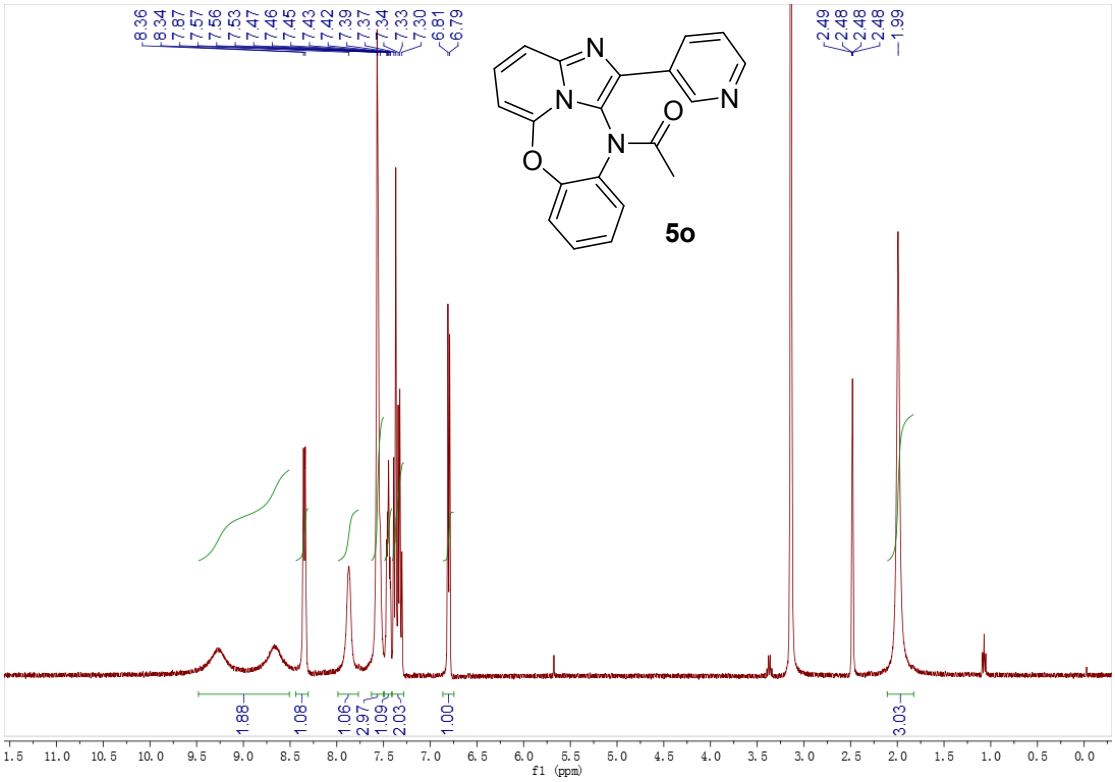
^{1}H NMR spectrum of **5n** in $CDCl_3$



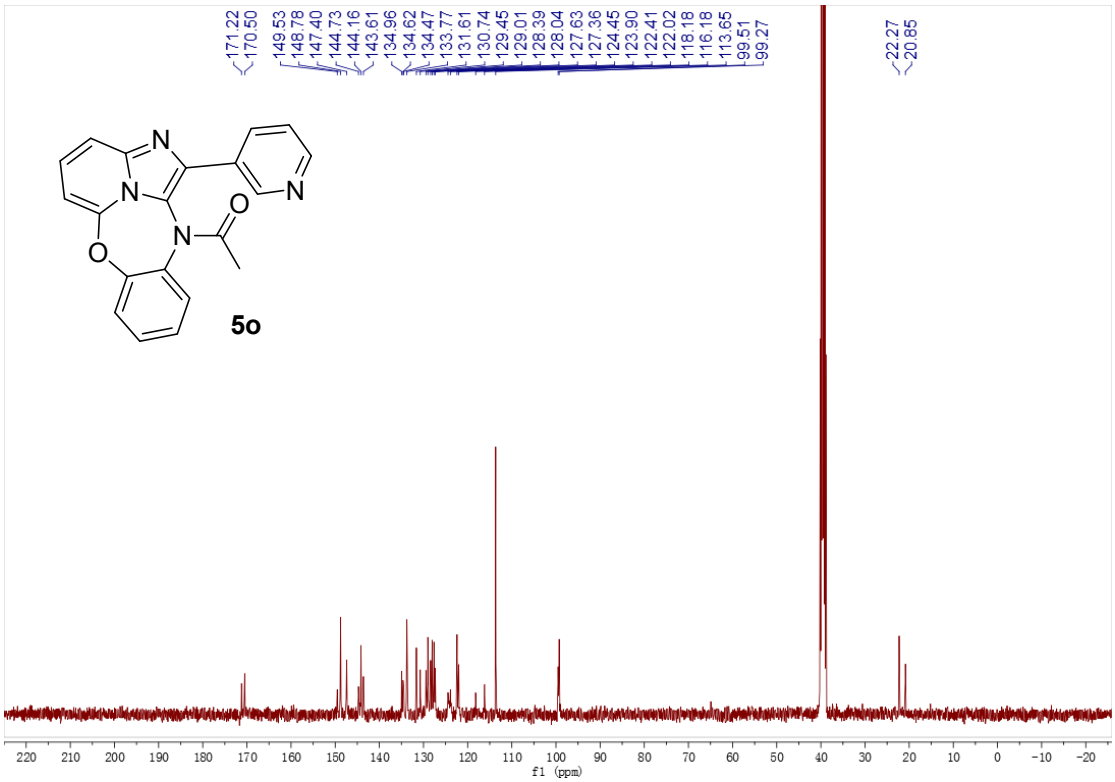
^{13}C NMR spectrum of **5n** in $CDCl_3$



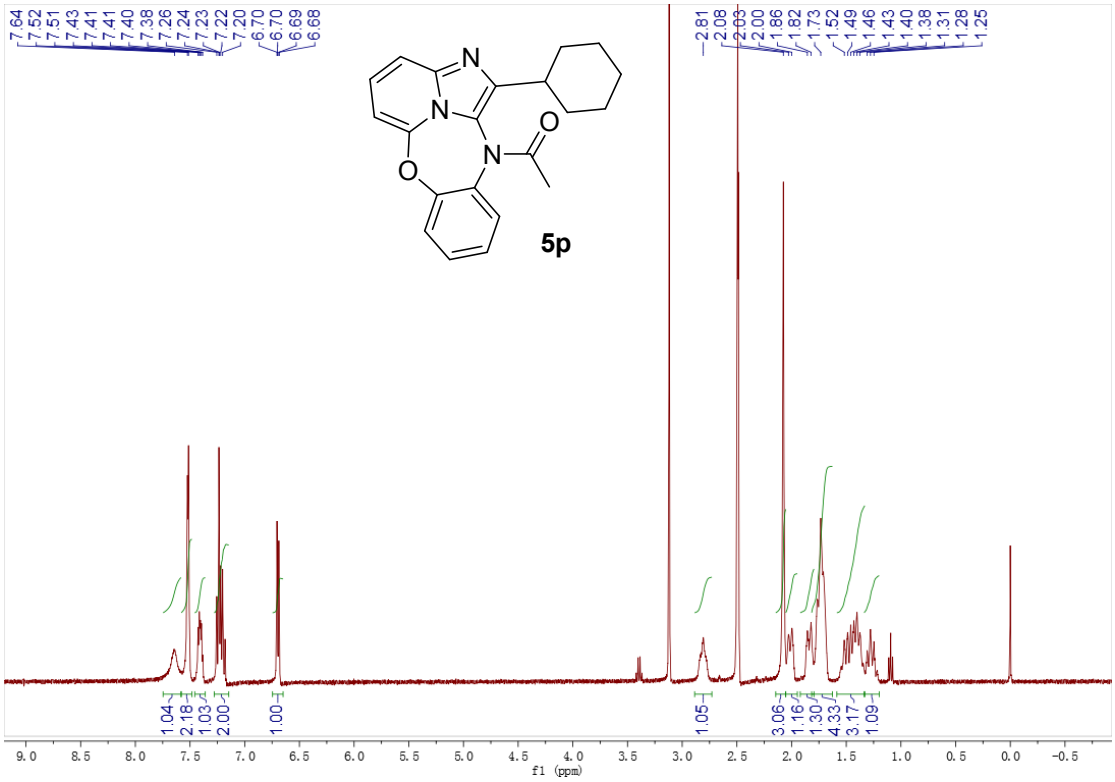
^{1}H NMR spectrum of **5o** in DMSO-d_6 70 °C



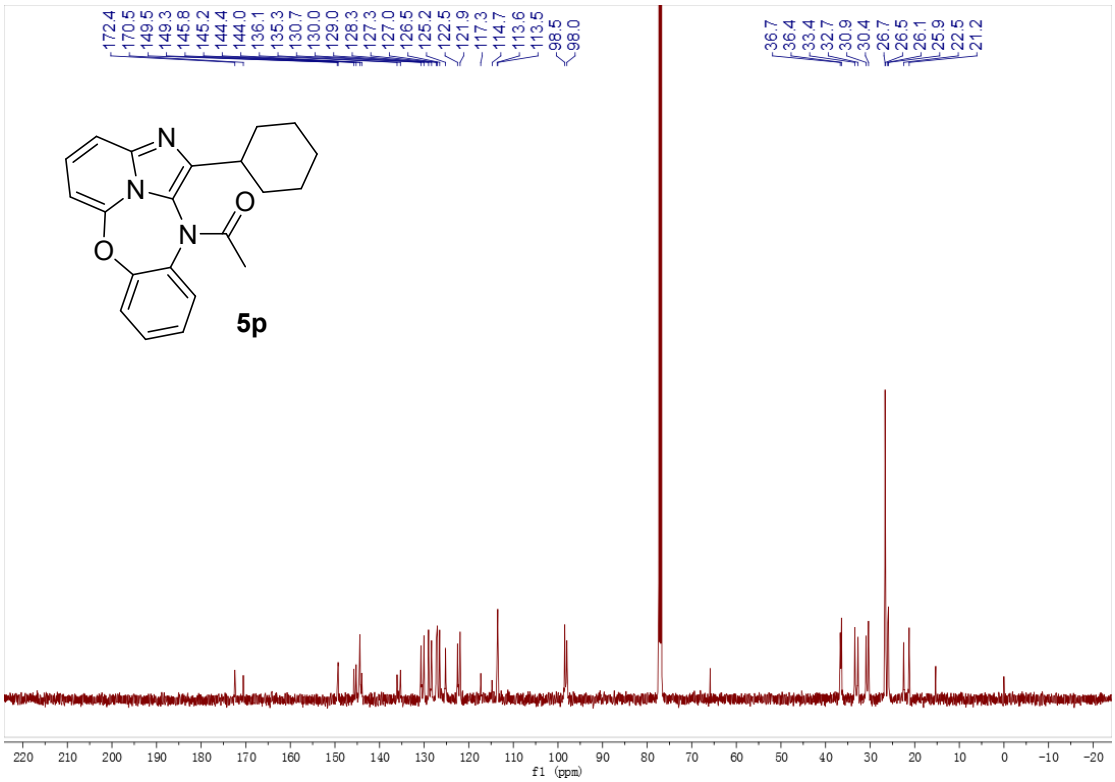
^{13}C NMR spectrum of **5o** in $CDCl_3$



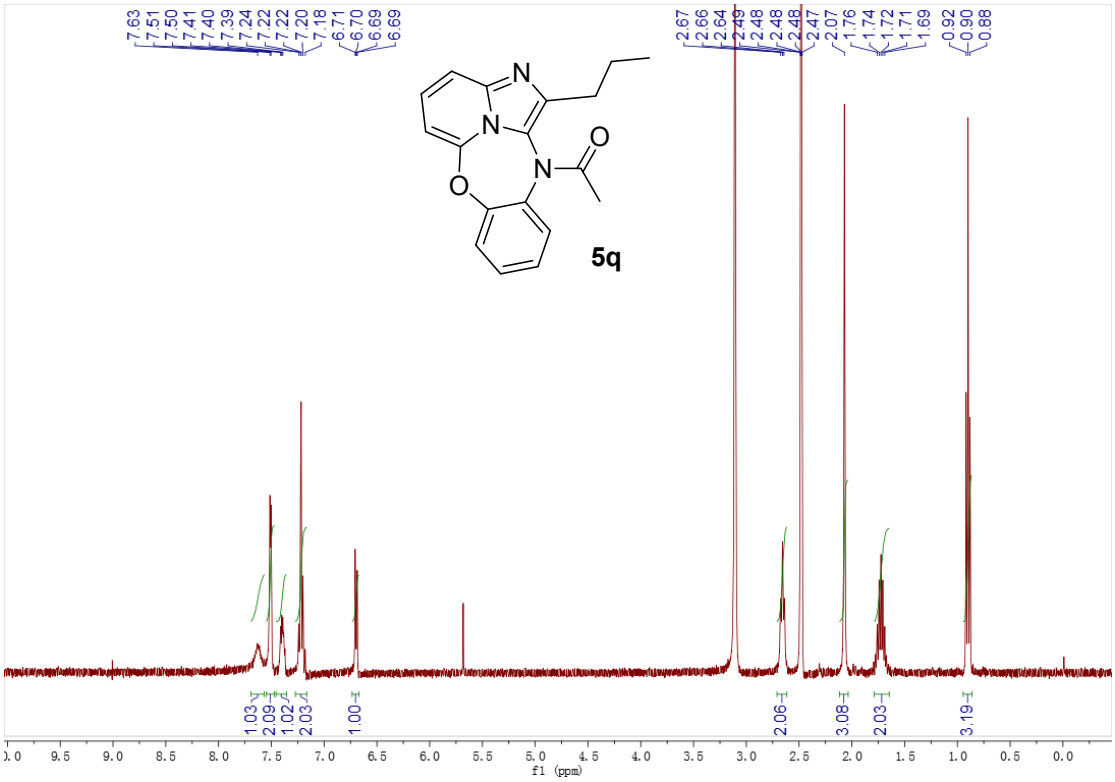
^{1}H NMR spectrum of **5p** in DMSO-d_6 70 °C



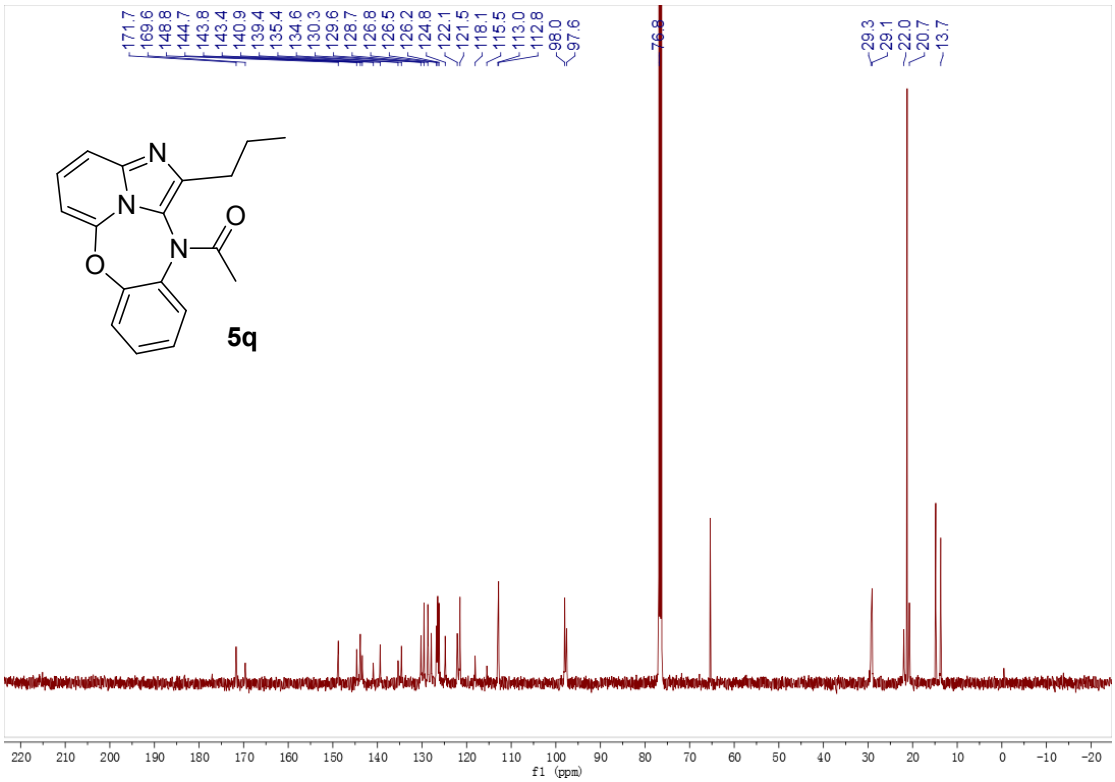
^{13}C NMR spectrum of **5p** in $CDCl_3$



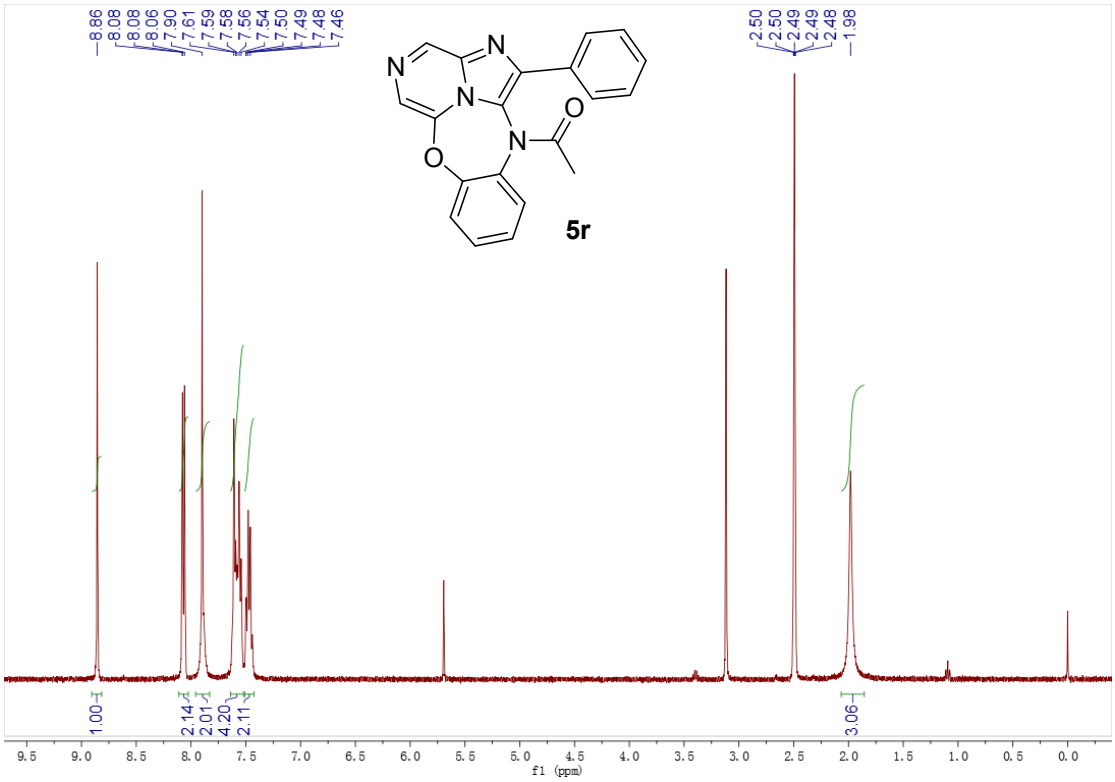
^{1}H NMR spectrum of **5q** in DMSO-d_6 70 °C



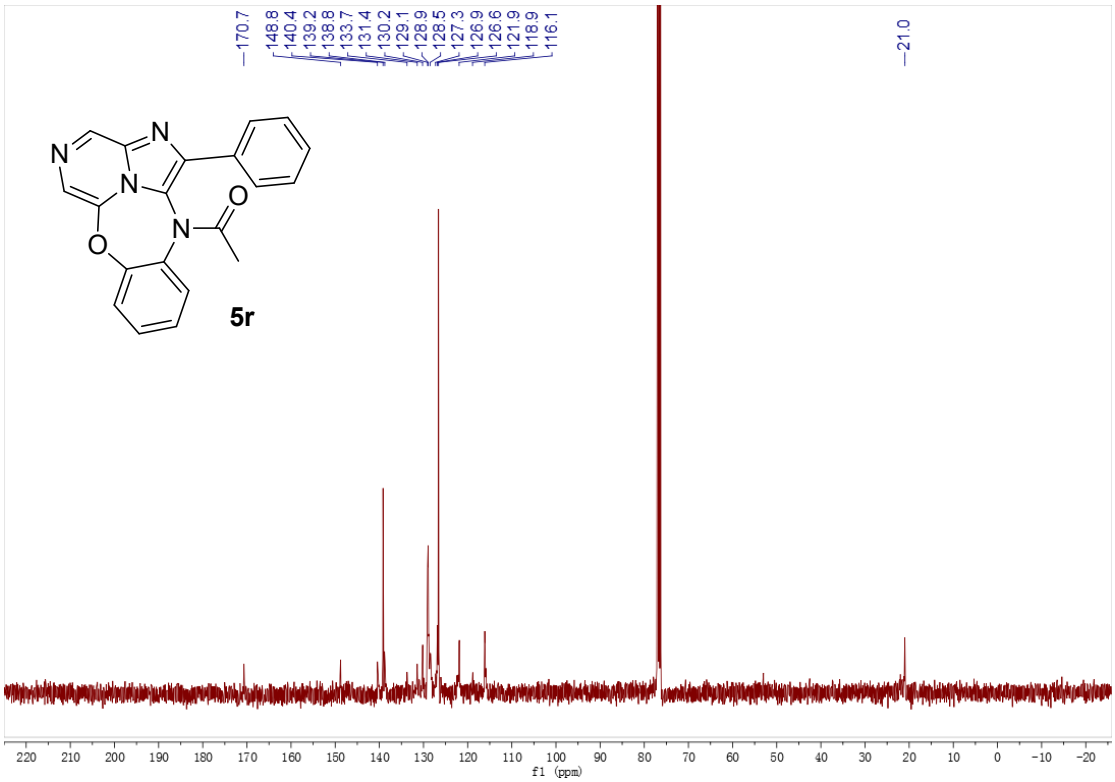
^{13}C NMR spectrum of **5q** in $CDCl_3$



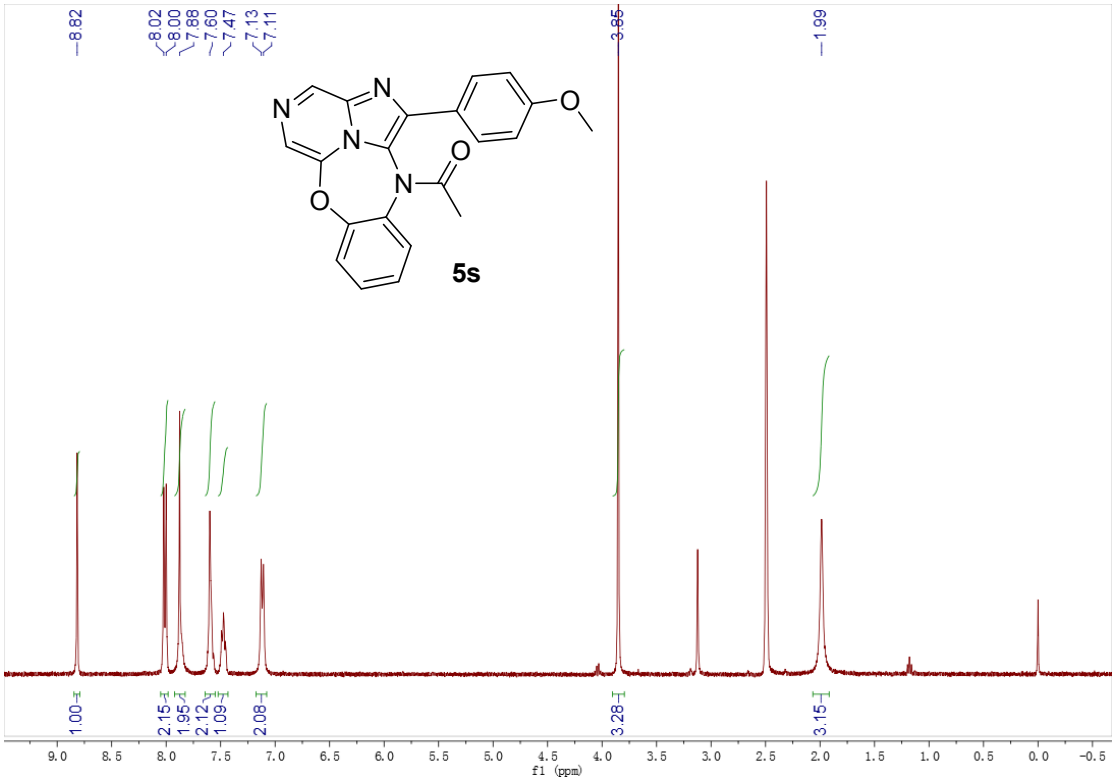
^{1}H NMR spectrum of **5r** in DMSO-d_6 70 °C



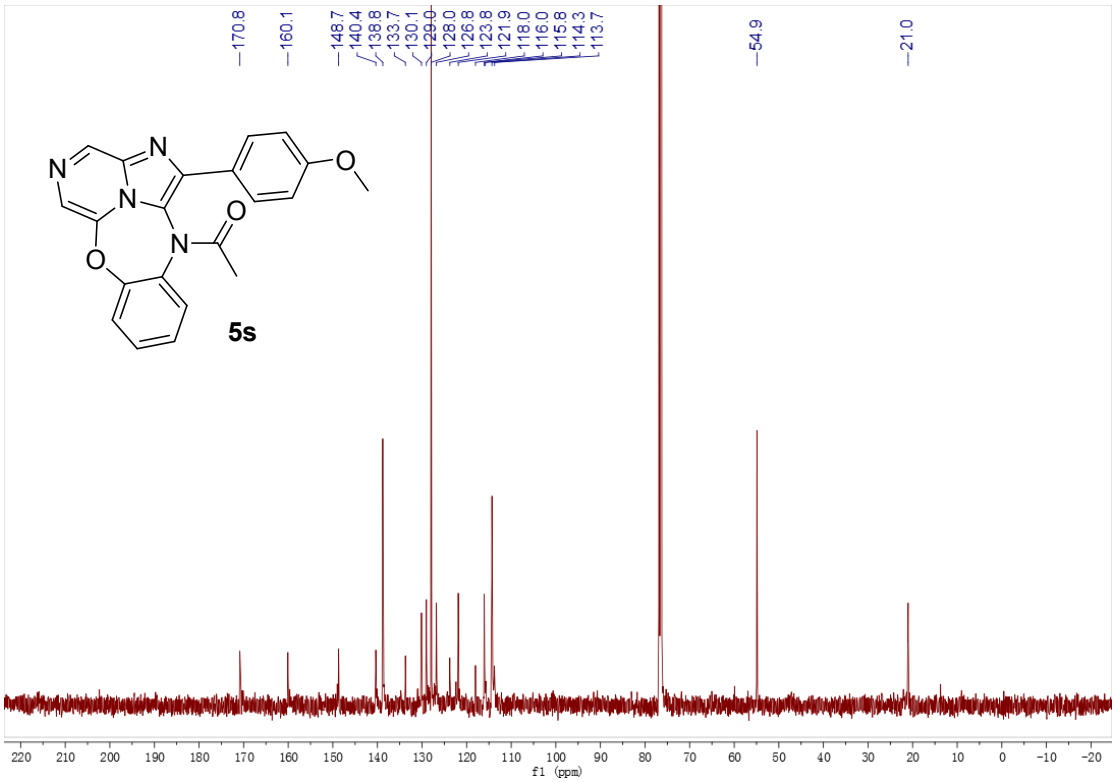
^{13}C NMR spectrum of **5r** in $CDCl_3$



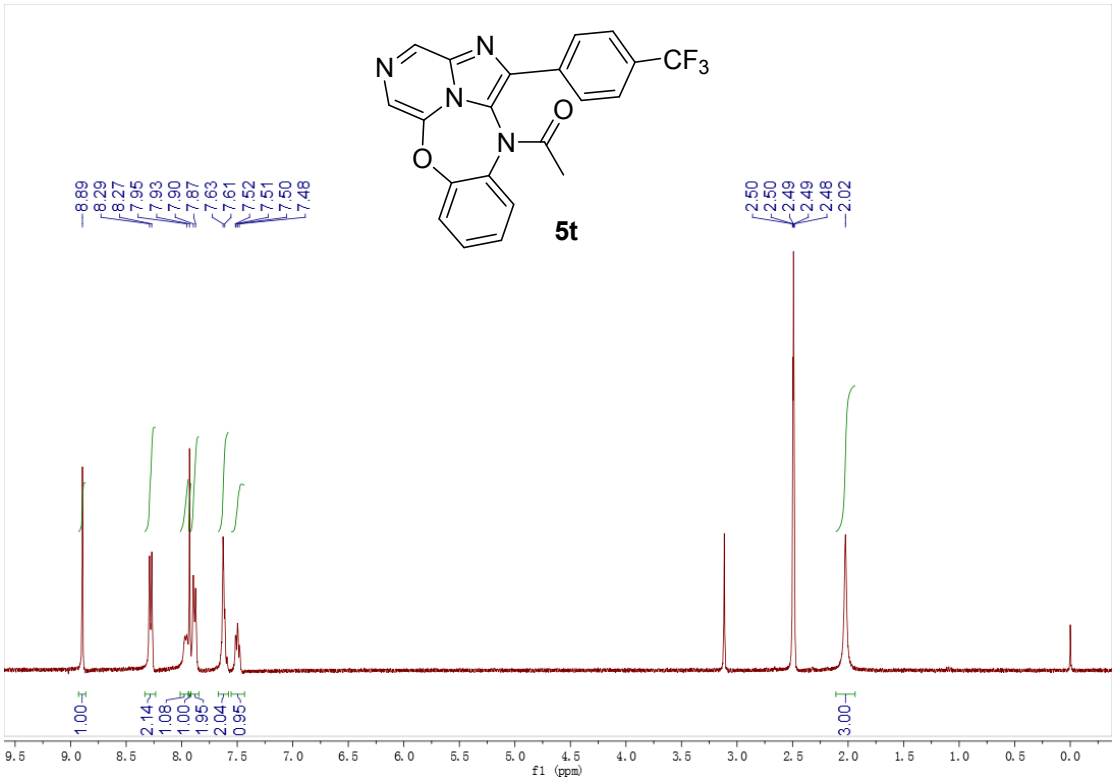
^{1}H NMR spectrum of **5s** in DMSO-d_6 70 °C



^{13}C NMR spectrum of **5s** in $CDCl_3$

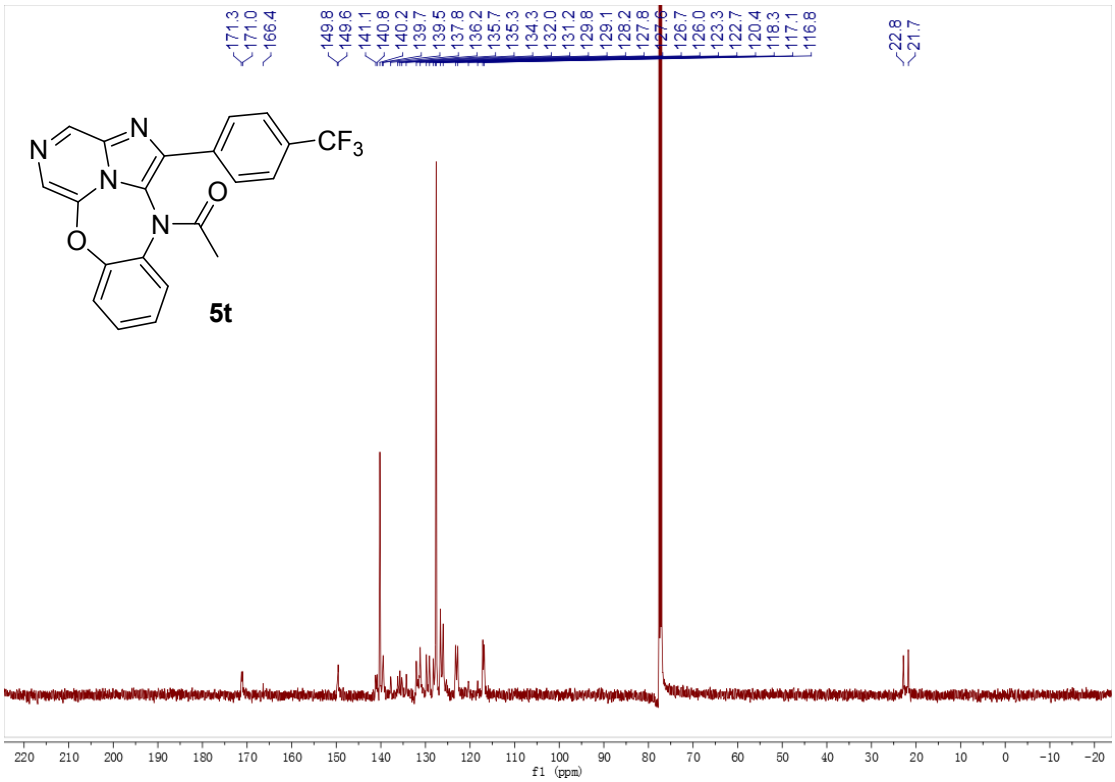


^{1}H NMR spectrum of **5t** in DMSO-d_6 70 °C



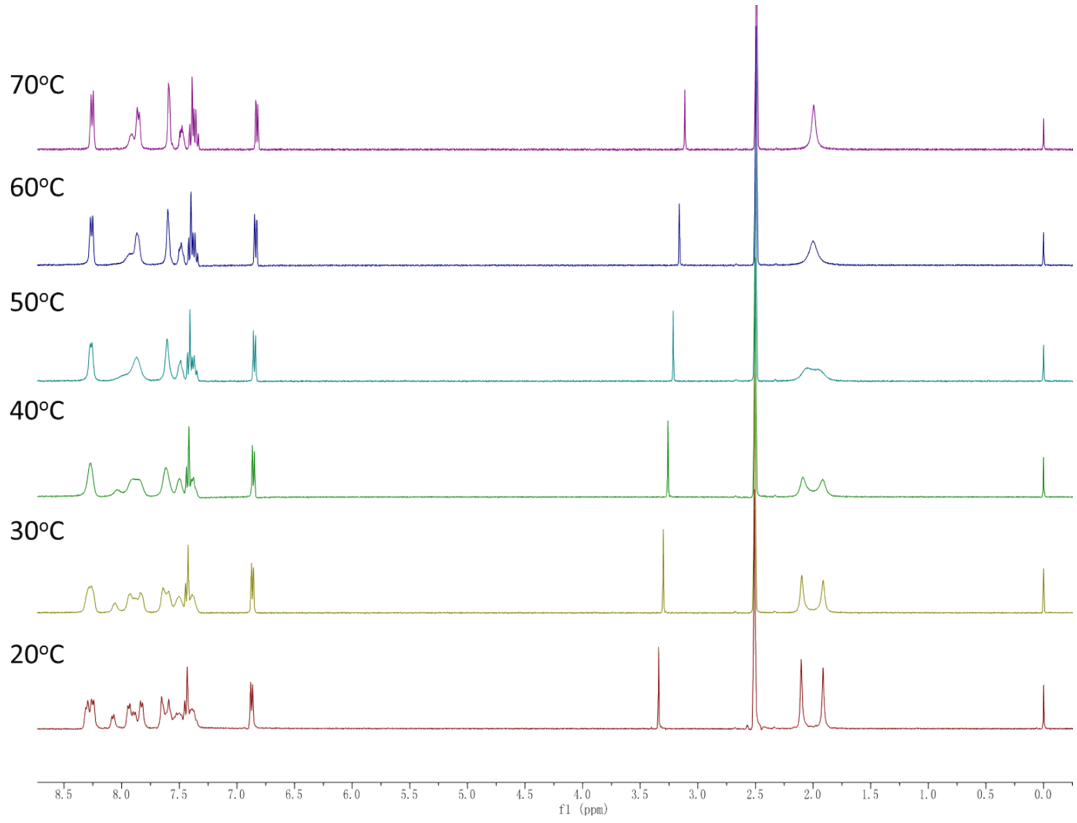
5t

^{13}C NMR spectrum of **5t** in $CDCl_3$



5t

Variable-temperature 400 MHz ^{1}H NMR spectra in d_6-DMSO study of **5c**



At room temperatures, the rate of rotation around the aryl-N(C=O) bonds would be slowed down, and in fact well separated multiple signals corresponding to a mixture of two conformers were observed, specially the acetyl signal was splitted into doublet. As shown in the figure above, the doublet of acetyl signal was merging into singlet as the temperature rising up to 70 °C.

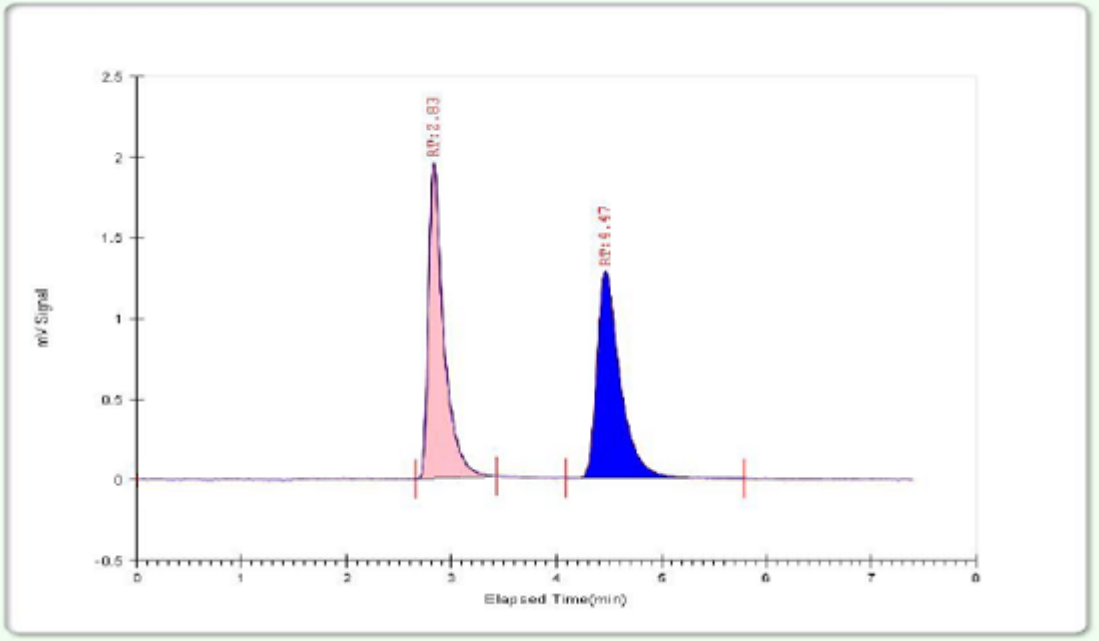
Resolution and measurement of rotation barriers of 5c

Semi-preparative method:

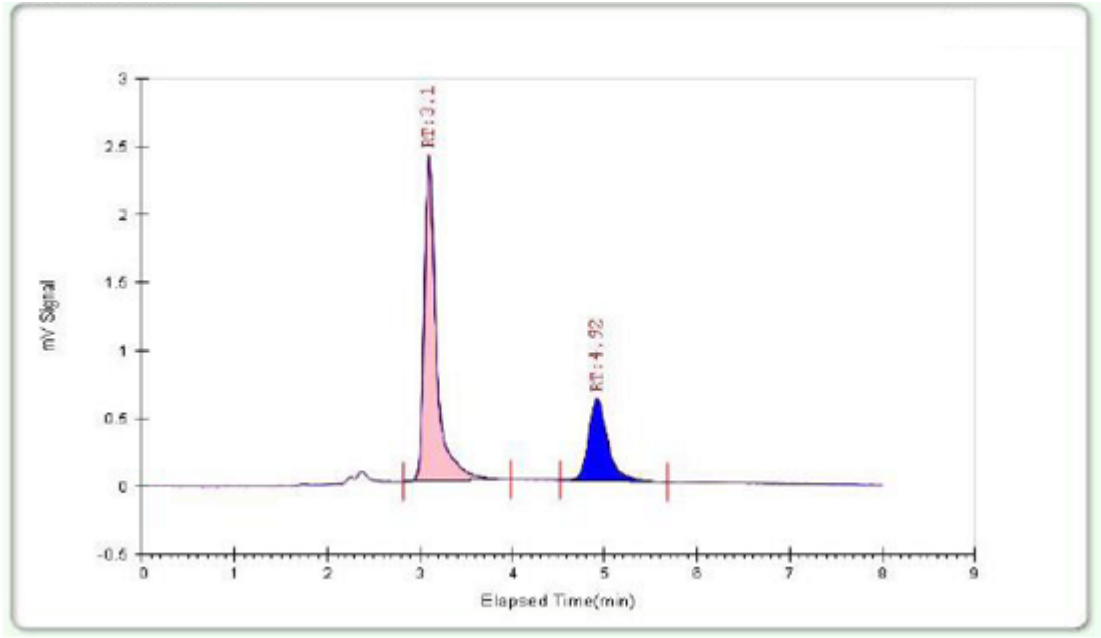
Column: Chiralpak IC, 4.6 mm I.D. * 250 mm Length, 5 um particle size
Mobile phase: CO_2 / MeOH = 60 / 40 (v/v)
Flow rate: 2.4 ml/min
Wave length: UV 220 nm
Temperature: 20 °C

CHROMATOGRAPHY REPORT

Column	:	IC
Column size	:	0.46 cm I.D. × 25 cm L
Injection	:	
Mobile phase	:	CO2/MeOH=60/40 (v/v)
Flow rate	:	2.4 ml/min
Wave length	:	UV 220 nm
Temperature	:	20 °C
Sample structure	:	Racemates of 5c



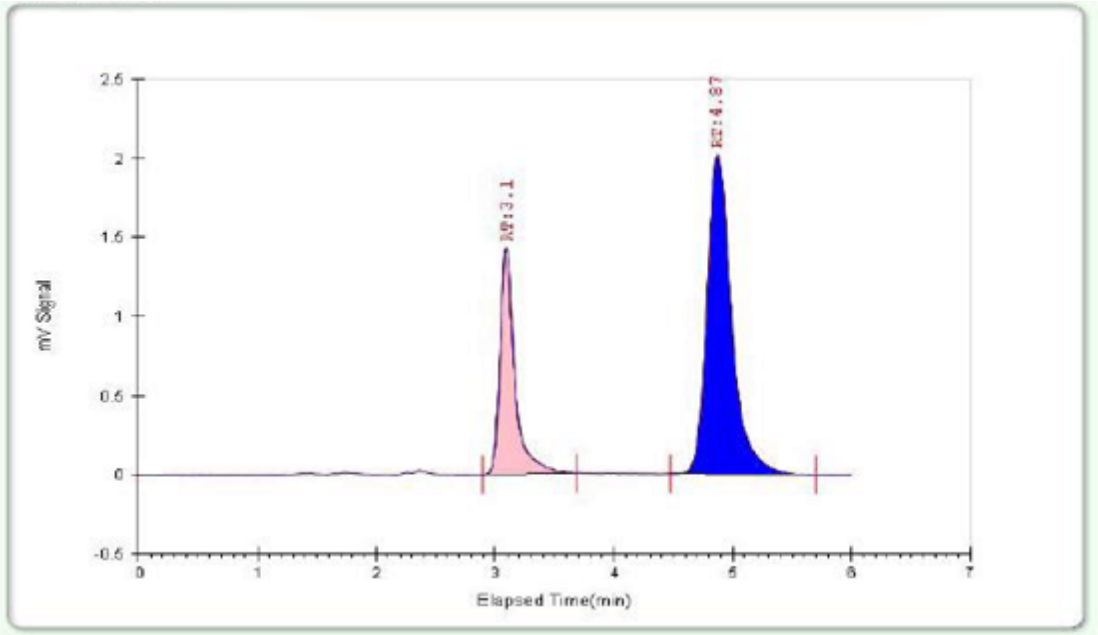
Column	:	IC
Column size	:	0.46 cm I.D. × 25 cm L
Injection	:	
Mobile phase	:	CO_2/MeOH=60/40 (v/v)
Flow rate	:	2.4 ml/min
Wave length	:	UV 220 nm
Temperature	:	20 °C
Sample structure	:	Peak 1 of 5c



Peak table:

No.	t_R(min)	Area%	T.Plates
1	3.1	71.85	7945
2	4.92	28.15	7621

Column	:	IC
Column size	:	0.46 cm I.D. × 25 cm L
Injection	:	
Mobile phase	:	CO_2/MeOH=60/40 (v/v)
Flow rate	:	2.4 ml/min
Wave length	:	UV 220 nm
Temperature	:	20 °C
Sample structure	:	Peak 2 of 5c



Peak table:

No.	t_R(min)	Area%	T.Plates
1	3.1	30.34	8031
2	4.87	69.66	7759

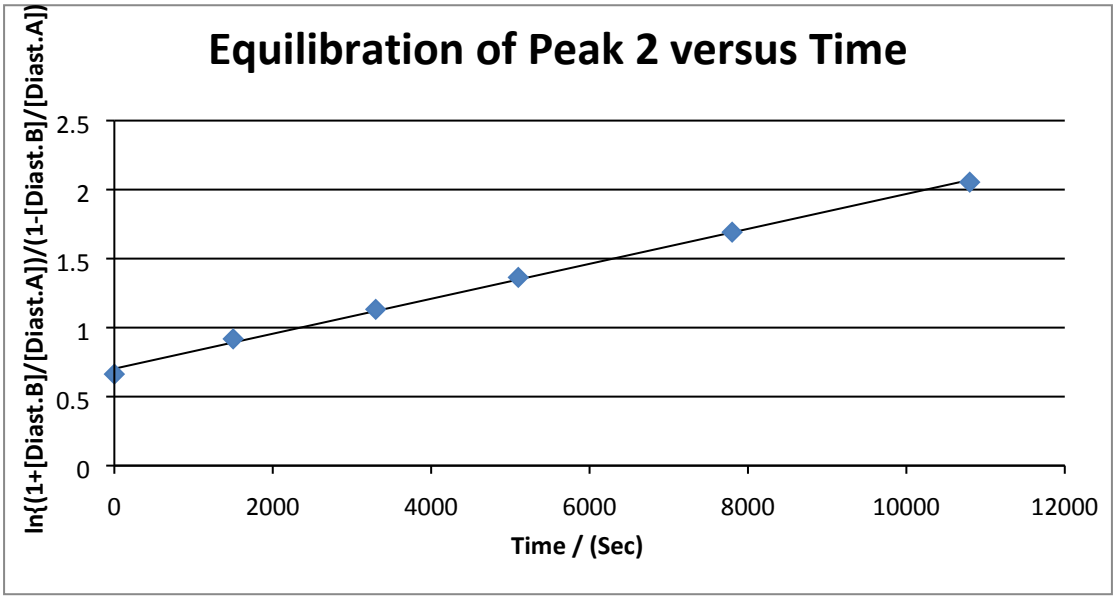
Measurement of rotation barriers of 5c

Column: Chiralpak AD-H, 4.6 mm I.D. * 250 mm Length, 5 um particle size
Mobile phase:Hexane / MeOH = 60 / 40 (v/v)
Flow rate: 0.8 ml/min
Wave length: UV 220 nm
Temperature: 22 °C

Injection volume: 20 μl

Peak 2 was dissolved in hexane : MeOH = 6 : 4 (5 μg/mL) and stirred at 298 K. At the given intervals of time, 20 μL of the solution was injected into the HPLC and the e.e% was measured by using peak integrations.

Peak 2	T = 298 K
Time (sec)	ee (%)
0	51.53
1500	39.93
3300	32.23
5100	25.57
7800	18.42
10800	12.82



$$\ln\left[\frac{1+[Diast.B]/[Diast.A]}{1-[Diast.B]/[Diast.A]}\right] = 2kt + c$$

Plot $\ln\left[\frac{1+[Diast.B]/[Diast.A]}{1-[Diast.B]/[Diast.A]}\right]$ vs Time (seconds)

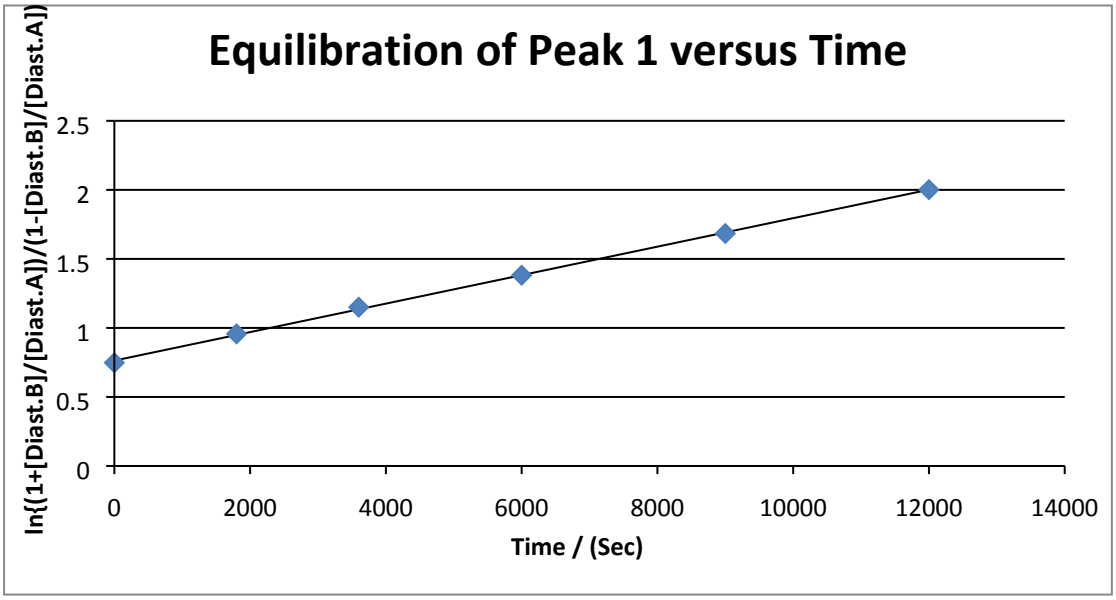
Where
-slope = 2k
-c is equal to zero if starting material se is 100%
-Diast. A represents the most prominent epimer in solution during the experiment (Diast. B the least)

k = 1/2 slope = 5.0E-05 S^{-1}
$K^{\ddagger}$ = kh / *k*T = (5.0E-05 S^{-1})(6.626 E-34 JS)/(1.381E-23 J/K)(298K)
$K^{\ddagger}$ = 8.05E-18 and ΔG = - RTlnK
$\Delta G^{\ddagger}_{rot} = 9.75\times10^{4}$ J/mol

Peak 1 was dissolved in hexane : MeOH = 6 : 4 (5 μg/mL) and stirred at 298 K. At the

given intervals of time, 20 μL of the solution was injected into the HPLC and the e.e% was measured by using peak integrations.

Peak1	T = 298 K
Time (sec)	ee (%)
0	47.32
1800	38.41
3600	31.66
6000	25.11
9000	18.56
12000	13.51



In an analogous fashion to the above example, the rotational barrier of Peak 1 was found to be $\Delta G^{\ddagger}_{rot} = 9.75\times10^{4}$ J/mol.

Crystal structure data for the compound 5a

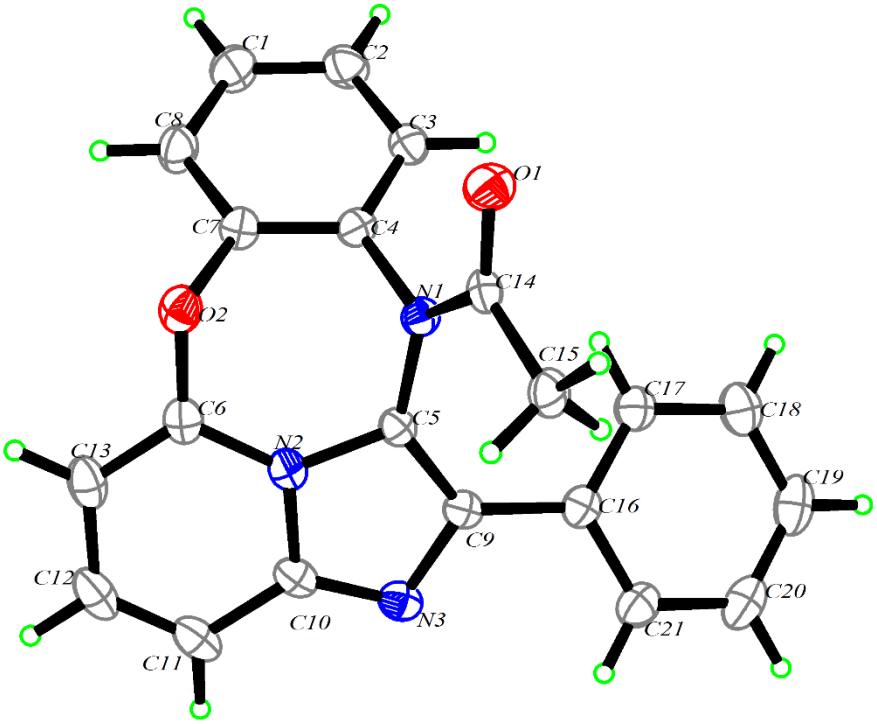
Relevant crystal data and structure refinement parameters are provided in Table S1. CCDC 1007734 (5a) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data. Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table S1. Sample and crystal data for 1007734.

Identification code	1007734	
Chemical formula	$C_{21}H_{15}N_3O_2$	
Formula weight	341.36	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal size	0.100 x 0.150 x 0.300 mm	
Crystal system	orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 8.4445(6) Å	α = 90°
	b = 19.2694(14) Å	β = 90°
	c = 20.5785(16) Å	γ = 90°
Volume	3348.5(4) $Å^3$	
Z	8	
Density (calculated)	1.354 Mg/cm^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	1424	
Theta range for data collection	1.98 to 27.56°	
Index ranges	-10<=h<=10, -25<=k<=23, -26<=l<=21	
Reflections collected	26324	
Independent reflections	3865 [R(int) = 0.0319]	
Coverage of independent reflections	99.9%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9911 and 0.9736	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3865 / 0 / 236	
Goodness-of-fit on F^2	2.671	

Δ/σ_{max}	0.001	
Final R indices	2824 data; I>2σ(I)	R1 = 0.0448, wR2 = 0.0697
	all data	R1 = 0.0660, wR2 = 0.0710
Weighting scheme	w=1/[$\sigma^2(F_o^2)$+(0.0000P)^2+0.0000P] where P=(F_o^2+2F_c^2)/3	
Largest diff. peak and hole	0.190 and -0.175 eÅ^{-3}	
R.M.S. deviation from mean	0.035 eÅ^{-3}	

Figure S1. An ORTEP view of compound 5a with atom numbering scheme.



Crystal structure data for the compound 5c

Relevant crystal data and structure refinement parameters are provided in Table S2. CCDC 1007733 (5c) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data. Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table S2. Sample and crystal data for 1007733.

Identification code	1007733	
Chemical formula	$C_{44}H_{29}F_6N_6O_4$	
Formula weight	819.73	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal size	0.050 x 0.070 x 0.200 mm	
Crystal system	orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 17.511(14) Å	α = 90°
	b = 8.066(6) Å	β = 90°
	c = 26.88(2) Å	γ = 90°
Volume	3797.(5) $Å^3$	
Z	4	
Density (calculated)	1.434 Mg/cm^3	
Absorption coefficient	0.114 mm^{-1}	
F(000)	1684	
Theta range for data collection	1.52 to 27.52°	
Index ranges	-22<=h<=22, -9<=k<=10, -34<=l<=34	
Reflections collected	35922	
Independent reflections	8610 [R(int) = 0.0843]	
Coverage of independent reflections	99.2%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9943 and 0.9776	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	8610 / 1 / 543	
Goodness-of-fit on F^2	0.998	

Δ/σ_{max}	0.083	
Final R indices	4398 data; I>2σ(I)	R1 = 0.0643, wR2 = 0.1112
	all data	R1 = 0.1511, wR2 = 0.1372
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0473P)^2+0.6173P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	1.1(12)	
Largest diff. peak and hole	0.248 and -0.232 eÅ^{-3}	
R.M.S. deviation from mean	0.045 eÅ^{-3}	

Figure S2. An ORTEP view of compound 5c with atom numbering scheme.