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Petasis adducts of tryptanthrin – synthesis, biological activity evaluation and druglikeness assessment

Pedro Brandão, Carolina Marques, Eugénia Pinto, Marta Pineiro, Anthony J. Burke

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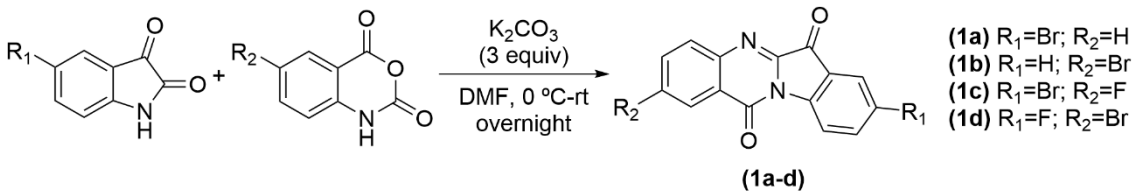
Experimental Section:

General Remarks: Reagents were obtained from Sigma–Aldrich, Acros, Strem and Alfa Aesar and were used as received. The solvents used were dried using current laboratory techniques.[1] Borylation reactions and Petasis reactions were conducted in a Radley's® 12-position carousel reactor under a nitrogen atmosphere or in round-bottom flasks. The 4Å molecular sieves (1-2 mm, 0.04-0.08 in) were obtained from Alfa Aesar (used as received). Column chromatography was carried out on silica flash (Carlo Erba, 40–63 µm, 60Å). Thin-layer chromatography (TLC) was carried out on aluminum-backed Kieselgel 60 F254 plates (Merck and Machery Nagel). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. Melting points (m.p.) were determined with a Barnstead Electrothermal 9100 apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance III instrument (400 MHz). The chemical shifts (δ) were quoted in parts per million (ppm) with respect to the solvent ($CDCl_3$, ^1H: δ = 7.26 ppm, ^{13}C: δ = 77.2 ppm; [*d*6]DMSO, 1H: δ = 2.50 ppm, 13C: δ = 39.5 ppm). Coupling constants (J) are reported in Hz and refer to apparent peak multiplicities. Splitting patterns are reported as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; m, multiplet; br, broad. Mass spectra (MS) were recorded with a quadrupole mass spectrometer Waters ZQ4000. The ionization was performed by ESI and the samples were infused in methanol. High-performance liquid chromatographic (HPLC) analysis was carried out with a Hitachi Primaide instrument, equipped with a 1410 series UV detector. Daicel Chiralpak IA column was used as stationary phase, n-hexane/ethanol as mobile phase and 254 nm was used as wavelength in the UV light detector.

B_2NPG_2 = bis(neopentyl glycolato)diboron.

1. Synthesis of tryptanthrin derivatives (1a-d):



Scheme S1. Synthesis of tryptanthrin derivatives.

General procedure: In a round-bottomed flask placed in an ice bath, (un)substituted isatin (1 equiv.) was dissolved in DMF (20 mL). Potassium carbonate (3 equiv.) was slowly added, and allowed to stir, leading to a colour change and hydrogen release.

Once gas production ceased, the suspension was kept at room temperature and (un)substituted isatoic anhydride (1.2 equiv.) was added. The reaction was allowed to proceed overnight, with stirring at room temperature and monitored by TLC. When the reaction was complete, the formed solid was washed with water (3 x 50 mL) and ethanol (2 x 20 mL) and the corresponding tryptanthrin used in the next step without further purification.

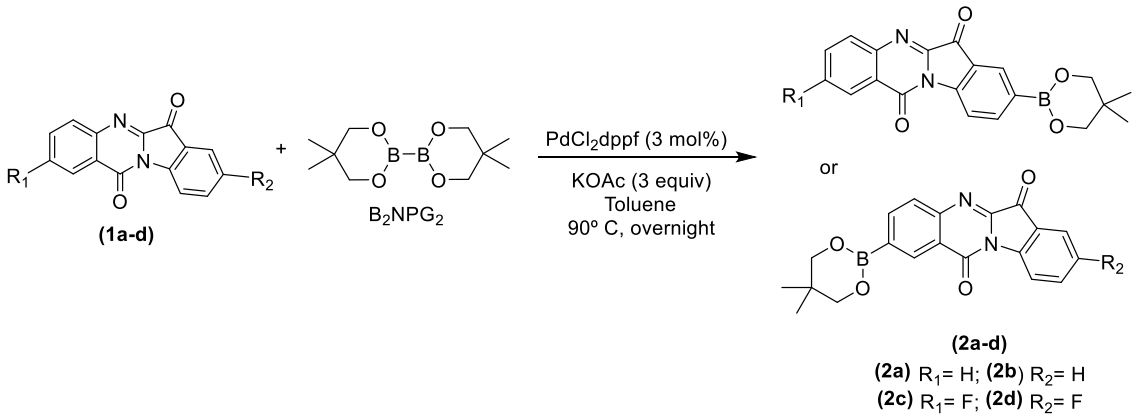
8-Bromo-tryptanthrin (8-bromoindolo[2,1-b]quinazoline-6,12-dione) (**1a**)[2]: 5-bromo-isatin (1.0 g, 1 equiv.), isatoic anhydride (0.866 g, 1.2 equiv.), K_2CO_3 (1.830 g, 3 equiv.) and DMF (20 mL) were used. The corresponding **1a** was obtained as a yellow solid (1.23 g, 85% yield).

2-Bromo-tryptanthrin (2-bromoindolo[2,1-b]quinazoline-6,12-dione) (**1b**)[2]: isatin (0.75 g, 1 equiv.), 5-bromoisatoic anhydride (1.48 g, 1.2 equiv.), K_2CO_3 (2.11 g, 3 equiv.) and DMF (20 mL) were used. The corresponding **1b** was obtained as a yellow solid (1.59 g, 95% yield).

8-Bromo-2-fluoro-tryptanthrin (8-bromo-2-fluoroindolo[2,1-b]quinazoline-6,12-dione) (**1c**): 5-bromoisatin (1.50 g, 1 equiv.), 5-fluoroisatoic anhydride (1.44 g, 1.2 equiv.), K_2CO_3 (2.75 g, 3 equiv.) and DMF (20 mL) were used. The corresponding **1c** was obtained as a yellow solid (1.69 g, 74% yield).

2-Bromo-8-fluoro-tryptanthrin (2-bromo-8-fluoroindolo[2,1-b]quinazoline-6,12-dione) (**1d**): 5-fluoroisatin (1.0 g, 1 equiv.), 5-bromoisatoic anhydride (1.76 g, 1.2 equiv.), K_2CO_3 (2.75 g, 3 equiv.) and DMF (20 mL) were used. The corresponding **1d** was obtained as a yellow solid (1.70 g, 81% yield).

2. Synthesis of boronate-tryptanthrin derivatives (2a-d)



Scheme S2. Synthesis boronate-tryptanthrin derivatives (2a-d).

General procedure[3]**:** In a round-bottom flask or in a Radley's® 12 position carousel reactor tube under nitrogen atmosphere was added the halide derivatives (**1**), B_2NPG_2 (1.1 equiv.), $PdCl_2$(dppf) (3 mol%), KOAc (3 equiv.) and toluene. The reaction was stirred at 90ºC (in an oil bath when a round-bottom flask was used) overnight and monitored by TLC. The reaction was quenched with brine (30 mL) followed by extraction with $CHCl_3$ (3 x 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent evaporated on the rotative evaporator. The crude mixture was filtered over a porous plate glass filter funnel packed with a layer of celite and a layer of SiO_2 and eluted with $CHCl_3$ until the washings became colourless. After evaporation of the solvent the corresponding product (**2**) was obtained and used in the next steps.

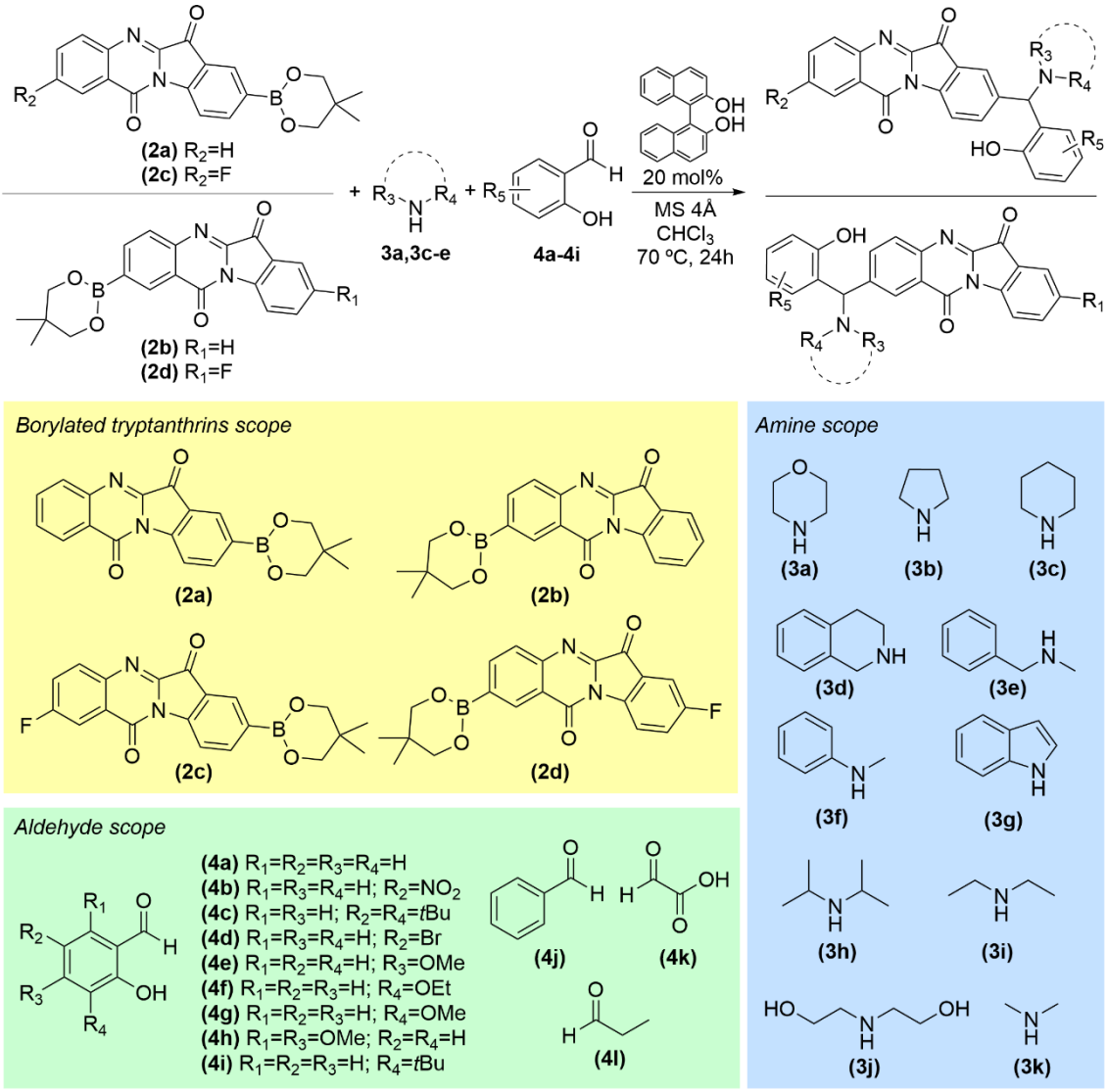
8-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)indolo[2,1-b]quinazoline-6,12-dione (**2a**): 8-bromoindolo[2,1-*b*]quinazoline-6,12-dione (**1a**) (301.7 mg, 0.92 mmol), B_2NPG_2 (228 mg, 1.0 mmol, 1.1 equiv.), $PdCl_2$(dppf) (20.1 mg, 0.028 mmol, 3 mol%), KOAc (270 mg, 2.8 mmol, 3 equiv.) and toluene (4 mL) were used. The corresponding **2a** was obtained as a yellow-green solid (275.2 mg, 87% yield). m.p.= >220°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04 (s, CH_3, 6H), 3.79 (s, CH_2, 4H), 7.63-7.67 (t, *J*= 8 Hz, Ar, 1H), 7.81-7.85 (t, *J*= 8 Hz, Ar, 1H), 8.00-8.02 (d, *J*= 8 Hz, Ar, 1H), 8.18-8.20 (d, *J*= 8 Hz, Ar, 1H), 8.34 (s, Ar, 1H), 8.41-8.43 (d, *J*= 8 Hz, Ar, 1H), 8.53-8.55 (d, *J*= 8 Hz, Ar, 1H).^{13}C{1H} APT NMR ($CDCl_3$, 100 MHz): δ 22.00, 32.08, 72.57, 117.02, 121.42, 123.84, 127.67, 130.24, 130.80, 131.27, 135.21, 144.21, 146.78, 147.90, 158.25, 182.80. HRMS (ESI-TOF) m/z: calcd. for $C_{20}H_{18}BN_2O_4$ [M]+ 361.1760, found 361.0960.

2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)indolo[2,1-b]quinazoline-6,12-dione (**2b**): 2-bromoindolo[2,1-*b*]quinazoline-6,12-dione (**1b**) (373 mg, 0.9 mmol), B_2NPG_2 (228 mg, 1.0 mmol, 1.1 equiv.), $PdCl_2$(dppf) (20.1 mg, 0.028 mmol, 3 mol%), KOAc (270 mg, 2.8 mmol, 3 equiv.) and toluene (4 mL) were used. The corresponding **2b** was obtained as a yellow solid (369.6 mg, >99% yield). m.p.= >220°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 (s, CH_3, 6H), 3.83 (s, CH_2, 4H), 7.39-7.43 (t, *J*= 8 Hz, Ar, 1H), 7.76-7.80 (t, *J*= 8 Hz, Ar, 1H), 7.90-7.91 (d, *J*= 8 Hz, Ar, 1H), 7.96-7.98 (d, *J*= 8 Hz, Ar, 1H), 8.22-8.24 (d, *J*= 8 Hz, Ar, 1H), 8.64-8.66 (d, *J*= 8 Hz, Ar, 1H), 8.88 (s, Ar, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 22.03, 32.11, 72.62, 118.18, 122.05, 122.91, 125.48, 127.20, 129.76, 133.75, 138.39, 140.28, 144.80, 146.60, 148.24, 158.44, 182.87. HRMS (ESI-TOF) m/z: calcd. for $C_{20}H_{18}BN_2O_4$ [M]+ 361.1760, found 361.0957.

8-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-fluoroindolo[2,1-b]quinazoline-6,12-dione (**2c**): 8-bromo-2-fluoroindolo[2,1-*b*]quinazoline-6,12-dione (**1c**) (332 mg, 0.8 mmol), B_2NPG_2 (216 mg, 0.9 mmol, 1.1 equiv.), $PdCl_2$(dppf) (19.1 mg, 0.026 mmol, 3 mol%), KOAc (256 mg, 2.6 mmol, 3 equiv.) and toluene (4 mL) were used. The corresponding **2c** was obtained as a yellow solid (292.8 mg, 80% yield). m.p.= >220°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04 (s, CH_3, 6H), 3.80 (s, CH_2, 4H), 7.55-7.58 (m, Ar, 1H), 8.02-8.09 (m, Ar, 2H), 8.20-8.22 (d, *J*= 8 Hz, Ar, 1H), 8.36 (s, Ar, 1H), 8.54-8.56 (d, *J*= 8 Hz, Ar, 1H).^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 22.01, 32.11, 72.60, 113.27, 113.55, 117.08, 118.17, 121.50, 123.37, 123.61, 125.65, 127.61, 131.37, 133.26, 138.48, 143.43, 144.27, 147.66, 157.34, 182.31. HRMS (ESI-TOF) m/z: calcd. for $C_{20}H_{17}BFN_2O_4$ [M]+ 379.1740, found 379.0864.

2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-8-fluoroindolo[2,1-b]quinazoline-6,12-dione (**2d**): 2-bromo-8-fluoroindolo[2,1-*b*]quinazoline-6,12-dione (**1d**) (297 mg, 0.8 mmol), B_2NPG_2 (216 mg, 0.9 mmol, 1.1 equiv.), $PdCl_2$(dppf) (19.1 mg, 0.026 mmol, 3 mol%), KOAc (256 mg, 2.6 mmol, 3 equiv.) and toluene (4 mL) were used. The corresponding **2d** was obtained as a yellow solid (302 mg, 93% yield). m.p.= >220°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 (s, CH_3, 6H), 3.83 (s, CH_2, 4H), 7.46-7.50 (t, *J*= 8 Hz, Ar, 1H), 7.56-7.58 (d, *J*= 8 Hz, Ar, 1H), 7.96-7.98 (d, *J*= 8 Hz, Ar, 1H), 8.23-8.25 (d, *J*= 8 Hz, Ar, 1H), 8.65-8.66 (m, Ar, 1H), 8.87 (s, Ar, 1H).^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 22.03, 32.11, 72.62, 118.18, 122.05, 122.91, 124.31, 125.48, 127.20, 129.76, 132.72, 133.75, 138.39, 140.28, 144.80, 146.60, 148.24, 158.44, 182.87. MS (ESI) m/z: 333.09 (M-OHNa)+.

3. Petasis 3-MCR



Scheme S3. Synthesis of new tryptanthrin derivatives *via* Petasis MCR and reaction scope.

3.1. Library generation *via* Petasis 3-MCR

General Procedure: In a round-bottom flask or in a Radley's® 12 position carousel reactor tube was added the borylated tryptanthrin derivatives (2) (0.3 mmol, 1.0 equiv.), the amine (3.9 equiv.), the aldehyde (3.3 equiv.), BINOL (20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL). The reaction was stirred at 70 ºC for 24 hours. After cooling down, the reaction mixture was filtered with a porous plate glass funnel packed with a celite layer and washed with $CHCl_3$. The solvent was evaporated under reduced pressure and

the crude product purified by silica gel flash chromatography using hexane/AcOEt from (5:1) to (1:1) as eluents.

8-((2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aaa**): **2a** (112 mg, 0.3 mmol, 1 equiv.), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5aaa** as a yellow solid (89.9 mg, 66% yield). m.p.= >220°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.48-2.51 (m, CH_2, 2H), 2.65 (s br, CH_2, 2H), 3.79 (s, CH_2, 4H), 4.50 (s, CH, 1H), 6.74-6.78 (t, *J*= 8 Hz, Ar, 1H), 6.88-6.90 (d, *J*= 8 Hz, Ar, 1H), 6.95-6.97 (d, *J*= 8 Hz, Ar, 1H), 7.14-7.18 (t, *J*= 8 Hz, Ar, 1H), 7.63-7.66 (t, Ar, 1H), 7.81-7.85 (t, *J*= 8 Hz, Ar, 1H), 7.87-7.89 (m, Ar, 1H), 7.96-8.00 (m, Ar, 2H), 8.38-8.40 (d, *J*= 8 Hz, Ar, 1H), 8.54-8.56 (d, *J*= 8 Hz, Ar, 1H), 11.29 (s br, OH, 1H). ^{13}C{1H} APT NMR ($CDCl_3$, 100 MHz): δ 52.47, 66.86, 76.15, 117.12, 118.66, 120.21, 122.53, 123.70, 125.30, 127.71, 129.22, 129.52, 130.52, 130.92, 135.35, 138.36, 139.26, 144.39, 145.98, 146.63, 155.91, 157.99, 182.23. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{22}O_4N_3$ [M]+ 440.16048, found 440.1597.

8-((2-hydroxyphenyl)(piperidin-1-yl)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aca**): **2a** (100 mg, 0.3 mmol, 1 equiv.), **3c** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5aca** as a green solid (32.1 mg, 26% yield). m.p.= 216.8°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.49-1.67 (m, CH_2, 6H), 2.37-2.44 (m, CH_2, 4H), 4.55 (s, CH, 1H), 6.70-6.73 (t, Ar, 1H), 6.86-6.89 (m, Ar, 2H), 7.11-7.15 (t, *J*= 8 Hz, Ar, 1H), 7.61-7.64 (t, Ar, 1H), 7.79-7.84 (m, Ar, 2H), 7.92 (s, Ar, 1H), 7.97-7.99 (d, *J*= 8 Hz, Ar, 1H), 8.36-8.38 (d, *J*= 8 Hz, Ar, 1H), 8.51-8.53 (d, *J*= 8 Hz, Ar, 1H), 12.06 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 24.08, 26.08, 52.84, 75.85, 117.51, 118.44, 119.62, 122.33, 123.71, 124.44, 125.47, 127.66, 128.96, 129.10, 130.42, 130.86, 135.27, 138.57, 139.57, 144.48, 145.81, 146.65, 156.86, 157.96, 182.43. HRMS (ESI-TOF) m/z: calcd. for $C_{27}H_{24}O_3N_3$ [M]+ 438.18122, found 438.1803.

8-((3,4-dihydroisoquinolin-2(1H)-yl)(2-hydroxyphenyl)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5ada**): **2a** (122 mg, 0.3 mmol), **3d** (0.14 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5ada** as a yellow solid (19.1 mg, 12% yield). m.p.= 215°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.82-3.10 (m, CH_2, 4H), 3.71 (s, CH_2, 2H), 4.71 (s, CH, 1H), 6.76-6.80 (t, *J*= 8 Hz, Ar, 1H), 6.90-6.92 (m, Ar, 2H), 6.99-7.00 (m, Ar, 1H), 7.09-7.21 (m, Ar, 4H), 7.63-7.67 (t, *J*= 8 Hz, Ar, 2H), 7.81-7.85 (t,

J= 8 Hz, Ar, 1H), 7.96-8.02 (m, Ar, 3H), 8.39-8.41 (d, *J*= 8 Hz, Ar, 1H), 8.56-8.58 (d, *J*= 8 Hz, Ar, 1H), 11.49 (s br, OH, 1H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 100 MHz): δ 28.59, 49.23, 54.62, 75.16, 117.81, 118.70, 119.98, 122.51, 123.74, 124.34, 125.22, 126.27, 126.92, 127.02, 127.71, 128.78, 129.05, 129.38, 130.48, 130.92, 132.94, 133.44, 135.32, 138.24, 139.93, 144.47, 145.99, 146.67, 156.47, 158.01, 182.38. HRMS (ESI-TOF) m/z: calcd. for $C_{31}H_{24}O_3N_3$ [M]+ 486.18122, found 486.1805.

8-((3,5-di-tert-butyl-2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aac**): **2a** (88 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4c** (215 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5aac** as a yellow solid (60.5 mg, 45% yield). m.p.= 217.2°C decomp. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.21 (s, CH_3, 9H), 1.44 (s, CH_3, 9H), 2.50-2.60 (m, CH_2, 4H), 3.79 (s, CH_2, 4H), 4.46 (s, CH, 1H), 6.80 (s, Ar, 1H), 7.20 (s, Ar, 1H), 7.63-7.67 (t, *J*= 8 Hz, Ar, 1H), 7.81-7.85 (t, *J*= 8 Hz, Ar, 1H), 7.95-8.02 (m, Ar, 3H), 8.40-8.42 (d, *J*= 8 Hz, Ar, 1H), 8.54-8.56 (d, *J*= 8 Hz, Ar, 1H), 11.45 (s br, OH, 1H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 100 MHz): δ 29.68, 31.72, 34.33, 35.23, 66.82, 77.05, 118.69, 122.45, 122.83, 123.76, 125.46, 127.74, 130.46, 130.93, 135.31, 137.08, 138.44, 139.79, 141.72, 144.51, 145.92, 146.71, 152.35, 158.03, 182.44. HRMS (ESI-TOF) m/z: calcd. for $C_{34}H_{38}O_4N_3$ [M]+ 552.2857, found 552.2850.

8-((5-bromo-2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aad**): **2a** (177 mg, 0.5 mmol), **3a** (0.17 mL, 1.9 mmol, 3.9 equiv.), **4d** (332 mg, 1.7 mmol, 3.3 equiv.), BINOL (28.6 mg, 0.1 mmol, 20 mol%), MS 4Å (300 mg) and $CHCl_3$ (5 mL) were used to obtain the corresponding **5aad** as a green solid (147.4 mg, 58% yield). m.p.= 170°C decomp. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.29-2.62 (m, CH_2, 4H), 3.77 (s br, CH_2, 4H), 4.45 (s, CH, 1H), 6.77-6.79 (d, *J*= 8 Hz, Ar, 1H), 7.07 (s, Ar, 1H), 7.23-7.26 (m, Ar, 1H), 7.62-7.66 (t, *J*= 8 Hz, Ar, 1H), 7.82-7.84 (m, Ar, 2H), 7.93 (s, Ar, 1H), 7.97-7.99 (d, *J*= 8 Hz, Ar, 1H), 8.36-8.38 (d, *J*= 8 Hz, Ar, 1H), 8.55-8.57 (d, *J*= 8 Hz, Ar, 1H), 11.47 (s br, OH, 1H). $^{13}C\{1H\}$ NMR ($CDCl_3$, 100 MHz): δ 66.77, 75.64, 111.78, 118.79, 119.66, 122.64, 123.68, 125.24, 125.73, 127.74, 130.58, 130.95, 131.73, 132.32, 135.41, 138.28, 138.45, 144.31, 146.16, 146.61, 155.18, 158.00, 182.23. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{21}O_4N_3Br$ [M]+ 518.0710, found 518.0701.

8-((3-ethoxy-2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aaf**): **2a** (93 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4f** (152 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5aaf** as a yellow solid (13.6 mg, 11% yield). m.p.=

137.5-138.2°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.47-1.50 (t, CH_3, 3H), 2.48-2.62 (m, CH_2, 4H), 3.77 (m, CH_2, 4H), 4.05-4.12 (q, CH_2, 2H), 4.58 (s, CH, 1H), 6.67-6.77 (m, Ar, 3H), 7.62-7.66 (t, *J*= 8 Hz, Ar, 1H), 7.80-7.84 (t, *J*= 8 Hz, Ar, 1H), 7.90-8.00 (m, Ar, 3H), 8.37-8.39 (d, *J*= 8 Hz, Ar, 2H), 8.51-8.53 (d, *J*= 8 Hz, Ar, 1H), 10.27 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 15.01, 52.48, 64.40, 66.96, 73.93, 111.84, 118.54, 119.91, 120.47, 122.35, 123.70, 124.51, 125.31, 127.67, 130.45, 130.87, 135.30, 138.35, 139.97, 144.44, 145.05, 145.80, 146.61, 147.62, 157.95, 182.42. HRMS (ESI-TOF) m/z: calcd. for $C_{28}H_{26}O_5N_3$ [M]+ 484.1867, found 484.1858.

8-((2-hydroxy-3-methoxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aag**): **2a** (121 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4g** (140 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5aag** as a yellow solid (18.0 mg, 11% yield). m.p.= 165.2-167°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.49-2.64 (m, CH_2, 4H), 3.78 (s br, CH_2, 4H), 3.88 (s, OMe, 3H), 4.57 (s, CH, 1H), 6.66 (m, Ar, 1H), 6.74-6.78 (t, *J*= 8 Hz, Ar, 2H), 7.62-7.66 (t, *J*= 8 Hz, Ar, 1H), 7.80-7.84 (t, *J*= 8 Hz, Ar, 1H), 7.89-8.00 (m, Ar, 3H), 8.36-8.38 (d, *J*= 8 Hz, Ar, 1H), 8.51-8.53 (m, Ar, 1H), 10.75 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 52.45, 56.00, 66.94, 74.51, 110.81, 118.61, 119.98, 120.63, 122.37, 123.68, 125.32, 127.68, 130.48, 130.88, 135.32, 138.36, 144.39, 145.00, 146.60, 157.95, 182.36. HRMS (ESI-TOF) m/z: calcd. for $C_{27}H_{24}O_5N_3$ [M]+ 470.1711, found 470.1702.

8-((3-(tert-butyl)-2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aai**): **2a** (102 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4i** (163 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5aai** as a yellow solid (50 mg, 36% yield). m.p.= 254°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, CH_3, 9H), 2.45-2.70 (m, CH_2, 4H), 3.80 (s, CH_2, 4H), 4.49 (s, CH, 1H), 6.68-6.72 (t, *J*=8 Hz, Ar, 1H), 6.82-6.84 (*d*, *J*= 8 Hz, Ar, 1H), 7.17-7.19 (d, *J*= 8 Hz, Ar, 1H), 7.65-7.69 (t, *J*= 8 Hz, Ar, 1H), 7.83-7.87 (t, *J*= 8 Hz, Ar, 1H), 7.92-8.03 (m, Ar, 3H), 8.41-8.43 (d, *J*= 8 Hz, Ar, 1H), 8.55-8.57 (d, *J*= 8 Hz, Ar, 1H), 11.73 (s, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 29.40, 34.91, 66.68, 76.51, 118.54, 119.23, 123.54, 123.63, 125.25, 126.53, 127.08, 127.61, 130.35, 130.82, 135.20, 137.97, 138.16, 139.29, 145.82, 154.94, 163.24, 182.23. HRMS (ESI-TOF) m/z: calcd. for $C_{30}H_{29}O_4N_3Na$ [M]+ 518.2050, found 518.2042.

2-((2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5baa**): **2b** (103 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.),

BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5baa** as a yellow solid (100.9 mg, 80% yield). m.p.= 211.5°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.45-2.65 (m, CH_2, 4H), 3.71-3.76 (m, CH_2, 4H), 4.60 (s, CH, 1H), 6.71-6.74 (t, Ar, 1H), 6.85-6.87 (d, *J*= 8 Hz, Ar, 1H), 6.97-6.99 (m, Ar, 1H), 7.10-7.14 (t, *J*= 8 Hz, Ar, 1H), 7.37-7.41 (t, *J*= 8 Hz, Ar, 1H), 7.73-7.77 (t, *J*= 8 Hz, Ar, 1H), 7.85-7.87 (d, *J*= 8 Hz, Ar, 1H), 7.93-7.95 (d, *J*= 8 Hz, Ar, 2H), 7.99 (m, Ar, 1H), 8.39 (s, Ar, 1H), 8.55-8.58 (d, *J*= 8 Hz, Ar, 1H), 11.37 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 52.55, 66.86, 76.41, 117.64, 118.08, 120.20, 122.06, 123.71, 124.02, 125.62, 127.47, 127.51, 129.45, 129.53, 131.87, 134.87, 138.48, 142.37, 144.62, 146.31, 146.52, 155.94, 157.95, 182.46. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{22}O_4N_3$ [M]+ 440.1605, found 440.1598.

2-((2-hydroxyphenyl)(piperidin-1-yl)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5bca**): **2b** (85 mg, 0.3 mmol), **3c** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5bca** as a green solid (61.8 mg, 60% yield). m.p.= 197.8°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (s br, CH_2, 2H), 1.65 (s br, CH_2, 4H), 2.42-2.62 (m, CH_2, 4H), 4.65 (s, CH, 1H), 6.68-6.71 (t, Ar, 1H), 6.85-6.87 (d, *J*= 8 Hz, Ar, 1H), 6.90-6.92 (d, *J*= 8 Hz, Ar, 1H), 7.09-7.13 (t, *J*= 8 Hz, Ar, 1H), 7.35-7.39 (t, *J*= 8 Hz, Ar, 1H), 7.70-7.74 (t, *J*= 8 Hz, Ar, 1H), 7.84-7.85 (d, *J*= 4 Hz, Ar, 1H), 7.92-7.97 (m, Ar, 2H), 8.36 (s, Ar, 1H), 8.54-8.56 (d, *J*= 8 Hz, Ar, 1H), 11.90 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 24.06, 26.06, 76.10, 117.38, 117.93, 119.53, 121.97, 123.75, 124.51, 125.45, 127.34, 127.44, 129.01, 129.14, 131.50, 138.32, 142.80, 144.40, 146.21, 146.22, 156.83, 157.95, 182.40. HRMS (ESI-TOF) m/z: calcd. for $C_{27}H_{24}O_4N_3$ [M]+ 438.1812, found 438.1802.

2-((benzyl(methyl)amino)(2-hydroxyphenyl)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5bea**): **2b** (107 mg, 0.3 mmol), **3e** (0.14 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5bea** as a yellow solid (21.4 mg, 15% yield). m.p.= 194°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.21 (s, CH_3, 3H), 3.56-3.79 (m, CH_2, 2H), 4.86 (s, CH, 1H), 6.74-6.78 (t, *J*= 8 Hz, Ar, 1H), 6.93-6.99 (m, Ar, 2H), 7.15-7.19 (t, *J*= 8 Hz, Ar, 1H), 7.27-7.37 (m, Ar, 5H), 7.39-7.43 (t, *J*= 8 Hz, Ar, 1H), 7.75-7.79 (t, *J*= 8 Hz, Ar, 1H), 7.88-7.90 (d, *J*= 8 Hz, Ar, 1H), 7.99-8.01 (m, Ar, 1H), 8.09-8.11 (m, Ar, 1H), 8.46 (s, Ar, 1H), 8.59-8.61 (d, *J*= 8 Hz, Ar, 1H), 11.95 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 39.67, 60.01, 75.32, 117.60, 118.06, 119.83, 122.05, 123.94, 124.51, 125.58, 127.45, 127.63, 127.95, 128.85, 129.13, 129.40, 129.46, 131.69,

135.16, 138.52, 138.44, 142.49, 144.56, 146.31, 146.44, 156.63, 158.01, 182.48. HRMS (ESI-TOF) m/z: calcd. for $C_{30}H_{24}O_3N_3$ [M]+ 474.1812, found 474.1804.

2-((3,5-di-tert-butyl-2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5bac**): **2b** (96 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4c** (215 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5bac** as a yellow solid (20.3 mg, 14% yield). m.p.= 115.3-117°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (s, CH_3, 9H), 1.45 (s, CH_3, 9H), 2.46-2.47 (m, CH_2, 4H), 3.74-3.78 (m, CH_2, 4H), 4.57 (s, CH, 1H), 6.83-6.84 (d, *J*= 8 Hz, Ar, 1H), 7.19-7.20 (d, *J*= 8 Hz, Ar, 1H), 7.38-7.41 (t, Ar, 1H), 7.72-7.77 (m, Ar, 1H), 7.87-7.88 (d, *J*= 4 Hz, Ar, 1H), 7.93-7.95 (d, *J*= 8 Hz, Ar, 1H), 8.05-8.09 (m, Ar, 1H), 8.46 (s br, Ar, 1H), 8.57-8.59 (d, *J*= 8 Hz, Ar, 1H), 11.60 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 29.67, 31.70, 34.29, 35.22, 66.83, 77.30, 118.04, 122.01, 122.81, 123.70, 123.91, 124.00, 125.55, 127.41, 127.59, 129.60, 131.74, 135.11, 136.95, 138.42, 141.55, 142.95, 144.48, 146.28, 146.31, 152.42, 158.01, 182.52. HRMS (ESI-TOF) m/z: calcd. for $C_{34}H_{38}O_4N_3$ [M]+ 552.2857, found 552.2844.

2-((5-bromo-2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5bad**): **2b** (95 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4d** (184 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5bad** as a green solid (80.3 mg, 59% yield). m.p.= 179.1-183°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.45-2.64 (m, CH_2, 4H), 3.77 (m, CH_2, 4H), 4.55 (s, CH, 1H), 6.77-6.79 (d, *J*= 8 Hz, Ar, 1H), 7.09-7.10 (d, *J*= 4 Hz, Ar, 1H), 7.22-7.24 (d, *J*= 8 Hz, Ar, 1H), 7.40-7.44 (t, *J*= 8 Hz, Ar, 1H), 7.76-7.80 (t, *J*= 8 Hz, Ar, 1H), 7.88-7.90 (d, *J*= 8 Hz, Ar, 1H), 7.97-7.99 (m, Ar, 2H), 8.39 (s, Ar, 1H), 8.58-8.60 (d, *J*= 8 Hz, Ar, 1H), 11.56 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 66.78, 75.91, 117.71, 118.06, 119.57, 121.99, 124.11, 125.63, 125.76, 127.45, 127.55, 131.89, 131.95, 132.27, 134.73, 138.52, 141.55, 144.71, 146.24, 146.68, 155.19, 157.83, 182.40. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{21}O_4N_3Br$ [M]+ 518.0710, found 518.0701.

2-((3-ethoxy-2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5baf**): **2b** (99 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4f** (152 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5baf** as a yellow solid (47.7 mg, 36% yield). m.p.= 99.8-101.2°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44-1.48 (t, *J*= 8 Hz, CH_3, 3H), 2.44-2.63 (m, CH_2, 4H), 3.71-3.80 (m, CH_2, 4H), 4.02-4.07 (q, CH_2, 2H), 4.67 (s, CH, 1H), 6.68-6.75 (m, Ar, 3H), 7.34-7.38 (t, *J*= 8 Hz, Ar, 1H), 7.70-7.74 (t, *J*= 8 Hz, Ar, 1H), 7.82-7.84

(d, *J*= 8 Hz, Ar, 1H), 7.90-7.92 (d, *J*= 8 Hz, Ar, 1H), 8.02-8.06 (m, Ar, 1H), 8.38 (s, Ar, 1H), 8.52-8.54 (d, *J*= 8 Hz, Ar, 1H), 10.61 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 14.95, 52.45, 64.29, 66.87, 74.51, 111.87, 117.90, 119.77, 120.71, 121.92, 123.73, 124.39, 125.44, 127.30, 127.33, 131.63, 134.75, 138.31, 142.93, 144.36, 145.09, 146.15, 146.20, 147.60, 157.86, 182.36. HRMS (ESI-TOF) m/z: calcd. for $C_{28}H_{26}O_5N_3$ [M]+ 484.1867, found 484.1859.

2-((2-hydroxy-3-methoxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5bag**): **2b** (94 mg, 0.3 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4g** (140 mg, 0.9 mmol, 3.3 equiv.), BINOL (15.9 mg, 0.06 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5bag** as a yellow solid (22.3 mg, 18% yield). m.p.= 133.8-135°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.46-2.66 (m, CH_2, 4H), 3.77-3.81 (m, CH_2, 4H), 3.87 (s, OMe, 3H), 4.67 (s, CH, 1H), 6.66-6.77 (m, Ar, 3H), 7.38-7.42 (t, *J*= 8 Hz, Ar, 1H), 7.74-7.78 (t, *J*= 8 Hz, Ar, 1H), 7.86 (m, Ar, 1H), 7.93-7.95 (d, *J*= 8 Hz, Ar, 1H), 8.03-8.08 (m, Ar, 1H), 8.39-8.40 (m, Ar, 1H), 8.57-8.59 (d, *J*= 8 Hz, Ar, 1H), 11.04 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 52.50, 55.96, 66.92, 75.11, 110.83, 118.00, 119.90, 120.90, 121.99, 123.84, 124.24, 125.55, 127.41, 127.43, 129.57, 134.79, 138.42, 142.68, 144.48, 145.07, 146.24, 146.36, 148.42, 157.93, 182.44. HRMS (ESI-TOF) m/z: calcd. for $C_{27}H_{24}O_5N_3$ [M]+ 470.1711, found 470.1702.

2-fluoro-8-((2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5caa**): **2c** (108 mg, 0.26 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (14.9 mg, 0.05 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5caa** as a yellow solid (12.7 mg, 10% yield). m.p.= 210.3°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.48-2.51 (m, CH_2, 2H), 2.65 (m, CH_2, 2H), 3.79 (m, CH_2, 4H), 4.51 (s, CH, 1H), 6.75-6.78 (t, Ar, 1H), 6.88-6.90 (d, *J*= 8 Hz, Ar, 1H), 6.96-6.98 (d, *J*= 8 Hz, Ar, 1H), 7.14-7.18 (t, *J*= 8 Hz, Ar, 1H), 7.52-7.57 (m, Ar, 1H), 7.89-7.91 (d, *J*= 8 Hz, Ar, 1H), 7.97-8.05 (m, Ar, 3H), 8.53-8.55 (d, *J*= 8 Hz, Ar, 1H), 11.29 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 52.50, 66.84, 76.13, 113.36, 113.60, 117.75, 118.73, 120.26, 122.63, 123.48, 123.64, 123.72, 125.39, 125.56, 125.65, 129.11, 129.58, 133.31, 133.40, 138.39, 139.54, 143.25, 143.93, 145.73, 155.89, 157.13, 162.07, 164.60, 182.00. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{21}O_4N_3F$ [M]+ 458.1511, found 458.1503.

8-((3-(tert-butyl)-2-hydroxyphenyl)(morpholino)methyl)-2-fluoroindolo[2,1-b]quinazoline-6,12-dione (**5cai**): **2c** (100 mg, 0.26 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4i** (155 mg, 0.9 mmol, 3.3 equiv.), BINOL (14.9 mg, 0.05 mmol, 20 mol%), MS 4Å (200 mg) and

$CHCl_3$ (3 mL) were used to obtain the corresponding **5cai** as a yellow solid (21 mg, 16% yield). m.p.= 253°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): 1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (s, CH_3, 9H), 2.51-2.66 (m, CH_2, 4H), 3.80 (s, CH_2, 4H), 4.49 (s, CH, 1H), 6.68-6.72 (t, *J*= 8 Hz, Ar, 1H), 6.81-6.83 (d, *J*= 8 Hz, Ar, 1H), 7.17-7.19 (d, *J*= 8 Hz, Ar, 1H), 7.53-7.57 (t, *J*= 8 Hz, Ar, 1H), 7.93-8.07 (m, Ar, 4H), 8.54-8.56 (d, *J*= 8 Hz, Ar, 1H), 11.71 (s, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 29.39, 34.91, 66.67, 76.51, 113.23, 113.48, 118.58, 119.25, 123.32, 123.50, 123.56, 125.32, 126.56, 127.07, 133.18, 133.27, 138.01, 138.18, 139.61, 143.19, 143.81, 143.84, 145.54, 154.93, 181.90. HRMS (ESI-TOF) m/z: calcd. for $C_{30}H_{27}O_4N_3F$ [M]- 512.1991, found 512.1990.

8-fluoro-2-((2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5daa**): **2d** (90 mg, 0.26 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (14.9 mg, 0.05 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5daa** as a yellow solid (22.1 mg, 20% yield). m.p.= 193.5°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.52-2.69 (m, CH_2, 4H), 3.80 (m, CH_2, 4H), 4.68 (s, CH, 1H), 6.74-6.78 (t, *J*= 8 Hz, Ar, 1H), 6.88-6.90 (d, *J*= 8 Hz, Ar, 1H), 7.05 (s, Ar, 1H), 7.13-7.17 (t, *J*= 8 Hz, Ar, 1H), 7.44-7.49 (m, Ar, 1H), 7.53-7.56 (m, Ar, 1H), 7.94-7.96 (d, *J*= 8 Hz, Ar, 1H), 8.07 (s, Ar, 1H), 8.41 (s, Ar, 1H), 8.57-8.60 (m, Ar, 1H), 11.45 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 52.52, 66.64, 112.15, 112.40, 117.59, 119.71, 119.79, 120.28, 123.41, 123.49, 123.94, 124.89, 125.12, 127.46, 129.40, 129.61, 131.96, 134.98, 142.39, 144.56, 146.34, 155.82, 157.66, 160.04, 162.54, 181.54. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{21}O_4N_3F$ [M]+ 458.1511, found 458.1501.

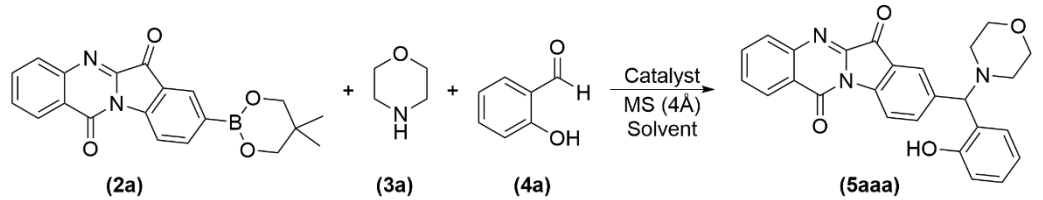
8-fluoro-2-((2-hydroxyphenyl)(piperidin-1-yl)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5dca**): **2d** (77 mg, 0.26 mmol), **3c** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4a** (0.1 mL, 0.9 mmol, 3.3 equiv.), BINOL (14.9 mg, 0.05 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5dca** as a yellow solid (32 mg, 34% yield). m.p.= 209.9°C decomp. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.49-1.67 (m, CH_2, 6H), 2.45 (m, CH_2, 4H), 4.69 (s, CH, 1H), 6.69-6.73 (t, *J*= 8 Hz, Ar, 1H), 6.86-6.88 (d, *J*= 8 Hz, Ar, 1H), 6.95 (s, Ar, 1H), 7.10-7.14 (t, *J*= 8 Hz, Ar, 1H), 7.43-7.48 (m, Ar, 1H), 7.53-7.55 (m, Ar, 1H), 7.93-7.95 (d, *J*= 8 Hz, Ar, 1H), 8.02 (s, Ar, 1H), 8.37 (s, Ar, 1H), 8.57-8.61 (m, Ar, 1H), 12.13 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 24.02, 25.94, 52.97, 75.89, 112.09, 112.34, 117.44, 119.70, 119.77, 113.43, 123.51, 123.78, 124.35, 124.83, 125.07, 127.47, 129.16, 131.73, 135.22, 142.41, 142.43, 143.06, 144.41, 146.16, 156.74, 157.78, 160.00, 162.49, 181.58. HRMS (ESI-TOF) m/z: calcd. for $C_{27}H_{23}O_3N_3F$ [M]+ 456.1718, found 456.1709.

2-((5-bromo-2-hydroxyphenyl)(morpholino)methyl)-8-fluoroindolo[2,1-b]quinazoline-6,12-dione (**5dad**): **2d** (75 mg, 0.26 mmol), **3a** (0.1 mL, 1.1 mmol, 3.9 equiv.), **4d** (172.5 mg, 0.9 mmol, 3.3 equiv.), BINOL (14.9 mg, 0.05 mmol, 20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were used to obtain the corresponding **5dad** as a yellow solid (16.5 mg, 16% yield). m.p.= 192.2-194°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.54-2.69 (m, CH_2, 4H), 3.81 (s, CH_2, 4H), 4.62 (s, CH, 1H), 6.81-6.83 (d, *J*= 8 Hz, Ar, 1H), 7.17 (s br, Ar, 1H), 7.24 (s, Ar, 1H), 7.48-7.52 (m, Ar, 1H), 7.56-7.58 (m, Ar, 1H), 7.97-8.03 (m, Ar, 2H), 8.42 (s, Ar, 1H), 8.59-8.62 (m, Ar, 1H), 11.62 (s br, OH, 1H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz): δ 52.53, 66.58, 75.71, 111.87, 112.26, 112.50, 119.60, 119.79, 119.87, 123.41, 123.49, 124.13, 125.01, 125.25, 127.51, 131.92, 132.15, 132.47, 142.39, 144.71, 146.61, 155.11, 157.61, 160.12, 162.61, 181.57. HRMS (ESI-TOF) m/z: calcd. for $C_{26}H_{20}O_4N_3BrF$ [M]+ 536.0616, found 536.0609.

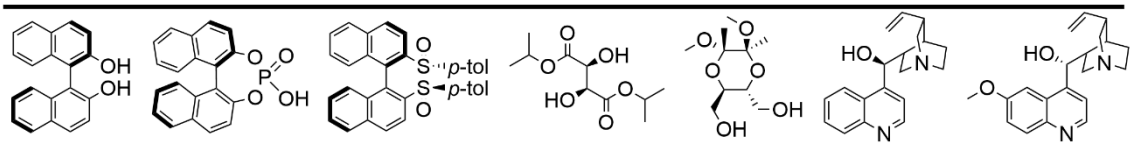
3.2. Asymmetric version:

General Procedure: In a round-bottom flask or in a Radley's® 12 position carousel reactor tube was added (2a) (0.3 mmol, 1.0 equiv.), (3a) (3.9 equiv.), (4a) (3.3 equiv.), chiral organocatalyst (20 mol%), MS 4Å (200 mg) and solvent (3 mL). The reaction was stirred at the indicated temperature and monitored by TLC. After cooling down, the reaction mixture was filtered with a porous plate glass funnel packed with a celite layer and washed with $CHCl_3$. The solvent was evaporated under reduced pressure and the crude product purified by silica gel flash chromatography using hexane/AcOEt (5:1) to (1:1) as eluents.

Table S1. Reaction scope.



(2a) (3a) (4a) (5aaa)



(*R*)-BINOL (*R*)-BNPPA (*M,S,S*)-*p*-tol-BINASO (+)-DT Diolane (+)-Cinchonine (-)-Quinine

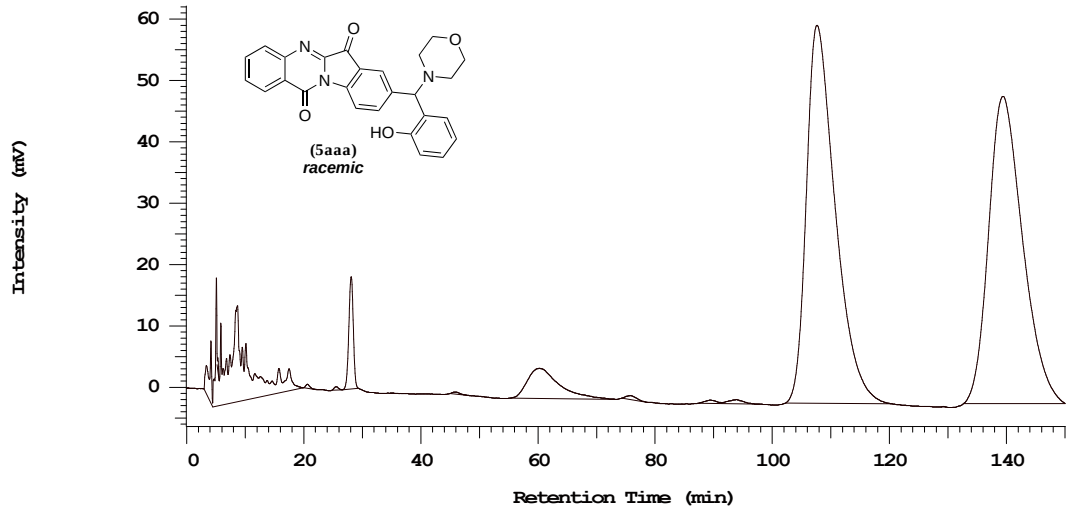
Entry[a]	Catalyst	Solvent	Temp.(ºC)	Time(h)	Yield(%)[b]	ee(%)[c]
1	(*R*)-BINOL	$CHCl_3$	70	24	71	99
2	(*R*)-BNPPA	$CHCl_3$	70	24	41	<10
3	*L*-(+)-DT	$CHCl_3$	70	24	40	86
4	(+)-Cinchonine	$CHCl_3$	70	24	42	<5
5	(-)-Quinine	$CHCl_3$	70	24	29	<5
6	Diolane	$CHCl_3$	70	24	32	59
7	(*M,S,S*)-*p*-Tol-BINASO	$CHCl_3$	70	24	32	<5
8[d]	(*R*)-BINOL	$CHCl_3$	70	24	53	75
9	(*R*)-BINOL	CH_2Cl_2	50	24	56	<10
10	(*R*)-BINOL	MeTHF	90	24	15	55
11	(*R*)-BINOL	DCE	rt	96	19	65
12	(*R*)-BINOL	DCE	90	24	28	86

[a]Reaction conditions: (**2a**) (0.3 mmol), (**3a**) (1.1 mmol), (**4a**) (0.92 mmol), Catalyst (20 mol%), MS 4Å (200 mg) and $CHCl_3$ (3 mL) were added to a Radley's® 12 position carousel reactor tube under a nitrogen atmosphere and stirred at 70 ºC for 24 hours. [b]Isolated yield. [c]Determined by chiral stationary phase HPLC (see Supporting Information for further details). [d]Reaction run with 1.2 equiv of (**3a**) and 1.2 equiv of (**4a**).

HPLC data:

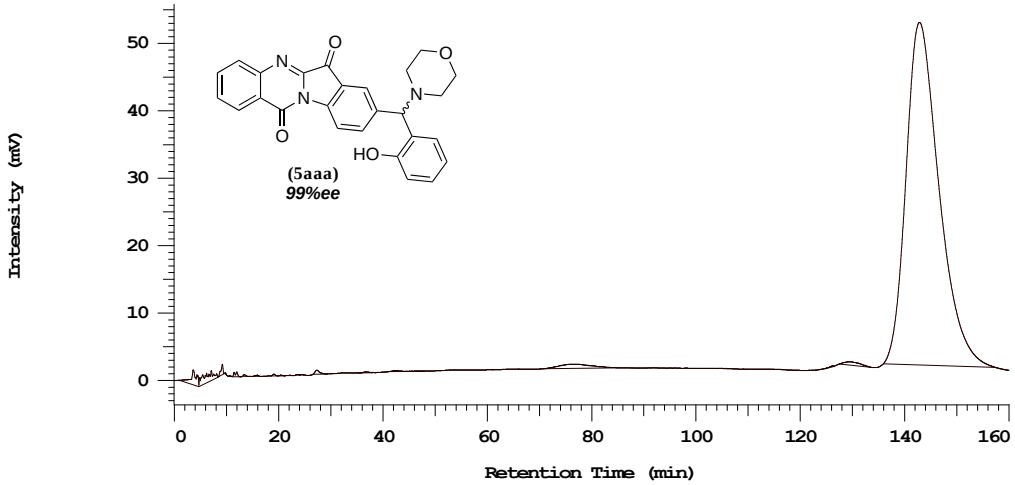
8-((2-hydroxyphenyl)(morpholino)methyl)indolo[2,1-b]quinazoline-6,12-dione (**5aaa**): Daicel Chiralpak IA column, *n*-hexane/ethanol = 70:30, 0.8 mL/min, 254 nm, retention time: 129.440 (minor), 142.827 min (major).

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
31	107.633	20930378	43.283	BB
33	139.407	20037671	41.437	BB

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
32	129.440	113936	0.495	BB
33	142.827	22148810	96.140	BB

4. References:

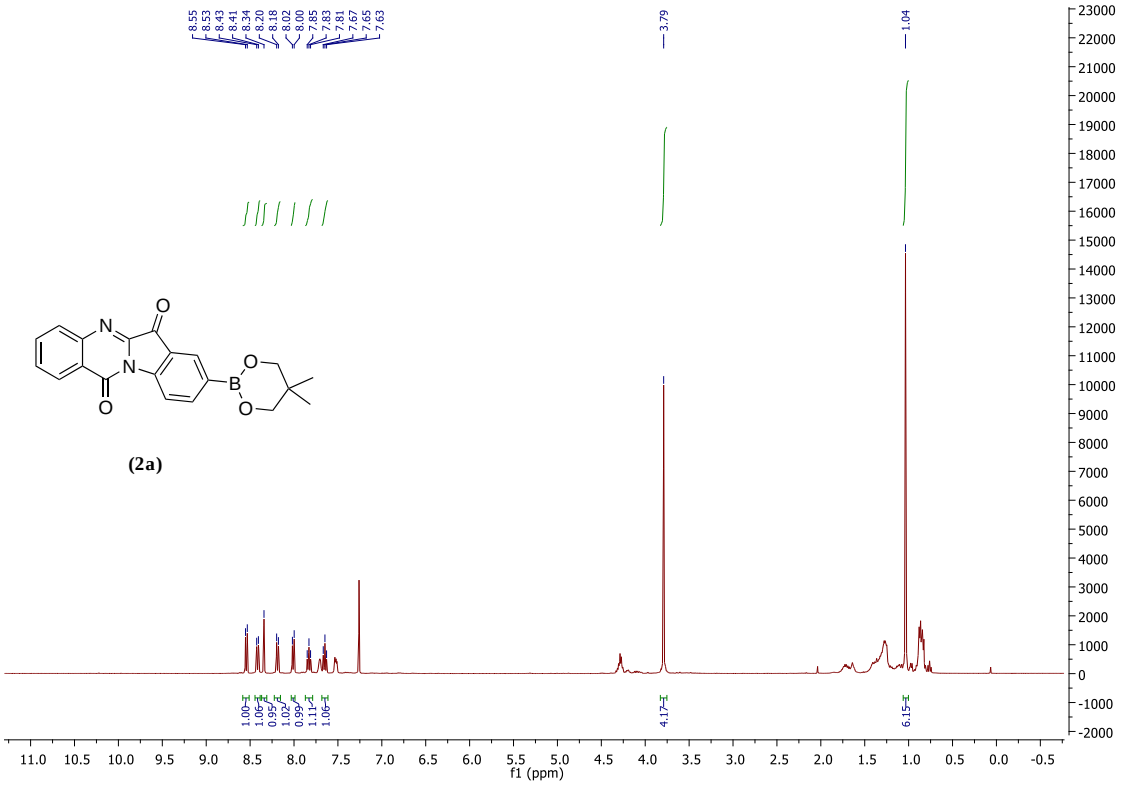
[1]. W. L. F. Amarego, D. D. Perrin in Purification of Laboratory Chemicals, 4th ed., Butterworth Heinemann, Oxford, UK, 1996.

[2]. A. Kumar, V. D. Tripathi, P. Kumar, Green Chem., 2011, 13, 51-54; L. A. Onambele, H. Riepl, R. Fischer, G. Pradel, A. Prokop, M. N. Aminake, Int. J. Parasit. Drugs Drug Resist., 2015, 5, 48-57.

[3]. T. Ishiyama, M. Murata, N. Miyaura, J. Org. Chem. 1995, 60, 7508-7510.

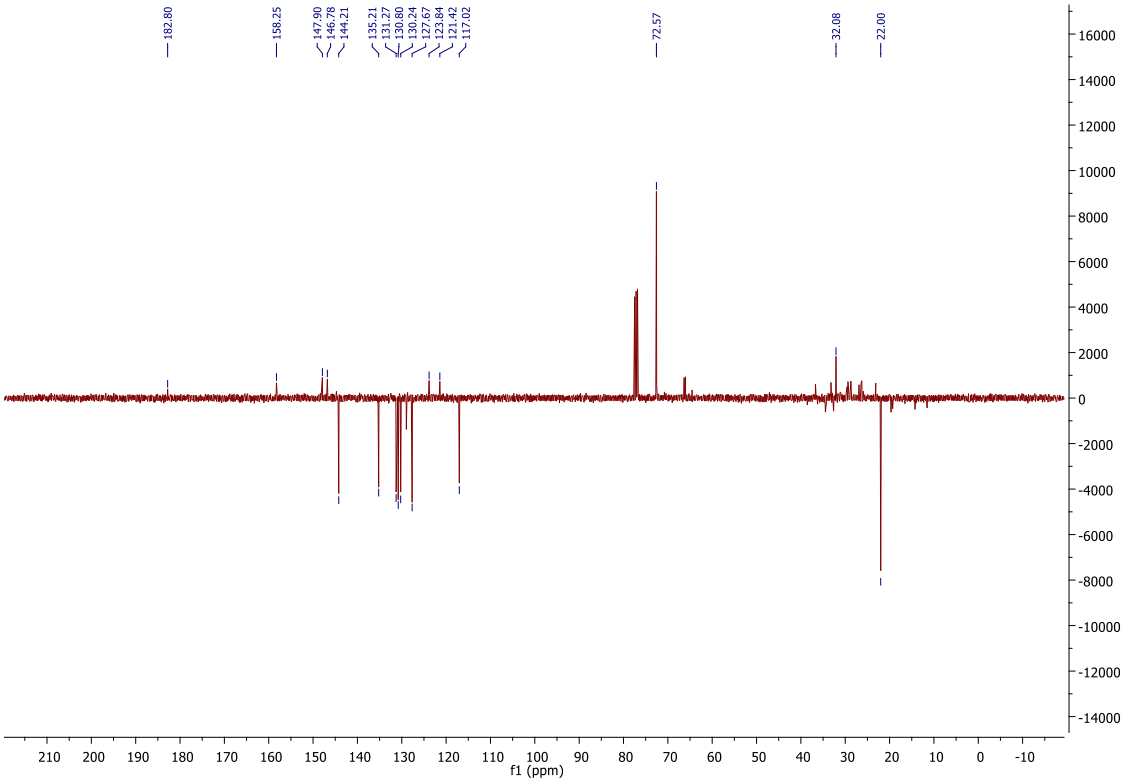
NMR Spectra

^{1}H NMR Spectra of **(2a)** (400 MHz, $CDCl_3$):

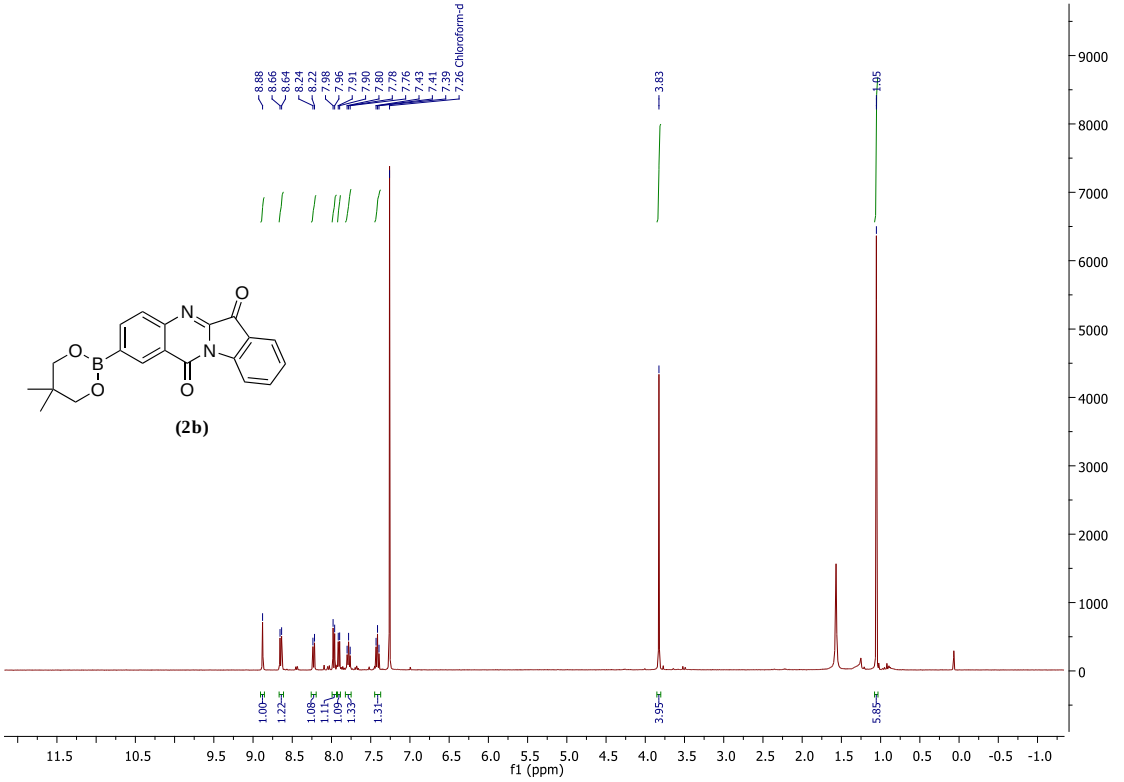


(2a)

^{13}C{^{1}H} APT NMR spectra of **(2a)** ($CDCl_3$, 100 MHz):

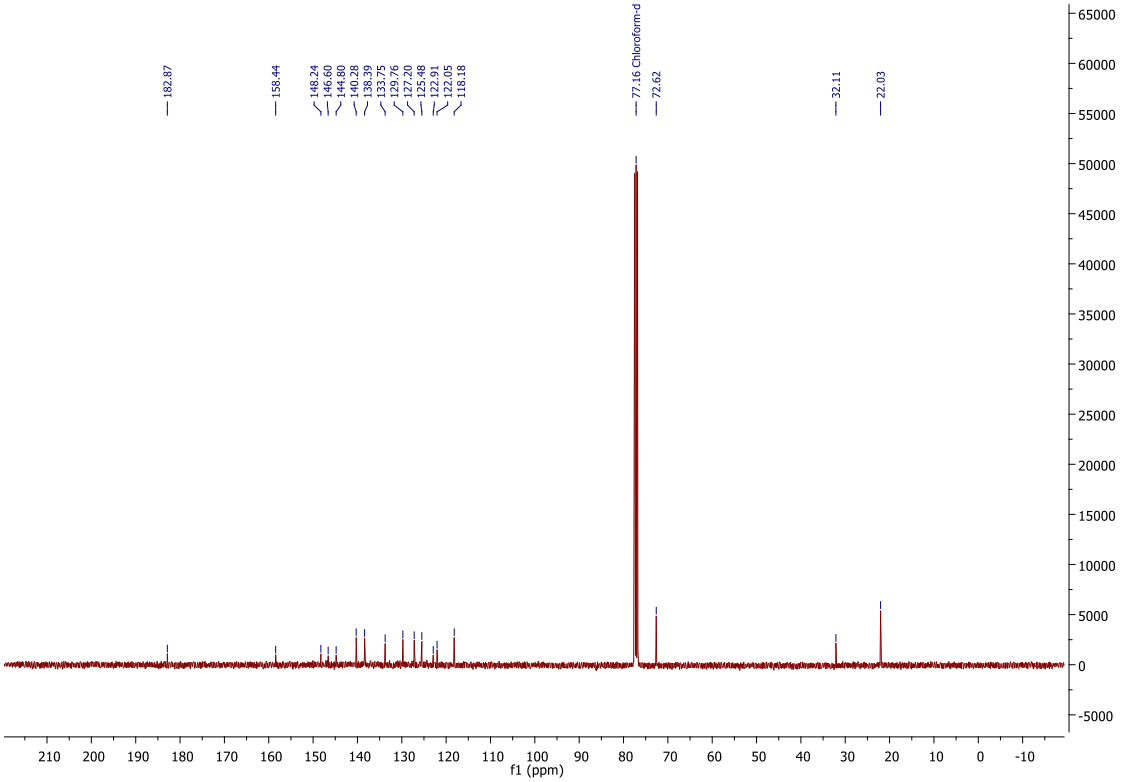


^{1}H NMR Spectra of **(2b)** (400 MHz, $CDCl_3$):

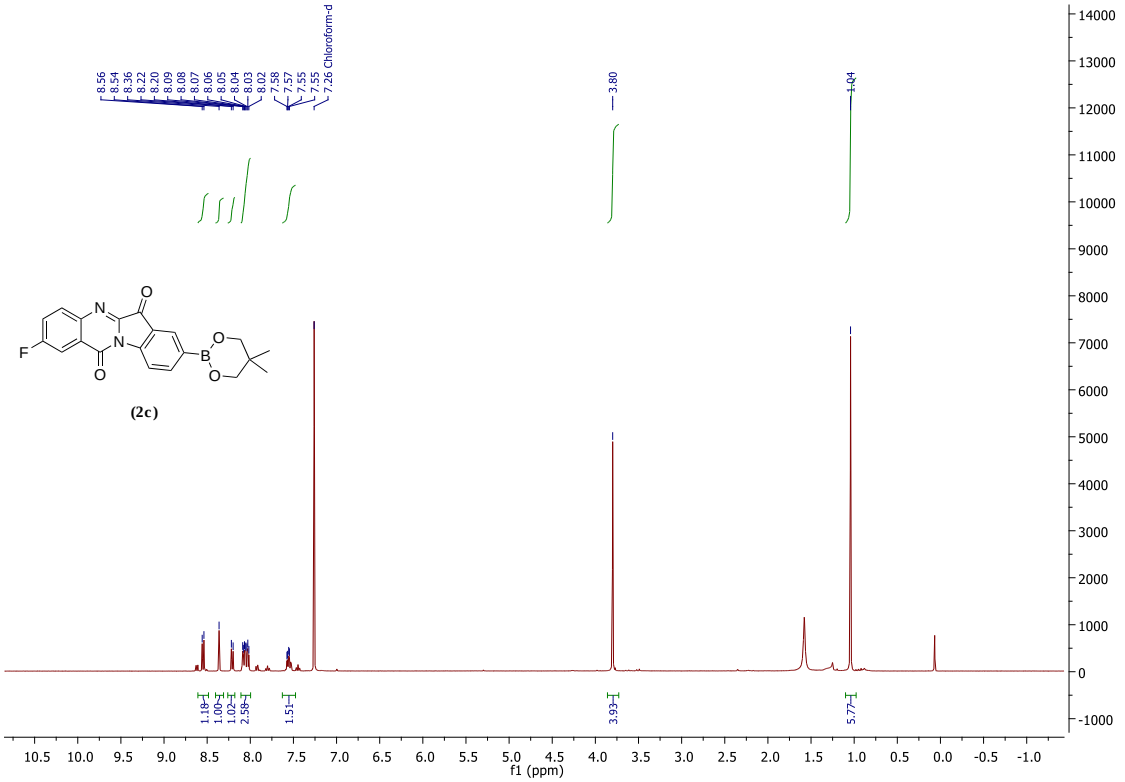


(2b)

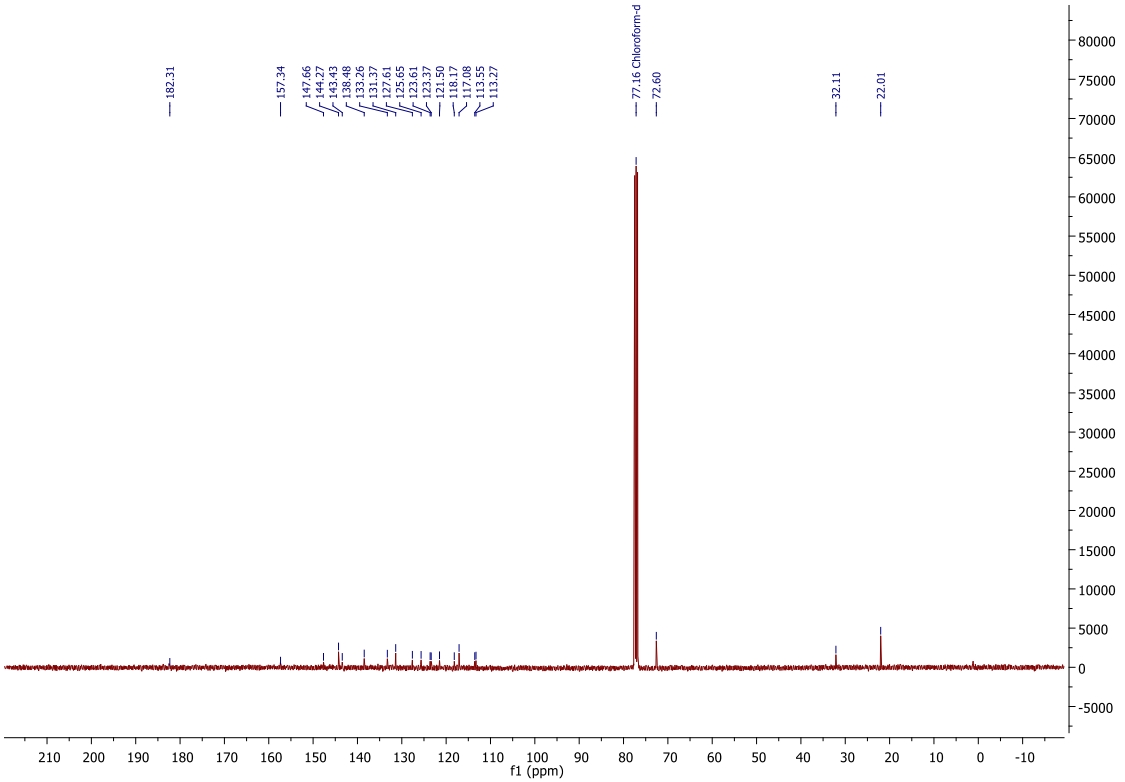
^{13}C{^{1}H} NMR spectra of **(2b)** ($CDCl_3$, 100 MHz):



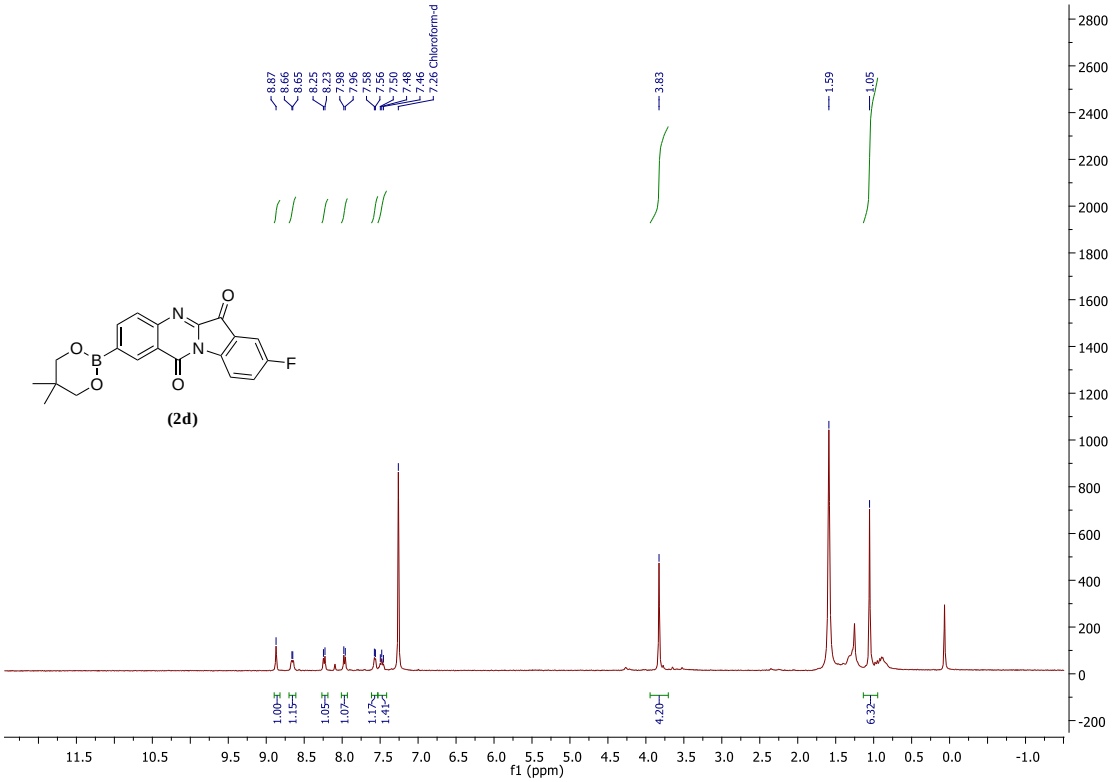
^{1}H NMR Spectra of **(2c)** (400 MHz, $CDCl_3$):



^{13}C{^{1}H} NMR spectra of **(2c)** ($CDCl_3$, 100 MHz):

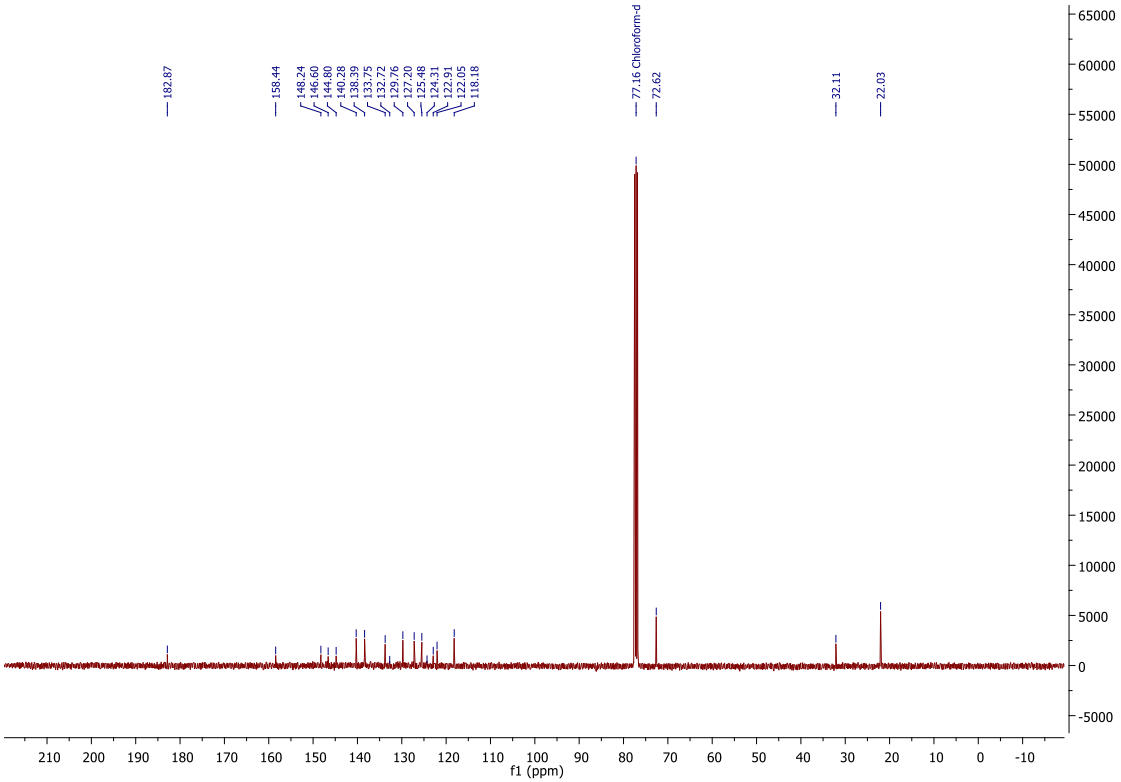


^{1}H NMR Spectra of **(2d)** (400 MHz, $CDCl_3$):

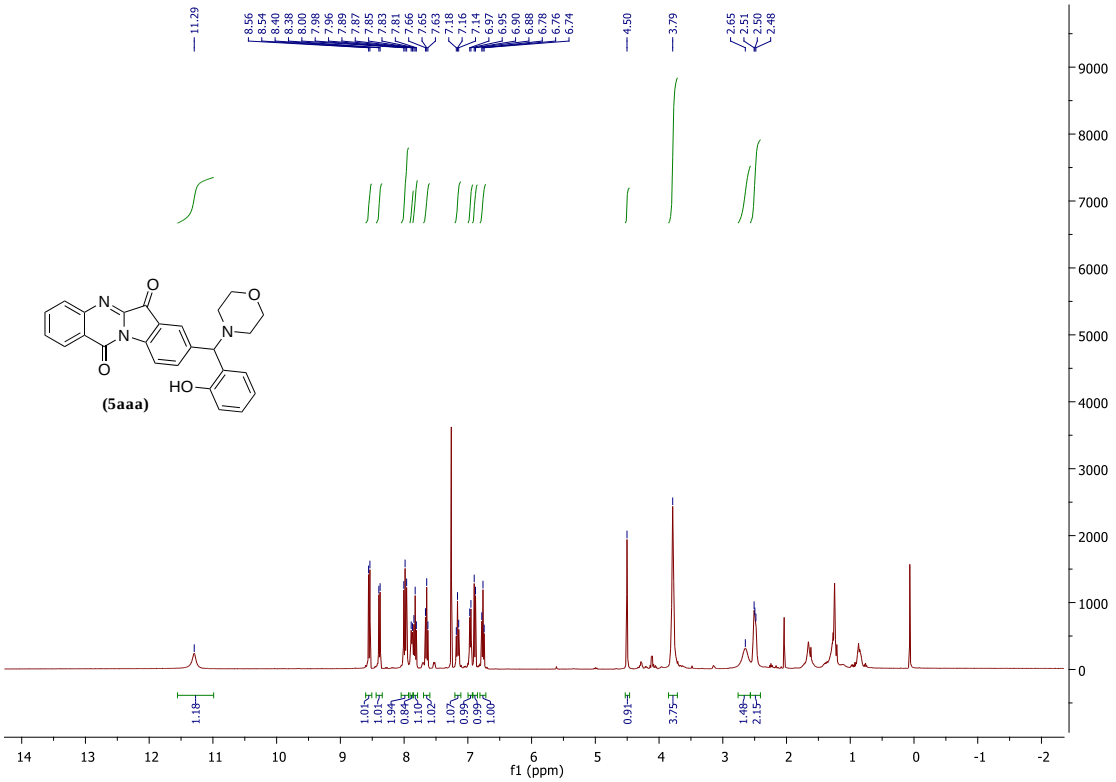


(2d)

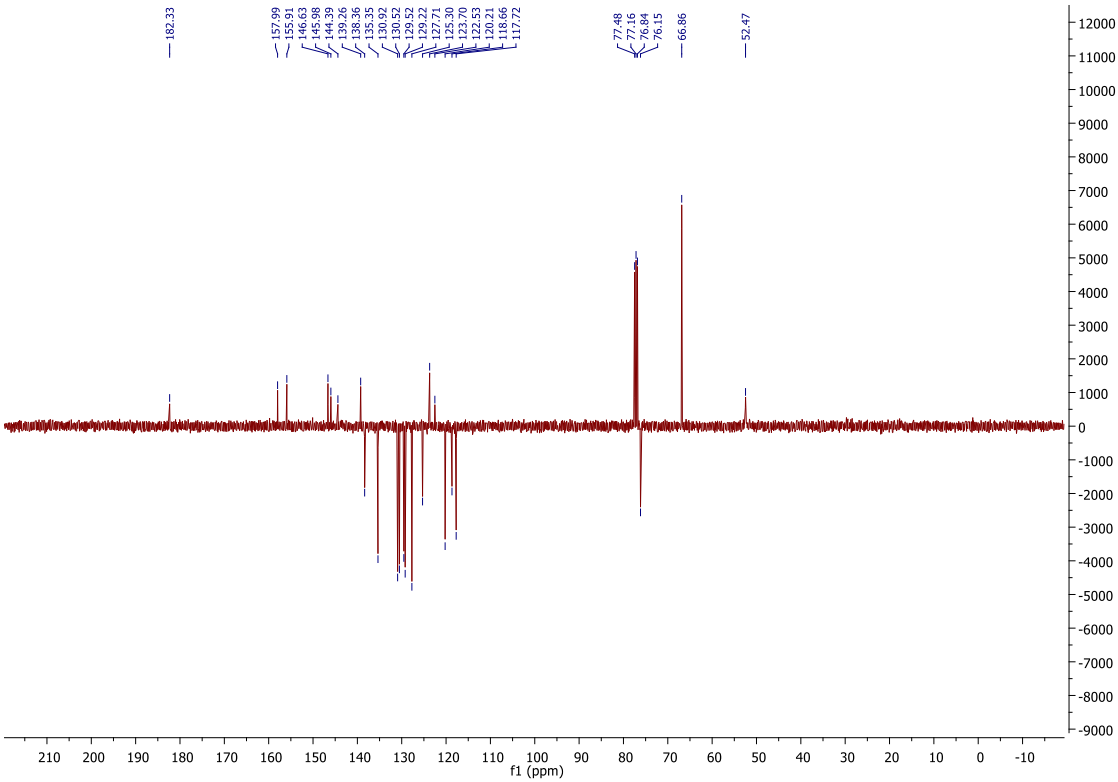
^{13}C{^{1}H} NMR spectra of **(2d)** ($CDCl_3$, 100 MHz):



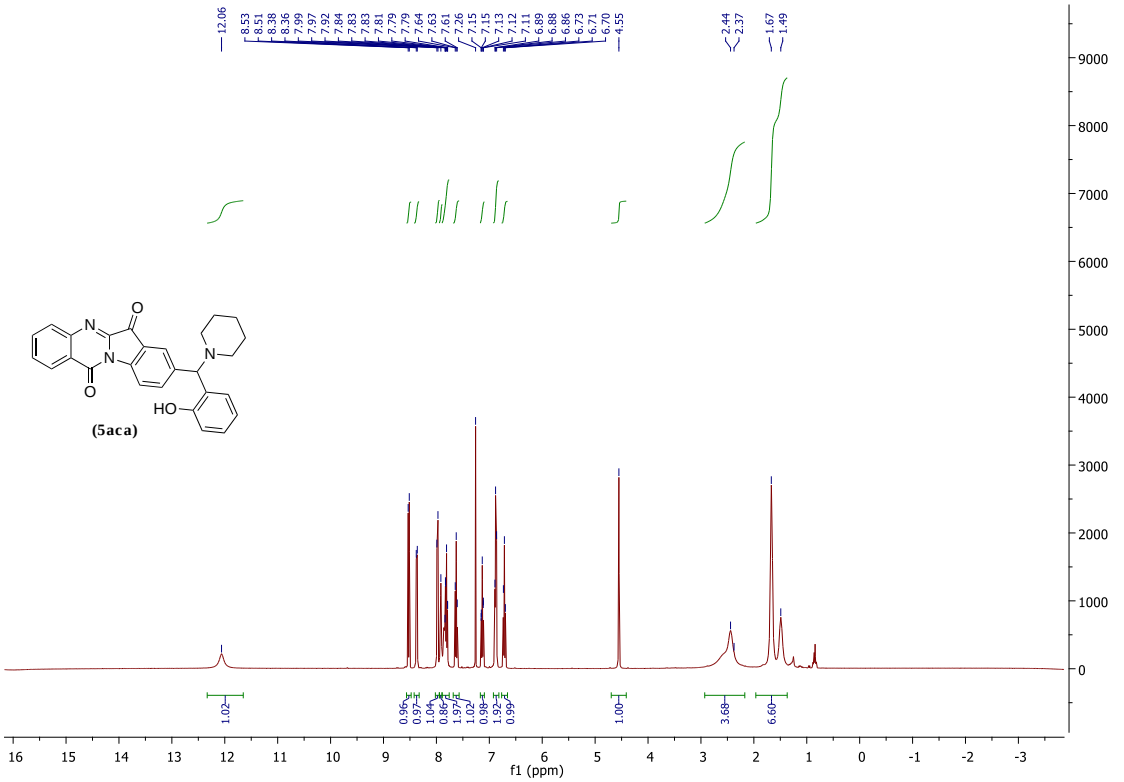
^{1}H NMR Spectra of **(5aa)** (400 MHz, $CDCl_3$):



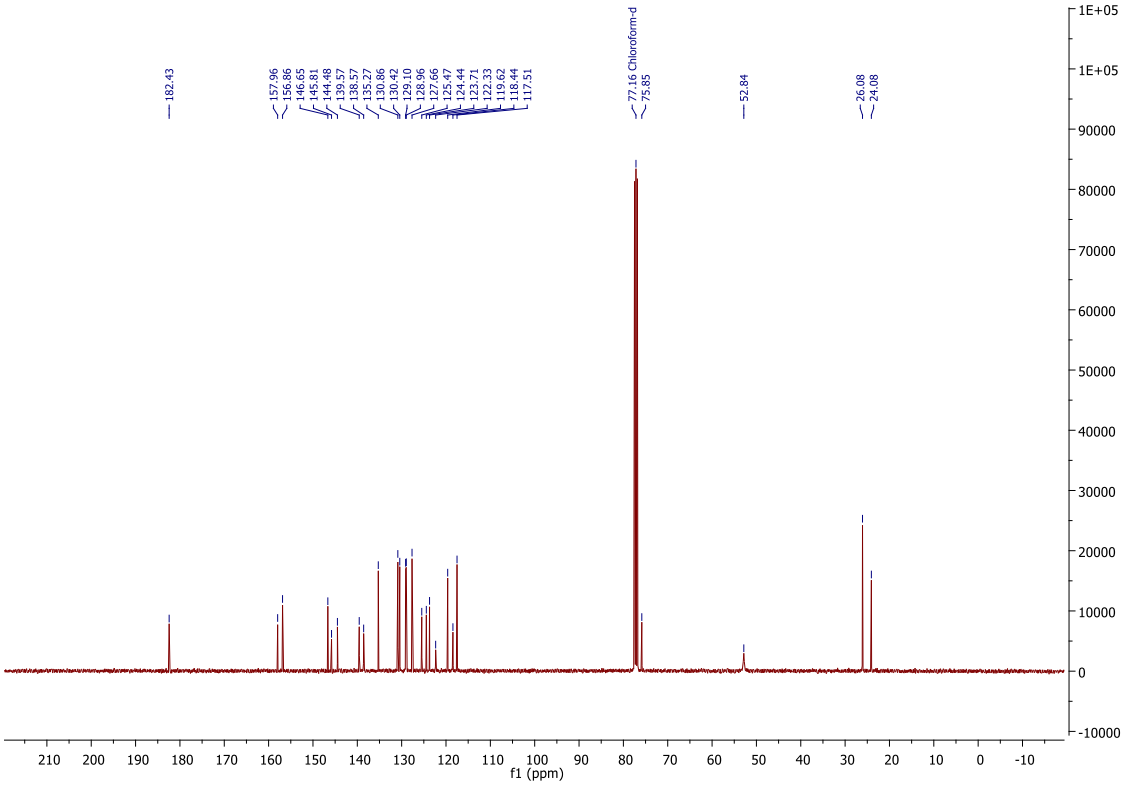
^{13}C{^{1}H} APT NMR spectra of **(5aa)** ($CDCl_3$, 100 MHz):



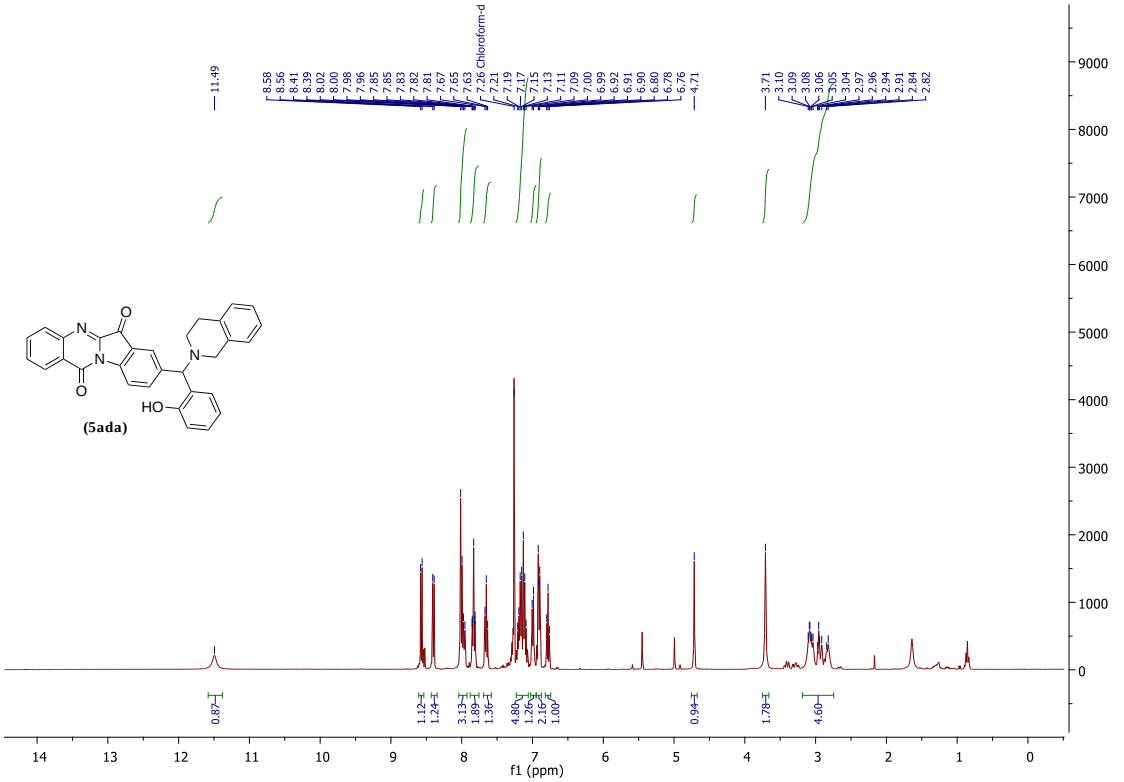
^{1}H NMR Spectra of **(5aca)** (400 MHz, $CDCl_3$):



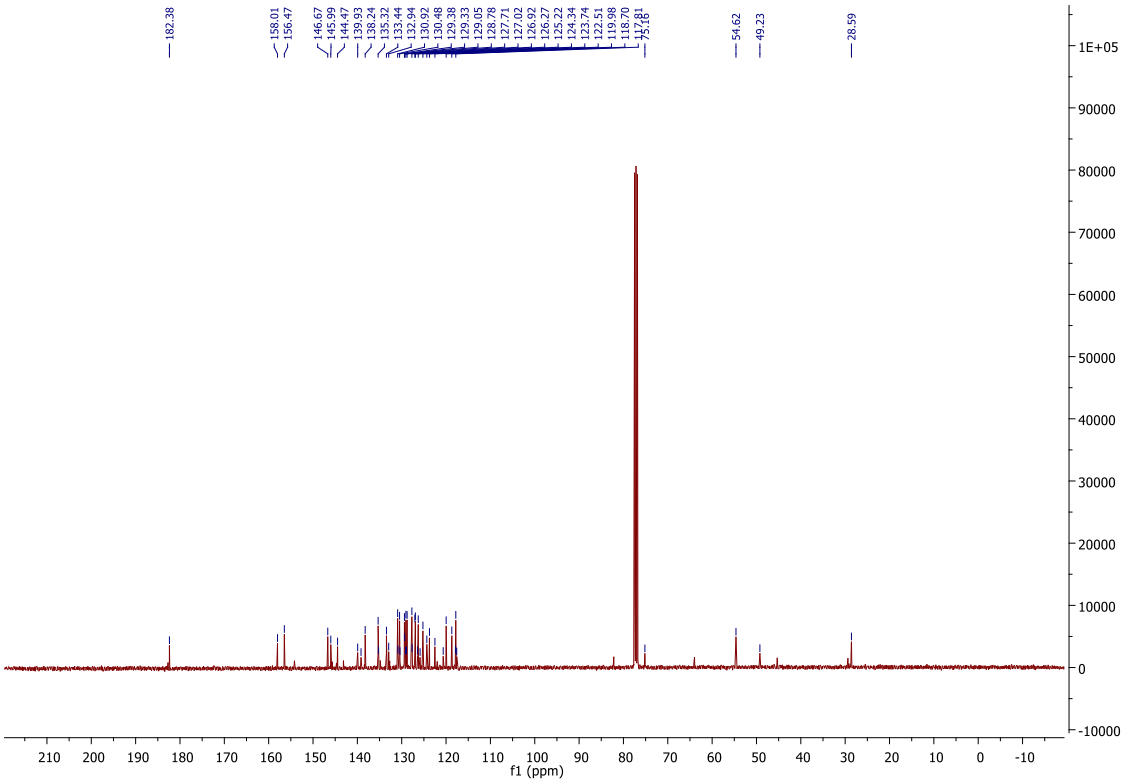
^{13}C{^{1}H} NMR spectra of **(5aca)** ($CDCl_3$, 100 MHz):



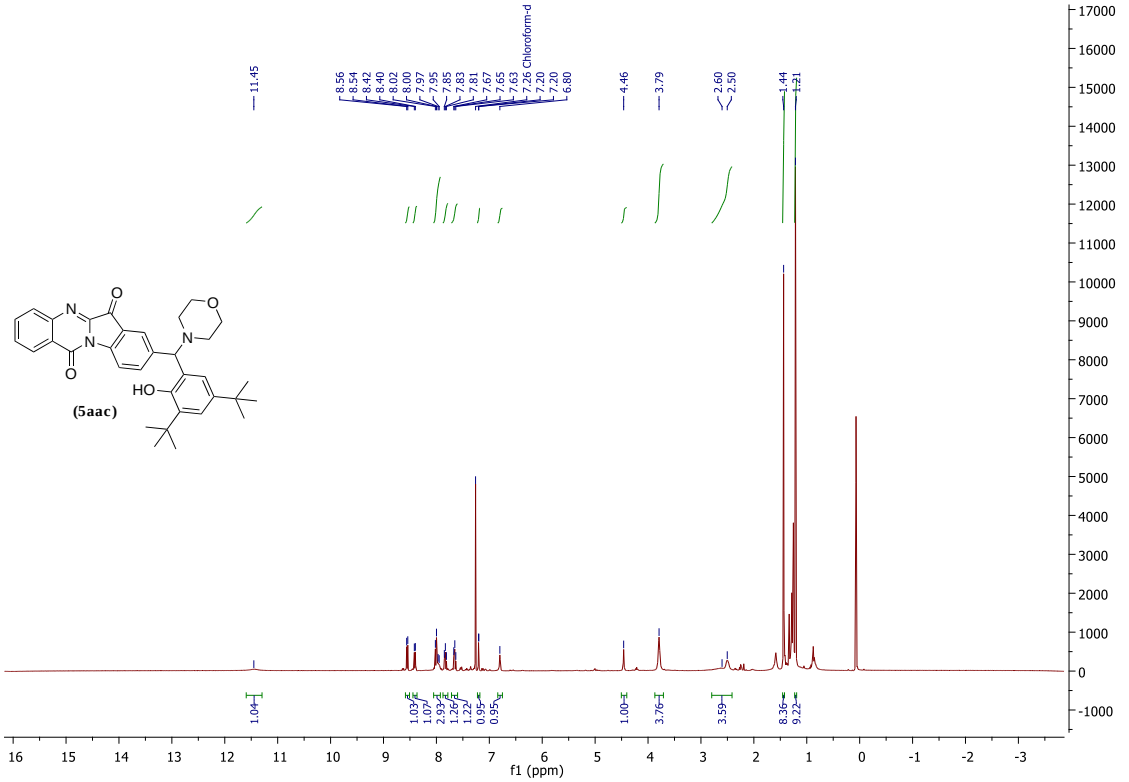
^{1}H NMR Spectra of **(5ada)** (400 MHz, $CDCl_3$):



^{13}C{^{1}H} NMR spectra of **(5ada)** ($CDCl_3$, 100 MHz):

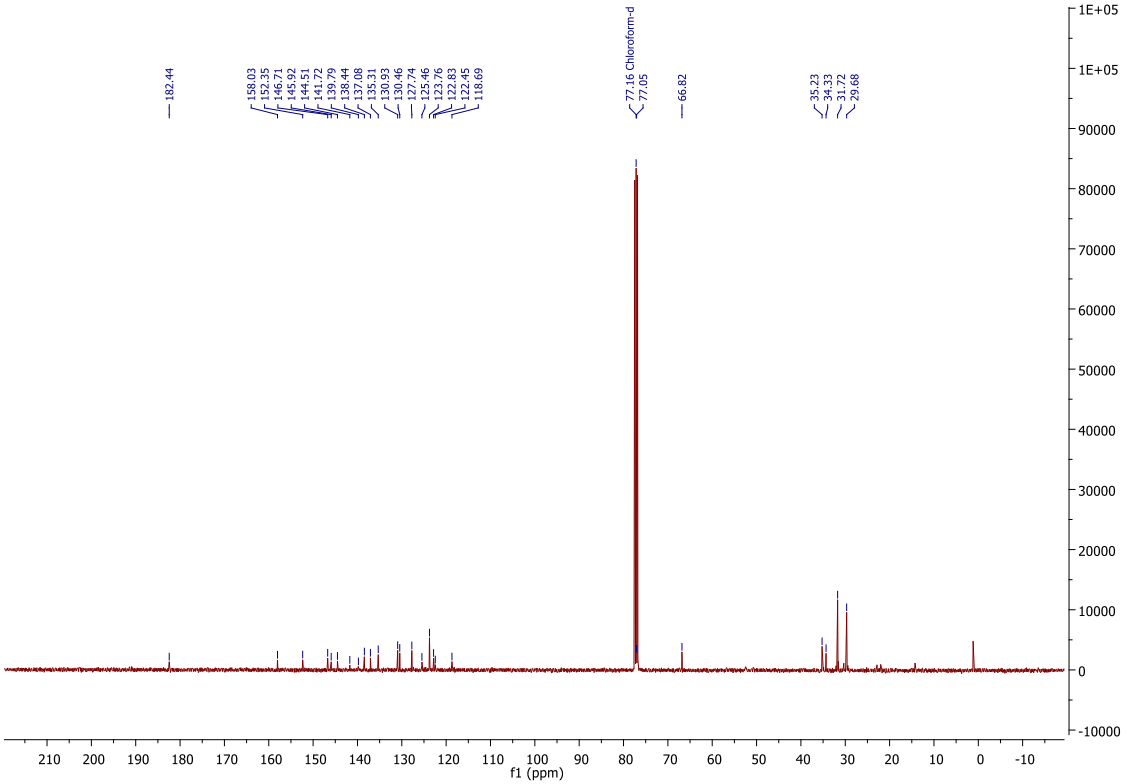


^{1}H NMR Spectra of **(5aac)** (400 MHz, $CDCl_3$):

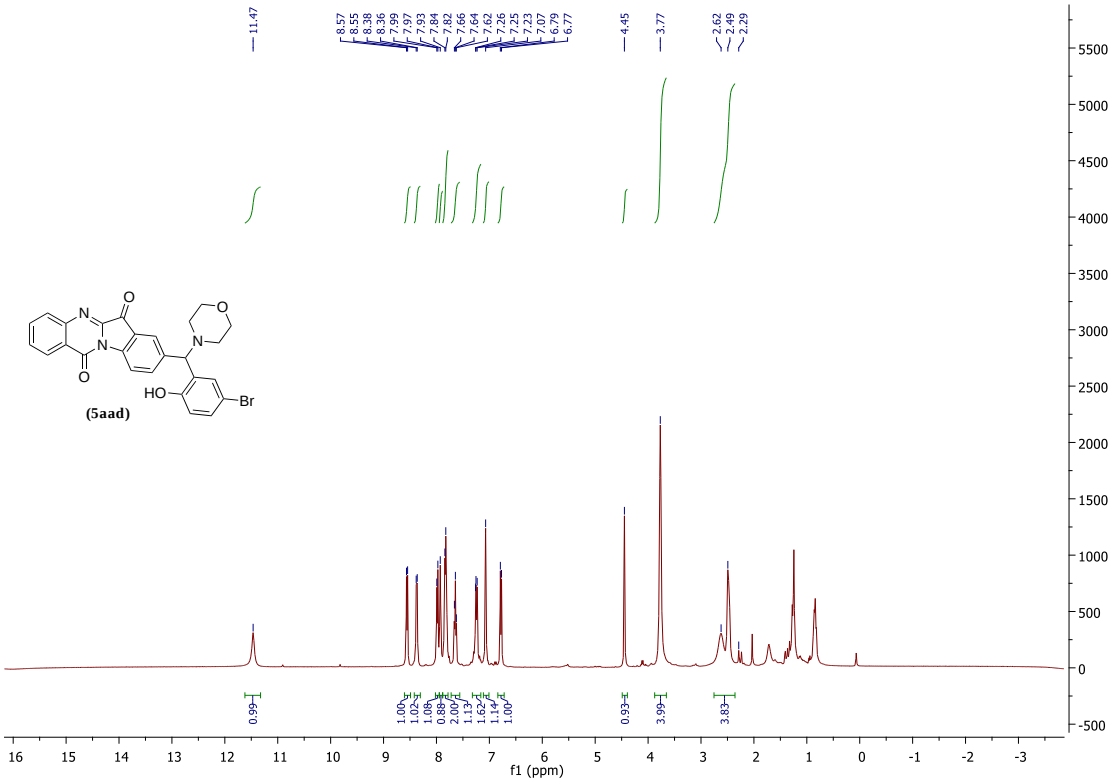


(5aac)

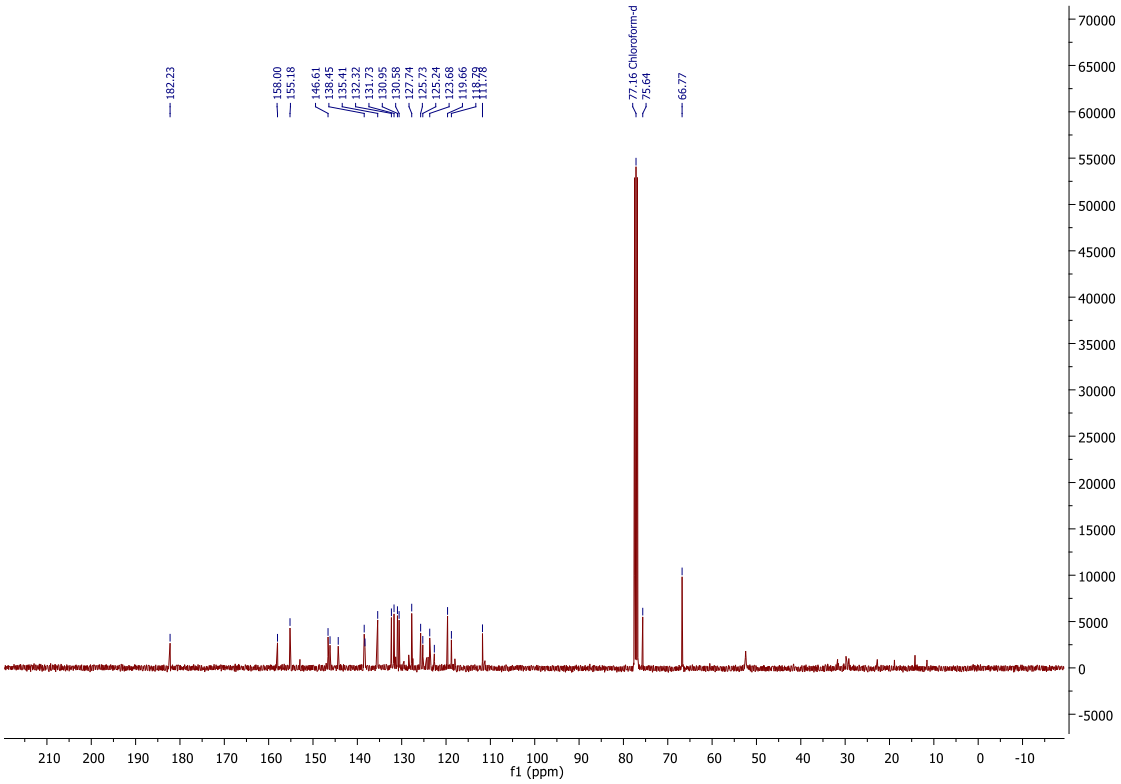
^{13}C{^{1}H} NMR spectra of **(5aac)** ($CDCl_3$, 100 MHz):



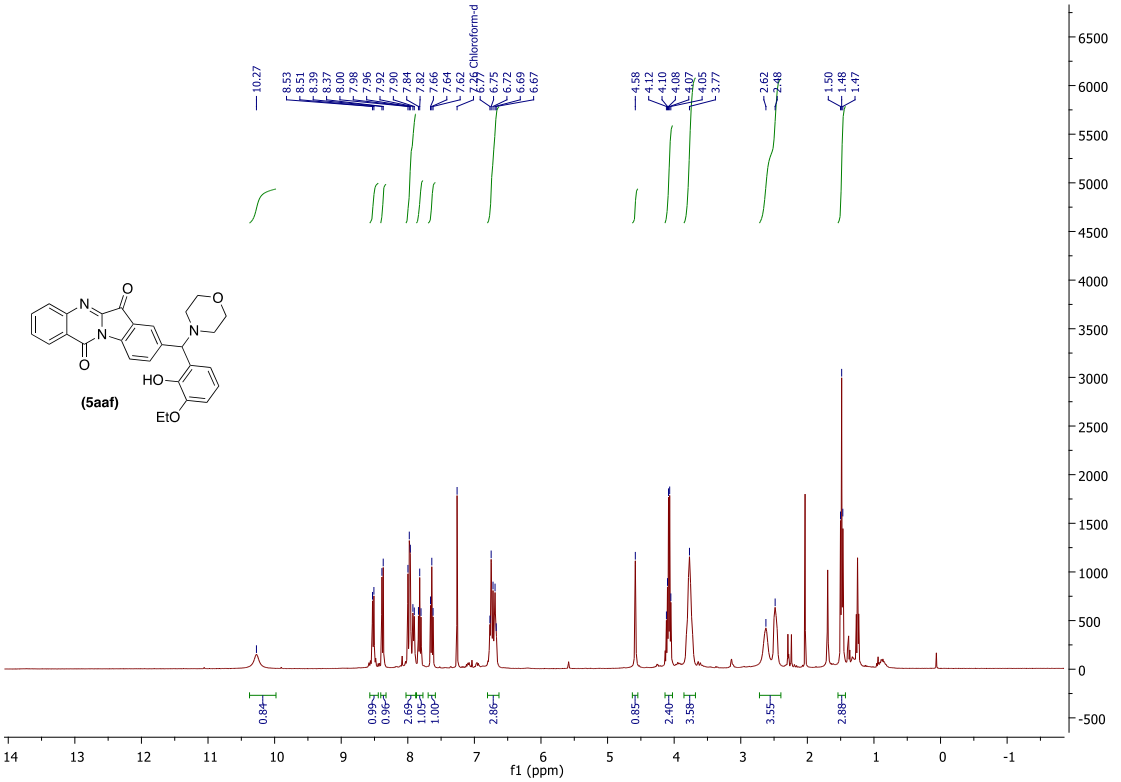
^{1}H NMR Spectra of **(5aad)** (400 MHz, $CDCl_3$):



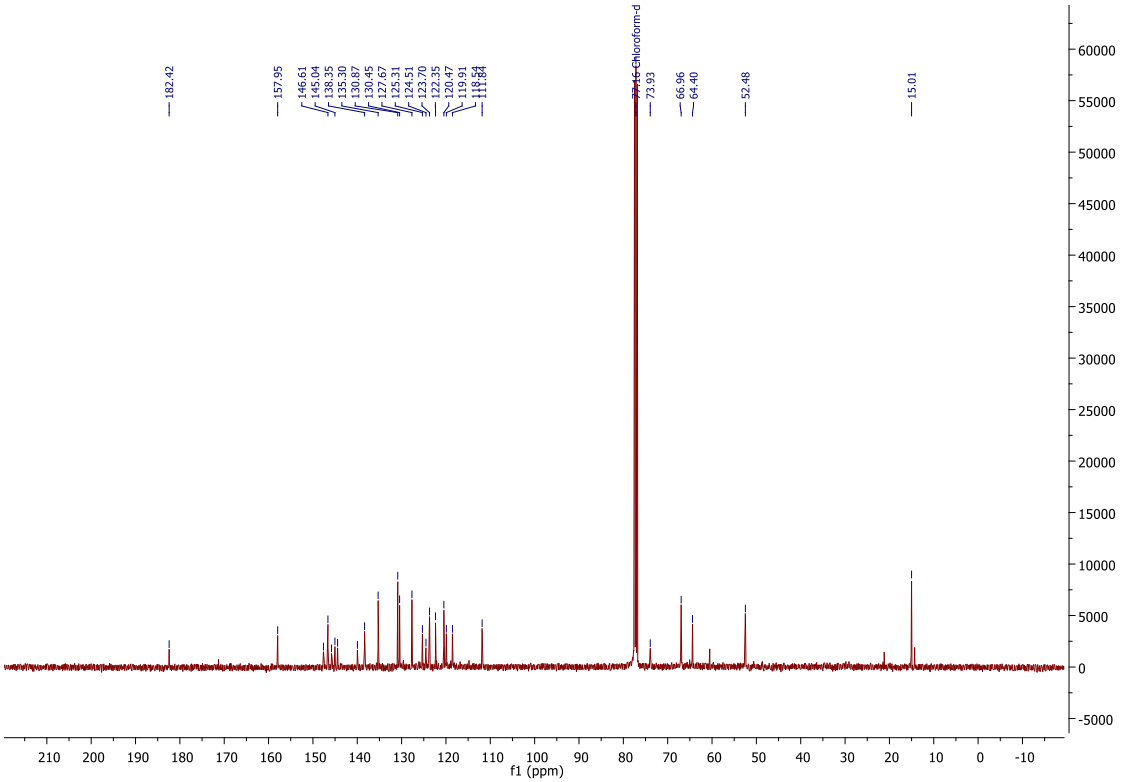
^{13}C{^{1}H} NMR spectra of **(5aad)** ($CDCl_3$, 100 MHz):



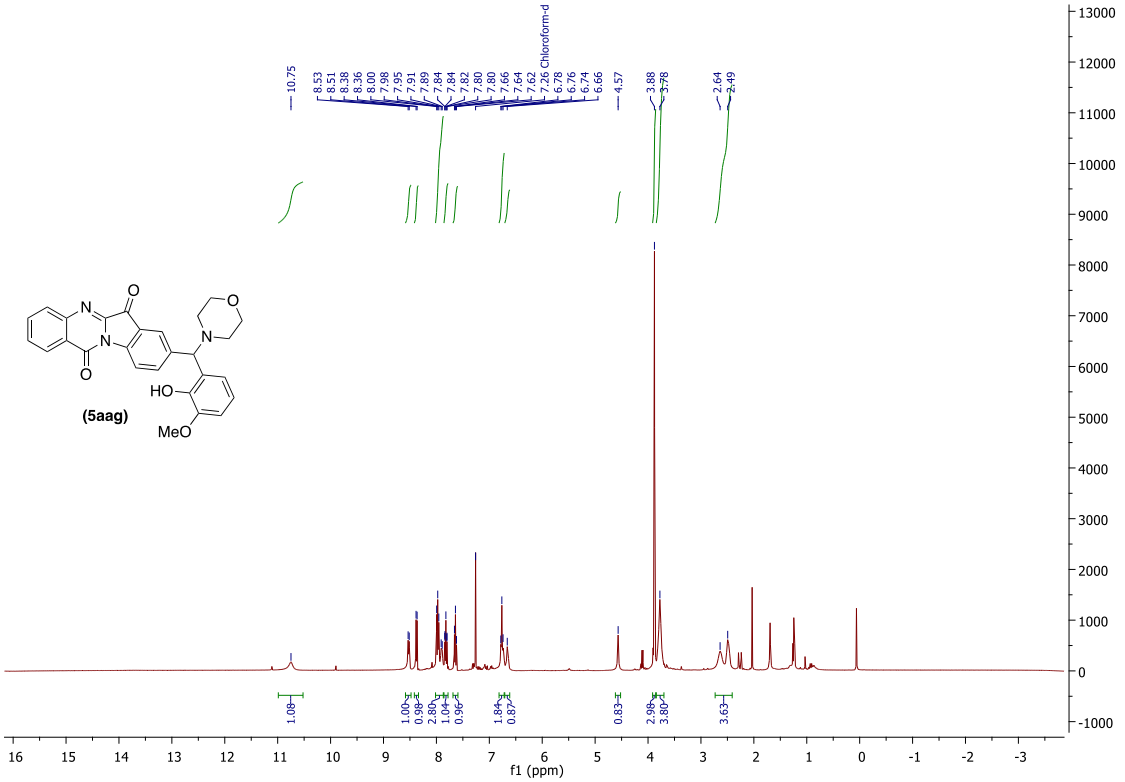
^{1}H NMR Spectra of **(5aaf)** (400 MHz, $CDCl_3$):



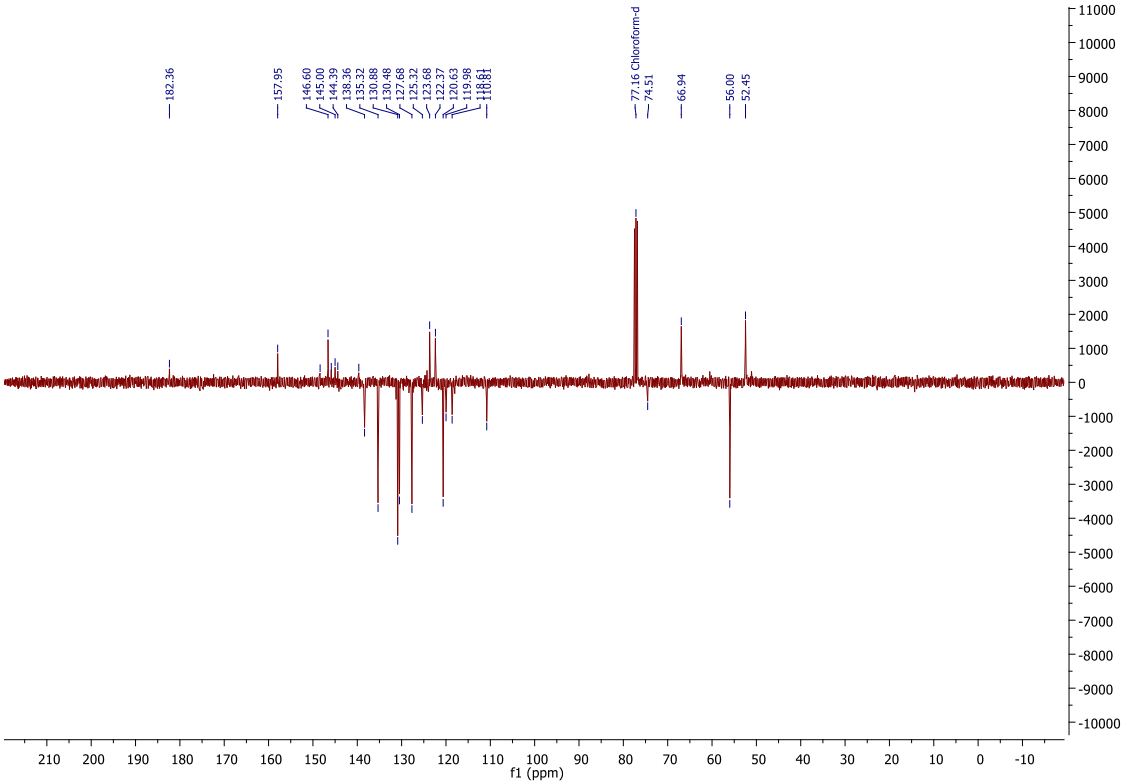
^{13}C{^{1}H} NMR spectra of **(5aaf)** ($CDCl_3$, 100 MHz):



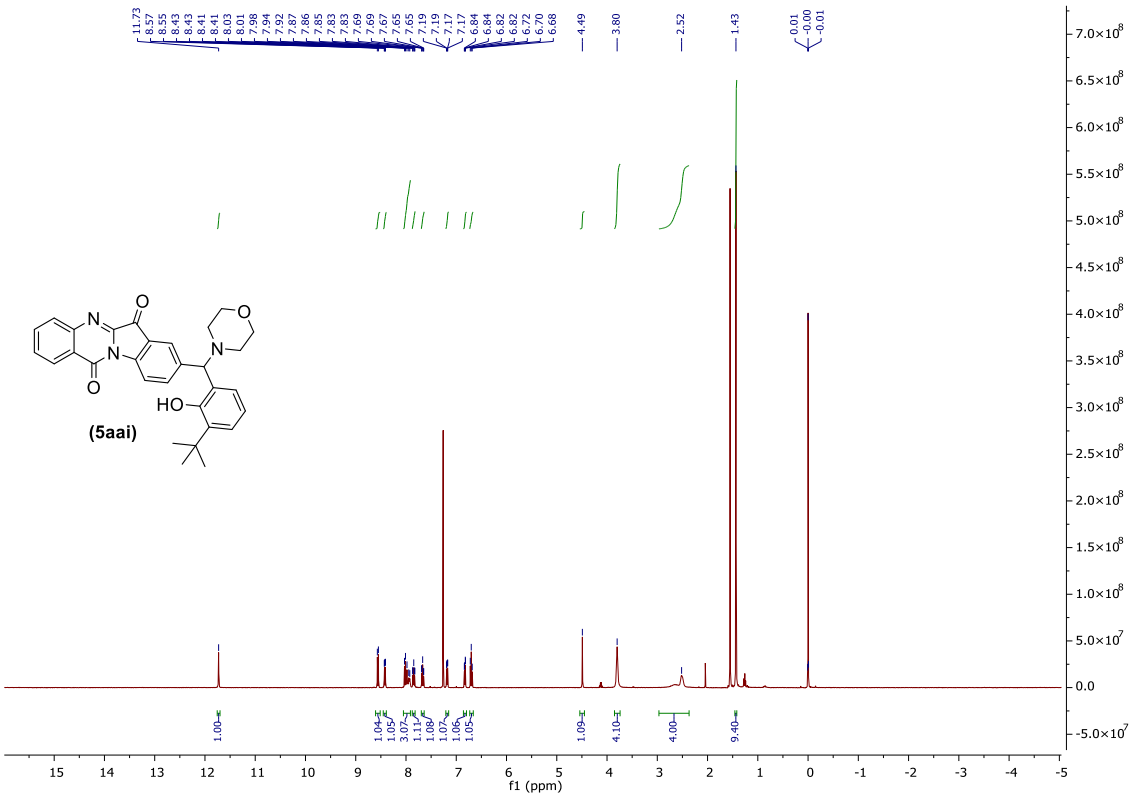
^{1}H NMR Spectra of **(5aag)** (400 MHz, $CDCl_3$):



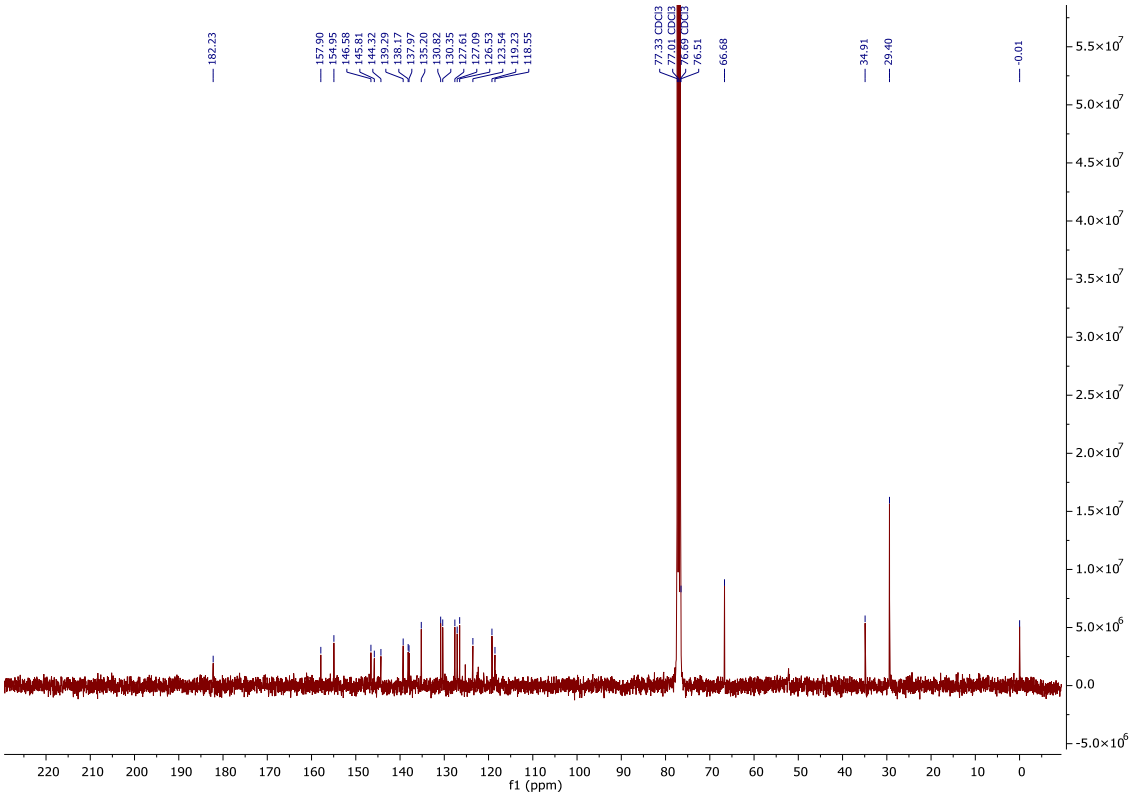
^{13}C{^{1}H} NMR spectra of **(5aag)** ($CDCl_3$, 100 MHz):



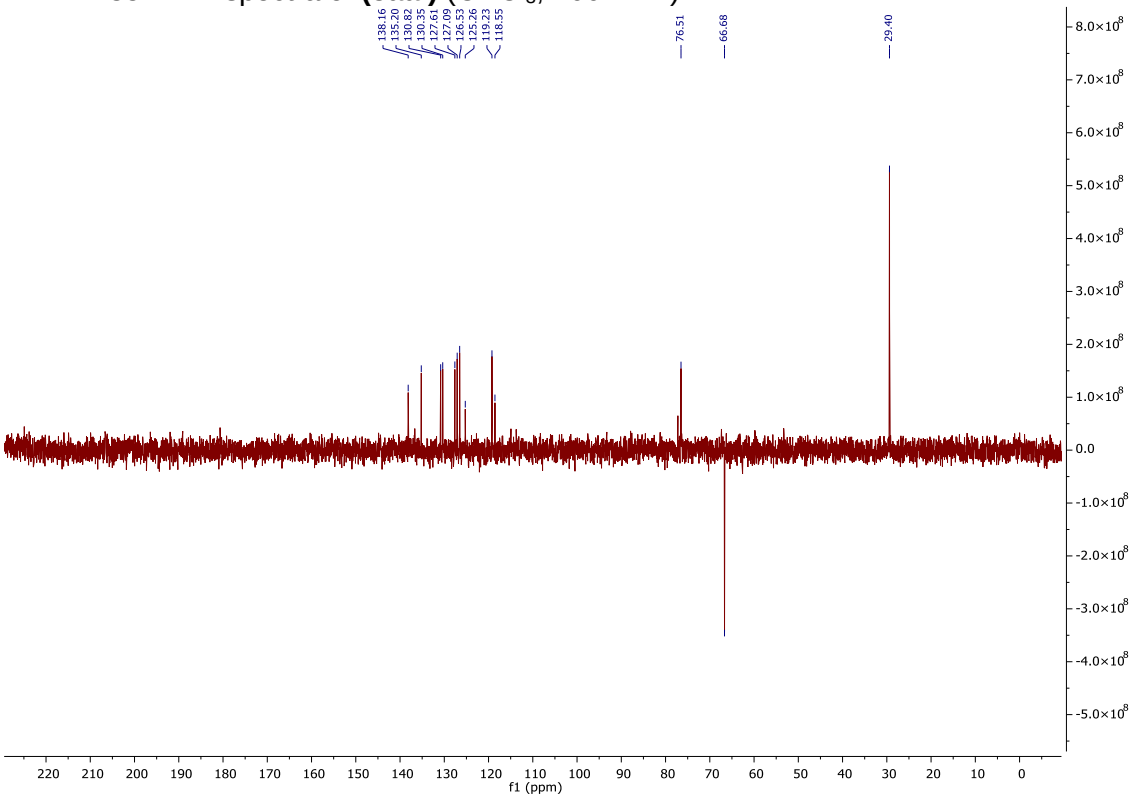
^{1}H NMR Spectra of **(5aai)** (400 MHz, $CDCl_3$):



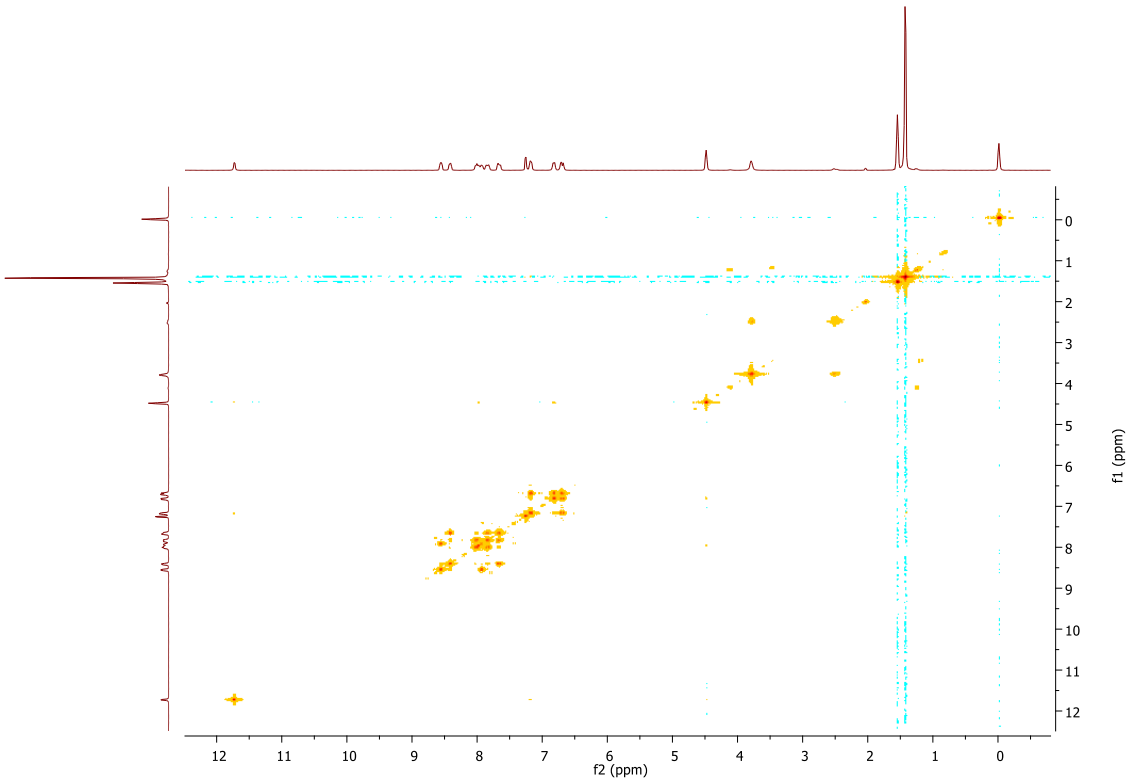
^{13}C{^{1}H} NMR spectra of **(5aai)** ($CDCl_3$, 100 MHz):



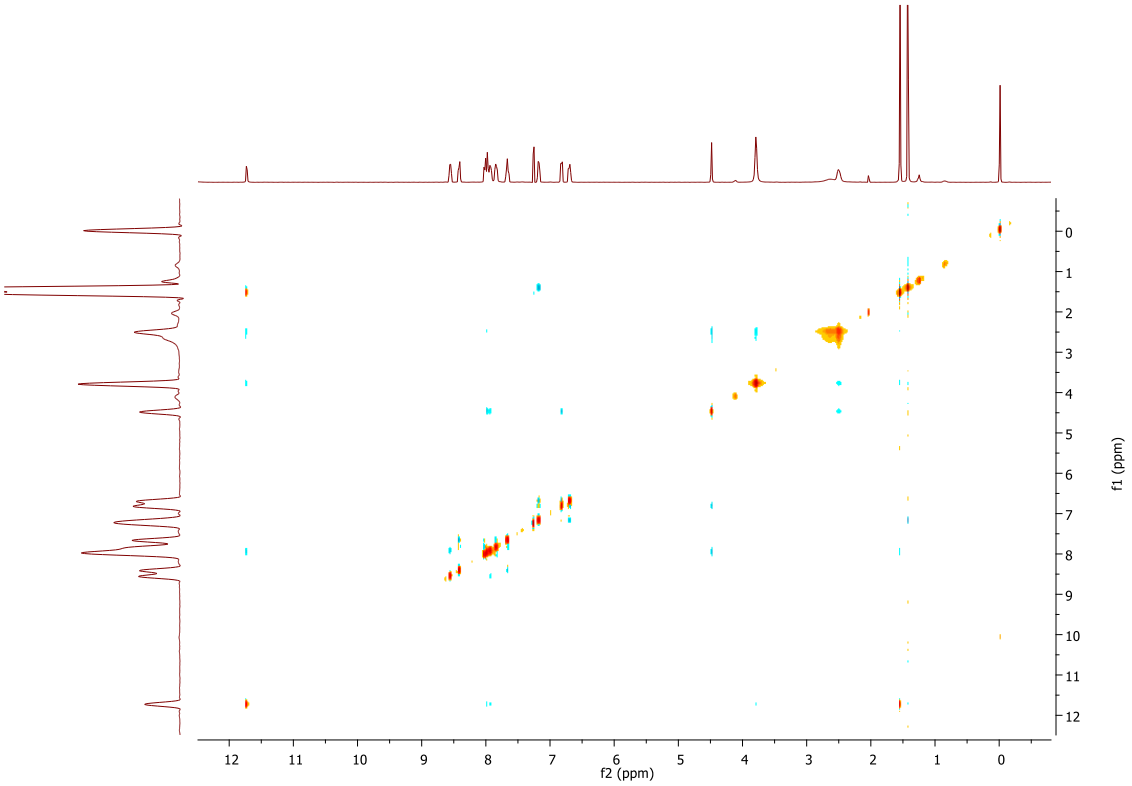
DEPT-135 NMR spectra of **(5aai)** ($CDCl_3$, 100 MHz):



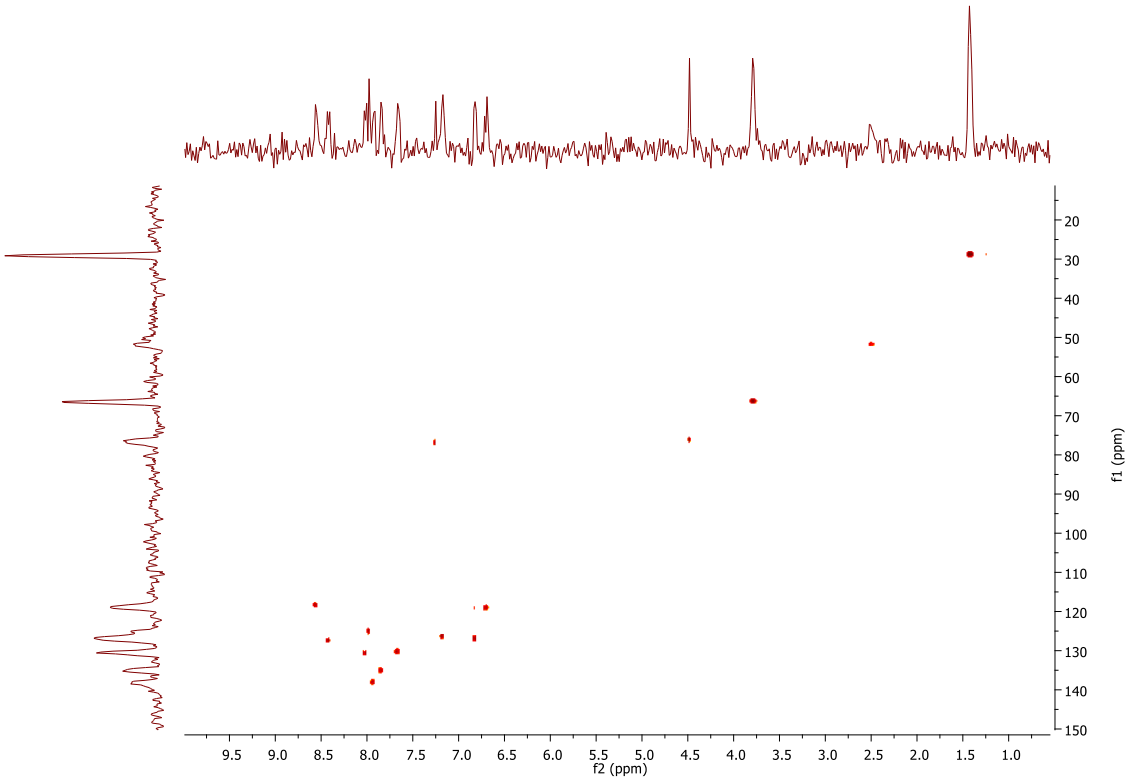
COSY NMR spectra of **(5aai)** ($CDCl_3$, 400 MHz):



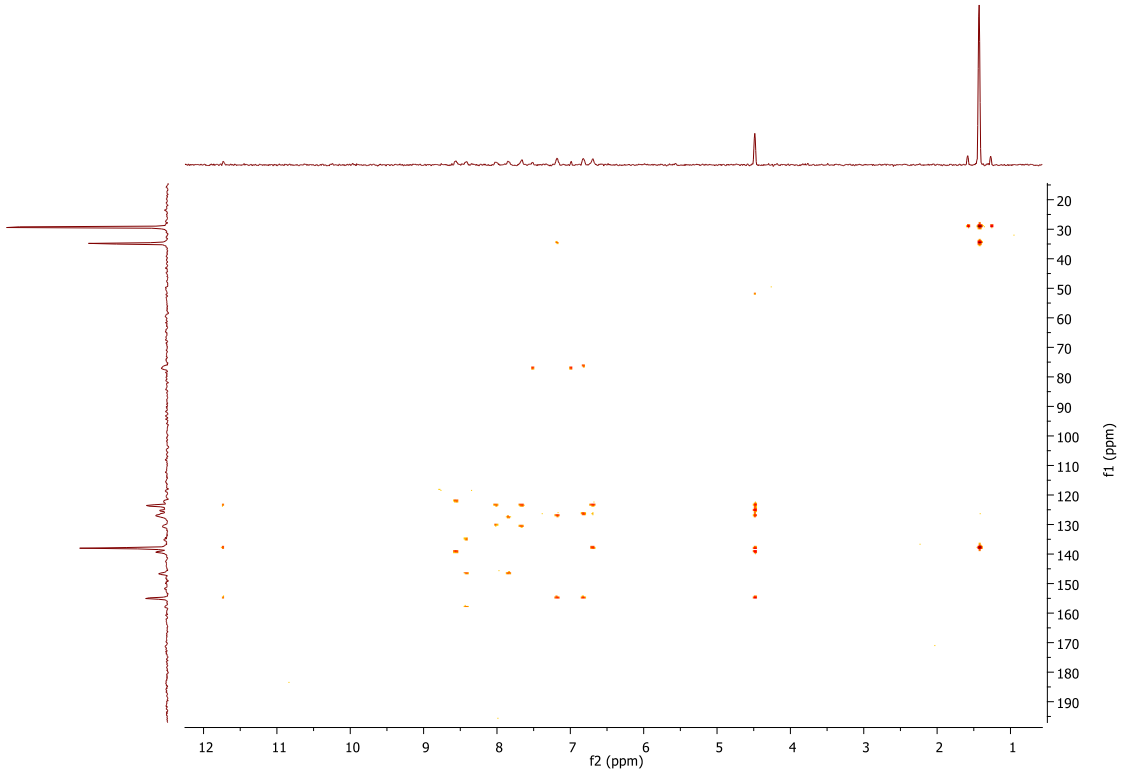
NOESY NMR spectra of **(5aai)** ($CDCl_3$, 400 MHz):



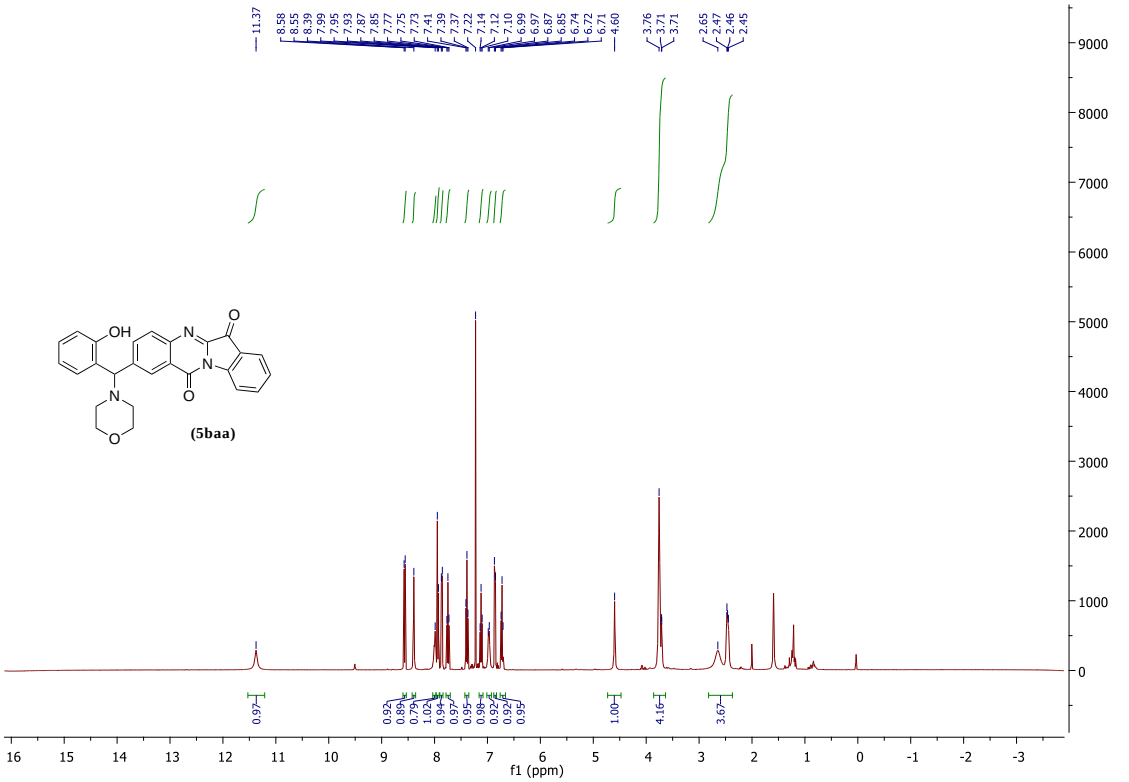
HSQC NMR spectra of **(5aai)** ($CDCl_3$):



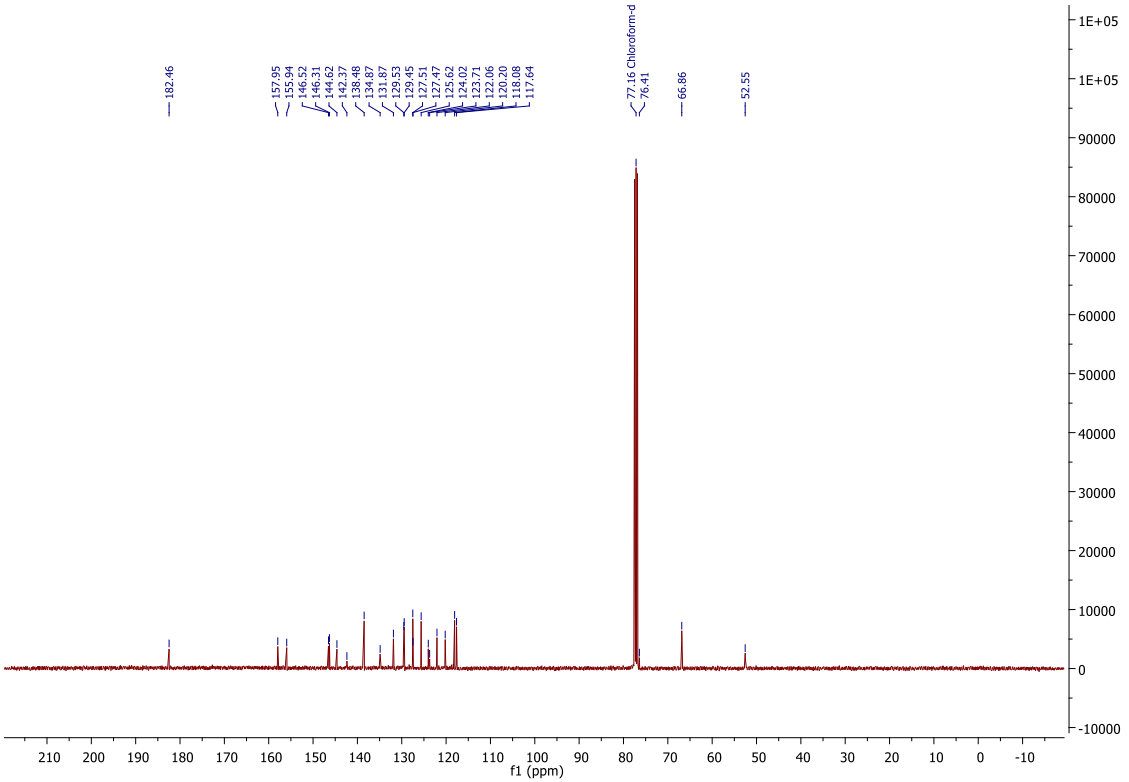
HMBC NMR spectra of **(5aai)** ($CDCl_3$):



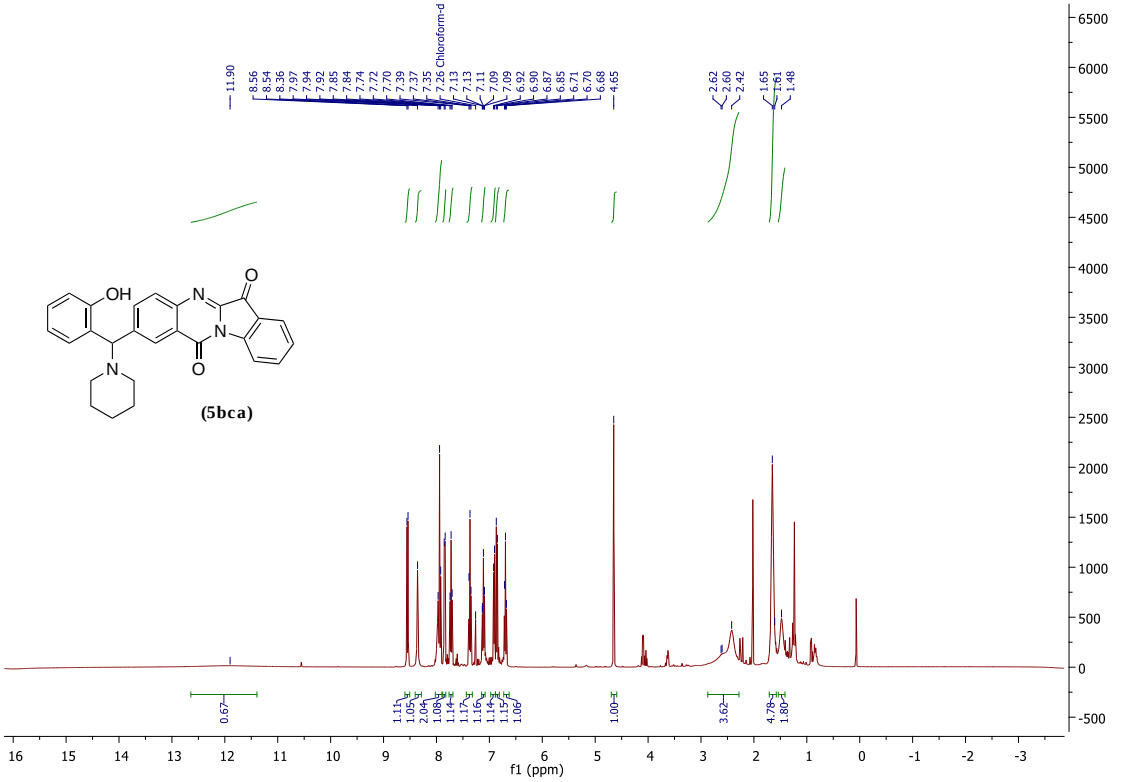
^{1}H NMR Spectra of **(5baa)** (400 MHz, $CDCl_3$):



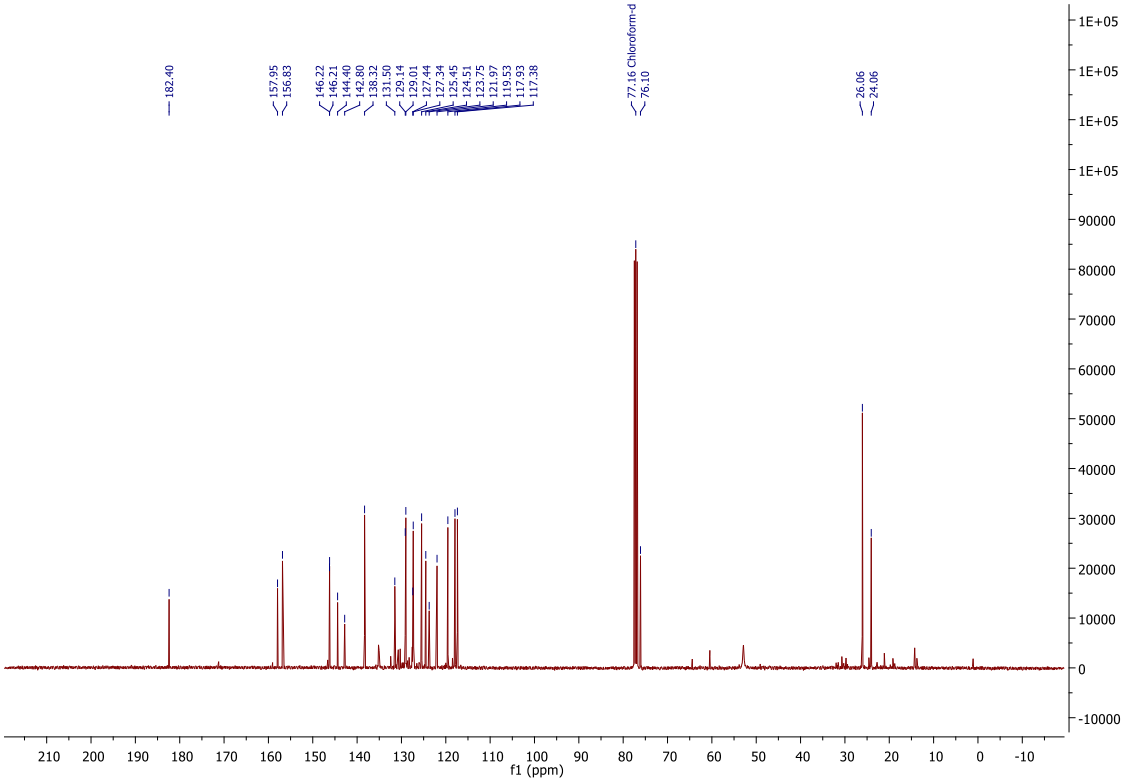
^{13}C{^{1}H} NMR spectra of **(5baa)** ($CDCl_3$, 100 MHz):



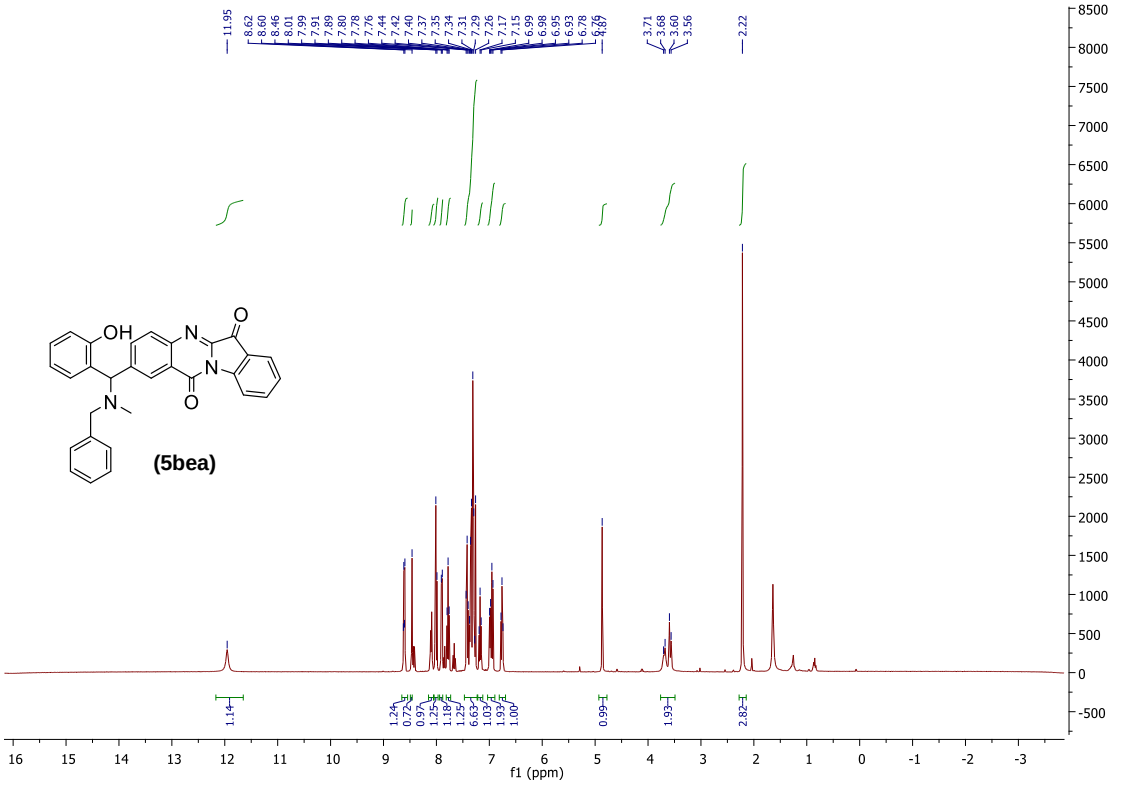
^{1}H NMR Spectra of **(5bca)** (400 MHz, $CDCl_3$):



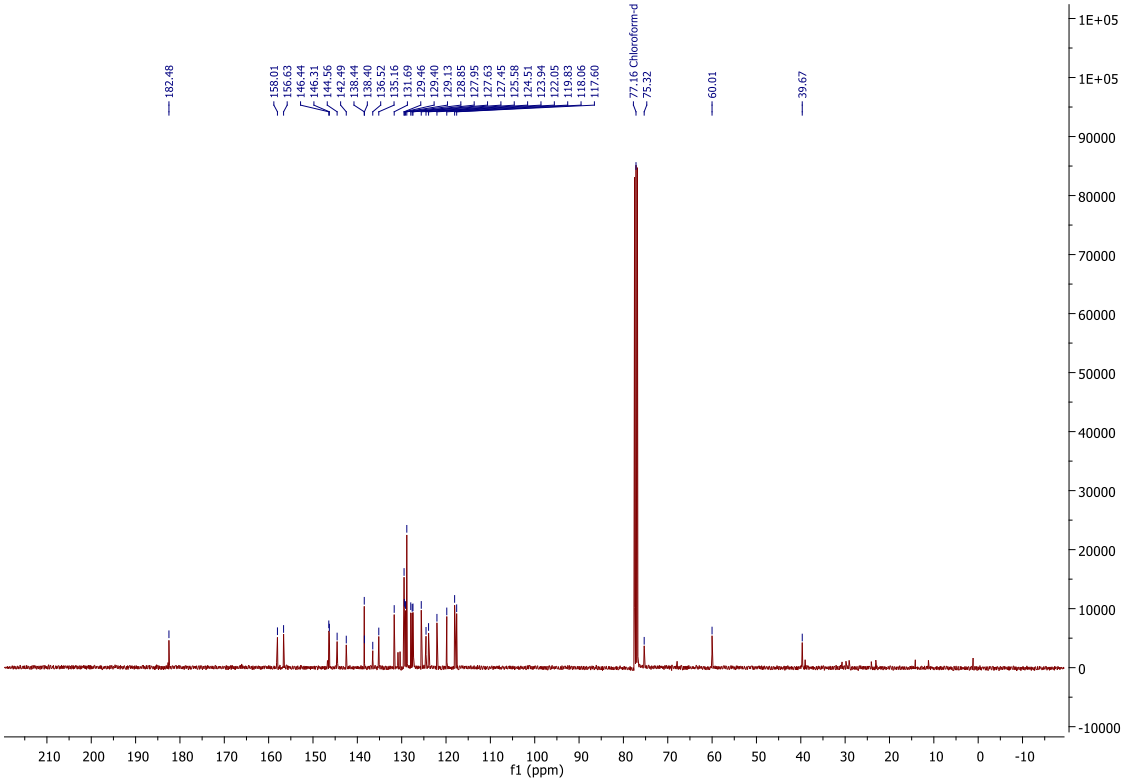
^{13}C{^{1}H} NMR spectra of **(5bca)** ($CDCl_3$, 100 MHz):



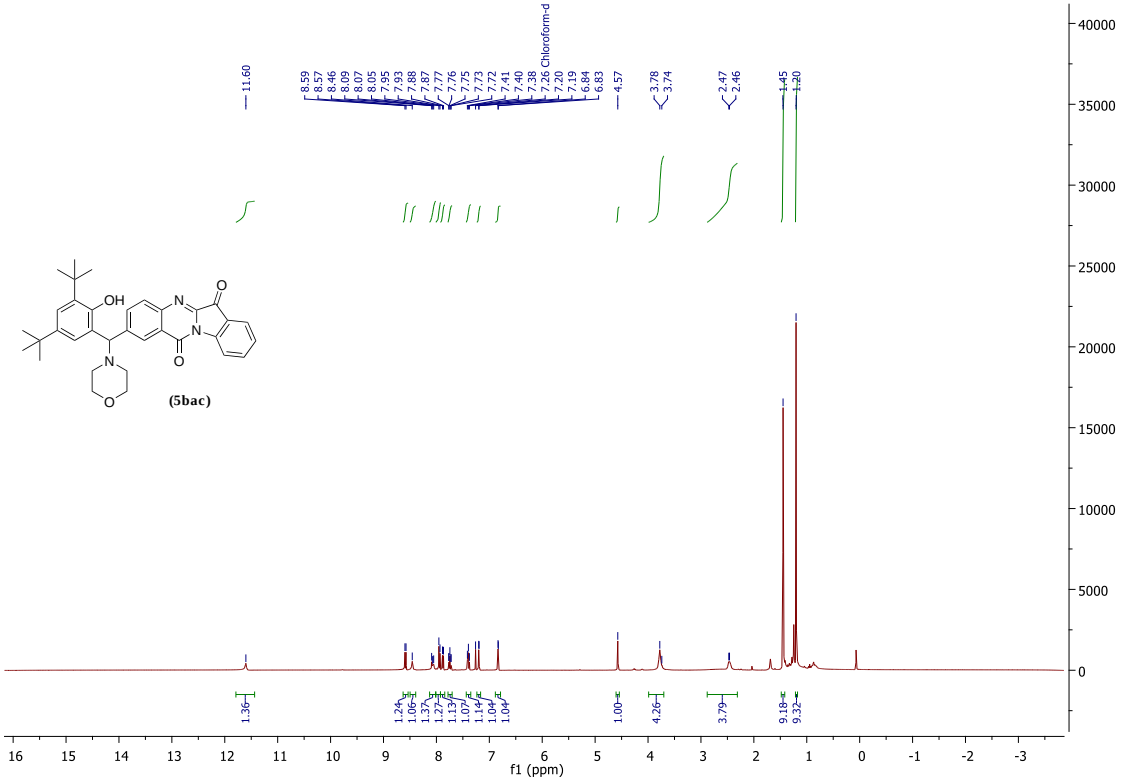
^{1}H NMR Spectra of **(5bea)** (400 MHz, $CDCl_3$):



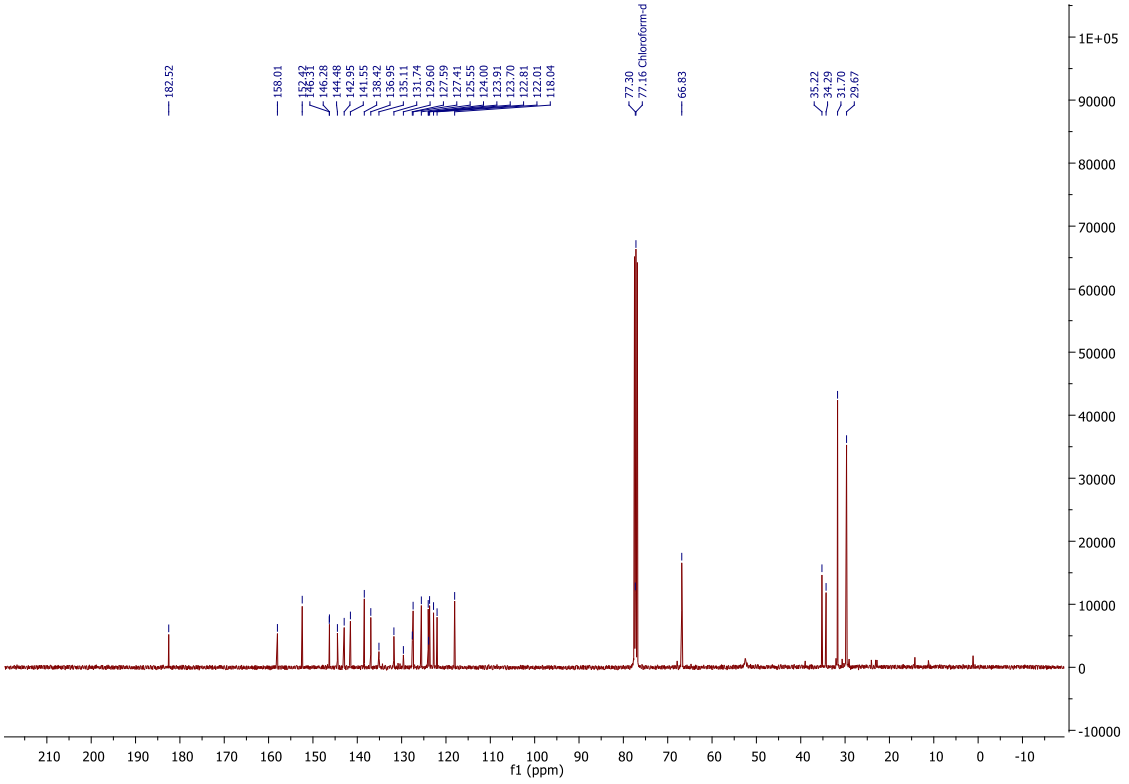
^{13}C{^{1}H} NMR spectra of **(5bea)** ($CDCl_3$, 100 MHz):



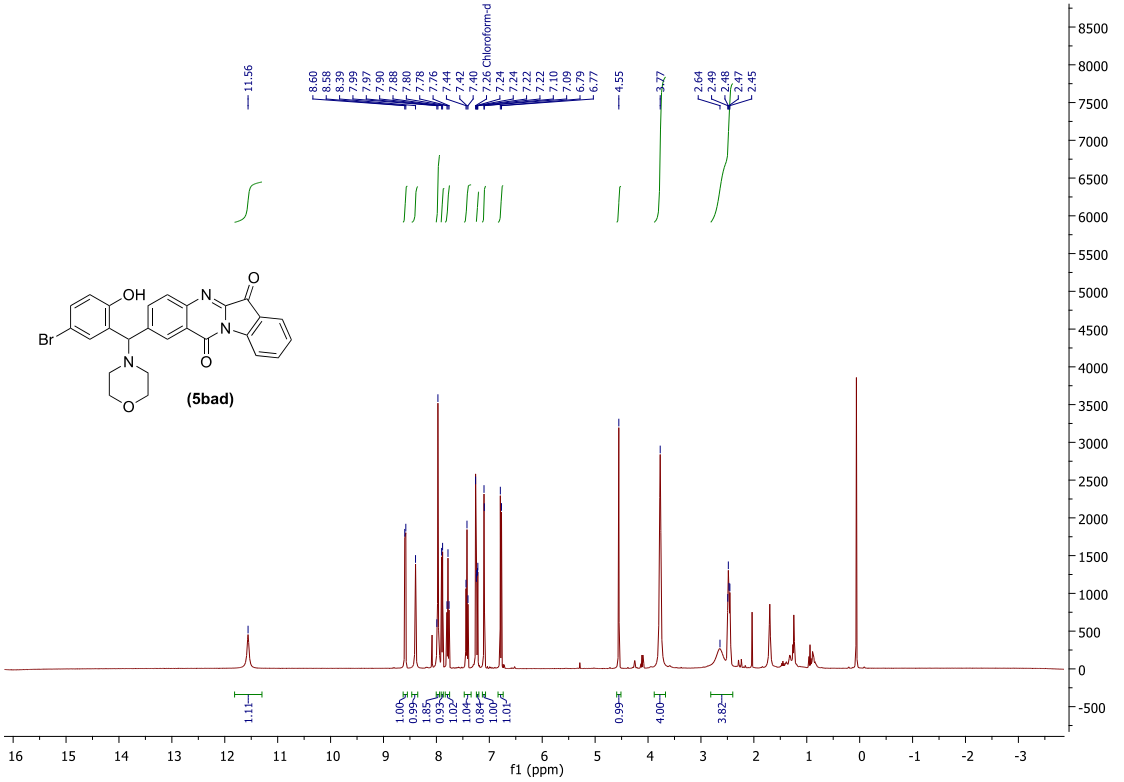
^{1}H NMR Spectra of **(5bac)** (400 MHz, $CDCl_3$):



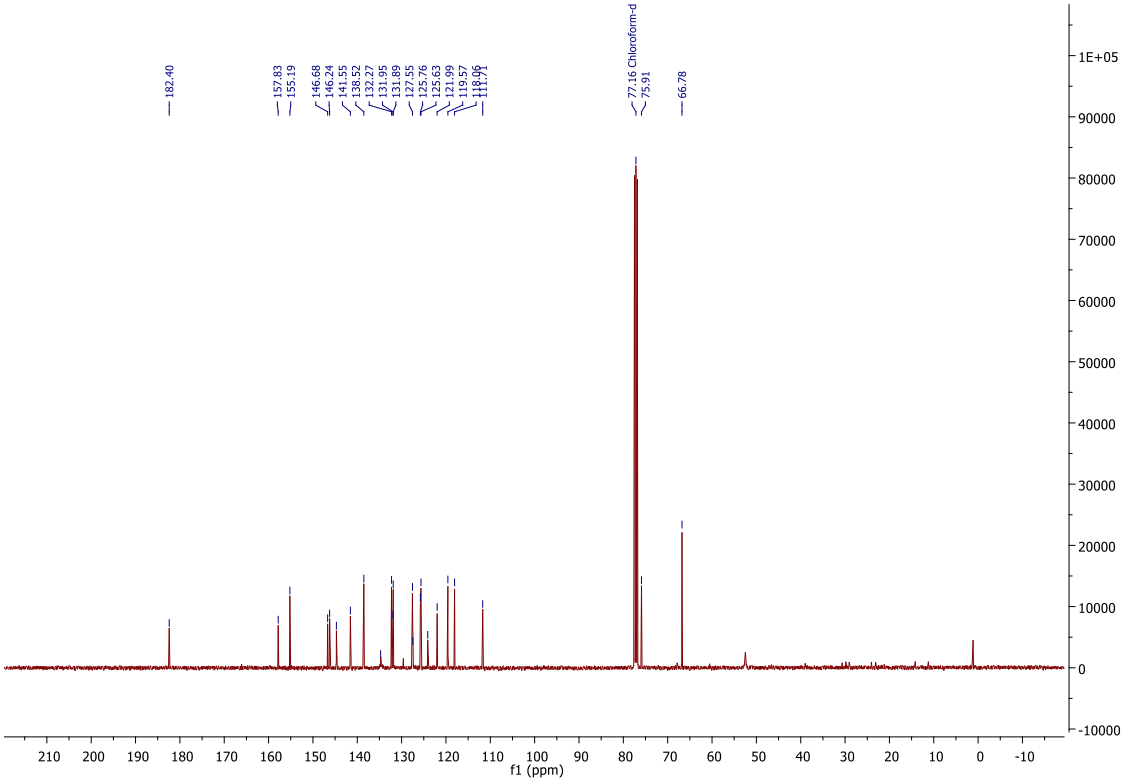
^{13}C{^{1}H} NMR spectra of **(5bac)** ($CDCl_3$, 100 MHz):



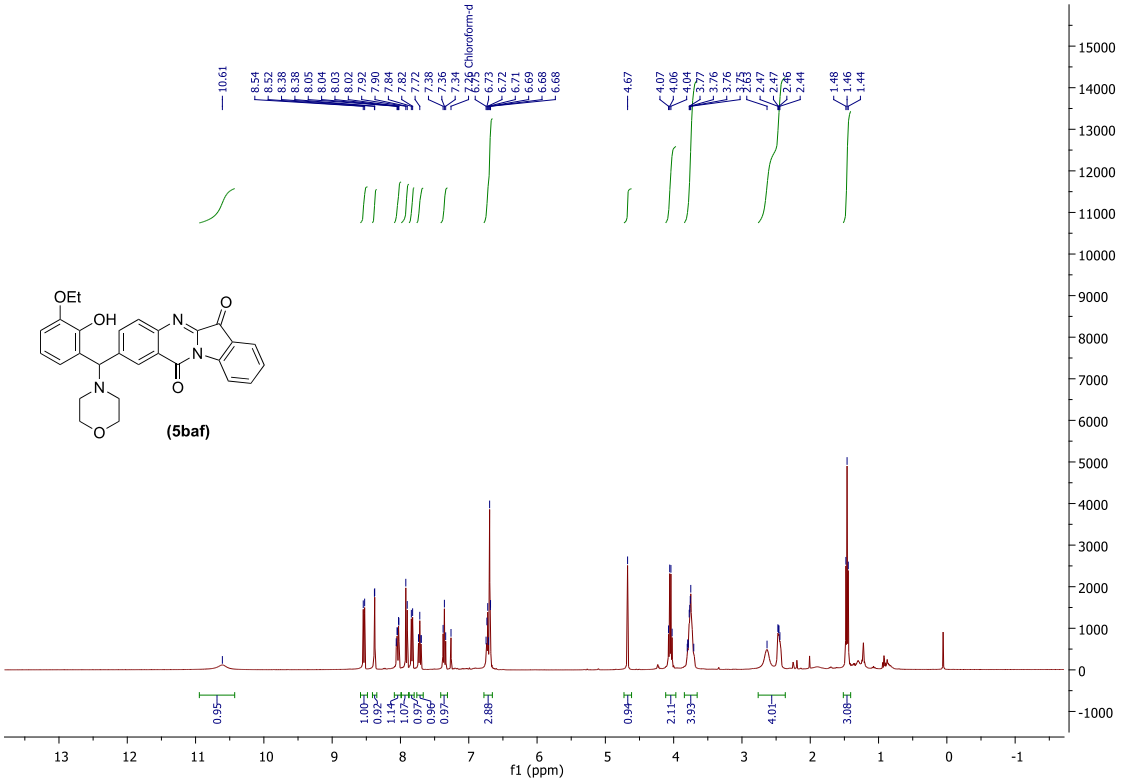
^{1}H NMR Spectra of **(5bad)** (400 MHz, $CDCl_3$):



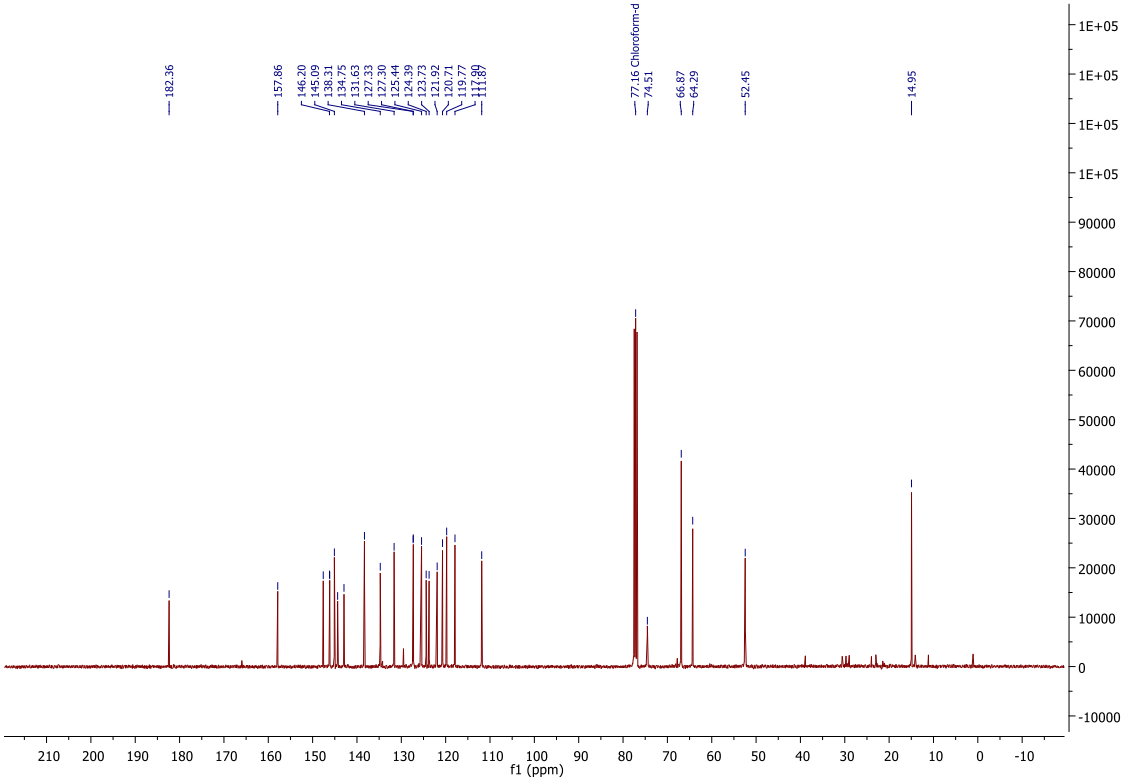
^{13}C{^{1}H} NMR spectra of **(5bad)** ($CDCl_3$, 100 MHz):



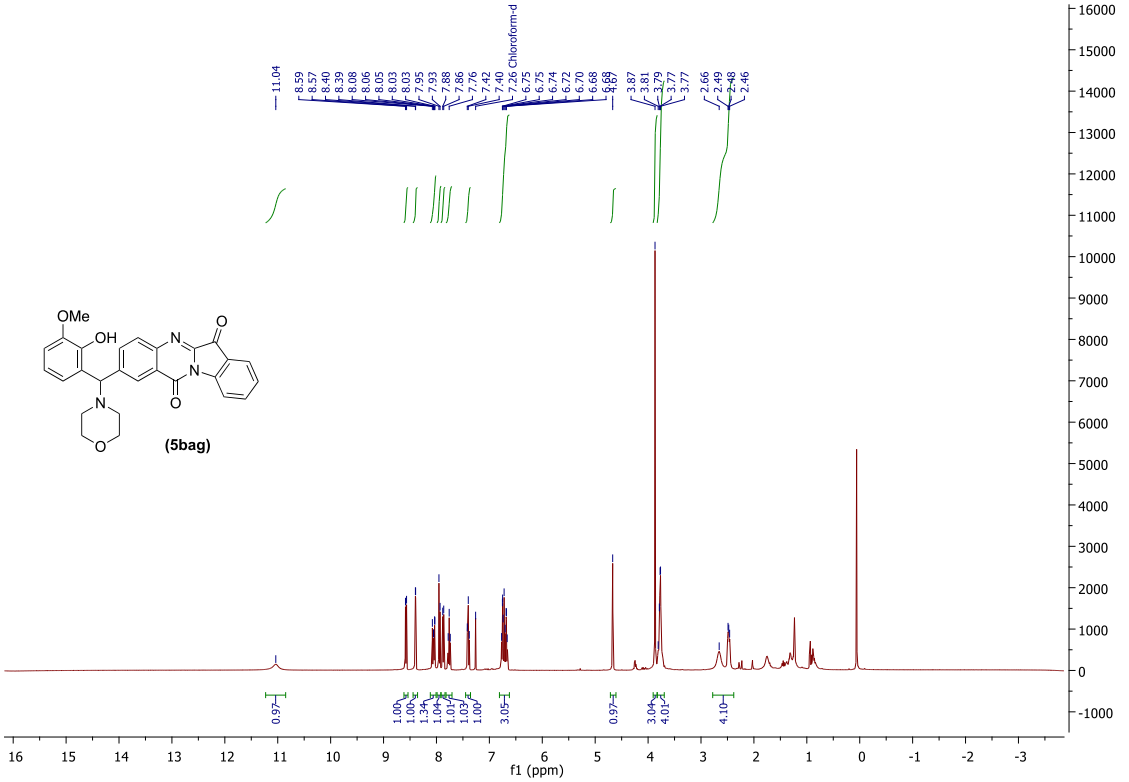
^{1}H NMR Spectra of **(5baf)** (400 MHz, $CDCl_3$):



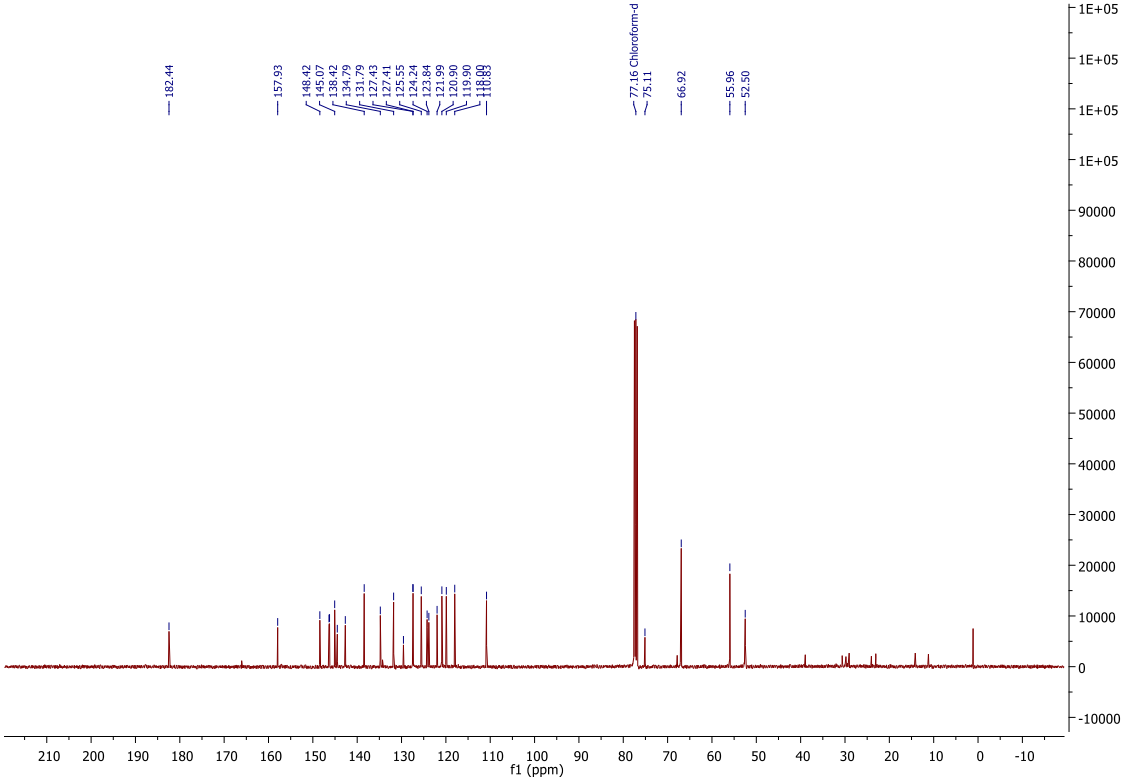
^{13}C{^{1}H} NMR spectra of **(5baf)** ($CDCl_3$, 100 MHz):



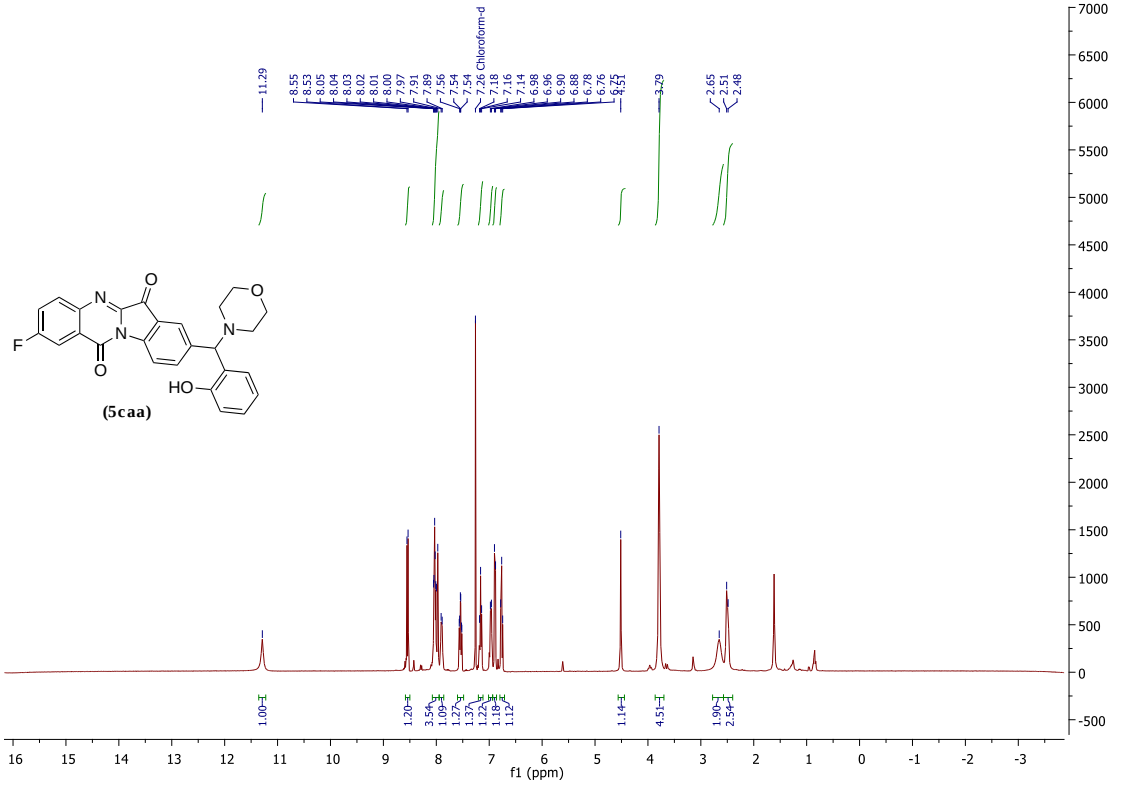
^{1}H NMR Spectra of **(5bag)** (400 MHz, $CDCl_3$):



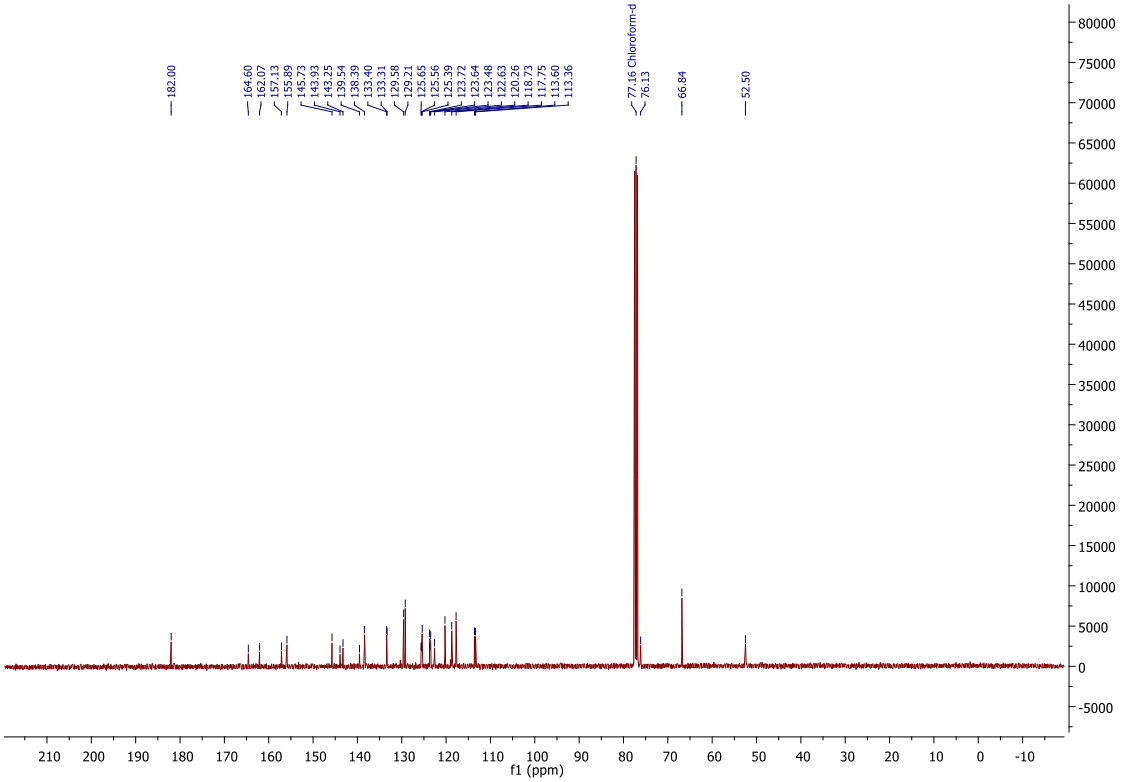
^{13}C{^{1}H} NMR spectra of **(5bag)** ($CDCl_3$, 100 MHz):



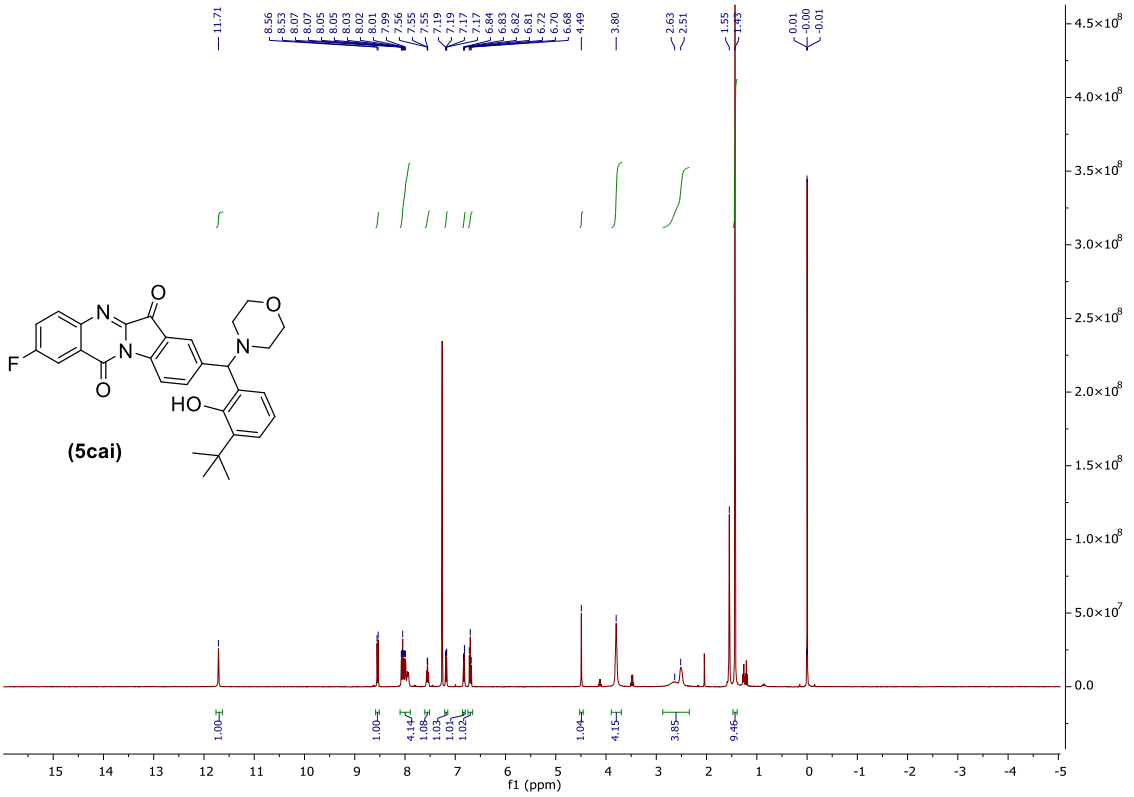
^{1}H NMR Spectra of **(5caa)** (400 MHz, $CDCl_3$):



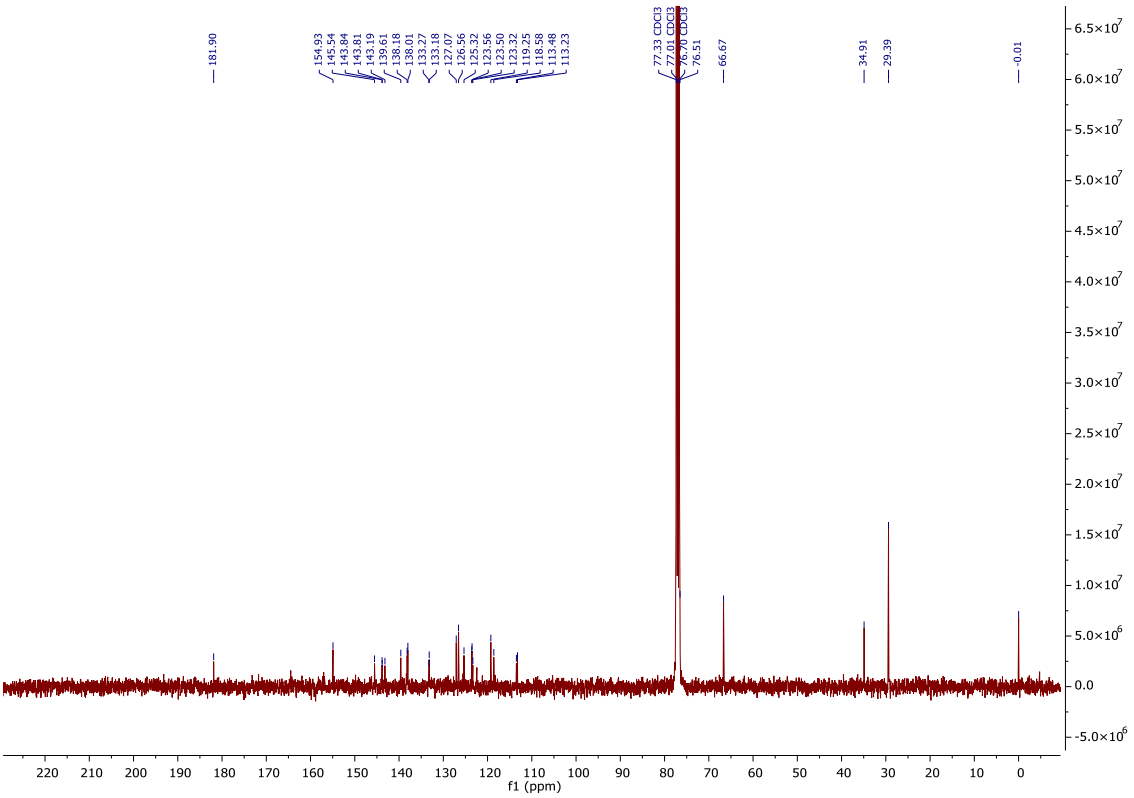
^{13}C{^{1}H} NMR spectra of **(5caa)** ($CDCl_3$, 100 MHz):



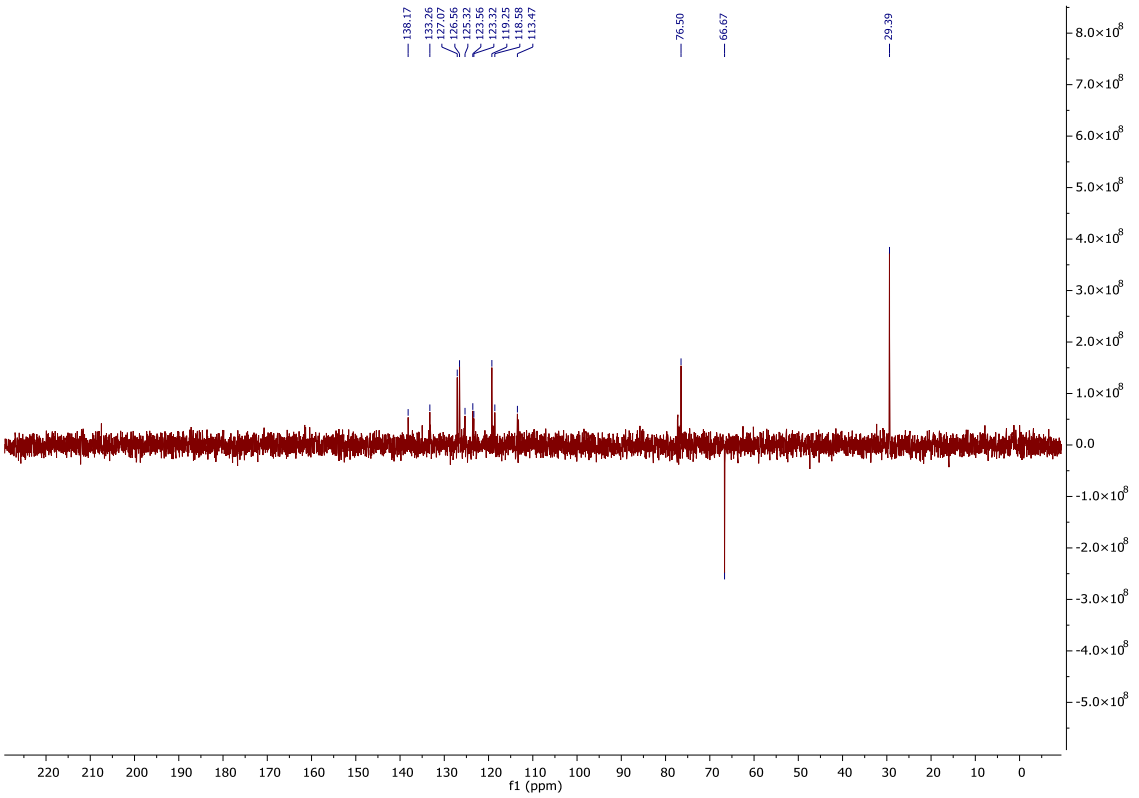
^{1}H NMR Spectra of **(5cai)** (400 MHz, $CDCl_3$):



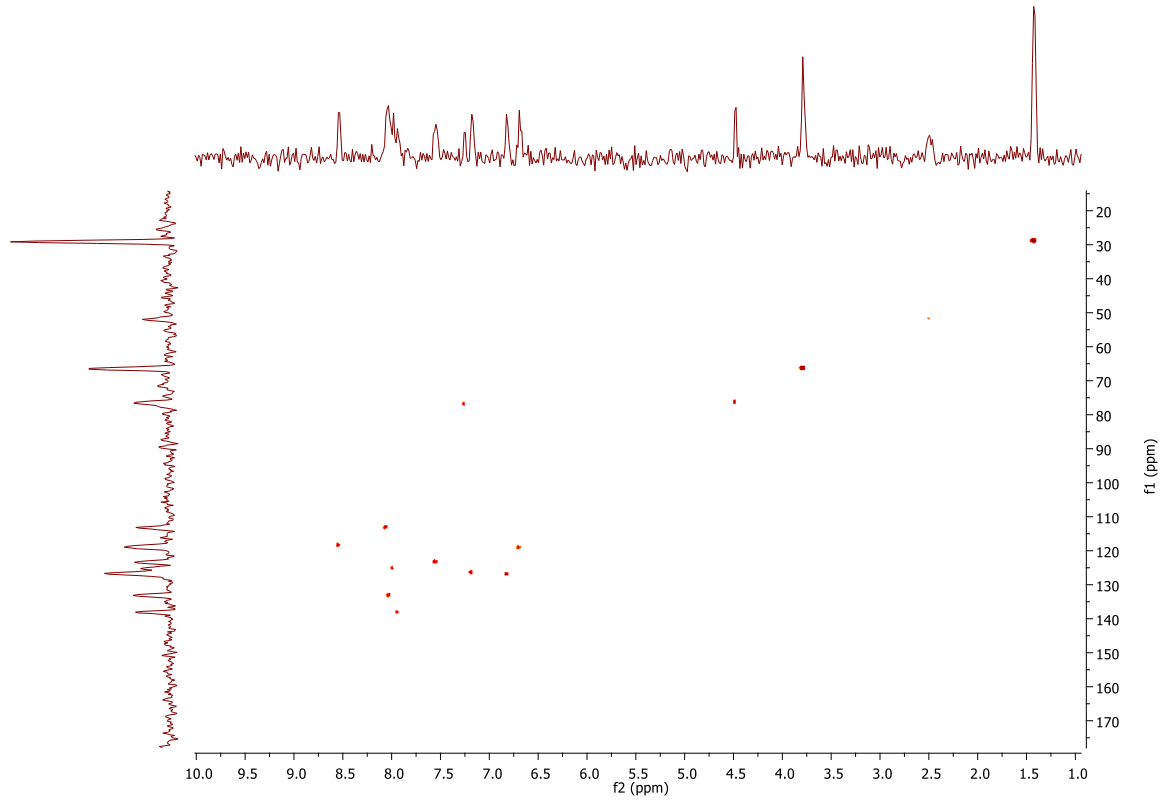
^{13}C{^{1}H} NMR spectra of **(5cai)** ($CDCl_3$, 100 MHz):



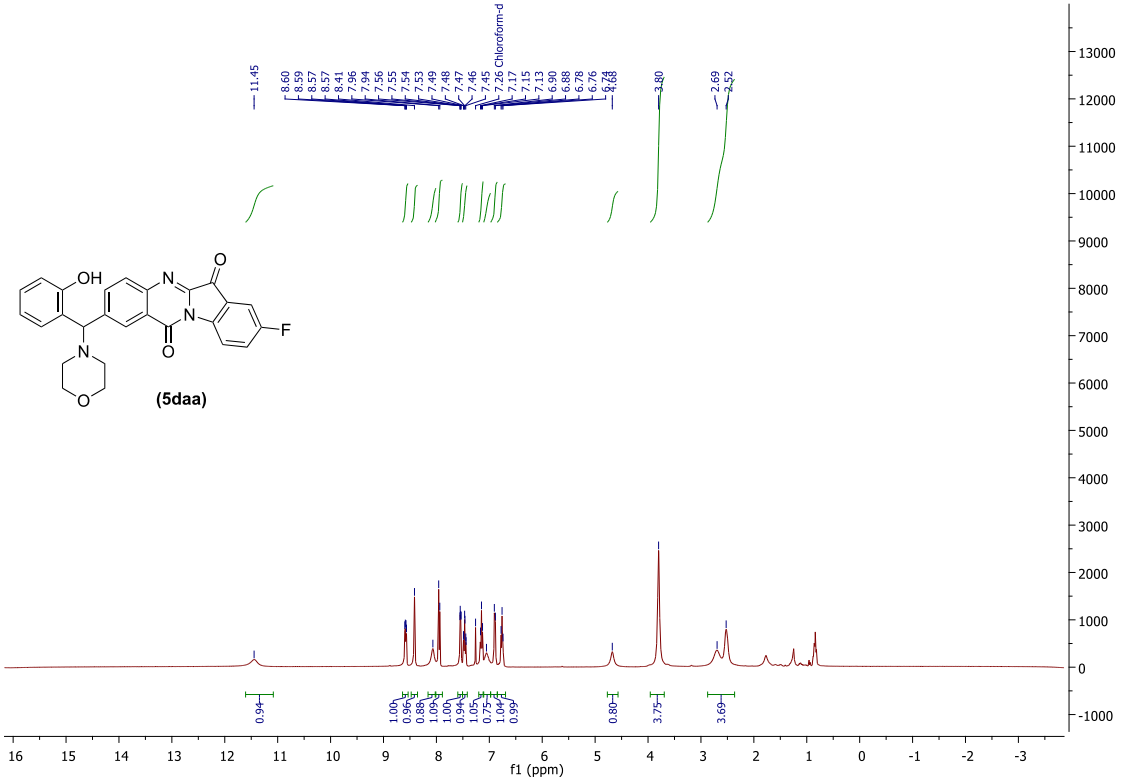
DEPT-135 NMR spectra of **(5cai)** ($CDCl_3$, 100 MHz):



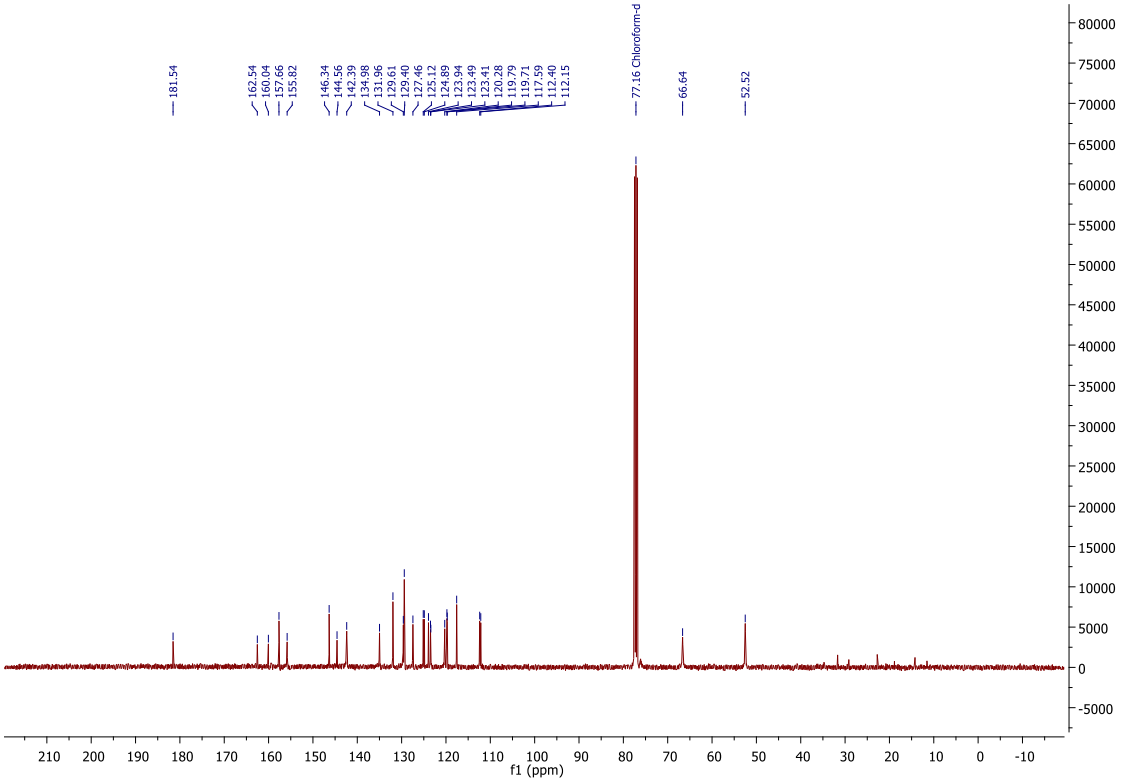
HSQC NMR spectra of **(5cai)** ($CDCl_3$)



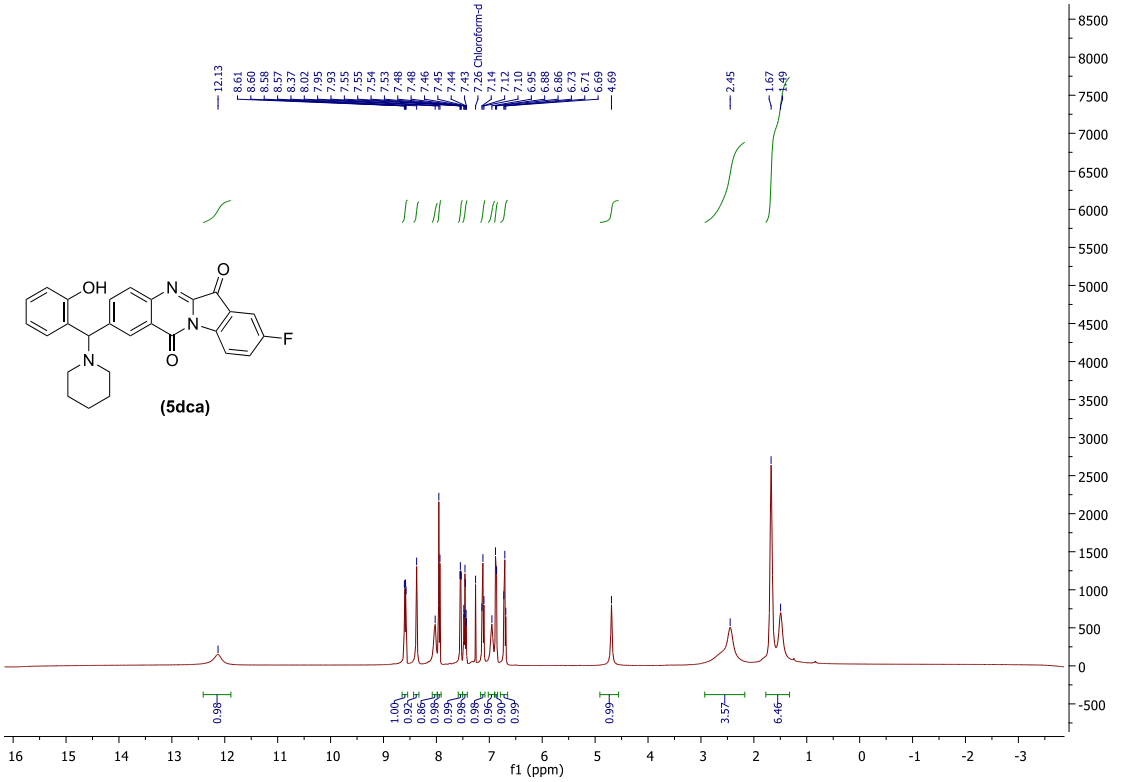
^{1}H NMR Spectra of **(5daa)** (400 MHz, $CDCl_3$):



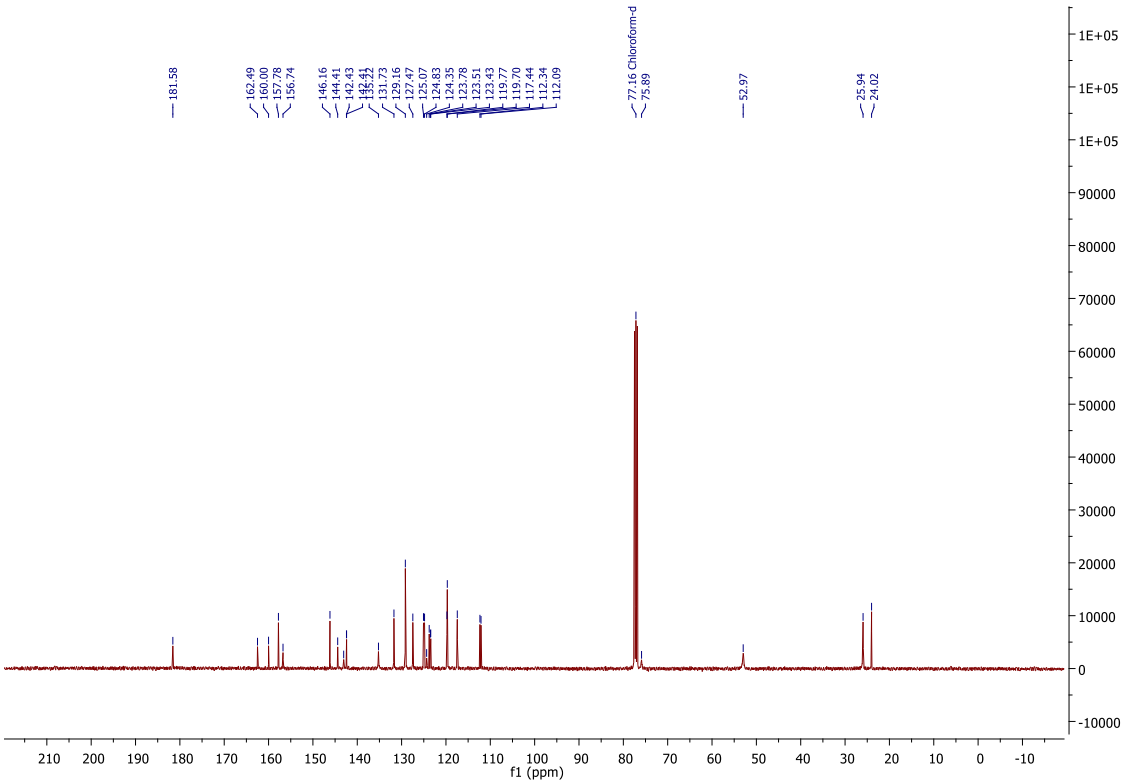
^{13}C{^{1}H} NMR spectra of **(5daa)** ($CDCl_3$, 100 MHz):



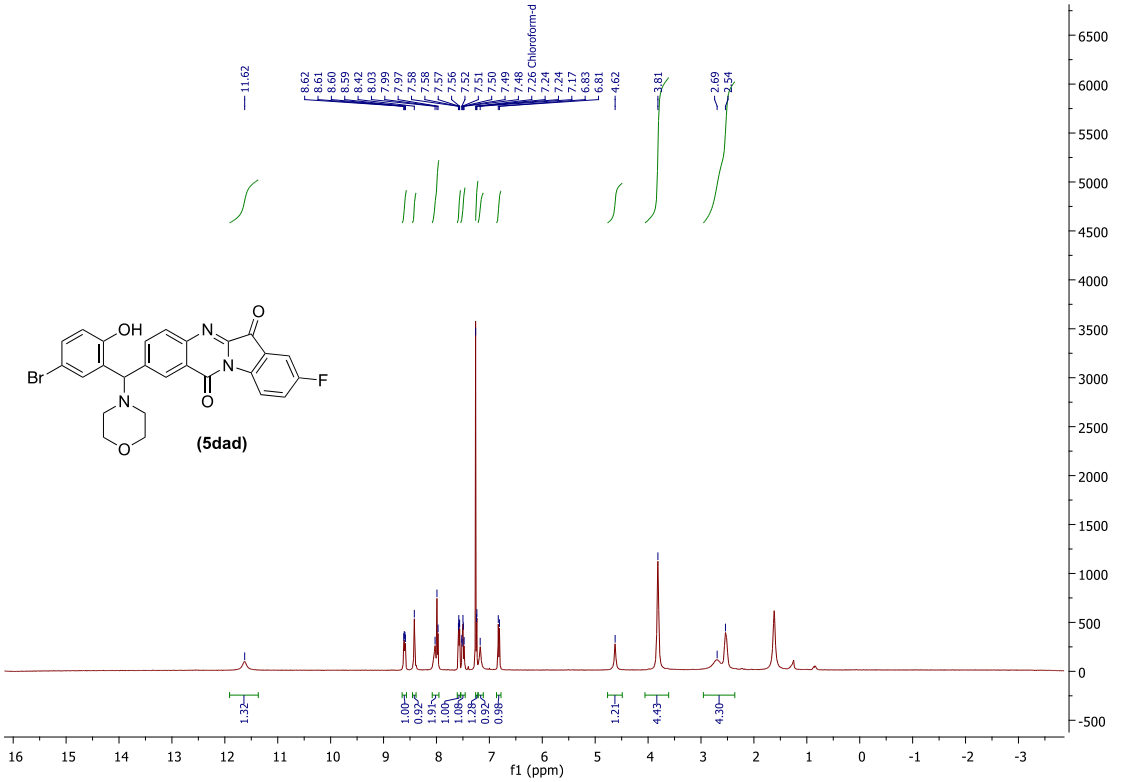
^{1}H NMR Spectra of **(5dca)** (400 MHz, $CDCl_3$):



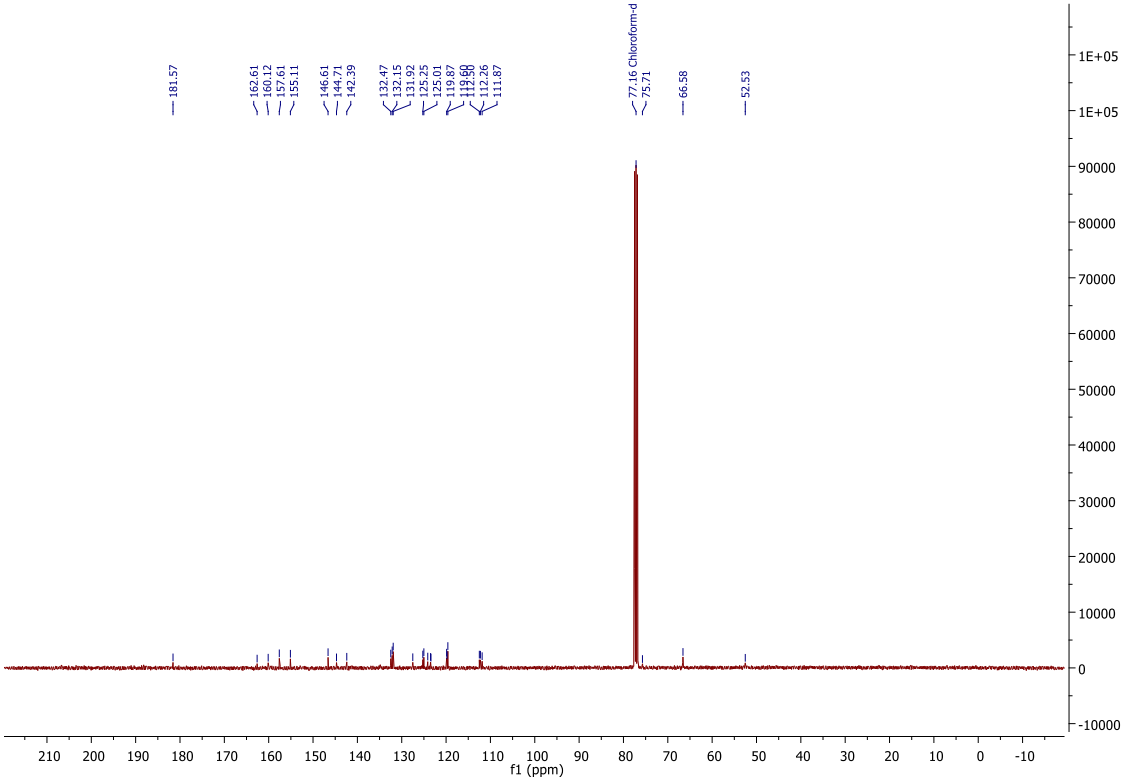
^{13}C{^{1}H} NMR spectra of **(5dca)** ($CDCl_3$, 100 MHz):



^{1}H NMR Spectra of **(5dad)** (400 MHz, $CDCl_3$):



^{13}C{^{1}H} NMR spectra of **(5dad)** ($CDCl_3$, 100 MHz):



6. Antimicrobial Activity Evaluation

Media and microbial strains

To guarantee the purity and optimal growth, the fungal and bacterial strains were sub-cultured before each assay: yeasts and filamentous fungi on Sabouraud dextrose agar (SDA, bioMérieux, Marcy l'Etoile, France), incubated at 35 °C/24-48 h; dermatophytes on Mycosel agar (MYC, Becton Dickinson, Maryland, USA), incubated for 5–7 days/25 °C; bacteria on Mueller–Hinton agar (MHA, Liofilchem, Roseto degli Abruzzi, Italy), incubated for 24 h/35 °C. RPMI-1640 broth medium, with L-glutamine and without NaHCO3 (Biochrom GmbH, Berlin, Germany), was buffered with 0.165 mol/L of 3-(N-morpholino)-propanesulfonic acid (MOPS, Sigma-Aldrich, St. Louis, MO, USA) and used on the evaluation of antifungal activity, after pH being adjusted to 7.0 ± 0.2 with 1 mol/L NaOH. Antibacterial activity was tested using Mueller–Hinton broth 2 (MHB2, Becton Dickinson, Maryland, US).

The antifungal activity was evaluated against nine fungal strains: two yeasts (Candida albicans ATCC 10231 and Candida krusei ATCC 6258); three filamentous fungi (Aspergillus fumigatus ATCC 204305, Aspergillus niger ATCC 16404 and Mucor spp.); four clinical dermatophyte strains Trichophyton rubrum FF5, Trichophyton mentagrophytes FF7, Microsporum canis FF1, and Nannizzia gypsea FF3 (formerly Microsporum gypseum). The antibacterial activity was evaluated against Gram-negative bacteria (Escherichia coli ATCC 25922) and Gram-positive bacteria (Staphylococcus aureus ATCC 25923).

Antimicrobial susceptibility testing

The minimum inhibitory concentrations (MICs) and minimal lethal concentrations (MLCs) were used for defining the antimicrobial activity in agreement with the references of the Clinical and Laboratory Standards Institute (CLSI) for broth microdilution tests, with minor modifications [1]: M27-A3 for yeasts, M38-A2 for filamentous fungi and dermatophytes and M100-A25 for bacteria.

A stock solution of the tryptanthrin derivatives was prepared in dimethylsulfoxide (DMSO, Sigma-Aldrich, St. Louis, MO, US). Two-fold serial dilutions in RPMI for fungi and in MHB2 for bacteria were prepared (concentration range 32-512 µg/mL) and distributed in sterile and disposable 96 flat bottom wells microtiter plates. The final concentration of DMSO, used in growth control, did not interfere on the bacterial/fungal growth. Furthermore, other two controls were performed: a sterility control and a quality control, performed with an ATCC reference strain, bacteria with gentamicin (Sigma-Aldrich,

Seelze, Germany) and yeast with voriconazole (kindly provided by Pfizer). Equal volumes of cell suspension and sample dilutions were added in the wells.
MICs were determined as the lowest concentrations resulting in 100% growth inhibition, in comparison to the sample-free controls. From wells showing no visible growth, 10 µL of culture were collected and deposited on MHA plates (for bacteria) and SDA (for fungi) to evaluate the MLC, defined as the lowest concentration at which no colonies grew after an incubation of 16–18 h/35 °C for bacteria, 48 h/35 °C for yeasts, Aspergillus and Mucor, and 5 days/25 °C for dermatophytes.
The compounds were tested at least two times.

Antibacterial Susceptibility Testing

Pure cultures on MHA/24 h were used to obtain a cell suspensions in sterile saline at a MacFarland standard of 0.5 (530 nm), corresponding to 1-5 × 106 cells/mL. The suspension was then diluted in MHB2 to get an inoculum suspension of 1-5 × 104 CFU/mL. The plates were incubated aerobically/35 °C/24 h. Gentamicine (0.06–4 µg/mL) and E. coli (ATCC 25922) were used as a quality control, results being within the recommended limits defined by CLSI.

Antifungal Susceptibility Testing

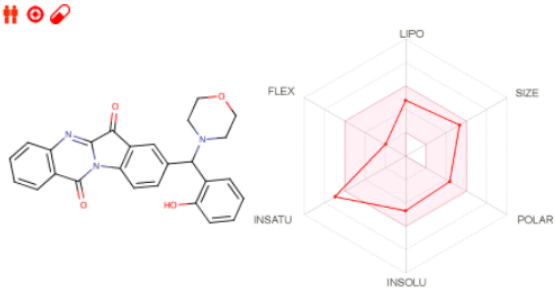
Yeast cells suspensions were prepared from pure cultures on SDA/24 h, in sterile saline solution and adjusted to MacFarland standard of 0.5 at 530 nm, corresponding to an initial suspension of 1-5 × 106 CFU/mL. This suspension was diluted in RPMI to obtain an inoculum of 1-5 × 103 CFU/mL. For filamentous fungi, a spore suspension was prepared from pure culture with spores in SDA (Aspergillus and Mucor) or MYC (dermatophytes) in sterile saline with one drop of TW20 added. The spores density was evaluated by the spore count and diluted in RPMI to obtain 1-3 × 103 CFU/mL for dermatophytes and 0.4-5 × 104 CFU/mL for Aspergillus and Mucor. The plates were incubated aerobically at 35 °C/48 h for C. albicans, Aspergillus and Mucor, and at 25 °C/5–7 days for the dermatophytes. Voriconazole (0.06–2 µg/mL) and C. krusei ATCC 6258 were used as a quality control, results being within the recommended limits defined by CLSI.

References:

[1] CLSI. Clinical and Laboratory Standard Institute, Reference Method for Dilution Antimicrobial Susceptibility Tests. Wayne, PA. Clin. Lab. Stand. Inst. 28. CLSI Document M07-A8 for bacteria, M27-A3 for yeasts and M38–A2 for filamentous fungi.

7. SwissADME evaluation of the tryptanthrin-based Petasis adducts

5aaa

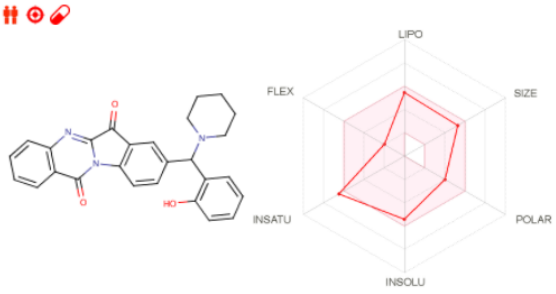


SMILES Oc1ccccc1C(c1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)cccc2)N1CCOCC1

Physicochemical Properties	
Formula	C26H21N3O4
Molecular weight	439.46 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	127.26
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.23
Log $P_{o/w}$ (XLOGP3)	2.85
Log $P_{o/w}$ (WLOGP)	2.35
Log $P_{o/w}$ (MLOGP)	1.90
Log $P_{o/w}$ (SILICOS-IT)	3.61
Consensus Log $P_{o/w}$	2.79

Water Solubility	
Log *S* (ESOL)	-4.66
Solubility	9.71e-03 mg/ml ; 2.21e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.29
Solubility	2.27e-02 mg/ml ; 5.17e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.15
Solubility	3.11e-05 mg/ml ; 7.08e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.96 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.89

5aca

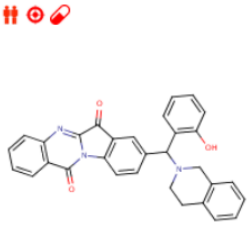


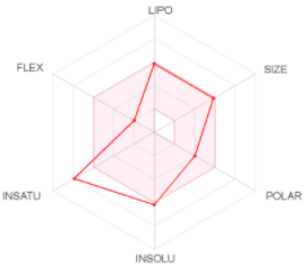
SMILES Oc1ccccc1C(c1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)cccc2)N1CCCCC1

Physicochemical Properties	
Formula	C27H23N3O3
Molecular weight	437.49 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	3
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	130.98
TPSA	75.43 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.49
Log $P_{o/w}$ (XLOGP3)	4.07
Log $P_{o/w}$ (WLOGP)	3.51
Log $P_{o/w}$ (MLOGP)	2.90
Log $P_{o/w}$ (SILICOS-IT)	4.26
Consensus Log $P_{o/w}$	3.65

Water Solubility	
Log *S* (ESOL)	-5.41
Solubility	1.69e-03 mg/ml ; 3.87e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.36
Solubility	1.92e-03 mg/ml ; 4.38e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.69
Solubility	8.93e-06 mg/ml ; 2.04e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.08 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.93

5ada



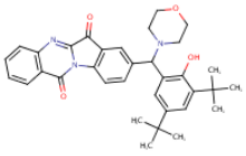


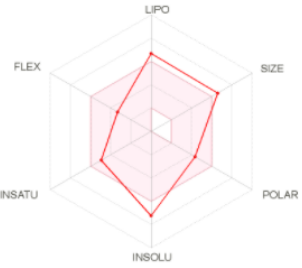
SMILES Oc1ccccc1C(c1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)cccc2)N1CCc2c(C1)cccc2

Physicochemical Properties	
Formula	C31H23N3O3
Molecular weight	485.53 g/mol
Num. heavy atoms	37
Num. arom. heavy atoms	28
Fraction Csp3	0.13
Num. rotatable bonds	3
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	146.01
TPSA	75.43 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.76
Log $P_{o/w}$ (XLOGP3)	4.76
Log $P_{o/w}$ (WLOGP)	3.93
Log $P_{o/w}$ (MLOGP)	3.48
Log $P_{o/w}$ (SILICOS-IT)	5.09
Consensus Log $P_{o/w}$	4.20

Water Solubility	
Log *S* (ESOL)	-6.21
Solubility	2.99e-04 mg/ml ; 6.15e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-6.07
Solubility	4.09e-04 mg/ml ; 8.42e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.60
Solubility	1.22e-07 mg/ml ; 2.52e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.88 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.16

5aac



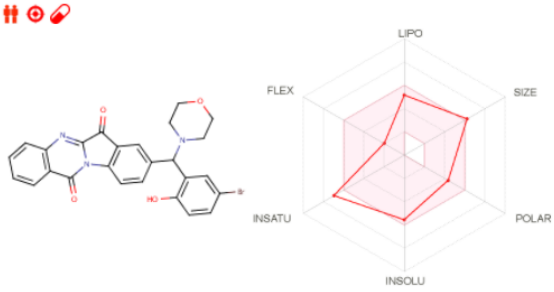


SMILES O=C1c2nc3ccccc3c(=O)n2c2c1cc(cc2)C(c1cc(cc(c1O)C(C)(C)C)C(C)(C)C)N1CCOCC1

Physicochemical Properties	
Formula	C34H37N3O4
Molecular weight	551.68 g/mol
Num. heavy atoms	41
Num. arom. heavy atoms	22
Fraction Csp3	0.38
Num. rotatable bonds	5
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	165.80
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.63
Log $P_{o/w}$ (XLOGP3)	6.20
Log $P_{o/w}$ (WLOGP)	4.95
Log $P_{o/w}$ (MLOGP)	3.44
Log $P_{o/w}$ (SILICOS-IT)	6.44
Consensus Log $P_{o/w}$	5.13

Water Solubility	
Log *S* (ESOL)	-7.23
Solubility	3.22e-05 mg/ml ; 5.84e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.76
Solubility	9.53e-06 mg/ml ; 1.73e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.45
Solubility	1.98e-07 mg/ml ; 3.59e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.26 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.84

5aad

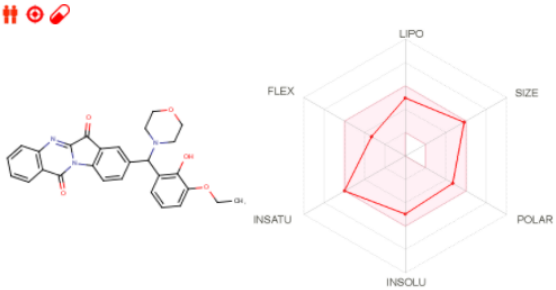


SMILES Brc1ccc(c(c1)C(c1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)cccc2)N1CCOCC1)O

Physicochemical Properties	
Formula	C26H20BrN3O4
Molecular weight	518.36 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	134.96
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.55
Log $P_{o/w}$ (XLOGP3)	3.54
Log $P_{o/w}$ (WLOGP)	3.11
Log $P_{o/w}$ (MLOGP)	2.20
Log $P_{o/w}$ (SILICOS-IT)	4.29
Consensus Log $P_{o/w}$	3.34

Water Solubility	
Log *S* (ESOL)	-5.56
Solubility	1.41e-03 mg/ml ; 2.72e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.00
Solubility	5.15e-03 mg/ml ; 9.94e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.92
Solubility	6.28e-06 mg/ml ; 1.21e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.95 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.95

5aaf

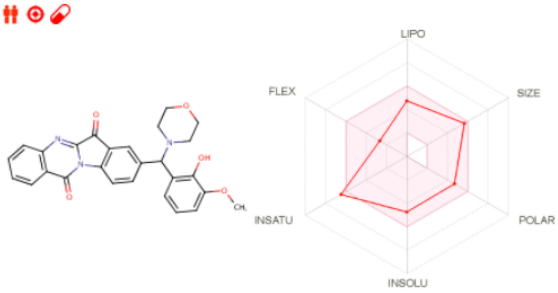


SMILES CCOc1cccc(c1O)C(c1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)cccc2)N1CCOCC1

Physicochemical Properties	
Formula	C28H25N3O5
Molecular weight	483.52 g/mol
Num. heavy atoms	36
Num. arom. heavy atoms	22
Fraction Csp3	0.25
Num. rotatable bonds	5
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	138.56
TPSA	93.89 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.70
Log $P_{o/w}$ (XLOGP3)	3.19
Log $P_{o/w}$ (WLOGP)	2.75
Log $P_{o/w}$ (MLOGP)	1.78
Log $P_{o/w}$ (SILICOS-IT)	4.07
Consensus Log $P_{o/w}$	3.10

Water Solubility	
Log *S* (ESOL)	-4.97
Solubility	5.18e-03 mg/ml ; 1.07e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.83
Solubility	7.10e-03 mg/ml ; 1.47e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.64
Solubility	1.12e-05 mg/ml ; 2.31e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.98 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	4.20

5aagc

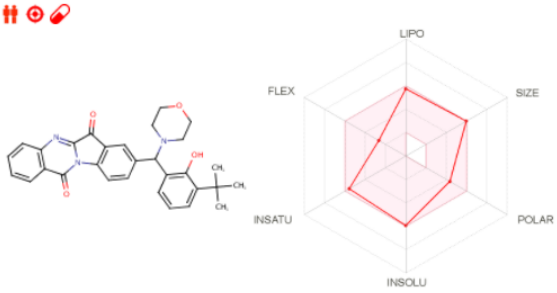


SMILES COc1cccc(c1O)C(c1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)cccc2)N1CCOCC1

Physicochemical Properties	
Formula	C27H23N3O5
Molecular weight	469.49 g/mol
Num. heavy atoms	35
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	4
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	133.75
TPSA	93.89 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.45
Log $P_{o/w}$ (XLOGP3)	2.82
Log $P_{o/w}$ (WLOGP)	2.36
Log $P_{o/w}$ (MLOGP)	1.58
Log $P_{o/w}$ (SILICOS-IT)	3.67
Consensus Log $P_{o/w}$	2.78

Water Solubility	
Log *S* (ESOL)	-4.73
Solubility	8.77e-03 mg/ml ; 1.87e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.45
Solubility	1.67e-02 mg/ml ; 3.55e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.25
Solubility	2.66e-05 mg/ml ; 5.66e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.16 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	4.08

5aai

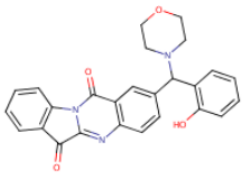


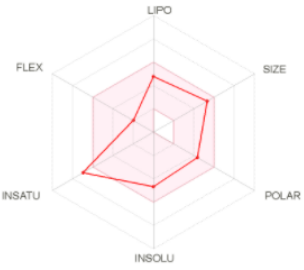
SMILES O=C1c2nc3ccccc3c(=O)n2c2c1cc(cc2)C(c1cccc(c1O)C(C)(C)C)N1CCOCC1

Physicochemical Properties	
Formula	C30H29N3O4
Molecular weight	495.57 g/mol
Num. heavy atoms	37
Num. arom. heavy atoms	22
Fraction Csp3	0.30
Num. rotatable bonds	4
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	146.53
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.99
Log $P_{o/w}$ (XLOGP3)	4.53
Log $P_{o/w}$ (WLOGP)	3.65
Log $P_{o/w}$ (MLOGP)	2.69
Log $P_{o/w}$ (SILICOS-IT)	5.01
Consensus Log $P_{o/w}$	3.97

Water Solubility	
Log *S* (ESOL)	-5.94
Solubility	5.66e-04 mg/ml ; 1.14e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.03
Solubility	4.63e-04 mg/ml ; 9.34e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.30
Solubility	2.48e-06 mg/ml ; 5.00e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.11 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.36

5baa



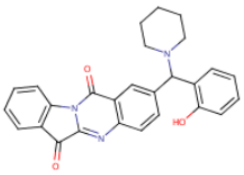


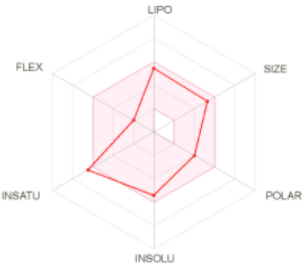
SMILES Oc1ccccc1C(c1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1cccc2)N1CCOCC1

Physicochemical Properties	
Formula	C26H21N3O4
Molecular weight	439.46 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	127.26
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.21
Log $P_{o/w}$ (XLOGP3)	2.85
Log $P_{o/w}$ (WLOGP)	2.35
Log $P_{o/w}$ (MLOGP)	2.31
Log $P_{o/w}$ (SILICOS-IT)	3.61
Consensus Log $P_{o/w}$	2.87

Water Solubility	
Log *S* (ESOL)	-4.66
Solubility	9.71e-03 mg/ml ; 2.21e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.29
Solubility	2.27e-02 mg/ml ; 5.17e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.15
Solubility	3.11e-05 mg/ml ; 7.08e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.96 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.86

5bca





SMILES Oc1ccccc1C(c1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1cccc2)N1CCCCC1

Physicochemical Properties	
Formula	C27H23N3O3
Molecular weight	437.49 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	3
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	130.98
TPSA	75.43 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.49
Log $P_{o/w}$ (XLOGP3)	4.07
Log $P_{o/w}$ (WLOGP)	3.51
Log $P_{o/w}$ (MLOGP)	3.31
Log $P_{o/w}$ (SILICOS-IT)	4.26
Consensus Log $P_{o/w}$	3.73

Water Solubility	
Log *S* (ESOL)	-5.41
Solubility	1.69e-03 mg/ml ; 3.87e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.36
Solubility	1.92e-03 mg/ml ; 4.38e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.69
Solubility	8.93e-06 mg/ml ; 2.04e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.08 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.90

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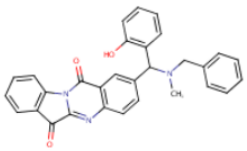
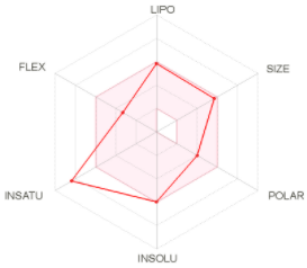


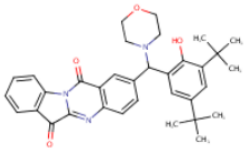


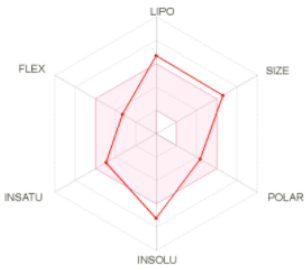
SMILES Oc1ccccc1C(c1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1cccc2)N(Cc1ccccc1)C

Physicochemical Properties	
Formula	C30H23N3O3
Molecular weight	473.52 g/mol
Num. heavy atoms	36
Num. arom. heavy atoms	28
Fraction Csp3	0.10
Num. rotatable bonds	5
Num. H-bond acceptors	5
Num. H-bond donors	1
Molar Refractivity	139.25
TPSA	75.43 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.43
Log $P_{o/w}$ (XLOGP3)	4.72
Log $P_{o/w}$ (WLOGP)	4.38
Log $P_{o/w}$ (MLOGP)	3.69
Log $P_{o/w}$ (SILICOS-IT)	4.85
Consensus Log $P_{o/w}$	4.21

Water Solubility	
Log *S* (ESOL)	-5.99
Solubility	4.79e-04 mg/ml ; 1.01e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-6.03
Solubility	4.39e-04 mg/ml ; 9.26e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.57
Solubility	1.26e-07 mg/ml ; 2.67e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.84 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.05

5bac



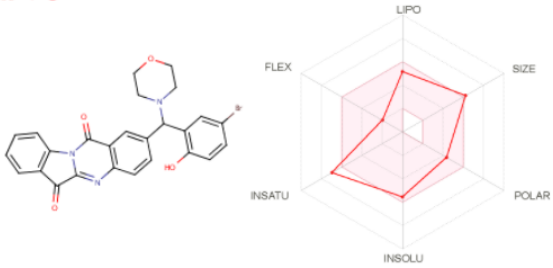


SMILES O=C1c2nc3ccc(cc3c(=O)n2c2c1cccc2)C(c1cc(cc(c1O)C(C)(C)C)C(C)(C)C)N1CCOCC1

Physicochemical Properties	
Formula	C34H37N3O4
Molecular weight	551.68 g/mol
Num. heavy atoms	41
Num. arom. heavy atoms	22
Fraction Csp3	0.38
Num. rotatable bonds	5
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	165.80
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.72
Log $P_{o/w}$ (XLOGP3)	6.20
Log $P_{o/w}$ (WLOGP)	4.95
Log $P_{o/w}$ (MLOGP)	3.84
Log $P_{o/w}$ (SILICOS-IT)	6.44
Consensus Log $P_{o/w}$	5.23

Water Solubility	
Log *S* (ESOL)	-7.23
Solubility	3.22e-05 mg/ml ; 5.84e-08 mol/l
Class	Poorly soluble
Log *S* (Ali)	-7.76
Solubility	9.53e-06 mg/ml ; 1.73e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-9.45
Solubility	1.98e-07 mg/ml ; 3.59e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-5.26 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.84

5bad

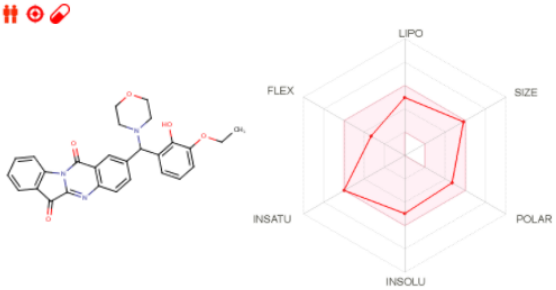


SMILES Brc1ccc(c(c1)C(c1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1cccc2)N1CCOCC1)O

Physicochemical Properties	
Formula	C26H20BrN3O4
Molecular weight	518.36 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	134.96
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.61
Log $P_{o/w}$ (XLOGP3)	3.54
Log $P_{o/w}$ (WLOGP)	3.11
Log $P_{o/w}$ (MLOGP)	2.88
Log $P_{o/w}$ (SILICOS-IT)	4.29
Consensus Log $P_{o/w}$	3.49

Water Solubility	
Log *S* (ESOL)	-5.56
Solubility	1.41e-03 mg/ml ; 2.72e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.00
Solubility	5.15e-03 mg/ml ; 9.94e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.92
Solubility	6.28e-06 mg/ml ; 1.21e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.95 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.92

5baf

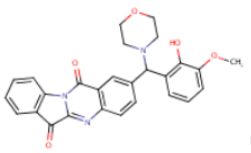


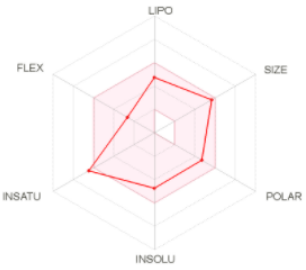
SMILES CCOc1cccc(c1O)C(c1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1cccc2)N1CCOCC1

Physicochemical Properties	
Formula	C28H25N3O5
Molecular weight	483.52 g/mol
Num. heavy atoms	36
Num. arom. heavy atoms	22
Fraction Csp3	0.25
Num. rotatable bonds	5
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	138.56
TPSA	93.89 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.73
Log $P_{o/w}$ (XLOGP3)	3.19
Log $P_{o/w}$ (WLOGP)	2.75
Log $P_{o/w}$ (MLOGP)	2.19
Log $P_{o/w}$ (SILICOS-IT)	4.07
Consensus Log $P_{o/w}$	3.19

Water Solubility	
Log *S* (ESOL)	-4.97
Solubility	5.18e-03 mg/ml ; 1.07e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.83
Solubility	7.10e-03 mg/ml ; 1.47e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.64
Solubility	1.12e-05 mg/ml ; 2.31e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.98 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	4.17

5bag



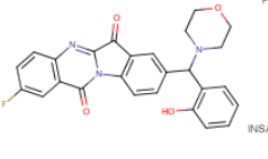


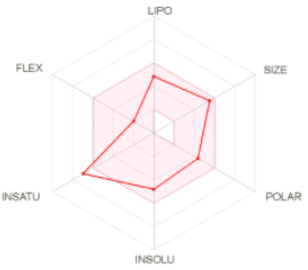
SMILES COc1cccc(c1O)C(c1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1cccc2)N1CCOCC1

Physicochemical Properties	
Formula	C27H23N3O5
Molecular weight	469.49 g/mol
Num. heavy atoms	35
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	4
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	133.75
TPSA	93.89 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.39
Log $P_{o/w}$ (XLOGP3)	2.82
Log $P_{o/w}$ (WLOGP)	2.36
Log $P_{o/w}$ (MLOGP)	1.99
Log $P_{o/w}$ (SILICOS-IT)	3.67
Consensus Log $P_{o/w}$	2.85

Water Solubility	
Log *S* (ESOL)	-4.73
Solubility	8.77e-03 mg/ml ; 1.87e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.45
Solubility	1.67e-02 mg/ml ; 3.55e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.25
Solubility	2.66e-05 mg/ml ; 5.66e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.16 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	4.05

5caa



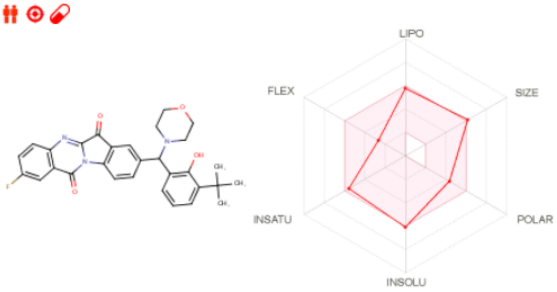


SMILES Fc1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1ccc(c2)C(c1ccccc1O)N1CCOCC1

Physicochemical Properties	
Formula	C26H20FN3O4
Molecular weight	457.45 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	3
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	127.22
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.29
Log $P_{o/w}$ (XLOGP3)	2.95
Log $P_{o/w}$ (WLOGP)	2.91
Log $P_{o/w}$ (MLOGP)	2.27
Log $P_{o/w}$ (SILICOS-IT)	4.03
Consensus Log $P_{o/w}$	3.09

Water Solubility	
Log *S* (ESOL)	-4.82
Solubility	7.00e-03 mg/ml ; 1.53e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.39
Solubility	1.86e-02 mg/ml ; 4.07e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.41
Solubility	1.78e-05 mg/ml ; 3.88e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.00 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.92

5cai



SMILES Fc1ccc2c(c1)c(=O)n1c(n2)C(=O)c2c1ccc(c2)C(c1cccc(c1O)C(C)(C)C)N1CCOCC1

Physicochemical Properties	
Formula	C30H28FN3O4
Molecular weight	513.56 g/mol
Num. heavy atoms	38
Num. arom. heavy atoms	22
Fraction Csp3	0.30
Num. rotatable bonds	4
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	146.49
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.03
Log $P_{o/w}$ (XLOGP3)	4.63
Log $P_{o/w}$ (WLOGP)	4.21
Log $P_{o/w}$ (MLOGP)	3.05
Log $P_{o/w}$ (SILICOS-IT)	5.43
Consensus Log $P_{o/w}$	4.27

Water Solubility	
Log *S* (ESOL)	-6.11
Solubility	4.03e-04 mg/ml ; 7.85e-07 mol/l
Class	Poorly soluble
Log *S* (Ali)	-6.13
Solubility	3.78e-04 mg/ml ; 7.35e-07 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-8.56
Solubility	1.41e-06 mg/ml ; 2.75e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.15 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	4.39

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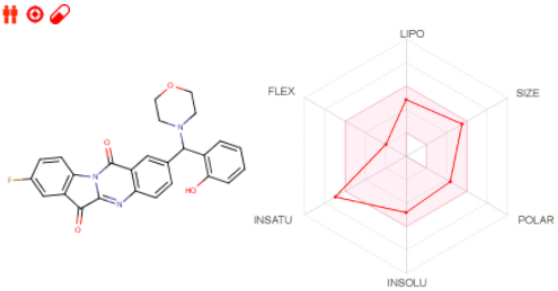
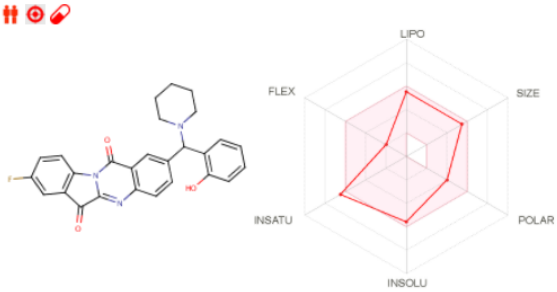


SMILES Fc1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)ccc(c2)C(c1ccccc1O)N1CCOCC1

Physicochemical Properties	
Formula	C26H20FN3O4
Molecular weight	457.45 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	3
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	127.22
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.31
Log $P_{o/w}$ (XLOGP3)	2.95
Log $P_{o/w}$ (WLOGP)	2.91
Log $P_{o/w}$ (MLOGP)	2.68
Log $P_{o/w}$ (SILICOS-IT)	4.03
Consensus Log $P_{o/w}$	3.17

Water Solubility	
Log *S* (ESOL)	-4.82
Solubility	7.00e-03 mg/ml ; 1.53e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.39
Solubility	1.86e-02 mg/ml ; 4.07e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.41
Solubility	1.78e-05 mg/ml ; 3.88e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.00 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	3.89

5dca



SMILES Fc1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)ccc(c2)C(c1ccccc1O)N1CCCCC1

Physicochemical Properties	
Formula	C27H22FN3O3
Molecular weight	455.48 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	22
Fraction Csp3	0.22
Num. rotatable bonds	3
Num. H-bond acceptors	6
Num. H-bond donors	1
Molar Refractivity	130.94
TPSA	75.43 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.60
Log $P_{o/w}$ (XLOGP3)	4.17
Log $P_{o/w}$ (WLOGP)	4.07
Log $P_{o/w}$ (MLOGP)	3.68
Log $P_{o/w}$ (SILICOS-IT)	4.67
Consensus Log $P_{o/w}$	4.04

Water Solubility	
Log *S* (ESOL)	-5.57
Solubility	1.22e-03 mg/ml ; 2.68e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.46
Solubility	1.57e-03 mg/ml ; 3.45e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-7.95
Solubility	5.09e-06 mg/ml ; 1.12e-08 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.12 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.93

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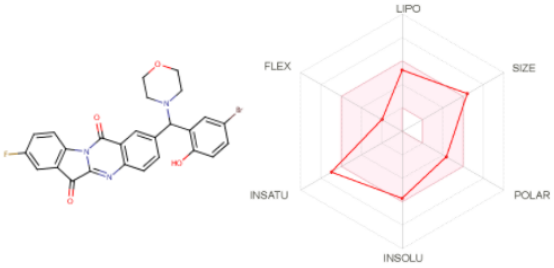

SMILES Fc1ccc2c(c1)C(=O)c1n2c(=O)c2c(n1)ccc(c2)C(c1cc(Br)ccc1O)N1CCOCC1

Physicochemical Properties	
Formula	C26H19BrFN3O4
Molecular weight	536.35 g/mol
Num. heavy atoms	35
Num. arom. heavy atoms	22
Fraction Csp3	0.19
Num. rotatable bonds	3
Num. H-bond acceptors	7
Num. H-bond donors	1
Molar Refractivity	134.92
TPSA	84.66 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.70
Log $P_{o/w}$ (XLOGP3)	3.65
Log $P_{o/w}$ (WLOGP)	3.67
Log $P_{o/w}$ (MLOGP)	3.24
Log $P_{o/w}$ (SILICOS-IT)	4.70
Consensus Log $P_{o/w}$	3.79

Water Solubility	
Log *S* (ESOL)	-5.73
Solubility	9.94e-04 mg/ml ; 1.85e-06 mol/l
Class	Moderately soluble
Log *S* (Ali)	-5.12
Solubility	4.10e-03 mg/ml ; 7.64e-06 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-8.18
Solubility	3.58e-06 mg/ml ; 6.68e-09 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-6.98 cm/s
Druglikeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 2 violations: MW>480, MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	1 alert: mannich_A
Brenk	0 alert
Leadlikeness	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.95