Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Twisting the Ethano-Tröger's Base: The Bisamide

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Supporting Information

1. GENERAL

All reactions were performed in dried apparatus with magnetic stirring under an inert atmosphere of argon or nitrogen. All solvents and chemicals were used as purchased unless stated otherwise. All NMR spectra were recorded on Bruker AV400, AVIII400, AVIIIHD 500 or AVIIIHD 600 spectrometers. ^{1}H and ^{13}C NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to residual unlabelled solvent peak using the Bruker internal referencing procedure (edlock). ^{15}N spectra are referenced relative to NH_3 and the ^{19}F NMR spectra are referenced relative to $CFCl_3$. Coupling constants (*J*) are reported in units of hertz (Hz) and are rounded off. The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), apt (apparent triplet). High-resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI) or on a Waters GC-TOF spectrometer using electron impact (EI). Infrared spectra were recorded as neat compounds using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were generated using ChemDraw Professional 15.0. All solvents were dried on a column of alumina prior to use. Thin layer chromatography (TLC) was performed using Merck aluminium-foil baked plates coated with Kieselgel 60 F245. The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. Flash column chromatography was performed over Merck silica gel C60 (40-60 µm) using eluent systems as described for each experiment.

Low temperature[1] (150 K) single-crystal X-ray diffraction data for **6a**, **6d**, **7a** and **10a** were collected using an Oxford Diffraction (Agilent) SuperNova A diffractometer. Raw frame data were reduced using the instrument manufacturer supplied software CrysAlisPro.[2] All structures could be solved ab initio using SuperFlip,[3] and full-matrix least-squares refinement was carried out using CRYSTALS.[4,5,6] All non-hydrogen atoms were refined using anisotropic displacement ellipsoids, and hydrogen atoms were visible in the difference map. Once the heavy atoms structure was complete, hydrogen atoms were positioned geometrically then refined separately using soft restraints prior to inclusion in the final refinement using a riding model.[7] X-ray structure of **5f** was measured on a Bruker APEX2 CCD area detector diffractometer with Mo-Kα radiation. Single crystal was coated at room temperature with perfluoroalkylether oil and mounted on a polymer pin. The structures were solved by direct methods in SHELXTL and successive interpretation of the difference Fourier maps, followed

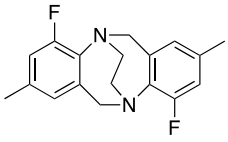
by full-matrix least-squares refinement (against F2). CCDC 1442060 **6a**, CCDC 1442061 **6d**, CCDC 1442062 **7a**, CCDC 1442063 **10a** and CCDC 1450259 **5f** contain the supplementary crystallographic data for this paper These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif and are also available in the supporting information for this article.

2. SYNTHESIS

2.1 Synthesis of Ethano-Tröger's Base analogues

5a,[8] **5b**, [8] **5c**, [9] **5d**, [10] **5e**[8] and **13f**[11] were synthesized according to literature procedures.

2.1. Synthesis of **5f**

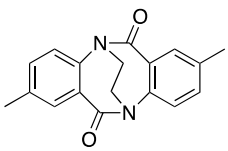


4,10-difluoro-2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, **13f** (1.14 g, 4.00 mmol) was stirred with Li_2CO_3 (1.47 g, 20.0 mmol, 5.00 equiv) and 1,2-dibromoethane (1.55 mL, 18.0 mmol, 4.50 equiv) in DMF (10 mL) for 48 hours at 125 °C. The reaction slurry was diluted with ethyl acetate (100 mL) and then adsorbed onto silica gel (10 g). The solvents were removed under reduced pressure to give a free flowing powder, which was purified *via* flash column chromatography [silica gel (50 g), ethyl acetate/hexane (30:80) containing 0.5% Et_3N] to give **5f** (4.8 g, 45%) as a white solid.

MP = 242 °C; IR (ATR, neat): ν [cm^{-1}] = 2962, 1475, 1341, 1326, 1167, 1134, 1031, 851, 822, 744, 735, 663, 636; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.16 (s, 6H,CH_3), 3.60 (m, 4H, NCH_2CH_2N),), 4.38 (d, *J* = 17.5 Hz, 4H, NCH_2Ar), 4.49 (d, *J* = 17.5 Hz, 4H, NCH_2Ar), 6.52 (s, 2H, Ar-*H*), 6.65 (d, $^2J_{H\text{-}F}$ = 11.2 Hz, 2H,Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 20.8 (d, *J* = 1.6 Hz), 55.6, 55.6 (d, *J* = 1.5 Hz), 114.6 (d, *J* = 21.4 Hz), 124.4 (d, *J* = 3.1 Hz), 134.5 (d, *J* = 11.9 Hz), 135.6 (d, *J* = 8.3 Hz), 139.0, 158.3 (d, *J* = 244.9 Hz) ; ^{19}F NMR (272 MHz, $CDCl_3$): δ [ppm] = -125.6; HRMS (EI): m/z $[M]^+$ calc. for $C_{18}H_{18}F_2N_2$: 300.1433; found 300.1438.

2.2 Synthesis of bis-amide products **6a**-**d**

2.2.1 Synthesis of **6a**

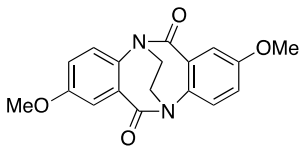


A 50 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dimethyl-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine **5a** (528 mg, 2.00 mmol), $KMnO_4$ (2.84 g, 18.0 mmol, 9.00 equiv) and $BnEt_3NCl$ (4.08 g, 18.0 mmol, 9.00 equiv). HPLC grade DCM (20 mL) was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of $NaHSO_3$ was added (30 mL) until the reaction turned white and biphasic. The reaction was diluted with DCM (20 mL) and phases were separated and the aqueous phase was extracted with DCM (75 mL × 2). The

combined organic phase was rinsed with water (20 mL × 2) and then with brine (20 mL × 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield an orange powder that was purified *via* column chromatography (15 g silica column; 5% ethyl acetate in methylene chloride) to yield 2,8-dimethyl-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine-6,12-dione **6a** as a white powder with a faint yellow tinge (271 mg, 47%).

MP = 320 °C (decomposes); IR (ATR, neat): ν [cm^{-1}] = 1674 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.40 (s, 6H, C*H*$_3$), 3.39 (m, 2H, NC*H*$_2$CH$_2$N), 3.75 (m, 2H, NCH$_2$C*H*$_2$N), 7.32 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 7.38 (dd, *J* = 7.9, 1.8 Hz, 2H, Ar-*H*), 7.46 (d, *J* = 1.8 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 21.3, 49.7, 128.5, 130.0, 134.0, 135.7, 139.8, 140.1, 179.1; HRMS (ESI): m/z $[M+H]^+$ calc. for $C_{18}H_{17}N_2O_2$: 293.1285; found: 293.1279;

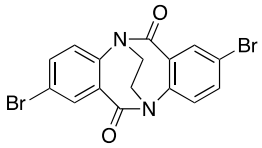
2.2.2 Synthesis of **6b**



A 50 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dimethoxy-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine **5b** (592 mg, 2.00 mmol), $KMnO_4$ (2.85 g, 18.0 mmol, 9.00 equiv) and $BnEt_3NCl$ (4.09 g, 18.0 mmol, 9.00 equiv). HPLC grade DCM (20 mL) was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of $NaHSO_3$ was added (30 mL) until the reaction turned white and biphasic. The reaction was diluted with DCM (20 mL) and phases were separated and the aqueous phase was extracted with DCM (75 mL × 2). The combined organic phase was rinsed with water (20 mL × 2) and then with brine (20 mL × 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield an orange powder that was purified *via* column chromatography (15 g silica column; 7.5% ethyl acetate in methylene chloride) to yield 2,8-dimethoxy-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine-6,12-dione **6b** as a white powder with a faint yellow tinge (337 mg, 52%).

MP = 245 °C (decomposes); IR (ATR, neat): ν [cm^{-1}] = 1683 (C=O); ^{1}H NMR: (400 MHz, $CDCl_3$): δ [ppm] = 3.39 (m, 2H, NC*H*$_2$CH$_2$N), 3.72 (m, 2H, NCH$_2$C*H*$_2$N), 3.83 (s, 6H, OC*H*$_3$), 7.07 (dd, *J* = 8.6, 3.0 Hz, 2H, Ar-*H*), 7.15 (d, *J* = 3.0 Hz, 2H, Ar-*H*), 7.35 (d, *J* = 8.6 Hz, 2H, Ar-*H*); ^{13}C NMR: (100 MHz, $CDCl_3$): δ [ppm] = 49.8, 55.9, 113.8, 119.2, 129.8, 135.2, 136.8, 160.1, 178.7; HRMS (ESI): m/z $[M+H]^+$ calc. for $C_{18}H_{17}N_2O_4$: 325.1183; found: 325.1184.

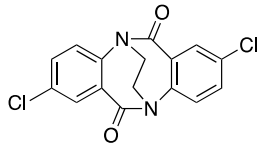
2.2.3 Synthesis of **6c**



A 100 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dibromo-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine **5c** (1.57 g, 4.00 mmol), $KMnO_4$ (5.69 g, 36.0 mmol, 9.00 equiv) and $BnEt_3NCl$ (8.20 g, 36.0 mmol, 9.00 equiv). HPLC grade DCM was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of $NaHSO_3$ was added (60 mL) until the reaction turned white and biphasic. The reaction was diluted with DCM (40 mL) and phases were separated and the aqueous phase was extracted with DCM (100 mL × 2). The combined organic phase was rinsed with water (30 mL × 2) and then with brine (30 mL × 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield an orange powder that was purified *via* column chromatography (25 g silica column; 7.5% ethyl acetate in methylene chloride) to yield 2,8-dibromo-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine-6,12-dione **6c** as a pale yellow powder (500 mg, 30%).

MP = 314 °C (decomposes); IR (ATR, neat): ν [cm^{-1}] = 1676 (C=O); ^{1}H NMR: (400 MHz, $CDCl_3$): δ [ppm] = 3.44 (m, 2H, NC*H*$_2$CH$_2$N), 3.77 (m, 2H, NC*H*$_2$CH$_2$N), 7.34 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.73 (dd, *J* = 8.3, 2.3 Hz, 2H, Ar-*H*), 7.80 (d, *J* = 2.3 Hz, 2H, Ar-*H*); ^{13}C NMR: (100 MHz, DMSO-d_6): δ [ppm] = 39.52, 48.57, 121.97, 130.88, 131.79, 135.89, 137.44, 141.21, 176.39; HRMS (ESI): m/z $[M+H]^+$ calc. for $C_{16}H_{11}Br_2N_2O_2$: 420.9182; found: 420.9183.

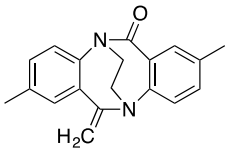
2.2.4 Synthesis of **6d**



A 50 mL round bottomed flask fitted with a water cooled reflux condenser was charged with 2,8-dichloro-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine **5d** (610 mg, 2.00 mmol), $KMnO_4$ (2.84 g, 18.0 mmol, 9.00 equiv) and $BnEt_3NCl$ (4.08 g, 18.0 mmol, 9.00 equiv). HPLC grade DCM (20 mL) was added and then the reaction was allowed to stir at 50 °C for 18 hours. The flask was cooled to 0 °C and then a saturated aqueous solution of $NaHSO_3$ was added (30 mL) until the reaction turned white and biphasic. The reaction was diluted with DCM (20 mL) and phases were separated and the aqueous phase was extracted with DCM (75 mL × 2). The combined organic phase was rinsed with water (20 mL × 2) and then with brine (20 mL × 2). The organic volatiles were removed under reduced pressure and then dried under high vacuum to yield a brown powder that was purified *via* column chromatography (15 g silica column; 5% ethyl acetate in methylene chloride) to yield 2,8-dichloro-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine-6,12-dione **6d** as a white powder (200 mg, 30%).

MP= 278 °C (decomposes); IR (ATR, neat): ν [cm^{-1}] = 1666 (C=O); ^{1}H NMR: (400 MHz, $CDCl_3$) δ [ppm] = 3.48 (m, 2H, NCH_2CH_2N), 3.71 (m, 2H, NCH_2CH_2N), 7.40 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.57 (dd, *J* = 8.3, 2.4 Hz, 2H, Ar-*H*), 7.65 (d, *J* = 2.4 Hz, 2H, Ar-*H*); ^{13}C NMR: (100 MHz, $CDCl_3$) δ [ppm] = 49.3, 129.8, 130.3, 133.5, 135.8, 137.1, 140.7, 176.9; HRMS (ESI): m/z $[M+H]^+$ calc. for $C_{16}H_{11}Cl_2N_2O_2$: 333.0192, found: 333.0197.

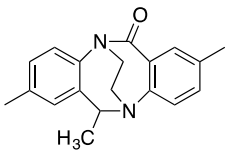
2.3 Synthesis of **7a**



A 100 mL pressure tube under argon was charged with **6a** (292 mg, 1.00 mmol) and dry methylene chloride (20 mL), after which a solution (0.23 M in toluene) of Cp_2TiMe_2 (13.5 mL, 3.00 mmol, 3.00 equiv) was injected. The reaction was warmed to 70 °C and allowed to stir for 18 hours. The reaction was cooled to room temperature and diluted with methylene chloride (20 mL) and then rinsed with water (15 mL). The organic phase was then dried over $MgSO_4$. The volatiles were removed under reduced pressure and then purified *via* flash column chromatography (15 g silica column; ethyl acetate/pentane 10/90 to 30/70) to yield 2,8-dimethyl-12-methylene-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocin-6-one **7a** as a tan solid (72 mg, 25%).

MP = 125 °C; IR (ATR, neat): ν [cm^{-1}] = 1667 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.37 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.13 (m, 1H, NCH_2CH_2N), 3.29 (m, 1H, NCH_2CH_2N), 3.39 (m, 1H, NCH_2CH_2N), 3.64 (m, 1H, NCH_2CH_2N), 4.59 (s, 1H, NC=CH_2), 4.65 (s, 1H, NC=CH_2), 7.22 (m, 2H, Ar-*H*), 7.25 (m, 2H, Ar-*H*), 7.30 (m, 1H, Ar-*H*), 7.48 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 21.6, 21.4, 49.1, 50.6, 105.3, 128.2, 128.7, 129.6, 130.0, 130.9, 133.4, 135.6, 137.9, 138.3, 138.8, 146.8, 155.5, 179.9; HRMS (ESI) m/z $[M+H]^+$ calc. for $C_{19}H_{19}N_2O$: 291.1491, found: 291.1492.

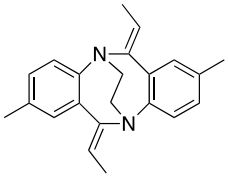
2.4 Synthesis of **8a**



A 250 mL round bottomed flask was charged with **7a** (500 mg, 1.72 mmol) and Pd/C (10%) (183 mg, 0.172 mmol, 10 mol%). The flask was evacuated and refilled with nitrogen (3x). Dry MeOH (75 mL) was injected after which a balloon filled with hydrogen was introduced and the reaction was stirred for 90 minutes. The hydrogen was vented, and the reaction was filtered through a celite plug (2 cm × 3 cm) after which it was purified *via* column chromatography (25 g silica column; ethyl acetate/methylene chloride 0/100 to 5/95) to yield 2,8,12-trimethyl-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocin-6-one **8a** as a white solid (375 mg, 75%).

MP = 115 °C; IR (ATR, neat): ν [cm^{-1}] = 1667 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 1.07 (d, *J* = 7.5 Hz, 3H, NCHC*H*$_3$), 2.34 (s, 3H, C*H*$_3$), 2.38 (s, 3H, C*H*$_3$), 3.15 (m, 1H, NC*H*$_2$CH$_2$N), 3.29 (m, 2H, NC*H*$_2$CH$_2$N), 3.60 (m, 1H, NC*H*$_2$CH$_2$N), 4.71 (*q*, *J* = 7.5 Hz, 1H, NC*H*CH$_3$), 6.88 (s, 1H, Ar-*H*), 7.04 (dd, *J* = 7.8, 1.9 Hz, 2H, Ar-*H*), 7.22 (m, 2H, Ar-*H),* 7.44 (d, *J* = 2.0 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm] = 21.1, 21.3, 48.9, 51.2, 63.4, 77.1, 128.9, 129.1, 129.3, 129.9, 131.9, 133.7, 137.0, 137.9, 138.1, 138.4, 143.1, 144.4, 181.3; HRMS (ESI) m/z $[M+H]^+$ calc. for $C_{19}H_{21}N_2O$: 293.1648, found: 293.1647.

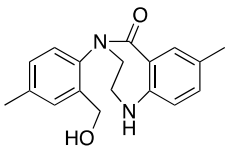
2.5 Synthesis of **9a**



Dry DCM (12.6 mL) was added into a 20 ml Schlenk flask under an argon atmosphere. $TiCl_4$ (1.34 mL, 12.2 mmol, 24.0 equiv.) was added at room temperature and the resulting solution was added slowly at 0 °C into a Schlenk flask containing THF (33 mL) under an argon atmosphere to form a yellow solution. TMEDA (3.67 mL, 24.5 mmol, 48.0 equiv.) was added at room temperature and it was stirred for 10 min to form a slightly brown orange solution. Subsequently, zinc powder (1.80 g, 27.5 mmol, 54.0 equiv.) was added at room temperature and it was stirred for 30 min. The colour turned to dark greenish blue. Bisamide **6a** (0.15 g, 0.51 mmol) was dissolved in dry DCM (10 mL) and the solution was added dropwise to the solution above followed by 1,1-dibromoethane (602 µL, 6.73 mmol, 13.2 equiv.). The reaction mixture was stirred overnight to form a greenish black mixture. It was then cooled to 0 °C and sodium methoxide (661 mg, 12.2 mmol, 24.0 equiv.) was added and the mixture was stirred for 20 min. It was then diluted with DCM (20 mL) and filtered through a pad of silica and celite to give a clear yellow solution. It was absorbed on silica, evaporated and purified by flash column chromatography (SiO_2 (50 g), Hex:EA = 4:1) to give 6,12-diethylidene-2,8-dimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine **9a** as a pale brown sensitive oil (50 mg, 31%), which contained minor impurities, but additional purification led only to the further decomposition of the product**.**

MP = given the instability of the compound, it was not possible to record the melting point. IR (ATR, neat): ν [cm^{-1}] = 2914, 2854, 1481, 1438, 1343, 1177, 1141, 1127, 907, 822, 810, 760, 730, 661, 646. ^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.85 (d, ^{3}*J* = 5.2 Hz, 6H, =CHC*H*$_3$), 2.26 (s, 6H, C*H*$_3$), 3.36 (bs, 4H, C*H*$_2$), 5.48 (bs, 2H, C*H*CH$_3$), 6.93 (d, ^{3}*J* = 7.3 Hz, 2H, Ar-*H*), 6.99 (d, ^{3}*J* = 7.8 Hz, 2H, Ar-*H*), 7.09 (bs, 2H, Ar-*H*). ^{13}C-NMR (75 MHz, $CDCl_3$): δ [ppm] = given the instability of the compound, it was not possible to record a ^{13}C-NMR spectrum of sufficient quality. HRMS (ESI): m/z $[M]^+$ calc. for $C_{22}H_{25}N_2$: 317.2012; found: 317.2016.

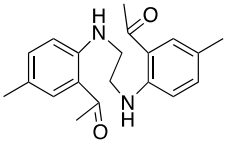
2.6 Synthesis of **10a**



A dry 50 mL round bottomed flask under nitrogen was charged with **6a** (292 mg, 1.00 mmol), $NaBH_4$ (228 mg, 6.00 mmol, 6.00 equiv), methanol (10 mL) and DCM (40 mL). The reaction was stirred under a nitrogen atmosphere for 24 hours after which it was quenched with NH_4Cl (sat. aq.) (10 mL) The reaction was diluted with DCM (50 mL) and the phases were separated. The aqueous phase was extracted with DCM (25 mL × 2). The combined DCM phases were rinsed with water (25 mL × 2) dried over $MgSO_4$ and then purified *via* column chromatography (25 g silica column; ethyl acetate/pentane 50/50) to yield 4-(2-(hydroxymethyl)-4-methylphenyl)-7-methyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one **10a** as a white solid (250 mg, 89%).

MP = 105-108 °C; IR (ATR, neat): ν [cm^{-1}] = 1646 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.29 (s, 3H, C*H*$_3$), 2.38 (s, 3H, C*H*$_3$), 3.64 (m, 2H, NC*H*$_2$CH$_2$N), 3.88 (m, 2H, NCH$_2$C*H*$_2$N), 4.49 (d, *J* = 12.0 Hz, 1H, NC*H*OH), 4.62 (d, *J* = 12.0 Hz, 1H, NC*H*OH), 6.65 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 7.11 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.13 (dd, *J* = 9.4, 1.3 Hz, 1H, Ar-*H*), 7.21 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-*H*), 7.62 (d, *J* = 1.5 Hz, 1H, Ar-*H*), 7.33 (d, *J* = 1.7 Hz, 1H, Ar-*H*) Note: The –OH and –NH peaks are under NC*H*$_2$C*H*$_2$N peaks.; ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] = 20.5, 21.1, 49.8, 50.2, 62.6, 119.9, 123.8, 126.2, 130.3, 131.8, 131.9, 133.9, 137.9, 138.2, 139.5, 142.6, 171.5; HRMS (EI) m/z $[M]^+$ calc. for $C_{18}H_{20}N_2O_2$: 296.1525, found: 296.1529.

2.7 Synthesis of **12a**



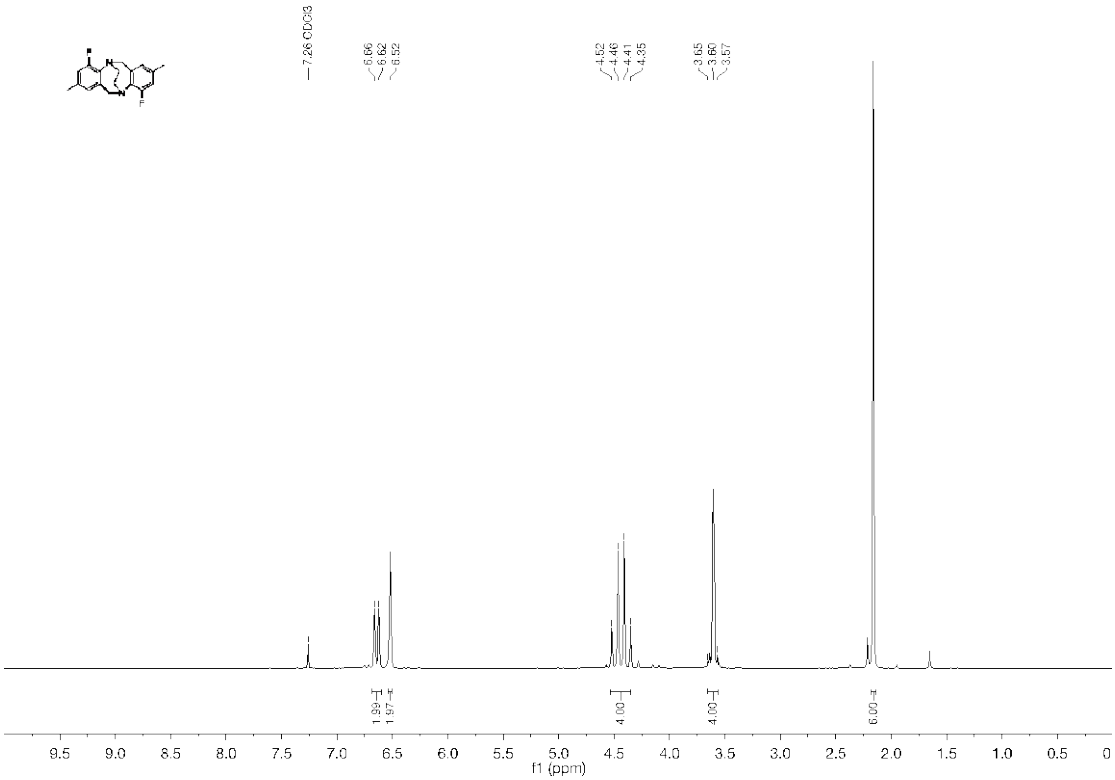
A dry 50 mL flask under nitrogen was charged with **6a** (73 mg, 0.25 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (123 mg, 0.60 mmol, 2.40 equiv). Dry DCM (10 mL) was injected and the contents were stirred at room temperature until a clear solution resulted [Gentle heating was required]. The flask was cooled to -78 °C in a dry ice-acetone bath, and then Tf_2O (101 µL, 0.60 mmol, 2.40 equiv) was injected dropwise over five minutes. After 45 minutes at -78 °C, MeMgBr (3 M in Et_2O; 500 µL, 1.50 mmol, 6.00 equiv) was injected and the reaction was stirred at -78 °C for 90 minutes after which it was allowed to reach room temperature over the course of an hour. The reaction was quenched with a saturated solution of NH_4Cl (5 mL), and then diluted with DCM (30 mL). The phases were separated and the aqueous phase was extracted with DCM (15 mL x 2). The combined DCM phases were rinsed with water (15 mL × 2) dried over $MgSO_4$ and then purified *via* column chromatography (5 g silica column; 10%

ethyl acetate in hexane) to yield 1,1'-((ethane-1,2-diylbis(azanediyl))bis(5-methyl-2,1-phenylene))bis(ethan-1-one) **12a** as a viscous yellow oil (42 mg, 52%)

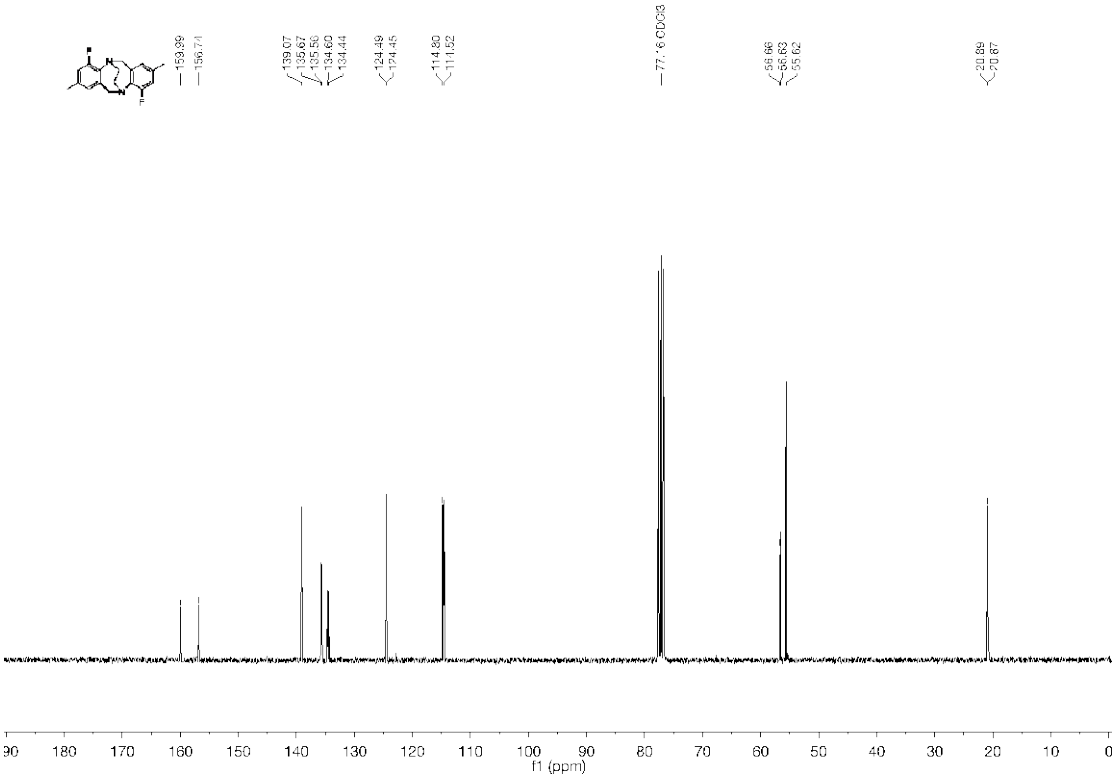
^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 2.19 (s, 6H, C*H*$_3$), 2.49 (s, 6H, CH_3), 3.43 (m, 4H NC*H*$_2$C*H*$_2$N), 6.60 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.12 (dd, *J* = 8.6, 2.0 Hz, 2H, Ar-*H*), 7.46 (s, 2H, Ar-*H*), 8.76 (brs, 2H, N*H*). ^{13}C NMR (100 MHz, CDCl): δ [ppm] = 49.1, 50.1, 61.6, 111.7, 121.3, 122.1, 122.8, 128.1, 132.5, 133.6, 134.8, 135.9, 140.2, 144.3, 169.5; IR (ATR, neat): ν [cm^{-1}] = 3278 (N-H), 1630 (C=O); HRMS (ESI): m/z $[M]^+$ calc. for $C_{20}H_{25}N_2O_2$: 325.1091; found: 325.1087.

3. NMR SPECTRA

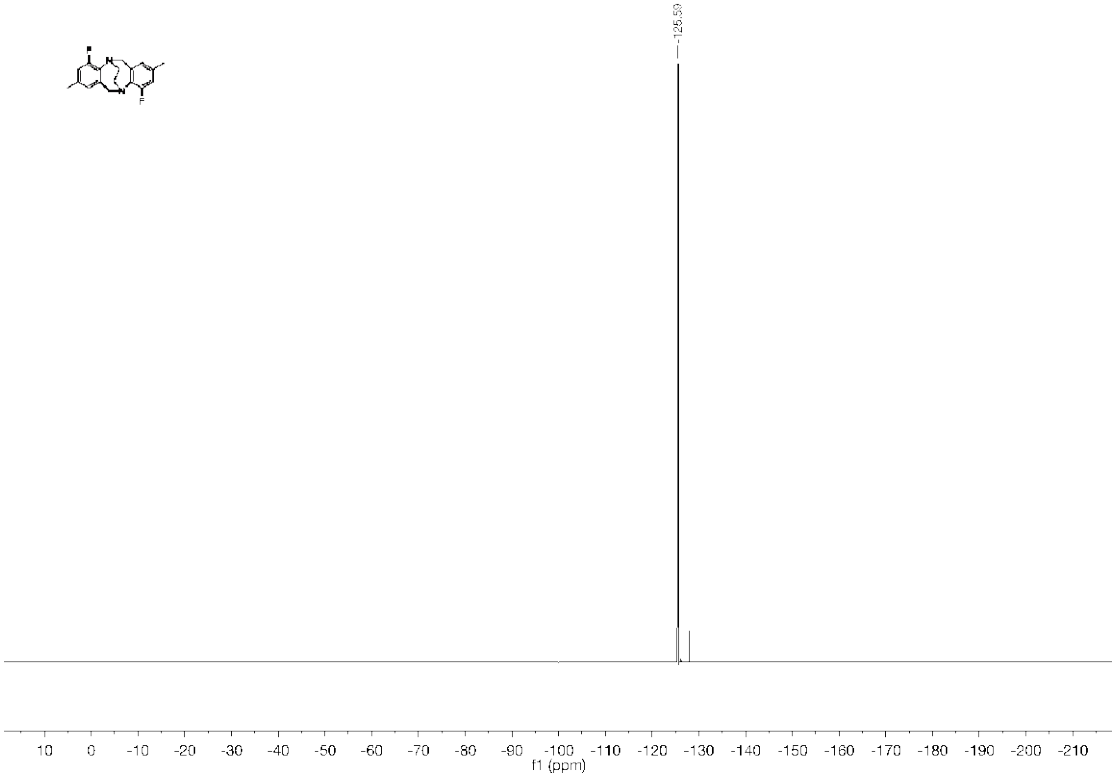
^{1}H NMR (300 MHz, $CDCl_3$) of **5f**



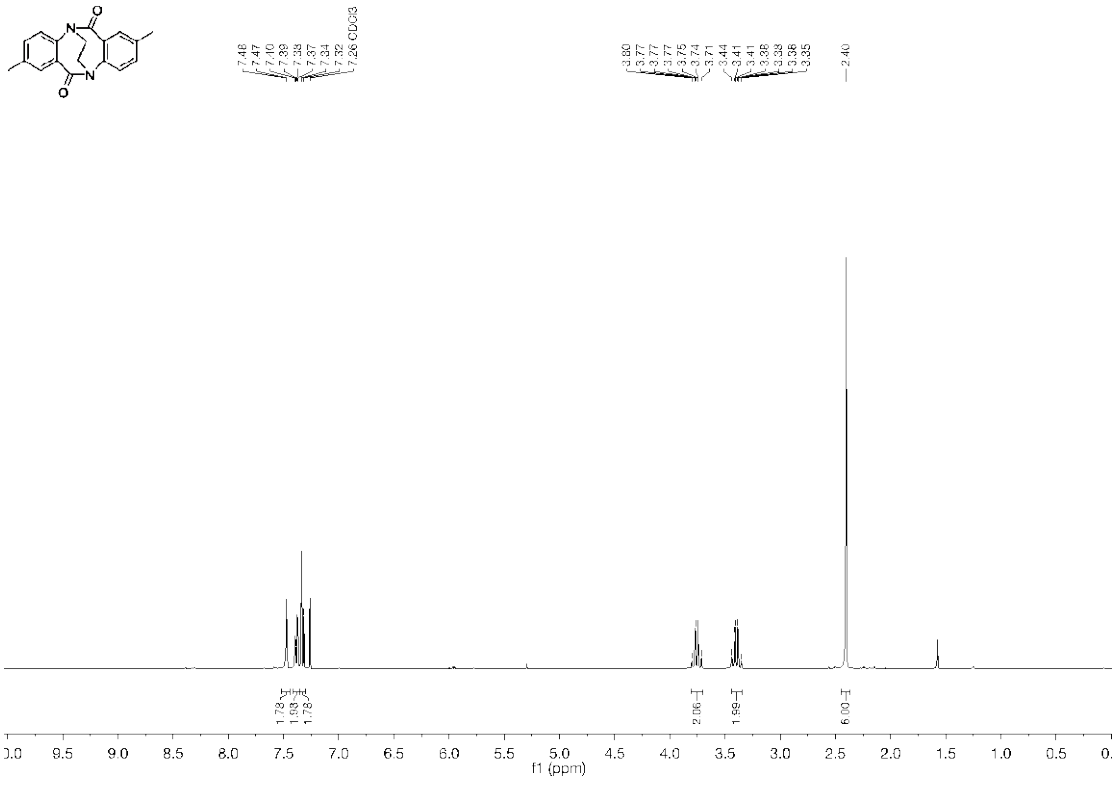
^{13}C NMR (75 MHz, $CDCl_3$) of **5f**



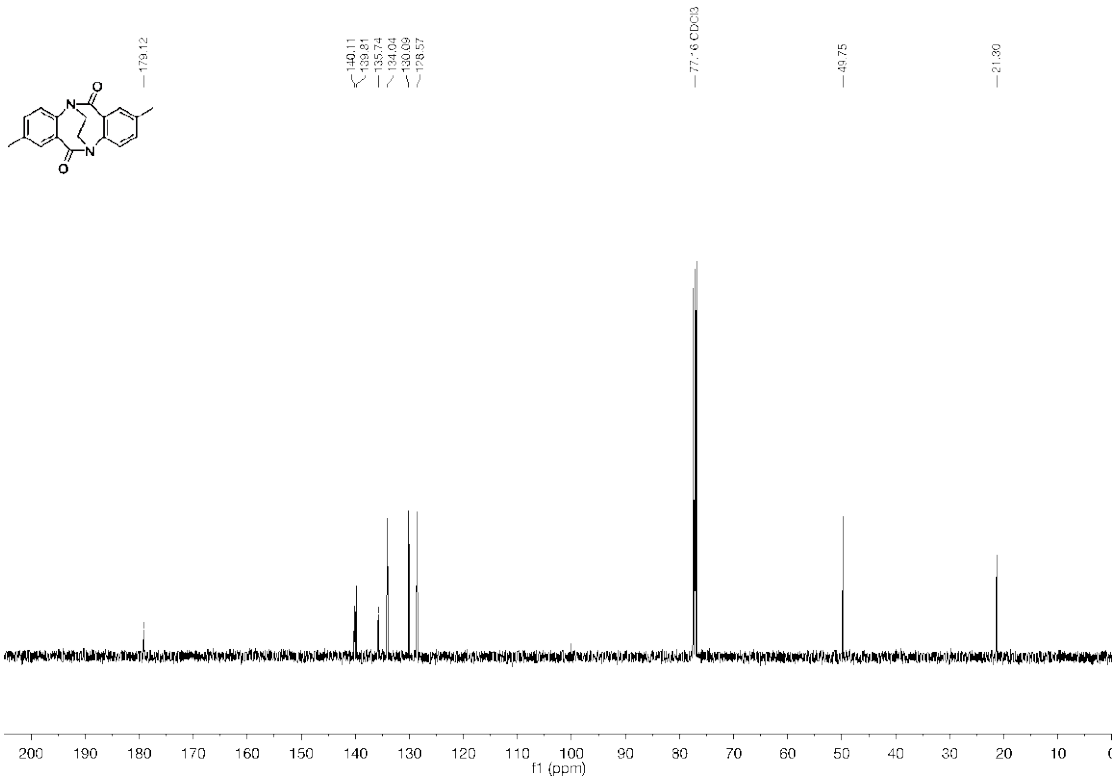
^{19}F NMR (272 MHz, $CDCl_3$) of **5f**



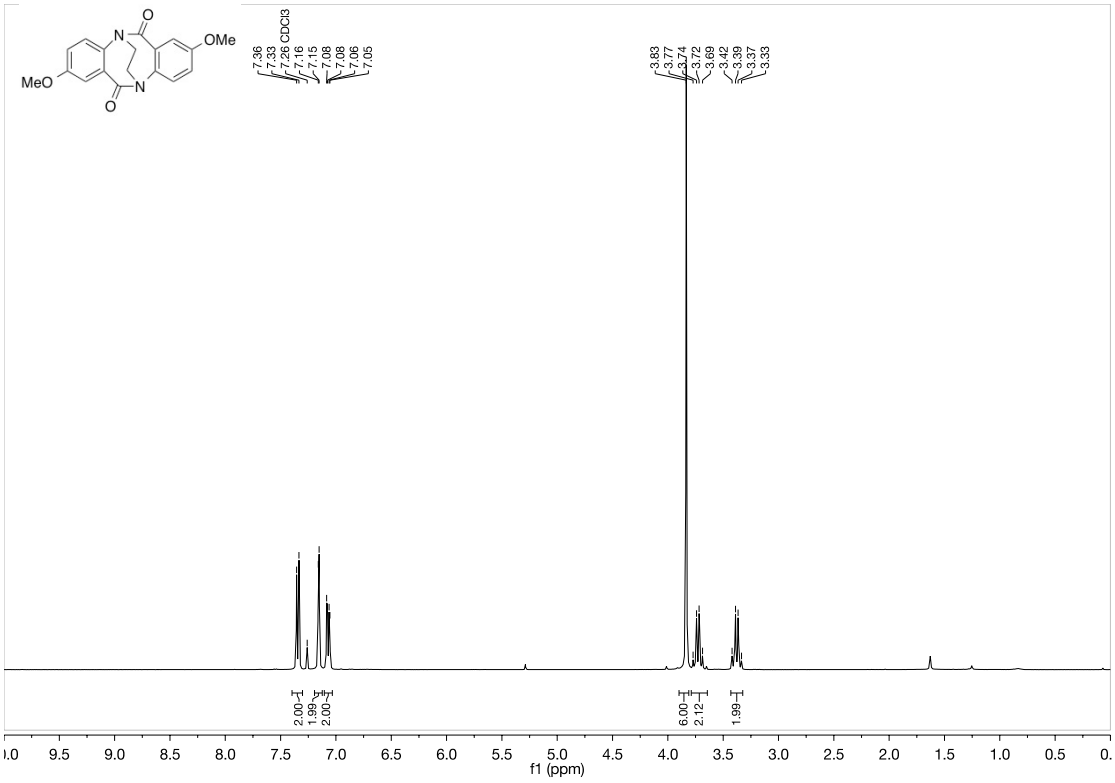
^{1}H NMR (400 MHz, $CDCl_3$) of **6a**



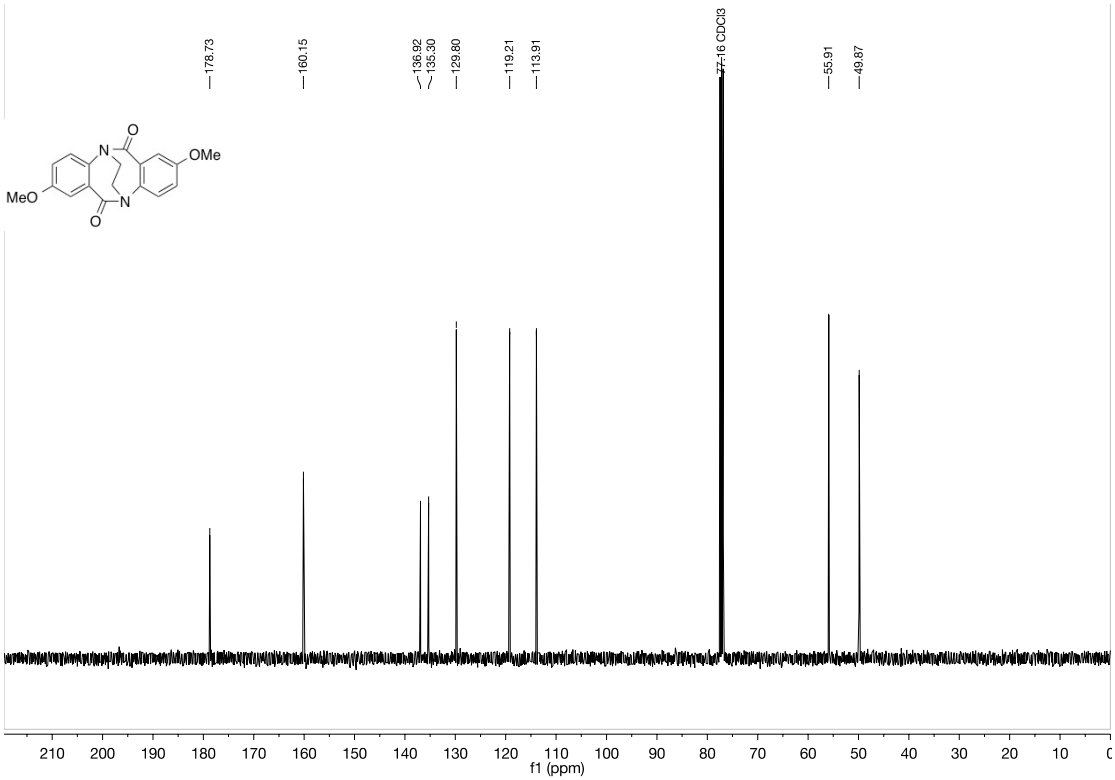
^{13}C NMR (100 MHz, $CDCl_3$) of **6a**



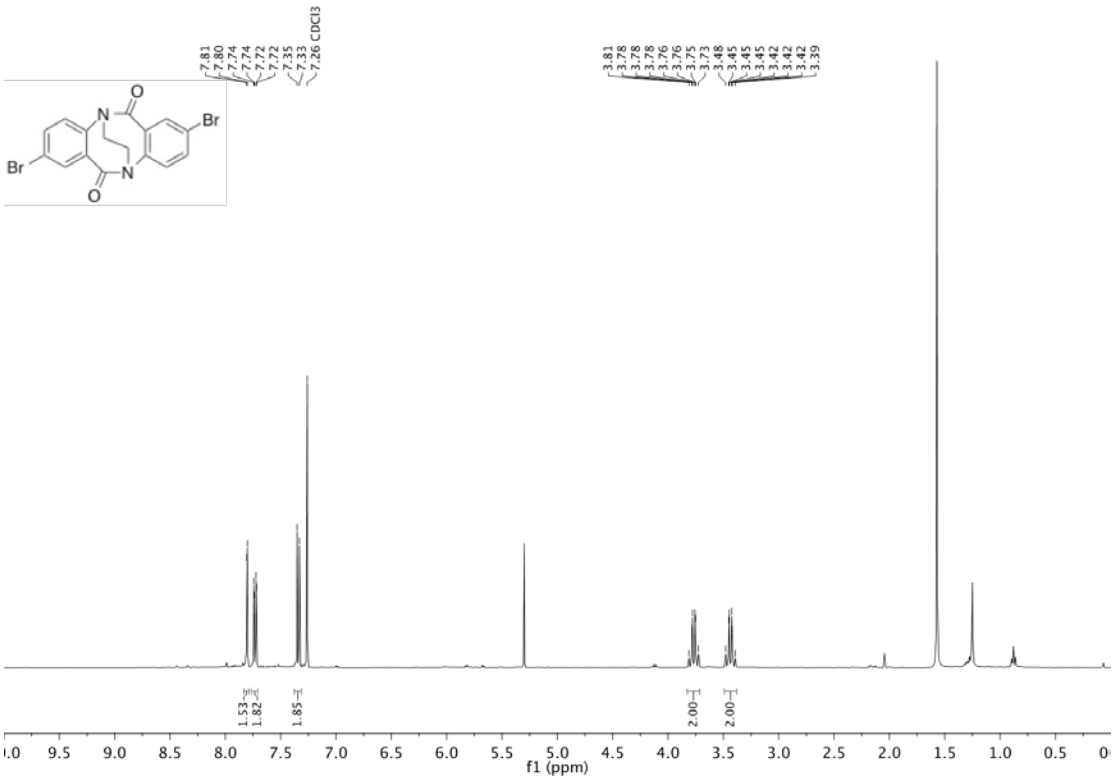
^{1}H NMR (400 MHz, $CDCl_3$) of **6b**



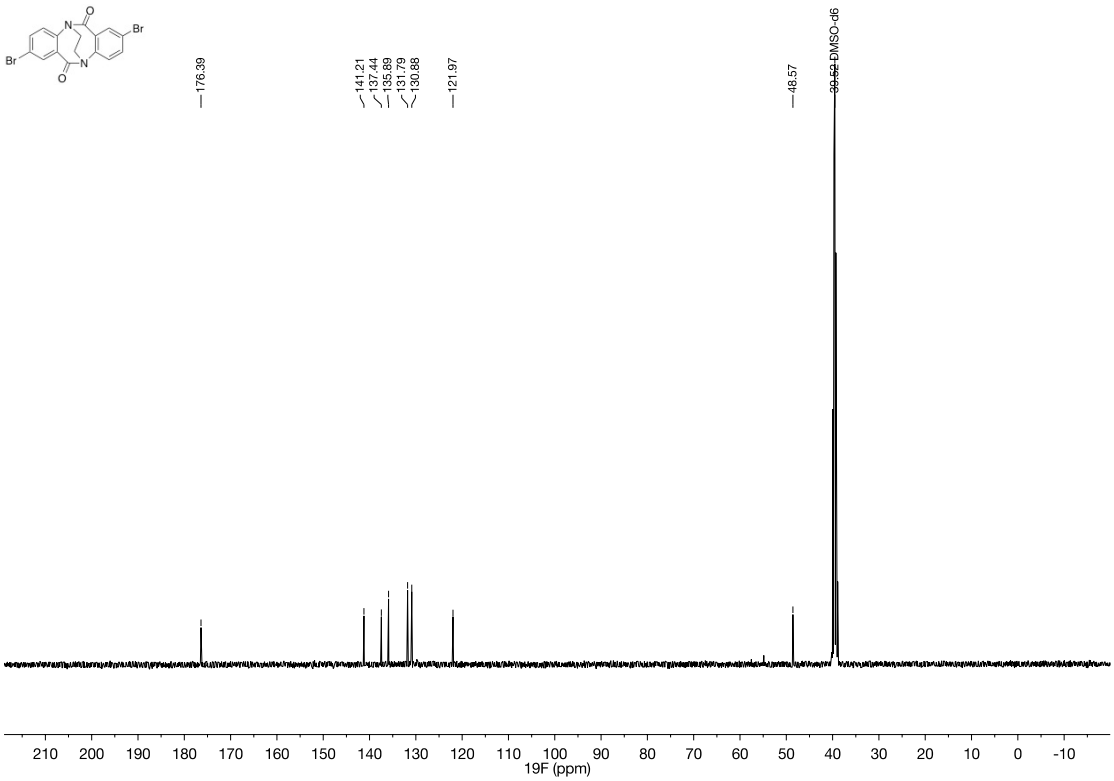
^{13}C NMR (100 MHz, $CDCl_3$) of **6b**



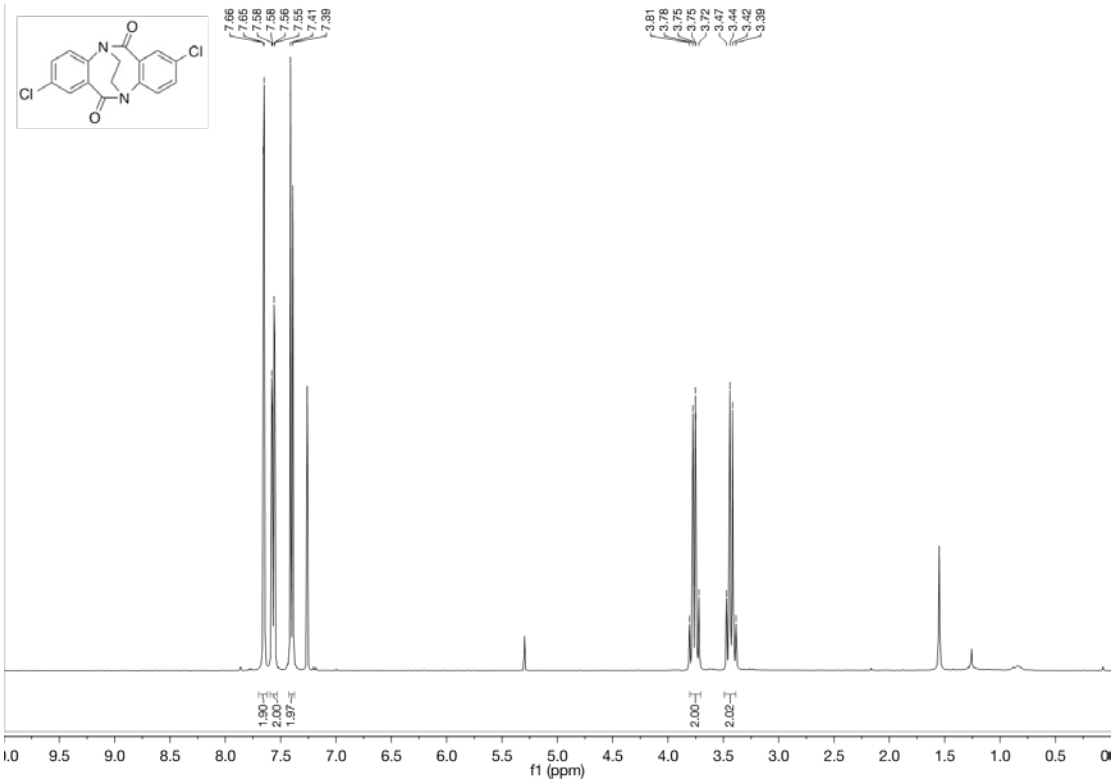
^{1}H NMR (400 MHz, $CDCl_3$) of **6c**



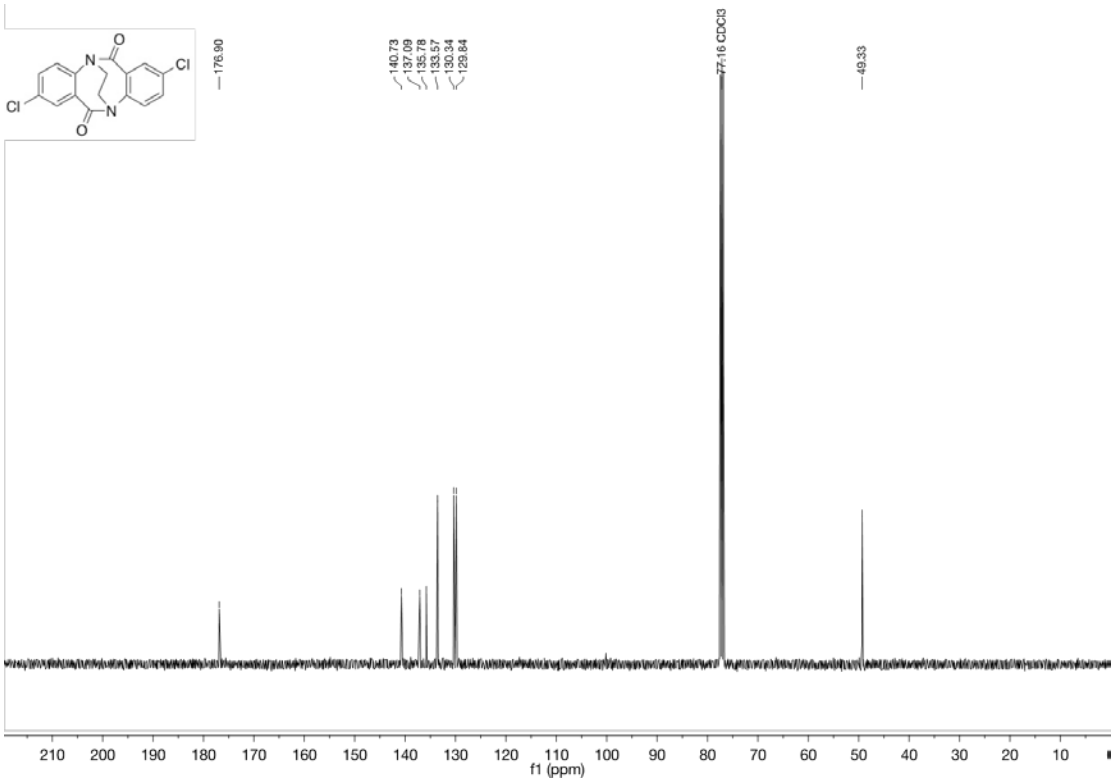
^{13}C NMR (100 MHz, DMSO-d_6) of **6c**



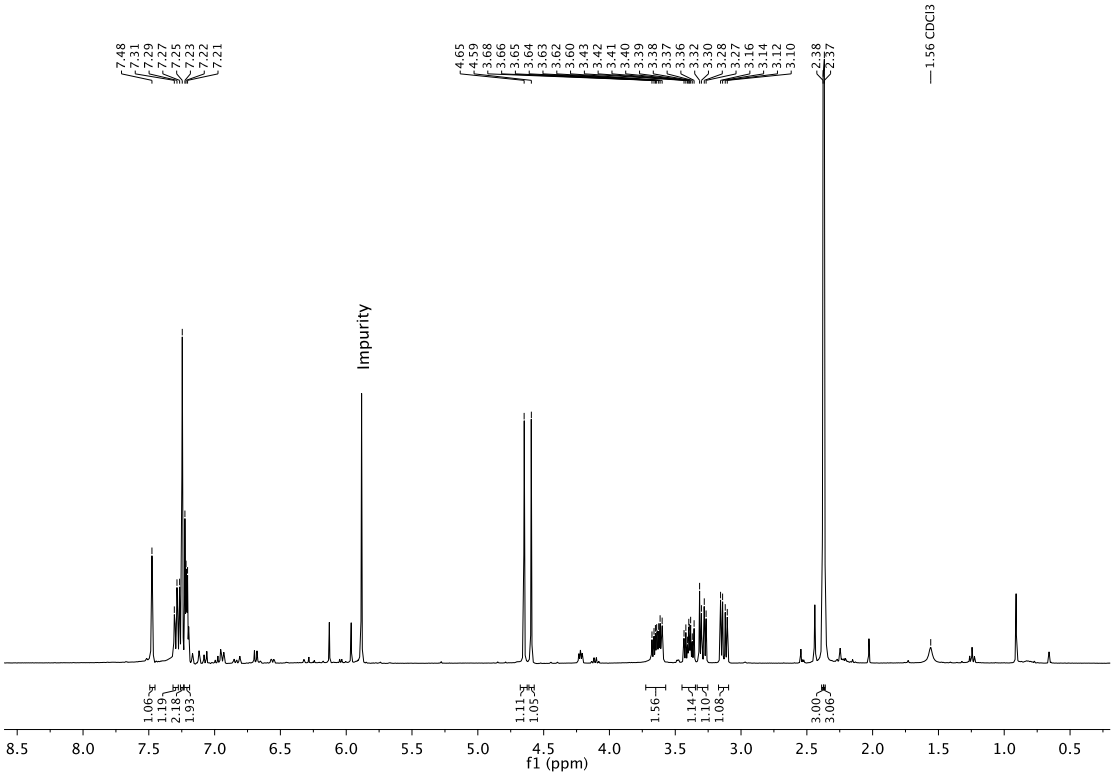
^{1}H NMR (400 MHz, $CDCl_3$) of **6d**



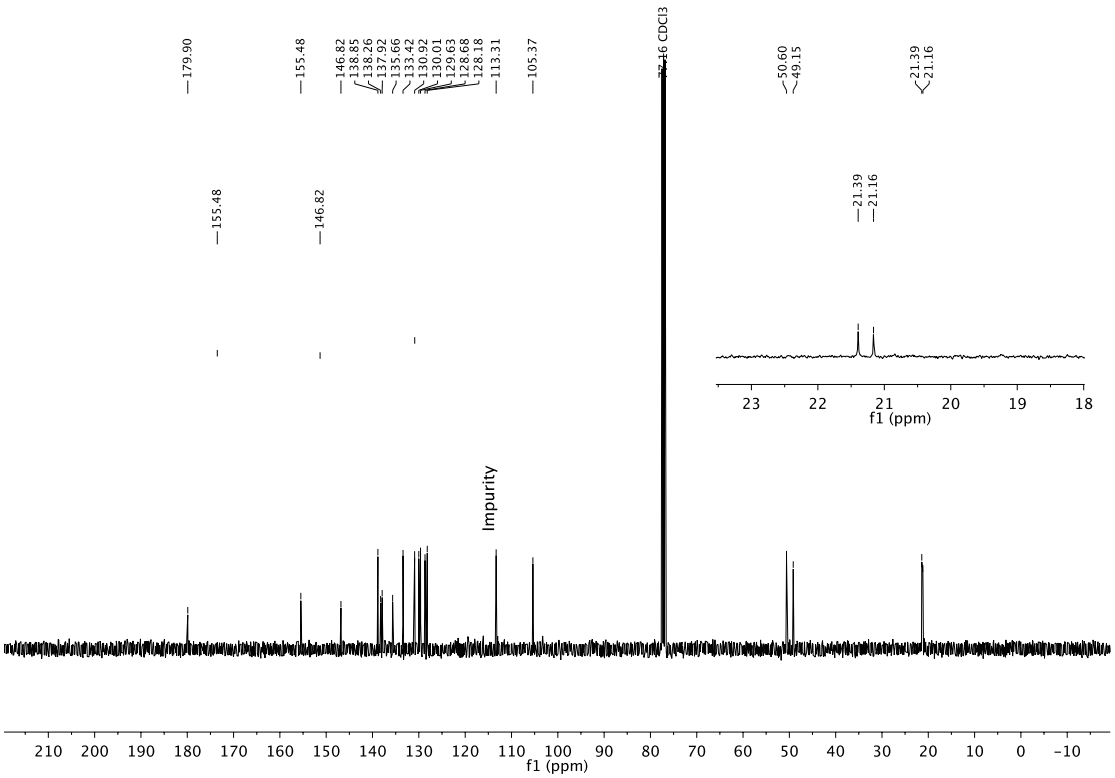
^{13}C NMR (100 MHz, $CDCl_3$) of **6d**



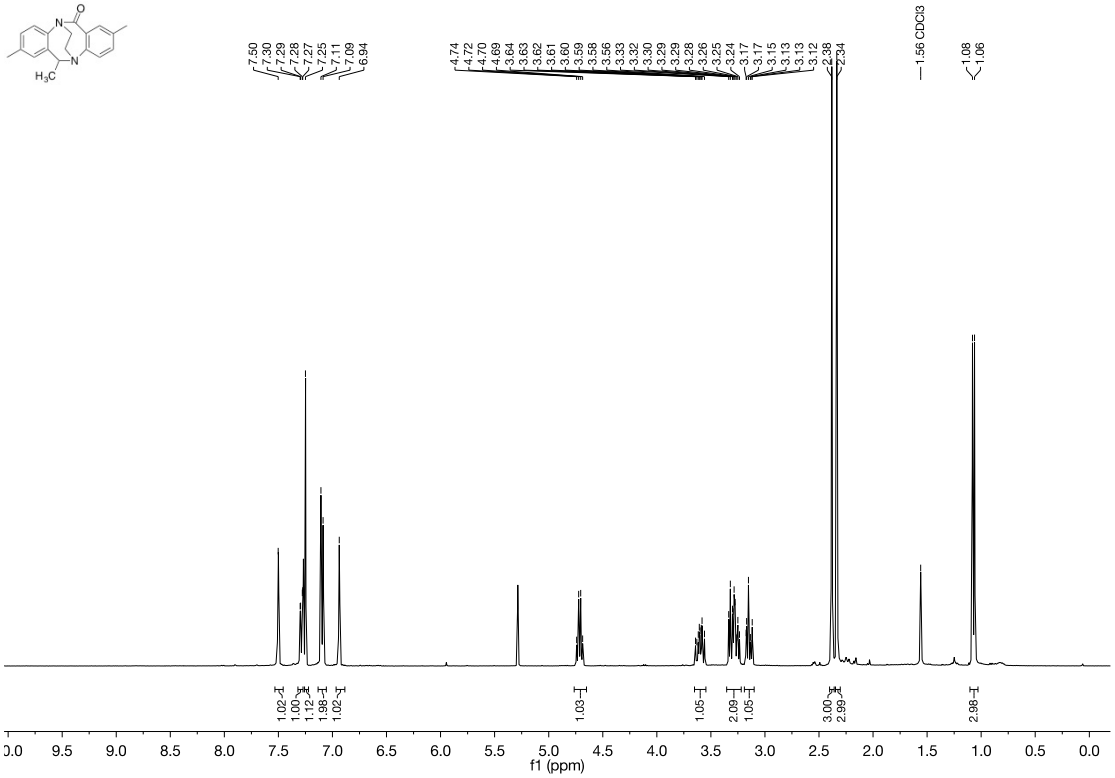
^{1}H NMR (400 MHz, $CDCl_3$) of **7a**



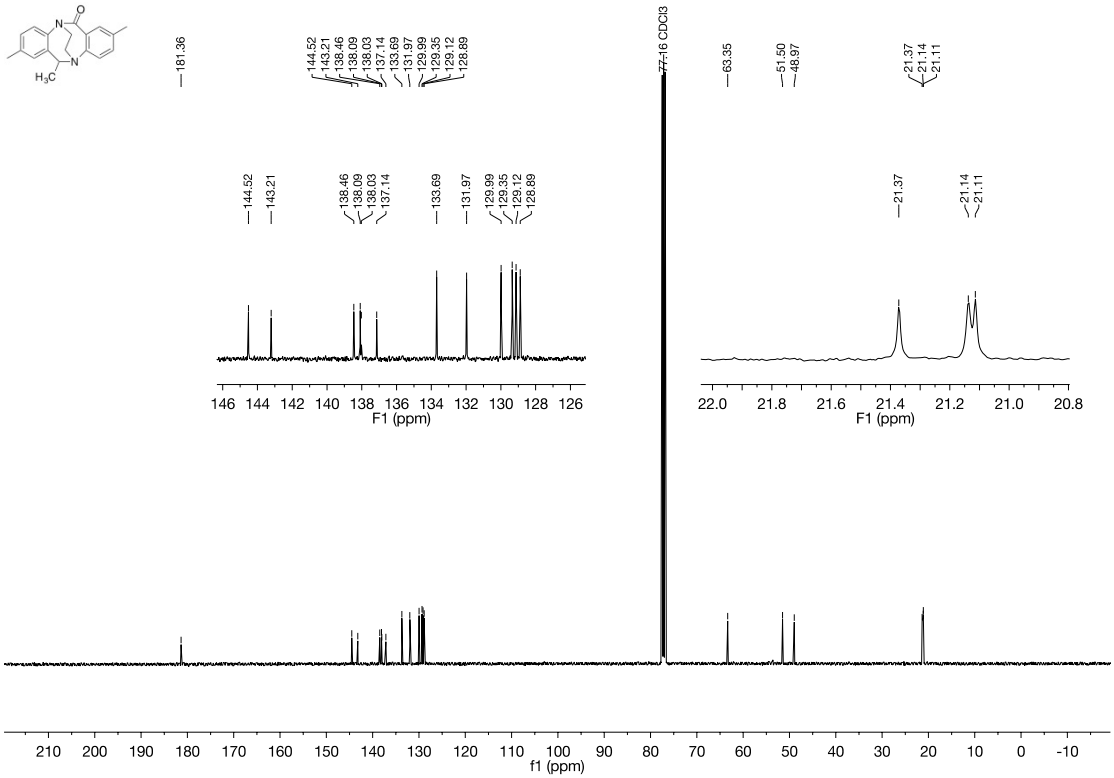
^{13}C NMR (100 MHz, $CDCl_3$) of **7a**



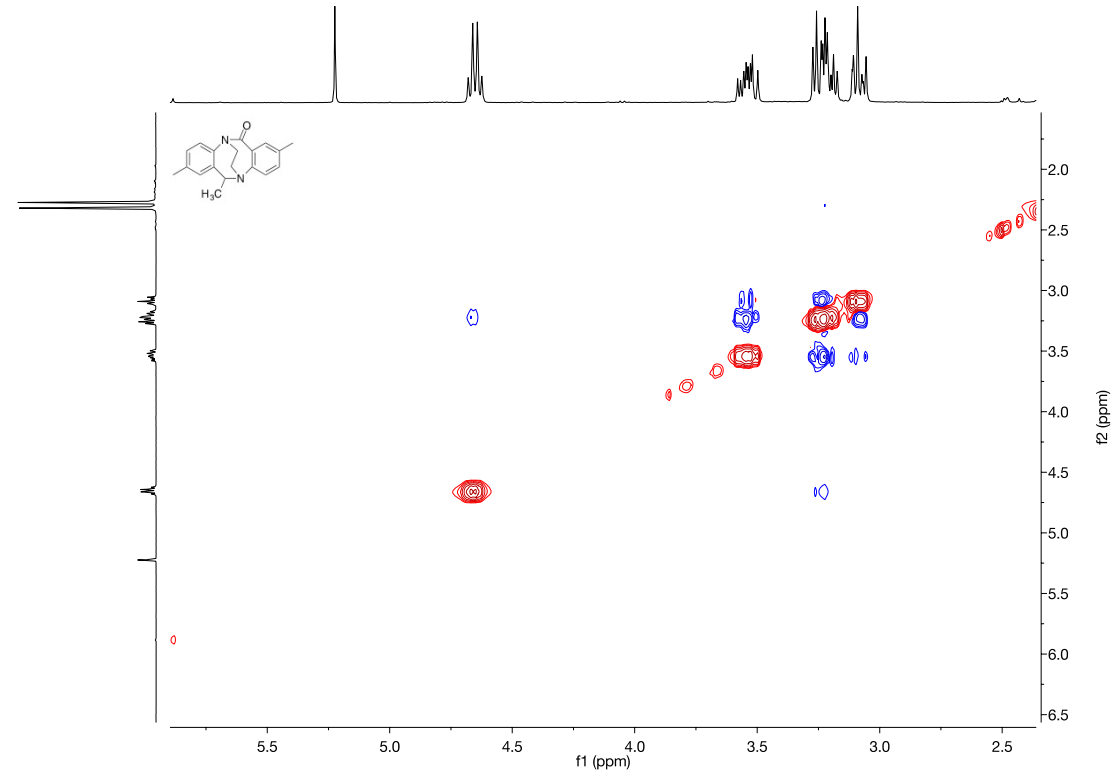
^{1}H NMR (400 MHz, $CDCl_3$) of **8a**



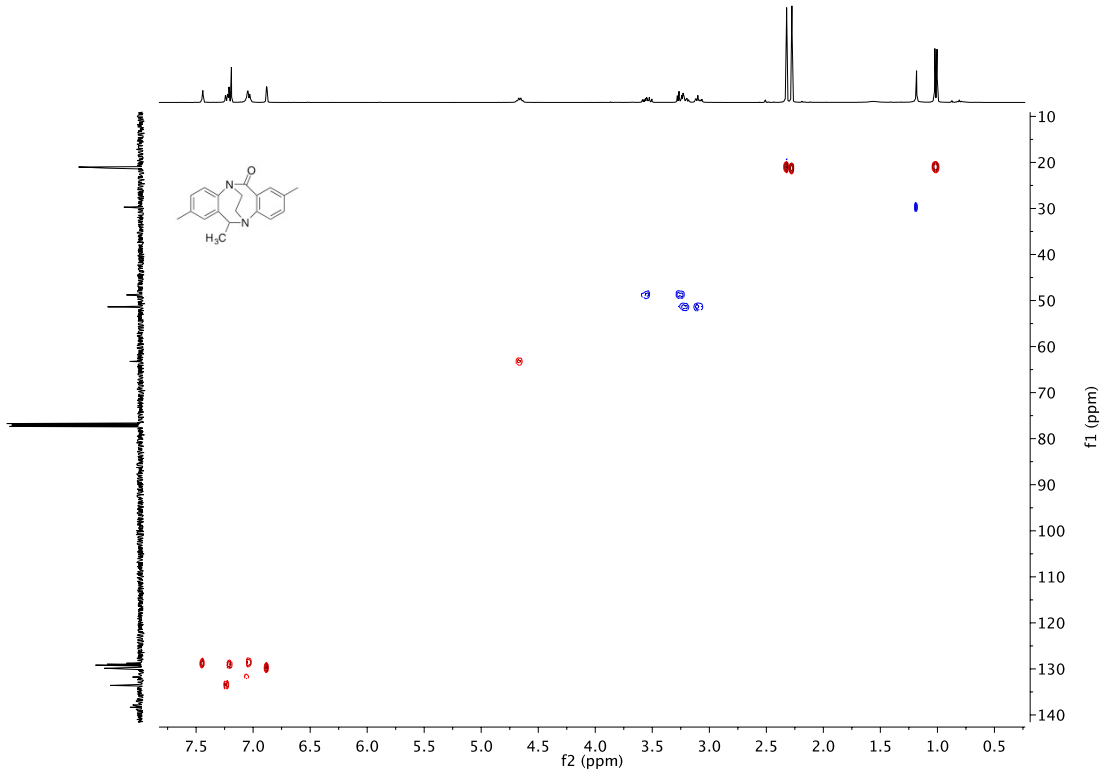
^{13}C NMR (100 MHz, $CDCl_3$) of **8a**



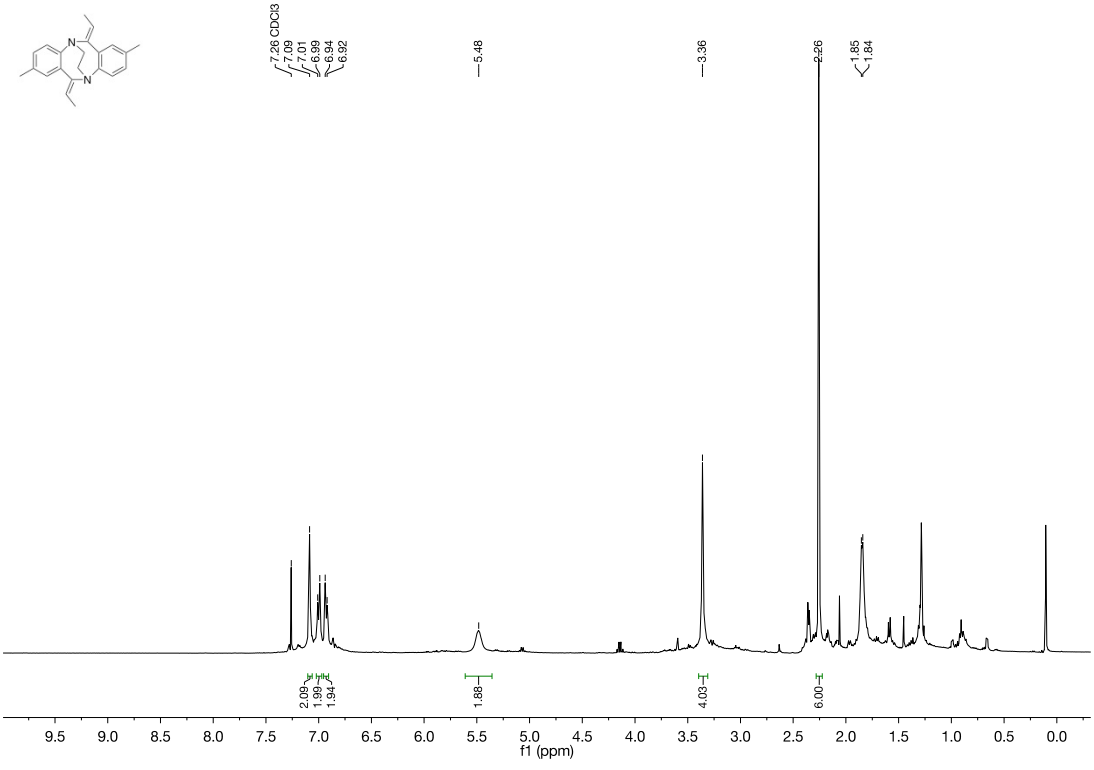
^{1}H-^{1}H NOESY(400 MHz, $CDCl_3$) of **8a**



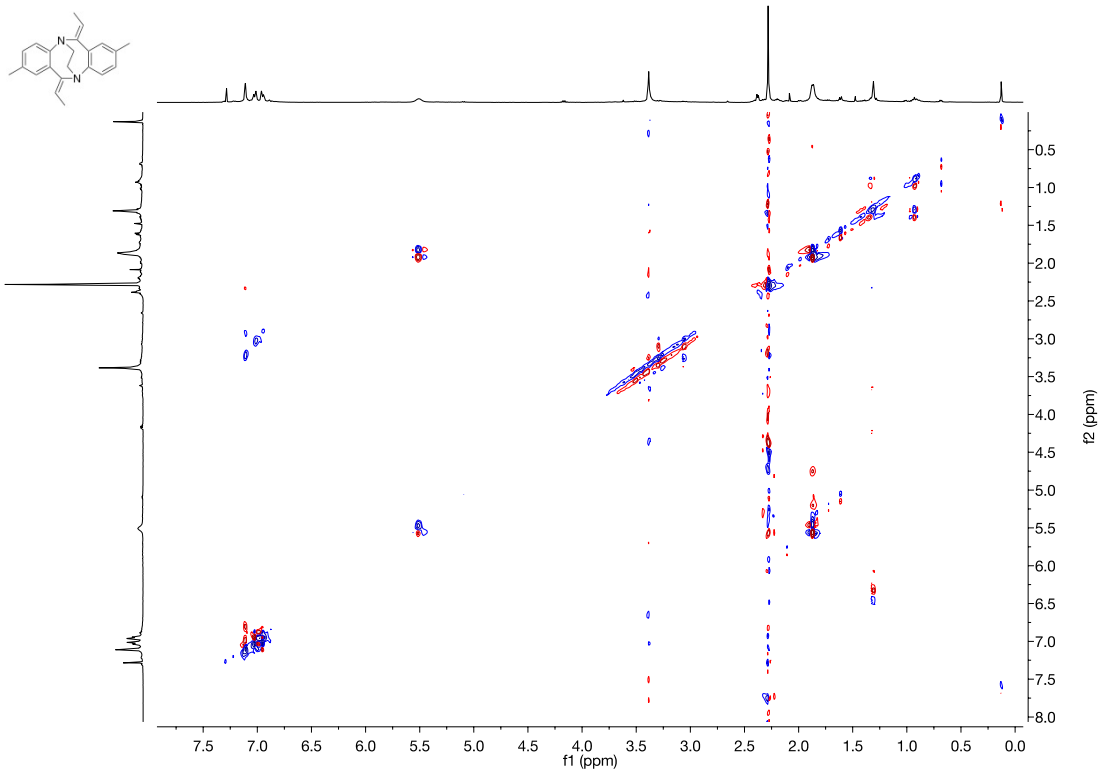
^{1}H-^{13}C HSQC (400 MHz, 100MHz $CDCl_3$) of of **8a**



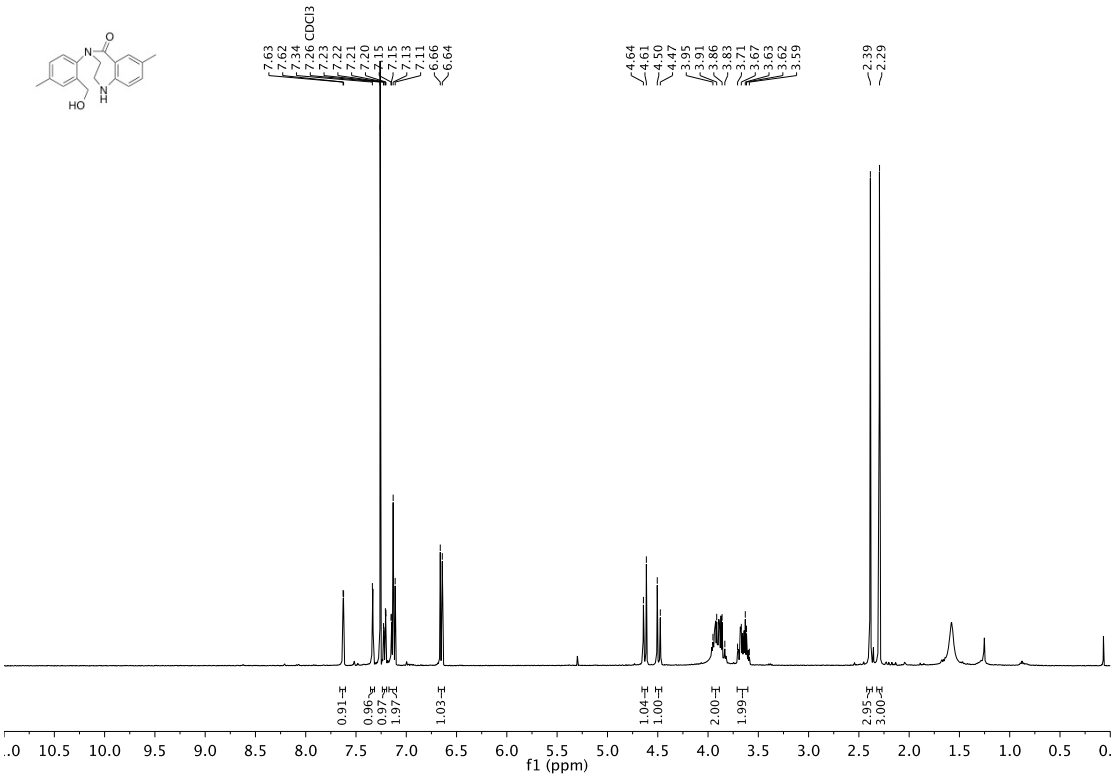
^{1}H NMR (400 MHz, $CDCl_3$) of **9a**



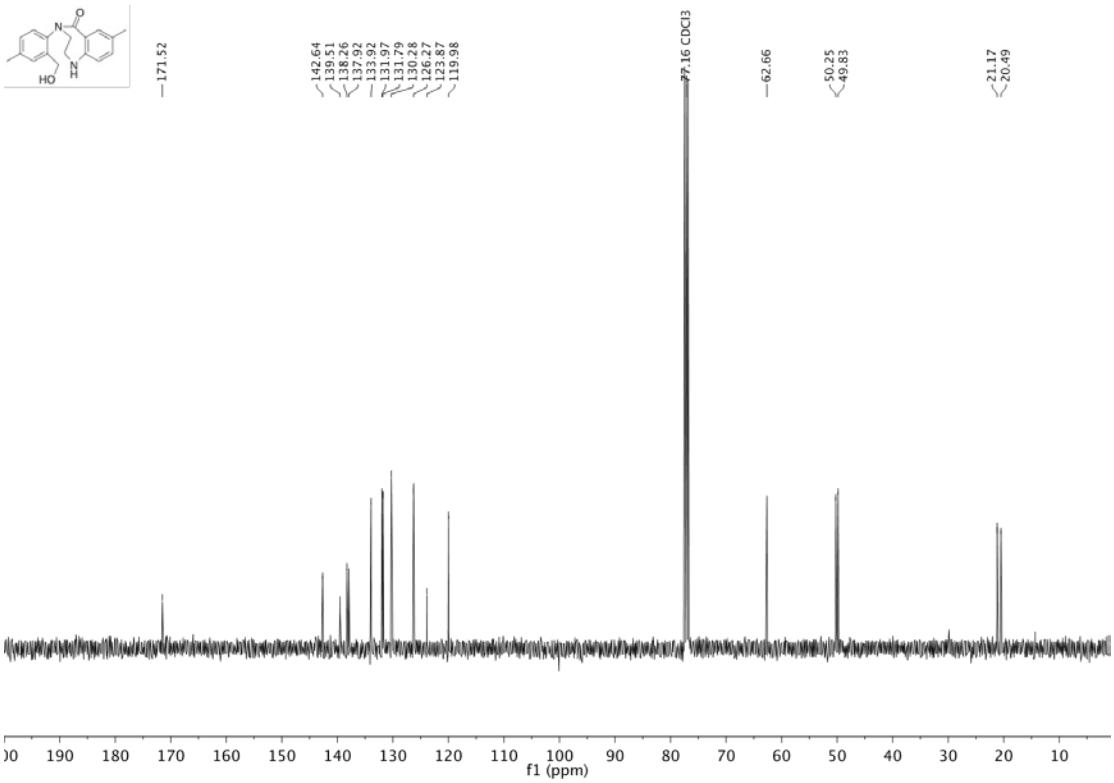
^{1}H-^{1}H COSY (400 MHz, $CDCl_3$) of **9a**



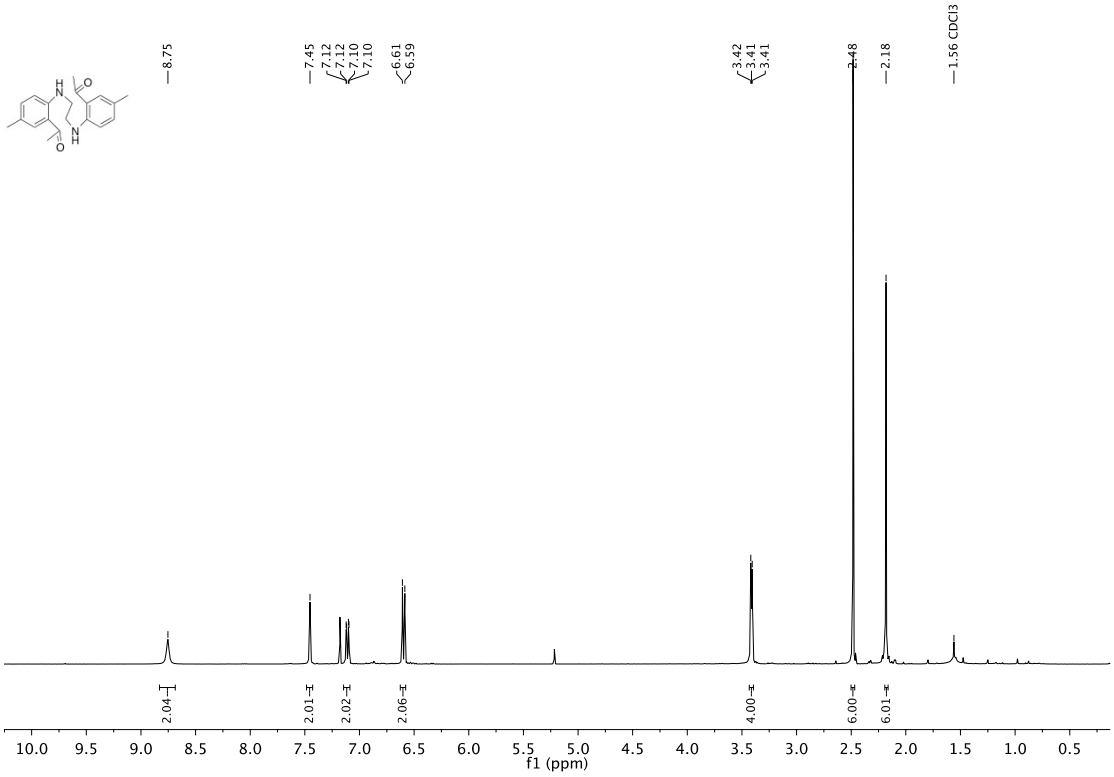
^{1}H NMR (400 MHz, $CDCl_3$) of **10a**



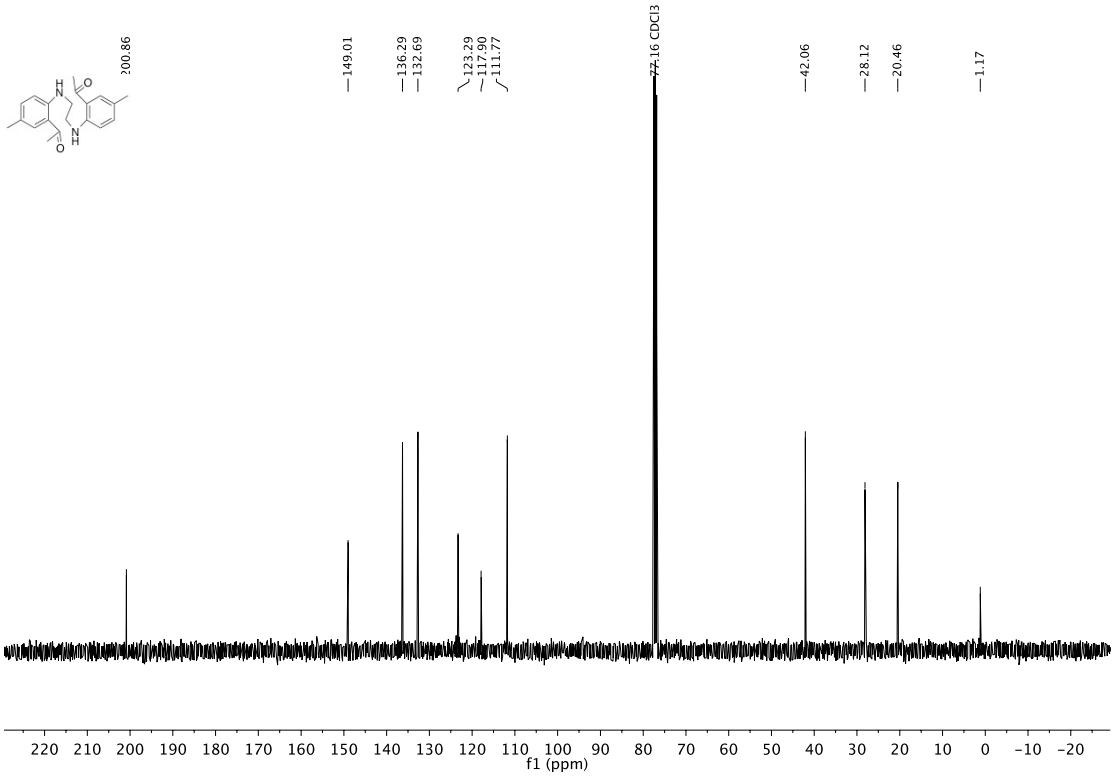
^{13}C NMR(100 MHz, $CDCl_3$) of **10a**



^{1}H NMR (400 MHz, $CDCl_3$) of **12a**



^{13}C NMR (100 MHz, $CDCl_3$) of **12a**



4. X-Ray Data

	6a	**6d**
Formula	$C_{18}H_{16}N_2O_2$	$C_{16}H_{10}Cl_2N_2O_2$
M_r	292.34	333.17
T [K]	150	150
Crystal system	orthorhombic	orthorhombic
Space group	Pnc2	Pbcn
Crystal dimensions [mm]	0.10 x 0.15 x 0.15	0.18 x 0.20 x 0.25
a [Å], α [°]	7.37910(10), 90	13.5987(2), 90
b [Å], β [°]	12.5501(2), 90	7.23440(10), 90
c [Å], γ [°]	7.49810(10), 90	13.7418(2), 90
V [Å^3]	694, 387(17)	1351.90(3)
Z, ρ [mg m^{-3}]	2, 1.398	4, 1.637
μ [mm^{-1}]	0.744	4.402
F(000)	308	680
Index ranges	$-9 \le h \le 9$, $-15 \le k \le 15$, $-9 \le l \le 9$	$-14 \le h \le 17$, $-7 \le k \le 9$, $-17 \le l \le 17$
θ range [°]	5.997 to 76.363	6.442 to 76.293
Completeness to θ [%]	100	99.6
Reflections collected	13587	11819
Independent reflections	1461 [R(int) = 0.017]	1413 [R(int) = 0.024]
Absorption correction	multi-scan	multi-scan
Max. and min. transmission	0.93 and 0.76	0.45 and 0.29
Refinement method	Full matrix least-squares on F^2	Full matrix least-squares on F^2
Data / restraints / parameters	1455 / 1 / 101	1406 / 0 / 100
Goodness-of-fit on F^2	1.0136	1.0054
Final R indices [$I>2\sigma(I)$]	R1 = 0.0252, wR2 = 0.0691	R1 = 0.0274, wR2 = 0.0748
R indices (all data)	R1 = 0.0253, wR2 = 0.0692	R1 = 0.0287, wR2 = 0.0768
Largest diff. peak and hole [e.Å-3]	0.16 and -0.13	0.31 and -0.33

	7a	**10a**
Formula	$C_{19}H_{18}N_2O_1$	$C_{18}H_{20}N_2O_2$
M_r	290.36	296.37
T [K]	150	150
Crystal system	monoclinic	monoclinic
Space group	P 21/n	P21/c
Crystal dimensions [mm]	0.18 x 0.20 x 0.20	0.15 x 0.18 x 0.22
a [Å], α [°]	9.6458(2), 90	7.32920(10), 90
b [Å], β [°]	14.7532(2), 109.3728(18)	19.7192(3), 97.9329(17)
c [Å], γ [°]	11.0237(2), 90	10.6272(2), 90
V [Å^3]	1479.92(5)	1521.21(4)
Z, ρ [mg m^{-3}]	4, 1.303	4, 1.294
μ [mm^{-1}]	0.641	0.680
F(000)	616	632
Index ranges	$-10 \le h \le 12$, $-18 \le k \le 17$, $-13 \le l \le 13$	$-8 \le h \le 9$, $-24 \le k \le 24$, $-13 \le l \le 13$
θ range [°]	5.204 to 76.404	4.484 to 76.540
Completeness to θ [%]	99.4	99.7
Reflections collected	13631	31065
Independent reflections	3080 [R(int) = 0.019]	3194 [R(int) = 0.024]
Absorption correction	multi-scan	multi-scan
Max. and min. transmission	0.89 and 0.83	0.90 and 0.79
Refinement method	Full matrix least-squares on F^2	Full matrix least-squares on F^2
Data / restraints / parameters	3068 / 0 / 199	3182 / 0 / 199
Goodness-of-fit on F^2	0.9881	0.9886
Final R indices [$I>2\sigma(I)$]	R1 = 0.0382, wR2 = 0.0962	R1 = 0.0538, wR2 = 0.1358
R indices (all data)	R1 = 0.0406, wR2 = 0.0984	R1 = 0.0557, wR2 = 0.1376
Largest diff. peak and hole [e.Å-3]	0.27 and -0.21	0.43 and -0.29

	5f
Formula	$C_{18}H_{18}N_2F_2$
M_r	300.34
T [K]	99
Crystal system	monoclinic
Space group	P 21/c
Crystal dimensions [mm]	0.18 x 0.20 x 0.20
a [Å], α [°]	12.2306(7), 90
b [Å], β [°]	13.6348(8), 93.658(1)
c [Å], γ [°]	8.4844(2), 90
V [$Å^3$]	1411.99(14)
Z, ρ [mg m^{-3}]	4, 1.413
μ [mm^{-1}]	0.102
F(000)	632.0
Index ranges	h: -16 – 16, k: -18 – 18, l: -11 – 11
θ range [°]	1.67 – 28.70
Completeness to θ [%]	1.000
Reflections collected	20793
Independent reflections	3287 [R(int) = 0.0406]
Absorption correction	multi-scan
Max. and min. transmission	0.9665, 0.9486
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	3657, 0, 201
Goodness-of-fit on F^2	1.033
Final R indices [I>2σ(I)]	R1 = 0.0406, wR2 = 0.1138
R indices (all data)	R1 = 0.0447, wR2 = 0.1174
Largest diff. peak and hole [e.Å-3]	0.605; -0.251

5. REFERENCES

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