

Development of a Late-Stage Diversification Strategy for the 4- and 5-Positions of 4,5,6-Trisubstituted Indazoles

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I. General Experimental Details

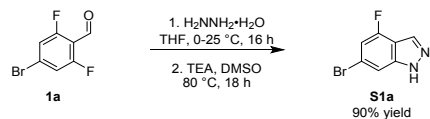
All commercially obtained reagents were used as received. **S1b** was purchased from Combi-Blocks Inc. Inhibitor free anhydrous THF was used as received from Sigma Aldrich. Lithium chloride solution (0.5 M) in anhydrous THF was used as received from Sigma Aldrich. Titration of *n*BuLi solution using *N*-benzylbenzamide was done before use, and the *n*BuLi solution (2.5 M) in hexanes was otherwise used as received from Sigma Aldrich. Lithium diisopropylamide (LDA) was generated fresh from *N,N*-diisopropylamine and *n*BuLi for each lithiation reaction. Anhydrous DMSO was used as received from Millipore Sigma. Reaction temperatures were controlled using an IKA mag temperature modulator, and if necessary, reactions were heated using an IKA RCT basic stir plate equipped with aluminum heating blocks. Unless otherwise stated, reactions were performed at room temperature (rt, approximately 25 °C). Thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F254) and visualized using UV light. Preparative silica-gel column chromatography was performed using Isco systems in conjunction with pre-packed cartridges. Reverse phase chromatography was performed using Isco systems in conjunction with Phenomenex Luna Omega Polar C18 columns. Uncorrected melting points were measured using an Optimelt/Meltview melting point apparatus. ¹H NMR spectra were recorded on Bruker spectrometers (at 400 MHz) and are reported relative to the residual solvent signal. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ¹³C NMR spectra were recorded on Bruker spectrometers (at 101 MHz) and are reported relative to the residual solvent signal. Data for proton-carbon decoupled ¹³C NMR spectra are reported in terms of chemical shift and, when necessary, multiplicity, and coupling constant (Hz) and integration. ¹⁹F NMR spectra were recorded on Bruker spectrometers (at 376 MHz) and reported in terms of chemical shift (δ ppm) and, when necessary, multiplicity, coupling constant (Hz), and integration. ¹¹B NMR were recorded on Bruker spectrometers (128 MHz) and reported in terms of chemical shift (δ ppm). Atropisomeric peaks reported as XX|YY. High resolution mass spectra were obtained using an Agilent 6230 Accurate Mass TOF LC/MS. Accurate masses are reported for the molecular ion [M+H]⁺ or a suitable ion fragment. Compound numbers used in the experimental section correspond to those employed in the main paper.

II. General Safety Information

The nucleophilic substitutions are carried out in DMSO under basic conditions. DMSO is known to undergo exothermic decomposition under basic reaction conditions.¹ Please **USE CAUTION** when performing these reactions.

General Experimental Procedures

a. Experimental Procedures for Indazole Formation to Form **S1a–d**



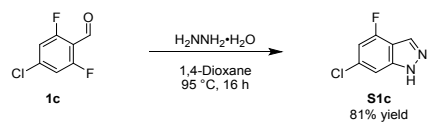
6-Bromo-4-fluoro-1H-indazole

This compound has been previously reported.²

To a stirred solution of 4-bromo-2,6-difluorobenzaldehyde (6.0 g, 27.1 mmol, 1.0 equiv) in THF (24.5 mL, 1.1 M with respect to benzaldehyde) was added hydrazine hydrate (1.95 g, 40.65 mmol, 1.5 equiv) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred at 25 °C for 16 h. The solvent was removed under reduced pressure. The residual solid was dissolved in DMSO (33.5 mL, 0.8 M with respect to benzaldehyde). Triethylamine (7.5 mL, 54.2 mmol, 2.0 equiv) was added, and the mixture was stirred at 80 °C for 18 h. The reaction was cooled and quenched with water. The resulting mixture was extracted with ethyl acetate (3x). The organic layers were combined, washed with water, brine, dried (Na_2SO_4), filtered, and concentrated to give the crude product. The crude product was purified by flash column chromatography (0–10% ethyl acetate:petroleum ether) to give title compound **S1a** (5.2 g, 90% yield) as a white solid.

¹H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.51 (s, 1H), 8.21 (t, $J = 1.4$ Hz, 1H), 7.64 (t, $J = 1.2$ Hz, 1H), 7.16 (dd, $J = 9.7, 1.3$ Hz, 1H).

¹⁹F NMR (376 MHz, $\text{DMSO}-d_6$) δ -115.73 (s, 1F).



6-Chloro-4-fluoro-1H-indazole

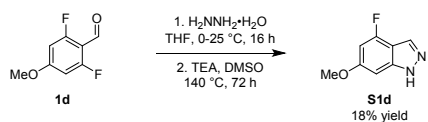
To a round-bottom flask equipped with a magnetic stir bar were added 4-chloro-2,6-difluorobenzaldehyde (5000 mg, 28.32 mmol, 1.0 equiv), 1,4-Dioxane (18.9 mL, 1.5 M with respect to benzaldehyde), and hydrazine hydrate (3900 mg, 77.9 mmol, 2.75 equiv), and the reaction mixture was stirred for 16 h at 95 °C. The reaction mixture was cooled to rt and slowly added to 250 mL of water. The solids were filtered off and washed an additional time with water then dried. The solid was triturated with MTBE (3x50 mL), diluted with ethyl acetate (50 mL), dried (Na_2SO_4), and concentrated to deliver **S1c** (3.91 g, 81% yield) as an off-white amorphous solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.51 (s, 1H), 8.21 (t, *J* = 1.3 Hz, 1H), 7.50 (t, *J* = 1.3 Hz, 1H), 7.05 (dd, *J* = 9.9, 1.5 Hz, 1H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 154.4 (d, *J* = 252.9 Hz, 1C), 142.3 (d, *J* = 10.6 Hz, 1C), 131.0 (d, *J* = 9.9 Hz, 1C), 130.0 (d, *J* = 2.8 Hz, 1C), 111.9 (d, *J* = 22.9 Hz, 1C), 106.6 (d, *J* = 4.4 Hz, 1C), 106.0 (d, *J* = 22.5 Hz, 1C).

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -115.74 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₇H₄ClFN₂ 171.0120; Found 171.0114.



4-Fluoro-6-methoxy-1H-indazole

To a stirred solution of 2,6-difluoro-4-methoxybenzaldehyde (1.0 g, 5.81 mmol, 1.0 equiv) in THF (5.3 mL, 1.1 M with respect to benzaldehyde) was added hydrazine hydrate (0.436 g, 8.72 mmol, 1.5 equiv) at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred at 25 °C for 16 h. The solvent was removed under reduced pressure. The residual solid was dissolved in DMSO (10 mL, 0.6 M with respect to benzaldehyde). Triethylamine (2.5 mL, 11.6 mmol, 2.0 equiv) was added, and the mixture was stirred at 140 °C for 72 h. The reaction was cooled and quenched with water. The resulting mixture was extracted with ethyl acetate (3x). The organic layers were combined, washed with water, brine, dried (Na₂SO₄), filtered, and concentrated to give the crude product. The crude product was purified by flash column chromatography (0–10% ethyl acetate:petroleum ether) to give title compound **S1d** (0.17 g, 18% yield) as an amorphous yellow solid.

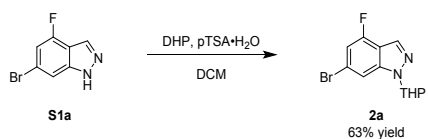
¹H NMR (400 MHz, DMSO-*d*₆) δ 13.11 (s, 1H), 8.02 (t, *J* = 1.3 Hz, 1H), 6.78 (dd, *J* = 1.8, 1.0 Hz, 1H), 6.57 (dd, *J* = 11.7, 1.8 Hz, 1H), 3.83 (s, 3H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.4 (d, *J* = 11.2 Hz, 1C), 154.8 (d, *J* = 248.2 Hz, 1C), 143.0 (d, *J* = 11.4 Hz, 1C), 129.6 (d, *J* = 2.9 Hz, 1C), 107.9 (d, *J* = 23.7 Hz, 1C), 96.9 (d, *J* = 21.4 Hz, 1C), 87.6 (d, *J* = 3.8 Hz, 1C), 55.8.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -117.57 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₈H₇FN₂O 167.0615; Found 167.0613.

b. Experimental Procedures for THP Protection to Form **2a–d**

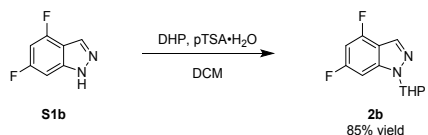


6-bromo-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

*This compound has been previously reported.*³

To a stirred solution of **S1a** (26.2 g, 0.122 mol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (2.32 g, 0.0122 mol, 0.1 equiv) in DCM (260 mL, 0.5 M with respect to indazole) was added 2H-3,4-dihydropyran (22.3 mL, 0.244 mol, 2.0 equiv). The resulting mixture was stirred at 25 °C for 20 h. The reaction was quenched with sat NaHCO₃ (aq) and extracted with DCM (2x). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated to give the crude product. The crude product was triturated with MeOH to give title compound **2a** (24.0 g, 63% yield) as yellow solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 – 8.24 (m, 1H), 7.94 (t, *J* = 1.1 Hz, 1H), 7.26 (dd, *J* = 9.5, 1.3 Hz, 1H), 5.90 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.87 (dtd, *J* = 11.3, 3.9, 1.6 Hz, 1H), 3.77 (ddd, *J* = 11.5, 8.1, 5.9 Hz, 1H), 2.43 – 2.28 (m, 1H), 2.01 (dddt, *J* = 22.8, 13.1, 7.1, 4.0 Hz, 2H), 1.72 (dddd, *J* = 15.7, 14.3, 7.0, 4.1 Hz, 1H), 1.58 (tq, *J* = 8.1, 3.9 Hz, 2H).



4,6-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

To a round bottom flask equipped with a magnetic stir bar were added **S1b** (10 g, 64.8 mmol, 1.0 equiv), DCM (200 mL, 0.3 M with respect to indazole), 2H-3,4-dihydropyran (8.88 mL, 97.3 mmol, 1.5 equiv), and *p*-toluenesulfonic acid monohydrate (1.23 g, 6.49 mmol, 0.1 equiv), and the reaction mixture was stirred at 25 °C for 17 h. TLC revealed the reaction had occurred. The reaction mixture was quenched with sat NaHCO₃ (aq). The mixture was separated, and the aqueous was extracted with DCM (2x). The organics were combined, dried (MgSO₄), concentrated, and purified by flash column chromatography (0–30% ethyl acetate:heptane) to deliver title compound **2b** (13.1 g, 85% yield) as a white solid.

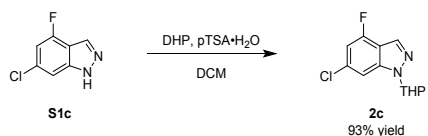
mp: 48.7 – 50.5 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24 (d, *J* = 0.8 Hz, 1H), 7.51 (dd, *J* = 9.7, 1.9 Hz, 1H), 7.05 (td, *J* = 10.0, 1.9 Hz, 1H), 5.83 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.87 (dtd, *J* = 11.5, 3.8, 1.6 Hz, 1H), 3.75 (ddd, *J* = 11.5, 8.2, 6.1 Hz, 1H), 2.44 – 2.29 (m, 1H), 2.09 – 1.91 (m, 2H), 1.80 – 1.66 (m, 1H), 1.58 (hept, *J* = 4.0 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 161.2 (dd, *J* = 243.6, 11.5 Hz, 1C), 154.5 (dd, *J* = 252.4, 16.1 Hz, 1C), 141.1 (dd, *J* = 15.1, 11.1 Hz, 1C), 129.9 (d, *J* = 2.9 Hz, 1C), 111.0 (d, *J* = 23.2 Hz, 1C), 96.9 (dd, *J* = 30.7, 22.8 Hz, 1C), 93.2 (dd, *J* = 27.3, 4.8 Hz, 1C), 84.1, 66.5, 28.7, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -111.40 (d, *J* = 8.0 Hz, 1F), -114.50 (d, *J* = 7.1 Hz, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₂H₁₂F₂N₂O 239.0991; Found 239.0987.



6-chloro-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

To a round bottom flask equipped with a magnetic stir bar were added **S1c** (3.91 g, 22.92 mmol, 1.0 equiv), DCM (30.5 mL, 0.75 M with respect to indazole), *p*-toluenesulfonic acid monohydrate (436 mg, 2.29 mmol, 0.1 equiv), and 2H-3,4-dihydropyran (3.14 mL, 34.4 mmol, 1.5 equiv), and the mixture was stirred for 1 h at 25 °C. TLC revealed the reaction had occurred. The reaction mixture was quenched with sat NaHCO₃ (aq). The mixture was separated, and the aqueous was extracted with DCM (2x). The organics were combined, dried (MgSO₄), concentrated, and purified by flash column chromatography (0–30% ethyl acetate:heptane) to deliver title compound **2c** (5.42 g, 93% yield) of a pale yellow solid.

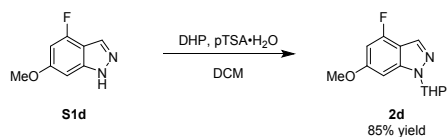
mp: 69.6 – 71.9 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 (d, *J* = 0.9 Hz, 1H), 7.77 (t, *J* = 1.2 Hz, 1H), 7.12 (dd, *J* = 9.8, 1.5 Hz, 1H), 5.87 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.91 – 3.81 (m, 1H), 3.81 – 3.71 (m, 1H), 2.43 – 2.28 (m, 1H), 2.07 – 1.91 (m, 2H), 1.82 – 1.63 (m, 1H), 1.63 – 1.48 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 154.2 (d, *J* = 253.7 Hz, 1C), 141.6 (d, *J* = 10.3 Hz, 1C), 131.7 (d, *J* = 9.9 Hz, 1C), 129.8 (d, *J* = 2.4 Hz, 1C), 112.9 (d, *J* = 23.2 Hz, 1C), 106.9 – 107.1 (m, 2C), 84.0, 66.3, 28.1, 24.0, 21.1.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -115.83 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₂H₁₂ClFN₂O 255.0695; Found 255.0683.



4-fluoro-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

To a stirred solution of **S1d** (170 mg, 1.02 mmol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (19.4 mg, 0.102 mmol, 0.1 equiv) in DCM (4.0 mL, 0.25 M with respect to indazole) was added 2*H*-3,4-dihydropyran (172 mg, 2.04 mol, 2.0 equiv). The resulting mixture was stirred at 25 °C for 20 h. TLC revealed the reaction had occurred. The reaction mixture was quenched with sat NaHCO₃ (aq). The mixture was separated, and the aqueous was extracted with DCM (2x). The organics were combined, dried (MgSO₄), concentrated, and purified by flash column chromatography (0–30% ethyl acetate:heptane) to deliver title **2d** (270 mg, 85 % yield) as a white solid.

mp: 94.3 – 99.1 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 (d, *J* = 0.8 Hz, 1H), 7.05 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.65 (dd, *J* = 11.6, 1.8 Hz, 1H), 5.83 (dd, *J* = 9.6, 2.6 Hz, 1H), 3.92 – 3.82 (m, 4H), 3.76 (ddd, *J* = 11.5, 8.1, 6.1 Hz, 1H), 2.39 (dddd, *J* = 13.6, 12.1, 9.6, 4.1 Hz, 1H), 2.04 (dtd, *J* = 13.1, 4.1, 1.7 Hz, 1H), 1.94 (dq, *J* = 13.1, 3.7 Hz, 1H), 1.83 – 1.64 (m, 1H), 1.57 (tq, *J* = 8.2, 3.9 Hz, 2H).

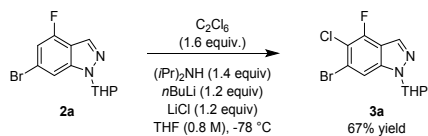
¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.9 (d, *J* = 11.2 Hz, 1C), 154.6 (d, *J* = 248.7 Hz, 1C), 142.5 (d, *J* = 11.2 Hz, 1C), 129.5 (d, *J* = 2.4 Hz, 1C), 108.7 (d, *J* = 23.8 Hz, 1C), 97.6 (d, *J* = 21.4 Hz, 1C), 88.5 (d, *J* = 3.9 Hz, 1C), 83.6, 66.4, 56.1, 28.9, 24.7, 22.1.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -117.72 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₃H₁₅FN₂O₂ 251.1190; Found 251.1192.

c. Experimental Procedures for C–H functionalization to Form **3a–i**

i. General Procedure A for C–H functionalization (Synthesis of **3a** used as an example)



6-bromo-5-chloro-4-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

To an oven dried vial under an atmosphere of nitrogen and equipped with a magnetic stir bar were added *N,N*-diisopropylamine (142 mg, 1.40 mmol, 0.196 mL, 1.4 equiv) and THF (1.25 mL, 0.8 M with respect to indazole), and the solution was cooled to 0 °C. *n*BuLi (0.522 mL, 2.3 M in hexanes, 1.20 mmol, 1.2 equiv with respect to indazole) was added to the solution, and the solution was stirred at 0 °C for 15 min, then cooled to -78 °C for transfer.

To an oven dried vial under an atmosphere of nitrogen and equipped with a magnetic stir bar were added **2a** (299 mg, 1.0 mmol, 1.0 equiv) and lithium chloride (2.40 mL, 0.5 M in THF, 1.20 mmol, 1.2 equiv), and the solution was cooled to -78 °C. The basic solution was then added to the substrate (**SLOWLY**). The reaction mixture was stirred for 2 h at -78 °C.

To an oven dried vial under an atmosphere of nitrogen and equipped with a magnetic stir were added hexachloroethane (379 mg, 1.60 mmol, 1.6 equiv) and THF (2.0 mL, 0.5 M with respect to indazole), and the solution was cooled to -78 °C. The anion was quickly cannula transferred to the electrophile, and stirring was continued at -78 °C for 1 h. The reaction was quenched with sat NH₄Cl (aq), extracted with ethyl acetate (2x), dried (Na₂SO₄), and concentrated to give an orange residue. The crude material was purified by flash column chromatography (0–30% ethyl acetate:heptane) to deliver title compound **3a** (225 mg, 67% yield) as a white solid.

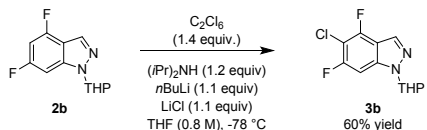
mp: 119.3 – 122.2 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (d, *J* = 0.9 Hz, 1H), 8.22 – 8.17 (m, 1H), 5.92 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.87 (dtd, *J* = 11.5, 3.9, 1.5 Hz, 1H), 3.83 – 3.73 (m, 1H), 2.42 – 2.27 (m, 1H), 2.09 – 1.92 (m, 2H), 1.80 – 1.63 (m, 1H), 1.63 – 1.52 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 150.1 (d, *J* = 255.2 Hz, 1C), 140.0 (d, *J* = 9.7 Hz, 1C), 129.8 (d, *J* = 2.6 Hz, 1C), 120.5, 113.8 (d, *J* = 23.0 Hz, 1C), 112.7 – 110.2 (m, 2C), 84.0, 66.5, 28.8, 24.6, 21.9.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -112.94 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₂H₁₂BrClFN₂O 332.9800; Found 332.9799.



5-chloro-4,6-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

Following general procedure A for C–H functionalization using **2b** (5.0 g, 20.99 mmol, 1.0 equiv), *N,N*-diisopropylamine (1.2 equiv), *n*BuLi (1.1 equiv), lithium chloride (1.1 equiv), and THF (0.8 M with respect to indazole), purified by flash column chromatography (0–40% ethyl acetate:heptane) then slurrying in isopropanol (4V) and filtered to deliver title compound **3b** (3.4 g, 60% yield) as a white solid.

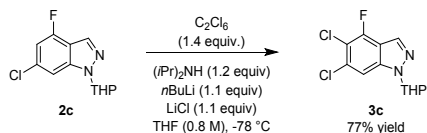
mp: 86.8 – 88.4 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (d, *J* = 1.0 Hz, 1H), 7.82 (dt, *J* = 9.3, 1.2 Hz, 1H), 5.86 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.87 (dtd, *J* = 11.6, 3.9, 1.6 Hz, 1H), 3.76 (ddd, *J* = 11.5, 7.3, 5.4 Hz, 1H), 2.42 – 2.28 (m, 1H), 2.09 – 1.92 (m, 2H), 1.80 – 1.69 (m, 1H), 1.58 (hept, *J* = 3.9 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 150.4 (d, *J* = 254.4 Hz, 1C), 139.1 (d, *J* = 10.2 Hz, 1C), 130.4, 129.8 (d, *J* = 2.8 Hz, 1C), 113.3 (d, *J* = 22.8 Hz, 1C), 110.0 (d, *J* = 18.0 Hz, 1C), 108.4 (d, *J* = 4.4 Hz, 1C), 84.0, 66.5, 28.7, 24.6, 21.9.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -115.05 (s, 1F), -117.17 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+Na]⁺ calcd for C₁₂H₁₁ClF₂N₂ONa 295.0420; Found 295.0417.



5,6-dichloro-4-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

Following general procedure A for C–H functionalization using **2c** (49.0 g, 192.4 mmol, 1.0 equiv), *N,N*-diisopropylamine (1.2 equiv), *n*BuLi (1.1 equiv), lithium chloride (1.1 equiv), and THF (0.8 M with respect to indazole), purified by slurrying in isopropanol (4V) and filtering to deliver title compound **3c** (42.6 g, 77% yield) as a white solid.

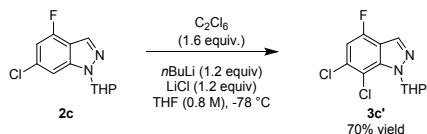
mp: 94.0 – 95.7 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 (d, *J* = 0.9 Hz, 1H), 8.09 (t, *J* = 1.1 Hz, 1H), 5.93 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.93 – 3.84 (m, 1H), 3.78 (ddd, *J* = 11.5, 7.9, 5.8 Hz, 1H), 2.43 – 2.28 (m, 1H), 2.09 – 1.94 (m, 2H), 1.81 – 1.66 (m, 1H), 1.63 – 1.54 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 150.4 (d, *J* = 254.5 Hz, 1C), 139.2 (d, *J* = 10.3 Hz, 1C), 130.4, 129.9 (d, *J* = 2.8 Hz, 1C), 113.4 (d, *J* = 22.8 Hz, 1C), 110.0 (d, *J* = 18.0 Hz, 1C), 108.5 (d, *J* = 4.4 Hz, 1C), 84.0, 66.5, 28.7, 24.6, 21.9.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.01 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₂H₁₁Cl₂FN₂O 289.0305; Found 289.0303.



6,7-dichloro-4-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

Following general procedure A for C–H functionalization using **2c** (255 mg, 1.0 mmol) and *n*BuLi as base (*not LDA*), purified by reverse phase HPLC (31x250 mm, Flow Rate 65 mL/min, 20–80% MeCN:H₂O + 0.05% AcOH) to deliver title compound **3c'** (201 mg, 70% yield) as a white solid in a 5:1 ratio of **3c'**:**3c**.

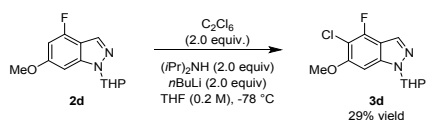
mp: 84.5 – 93.2 °C (mixture of isomers)

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 (s, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 6.29 (dd, *J* = 9.7, 2.2 Hz, 1H), 3.94 – 3.83 (m, 1H), 3.77 – 3.68 (m, 1H), 2.48 – 2.38 (m, 1H), 2.15 – 1.98 (m, 2H), 1.81 – 1.67 (m, 1H), 1.64 – 1.48 (m, 3H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.6 (d, *J* = 253.4 Hz, 1C), 137.8 (d, *J* = 9.7 Hz, 1C), 131.3 (d, *J* = 10.4 Hz, 1C), 130.6 (d, *J* = 2.2 Hz, 1C), 115.6 (d, *J* = 24.4 Hz, 1C), 110.3 (d, *J* = 4.9 Hz, 1C), 108.9 (d, *J* = 23.5 Hz, 1C), 84.6, 66.4, 28.7, 24.6, 22.4.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -118.15 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+Na]⁺ calcd for C₁₂H₁₁Cl₂FN₂ONa 311.0125; Found 311.0116.



5-chloro-4-fluoro-6-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

To a stirred solution of *N,N*-diisopropylamine (243 mg, 2.40 mmol, 2.0 equiv) in THF (5.0 mL 0.2 M with respect to indazole) under an atmosphere of nitrogen was added *n*BuLi (1.05 mL, 2.5 M in hexanes, 2.6 mmol, 2.2 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min then cooled to -78 °C. **2d** (300 mg, 1.20 mmol, 1.0 equiv) in THF (5.0 mL, 0.2 M with respect to indazole) was added dropwise to the mixture and stirred for 1 h. Hexachloroethane (568 mg, 2.40 mmol, 2.0 equiv) in THF (5.0 mL, 0.2 M with respect to indazole) was added to the mixture. The reaction was stirred for 30 min and warmed to rt. The reaction was quenched with sat NH₄Cl (aq), extracted with ethyl acetate (2x), dried (Na₂SO₄), and concentrated to give an orange residue. The crude material was purified by reverse phase HPLC (31x250 mm, Flow Rate 65 mL/min, 20–80% MeCN:H₂O + 0.05% AcOH) to deliver title compound **3d** (100 mg, 29% yield) as a white solid.

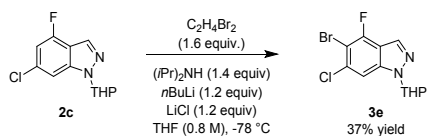
mp: 101.6 – 106.6 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (s, 1H), 7.27 (s, 1H), 5.90 (dd, *J* = 9.6, 2.6 Hz, 1H), 3.98 (s, 3H), 3.93 – 3.84 (m, 1H), 3.83 – 3.72 (m, 1H), 2.38 (tdd, *J* = 13.2, 9.6, 4.1 Hz, 1H), 2.10 – 2.00 (m, 1H), 1.95 (dq, *J* = 12.8, 3.5 Hz, 1H), 1.82 – 1.66 (m, 1H), 1.59 (dq, *J* = 10.0, 5.8, 4.7 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 154.8 (d, *J* = 2.5 Hz, 1C), 150.3 (d, *J* = 250.2 Hz, 1C), 139.8 (d, *J* = 10.8 Hz, 1C), 129.5 (d, *J* = 2.6 Hz, 1C), 108.5 (d, *J* = 23.1 Hz, 1C), 102.9 (d, *J* = 17.3 Hz, 1C), 88.8 (d, *J* = 3.6 Hz, 1C), 83.4, 66.4, 57.1, 28.9, 24.7, 22.1.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -118.63 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₃H₁₅ClFN₂O₂ 285.0801; Found 285.0799.



5-bromo-6-chloro-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

Following general procedure A for C–H functionalization using **2c** (255 mg, 1.0 mmol) and dibromoethane (1.6 equiv) as the electrophile, purified by reverse phase HPLC (31x250 mm, Flow Rate 65 mL/min, 20–80% MeCN:H₂O + 0.05% AcOH) to deliver title compound **3e** (125 mg, 37% yield) as a white solid.

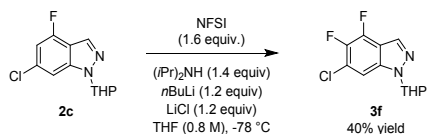
mp: 95.3 – 97.5 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (d, *J* = 0.9 Hz, 1H), 8.07 (d, *J* = 1.0 Hz, 1H), 5.92 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.77 (ddd, *J* = 11.4, 7.9, 5.8 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.08 – 1.89 (m, 2H), 1.80 – 1.64 (m, 1H), 1.59 (dq, *J* = 9.1, 4.0 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.6 (d, *J* = 252.3 Hz, 1C), 140.0 (d, *J* = 10.3 Hz, 1C), 132.0, 129.7 (d, *J* = 3.0 Hz, 1C), 113.4 (d, *J* = 24.3 Hz, 1C), 108.4 (d, *J* = 4.3 Hz, 1C), 100.0 (d, *J* = 21.3 Hz, 1C), 84.1, 66.5, 28.7, 24.6, 21.9.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -104.62 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+Na]⁺ calcd for C₁₂H₁₂BrClFNa 354.9620; Found 354.9611.



6-chloro-4,5-difluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

Following general procedure A for C–H functionalization using **2c** (255 mg, 1.0 mmol) and NFSI (1.6 equiv) as the electrophile, purified by reverse phase HPLC (31x250 mm, Flow Rate 65 mL/min, 20–80% MeCN:H₂O + 0.05% AcOH) to deliver title compound **3f** (110 mg, 40% yield) as a white solid.

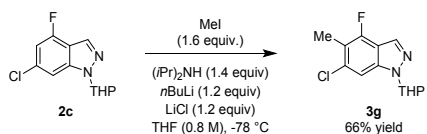
mp: 79.5 – 81.8 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.37 (s, 1H), 8.02 – 7.96 (m, 1H), 5.90 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.87 (dtd, *J* = 11.6, 3.9, 1.5 Hz, 1H), 3.77 (ddd, *J* = 11.5, 7.9, 5.7 Hz, 1H), 2.42 – 2.26 (m, 1H), 2.08 – 1.93 (m, 2H), 1.80 – 1.65 (m, 1H), 1.59 (dq, *J* = 8.9, 4.1 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 141.9 (dd, *J* = 153.5, 14.1 Hz, 1C), 139.5 (dd, *J* = 138.4, 15.2 Hz, 1C), 136.3 (d, *J* = 8.7 Hz, 1C), 130.2 (dd, *J* = 5.8, 2.4 Hz, 1C), 121.3 (d, *J* = 18.0 Hz, 1C), 113.4 (d, *J* = 19.4 Hz, 1C), 107.6 (d, *J* = 4.4 Hz, 1C), 84.0, 66.5, 28.7, 24.6, 21.9.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -141.28 (d, *J* = 21.3 Hz, 1F), -150.88 (d, *J* = 21.6 Hz, 1F).

HRMS (ESI/TOF) *m/z*: [M+Na]⁺ calcd for C₁₂H₁₁ClF₂N₂ONa 295.0420; Found 295.0410.



6-chloro-4-fluoro-5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

Following general procedure A for C–H functionalization using **2c** (255 mg, 1.0 mmol) and MeI (1.6 equiv) as the electrophile, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **3g** (178 mg, 66% yield) as a white solid.

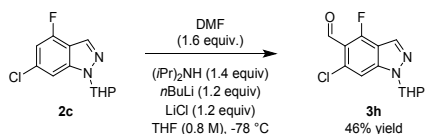
mp: 58.6 – 60.7 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 (s, 1H), 7.81 (s, 1H), 5.87 (dd, *J* = 9.6, 2.5 Hz, 1H), 3.86 (dtd, *J* = 11.5, 3.9, 1.6 Hz, 1H), 3.76 (ddd, *J* = 11.4, 8.0, 5.8 Hz, 1H), 2.42 – 2.28 (m, 4H), 2.07 – 1.91 (m, 2H), 1.72 (dddd, *J* = 20.5, 8.3, 6.6, 3.3 Hz, 1H), 1.57 (tq, *J* = 8.2, 4.0 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.0 (d, *J* = 249.7 Hz, 1C), 139.4 (d, *J* = 10.5 Hz, 1C), 133.3 (d, *J* = 5.5 Hz, 1C), 129.4 (d, *J* = 2.2 Hz, 1C), 113.4 (d, *J* = 17.2 Hz, 1C), 113.1 (d, *J* = 24.9 Hz, 1C), 107.1 (d, *J* = 4.5 Hz, 1C), 84.0, 66.4, 28.8, 24.6, 22.0, 11.2 (d, *J* = 3.7 Hz, 1C).

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -118.05 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₃H₁₅ClFN₂O 269.0852; Found 269.0845.



6-chloro-4-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-5-carbaldehyde

Following general procedure A for C–H functionalization using **2c** (255 mg, 1.0 mmol) and DMF (1.6 equiv) as the electrophile, purified by flash chromatography (2 mm chromatron plate, 5–25% ethyl acetate:heptane) to deliver title compound **3h** (130 mg, 46% yield) as a white solid.

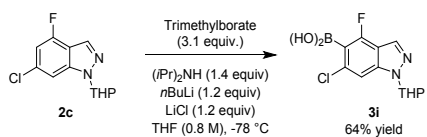
mp: 98.0 – 100.0 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.38 (d, *J* = 1.0 Hz, 1H), 8.50 (d, *J* = 0.9 Hz, 1H), 7.95 (d, *J* = 0.9 Hz, 1H), 5.96 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.83 – 3.75 (m, 1H), 2.41 – 2.27 (m, 1H), 2.08 – 1.93 (m, 2H), 1.81 – 1.66 (m, 1H), 1.64 – 1.53 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 186.7 (d, *J* = 2.9 Hz, 1C), 156.6 (d, *J* = 272.1 Hz, 1C), 142.4 (d, *J* = 11.8 Hz, 1C), 132.5 (d, *J* = 3.5 Hz, 1C), 132.4, 113.4 (d, *J* = 6.4 Hz, 1C), 113.1 (d, *J* = 22.0 Hz, 1C), 109.0 (d, *J* = 4.0 Hz, 1C), 84.1, 66.6, 28.7, 24.5, 21.8.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -116.5 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₃H₁₃ClFN₂O₂ 283.0644; Found: 283.0639.



(6-chloro-4-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)boronic acid

Following general procedure A for C–H functionalization using **2c** (255 mg, 1.0 mmol) and trimethylborate (3.1 equiv) as the electrophile and adding the electrophile to the anion, purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **3i** (188 mg, 64% yield) as a colorless oil.

¹H NMR (400 MHz, Methanol-*d*₄) δ 8.01 (d, *J* = 0.9 Hz, 1H), 7.54 (d, *J* = 1.0 Hz, 1H), 5.68 (dd, *J* = 9.4, 2.7 Hz, 1H), 3.88 (dtd, *J* = 11.6, 4.0, 1.8 Hz, 1H), 3.71 (ddd, *J* = 11.6, 9.7, 3.5 Hz, 1H), 2.37 (dddd, *J* = 13.4, 11.6, 9.3, 4.0 Hz, 1H), 2.03 (dtd, *J* = 13.1, 4.2, 1.6 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.78 – 1.65 (m, 1H), 1.59 (dddt, *J* = 13.8, 9.3, 4.9, 3.7 Hz, 2H).

¹³C NMR (101 MHz, Methanol-*d*₄) δ 157.4 (d, *J* = 248.5 Hz, 1C), 143.7 (d, *J* = 10.4 Hz, 1C), 135.8 (d, *J* = 12.7 Hz, 1C), 130.9 (d, *J* = 2.5 Hz, 1C), 114.4 (d, *J* = 26.0 Hz, 1C), 108.3 (d, *J* = 4.6 Hz, 1C), 86.7, 68.3, 49.9, 30.3, 26.2, 23.3.

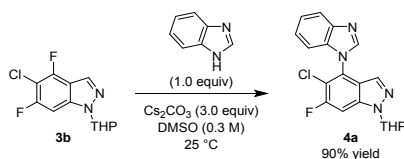
¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -110.80 (s, 1F).

¹¹B NMR (128 MHz, Methanol-*d*₄) δ 28.46 (br s, 1B).

HRMS (ESI/TOF) *m/z*: [M-H]⁻ calcd for C₁₂H₁₂BClFN₂O₃ 297.0621; Found 297.0617.

d. Experimental Procedures for the Nucleophilic Substitution to Form **4a–o**

i. General Procedure B for Nucleophilic Substitution (Synthesis of **4a** used as an example)



4-(1*H*-benzo[d]imidazol-1-yl)-5-chloro-6-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

To an oven dried vial equipped with a magnetic stir bar were added **3b** (81.8 mg, 0.3 mmol), benzimidazole (42.5 mg, 0.36 mmol, 1.2 equiv), and cesium carbonate (293 mg, 0.9 mmol, 3.0 equiv). The solids were purged with nitrogen. DMSO (1.0 mL, 0.3 M with respect to indazole) was added to the solids. The vial was capped and stirred at 25 °C for 2 h. The reaction was diluted with ethyl acetate, washed with water (2x), brine, dried (MgSO₄), and concentrated to give a crude residue. The crude material was purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **4a** (100 mg, 90% yield) as an amorphous solid and atropisomeric mixture.

¹H NMR (400 MHz, DMF-*d*₇, 100 °C) δ 8.51 – 8.39 (m, 1H), 8.06 – 8.00 (m, 1H), 7.88 – 7.80 (m, 1H), 7.75 (s, 1H), 7.38 – 7.26 (m, 2H), 7.24 – 7.13 (m, 1H), 5.96 (dd, *J* = 9.1, 2.4 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.90 – 3.79 (m, 1H), 2.54 – 2.35 (m, 1H), 2.19 – 2.04 (m, 2H), 1.90 – 1.75 (m, 1H), 1.76 – 1.55 (m, 2H).

¹³C NMR (101 MHz, DMF-*d*₇, 100 °C) δ 158.2 (d, *J* = 246.8 Hz), 145.1, 144.8|144.7, 139.4, 135.6, 132.4, 128.3, 124.9|124.9, 123.9, 121.4, 121.2, 114.9 (d, *J* = 22.6 Hz), 112.1|112.0, 100.1 (d, *J* = 27.8 Hz), 86.9, 68.0, 26.2, 23.1, (18 of 19 reported)

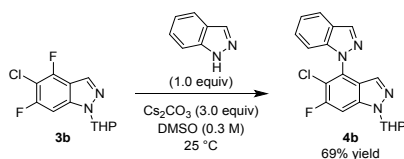
¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -113.23|-113.27 (s, 1F).

Note: (18 of 19 reported) 1 missing carbon under DMF peak, HSQC reveals correlation to 2 protons for a carbon peak at ~29.1 ppm.

A range of temperature explored - Unable to observe total coalescence of atropisomeric doublet of H9 (8.6 – 8.4 ppm) at 147 °C, near the maximum temperature allowed (150 °C) for our instruments.

Key evidence for C4-N8 regiochemistry was observed NOE between H3 and H9.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₁₇ClFN₄O 371.1069; Found 371.1089.



5'-chloro-6'-fluoro-1'-(tetrahydro-2*H*-pyran-2-yl)-1'*H*-1,4'-biindazole

Following general procedure B using **3b** (0.3 mmol), 1*H*-indazole (1.0 equiv), and DMSO (0.3 M with respect to **3b**), purified by flash column chromatography (10% ethyl acetate:heptane) to deliver title compound **4b** (76 mg, 69% yield) as a white solid and atropisomeric mixture.

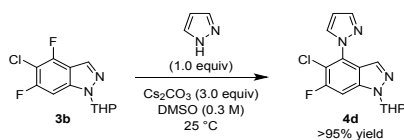
mp: 46.4 – 54.1 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.55 (s, 1H), 8.18 – 8.13 (m, 1H), 7.98 – 7.94 (m, 1H), 7.77 (s, 1H), 7.51 – 7.44 (m, 1H), 7.36 – 7.28 (m, 2H), 5.94 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.98 – 3.85 (m, 1H), 3.85 – 3.74 (m, 1H), 2.44 – 2.30 (m, 1H), 2.11 – 1.94 (m, 3H), 1.84 – 1.65 (m, 1H), 1.62 – 1.58 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 156.3 (d, *J* = 245.7 Hz), 139.7, 137.8 (d, *J* = 12.8 Hz), 137.1, 131.7, 129.6 (d, *J* = 3.2 Hz), 127.5, 124.1, 121.9, 121.5, 119.1, 112.1 (d, *J* = 22.5 Hz), 110.7, 98.4 (d, *J* = 27.7 Hz), 84.2, 66.6, 28.7, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -113.41|-113.46.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₁₆ClFN₄O: 370.0997; found: 370.1011.



5-chloro-6-fluoro-4-(1*H*-pyrazol-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

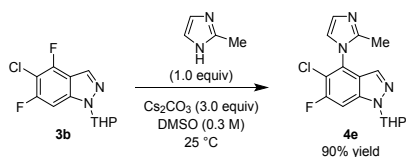
Following general procedure B using **3b** (0.3 mmol), pyrazole (1.0 equiv), and DMSO (0.3 M with respect to **3b**), purified by flash column chromatography (10% ethyl acetate:heptane) to deliver title compound **4d** (91 mg, >95% yield) as a colorless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.34 (d, *J* = 2.5 Hz, 1H), 8.04 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.98 (d, *J* = 0.9 Hz, 1H), 7.93 (d, *J* = 1.8 Hz, 1H), 6.69 – 6.64 (m, 1H), 5.90 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.83 – 3.72 (m, 1H), 2.43 – 2.30 (m, 1H), 2.09 – 1.93 (m, 2H), 1.81 – 1.67 (m, 1H), 1.59 (p, *J* = 4.6 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 156.2 (d, *J* = 244.9 Hz), 141.6, 137.7 (d, *J* = 13.5 Hz), 132.7, 132.3, 131.0 (d, *J* = 3.3 Hz), 117.7, 109.4 (d, *J* = 23.0 Hz), 107.3, 97.6 (d, *J* = 27.8 Hz), 84.2, 66.6, 28.7, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -113.14 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₅H₁₄ClFN₄O 320.0840; Found 320.0852.



5-chloro-6-fluoro-4-(2-methyl-1*H*-imidazol-1-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

Following general procedure B using **3b** (0.3 mmol), 2-methylimidazole (1.0 equiv), and DMSO (0.3 M with respect to **3b**), purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **4e** (88 mg, 90% yield) as a white solid and atropisomeric mixture.

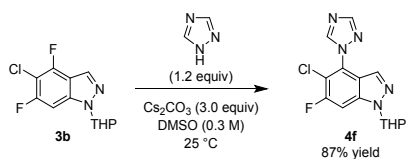
mp: 153.4 – 154.5 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 – 8.06 (m, 1H), 7.90 – 7.83 (m, 1H), 7.37 – 7.29 (m, 1H), 7.09 – 7.02 (m, 1H), 5.96 – 5.87 (m, 1H), 3.95 – 3.84 (m, 1H), 3.83 – 3.73 (m, 1H), 2.44 – 2.30 (m, 1H), 2.13 – 2.07 (m, 3H), 2.07 – 1.95 (m, 2H), 1.82 – 1.67 (m, 1H), 1.59 (p, *J* = 4.6 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 156.1|156.1 (d, *J* = 247.5 Hz, 1C), 144.4|144.3, 137.6|137.5, 131.2|131.2, 128.3 – 128.2 (m, 1C), 128.1|128.1, 121.1|121.0, 119.4|119.3, 113.4 (d, *J* = 22.0 Hz, 1C), 98.8|98.8 (d, *J* = 27.6 Hz, 1C), 84.2|84.2, 66.6|66.5, 28.7|28.6, 24.6. 22.0|21.9, 12.7|12.7.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -113.57|113.60 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₁₇ClFN₄O 335.1075; Found 335.1079.



5-chloro-6-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-4-(1*H*-1,2,4-triazol-1-yl)-1*H*-indazole

Following general procedure B using **3b** (0.3 mmol), 1*H*-1,2,4-triazole (1.2 equiv), and DMSO (0.3 M with respect to **3b**) and stirring at 50 °C for 24 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **4f** (84 mg, 87% yield) as a white solid.

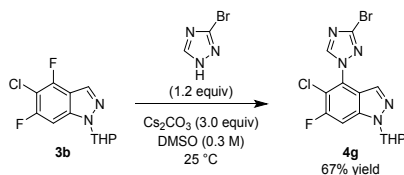
mp: 145.8 – 148.4 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.19 (s, 1H), 8.43 (s, 1H), 8.16 (dd, *J* = 0.7, 9.2 Hz, 1H), 8.02 (s, 1H), 5.93 (dd, *J* = 2.3, 9.5 Hz, 1H), 4.00 - 3.85 (m, 1H), 3.84 - 3.71 (m, 1H), 2.45 - 2.28 (m, 1H), 2.11 - 1.94 (m, 2H), 1.84 - 1.67 (m, 1H), 1.66 - 1.52 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 156.0 (d, *J* = 245.8 Hz, 1C), 152.7, 146.3, 137.7 (d, *J* = 13.2 Hz, 1C), 131.8, 127.5 (d, *J* = 2.9 Hz, 1C), 117.7, 110.9 (d, *J* = 23.5 Hz, 1C), 98.9 (d, *J* = 27.1 Hz, 1C), 84.2, 66.6, 28.7, 24.5, 21.9.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -113.29 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+Na]⁺ calcd for C₁₄H₁₃ClF₂N₅ONa 344.0685; Found 344.0688.



4-(3-bromo-1H-1,2,4-triazol-1-yl)-5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

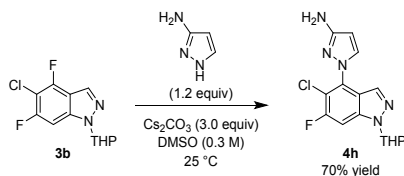
Following general procedure B using **3b** (0.3 mmol), 3-bromo-1H-1,2,4-triazole (1.2 equiv), and DMSO (0.3 M with respect to **3b**) and stirring at 50 °C for 24 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **4g** (81 mg, 67% yield) as a white amorphous solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.21 (s, 1H), 8.20 (dd, *J* = 0.9, 9.2 Hz, 1H), 8.11 (d, *J* = 0.6 Hz, 1H), 5.93 (dd, *J* = 2.3, 9.5 Hz, 1H), 3.96 - 3.84 (m, 1H), 3.83 - 3.71 (m, 1H), 2.45 - 2.28 (m, 1H), 2.12 - 1.93 (m, 2H), 1.83 - 1.66 (m, 1H), 1.65 - 1.52 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 155.8 (d, *J* = 245.8 Hz, 1C), 148.6, 141.0, 137.6 (d, *J* = 13.2 Hz, 1C), 131.6, 126.5 (d, *J* = 2.9 Hz, 1C), 117.8, 111.6 (d, *J* = 23.5 Hz, 1C), 99.7 (d, *J* = 27.9 Hz, 1C), 84.2, 66.6, 28.7, 24.5, 21.9.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -113.37 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₁₃BrClFN₅O 399.9971; Found 399.9987.



1-(5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-1H-pyrazol-3-amine

Following general procedure B using **3b** (0.3 mmol), 3-amino-pyrazole (1.2 equiv), and DMSO (0.3 M with respect to **3b**), purified by reverse phase HPLC (21x250 mm, Flow Rate 65 mL/min, 20–80% MeCN:H₂O + 0.05% AcOH) to deliver title compound **4h** (68 mg, 70% yield) as a white solid.

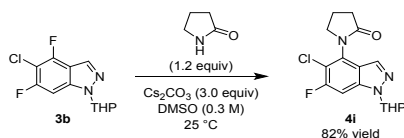
mp: 143.4 – 147.7 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.21 (s, 1H), 8.03 (d, *J* = 2.6 Hz, 1H), 7.80 (dd, *J* = 9.3, 1.0 Hz, 1H), 5.88 (d, *J* = 2.7 Hz, 1H), 5.84 (dd, *J* = 9.6, 2.5 Hz, 1H), 5.23 (s, 2H), 3.88 (dq, *J* = 11.6, 2.9 Hz, 1H), 3.82 – 3.71 (m, 1H), 2.36 (tdd, *J* = 13.1, 10.3, 3.8 Hz, 1H), 2.06 – 1.91 (m, 2H), 1.73 (t, *J* = 10.2 Hz, 1H), 1.59 (dq, *J* = 8.3, 4.2 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 157.6, 156.5 (d, *J* = 244.4 Hz, 1C), 138.0, 137.9 (d, *J* = 14.4 Hz, 1C), 133.1, 131.5 (d, *J* = 4.0 Hz, 1C), 116.5, 106.1 (d, *J* = 23.2 Hz, 1C), 96.7, 95.2 (d, *J* = 28.3 Hz, 1C), 84.1, 66.6, 28.8, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -112.78 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₅H₁₆ClFN₅O 336.1022; Found 336.1037.



1-(5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)pyrrolidin-2-one

Following general procedure B using **3b** (0.3 mmol), pyrrolidinone (1.2 equiv), DMSO (0.3 M with respect to **3b**), and stirring for 24 h, purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **4i** (83 mg, 82% yield) as a white solid and atropisomeric mixture.

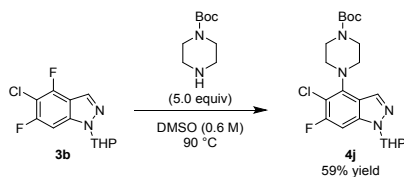
mp: 139.9 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.17 (s, 1H), 7.94 – 7.91 (m, 1H), 5.85 (dd, *J* = 2.1, 9.6 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.85 – 3.73 (m, 3H), 2.65 – 2.54 (m, 1H), 2.49 – 2.42 (m, 1H), 2.42 – 2.16 (m, 3H), 2.07 – 1.92 (m, 2H), 1.80 – 1.66 (m, 1H), 1.63 – 1.53 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 174.1, 156.3 (d, *J* = 245.8 Hz, 1C), 137.6|137.5, 132.2, 130.4|130.3, 119.2, 113.3 (d, *J* = 21.3 Hz, 1C), 97.4 (d, *J* = 27.1 Hz, 1C), 84.1, 66.6, 48.9, 30.3, 28.8, 24.6, 22.0, 19.2.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -114.19|-114.22 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₁₈ClFN₃O₂ 338.1066; Found: 338.1069.



tert-butyl 4-(5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)piperazine-1-carboxylate

See general safety information concerning DMSO!!!

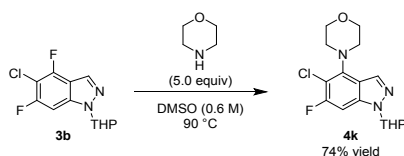
To an oven dried vial equipped with a magnetic stir bar were added **3b** (82 mg, 0.3 mmol), 1-Boc-piperazine (279 mg, 0.15 mmol, 5.0 equiv), and the solids were purged with nitrogen. DMSO (0.5 mL, 0.6 M with respect to indazole) was added to the solids. The vial was capped and stirred at 90 °C for 20 h. The reaction was diluted with ethyl acetate, washed with water (2x), brine, dried (MgSO₄), and concentrated to give a crude residue. The crude material was purified by flash column chromatography (0–80% ethyl acetate:heptane) to deliver title compound **4j** (78 mg, 59% yield) as a white amorphous solid.

¹H NMR (400 MHz, DMSO-*d*₆, 80 °C) δ = 8.28 (d, *J* = 0.9 Hz, 1H), 7.40 (dd, *J* = 9.2, 1.0 Hz, 1H), 5.76 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.92 – 3.82 (m, 1H), 3.80 – 3.69 (m, 1H), 3.55 (dd, *J* = 6.3, 3.7 Hz, 4H), 3.36 (dd, *J* = 6.1, 3.8 Hz, 4H), 2.45 – 2.28 (m, 1H), 2.13 – 2.01 (m, 1H), 2.01 – 1.92 (m, 1H), 1.83 – 1.67 (m, 1H), 1.67 – 1.55 (m, 2H), 1.47 (s, 9H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 157.0 (d, *J* = 243.0 Hz, 1C), 153.9, 142.9 (d, *J* = 3.7 Hz, 1C), 138.3 (d, *J* = 14.7 Hz, 1C), 132.9, 116.3, 107.5 (d, *J* = 20.4 Hz, 1C), 91.7 (d, *J* = 28.2 Hz, 1C), 83.8, 79.0 (s, 2C), 66.4, 51.0, 44.3 (br s, 1C), 43.7 (br s, 1C), 28.7, 28.0 (3C), 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -112.61 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₈FCIN₄O₃ 439.1907; Found 439.1922.



4-(5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)morpholine

See general safety information concerning DMSO!!!

To an oven dried vial equipped with a magnetic stir bar was added **3b** (82 mg, 0.3 mmol), and the solid was purged with nitrogen. DMSO (0.5 mL, 0.6 M with respect to indazole) and morpholine (0.133 mL, 0.15 mmol, 5.0 equiv) were added to the solids. The vial was capped and stirred at 90 °C for 20 h. The reaction was diluted with ethyl acetate, washed with water (2x), brine, dried (MgSO₄), and concentrated to give a crude residue. The crude material was purified by flash

SI20

column chromatography (0–80% ethyl acetate:heptane) to deliver title compound **4k** (75 mg, 74% yield) as a white solid.

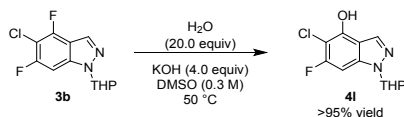
mp: 118.2 – 121.6 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.37 (s, 1H), 7.48 (dd, *J* = 9.1, 0.9 Hz, 1H), 5.77 (dd, *J* = 9.6, 2.6 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.82 – 3.69 (m, 5H), 3.39 (dd, *J* = 5.4, 3.6 Hz, 4H), 2.35 (tdd, *J* = 13.2, 8.8, 4.9 Hz, 1H), 2.09 – 1.97 (m, 1H), 1.97 – 1.88 (m, 1H), 1.79 – 1.64 (m, 1H), 1.57 (dt, *J* = 9.0, 4.6 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 157.0 (d, *J* = 243.0 Hz, 1C), 142.9 (d, *J* = 3.8 Hz, 1C), 138.4 (d, *J* = 14.8 Hz, 1C), 132.9, 116.2, 107.4 (d, *J* = 20.4 Hz, 1C), 91.6 (d, *J* = 28.1 Hz, 1C), 83.8, 66.7 (s, 2C), 66.4, 51.5 (s, 2C), 28.7, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -112.57 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₁₉ClFN₃O₂ 340.1223; Found 340.1229.



5-chloro-6-fluoro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-ol

Following general procedure B using **3b** (1.0 mmol), water (20.0 equiv), potassium hydroxide (4.0 equiv), and DMSO (0.3 M with respect to **3b**), stirring at 50 °C for 24 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **4l** (260 mg, >95% yield) as a white solid.

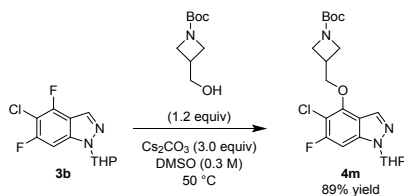
mp: 130.2 – 132.9 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.35 (s, 1H), 8.25 (d, *J* = 0.9 Hz, 1H), 7.25 (dd, *J* = 9.5, 1.0 Hz, 1H), 5.73 (dd, *J* = 9.7, 2.6 Hz, 1H), 3.86 (dtd, *J* = 11.4, 3.8, 1.6 Hz, 1H), 3.72 (ddd, *J* = 11.5, 8.0, 5.8 Hz, 1H), 2.41 – 2.27 (m, 1H), 2.06 – 1.97 (m, 1H), 1.97 – 1.89 (m, 1H), 1.78 – 1.64 (m, 1H), 1.59 – 1.52 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 157.4 (d, *J* = 242.4 Hz, 1C), 147.6 (d, *J* = 5.5 Hz, 1C), 138.1 (d, *J* = 15.1 Hz, 1C), 131.7, 112.6, 99.1 (d, *J* = 22.4 Hz, 1C), 88.4 (d, *J* = 27.9 Hz, 1C), 84.0, 66.4, 28.7, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -114.61.

HRMS -(ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₂H₁₃ClFN₂O₂ 271.0644; Found 271.0633.



tert-butyl 3-(((5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)methyl)azetidine-1-carboxylate

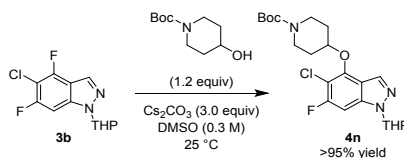
Following general procedure B using **3b** (0.3 mmol), 1-Boc-azetidine-3-yl-methanol (1.2 equiv), and DMSO (0.3 M with respect to **3b**), stirring at 50 °C for 16 h, purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **4m** (117 mg, 89% yield) as a white gum and atropisomeric mixture.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.42 (s, 1H), 7.52 – 7.50 (m, 1H), 5.79 (dd, *J* = 9.6, 2.6 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 4.01 – 3.91 (m, 2H), 3.90 – 3.69 (m, 4H), 3.01 (tp, *J* = 8.4, 5.7 Hz, 1H), 2.42 – 2.30 (m, 1H), 2.07 – 1.98 (m, 1H), 1.98 – 1.90 (m, 1H), 1.79 – 1.65 (m, 1H), 1.63 – 1.53 (m, 2H), 1.38 (s, 9H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 158.0, 155.6, 148.5 (d, *J* = 5.1 Hz), 138.7|138.6, 131.9, 113.0, 103.2 (d, *J* = 22.1 Hz), 91.2 (d, *J* = 27.6 Hz), 83.9, 78.4, 73.9, 66.5, 51.5 (br s, 1C), 50.6 (br s, 1C), 28.7, 28.2, 28.0, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -114.36|-114.38 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₇ClFN₃O₄ 440.1747; Found 440.1765.



tert-butyl 4-(((5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)piperidine-1-carboxylate

Following general procedure B using **3b** (0.3 mmol), *N*-Boc-4-hydroxy piperidine (1.2 equiv), and DMSO (0.3 M with respect to **3b**), stirring at 25 °C for 20 h, purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **4n** (135 mg, >95% yield) as a white foam.

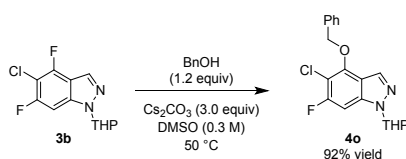
¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.33 (s, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 5.81 (dd, *J* = 2.3, 9.5 Hz, 1H), 4.93 (td, *J* = 3.9, 7.6 Hz, 1H), 3.94 - 3.82 (m, 1H), 3.82 - 3.63 (m, 3H), 3.28 - 3.17 (m, 2H), 2.44 - 2.28 (m, 1H), 2.03 (d, *J* = 9.1 Hz, 1H), 2.00 - 1.88 (m, 3H), 1.78 - 1.64 (m, 3H), 1.62 - 1.52 (m, 2H), 1.42 (s, 9H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 157.3 (d, *J* = 244.3 Hz, 1C), 154.3, 147.5 (d, *J* = 4.4 Hz, 1C), 138.9 (d, *J* = 14.7 Hz, 1C), 132.0, 115.1, 106.1 (d, *J* = 22.0 Hz, 1C), 92.8 (d, *J* = 27.9 Hz, 1C), 84.5, 79.3, 78.4, 67.0, 31.4, 29.2, 28.5, 25.1, 22.5.

Note: (17 of 18 reported) 1 missing carbon under DMSO peak, HSQC reveals correlation to 4 protons for a carbon peak at ~40.8 ppm.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -113.95 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₂₂H₃₀ClFN₃O₄ 454.1903; Found: 454.1901.



4-(benzyloxy)-5-chloro-6-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

Following general procedure B using **3b** (0.3 mmol), benzyl alcohol (1.2 equiv), and DMSO (0.3 M with respect to **3b**), stirring at 50 °C for 20 h, purified by flash column chromatography (0–40% ethyl acetate:heptane) to deliver title compound **4o** (100 mg, 92% yield) as a white solid and atropisomeric mixture.

mp: 87.0 °C

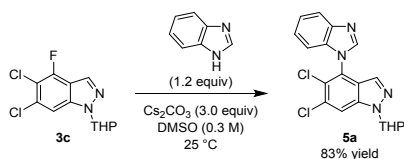
¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.47 (s, 1H), 7.58 – 7.49 (m, 3H), 7.45 – 7.39 (m, 2H), 7.39 – 7.33 (m, 1H), 5.79 (dd, *J* = 9.6, 2.5 Hz, 1H), 5.62 (s, 2H), 3.91 – 3.83 (m, 1H), 3.80 – 3.69 (m, 1H), 2.43 – 2.29 (m, 1H), 2.08 – 1.99 (m, 1H), 1.99 – 1.91 (m, 1H), 1.80 – 1.65 (m, 1H), 1.64 – 1.50 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 156.8 (d, *J* = 243.6 Hz), 148.4 (d, *J* = 5.1 Hz), 138.7|138.6, 136.4, 132.1, 128.4, 128.2, 127.8, 113.1, 103.4 (d, *J* = 22.1 Hz), 91.2 (d, *J* = 27.6 Hz), 83.9, 74.1, 66.5, 28.7, 24.6, 22.0.

¹⁹F NMR (376 MHz, DMSO-*d*₆) δ = -114.23|114.26 (s, 1F).

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₁₈ClFN₂O₂ 361.1114; Found 361.1128.

e. Experimental Procedures for the Nucleophilic Substitution to Form **5a–o**



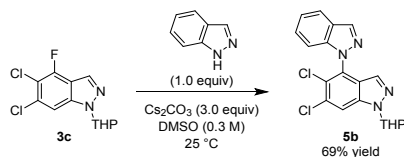
4-(1*H*-benzo[d]imidazol-1-yl)-5,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

Following general procedure B using **3c** (0.3 mmol), benzimidazole (1.2 equiv), and DMSO (0.3 M with respect to **3c**), purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5a** (96 mg, 83% yield) as a colorless oil and atropisomeric mixture.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 – 8.54 (m, 1H), 8.48 – 8.44 (m, 1H), 7.88 – 7.79 (m, 2H), 7.39 – 7.25 (m, 2H), 7.22 – 7.10 (m, 1H), 6.02 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.97 – 3.87 (m, 1H), 3.87 – 3.77 (m, 1H), 2.44 – 2.28 (m, 1H), 2.11 – 1.94 (m, 2H), 1.85 – 1.67 (m, 1H), 1.66 – 1.54 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 143.9|143.8, 142.9, 138.2|138.2, 133.6|133.6, 131.3|131.3, 130.7|130.7, 126.5|126.5, 123.7|123.7, 122.7, 122.5, 121.7|121.7, 120.0, 113.1|113.1, 110.8|110.8, 84.1, 66.6|66.6, 28.8|28.7, 24.6, 22.0|21.9.

HRMS (ESI/TOF) *m/z*: [M+Na]⁺ calcd for C₁₉H₁₆Cl₂N₄ONa 409.0593; Found 409.0595.



5',6'-dichloro-1'-(tetrahydro-2*H*-pyran-2-yl)-1'*H*-1,4'-biindazole

Following general procedure B using **3c** (0.3 mmol), 1*H*-indazole (1.0 equiv), and DMSO (0.3 M with respect to **3c**), stirred for 20 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5b** (80 mg, 69% yield) as a white solid and atropisomeric mixture.

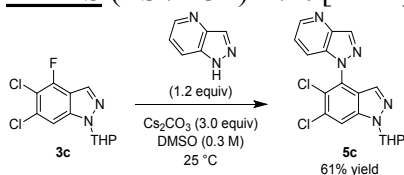
mp: 56.6 – 64.4 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 – 8.51 (m, 1H), 8.45 – 8.39 (m, 1H), 7.99 – 7.93 (m, 1H), 7.74 (s, 1H), 7.51 – 7.42 (m, 1H), 7.34 – 7.21 (m, 2H), 6.03 – 5.98 (m, 1H), 3.96 – 3.86 (m, 1H), 3.86 – 3.77 (m, 1H), 2.43 – 2.29 (m, 1H), 2.10 – 1.96 (m, 2H), 1.82 – 1.67 (m, 1H), 1.66 – 1.54 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 139.7|139.6, 138.3|138.2, 137.0|136.9, 131.7|131.7, 130.7, 129.8, 127.5, 124.1, 121.8, 121.8|121.8, 121.6|121.6, 121.5|121.4, 112.84, 110.6|110.6, 84.1|84.1, 66.6, 28.7, 24.6, 22.0.

Regiochemistry confirmed by ^{15}N HMBC data showing relationship between N16 and N17 with C18 (^1H - ^{15}N HMBC, 400 MHz, $\text{DMSO-}d_6$).

HRMS (ESI/TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}$: 386.0701; Found: 386.0718.



1-(5,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-1H-pyrazolo[4,3-b]pyridine

Following general procedure B using **3c** (0.3 mmol), 1H-pyrazolo[4,3-b]pyridine (1.2 equiv), and DMSO (0.3 M with respect to **3c**), purified by SFC (5–60% methanol: carbon dioxide) to deliver title compound **5c** (71 mg, 61% yield) as a white solid and atropisomeric mixture.

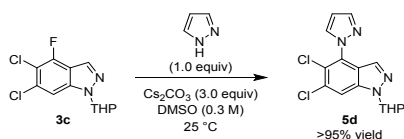
mp: 69.0 – 72.0 °C

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 8.77 (s, 1H), 8.73 – 8.65 (m, 1H), 8.47 – 8.40 (m, 1H), 7.88 – 7.78 (m, 2H), 7.52 – 7.46 (m, 1H), 6.00 (d, J = 9.3 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.85 – 3.76 (m, 1H), 2.42 – 2.31 (m, 1H), 2.06 – 1.95 (m, 2H), 1.77 – 1.68 (m, 1H), 1.64 – 1.54 (m, 2H).

^{13}C NMR (176 MHz, $\text{DMSO-}d_6$) δ = 146.5, 141.7, 138.3|138.3, 137.2|137.2, 133.0|132.9, 131.7|131.7, 130.7|130.7, 129.2, 122.0, 121.7|121.7, 121.6|121.5, 119.1|119.1, 113.1, 84.1, 66.6, 28.8, 24.6, 21.9.

Regiochemistry confirmed by ^{15}N HMBC data showing relationship between N42 and N43 with C44 (^1H - ^{15}N HMBC, 700 MHz, $\text{DMSO-}d_6$).

HRMS (ESI/TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{N}_5\text{O}$ 388.0726, found 388.0734.



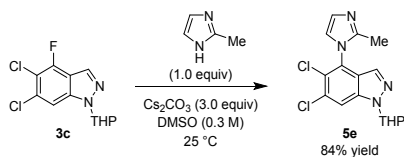
5,6-dichloro-4-(1H-pyrazol-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

Following general procedure B using **3c** (0.3 mmol), pyrazole (1.0 equiv), and DMSO (0.3 M with respect to **3c**), stirred for 16 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5d** (100 mg, >95% yield) as a colorless gum.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ = 8.31 (d, J = 2.2 Hz, 2H), 7.97 – 7.83 (m, 2H), 6.64 (t, J = 2.2 Hz, 1H), 5.97 (dd, J = 9.6, 2.4 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.84 – 3.74 (m, 1H), 2.43 – 2.28 (m, 1H), 2.01 (td, J = 14.5, 13.3, 6.4 Hz, 2H), 1.82 – 1.65 (m, 1H), 1.65 – 1.53 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 141.5, 138.1, 132.8, 132.2, 131.3, 130.6, 120.6, 119.1, 112.1, 107.1, 84.0, 66.5, 28.8, 24.6, 21.9.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₅H₁₄Cl₂N₄O: 336.0545; Found: 336.0560.



5,6-dichloro-4-(2-methyl-1H-imidazol-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

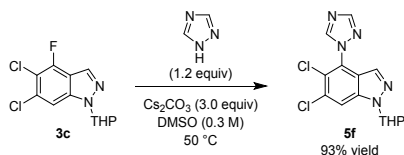
Following general procedure B using **3c** (0.3 mmol), 2-methylimidazole (1.0 equiv), and DMSO (0.3 M with respect to **3c**), purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5e** (88 mg, 84% yield) as a white solid and atropisomeric mixture.

mp: 156.2 – 157.8 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.43 – 8.34 (m, 1H), 7.90 – 7.81 (m, 1H), 7.37 – 7.26 (m, 1H), 7.09 – 7.00 (m, 1H), 6.03 – 5.92 (m, 1H), 3.93 – 3.85 (m, 1H), 3.85 – 3.73 (m, 1H), 2.42 – 2.30 (m, 1H), 2.11 – 2.06 (m, 3H), 2.06 – 1.95 (m, 2H), 1.81 – 1.67 (m, 1H), 1.64 – 1.54 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 144.3|144.2, 138.0|138.0, 131.2|131.2, 130.4|130.4, 128.4|128.4, 128.0|128.0, 122.7, 121.9|121.8, 121.1|121.0, 113.1|113.0, 84.1|84.1, 66.6|66.5, 28.8|28.7, 24.6, 22.0|21.9, 12.7.

HRMS (ESI/TOF) *m/z*: [M+Na]⁺ calcd for C₁₆H₁₆Cl₂N₄ONa 373.0593; Found 373.0575.



5,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-4-(1H-1,2,4-triazol-1-yl)-1H-indazole

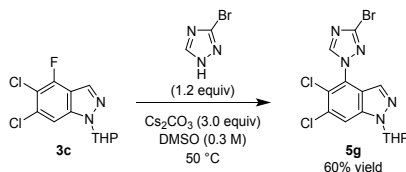
Following general procedure B using **3c** (0.3 mmol), 1H-1,2,4-triazole (1.2 equiv), and DMSO (0.3 M with respect to **3c**), stirring at 50 °C for 24 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5f** (94 mg, 93% yield) as a white solid.

mp: Sample shows decomposition to another solid from 75.7 – 79.8 °C followed by melting from 127.3 – 129.6 °C.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.17 (s, 1H), 8.50 - 8.35 (m, 2H), 7.99 (s, 1H), 5.99 (dd, *J* = 2.3, 9.5 Hz, 1H), 3.96 - 3.85 (m, 1H), 3.84 - 3.73 (m, 1H), 2.44 - 2.29 (m, 1H), 2.10 - 1.94 (m, 2H), 1.82 - 1.66 (m, 1H), 1.64 - 1.54 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 152.6, 146.3, 138.1, 131.7, 130.5, 127.8, 120.5, 120.4, 113.3, 84.1, 66.6, 28.7, 24.6, 21.9.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₁₄Cl₂N₅O 338.0567; Found 338.0584.



4-(3-bromo-1H-1,2,4-triazol-1-yl)-5,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

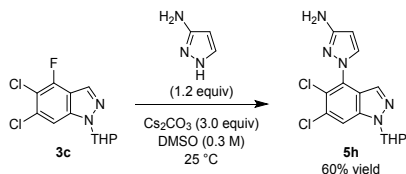
Following general procedure B using **3c** (0.3 mmol), 3-bromo-1H-1,2,4-triazole (1.2 equiv), and DMSO (0.3 M with respect to **3c**), stirring at 50 °C for 24 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5g** (75 mg, 60% yield) as a white solid.

mp: 126.4 – 129.4 °C.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.19 (s, 1H), 8.47 (d, *J* = 0.9 Hz, 1H), 8.09 (d, *J* = 0.6 Hz, 1H), 6.00 (dd, *J* = 2.3, 9.5 Hz, 1H), 3.96 - 3.85 (m, 1H), 3.84 - 3.73 (m, 1H), 2.45 - 2.27 (m, 1H), 2.12 - 1.92 (m, 2H), 1.85 - 1.65 (m, 1H), 1.64 - 1.51 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 148.6, 140.8, 138.0, 131.5, 130.4, 126.8, 121.1, 120.5, 114.0, 84.1, 66.6, 28.7, 24.5, 21.9.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₄H₁₃BrCl₂N₅O 415.9675; Found 415.9691.



1-(5,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-1H-pyrazol-3-amine

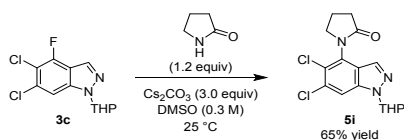
Following general procedure B using **3c** (0.3 mmol), 3-amino-pyrazole (1.2 equiv), and DMSO (0.3 M with respect to **3c**), purified by reverse phase HPLC (21x250 mm, Flow Rate 65 mL/min, 20–80% MeCN:H₂O + 0.05% AcOH) to deliver title compound **5h** (66 mg, 60% yield) as a white solid.

mp: 144.9 – 151.6 °C.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.14 (d, *J* = 0.9 Hz, 1H), 8.10 (d, *J* = 0.9 Hz, 1H), 7.99 (d, *J* = 2.6 Hz, 1H), 5.91 (dd, *J* = 9.6, 2.5 Hz, 1H), 5.86 (d, *J* = 2.6 Hz, 1H), 5.19 (s, 2H), 3.92 – 3.84 (m, 1H), 3.78 (ddd, *J* = 11.5, 7.9, 5.8 Hz, 1H), 2.35 (dddd, *J* = 16.0, 13.3, 9.7, 3.8 Hz, 1H), 2.06 – 1.93 (m, 3H), 1.73 (ddt, *J* = 15.7, 12.1, 6.2 Hz, 1H), 1.58 (tq, *J* = 7.9, 3.8 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 157.5, 138.2, 133.4, 133.3, 131.8, 130.9, 119.6, 116.0, 109.9, 96.4, 83.9, 66.5, 28.8, 24.6, 22.0.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₅H₁₅Cl₂N₅O 352.0726; Found 352.0740.



1-(5,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)pyrrolidin-2-one

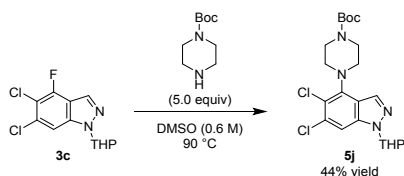
Following general procedure B using **3c** (0.3 mmol), pyrrolidinone (1.2 equiv), DMSO (0.3 M with respect to **3c**), stirring for 24 h, purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **5i** (69 mg, 65% yield) as a white solid and atropisomeric mixture.

mp: 160.7 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.20 – 8.19 (m, 2H), 5.96 – 5.86 (m, 1H), 3.95 – 3.70 (m, 4H), 2.67 – 2.54 (m, 1H), 2.49 – 2.43 (m, 1H), 2.42 – 2.16 (m, 3H), 2.09 – 1.92 (m, 2H), 1.81 – 1.66 (m, 1H), 1.64 – 1.54 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 174.1|174.1, 138.0, 132.2, 130.4, 130.3, 122.8, 121.8, 111.7, 84.0|84.0, 66.6|66.5, 48.8, 30.3, 28.8, 24.6, 22.0, 19.1.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₁₈Cl₂N₃O₂ 354.0771; Found: 354.0776.



tert-butyl 4-(5,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)piperazine-1-carboxylate

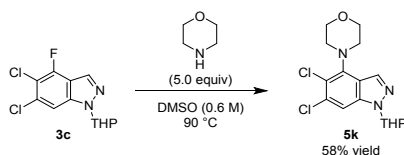
See general safety information concerning DMSO!!!

To an oven dried vial equipped with a magnetic stir bar were added **3c** (82 mg, 0.3 mmol), 1-Boc-piperazine (279 mg, 0.15 mmol, 5.0 equiv), and the solids were purged with nitrogen. DMSO (0.5 mL, 0.6 M with respect to indazole) was added to the solids. The vial was capped and stirred at 90 °C for 20 h. The reaction was diluted with ethyl acetate, washed with water (2x), brine, dried (MgSO₄), and concentrated to give a crude residue. The crude material was purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5j** (60 mg, 44% yield) as a white amorphous solid.

¹H NMR (400 MHz, DMSO-*d*₆) 80 °C) δ = 8.31 (d, *J* = 1.0 Hz, 1H), 7.72 (d, *J* = 1.0 Hz, 1H), 5.82 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.81 – 3.72 (m, 1H), 3.60 – 3.50 (m, 4H), 3.34 (dd, *J* = 5.9, 4.0 Hz, 4H), 2.43 – 2.28 (m, 1H), 2.10 – 2.01 (m, 1H), 2.01 – 1.92 (m, 1H), 1.83 – 1.68 (m, 1H), 1.61 (dq, *J* = 8.6, 4.4 Hz, 2H), 1.47 (s, 9H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 153.9, 143.0, 138.7, 132.8, 131.1, 119.1, 117.7, 106.2, 83.7, 79.0, 66.4, 51.0 (s, 2C), 44.3 (br s, 1C) 42.7 (br s, C), 28.7, 28.0 (s, 3C), 24.7, 22.0.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₉Cl₂N₄O₃ 455.1611; Found 455.1631.



4-(5,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)morpholine

See general safety information concerning DMSO!!!

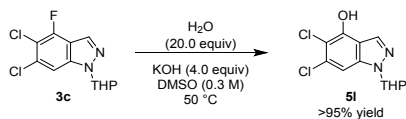
To an oven dried vial equipped with a magnetic stir bar was added **3c** (82 mg, 0.3 mmol), and the solid was purged with nitrogen. DMSO (0.5 mL, 0.6 M with respect to indazole) and morpholine (0.133 mL, 0.15 mmol, 5.0 equiv) were added to the solids. The vial was capped and stirred at 90 °C for 20 h. The reaction was diluted with ethyl acetate, washed with water (2x), brine, dried (MgSO₄), and concentrated to give a crude residue. The crude material was purified by flash column chromatography (0–80% ethyl acetate:heptane) to deliver title compound **5k** (62 mg, 58% yield) as a white solid.

mp: 106.3 – 108.8 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.40 (s, 1H), 7.78 (s, 1H), 5.84 (dd, *J* = 9.5, 2.6 Hz, 1H), 3.90 – 3.69 (m, 6H), 3.36 (t, *J* = 4.5 Hz, 4H), 2.42 – 2.28 (m, 1H), 2.09 – 1.98 (m, 1H), 1.98 – 1.89 (m, 1H), 1.81 – 1.65 (m, 1H), 1.65 – 1.52 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 143.0, 138.8, 132.8, 131.1, 119.0, 117.6, 106.2, 83.7, 66.7 (2C), 66.4, 51.5 (2C), 28.7, 24.7, 22.0.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₂₀Cl₂N₃O₂ 356.0927; Found 356.0936.



5,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-ol

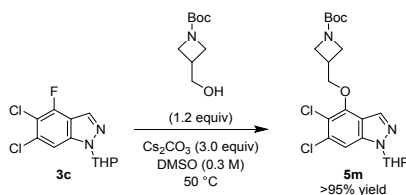
Following general procedure B using **3c** (1.0 mmol), water (20.0 equiv), potassium hydroxide (4.0 equiv), and DMSO (0.3 M with respect to **3c**), stirring at 50 °C for 24 h, purified by flash column chromatography (0–50% ethyl acetate:heptane) to deliver title compound **5l** (281 mg, >95% yield) as a white solid.

mp: 164.2 – 166.8 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.28 (s, 1H), 8.26 (d, *J* = 0.9 Hz, 1H), 7.53 (d, *J* = 0.9 Hz, 1H), 5.79 (dd, *J* = 9.6, 2.6 Hz, 1H), 3.86 (dtd, *J* = 11.5, 3.8, 1.6 Hz, 1H), 3.74 (ddd, *J* = 11.5, 8.1, 6.1 Hz, 1H), 2.40 – 2.26 (m, 1H), 2.05 – 1.97 (m, 1H), 1.93 (dq, *J* = 13.0, 3.4 Hz, 1H), 1.78 – 1.64 (m, 1H), 1.56 (tq, *J* = 8.2, 3.9 Hz, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 147.4, 138.7, 131.7, 130.9, 115.0, 108.5, 102.6, 83.9, 66.4, 28.8, 24.7, 22.0.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₂H₁₃Cl₂N₂O₂ 287.0349; Found 287.0339.



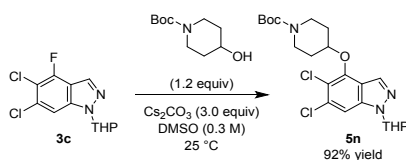
tert-butyl 3-(((5,6-dichloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)oxy)methyl)azetidine-1-carboxylate

Following general procedure B using **3c** (0.3 mmol), 1-Boc-azetidine-3-yl-methanol (1.2 equiv), and DMSO (0.3 M with respect to **3c**), stirring at 50 °C for 16 h, purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **5m** (134 mg, >95% yield) as a white gum.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.42 (s, 1H), 7.78 (d, *J* = 0.9 Hz, 1H), 5.85 (dd, *J* = 9.5, 2.6 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 2H), 4.03 – 3.92 (m, 2H), 3.90 – 3.73 (m, 4H), 3.01 (tp, *J* = 8.4, 5.7 Hz, 1H), 2.35 (dddd, *J* = 16.0, 13.1, 9.7, 4.0 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.79 – 1.66 (m, 1H), 1.63 – 1.53 (m, 2H), 1.38 (s, 9H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 155.6, 148.5, 139.1, 131.8, 130.6, 115.5, 112.8, 105.4, 83.8, 78.3, 73.9, 66.4, 51.5 (br s, 1C), 50.6 (br s, 1C), 28.7, 28.3, 28.0 (s, 3C), 24.6, 22.0.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₈Cl₂N₃O₄ 456.1451; Found 456.1453.



tert-butyl 4-((5,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)piperidine-1-carboxylate

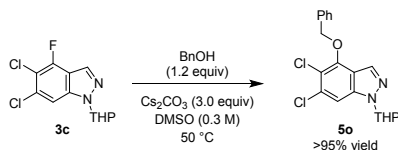
Following general procedure B using **3c** (0.3 mmol), *N*-Boc-4-hydroxy piperidine (1.2 equiv), and DMSO (0.3 M with respect to **3c**), stirring at 25 °C for 20 h, purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **5n** (13 mg, 92% yield) as a white foam.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.35 (s, 1H), 7.87 - 7.85 (m, 1H), 5.87 (dd, *J* = 2.4, 9.6 Hz, 1H), 4.93 - 4.86 (m, 1H), 3.90 - 3.84 (m, 1H), 3.82 - 3.75 (m, 1H), 3.74 - 3.65 (m, 2H), 3.21 (br t, *J* = 9.3 Hz, 2H), 2.36 (br d, *J* = 12.1 Hz, 1H), 2.08 - 1.87 (m, 4H), 1.79 - 1.64 (m, 3H), 1.64 - 1.53 (m, 2H), 1.42 (s, 9H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 154.3, 147.5, 139.4, 132.0, 131.2, 117.7, 115.7, 107.0, 84.3, 79.3, 78.6, 67.0, 31.4, 29.2, 28.5, 25.1, 22.5.

Note: (17 of 18 reported) 1 missing carbon under DMSO peak, HSQC reveals correlation to 4 protons for a carbon peak at ~40.8 ppm

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₂₂H₃₀Cl₂N₃O₄ 470.1608; Found: 470.1608.



4-(benzyloxy)-5,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

Following general procedure B using **3c** (0.3 mmol), benzyl alcohol (1.2 equiv), and DMSO (0.3 M with respect to **3c**), stirring at 50 °C for 20 h, purified by flash column chromatography (0–40% ethyl acetate:heptane) to deliver title compound **5o** (110 mg, >95% yield) as a white solid.

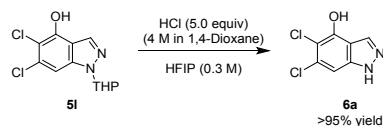
mp: 108.0 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.46 (s, 1H), 7.79 (d, *J* = 1.0 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.44 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 5.85 (dd, *J* = 9.6, 2.6 Hz, 1H), 5.59 (s, 2H), 3.86 (dtd, *J* = 11.5, 3.8, 1.6 Hz, 1H), 3.76 (ddd, *J* = 11.5, 8.0, 6.0 Hz, 1H), 2.35 (dddd, *J* = 16.1, 13.2, 9.8, 3.9 Hz, 1H), 2.11 – 1.89 (m, 2H), 1.83 – 1.63 (m, 1H), 1.63 – 1.51 (m, 2H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 148.4, 139.2, 136.4, 132.0, 130.7, 128.4 (2C), 128.2, 127.8 (2C), 115.6, 113.1, 105.4, 83.8, 74.2, 66.4, 28.7, 24.6, 22.0.

HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₁₉Cl₂N₂O₂ 377.0818; Found 377.0817.

f. Experimental Procedures for the Deprotection to Form **6a**



5,6-dichloro-1H-indazol-4-ol

To a vial equipped with a magnetic stir bar were added **5l** (86 mg, 0.3 mmol), 1,1,1,3,3,3-hexafluoro-2-propanol (1.0 mL, 0.3 M with respect to **5l**), and HCl (0.375 mL, 4 M in 1,4-dioxane, 1.50 mmol, 5.0 equiv). The vial was capped and stirred at 25 °C for 1 h. The reaction was quenched with sat NaHCO₃ (aq), extracted with ethyl acetate (2x), dried (MgSO₄), and concentrated to give a crude residue. The crude material was purified by flash column chromatography (0–100% ethyl acetate:heptane) to deliver title compound **6a** (58 mg, >95% yield) as a white solid.

mp: Material began to decompose at 140 °C

¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.08 (s, 1H), 11.06 (s, 1H), 8.15 (t, *J* = 1.4 Hz, 1H), 7.19 (d, *J* = 1.0 Hz, 1H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ = 147.3, 139.2, 131.8, 130.2, 114.1, 107.4, 102.2.

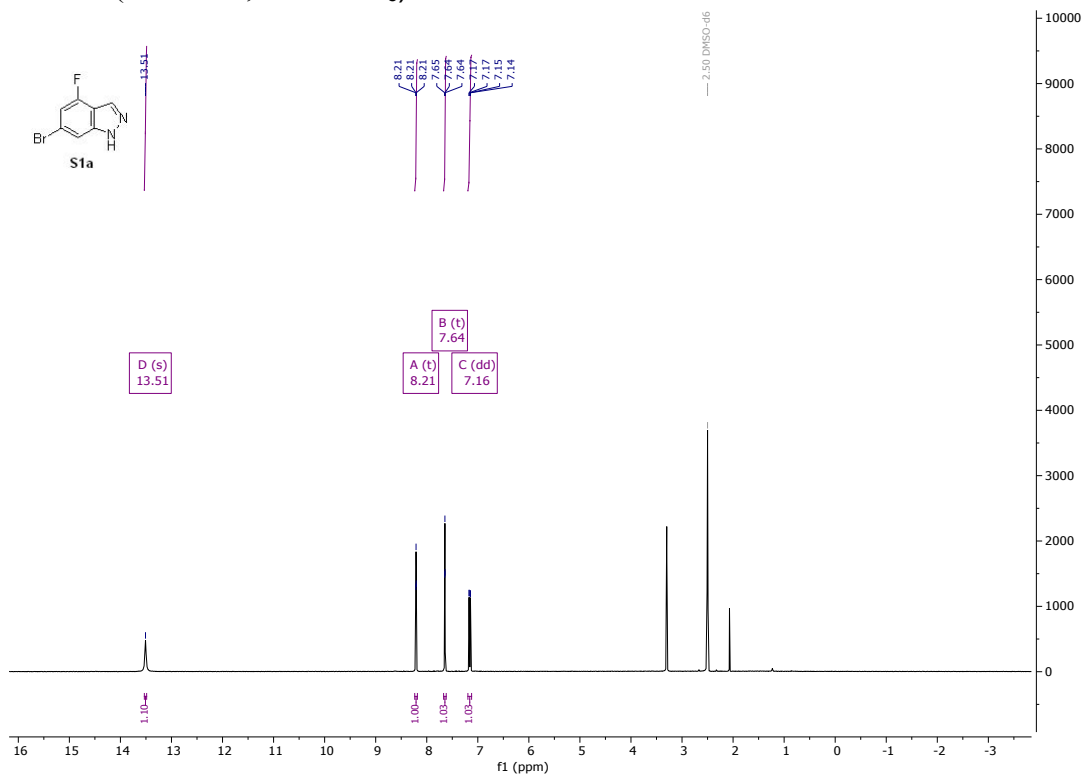
HRMS (ESI/TOF) *m/z*: [M+H]⁺ calcd for C₇H₄Cl₂N₂O 202.9773; Found 202.9773.

III. References

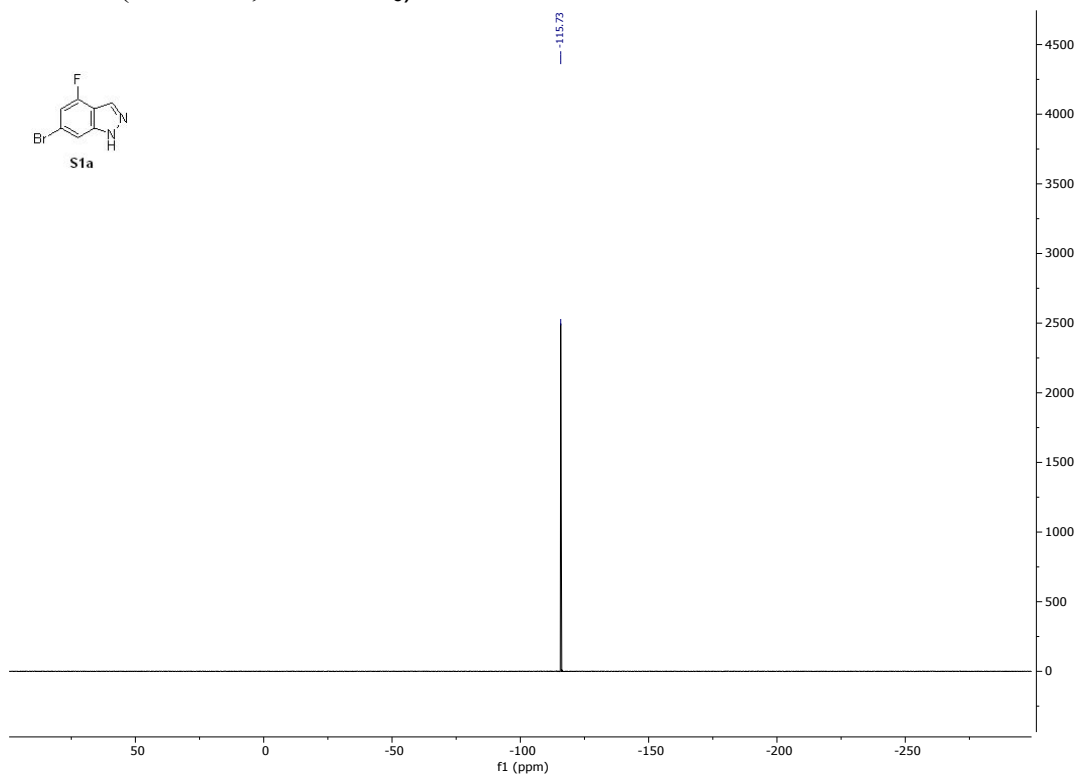
- (1) Lam, T. T.; Vickery, T.; Tuma, L. Thermal Hazards and Safe Scale-up of Reactions Containing Dimethyl Sulfoxide. *J. Therm. Anal. Calorim.* **2006**, *85* (1), 25–30. <https://doi.org/10.1007/s10973-005-7338-8>.
- (2) Qian, S.; He, T.; Wang, W.; He, Y.; Zhang, M.; Yang, L.; Li, G.; Wang, Z. Discovery and Preliminary Structure–Activity Relationship of 1H-Indazoles with Promising Indoleamine-2,3-Dioxygenase 1 (IDO1) Inhibition Properties. *Bioorg. Med. Chem.* **2016**, *24* (23), 6194–6205. <https://doi.org/10.1016/j.bmc.2016.10.003>.
- (3) FENSTER, E.; LAM, T. M.; Loo, M.; Mckinnell, R. M.; PALERMO, A. F.; WANG, D. J.; FRAGA, B.; NZEREM, J.; Dabros, M.; Thalladi, V. R.; Rapta, M. Pyrazolo and Triazolo Bicyclic Compounds as Jak Kinase Inhibitors. WO2019027960A1, February 7, 2019.

VII. Spectra

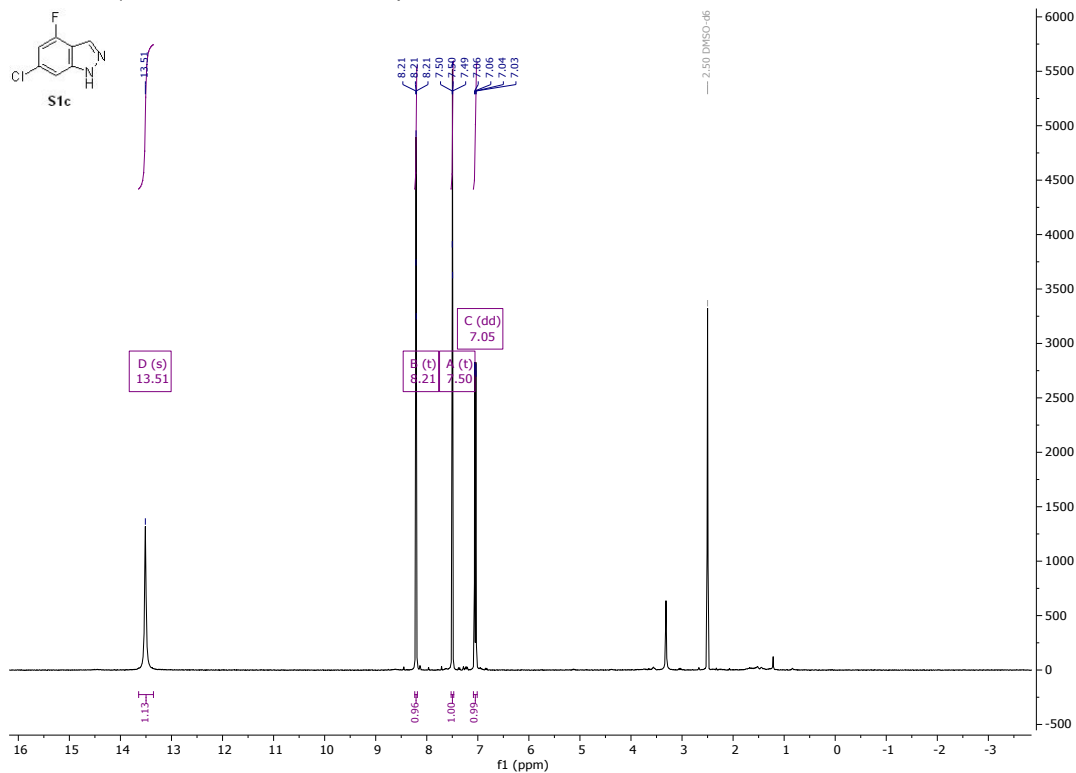
S1a ¹H NMR (400 MHz, DMSO-*d*₆)



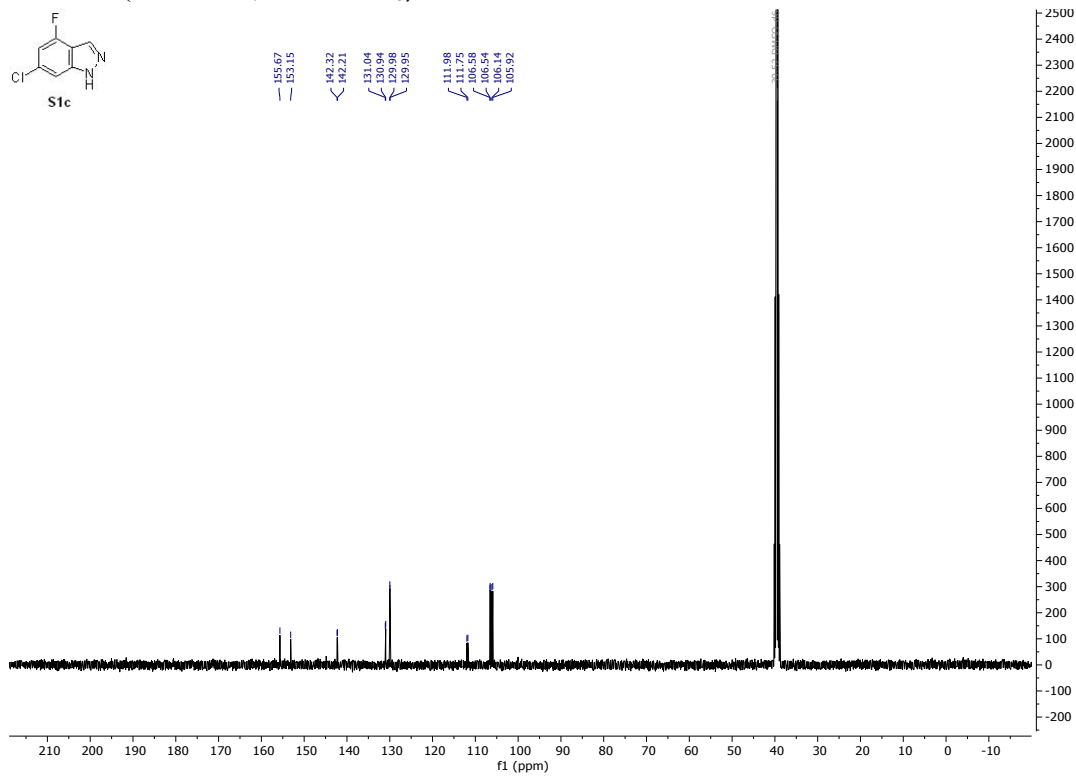
S1a ¹⁹F NMR (376 MHz, DMSO-*d*₆)



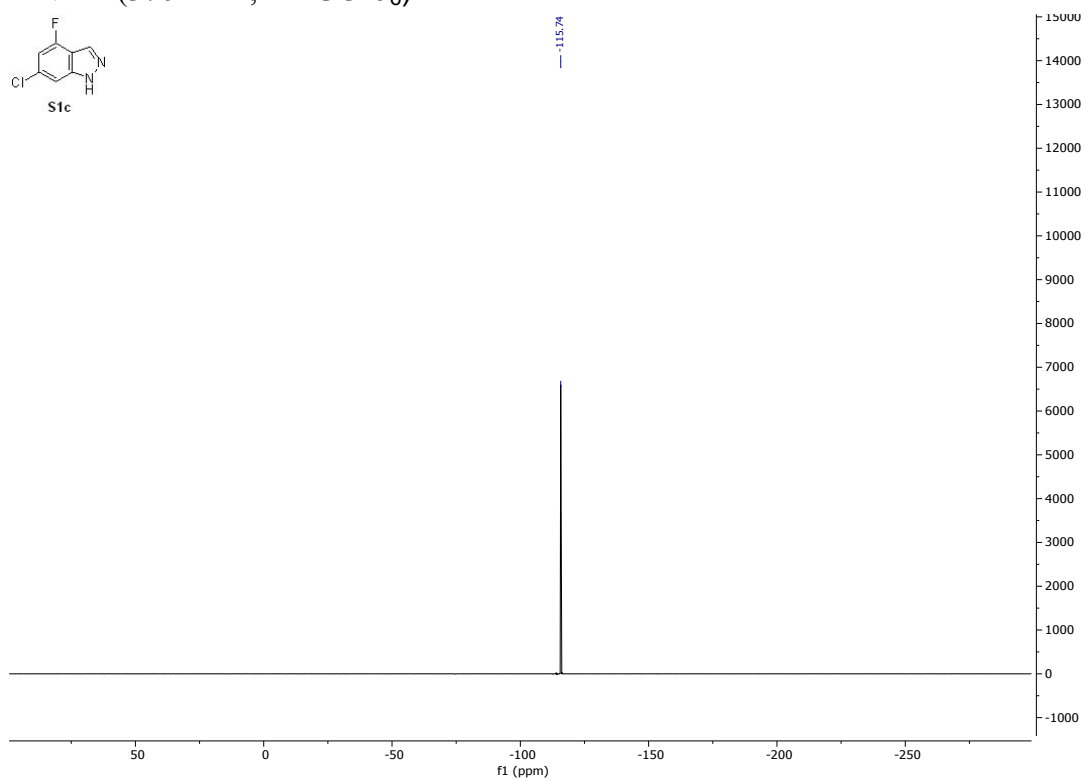
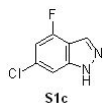
S1c ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



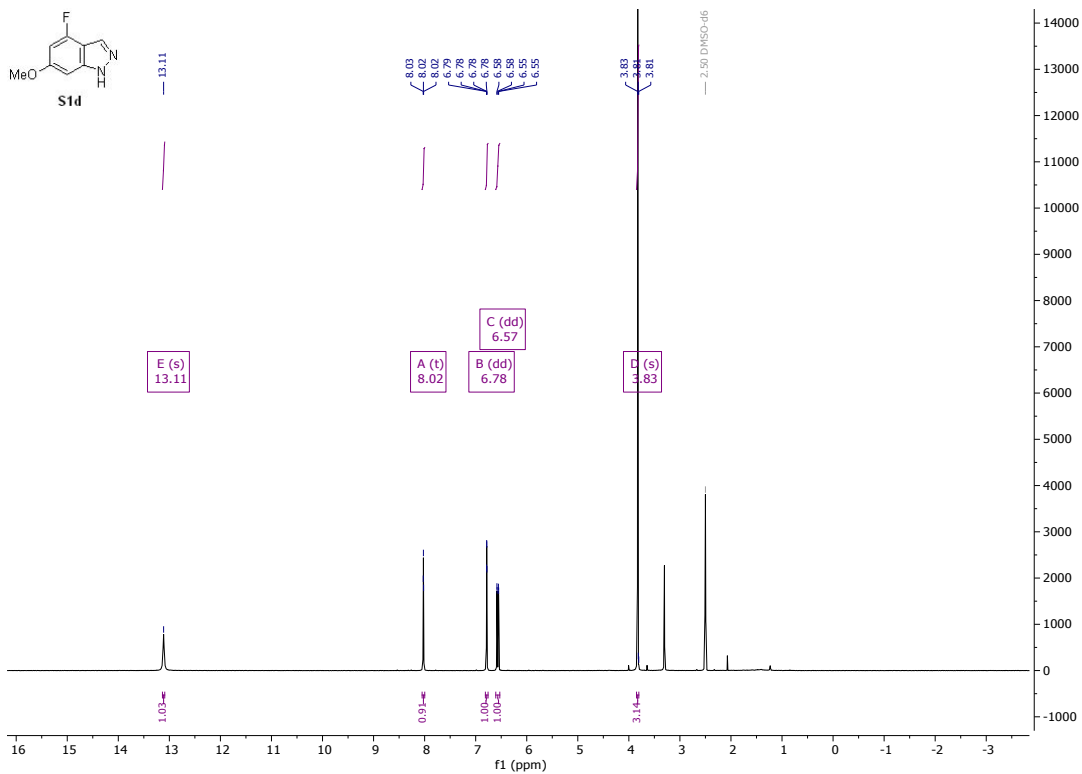
S1c ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)



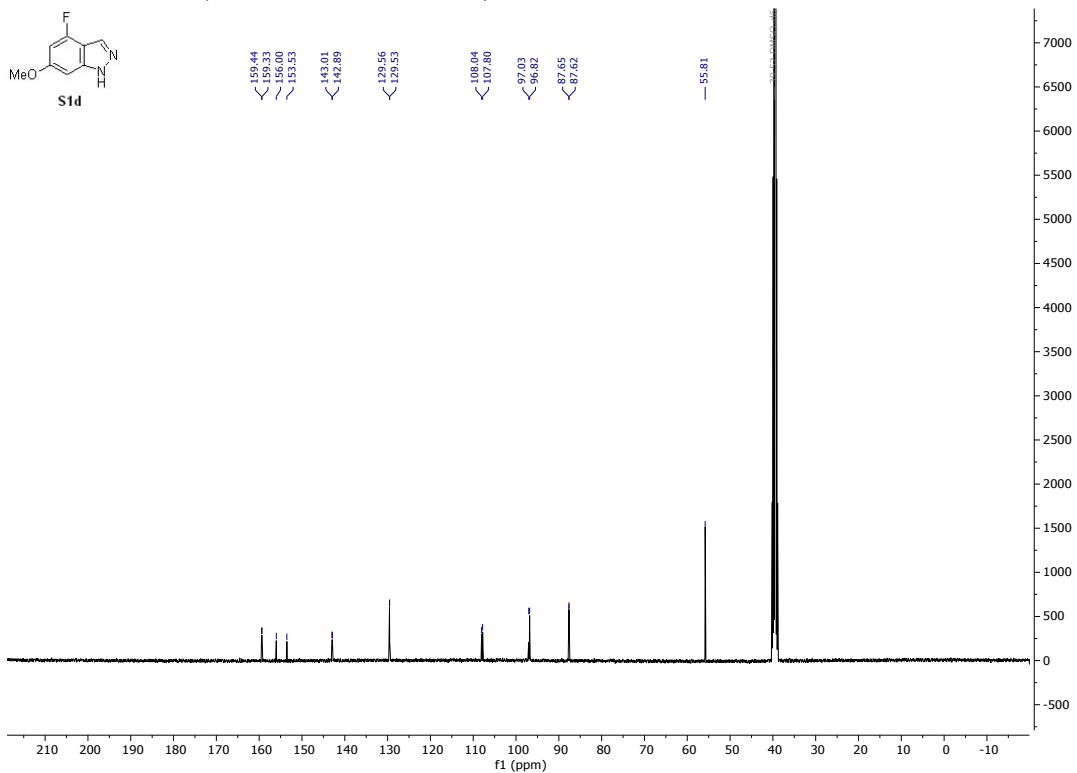
S1c ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$)



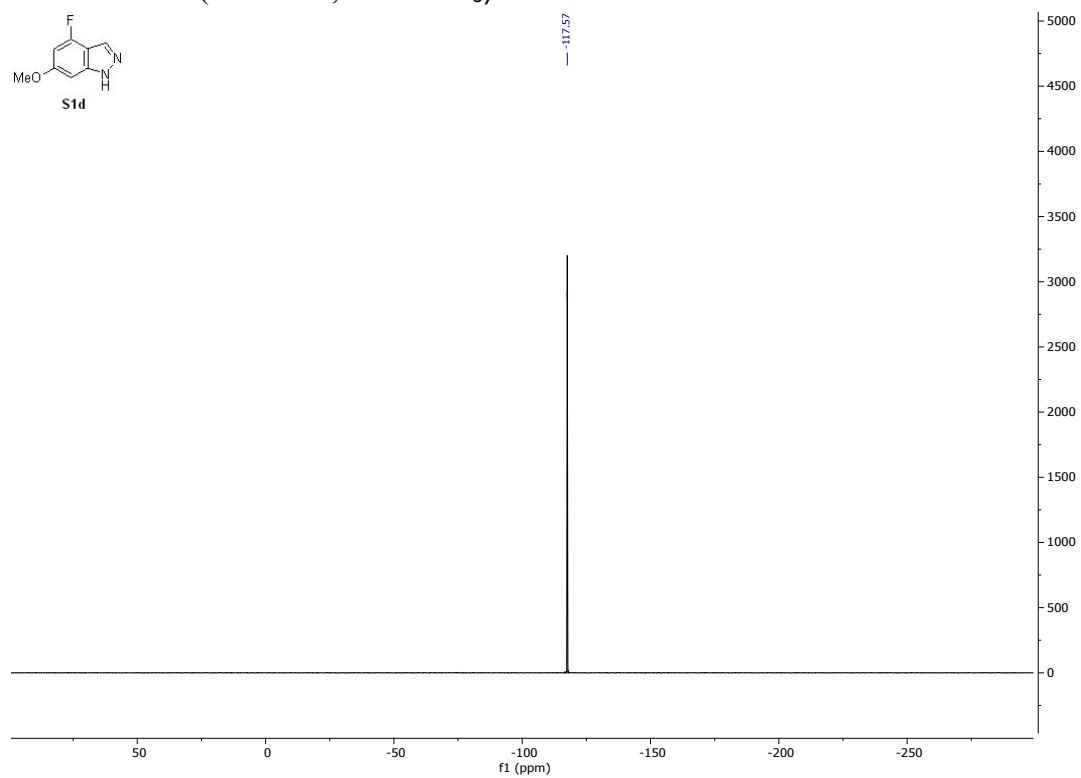
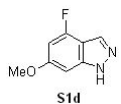
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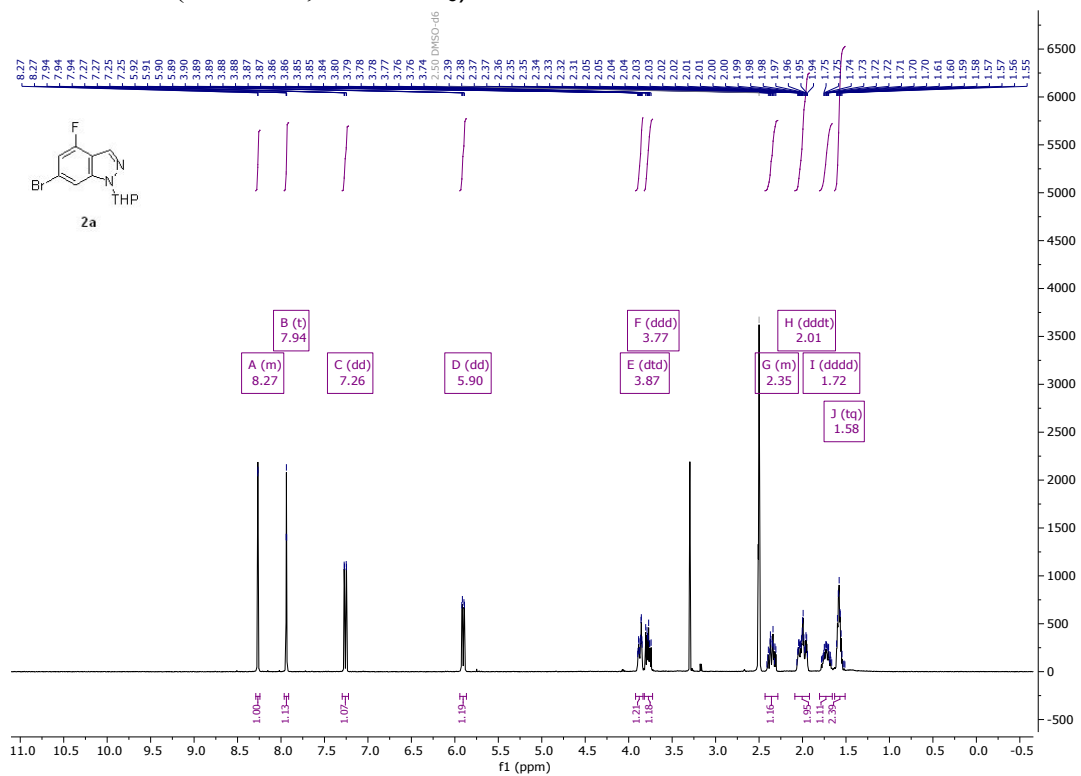
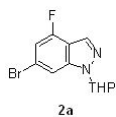
S1d ^{13}C NMR (101 MHz, DMSO- d_6)



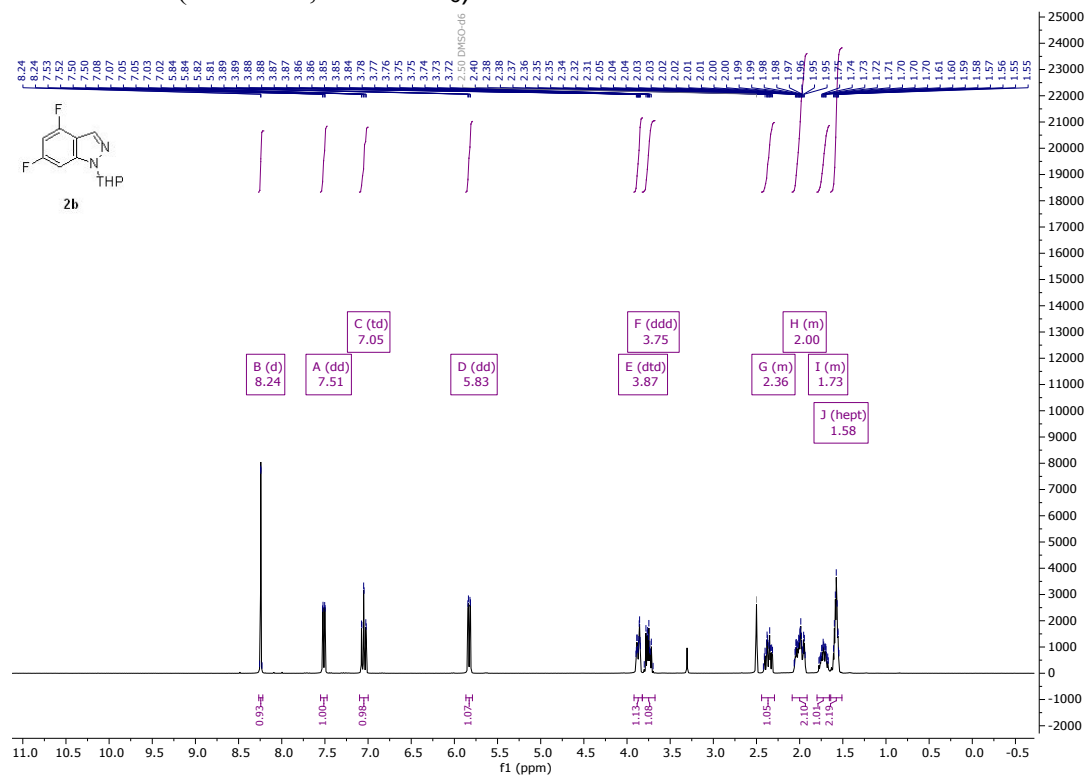
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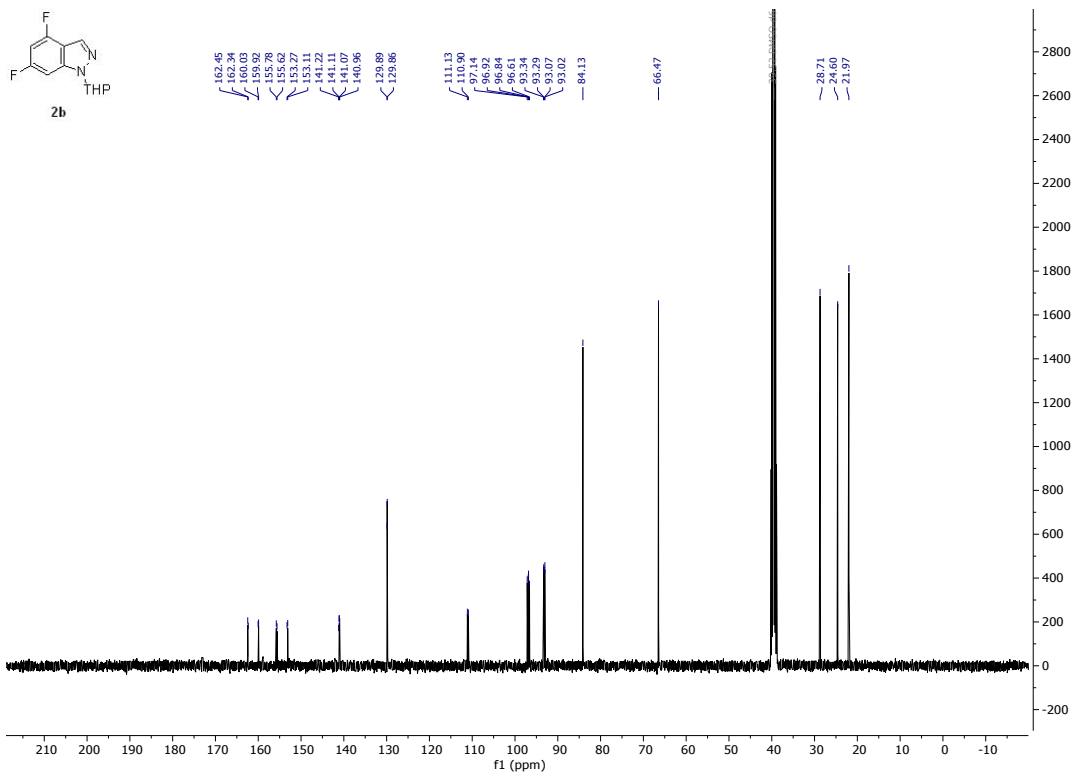
2a ^1H NMR (400 MHz, $\text{DMSO-}d_6$)



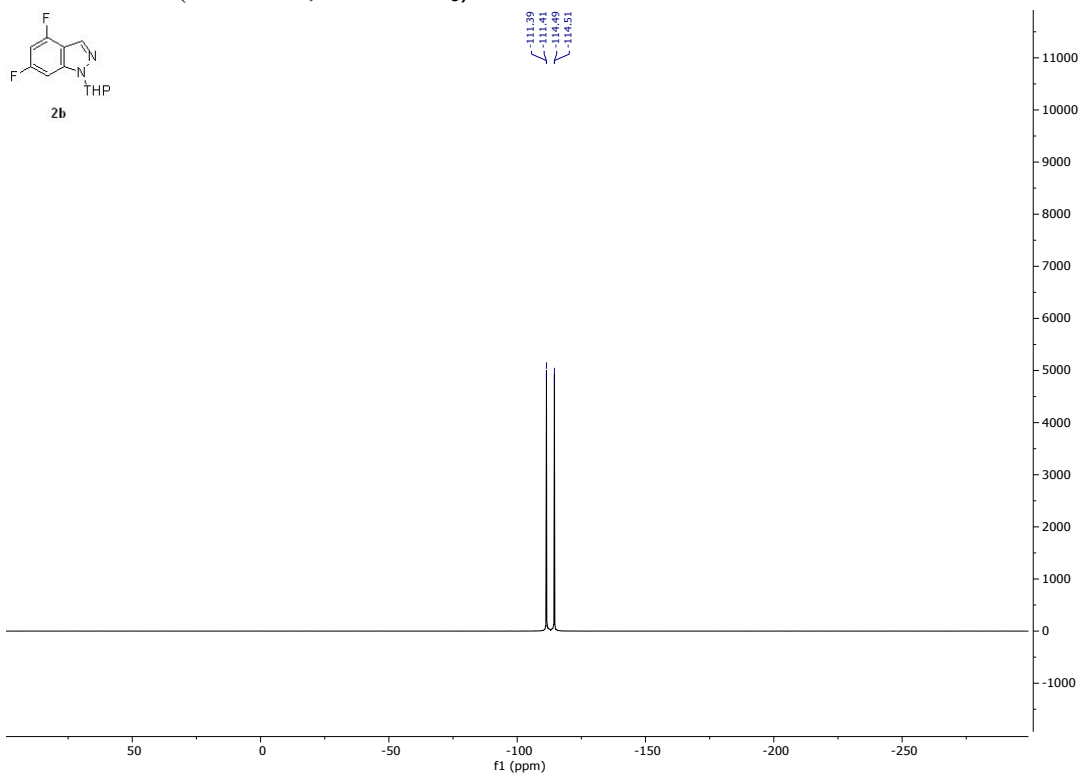
2b ^1H NMR (400 MHz, $\text{DMSO-}d_6$)



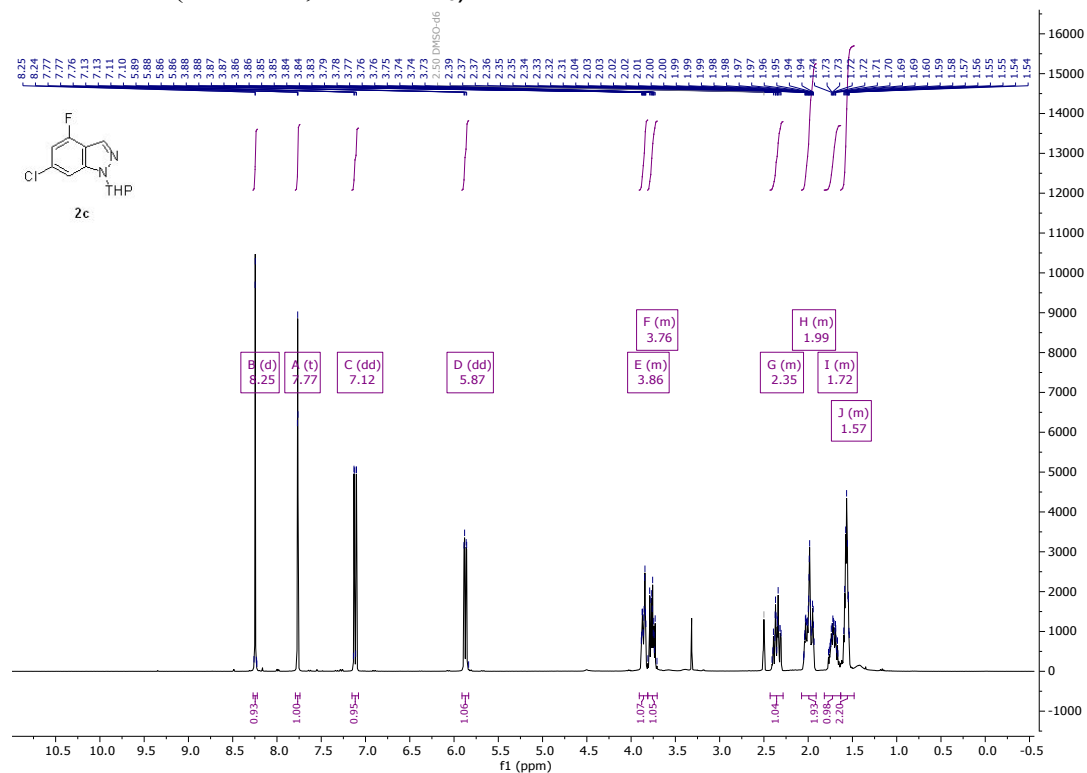
2b ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$)



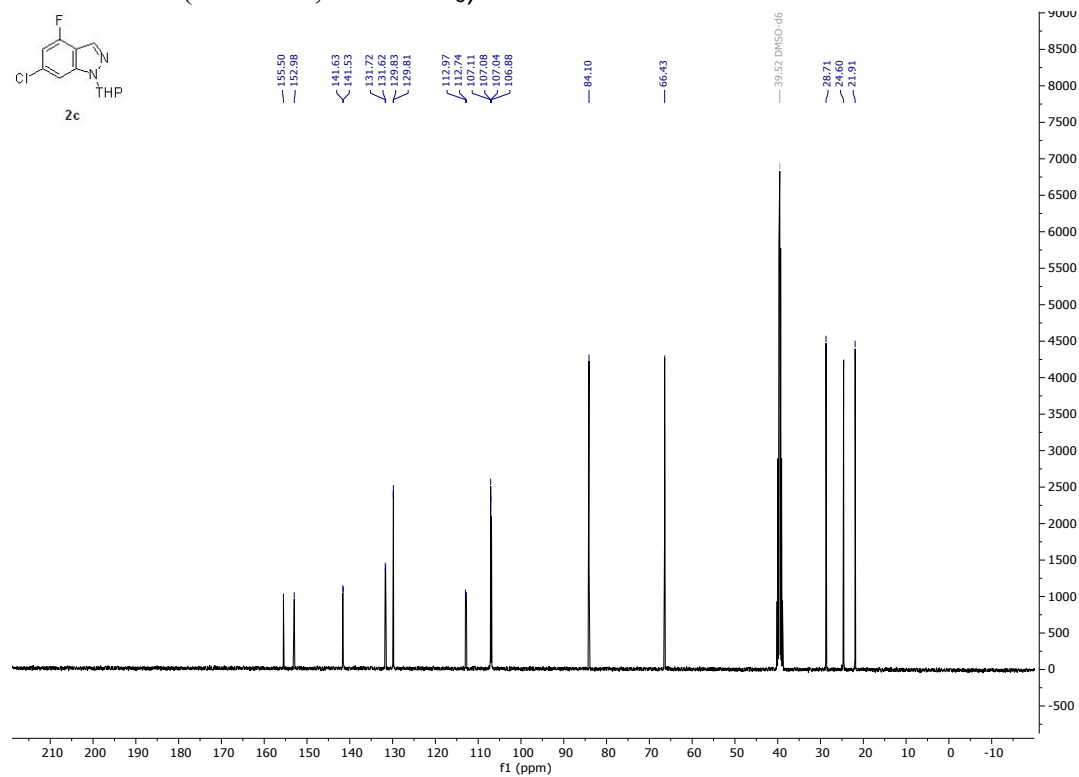
2b ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)



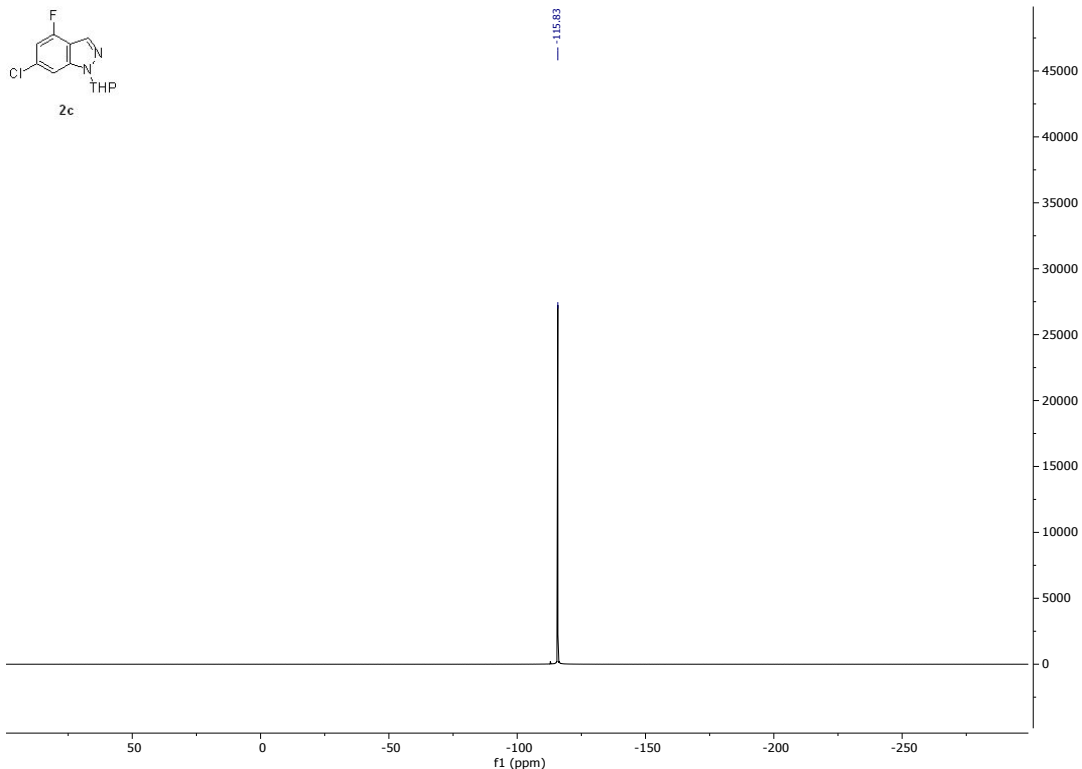
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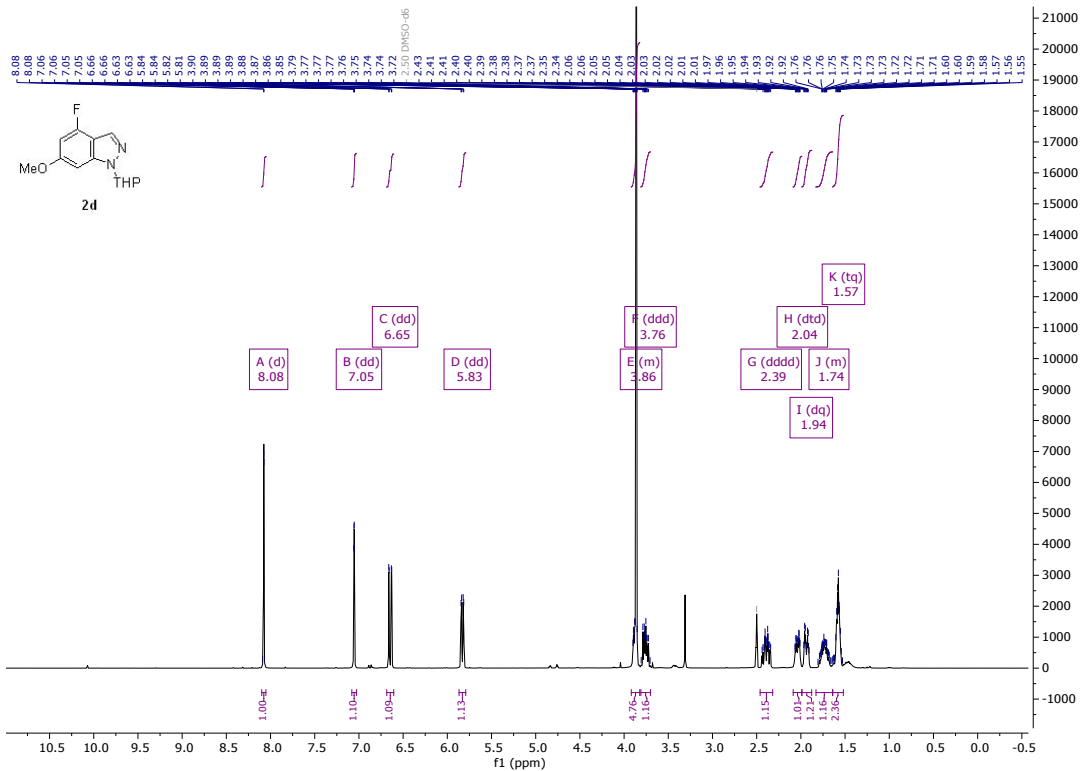
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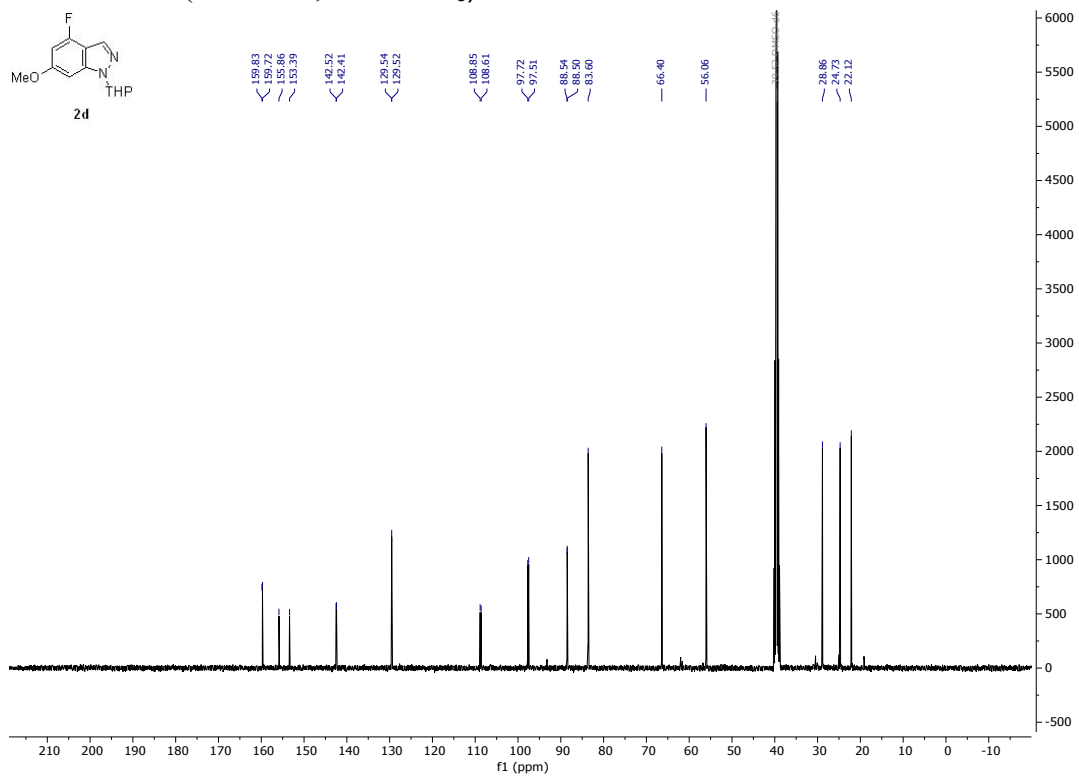
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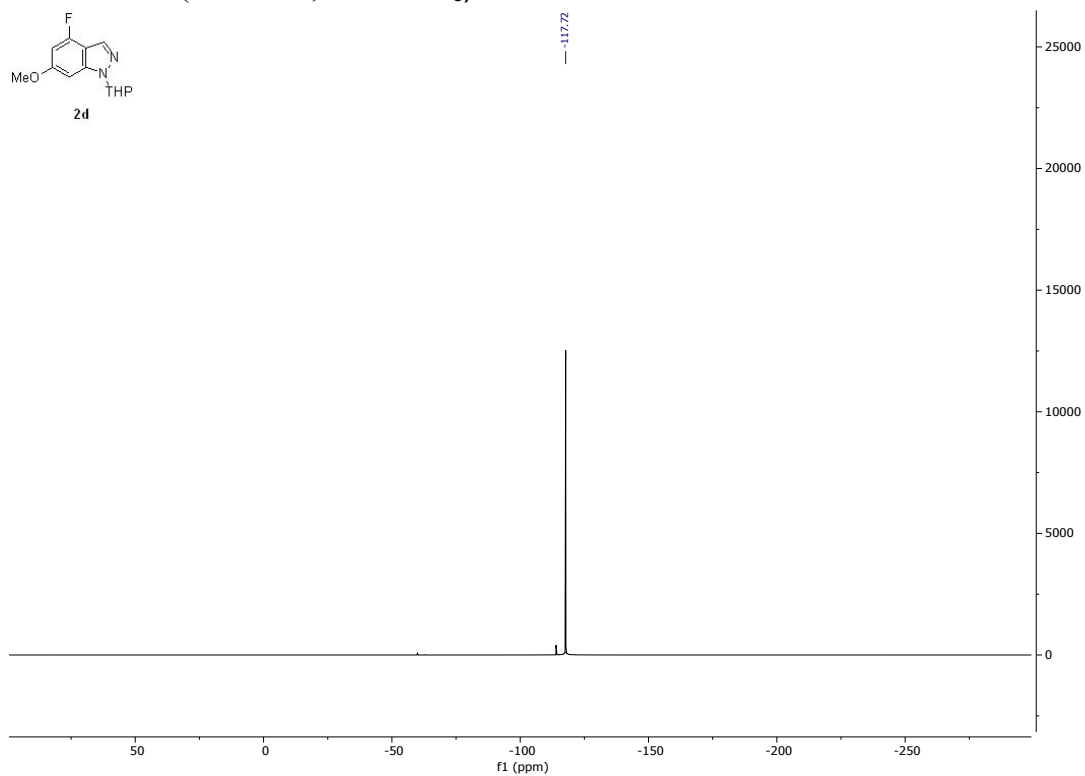
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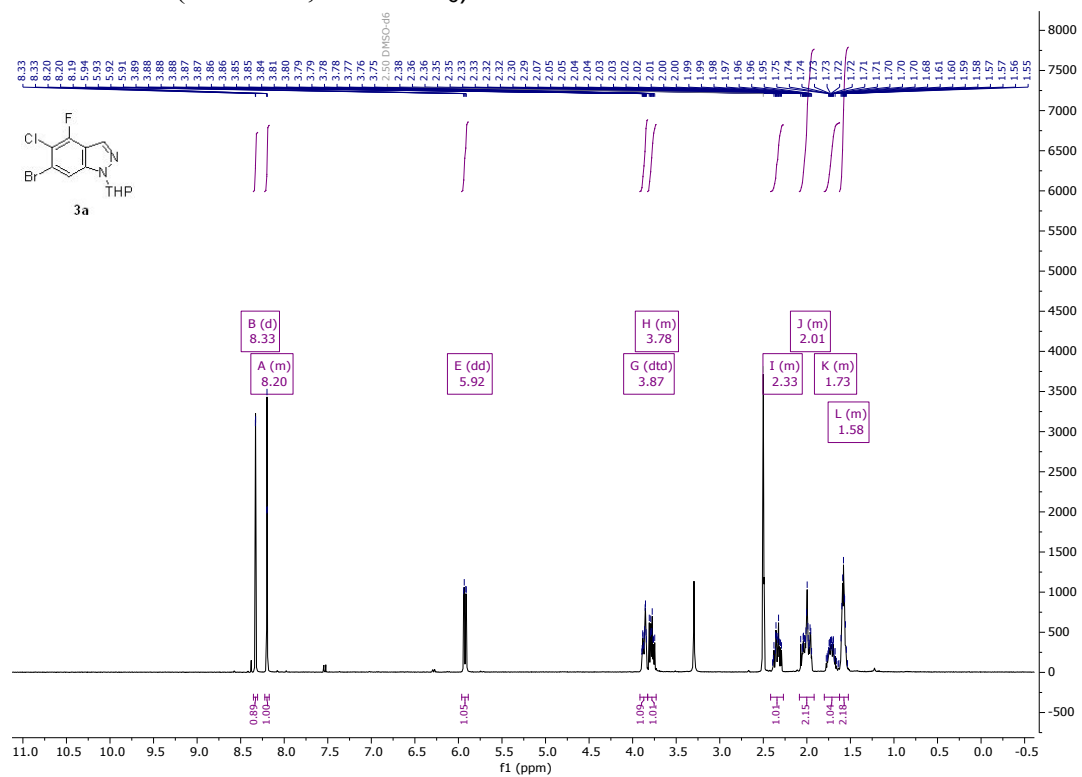
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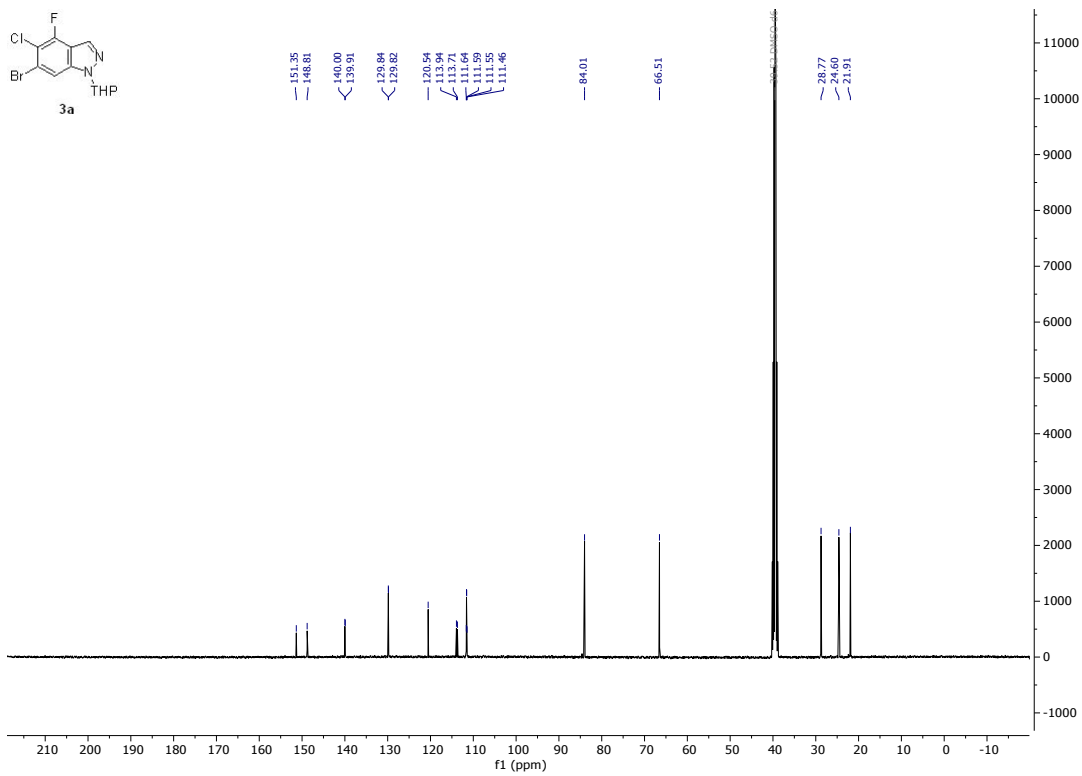
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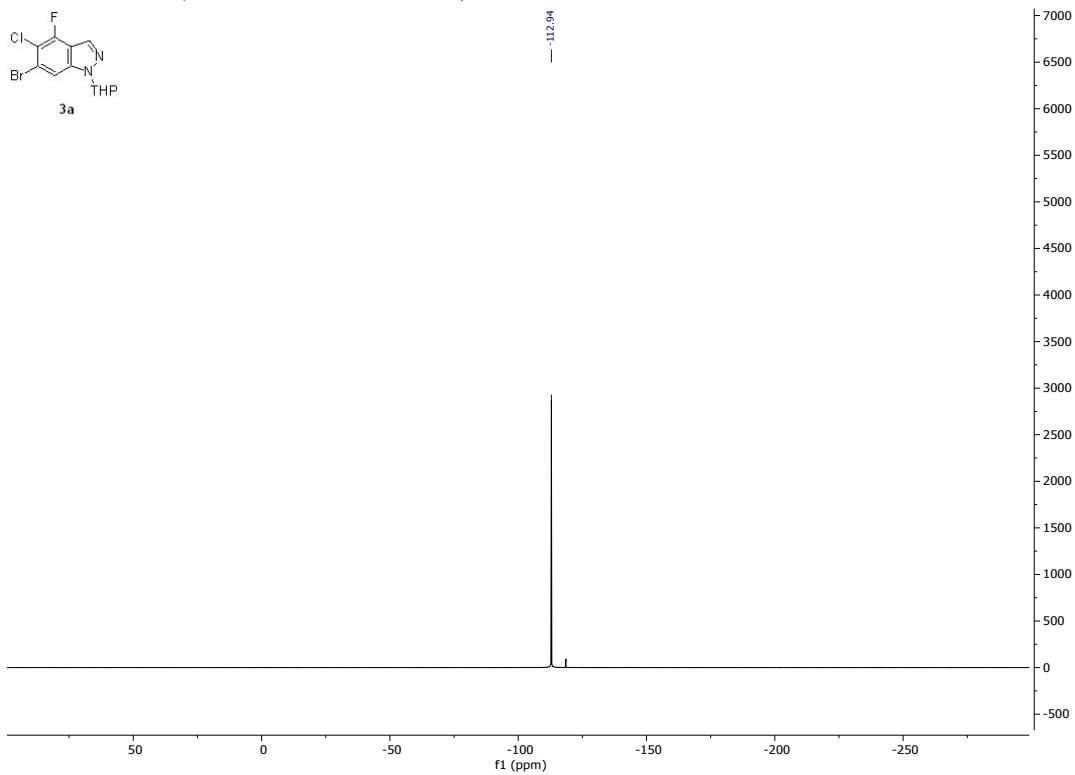
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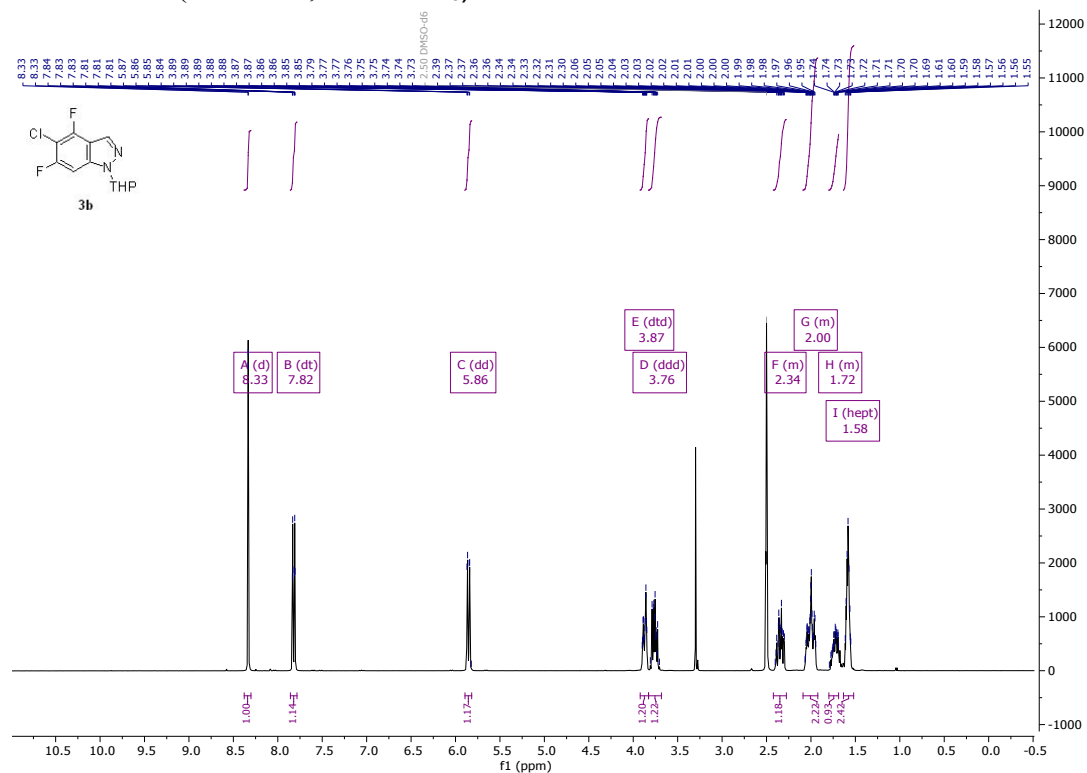
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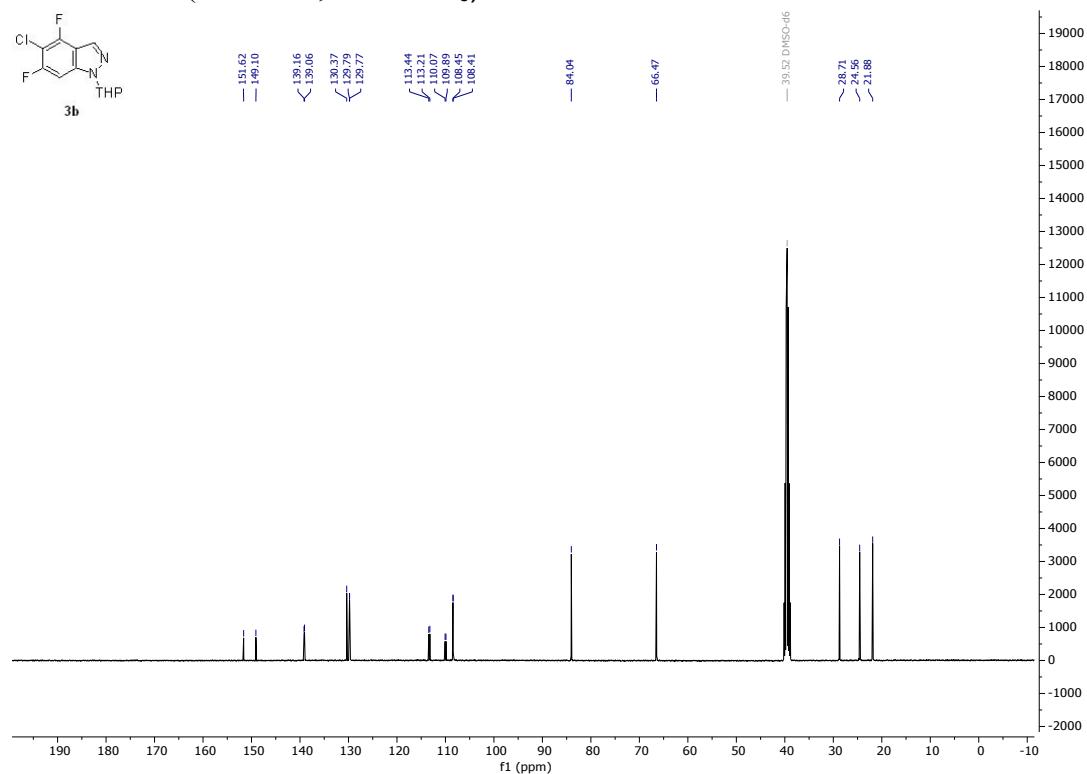
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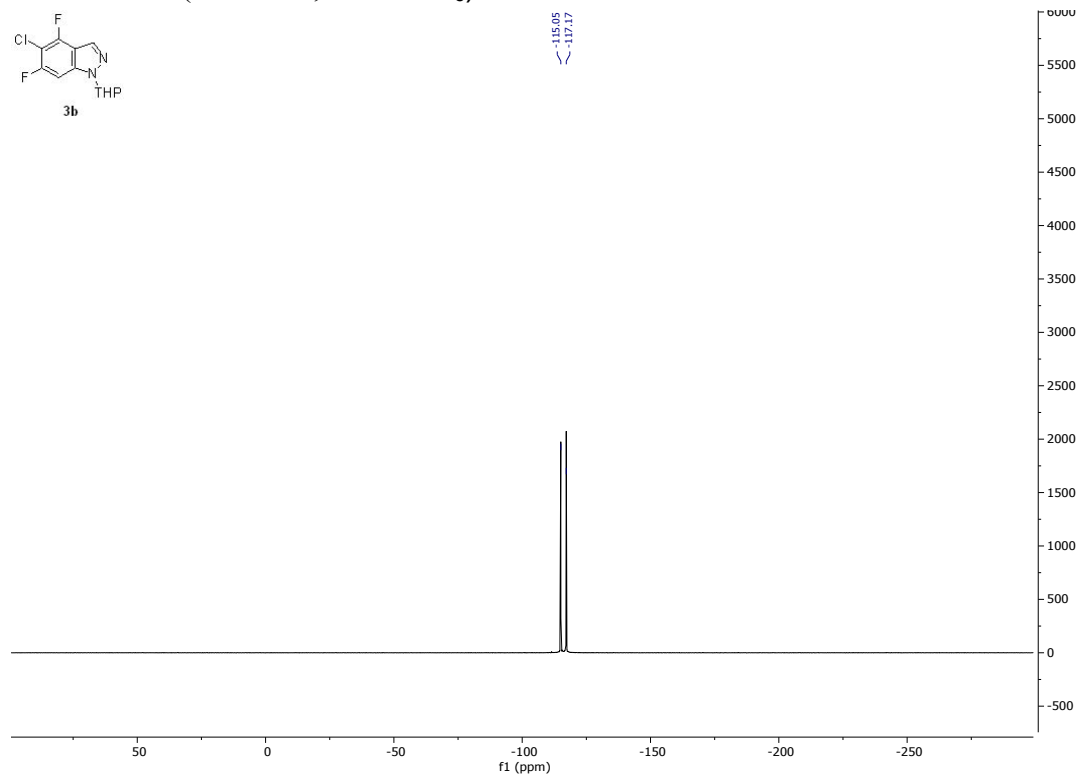
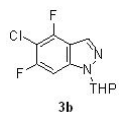
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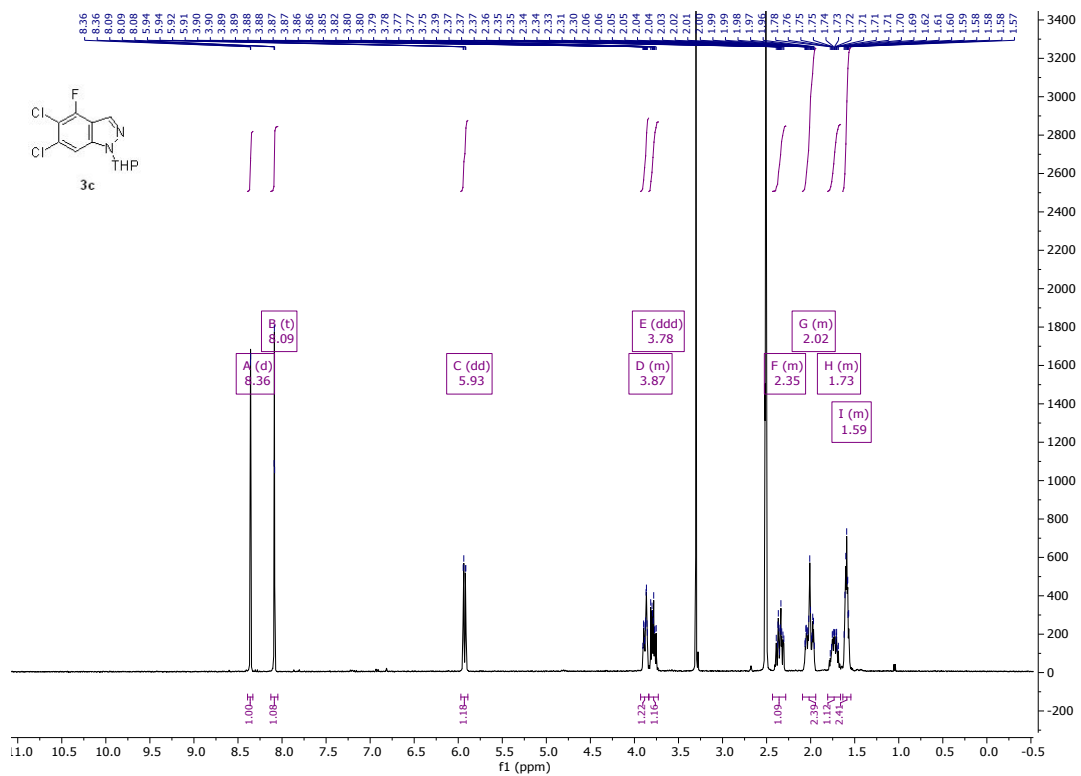
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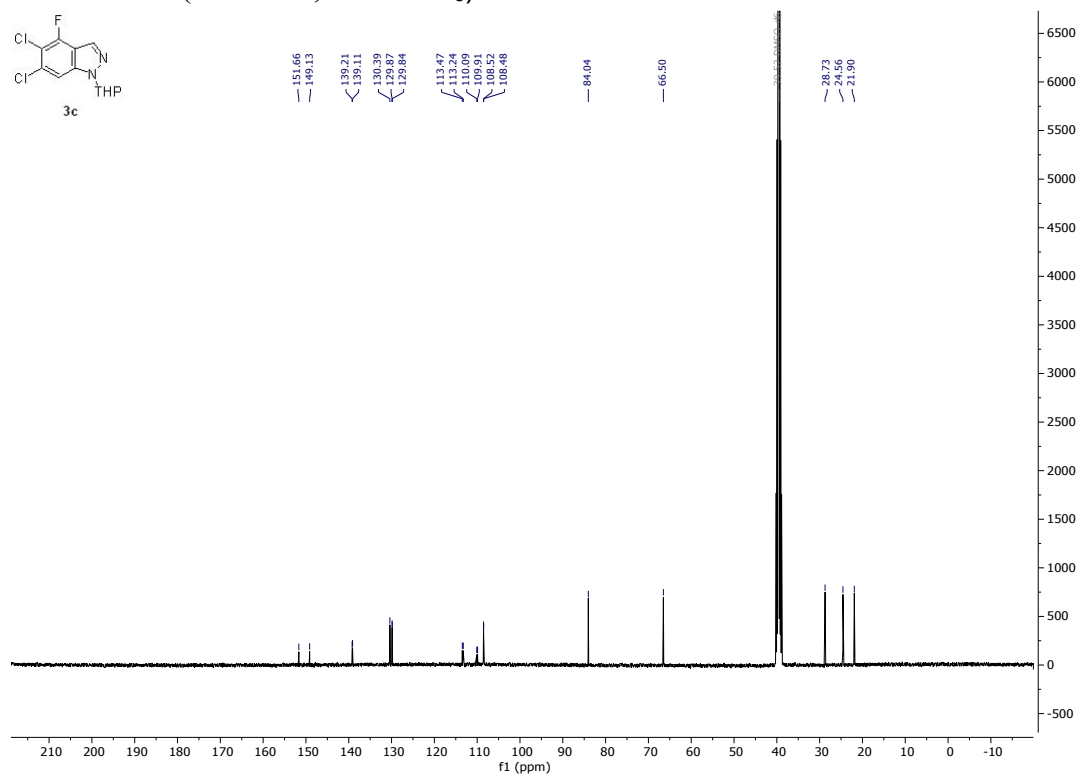
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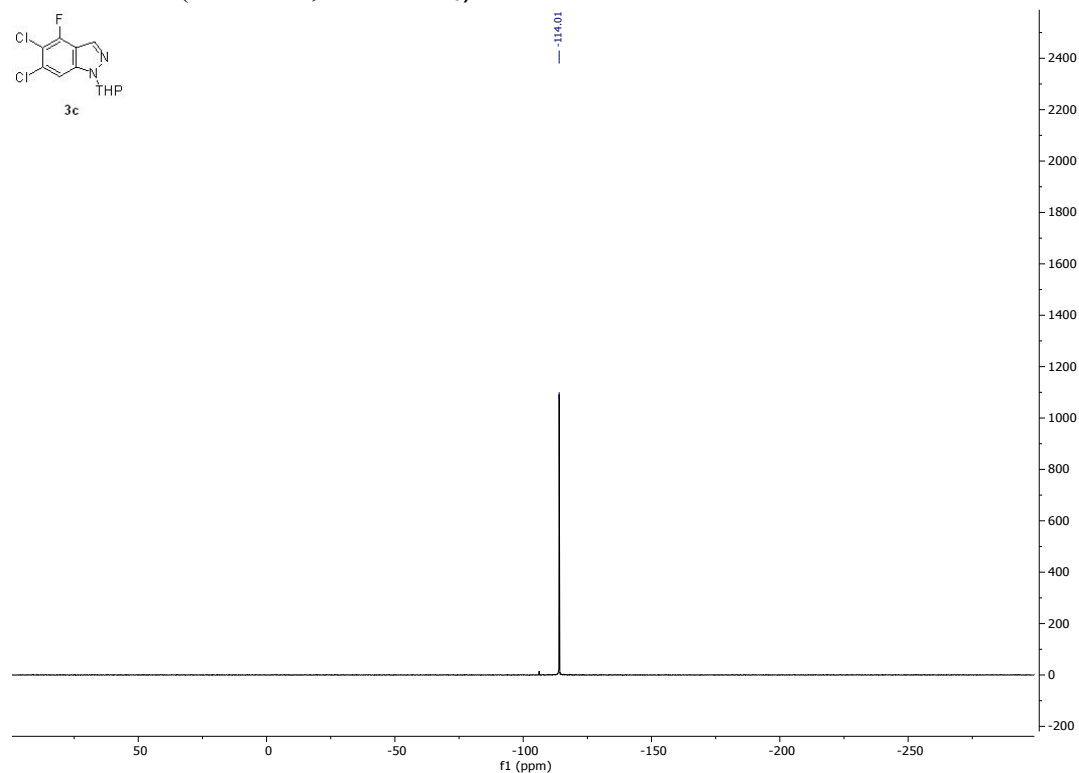
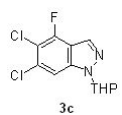
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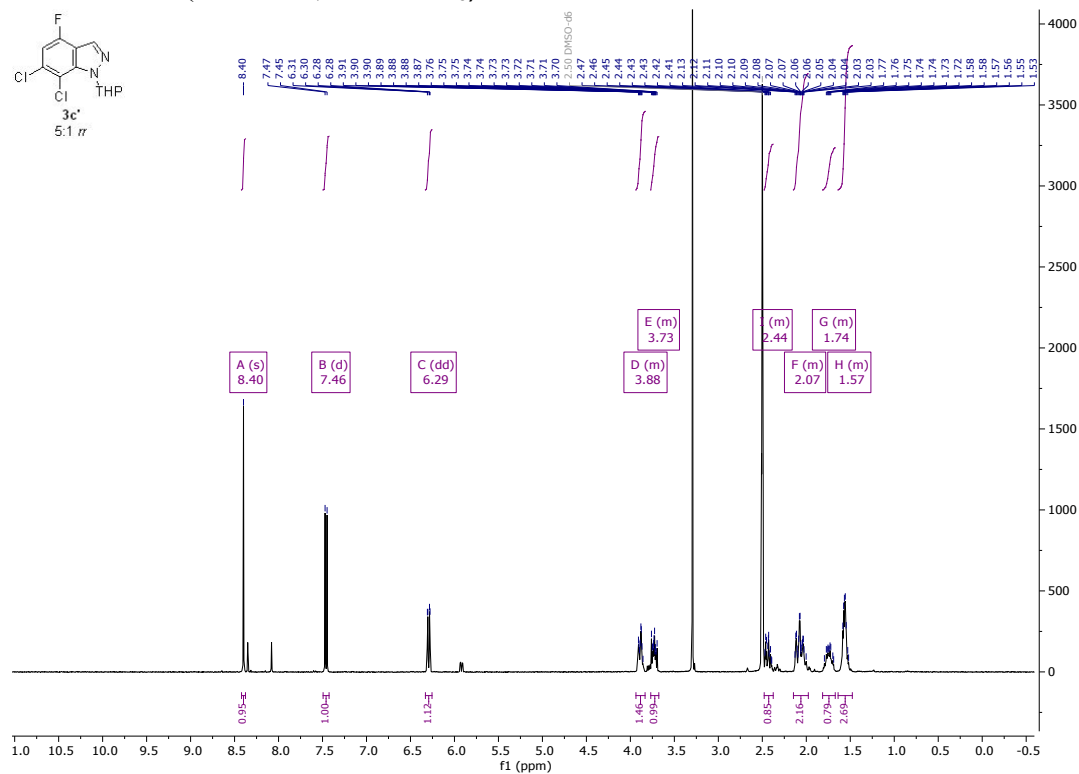
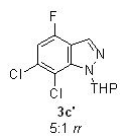
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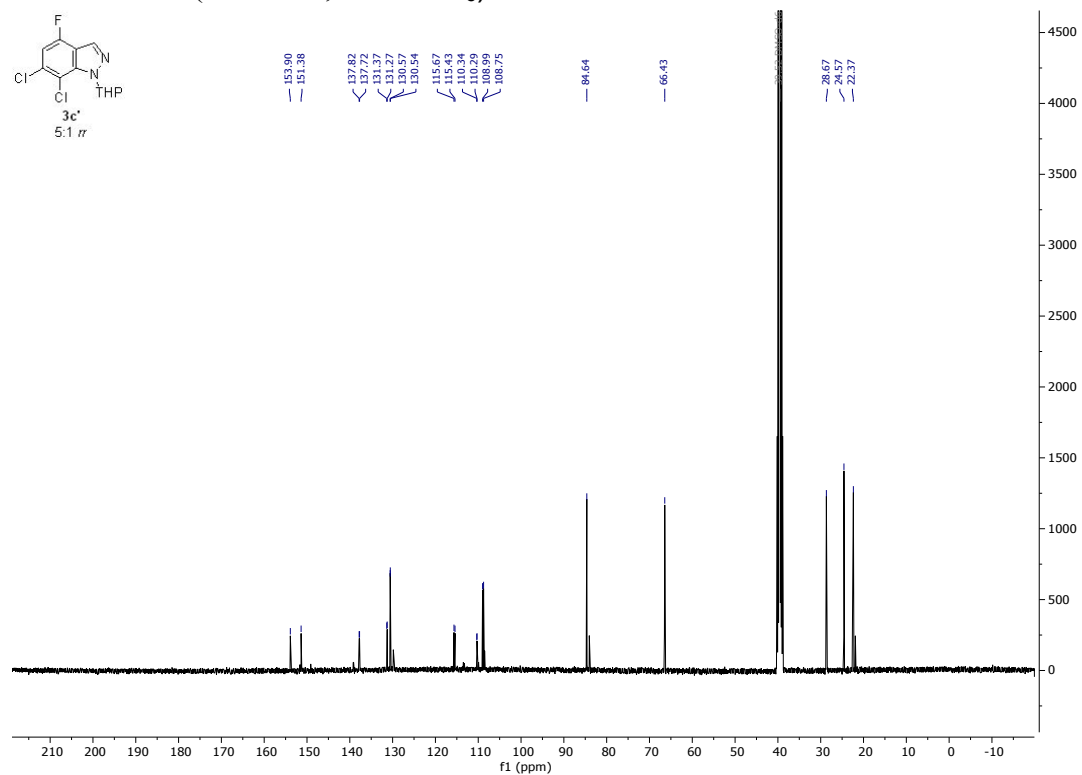
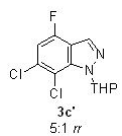
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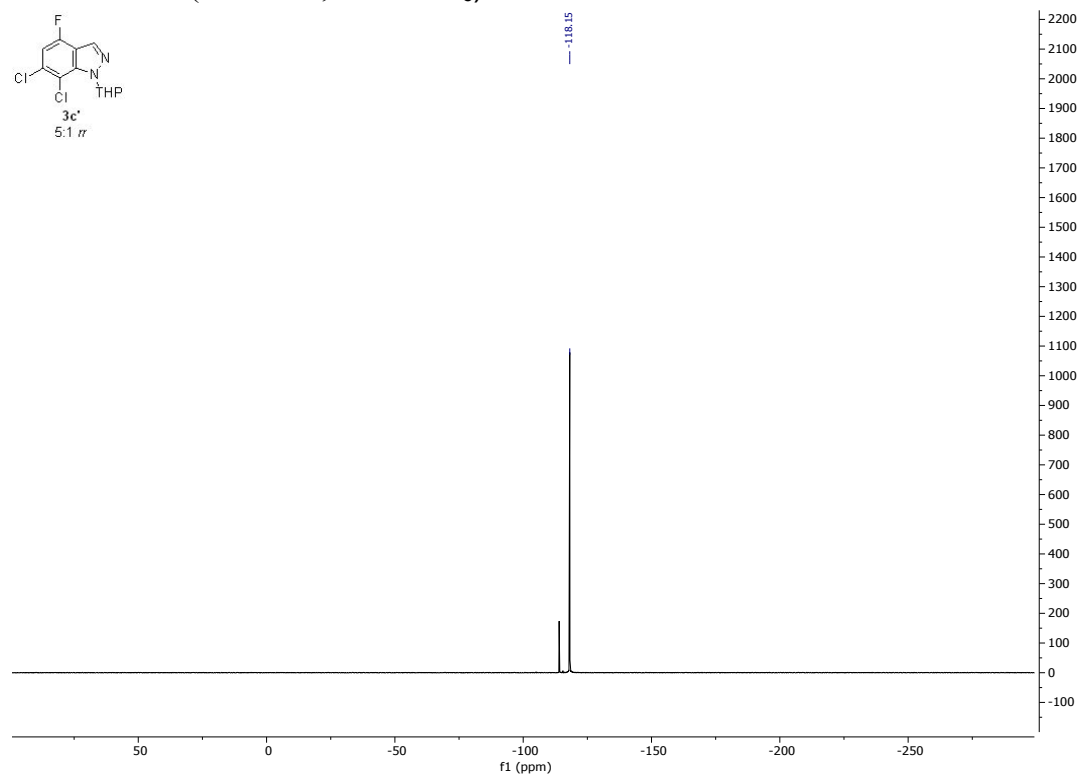
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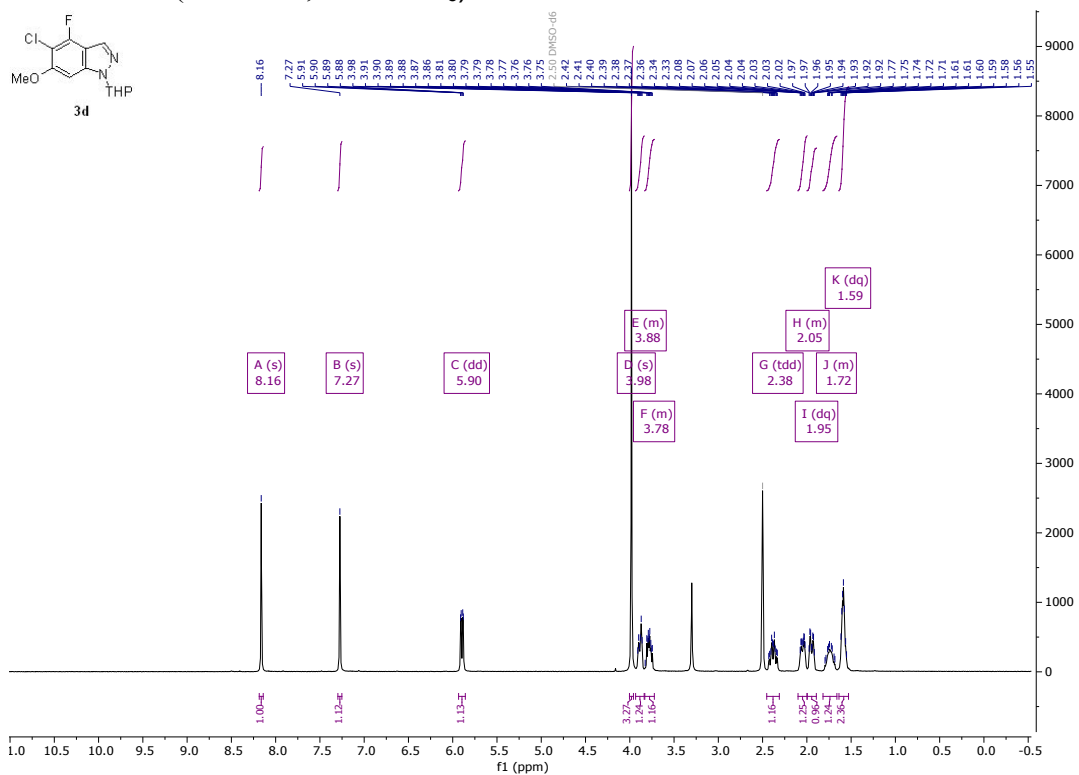
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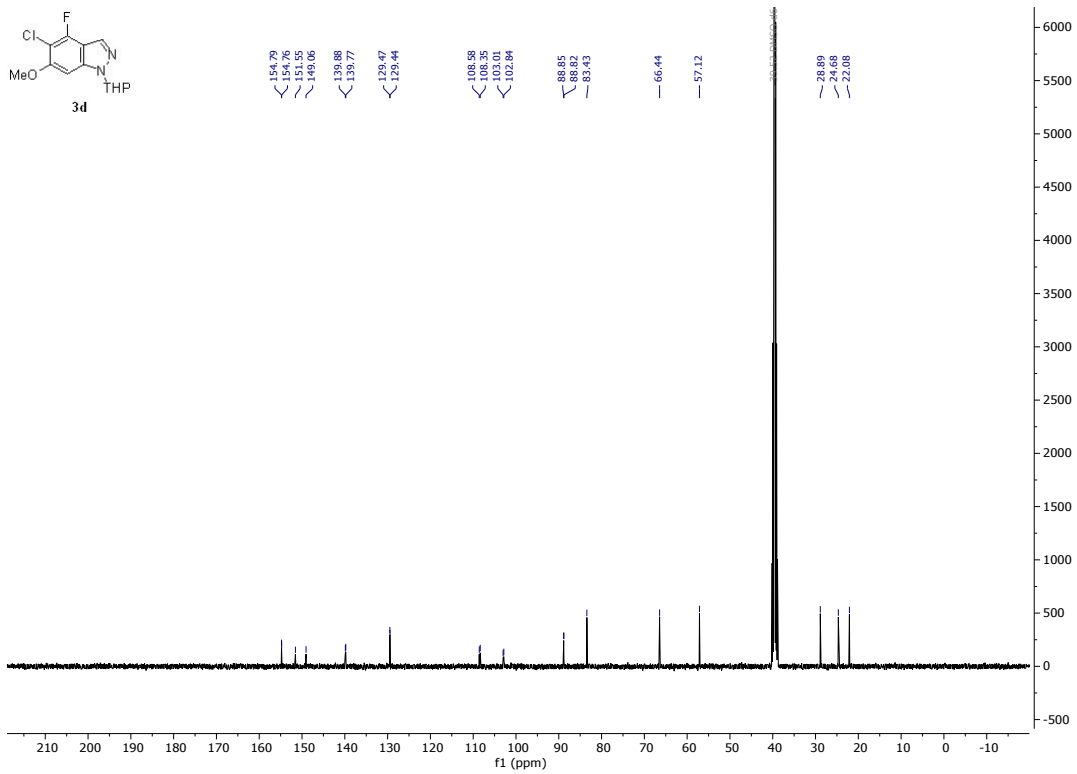
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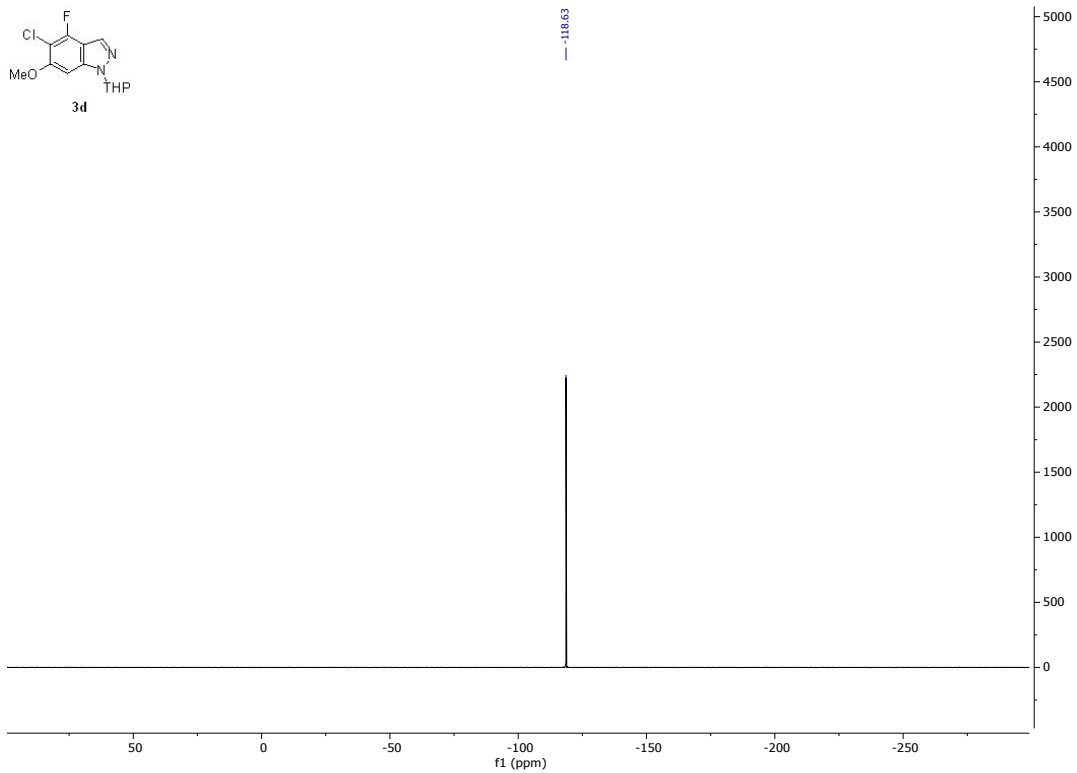
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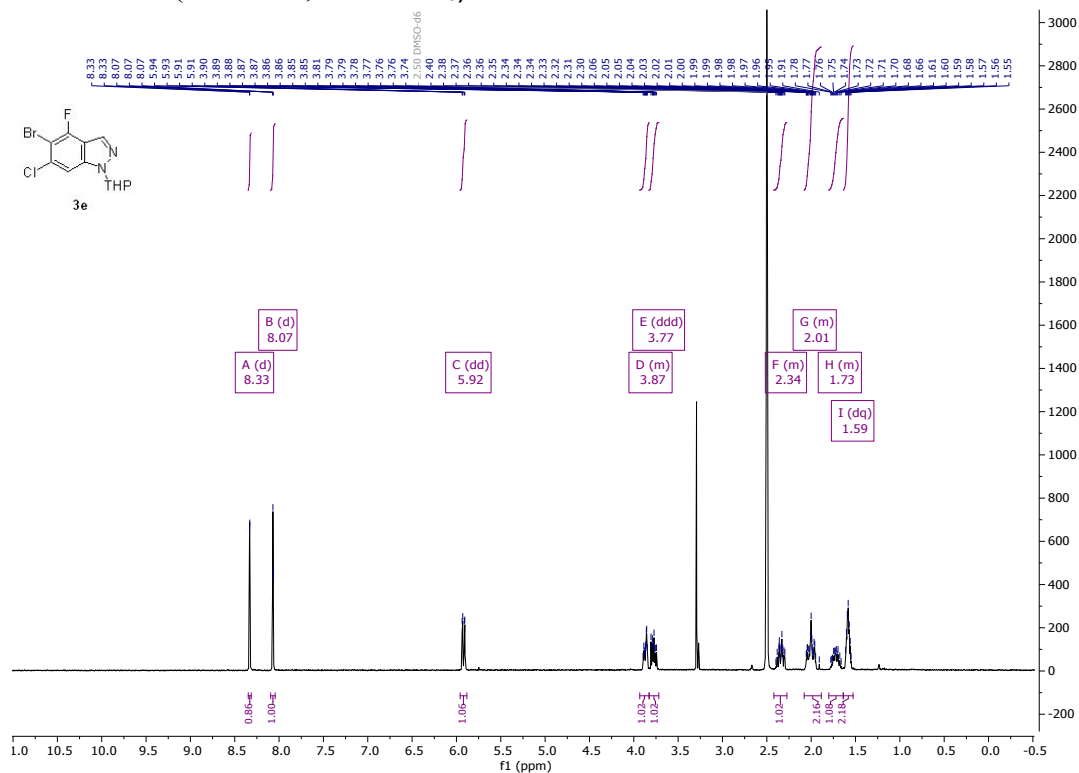
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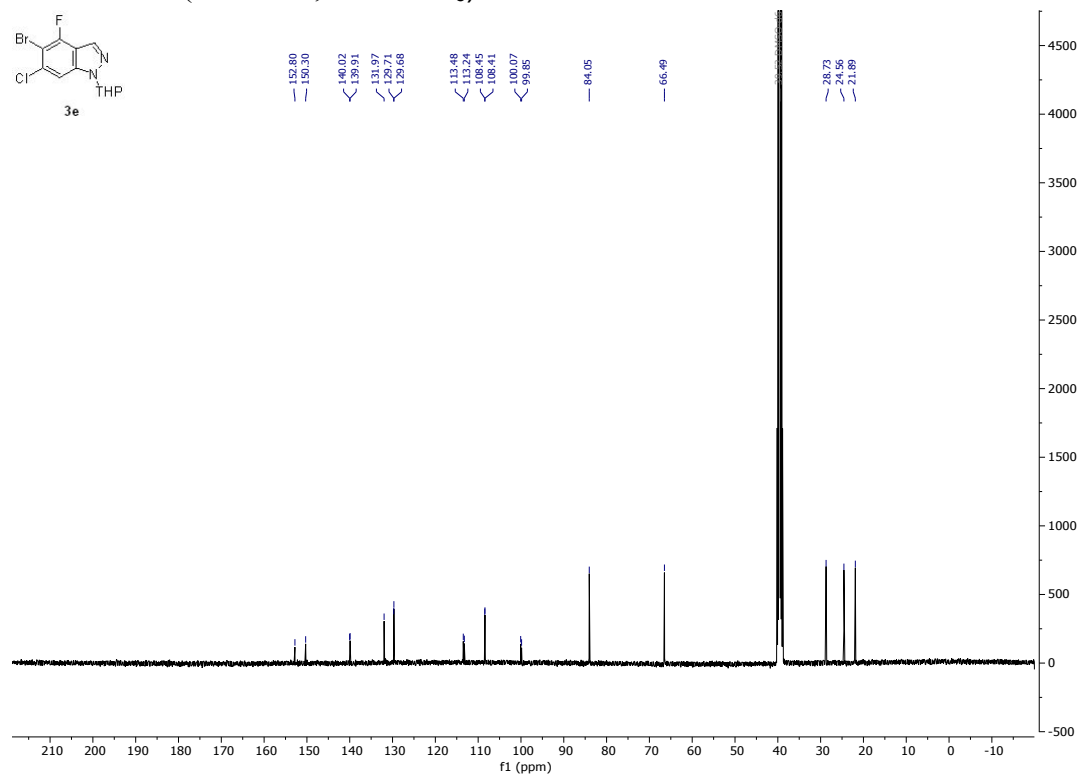
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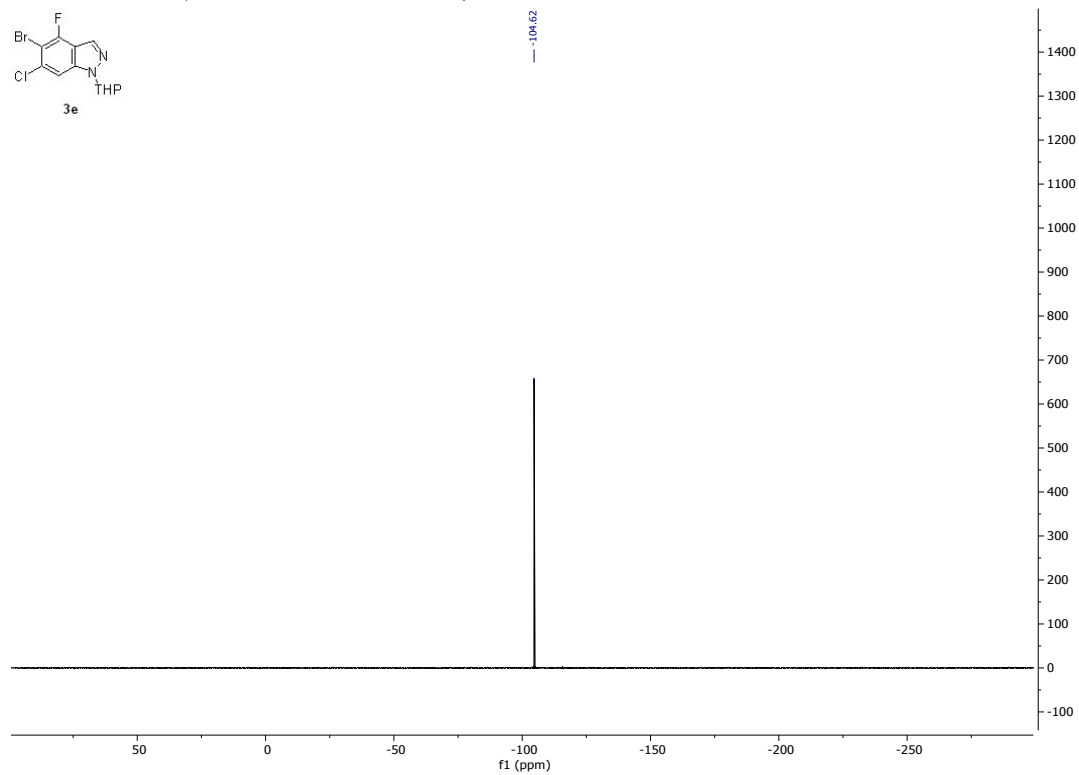
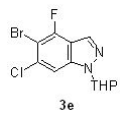
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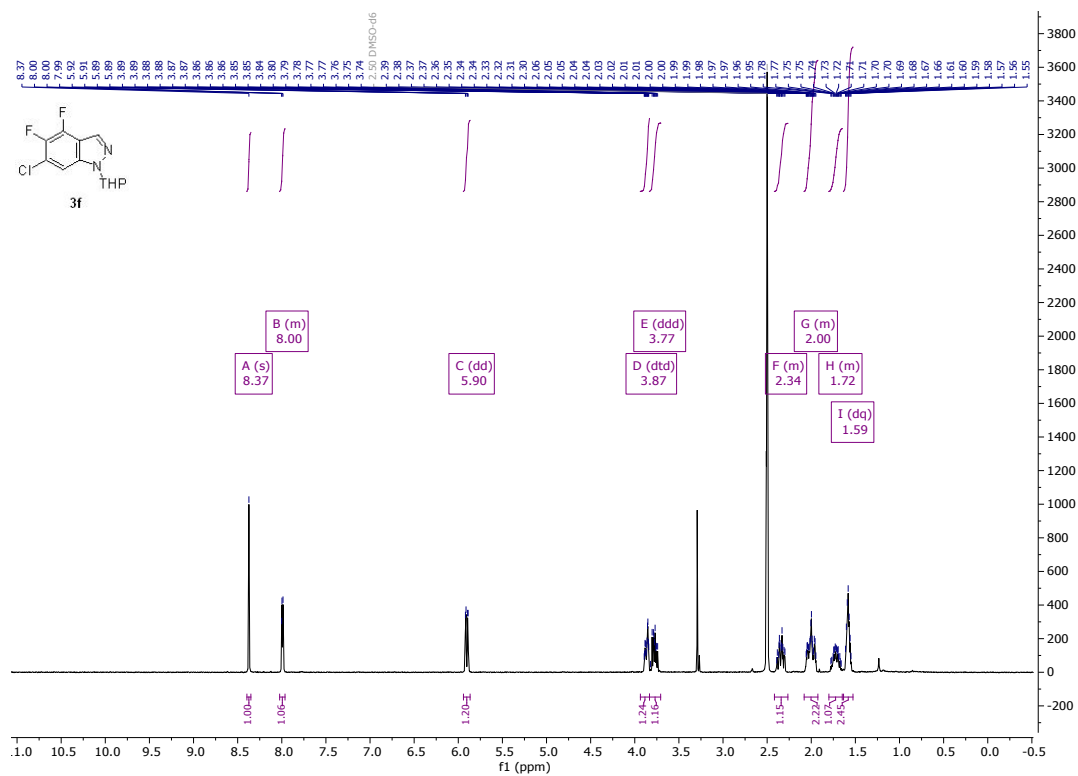
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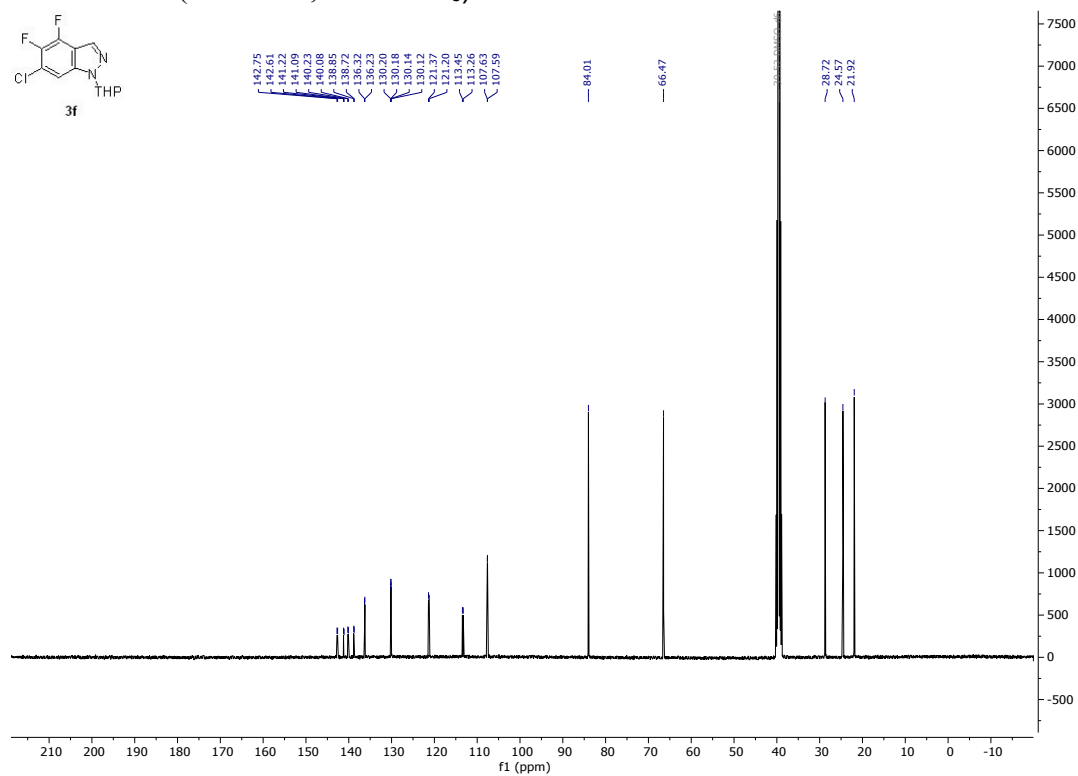
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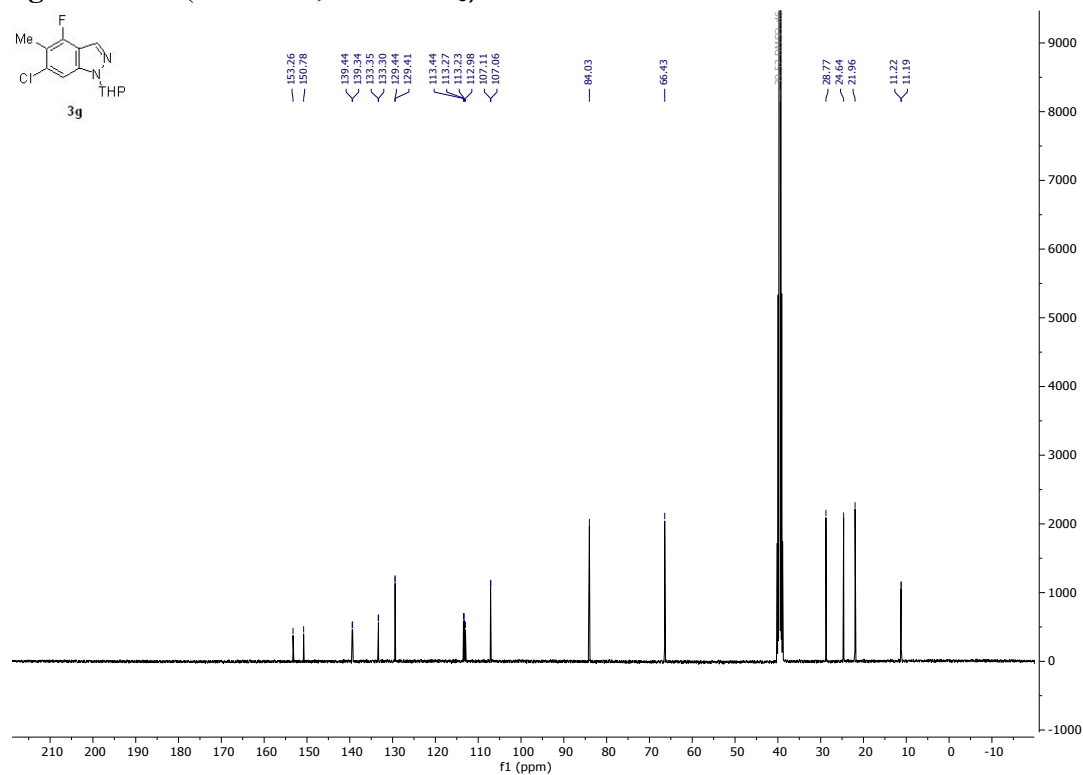
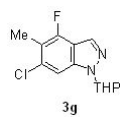
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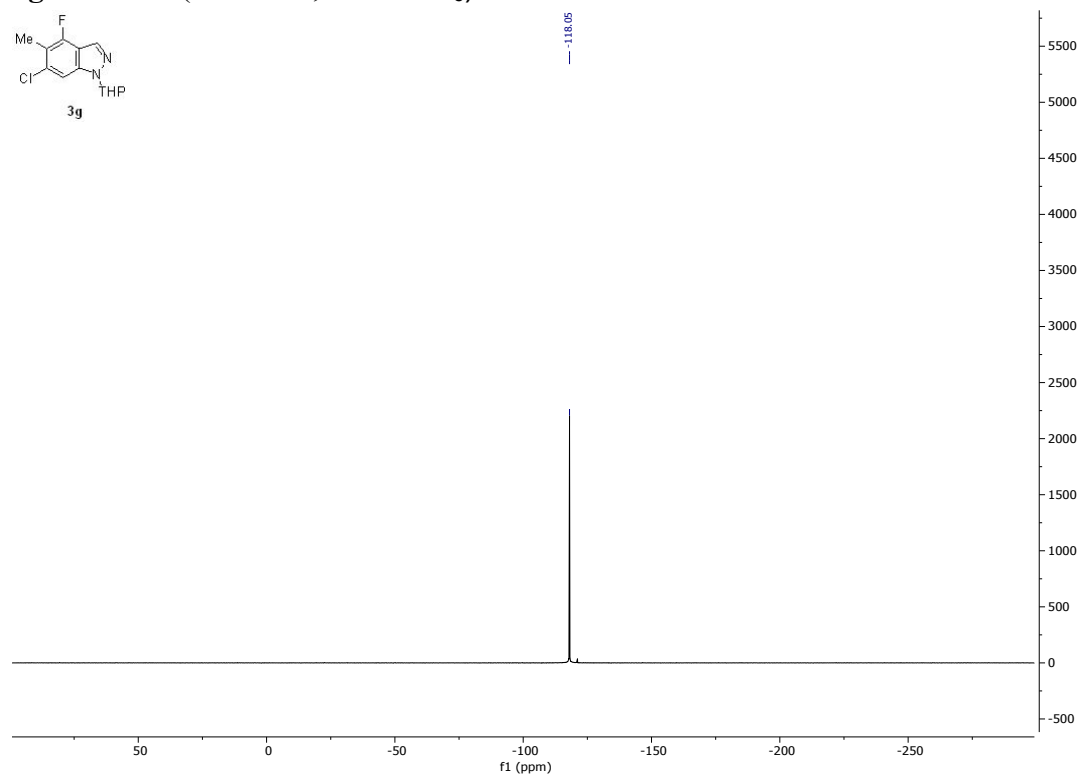
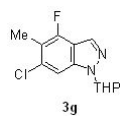
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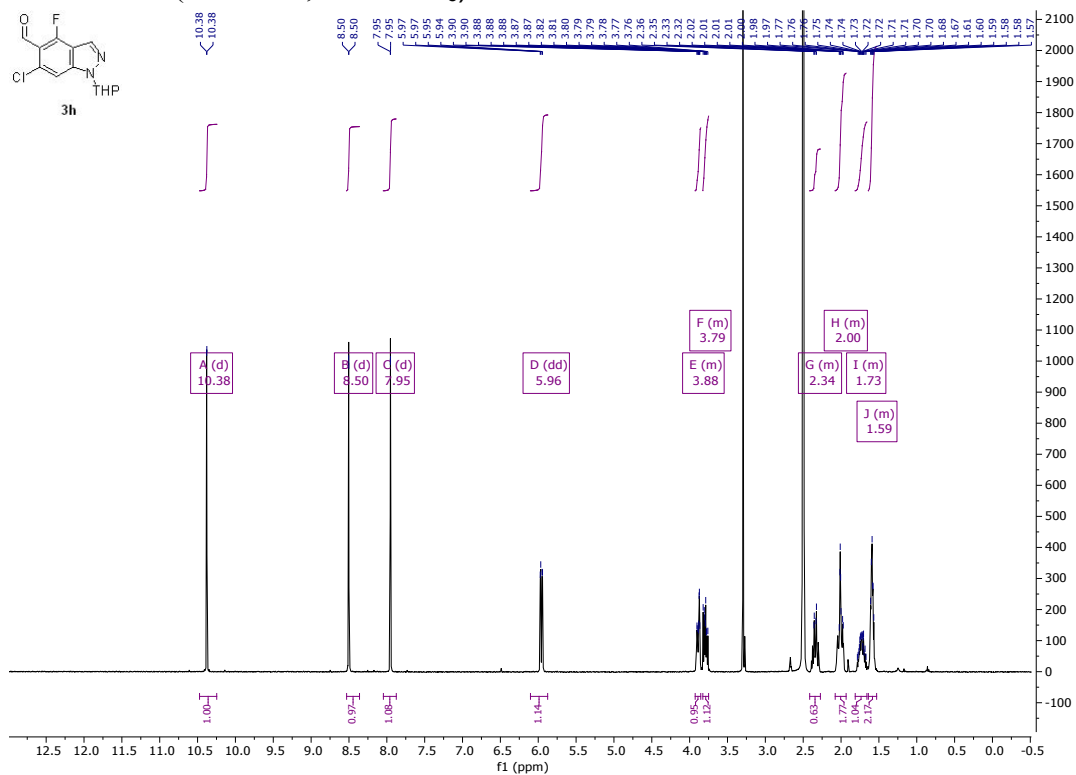
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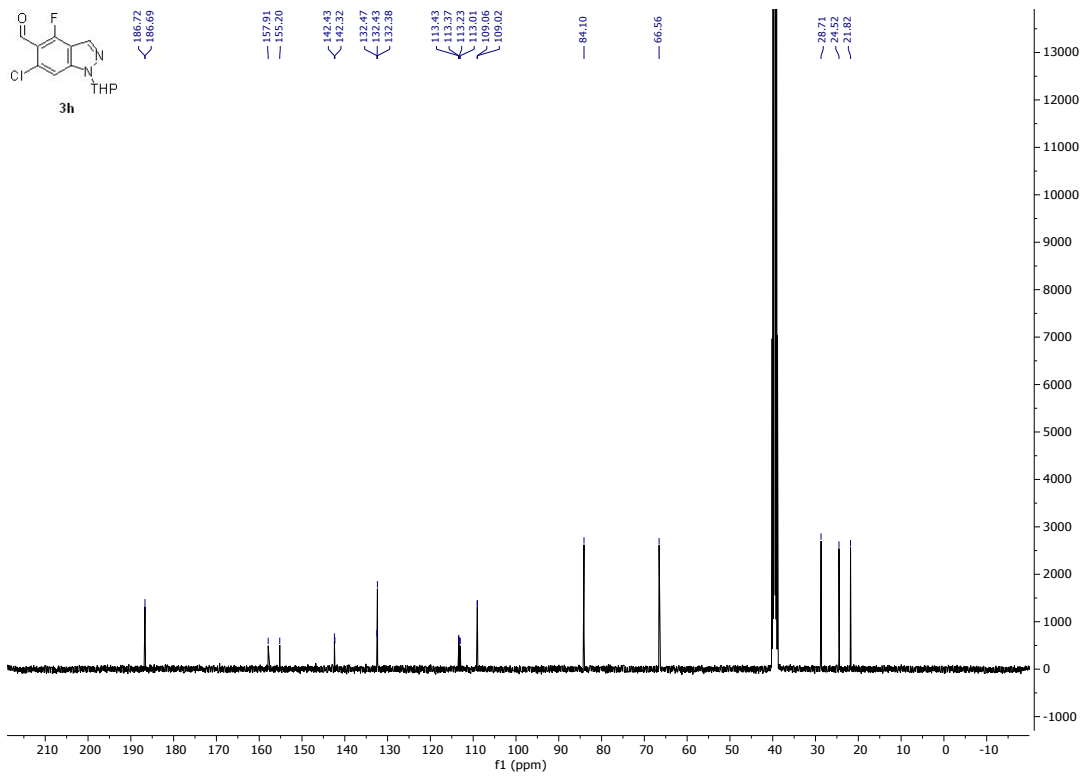
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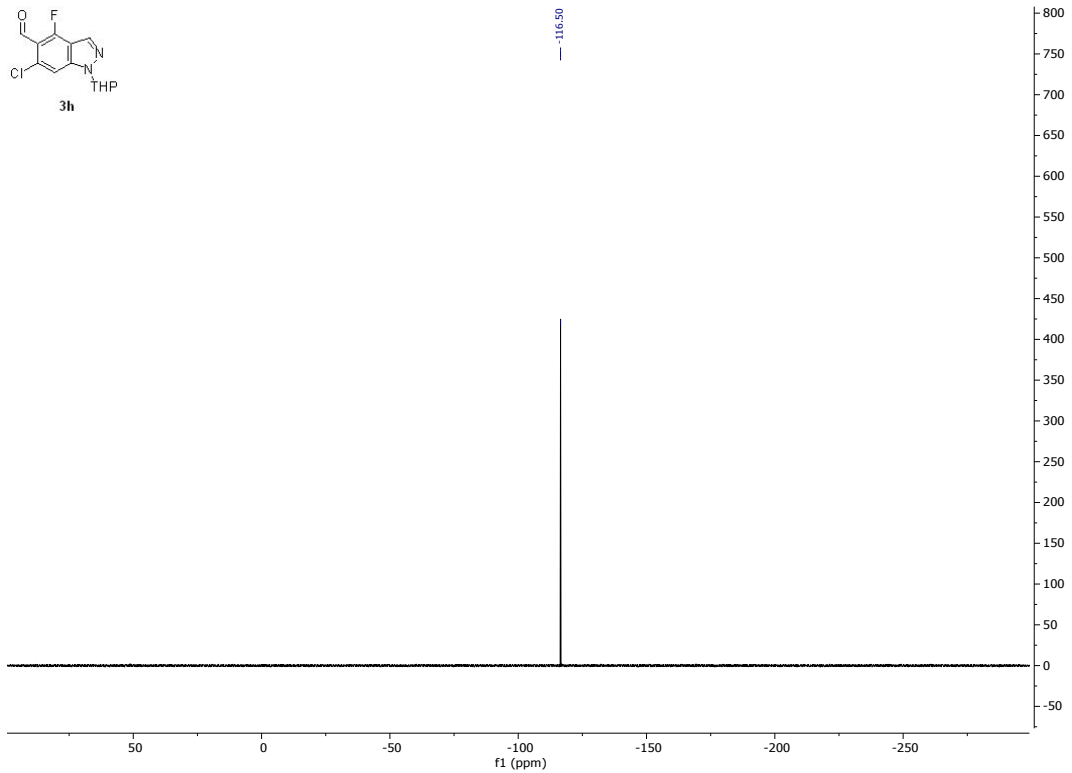
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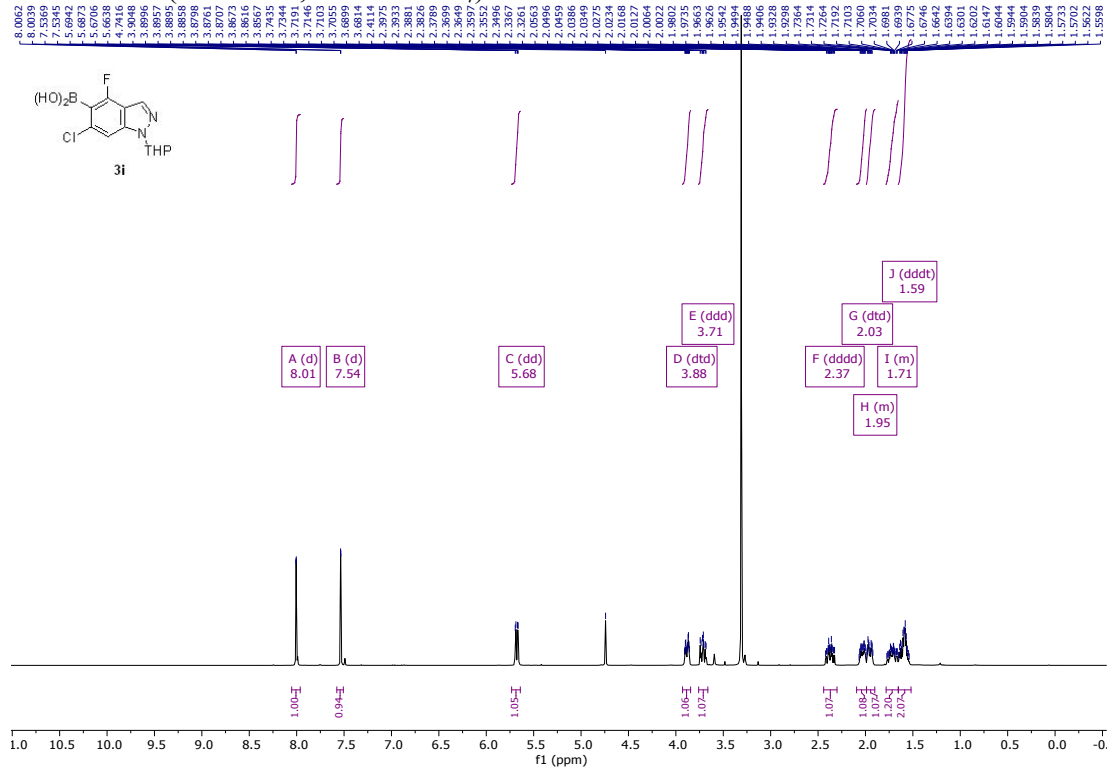
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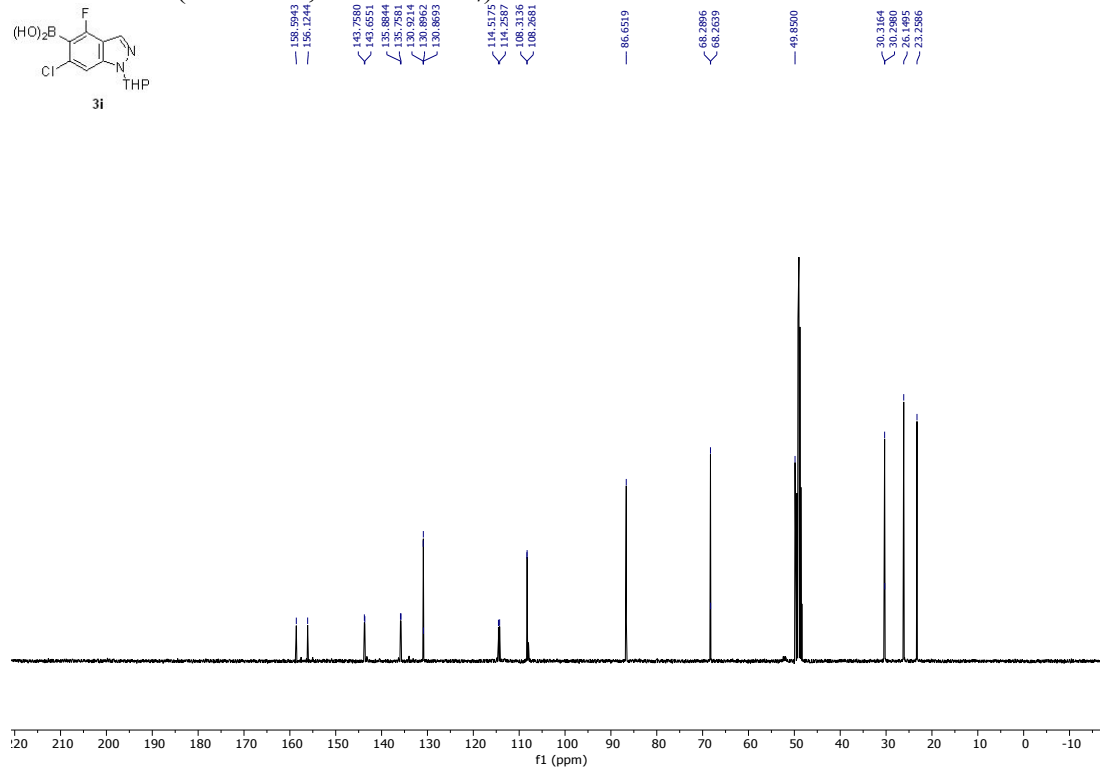
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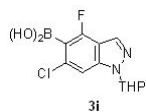
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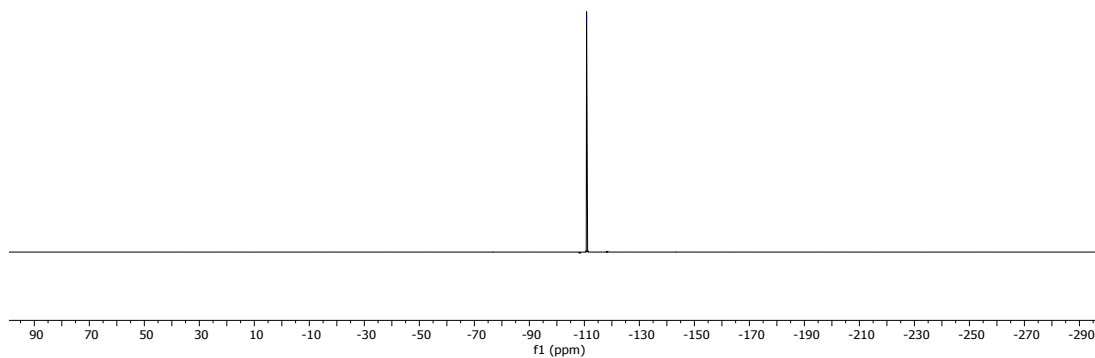
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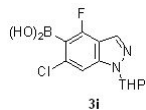
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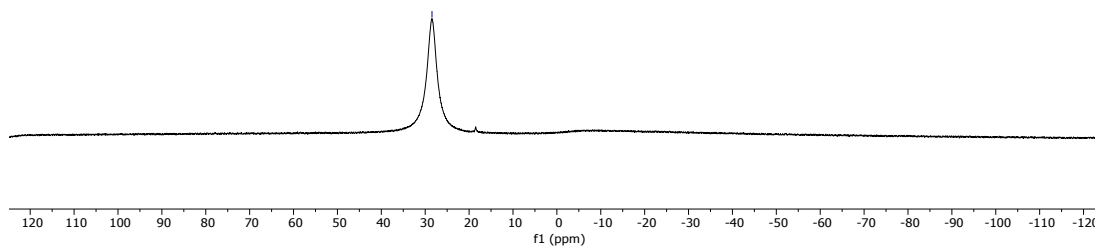
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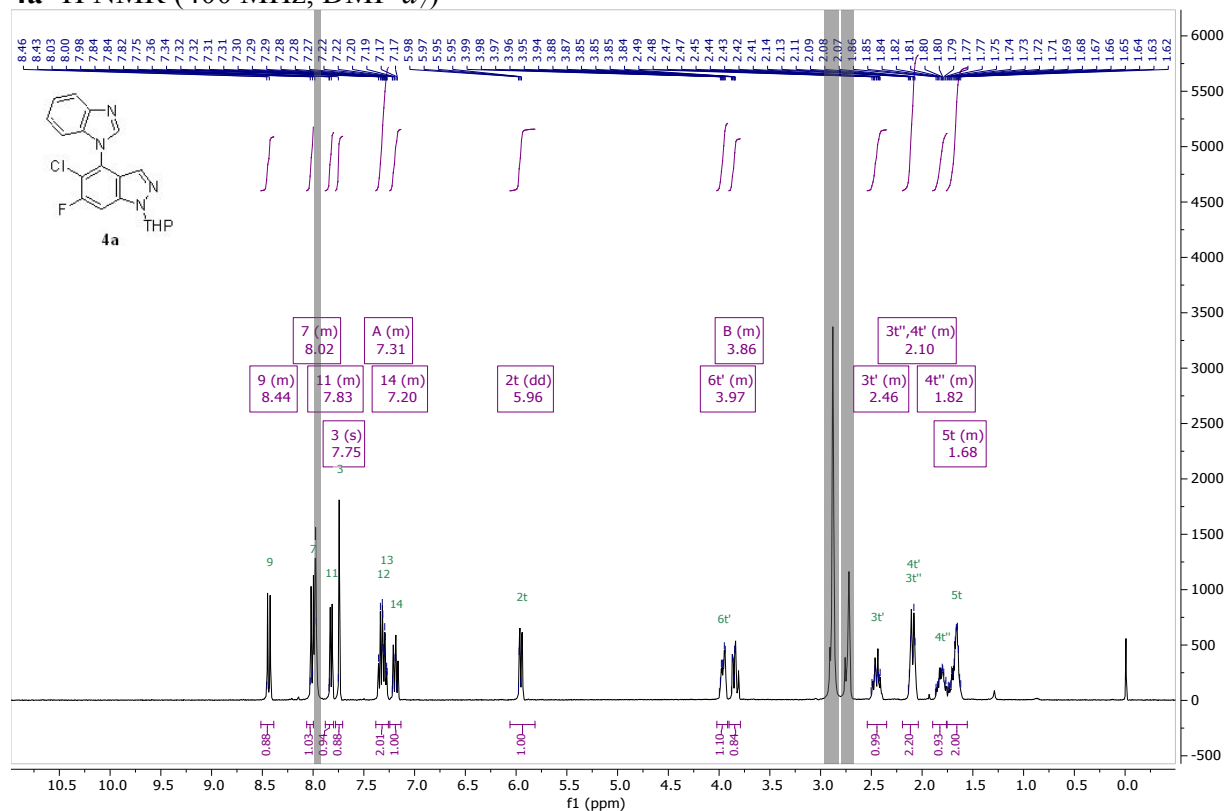
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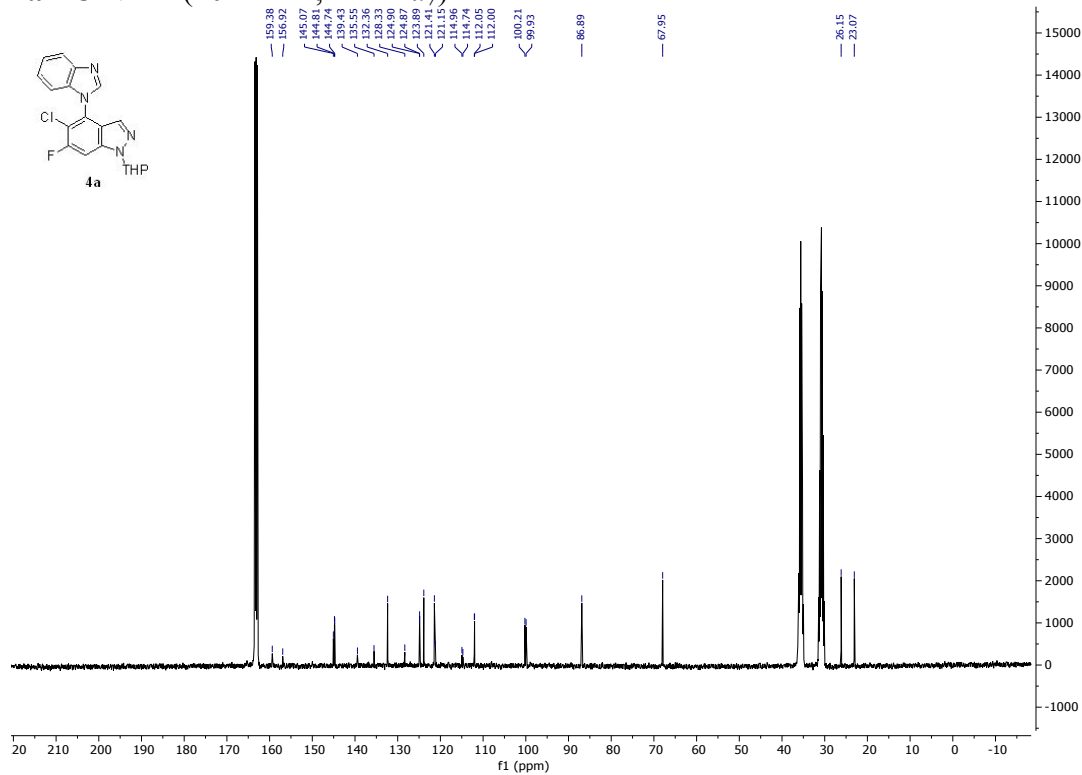
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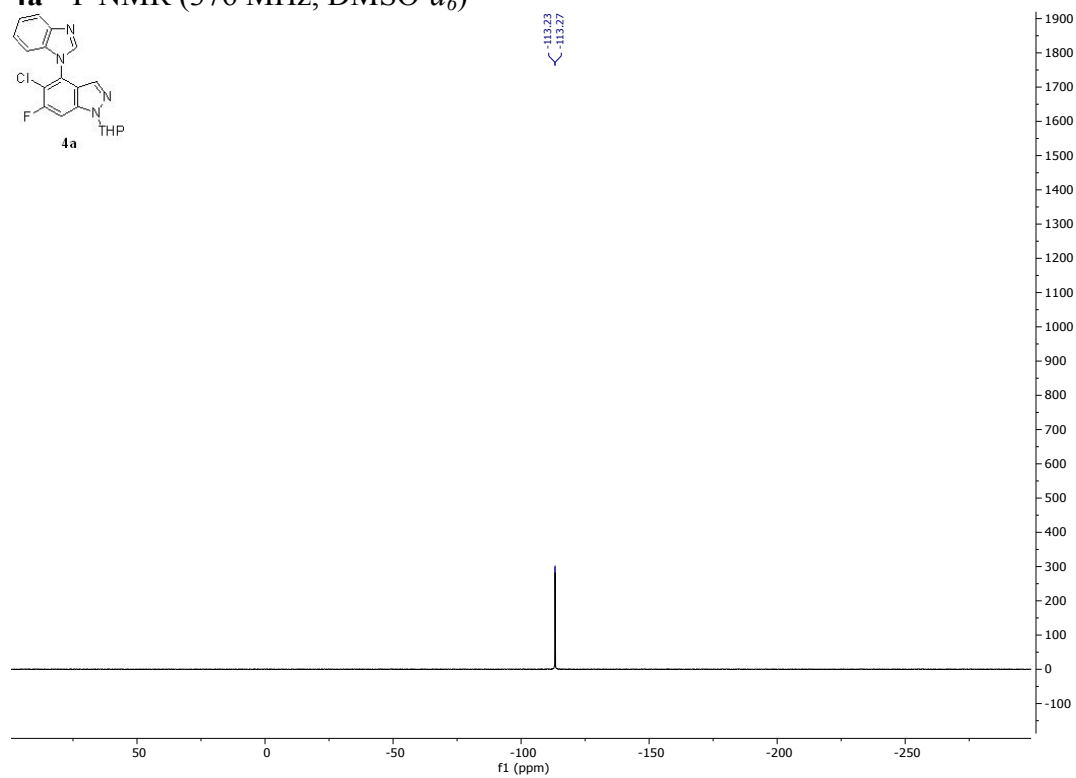
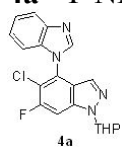
4a ¹H NMR (400 MHz, DMF-d₇)



4a ¹³C NMR (101 MHz, DMF-d₇)

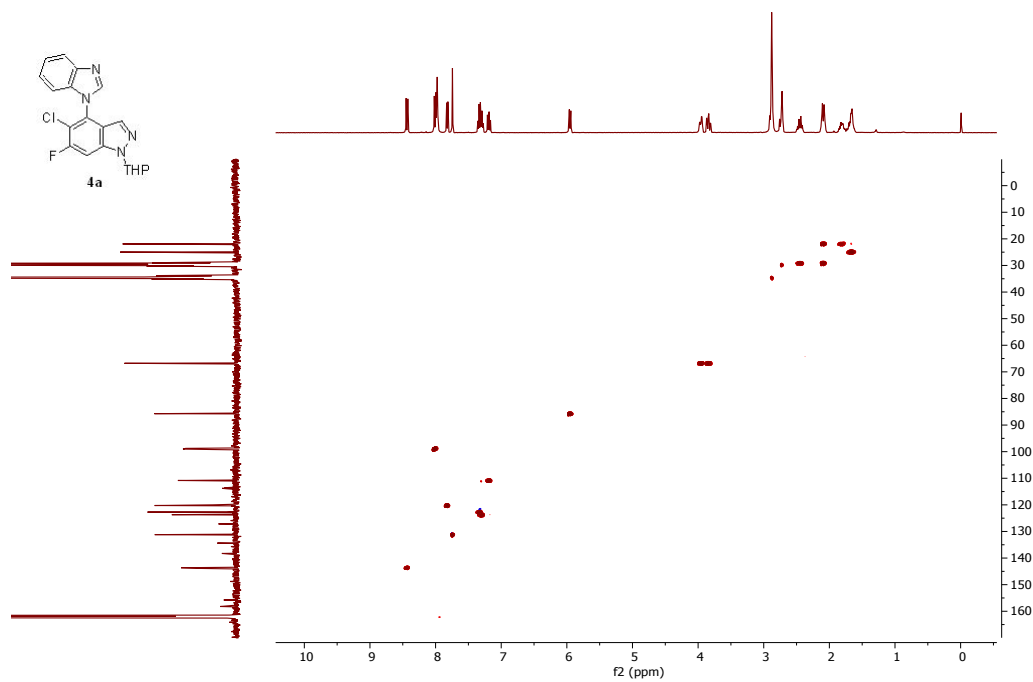


4a ¹⁹F NMR (376 MHz, DMSO-*d*₆)

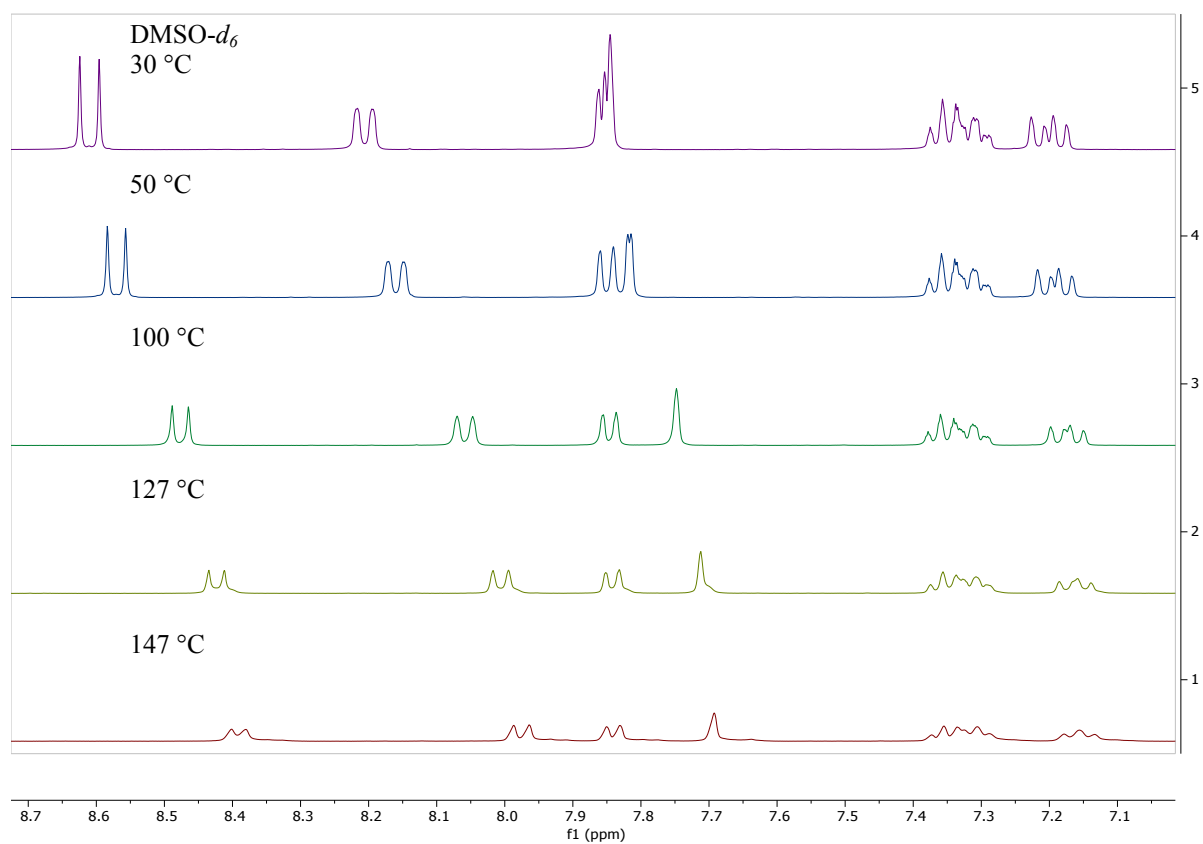


4a HSQC (¹H 400 MHz, DMF-*d*₇)

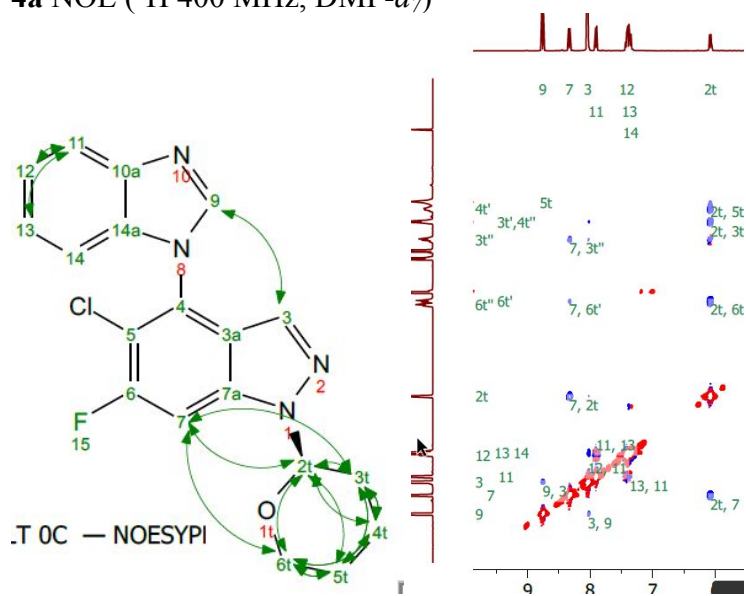
79811-5-DMF-100C.803.ser — NMR SYSTEM HOKI — 00712459-561-002 10.35mg 600 ul DMF-d7 Hoki#16 100C — 80C_gHSQC DMF C:\\ wang16 16



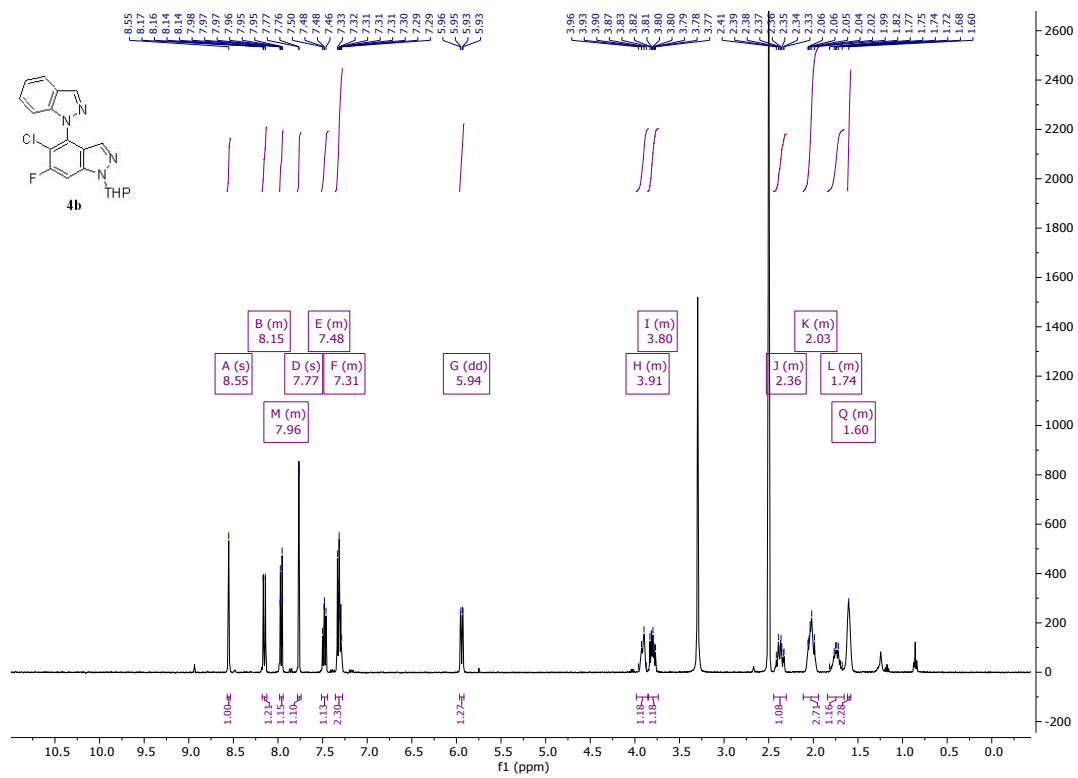
4a Overlay (¹H 400 MHz, DMSO-*d*₆)



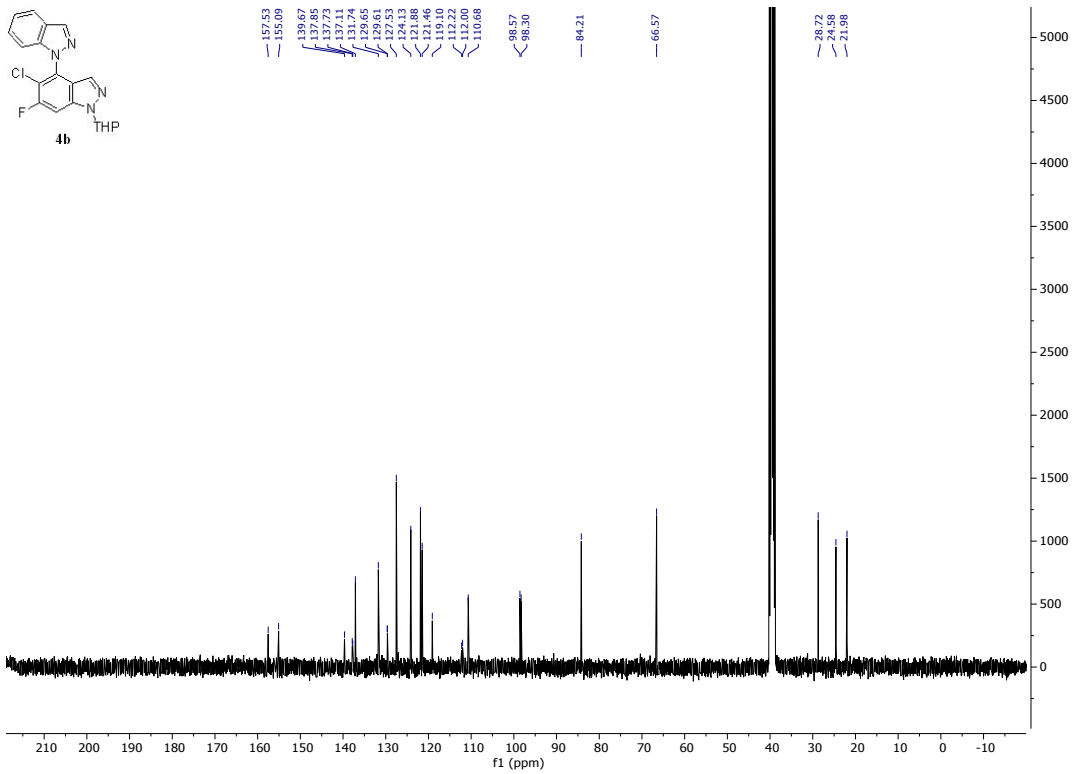
4a NOE (^1H 400 MHz, DMF- d_7)



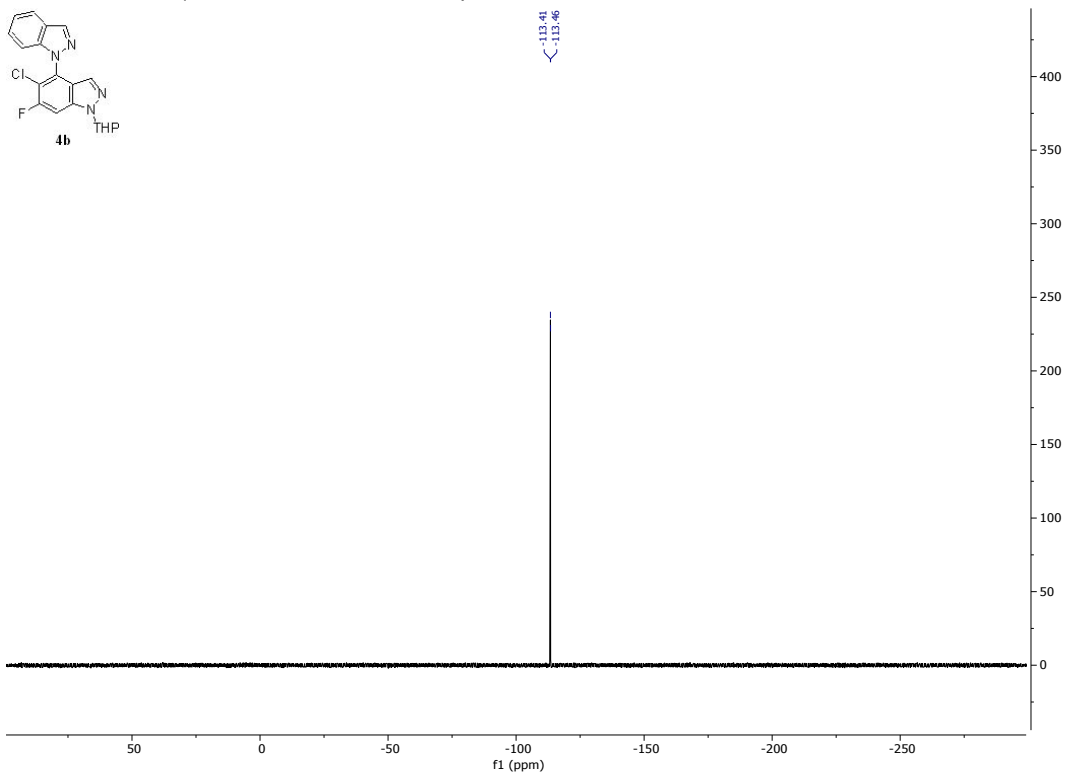
4b ^1H NMR (400 MHz, DMSO- d_6)



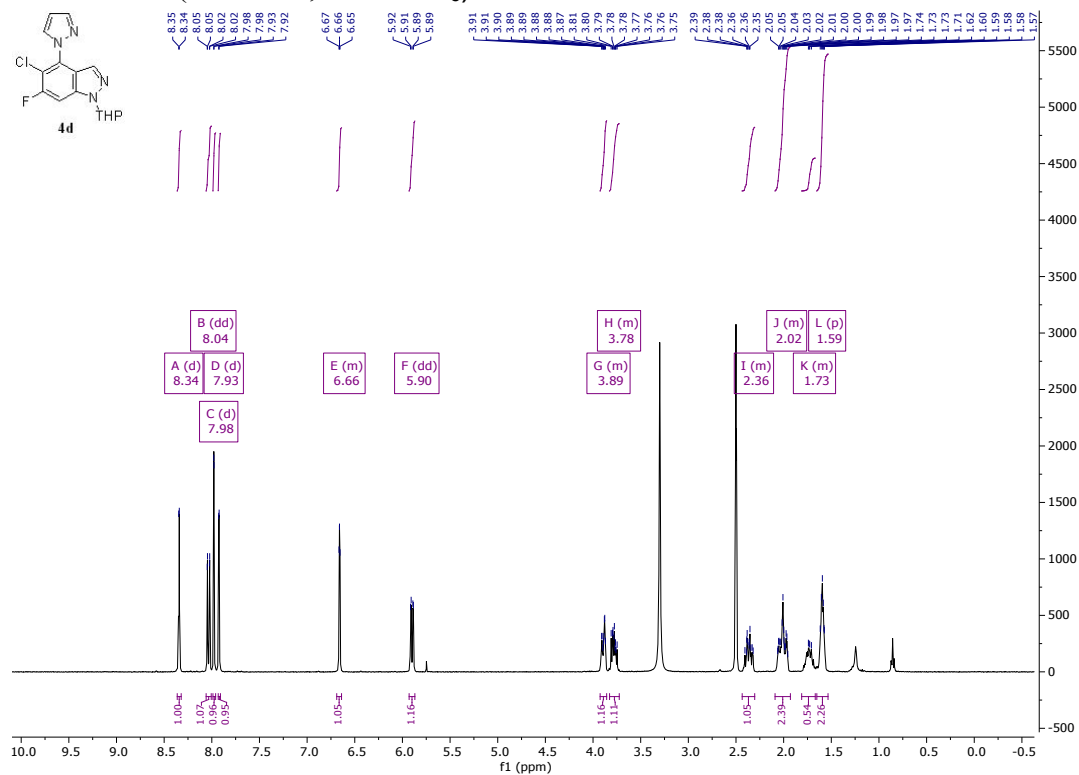
4b ¹³C NMR (101 MHz, DMSO-*d*₆)



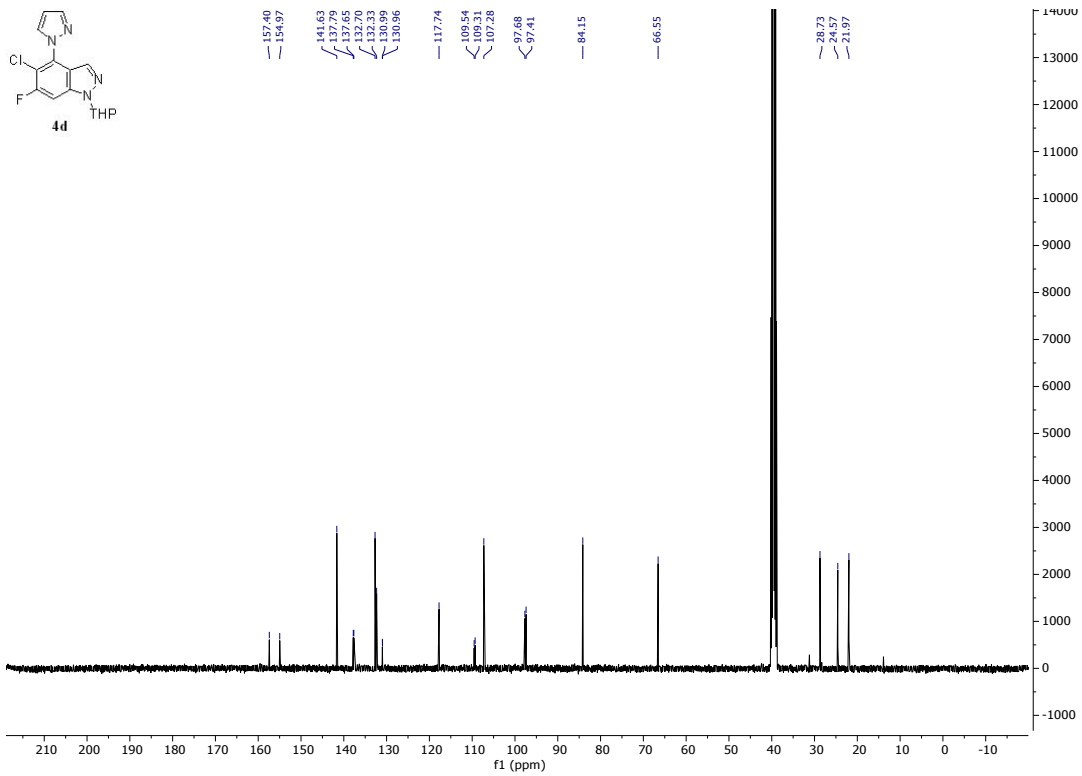
4b ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)



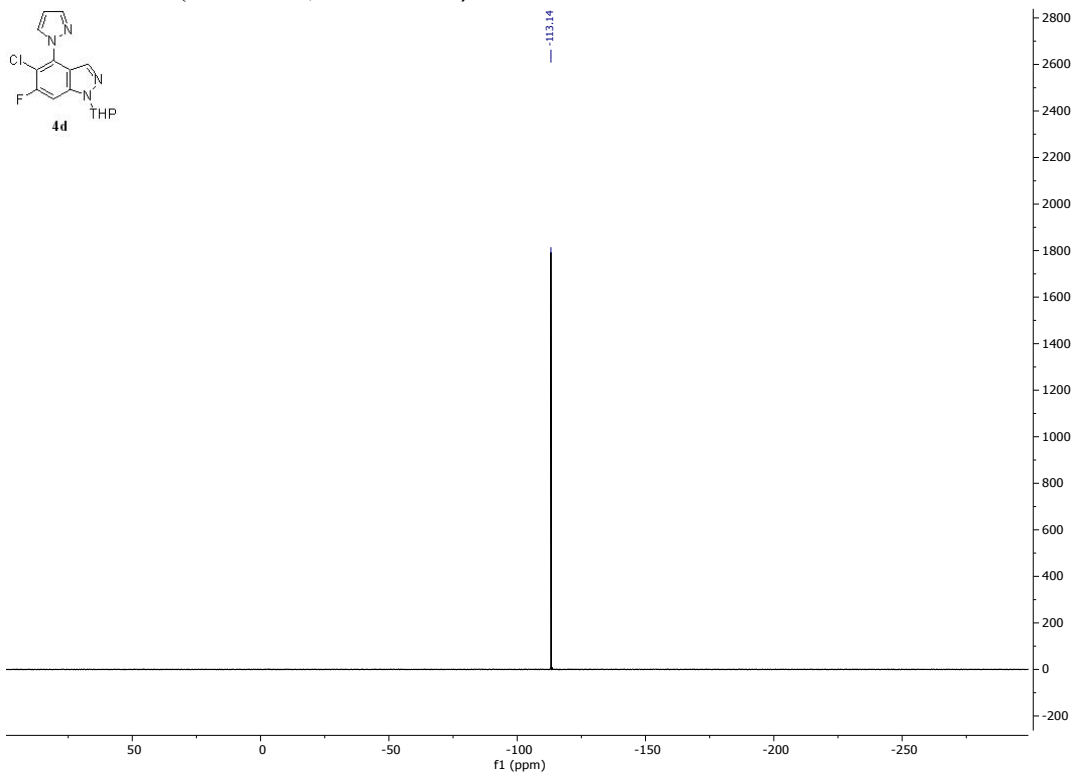
4d ¹H NMR (400 MHz, DMSO-*d*₆)



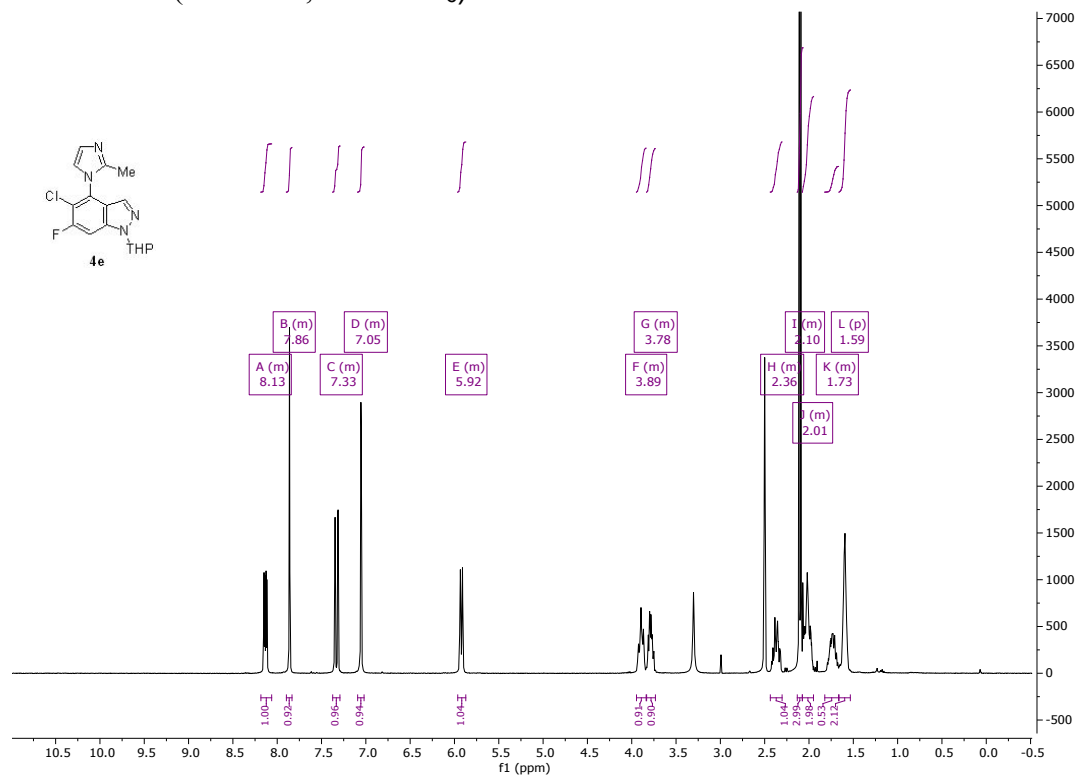
4d ¹³C NMR (101 MHz, DMSO-*d*₆)



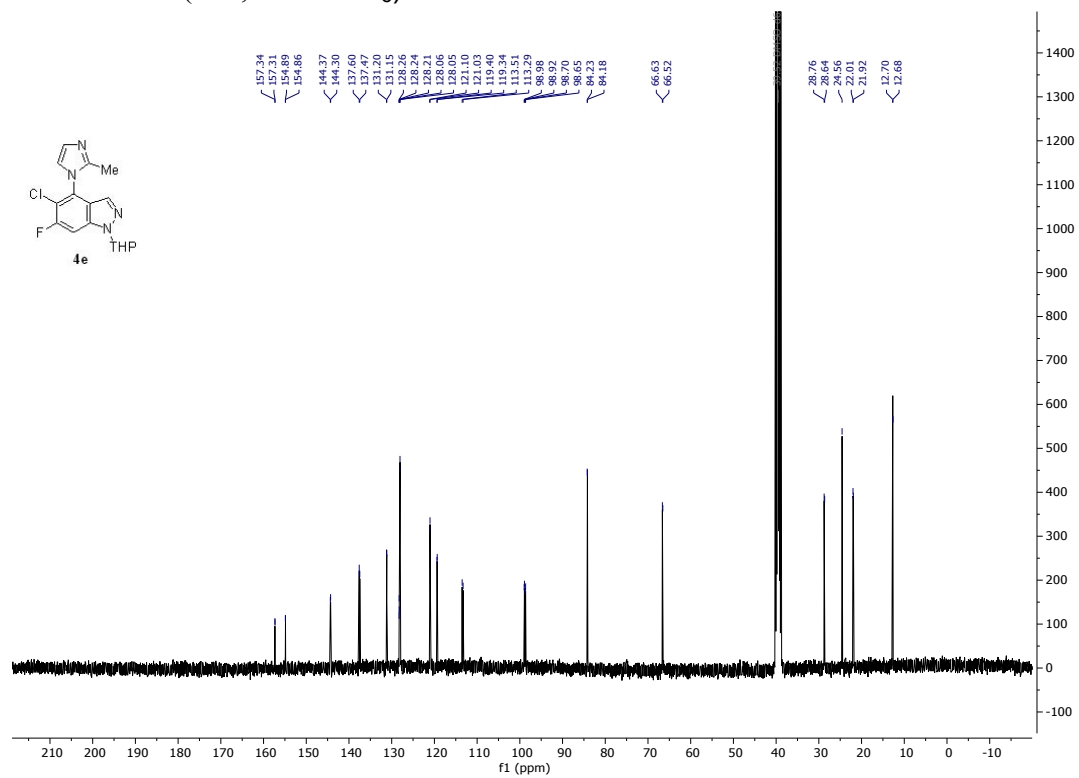
4d ¹⁹F NMR (376 MHz, DMSO-*d*₆)



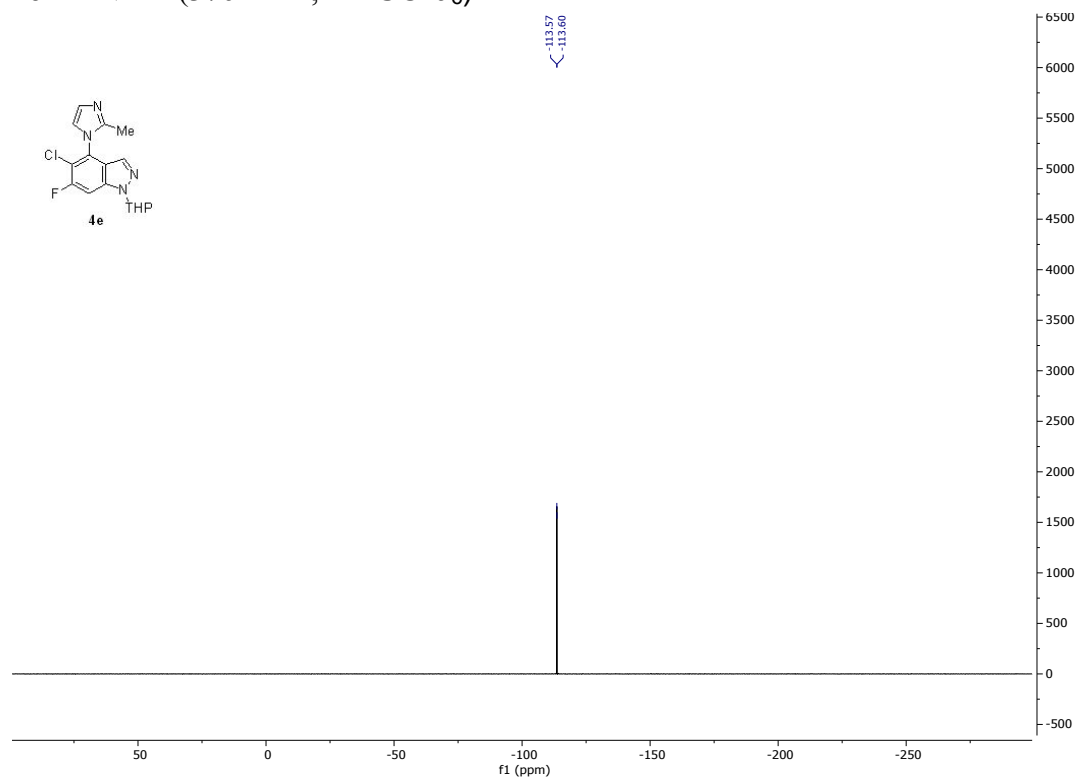
4e ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



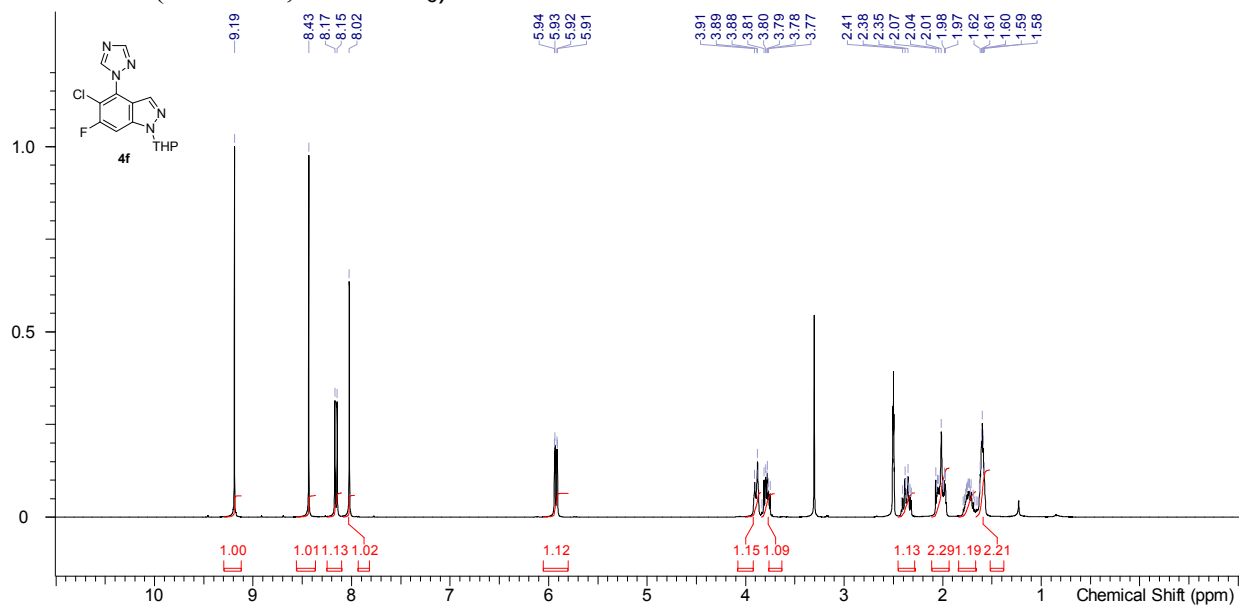
4e ^{13}C NMR (101, $\text{DMSO}-d_6$)



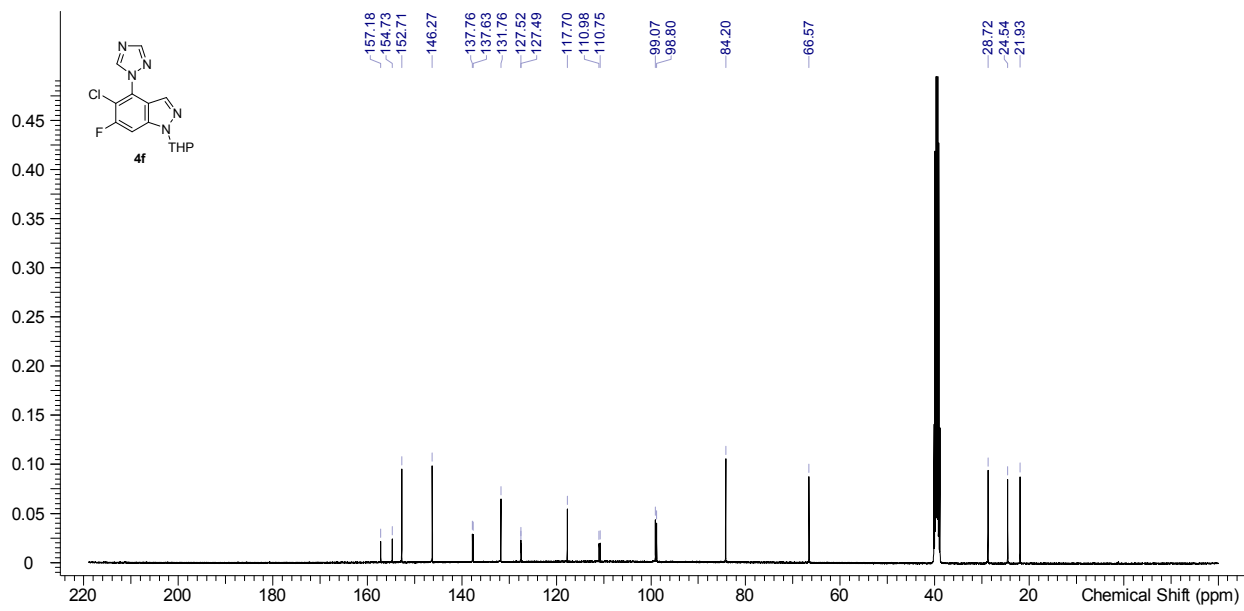
4e ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)



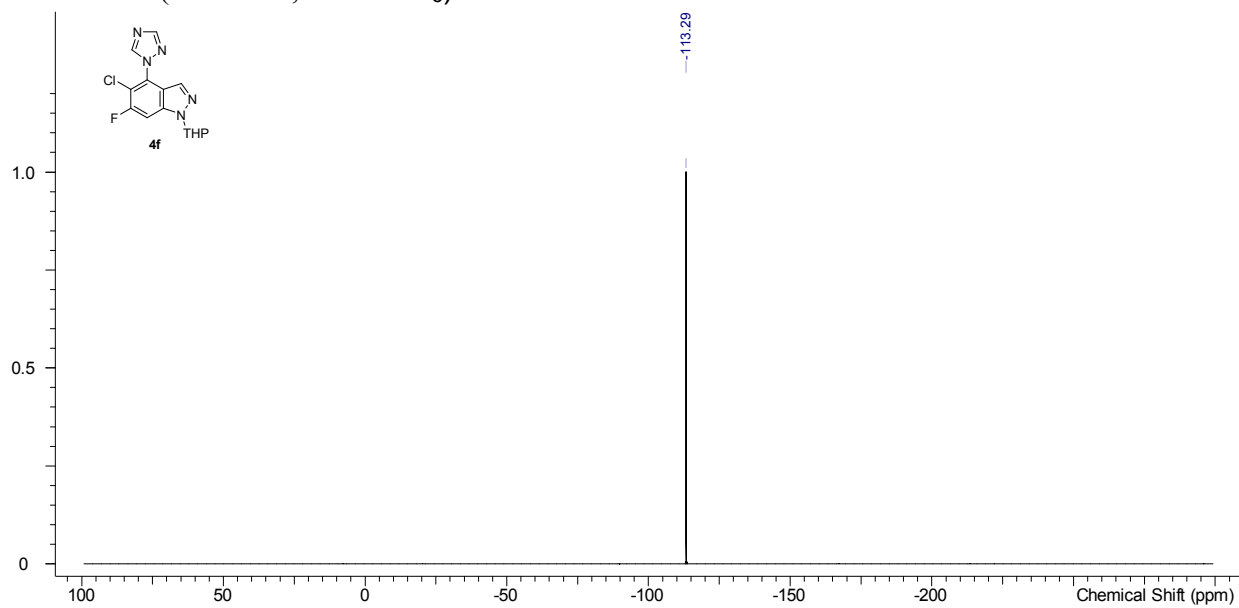
4f ^1H NMR (400 MHz, $\text{DMSO-}d_6$)



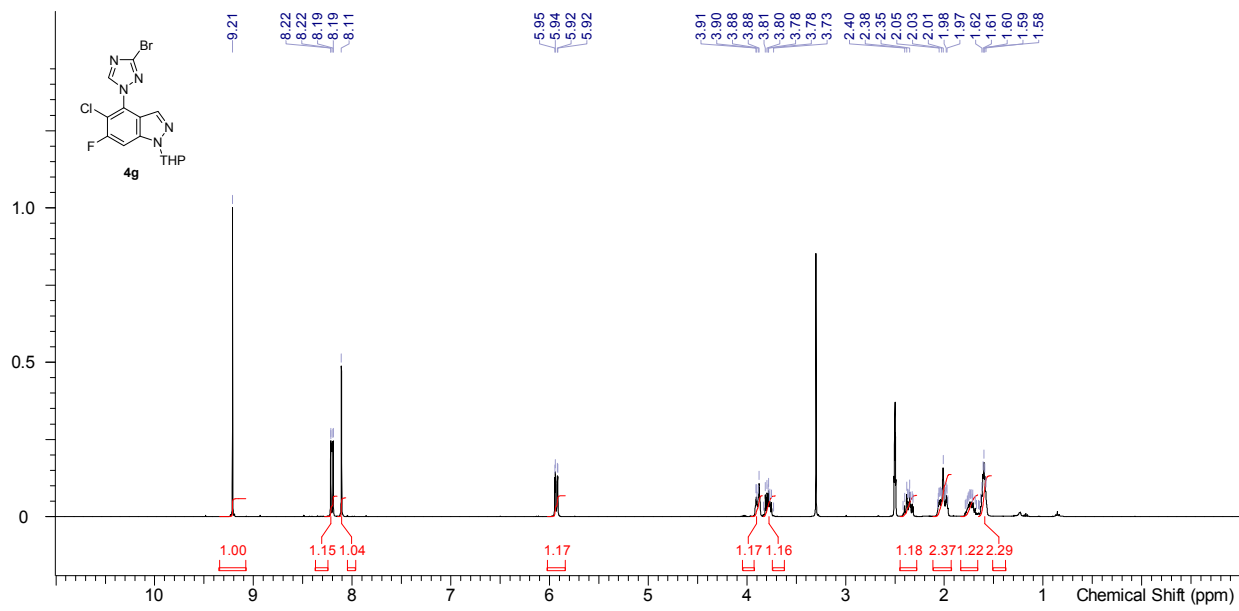
4f ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$)



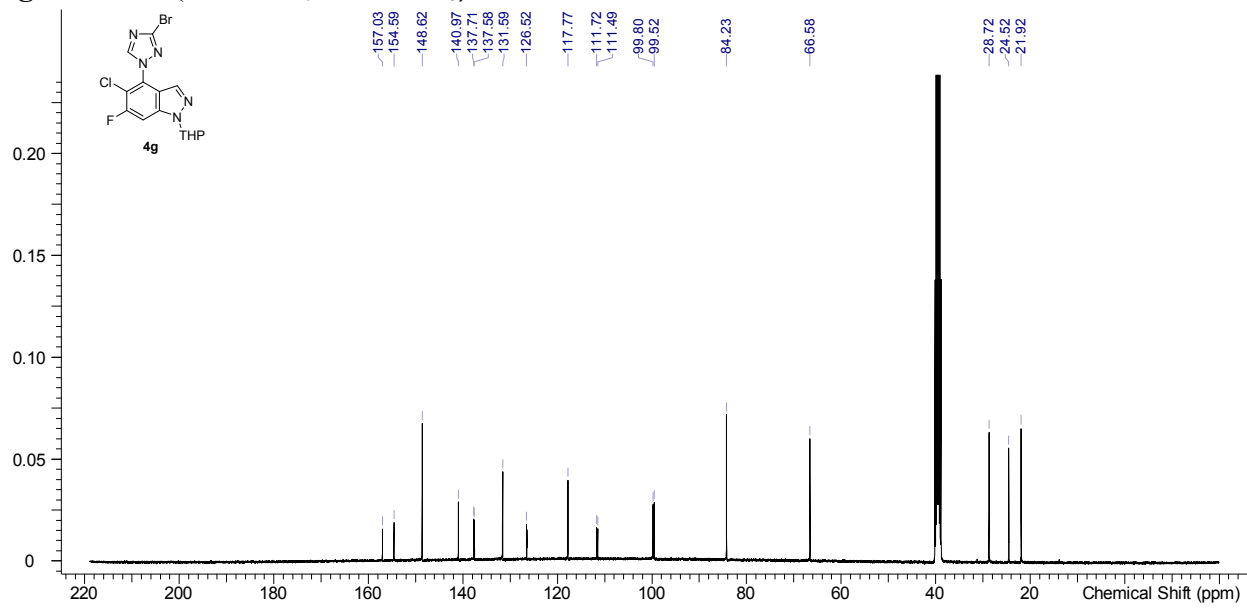
4f ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$)



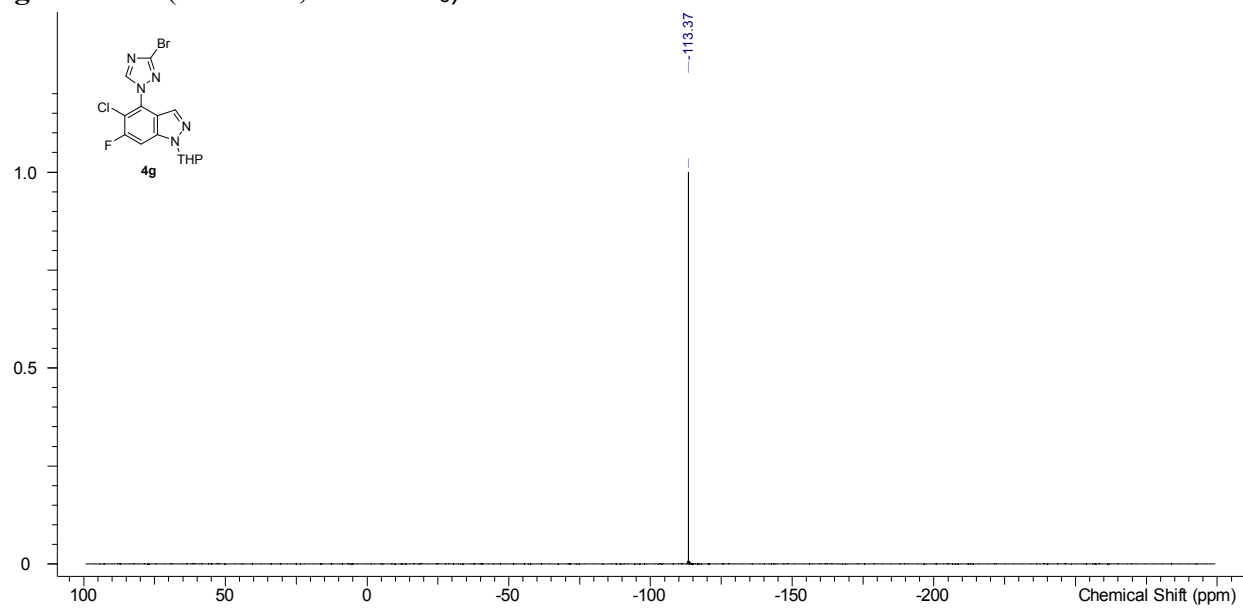
4g ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



4g ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)

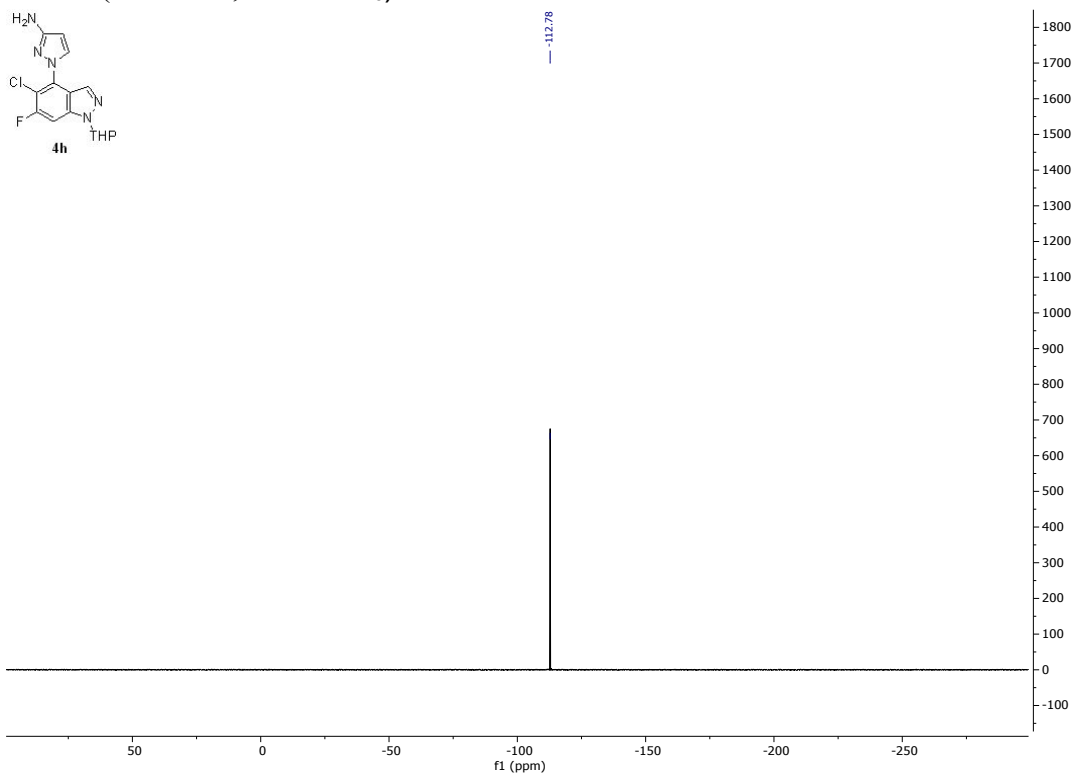


4g ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)

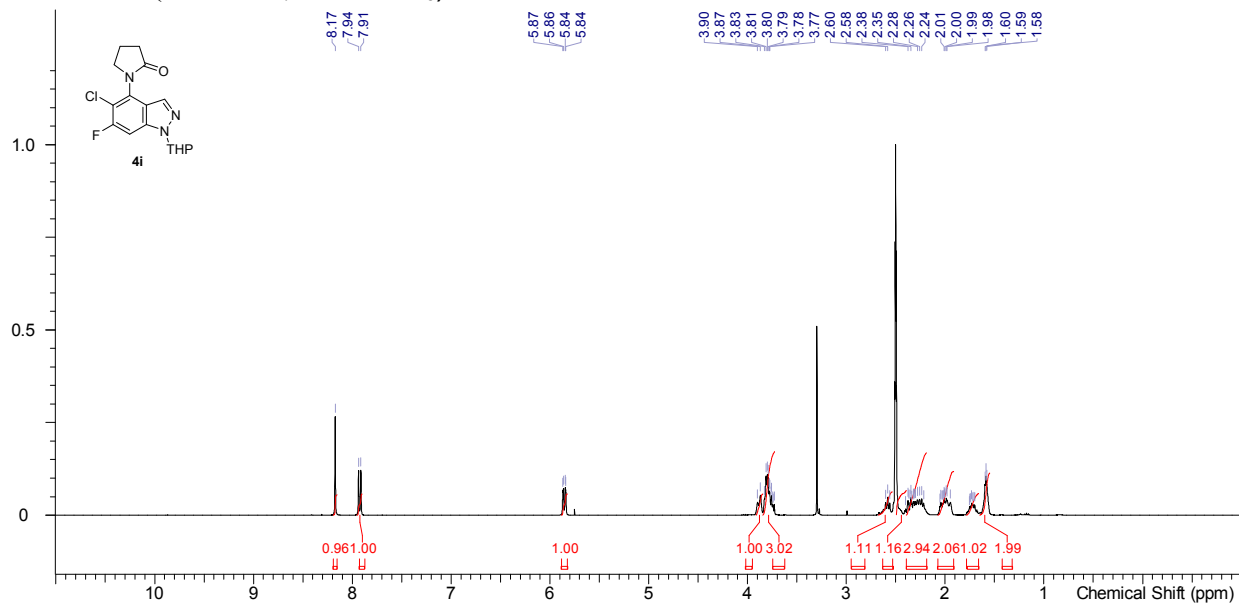


4h ^1H NMR (400 MHz, $\text{DMSO-}d_6$)

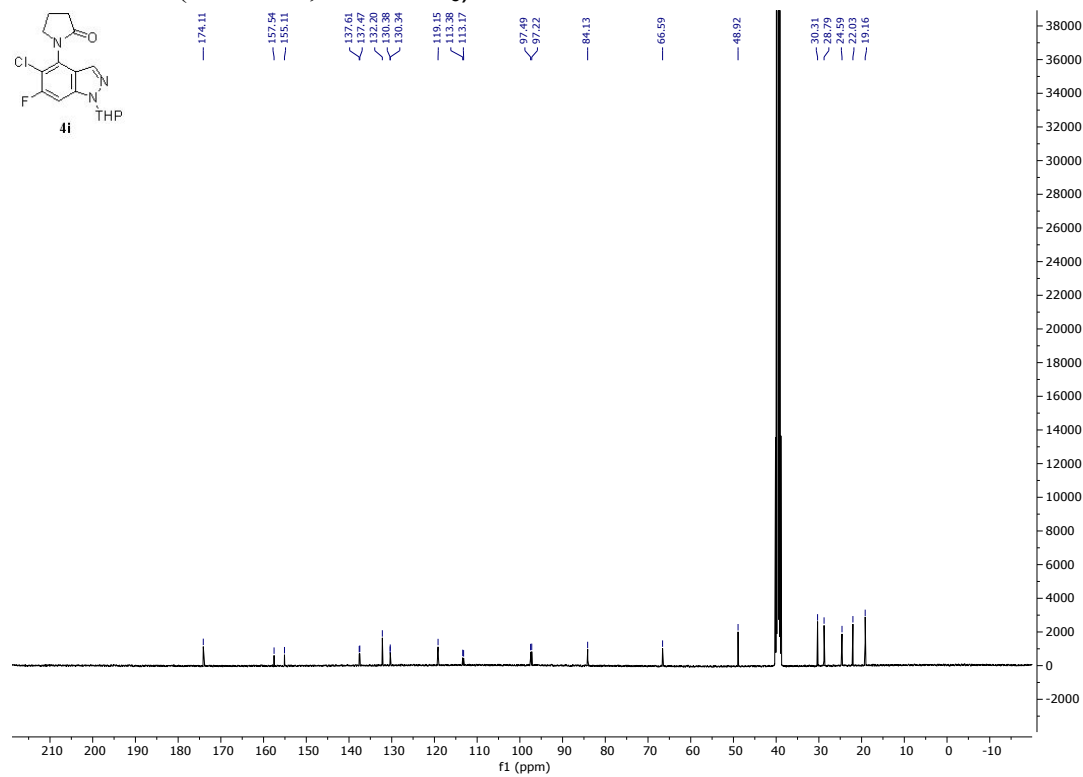
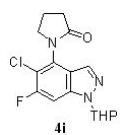
4h ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$)



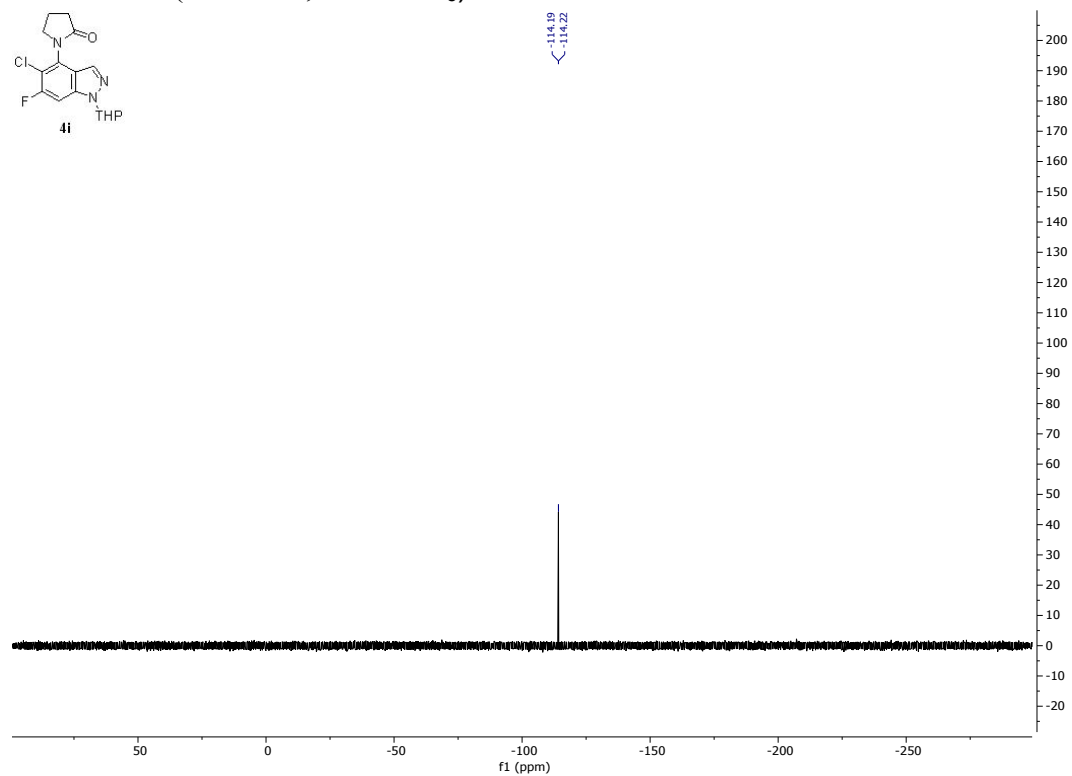
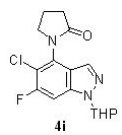
4i ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



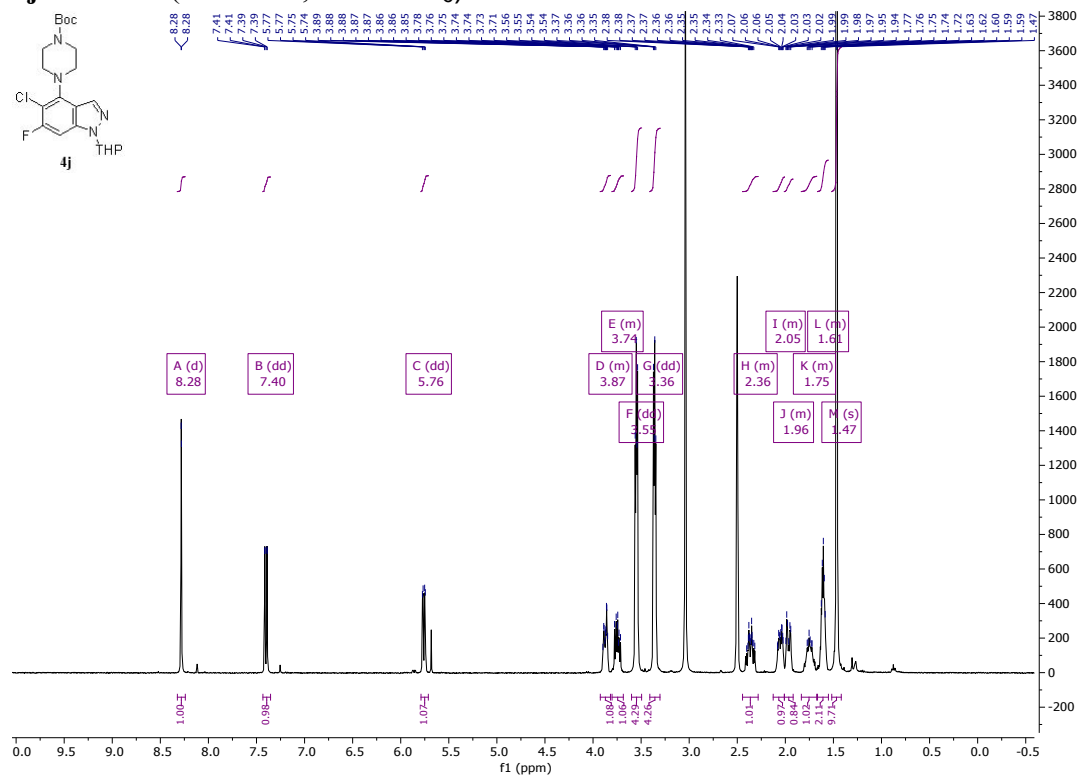
4i ¹³C NMR (101 MHz, DMSO-*d*₆)



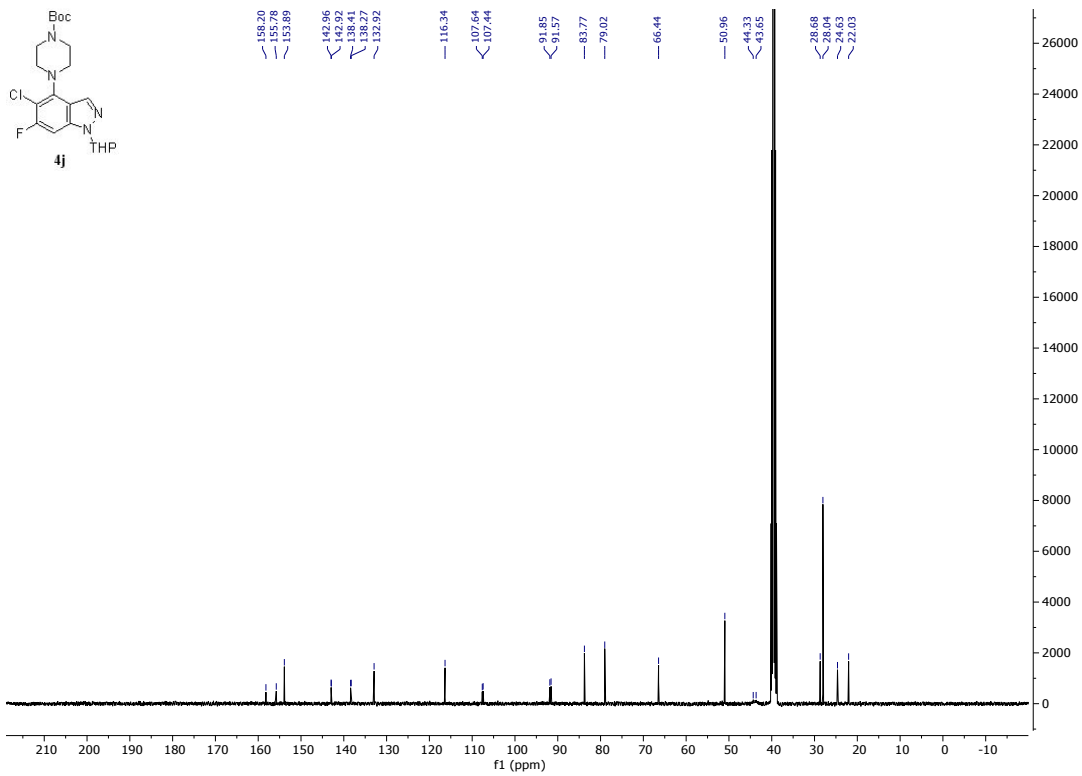
4i ¹⁹F NMR (376 MHz, DMSO-*d*₆)



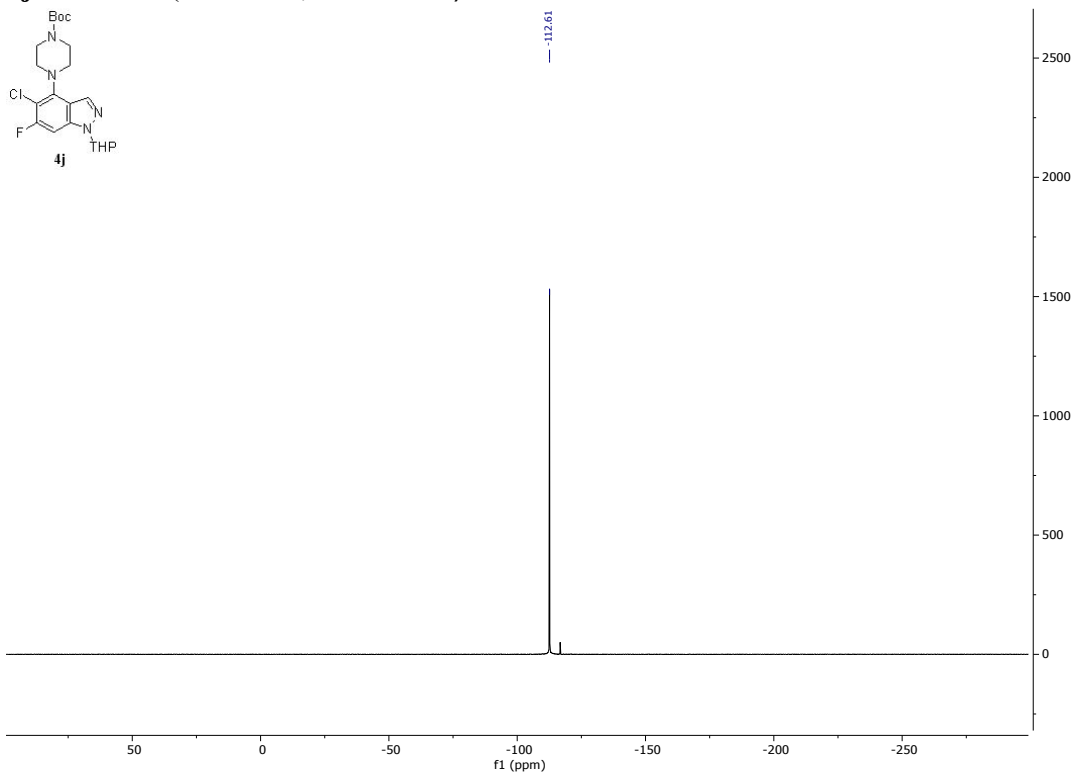
4j ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



4j ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)

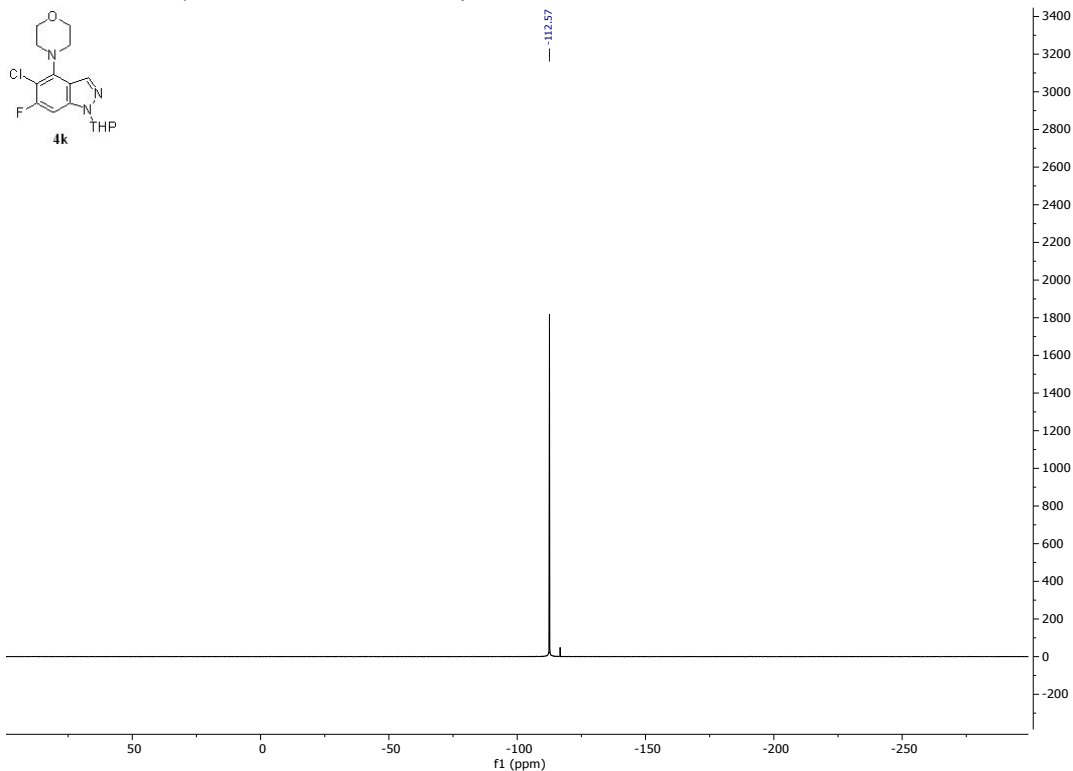


4j ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$)

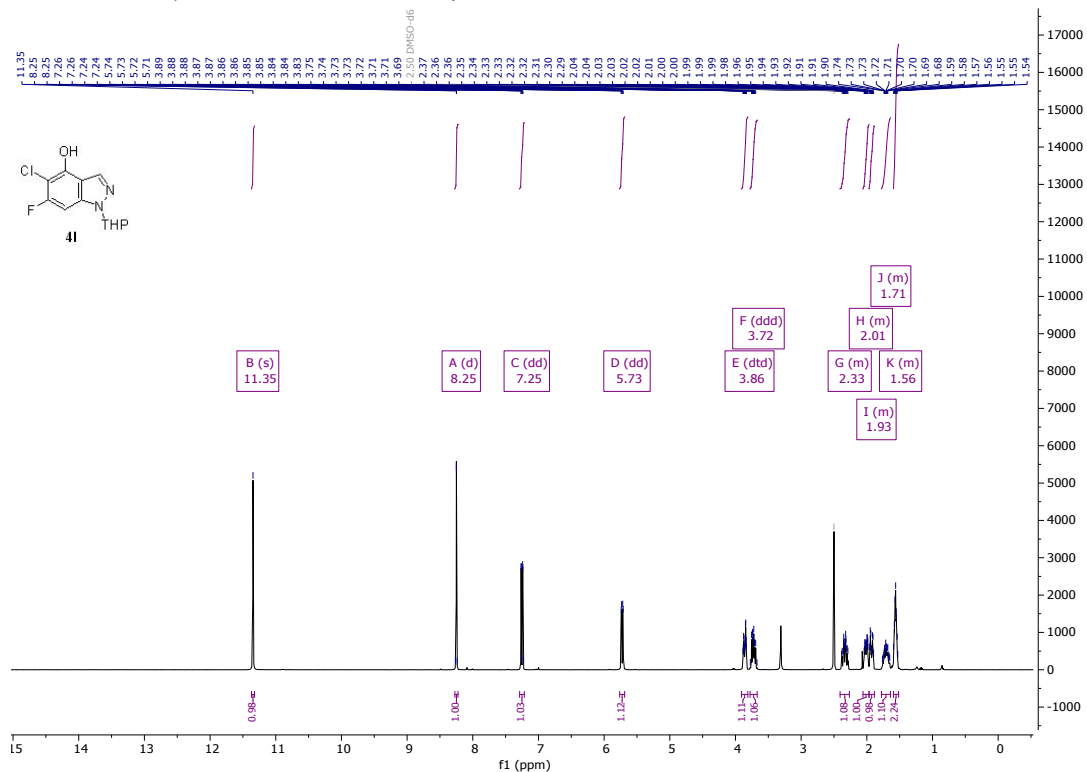


4k ^1H NMR (400 MHz, $\text{DMSO}-d_6$)

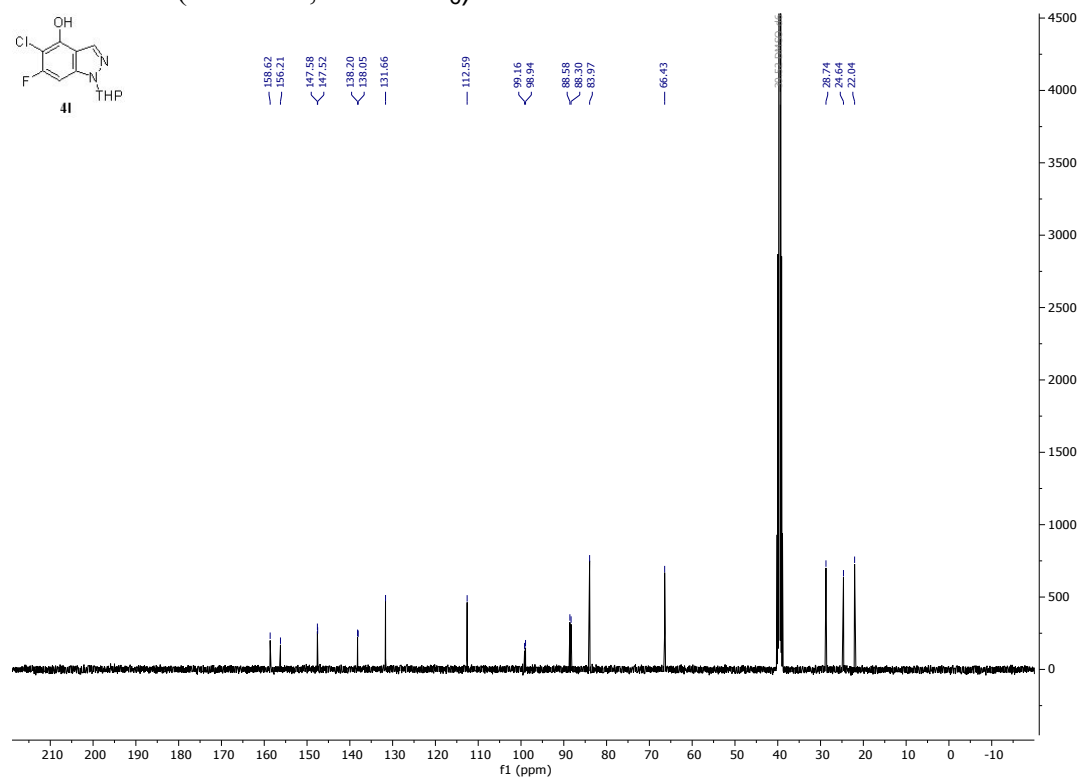
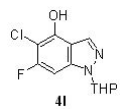
4k ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)



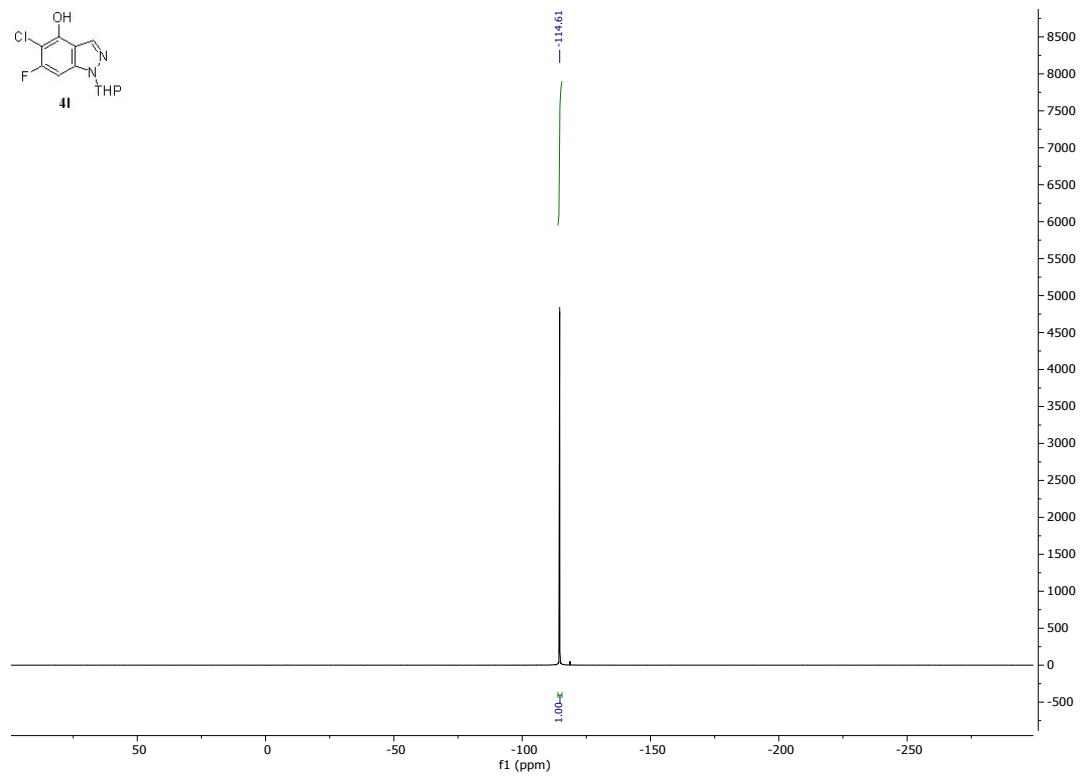
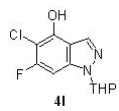
4l ^1H NMR (400 MHz, $\text{DMSO-}d_6$)



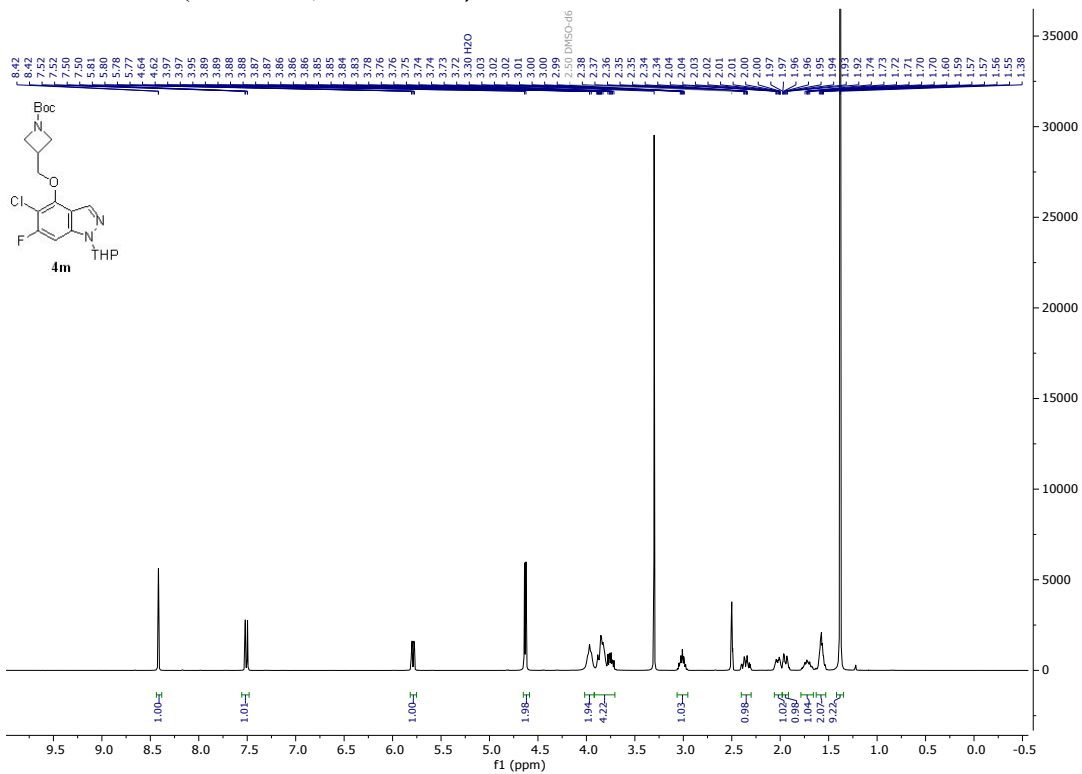
41 ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$)



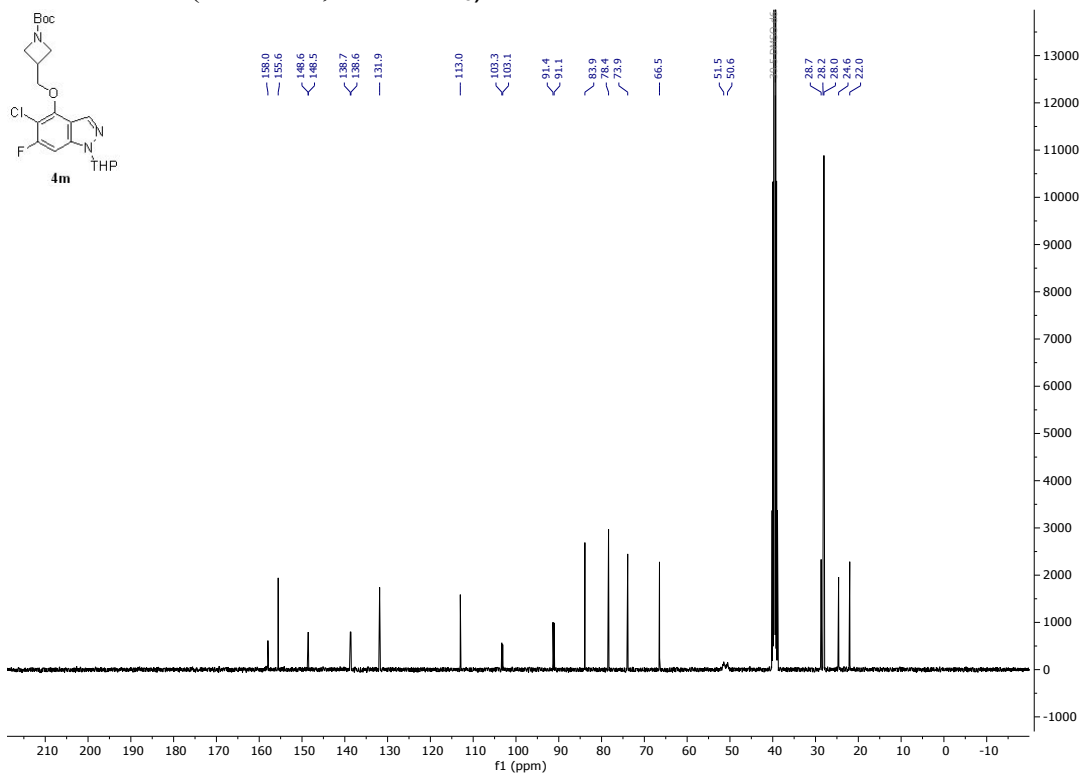
41 ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)



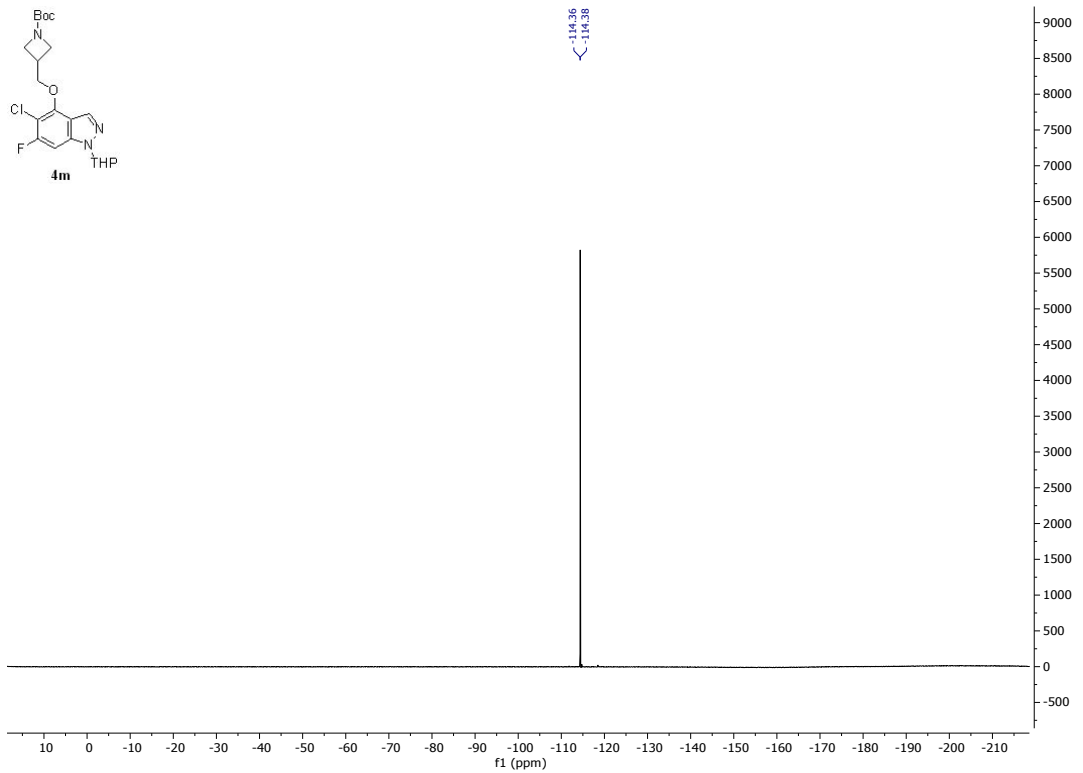
4m ¹H NMR (400 MHz, DMSO-*d*₆)



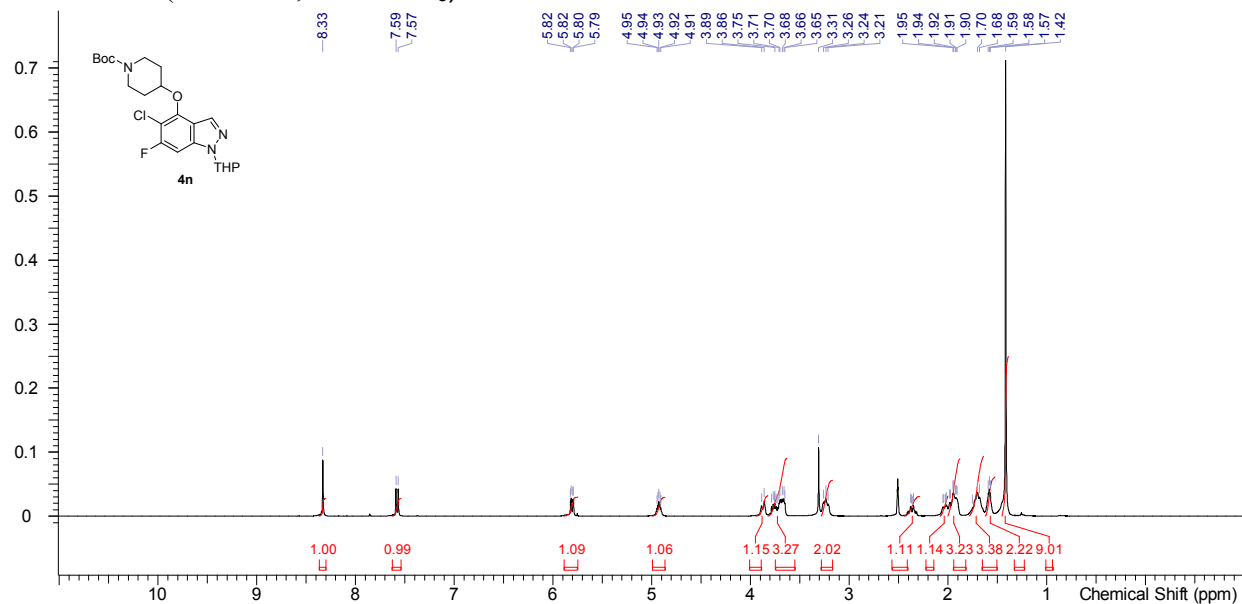
4m ¹³C NMR (101 MHz, DMSO-*d*₆)



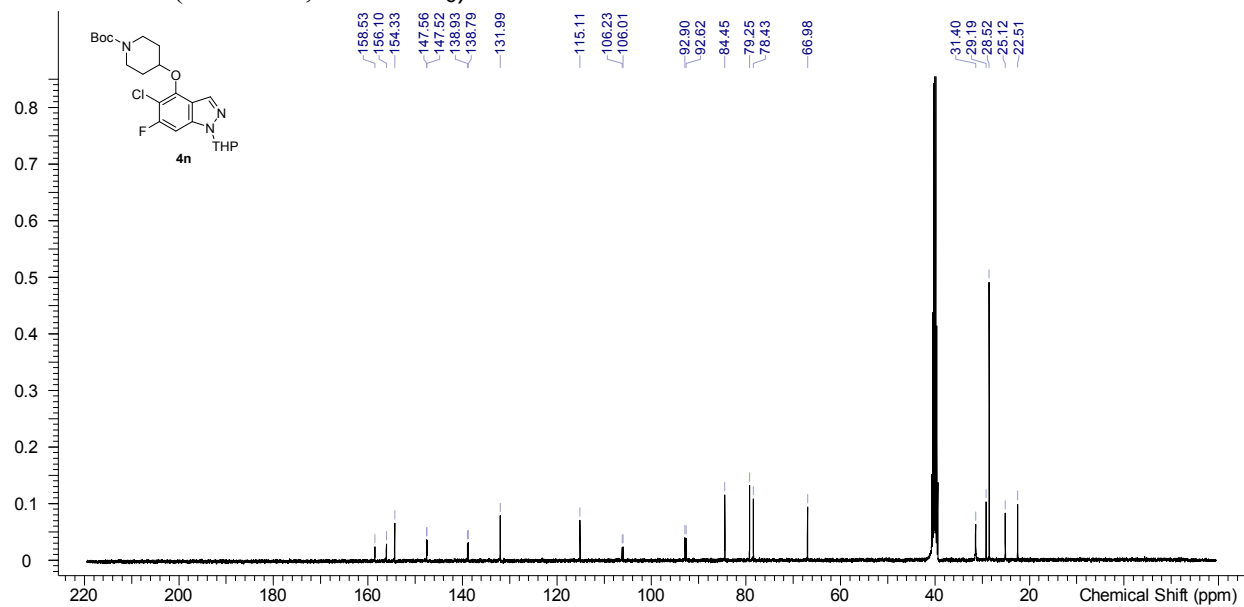
4m ¹⁹F NMR (376 MHz, DMSO-*d*₆)



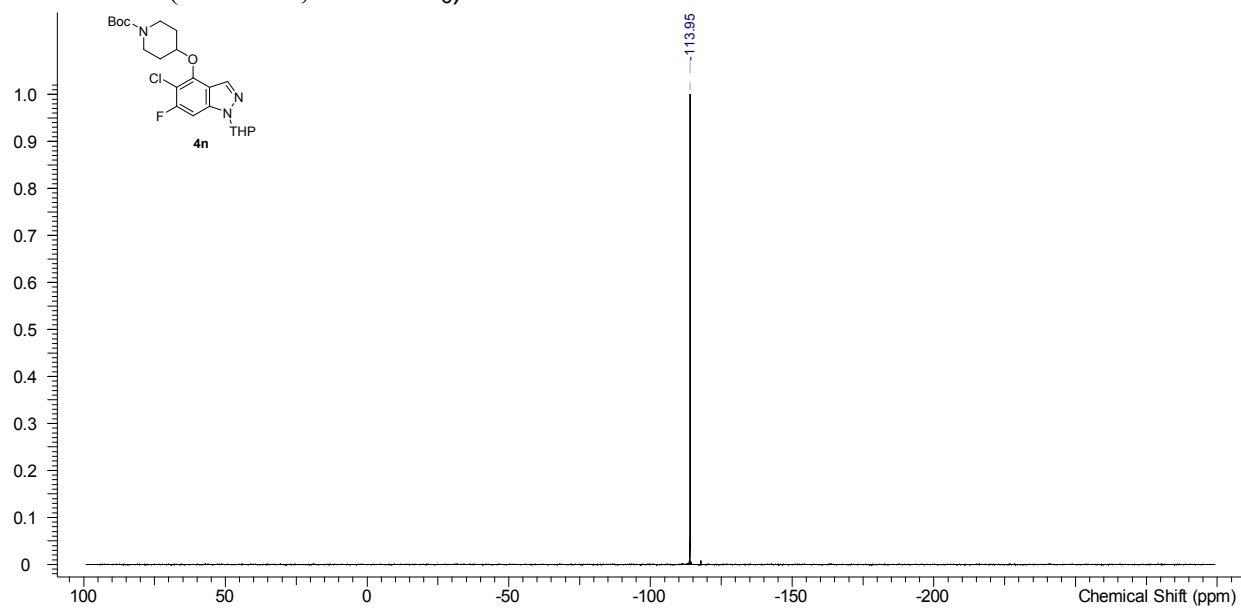
4n ¹H NMR (400 MHz, DMSO-*d*₆)



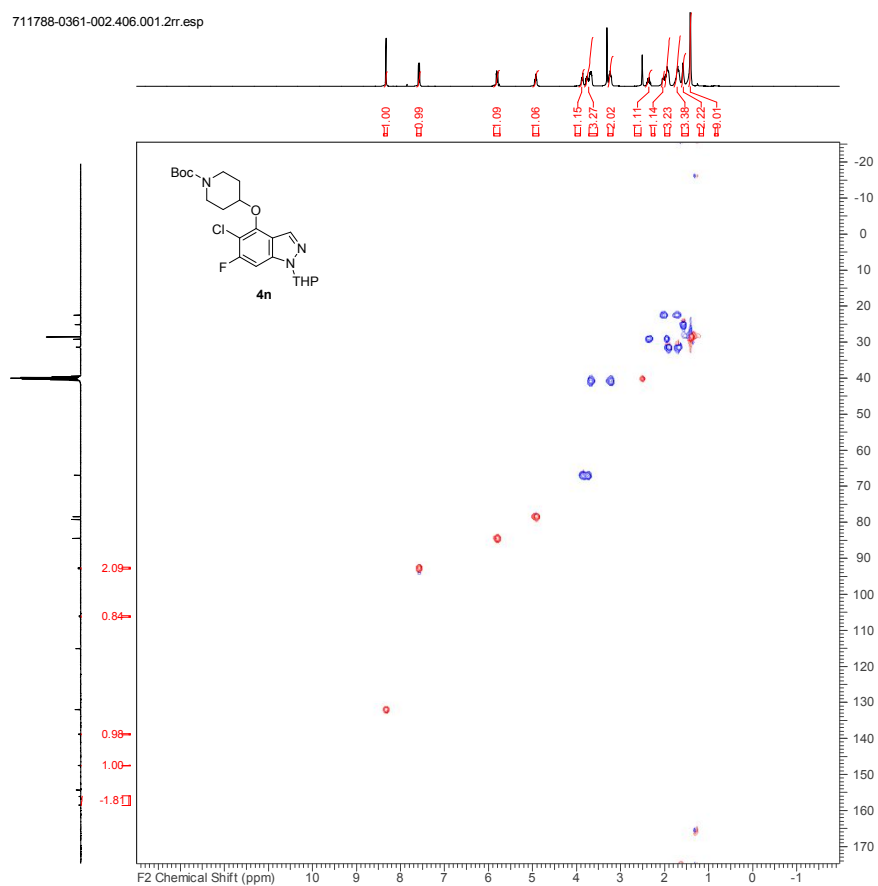
4n ¹³C NMR (101 MHz, DMSO-*d*₆)



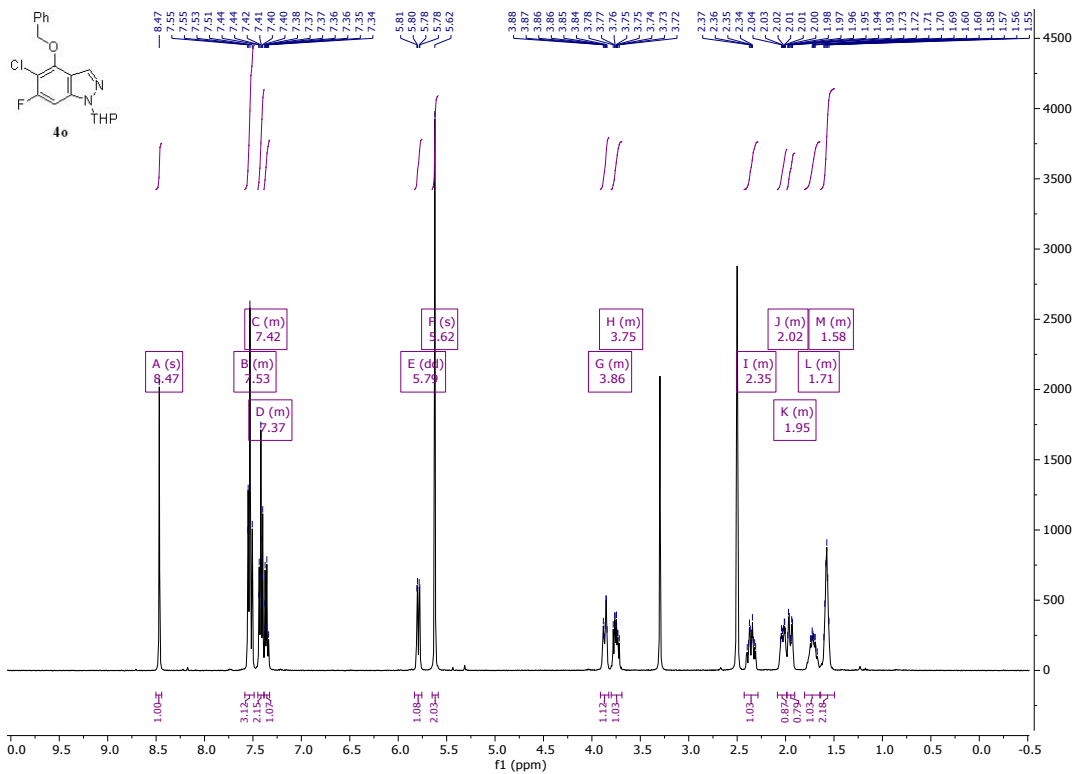
4n ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$)



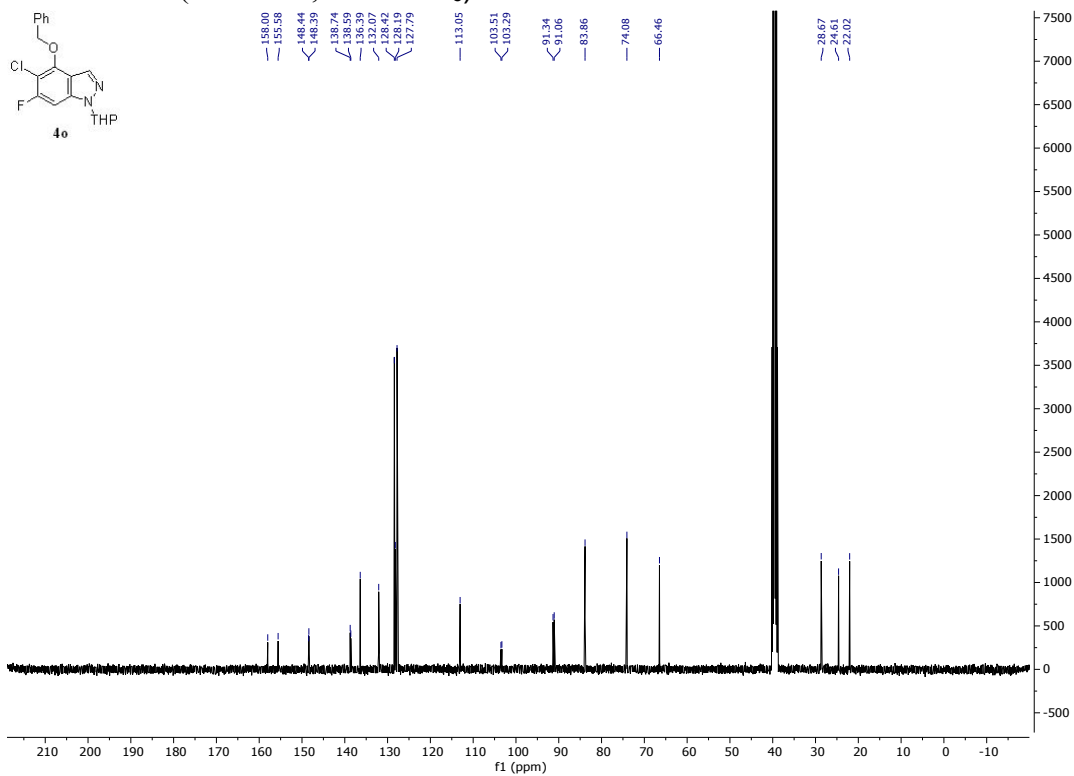
4n HSQC (^1H 400 MHz, $\text{DMSO-}d_6$)



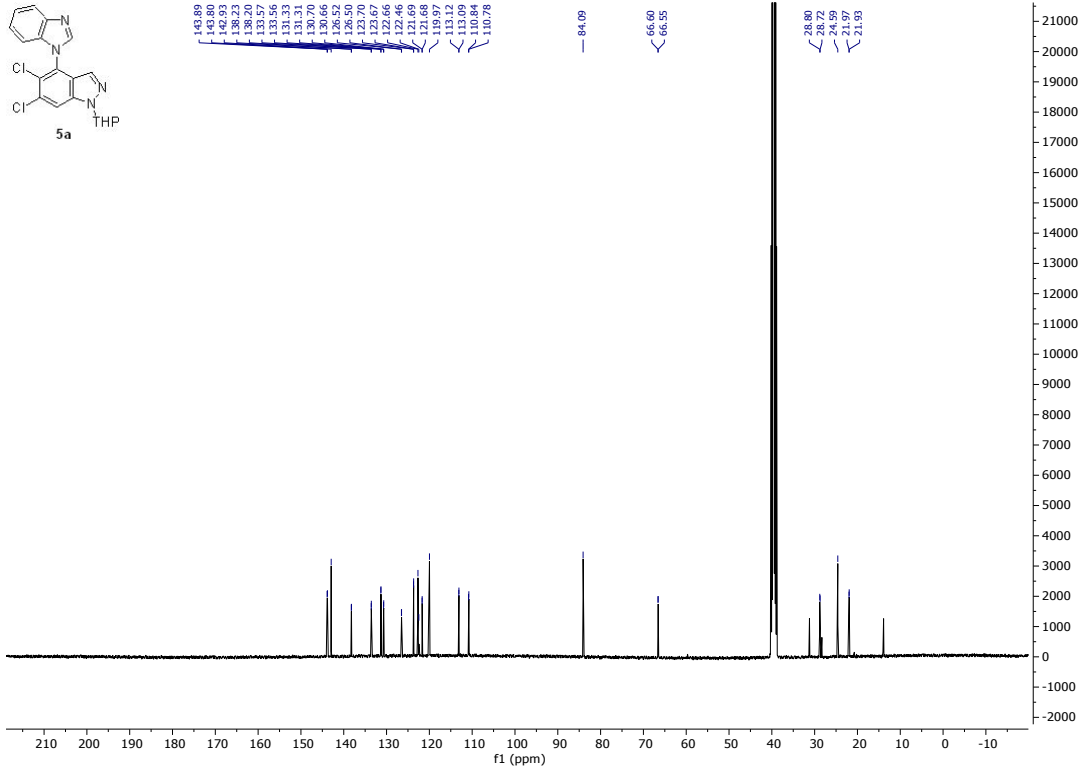
4n ¹H NMR (400 MHz, DMSO-*d*₆)



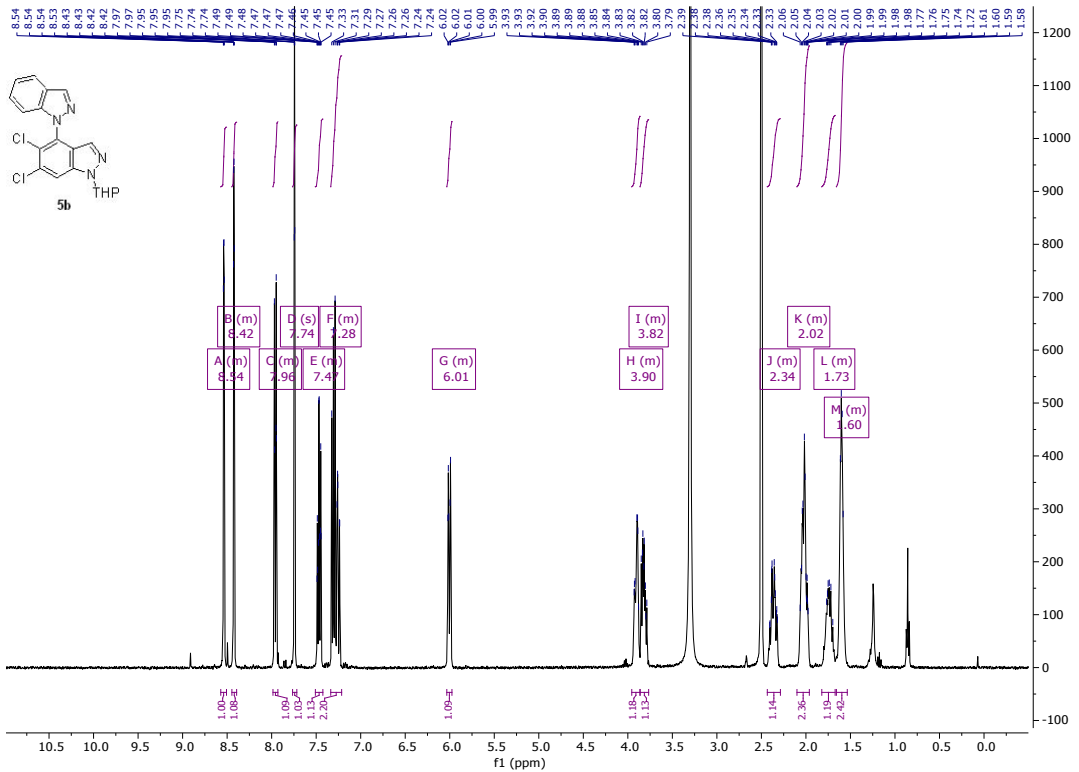
4o ¹³C NMR (101 MHz, DMSO-*d*₆)



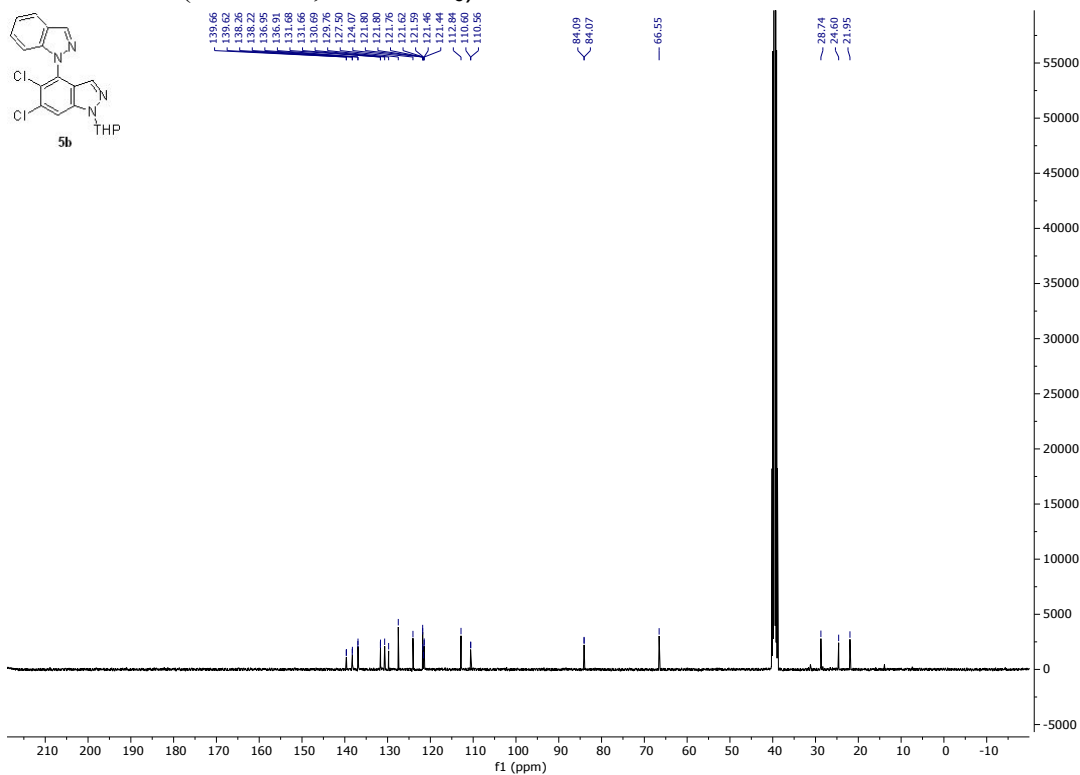
5a ¹³C NMR (101 MHz, DMSO-*d*₆)



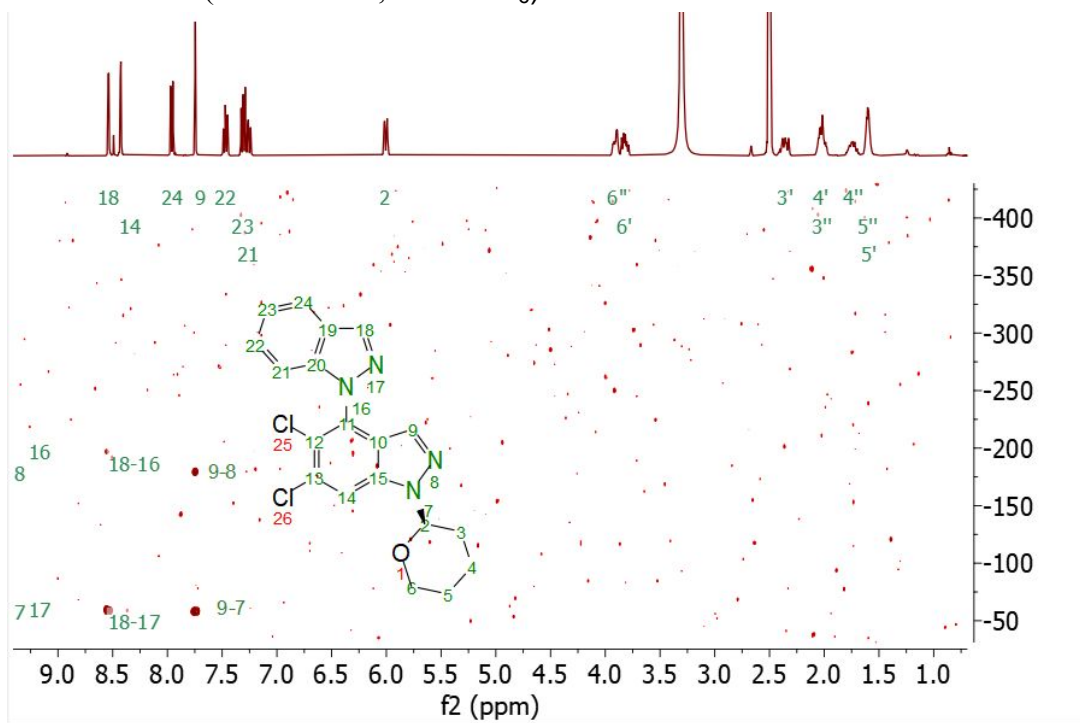
5b ¹H NMR (400 MHz, DMSO-*d*₆)



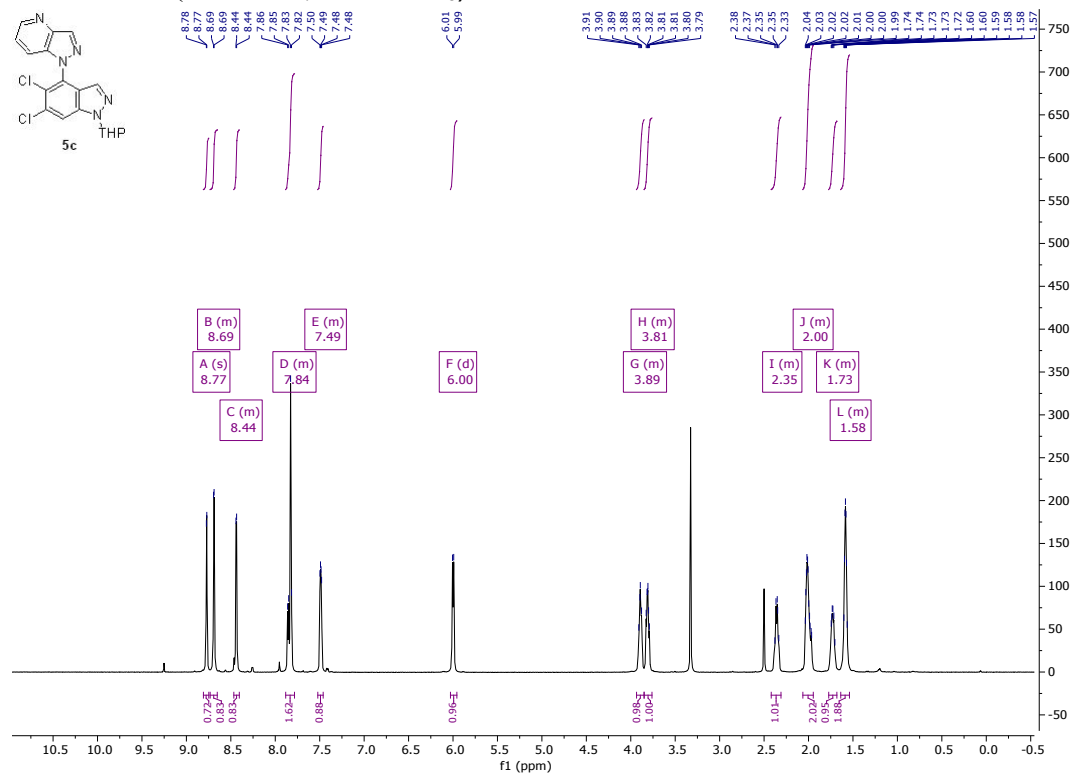
5b ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)



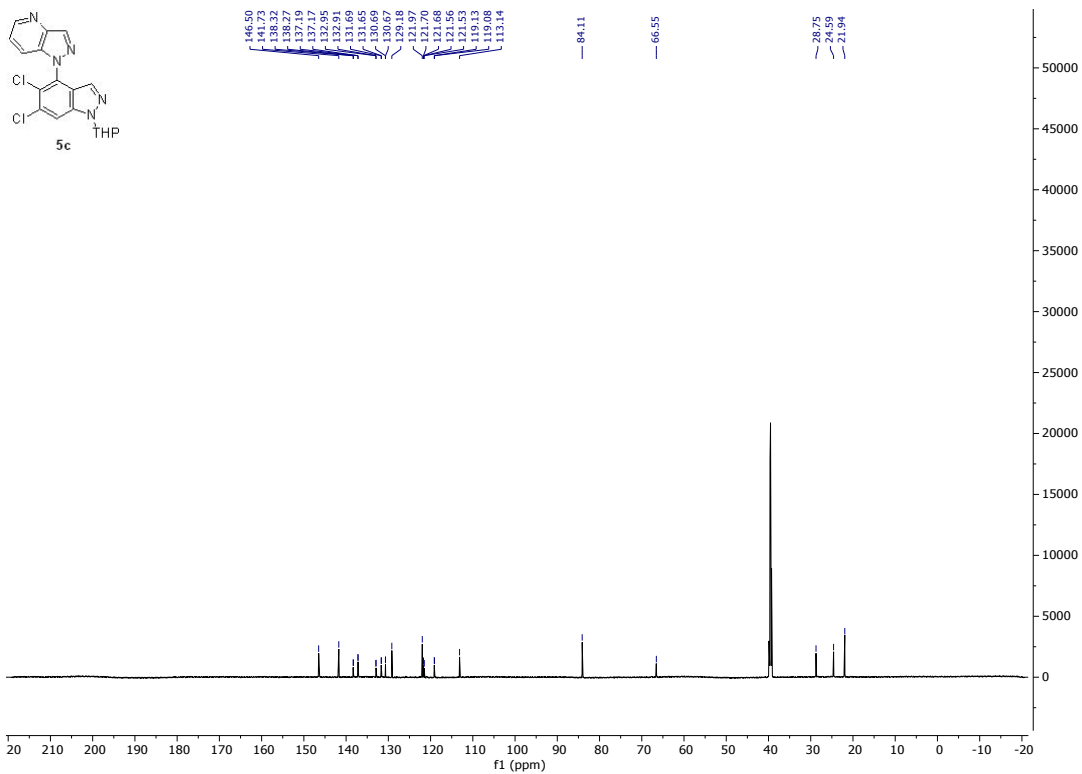
5b ^{15}N HMBC (^1H 400 MHz, $\text{DMSO}-d_6$)



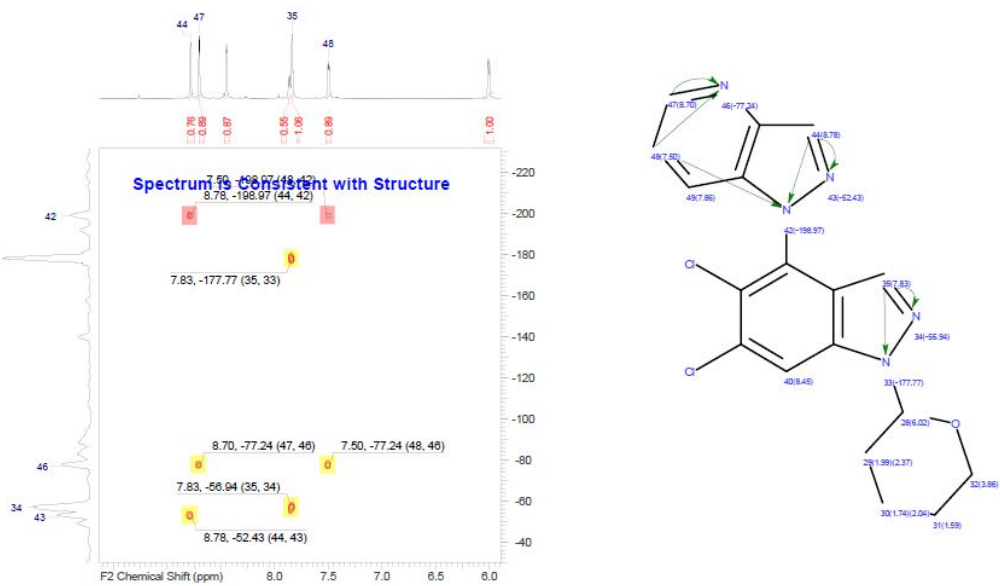
5c ¹H NMR (400 MHz, DMSO-*d*₆)



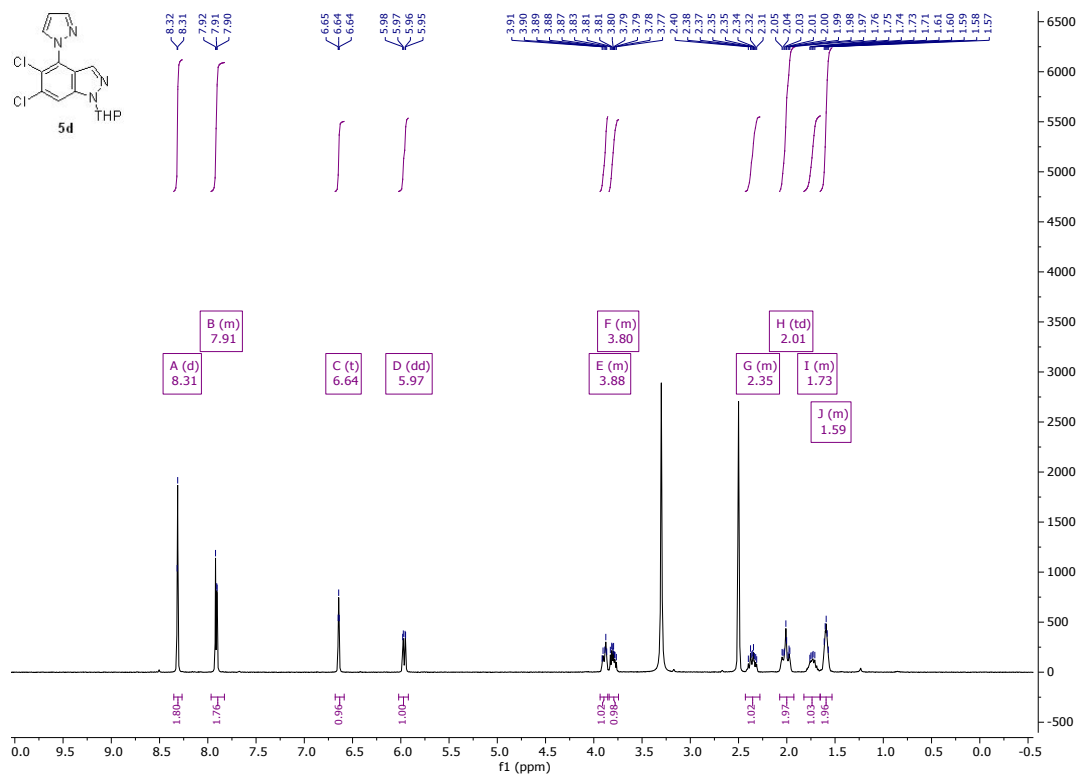
5c ¹³C NMR (176 MHz, DMSO-*d*₆)



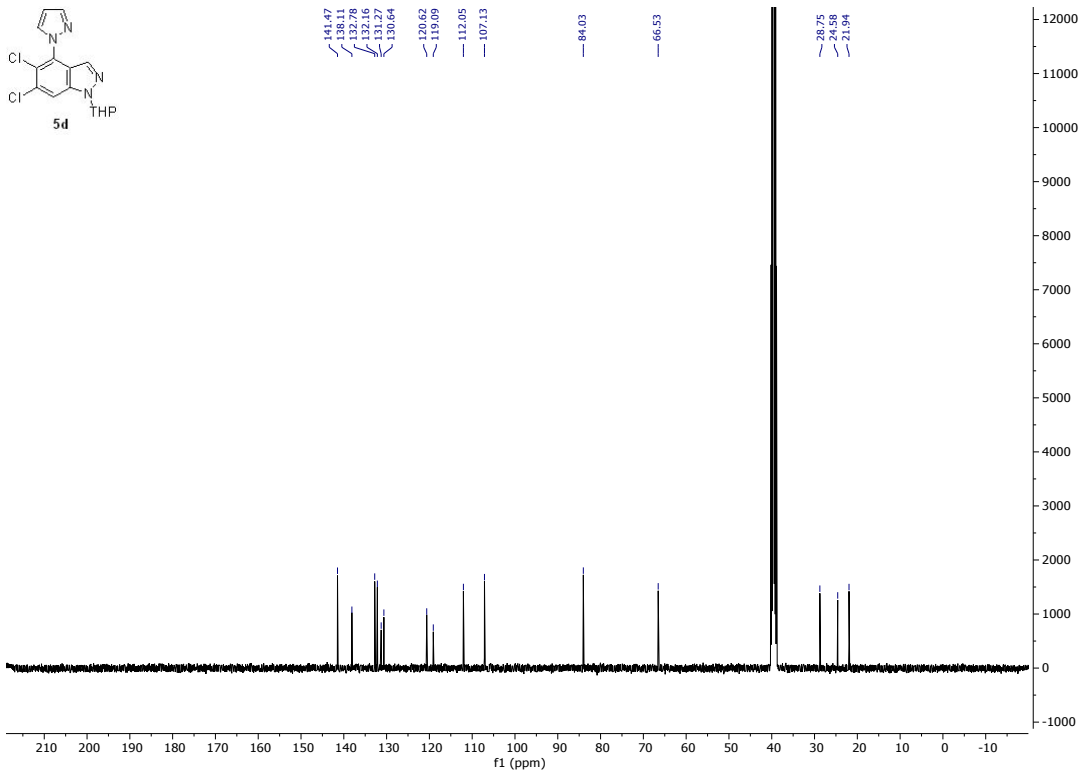
5c ^{15}N HMBC (^1H 700 MHz, $\text{DMSO-}d_6$)



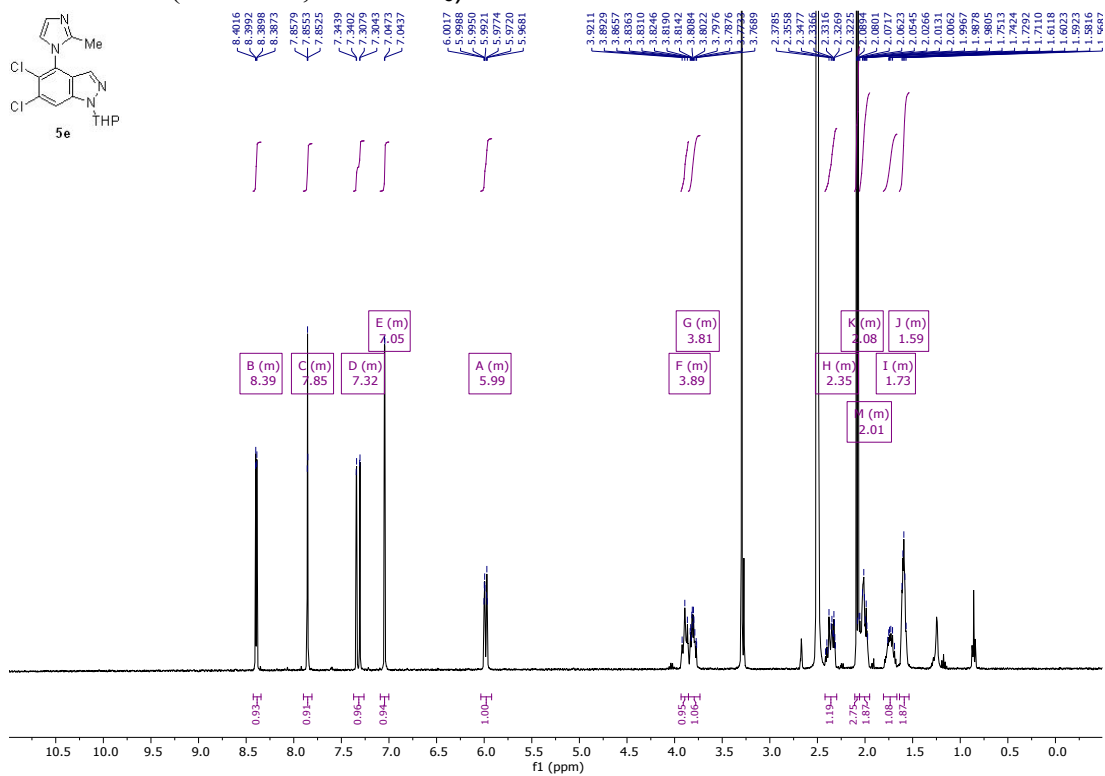
5d ^1H NMR (400 MHz, $\text{DMSO-}d_6$)



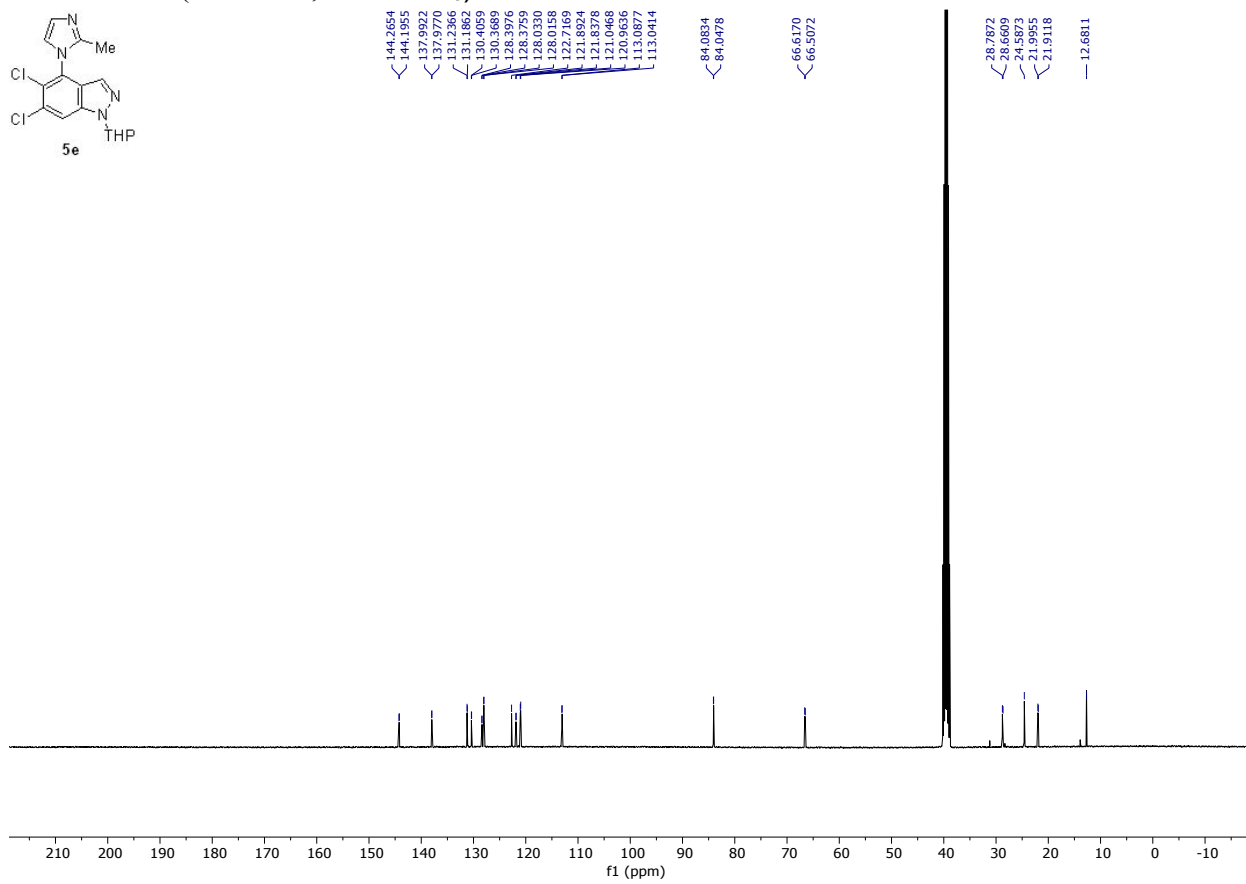
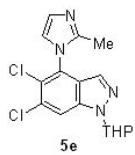
5d ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)



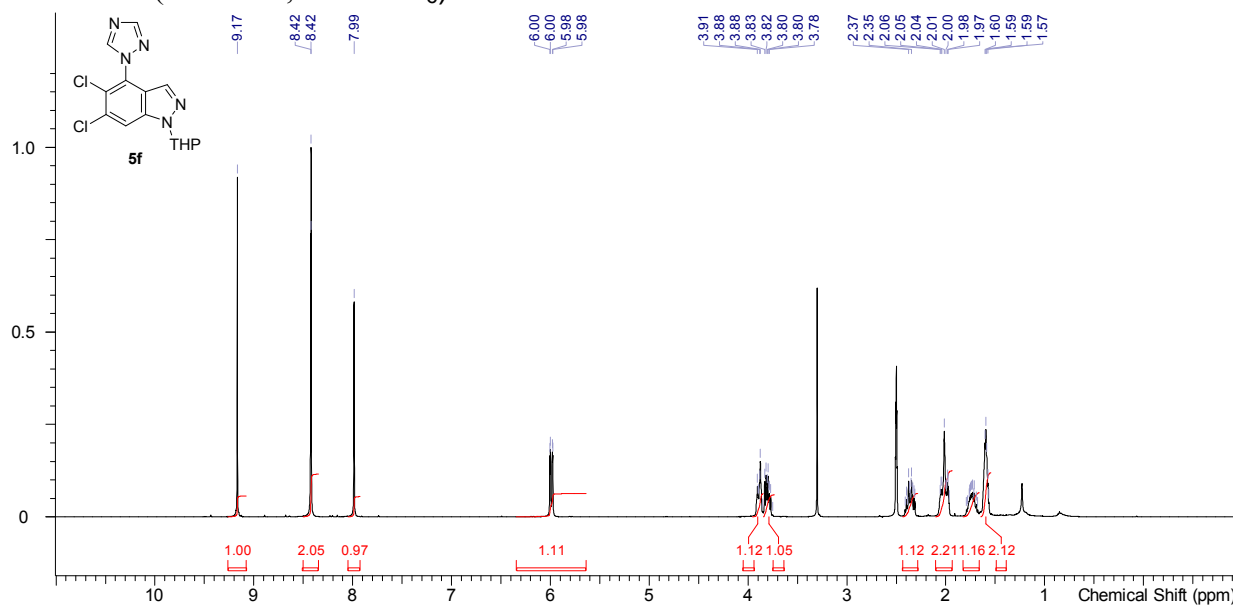
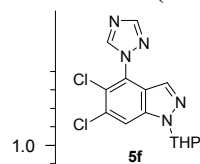
5e ¹H NMR (400 MHz, DMSO-*d*₆)



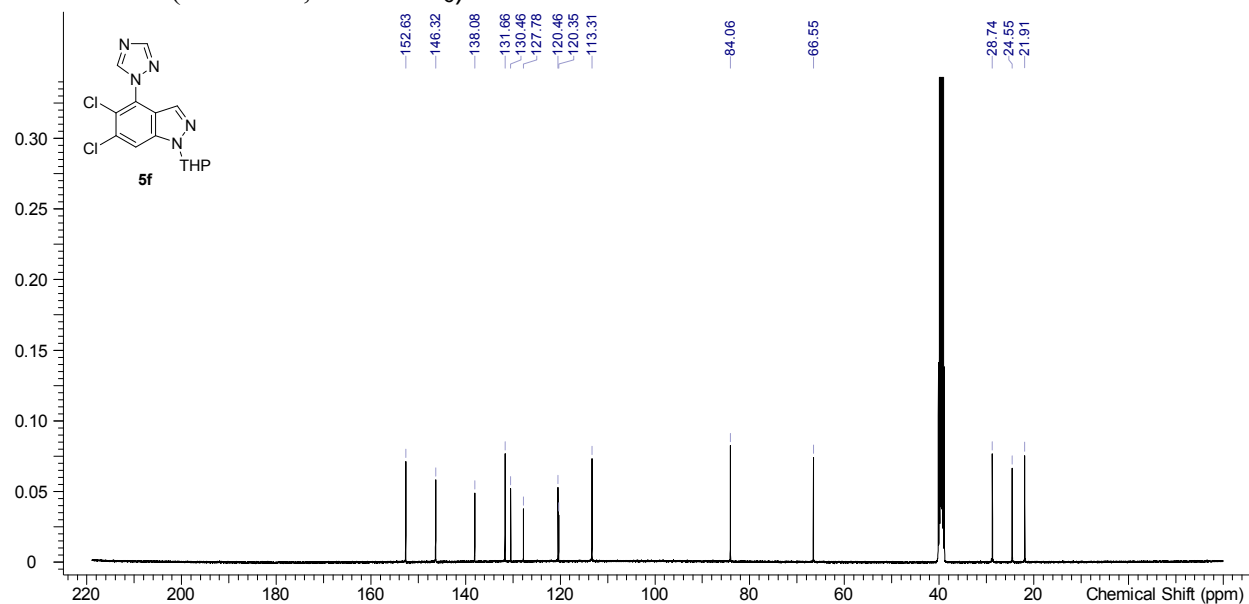
5e ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)



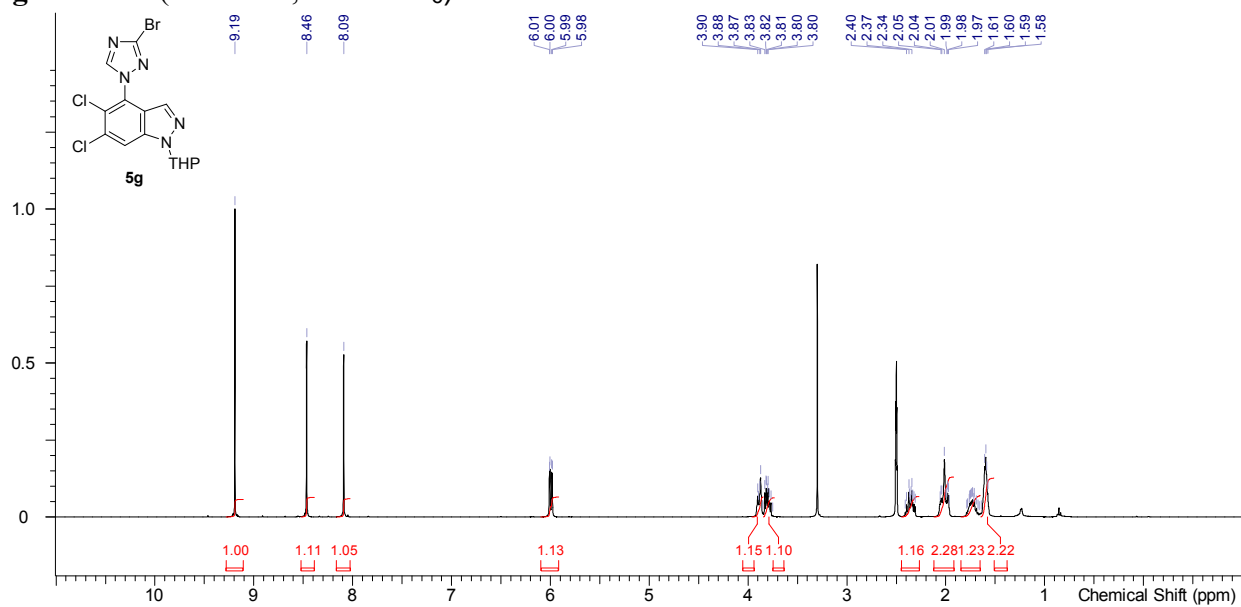
5f ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



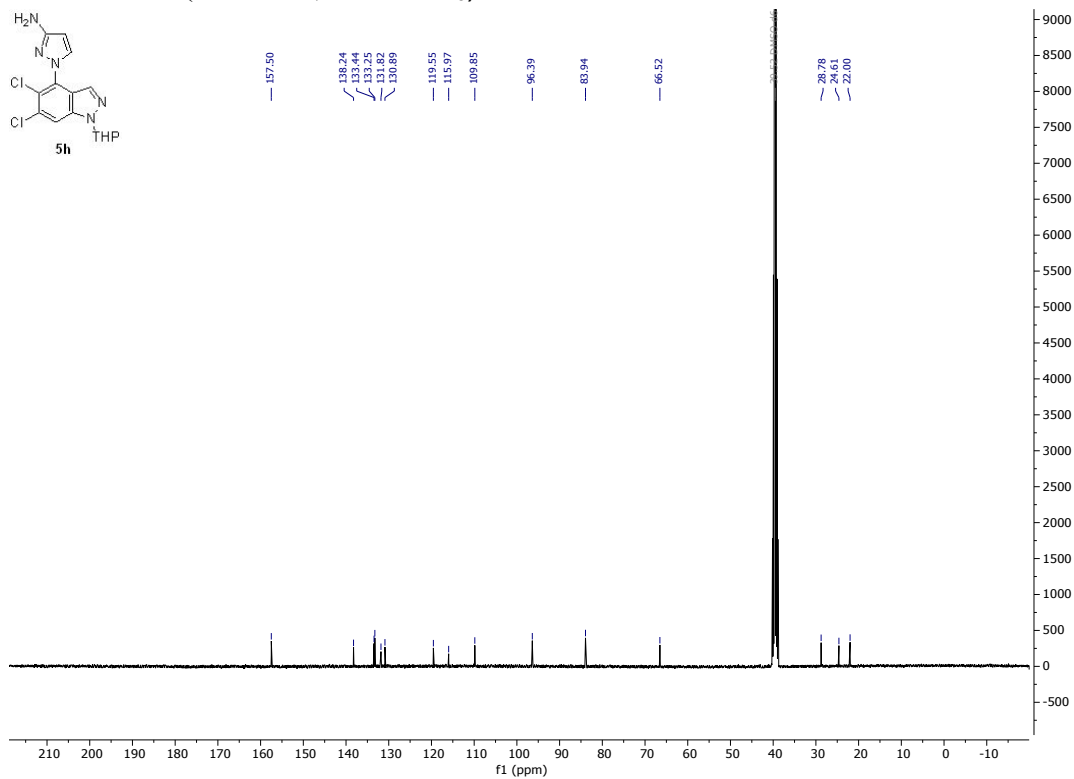
5f ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)



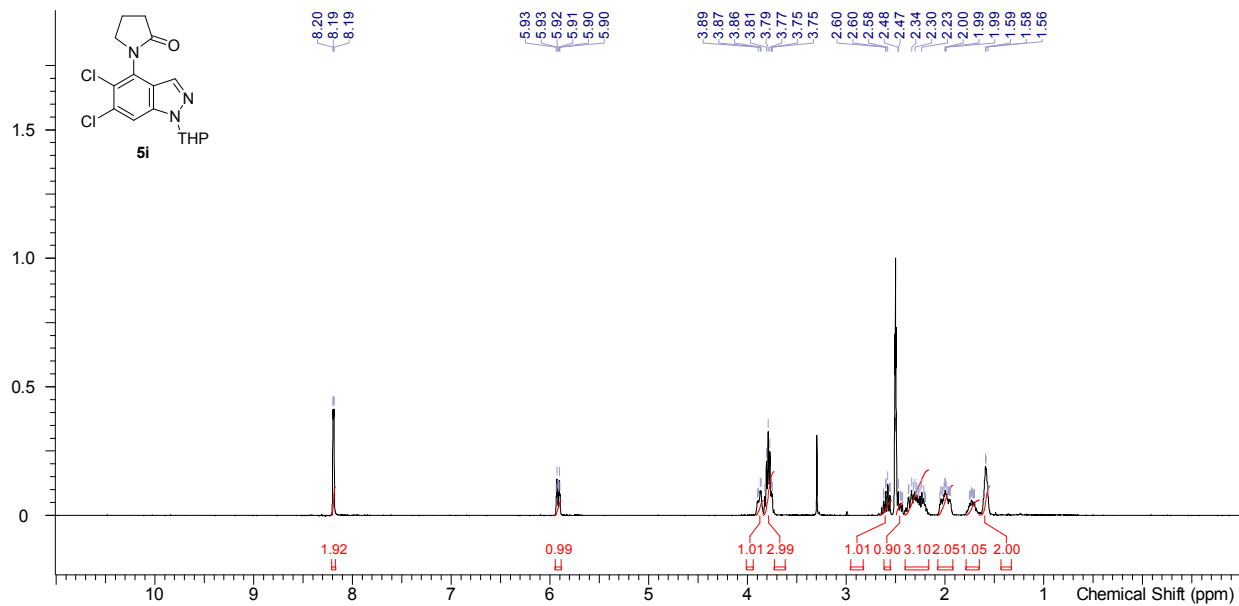
5g ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



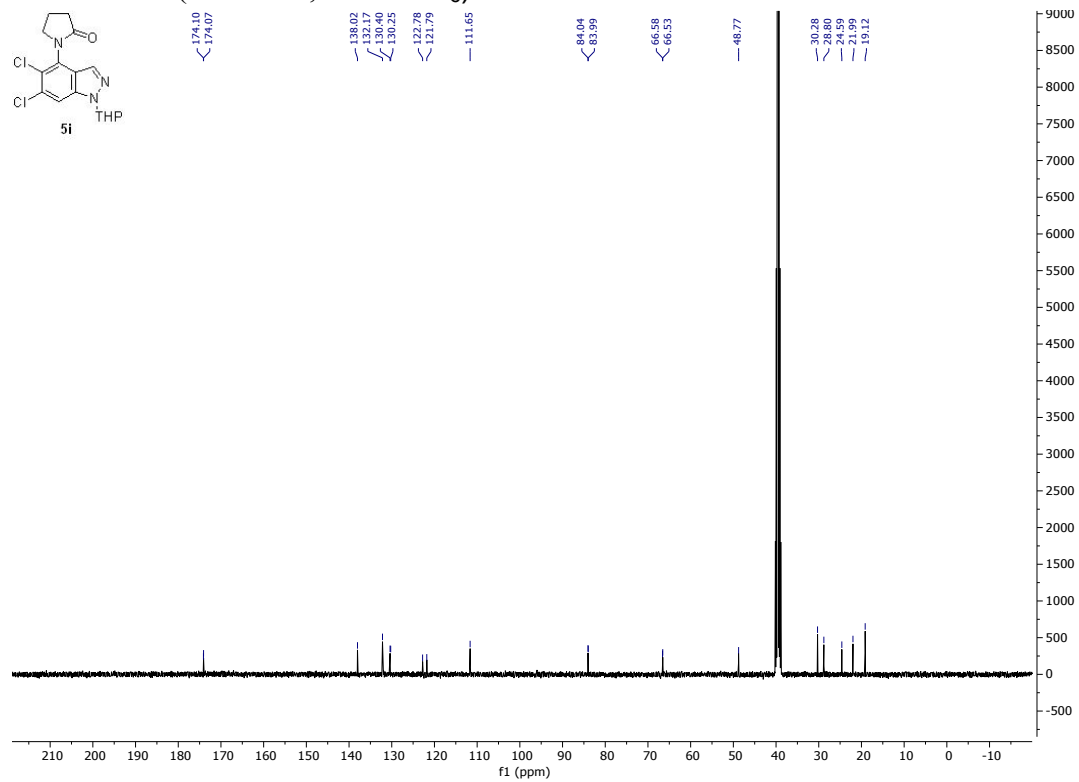
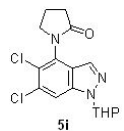
5h ¹³C NMR (101 MHz, DMSO-d₆)



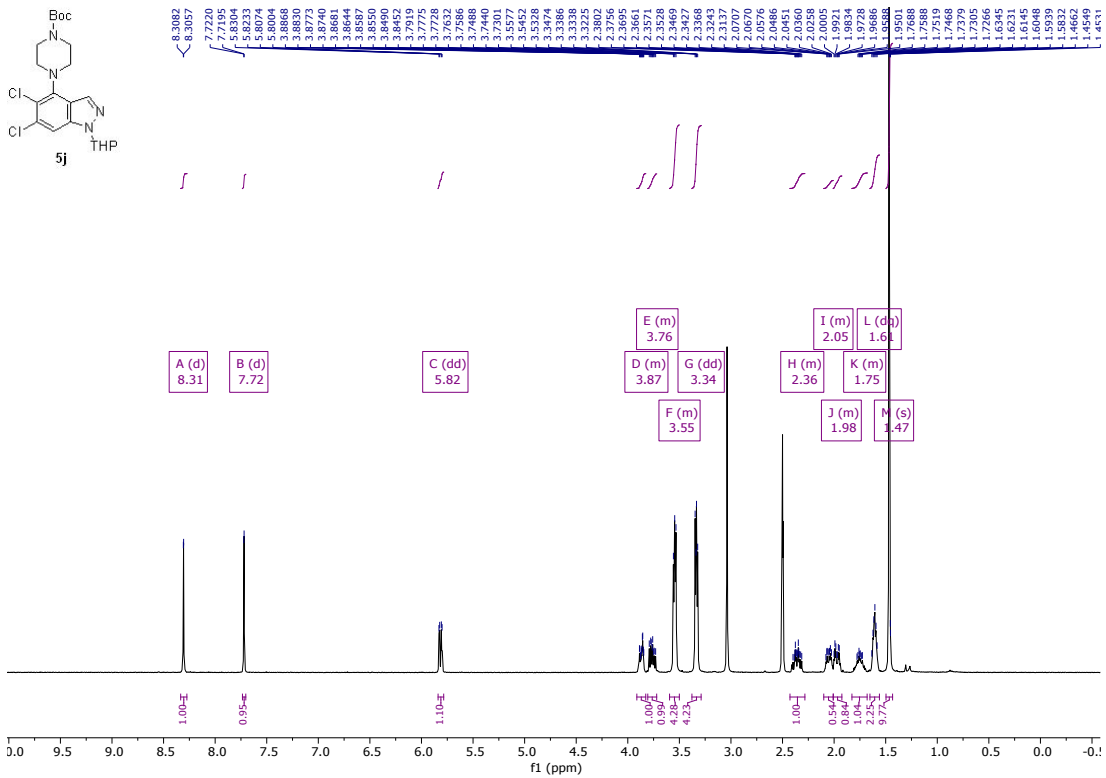
5i ¹H NMR (400 MHz, DMSO-d₆)



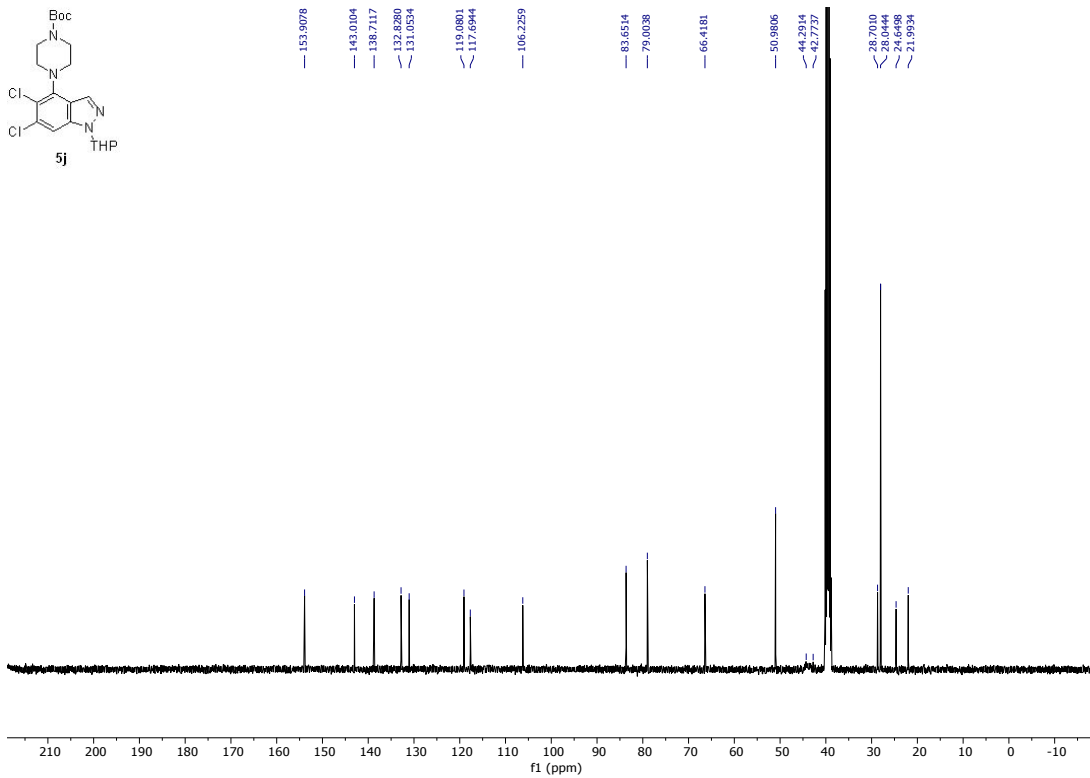
5i ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)



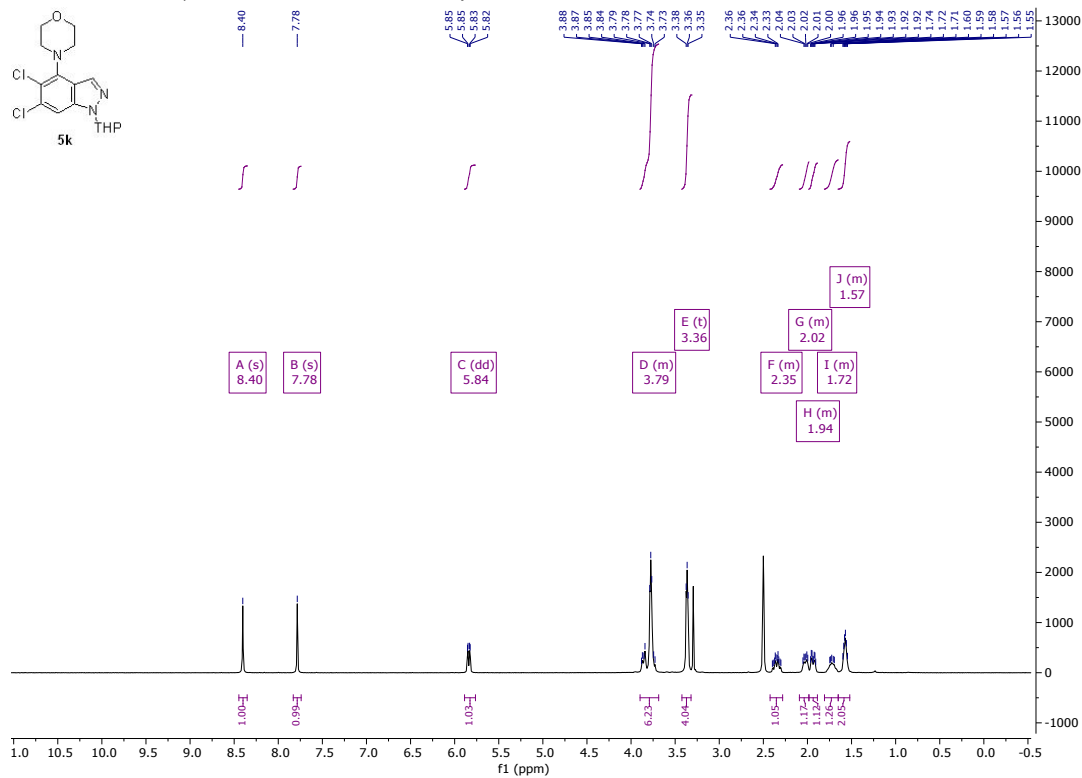
5j ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



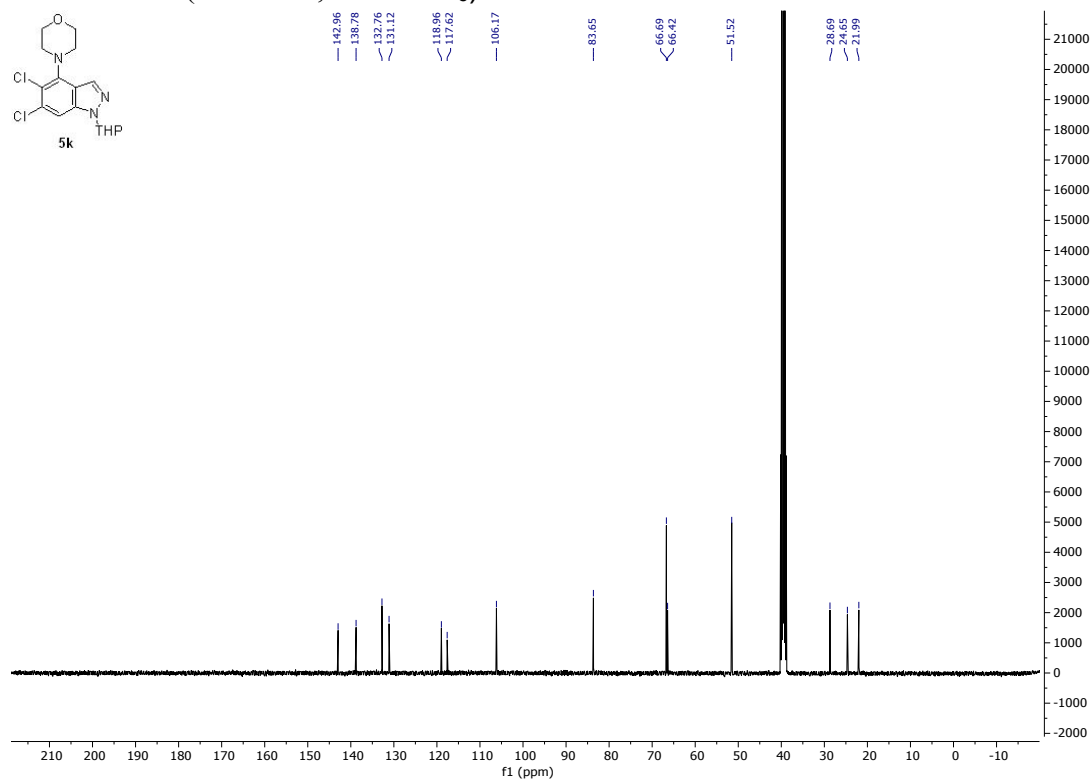
5j ¹³C NMR (101 MHz, DMSO-*d*₆)

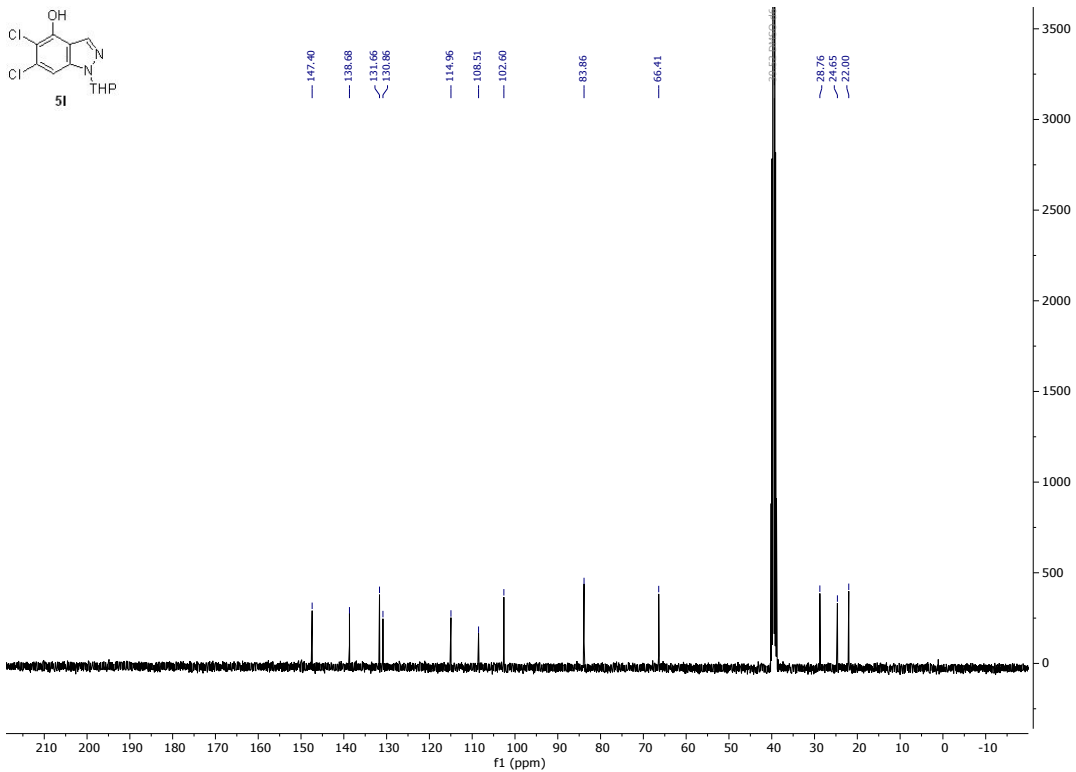


5k ¹H NMR (400 MHz, DMSO-*d*₆)

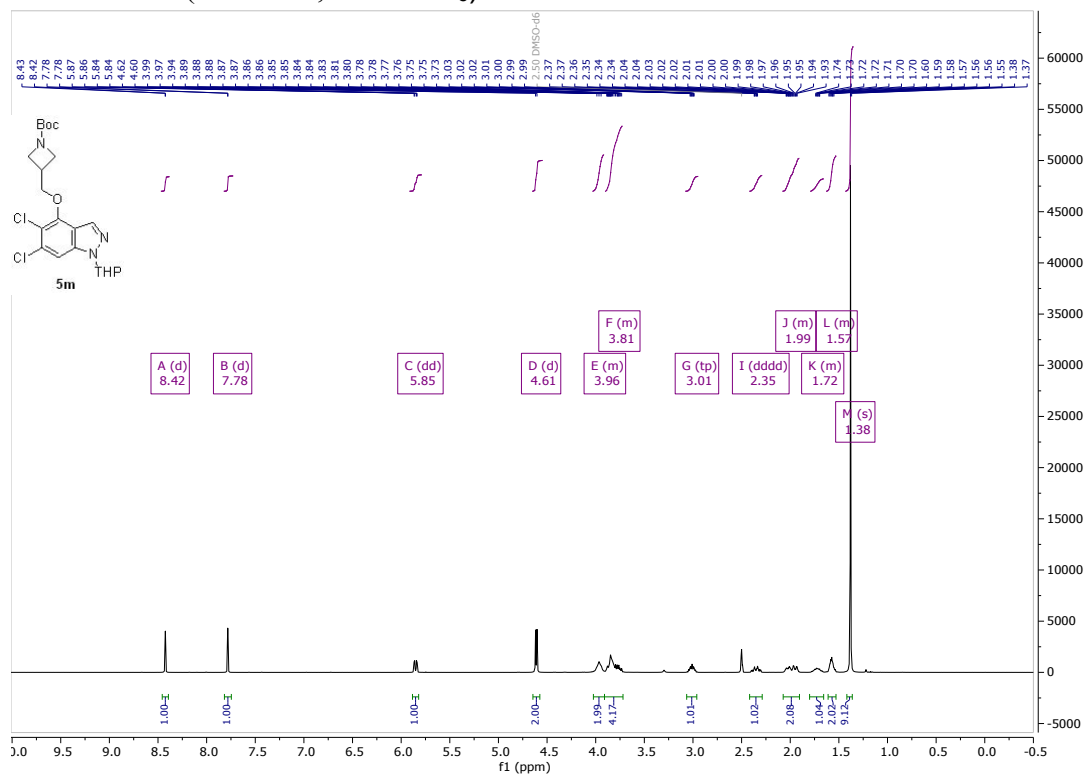


5k ¹³C NMR (101 MHz, DMSO-*d*₆)

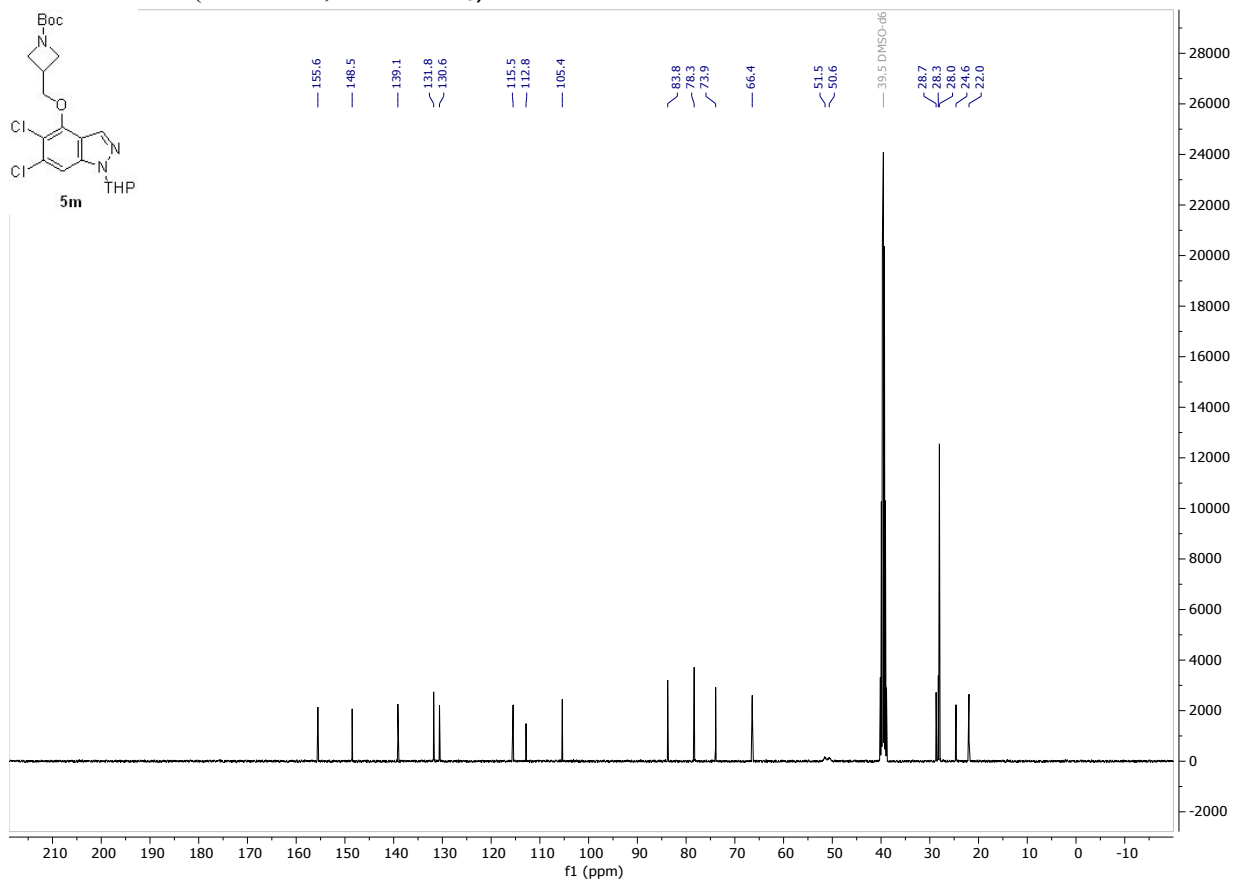




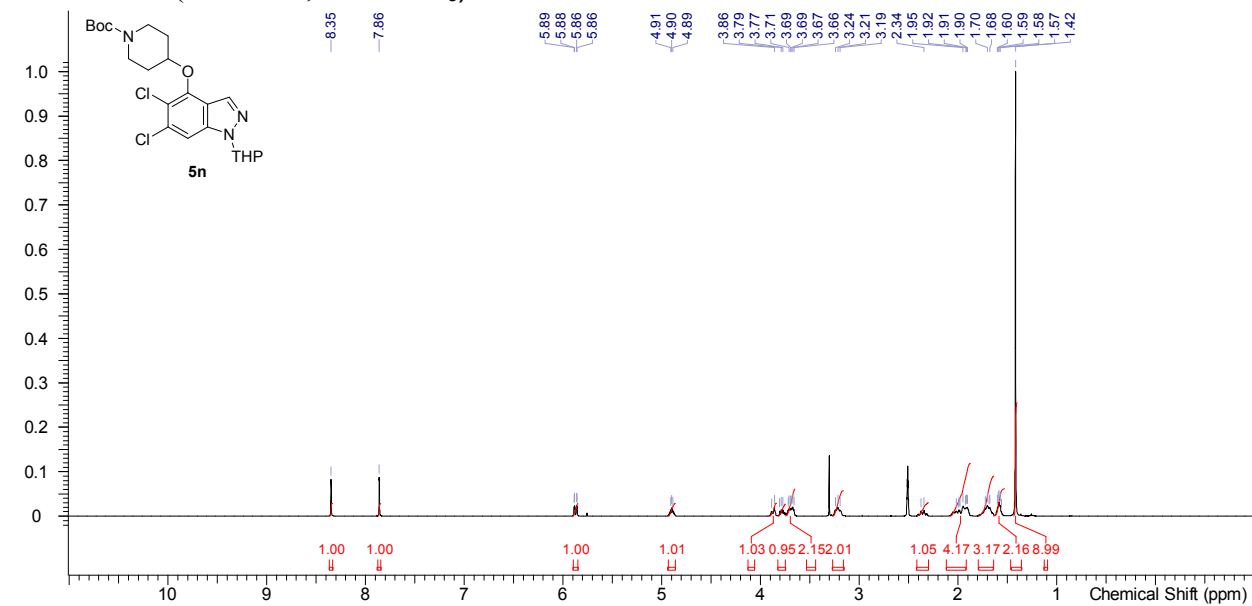
5m ^1H NMR (400 MHz, $\text{DMSO-}d_6$)



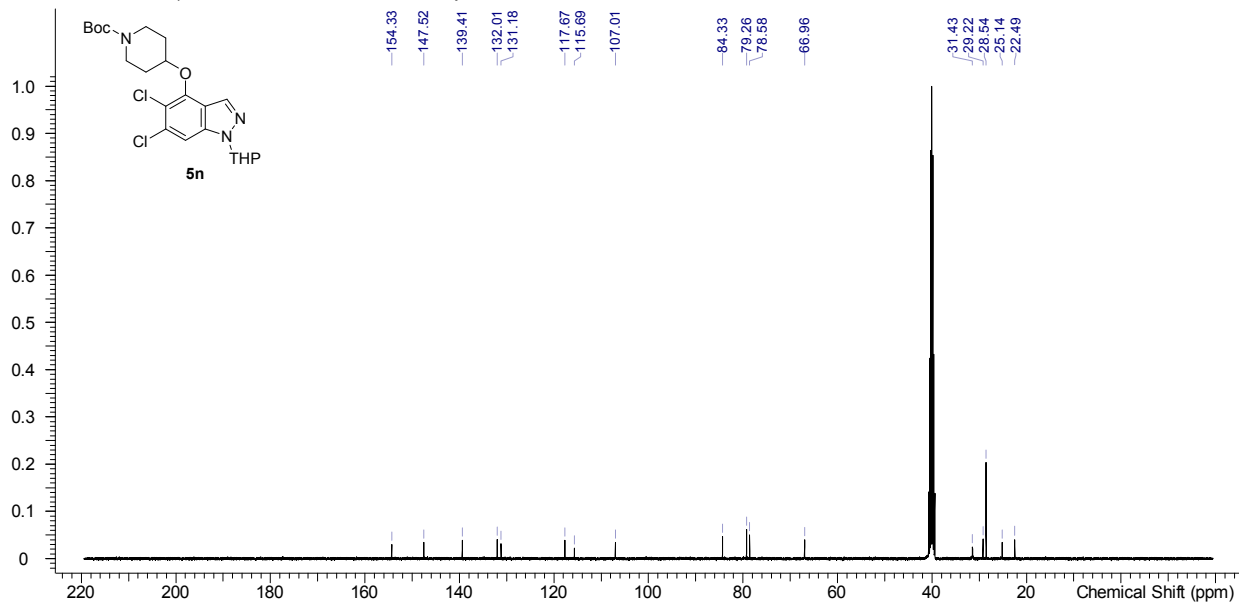
5m ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$)



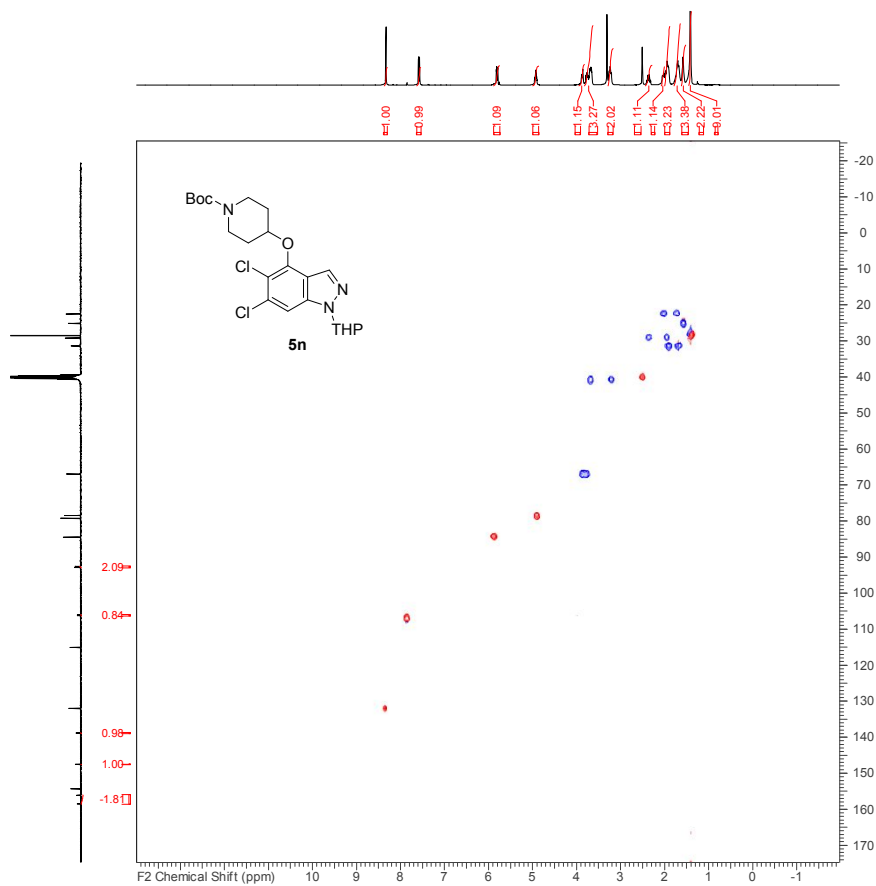
5n ^1H NMR (400 MHz, $\text{DMSO-}d_6$)



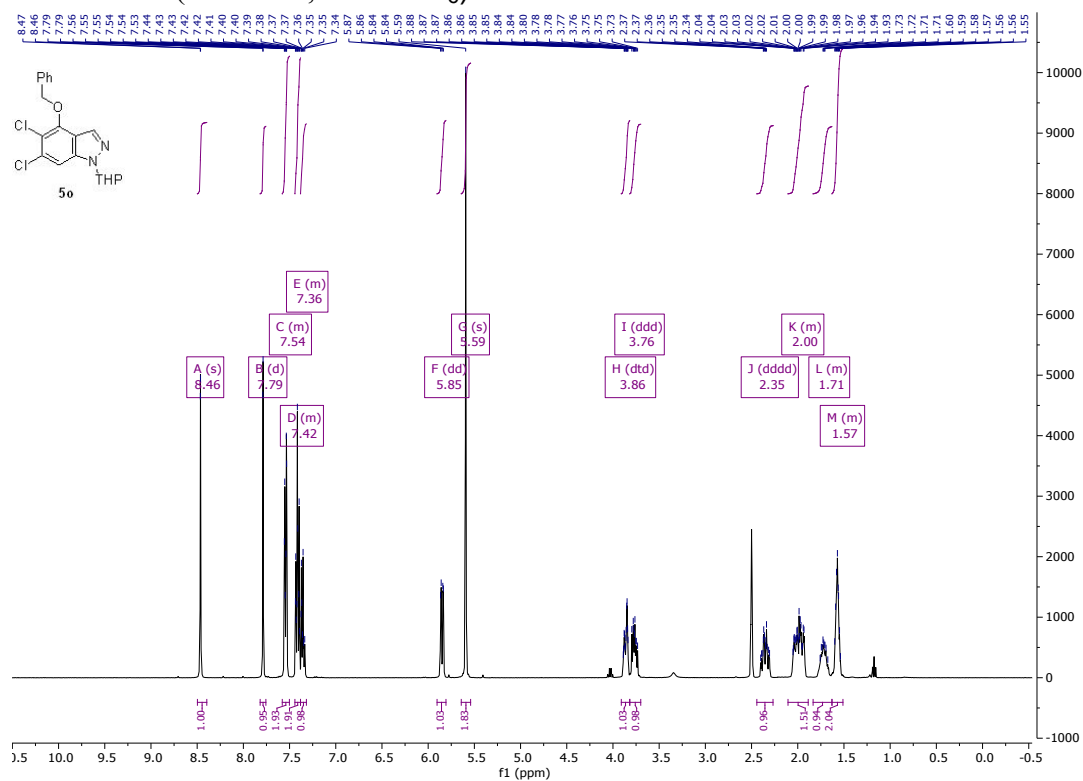
5n ¹³C NMR (101 MHz, DMSO-d₆)



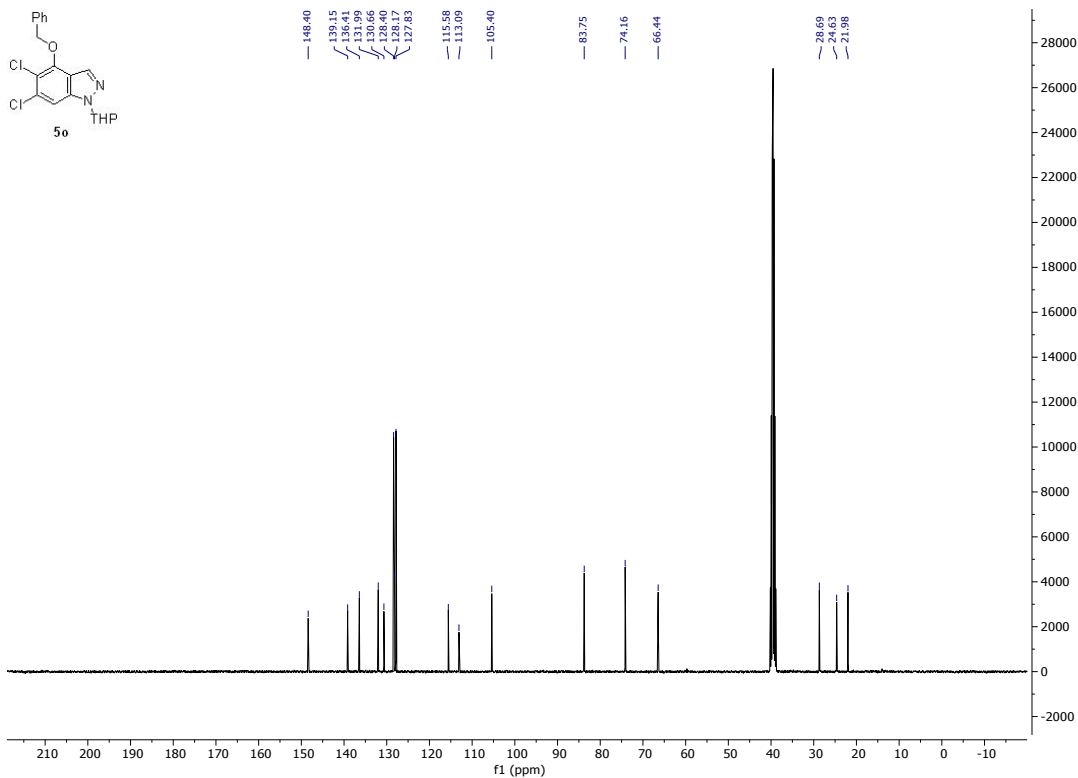
5n HSQC (¹H 400 MHz, DMSO-d₆)



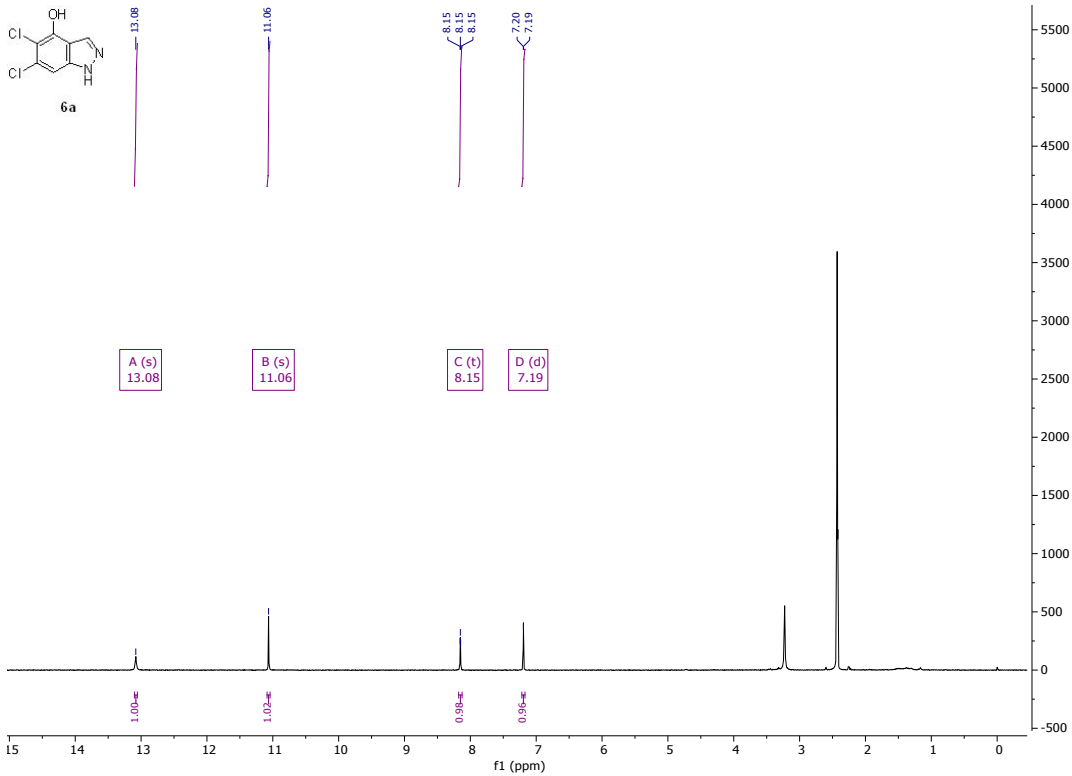
5o ¹H NMR (400 MHz, DMSO-*d*₆)



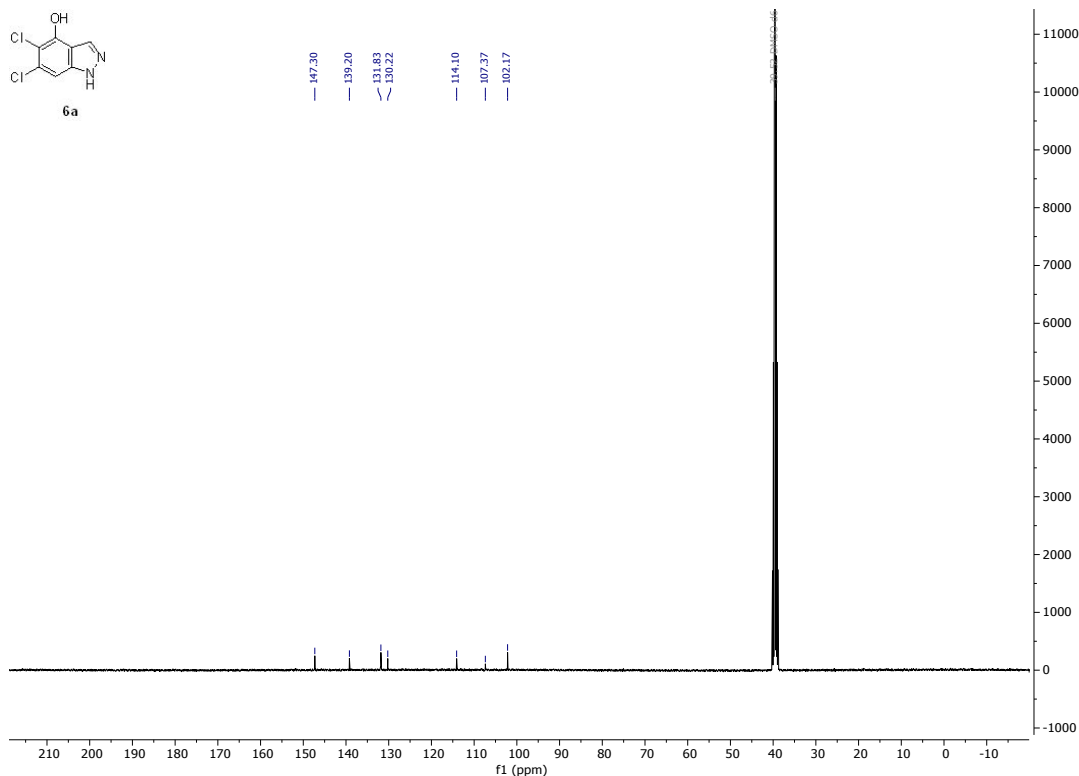
5o ¹³C NMR (101 MHz, DMSO-*d*₆)



6a ^1H NMR (400 MHz, $\text{DMSO}-d_6$)



6a ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$)



VIII. X-ray Crystallographic Data for **4g**

a. Crystal data and structure refinement for **4g**

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker APEX II

CCD diffractometer equipped with Cu K $_{\alpha}$ radiation ($\lambda = 1.54178$).

Crystal where grown by vapor diffusion from DCM/Pentane.

A 0.300 x 0.090 x 0.060 mm colorless crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans.

Crystal-to-detector distance was 40 mm using exposure time 1, 2, 3, and 4s (depending

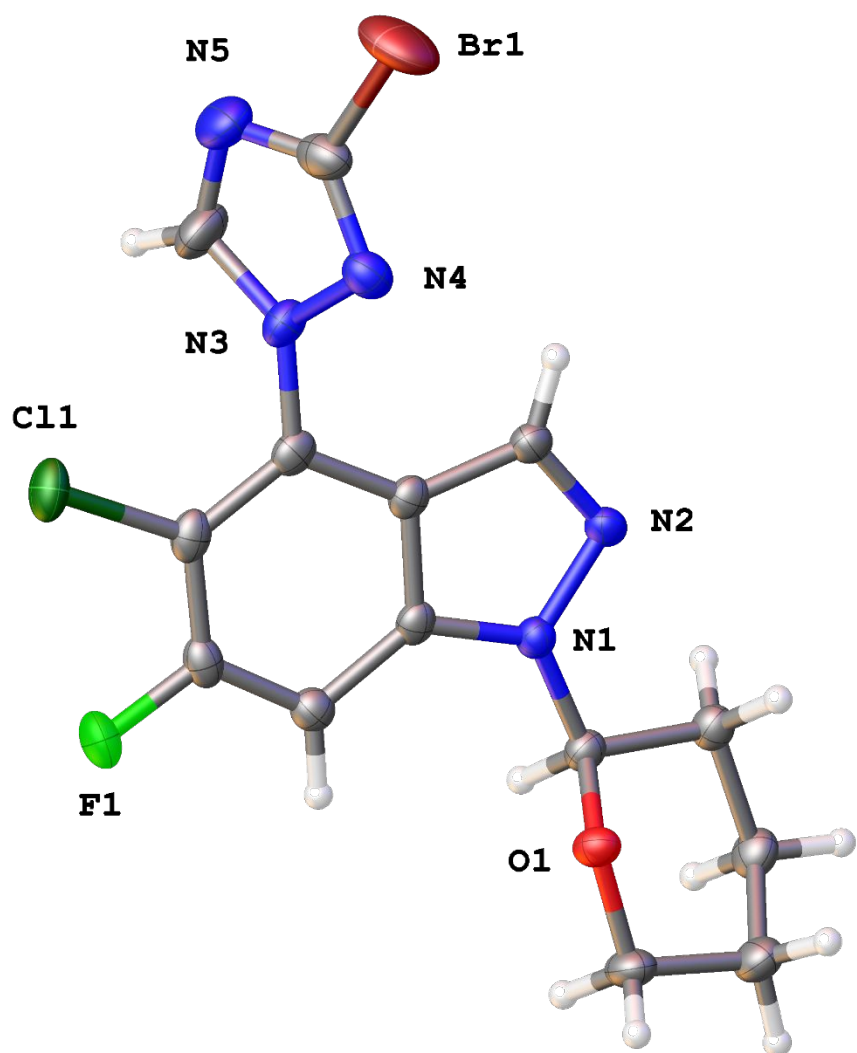
on the 2 theta range) with a scan width of 1.25°. Data collection was 99.8% complete to 67.500° in θ . A total of 18105 reflections were collected covering the indices, $-15 \leq h \leq 15$, $-21 \leq k \leq 21$, $-8 \leq l \leq 8$. 2982 reflections were found to be symmetry independent, with a R_{int} of 0.0422. Indexing and unit cell refinement indicated a **Primitive, Monoclinic** lattice. The space group was found to be $P2_1/c$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

(Positions of the N-H and O-H hydrogen atoms have been refined using appropriate HFIX commands.)

Crystallographic data are summarized in Table 1.

Notes: Excellent data and refinement.



Displacement ellipsoids are drawn at 50% probability level.

Table 1. Crystal data and structure refinement for PFLJ540.

Report date	2020-02-12	
Identification code	pflj540	
Empirical formula	C ₁₄ H ₁₂ Br Cl F N ₅ O	
Molecular formula	C ₁₄ H ₁₂ Br Cl F N ₅ O	
Formula weight	400.65	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 12.7399(6) Å	α = 90°.
	b = 17.5425(9) Å	β = 100.555(4)°.
	c = 7.1356(5) Å	γ = 90°.
Volume	1567.75(16) Å ³	
Z	4	
Density (calculated)	1.697 Mg/m ³	
Absorption coefficient	5.351 mm ⁻¹	
F(000)	800	
Crystal size	0.3 x 0.09 x 0.06 mm ³	
Crystal color, habit	colorless needle	
Theta range for data collection	3.529 to 70.899°.	
Index ranges	-15 ≤ h ≤ 15, -21 ≤ k ≤ 21, -8 ≤ l ≤ 8	
Reflections collected	18105	

Independent reflections	2982 [R(int) = 0.0422]
Completeness to theta = 67.500°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6619 and 0.4604
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2982 / 0 / 208
Goodness-of-fit on F ²	1.058
Final R indices [I > 2sigma(I)]	R1 = 0.0368, wR2 = 0.0847
R indices (all data)	R1 = 0.0434, wR2 = 0.0885
Largest diff. peak and hole	0.798 and -0.561 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$)

for PFLJ540. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
Br(1)	1701(1)	3336(1)	5524(1)	64(1)
Cl(1)	5187(1)	5158(1)	2493(1)	31(1)
F(1)	7361(1)	4812(1)	2133(2)	33(1)
O(1)	8724(1)	1986(1)	4226(2)	24(1)
N(1)	6964(2)	2087(1)	2757(3)	21(1)
N(2)	6101(2)	1651(1)	2974(3)	22(1)
N(3)	4036(2)	3662(1)	2819(3)	25(1)
N(4)	3651(2)	3379(1)	4343(3)	30(1)
N(5)	2314(2)	3904(2)	2177(4)	45(1)
C(1)	9788(2)	1760(2)	4062(4)	30(1)
C(2)	9867(2)	904(2)	3876(4)	32(1)
C(3)	9048(2)	614(1)	2191(4)	29(1)
C(4)	7936(2)	895(1)	2381(4)	24(1)
C(5)	7978(2)	1757(1)	2567(3)	22(1)
C(6)	6710(2)	2846(1)	2675(3)	20(1)
C(7)	7332(2)	3486(1)	2426(3)	23(1)
C(8)	6811(2)	4170(1)	2356(3)	24(1)
C(9)	5733(2)	4254(1)	2519(3)	24(1)

C(10)	5139(2)	3612(1)	2735(3)	22(1)
C(11)	5637(2)	2895(1)	2845(3)	21(1)
C(12)	5310(2)	2128(1)	3033(3)	22(1)
C(13)	3226(2)	3965(2)	1560(5)	41(1)
C(14)	2633(2)	3553(2)	3868(4)	34(1)

Table 3. Bond lengths [\AA] and angles [$^\circ$] for PFLJ540.

Br(1)-C(14)	1.862(3)	C(3)-H(3A)	0.9900
Cl(1)-C(9)	1.730(2)	C(3)-H(3B)	0.9900
F(1)-C(8)	1.352(3)	C(3)-C(4)	1.529(3)
O(1)-C(1)	1.438(3)	C(4)-H(4A)	0.9900
O(1)-C(5)	1.433(3)	C(4)-H(4B)	0.9900
N(1)-N(2)	1.372(3)	C(4)-C(5)	1.519(3)
N(1)-C(5)	1.444(3)	C(5)-H(5)	1.0000
N(1)-C(6)	1.369(3)	C(6)-C(7)	1.404(3)
N(2)-C(12)	1.316(3)	C(6)-C(11)	1.396(3)
N(3)-N(4)	1.366(3)	C(7)-H(7)	0.9500
N(3)-C(10)	1.419(3)	C(7)-C(8)	1.368(3)
N(3)-C(13)	1.347(4)	C(8)-C(9)	1.408(4)
N(4)-C(14)	1.315(4)	C(9)-C(10)	1.381(4)
N(5)-C(13)	1.320(4)	C(10)-C(11)	1.405(3)
N(5)-C(14)	1.349(4)	C(11)-C(12)	1.422(3)
C(1)-H(1A)	0.9900	C(12)-H(12)	0.9500
C(1)-H(1B)	0.9900	C(13)-H(13)	0.9500
C(1)-C(2)	1.513(4)		
C(2)-H(2A)	0.9900	C(5)-O(1)-C(1)	110.39(18)
C(2)-H(2B)	0.9900	N(2)-N(1)-C(5)	122.41(19)
C(2)-C(3)	1.527(4)	C(6)-N(1)-N(2)	111.02(19)

C(6)-N(1)-C(5)	126.5(2)	C(4)-C(3)-H(3A)	109.8
C(12)-N(2)-N(1)	106.46(19)	C(4)-C(3)-H(3B)	109.8
N(4)-N(3)-C(10)	120.9(2)	C(3)-C(4)-H(4A)	110.1
C(13)-N(3)-N(4)	109.4(2)	C(3)-C(4)-H(4B)	110.1
C(13)-N(3)-C(10)	129.7(2)	H(4A)-C(4)-H(4B)	108.4
C(14)-N(4)-N(3)	101.0(2)	C(5)-C(4)-C(3)	108.1(2)
C(13)-N(5)-C(14)	101.3(2)	C(5)-C(4)-H(4A)	110.1
O(1)-C(1)-H(1A)	109.4	C(5)-C(4)-H(4B)	110.1
O(1)-C(1)-H(1B)	109.4	O(1)-C(5)-N(1)	106.24(18)
O(1)-C(1)-C(2)	111.1(2)	O(1)-C(5)-C(4)	110.99(19)
H(1A)-C(1)-H(1B)	108.0	O(1)-C(5)-H(5)	108.8
C(2)-C(1)-H(1A)	109.4	N(1)-C(5)-C(4)	113.0(2)
C(2)-C(1)-H(1B)	109.4	N(1)-C(5)-H(5)	108.8
C(1)-C(2)-H(2A)	109.5	C(4)-C(5)-H(5)	108.8
C(1)-C(2)-H(2B)	109.5	N(1)-C(6)-C(7)	130.4(2)
C(1)-C(2)-C(3)	110.6(2)	N(1)-C(6)-C(11)	106.5(2)
H(2A)-C(2)-H(2B)	108.1	C(11)-C(6)-C(7)	123.1(2)
C(3)-C(2)-H(2A)	109.5	C(6)-C(7)-H(7)	122.4
C(3)-C(2)-H(2B)	109.5	C(8)-C(7)-C(6)	115.1(2)
C(2)-C(3)-H(3A)	109.8	C(8)-C(7)-H(7)	122.4
C(2)-C(3)-H(3B)	109.8	F(1)-C(8)-C(7)	118.5(2)
C(2)-C(3)-C(4)	109.5(2)	F(1)-C(8)-C(9)	117.2(2)
H(3A)-C(3)-H(3B)	108.2	C(7)-C(8)-C(9)	124.3(2)

C(8)-C(9)-Cl(1)	119.43(19)
C(10)-C(9)-Cl(1)	121.4(2)
C(10)-C(9)-C(8)	119.1(2)
C(9)-C(10)-N(3)	121.4(2)
C(9)-C(10)-C(11)	119.0(2)
C(11)-C(10)-N(3)	119.6(2)
C(6)-C(11)-C(10)	119.3(2)
C(6)-C(11)-C(12)	105.0(2)
C(10)-C(11)-C(12)	135.7(2)
N(2)-C(12)-C(11)	111.0(2)
N(2)-C(12)-H(12)	124.5
C(11)-C(12)-H(12)	124.5
N(3)-C(13)-H(13)	124.5
N(5)-C(13)-N(3)	111.1(3)
N(5)-C(13)-H(13)	124.5
N(4)-C(14)-Br(1)	120.1(2)
N(4)-C(14)-N(5)	117.2(3)
N(5)-C(14)-Br(1)	122.6(2)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for PFLJ540. The anisotropic

displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	44(1)	65(1)	93(1)	-8(1)	36(1)	-19(1)
Cl(1)	47(1)	20(1)	29(1)	2(1)	10(1)	8(1)
F(1)	40(1)	20(1)	38(1)	3(1)	9(1)	-6(1)
O(1)	19(1)	24(1)	27(1)	-4(1)	1(1)	0(1)
N(1)	21(1)	18(1)	22(1)	0(1)	2(1)	-1(1)
N(2)	19(1)	22(1)	23(1)	1(1)	0(1)	-3(1)
N(3)	26(1)	25(1)	22(1)	2(1)	1(1)	6(1)
N(4)	29(1)	30(1)	29(1)	0(1)	4(1)	-6(1)
N(5)	31(1)	38(1)	64(2)	5(1)	4(1)	9(1)
C(1)	18(1)	31(1)	40(2)	-1(1)	2(1)	1(1)
C(2)	24(1)	29(1)	42(2)	1(1)	1(1)	5(1)
C(3)	29(1)	24(1)	33(1)	-1(1)	5(1)	6(1)
C(4)	25(1)	21(1)	24(1)	-2(1)	1(1)	1(1)
C(5)	21(1)	22(1)	21(1)	1(1)	1(1)	2(1)
C(6)	23(1)	20(1)	16(1)	1(1)	-1(1)	2(1)
C(7)	23(1)	24(1)	20(1)	0(1)	3(1)	-1(1)
C(8)	33(1)	20(1)	18(1)	0(1)	3(1)	-4(1)
C(9)	34(1)	21(1)	16(1)	0(1)	2(1)	4(1)

C(10)	24(1)	26(1)	15(1)	1(1)	0(1)	4(1)
C(11)	23(1)	22(1)	16(1)	1(1)	1(1)	2(1)
C(12)	20(1)	23(1)	21(1)	2(1)	1(1)	0(1)
C(13)	33(2)	44(2)	43(2)	13(1)	0(1)	14(1)
C(14)	27(1)	28(1)	49(2)	-7(1)	8(1)	-4(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$)

for PFLJ540.

	x	y	z	U(eq)
H(1A)	10296	1933	5202	36
H(1B)	9988	2007	2930	36
H(2A)	9740	658	5063	38
H(2B)	10594	765	3691	38
H(3A)	9058	50	2164	35
H(3B)	9231	804	983	35
H(4A)	7408	745	1244	29
H(4B)	7721	665	3521	29
H(5)	8206	1977	1413	26
H(7)	8062	3446	2315	27
H(12)	4613	1980	3181	26
H(13)	3302	4192	384	49