Electronic Supporting Information for

Dearomatization of 3-Cyanoindoles by (3+2) Cycloaddition: From Batch to Flow Chemistry

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1. General:

High field ^{1}H NMR studies were recorded on a 300 MHz Bruker Spectrospin spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS, $CDCl_3$ or $(CD_3)_2CO$. Coupling constants (*J)* are given in Hertz. High resolution mass spectra were acquired on a Shimadzu QP2010 hybrid ionisation apparatus (HP5-MS stationary phase, l = 30 m, d = 0.25 mm, film thickness = 0.25 µm). Infrared spectra were recorded on a Perkin Elmer ATR universal sampler 100 spectrum. Melting points were measured on a Stuart SMP30 Digital Melting Point apparatus.

2. Procedures and data for the synthesis of starting materials:

General procedure A for the Suzuki coupling on 5-bromo-3-cyanoindole :

An oven dried vessel was charged with 5-bromo-3-cyanoindole (3 mmol, 1.0 equiv), boronic acid (6 mmol, 2 equiv), XPhosPdG2 (6 mol%), and K_3PO_4 (6 mmol, 2.0 equiv). The reaction vessel was evacuated and backfilled with argon three times. Dioxane (0.25 M) and H_2O (1.25 M) were degassed with argon for 30 minutes and then added with a syringe and the resulting mixture was heated at 100 °C overnight. It was then cooled to room temperature and filtered through a short plug of celite. The filter cake was washed with EtOAc. The resulting solution was dried over Na_2SO_4 and solvents were removed in vacuo. The crude was purified by flash chromatography to afford the desire product.

General procedure B for the triflation of NH-cyanoindole derivatives:

To a solution of 1*H*-3-cyanoindole derivative (2 mmol, 1.0 equiv), Et_3N (8 mmol, 4 equiv), DMAP (2 mmol, 1.0 equiv) in dry CH_2Cl_2 (0.25 M) at 0 °C was added dropwise Tf_2O (6 mmol, 3 equiv.). The mixture was allowed to stir at 0 °C for 30 min. The reaction was then quenched by addition of an ice-water mixture. The resulting mixture was extracted with EtOAc (3x). Then, the organic phases were washed with H_2O and brine. The organic phase was dried over Na_2SO_4, concentrated and purified by flash chromatography to afford the *N*-Tf-3-cyanoindole derivatives.

General procedure C for the (3+2) cycloaddition reaction between cyanoindole derivatives and hemiaminal 1 in batch conditions:

A solution of TFA in dry CH_2Cl_2 (0.36 mmol, 0.18 M) was added dropwise at 0 °C, over 30 min, to a solution of hemiaminal **1** (3 mmol, 6.0 equiv) and the requisite cyanoindole derivative **2** (0.5 mmol, 1.0 equiv) in dry CH_2Cl_2 (0.25 M). The resultant mixture was allowed to warm to room temperature and was kept under an inert atmosphere for 2 hours. The crude mixture was then concentrated under reduced pressure. The crude material was purified by chromatography to afford the product.

General procedure D for the (3+2) cycloaddition reaction between cyanoindole derivatives and hemiaminal 1 in flow conditions (set-up A in the manuscript):

The set up was prepared using two 2 mL loading loops 1/16 inch I.D. PFA tubing, one reactor of 20 mL 1/8 inch I.D. PFA tubing, one PEEK micromixer 0.02 inch I.D. 0.57 μL swept volume, two 50 mL SGE gastight glass syringes, two Harvard apparatus PHD Ultra syringe pumps.

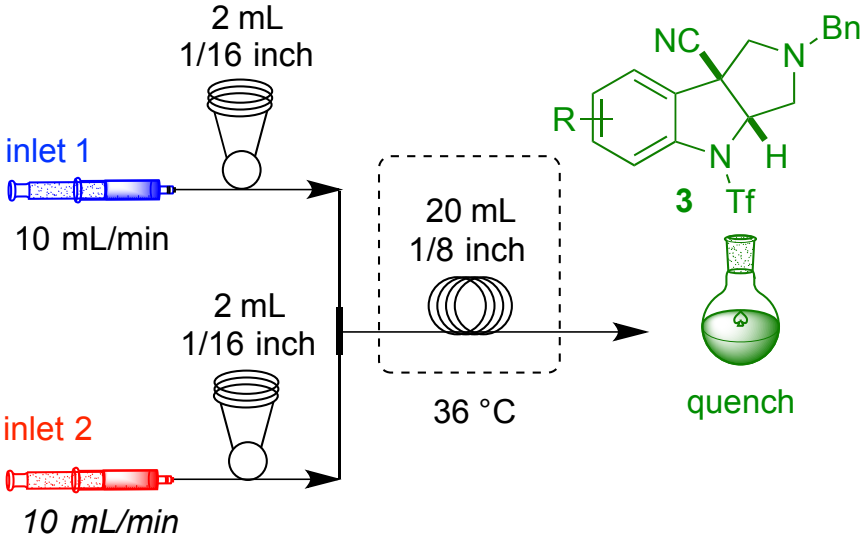
A solution of TFA in dry CH_2Cl_2 (0.12 mmol, 0.06 M) was introduced in a 2mL loading loop on a first channel. A solution of hemiaminal **1** (1.5 mmol, 3.0 equiv.) and the requisite cyanoindole derivative **2** (0.5 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.25 M) was introduced in 2 mL loading loop inch on a second channel. Once all the solutions loaded, both channels were connected to 50 mL syringe containing dry CH_2Cl_2 actioned by syringe pump. The two channels were connected by a mixer. The latest were connected to a 20 mL reactor heated at 36 °C by a water bath. The syringe pump was set up to 10mL/min for each syringe. The reaction mixture was collected in round bottom. At the end of the reaction the mixture was quenched with Et_3N (0.12 mmol).

General procedure E for the (3+2) cycloaddition reaction between cyanoindole derivatives and hemiaminal 1 in flow conditions (set-up B in the manuscript):

The set up was prepared using two 2 mL loading loops 1/16 inch I.D. PFA tubing, one reactor of 20 mL 1/8 inch I.D. PFA tubing, one PEEK micromixer 0.02 inch I.D. 0.57 μL swept volume, two 50 mL SGE gastight glass syringes, two Harvard apparatus PHD Ultra syringe pumps.

A solution of hemiaminal **1** in dry CH_2Cl_2 (1.5 mmol, 3.0 equiv.) was introduced in a 2mL loading loop on a first channel. A solution of TFA (0.12 mmol, 0.06 M) and the requisite cyanoindole derivative **2** (0.5 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.25 M) was introduced in 2

mL loading loop inch on a second channel. Once all the solutions loaded, both channels were connected to 50 mL syringe containing dry CH_2Cl_2 actioned by syringe pump. The two channels were connected by a mixer. The latest were connected to a 20 mL reactor heated at 36 °C by a water bath. The syringe pump was set up to 10mL/min for each syringe. The reaction mixture was collected in round bottom. At the end of the reaction the mixture was quenched with Et_3N (0.12 mmol).



Procedure C (Set-up A)

TFA

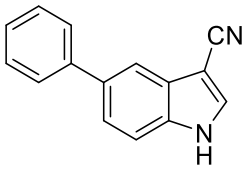
Hemiaminal **1**, Cyanoindole **2**

Procedure D (Set-up B)

TFA, Cyanoindole **2**

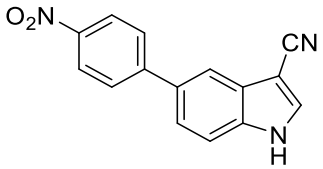
Hemiaminal **1**

5-phenyl-1*H*-indole-3-carbonitrile (1i)



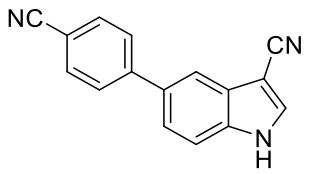
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.34 Toluene / Ethyl Acetate 8:2) to afford the desired product as brown solid (648 mg, 99% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.25 (broad s, 1H), 8.17 – 8.12 (m, 1H), 7.92 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.77 – 7.65 (m, 3H), 7.62 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.40 – 7.31 (m, 1H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 142.3, 136.2, 135.9, 134.9, 129.7 (2C), 128.7, 128.1 (2C), 127.8, 124.2, 117.7, 116.3, 114.0, 87.2 ppm. IR (neat) nmax = 3242, 2924, 2221, 1470, 1420, 815, 763, 749, 688 cm^{-1} HRMS TOF MS ES- m/z calcd for $C_{15}H_9N_2$: 217.0766 $[M-H]^-$; found: 217.0762. Mp = 215 °C.

5-(4-nitrophenyl)-1*H*-indole-3-carbonitrile (1j)



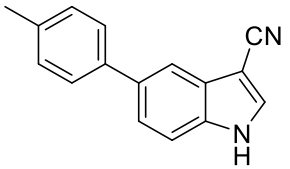
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.25 Toluene / Ethyl Acetate 8:2) to afford the desired product as yellow solid (240 mg, 80% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.40 (s, 1H), 8.39 – 8.32 (m, 2H), 8.23 – 8.20 (m, 1H), 8.12 – 8.03 (m, 3H), 7.78-7.30 (m, 2H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 148.7, 147.7, 136.7, 135.5, 133.5, 128.8 (2C), 128.7, 124.8 (2C), 124.1, 118.7, 116.1, 114.4, 87.5 ppm. IR (neat) nmax = 3418, 2222, 1594, 1514, 1341, 1108, 806, 613 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{15}H_8N_3O_2$: 262.0617 $[M-H]^-$; found: 262.0612. Mp = 240 °C.

5-(4-cyanophenyl)-1*H*-indole-3-carbonitrile (1k)



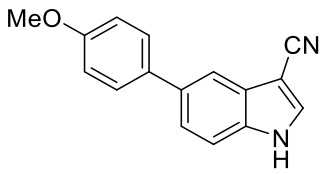
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.36 Toluene / Ethyl Acetate 8:2) to afford the desired product as pinkish solid (571 mg, 78% yield). ^{1}H NMR (300 MHz, Acetone-d_6) δ 11.36 (s, 1H), 8.20 (s, 1H), 8.04 (dd, *J* = 1.8, 0.8 Hz, 1H), 8.02 – 7.96 (m, 2H), 7.91 – 7.85 (m, 2H), 7.75 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.70 (dd, *J* = 8.6, 1.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 146.7, 136.6, 135.5, 135.3, 134.0, 133.5 128.8 , 128.7, 124.1, 119.5, 118.4, 116.1, 114.4, 114.3, 111.3, 87.5 ppm. IR (neat) nmax = 3248, 3128, 2221, 1606, 1472, 1434, 1250, 835, 793 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{16}H_8N_3$: 242.0718 $[M-H]^-$; found: 242.0720. Mp = 268 ° C.

5-(p-tolyl)-1*H*-indole-3-carbonitrile (1l)



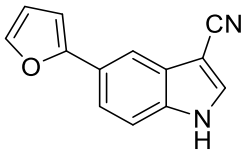
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.36 Toluene / Ethyl Acetate 8:2) to afford the desired product as pinkish solid (669 mg, 96% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.25 (s, 1H), 8.15 – 8.12 (m, 1H), 7.89 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.70 – 7.56 (m, 4H), 7.29 (dt, *J* = 7.9, 0.7 Hz, 2H), 2.38 (s, 3H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 138.5, 136.4, 135.2, 134.9, 133.9, 129.5 (2C), 127.8, 127.0 (2C), 123.2, 116.5, 115.5, 113.1, 86.2, 20.2 ppm. IR (neat) nmax = 3226, 3138, 2216, 1459, 1427, 1207, 1111, 886, 842, 640, 587 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{16}H_{11}N_2$: 231.0922 $[M-H]^-$; found: 231.0927. Mp = 214 ° C.

5-(4-methoxyphenyl)-1*H*-indole-3-carbonitrile (1m)



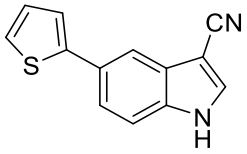
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.36 Toluene / Ethyl Acetate 8:2) to afford the desired product as pinkish solid (745 mg, 89% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.25 (s, 1H), 8.14 – 8.10 (m, 1H), 7.86 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.70 – 7.62 (m, 3H), 7.57 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.08 – 6.99 (m, 2H), 3.85 (s, 3H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 160.1, 135.9, 135.6, 134.7, 134.7, 129.0 (2C), 128.7, 123.9, 117.1, 116.4, 115.1 (2C), 113.9, 87.0, 55.6 ppm. IR (neat) nmax = 3237, 2218, 1607, 1470, 1238, 1179, 1033, 837, 796, 647, 585, 431 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{16}H_{11}N_2O$: 247.0871 $[M-H]^-$; found: 247.0875. Mp = 237 ° C.

5-(furan-2-yl)-1*H*-indole-3-carbonitrile (1n)



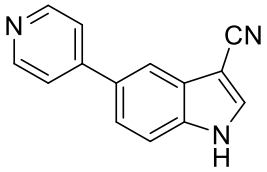
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.29 Toluene / Ethyl Acetate 8:2) to afford the desired product as pinkish solid (561 mg, 90% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.28 (s, 1H), 8.15 – 8.10 (m, 1H), 8.05 – 7.99 (m, 1H), 7.71 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.64 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.64 (dd, *J* = 8.6, 0.8 Hz, 1H), 6.90 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.56 (dd, *J* = 3.4, 1.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 155.1, 142.9, 135.8, 134.9, 128.4, 126.2, 121.1, 116.2, 114.4, 114.1, 112.6, 105.4, 87.1 ppm. IR (neat) nmax = 3234, 2219, 1523, 1447, 1430, 1302, 1239, 1114, 1007, 871, 786, 718, 675, 618, 430 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{13}H_7N_2O$: 207.0558 $[M-H]^-$; found: 207.0556. Mp = 221 ° C.

5-(thiophen-2-yl)-1*H*-indole-3-carbonitrile (1o)



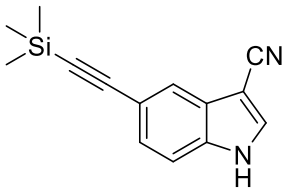
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.28 Toluene / Ethyl Acetate 8:2) to afford the desired product as pinkish solid (676 mg, 99% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.32 (s, 1H), 8.15 – 8.10 (m, 1H), 7.96-7.93 (m, 1H), 7.62-7.66 (m, 2H), 7.51 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.43 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 145.4, 135.9, 135.2, 129.5, 129.1, 128.6, 125.4, 123.9, 123.1, 116.3, 116.2, 114.3, 87.0 ppm. IR (neat) nmax = 3249, 2216, 1521, 1427, 1241, 1121, 870, 849, 804, 696, 639, 583, 414 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{13}H_7N_2S$: 223.0330 $[M-H]^-$; found: 223.0321. Mp = 237 ° C.

5-(pyridin-4-yl)-1*H*-indole-3-carbonitrile (1p)



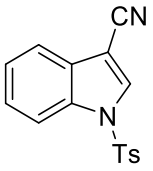
The target compound was prepared according to the general procedure A. The crude mixture was purified by flash chromatography on silica gel (Dichloromethane/MeOH 95:5, R_f = 0.33 Dichloromethane/MeOH 95:5) to afford the desired product as pinkish solid (554 mg, 84% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.39 (s, 1H), 8.72 – 8.56 (m, 2H), 8.24 – 8.16 (m, 1H), 8.09 (d, *J* = 1.2 Hz, 1H), 7.84 – 7.70 (m, 4H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 151.2 (2C), 149.1, 136.9, 135.5, 132.9, 128.7, 123.7 (2C), 122.4, 118.2, 116.1, 114.5, 87.5 ppm. IR (neat) nmax = 2857, 2219, 1601, 1063, 821, 787, 641 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{14}H_8N_3$: 218.0718 $[M-H]^-$; found: 218.0710. Mp = 249 ° C.

5-((trimethylsilyl)ethynyl)-1*H*-indole-3-carbonitrile (1q)



The 3-cyano-5-bromo-indole (3 mmol, 1equiv.), $Pd(PPh3)_4$ (0.06 mmol, 2 mol%), CuI (0.12 mmol, 4 mol%), ethynyltrimethylsilane (3.6 mmol, 1.2 equiv.), Et_2NH/DMF (4 :1 v/v) were mixed and stirred under argon in at 120°C for 2 hours. Then, the reaction was poured into a 1M aqueous HCl solution and extracted three times with Et_2O. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ and brine, then the organic phase was dried over $MgSO_4$, concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 8:2, R_f = 0.33 Toluene / Ethyl Acetate 8:2) to afford the desired product as pale yellow solid (519 mg, 73% yield). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 11.36 (s, 1H), 8.21 – 8.14 (m, 1H), 7.78 (dd, *J* = 1.5, 0.8 Hz, 1H), 7.60 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.38 (dd, *J* = 8.5, 1.5 Hz, 1H), 0.25 (s, 9H) ppm. ^{13}C (NMR (75 MHz, $(CD_3)_2CO$) δ = 136.1, 135.5, 128.0, 127.9, 123.4, 117.5, 115.7, 113.9, 106.6, 93.0, 87.1, 0.10 (3C) ppm. IR (neat) nmax = 3294, 2223, 2154, 1520, 1472, 1421, 1236, 933, 869, 838, 636, 412 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{14}H_{13}N_2Si$: 237.0848 $[M-H]^-$; found: 237.0849. Mp = 159 ° C.

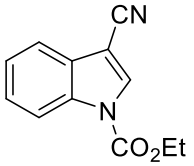
1-tosyl-1*H*-indole-3-carbonitrile (2a)



A mixture of 1-tosyl-1H-indole-3-carbaldehyde (15 mmol, 1 equiv.) and $NH_2OH.HCl$ (16.5 mmol, 1.1 equiv.) in DMSO (0.25 M) was stirred at 90 °C for 2h. The mixture was cooled at room temperature and diluted with water. The resulting mixture was extracted with EtOAc (3x). Then, the combined organic phases were washed with H_2O and brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (Toluene/Cyclohexane 9:1, R_f = 0.41) to afford the product as a white solid (4.1 g, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ

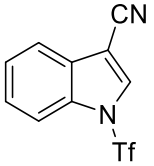
= 8.10 (s, 1H), 8.01-7.97 (m, 1H), 7.84-7.81 (m, 2H), 7.70 ((ddd, *J* = 7.6, 1.5, 0.8 Hz, 1H), 7.45-7.35 (m, 2H), 7.32-7.29 (m, 2H), 2.39 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 146.4, 134.0, 133.6, 133.2, 130.4 (2C), 128.3, 127.2 (2C), 126.5, 124.8, 120.2, 112.8, 113.5, 93.6, 21.6 ppm. IR (neat) nmax = 3144, 2233, 1175, 960, 755, 666, 569, 535 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{16}H_{11}N_2O_2S$: 295.0541 $[M-H]^-$; found: 295.0539. Mp = 154 °C

Ethyl 3-cyano-1*H*-indole-1-carboxylate (2c)



To a stirred suspension of NaH (2 mmol, 2 equiv.) in DMF (0.4 M) was added a solution of 3-cyanoindole (1 mmol, 1 equiv.) in DMF (0.2 M). The reaction mixture was stirred for 2h at 0 °C. Then, the ethyl chloroformate was added slowly to the solution. The reaction was warmed up to room temperature and stirred for 16h. The reaction mixture was quenched by adding cooled distilled water. The resulting mixture was extracted with ether (3x). The organic phase was washed with brine and dried over Na_2SO_4, and concentrated in vacuo, furnishing the desire product as a white solid without further purification (214 mg, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.22 (ddd, *J* = 8.3, 1.1, 0.8 Hz, 1H), 8.16 (s, 1H), 7.74 (ddd, *J* = 7.6, 1.5, 0.8 Hz, 1H), 7.51 – 7.36 (m, 2H), 4.56 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 149.8, 134.4, 133.0, 128.1, 126.6, 124.7, 119.9, 115.8, 114.0, 93.2, 64.7, 14.4 ppm. IR (neat) nmax = 3149, 2919, 2227, 1739, 1449, 1380, 1257, 1225, 1025, 756, 739, 422 cm^{-1}. HRMS TOF MS AP- m/z calcd for $C_9H_5N_2$: 141.0453 $[M-CO_2CH_2CH_3]^-$; found: 141.0456. Mp = 76 °C

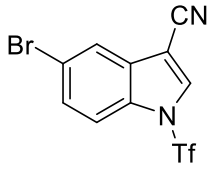
1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2d)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 8:2, R_f = 0.27 Toluene/Cyclohexane 8:2) to afford the desired product as white crystals (504 mg, 92%

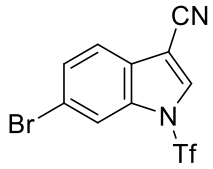
yield). ^{1}H NMR (300MHz,$CDCl_3$) d = 7.97-7.94 (m, 1H), 7.92 (s, 1H), 7.84-7.80 (m, 1H), 7.60-7.52 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 134.5, 133.2, 128.1, 128.0, 126.4, 120.8, 119.3 (q, *J* = 324 Hz), 114.1, 112.1, 97.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.6 ppm IR (neat) nmax = 3133, 3089, 2919, 2233, 1739, 1558, 1421, 1203, 1111, 755, 740 524 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_9H_5N_2$: 141.0453 $[M\text{-}CF_3O_2S]^-$; found: 141.0450. Mp = 94 °C

5-Bromo-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2e)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 8:2, R_f = 0.81 Toluene/Cyclohexane 9:1) to afford the desired product as brown solid (678 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) NMR 7.98 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.92 (s, 1H), 7.82 (dd, *J* = 9.0, 0.6 Hz, 1H), 7.68 (ddd, *J* = 9.0, 1.9, 0.6), 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 134.1, 133.3, 131.3, 129.7, 123.7, 120.3, 119.3 (q, *J* = 324 Hz), 115.6, 111.5, 97.1 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.7 ppm. IR (neat) nmax = 3670, 2984, 2902, 2227, 1739, 1423, 1214, 1089, 611 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{10}H_4N_2O_2F_3SBr$: 368.9156 $[M+HO]^-$; found: 368.9150. Mp = 83 °C.

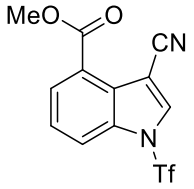
6-Bromo-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2f)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 9:1, R_f = 0.70) to afford the desired product as white solid (473 mg, 68% yield) . ^{1}H NMR (300 MHz, $CDCl_3$) δ

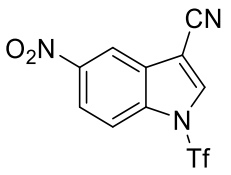
= 8.11 (s, 1H), 7.90 (s, 1H), 7.70-7.62 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.2, 133.4, 130.2, 127.0, 122.1, 122.0, 119.3 (q, *J* = 324 Hz), 117.4, 111.7, 97.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.7 ppm. IR (neat) nmax = 3676, 2988, 2902, 1601, 1547, 1435, 1221, 1124, 1080, 972, 812, 615, 567, 514 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{10}H_4N_2O_2F_3SBr$: 368.9156 $[M+HO]^-$; found: 368.9155. Mp = 97 °C.

Methyl 3-cyano-1-((trifluoromethyl)sulfonyl)-1*H*-indole-4-carboxylate (2g)



To a solution of methyl 3-cyano-1H-indole-4-carboxylate (2 mmol, 1 equiv.) in dry CH_2Cl_2 (0.2 M), DIPEA (4 mmol, 2 equiv.), and 4-DMAP (0.2 mmol, 0.1 equiv.) are added under argon atmosphere. Then, a solution of $PhNTf_2$ (2.6 mmol, 1.3 equiv.) in dry CH_2Cl_2 (0.8 M) is added to the mixture. The resulting mixture is allowed to stir at room temperature until the reaction is complete. The reaction is quenched with a saturated aqueous solution of $NaHCO_3$, extracted 3 times with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The crude mixture is purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 9:1, R_f = 0.60 Toluene / Ethyl Acetate 9:1) to afford the desired product as white solid (520 mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) NMR 8.20-8.18 (m, 1H), 8.17 (m, 1H), 8.13 (s, 1H), 7.64 (m, 1H), 4.08 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 165.5, 137.03, 135.48, 129.14, 127.46, 125.42, 125.00, 119.29 (q, *J* = 324 Hz), 118.15, 113.11, 98.36, 51.87 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR -74.6 ppm. IR (neat) nmax = 3127, 2919, 2233, 1711, 1417, 1204, 1133, 1028, 754, 618 cm^{-1}. HRMS TOF MS AP+ m/z calcd for $C_{12}H_8N_2O_4F_3S$: 333.0157 $[M+H]^+$; found: 333.0168. Mp = 113°C.

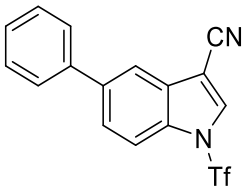
5-Nitro-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2h)



To a solution of 5-nitro-1H-indole-3-carbonitrile (1 equiv.) in dry CH_2Cl_2 (0.2 M), DIPEA (2 equiv.), and 4-DMAP (0.1 equiv.) are added under argon atmosphere. Then, a solution of

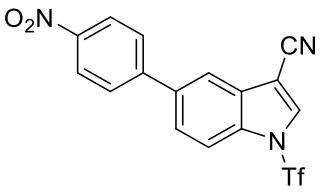
$PhNTf_2$ (1.3 equiv.) in dry CH_2Cl_2 (0.8 M) is added to the mixture. The resulting mixture is allowed to stir at room temperature until the reaction is complete. The reaction is quenched with a saturated aqueous solution of $NaHCO_3$, extracted 3 times with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (Toluene / Ethyl Acetate 9:1, R_f = 0.52 100% Toluene) to afford the desired product as white solid (536 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.76 (dd, *J* = 2.2, 0.6 Hz, 1H), 8.48 (dd, *J* = 9.2, 2.2 Hz, 1H), 8.14 – 8.09 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.4, 137.3, 135.9, 128.6, 123.2, 119.3 (q, *J* = 324 Hz), 117.3, 115.1, 110.9, 98.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR -74.5 ppm. IR (neat) nmax = 3144, 2249, 1530, 1426, 1211, 1111, 783, 733, 609, 581 cm^{-1}. HRMS TOF MS AP- m/z calcd for $C_{10}H_5N_3O_5F_3S$: 335.9902 $[M+H_2O-H]^-$; found: 335.9915. Mp = 101°C.

5-Phenyl-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2i)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 5:5, R_f = 0.5 Toluene / Cyclohexane 5:5) to afford the desired product as white solid (625 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) NMR 7.96 – 7.89 (m, 2H), 7.87 (s, 1H), 7.72 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.49 – 7.30 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.3, 139.6, 133.8 (2C), 133.6, 129.2 (2C), 128.8, 128.2, 127.5 (2C), 119.4 (q, *J* = 324 Hz), 119.0, 114.4, 112.2, 97.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR -74.8 ppm. IR (neat) nmax = 3154, 2233, 1419 1215, 1195, 1141, 1118, 1085, 761, 611, 595 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{16}H_9F_3N_2O_2S$: 367.0364 $[M+ H_2O-H]^-$; found: 367.0359. Mp = 111°C.

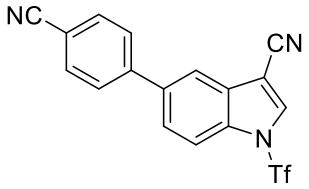
5-(4-Nitrophenyl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2j)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 7:3 to 9:1, R_f =

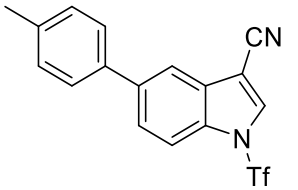
0.4 Toluene / Cyclohexane 8:2) to afford the desired product as white yellowish solid (563 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.39-8.36 (m, 2H), 8.07 (d, *J* = 8.8 Hz, 1H), 8.03 (dd, *J* = 1.8, 0.7 Hz, 1H), 8.00 (s, 1H), 7.84 – 7.81 (m, 2H), 7.81 – 7.78 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 147.8, 146.0, 137.8, 134.6, 134.1, 128.9, 128.4 (2C), 127.6, 124.5 (2C), 119.7, 119.38 (q, *J* = 324 Hz), 115.0, 111.9, 97.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.7 ppm. IR (neat) nmax = 3122, 3089, 2244, 1425, 1346, 1214, 1142, 1116, 1082, 807, 752, 618, 583 cm^{-1}. HRMS TOF MS AP- m/z calcd for $C_{16}H_9N_3O_5F_3S$: 412.0215 $[M+H_2O-H]^{- -}$; found: 412.0203. Mp = 197 °C.

5-(4-Cyanophenyl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2k)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 9:1, R_f = 0.53 Toluene / Cyclohexane 9:1) to afford the desired product as white solid (665 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 8.8 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.84 – 7.71 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.0, 138.1, 134.4, 134.1, 132.9 (2C), 128.9, 128.2 (2C), 127.4, 119.5, 119.31 (q, *J* = 324 Hz), 118.6, 114.8, 112.0, 111.9, 97.9 ppm ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.7 ppm. IR (neat) nmax = 3305, 3104, 2957, 2225, 1421, 1232, 1204, 1138, 1109, 976, 852, 833, 804, 620 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{17}H_9N_3O_3F_3S$: 392.0317 $[M+H_2O-H]^{-}$; found: 392.0320. Mp = 173 °C.

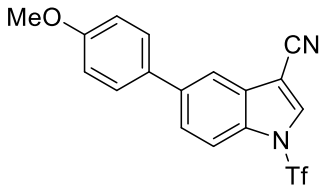
5-(*p*-Tolyl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2l)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 9:1, R_f = 0.59 Toluene / Cyclohexane 9:1) to afford the desired product as white solid (646 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00 – 7.94 (m, 2H), 7.93 (s, 1H), 7.77 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H) ppm. ^{13}C NMR (75 MHz,

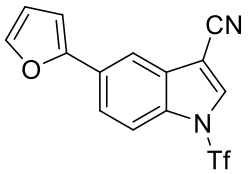
$CDCl_3$) d = 140.2, 138.2, 136.7, 133.6, 133.5, 129.9 (2C), 128.8, 127.4, 127.4 (2C), 119.41 (q, *J* = 324 Hz), 118.7, 114.34, 112.2, 97.9, 21.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.8 ppm. IR (neat) nmax = 3154, 2238, 1420, 1216, 1114, 975, 802, 622, 582 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{17}H_{12}N_2O_3F_3S$: 381.0521 $[M+H_2O-H]^-$; found: 381.0512. Mp = 106 °C.

5-(4-Methoxyphenyl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2m)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 9:1, R_f = 0.51 Toluene / Cyclohexane 9:1) to afford the desired product as white solid (655 mg, 86% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.9 Hz, 1H), 7.94-7.91 (m, 2H), 7.74 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.08 – 6.98 (m, 2H), 3.88 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 159.9, 139.9, 133.5, 133.4, 132.0, 128.8, 128.6 (2C), 127.2, 119.39 (q, *J* = 324 Hz), 118.4, 114.6 (2C), 114.3, 112.2, 97.9, 55.5 ppm ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.8 ppm. IR (neat) nmax = 3120, 3082, 2235, 1423, 1234, 199, 1165, 1117, 1082, 832, 801, 618, 582, 525 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{17}H_{12}N_2O_4F_3S$: 397.0470 $[M+H_2O-H]^-$; found: 397.0459. Mp = 146 °C.

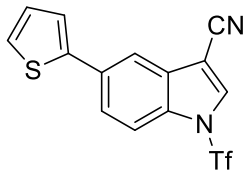
5-(Furan-2-yl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2n)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 8:2, R_f = 0.65 Toluene / Cyclohexane 8:2) to afford the desired product as yellow solid (598 mg, 88% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 8.07 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.97 – 7.89 (m, 2H), 7.86 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.54 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.79 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.3, 143.2, 133.7, 133.4, 129.8, 128.7, 124.1, 119.4 (q, *J* = 324 Hz), 115.5, 114.5, 112.2, 112.1, 106.7, 97.9 ppm ^{19}F NMR

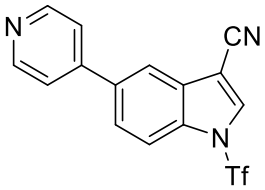
(282 MHz, $CDCl_3$) δ = -74.8 ppm. IR (neat) nmax = 3147, 2946, 2240, 1425, 1204, 1115, 975, 807, 798, 733, 626, 619, 580 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{13}H_7N_2O$: 207.0558 $[M\text{-}CF_3O_2S]^-$; found: 207.0565. Mp = 92°C.

5-(Thiophen-2-yl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2o)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 8:2, R_f = 0.67 Toluene / Cyclohexane 8:2) to afford the desired product as white solid (632 mg, 89% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.99 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.80 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.41 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.38 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.5, 133.8, 133.6, 133.5, 128.8, 128.52, 126.4, 126.3, 124.5, 119.38 (q, *J* = 324 Hz), 117.6, 114.6, 112.1, 97.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.8 ppm. IR (neat) nmax = 3158, 3104, 2973, 2859, 2235, 1600, 1464, 1418, 1212, 1141, 1114, 965, 809, 612 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{13}H_7N_2S$: 223.0330 $[M\text{- }CF_3O_2S]^-$; found: 223.0323. Mp = 132 °C.

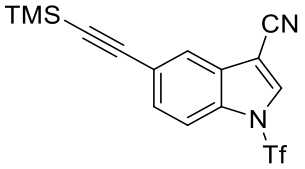
5-(Pyridin-4-yl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole-3-carbonitrile (2p)



To a solution of methyl 3-cyano-1H-indole-4-carboxylate (2 mmol, 1 equiv.) in dry CH_2Cl_2 (0.2 M), DIPEA (4 mmol, 2 equiv.), and 4-DMAP (0.2 mmol, 0.1 equiv.) are added under argon atmosphere. Then, a solution of $PhNTf_2$ (2.6 mmol, 1.3 equiv.) in dry CH_2Cl_2 (0.8 M) is added to the mixture. The resulting mixture is allowed to stir at room temperature until the reaction is complete. The reaction is quenched with a saturated aqueous solution of $NaHCO_3$, extracted 3 times with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 6:5 then DCM/MeOH 99:1, R_f = 0.35 DCM/MeOH 99:1) to afford the desired product as white solid (553 mg, 79% yield). ^1H NMR (300 MHz, $CDCl_3$) δ = 8.77 – 8.71 (m, 2H), 8.09 – 8.02 (m,

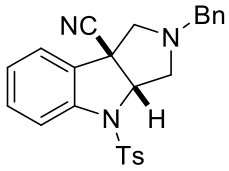
2H), 7.99 (s, 1H), 7.82 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.59 – 7.53 (m, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.7 ppm^{13}C NMR (75 MHz, $CDCl_3$) δ =150.6 (2C), 146.7, 137.1, 134.7, 134.0, 128.9, 127.1 (2C), 121.9, 119.3 (q, *J* = 324 Hz), 119.2, 114.8, 111.8, 97.8 ppm IR (neat) nmax = 2979, 2859, 2235, 1420, 1209, 1120, 974, 809, 690, 611 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{14}H_8N_3$: 218.0718 [M- CF_3O_2S]$^-$; found: 218.0713. Mp = 186 °C.

1-((Trifluoromethyl)sulfonyl)-5-((trimethylsilyl)ethynyl)-1*H*-indole-3-carbonitrile (2q)



The target compound was prepared according to the general procedure B. The crude mixture was purified by flash chromatography on silica gel (Toluene / Cyclohexane 8:2 to 9:1, R_f = 0.64 Toluene / Cyclohexane 9:1) to afford the desired product as white solid (673 mg, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 – 7.90 (m, 2H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 0.28 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) d = 133.9, 133.8, 131.7, 128.2, 124.4, 122.1, 119.3 (q, *J* = 324 Hz), 114.1, 111.7, 103.1, 97.6, 96.6, -0.06 (3C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -74.8 ppm. IR (neat) nmax = 3138, 2238, 2150, 1459, 1426, 1207, 1112, 885, 842, 813, 611, 588, 524 cm^{-1}. HRMS TOF MS AP- m/z calcd for $C_{15}H_{14}N_2O_3F_3Si$: 387.0447 [M+H_2O-H]$^{--}$; found: 387.0455. Mp = 91 °C.

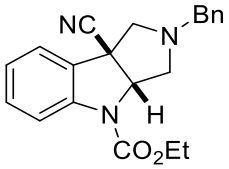
(3a*R,8b*S**)-2-Benzyl-4-tosyl-2,3,3a,4-tetrahydropyrrolo[3,4-b]indole-8b(1*H*)-carbonitrile (3a)**



The target compound was prepared according to the general procedure C. The crude mixture was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 8:2) followed by a second purification on silica gel (Cyclohexane/EtOAc/DCM 3:1:1, R_f = 0.64 Dichloromethane 100%) to afford the desired product as white solid (94 mg, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.06 (m, 10H), 4.83 (dd, *J* = 5.5, 4.0 Hz, 1H), 3.63 (s, 2H), 3.16 – 3.10 (m, 2H), 3.06 (d, *J* = 9.3

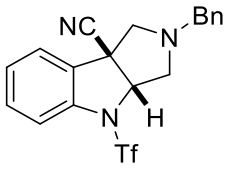
Hz, 1H), 2.94 (d, *J* = 9.3 Hz, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.1, 142.3, 137.0, 133.5, 130.4, 130.1 (2C), 129.9, 128.6 (4C), 127.6, 127.2 (2C), 125.5, 124.3, 119.7, 116.3, 70.6, 64.5, 61.8, 58.0, 47.3, 21.7. IR (neat) ν max = 1757, 1549,1487, 1357, 1171 cm^{-1}. HMRS TOF MS ES+ m/z calcd for $C_{25}H_{24}N_3O_2S$: 430.1584 $[M+H]^+$; found :430.1576. Mp = 163 °C.

Ethyl (3a*R,8b*S**)-2-benzyl-8b-cyano-2,3,3a,8b-tetrahydropyrrolo[3,4-b]indole-4(1*H*)-carboxylate (3c)**



The target compound was prepared according to the general procedure C. The crude mixture was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 9:1) followed by a second purification on silica gel (Cyclohexane/EtOAc/DCM 9:0.5:0.5, R_f = 0.22 Cyclohexane/EtOAc 9:1) to afford the desired product as yellowish oil (71 mg, 41 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 – 7.35 (m, 2H), 7.35 – 7.25 (m, 4H), 7.24 – 7.16 (m, 2H), 7.10 (td, *J* = 7.5, 1.1 Hz, 1H), 5.16 – 5.03 (m, 1H), 4.32 (m, 2H), 3.65 (s, 2H), 3.21 – 2.93 (m, 2H), 1.33 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.1, 130.2, 128.5 (4C), 127.4 (2C), 123.7 (2C), 120.6, 115.2 (2C), 100.0, 68.4, 65.1, 62.0, 61.2, 58.0, 14.6 ppm. (NCO2Et not observed) IR (neat) nmax = 2979, 2801, 2238, 1704, 1601, 1485, 1403, 1381, 1255, 1153, 1068, 750, 698 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{21}H_{22}N_3O_2$: 348.1712 $[M+H]^+$; found: 348.1706.

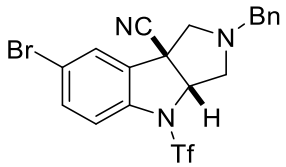
(3a*R,8b*S**)-2-Benzyl-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3d)**



The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene 100%, , R_f = 0.43 Toluene 100%) to afford the desired product as colorless oil (163-179 mg, 80-88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) NMR 7.51 (d, *J* = 8.3 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.34-7.23 (m,

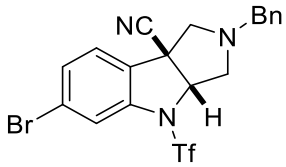
4H), 7.19 – 7.11 (m, 2H), 5.15 (dd, *J* = 6.3, 2.7 Hz, 1H), 3.66 (d, *J* = 15 Hz, 1H), 3.61 (d, *J* = 15 Hz, 1H), 3.18 – 3.12 (m, 2H), 3.12 – 3.00 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.8, 136.6, 130.8, 129.2, 128.6 (2C), 128.5 (2C), 127.7 (2C), 126.6, 124.7, 120.1 (q, *J* = 325 Hz), 119.1, 114.9, 71.4, 64.4, 57.7, 47.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR (282 MHz, CDCl64.4, 5nmax = 2807, 2238, 1481, 1462, 1402, 1227, 1196, 1141, 1049, 750, 699, 602, 573, 526 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{19}H_{17}N_3F_3O_2S$: 408.0994 $[M+H]^+$; found: 408.0989.

(3a*R,8b*S**)-2-Benzyl-7-bromo-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-b]indole-8b(1*H*)-carbonitrile (3e)**



The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene/Ethyl Acetate 9:1, R_f = 0.40 Cyclohexane/Ethyl acetate 9:1) to afford the desired product as white solid (C: 224 mg, 92% yield. D: 209 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) NMR 7.54 – 7.47 (m, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.27 (m, 3H), 7.17 – 7.10 (m, 2H), 5.12 (d, *J* = 5.8 Hz, 1H), 3.67 – 3.61 (m, 2H), 3.19 – 3.11 (m, 2H), 3.06 (d, *J* = 9.6 Hz, 1H), 2.97 (dd, *J* = 11.1, 5.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.1, 136.3, 133.9, 131.2, 128.7 (2C), 128.5 (2C), 127.8 (2C), 119.9 (q, *J* = 326 Hz), 119.2, 118.4, 116.3, 71.8, 64.2, 61.2, 57.6, 47.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR (282 MHz, CDCl, 71.8,nmax = 2811, 2249, 1473, 1403, 1227, 1198, 1143, 731, 600, 576 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{19}H_{16}BrN_3F_3O_2S$: 486.0099 $[M+H]^+$; found: 486.0082. Mp = 49 ° C.

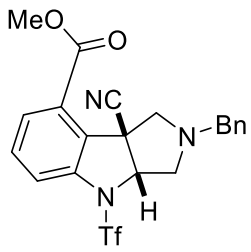
(3a*R,8b*S**)-2-Benzyl-6-bromo-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3f)**



The target compound was prepared according to the general procedure C. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 9:1, R_f = 0.48 Toluene/Cyclohexane 9:1) to afford the desired product as white solid (192 mg, 79% yield).

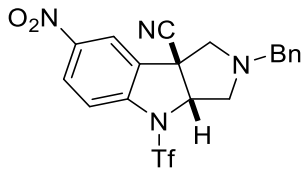
^{1}H NMR (300 MHz, , $CDCl_3$) δ = 7.68-7.61 (m, 1H), 7.40 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.14 (m, 2H), 5.17-5.07 (m, 1H), 3.66 (d, *J* = 13.2 Hz, 1H), 3.61 (d, *J* = 13.2 Hz, 1H), 3.17 (dd, *J* = 11.0, 2.3 Hz, 1H), 3.13 (d, *J* = 9.5 Hz, 1H), 3.03 (d, *J* = 9.5Hz, 1H), 2.97 (dd, *J* = 11.0, 5.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.1, 136.3, 129.8, 128.6 (2C), 128.4 (2C), 128.3, 127.7, 125.7, 124.6, 119.9 (q, *J* = 326.0 Hz), 118.4, 118.1, 71.9, 64.1, 61.2, 57.6, 47.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -72.3 ppm. IR (neat) nmax = 2811, 2244, 1594, 1477, 1404, 1227, 1198, 1141, 1049, 736, 699, 609, 576 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{19}H_{16}BrN_3F_3O_2S$: 486.0099 $[M+H]^+$; found: 486.0099. Mp = 49 ° C.

Methyl (3a*R,8b*S**)-2-benzyl-8b-cyano-4-((trifluoromethyl)sulfonyl)-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole-8-carboxylate (3g)**



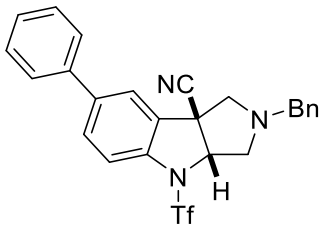
The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene/Ethyl acetate 95:5, R_f = 0.41 Toluene/Cyclohexane 95:5) to afford the desired product as a colorless oil (C: 231 mg, 93% yield. D: 205 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.95 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.23 – 7.16 (m, 2H), 5.18 (dd, *J* = 6.2, 4.7 Hz, 1H), 3.96 (s, 3H), 3.68 – 3.58 (m, 3H), 3.24 (dd, *J* = 10.4, 6.2 Hz, 1H), 3.04 (d, *J* = 10.4 Hz, 1H), 2.81 (dd, *J* = 10.4, 4.7 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.6, 141.1, 136.7, 131.3, 129.8, 128.6 (2C), 128.5 (2C), 128.4, 127.7, 127.4, 120.0 (q, *J* = 326 Hz), 119.5, 119.3, 72.1, 65.2, 60.5, 57.7, 52.7, 48.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -72.1 ppm. IR (neat) nmax = 2923, 2853, 1725, 1451, 1404, 1282, 1196, 1136, 1066, 756, 700, 606, 575 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{21}H_{19}N_3F_3O_4S$: 466.1048 $[M+H]^+$; found: 466.1032.

(3a*R,8b*S**)-2-Benzyl-7-nitro-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3h)**



The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 9:1, R_f = 0.36 Toluene/Cyclohexane 9:1) to afford the desired product as a white solid (C: 121 mg, 73% yield. D: 170 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.33 (dd, *J* = 9.0, 2.3 Hz, 1H), 8.27 (dd, *J* = 2.3, 0.5 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.33-7.27 (m, 3H), 7.16 – 7.09 (m, 2H), 5.21 (d, *J* = 5.8 Hz, 1H), 3.66 (s, 2H), 3.32 – 3.23 (m, 2H), 3.06 (d, *J* = 9.7 Hz, 1H), 2.95 (dd, *J* = 11.4, 5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.9, 145.1, 135.9, 130.8, 128.7 (2C), 128.5 (2C), 128.0 (2C), 127.0, 120.8, 117.8, 114.7, 72.6, 64.3, 57.5, 47.0, 29.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR (282 MHz, CDCl8, 114.nmax = 2918, 2851, 1731, 1523, 1342, 1228, 1197, 1128, 1043, 704, 604, 579 cm^{-1}. HRMS TOF MS ES- m/z calcd for $C_{19}H_{14}N_4F_3O_4S$: 451.0688 $[M-H]^-$; found: 451.0676. Mp = 183 ° C.

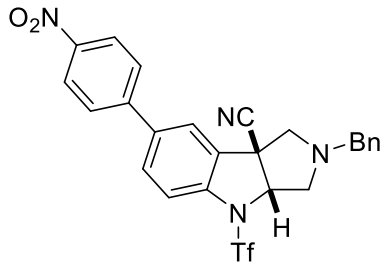
(3a*R,8b*S**)-2-Benzyl-7-phenyl-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3i)**



The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 9:1, R_f = 0.36 Toluene/Cyclohexane 9:1) to afford the desired product as white solid (C: 234 mg, 97% yield. D: 234 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.62 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.58 – 7.50 (m, 3H), 7.50 – 7.42 (m, 2H), 7.42 – 7.35 (m, 1H), 7.33 – 7.27 (m, 3H), 7.14-7.17 (m, 3H), 5.17 (m, 1H), 3.66 (s, 2H), 3.19 (d, *J* = 9.4 Hz, 1H), 3.16 – 3.10 (m, 2H), 3.05 (dd, *J* = 10.9, 6.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.3, 139.3, 139.1, 136.6, 129.9, 129.8, 129.1 (2C), 128.7 (2C), 128.5 (2C), 128.1, 127.8, 127.1 (2C), 123.2, 120.2 (q, *J* = 327 Hz), 119.2, 115.2, 71.8, 64.5, 61.4, 57.7, 47.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -72.3

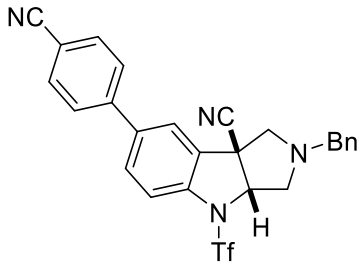
ppm. IR (neat) nmax = 2809, 1479, 1402, 1227, 1200, 1145, 1051, 761, 697, 574 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{25}H_{21}F_3N_3O_2S$: 484.1307 $[M+H]^+$; found: 484.1318. Mp = 62 ° C.

(3a*R,8b*S**)-2-Benzyl-7-(4-nitrophenyl)-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3j)**



The target compound was prepared according to the general procedure C and E. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 9:1, R_f = 0.19 Toluene/Cyclohexane 9:1) to afford the desired product as a yellow powder (C: 238 mg, 95% yield. E: 227 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.33 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.68 – 7.57 (m, 3H), 7.28 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.14-7.16 (m, 2H), 5.18-5.20 (m, 1H), 3.67 (s, 2H), 3.24 – 3.17 (m, 2H), 3.13 (d, *J* = 9.5 Hz, 1H), 3.04 (dd, *J* = 11.0, 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.5, 145.5, 140.5, 137.5, 136.4, 130.5, 130.1, 128.6, 128.5 (2C), 127.8 (2C), 127.7 (2C), 124.4 (2C), 123.5, 118.8, 115.4, 71.9, 64.4, 61.3, 57.6, 47.5 ppm (CF_3 non observed). ^{19}F NMR (282 MHz, $CDCl_3$) δ = ppm. IR (neat) nmax = 2822, 1594, 1510, 1479, 1510, 1389, 1337, 1226, 1142, 1050, 821, 754, 703, 630, 616, 599, 578 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{25}H_{20}F_3N_4O_4S$: 529.1157 $[M+H]^+$; found: 529.1151. Mp = 189 ° C.

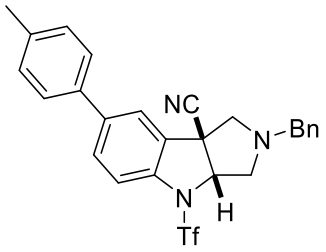
(3a*R,8b*S**)-2-Benzyl-7-(4-cyanophenyl)-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3k)**



The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene/Ethyl Acetate 95:5 R_f =

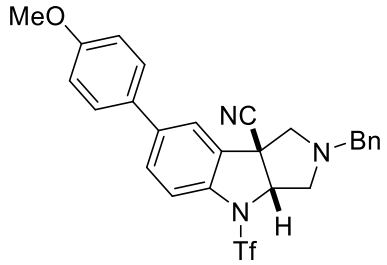
0.47 Toluene/Ethyl Acetate 95:5) to afford the desired product as a white solid (C: 238 mg, 94% yield. D: 215 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.62 – 7.53 (m, 3H), 7.37 – 7.27 (m, 3H), 7.14 (dd, *J* = 6.9, 2.7 Hz, 2H), 5.16-5.20 (m, 1H), 3.66 (s, 2H), 3.24 – 3.07 (m, 3H), 3.04 (dd, *J* = 11.1, 6.2 Hz, 1H). ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.6, 140.3, 137.9, 136.4, 132.9 (2C), 130.5, 129.9, 128.6 (2C), 128.5 (2C), 127.8, 127.7 (2C), 125.7, 123.4, 120.0 (q, *J* = 324 Hz), 118.9, 118.7, 115.4, 111.7, 71.9, 64.4, 57.6, 47.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR -72.4 ppm. IR (neat) nmax = 2924, 2221, 1606, 1483, 1409, 1208, 1147, 822, 698, 597 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{26}H_{20}F_3N_4O_2S$: 509.1259 $[M+H]^+$; found: 509.1247. Mp = 159 ° C.

(3a*R,8b*S**)-2-Benzyl-7-(*p*-tolyl)-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3l)**



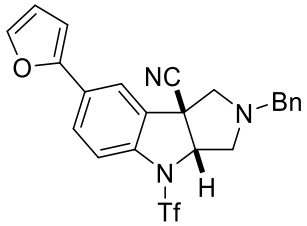
The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene 100% R_f = 0.52 Toluene/Cyclohexane 9:1) to afford the desired product as a white solid (C: 205 mg, 91% yield. D: 214 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.59 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.27 (m, 5H), 7.15 (m, 2H), 5.15-5.17 (m, 1H), 3.66 (s, 2H), 3.16-3.12 (m, 3H), 3.06 (dd, *J* = 10.9, 6.0 Hz, 1H), 2.41 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.2, 138.7, 137.9, 136.5, 136.4, 129.8 (2C), 129.5 (2C), 128.6 (2C), 128.5 (2C), 127.7 (2C), 126.8 (2C), 122.9, 119.2, 115.1, 71.7, 64.5, 57.7, 47.6, 21.2 ppm (CF_3 not observed). ^{19}F NMR (282 MHz, $CDCl_3$) δ = -72.2 ppm. IR (neat) nmax = 2924, 2806, 2214, 1481, 1401, 1231, 1196, 1101, 1058, 810, 701, 592, 572 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{26}H_{23}F_3N_3O_2S$: 498.1463 $[M+H]^+$; found: 498.1449. Mp = 137 ° C.

(3a*R,8b*S**)-2-benzyl-7-(4-methoxyphenyl)-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3m)**



The target compound was prepared according to the general procedure C. The crude mixture was purified by flash chromatography on silica gel (Toluene 100% R_f = 0.52 Toluene/Cyclohexane 9:1) to afford the desired product as a white solid (C: 239 mg, 93% yield, D: 208 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.25-7.30 (m, 4H), 7.19 – 7.14 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 5.14-5.18 (m, 1H), 3.86 (s, 3H), 3.66 (s, 2H), 3.17-3.12 (m, 3H), 3.06 (dd, *J* = 10.9, 6.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.7, 139.9, 138.4, 136.6, 131.8, 129.9, 129.2, 128.6 (2C), 128.5 (2C), 128.1 (2C), 127.7, 122.6, 122.3, 120.2 (q, *J* = 325 Hz), 119.2, 115.2, 114.5,71.8, 64.4, 61.3, 57.7, 55.4, 47.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -72.5 ppm. IR (neat) nmax = 3101, 3042, 2988, 2806, 2220, 1608, 1481, 1352, 1228, 1103, 1061, 942 ,810, 573 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{26}H_{23}F_3N_3O_3S$: 514.1412 $[M+H]^+$; found: 514.1415. Mp = 67 ° C.

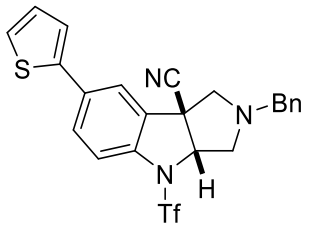
(3a*R,8b*S**)-2-Benzyl-7-(furan-2-yl)-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3n)**



The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 8:2 R_f = 0.33 Toluene/Cyclohexane 8:2) to afford the desired product as a white solid (C: 225mg, 95% yield. D: 204 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 – 7.64 (m, 2H), 7.52 – 7.45 (m, 2H), 7.31 – 7.26 (m, 3H), 7.15 (dd, *J* = 7.3, 2.2 Hz, 2H), 6.66 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.49 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.15 (d, *J* = 5.9 Hz, 1H), 3.71-3.57 (m, 2H), 3.21 – 3.09 (m, 3H), 3.03 (dd, *J* = 10.8, 5.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.2, 142.7,

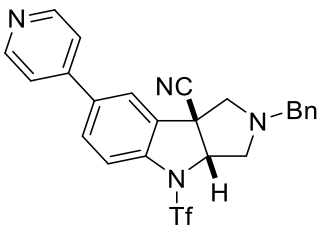
138.5, 136.5, 129.9, 129.8, 128.6 (2C), 128.5 (2C), 127.7, 126.3, 120.1 (q, J = 327 Hz), 119.8, 119.0, 115.2, 112.0, 105.9, 71.7, 64.4, 61.2, 57.7, 47.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR (282 MHz, CDCl, 112.0nmax = 3119, 2821, 2220, 1472, 1403, 1197, 1143, 1004, 733, 699, 618, 600 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{23}H_{19}F_3N_3O_3S$: 474.1099 $[M+H]^+$; found: 474.1087. Mp = 69 ° C.

(3a*R,8b*S**)-2-benzyl-7-(thiophen-2-yl)-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3o)**



The target compound was prepared according to the general procedure C. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 9:1 R_f = 0.41 Toluene/Cyclohexane 9:1) to afford the desired product as a white solid (C: 233 mg, 95% yield. D: 211 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.63 (dd, J = 8.6, 1.9 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.20 – 7.14 (m, 3H), 7.10 (dd, J = 5.1, 3.7 Hz, 1H), 5.15 (d, J = 5.9 Hz, 1H), 3.72-3.59 (m, 2H), 3.22 – 3.09 (m, 3H), 3.06 (dd, J =10.8, 5.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.2, 138.8, 136.4, 133.4, 130.1, 128.6 (2C), 128.4 (2C), 128.3, 127.7, 125.6, 123.9, 121.8, 120.1 (q, J = 326 Hz), 118.9, 115.2, 77.4, 71.7, 64.3, 61.1, 57.6, 47.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) NMR (282 MHz, CDCl(2C), 1nmax = 2810, 2214, 1484, 1399, 1232, 1195, 1141, 731, 699, 599, 576 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{23}H_{19}F_3N_3O_2S_2$: 490.0871 $[M+H]^+$; found: 490.0876. Mp = 96 ° C.

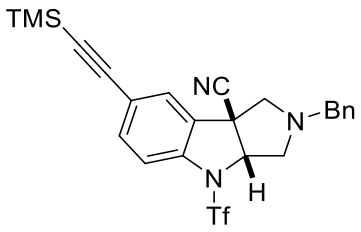
(3a*R,8b*S**)-2-Benzyl-7-(pyridin-4-yl)-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile. (3p)**



The target compound was prepared according to the general procedure C or D. The crude mixture was purified by flash chromatography on silica gel (Toluene/Ethyl Acetate 5:5 R_f =

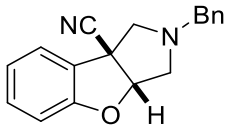
0.47 DCM/MeOH 1%) followed by a second purification (DCM/MeOH 1%) to afford the desired product as a white solid (C: 235 mg, 97% yield. D: 225 mg, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.70 (d, *J* = 5.6 Hz, 2H), 7.68 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.51 – 7.44 (m, 2H), 7.32-7.26 (m, 3H), 7.15 (dd, *J* = 7.1, 2.5 Hz, 2H), 5.19 (d, *J* = 5.9 Hz, 1H), 3.66 (s, 2H), 3.27 – 3.09 (m, 3H), 3.04 (dd, *J* = 11.0, 5.9 Hz, 1H). ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.2, 138.8, 136.4, 133.4 (2C), 130.1 (2C), 128.6 (2C), 128.4 (2C), , 127.7 (2C), 125.6, 123.9, 121.8, 120.1 (q, *J* = 326 Hz), 118.9, 115.2, 71.7, 64.3, 61.1, 57.6, 47.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -72.3 ppm. IR (neat) nmax = 3024, 2815, 1597, 1481, 1397, 1229, 1198, 1144, 1008, 808, 693, 611, 601 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{24}H_{20}F_3N_4O_2S$: 485.1259 $[M+H]^+$; found: 485.1259. Mp = 136 ° C.

(3a*R,8b*S**)-2-benzyl-4-((trifluoromethyl)sulfonyl)-7-((trimethylsilyl)ethynyl)-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indole-8b(1*H*)-carbonitrile (3q)**



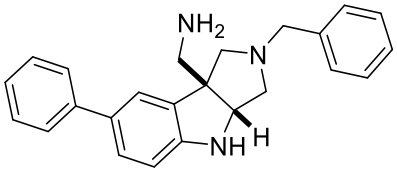
The target compound was prepared according to the general procedure C. The crude mixture was purified by flash chromatography on silica gel (Toluene/Cyclohexane 8:2, R_f = 0.44 Toluene/Cyclohexane 8:2) to afford the desired product as a colorless solid (C: 232 mg, 92% yield. D: 229 mg, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51 – 7.45 (m, 2H), 7.41-7.39 (m, 1H), 7.35 – 7.27 (m, 3H), 7.16-7.10 (m, 2H), 5.11 (d, *J* = 6.0 Hz, 1H), 3.63 (s, 2H), 3.19 – 3.09 (m, 2H), 3.06 (d, *J* = 9.5 Hz, 1H), 2.97 (dd, *J* = 11.0, 6.0 Hz, 1H), 0.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.7, 136.4, 134.6, 129.6, 128.6 (2C), 128.5 (2C), 128.2, 127.8, 121.7, 120.0 (q, *J* = 326 Hz), 118.6, 114.7, 103.1, 96.1, 71.8, 64.4, 61.2, 57.7, 47.3, -0.11 (3C). ^{19}F NMR (282 MHz, $CDCl_3$) δ = -72.4 ppm. IR (neat) nmax = 2960, 2804, 2163, 1482, 1404, 1208, 1143, 1049, 867, 840, 758, 699, 602, 573 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{24}H_{25}F_3N_3O_2SSi$: 504.1389 $[M+H]^+$; found: 504.1395. Mp = 50 ° C.

(3a*R,8b*R**)-2-Benzyl-1,2,3,3a-tetrahydro-8b*H*-benzofuro[2,3-*c*]pyrrole-8b-carbonitrile (3r)**



The target compound was prepared according to the general procedure C. The crude mixture was purified by flash chromatography on silica gel (Toluene/Ethyl Acetate 9:1 R_f = 0.62 Toluene/Ethyl Acetate 9:1) followed by a second purification (DCM/MeOH 1%) to afford the desired product as a white solid (125 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.32 – 7.26 (m, 3H), 7.26 – 7.23 (m, 2H), 7.21 – 7.14 (m, 2H), 6.97 (td, *J* = 7.5, 1.0 Hz, 1H), 6.83 (dt, *J* = 8.1, 0.8 Hz, 1H), 5.42 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.65 (s, 2H), 3.25 – 3.15 (m, 2H), 2.96 (d, *J* = 9.5 Hz, 1H), 2.82 – 2.74 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.4, 137.1, 130.7, 128.5 (2C), 128.4 (2C), 127.5, 125.3, 124.0, 121.7, 120.2, 110.0, 90.1, 60.9, 60.6, 58.1, 49.1 ppm. IR (neat) nmax = 2958, 2923, 2786, 2244, 1597, 1480, 1461, 1251, 866, 763, 747, 701 462 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{18}H_{17}N_2O$: 277.1341 $[M+H]^+$; found: 277.1340. Mp = 93 ° C.

((3a*R,8b*S**)-2-Benzyl-7-phenyl-2,3,3a,4-tetrahydropyrrolo[3,4-*b*]indol-8b(1*H*)-yl)methanamine (5e)**

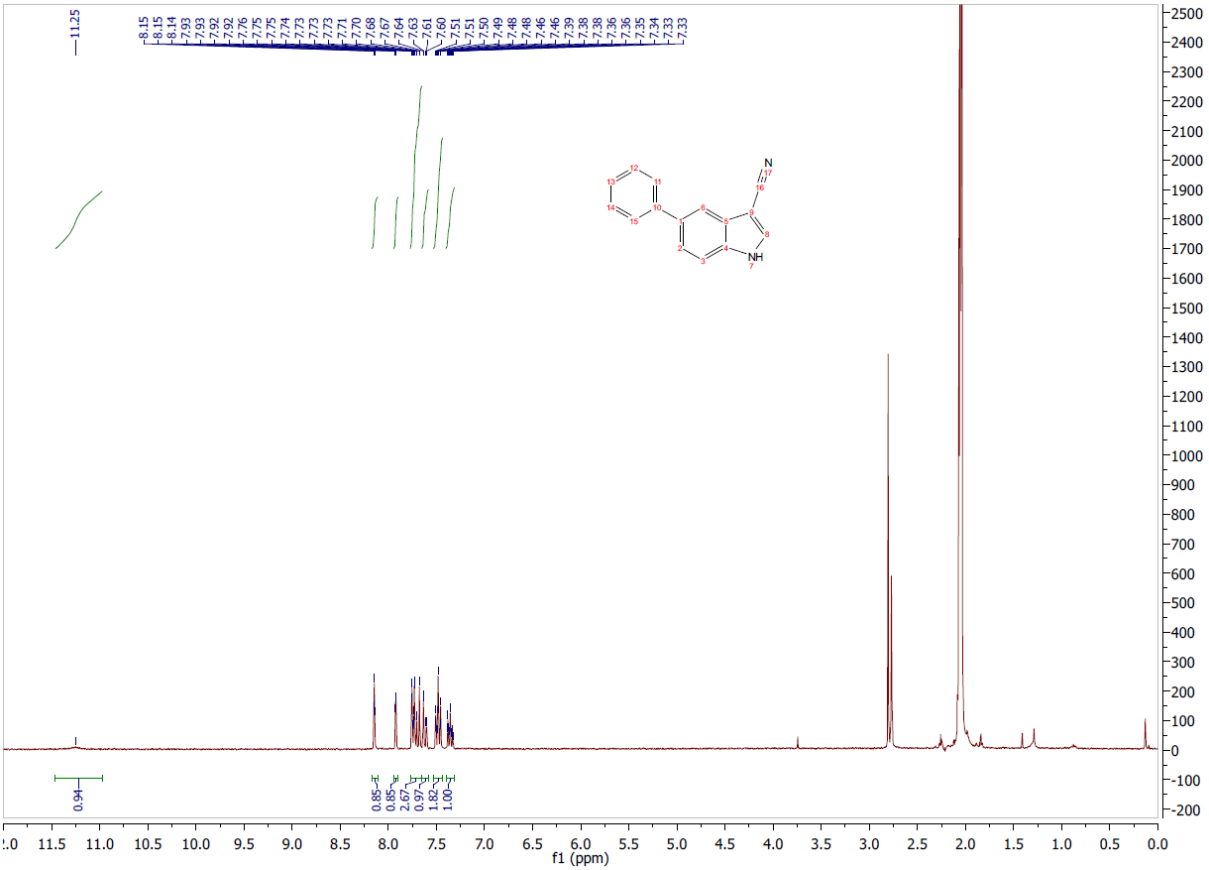


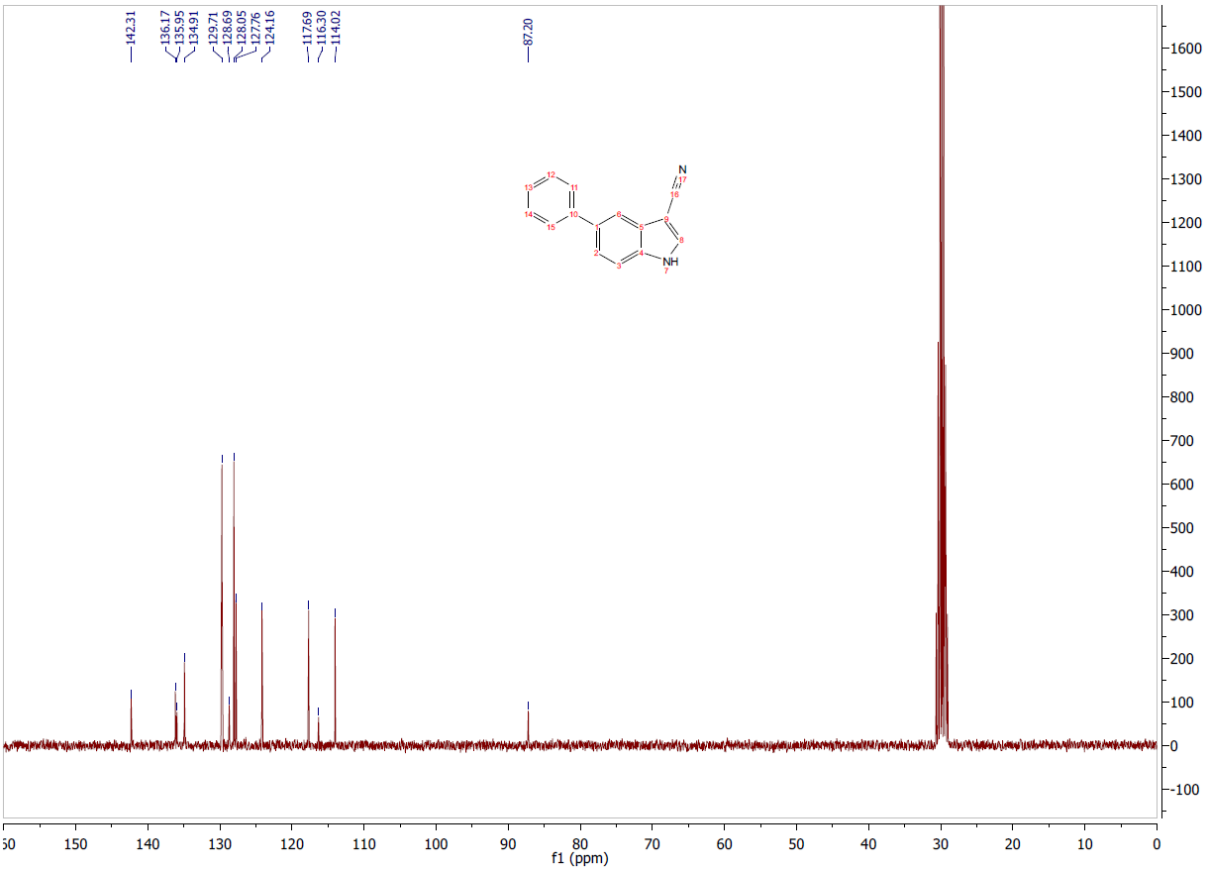
A solution of (3a*R**,8bI)*-2-benzyl-7-phenyl-4-((trifluoromethyl)sulfonyl)-2,3,3a,4-tetrahydropyrrolo[3,4-b]indole-8b(1H)-carbonitrile (0.25 mmol, 1 equiv.) in dry THF (2.5 mL) is added dropwise to a suspension of $LiAlH_4$ (1.00 mmol, 4 equiv.) in dry THF (2.5 mL) at 0°C. The reaction was then refluxed for 16h. Once completed, the reaction is quenched with water (1 mL), then NaOH 2N (1 mL) and H_2O (1 mL). The reaction mixture is dried over $MgSO_4$, filtered on celite and concentrated. The crude mixture was purified on silica gel (starting DCM/MeOH 1% to MeOH 100%), followed by a second purification on inverse phase (H_2O (w/ formic acid 0.5 %)/MeCN, starting from 95:5 to 100% MeCN over 30 min) to afford a white solid (66 mg, 95 % yield). ^{1}H NMR (300 MHz, CD_3CN) δ = 7.58 – 7.50 (m, 2H), 7.41 – 7.32 (m, 2H), 7.31 – 7.25 (m, 4H), 7.25 – 7.16 (m, 4H), 6.54 (dd, *J* = 7.6, 1.0 Hz,

1H), 4.65 (bs, 2H), 4.10 (dd, *J* = 5.7, 2.1 Hz, 1H), 3.59 (d, *J* = 13.0 Hz, 1H), 3.48 (d, *J* = 13.0 Hz, 1H), 2.98 (d, *J* = 12.9 Hz, 1H), 2.91 (d, *J* = 9.0 Hz, 1H), 2.80 (d, *J* = 12.9 Hz, 1H), 2.74 (dd, *J* = 9.7, 2.1 Hz, 1H), 2.53 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.48 (d, *J* = 9.0 Hz, 1H) ppm. (NH missing) ^{13}C NMR (75 MHz, CD_3CN) δ = 153.4, 142.7, 140.2, 135.5, 131.2, 129.8, 129.7 (2C), 129.1 (2C), 127.8, 127.6, 126.9 (2C), 126.8 (2C), 122.8 (2C), 109.1, 66.1 (2C), 64.3, 60.5, 49.6 ppm IR (neat) nmax = 3030, 2917, 2791, 1573, 1481, 1454, 1339, 1262, 762, 697 cm^{-1}. HRMS TOF MS ES+ m/z calcd for $C_{24}H_{26}N_3$: 356.2127 $[M+H]^+$; found: 356.2130. Mp = 57 ° C.

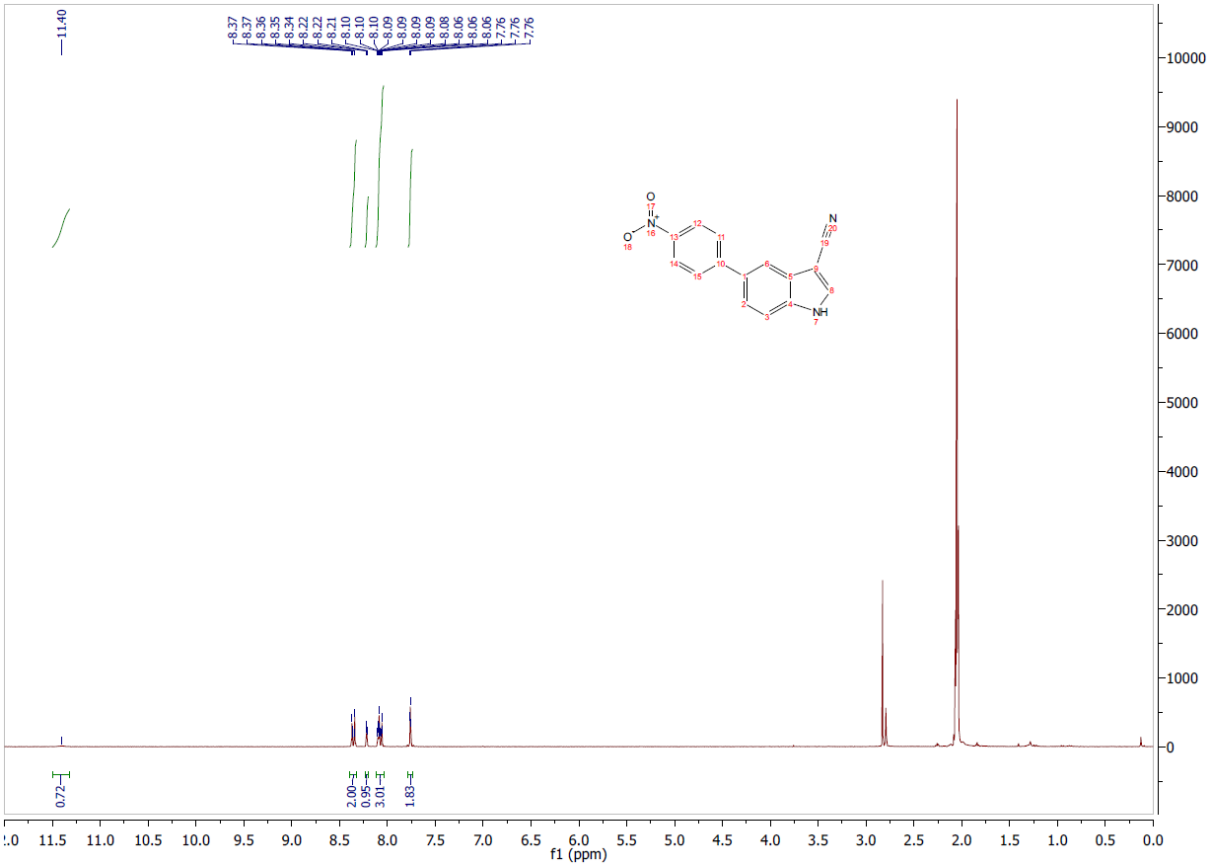
3. ^{1}H and ^{13}C NMR Spectra of all synthesized compounds:

1i:





1j: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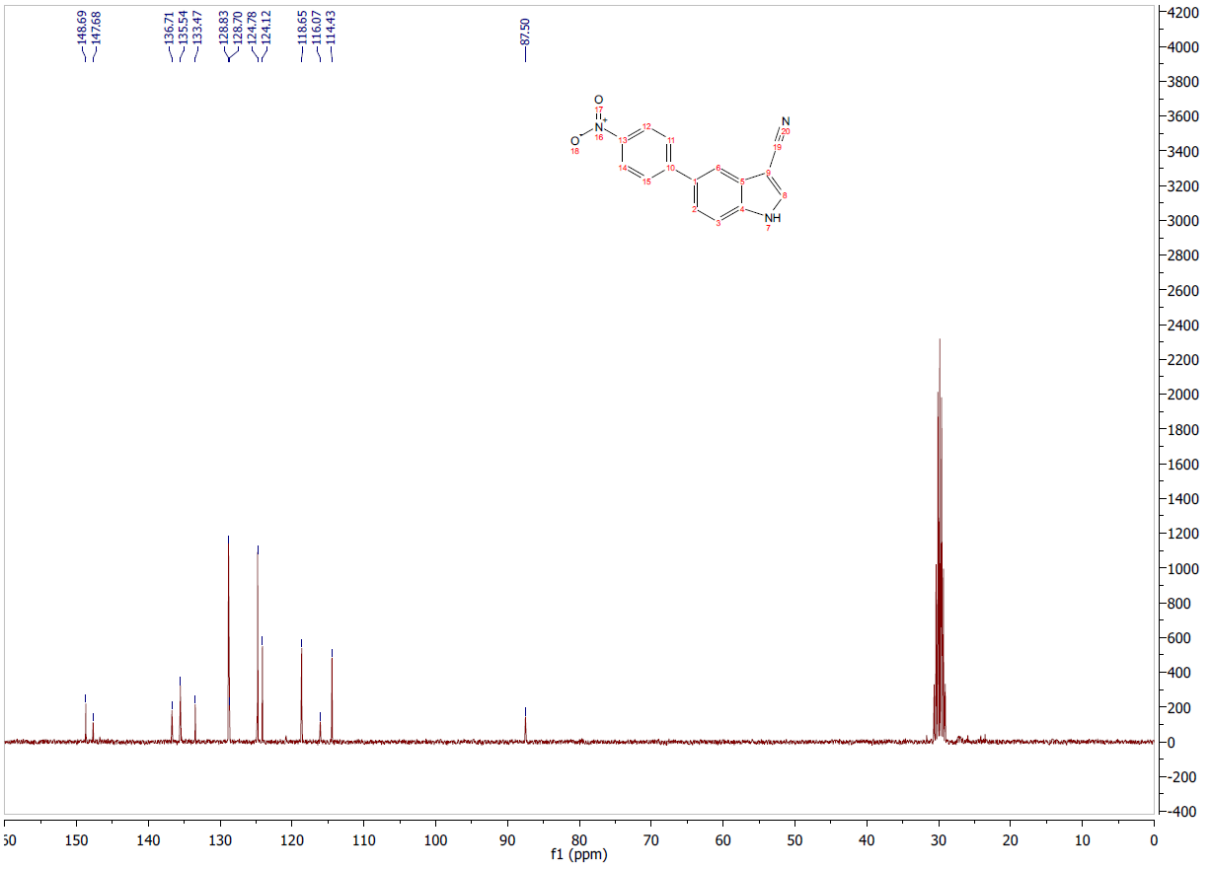
8.36
8.35
8.34
8.22
8.22
8.21
8.10
8.10
8.10
8.09
8.09
8.09
8.09
8.09
8.08
8.06
8.06
8.06
7.76
7.76
7.76
0.72
2.00
0.95
3.01
1.83
f1 (ppm)


148.69
147.68
136.71
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133.47
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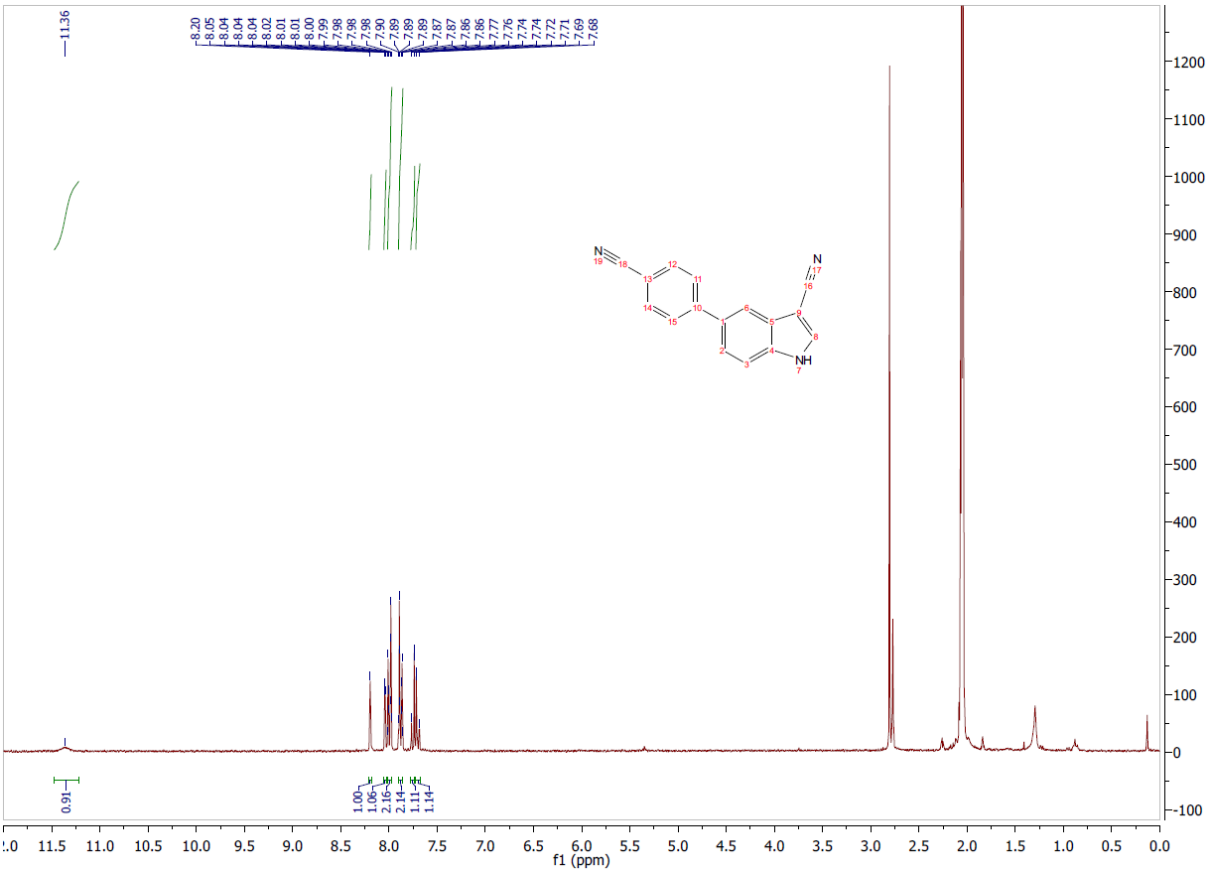
128.70
124.78
124.12
118.65
116.07
114.43
87.50
f1 (ppm)

1k: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8.04
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8.01
8.01
8.00
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7.98
7.90
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7.89
7.89
7.87
7.87
7.86
7.86
7.77
7.76
7.74
7.74
7.72
7.71
7.69
7.68
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1.00
1.06
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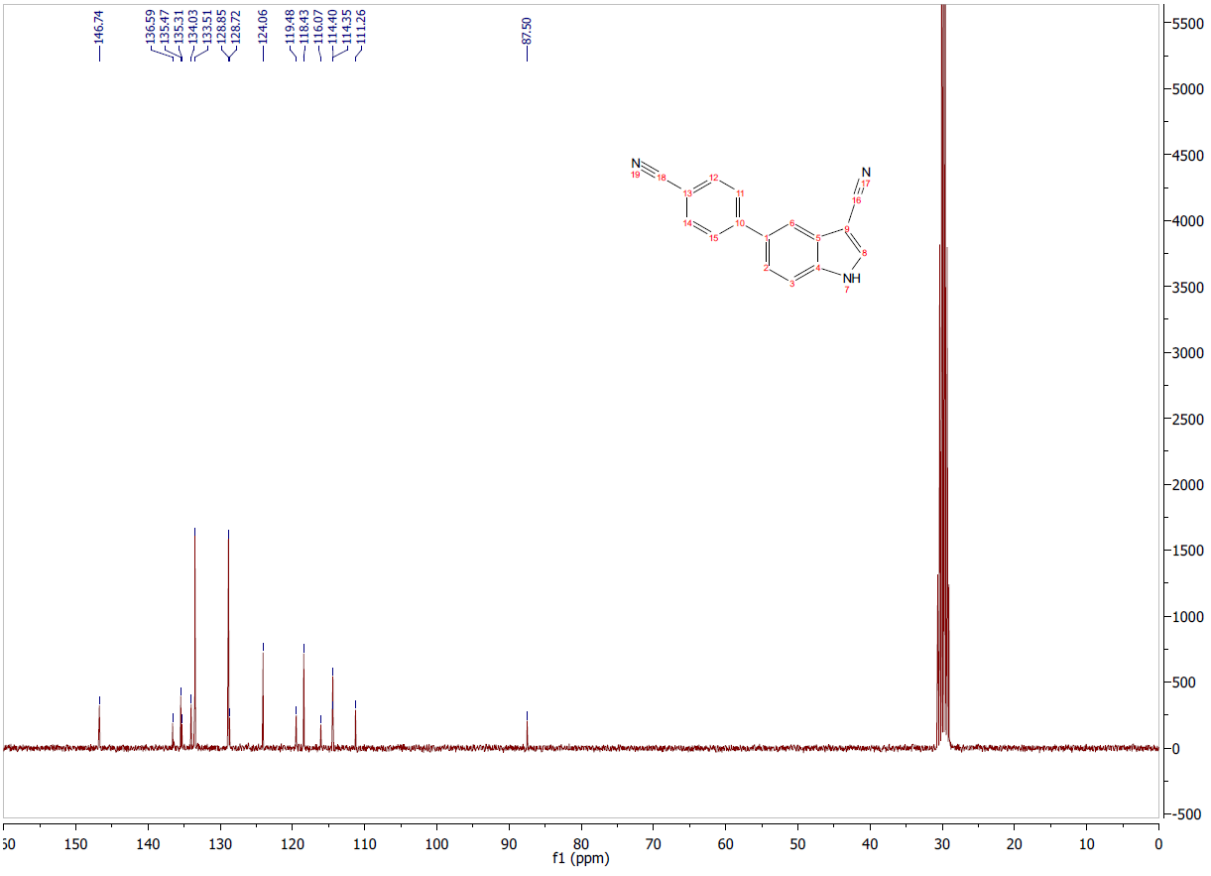
2.14
1.11
1.14
f1 (ppm)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133.51
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118.43
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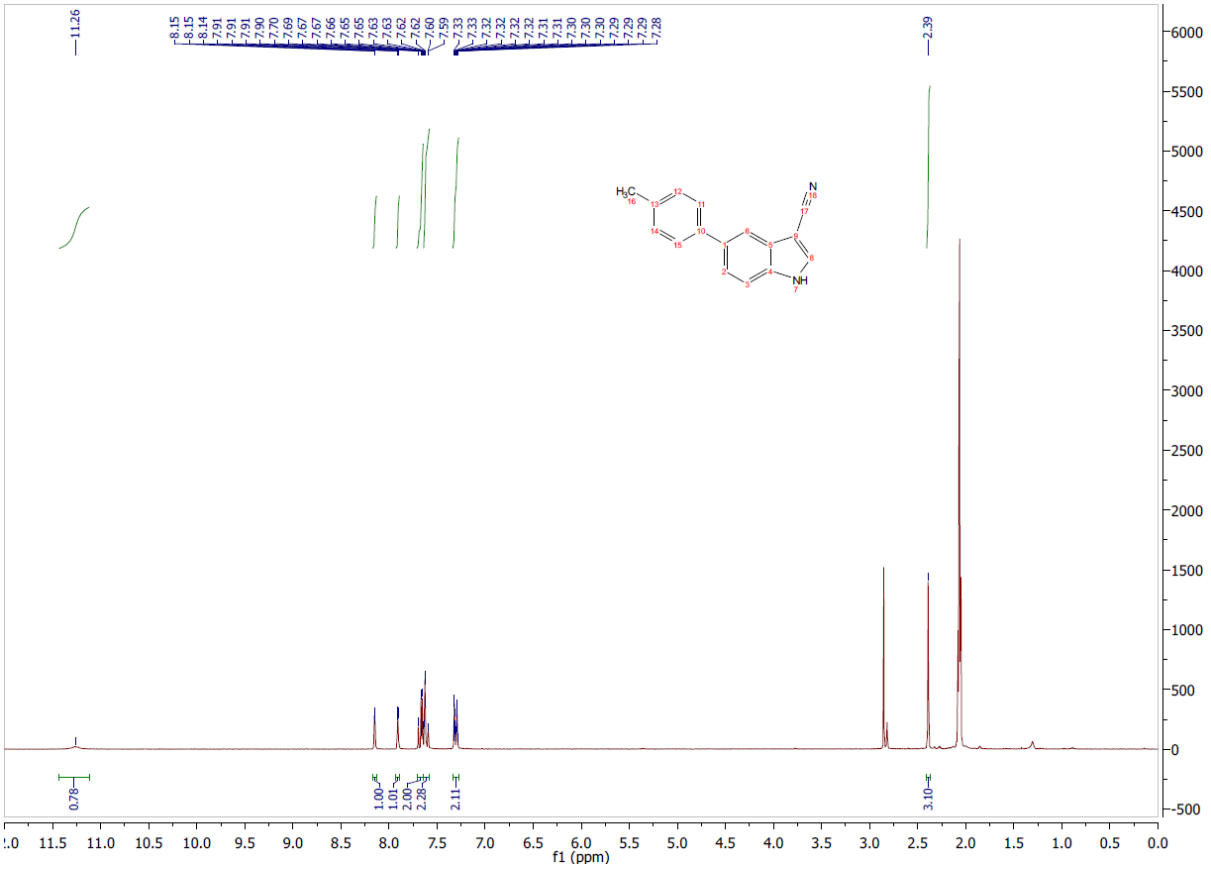
114.35
111.26
87.50
f1 (ppm)

1l: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7.90
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7.69
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7.63
7.63
7.62
7.62
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7.59
7.33
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.29
7.28
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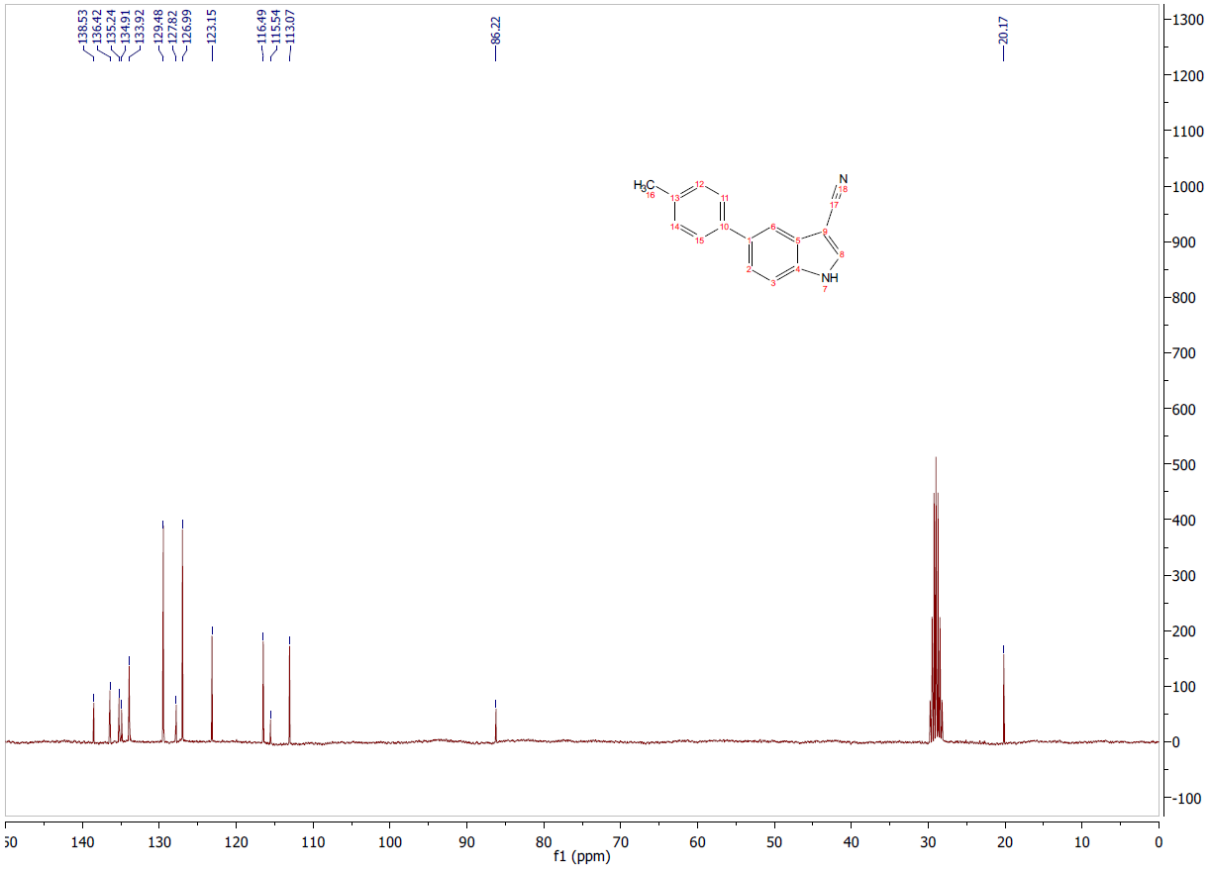
1.00
1.01
2.00
2.28
2.11
3.10
f1 (ppm)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134.91
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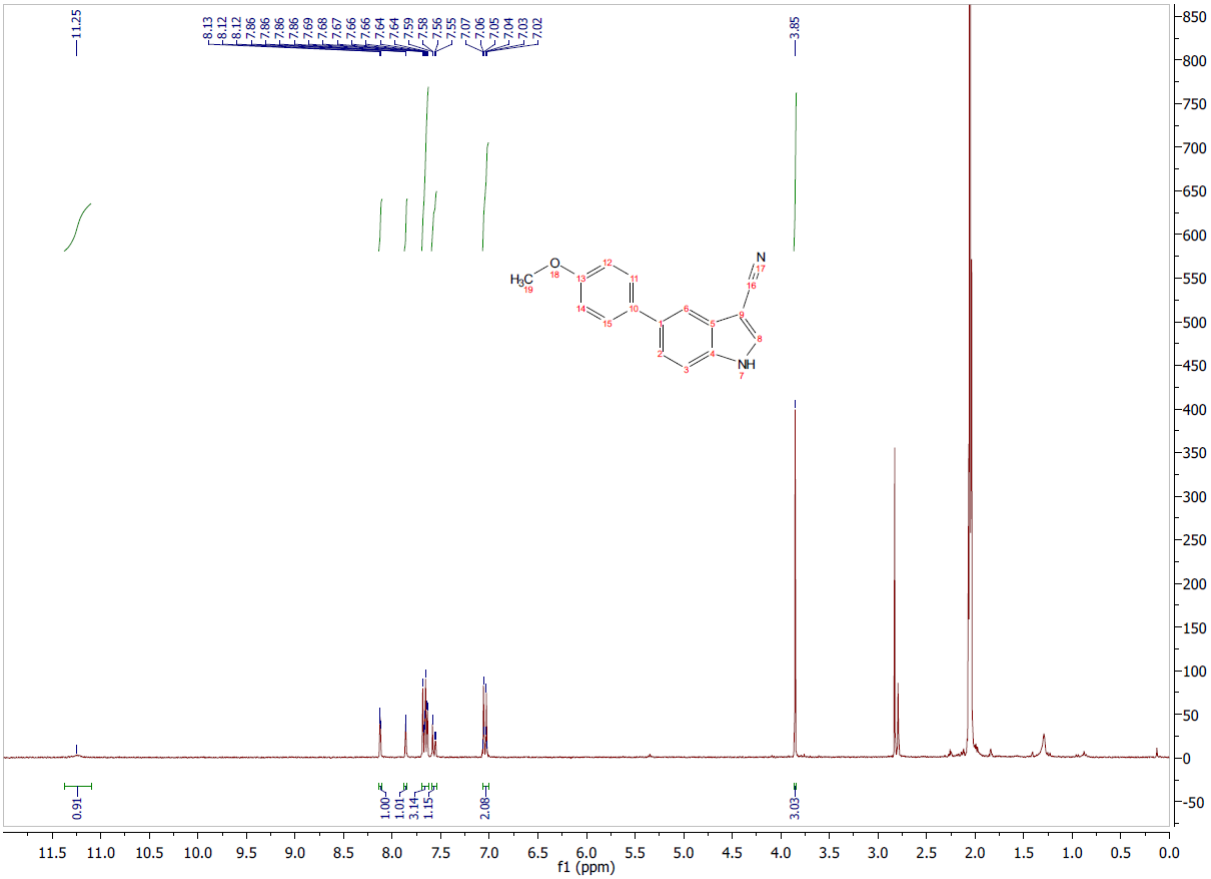
126.99
123.15
116.49
115.54
113.07
86.22
20.17
f1 (ppm)

1m: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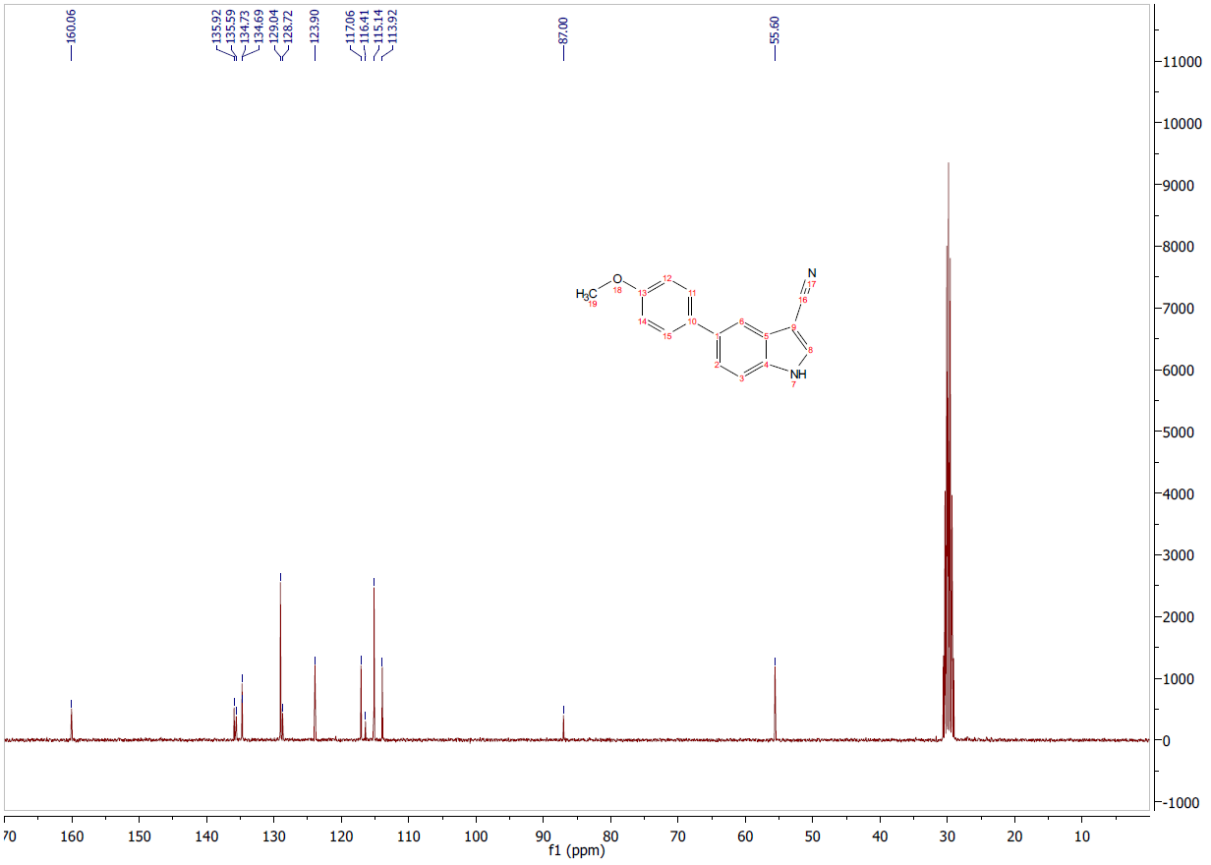
7.64
7.59
7.58
7.56
7.55
7.07
7.06
7.05
7.04
7.03
7.02
3.85
0.91
1.00
1.01
3.14
1.15
2.08
3.03
f1 (ppm)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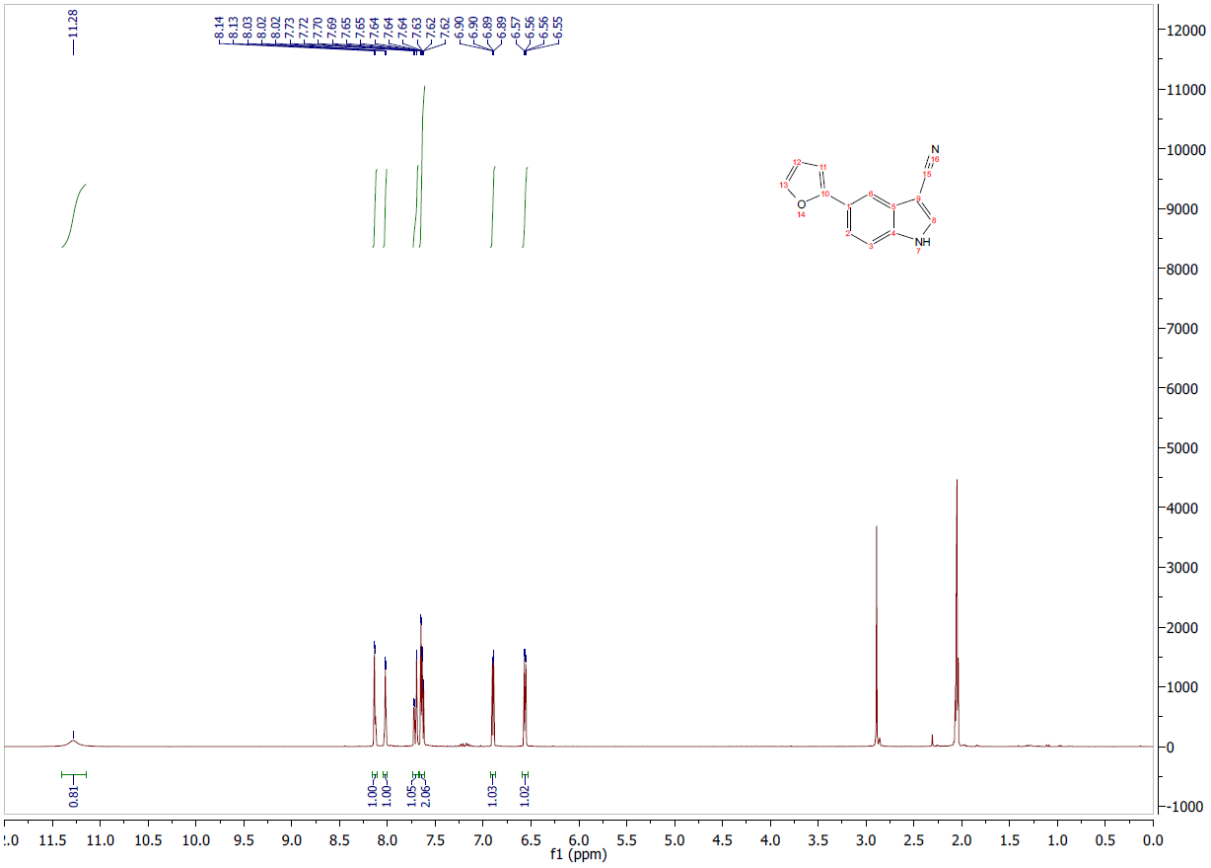
129.04
128.72
123.90
117.06
116.41
115.14
113.92
67.00
55.60
f1 (ppm)

1n: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8.02
8.02
7.73
7.72
7.70
7.69
7.65
7.65
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7.64
7.64
7.63
7.62
7.62
6.90
6.90
6.89
6.89
6.57
6.56
6.56
6.55
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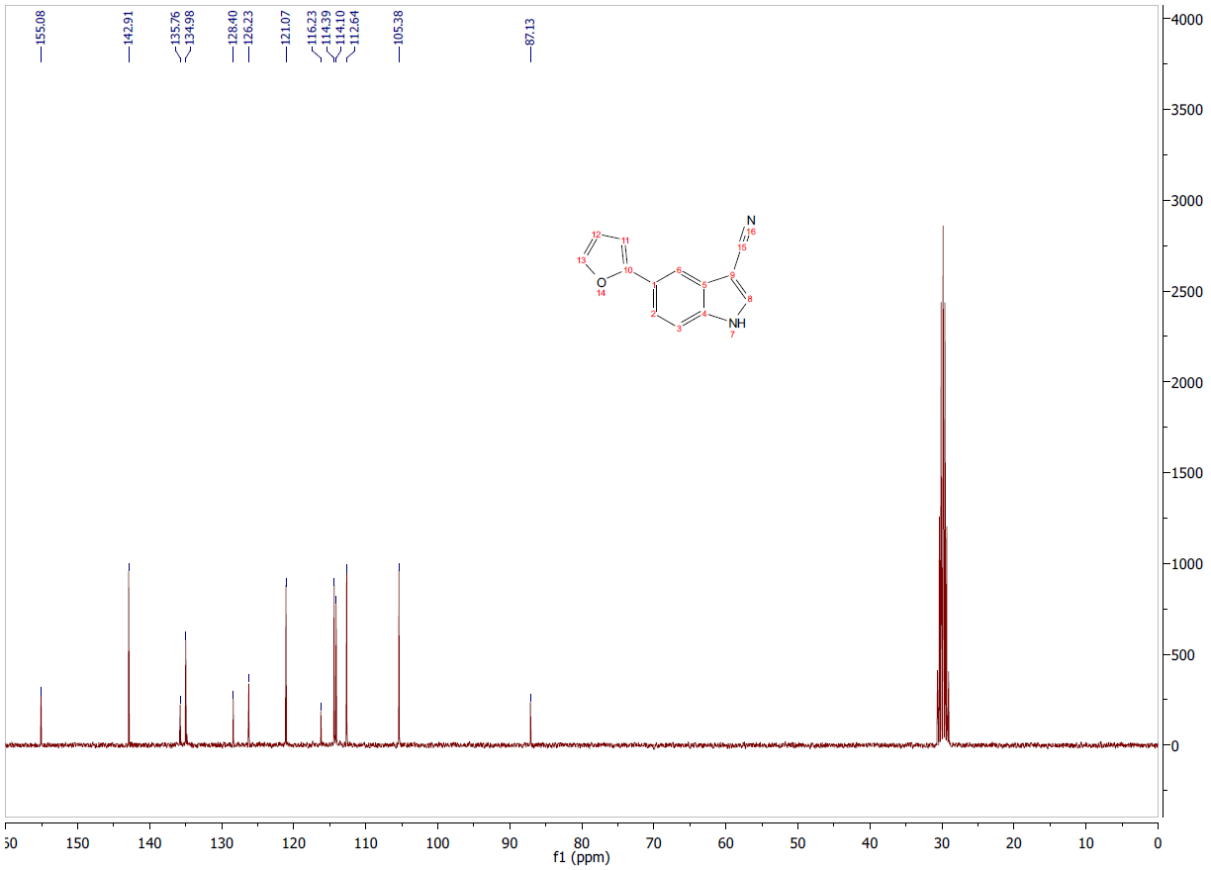
1.00
1.00
1.05
2.06
1.03
1.02
f1 (ppm)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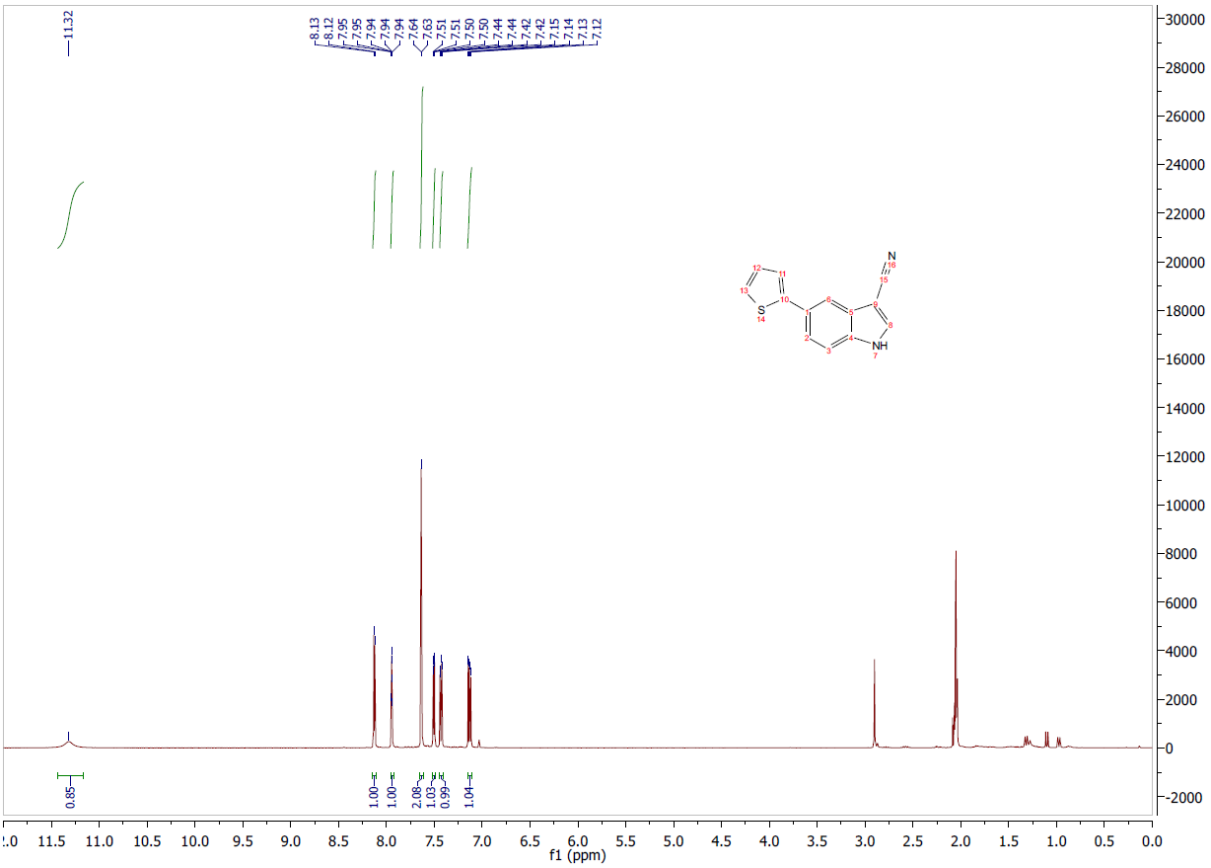
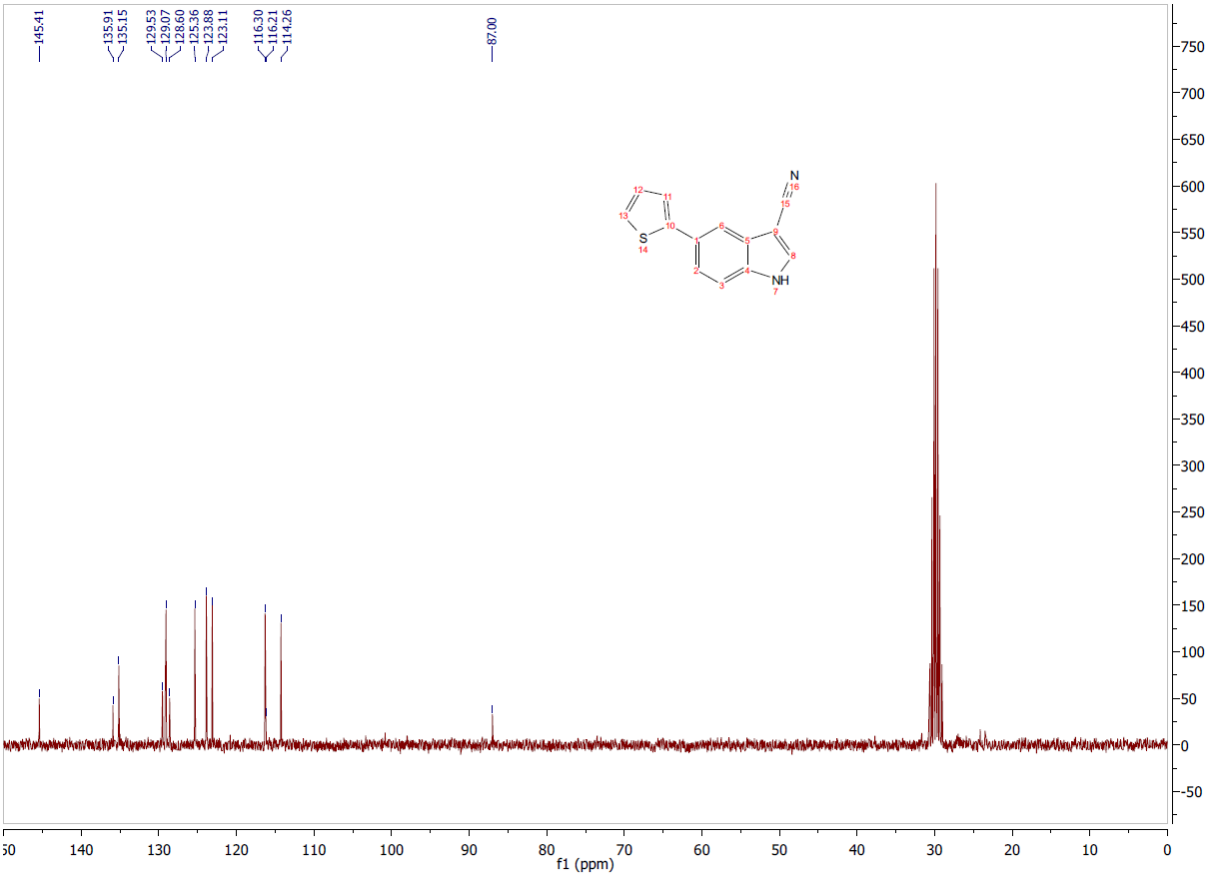
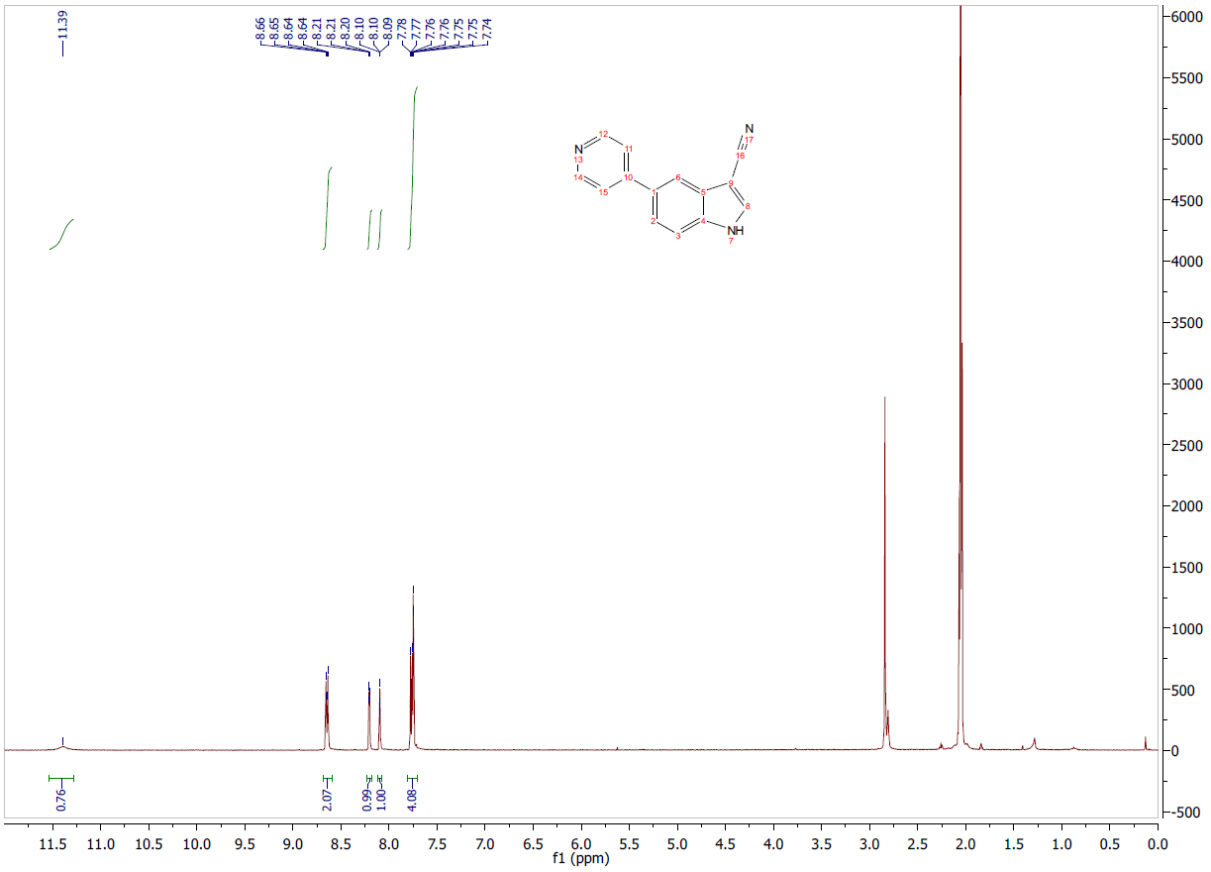
128.40
126.23
121.07
116.23
114.39
114.10
112.64
105.38
87.13
f1 (ppm)

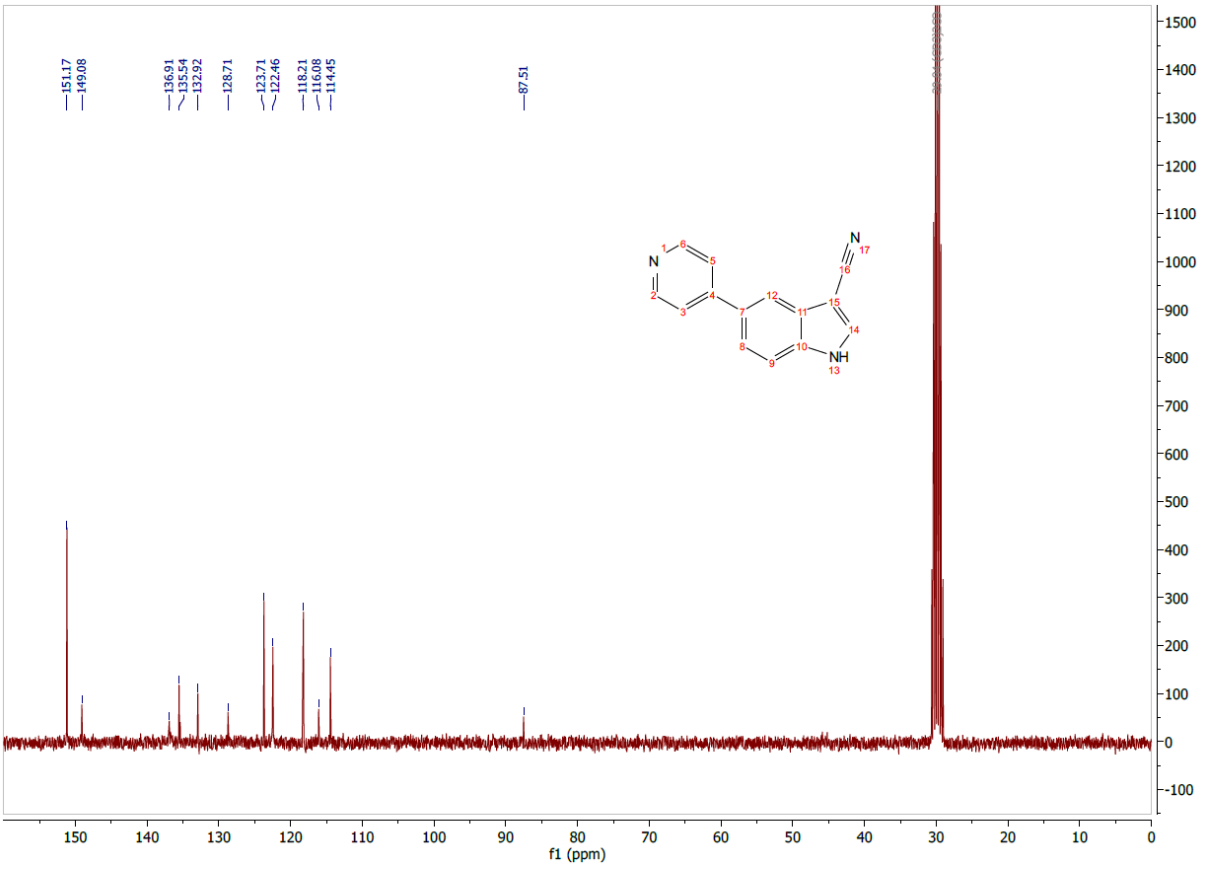
1o:


11.32
8.13
8.12
7.95
7.95
7.94
7.94
7.94
7.94
7.64
7.63
7.51
7.51
7.50
7.50
7.44
7.44
7.42
7.42
7.15
7.14
7.13
7.12
0.85
1.00
1.00
2.08
1.03
0.99
1.04
f1 (ppm)

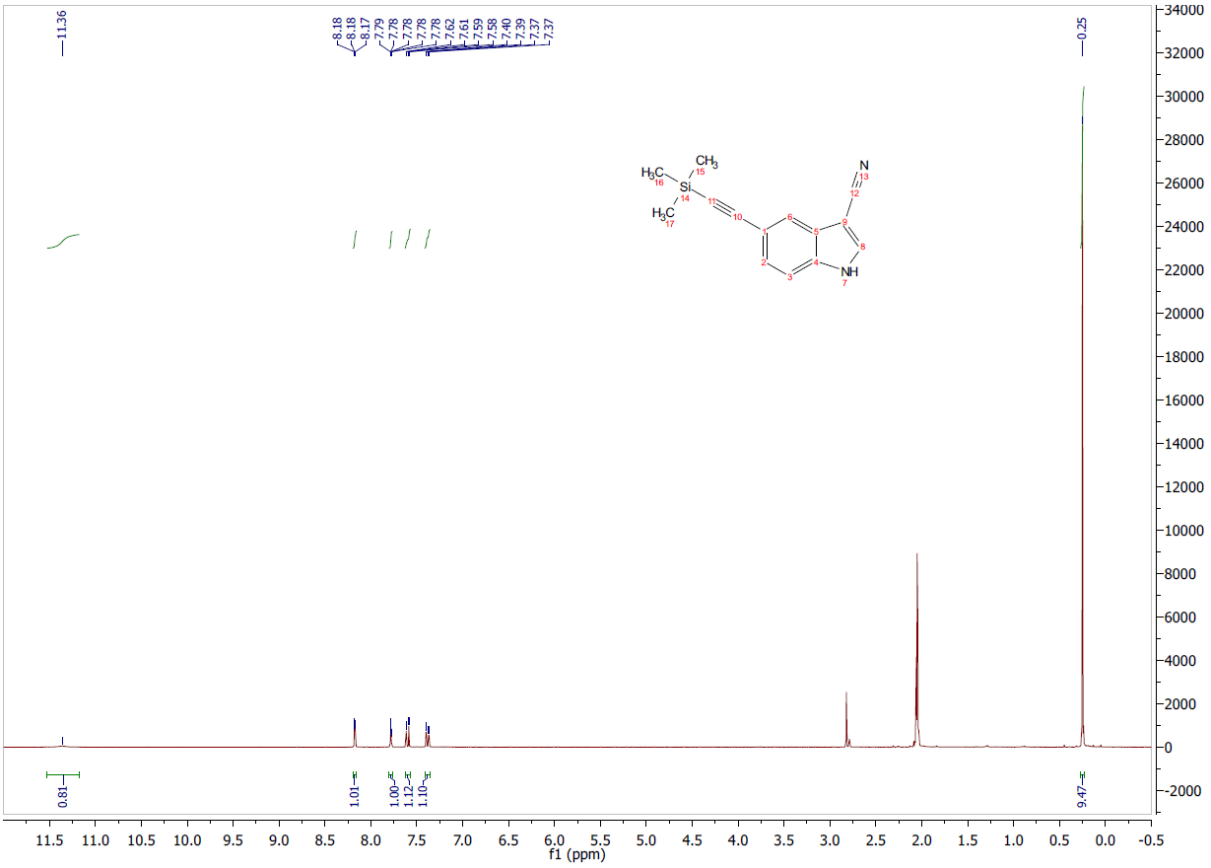

145.41
135.91
135.15
129.53
129.07
128.60
125.36
123.88
123.11
116.30
116.21
114.26
87.00
f1 (ppm)

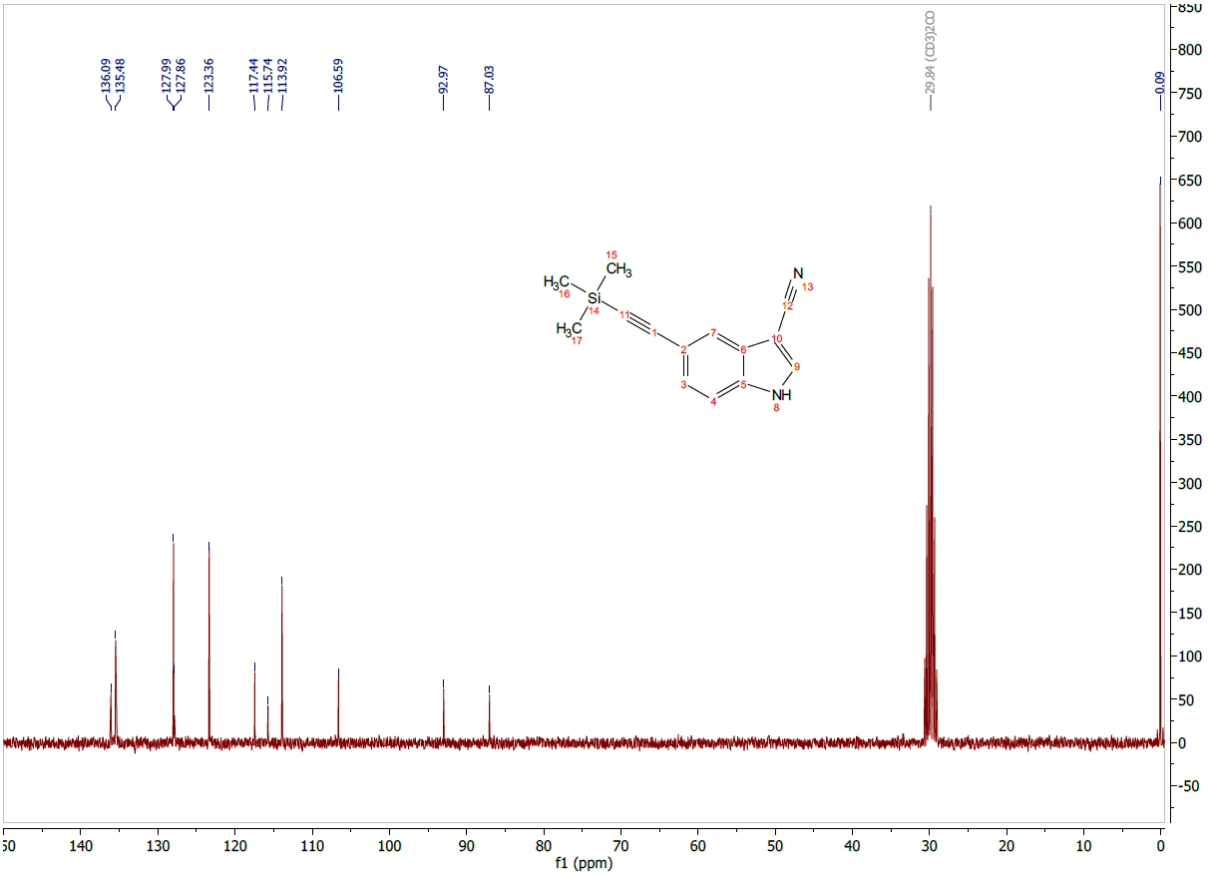
1p:


11.39
8.66
8.65
8.64
8.64
8.21
8.21
8.20
8.10
8.10
8.09
7.78
7.77
7.76
7.76
7.75
7.75
7.74
0.76
2.07
0.99
1.00
4.08
f1 (ppm)

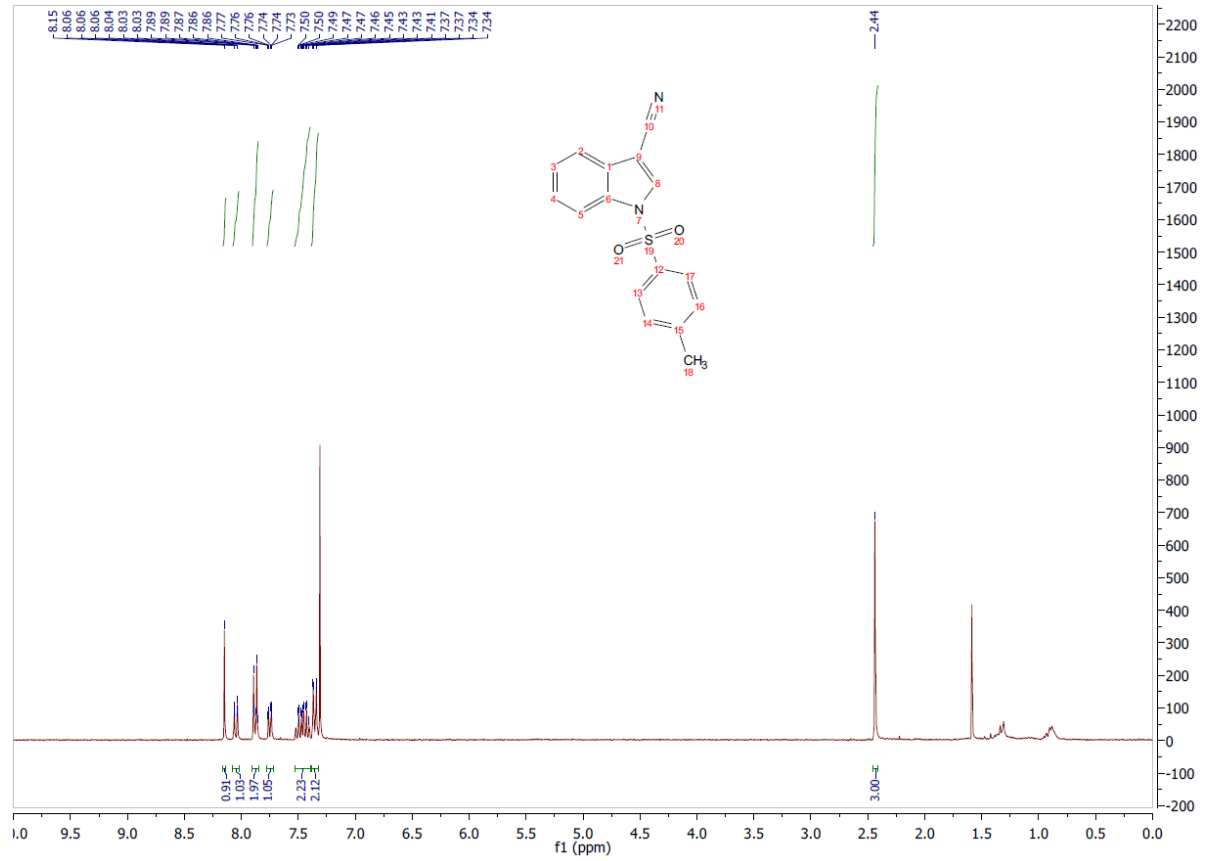

151.17
149.08
136.91
135.54
132.92
128.71
123.71
122.46
118.21
116.08
114.45
87.51
f1 (ppm)

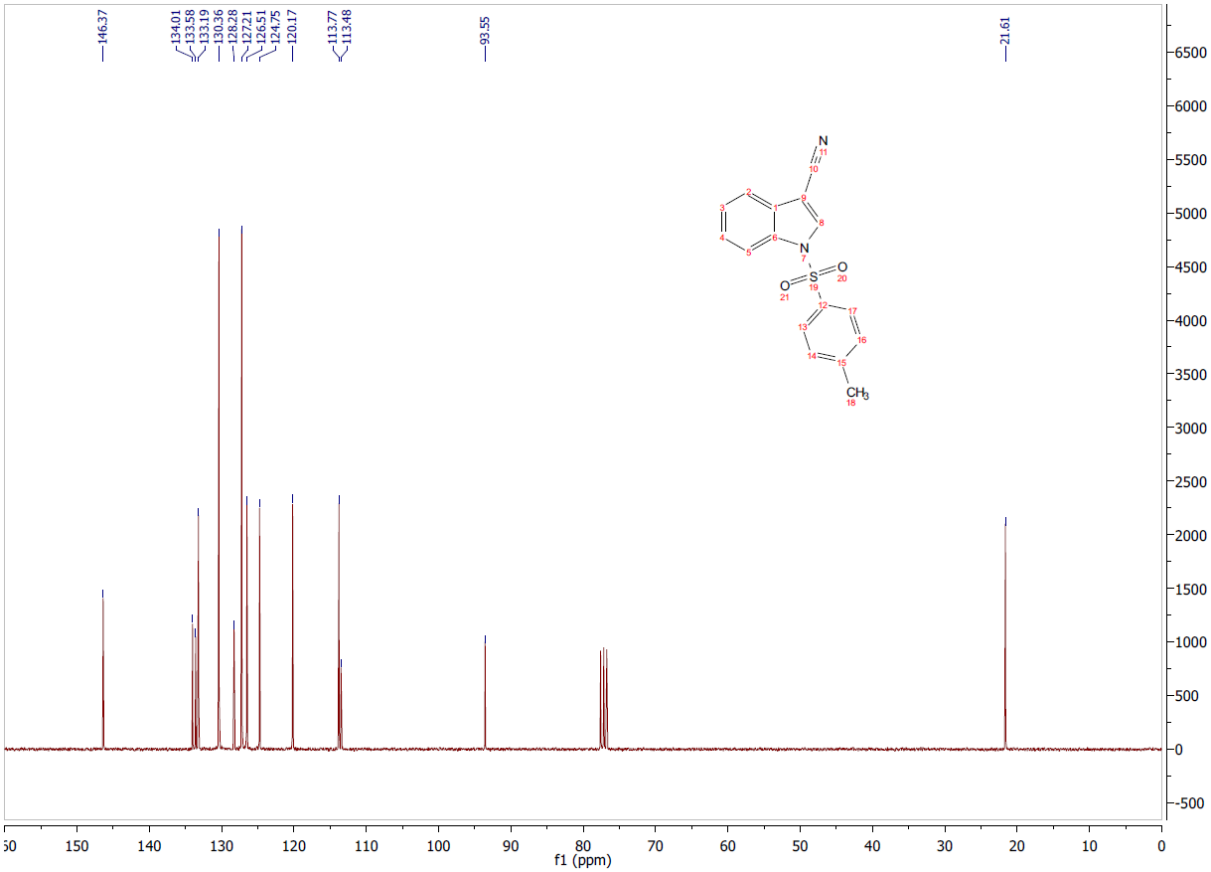
1q:


11.36
8.18
8.18
8.17
7.79
7.78
7.78
7.78
7.78
7.62
7.61
7.59
7.58
7.40
7.39
7.37
7.37
0.25
0.81
1.01
1.00
1.12
1.10
9.47
f1 (ppm)

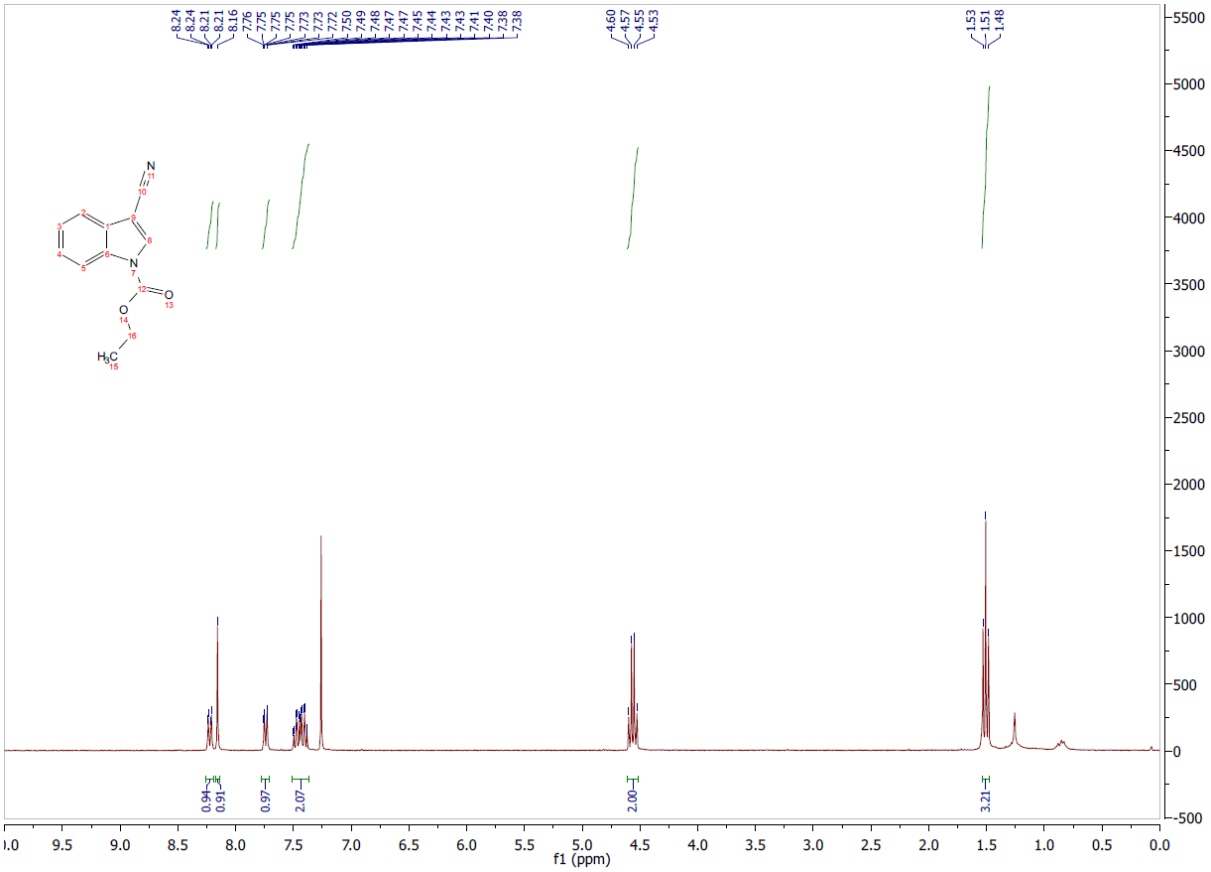

136.09
135.48
127.99
127.86
123.36
117.44
115.74
113.92
106.59
92.97
87.03
29.84 (CD3)2CO
0.09
f1 (ppm)

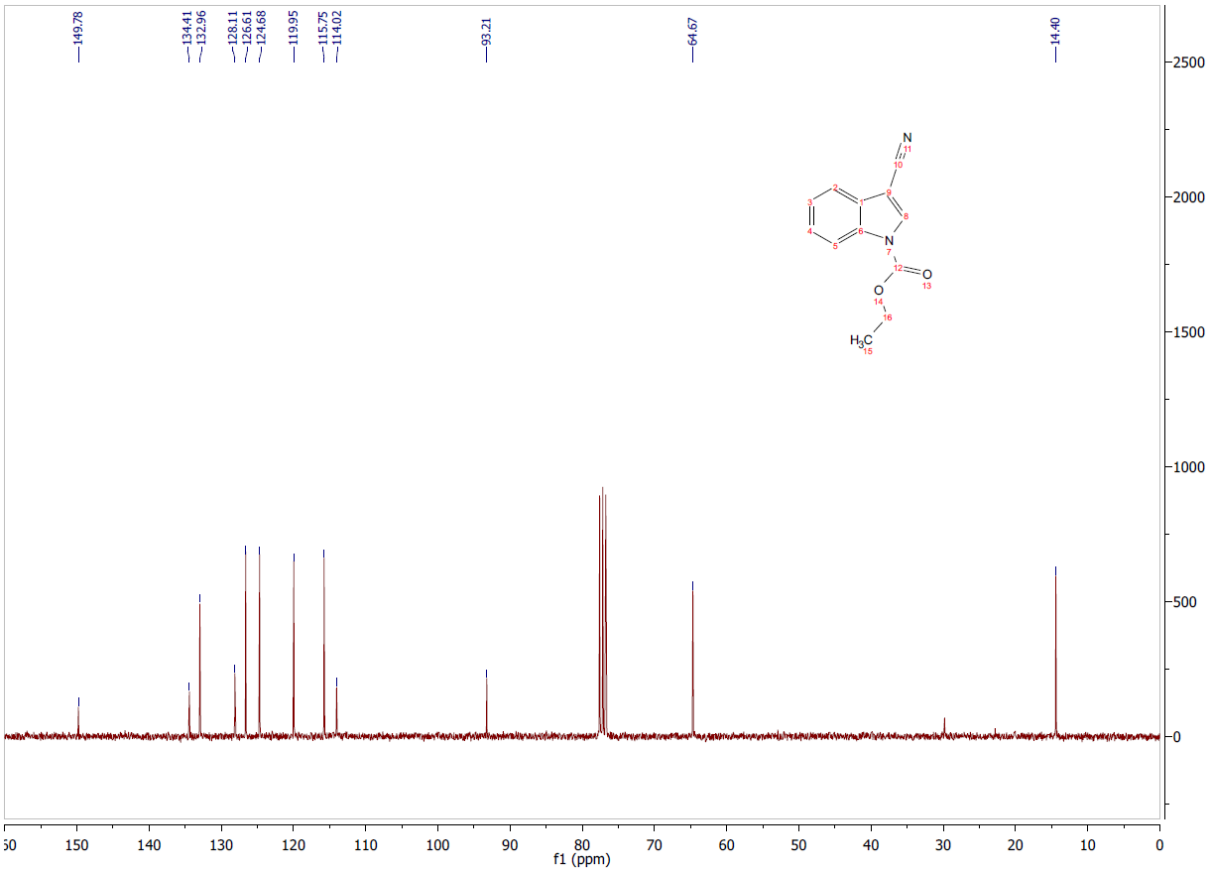
2a:


8.15
8.06
8.06
8.06
8.04
8.03
8.03
7.89
7.89
7.87
7.86
7.86
7.77
7.76
7.76
7.74
7.74
7.73
7.50
7.50
7.49
7.47
7.47
7.46
7.45
7.43
7.43
7.41
7.37
7.37
7.34
7.34
2.44
0.91
1.03
1.97
1.05
2.23
2.12
3.00
f1 (ppm)

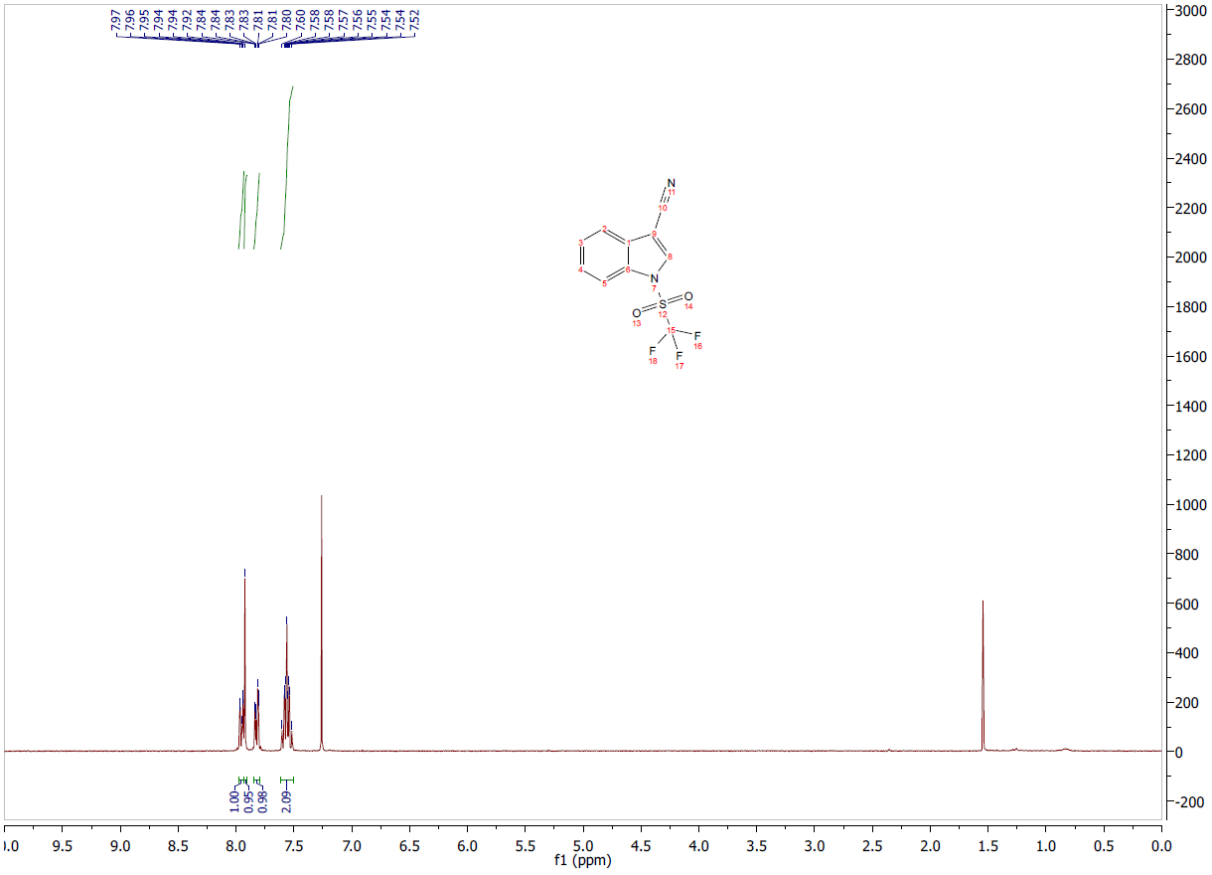

146.37
134.01
133.58
133.19
130.36
128.28
127.21
126.51
124.75
120.17
113.77
113.48
93.55
21.61
f1 (ppm)

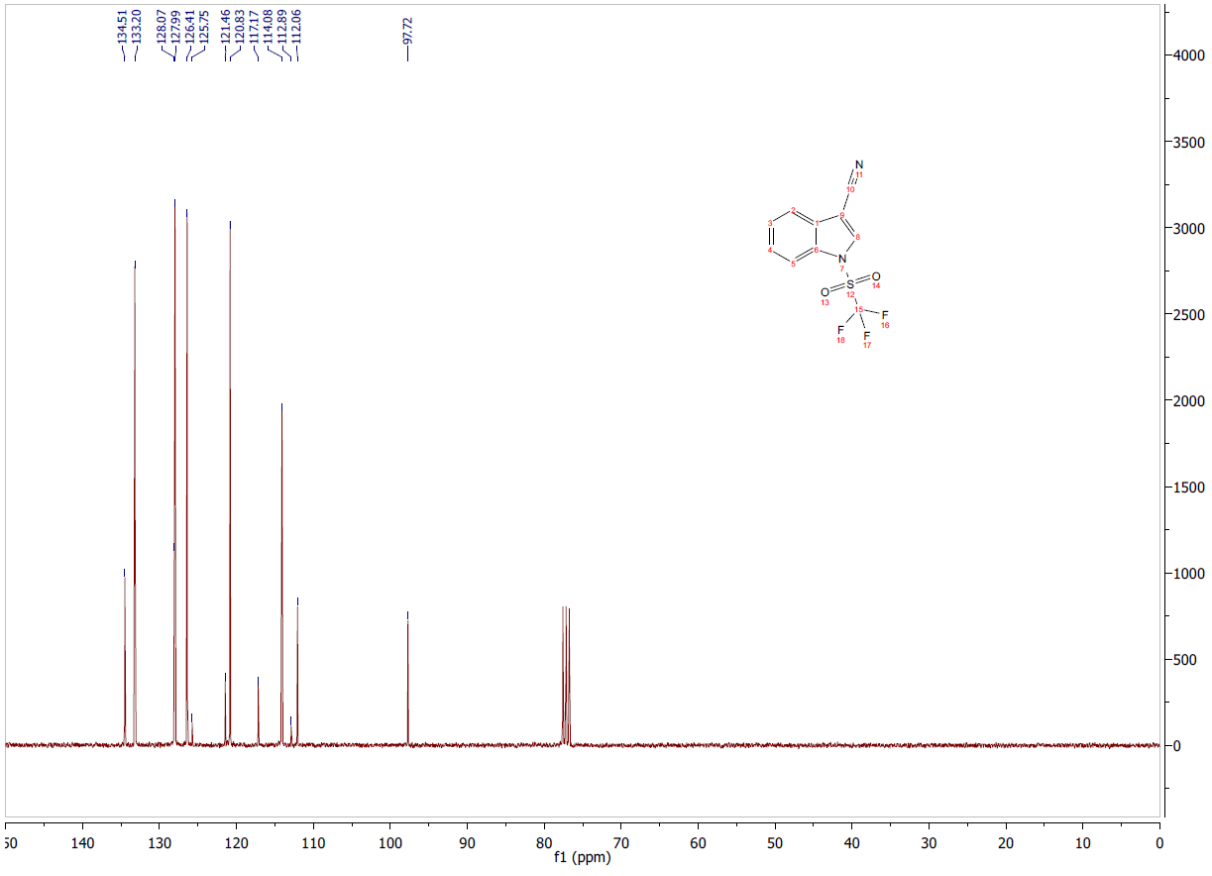
2c:


8.24
8.24
8.21
8.21
8.16
7.76
7.75
7.75
7.75
7.73
7.73
7.72
7.50
7.49
7.48
7.47
7.47
7.45
7.44
7.43
7.43
7.41
7.40
7.38
7.38
4.60
4.57
4.55
4.53
1.53
1.51
1.48
0.94
0.91
0.97
2.07
2.00
3.21
f1 (ppm)

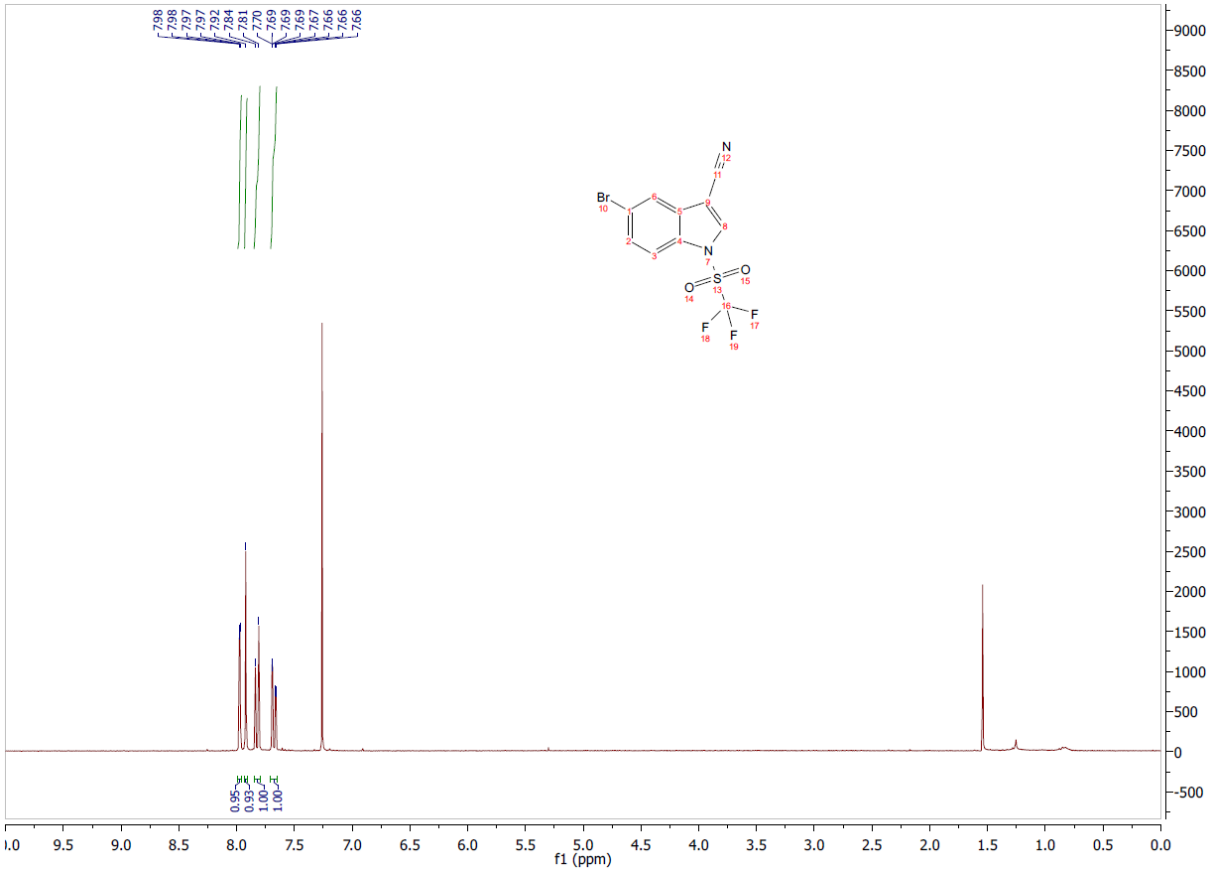

149.78
134.41
132.96
128.11
126.61
124.68
119.95
115.75
114.02
93.21
64.67
14.40
f1 (ppm)

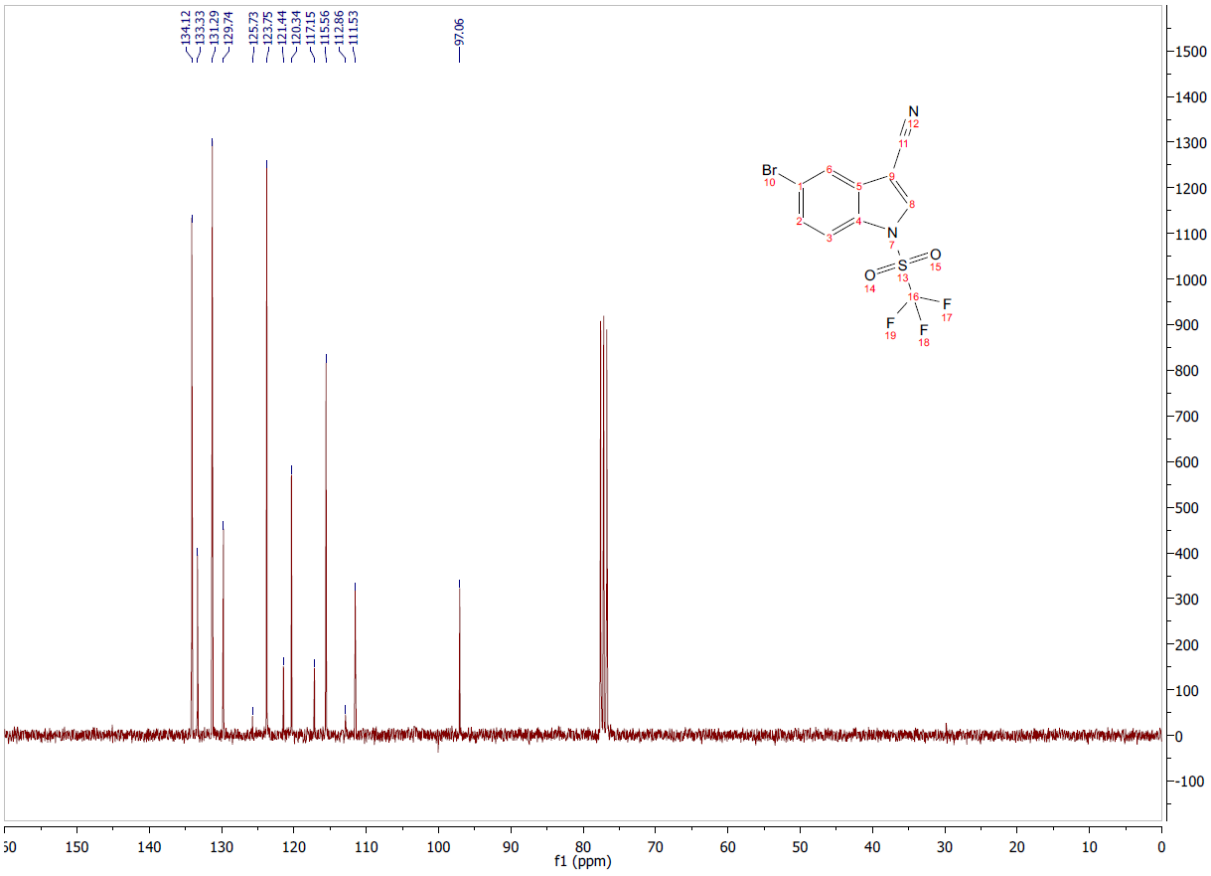
2d:


7.97
7.96
7.95
7.94
7.94
7.92
7.84
7.84
7.83
7.83
7.81
7.81
7.80
7.60
7.58
7.58
7.57
7.56
7.55
7.54
7.54
7.52
1.00
0.95
0.98
2.09
f1 (ppm)

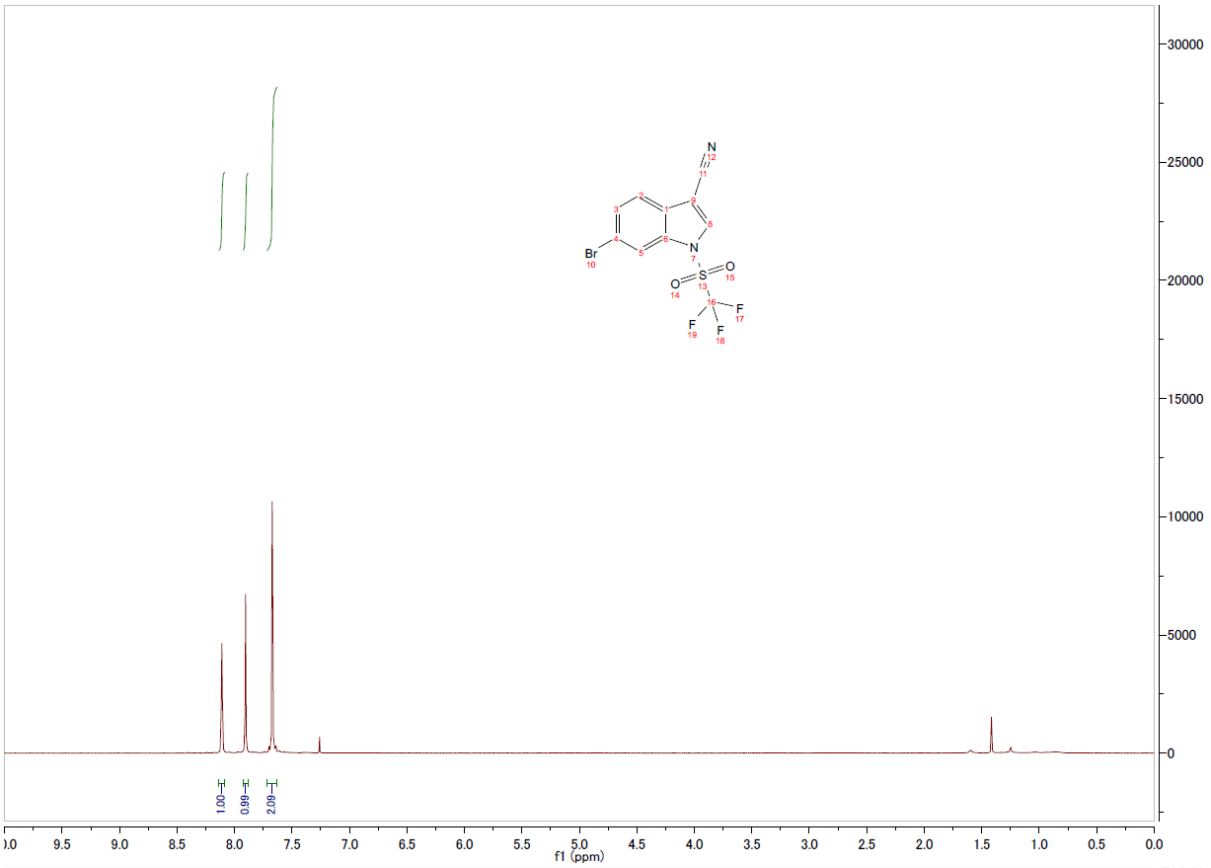

134.51
133.20
128.07
127.99
126.41
125.75
121.46
120.83
117.17
114.08
112.89
112.06
97.72
f1 (ppm)

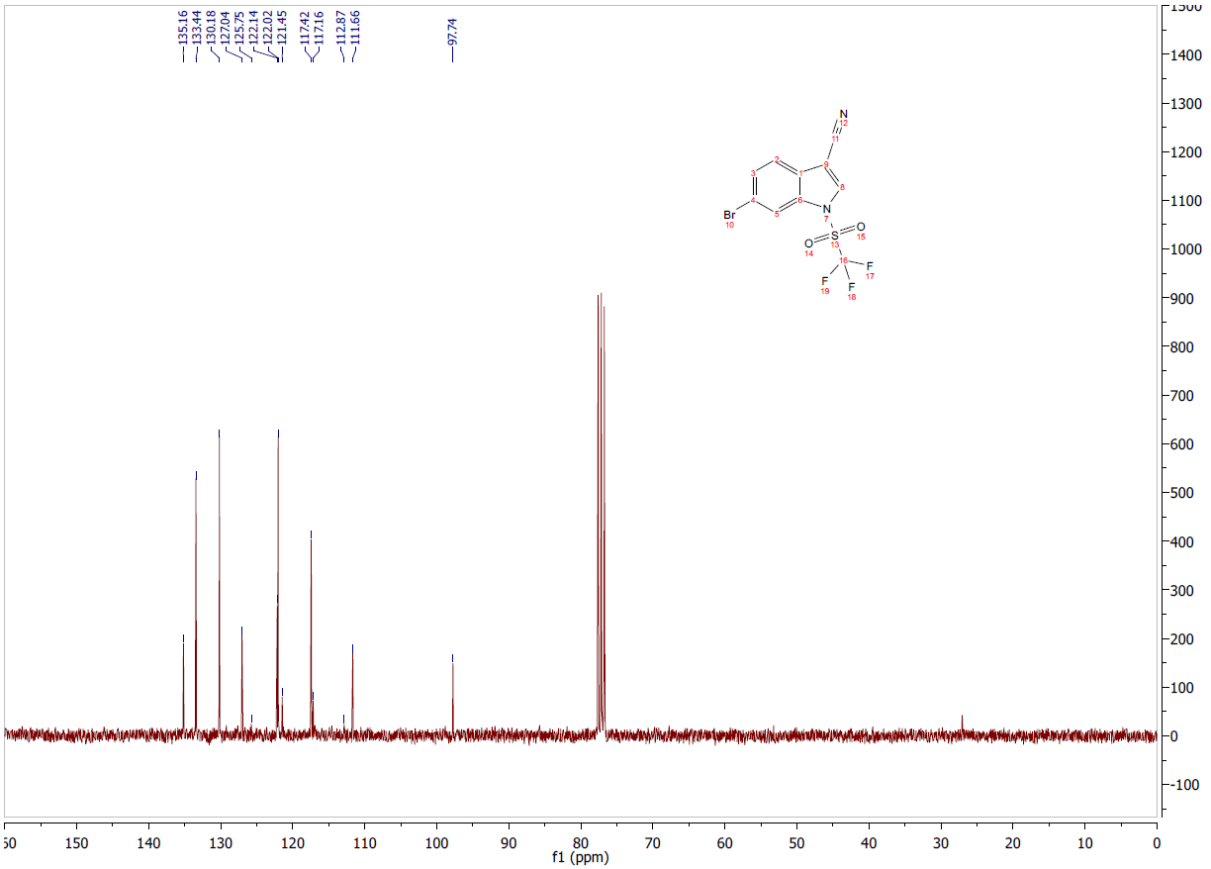
2e:


798
798
797
797
792
784
781
770
769
769
769
767
766
766
766
0.95
0.93
1.00
1.00
f1 (ppm)

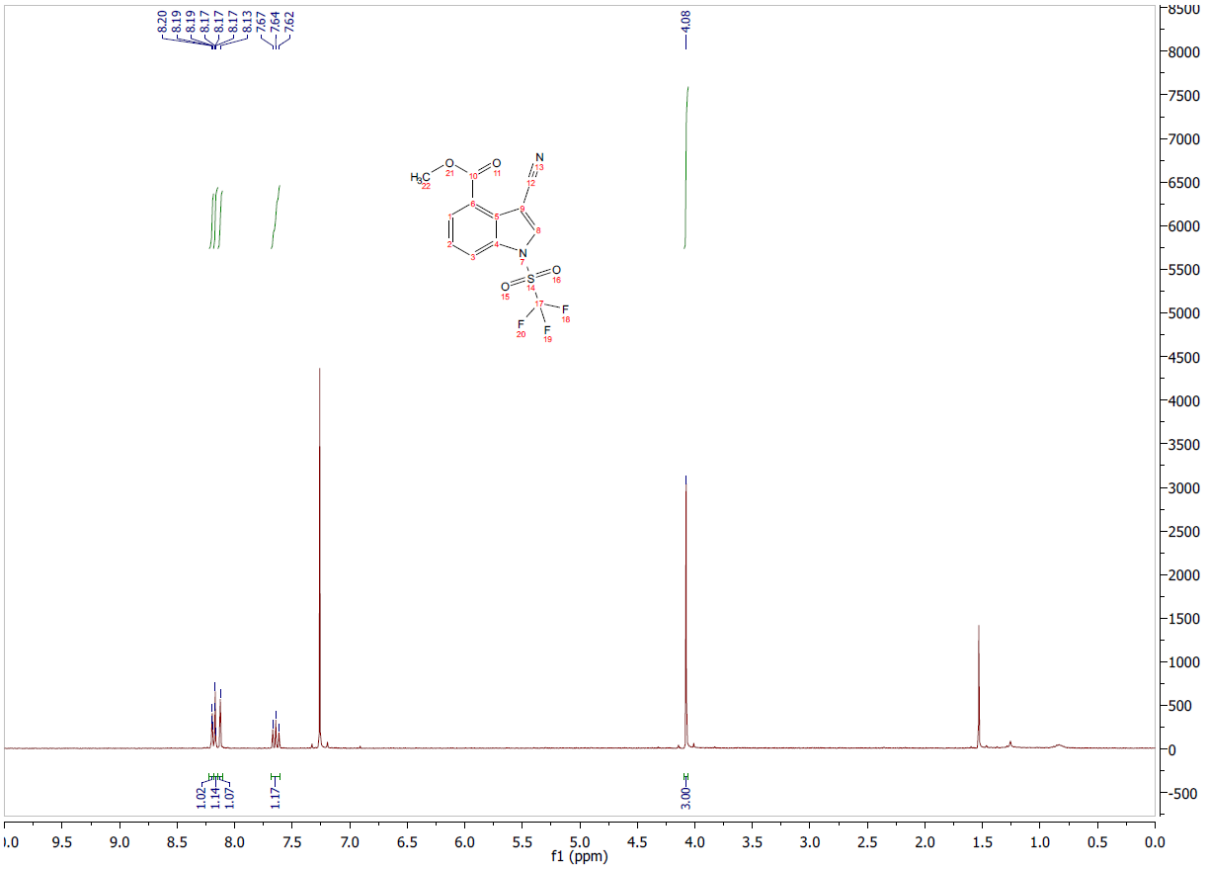

134.12
133.33
131.29
129.74
125.73
123.75
121.44
120.34
117.15
115.56
112.86
111.53
97.06
f1 (ppm)

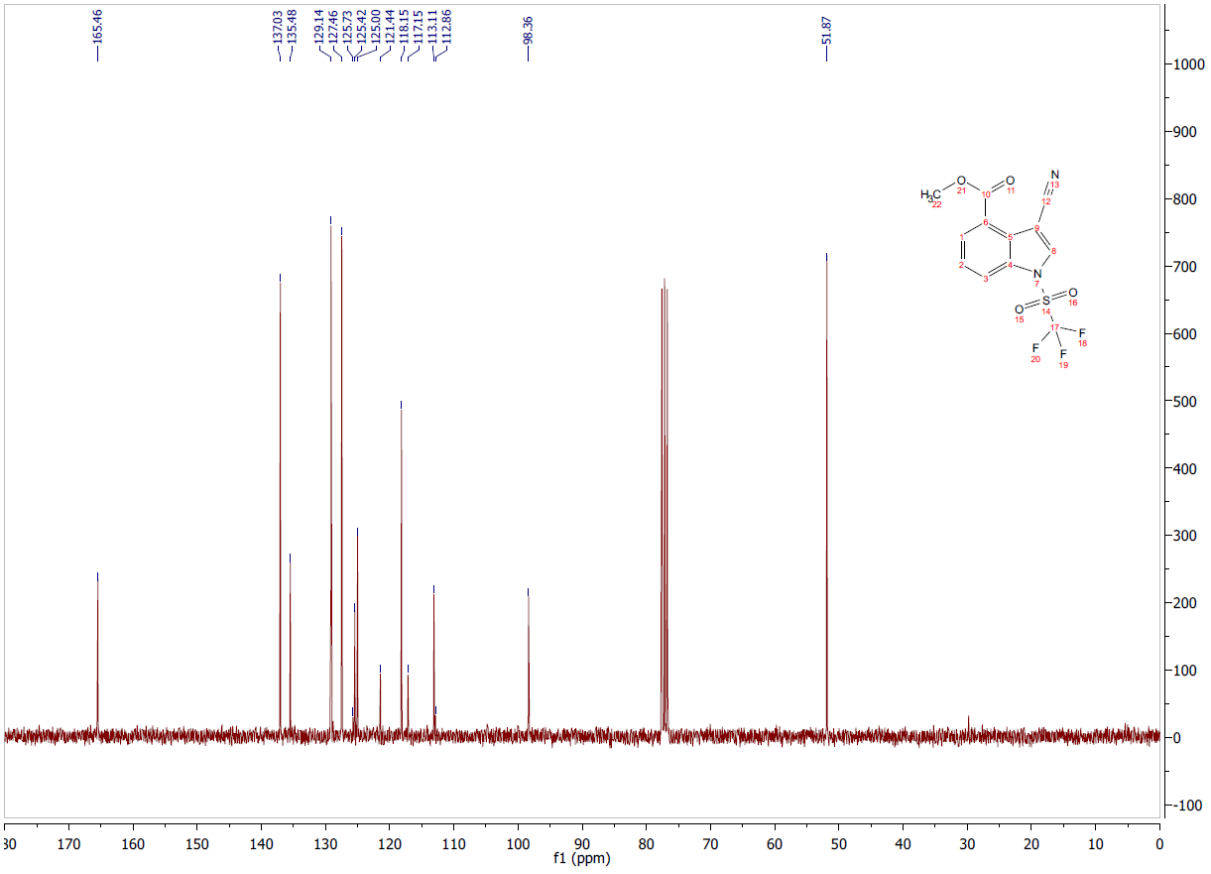
2f:


1.00
0.99
2.09
f1 (ppm)

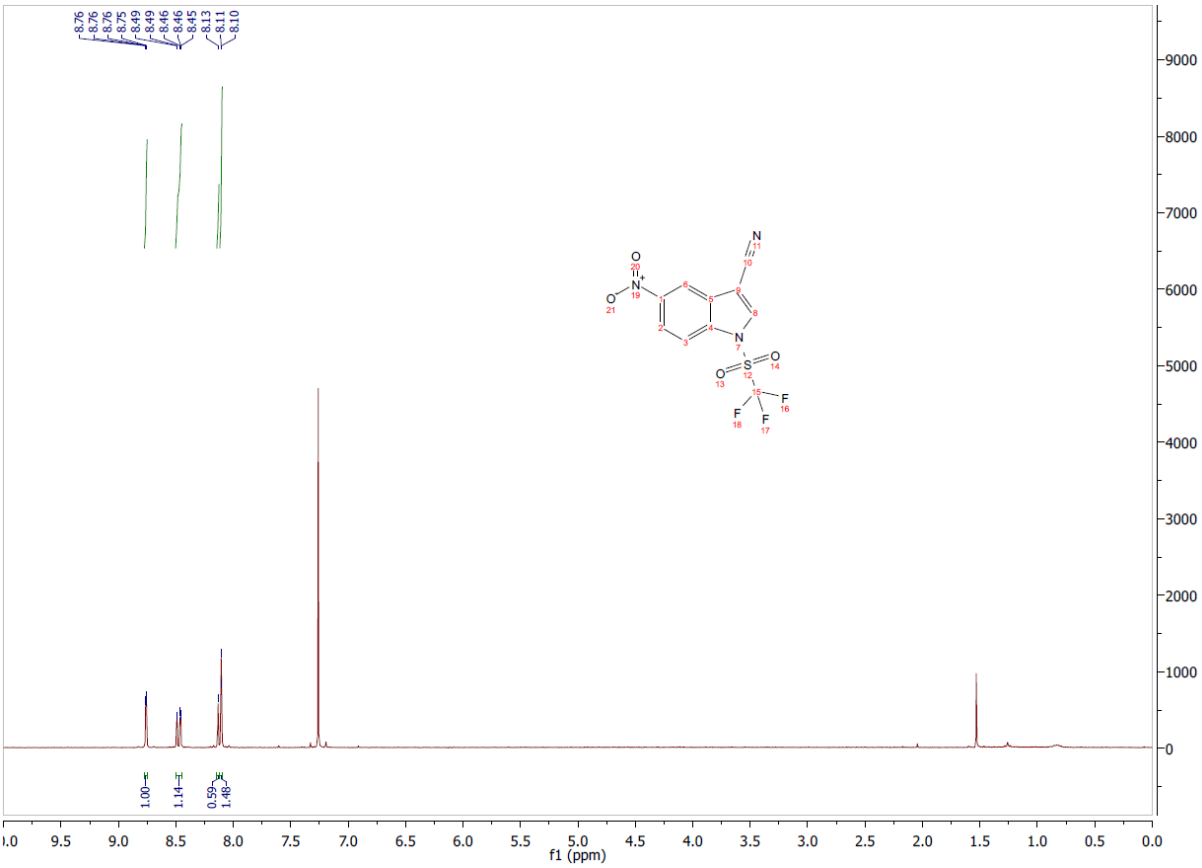

135.16
133.44
130.18
127.04
125.75
122.14
122.02
121.45
117.42
117.16
112.87
111.66
97.74
f1 (ppm)

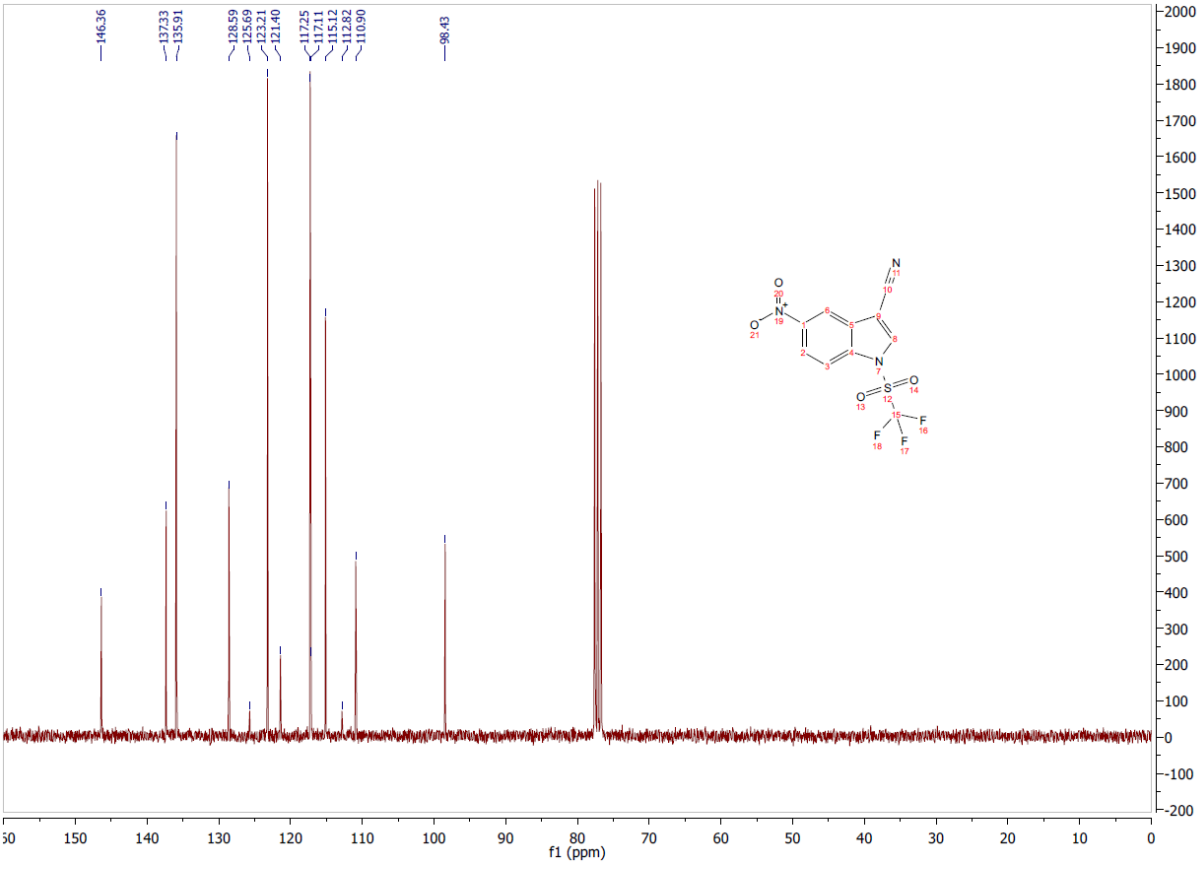
2g:


8.20
8.19
8.19
8.17
8.17
8.17
8.13
7.67
7.64
7.62
4.08
1.02
1.14
1.07
1.17
3.00
f1 (ppm)

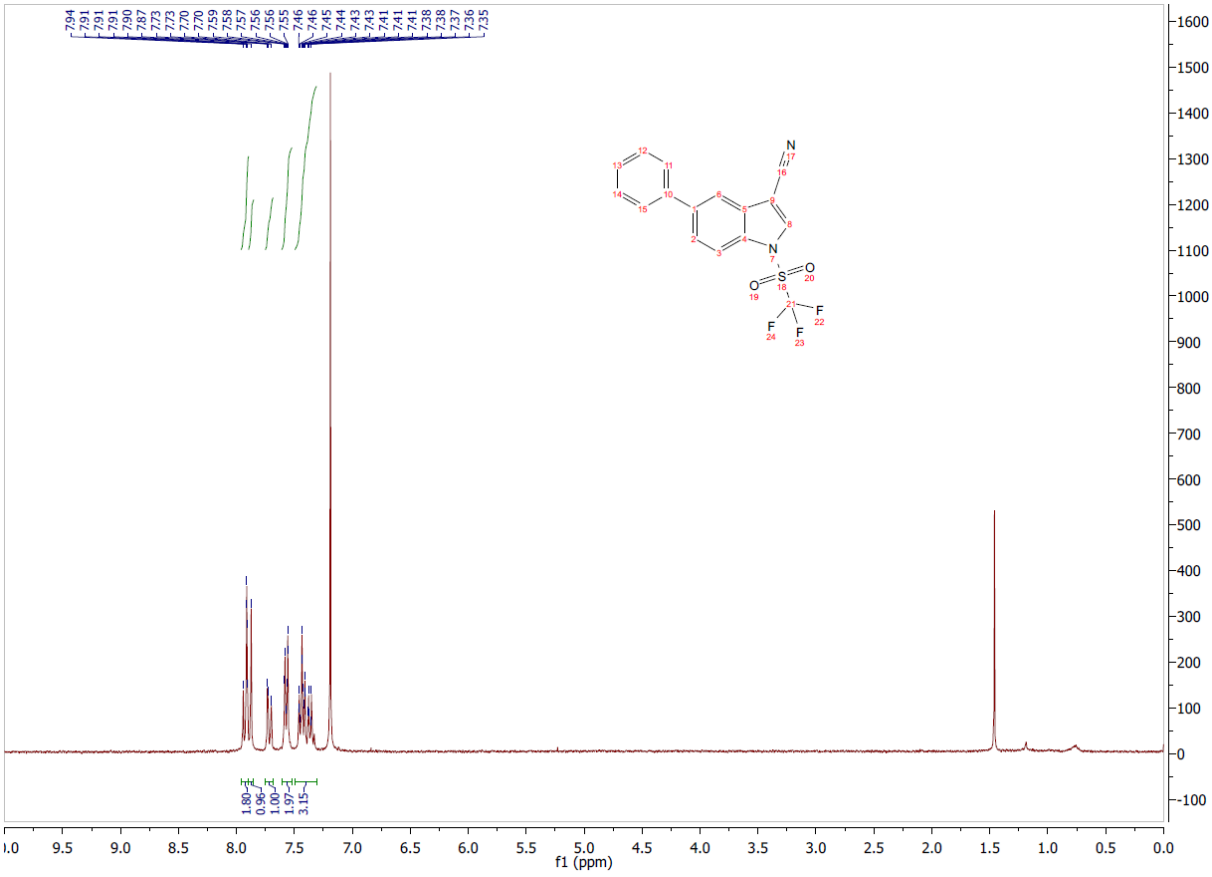

165.46
137.03
135.48
129.14
127.46
125.73
125.42
125.00
121.44
118.15
117.15
113.11
112.86
98.36
51.87
f1 (ppm)

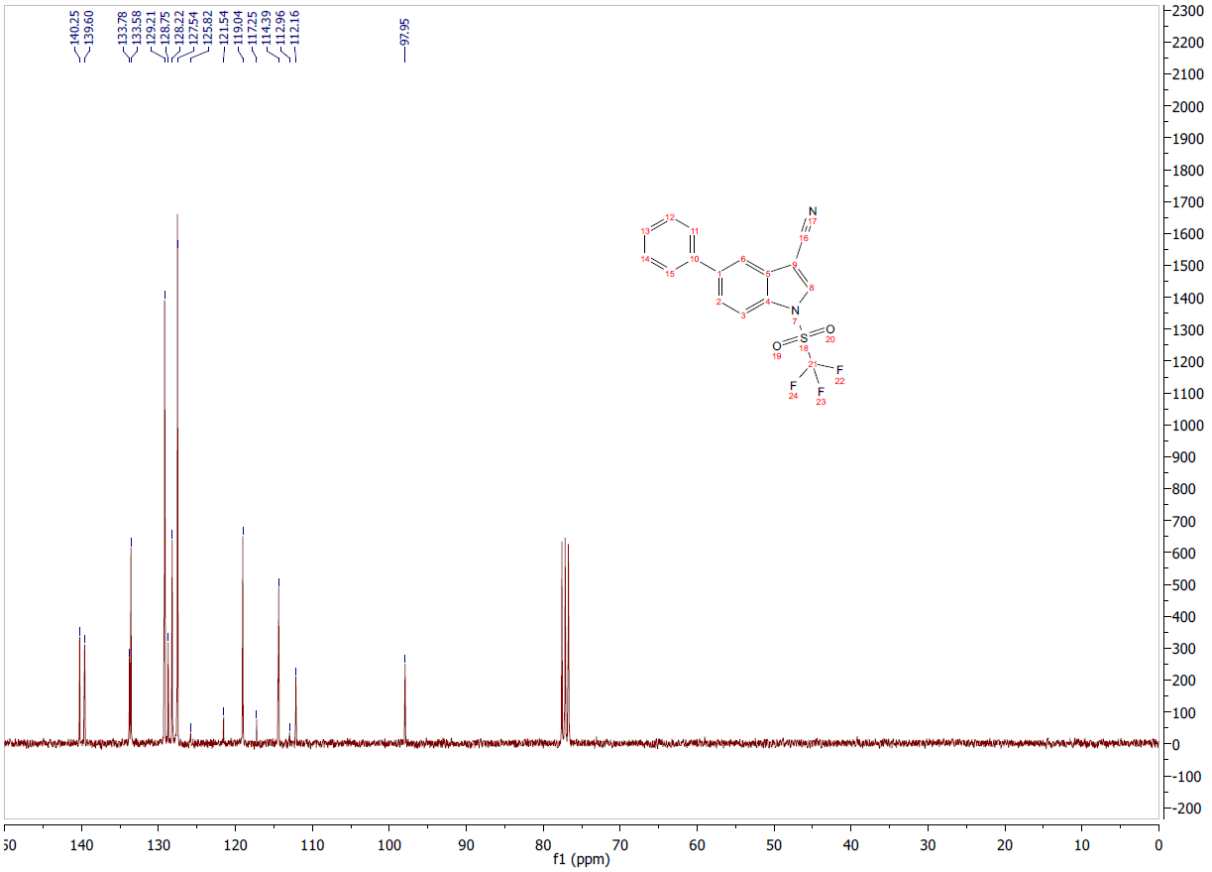
2h:


8.76
8.76
8.76
8.75
8.49
8.49
8.46
8.46
8.45
8.13
8.11
8.10
1.00
1.14
0.59
1.48
f1 (ppm)

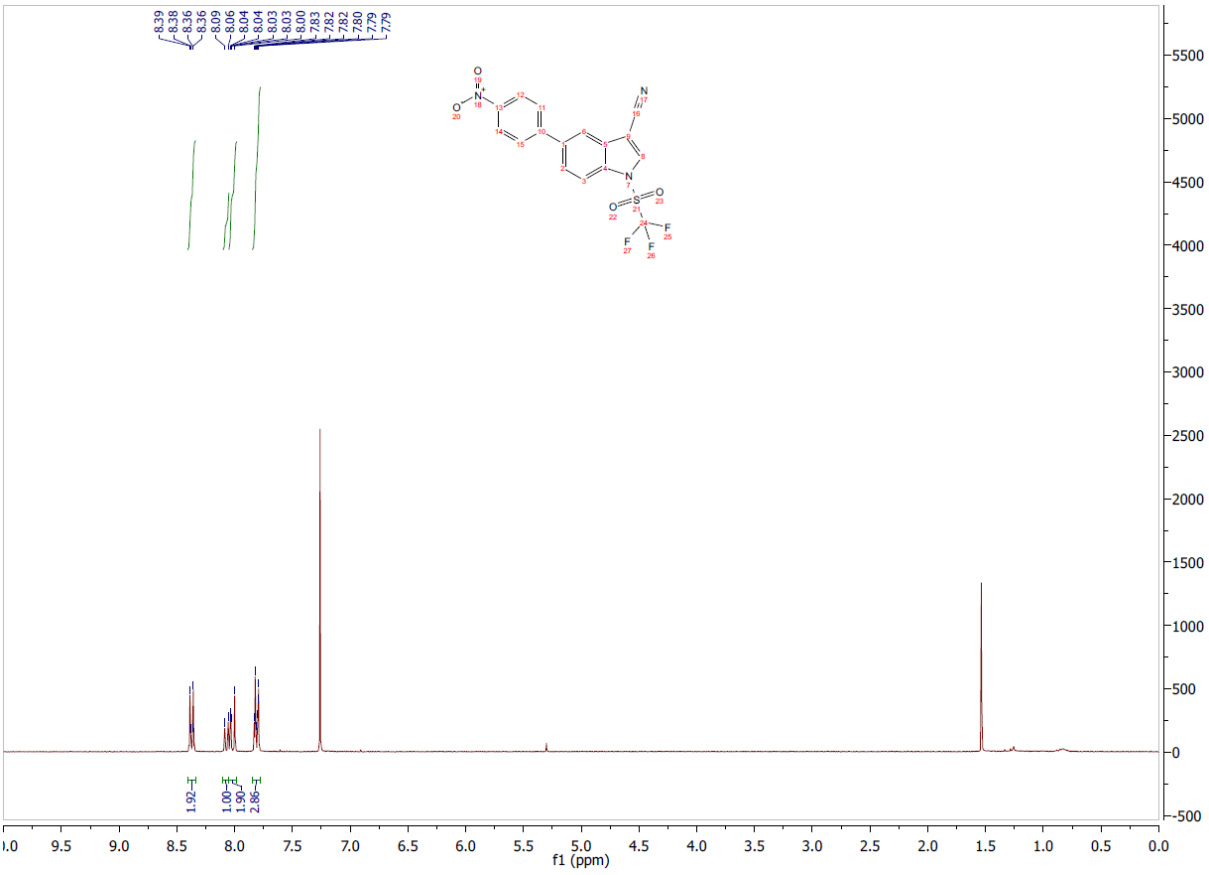

146.36
137.33
135.91
128.59
125.69
123.21
121.40
117.25
117.11
115.12
112.82
110.90
98.43
f1 (ppm)

2i:


7.94
7.91
7.91
7.91
7.90
7.87
7.73
7.73
7.70
7.70
7.59
7.58
7.57
7.56
7.56
7.55
7.46
7.46
7.45
7.44
7.43
7.43
7.41
7.41
7.41
7.38
7.38
7.37
7.36
7.35
1.80
0.96
1.00
1.97
3.15
f1 (ppm)


140.25
139.60
133.78
133.58
129.21
128.75
128.22
127.54
125.82
121.54
119.04
117.25
114.39
112.96
112.16
97.95
f1 (ppm)

2j:


8.39
8.38
8.36
8.36
8.09
8.06
8.04
8.04
8.03
8.03
8.00
7.83
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7.82
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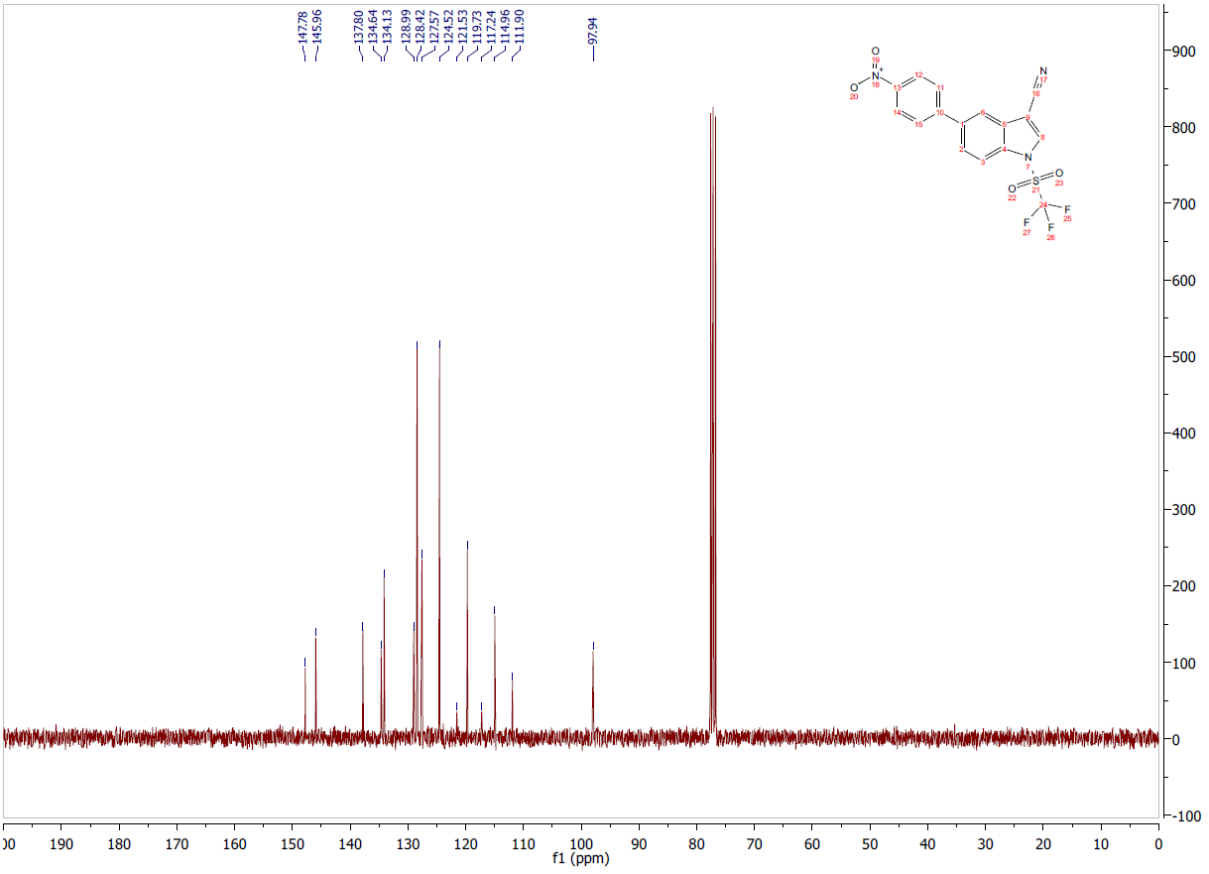
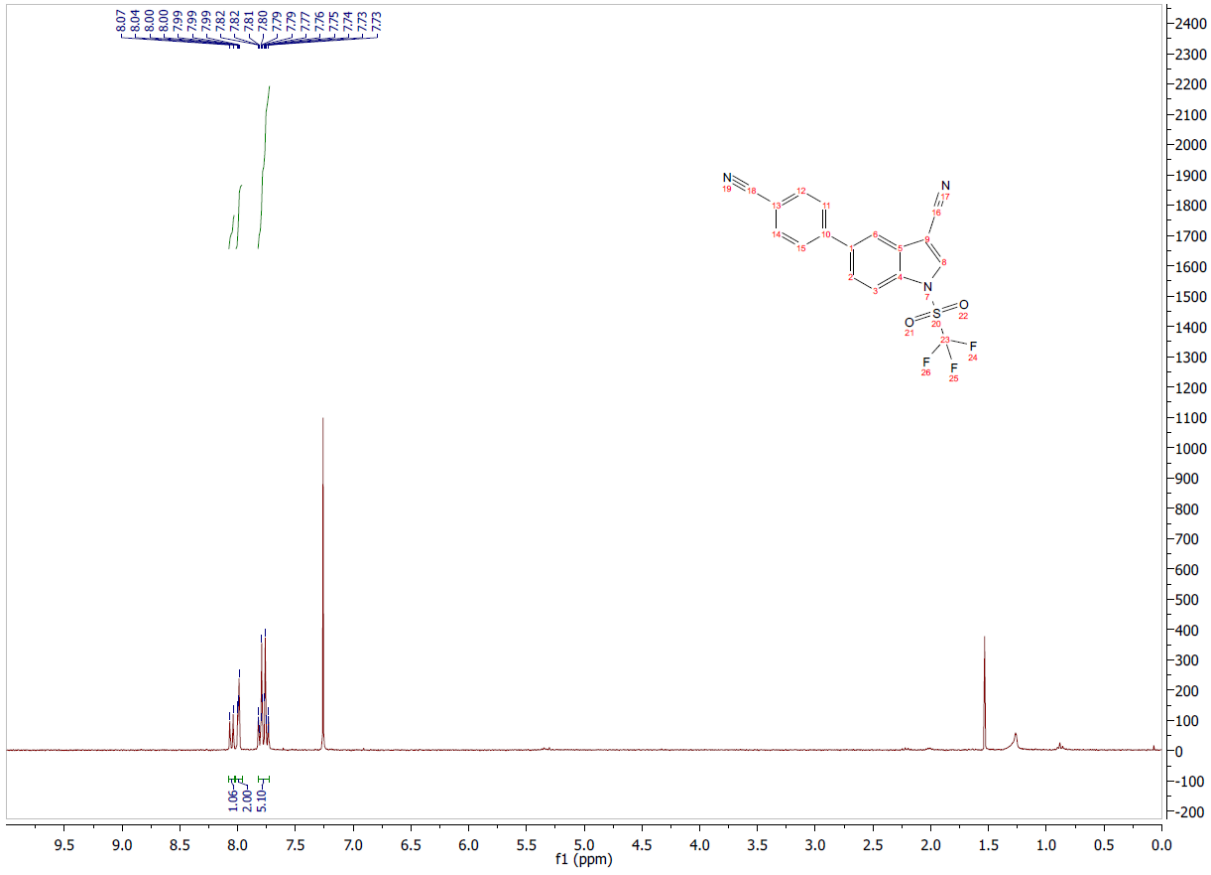
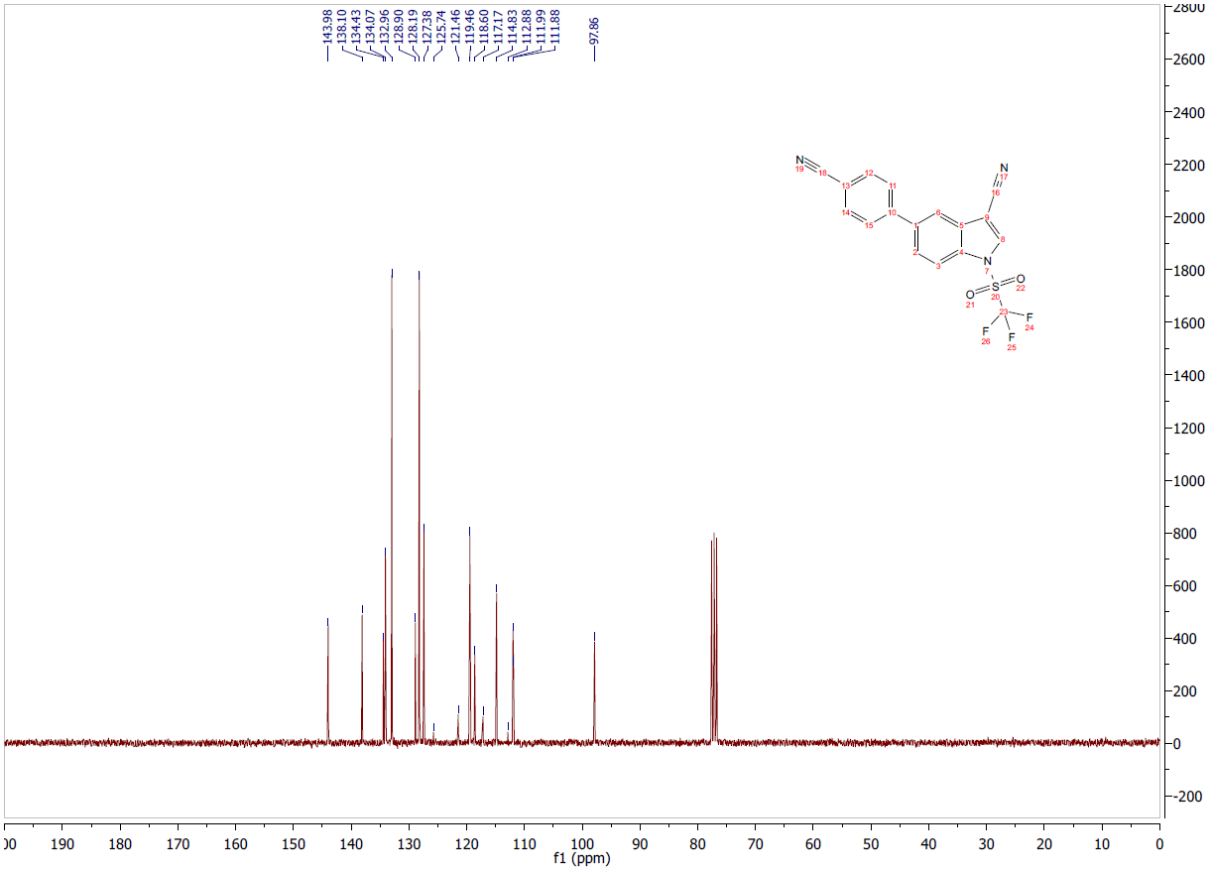
7.79
1.92
1.00
1.90
2.86
f1 (ppm)

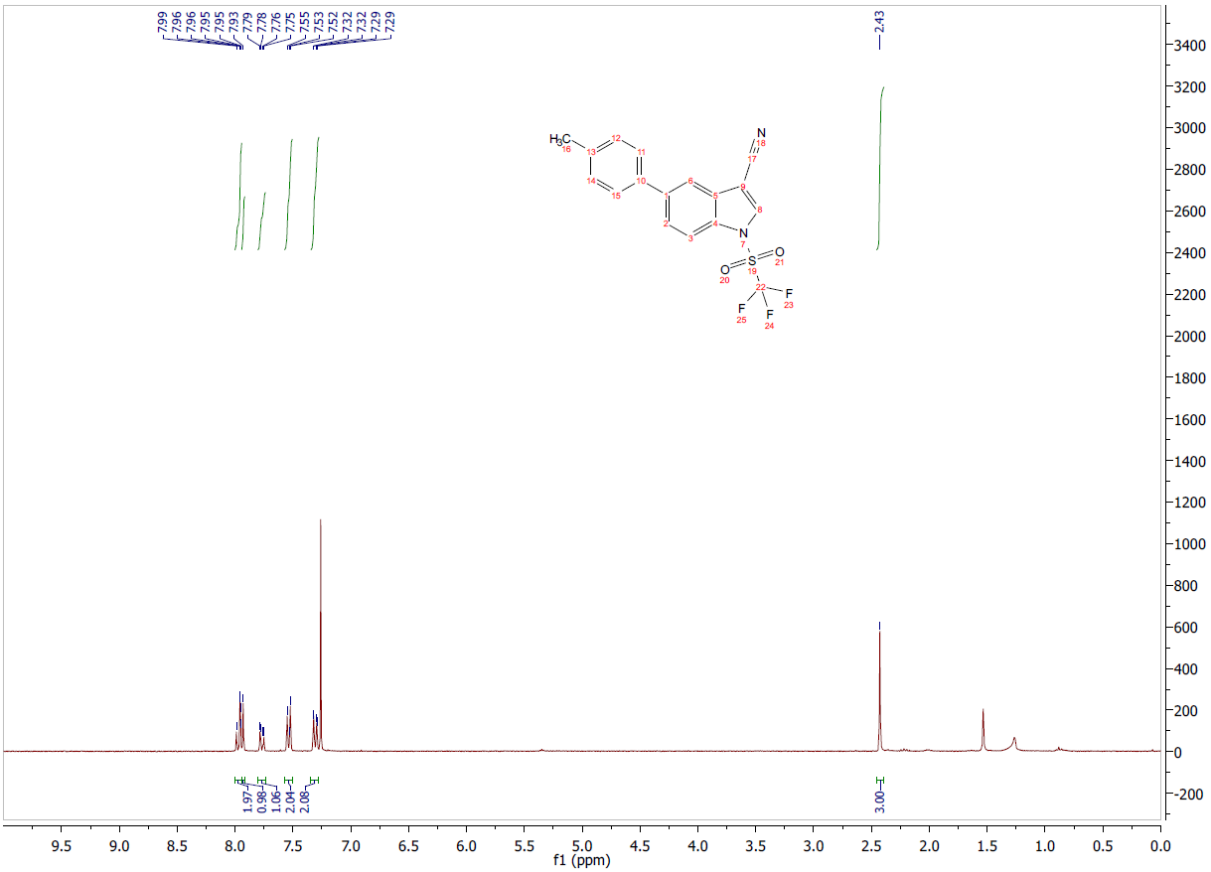

147.78
145.96
137.80
134.64
134.13
128.99
128.42
127.57
124.52
121.53
119.73
117.24
114.96
111.90
97.94
f1 (ppm)

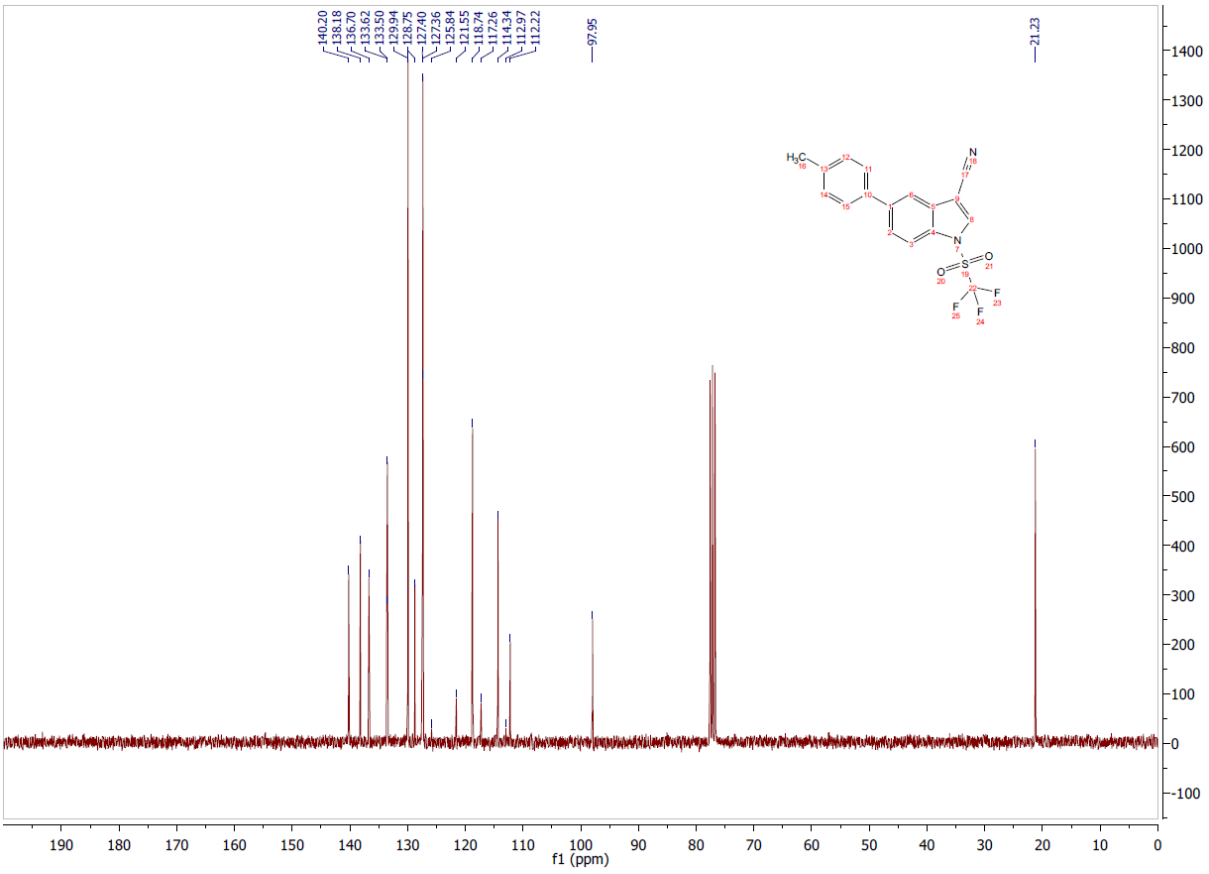
2k:


8.07
8.04
8.00
8.00
8.00
7.99
7.99
7.99
7.82
7.82
7.81
7.80
7.79
7.79
7.77
7.76
7.75
7.74
7.73
7.73
1.06
2.00
5.10
f1 (ppm)

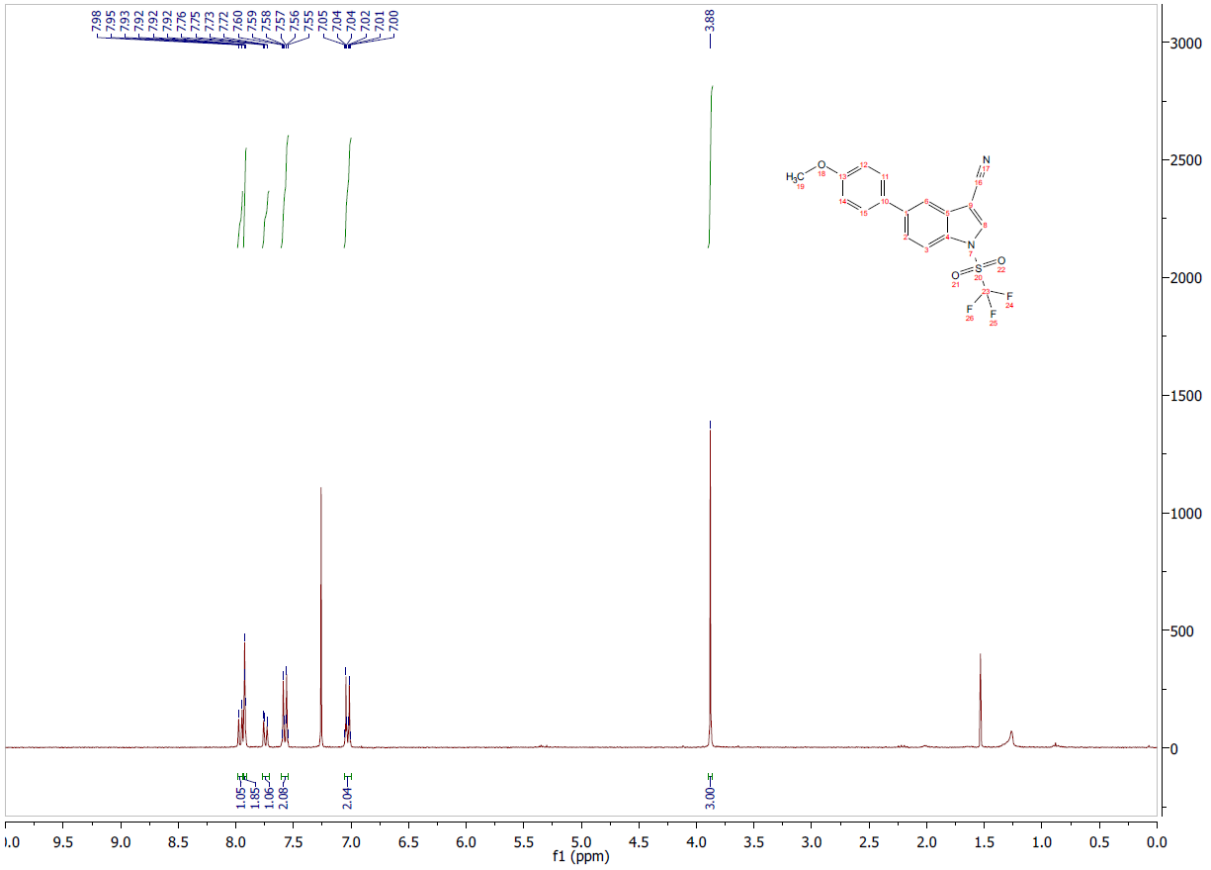

143.98
138.10
134.43
134.07
132.96
128.90
128.19
127.38
125.74
121.46
119.46
118.60
117.17
114.83
112.88
111.99
111.88
97.86
f1 (ppm)

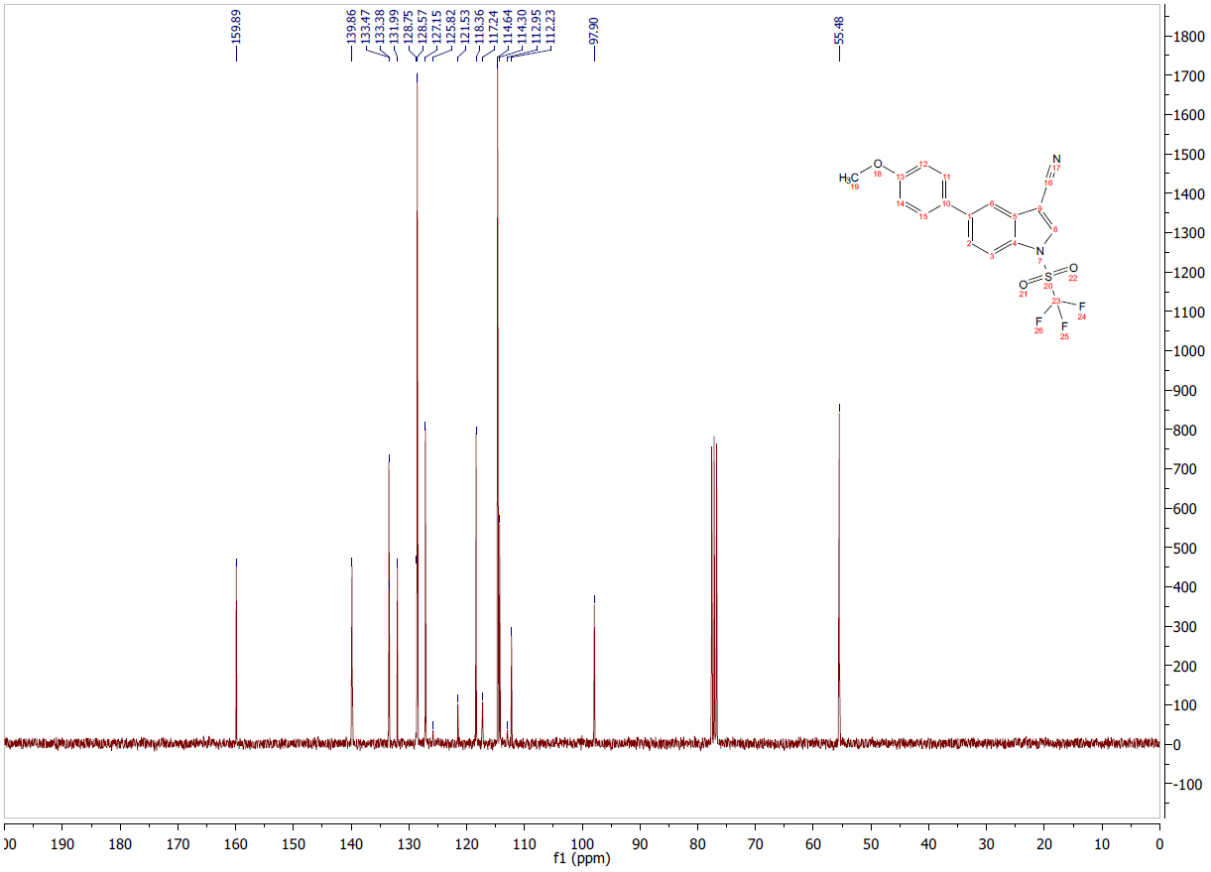
2l:


7.99
7.96
7.96
7.95
7.95
7.93
7.79
7.78
7.76
7.75
7.55
7.53
7.52
7.32
7.32
7.29
7.29
2.43
1.97
0.98
1.06
2.04
2.08
3.00
f1 (ppm)

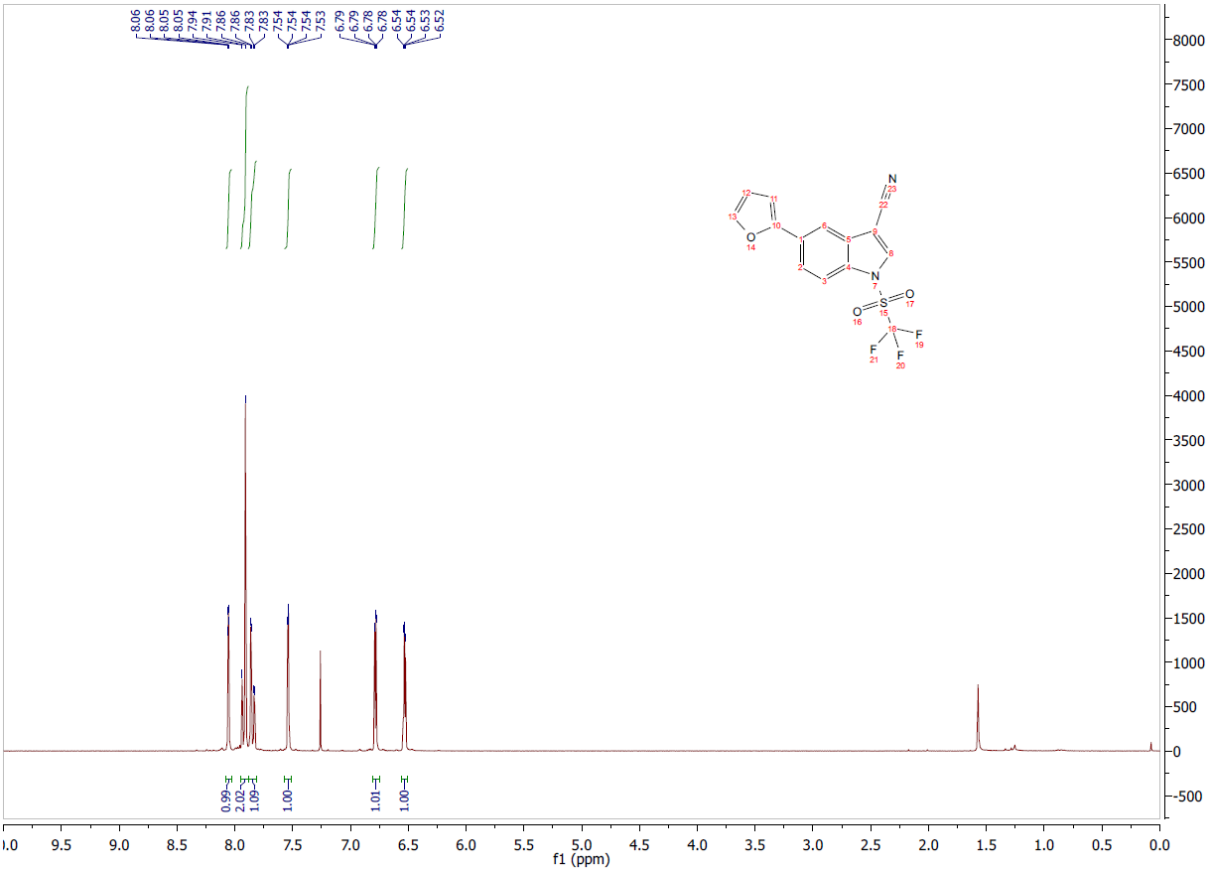

140.20
138.18
136.70
133.62
133.50
129.94
128.75
127.40
127.36
125.84
121.55
118.74
117.26
114.34
112.97
112.22
97.95
21.23
f1 (ppm)

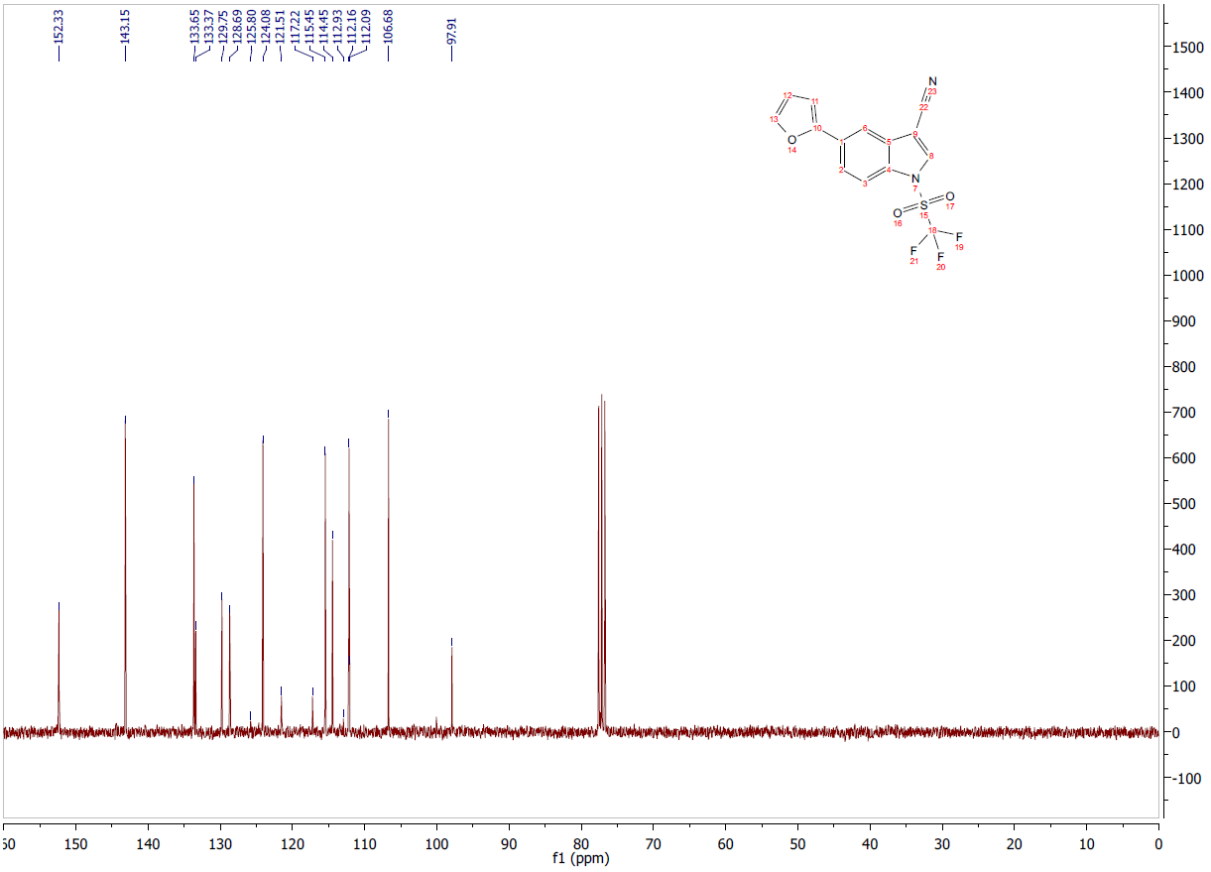
2m:


7.98
7.95
7.93
7.92
7.92
7.92
7.76
7.75
7.73
7.72
7.60
7.59
7.58
7.57
7.56
7.55
7.05
7.04
7.04
7.02
7.01
7.00
3.88
1.05
1.85
1.06
2.08
2.04
3.00
f1 (ppm)

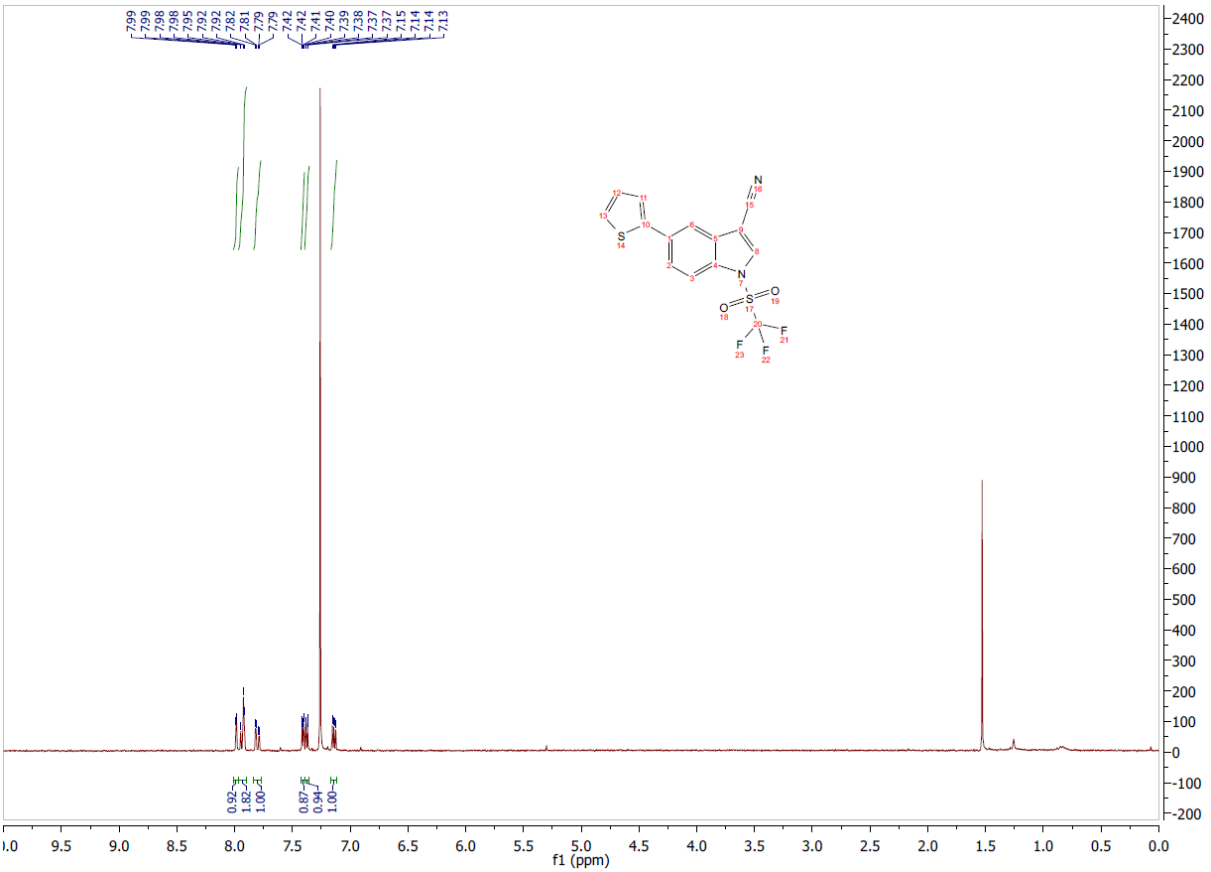

159.89
139.86
133.47
133.38
131.99
128.75
128.57
127.15
125.82
121.53
118.36
117.24
114.64
114.30
112.95
112.23
97.90
55.48
f1 (ppm)

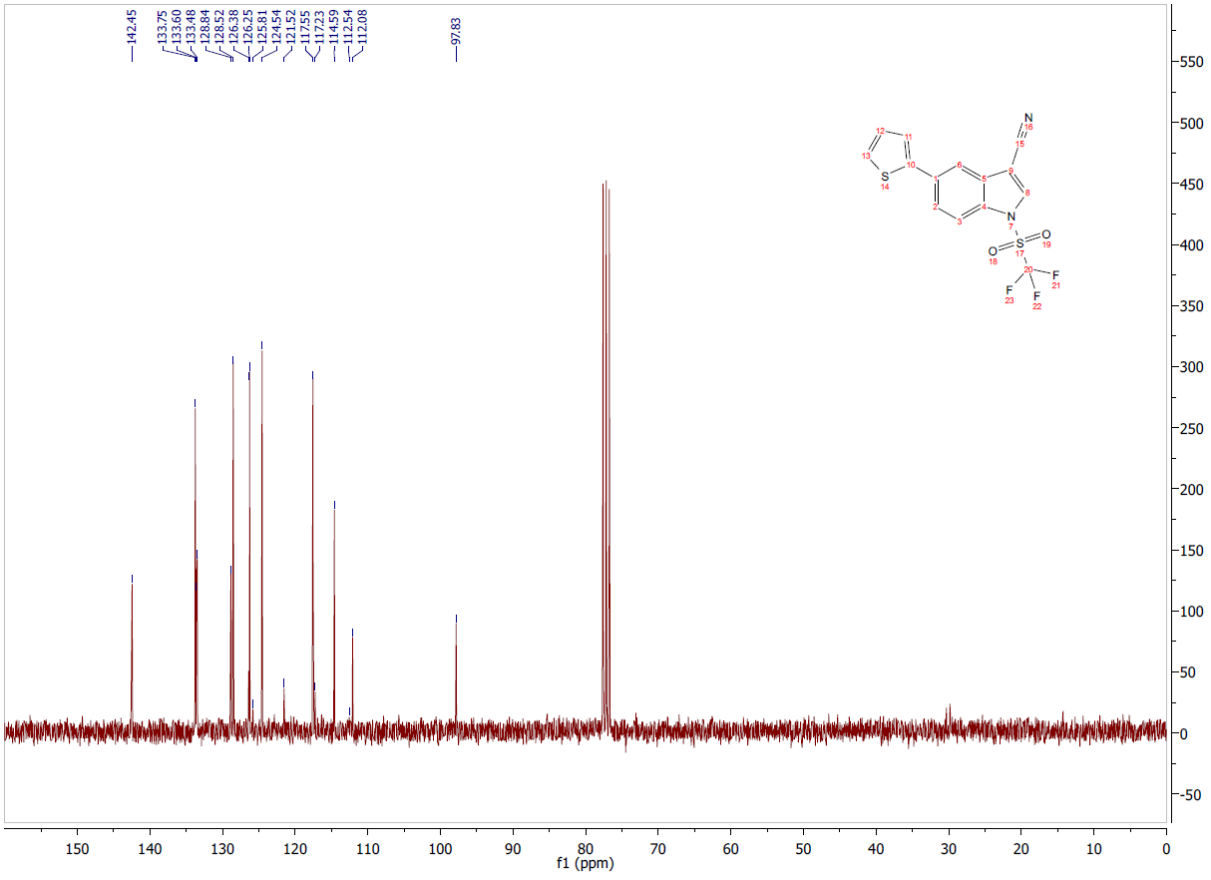
2n:


8.06
8.06
8.05
8.05
7.94
7.91
7.86
7.86
7.83
7.83
7.54
7.54
7.54
7.53
6.79
6.79
6.78
6.78
6.54
6.54
6.53
6.52
0.99
2.02
1.09
1.00
1.01
1.00
f1 (ppm)

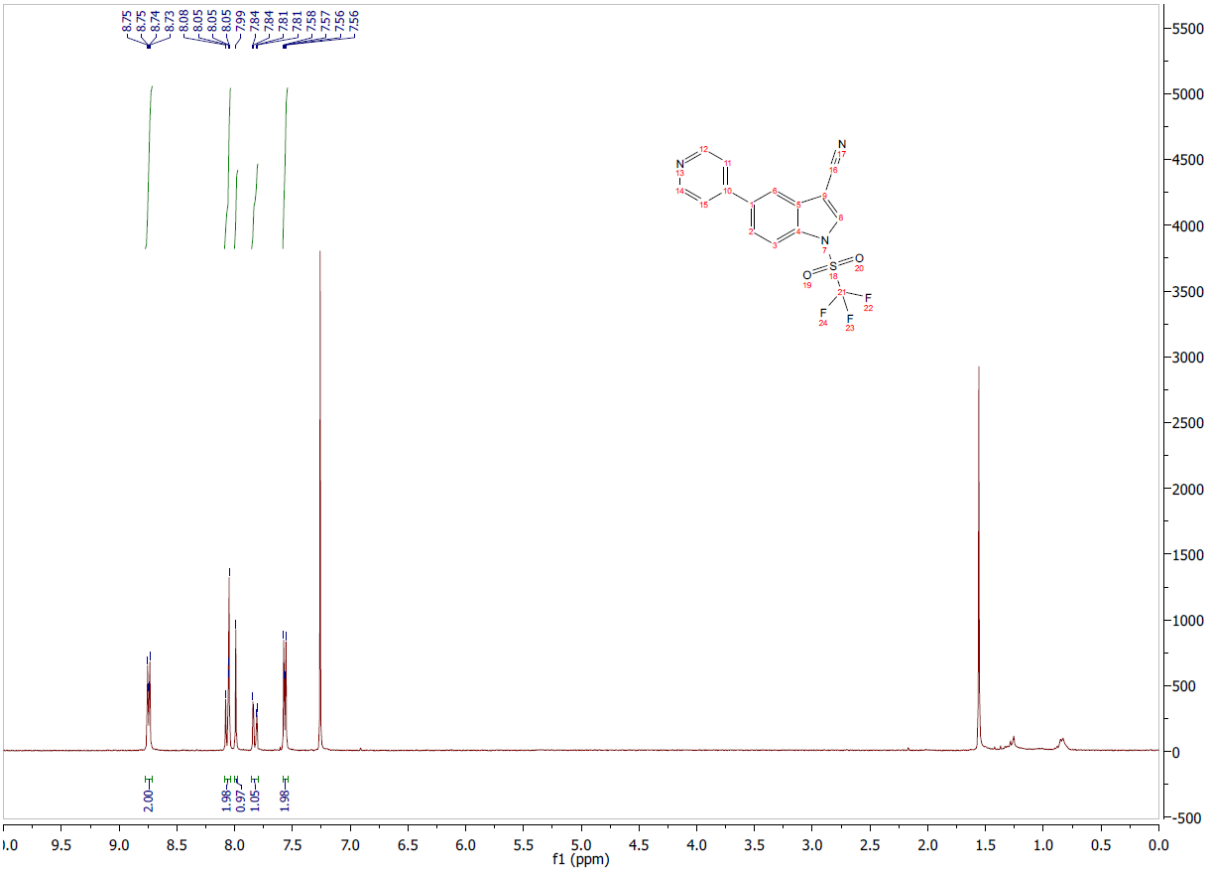

152.33
143.15
133.65
133.37
129.75
128.69
125.80
124.08
121.51
117.22
115.45
114.45
112.93
112.16
112.09
106.68
97.91
f1 (ppm)

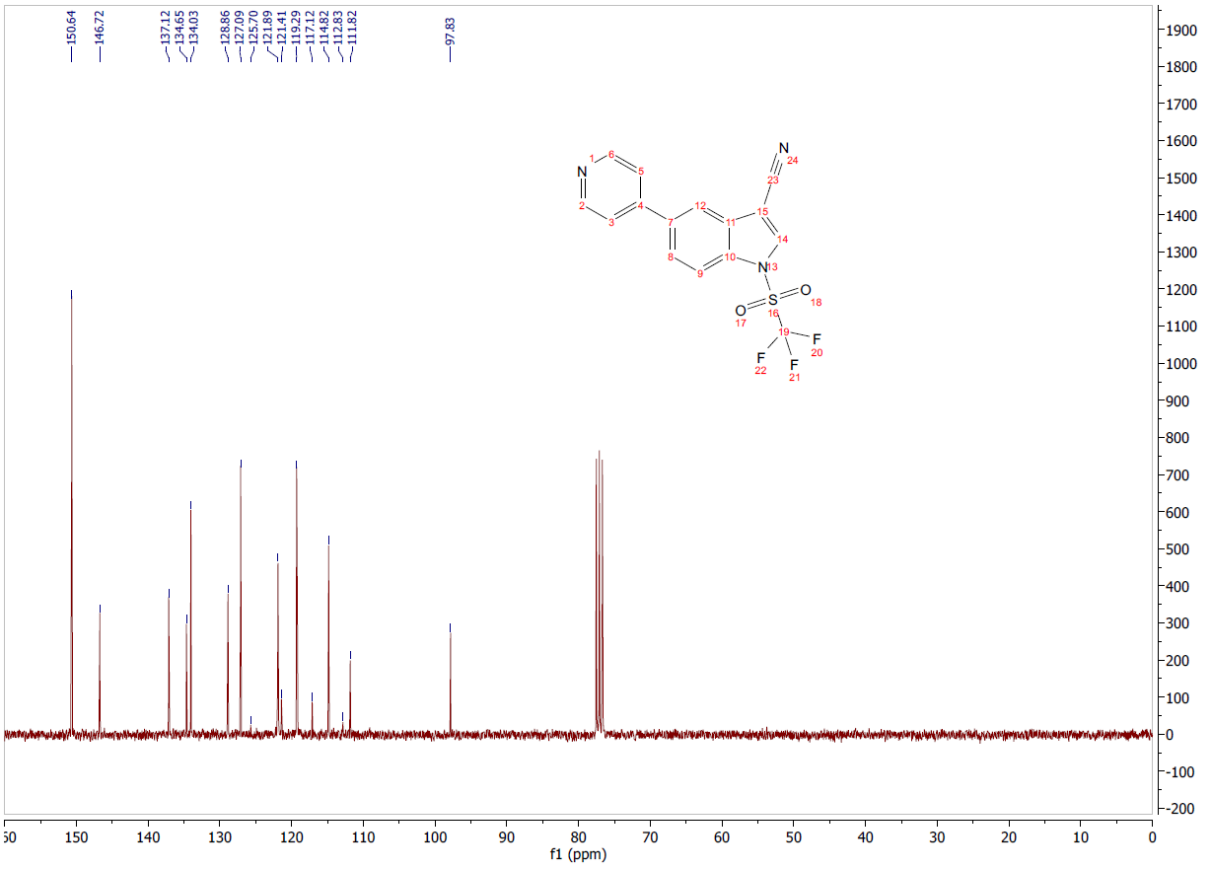
2o:


7.99
7.99
7.98
7.98
7.95
7.92
7.92
7.82
7.81
7.79
7.79
7.42
7.42
7.41
7.40
7.39
7.38
7.37
7.37
7.15
7.14
7.14
7.13
0.92
1.82
1.00
0.87
0.94
1.00
f1 (ppm)


142.45
133.75
133.60
133.48
128.84
128.52
126.38
126.25
125.81
124.54
121.52
117.55
117.23
114.59
112.54
112.08
97.83
f1 (ppm)

2p:


8.75
8.75
8.74
8.73
8.08
8.05
8.05
8.05
7.99
7.84
7.84
7.81
7.81
7.58
7.57
7.56
7.56
2.00
1.98
0.97
1.05
1.98
f1 (ppm)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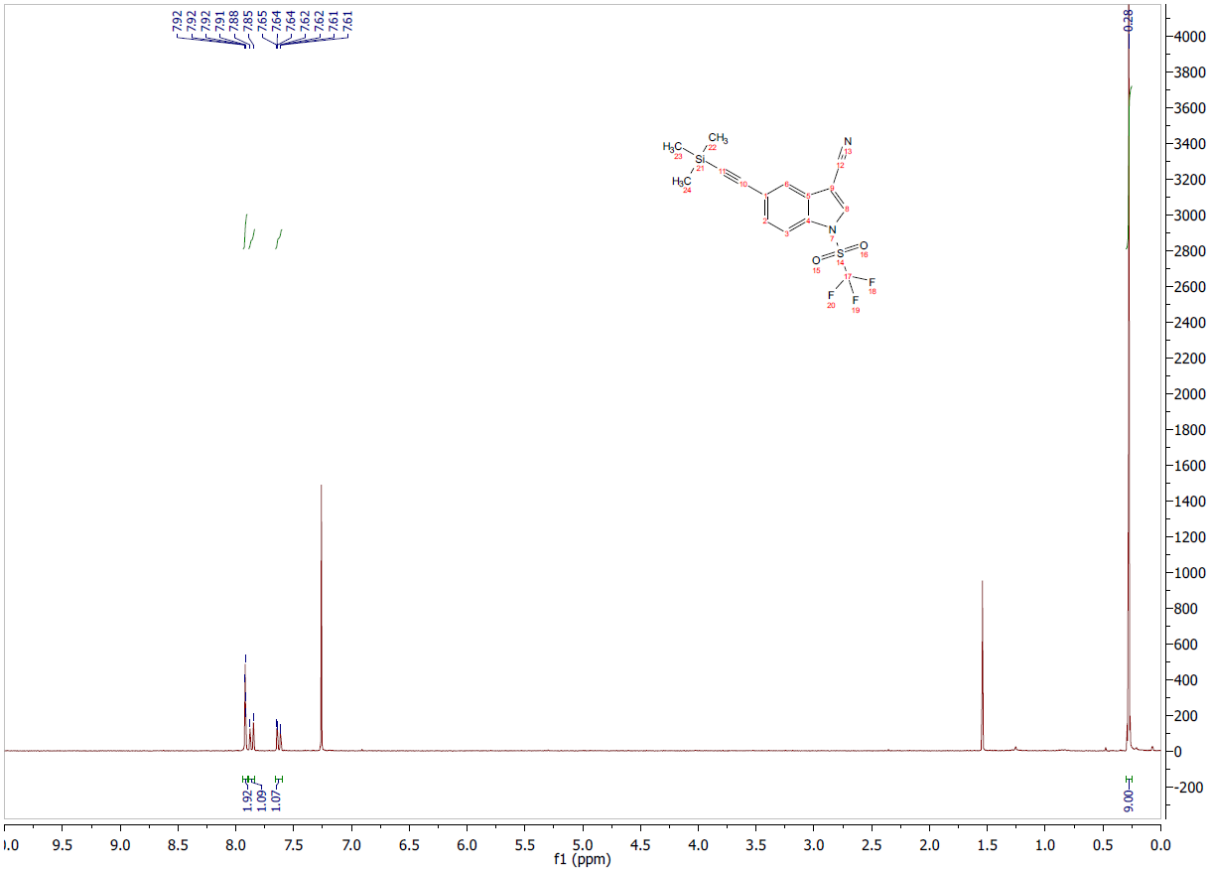
146.72
137.12
134.65
134.03
128.86
127.09
125.70
121.89
121.41
119.29
117.12
114.82
112.83
111.82
97.83
f1 (ppm)

2q:


7.92
7.92
7.92
7.91
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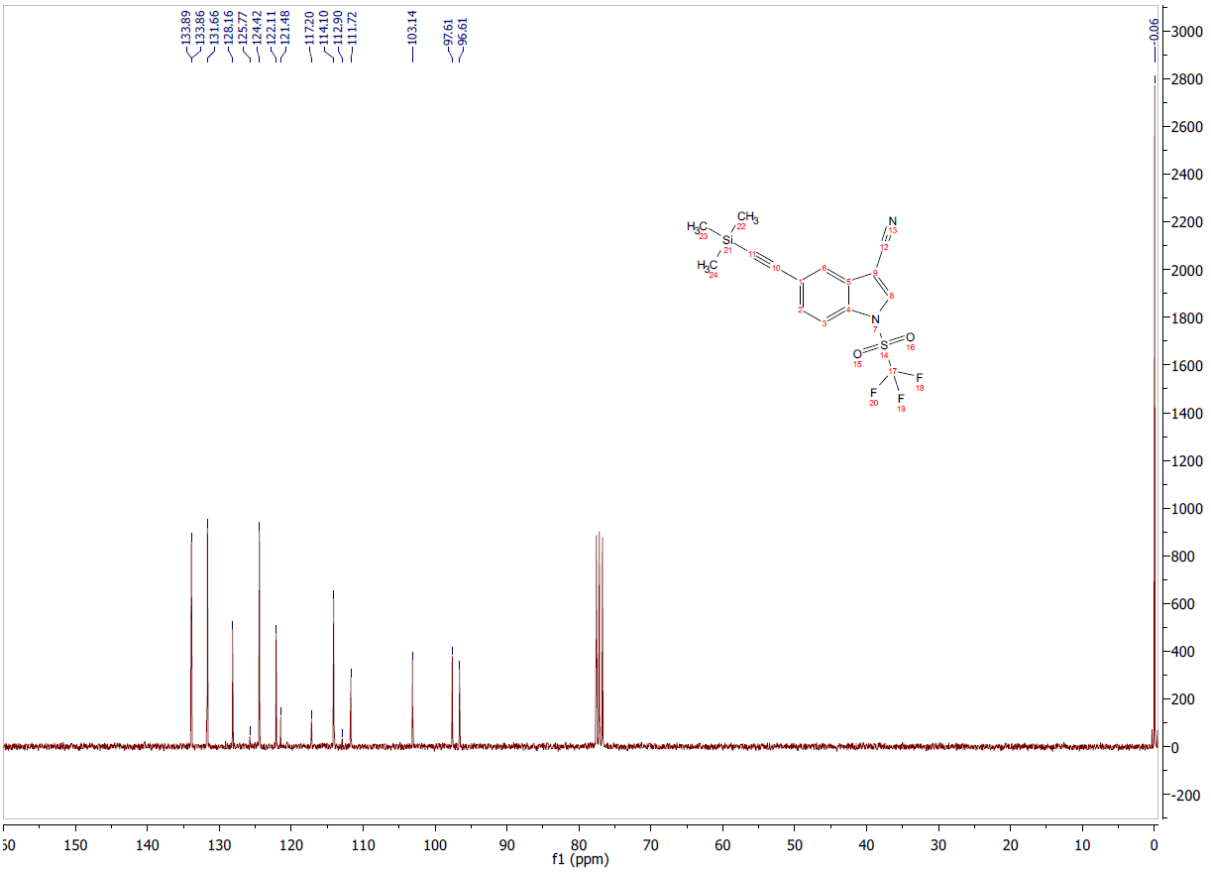
7.85
7.65
7.64
7.64
7.62
7.62
7.61
7.61
0.28
1.92
1.09
1.07
9.00
f1 (ppm)


133.89
133.86
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125.77
124.42
122.11
121.48
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114.10
112.90
111.72
103.14
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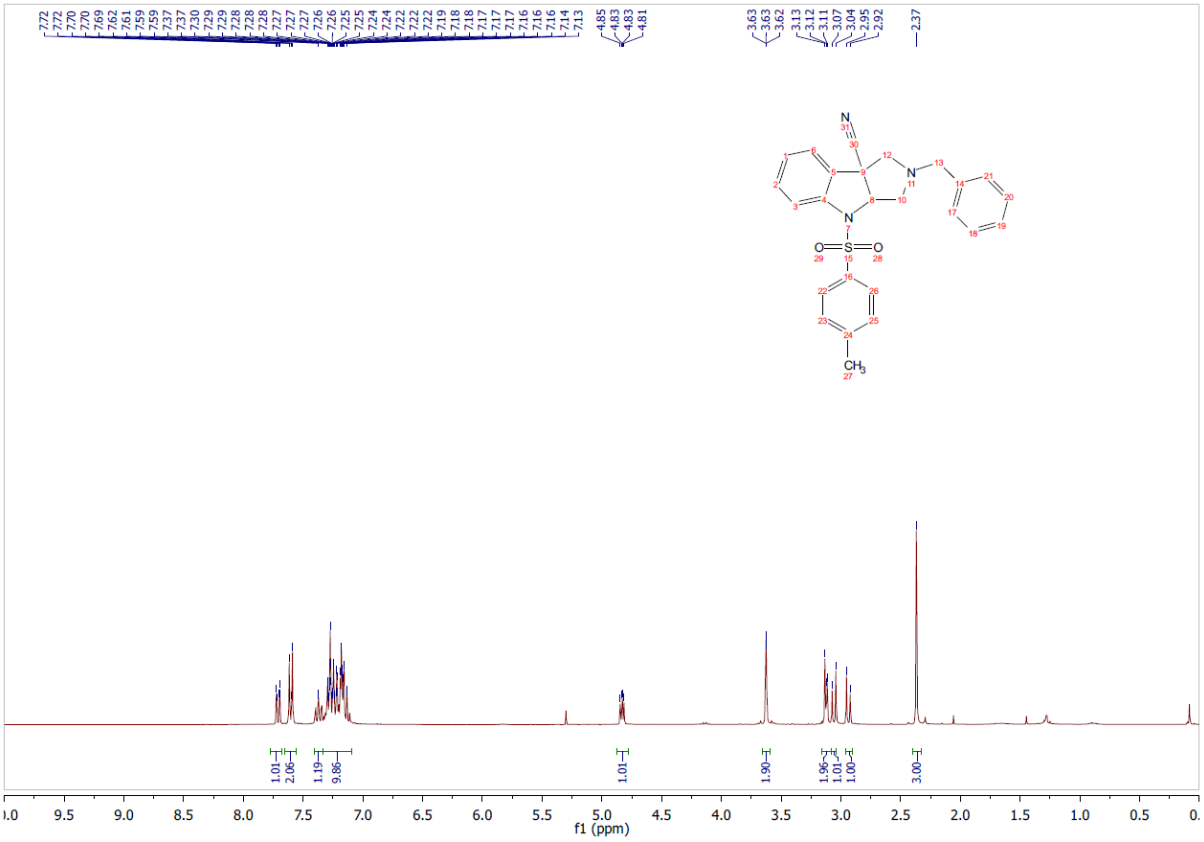
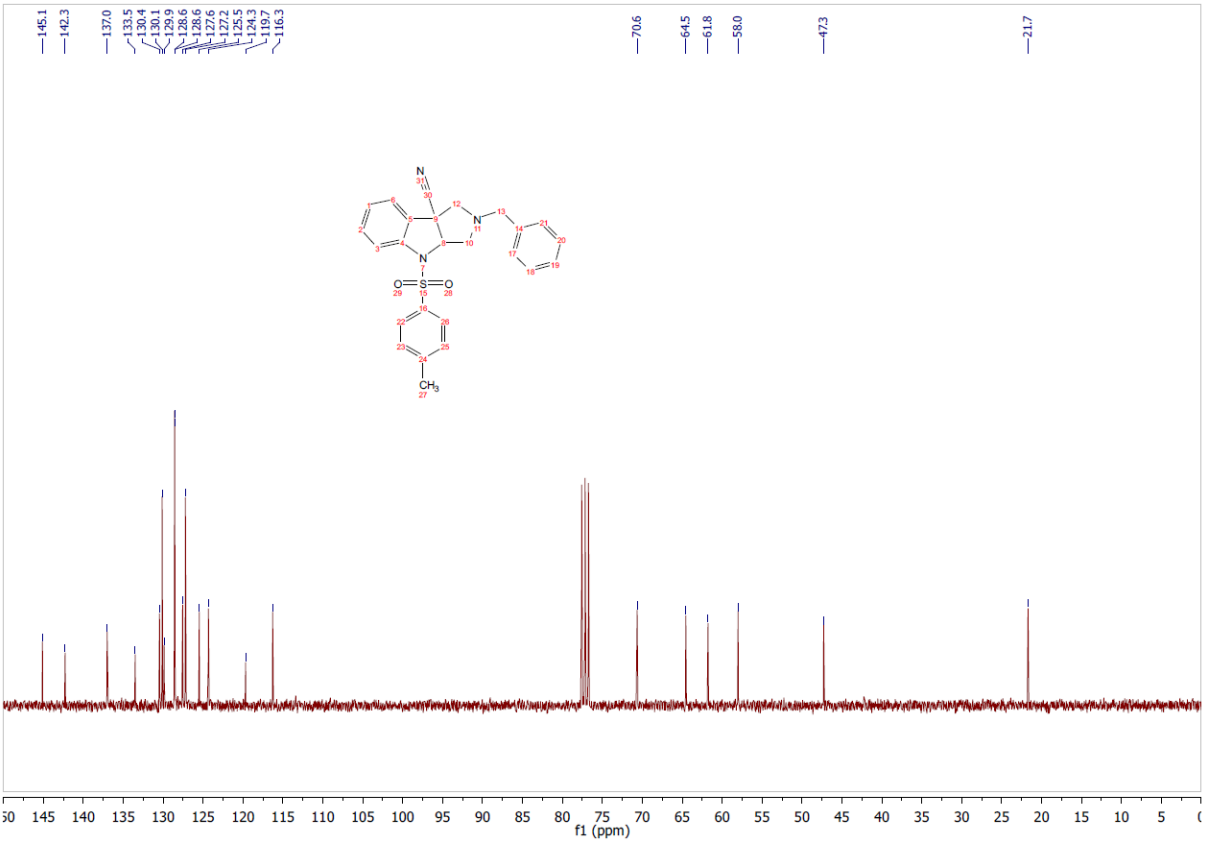
96.61
0.06
f1 (ppm)

3a:





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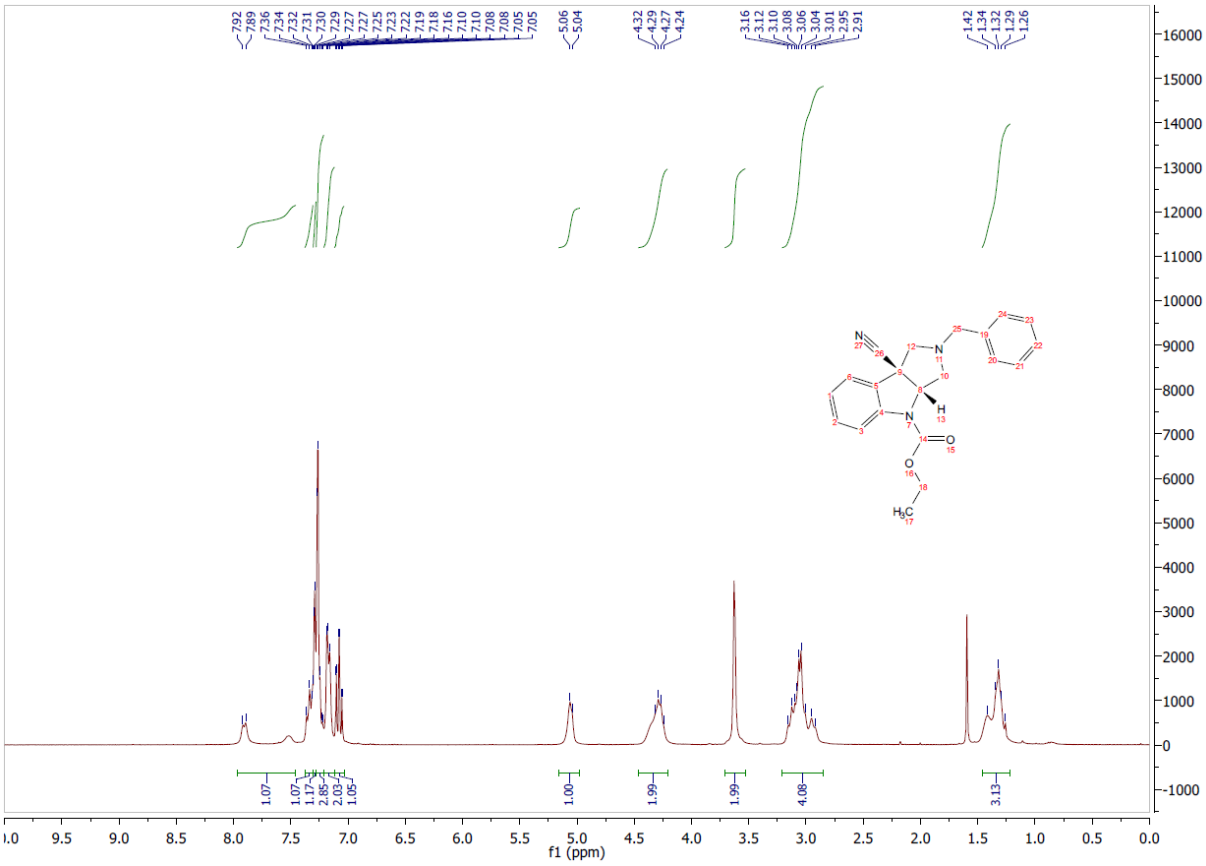
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7.29
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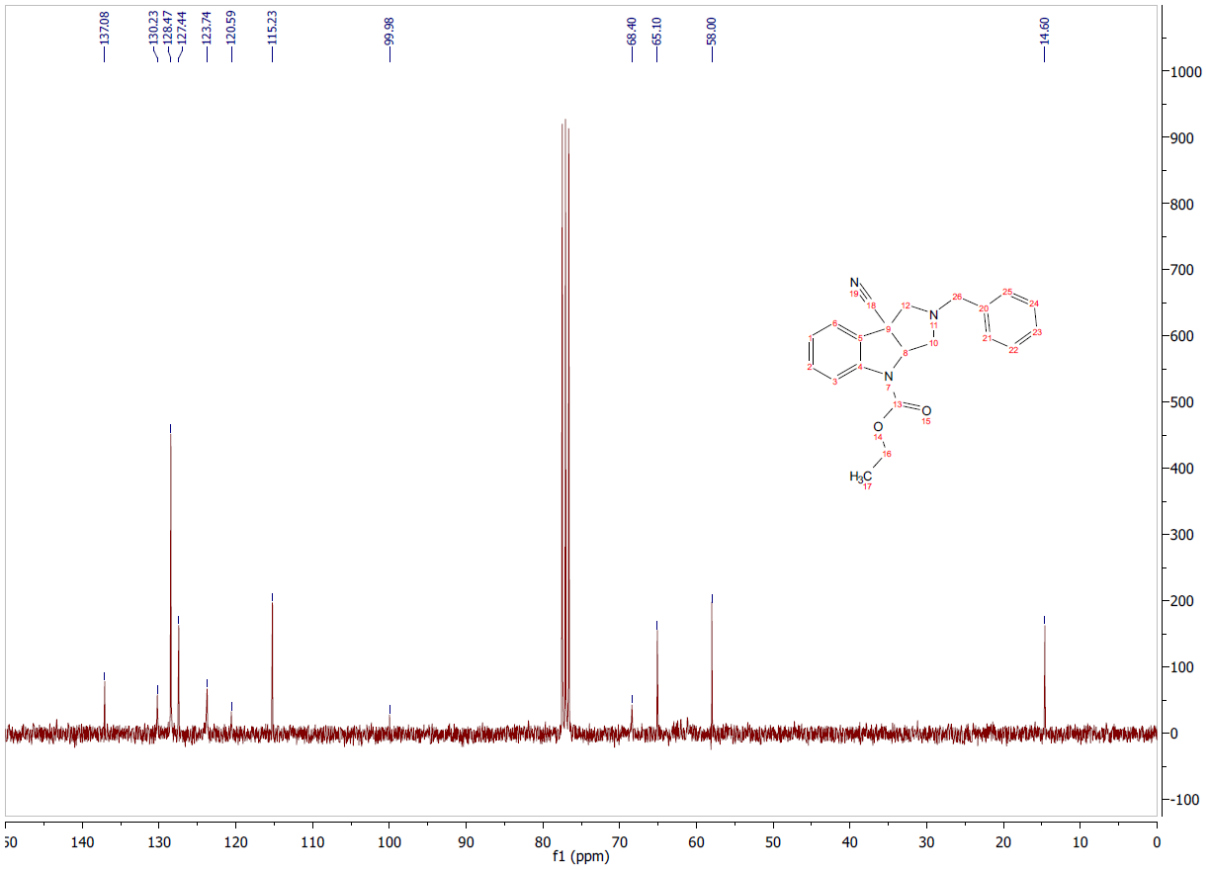
7.27
7.25
7.23
7.22
7.19
7.18
7.16
7.10
7.10
7.08
7.08
7.05
7.05
5.06
5.04
4.32
4.29
4.27
4.24
3.16
3.12
3.10
3.08
3.06
3.04
3.01
2.95
2.91
1.42
1.34
1.32
1.29
1.26
1.07
1.07
1.17
2.85
2.03
1.05
1.00
1.99
1.99
4.08
3.13
f1 (ppm)


137.08
130.23
128.47
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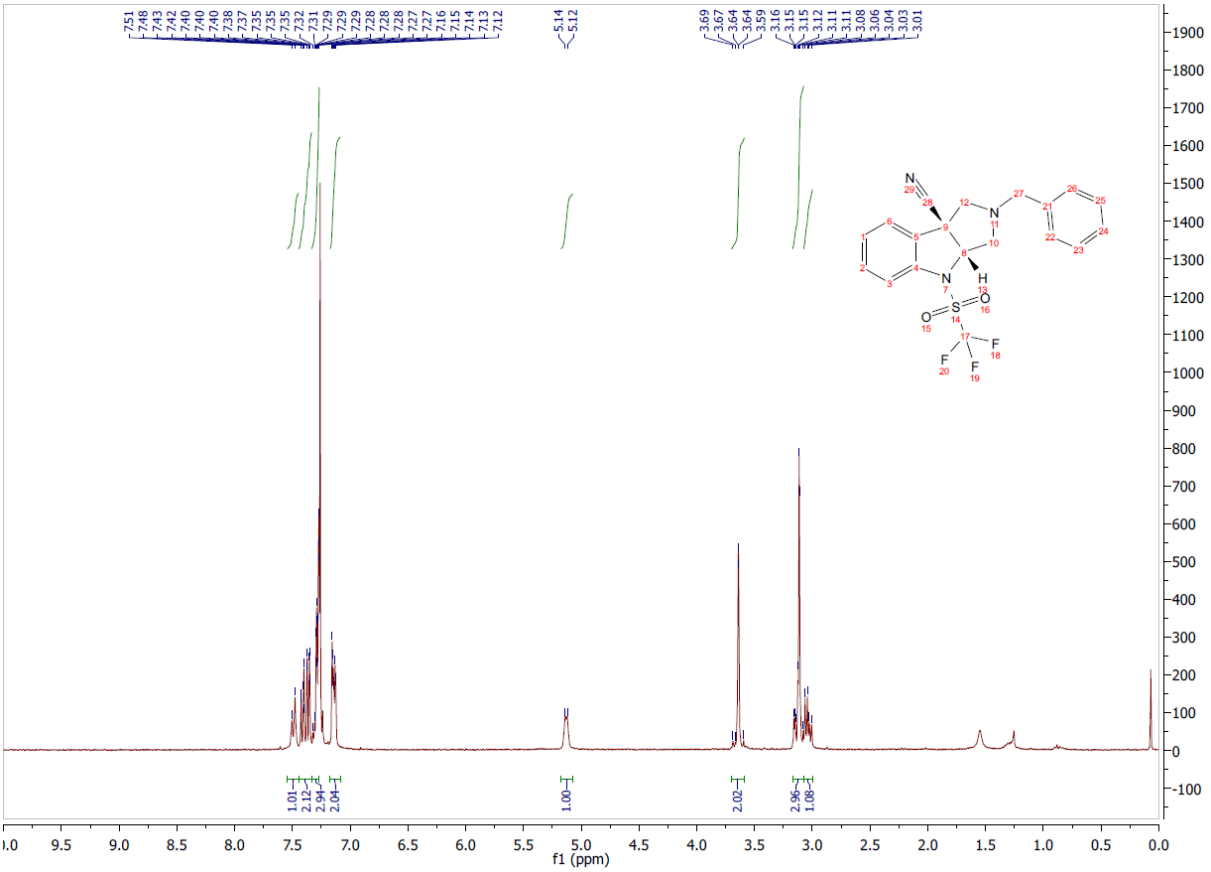
123.74
120.59
115.23
99.98
68.40
65.10
58.00
14.60
f1 (ppm)

3d: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7.40
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7.37
7.35
7.35
7.35
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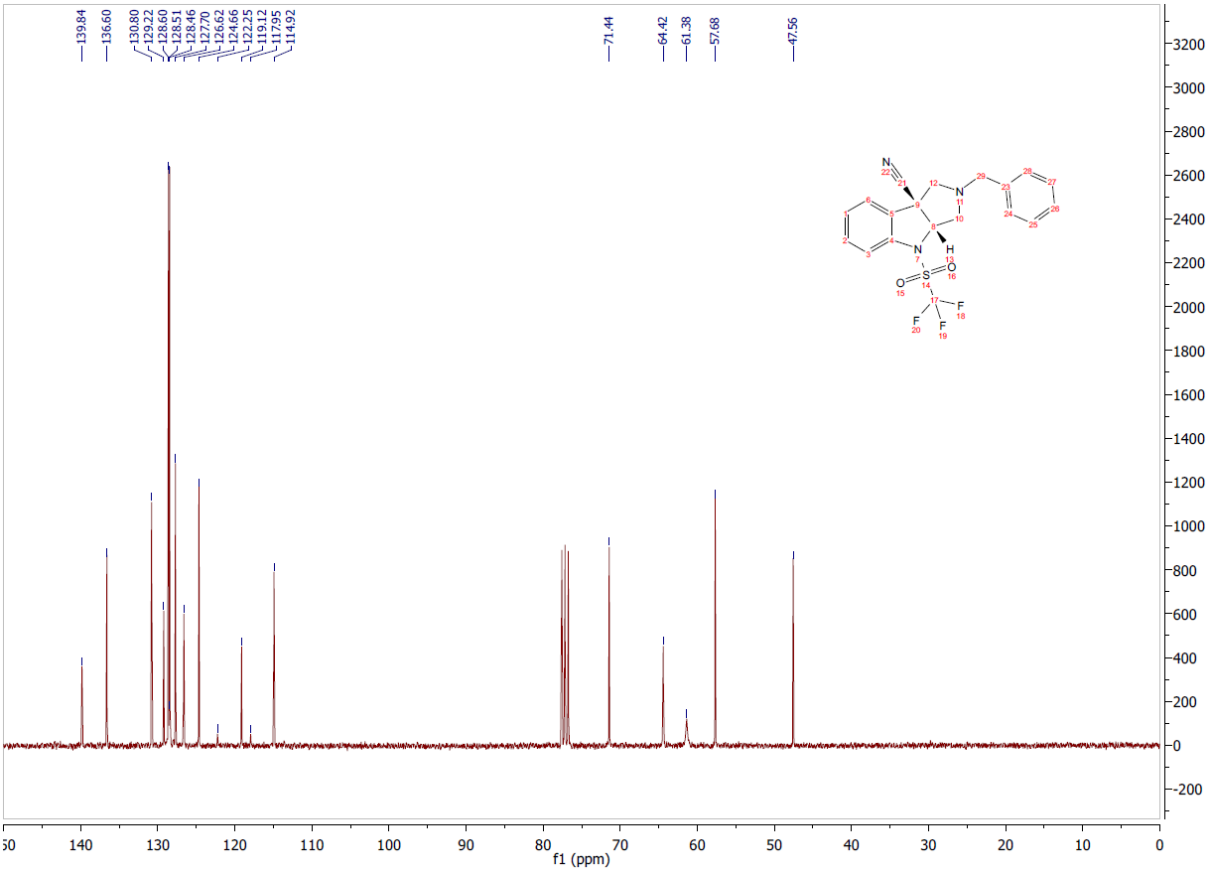
7.31
7.29
7.29
7.29
7.28
7.28
7.28
7.27
7.27
7.16
7.15
7.14
7.13
7.12
5.14
5.12
3.69
3.67
3.64
3.64
3.59
3.16
3.15
3.15
3.12
3.11
3.11
3.08
3.06
3.04
3.03
3.01
1.01
2.12
2.94
2.04
1.00
2.02
2.96
1.08
f1 (ppm)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128.60
128.51
128.46
127.70
126.62
124.66
122.25
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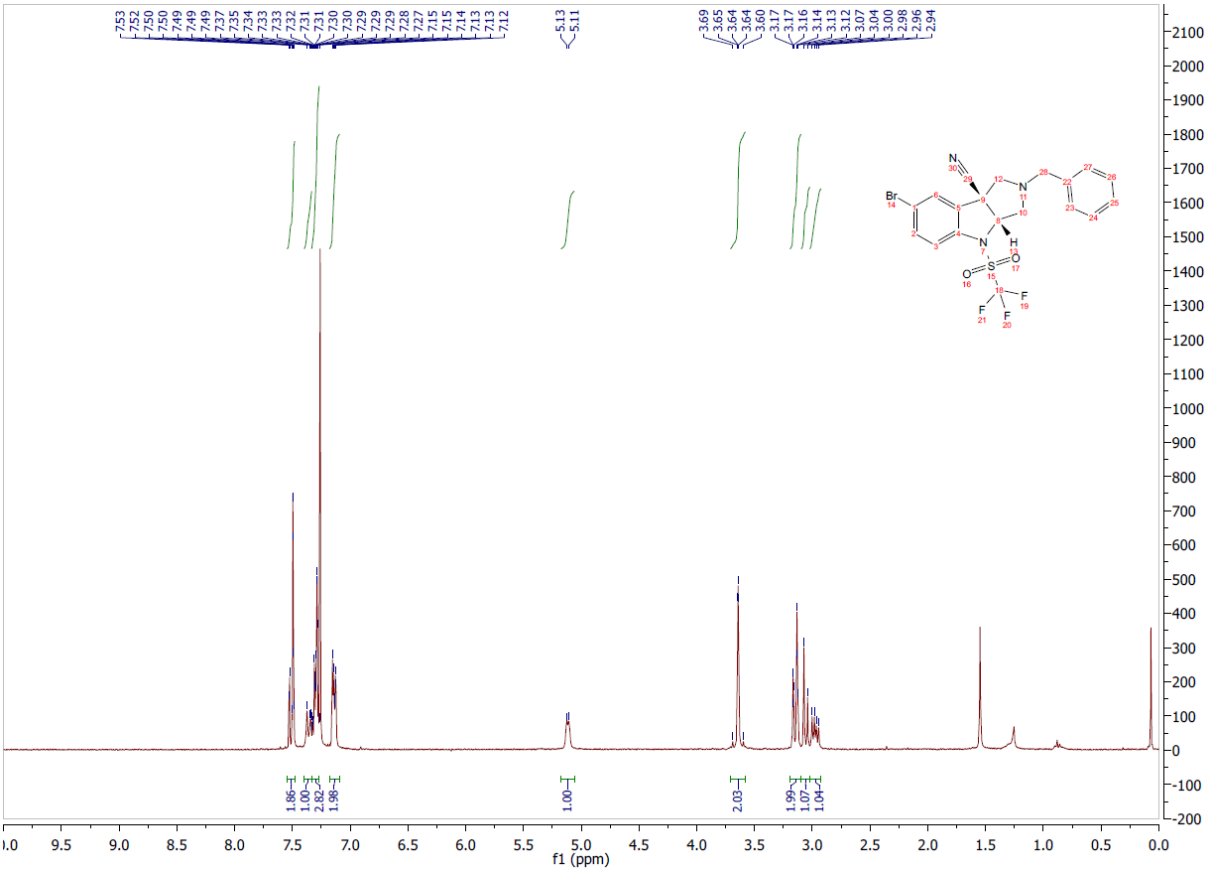
117.95
114.92
71.44
64.42
61.38
57.68
47.56
f1 (ppm)

3e: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7.49
7.37
7.35
7.34
7.33
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7.30
7.29
7.29
7.29
7.28
7.27
7.15
7.15
7.14
7.13
7.13
7.12
5.13
5.11
3.69
3.65
3.64
3.64
3.60
3.17
3.17
3.16
3.14
3.13
3.12
3.07
3.04
3.00
2.98
2.96
2.94
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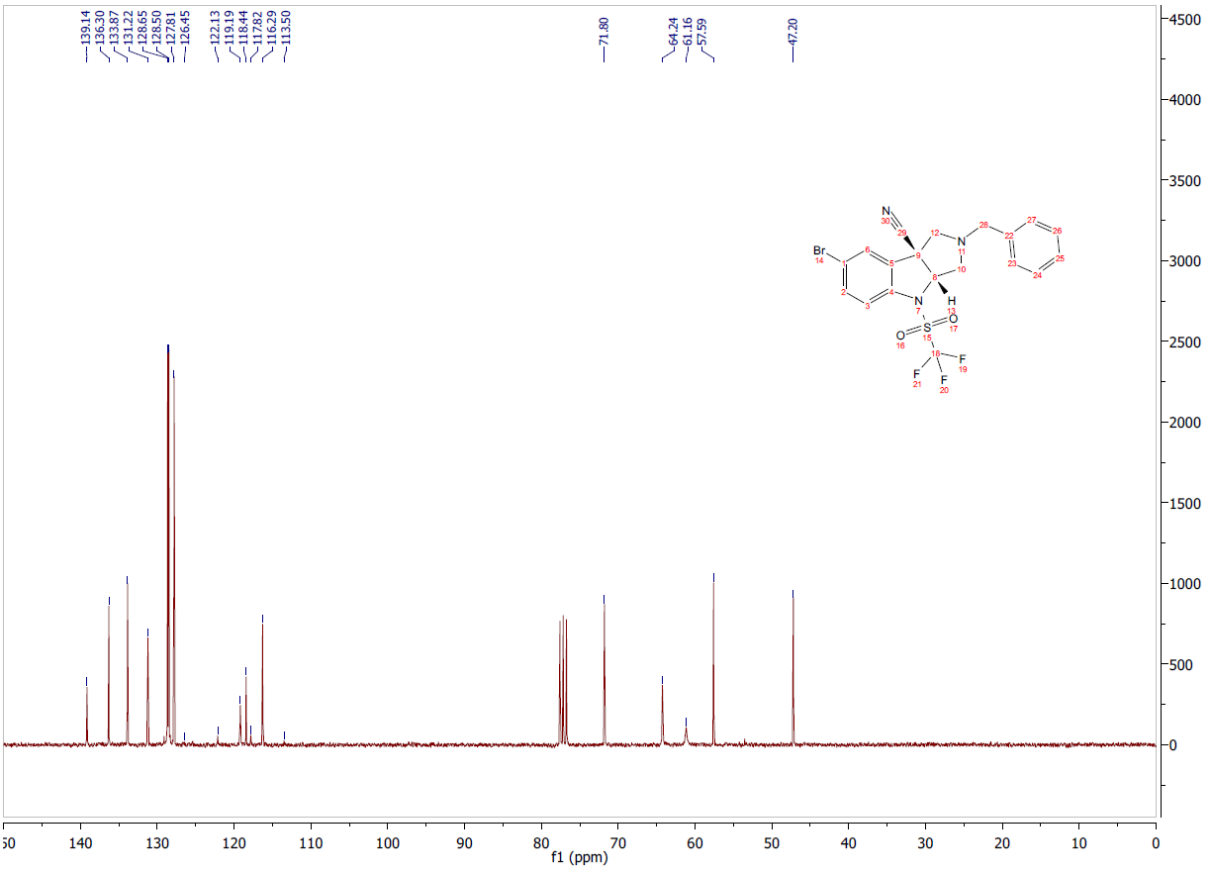
1.00
2.82
1.98
1.00
2.03
1.99
1.07
1.04
f1 (ppm)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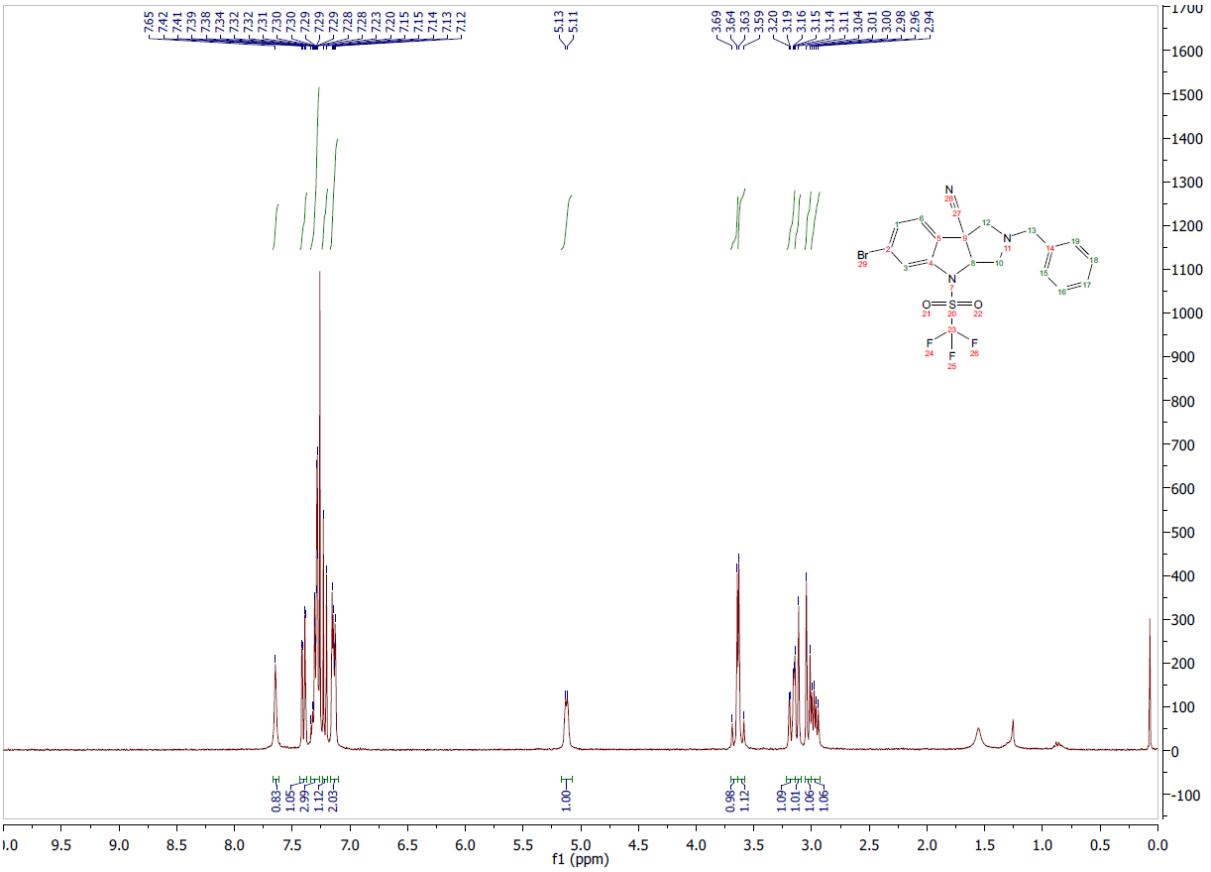
136.30
133.87
131.22
128.65
128.50
127.81
126.45
122.13
119.19
118.44
117.82
116.29
113.50
71.80
64.24
61.16
57.59
47.20
f1 (ppm)

3f: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7.38
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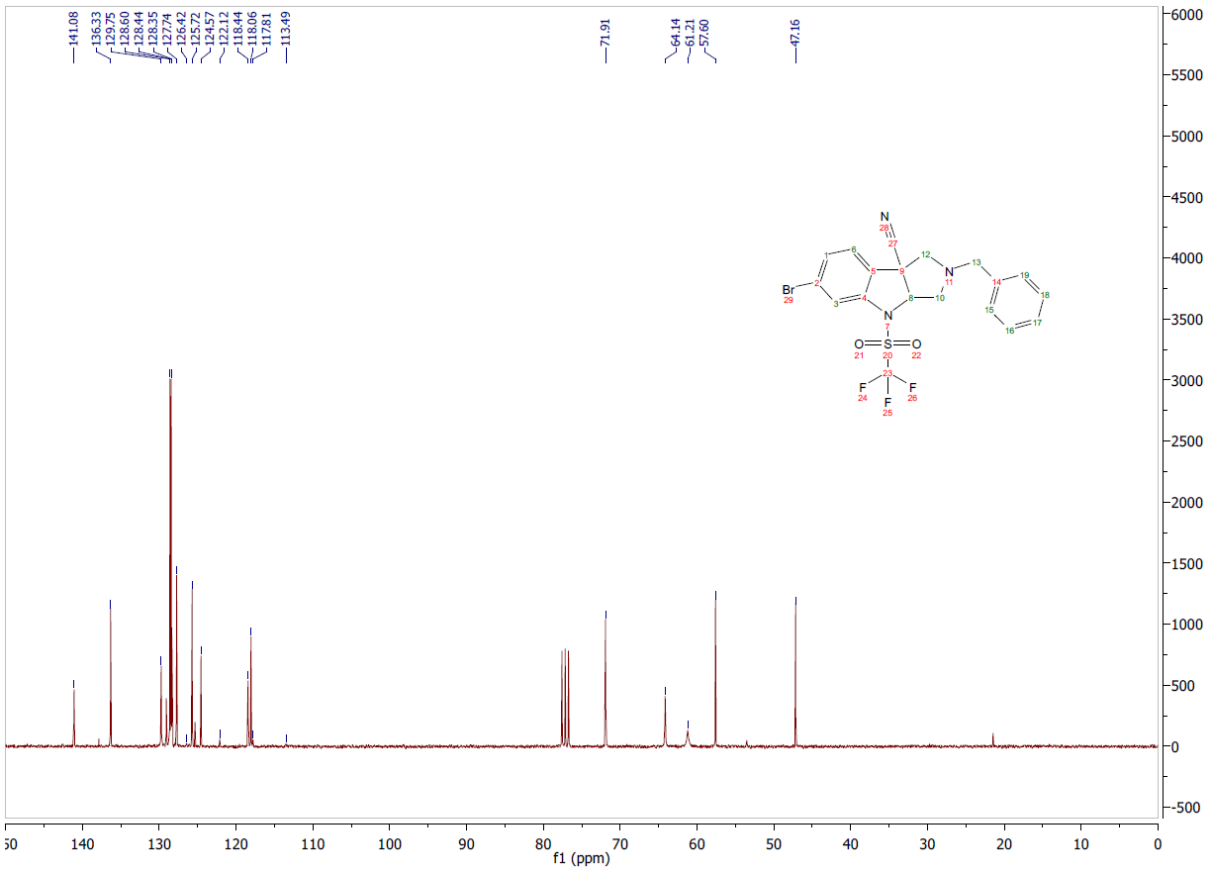
7.32
7.32
7.31
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.23
7.20
7.15
7.15
7.14
7.13
7.12
5.13
5.11
3.69
3.64
3.63
3.59
3.20
3.19
3.16
3.15
3.14
3.11
3.04
3.01
3.00
2.98
2.96
2.94
0.83
1.05
2.99
1.12
2.03
1.00
0.98
1.12
1.09
1.01
1.06
1.06
f1 (ppm)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129.75
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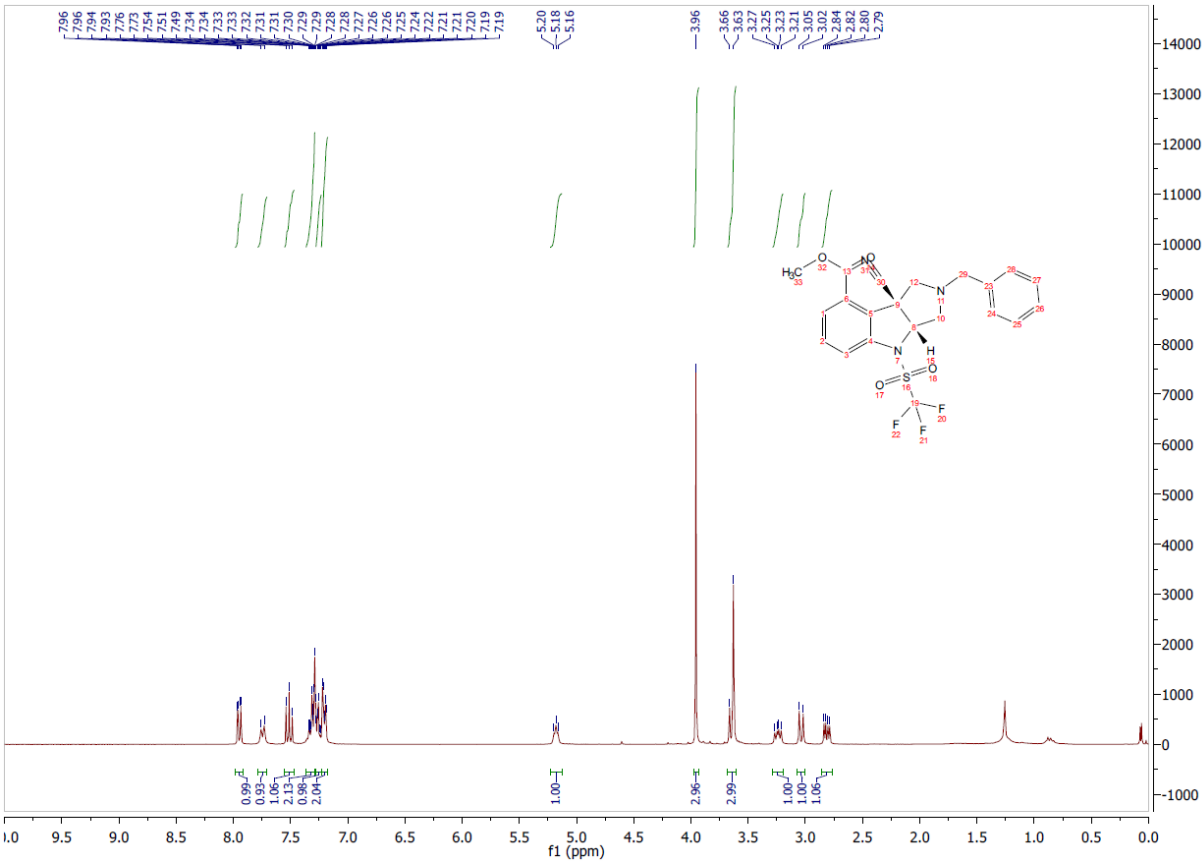
128.44
128.35
127.74
126.42
125.72
124.57
122.12
118.44
118.06
117.81
113.49
71.91
64.14
61.21
57.60
47.16
f1 (ppm)

3g: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7.73
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7.51
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7.32
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7.31
7.30
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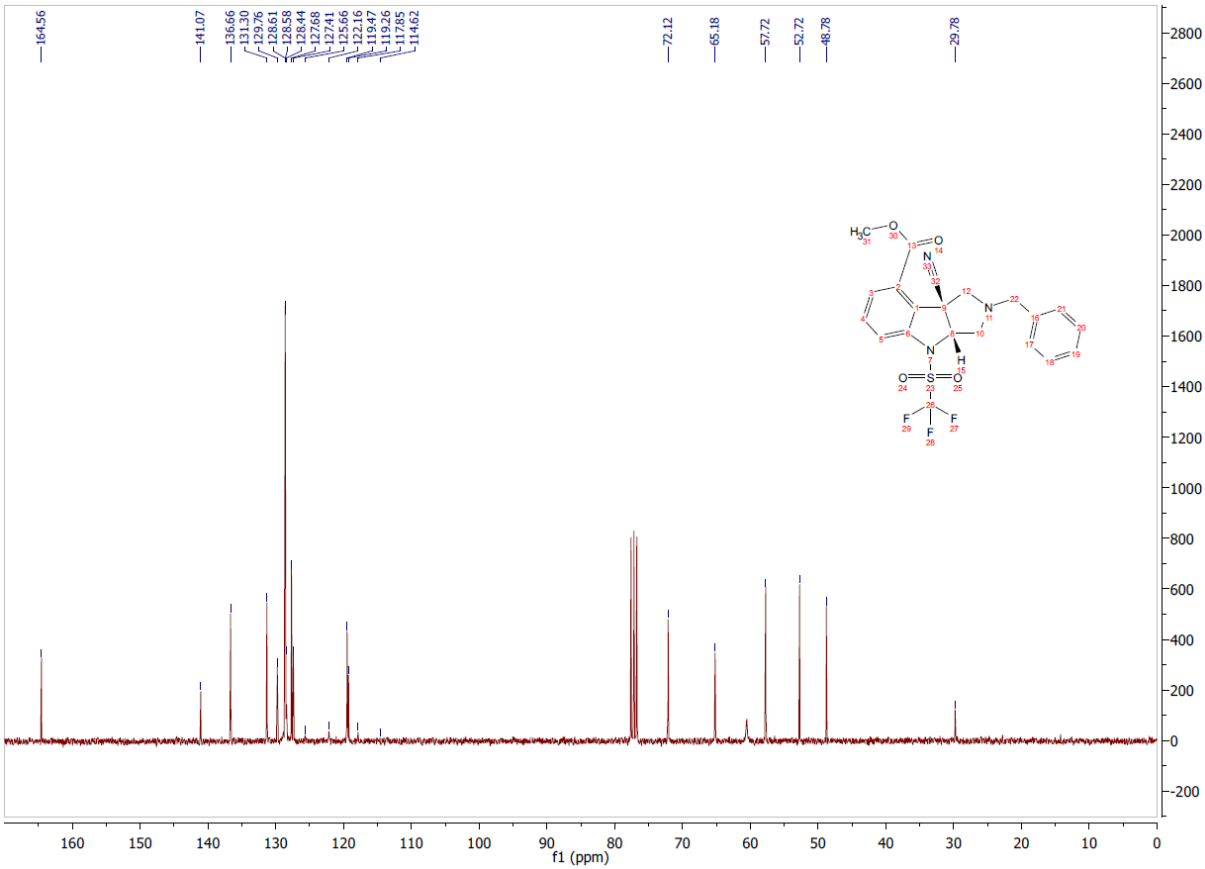
7.29
7.28
7.28
7.27
7.26
7.26
7.25
7.24
7.22
7.21
7.21
7.20
7.19
7.19
5.20
5.18
5.16
3.96
3.66
3.63
3.27
3.25
3.23
3.21
3.05
3.02
2.84
2.82
2.80
2.79
0.99
0.93
1.05
2.13
0.98
2.04
1.00
2.96
2.99
1.00
1.00
1.06
f1 (ppm)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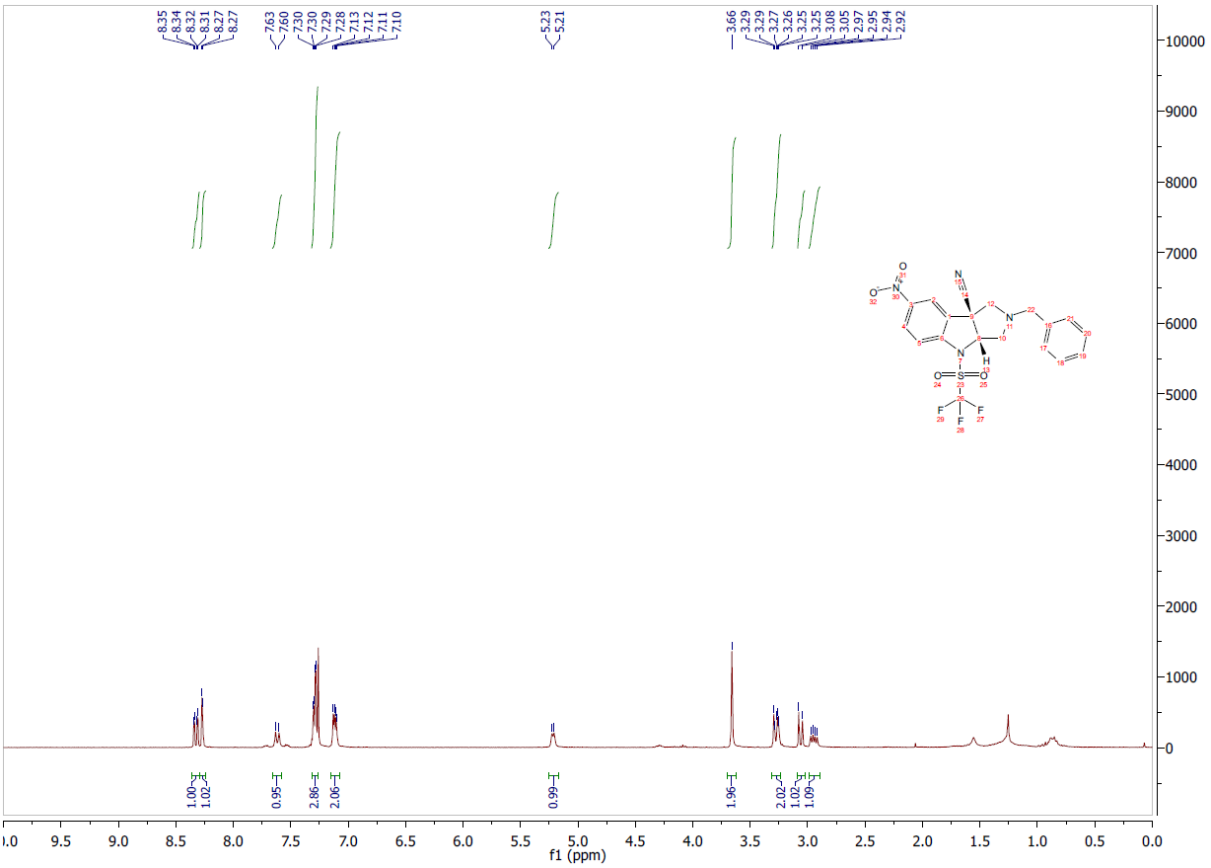
128.61
128.58
128.44
127.68
127.41
125.66
122.16
119.47
119.26
117.85
114.62
72.12
65.18
57.72
52.72
48.78
29.78
f1 (ppm)

3h: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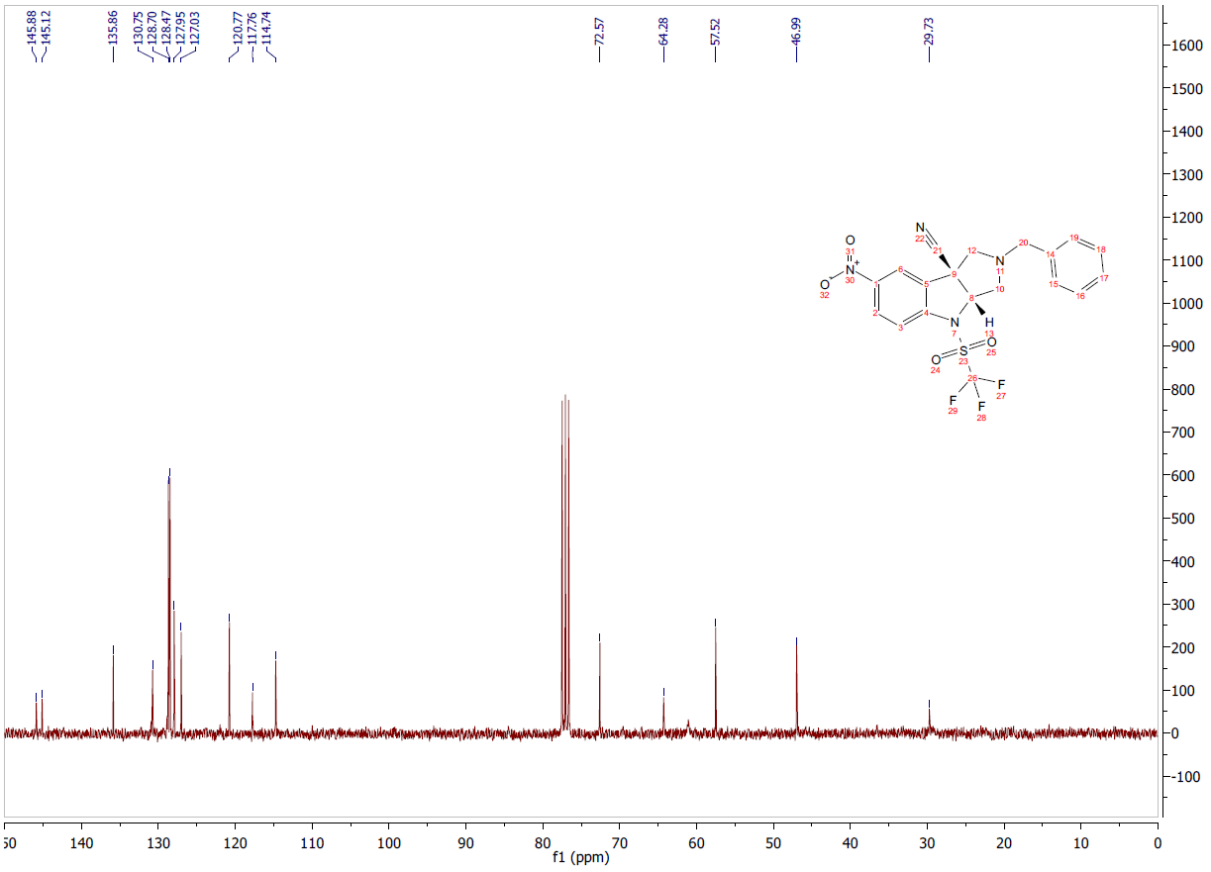
8.27
7.63
7.60
7.30
7.30
7.29
7.28
7.13
7.12
7.11
7.10
5.23
5.21
3.66
3.29
3.29
3.27
3.26
3.25
3.25
3.08
3.05
2.97
2.95
2.94
2.92
1.00
1.02
0.95
2.86
2.06
0.99
1.96
2.02
1.02
1.09
f1 (ppm)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127.03
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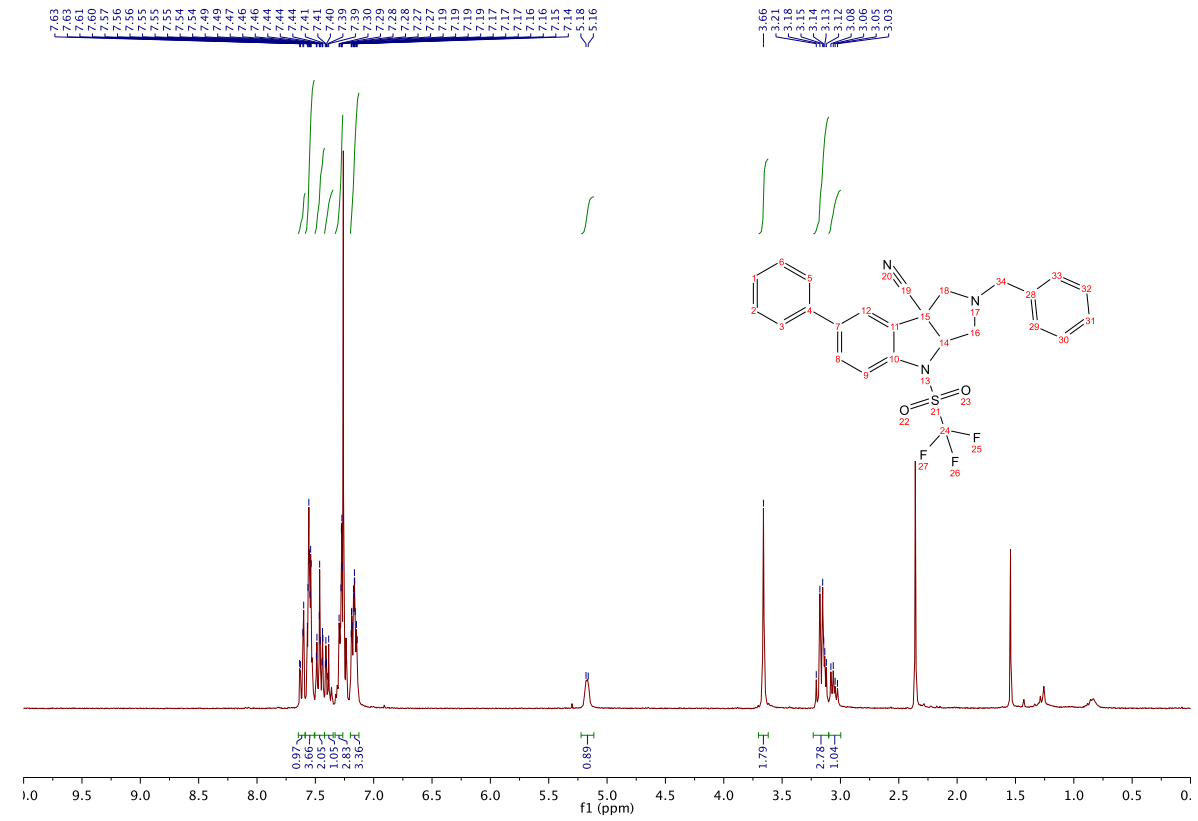
114.74
72.57
64.28
57.52
46.99
29.73
f1 (ppm)

3i: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7.47
7.46
7.44
7.41
7.40
7.39
7.30
7.29
7.28
7.27
7.19
7.17
7.16
7.15
7.14
5.18
5.16
3.66
3.21
3.18
3.15
3.14
3.13
3.12
3.08
3.06
3.05
3.03
0.97
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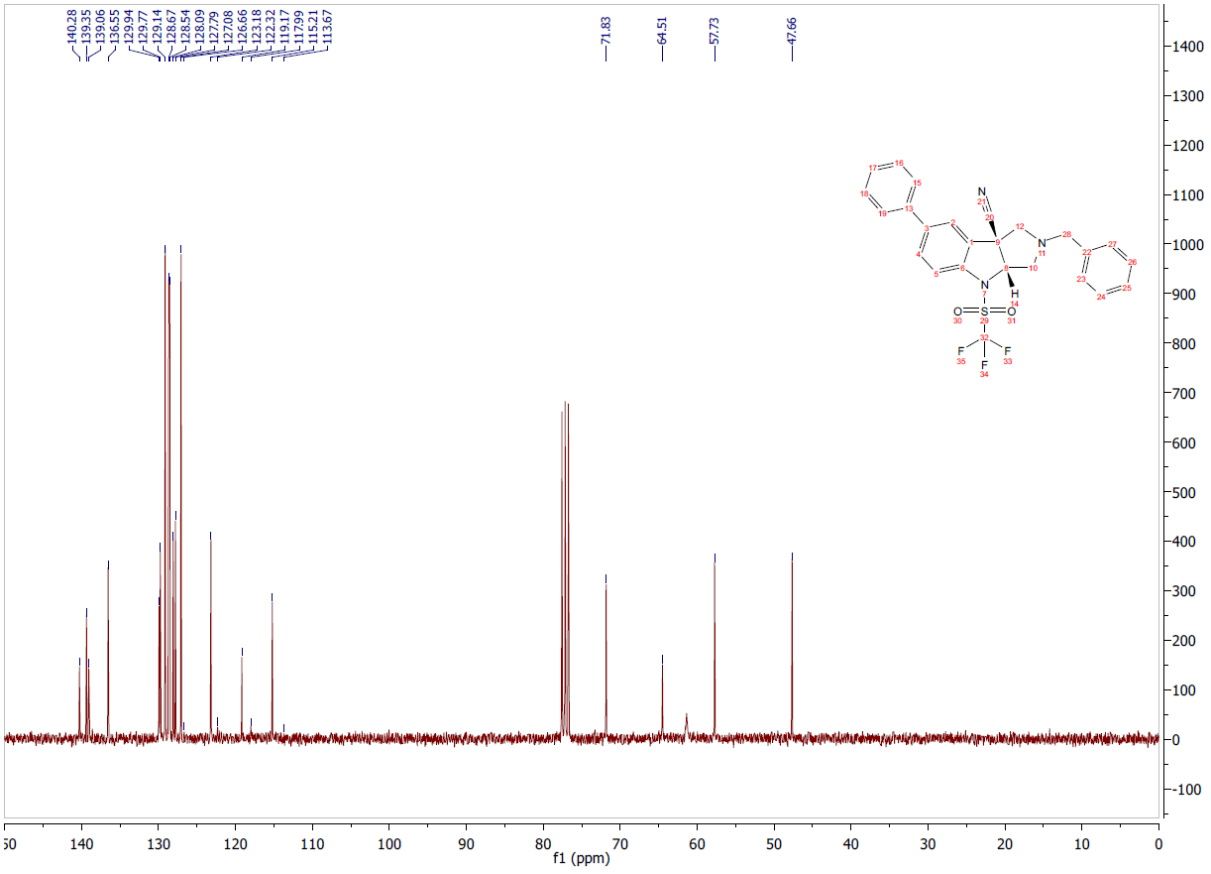
2.05
1.05
2.83
3.36
0.89
1.79
2.78
1.04
f1 (ppm)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128.54
128.09
127.79
127.08
126.66
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122.32
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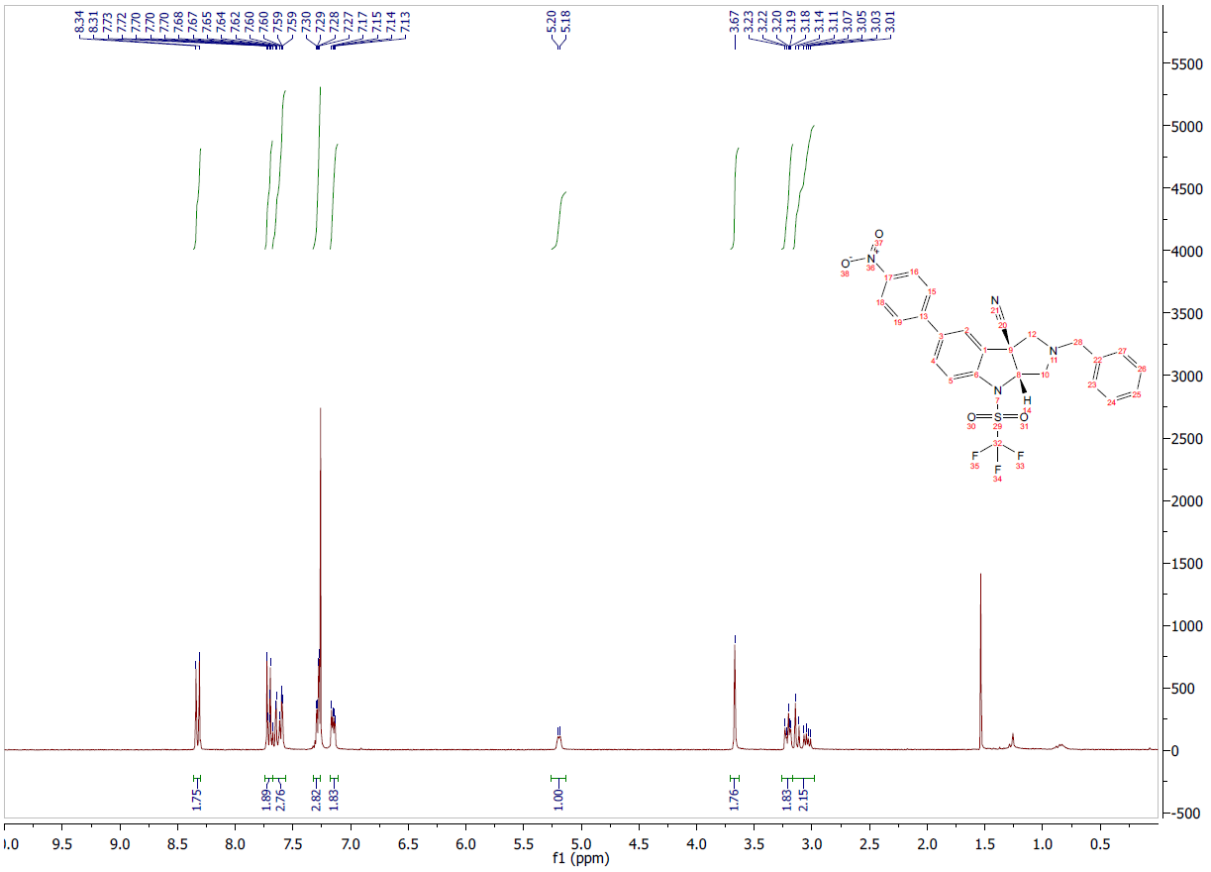
117.99
115.21
113.67
71.83
64.51
57.73
47.66
f1 (ppm)

3j: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7.67
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7.64
7.62
7.60
7.60
7.59
7.59
7.30
7.29
7.28
7.27
7.17
7.15
7.14
7.13
5.20
5.18
3.67
3.23
3.22
3.20
3.19
3.16
3.14
3.11
3.07
3.05
3.03
3.01
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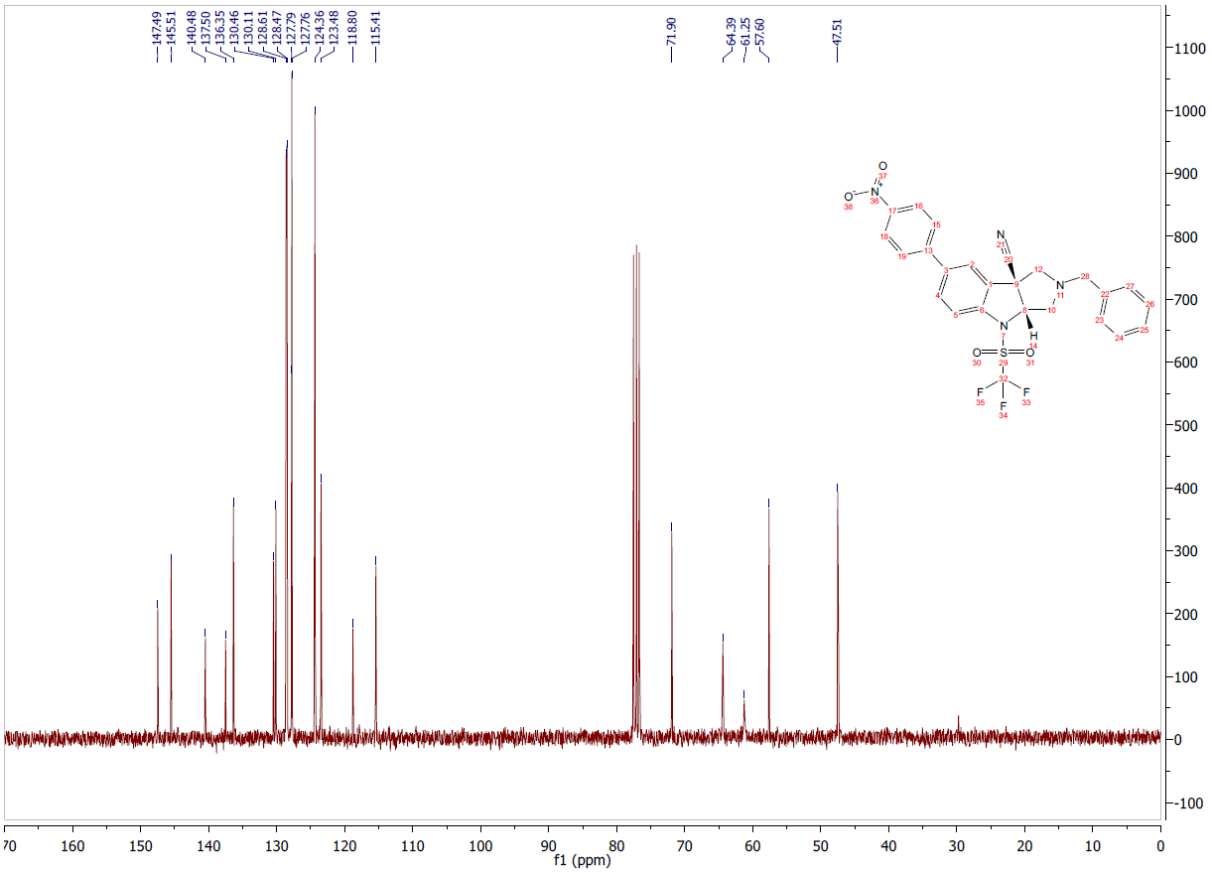
1.89
2.76
2.82
1.83
1.00
1.76
1.83
2.15
f1 (ppm)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130.46
130.11
128.61
128.47
127.79
127.76
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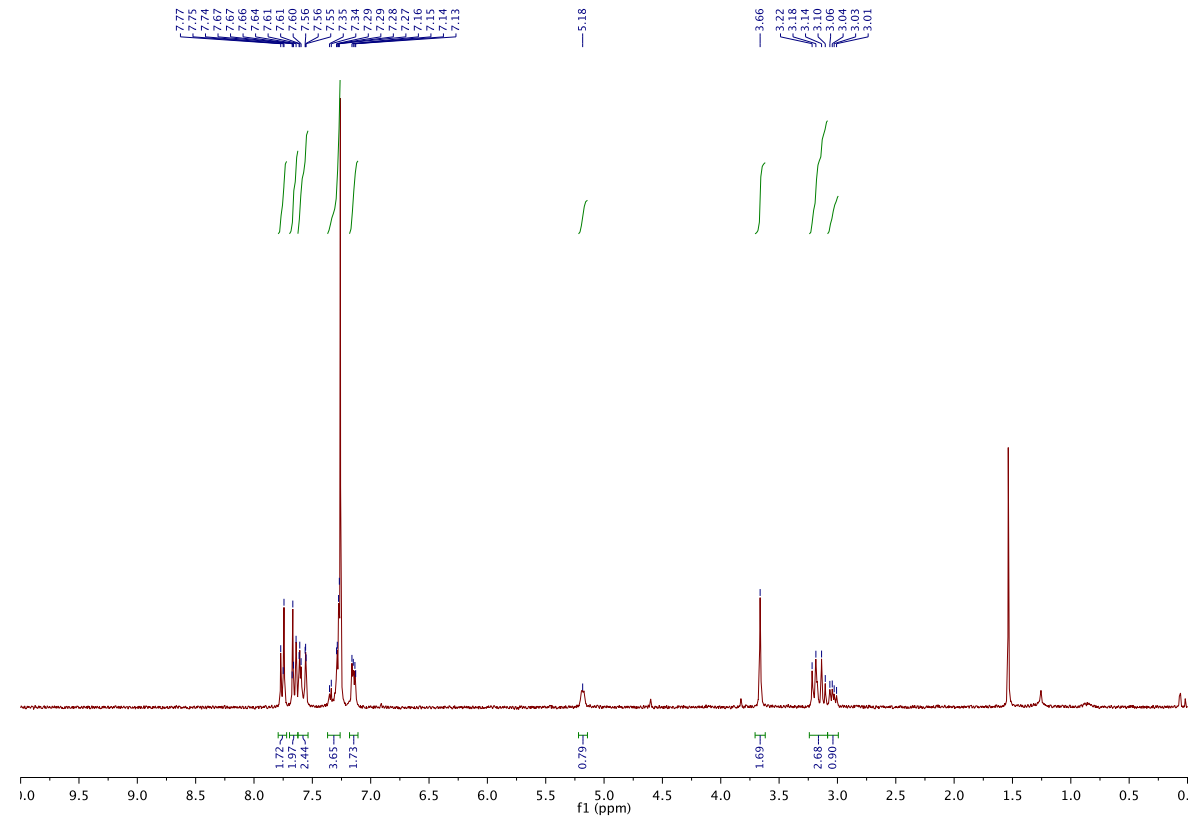
118.80
115.41
71.90
64.39
61.25
57.60
47.51
f1 (ppm)

3k: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7.35
7.35
7.34
7.29
7.29
7.28
7.27
7.16
7.15
7.14
7.13
5.18
3.66
3.22
3.18
3.14
3.10
3.06
3.04
3.03
3.01
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3.65
1.73
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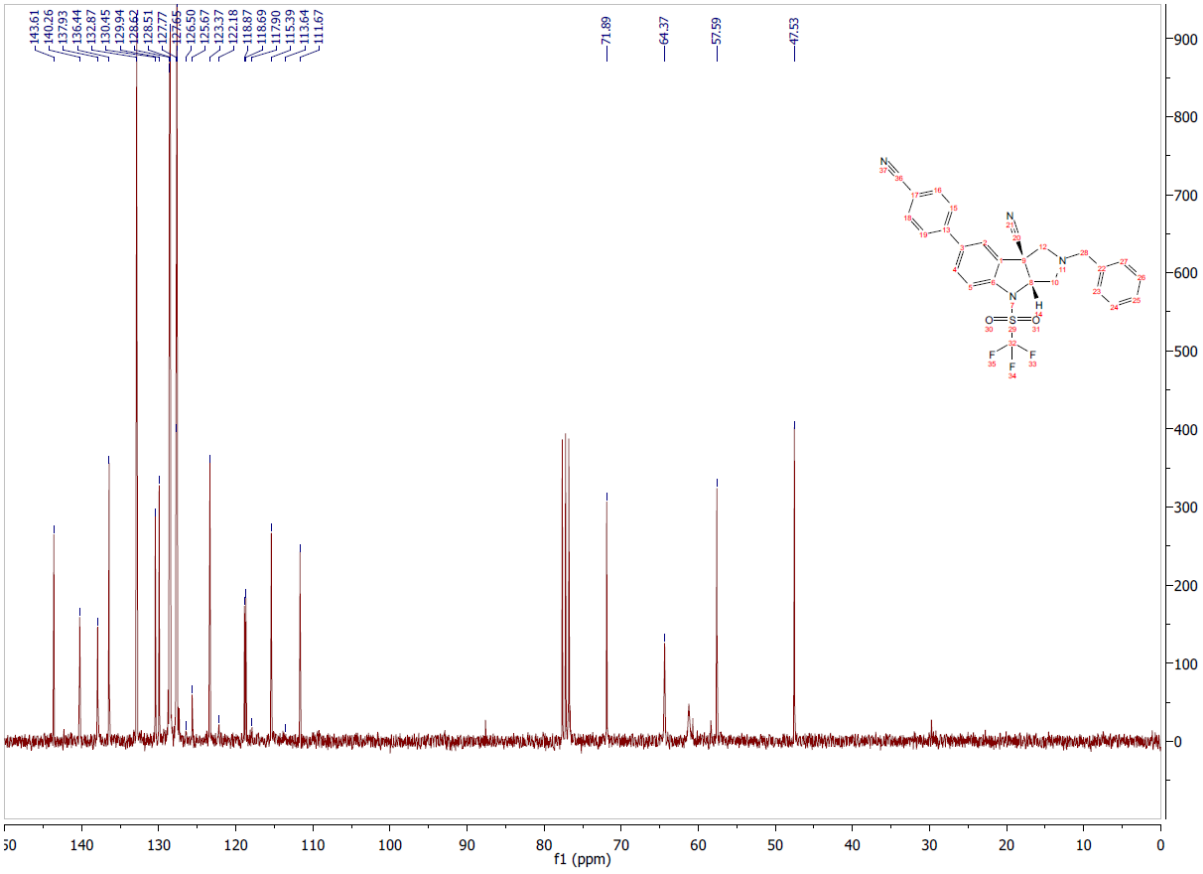
1.69
2.68
0.90
f1 (ppm)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127.77
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125.67
123.37
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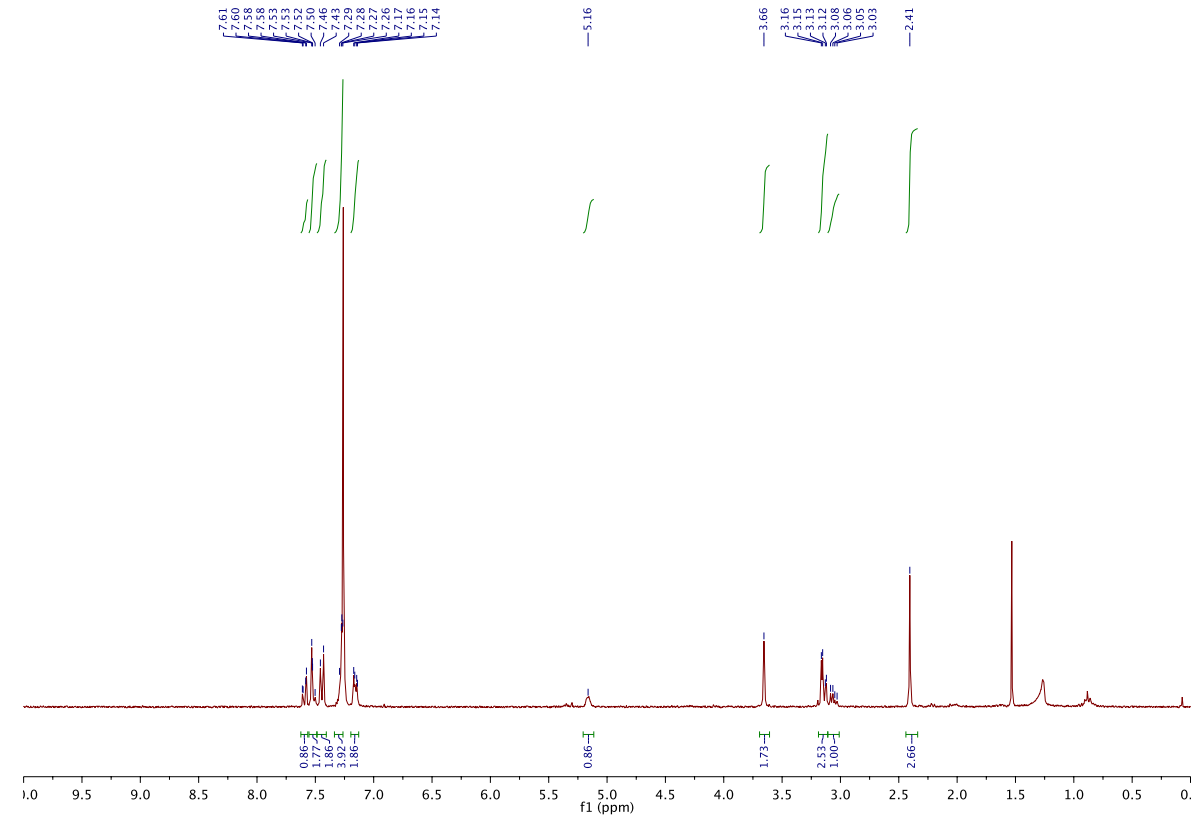
64.37
57.59
47.53
f1 (ppm)

3l: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7.52
7.50
7.46
7.43
7.29
7.28
7.27
7.26
7.17
7.16
7.15
7.14
5.16
3.66
3.16
3.15
3.13
3.12
3.08
3.06
3.05
3.03
2.41
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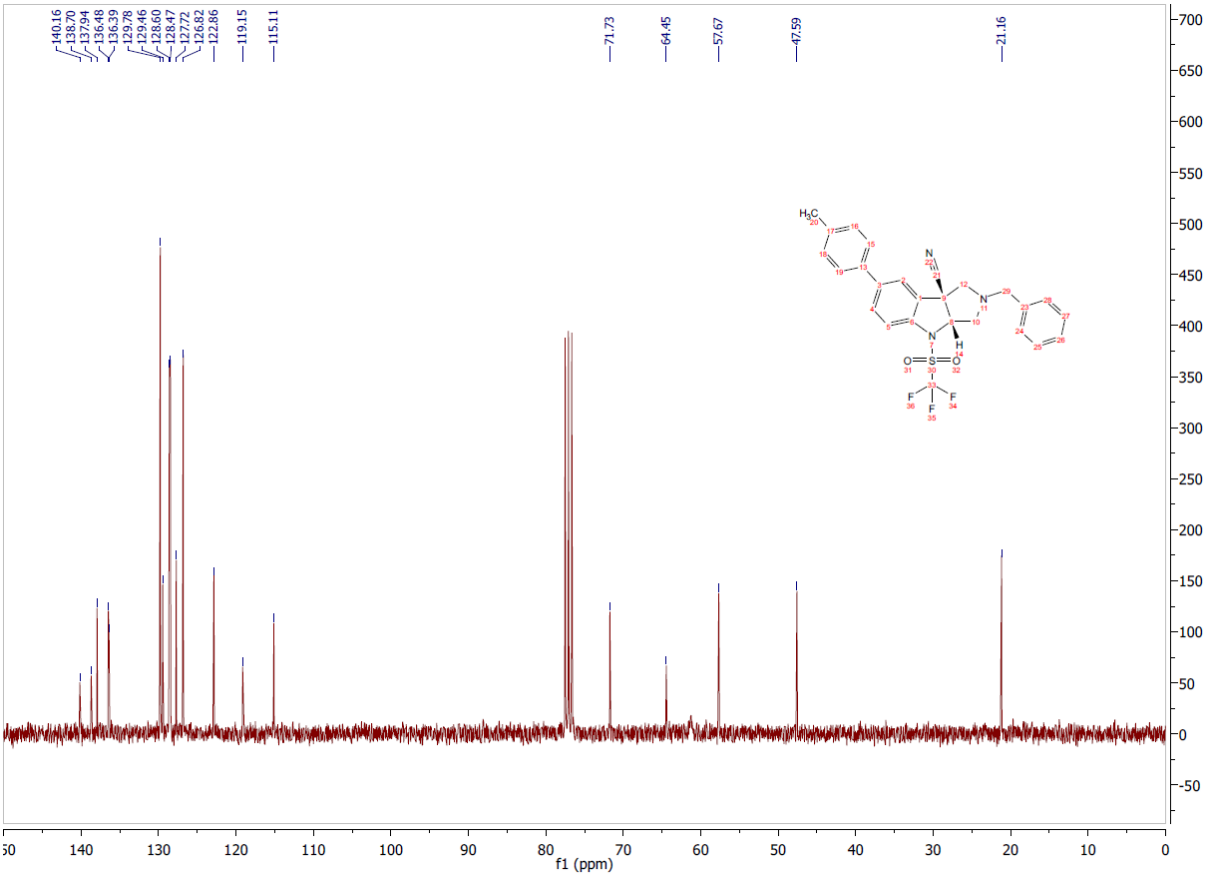
1.86
3.92
1.86
0.86
1.73
2.53
1.00
2.66
f1 (ppm)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129.78
129.46
128.60
128.47
127.72
126.82
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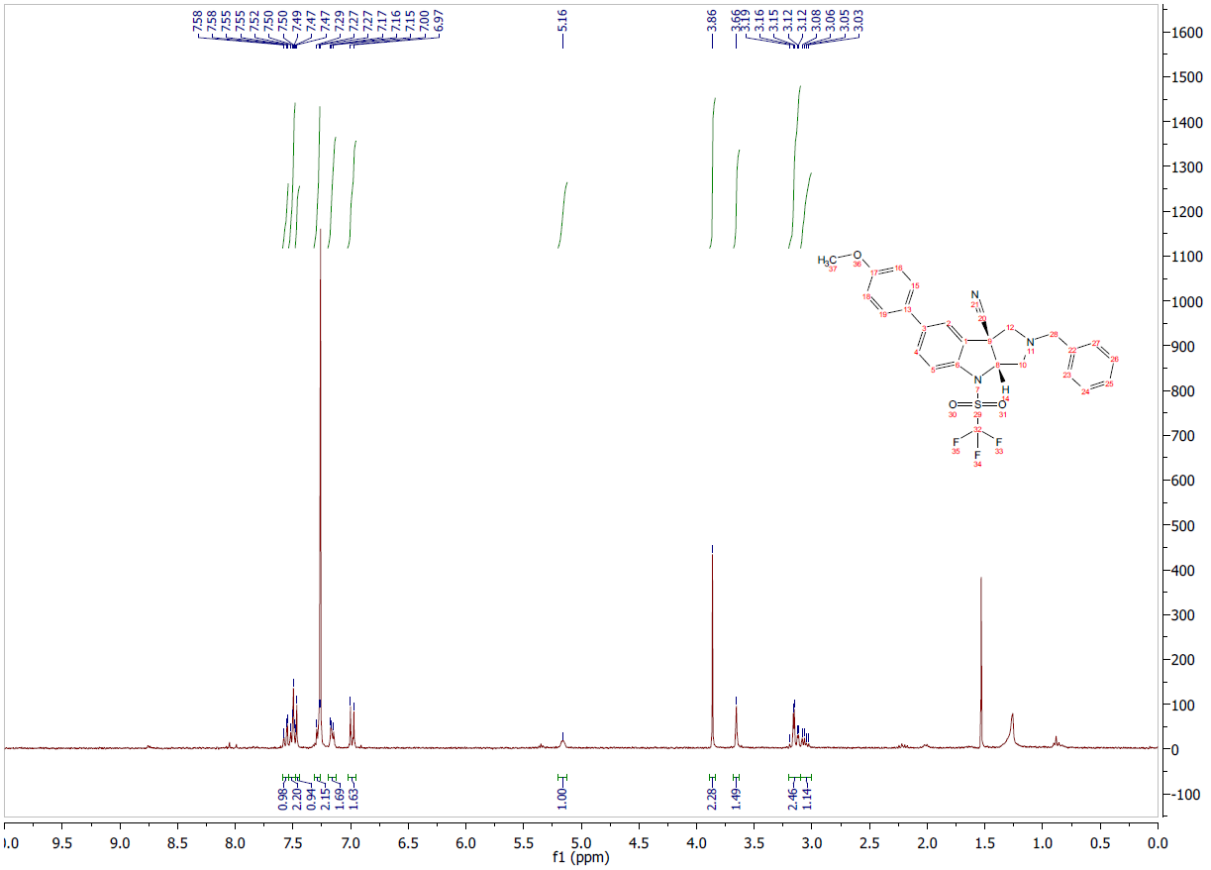
119.15
115.11
71.73
64.45
57.67
47.59
21.16
f1 (ppm)

3m: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7.55
7.55
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7.50
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7.47
7.47
7.29
7.27
7.27
7.17
7.16
7.15
7.00
6.97
5.16
3.86
3.66
3.65
3.16
3.15
3.12
3.08
3.06
3.05
3.03
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2.20
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2.15
1.69
1.63
1.00
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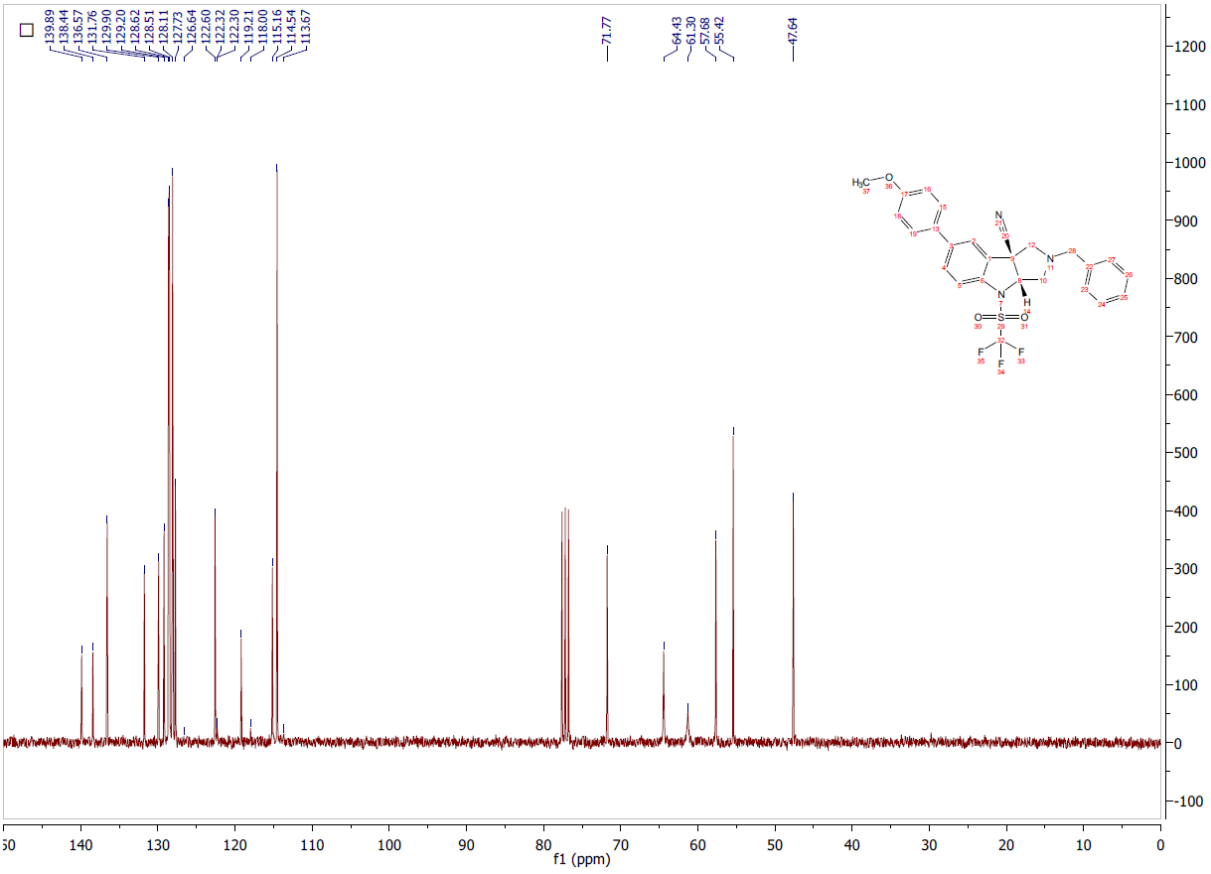
1.49
2.46
1.14
f1 (ppm)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129.90
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128.62
128.51
128.11
127.73
126.64
122.60
122.32
122.30
119.21
118.00
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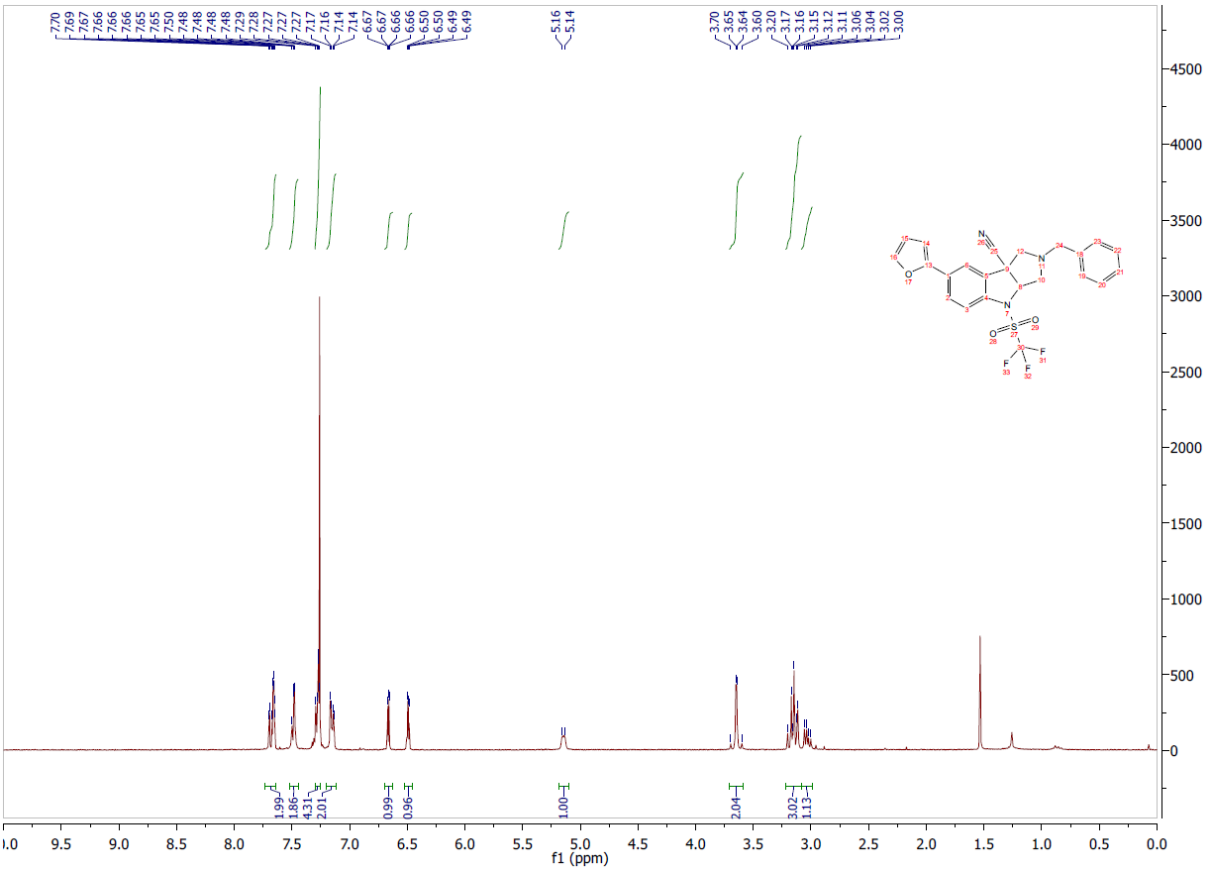
113.67
71.77
64.43
61.30
57.68
55.42
47.64
f1 (ppm)

3n: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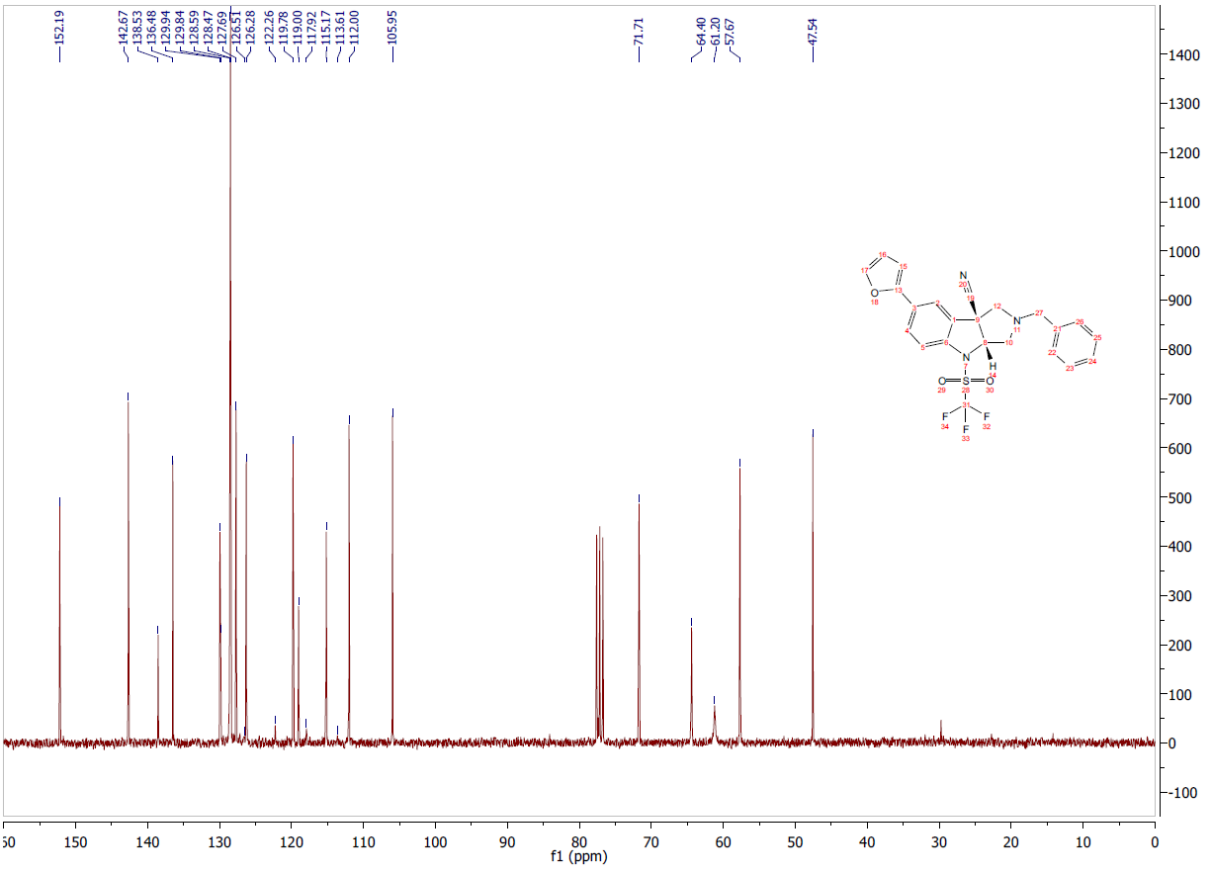
7.48
7.29
7.28
7.27
7.27
7.27
7.17
7.16
7.14
7.14
6.67
6.67
6.66
6.66
6.50
6.50
6.49
6.49
5.16
5.14
3.70
3.65
3.64
3.60
3.20
3.17
3.16
3.15
3.12
3.11
3.06
3.04
3.02
3.00
1.99
1.86
4.31
2.01
0.99
0.96
1.00
2.04
3.02
1.13
f1 (ppm)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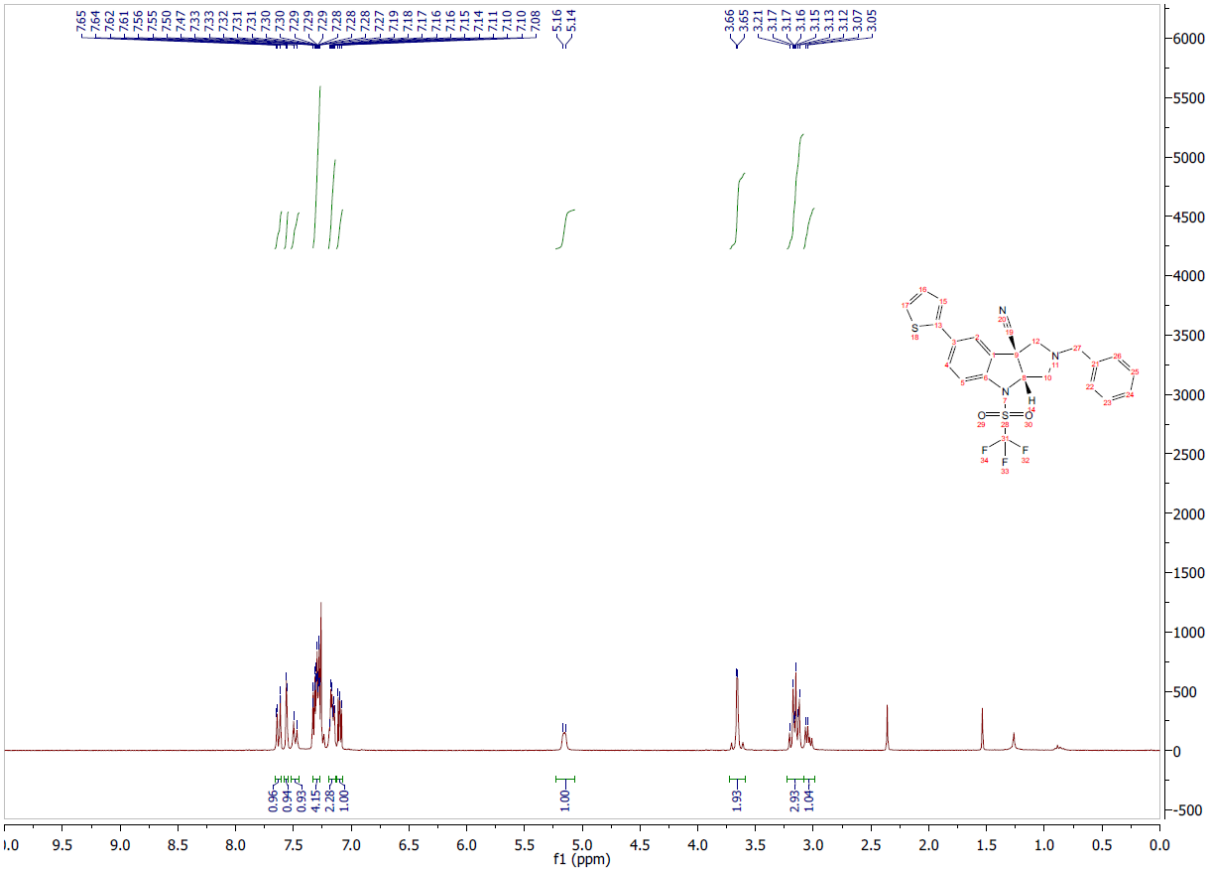
126.51
126.28
122.26
119.78
119.00
117.92
115.17
113.61
112.00
105.95
71.71
64.40
61.20
57.67
47.54
f1 (ppm)

3o: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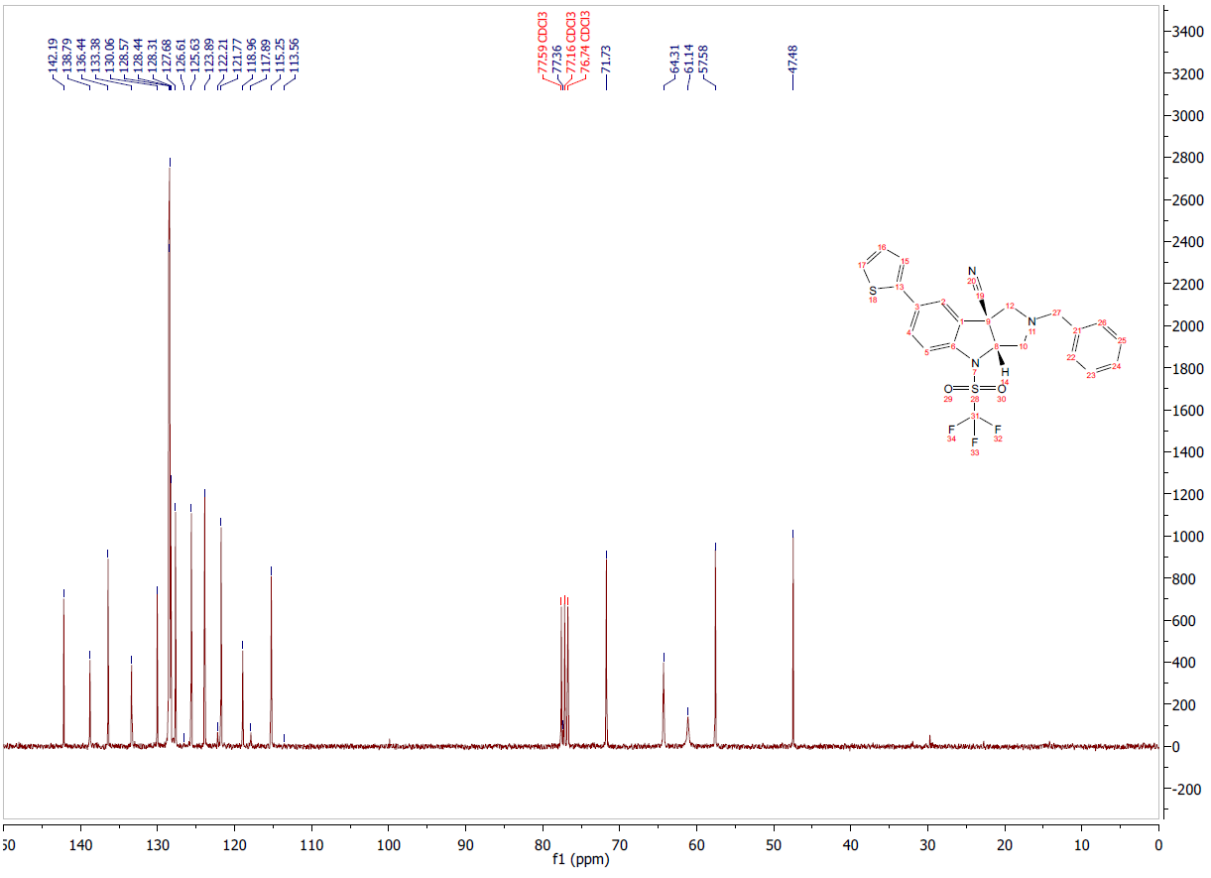
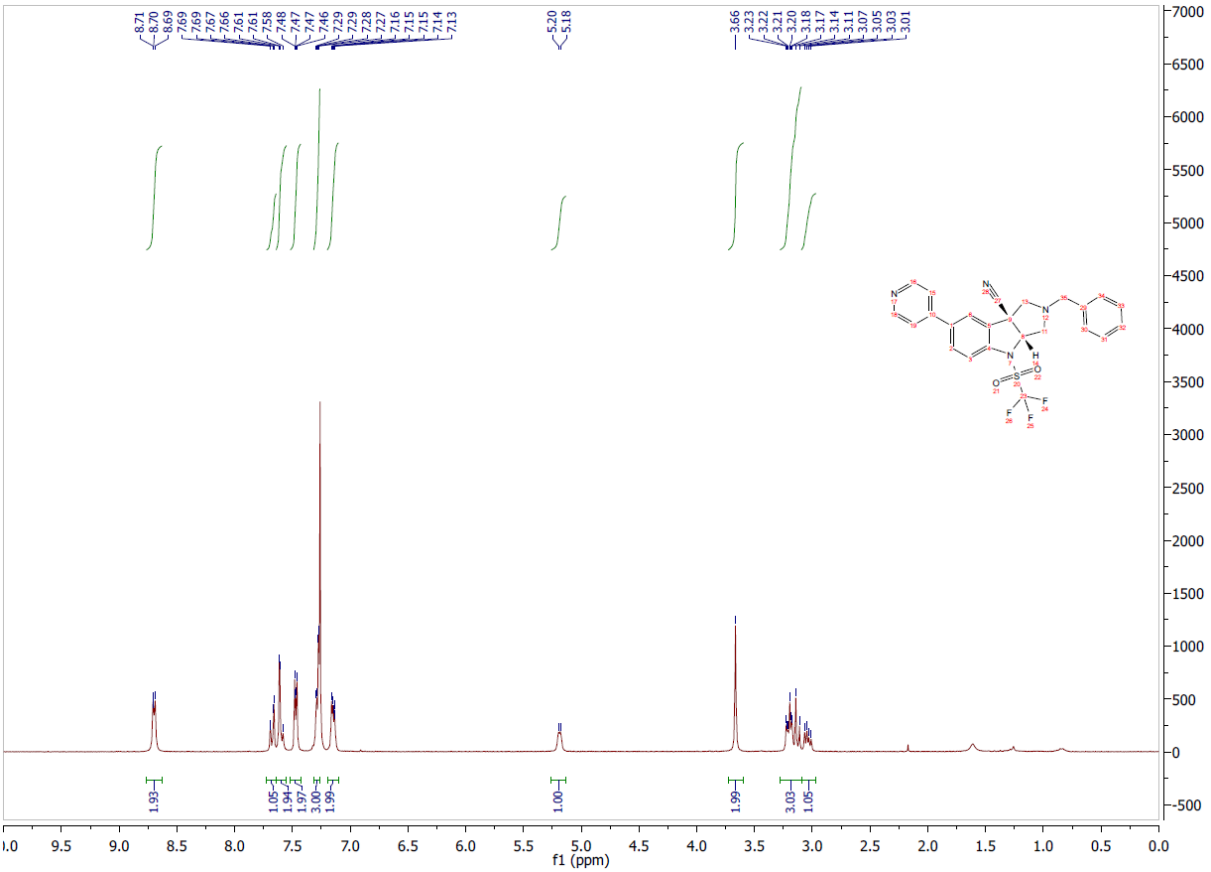
5.16 5.14
3.66 3.65 3.21 3.17 3.17 3.16 3.15 3.13 3.12 3.07 3.05
0.96 0.94 0.93 4.15 2.28 1.00
1.00
1.93
2.93 1.04
f1 (ppm)


142.19 138.79 136.44 133.38 130.06 128.57 128.44 128.31 127.68 126.61 125.63 123.89 122.21 121.77 118.96 117.89 115.25 113.56
77.59 CDCl3 77.36 77.16 CDCl3 76.74 CDCl3
71.73
64.31 61.14 57.58
47.48
f1 (ppm)

3p: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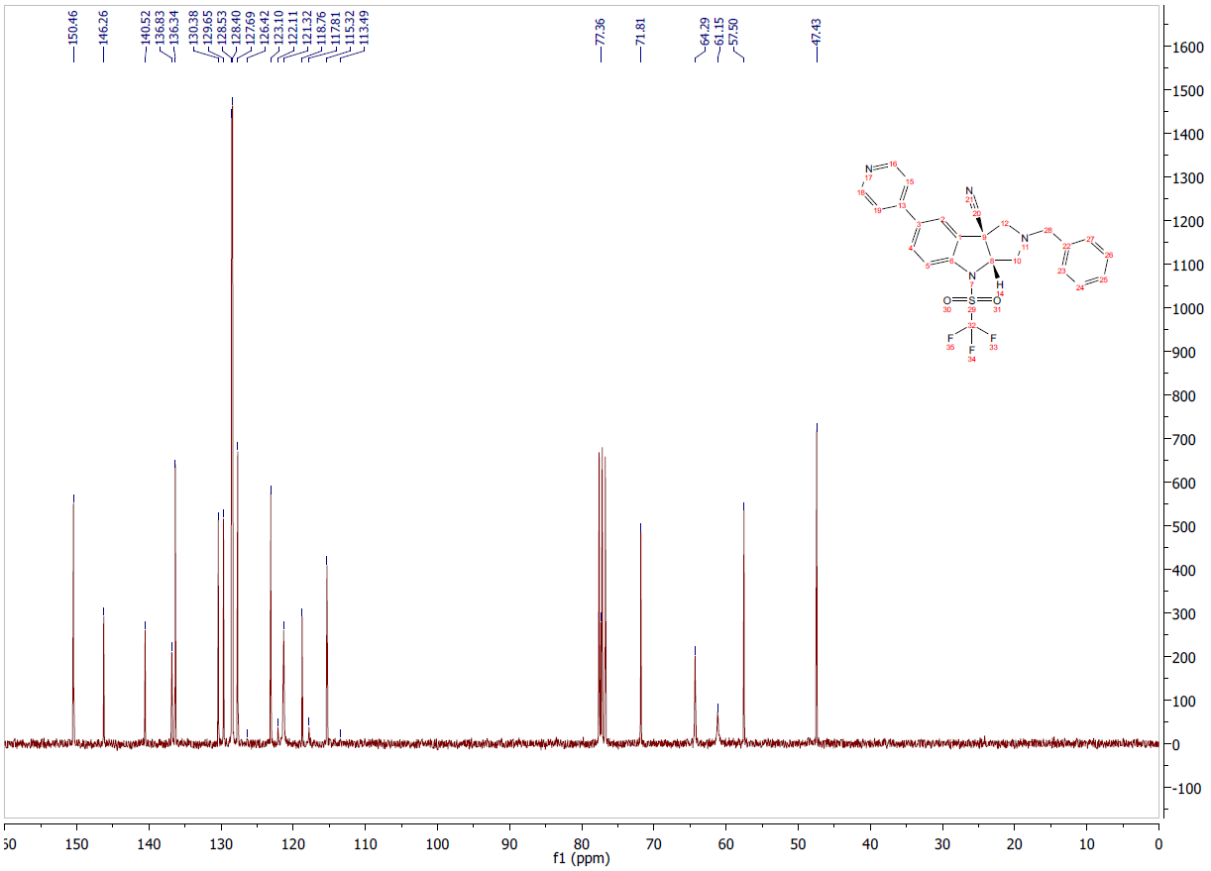
7.69
7.69
7.67
7.66
7.61
7.61
7.58
7.48
7.47
7.47
7.46
7.29
7.29
7.28
7.27
7.16
7.15
7.15
7.14
7.13
5.20
5.18
3.66
3.23
3.22
3.21
3.20
3.18
3.17
3.14
3.11
3.07
3.05
3.03
3.01
1.93
1.05
1.94
1.97
3.00
1.99
1.00
1.99
3.03
1.05
f1 (ppm)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140.52
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128.53
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123.10
122.11
121.32
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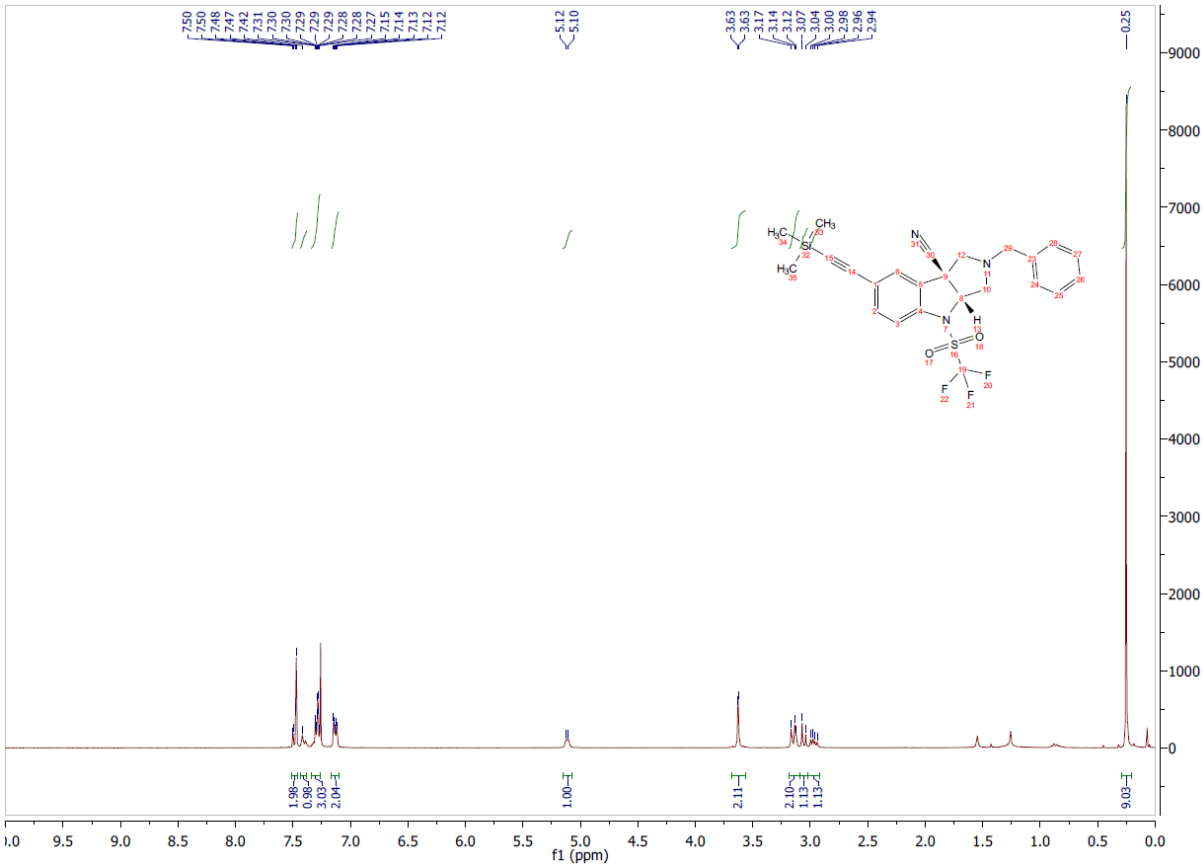
113.49
77.36
71.81
64.29
61.15
57.50
47.43
f1 (ppm)

3q: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7.48
7.47
7.42
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7.30
7.29
7.29
7.29
7.28
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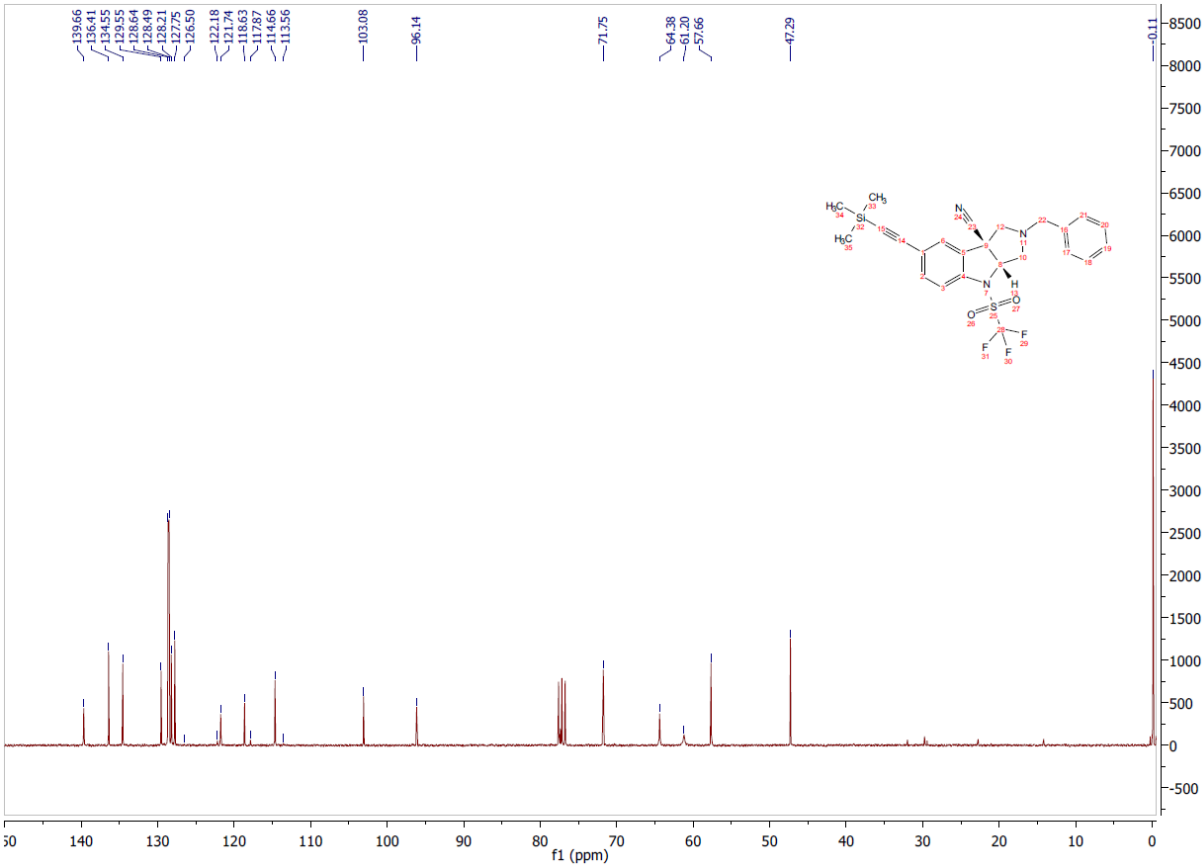
7.27
7.15
7.14
7.13
7.12
7.12
5.12
5.10
3.63
3.63
3.17
3.14
3.12
3.07
3.04
3.00
2.98
2.96
2.94
0.25
1.98
0.98
3.03
2.04
1.00
2.11
2.10
1.13
1.13
9.03
f1 (ppm)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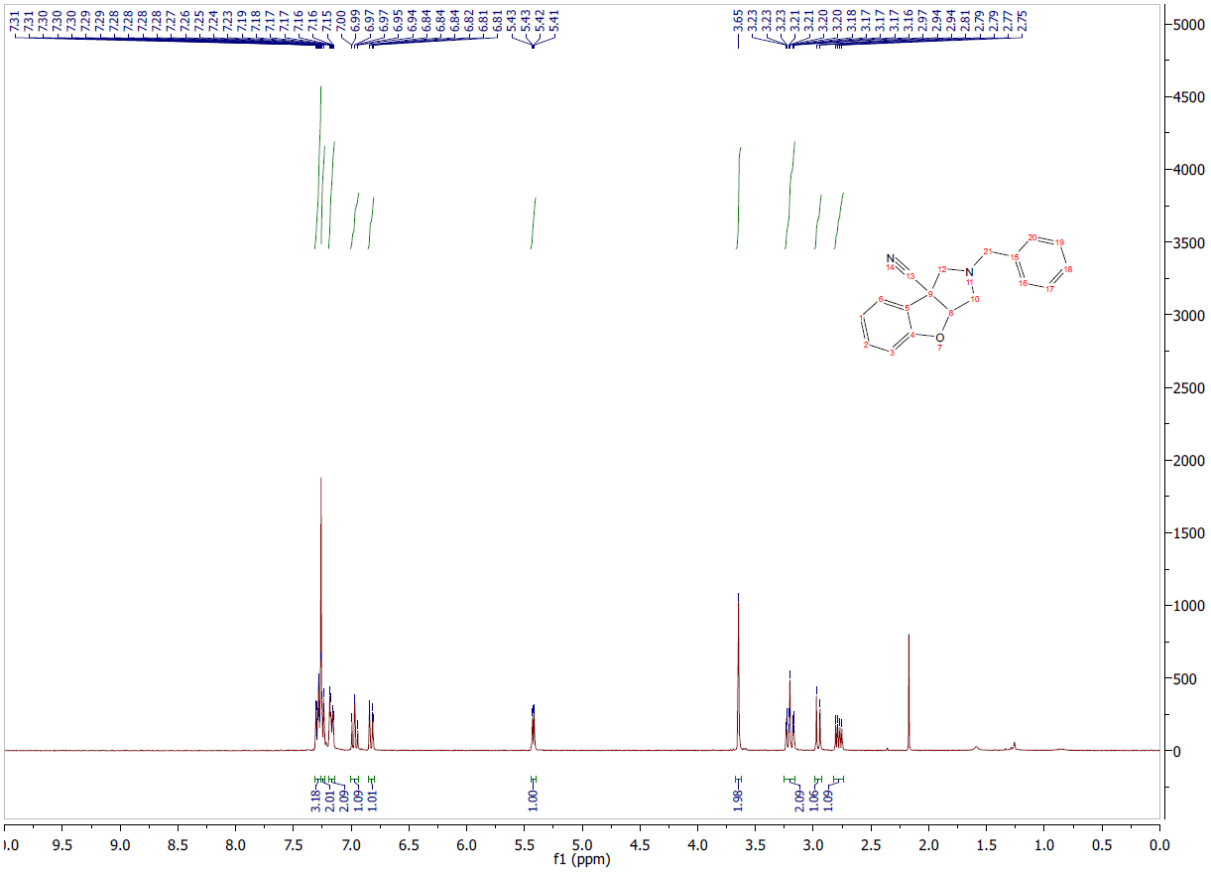
134.55
129.55
128.64
128.49
128.21
127.75
126.50
122.18
121.74
118.63
117.87
114.66
113.56
103.08
96.14
71.75
64.38
61.20
57.66
47.29
0.11
f1 (ppm)

3r: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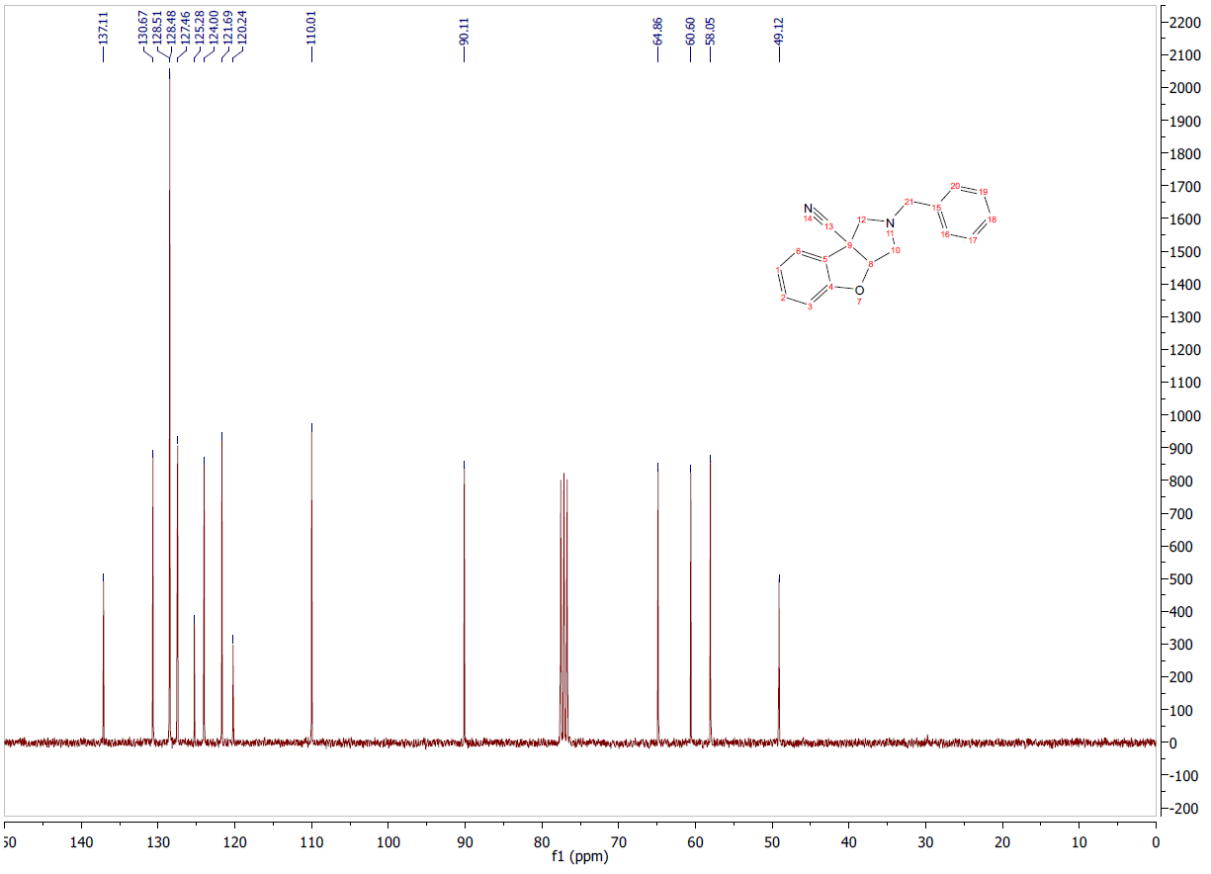
7.28
7.27
7.26
7.25
7.24
7.23
7.19
7.18
7.17
7.17
7.17
7.16
7.16
7.15
7.00
6.99
6.97
6.97
6.95
6.94
6.84
6.84
6.84
6.82
6.81
6.81
5.43
5.43
5.42
5.41
3.65
3.23
3.23
3.23
3.21
3.21
3.20
3.20
3.18
3.17
3.17
3.17
3.16
2.97
2.94
2.94
2.81
2.79
2.79
2.77
2.75
3.18
2.01
2.09
1.09
1.01
1.00
1.98
2.09
1.06
1.09
f1 (ppm)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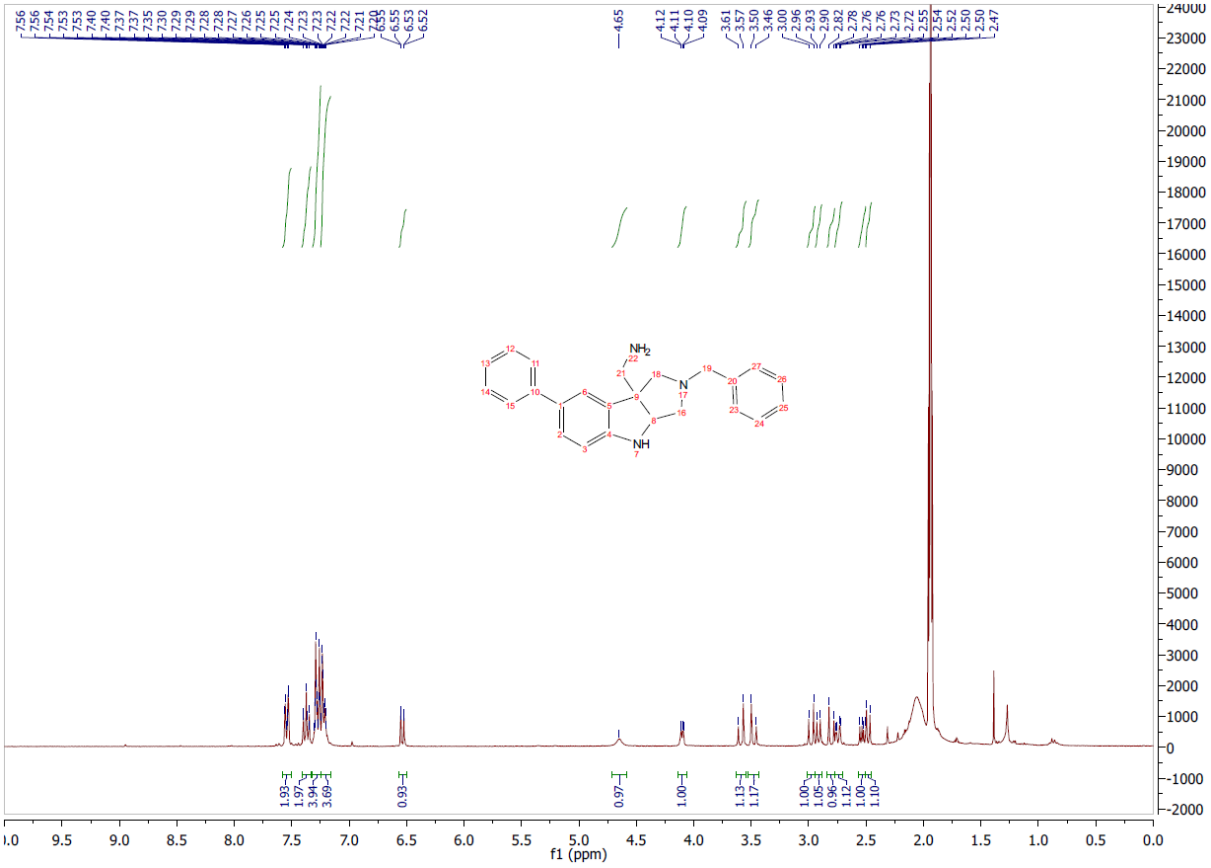
128.51
128.48
127.46
125.28
124.00
121.69
120.24
110.01
90.11
64.86
60.60
58.05
49.12
f1 (ppm)

5e: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7.29
7.28
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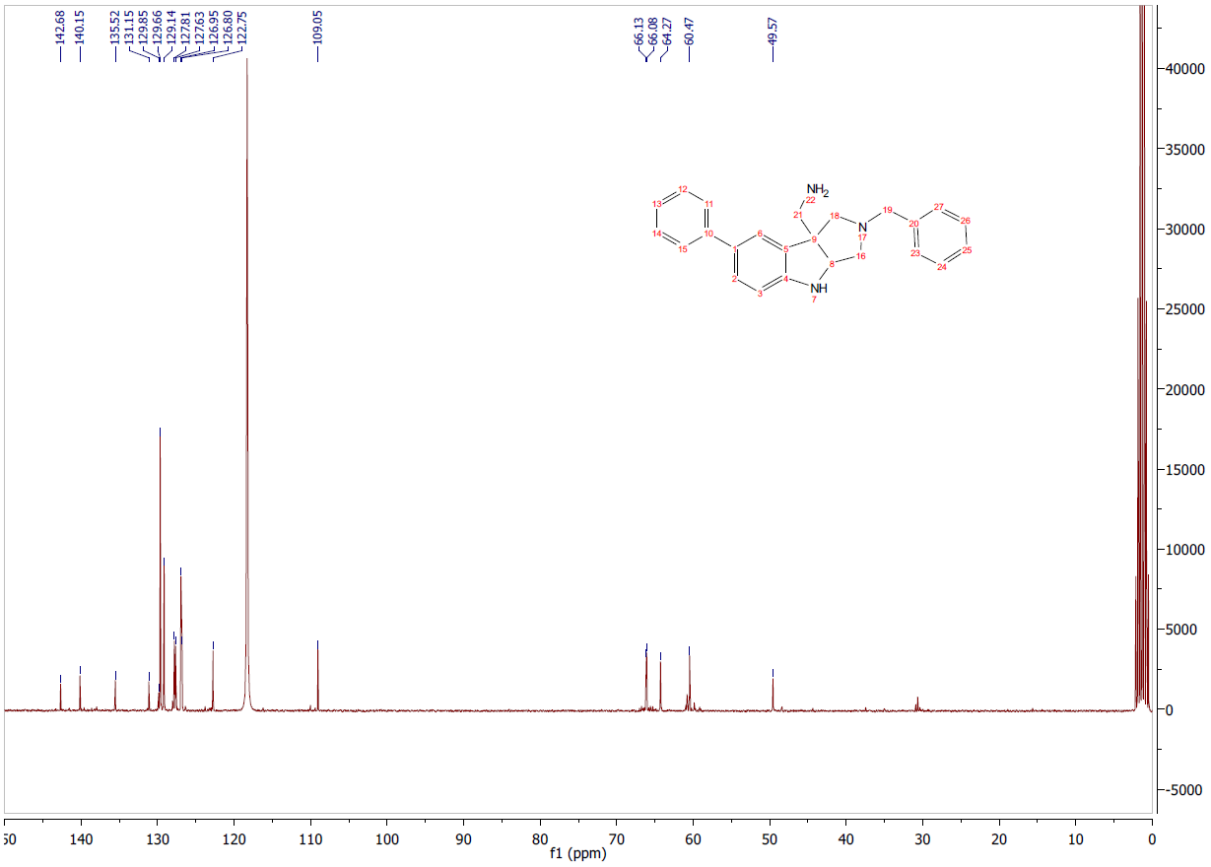
7.27
7.26
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.21
6.55
6.53
6.52
4.65
4.12
4.11
4.10
4.09
3.61
3.57
3.50
3.46
3.00
2.96
2.93
2.90
2.82
2.78
2.76
2.76
2.73
2.72
2.55
2.54
2.52
2.50
2.50
2.47
NH2
NH
N
1.93
1.97
3.94
3.69
0.93
0.97
1.00
1.13
1.17
1.00
1.05
0.96
1.12
1.00
1.10
f1 (ppm)


142.68
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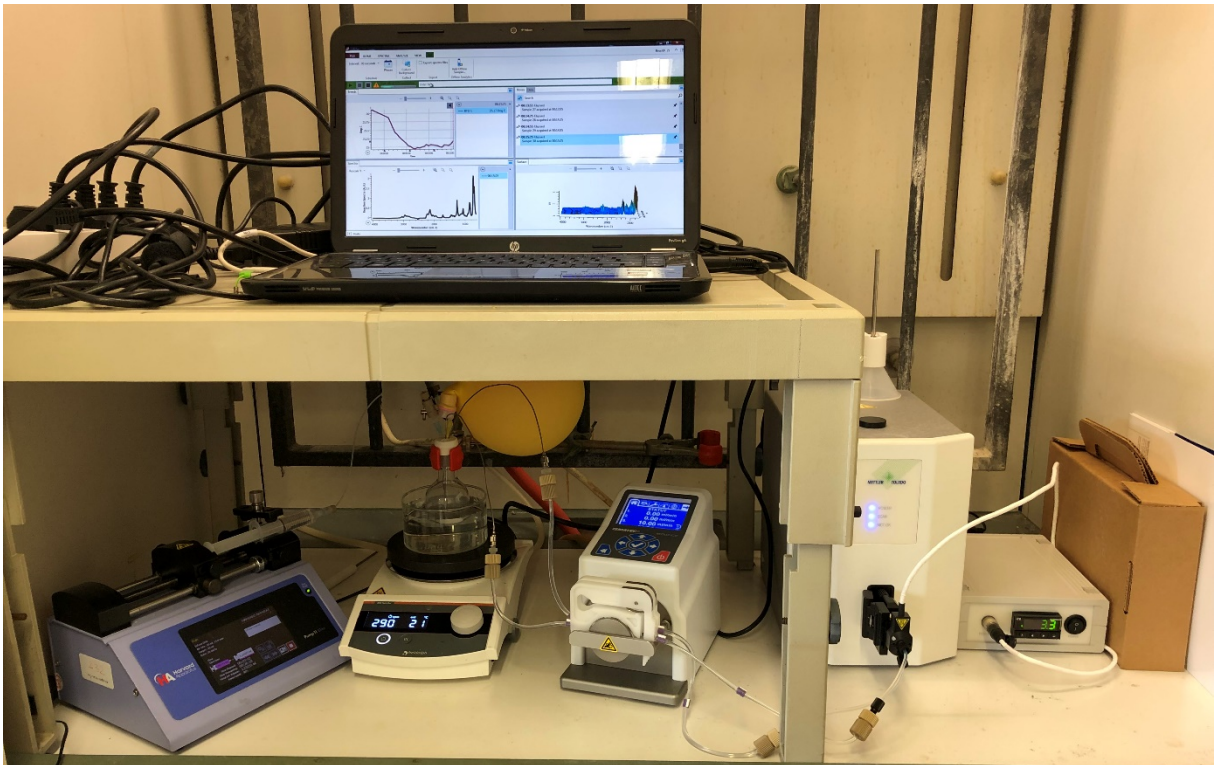
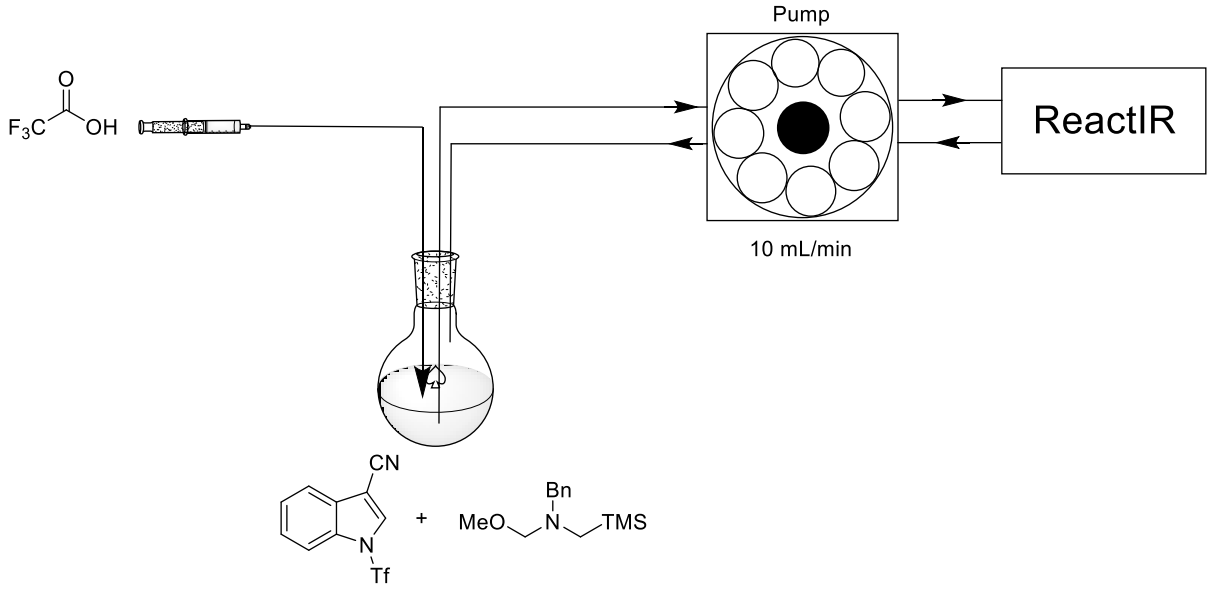
135.52
131.15
129.85
129.66
129.14
127.81
127.63
126.95
126.80
122.75
109.05
66.13
66.08
64.27
60.47
49.57
NH2
NH
N
f1 (ppm)

4. Procedure for the infrared in-line analysis of the (3+2) cycloaddition reaction between 2d and 1.

The procedure was performed according to the general procedure A, additionaly using ISAMATEC Reglo ICC digital peristaltic pump and an *in situ*, monitoring Fourier Transform Infrared Spectroscopy (FTIR) instrument ReactIR Mettler Toledo with 4000-650 cm^{-1} optical range, operating temperature at 20°C, and Diamond cell. The reaction mixture was analyzed using the peristaltic pump set at 10 mL/min to bring the reaction mixture to the FTIR and put it back to the reactor.





5. Data analysis obtained for the infrared in line analysis of the (3+2) cycloaddition reaction between 2d and 1: