Synergetic Copper/Zinc Catalysis: Synthesis of Aryl/Heteroaryl-Fused 1*H*-Pyrrolo[3,2-c]pyridines

Gayyur,[a] Shivani Choudhary,[a,b] Ruchir Kant,[c] and Nayan Ghosh[a,b] *

[a]*Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow-226031, U.P., India*
[b]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India*
[c]*Molecular and Structural Biology Division, CSIR-Central Drug Research Institute, Lucknow-226031, U.P., India*

E-mail: *nayan.ghosh@cdri.res.in*

SUPPORTING INFORMATION

Table of Contents **Page**

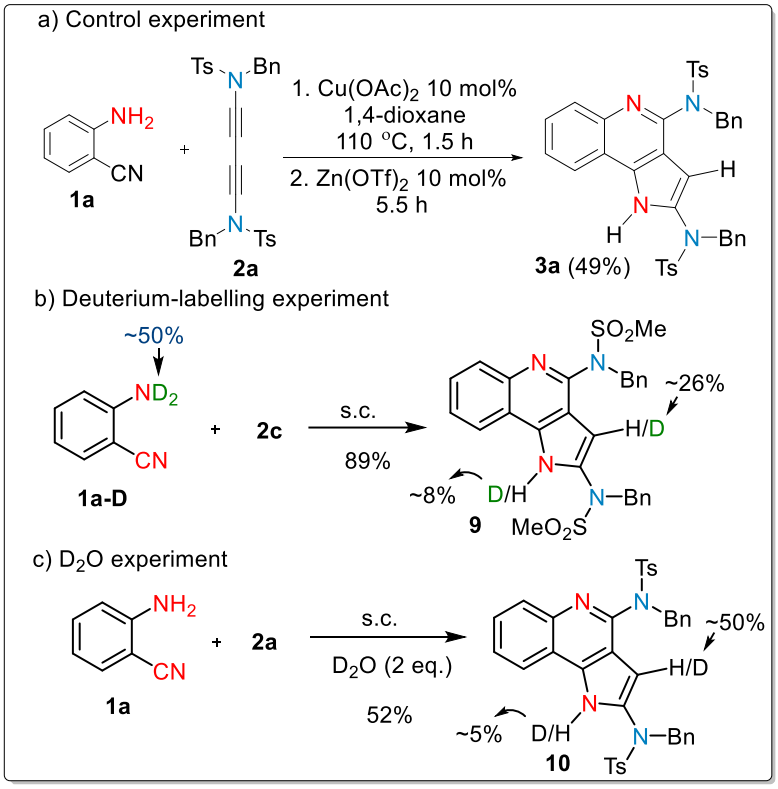
General Experimental

All the reactions were performed in an oven-dried Schlenk flask under an argon atmosphere. Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (CH_2Cl_2), acetonitrile, ethyl acetate, acetone and dichloroethane (DCE) were distilled over CaH_2. THF, toluene, 1,4-dioxane was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. TMEDA was distilled over KOH. Column chromatography was performed using silica gel (100-200 Mesh) eluting with hexanes and ethyl acetate mixture. Flash column chromatography was performed using silica gel (230-400 Mesh) eluting with hexanes and ethyl acetate mixture. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining over I_2 chamber or an aqueous alkaline $KMnO_4$ solution followed by heating.

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Bruker Avance 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz; ^{19}F NMR, 376 MHz) spectrometer, having solvent resonance as internal standard (^{1}H NMR, $CDCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Few cases tetramethylsilane (TMS) at 0.00 ppm was used as reference standard. All the catalysts used in this reaction were procured directly from commercial sources. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; br s = broad singlet; d = doublet; br d = broad doublet, t = triplet; br t = broad triplet; q = quartet; m = multiplet), coupling constants, *J*, in (Hz), and integration. Data for ^{13}C NMR, ^{19}F NMR were reported in terms of chemical shift (ppm). IR spectra were recorded on FT/IR-5300 spectrometer and reported in cm^{-1}. High resolution mass spectra were obtained in ESI mode. Melting points were determined by electro-thermal heating and are uncorrected. X-Ray data was collected at 298K on the Bruker APEX-II CCD single crystal diffractometer.

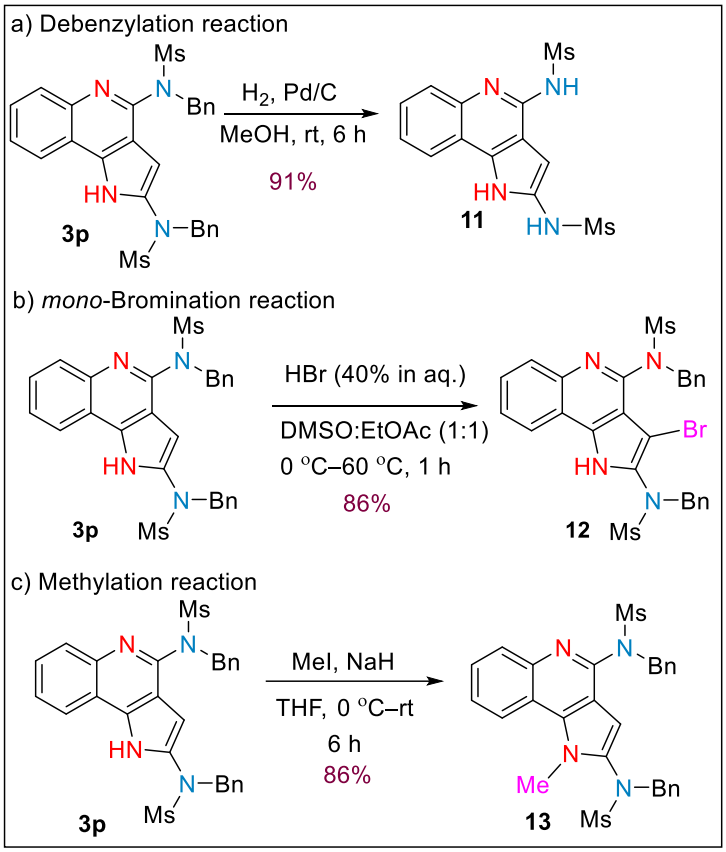
The role of Cu(II) and Zn(II) salts was investigated (Scheme S1a). At first, Cu(II) was added in a mixture of **1a** and **2a** and stirred at 110 °C for 2 h until the disappearance of **2a**. Subsequently, the reaction mixture was stirred another 5 h at 110 °C upon addition of Zn(II) and **3a** was isolated in 49% yield. However, only $Cu(OAc)_2$ (10 mol%) produced 31% of **3a** (entry 7, Table 1). These results further highlight about catalytic synergy of Cu(II) and Zn(II) salts in this protocol. Next, we moved towards deuterium-labelling experiments. When **1a-D** and **2c** reacted under the optimized conditions, deuterium incorporation was noticed into the final product **9**; thus confirming the origin of proton (Scheme S1b). In addition, when **1a** and **2a** reacted upon addition of D_2O (2 equiv.) under standard conditions, desired product **10** was isolated in 52% yield with 50% deuterium incorporation (Scheme S1c).

Scheme S1. Control Experiment and Deuterium-Labelling Studies



To highlight the importance of the final product further, structural modifications of **3p** were executed via routine synthetic manipulation, delivering products **11**, **12** and **13** in excellent yields (Scheme S2)**.**

Scheme S2. Chemical Elaboration of 3p



2-Amino arylnitriles (1)

Starting materials (**1a-1g)** were purchased from commercial sources and used in the reaction. In addition, other starting substrates (**1h-1k**) were prepared following literature reports.[1]

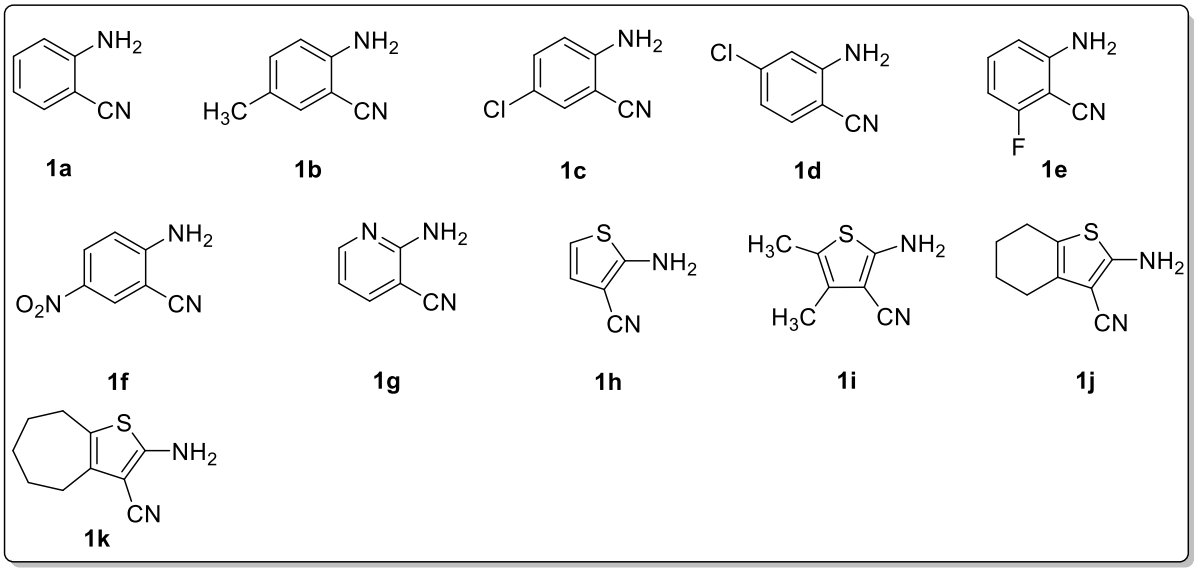
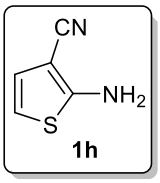


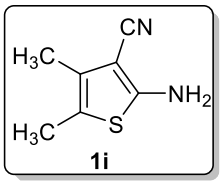
Figure S1. Various 2-amino arylnitriles employed in cyclization reaction (**1**)

2-Aminothiophene-3-carbonitrile (**1h**)



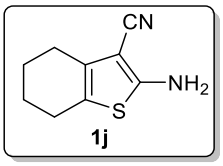
Following literature procedure, compound **1h** (1.16 g) was obtained in 71% yield as light green crystalline solid; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.65 (d, J = 6.0 Hz, 1H), 6.27 (d, J = 5.6 Hz, 1H), 4.76 (brs, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.6, 125.7, 115.5, 110.4, 88.3; **IR (Neat)** ν_{max} 3413, 3331, 2206, 1625, 1527, 1383 cm^{-1}.

2-Amino-4,5-dimethylthiophene-3-carbonitrile (1i)



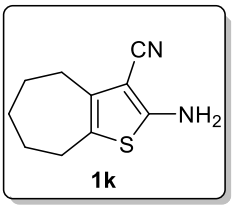
Following literature procedure, compound **1i** (1.73 g) was obtained in 82% yield as brown solid; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.50 (brs, 2H), 2.08 (s, 3H), 1.99 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.1, 129.6, 117.2, 115.9, 90.7, 12.8, 12.4; **IR (Neat)** ν_{max} 3418, 2201, 1627, 1526, 1384, 1055 cm^{-1}.

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (1j)



Following literature procedure, compound **1j** (1.01 g) was obtained in 66% yield as pale yellow solid; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.61 (brs, 2H), 2.51–2.48 (m, 4H), 1.83–1.76 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.0, 132.3, 120.6, 115.5, 88.7, 24.5, 24.1, 23.3, 22.1; **IR (Neat)** ν_{max} 3423, 3329, 2921, 2198, 1624, 1521, 1387, 1073 cm^{-1}.

2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carbonitrile (1k)



Following literature procedure, compound **1k** (1.2 g) was obtained in 70% yield as pale yellow solid; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.51 (brs, 2H), 2.63–2.52 (m, 4H), 1.85–1.79 (m, 2H), 1.68–1.61 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.0, 136.9, 123.8, 115.9, 91.9, 31.9, 29.4, 29.1, 28.1, 27.2; **IR (Neat)** ν_{max} 3437, 2199, 1637, 722 cm^{-1}.

General procedure for the synthesis of ynamide-derived buta-1,3-diynes (2) (GP-1):

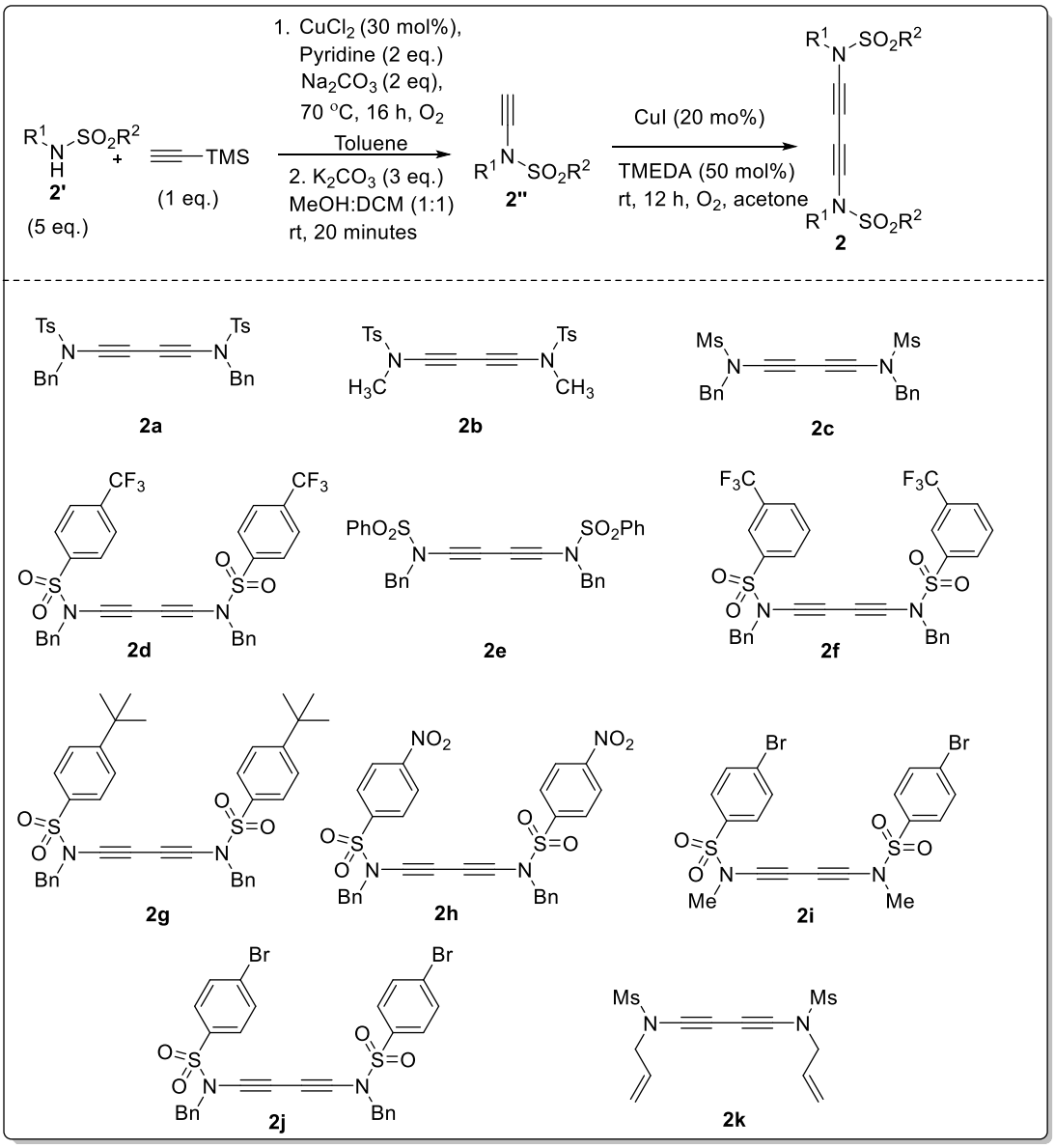
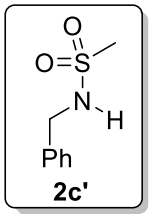


Figure S2. Various ynamide-derived buta-1,3-diynes employed in cyclization reaction (**2**)

At first, **2''** was synthesized applying literature method from **2'** and Trimethylsilylacetylene and further subjected compound **2''** in the above reaction conditions to obtain various ynamide-derived buta-1,3-diynes (**2**).[2,3]

In an oven-dried Schlenk flask, CuI (20 mol%) and TMEDA (50 mol%) were added successively in dry acetone (10 mL) under O_2 atmosphere at rt. Upon stirring for 15 min at rt, a solution of **2''** (1eq.) in acetone (10 mL) was slowly added and the mixture was vigorously stirred under O_2 atmosphere until full consumption of the starting material **2''** (12 h). After solvent removal, the crude residue was purified by column chromatography on silica gel to obtain pure **2a-2k**.

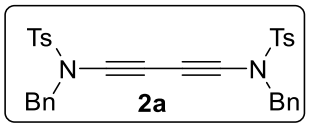
***N*-Benzylmethanesulfonamide (2c')**[4]



2c'

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 4H), 7.25–7.22 (m, 1H), 4.98 (brs, 1H), 4.23 (d, J = 6.0 Hz, 2H), 2.77 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.7, 128.8, 128.0, 127.9, 47.1, 41.0.

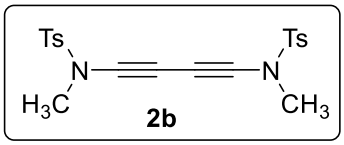
***N*,*N*'-(Buta-1,3-diyne-1,4-diyl)bis(*N*-benzyl-4-methylbenzenesulfonamide) (2a)**



2a

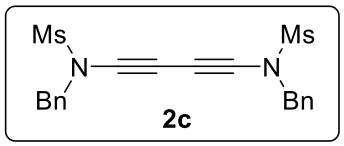
Following the general procedure of GP-1, compound **2a** (630 mg) was obtained in 70% yield as colorless solid from 3.15 mmol of **2a''**; mp = 153–155 °C; R_f = 0.44 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.67 (d, J = 8.4 Hz, 4H), 7.29–7.22 (m, 14H), 4.52 (s, 4H), 2.44 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 144.9, 134.7, 134.1, 129.8, 128.6, 128.5, 128.3, 127.6, 75.9, 60.0, 55.8, 21.6; **IR (Neat)** ν_{max} 3385, 2200, 1621, 1382, 1163, 1079, 707 cm^{-1}; HRMS (ESI) for $C_{32}H_{29}N_2O_4S_2$ $(M+H)^+$: calcd 569.1569, found 569.1557.

***N*,*N*'-(Buta-1,3-diyne-1,4-diyl)bis(*N*,4-dimethylbenzenesulfonamide) (2b)**



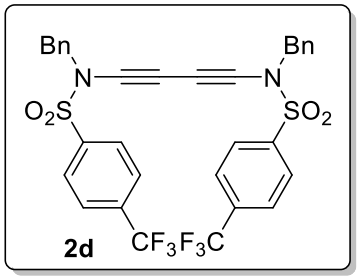
Following the general procedure of GP-1, compound **2b** (750 mg) was obtained in 58% yield as pale yellow solid from 6.22 mmol of **2b''**; mp = 120–122 °C; R_f = 0.37 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.79 (d, J = 8.4 Hz, 4H), 7.38 (d, J = 8.0 Hz, 4H), 3.11 (s, 6H), 2.47 (s, 6H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 145.2, 133.4, 130.0, 127.7, 57.7, 39.1, 21.7; **IR (Neat)** ν_{max} 3390, 2170, 1370, 1168, 1086, 943, 680 cm^{-1}; HRMS (ESI) for $C_{20}H_{21}N_2O_4S_2$ $(M+H)^+$: calcd 417.0943, found 417.0935.

***N*,*N*'-(Buta-1,3-diyne-1,4-diyl)bis(*N*-benzylmethanesulfonamide) (2c)**



Following the general procedure of GP-1, compound **2c** (980 mg) was obtained in 77% yield as colorless solid from 6.0 mmol of **2c''**; mp = 136–138 °C; R_f = 0.22 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.41–7.36 (m, 10H), 4.65 (s, 4H), 2.88 (s, 6H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 134.1, 128.9, 128.8, 128.7, 75.7, 60.1, 56.1, 39.8; **IR (Neat)** ν_{max} 3385, 1379, 1159, 1069, 771 cm^{-1}; HRMS (ESI) for $C_{20}H_{21}N_2O_4S_2$ $(M+H)^+$: calcd 417.0943, found 417.0936.

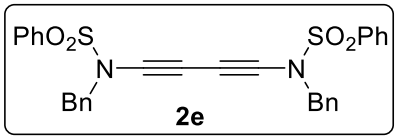
***N*,*N*'-(buta-1,3-diyne-1,4-diyl)bis(*N*-benzyl-4-(trifluoromethyl)benzenesulfonamide) (2d)**



Following the general procedure of GP-1, compound **2d** (1.3 mg) was obtained in 82% yield as pale yellow solid from 4.71 mmol of **2d''**; mp = 115–117 °C; R_f = 0.36 (9:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.85 (d, J = 6.8 Hz, 4H), 7.71 (d, J = 6.8 Hz, 4H), 7.32–7.27 (m, 6H), 7.21 (d, J = 5.6 Hz, 4H), 4.61 (s, 4H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 141.1, 135.5, 135.2, 133.5, 128.8, 128.7, 128.6, 128.1, 126.3 (q, J = 3.0 Hz, 1C), 124.1, 121.9, 75.7, 60.0, 56.4; **^{19}F NMR (376 MHz, CDCl$_3$)** δ –63.3; **IR (Neat)** ν_{max} 3416,

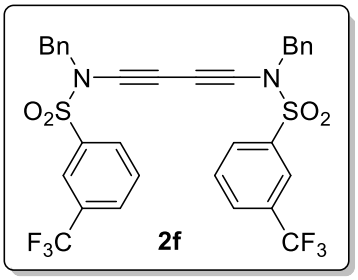
1629, 1372, 1323, 1169, 758 cm^{-1}; HRMS (ESI) for $C_{32}H_{23}F_6N_2O_4S_2$ $(M+H)^+$: calcd 677.1003, found 677.1007.

***N,N'*-(Buta-1,3-diyne-1,4-diyl)bis(*N*-benzylbenzenesulfonamide) (2e)**



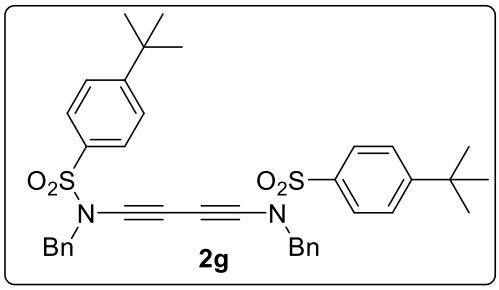
Following the general procedure of GP-1, compound **2e** (470 mg) was obtained in 59% yield as colorless solid from 2.94 mmol of **2e''**; mp = 140–142 °C; R_f = 0.37 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, J = 8.4 Hz, 4H), 7.63 (t, J = 7.6 Hz, 2H), 7.49 (t, J = 7.6 Hz, 4H), 7.29–7.21 (m, 10H), 4.55 (s, 4H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 137.7, 133.9, 133.8, 129.2, 128.6, 128.4, 127.5, 75.8, 60.0, 55.9; **IR (Neat)** ν_{max} 3393, 2166, 1375, 1167, 1083, 765 cm^{-1}; HRMS (ESI) for $C_{30}H_{25}N_2O_4S_2$ $(M+H)^+$: calcd 541.1256, found 541.1252.

***N,N'*-(Buta-1,3-diyne-1,4-diyl)bis(*N*-benzyl-3-(trifluoromethyl)benzenesulfonamide) (2f)**



Following the general procedure of GP-1, compound **2f** (620 mg) was obtained in 78% yield as pale yellow solid from 2.35 mmol of **2f''**; mp = 90–92 °C; R_f = 0.62 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 (brs, 4H), 7.65 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.11–7.03 (m, 10H), 4.44 (s, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 138.8, 133.4, 131.6 (q, J = 34.3 Hz, 1C), 130.7, 130.3 (2C), 129.9, 128.7, 128.6, 128.5, 124.6, 124.5, 124.2, 121.5, 75.7, 59.9, 56.5; **^{19}F NMR (376 MHz, $CDCl_3$)** δ –62.8; **IR (Neat)** ν_{max} 3385, 1381, 1323, 1158, 1051 cm^{-1}; HRMS (ESI) for $C_{32}H_{23}F_6N_2O_4S_2$ $(M+H)^+$: calcd 677.1003, found 677.1002.

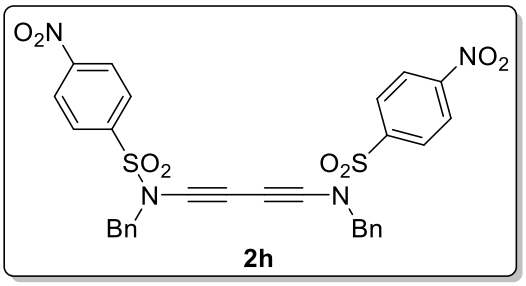
***N,N'*-(Buta-1,3-diyne-1,4-diyl)bis(*N*-benzyl-4-(tert-butyl)benzenesulfonamide) (2g)**



2g

Following the general procedure of GP-1, compound **2g** (730 mg) was obtained in 73% yield as colorless solid from 3.05 mmol of **2g''**; mp = 131–133 °C; R_f = 0.64 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.72 (d, J = 8.4 Hz, 4H), 7.48 (d, J = 8.8 Hz, 4H), 7.27–7.20 (m, 10H), 4.54 (s, 4H), 1.35 (s, 18H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 157.7, 134.8, 134.0, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.4, 127.0, 126.2, 126.1, 76.0, 60.0, 55.9, 35.2, 31.0; **IR (Neat)** ν_{max} 3392, 2962, 2167, 1368, 1170, 1084, 769 cm^{-1}; HRMS (ESI) for $C_{38}H_{41}N_2O_4S_2$ $(M+H)^+$: calcd 653.2508, found 653.2498.

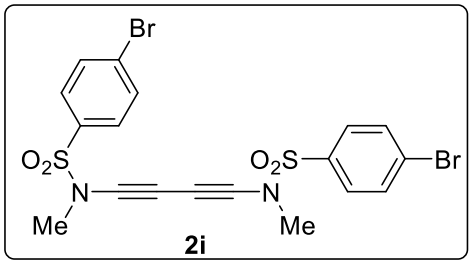
***N*,*N*'-(Buta-1,3-diyne-1,4-diyl)bis(*N*-benzyl-4-nitrobenzenesulfonamide) (2h)**



2h

Following the general procedure of GP-1, compound **2h** (615 mg) was obtained in 51% yield as yellow solid from 3.8 mmol of **2h''**; mp = 154–155 °C; R_f = 0.55 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.27 (d, J = 9.2 Hz, 4H), 7.88 (d, J = 9.2 Hz, 4H), 7.35–7.22 (m, 10H), 4.64 (s, 4H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 150.6, 142.9, 133.3, 128.9, 128.8 (2C), 128.7, 124.3, 75.7, 60.1, 56.7; **IR (Neat)** ν_{max} 3389, 1530, 1380, 1169, 1069, 763, 605 cm^{-1}; HRMS (ESI) for $C_{30}H_{23}N_4O_8S_2$ $(M+H)^+$: calcd 631.0957, found 631.0940.

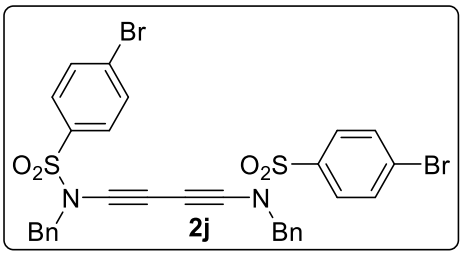
***N*,*N*'-(Buta-1,3-diyne-1,4-diyl)bis(4-bromo-*N*-methylbenzenesulfonamide) (2i)**



2i

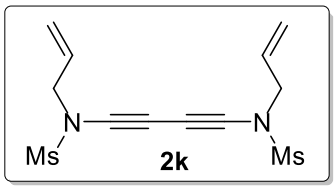
Following the general procedure of GP-1, compound **2i** (720 mg) was obtained in 60% yield as colorless solid from 4.37 mmol of **2i''**; mp = 131–133 °C; R_f = 0.48 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78–7.73 (m, 8H), 3.14 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.3, 132.7, 129.4, 129.1, 76.3, 57.8, 39.2; **IR (Neat)** ν_{max} 3388, 1382, 1152, 1073, 746 cm^{-1}; HRMS (ESI) for $C_{18}H_{15}Br_2N_2O_4S_2$ $(M+H)^+$: calcd 544.8840, found 544.8833.

***N,N'*-(Buta-1,3-diyne-1,4-diyl)bis(*N*-benzyl-4-bromobenzenesulfonamide) (2j)**



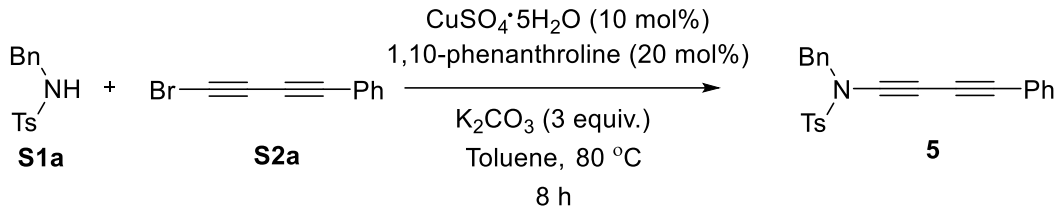
Following the general procedure of GP-1, compound **2j** (560 mg) was obtained in 70% yield as colorless solid from 2.3 mmol of **2j''**; mp = 150–152 °C; R_f = 0.6 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.60 (s, 8H), 7.33–7.28 (m, 6H), 7.27–7.22 (m, 4H), 4.57 (s, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.6, 133.8, 132.5, 129.2, 129.1, 128.7, 128.6, 128.5, 75.8, 60.1, 56.2; **IR (Neat)** ν_{max} 3381, 1380, 1166, 1072, 746, 603 cm^{-1}; HRMS (ESI) for $C_{30}H_{23}Br_2N_2O_4S_2$ $(M+H)^+$: calcd 696.9466, found 696.9457.

***N,N'*-(Buta-1,3-diyne-1,4-diyl)bis(*N*-allylmethanesulfonamide) (2k)**



Following the general procedure of GP-1, compound **2k** (273 mg) was obtained in 69% yield as colorless solid from 2.5 mmol of **2k''**; mp = 87–89 °C; R_f = 0.45 (3:2 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.97–5.87 (m, 2H), 5.38 (dt, J = 1.2, 6.0 Hz, 4H), 4.12 (s, 2H), 4.10 (s, 2H), 3.12 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 130.4, 121.0, 75.1, 59.7, 54.5, 39.8; **IR (Neat)** ν_{max} 3414, 2927, 2168, 1639, 1357, 1163, 771 cm^{-1}.

Synthesis of *N*-Benzyl-4-methyl-*N*-(phenylbuta-1,3-diyn-1-yl)benzenesulfonamide (5)

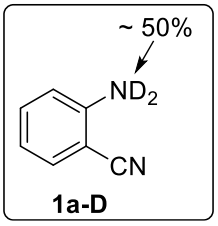


To a mixture of **S1a** (210 mg, 0.80 mmol), $CuSO_4 \cdot 5H_2O$ (20 mg, 0.080 mmol), 1,10-phenanthroline (29 mg, 0.16 mmol) and K_2CO_3 (333 mg, 2.4 mmol) in a Schlenck tube under the argon atmosphere, 5.0 mL of anhydrous toluene was added at room temperature. Upon stirring for 2 minutes, (bromobuta-1,3-diyn-1-yl)benzene **S2a** (197 mg, 0.96 mmol) was subsequently introduced into the Schlenck tube. The reaction mixture was heated at 80 °C under the argon atmosphere. Progress of the reaction was monitored periodically by TLC. Upon full consumption of **S1a**, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL). The crude mixture was filtered through a small pad of Celite and concentrated. The crude residue was purified using column chromatography on silica gel to provide **5**.

Compound **5** (220 mg) was obtained in 71% yield as pale yellow solid; mp = 65–67 °C; R_f = 0.57 (9:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.24–7.16 (m, 10H), 4.48 (s, 2H), 2.35 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.1, 134.7, 134.0, 132.4, 129.9, 129.0, 128.7 (2C), 128.5, 128.4, 127.7, 122.0, 81.3, 74.3, 73.5, 58.8, 55.7, 21.7; **IR (Neat)** ν_{max} 3436, 2089, 1637, 1050, 771, cm^{-1}; HRMS (ESI) for $C_{24}H_{20}NO_2S$ $(M+H)^+$: calcd 386.1215, found 386.1216.

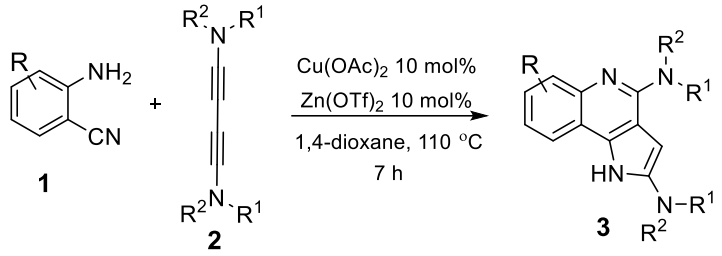
Synthesis of 1a-D

2-amino benzonitrile **1a** (0.84 mmol) was dissolved in 1 mL of CD_3OD under argon atmosphere and stirred for 12 h at room temperature. Next, the reaction mixture was concentrated under reduced pressure to afford **1a-D** in quantitative yield.



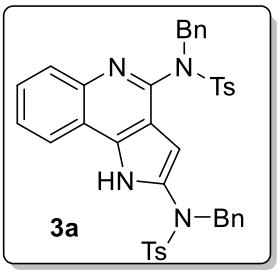
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 2.0, 6.8 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.68–6.64 (m, 2H), 4.31 (brs, 1H).

General procedure for cyclization reaction (GP-2):



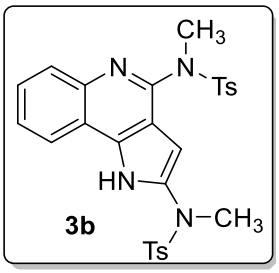
In an oven-dried 15 mL Schlenk flask, **1** (0.15 mmol), **2** (0.14 mmol), $Cu(OAc)_2$ (0.014 mmol), and $Zn(OTf)_2$ (0.014 mmol) were taken and anhydrous 1,4-dioxane (2 mL) was added into the reaction mixture under argon atmosphere. Subsequently, the Schlenk flask was placed in oil bath at 110 °C with stirring. The progress of the reaction was routinely monitored by TLC. Upon full conversion of starting material **2**, the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure and the crude residue was purified through silica gel column chromatography to obtain **3**.

***N*,*N*'-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-4-methylbenzenesulfonamide) (3a)**



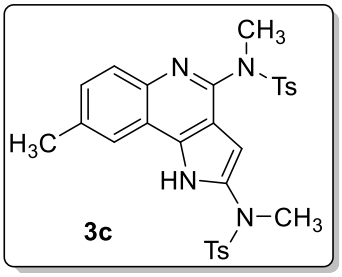
Following the general procedure of GP-2, compound **3a** (65 mg) was obtained in 68% yield as pale yellow solid; mp = 143–145 °C; R_f = 0.42 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.57 (s, 1H), 7.78 (d, J = 6.8 Hz, 2H), 7.61 (d, J = 6.4 Hz, 2H), 7.56 (d, J = 6.8 Hz, 2H), 7.52 (dt, J = 1.2, 5.6 Hz, 1H), 7.35–7.31 (m, 4H), 7.30–7.24 (m, 3H), 7.23–7.15 (m, 5H), 7.05–7.03 (m, 3H), 6.44 (d, J = 2.4 Hz, 1H), 4.90 (s, 2H), 4.65 (s, 2H), 2.46 (s, 3H), 2.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 146.9, 144.5, 143.5, 142.7, 136.6, 135.2, 135.0, 134.5, 133.1, 132.8, 129.8, 129.7, 129.3, 128.8, 128.6, 128.5, 128.4, 128.3 (2C), 128.1, 127.9, 127.8, 127.6, 127.1, 126.7, 125.9, 119.8, 119.7, 116.5, 99.1, 54.8, 52.7, 21.6, 21.5; **IR (Neat)** ν_{max} 3377, 1384, 1156, 1069 cm^{-1}; HRMS (ESI) for $C_{39}H_{35}N_4O_4S_2$ $(M+H)^+$: calcd 687.2100, found 687.2092.

***N*,*N*'-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*,4-dimethylbenzenesulfonamide) (3b)**



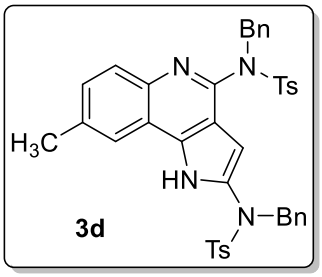
Following the general procedure of GP-2, compound **3b** (45 mg) was obtained in 60% yield as colorless solid; mp = 170–172 °C; R_f = 0.32 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.88 (s, 1H), 8.00–7.98 (m, 1H), 7.80–7.78 (m, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.50–7.47 (m, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.19–7.16 (m, 4H), 6.24 (d, J = 2.4 Hz, 1H), 3.17 (s, 6H), 2.35 (s, 3H), 2.35 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 148.3, 144.8, 143.6, 142.7, 135.6, 134.4, 133.8, 131.4, 129.8, 129.4, 129.2, 128.6, 127.7, 126.9, 126.1, 119.6, 118.2, 116.5, 94.9, 37.4, 36.9, 21.6, 21.5; **IR (Neat)** ν_{max} 3371, 1384, 1352, 1160, 1078 cm^{-1}; HRMS (ESI) for $C_{27}H_{27}N_4O_4S_2$ $(M+H)^+$: calcd 535.1474, found 535.1464.

***N*,*N*'-(8-methyl-1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*,4-dimethylbenzenesulfonamide) (3c)**



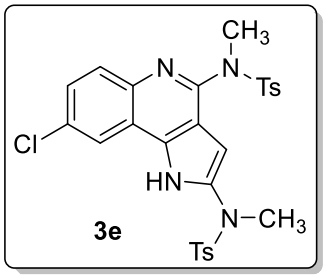
Following the general procedure of GP-2, compound **3c** (50 mg) was obtained in 65% yield as pale yellow solid; mp = 80–82 °C; R_f = 0.51 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.89 (s, 1H), 7.84 (s, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.58 (d, J = 6.4 Hz, 2H), 7.48 (d, J = 6.8 Hz, 2H), 7.38 (d, J = 6.8 Hz, 1H), 7.25–7.22 (m, 4H), 6.28 (d, J = 2.0 Hz, 1H), 3.24 (s, 3H), 3.23 (s, 3H), 2.57 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 147.6, 144.8, 143.6, 141.1, 136.2, 135.5, 134.2, 133.9, 131.5, 129.9, 129.2, 129.0, 128.6, 127.7, 118.9, 118.3, 116.4, 94.7, 37.4, 37.0, 21.7, 21.6 (2C); **IR (Neat)** ν_{max} 3367, 1384, 1355, 1160, 1081 cm^{-1}; HRMS (ESI) for $C_{28}H_{29}N_4O_4S_2$ $(M+H)^+$: calcd 549.1630, found 549.1601.

***N*,*N*'-(8-Methyl-1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-4-methylbenzenesulfonamide) (3d)**



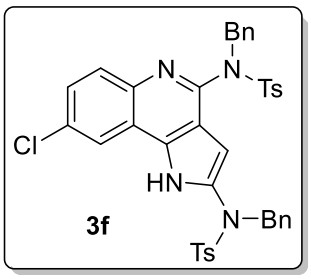
Following the general procedure of GP-2, compound **3d** (61 mg) was obtained in 62% yield as pale yellow solid; mp = 150–152 °C; R_f = 0.41 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.36 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.33 (dd, J = 1.6, 8.4 Hz, 1H), 7.32–7.28 (m, 4H), 7.24 (d, J = 8.0 Hz, 2H), 7.21–7.17 (m, 5H), 7.05–7.02 (m, 3H), 6.40 (d, J = 2.0 Hz, 1H), 4.88 (s, 2H), 4.64 (s, 2H), 2.49 (s, 3H), 2.46 (s, 3H), 2.43 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.2, 144.6, 143.5, 141.1, 136.7, 136.1, 135.3, 135.1, 134.1, 133.1, 132.8, 129.9, 129.3, 129.1, 128.9, 128.8, 128.5, 128.4, 128.2, 127.9, 127.8, 127.1, 119.8, 119.1, 116.5, 98.9, 54.8, 52.8, 21.7, 21.6 (2C); **IR (Neat)** ν_{max} 3366, 1383, 1354, 1161, 1088 cm^{-1}; HRMS (ESI) for $C_{40}H_{37}N_4O_4S_2$ $(M+H)^+$: calcd 701.2256, found 701.2249.

***N*,*N*'-(8-Chloro-1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*,4-dimethylbenzenesulfonamide) (3e)**



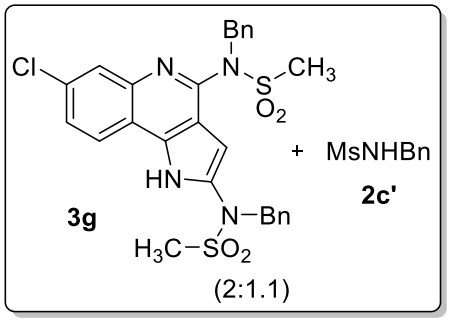
Following the general procedure of GP-2, compound **3e** (42 mg) was obtained in 53% yield as colorless solid; mp = 214–216 °C; R_f = 0.66 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.0 (s, 1H), 7.93 (s, 1H), 7.67 (d, J = 6.8 Hz, 1H), 7.49–7.45 (m, 4H), 7.37 (d, J = 7.2 Hz, 1H), 7.21–7.16 (m, 4H), 6.27 (d, J = 1.6 Hz, 1H), 3.18 (s, 3H), 3.16 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 148.4, 144.9, 143.7, 140.9, 136.1, 133.6, 133.4, 131.7, 131.5, 130.8, 129.9, 129.2, 128.5, 127.7, 127.5, 118.9, 118.7, 117.1, 95.2, 37.5, 36.9, 21.6, 21.5; **IR (Neat)** ν_{max} 3358, 1377, 1352, 1161, 1082 cm^{-1}; HRMS (ESI) for $C_{27}H_{26}ClN_4O_4S_2$ $(M+H)^+$: calcd 569.1084, found 569.1074.

***N*,*N*'-(8-Chloro-1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-4-methylbenzenesulfonamide) (3f)**



Following the general procedure of GP-2, compound **3f** (68 mg) was obtained in 67% yield as colorless solid; mp = 190–192 °C; R_f = 0.84 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.46 (s, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.57 (dd, J = 1.6, 6.4 Hz, 2H), 7.54 (dd, J = 1.6, 6.4 Hz, 2H), 7.42 (dd, J = 2.4, 9.2 Hz, 1H), 7.32–7.29 (m, 4H), 7.25 (d, J = 8.0 Hz, 2H), 7.22–7.19 (m, 3H), 7.18–7.15 (m, 2H), 7.06–7.02 (m, 3H), 6.43 (d, J = 2.0 Hz, 1H), 4.88 (s, 2H), 4.65 (s, 2H), 2.47 (s, 3H), 2.44 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.2, 144.6, 143.6, 141.0, 136.5, 135.1, 135.0, 133.5, 133.2, 131.7, 130.8, 129.9, 129.4, 128.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.5, 127.2, 120.3, 119.5, 117.4, 99.3, 54.9, 52.8, 21.7, 21.6; **IR (Neat)** ν_{max} 3370,, 1384, 1160, 1080 cm^{-1}; HRMS (ESI) for $C_{39}H_{34}ClN_4O_4S_2$ $(M+H)^+$: calcd 721.1710, found 721.1703.

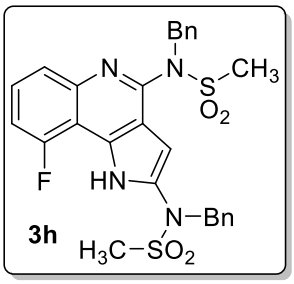
***N*,*N*'-(7-Chloro-1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzylmethanesulfonamide) (3g) + *N*-Methylmethanesulfonamide (2c')**



Following the general procedure of GP-2, an inseparable mixture of compound **3g** (36 mg) and **2c'** (6 mg) was obtained in 45% and 11% yields as pale yellow solid; mp = 75–76 °C; R_f = 0.41 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.74 (s, 1H), 7.96 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.39–7.31 (m, 4H), 7.27–7.24 (m, 7H), 7.12 (t, J = 3.6 Hz, 3H), 6.55 (d, J = 2.0 Hz, 1H), 5.08 (s, 2H), 4.82 (s, 2H), 4.79 (s, 0.5H), 4.32 (d, J = 6.4 Hz, 1.1H), 3.20 (s, 3H), 2.96 (s, 3H), 2.87 (s, 1.7H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 148.1, 143.4, 136.7, 136.1, 135.0, 134.8, 133.0, 132.8, 128.9, 128.7 (2C), 128.6, 128.4, 128.3, 128.2, 128.1, 127.9,

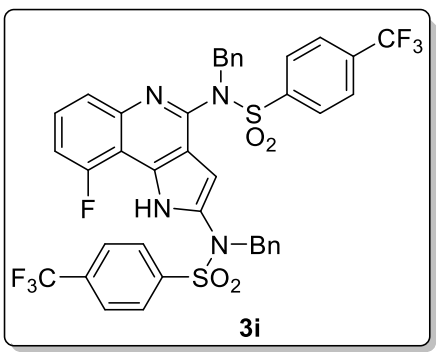
127.7, 127.0, 121.1, 119.2, 115.0, 98.4, 55.1, 53.9, 47.2, 41.1, 38.1, 37.4; **IR (Neat)** ν_{max} 3403, 2926, 1631, 1340, 1153, 1065, 762 cm^{-1}; HRMS (ESI) for $C_{27}H_{26}ClN_4O_4S_2$ $(M+H)^+$: calcd 569.1084, found 569.1106.

***N*,*N*'-(9-Fluoro-1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzylmethanesulfonamide) (3h)**



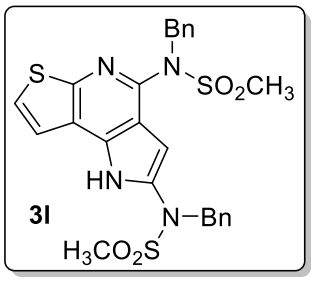
Following the general procedure of GP-2, compound **3h** (85 mg) was obtained in 80% yield in presence of 4 Å MS (20 mg) in THF at 100 °C for 4 h as pale yellow solid. $Cu(OAc)_2$ (0.028 mmol, 5.0 mg) was used; 0.19 mmol of **2c** (80 mg) was used for this reaction; mp = 90–92 °C; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.60 (s, 1H), 7.83 (d, J = 6.8 Hz, 1H), 7.49 (q, J = 6.4 Hz, 1H), 7.31–7.24 (m, 7H), 7.11 (dd, J = 1.6, 6.4 Hz, 1H), 7.11 (t, J = 2.4 Hz, 3H), 6.54 (d, J = 1.6 Hz, 1H), 5.11 (s, 2H), 4.84 (s, 2H), 3.20 (s, 3H), 2.94 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 157.1 (d, J = 200 Hz, 1C), 148.1, 144.3, 136.2, 135.1, 133.4, 131.8, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.7, 126.4 (d, J = 7.1 Hz, 1C), 125.0 (d, J = 3.5 Hz, 1C), 119.3, 110.6 (d, J = 15.1.0 Hz, 1C), 97.0, 54.8, 53.9, 38.2, 37.4; **^{19}F NMR (376 MHz, $CDCl_3$)** δ −118.6; **IR (Neat)** ν_{max} 3412, 2925, 1638, 1344, 1153, 1065, 759 cm^{-1}; HRMS (ESI) for $C_{27}H_{26}FN_4O_4S_2$ $(M+H)^+$: calcd 553.1379, found 553.1391.

***N*,*N*'-(9-fluoro-1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-4-(trifluoromethyl)benzenesulfonamide) (3i)**



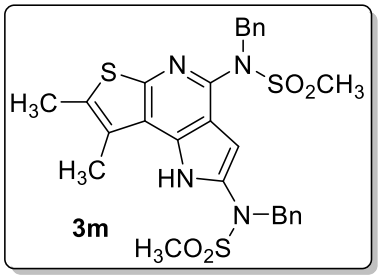
Following the general procedure of GP-2, compound **3i** (86 mg) was obtained in 72% yield as pale yellow solid from 0.14 mmol of **2d** in presence of 4 Å MS (20 mg) in THF at 100 °C for 4 h. $Cu(OAc)_2$ (0.02 mmol, 4.0 mg) was used**;** mp = 130–132 °C; R_f = 0.44 (9:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.54 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.77 (br s, 4H), 7.74 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.74 (q, J = 8.4 Hz, 1H), 7.29–7.25 (m, 2H), 7.24–7.22 (m, 4H), 7.18 (dd, J = 1.6, 7.6 Hz, 2H), 7.10–7.03 (m, 3H), 6.42 (d, J = 2.0 Hz, 1H), 4.90 (s, 2H), 4.70 (s, 2H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 157.3 (d, J = 200 Hz, 1C), 147.4, 144.2, 141.6, 139.8, 135.7, 135.0 (q, J = 27.3 Hz, 1C), 134.4, 132.8, 131.6, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 127.5, 126.6 (d, J = 8.1 Hz, 1C), 126.4, 125.8 (d, J = 2.0 Hz, 1C), 124.9, 124.3 (d, J = 16.1 Hz, 1C), 122.2 (d, J = 16.2 Hz, 1C), 119.8, 110.7 (d, J = 15.1 Hz, 1C), 107.5 (d, J = 12.1 Hz, 1C), 98.8, 55.2, 53.2; **^{19}F NMR (376 MHz, $CDCl_3$)** δ –63.0, –63.1, –118.4; **IR (Neat)** ν_{max} 3422, 1635, 1063, 771 cm^{-1}; HRMS (ESI) for $C_{39}H_{28}F_7N_4O_4S_2$ $(M+H)^+$: calcd 813.1440, found 813.1436.

<u>*N*,*N*'-(1*H*-Pyrrolo[2,3-d]thieno[2,3-b]pyridine-2,4-diyl)bis(*N*-benzylmethanesulfonamide) (3l)</u>



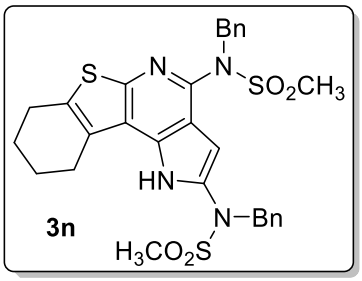
In this reaction, 0.19 mmol of **2c**, 0.21 mmol of **1h**, $Cu(OAc)_2$ (0.019 nnmol), and $Zn(OTf)_2$ (0.019 mmol) were was used in THF (2 mL) at 90 °C for 7 h in presence of 4 Å MS (20 mg). The compound **3l** (50 mg) was obtained in 48% yield as brown solid; mp = 186–188 °C; R_f = 0.48 (3:2 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.21 (s, 1H), 7.37 (d, J = 6.0 Hz, 1H), 7.26–7.23 (m, 7H), 7.11 (d, J = 6.0 Hz, 1H), 7.11 (t, J = 2.4 Hz, 3H), 6.48 (t, J = 2.4 Hz, 1H), 5.04 (s, 2H), 4.80 (s, 2H), 3.16 (s, 3H), 2.91 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 153.6, 143.7, 136.3, 135.1, 134.2, 132.9, 128.7 (2C), 128.6, 128.3, 128.2, 127.6, 125.9, 119.9, 117.9, 117.1, 97.0, 54.9, 54.2, 37.7, 37.1; **IR (Neat)** ν_{max} 3400, 1384, 1060, 771 cm^{-1}; HRMS (ESI) for $C_{25}H_{25}N_4O_4S_3$ $(M+H)^+$: calcd 541.1038, found 541.1044.

<u>*N*,*N*'-(7,8-Dimethyl-1*H*-pyrrolo[2,3-d]thieno[2,3-b]pyridine-2,4-diyl)bis(*N*-benzylmethanesulfonamide) (3m)</u>



In this reaction, 0.24 mmol of **2c**, 0.26 mmol of **1i**, $Cu(OAc)_2$ (0.024 nnmol), and $Zn(OTf)_2$ (0.024 mmol) were used in THF (2 mL) at 90 °C for 7 h. **3m** (27 mg) was obtained in 20% yield as pale yellow solid; mp = 130–132 °C; R_f = 0.6 (3:2 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.02 (s, 1H), 7.29–7.22 (m, 7H), 7.09 (t, J = 3.2 Hz, 3H), 6.35 (d, J = 2.4 Hz, 1H), 5.01 (s, 2H), 4.80 (s, 2H), 3.14 (s, 3H), 2.91 (s, 3H), 2.45 (s, 3H), 2.35 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 150.9, 142.4, 136.4, 135.2, 134.0, 133.2, 133.1, 128.7 (2C), 128.6, 128.3, 128.1, 127.5, 123.1, 120.6, 119.5, 95.9, 54.6, 54.2, 37.5, 37.4, 13.5, 13.2; **IR (Neat)** ν_{max} 3400, 2923, 1383, 1153, 770 cm^{-1}; HRMS (ESI) for $C_{27}H_{29}N_4O_4S_3$ $(M+H)^+$: calcd 569.1351, found 569.1377.

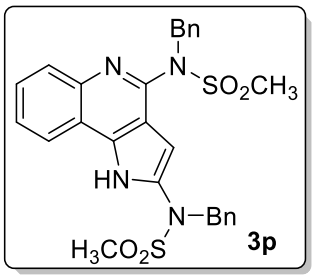
<u>*N*,*N*'-(7,8,9,10-tetrahydro-1*H*-benzo[4,5]thieno[2,3-b]pyrrolo[2,3-d]pyridine-2,4-diyl)bis(*N*-benzylmethanesulfonamide) (3n)</u>



In this reaction, 0.36 mmol of **2c**, 0.4 mmol of **1j**, $Cu(OAc)_2$ (0.036 nnmol), $Zn(OTf)_2$ (0.036 mmol), and 4 Å MS (20 mg) were used in 1,4-dioxane (2.5 mL). The desired product **3n** (43 mg) was obtained in 30% yield.

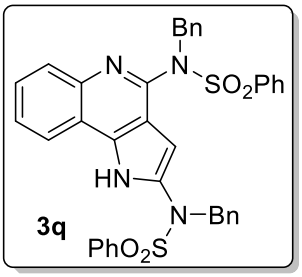
Brown semi-solid; R_f = 0.29 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.91 (s, 1H), 7.27 (br s, 5H), 7.24–7.22 (m, 2H), 7.09 (t, J = 2.8 Hz, 3H), 6.41 (d, J = 2.0 Hz, 1H), 5.01 (s, 2H), 4.80 (s, 2H), 3.14 (s, 3H), 2.90 (s, 3H), 2.79 (brs, 4H), 1.90 (t, J = 2.4 Hz, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 151.6, 142.3, 136.5, 136.4, 135.2, 133.9, 133.1, 128.8, 128.7, 128.6128.3, 128.1, 127.5, 120.5, 118.2, 95.7, 54.5, 54.2, 37.5, 37.2, 25.6, 25.1, 23.0, 22.3; **IR (Neat)** ν_{max} 3406, 2925, 1628, 1342, 1153, 1059, 771 cm^{-1}; HRMS (ESI) for $C_{29}H_{31}N_4O_4S_3$ $(M+H)^+$: calcd 595.1507, found 595.1511.

***N*,*N*'-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzylmethanesulfonamide) (3p)**



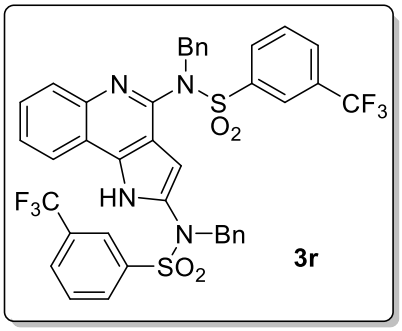
Following the general procedure of GP-2, compound **3p** (67 mg) was obtained in 90% yield as pale yellow solid; mp = 185–187 °C; R_f = 0.37 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.43 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 0.8, 8.0 Hz, 1H), 7.55 (dt, J = 1.2, 8.0 Hz, 1H), 7.46 (dt, J = 1.2, 7.6 Hz, 1H), 7.30–7.24 (m, 7H), 7.13–7.11 (m, 3H), 6.52 (d, J = 2.4 Hz, 1H), 5.11 (s, 2H), 4.82 (s, 2H), 3.20 (s, 3H), 2.93 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 147.1, 143.0, 136.4, 135.2, 135.0, 132.8, 130.0, 129.5, 128.7 (3C), 128.6, 128.3, 128.2. 127.6, 127.2, 126.4, 119.9, 119.1, 116.6, 98.1, 55.0, 53.9, 38.1, 37.2; **IR (Neat)** ν_{max} 3384, 1374, 1339, 1153, 1061 cm^{-1}; HRMS (ESI) for $C_{27}H_{27}N_4O_4S_2$ $(M+H)^+$: calcd 535.1474, found 535.1469.

***N*,*N*'-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzylbenzenesulfonamide) (3q)**



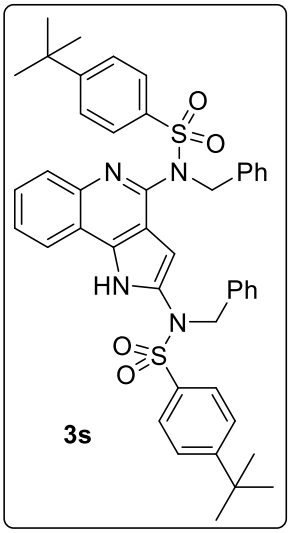
Following the general procedure of GP-2, compound **3q** (63 mg) was obtained in 68% yield as colorless solid; mp = 132–134 °C; R_f = 0.51 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.35 (s, 1H), 7.83 (dd, J = 1.2, 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.74–7.65 (m, 3H), 7.58 (t, J = 7.6 Hz, 1H), 7.53–7.44 (m, 7H), 7.33–7.27 (m, 2H), 7.23–7.17 (m, 5H), 7.10–7.01 (m, 2H), 6.41 (d, J = 2.0 Hz, 1H), 4.92 (s, 2H), 4.67 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.8, 142.8, 138.2, 136.5, 136.0, 134.9, 134.4, 133.6, 132.8, 132.7, 129.2, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.1, 126.9, 126.1, 119.7, 116.5, 99.0, 54.8, 52.9; **IR (Neat)** ν_{max} 3358, 1352, 1164, 1089 cm^{-1}; HRMS (ESI) for $C_{37}H_{31}N_4O_4S_2$ $(M+H)^+$: calcd 659.1787, found 659.1778.

***N,N'*-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-3-(trifluoromethyl)benzenesulfonamide) (3r)**



Following the general procedure of GP-2, compound **3r** (70 mg) was obtained in 63% yield as colorless solid; mp = 93–95 °C; R_f = 0.53 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.41 (s, 1H), 8.10 (s, 2H), 7.94–7.85 (m, 5H), 7.66–7.60 (m, 3H), 7.55–7.49 (m, 2H), 7.24–7.15 (m, 7H), 7.07–7.02 (m, 3H), 6.35 (d, J = 2.4 Hz, 1H), 4.87 (s, 2H), 4.69 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.5, 142.8, 139.6, 137.5, 135.8, 135.0, 134.5, 132.2, 131.5 (q, J = 12.1 Hz), 130.2, 129.4, 129.3, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 127.5, 127.4, 126.5, 125.6, 124.5, 119.8, 119.4, 116.5, 99.4, 55.5, 53.4; **^{19}F NMR (376 MHz, $CDCl_3$)** δ –62.8, –62.7; **IR (Neat)** ν_{max} 3336, 2926, 1361, 1325, 1167, 1135, cm^{-1}; HRMS (ESI) for $C_{39}H_{29}F_6N_4O_4S_2$ $(M+H)^+$: calcd 795.1534, found 795.1526.

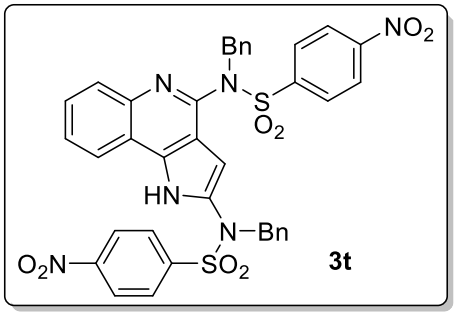
***N,N'*-(1*H*-pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-4-(tert-butyl)benzenesulfonamide) (3s)**



Following the general procedure of GP-2, **3s** (50 mg) was obtained in 46% yield as pale yellow solid; mp = 109–111 °C; R_f = 0.54 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400**

MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.84 (dt, J = 0.8, 7.6 Hz, 2H), 7.68 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.54 (s, 1H), 7.52–7.49 (m, 2H), 7.48–7.44 (m, 2H), 7.29 (dd, J = 2.8, 7.6 Hz, 3H), 7.25–7.18 (m, 5H), 7.05–7.02 (m, 3H), 6.43 (d, J = 2.0 Hz, 1H), 4.92 (s, 2H), 4.68 (s, 2H), 1.37 (s, 9H), 1.35 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 157.5, 156.5, 147.0, 142.8, 136.7, 135.5, 135.1, 134.4, 133.3, 133.0, 129.4, 128.8, 128.5, 128.2, 128.0, 127.7, 127.1, 126.8, 126.3, 126.1, 126.0, 125.7, 119.8 (2C), 116.5, 98.8, 54.8, 52.8, 35.3, 35.2, 31.1, 31.0; **IR (Neat)** ν_{max} 3411, 2938, 1637, 1348, 1163, 756 cm^{-1}; HRMS (ESI) for $C_{45}H_{47}N_4O_4S_2$ $(M+H)^+$: calcd 771.3039, found 771.3031.

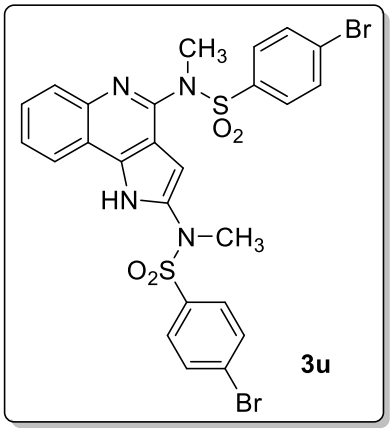
***N*,*N*'-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-4-nitrobenzenesulfonamide) (3t)**



Following the general procedure of GP-2, compound **3t** (69 mg) was obtained in 66% yield as pale yellow solid; mp = 180–182 °C; R_f = 0.33 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.34 (s, 1H), 8.27–8.22 (m, 4H), 7.85–7.70 (m, 6H), 7.50–7.39 (m, 2H), 7.18–7.05 (m, 7H), 7.03–6.97 (m, 3H), 6.29 (d, J = 2.0 Hz, 1H), 4.84 (s, 2H), 4.62 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.6, 150.2, 146.1, 143.8, 142.9, 141.5, 135.6, 134.9, 134.2, 131.9, 129.6, 129.5, 129.1, 128.9, 128.7, 128.5, 128.4, 128.2, 127.6, 126.7, 124.4, 123.9, 119.8, 119.4, 116.5, 99.7, 55.5, 53.4; **IR (Neat)** ν_{max} 3377, 2923, 1529, 1366, 1165, 1082 cm^{-1}; HRMS (ESI) for $C_{37}H_{29}N_6O_8S_2$ $(M+H)^+$: calcd 749.1488, found 749.1482.

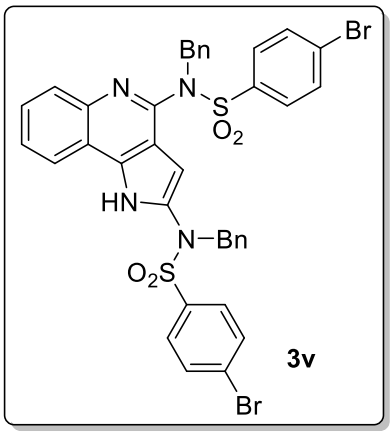
When a mixture of **1a** and **2h** was stirred for 15 h under the standard reaction conditions, the desired product (**3t**) was isolated in 68% yield (71mg).

***N*,*N*'-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(4-bromo-*N*-methylbenzenesulfonamide) (3u)**



Following the general procedure of GP-2, compound **3u** (54 mg) was obtained in 58% yield as pale yellow solid; mp = 188–190 °C; R_f = 0.66 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.84 (s, 1H), 8.08–8.05 (m, 1H), 7.89–7.86 (m, 1H), 7.63–7.56 (m, 8H), 7.46 (d, J = 8.0 Hz, 2H), 6.33 (d, J = 2.0 Hz, 1H), 3.27 (s, 3H), 3.26 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 147.9, 142.7, 135.8, 135.1, 134.7, 133.3, 132.5, 132.4, 131.8, 130.1, 129.5, 129.2, 128.8, 128.0, 127.3, 126.4, 119.8, 118.0, 116.5, 95.4, 37.8, 37.1; **IR (Neat)** ν_{max} 3356, 1573, 1380, 1355, 1162, 1071 cm^{-1}; HRMS (ESI) for $C_{25}H_{21}Br_2N_4O_4S_2$ $(M+H)^+$: calcd 662.9371, found 662.9366.

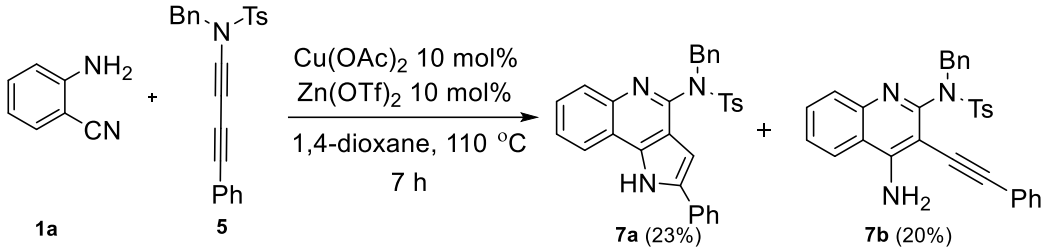
***N*,*N*'-(1*H*-Pyrrolo[3,2-c]quinoline-2,4-diyl)bis(*N*-benzyl-4-bromobenzenesulfonamide) (3v)**



Following the general procedure of GP-2, compound **3v** (73 mg) was obtained in 64% yield as pale yellow solid; mp = 148–150 °C; R_f = 0.62 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.47 (s, 1H), 7.84 (dd, J = 4.8, 7.6 Hz, 2H), 7.65–7.57 (m, 6H), 7.50–7.45 (m, 3H), 7.28–7.24 (m, 3H), 7.19 (dd, J = 2.0, 6.8 Hz, 5H), 7.09 (t, J = 7.2 Hz, 3H), 6.41 (d, J = 2.0 Hz, 1H), 4.90 (s, 2H), 4.65 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 146.6,

142.8, 137.2, 136.2, 135.0, 134.7 (2C), 132.6, 132.5, 132.0, 129.9, 129.5, 129.3, 128.9, 128.8, 128.6, 128.4, 128.2, 128.1, 127.9, 127.4, 127.2, 126.4, 119.9, 119.6, 116.5, 99.3, 55.1, 53.0; **IR (Neat)** ν_{max} 3370, 1531, 1384, 1162, 1072, cm^{-1}; HRMS (ESI) for $C_{37}H_{29}Br_2N_4O_4S_2$ $(M+H)^+$: calcd 814.9997, found 814.9988.

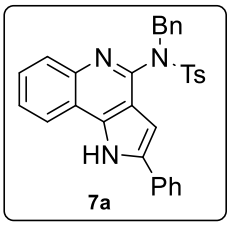
Synthesis of 7a and 7b



1a **5** **7a** (23%) **7b** (20%)

In an oven-dried Schlenk flask, **1a** (0.23 mmol, 27 mg)**, 5** (0.21 mmol, 80 mg), $Cu(OAc)_2$ (0.021 mmol, 4.0 mg), and $Zn(OTf)_2$ (0.021 mmol, 8.0 mg) were taken and subsequently anhydrous 1,4-dioxane (2 mL) was introduced into the Schlenk flask under argon atmosphere. The reaction mixture was heated at 110 °C for 7 h before diluting with dichloromethane (10 mL). Subsequently, the reaction mixture was filtered through a small pad of Celite and the filtrate was concentrated. The crude residue was purified through silica gel column chromatography to obtain pure **7a** and **7b** in 23% (24 mg) and 20% (21 mg) yields, respectively.

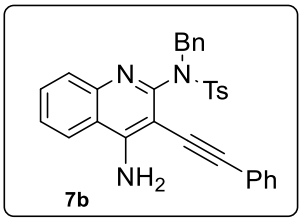
***N*-Benzyl-4-methyl-*N*-(2-phenyl-1*H*-pyrrolo[3,2-c]quinolin-4-yl)benzenesulfonamide (7a)**



7a

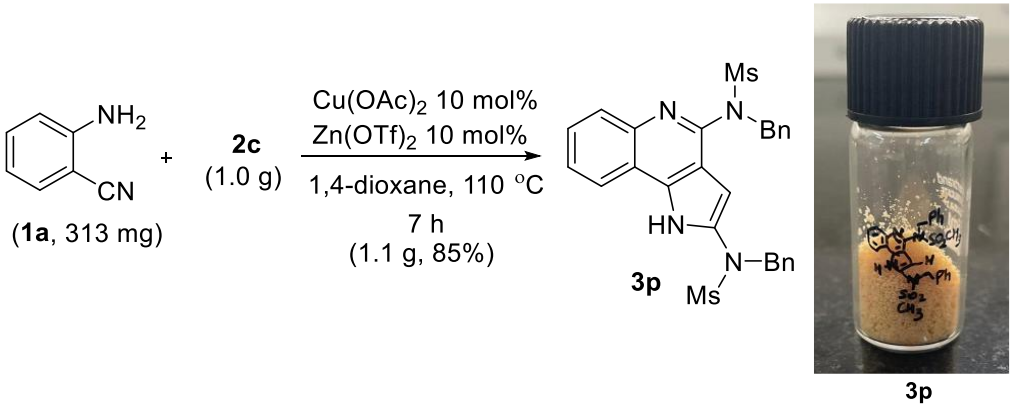
Pale yellow solid; mp = 220–222 °C; R_f = 0.62 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.27 (s, 1H), 7.92–7.89 (m, 1H), 7.83–7.79 (m, 3H), 7.57 (d, J = 7.6 Hz, 2H), 7.46–7.43 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.34–7.29 (m, 5H), 7.09–7.01 (m, 4H), 4.95 (s, 2H), 2.48 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 147.1, 143.6, 142.7, 137.6, 137.3, 136.4, 135.9, 131.4, 129.4 (2C), 128.9, 128.6, 128.5, 128.1, 127.8, 127.3, 126.6, 125.9, 125.2, 121.8, 119.7, 116.9, 101.4, 53.1, 21.6; **IR (Neat)** ν_{max} 3408, 2924, 1639, 1343, 1089, 759 cm^{-1}; HRMS (ESI) for $C_{31}H_{26}N_3O_2S$ $(M+H)^+$: calcd 504.1746, found 504.1752.

***N*-(4-Amino-3-(phenylethynyl)quinolin-2-yl)-*N*-benzyl-4-methylbenzenesulfonamide (7b)**



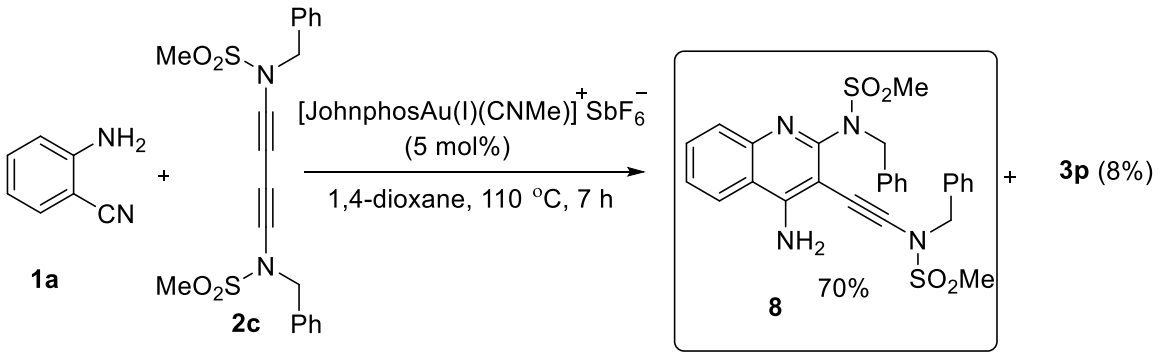
Pale yellow solid; mp = 171–173 °C; R_f = 0.52 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 3.2 Hz, 2H), 7.53 (t, J = 8.4 Hz, 2H), 7.35–7.25 (m, 8H), 7.06 (t, J = 3.2 Hz, 3H), 5.45 (s, 2H), 4.81 (s, 2H), 2.44 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 152.6, 152.5, 145.9, 143.4, 136.4, 136.0, 131.5, 129.9, 129.5, 129.3, 128.7, 128.4, 128.3, 127.9, 127.3, 125.5, 123.4, 120.5, 116.4, 99.8, 83.3, 53.5, 21.6; **IR (Neat)** ν_{max} 3417, 2924, 1636, 1365, 1082, 763 cm^{-1}; HRMS (ESI) for $C_{31}H_{26}N_3O_2S$ $(M+H)^+$: calcd 504.1746, found 504.1757.

Procedure for gram-scale reaction



In an oven-dried 15 mL Schlenk flask, **1a** (313 mg, 2.6 mmol), **2c** (1.0 g, 2.4 mmol), $Cu(OAc)_2$ (44 mg, 0.24 mol), and $Zn(OTf)_2$ (87 mg, 0.24 mmol) were taken and anhydrous 1,4-dioxane (20 mL) was added in the reaction mixture under argon atmosphere. Subsequently, the reaction mixture was heated at 110 °C for 7 h. Upon full consumption of **2c**, the reaction mixture was diluted with dichloromethane (30 mL) and filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure and the crude residue was purified through silica gel column chromatography to obtain pure **3p** in 85% yield (1.1 g).

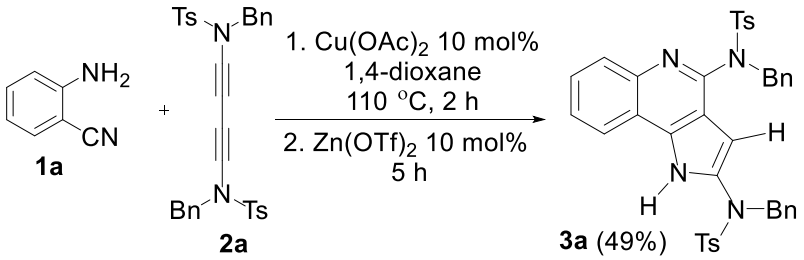
Procedure for the synthesis of *N*-((4-amino-2-(*N*-benzylmethylsulfonamido)quinolin-3-yl)ethynyl)-*N*-benzylmethanesulfonamide (8)



A mixture of **1a** (23 mg, 0.21 mmol), **2c** (80 mg, 0.19 mmol), and Au(I) (5 mol%, 7.4 mg) was taken in an oven-dried 15 mL Schlenk flask under argon atmosphere, and subsequently 1 mL of anhydrous 1,4-dioxane was poured into the reaction mixture via syringe. Next, the Schlenk flask was heated at 110 °C for 7 h. Upon full consumption of 2c the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure and purified through silica gel column chromatography to obtain pure **3p** (8 mg) and **8** (72 mg) in 8% and 70% yields, respectively.

pale yellow solid; mp = 155–157 °C; R_f = 0.28 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.60 (t, J = 7.2 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.32 (brs, 11H), 6.01 (s, 2H), 4.70 (d, J = 14.4 Hz, 2H), 4.55 (d, J = 14.4 Hz, 2H), 2.63 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 137.9, 135.2, 133.7, 133.0, 132.4, 130.0, 129.5, 128.6, 128.5, 128.3, 116.9, 107.7, 56.2, 39.1; **IR (Neat)** ν_{max} 3427, 1634, 1341, 1154, 770 cm^{-1}; HRMS (ESI) for $C_{27}H_{26}KN_4O_4S_2$ $(M+K)^+$: calcd 573.1033, found 573.1041.

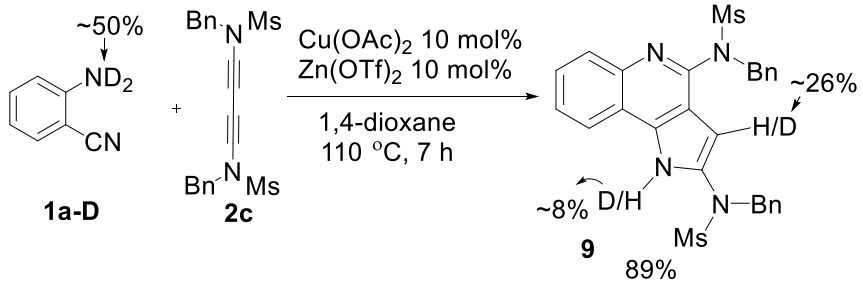
Control experiment



In an oven-dried 15 mL Schlenk flask, **1a** (18 mg, 0.15 mmol), **2a** (80 mg, 0.14 mmol), and $Cu(OAc)_2$ (3.0 mg, 0.014 mmol) were taken and anhydrous 1,4-dioxane (2 mL) was added in

the reaction mixture under argon atmosphere. Subsequently, the reaction mixture was heated at 110 °C for 2 h. Upon full consumption of **2a**, the reaction mixture was cooled to room temperature and $Zn(OTf)_2$ (5.0 mg, 0.014 mmol) was added under argon atmosphere. Thereafter, the reaction mixture was stirred at 110 °C for an additional 5 h before diluting with dichloromethane (10 mL). The diluted reaction mixture was filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure and the crude residue was purified through silica gel column chromatography. The desired product **3a** was isolated in 49% yield (48 mg).

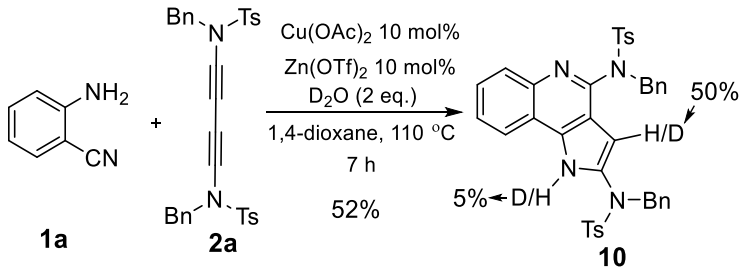
Deuterium-labelling experiment



Following general procedurae GP-2, reaction between **1a-D** (31 mg, 0.26 mmol) and **2c** (100 mg, 0.24 mmol) in presence of $Cu(OAc)_2$ (5.0 mg, 0.024 mmol) and $Zn(OTf)_2$ (9.0 mg, 0.024 mmol) furnished the desired product **9** (114 mg) in 89% yield as pale yellow solid.

mp = 205–207 °C; R_f = 0.23 (4:1 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.52 (s, 0.92H), 8.00 (d, J = 8.0 Hz, 1H), 7.78 (dd, J = 0.8, 8.4 Hz, 1H), 7.53 (dt, J = 1.6, 7.2 Hz, 1H), 7.42 (dt, J = 1.2, 6.8 Hz, 1H), 7.29–7.23 (m, 7H), 7.13–7.10 (m, 3H), 6.52 (d, J = 2.4 Hz, 0.74H), 5.11 (s, 2H), 4.81 (s, 2H), 3.20 (s, 3H), 2.91 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.1, 143.0, 136.4, 135.2, 135.0, 132.8, 129.5, 128.7, 128.3, 128.2, 127.6, 127.2, 126.4, 119.8, 119.1, 116.6, 98.0, 55.0, 53.9, 38.1, 37.2; **IR (Neat)** ν_{max} 3407, 2926, 1637, 1340, 1152, 1065, 756 cm^{-1}; HRMS (ESI) for $C_{27}H_{26}DN_4O_4S_2$ $(M+H)^+$: calcd 536.1536, found 536.1528.

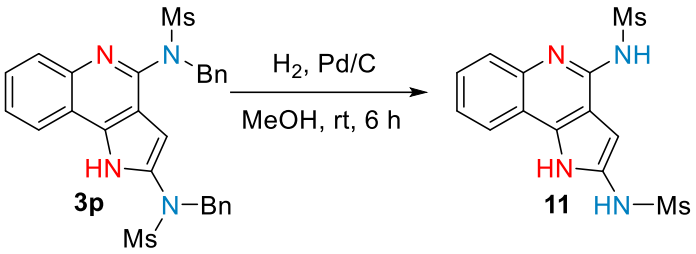
D_2O experiment



In an oven-dried 15 mL Schlenk flask, **1a** (18 mg, 0.15 mmol), **2a** (80 mg, 0.14 mmol), $Cu(OAc)_2$ (3.0 mg, 0.014 mmol), and $Zn(OTf)_2$ (5.2 mg, 0.014 mmol) were taken and anhydrous 1,4-dioxane (2 mL) was added in the reaction mixture under argon atmosphere. Next, D_2O (6.0 μL, 0.28 mmol) was introduced into the flask via micro syringe and subsequently the Schlenk flask was placed inside oil bath at 110 °C with stirring. Upon full conversion of starting material **2a**, the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure and purified through silica gel column chromatography to obtain pure **10** (50mg) in 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 0.95H), 7.83 (t, J = 8.8 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.52–7.43 (m, 2H), 7.30 (d, J = 8.0 Hz, 4H), 7.25 (d, J = 8.0 Hz, 2H), 7.22–7.18 (m, 5H), 7.08–7.02 (m, 3H), 6.43 (d, J = 2.0 Hz, 0.5H), 4.90 (s, 2H), 4.64 (s, 2H), 2.47 (s, 3H), 2.44 (s, 3H).

Debenzylation of 3p

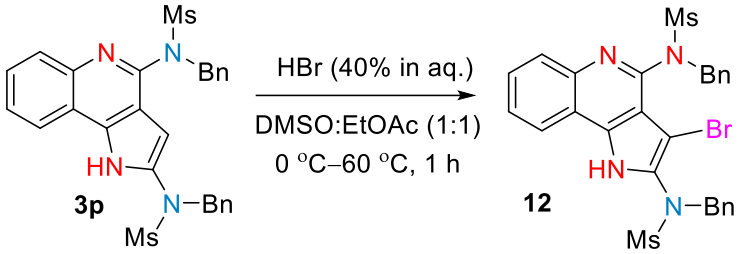


In an oven-dried 10 mL Schlenk flask, **3p** (80 mg, 0.14 mmol) and Pd/C (31 mg, 0.29 mmol), were taken and MeOH (3 mL) was added under H_2 atmosphere. Later, the reaction mixture was stirred for 6 h under H_2 balloon condition and upon full conversion of **3p**, the reaction mixture was evaporated under reduced pressure. Then, the crude reaction mixture was purified through silica gel column chromatography to obtain pure **11** (48mg) in 91% yield.

colorless solid; mp = 220–222 °C; R_f = 0.44 (1:1 hexane/acetone); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, d_6-DMSO)** δ 12.78 (s, 1H), 11.67 (s, 1H), 10.0 (s, 1H), 8.25 (d, J = 7.6 Hz, 1H),

7.73 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 6.83 (s, 1H), 3.09 (s, 3H), 3.04 (s, 3H); **^{13}C NMR (101 MHz, d_6-DMSO)** δ 150.5, 134.4, 133.4, 130.8, 128.7, 124.2, 121.6, 118.3, 113.4, 112.4, 101.9, 43.1; **IR (Neat)** ν_{max} 3395, 2923, 1634, 1593, 1383, 1102 cm^{-1}; HRMS (ESI) for $C_{13}H_{15}N_4O_4S_2$ $(M+H)^+$: calcd 355.0535, found 355.0524.

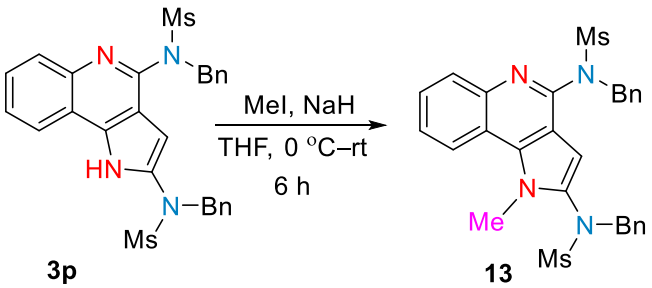
Bromination of 3p



In an oven-dried 10 mL Schlenk flask, **3p** (55 mg, 0.10 mmol) was dissolve in DMSO: EtOAc (1:1, 2mL) at 0 °C and subsequently HBr (25 µL, 1.0 mmol) was added in the reaction mixture. Later, the mixture was heated to 60 °C and stirred for 1 h. Upon full conversion of **3p**, H_2O (5 mL) was poured into the Schlenk flask and the reaction mixture was extracted with EtOAc (5 mL X 3). The organic extract was concentrated under reduced pressure and the crude residue was purified through silica gel column chromatography to obtain pure **12** (54mg) in 86% yield.

Pale yellow solid; mp = 105–107 °C; R_f = 0.5 (4:1 hexane/acetone); [Silica, UV and I_2]; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.61 (s, 1H), 7.94 (d, J = 7.2 Hz, 1H), 7.62 (t, J = 6.4 Hz, 1H), 7.52 (t, J = 5.6 Hz, 1H), 7.37 (t, J = 6.0 Hz, 1H), 7.31 (t, J = 3.2 Hz, 2H), 7.19–7.16 (m, 8H), 5.06 (s, 2H), 4.94 (s, 2H), 3.17 (s, 3H), 3.14 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 146.7, 142.7, 135.5, 135.4, 135.1, 129.9, 129.4, 129.1, 129.0, 128.7, 128.3, 128.1, 127.9, 127.8, 126.9, 119.7, 116.4, 116.2, 90.3, 55.0, 53.8, 40.7, 38.5; **IR (Neat)** ν_{max} 3395, 2924, 1621, 1384, 1152 cm^{-1}; HRMS (ESI) for $C_{27}H_{26}BrN_4O_4S_2$ $(M+H)^+$: calcd 613.0579, found 613.0575.

Methylation of free -NH group in 3p



In an oven-dried 10 mL Schlenk flask, NaH (12 mg 60% in oil, 0.29 mmol) was taken under argon atmosphere and anhydrous THF (4 mL) was introduced into the Schlenk flask. Subsequently, **3p** (80 mg, 0.14 mmol) was added in one portion at 0 °C and stirred for 10 min. Later, MeI (0.2 mL, 2.9 mmol) was introduced into the reaction mixture at 0 °C and stirred for 6 h at rt. Upon full conversion of **3p**, the reaction mixture was quenched with H_2O (5 mL) at 0 °C and extracted with DCM (10 mL X 3). The organic extract was concentrated under reduced pressure and the crude residue was purified through silica gel column chromatography (acetone:hexane) (3:1) to obtain pure **13** (71mg) in 86% yield.

colorless solid; mp = 110–112 °C; R_f = 0.52 (3:1 hexane/acetone); [Silica, UV and I_2]; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.22 (t, J = 8.0 Hz, 1H), 8.10 (dd, J = 1.6, 8.0 Hz, 1H), 7.60 (dt, J = 1.2, 7.2 Hz, 1H), 7.51 (dt, J = 1.2, 6.8 Hz, 1H), 7.31 (dd, J = 2.0, 8.0 Hz, 2H), 7.23–7.15 (m, 6H), 7.14–7.10 (m, 2H), 6.70 (s, 1H), 5.12 (q, J = 13.2 Hz, 2H), 4.98 (d, J = 13.2 Hz, 1H), 4.41 (d, J = 13.2 Hz, 1H), 3.67 (s, 3H), 3.21 (s, 3H), 2.96 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.6, 144.0, 136.6, 135.0, 134.5, 134.0, 130.1, 129.5, 128.9, 128.7, 128.6, 128.2, 127.7, 126.8, 126.3, 120.8, 118.7, 118.4, 100.7, 57.3, 54.1, 37.8, 36.6, 32.9; **IR (Neat)** ν_{max} 3398, 2924, 1346, 1154, 1085 cm^{-1}; HRMS (ESI) for $C_{28}H_{29}N_4O_4S_2$ $(M+H)^+$: calcd 549.1630, found 549.1637.

X-Ray Data Collection and Structure Refinement Details for compound 3p

A good quality single crystal of size 0.36x 0.32x 0.21mm was selected under a polarizing microscope and was mounted on a glass fiber for data collection. Single crystal X-ray data for compound **3p** were collected on the Bruker APEX-II CCD area-detector at 100(2) K. Data collection was performed using ω-scans at 100(2) K by Bruker APEX2[1]. Cell determination, and data reduction was performed using the Bruker SAINT software. Structure solution and refinement were performed by using SHELX-97[2]. Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms were carried out by the full-matrix least-squares method. The hydrogen atoms attached to carbon atoms were generated with idealized geometries and isotropically refined using a riding model.

Crystallization: Crystals of compound **3p** (8 mg) were grown in a 1 mL mixture of solvents *n*-hexane:ethyl acetate (1:9) by slow evaporation method for 3 days.

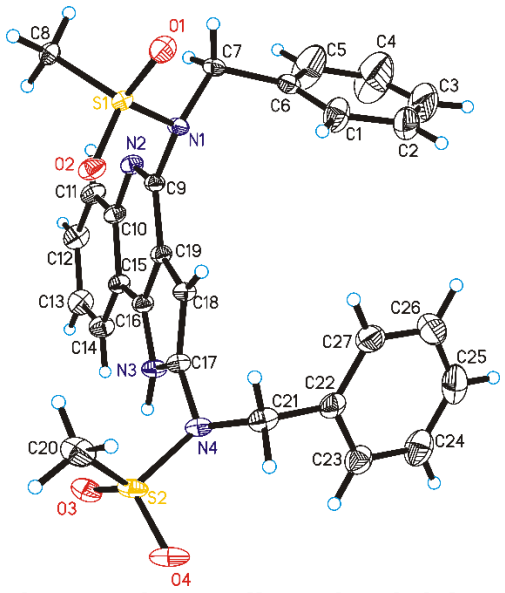


Figure S3 ORTEP diagram drawn with 50% ellipsoid probability for non-H atoms of the crystal structure of compound **3p** determined at 273K.

Table S1 Crystal data and structure refinement details for **3p**.

Compound	**3p**
Empirical formula	$C_{27}H_{26}N_4O_4S_2$
Formula weight	534.64
Crystal System	Triclinic
Space group	*P*-1
a (Å)	11.8340(3)
b (Å)	13.5204(3)
c (Å)	16.9352(4)
α (°)	90.4110(10)
β (°)	91.3210(10)
γ (°)	97.8180(10)
V (Å^3)	2683.59(11)
Z	4
D_c (g/cm^3)	1.323
F_{000}	1120
μ (mm^{-1})	0.238
θ_{max} (°)	28.34
Total reflections	45794
Unique reflections	13378
Reflections [$I > 2\sigma(I)$]	10771
Parameters	679
R_{int}	0.0488
Goodness-of-fit	1.024

R [$F^2 > 2\sigma(F^2)$]	0.0695
wR (F^2, all data)	0.1967
CCDC No.	2101673

References:

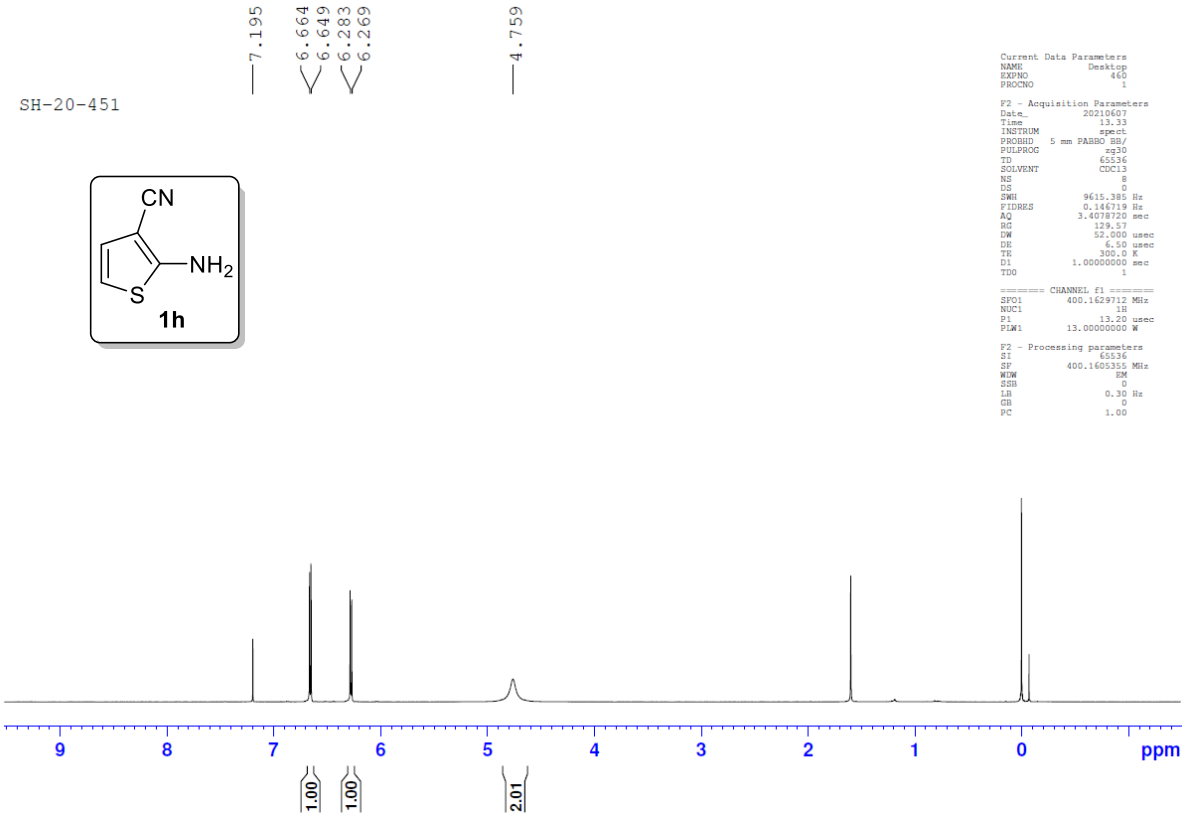
1. (a) Ramya, P. V. S.; Thatikonda, S.; Angapelly, S.; Babu, B. N.; Naidu, V. G. M.; Kamal, A. Synthesis and Biological Evaluation of Thieno[2, 3-d]pyrimidine-amides as Potential Anticancer Agents. *ChemistrySelect*, **2018**, *3*, 3101–3106. (b) Salem, Mohamed S. H.; Abdel Aziz, Yasmine M.; Elgawish, Mohamed S.; Said, Mohamed M.; Abouzid, Khaled A. M. Design, synthesis, biological evaluation and molecular modeling study of new thieno[2,3-d] pyrimidines with anti-proliferative activity on pancreatic cancer cell lines. B*ioorganic Chemistry* **2020**, *94*, 103472.

2. Tian, X.; Song, L.; Rudolph, M.; Rominger, F.; Oeser, T.; Hashmi, A. S. K. Sulfilimines as Versatile Nitrene Transfer Reagents: Facile Access to Diverse Aza-Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 3589–3593.

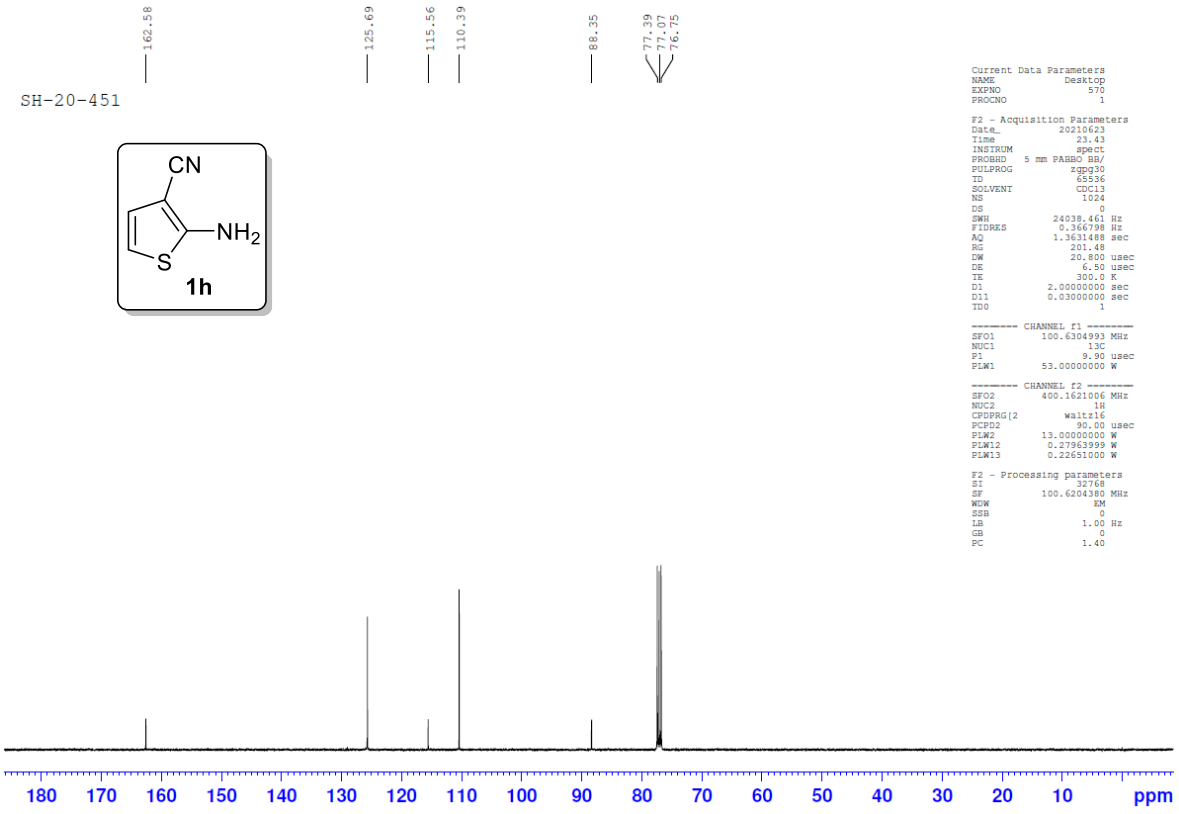
3. (a) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. Coupling and cycloaddition of ynamides: homo- and Negishi coupling of tosylynamides and intramolecular [4D2] cycloaddition of N-(o-ethynyl)phenyl ynamides and arylynamides. *Tetrahedron* **2006**, *62*, 3843–3855. (b) Kramer, S.; Madsen, J. L. H.; Rottländer, M.; Skrydstrup, T. Access to 2,5-Diamidopyrroles and 2,5-Diamidofurans by Au(I)-Catalyzed Double Hydroamination or Hydration of 1,3-Diynes. *Org. Lett.* **2010**, *12*, 2758–2761. (c) Rodríguez, D.; Castedo, L.; Saá, C. Homocoupling of 1-Alkynyl Tosylamides. *Synlett* **2004**, 377–379.

4. Andna, L.; Miesch, L. Metal-free synthesis of activated ynesulfonamides and tertiary enesulfonamides. *Org. Biomol. Chem.* **2019**, *17*, 5688–5692.

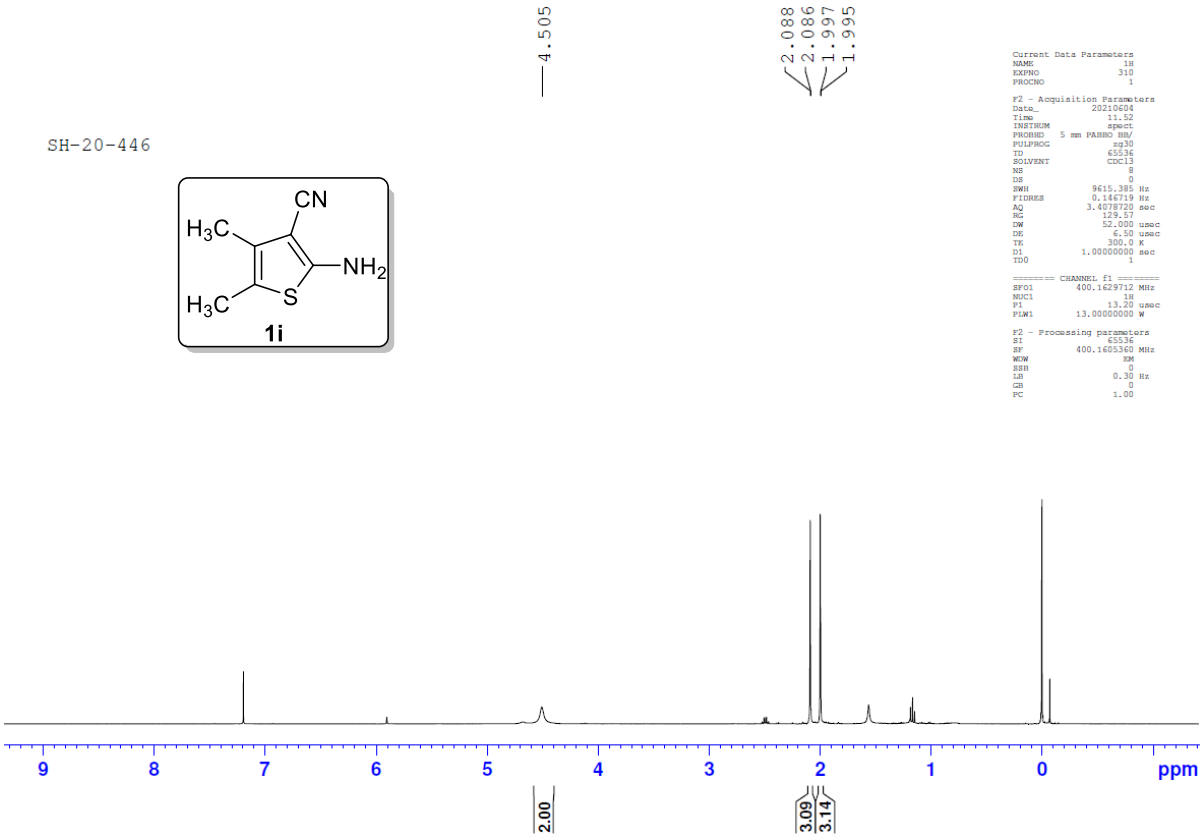
^{1}H NMR, $CDCl_3$, 400 MHz



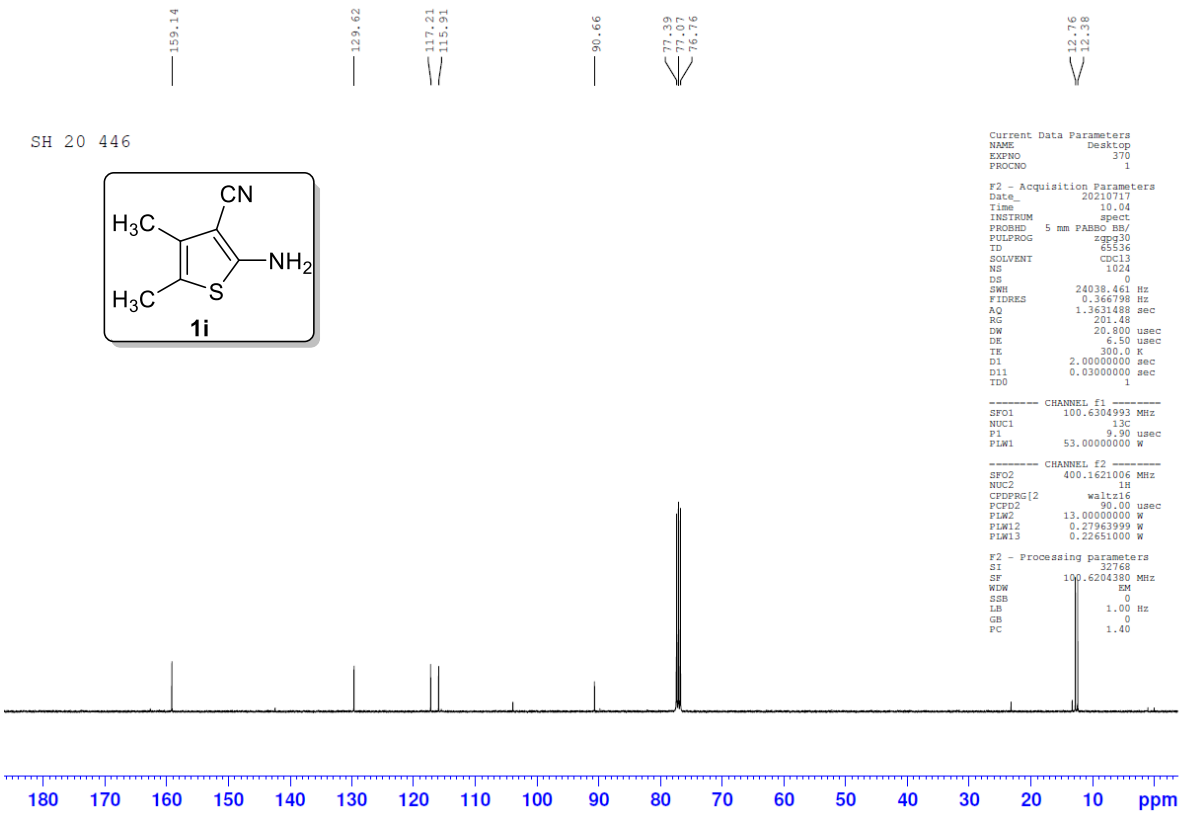
^{13}C NMR, $CDCl_3$, 101 MHz



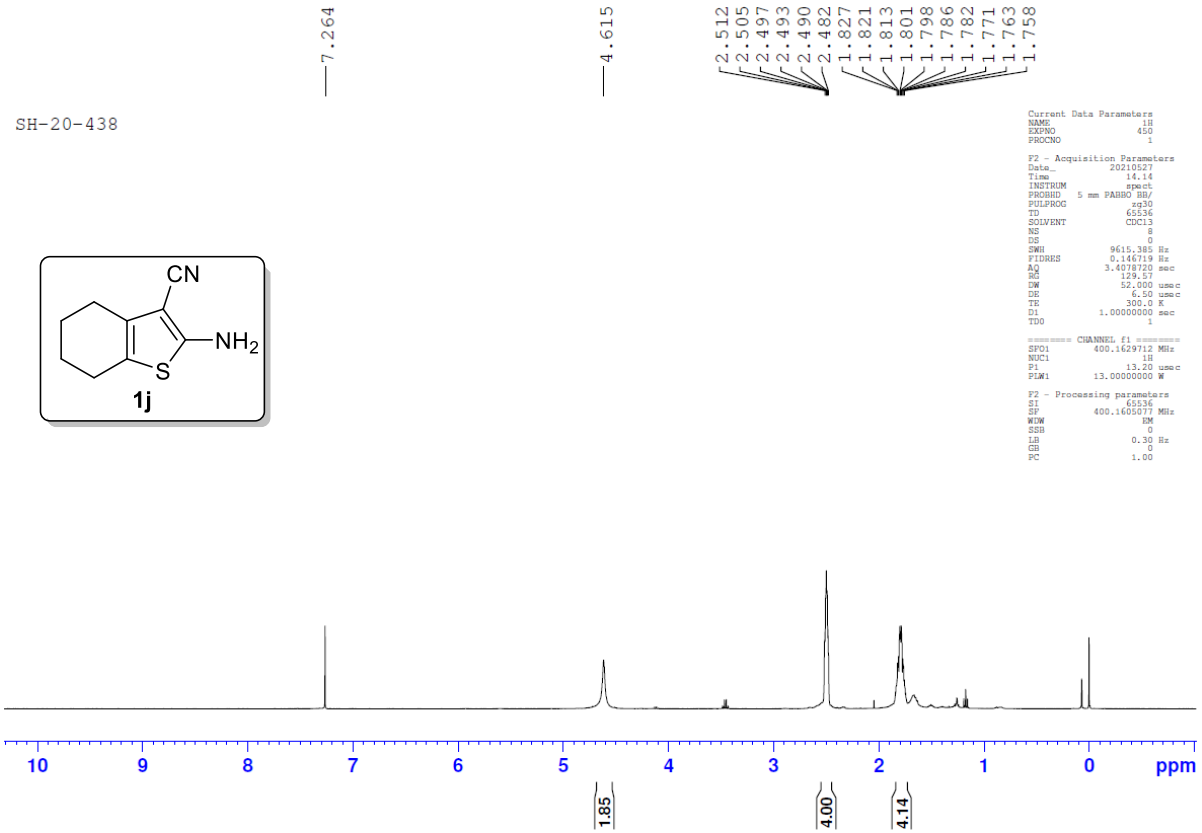
^{1}H NMR, $CDCl_3$, 400 MHz



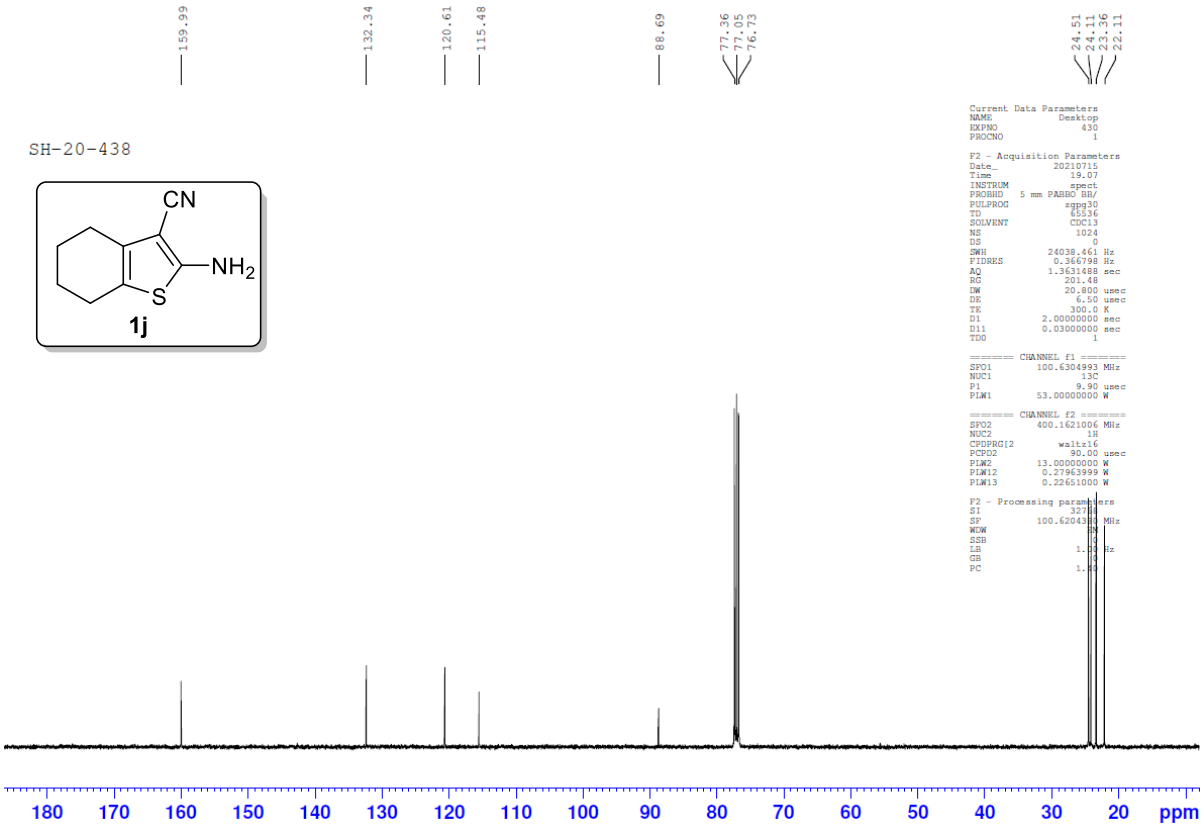
^{13}C NMR, $CDCl_3$, 101 MHz



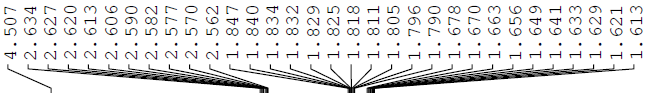
^{1}H NMR, $CDCl_3$, 400 MHz



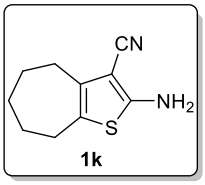
^{13}C NMR, $CDCl_3$, 101 MHz

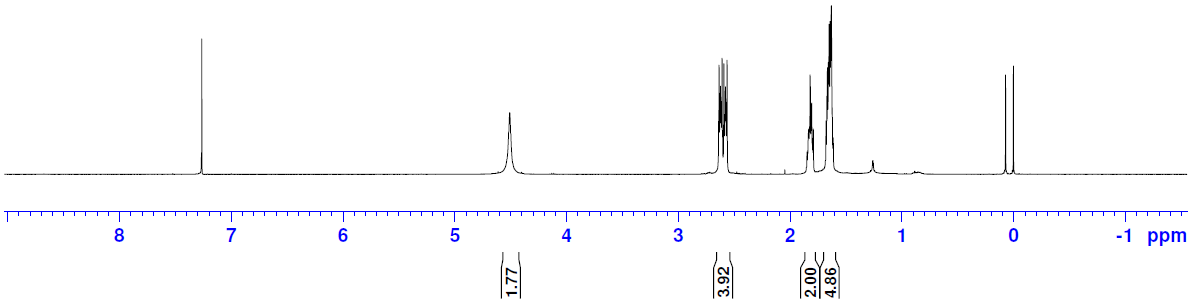


^{1}H NMR, $CDCl_3$, 400 MHz



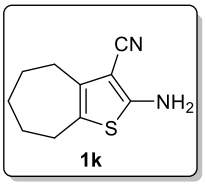
SH-20-449

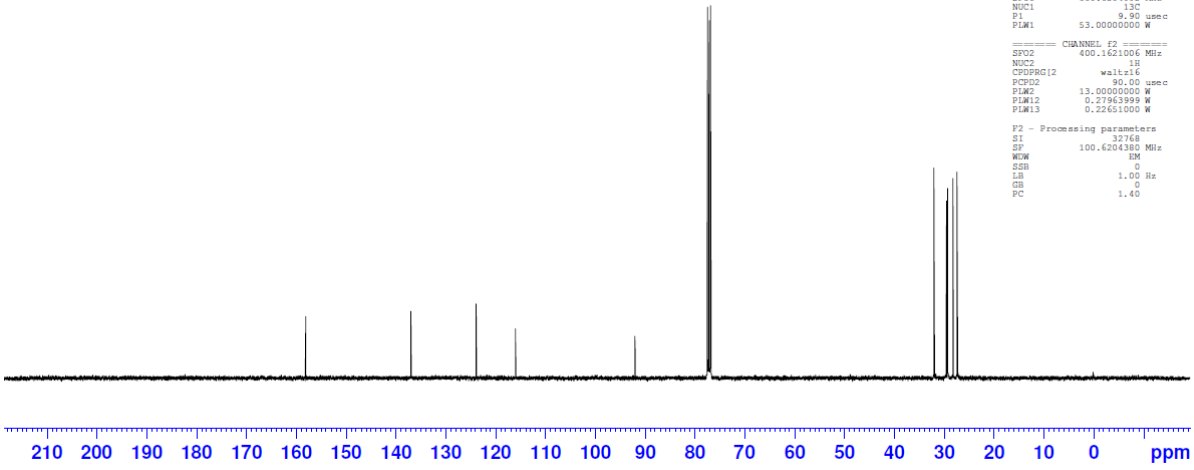




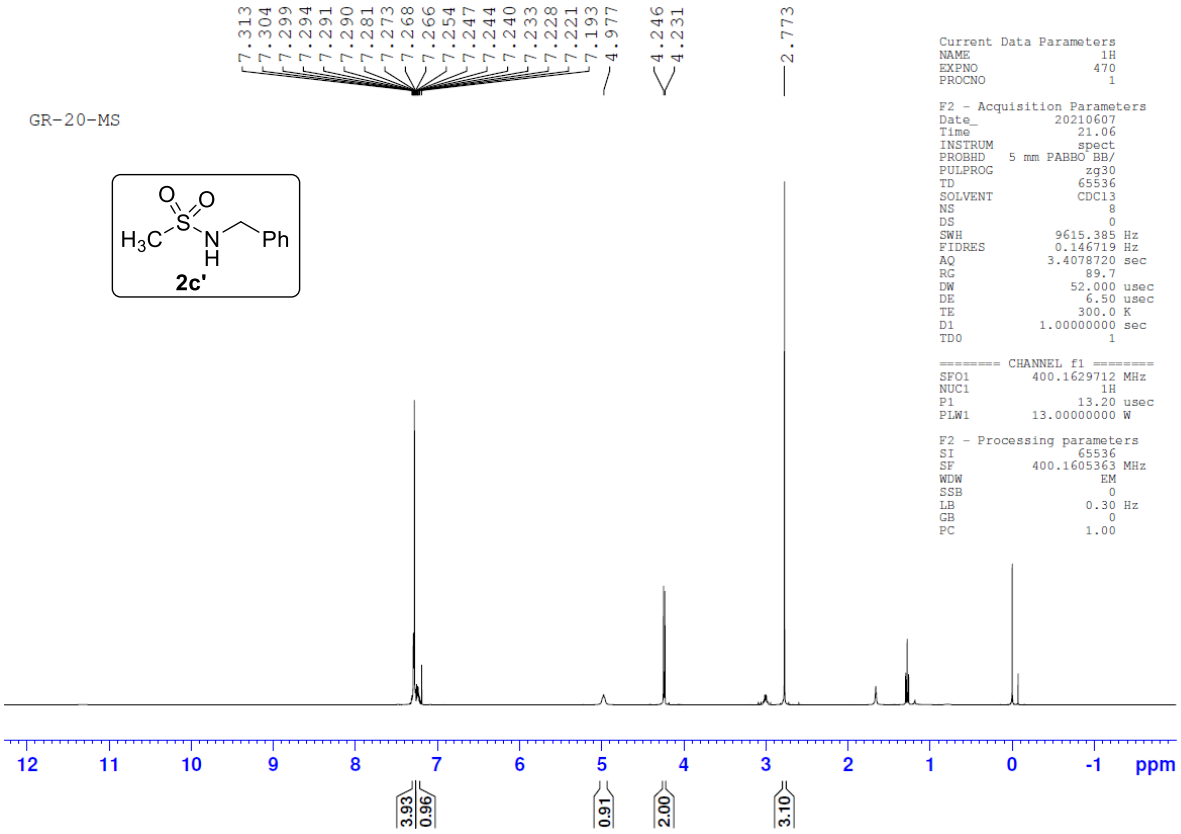
^{13}C NMR, $CDCl_3$, 101 MHz

SH-20-449

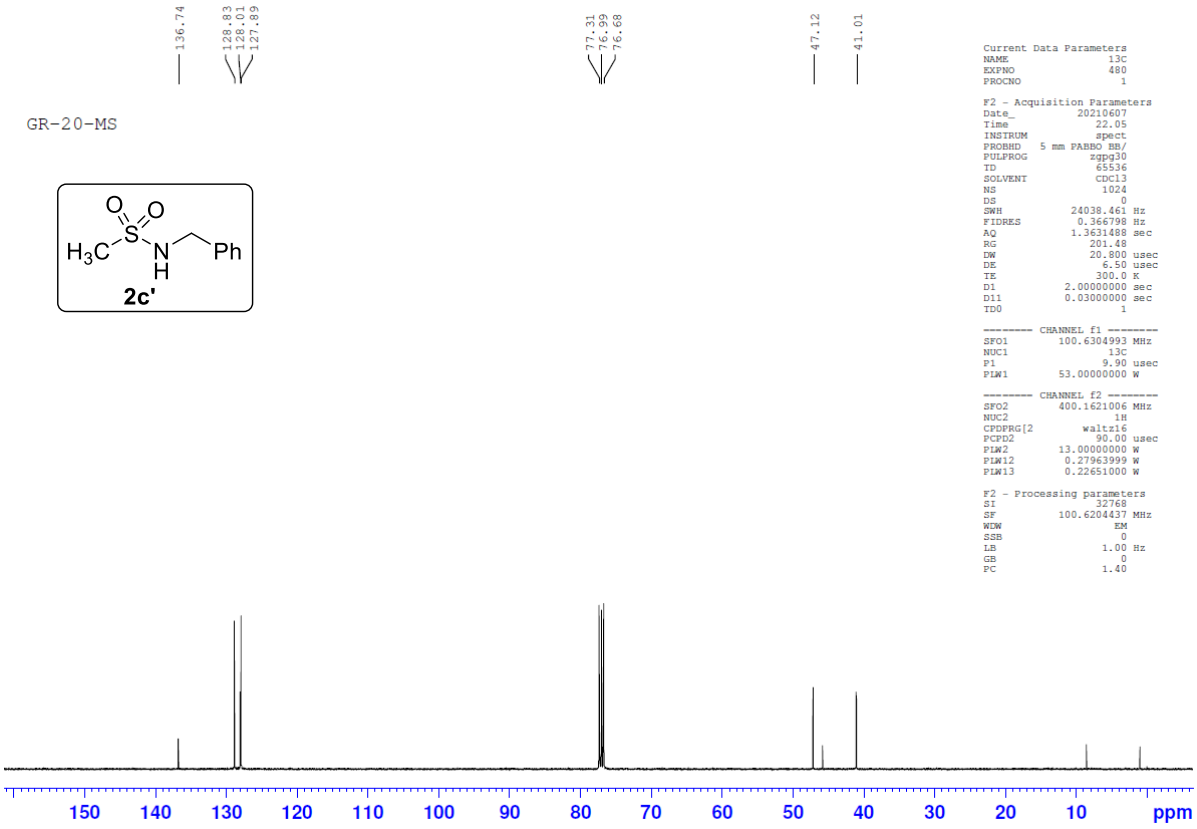




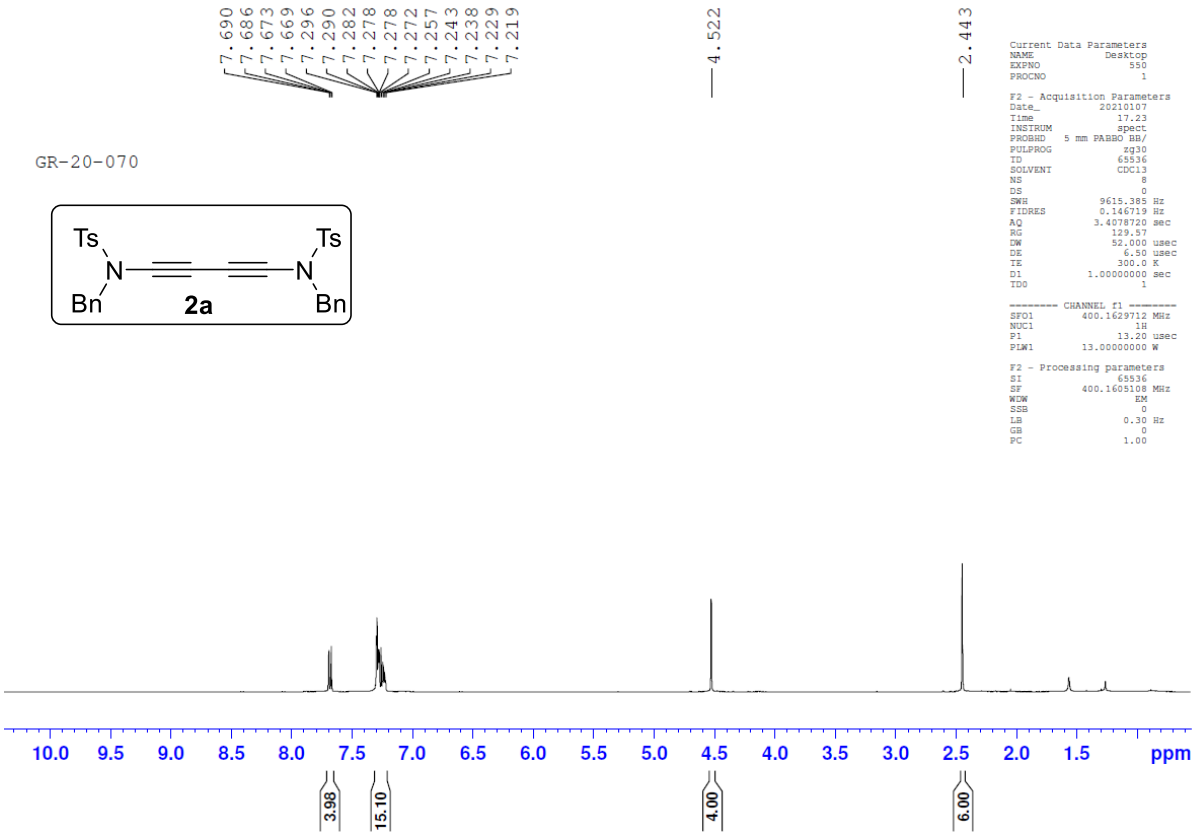
^{1}H NMR, $CDCl_3$, 400 MHz



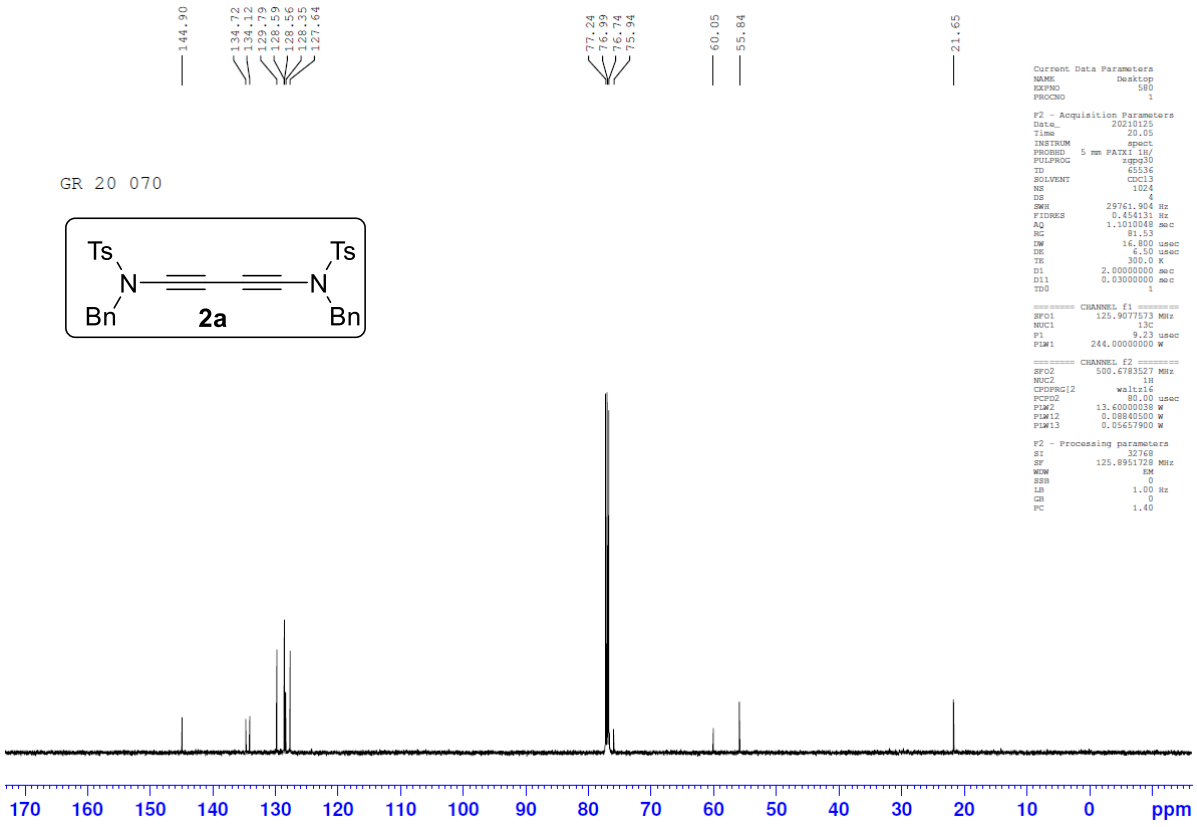
^{13}C NMR, $CDCl_3$, 101 MHz



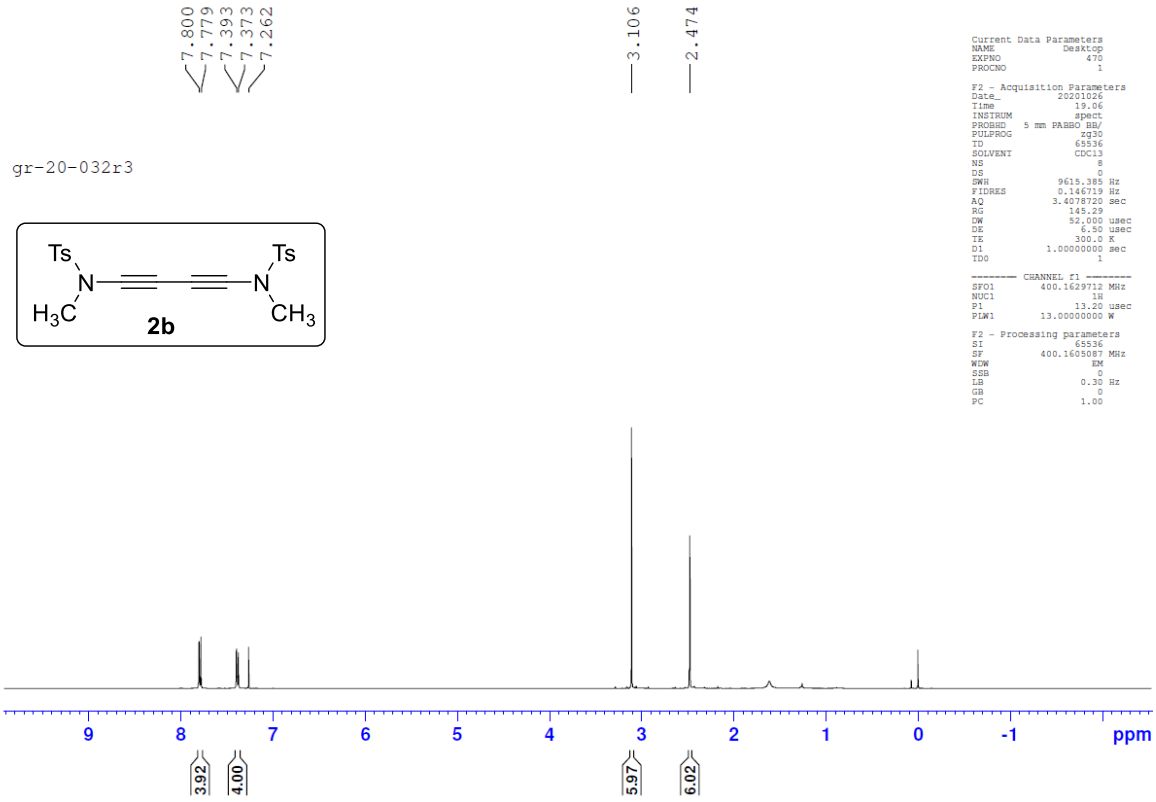
^{1}H NMR, $CDCl_3$, 400 MHz



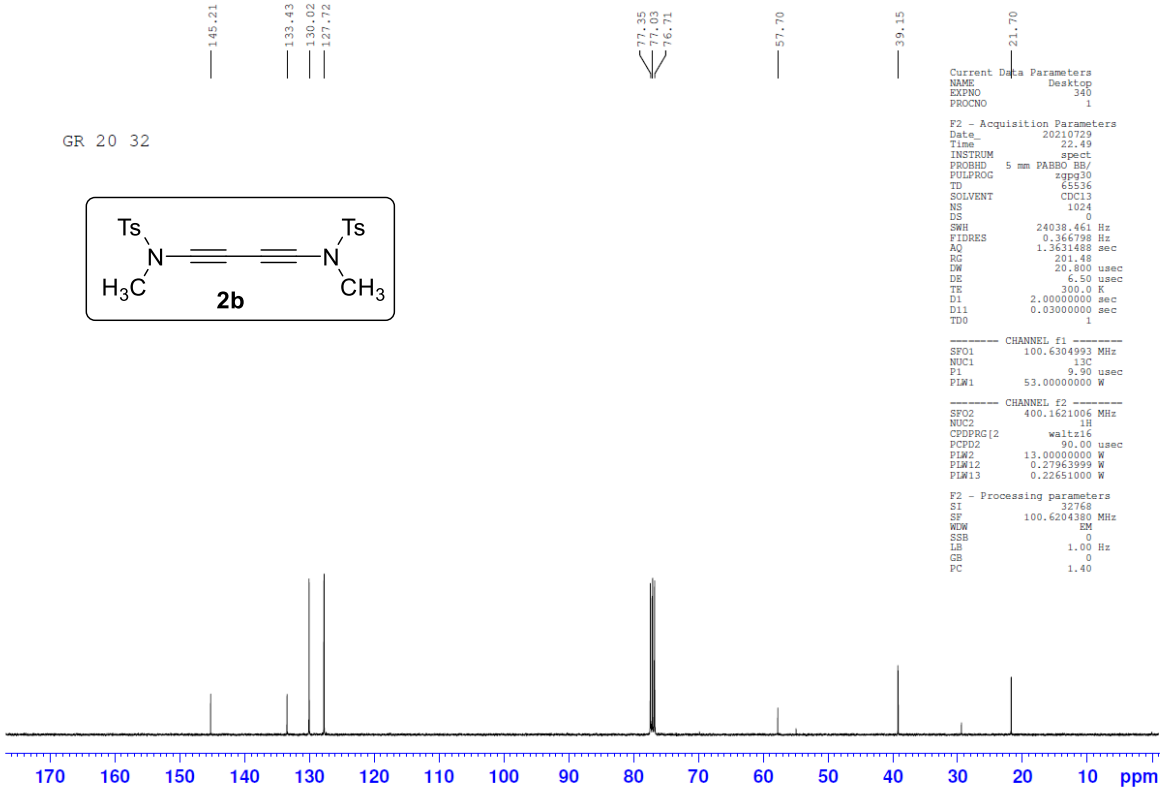
^{13}C NMR, $CDCl_3$, 125 MHz



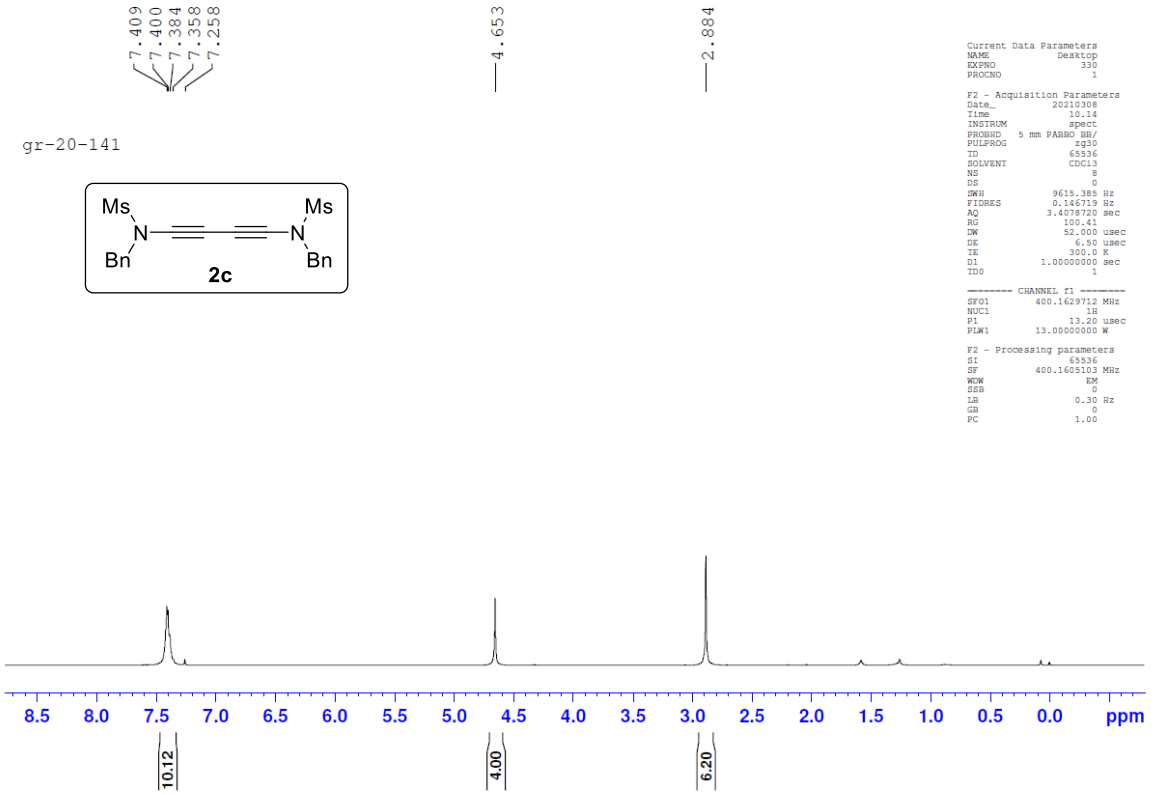
^{1}H NMR, $CDCl_3$, 400 MHz



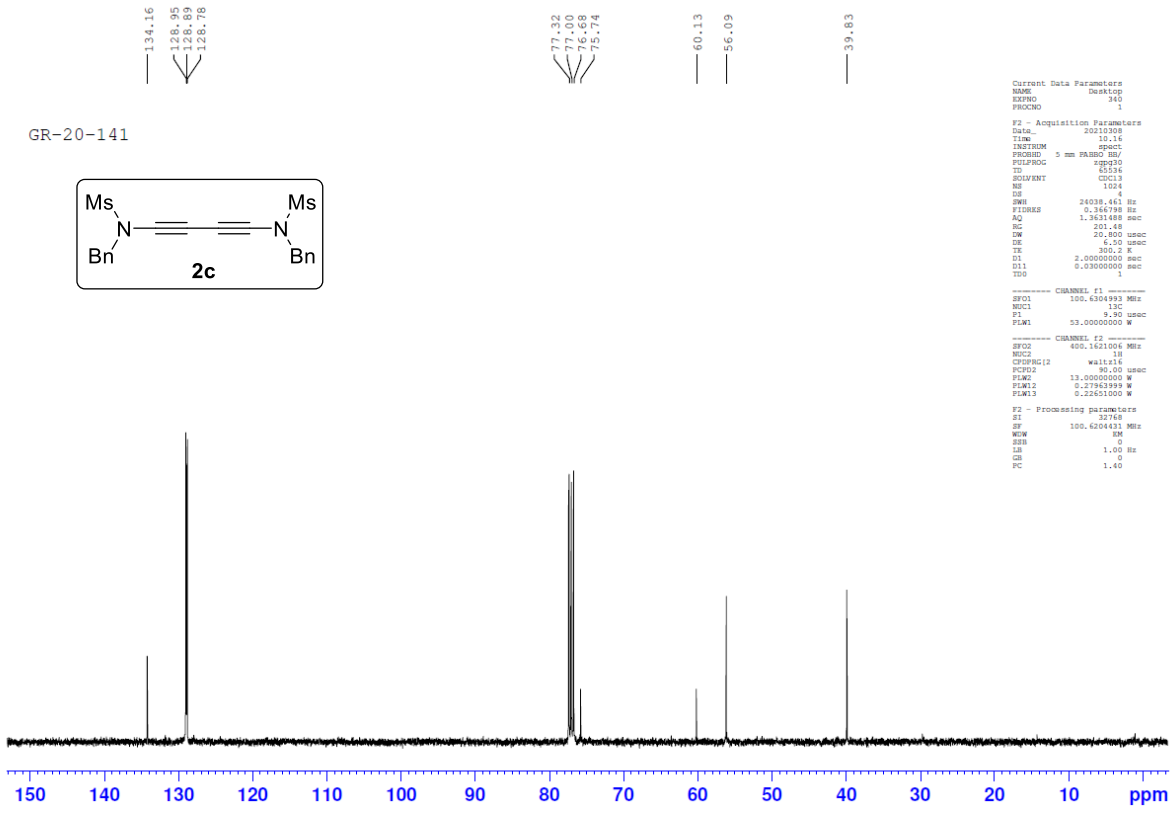
^{13}C NMR, $CDCl_3$, 101 MHz



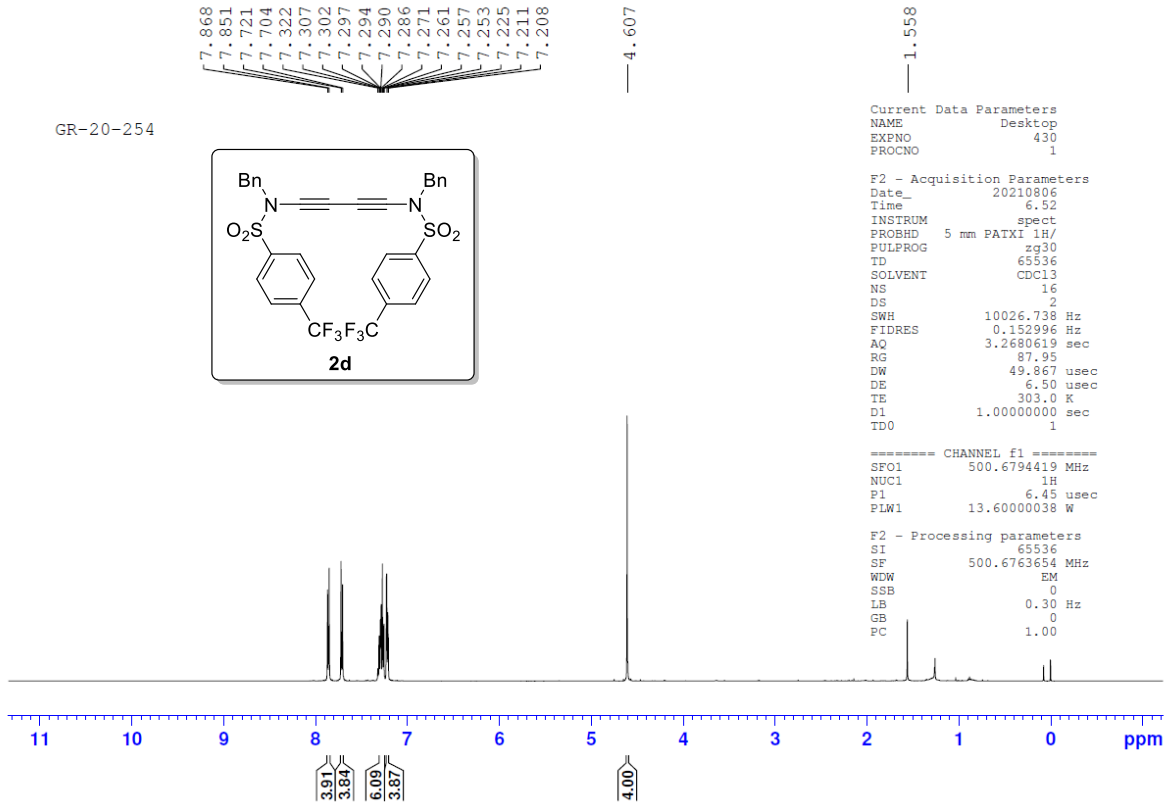
^{1}H NMR, $CDCl_3$, 400 MHz



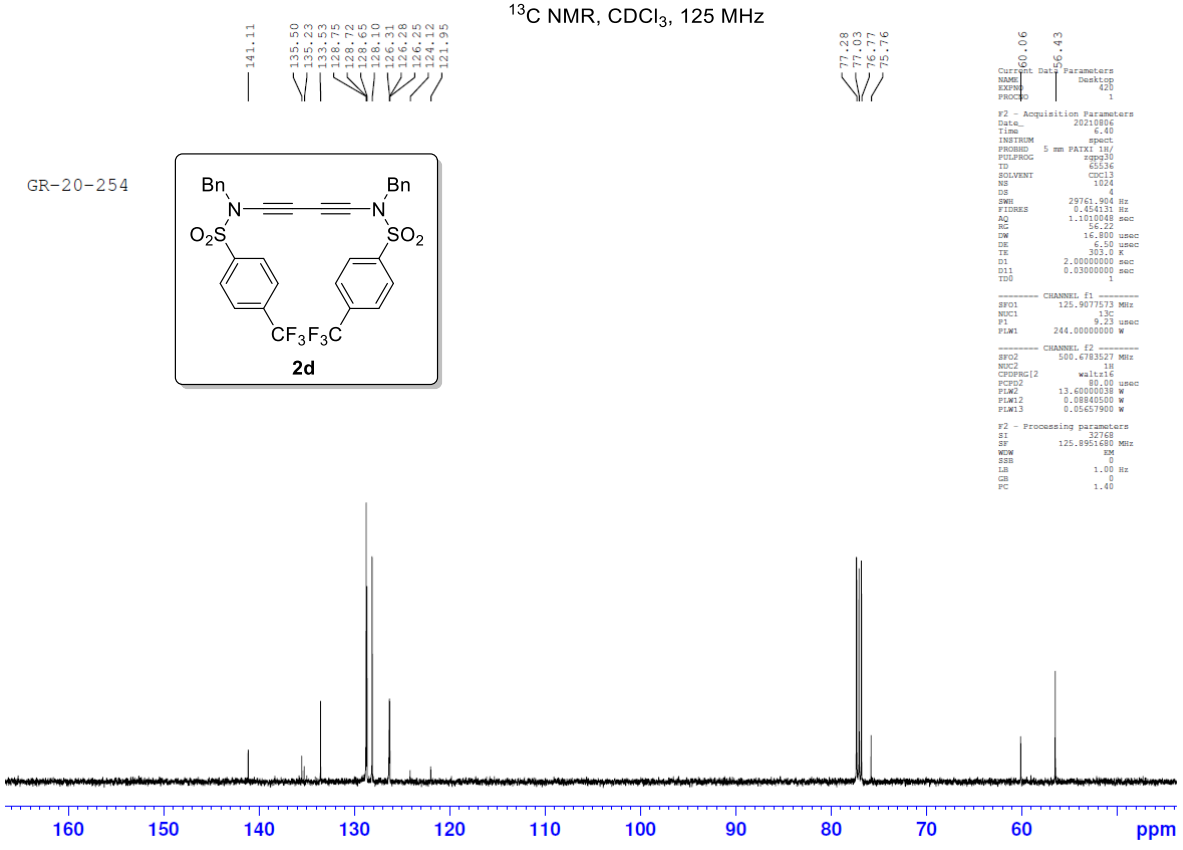
^{13}C NMR, $CDCl_3$, 101 MHz



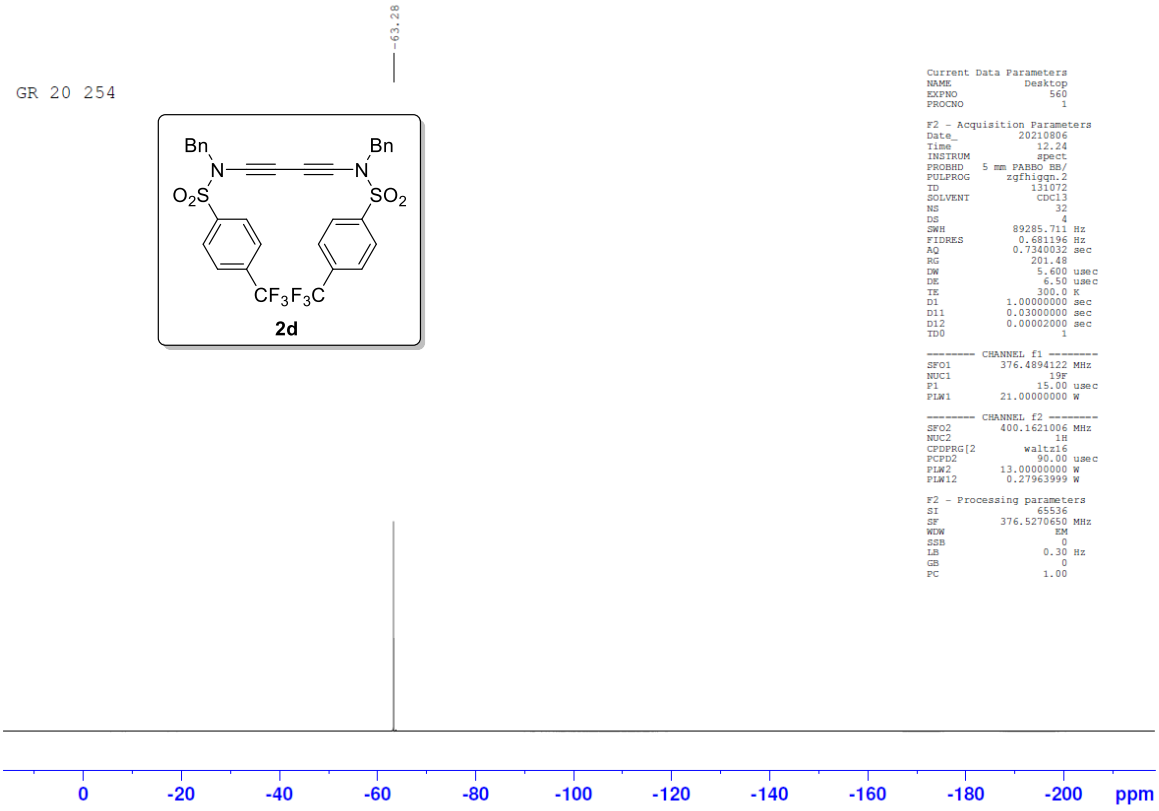
^{1}H NMR, $CDCl_3$, 500 MHz



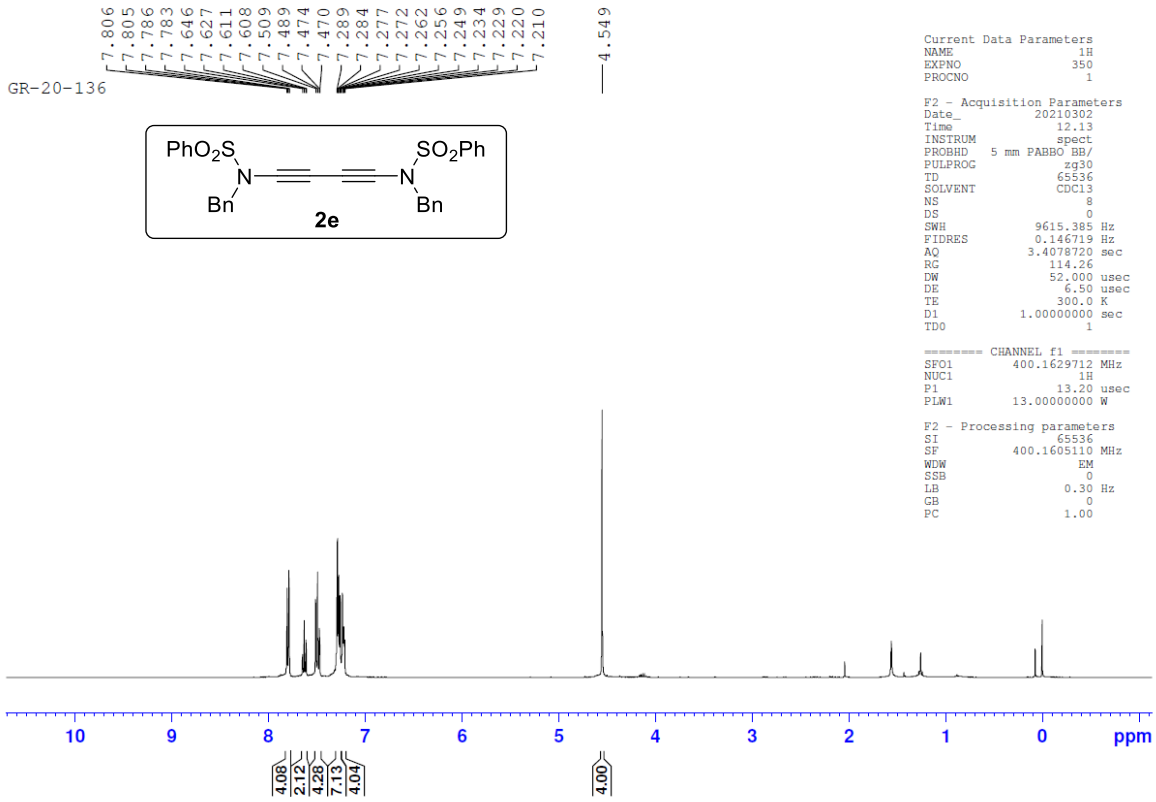
^{13}C NMR, $CDCl_3$, 125 MHz



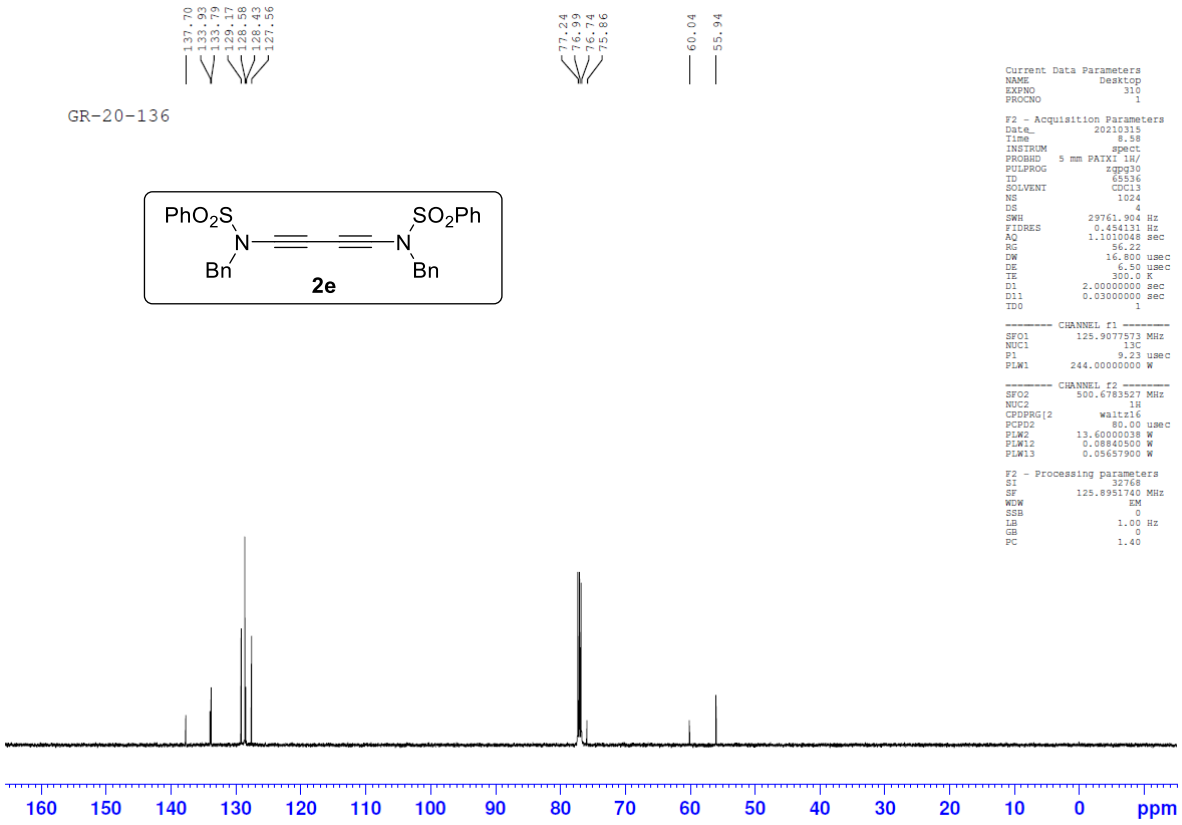
^{19}F NMR, $CDCl_3$, 376 MHz



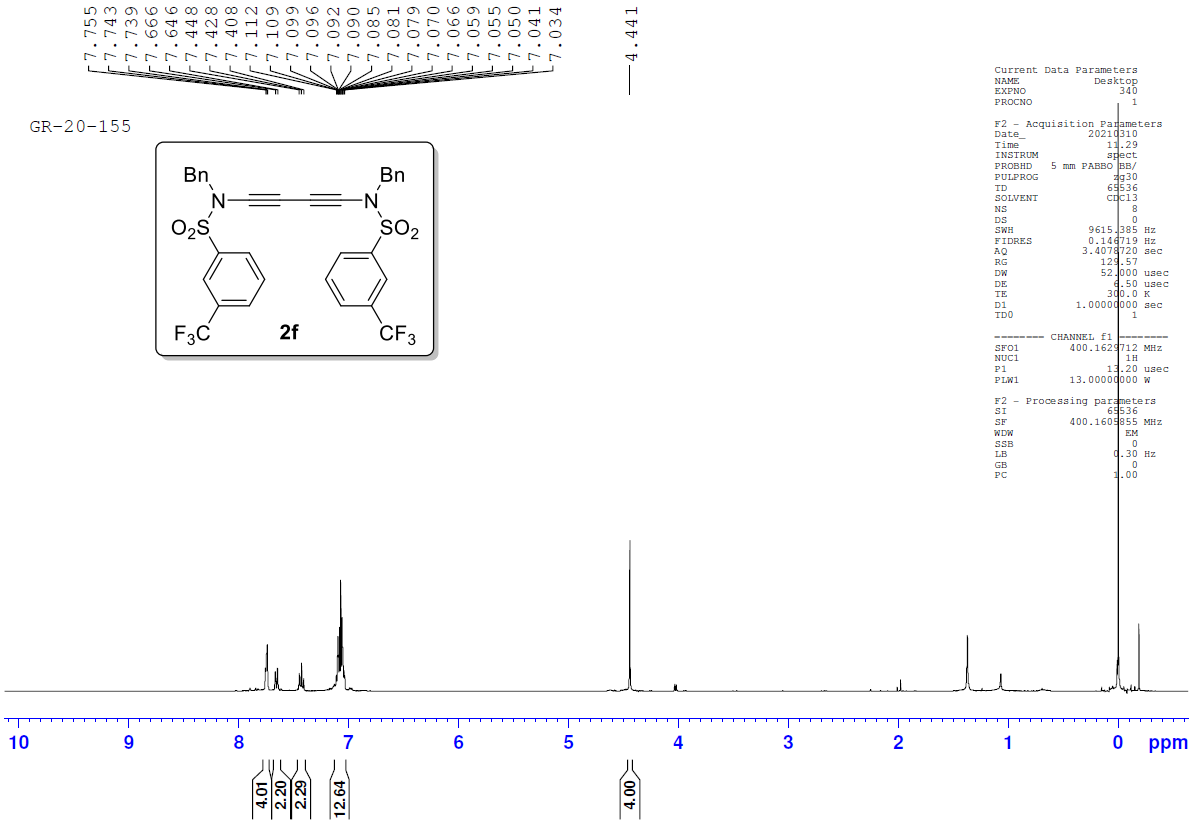
^{1}H NMR, $CDCl_3$, 400 MHz



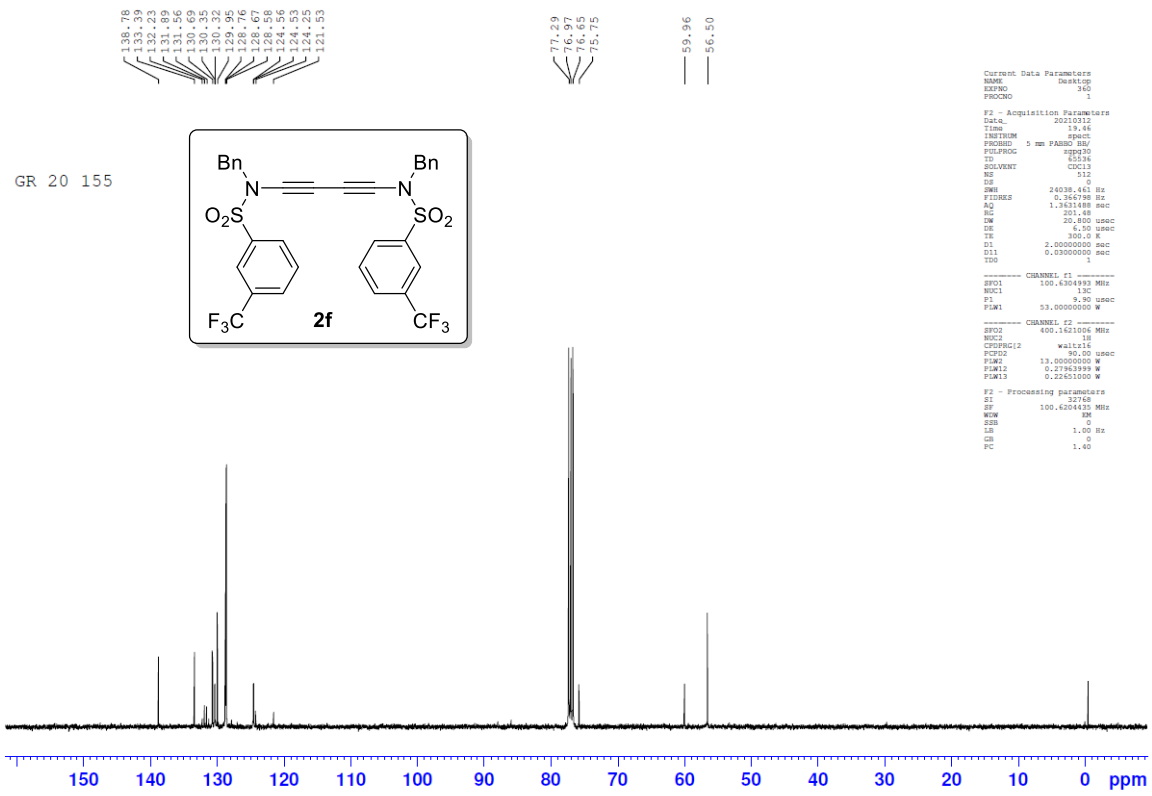
^{13}C NMR, $CDCl_3$, 125 MHz



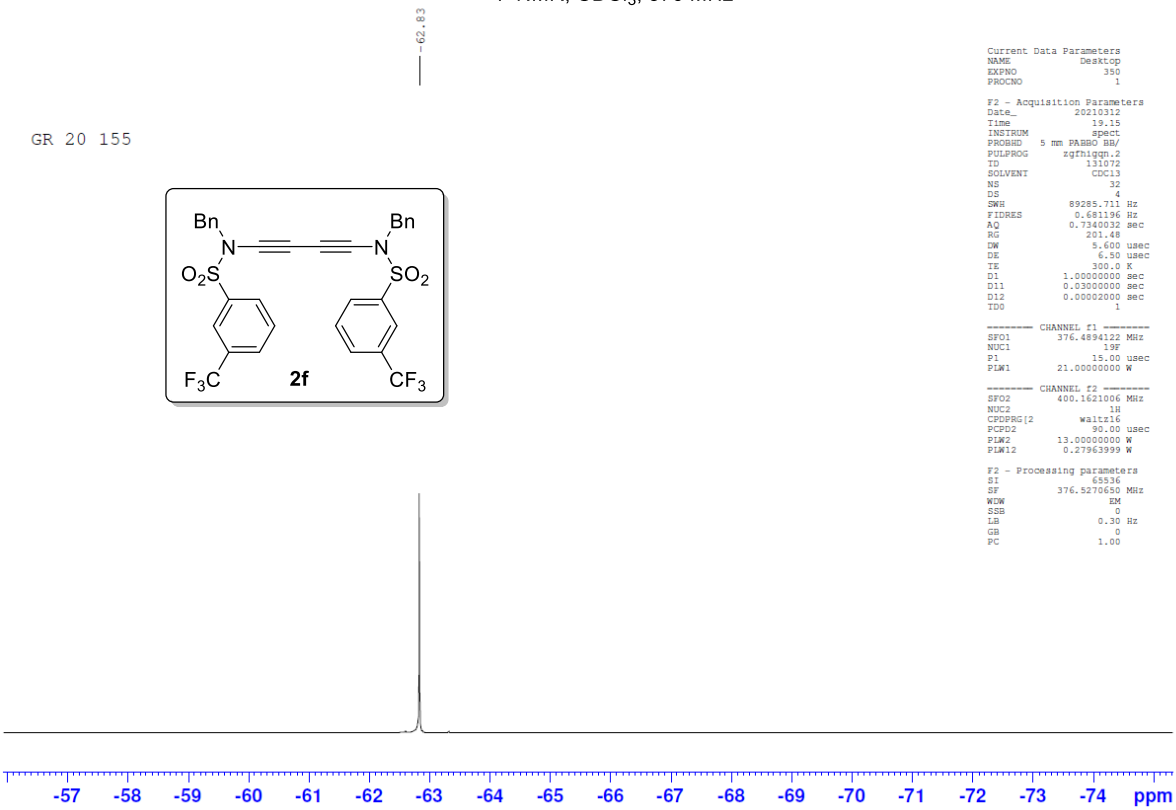
^{1}H NMR, $CDCl_3$, 400 MHz



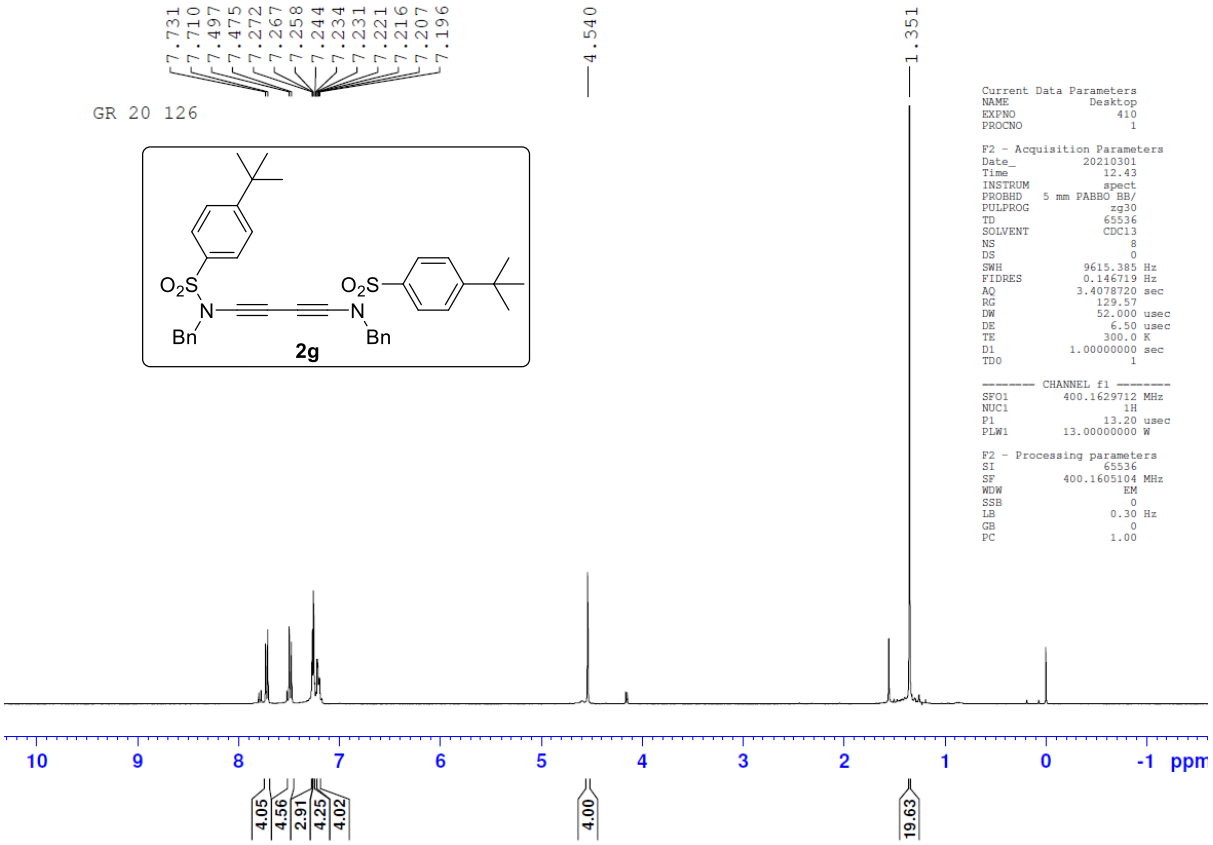
^{13}C NMR, $CDCl_3$, 101 MHz



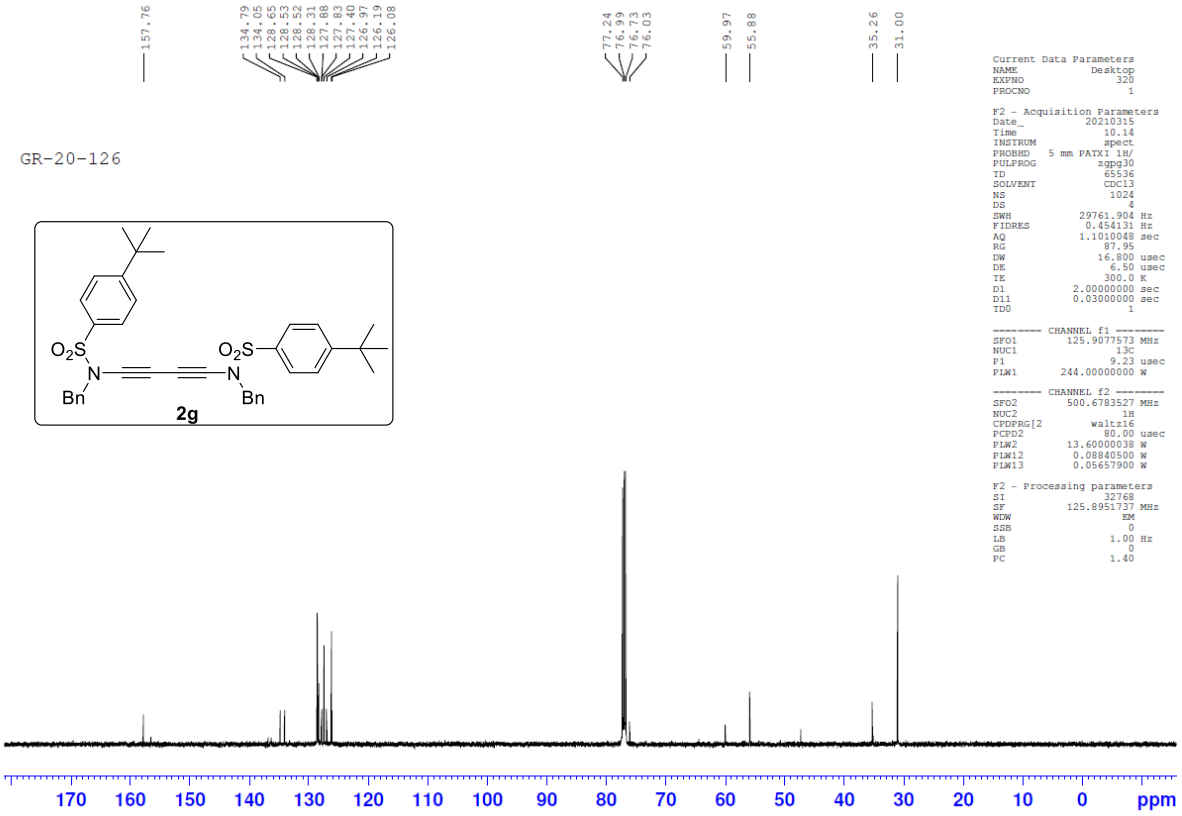
^{19}F NMR, $CDCl_3$, 376 MHz



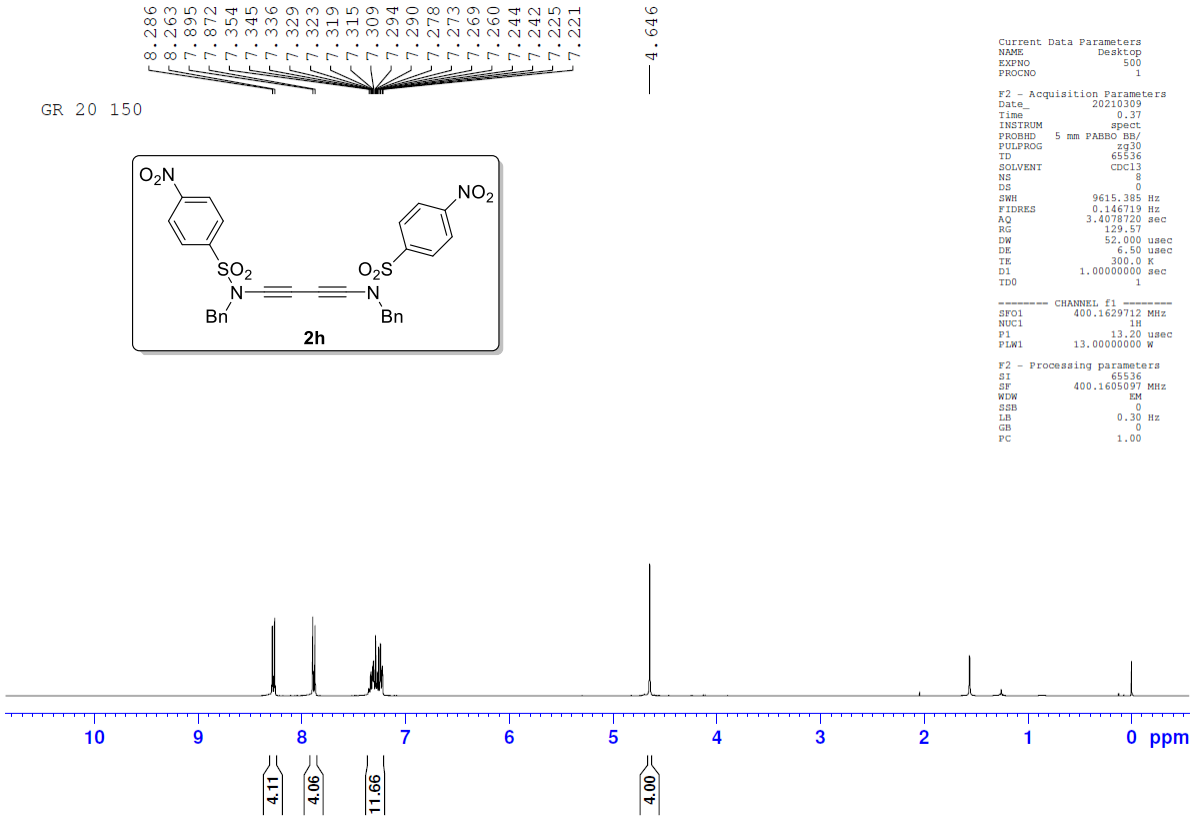
^{1}H NMR, $CDCl_3$, 400 MHz



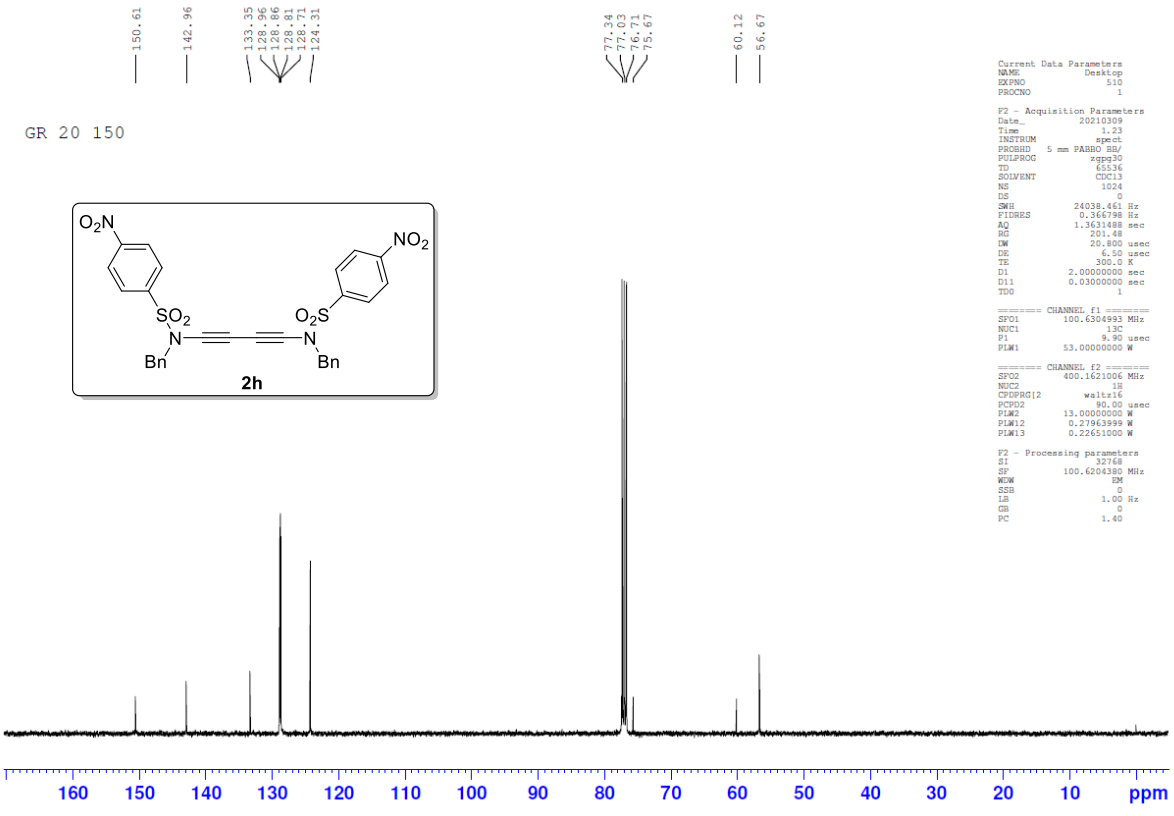
^{13}C NMR, $CDCl_3$, 125 MHz



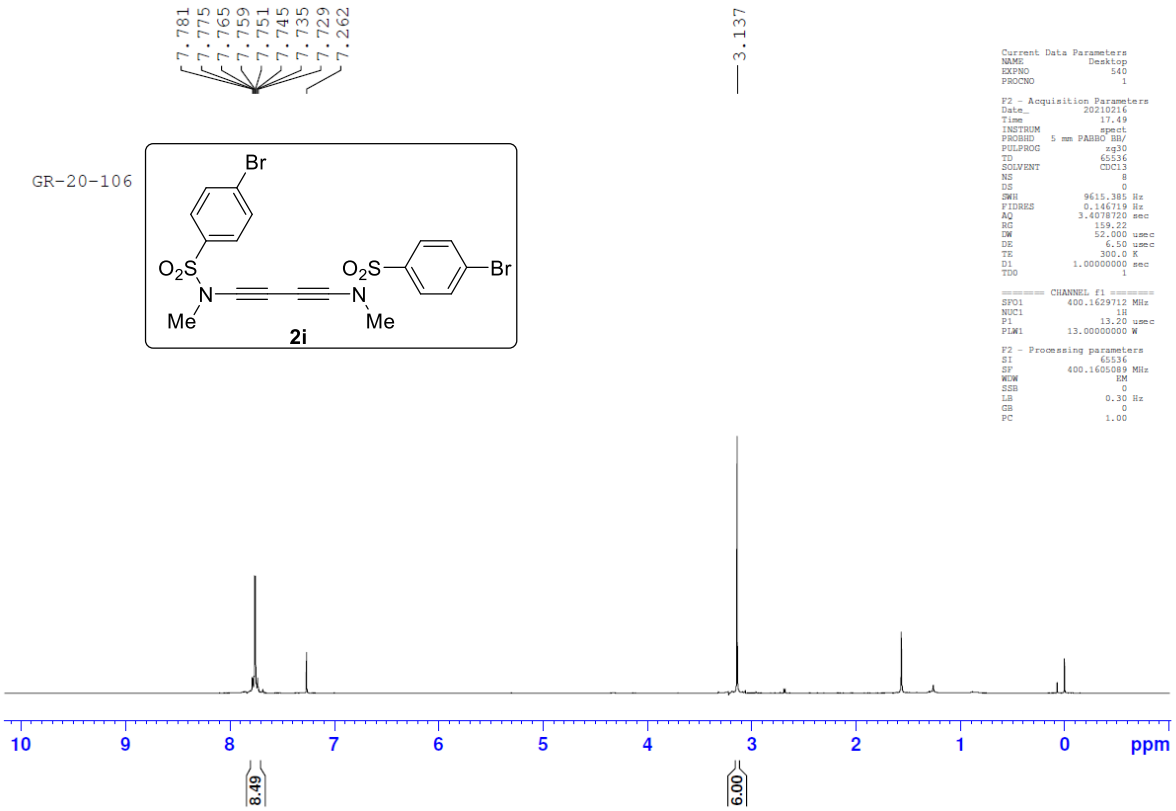
^{1}H NMR, $CDCl_3$, 400 MHz



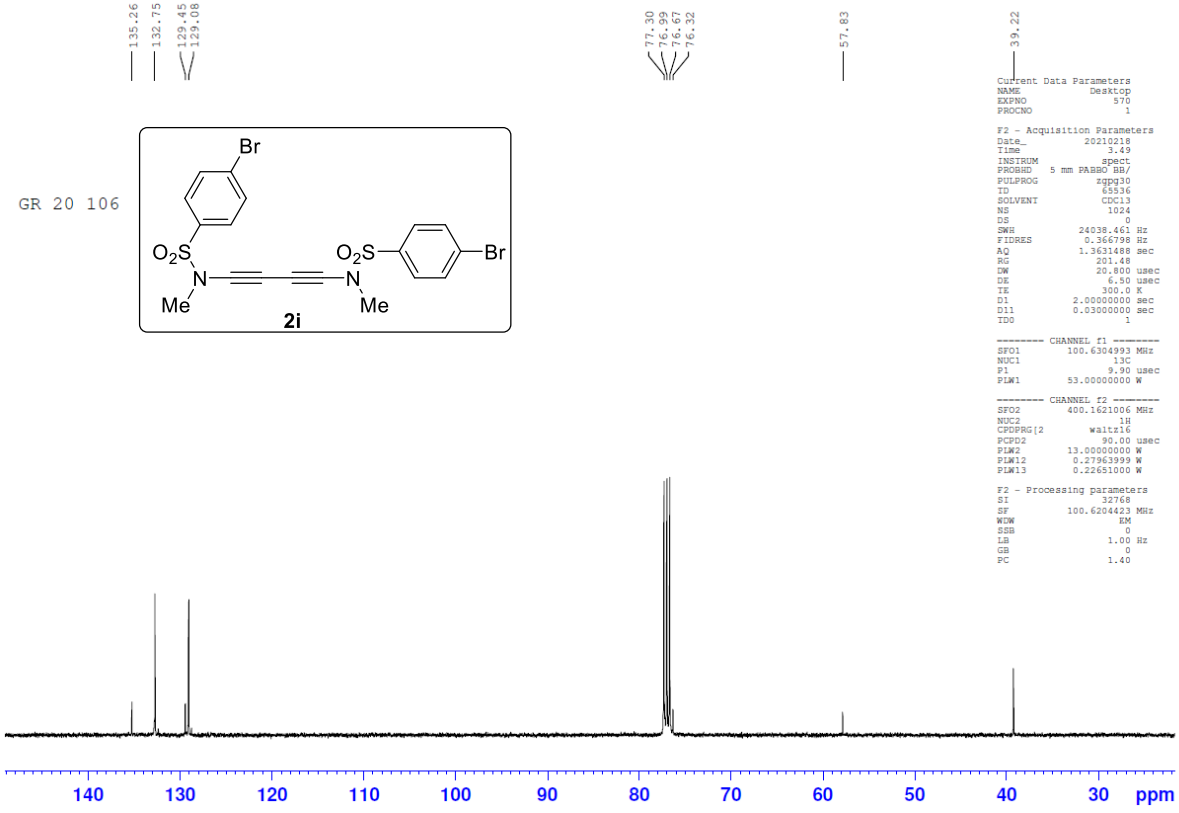
^{13}C NMR, $CDCl_3$, 101 MHz



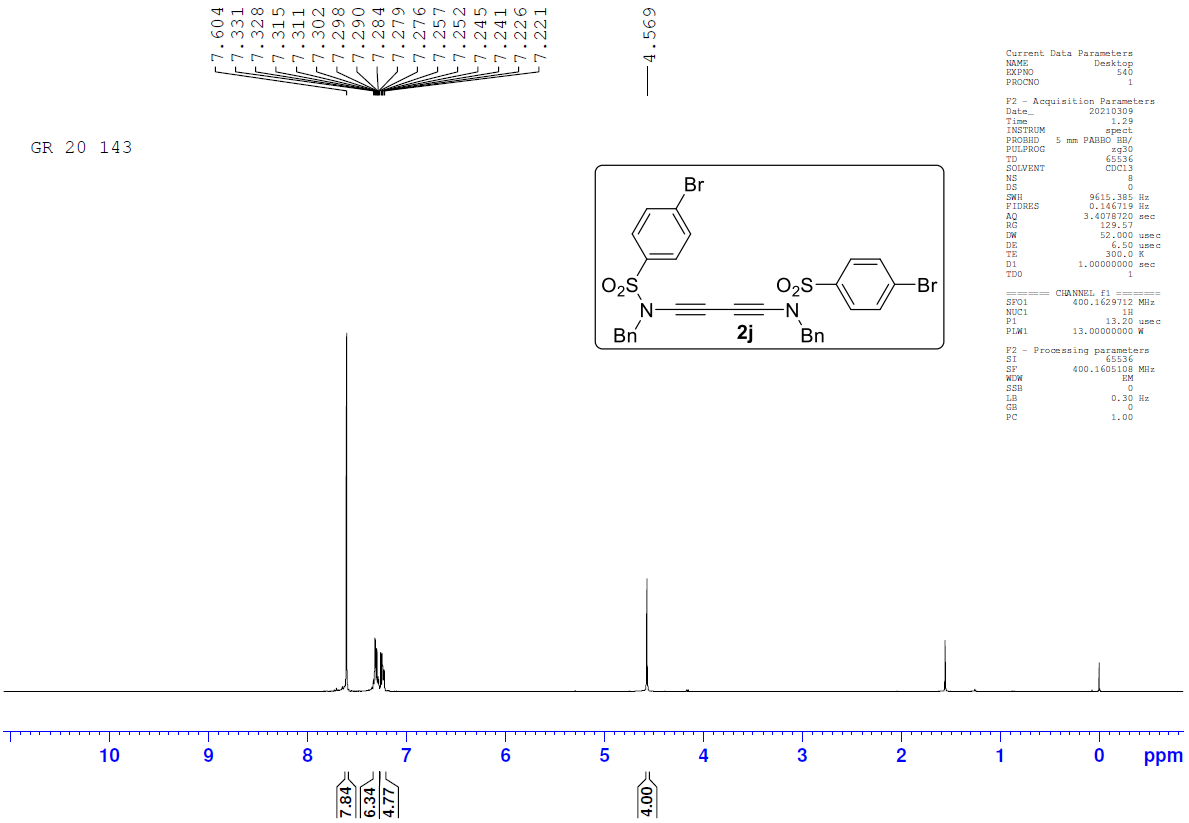
^{1}H NMR, $CDCl_3$, 400 MHz



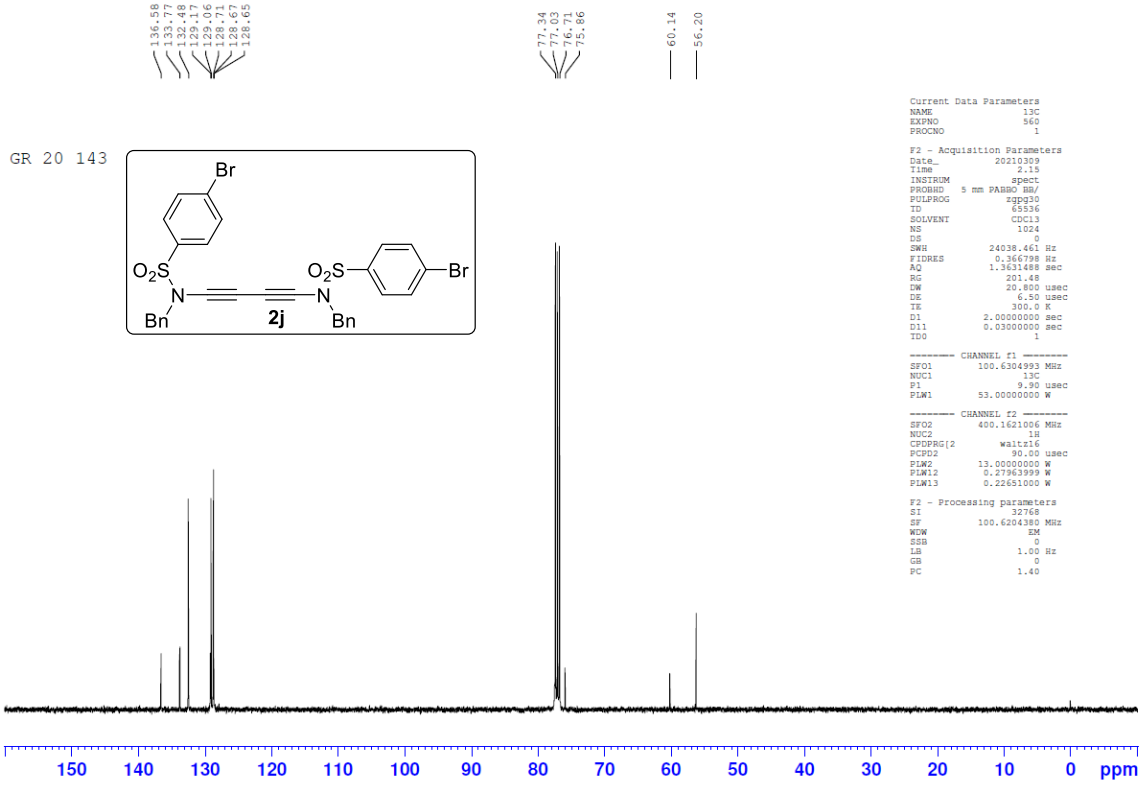
^{13}C NMR, $CDCl_3$, 101 MHz



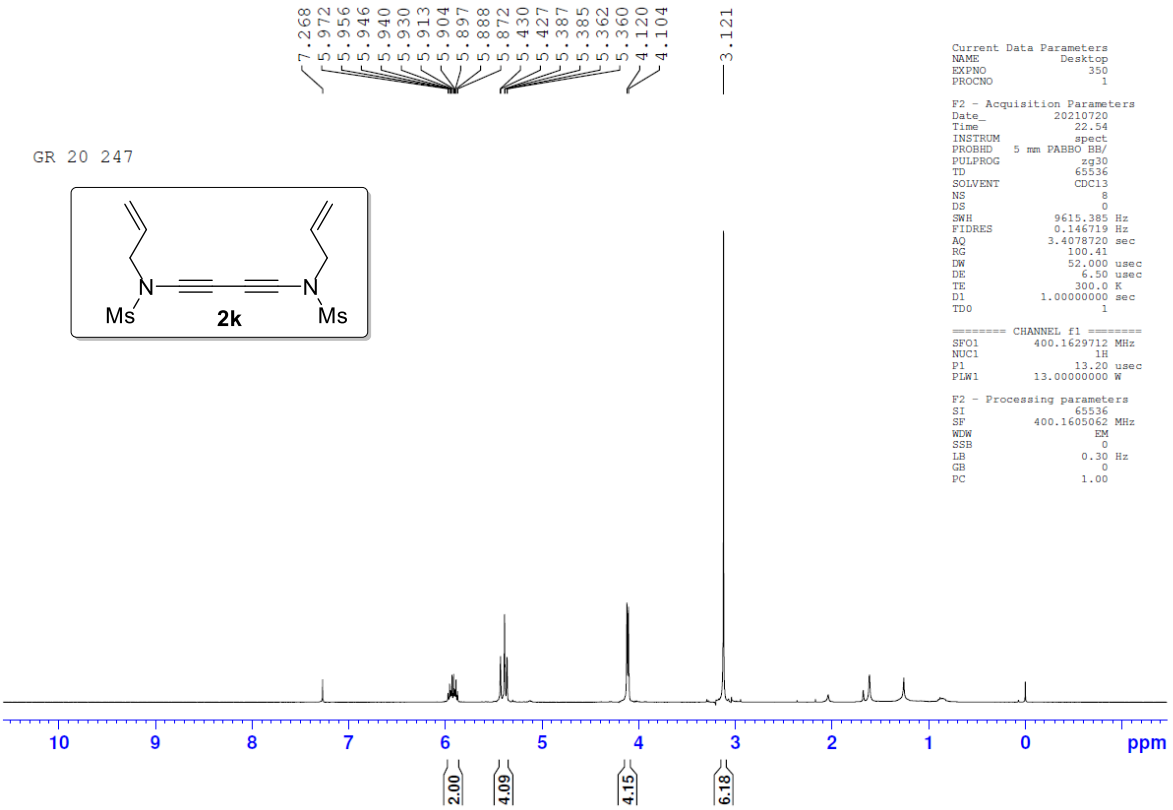
^{1}H NMR, $CDCl_3$, 400 MHz



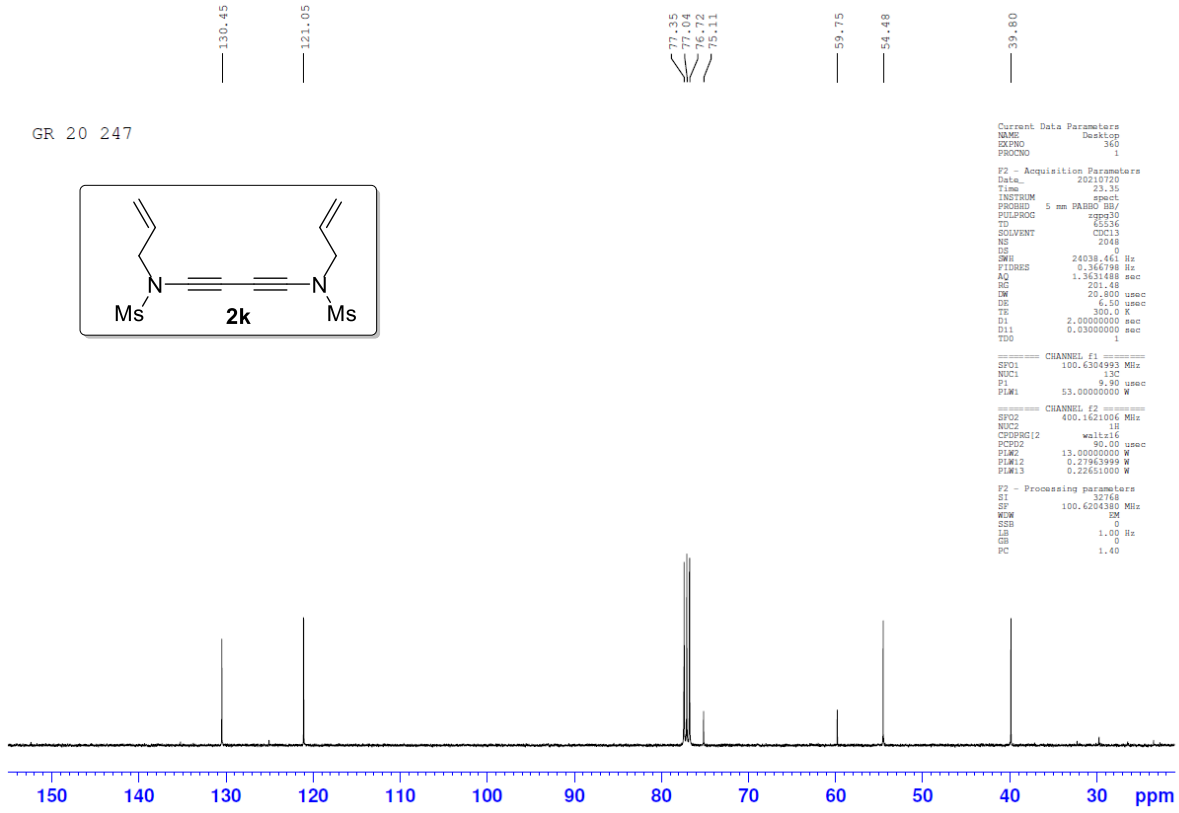
^{13}C NMR, $CDCl_3$, 101 MHz



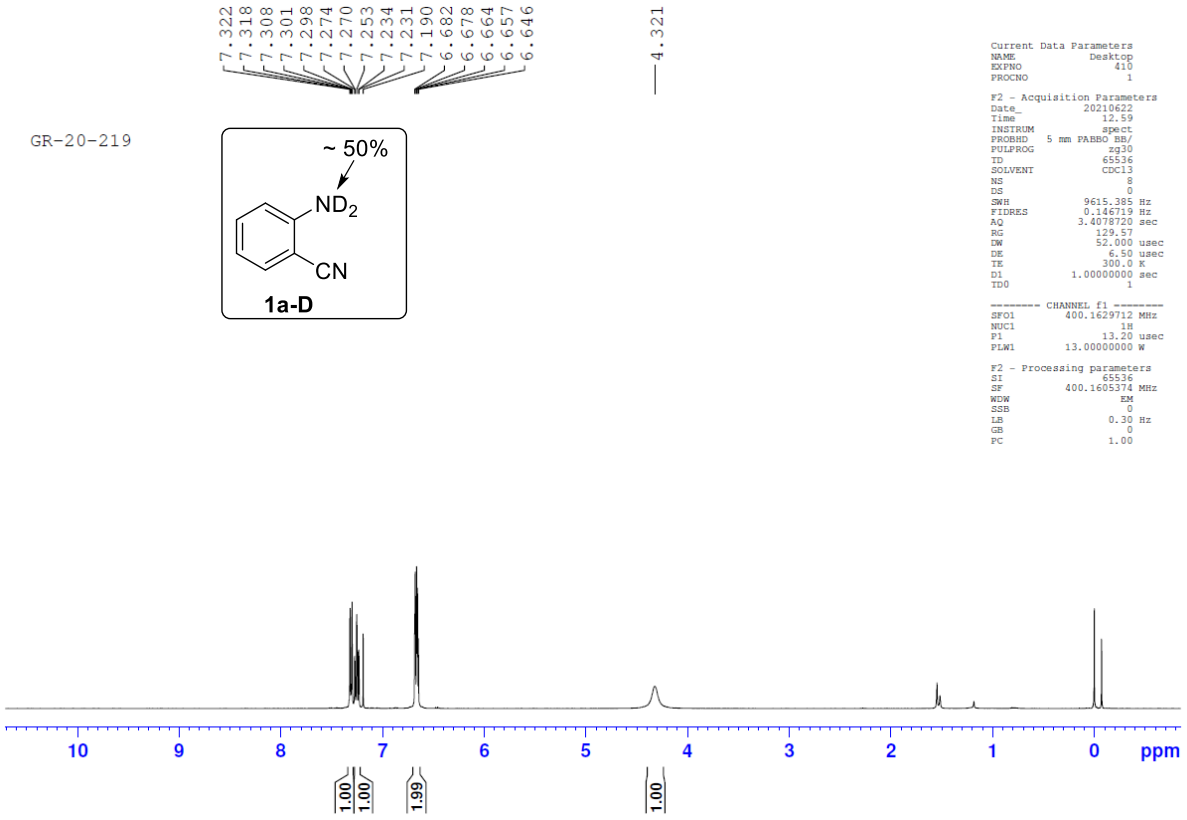
^{1}H NMR, $CDCl_3$, 400 MHz



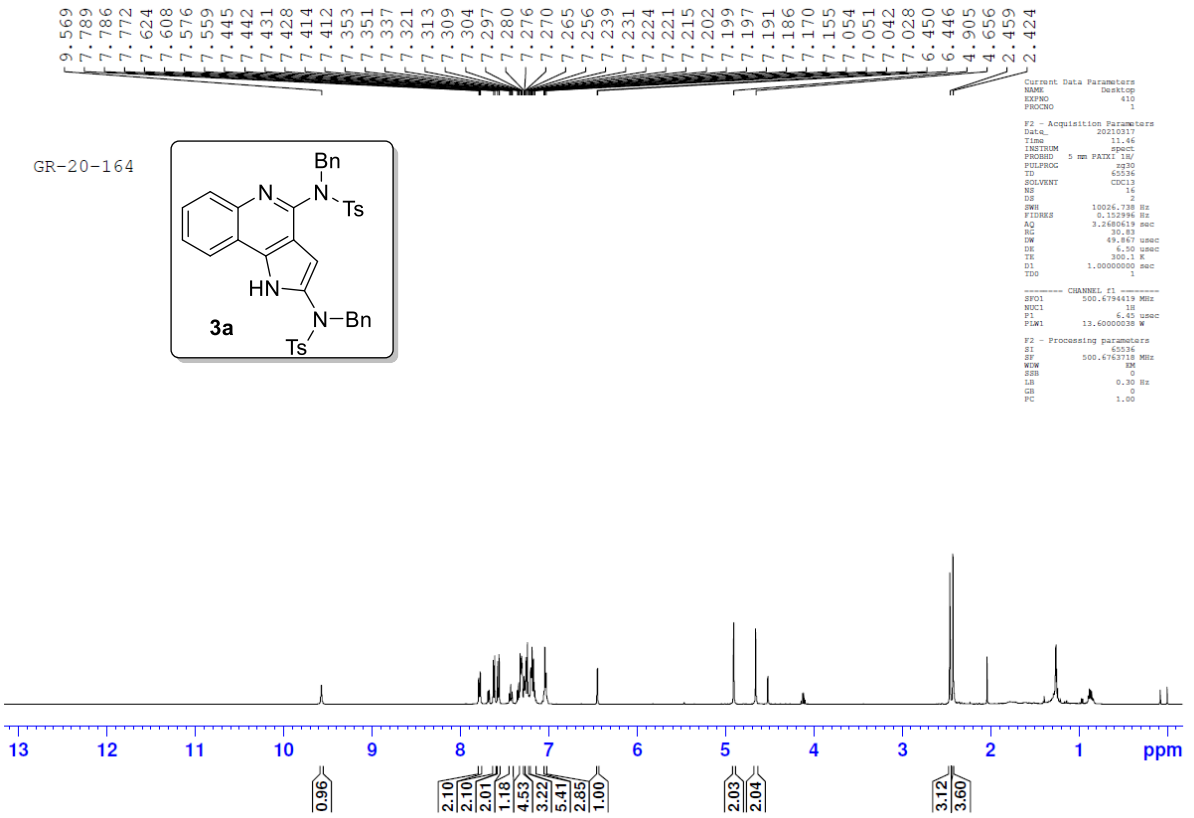
^{13}C NMR, $CDCl_3$, 101 MHz



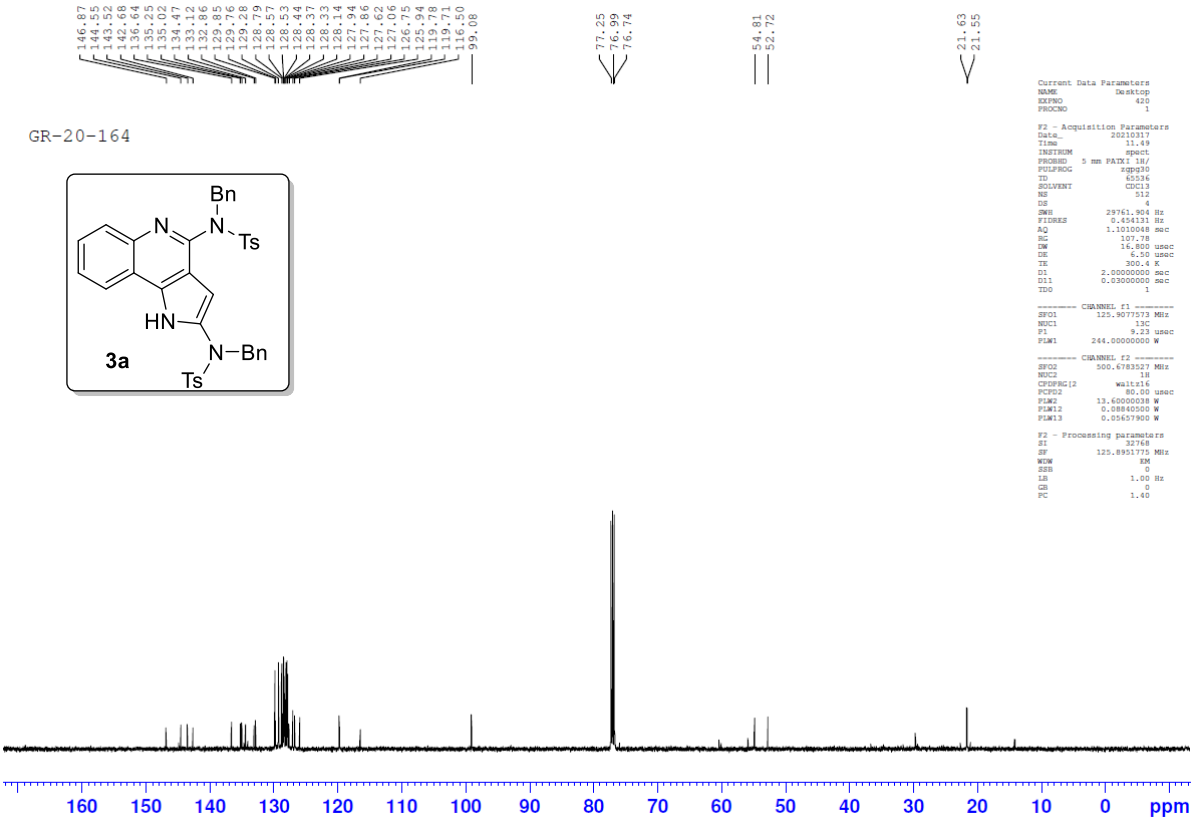
^{1}H NMR, $CDCl_3$, 400 MHz



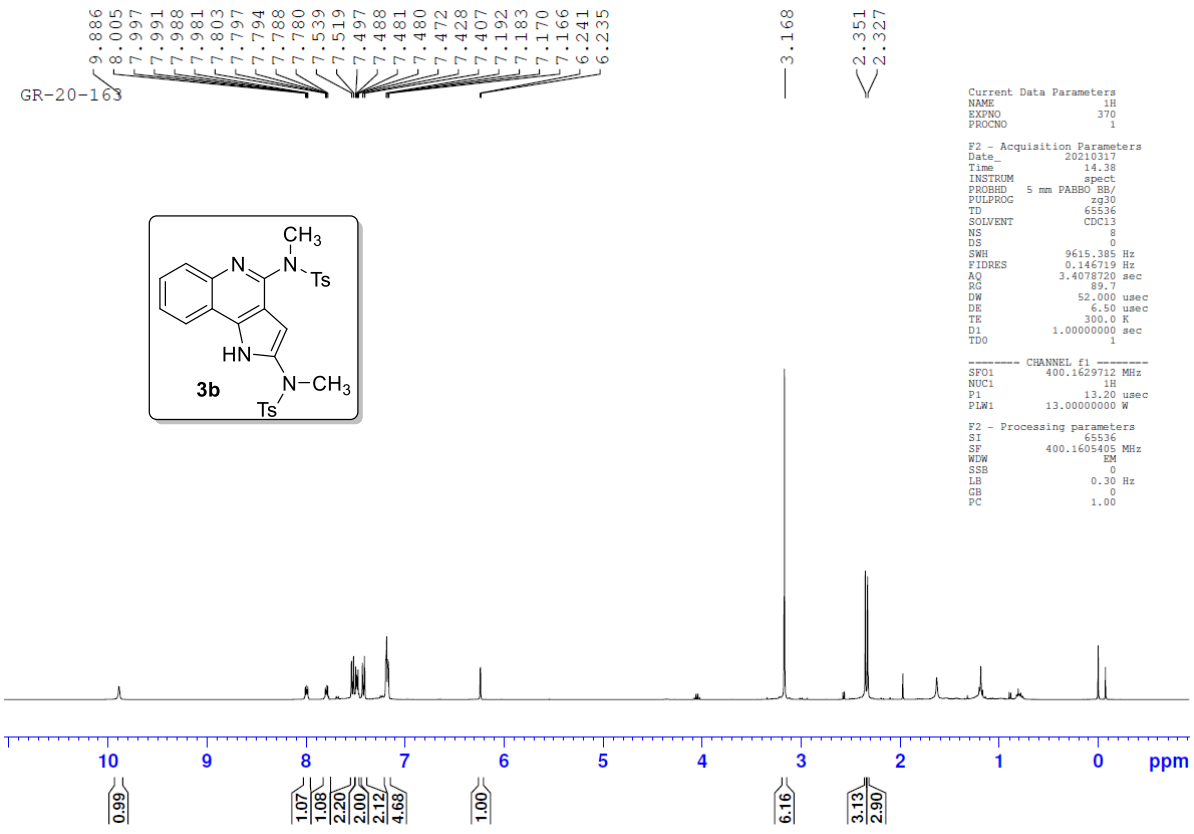
^{1}H NMR, $CDCl_3$, 500 MHz



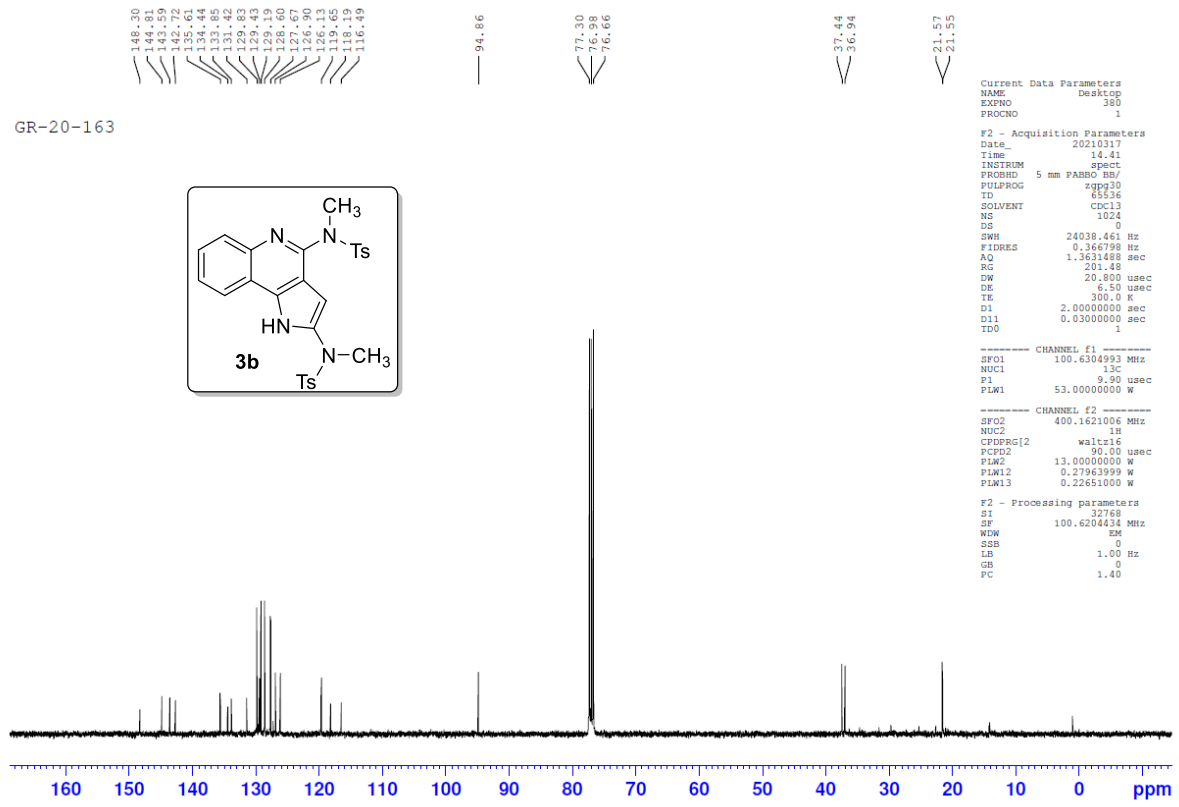
^{13}C NMR, $CDCl_3$, 125 MHz



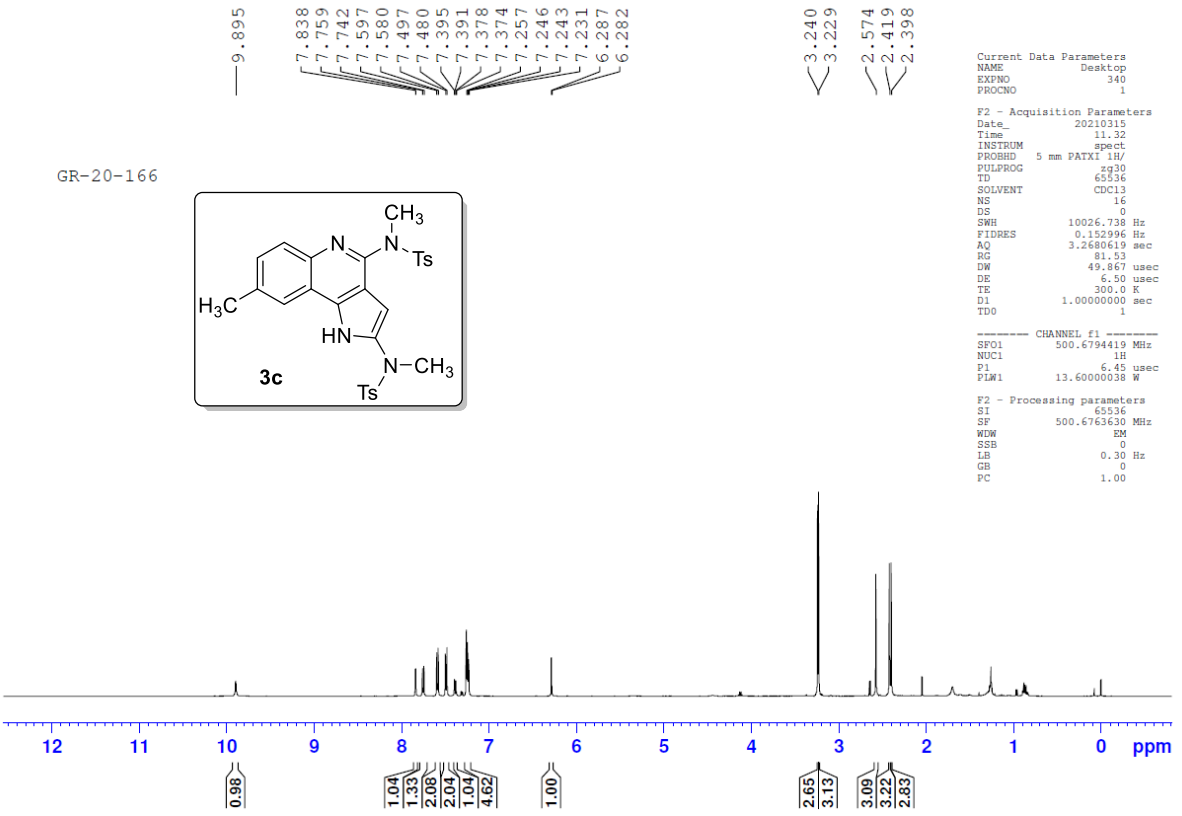
^{1}H NMR, $CDCl_3$, 400 MHz



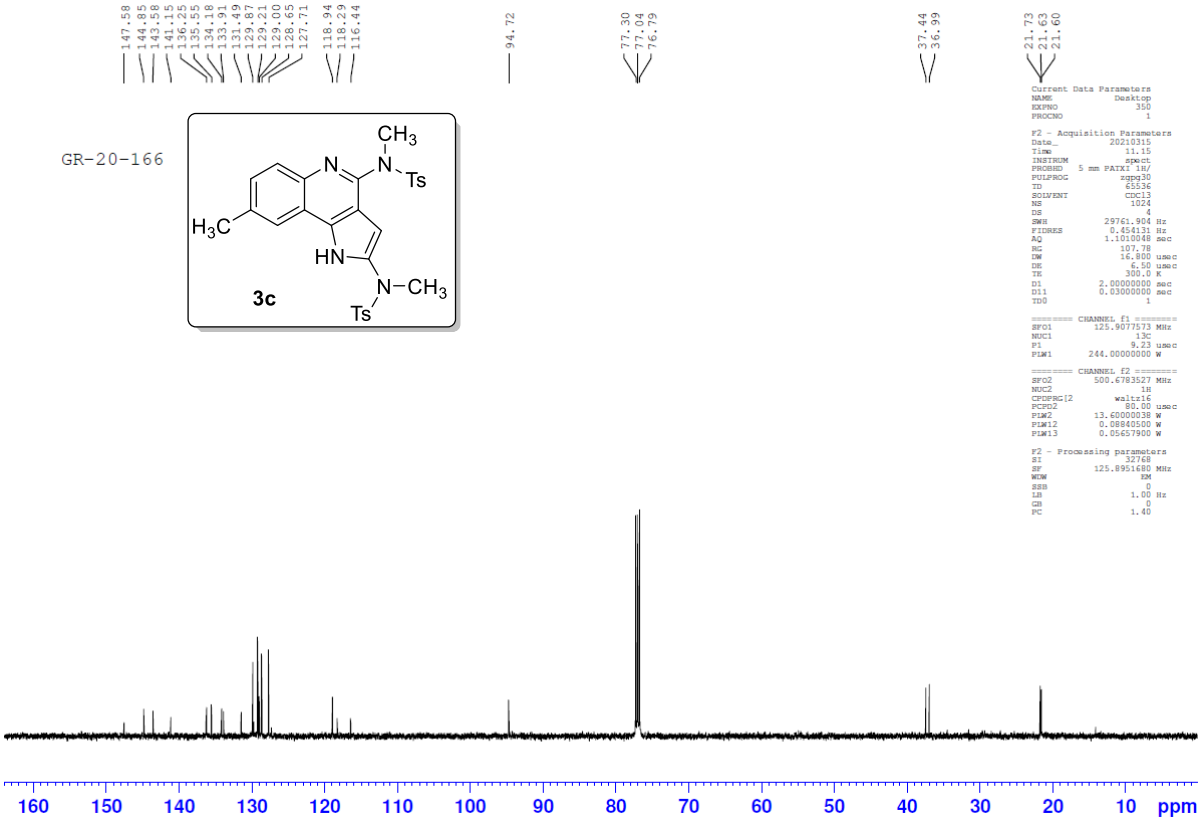
^{13}C NMR, $CDCl_3$, 101 MHz



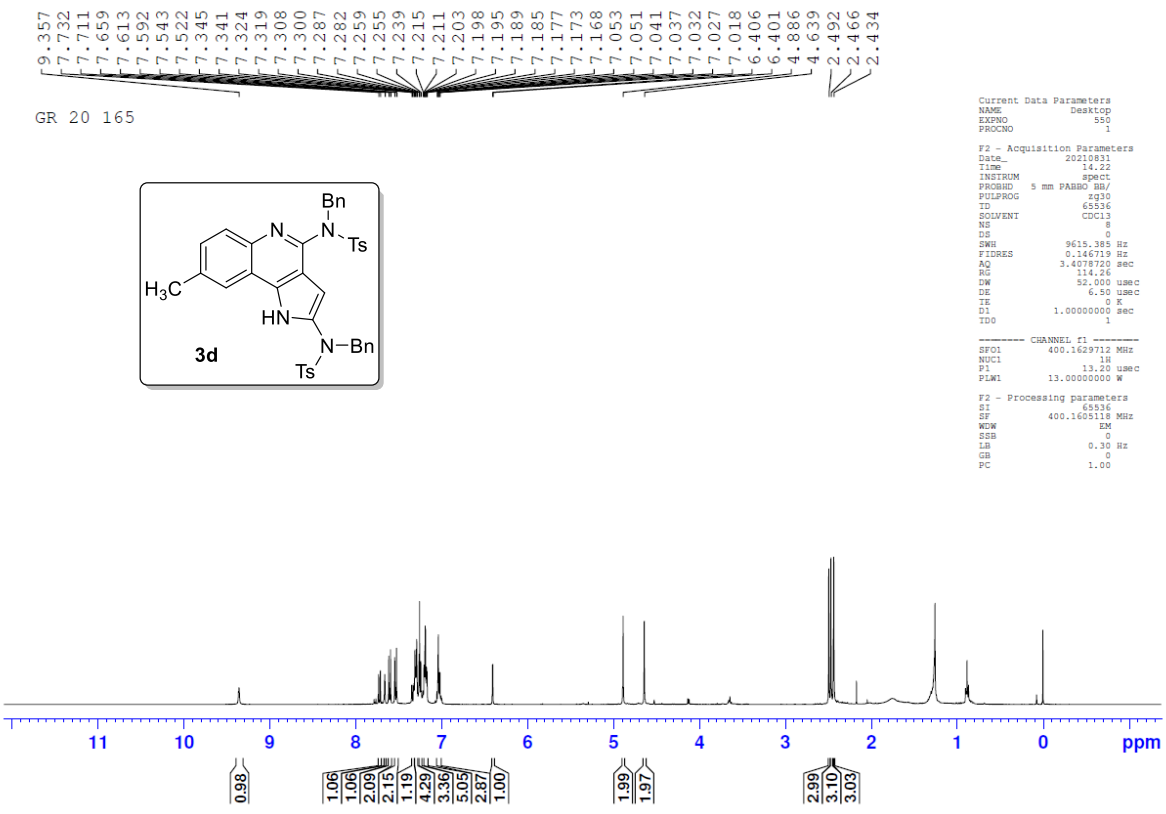
^{1}H NMR, $CDCl_3$, 500 MHz



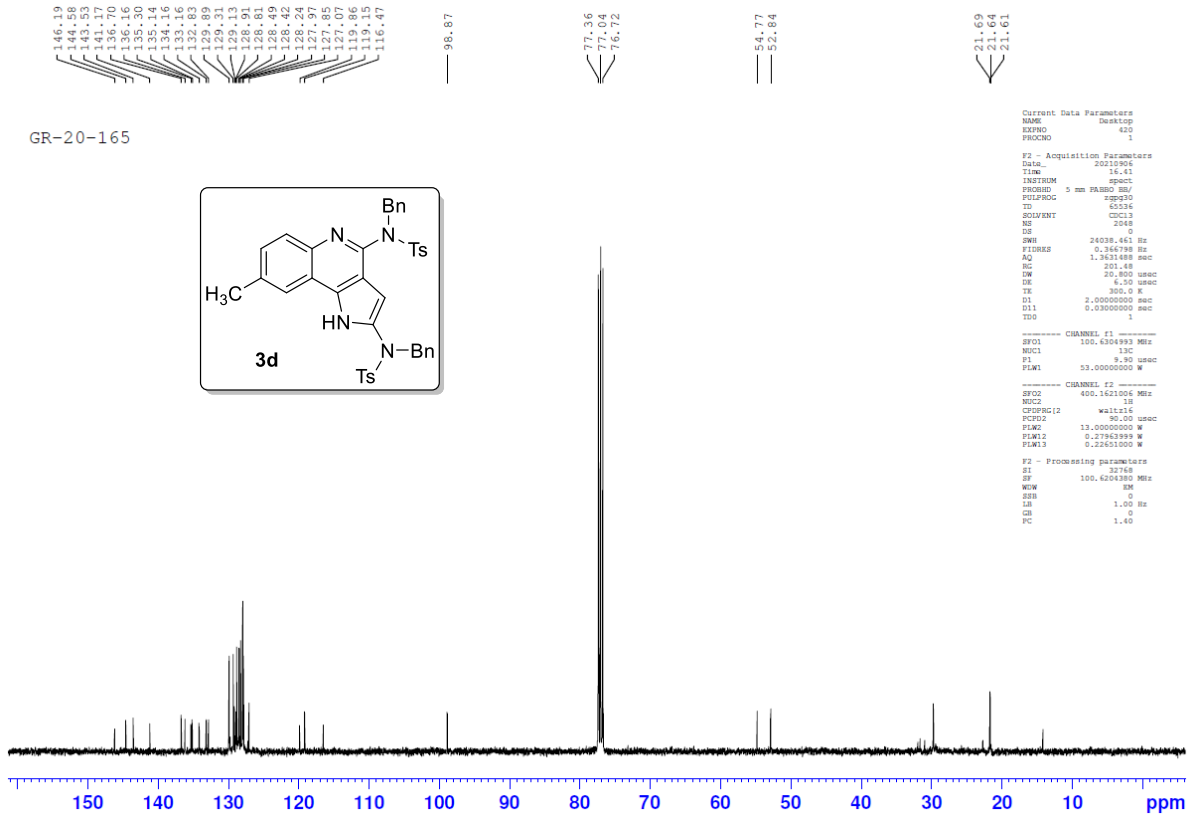
^{13}C NMR, $CDCl_3$, 125 MHz



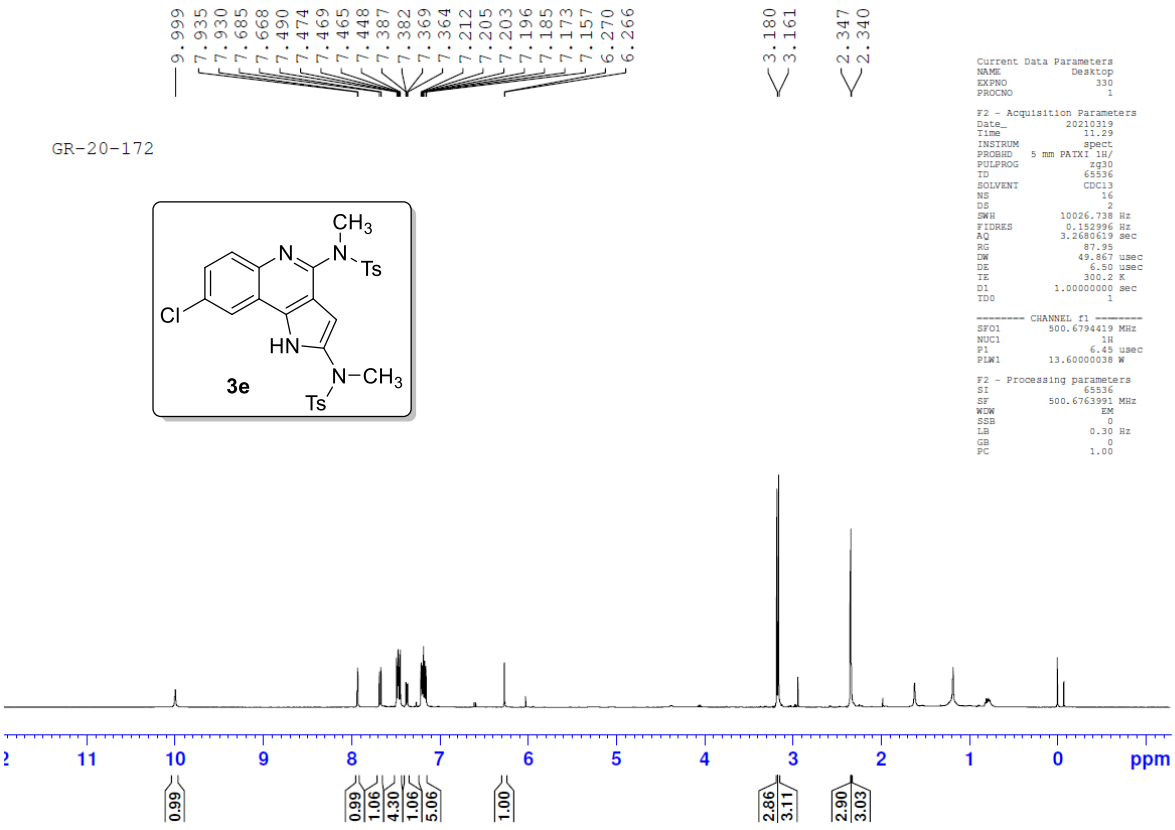
^{1}H NMR, $CDCl_3$, 400 MHz



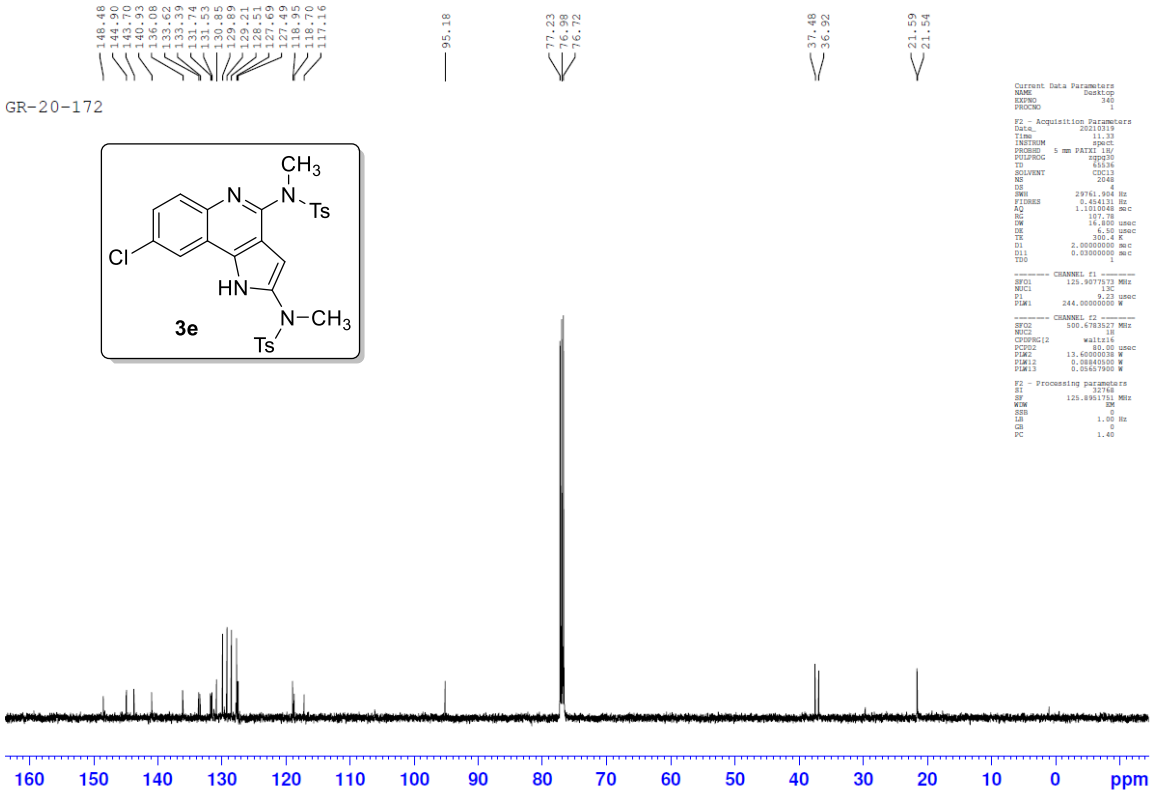
^{13}C NMR, $CDCl_3$, 101 MHz



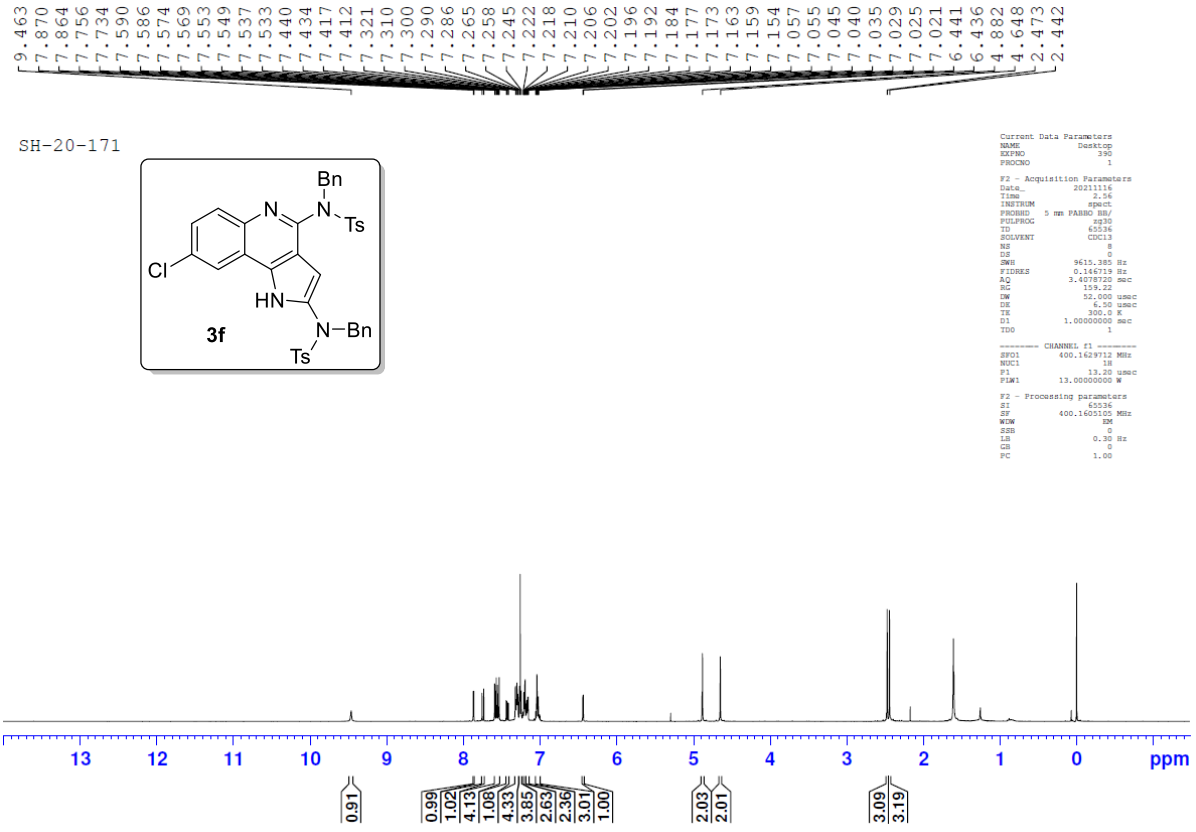
^{1}H NMR, $CDCl_3$, 500 MHz



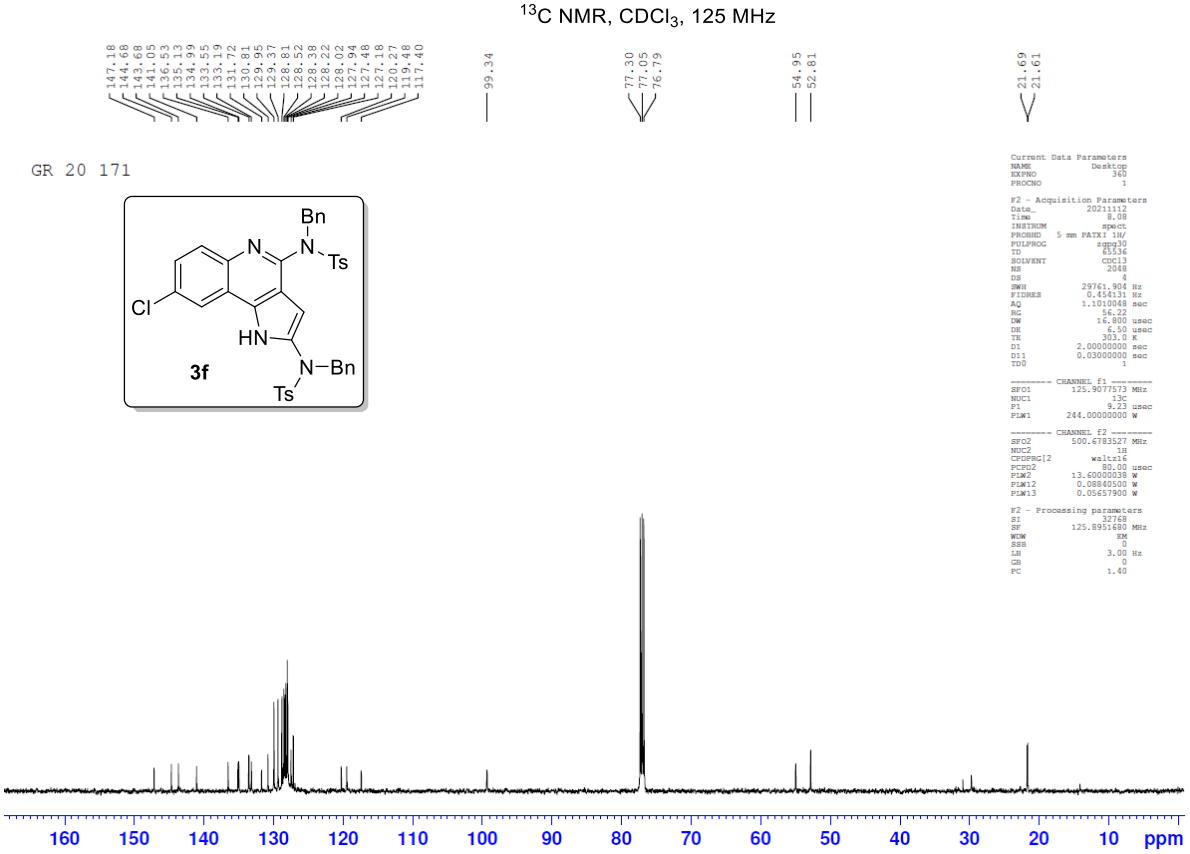
^{13}C NMR, $CDCl_3$, 125 MHz



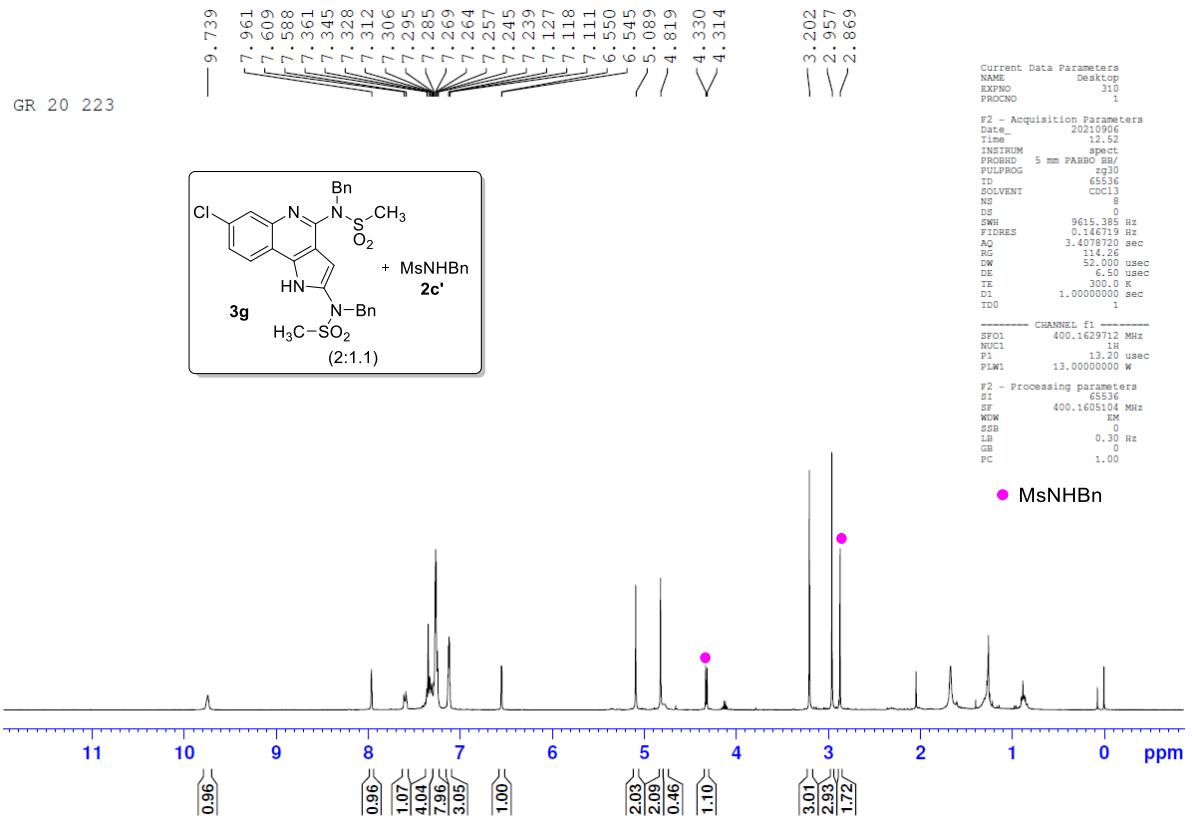
^{1}H NMR, $CDCl_3$, 400 MHz



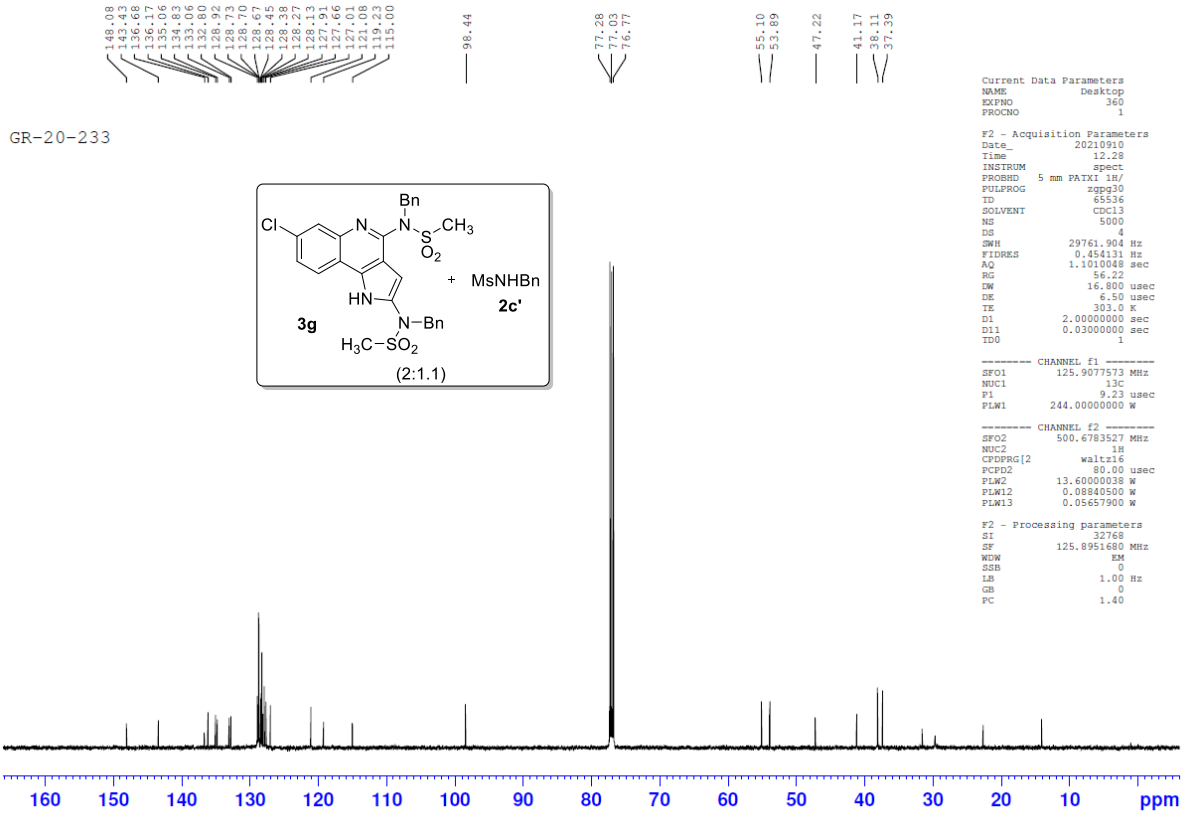
^{13}C NMR, $CDCl_3$, 125 MHz



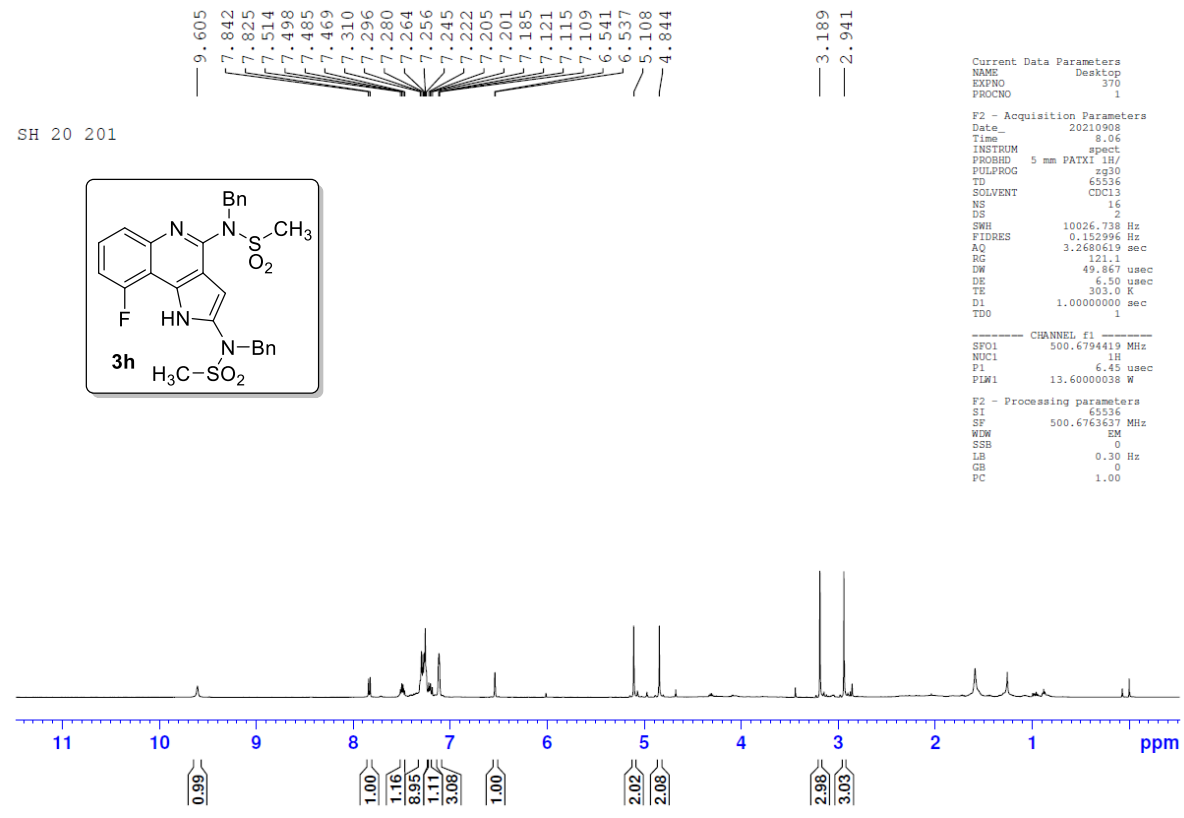
^{1}H NMR, $CDCl_3$, 400 MHz



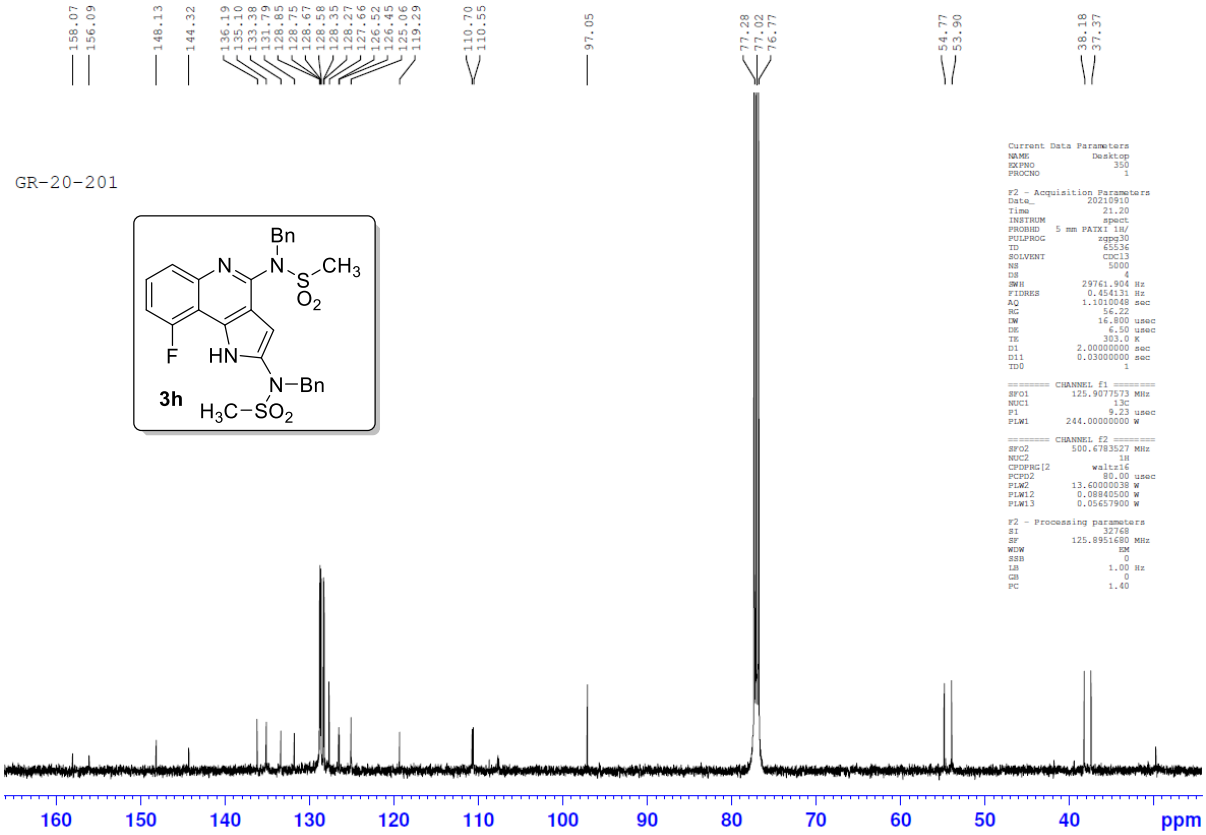
^{13}C NMR, $CDCl_3$, 125 MHz



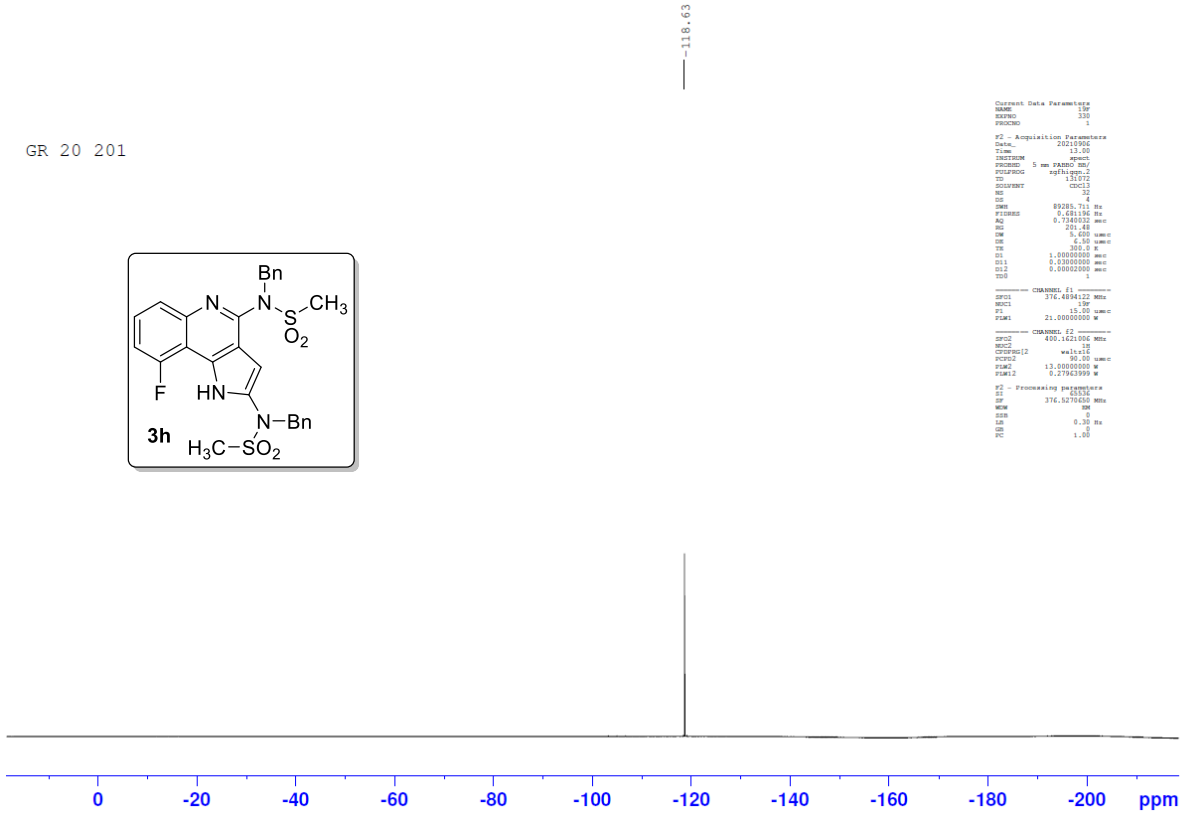
^{1}H NMR, $CDCl_3$, 500 MHz



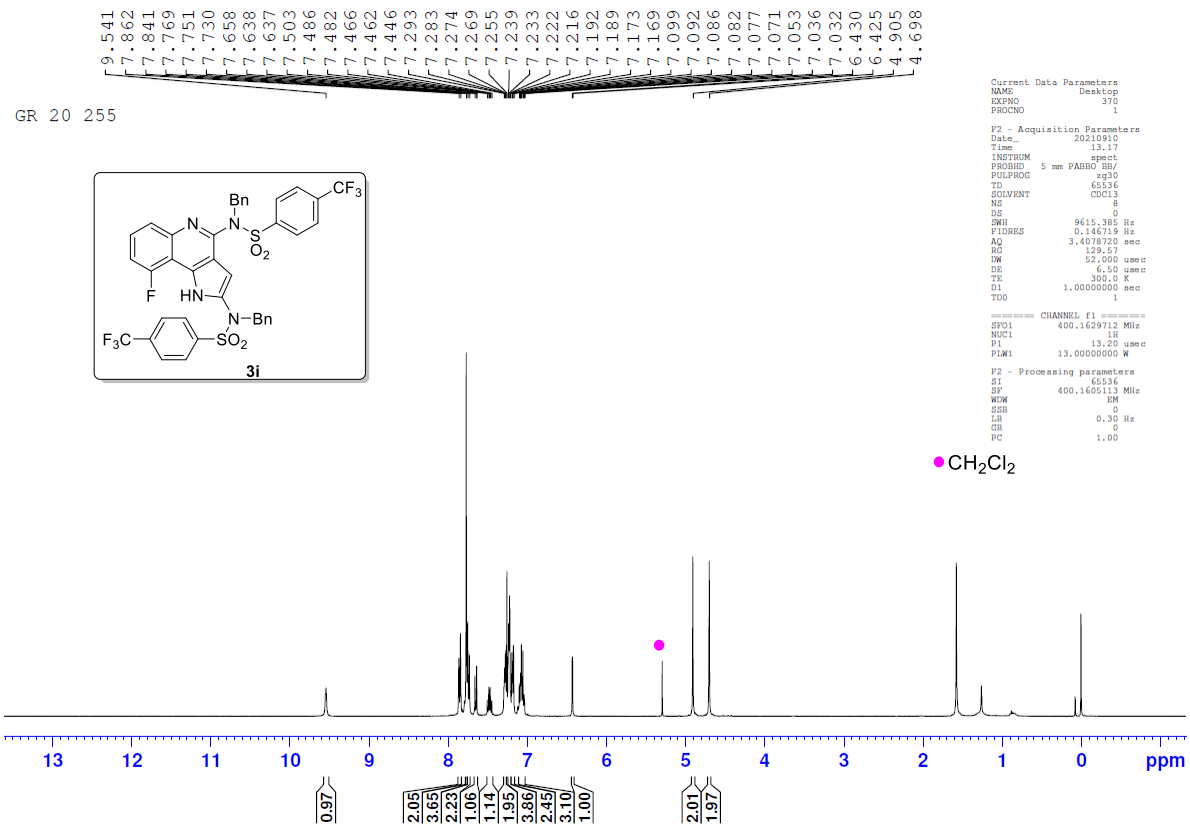
^{13}C NMR, $CDCl_3$, 125 MHz



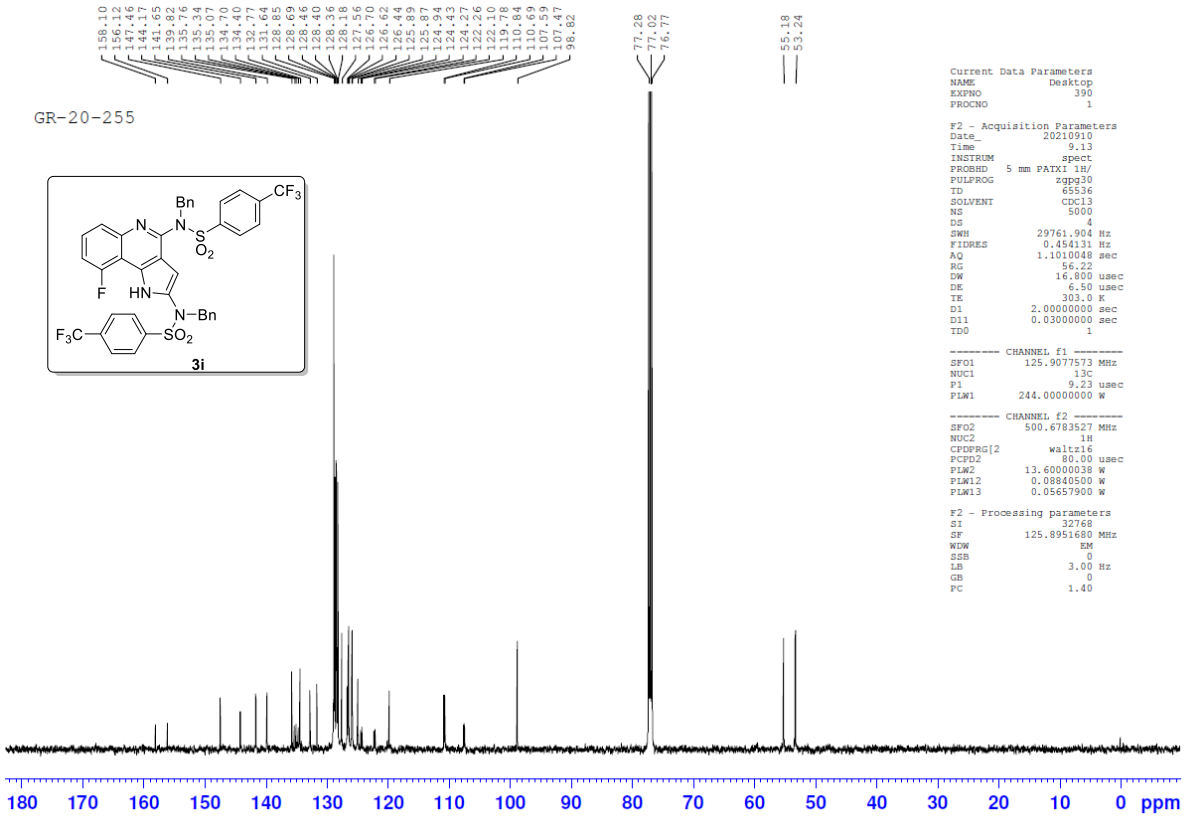
^{19}F NMR, $CDCl_3$, 376 MHz



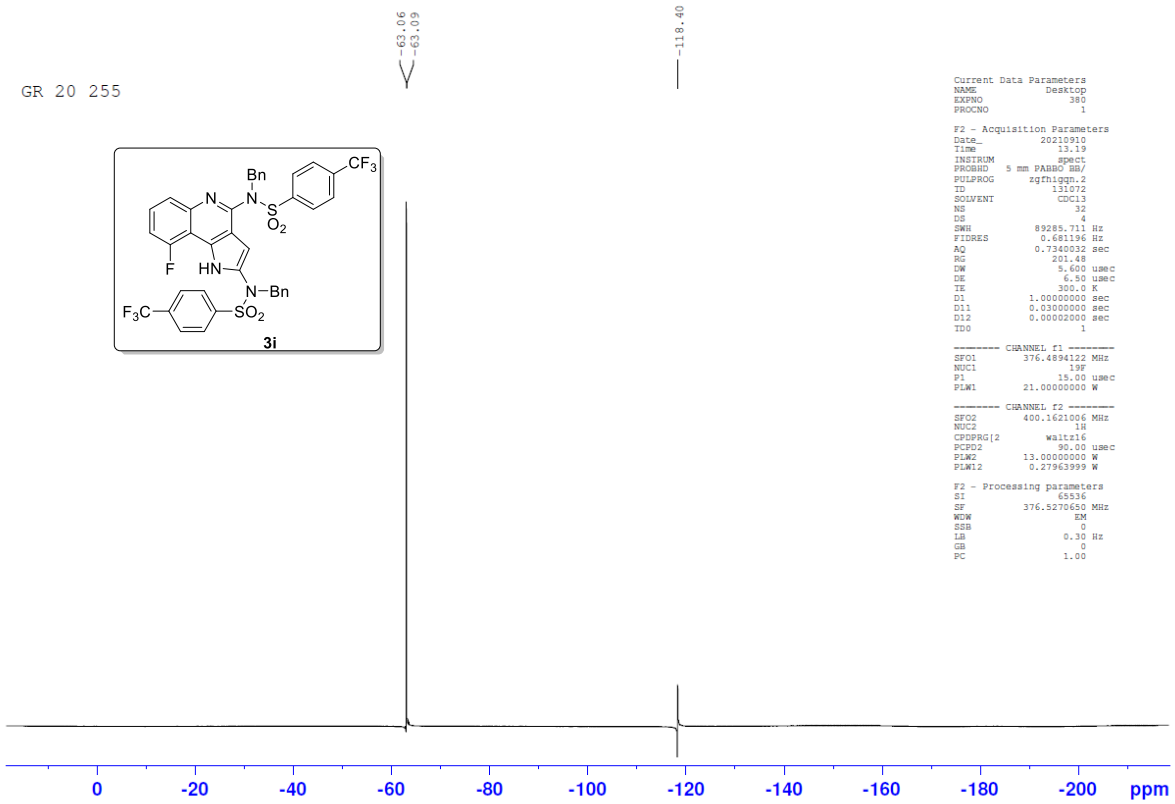
^{1}H NMR, $CDCl_3$, 400 MHz



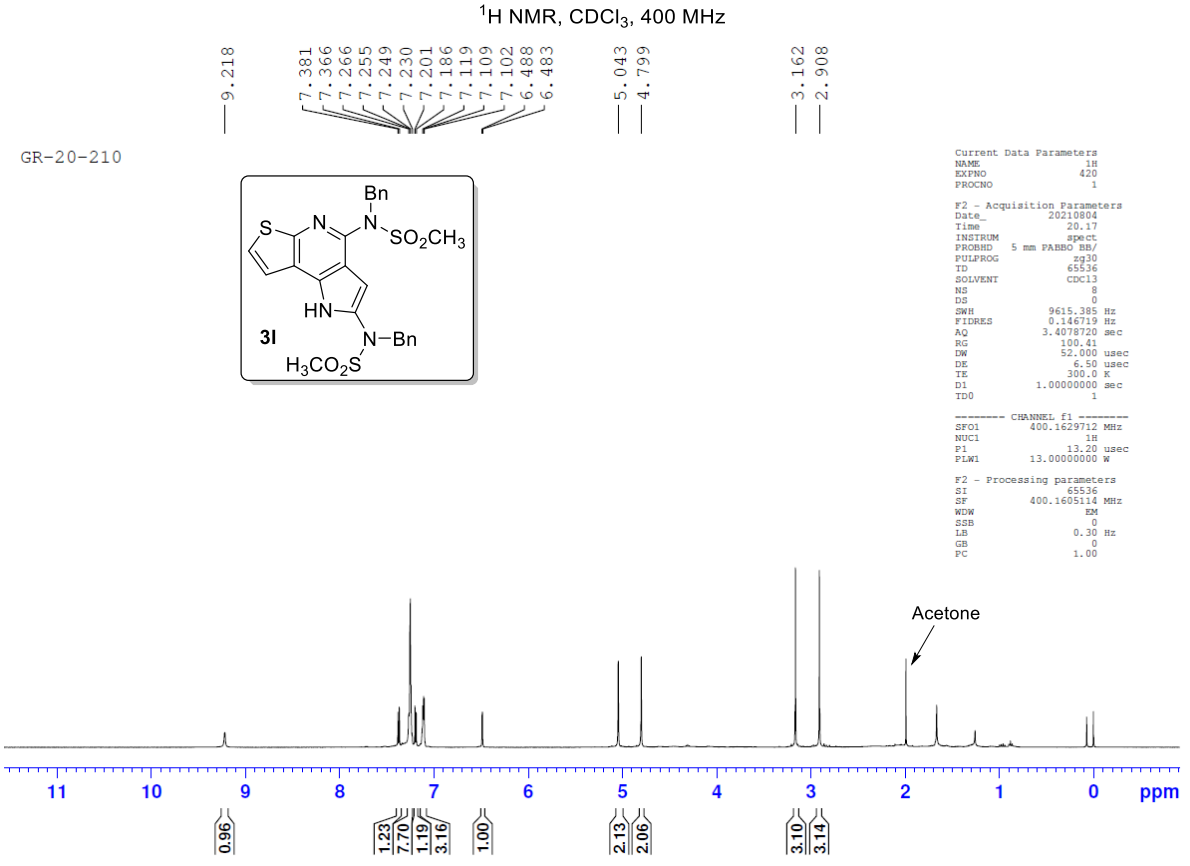
^{13}C NMR, $CDCl_3$, 125 MHz



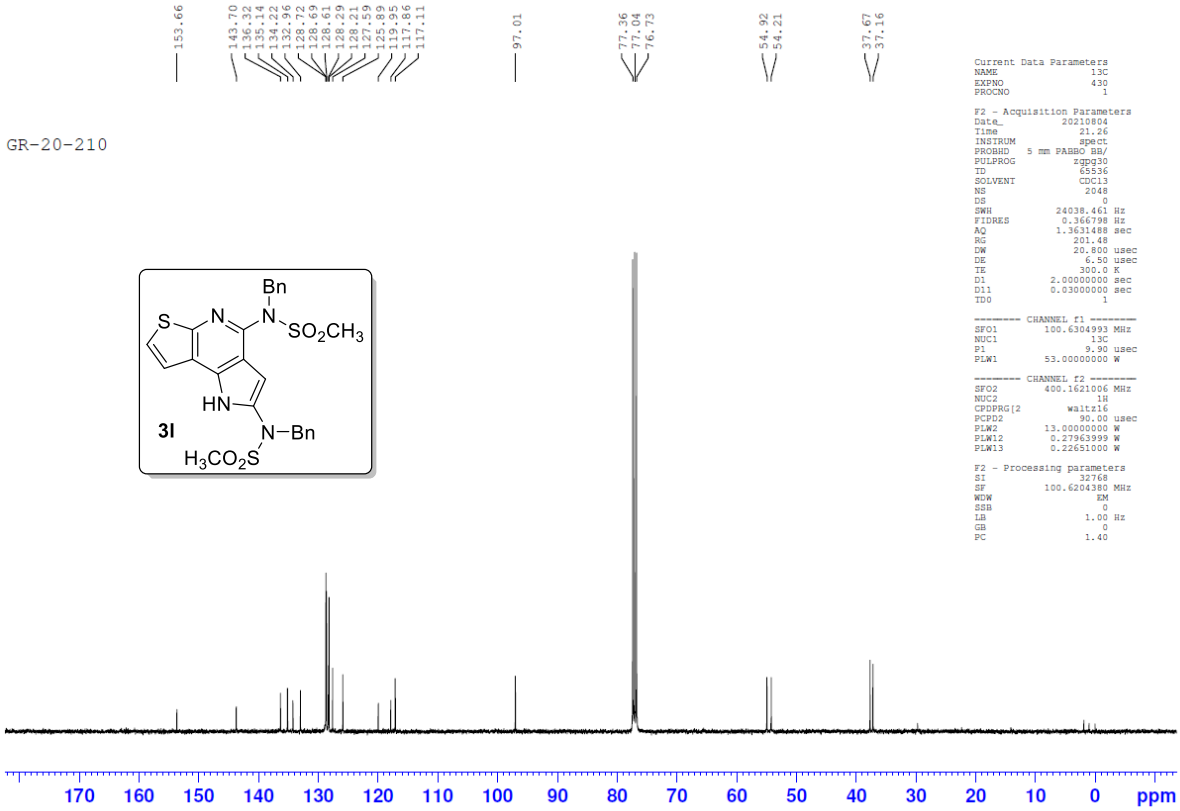
^{19}F NMR, $CDCl_3$, 376 MHz



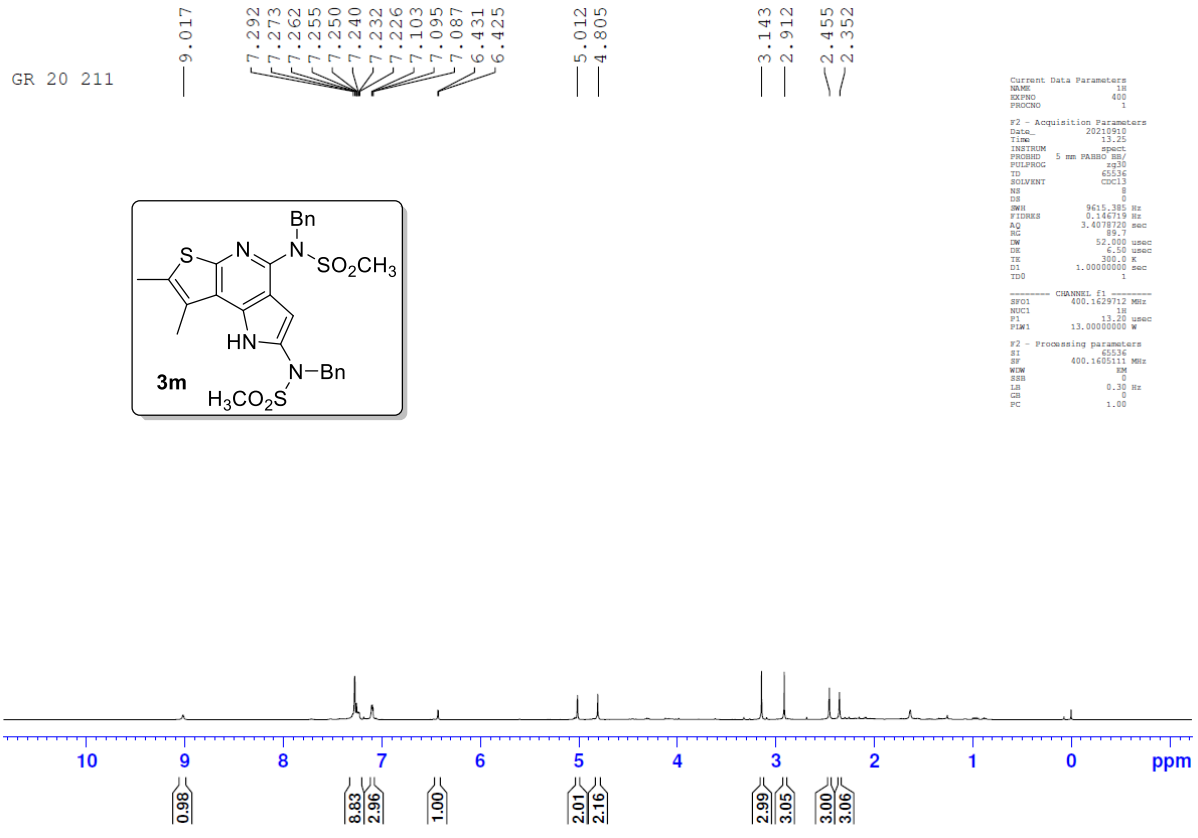
^{1}H NMR, $CDCl_3$, 400 MHz



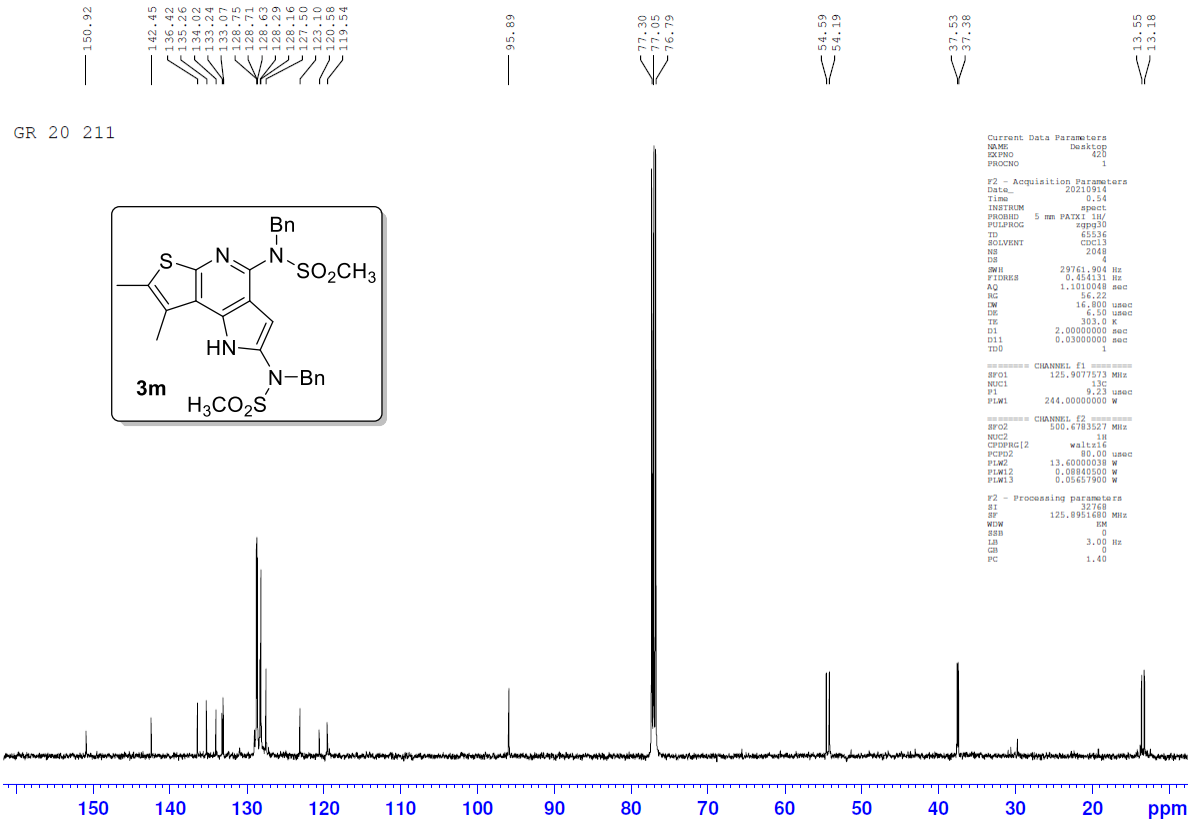
^{13}C NMR, $CDCl_3$, 101 MHz



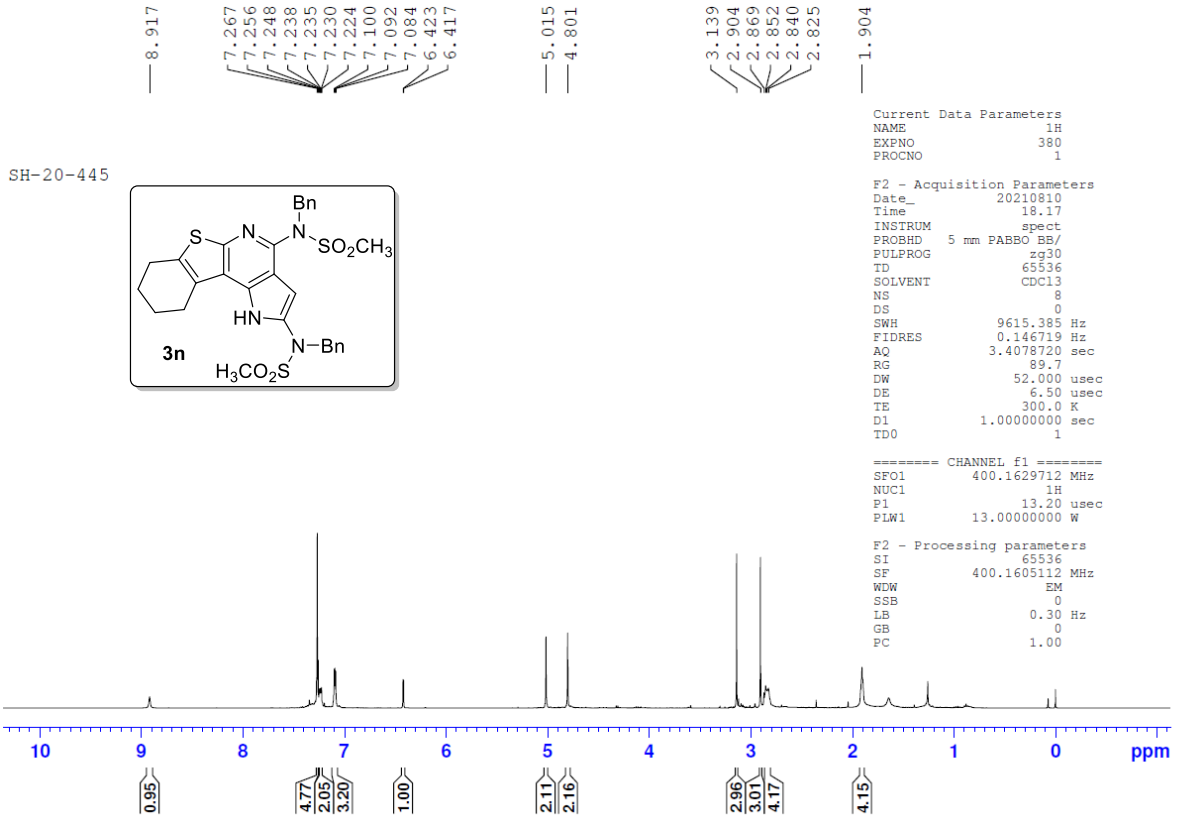
^{1}H NMR, $CDCl_3$, 400 MHz



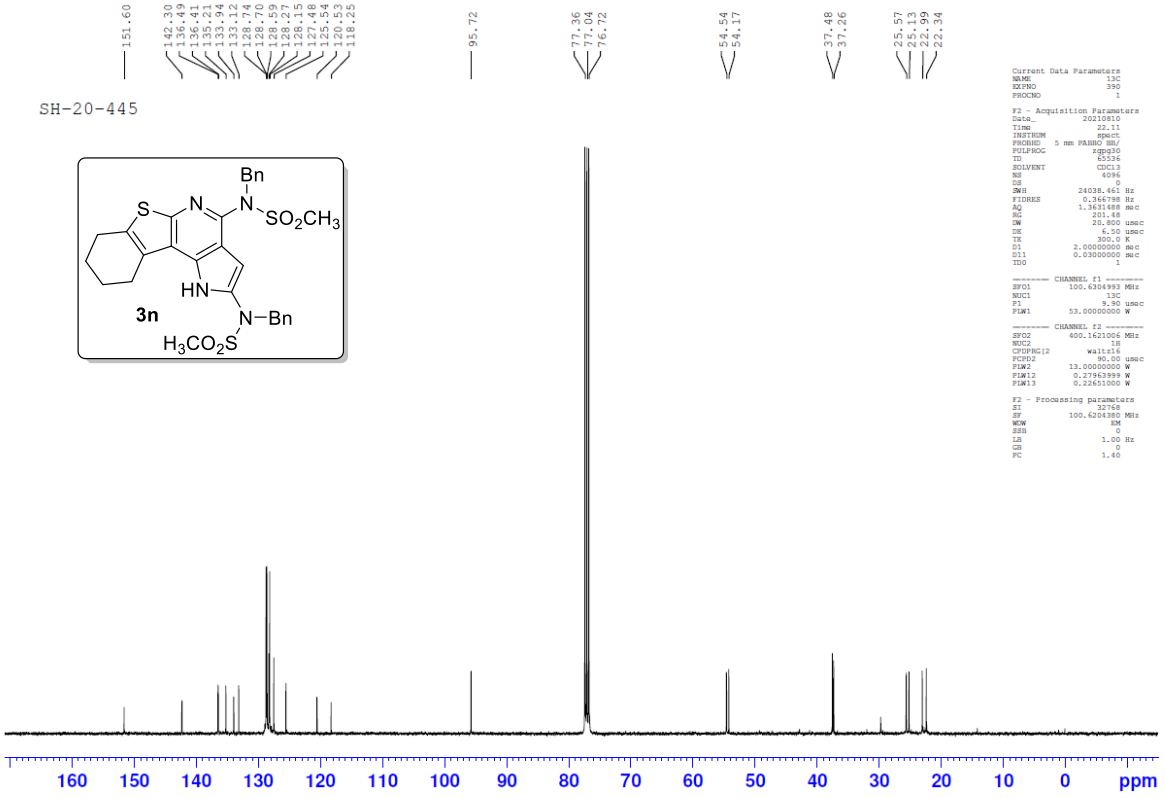
^{13}C NMR, $CDCl_3$, 125 MHz



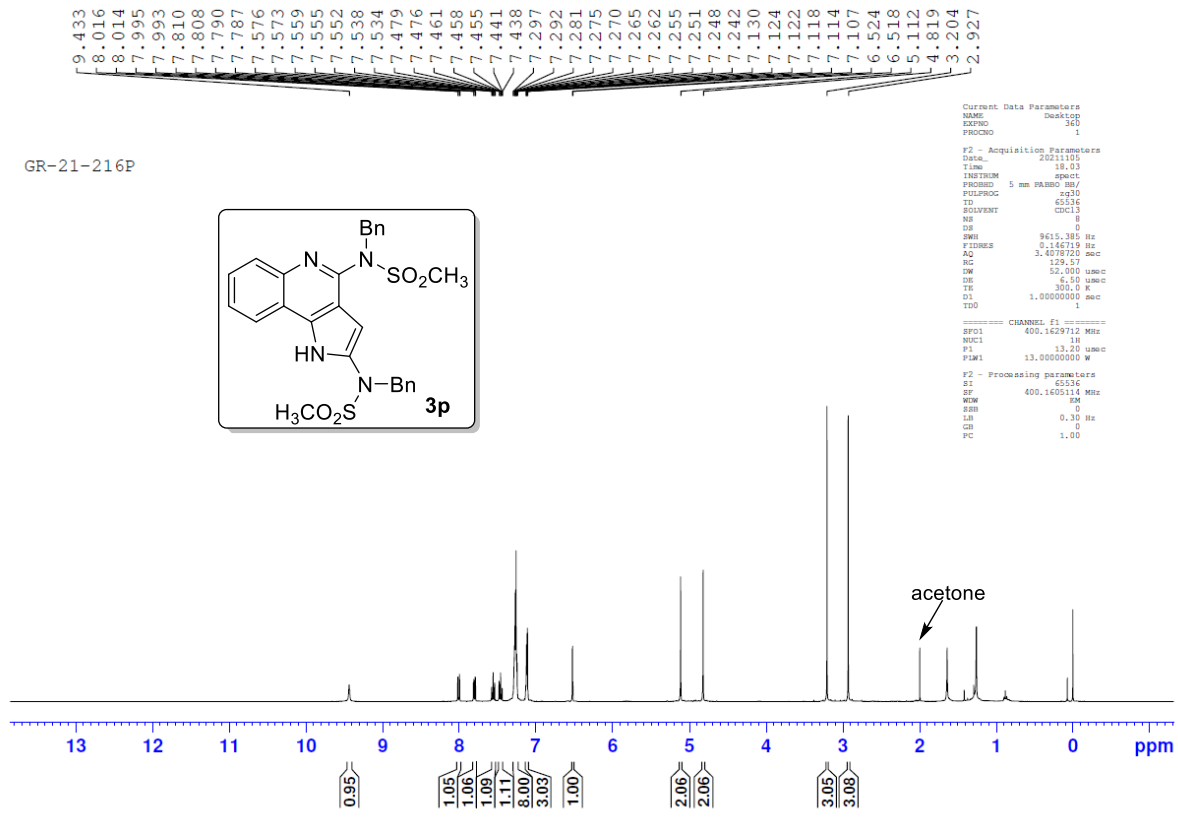
^{1}H NMR, $CDCl_3$, 400 MHz



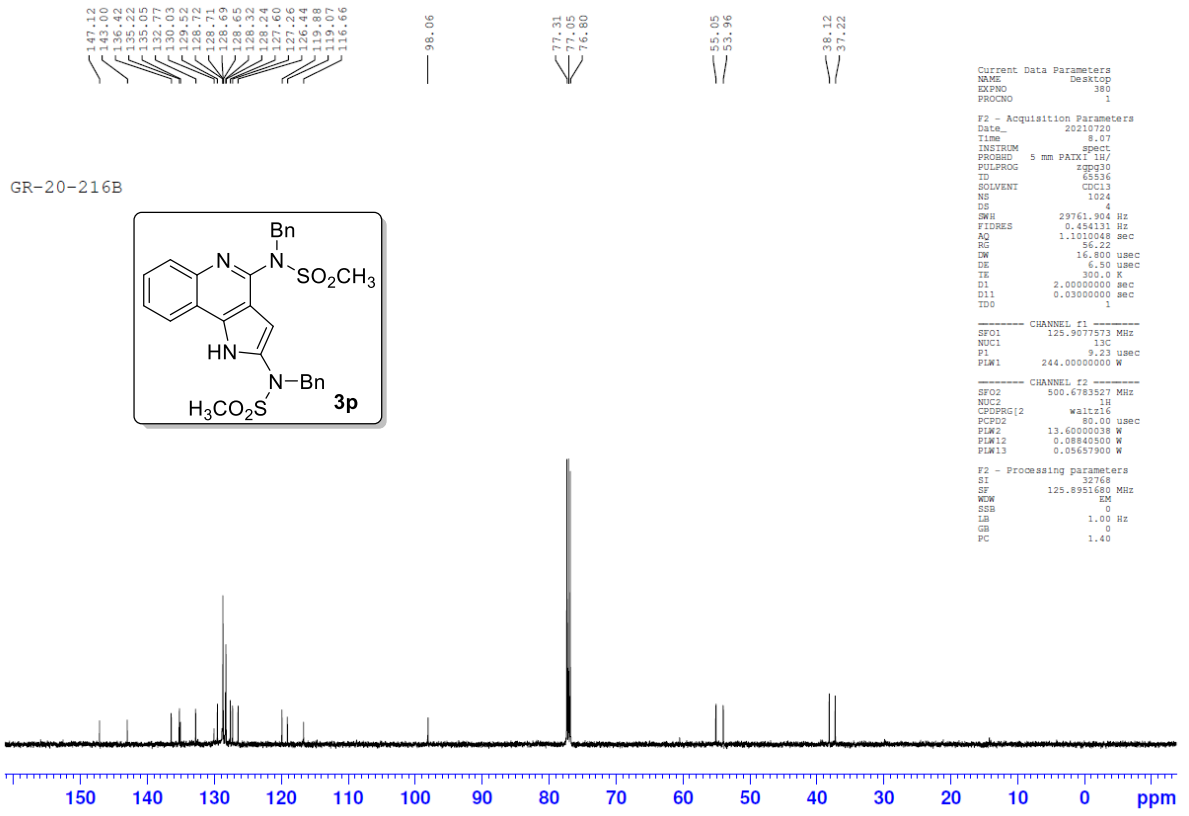
^{13}C NMR, $CDCl_3$, 101 MHz



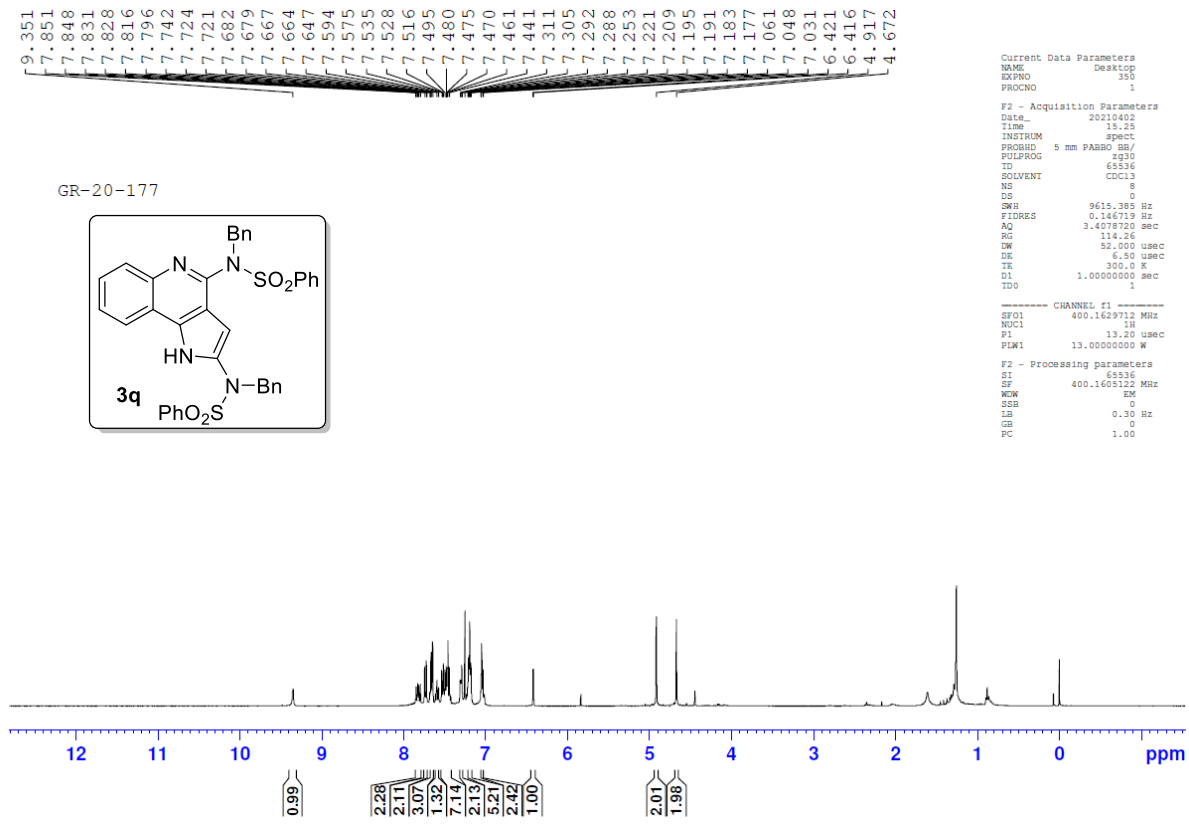
^{1}H NMR, $CDCl_3$, 400 MHz



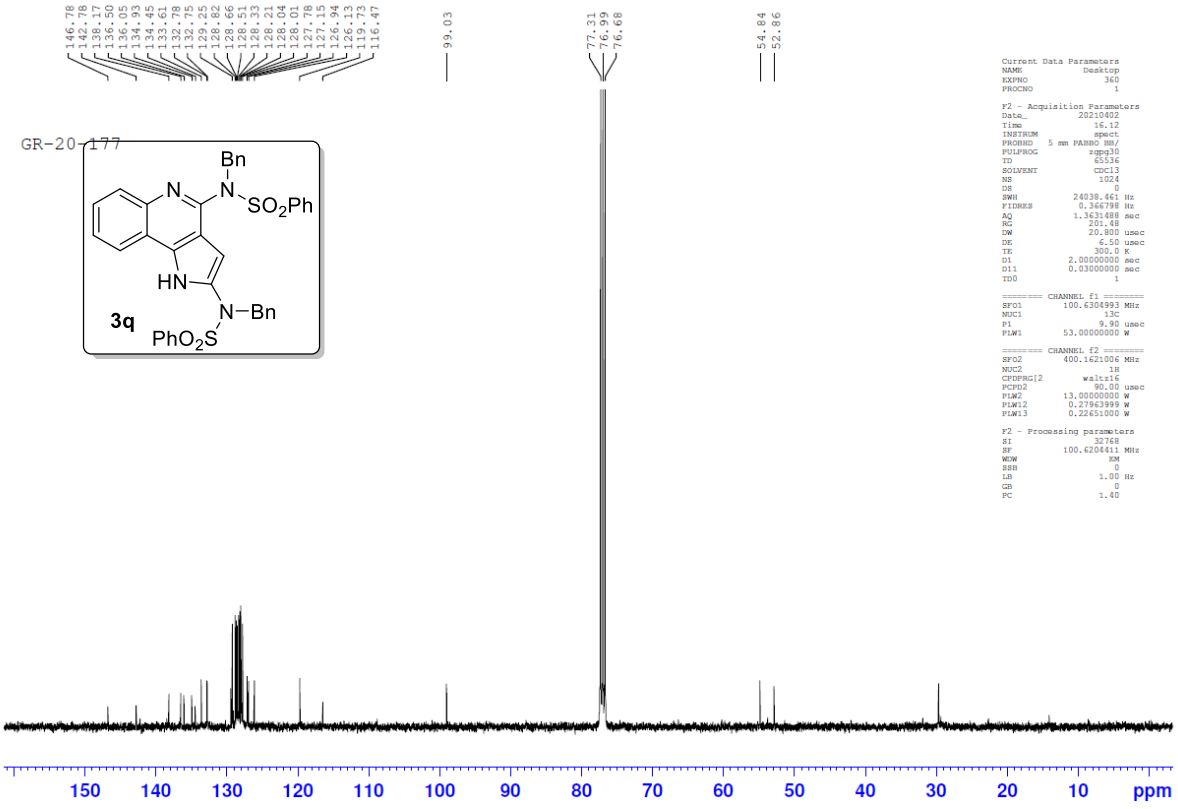
^{13}C NMR, $CDCl_3$, 125 MHz



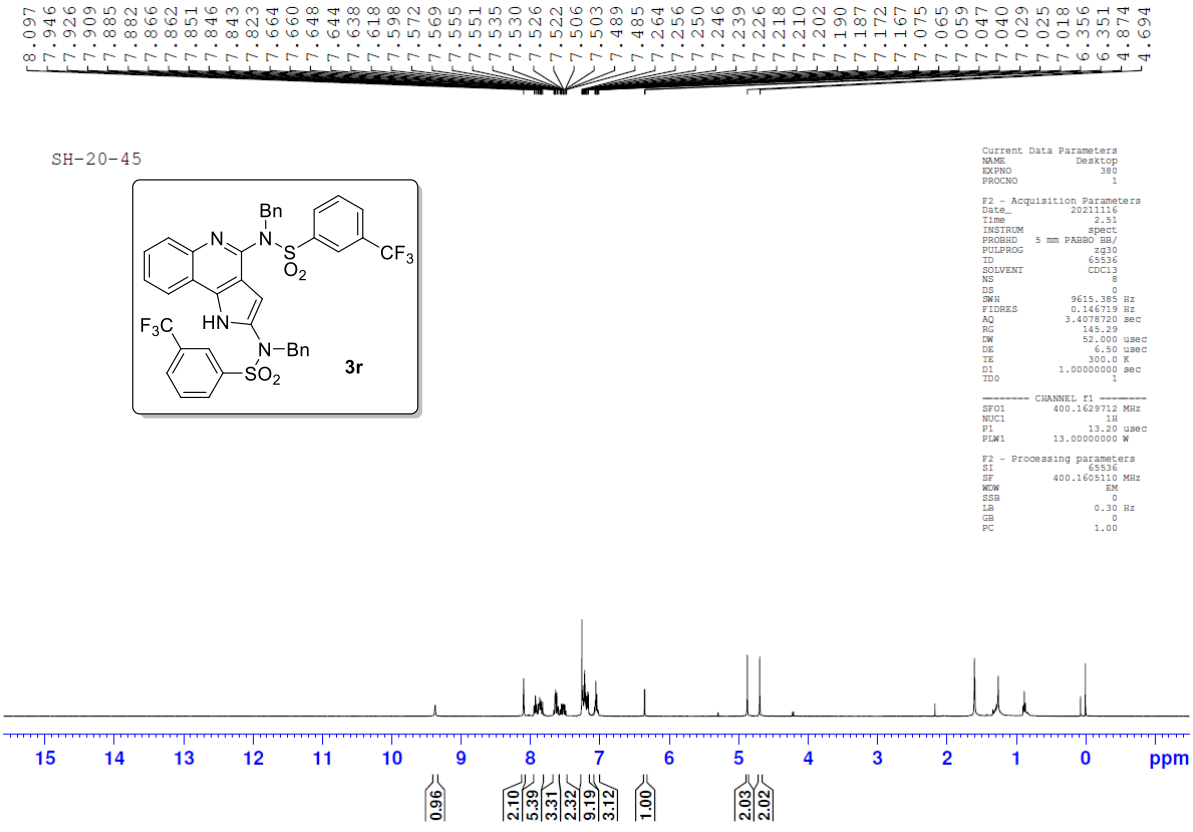
^{1}H NMR, $CDCl_3$, 400 MHz



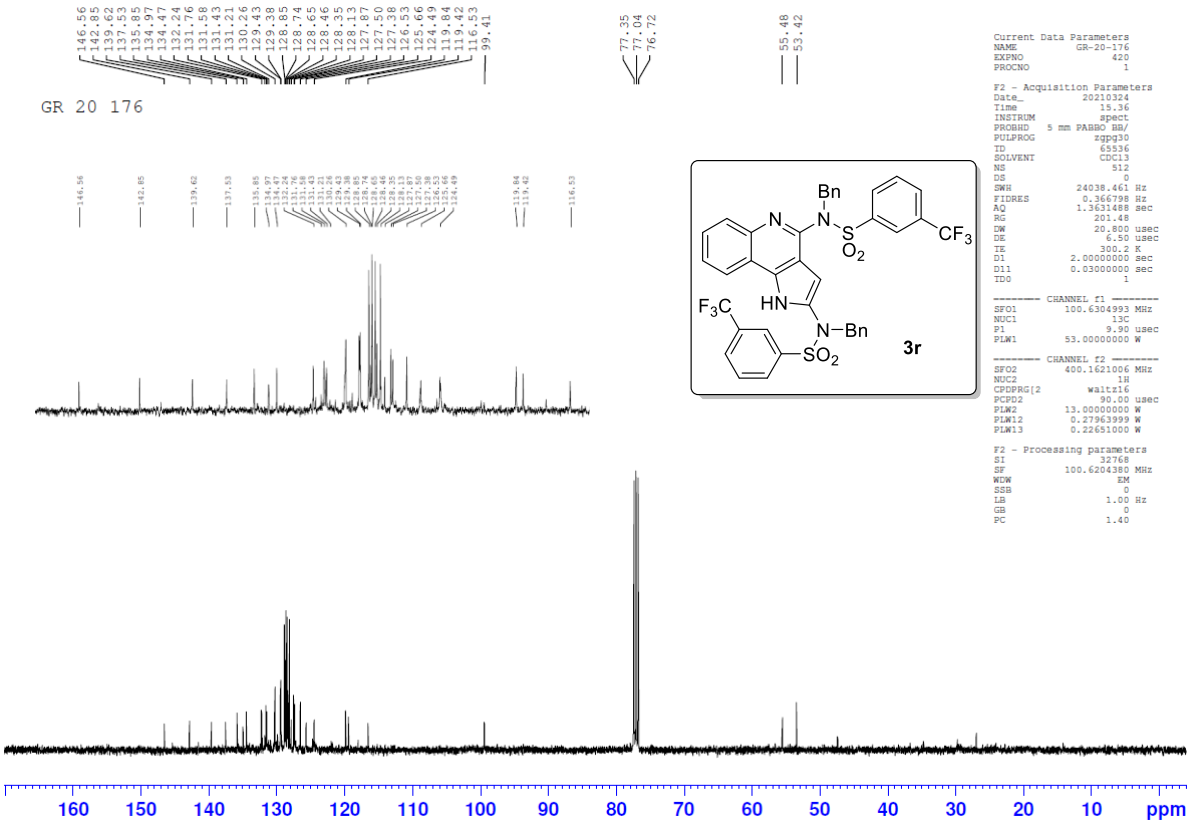
^{13}C NMR, $CDCl_3$, 101 MHz



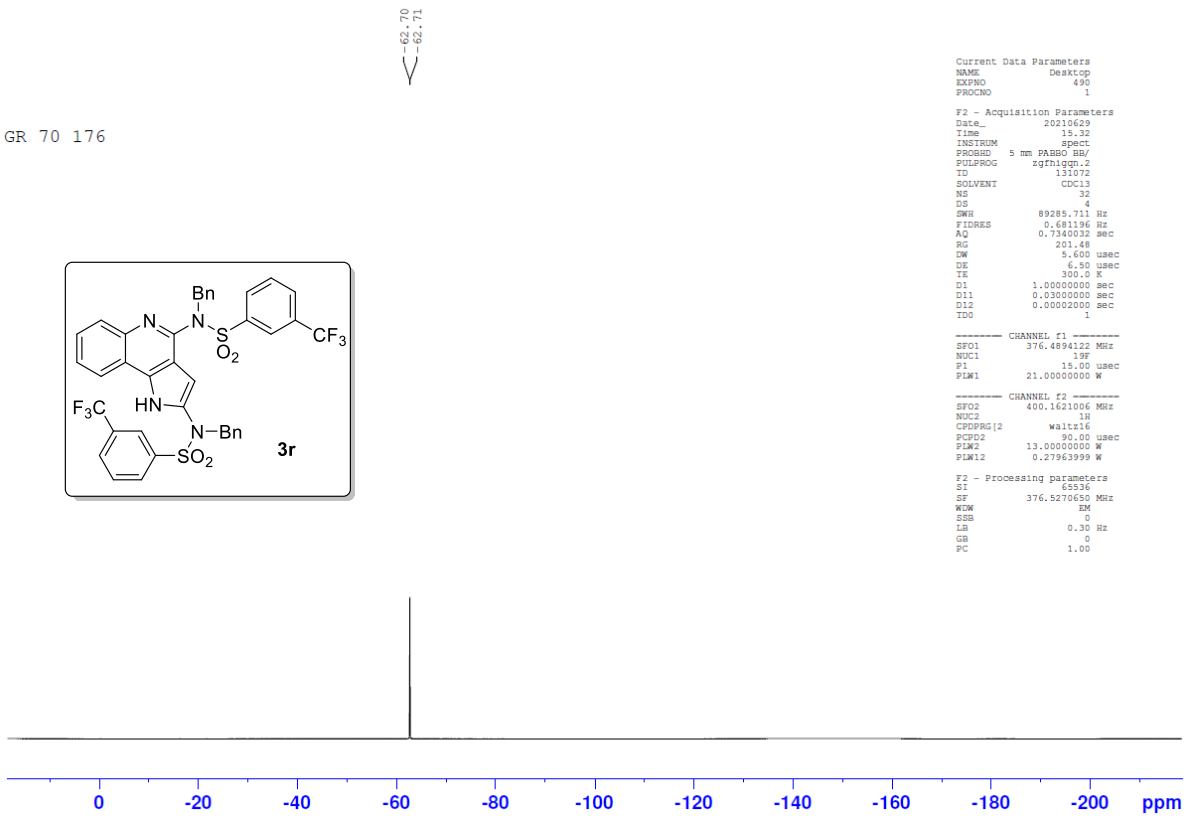
^{1}H NMR, $CDCl_3$, 400 MHz



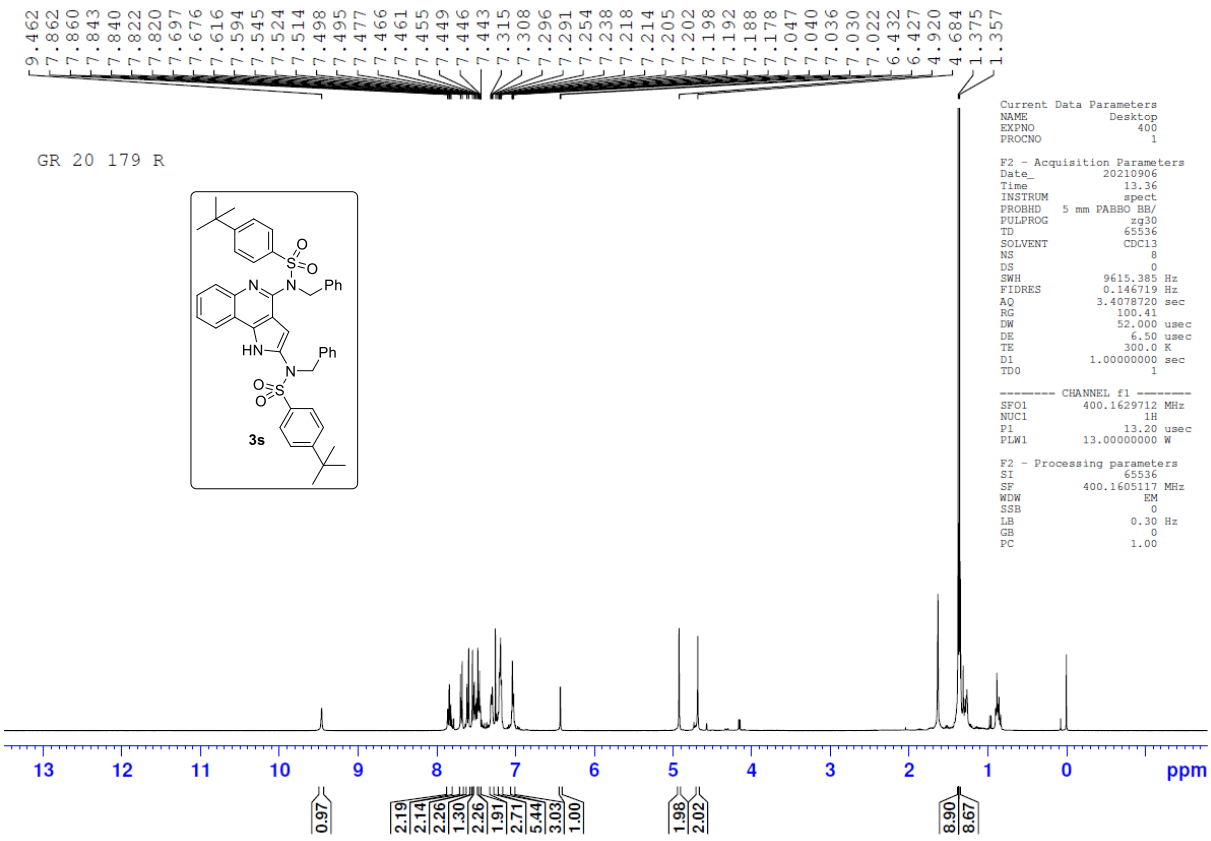
^{13}C NMR, $CDCl_3$, 101 MHz



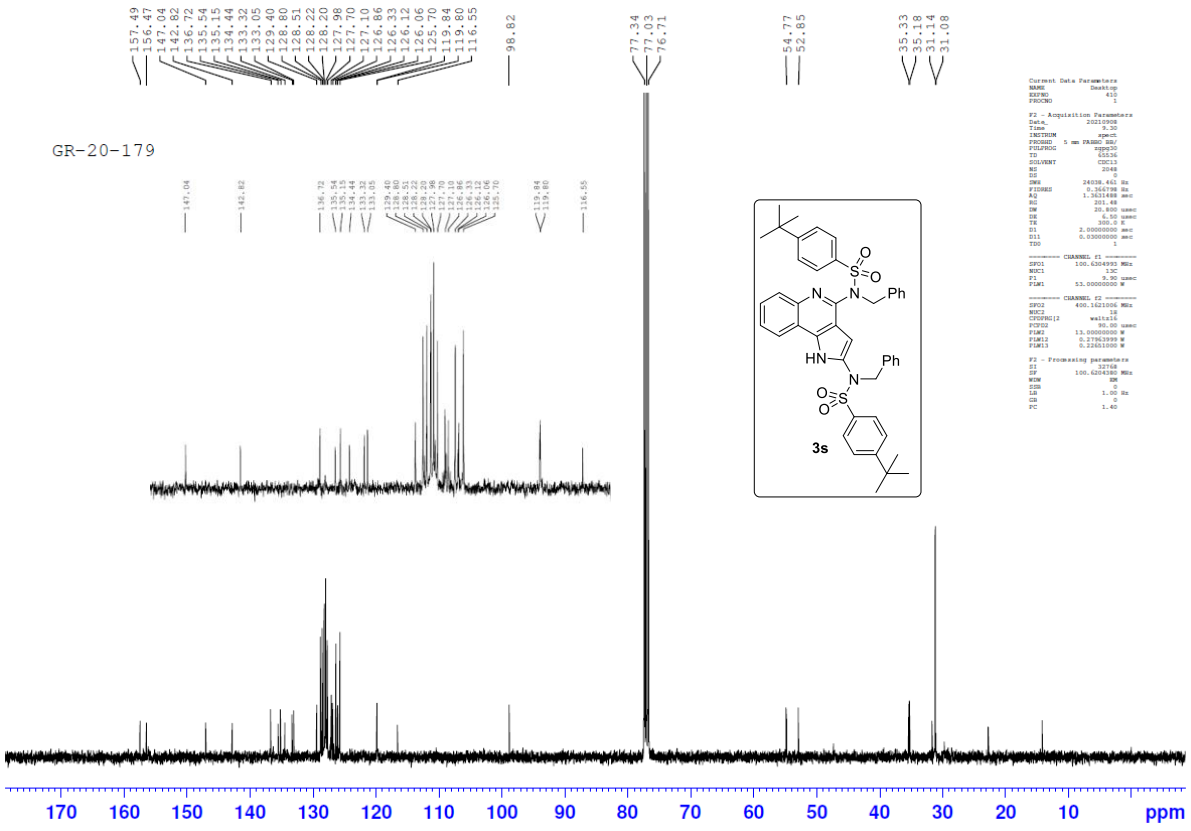
^{19}F NMR, $CDCl_3$, 376 MHz



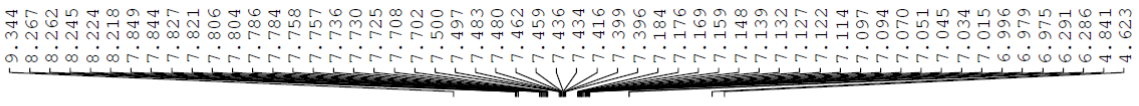
^{1}H NMR, $CDCl_3$, 400 MHz



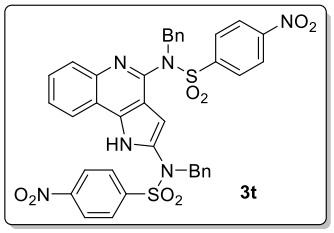
^{13}C NMR, $CDCl_3$, 101 MHz

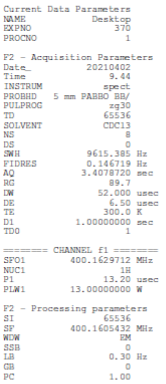


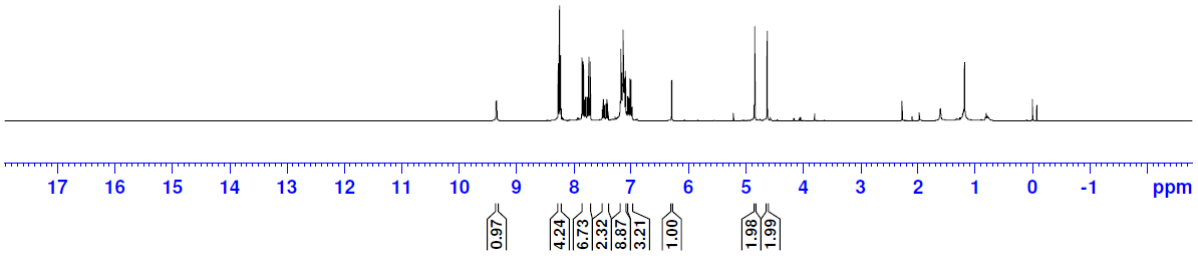
^{1}H NMR, $CDCl_3$, 400 MHz



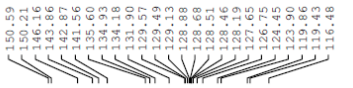
GR-20-156



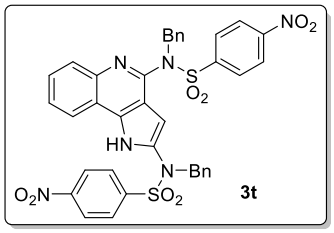


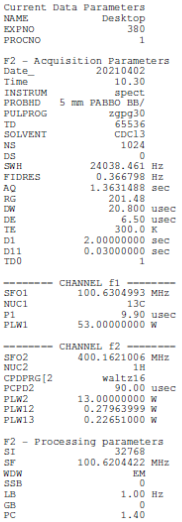


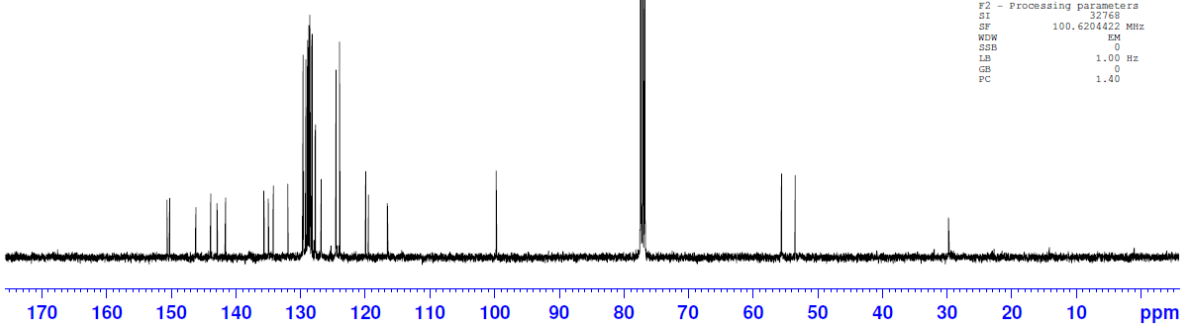
^{13}C NMR, $CDCl_3$, 101 MHz



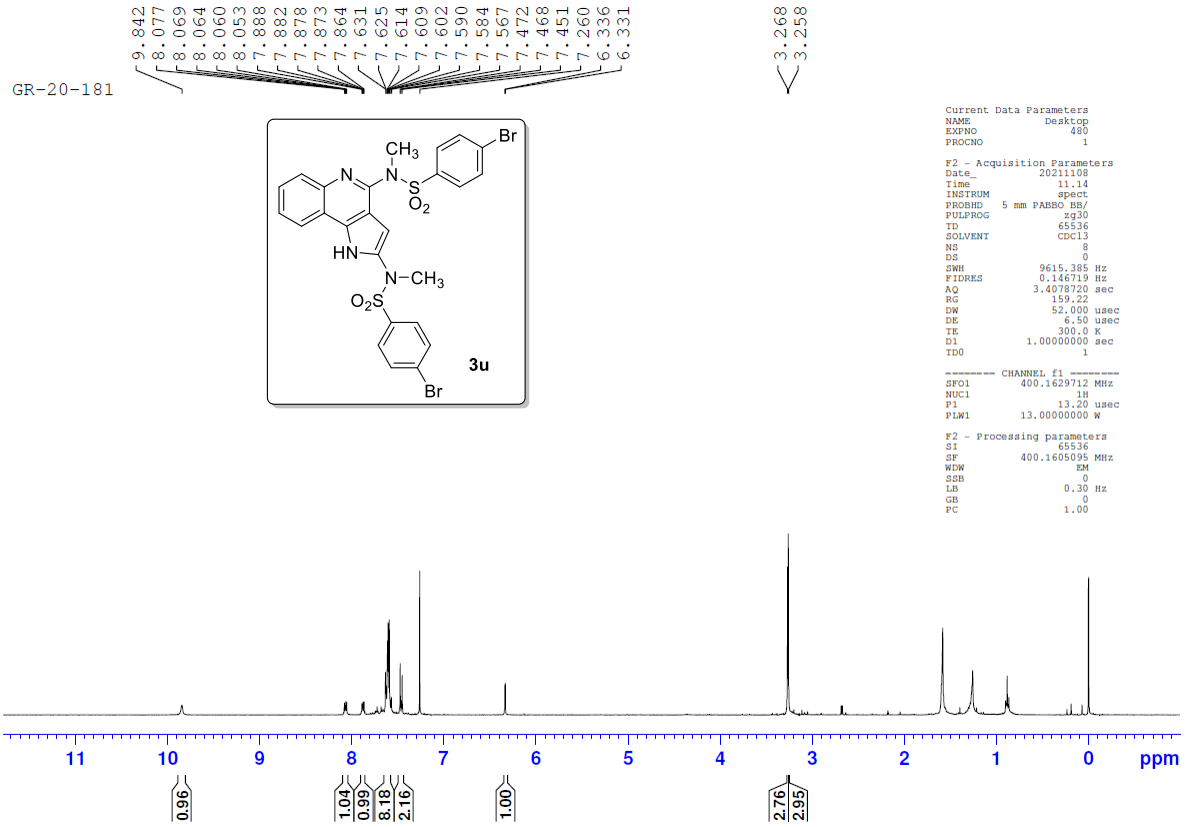
GR-20-156



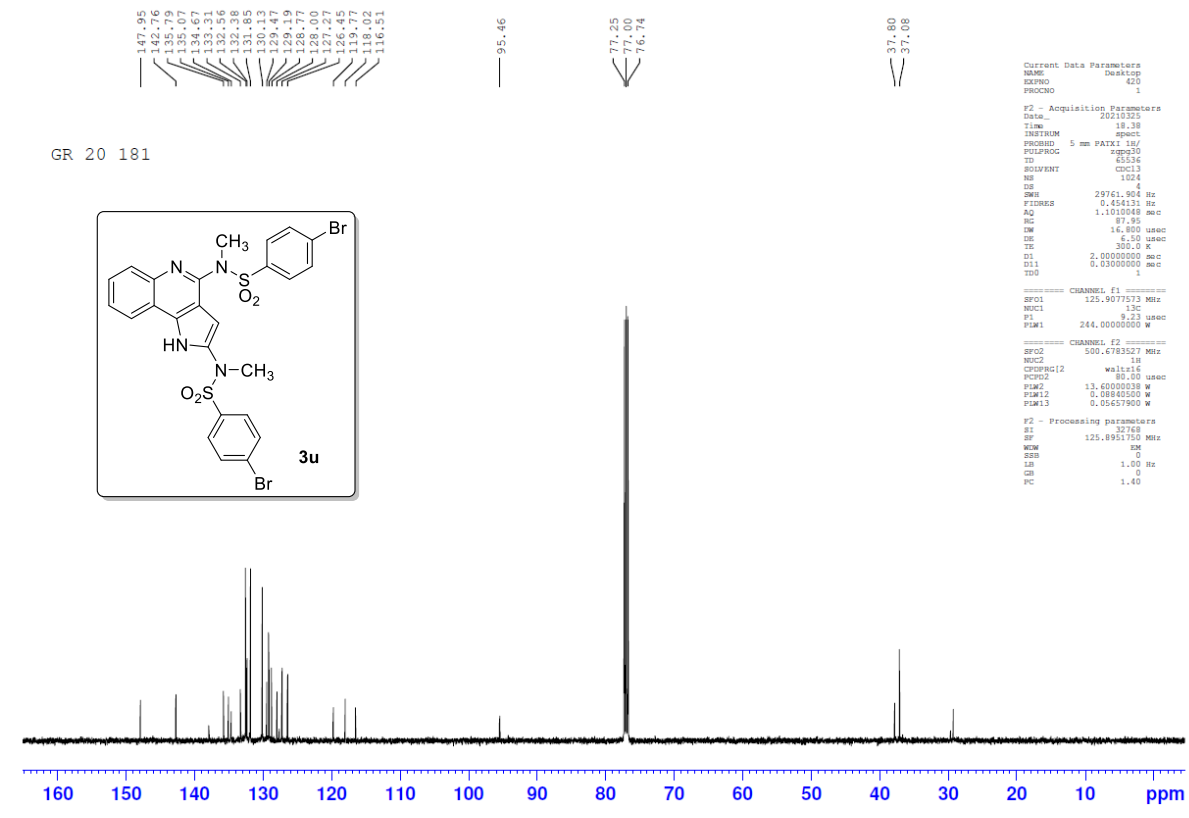




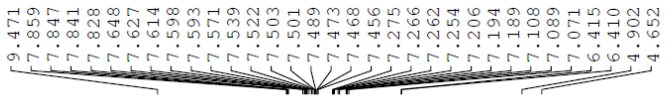
^{1}H NMR, $CDCl_3$, 400 MHz



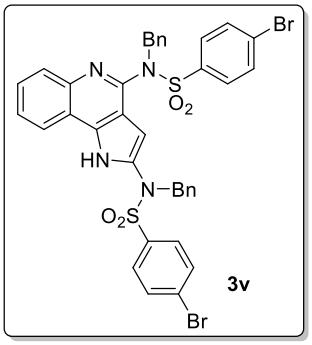
^{13}C NMR, $CDCl_3$, 125 MHz

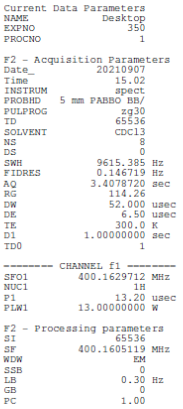


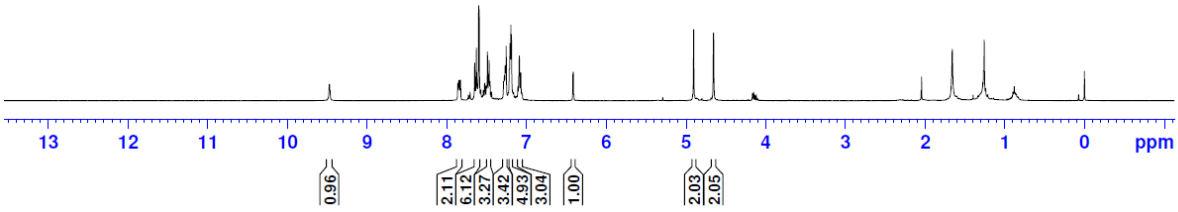
^{1}H NMR, $CDCl_3$, 400 MHz



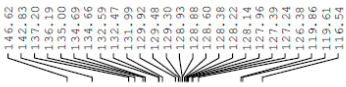
GR-20-180R



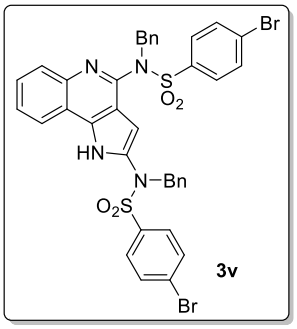


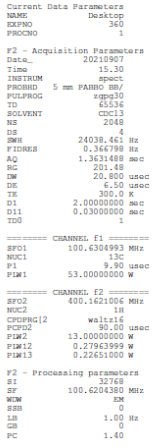


^{13}C NMR, $CDCl_3$, 101 MHz

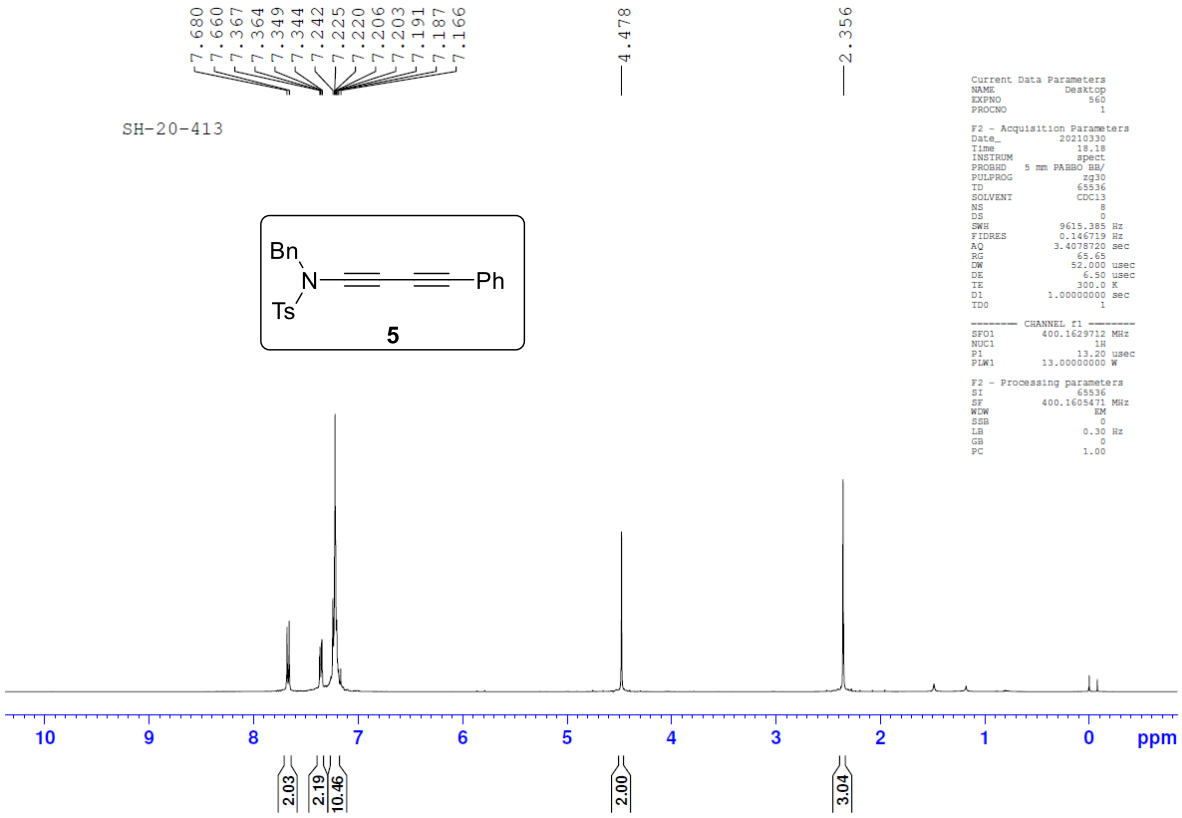


GR-20-180R

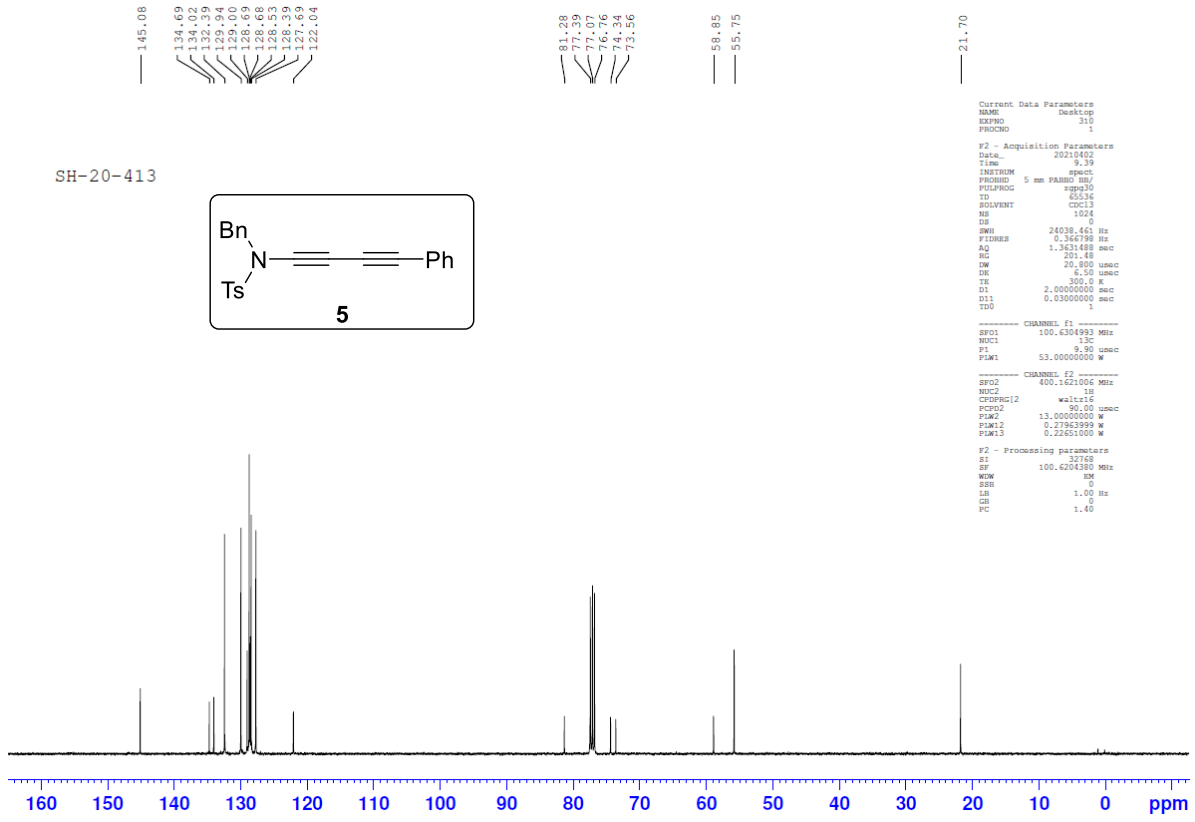




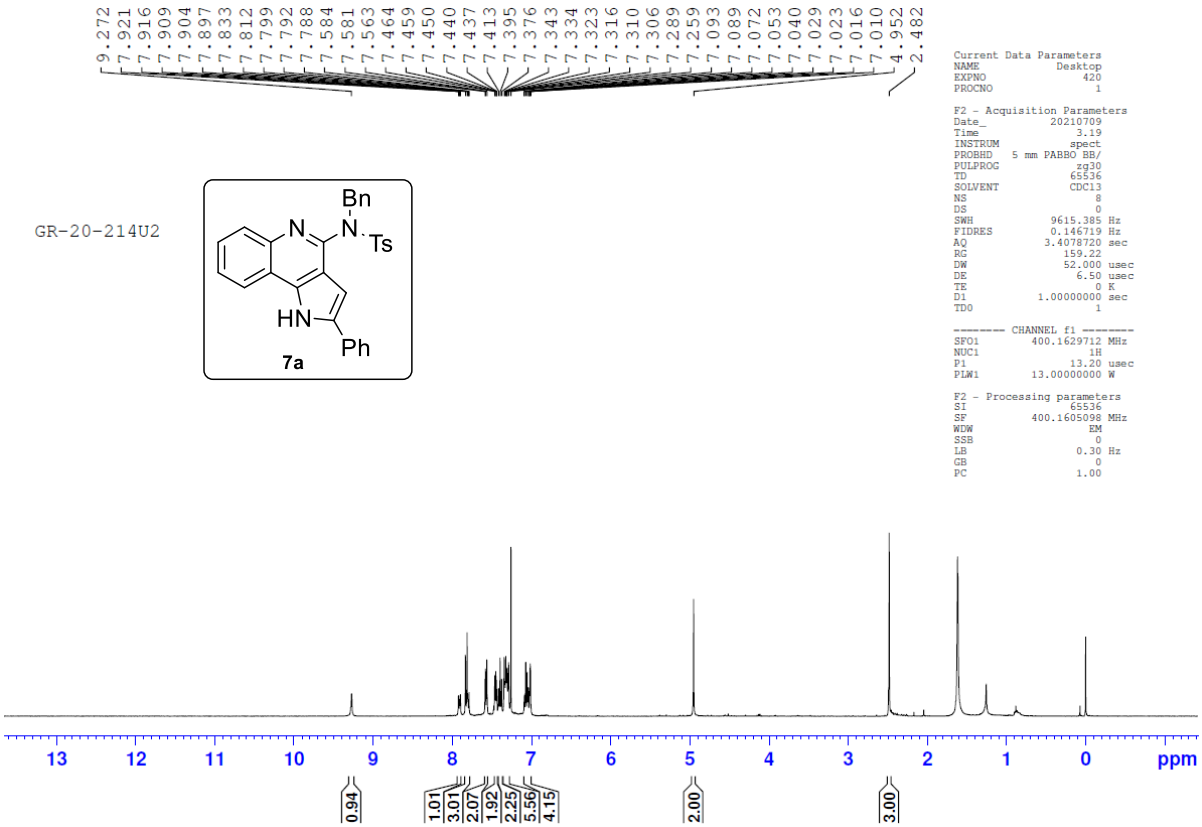
^{1}H NMR, $CDCl_3$, 400 MHz



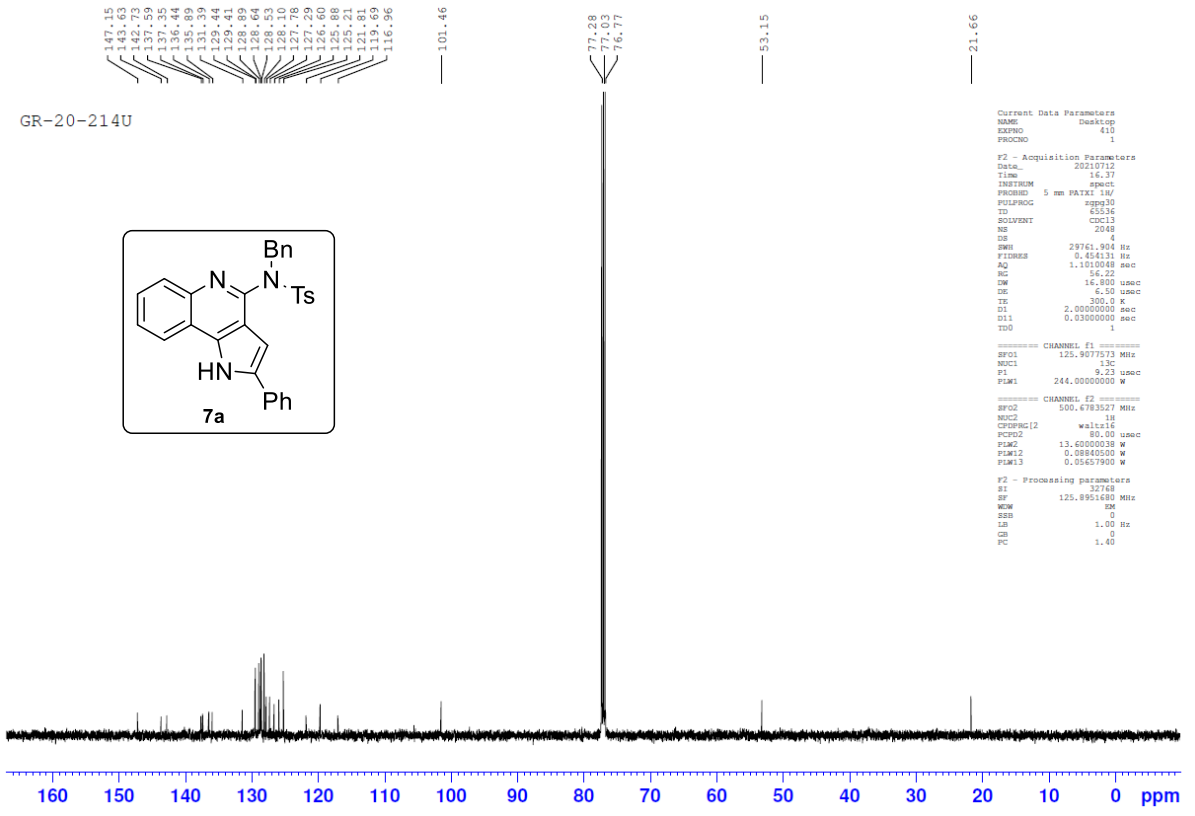
^{13}C NMR, $CDCl_3$, 101 MHz



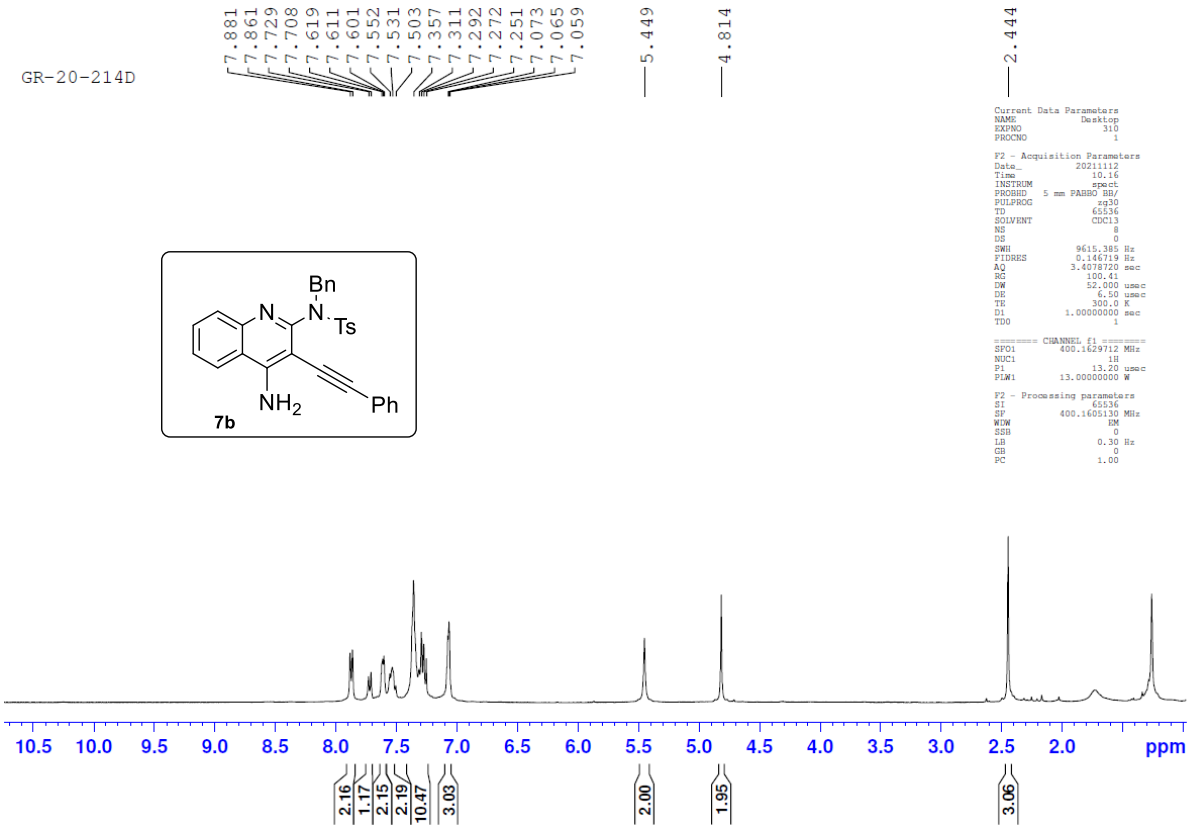
^{1}H NMR, $CDCl_3$, 400 MHz



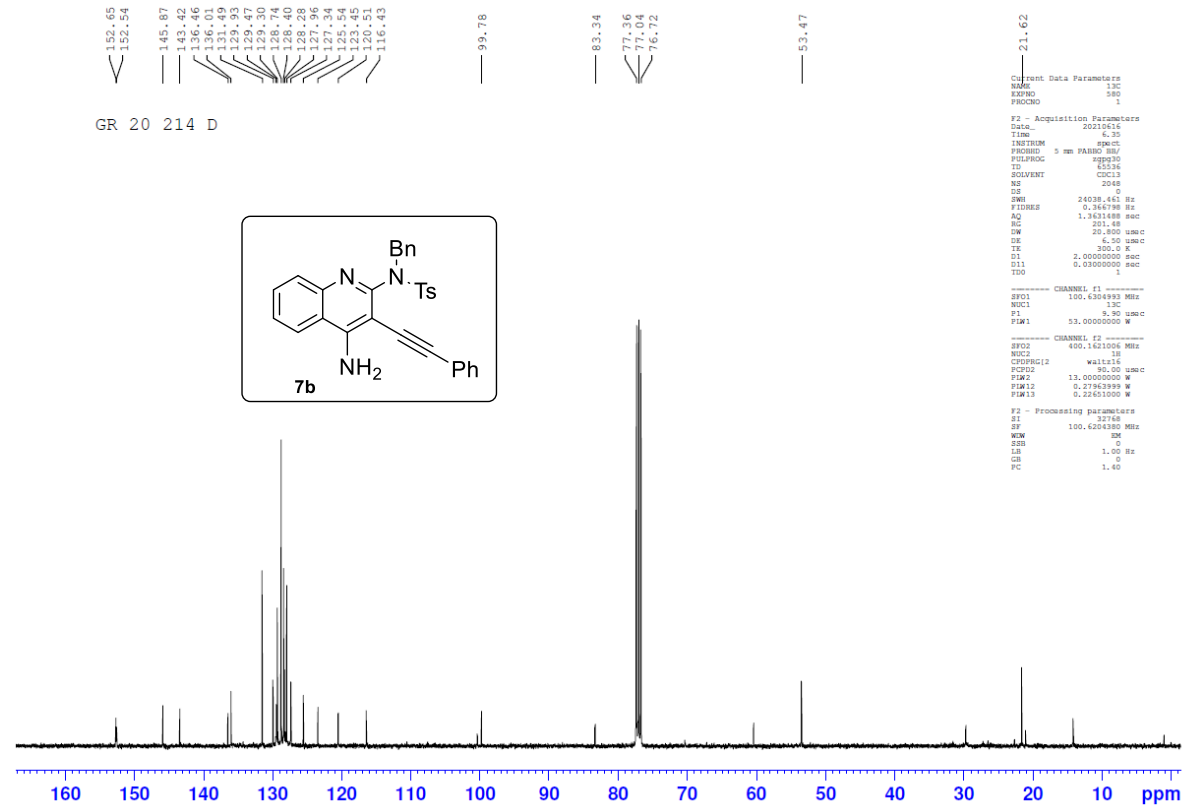
^{13}C NMR, $CDCl_3$, 125 MHz



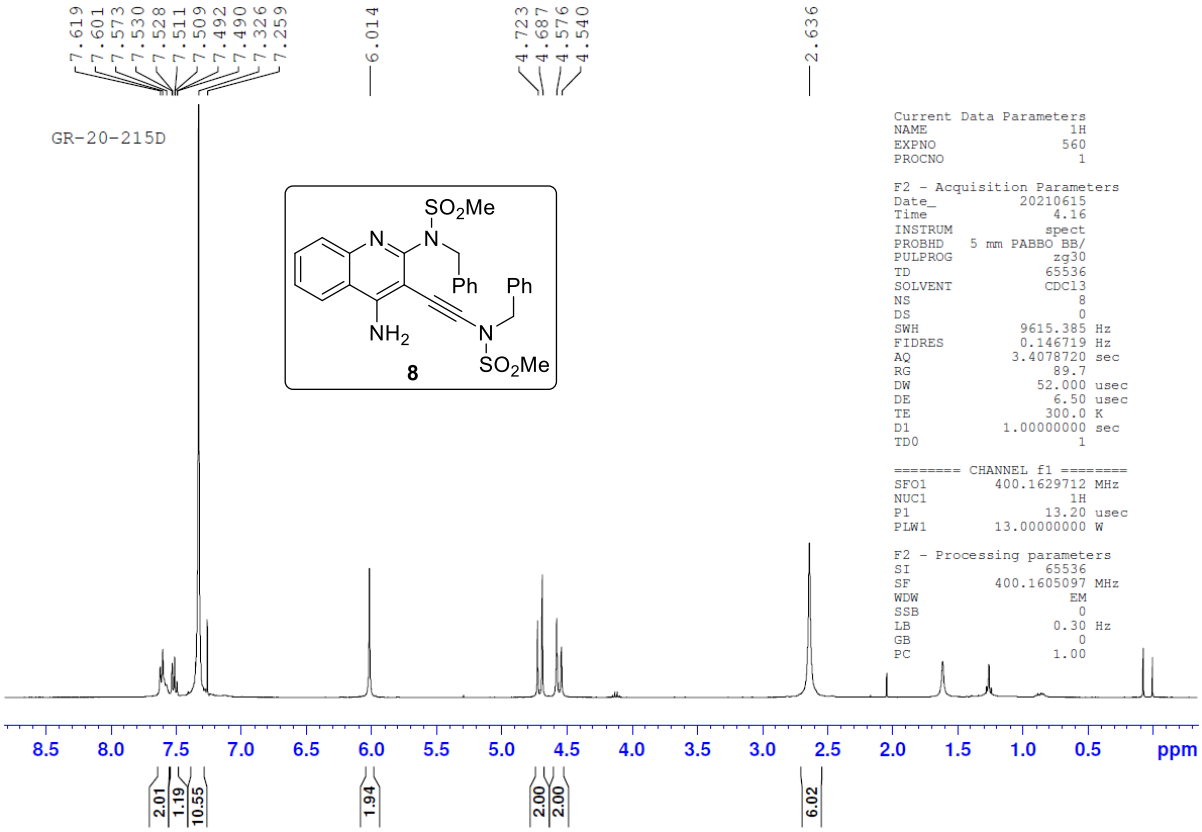
^{1}H NMR, $CDCl_3$, 400 MHz



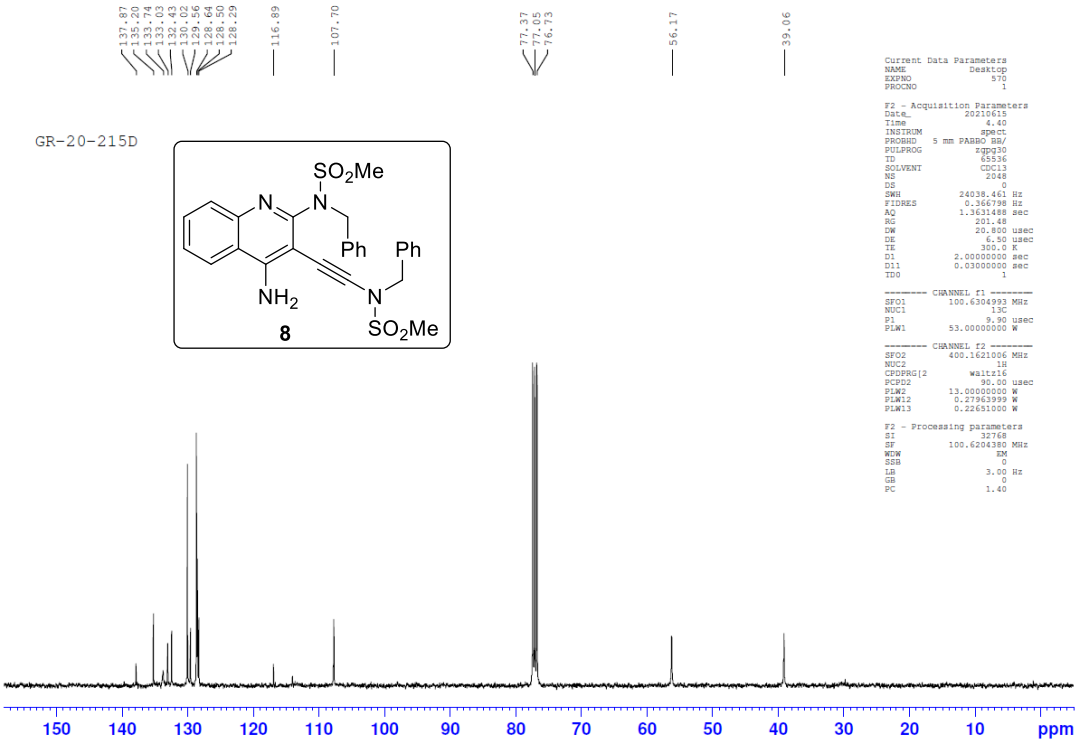
^{13}C NMR, $CDCl_3$, 101 MHz



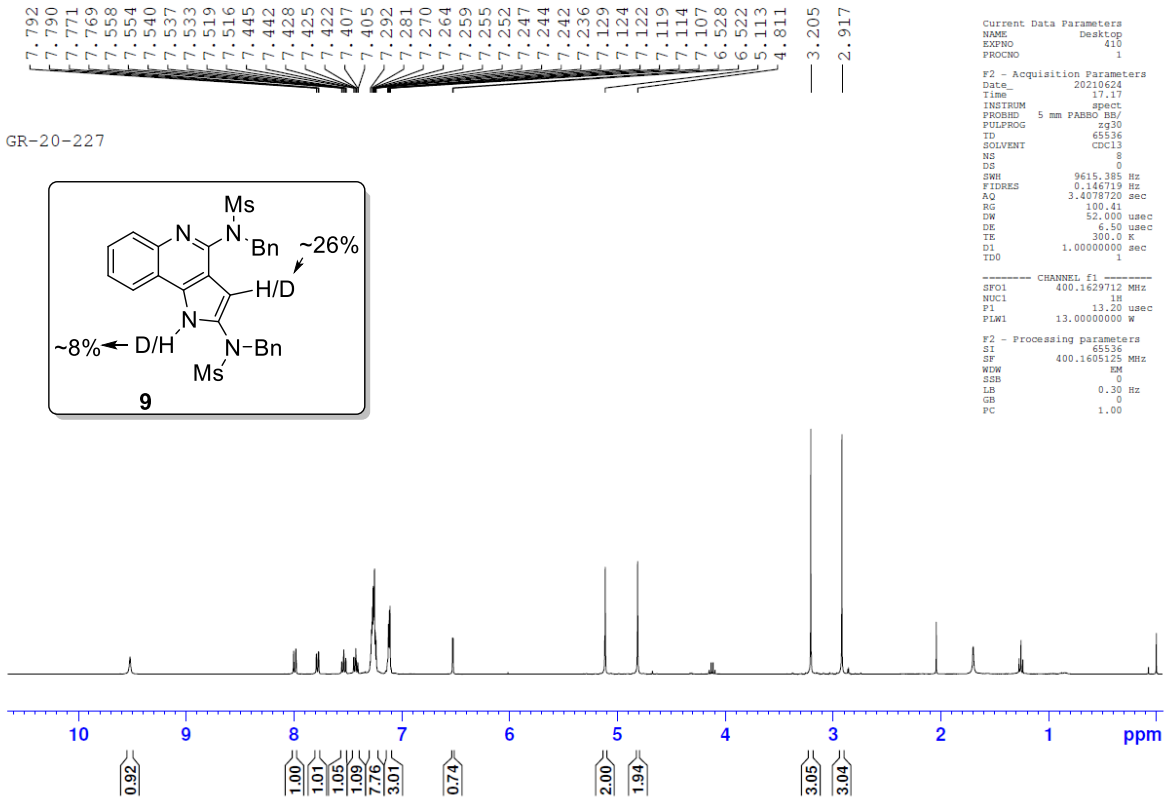
^{1}H NMR, $CDCl_3$, 400 MHz



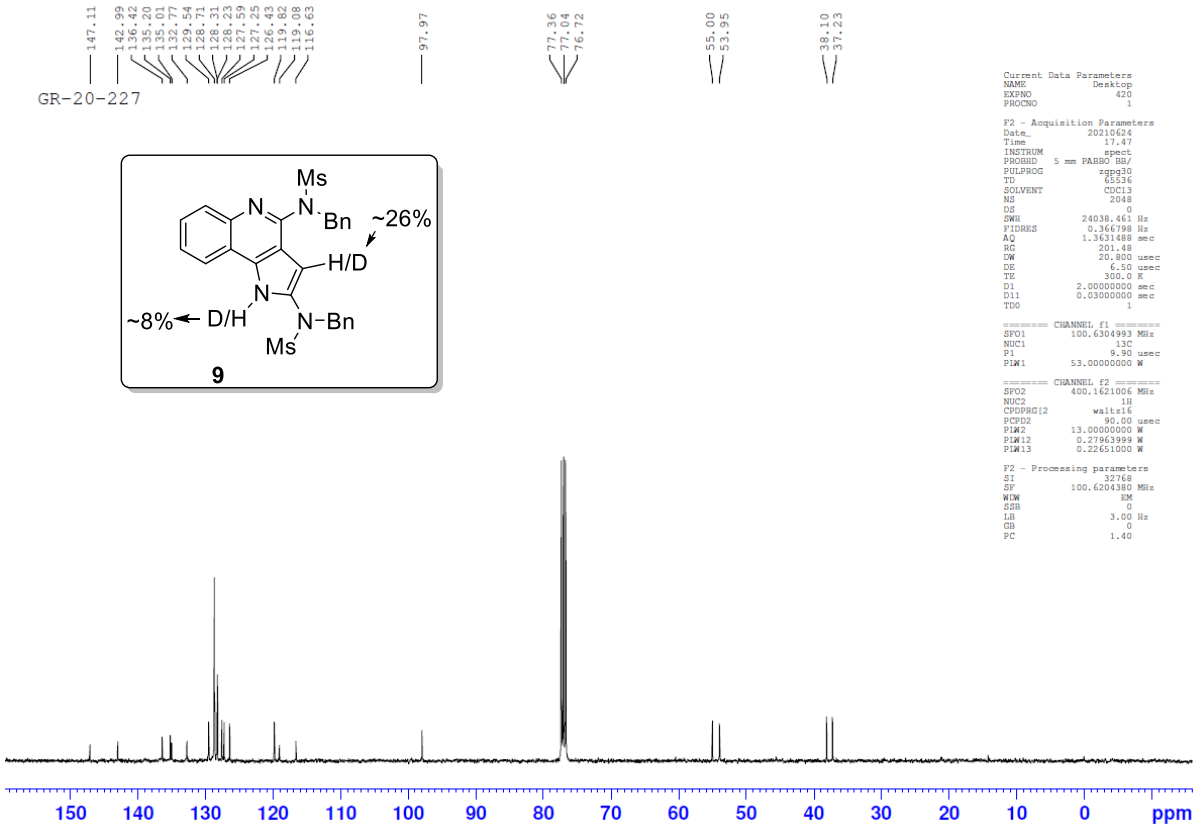
^{13}C NMR, $CDCl_3$, 101 MHz



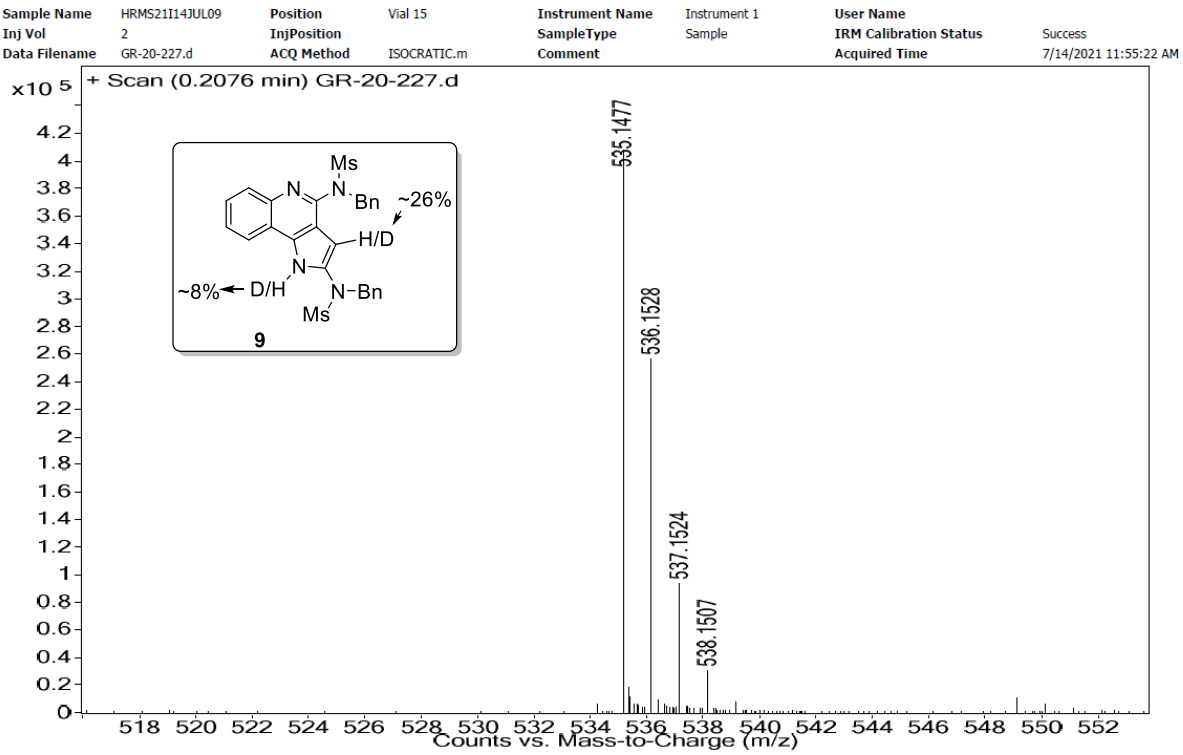
^{1}H NMR, $CDCl_3$, 400 MHz



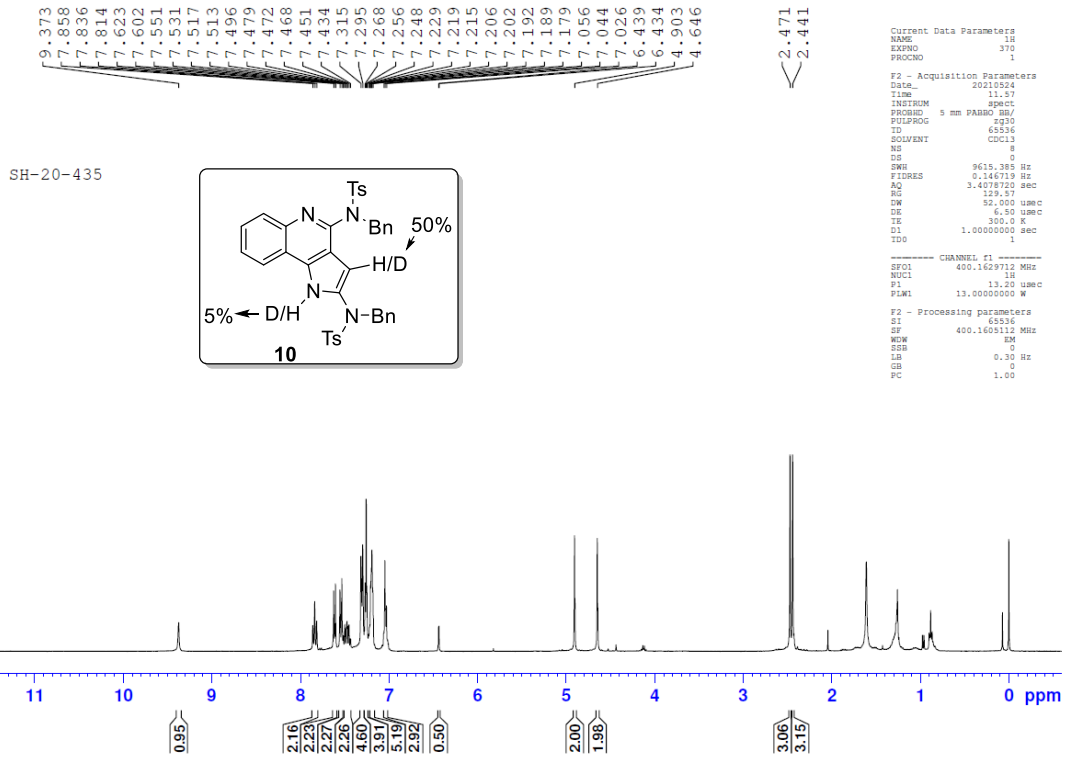
^{13}C NMR, $CDCl_3$, 101 MHz



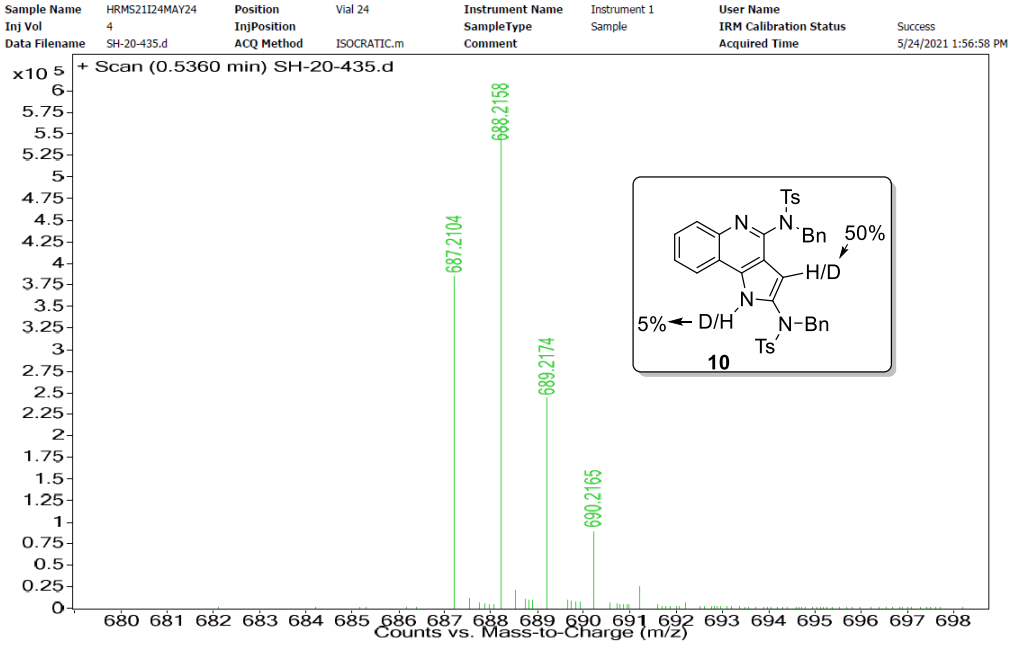
HRMS of compound **9**



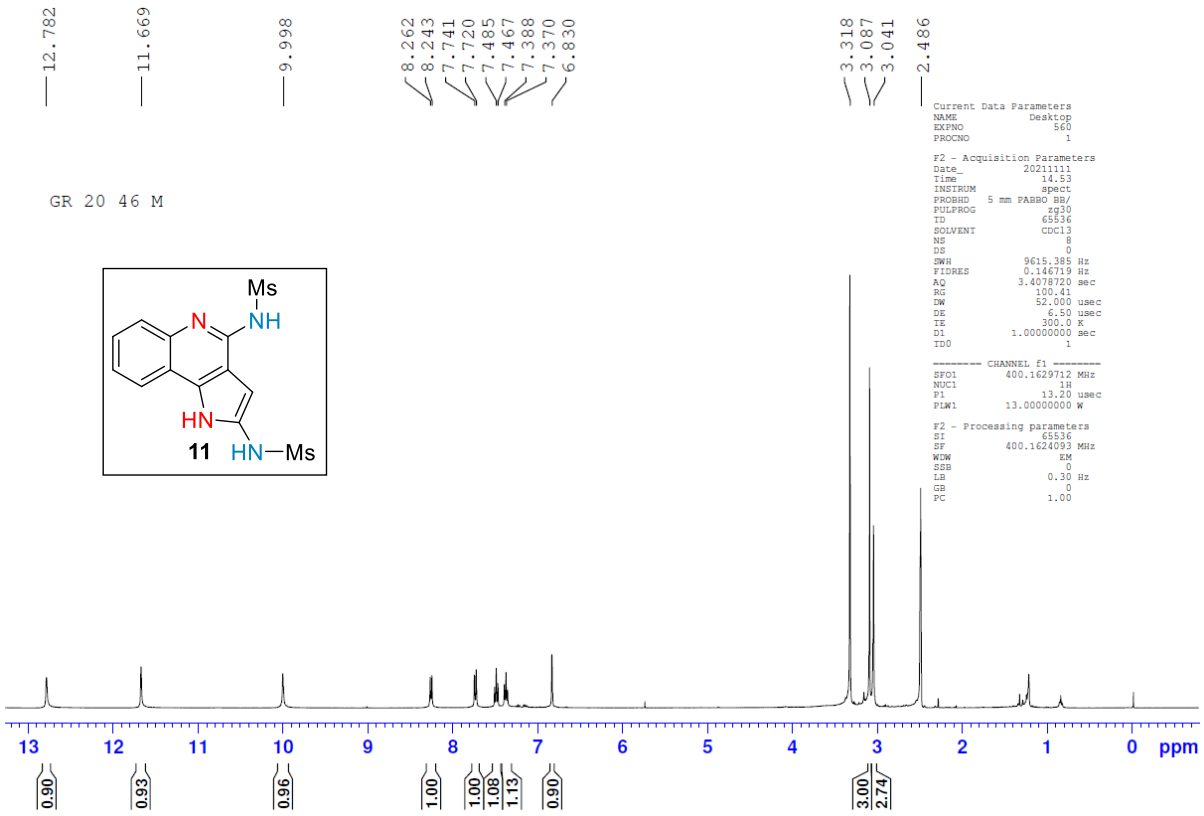
^{1}H NMR, $CDCl_3$, 400 MHz



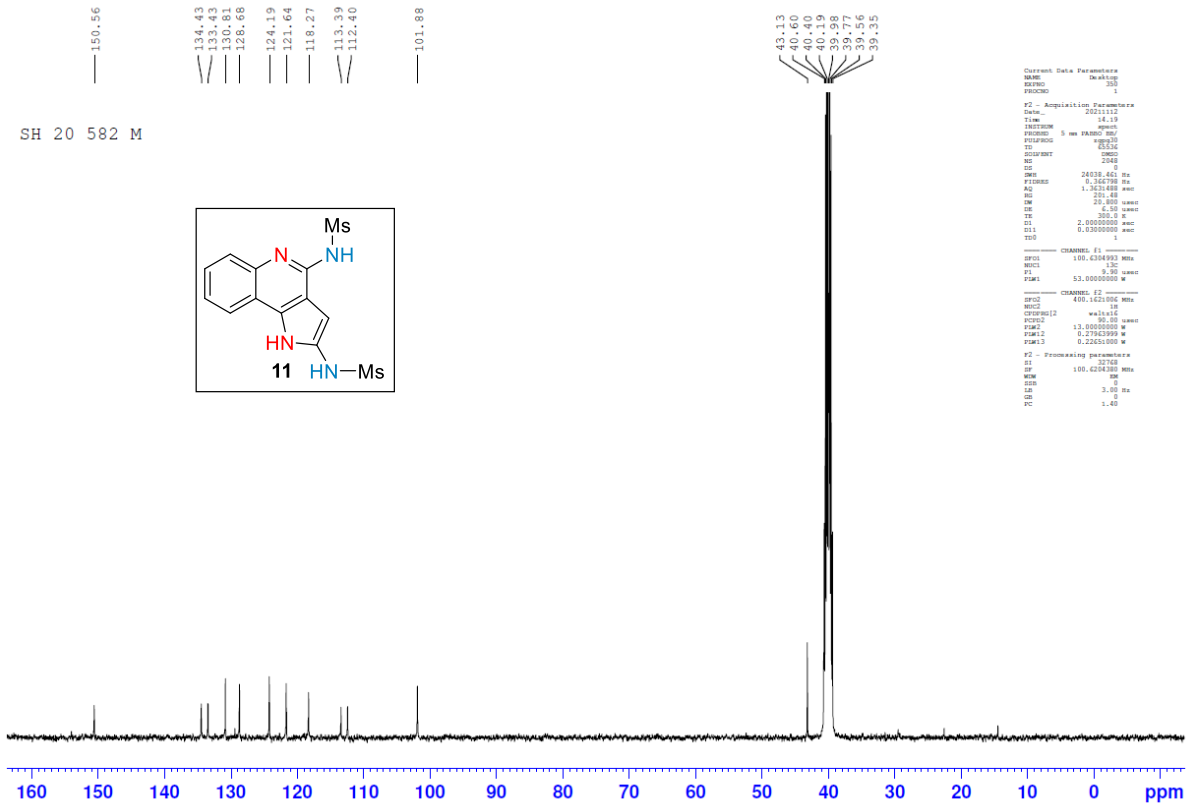
HRMS of compound **10**



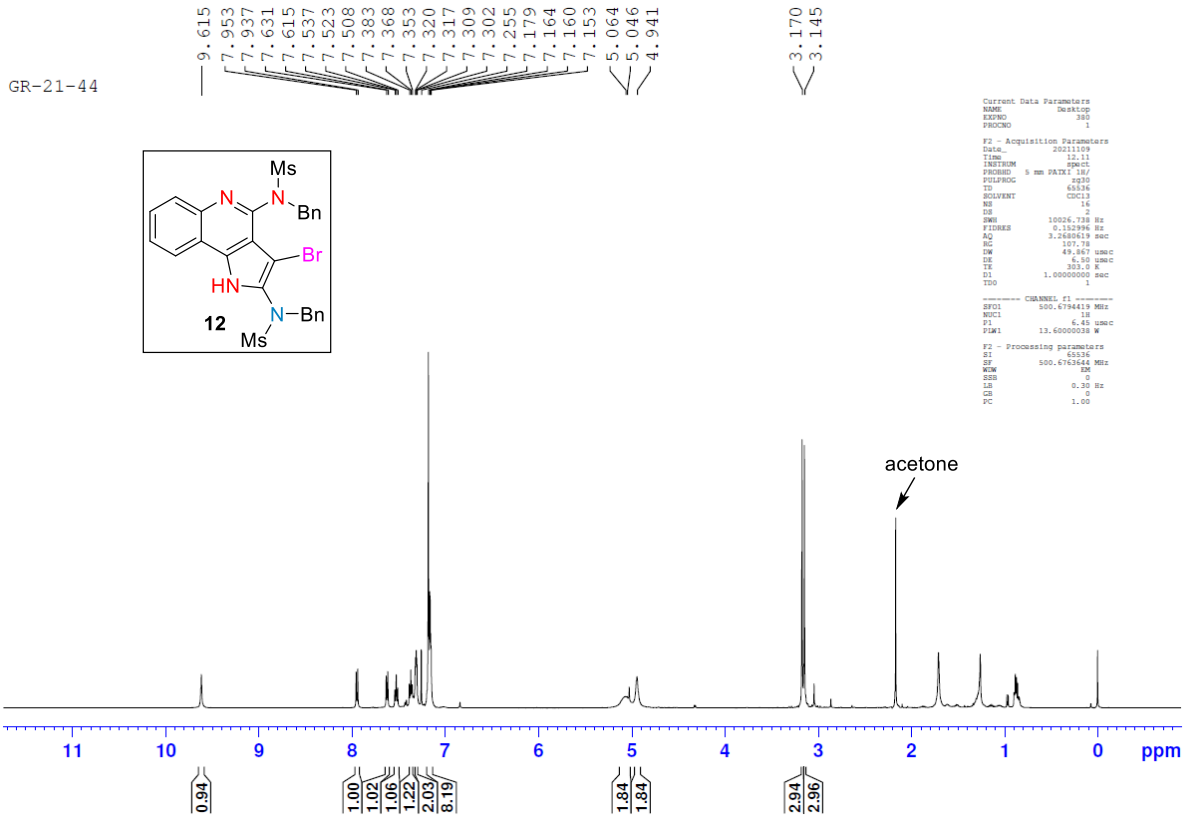
^{1}H NMR, d_6-DMSO, 400 MHz



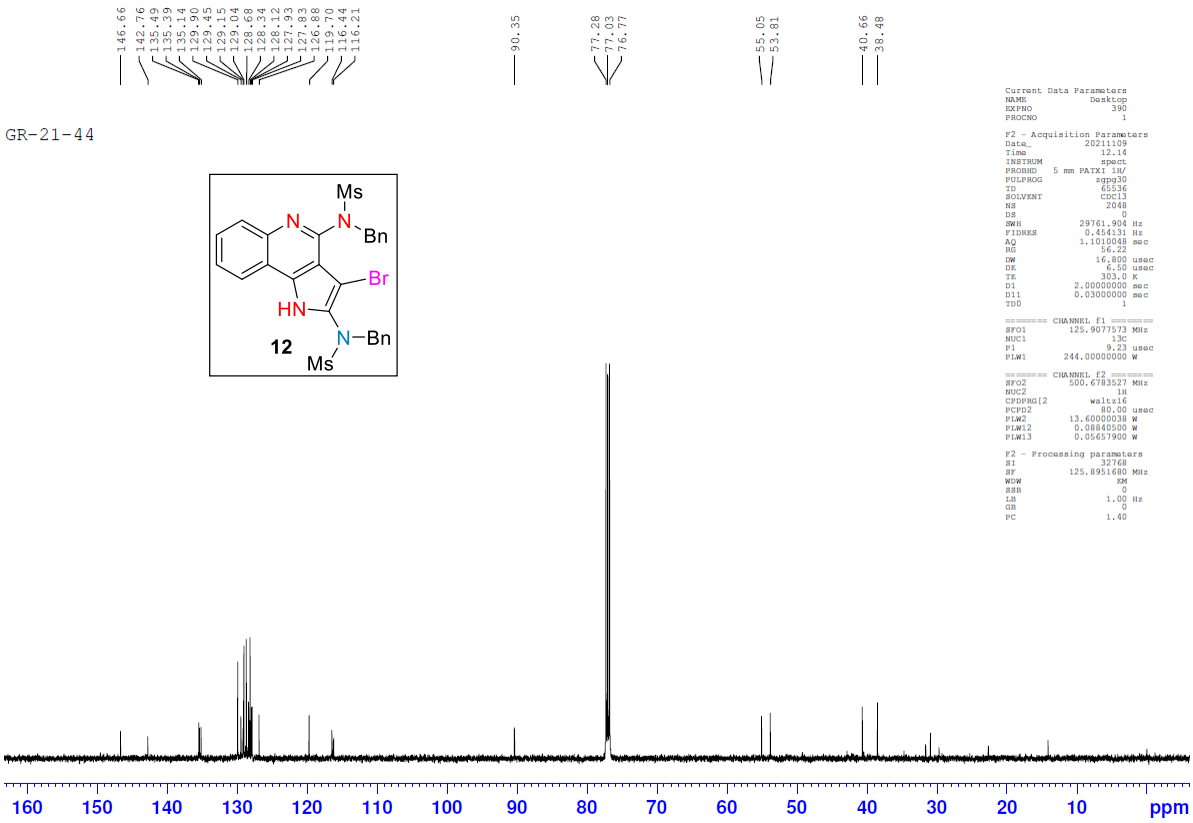
^{1}H NMR, d_6-DMSO, 101 MHz



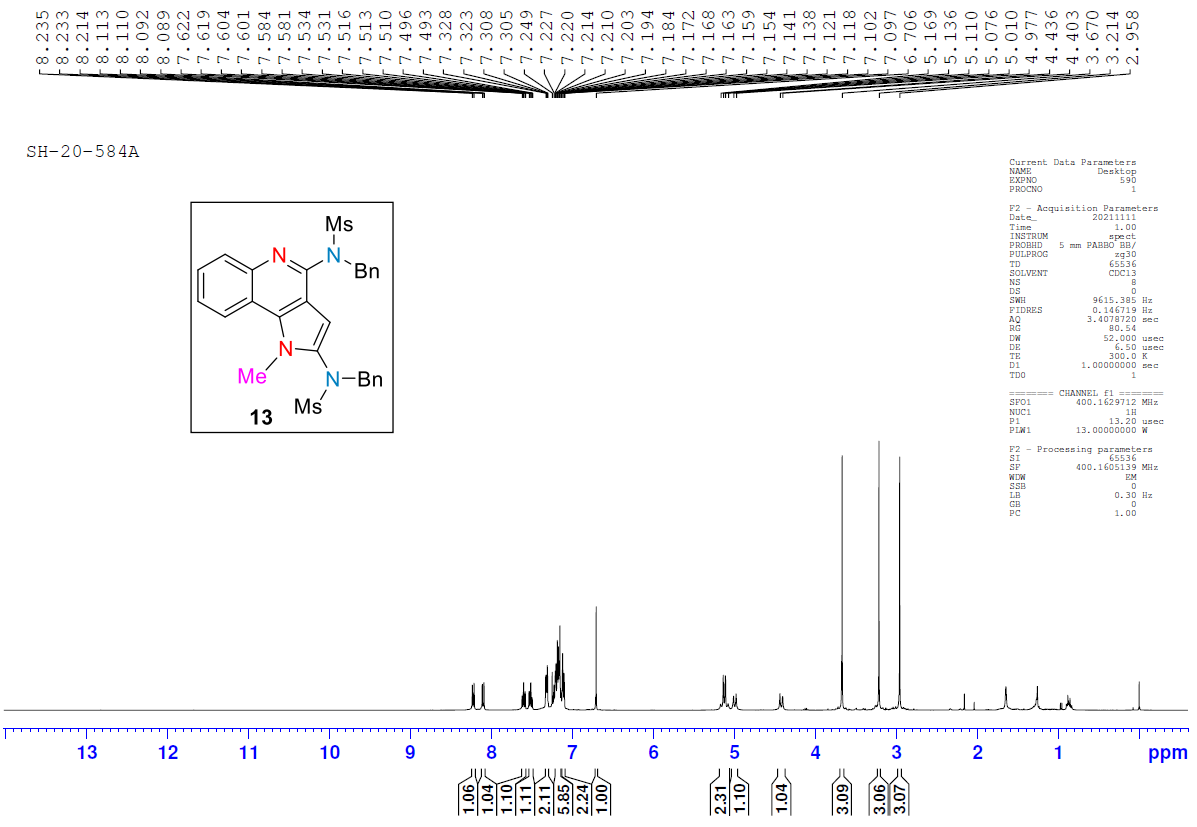
^{1}H NMR, $CDCl_3$, 500 MHz



^{13}C NMR, $CDCl_3$, 125 MHz



^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz