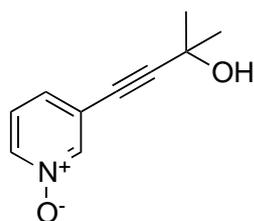


Preparation and characterization of selenopheno[2,3-*b*]pyridine *N*-oxides

**Pavel Arsenyan, Jelena Vasiljeva, Sergey Belyakov, Marina Petrova
and Edvards Liepinsh**

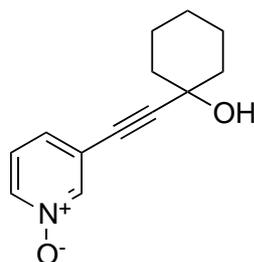
Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using MERCK Silica gel 60 F254 plates and visualized by UV (254 nm) fluorescence. ZEOCHEM silica gel (ZEOprep 60/35-70 microns – SI23501) was used for column chromatography. ^1H NMR monitoring was run on a Varian-Mercury 400 MHz spectrometer in dioxane at 25°C. The one-dimensional ^1H - and ^{13}C - and two-dimensional ^{13}C - ^1H HMBC, ^{13}C - ^1H HSQC spectra of compounds were recorded on a Varian-Mercury 400 and Varian-MR 400 MHz spectrometers. Spectra were acquired using the standard pulse sequences provided by Varian spectrometer library. The chemical shifts of the hydrogen and carbon atoms are presented in ppm and were indirectly referred to the internal spectrometer reference of Me_4Si in CDCl_3 . ^{77}Se NMR spectra were recorded at 76.36 MHz at 25°C on a Varian MR 400 MHz spectrometer and were indirectly referred to the internal spectrometer reference of Me_2Se in C_6D_6 . ^{15}N NMR spectra were recorded at 25°C on a Varian UNITY INOVA 600 MHz spectrometer equipped with a cryoprobe. The ^{15}N spectra were recorded at 60.81 MHz, using HSQC technique with pulsed-field gradients. The magnetization from ^1H to ^{15}N in HSQC spectra were transferred from 3,5-pyridine protons to nitrogen using coupling constants $^n\text{J}(^1\text{H}, ^{15}\text{N}) = 3$ Hz. ^{15}N spectra were indirectly referenced to the internal spectrometer reference liquid ammonia. The melting points were determined on a “Digital melting point analyser” (Fisher), and the results are given without correction. Diffraction data were collected on a Nonius KappaCCD diffractometer using graphite monochromated Mo- $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The crystal structures were solved by direct methods and refined by full-matrix least squares. Dioxane was dried over sodium; CH_2Cl_2 , CHCl_3 and CCl_4 were dried over CaH_2 . 3-Ethynylpyridines were prepared from 3-bromopyridine using Sonogashira reaction conditions. Oxidation has been done according to [D. H. Bremner, K. R. Sturrock, G. Wishart, S. R. Mitchell, S. M. Nicoll and G. Jones, *Synth. Commun.*, 1997, **27**, 1535-1542].

3-(3-Hydroxy-3-methylbut-1-ynyl)pyridine 1-oxide (3a)



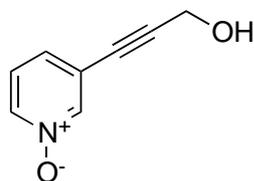
Yield: 77%, mp = 138-140° C. ¹H NMR (DMSO-d₆, 400 MHz) δ (ppm): 1.46 (s, 6H, CH₃), 5.60 (br s, 1H, OH), 7.32-7.35 (m, 1H, 6-CH), 7.38-7.42 (m, 1H, 2-CH), 8.19-8.23 (m, 2H, 4,5-CH). ¹³C NMR (DMSO-d₆, 100.6 MHz) δ (ppm): 31.1, 63.5, 75.2, 100.3, 122.2, 126.5, 127.5, 138.7, 139.9. LC-MS *m/z* 177 [M]. Anal. Calcd for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.61; H, 6.02; N, 8.11.

1-(1-Oxidopyrid-3-yl)-1-ethynylcyclohexanol (3b)



Yield: 50%. ¹H NMR (CDCl₃/TMS, 400 MHz,) δ (ppm): 1.21-1.31 (m, 1H, cyclohexane), 1.42-1.54 (m, 3H, cyclohexane), 1.62-1.75 (m, 4H, cyclohexane), 1.93-1.98 (m, 2H, cyclohexane), 7.05 (br s, 1H, OH), 7.38-7.41 (m, 1H, 6-CH), 7.49-7.51 (m, 1H, 2-CH), 8.33-8.35 (m, 1H, 5-CH), 8.40-8.42 (m, 1H, 4-CH). ¹³C NMR (100.6 MHz, CDCl₃/TMS) δ (ppm): 23.0, 24.9, 39.3, 68.4, 101.0, 123.9, 126.2, 133.4, 138.5, 141.2. LC-MS *m/z* 177 [M]. Anal. Calcd for C₁₃H₁₅NO₂: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.59; H, 6.75; N, 6.68.

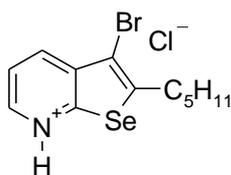
3-(1-Oxidopyrid-3-yl)prop-2-yn-1-ol (3c)



Yield: 70%. ¹H NMR (DMSO-d₆, 400 MHz) δ (ppm): 4.32 (d, *J* = 5.4 Hz, 2H, CH₂), 5.46 (t, *J* = 5.8 Hz, 1H, OH), 7.36-7.43 (m, 2H, 2,6-CH), 8.22 (dt, *J* = 1.7 Hz, *J* = 6.0 Hz, 1H, 5-CH), 8.27-8.28 (m, 1H, 4-CH). ¹³C NMR (DMSO-d₆, 100.6 MHz) δ (ppm): 49.2, 78.2, 94.3, 122.0, 126.6, 127.6, 138.9, 140.1. LC-MS *m/z* 149 [M]. Anal. Calcd for C₈H₇NO₂: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.26; H, 4.56; N, 9.45.

3-Bromo-2-pentylselenopheno[2,3-*b*]pyridinium hydrochloride (2)

To the solution of selenium dioxide (0.444 g, 4.00 mmol) in HBr (0.45 ml) 2-(hept-1-yn-1-yl)pyridine **1** (1.00 mmol) in dioxane (10 ml) was added and the mixture was stirred at room temperature for 48 h. After the consumption of substrate (LC-MS), ethyl acetate (100 ml) and water NaHCO₃ were added (to pH 9). The organic phase was separated, washed with water (2x50 ml) and dried over anhydrous Na₂SO₄. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using dichloromethane:ethyl acetate (gradient elution 1:0 to 10:1) as eluent. Hydrochloride **2** was precipitated as the yellowish crystals after addition of HCl to the solution in CH₂Cl₂.

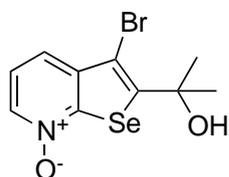


Yield: 6%, mp = 102-103 °C. ^1H NMR (DMSO- d_6 , 400 MHz) δ (ppm): 0.87 (t, $J = 7.2$ Hz, 3H, CH_3), 1.30-1.40 (m, 4H, CH_2), 1.65-1.72 (m, 2H, CH_2), 2.99 (t, $J = 7.2$ Hz, 2H, CH_2), 7.56 (dd, $J = 4.5$ Hz, $J = 8.0$ Hz, 1H, 5- CH), 8.04 (dd, $J = 1.5$ Hz, $J = 8.0$ Hz, 1H, 4- CH), 8.55 (dd, $J = 1.5$ Hz, $J = 4.5$ Hz, 1H, 6- CH). ^{13}C NMR (DMSO- d_6 , 100.6 MHz) δ (ppm): 13.7, 21.7, 30.1, 30.5, 31.6, 104.2, 121.1, 131.9, 134.5, 145.9, 146.7, 160.1. LC-MS m/z 333 [M]. Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{ClBrNSe}$: C, 39.07; H, 4.07; N, 3.80. Found: C, 38.96; H, 3.92; N, 3.67.

General procedure for the preparation of selenopheno[2,3-*b*]pyridine *N*-oxides 4a-c.

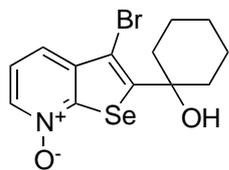
Ethynylpyridine *N*-oxide **3** (1.00 mmol) and cyclohexene (0.05 g, 0.60 mmol) in dioxane was added dropwise to the mixture of SeO_2 (0.133 g, 1.20 mmol) in HBr (0.6 ml). The reaction mixture was stirred at room temperature for 24-48 h and controlled by TLC. After the disappearing of the starting material, ethyl acetate (100 ml) and water NaHCO_3 were added (to pH 9). The organic phase was separated, washed with water (2x50 ml) and dried over anhydrous Na_2SO_4 . After evaporation of the solvent, crude product was purified by column chromatography on silica gel using dichloromethane–ethyl acetate (gradient elution 1:0 to 20:1) as eluent. Dibromo derivative **5** was isolated and characterized from the experiment with the absence of cyclohexene.

3-Bromo-2-(2-hydroxy-2-methylethyl)selenopheno[2,3-*b*]pyridine *N*-oxide (4a)



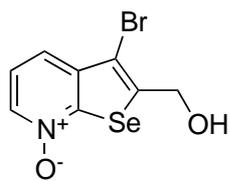
Yield: 52 %, mp > 200° C. ^1H NMR (DMSO- d_6 , 400 MHz) δ (ppm): 1.82 (s, 6H, CH_3), 3.56 (br s, 1H, OH), 7.38 (dd, $J = 6.2$ Hz, $J = 8.0$ Hz, 1H, 6- CH), 7.64 (dd, $J = 0.8$ Hz, $J = 8.0$ Hz, 1H, 5- CH), 8.26 (dd, $J = 0.8$ Hz, $J = 6.2$ Hz, 1H, 4- CH). ^{13}C NMR (DMSO- d_6 , 100.6 MHz) δ (ppm): 28.4, 74.4, 98.6, 122.3, 130.1, 135.9, 141.8, 150.2, 161.1. LC- MS m/z 335 [M]. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{BrNO}_2\text{Se}$: C, 35.85, H, 3.01, N, 4.18. Found: C, 35.74, H, 2.97, N, 4.17.

3-Bromo-2-(1-hydroxycyclohexyl)selenopheno[2,3-*b*]pyridine *N*-oxide (4b)



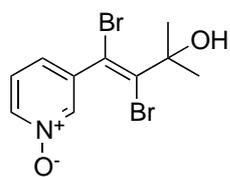
Yield: 28%, mp > 200° C. ^1H NMR (DMSO- d_6 , 400 MHz) δ (ppm): 1.21-1.33 (m, 1H, cyclohexane), 1.57-1.75 (m, 7H, cyclohexane), 2.34-2.42 (m, 2H, cyclohexane), 7.53 (dd, $J = 4.6$ Hz, $J = 8.0$ Hz, 1H, 6- CH), 8.04 (dd, $J = 1.4$ Hz, $J = 8.0$ Hz, 1H, 5- CH), 8.55 (dd, $J = 1.4$ Hz, $J = 4.6$ Hz, 1H, 4- CH). ^{13}C NMR (DMSO- d_6 , 100.6 MHz) δ (ppm): 21.0, 24.6, 34.1, 73.7, 96.9, 120.7, 131.7, 136.8, 146.5, 159.3, 159.9. LC-MS m/z 375 [M]. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{BrNO}_2\text{Se}$: C, 41.62; H, 3.76; N, 3.73. Found: C, 41.43; H, 3.67; N, 3.76.

3-Bromo-2-(hydroxymethyl)selenopheno[2,3-*b*]pyridine *N*-oxide (4c)



Yield: 15%, mp = 147-149° C. ¹H NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 4.74 (d, J = 5.5 Hz, 2H, CH₂), 6.40 (t, J = 5.5 Hz, 1H, OH), 7.58-7.62 (m, 1H, 6-CH), 7.66 (dd, J = 1.0 Hz, J = 8.2 Hz, 1H, 5-CH), 8.42 (dd, J = 1.0 Hz, J = 6.1 Hz, 1H, 4-CH). ¹³C NMR (DMSO-*d*₆, 100.6 MHz) δ (ppm): 60.1, 99.6, 120.9, 123.6, 134.0, 138.0, 147.0, 151.7. LC-MS m/z 333 [M]. Anal. Calcd for C₈H₆BrNO₂Se: C, 31.30; H, 1.97; N, 4.56. Found: C, 31.19; H, 1.78; N, 4.47.

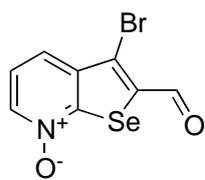
3,4-Dibromo-2-methyl-4-(1-oxidopyrid-3-yl)-but-3-en-2-ol (5)



Yield: 52%, mp = 160-161° C. ¹H NMR (CDCl₃/TMS, 400 MHz) δ (ppm): 1.72 (s, 6H, 2CH₃), 3.36 (s, 1H, OH), 7.15-7.18 (m, 1H, 6-CH), 7.27-7.31 (m, 1H, 2-CH), 8.12-8.14 (m, 2H, 4,5-CH). ¹³C NMR (DMSO-*d*₆, 100.6 MHz) δ (ppm): 29.5, 76.0, 106.5, 125.9, 134.8, 138.67, 138.68, 139.2, 142.6. Anal. Calcd for C₁₀H₁₁Br₂NO₂: C, 35.64; H, 3.29; N, 4.16. Found: C, 35.63; H, 3.23; N, 4.11.

3-Bromoselenopheno[2,3-*b*]pyridine-2-carbaldehyde *N*-oxide (6)

Solution of 3-bromo-2-(hydroxymethyl)selenopheno[2,3-*b*]pyridine *N*-oxide **4c** (0.10 g, 0.32 mmol) in dry CH₂Cl₂ was added to the suspension of MnO₂ (0.11 g, 1.30 mmol) in dry CH₂Cl₂ (20 ml) at 0° C. Then the mixture was left warmed to room temperature and stirred for 12 h. After the consumption of the reaction (controlled by TLC), the mixture was filtered through the short pad of silica gel. The solvent was evaporated to leave a pure product as green-yellow needles.



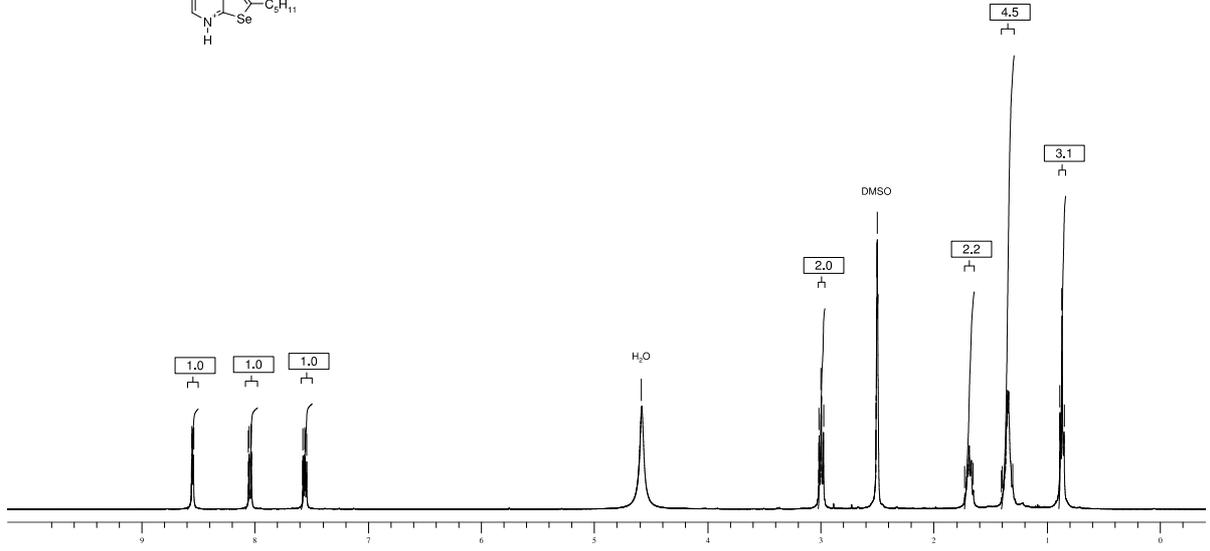
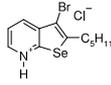
Yield: 80%, mp = 147-149° C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.47 (dd, J = 4.6 Hz, J = 8.0 Hz, 1H, 6-CH), 8.30 (dd, J = 1.7 Hz, J = 8.0 Hz, 1H, 5-CH), 8.68 (dd, J = 1.7 Hz, J = 4.6 Hz, 1H, 4-CH), 10.21 (s, 1H, CHO). ¹³C NMR (CDCl₃, 100.6 MHz) δ (ppm): 117.3, 121.1, 134.4, 135.2, 140.4, 150.7, 163.6, 186.0. ⁷⁷Se NMR (CDCl₃, 76.36 MHz) δ (ppm): 575.9. LC-MS m/z 305 [M]. Anal. Calcd for C₈H₄BrNO₂Se: C, 31.51; H, 1.32; N, 4.59. Found: C, 31.42; H, 1.27; N, 4.42.

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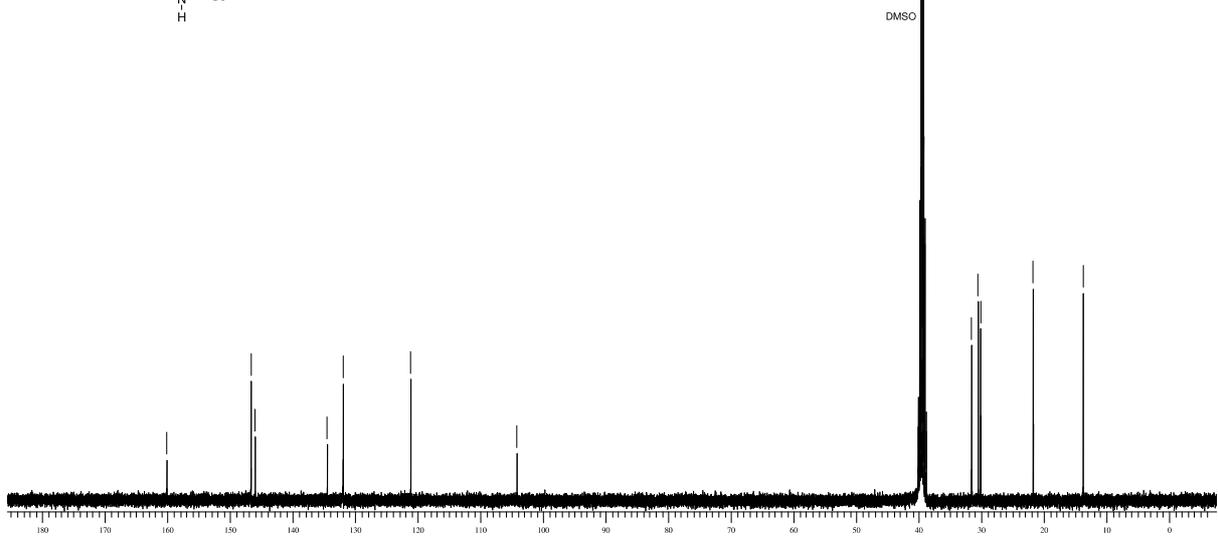
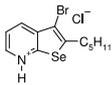
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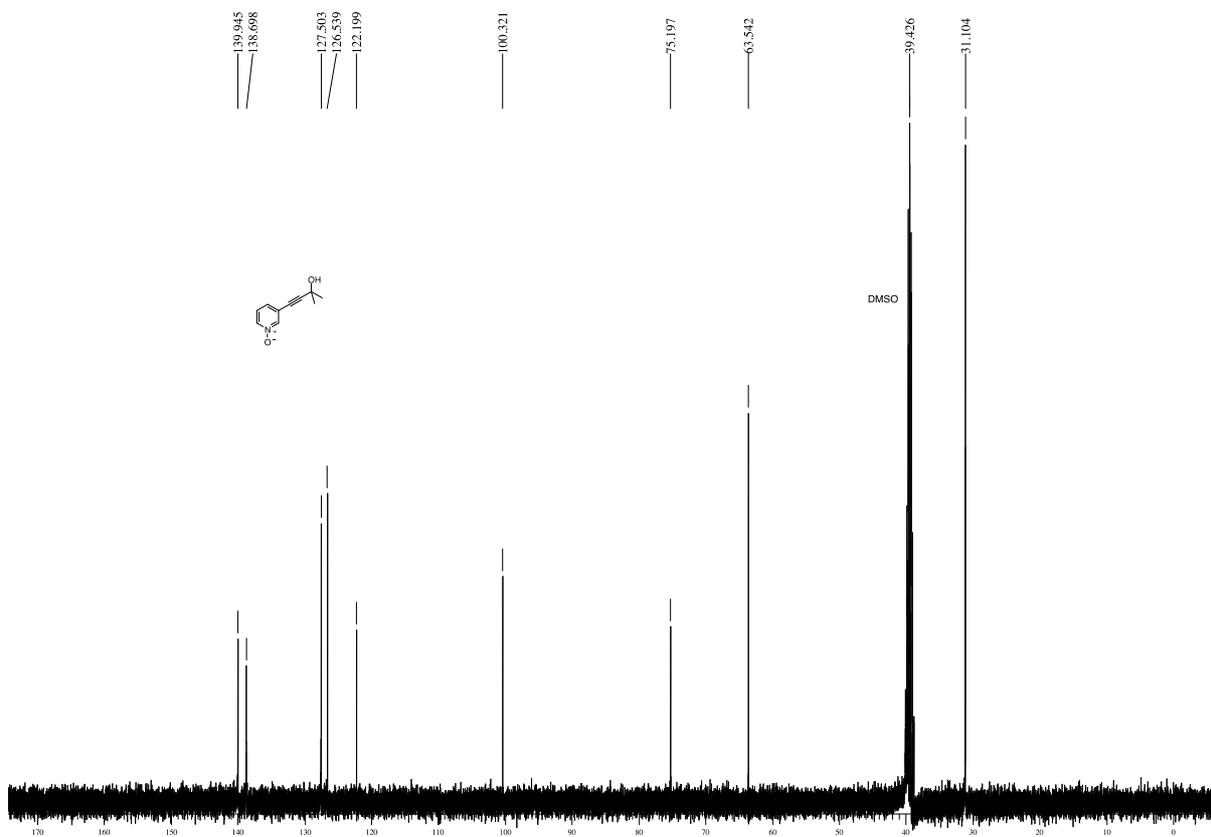
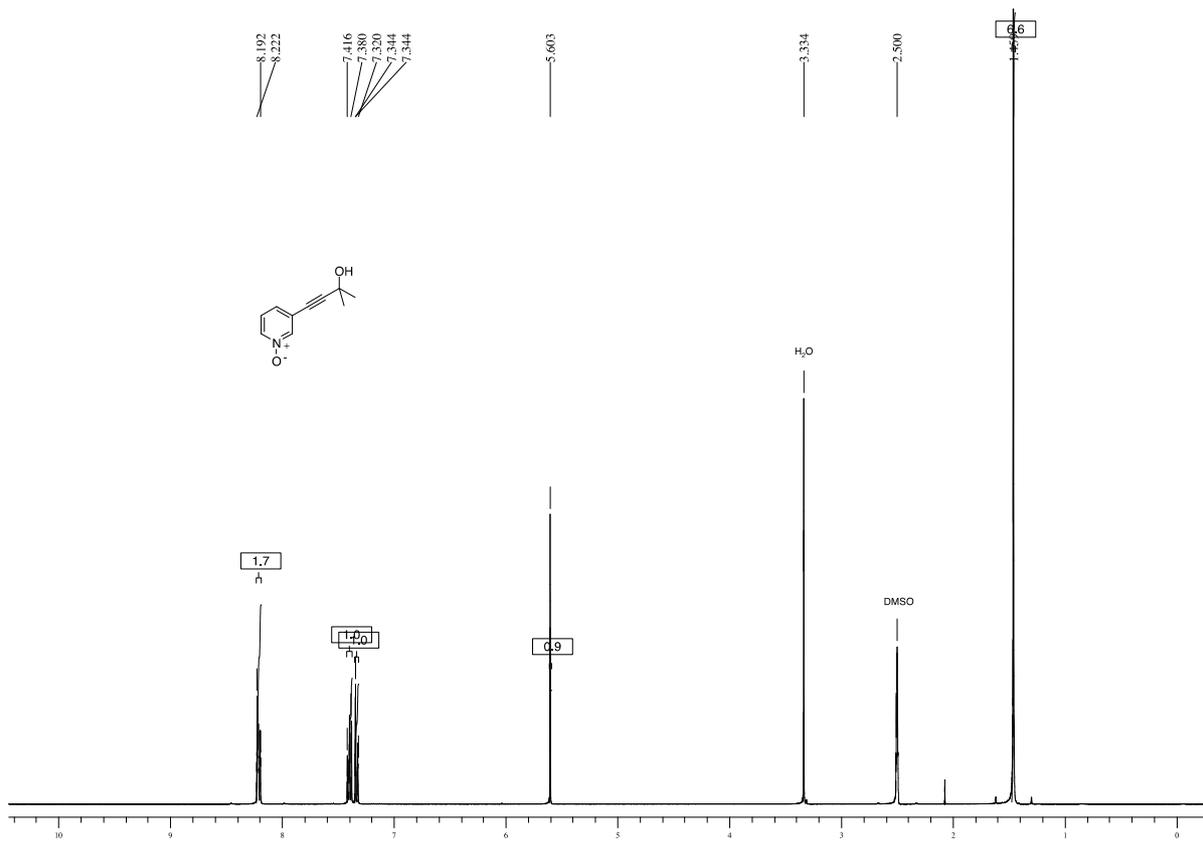
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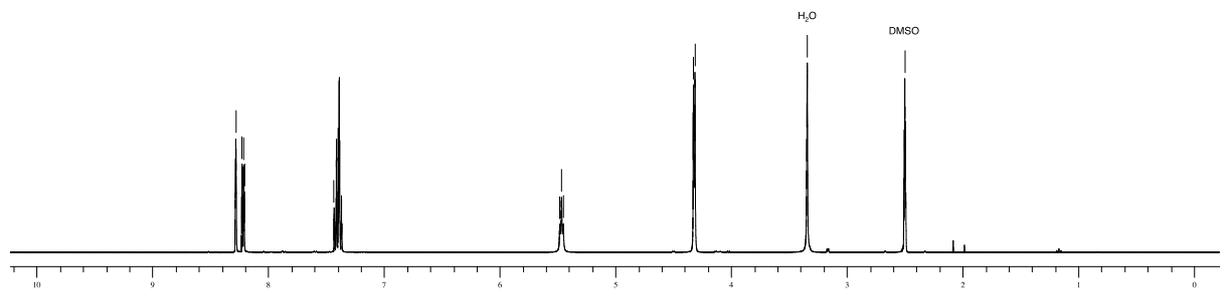
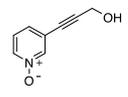
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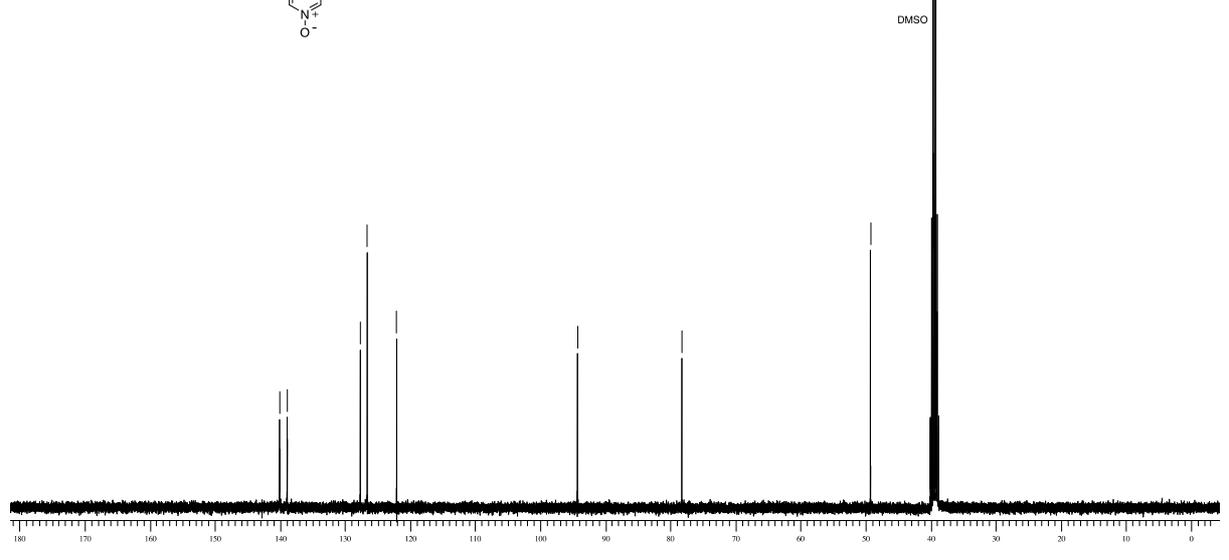
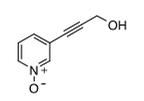
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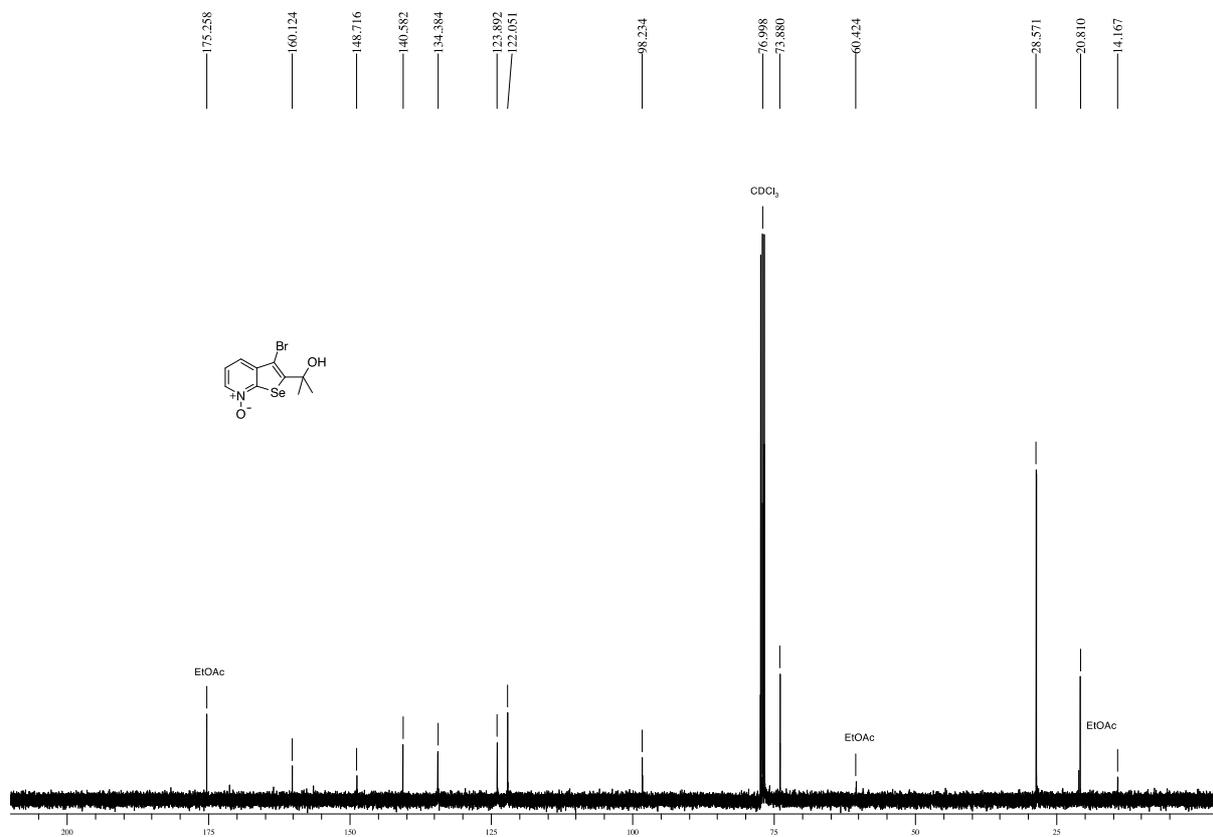
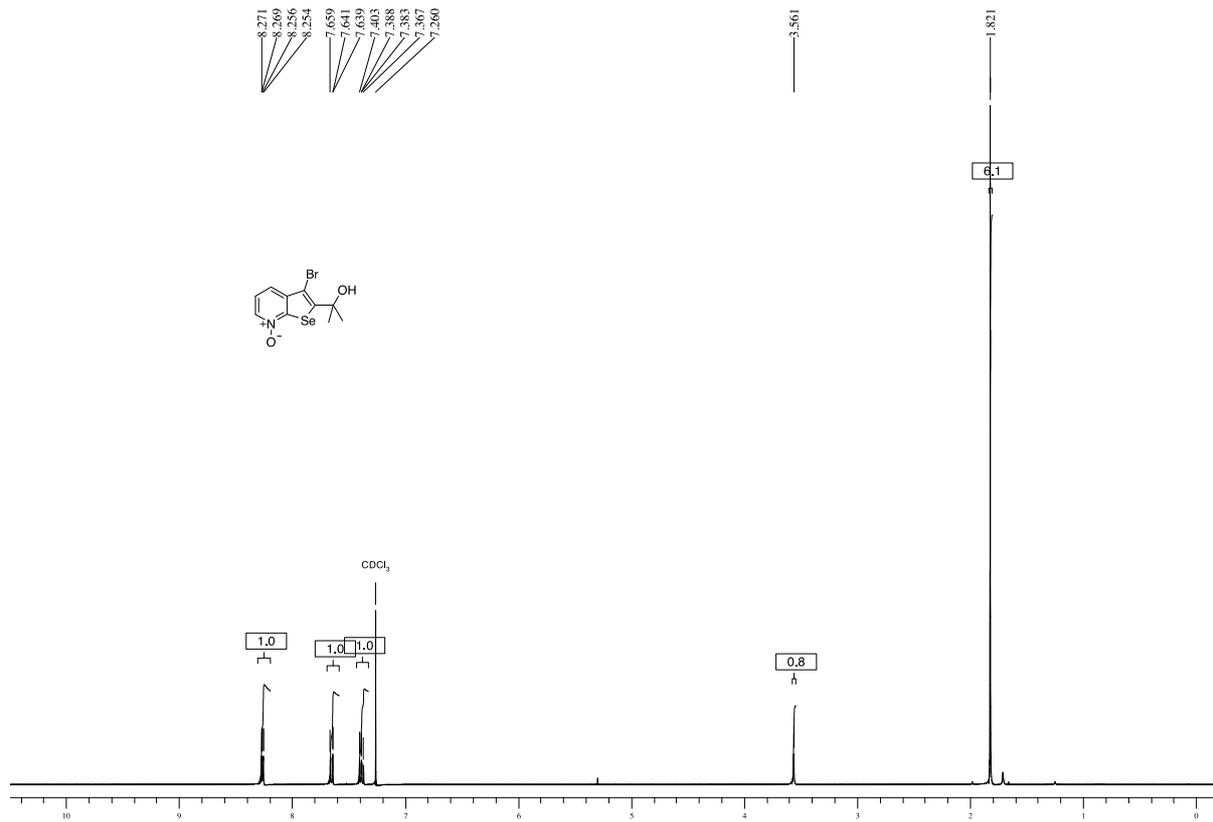
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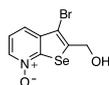
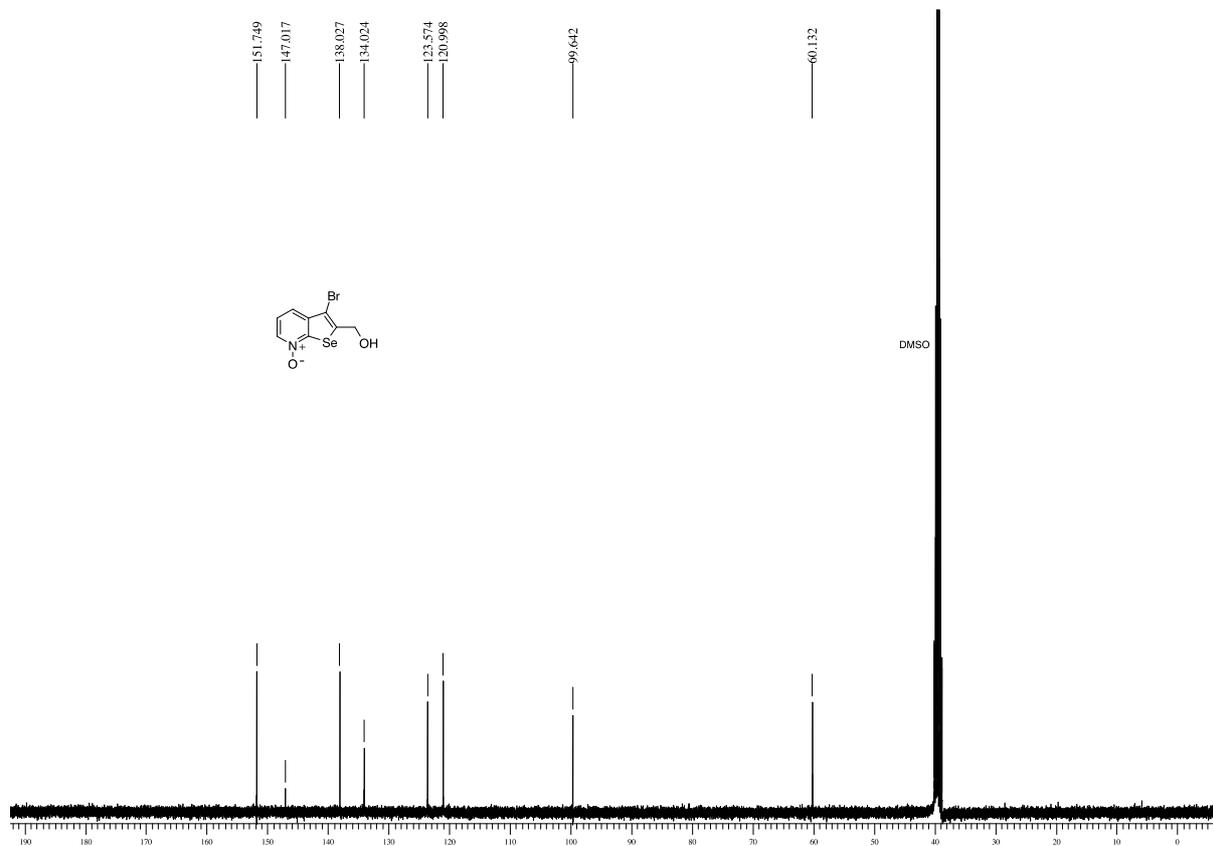
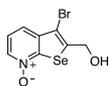
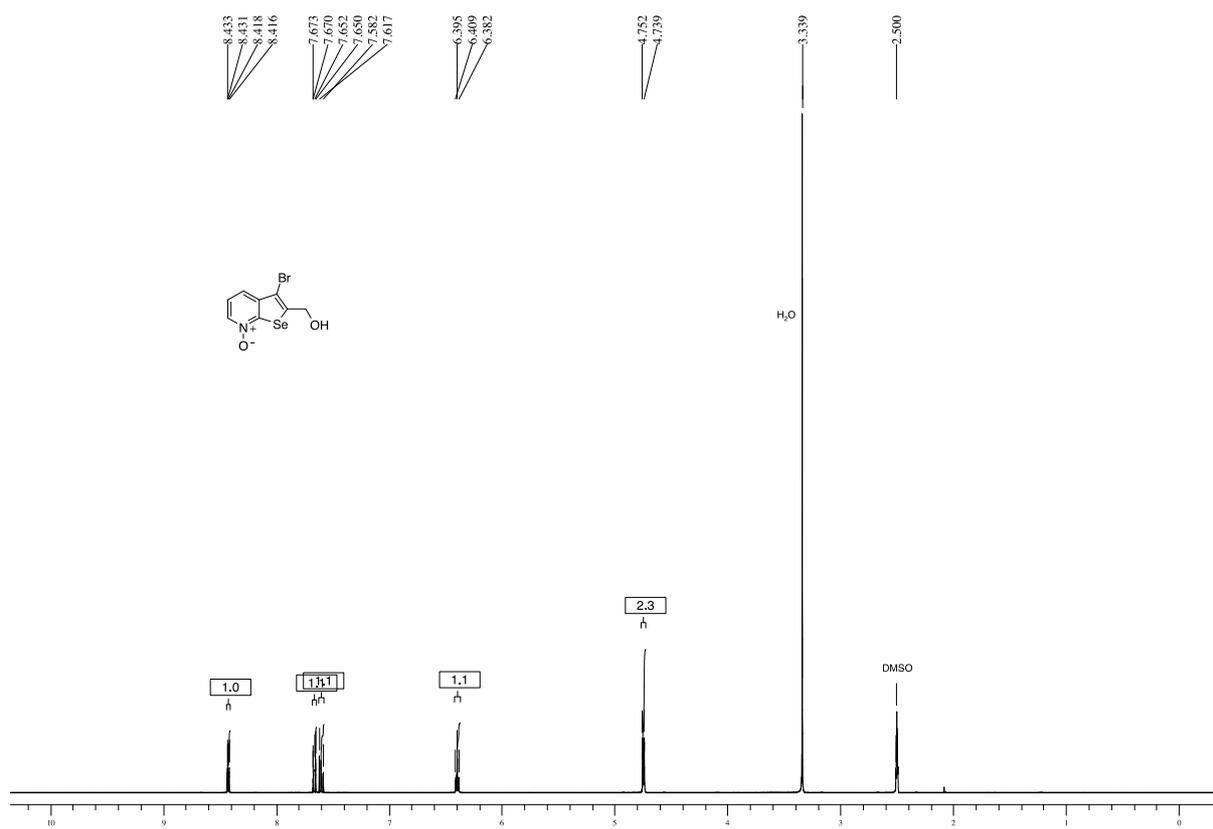
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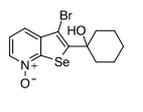
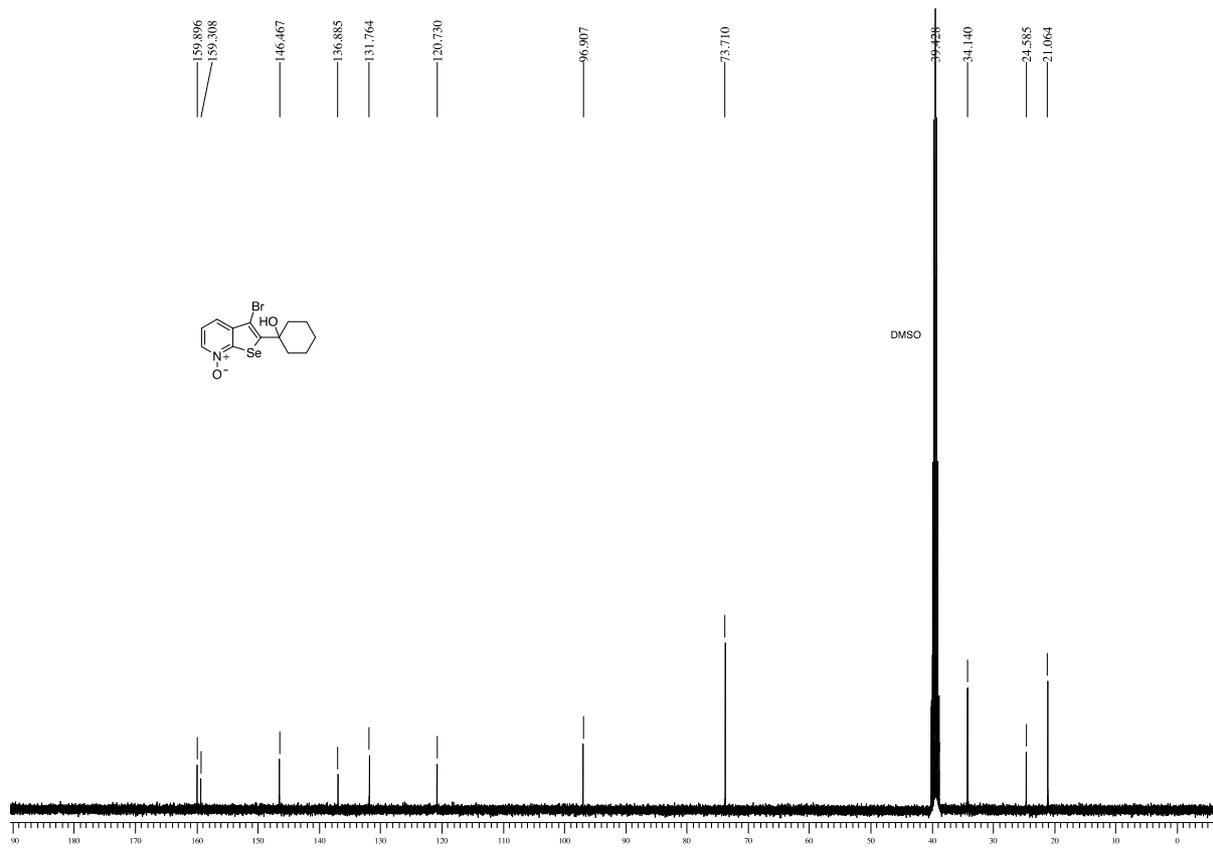
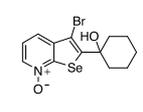
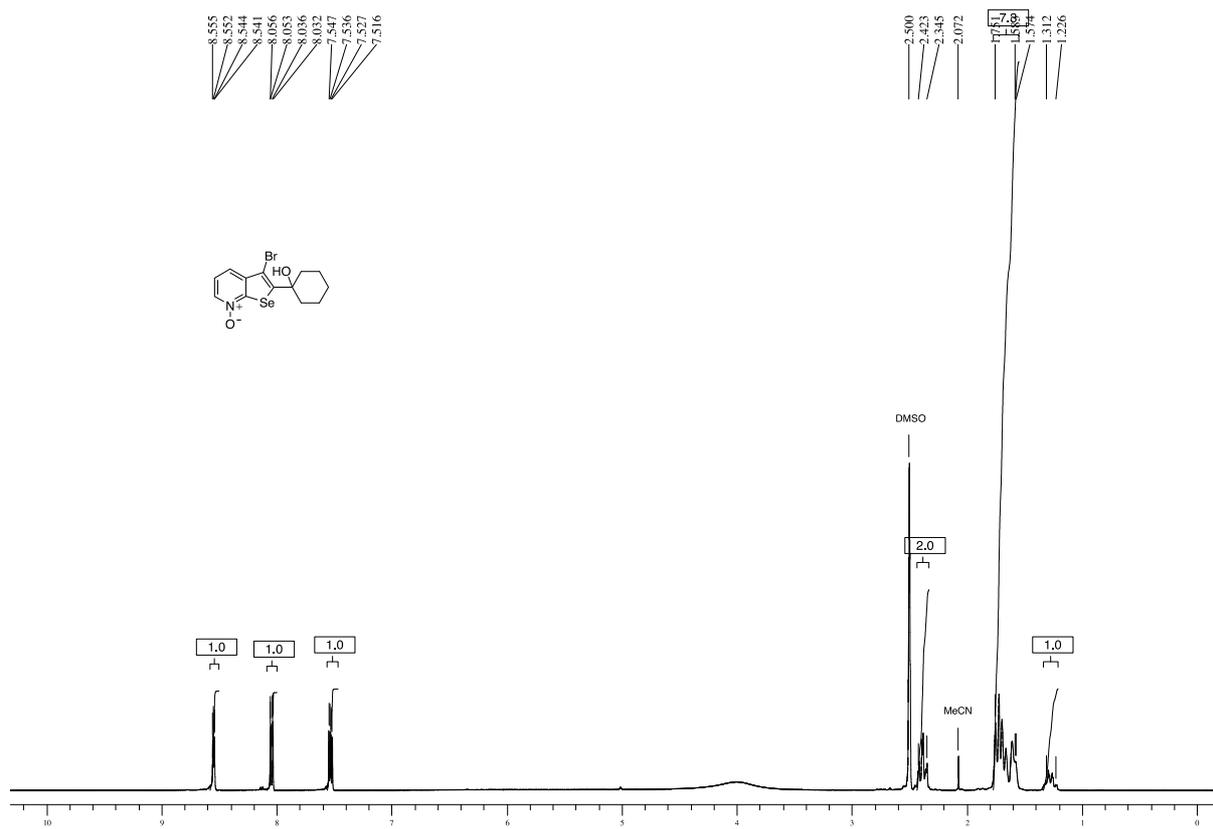
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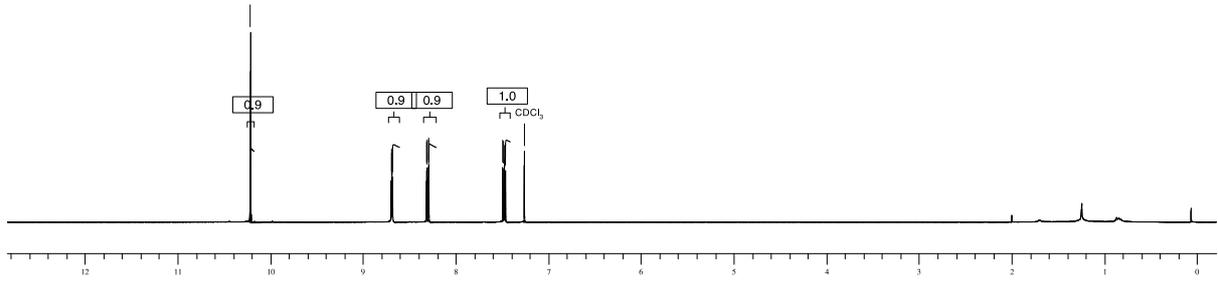








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