Diastereoselective Synthesis of Tetrahydropyrrolo[1,2-*d*]oxadiazoles from Functionalized Δ^1-Pyrrolines and *in situ* Generated Nitrile Oxides

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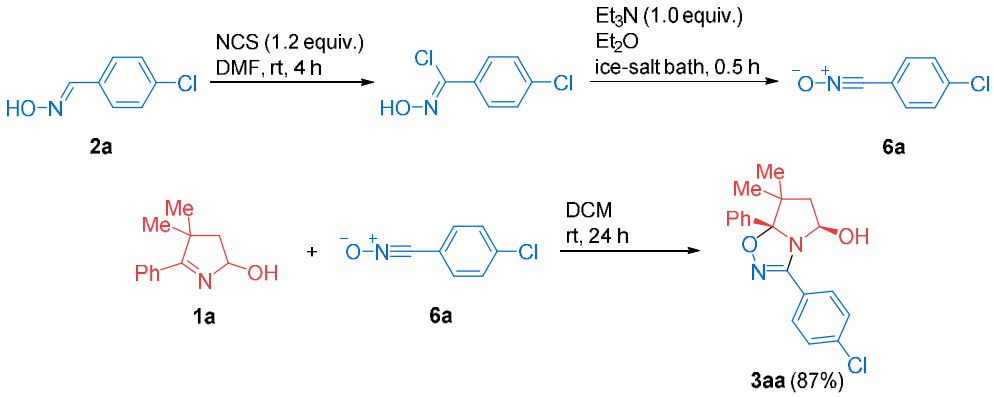
Table of contents

Reaction of pyrroline 1a with nitrile oxide 6a

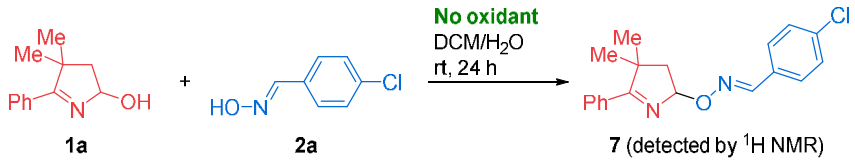


A 5-mL round-bottom flask with a stir bar was charged with aldoxime **2a** (155 mg, 1.0 mmol) and DMF (3 mL). Then N-chlorosuccinimide (160 mg, 1.2 mmol) was added, the reaction flask was capped with a glass stopper, and the reaction mixture was stirred at room temperature for 4 h. After the completion of the reaction, the mixture was diluted with water (10 mL), and the water layer was extracted with diethyl ether (3 × 10 mL). The organic layers were combined, washed with water (3 × 10 mL) and dried over $CaCl_2$.

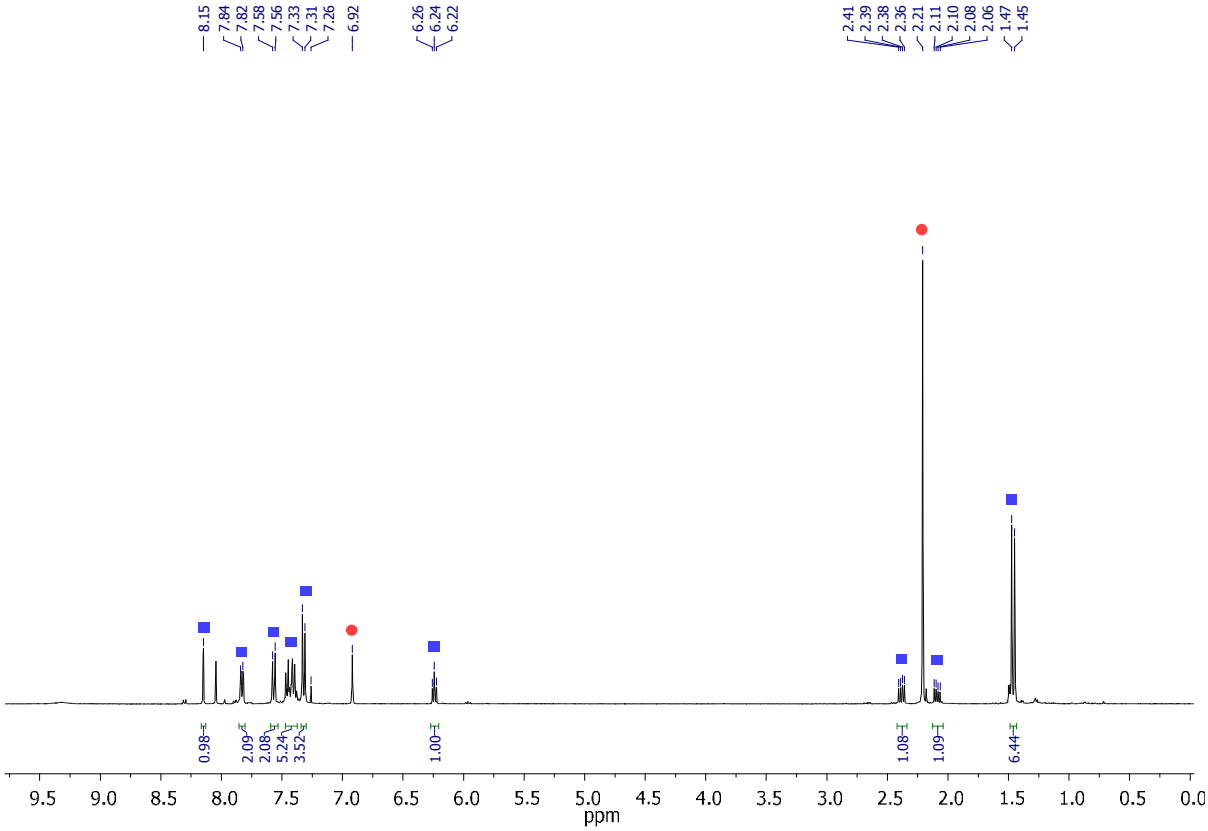
The residue after solvent evaporation without additional purification, 4-chloro-N-hydroxybenzimidoyl chloride (170 mg, 0.9 mmol), was placed in a 25-mL round-bottom flask with a stir bar immersed in an ice-salt bath. Then diethyl ether (10 mL) and triethylamine (91 mg, 0.9 mmol) were sequentially added, and the obtained reaction mixture was stirred for 0.5 h. A white precipitate was filtered off and washed with diethyl ether (2 × 5 mL). Further evaporation of the mother solution under reduced pressure at room temperature afforded nitrile oxide **6a** (132 mg) as an oily solid with acceptable purity.

Thus pre-synthesized nitrile oxide **6a** was dissolved in DCM (3 mL), and pyrroline **1a** (47 mg, 0.25 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. After reaction completion the solvent was evaporated. The residue was analyzed by ^{1}H NMR using durene as an internal standard to reveal the formation of fused 1,2,4-oxadiazoline **3aa** in 87% yield with total diastereoselectivity.

Reaction of pyrroline 1a with aldoxime 2a in the absence of oxidant



Characteristic signals of product **7**: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.84-7.82 (m, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.46-7.40 (m, 3H), 7.32 (d, J = 8.5 Hz, 2H), 6.24 (t, J = 6.5 Hz, 1H), 2.38 (dd, J = 13.2 Hz, J = 6.6 Hz, 1H), 2.09 (dd, J = 13.2 Hz, J = 6.5 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H).



^{1}H NMR Spectrum of crude (400.1 MHz, $CDCl_3$). Characteristic signals of product **7** (blue squares) and signals of internal standard (durene, red circles) are represented.

X-Ray diffraction analysis for 3aa

The determination of the unit cell and the data collection for (*5R*,7aS**)-3-(4-chlorophenyl)-7,7-dimethyl-7a-phenyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazol-5-ol (**3aa**) was performed on a Bruker D8 VENTURE PHOTON 100 CMOS diffractometer with MoK_α radiation (λ = 0.71073) at 293.0(2) K using the ω–φ scan technique. A specimen of **3aa** ($C_{19}H_{19}ClN_2O_2$), approximate dimensions 0.05 mm x 0.15 mm x 0.39 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The integration of the data using a monoclinic unit cell with *P2₁/c* space group yielded a total of 72219 reflections to a maximum θ angle of 26.1° (0.81 Å resolution), of which 7036 were independent (completeness = 100.0%, Rint = 12.68%, Rsig = 5.95%) and 3969 were greater than 2σ(F2). The final cell constants of **a** = 9.286(6) Å, **b** = 21.161(16) Å, **c** = 18.146(13) Å, Z= 4, volume = 3566(4) $Å^3$. Data were corrected for absorption effects using the multi-scan method (SADABS).[1] The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.961 and 0.988. The structure was solved using the Bruker SHELXTL Software Package[2] and refined using Olex2 package.[3] All H atoms were treated by mixed method.

The final anisotropic full-matrix least-squares refinement on F2 with 444 variables converged at R1 = 5.00%, for the observed data and wR2 = 11.72% for all data. The goodness-of-fit was 1.02. The largest peak in the final difference electron density synthesis was 0.23 e-/$Å^3$ and the largest hole was -0.30 e-/$Å^3$. On the basis of the final model, the calculated density was 1.277 g/cm^3 and F(000), 1440 e-.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC) and allocated the deposition numbers CCDC **2220955**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

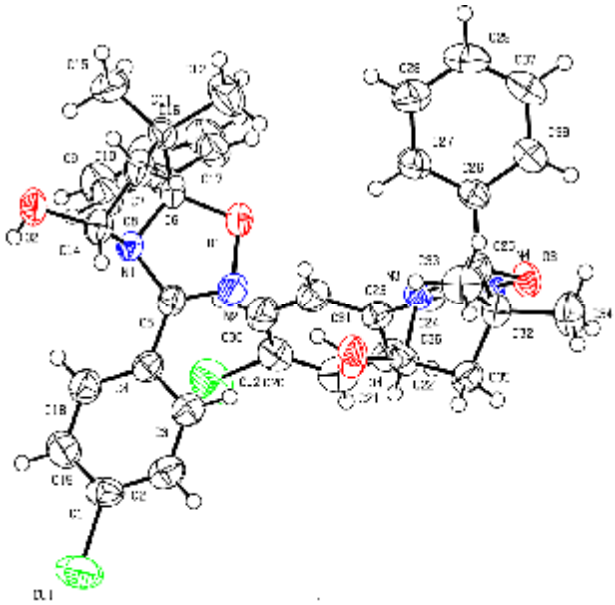


Figure 1. X-ray structure of (*5R*,7aS**)-3-(4-chlorophenyl)-7,7-dimethyl-7a-phenyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazol-5-ol (**3aa**). Thermal ellipsoids set at 50% probability.

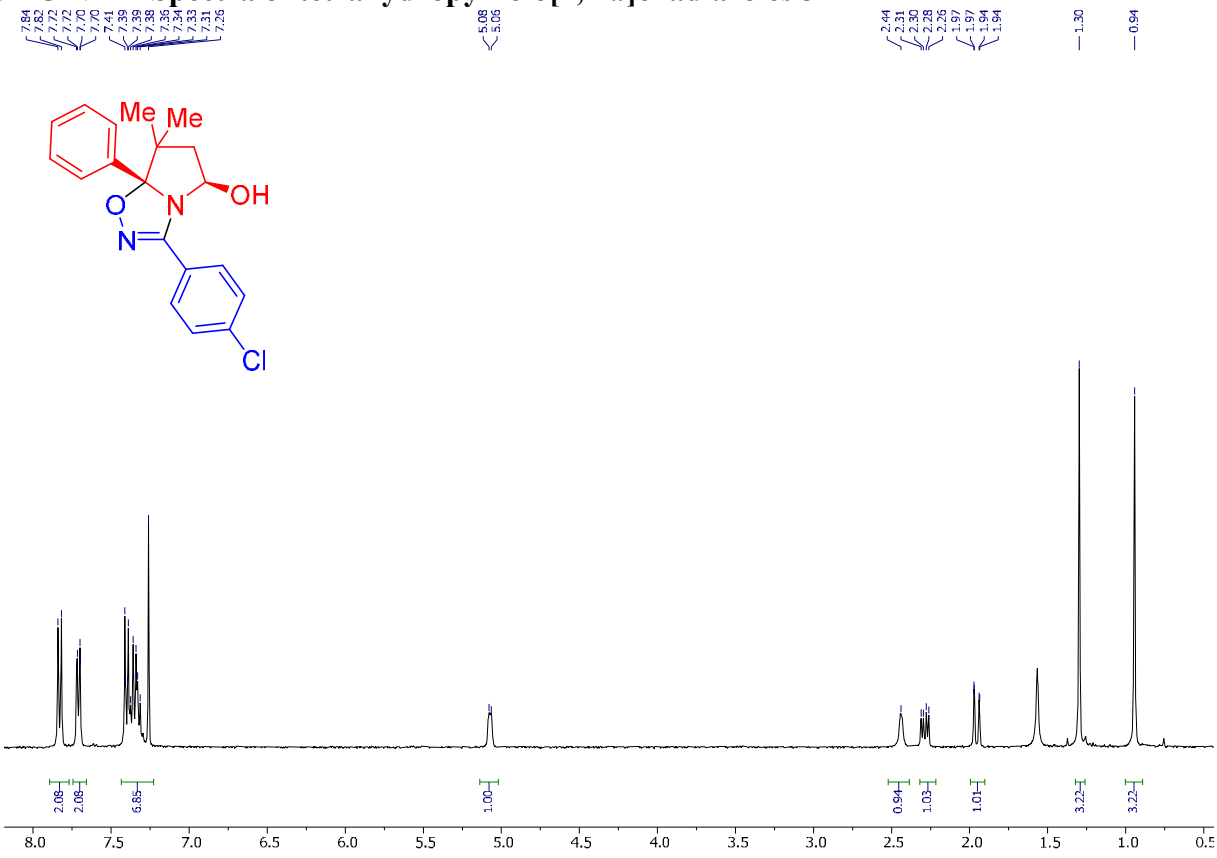
References

1. G. M. Sheldrick, SADABS, Version 2008/1, 2008, Bruker AXS Inc., Germany.

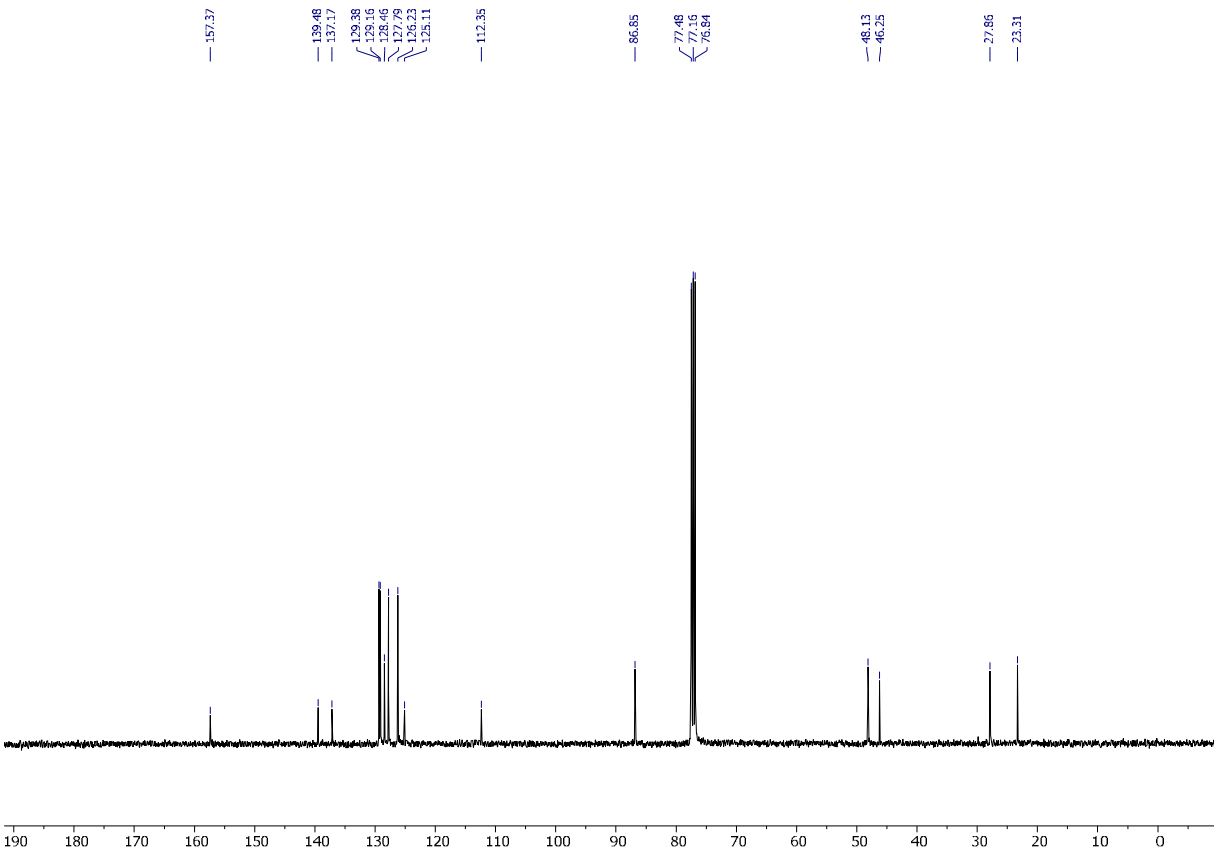
2. G.M. Sheldrick, *Acta Crystallogr.*, 2008, **D64**, 112-122.

3. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.,* 2009, **42,** 339-341.

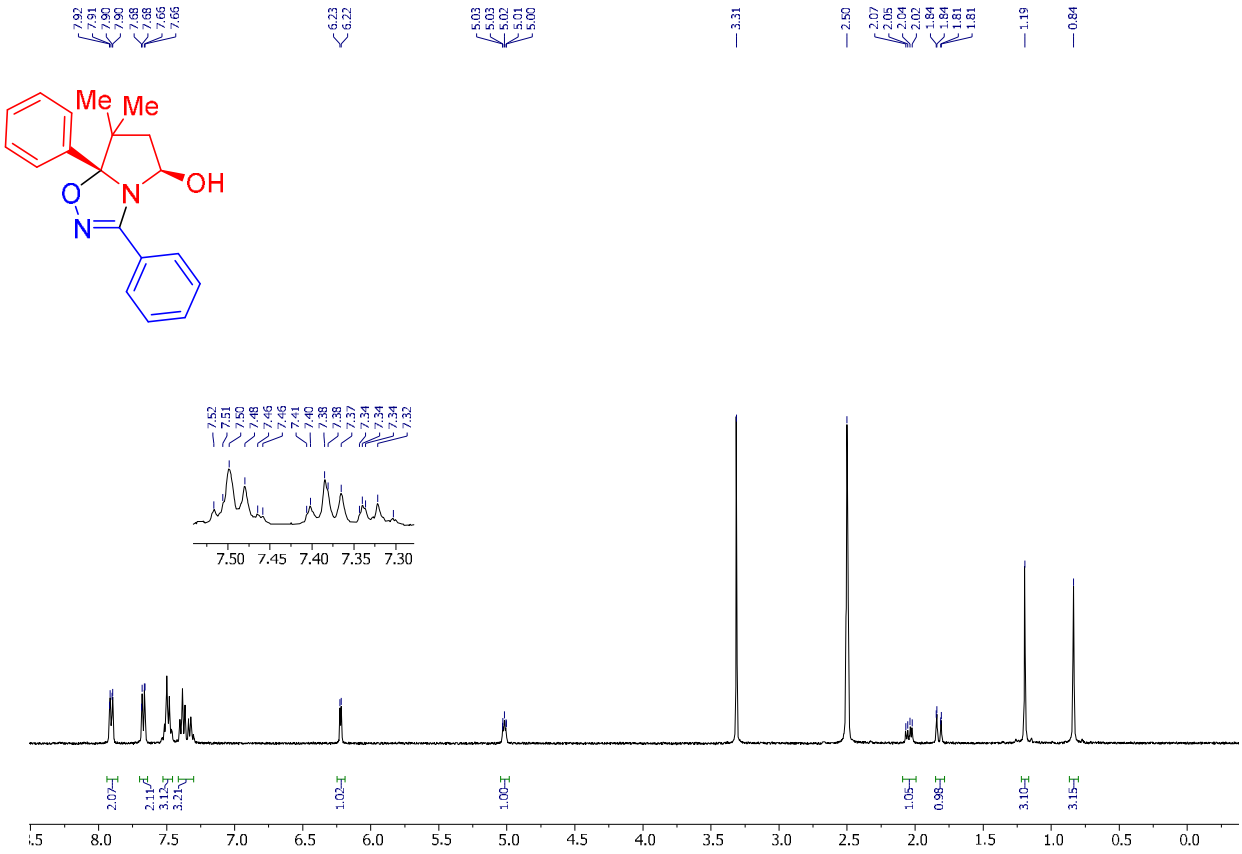
^{1}H and ^{13}C NMR Spectra of tetrahydropyrrolo[1,2-*d*]oxadiazoles 3



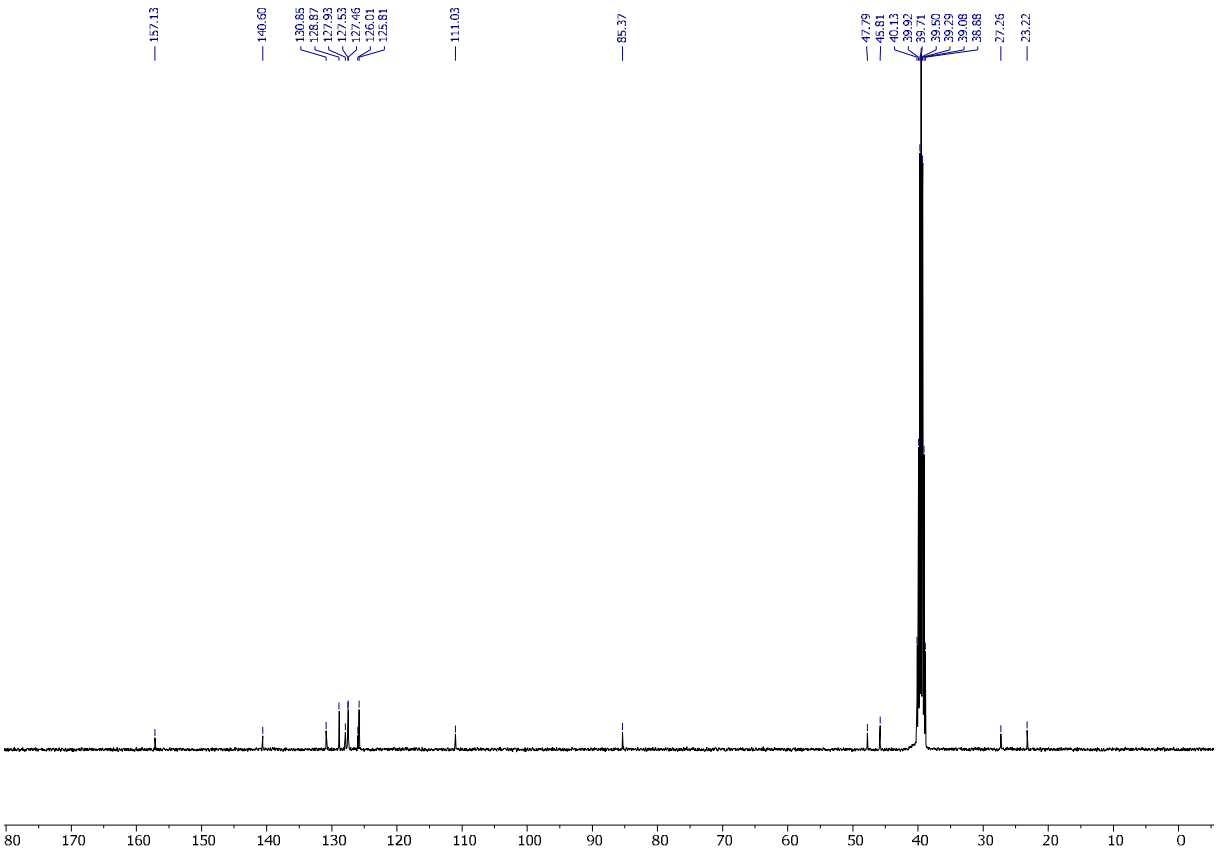
^{1}H NMR Spectrum of **3aa** (400.1 MHz, $CDCl_3$)



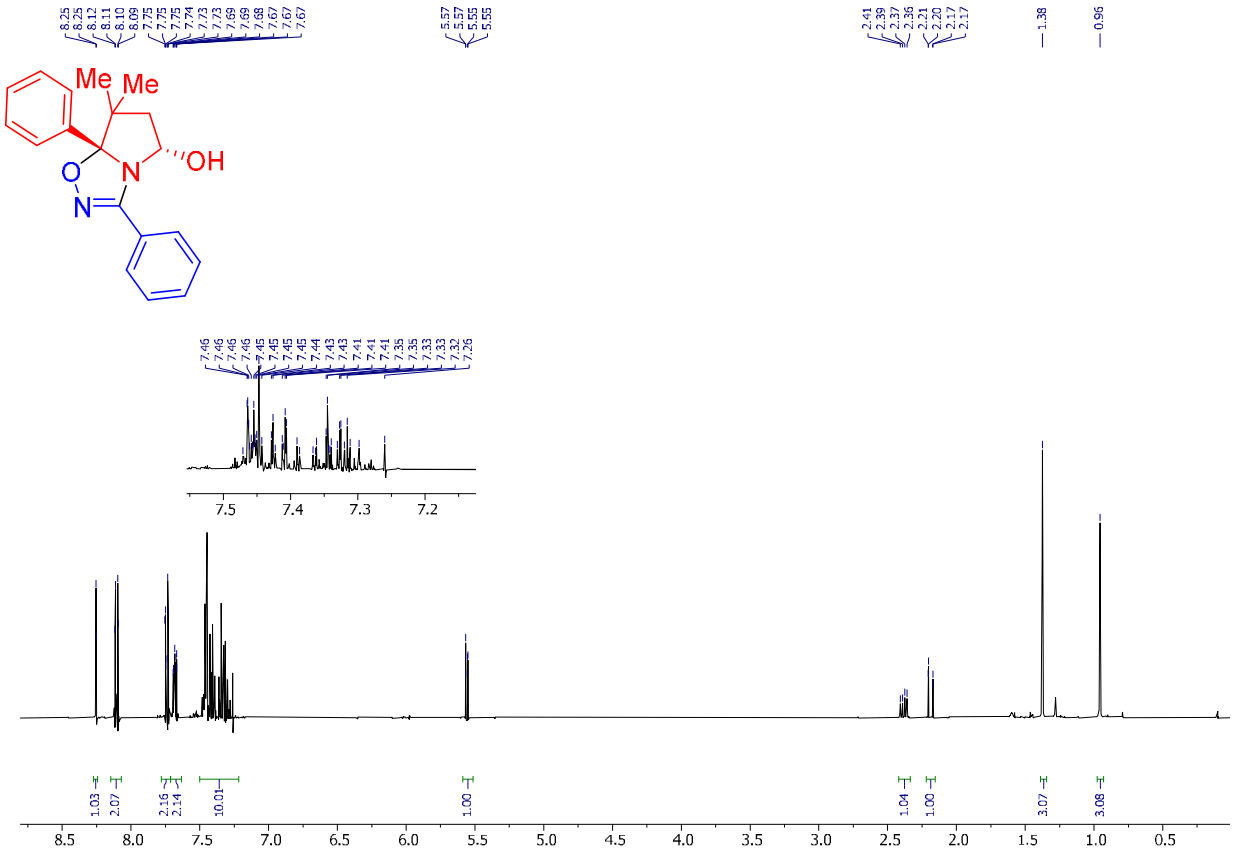
^{13}C NMR Spectrum of **3aa** (100.6 MHz, $CDCl_3$)



^{1}H NMR Spectrum of 3**ab** major isomer (400.1 MHz, DMSO-d_6)



^{13}C NMR Spectrum of **3ab** major isomer (100.6 MHz, DMSO-d_6)



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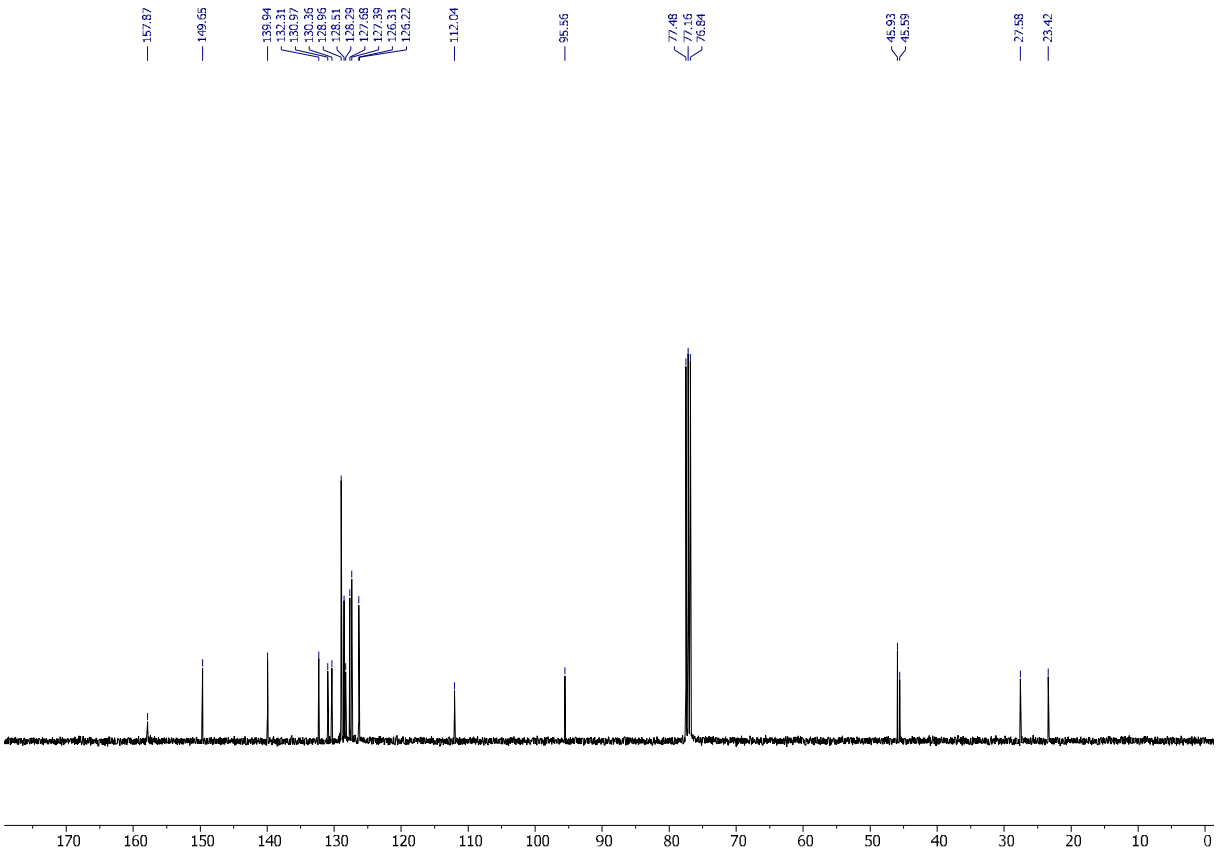
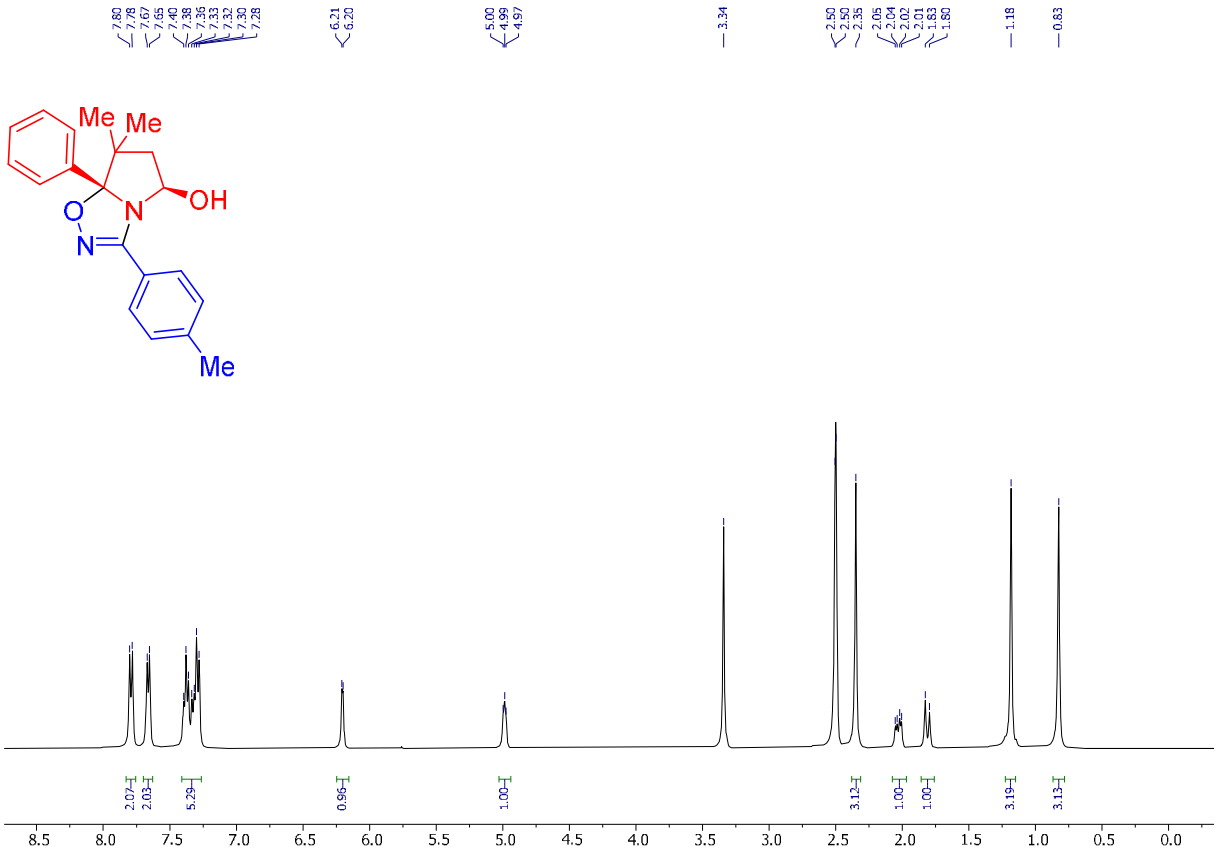
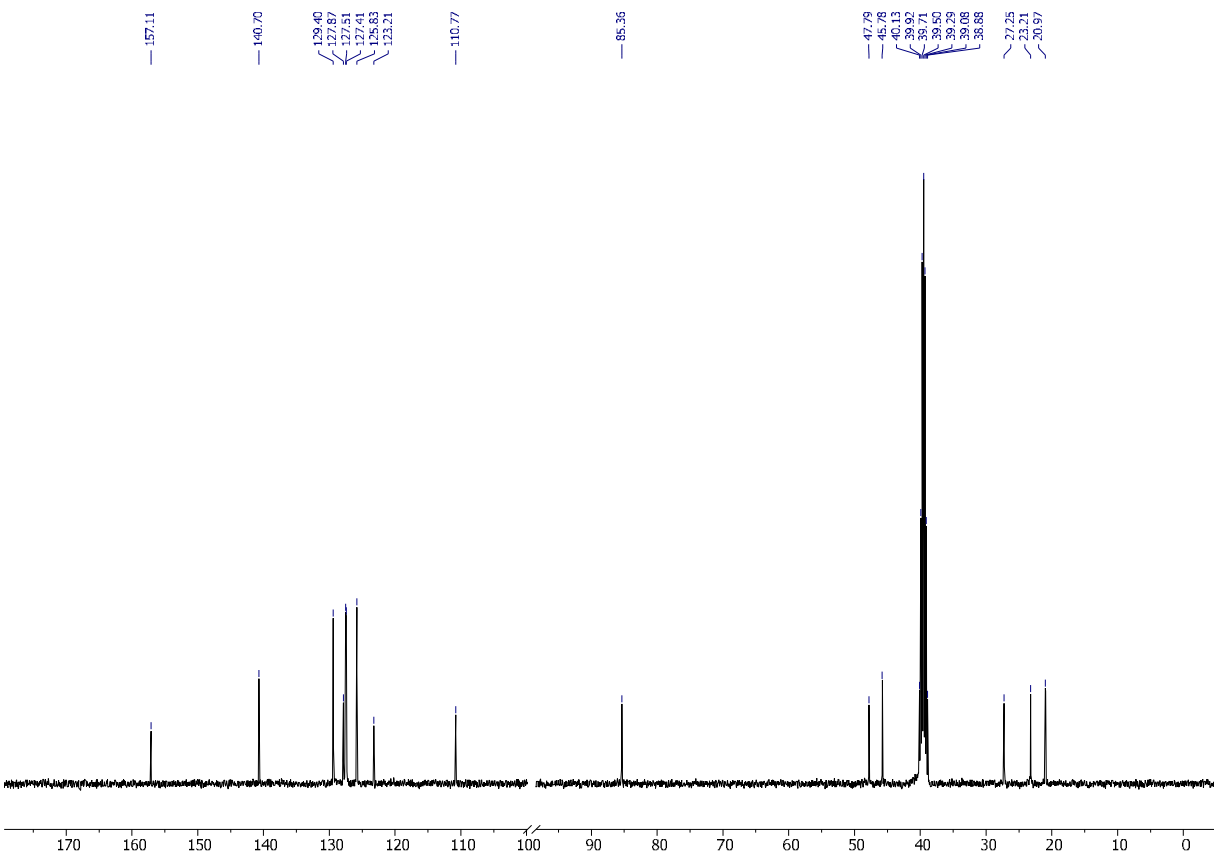


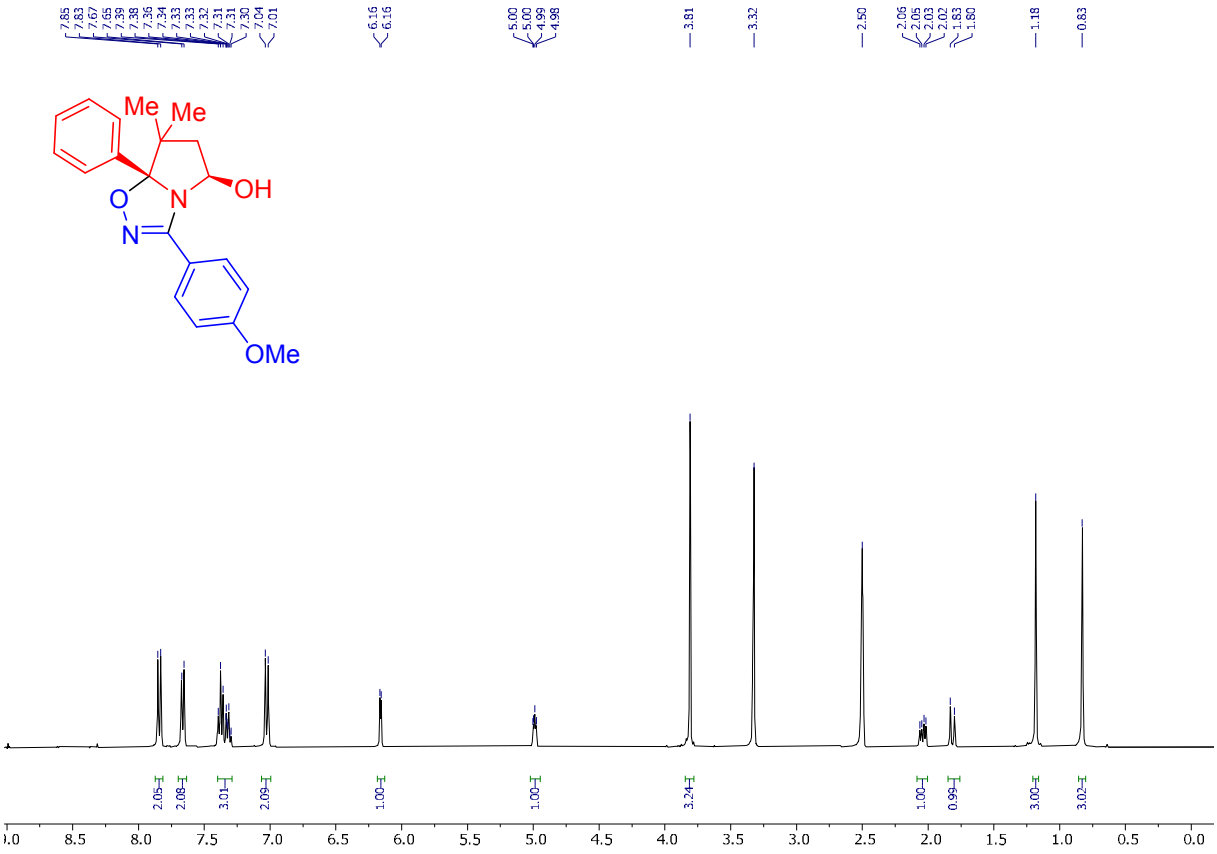
^{13}C NMR Spectrum of **3ab** minor isomer (100.6 MHz, DMSO-d_6)



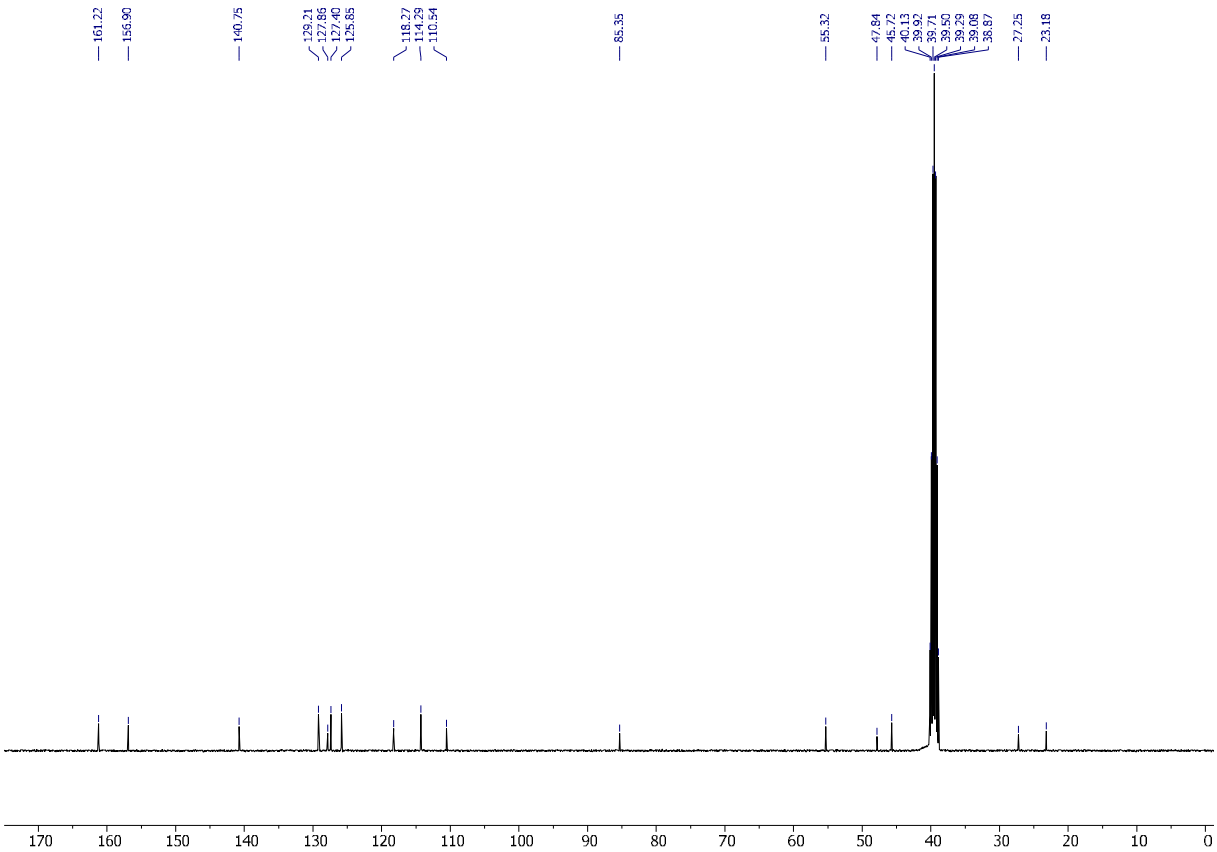
^{1}H NMR Spectrum of **3ac** (400.1 MHz, DMSO-d_6)



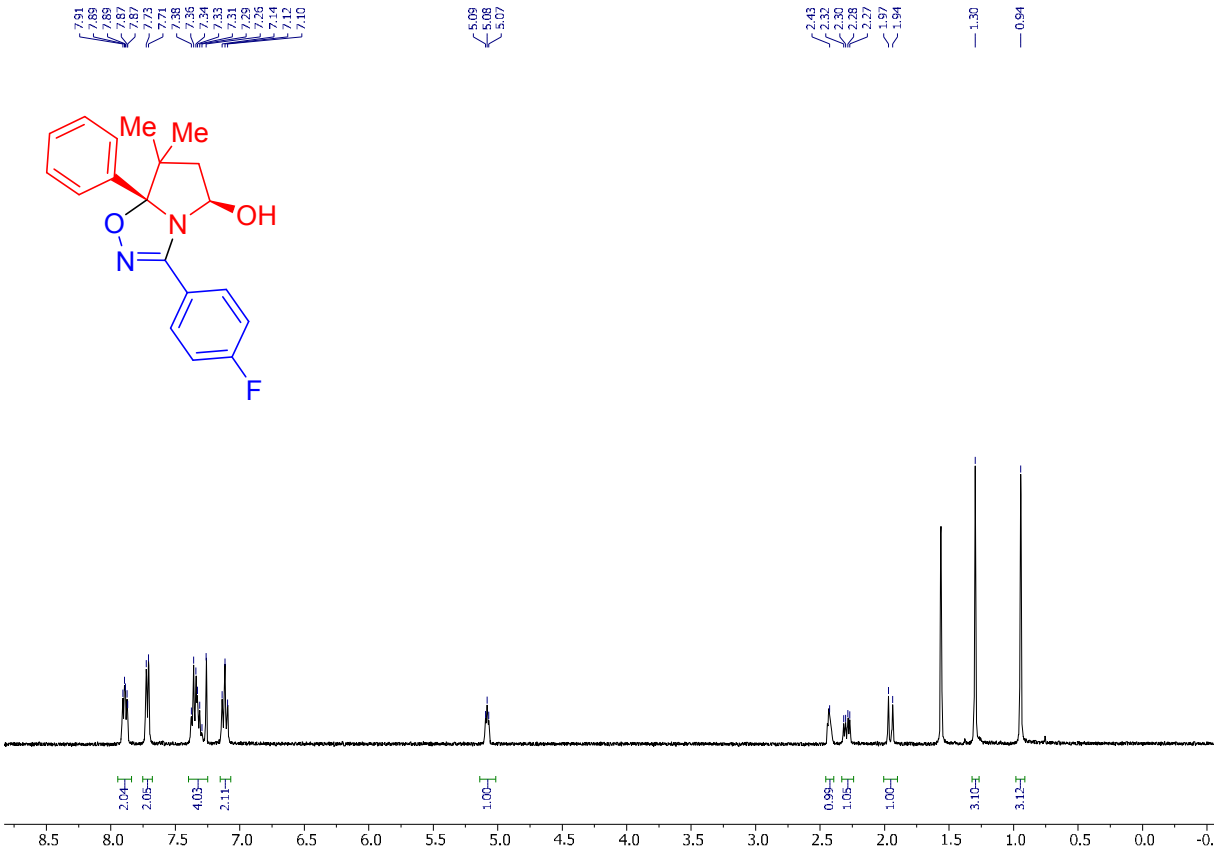
^{13}C NMR Spectrum of **3ac** (100.6 MHz, DMSO-d_6)



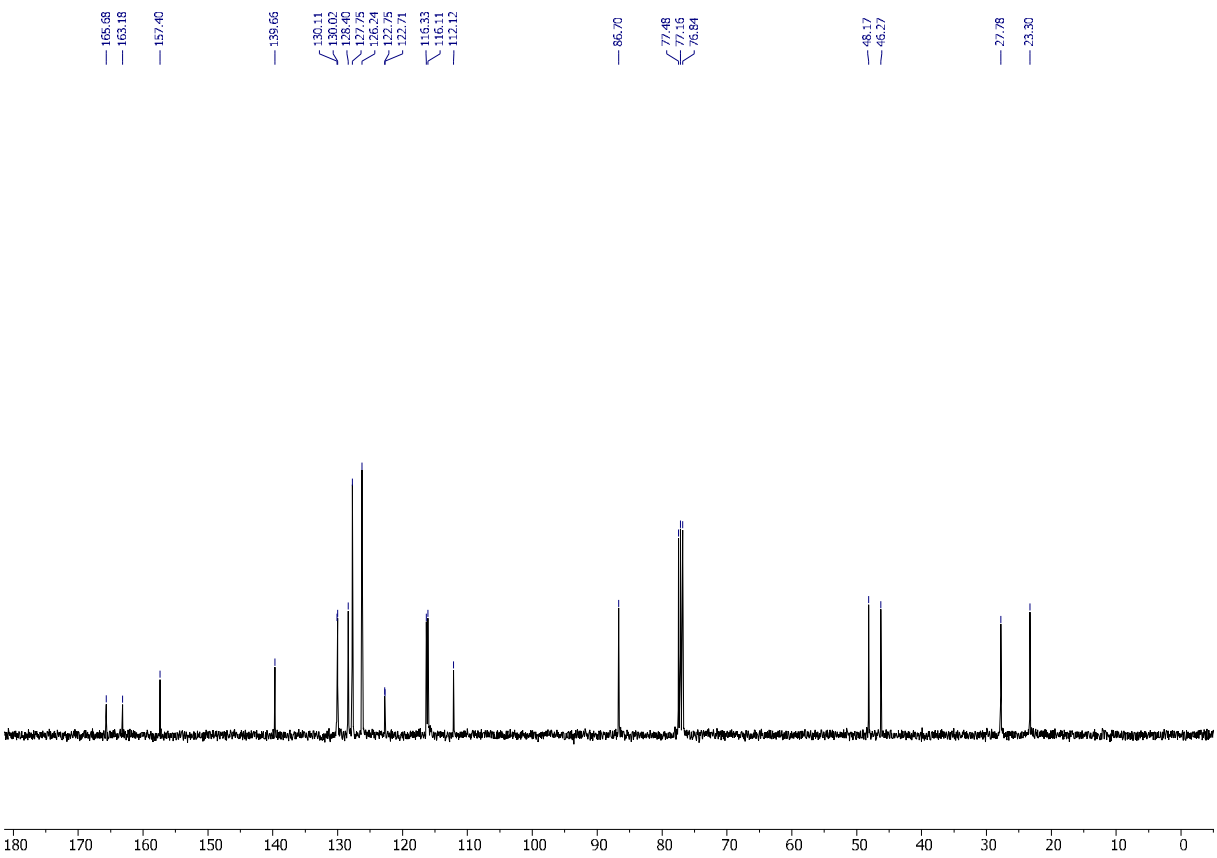
^{1}H NMR Spectrum of **3ad** (400.1 MHz, DMSO-d_6)



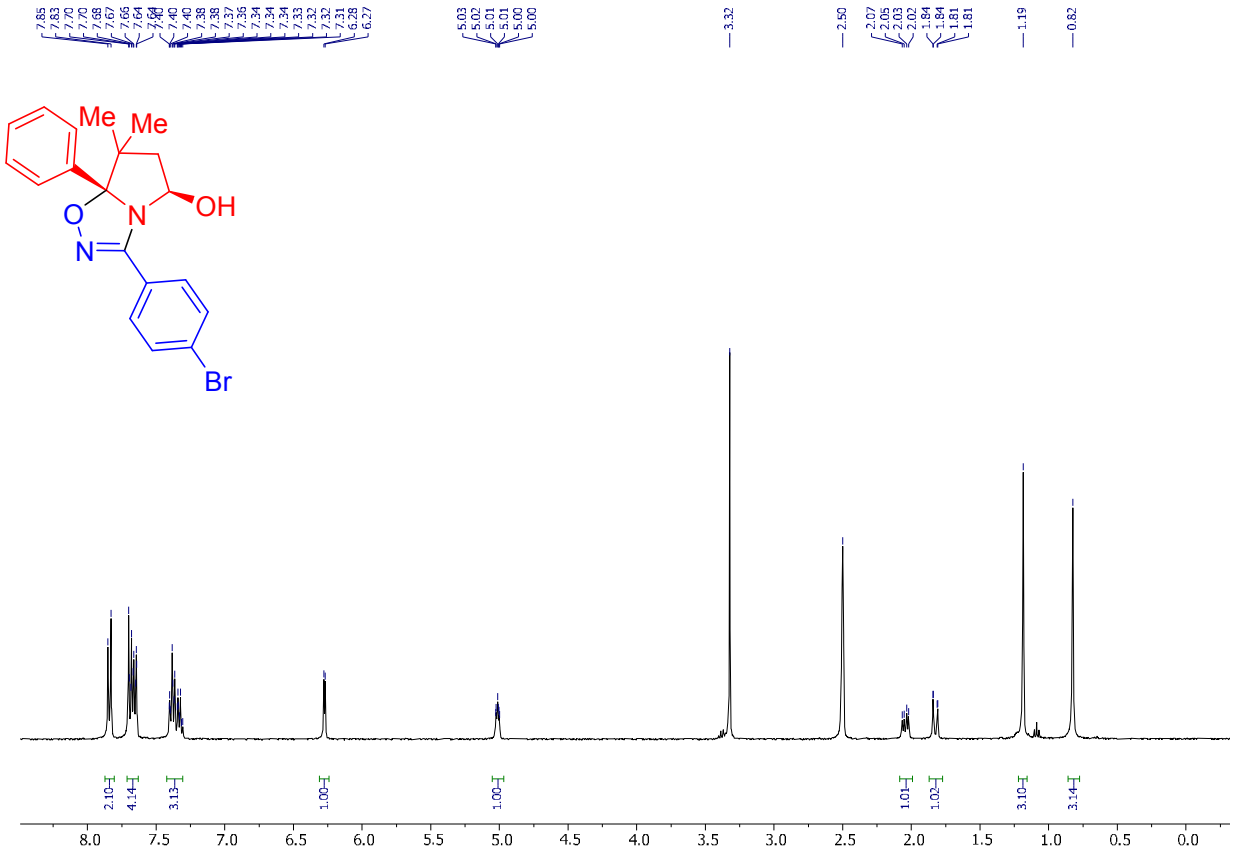
^{13}C NMR Spectrum of **3ad** (100.6 MHz, DMSO-d_6)



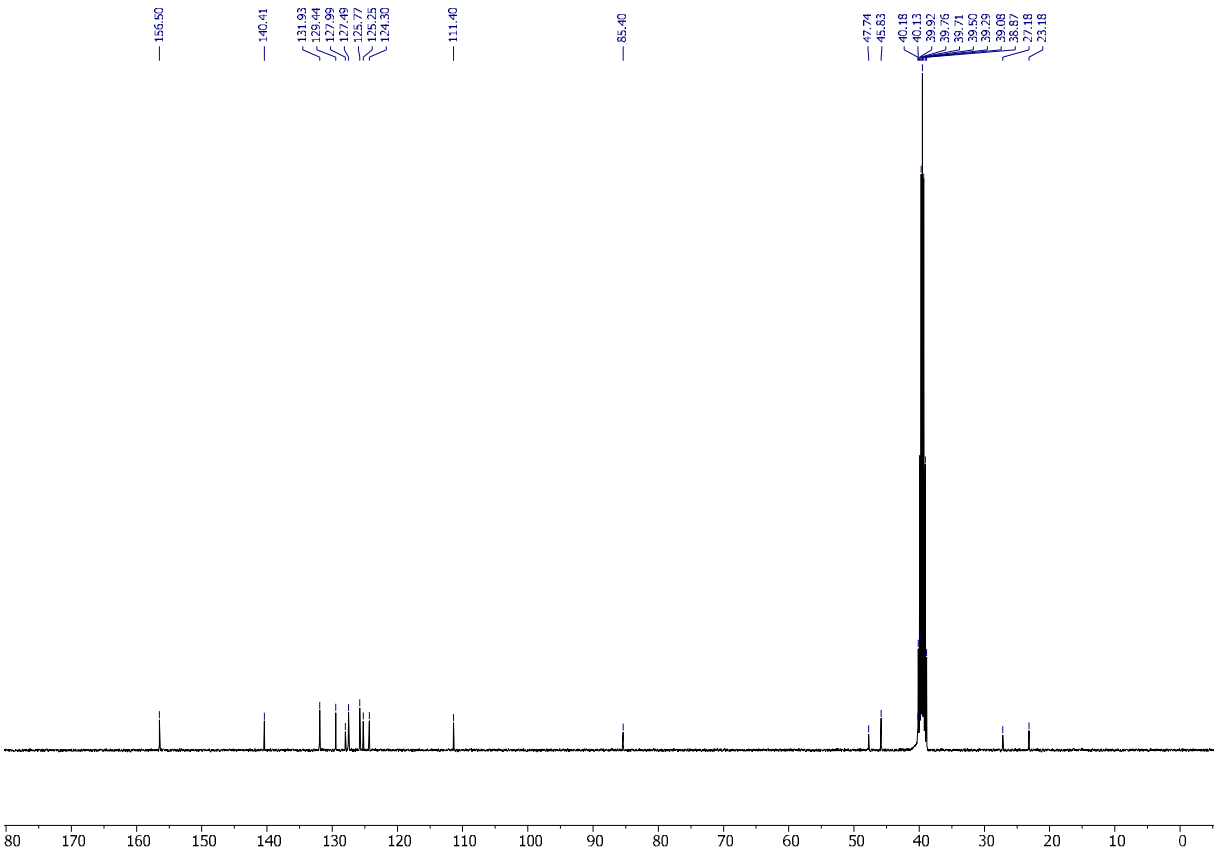
^{1}H NMR Spectrum of **3ae** (400.1 MHz, $CDCl_3$)



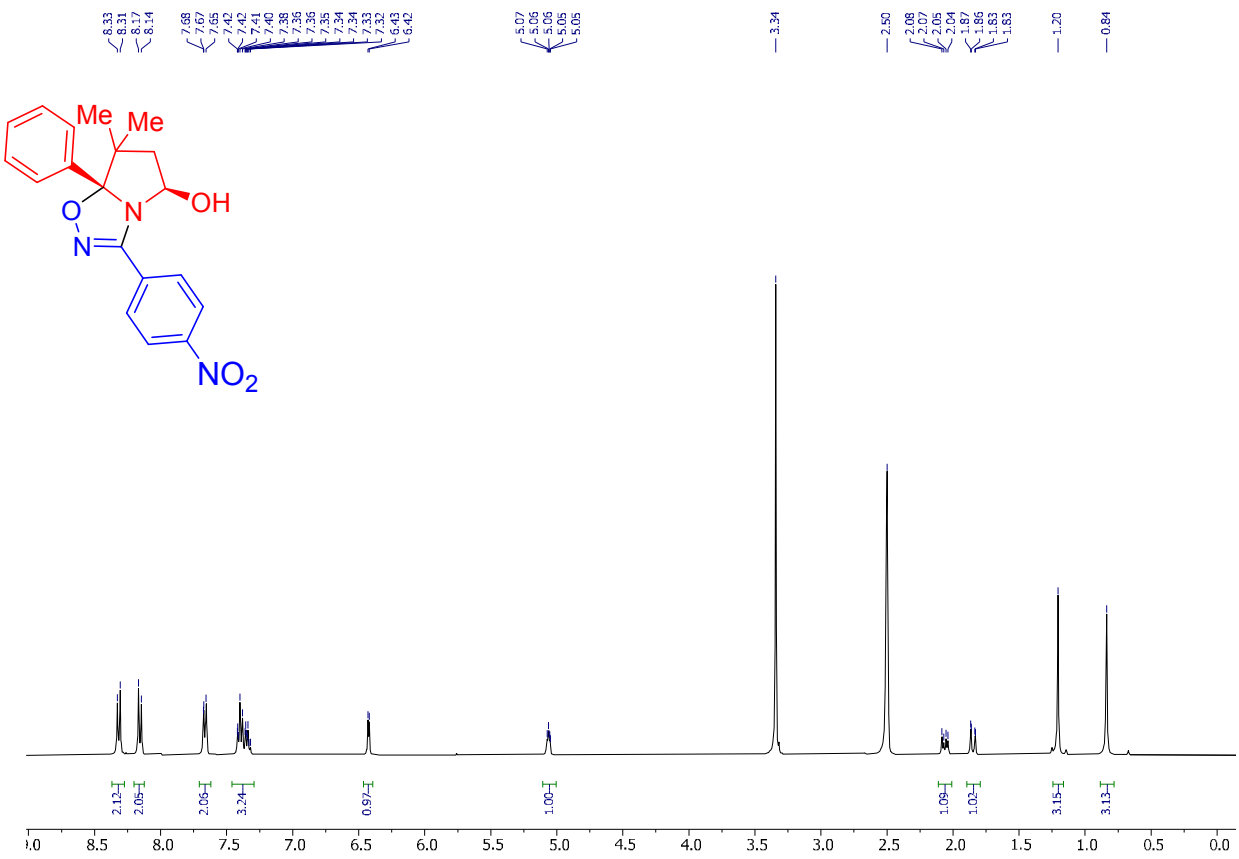
^{13}C NMR Spectrum of **3ae** (100.6 MHz, $CDCl_3$)



^{1}H NMR Spectrum of **3af** (400.1 MHz, DMSO-d_6)



^{13}C NMR Spectrum of **3af** (100.6 MHz, DMSO-d_6)



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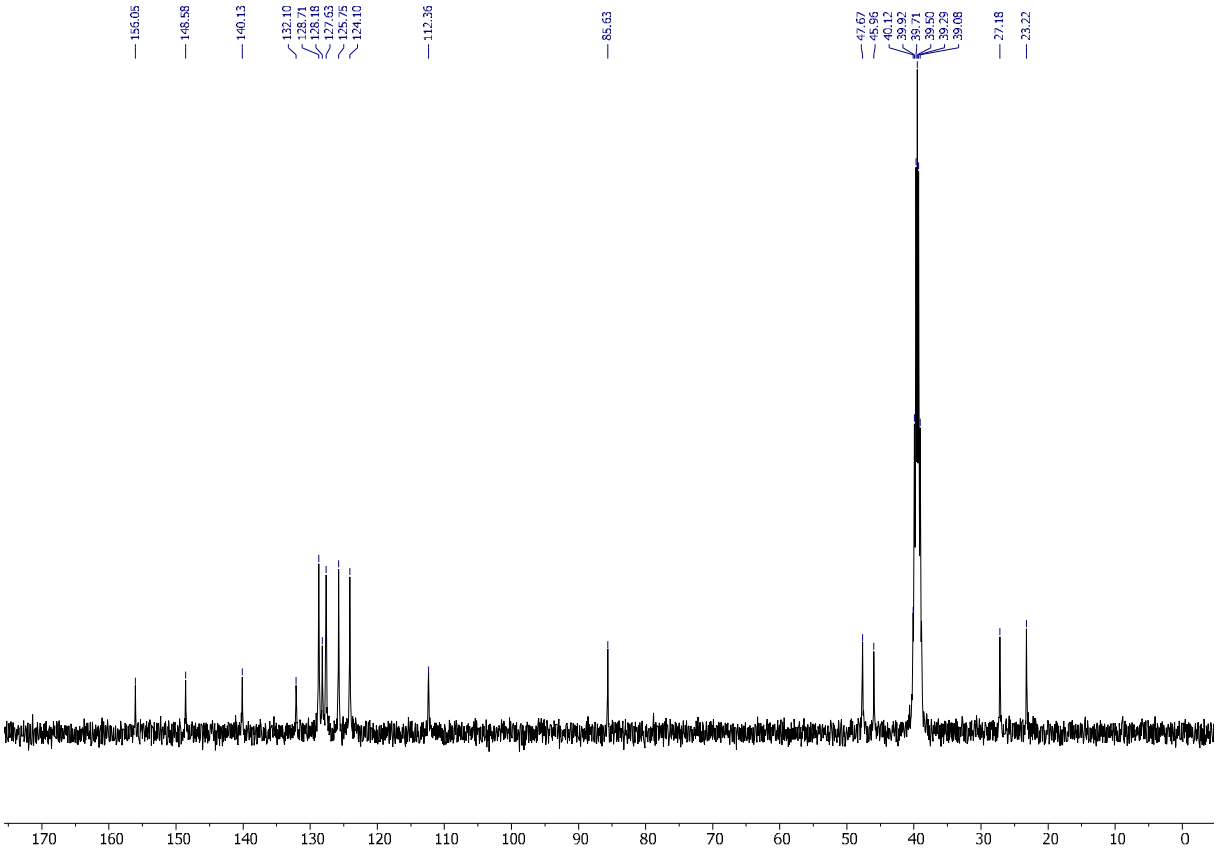
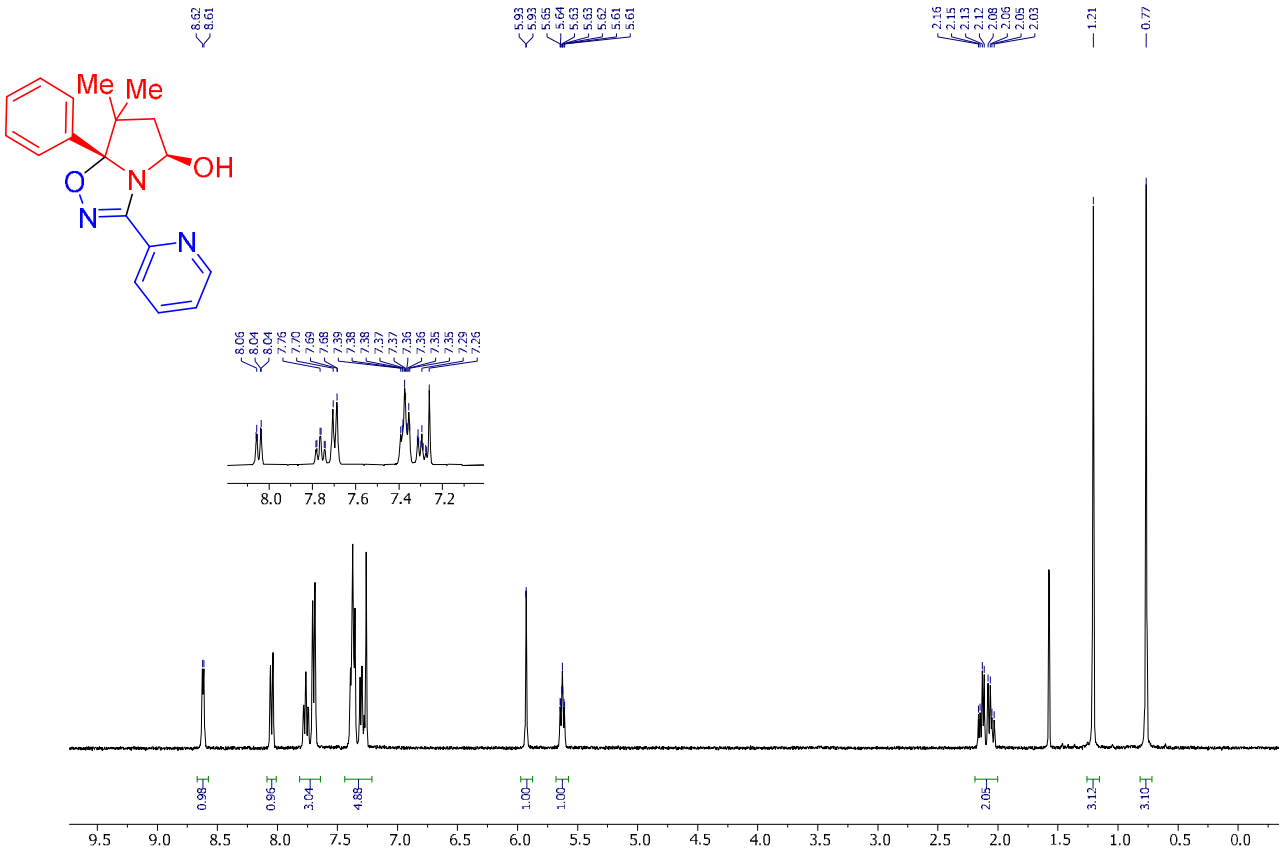


^{13}C NMR Spectrum of **3ag** (100.6 MHz, DMSO-d_6)



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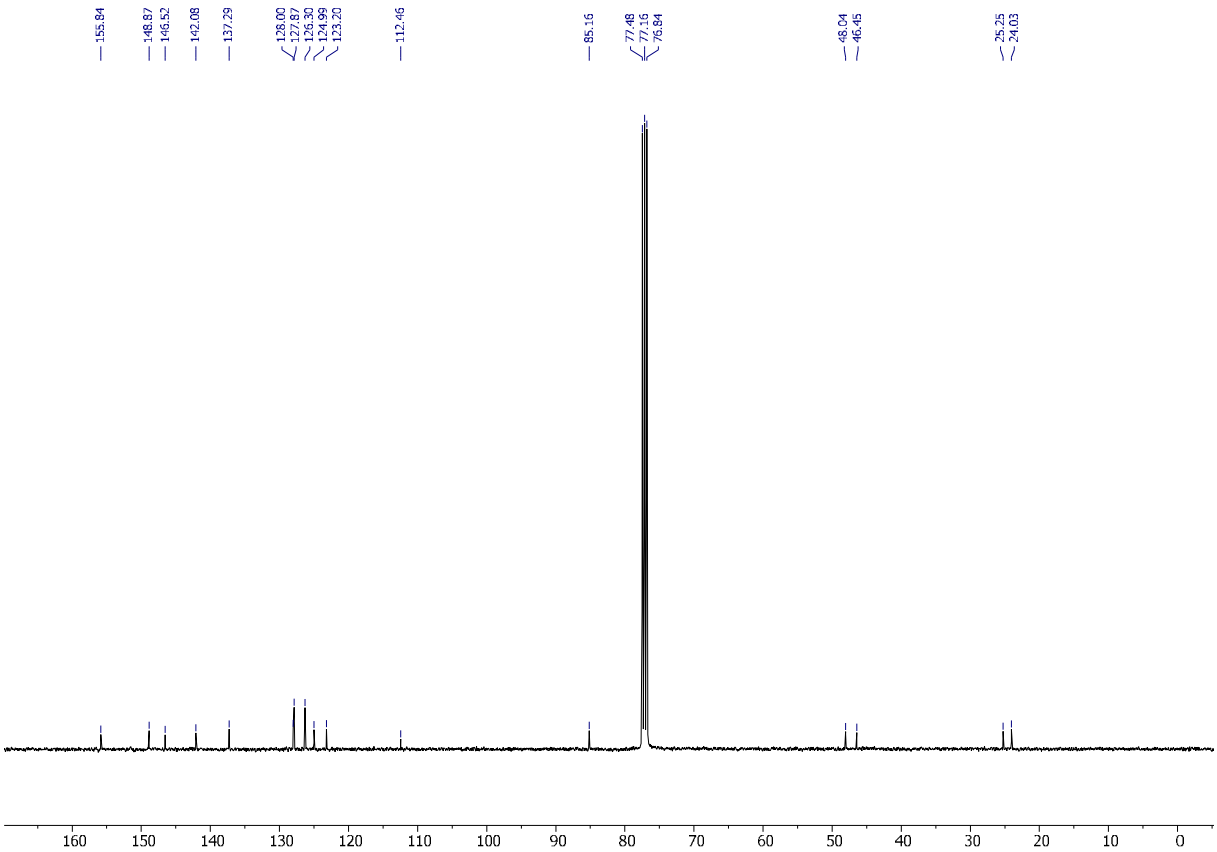
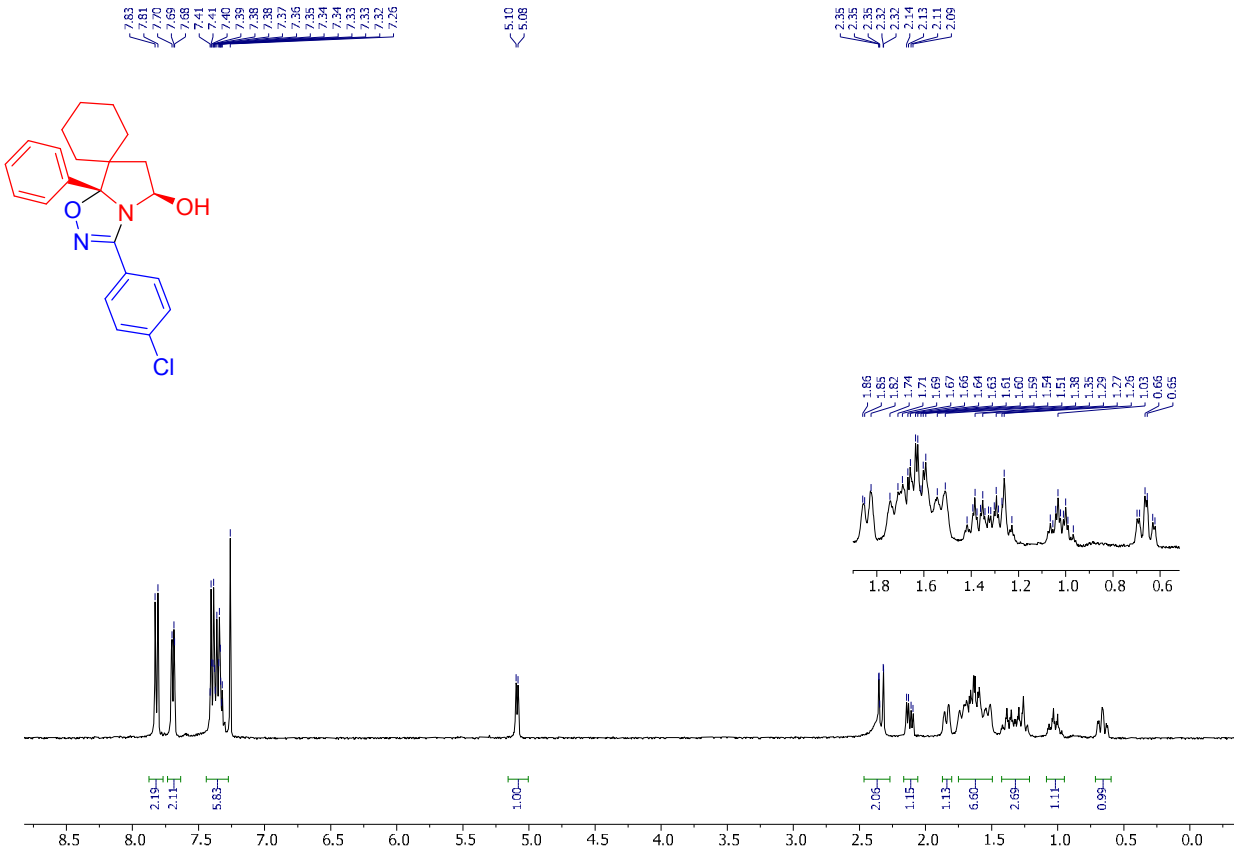


^{13}C NMR Spectrum of **3ah** (100.6 MHz, $CDCl_3$)



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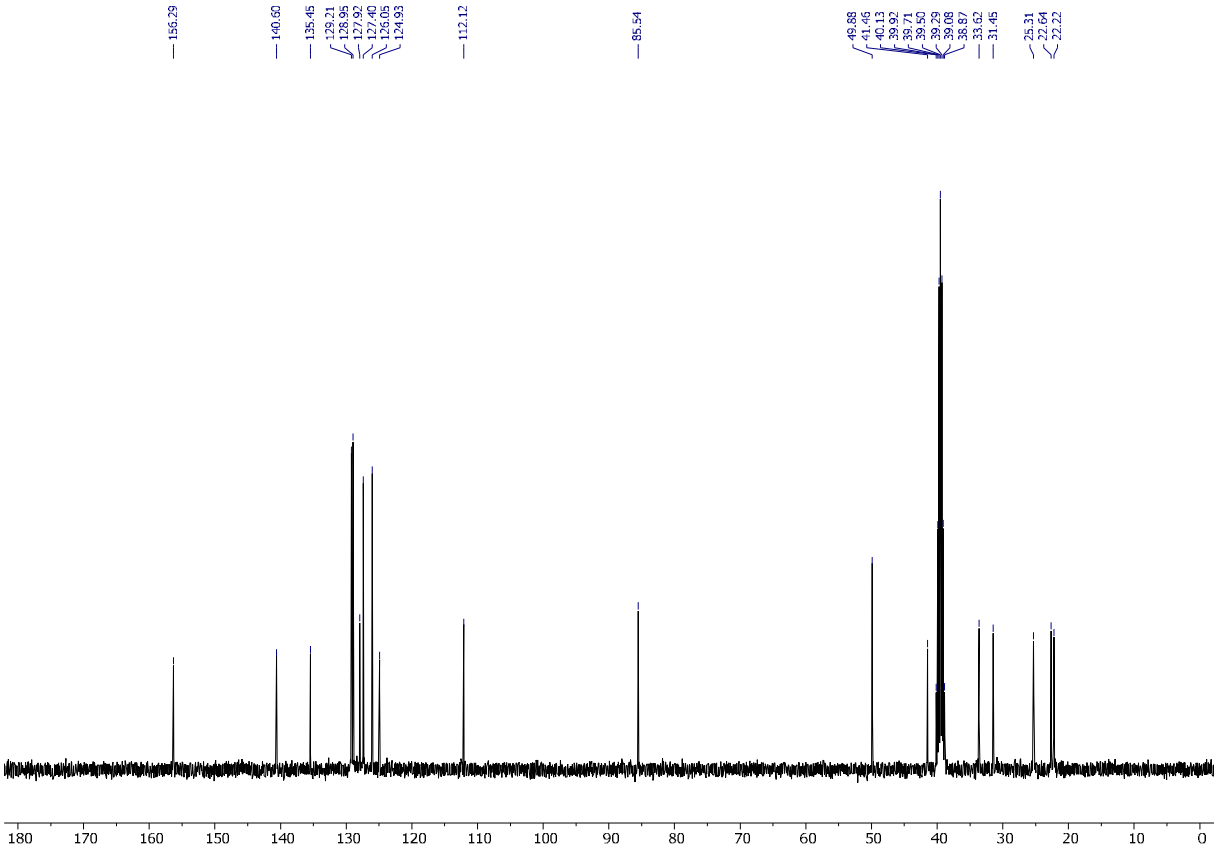

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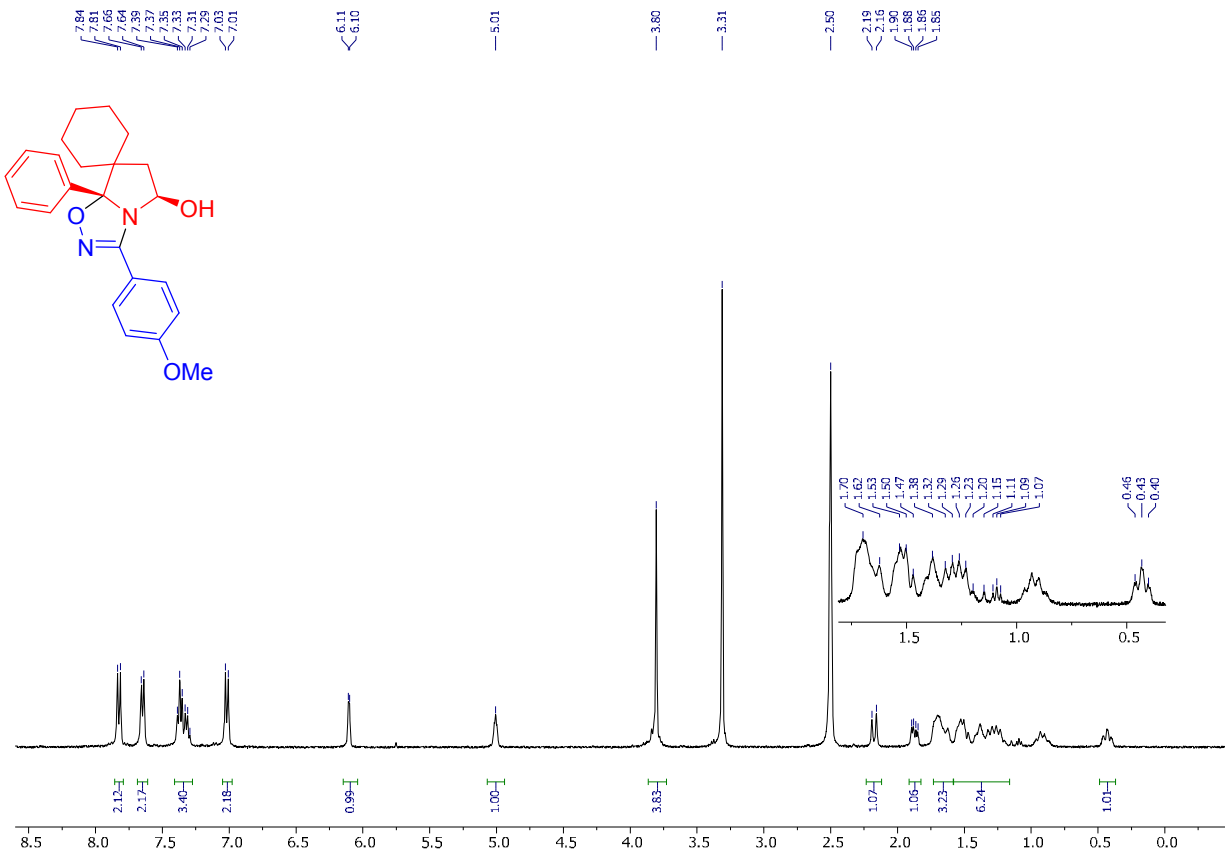

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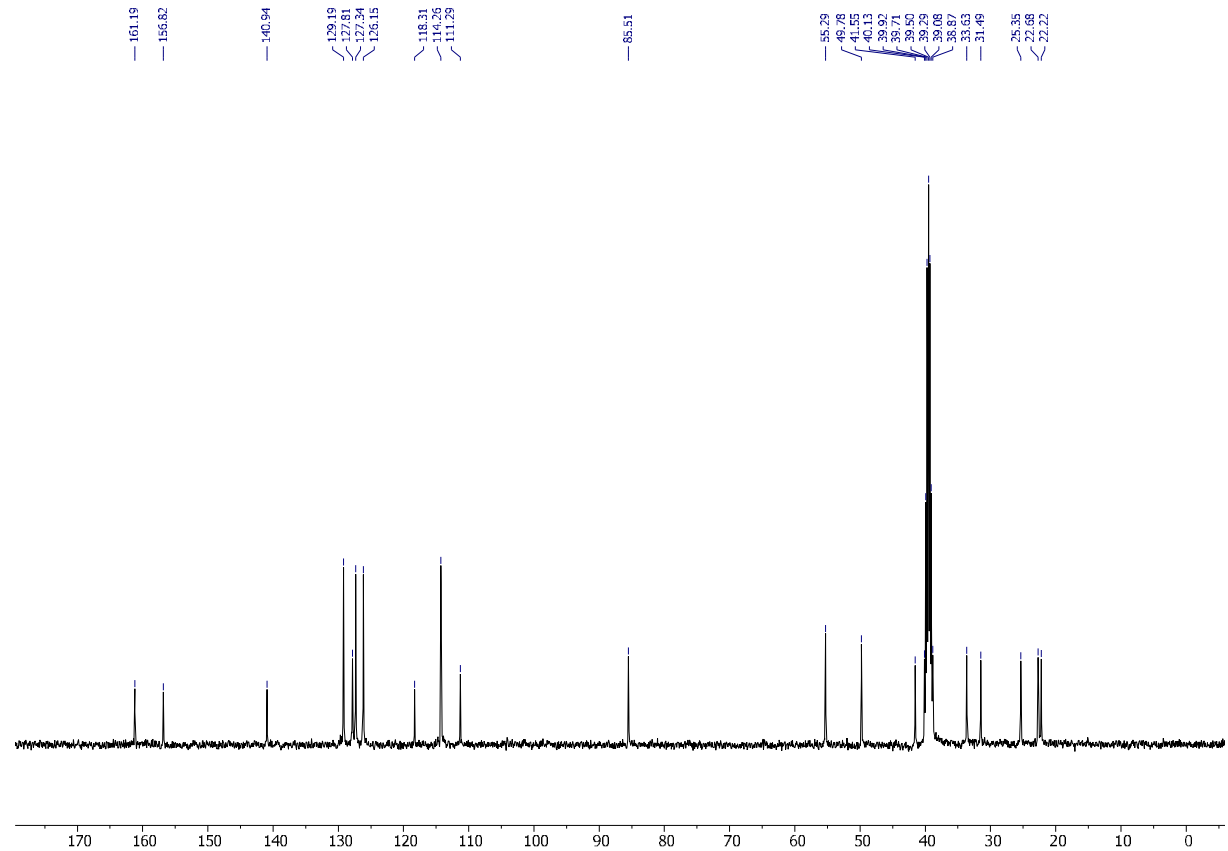
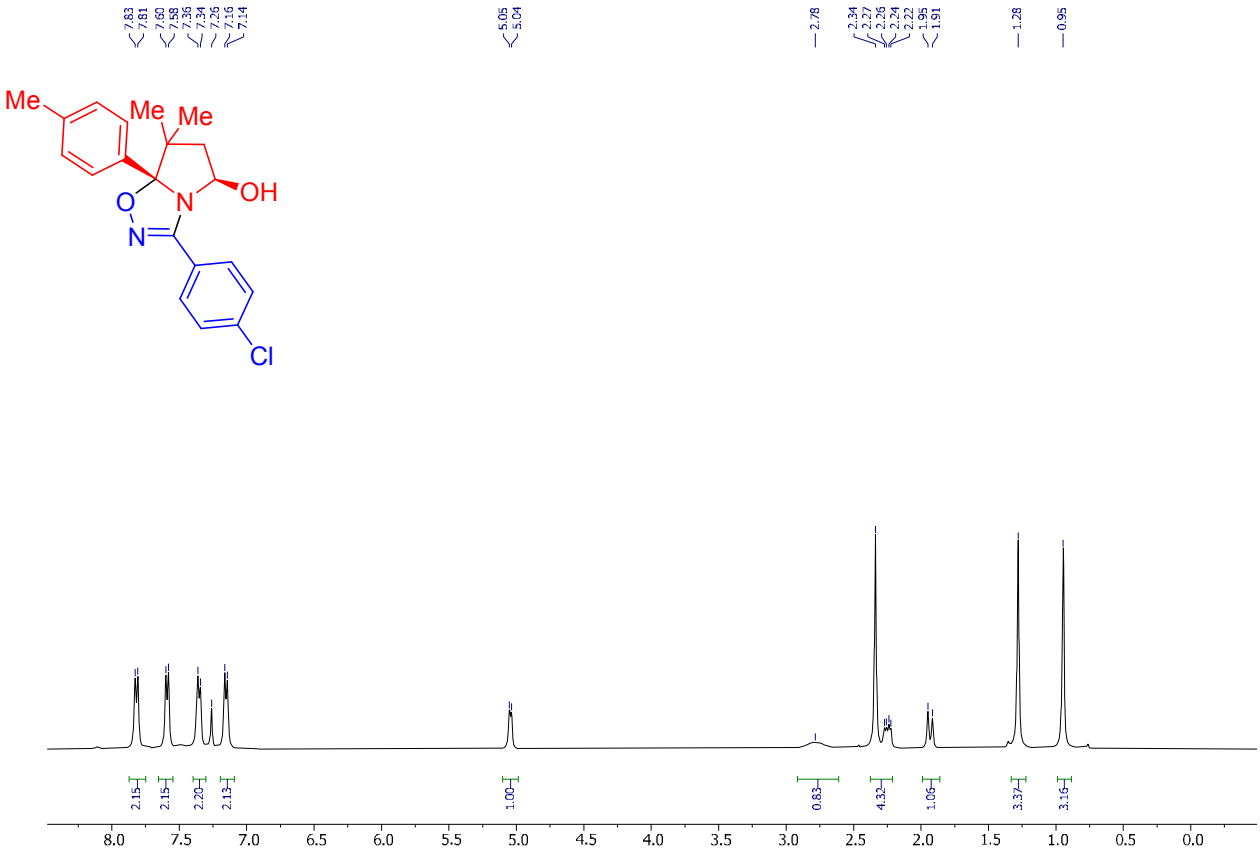
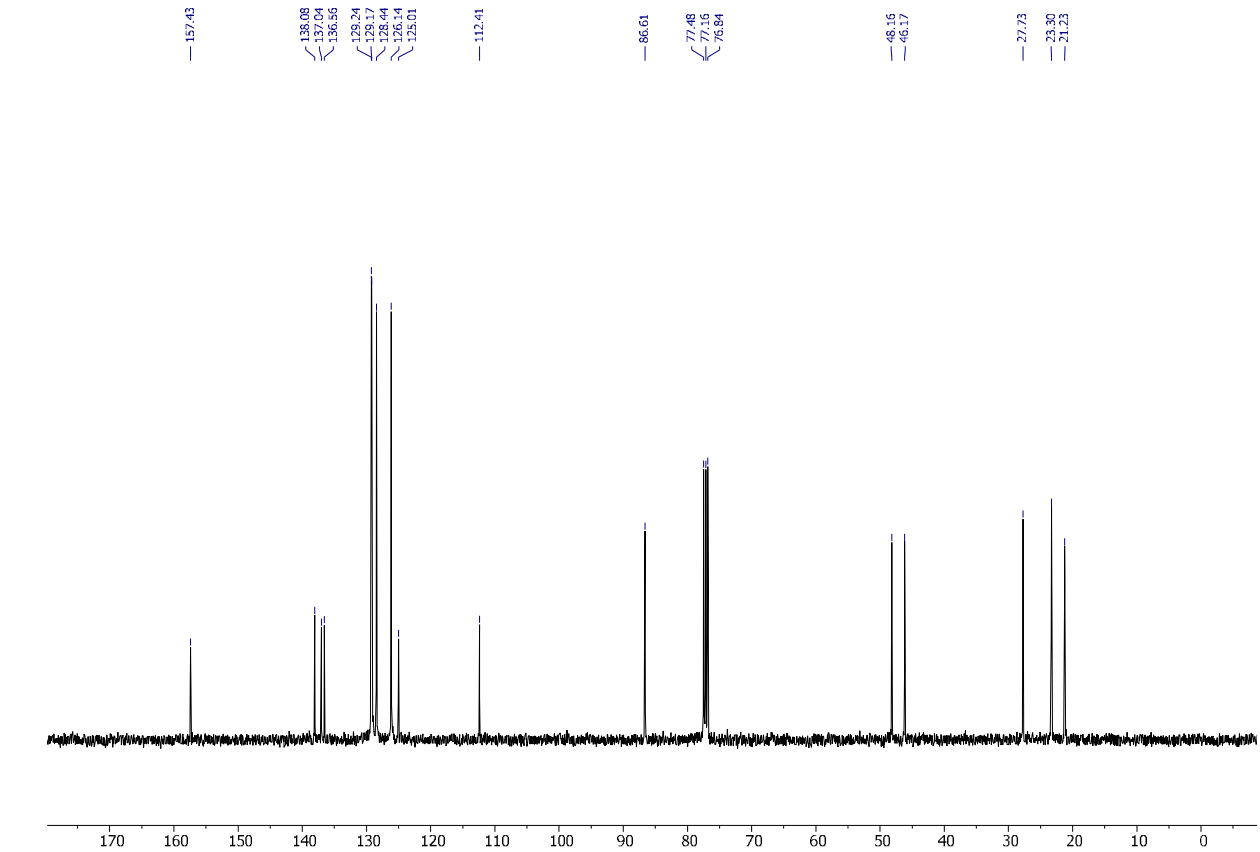


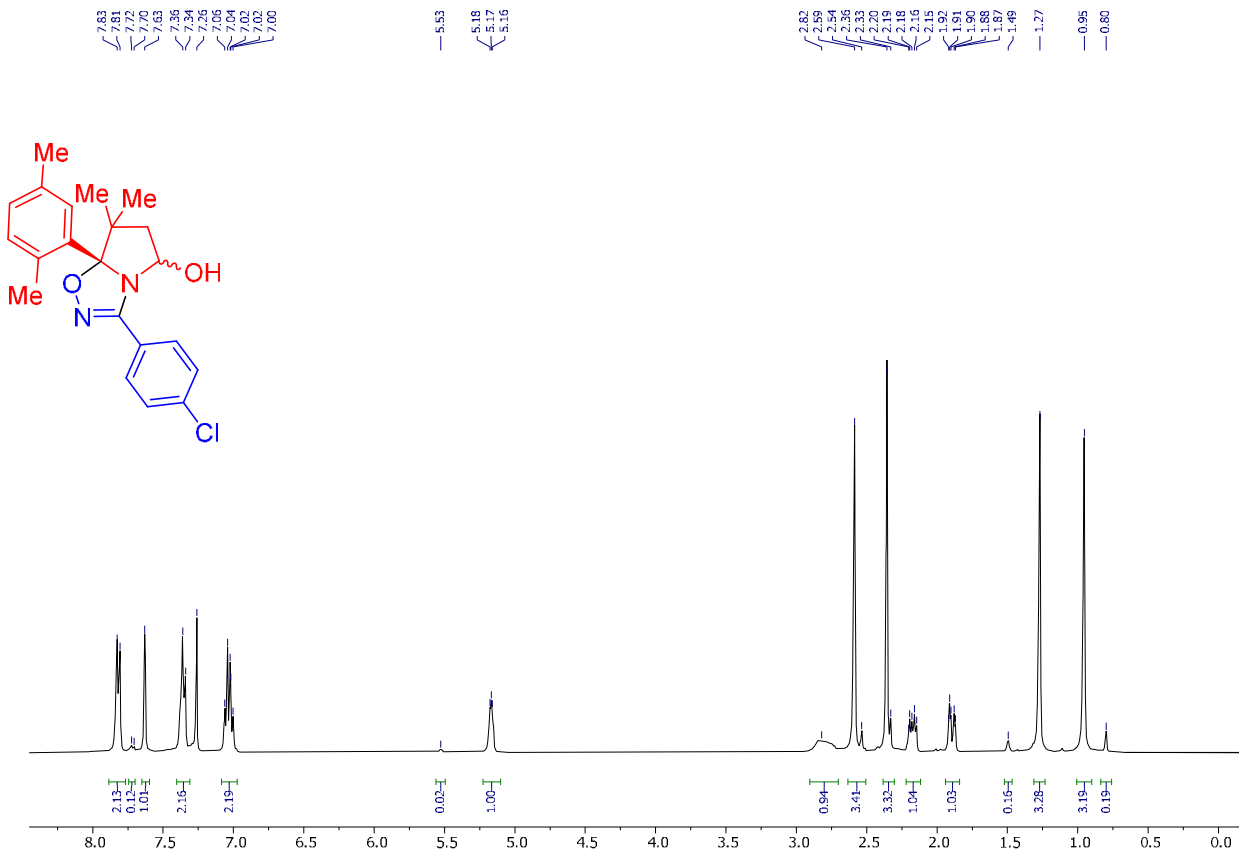
^{13}C NMR Spectrum of **3bd** (100.6 MHz, DMSO-d_6)



^{1}H NMR Spectrum of **3ca** (400.1 MHz, $CDCl_3$)



^{13}C NMR Spectrum of **3ca** (100.6 MHz, $CDCl_3$)



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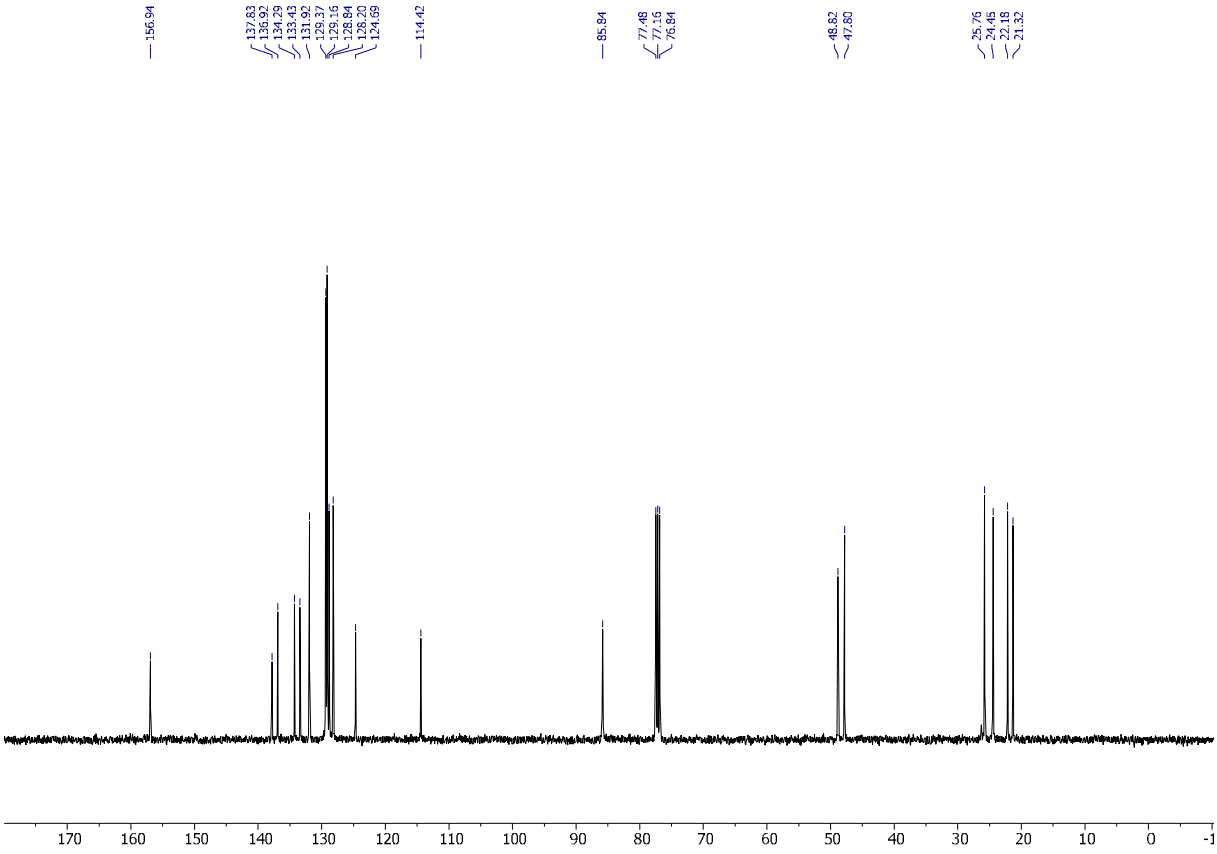
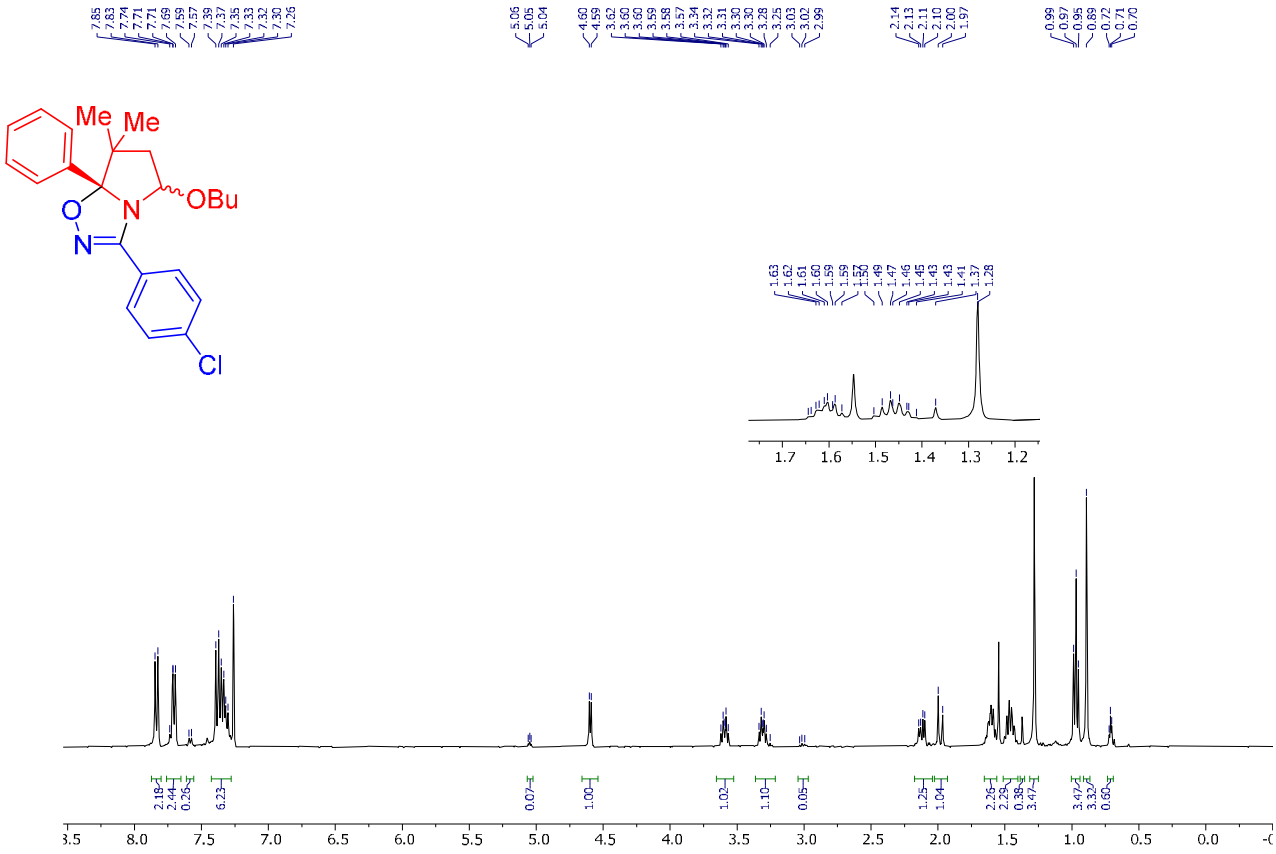
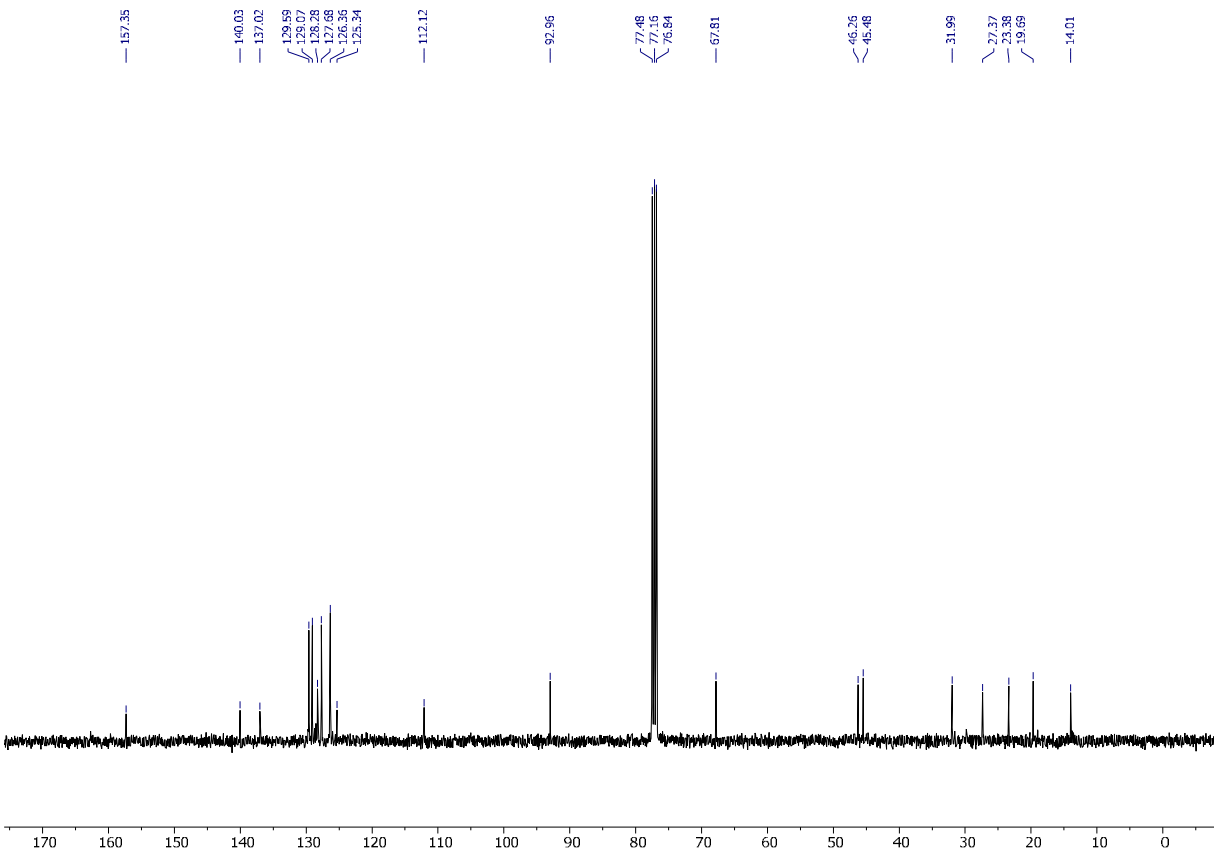


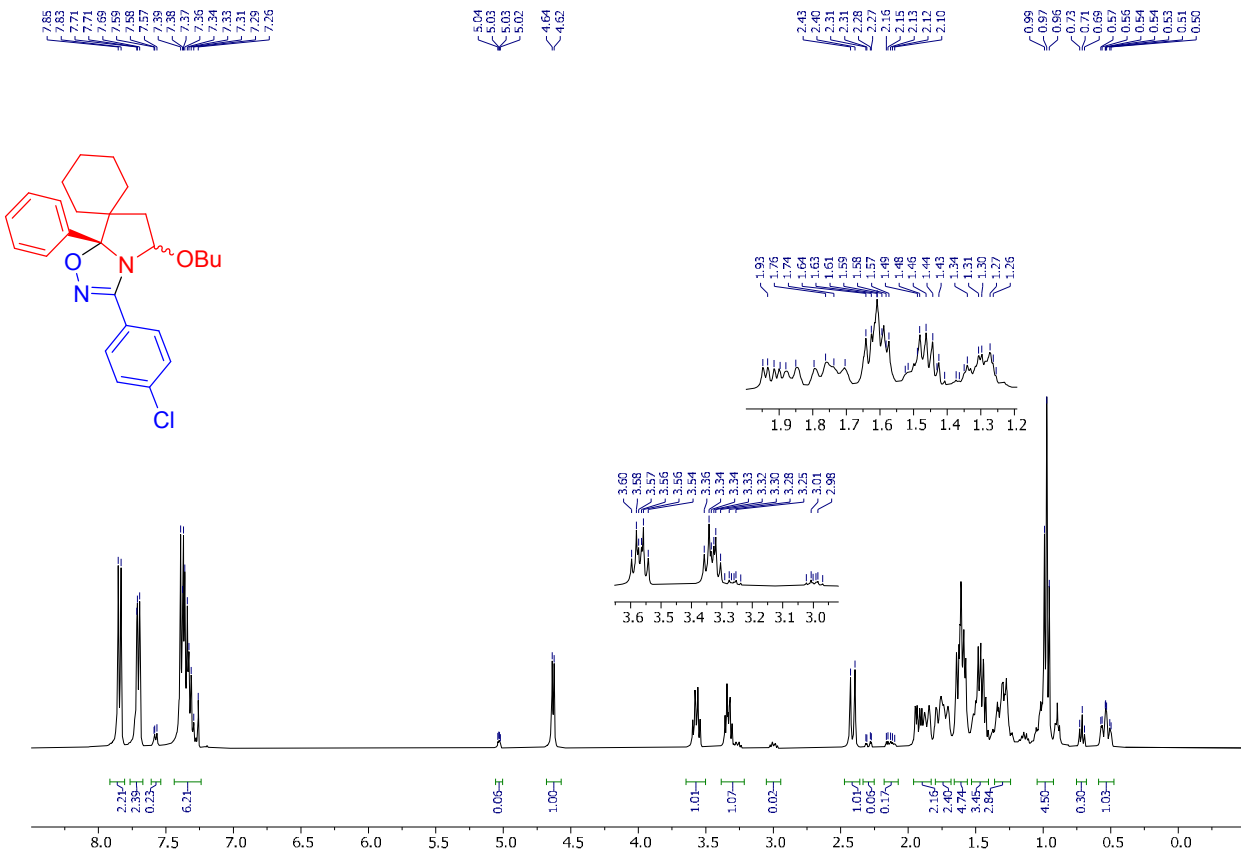
^{13}C NMR Spectrum of **3da** (100.6 MHz, $CDCl_3$)



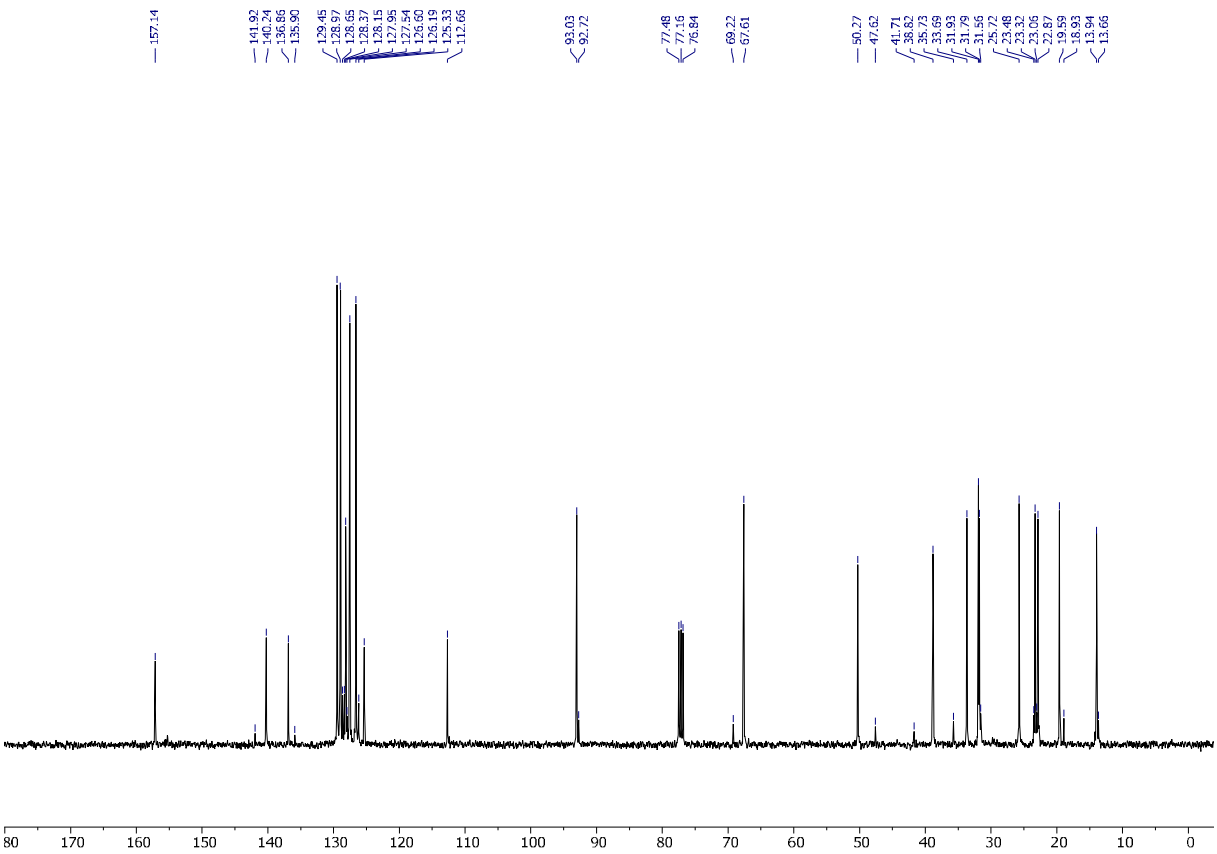
^{1}H NMR Spectrum of **3ea** (400.1 MHz, $CDCl_3$)



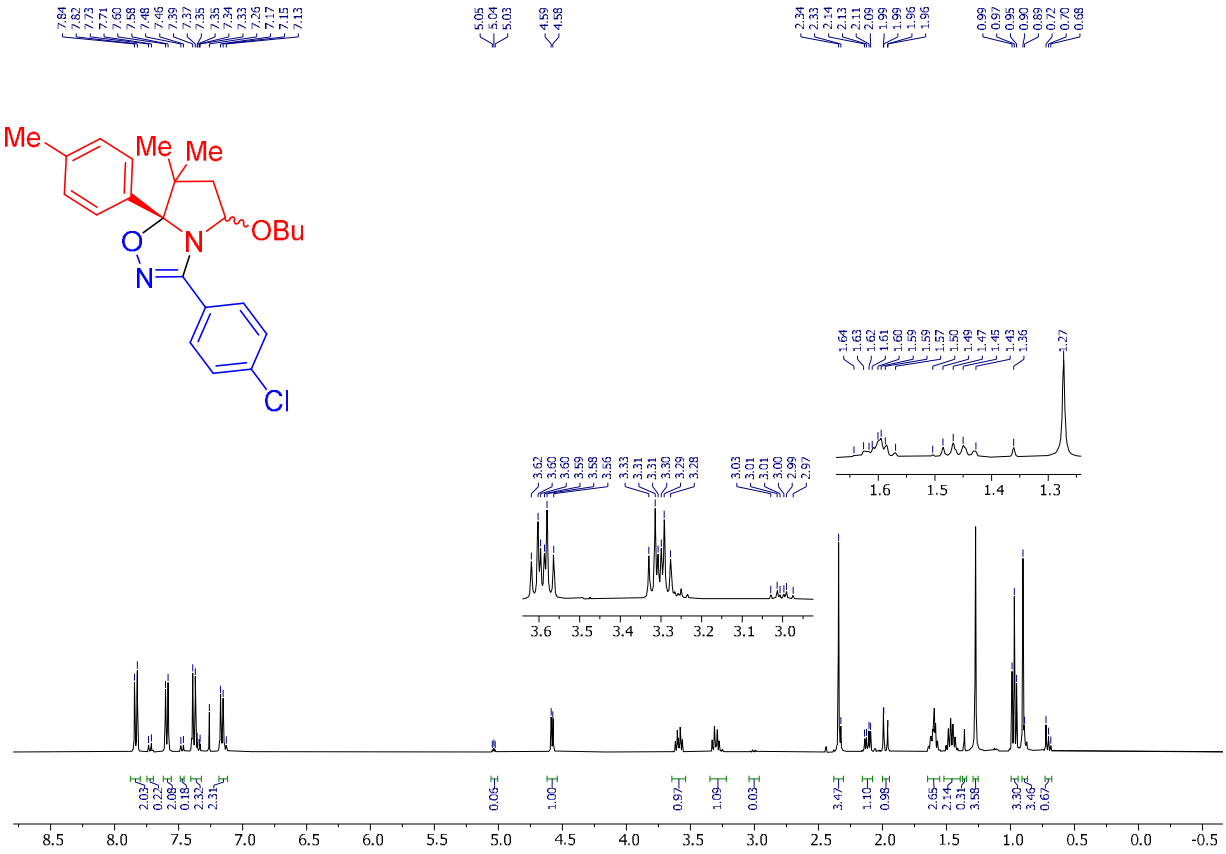
^{13}C NMR Spectrum of **3ea** (100.6 MHz, $CDCl_3$)



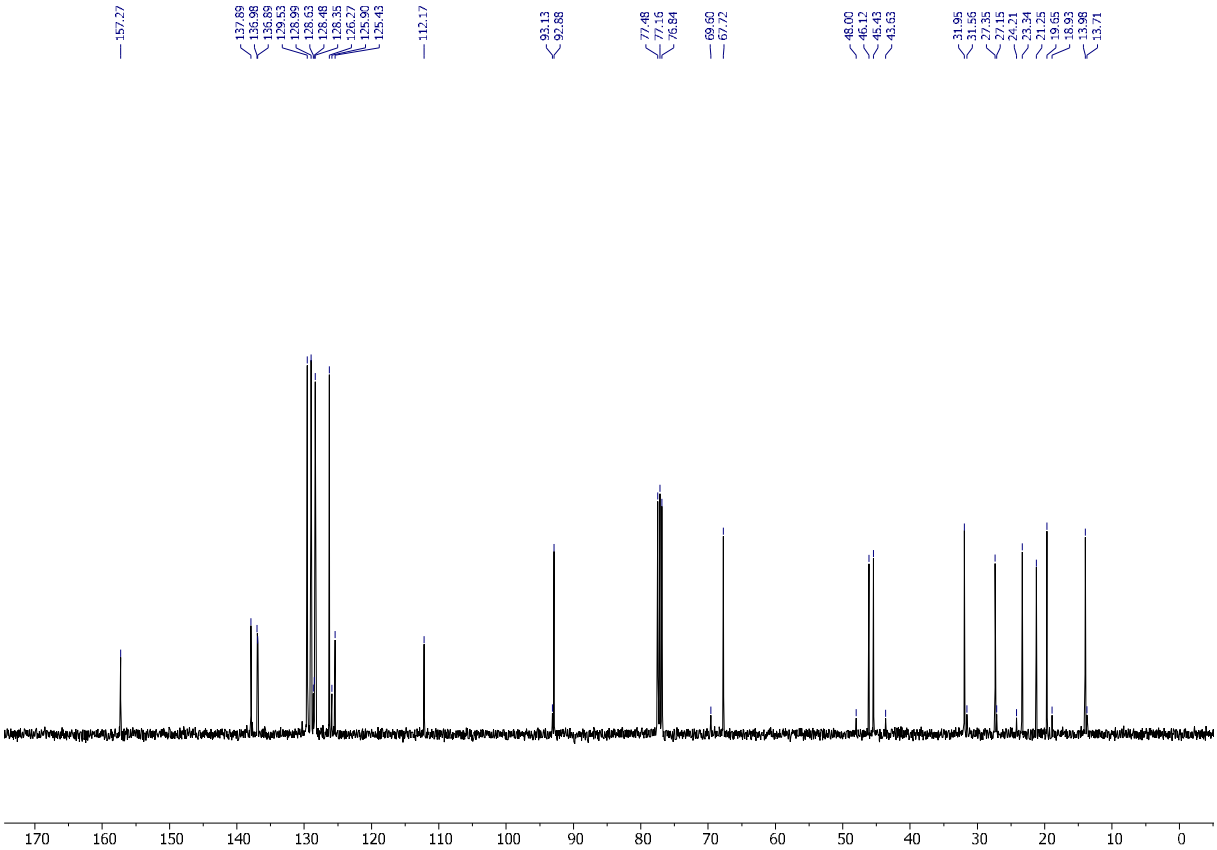
^{1}H NMR Spectrum of **3fa** (400.1 MHz, $CDCl_3$)



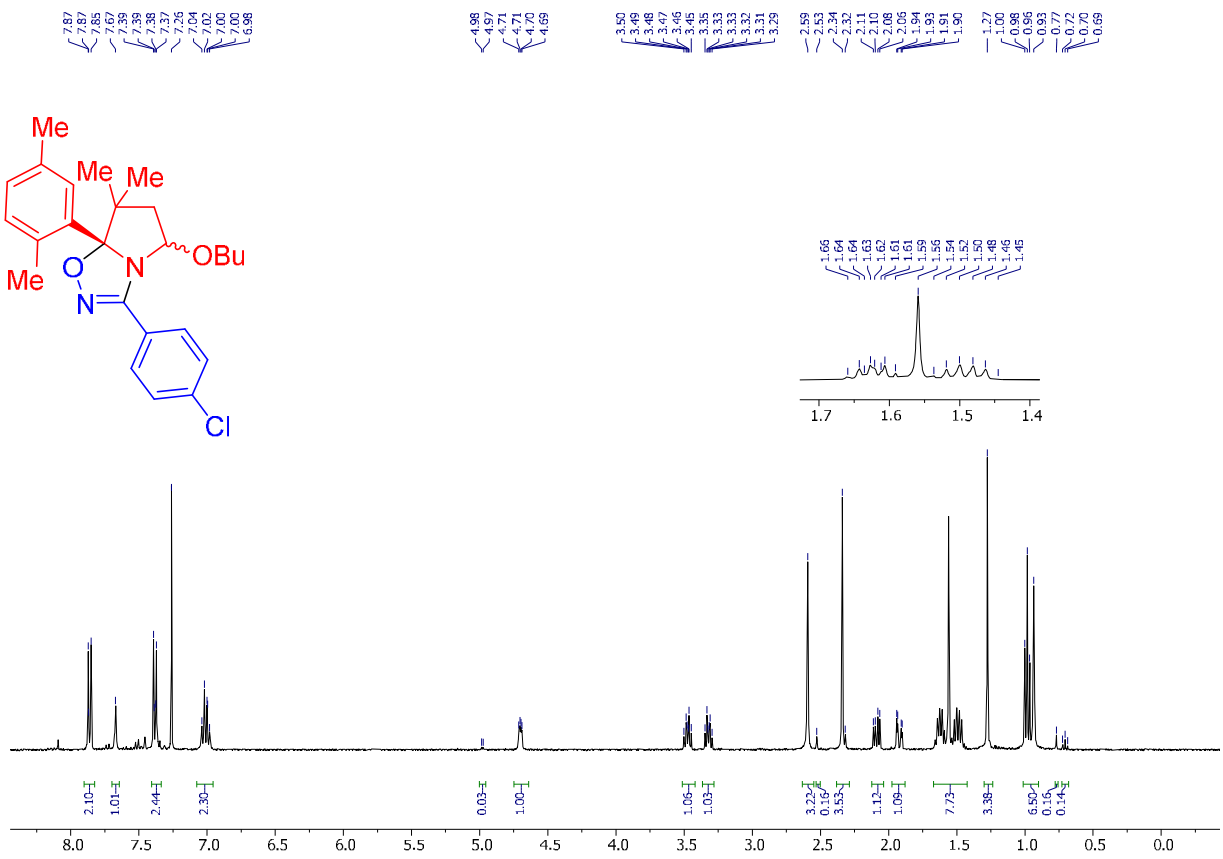
^{13}C NMR Spectrum of **3fa** (100.6 MHz, $CDCl_3$)



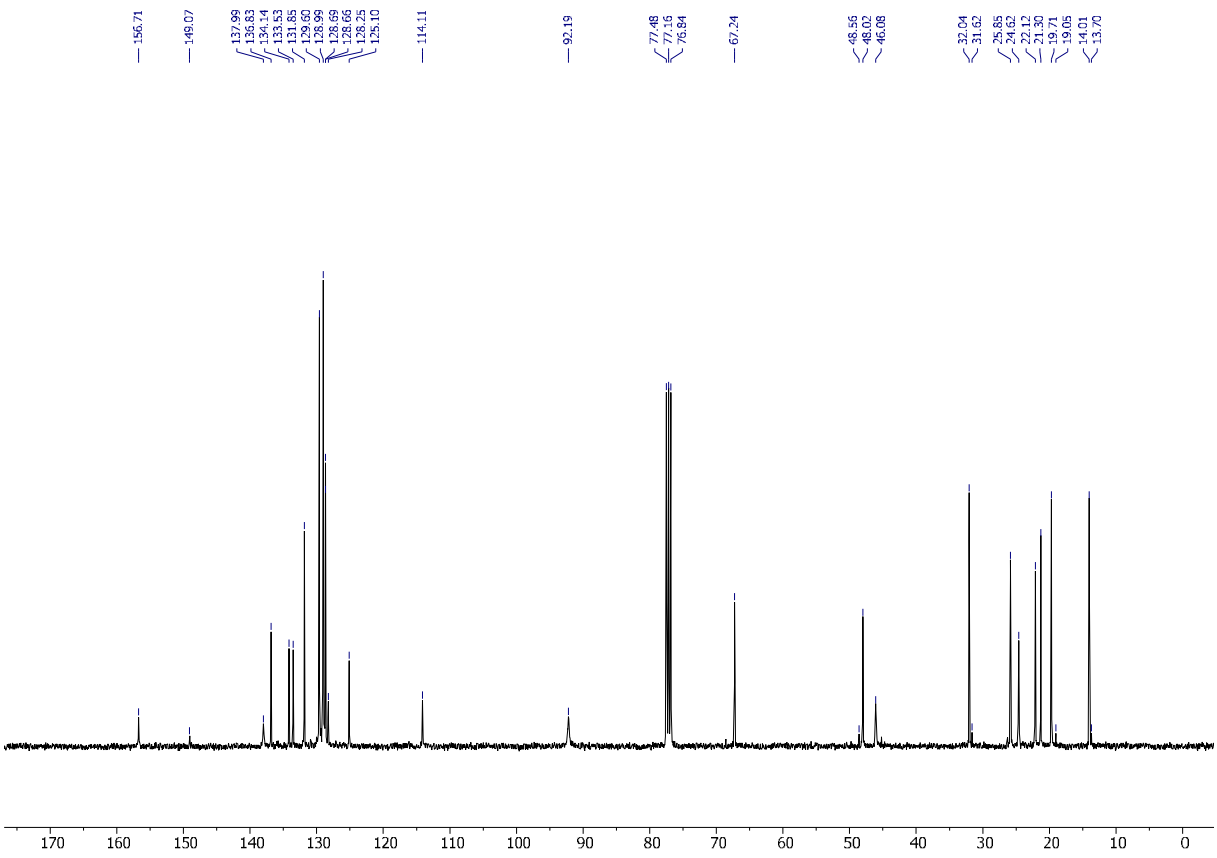
^{1}H NMR Spectrum of **3ga** (400.1 MHz, $CDCl_3$)



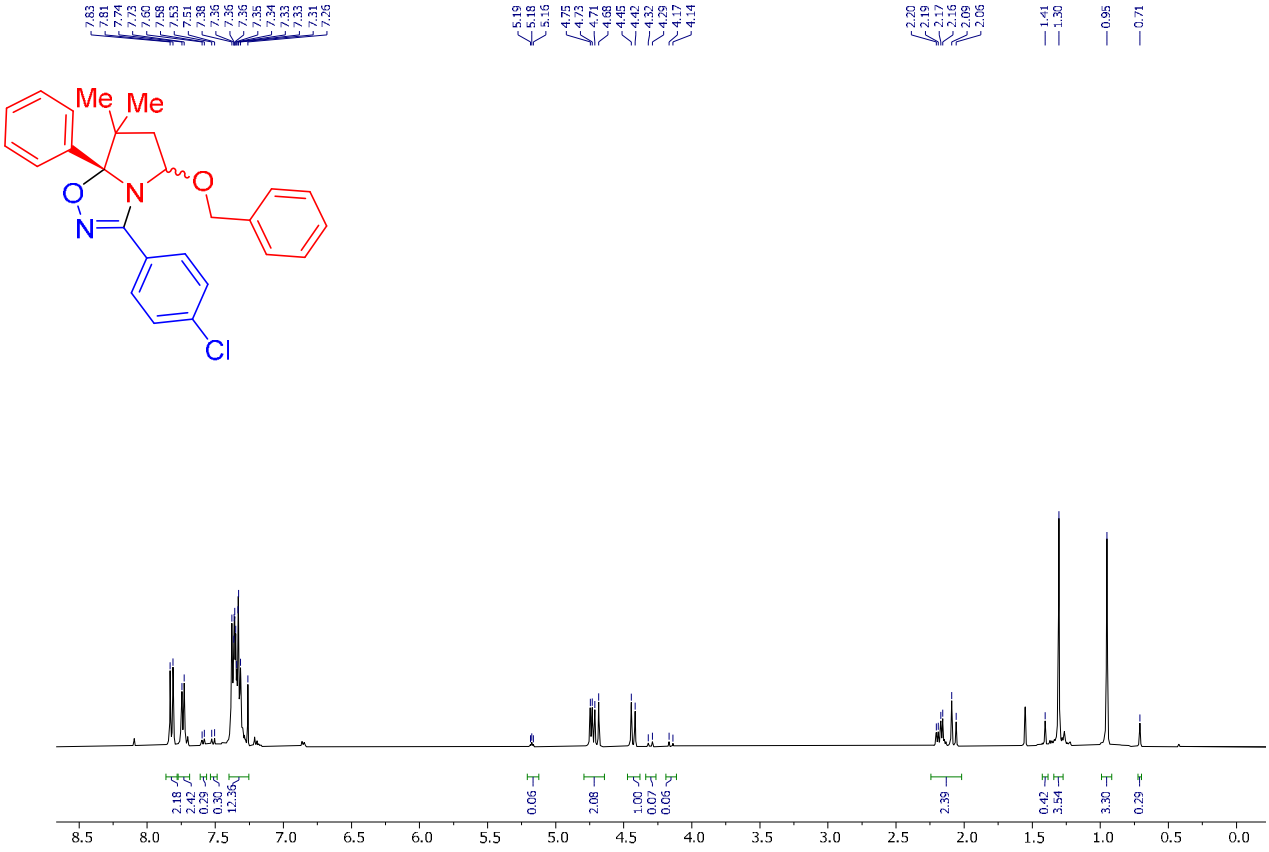
^{13}C NMR Spectrum of **3ga** (100.6 MHz, $CDCl_3$)



^{1}H NMR Spectrum of **3ha** (400.1 MHz, $CDCl_3$)



^{13}C NMR Spectrum of **3ha** (100.6 MHz, $CDCl_3$)



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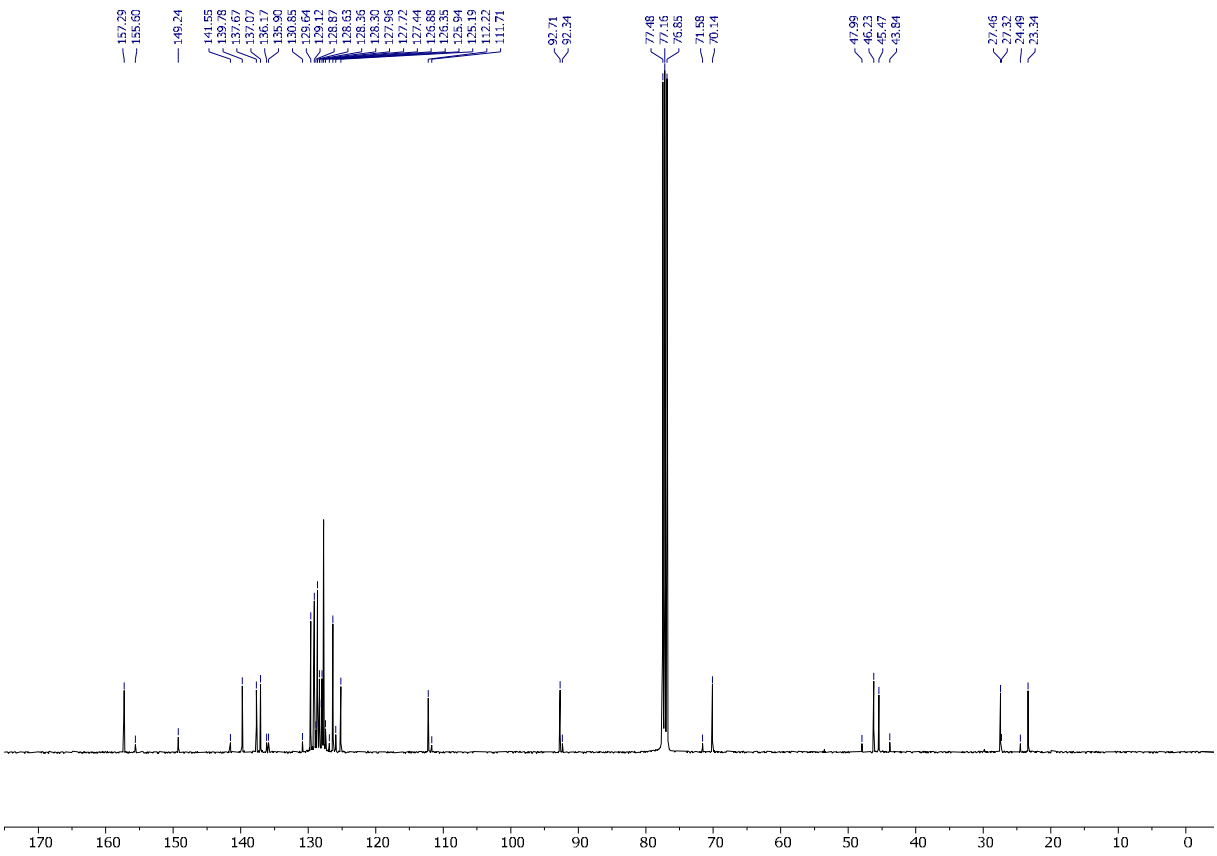
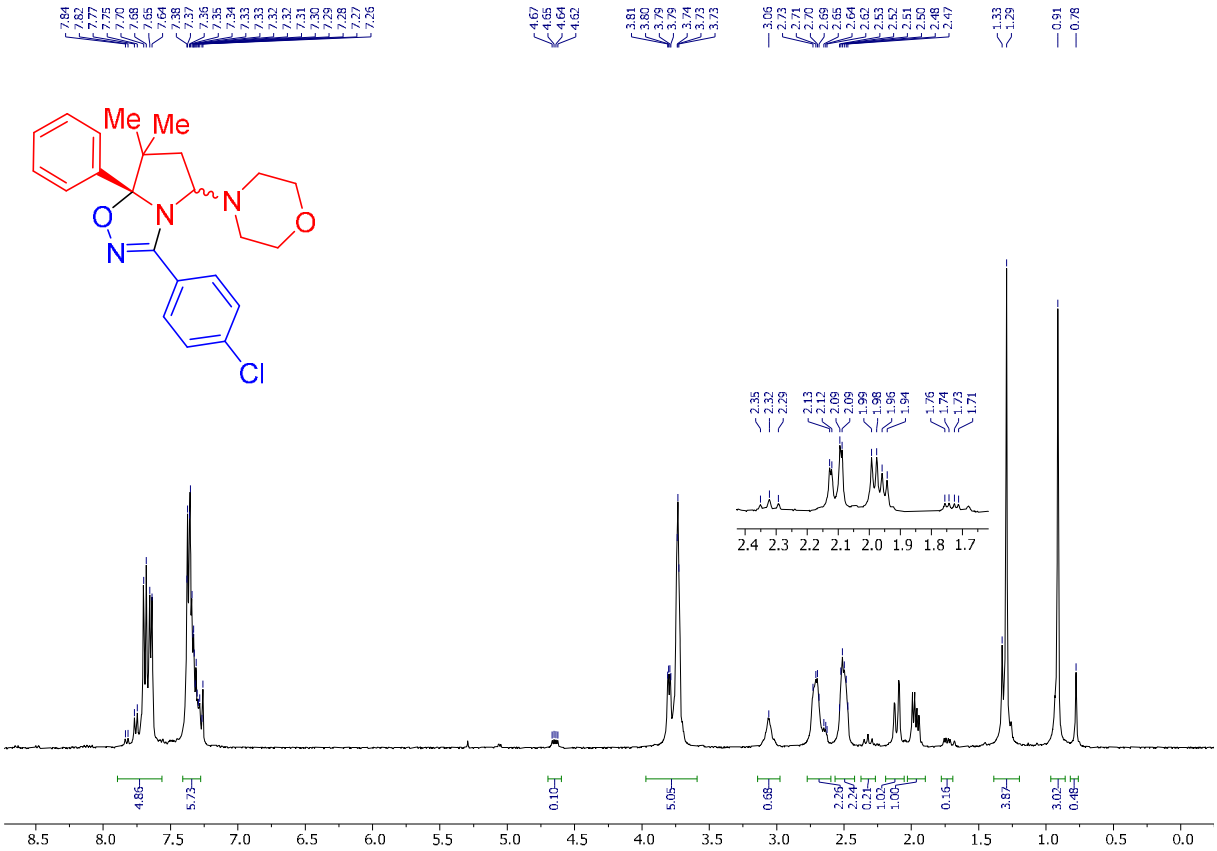
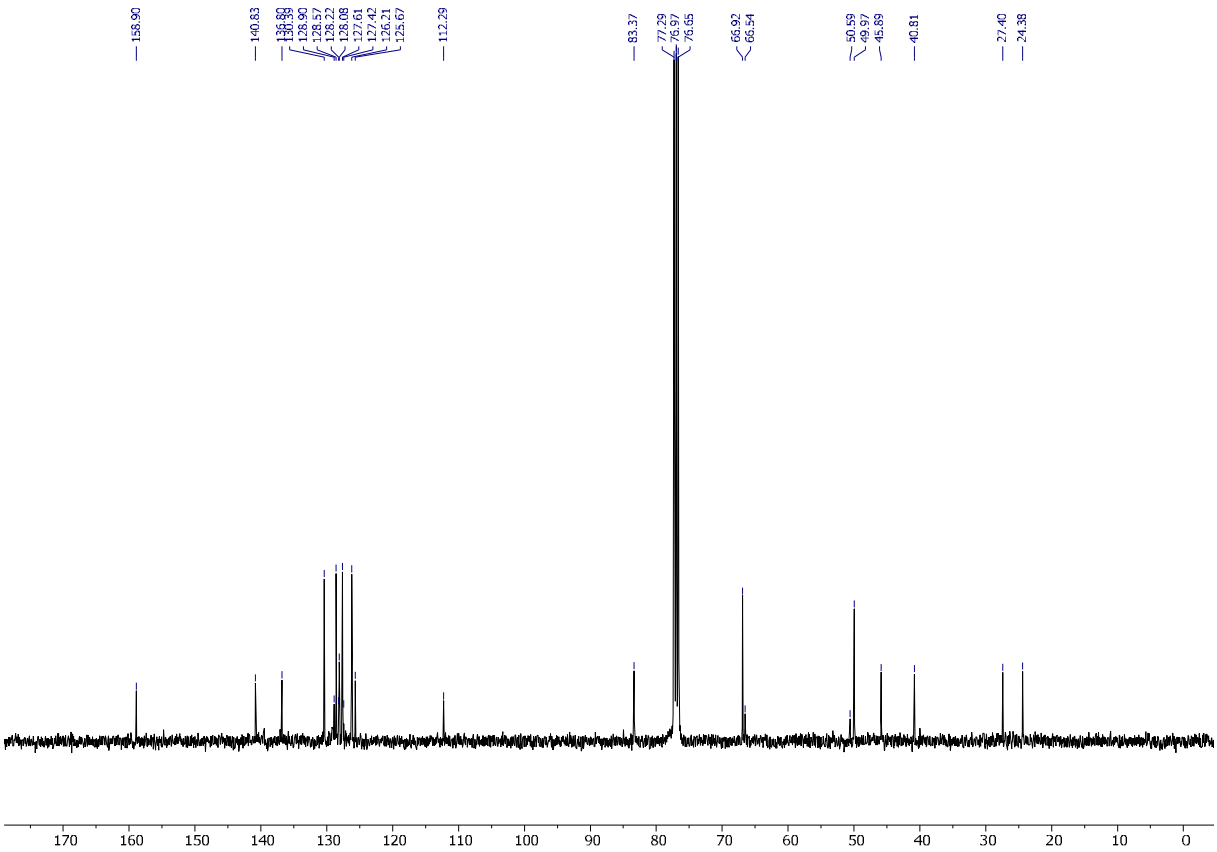


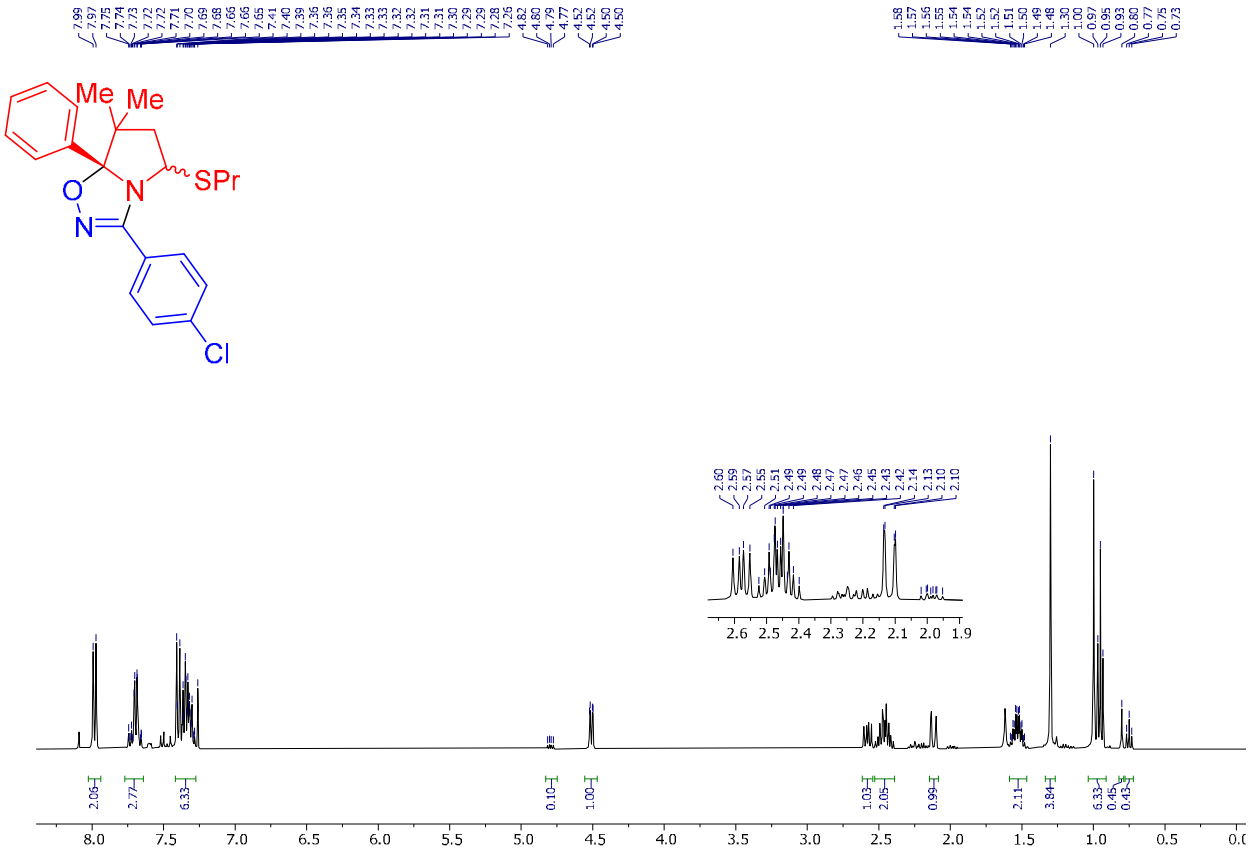
^{13}C NMR Spectrum of **3ia** (100.6 MHz, $CDCl_3$)



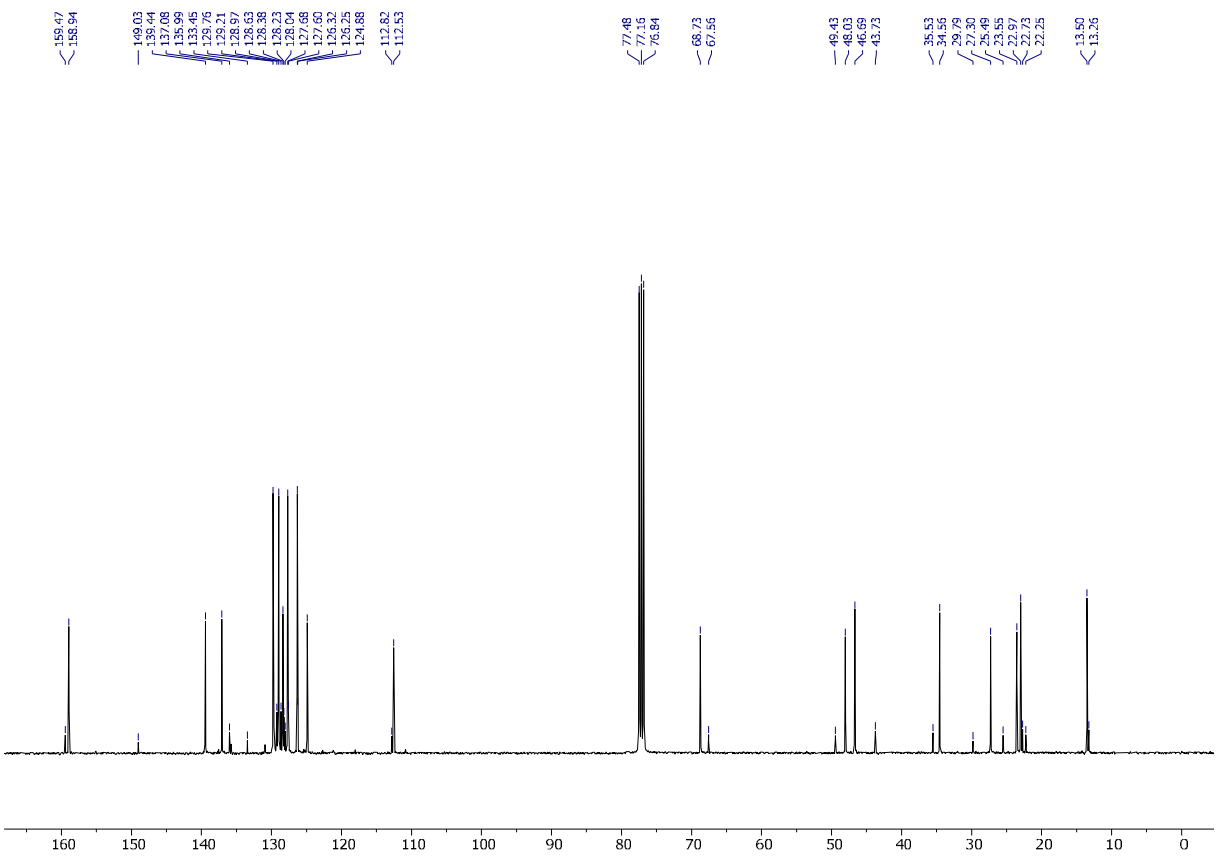
^{1}H NMR Spectrum of **3ja** (400.1 MHz, $CDCl_3$)



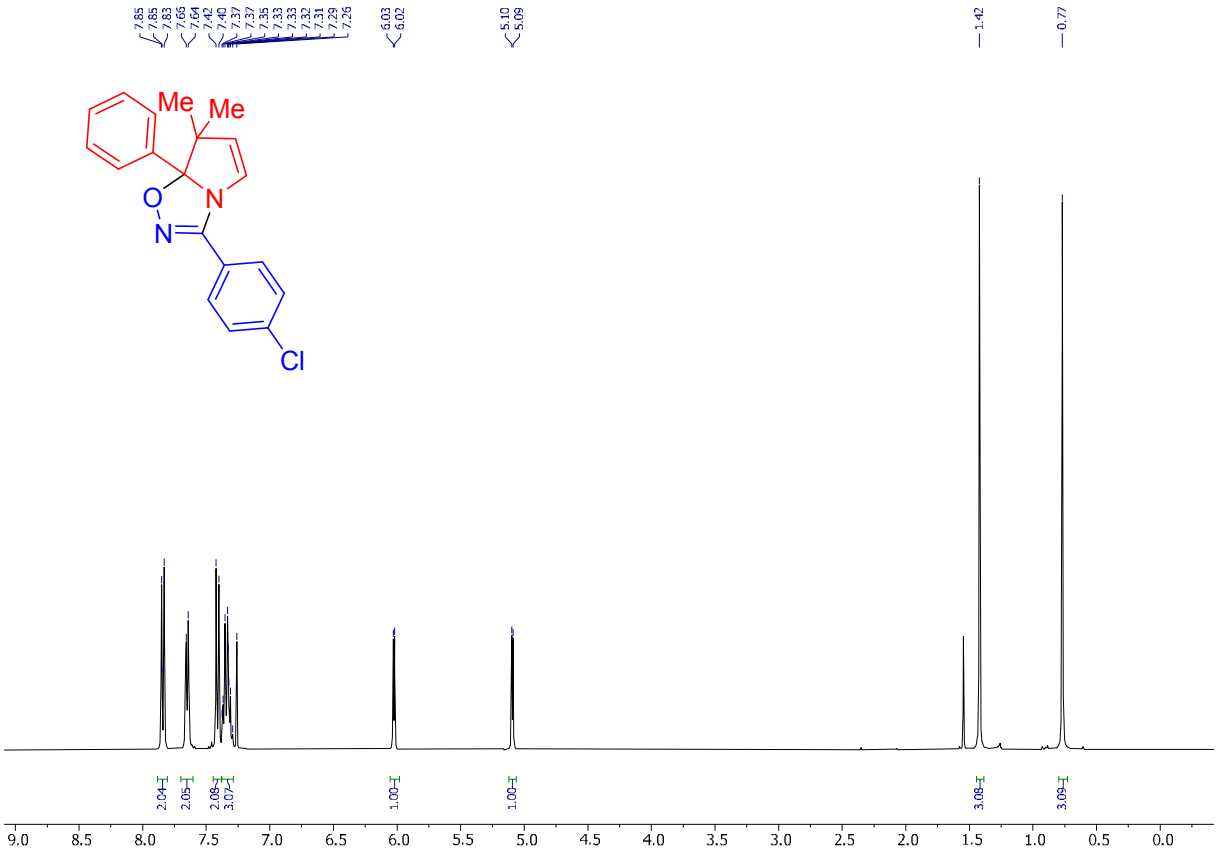
^{13}C NMR Spectrum of **3ja** (100.6 MHz, $CDCl_3$)



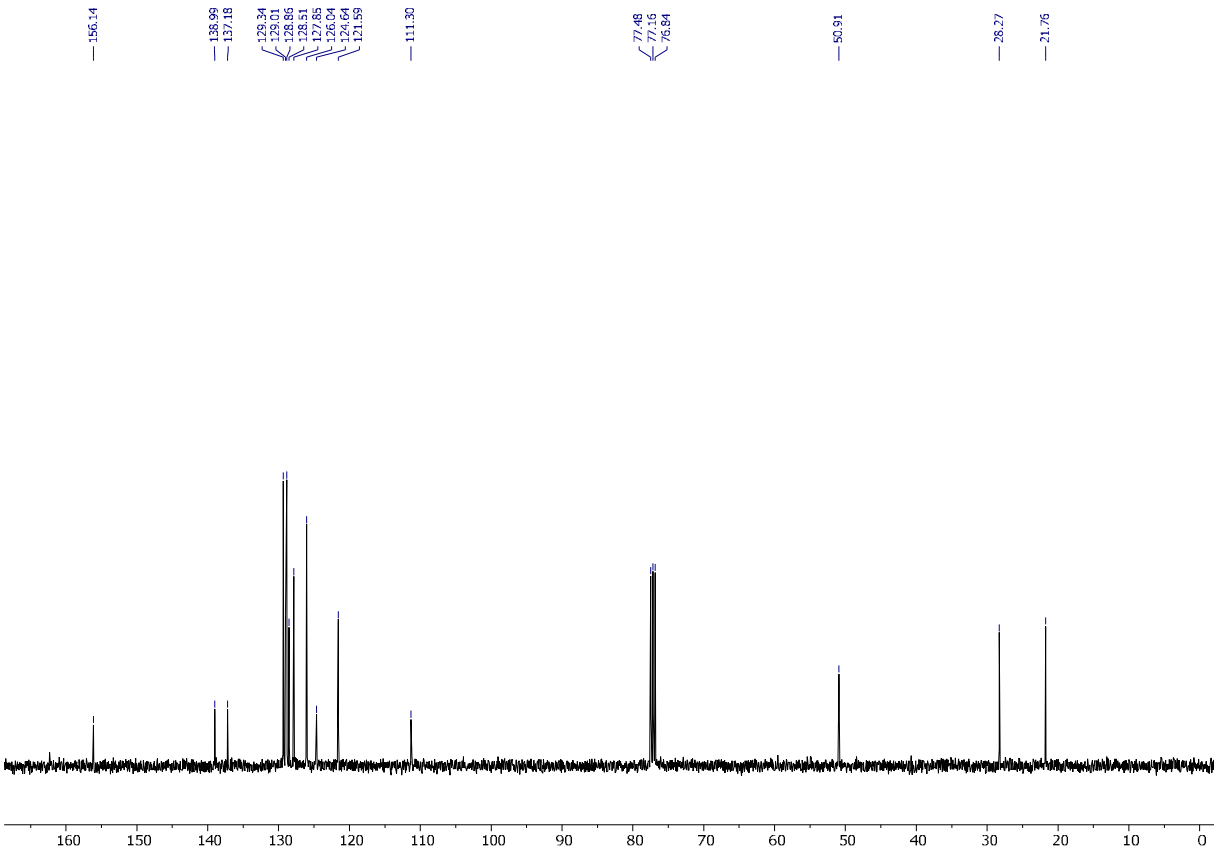
^{1}H NMR Spectrum of **3ka** (400.1 MHz, $CDCl_3$)



^{13}C NMR Spectrum of **3ka** (100.6 MHz, $CDCl_3$)

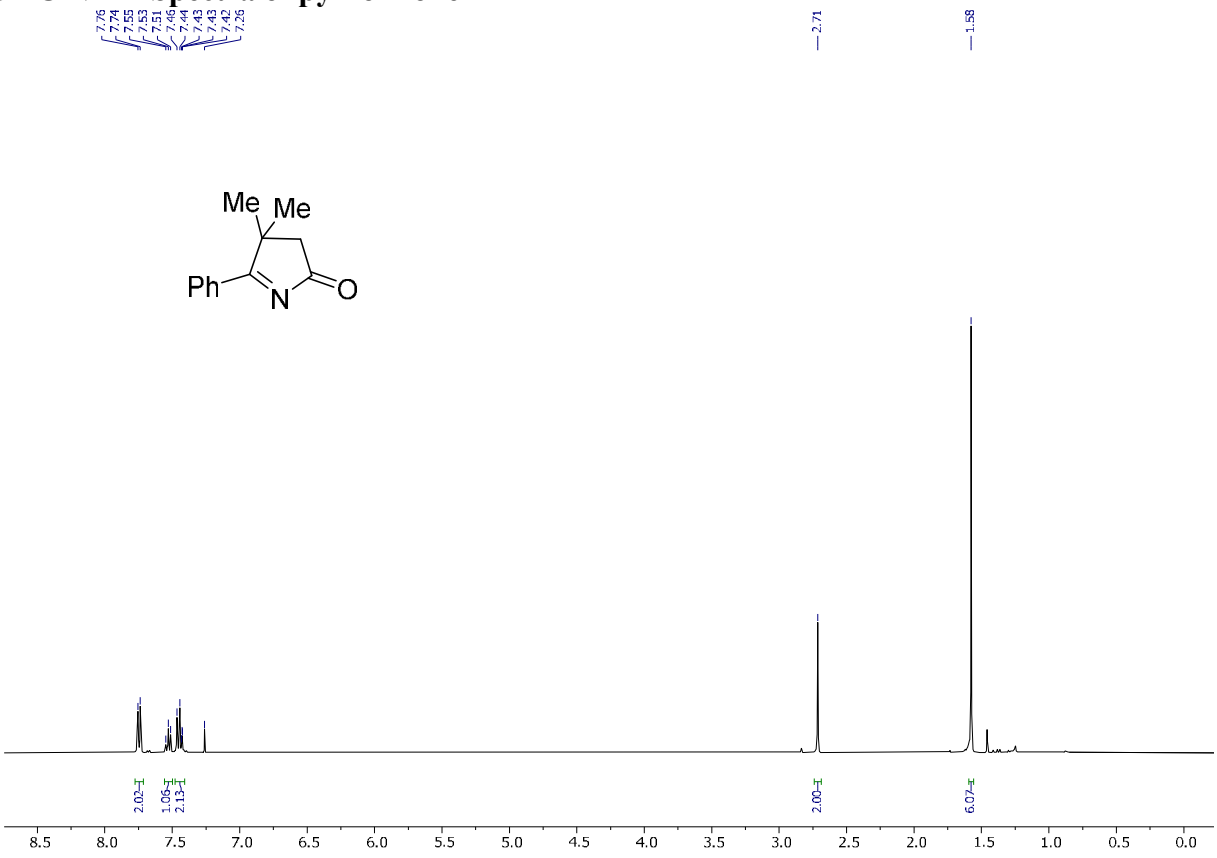


^{1}H NMR Spectrum of **3la** (400.1 MHz, $CDCl_3$)

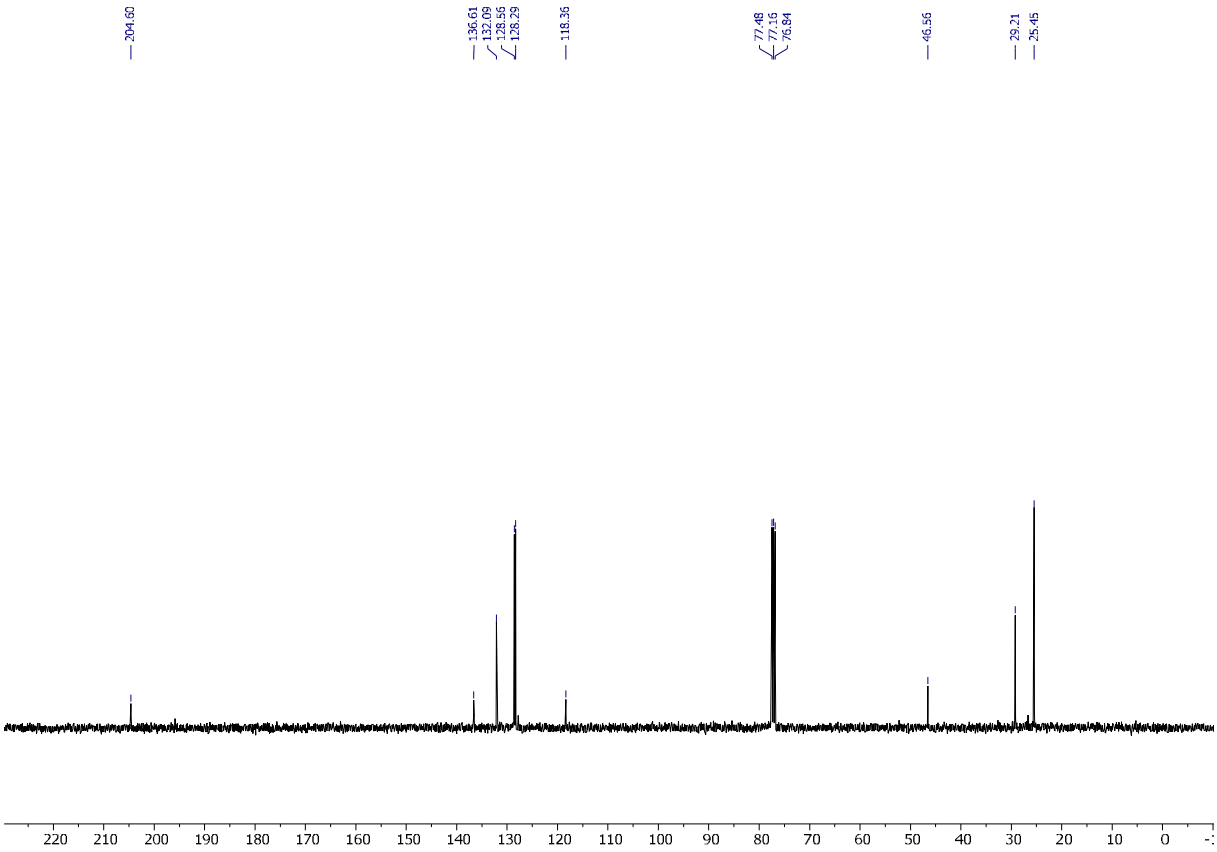


^{13}C NMR Spectrum of **3la** (100.6 MHz, $CDCl_3$)

^{1}H and ^{13}C NMR Spectra of pyrrolinone 4

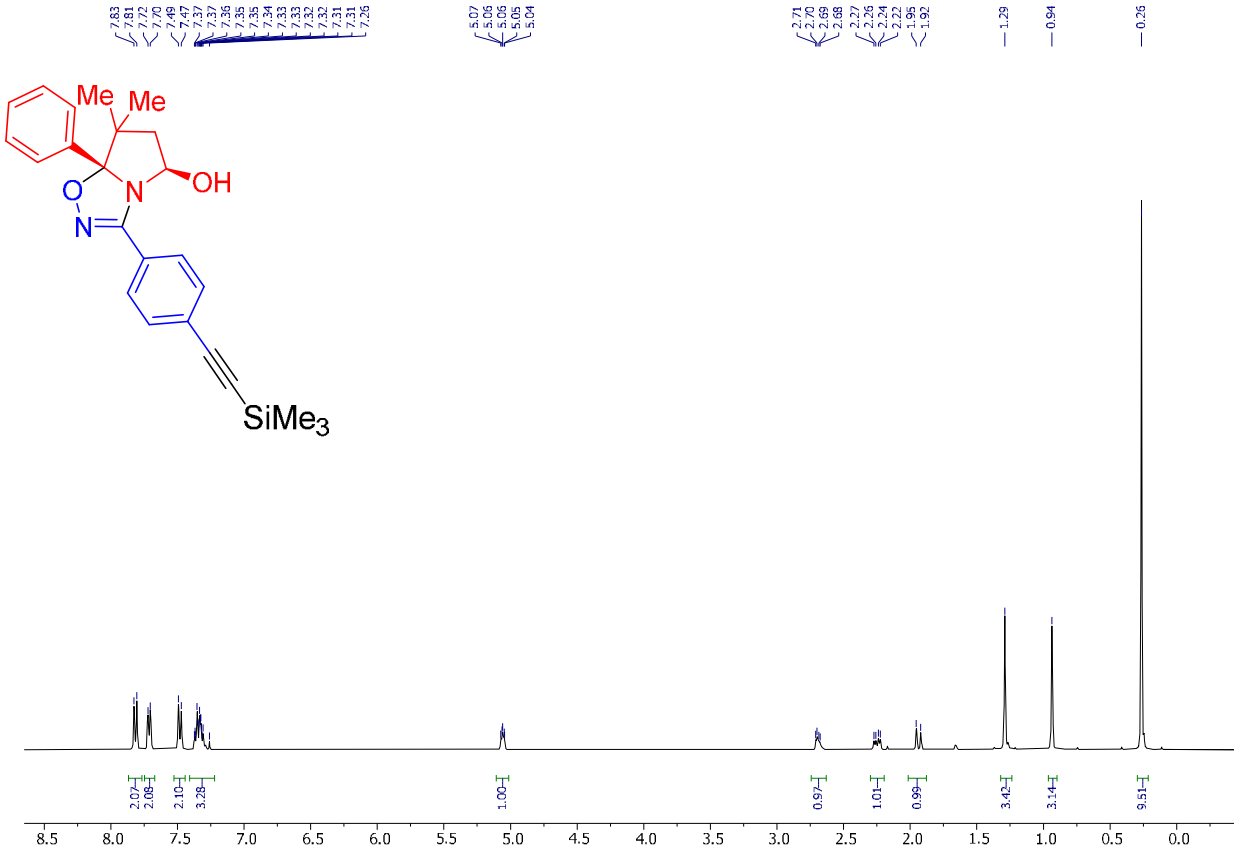


^{1}H NMR Spectrum of **4** (400.1 MHz, $CDCl_3$)

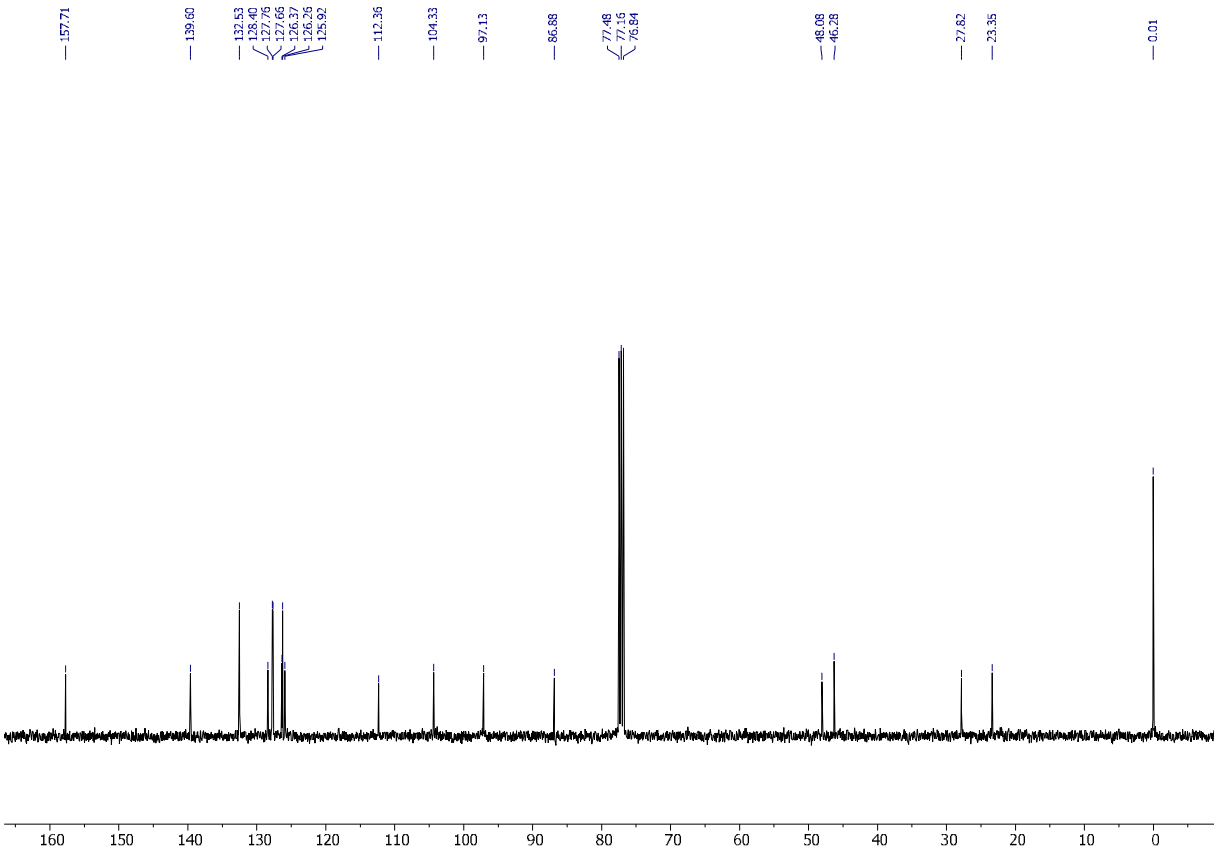


^{13}C NMR Spectrum of **4** (100.6 MHz, $CDCl_3$)

^{1}H and ^{13}C NMR Spectra of tetrahydropyrrolo[1,2-*d*]oxadiazole 5



^{1}H NMR Spectrum of **5** (400.1 MHz, $CDCl_3$)



^{13}C NMR Spectrum of **5** (100.6 MHz, $CDCl_3$)