

A facile green chemistry approaches towards the synthesis of bis-Schiff bases using ultrasound versus microwave and conventional method without catalyst

Wael A. A. Arafa,^{a*} Raafat M. Shaker^b

^a Chemistry Department, Faculty of Science, Fayoum University 63514, Fayoum, Egypt

^b Chemistry Department, Faculty of Science, Minia University, 61519 Minia, Egypt

E-mail: waa00@fayoum.edu.eg

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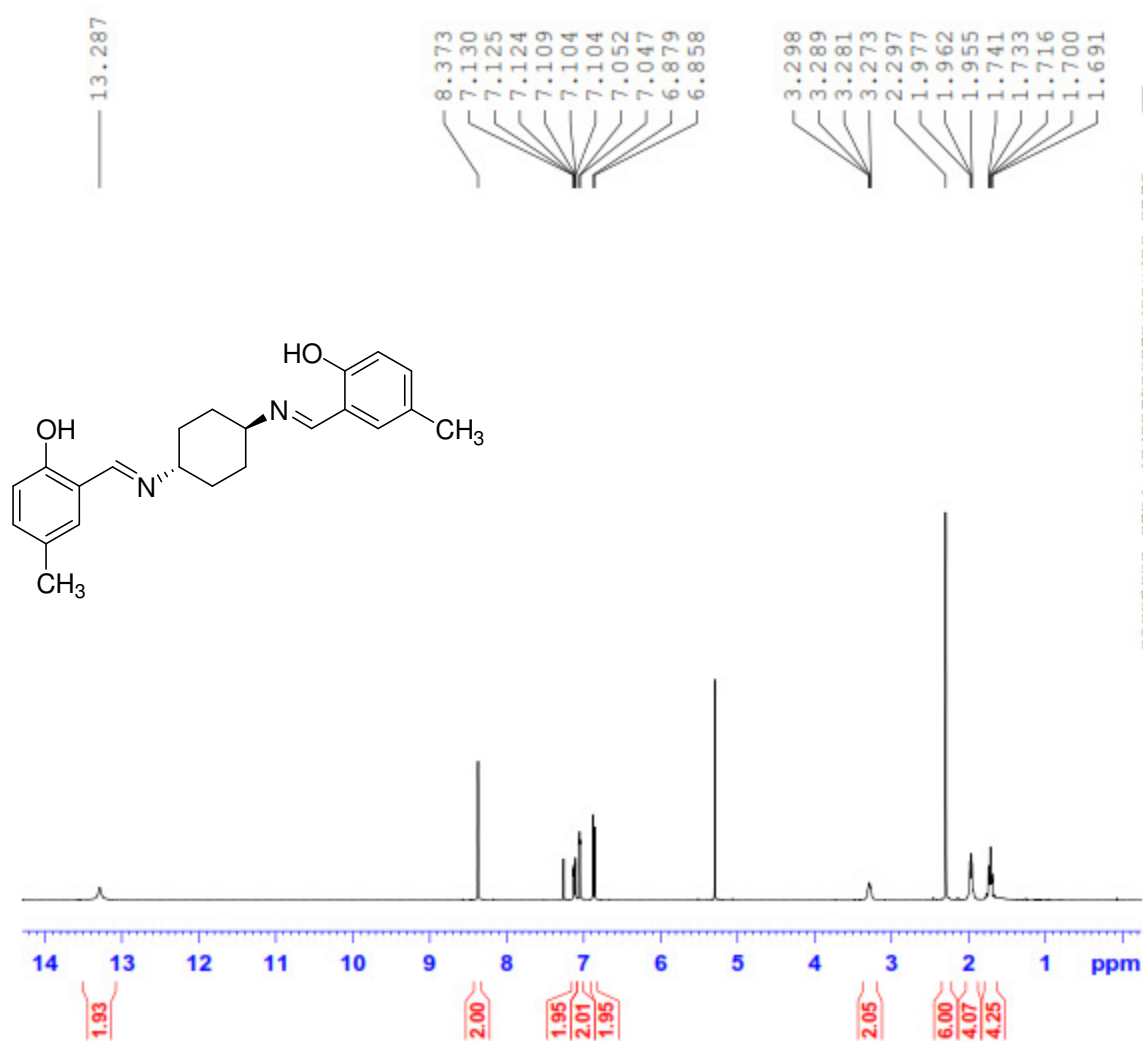


Figure S1. 3a, ¹H NMR.

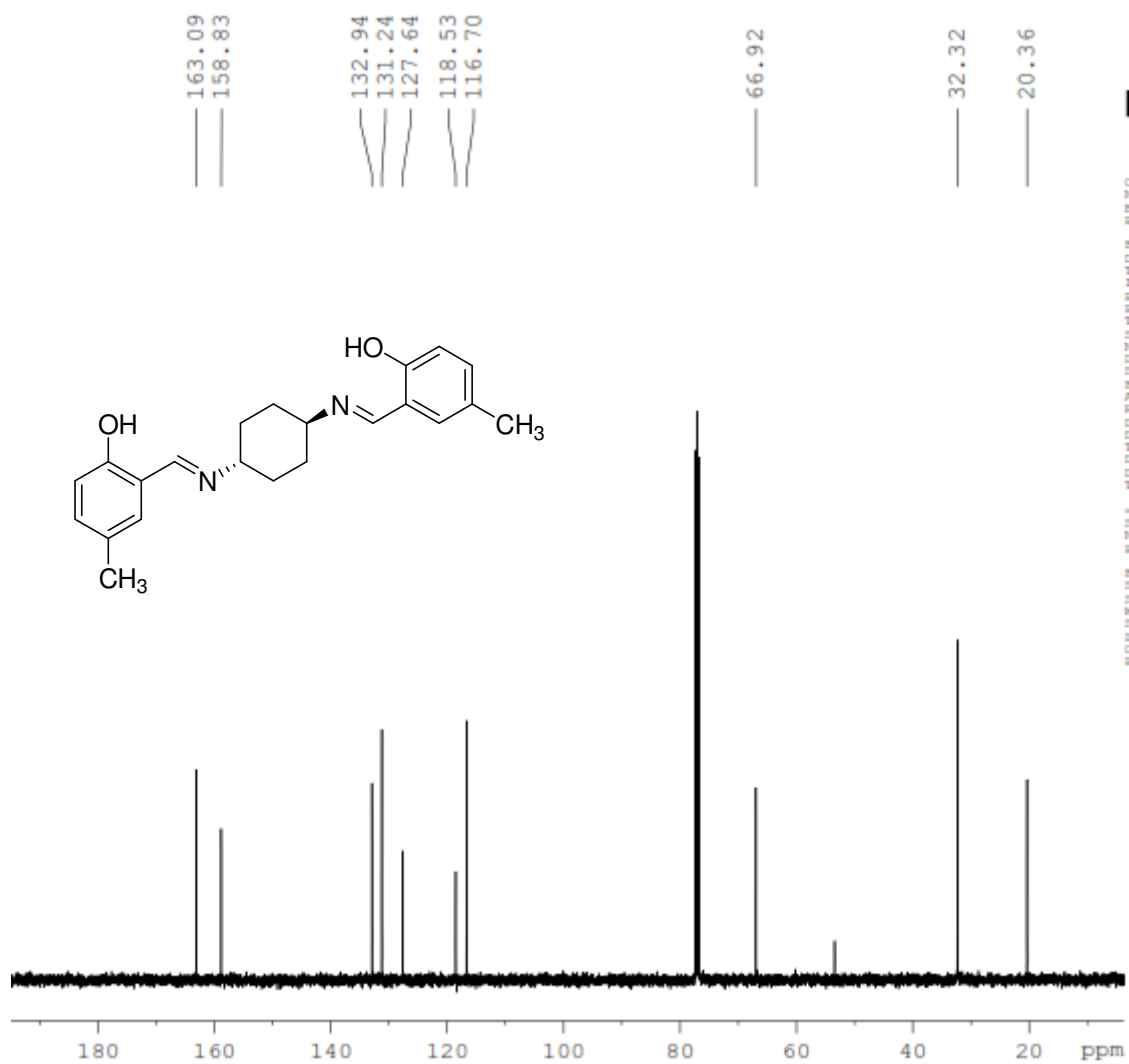
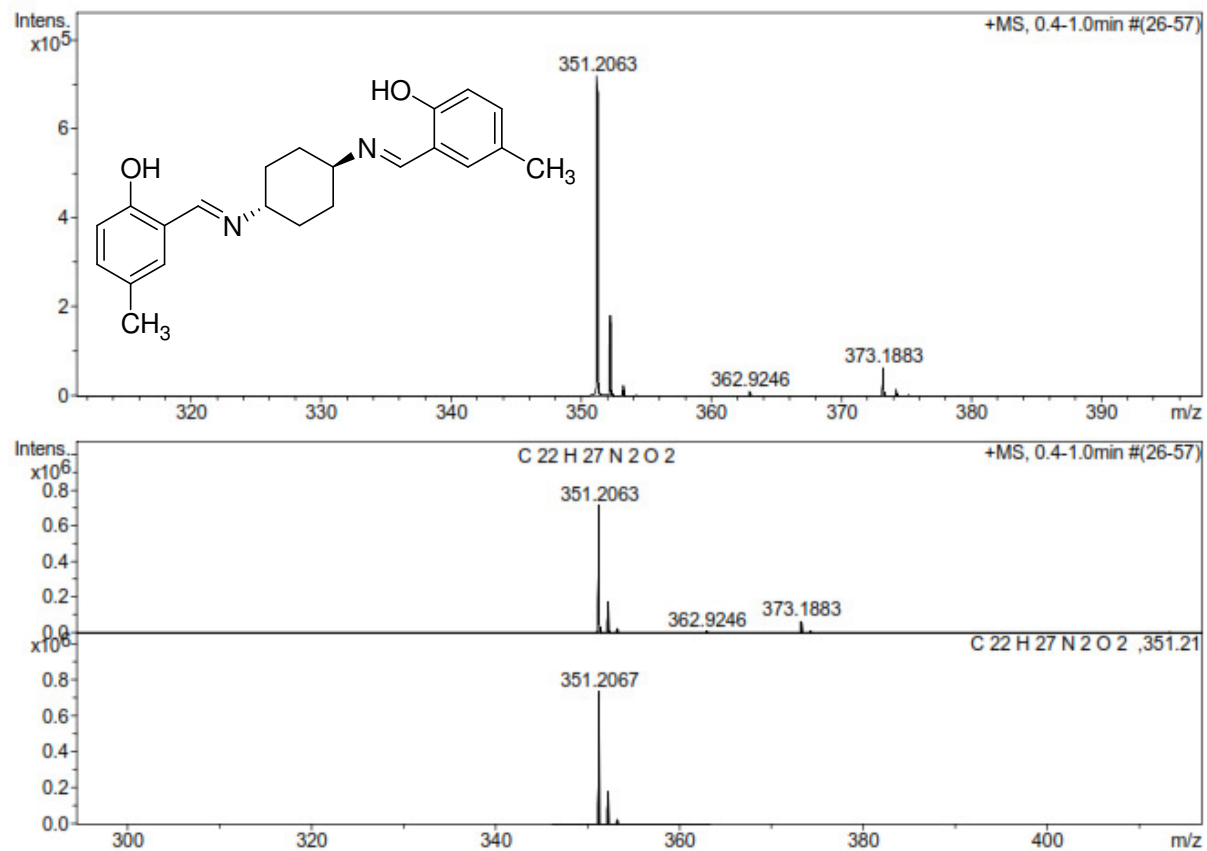


Figure S2. **3a**, ^{13}C NMR.

**Figure S3. 3a, HRMS.**

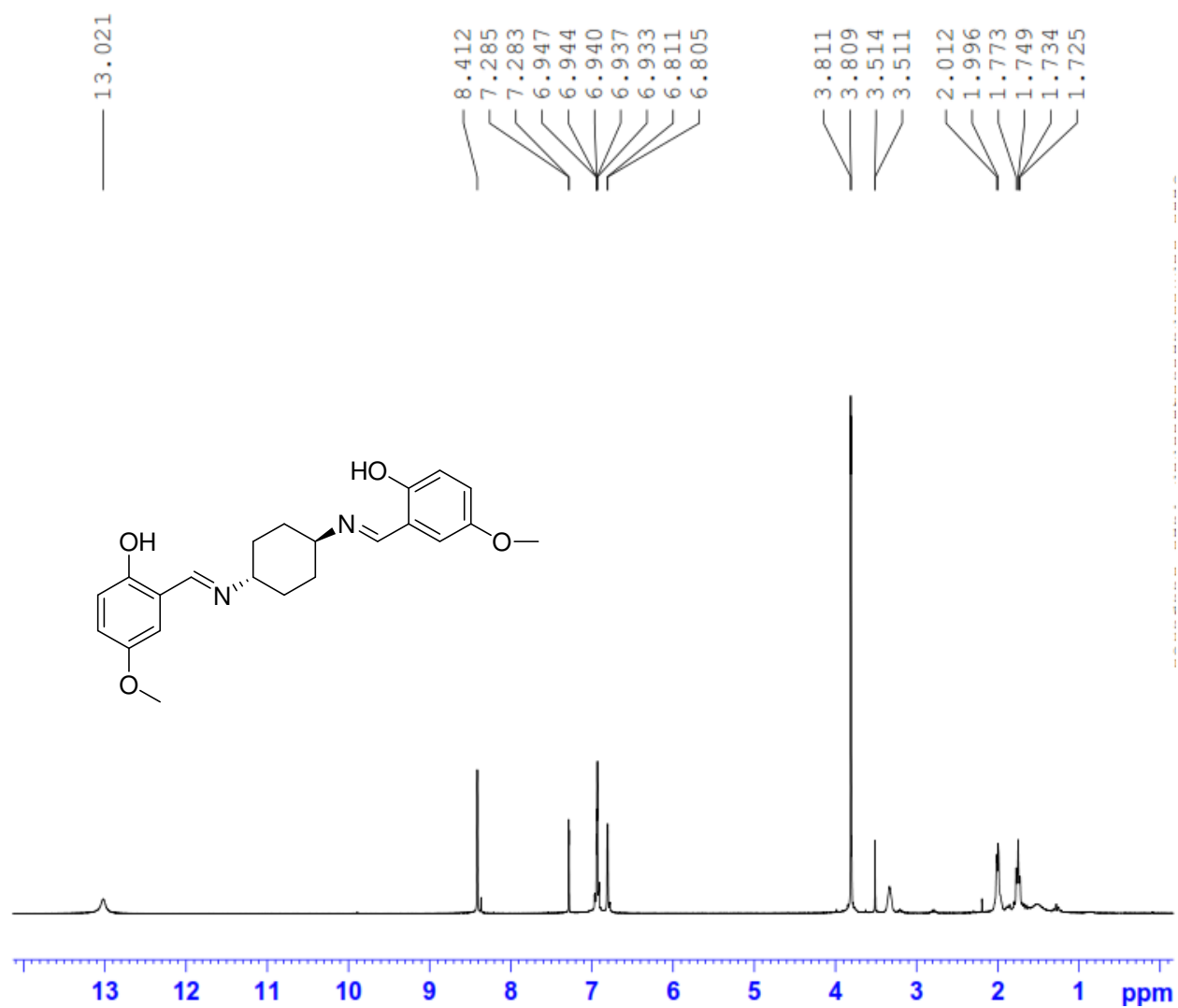


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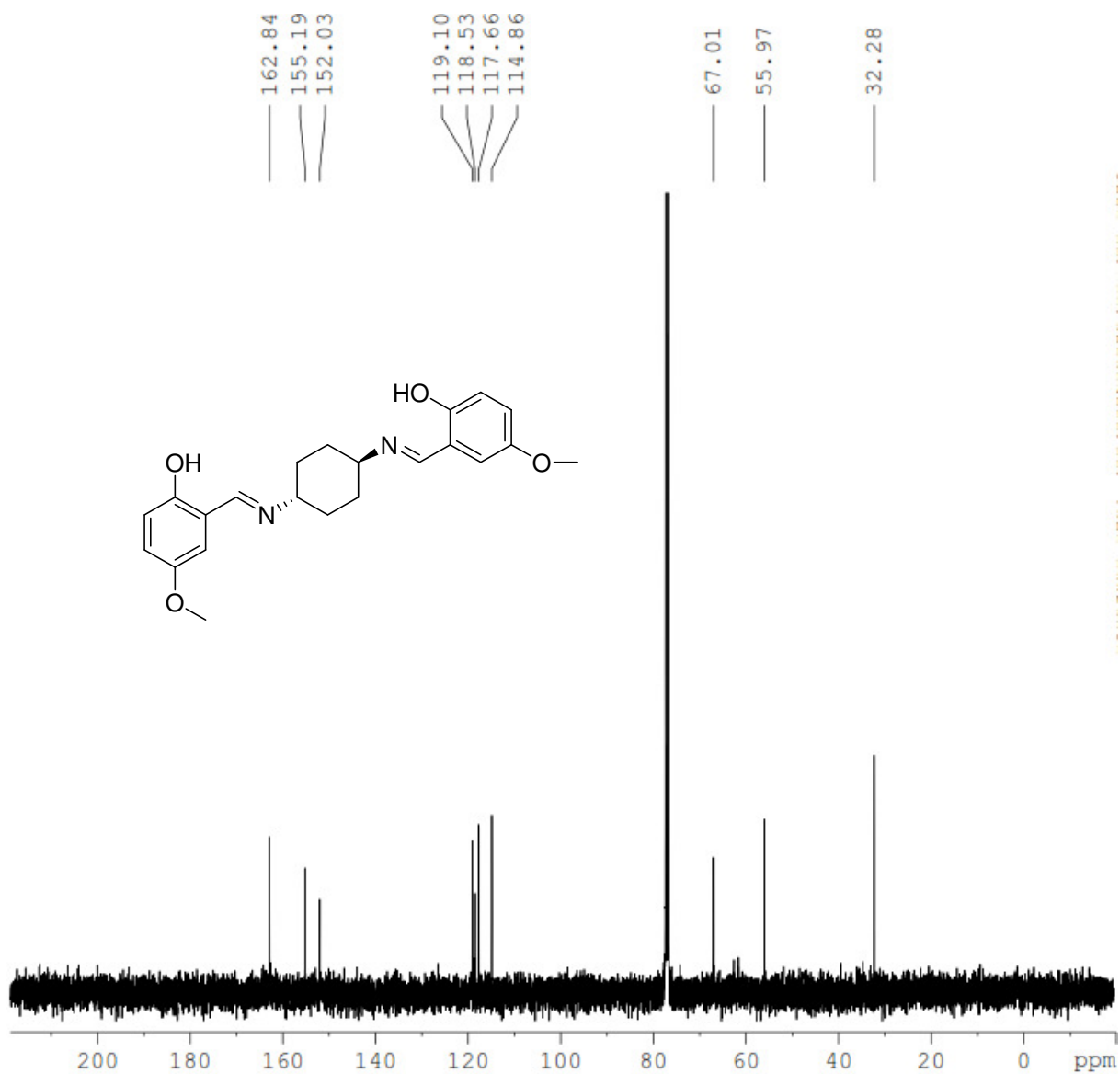


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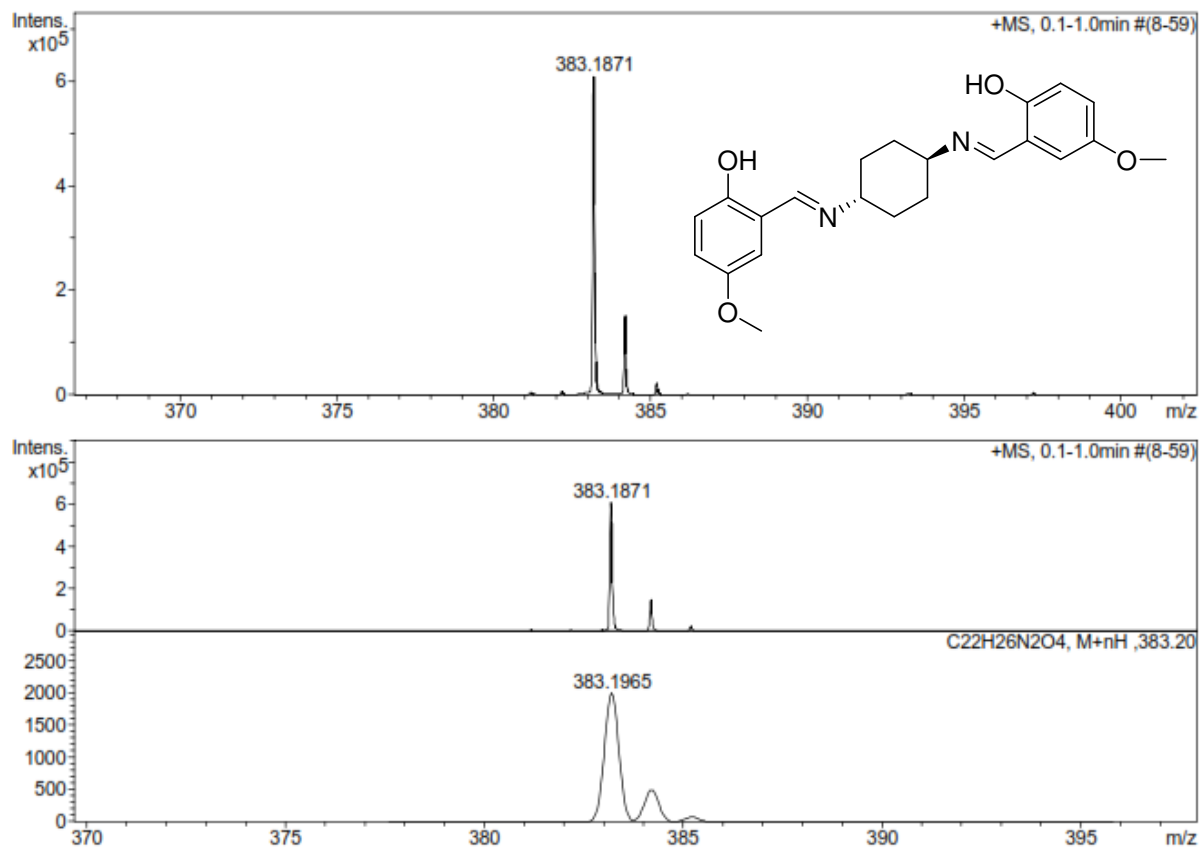


Figure S6. 3b, HRMS.

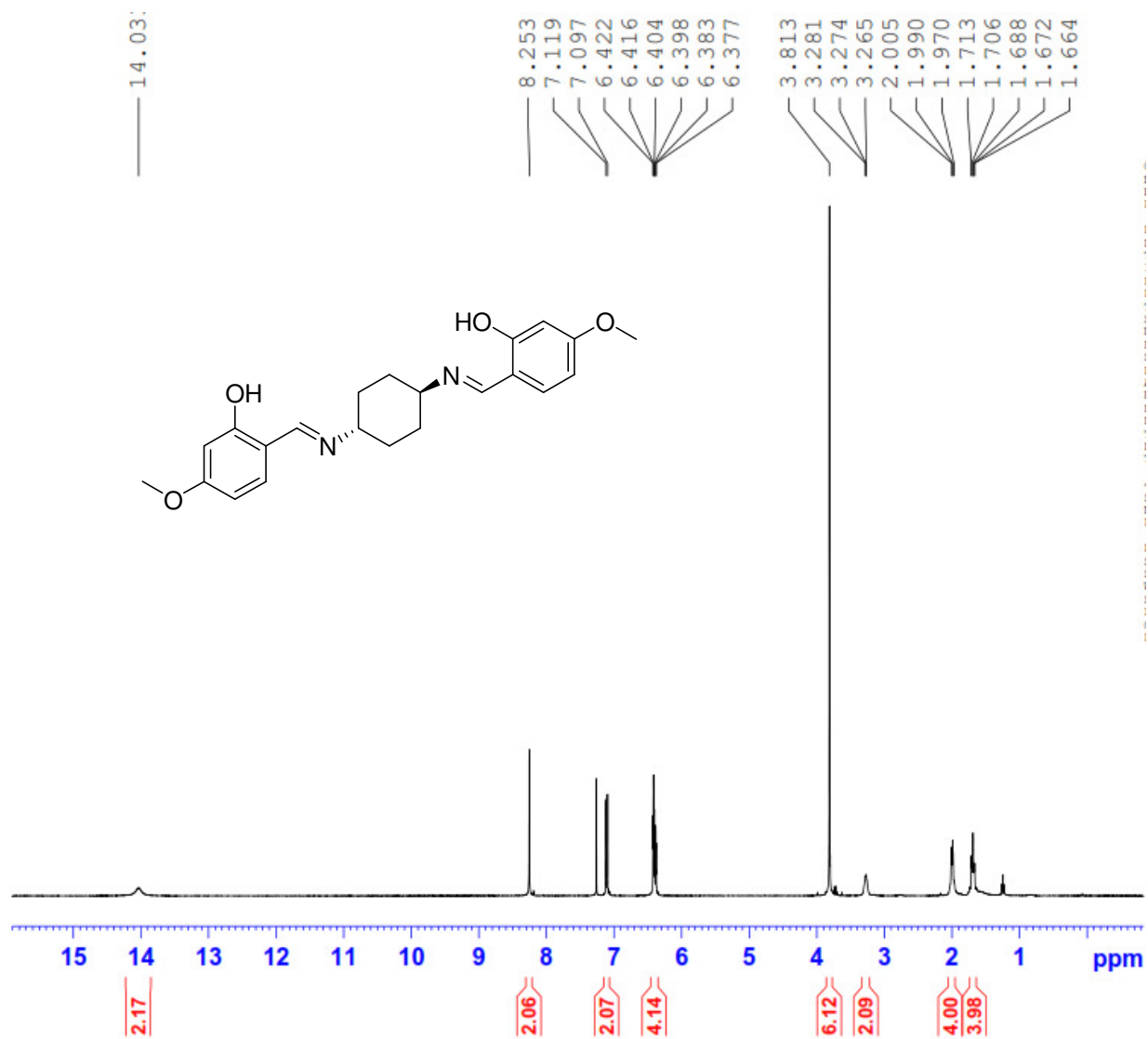


Figure S7. 3c, ¹H NMR.

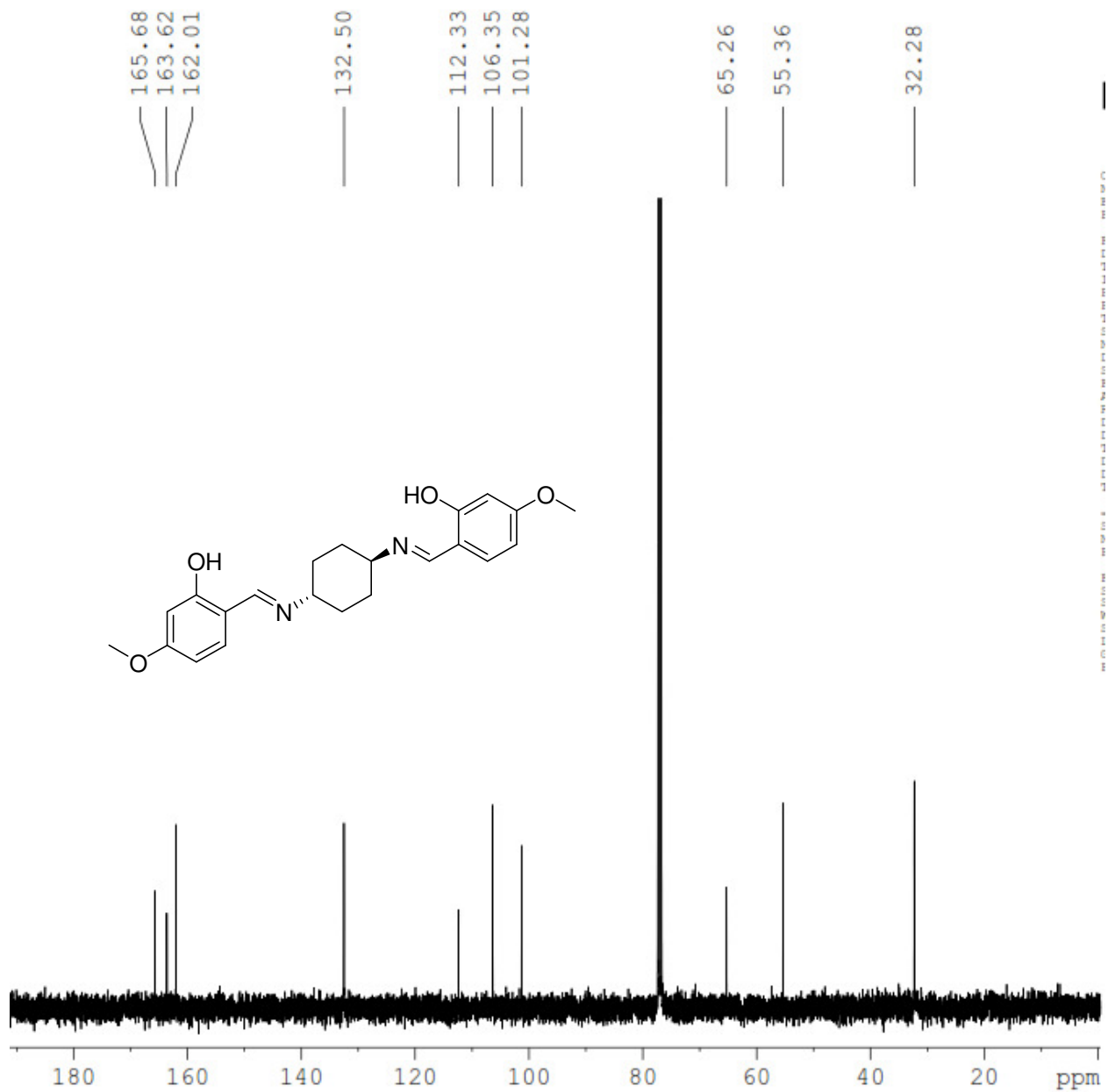


Figure S8. 3c, ¹³C NMR.

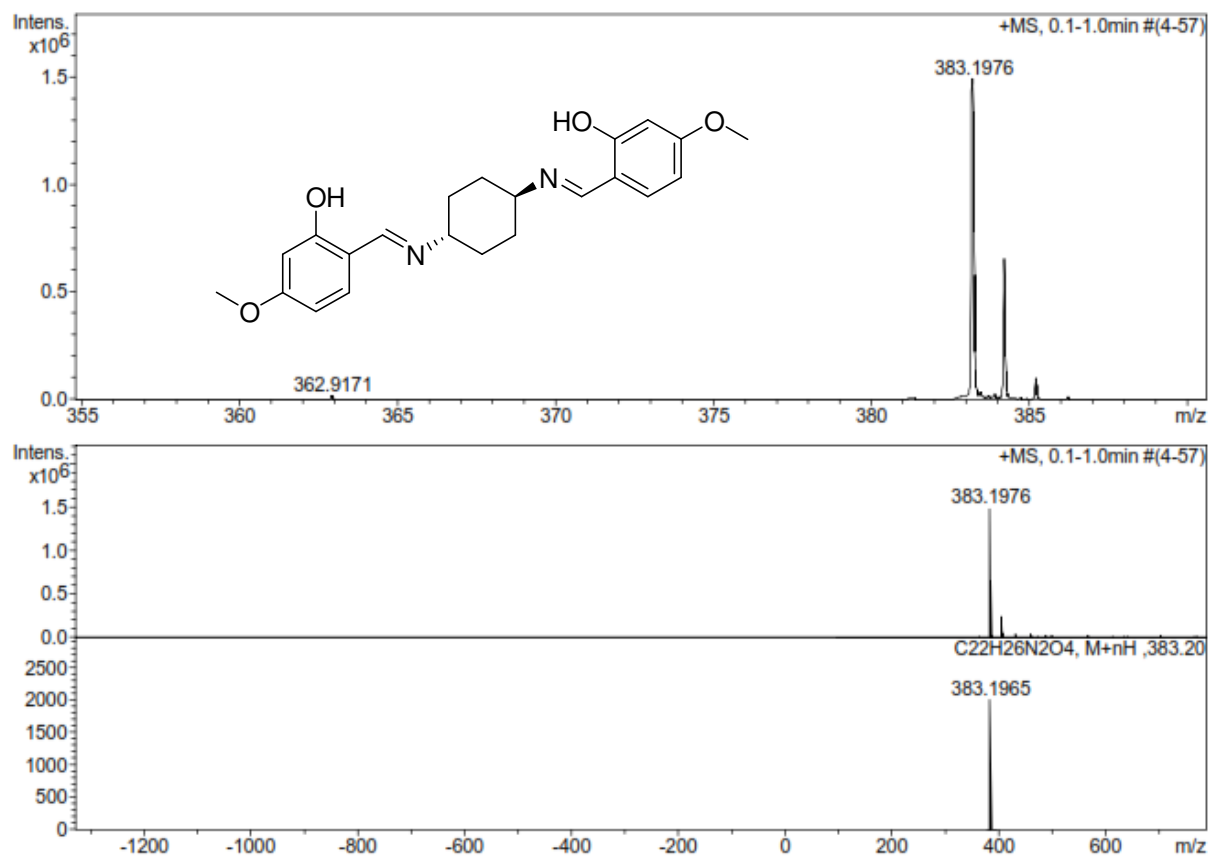


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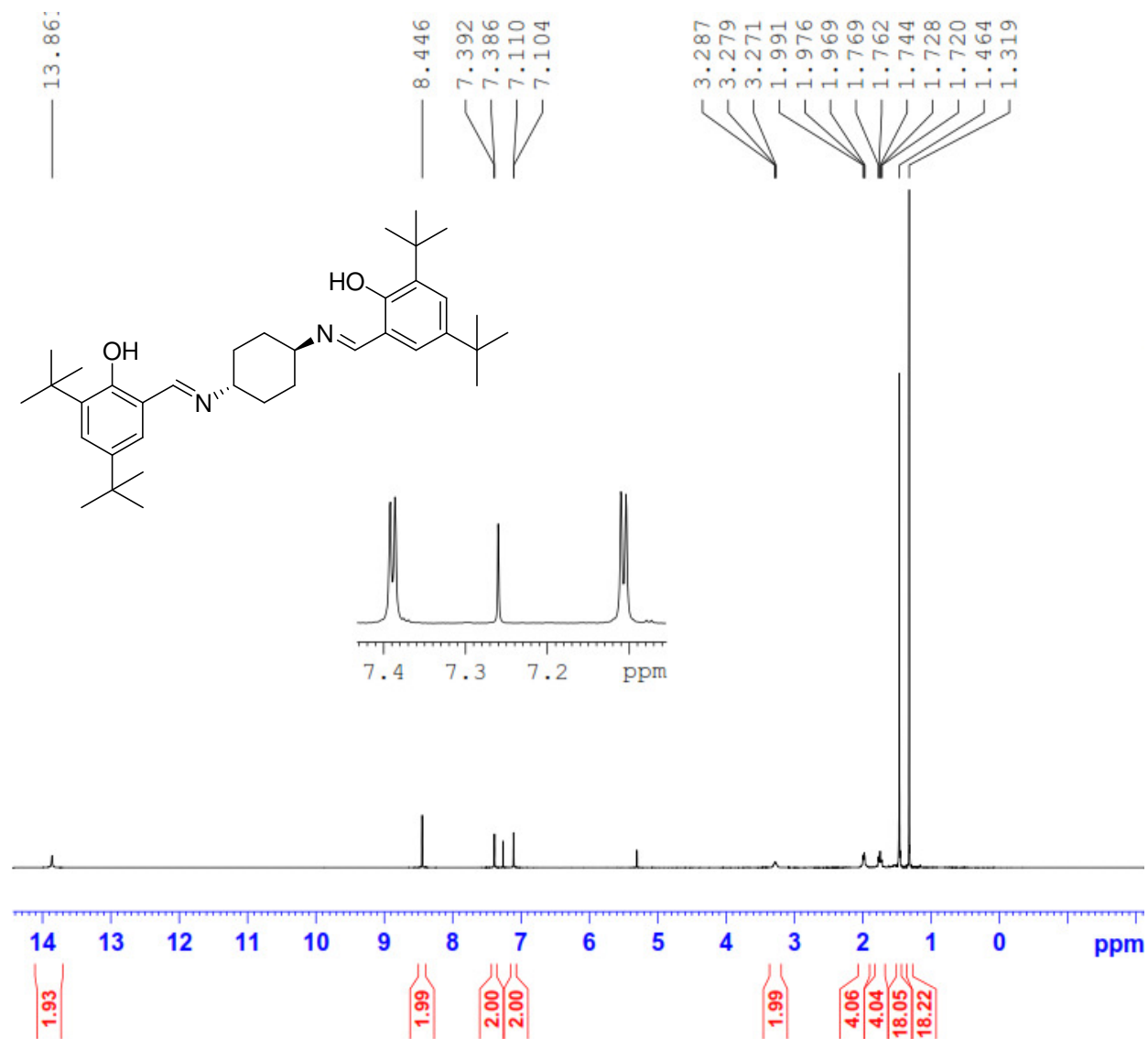


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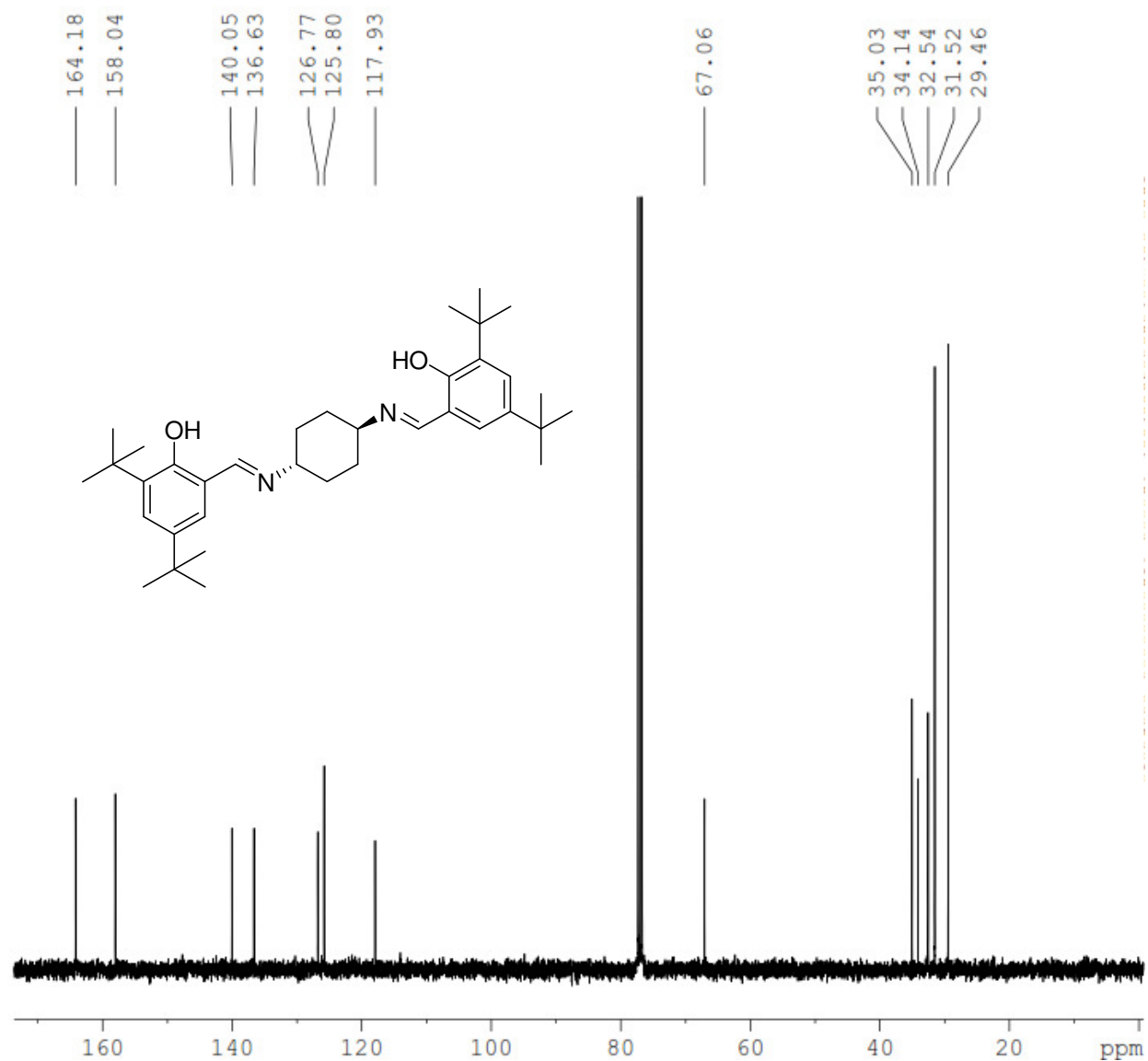


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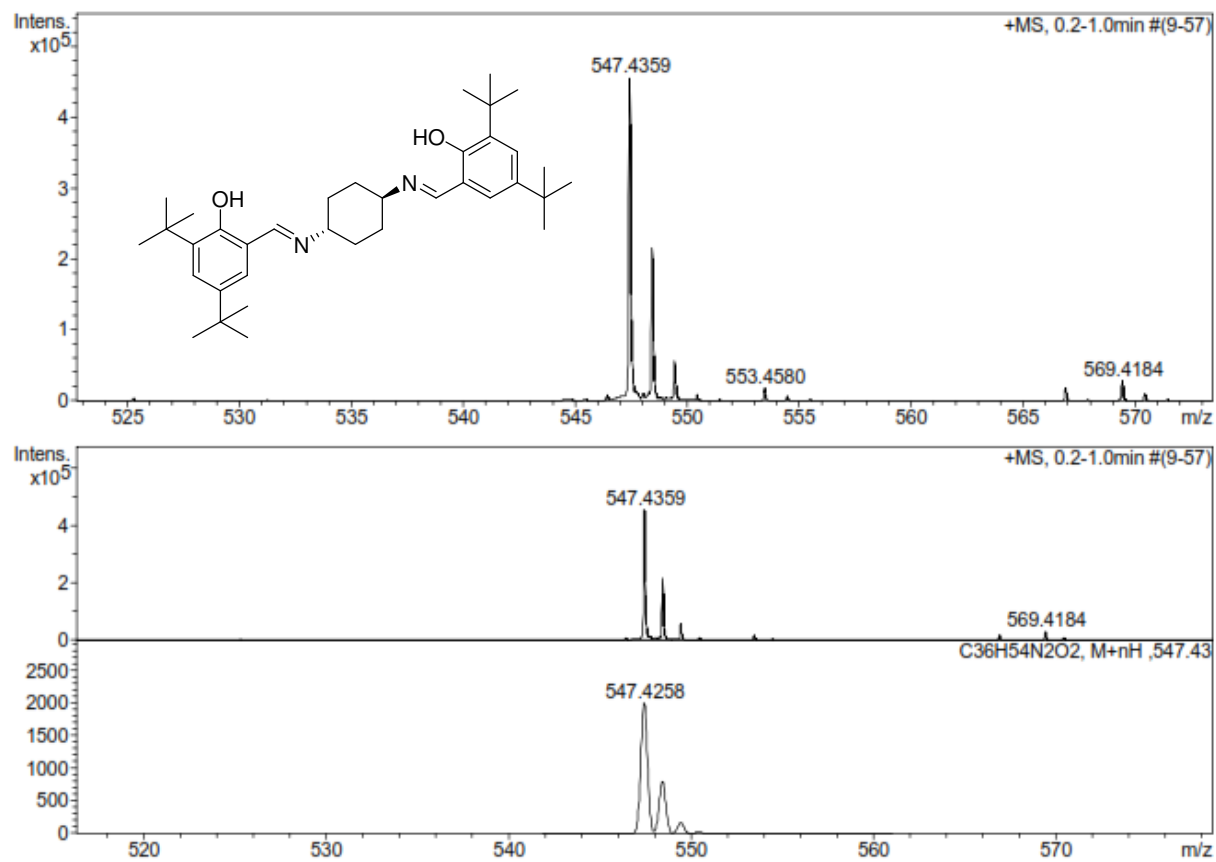


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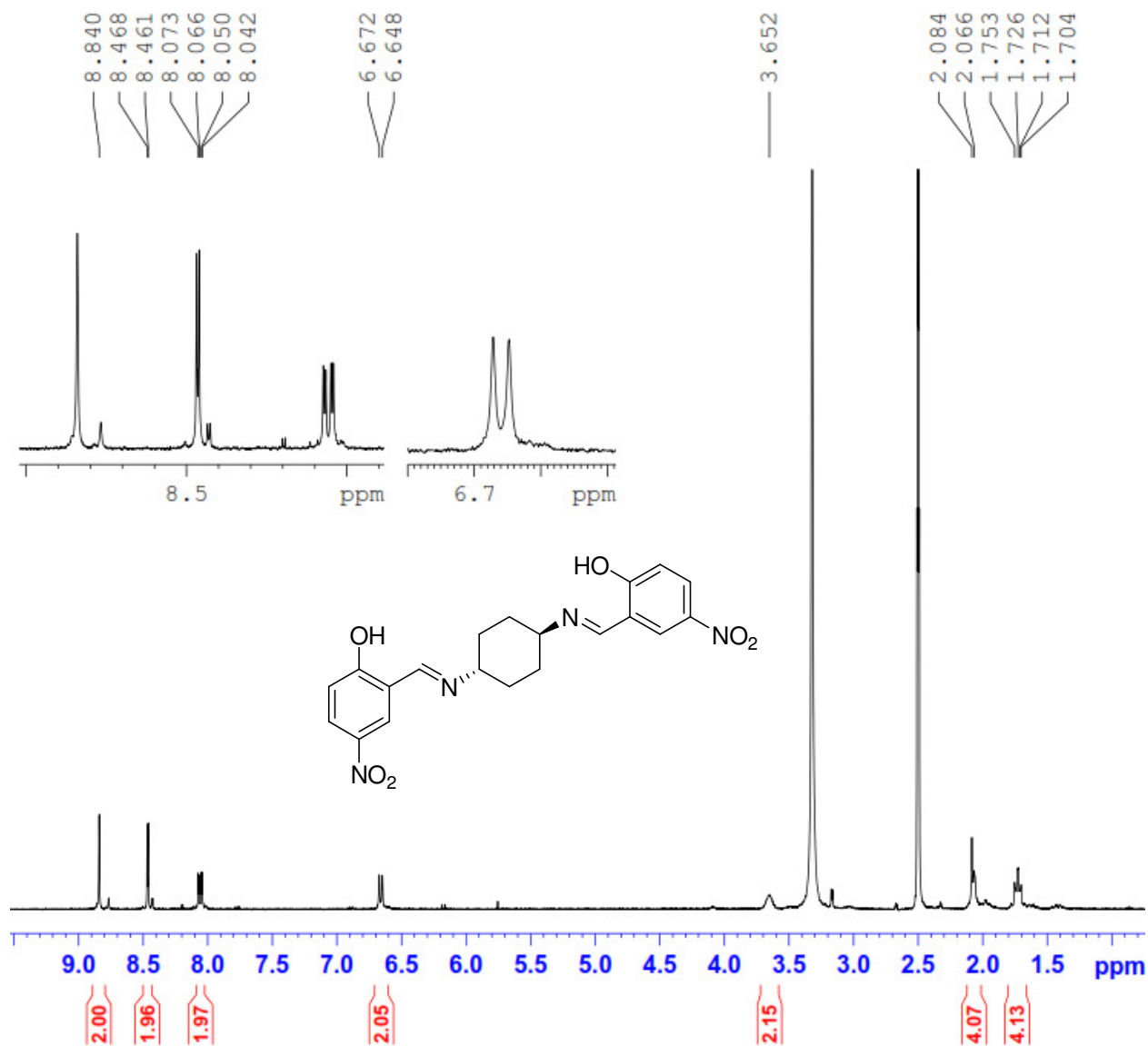


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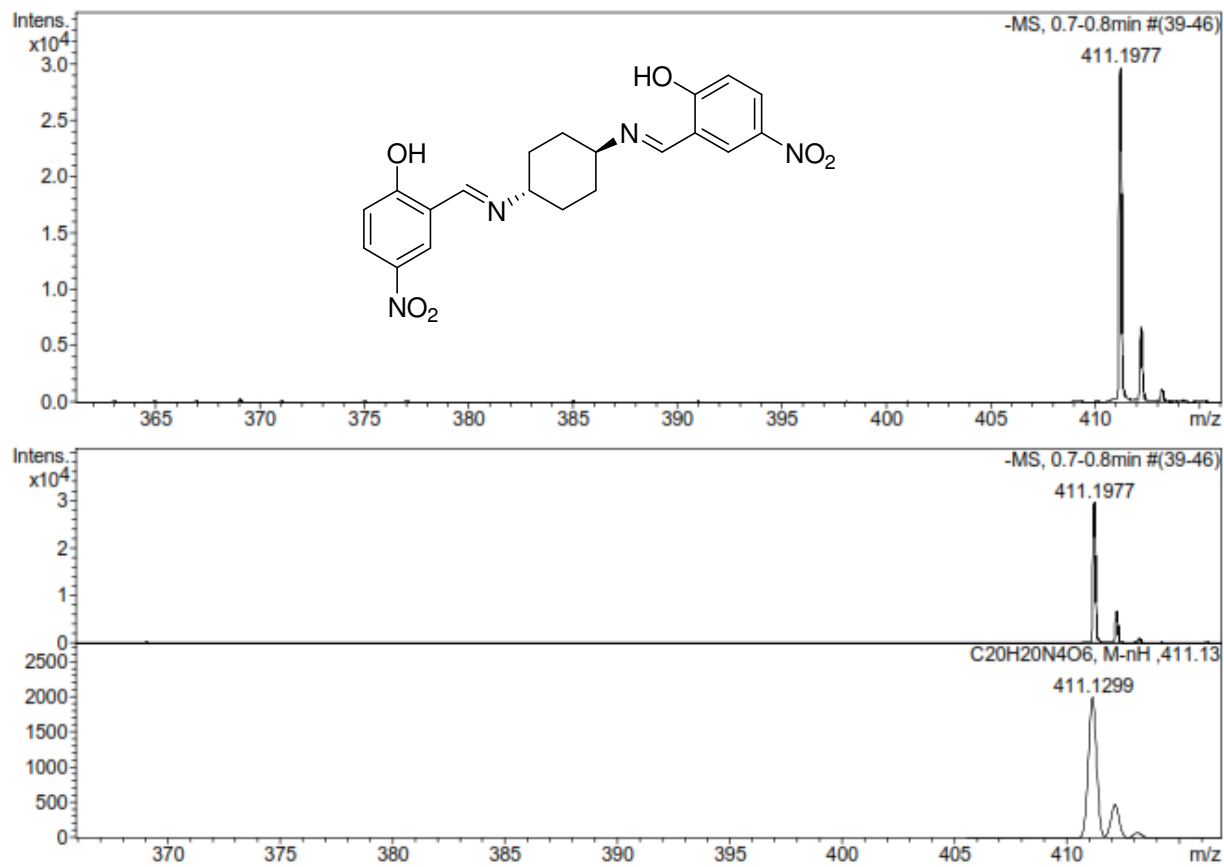


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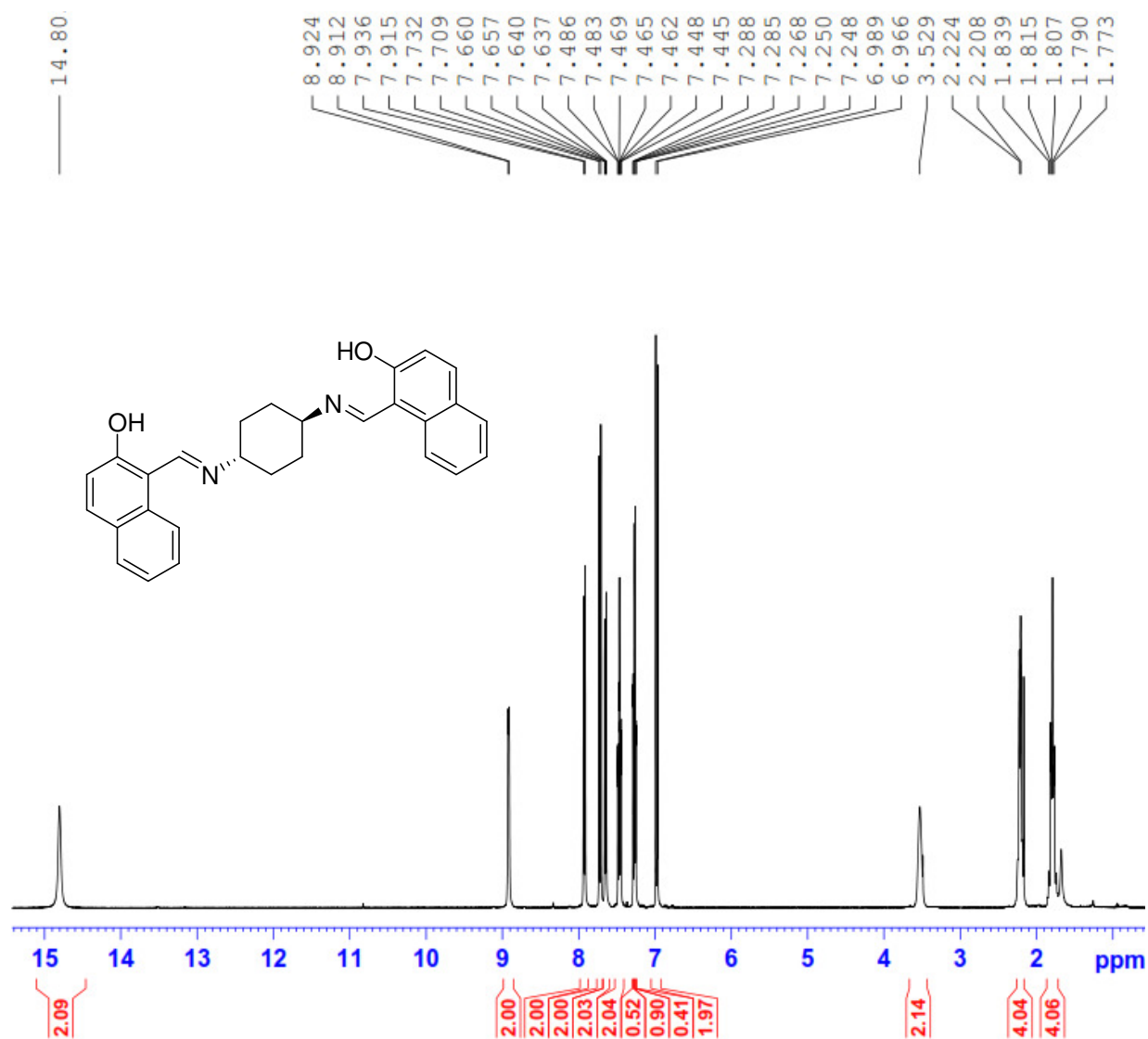


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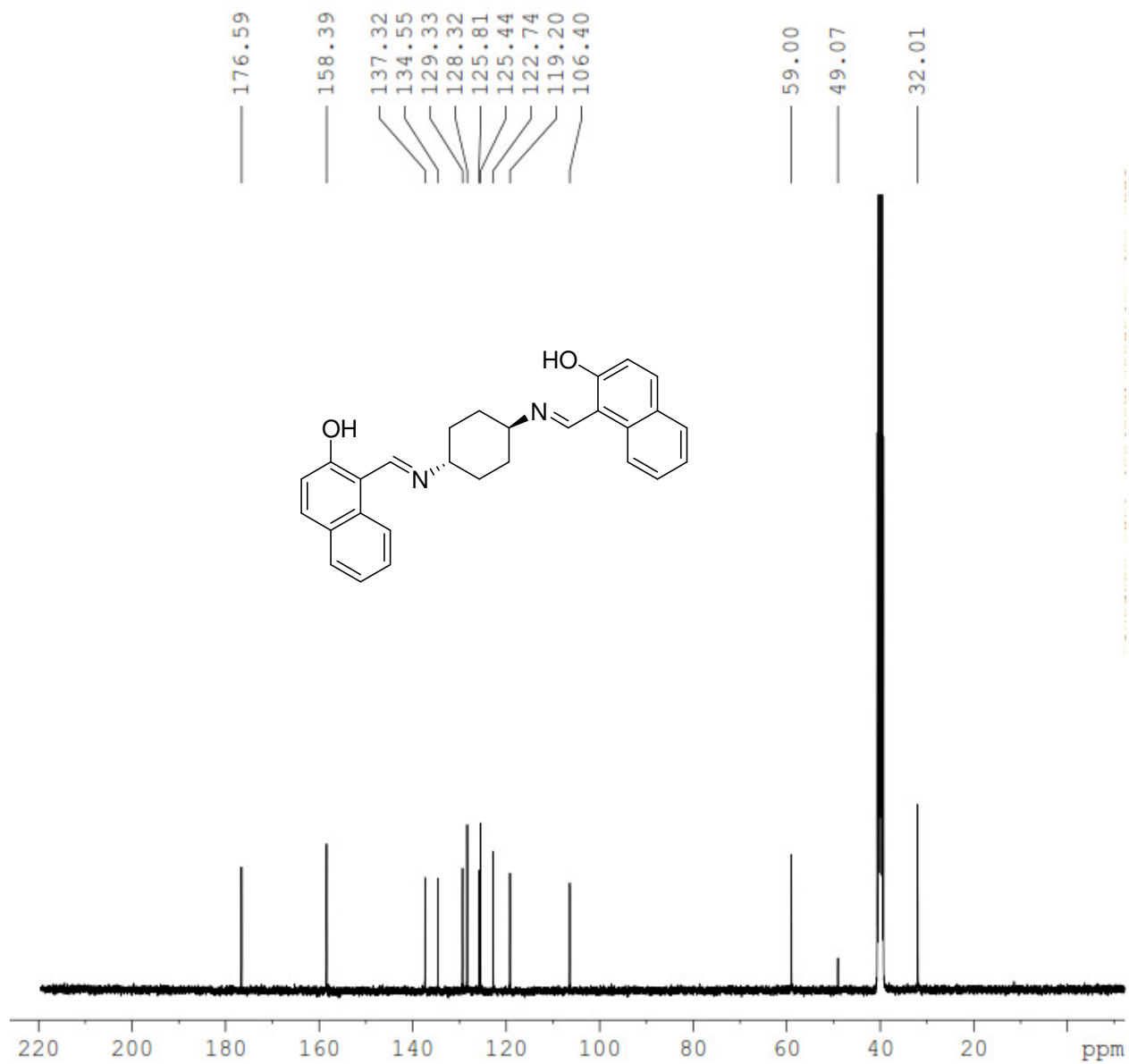


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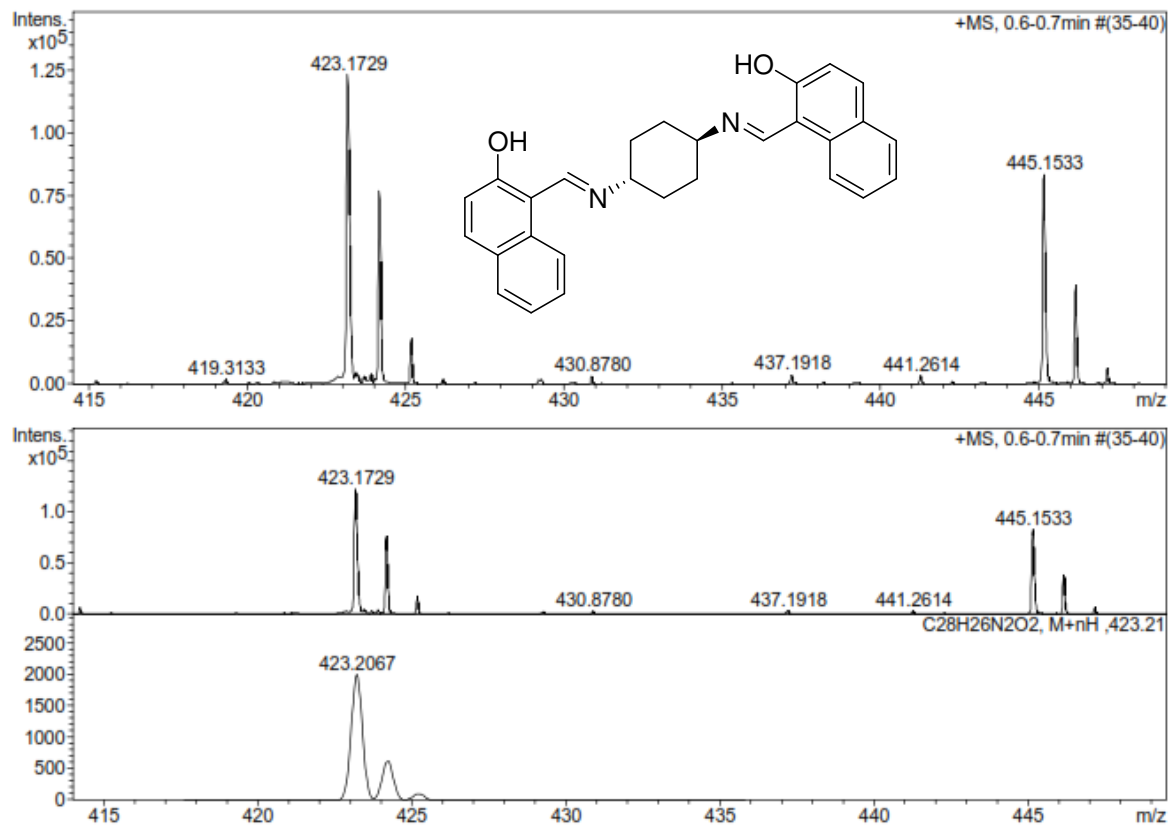


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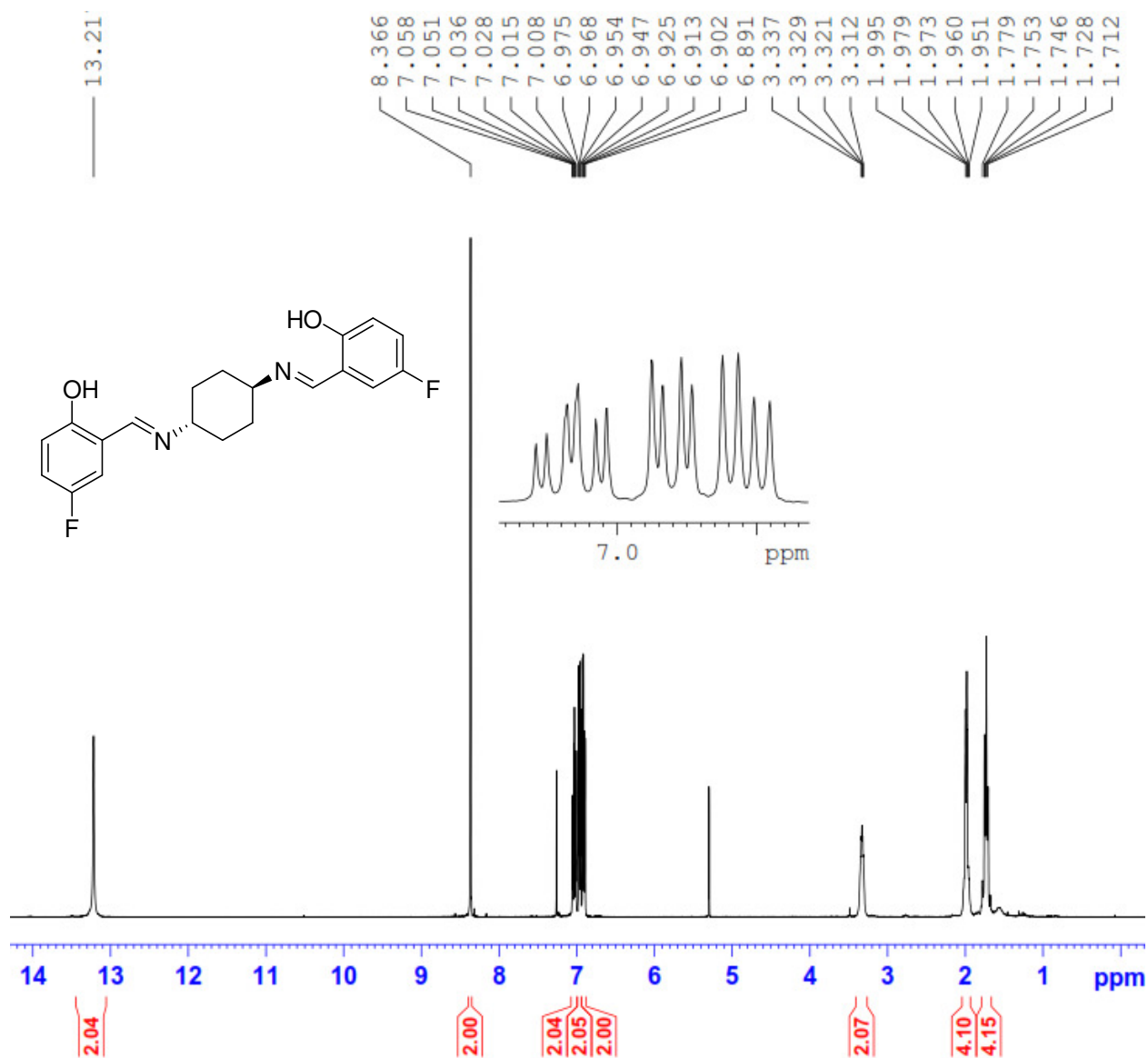


Figure S17. 3g, ¹H NMR.

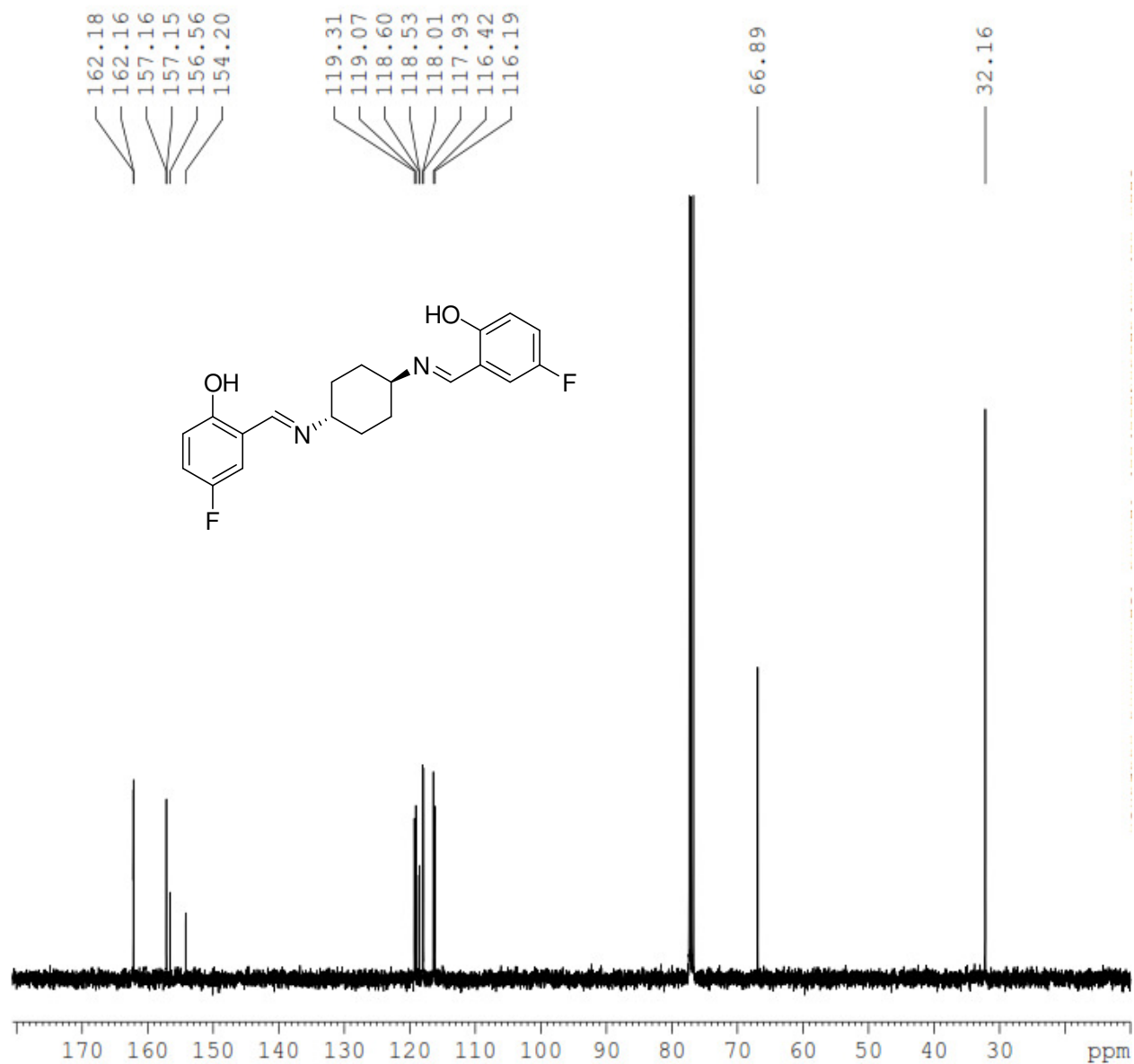


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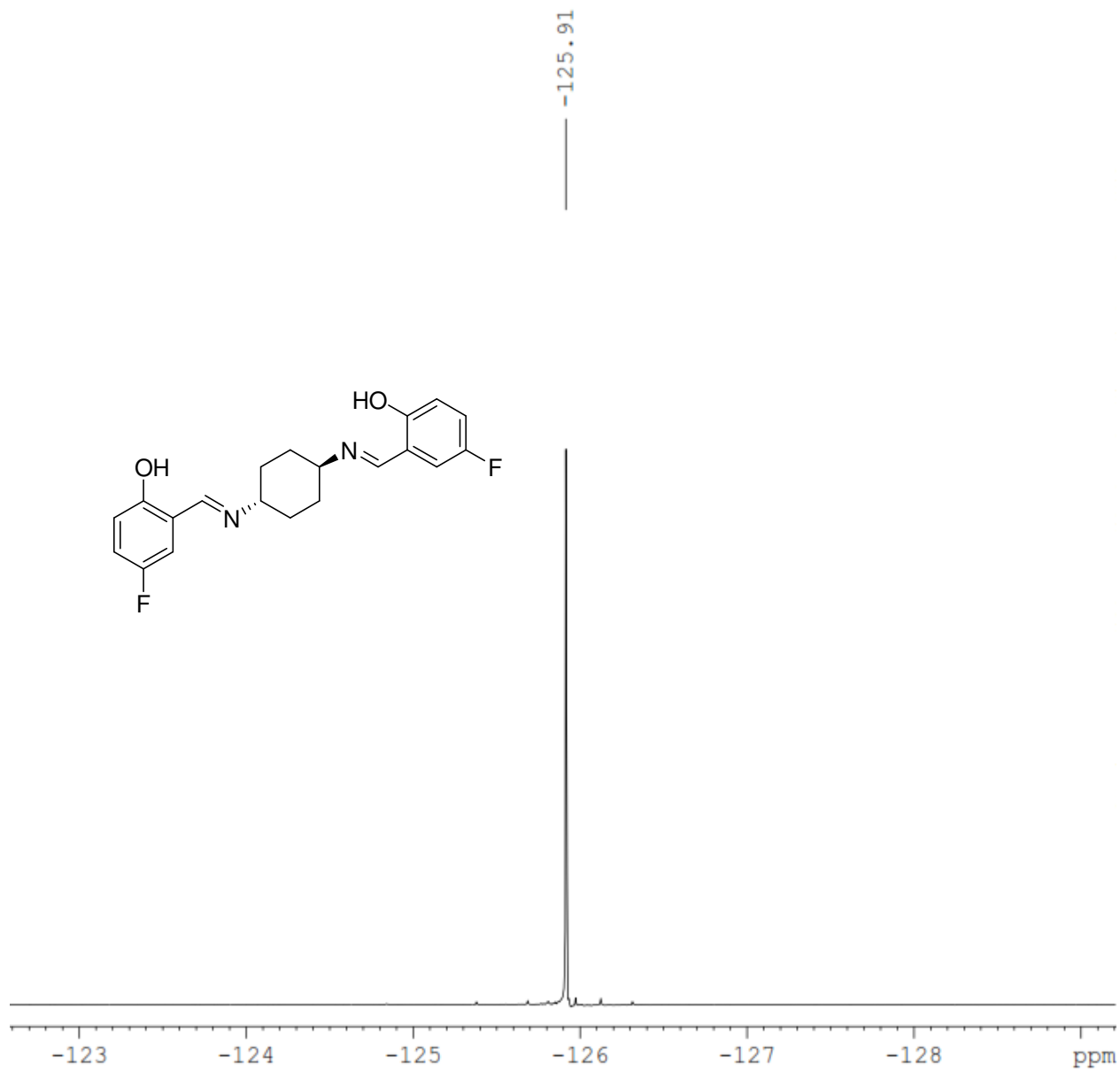


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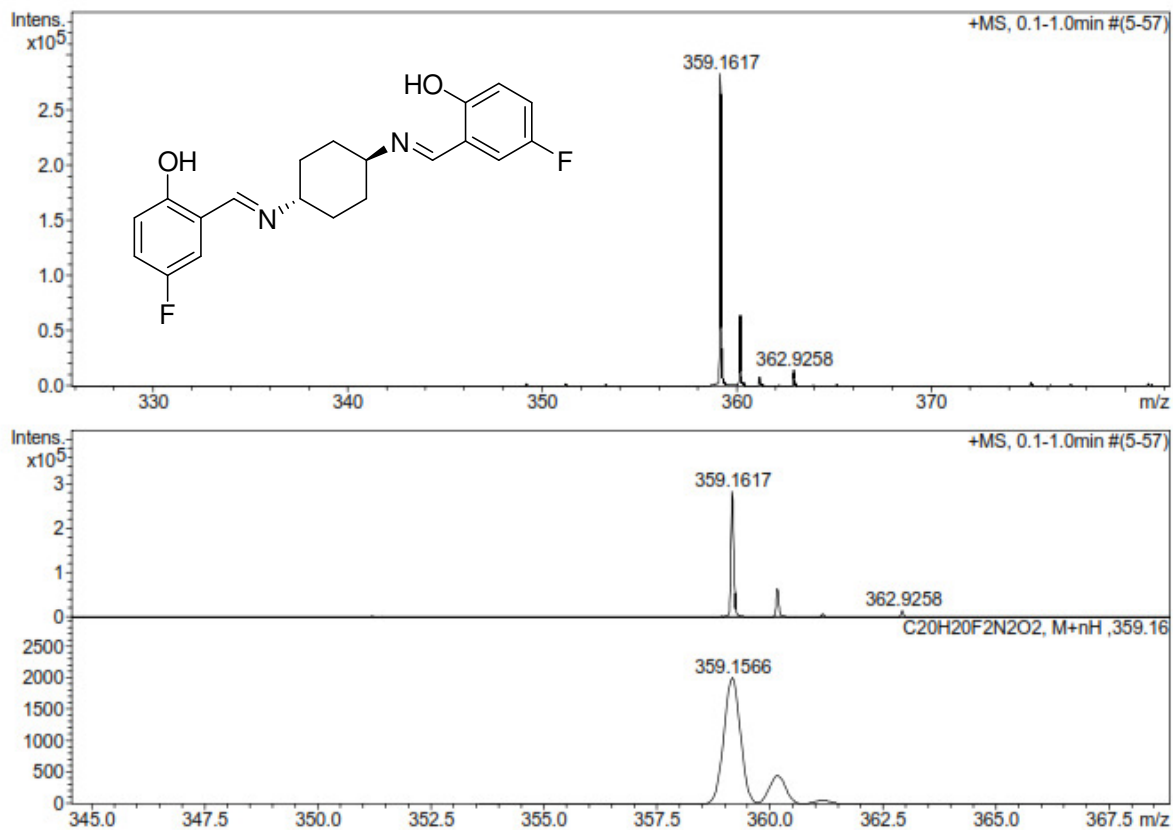


Figure S20. 3g, HRMS.

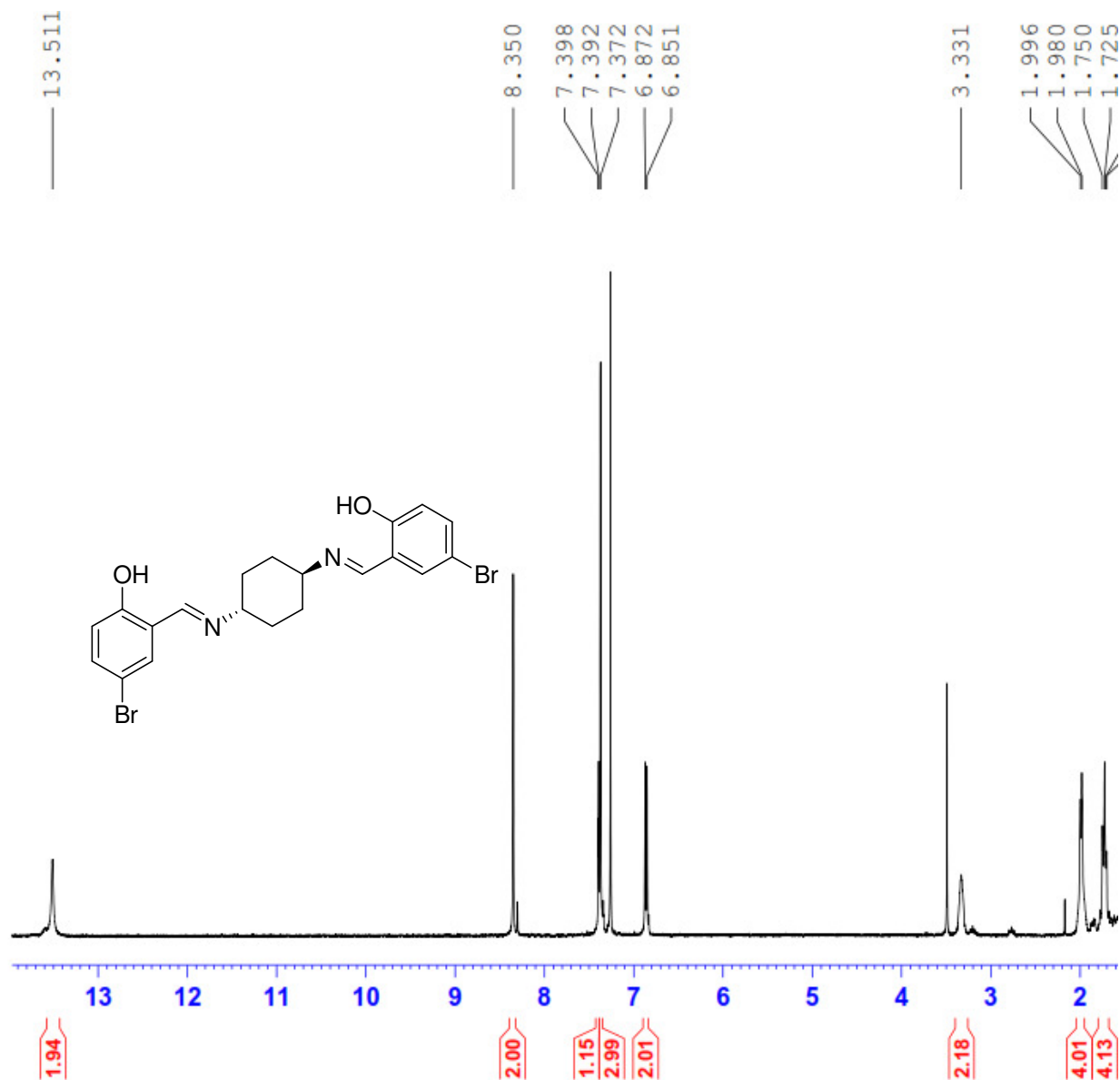


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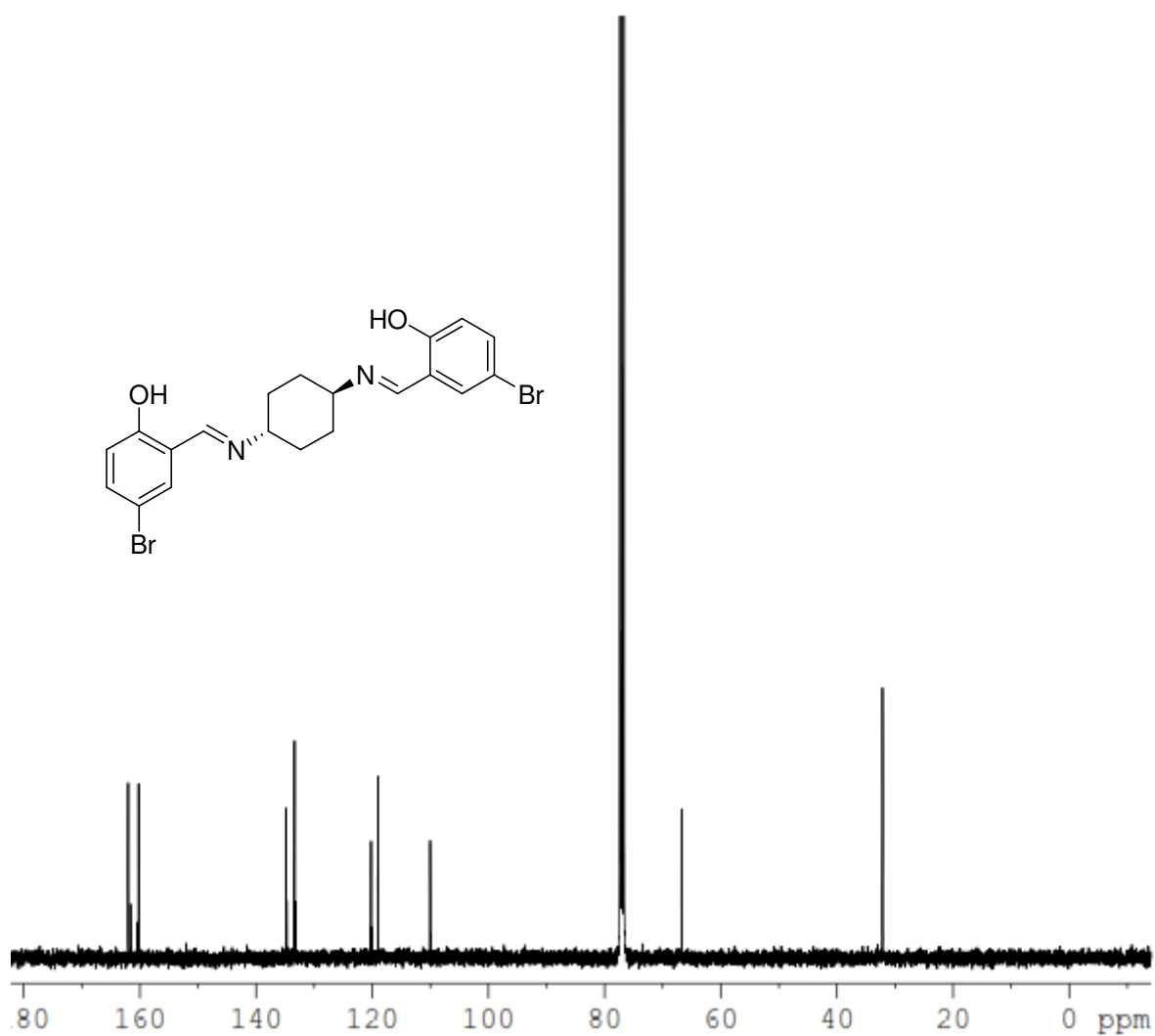


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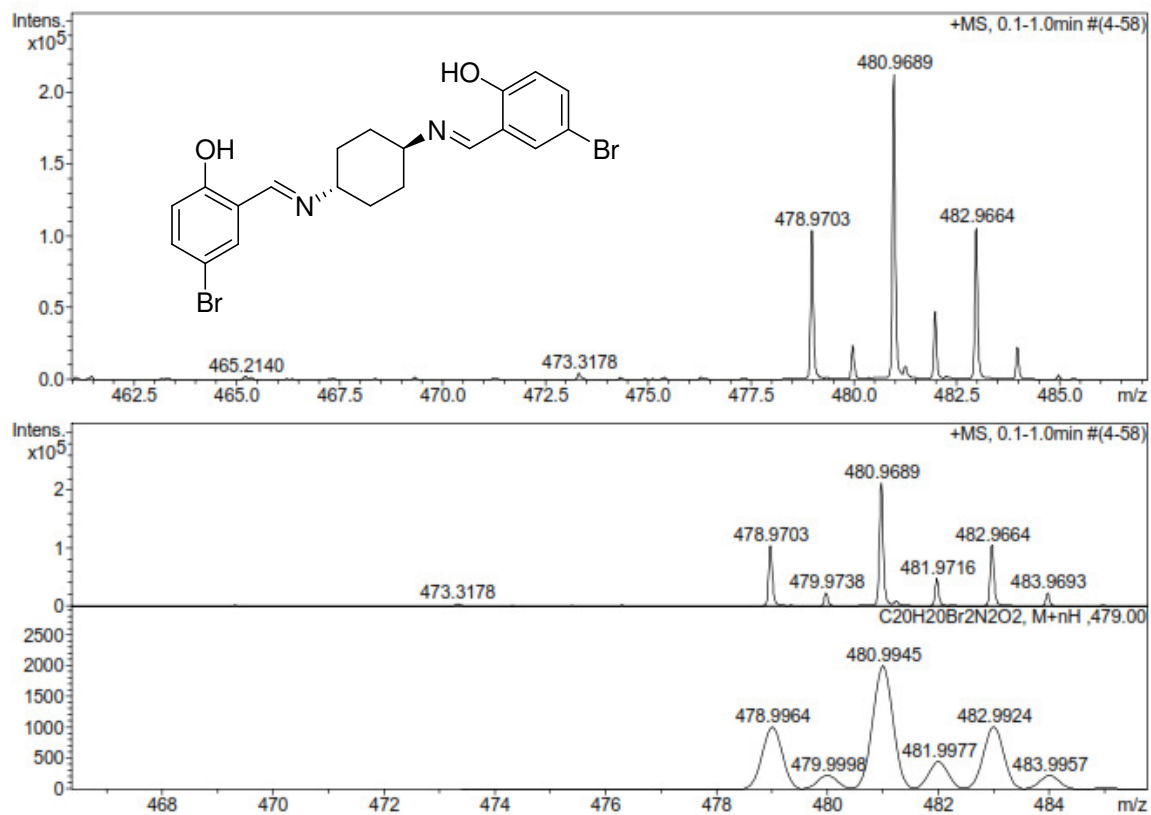


Figure S23. **3h**, HRMS.

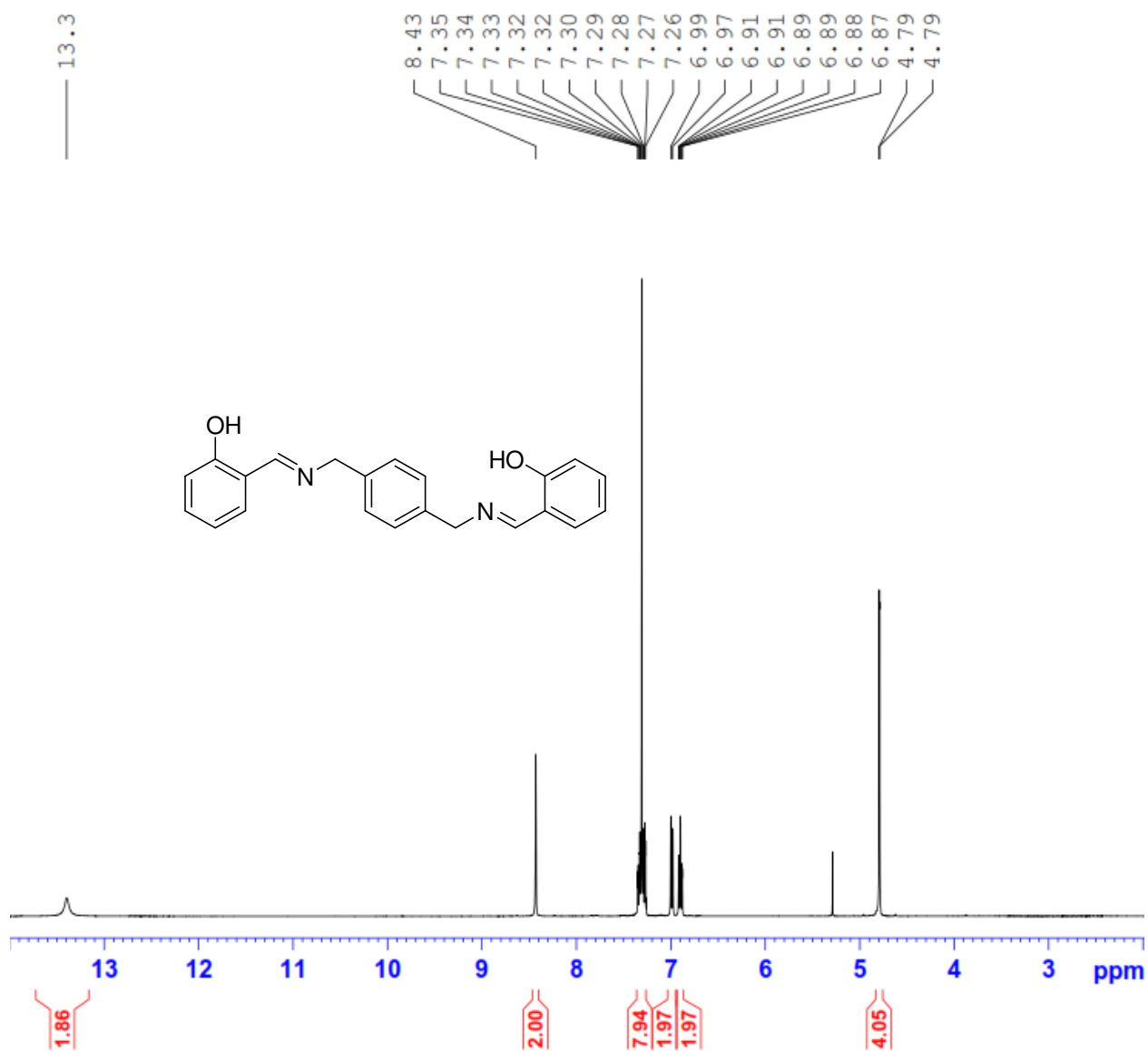


Figure S24. 4a, ¹H NMR.

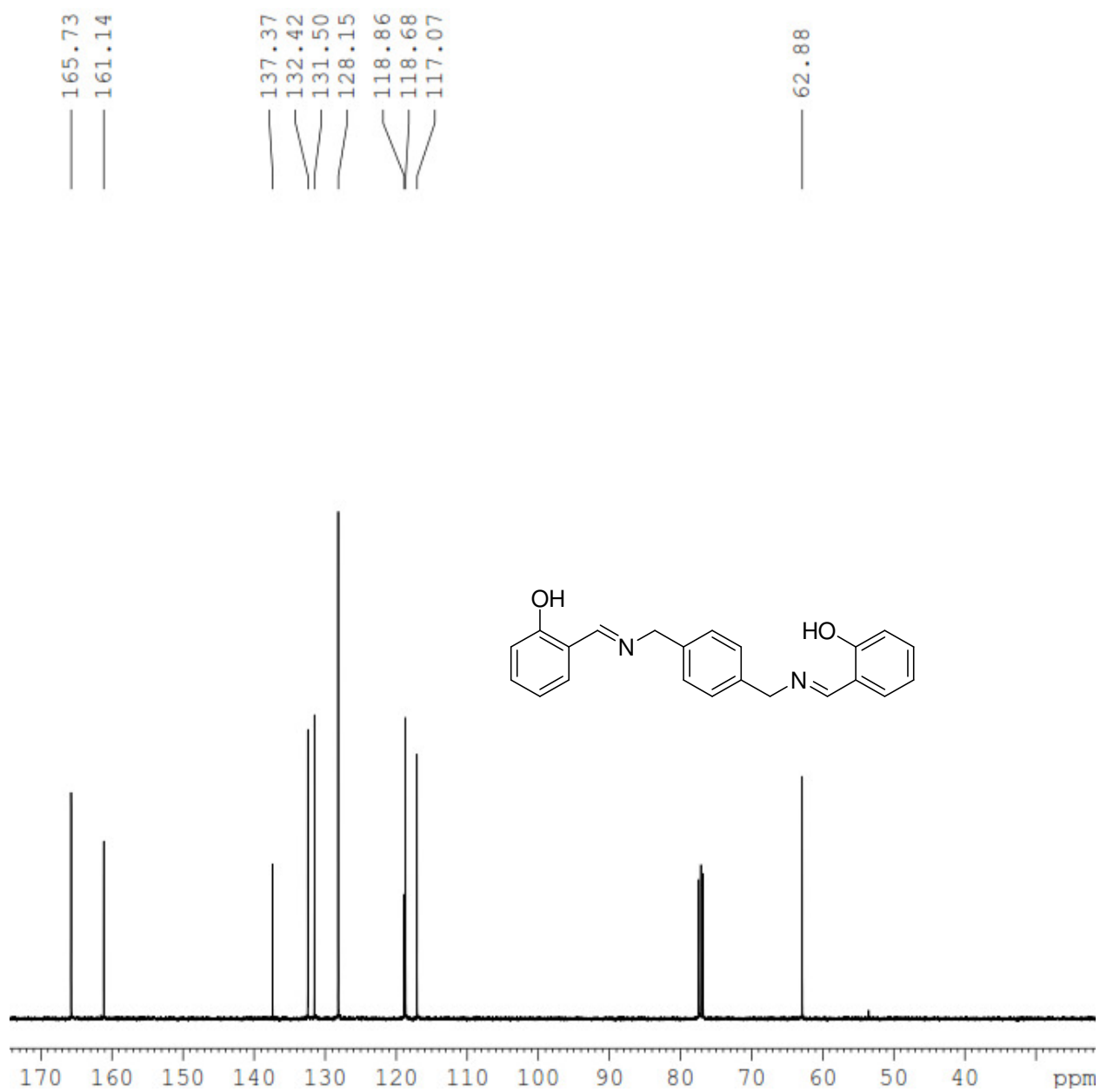


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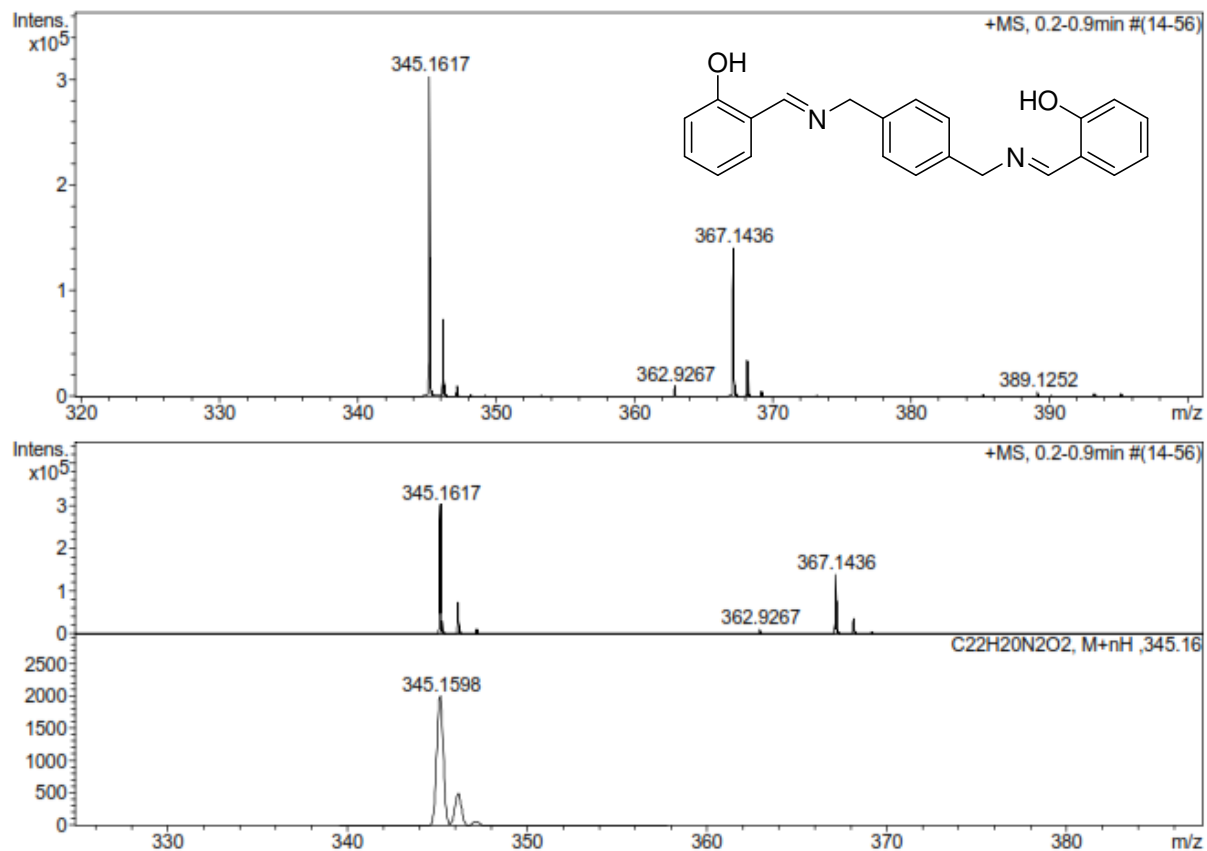


Figure S26. 4a, HRMS.

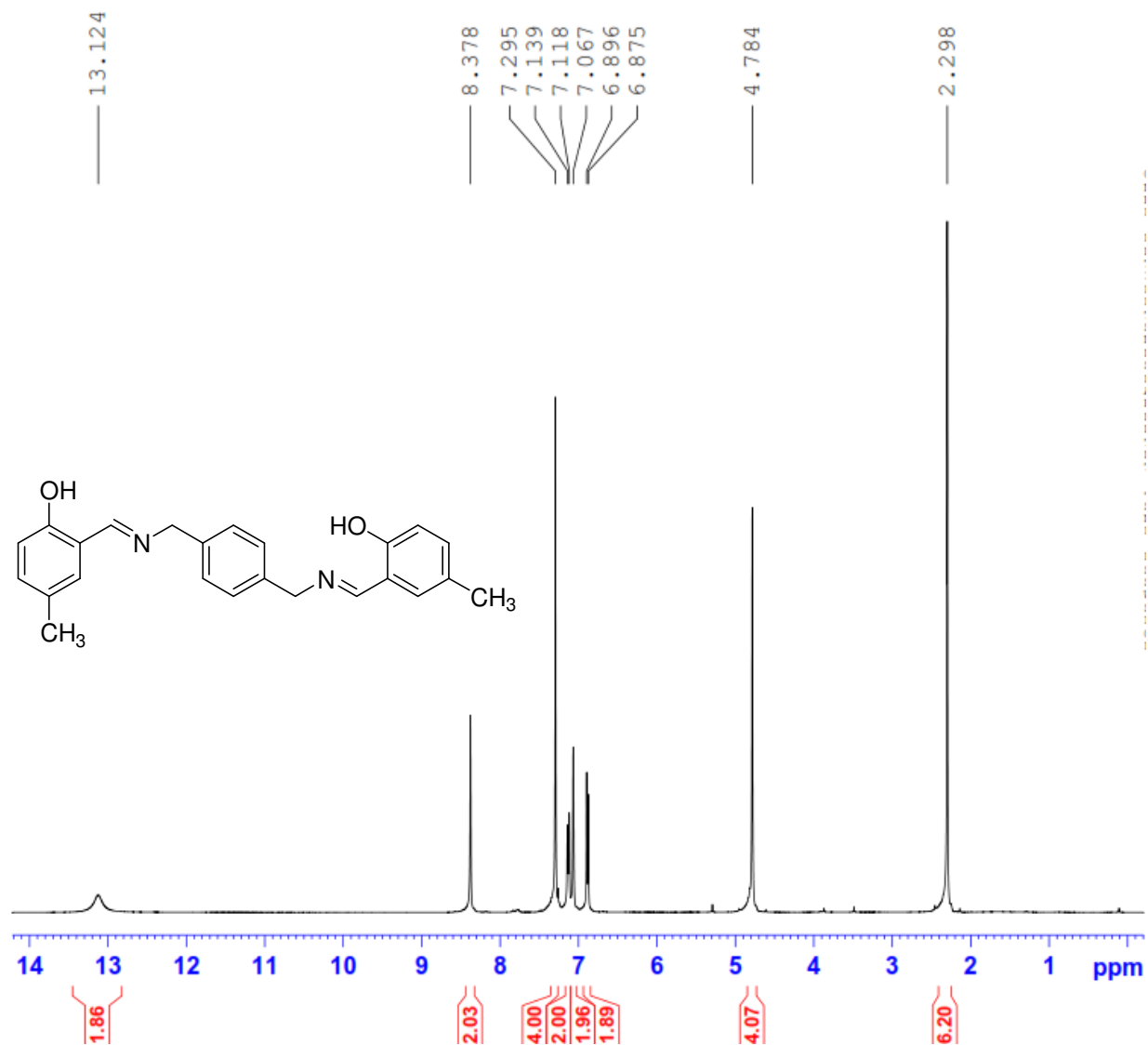


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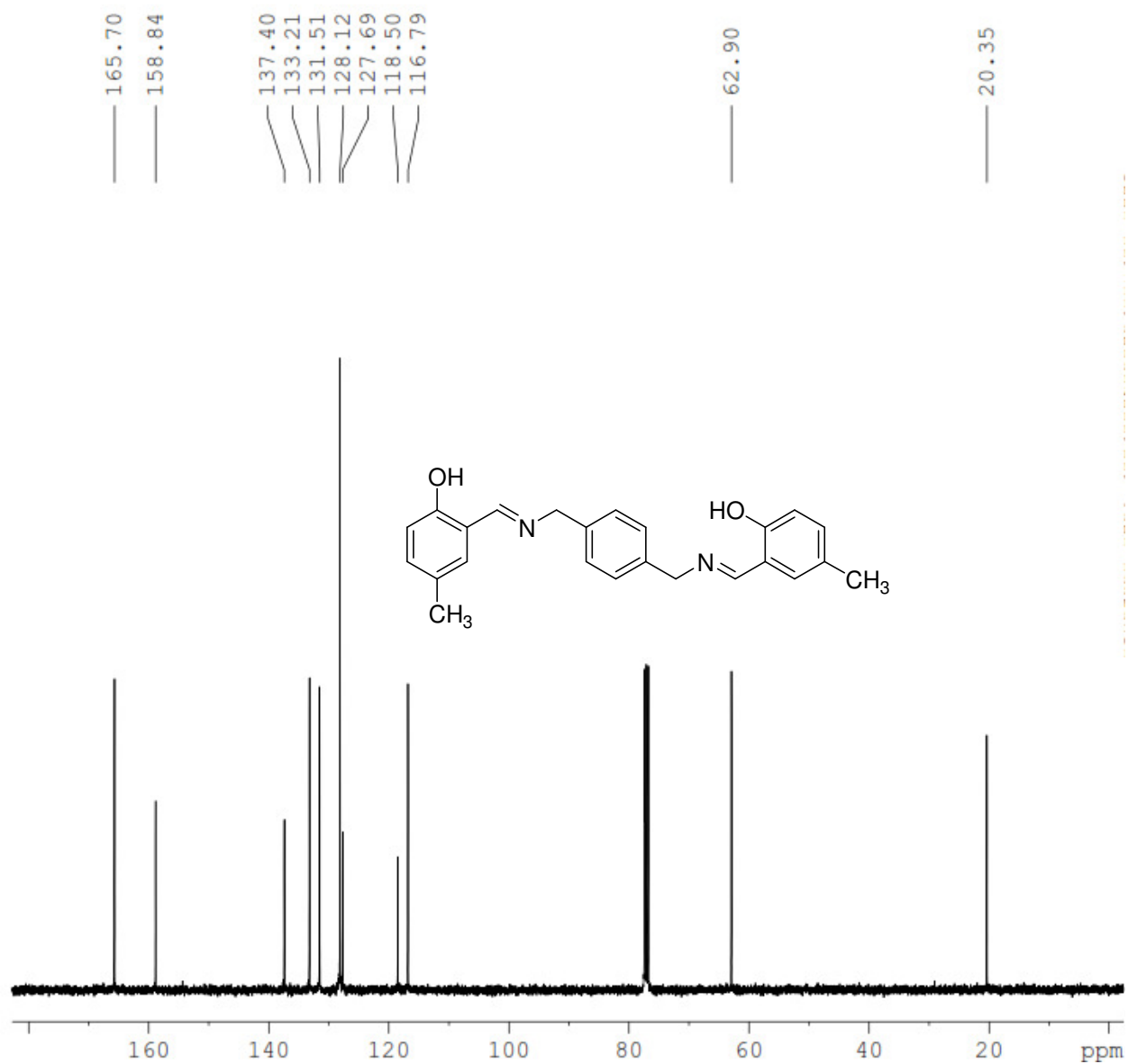


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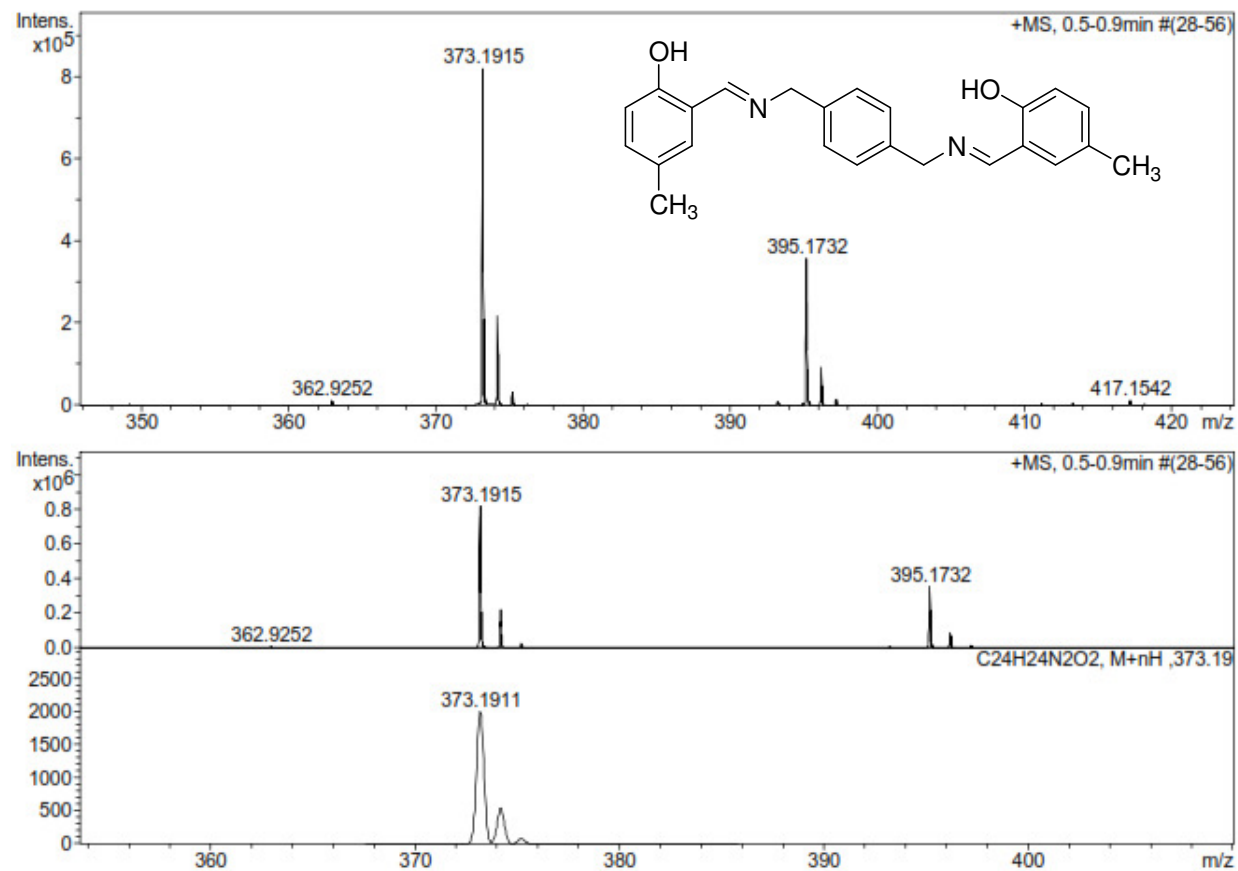


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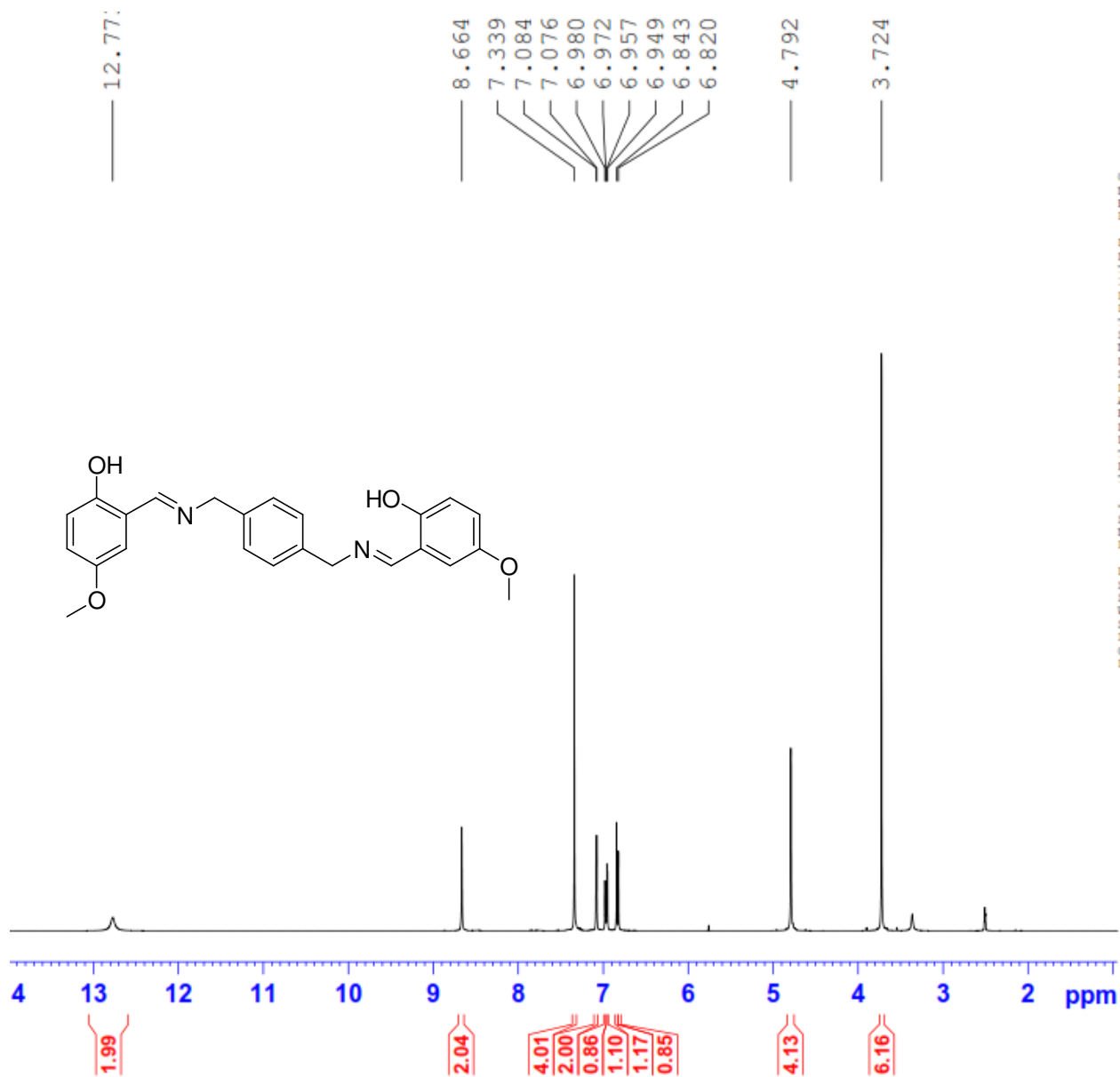


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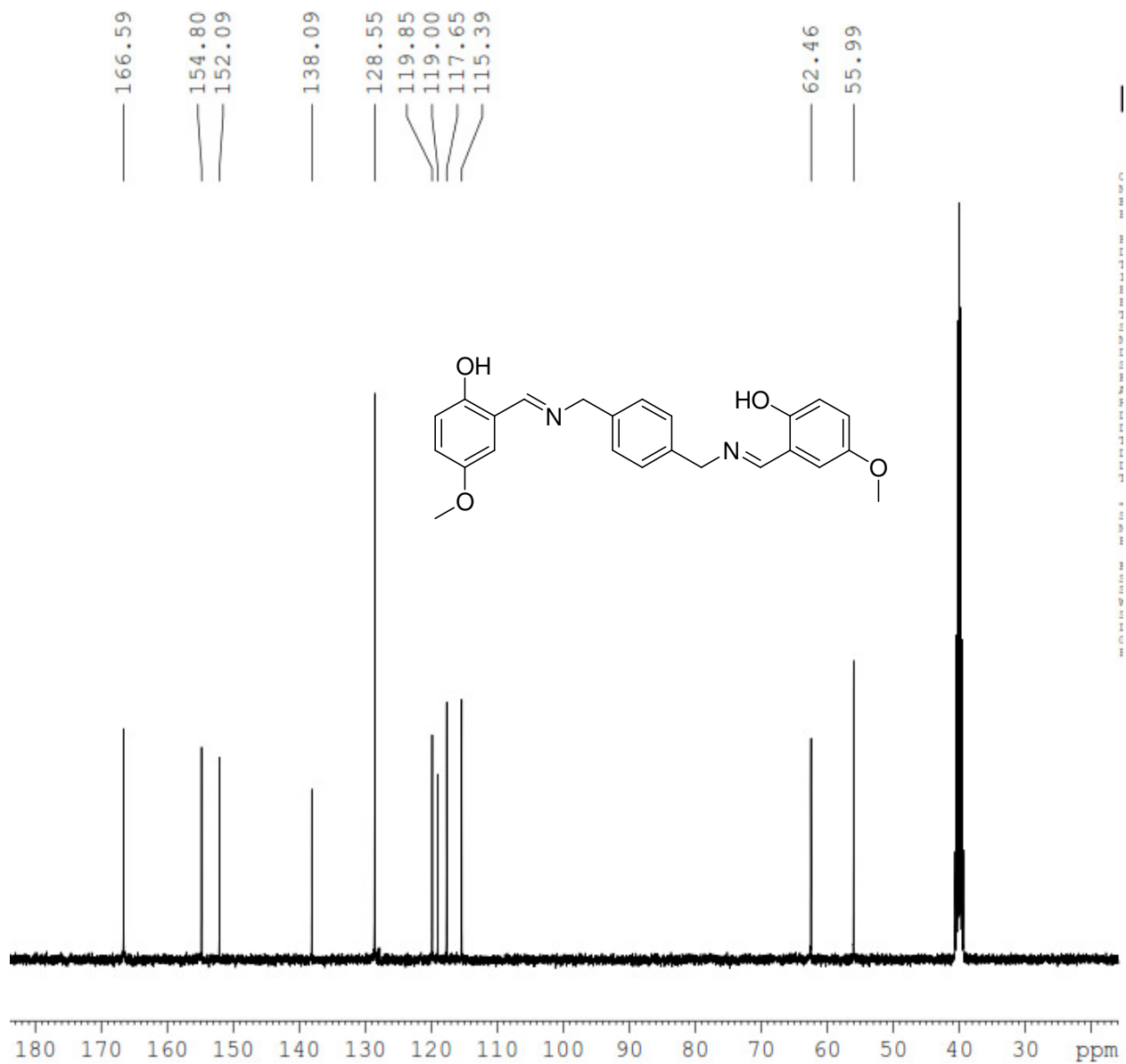


Figure S31. **4c**, ^{13}C NMR.

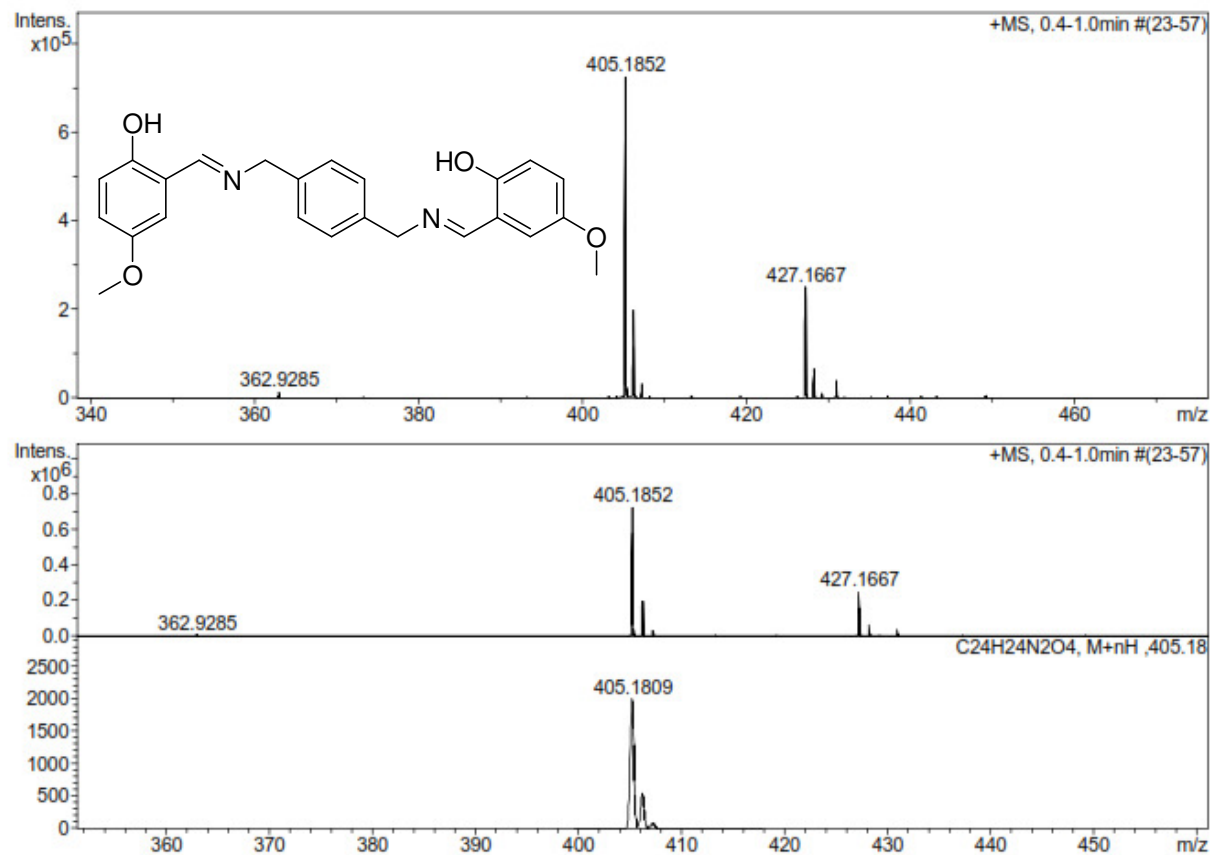


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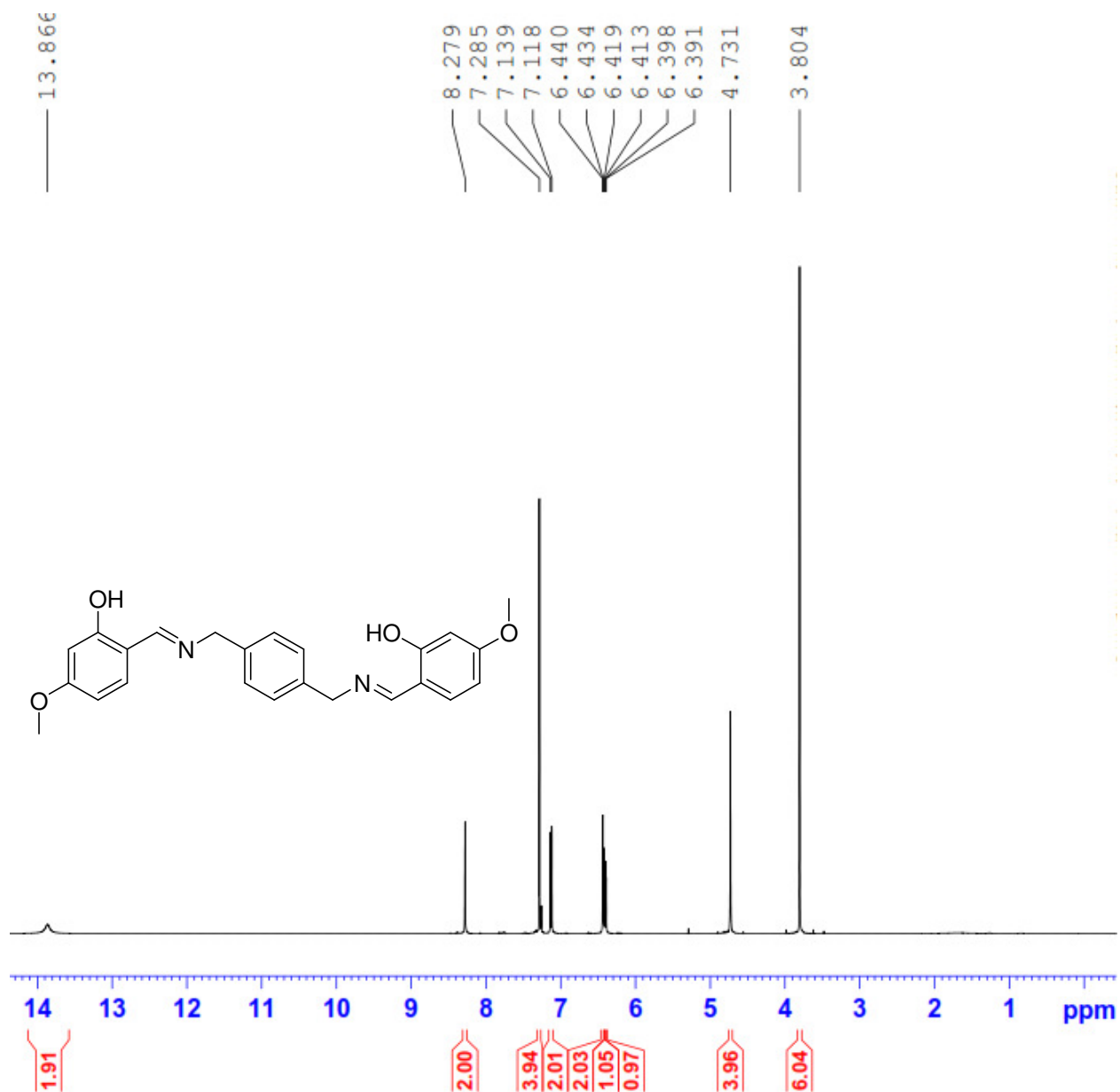


Figure S33. 4d, ¹H NMR.

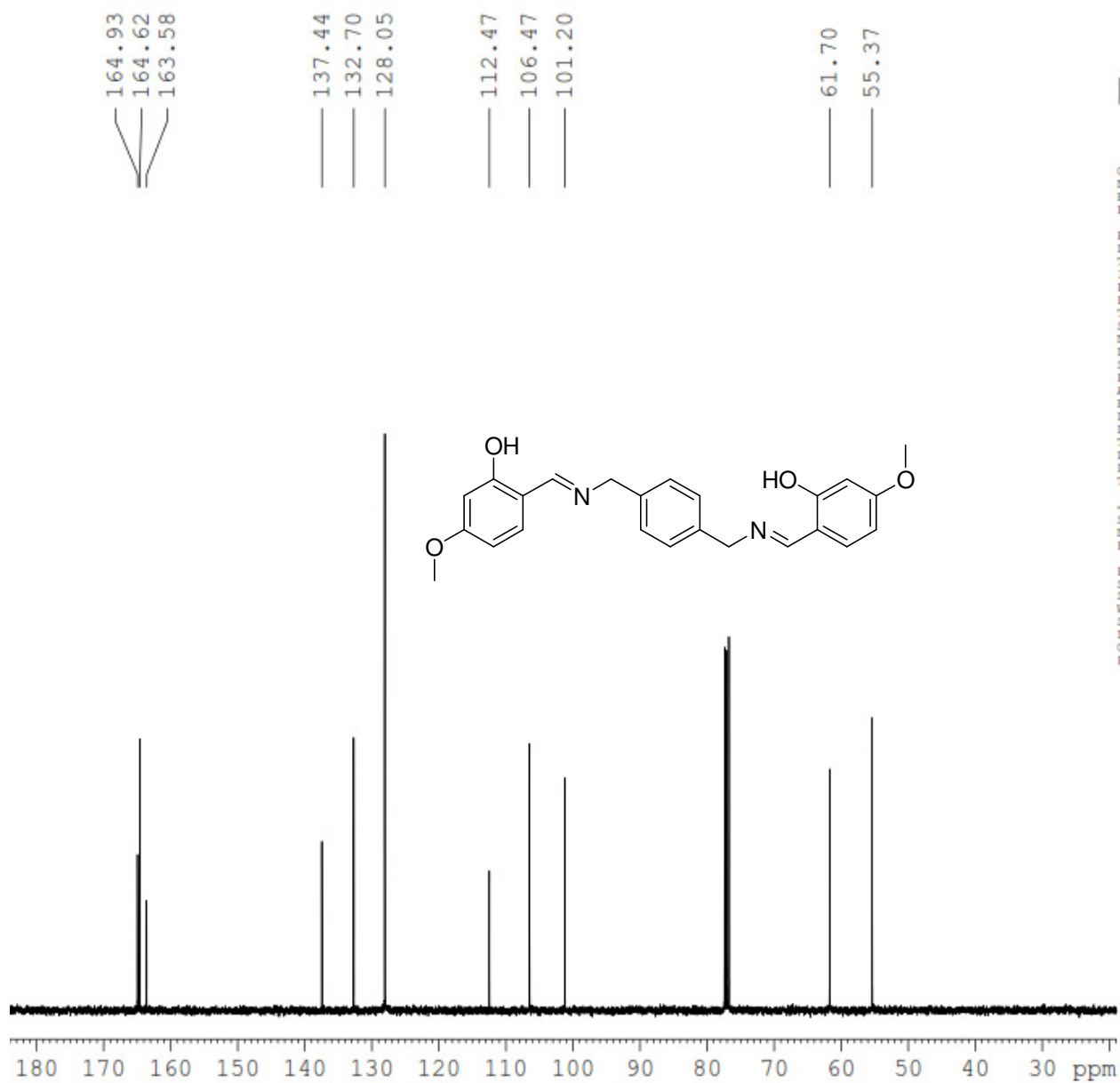


Figure S34. 4d, ¹³C NMR.

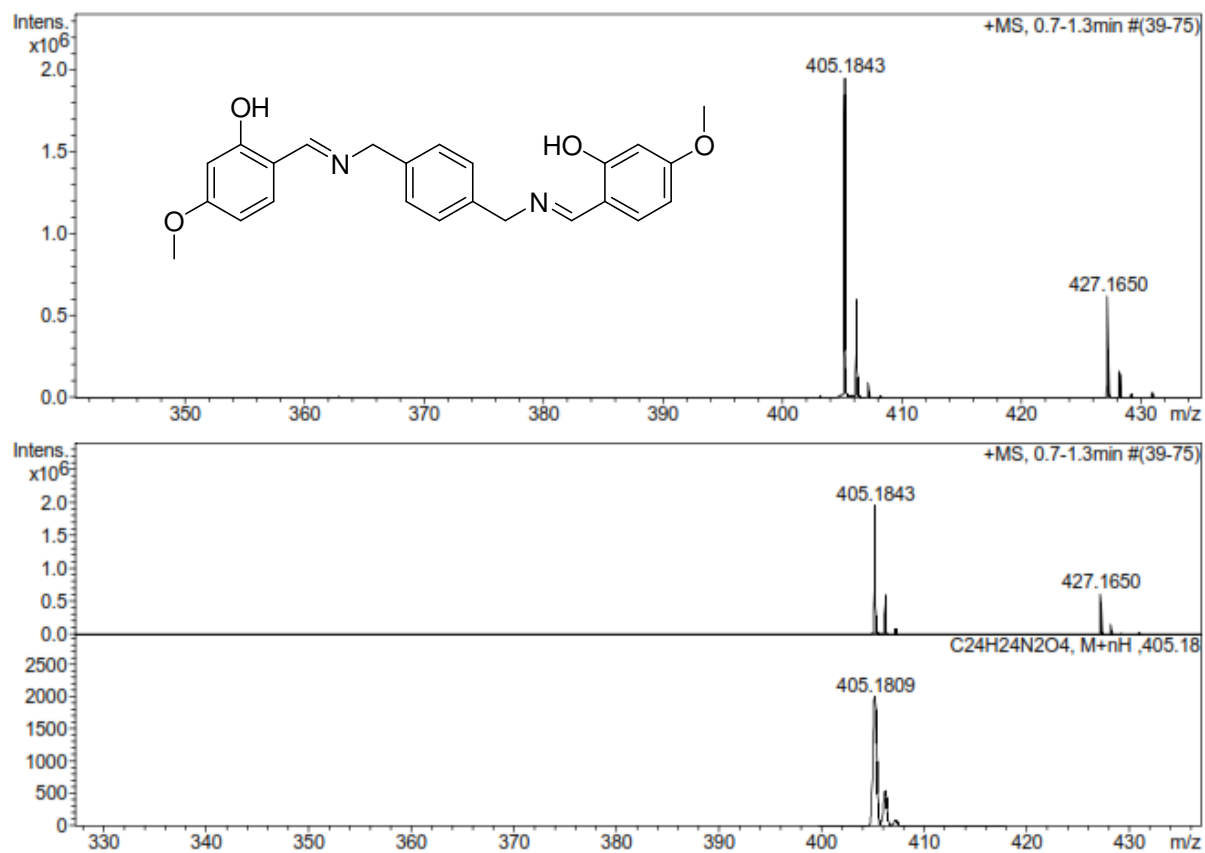


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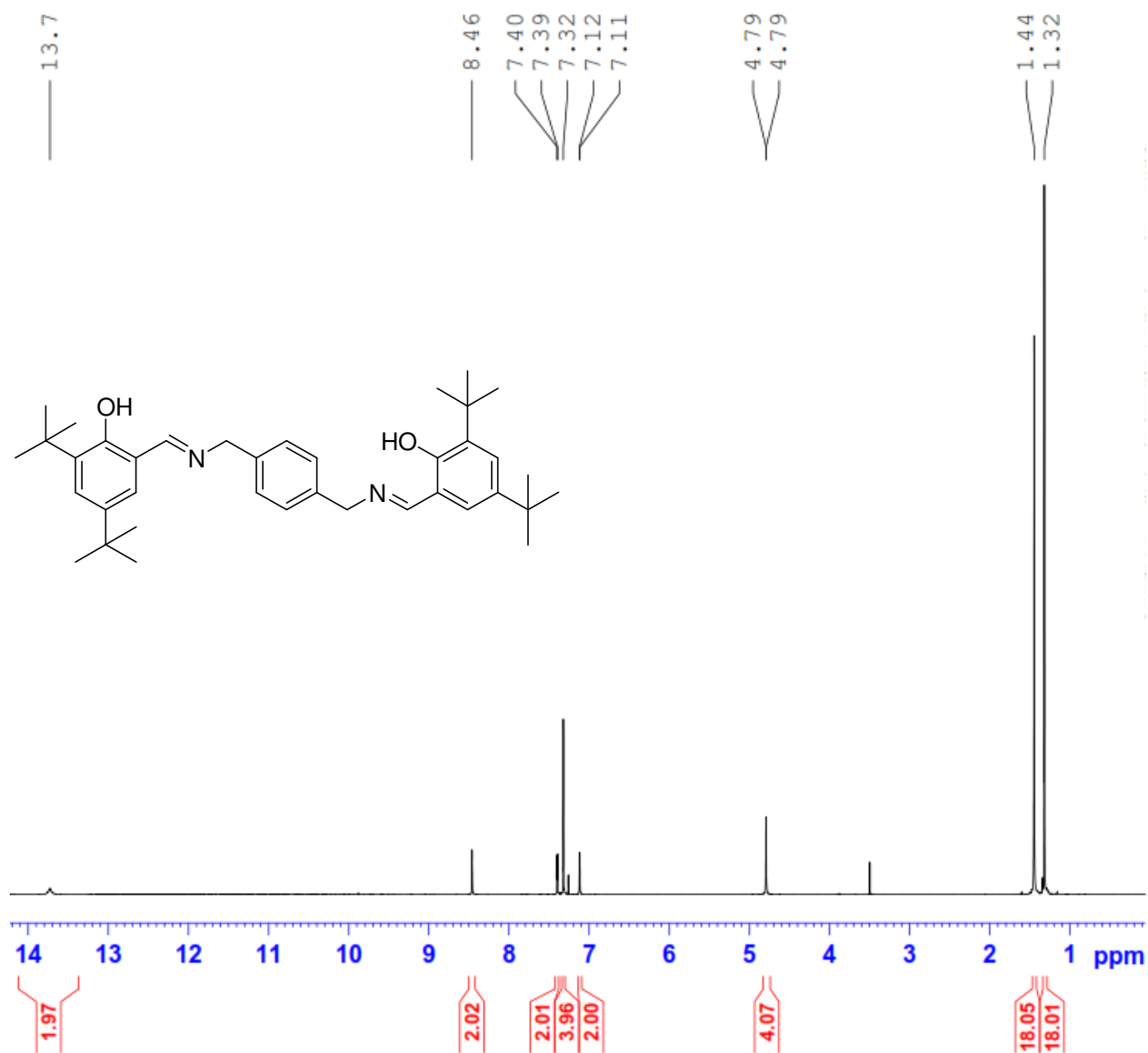


Figure S36. 4e, ¹H NMR.

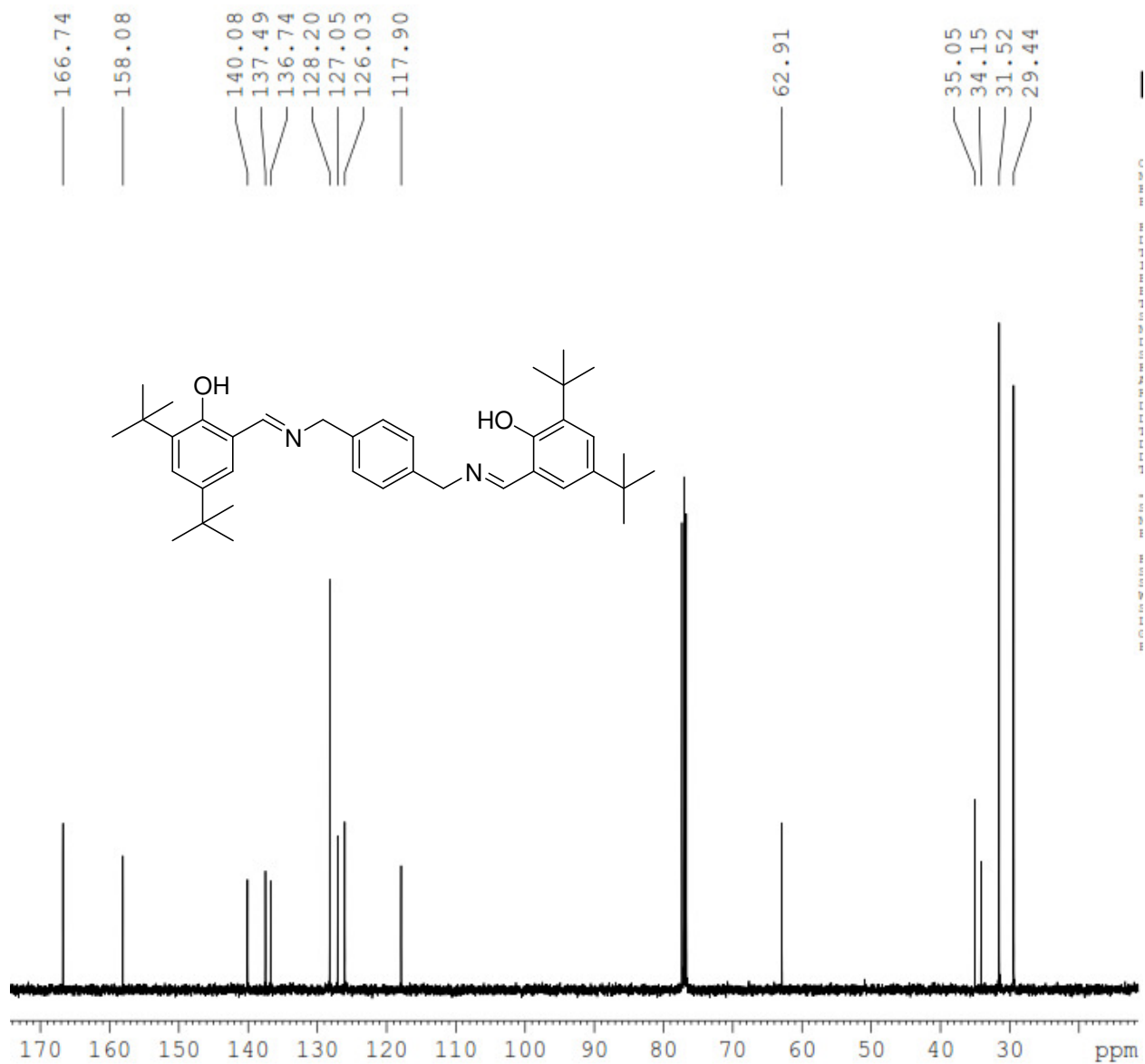


Figure S37. **4e**, ¹³C NMR.

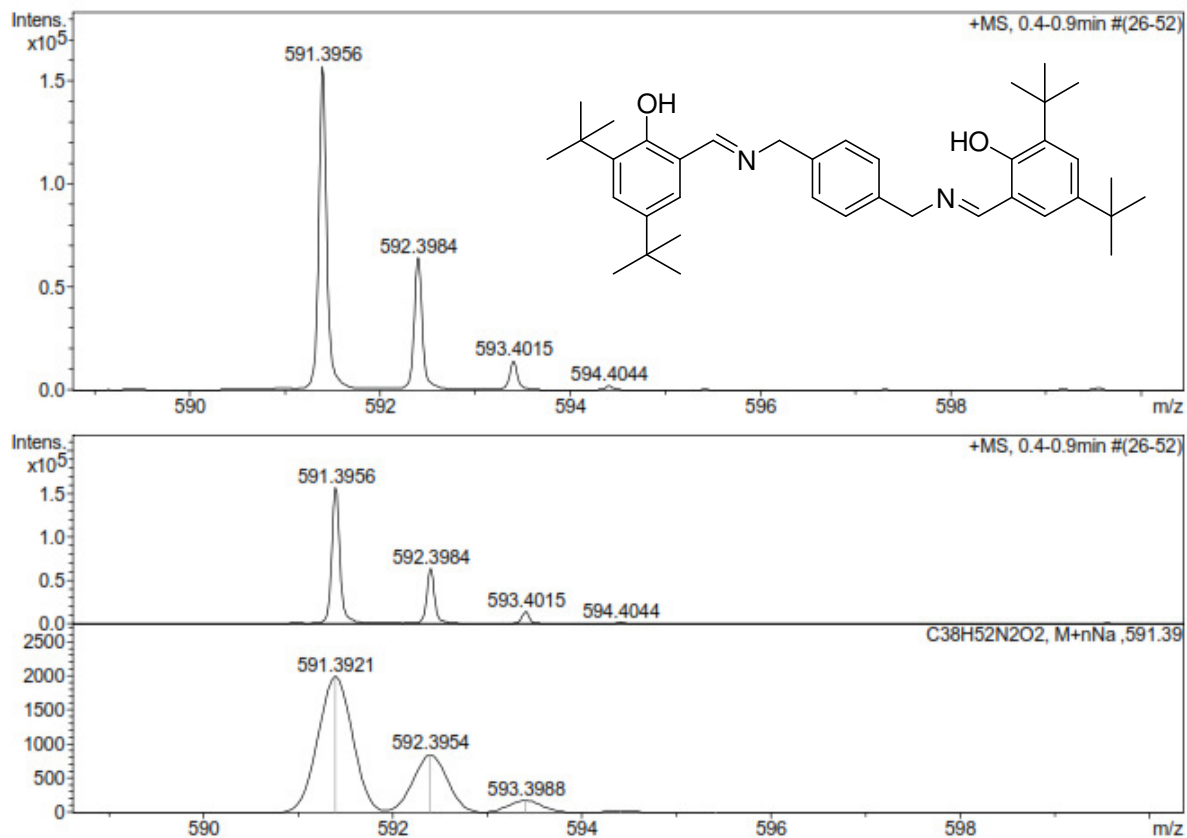


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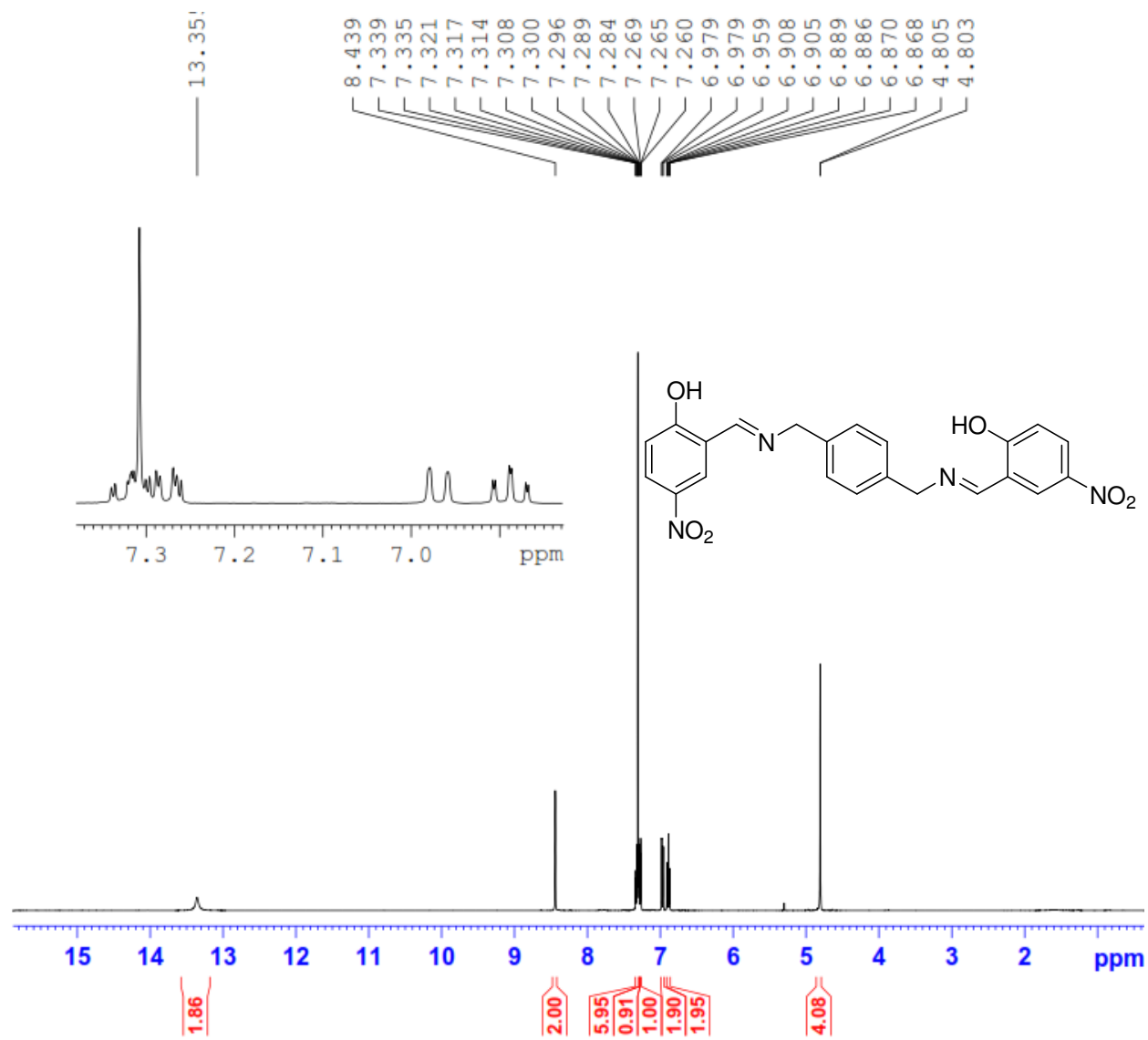


Figure S39. 4f, ¹H NMR.

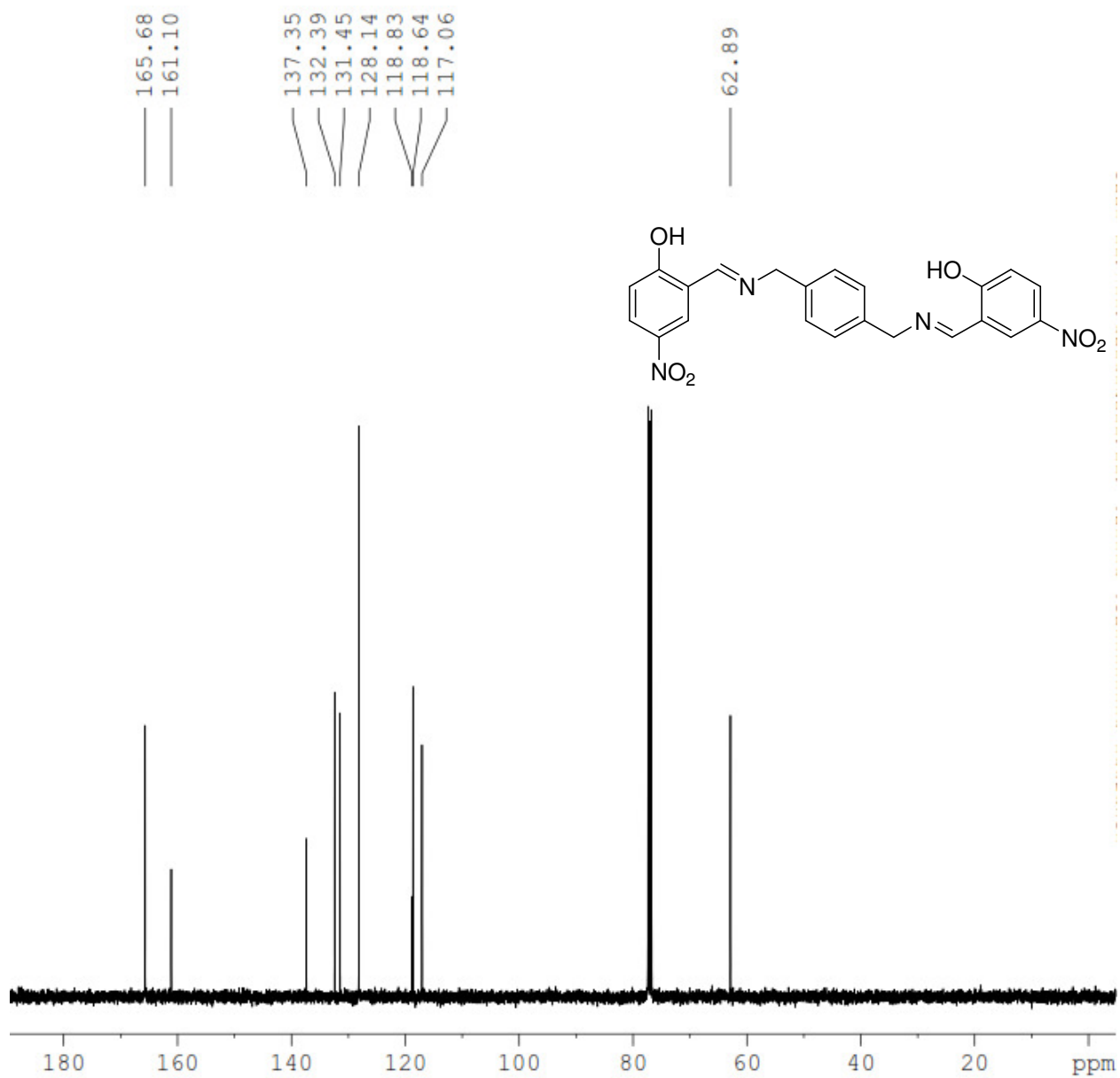


Figure S39. 4f, ¹³C NMR.

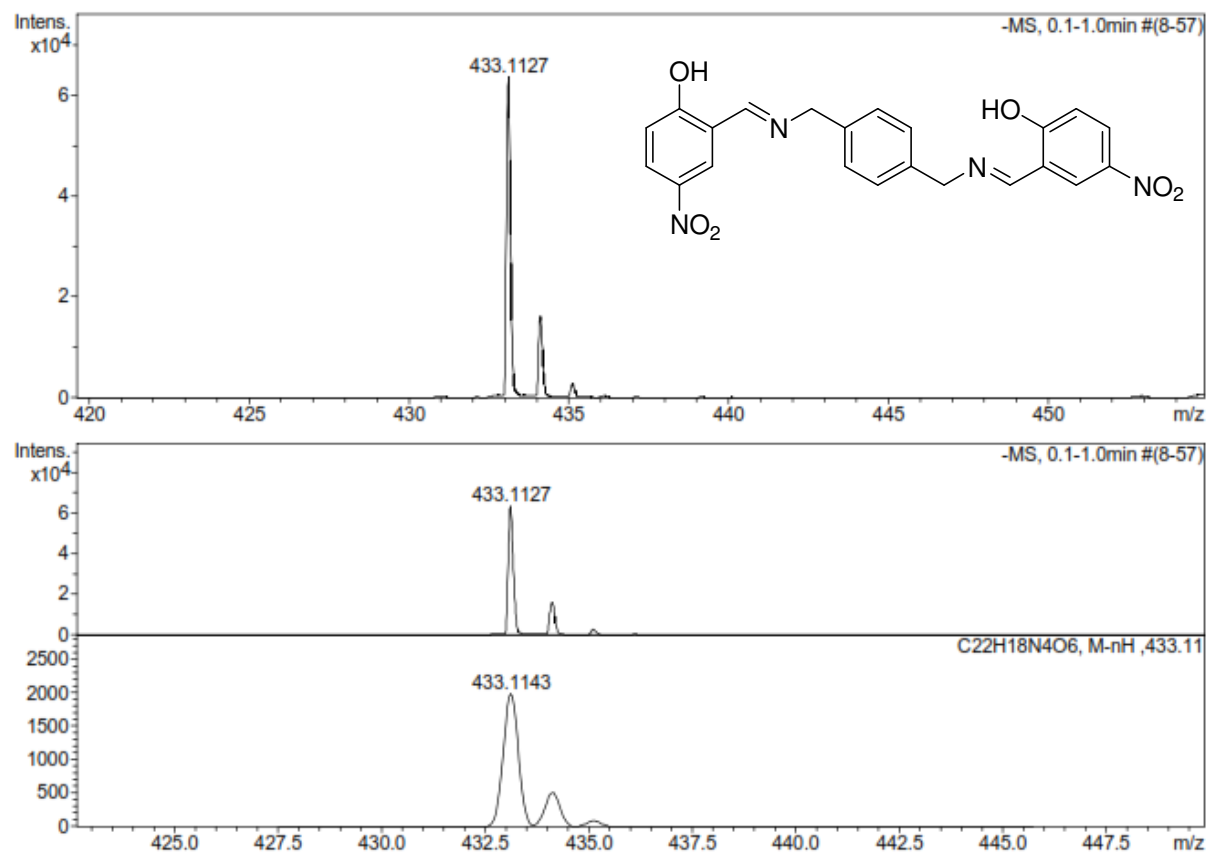


Figure S40. 4f, HRMS.

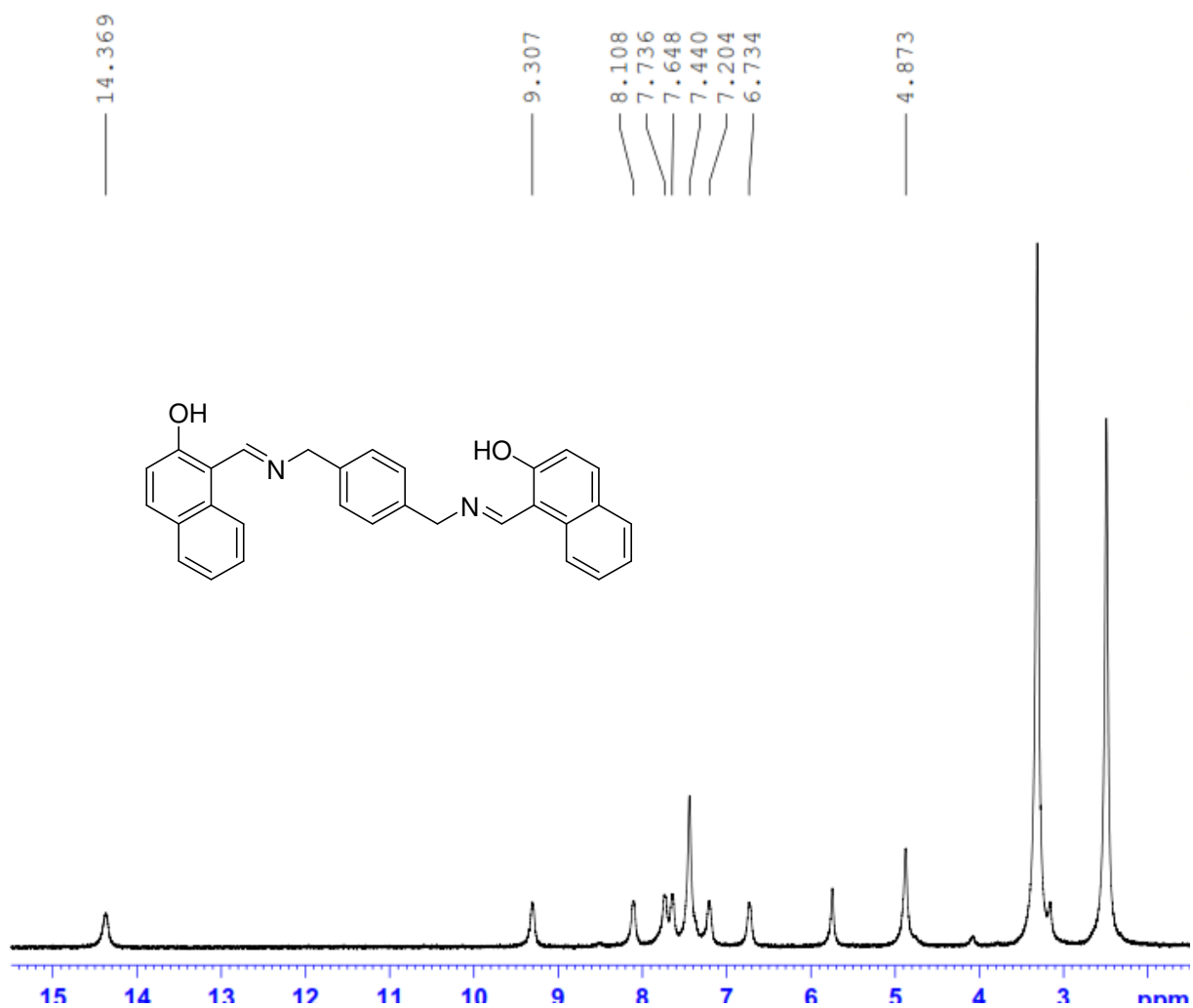


Figure S41. 4g, ^1H NMR.

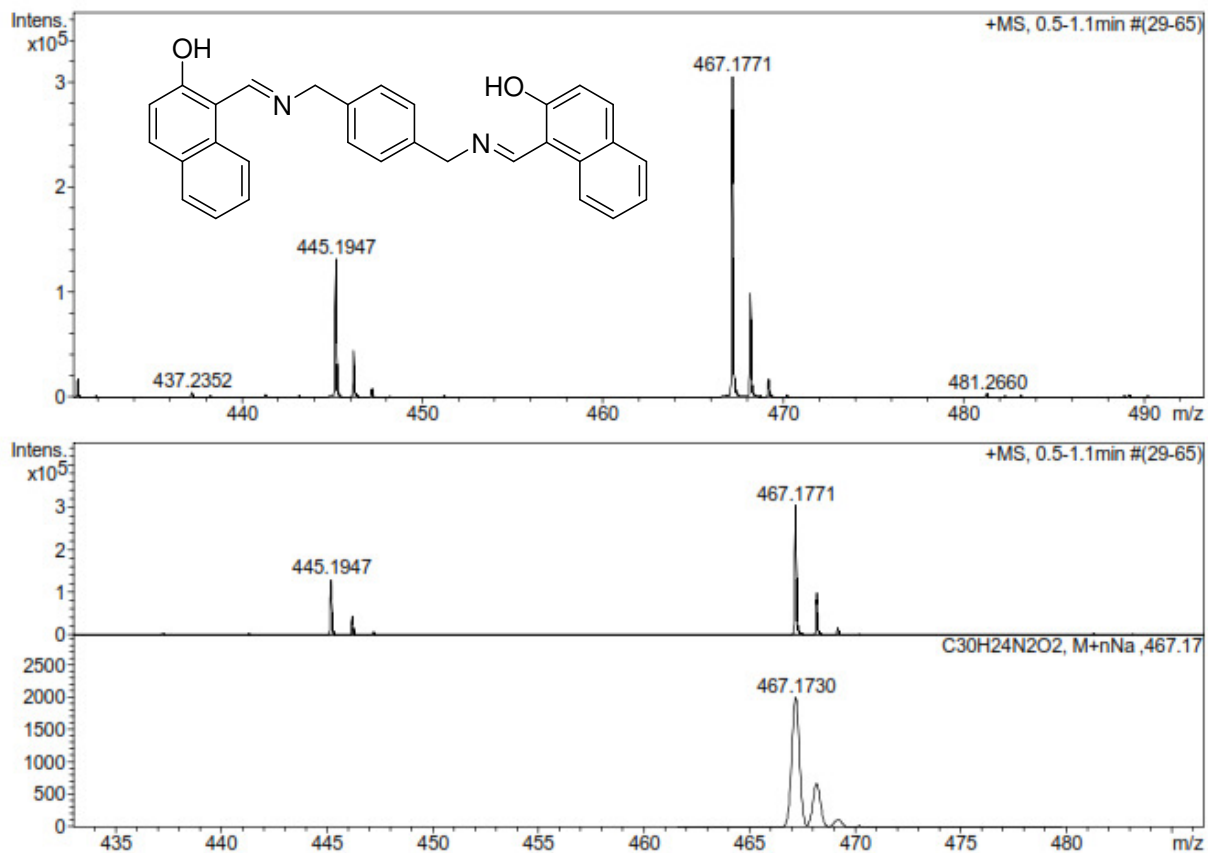


Figure S42. 4g, HRMS.

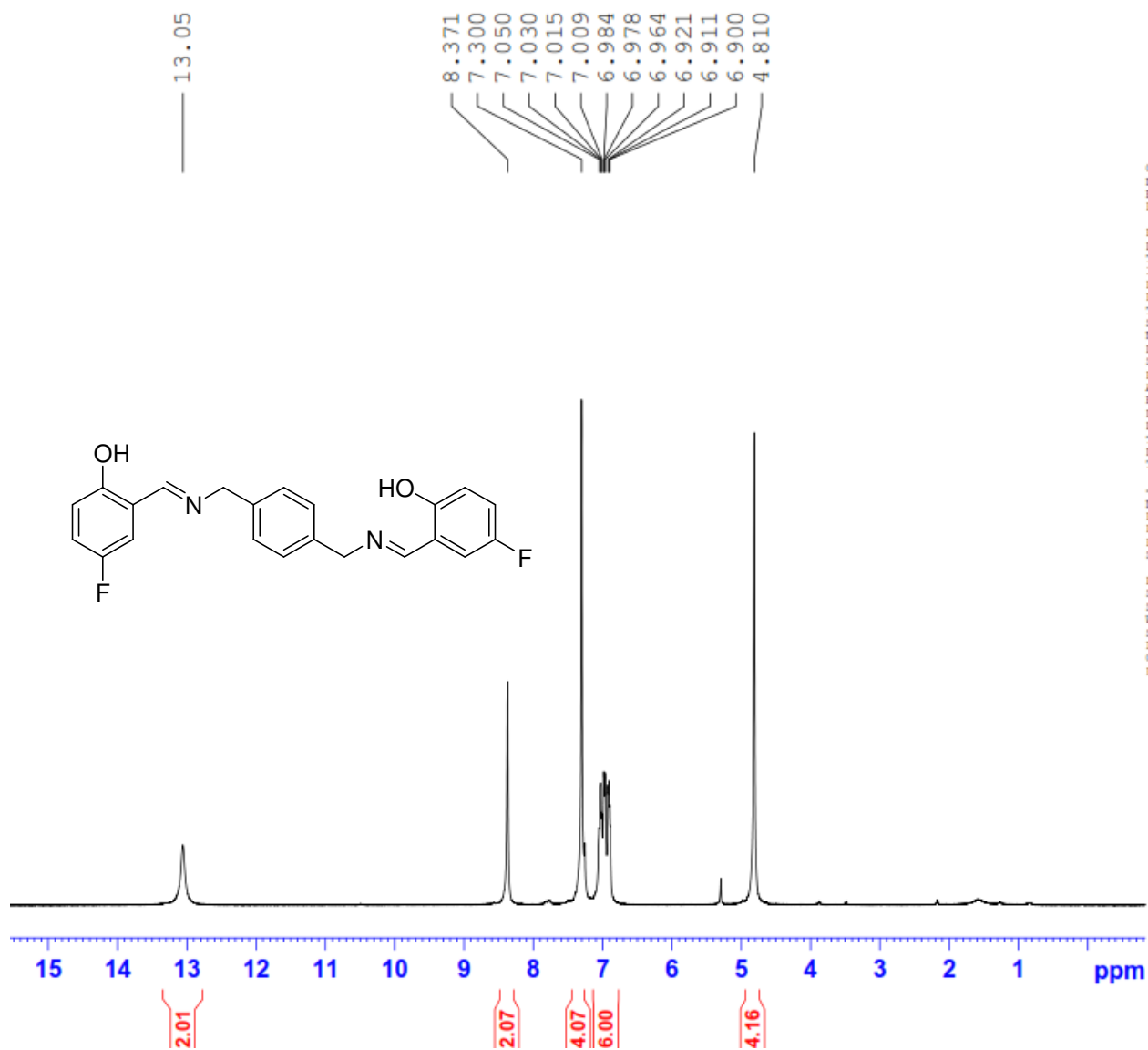


Figure S43. 4h, ¹H NMR.

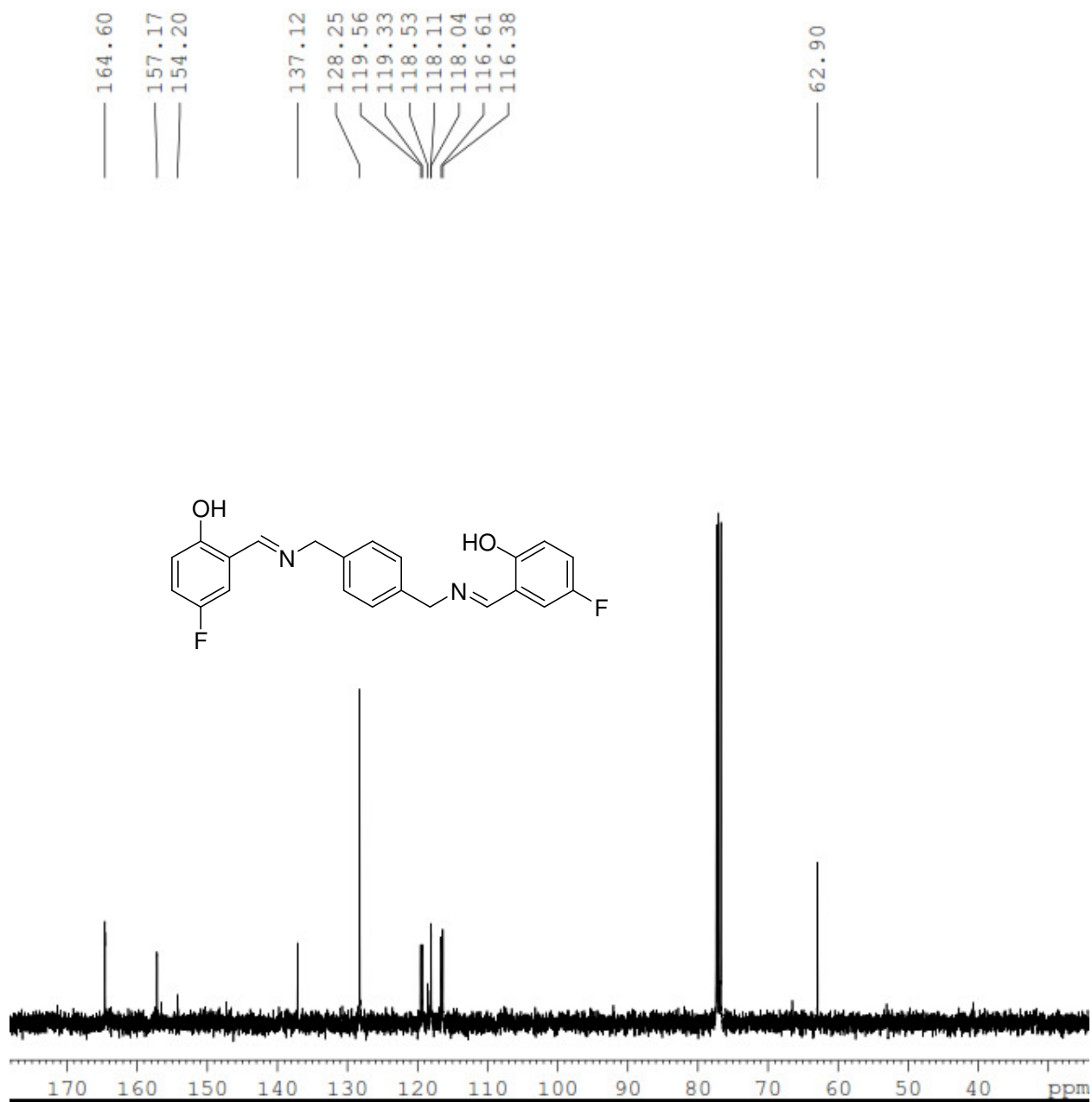


Figure S44. 4h, ^{13}C NMR.

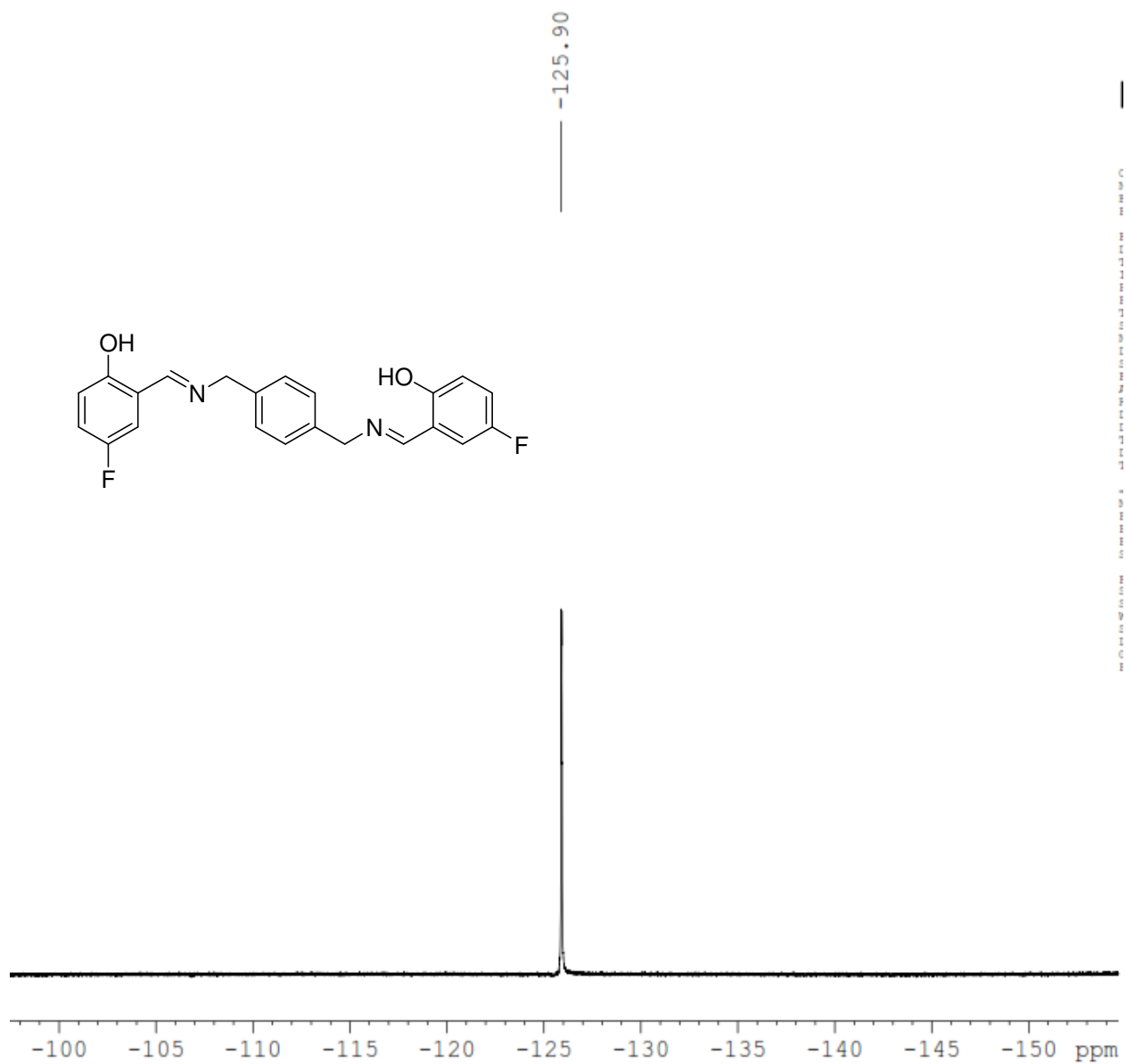


Figure S45. 4h, ^{19}F NMR.

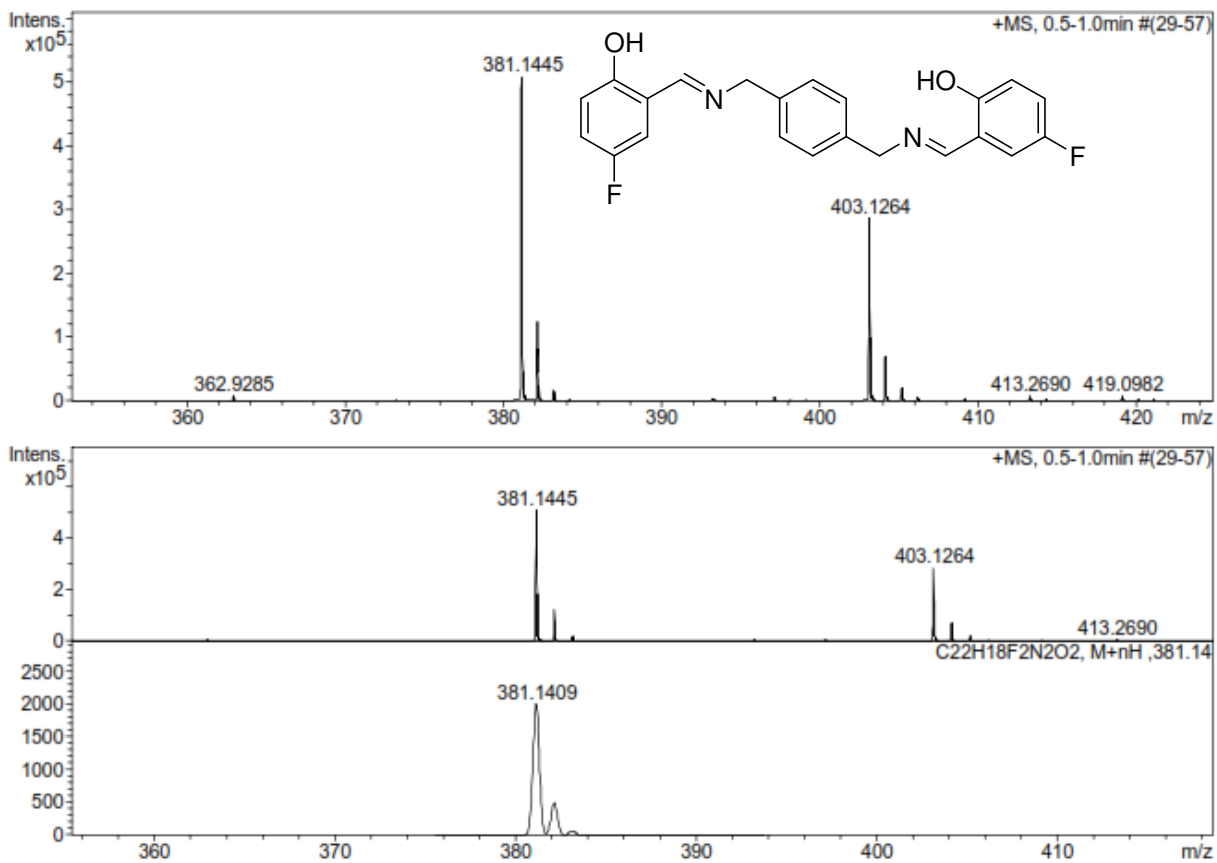


Figure S46. 4h, HRMS.

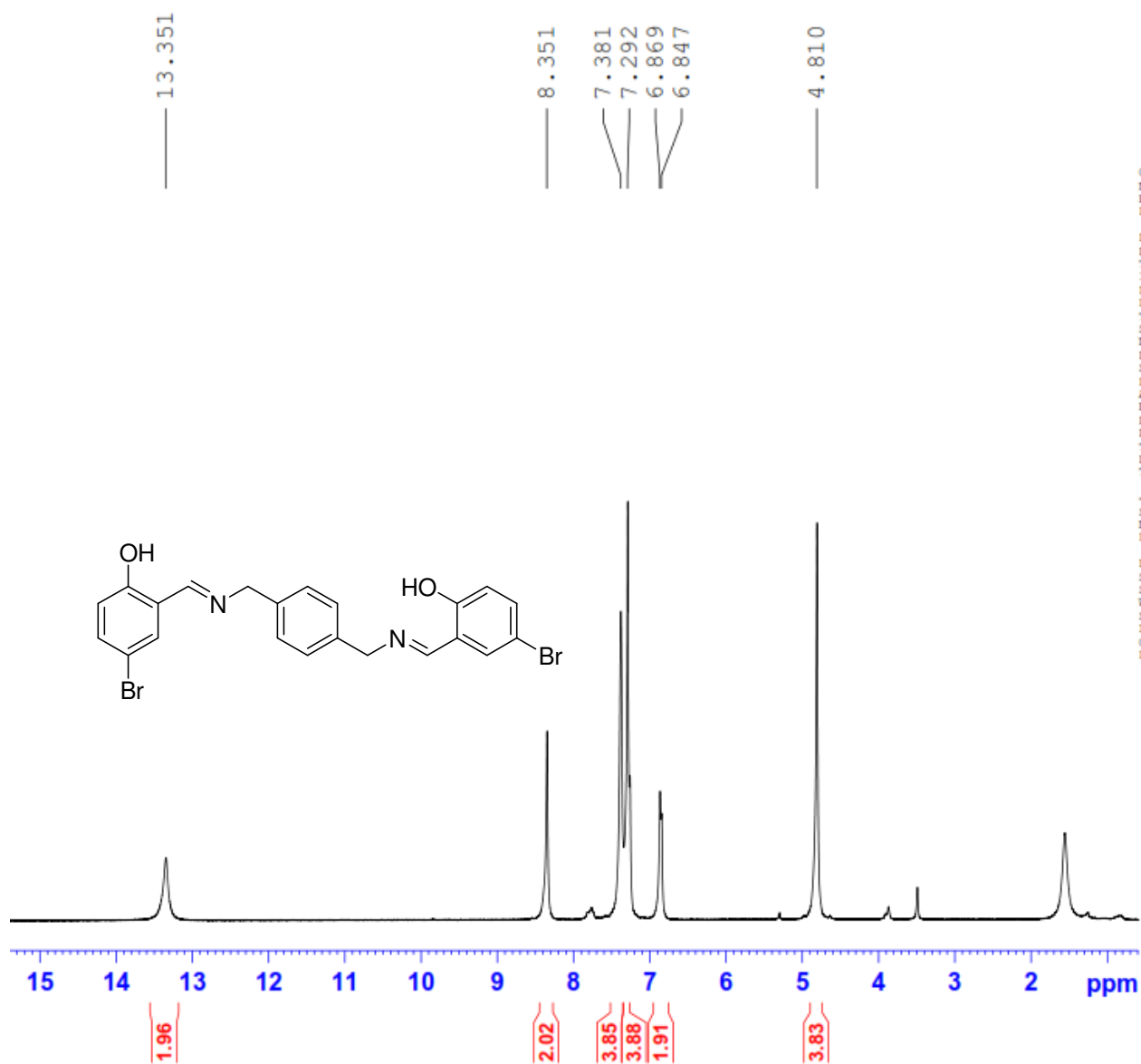


Figure S47. 4i, ^1H NMR.

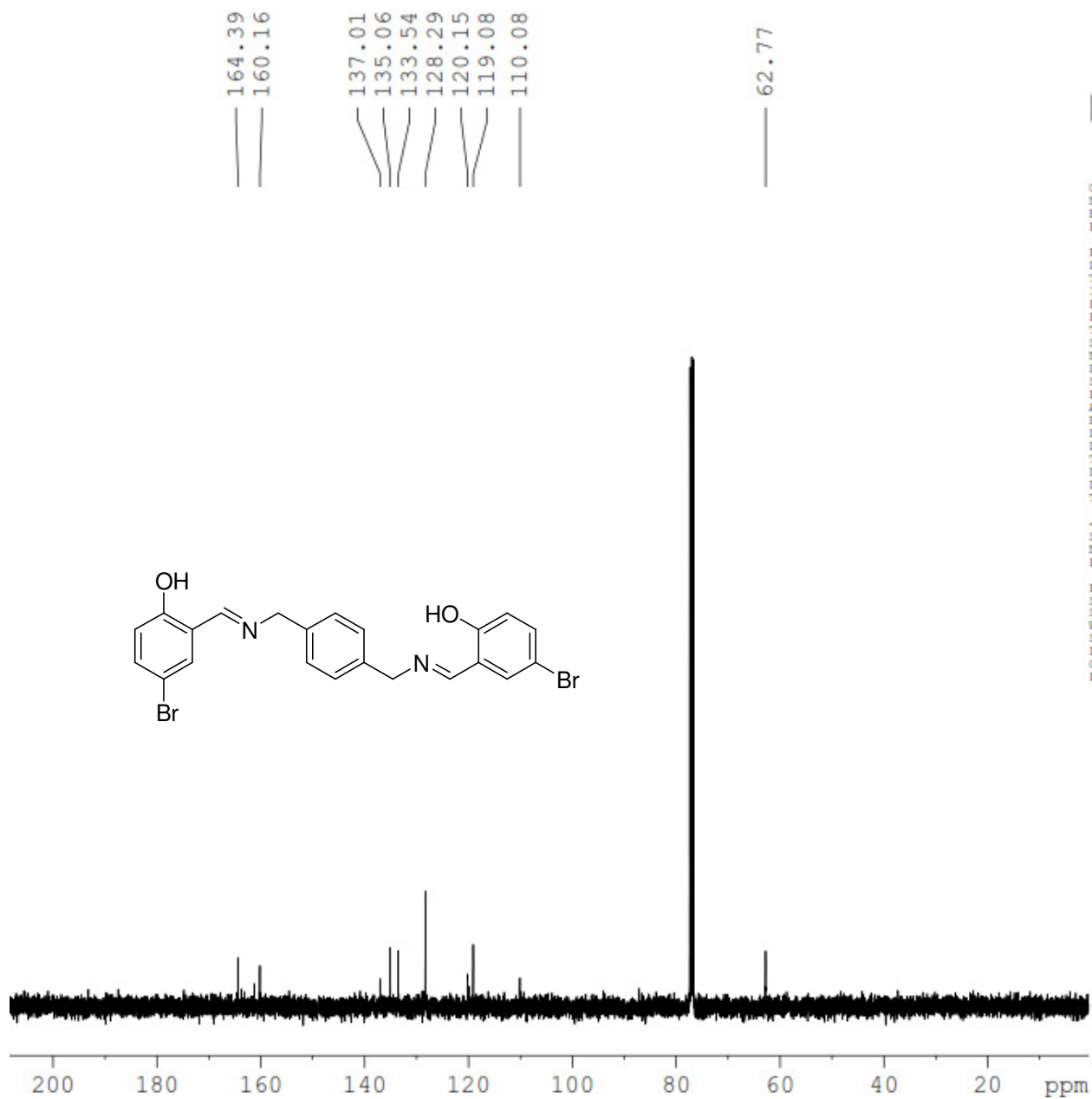
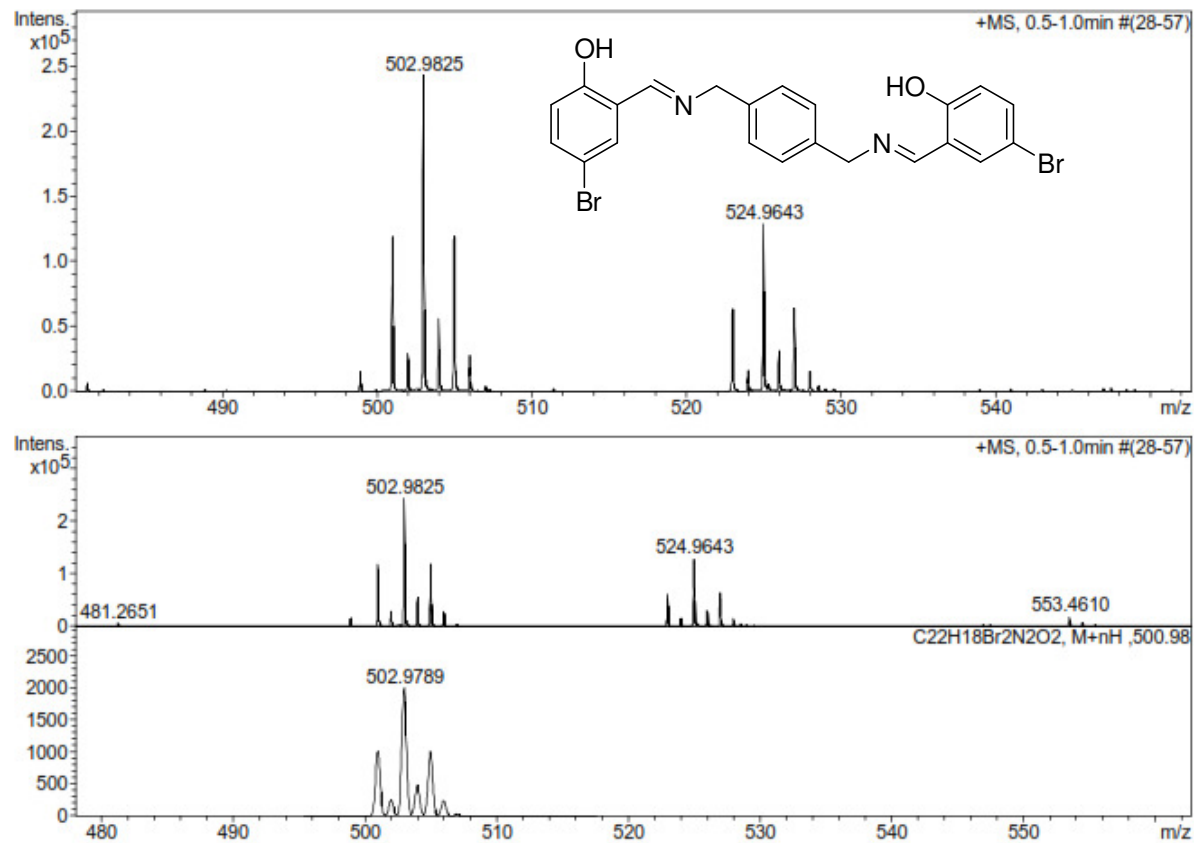


Figure S48. 4i, ¹³C NMR.

**Figure S49. 4i, HRMS.**

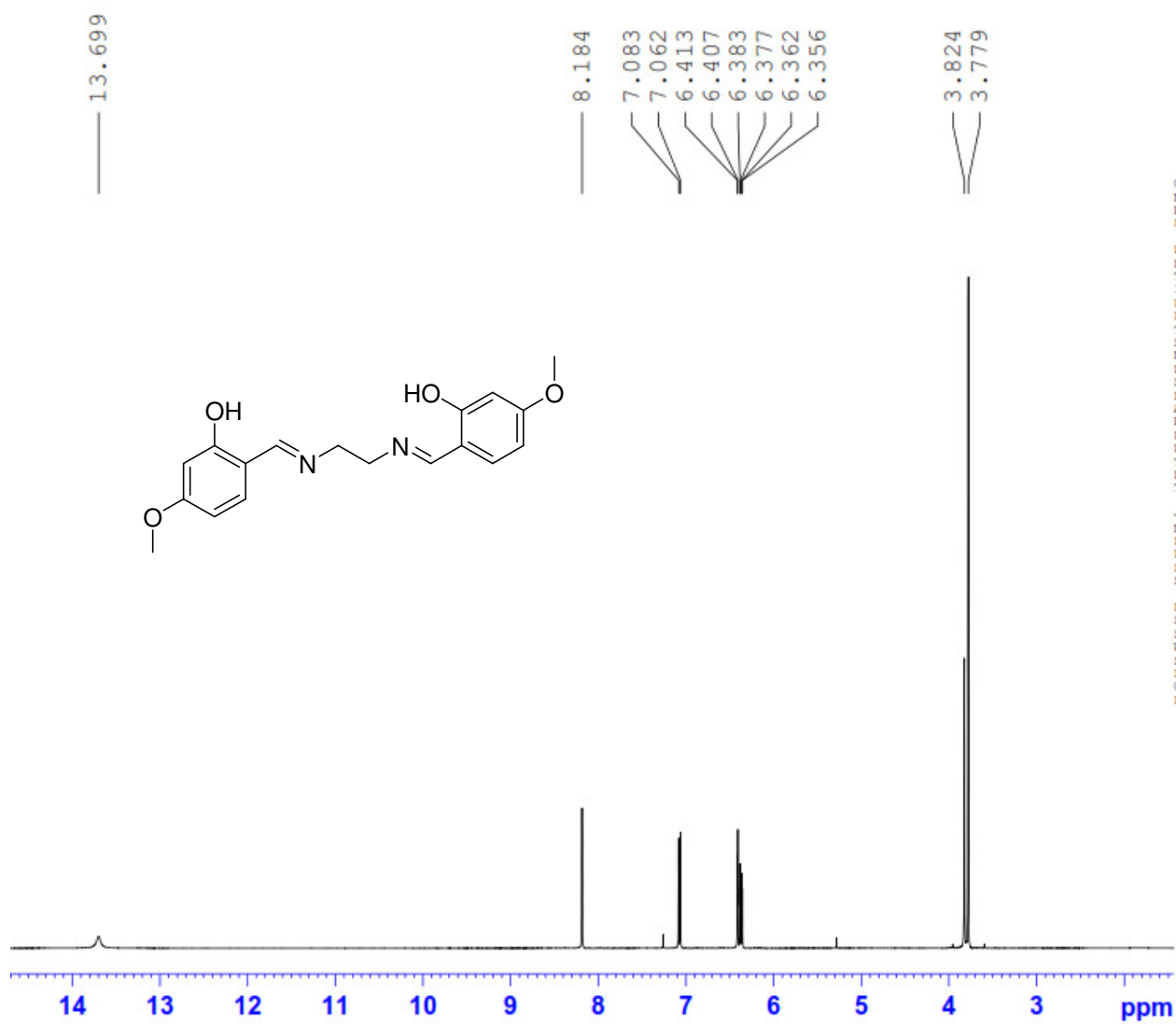


Figure S50. 5, ¹H NMR.

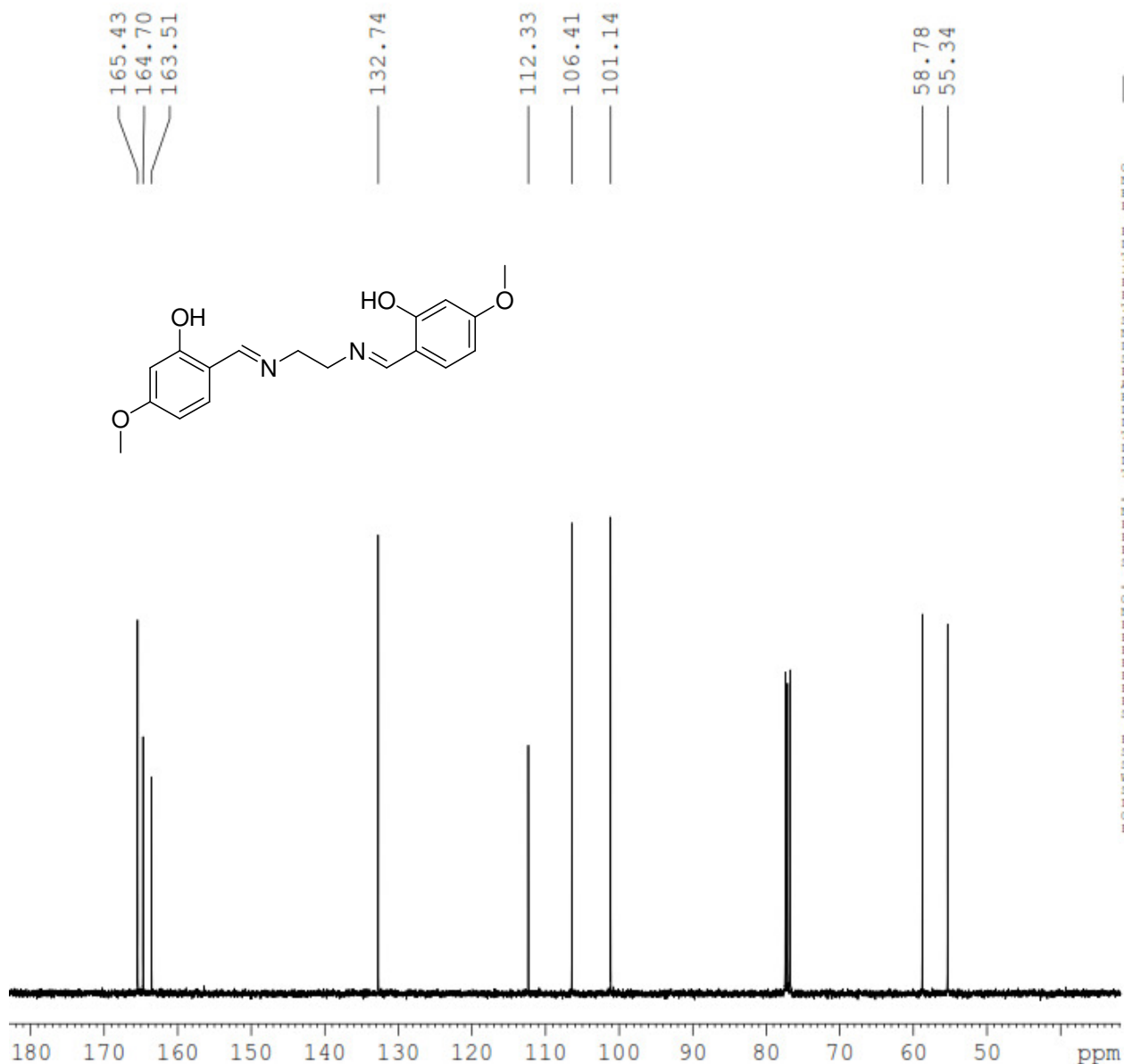


Figure S51. 5, ¹³C NMR.

Synthesis of 5-bromo-2-hydroxybenzaldehyde (II)¹

4-Bromophenol (1.47 g, 8.49 mmol) and hexamethylenetetramine (9.52 g, 67.9 mmol) were dissolved in anhydrous CF₃COOH (25 mL) and the yellow solution was heated at 110 °C for 18 h. After cooling to room temperature, the mixture was added to aqueous HCl (4 M, 50 mL) and stirred for 5 h. Filtration and washing with H₂O (3 × 15 mL) afforded the product as a yellow

solid. **II** was obtained following silica gel flash chromatography ($R_f = 0.35$ in 20% DCM/Pentane) as colorless crystals. ^1H NMR (400 MHz, CDCl_3): δ_{H} 10.92 (s, 1 H), 9.84 (s, 1 H), 7.67 (d, J 2.5 Hz, 1 H), 7.60 (dd, J 8.8, 2.5 Hz, 1 H), 6.91 (d, J 8.8, 1 H). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 195.6, 160.7, 139.9, 135.8, 121.9, 120.0, 111.5.

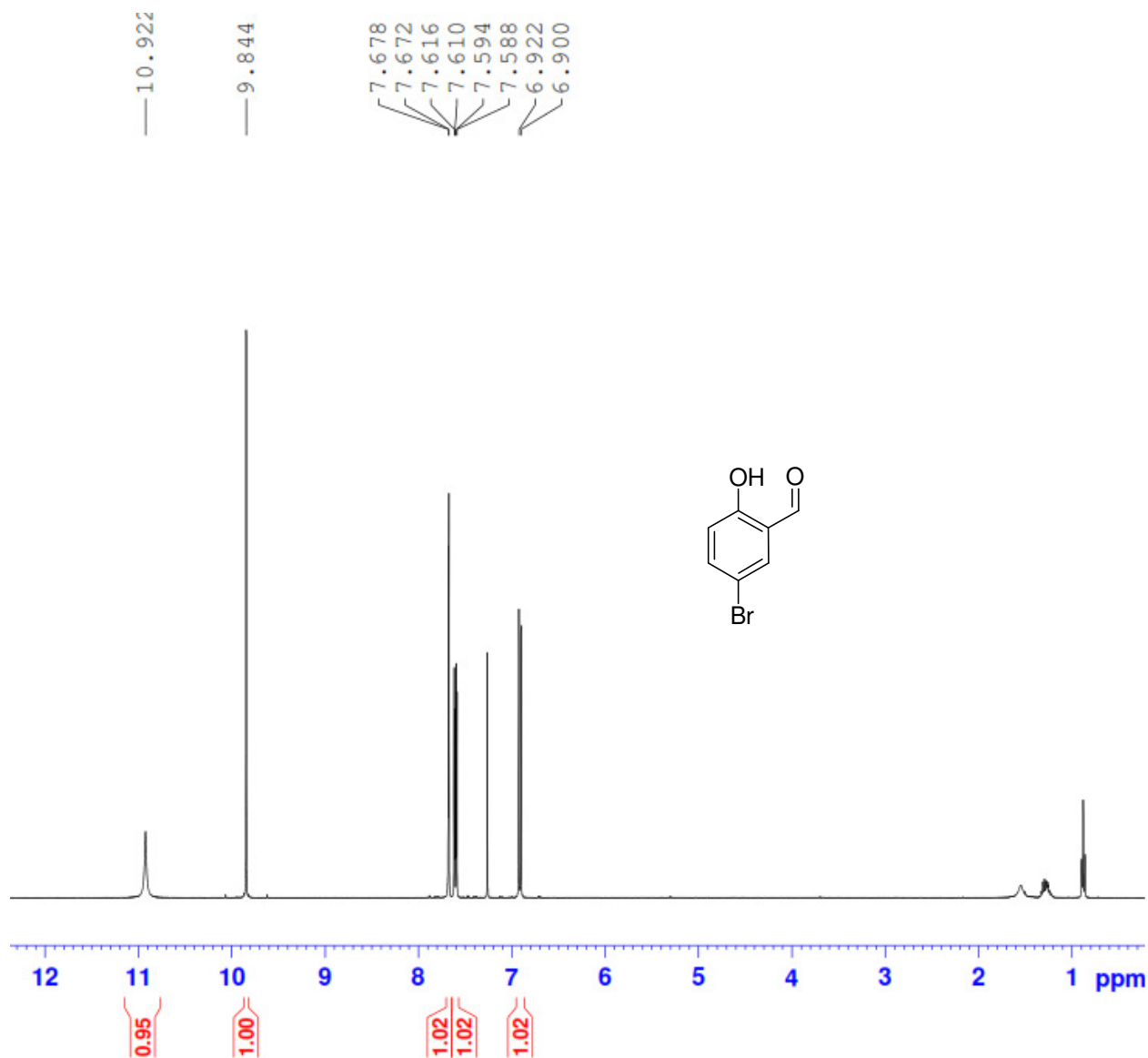


Figure S52. **II**, ^1H NMR.

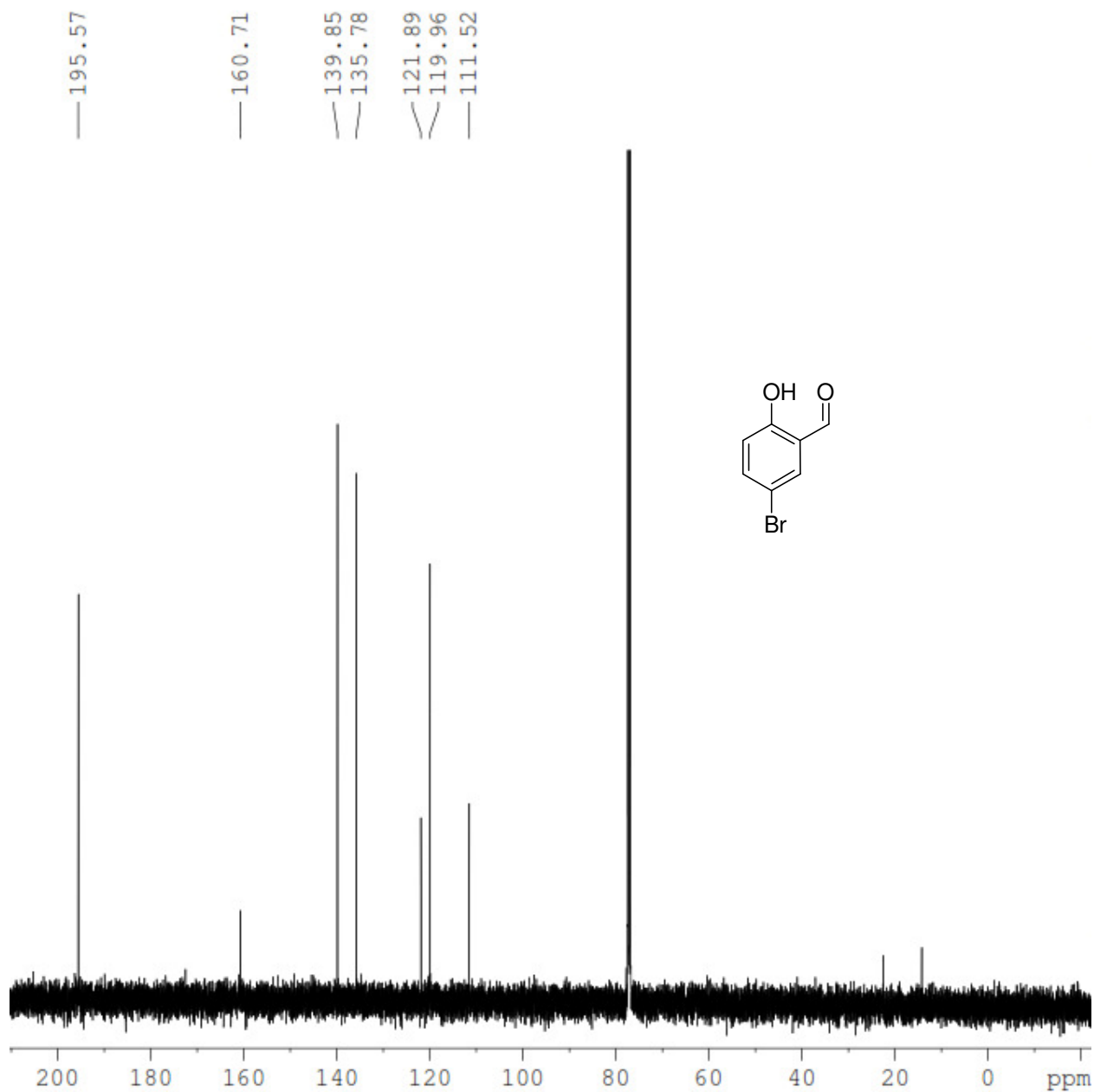


Figure S53. I1, ^{13}C NMR.

Synthesis of 2-hydroxy-5-(2-(trimethylsilyl)ethynyl)benzaldehyde (I2)²

To a mixture of 5-bromosalicylaldehyde (5.00 g, 24.87 mmol), Pd(PPh₃)₂Cl₂ (0.52 g, 0.74 mmol), PPh₃ (0.74 mmol) and CuI (0.15 g, 0.75 mmol) in 80 mL of Et₃N (0.7255 g/mL), trimethylsilylacetylene (5.5 mL, 38.72 mmol, 0.69 g/mL) was added. The mixture refluxed for 8 h under an atmosphere of argon. After cooling, CH₂Cl₂ (100 mL) was added and filtered. Solvent was removed under vacuum and the residue was purified by chromatography on silica gel with pentane/DCM (2:1) as eluent. Removal of solvent under vacuum afforded a yellow powder, and the product was identified as 5-trimethylsilylethynylsalicylaldehyde (4.8 g, 88.51 %). ¹H NMR (400 MHz, CDCl₃): δ_H 11.09 (s, 1 H, OH), 9.84 (s, 1H, CHO), 7.69 (d, *J* 2.0 Hz, 1H, Ar-H), 7.60 (dd, *J* 8.6, 2.0 Hz, 1H, Ar-H), 6.92 (d, *J* 8.6 Hz, 1H, Ar-H), 0.24 (s, 9H, 3CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 196.1, 161.6, 140.2, 137.5, 120.5, 115.2, 118.1, 103.3, 93.9, 0.07.

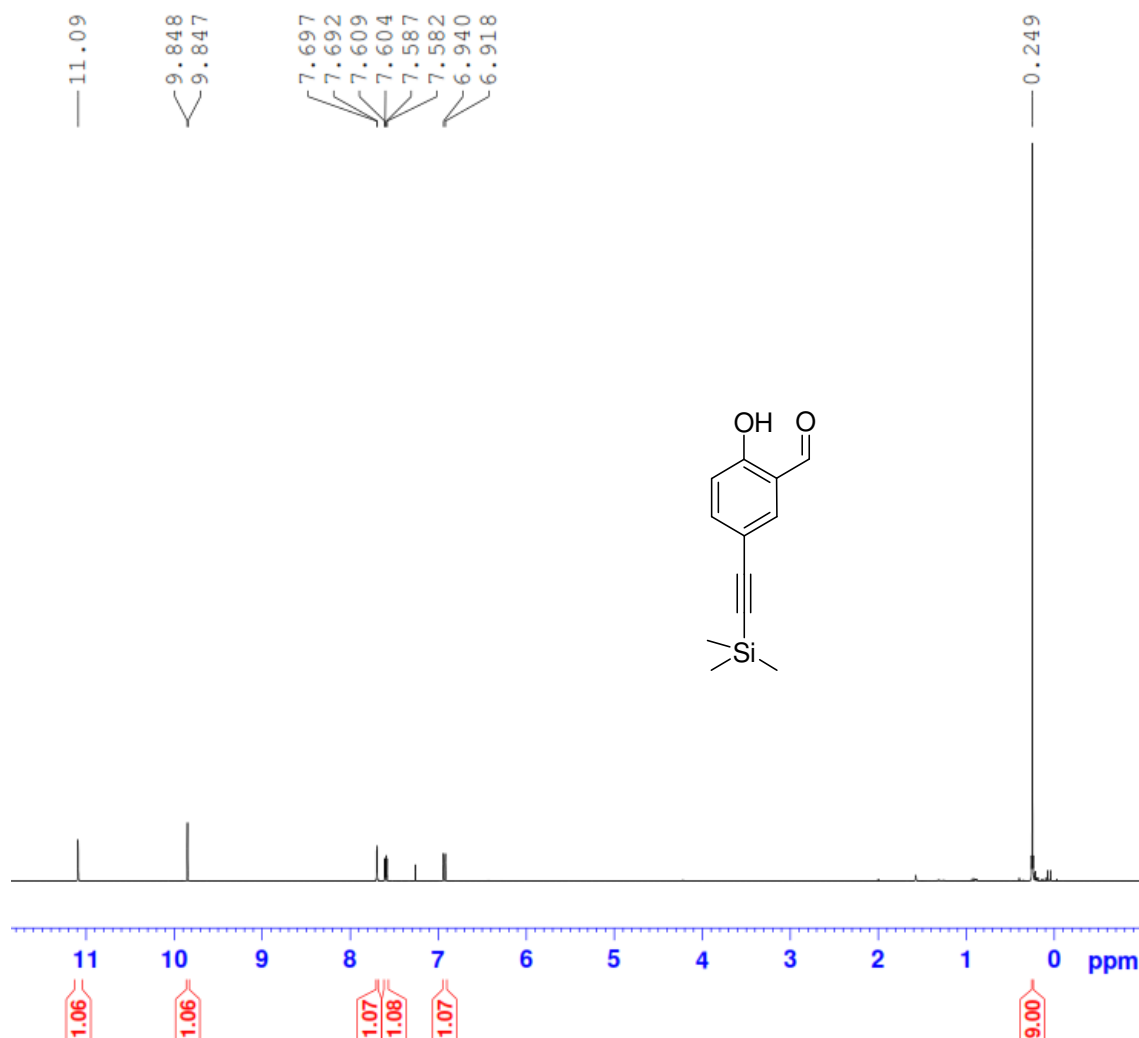


Figure S54. I2, ¹H NMR.

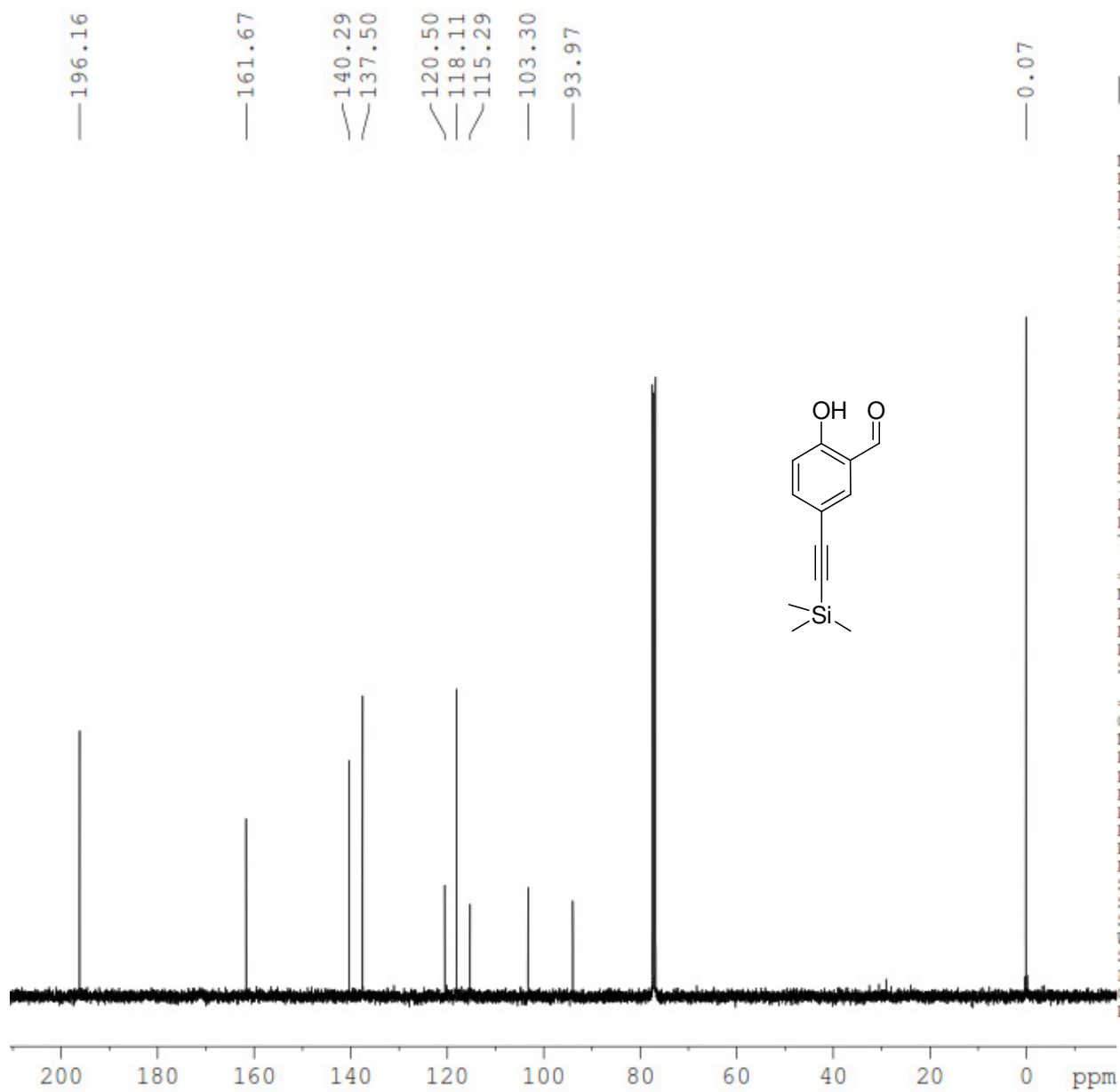


Figure S55. **12**, ¹³C NMR.

Synthesis of 5-ethynyl-2-hydroxybenzaldehyde (I3)²

5-Ethynyltrimethylsilylsalicylaldehyde (4.945 g, 22.6 mmol) was dissolved in CH₂Cl₂ (30 mL). Potassium hydroxide (1.268 g, 22.6 mmol) was dissolved in MeOH (15 mL) and added to the CH₂Cl₂ solution. The reaction mixture was stirred at room temperature overnight, and then the solvent was removed under reduced pressure. The residue was dissolved in H₂O (15 mL) and acidified with 0.05 M HCl. The mixture was extracted with CH₂Cl₂ (3 x 20). The organic phase was dried over MgSO₄, filtered, and the solvent was removed by rotary evaporation to obtain 3.15 g (95.11%) of light yellow powder. ¹H NMR (400 MHz, CDCl₃): δ_H 11.12 ppm (s, 1 H, OH), 9.86 (s, 1H, CHO), 7.72 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.62 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar-H), 6.96 (d, *J* = 8.6 Hz, 1H, Ar-H), 3.03 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_C 196.1, 161.9, 140.3, 137.6, 120.5, 118.3, 114.1, 82.0, 76.9 ppm. ESI-HRMS *m/z* calcd. for C₉H₆O₂ (M - H)⁺: 145.0284; found 145.0288.

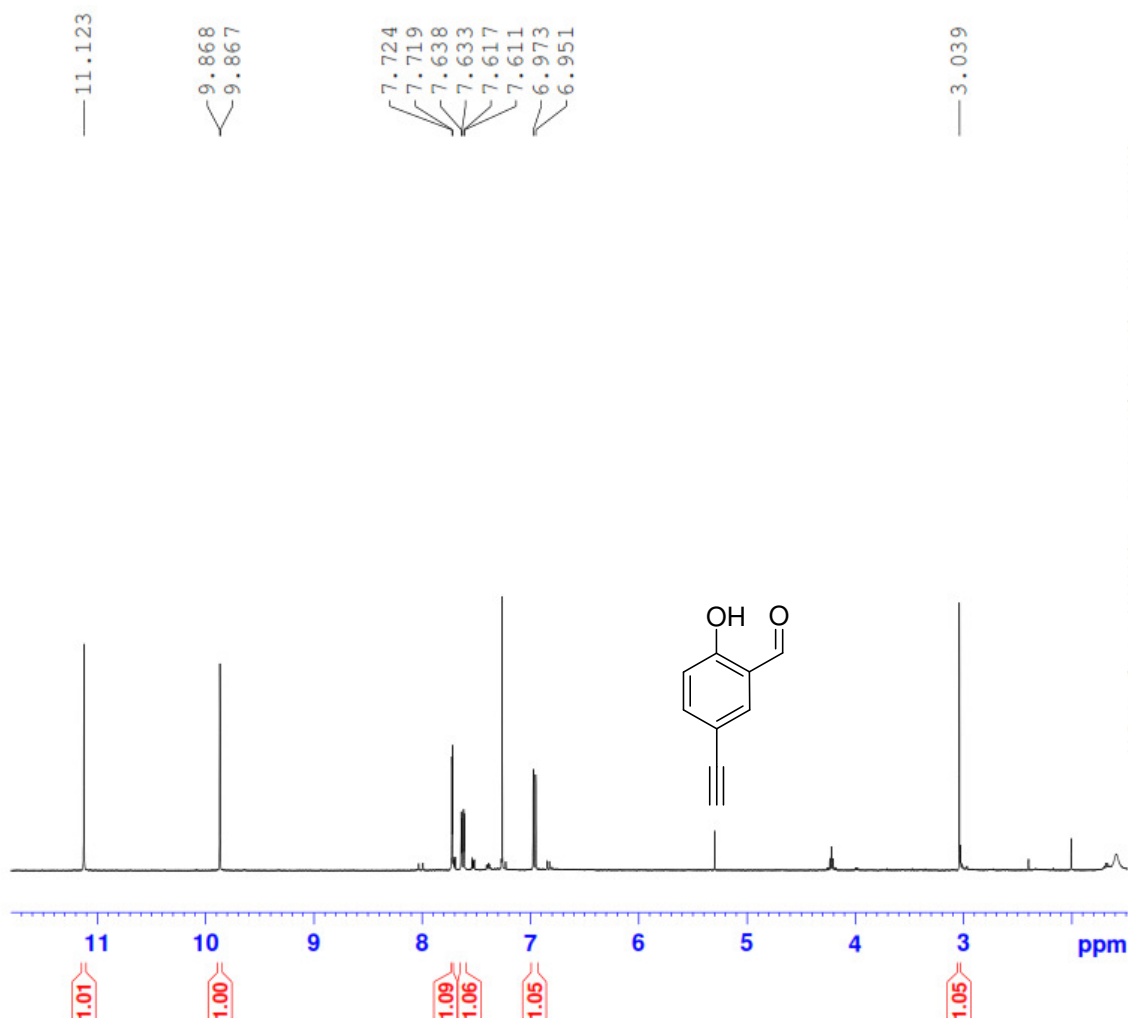


Figure S56. I3, ¹H NMR.

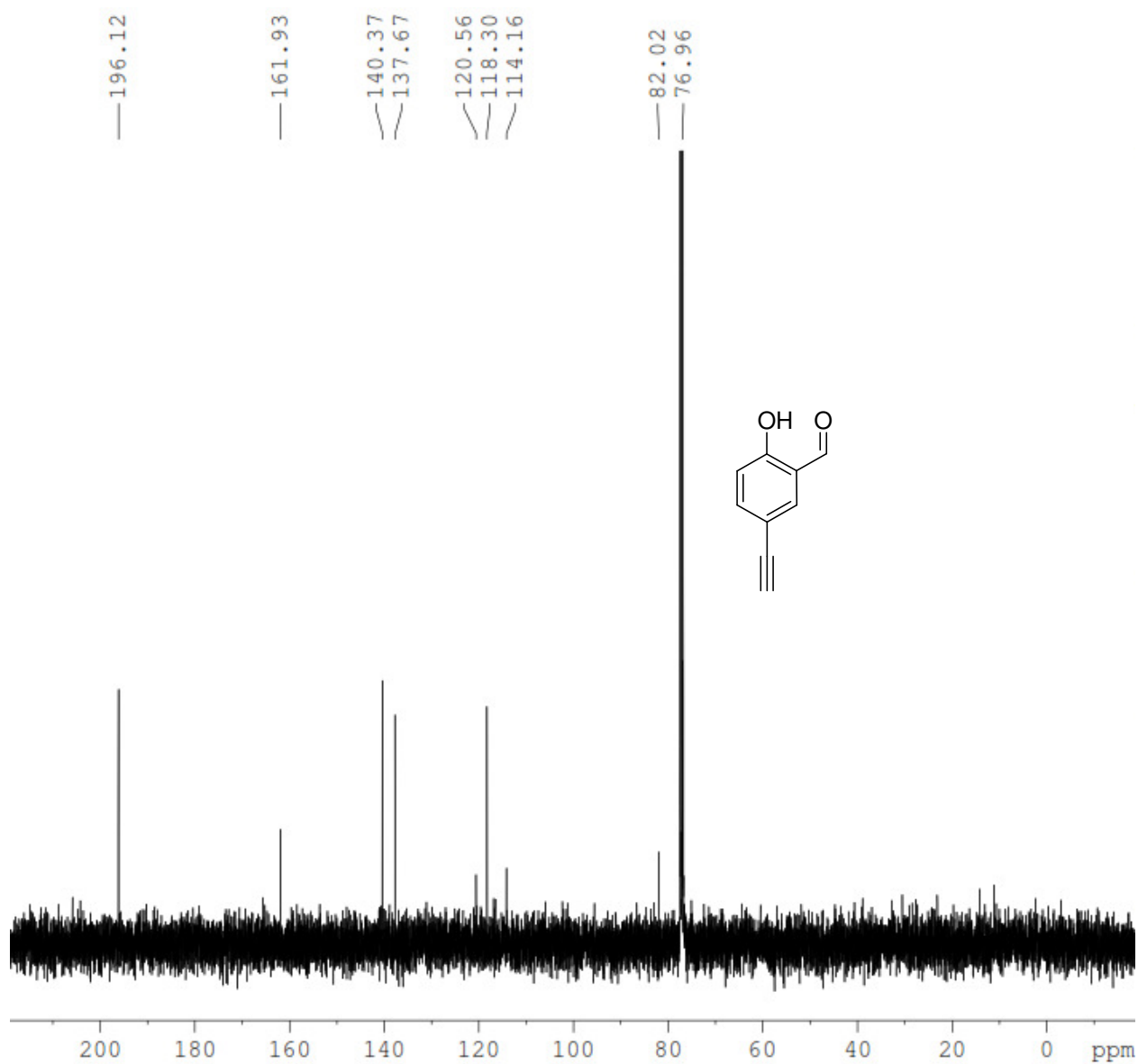


Figure S57. I3, ^{13}C NMR.

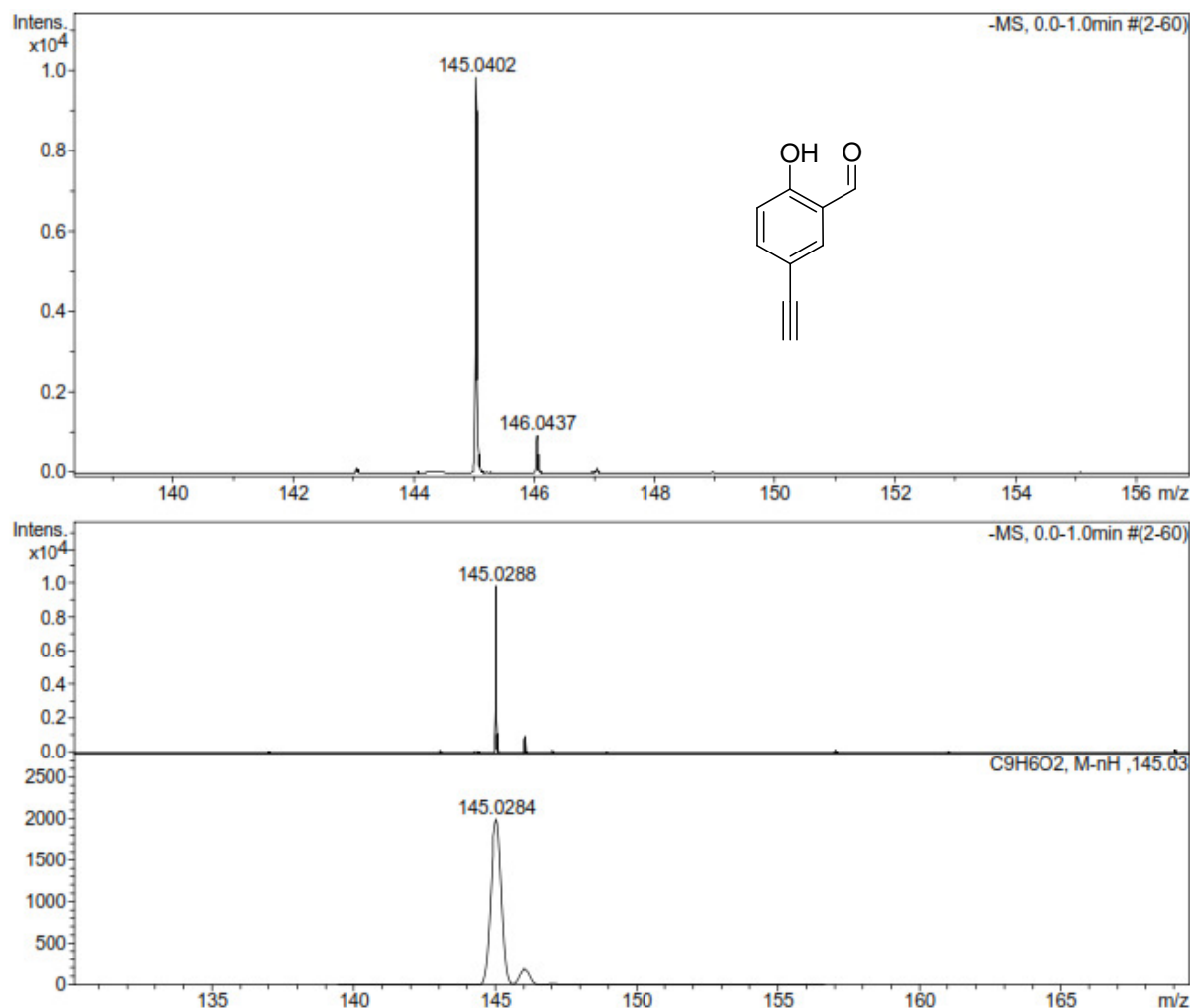


Figure S58. I3, HRMS.

Synthesis of 2,2'-bipyridine-*N*'-oxide (**I4**)^{3,4}

2,2'-Bipyridine (10 g, 64 mmol) was dissolved in 50 mL trifluoroacetic acid and cooled to 5 °C. To the cold solution, 10 mL of hydrogen peroxide (30 mass %, 77.5 mmol, 1.11 g/mL) was added and the obtained mixture was stirred at room temperature for 4 h. The product was extracted with chloroform (3 x 100 mL), and the combined organic extracts were washed with 3 M NaOH (3 x 50 mL) then dried with MgSO₄ and evaporated to give 11.0 g of white solid. ¹H NMR (400 MHz, CDCl₃): δ_H 8.84 (br d, *J* 8.0 Hz, 1 H), 8.66 (m, 1 H), 8.25 (dd, *J* 6.5, 1.0 Hz, 1H), 8.11 (dd, *J* 8.0, 2.1 Hz, 1H), 7.76 (ddd, *J* 9.4, 7.8, 1.8 Hz, 1H), 7.31 - 7.26 (m, 2 H), 7.20 (ddd, *J* 8.8, 7.5, 2.1 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ_C 149.6, 149.3, 147.3, 140.6, 136.2, 127.8, 125.6, 125.4, 125.2, 124.2.

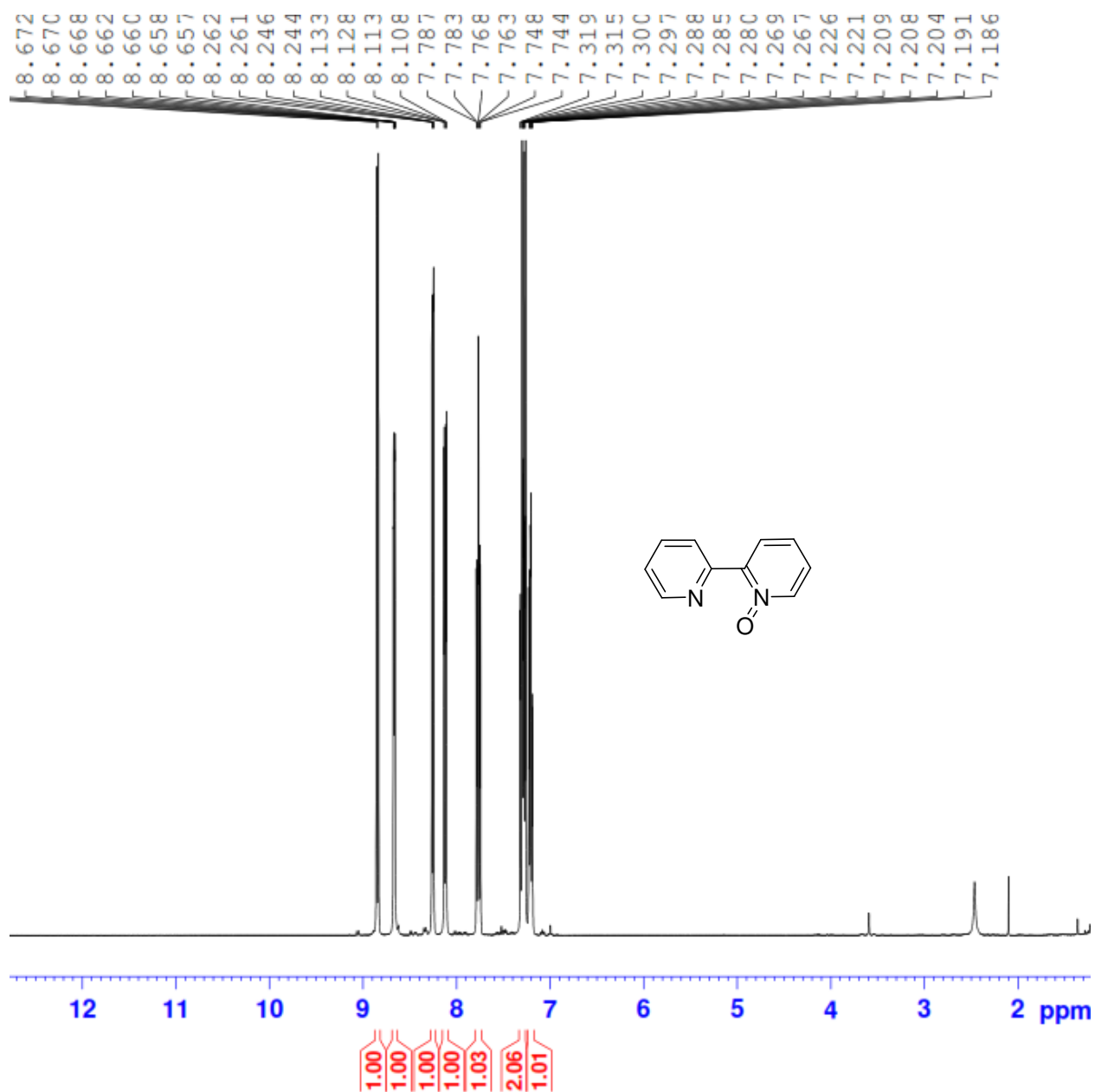


Figure S59. I4, ¹H NMR.

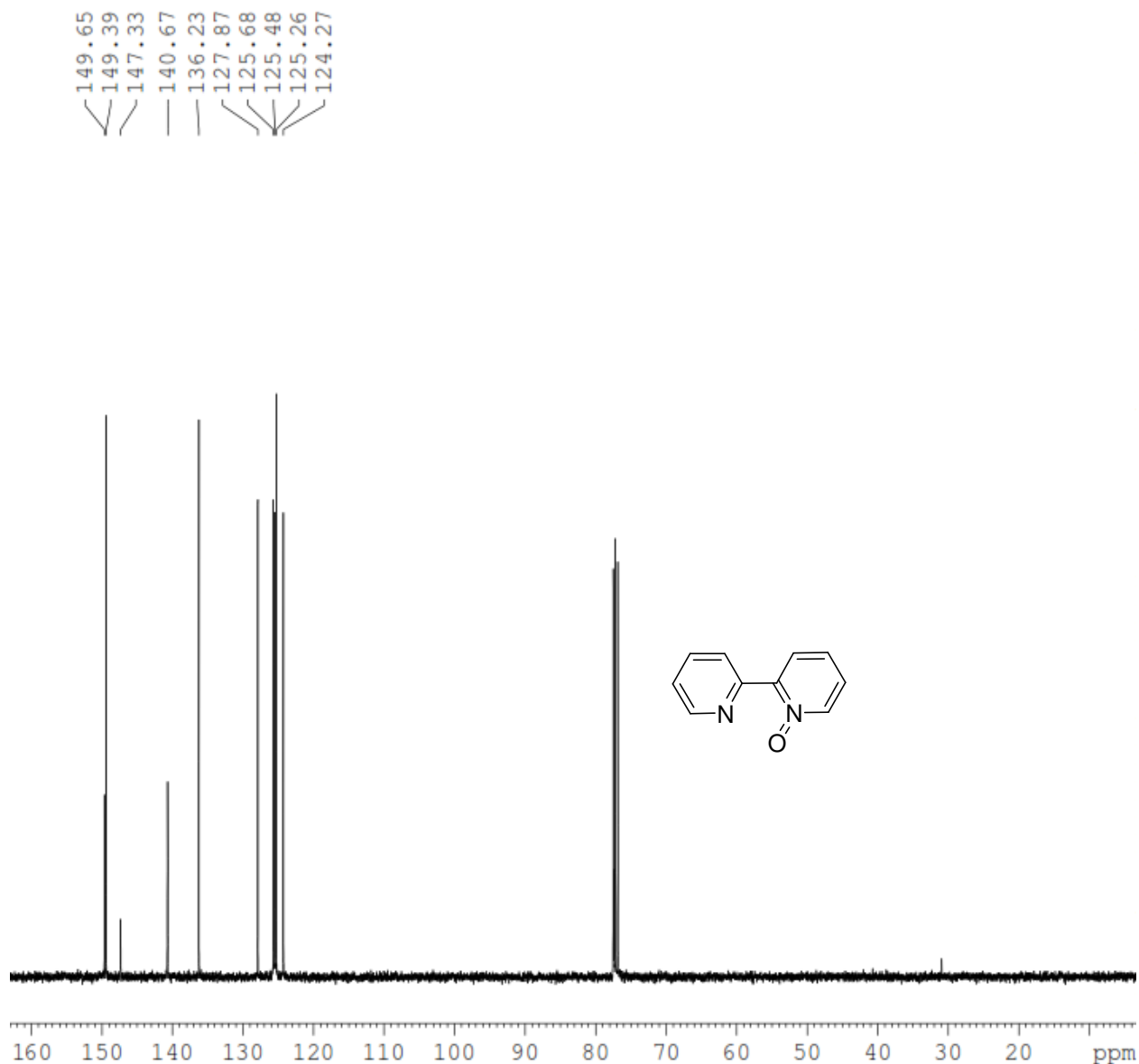


Figure S60. 14, ¹³C NMR.

Synthesis of 4'-nitro-2,2'-bipyridine-N'-oxide (15)^{3,4}

2,2'-Bipyridine-N'-oxide (9 g, 51 mmol) was dissolved in concentrated sulphuric acid (57 mL, 3.5 mol, 1.84 g/mL) under stirring. A mixture of fuming nitric acid (90 mL, 2.08 mol, 1.48 g/mL) and concentrated sulphuric acid (42 mL, 0.78 mol, 1.84 g/mL) was added dropwise over 30 min. and then the reaction mixture was heated at 100 °C for 5h. After cooling to room temperature, pour the reaction mixture onto ice/water mixture (500 mL) and the pH was adjusted using 4 M NaOH. Filter the formed precipitate and wash with water (3 x 100 mL). The solid was suspended in water and extracted with DCM (3 x 100 mL). The combined organic extracts were

washed with water (100 mL) and dried with MgSO_4 . After the solvent was evaporated, the product (7.2 g) was obtained as light yellow solid. ^1H NMR (400 MHz, CDCl_3): δ_{H} 9.15 (d, J 3.2 Hz, 1 H), 8.88 (d, J 8.0 Hz, 1 H), 8.78 (dd, J 4.5, 0.6 Hz, 1H), 8.35 (d, J 7.1 Hz, 1H), 8.05 (dd, J 7.1, 3.2 Hz, 1H), 7.87 (ddd, J 9.5, 7.9, 1.8 Hz, 1H), 7.44-7.40 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 149.96, 148.40, 147.72, 142.60, 142.07, 136.81, 125.48, 125.23, 122.74, 119.00. ESI-HRMS m/z calcd. for $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_3$ ($\text{M} + \text{Na}$) $^+$: 240.0380; found 240.0395.

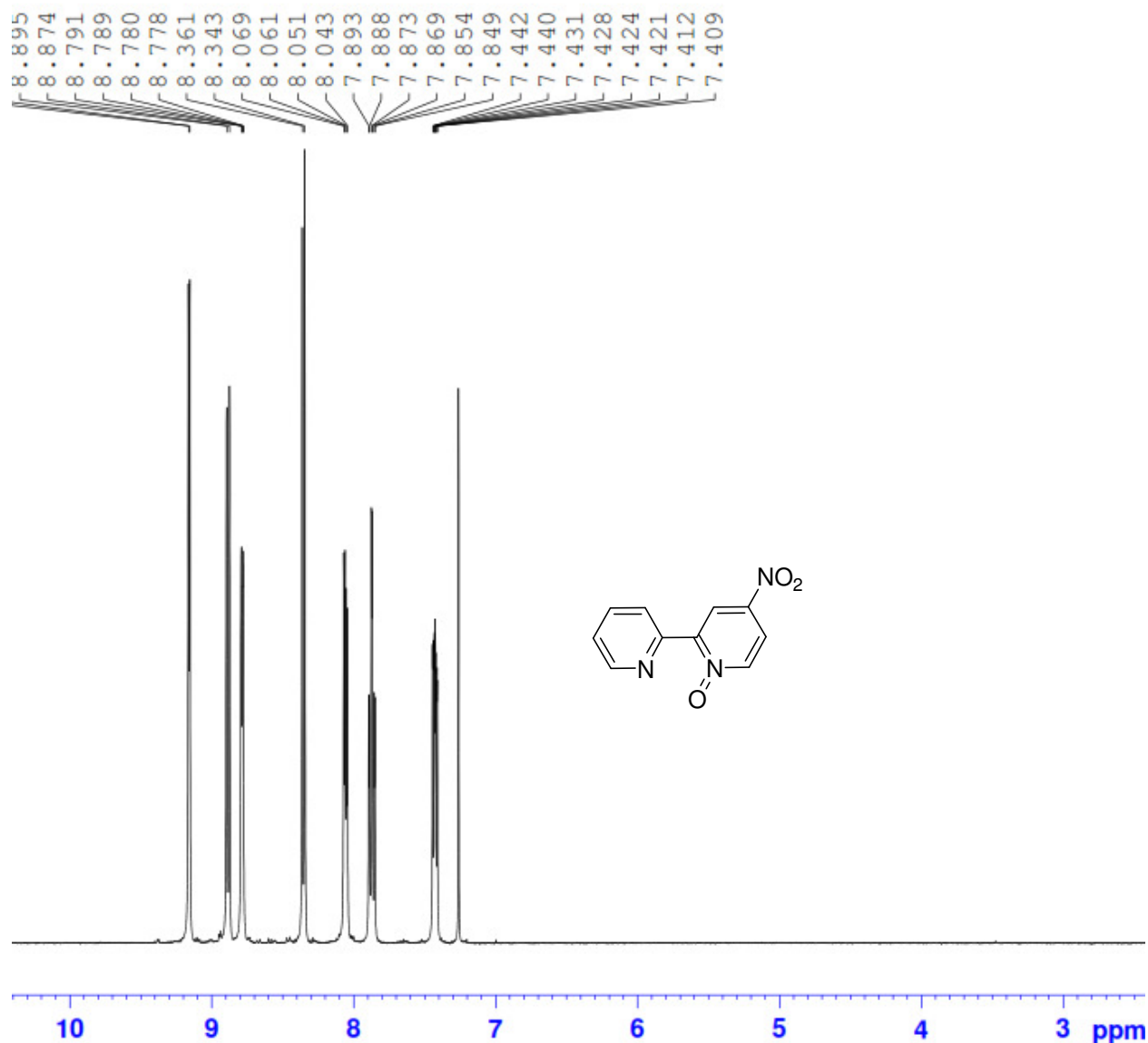


Figure S61. I5, ^1H NMR.

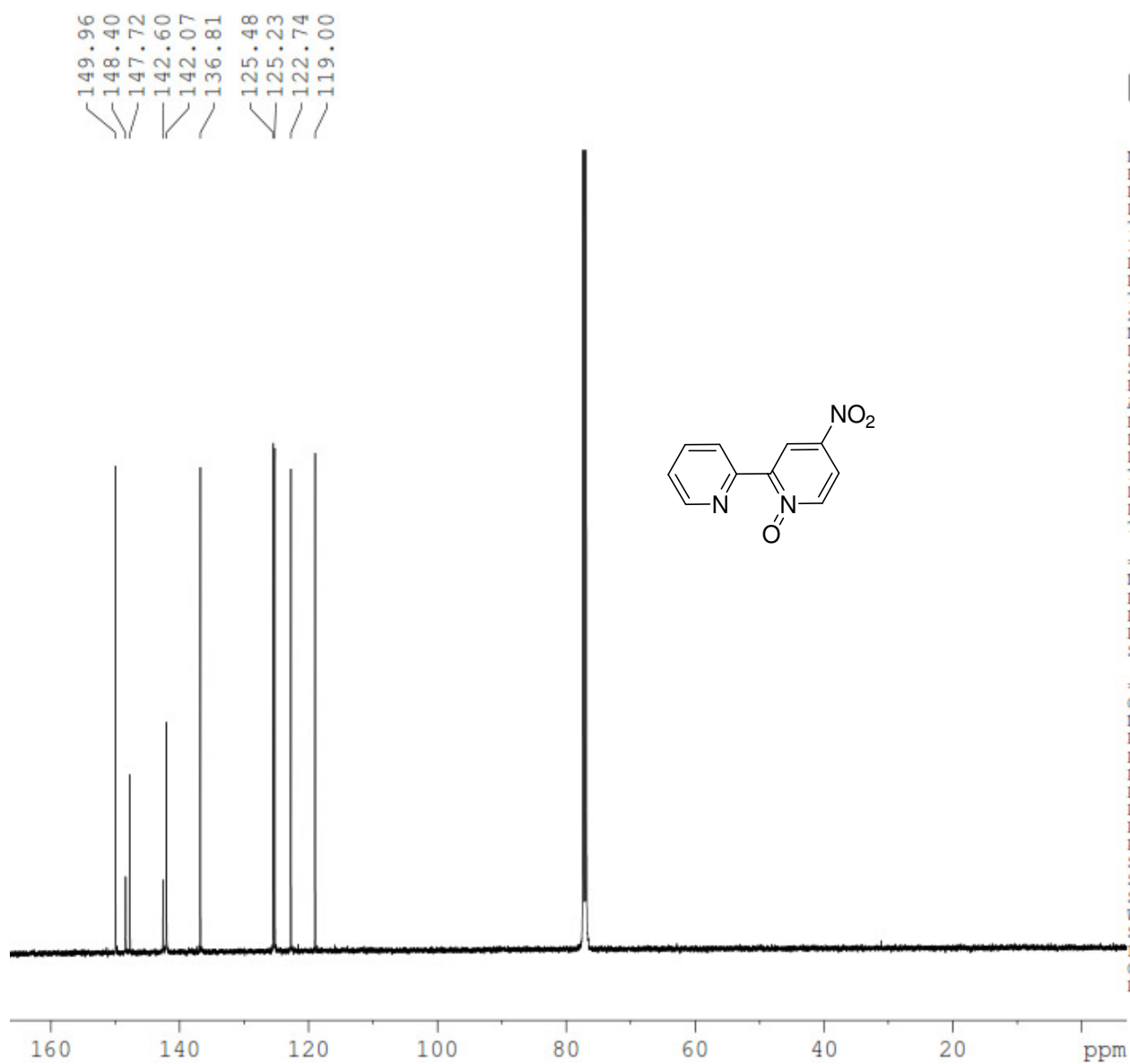


Figure S62. I5, ¹³C NMR.

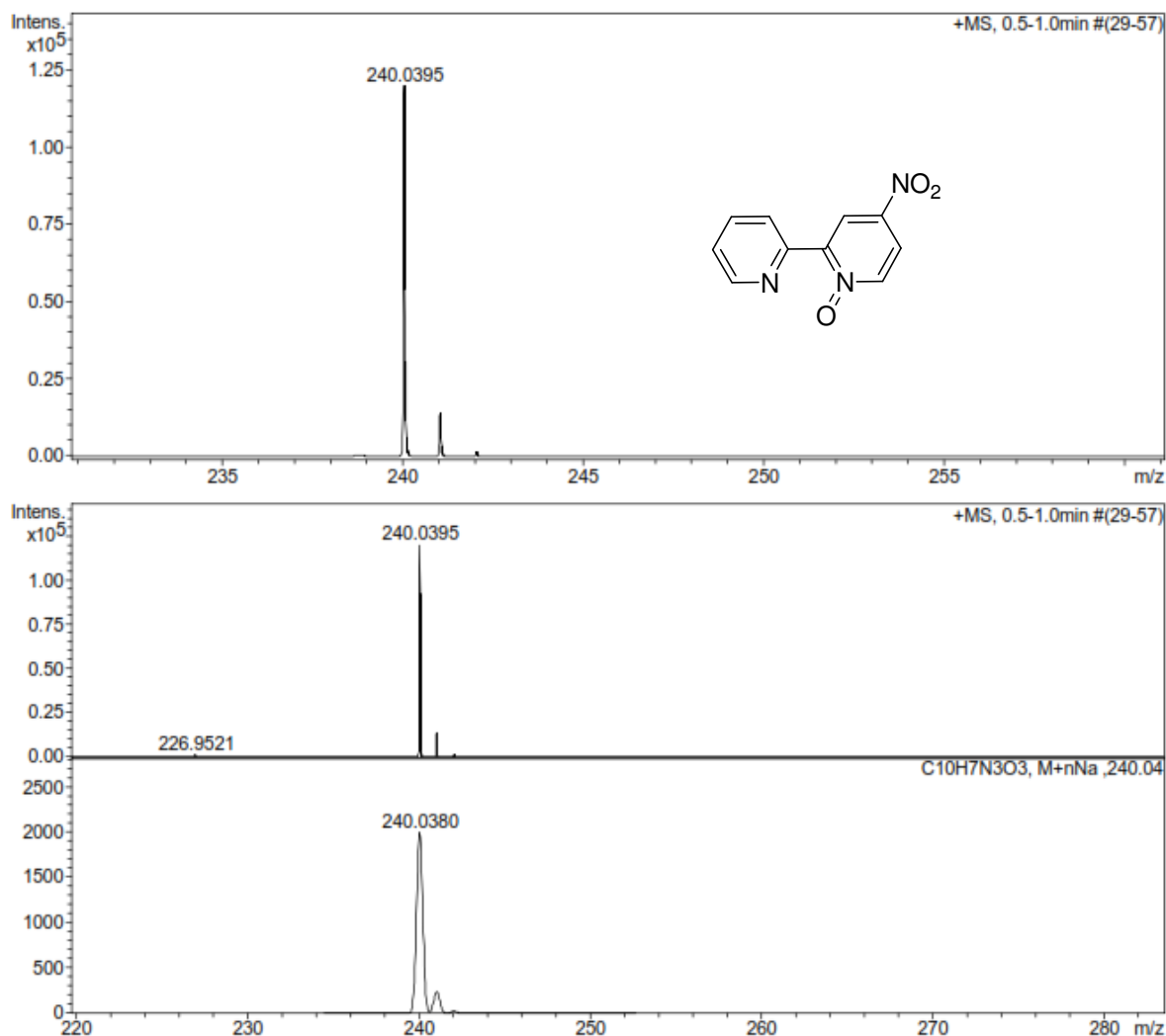


Figure S63. I5, HRMS.

Synthesis of 4'-azido-2,2'-bipyridine-N'-oxide (I6)^{3,4}

4'-Nitro-2,2'-bipyridine-N'-oxide (3.27 g, 15 mmol) and sodium azide (3.51 g, 54 mmol) were suspended in dry DMF (100 mL) at ambient temperature. The reaction mixture was heated at 80 °C for 48 h. After the removal of the solvent, 100 mL water was added and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried with MgSO₄, and the solvent was evaporated. The product (3.1 g) was obtained as orange solid. ¹H NMR (400 MHz, CDCl₃): δ_H 9.01-8.98 (m, 1 H), 8.72-8.71 (m, 1 H), 8.22 (dd, *J* 7.3, 0.2 Hz, 1H), 7.95 (d, *J* 3.2 Hz, 1H), 7.83 (ddd, *J* 9.5, 7.9, 1.8 Hz, 1H), 7.38-7.35 (m, 1H), 6.8 (dd, *J* 7.0, 3.3 Hz, 1H), ¹³C NMR (100 MHz, CDCl₃): δ_C 149.5, 148.8, 148.0, 141.9, 138.5, 136.6, 125.7, 124.9, 117.6, 116.2. ESI-HRMS *m/z* calcd. for C₁₀H₇N₅O (M + Na)⁺: 236.0543; found 236.0546.

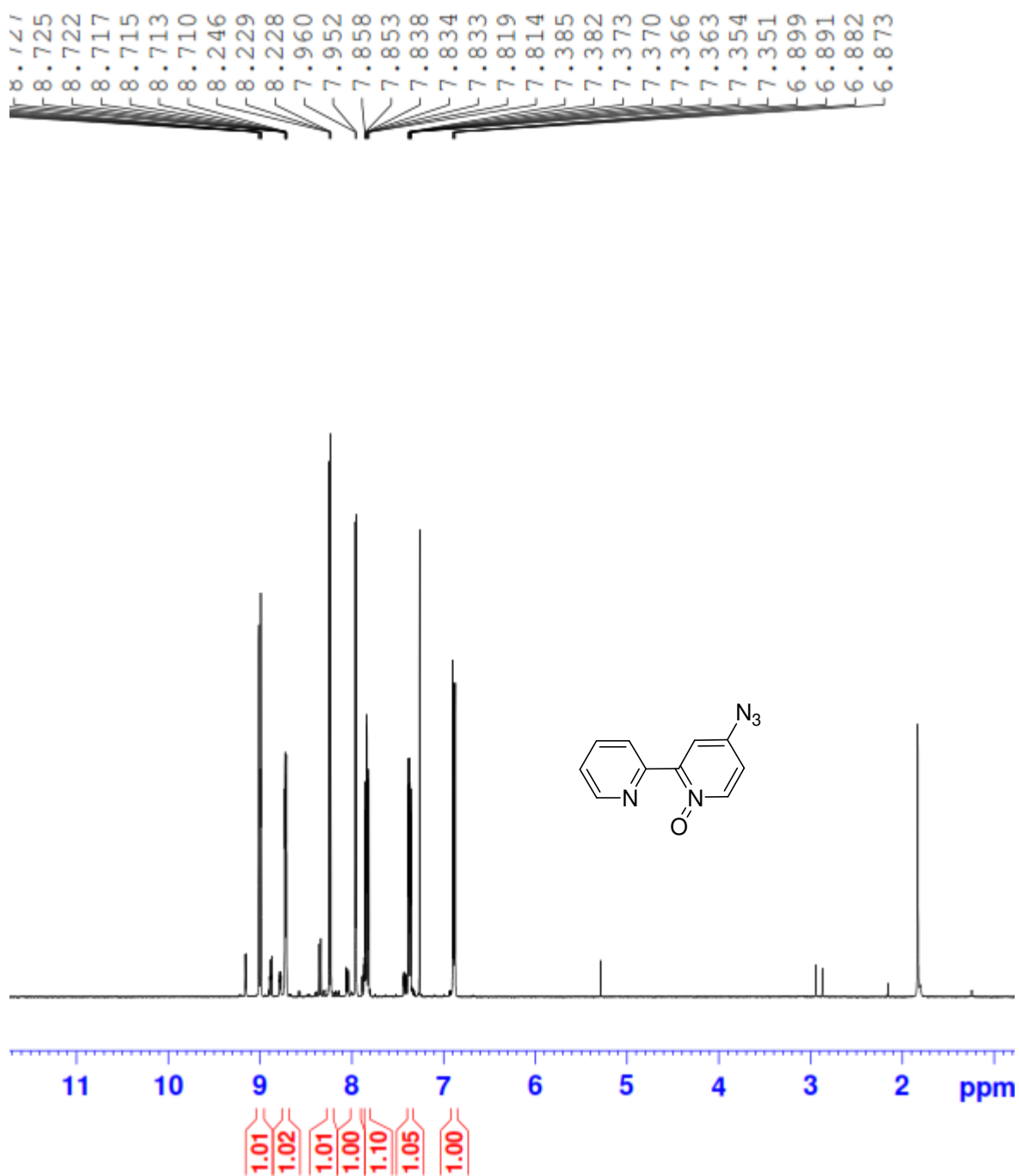


Figure S64. I6, ¹H NMR.

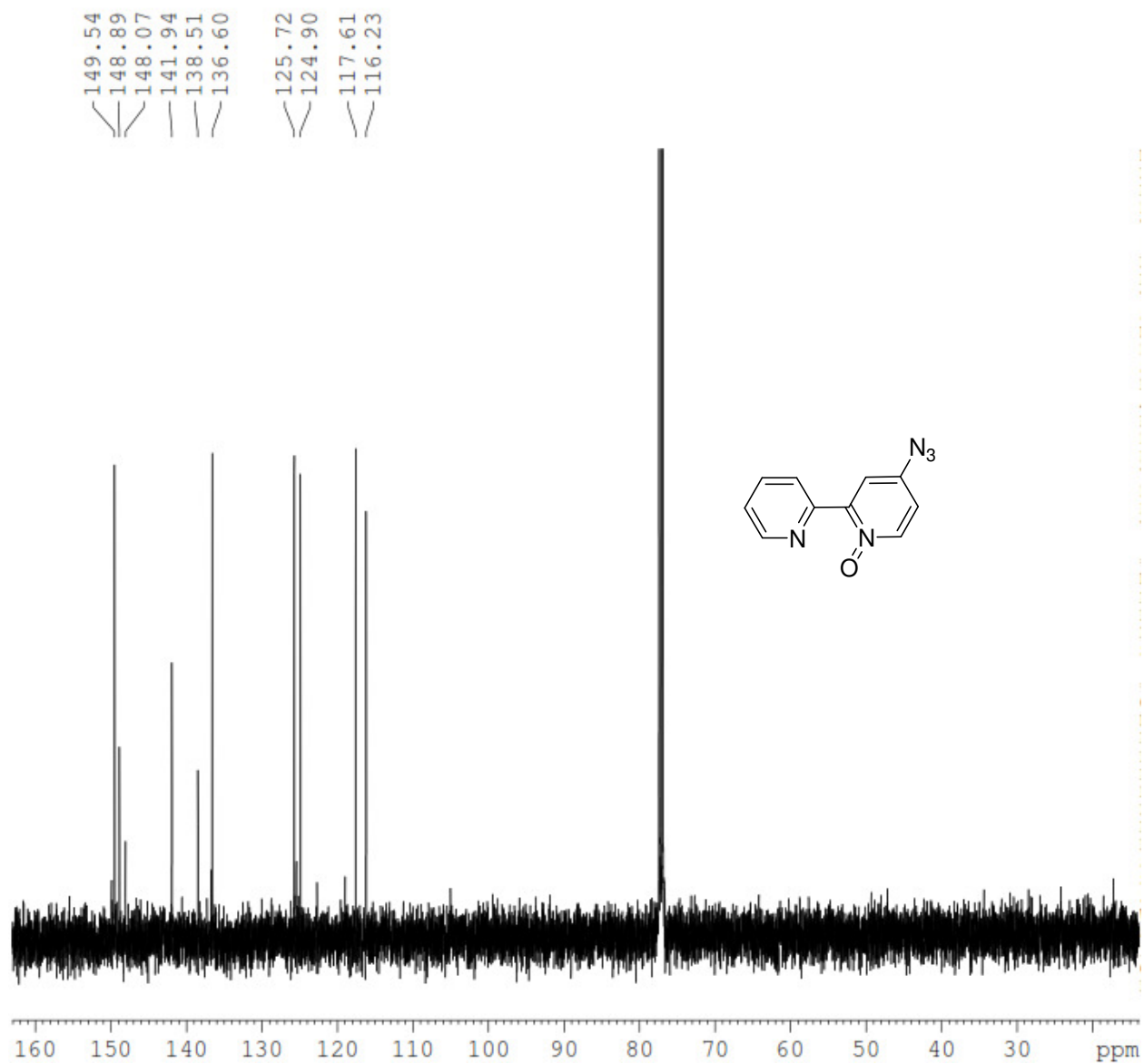


Figure S65. I6, ¹³C NMR.

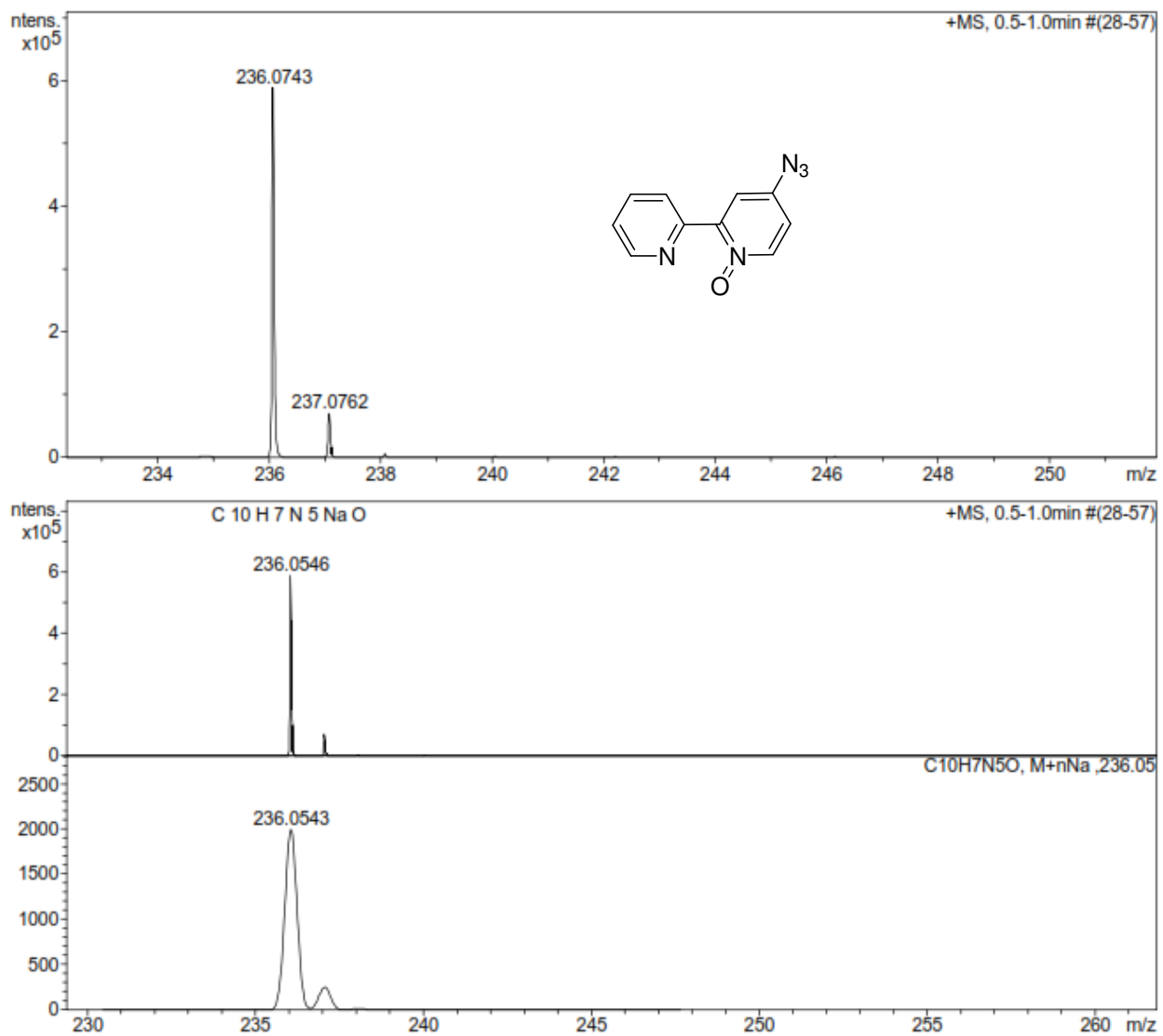


Figure S66. 16, HRMS.

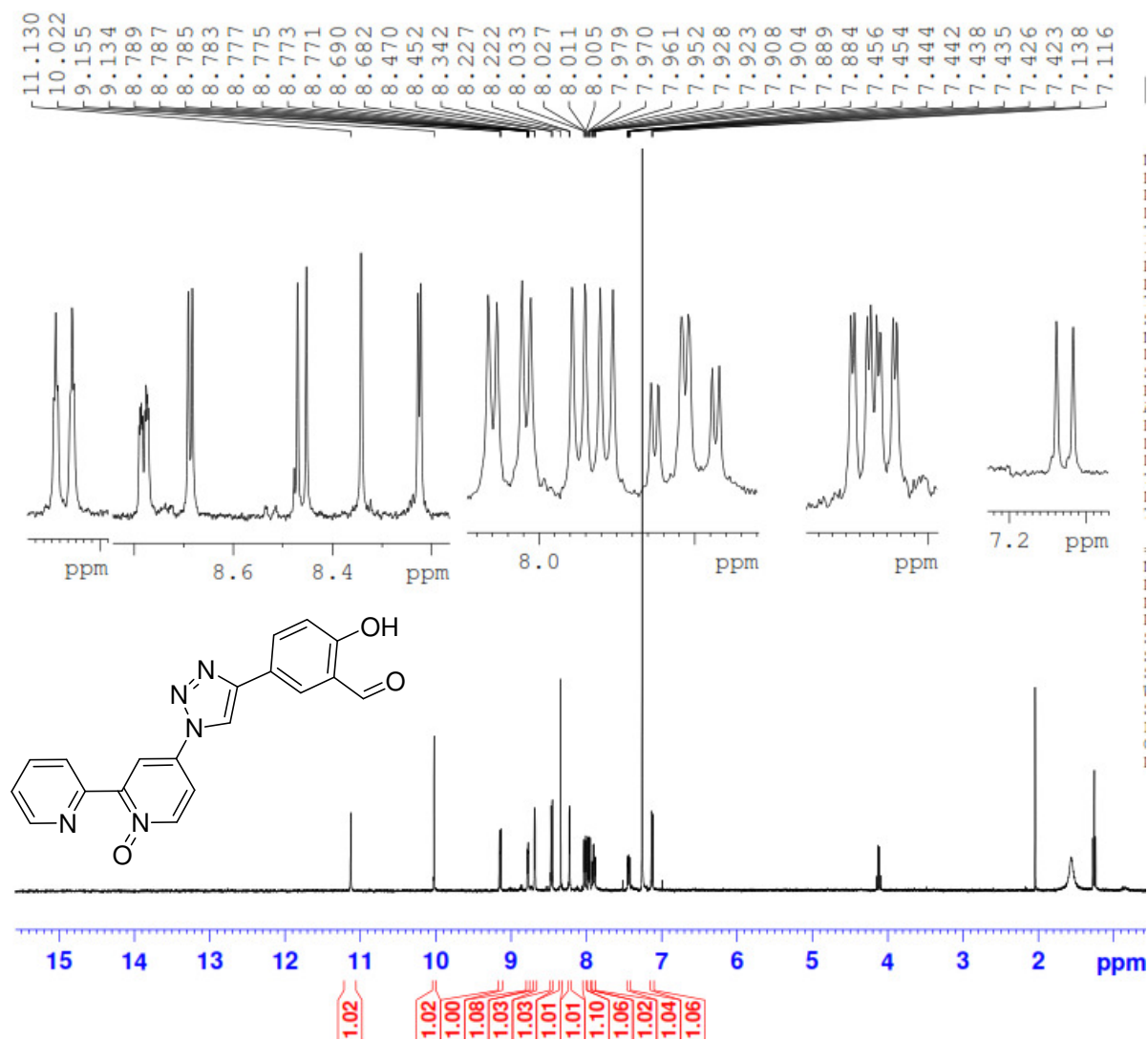


Figure S67. 8, ^1H NMR.

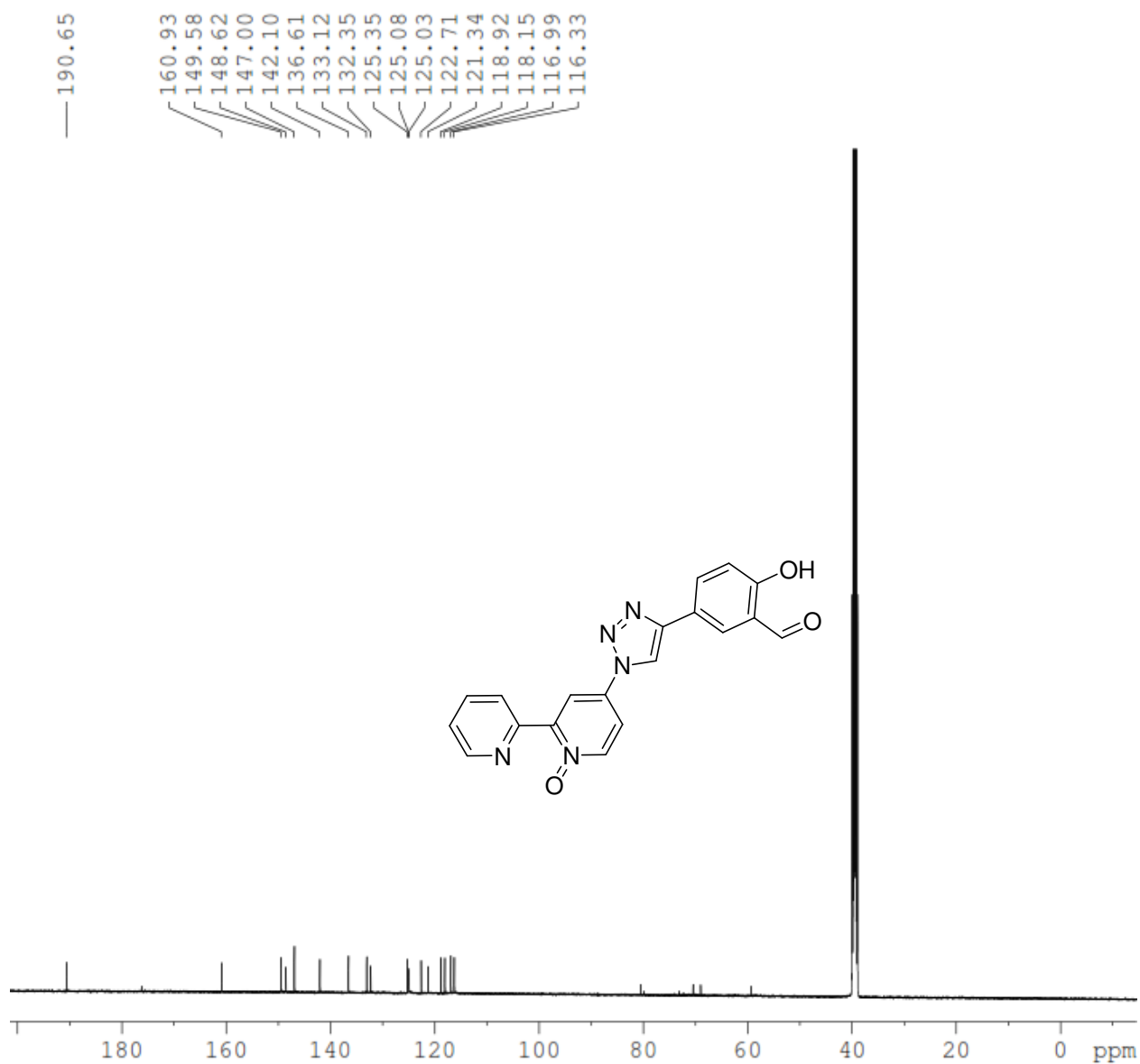


Figure S68. 8, ^{13}C NMR.

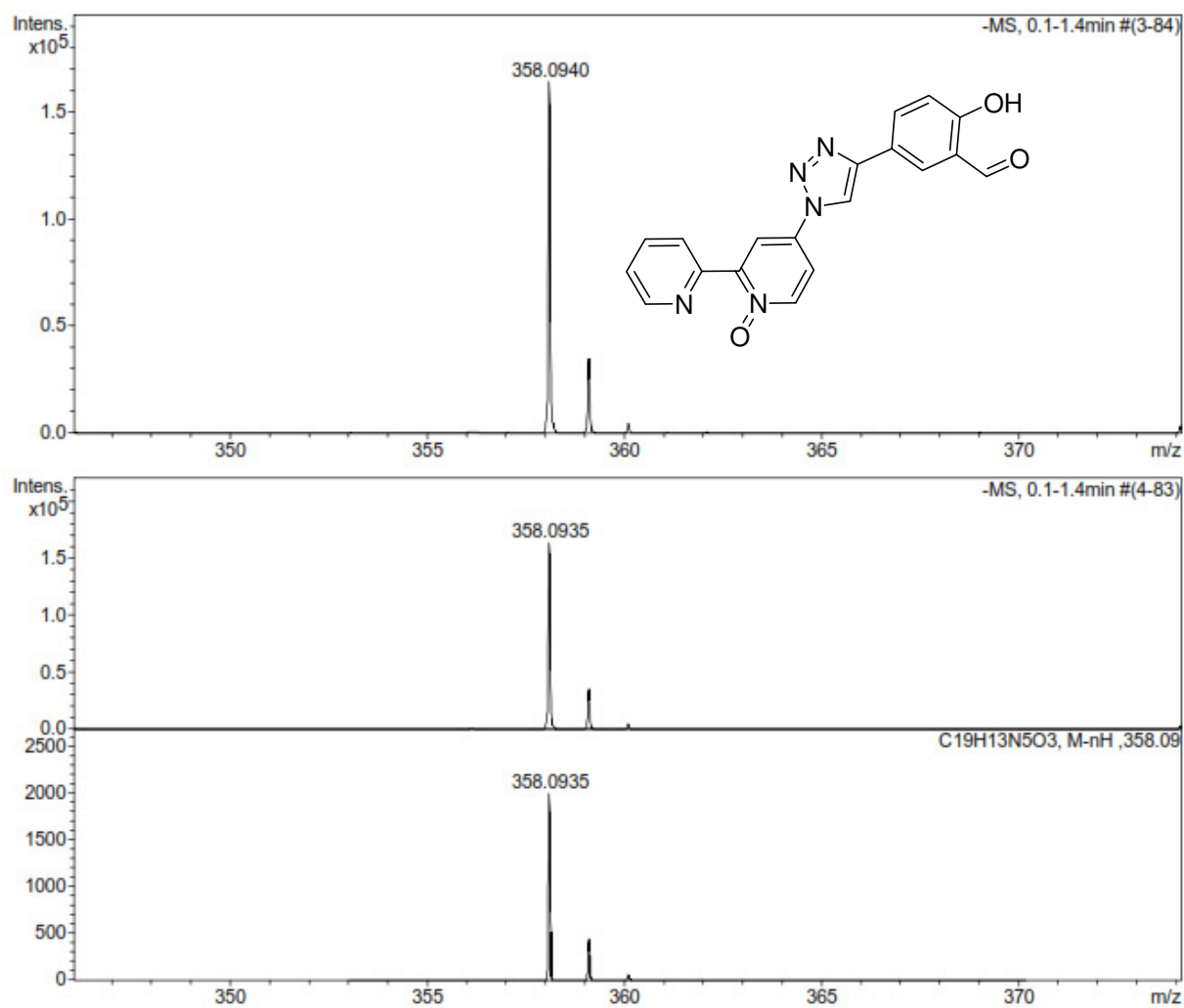


Figure S69. 8, HRMS.

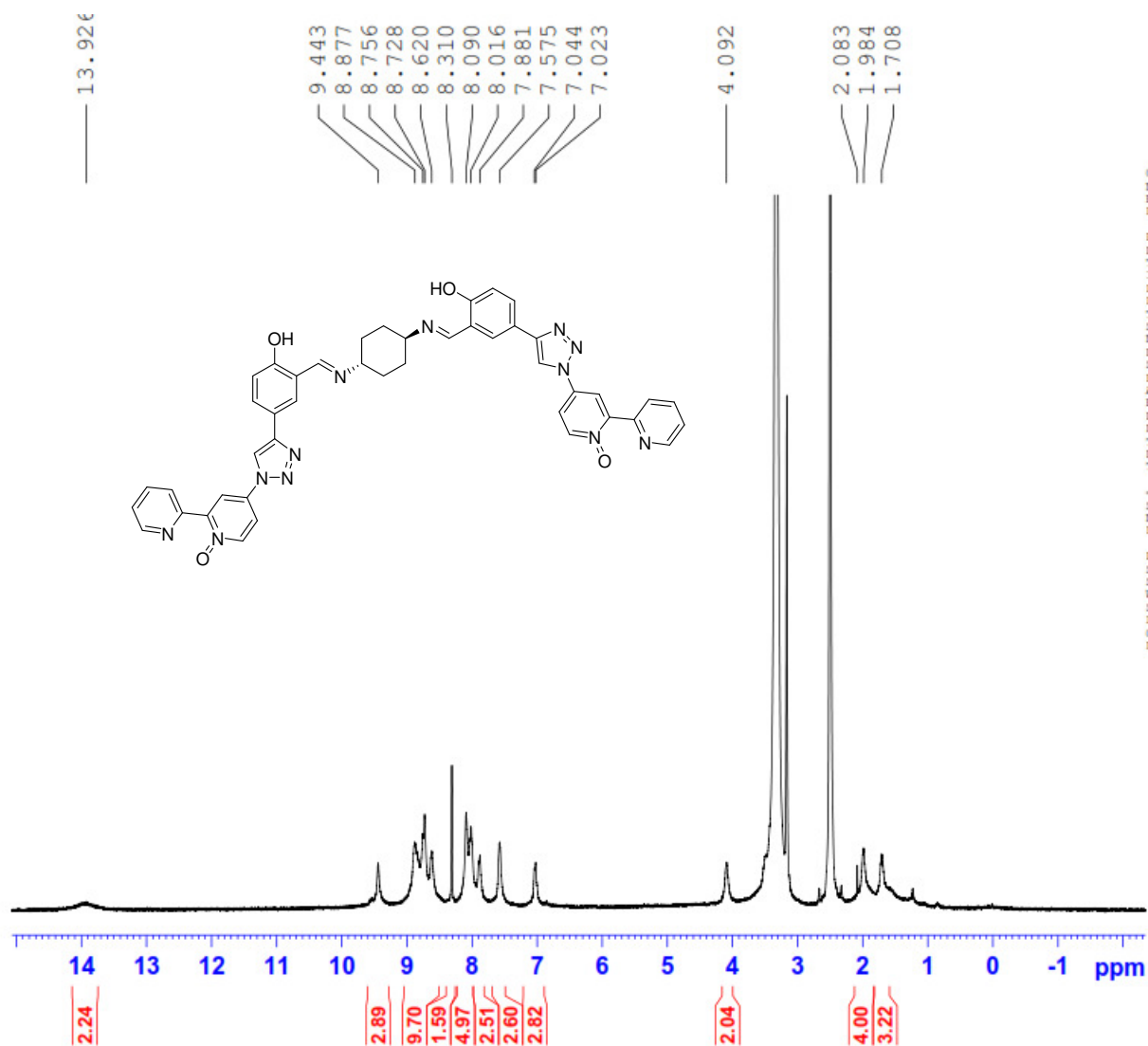


Figure S70. 9a, ¹H NMR.

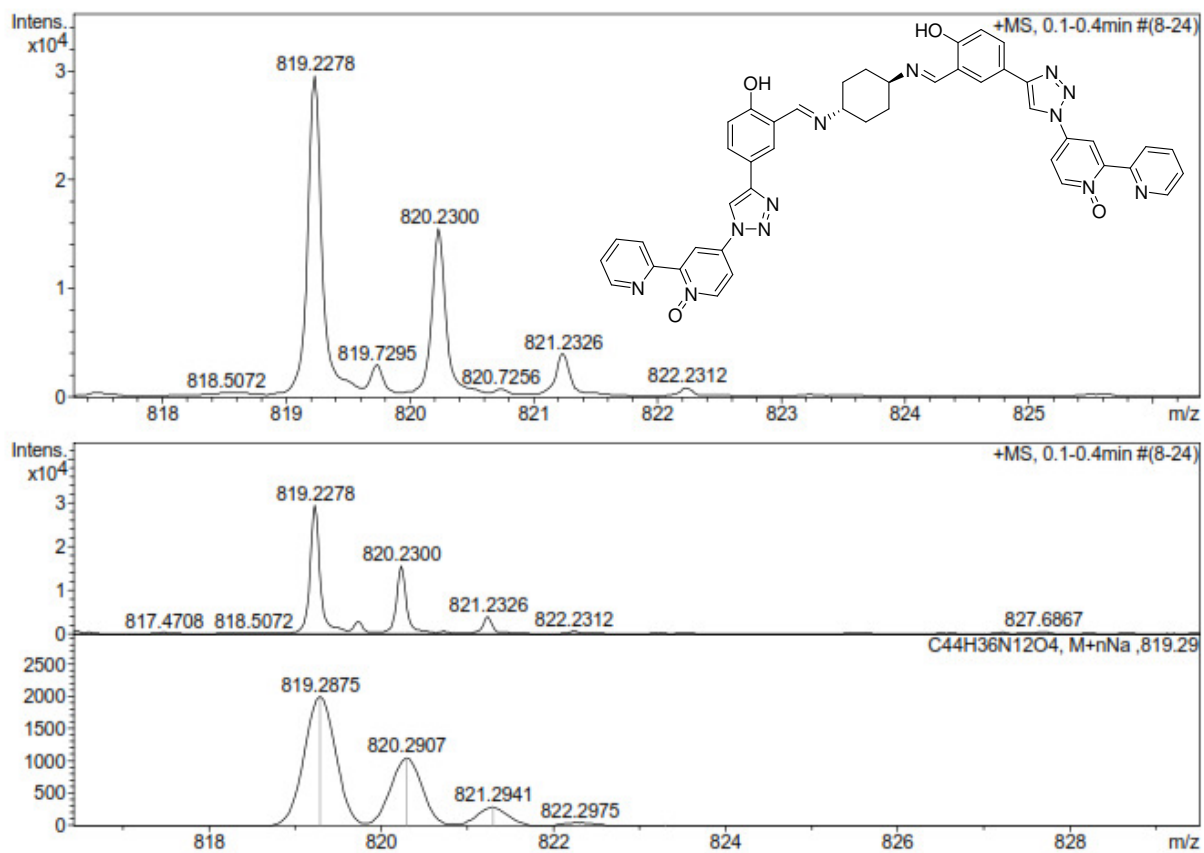


Figure S71. 9a, HRMS.

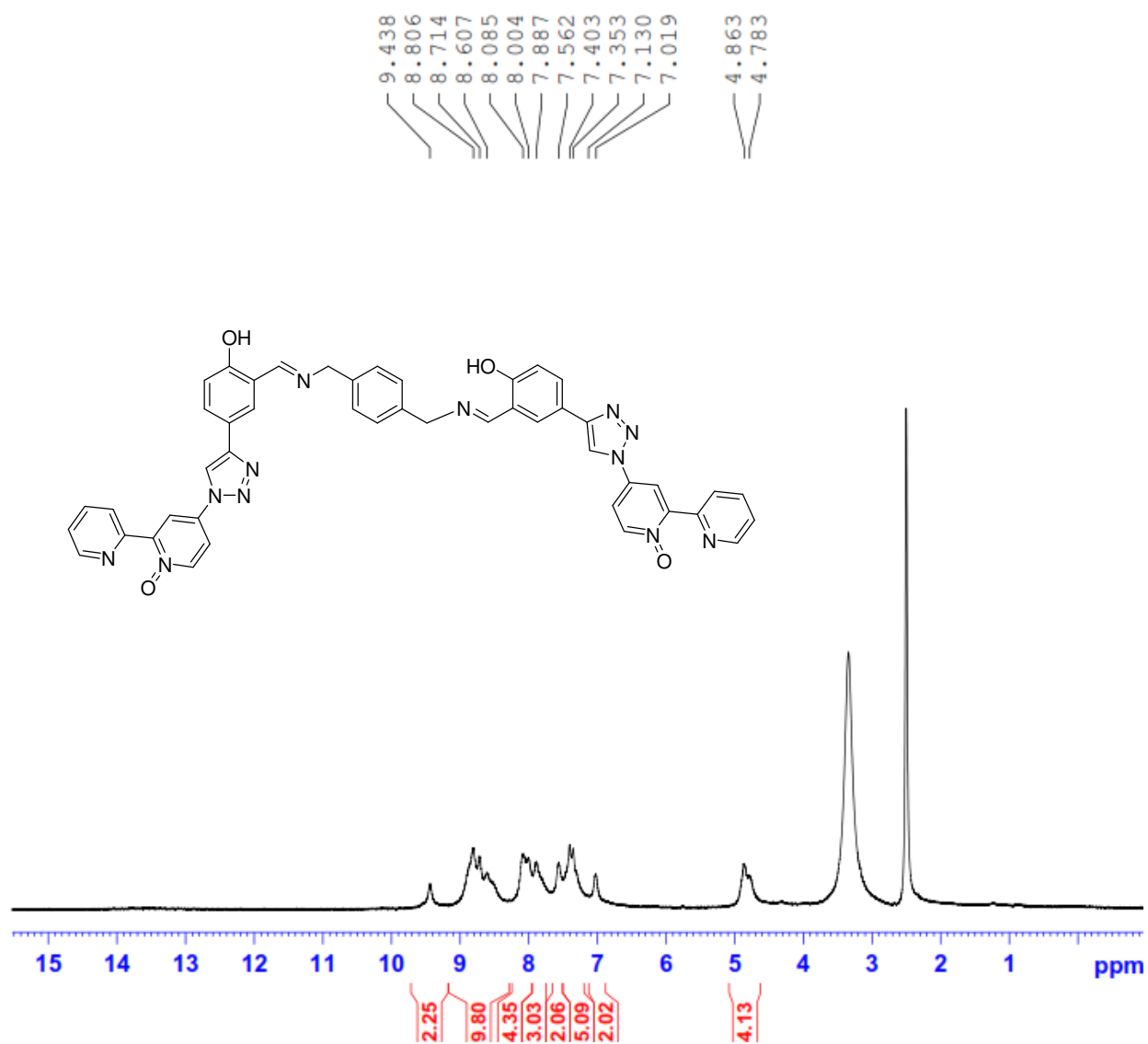


Figure S72. 9b, ^1H NMR.

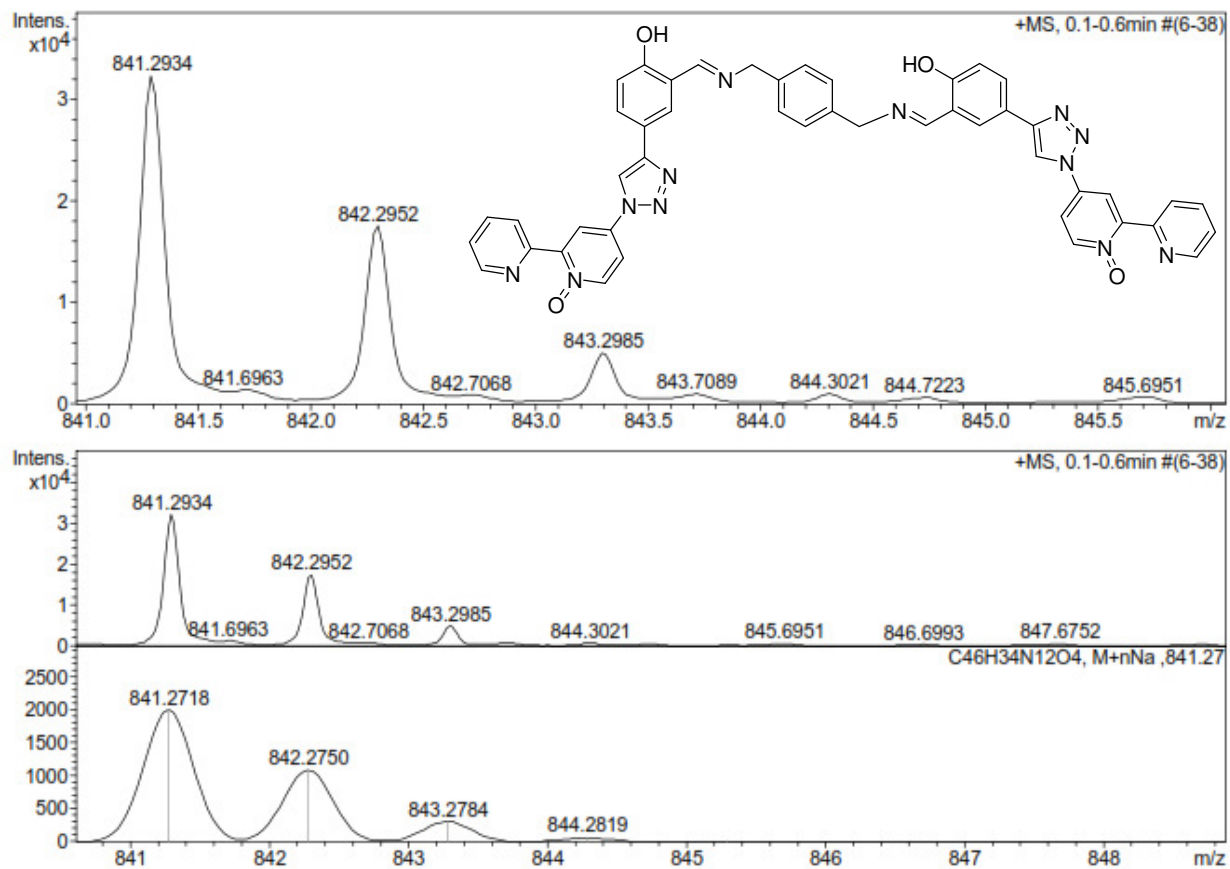


Figure S73. 9b, HRMS.

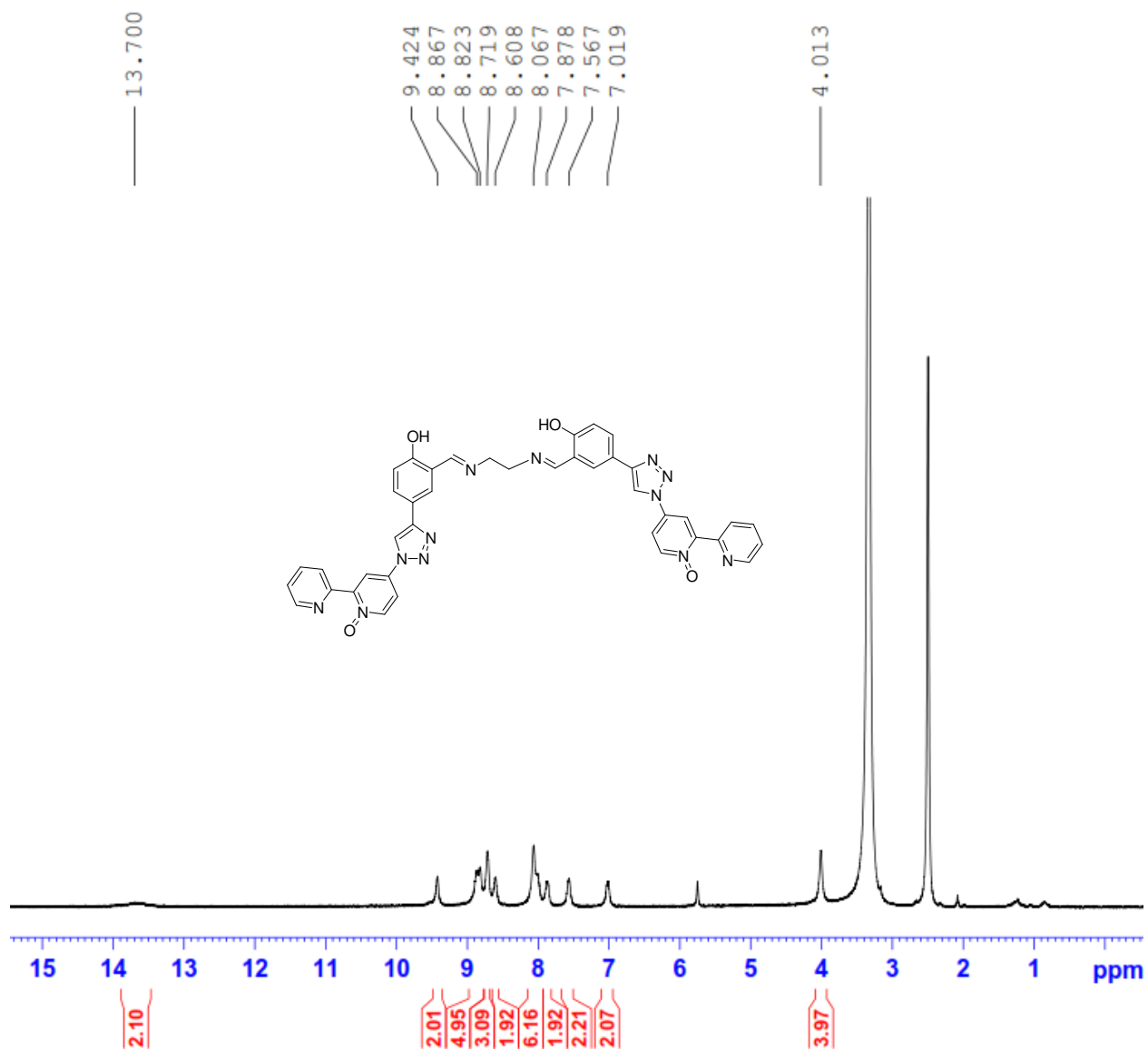


Figure S74.9c, ¹H NMR.

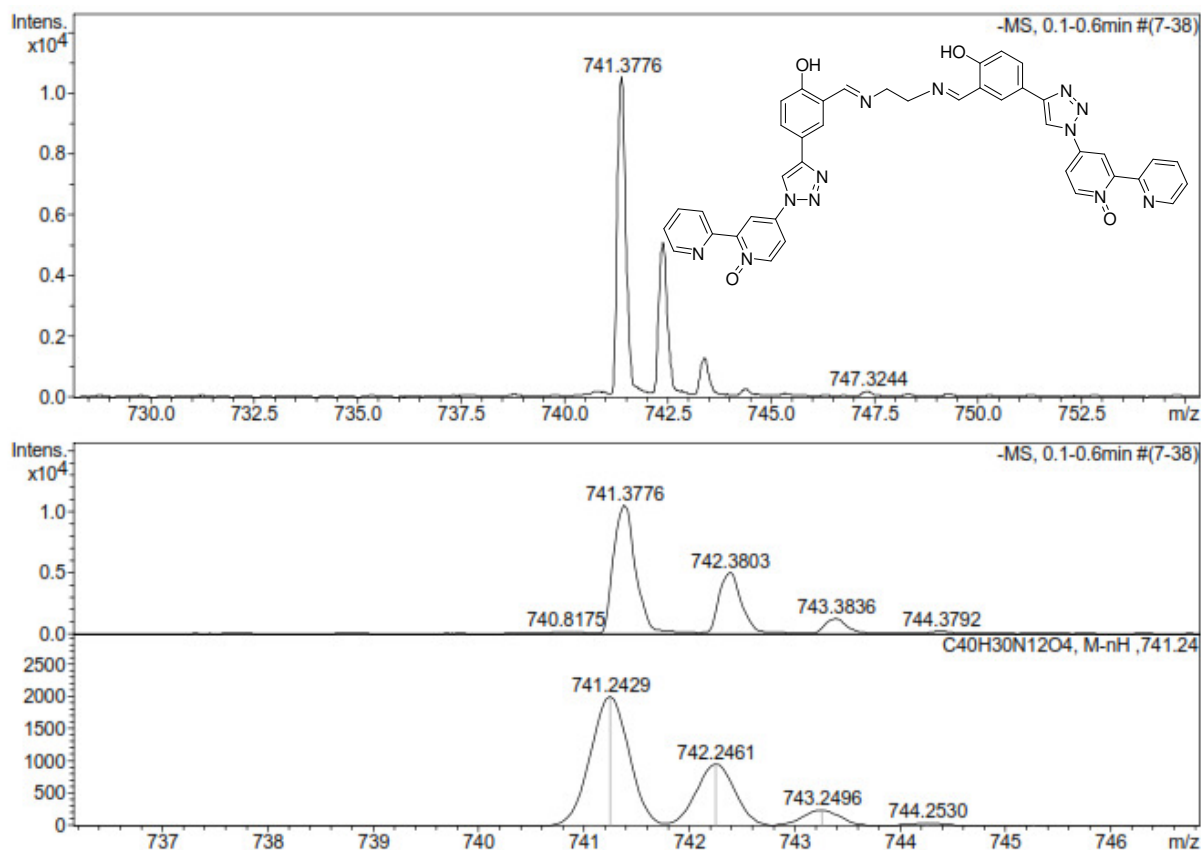


Figure S75. 9c, HRMS.

References

1. Arafa, W. A. A.; Kärkäs, M. D.; Lee, B. L.; Åkermark, T.; Liao, R. Z.; Siegbahn, P. E. M.; Åkermark, B. *Phys. Chem. Chem.* **2014**, *16*, 11950.
2. Xu, Y.; Meng, J.; Meng, L.; Dong, Y.; Cheng, Y.; Zhu, C. *Eur. J.* **2010**, *16*, 12898.
3. Demnitz, F. W.; d'Heni, J. M. B. *OPPI BRIEFS* **1998**, *30*, 4.
4. Baron, A.; Herrero, C.; Quaranta, A.; Charlot, M. F.; Leibl, W.; Vauzeilles. B.; Aukauloo, A. *Chem. Commun.* **2011**, *47*, 11011.