Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Chemo- and regioselective cross-dehydrogenative coupling reaction of 3-hydroxycarbazoles with arenols catalyzed by a mesoporous silica-supported oxovanadium

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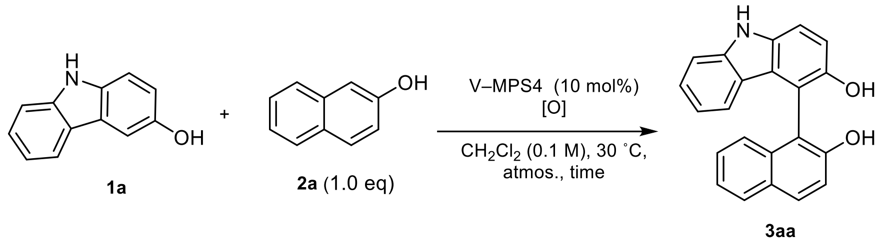
1. General information

All reactions were monitored by thin-layer chromatography (TLC) on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm). All new products were fully characterized by ^{1}H and ^{13}C NMR spectra, infrared (IR) absorption spectrum, and high-resolution mass spectrum (HRMS). IR spectra were recorded on a SHIMADZU IRAffinity-1S spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-ECA500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) instrument. Chemical shifts were reported in δ (ppm) relative to tetramethylsilane (0.00 ppm) or the residual nondeuterated solvent signal for ^{1}H ($CDCl_3$: $\delta = 7.26$ ppm, acetone-d_6: $\delta = 2.05$ ppm) and relative to the solvent signal for ^{13}C ($CDCl_3$: $\delta = 77.00$ ppm, acetone-d_6: $\delta = 29.84$ ppm). High-resolution mass spectra (HRMS) were measured on a JEOL JMS-S3000 (MALDI) with a TOF mass analyzer. Vanadium content was measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES, Agilent 720 ICP) analysis. Electron spin resonance (ESR) spectra were recorded on a Bruker EMXmicro instrument (modulation amplitude: 1.0 G, modulation frequency: 100.0 KHz, conversion: 30.00 ms, time constant: 10.2 ms).

All reagents and solvents were purchased from FUJIFILM Wako Pure Chemical, Tokyo Chemical Industry, Sigma-Aldrich, Nacalai Tesque, Kishida Chemical, Chem Impex International, Oakwood Products and Combi Blocks, and used without further purification. Flash chromatography was performed on silica gel 60N (particle size 40–50 μm) purchased from Kanto Chemical Co., Inc. Mesoporous silica (TMPS-4R) was kindly supplied by Taiyo Kagaku Co., Ltd. (Tokyo, Japan).

2. Screening of reaction conditions

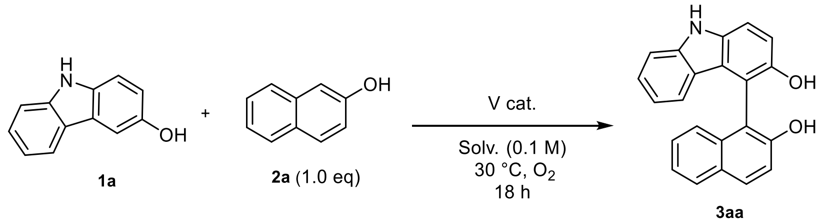
Table S1. Screening of reoxidants.



entry	[O] (eq.)	atmos.	time	yield of **3aa**
1	none	O_2	4 h	83%
2	Oxone (2.0)	Ar	6 h	15%
3	mCPBA (2.0)	Ar	6 h	trace
4	NMO (2.0)	Ar	6 h	10%
5	NaClO·5H_2O (2.0)	Ar	6 h	11%

The yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. mCPBA = *m*-chloroperoxybenzoic acid, NMO = 4-methylmorpholine,

Table S2. Screening of solvents and vanadium catalysts.

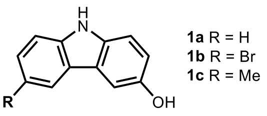


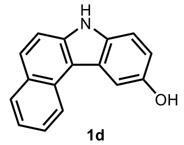
Entry	V cat. (mol%)	Solv.	Yield of **3aa**
1	V-MPS4 (10)	MeOH	trace
2	V-MPS4 (10)	THF	trace
3	V-MPS4 (10)	DME	6%
4	V-MPS4 (10)	acetone	15%
5	V-MPS4 (10)	TBME	16%
6	V-MPS4 (10)	CPME	20%
7	V-MPS4 (10)	MeCN	26%
8	V-MPS4 (10)	CCl_4	60%
9	V-MPS4 (10)	$CHCl_3$	85%
10	V-MPS4 (10)	toluene	86%
11	V_2O_5 (5)	CH_2Cl_2	no reaction
12	$VOSO_4$•nH_2O (10)	CH_2Cl_2	no reaction
13[b]	V-MPS4 (4)	CH_2Cl_2	48%
Table 1,[b] Entry 1	V-MPS4 (10)	CH_2Cl_2	87% (93%)[b]

[a] The yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. [b] Reaction time was 12 h. [c] Isolated yield. THF = tetrahydrofuran, DME = 1,2-dimethoxyethane, TBME = *tert*-butyl methyl ether, CPME = cyclopentyl methyl ether.

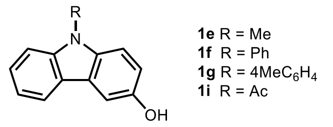
3. Substrate syntheses

3-1. Synthesis of hydroxycarbazoles 1



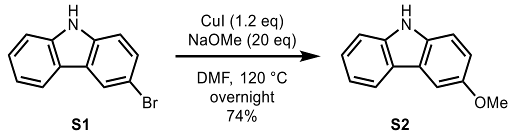


1d



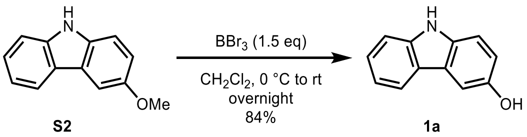
Compounds **1a**–**1d** were synthesized as described below. Compounds **1e**–**1i** ware prepared according to the literature procedure.[1–3]

3-Methoxy-9*H*-carbazole (**S2**)



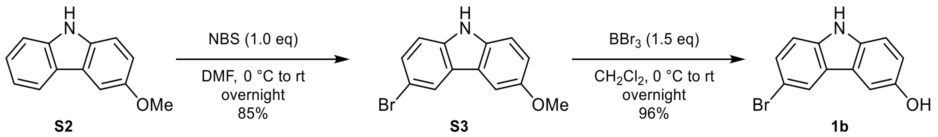
3-Bromo-9*H*-carbazole **S1** (9.8 g, 40 mmol) and CuI (9.1 g, 48 mmol) were dissolved in dry DMF (80 mL, 0.5 M) under Ar. A 5 M solution of NaOMe in MeOH (160 mL, 0.80 mol) was added at room temperature and the solution was stirred at 120 °C overnight. After cooling to room temperature, the solution was evaporated and then the residue was extracted with EtOAc two times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel chromatography (hexane/CH_2Cl_2 = 1:1) to give **S2** (3.64 g, 92% yield). Its ^{1}H NMR data were in good agreement with those reported in the literature.[4]

3-Hydroxycarbazole (**1a**) [**General procedure for *O*-demethylation**]



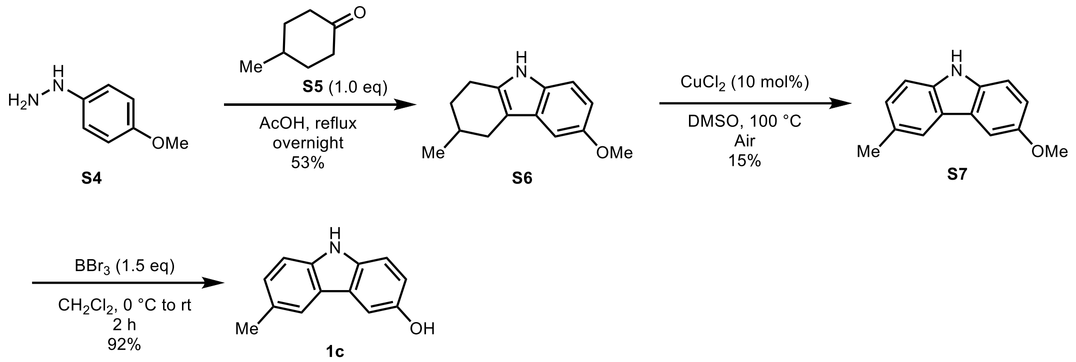
BBr_3 (1.0 M in CH_2Cl_2, 4.5 mL, 4.5 mmol) was added to a solution of **S2** (592 mg, 3.0 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred overnight at room temperature. After cooling to 0 °C, the reaction was quenched with sat. $NaHCO_3$. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuo. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give **1a** in (462 mg, 84% yield) as a colorless solid. Its ^{1}H NMR data were in good agreement with those reported in the literature.[1]

6-Bromo-9*H*-carbazol-3-ol (**1b**)



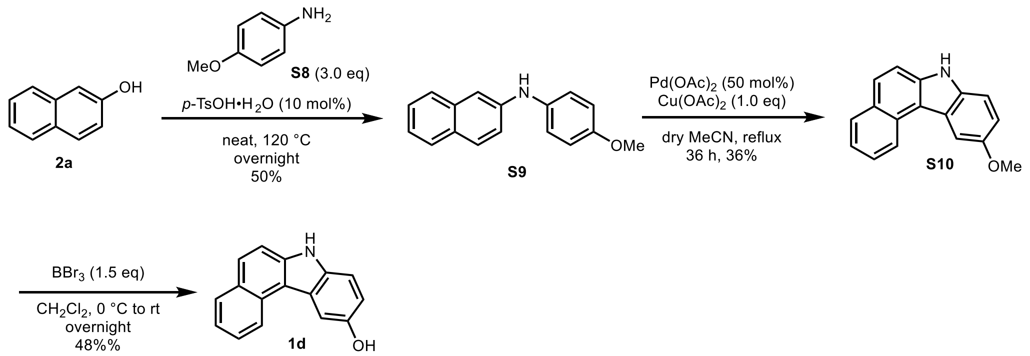
Compound **S3** was prepared according to the literature.[5] A solution of *N*-bromosuccinimide (NBS) (890 mg, 5.0 mmol) in DMF (5 mL) was slowly added into a solution of **S2** (986 mg, 5.0 mmol) in DMF (5 mL) at 0 °C. The resultant mixture was stirred overnight at room temperature. After complete consumption of **S2** was confirmed by TLC analysis, water was added and the mixture was filtered by using a Kiriyama funnel (H_2O). Then, the solid product left in the funnel was washed with water and recrystallized from EtOH to give **S3** (1.17 g, 85% yield). Its ^{1}H NMR data were in good agreement with those reported in the literature.[5] Deprotection of **S3** (690 mg, 2.5 mmol) was conducted according to the general *O*-demethylation procedure of **1a** to give **1b** (630 mg, 96% yield). Its ^{1}H NMR data were in good agreement with those reported in the literature.[6]

6-Methyl-9*H*-carbazol-3-ol (**1c**)



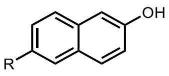
Compound **S6** (1.3 g, 53% yield) was prepared according to the literature[7] using **S4** (2.0 g, 11.5 mmol) and **S5** (1.4 mL, 11.5 mmol). Compound **S7** (159 mg, 15% yield) was prepared according to the literature[8] using **S6** (1.08 g, 5.0 mmol). Deprotection of **S7** (200 mg, 0.94 mmol) was conducted according to the general *O*-demethylation procedure of **1a** to give **1c** (171 mg, 92% yield). Its ^{1}H NMR data were in good agreement with those reported in the literature.[9]

7*H*-benzo[*c*]carbazol-10-ol (**1d**)

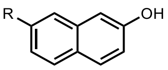


Compound **S9** was prepared from **2a** (1.44 g, 10.0 mmol) according to the literature[10] with a modification . A mixture of **S9** (230 mg, 0.92 mmol), $Pd(OAc)_2$ (104 mg, 0.46 mmol), and $Cu(OAc)_2$ (167 mg, 0.92 mmol) in dry MeCN (2.8 mL) was refluxed for 36 h. After cooling to room temperature, the reaction mixture was filtered through a pad of silica gel (hexane/EtOAc = 1:1) and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane/ EtOAc = 9:1) to give **S10** (81 mg, 36% yield). Deprotection of **S10** (247 mg, 1.0 mmol) was conducted according to the general *O*-demethylation procedure of **1a**, and the crude product was recrystallized from $CHCl_3$ to give **1d** (111 mg, 48% yield). Its ^1H NMR data were in good agreement with those reported in the literature.[6]

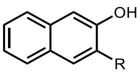
3-2. Synthesis of naphthols 2



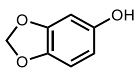
2a R = H
2b R = OMe
2c R = Br
1d R = CO_2Et



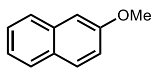
2e R = Br
2f R = OTBS
2g R = OMe



2h R = Me
2i R = Br



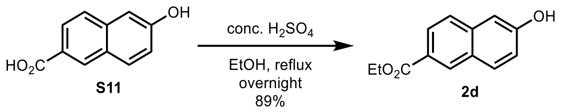
2j



2k

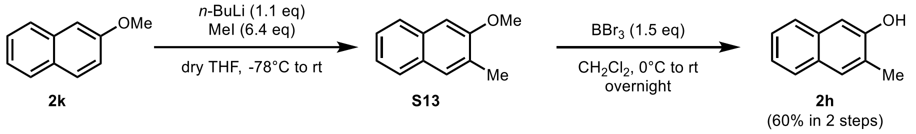
Compounds **2a-2c**, **2e**, **2g**, **2h**, **2j**, and **2k** were purchased from commercial suppliers. Compound **2f** was prepared according to the literature procedure.[11] Compounds **2d** and **2h** were synthesized as described below.

Ethyl 6-hydroxy-2-naphthoate (**2d**)



To a solution of 6-hydroxy-2-naphthoic acid **S11** (1.88 g, 10.0 mmol) in EtOH (50 mL) was added conc. H_2SO_4 (5 mL) at room temperature. The mixture was refluxed overnight and then cooled to room temperature. The solution was evaporated in vacuo and sat. $NaHCO_3$ was added to the residue. The mixture was extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to give **2d** (1.92g, 89% yield). Its ^1H NMR data were in good agreement with those reported in the literature.[12] As-prepared **2d** was used without further purification.

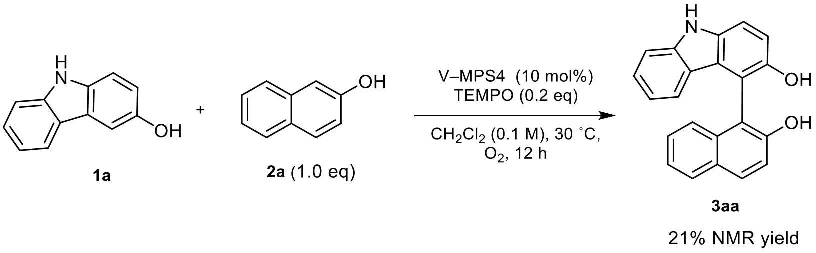
3-Methylnaphthalen-2-ol (**2h**)



2-Methoxy-3-methylnaphthalene **S13** was prepared according to the literature procedure.[13] Deprotection of **S13** was conducted according to the general *O*-demethylation procedure of **1a**, and the crude product was recrystallized from $CHCl_3$/hexane to give **2h** (475 mg, 60% yield in two steps). Its ^1H NMR data were in good agreement with those reported in the literature.[14]

4. Investigation of reaction mechanism

4-1. Radical trap experiment



Scheme S1. The addition of TEMPO as a radical scavenger.

4-2. ESR analysis

[Sample preparation (Figure 1a)] A Schlenk tube was charged with **1a** (18.3 mg, 0.10 mmol), **2a** (14.4 mg, 0.10 mmol), and V-MPS4 (10 mol% based on vanadium content) and the tube was purged with nitrogen. After that, CH_2Cl_2 (1.0 mL, 0.1 M) was added to the tube and then the mixture was stirred at 30 °C for 12 h under nitrogen atmosphere. The solvent was evaporated in vacuo at room temperature, and nitrogen was purged to the tube. The residue was transferred to an ESR sample tube under a nitrogen atmosphere.

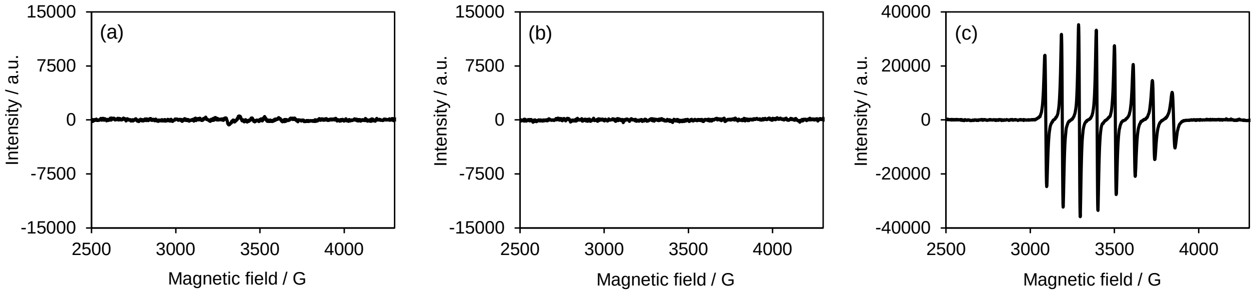


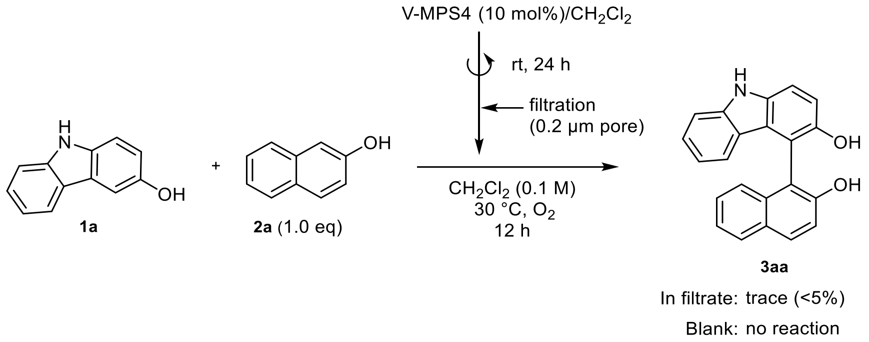
Figure S1. ESR spectra of (a) V-MPS4 before the reaction (solid state), (b) $VO(OSiPh_3)_3$ in toluene, and (c) $VO(acac)_2$ in toluene.

4-3. XANES analysis

X-ray absorption spectroscopy (XAS) experiments were performed at SPring-8 BL14B2 beamline using Si(111) double-crystal monochromatized synchrotron radiation. All XAS experiments were carried out using transmission mode with quick scan technique (QXAFS). Ionization chambers were used to measure the intensities of the incident (I_0) and transmitted (I) X-ray. E_0 value was defined as a fraction of the edge step of the normalized μ(E) spectrum, and that of V foil was set to 5465 eV for photon energy calibration. XAS analyses were conducted using Demeter package, a comprehensive system for processing and analysing X-ray absorption spectroscopy data.[15–17] Background removal by cubic spline method and normalization of raw data were performed using Athena software.

[Sample preparation] A mixture of a reagent and an appropriate amount of boron nitride (approx. 70–100 mg) were ground using an agate mortar over 45 min under ambient atmosphere. The resulting powder was pelletized using a tablet press (JASCO Corporation, φ = 10 mm) with the pressure ranging between 10 and 15 MPa. The thus-prepared pellets were packed in a gas barrier bag (thickness: 60 μm), and subjected to XAS measurement.

5. Leaching examination of V-MPS4



Scheme S2. Leaching examination of V-MPS4 in the CDC reaction.

6. Determination of the vanadium content of V-MPS4

To the V-MPS4 (ca. 20–30 mg) was added 60% nitric acid (2.0 mL), and the resultant mixture was stirred for 5 h at room temperature. Then, the mixture was diluted with distilled water in a 50-mL volumetric flask. After passing through a membrane filter (0.2-μm pore), the filtrate was analyzed by ICP-AES to determine the vanadium content. The result was 11.0±0.33 mg-V/g-V-MPS4 (0.216±0.0065 mmol/g).

7. References

1 M. Sako, A. Sugizaki and S. Takizawa, *Bioorg. Med. Chem.*, 2018, **28**, 2751–2753.

2 H. Kang, Y. E. Lee, P. V. G. Reddy, S. Dey, S. E. Allen, K. A. Niederer, P. Sung, K. Hewitt, C. Torruellas, M. R. Herling and M. C. Kozlowski, *Org. Lett.*, 2017, **19**, 5505–5508.

3 S. Xia, L. Gan, K. Wang, Z. Li and D. Ma, *J. Am. Chem. Soc.*, 2016, **138**, 13493–13496.

4 M. L. Louillat, A. Biafora, F. Legros and F. W. Patureau, *Angew. Chem. Int. Ed.*, 2014, **53**, 3505–3509.

5 M. Mao, M. G. Ren and Q. H. Song, *Chem. Eur. J.*, 2012, **18**, 15512–15522.

6 M. Sako, K. Higashida, G. T. Kamble, K. Kaut, A. Kumar, Y. Hirose, D. Zhou, T. Suzuki, M. Rueping, T. Maegawa, S. Takizawa and H. Sasai, *Org. Chem. Front.*, 2021, **8**, 4878–4885.

7 V. Humne, Y. Dangat, K. Vanka and P. Lokhande, *Org. Biomol. Chem.*, 2014, **12**, 4832–4836.

8 B. A. Dalvi and P. D. Lokhande, *Tetrahedron Lett.*, 2018, **59**, 2145–2149.

9 G. Karan, S. Sahu and M. S. Maji, *Chem. Commun.*, 2021, **57**, 5274–5277.

10 A. K. Mishra and S. Biswas, *J. Org. Chem.*, 2016, **81**, 2355–2363.

11 Y. F. Wong, Z. Wang and J. Sun, *Org. Biomol. Chem.*, 2016, **14**, 5751–5754.

12 K.-T. Lin, H.-M. Kuo, H.-S. Sheu and C. K. Lai, *Tetrahedron*, 2013, **69**, 9045–9055.

13 C. Zarate, M. Nakajima and R. Martin, *J. Am. Chem. Soc.*, 2017, **139**, 1191–1197.

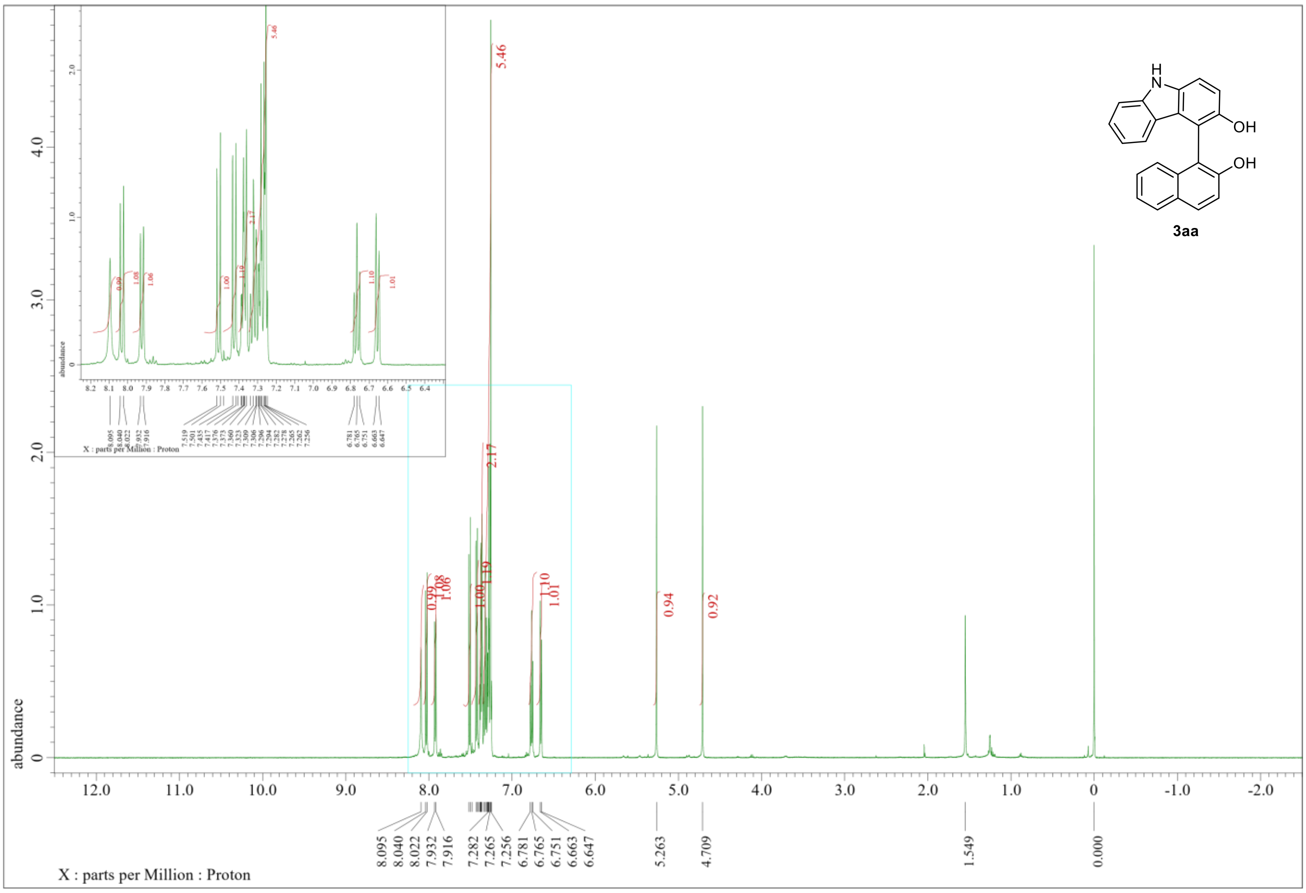
14 W. Zhang and J. M. Ready, *Angew. Chem. Int. Ed.*, 2014, **53**, 8980–8984.

15 B. Ravel and M. Newville, *J. Synchrotron Radiat.*, 2005, **12**, 537–541.

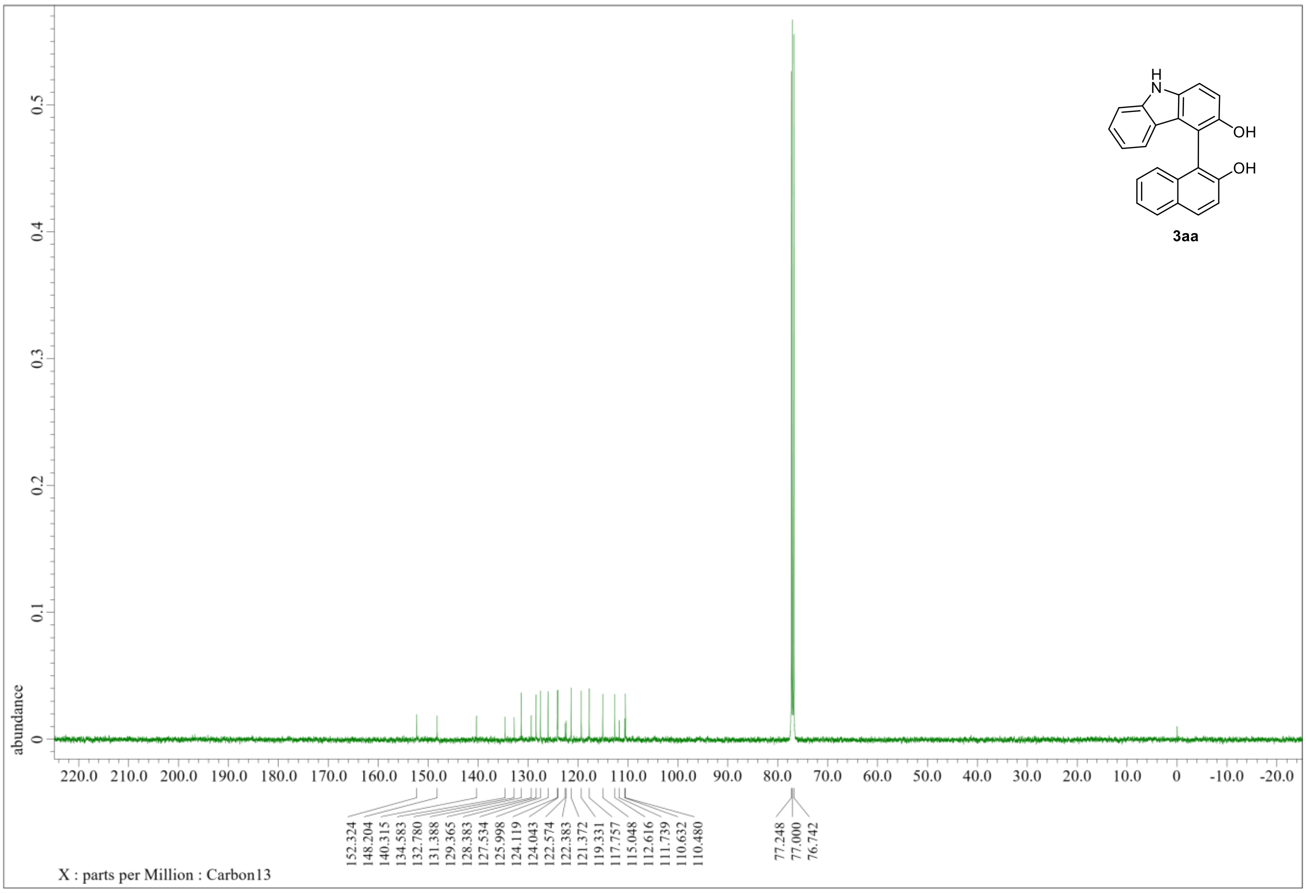
16 M. Newville, *J. Synchrotron Radiat.*, 2001, **8**, 322–324.

17 J. J. Rehr and R. C. Albers, *Rev. Mod. Phys.*, 2000, **72**, 621–654.

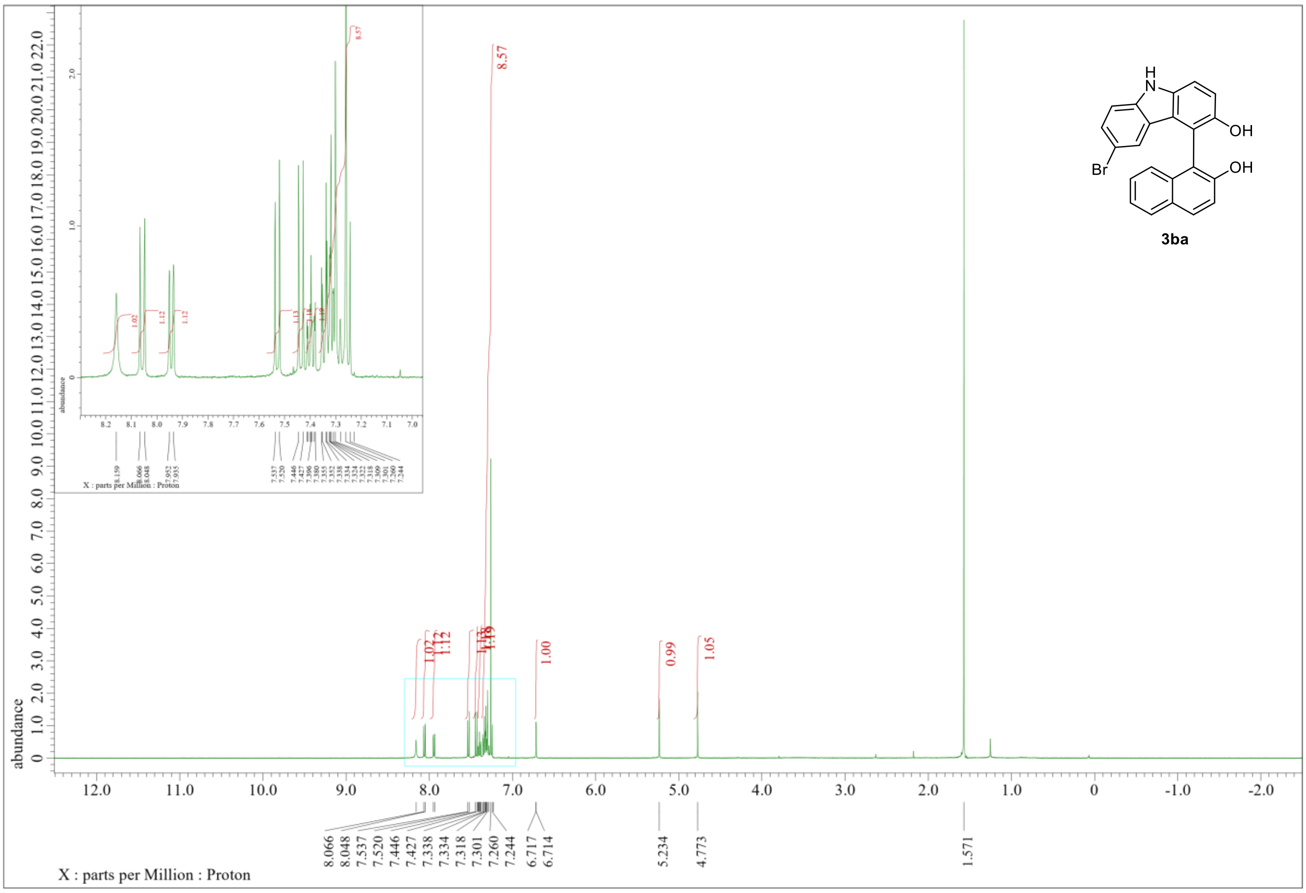
8. NMR spectra



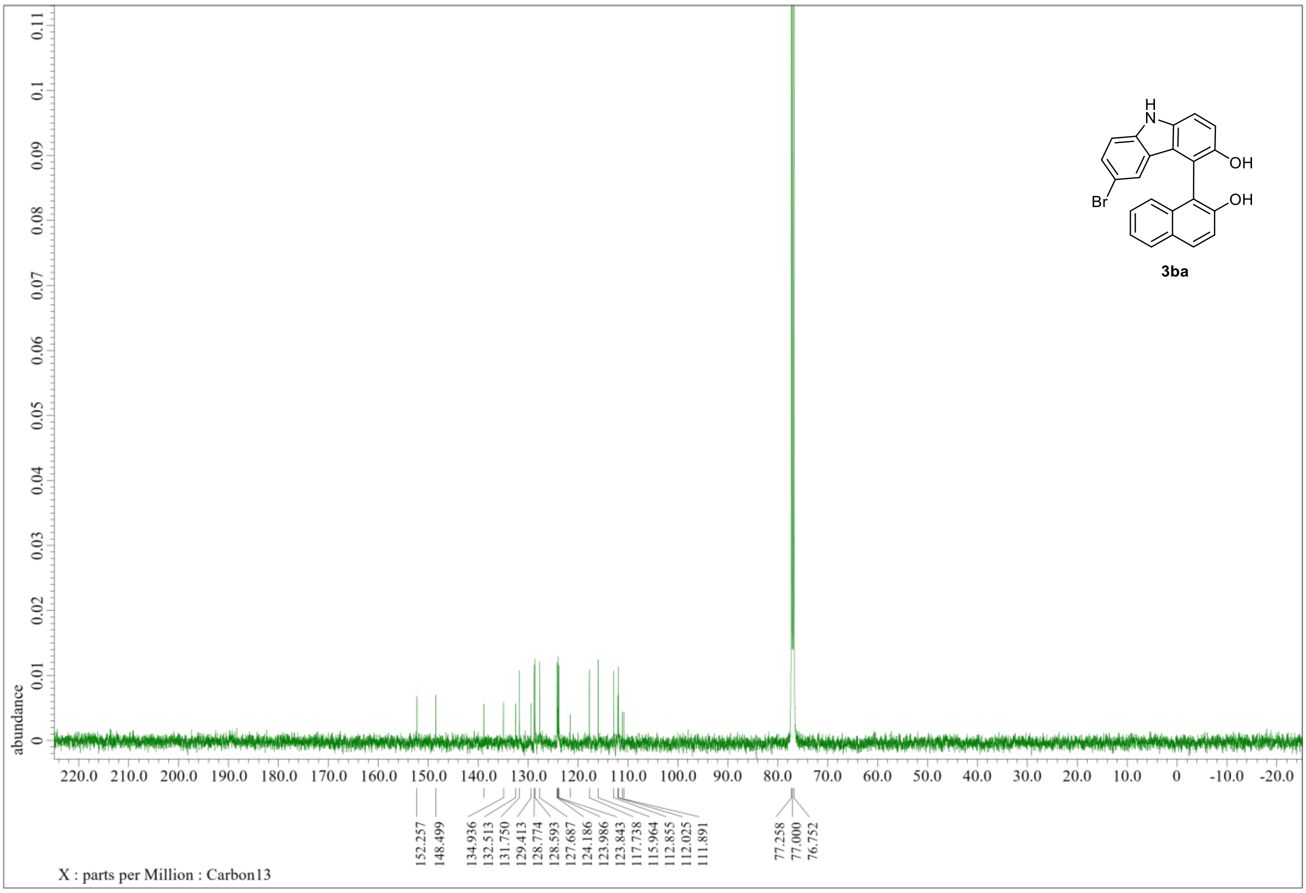
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3aa**



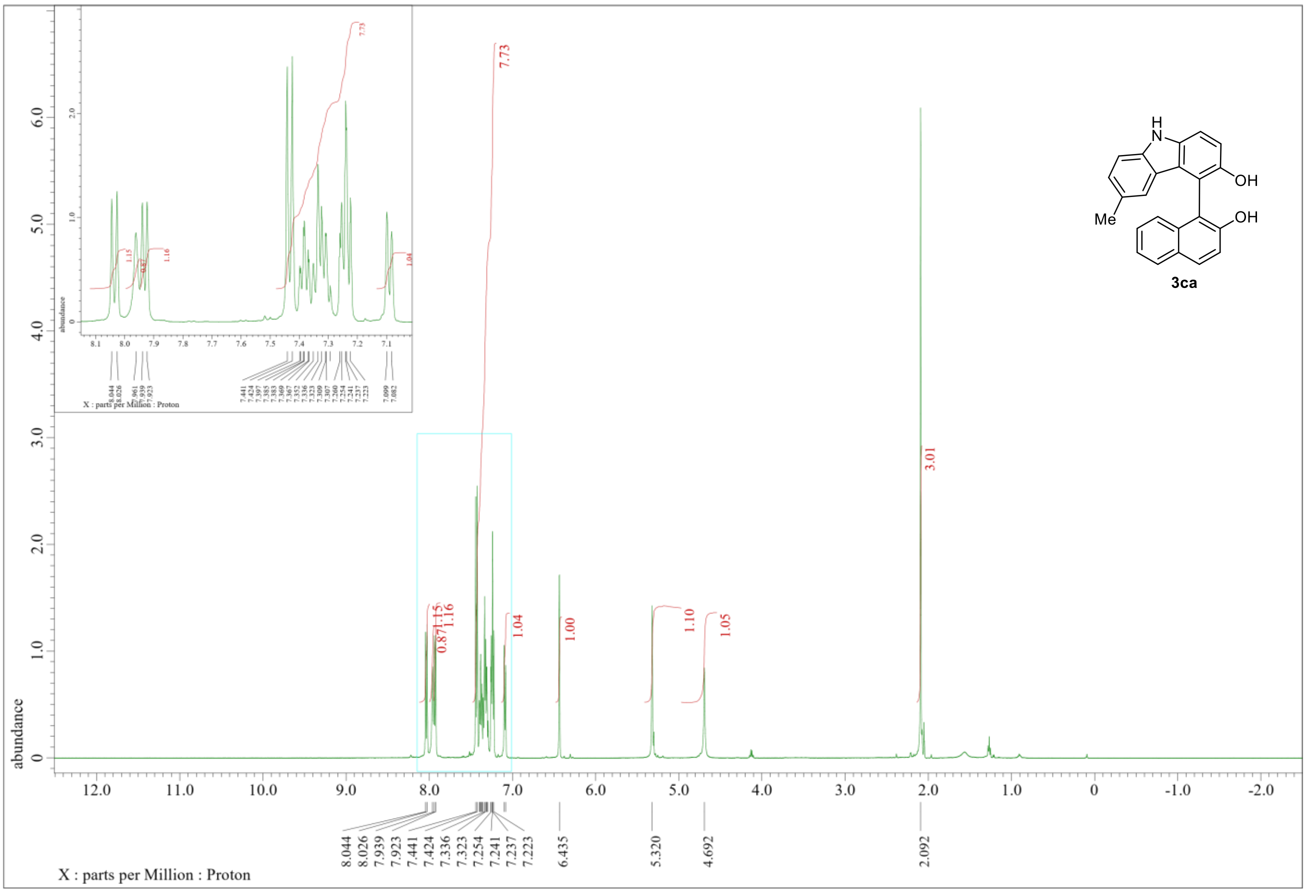
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3aa**



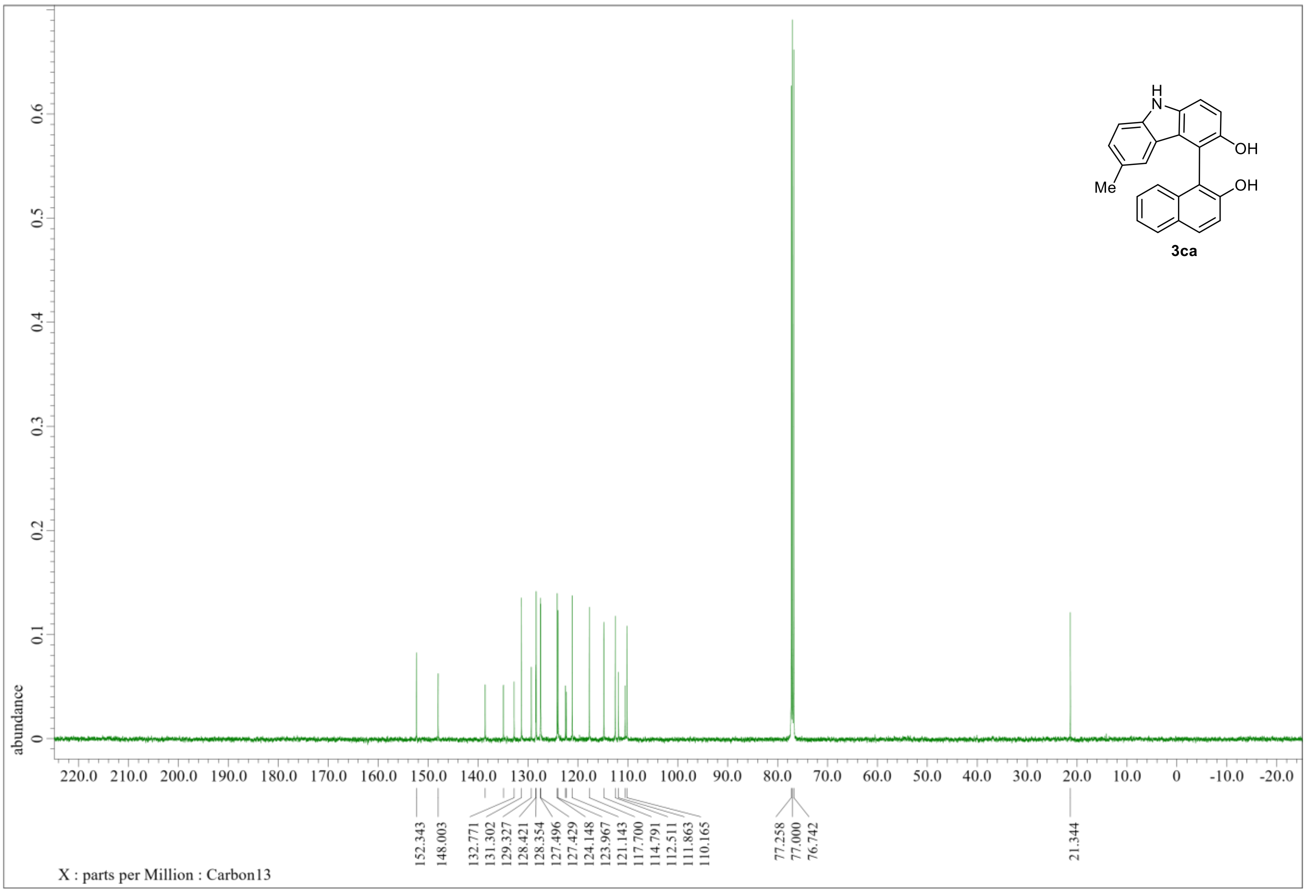
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ba**



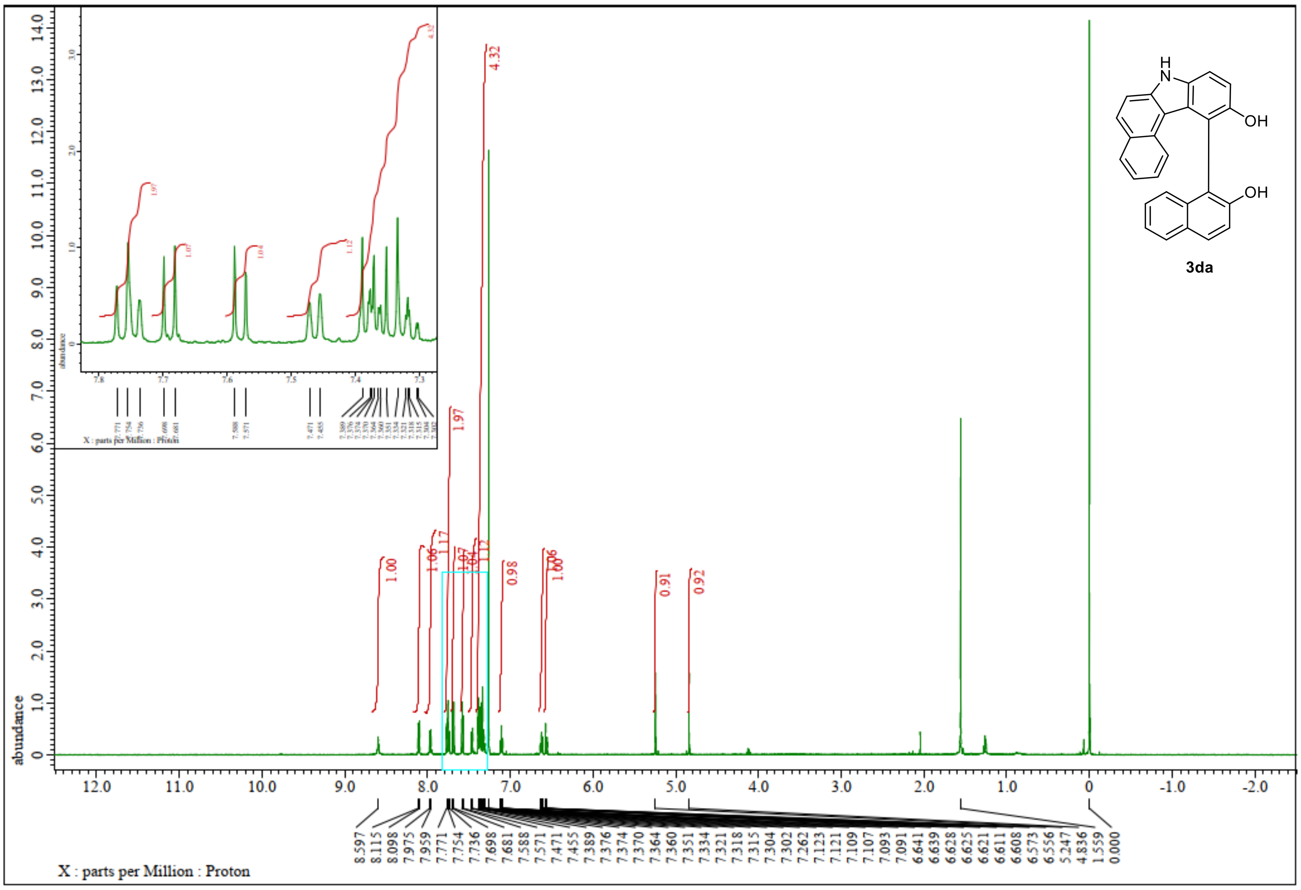
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ba**



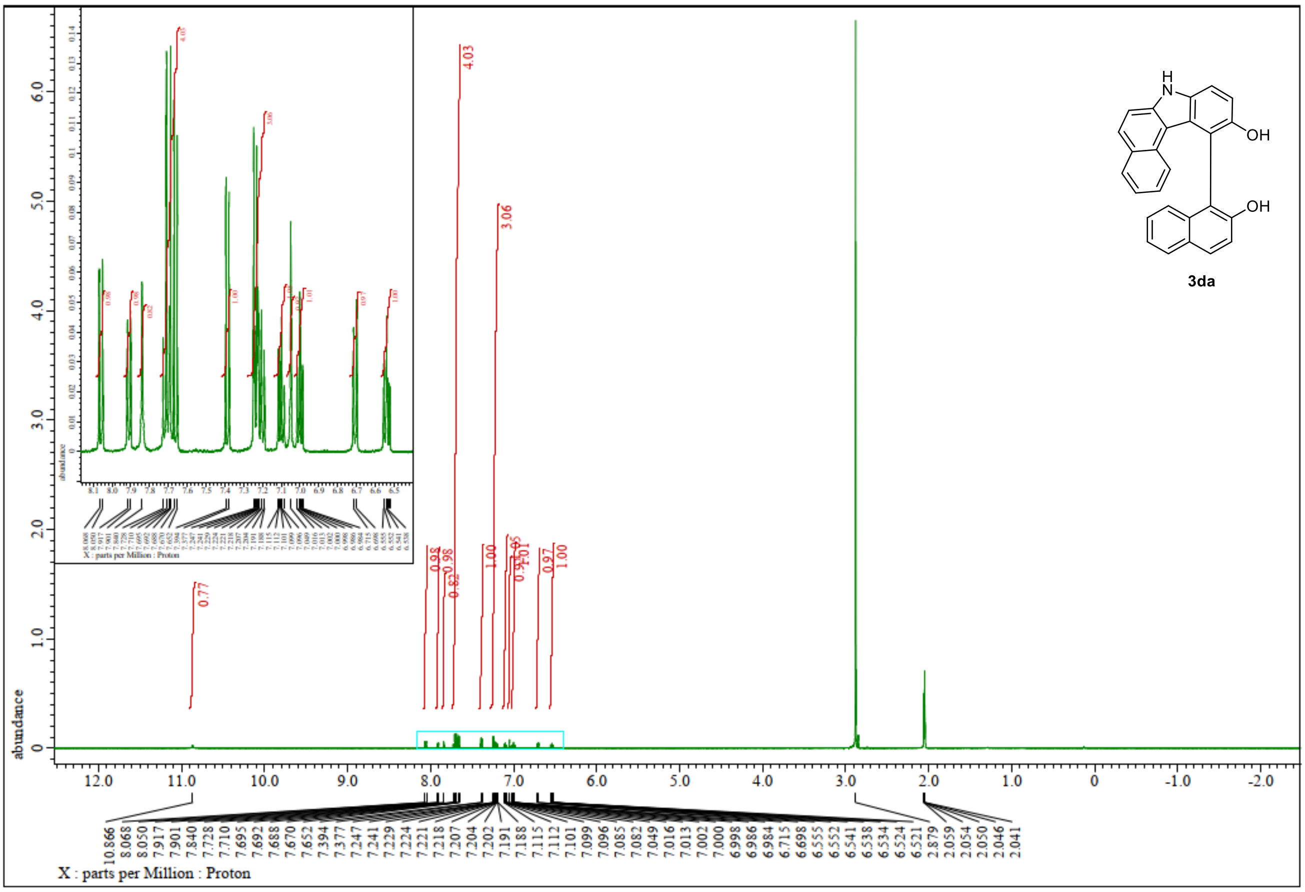
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ca**



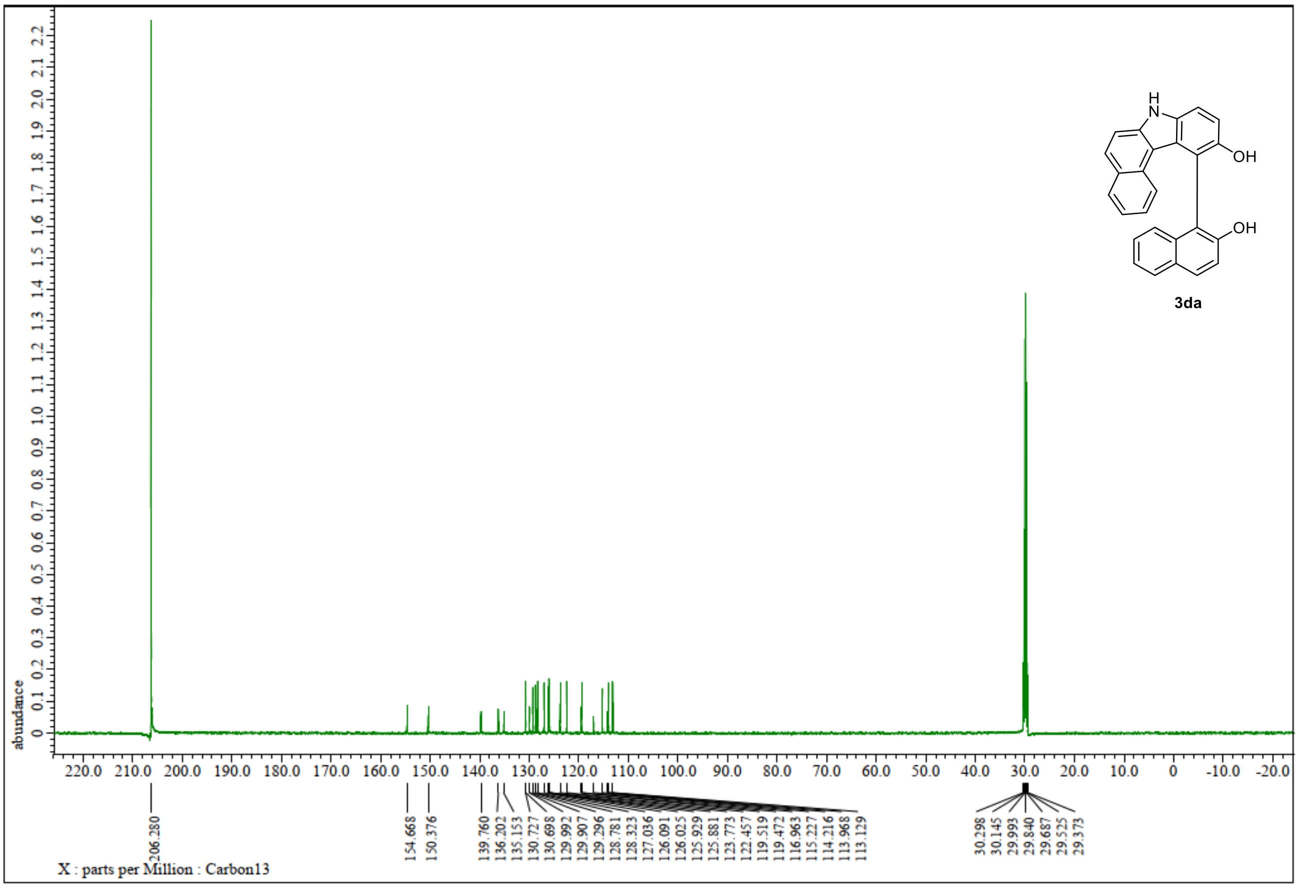
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ca**



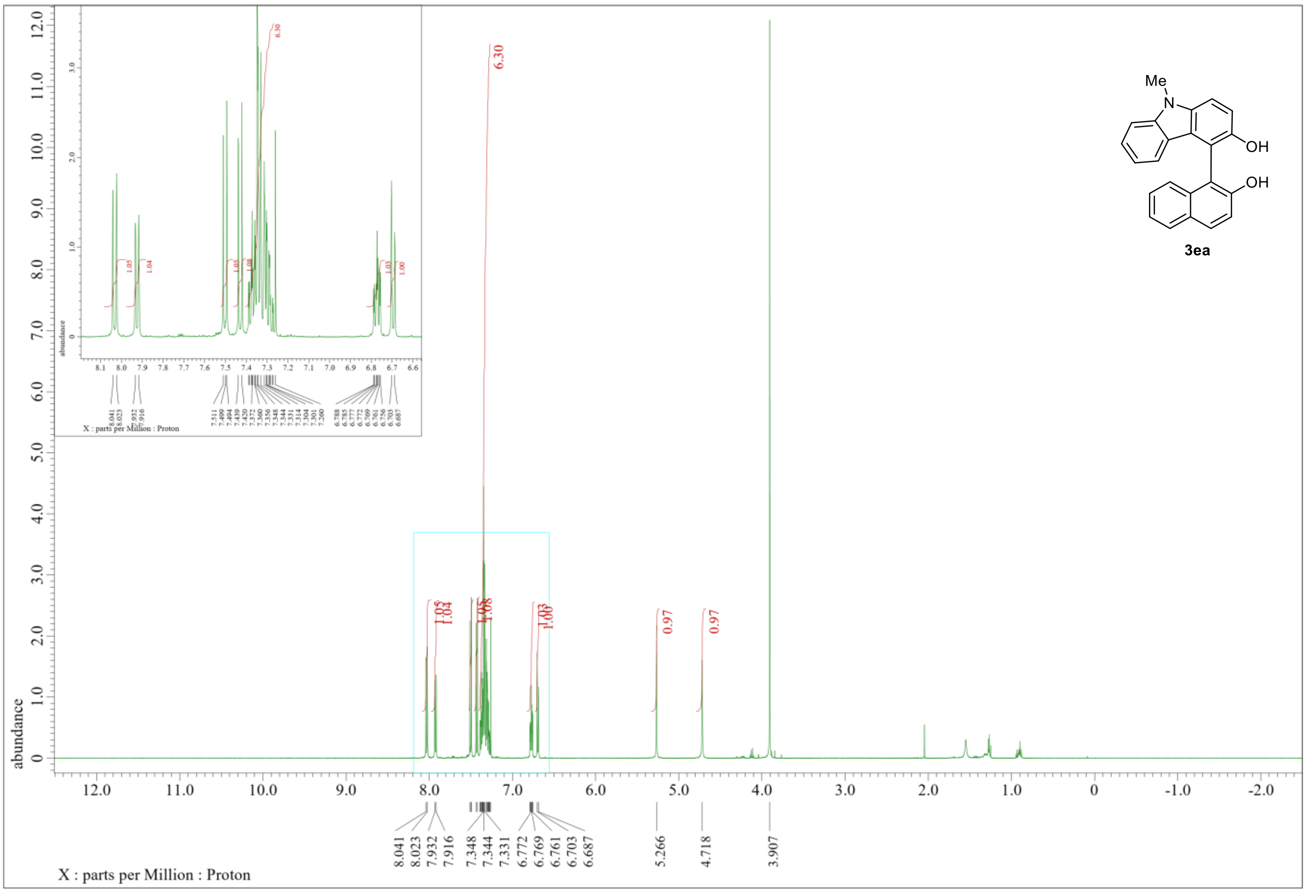
^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **3da**



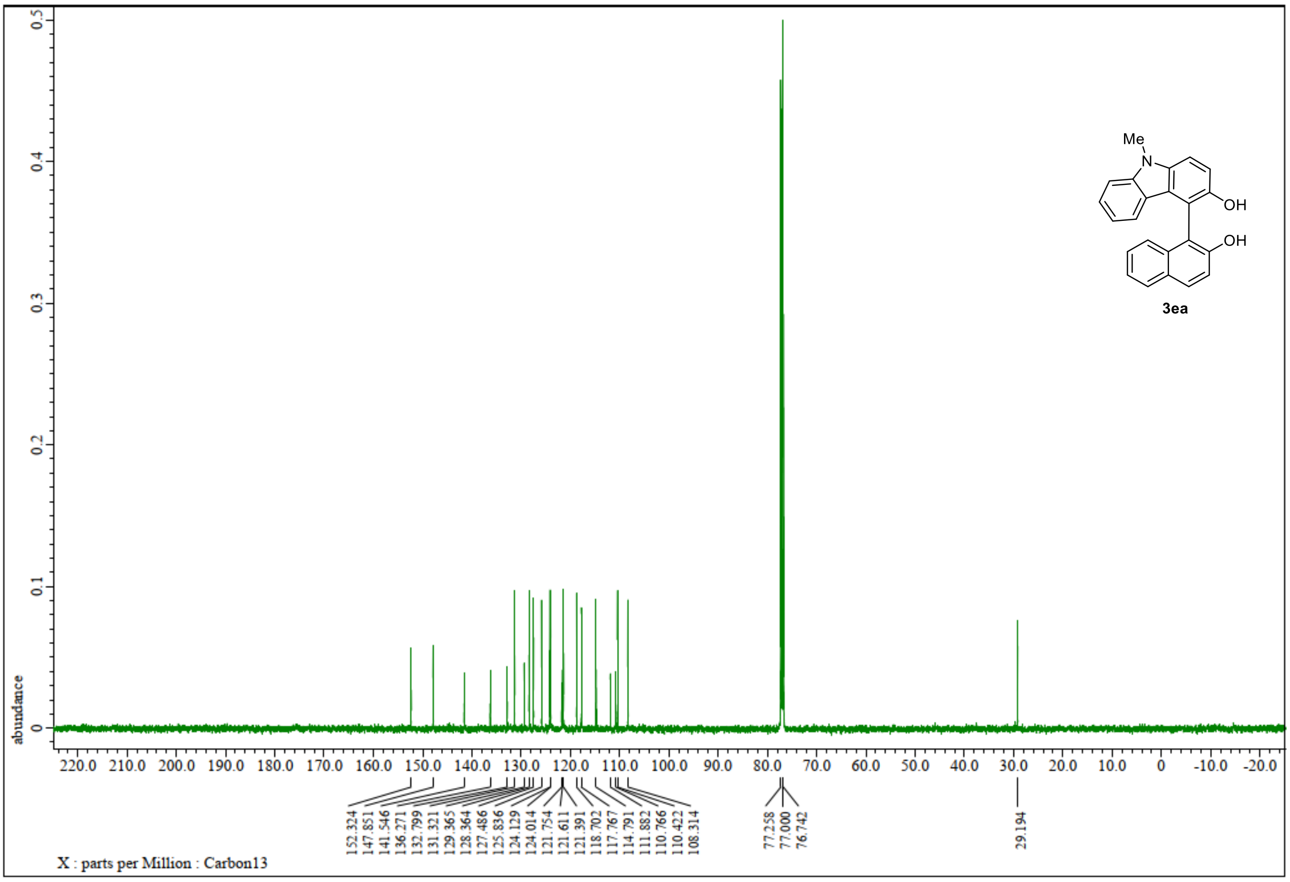
^{1}H NMR spectrum (500 MHz, acetone-d_6) of **3da**



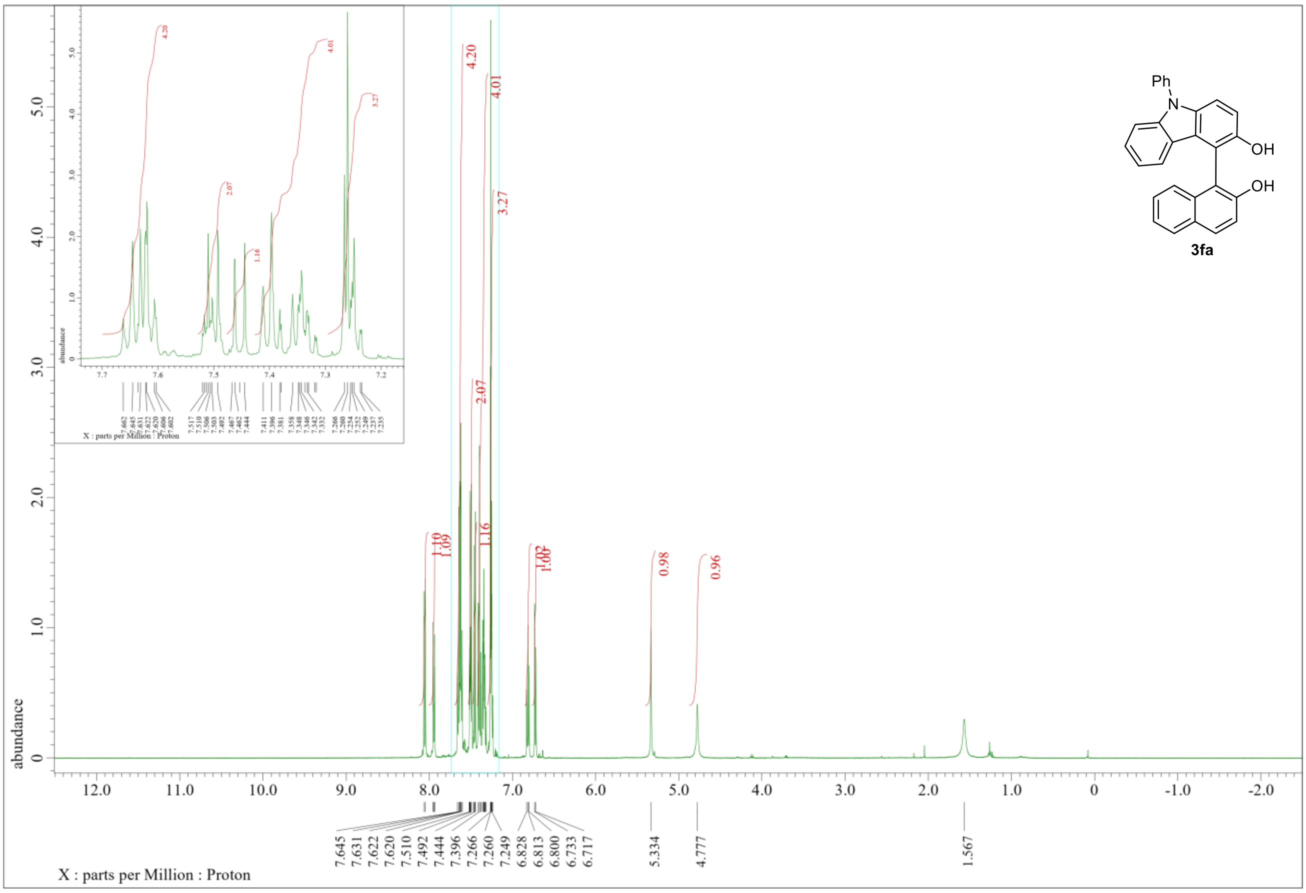
^{13}C NMR spectrum (125 MHz, acetone-d_6) of **3da**



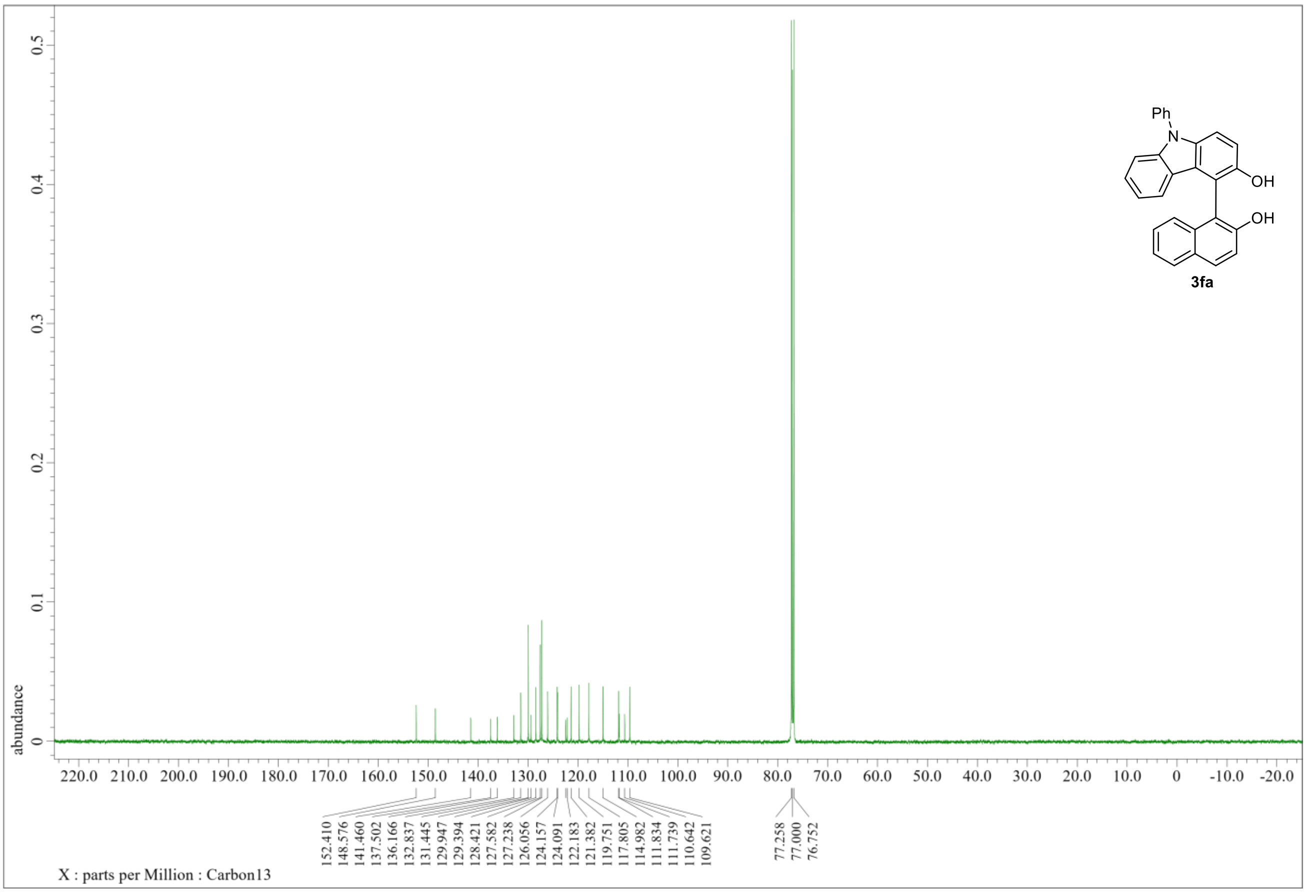
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ea**



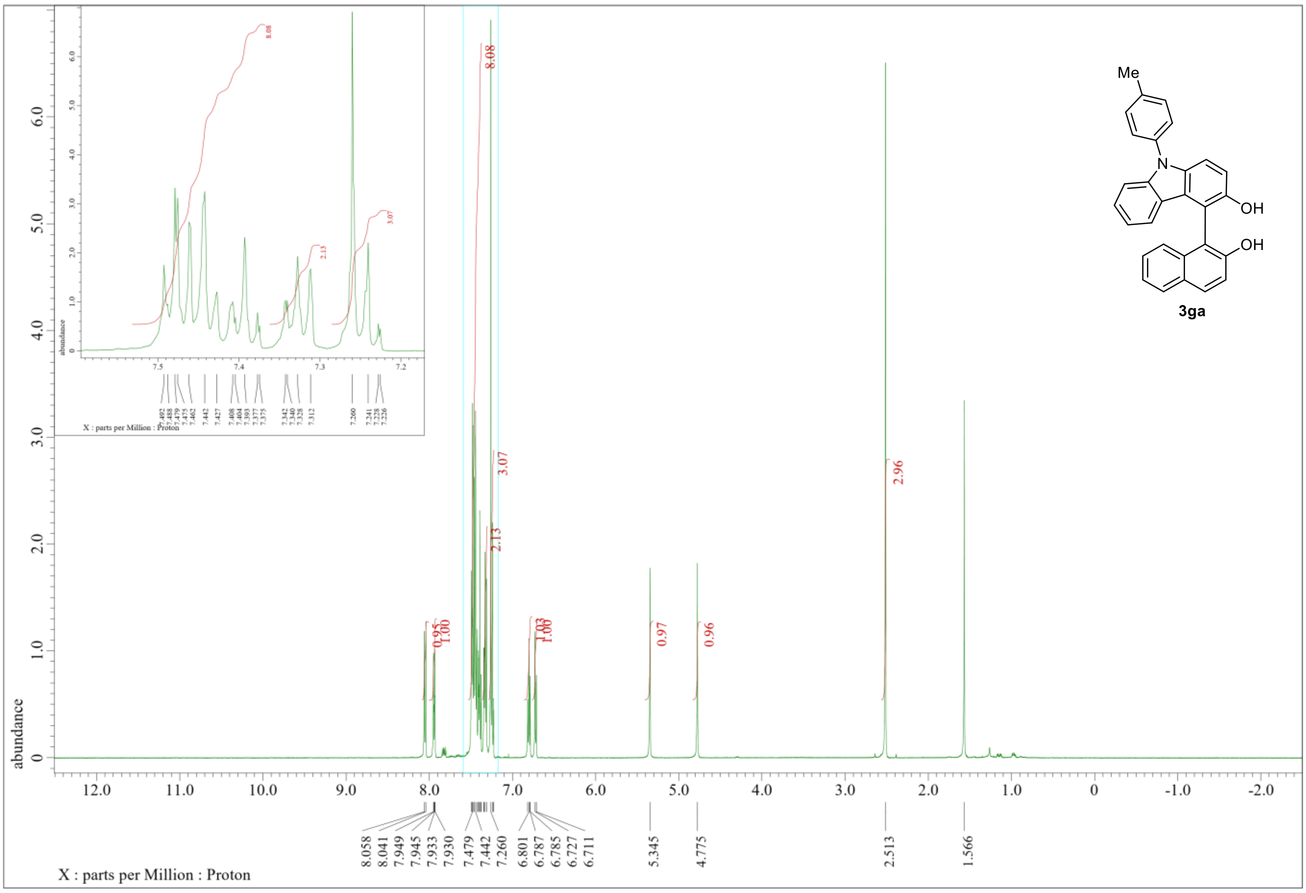
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ea**



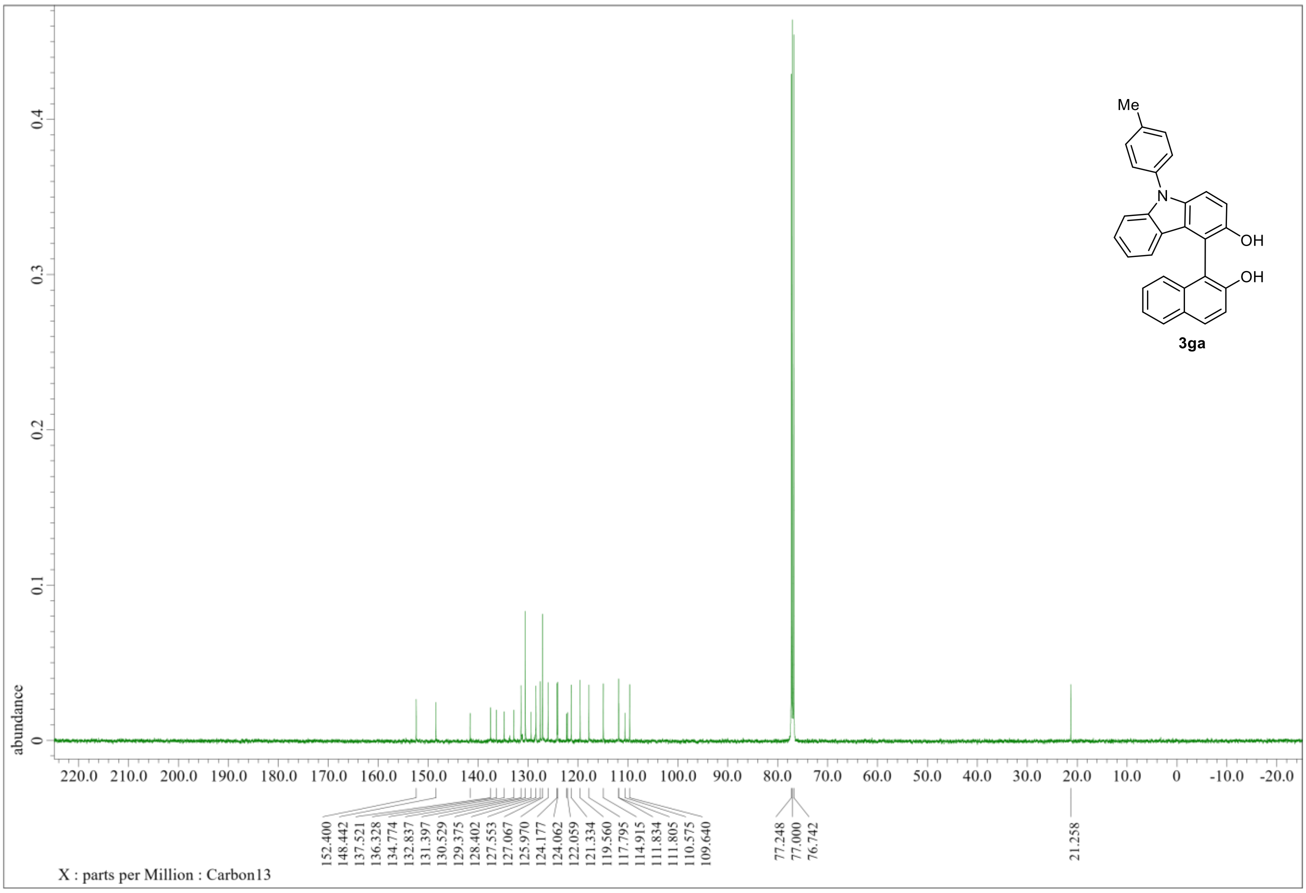
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3fa**



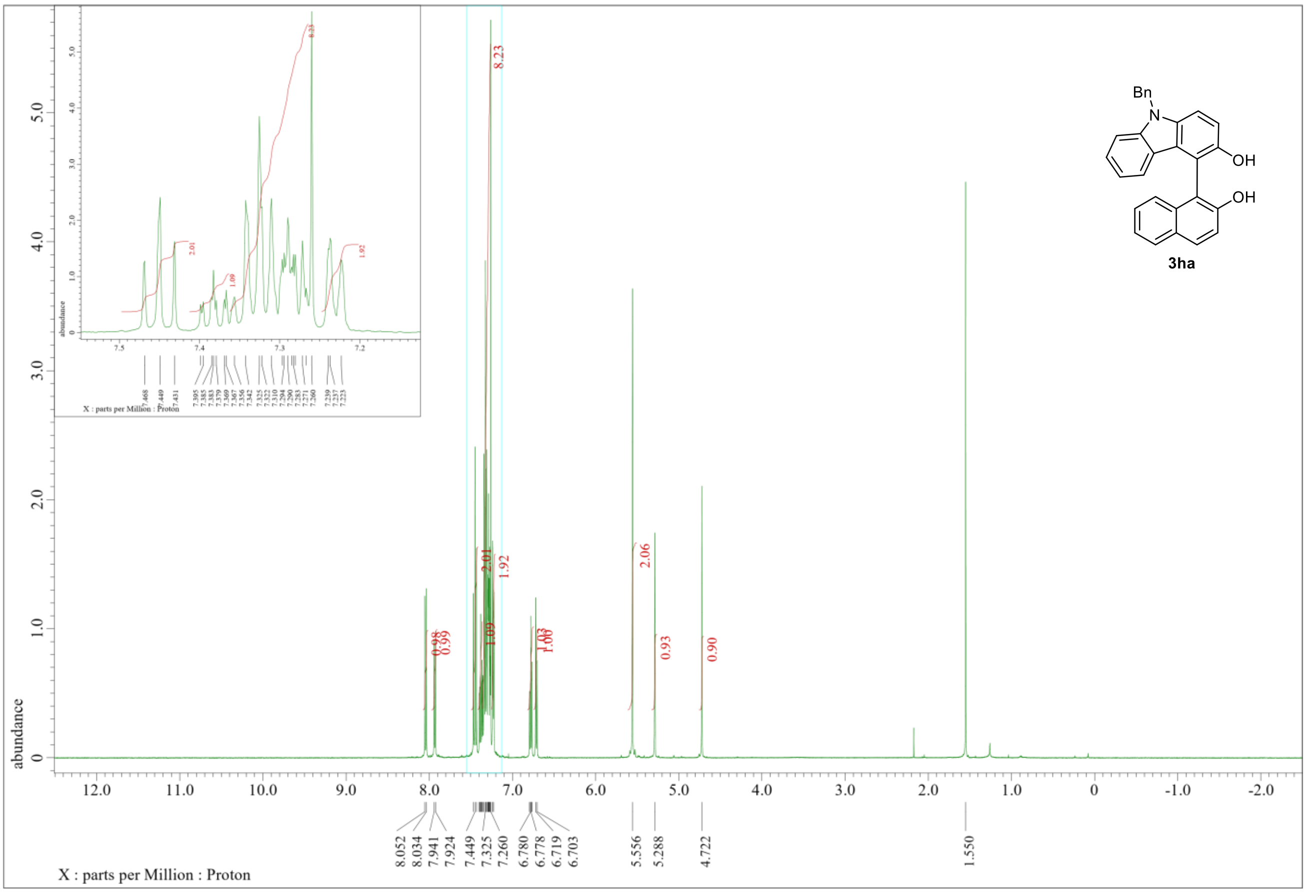
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3fa**



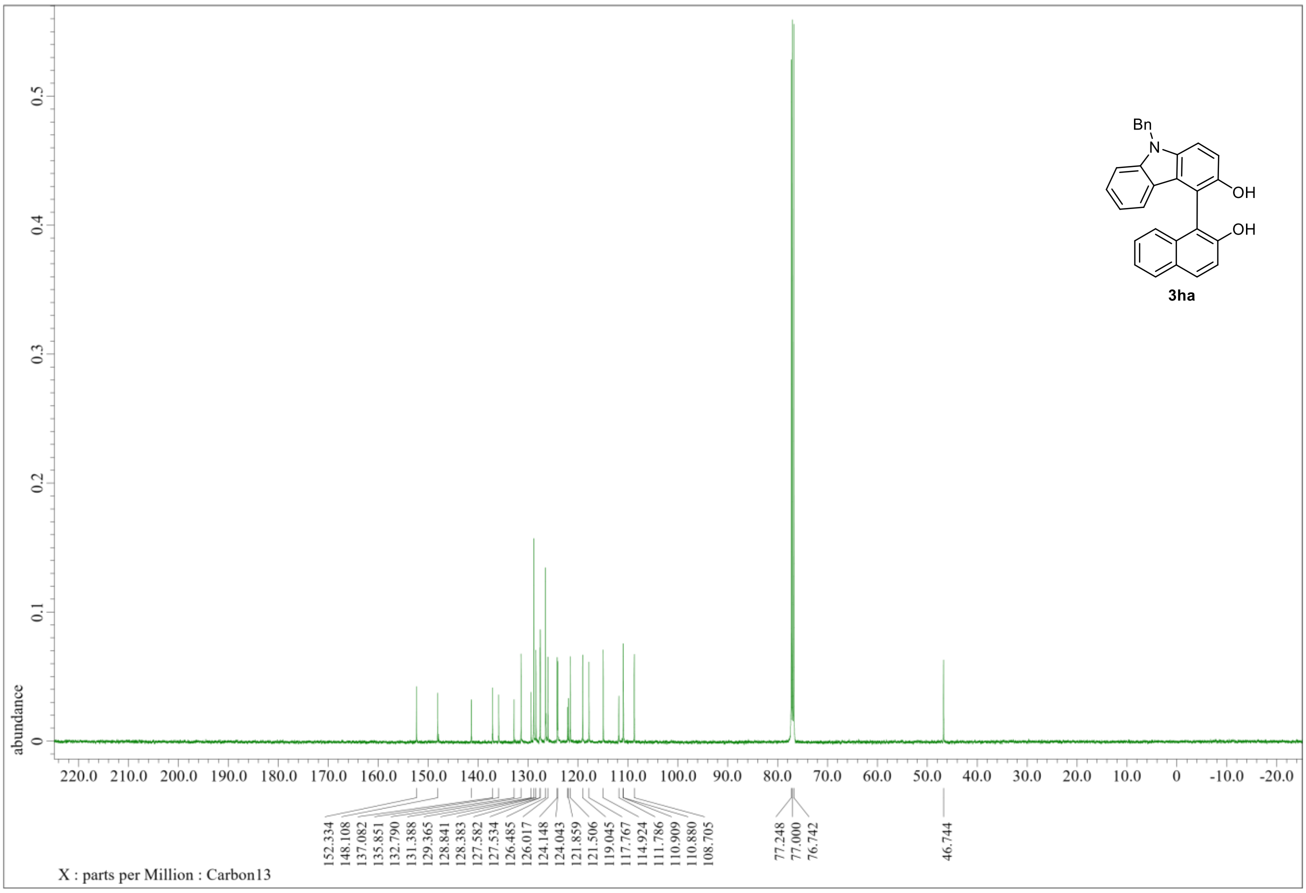
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ga**



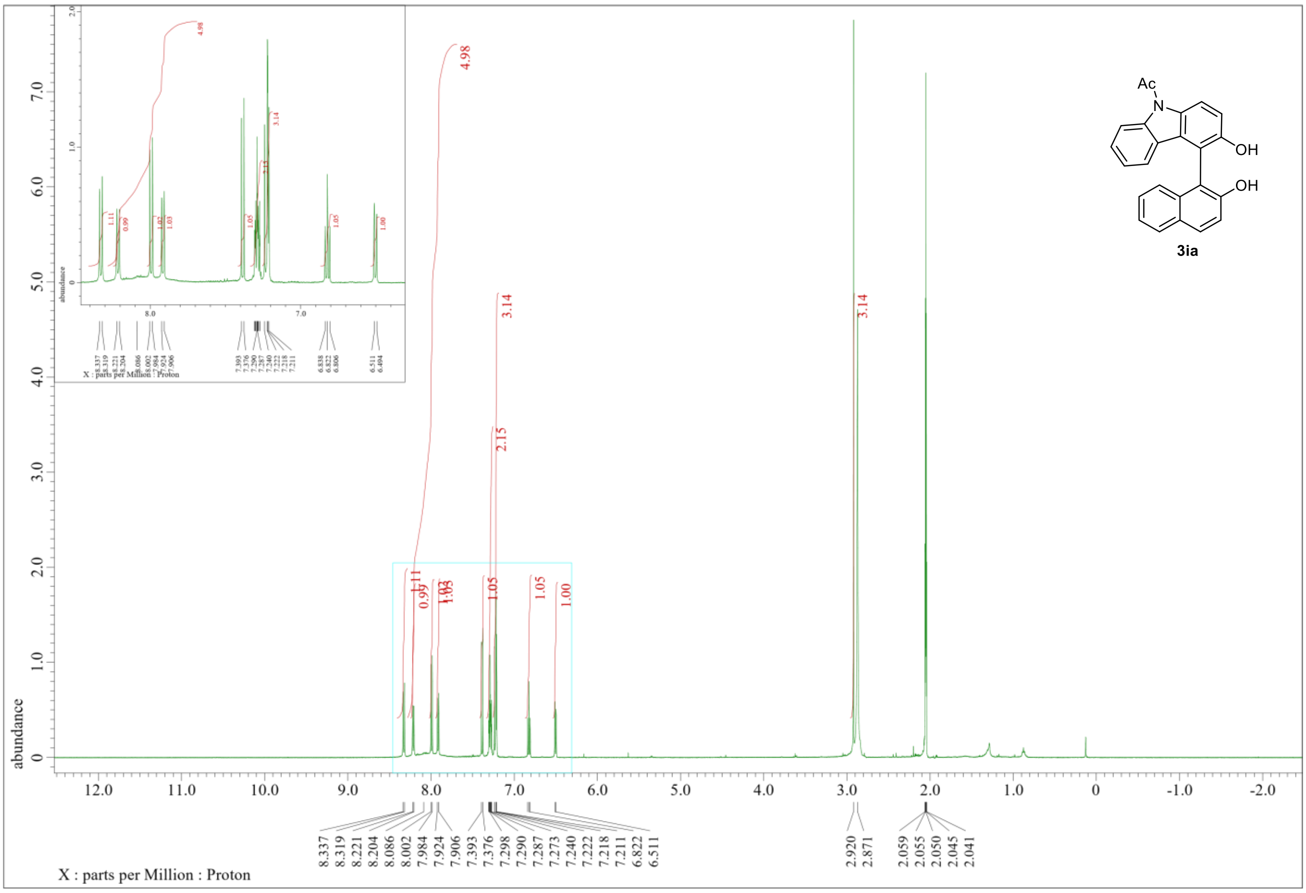
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ga**



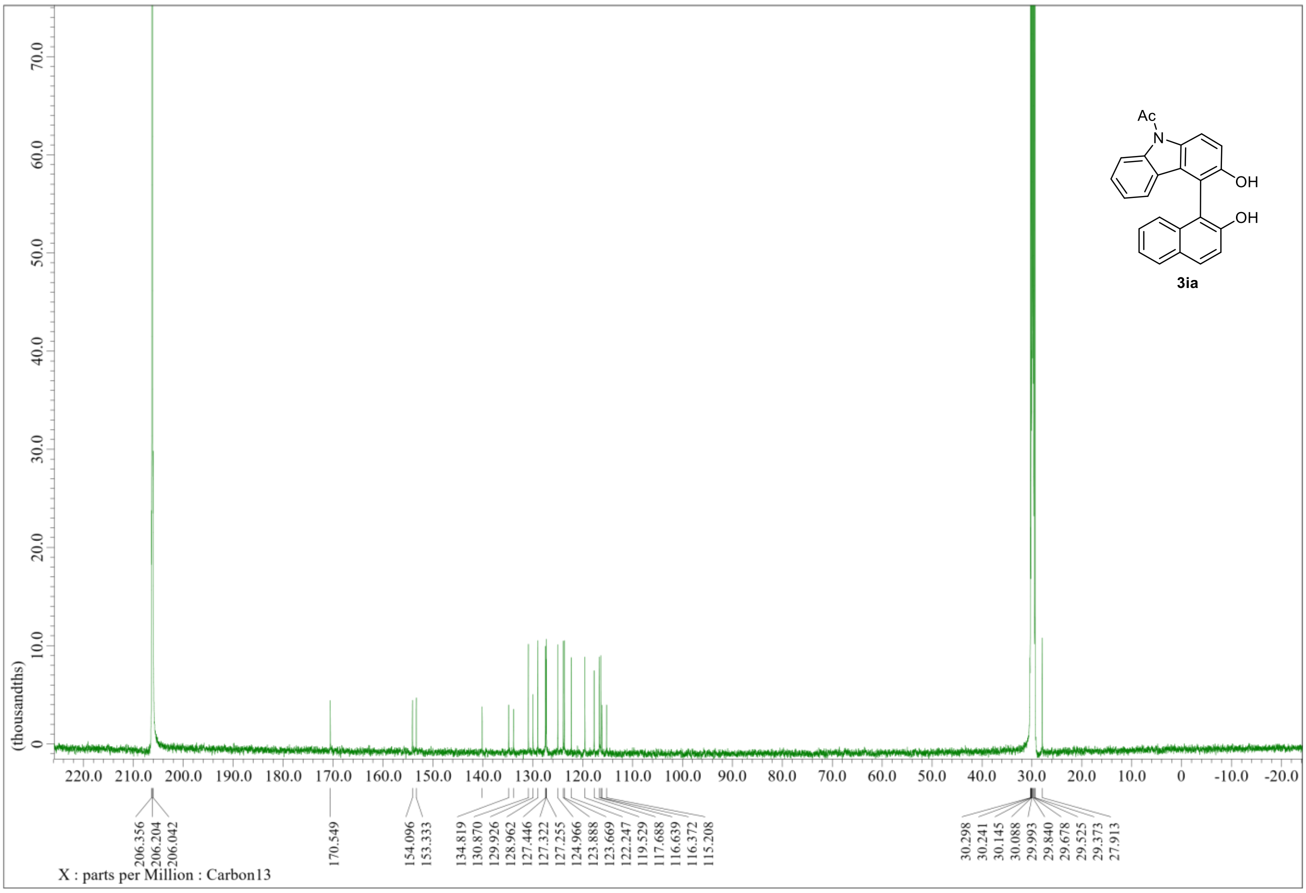
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ha**



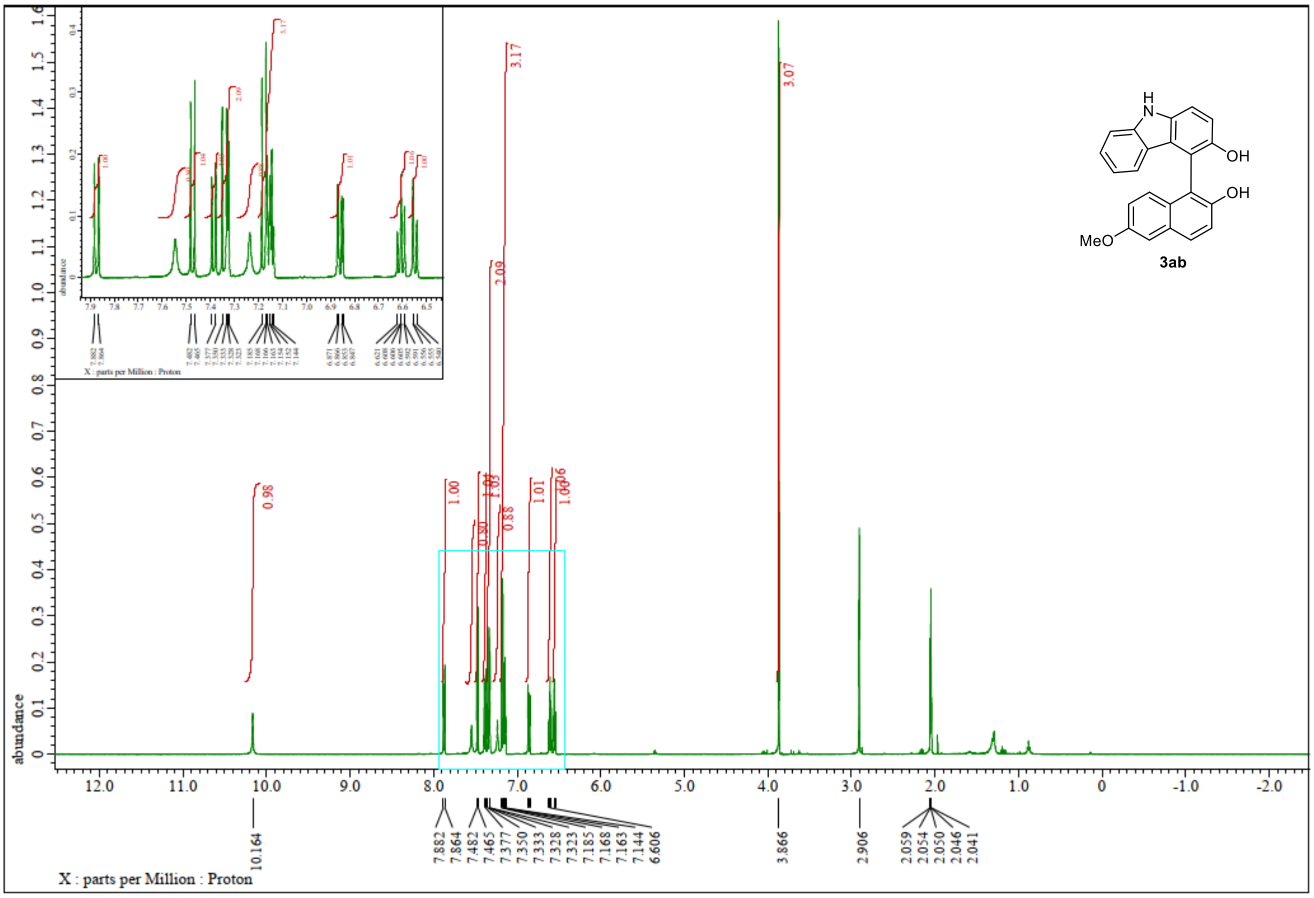
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ha**



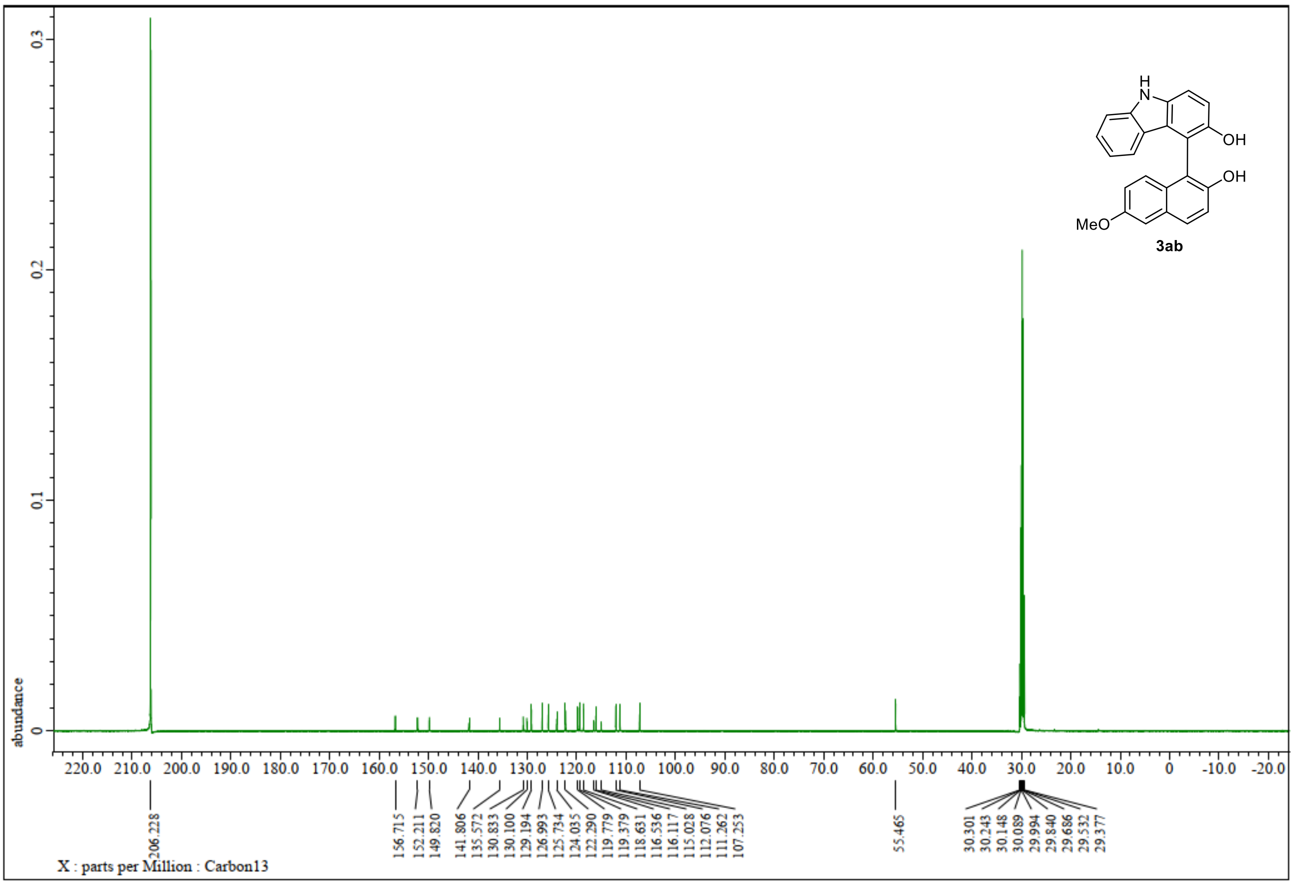
^{1}H NMR spectrum (500 MHz, acetone-d_6) of **3ia**



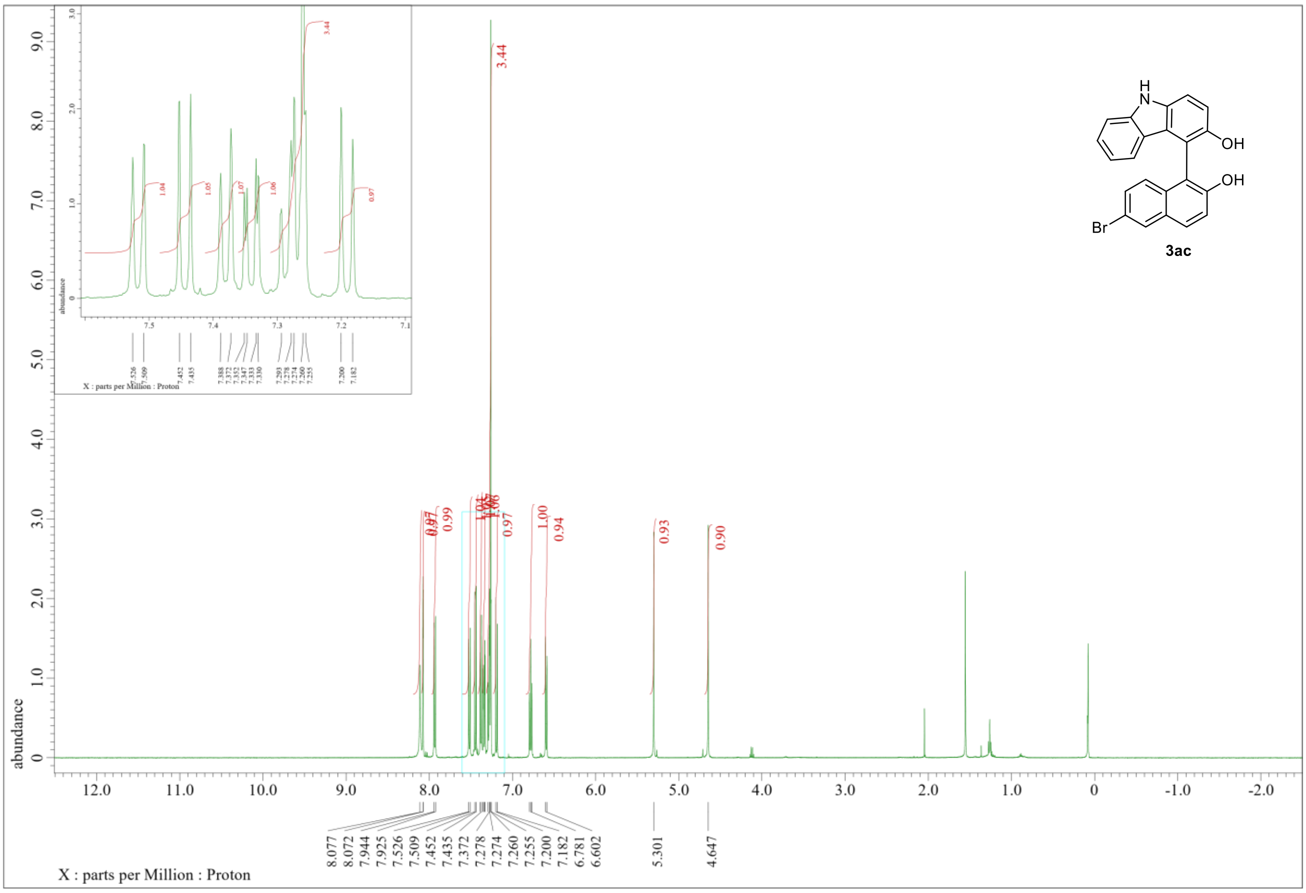
^{13}C NMR spectrum (125 MHz, acetone-d_6) of **3ia**



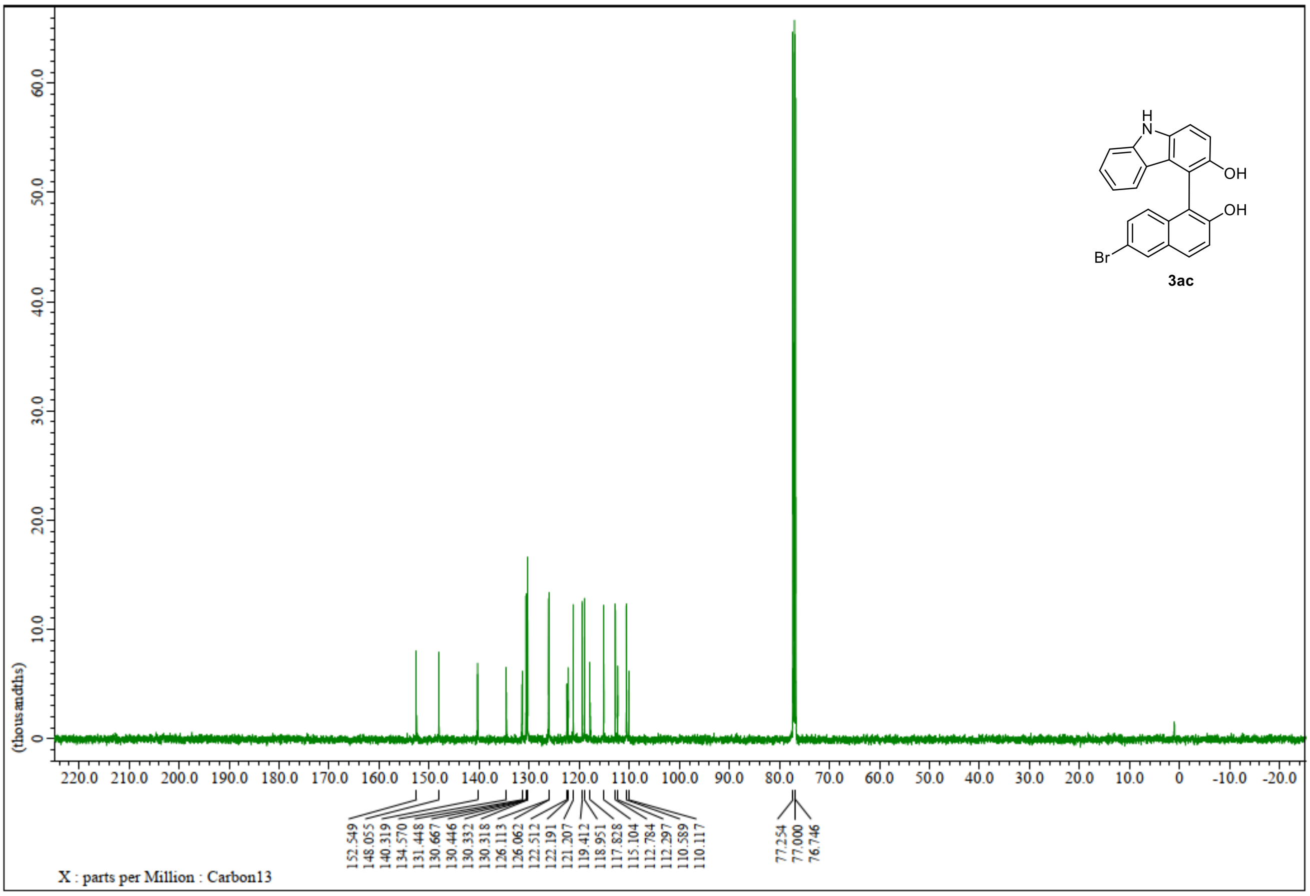
^{1}H NMR spectrum (500 MHz, acetone-d_6) of **3ab**



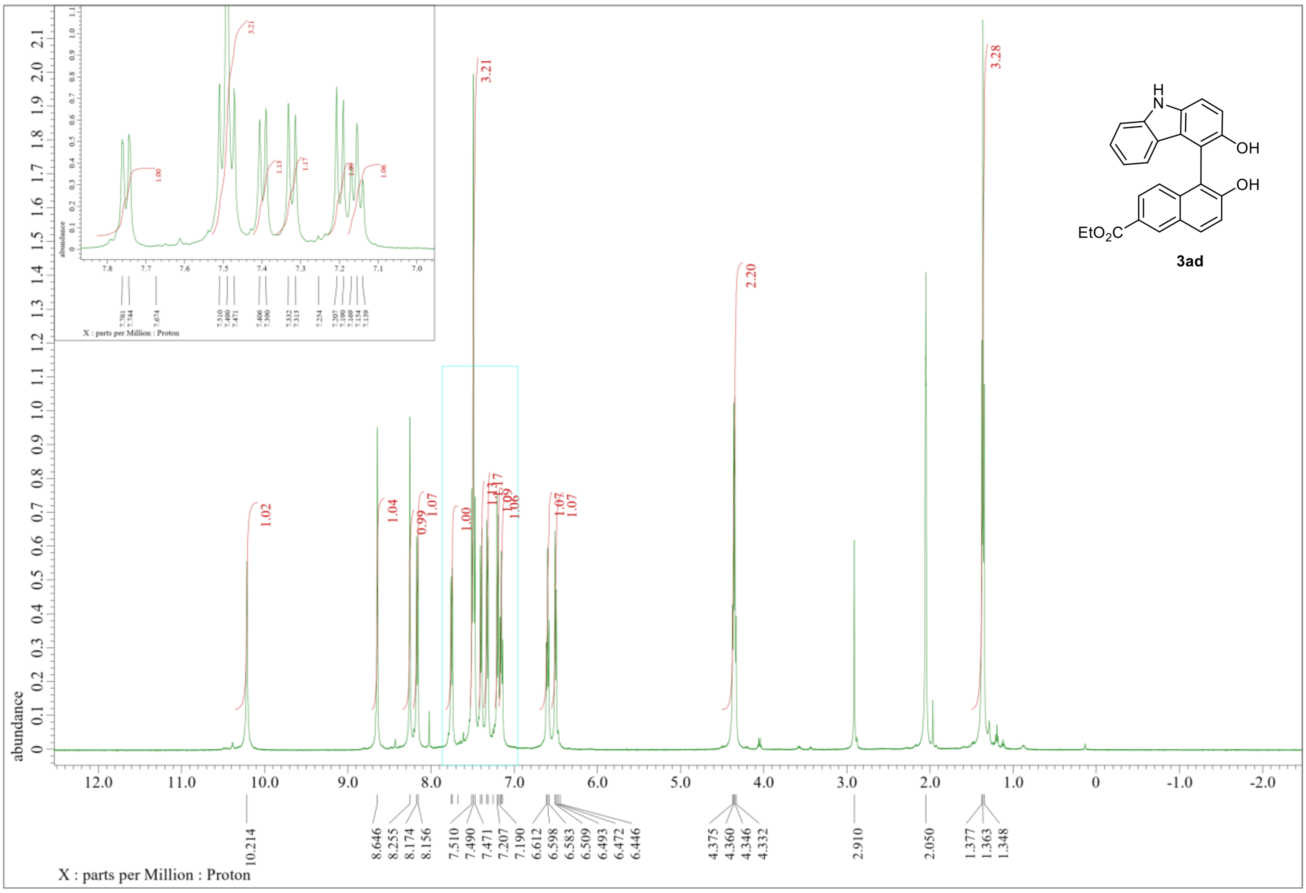
^{13}C NMR spectrum (125 MHz, acetone-d_6) of **3ab**



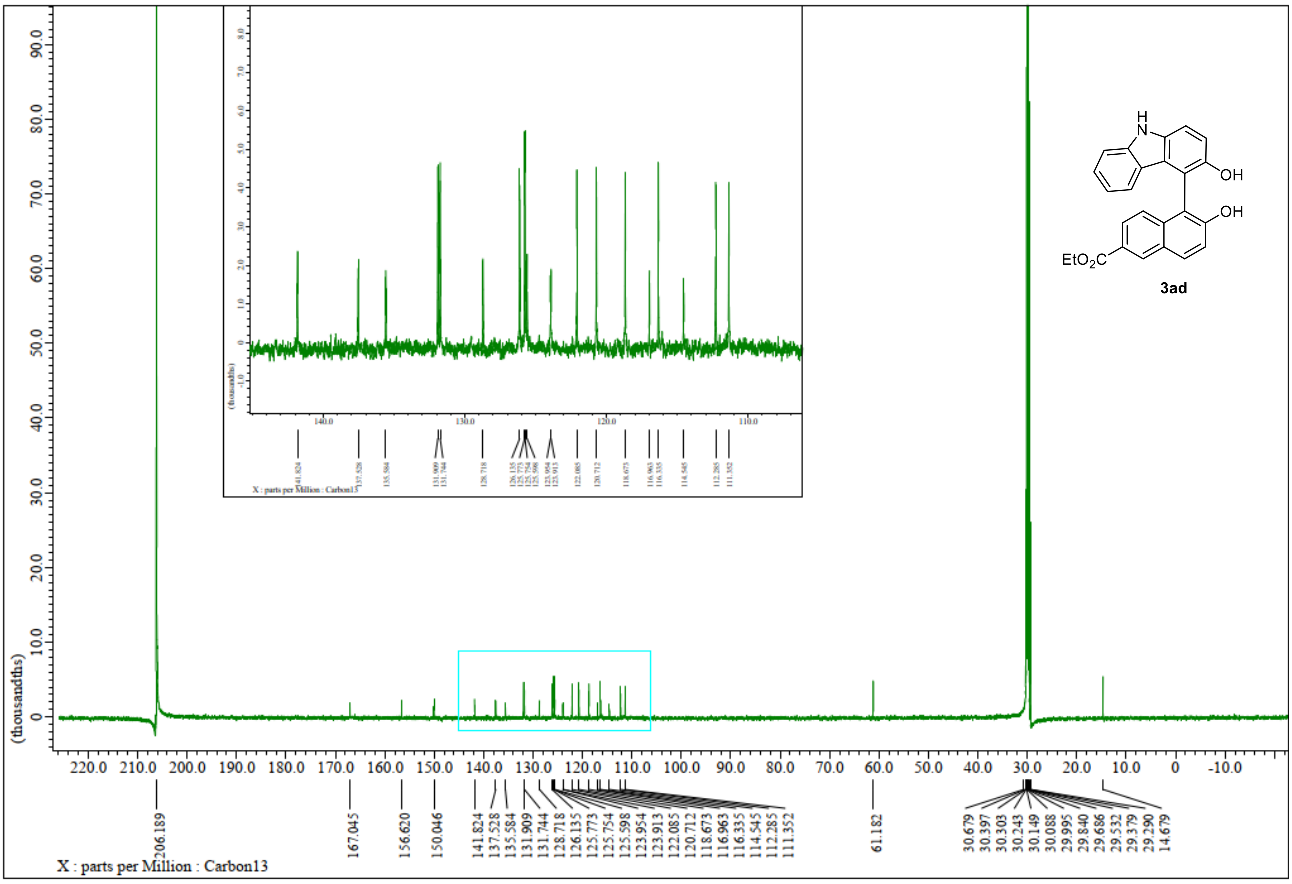
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ca**



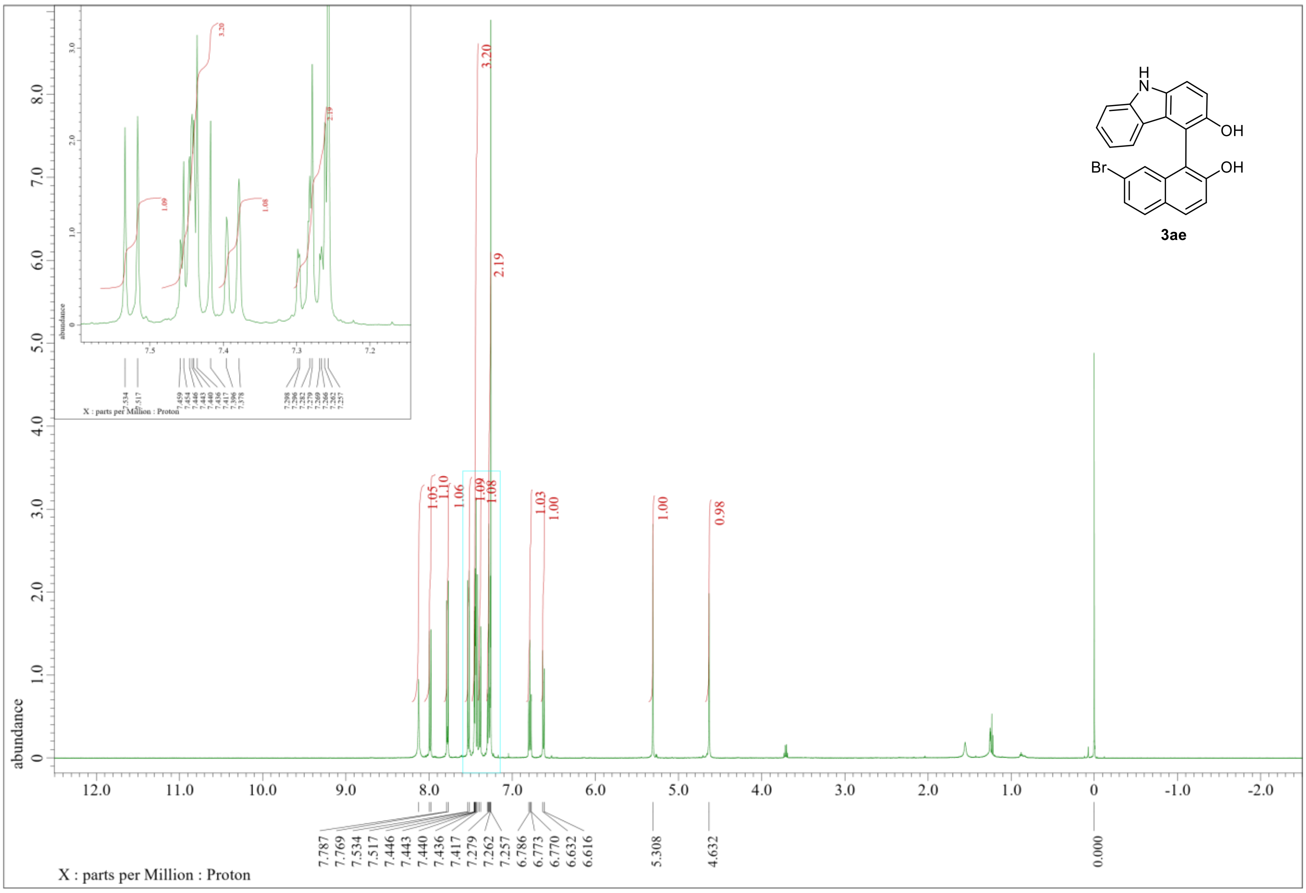
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ac**



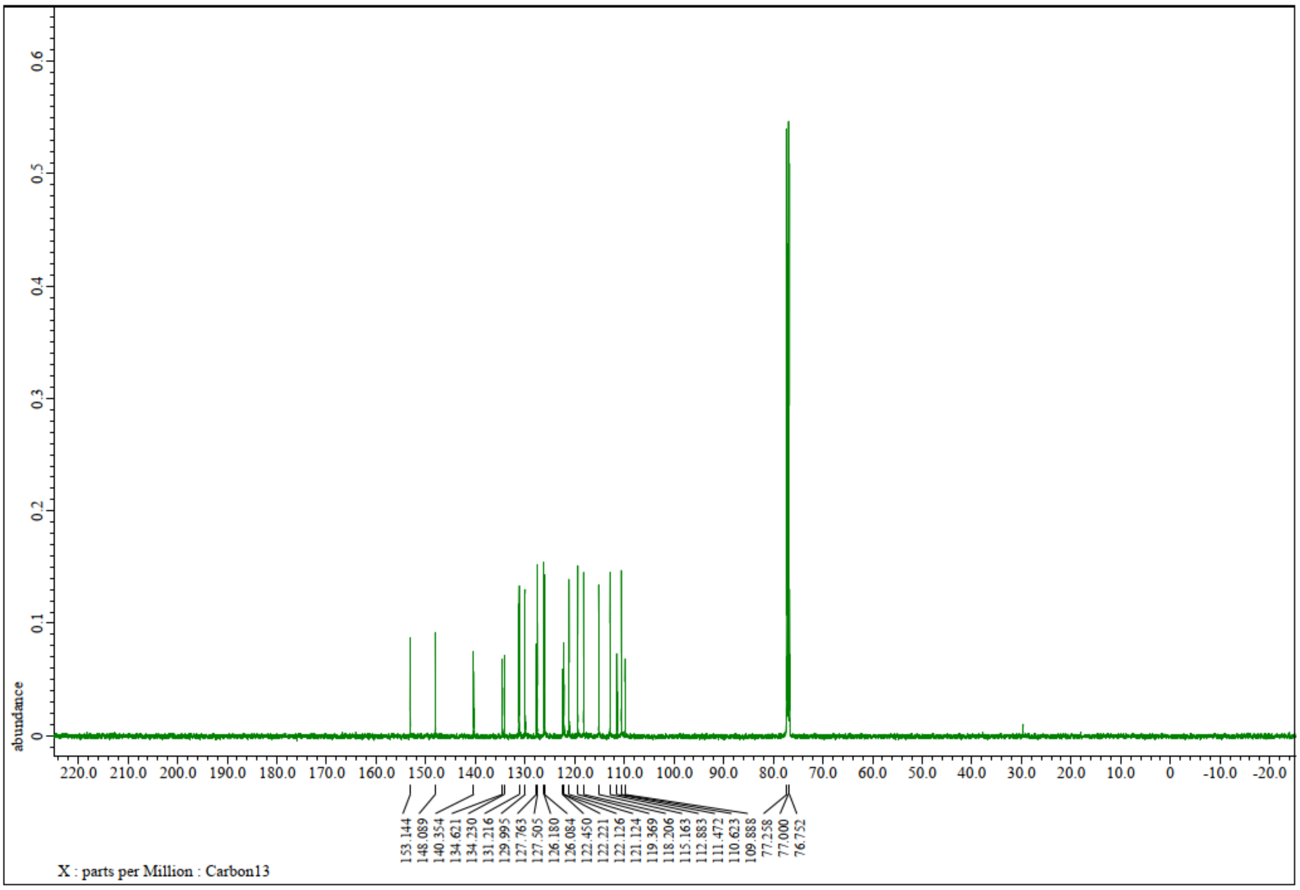
^{1}H NMR spectrum (500 MHz, acetone-d_6) of **3ad**



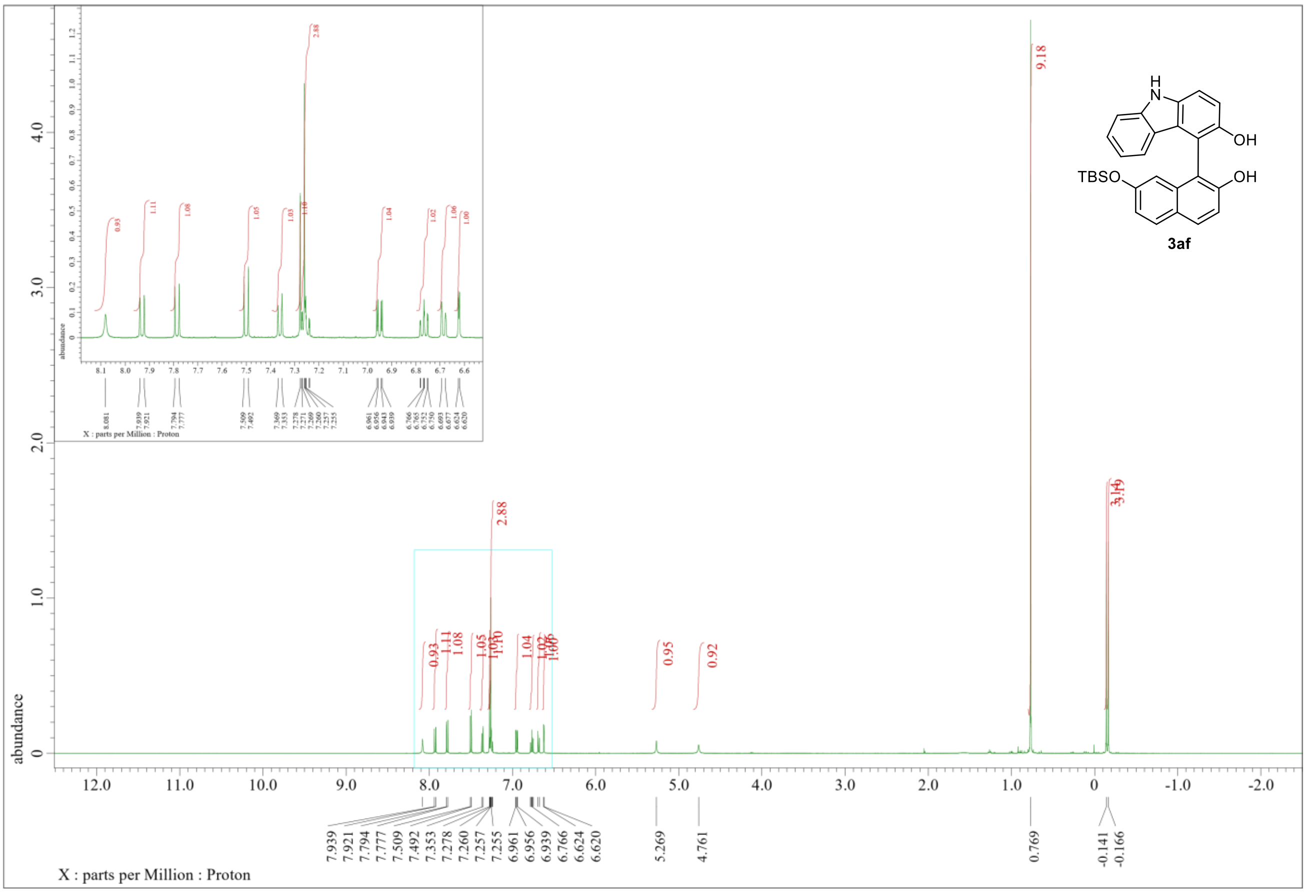
^{13}C NMR spectrum (125 MHz, acetone-d_6) of **3ad**



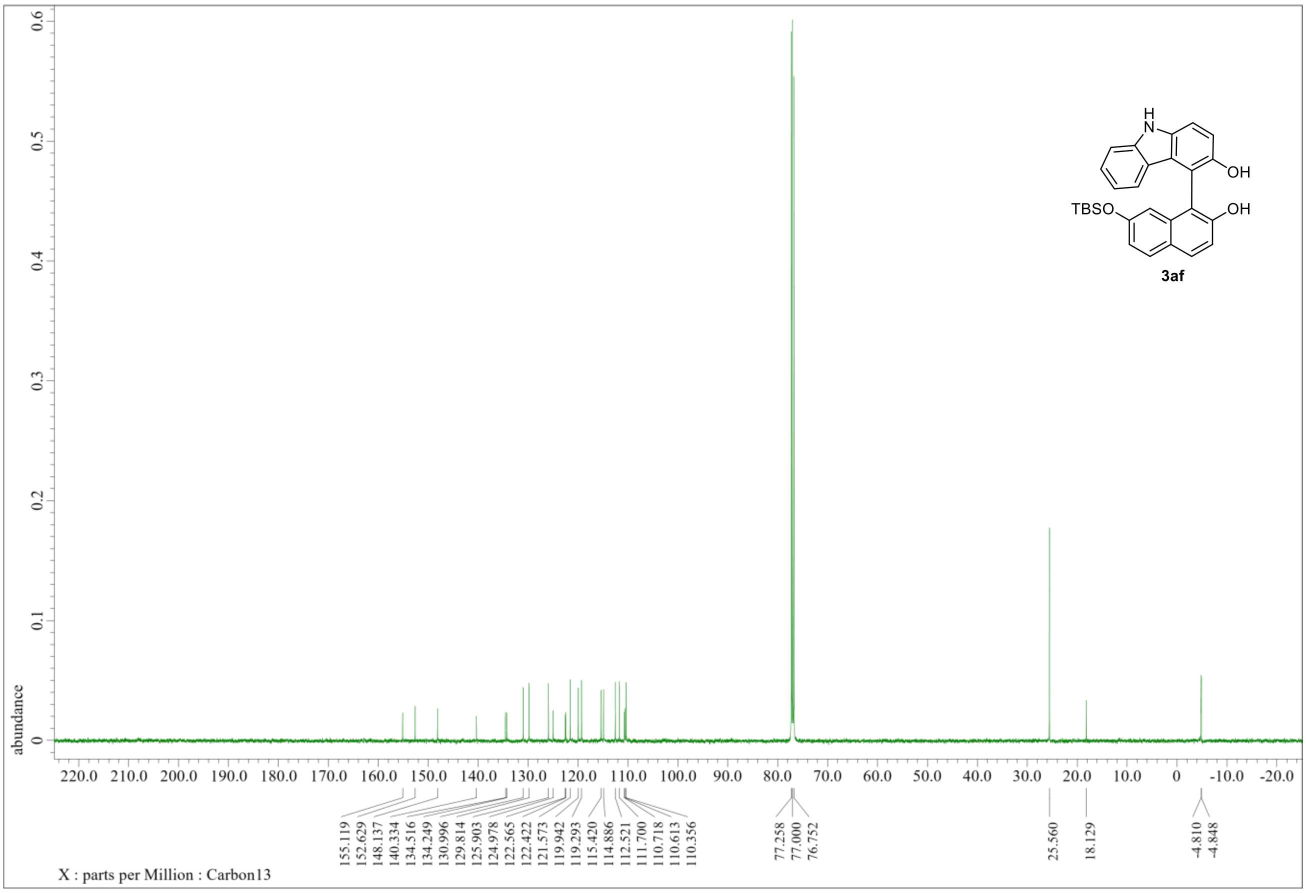
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ae**



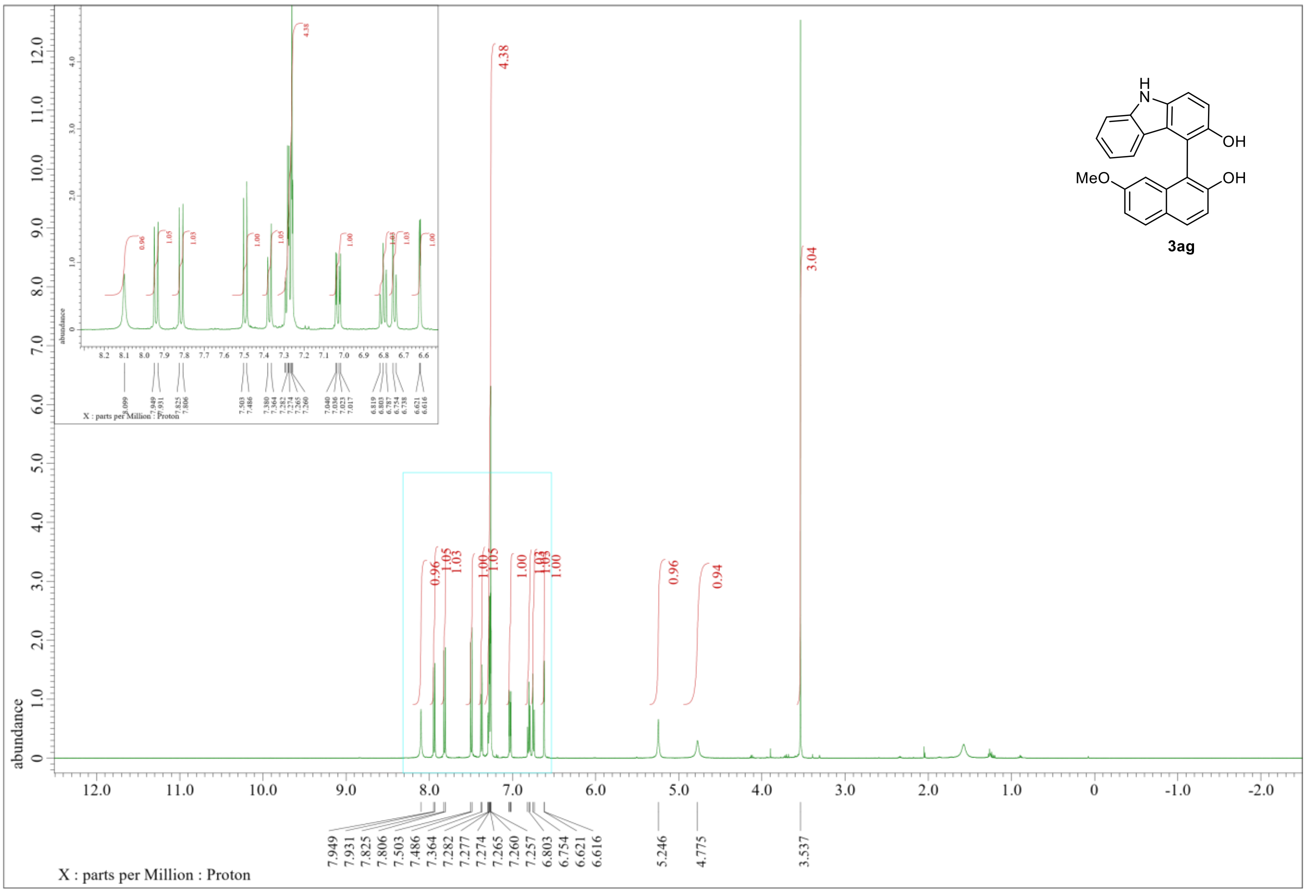
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ae**



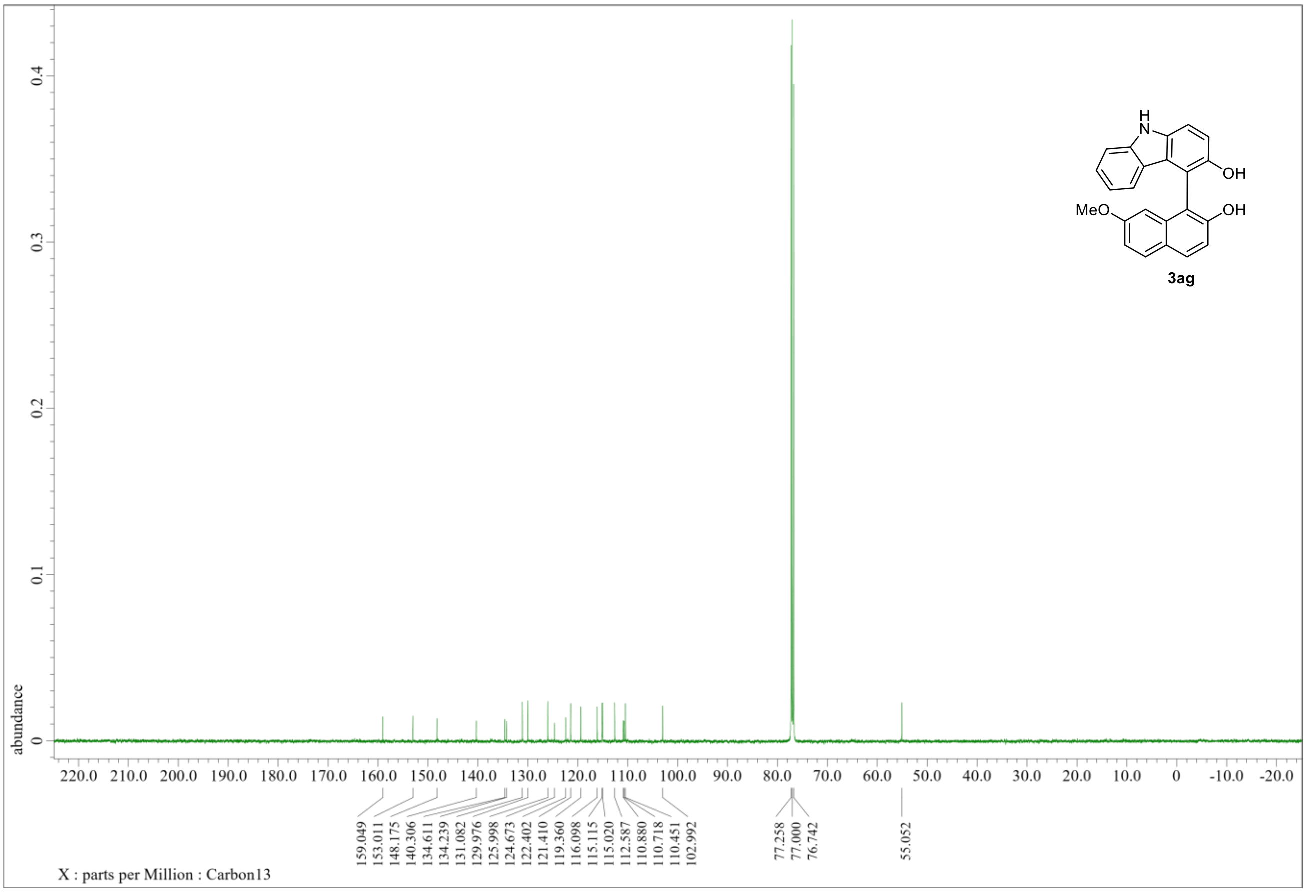
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3af**



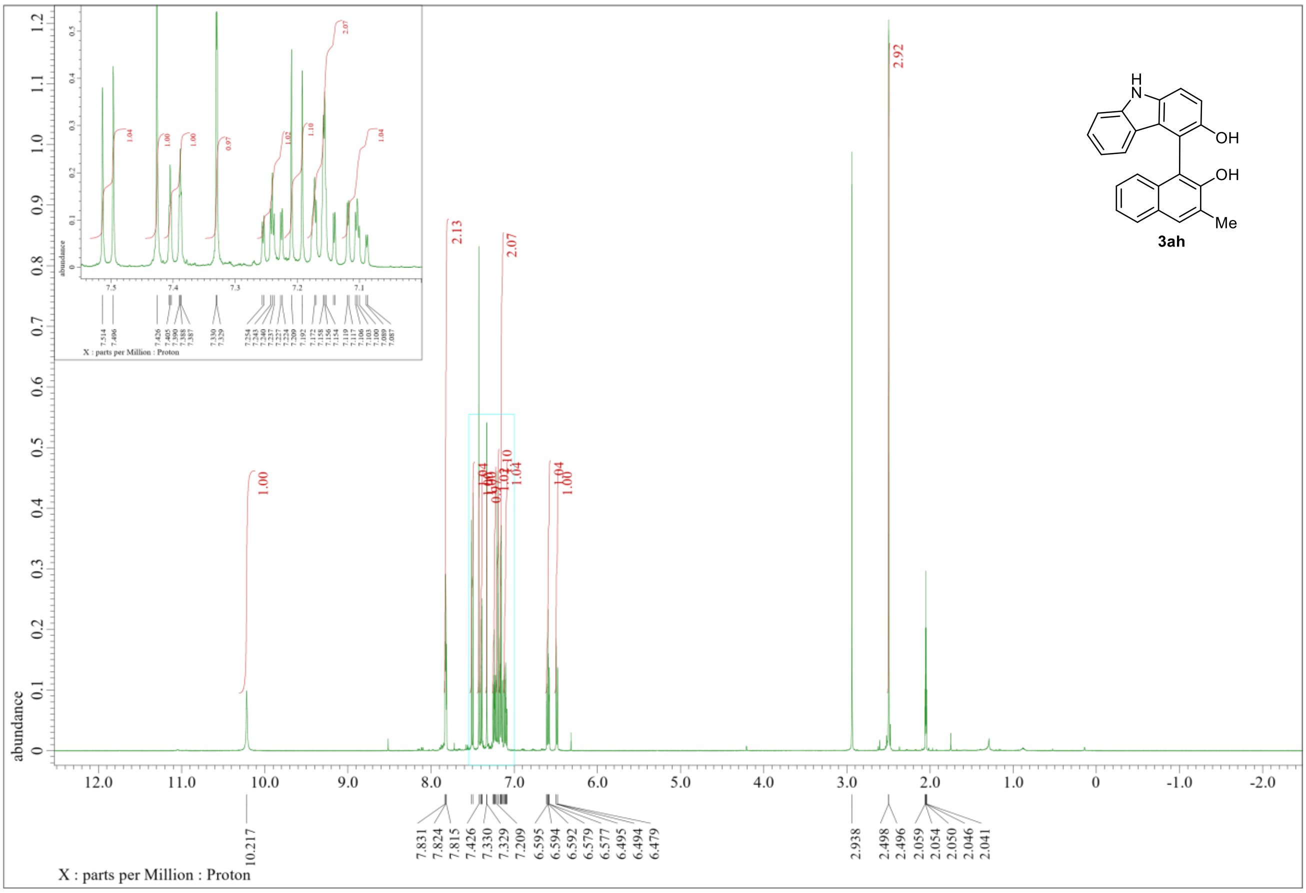
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3af**



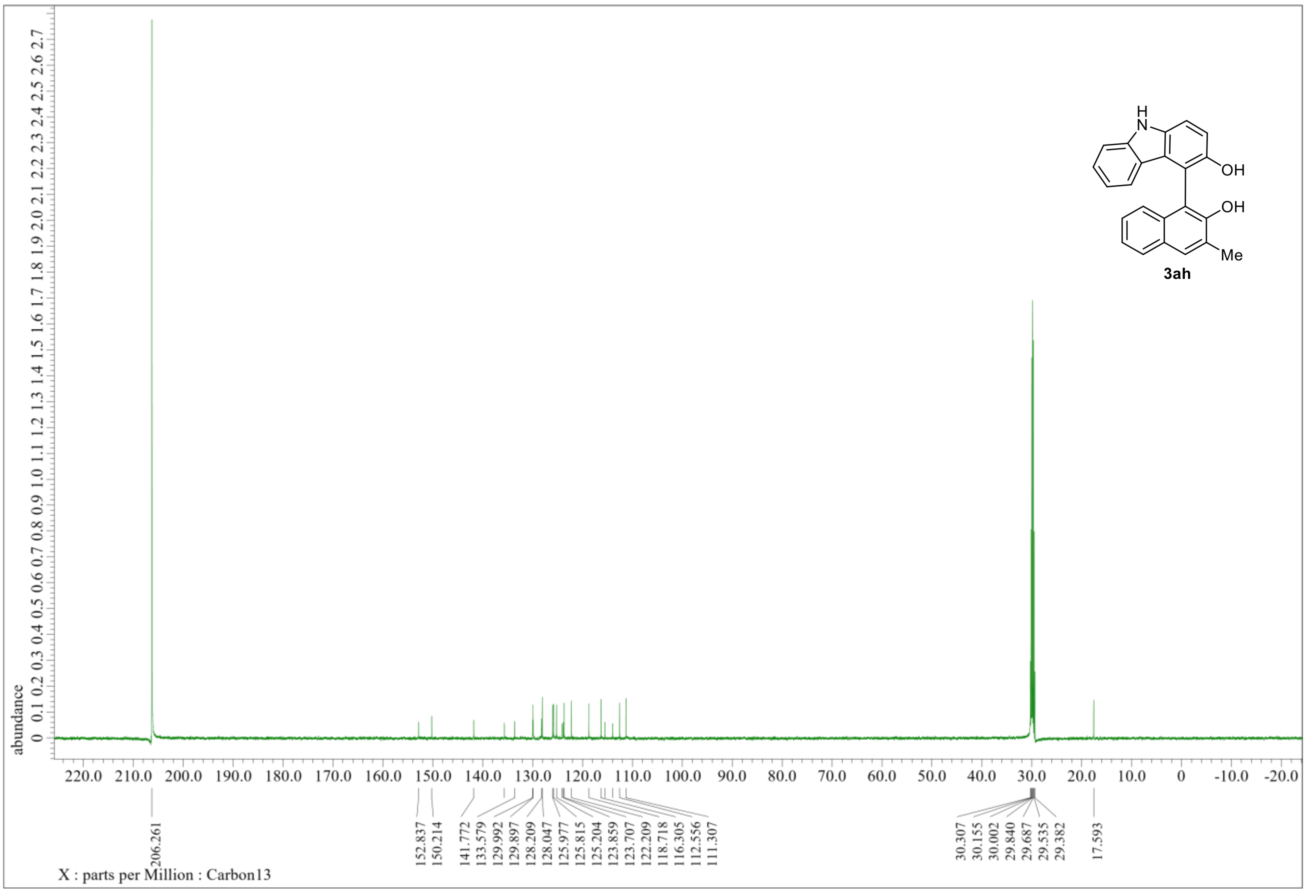
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3ag**



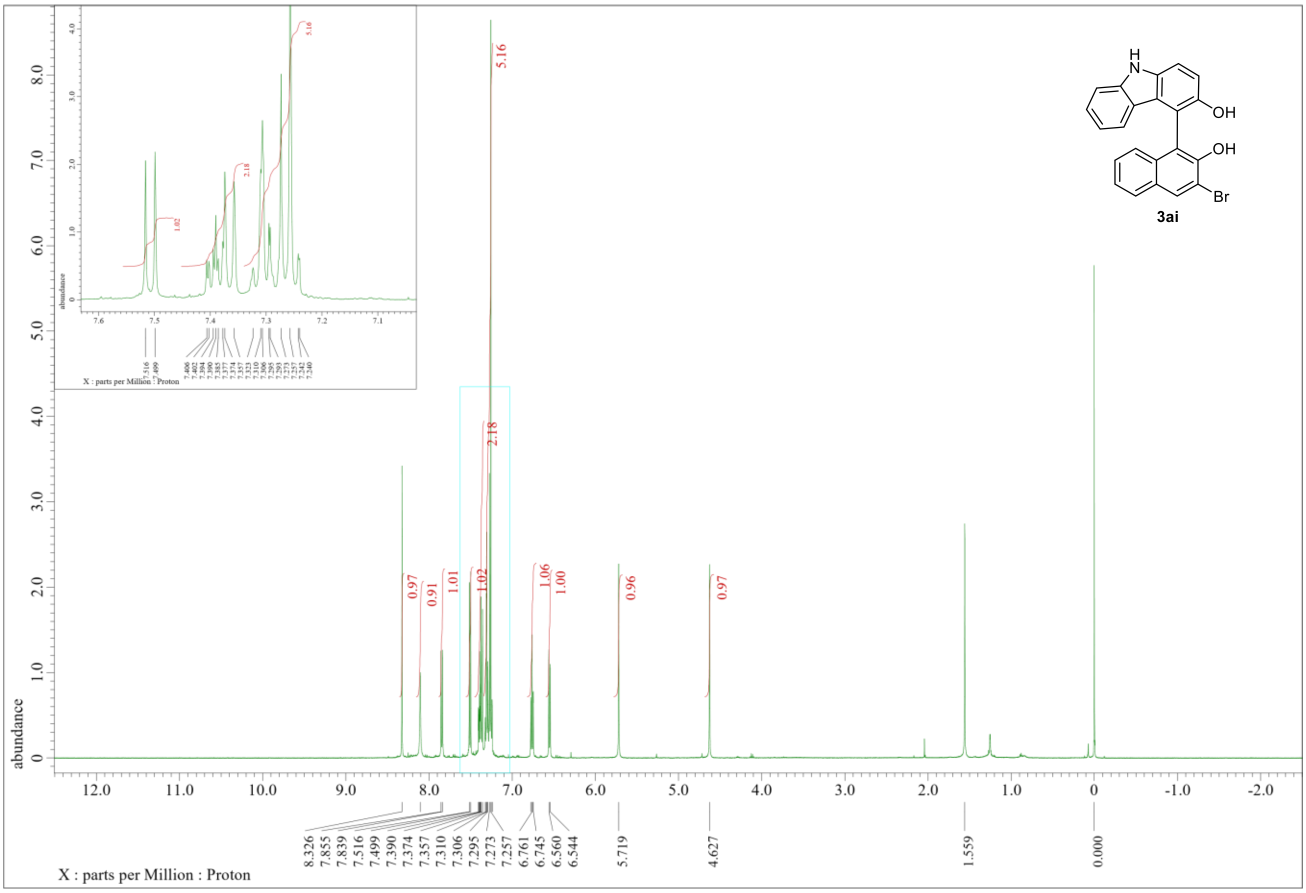
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3ag**



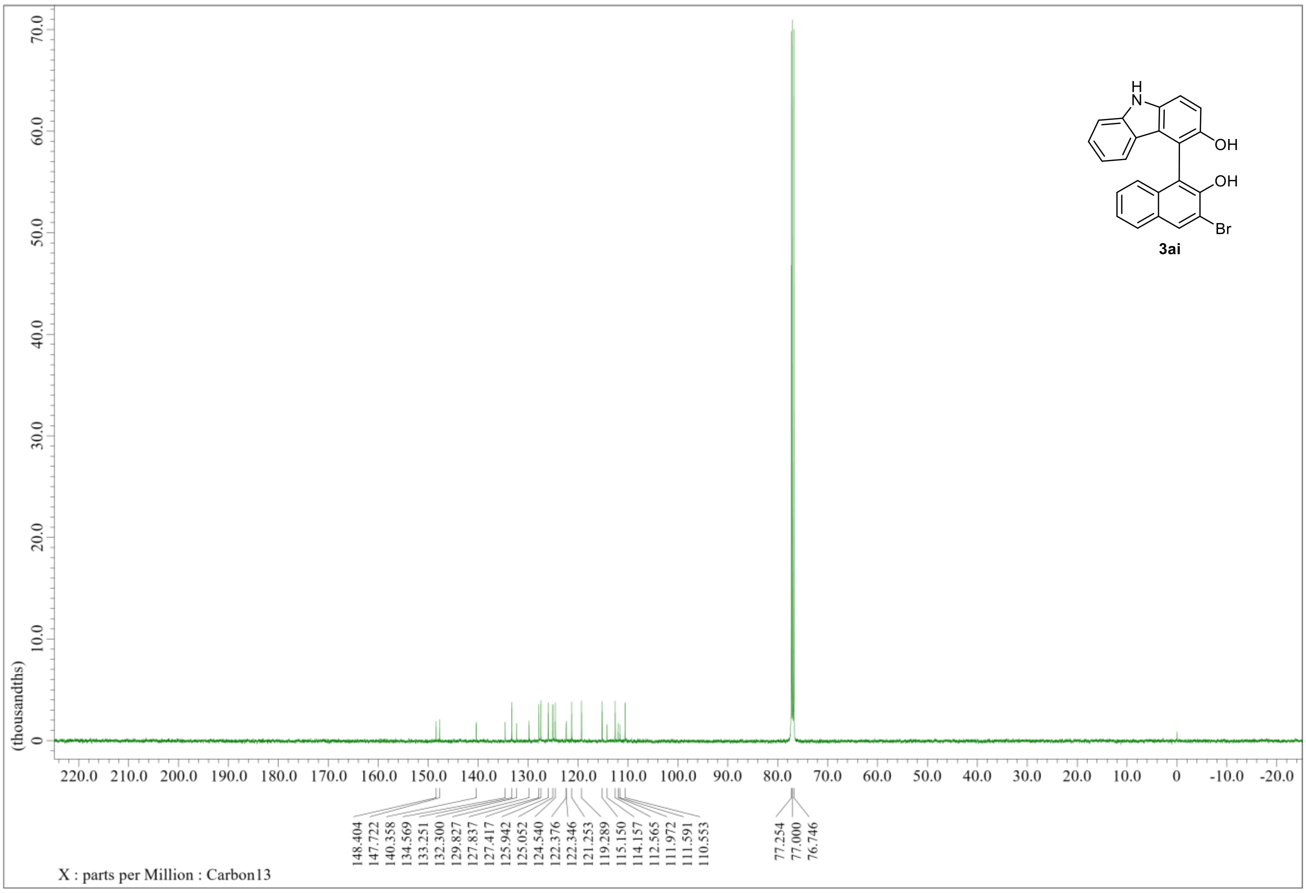
^{1}H NMR spectrum (500 MHz, acetone-d_6) of **3ah**



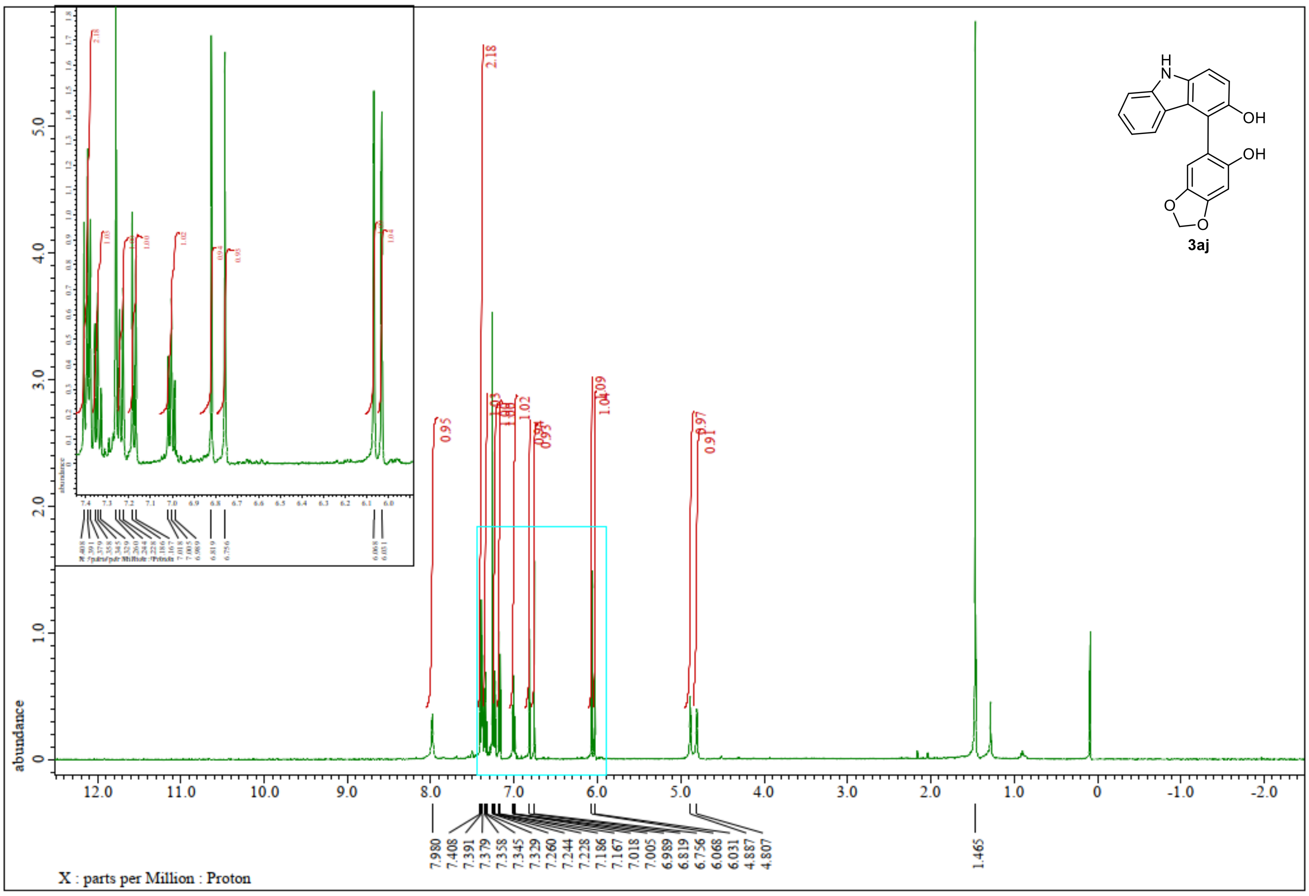
^{13}C NMR spectrum (125 MHz, acetone-d_6) of **3ah**



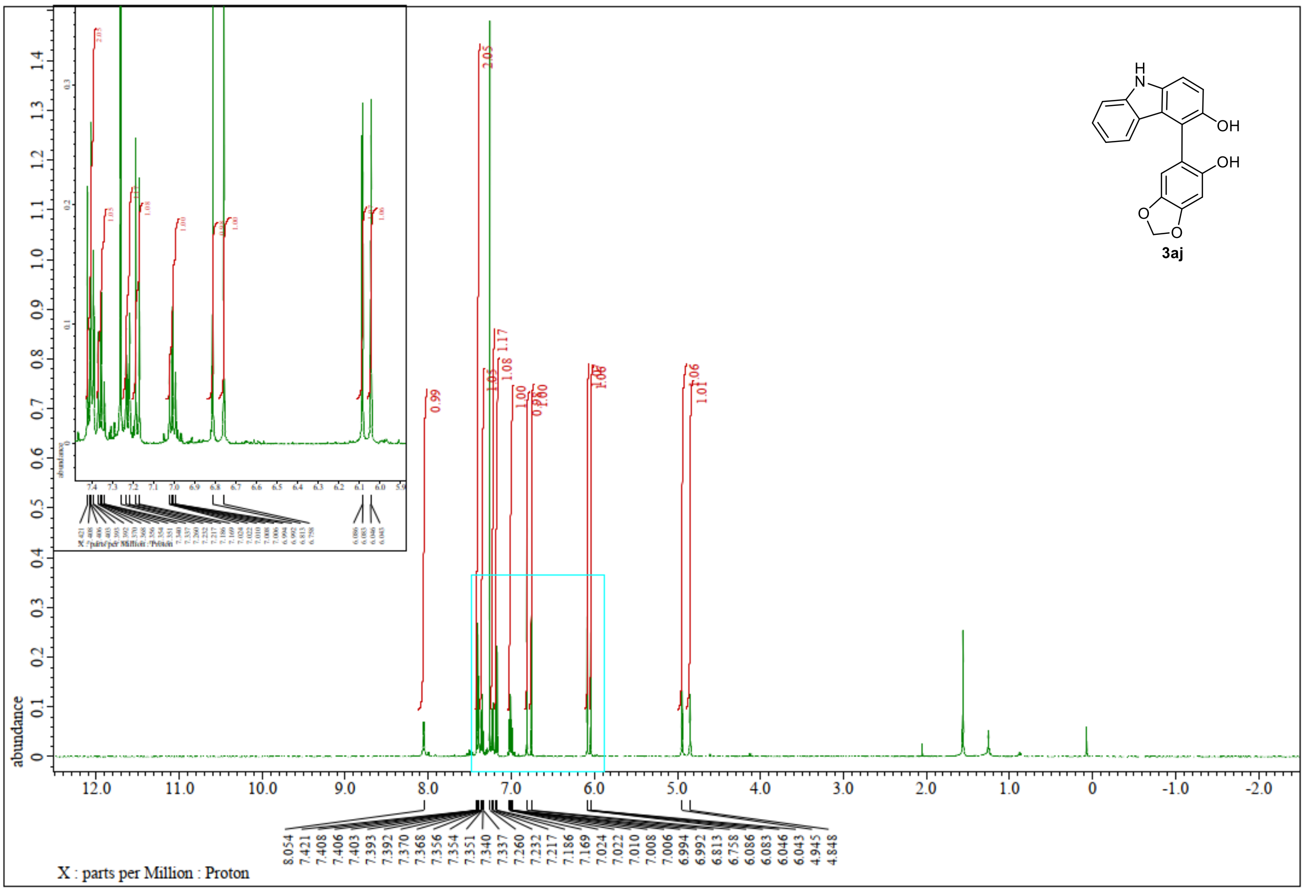
¹H NMR spectrum (500 MHz, $CDCl_3$) of **3ai**



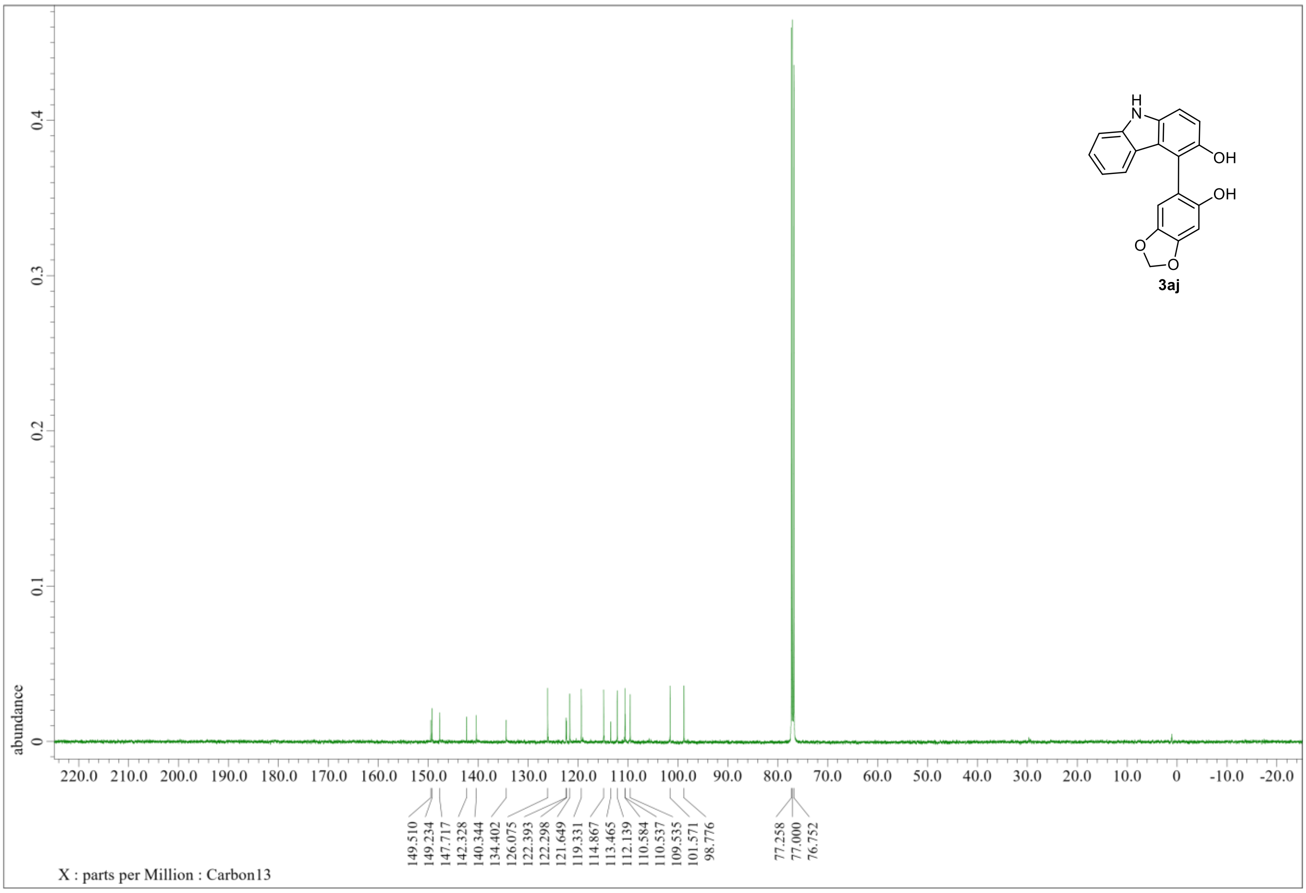
¹³C NMR spectrum (125 MHz, $CDCl_3$) of **3ai**



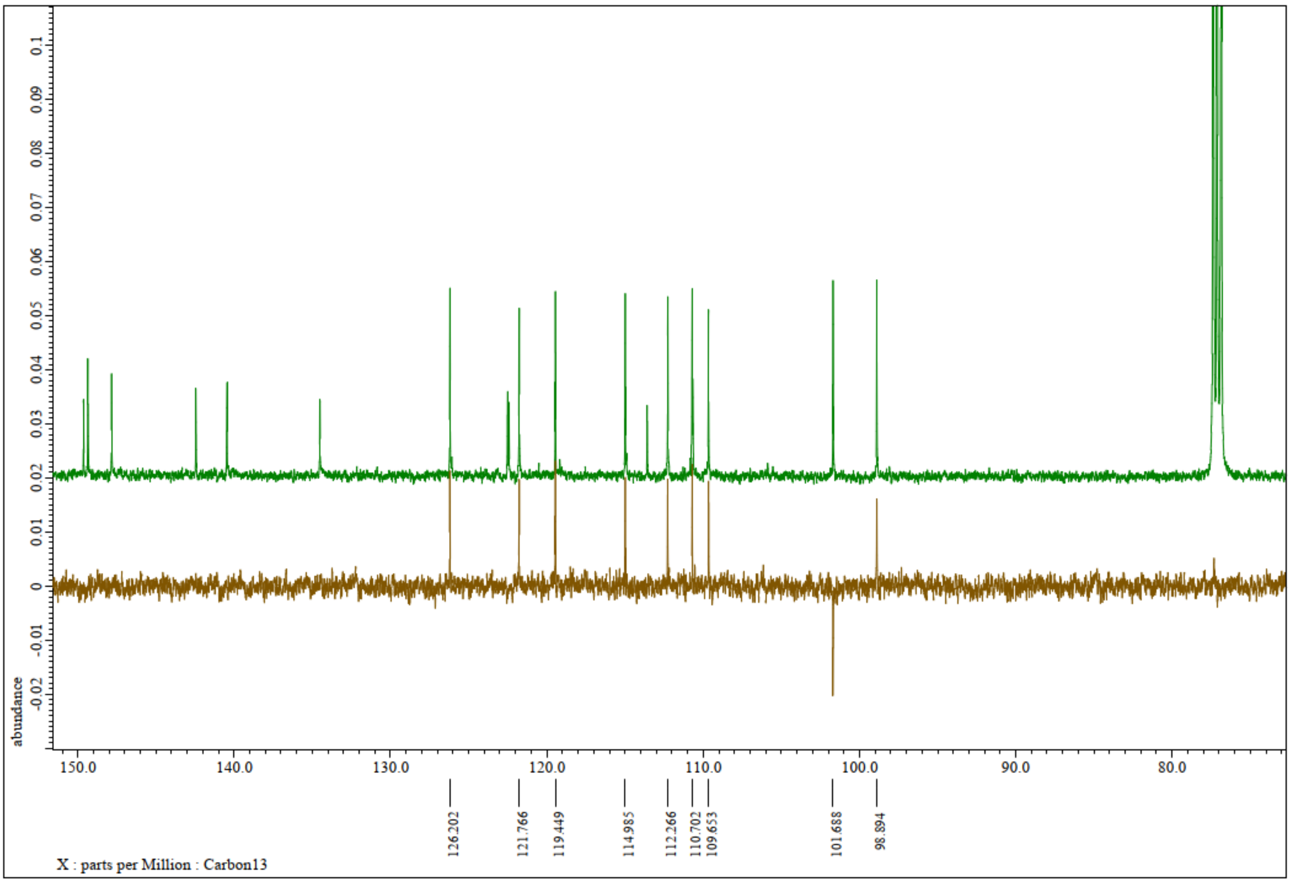
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3aj** at 60°C.



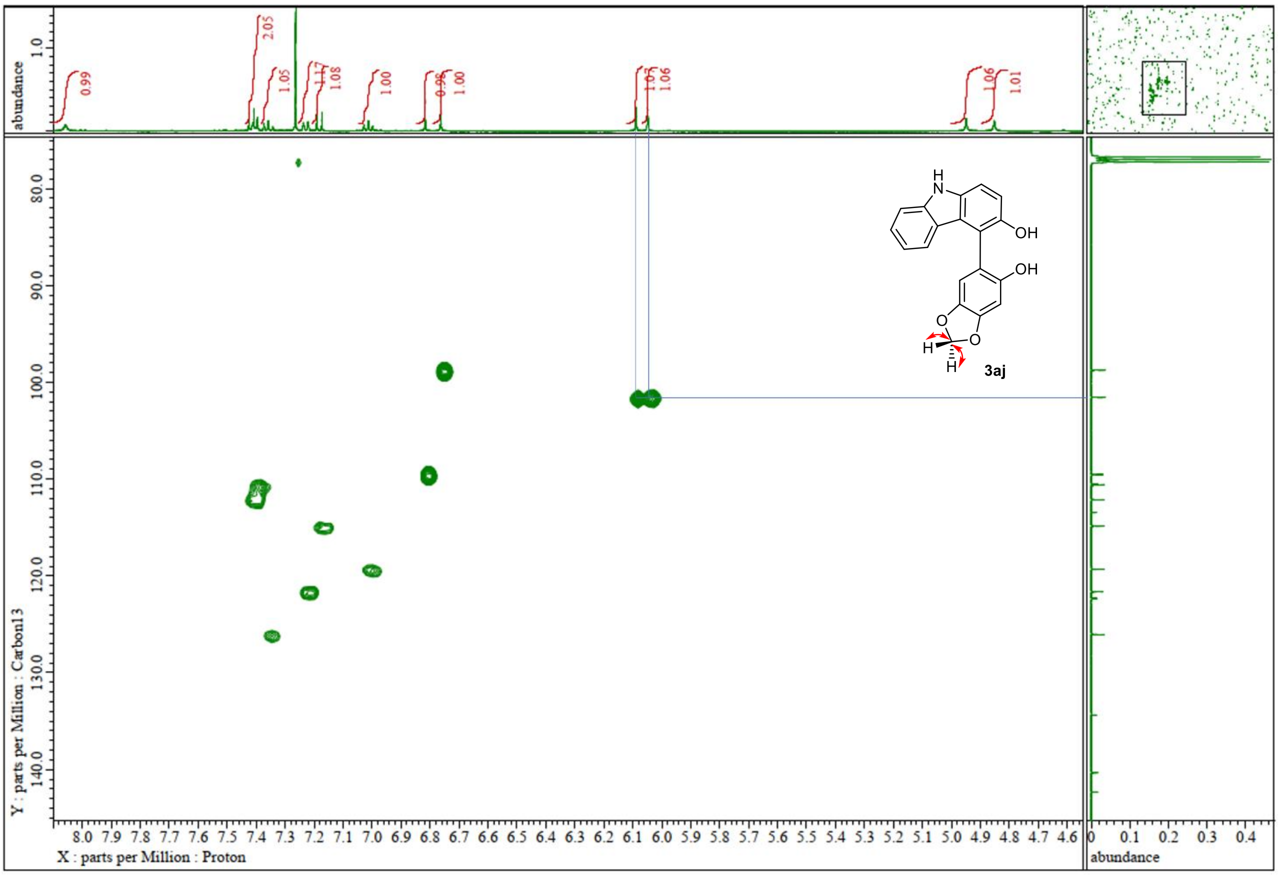
^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3aj** at 20°C.



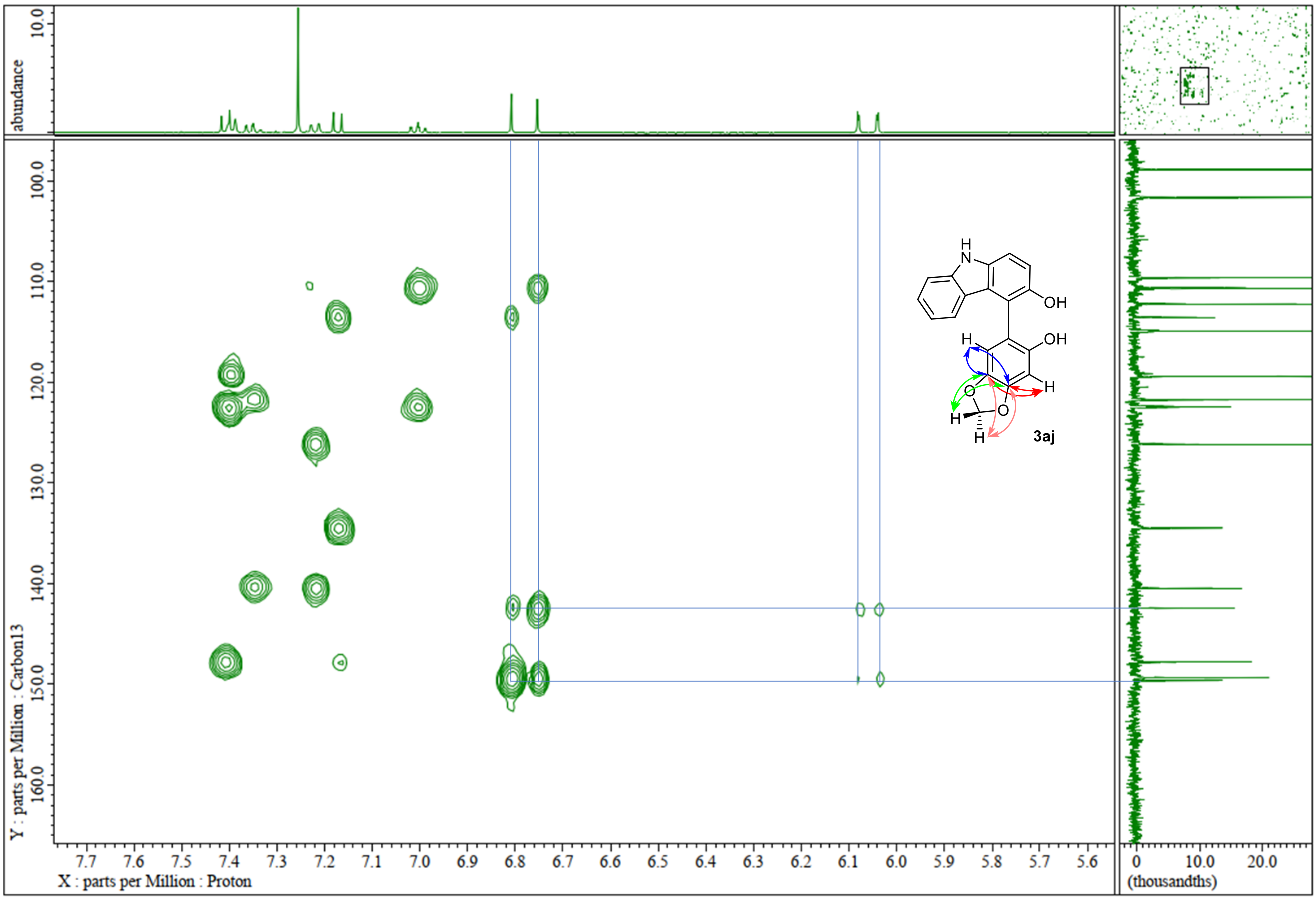
^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3aj**



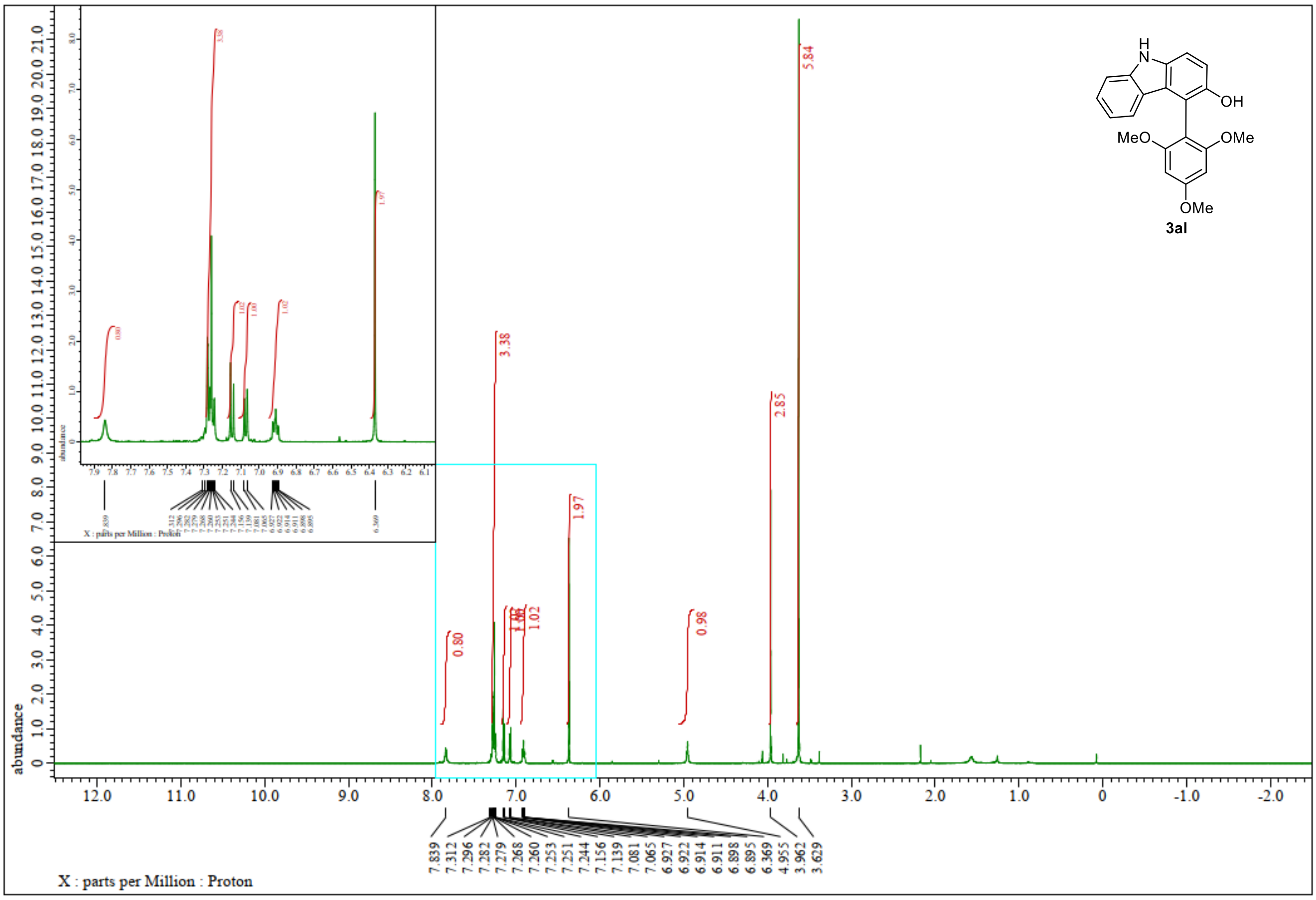
^{13}C NMR and DEPT135 spectrum (125 MHz, CDCl$_3$) of **3aj**



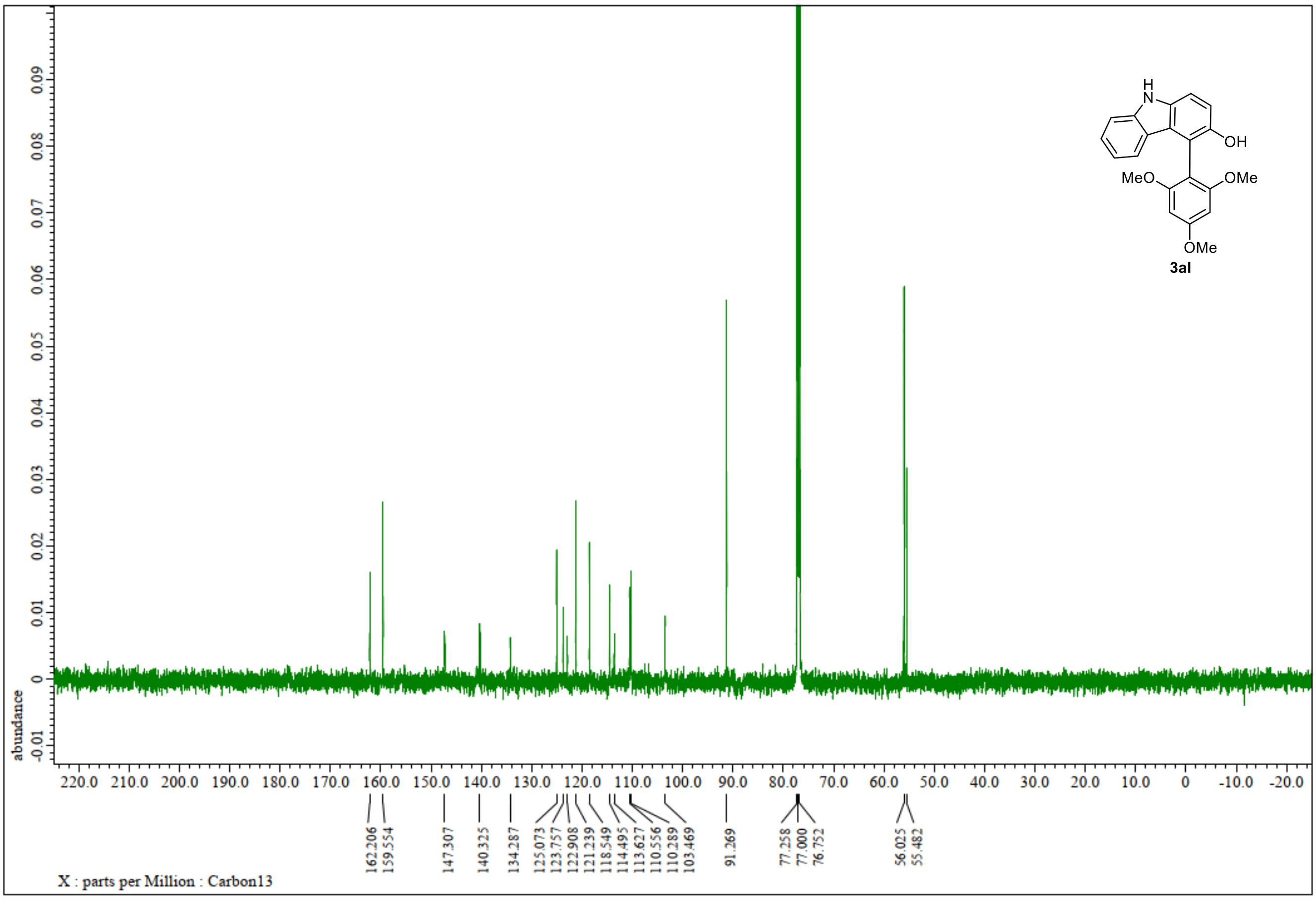
HMQC spectrum (CDCl3) of **3aj**



HMBC spectrum (CDCl3) of **3aj**



^{1}H NMR spectrum (500 MHz, CDCl$_3$) of **3aj**



^{13}C NMR spectrum (125 MHz, CDCl$_3$) of **3aj**