Highly efficient and sustainable HT@NC/Pd catalysts for Suzuki coupling and their application in Elacestrant synthesis

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1. General Information

Materials

The starting material is commercially available and can be used without further purification, except for the solvent. Aluminum chloride hexahydrate ($AlCl_3 \cdot 6H_2O$) and magnesium chloride ($MgCl_2$) were provided by Shanghai Darui Fine Chemical Co., LTD. Glucosamine was from Shanghai Darui Fine Chemical Co., LTD. (Shanghai, China). Palladium chloride ($PdCl_2$, 59.5%) was supplied by J&K Scientific Co. LTD. Other materials were analytical-grade and used as received.

Characterization

Transmission electron microscopy (SEM) images were obtained from a FEI T20 microscope. X-ray diffraction (XRD) measurements were performed at room temperature by using a Shimadzu XRD-6000 spectrometer (Japan). The magnetic properties of the nanoparticles were determined using a vibrating sample magnetometer (Lake Shore 7304, USA). X-ray photoelectron spectrographs (XPSs) were collected with an Axis Ultra DLD electron spectrometer (Kratos, UK) with the C1s=284.8 eV signal as the internal standard. ^{1}H and ^{13}C NMR spectra were measured with a Bruker Advance 400 spectrometer by using $CDCl_3$ or DMSO-*d6* as solvents and TMS as the internal standard.

2. Experimental Section

Preparation of HT nanoparticles

The HT nanoparticles were prepared by the coprecipitation method [1-3]. For this, 2.41 g of $AlCl_3 \cdot 6H_2O$ and 3.81 g of $MgCl_2$ were dissolved in 100 mL of deionized water with a magnetic stirrer, and the resulting solution was used as a salt solution. At the same time, 16g of NaOH and 15g of Na_2CO_3 were dissolved in 100ml of deionized water with a magnetic stirrer, and the resulting solution was used as a precipitating agent. After the

solution was completely dissolved, a three-neck flask containing the salt solution was placed in an electric thermostatic water bath at 75 ℃, and the precipitating agent was added to the salt solution with an automatic dropper at the rate of 30 drops per minute to maintain a pH of about 9. After titration, the temperature of the water bath was kept at 75 ℃ and stirred for 12 h, and the resulting product was filtered and washed in deionized water to a pH of about 7, dried at 70 ℃ for 24 h. Then, the sample was ground into a powder and calcined at 450 ℃ for 4h, then hydrated for 2h.

Preparation of HT/Pd nanoparticles

The HT/Pd was synthesized according to the literature procedure [4]. We weighed 0.95g of hydrotalcite into a 50 mL round-bottomed flask, added 40 mL ethanol, and ran an ultrasonic process for 30min. We then weighed 50 mg of $PdCl_2$, added it into the ethanol solution of the hydrotalcite, and performed an ultrasound for 1h. After the ultrasound was completed, 85 mg of $NaBH_4$ was added to the mixture, which was stirred at 60 °C for 2 h. After the reaction was completed, the black precipitated product was pumped, filtered and collected, washed with deionized water several times, then washed with ethanol several times, and finally dried in a vacuum at 70 °C for 24 h.

Preparation of HT@NC particles

The HT@NC was synthesized according to the literature procedure [5]. First, 0.8 g of HT nanoparticles was dispersed in 30 mL of water containing 0.8 g of glucosamine hydrochloride, and an ultrasound was performed for 30 min. The pH was adjusted to 8-9 with ammonia water, and then, the mixture was transferred to a stainless steel high-pressure reactor lined with tetrafluoroethylene and heated at 200 °C for 12 h. The solids were collected by filtration, washed with water several times, then washed with ethanol several times, and finally dried in a vacuum at 60 ℃ for 24 h.

Preparation of HT@NC/Pd catalyst

The HT@NC/Pd was prepared by a previously published method [6]. Here, 0.95g of HT @NC carrier was added to 40 mL of ethanol, and an ultrasound was performed for 30 mi n. Then, 50 mg of palladium chloride was added to the black suspension, and the ultrasou nd was continued for 1 h. We added 85 mg of $NaBH_4$ and stirred vigorously at 60 °C for 2 h. After the reaction was completed, the black precipitated product was collected by filtra tion, washed with ethanol several times, and finally dried in a vacuum at 60 °C for 24 h.

General procedure for the Suzuki coupling reactions

Aryl halides (1.0 mmol), aryl boronic acid (1.5 mmol), KOH (1.5 mmol), HT@NC/Pd (10 mg), and 3 mL of H_2O were put into a reaction flask and stirred at 90 ˚C under air. After the reaction was complete, the reaction was cooled to room temperature. Then, the mixture was extracted with ethyl acetate dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography on a silica gel using petroleum/ethyl acetate 100:1 to obtain the product.

General procedure for catalyst recovery

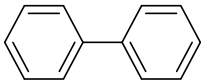
Iodobenzene (1.0 mmol), phenyl boronic acid (1.5 mmol), and HT@NC/Pd (10 mg) were mixed with H_2O (3.0 mL). We stirred the mixture at room temperature and under air. After the reaction was completed, the catalyst was separated by filtration, washed with water (3×2 mL) and ethanol (3×2 mL), and vacuum-dried, followed by the next round of use.

General procedure for the gram-scale synthesis of Elacestrant intermediate

The **ELA-7** (5.0 mmol), **ELC-7** (7.5 mmol), KOH (7.5 mmol), HT@NC/Pd (50 mg), 10 mL of ethanol, and 10 mL of H_2O were put into a reaction flask and stirred at 90 ˚C under air. After the reaction was complete, the mixture was cooled to room temperature. Then, the mixture was extracted with ethyl acetate, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography on a silica gel to obtain the Elacestrant intermediate **EL-1** 1.9 g (95%).

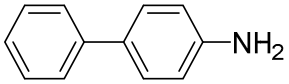
3. Characterization of Products [7].

Biphenyl 3a:



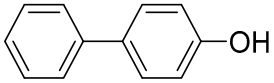
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 4H), 7.51 – 7.45 (m, 4H), 7.41 – 7.35 (m, 2H).

Biphenyl-4-amine 3b:



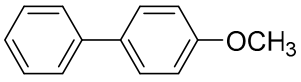
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.5 Hz, 1H), 7.56 (d, *J* = 1.3 Hz, 1H), 7.46 (s, 1H), 7.44 (d, *J* = 3.3 Hz, 2H), 7.41 (s, 1H), 7.32 – 7.28 (m, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 3.71 (s, 2H).

Biphenyl-4-ol 3c:



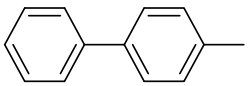
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.54 (d, *J* = 9.3 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 2H).

4-Methoxybiphenyl 3d:



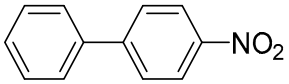
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 4H), 7.46 – 7.41 (m, 2H), 7.35 – 7.30 (m, 1H), 7.02 – 6.98 (m, 2H), 3.86 (s, 3H).

4-Methylbiphenyl 3e:



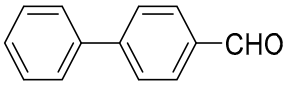
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.55 – 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.38 – 7.33 (m, 1H), 7.31 – 7.26 (m, 2H), 2.43 (s, 3H).

4-Nitrobiphenyl 3f:



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.66 – 7.63 (m, 2H), 7.54 – 7.50 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 1H).

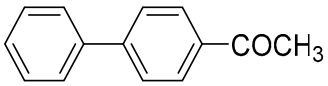
4-Phenylbenzaldehyde 3g:



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* =

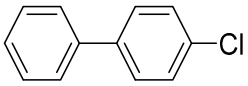
7.2 Hz, 1H).

4-Acetylbiphenyl 3h:



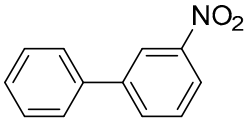
^{1}H NMR (400 MHz**,** $CDCl_3$**)** δ 8.04 (d, J = 3.9 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 3.9 Hz, 1H), 7.67 (d, J = 3.9 Hz, 1H), 7.63 (d, J = 2.2 Hz, 1H), 7.61 (d, J = 2.9 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.42 – 7.37 (m, 1H), 2.63 (s, 3H).

4-Chlorobiphenyl 3i:



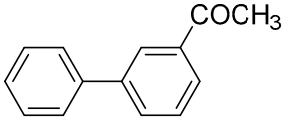
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 4H), 7.49 – 7.34 (m, 5H).

3-Nitrobiphenyl 3j:



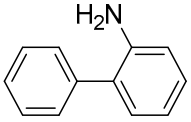
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (t, *J* = 2.0 Hz, 1H), 8.19 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.90 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.63 – 7.59 (m, 3H), 7.51 – 7.46 (m, 2H), 7.45 – 7.40 (m, 1H).

3-Acetylbiphenyl 3k:



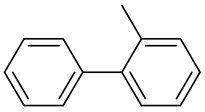
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 7.1 Hz, 1H), 2.62 (s, 3H).

2-Aminebiphenyl 3l:



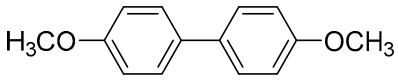
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (q, *J* = 7.2 Hz, 4H), 7.36 (t, *J* = 6.8 Hz, 1H), 7.16 (dd, *J* = 18.0, 7.7 Hz, 2H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.66 (s, 2H).

2-Methylbiphenyl 3m:



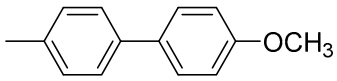
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.44 – 7.37 (m, 3H), 7.36 – 7.29 (m, 4H), 2.35 (s, 3H).

4,4'-Dimethoxybiphenyl 3n:



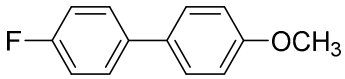
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.6 Hz, 4H), 6.93 (d, *J* = 8.6 Hz, 4H), 3.82 (s, 6H).

1-Methoxy-4-(4-methylphenyl)benzene 3o:



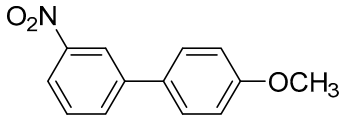
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 7.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 2.36 (s, 3H).

1-Fluoro-4-(4-methylphenyl)benzene 3p:



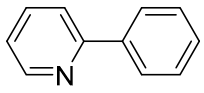
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 4H), 7.14 – 7.08 (m, 2H), 7.00 – 6.96 (m, 2H), 3.86 (s, 3H).

1-(4-Methoxyphenyl)-3-nitrobenzene 3q:



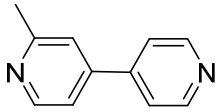
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 3H), 7.04 (d, *J* = 8.1 Hz, 2H), 3.89 (s, 3H).

2-Phenylpyridine 3r:



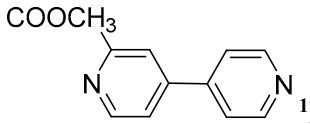
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 6.7 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 5.7 Hz, 1H).

3-Phenylquinoline 3s:



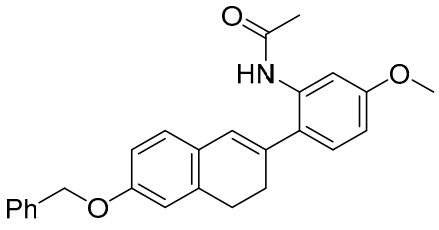
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 6.2 Hz, 2H), 8.63 (t, J = 5.8 Hz, 1H), 7.54 (d, J = 6.3 Hz, 2H), 7.42 (s, 1H), 7.37 – 7.29 (m, 1H), 2.68 (s, 3H).

3-Phenylquinoline 3t:



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 5.0 Hz, 1H), 8.82 (d, J = 6.1 Hz, 2H), 8.44 (d, J = 1.6 Hz, 1H), 7.77 (dd, J = 5.1, 1.9 Hz, 1H), 7.64 (d, J = 6.2 Hz, 2H), 4.09 (s, 3H).

Elacestrant intermediate EL-1：

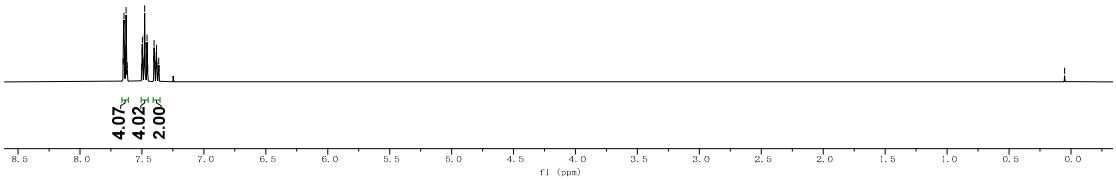


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.55 (s, 1H), 7.45 (dd, *J* = 14.0, 8.4 Hz, 4H), 7.39 (d, *J* = 6.0 Hz, 1H), 7.14 (s, 1H), 7.05 (s, 1H), 6.90 – 6.83 (m, 2H), 6.71 (s, 1H), 6.53 (s, 1H), 5.13 (s, 2H), 3.88 – 3.84 (m, 3H), 2.97 (s, 2H), 2.58 (s, 2H), 2.16 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.24, 159.22, 158.40, 137.02, 136.27, 135.53, 134.47, 128.84, 128.73, 128.67, 128.05, 127.60, 127.52, 127.48, 127.38, 127.29, 125.46, 119.97, 114.77, 112.53, 110.56, 70.12, 55.49, 28.93, 28.76, 24.92.

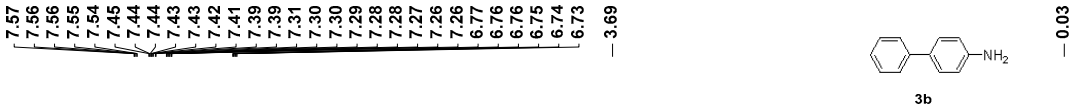
4. ^{1}H and ^{13}C NMR Spectra of The Compounds



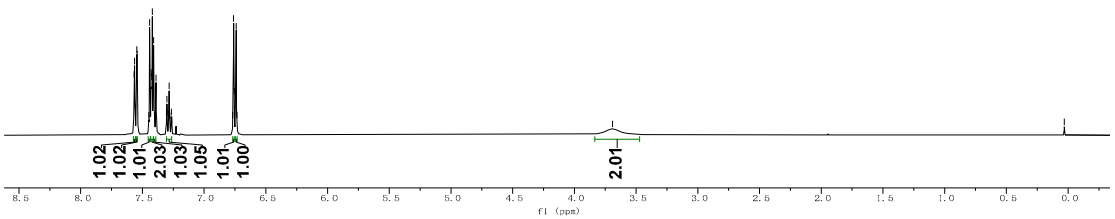
3a



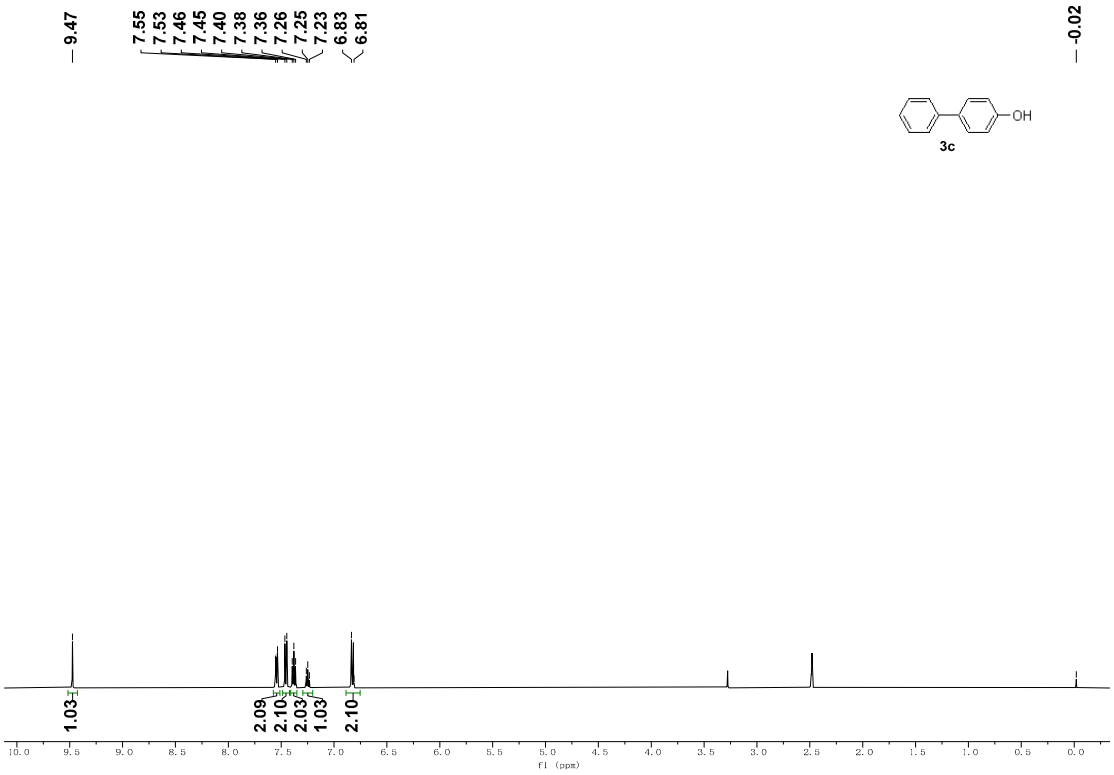
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3a.**



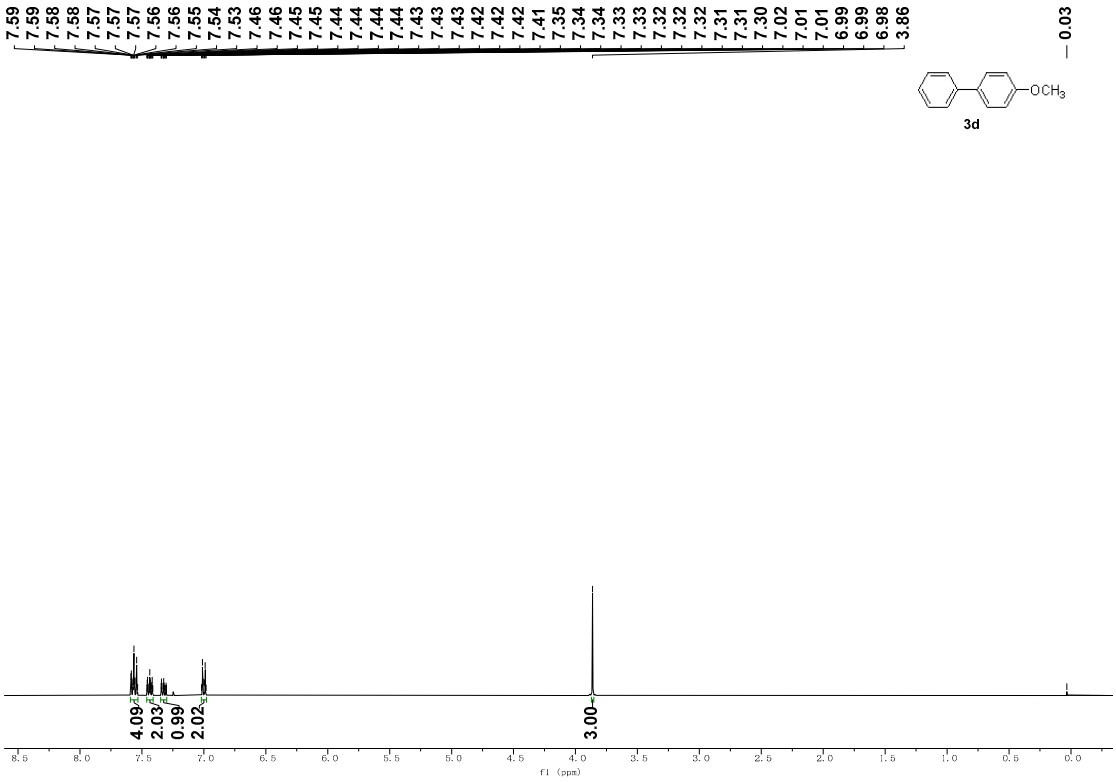
3b



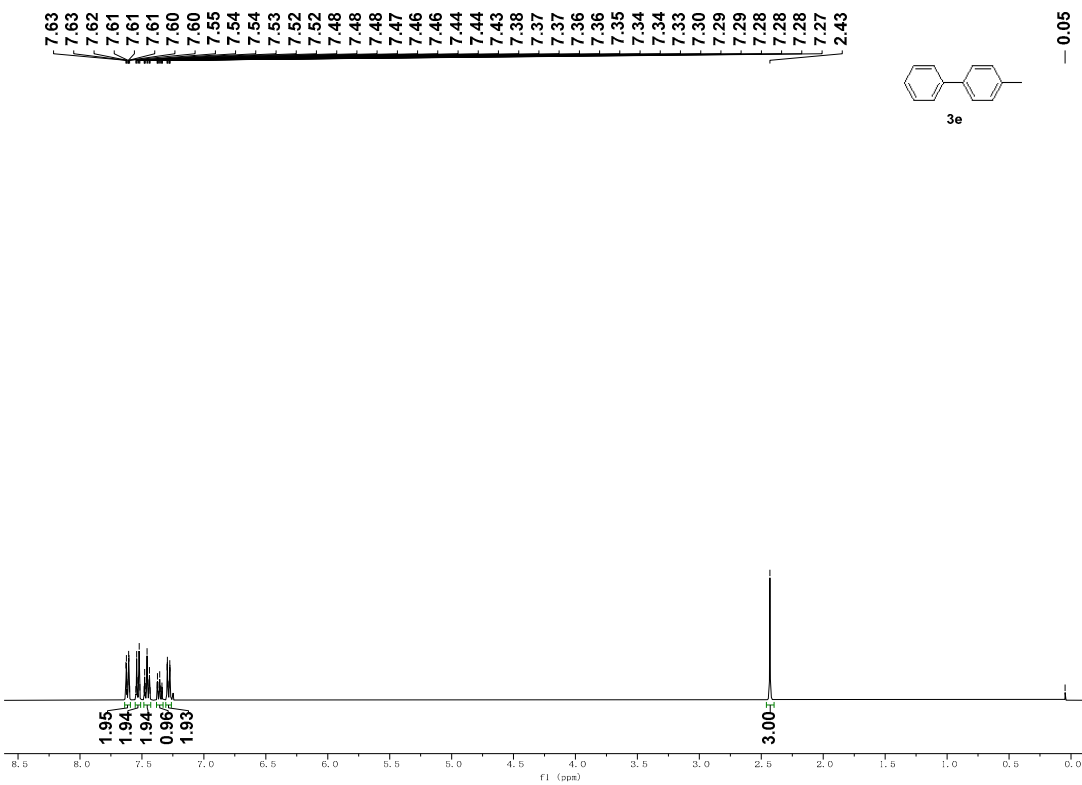
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3b.**



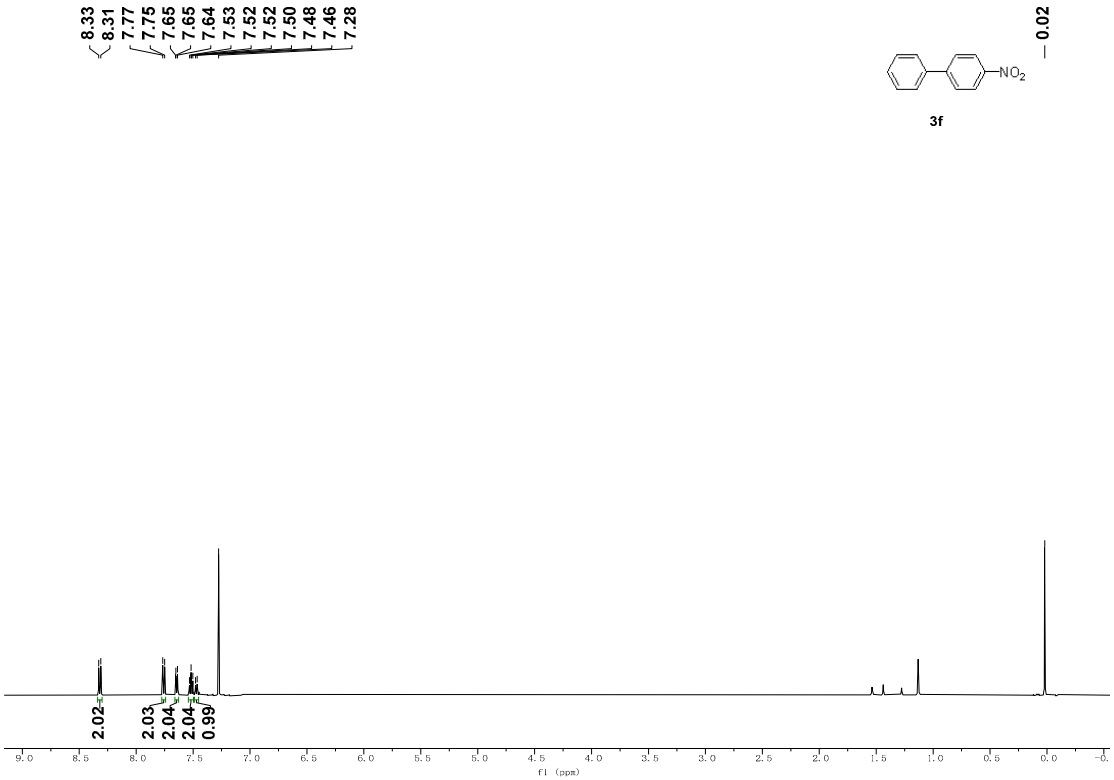
^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **3c.**



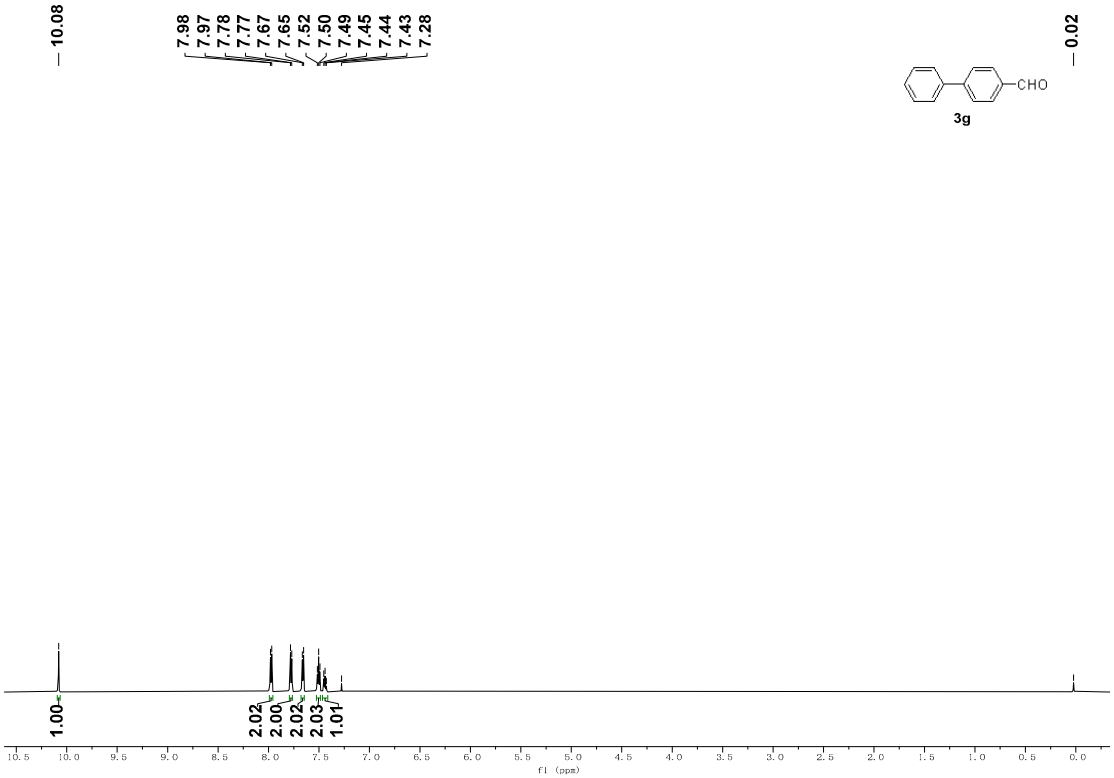
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3d.**



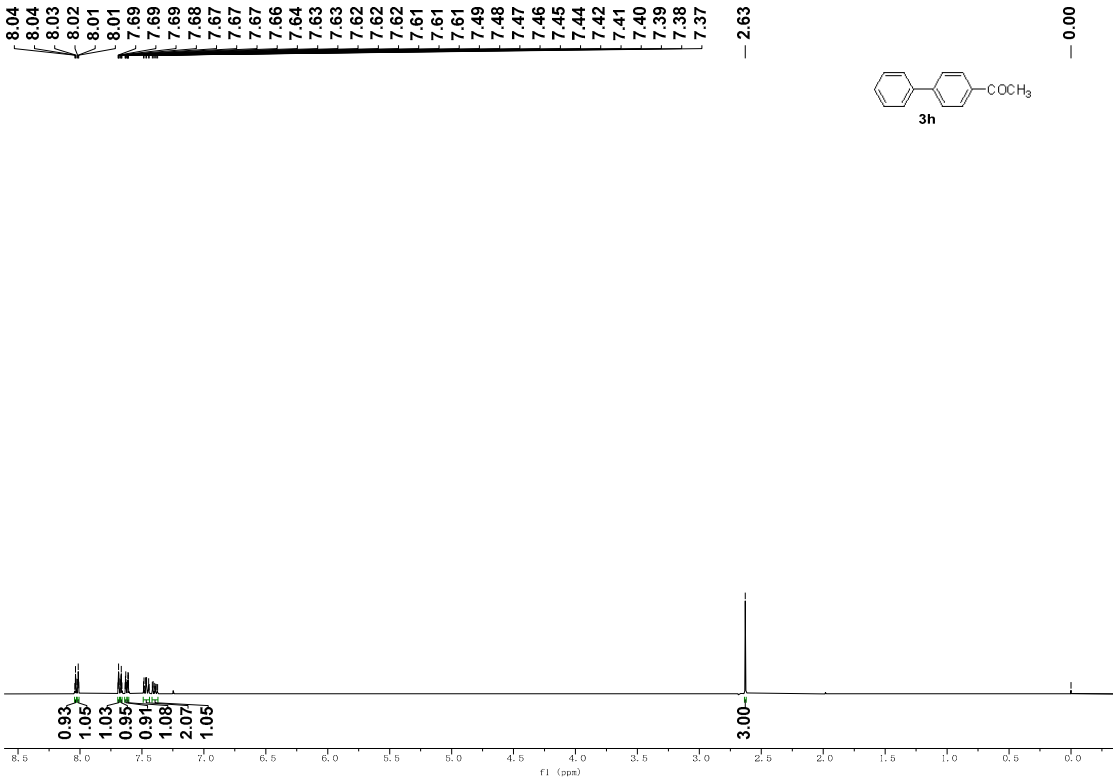
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3e.**



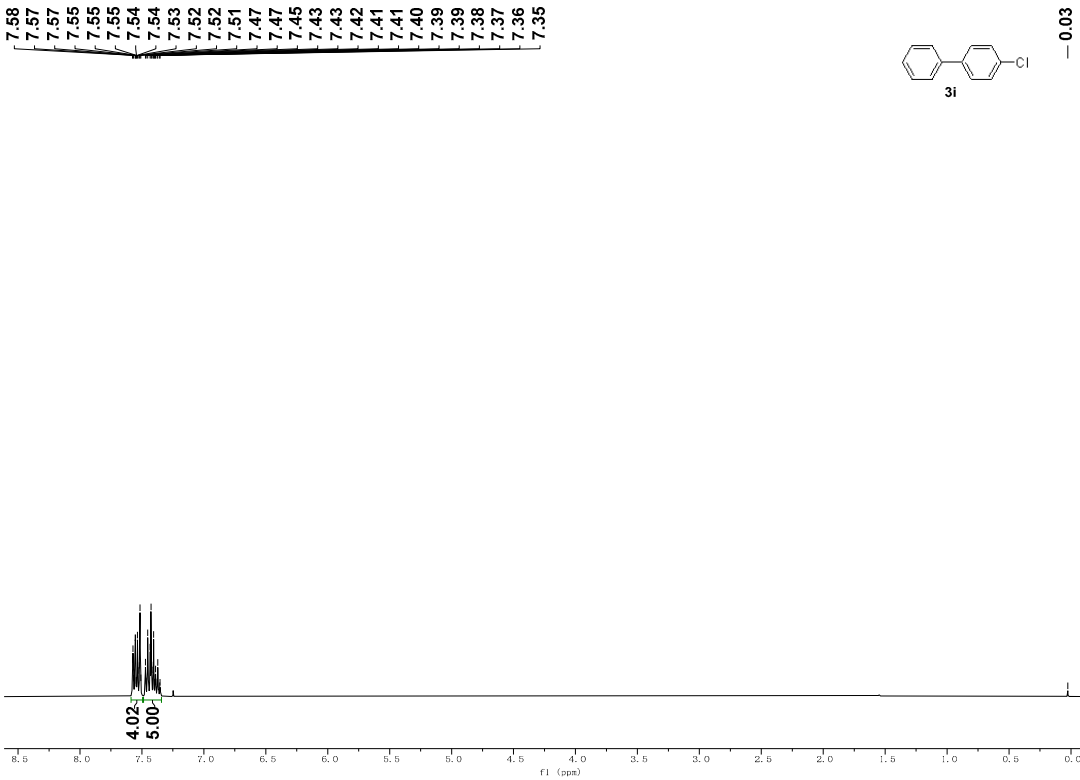
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3f.**



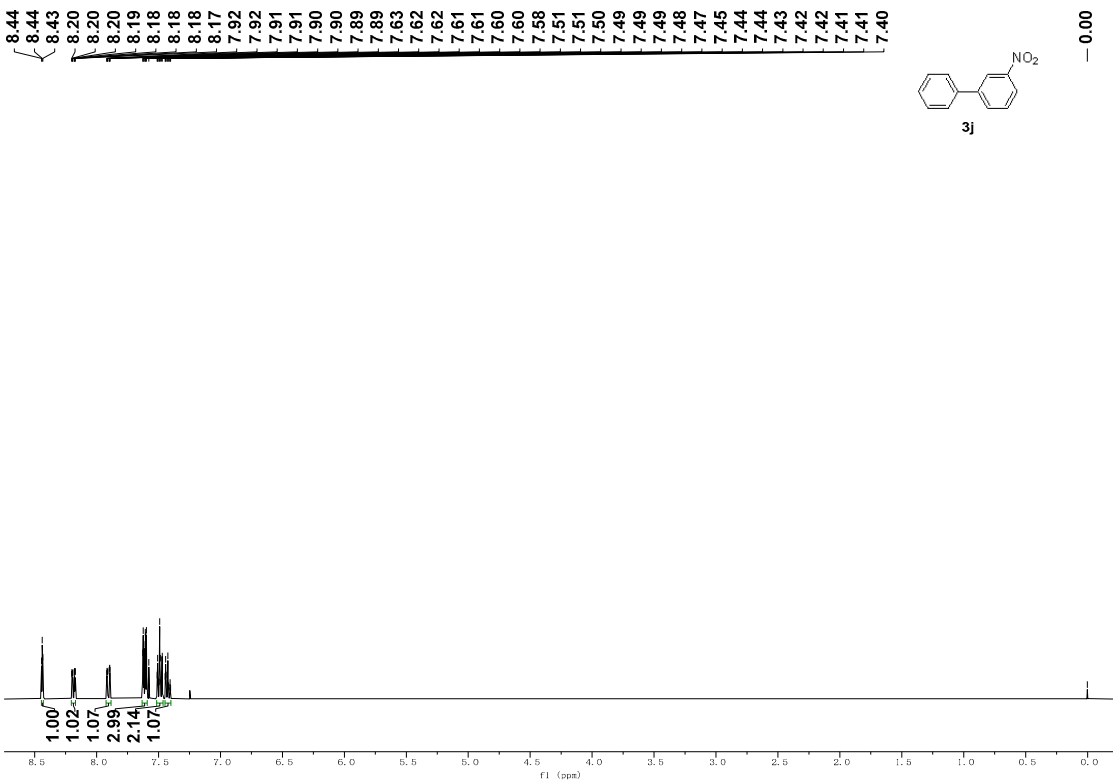
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3g.**



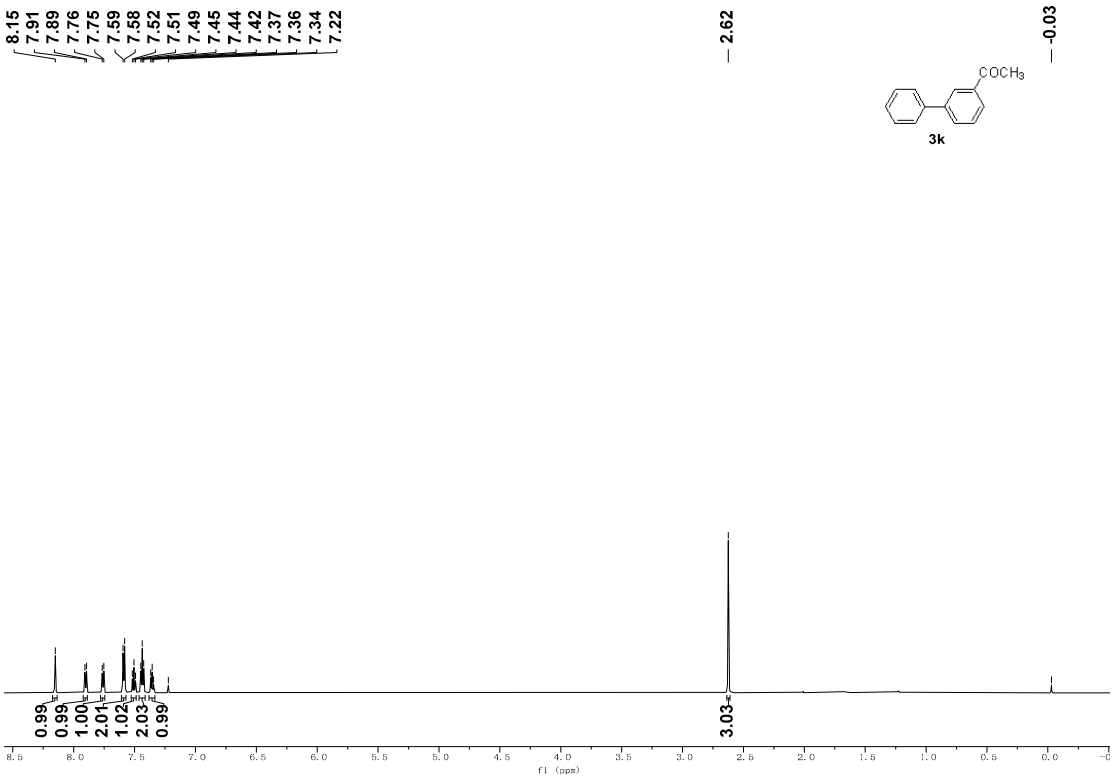
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3h.**



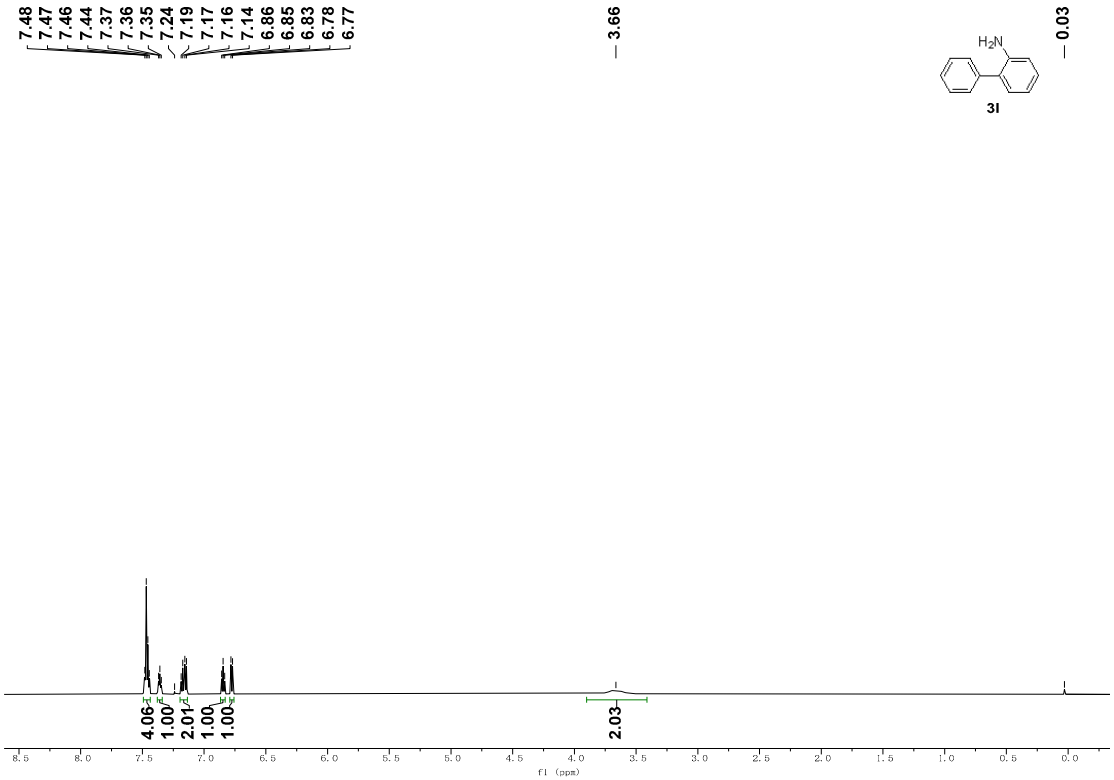
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3i.**



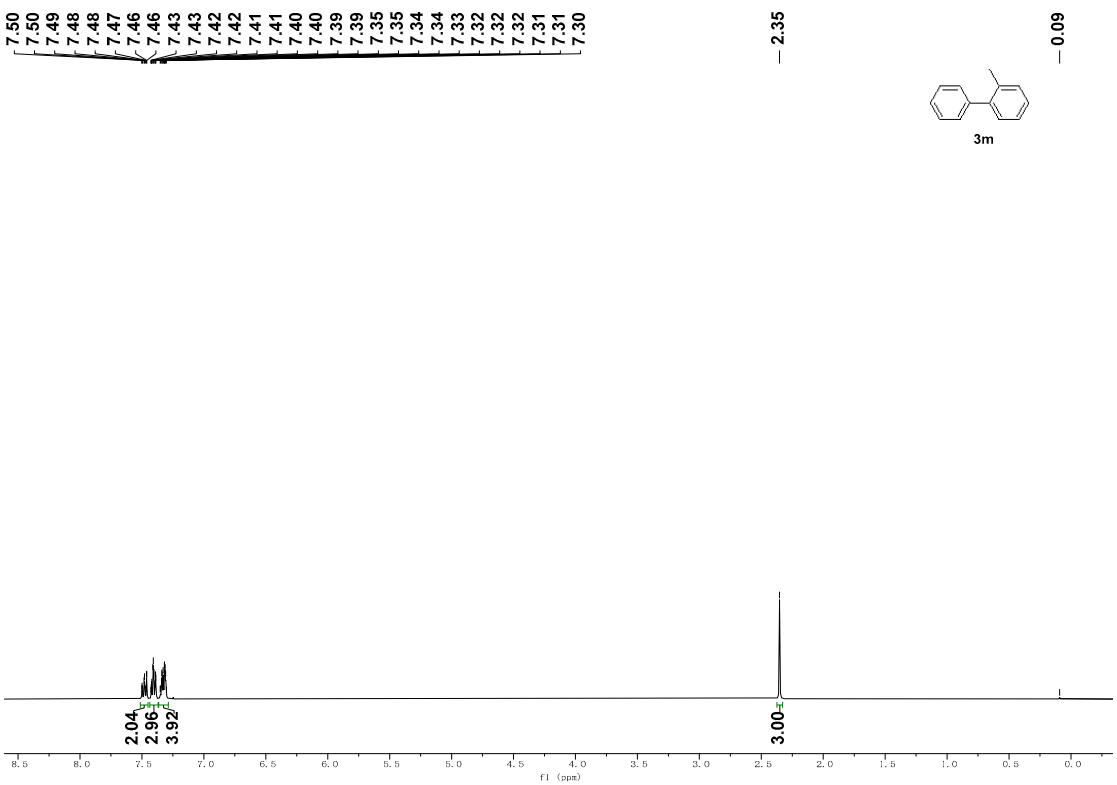
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3j.**



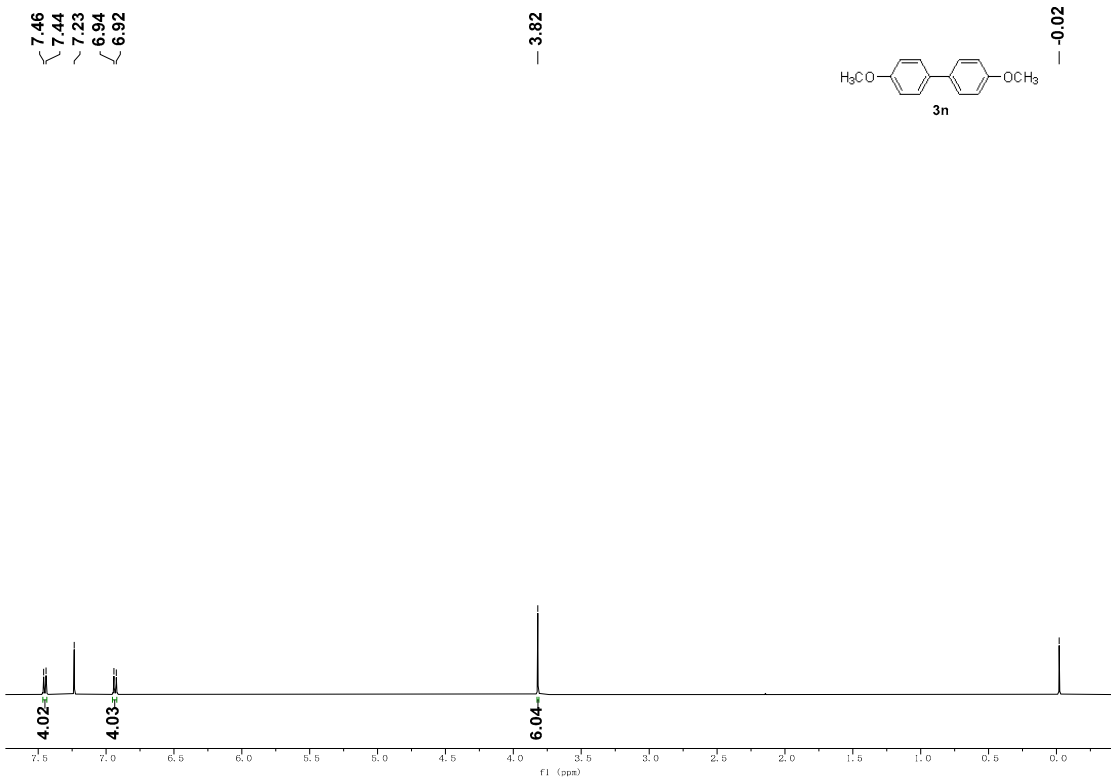
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3k.**



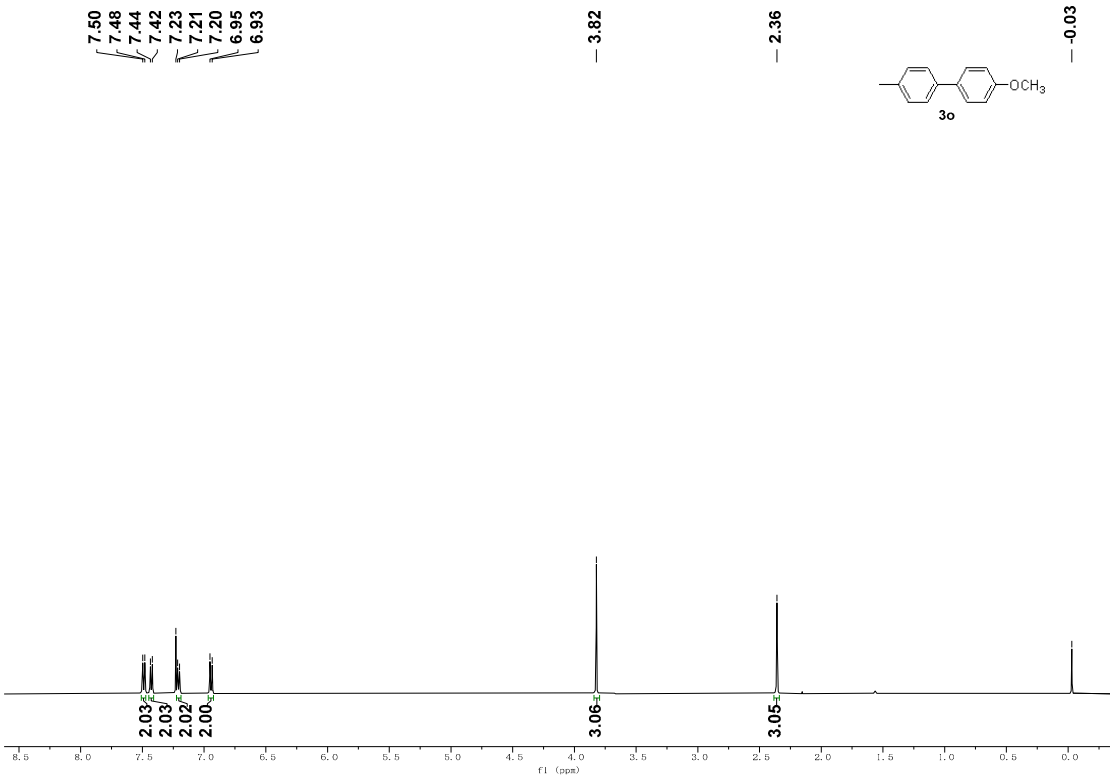
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3l.**



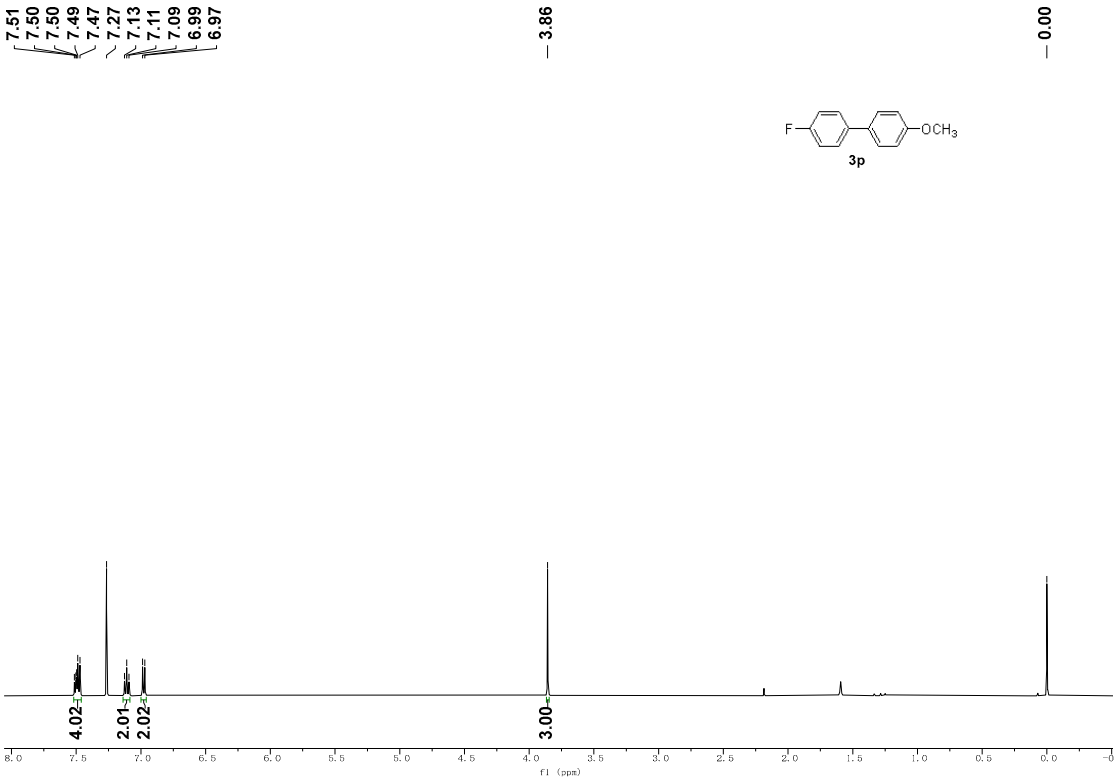
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3m.**



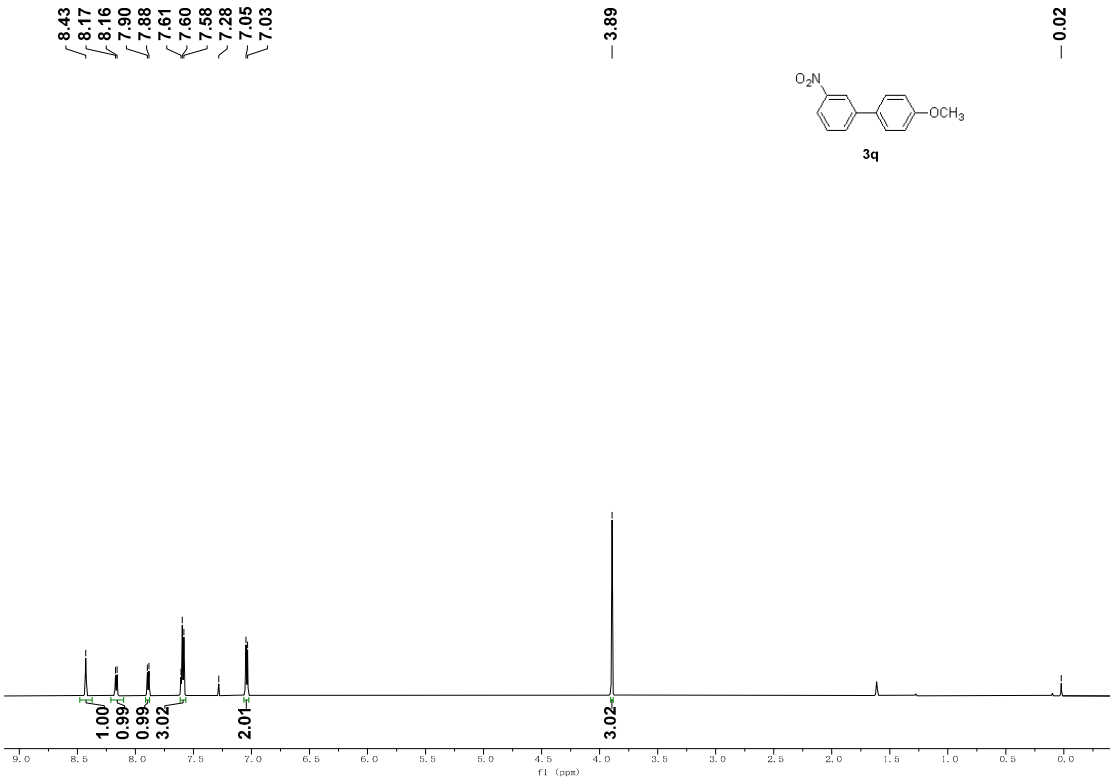
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3n.**



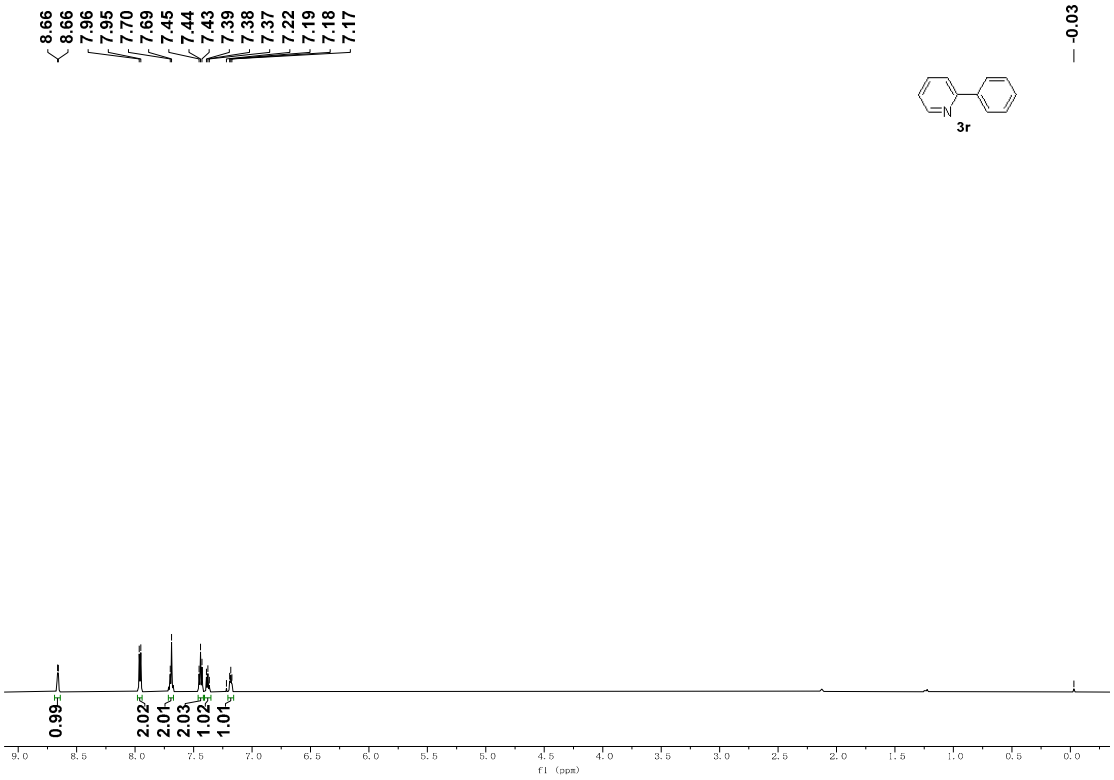
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3o.**



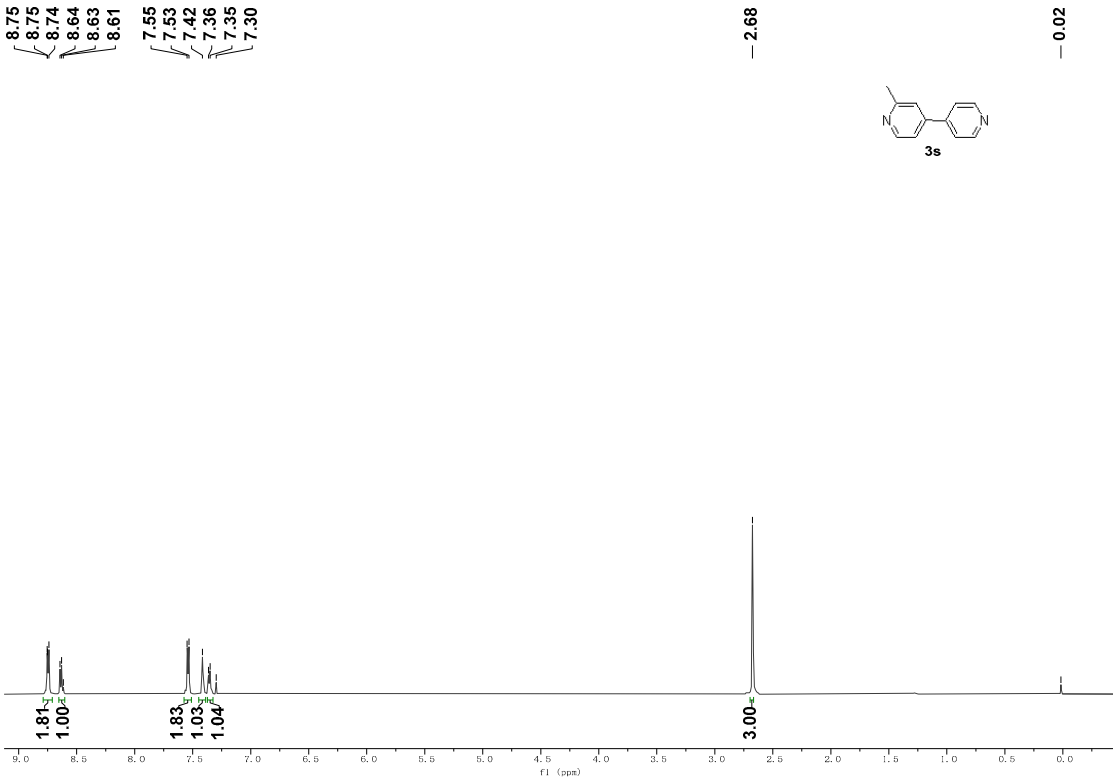
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3p.**



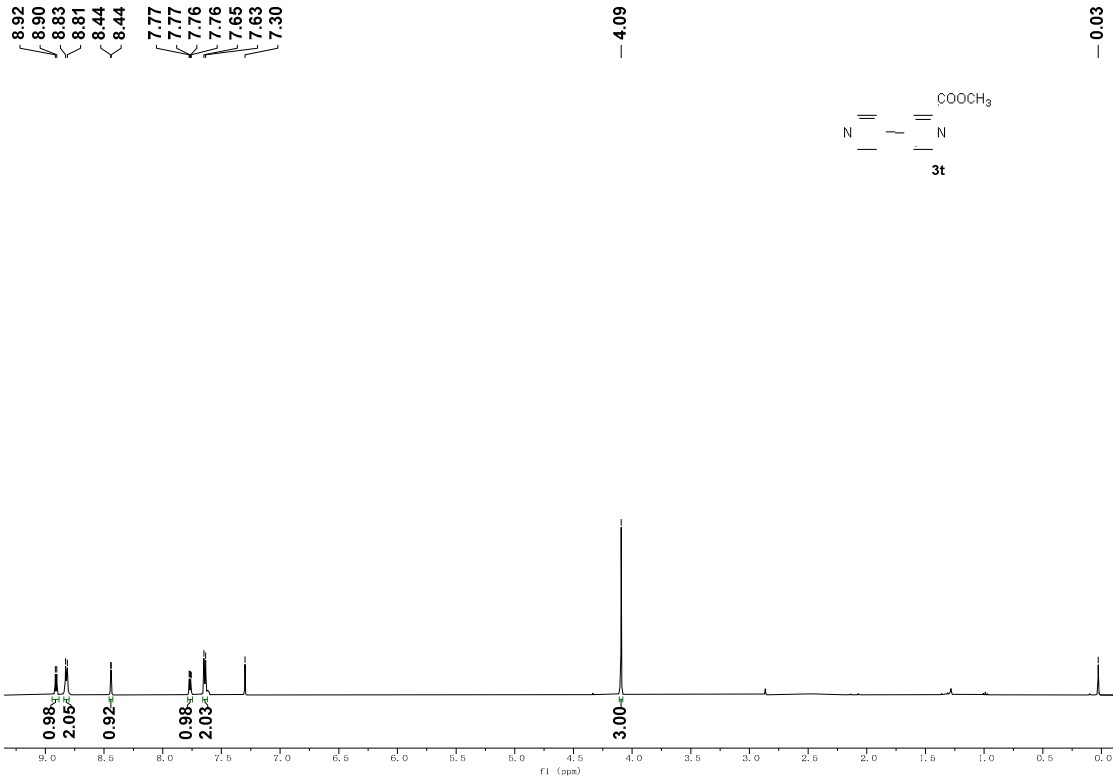
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3q.**



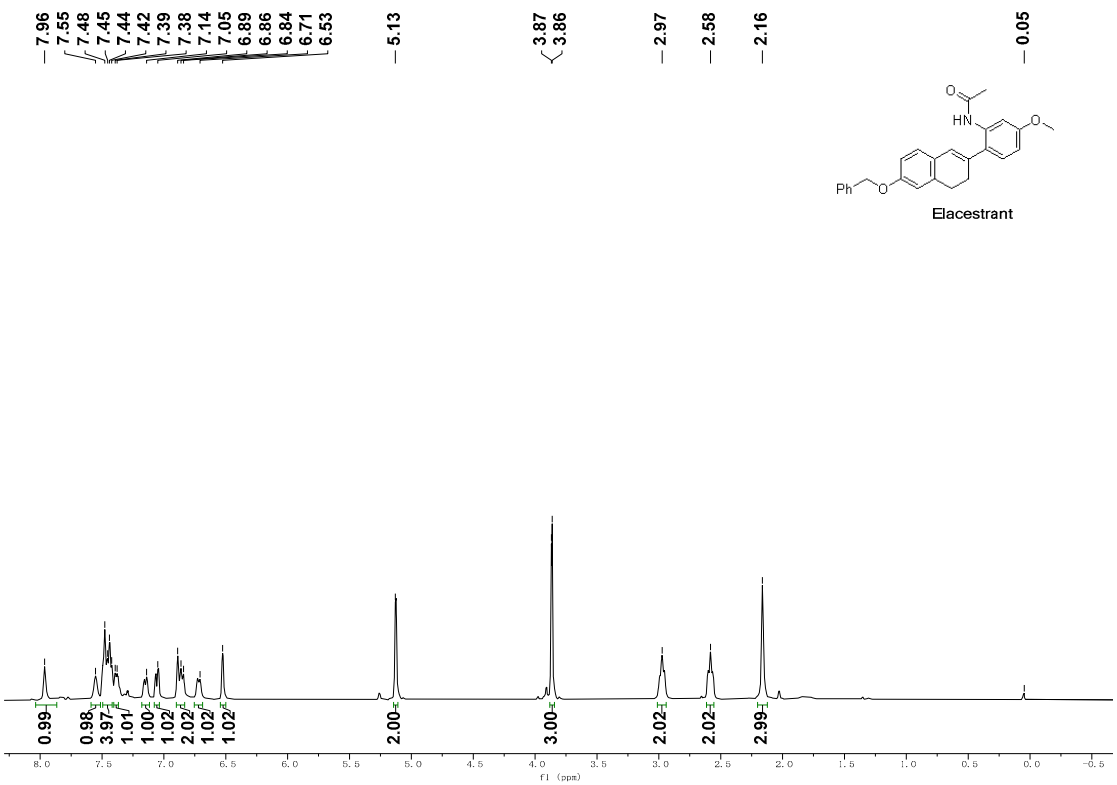
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3r.**



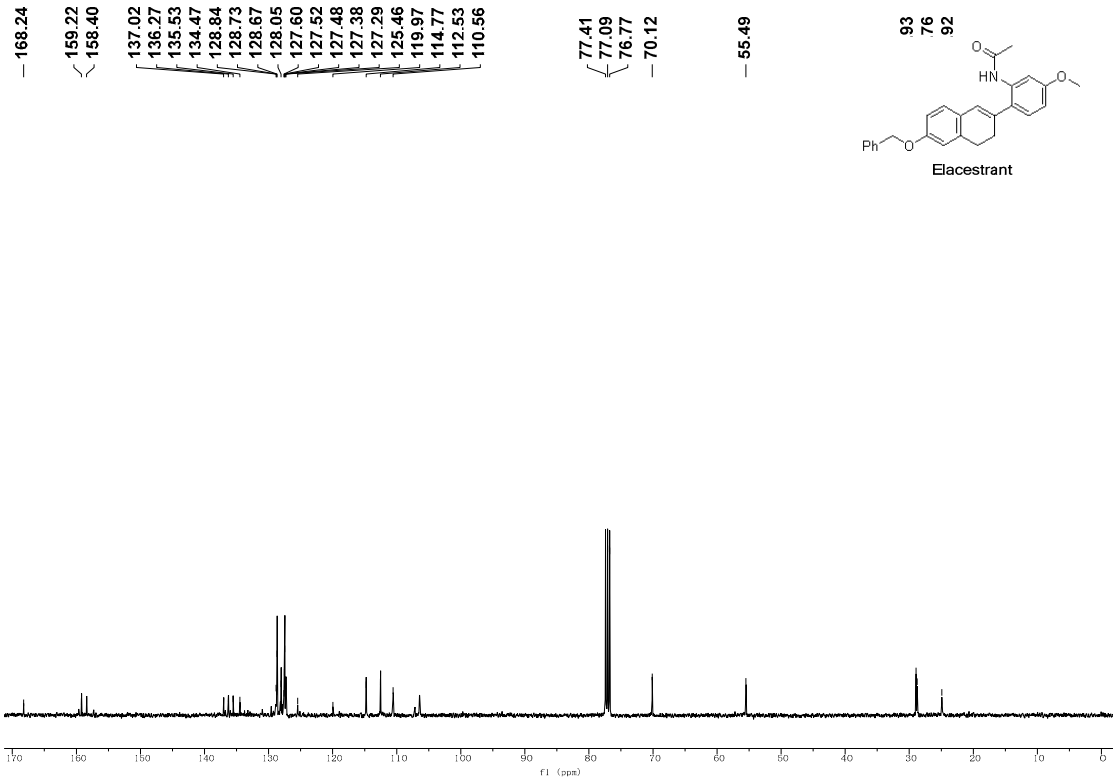
^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3s.**



^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **3t.**



^{1}H NMR (400 MHz, $CDCl_3$) spectra of compound **Elacestrant.**



^{13}C NMR (101 MHz, $CDCl_3$) spectra of compound **Elacestrant.**

5. References

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