

Novel Magnetically-Recyclable, Nitrogen-Doped Fe₃O₄@Pd NPs for Suzuki–Miyaura Coupling and Their Application in the Synthesis of Crizotinib

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1 General Information

Materials

The starting materials were commercially available and were used without further purification except solvents. Ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) was provided by Shanghai Darui Fine Chemicals Co. Ltd. Glucose was obtained from Chinasun Specialty Products Co. Ltd. Sodium acetate anhydrous and ethylene glycol were provided by Shanghai Ling Feng Chemical Reagent Co. Ltd. Polyvinyl pyrrolidone (PVP) and ethylenediamine (EDA) were supplied by Aladdin. Palladium(II) chloride (PdCl_2 , 59.5%) was provided by J&K Scientific Ltd. Other materials were of analytical grade and used as received.

Characterization

Fourier-transform infrared (FTIR) spectra were measured with a Bruker Tensor 27 FT-IR by using KBr pellets. Melting points were determined on an X-6 Data microscopic melting point apparatus. Transmission electron microscopy (TEM) 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 by a vibrating sample magnetometer (Lake Shore 7304, USA). X-ray photoelectron spectrographs (XPS) were collected with an Axis Ultra DLD electron spectrometer (Kratos, UK) with the $\text{C}1\text{s}=284.8$ eV signal as internal standard. Thermogravimetric analyses were performed with a Q600 simultaneous DSC-TGA at 20 °C/min in nitrogen atmosphere (150 ml/min). 10 mg of each sample in an alumina pan was analyzed in the 30 - 800 °C temperature range. ^1H and ^{13}C NMR spectra were measured with a Bruker Advance 400 spectrometer by using CDCl_3 or $\text{DMSO-}d_6$ as solvents and TMS as

the internal standard. The Pd content in the supported catalyst was determined by an Perkin-Elmer Optima 2100 DV.

2 Experimental Section

Preparation of Fe₃O₄ nanoparticles

Fe₃O₄ nanoparticles is synthesized by a solvothermal reaction method.^[11, 14a, 14b] Typically, FeCl₃·6H₂O (1.5 g) , NaAC (2 g) and PVP (1 g) were dissolved in ethylene glycol (30 mL) under magnetic stirring. The resultant solution was transferred into a Teflon lined stainless steel autoclave, sealed, and heated to 200 °C for 12 h. After the reaction was complete, the black Fe₃O₄ nanoparticles were separated by using a permanent magnet and washed several times with ethanol water. Finally, the resulting product is dried under vacuum at 60 °C for 24 h.

Preparation of Fe₃O₄@C nanoparticles

Fe₃O₄@C was synthesized by in situ carbonization of glucose in the presence of Fe₃O₄ under hydrothermal conditions.^[14a, 14c] Fe₃O₄ nanoparticles (100 mg) were dispersed in water (10 mL) containing glucose (1.6 g) by ultrasonication. Subsequently, It was transferred into a Teflon lined stainless steel autoclave, sealed, and heated at 180 °C for 10 h and cooled down at room temperature. After the reaction was complete, the resulting nanoparticles were collected by a permanent magnet and washed with ethanol followed by water. Finally, the black colored product was dried under vacuum for 24 h to give Fe₃O₄@C nanoparticles.

Preparation of Fe₃O₄@NC nanoparticles

Fe₃O₄@NC was prepared according to the literature procedure.^[14a, 14d] Fe₃O₄ nanoparticles (100 mg) were dispersed in water (10 mL) containing glucose (1.6 g) and ethylenediamine (EDA) (0.2 mL) ultrasonication. Subsequently, It was transferred into a Teflon lined stainless steel autoclave, sealed, and heated at 180 °C for 10 h and cooled down at room temperature. After the reaction was complete, the resulting nanoparticles were collected by a permanent magnet and washed with ethanol followed by water. Finally, the black colored product is dried under vacuum for 24 h to give Fe₃O₄@NC nanoparticles.

Preparation of Fe₃O₄@C/Pd and Fe₃O₄@NC/Pd catalyst

The Fe₃O₄@C/Pd and Fe₃O₄@NC/Pd catalyst were prepared using a published method.^[13a, 13e] Typically, Fe₃O₄@C and Fe₃O₄@NC (400 mg) was well dispersed in ethanol (40 mL) under ultrasonication for 0.5 h. The formed black suspension was ultrasonically mixed with PdCl₂ (35 mg) ethanol solution (3 ml) for 1 h, then an ascorbic acid ethanol solution (8 ml) was dropped into the above mixture with vigorous stirring under 60 °C. After 2 h of reduction, the products were separated by an external magnet and washed several times with water. The products were dried in vacuum to obtain Fe₃O₄@C/Pd and Fe₃O₄@NC/Pd.

General procedure for the Suzuki coupling reactions

Aryl halides (1.0 mmol), arylboronic acid (1.5 mmol), KOH (1.5 mmol), Fe₃O₄@NC/Pd (10 mg) and H₂O (3 mL) were added into a reaction flask and stirred at 90 °C under air. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was allowed to cool to room temperature. Then the aqueous phase was extracted with ethyl acetate for 3 times. Then the organic phases were combined, dried over anhydrous MgSO₄, concentrated

under vacuum and purified by column chromatography (petroleum/ethyl acetate 100:1) to afford the desired product.

General procedure for catalyst recovery

4-iodoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), KOH (1.5 mmol), and Fe₃O₄@NC/Pd (10 mg) were mixed in H₂O (3 mL). The mixture was stirred at 90 °C under air. After the reaction was complete, the supported catalyst was separated by an external magnet and washed with water (3×2 mL) and ethanol (3×2 mL), then dried in vacuum and directly used in the next run.

3. Characterization of the Catalysts and Prouducts

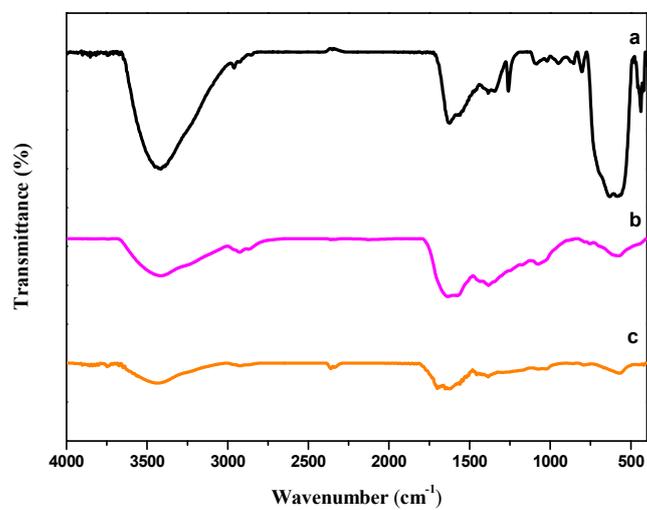


Figure S1 FTIR spectra of (a) Fe₃O₄; (b) Fe₃O₄@C; (c) Fe₃O₄@C/Pd

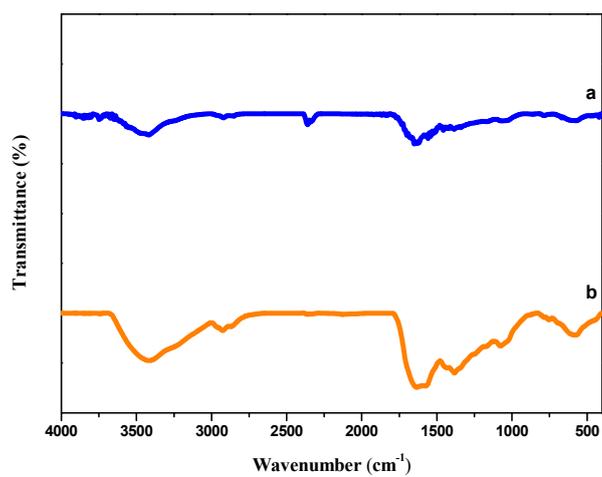


Figure S2 FTIR spectra of (a) fresh Fe₃O₄@NC/Pd and (b) used Fe₃O₄@NC/Pd.

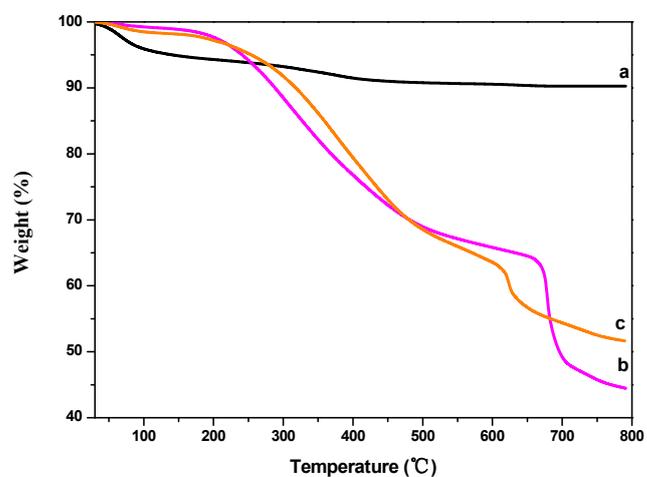


Figure S3 Thermogravimetric analysis graphs of (a) Fe₃O₄; (b) Fe₃O₄@C; (c) Fe₃O₄@C/Pd

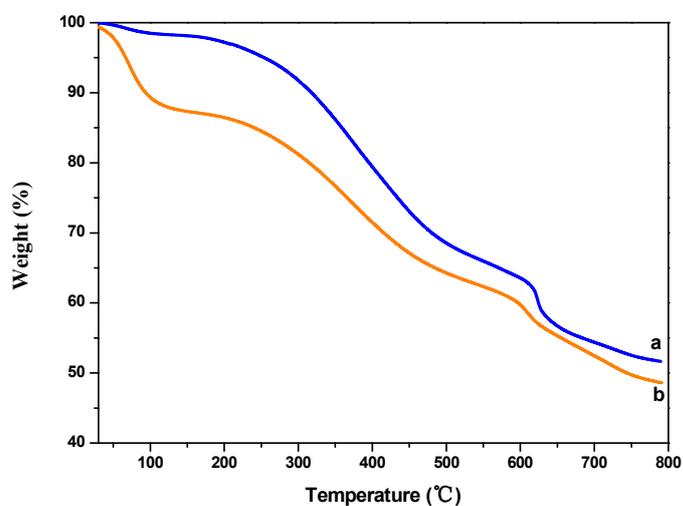
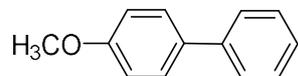


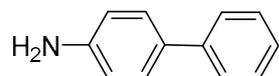
Figure S4 Thermogravimetric analysis graphs of (a) fresh Fe₃O₄@NC/Pd. and (b) used Fe₃O₄@NC/Pd.

4-Methoxybiphenyl 3a:



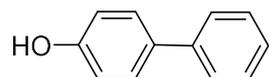
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.61 (d, $J = 7.5$ Hz, 2H), 7.59 (d, $J = 8.8$ Hz, 2H), 7.47 (t, $J = 7.7$ Hz, 2H), 7.36 (t, $J = 7.4$ Hz, 1H), 7.03 (d, $J = 8.7$ Hz, 2H), 3.90 (s, 3H).

4-Aminebiphenyl 3b:



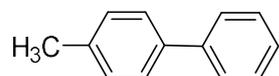
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.45 (d, $J = 7.1$ Hz, 2H), 7.39 – 7.25 (m, 4H), 7.18 (t, $J = 6.9$ Hz, 1H), 6.66 (d, $J = 7.6$ Hz, 2H), 3.61 (s, 2H).

Biphenyl-4-ol 3c:



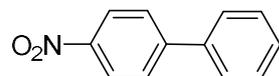
$^1\text{H NMR}$ (500 MHz, DMSO) δ 9.50 (s, 1H), 7.57 (d, $J = 7.2$ Hz, 2H), 7.49 (t, $J = 8.6$ Hz, 2H), 7.42 (d, $J = 7.6$ Hz, 2H), 7.28 (t, $J = 7.4$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 2H).

4-Methylbiphenyl 3d:



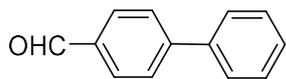
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.69 (d, $J = 8.0$ Hz, 2H), 7.59 (d, $J = 8.1$ Hz, 2H), 7.51 (t, $J = 8.0$ Hz, 2H), 7.45 – 7.42 (t, 1H), 7.34 (d, $J = 7.9$ Hz, 2H), δ 2.48 (s, 3H).

4-Nitrobiphenyl 3e:



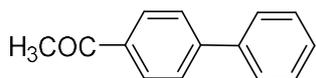
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.33 (d, $J = 8.9$ Hz, 2H), 7.77 (d, $J = 8.9$ Hz, 2H), 7.65 (d, $J = 7.1$ Hz, 2H), 7.53 (t, $J = 7.4$ Hz, 2H), 7.48 (t, $J = 7.3$ Hz, 1H).

[1,1'-Biphenyl]-4-carbaldehyde 3f:



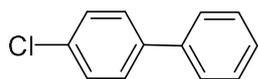
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 10.06 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.3 Hz, 1H).

1-([1,1'-biphenyl]-4-yl)ethan-1-one 3g:



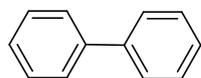
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.04 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 2.64 (s, 3H).

4-Chlorobiphenyl 3h:



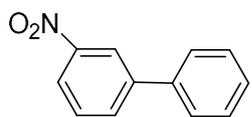
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.67 – 7.53 (m, 4H), 7.52 – 7.41 (m, 4H), 7.38 (t, J = 7.4 Hz, 1H).

Biphenyl 3i:



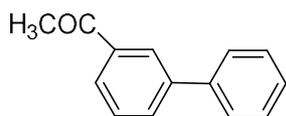
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.73 (dd, J = 8.2, 1.1 Hz, 4H), 7.56 (m, J = 7.7 Hz, 4H), 7.47 (t, J = 7.4 Hz, 2H).

3-Nitrobiphenyl 3j:



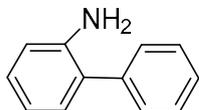
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.48 (d, J = 1.9 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.67 – 7.62 (m, 3H), 7.53 (t, J = 7.5 Hz, 2H), 7.46 (t, J = 7.3 Hz, 1H).

1-([1,1'-Biphenyl]-3-yl)ethan-1-one 3k:



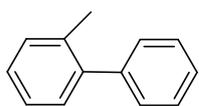
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.18 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 7.7 Hz, 2H), 7.53 (t, J = 7.7 Hz, 1H), 7.47 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 2.65 (s, 3H).

2-Aminebiphenyl 3l:



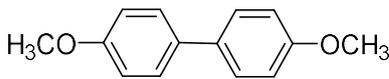
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.43 (m, $J = 7.2$ Hz, 4H), 7.33 (t, $J = 6.8$ Hz, 1H), 7.20 – 7.04 (m, 2H), 6.82 (t, $J = 7.4$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 3.64 (s, 2H).

2-Methylbiphenyl 3m:



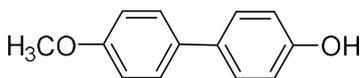
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.63 (d, $J = 7.9$ Hz, 1H), 7.47 (t, $J = 8.1$ Hz, 2H), 7.44 (m, $J = 7.4$ Hz, 2H), 7.37 (d, $J = 1.5$ Hz, 2H), 7.30 (m, $J = 2.7$ Hz, 2H), δ 2.31 (s, 3H).

4,4'-Dimethoxybiphenyl 3n:



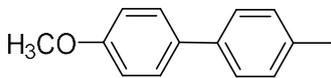
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.69 – 7.41 (m, 4H), 7.05 – 6.87 (m, 4H), 3.87 (s, 6H).

4'-Methoxybiphenyl-4-ol 3o:



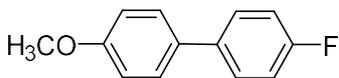
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.49 (d, $J = 8.8$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 3.87 (s, 3H).

4-Methoxy-4'-methylbiphenyl 3p:



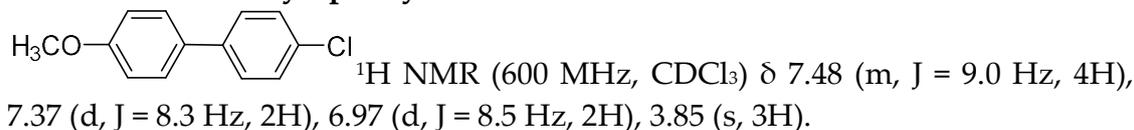
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.55 (d, $J = 8.8$ Hz, 2H), 7.48 (d, $J = 8.1$ Hz, 2H), 7.26 (d, $J = 7.9$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 3.88 (s, 3H), 2.42 (s, 3H).

4-Fluoro-4'-methoxybiphenyl 3q:

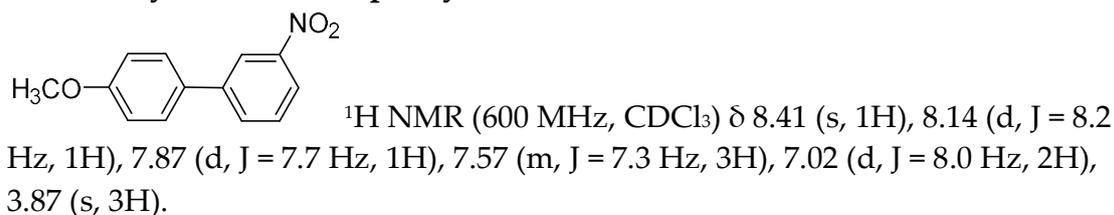


$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.66 – 7.38 (m, 4H), 7.13 (d, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 3.88 (s, 3H).

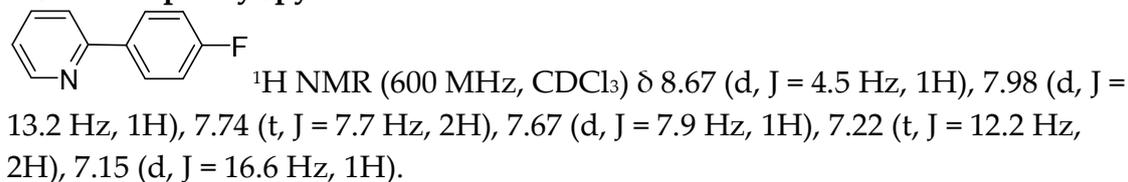
4-Chloro-4'-methoxybiphenyl 3r:



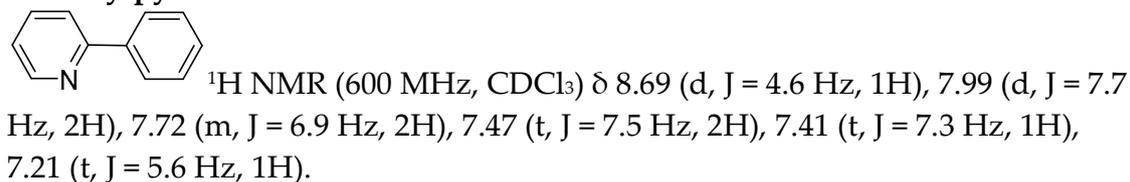
4'-Methoxy-3-nitro-1,1'-biphenyl 3s:



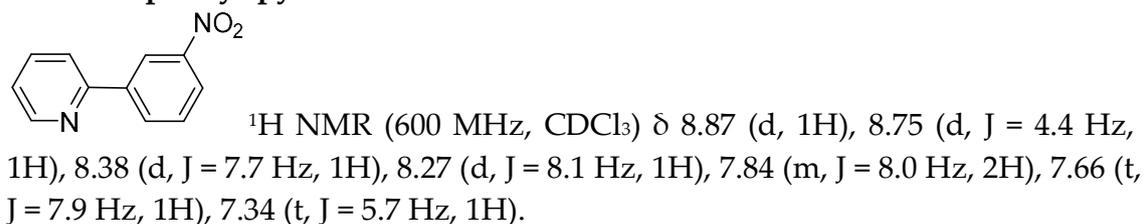
2-(4-Fluorophenyl)pyridine 3t:



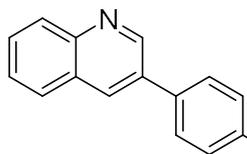
2-Phenylpyridine 3u:



2-(3-Nitrophenyl)pyridine 3v:

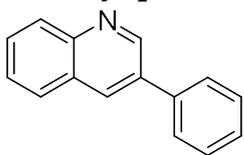


3-(4-Fluorophenyl)quinoline 3w:



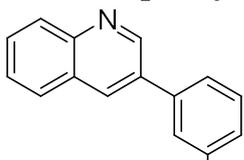
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.13 (s, 1H), 8.27 (s, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 7.6$ Hz, 1H), 7.67 (d, 2H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H).

3-Phenylquinoline 3x:



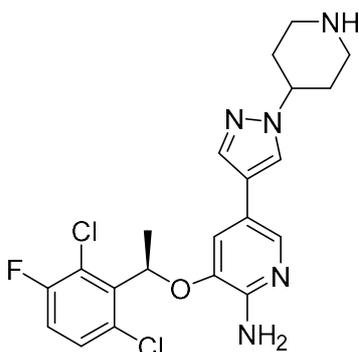
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.17 (s, 1H), 8.25 (s, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.69 (m, $J = 12.1, 7.6$ Hz, 3H), 7.54 (t, $J = 7.5$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 2H), 7.41 (t, $J = 7.4$ Hz, 1H).

3-(3-Nitrophenyl)quinoline 3y:



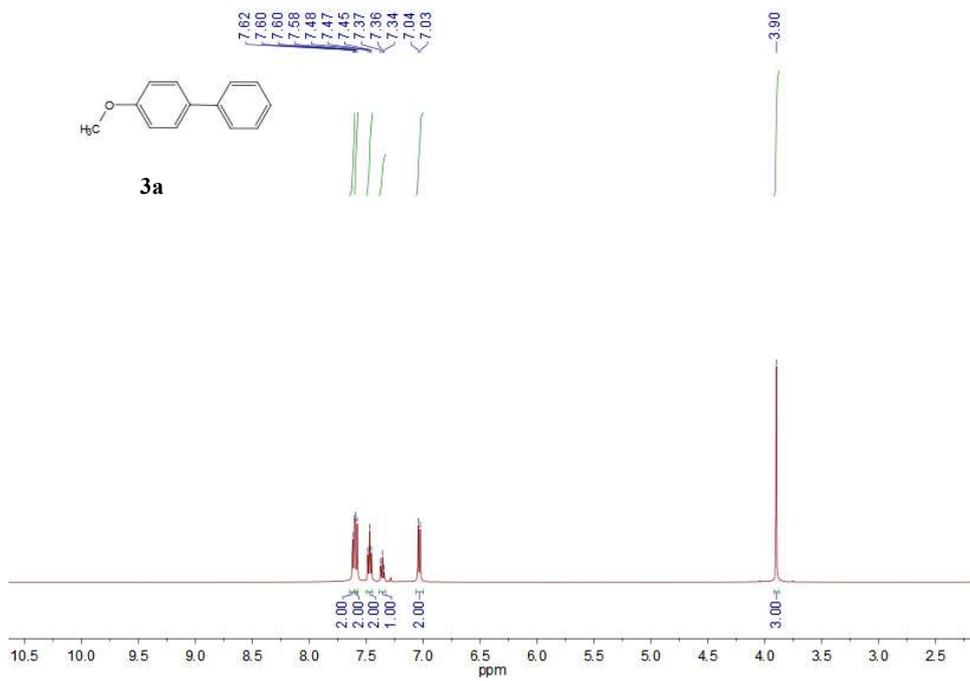
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.56 – 8.45 (m, 2H), 8.38 – 8.17 (m, 2H), 8.11 – 7.89 (m, 2H), 7.77 – 7.54 (m, 2H), 7.45 – 7.13 (m, 2H).

Crizotinib:

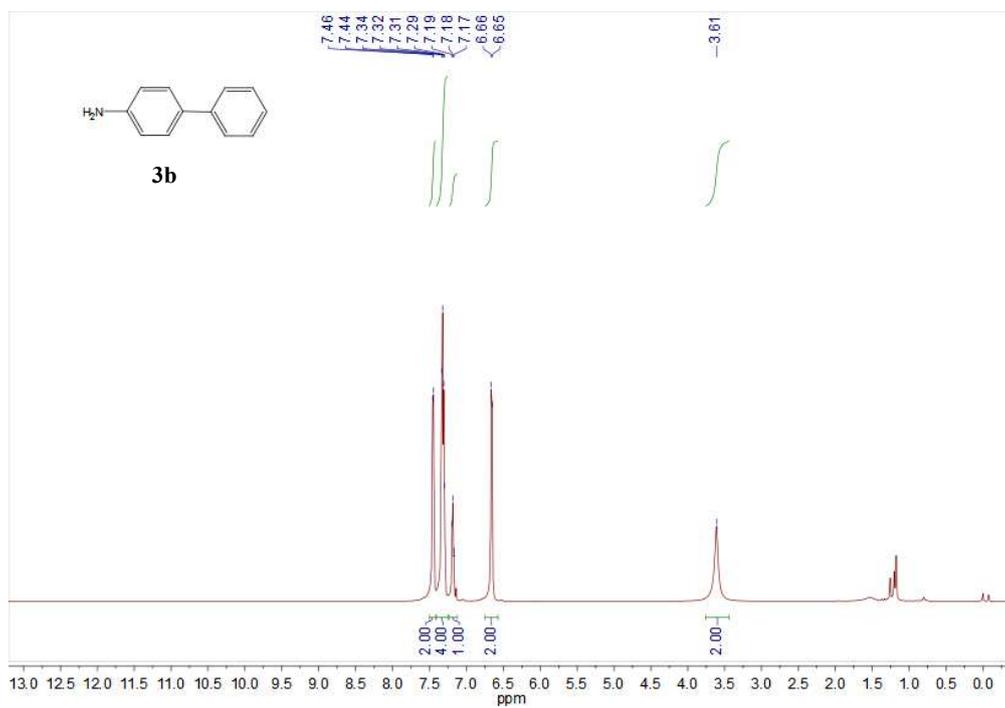


$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.77 (d, $J = 1.7$ Hz, 1H), 7.57 (s, 1H), 7.50 (s, 1H), 7.30 (s, 1H), 7.08 – 7.02 (m, 1H), 6.87 (d, $J = 1.6$ Hz, 1H), 6.07 (q, $J = 6.7$ Hz, 1H), 4.78 (s, 2H), 4.39 – 3.97 (m, 1H), 3.28 – 3.23 (m, 2H), 2.86 – 2.49 (m, 2H), 2.21 – 2.12 (m, 2H), 1.95 – 1.88 (m, 2H), 1.85 (d, $J = 6.7$ Hz, 3H). $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 148.86, 139.82, 136.98, 135.62, 135.61, 128.96, 128.93, 122.45, 122.12, 122.00, 119.90, 119.29, 116.78, 116.63, 114.93, 72.41, 59.75, 45.66, 33.90, 33.88, 18.93.

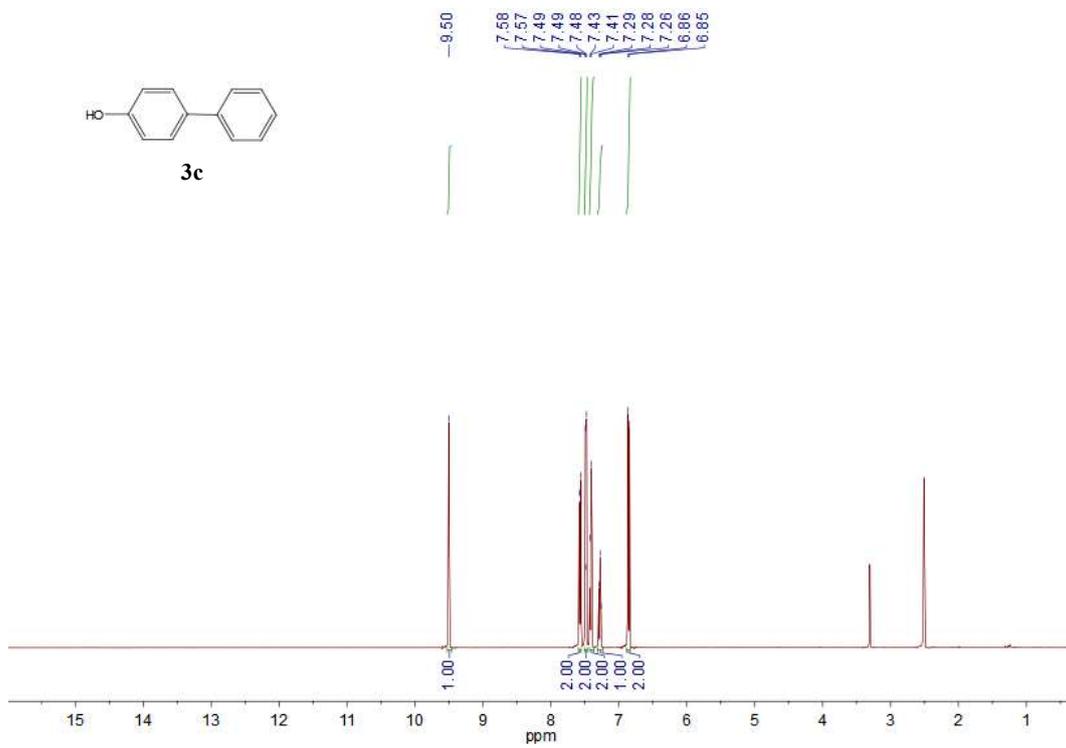
^1H NMR



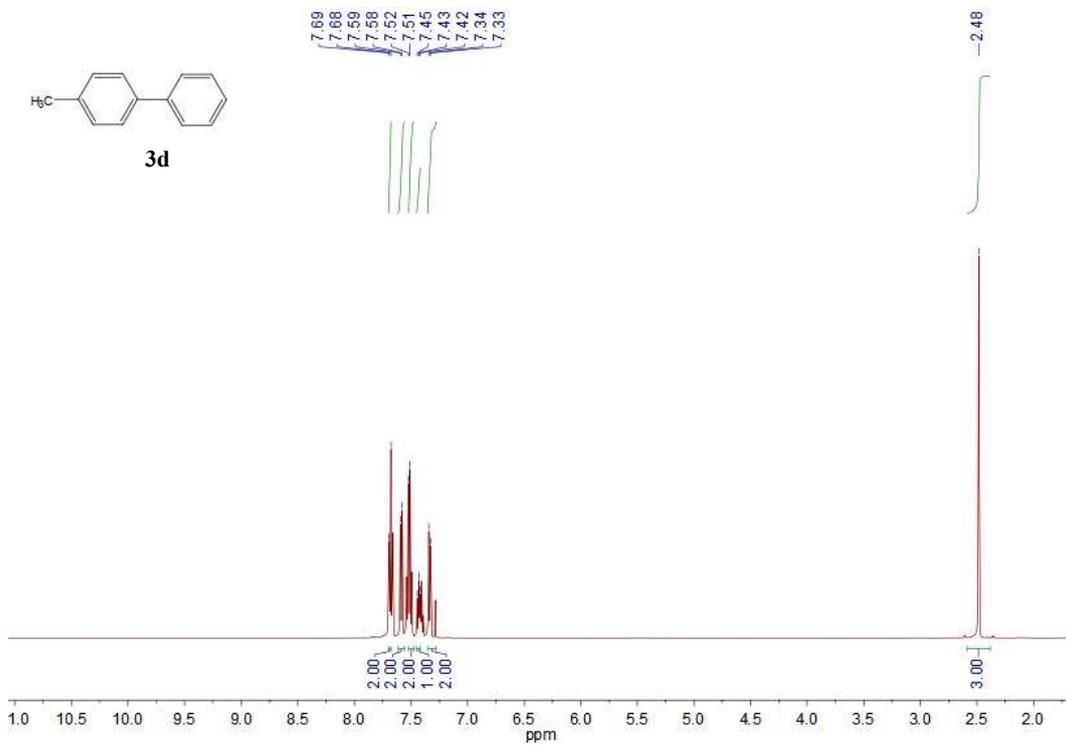
$^1\text{H NMR}$



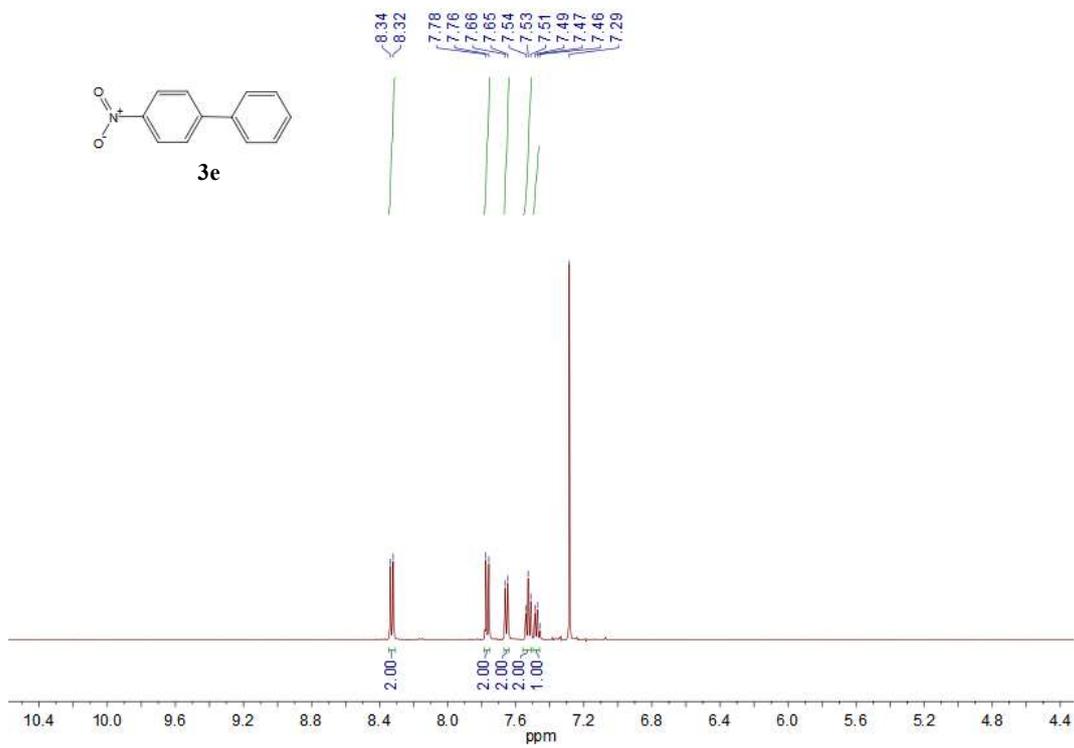
$^1\text{H NMR}$



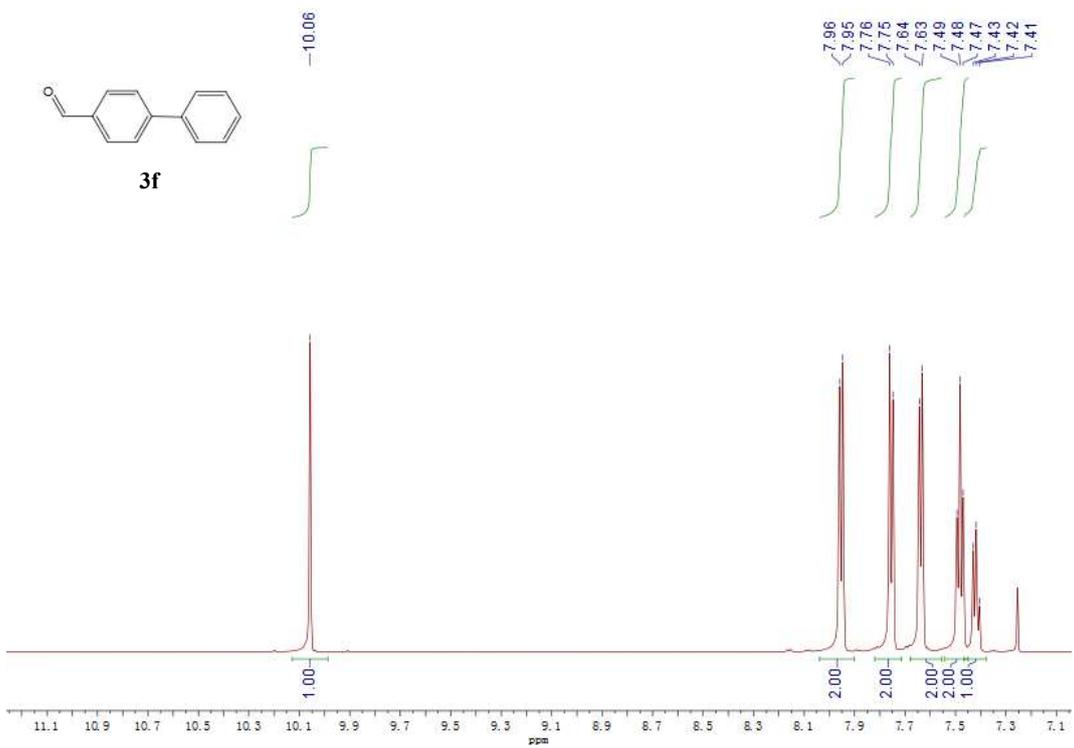
¹H NMR



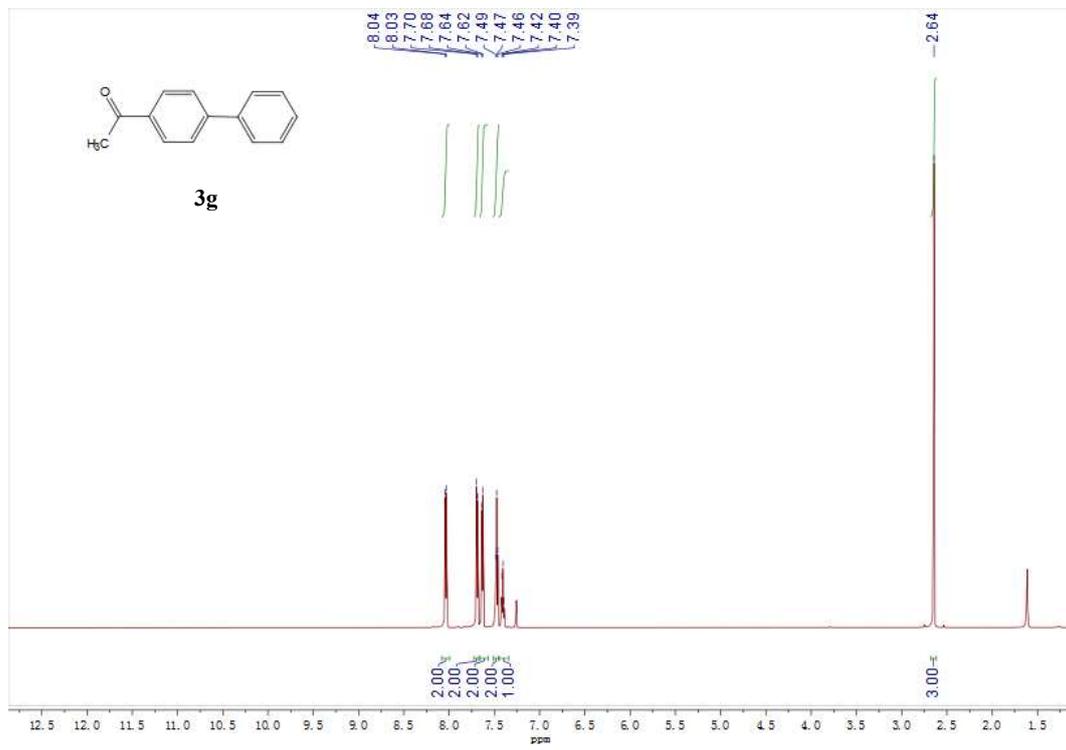
¹H NMR



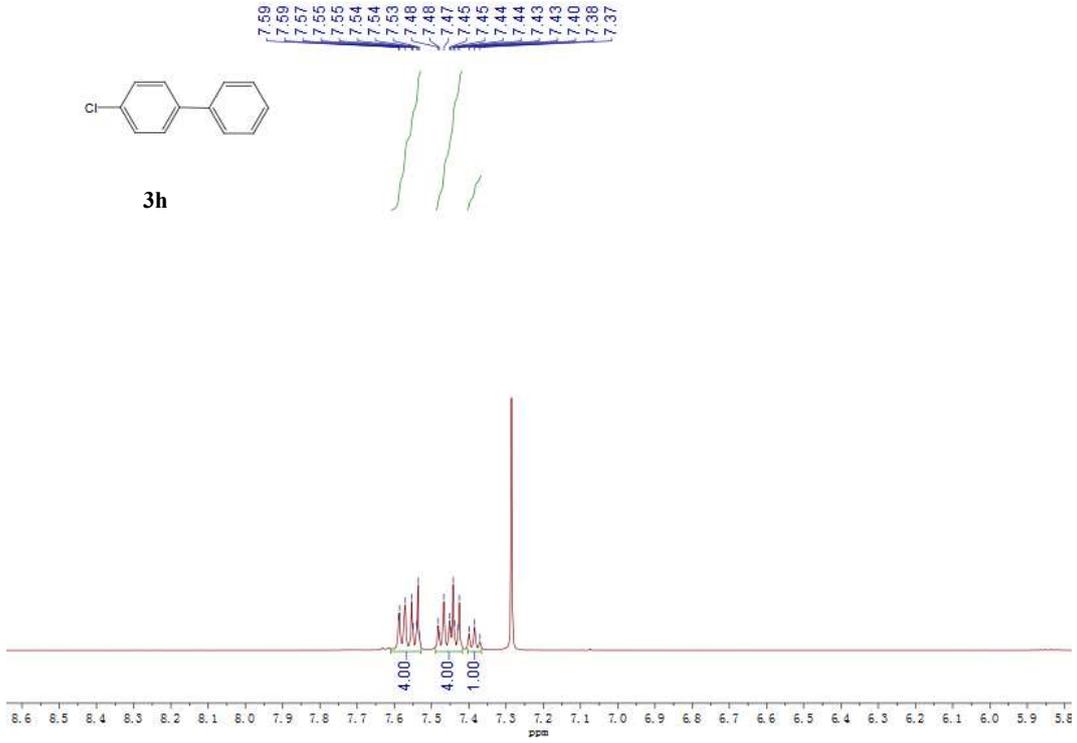
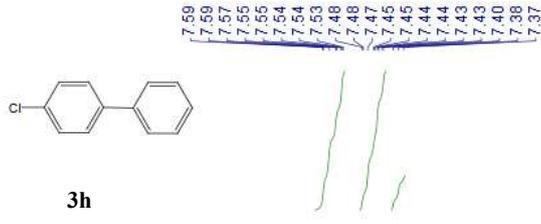
$^1\text{H NMR}$



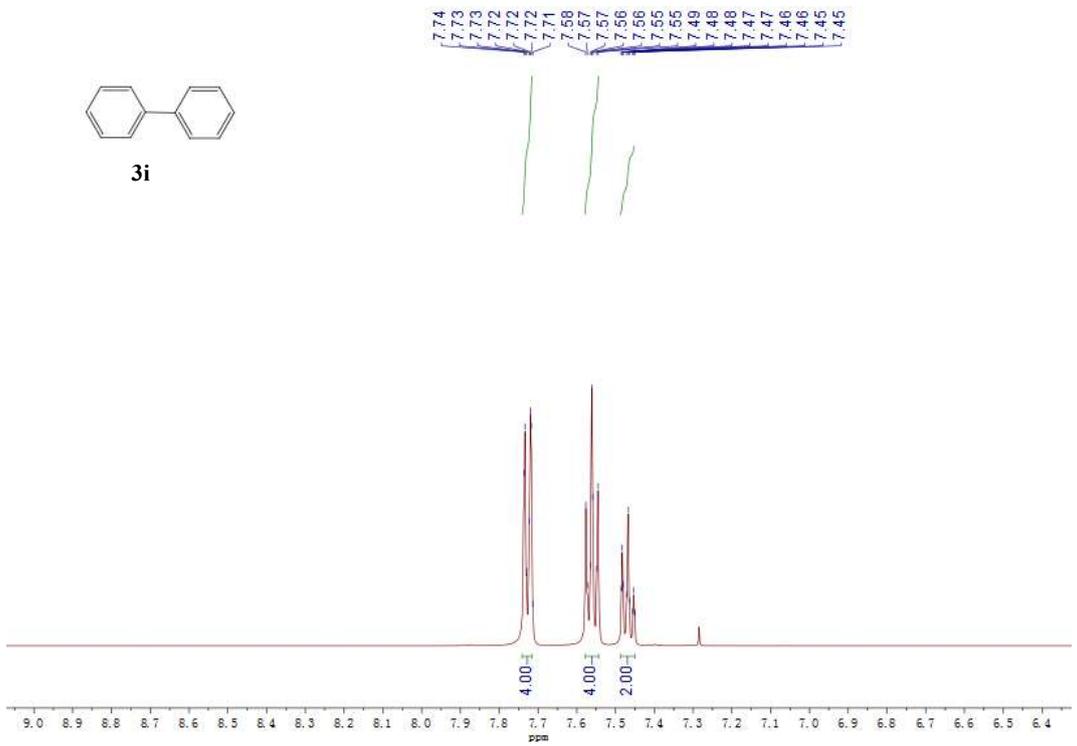
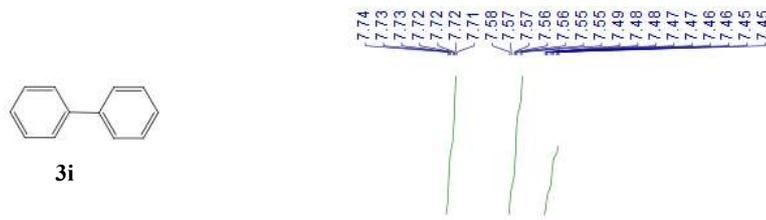
^1H NMR



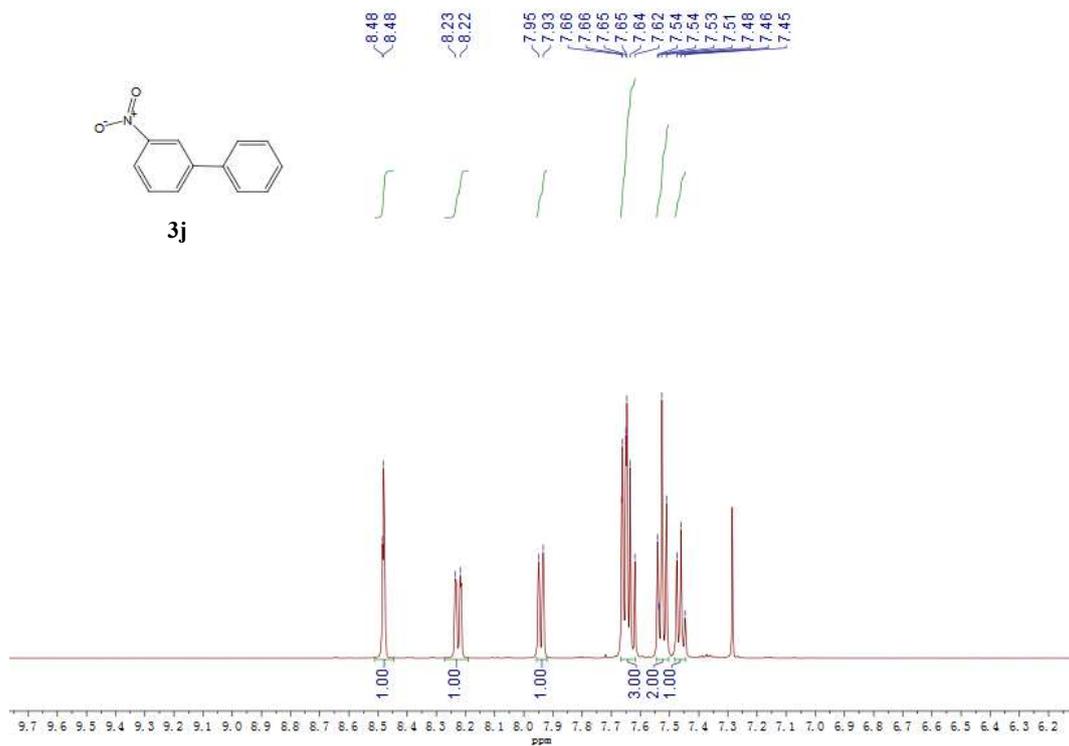
^1H NMR



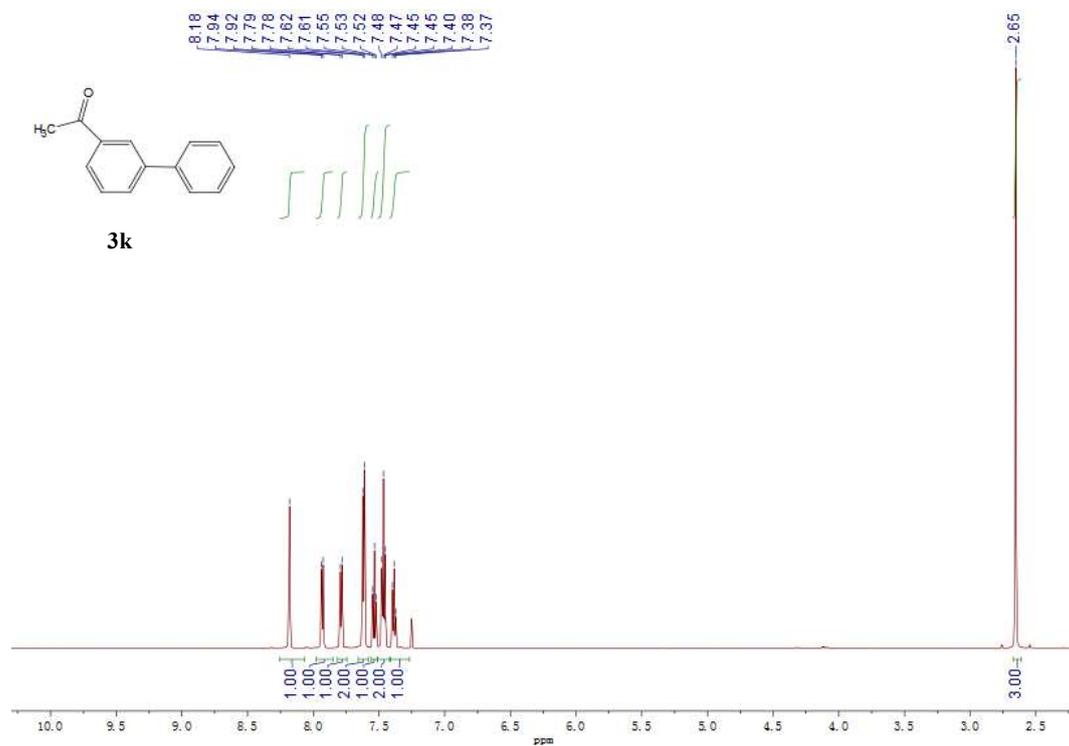
¹H NMR



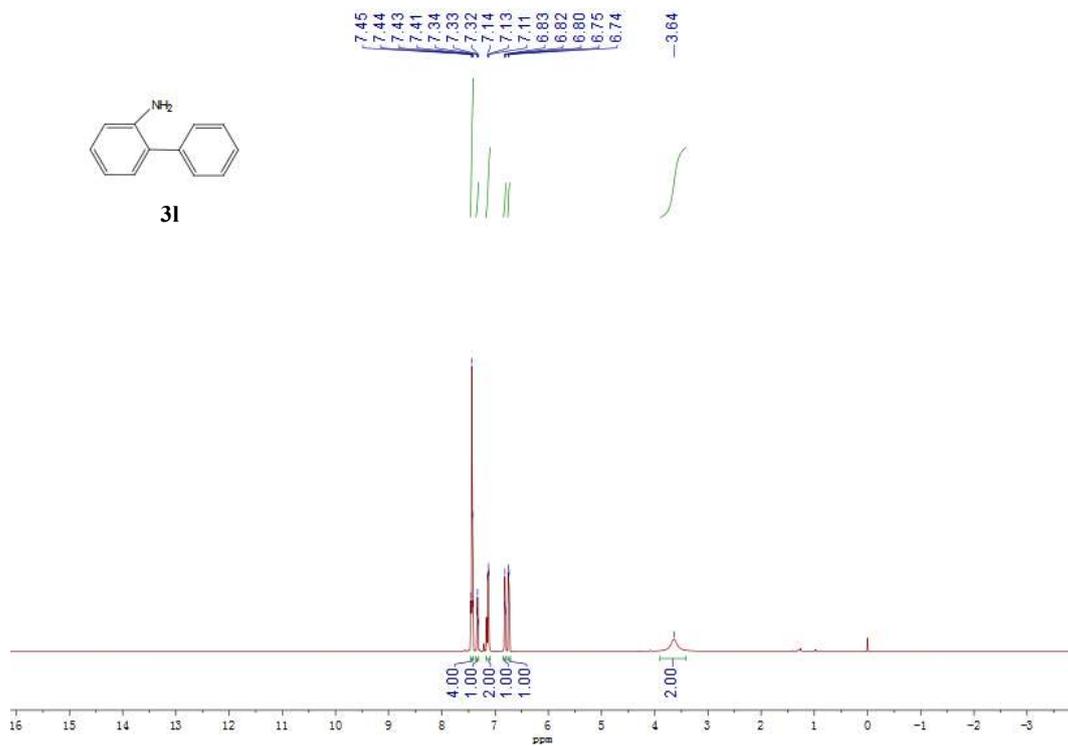
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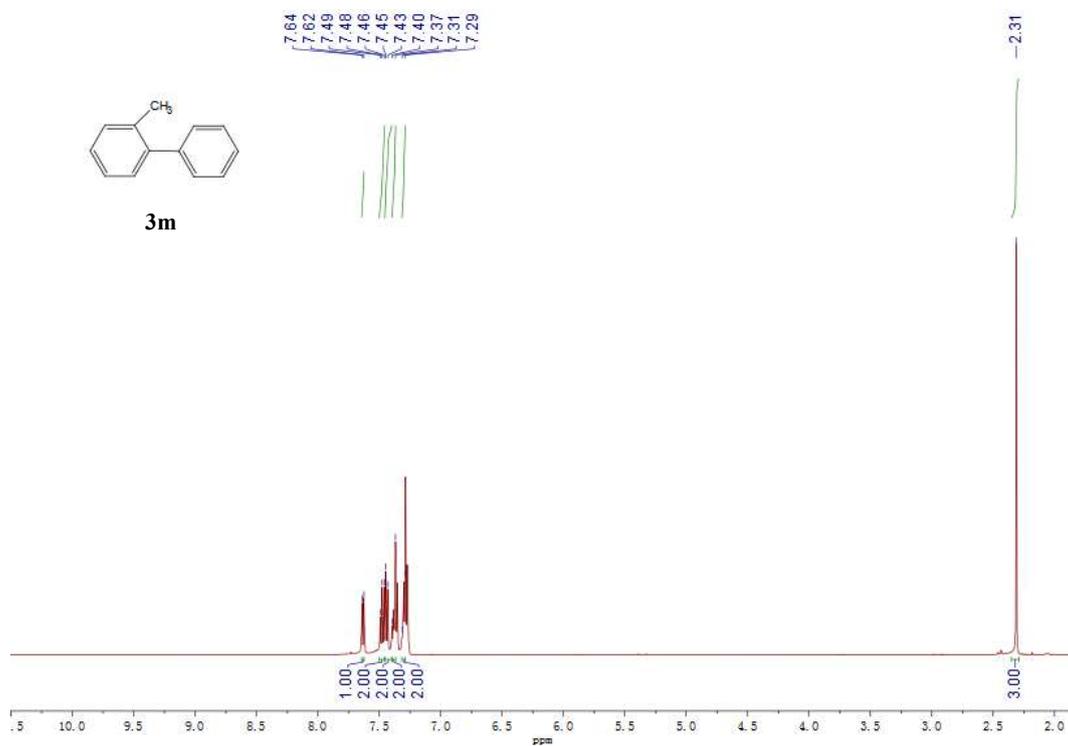
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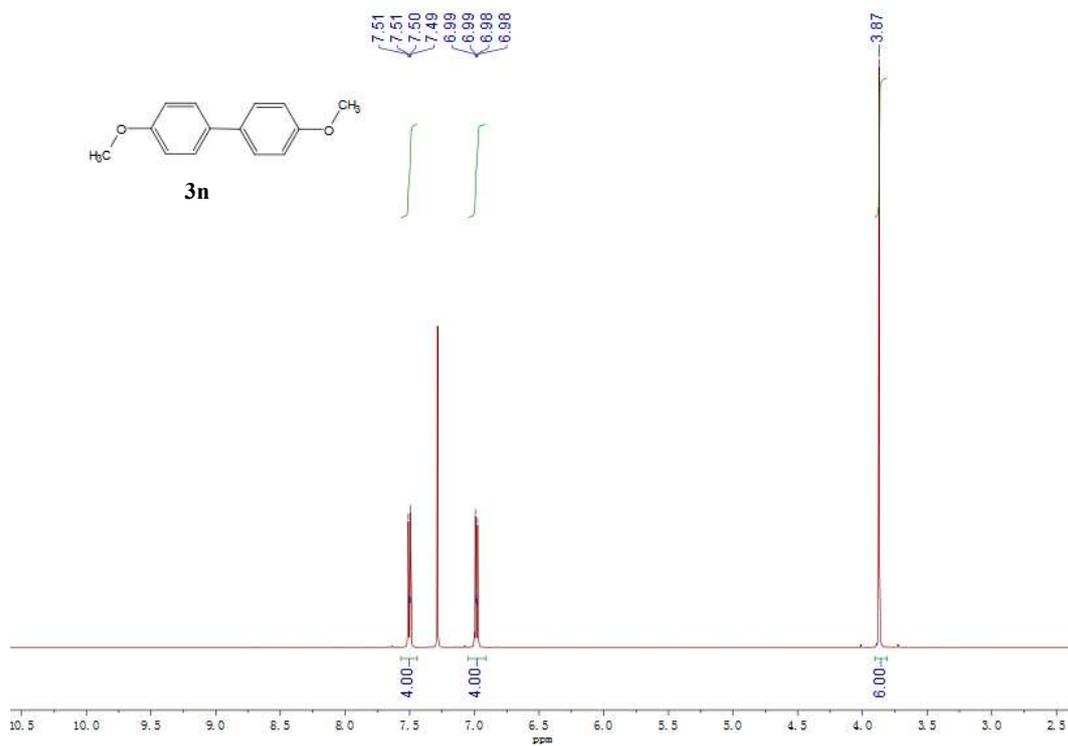
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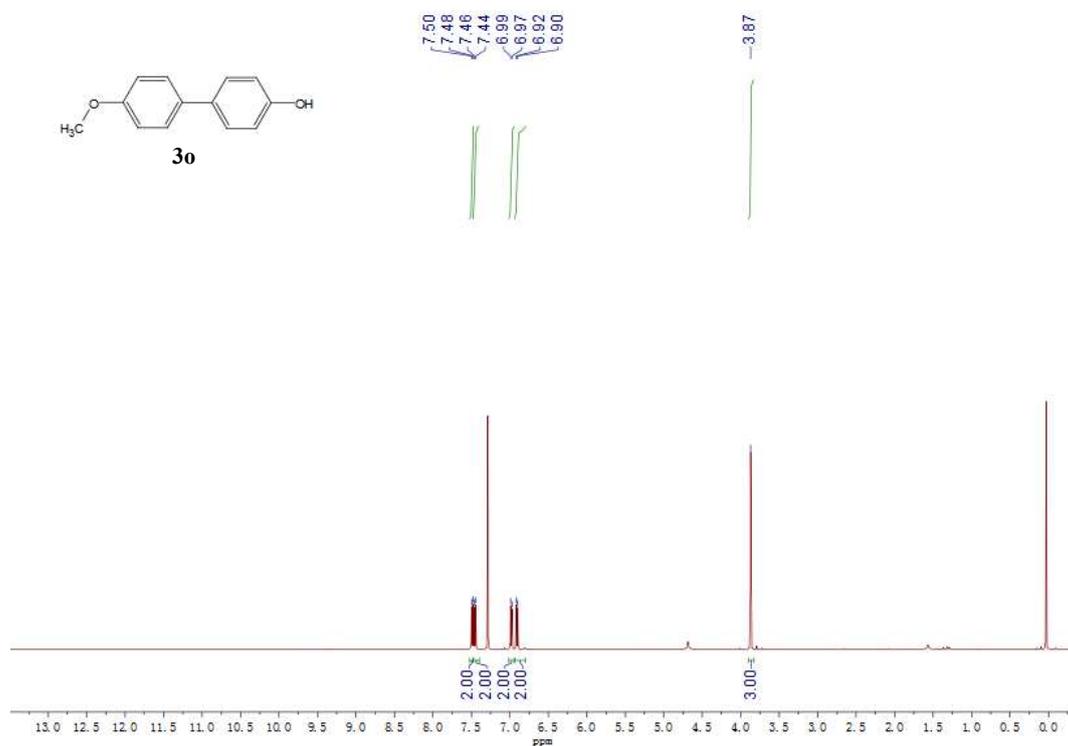
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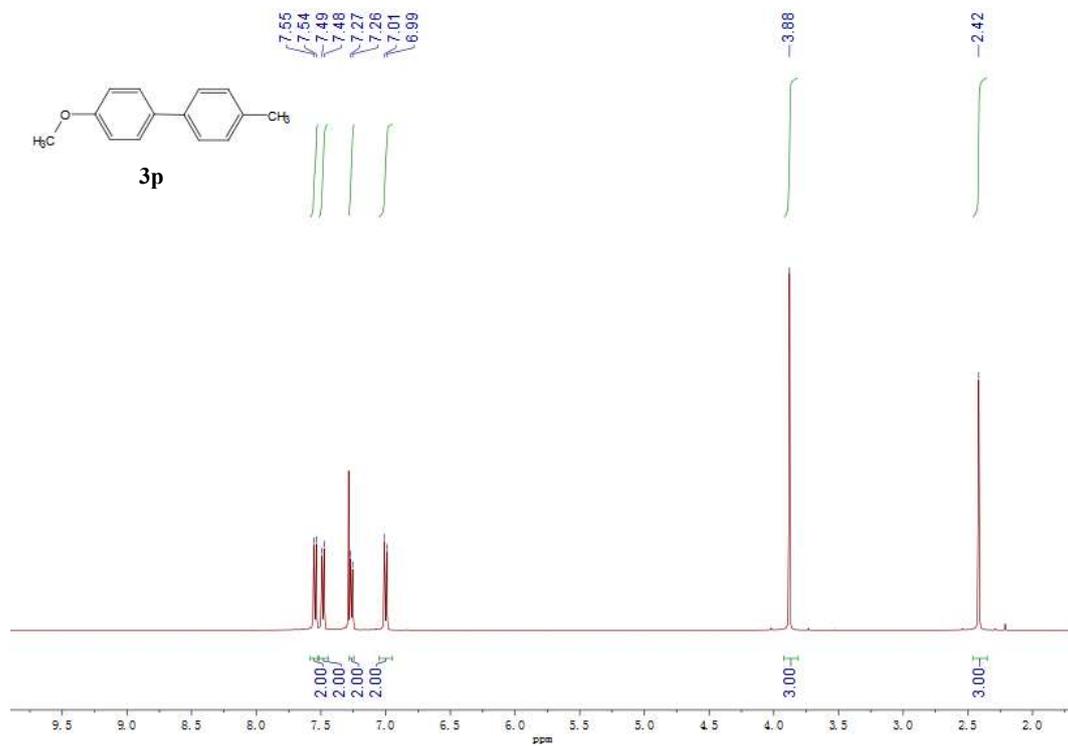
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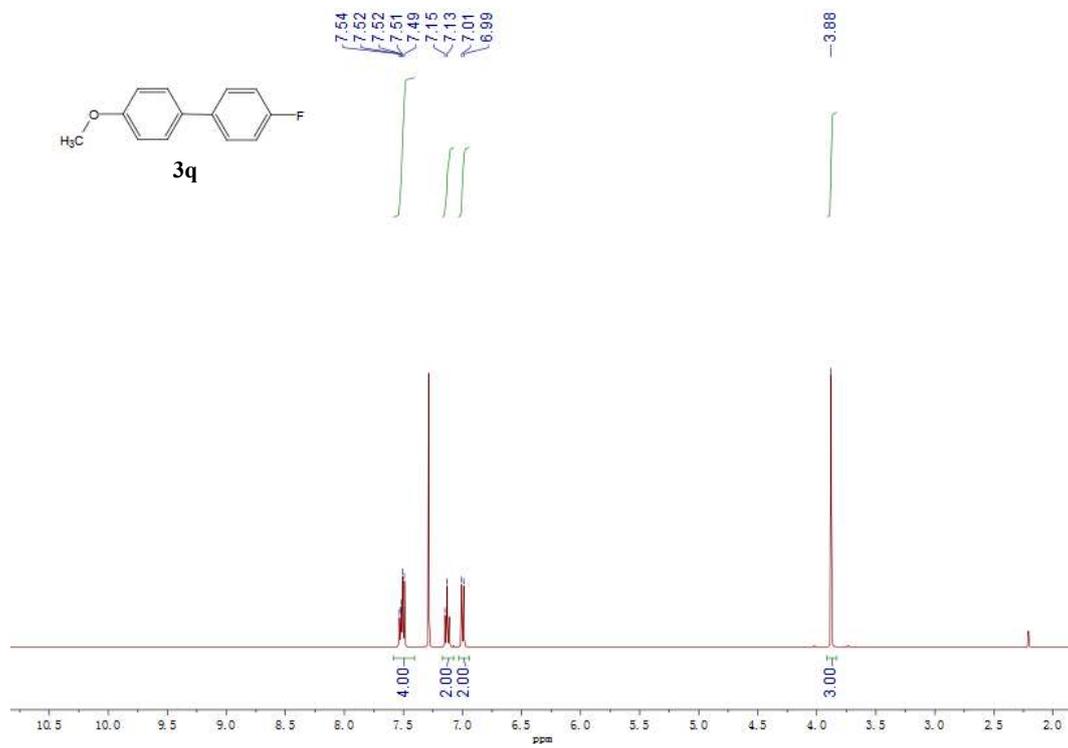
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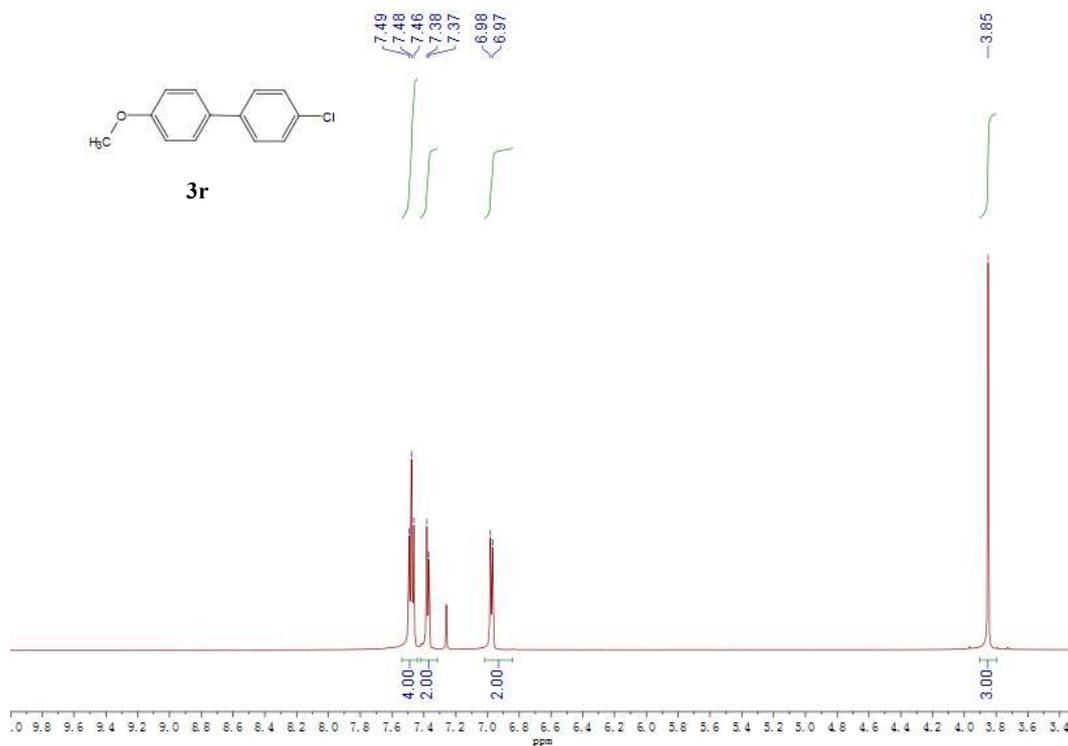
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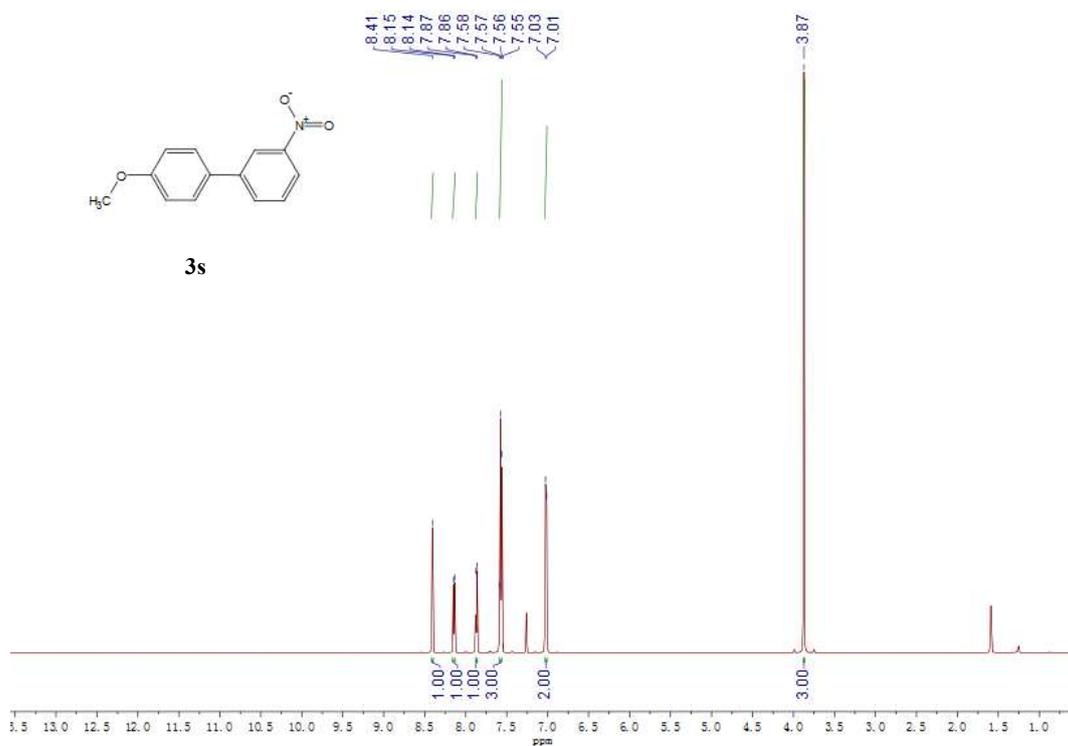
^1H NMR



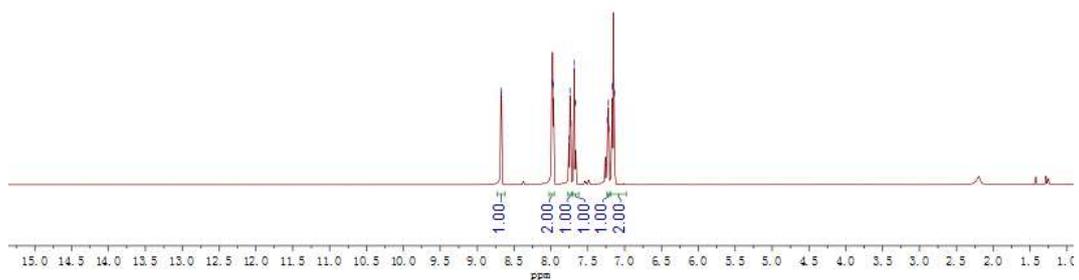
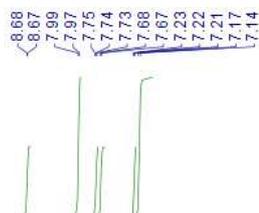
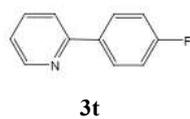
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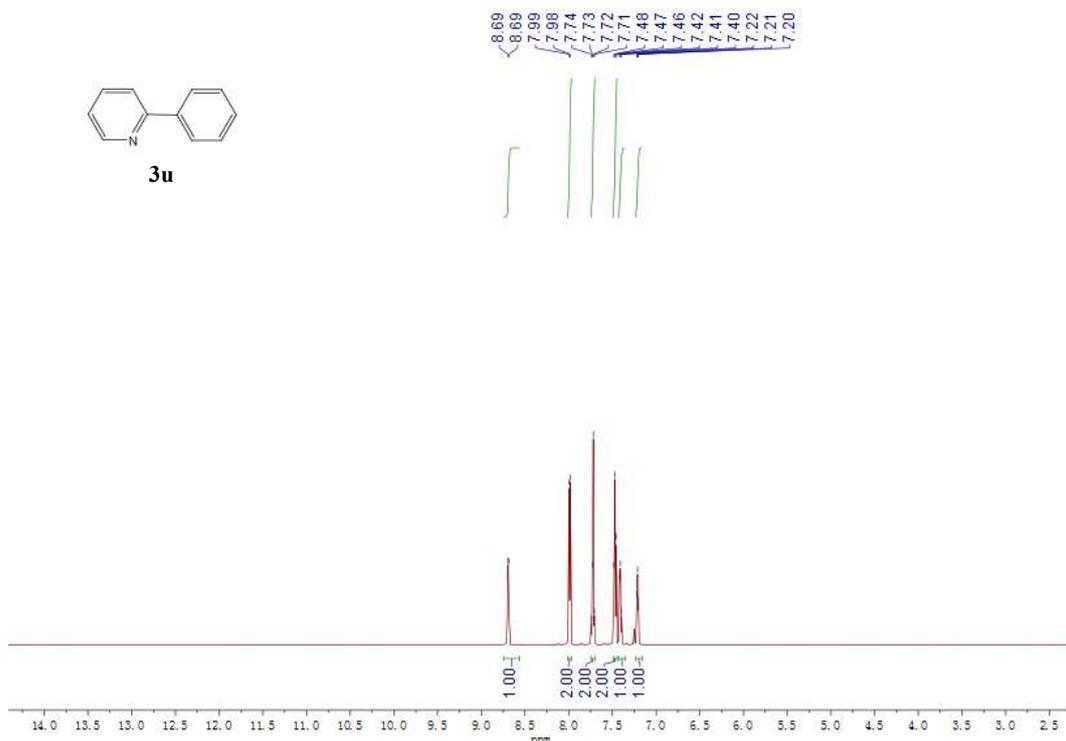
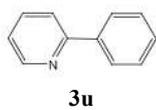
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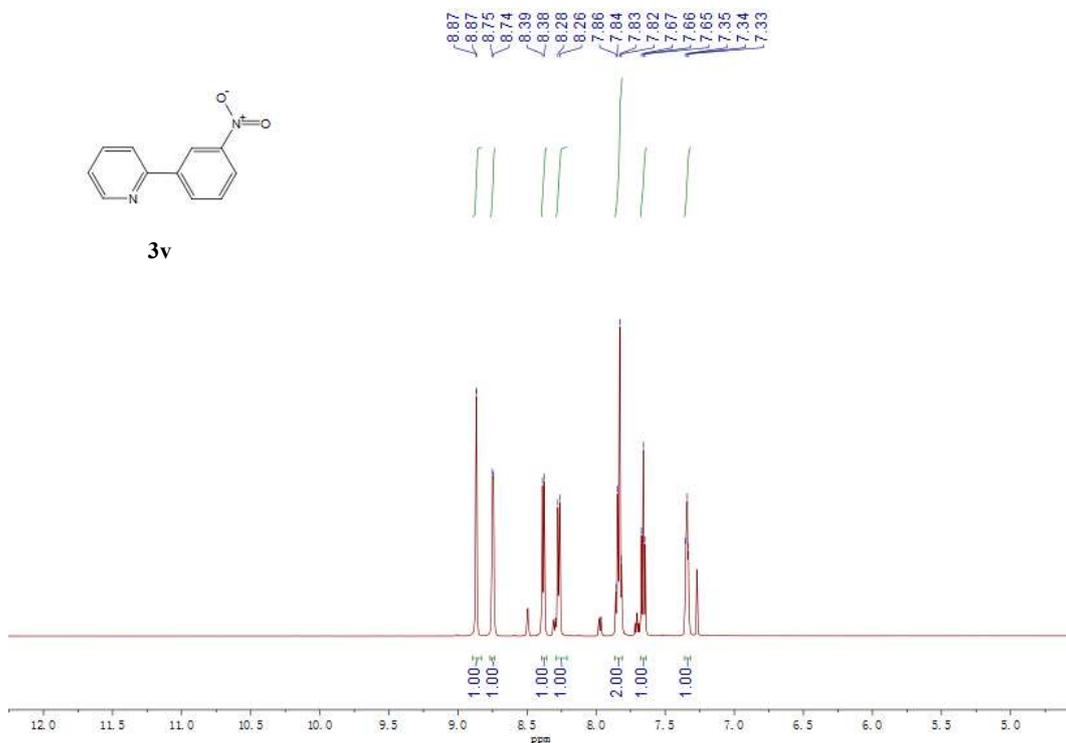
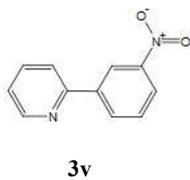
^1H NMR



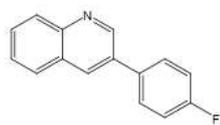
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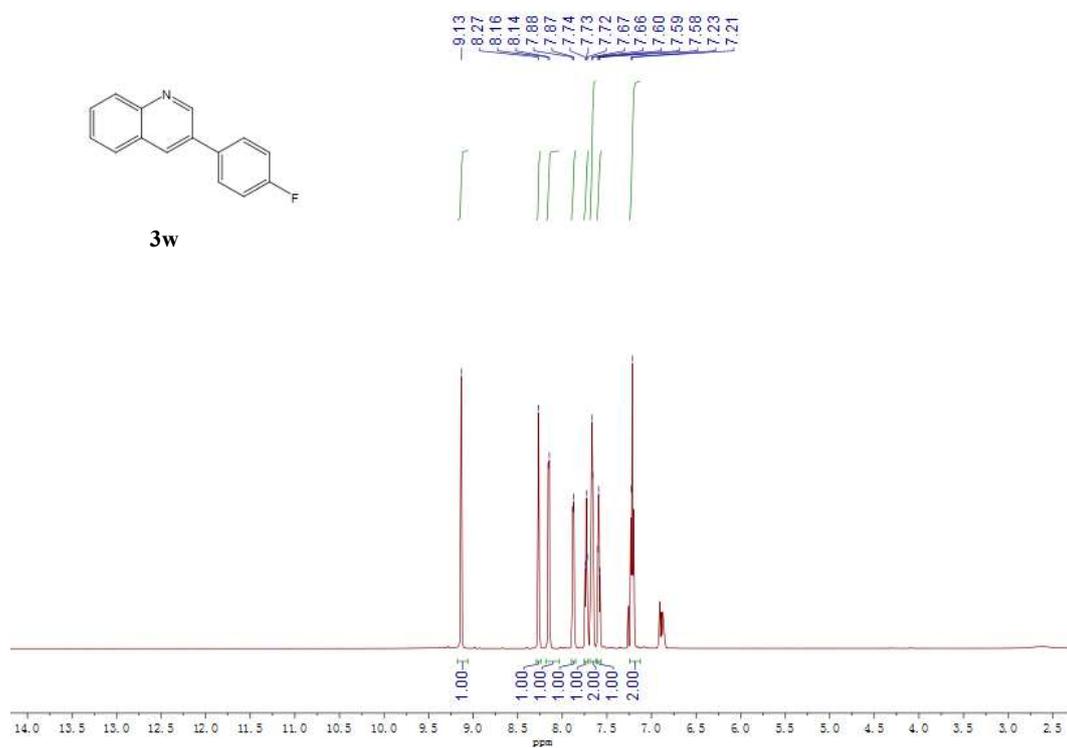
¹H NMR



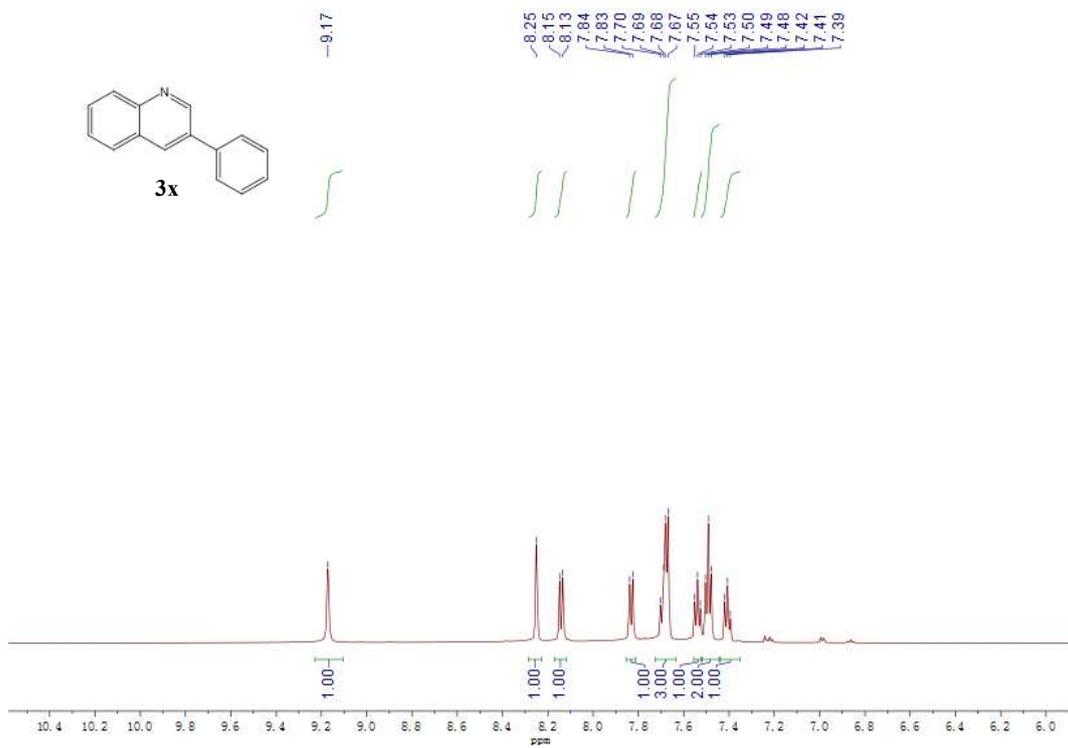
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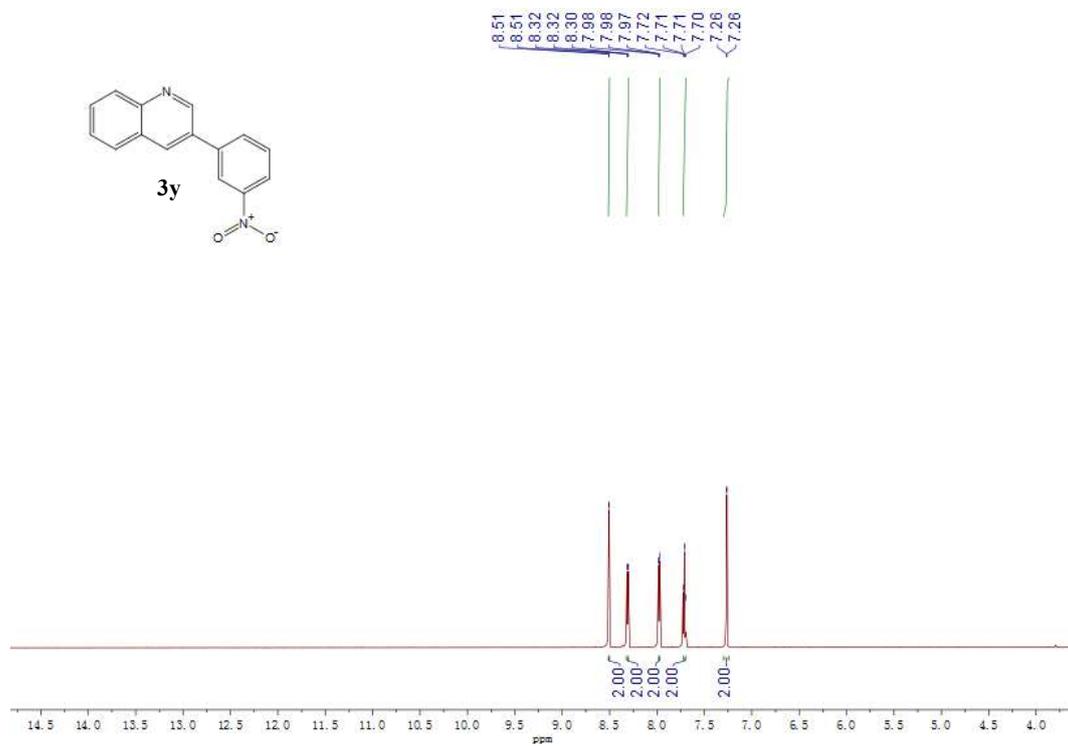
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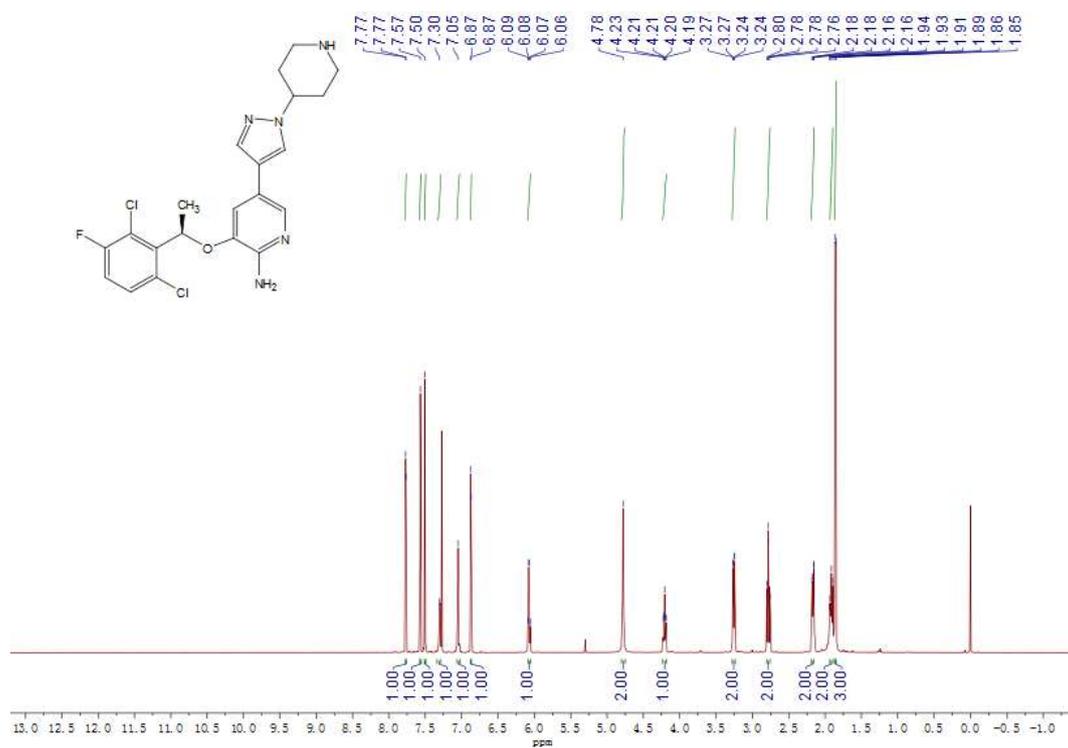
^1H NMR



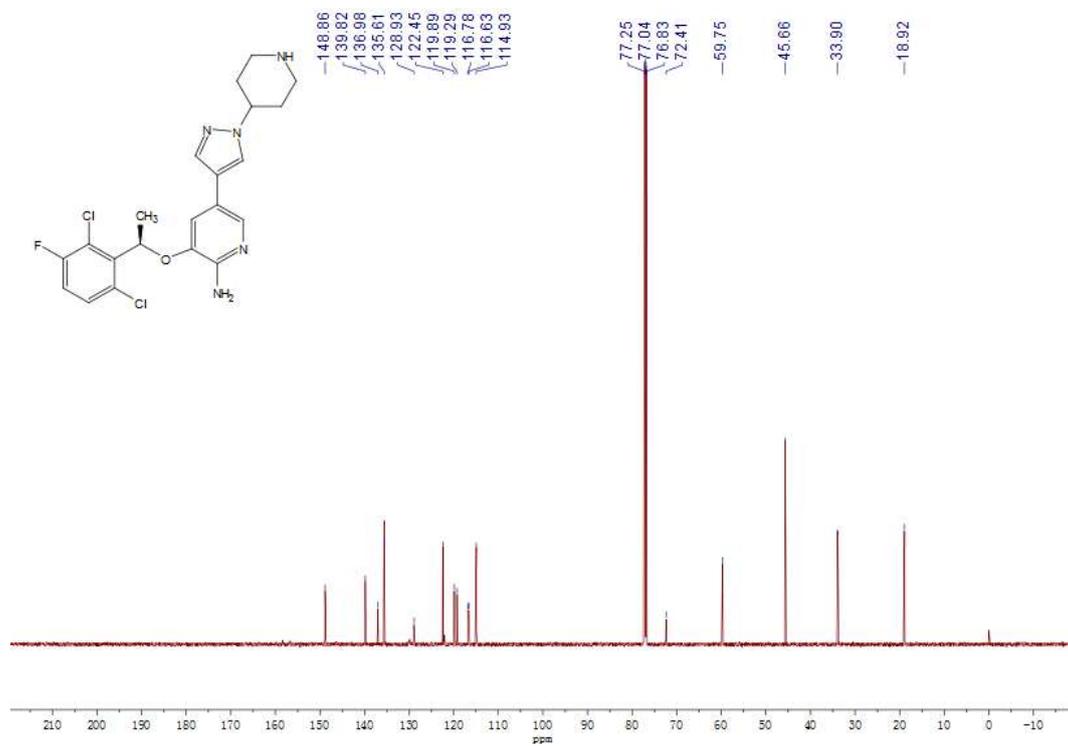
^1H NMR



¹H NMR



¹³C NMR



4、References

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