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Pd(II)/Mg-La mixed oxide catalyst for cyanation of aryl C–H bonds and tandem Suzuki-cyanation reactions

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1 General Information

All reagents were commercial grade materials and were used without further purification. All solvents were dried and distilled by standard methods as described in the literature.[1] Thin layer chromatography was performed on precoated silica gel 60-F_{254} plates. The ^{1}H NMR and ^{13}C NMR spectras were recorded on 200, 300 and 500 MHz spectrometer. Chemical shift (δ) values are reported in ppm, using TMS as an internal standard. X-ray photoelectron spectroscopy (XPS) was recorded on a KRATOS AXIS 165 equipped with Mg Kα radiation (1253.6 ev) at 75 W apparatus using Mg Kα anode and a hemi spherical analyzer. The C 1s line at 284.6 ev was used as an internal standard for the correction of binding energies. The X-ray diffraction (XRD) patterns of the fresh and used samples were obtained on a Rigaku Miniflex X-ray diffractometer using Ni filtered Cu K_α radiation (λ= 0.15406 nm) from 2θ = 10 to 80°, at a scan rate of 2° $\min^{-1}$, with the beam voltage and beam current of 30 kV and 15 mA respectively. Mass spectra were obtained at an ionisation potential of 70 eV [scanned on VG 70-70H (micro mass)]. Transmission electron micrographs (TEM) were carried out in a Philips Tecnai G^2 FEI F12 electron microscope. The samples were ultrasonically dispersed in ethanol before loading onto a carbon coated copper grid and then allowed to dry at room temperature before recording the micrographs. The elemental analysis of the fresh and used Pd(II)/Mg-La mixed oxide samples were analysed by atomic absorption spectroscopy (AAS) Perkin Elmer, Analyst-300.

2. Typical Experimental Procedures

Preparation of Pd(II)/Mg-La mixed oxide

Preparation of Mg-La mixed oxide: The Mg-La mixed oxide was obtained by co-precipitation method.[2] In a 1 L beaker, $Mg(NO_3)_2{\bullet}6H_2O$ (57.8 g, 0.39 mol) and $La(NO_3)_3{\bullet}6H_2O$ (56.2 g, 0.13 mol) were dissolved in 500 mL distilled water. This solution was transferred to an addition funnel and was labeled as solution A. Next, KOH (56.11 g, 1 mol) and K_2CO_3 (35.9 g, 0.26 mol) were dissolved in 520 mL of distilled water in a 1 L beaker. This solution was transferred to an addition funnel and was labeled as solution B. At room temperature, 500 mL of distilled water was taken in a 5 L beaker and both solutions (solution A and solution B) were added drop wise under constant stirring and at a pH of around 10. After completion of the addition, the obtained gel was stirred for another 30 minutes. Next, the gel was washed several times with distilled water until the pH of the filtrate becomes neutral. Finally, the gel was filtered and oven dried at 120 °C for 16 h. Subsequently it was calcined in static air at 750 °C for 5 h at a ramping rate of 10 °C/min.

Preparation of Pd(II)/Mg-La mixed oxide**:** The Pd was incorporated on Mg-La mixed oxide by impregnation method.[3] In a typical experiment, Mg-La mixed oxide (1.5 g) was suspended in 150 mL of aqueous palladium (II) nitrate hydrate (Pd $(NO_3)_2\cdot xH_2O$) [0.345 g, 1.5 mmol] solution and stirred at 25 °C for 12 h under a nitrogen atmosphere. After this, the solid was filtered, washed with distilled water (500 mL), oven dried at 100 °C and calcined at 350 °C for 5 h. The Pd content of the catalyst was measured by AAS and was found to be 9.76% (weight %).

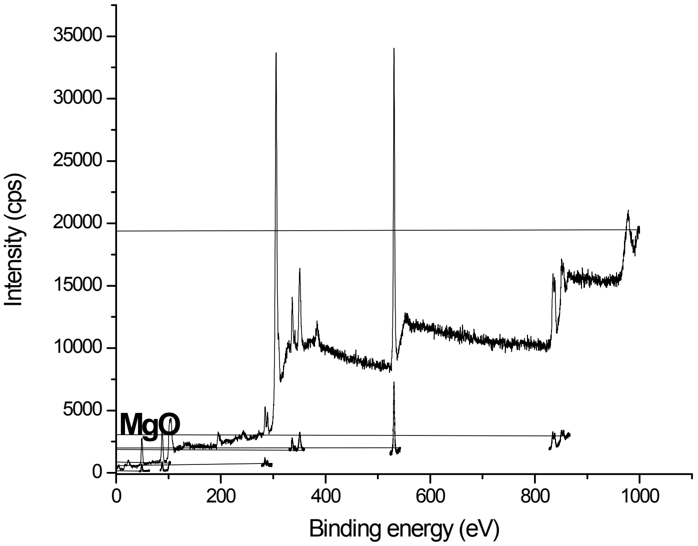


Figure 1. The XPS spectrum of Pd(II)/Mg-La mixed oxide.

Preparation of Substrates

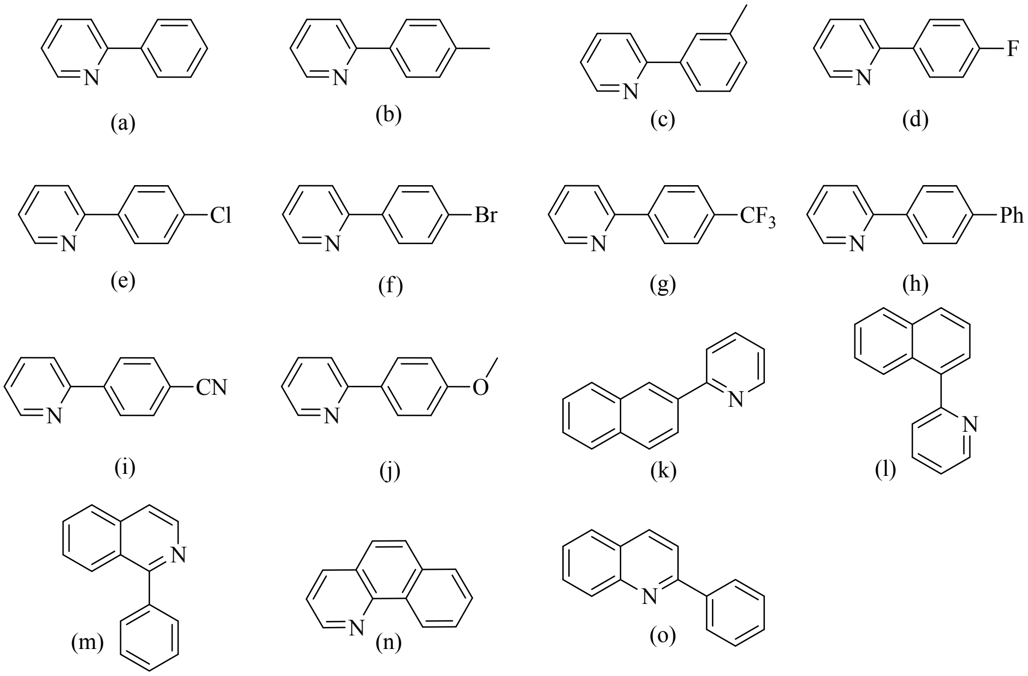
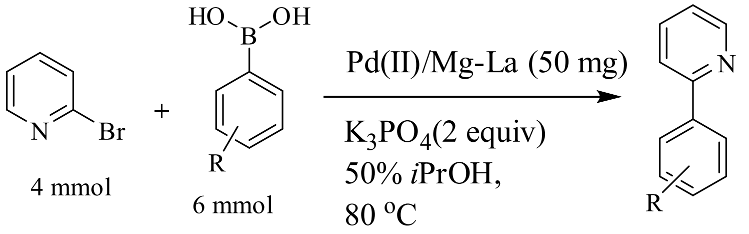


Figure 2. Substrates used for the cyanation reaction.

Substrates a, b and n (Figure 2) are commercially available and were purchased directly from Sigma-Aldrich. Other substrates (Figure 2, c-m, and o) were prepared by using Pd(II)/Mg-La mixed oxide catalyst via Suzuki coupling (Scheme 1).



Scheme 1. Synthesis of starting materials for the cyanation reaction.

General catalytic procedure for the preparation of starting materials by Suzuki coupling

Aryl bromide (4 mmol), arylboronic acid (6 mmol), Pd(II)/Mg-La (50 mg), $K_3PO_4\bullet 7H_2O$ (1.698 g, 8 mmol), 50% aqueous isopropanol (20 mL) was taken in a 50 mL round bottom flask (RB) and was stirred at 80 ° C. After the completion of the reaction (3 h), as monitored by TLC, the catalyst was separated by simple centrifugation and the reaction mixture was treated with brine (10 mL) and extracted with diethyl ether (4×15 mL). The combined organic extract was dried with anhydrous Na_2SO_4 (200 gm) and was concentrated under reduced pressure. The product was isolated by short column chromatography on silica gel column using ethyl acetate/hexane (5%) as eluent.[4]

General catalytic procedure for the cyanation reaction

A 10 mL round bottom flask was charged with 2-phenylpyridine (77.59 mg, 0.5 mmol), NH_4HCO_3 (83 mg, 1.05 mmol, 2.1 equiv.), Pd(II)/Mg-La (30 mg, 5.5 mol % of Pd), $Cu(NO_3)_2$•$3H_2O$ (187.5 mg, 1 mmol, 2 equiv.) and DMSO (2 mL). The reaction mixture was stirred at 140 ºC for 18 h. After the completion of the reaction, as monitored by TLC, 5 mL of ethyl acetate was added in the reaction mixture. The catalyst was separated by simple centrifugation and the reaction mixture was treated with brine (10 mL). The organic layer was separated and the aqueous layer was back extracted with ethyl acetate (3×5 mL). The combined ethyl acetate extract was dried with anhydrous Na_2SO_4 (50 gm) and was concentrated under reduced pressure. The pure product was isolated by flash column chromatography on silica gel using ethyl acetate/hexane (10%) as an eluent (pale yellow oil, 156 mg, 87% yield).

General catalytic procedure for the tandem Suzuki-cyanation reaction

A 25 mL round bottom flask was charged with 2-bromopyridine (96 mg, 1 mmol), phenylboronic acid (182 mg, 1.5 mmol), Pd(II)/Mg-La (40 mg), K_3PO_4•$7H_2O$ (424 mg, 2 mmol) and 50% aqueous isopropanol (3 mL). The reaction mixture was stirred at 80 ºC and was monitored by TLC. After the completion of the reaction (3 h), the reaction mixture was brought under room temperature and charged with NH_4HCO_3 (236 mg, 3 mmol), $Cu(NO_3)_2$•$3H_2O$ (454 mg, 2.5 mmol) and DMSO (2 mL). The reaction was continued at 140 ºC for another 18 h. After the completion of the reaction, as monitored by TLC, 10 mL of ethyl acetate was added and the catalyst was separated by simple centrifugation. The reaction mixture was treated with brine (10 mL) and the organic layer was separated. The aqueous layer was back extracted with ethyl acetate (3×5 mL). The combined ethyl acetate extract was dried with anhydrous Na_2SO_4 (50 gm) and was concentrated under reduced pressure. The pure product was isolated by flash column chromatography on silica gel using ethyl acetate/hexane (10%) as an eluent (pale yellow oil, 129 mg, 72% yield).

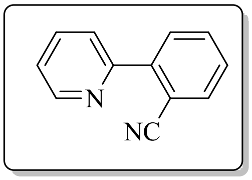
Recyclability test

The recyclability of the catalyst was checked using 2-phenylpyridine as the model substrate on 1.5 mmol scale. A 25 mL round bottom flask was charged with 2-phenylpyridine (232.7 mg, 1.5 mmol), Pd(II)/Mg-La catalyst (90 mg, 5.5 mol % of Pd), $Cu(NO_3)_2 \cdot 3H_2O$ (562.5 mg, 2 equiv), NH_4HCO_3 (249 mg, 2.1 equiv), DMSO (6 mL) and stirred at 140 °C for 18 h. After the completion of the reaction, as monitored by TLC, 15 mL of ethyl acetate was added in the reaction mixture. The catalyst was recovered by simple centrifugation, washed with water (100 mL), air-dried and used directly for the next cycle without further purification. The Pd(II)/Mg-La mixed oxide catalyst shows consistent activity and selectivity up to 4 cycles. Leaching of Pd species from the solid catalyst after the first cycle was determined by atomic absorption spectroscopy (AAS) and was found to be negligible. The Pd content of the fresh catalyst was 9.76% and in the case of used catalyst after the first cycle was found to be 9.68% as measured by AAS. Table 1 contains the Pd loading of the catalysts in each of the reaction cycles.

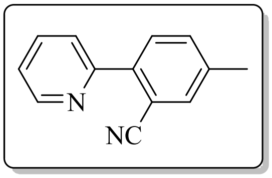
Table 1: AAS studies of Pd content of the catalysts in each cycle.

Cycle	% of Pd from AAS
Fresh	9.76
After 1st cycle	9.68
After 2nd cycle	9.66
After 3rd cycle	9.62
After 4th cycle	9.60

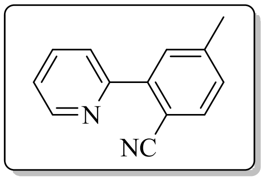
3. Analytical Data of all Products



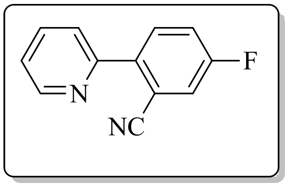
2-(Pyridin-2-yl)benzonitrile (Figure 4, **1,** 87% yield);[5] pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78-8.77 (m, 1H), 7.86-7.77 (m, 4H), 7.69 (td, *J* = 7.6, 1.3 Hz, 1H), 7.50 (td, *J* = 7.6, 1.2 Hz, 1H), 7.37-7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 149.8, 143.4, 136.8, 134.0, 132.7, 129.9, 128.7, 123.3, 123.2, 118.6, 111.0; MS (ESI) 181 (M+H).



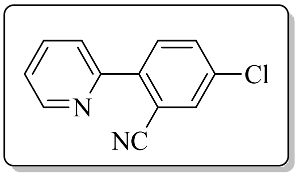
5-Methyl-2-(pyridin-2-yl)benzonitrile (Figure 4, **2,** 82% yield);[6] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76-8.75 (m, 1H), 7.8 (td, *J* = 7.9, 1.6 Hz, 1H), 7.77-7.73(m, 2H), 7.60 (d, *J* = 1.0 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.34- 7.32 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 149.7, 140.6, 139.0, 136.7, 134.3, 133.7, 129.8, 123.0, 122.8, 118.8, 110.6, 20.8; MS (ESI) 195 (M+H).



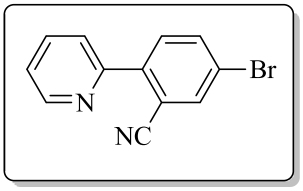
4-Methyl-2-(pyridin-2-yl)benzonitrile (Figure 4, **3**, 78% yield);[5] colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77-8.76 (m, 1H), 7.78-7.77 (m, 2H), 7.68-7.66 (m, 2H), 7.38-7.30 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 149.8, 143.8, 143.2, 136.7, 133.9, 130.6, 129.4, 123.2, 123.1, 118.9, 107.9, 21.7; MS (ESI) 195 (M+H).



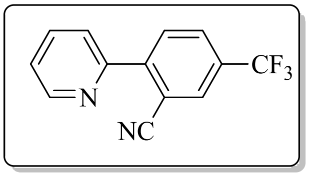
5-Fluoro-2-(pyridin-2-yl)benzonitrile (Figure 4, **4**, 76% yield);[6] colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77-8.66 (m, 1H), 7.87-7.83 (m, 2H), 7.77-7.75 (m, 1H), 7.50 (dd, J = 8.0, 2.7 Hz, 1H), 7.43-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, $J_{C\text{-}F}$ = 252.4 Hz), 154.2, 149.9, 139.8 (d, $J_{C\text{-}F}$ = 3.6 Hz), 136.9, 132.1 (d, $J_{C\text{-}F}$ = 8.1 Hz), 123.3, 123.0, 120.6 (d, $J_{C\text{-}F}$ = 25.4 Hz), 120.4, 117.4 (d, $J_{C\text{-}F}$ = 2.7 Hz), 112.3 (d, $J_{C\text{-}F}$ = 9.0 Hz); MS (ESI) 199 (M+H).



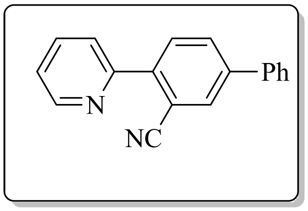
5-Chloro-2-(pyridin-2-yl)benzonitrile (Figure 4, **5**, 68% yield);[5] white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.78-8.71 (m, 1H), 7.86-7.77 (m, 4H), 7.66 (dd, J = 8.3, 2.1Hz, 1H), 7.39-7.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0, 150.0, 141.7, 136.9, 134.9, 133.5, 133.1, 131.2, 123.5, 123.0, 117.4, 112.3.



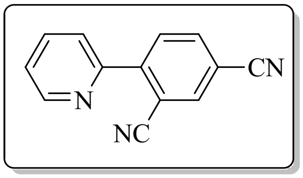
5-Bromo-2-(pyridin-2-yl)benzonitrile (Figure 4, **6,** 62% yield);[7] white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.77 (d, J = 4.3 Hz, 1H), 7.93 (d, J = 1.7 Hz, 1H), 7.87-7.73 (m, 4H), 7.40-7.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0, 150.0, 142.1, 136.9, 136.4, 136.0, 131.3, 123.5, 123.0, 122.5, 117.2, 112.6; MS (ESI) 260 (M+H).



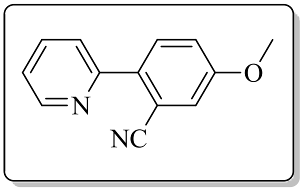
2-(Pyridin-2-yl)-4-(trifluoromethyl)benzonitrile (Figure 4, **7**, 62% yield);[8] white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.80 (d, J = 4.7 Hz, 1H), 8.05 (s, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.90 (t, J = 7.7 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.47–7.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 150.1, 146.4, 137.0, 131.8 (q, $J_{C\text{-}F}$ = 29.9 Hz), 130.9 (q, $J_{C\text{-}F}$ = 3.6 Hz), 130.6, 129.3 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.0, 123.2, 122.8 (q, $J_{C\text{-}F}$ = 272 Hz), 117.4, 112.0; MS (ESI) 249 (M+H).



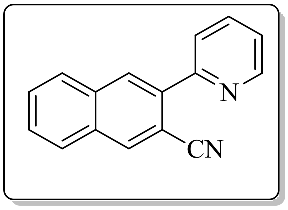
5-Phenyl-2-(pyridin-2-yl)benzonitrile (Figure 4, **8**, 75% yield);[5] yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80-8.79 (m, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.94-7.89 (m, 2H), 7.87-7.83 (m, 2H), 7.63-7.61 (m, 2H), 7.51-7.48 (m, 2H), 7.45-7.41 (m, 1H), 7.38-7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 149.9, 141.8, 141.8, 138.2, 136.8, 132.5, 131.3, 130.4, 129.1, 128.4, 126.9, 123.2, 123.1, 118.7, 111.3; MS (ESI) 257 (M+H).



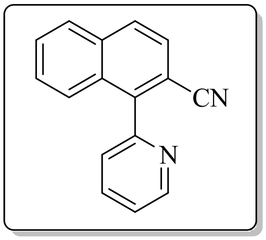
4-(pyridin-2-yl)isophthalonitrile (Figure 4, **9**, 72% yield);[9] white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.82-8.81 (m, 1H), 8.09 (d, J = 1.5 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.96 (dd, J = 1.6, 8.2 Hz, 1H), 7.90 (td, J = 1.6, 7.2 Hz, 1H), 7.86-7.84 (m, 1H), 7.46–7.43 (m, 1H). ^{13}CNMR ($CDCl_3$, 125 MHz) δ: 153.1, 150.2, 146.9, 137.3, 137.1, 135.7, 130.9, 124.3, 123.3, 116.6, 116.5, 113.2, 112.4; MS (ESI) 206 (M+H).



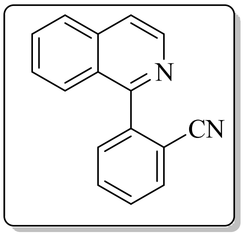
5-methoxy-2-(pyridin-2-yl)benzonitrile (Figure 4, **10**, 68% yield);[9] colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.5 Hz, 1H), 7.82-7.74 (m, 3H), 7.32-7.30 (m, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 2.7, 8.8 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 154.9, 149.7, 136.7, 135.9, 131.2, 122.7, 122.6, 119.3, 118.6, 118.4, 111.6, 55.6; MS (ESI) 211 (M+H).



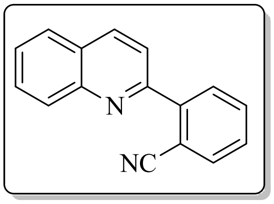
3-(pyridin-2-yl)naphthalene-2-carbonitrile (Figure 4, **11**, 53% yield);[5] white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82-8.81 (m, 1H), 8.40 (s, 1H), 8.28 (s, 1H), 7.95-7.34 (m, 2H), 7.87-7.86 (m, 2H), 7.66-7.61 (m, 2H), 7.39-7.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 149.8, 143.6, 136.7, 134.4, 132.9, 132.4, 131.7, 129.6, 128.8, 127.9, 127.7, 118.9, 108.6; MS (ESI) 231 (M+H).



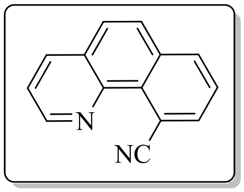
1-(Pyridin-2-yl)-2-naphthonitrile (Figure 4, **12**, 72% yield);[6] yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, *J* = 4.3, Hz, 1H), 7.99-7.90 (m, 3H), 7.74-7.70 (m, 2H), 7.66-7.60 (m, 2H), 7.56-7.53 (m, 1H), 7.50-7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 149.9, 144.4, 136.7, 135.0, 131.1, 129.4, 128.7, 128.3, 127.9, 126.8, 126.7, 125.6, 123.5, 118.5, 109.7; MS (ESI) 231 (M+H).



2-(Isoquinolin-1-yl)benzonitrile (Figure 4, **13**, 79% yield);[6] yellow solid; ^{1}H NMR (400 MHz, CDCl3) δ 8.66 (d, *J* = 5.6 Hz, 1H), 7.95-7,93 (m, 1H), 7.88 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.78-7.72 (m, 4H), 7.67-7.66 (m, 1H), 7.63-7.55 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.8, 142.8, 142.0, 136.6, 133.3, 132.2, 130.8, 130.4, 128.8, 127.7, 127.1, 126.7, 126.4, 121.3, 117.5, 113.0; MS (ESI) 231 (M+H).



2-(quinolin-2-yl)benzonitrile (Figure 4, **14**, 73% yield);[5] white solid; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.32 (d, *J* = 8.5 Hz , 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.89-7.84 (m, 3H), 7.79-7.72 (m, 2H), 7.62-7.59 (m, 1H), 7.56-7.53 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 155.1, 148.0, 143.6, 137.0, 134.2, 132.8, 130.1, 129.7, 189.9, 128.9, 127.5, 127.3, 127.2, 120.5, 118.6, 111.5; MS (ESI) 231 (M+H).



Benzo[*h*]quinoline-10-carbonitrile (Figure 4, **15,** 63% yield);[9] colorless solid; ^{1}H NMR (CDCl$_3$, 500 MHz) δ: 9.14 (dd, *J* = 4.4, 1.8Hz, 1H), 8.23 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.17-8.12 (m, 2H), 7.82 (q, J = 8.8 Hz, 2H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 8.0, 4.4 Hz, 1H). ^{13}CNMR (CDCl$_3$, 125 MHz) δ: 148.4, 144.4, 136.2, 135.6, 134.0, 132.6, 130.7, 127.3, 127.2, 127.0, 126.9, 123.0, 120.7, 108.9.

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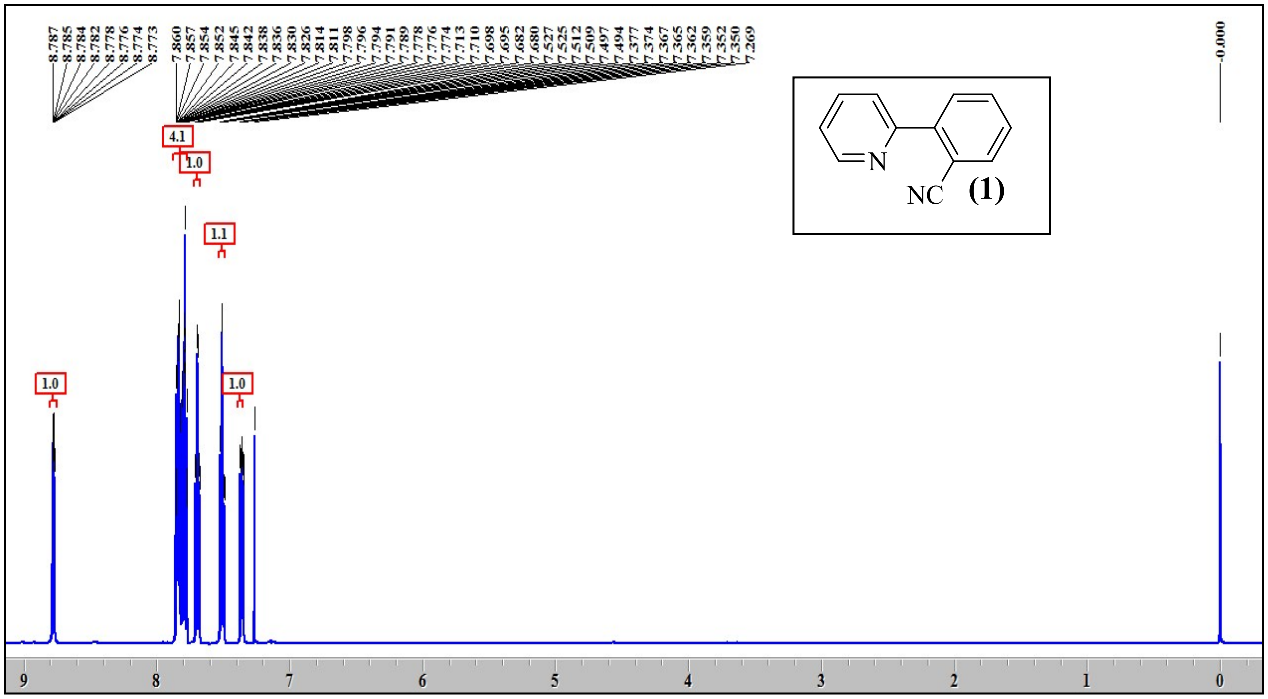
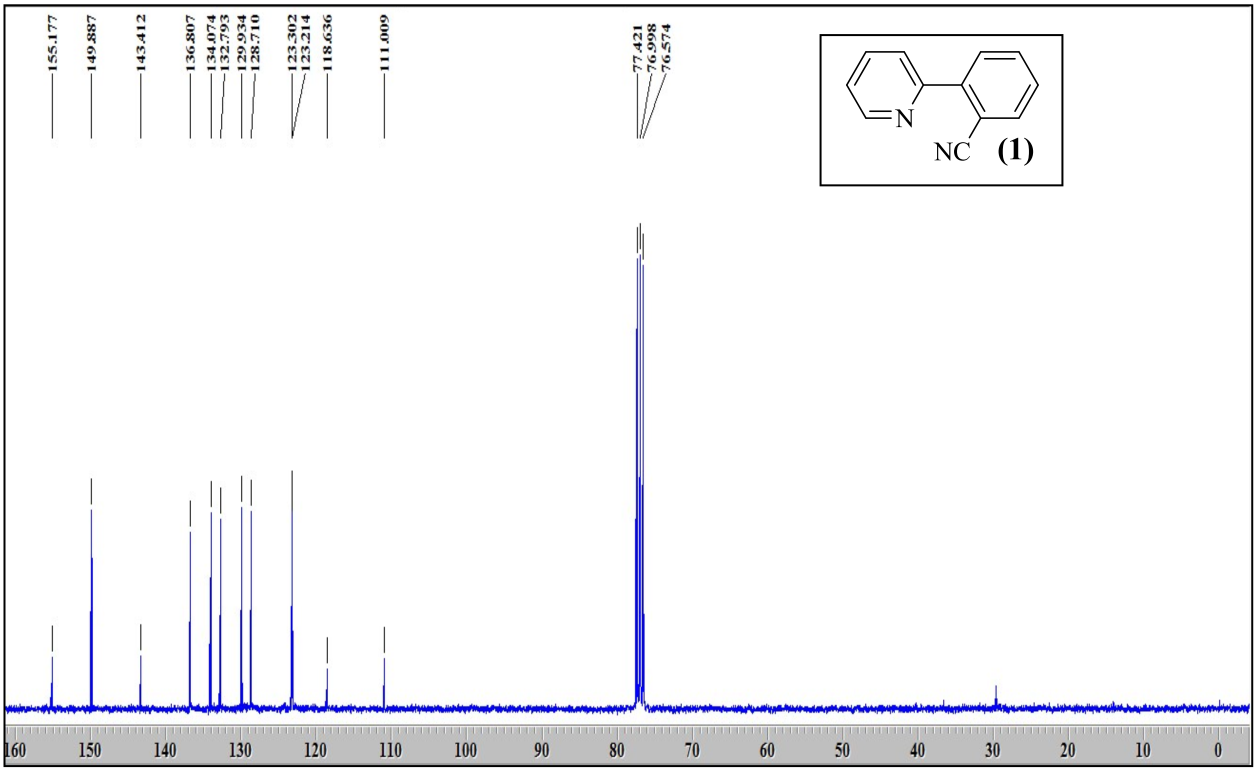
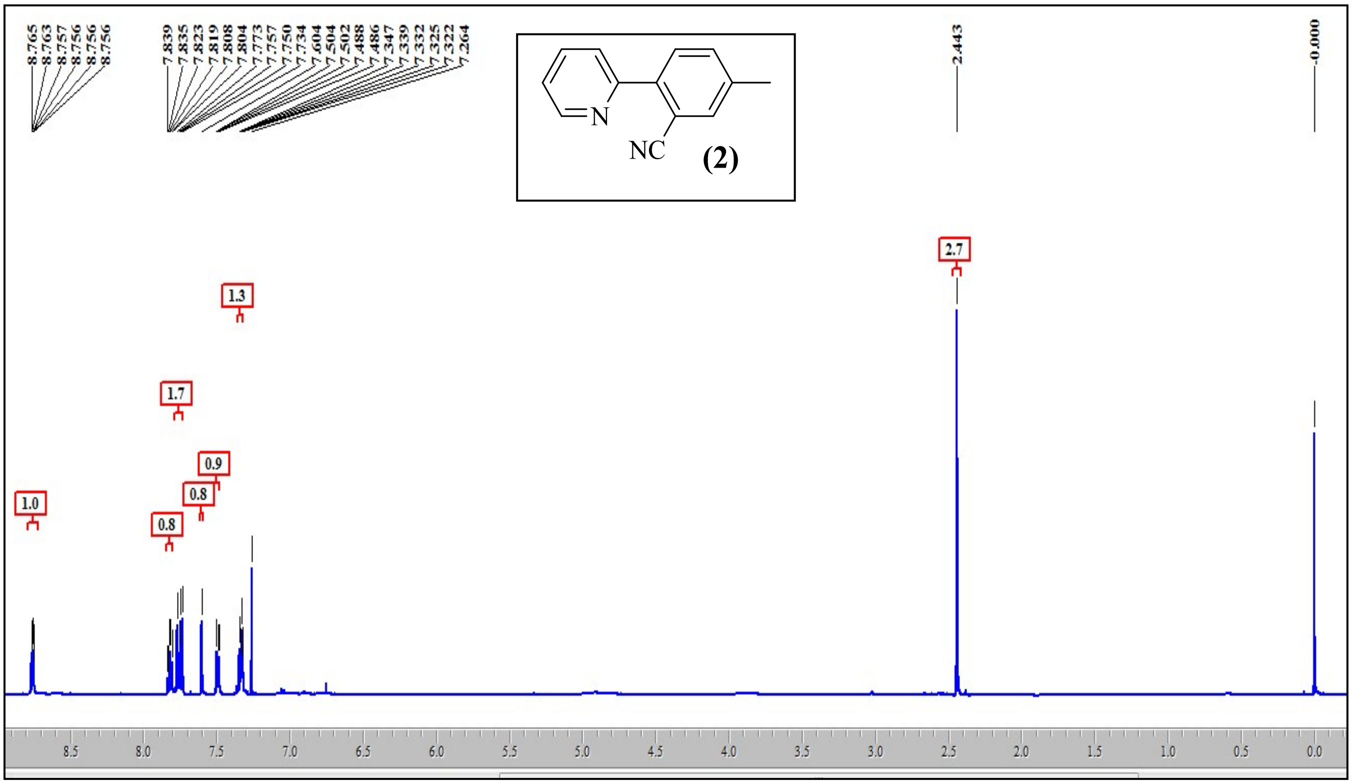
5. ^{1}H and ^{13}C NMR spectra of all products:

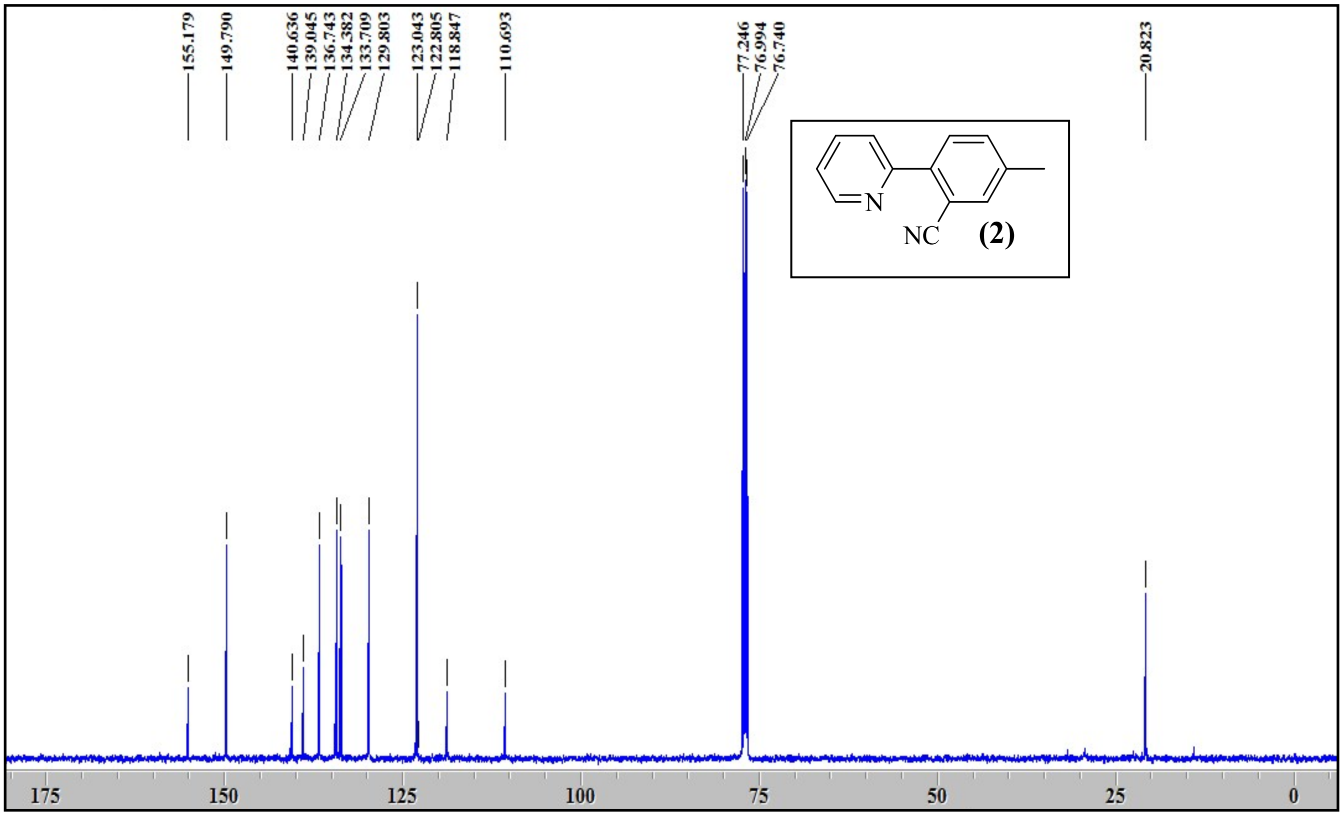
^{1}H and ^{13}C NMR Spectra of 2-(Pyridin-2-yl)benzonitrile (Figure 4, 1)



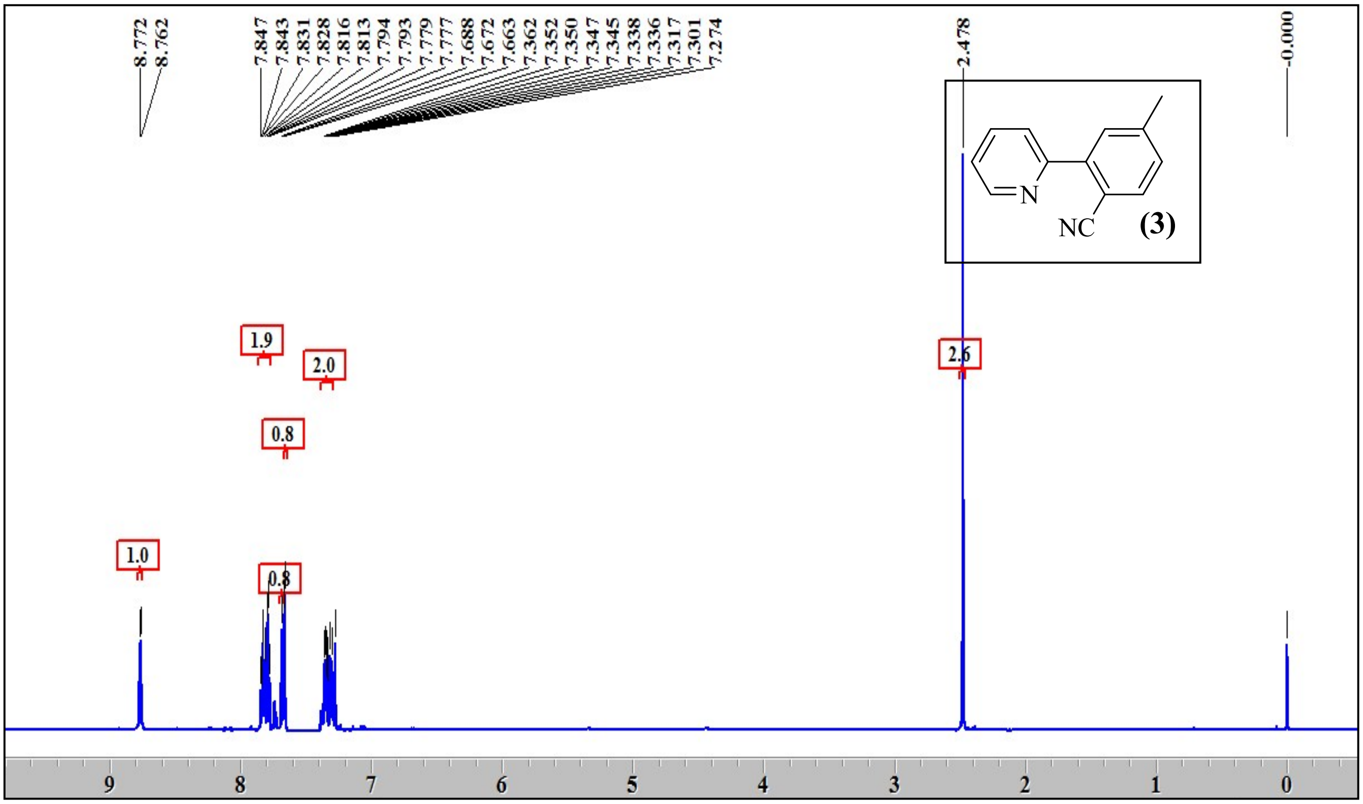


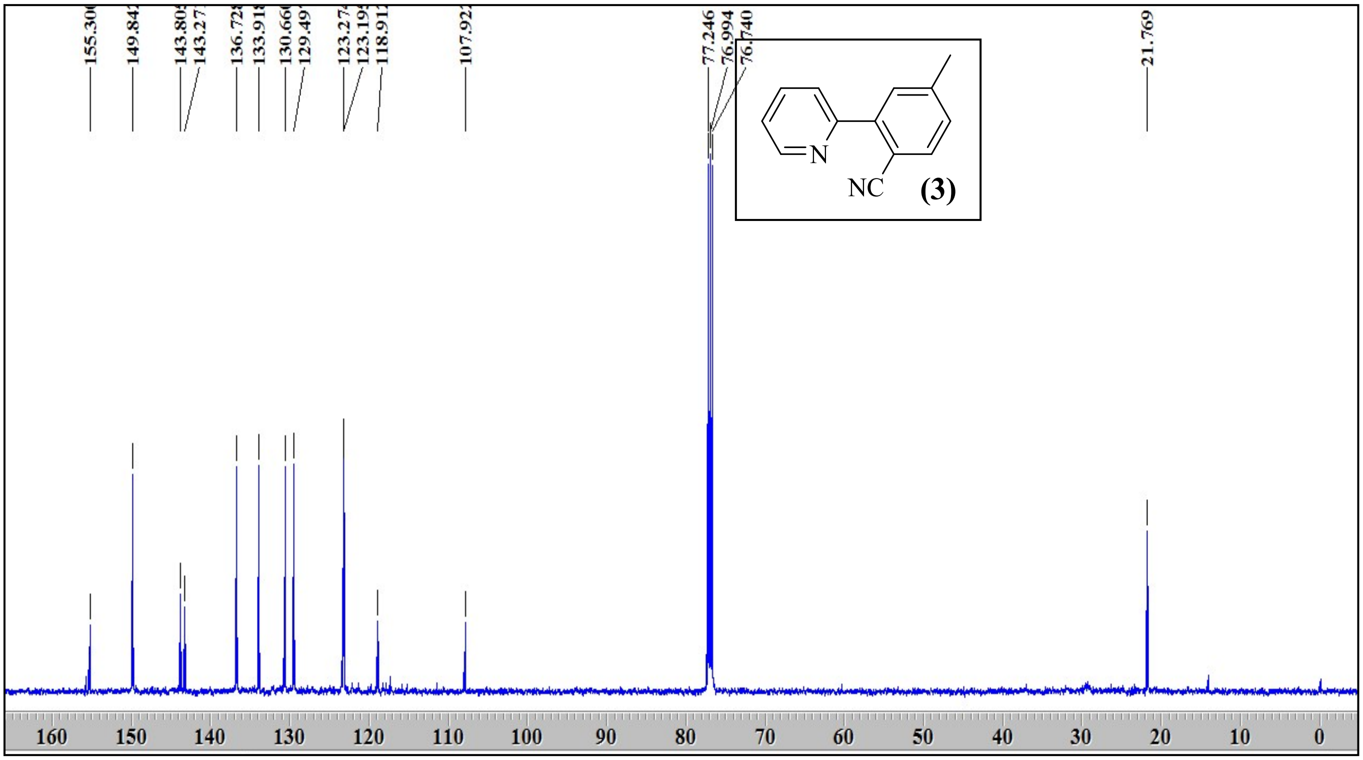
^{1}H and ^{13}C NMR Spectra of 5-Methyl-2-(pyridin-2-yl)benzonitrile (Figure 4, 2)



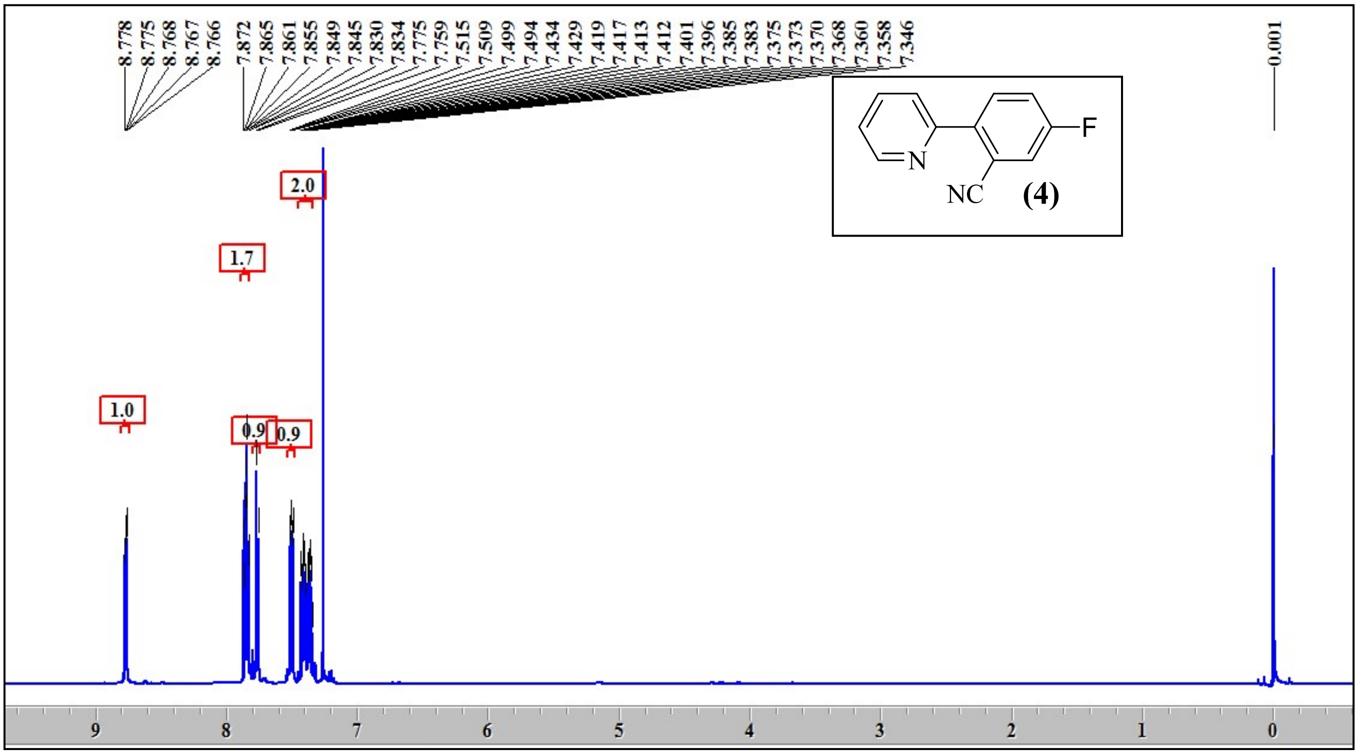


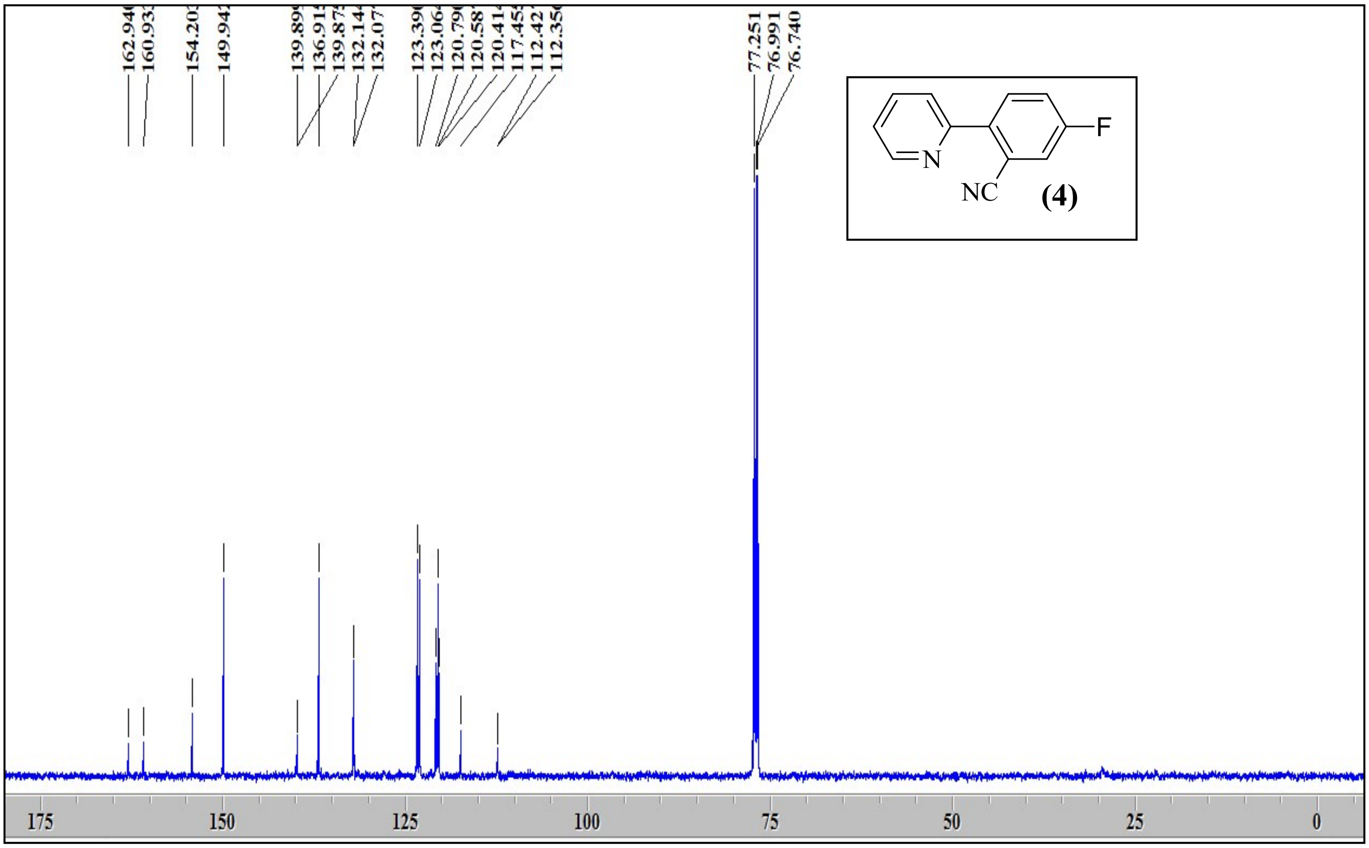
^{1}H and ^{13}C NMR Spectra of 4-Methyl-2-(pyridin-2-yl)benzonitrile (Figure 4, 3)



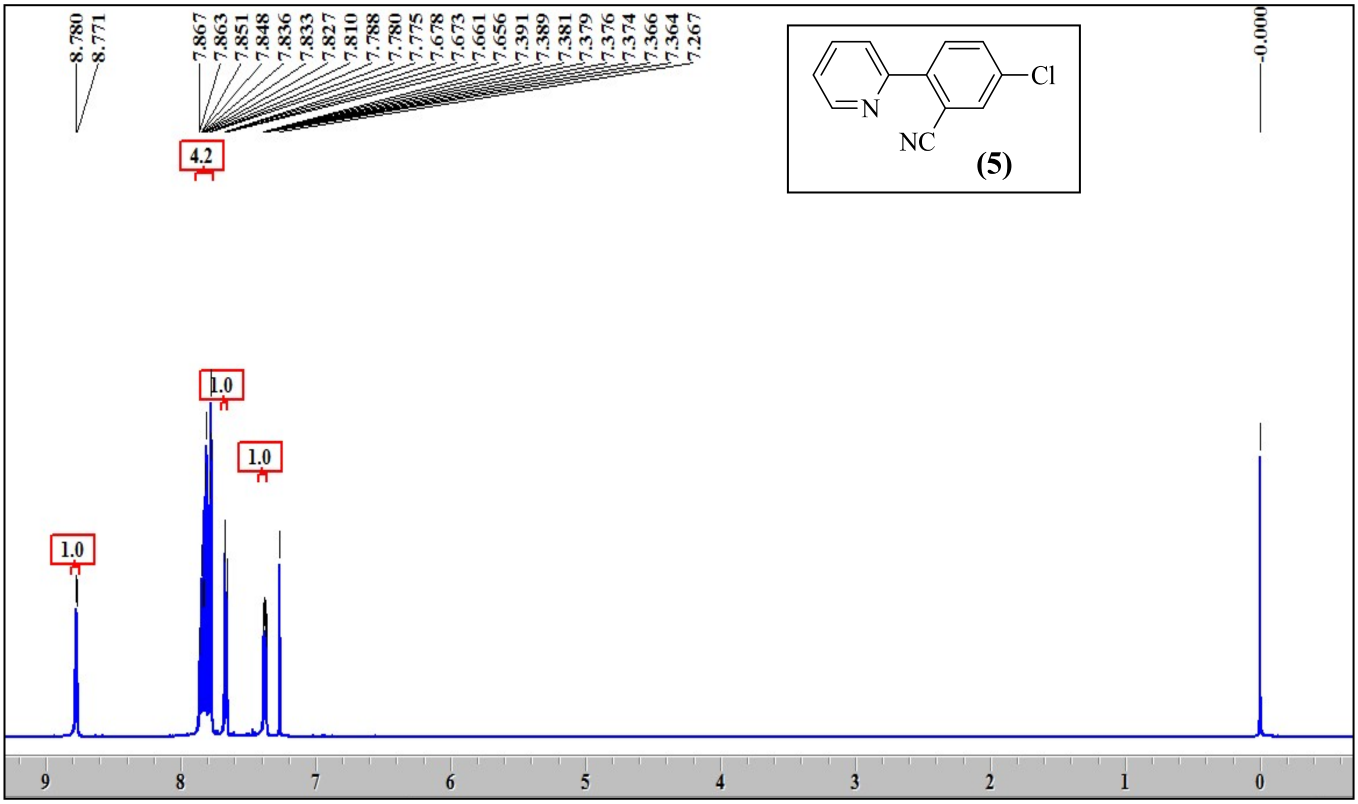


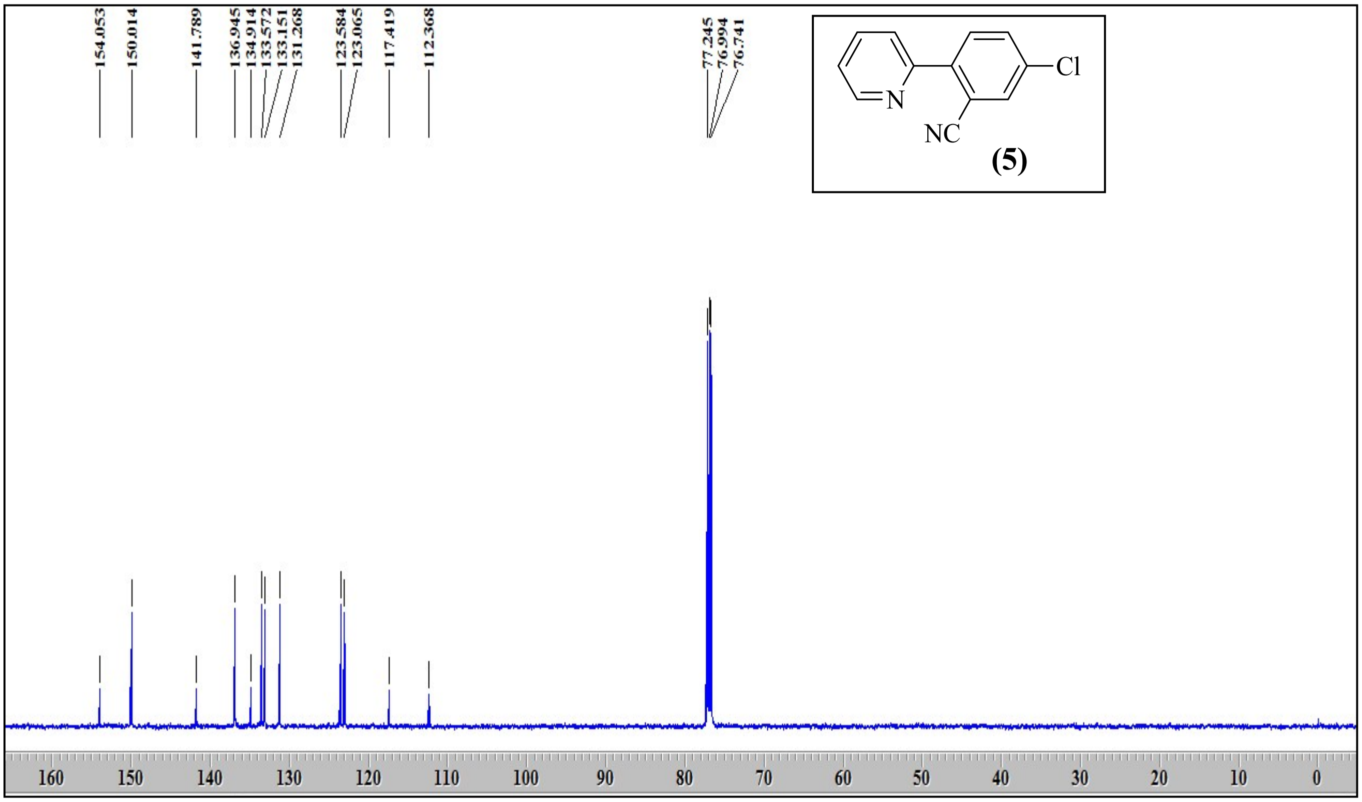
^1H and ^{13}C NMR Spectra of 5-Fluoro-2-(pyridin-2-yl)benzonitrile (Figure 4, 4)



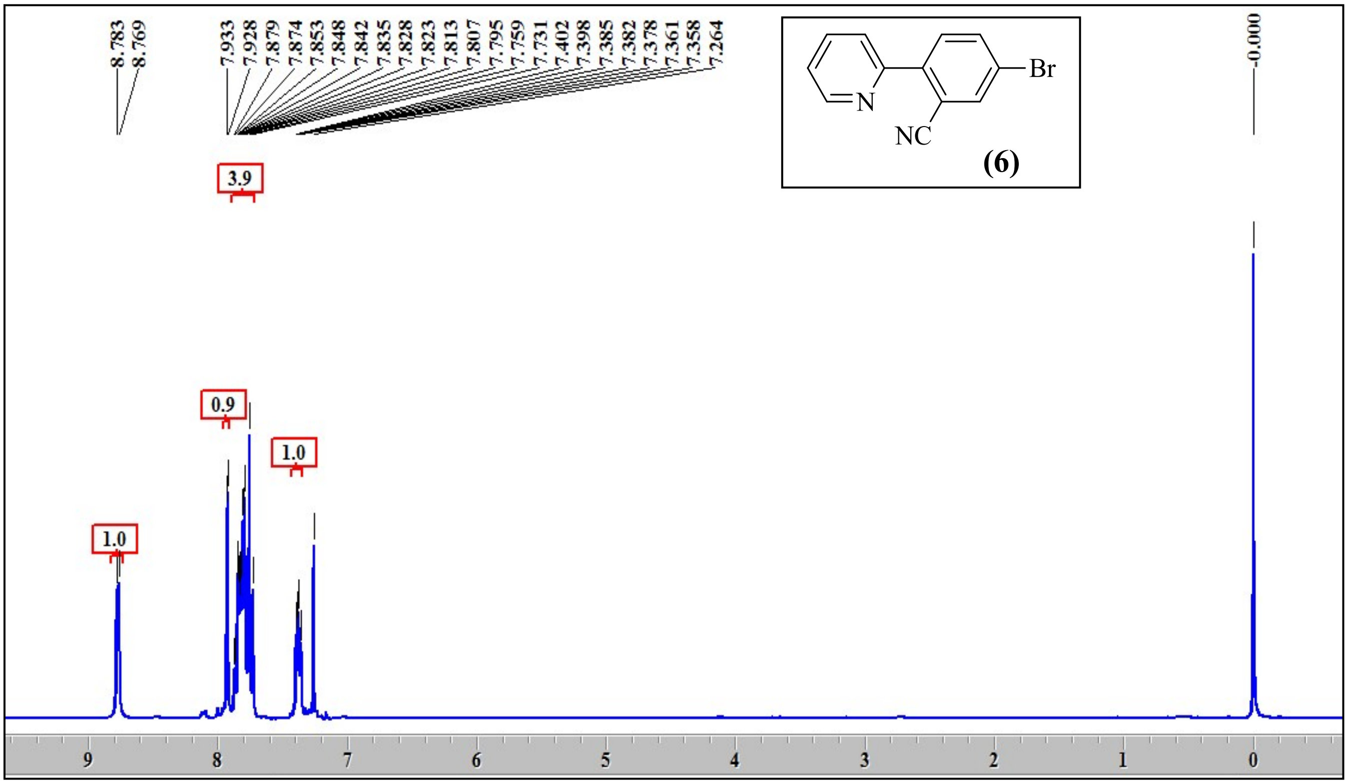


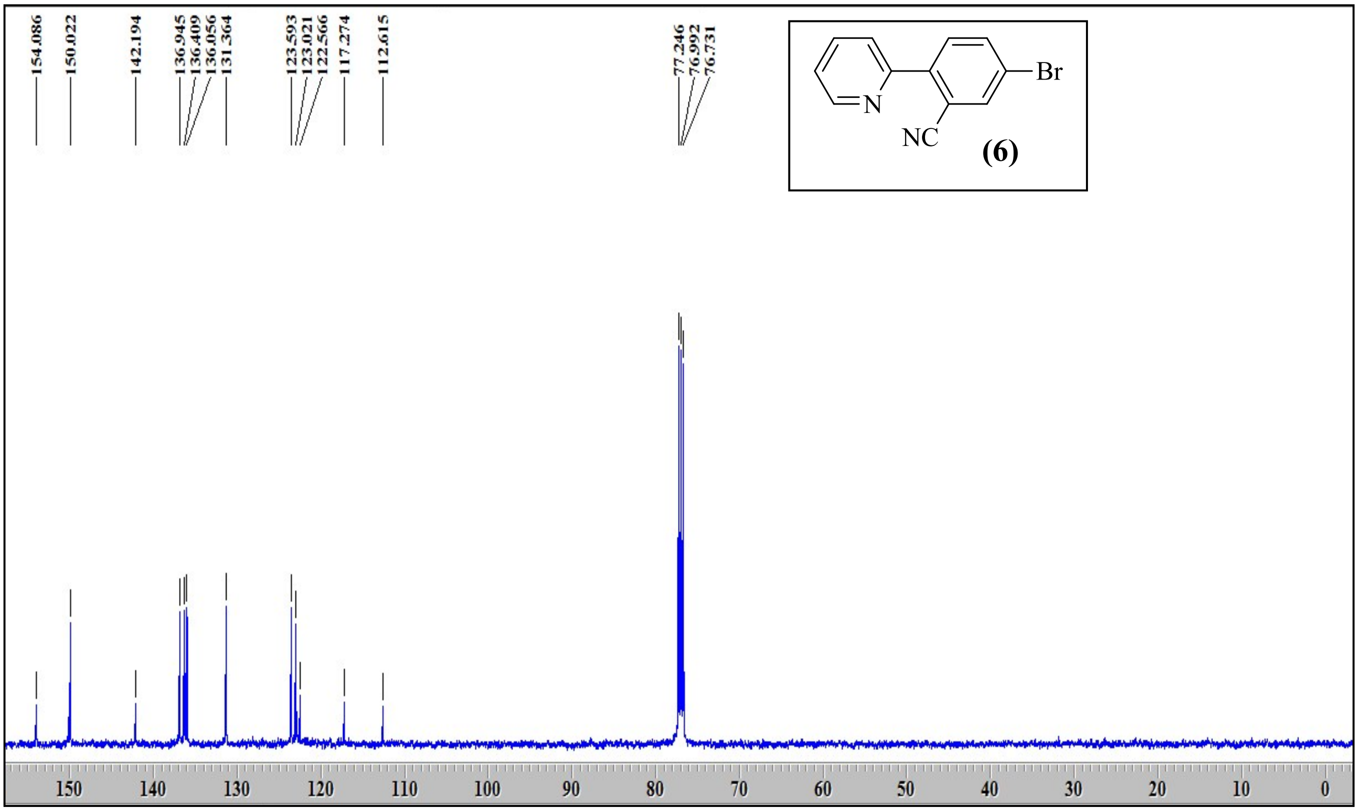
^1H and ^{13}C NMR Spectra of 5-Chloro-2-(pyridin-2-yl)benzonitrile (Figure 4, 5)



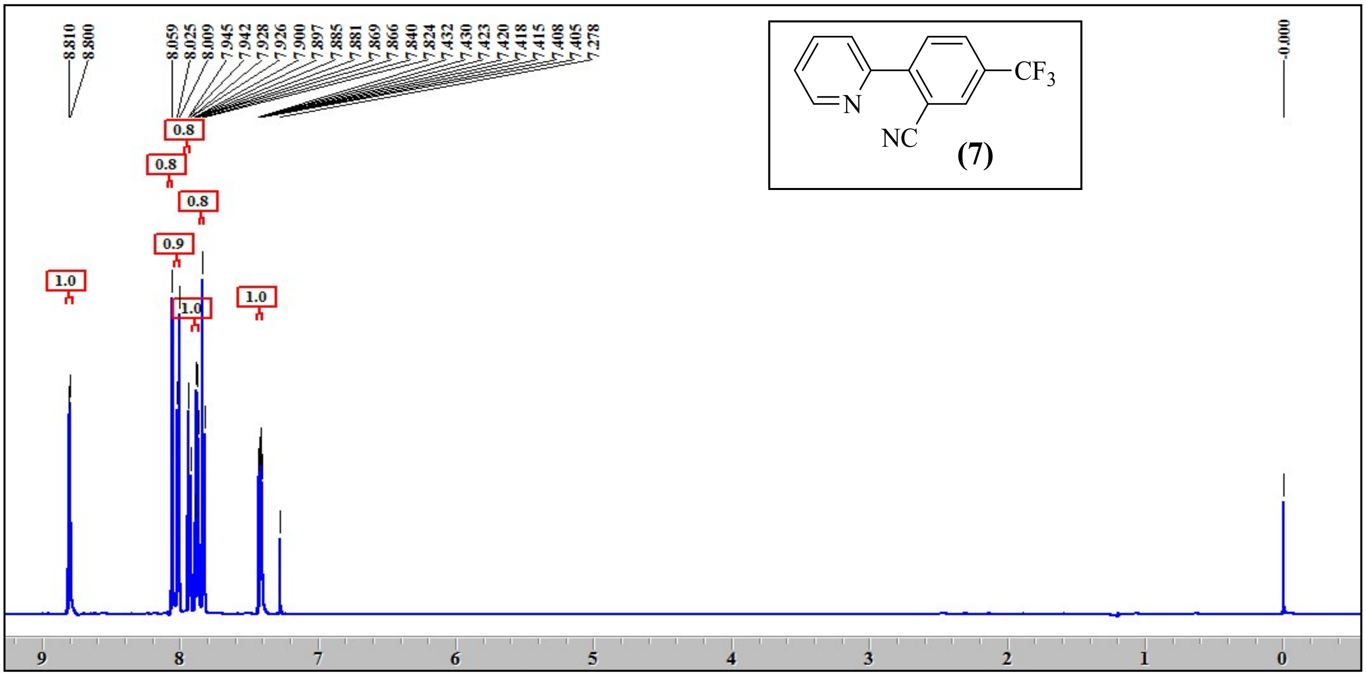


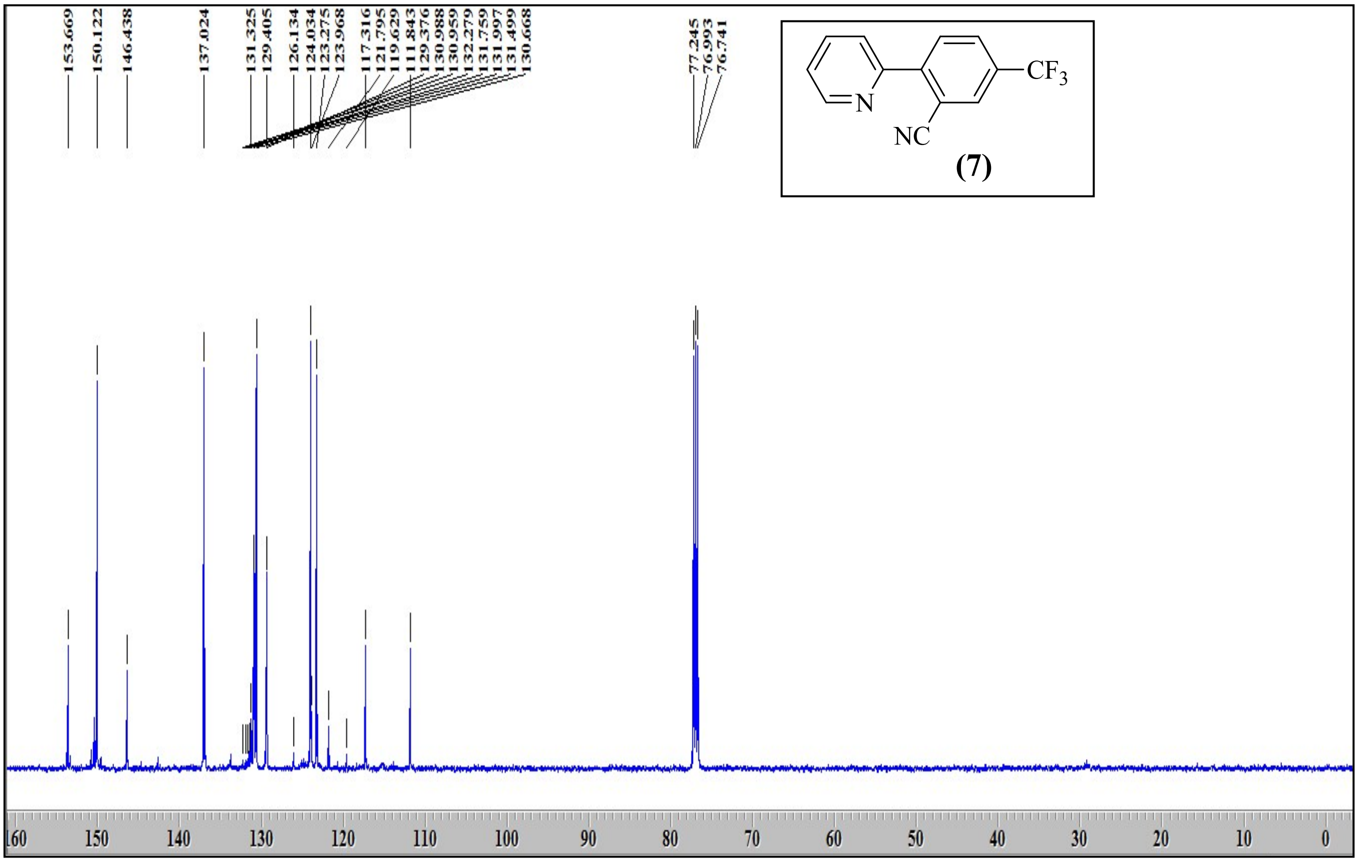
^{1}H and ^{13}C NMR Spectra of 5-Bromo-2-(pyridin-2-yl)benzonitrile (Figure 4, 6)



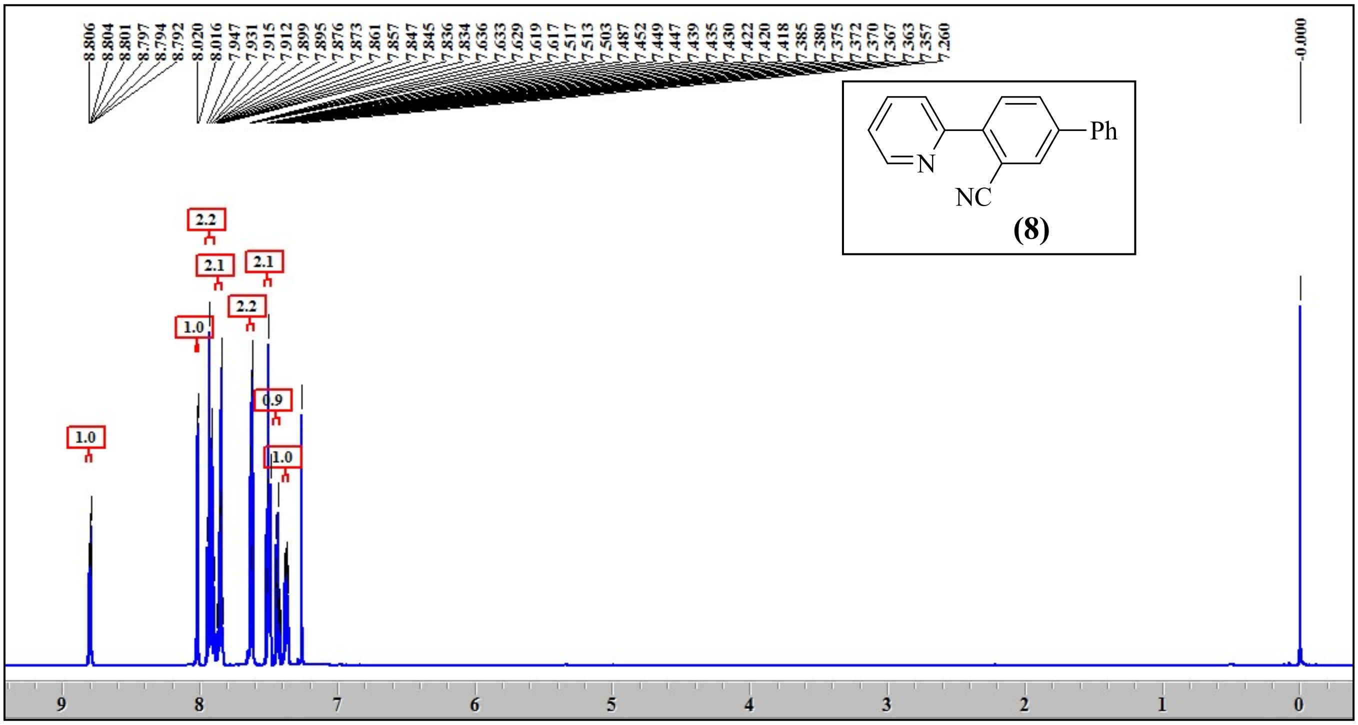


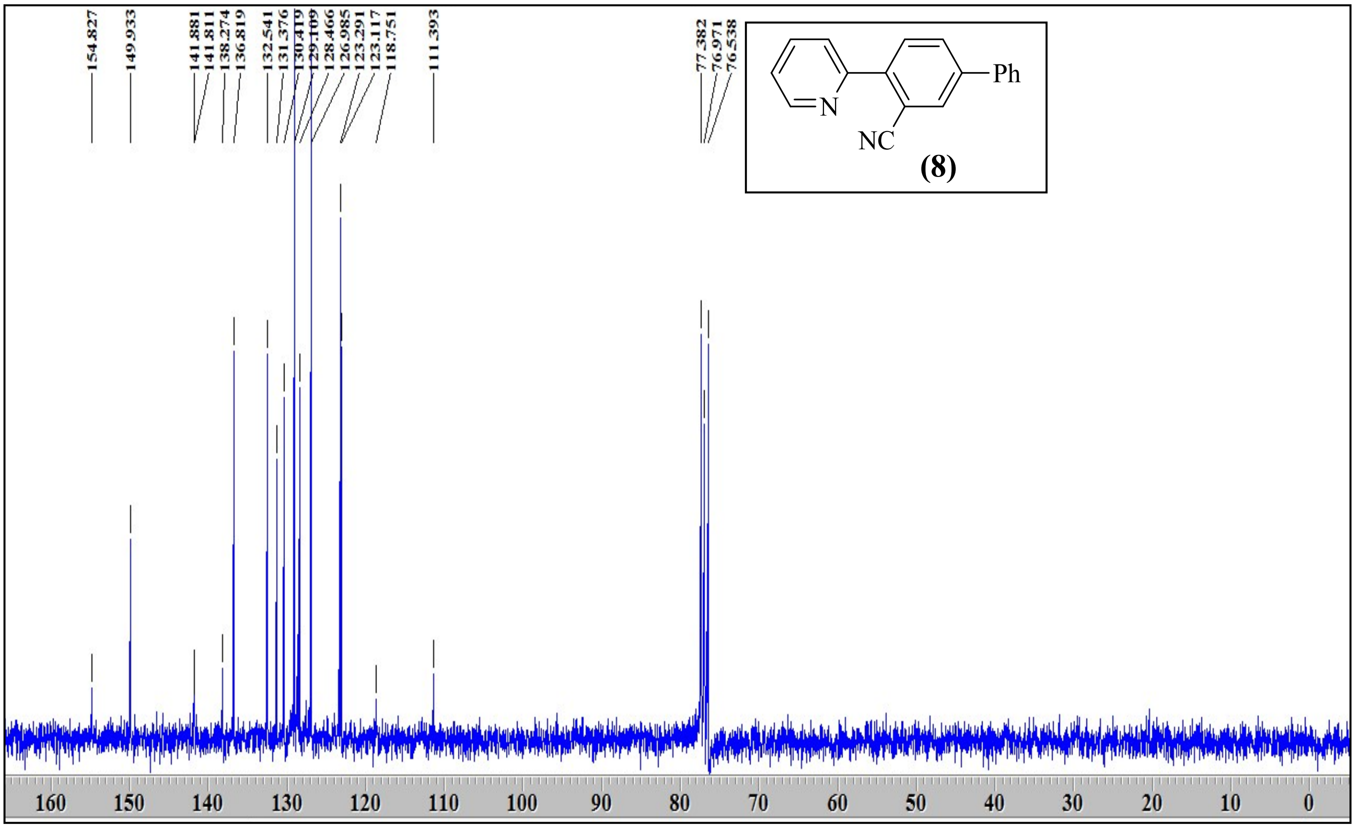
^{1}H and ^{13}C NMR Spectra of 2-(Pyridin-2-yl)-4-(trifluoromethyl)benzonitrile (Figure 4, 7)



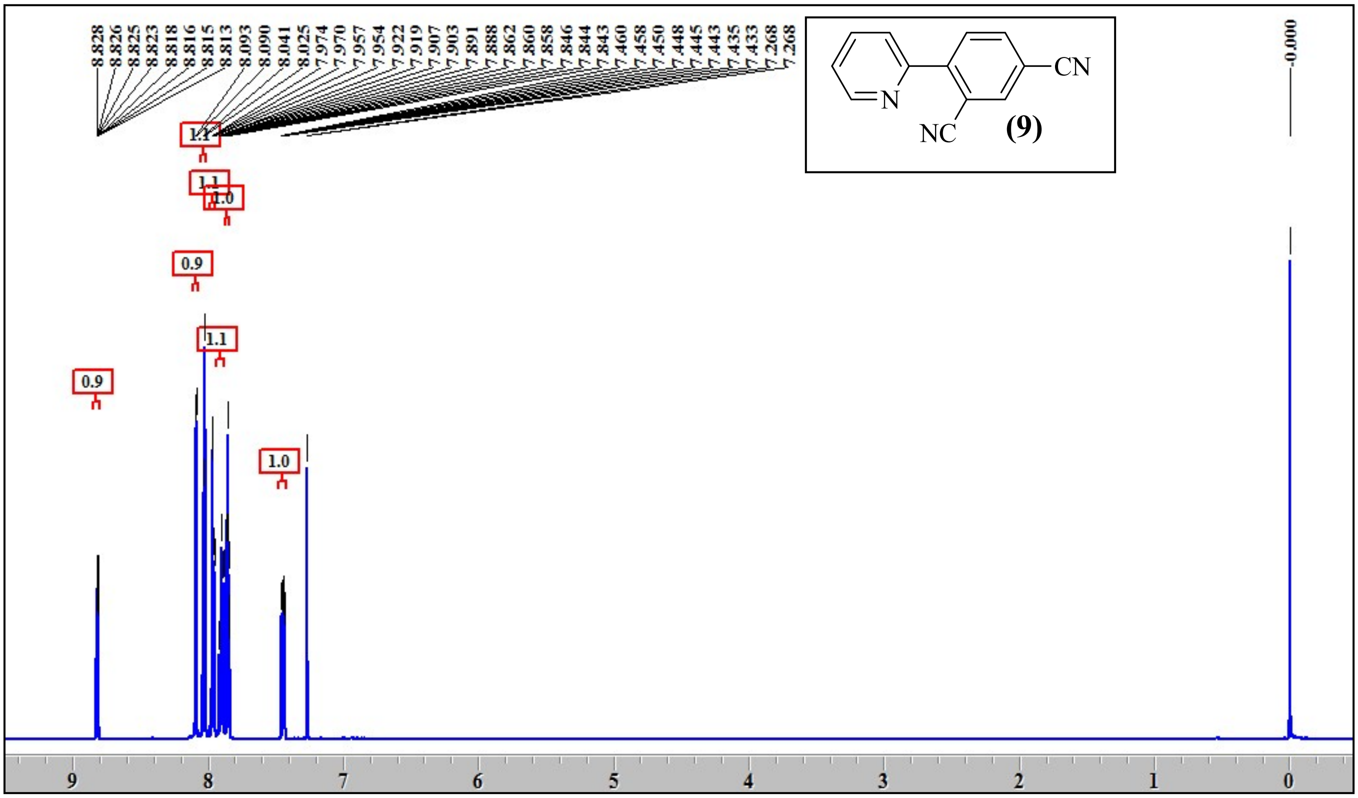


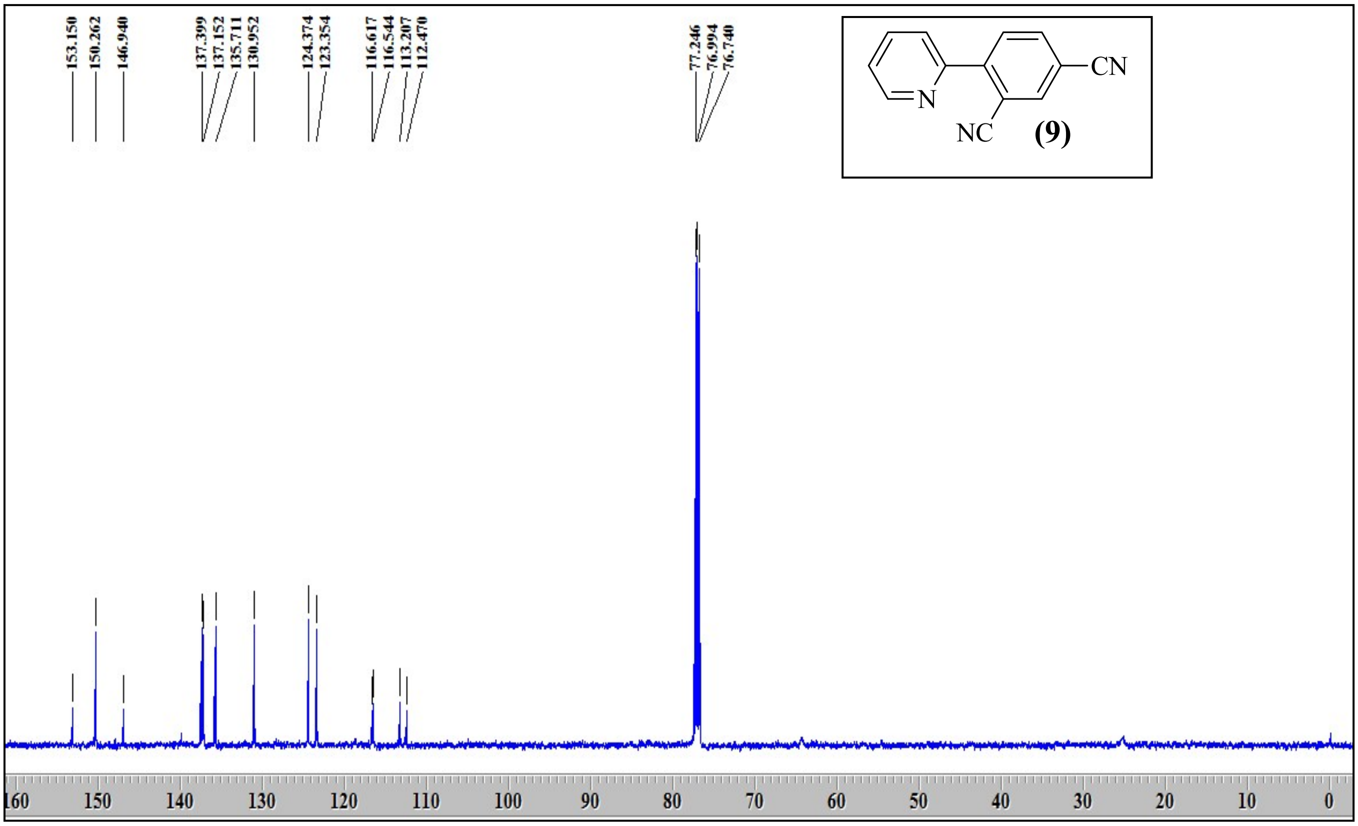
^{1}H and ^{13}C NMR Spectra of 5-Phenyl-2-(pyridin-2-yl)benzonitrile (Figure 4, 8)



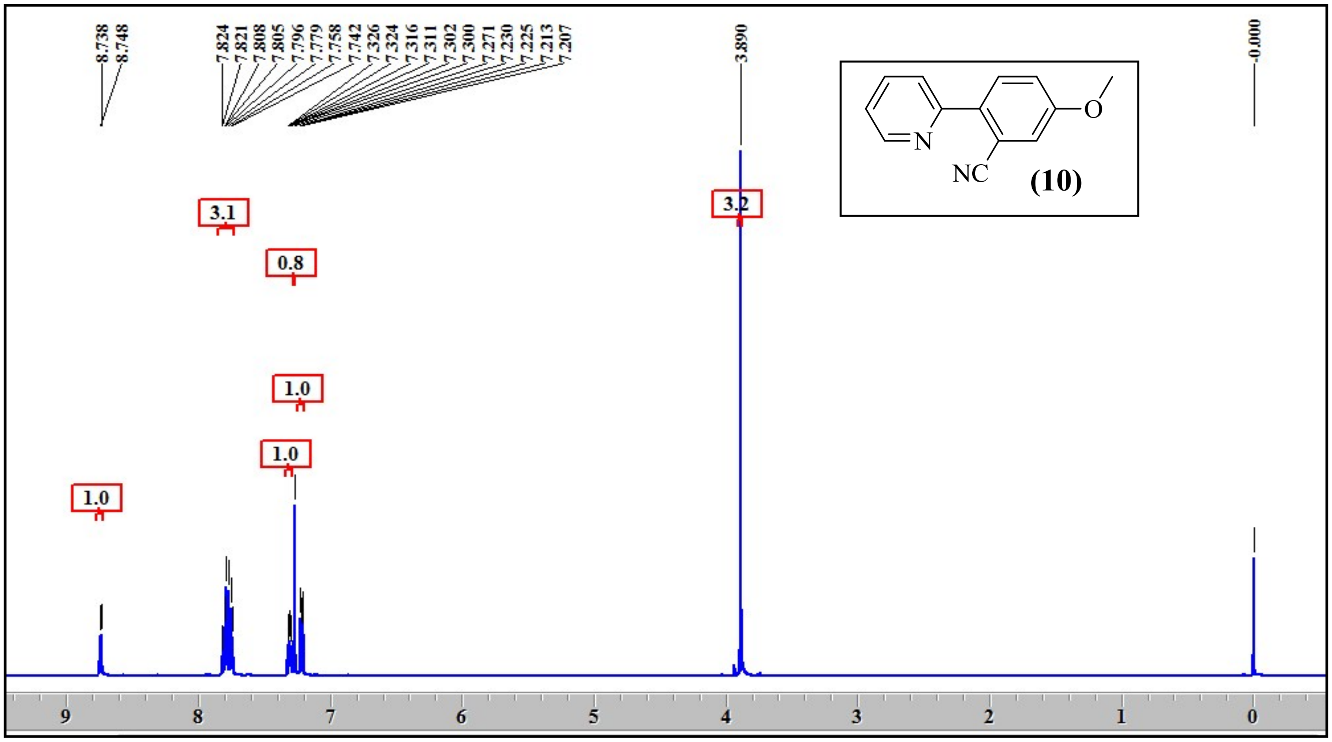


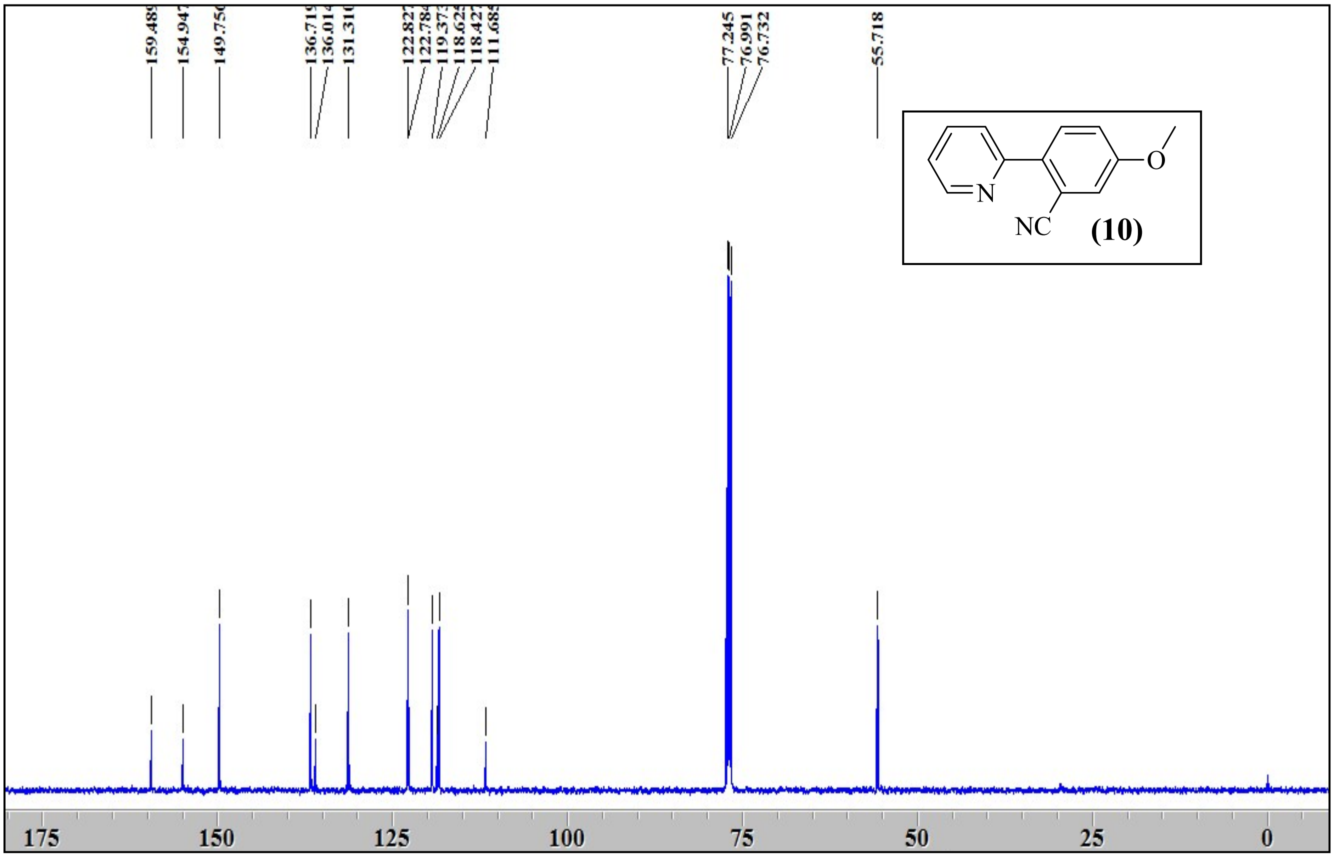
^{1}H and ^{13}C NMR Spectra of 4-(pyridin-2-yl)isophthalonitrile (Figure 4, 9)



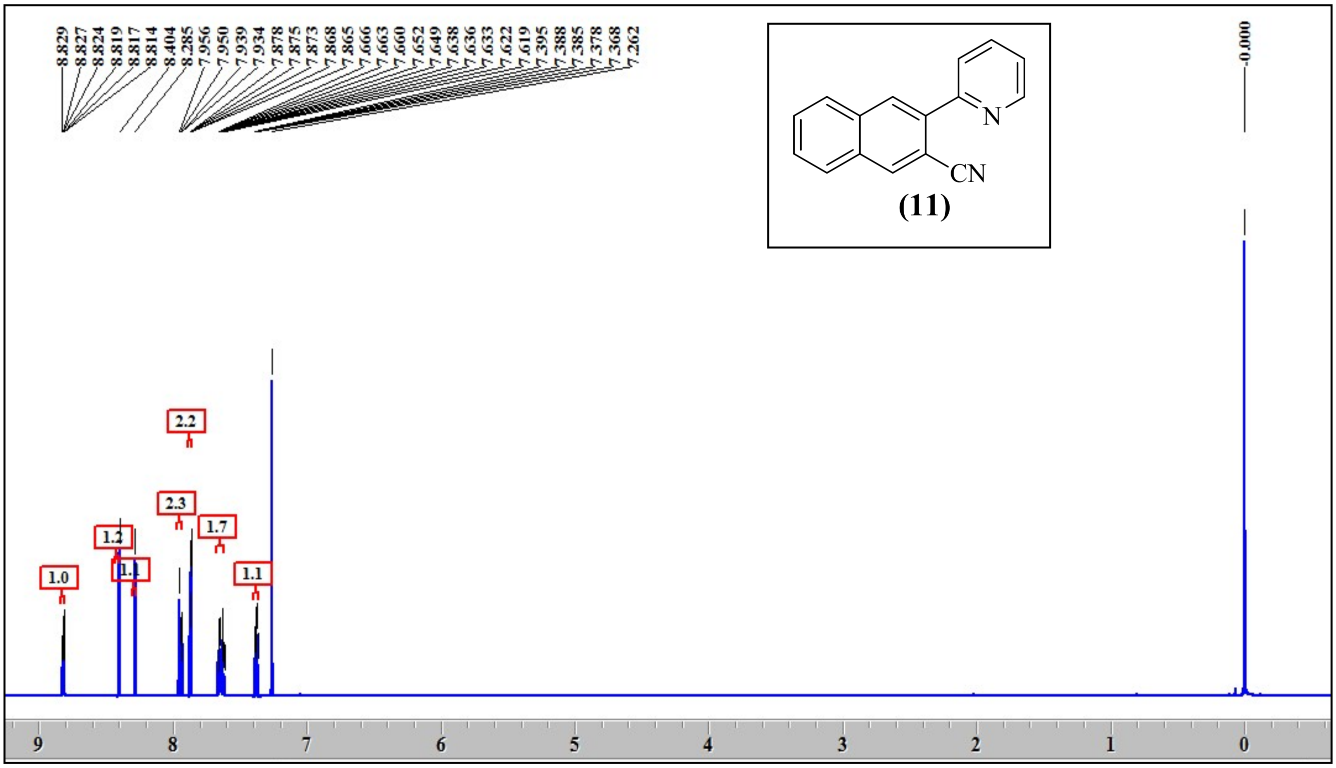


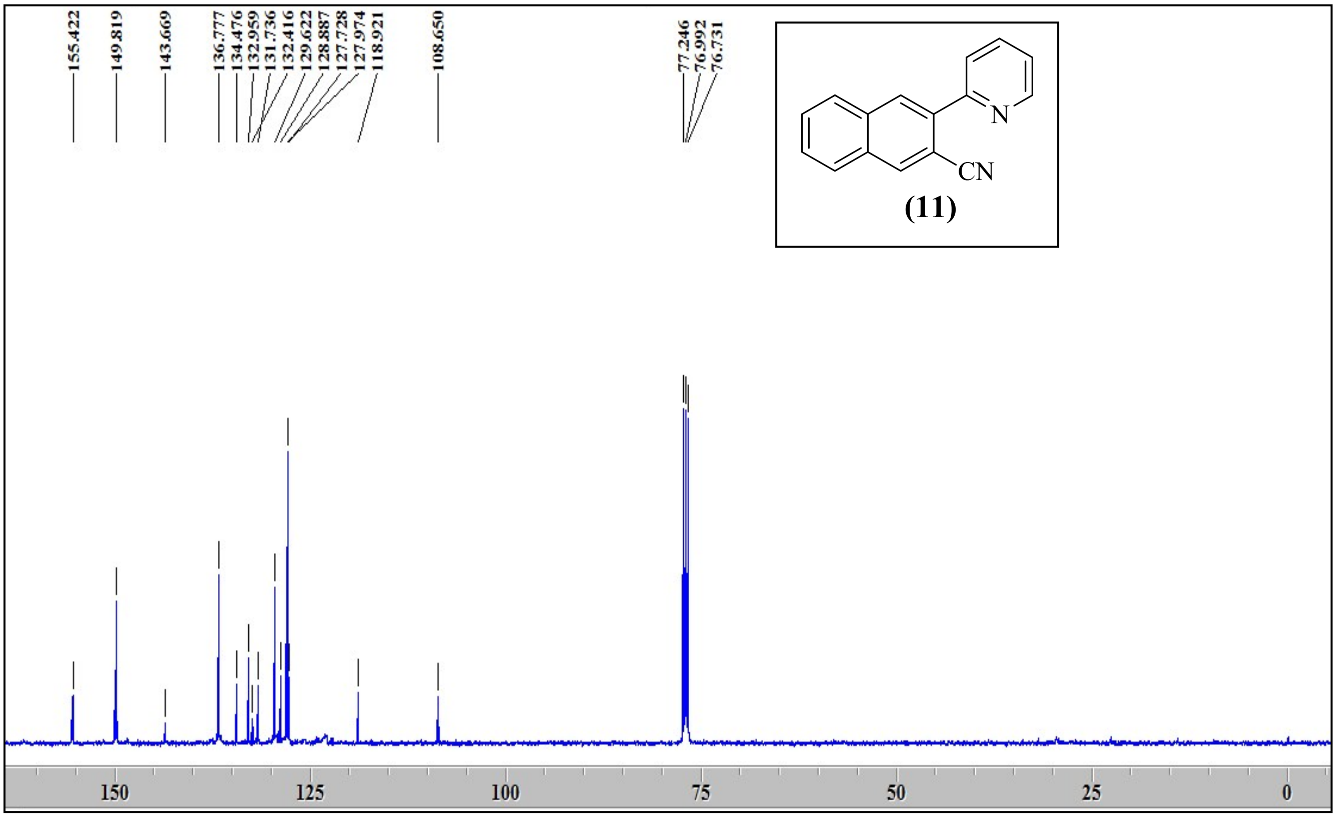
^1H and ^{13}C NMR Spectra of 5-methoxy-2-(pyridin-2-yl)benzonitrile (Figure 4, 10)



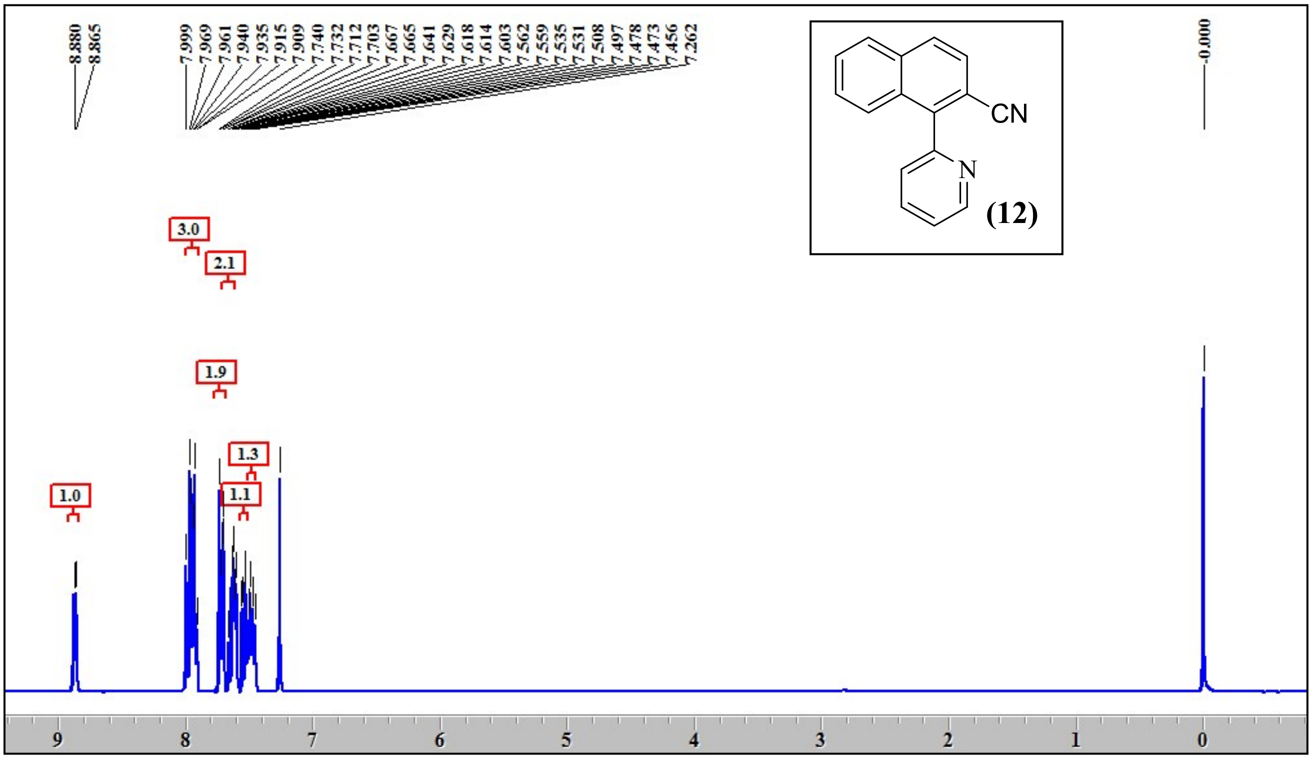


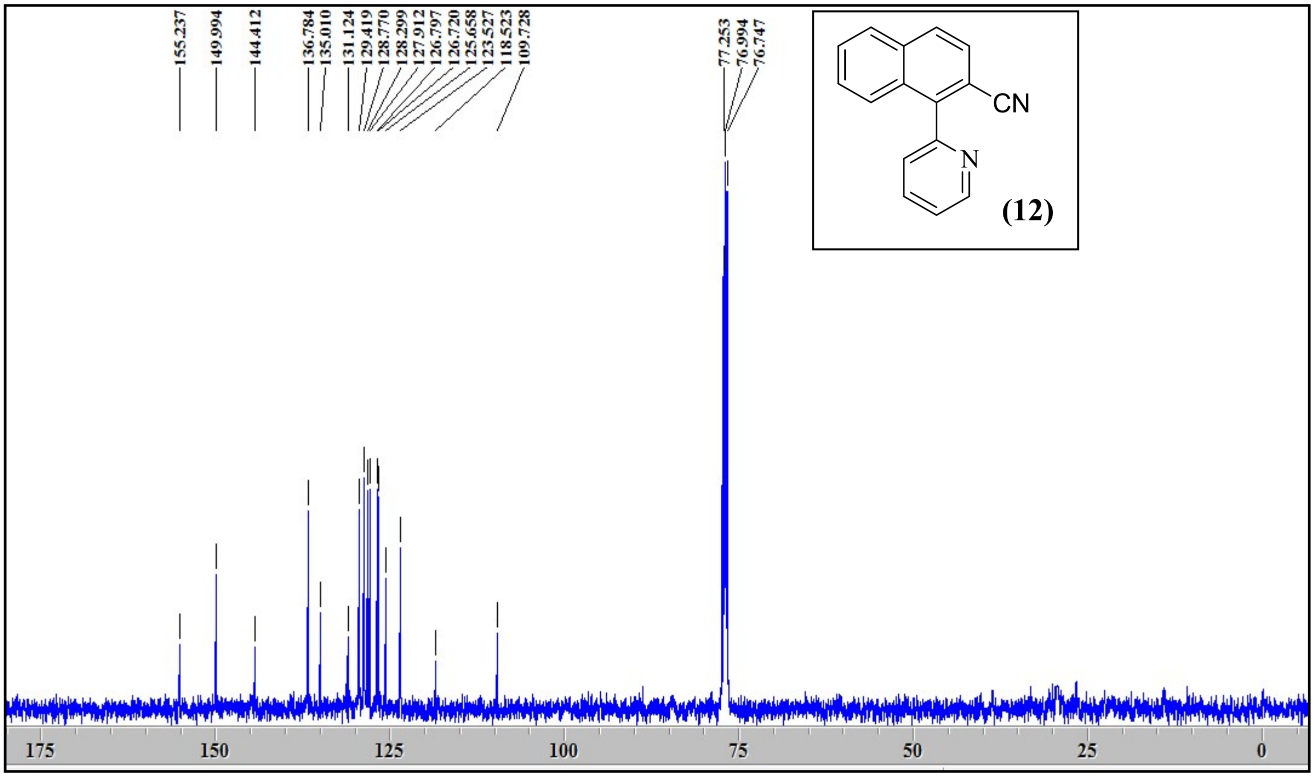
^{1}H and ^{13}C NMR Spectra of 3-(pyridin-2-yl)naphthalene-2-carbonitrile (Figure 4, 11)



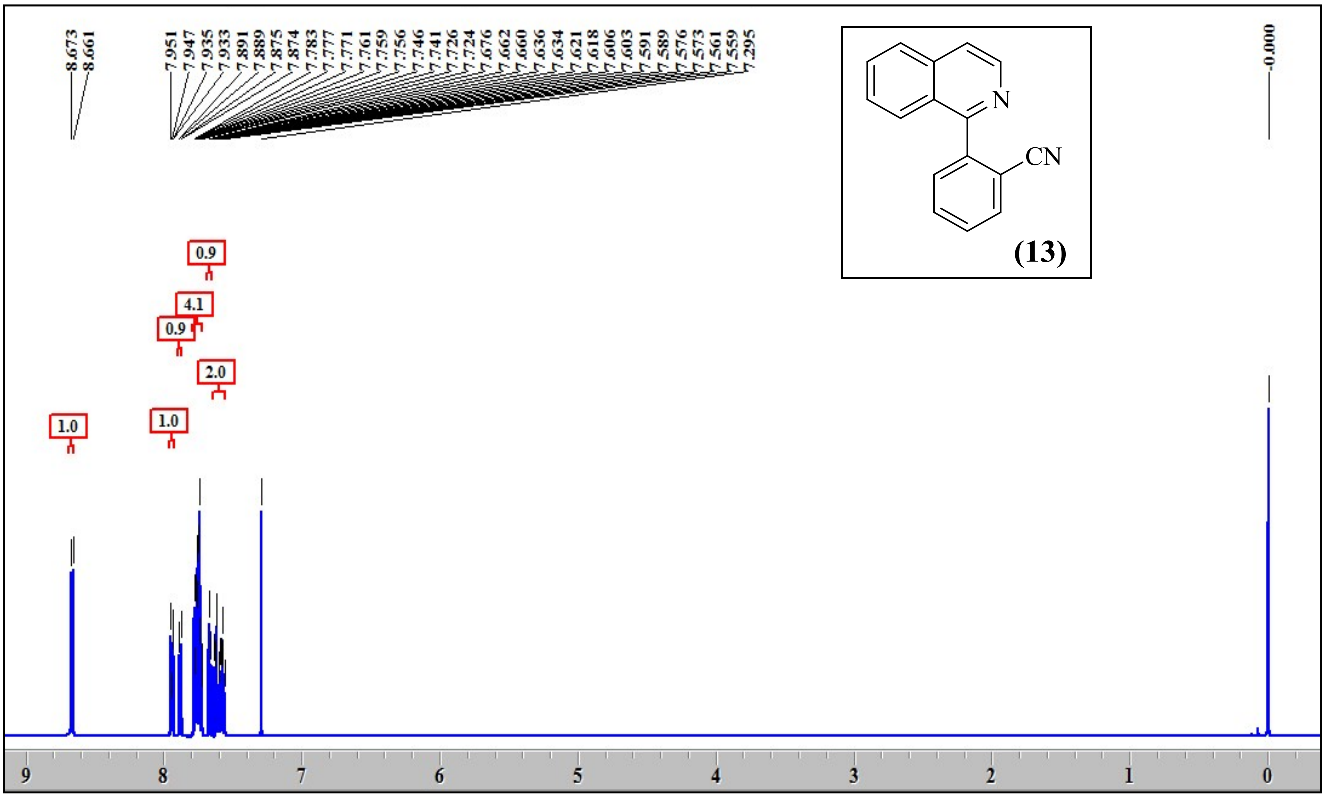


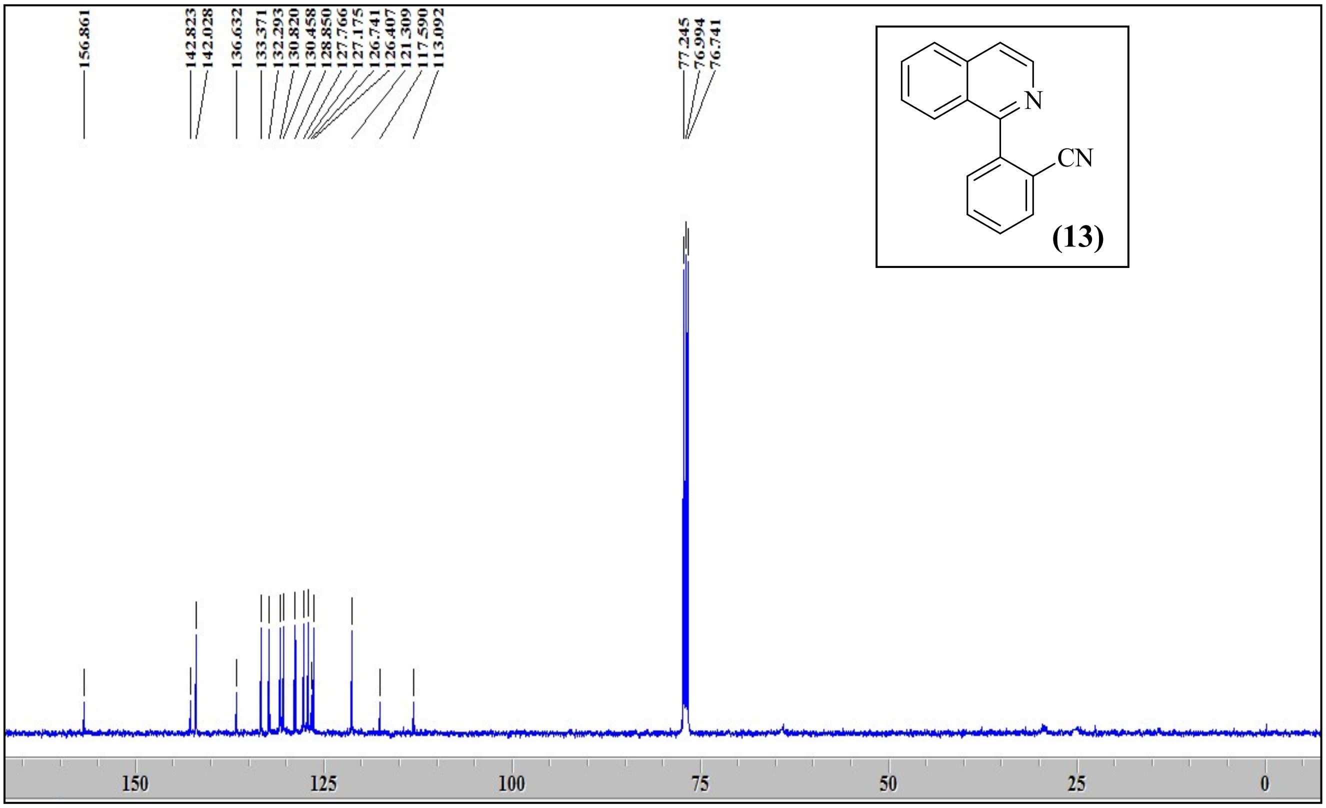
^{1}H and ^{13}C NMR Spectra of 1-(Pyridin-2-yl)-2-naphthonitrile (Figure 4, 12)



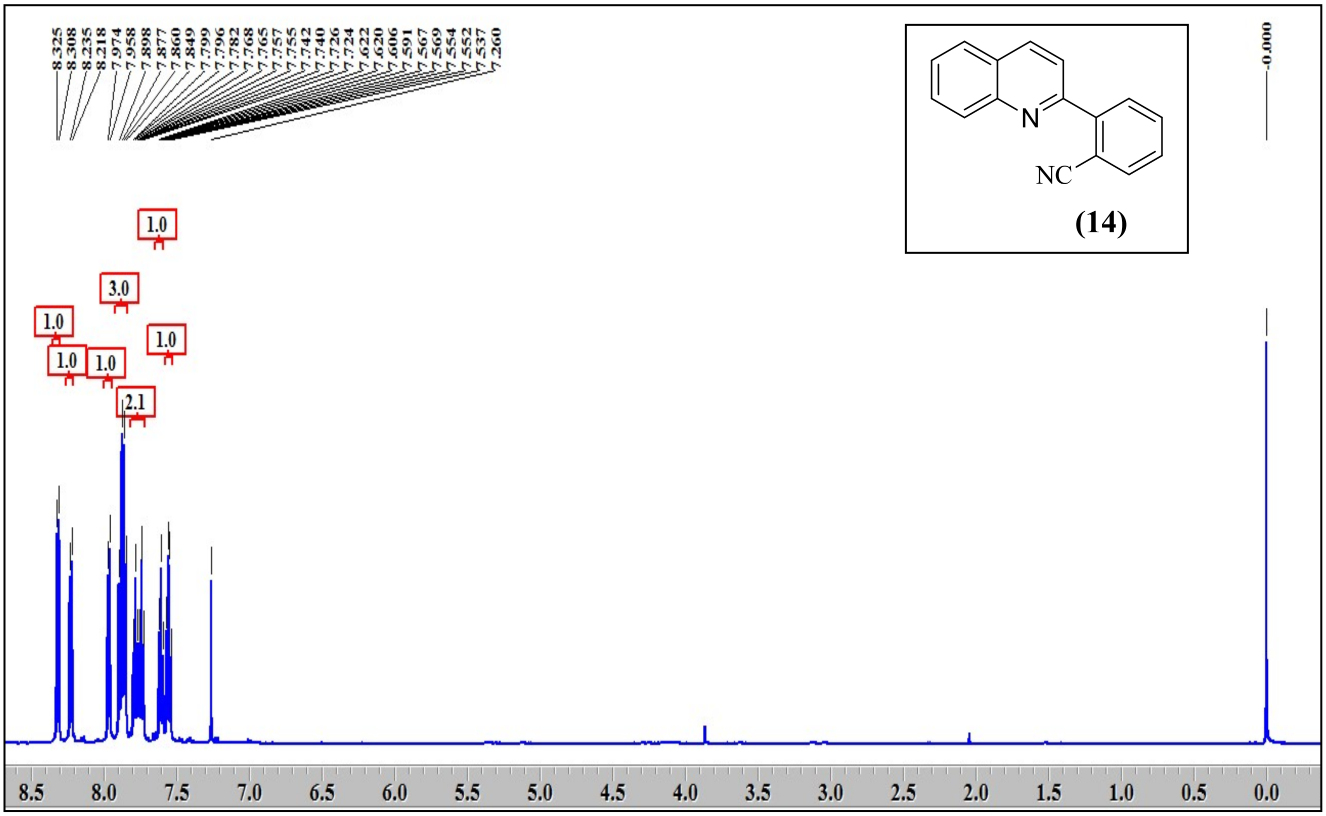


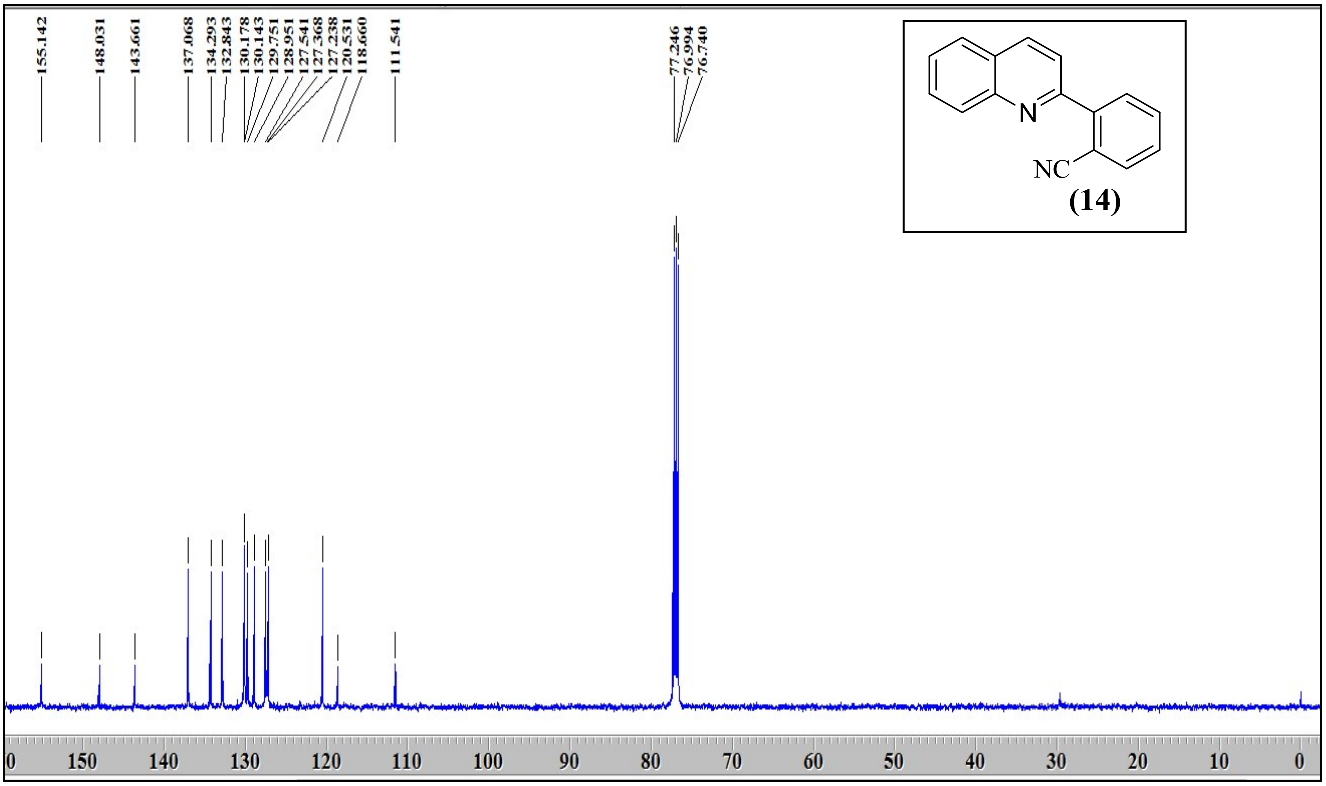
^{1}H and ^{13}C NMR Spectra of 2-(Isoquinolin-1-yl)benzonitrile (Figure 4, 13)





^1H and ^{13}C NMR Spectra of 2-(quinolin-2-yl)benzonitrile (Figure 4, 14)





^{1}H and ^{13}C NMR Spectra of Benzo[*h*]quinoline-10-carbonitrile (Figure 4, 15)