Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Copper-Mediated Three-Component Synthesis of 3-Cyanoimidazo[1,2-*a*]pyridines

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Table of Contents

1. General procedures

Unless otherwise indicated, all the reagents were purchased and used without further treatment. All the solvents (NMP, DMF, DMSO, DMAc, THF, and DCM) were dried and distilled before use. NMR spectra were tested at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR in $CDCl_3$. Chemical shifts of ^{1}H NMR were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane (TMS). Chemical shifts of ^{13}C NMR spectra were also quoted in parts per million (ppm) referenced to the center line of a triplet at 77.00 ppm of $CDCl_3$. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet. Coupling constants *J*, were reported in hertz unit (Hz). Melting points were recorded without correction. Infrared spectra were obtained on an FTIR spectrometer. HRMS spectra of all the unknown compounds were measured using EI method of ionization.

2. Procedures for the synthesis of 4.

Typical procedures for the synthesis of **4a**: In a 25 mL reaction tube was charged with 2-aminopyridine (56 mg, 0.6 mmol), acetophenone (60 mg, 0.5 mmol), CuI (95 mg, 0.5 mmol), and NMP (1 mL). Then benzyl cyanide (70 mg, 0.6 mmol) was added. The reaction mixture was stirred at 120 °C (oil bath) under ambient air conditions for 17 hours. After the completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and filtered through a pad of Celite. The filtrate was poured into 15 mL water and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel (petroleum ether/EtOAc = 1:5) to afford **4a** (80 mg, 73%) as a white solid.

Other compounds (**4b-4w**) were prepared according to the typical procedures of **4a**.

3. Procedures for the synthesis of saripidem (5)

Procedures for the synthesis of saripidem (**5**) from **4j** were referred to the previous literatures,[1,2,3] and are described as follows:

(1) To a stirred suspension of $LiAlH_4$ (76 mg, 2 mmol) in THF (2 mL) was added slowly the solution of **4j** (126 mg, 0.5 mmol) in anhydrous THF (2 mL) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 3 hours at room temperature. Upon completion, the solution was cooled and added H_2O (0.2 mL), NaOH (15%, 0.2 mL) and H_2O (0.2 mL) slowly and sequentially. The resulting solution was stirred for 0.5 h and filtered through Celite. The filtrate was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the crude product, which was directly subjected to the following step.

(2) The crude product obtain above was dissolved in DCM (2 mL). To the solution was added triethylamine (101 mg, 1 mmol) and 4-(dimethylamino)pyridine (6 mg, 0.05 mmol) at 0 °C. Then *n*-butyric anhydride (95 mg, 0.6 mmol) was added dropwise, and the mixture was stirred for 10 min at 0 °C and 30 min at room temperature. The reaction was washed with saturated aqueous $NaHCO_3$, 1 M HCl, water, and brine sequentially. The organic phase was collected, dried and

concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the corresponding amide product.

(3) In an ice bath, the crude amide product was dissolved in DMF (2 mL). To the solution was added NaH (60%, 45 mg, 1 mmol) in portion. The mixture was stirred at room temperature for 30 min. Then methyl iodide (107 mg, 0.75 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Upon completion, the reaction solution was poured into 10 mL water, and extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford saripidem **5** (106 mg, 62% yield over three steps) as a white solid.

4. Procedures for the synthesis of necopidem (6)

Procedures for the synthesis of saripidem (**6**) from **4t** were similar to that of **5**,[1,3] which are shown as follows:

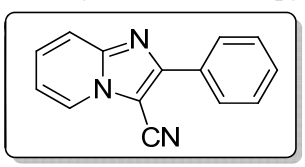
(1) To a stirred suspension of $LiAlH_4$ (76 mg, 2 mmol) in THF (2 mL) was added slowly the solution of **4t** (131 mg, 0.5 mmol) in anhydrous THF (2 mL) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 3 hours at room temperature. Upon completion, the solution was cooled and added H_2O (0.2 mL), NaOH (15%, 0.2 mL) and H_2O (0.2 mL) slowly and sequentially. The resulting solution was stirred for 0.5 h and filtered through Celite. The filtrate was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the crude product, which was directly subjected to the following step.

(2) The crude product obtain above was dissolved in DCM (2 mL). To the solution was added triethylamine (101 mg, 1 mmol) at 0 °C. Then 3-methylbutanoyl chloride (72 mg, 0.6 mmol) was added dropwise, and the mixture was stirred for 10 min at 0 °C and 30 min at room temperature. The reaction was poured into saturated aqueous $NaHCO_3$, and extracted with DCM. The organic phase was collected, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the corresponding amide product.

(3) In an ice bath, the crude amide product was dissolved in DMF (2 mL). To the solution was added NaH (60%, 45 mg, 1 mmol) in portion. The mixture was stirred at room temperature for 30 min. Then methyl iodide (107 mg, 0.75 mmol) was added, and the mixture was stirred at room temperature for 1 hour. Upon completion, the reaction solution was poured into 10 mL water, and extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford necopidem **6** (107 mg, 59% yield over three steps) as sticky oil.

5. Spectral data for all the compounds

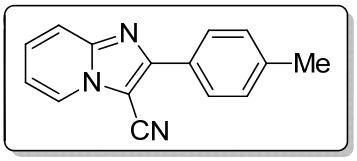
2-Phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (4a)



Known compound, white solid, mp 162–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (dt, *J* =

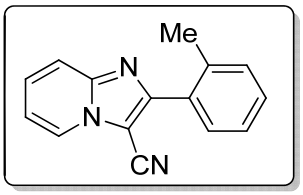
6.8, 1.2 Hz, 1H), 8.24–8.15 (m, 2H), 7.79 (d, J = 9.2 Hz, 1H), 7.58–7.43 (m, 4H), 7.11 (td, J = 6.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 146.7, 131.0, 130.2, 129.0, 128.9, 127.3, 125.6, 118.1, 114.8, 112.7, 93.9. IR (film): $\nu_{(C\equiv N)}$ 2208 cm^{-1}. The ^{1}H and ^{13}C NMR spectral data are in accordance with the literature.[5]

2-(*p*-Tolyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4b)



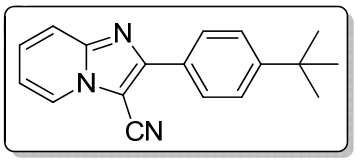
Unknown compound, white solid, mp 160–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 6.8 Hz, 1H), 8.10 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 9.2 Hz, 1H), 7.51–7.43 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.10 (td, J = 6.8, 0.8 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 146.7, 140.5, 129.7, 128.8, 128.2, 127.2, 125.6, 118.0, 114.7, 112.9, 93.5, 21.5. IR (film): $\nu_{(C\equiv N)}$ 2207 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}N_3$ [M$^+$], 233.0953; found, 233.0955.

2-(*o*-Tolyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4c)



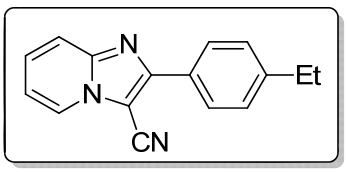
Unknown compound, white solid, mp 122–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 6.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.55–7.48 (m, 1H), 7.42–7.29 (m, 3H), 7.15 (t, J = 6.8 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 146.2, 137.3, 131.1, 130.4, 130.3, 129.8, 128.7, 126.0, 125.6, 118.2, 114.9, 112.0, 96.4, 20.4. IR (film): $\nu_{(C\equiv N)}$ 2207 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}N_3$ [M$^+$], 233.0953; found: 233.0952.

2-(4-(*tert*-Butyl)phenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4d)



Unknown compound, white solid, mp 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 6.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.50–7.43 (m, 1H), 7.09 (t, J = 6.8 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 153.4, 146.8, 128.7, 128.3, 127.1, 126.0, 125.6, 118.0, 114.6, 112.9, 93.5, 34.9, 31.2. IR (film): $\nu_{(C\equiv N)}$ 2208 cm^{-1}. HRMS: calcd. for $C_{18}H_{17}N_3$ [M$^+$], 275.1422; found: 275.1421.

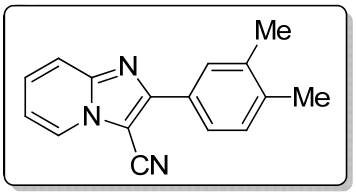
2-(4-Ethylphenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4e)



Unknown compound, white solid, mp 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 6.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.50–7.42 (m, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.09 (t, J = 6.8 Hz, 1H), 2.73 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100

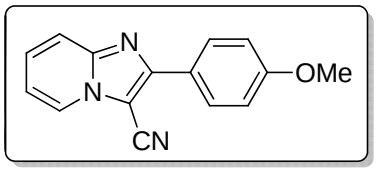
MHz, $CDCl_3$): δ 153.5, 146.8, 128.7, 128.5, 127.3, 125.6, 118.0, 114.6, 112.9, 93.5, 28.8, 15.3. IR (film): $\nu_{(C\equiv N)}$ 2204 cm^{-1}. HRMS: calcd. for $C_{16}H_{13}N_3$ [M^+], 247.1109; found: 247.1108.

2-(3,4-Dimethylphenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4f)



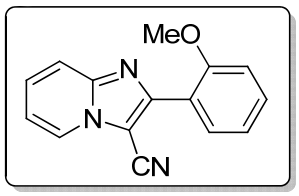
Unknown compound, white solid, mp 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.52–7.44 (m, 2H), 7.16 (s, 1H), 7.15–7.08 (m, 2H), 2.50 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 146.4, 139.6, 137.0, 131.9, 130.2, 128.4, 127.8, 126.8, 125.5, 118.2, 114.6, 112.2, 96.2, 21.3, 20.3. IR (film): $\nu_{(C\equiv N)}$ 2205 cm^{-1}. HRMS: calcd. for $C_{16}H_{13}N_3$ [M^+], 247.1109; found: 247.1111.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4g)



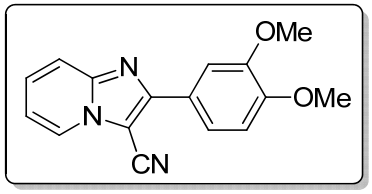
Unknown compound, yellow solid, mp 216–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 6.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 9.2 Hz, 1H), 7.49–7.42 (m, 1H), 7.10–7.01 (m, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 153.3, 146.7, 128.8, 128.7, 125.5, 123.7, 117.8, 114.5, 114.4, 113.1, 92.9, 55.4. IR (film): $\nu_{(C\equiv N)}$ 2205 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}N_3O$ [M^+], 249.0902; found: 249.0902.

2-(2-Methoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4h)



Unknown compound, white solid, mp 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 6.8 Hz, 1H), 7.81–7.71 (m, 3H), 7.51–7.39 (m, 2H), 7.10 (t, J = 6.8 Hz, 1H), 7.03 (dd, J = 8.0, 2.4 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 153.2, 146.7, 132.3, 130.1, 128.8, 125.6, 119.7, 118.1, 116.8, 114.8, 112.7, 111.8, 94.0, 55.4. IR (film): $\nu_{(C\equiv N)}$ 2204 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}N_3O$ [M^+], 249.0902; found: 249.0900.

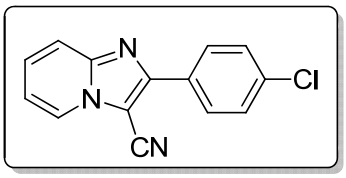
2-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4i)



Unknown compound, white solid, mp 181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dt, J = 6.8, 1.2 Hz, 1H), 7.82 (dd, J = 8.4, 2.0 Hz, 1H), 7.77–7.72 (m, 2H), 7.49–7.43 (m, 1H), 7.08 (td, J = 6.8, 1.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (100 MHz,

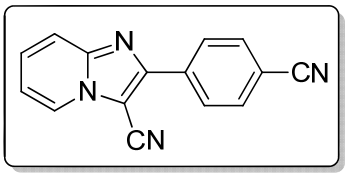
$CDCl_3$): δ 153.4, 150.6, 149.2, 146.8, 128.7, 125.5, 124.0, 120.3, 117.8, 114.5, 113.2, 111.2, 109.9, 93.1, 56.0, 55.9. IR (film): $\nu_{(C\equiv N)}$ 2203 cm^{-1}. HRMS: calcd. for $C_{16}H_{13}N_3O_2$ [M^+], 279.1008; found: 279.1011.

2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4j)



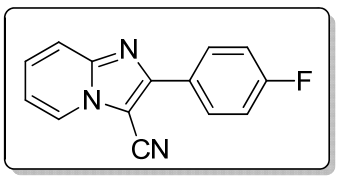
Unknown compound, white solid, mp 191–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 6.8 Hz, 1H), 8.14 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 9.2 Hz, 1H), 7.54–7.46 (m, 3H), 7.13 (td, J = 6.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 146.7, 136.2, 129.6, 129.3, 129.0, 128.5, 125.6, 118.2, 115.0, 112.5, 93.8. IR (film): $\nu_{(C\equiv N)}$ 2208 cm^{-1}. HRMS: calcd. for $C_{14}H_8ClN_3$ [M^+], 253.0407; found: 253.0408.

2-(4-Cyanophenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4k)



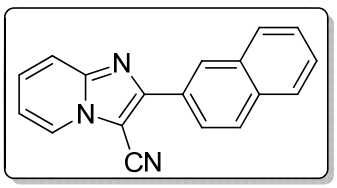
Unknown compound, white solid, mp 303–305 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (dt, J = 6.8, 1.2 Hz, 1H), 8.35–8.30 (m, 2H), 7.85–7.78 (m, 3H), 7.54 (ddd, J = 9.2, 7.2, 1.2 Hz, 1H), 7.17 (td, J = 6.8, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 146.9, 135.4, 132.8, 129.7, 127.7, 125.7, 118.5, 118.4, 115.4, 113.4, 112.2, 94.8. IR (film): $\nu_{(C\equiv N)}$ 2224, 2210 cm^{-1}. HRMS: calcd. for $C_{15}H_8N_4$ [M^+], 244.0749; found: 244.0750.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4l)



Unknown compound, white solid, mp 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 6.8 Hz, 1H), 8.25–8.16 (m, 2H), 7.78 (d, J = 9.2 Hz, 1H), 7.53–7.45 (m, 1H), 7.25–7.17 (m, 2H), 7.12 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (d, $^1J_{CF}$ = 249.3 Hz), 152.4, 146.8, 129.4 (d, $^3J_{CF}$ = 8.5 Hz), 129.0, 127.4 (d, $^4J_{CF}$ = 3.3 Hz), 125.7, 118.2, 116.2 (d, $^2J_{CF}$ = 21.7 Hz), 114.9, 112.7, 93.6. IR (film): $\nu_{(C\equiv N)}$ 2209 cm^{-1}. HRMS: calcd. for $C_{14}H_8FN_3$ [M^+], 237.0702; found: 237.0699.

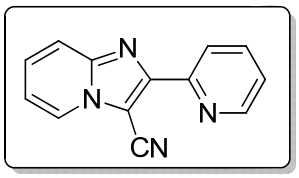
2-(Naphthalen-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4m)



Unknown compound, white solid, mp 219–221 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s,

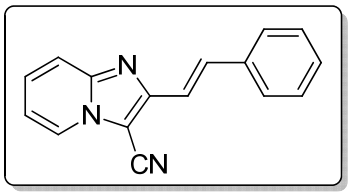
1H), 8.40 (d, J = 6.8 Hz, 1H), 8.30 (dd, J = 8.8, 1.6 Hz, 1H), 8.02–7.96 (m, 2H), 7.92–7.86 (m, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.58–7.52 (m, 2H), 7.52–7.46 (m, 1H), 7.11 (td, J = 6.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 146.9, 134.1, 133.3, 128.84, 128.83, 128.79, 128.5, 127.8, 127.21, 127.18, 126.7, 125.6, 124.2, 118.2, 114.8, 112.9, 94.1. IR (film): $\nu_{(C\equiv N)}$ 2213 cm^{-1}. HRMS: calcd. for $C_{18}H_{11}N_3$ [M^+], 269.0953; found: 269.0958.

2-(Pyridin-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4n)



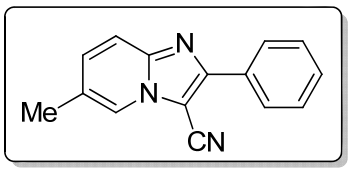
Unknown compound, white solid, mp 177–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 4.8 Hz, 1H), 8.45 (d, J = 6.8 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 7.86 (td, J = 7.6, 1.6 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.55–7.47 (m, 1H), 7.41–7.34 (m, 1H), 7.14 (td, J = 6.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 150.2, 149.9, 146.8, 136.9, 128.9, 125.7, 124.5, 121.5, 118.4, 115.1, 112.3, 96.0. IR (film): $\nu_{(C\equiv N)}$ 2214 cm^{-1}. HRMS: calcd. for $C_{13}H_8N_4$ [M^+], 220.0749; found: 220.0751.

(*E*)-2-styrylimidazo[1,2-*a*]pyridine-3-carbonitrile (4o)



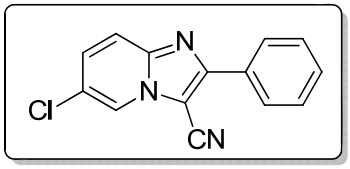
Unknown compound, white solid, mp 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 6.8 Hz, 1H), 7.80 (d, J = 16.0 Hz, 1H), 7.70 (d, J = 9.2 Hz, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.49–7.38 (m, 3H), 7.34 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 16.0 Hz, 1H), 7.05 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 147.0, 135.8, 129.0, 128.9, 128.8, 127.3, 125.6, 117.7, 116.7, 114.4, 111.7, 95.4. IR (film): $\nu_{(C\equiv N)}$ 2211 cm^{-1}. HRMS: calcd. for $C_{16}H_{11}N_3$ [M^+], 245.0953; found: 245.0954.

6-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (4p)



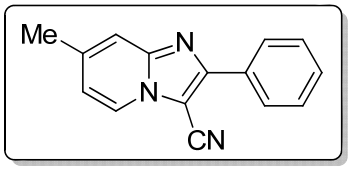
Unknown compound, white solid, mp 169–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21–8.13 (m, 3H), 7.66 (d, J = 9.2 Hz, 1H), 7.55–7.44 (m, 3H), 7.32 (dd, J = 9.2, 1.6 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 145.8, 131.8, 131.3, 130.0, 129.0, 127.2, 124.98, 123.4, 117.4, 113.0, 93.4, 18.2. IR (film): $\nu_{(C\equiv N)}$ 2208 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}N_3$ [M^+], 233.0953; found: 233.0956.

6-Chloro-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (4q)



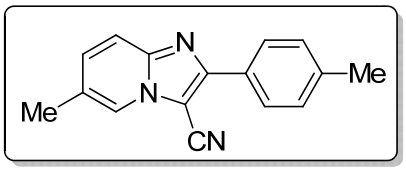
Unknown compound, white solid, mp 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.20–8.14 (m, 2H), 7.71 (dd, *J* = 9.6, 0.8 Hz, 1H), 7.57–7.48 (m, 3H), 7.44 (dd, *J* = 9.6, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 145.1, 130.7, 130.4, 130.3, 129.1, 127.3, 123.6, 123.3, 118.4, 112.2, 94.3. IR (film): $\nu_{(C\equiv N)}$ 2210 cm^{-1}. HRMS: calcd. for $C_{14}H_8ClN_3$ [M^+], 253.0407; found: 253.0410.

7-Methyl-2-phenylimidazo[1,2-*a*]pyridine-3-carbonitrile (4r)



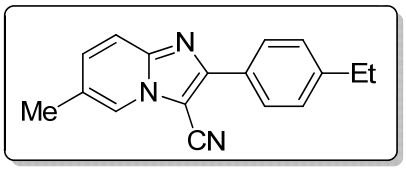
Unknown compound, white solid, mp 193–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 6.8 Hz, 1H), 8.22–8.16 (m, 2H), 7.59 (s, 1H), 7.56–7.45 (m, 3H), 6.97 (d, *J* = 6.8 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 147.2, 140.5, 131.2, 130.0, 129.0, 127.2, 124.7, 117.3, 116.7, 113.0, 93.2, 21.6. IR (film): $\nu_{(C\equiv N)}$ 2207 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}N_3$ [M^+], 233.0953; found: 233.0953.

6-Methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4s)



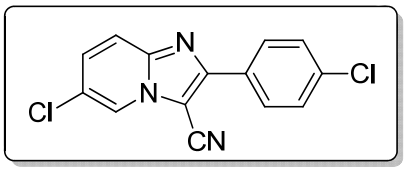
Unknown compound, white solid, mp 184–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.34–7.27 (m, 3H), 2.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 145.8, 140.2, 131.7, 129.7, 128.5, 127.1, 124.8, 123.4, 117.2, 113.2, 93.1, 21.4, 18.2. IR (film): $\nu_{(C\equiv N)}$ 2203 cm^{-1}. HRMS: calcd. for $C_{16}H_{13}N_3$ [M^+], 247.1109; found: 247.1111.

2-(4-Ethylphenyl)-6-methylimidazo[1,2-*a*]pyridine-3-carbonitrile (4t)



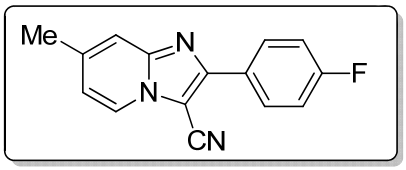
Unknown compound, white solid, mp 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 9.2 Hz, 1H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 146.5, 145.7, 131.7, 128.7, 128.5, 127.1, 124.8, 123.4, 117.2, 113.2, 93.1, 28.8, 18.2, 15.4. IR (film): $\nu_{(C\equiv N)}$ 2208 cm^{-1}. HRMS: calcd. for $C_{17}H_{15}N_3$ [M^+], 261.1266; found: 261.1268.

6-Chloro-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4u)



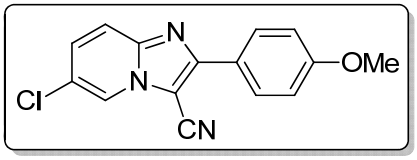
Unknown compound, white solid, mp 244–245 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.70 (dd, *J* = 9.6, 0.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.45 (dd, *J* = 9.6, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 145.1, 136.5, 130.5, 129.4, 129.3, 128.5, 123.6, 123.4, 118.4, 112.0, 94.3. IR (film): $\nu_{(C\equiv N)}$ 2215 cm^{-1}. HRMS: calcd. for $C_{14}H_7Cl_2N_3$ [M^+], 287.0017; found: 287.0018.

2-(4-Fluorophenyl)-7-methylimidazo[1,2-*a*]pyridine-3-carbonitrile (4v)



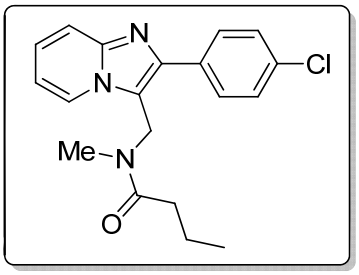
Unknown compound, white solid, mp 191–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 6.8 Hz, 1H), 8.20–8.13 (m, 2H), 7.51 (s, 1H), 7.23–7.16 (m, 2H), 6.93 (dd, *J* = 6.8, 1.2 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 ($^1J_{CF}$ = 249.0 Hz), 152.4, 147.2, 140.6, 129.2 ($^3J_{CF}$ = 8.5 Hz), 127.5 ($^4J_{CF}$ = 3.1 Hz), 124.7, 117.3, 116.7, 116.1 ($^2J_{CF}$ = 21.7 Hz), 112.9, 93.0, 21.6. IR (film): $\nu_{(C\equiv N)}$ 2205 cm^{-1}. HRMS: calcd. for $C_{15}H_{10}FN_3$ [M^+], 251.0859; found: 251.0859.

6-Chloro-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbonitrile (4w)



Unknown compound, white solid, mp 204–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 7.66 (dd, *J* = 9.6, 0.8 Hz, 1H), 7.41 (dd, *J* = 9.6, 2.0 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 153.7, 145.1, 130.1, 128.8, 123.5, 123.3, 122.9, 118.1, 114.4, 112.5, 93.4, 55.4. IR (film): $\nu_{(C\equiv N)}$ 2206 cm^{-1}. HRMS: calcd. for $C_{15}H_{10}ClN_3O$ [M^+], 283.0512; found: 283.0510.

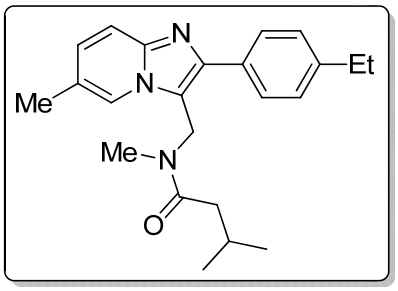
***N*-((2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)-*N*-methylbutyramide (5, Saripidem)**



Known compound, white solid, mp 172–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 6.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.30–7.23 (m, 1H), 6.85 (td, *J* = 6.8, 0.8 Hz, 1H), 5.19 (s, 2H), 2.60 (s, 3H), 2.29 (t, *J* = 7.2 Hz, 2H),

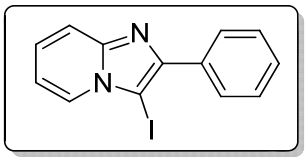
1.74–1.62 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 145.1, 144.6, 134.1, 132.6, 130.0, 128.9, 125.5, 125.5, 117.3, 116.0, 112.8, 38.5, 35.3, 33.6, 18.4, 13.9. The ^{1}H and ^{13}C NMR spectral data are in accordance with the literature.[3]

***N*-((2-(4-ethylphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methyl)-*N*,3-dimethylbutanamide (6, Necopidem)**



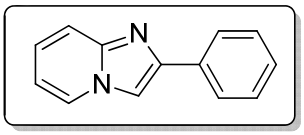
Known compound, sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 9.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.08 (dd, J = 9.2, 1.6 Hz, 1H), 5.19 (s, 2H), 2.71 (q, J = 7.6 Hz, 2H), 2.60 (s, 3H), 2.32 (s, 3H), 2.19 (s, 2H), 2.22–2.16 (m, 3H), 1.28 (t, J = 7.6 Hz, 3H), 0.96 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 145.8, 144.1, 144.0, 131.5, 128.7, 128.2, 128.1, 123.1, 122.1, 116.5, 115.2, 42.3, 38.6, 33.6, 28.6, 25.5, 22.6, 18.3, 15.4. The ^{1}H and ^{13}C NMR spectral data are in accordance with the literature.[4]

3-Iodo-2-phenylimidazo[1,2-*a*]pyridine (7)



Known compound, white solid, mp 168–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 6.8 Hz, 1H), 8.10–8.04 (m, 2H), 7.64 (d, J = 9.2 Hz, 1H), 7.46–7.53 (m, 2H), 7.44–7.38 (m, 1H), 7.31–7.24 (m, 1H), 6.94 (td, J = 6.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 147.9, 133.4, 128.5, 128.3, 126.5, 125.6, 117.5, 113.2, 59.5. The ^{1}H and ^{13}C NMR spectral data are in accordance with the literature.[6]

2-Phenylimidazo[1,2-*a*]pyridine (8)



Known compound, white solid, mp 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 6.4 Hz, 1H), 8.01–7.93 (m, 2H), 7.87 (s, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.48–7.41 (m, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.22–7.14 (m, 1H), 6.79 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 145.6, 133.6, 128.7, 128.0, 126.0, 125.6, 124.72, 117.5, 112.5, 108.1. The ^{1}H and ^{13}C NMR spectral data are in accordance with the literature.[6]

6. References

[1] W. Du, Q. Gu, Z. Li, D. Yang, *J. Am. Chem. Soc.* **2015**, *137*, 1130–1135.

[2] L. O. Dialer, S. V. Selivanova, C. J. Müller, A. Müller, T. Stellfeld, K. Graham, L. M. Dinkelborg, S. D. Krämer, R. Schibli, M. Reiher, S. M. Ametamey, *J. Med. Chem.* **2013**, *56*, 7552−7563.

[3] M. Chioua, E. Soriano, L. Infantes, M. L. Jimeno, J. Marco-Contelles, A. Samadi, *Eur. J. Org. Chem.* **2013**, 35–39.

[4] H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang, Q. Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5678–5681.

[5] X. Wang, L. Ma, W. Yu, *Synthesis* **2011**, 2445–2453.

[6] Y. Zhang, Z. Chen, W. Wu, Y. Zhang, W. Su, *J. Org. Chem.* **2013**, *78*, 12494−12504.

7. Copies of the compounds ^{1}H NMR and ^{13}C NMR

Figure 1 ^{1}H NMR spectrum of **4a**

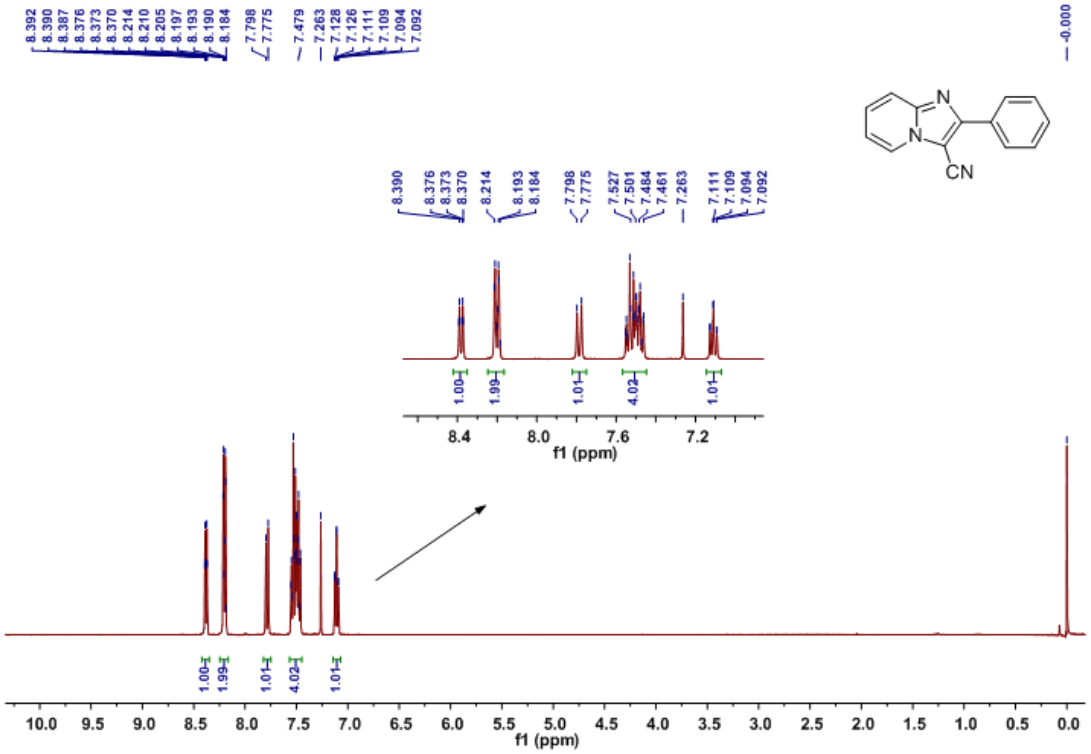


Figure 2 ^{13}C NMR spectrum of **4a**

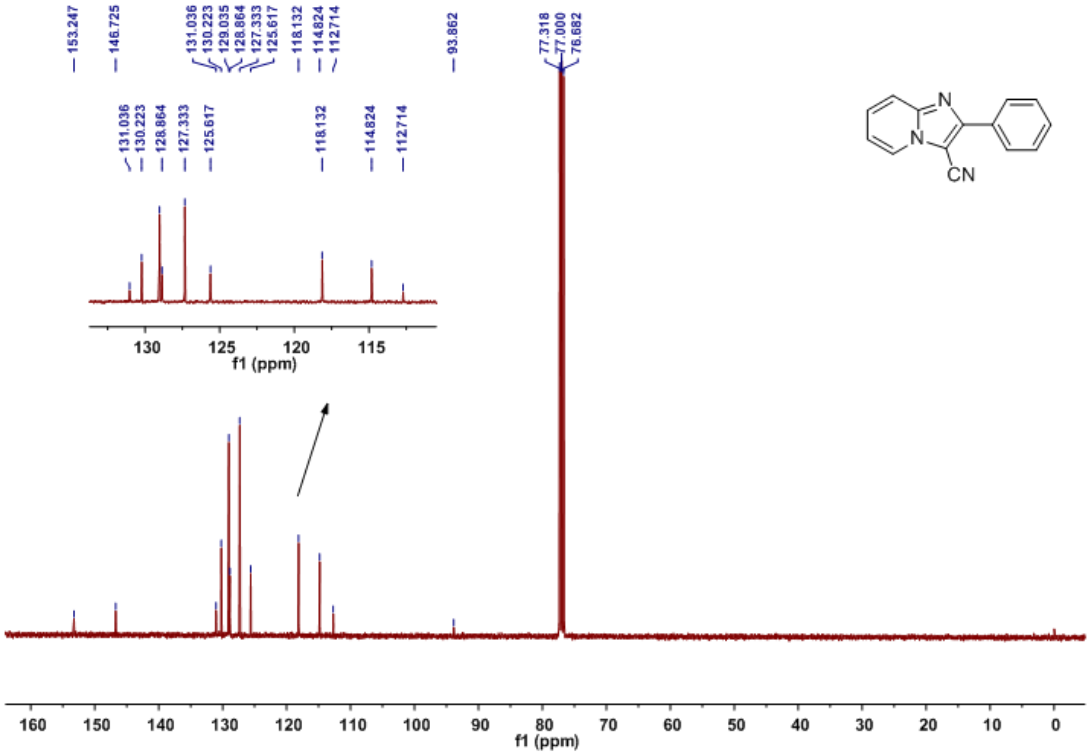


Figure 3 ^{1}H NMR spectrum of **4b**

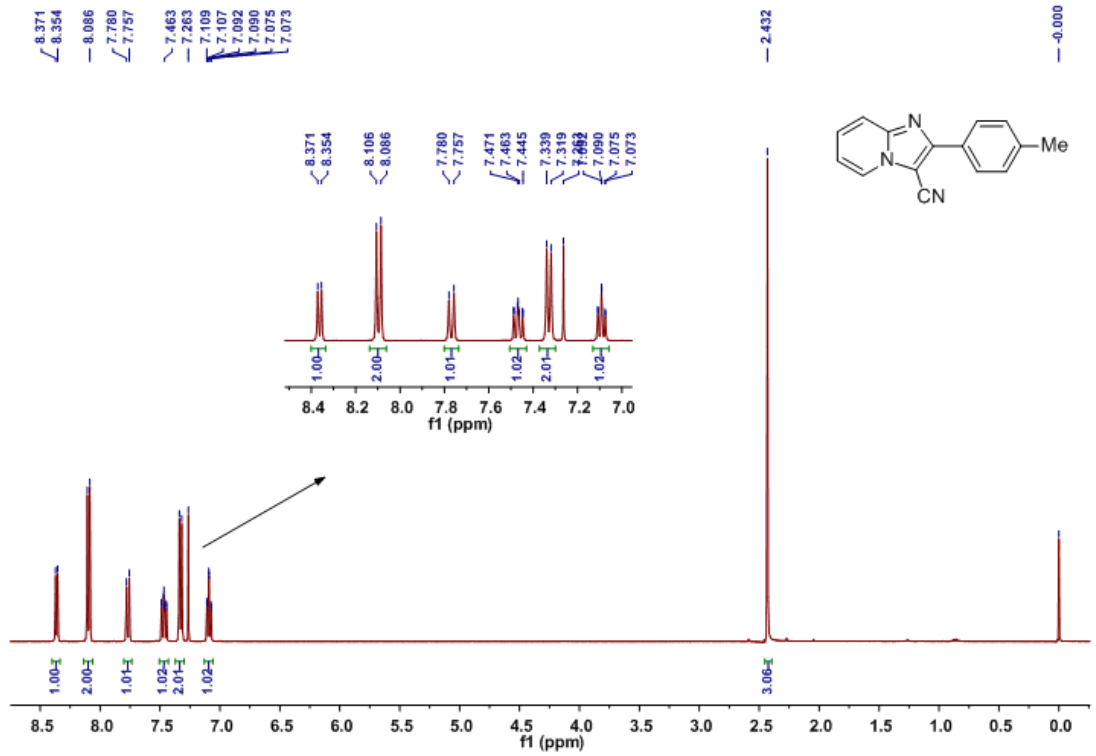


Figure 4 ^{13}C NMR spectrum of **4b**

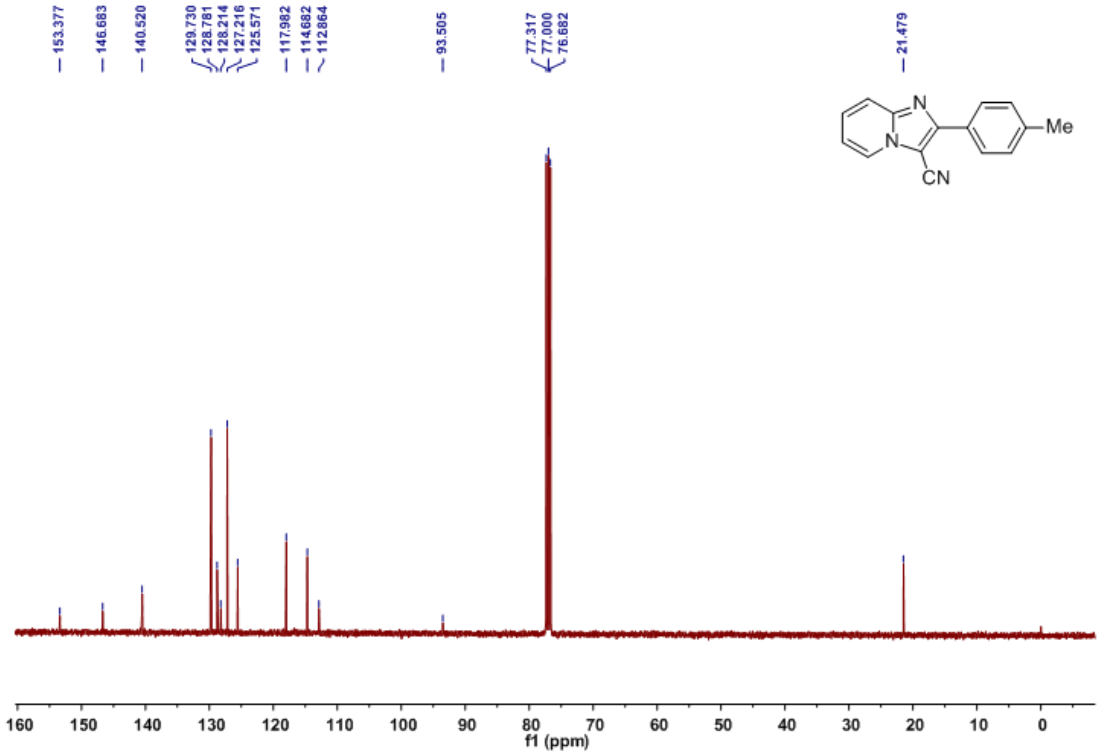


Figure 5 ^{1}H NMR spectrum of **4c**

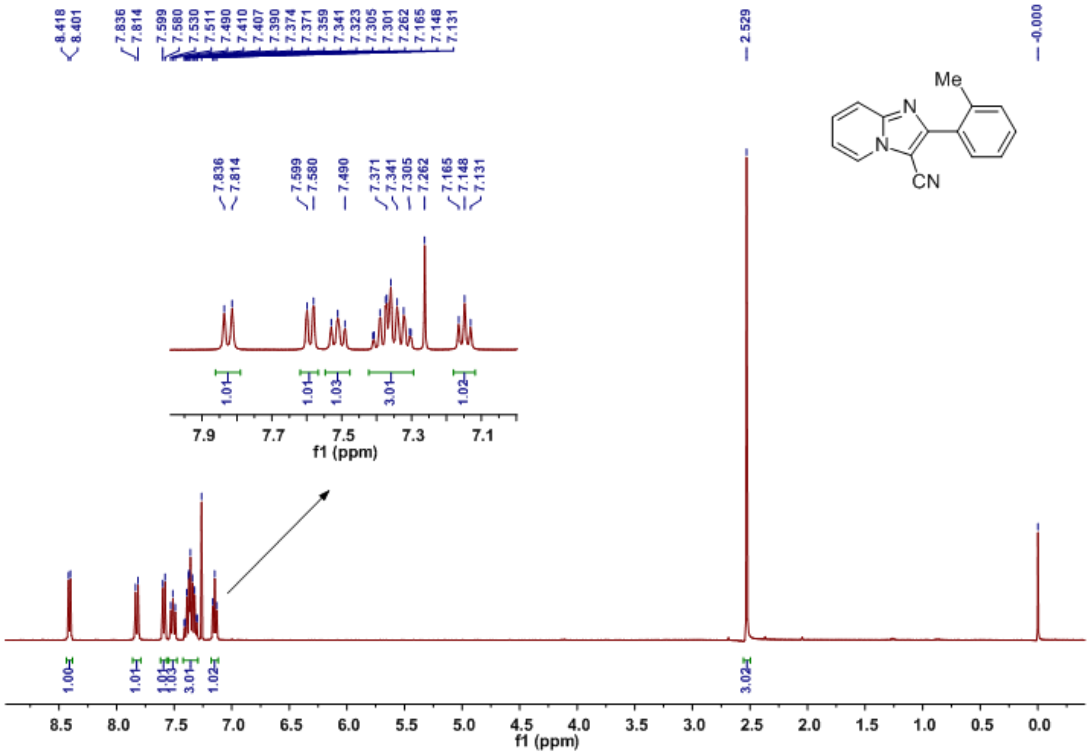


Figure 6 ^{13}C NMR spectrum of **4c**

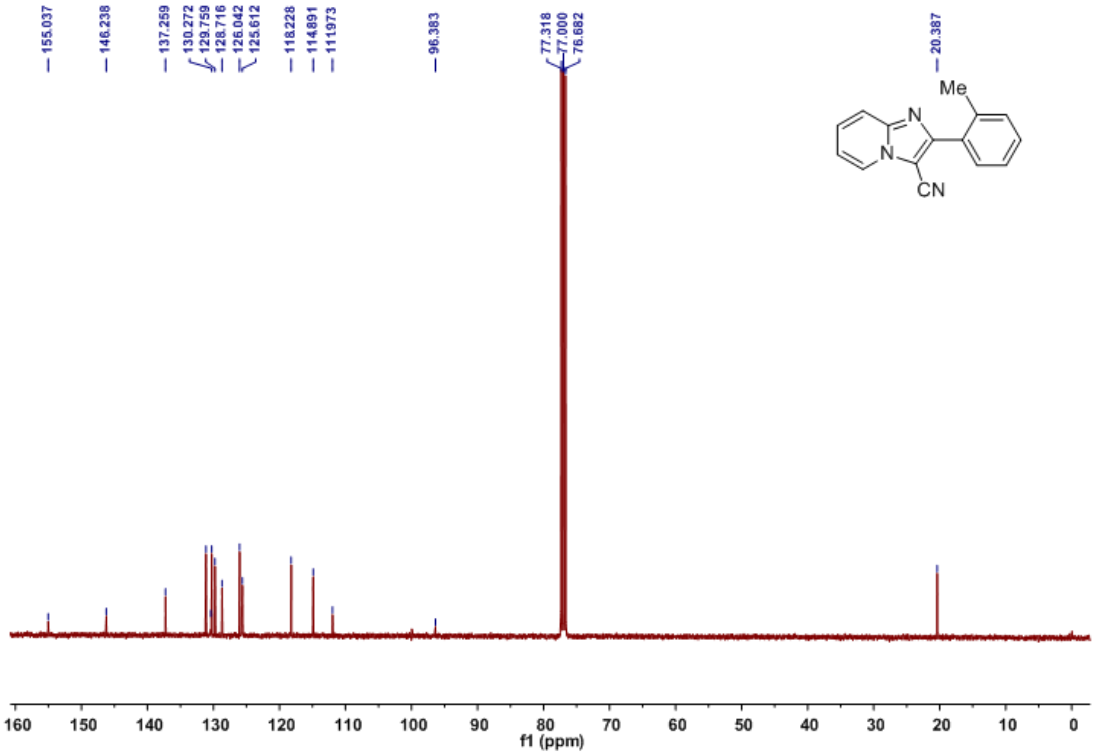


Figure 7 ^{1}H NMR spectrum of **4d**

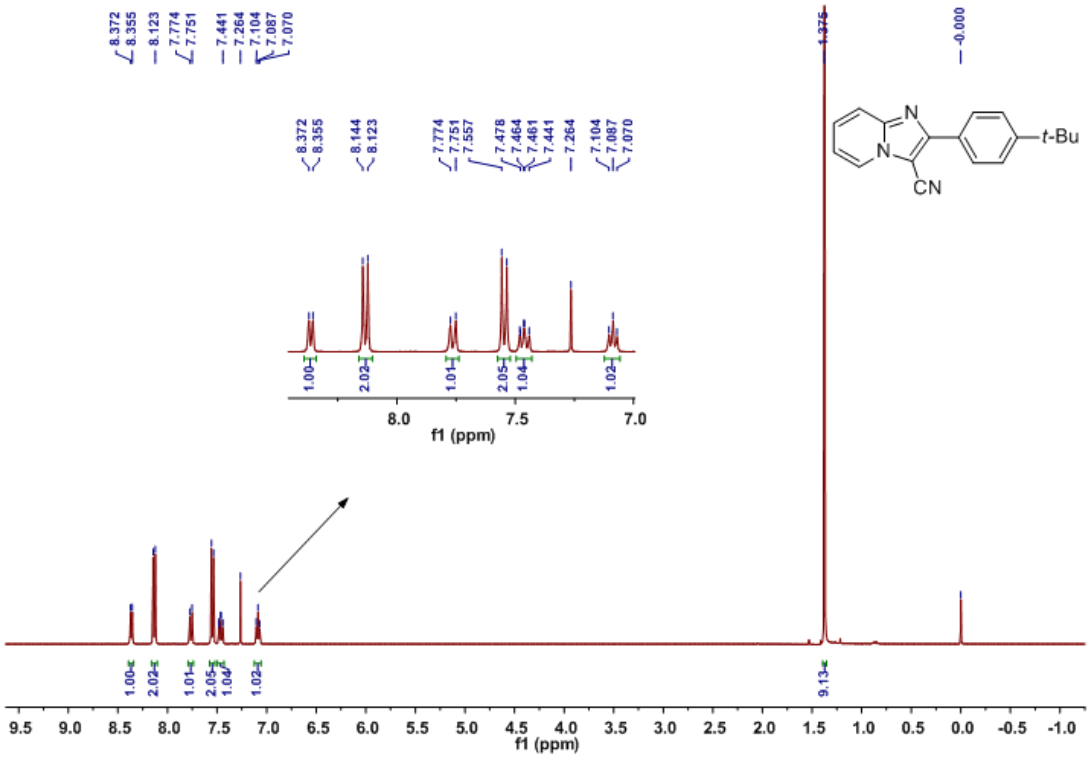


Figure 8 ^{13}C NMR spectrum of **4d**

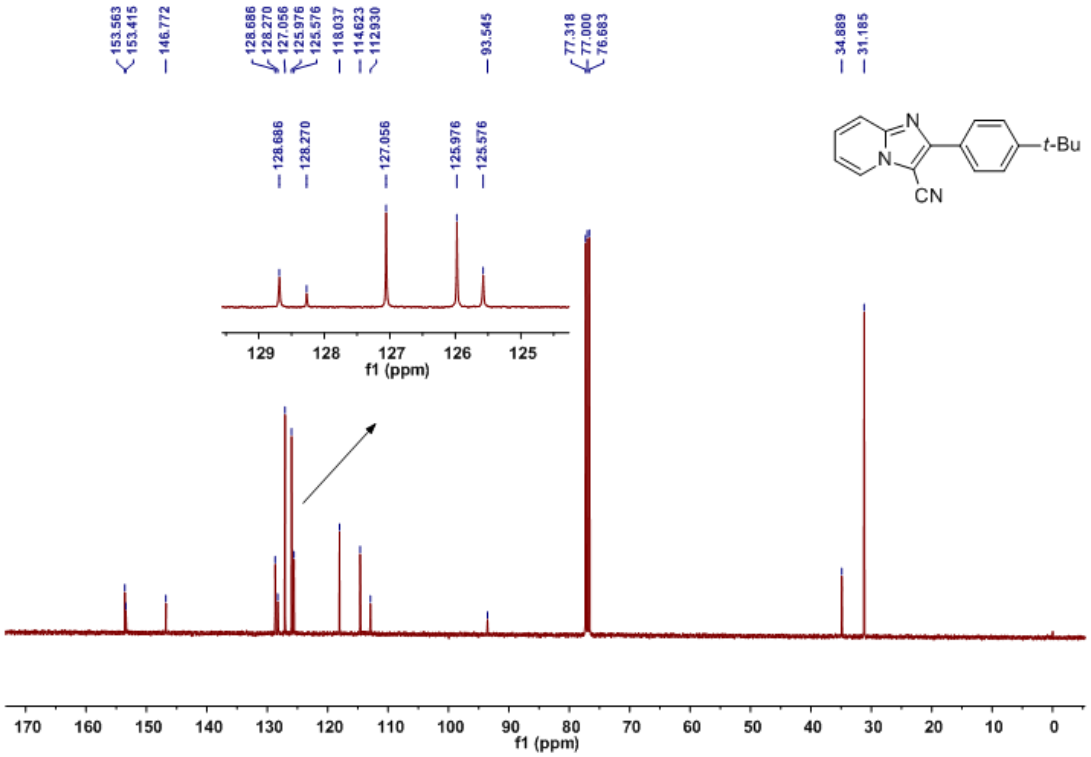


Figure 9 ^{1}H NMR spectrum of **4e**

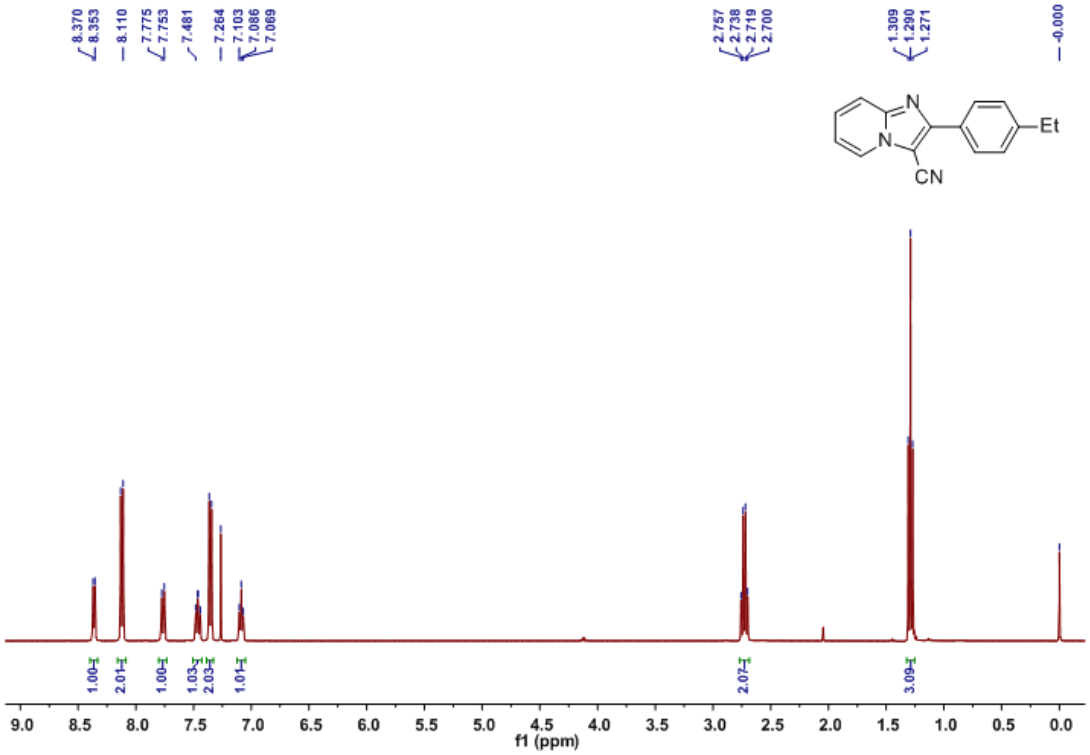


Figure 10 ^{13}C NMR spectrum of **4e**

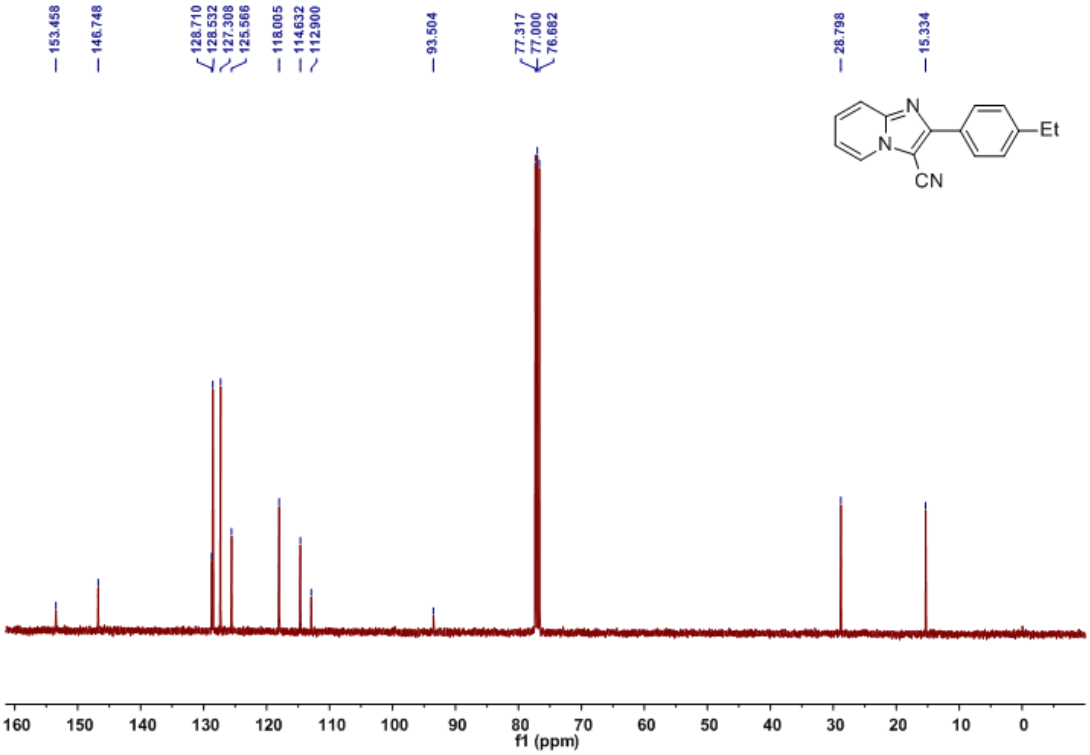


Figure 11 ^{1}H NMR spectrum of **4f**

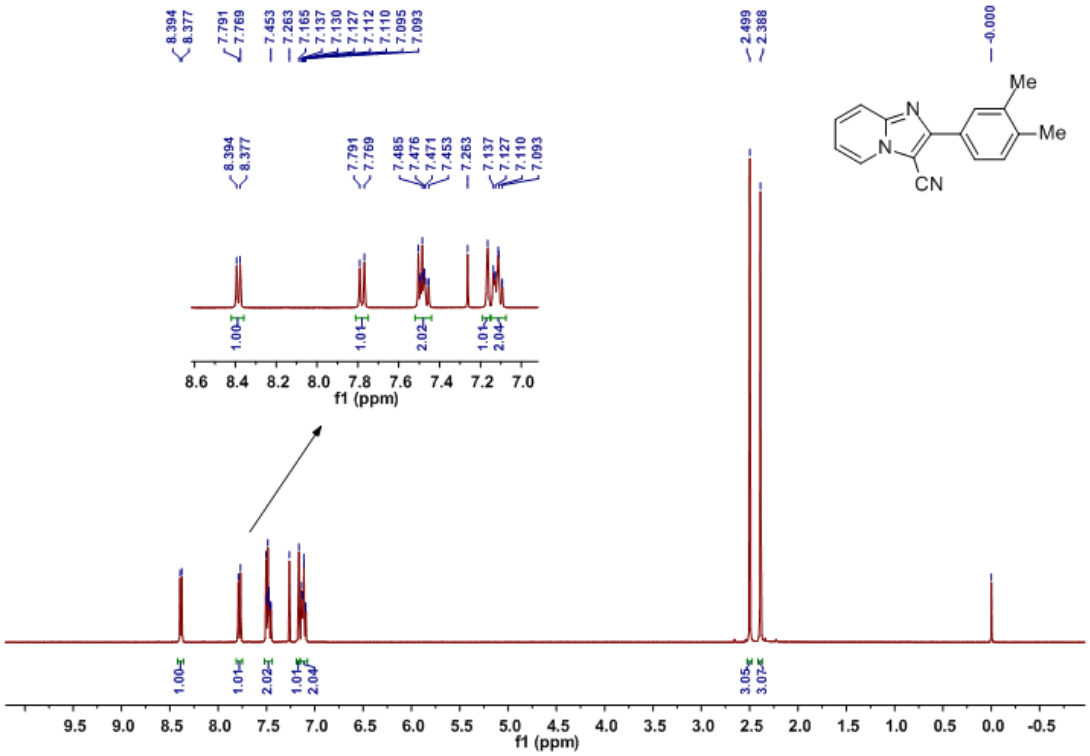


Figure 12 ^{13}C NMR spectrum of **4f**

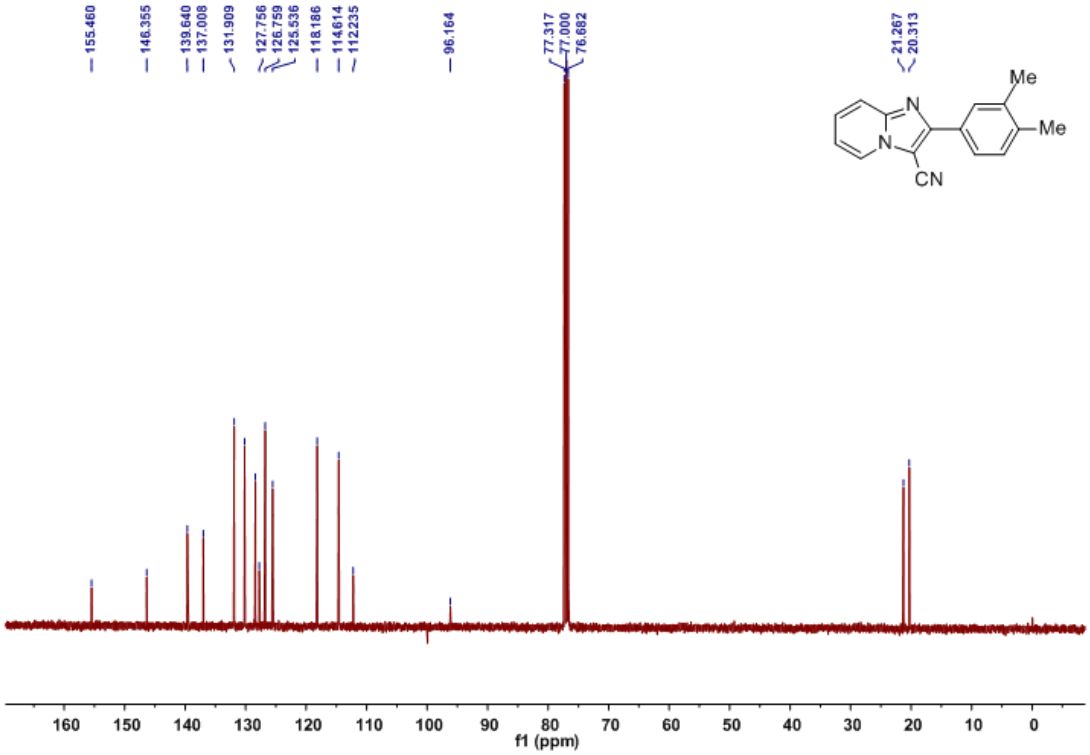


Figure 13 ^{1}H NMR spectrum of **4g**

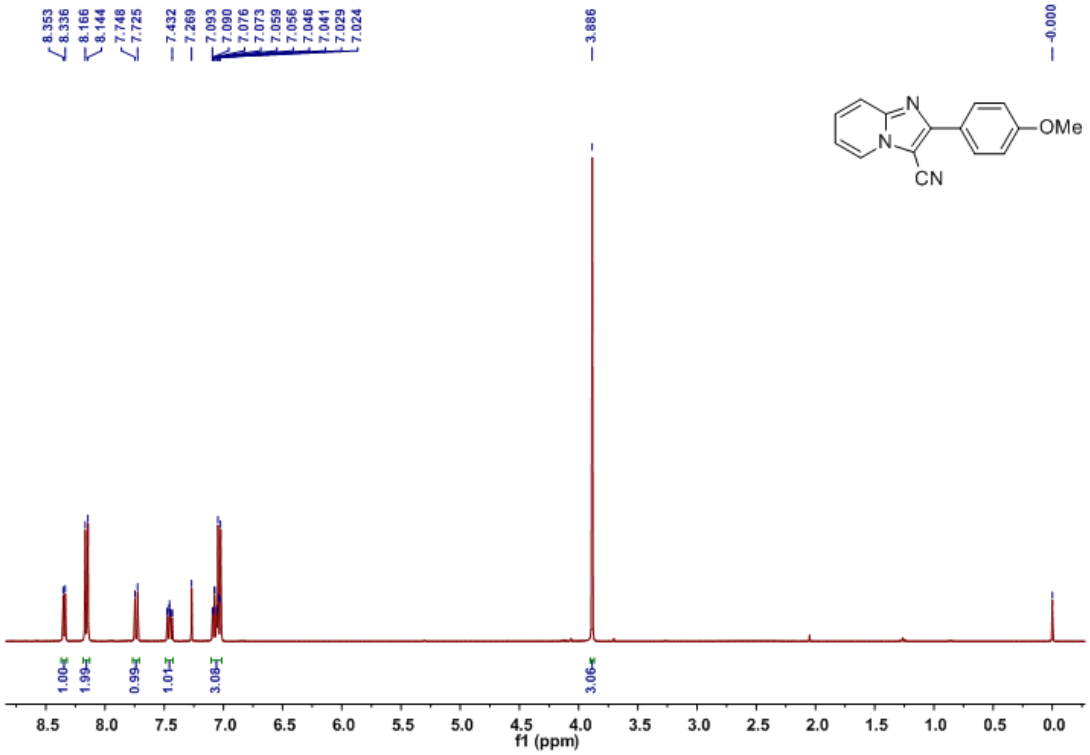


Figure 14 ^{13}C NMR spectrum of **4g**

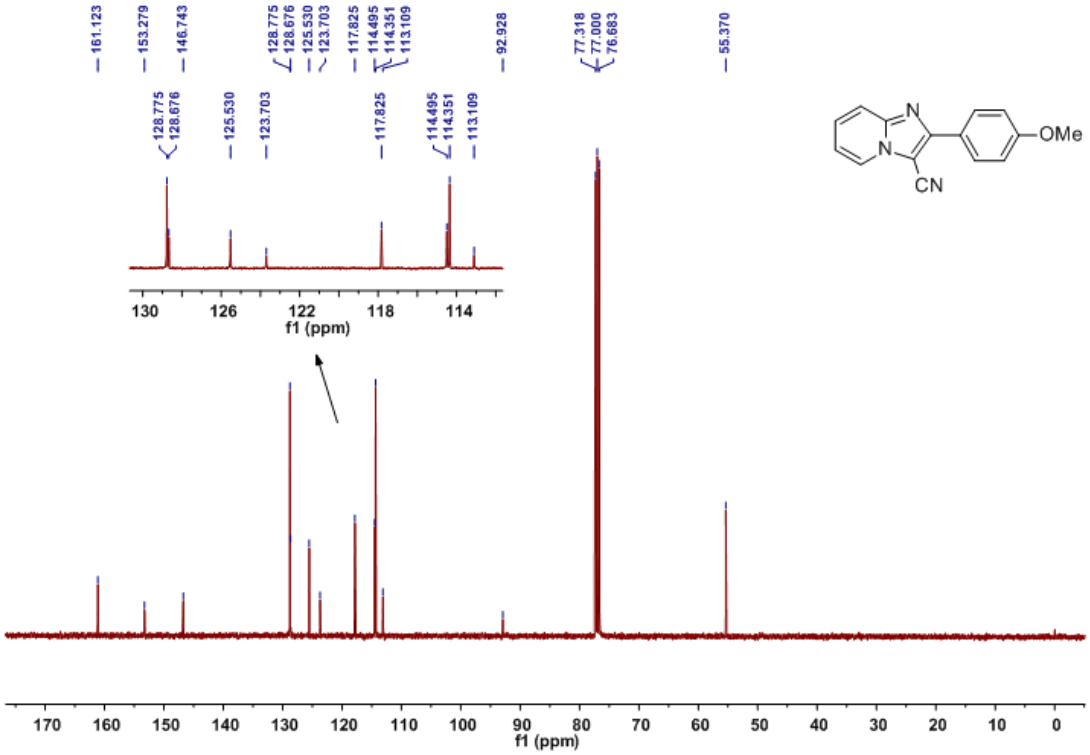


Figure 15 ^{1}H NMR spectrum of **4h**

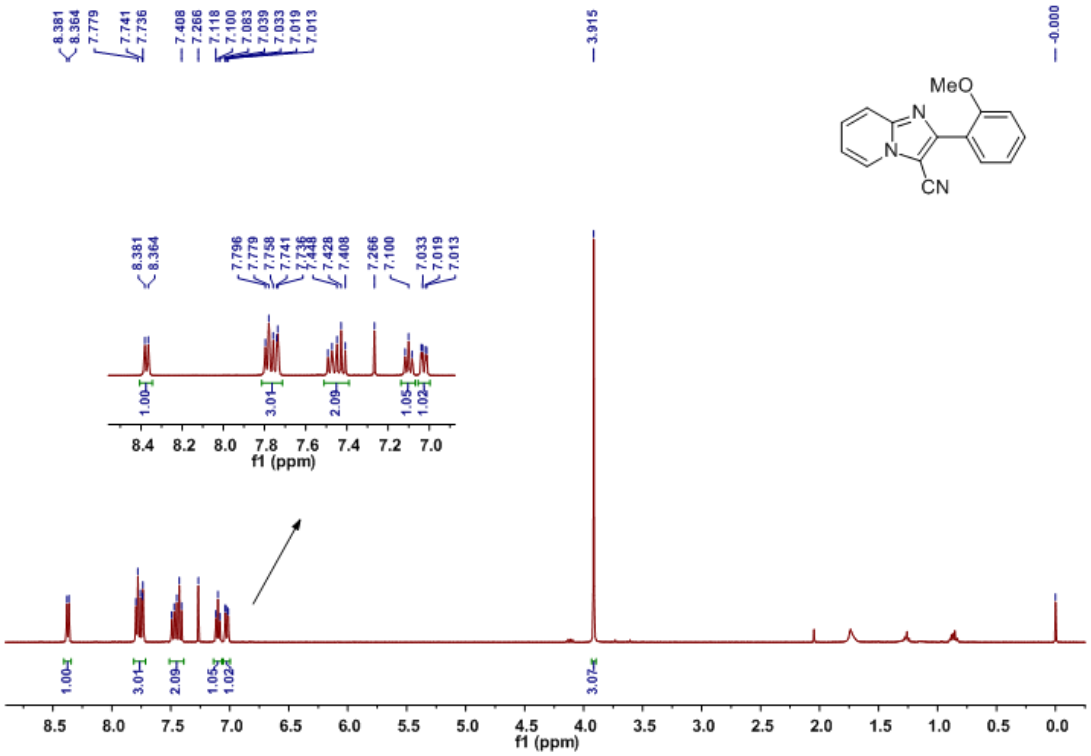


Figure 16 ^{13}C NMR spectrum of **4h**

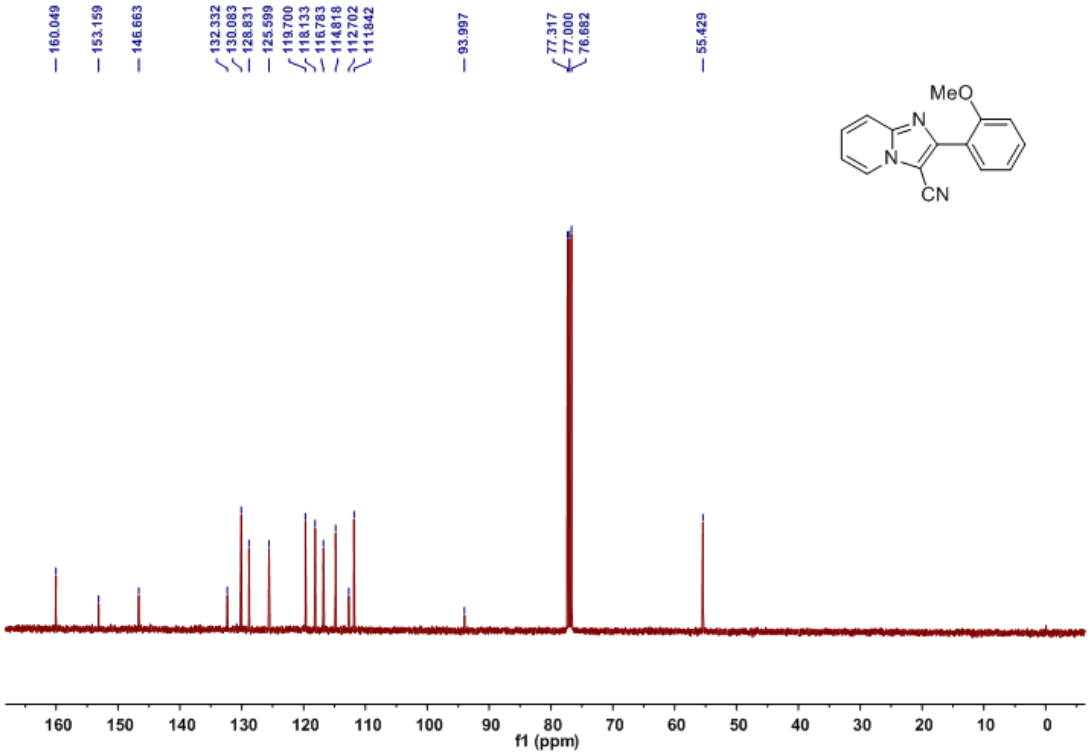


Figure 17 ^{1}H NMR spectrum of **4i**

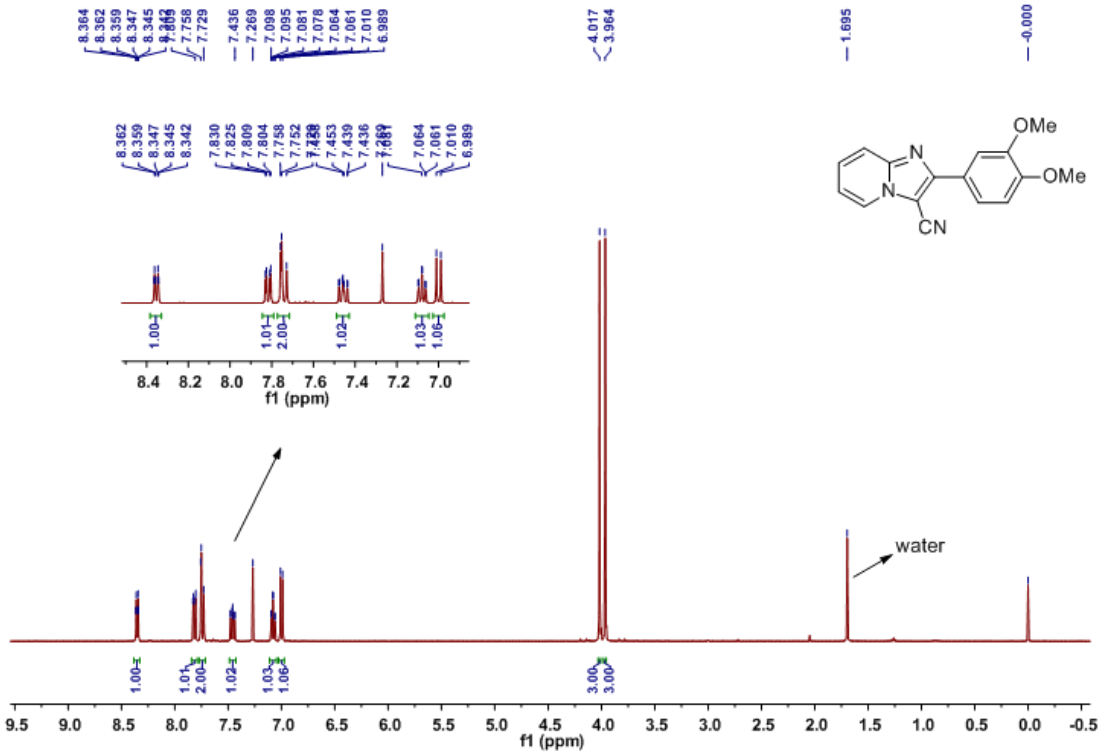


Figure 18 ^{13}C NMR spectrum of **4i**

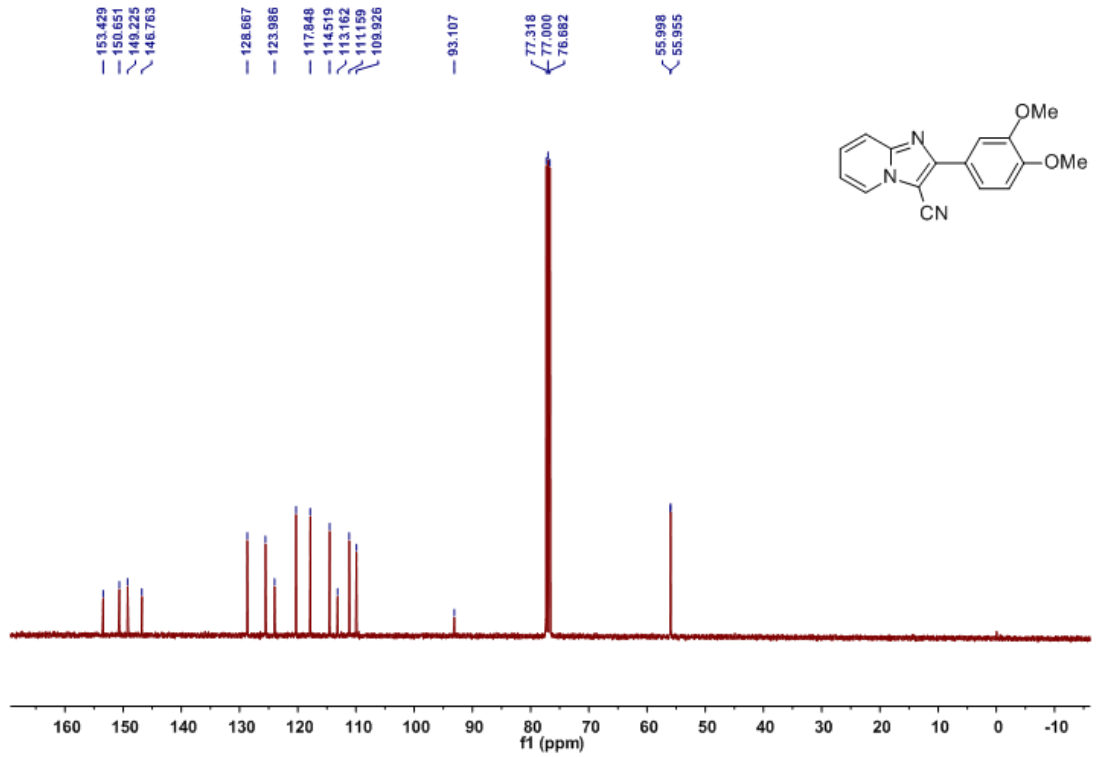


Figure 19 ^{1}H NMR spectrum of **4j**

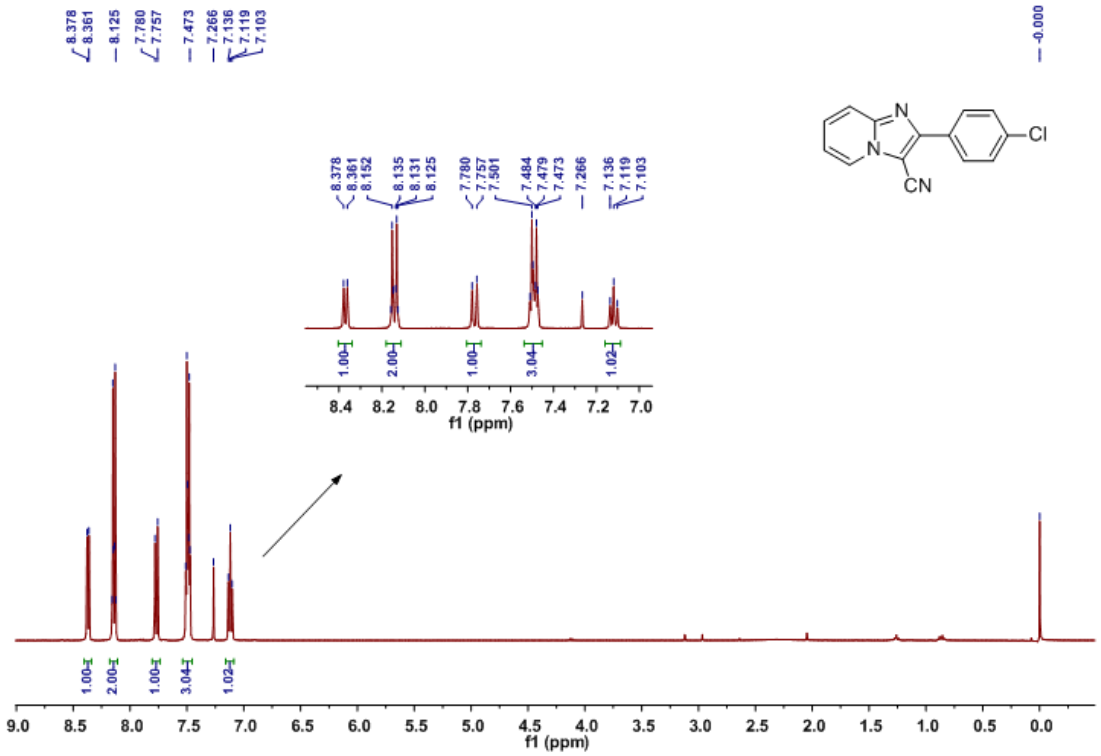


Figure 20 ^{13}C NMR spectrum of **4j**

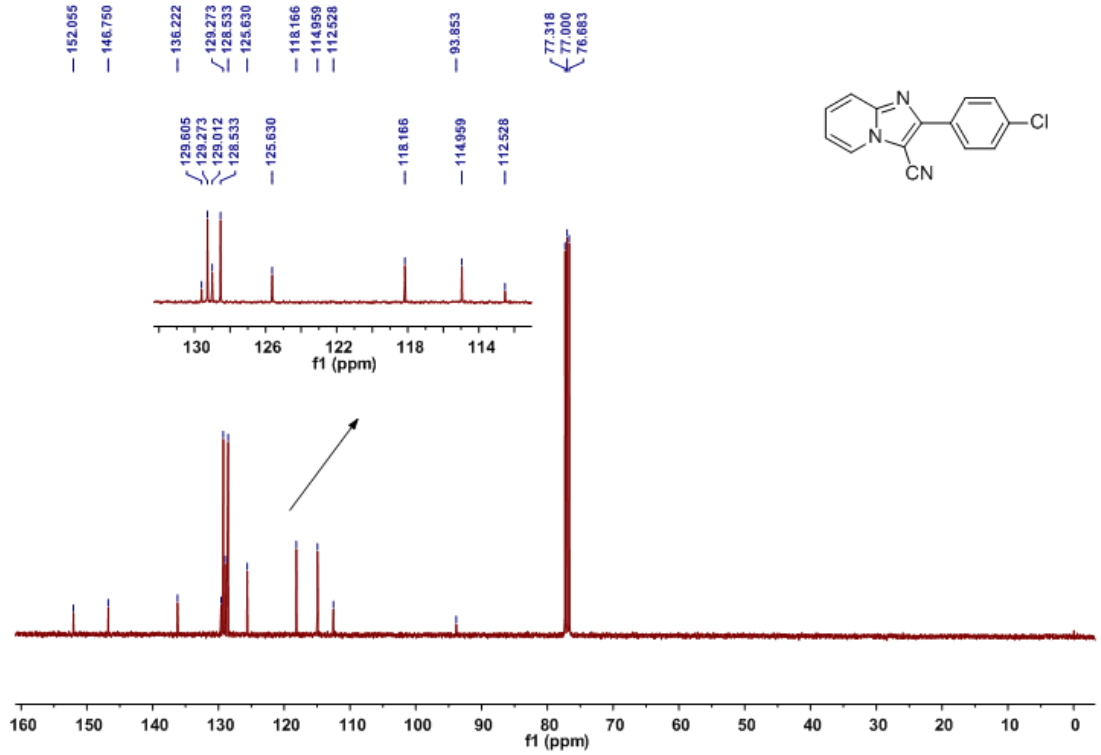


Figure 21 ^{1}H NMR spectrum of **4k**

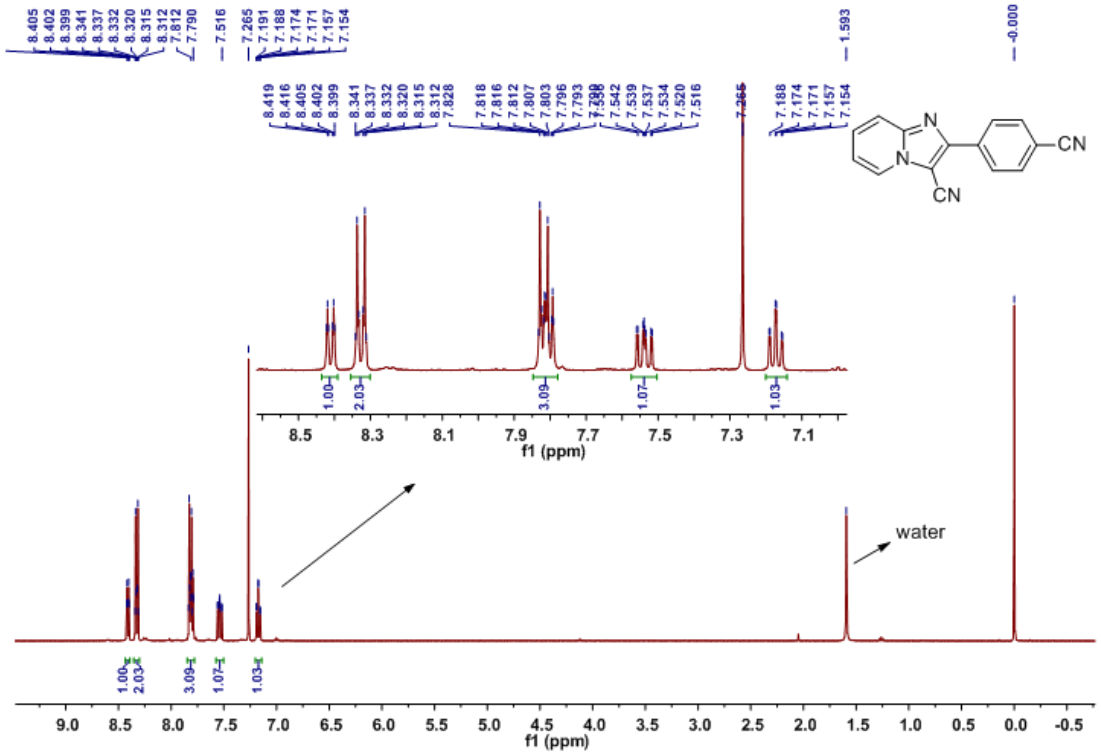


Figure 22 ^{13}C NMR spectrum of **4k**

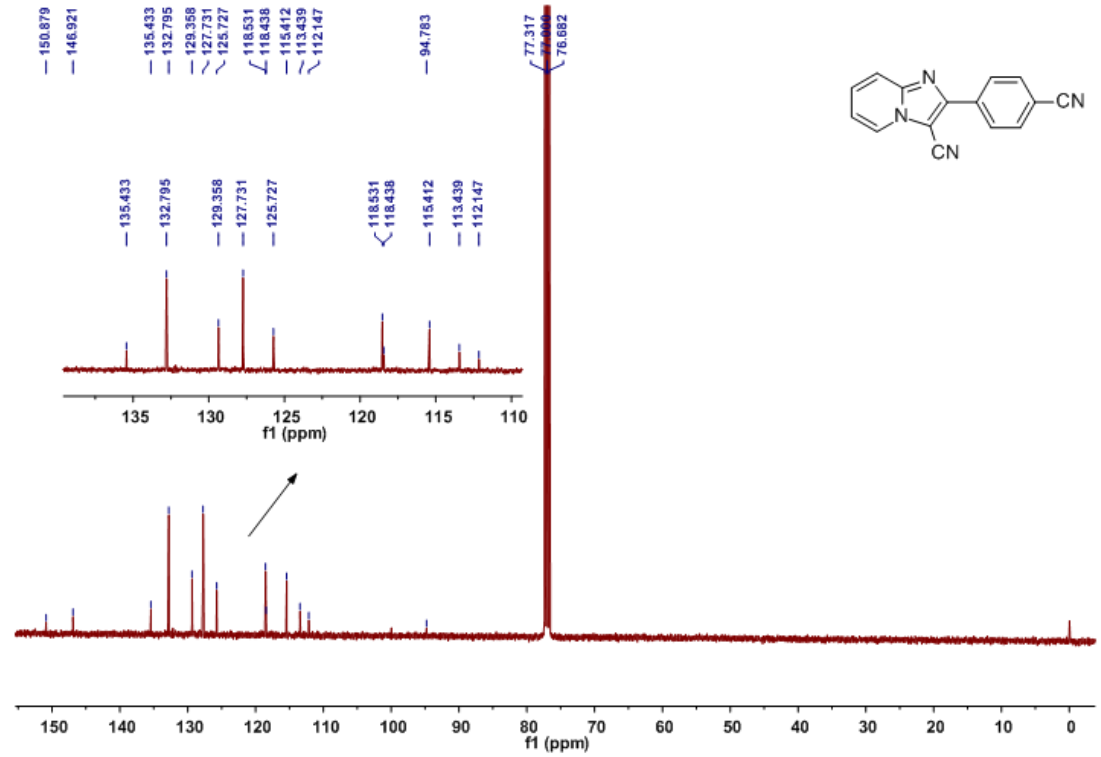


Figure 23 ^{1}H NMR spectrum of **4l**

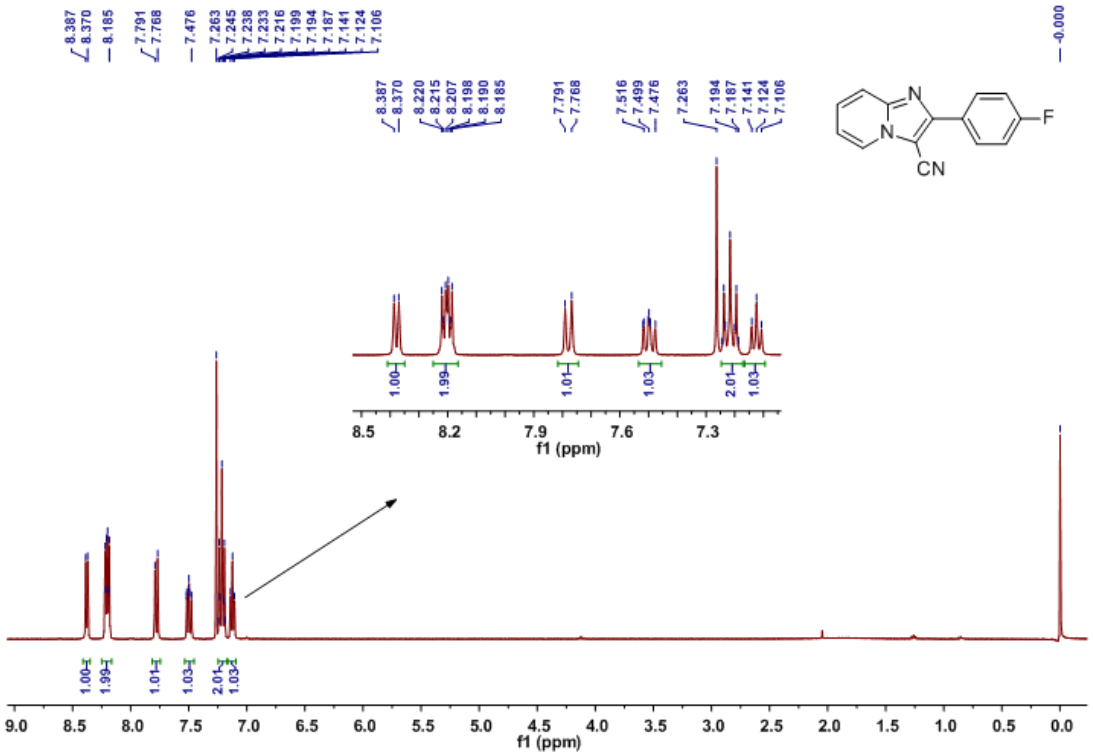


Figure 24 ^{13}C NMR spectrum of **4l**

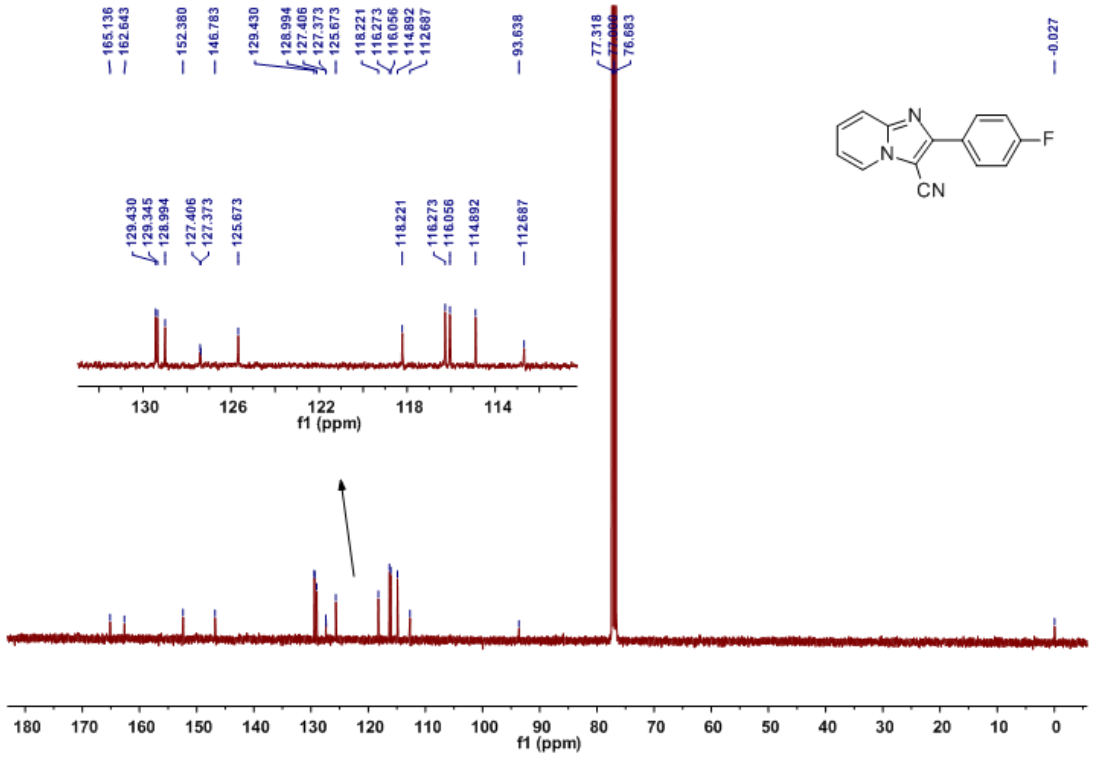


Figure 25 ^{1}H NMR spectrum of **4m**

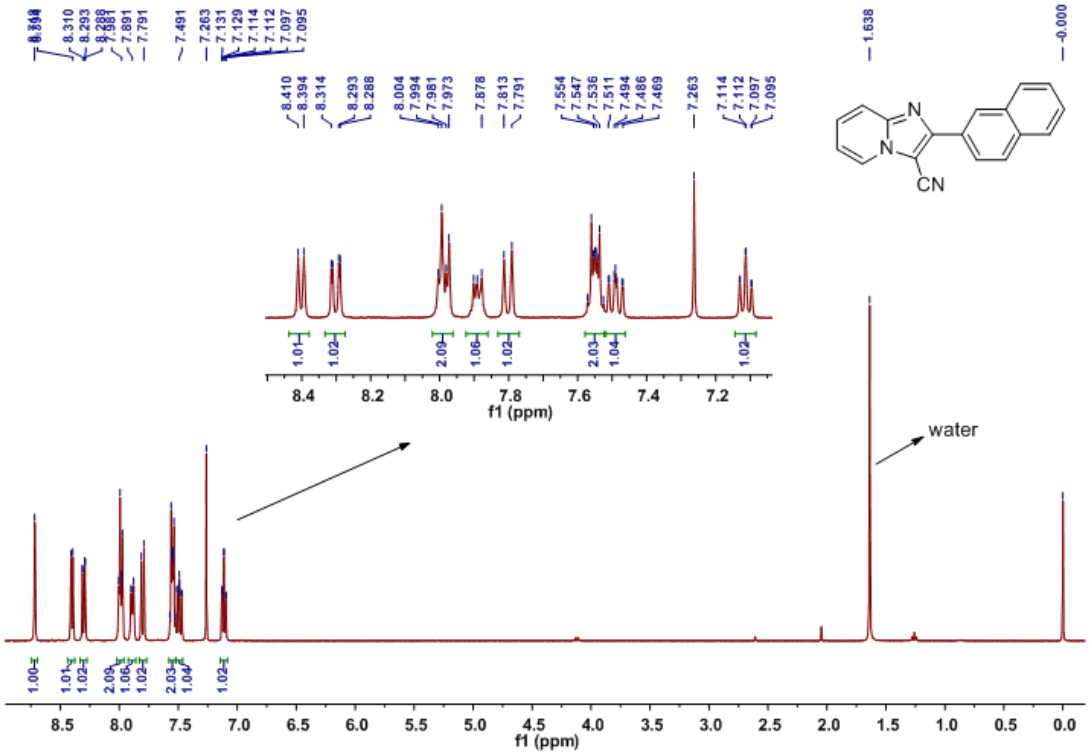


Figure 26 ^{13}C NMR spectrum of **4m**

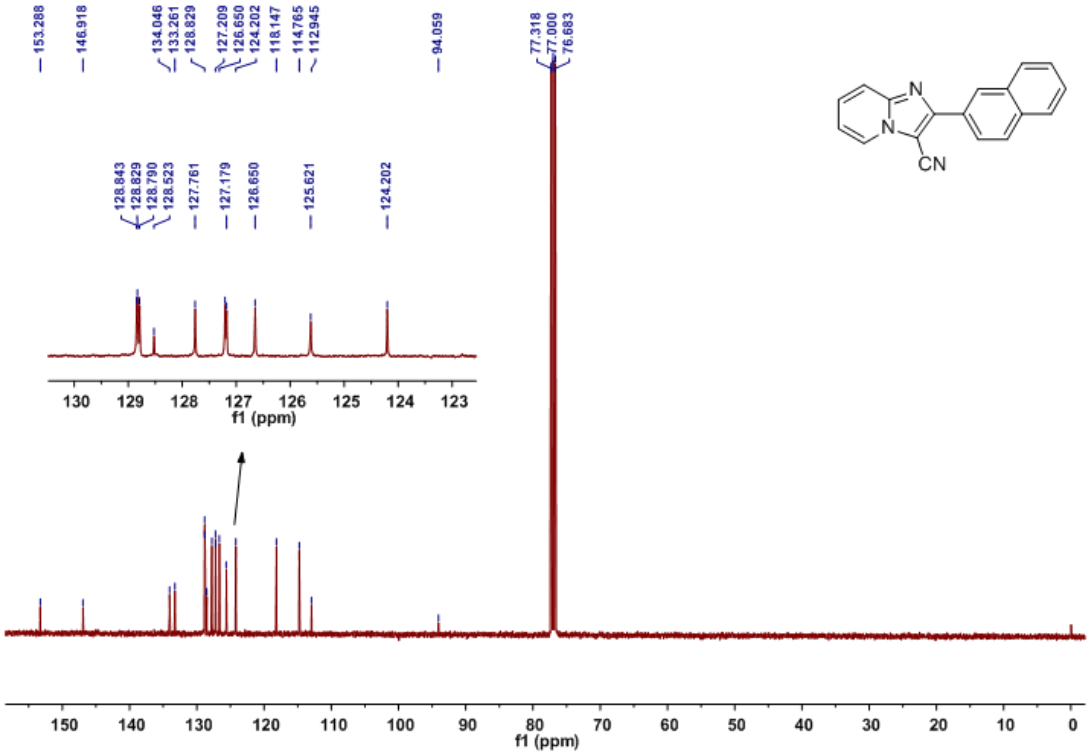


Figure 27 ^{1}H NMR spectrum of **4n**

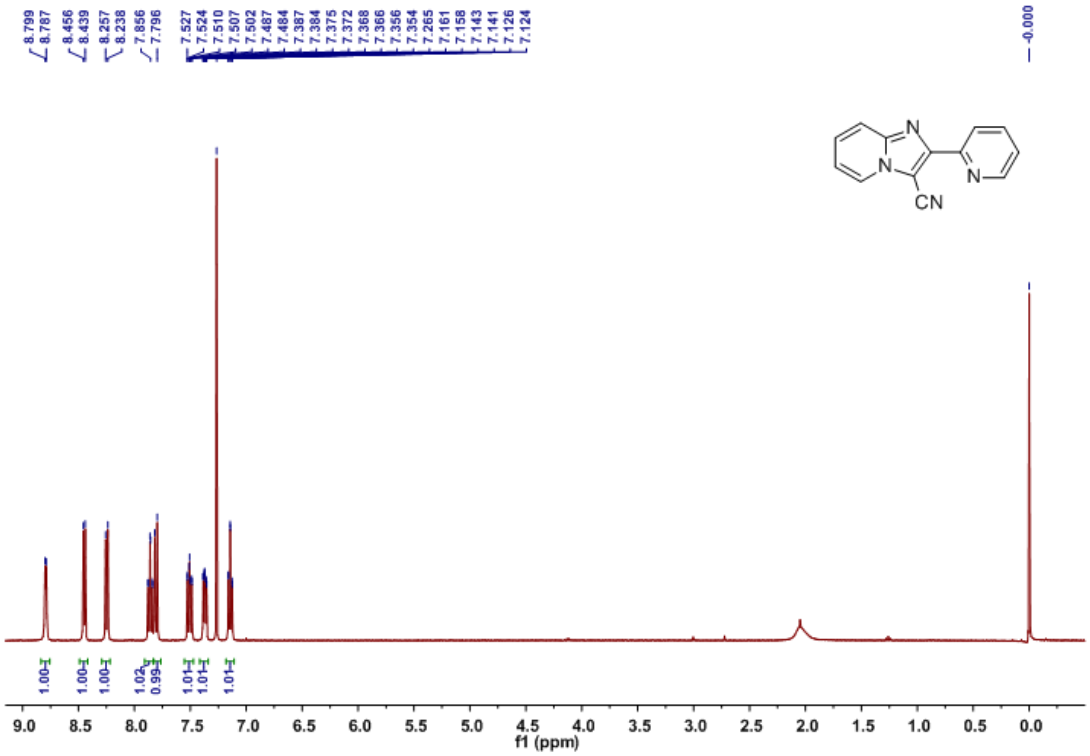


Figure 28 ^{13}C NMR spectrum of **4n**

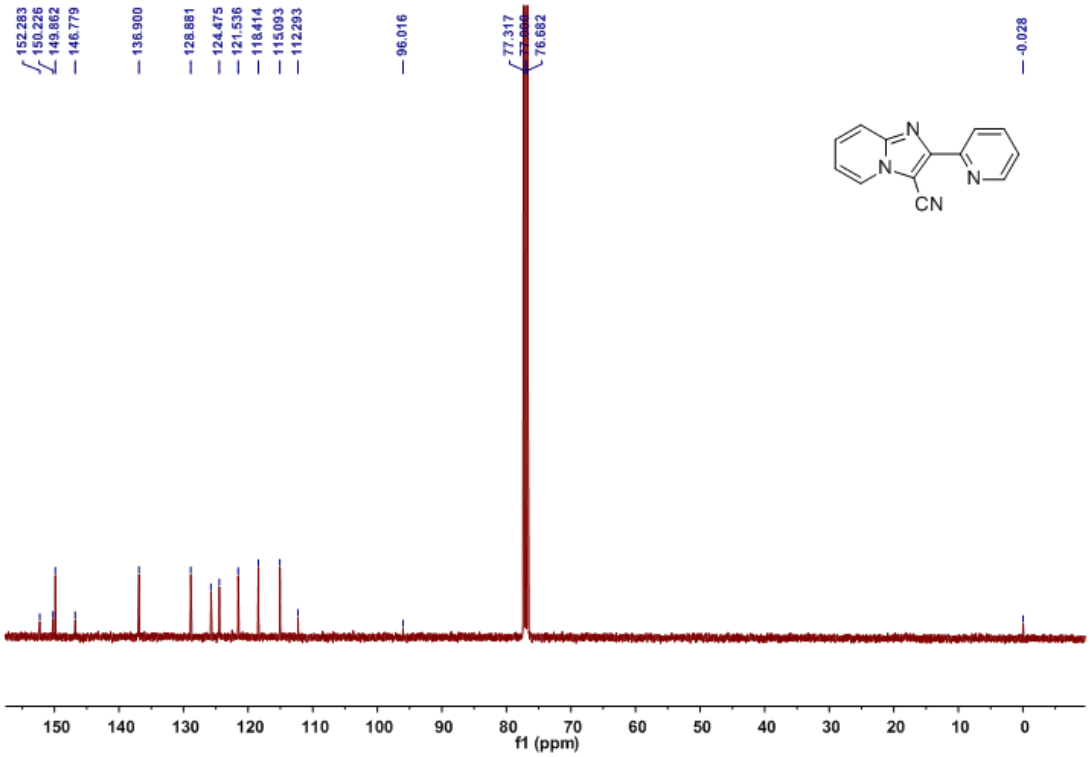


Figure 29 ^{1}H NMR spectrum of **4o**

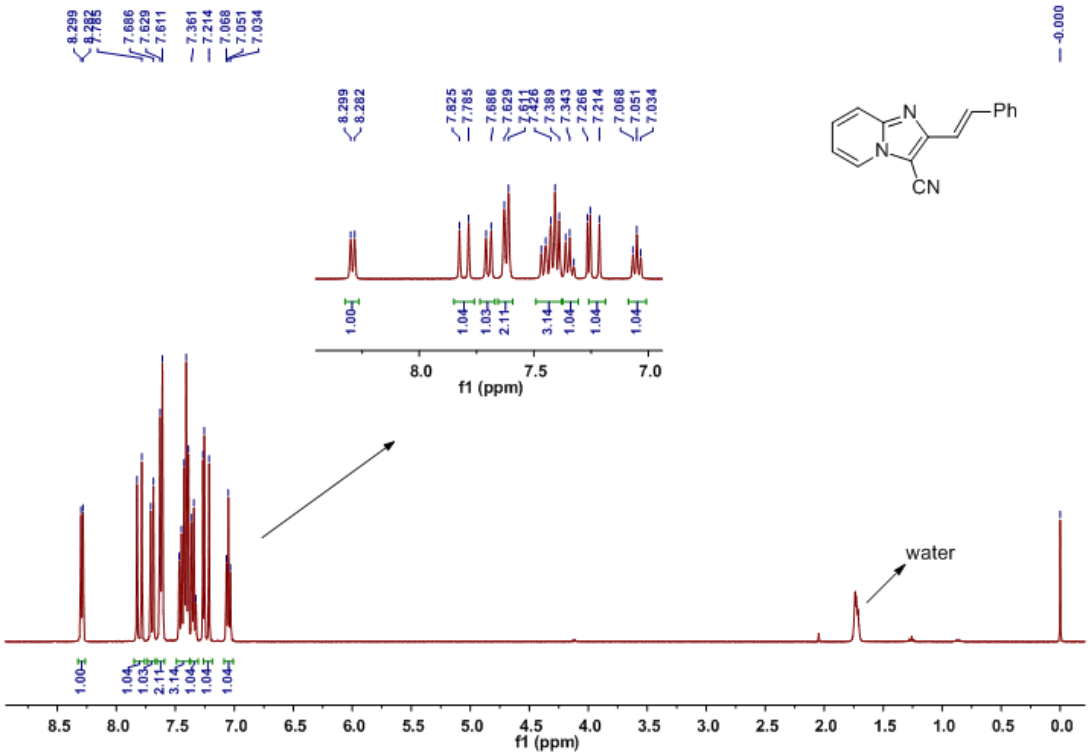


Figure 30 ^{13}C NMR spectrum of **4o**

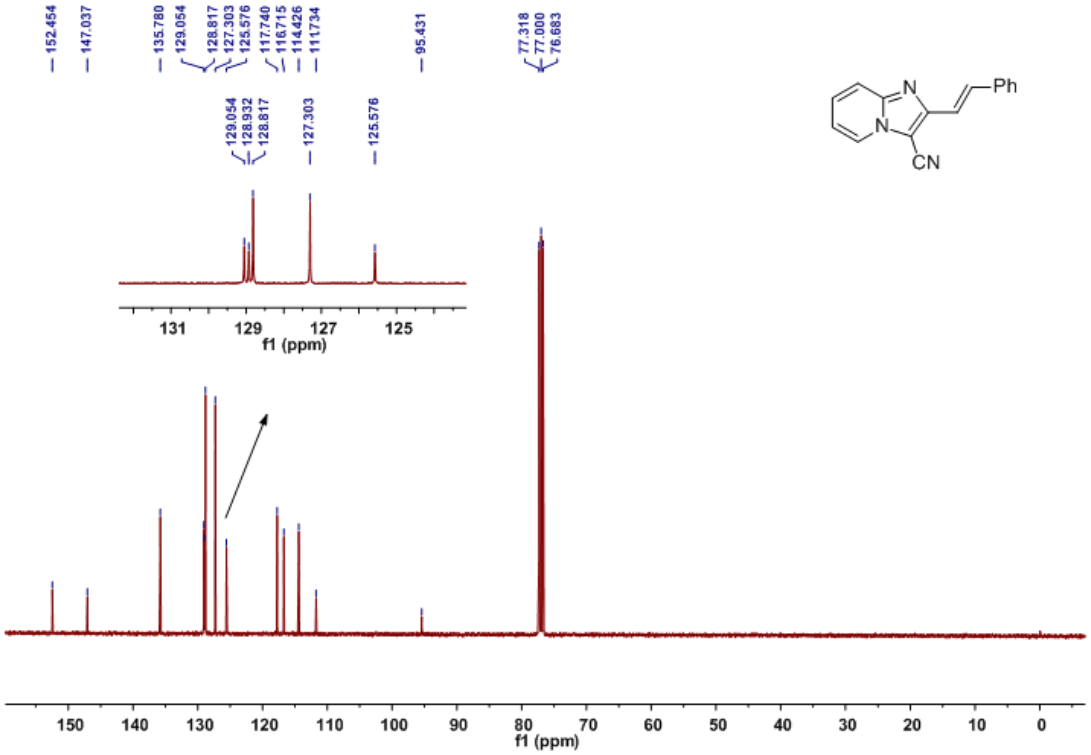


Figure 31 ^{1}H NMR spectrum of **4p**

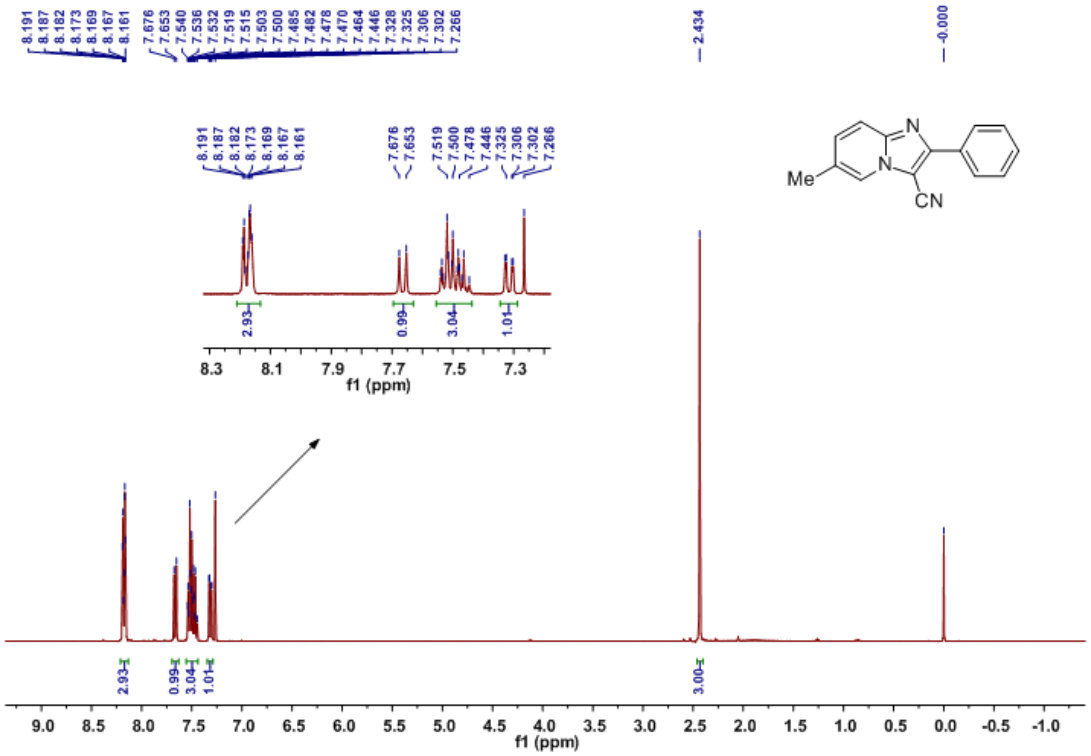


Figure 32 ^{13}C NMR spectrum of **4p**

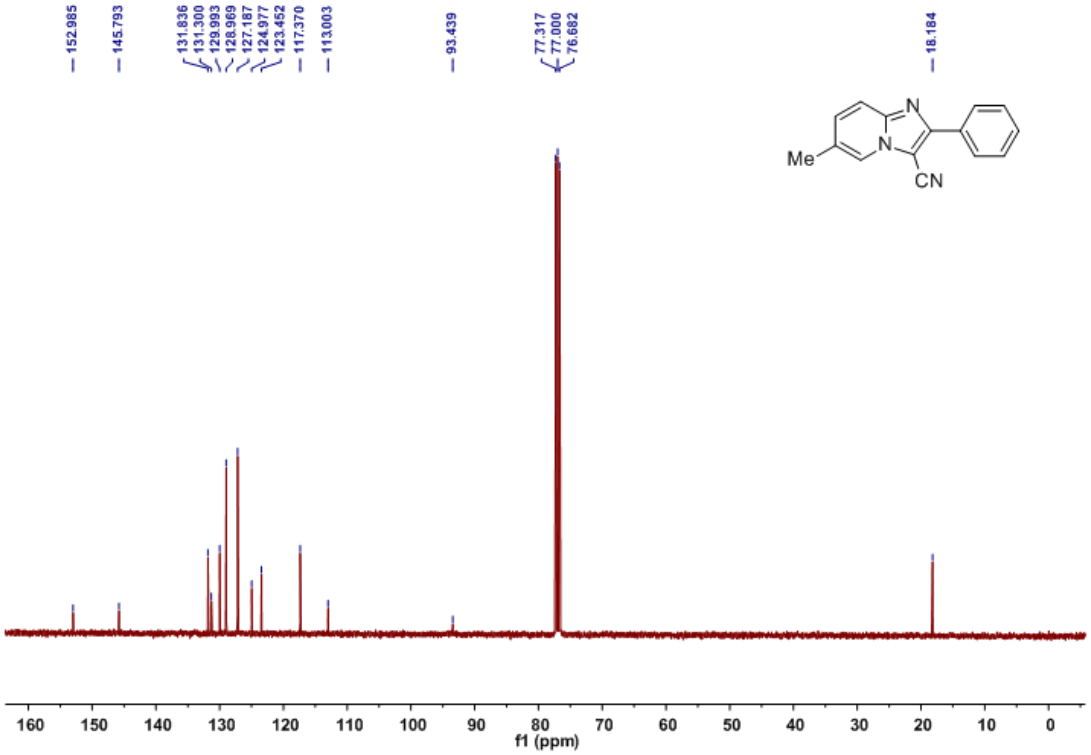


Figure 33 ^{1}H NMR spectrum of **4q**

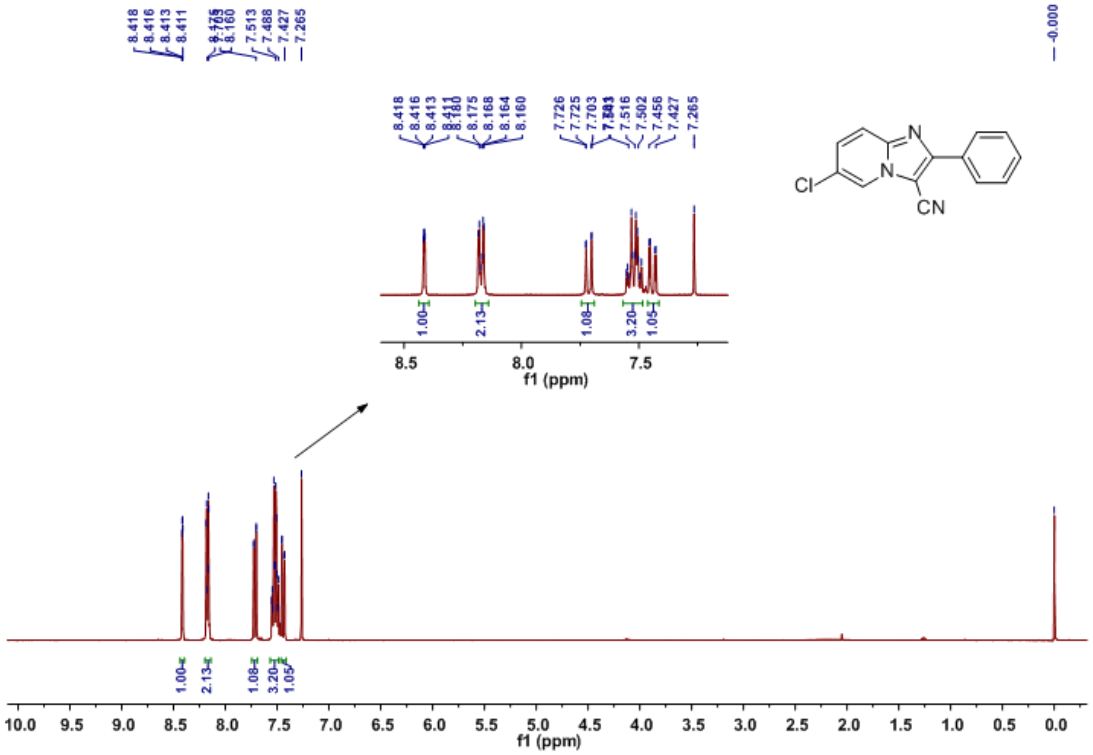


Figure 34 ^{13}C NMR spectrum of **4q**

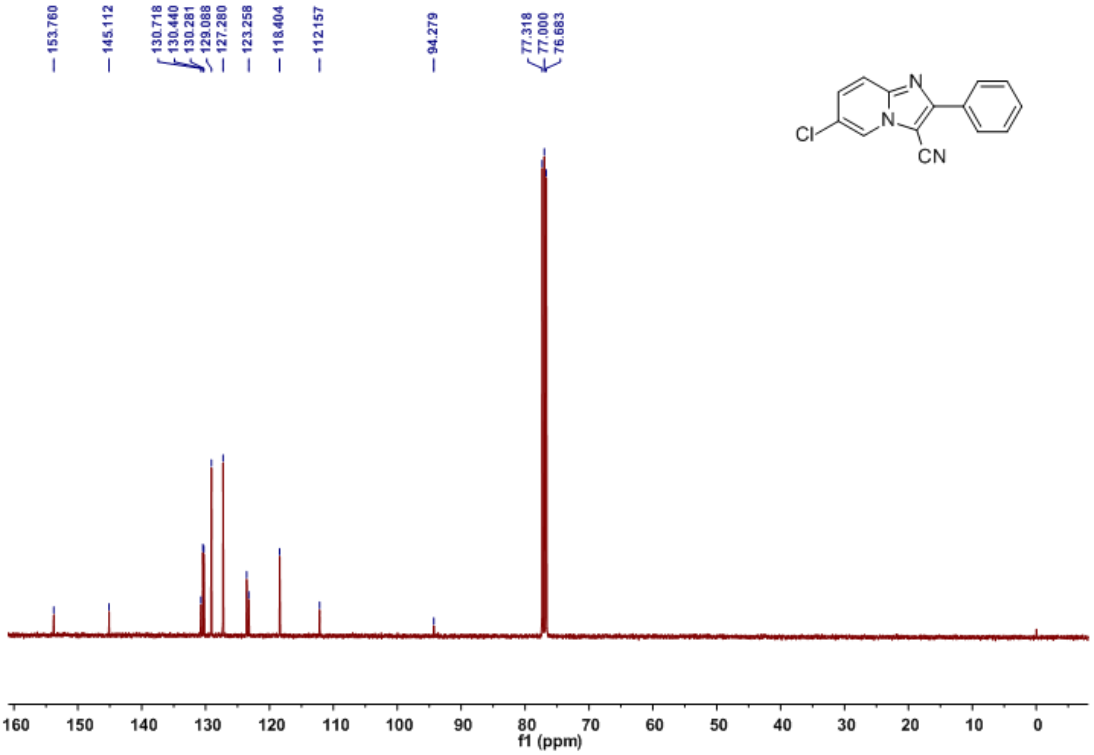


Figure 35 ^{1}H NMR spectrum of **4r**

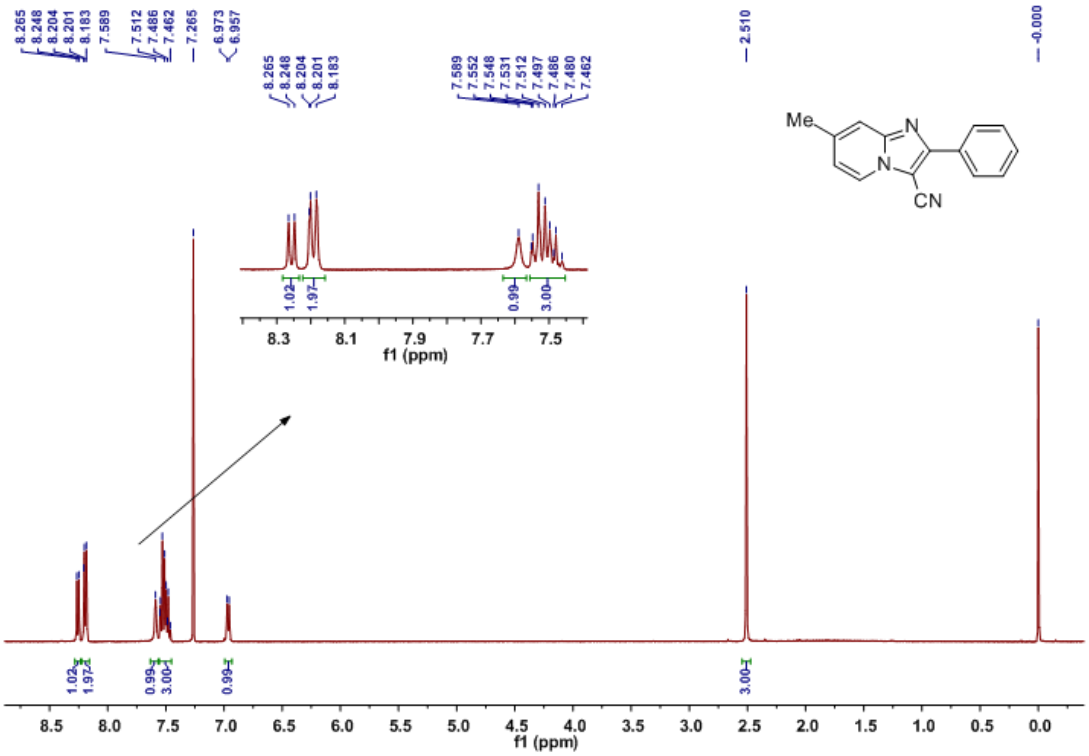


Figure 36 ^{13}C NMR spectrum of **4r**

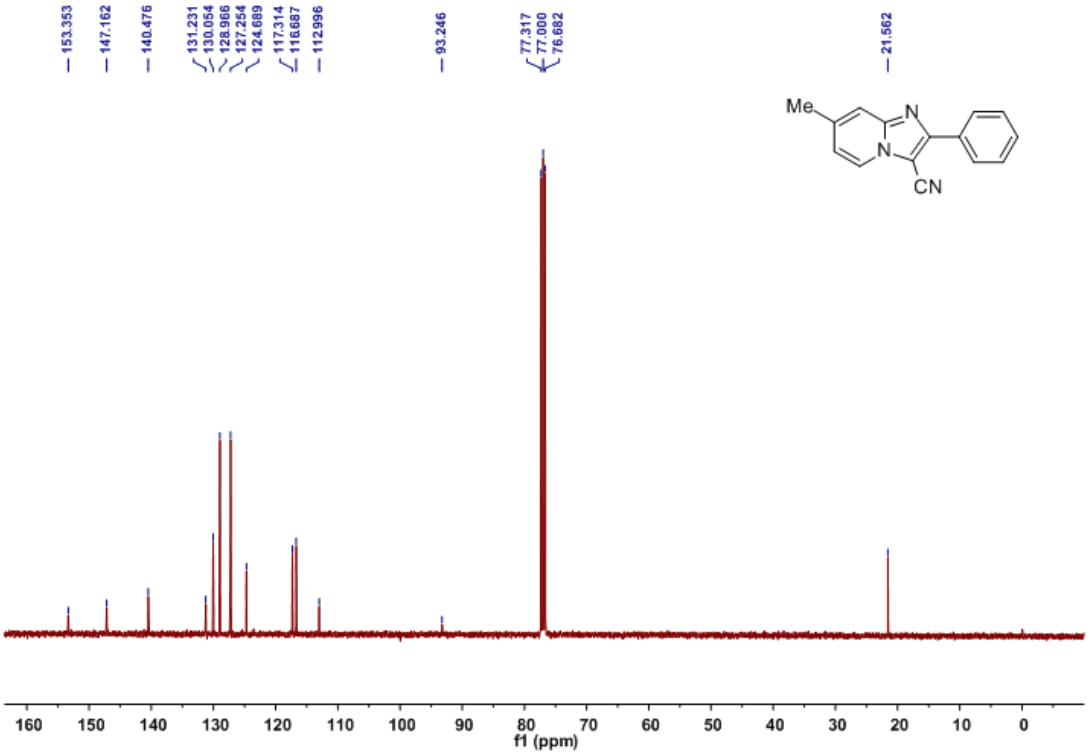


Figure 37 ^{1}H NMR spectrum of **4s**

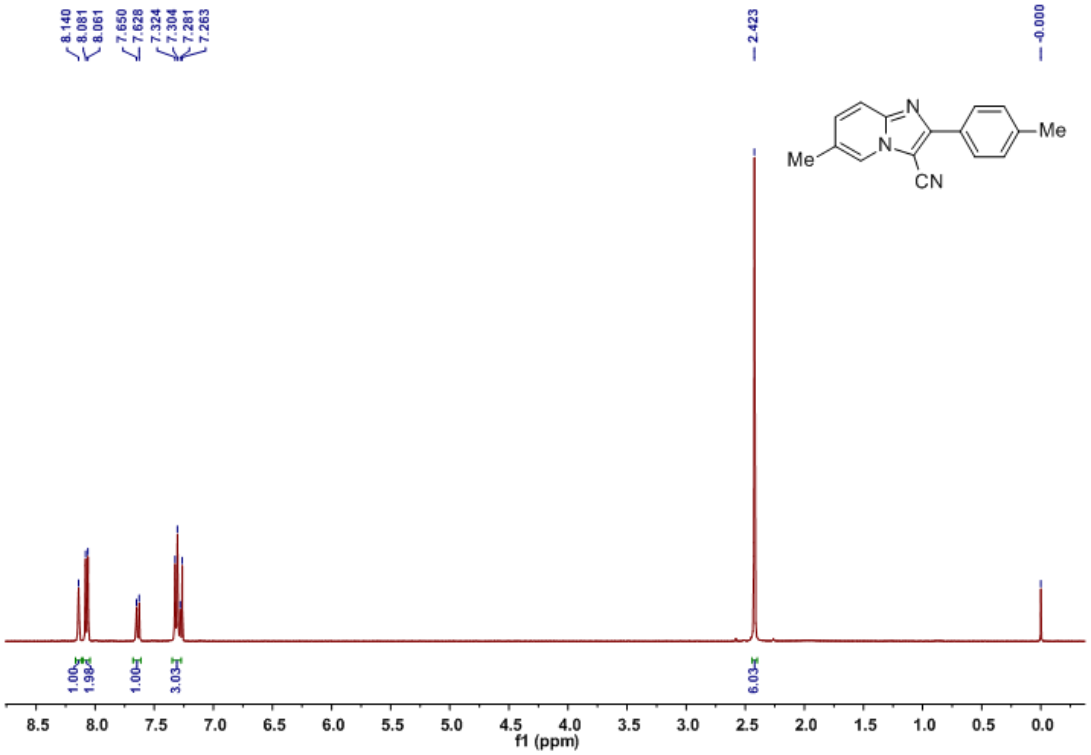


Figure 38 ^{13}C NMR spectrum of **4s**

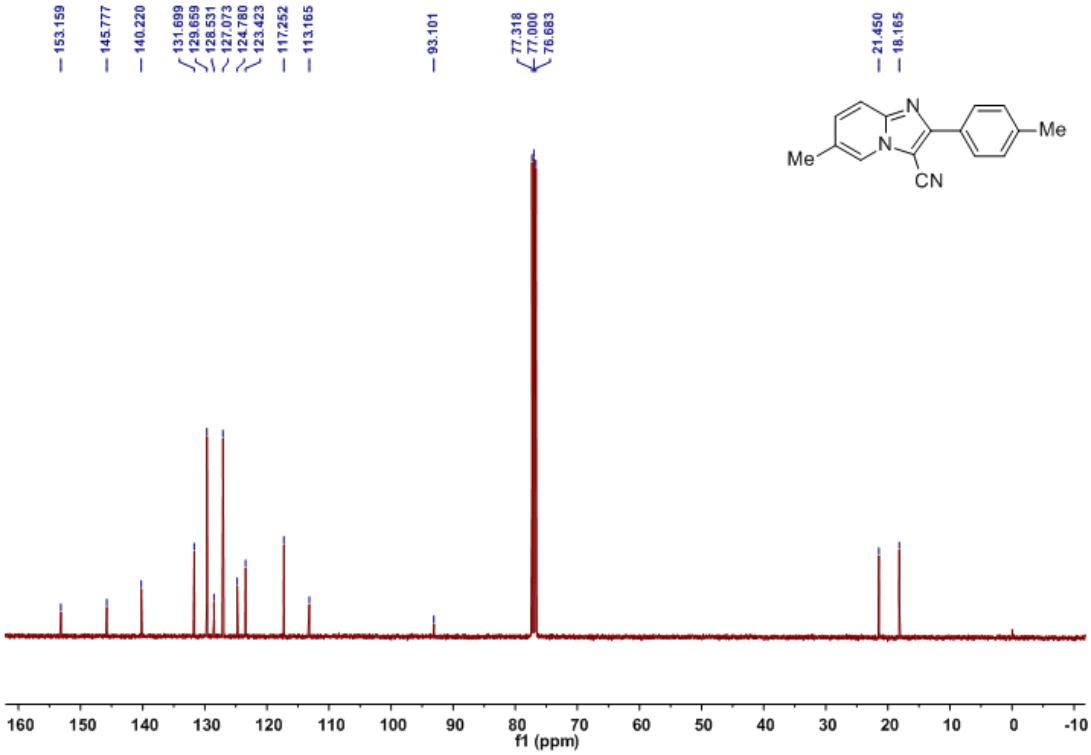


Figure 39 ^{1}H NMR spectrum of **4t**

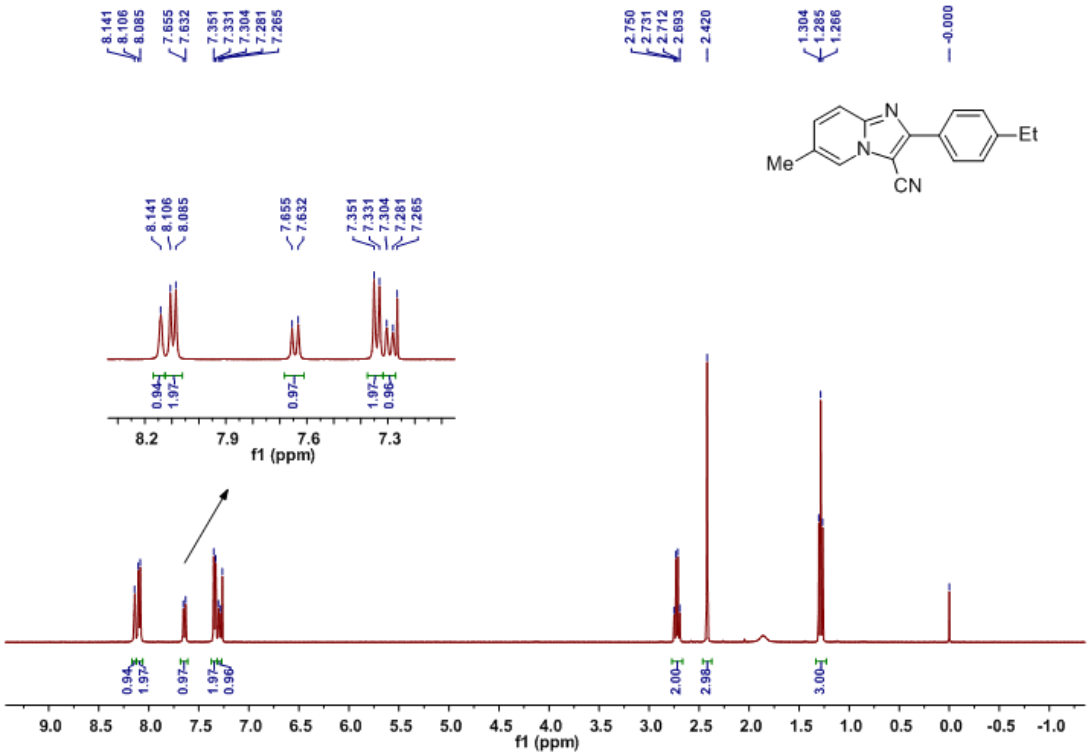


Figure 40 ^{13}C NMR spectrum of **4t**

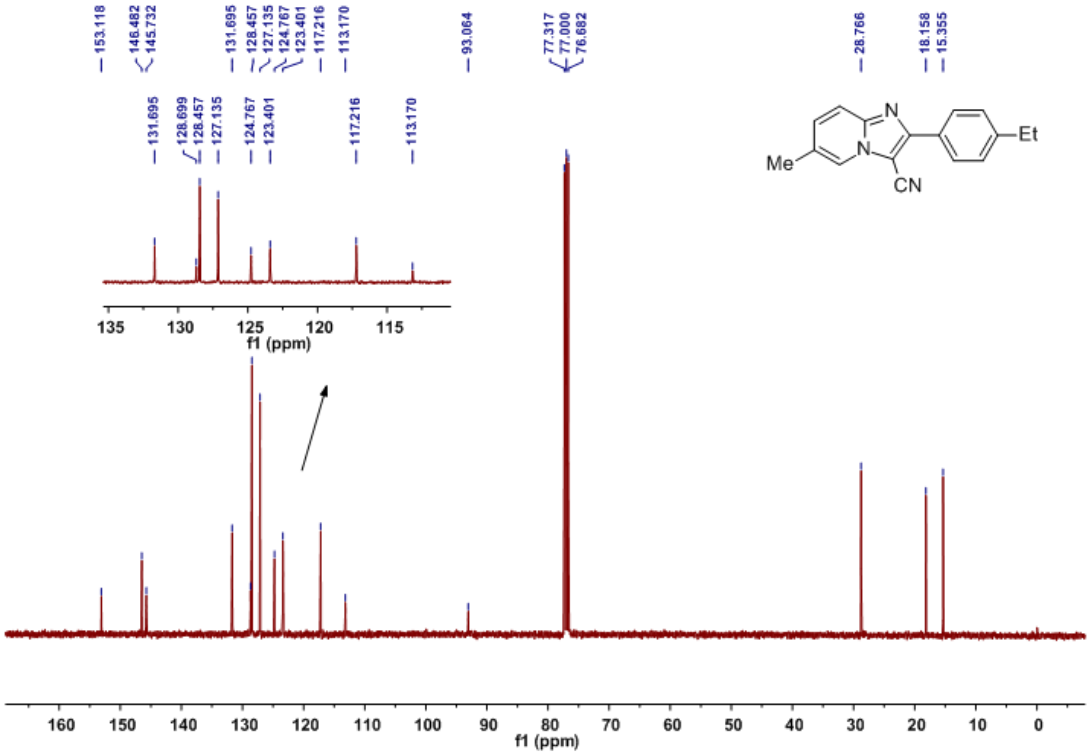


Figure 41 ^{1}H NMR spectrum of **4u**

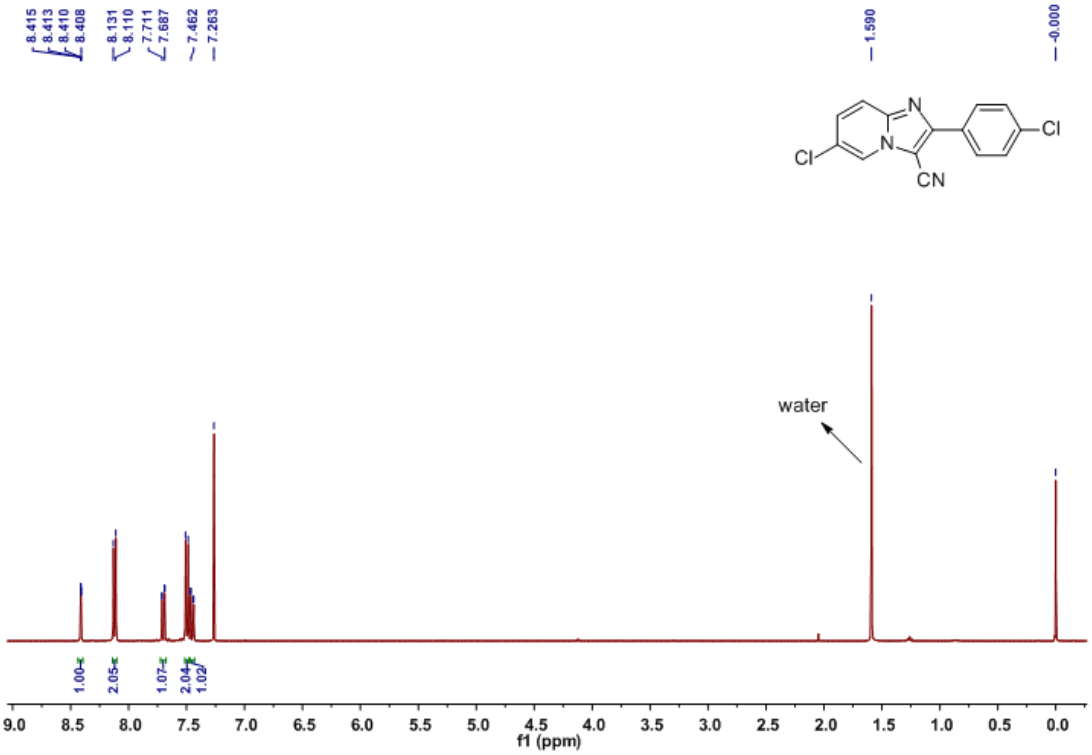


Figure 42 ^{13}C NMR spectrum of **4u**

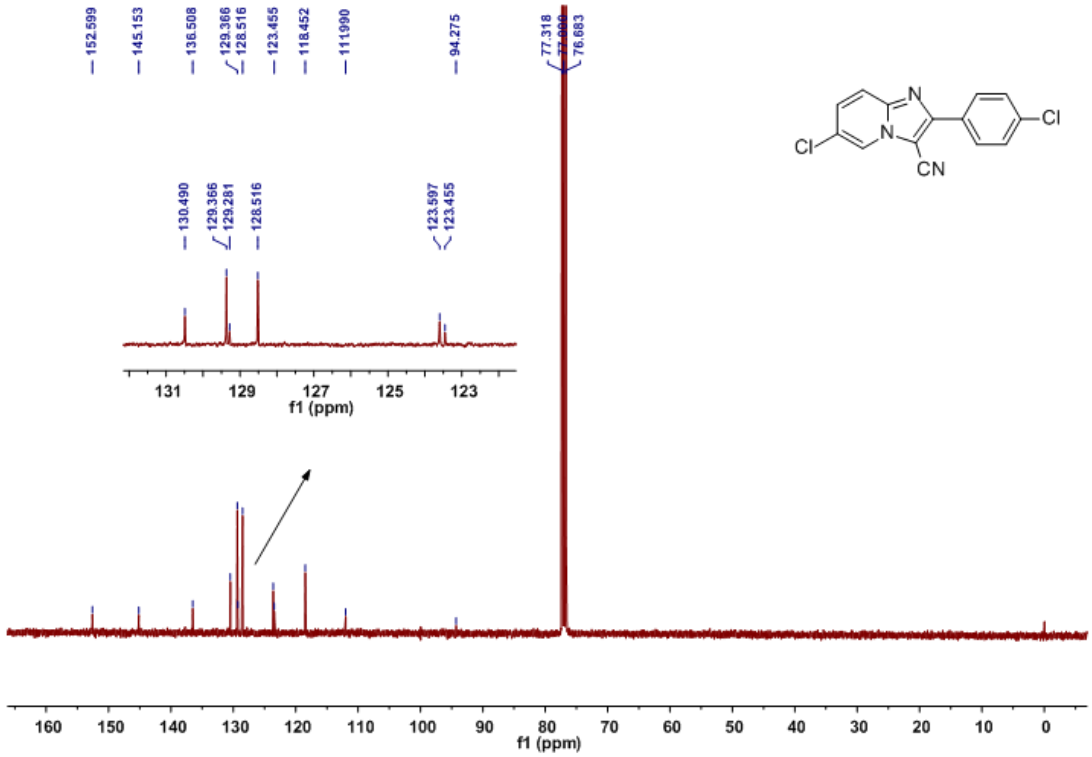


Figure 43 ^{1}H NMR spectrum of **4v**

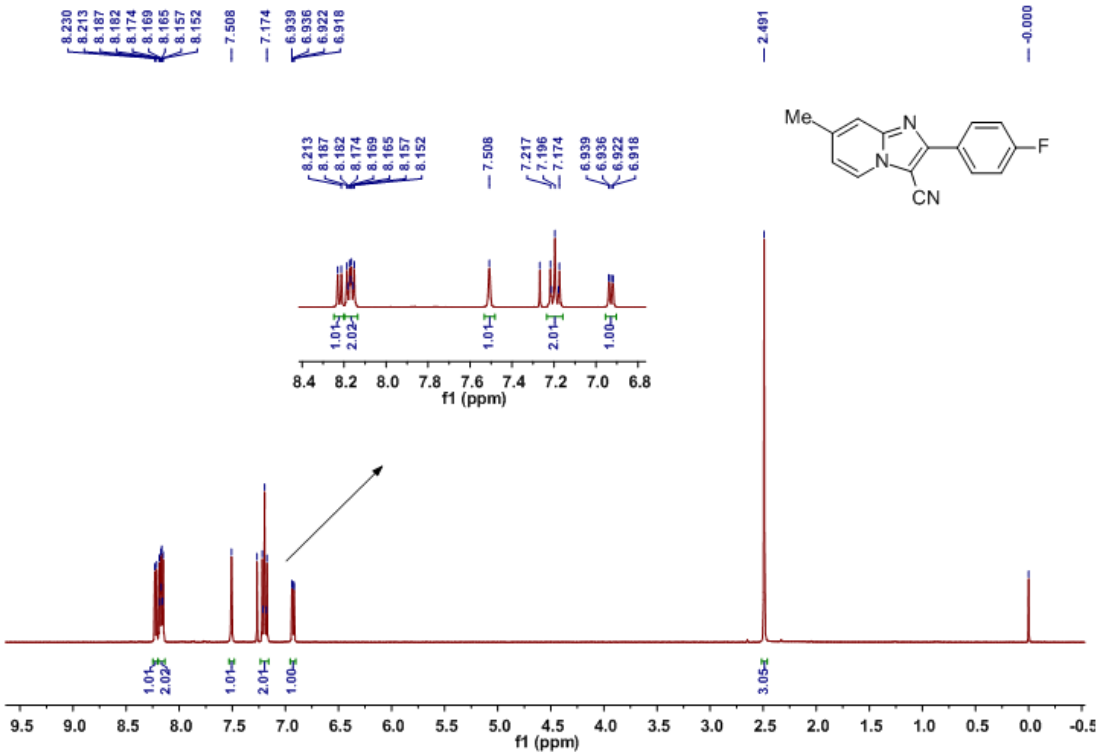


Figure 44 ^{13}C NMR spectrum of **4v**

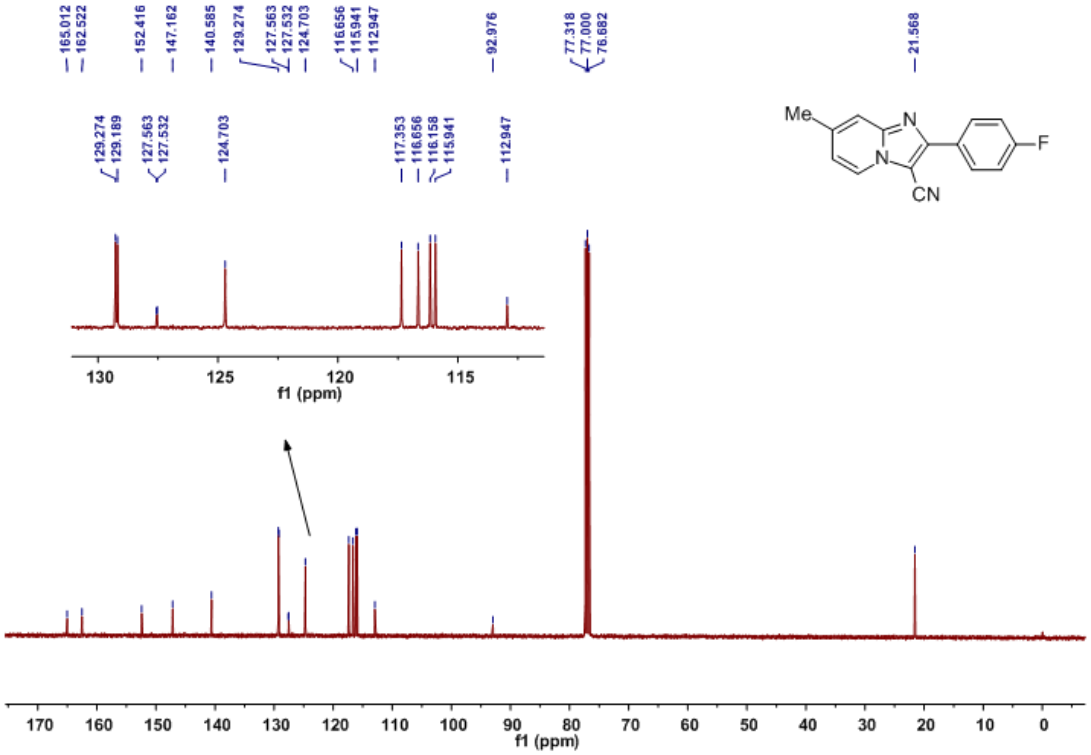


Figure 45 ^{1}H NMR spectrum of **4w**

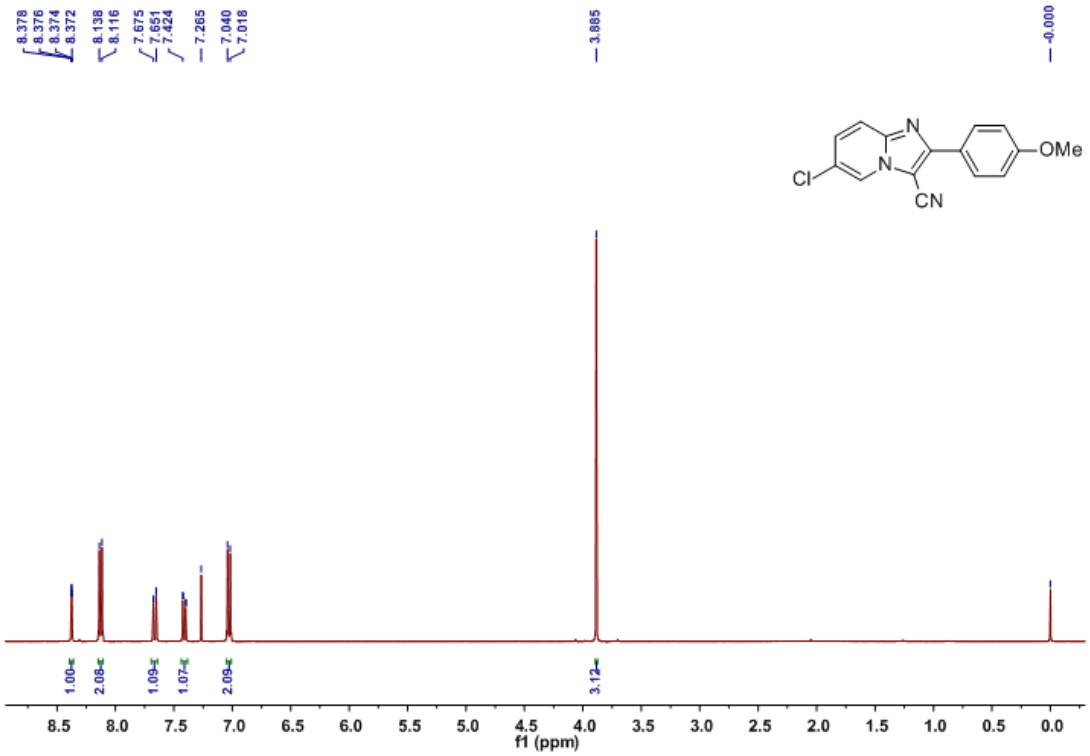


Figure 46 ^{13}C NMR spectrum of **4w**

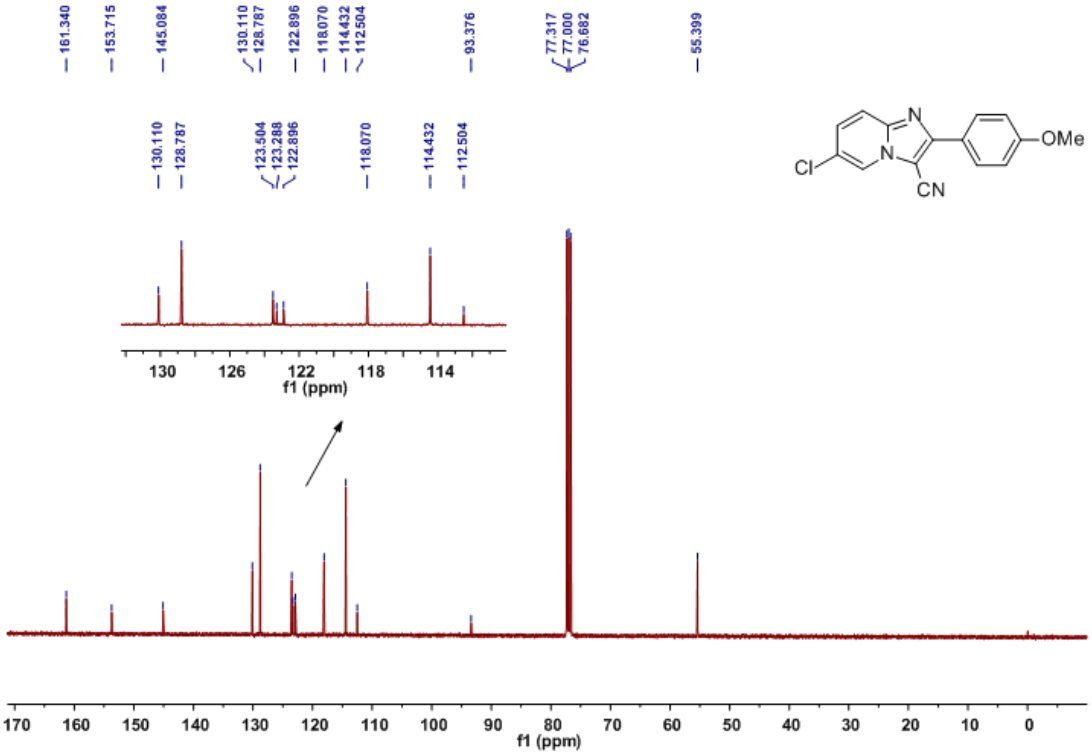


Figure 47 ^{1}H NMR spectrum of **5**

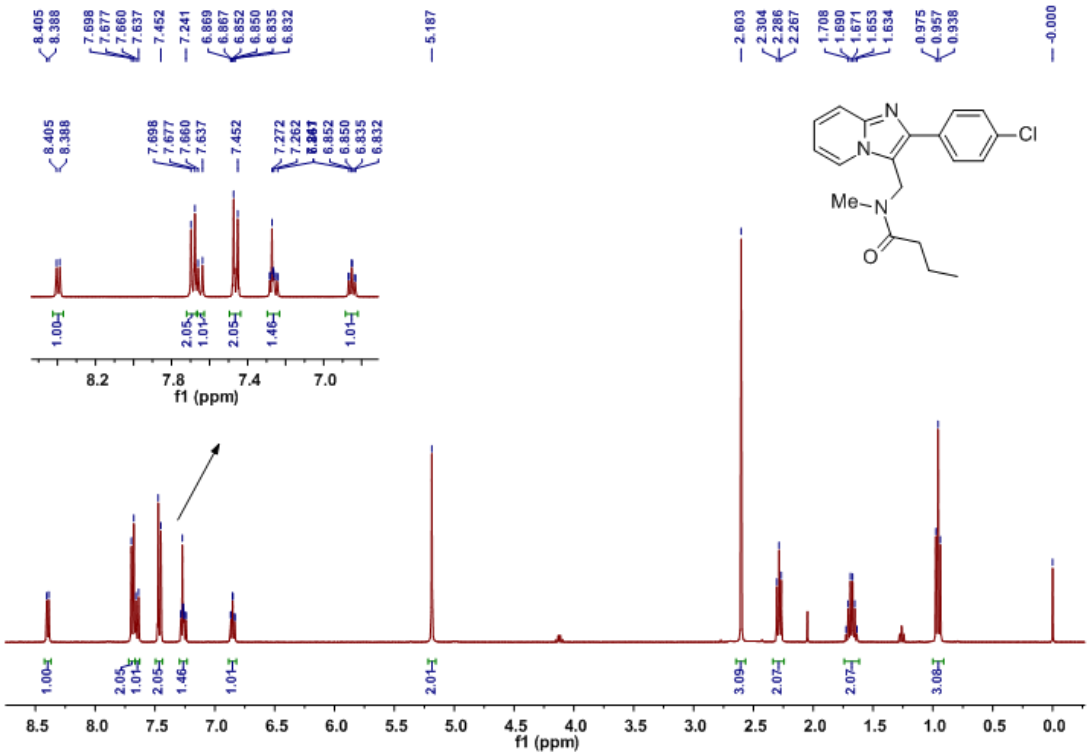


Figure 48 ^{13}C NMR spectrum of **5**

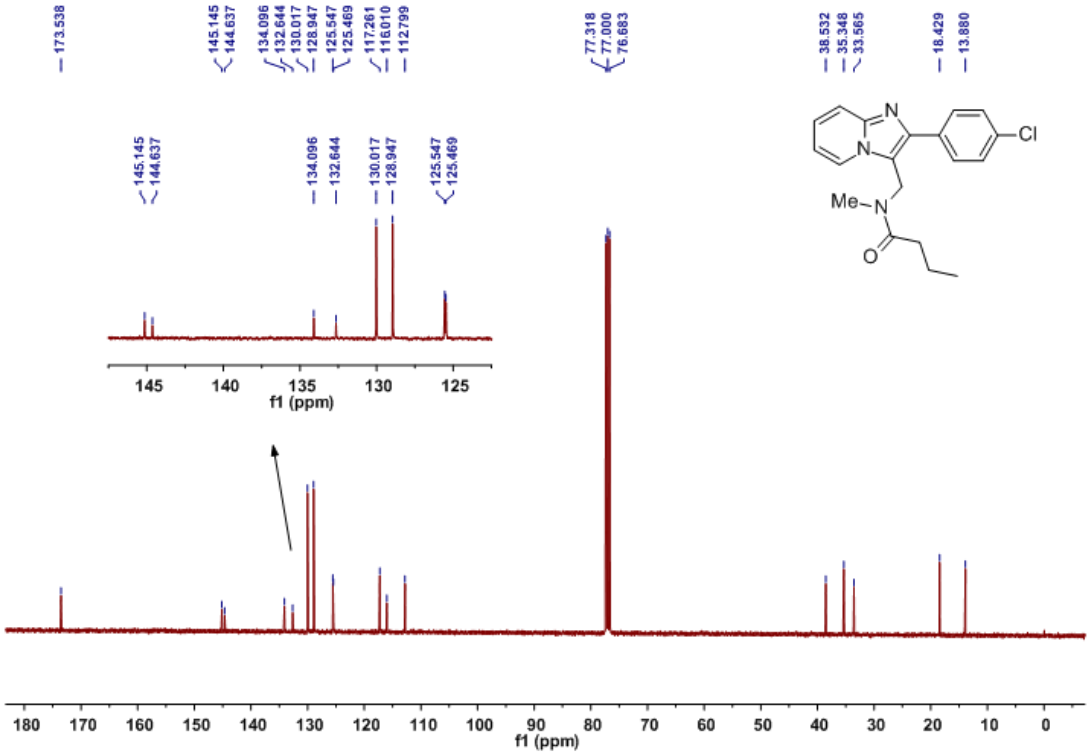


Figure 49 ^{1}H NMR spectrum of **6**

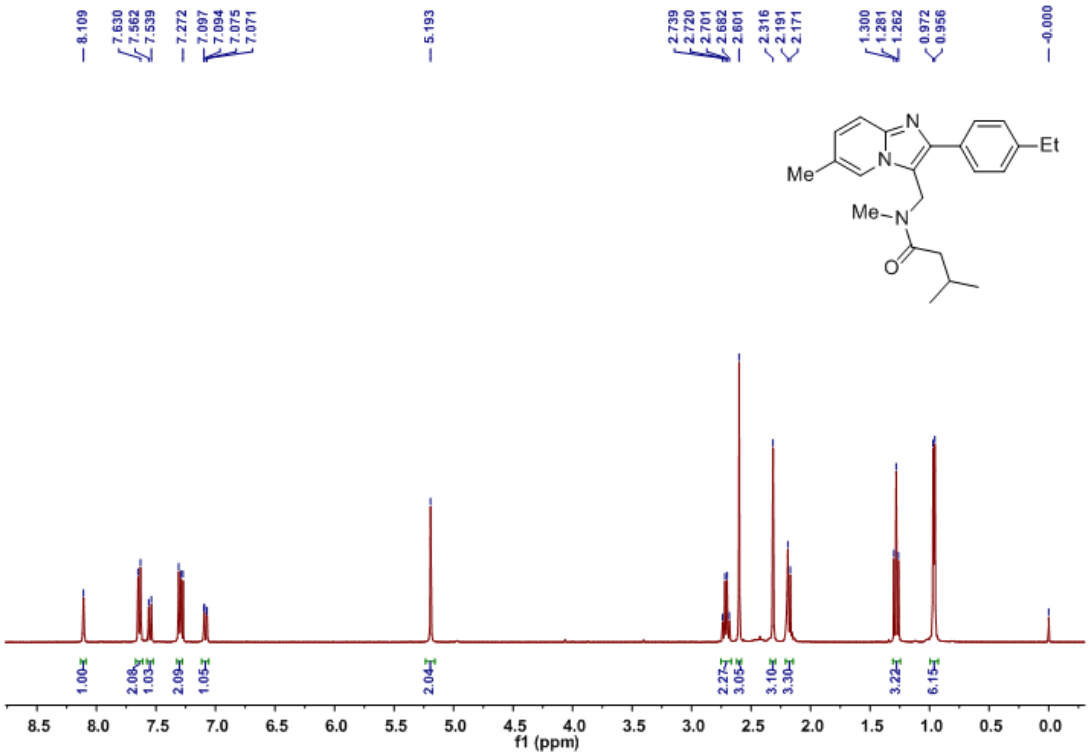


Figure 50 ^{13}C NMR spectrum of **6**

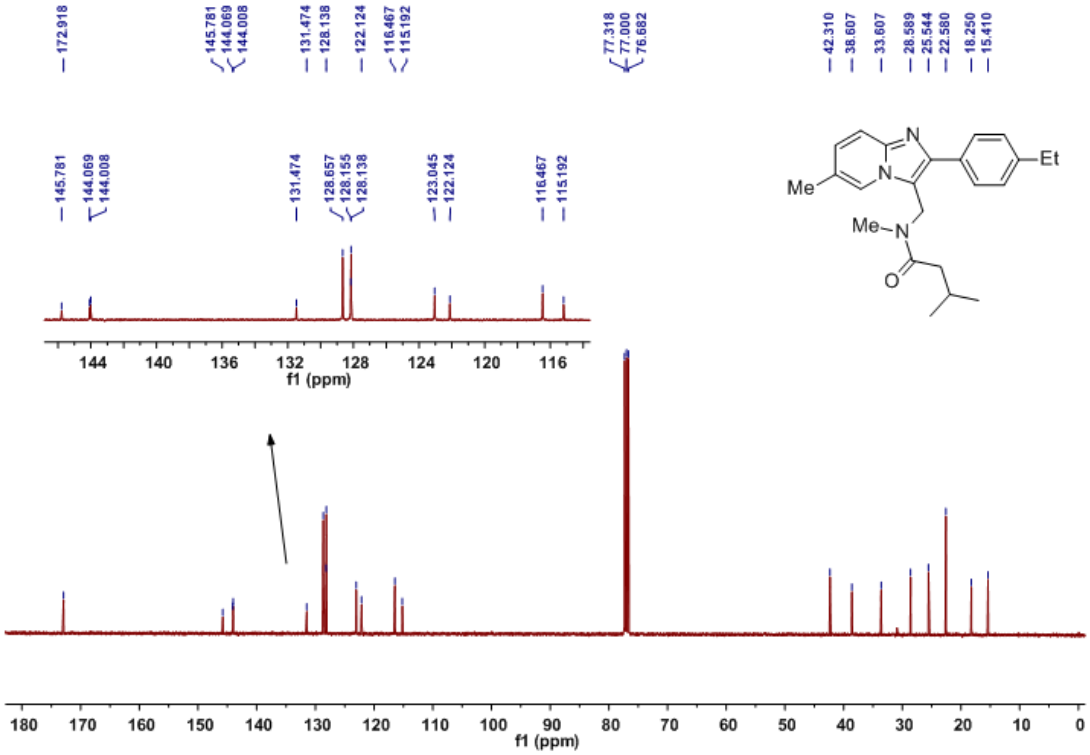


Figure 51 ^{1}H NMR spectrum of **7**

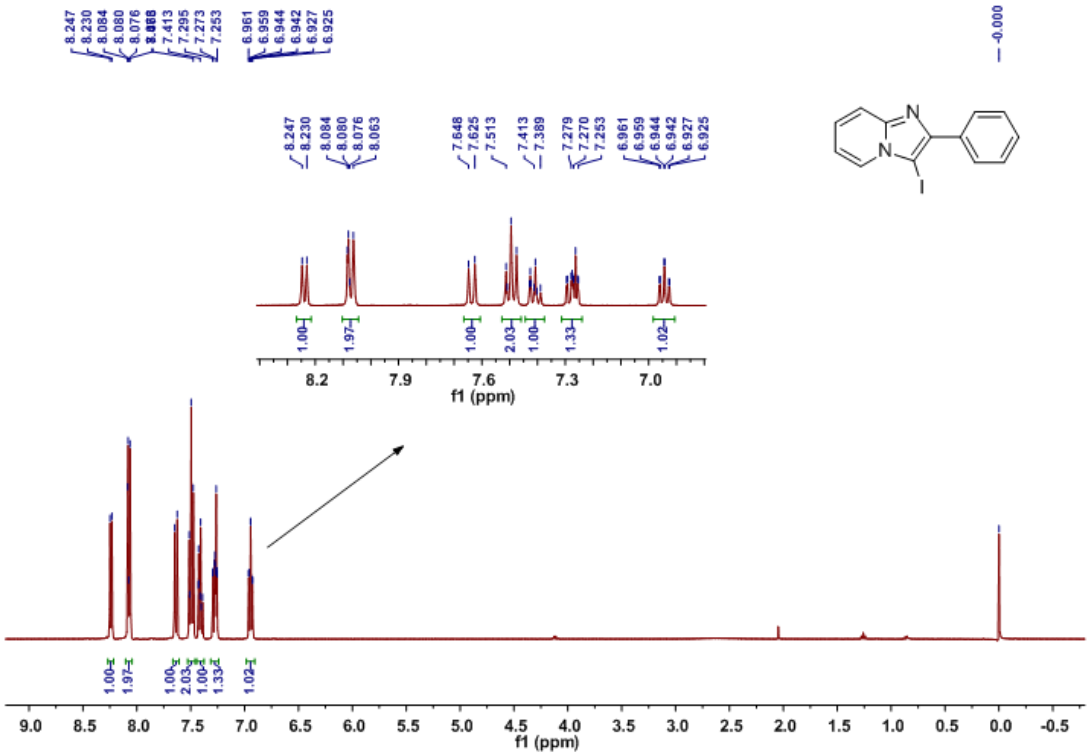


Figure 52 ^{13}C NMR spectrum of **7**

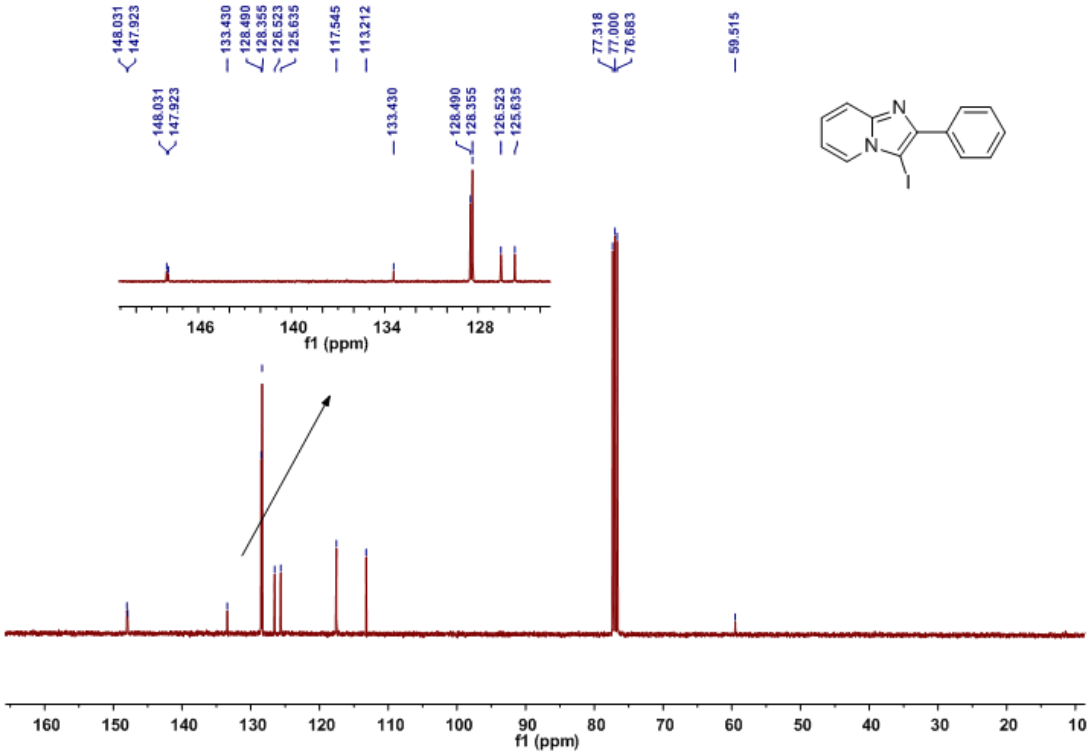


Figure 53 ^{1}H NMR spectrum of **8**

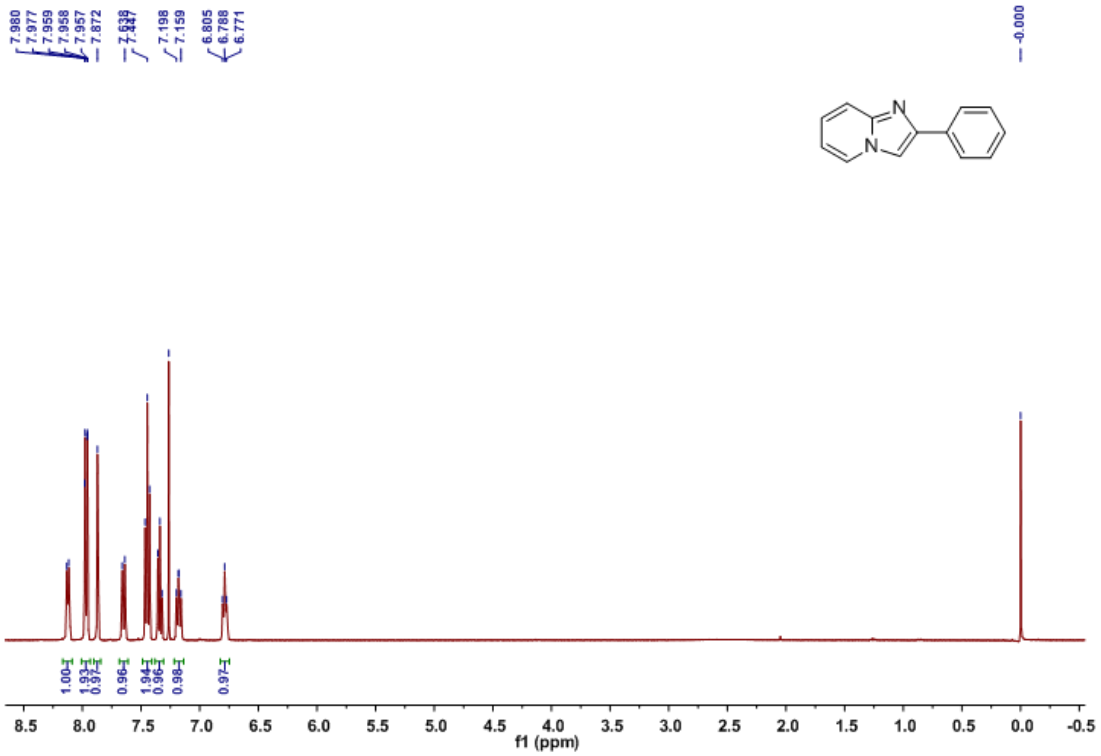


Figure 54 ^{13}C NMR spectrum of **8**