Visible-light-mediated nickel(II)-catalyzed C-N cross-coupling in water: a green and regioselective access for the synthesis of pyrazole-containing compounds

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Supporting Information

General Information

All commercial reagents were used as received. All products were isolated by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90°C) and ethyl acetate. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance DRX-500 spectrometers at ambient temperature with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. Compounds for HRMS were analyzed by positive mode electrospray ionization (ESI) using Agilent 6530 QTOF mass spectrometer. The ICP-MS measurement was performed in an Inductively Coupled Plasma Mass Spectrometer of the Elan DRC-e series (PerkinElmer Instruments, USA).

1. Experimental Section

General procedure for the synthesis of substrates 1

A mixture of naphthylamine (10 mmol), pyridine-2-carbonyl chloride (1.05 equiv), NEt_3 (3.0 equiv) in anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the desired amide products.

General procedure for the synthesis of products 3a-x

Amides **1** (0.2 mmol), pyrazole derivatives **2** (0.4 mmol), $NiSO_4{\bullet}6H_2O$ (15 mol %), Acr^+−Mes ClO_4^- (5 mol%), H_2O_2 (0.4 mmol) and H_2O (4 mL) were combined in a 25 mL tube. The mixture was then stirred for 24 hours at room temperature under the radiation of 12 W blue LED. After the conversion was completed as indicated by TLC, the mixture was extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified directly by flash column chromatography to give the products **3a-x**.

General procedure for the synthesis of products 3aa-ad

Amides **1** (0.2 mmol), pyrazole **2a** (0.8 mmol), $NiSO_4{\bullet}6H_2O$ (15 mol %), Acr^+−Mes ClO_4^- (5 mol%), H_2O_2 (0.8 mmol) and H_2O (4 mL) were combined in a 25 mL tube. The mixture was then stirred for 48 hours at room temperature under the radiation of 12 W blue LED. After the conversion was completed as indicated by TLC, the mixture was extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified directly by flash column chromatography to give the products **3aa-ad**.

General procedure for the synthesis of product 4a

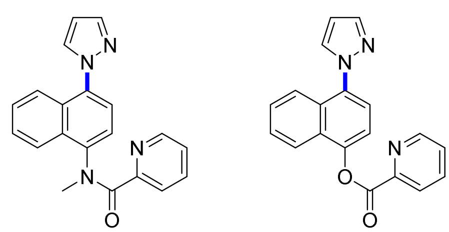
Compound **3a** (1.0 mmol), NaOH (6.0 mmol) and EtOH (10.0 mL) were combined in a 25 mL tube. The mixture was then stirred for 8 hours at 90 ^{o}C. After the conversion was completed as indicated by TLC, the mixture was cooled to room temperature and poured into water, extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified directly by flash column chromatography to give the product **4a**. Then 1 M HCl was added in aqueous layer until pH 4. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified directly by flash column chromatography to afford the 2-picolinic acid.

General procedure for the synthesis of product 5a

Compound **4a** (1.0 mmol), concentrated HCl (1.5 mmol) and water (5.0 mL) were combined in a 25 mL tube at 0 ^{o}C. Then, a solution of $NaNO_2$ (1.5 mmol) in water (1.0 mL) was slowly added. After stirring for 15 min, a solution of KI (1.5 mmol) in water (1.0 mL) was slowly added. Then the mixture was warmed to room temperature and stirred for 24 h. Subsequently, the solution was neutralized by adding 2 N NaOH and the organic phase was extracted with EtOAc (3 × 5 mL). The collected organic layer was washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified directly by flash column chromatography to give the product **5a**.

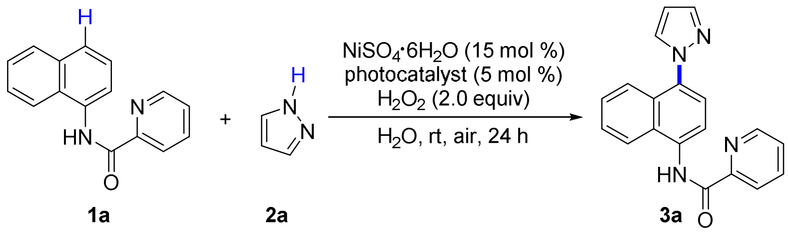
General procedure for the cycle experiment of catalyst-in-water

Amides **1a** (0.2 mmol), pyrazole derivatives **2a** (0.4 mmol), $NiSO_4$•$6H_2O$ (15 mol %), Acr^+−Mes ClO_4^- (5 mol %), H_2O_2 (0.4 mmol) and H_2O (4 mL) were combined in a 25 mL tube. The mixture was then stirred for 24 hours at room temperature under the radiation of 12 W blue LED. After the conversion was completed as indicated by TLC, the water in the flask was extracted directly, using EtOAc (3 × 5 mL) in which the nickel(II) salt is insoluble. According to the difference of the solubility to nickel(II) salt and organic product in H_2O and EtOAc, catalyst-in-water (contains nickel(II) salt and H_2O) could be retrieved by an easy phase separation from the organic layer. And the retrieved catalyst-in-water was reutilized in the next round by the addition of starting materials.



3ae, 0%　　**3af**, 0%

Table S1 Conditions screening[a,b]



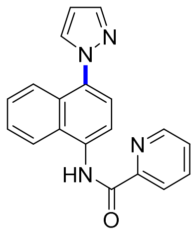
entry	photocatalyst	light source	yield [%][b]
1	Acr^+−Mes ClO_4^-	white LED	31
2	Acr^+−Mes ClO_4^-	green LED	28
3	Acr^+−Mes ClO_4^-	red LED	0
4	Acr^+−Mes ClO_4^-	dark	0
5	$Ru(bpy)_3Cl_2$	blue LED	0
6	$Ir(ppy)_3$	blue LED	18
7	Vitamin B2	blue LED	23
8	rhodamine B	blue LED	41

Table S2 ICP-Ms analysis on product for Ni content

product	Ni Content (ppm)
3a	3.6
3w	3.0

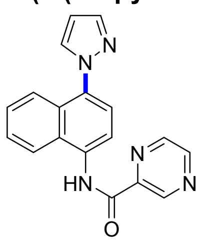
2. Characterization of Products

N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3a)



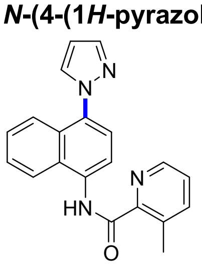
Faint yellow solid (45 mg, 72% yield), M.p. 148-149 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.89 (s, 1H), 8.70 (d, *J* = 4.2 Hz, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.93 (td, *J* = 7.7, 1.7 Hz, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.51 (m, 2H), 6.54 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.41, 149.84, 148.27, 140.91, 138.00, 134.23, 133.27, 132.00, 130.10, 127.38, 127.10, 126.88, 126.84, 124.29, 123.73, 122.70, 120.75, 117.51, 106.61. HRMS (ESI): Calculated for $C_{19}H_{14}N_4O^+$: 315.1241 $[M+H]^+$, Found: 315.1243.

N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)pyrazine-2-carboxamide (3b)



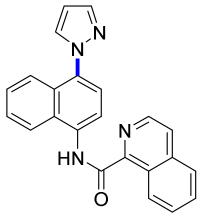
Faint yellow solid (43 mg, 69% yield), M.p. 153-154 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.52 (d, *J* = 1.1 Hz, 1H), 8.81 (d, *J* = 2.4 Hz, 1H), 8.63 (dd, *J* = 2.2, 1.6 Hz, 1H), 8.39 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.72 (d, *J* = 2.2 Hz, 1H), 7.58 (dd, *J* = 11.3, 4.0 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 6.48 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.05, 146.87, 143.86, 143.36, 141.54, 139.94, 133.71, 131.43, 130.82, 128.99, 126.38, 126.18, 125.79, 123.39, 122.49, 119.33, 117.03, 105.58. HRMS (ESI): Calculated for $C_{18}H_{13}N_5O^+$: 316.1193 $[M+H]^+$, Found: 316.1188.

N-(4-(1H-pyrazol-1-yl)naphthalen-1-yl)-3-methylpicolinamide (3c)



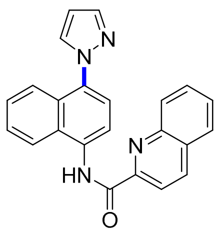
Faint yellow solid (39 mg, 60% yield), M.p. 155-156 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.50 (d, *J* = 4.1 Hz, 1H), 8.40 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 2.2 Hz, 2H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.37 (dd, *J* = 7.7, 4.6 Hz, 1H), 6.47 (t, *J* = 2.0 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.80, 145.65, 144.52, 140.51, 139.75, 135.50, 133.28, 132.90, 132.57, 130.88, 129.05, 126.17, 125.84, 125.31, 123.08, 122.63, 119.83, 116.22, 105.41, 19.84. HRMS (ESI): Calculated for $C_{20}H_{16}N_4O^+$: 329.1397 $[M+H]^+$, Found: 329.1394.

_N_-(4-(1_H_-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3d)



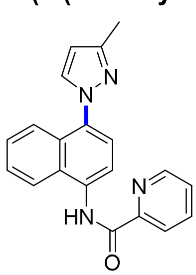
Faint yellow solid (34 mg, 47% yield), M.p. 148-149 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 11.27 (s, 1H), 9.82 (d, *J* = 8.1 Hz, 1H), 8.66 (d, *J* = 5.5 Hz, 1H), 8.53 (d, *J* = 8.1 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.96 – 7.92 (m, 2H), 7.86 – 7.75 (m, 5H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.60 – 7.55 (m, 1H), 6.56 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.93, 146.25, 139.82, 139.09, 136.77, 133.19, 132.47, 130.87, 129.79, 129.09, 128.15, 126.80, 126.47, 126.24, 126.14, 126.01, 125.94, 124.25, 123.16, 122.62, 119.92, 116.65, 105.45. HRMS (ESI): Calculated for $C_{23}H_{16}N_4O^+$: 365.1397 $[M+H]^+$, Found: 365.1392.

_N_-(4-(1_H_-pyrazol-1-yl)naphthalen-1-yl)quinoline-2-carboxamide (3e)



Faint yellow solid (38 mg, 52% yield), M.p. 169-170 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 3H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.70 (t, *J* = 6.4 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 6.56 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.49, 148.59, 145.32, 139.84, 137.08, 133.24, 132.20, 130.86, 129.47, 129.07, 128.86, 128.60, 127.36, 126.87, 126.27, 126.03, 125.90, 123.26, 122.65, 119.64, 117.82, 116.54, 105.48. HRMS (ESI): Calculated for $C_{23}H_{16}N_4O^+$: 365.1397 $[M+H]^+$, Found: 365.1391.

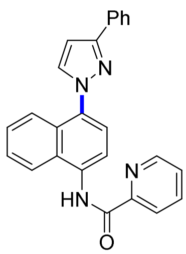
_N_-(4-(3-methyl-1_H_-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3i)



Faint yellow solid (43 mg, 66% yield), M.p. 160-161 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.73 (d, *J* = 4.5 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 7.7 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 1.9

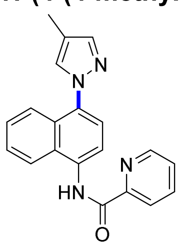
Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.59 – 7.54 (m, 3H), 6.32 (d, *J* = 1.9 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.34, 150.14, 149.85, 148.22, 137.88, 134.35, 132.86, 132.59, 130.06, 127.21, 126.93, 126.77, 126.75, 124.37, 123.55, 122.60, 120.60, 117.50, 106.30, 13.75. HRMS (ESI): Calculated for $C_{20}H_{16}N_4O^+$: 329.1397 [M+H]$^+$, Found: 329.1391.

_N_-(4-(3-phenyl-1_H_-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3j)



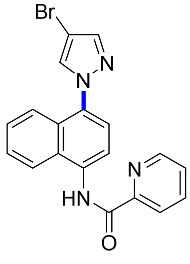
Faint yellow solid (48 mg, 62% yield), M.p. 173-174 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.91 (s, 1H), 8.76 – 8.73 (m, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.39 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.96 (dd, *J* = 10.3, 3.4 Hz, 4H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.58 – 7.54 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.36, 152.87, 149.83, 148.24, 137.90, 134.22, 133.37, 133.24, 133.22, 130.05, 128.69, 127.98, 127.33, 127.06, 126.83, 126.79, 125.91, 124.37, 123.72, 122.62, 120.63, 117.47, 103.91. HRMS (ESI): Calculated for $C_{25}H_{18}N_4O^+$: 391.1553 [M+H]$^+$, Found: 391.1546.

_N_-(4-(4-methyl-1_H_-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3m)



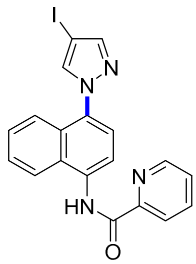
Faint yellow solid (48 mg, 74% yield), M.p. 148-149 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.71 (d, *J* = 4.3 Hz, 1H), 8.49 (d, *J* = 8.1 Hz, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.57 – 7.53 (m, 4H), 2.23 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.35, 149.82, 148.22, 141.56, 137.86, 134.43, 132.85, 130.54, 129.91, 127.14, 126.93, 126.81, 126.75, 124.39, 123.34, 122.58, 120.62, 117.53, 117.03, 8.96. HRMS (ESI): Calculated for $C_{20}H_{16}N_4O^+$: 329.1397 [M+H]$^+$, Found: 329.1398.

_N_-(4-(4-bromo-1_H_-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3n)



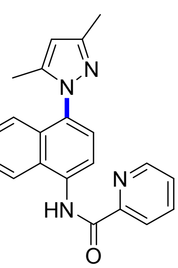
Faint yellow solid (40 mg, 51% yield), M.p. 172-173 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.74 (d, *J* = 4.7 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.98 (td, *J* = 7.7, 1.6 Hz, 1H), 7.82 – 7.77 (m, 3H), 7.68 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.33, 148.73, 147.22, 140.41, 136.90, 132.65, 132.46, 132.42, 130.87, 128.69, 126.51, 126.14, 125.81, 125.65, 122.79, 121.62, 119.70, 116.16, 93.43. HRMS (ESI): Calculated for $C_{19}H_{13}BrN_4O^+$: 393.0346 $[M+H]^+$, Found: 393.0345.

***N*-(4-(4-iodo-1*H*-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3o)**



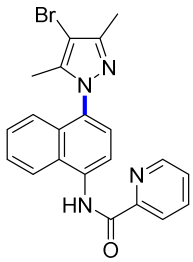
Faint yellow solid (53 mg, 60% yield), M.p. 144-145 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.76 (d, *J* = 4.2 Hz, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.01 – 7.98 (m, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.68 (m, 1H), 7.62 – 7.58 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.32, 149.71, 148.21, 145.85, 137.93, 136.13, 133.65, 133.28, 129.69, 127.52, 127.15, 126.83, 126.65, 123.83, 123.78, 122.65, 120.71, 117.17, 57.57. HRMS (ESI): Calculated for $C_{19}H_{13}IN_4O^+$: 441.0207 $[M+H]^+$, Found: 441.0200.

***N*-(4-(3,5-dimethyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3p)**



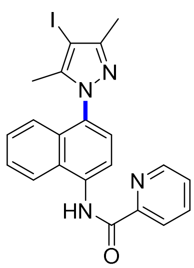
Faint yellow solid (44 mg, 65% yield), M.p. 155-156 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.72 (dd, *J* = 4.1, 0.6 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.96 (td, *J* = 7.7, 1.6 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.54 (dd, *J* = 10.1, 5.5 Hz, 3H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.08 (s, 1H), 2.36 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.26, 148.82, 147.99, 147.19, 140.74, 136.84, 132.38, 131.79, 130.55, 126.31, 125.85, 125.72, 125.60, 124.70, 123.16, 121.56, 119.53, 116.19, 104.35, 12.65, 10.43. HRMS (ESI): Calculated for $C_{21}H_{18}N_4O^+$: 343.1553 $[M+H]^+$, Found: 343.1549.

***N*-(4-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3q)**



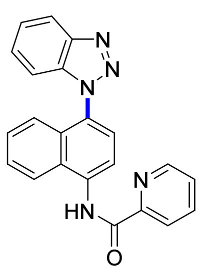
Faint yellow solid (50 mg, 60% yield), M.p. 179-180 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.72 (d, *J* = 4.7 Hz, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.96 (t, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.54 (dd, *J* = 14.2, 8.0 Hz, 3H), 7.37 (d, *J* = 8.4 Hz, 1H), 2.36 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.32, 149.74, 148.24, 147.64, 139.89, 137.91, 133.86, 132.53, 131.17, 127.58, 127.06, 126.83, 126.58, 125.78, 123.84, 122.62, 120.69, 117.08, 94.97, 12.53, 10.91. HRMS (ESI): Calculated for $C_{21}H_{17}BrN_4O^+$: 421.0659 $[M+H]^+$, Found: 421.0644.

***N*-(4-(4-iodo-3,5-dimethyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)picolinamide (3r)**



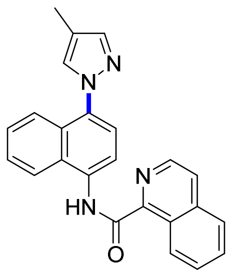
Faint yellow solid (60 mg, 64% yield), M.p. 182-183 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.70 (d, *J* = 4.3 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.94 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 3H), 7.35 (d, *J* = 8.4 Hz, 1H), 2.36 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.32, 150.85, 149.70, 148.24, 143.34, 137.91, 133.86, 132.71, 131.11, 127.60, 127.08, 126.84, 126.56, 125.74, 123.83, 122.61, 120.70, 117.07, 63.59, 14.29, 12.56. HRMS (ESI): Calculated for $C_{21}H_{17}IN_4O^+$: 469.0520 $[M+H]^+$, Found: 469.0521.

***N*-(4-(1*H*-benzo[d][1,2,3]triazol-1-yl)naphthalen-1-yl)picolinamide (3s)**



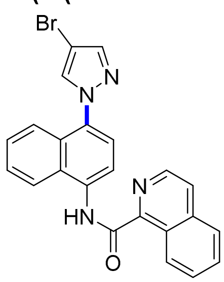
Faint yellow solid (32 mg, 44% yield), M.p. 152-153 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.77 (d, *J* = 4.7 Hz, 1H), 8.70 (d, *J* = 8.1 Hz, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 8.00 (td, *J* = 7.7, 1.6 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.73 – 7.70 (m, 1H), 7.60 – 7.57 (m, 1H), 7.53 (dd, *J* = 14.8, 7.8 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.42, 149.68, 148.29, 145.74, 137.98, 134.95, 134.60, 130.00, 129.03, 128.21, 127.74, 127.39, 126.93, 126.77, 125.17, 124.34, 123.67, 122.70, 120.88, 120.18, 117.23, 110.37. HRMS (ESI): Calculated for $C_{22}H_{15}N_5O^+$: 366.1349 $[M+H]^+$, Found: 366.1343.

***N*-(4-(4-methyl-1H-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3t)**



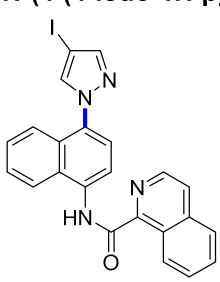
Faint yellow solid (37 mg, 49% yield), M.p. 159-160 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.82 (d, *J* = 7.9 Hz, 1H), 8.65 (d, *J* = 5.5 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.90 (m, 3H), 7.77 (ddd, *J* = 7.8, 6.3, 1.5 Hz, 2H), 7.68 – 7.63 (m, 2H), 7.59 (dd, *J* = 11.7, 7.9 Hz, 3H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.94, 146.28, 140.53, 139.10, 136.75, 133.44, 132.14, 129.76, 129.54, 129.51, 128.97, 128.12, 126.80, 126.45, 126.19, 126.10, 126.00, 125.87, 124.21, 123.32, 122.32, 119.90, 116.77, 7.93. HRMS (ESI): Calculated for $C_{24}H_{18}N_4O^+$: 379.1554 $[M+H]^+$, Found: 379.1559.

***N*-(4-(4-bromo-1H-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3u)**



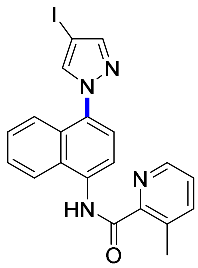
Faint yellow solid (29 mg, 33% yield), M.p. 184-185 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 11.24 (s, 1H), 9.74 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 5.5 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.87 (t, *J* = 6.0 Hz, 2H), 7.73 (dd, *J* = 13.4, 8.9 Hz, 5H), 7.61 (t, *J* = 7.1 Hz, 1H), 7.54 (dd, *J* = 7.6, 5.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.93, 146.12, 140.40, 139.09, 136.77, 132.99, 132.41, 131.58, 130.90, 129.82, 128.74, 128.21, 126.75, 126.51, 126.47, 126.11, 126.03, 124.33, 122.77, 122.74, 120.02, 116.38, 93.42. HRMS (ESI): Calculated for $C_{23}H_{15}BrN_4O^+$: 443.0502 $[M+H]^+$, Found: 443.05009.

***N*-(4-(4-iodo-1H-pyrazol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide (3v)**



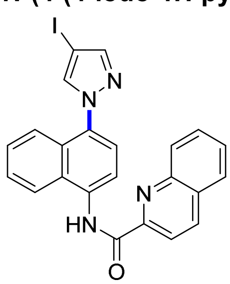
Faint yellow solid (38 mg, 39% yield), M.p. 169-170 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.23 (s, 1H), 9.73 (d, *J* = 7.9 Hz, 1H), 8.58 (d, *J* = 5.5 Hz, 1H), 8.47 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 6.7 Hz, 2H), 7.78 (d, *J* = 4.2 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 3H), 7.60 (t, *J* = 7.1 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.91, 146.11, 144.82, 139.08, 136.76, 135.12, 132.97, 132.25, 129.81, 128.72, 128.19, 126.74, 126.48, 126.45, 126.09, 126.02, 126.00, 124.31, 122.76, 122.74, 119.99, 116.34, 56.52. HRMS (ESI): Calculated for $C_{23}H_{15}IN_4O^+$: $[M+H]^+$ 491.0364, Found: 491.0368.

***N*-(4-(4-iodo-1H-pyrazol-1-yl)naphthalen-1-yl)-3-methylpicolinamide (3w)**



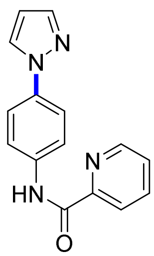
Faint yellow solid (26 mg, 29% yield), M.p. 167-168 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.55 (d, *J* = 4.0 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 9.7 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.43 (dd, *J* = 7.7, 4.6 Hz, 1H), 2.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.70, 145.49, 144.76, 144.42, 140.58, 135.53, 135.11, 133.02, 131.99, 128.65, 126.40, 125.98, 125.78, 125.35, 122.71, 122.67, 119.91, 115.95, 56.48, 19.80. HRMS (ESI): Calculated for $C_{20}H_{15}IN_4O^+$: 455.0364 $[M+H]^+$, Found: 455.0361.

***N*-(4-(4-iodo-1H-pyrazol-1-yl)naphthalen-1-yl)quinoline-2-carboxamide (3x)**



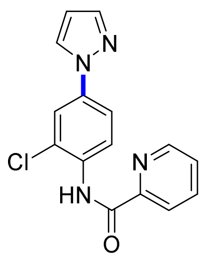
Faint yellow solid (30 mg, 31% yield), M.p. 173-174 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.14 (s, 1H), 8.57 (d, *J* = 8.1 Hz, 1H), 8.46 (q, *J* = 8.5 Hz, 2H), 8.29 (dd, *J* = 15.6, 8.5 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.86 (d, *J* = 2.2 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.52, 148.52, 144.86, 139.77, 137.16, 135.21, 135.13, 133.00, 132.35, 129.52, 128.87, 127.42, 126.90, 126.54, 126.21, 125.82, 124.05, 122.88, 122.81, 119.74, 117.84, 116.34, 56.55. HRMS (ESI): Calculated for $C_{23}H_{15}IN_4O^+$: 491.0364 $[M+H]^+$, Found: 491.0359.

***N*-(4-(1H-pyrazol-1-yl)phenyl)picolinamide (3aa)**



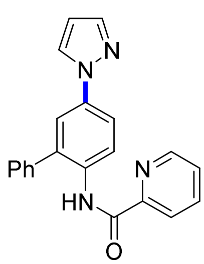
White solid (22 mg, 42% yield), M.p. 143-144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.63 (d, *J* = 4.7 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.92 – 7.88 (m, 4H), 7.73 – 7.70 (m, 3H), 7.52 – 7.49 (m, 1H), 6.47 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.00, 148.58, 146.99, 139.94, 136.75, 135.51, 135.19, 125.67, 125.57, 121.43, 119.46, 118.91, 106.52. HRMS (ESI): Calculated for $C_{15}H_{12}N_4O^+$: 265.1084 $[M+H]^+$, Found: 265.1084.

***N*-(2-chloro-4-(1H-pyrazol-1-yl)phenyl)picolinamide (3ab)**



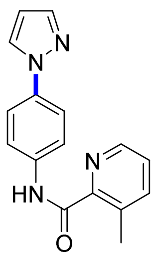
White solid (22 mg, 37% yield), M.p. 152-153 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.77 (d, *J* = 9.0 Hz, 1H), 8.68 (d, *J* = 4.1 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.90 (dd, *J* = 11.4, 2.5 Hz, 2H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.62 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.52 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.49 – 6.47 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.19, 149.51, 148.33, 141.33, 137.71, 136.38, 133.08, 126.75, 126.67, 124.26, 122.47, 121.47, 120.19, 117.95, 107.96. HRMS (ESI): Calculated for $C_{15}H_{11}ClN_4O^+$: 299.0694 $[M+H]^+$, Found: 299.0697.

***N*-(5-(1H-pyrazol-1-yl)-[1,1'-biphenyl]-2-yl)picolinamide (3ac)**



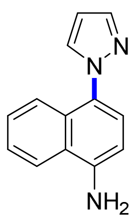
White solid (33 mg, 48% yield), M.p. 158-159 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.77 (d, *J* = 9.6 Hz, 1H), 8.38 (d, *J* = 4.1 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.88 – 7.85 (m, 1H), 7.73 – 7.71 (m, 3H), 7.52 (d, *J* = 3.2 Hz, 4H), 7.49 – 7.46 (m, 1H), 7.39 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.49 – 6.47 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.01, 148.77, 146.97, 139.98, 136.51, 136.25, 135.26, 132.63, 132.33, 128.44, 128.01, 127.24, 125.72, 125.23, 121.23, 120.42, 120.14, 117.85, 106.55. HRMS (ESI): Calculated for $C_{21}H_{16}N_4O^+$: 341.1397 $[M+H]^+$, Found: 341.1392.

***N*-(4-(1H-pyrazol-1-yl)phenyl)-3-methylpicolinamide (3ad)**



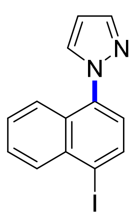
White solid (28 mg, 51% yield), M.p. 131-132 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.46 (d, *J* = 4.0 Hz, 1H), 7.91 (d, *J* = 2.3 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.72 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.38 (dd, *J* = 7.7, 4.5 Hz, 1H), 6.50 – 6.44 (m, 1H), 2.83 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.50, 146.48, 145.26, 141.44, 140.87, 136.57, 136.31, 136.29, 126.67, 126.14, 120.39, 119.86, 107.44, 20.80. HRMS (ESI): Calculated for $C_{16}H_{14}N_4O^+$: 279.1241 $[M+H]^+$, Found: 279.1247.

4-(1*H*-pyrazol-1-yl)naphthalen-1-amine (4a)



Light brown solid (186 mg, 89% yield), M.p. 88-89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.50 (d, *J* = 9.5 Hz, 1H), 7.41 (t, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.42 (t, *J* = 2.1 Hz, 1H), 4.26 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.10, 139.29, 130.95, 129.58, 128.07, 126.13, 124.47, 123.41, 122.59, 122.44, 119.96, 107.03, 104.92. HRMS (ESI): Calculated for $C_{13}H_{11}N_3^+$: 210.1026 $[M+H]^+$, Found: 210.1031.

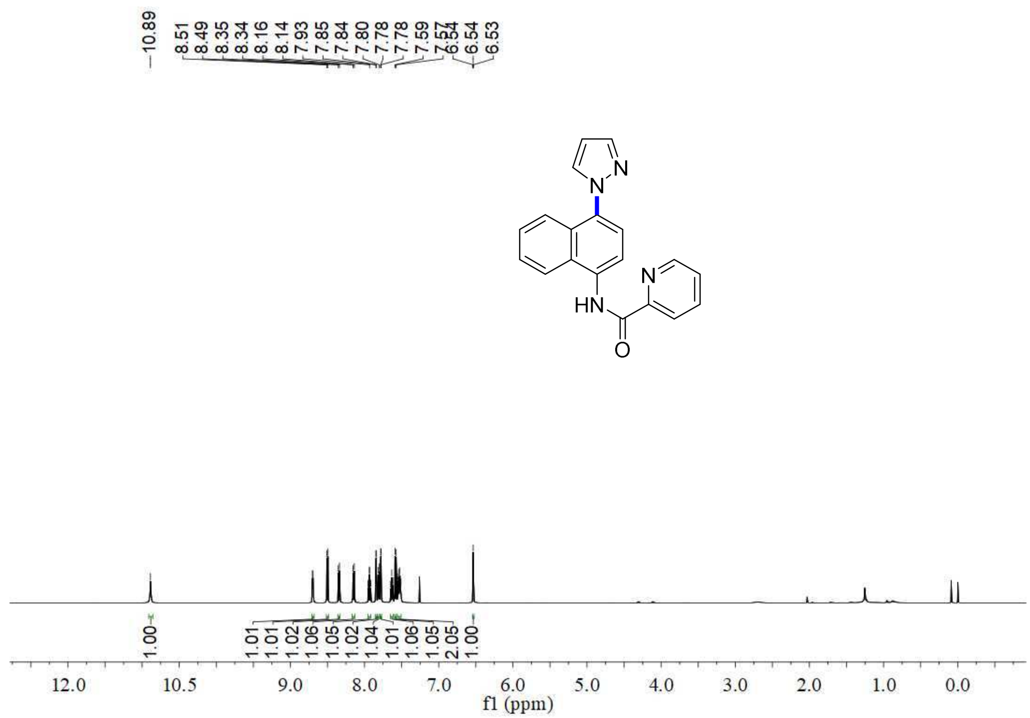
1-(4-iodonaphthalen-1-yl)-1H-pyrazole (5a)



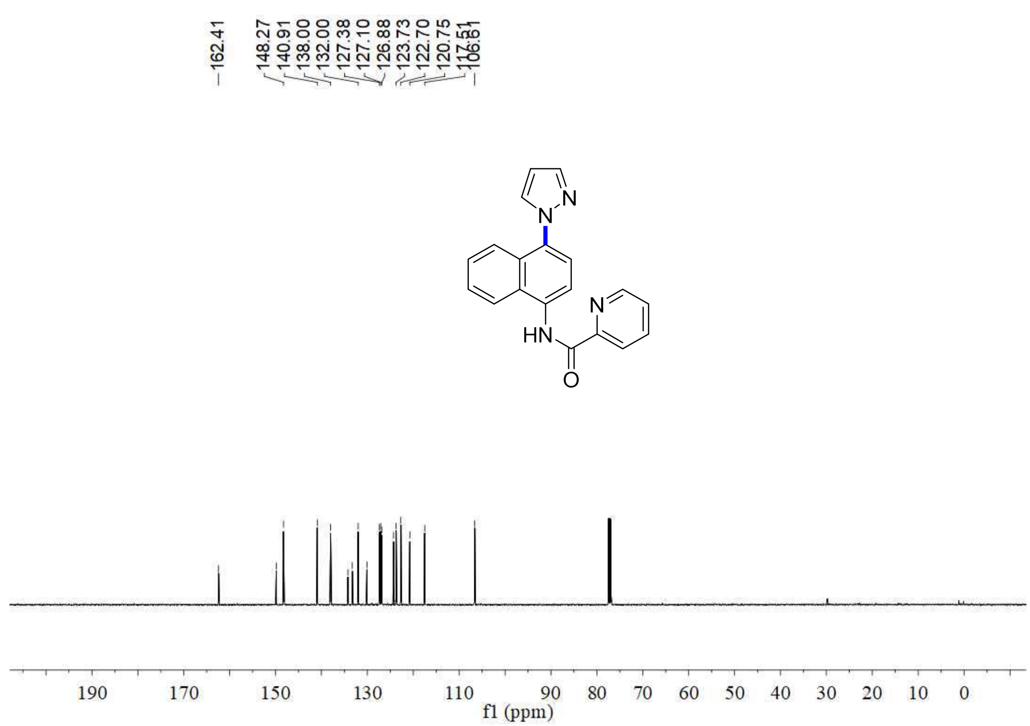
Faint yellow solid (240 mg, 75% yield), M.p. 123-124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 1.3 Hz, 1H), 7.77 – 7.72 (m, 2H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 6.55 – 6.51 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.13, 137.24, 135.55, 133.91, 131.55, 130.73, 128.76, 127.43, 126.99, 123.02, 122.90, 105.81, 99.03. HRMS (ESI): Calculated for $C_{13}H_9IN_2^+$: 320.9886 $[M+H]^+$, Found: 320.9883.

3. Copies of ^{1}H and ^{13}C NMR Spectra

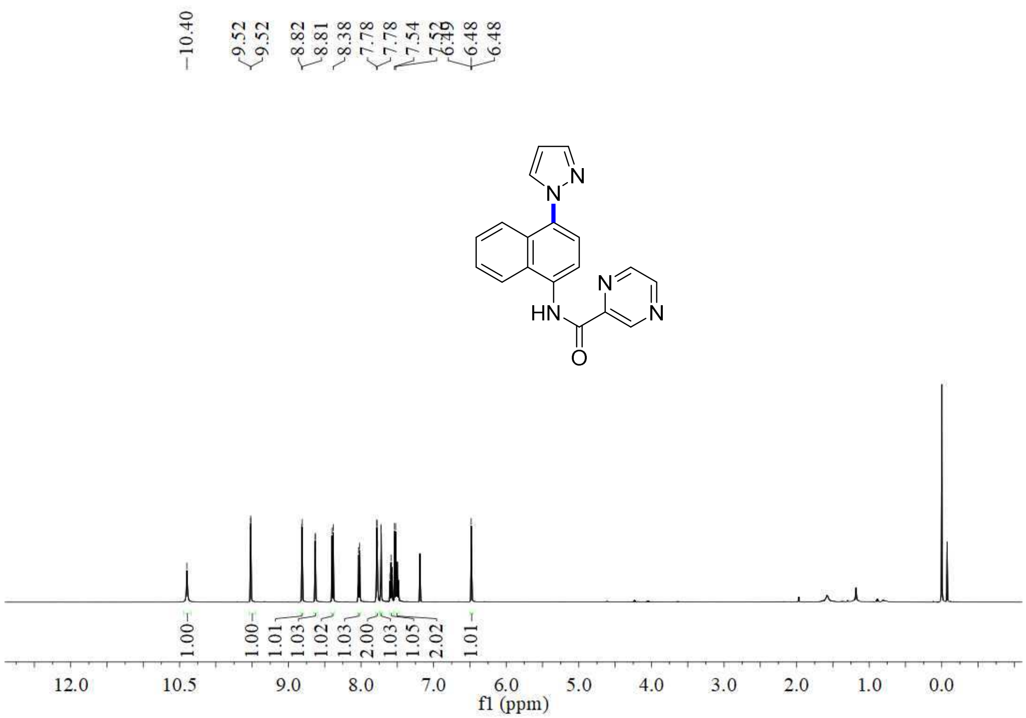
3a ^{1}H NMR



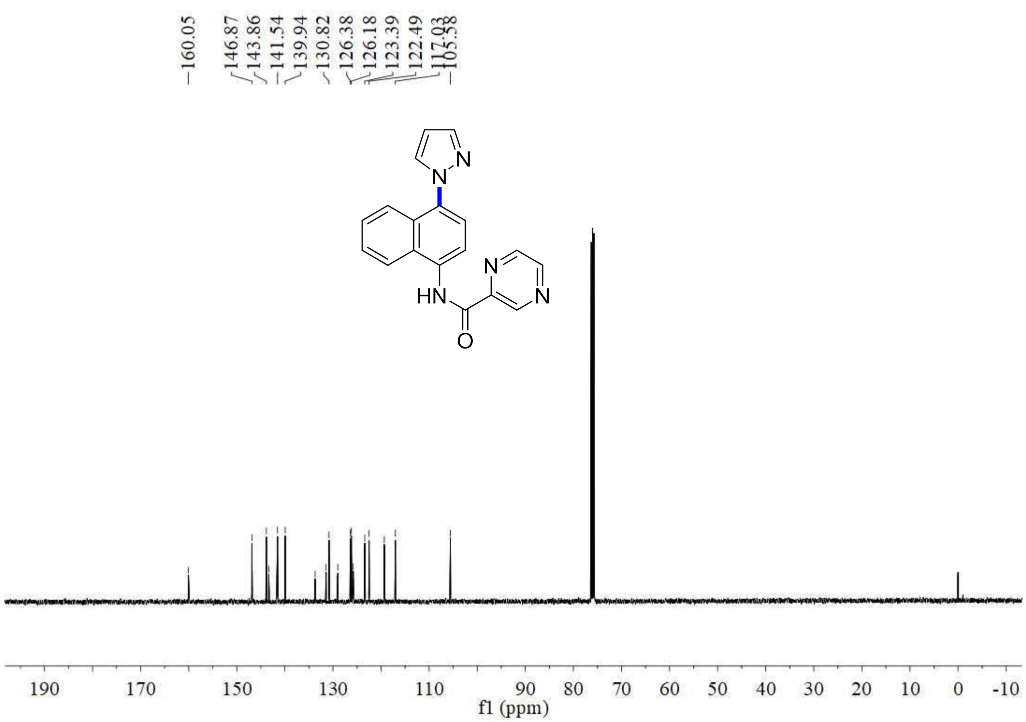
3a ^{13}C NMR



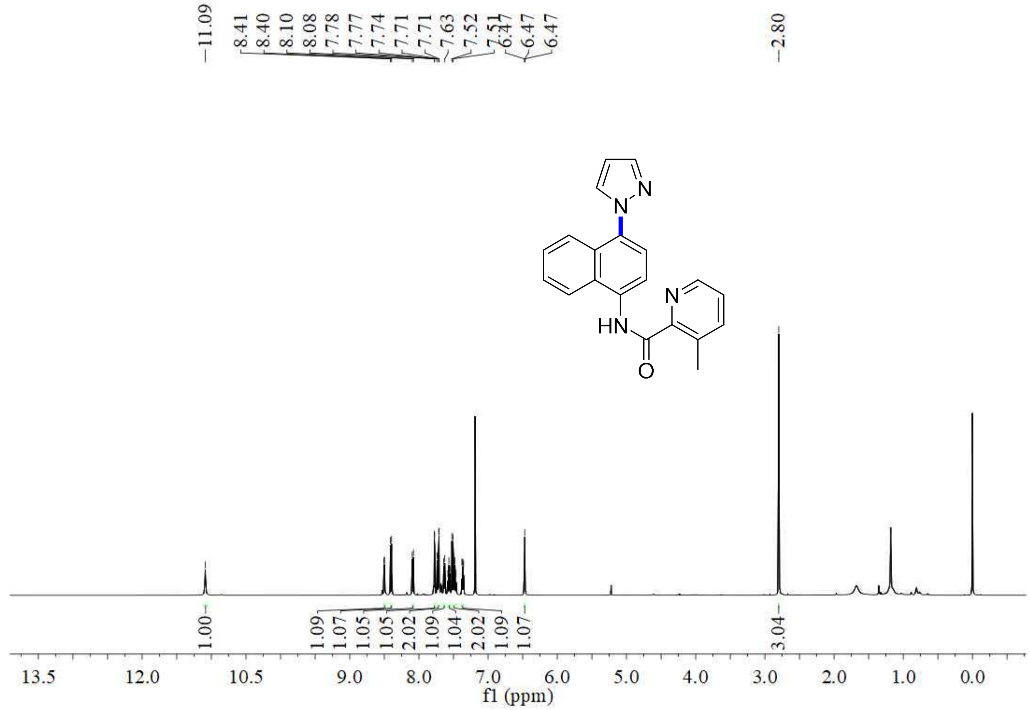
3b ^{1}H NMR



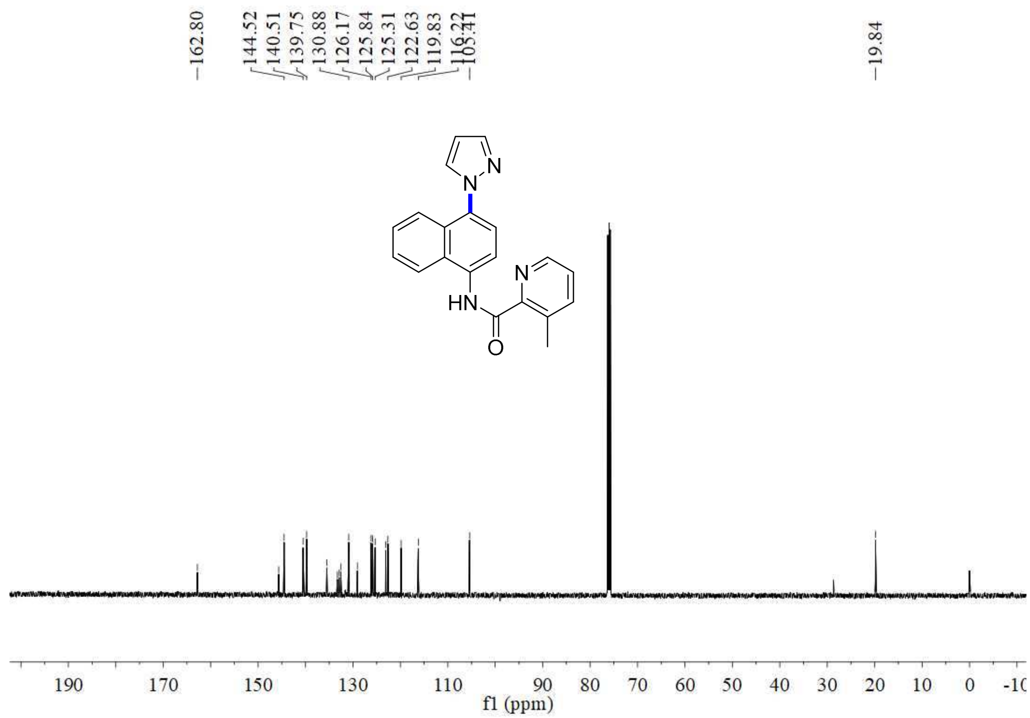
3b ^{13}C NMR



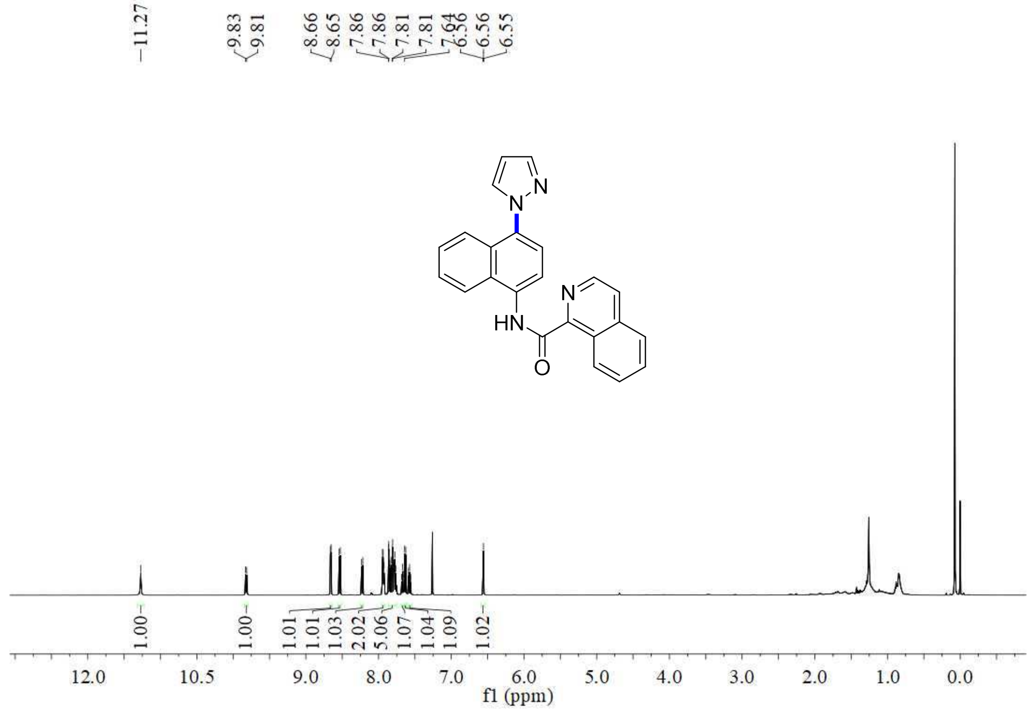
3c ^{1}H NMR



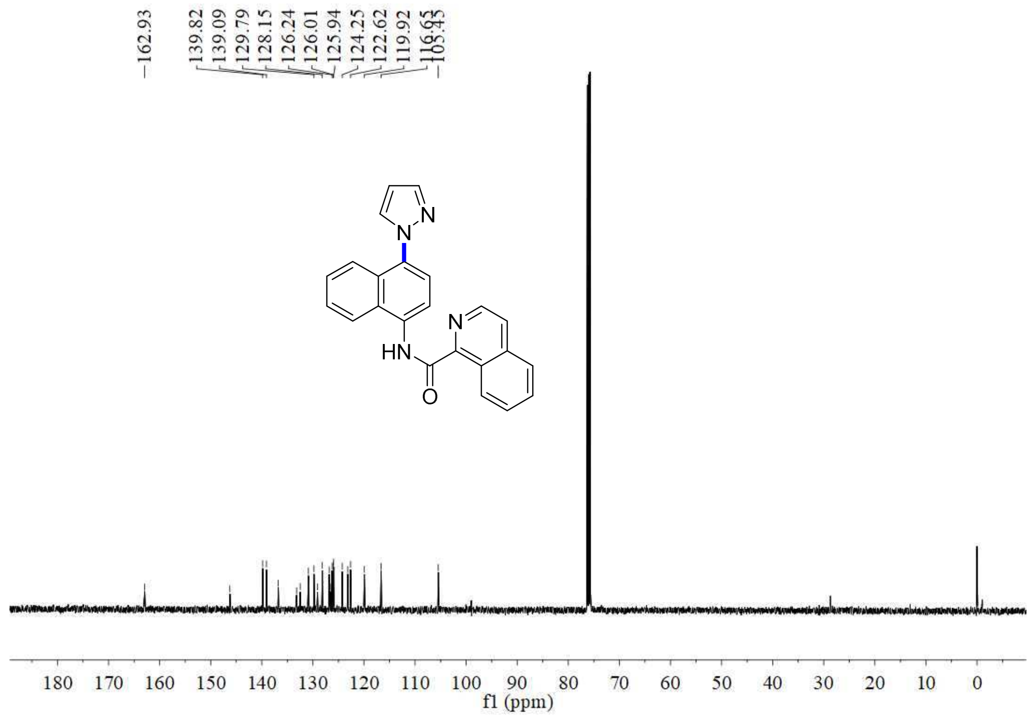
3c ^{13}C NMR



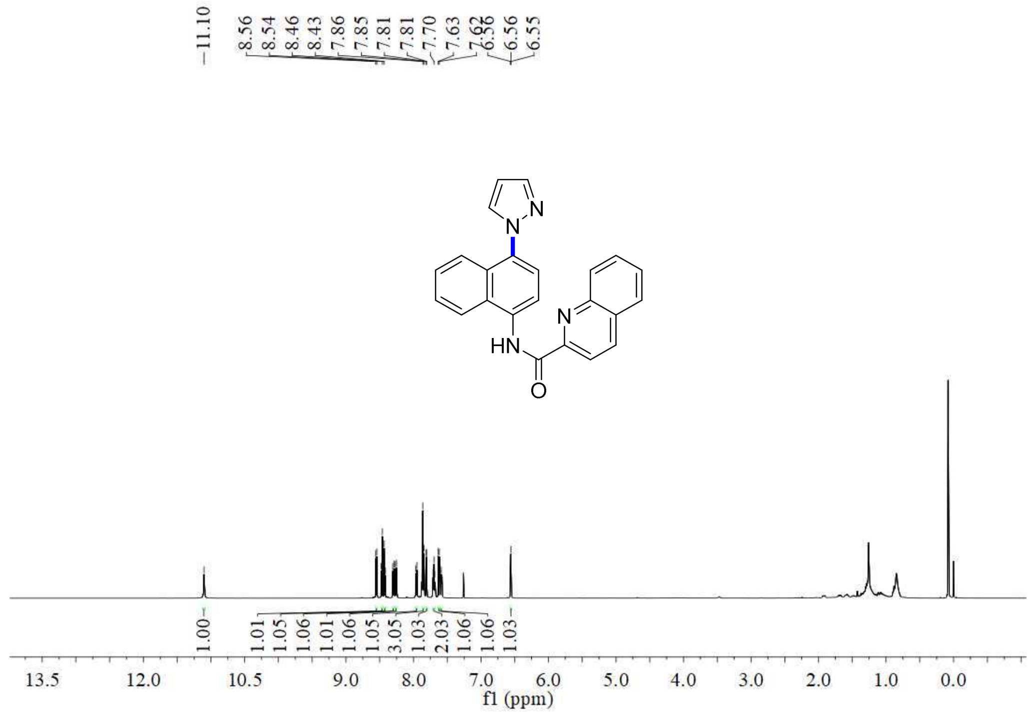
3d ^{1}H NMR



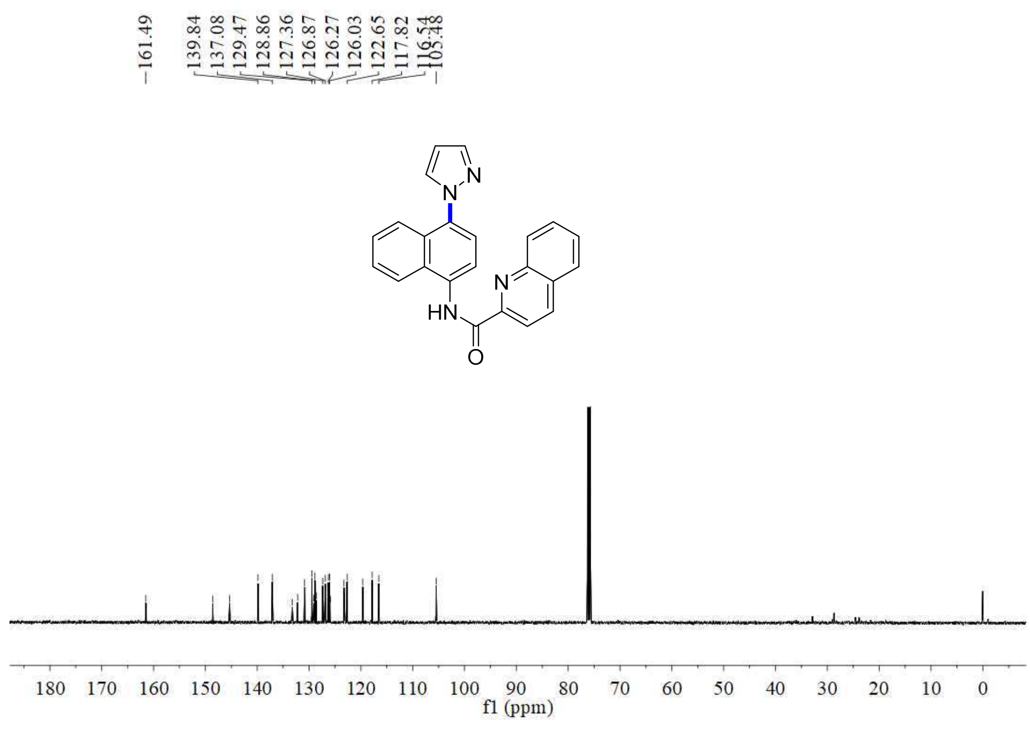
3d ^{13}C NMR



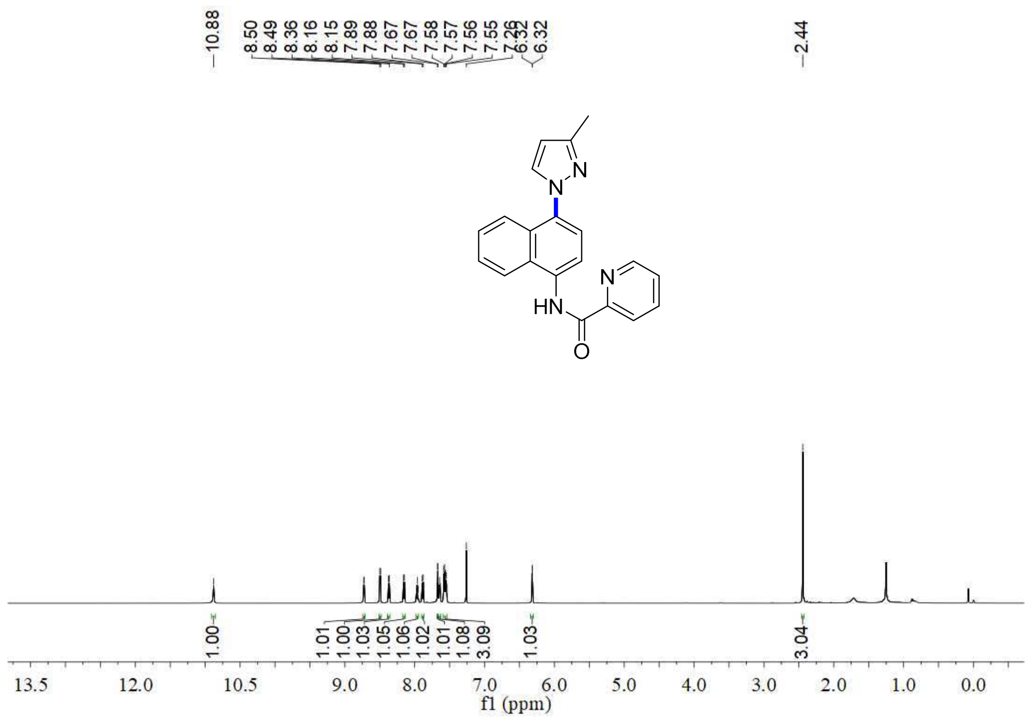
3e ^{1}H NMR



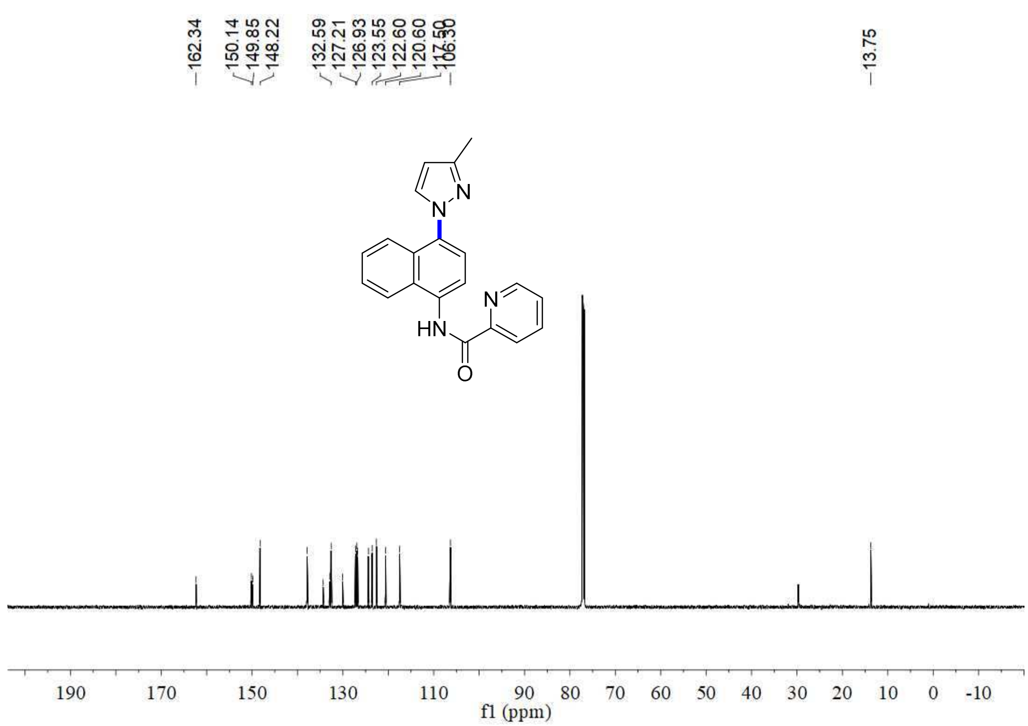
3e ^{13}C NMR



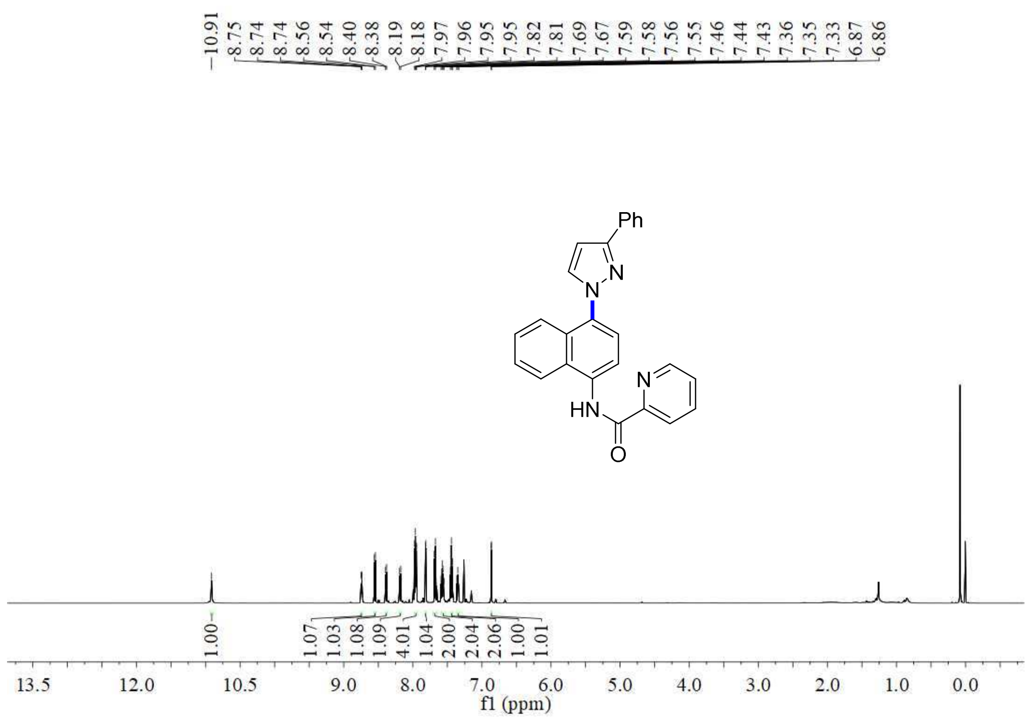
3i ^{1}H NMR



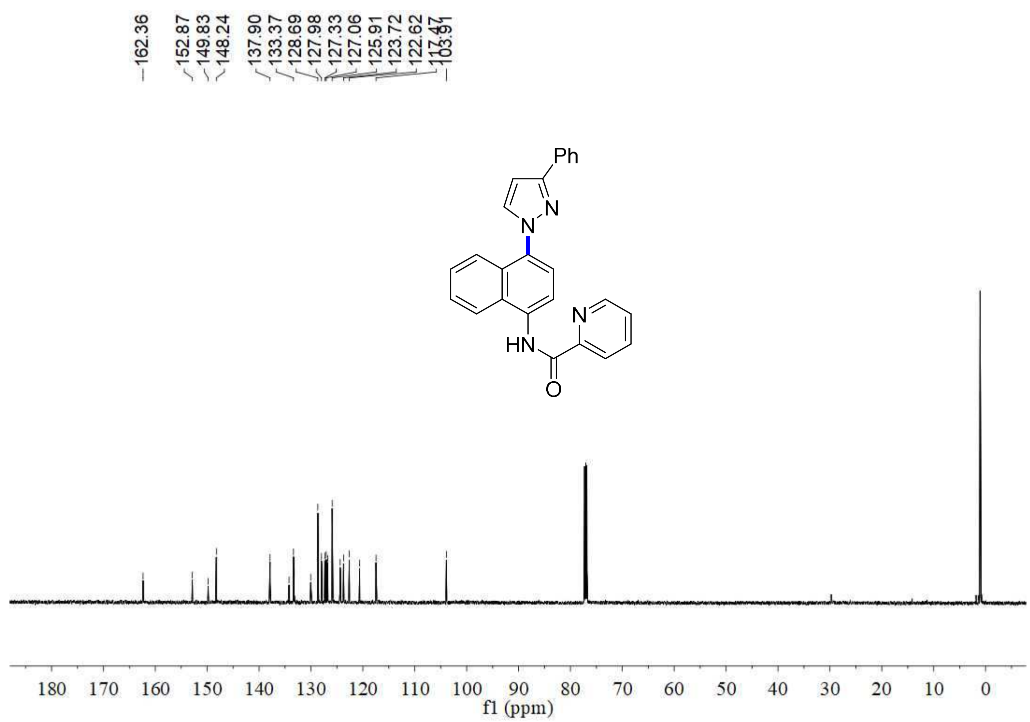
3i ^{13}C NMR



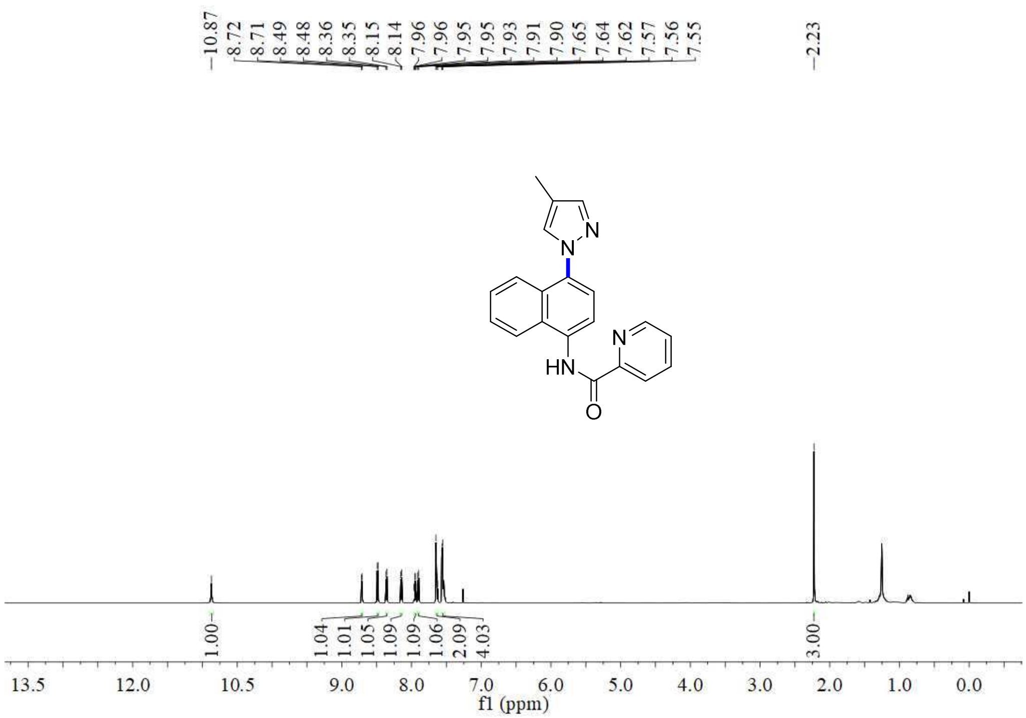
3j ¹H NMR



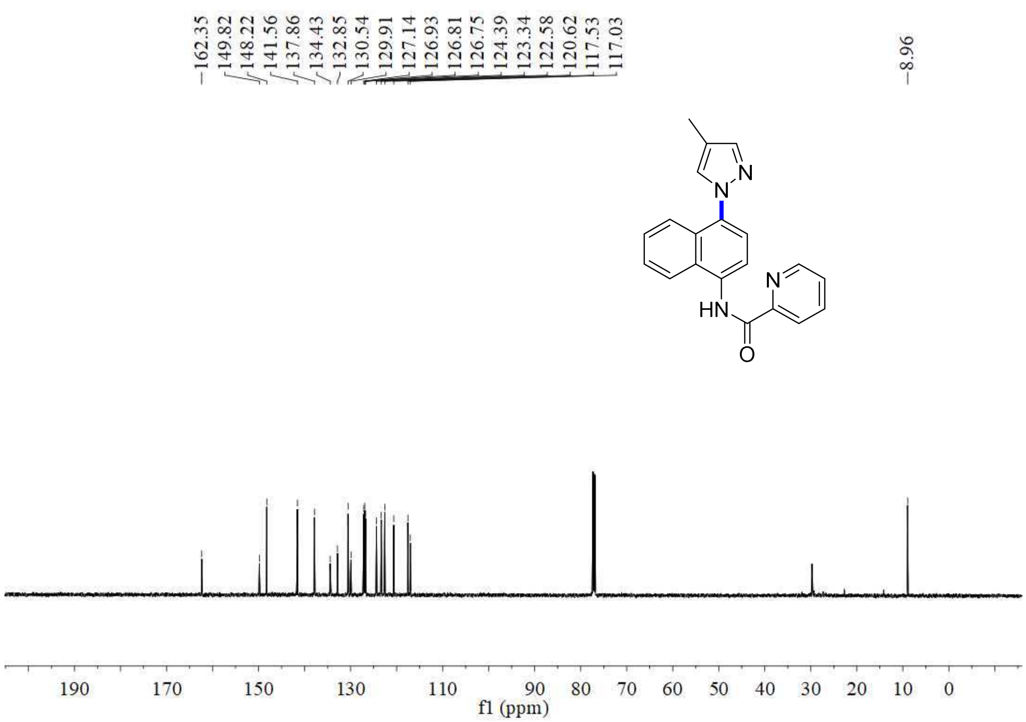
3j ¹³C NMR



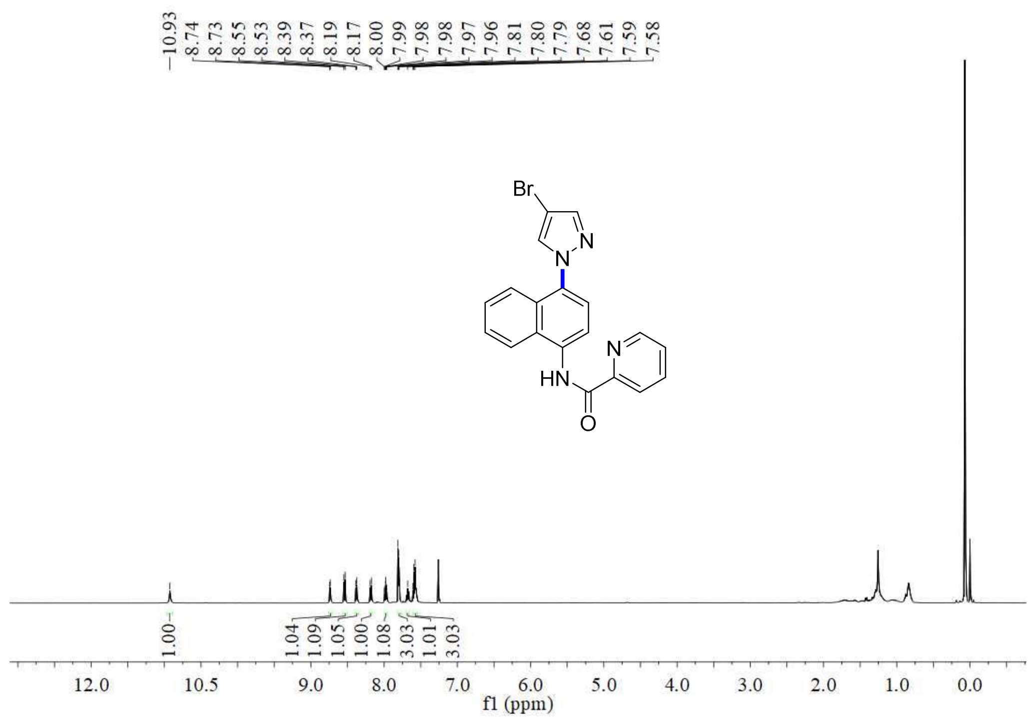
3m ^{1}H NMR



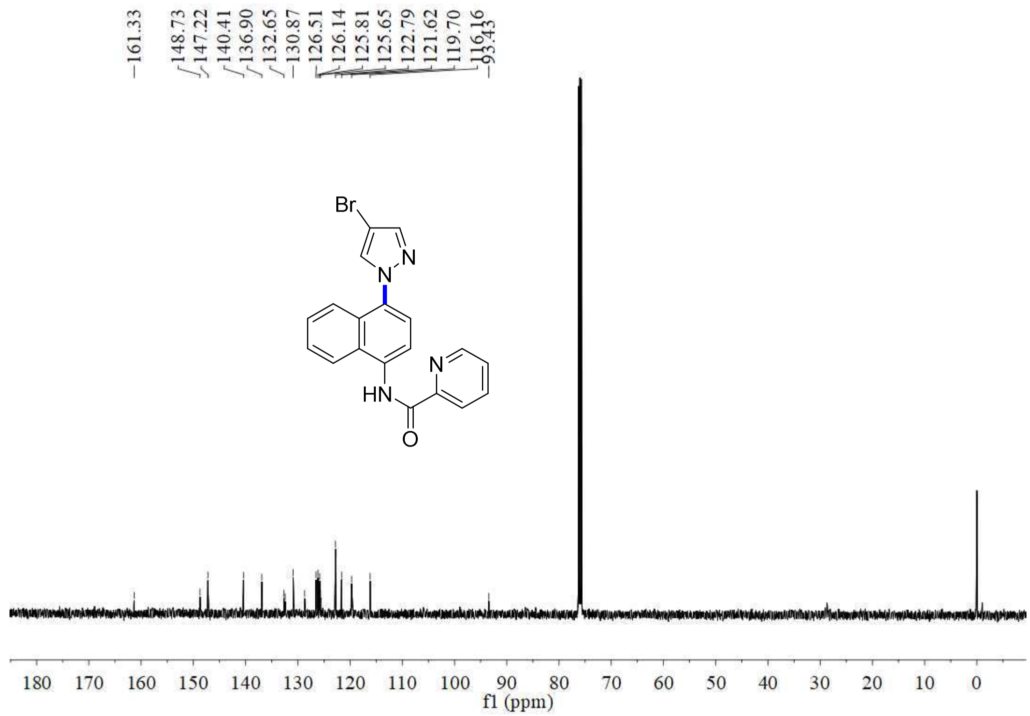
3m ^{13}C NMR



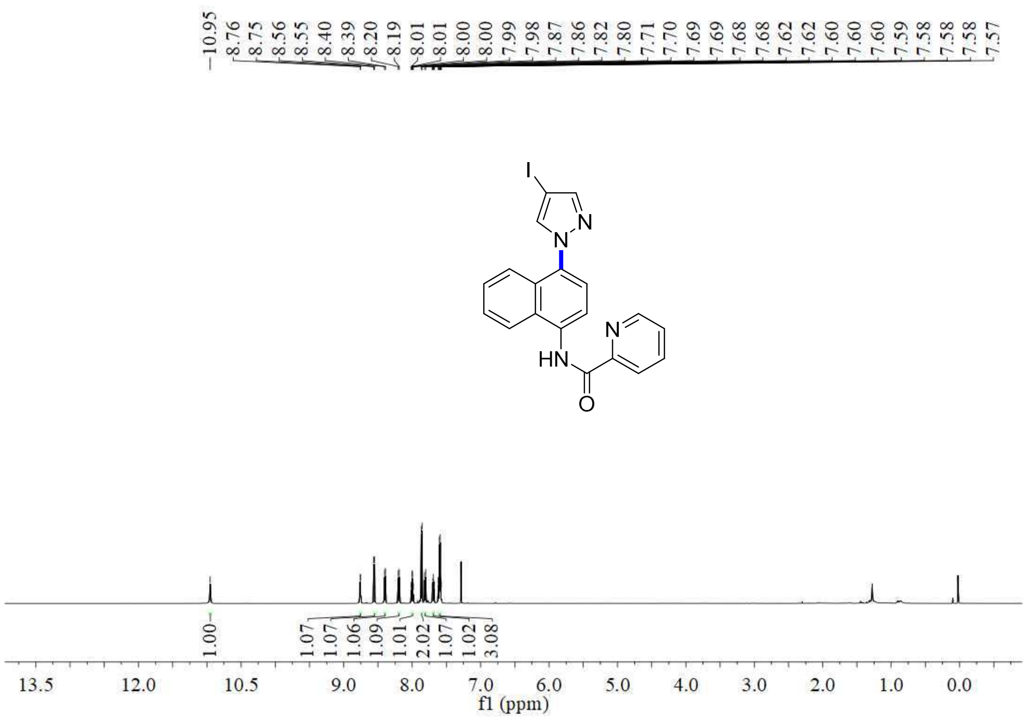
3n ^{1}H NMR



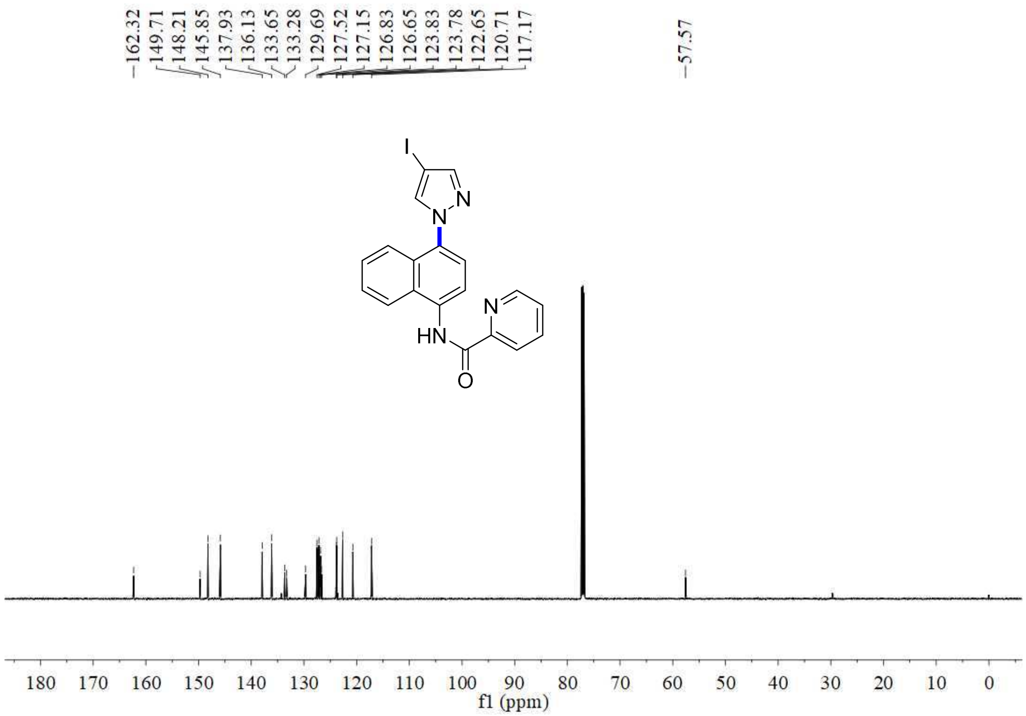
3n ^{13}C NMR



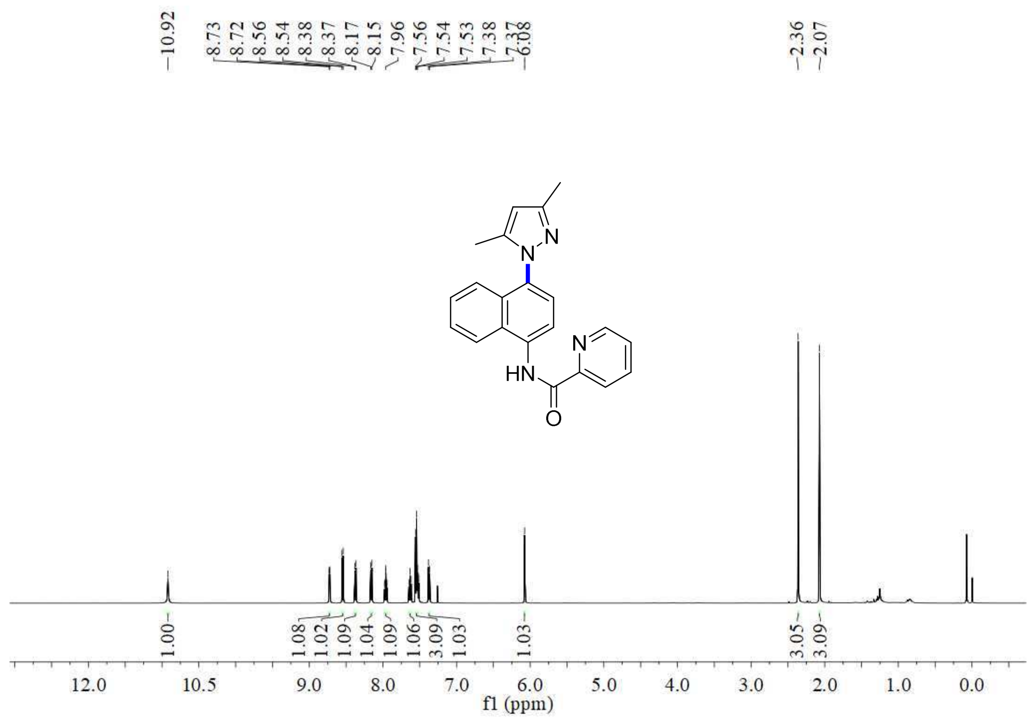
3o ^{1}H NMR



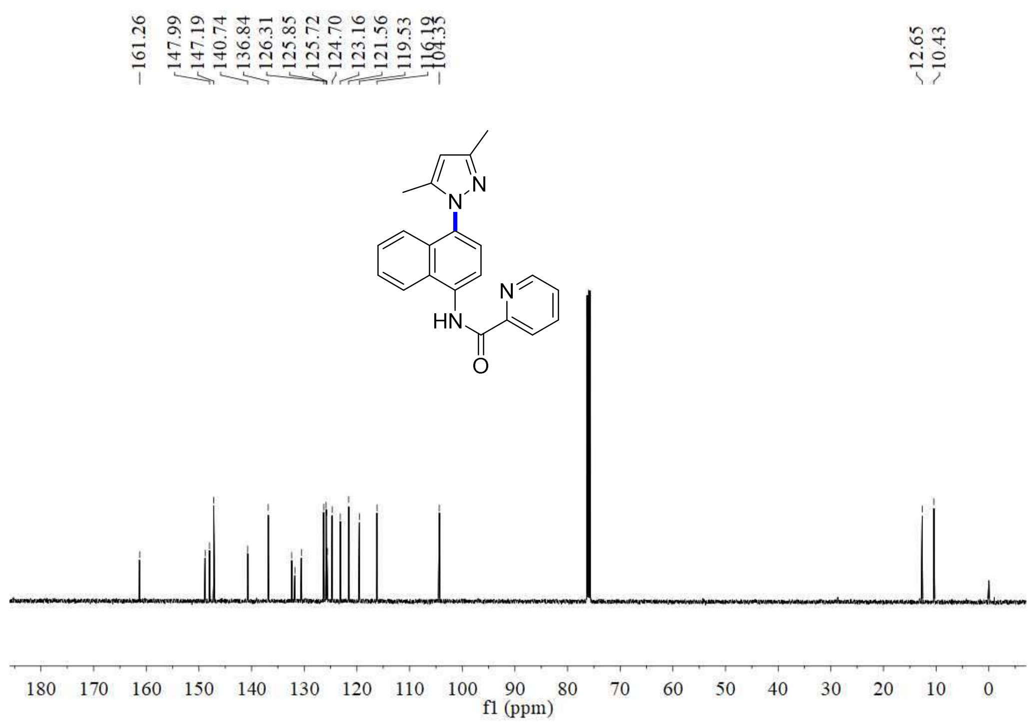
3o ^{13}C NMR



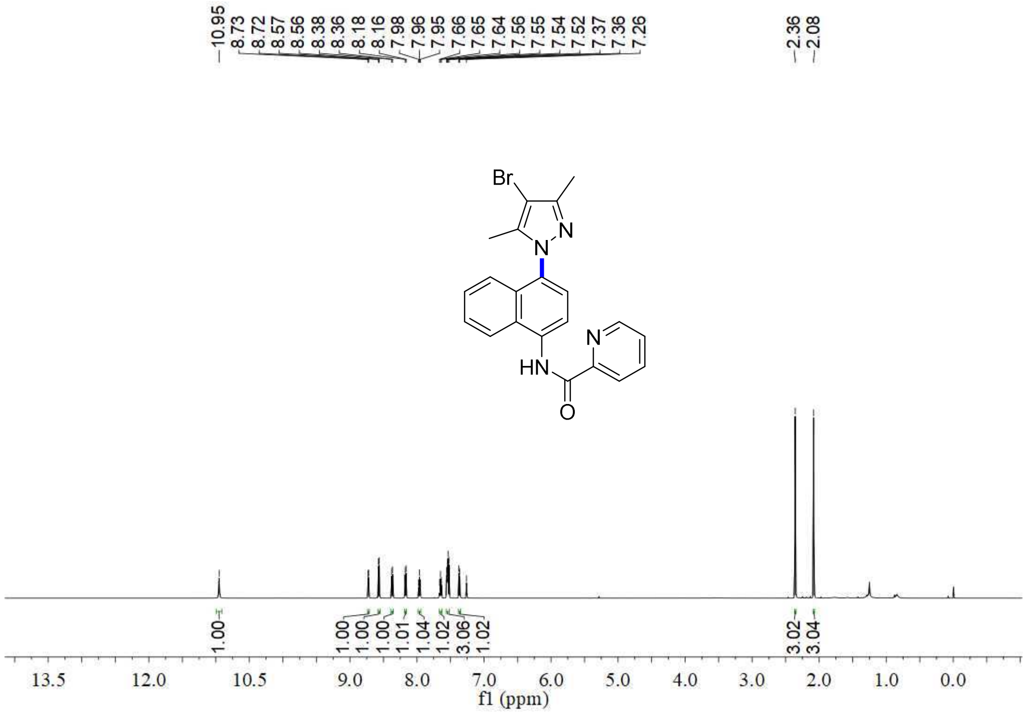
3p ^{1}H NMR



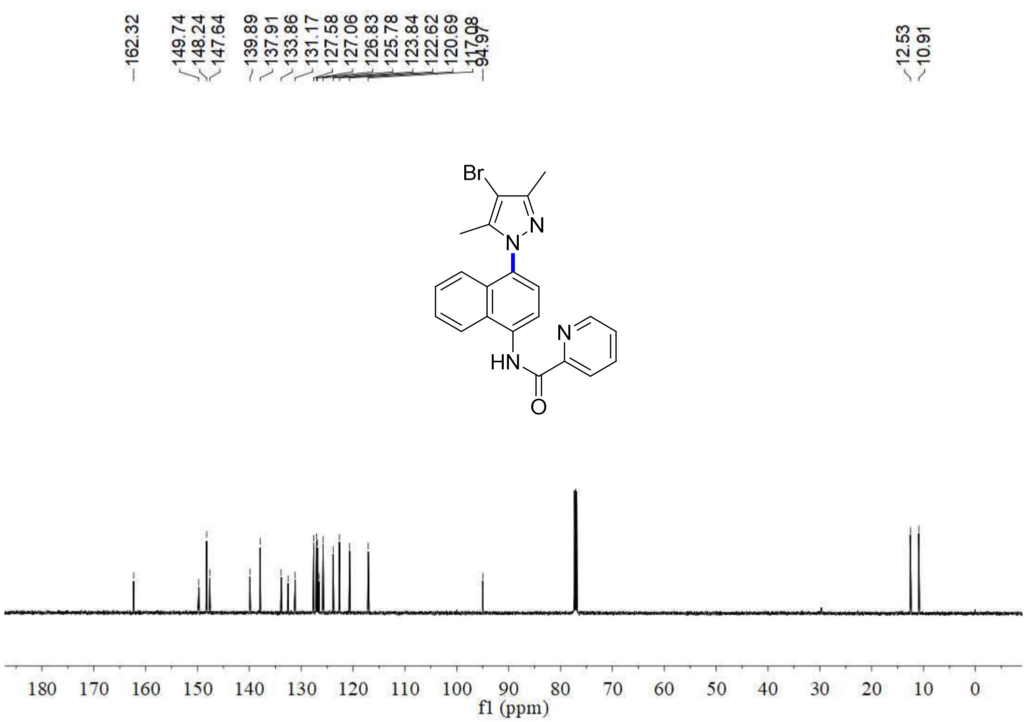
3p ^{13}C NMR



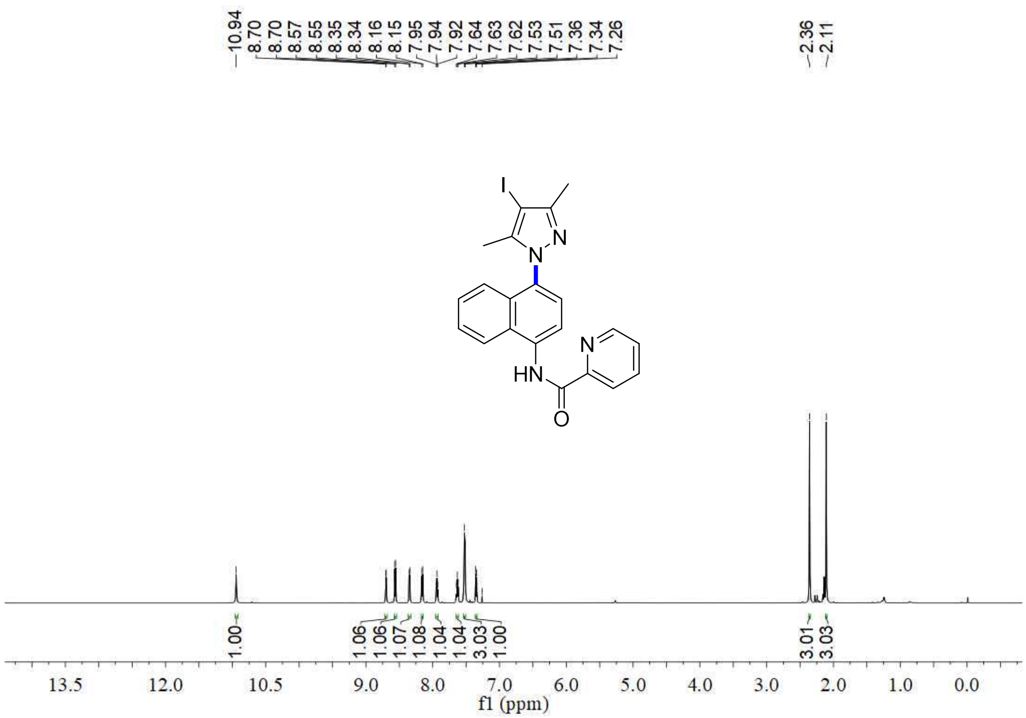
3q ^{1}H NMR



3q ^{13}C NMR



3r ^{1}H NMR



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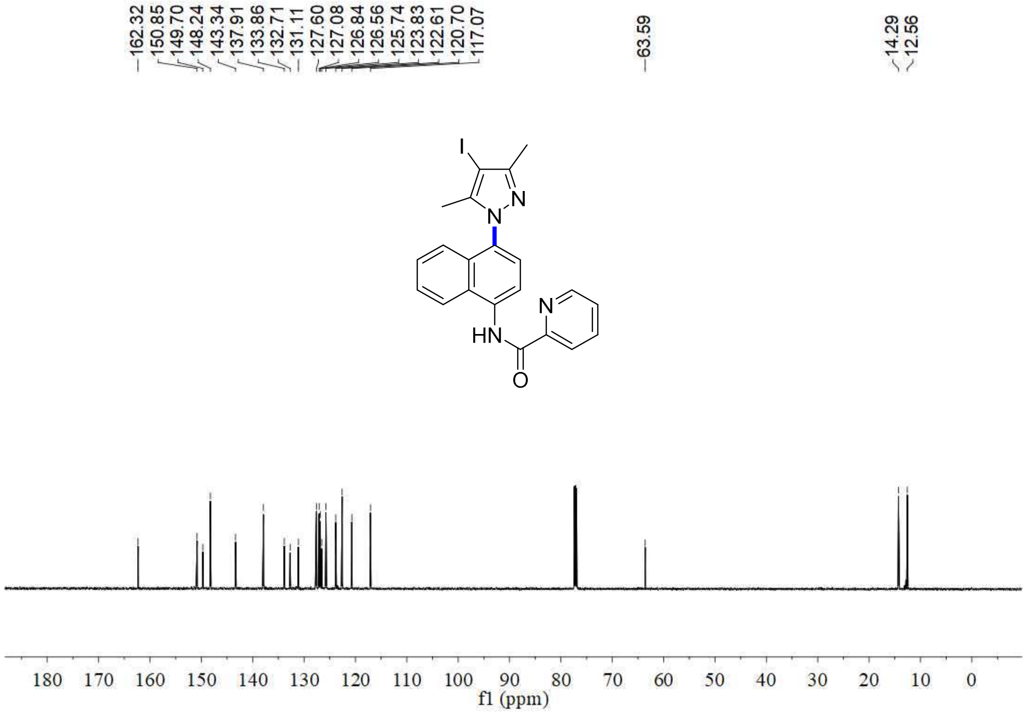

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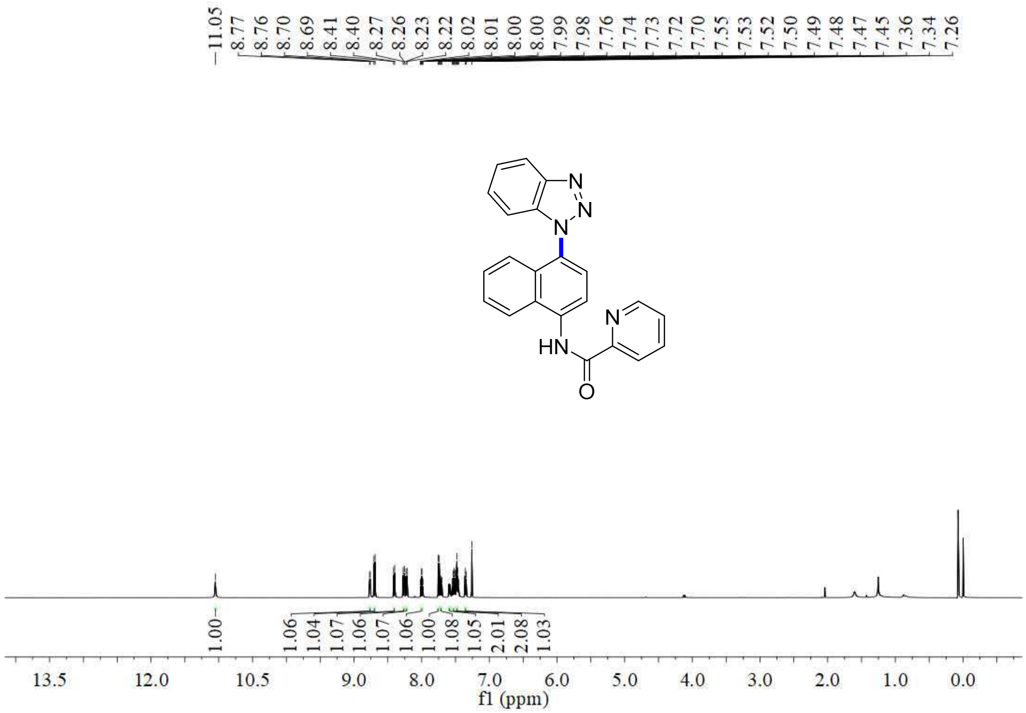
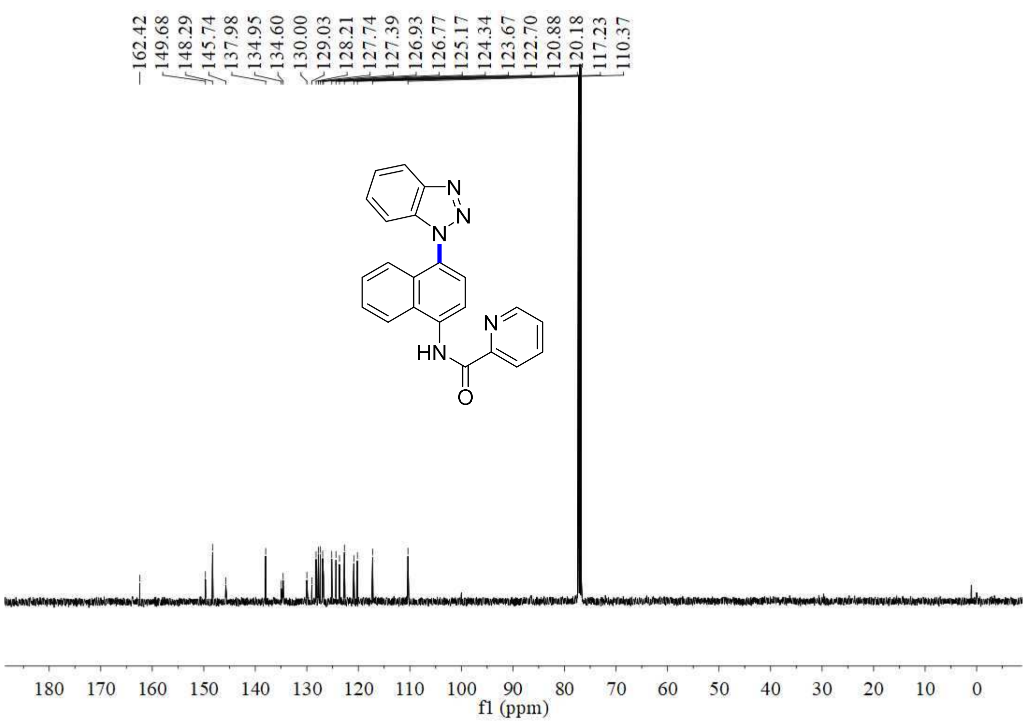
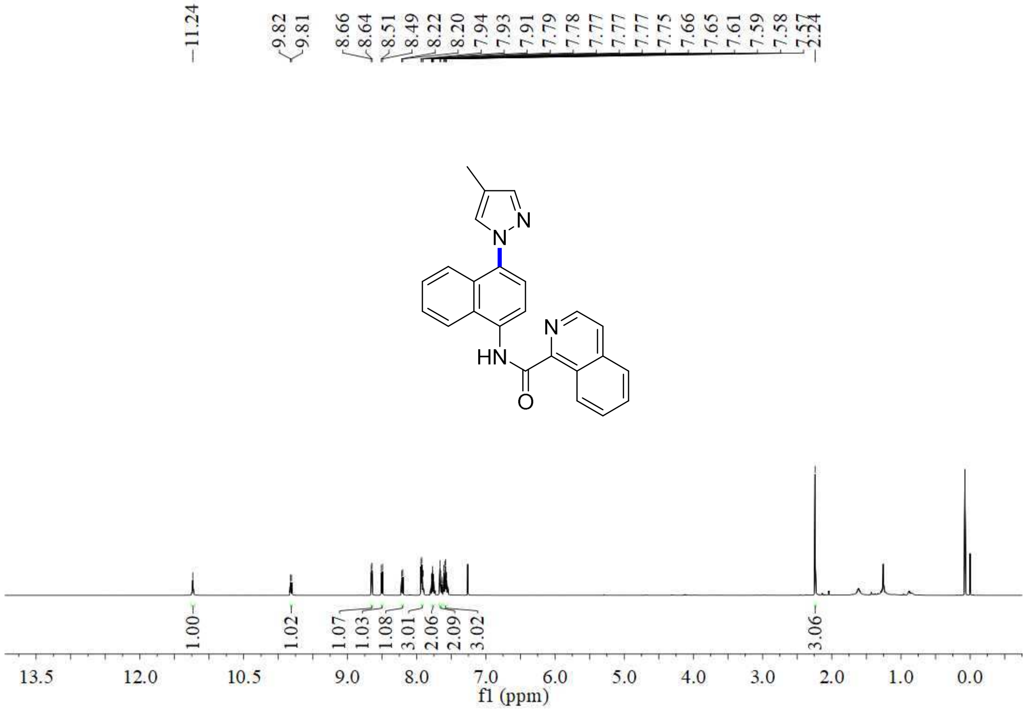


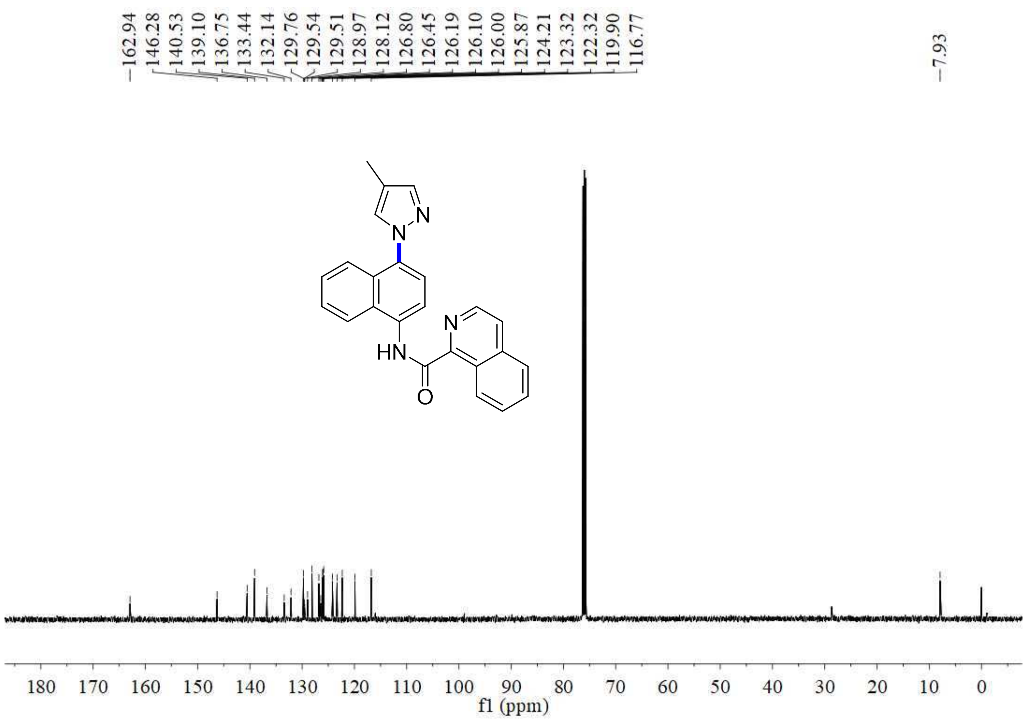
3s ^{13}C NMR



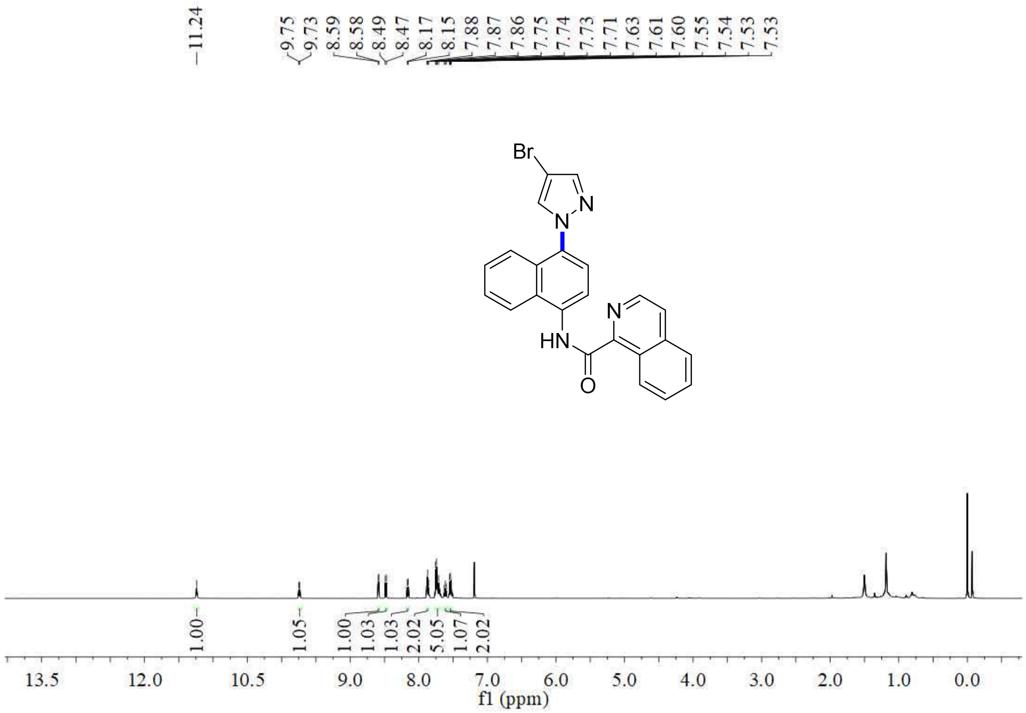
3t ^{1}H NMR



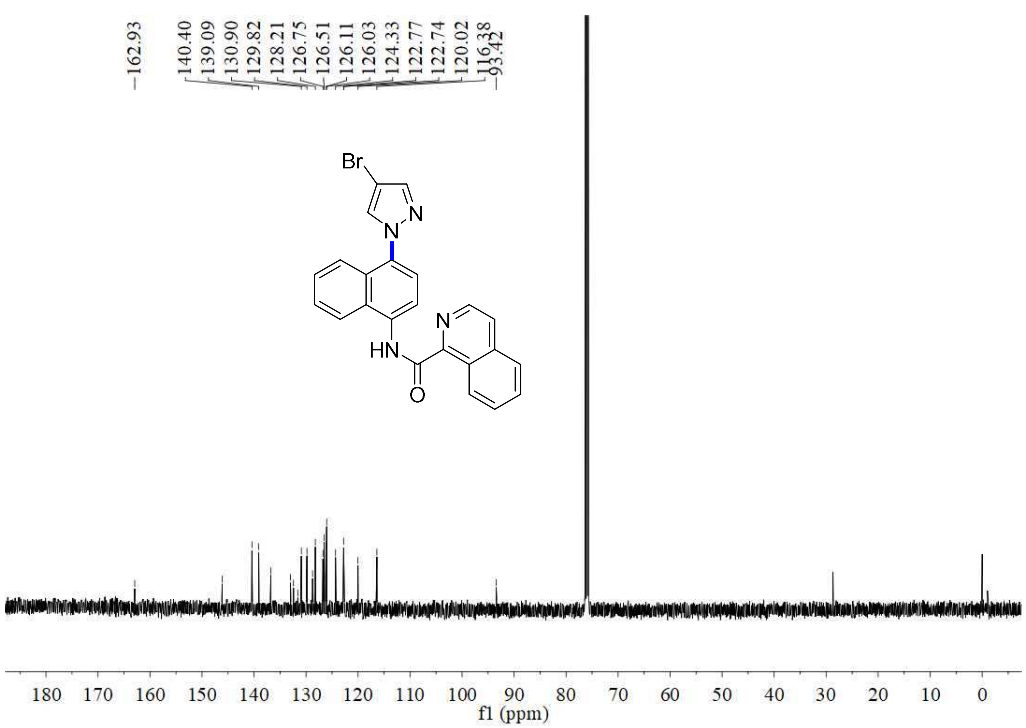
3t ^{13}C NMR



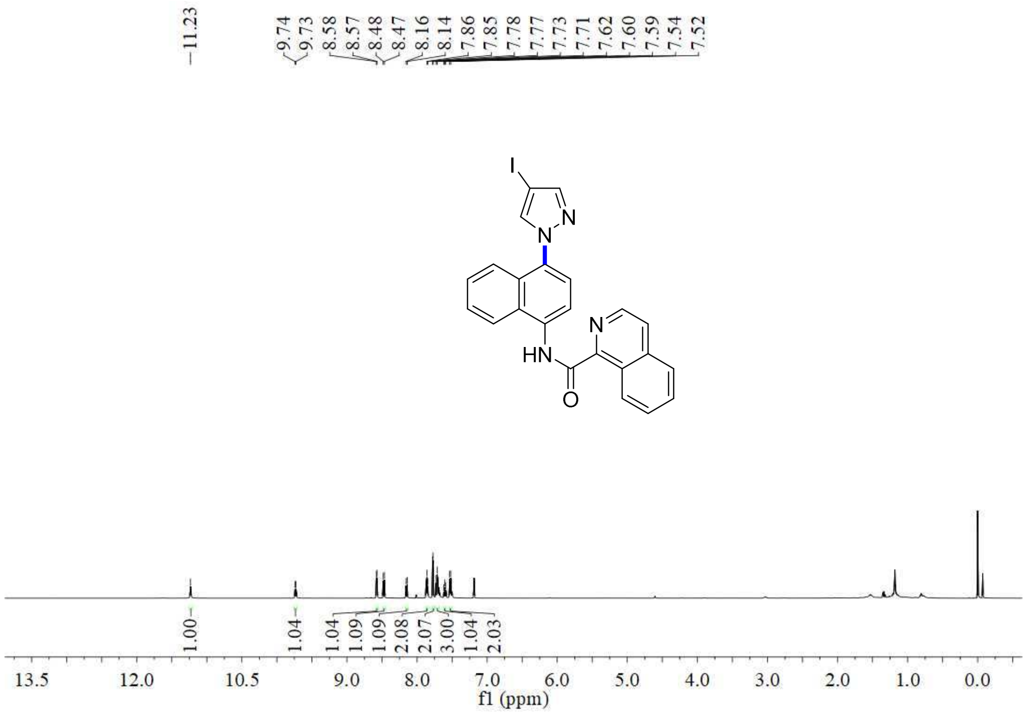
3u ^{1}H NMR



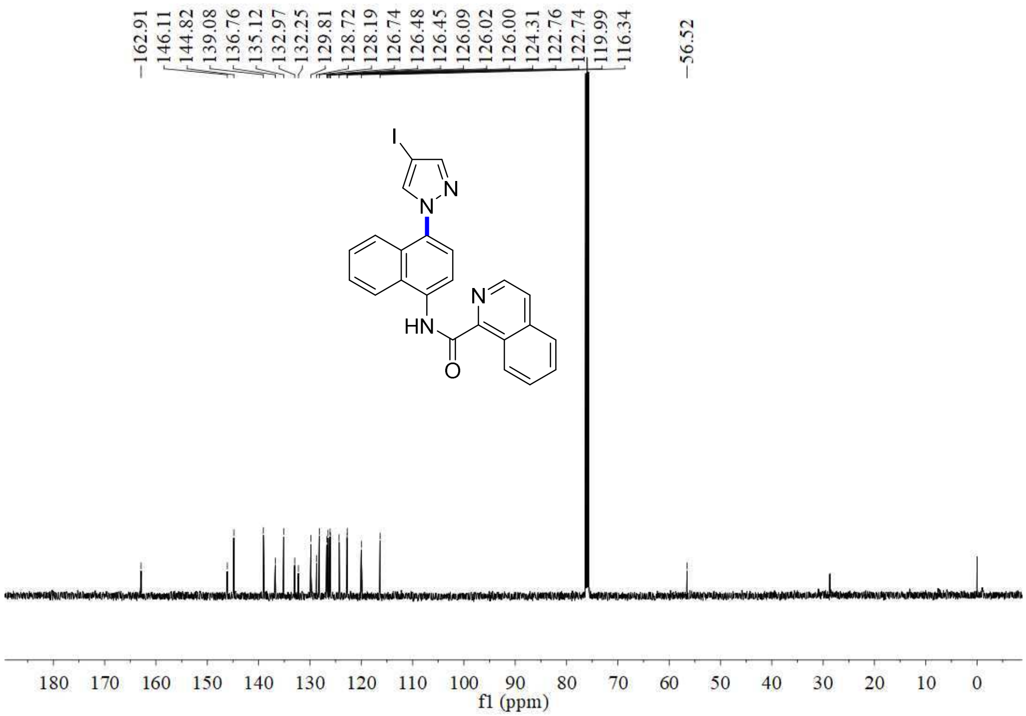
3u ^{13}C NMR



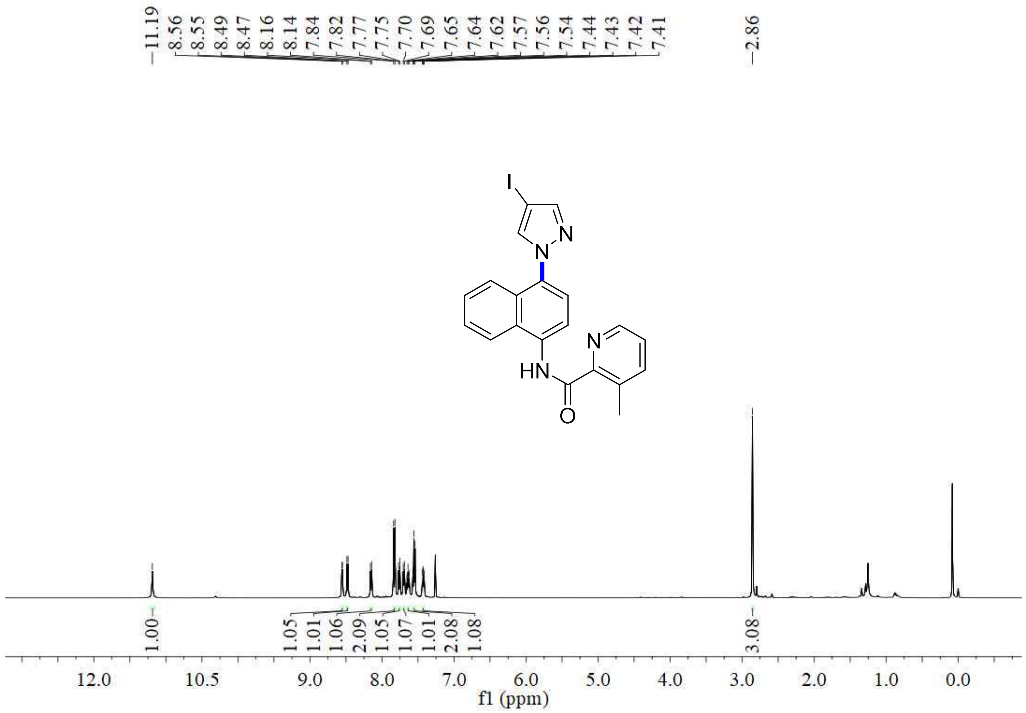
3v ^{1}H NMR



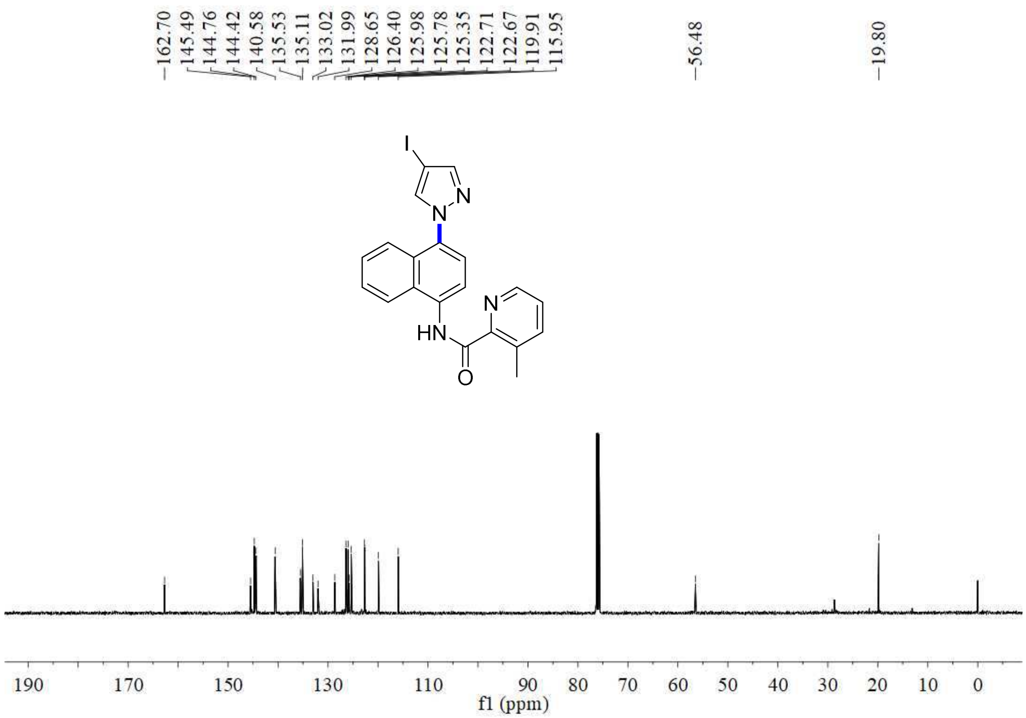
3v ^{13}C NMR



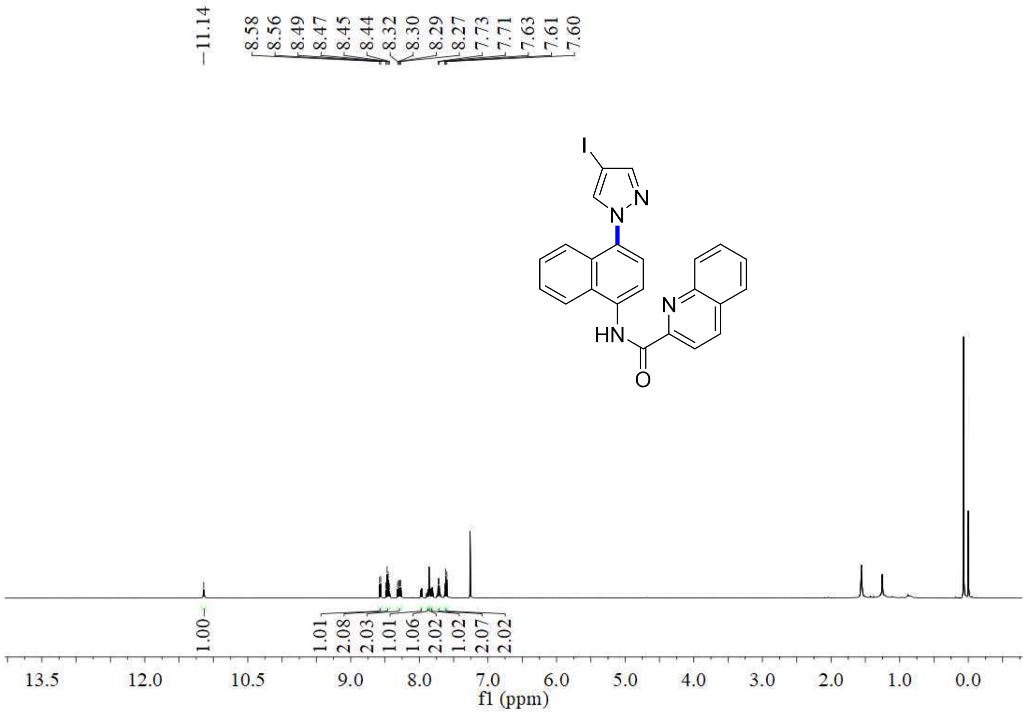
3w ^{1}H NMR



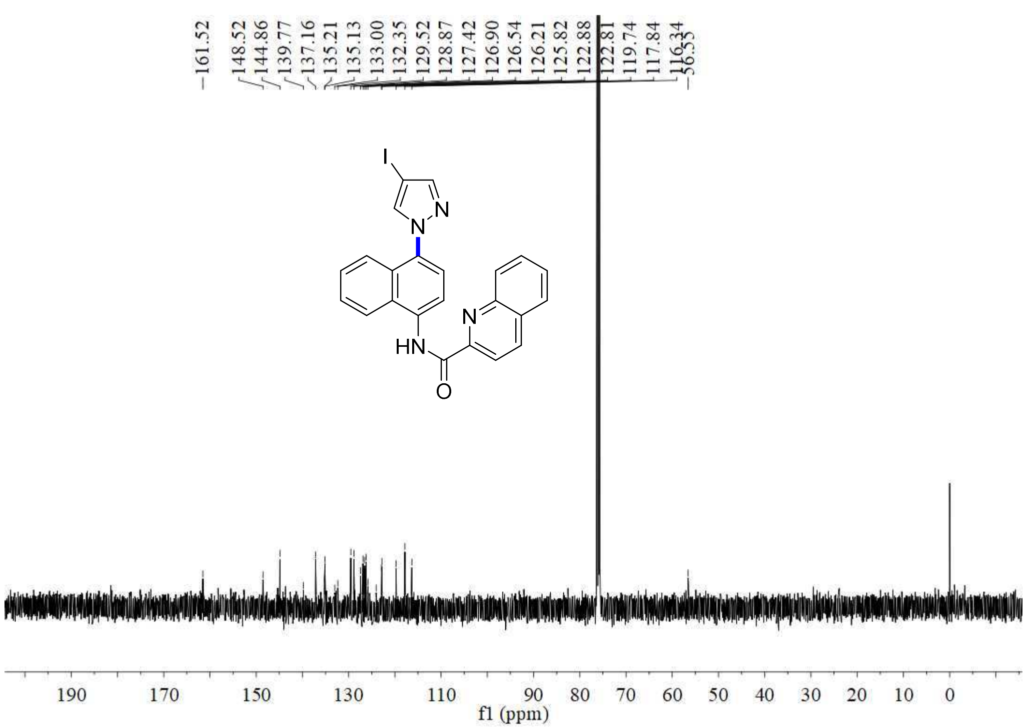
3w ^{13}C NMR



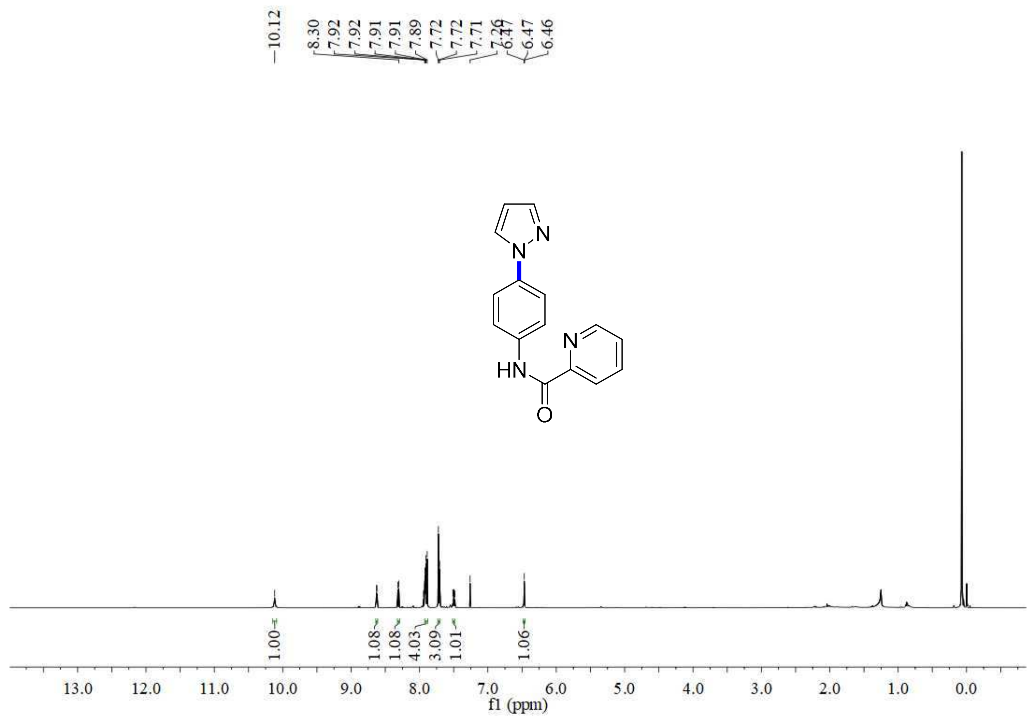
3x ^{1}H NMR



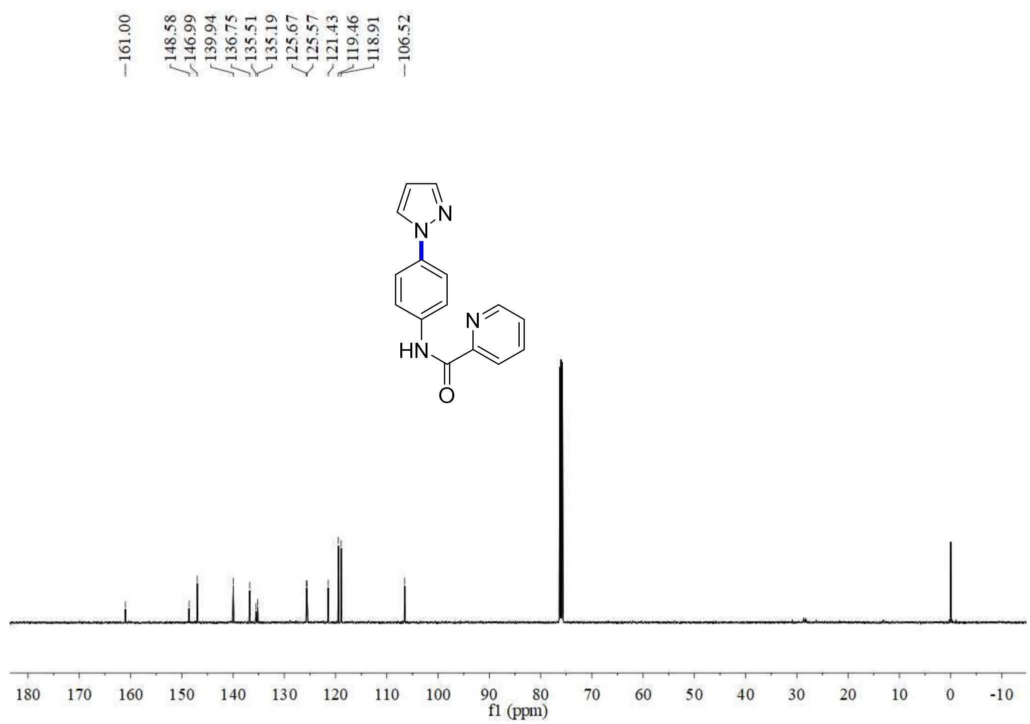
3x ^{13}C NMR



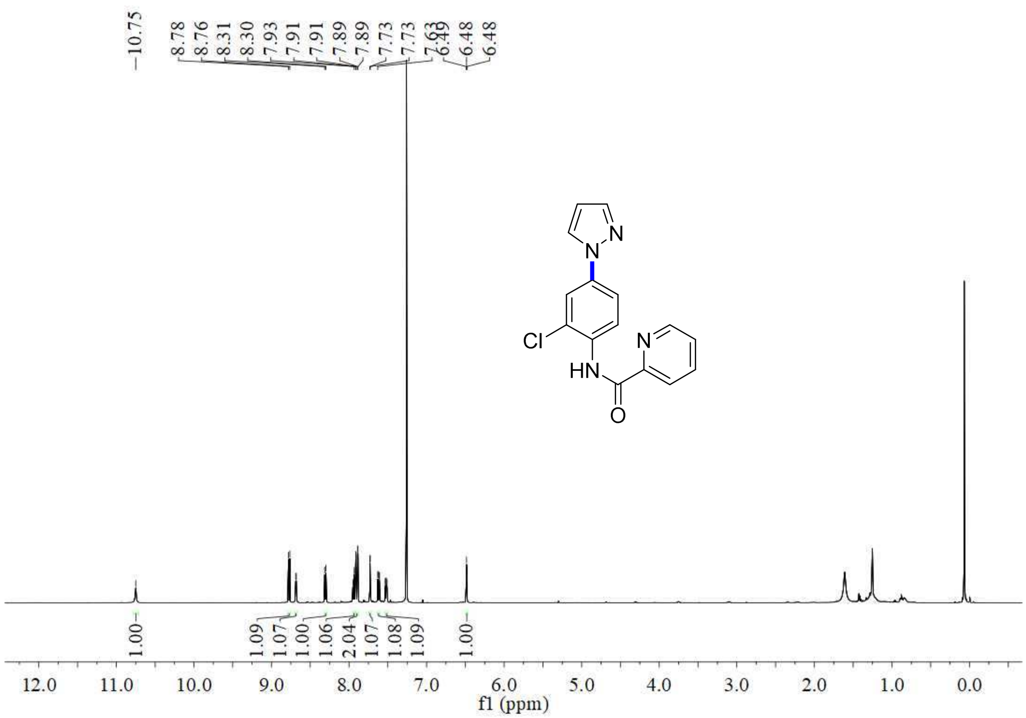
3aa ^{1}H NMR



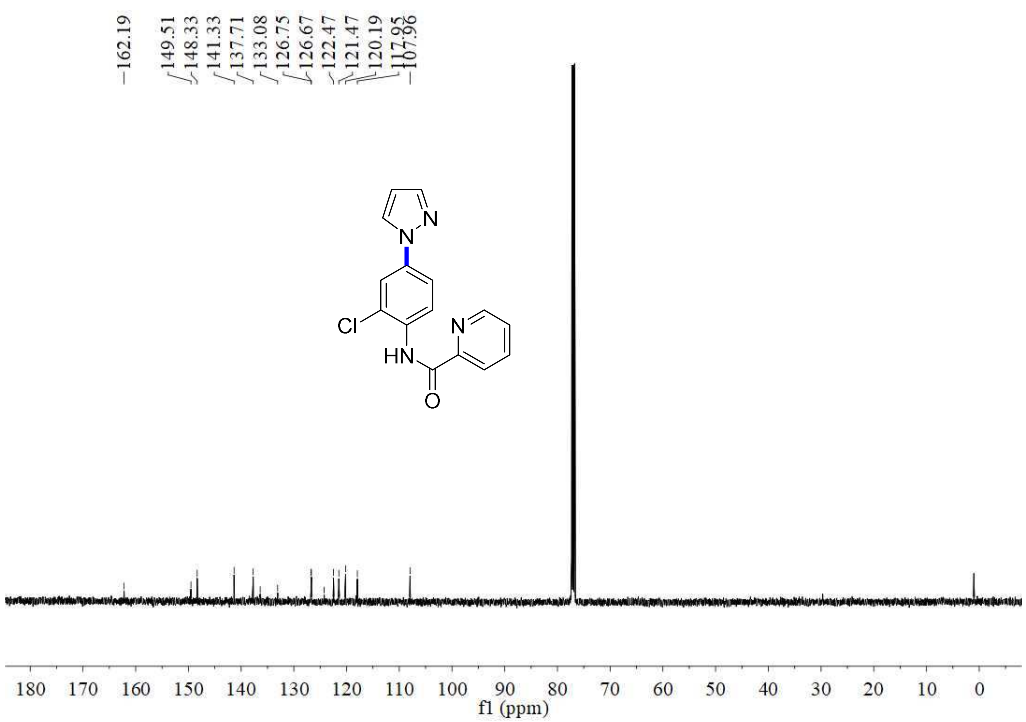
3aa ^{13}C NMR



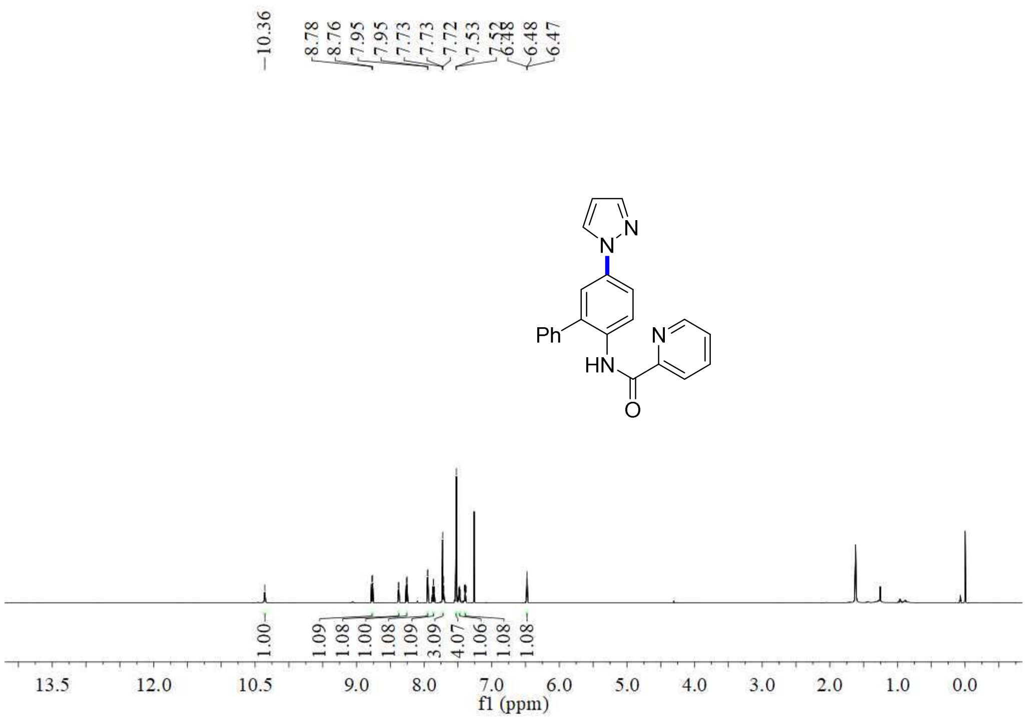
3ab ^{1}H NMR



3ab ^{13}C NMR



3ac ¹H NMR



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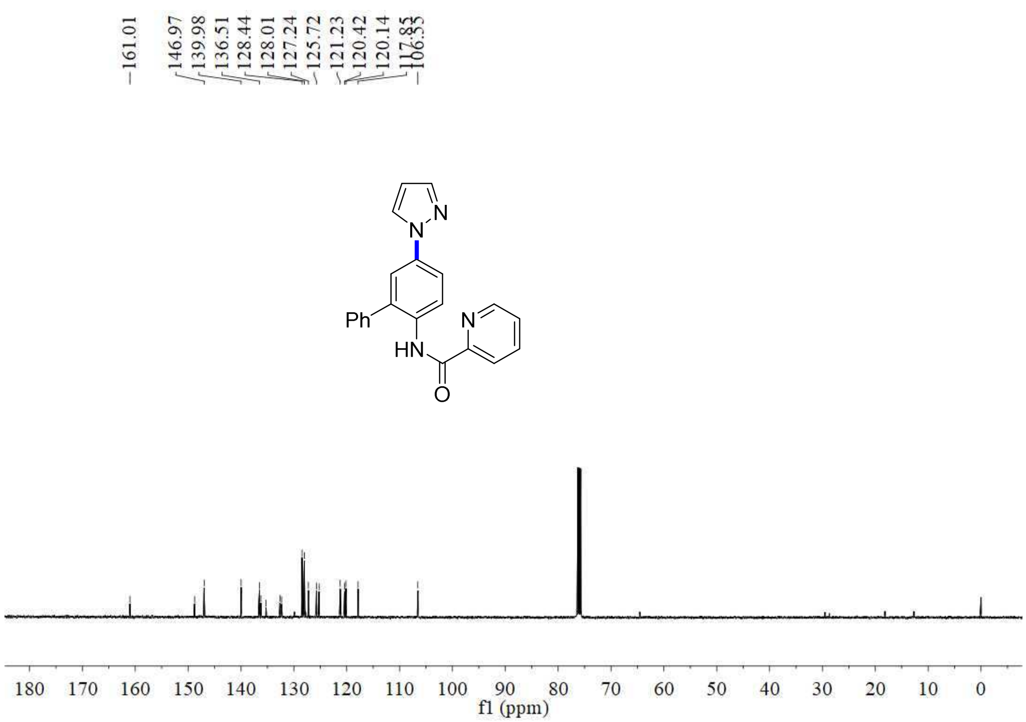
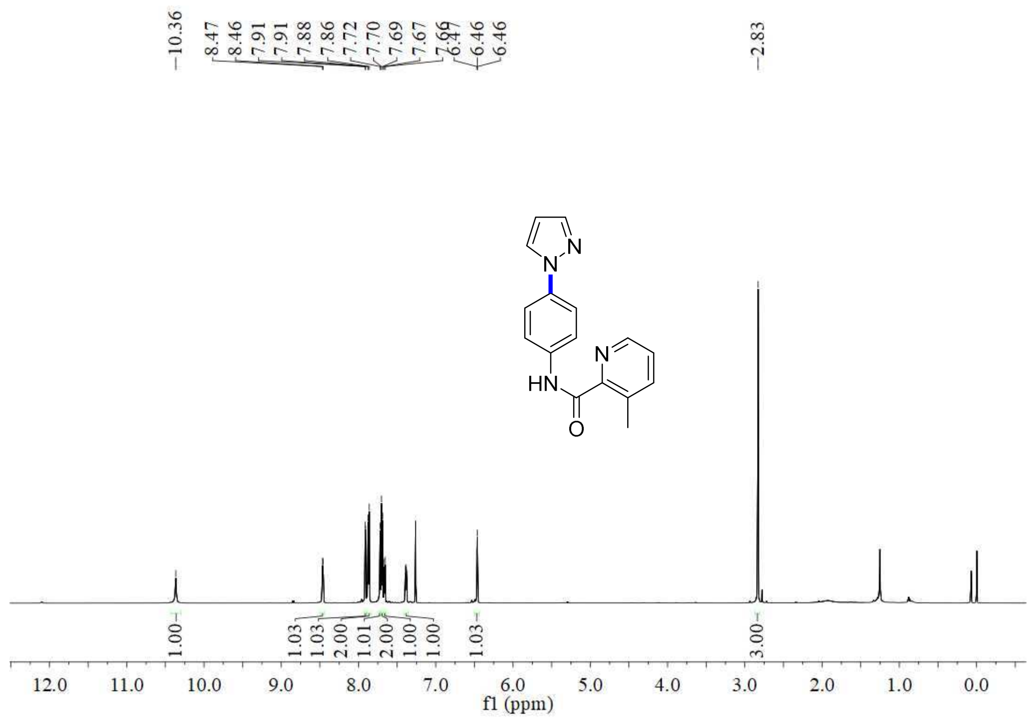
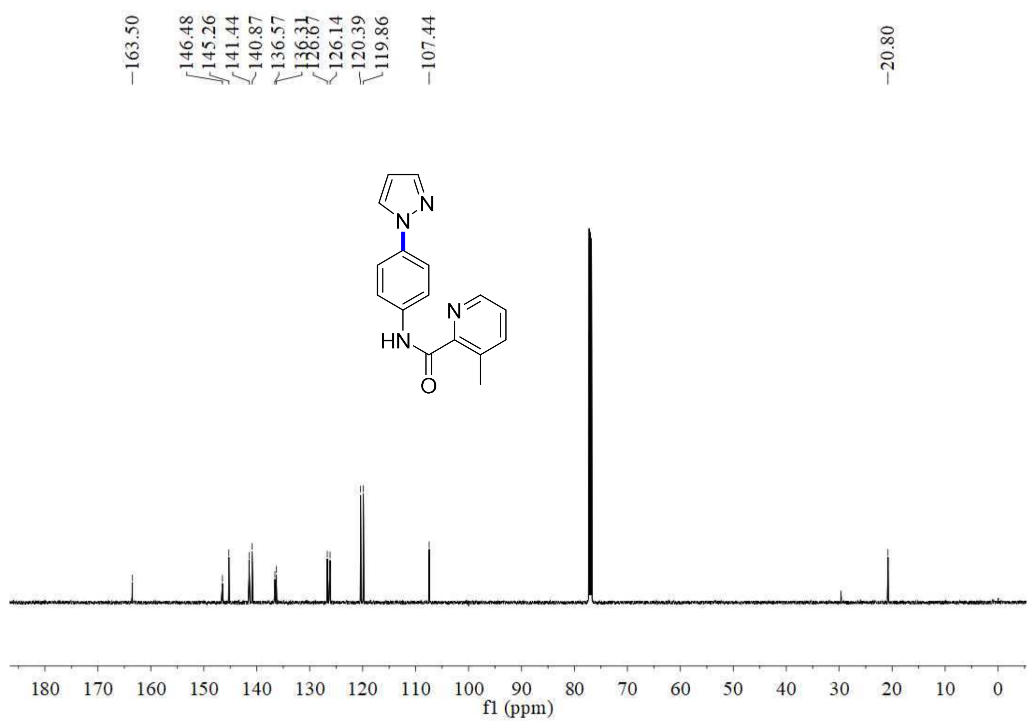


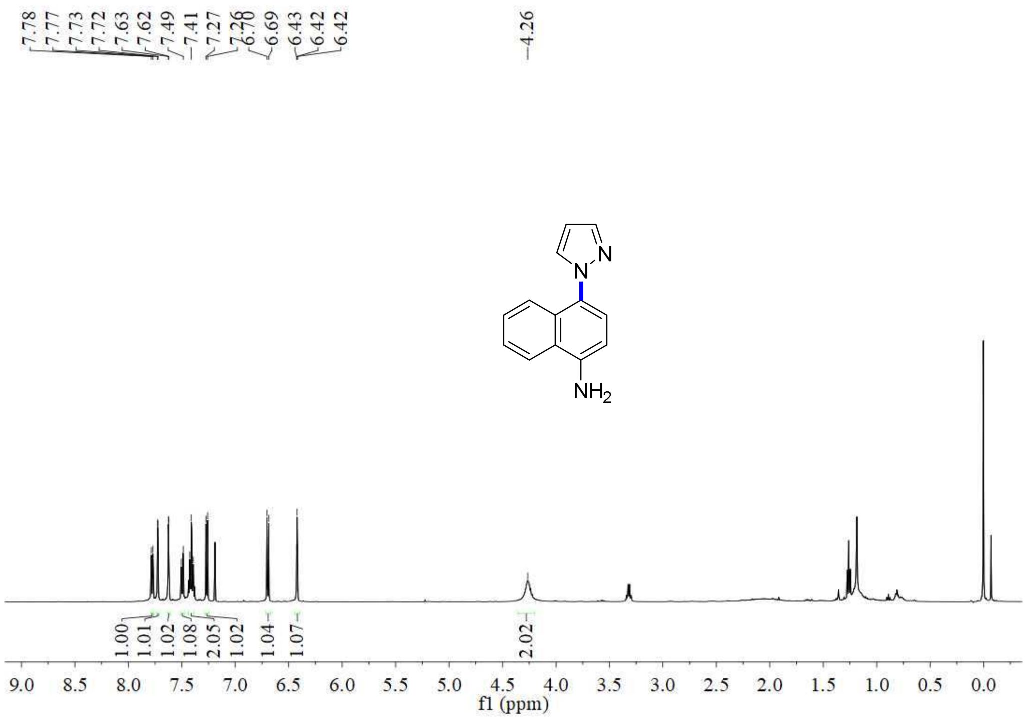
3ad ^{1}H NMR



3ad ^{13}C NMR



4a ^{1}H NMR



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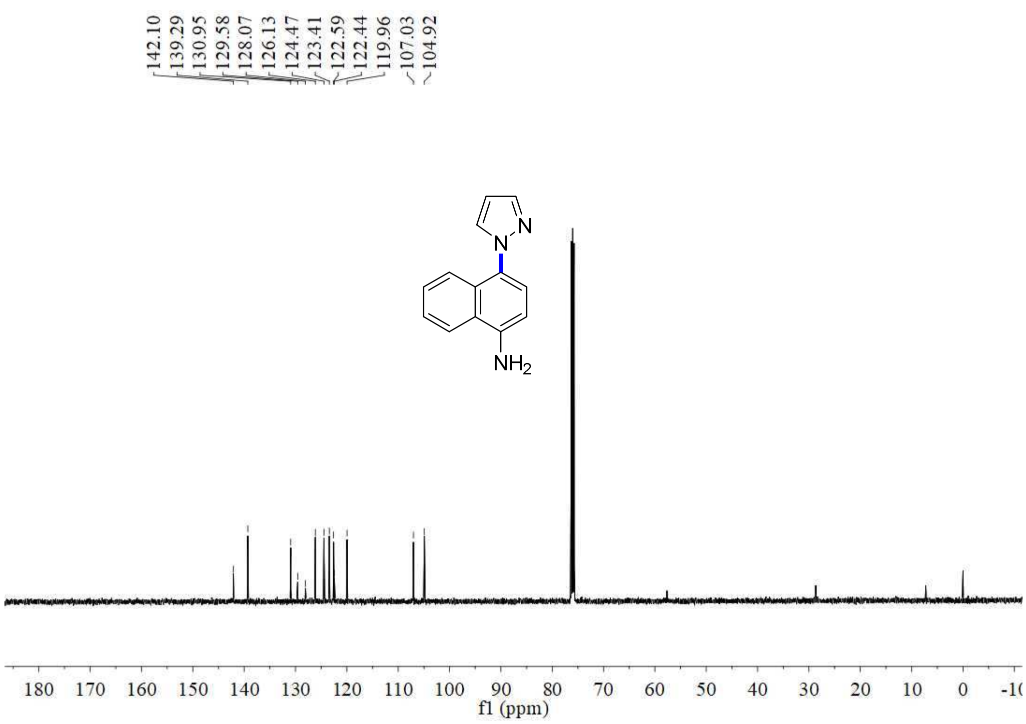
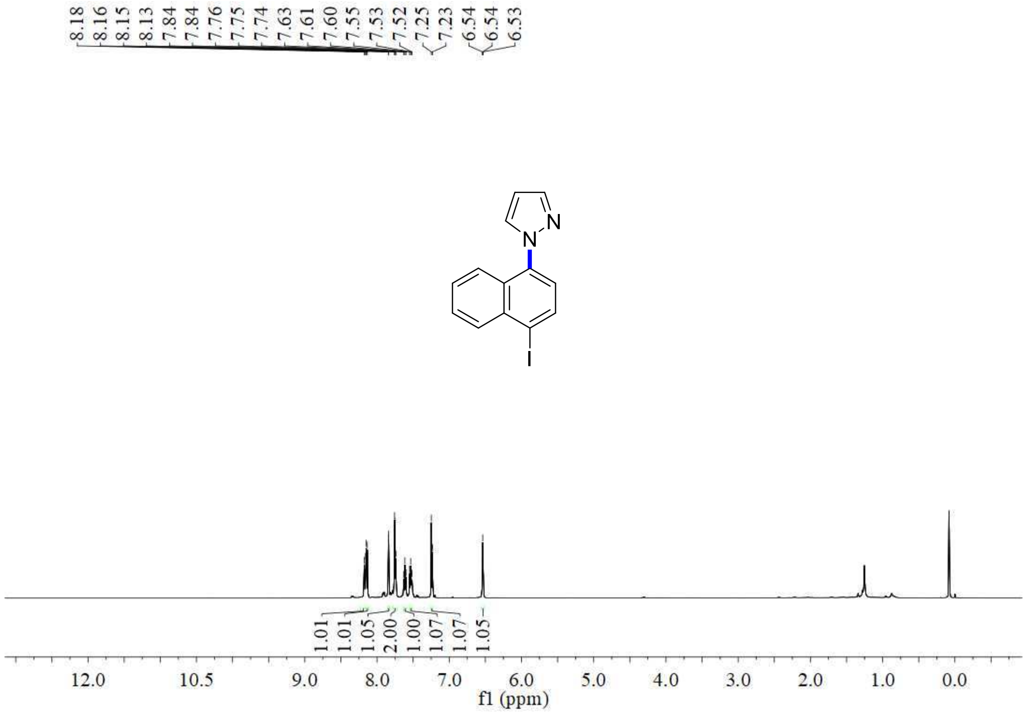


5a ^{1}H NMR



5a ^{13}C NMR