Saponin: A Green and Efficient Natural Surfactant for Suzuki-Miyaura Cross-Couplings of Heteroaryl Substrates in Aqueous Media at Ambient Conditions.

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Supporting Information

1. General Information:

Safety Statement:

No unusual or unexpected safety hazards were encountered or observed during the entire course of experiments.

Reagents and Surfactants:

All the reagents and solvents used in this study were purchased from BLD Pharma, Sigma-Aldrich, Tokyo Chemical Industry Co., Ltd (TCI), and Combi-Blocks. All the aryl, heteroaryl halides, and aryl, heteroaryl boron reagents used for this study were purchased from BLD pharma, Combi-blocks, and TCI-Chemicals. For this study, we used saponin (cas no: 8047-15-2) obtained from four different sources, TCI-Chemicals (S0019), Sigma-Aldrich (from Quillaja bark (S7900), and purified from quillaja bark (S4521)), and Indian soapberry nuts purchased from local supermarket at Hyderabad in India. Pd-catalysts were purchased from BLD Pharma.

Chromatography:

TLC plates: TLC silica gel 60 F_{254}; 25 Aluminium sheets purchased from Merck. The developed TLC plate was analysed by a UV lamp (254 nm). The TLC plates were further analyzed with the use of iodine, and an ethanolic phosphomolybdic acid stain with the help of a heat gun. Flash chromatography was performed by a combiflash column, and pre-packed silica gel (100−200 mesh and 230−400 mesh) was used for CombiFlash column chromatographic separations.

Analytical methods:

Nuclear Magnetic Resonance Spectroscopy (NMR), and Mass Spectrometry (MS):

All the ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-*d6* with residual $CHCl_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm) or DMSO-*d6* (^{1}H = 2.55 ppm, ^{13}C = 40.46 ppm) as the internal standard. Deuterated solvents were purchased from Cambridge Isotope Laboratories. Chemical shifts are reported in parts per million (ppm). The data presented will be reported as follows; chemical shift, multiplicity in Hertz (Hz) (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet, brs = broad singlet), coupling constant, and number of protons.

HRMS analysis (ESI-MS) mass spectral analysis was performed using Agilent Technologies 6540 UHD Accurate-mass Q-TOF LC/MS instrument.

Palladium residual assay was performed (ICP-MS method) using Agilent instrument, Model 7800.

All the reactions were monitored by Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) along with TLC analysis. The UPLC-MS analysis was performed using Waters: Acquity UPLC BEM 2.1 × 50 mμ C-18 column with acetonitrile/Water as a mobile system.

Scanning Electron Microscopy:

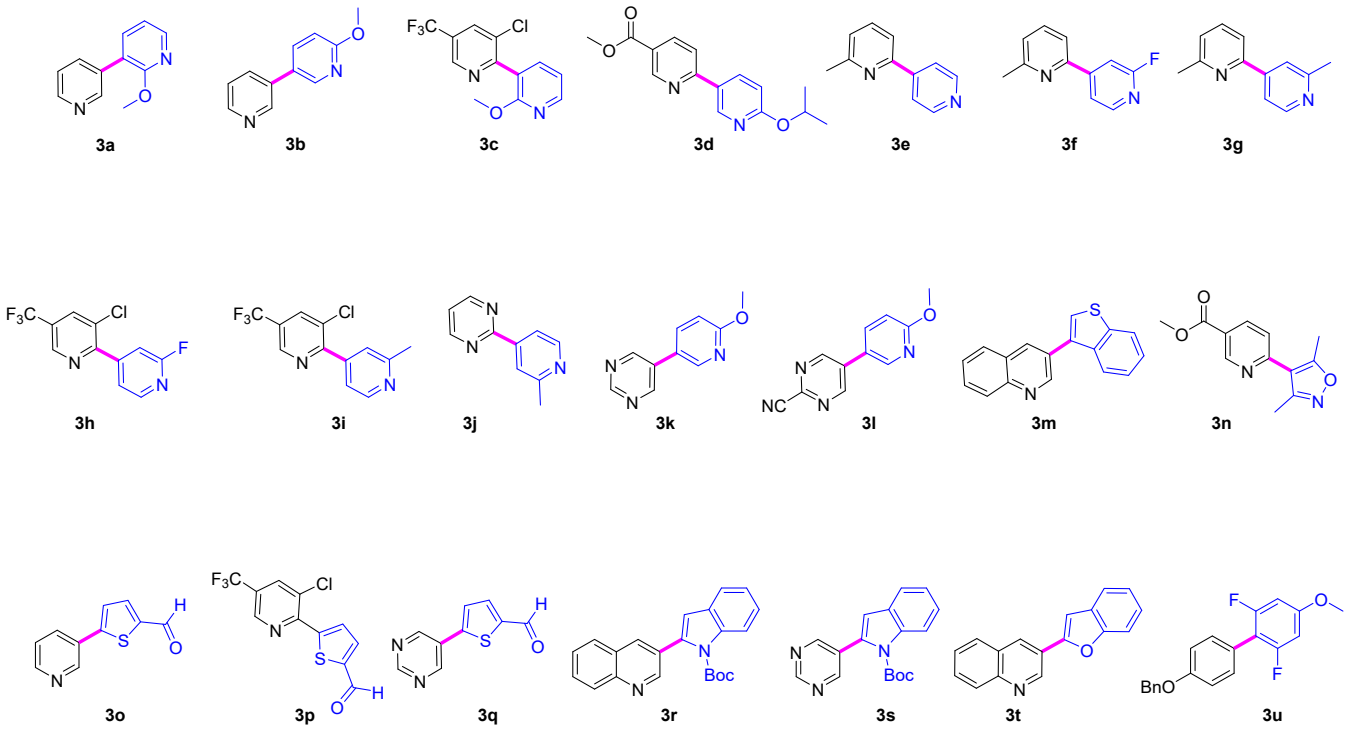
Instrument make: Joel; Model: JSM/7610F, compound with platinum coated.

Dynamic Light Scattering (DLS):

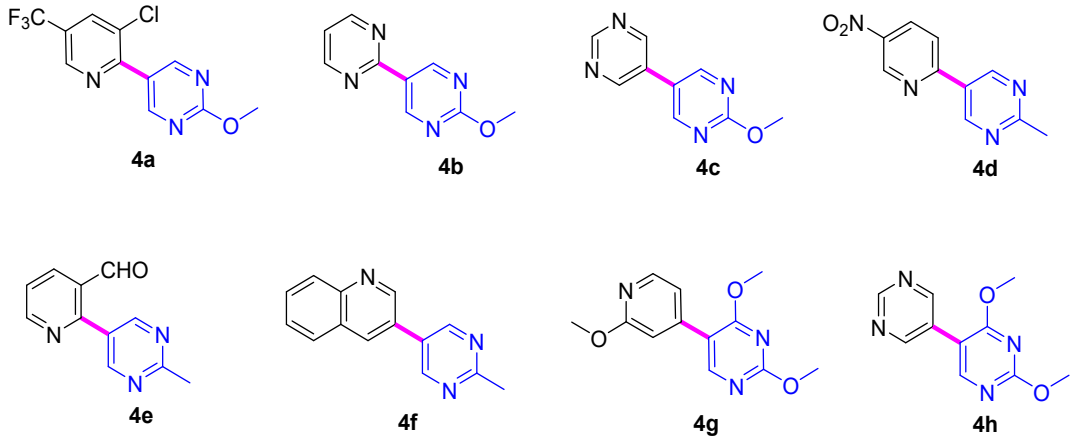
Instrument make: Malvern Instruments

2. List of Suzuki-Miyaura Cross-Coupling products

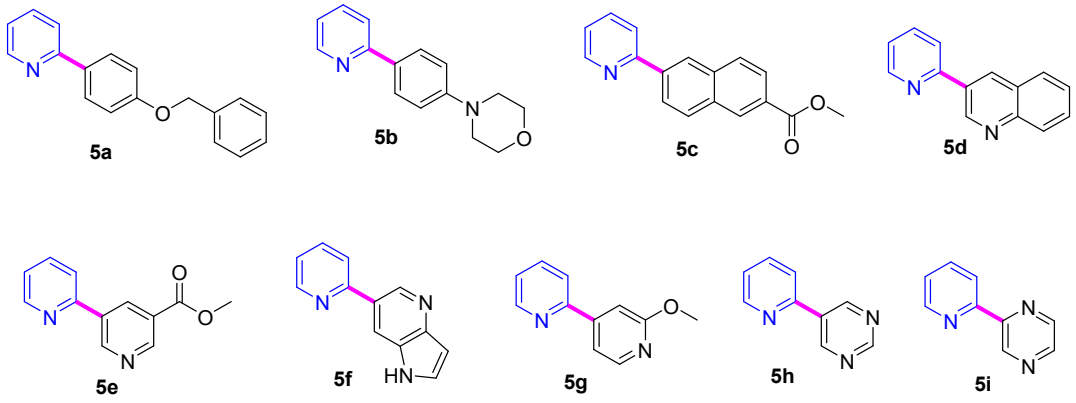
Scheme 1. SMC reaction of pyridyl boronic acids with heteroaryl bromides.



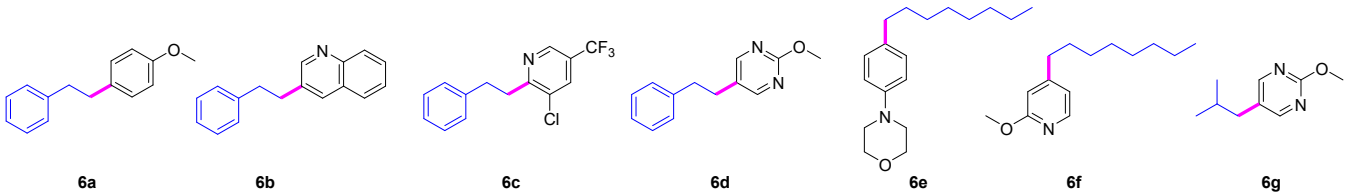
Scheme 2. SMC reaction of pyrimidine boronic acids with heteroaryl bromides.



Scheme 3. SMC reaction with 2-pyridyl boronic acid.[a]

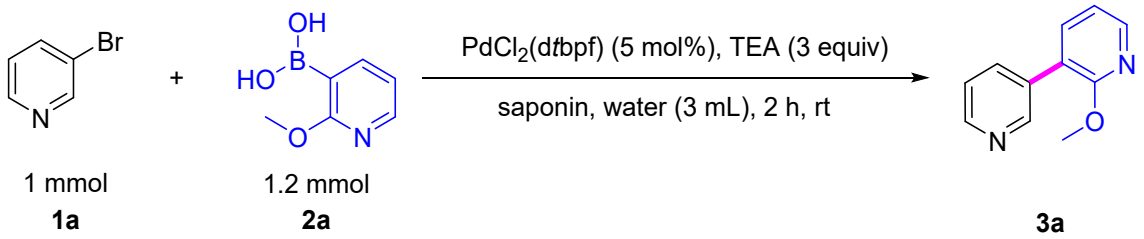


Scheme 4. SMC reaction of alkyl boronic acids with aryl halides.[a]



3. Optimization of the amount of saponin

Table-S1:



1 mmol **1a** + 1.2 mmol **2a** → **3a**

Entry	Source of saponin	Saponin quantity	Yield (%)[b]
1	Saponin from Sigma Aldrich (purified from quillaja bark)	10 wt %; 300 mg	62 %
2	Saponin from Sigma Aldrich (purified from quillaja bark)	5 wt %; 150 mg	82 %
3	Saponin from Sigma Aldrich (purified from quillaja bark)	2 wt %; 60 mg	88 %
4	Saponin from Sigma Aldrich (purified from quillaja bark)	1 wt %; 30 mg	76 %
5	Saponin from Sigma Aldrich (purified from quillaja bark)	0.5 wt %; 15 mg	62 %

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), $PdCl_2$(d*t*bpf) (5 mol %), TEA (3 equiv), Water (3.0 mL), saponin, rt, 2−6 h. [b]Yields determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

4. The general procedure A and B of SMC reactions

General procedure-A: Suzuki-Miyaura Cross-Coupling

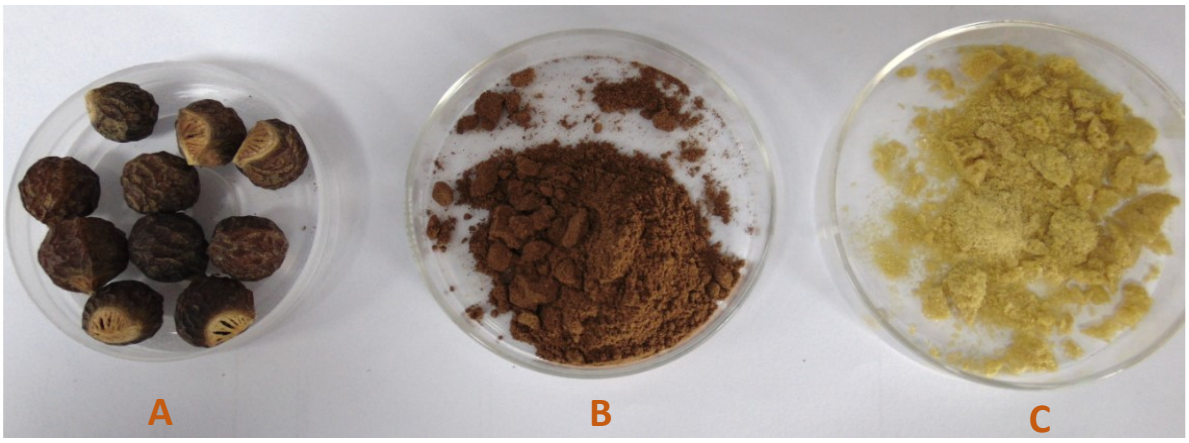
To a solution of heteroaryl bromide (1 mmol) **1a**, heteroaryl boronic acid (1.2 mmol, 1.2 equiv) **2a** in water (3.0 mL) was added TEA (0.42 mL, 3.0 mmol, 3.0 equiv) and saponin (60 mg) followed by $PdCl_2$(d*t*bpf) (33 mg, 0.5 mmol, 5 mol %). The reaction mixture was stirred for 2-6 h at ambient temperature. After the completion of the reaction, as observed by thin-layer chromatography (TLC) and UPLC-MS analysis, the reaction mixture was diluted with water (10 mL), and EtOAc (20 mL) and stirred for a couple of minutes. The emulsion was filtered through celite washed with EtOAc (20 mL) and separated the organic layer. The aqueous layer was re-extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude residue was purified by combiflash column chromatography using a mixture of hexanes/EtOAc (8:2) as an eluent to yield the corresponding cross-coupling product.

General procedure-B: Suzuki-Miyaura Cross-Coupling for 2-pyridyl boronic acid

To a solution of heteroaryl bromide (1 mmol), saponin (80 mg) in water (3.0 mL)/THF (1.0 mL) was added K_3PO_4 (636 mg, 3.0 mmol, 3 equiv), Cu(I)Cl (99 mg, 1.0 mmol, 1 equiv) and XPhos-Pd-G_2 (39.5 mg, 0.5 mmol, 5 mol %) followed by 2-pyridyl boronic acid (2.0 mmol, 2.0 equiv) The reaction mixture was stirred for 16 h at ambient temperature. After the completion of the reaction, as observed by thin-layer chromatography (TLC) and UPLC-MS analysis, the reaction mixture was diluted with water (10 mL), and EtOAc (20 mL) and stirred for a couple of minutes. The emulsion was filtered through celite washed with EtOAc (20 mL) and separated the organic layer. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude residue was purified by combiflash column chromatography using a mixture of hexanes/EtOAc (8:2) as an eluent to yield the corresponding cross-coupling product.

5. Saponin isolated from Indian soapberry nuts:

The soapnut is an ancient Indian herb used in Ayurveda, its botanical Name is Sapindus trifoliatus and its family name is Sapindaceae.[1] A dry soapnut is easily available across India. The dried nut was grinded as a fine powder to get brown color crude saponins. The crude material 10 g was washed with EtOAc (100 mL) three times to remove some non-polar impurities (~1 g of non-polar impurities obtained). The crude powder was used directly for the reaction as a surfactant (Entry-4 in Table 1). Later, the material was extracted with methanol (100 mL) three times and obtained 3 g of light yellow powder of saponins. The methanolic extracted material was tested as a surfactant (Entry-5 in Table 1). The ^{1}H-NMR of the methanolic extracted saponin from Indian soapberry nuts and saponin purchased from TCI-Japan and Sigma Aldrich (USA) is almost similar.

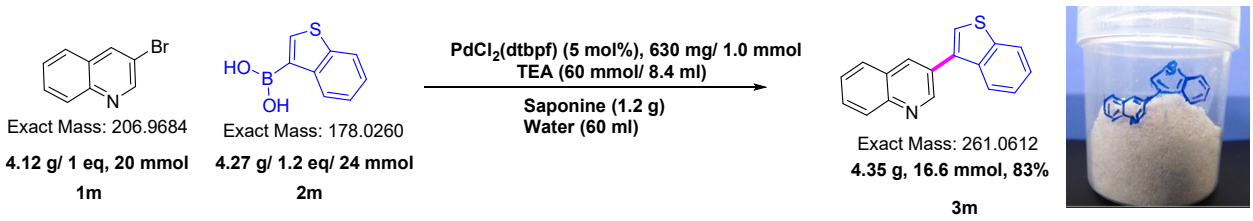


(A) Soapnut berries (B) powdered Soapnut berries/crude saponines (C) methanolic extracts of crude saponines.

1. (a) Panda, A.; Kumar, A.; Mishra, S.; Mohapatra, S. S. Soapnut: A replacement of synthetic surfactant for cosmetic and biomedical applications. *Sustainable Chem. Pharm*. **2020**, *17*, 100297. (b) Kommalapati, R. R.; Valsaraj, K. T.; Constant, W. D.; Roy, D. Soil flushing using colloidal gas aphron suspensions generated from a plant-based surfactant. *J. Hazard. Mater*. **1998**, *60*, 73.

6. Scale-up reactions:

Scale-up reaction-I



Synthesis of 3-(benzo[b]thiophen-3-yl)quinoline (3m):

To a solution of 3-bromoquinoline **1m** (4.12 g, 20 mmol), benzo[b]thiophen-3-ylboronic acid **2m** (4.27 g, 24 mmol, 1.2 equiv) in water (60.0 mL) was added TEA (8.4 mL, 60 mmol, 3.0 equiv) and saponin (1.2 g) followed by $PdCl_2$(d*t*bpf) (630 mg, 1.0 mmol, 5 mol %). The reaction mixture was stirred for 2 h at ambient temperature. After the completion of the reaction, as observed by thin-layer chromatography (TLC) and UPLC-MS analysis, the reaction mixture was diluted with water (100 mL), and EtOAc (200 mL) and stirred for a couple of minutes. The emulsion was filtered through celite washed with EtOAc (2 × 50 mL) and separated the organic layer. The aqueous layer was re-extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude residue was purified by combiflash column chromatography using a mixture of hexanes/EtOAc (8:2) as an eluent to yield **3-(benzo[b]thiophen-3-yl)quinoline (3m)** (4.35 g, 16.6 mmol) in 83 % yield as an off-white solid.

The residual palladium content of the above purified **3-(benzo[b]thiophen-3-yl)quinoline (3m)** was tested by IPC-MS analysis and found that 12.01 ppm Palladium is present in the material.

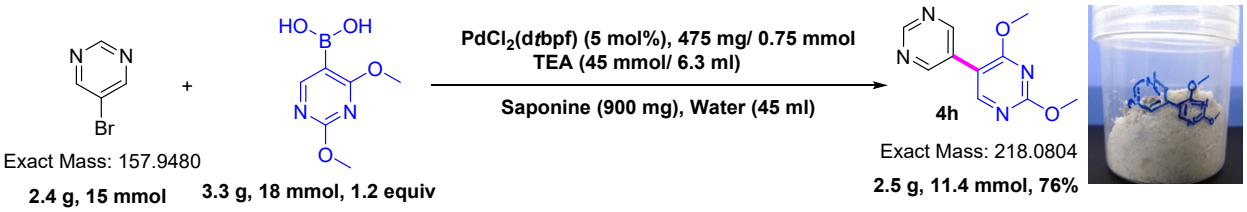
The same above reaction of synthesis of **3-(benzo[b]thiophen-3-yl)quinoline (3m)** was performed in a 5.0 mmol batch with a reduced amount of Pd-catalyst load 2.0 mol% of $PdCl_2$(d*t*bpf). The reaction was completed in 4 h and provided the desired product (**3m**) (1.04 g, 4.0 mmol) in 80% yield after column chromatography.

E-Factor calculation for the synthesis of 3-(benzo[b]thiophen-3-yl)quinoline (3m):

Entry	Total material used	Mass of the total material used	Mass of the product	E-Factor
1	Aryl Bromide	4.12 g	**4.35 g**	15.08 ÷4.35 = **3.46**
2	Boronic acid	4.27 g		
3	Pd-Catalyst	0.63 g		
4	Triethyl amine	6.06 g		
Total mass used		**15.08**		

The E-factor was calculated for only reaction and not for workup and column chromatography. Water is a safe solvent and saponin is a natural biodegradable surfactant therefore the amount of water and saponin are not included during the calculation of the total mass used.

Scale-up reaction-II



Synthesis of 2,4-dimethoxy-5,5'-bipyrimidine (4h)

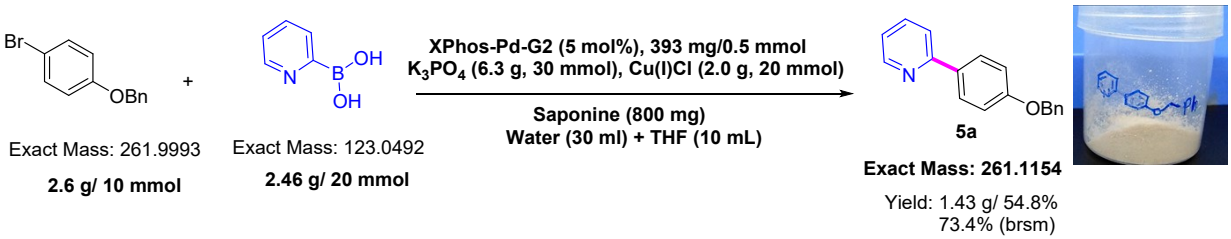
To a solution of 5-bromopyrimidine (2.4 g, 15 mmol), (2,4-dimethoxypyrimidin-5-yl)boronic acid (3.3 g, 18 mmol, 1.2 equiv) in water (45.0 mL) was added TEA (6.3 mL, 45 mmol, 3.0 equiv) and saponin (900 mg) followed by $PdCl_2$(d*t*bpf) (475 mg, 0.75 mmol, 5 mol %). The reaction mixture was stirred for 10 h at ambient temperature. After the completion of the reaction, as observed by thin-layer chromatography (TLC) and UPLC-MS analysis, the reaction mixture was diluted with water (100 mL), and EtOAc (200 mL) and stirred for a couple of minutes. The emulsion was filtered through celite washed with EtOAc (2 × 50 mL) and separated the organic layer. The aqueous layer was re-extracted with EtOAc (3 × 100 mL). The

combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude residue was purified by combiflash column chromatography using a mixture of hexanes/EtOAc (8:2) as an eluent to yield **2,4-dimethoxy-5,5'-bipyrimidine (4h)** (2.5 g, 11.4 mmol) in 76 % yield as an off-white solid.

The residual palladium content of the above purified material **2,4-dimethoxy-5,5'-bipyrimidine (4h)** was 41.2 ppm which was determined by IPC-MS analysis.

The same above reaction of synthesis of **2,4-dimethoxy-5,5'-bipyrimidine (4h)** was performed in a 5.0 mmol batch with a reduced amount of Pd-catalyst load 2.0 mol% of $PdCl_2$(d*t*bpf). The reaction was completed in 16 h and provided the desired product (**4h**) (850 mg, 3.9 mmol) in 78% yield after column chromatography.

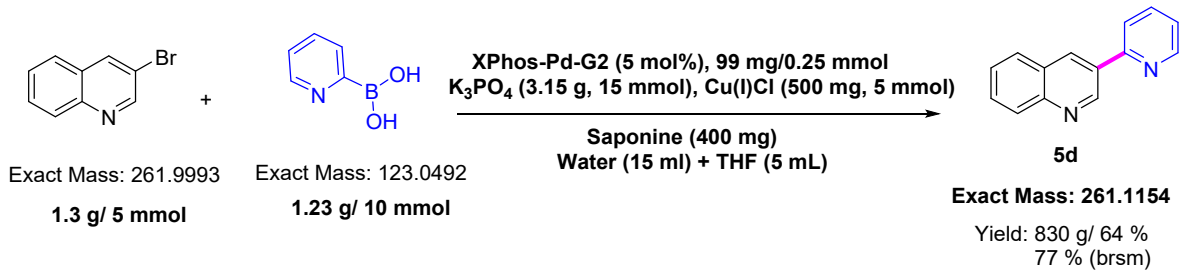
Scale-up reaction-III



Synthesis of 2-(4-(benzyloxy)phenyl)pyridine (5a):

To a solution of 1-(benzyloxy)-4-bromobenzene (2.6 g, 10 mmol, 1 equiv), saponin (800 mg) in water (30.0 mL)/THF (10.0 mL) was added K_3PO_4 (6.3 g, 30.0 mmol, 3 equiv), XPhos-Pd-G_2 (393 mg, 0.5 mmol, 5 mol %) followed by Cu(I)Cl (990 mg, 10 mmol, 1 equiv) and 2-pyridyl boronic acid (2.46 g, 20.0 mmol, 2.0 equiv). The reaction mixture was stirred for 16 h at ambient temperature. After 16 h, the reaction mixture was diluted with water (100 mL), and EtOAc (200 mL) and stirred for a couple of minutes. The emulsion was filtered through celite washed with EtOAc (100 mL) and separated the organic layer. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude residue was purified by combiflash column chromatography using a mixture of hexanes/EtOAc (8:2) as an eluent to yield the **2-(4-(benzyloxy)phenyl)pyridine (5a)** (1.43 g) in 54.8 % yield as an off-white solid along with unreacted bromo compound.

The above-purified compound **2-(4-(benzyloxy)phenyl)pyridine (5a)** was tested for its residual palladium content by ICP-MS analysis and found that 1.88 ppm amount of Palladium was present in the material.



Exact Mass: 261.9993

1.3 g/ 5 mmol

Exact Mass: 123.0492

1.23 g/ 10 mmol

5d

Exact Mass: 261.1154

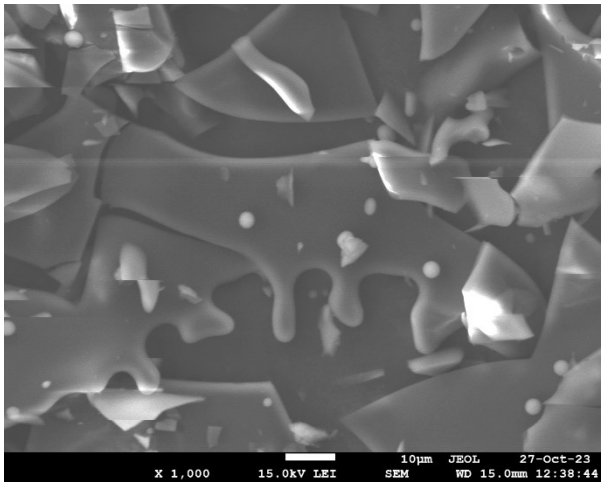
Yield: 830 g/ 64 %
77 % (brsm)

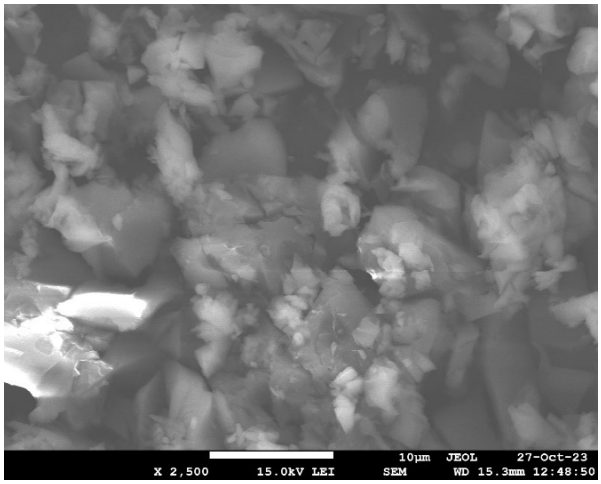
3-(pyridin-2-yl)quinoline (5d)

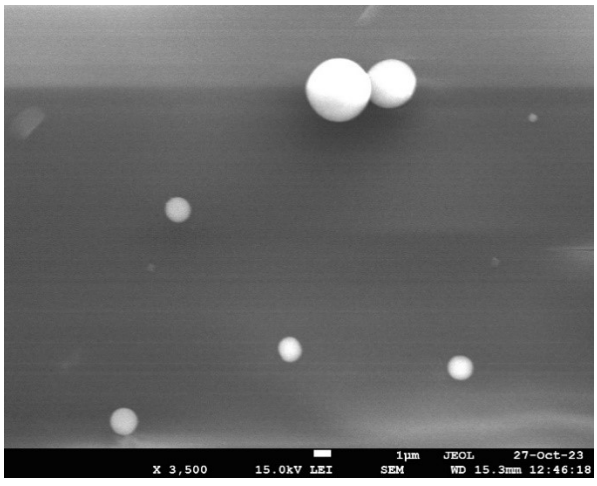
To a solution of 3-bromoquinoline (1.3 g, 5.0 mmol, 1 equiv), saponin (400 mg) in water (15.0 mL)/THF (5.0 mL) was added K_3PO_4 (3.15 g, 15.0 mmol, 3 equiv), XPhos-Pd-G_2 (79 mg, 0.1 mmol, 2.0 mol %) followed by Cu(I)Cl (490 mg, 5 mmol, 1 equiv) and 2-pyridyl boronic acid (1.23 g, 10.0 mmol, 2.0 equiv). The reaction mixture was stirred for 16 h at ambient temperature. After 16 h, the reaction mixture was diluted with water (50 mL), and EtOAc (100 mL) and stirred for a couple of minutes. The emulsion was filtered through celite washed with EtOAc (100 mL) and separated the organic layer. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude residue was purified by combiflash column chromatography using a mixture of hexanes/EtOAc (8:2) as an eluent to yield the **23-(pyridin-2-yl)quinoline (5d)** (830 mg, 3.2 mmol) in 64 % yield as an off-white solid along with unreacted bromo compound.

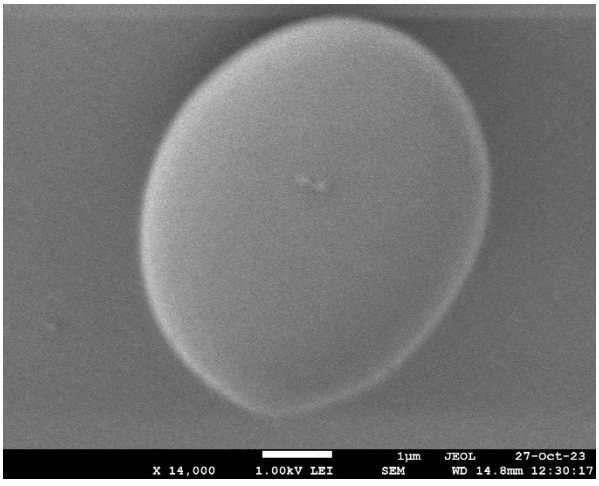
7. SEM, ELD, and DLS Spectras

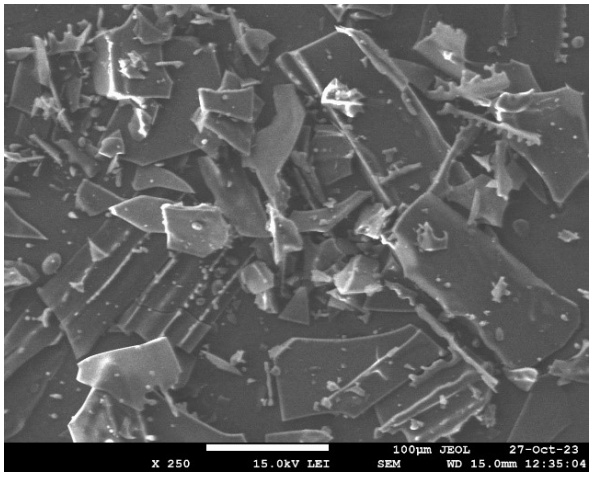
Field Emission Scanning Electron Microscopy (FE-SEM) of Saponin/Sigma Aldrich (cas no: 8047-15-2) Product code: S4521

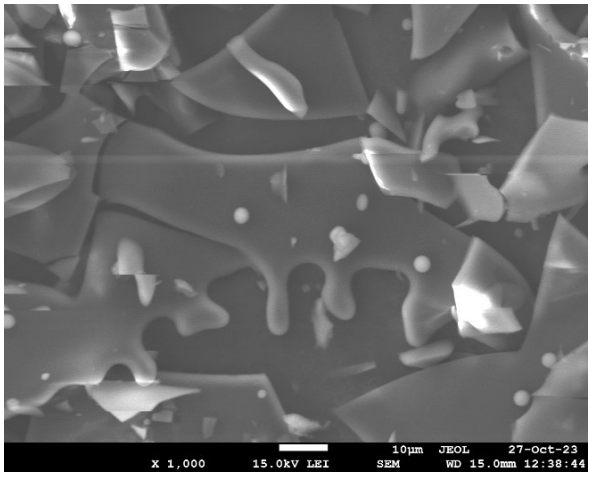




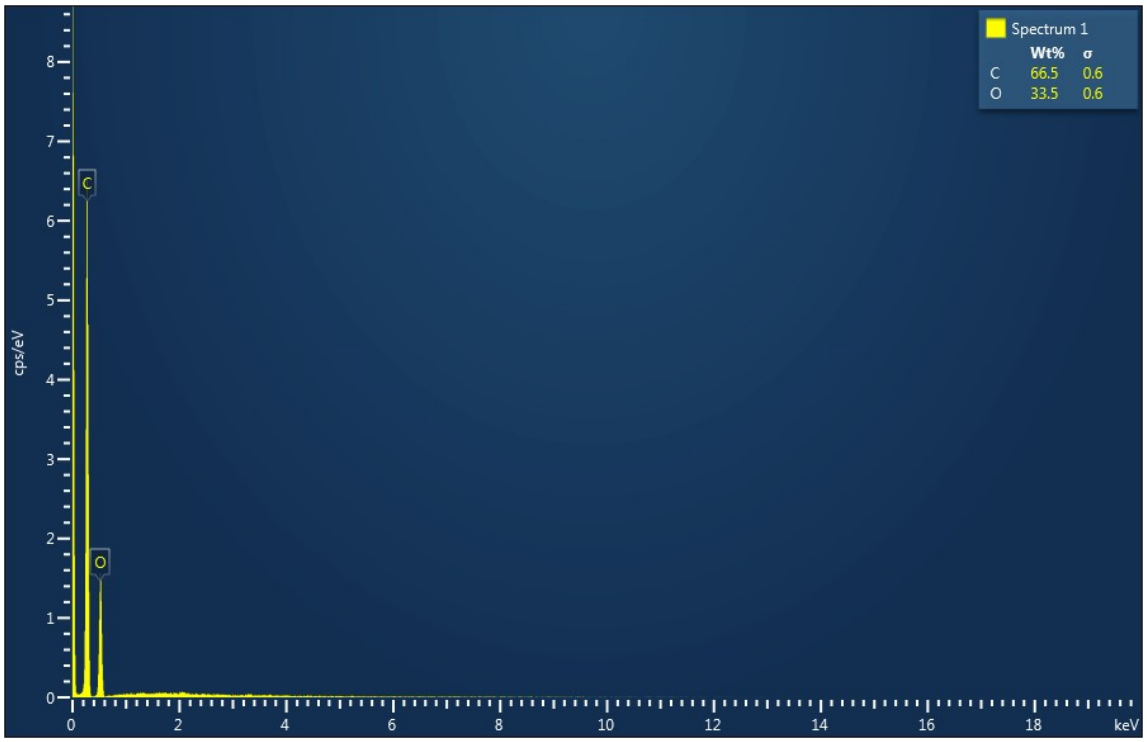








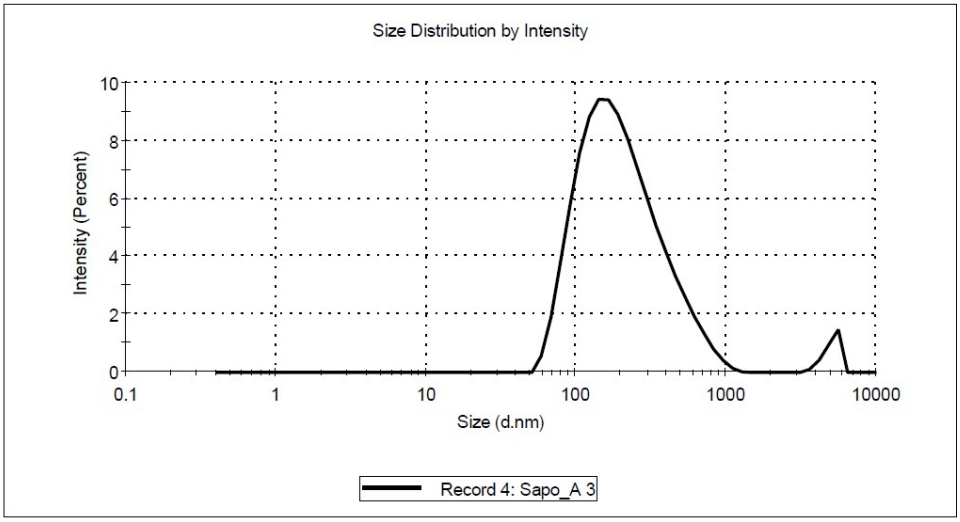
Energy Dispersive Spectroscopy (EDS) of Saponin /Sigma Aldrich (cas no: 8047-15-2) Product code: S4521



Dynamic Light Scattering (DLS**) of Saponin** /Sigma Aldrich (cas no: 8047-15-2) Product code: S4521

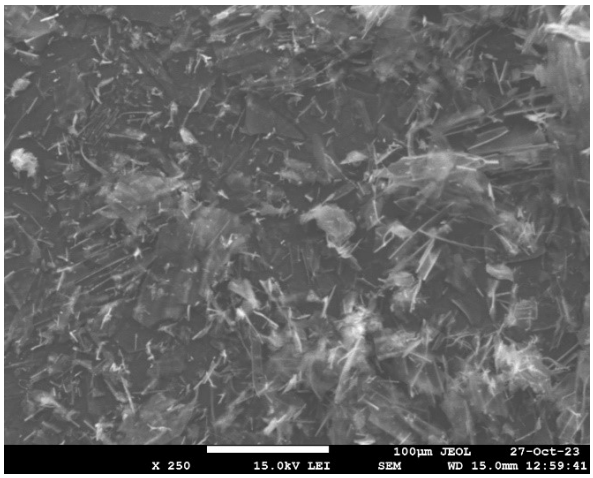
		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 165.5	Peak 1:	231.2	97.0	158.6
PdI: 0.396	Peak 2:	5039	3.0	591.5
Intercept: 0.953	Peak 3:	0.000	0.0	0.000

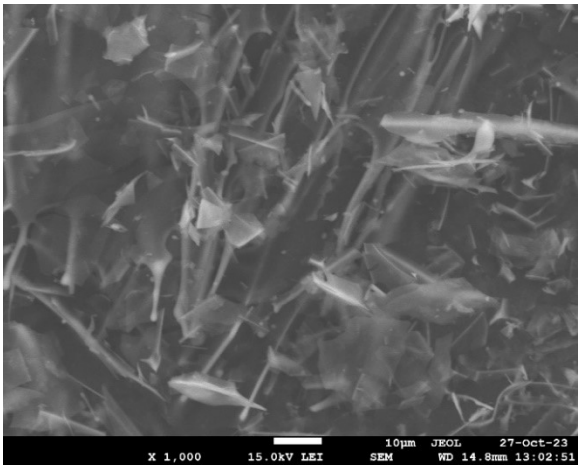
Result quality : Good

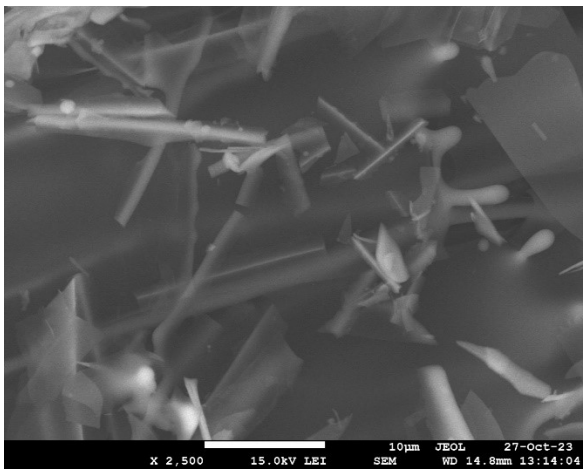


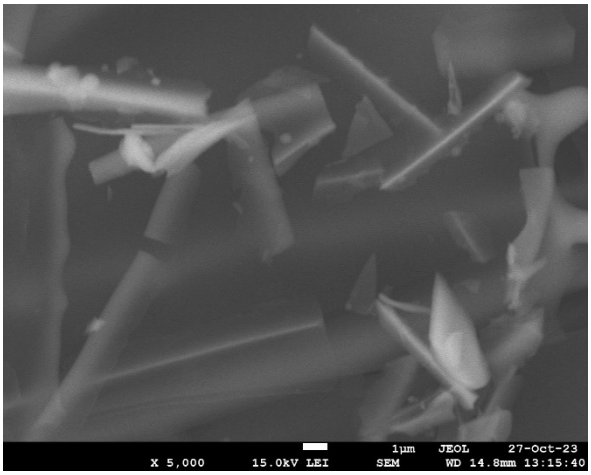
Field Emission Scanning Electron Microscopy (FE-SEM) of Saponin in water

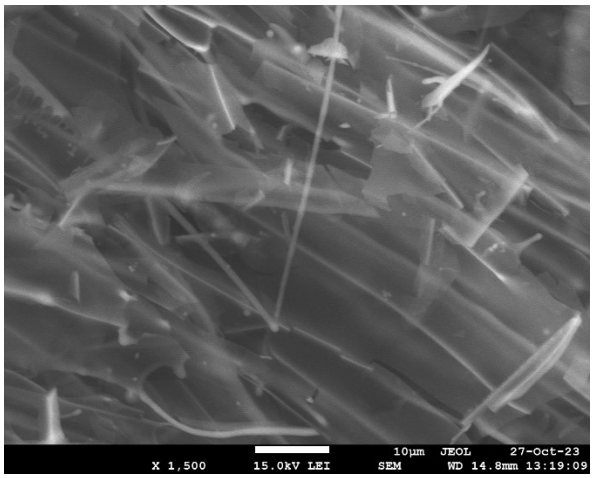
Sample preparation: 60 mg of Saponin (Sigma Aldrich (cas no: 8047-15-2) Product code: S4521) dissolved in 3 mL of DI water (Note: The saponin dissolved immediately and provided clear light brown color solution) and stirred for 5 minutes followed by lyophilization to get dry powder. This powder was used for FE-SEM, EDS, and DLS analysis to understand the effect of water.

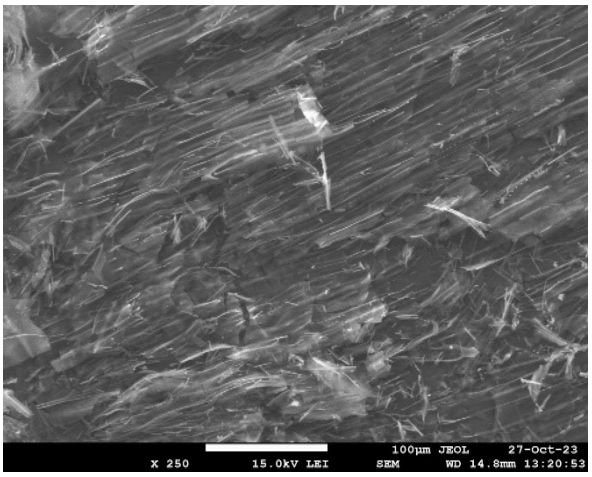




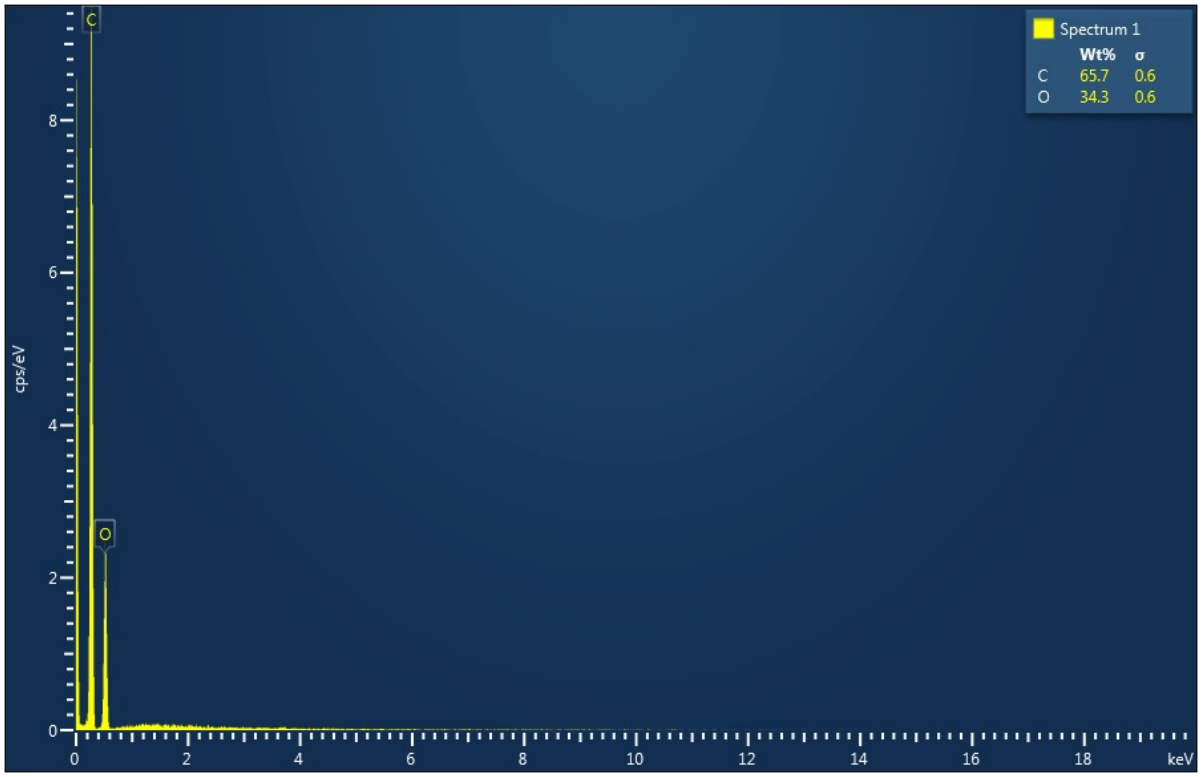






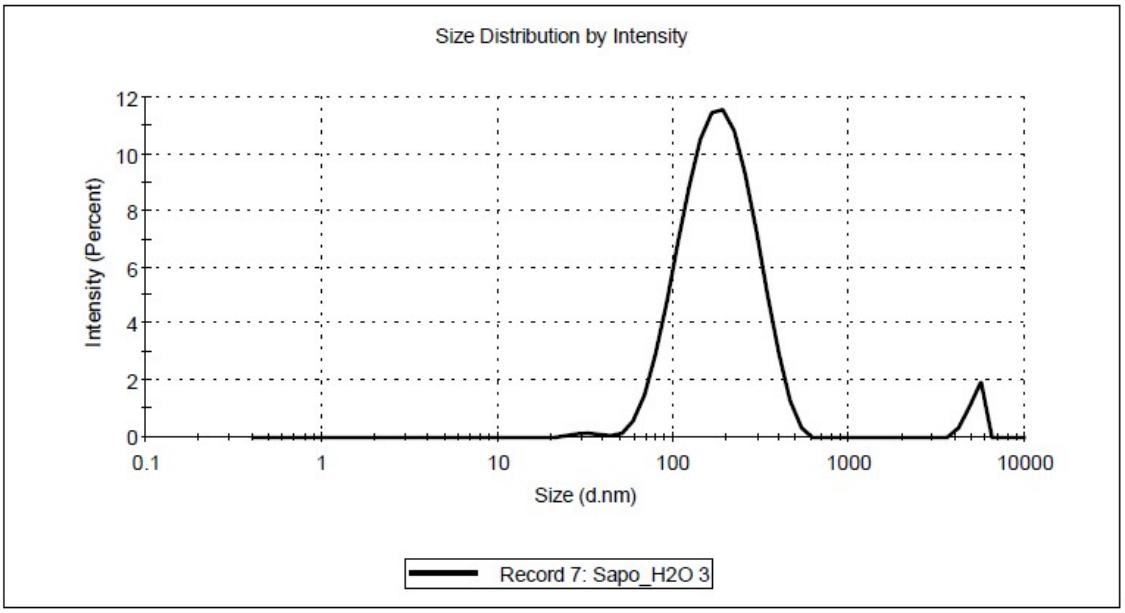


Energy Dispersive Spectroscopy (EDS) of Saponin in water



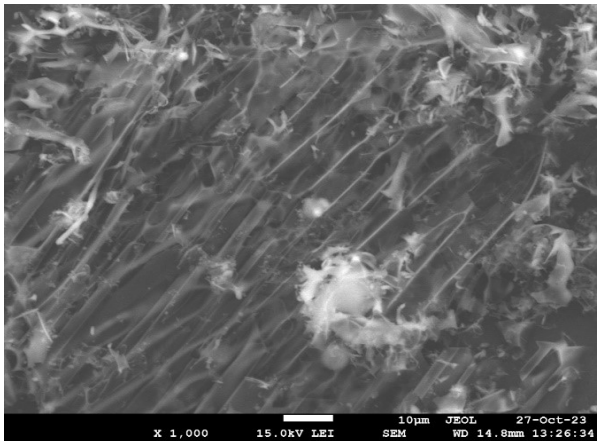
Dynamic Light Scattering (DLS) of Saponin in water

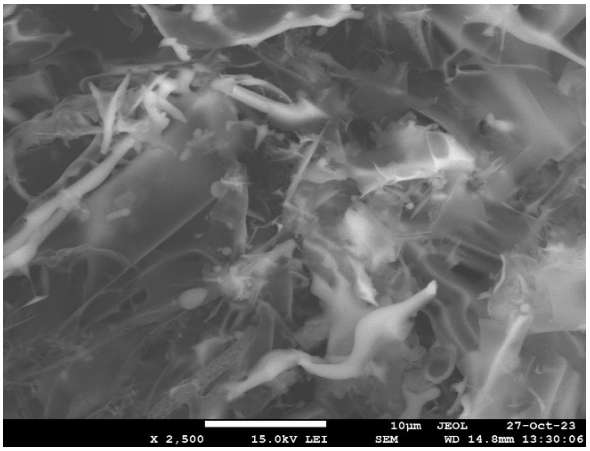
			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	168.5	Peak 1:	194.7	96.1	87.81
PdI:	0.346	Peak 2:	5174	3.4	488.8
Intercept:	0.952	Peak 3:	32.82	0.5	5.651
Result quality :	Good				

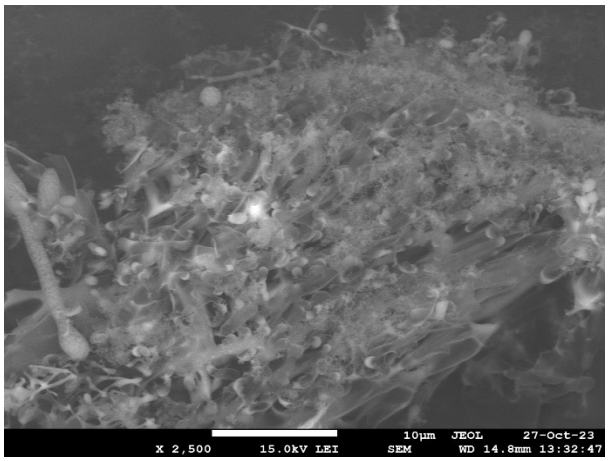


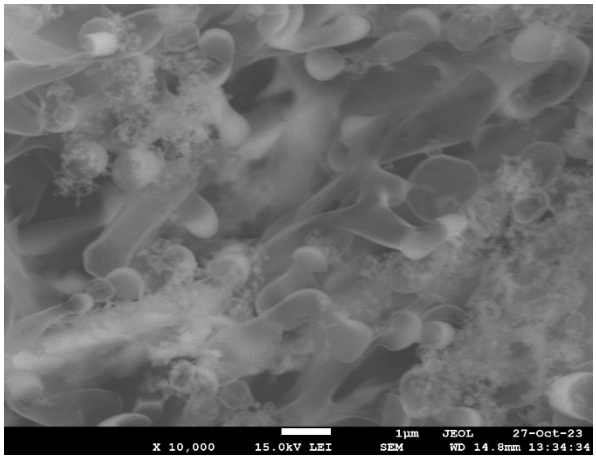
Field Emission Scanning Electron Microscopy (FE-SEM) of Saponin and $PdCl_2$(d*t*bpf) in water

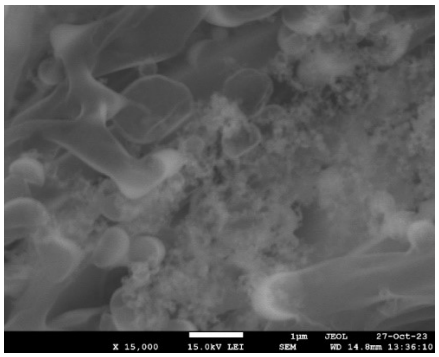
Sample preparation: 60 mg of Saponin and 33 mg of $PdCl_2$(d*t*bpf) were dissolved in 3 mL of DI water (Note: after the addition of Pd-catalyst, the solution became unclear brown color) and stirred for 5 minutes followed by lyophilization to get dry powder. This powder was used for FE-SEM, EDS, and DLS analysis.

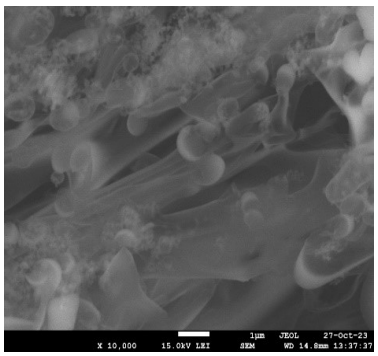


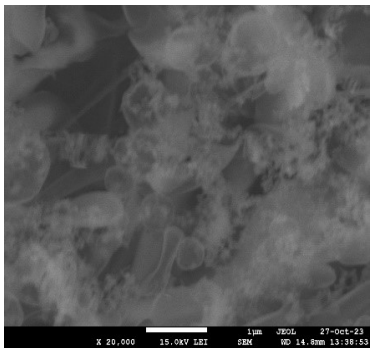




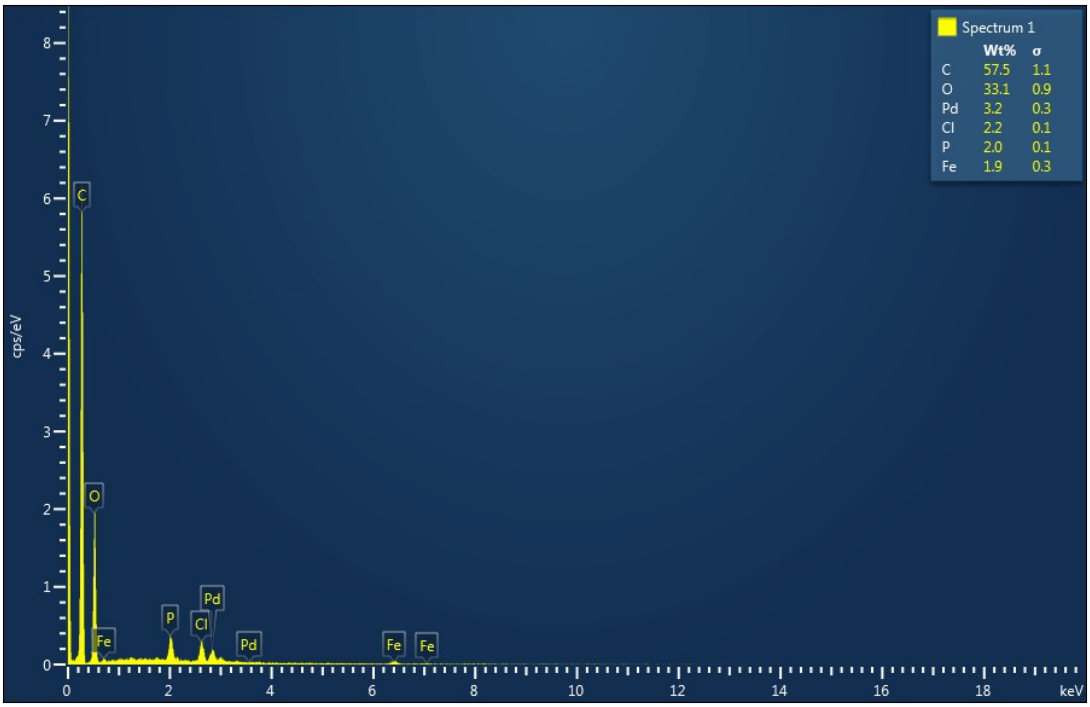






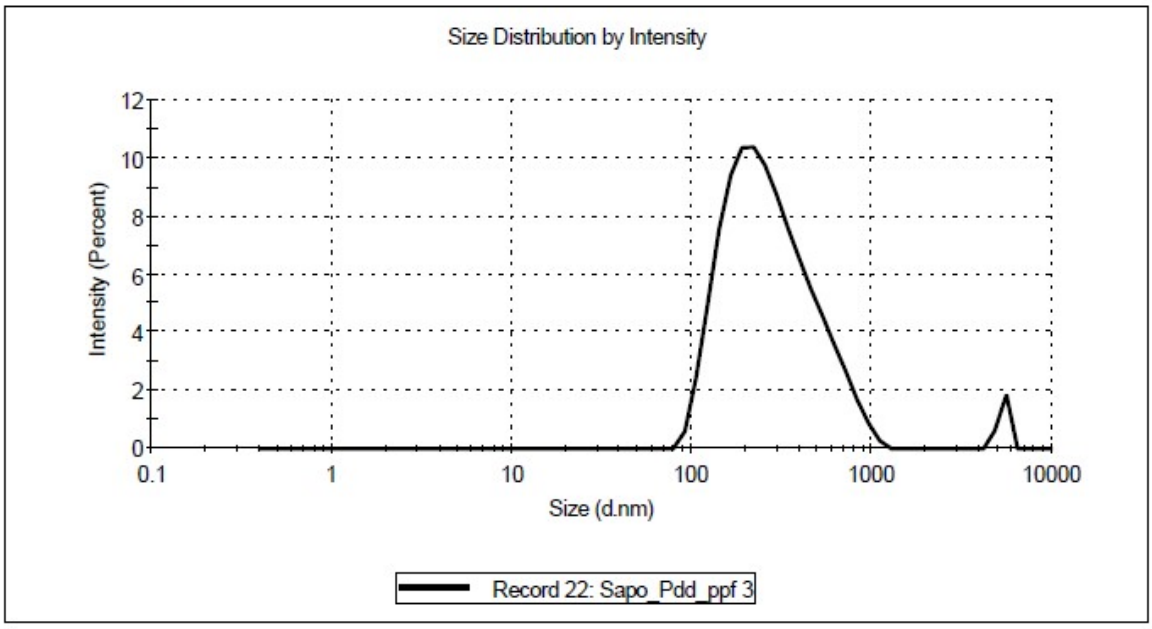


Energy Dispersive Spectroscopy (EDS) of Saponin and $PdCl_2$(d*t*bpf) in water



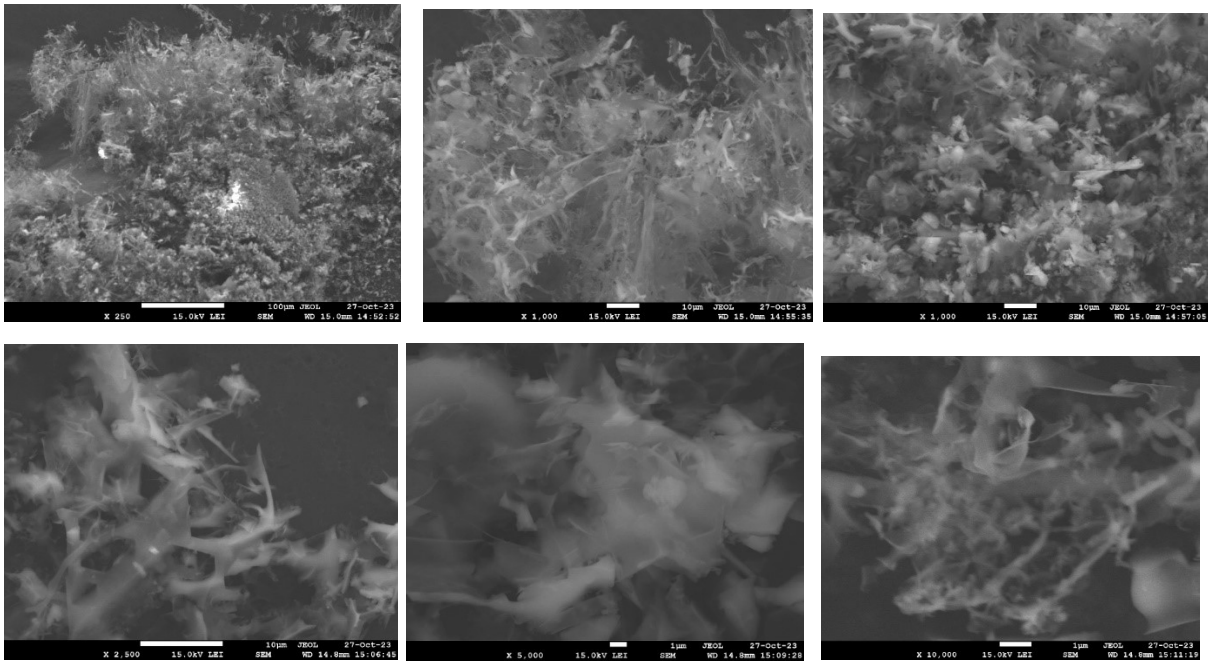
Dynamic Light Scattering (DLS) of Saponin and $PdCl_2$(d*t*bpf) in water

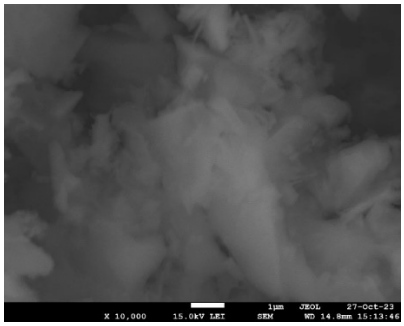
		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 264.6	Peak 1:	304.2	97.5	179.7
PdI: 0.368	Peak 2:	5369	2.5	328.9
Intercept: 0.973	Peak 3:	0.000	0.0	0.000
Result quality : Good				

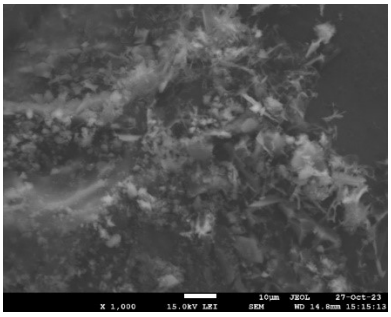


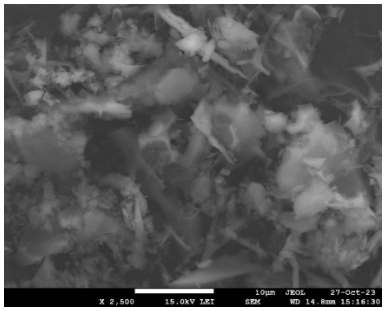
Field Emission Scanning Electron Microscopy (FE-SEM) of Saponin and XPhos-Pd-G2 in water

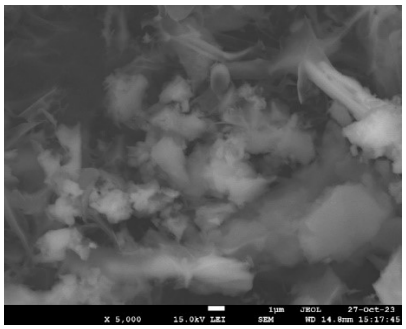
Sample preparation: 80 mg of Saponin and 39 mg of XPhos-Pd-G2 were dissolved in 3.0 mL of DI water and 1.0 mL of THF (Note: the mixture provided unclear solution) and stirred for 5 minutes followed by lyophilization to get dry powder. This powder was used for FE-SEM, EDS, and DLS analysis.

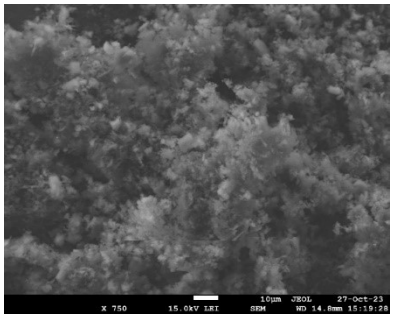


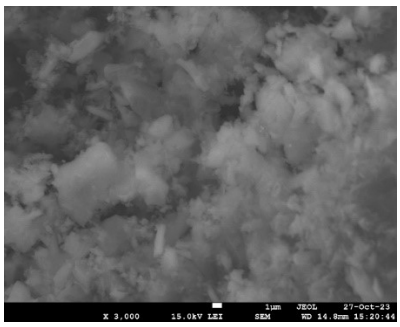




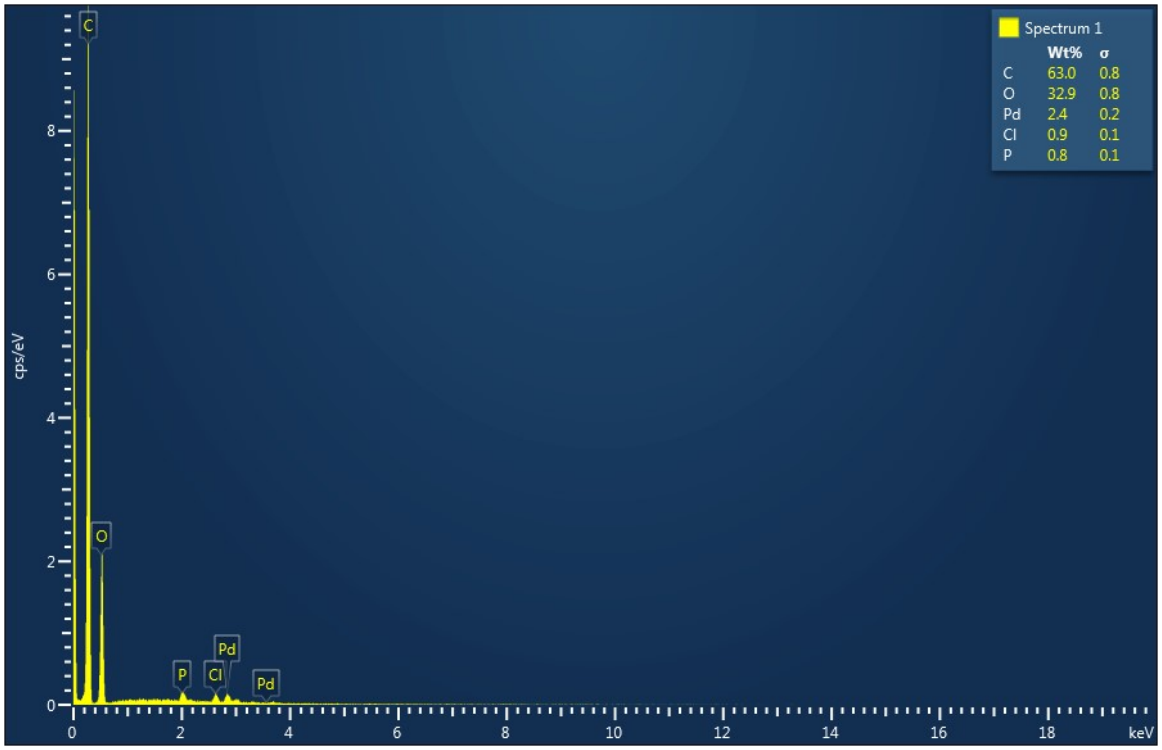








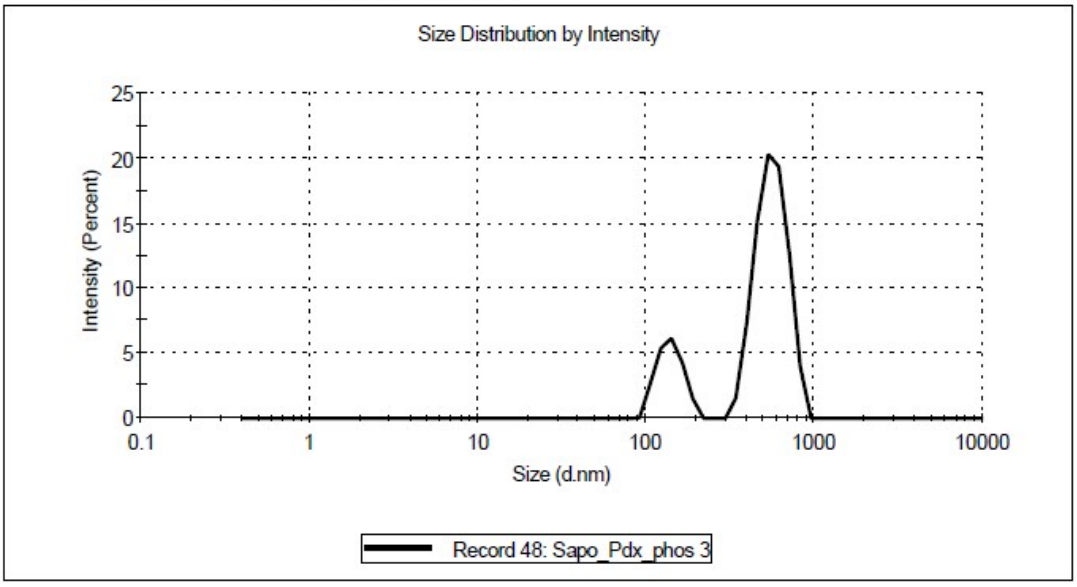
Energy Dispersive Spectroscopy (EDS) of Saponin and XPhos-Pd-G2 in water



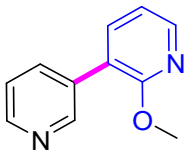
Dynamic Light Scattering (DLS) of Saponin and XPhos-Pd-G2 in water

			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	837.5	Peak 1:	564.6	80.0	115.6
PdI:	0.660	Peak 2:	140.3	20.0	23.64
Intercept:	0.933	Peak 3:	0.000	0.0	0.000

Result quality : Refer to quality report



8. Spectral data (^{1}H, ^{13}C, and ^{19}F-NMR) of SMC products (3a – 3u, 4a – 4h, 5a – 5k, 6a – 6g)



3a

2-methoxy-3,3'-bipyridine (3a)[1]

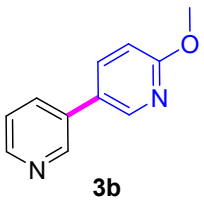
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 1.6 Hz, 1H), 8.58 (dd, *J* = 5.2 Hz, *J* = 1.6 Hz, 1H), 8.20 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1H), 7.90 (dt, *J* = 4.8 Hz, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 7.2 Hz, *J* = 2.0 Hz, 1H), 7.36-7.33 (m, 1H), 7.01 (dd, *J* = 7.2 Hz, *J* = 5.2 Hz, 1H), 3.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 149.7, 148.3, 146.6, 138.4, 136.5, 132.5, 123.0, 121.0, 117.2, 53.5.

Yield: 166 mg; 90 %

Physical appearance: High viscous oil.

Rf: 0.3 (10 % EtOAc in hexanes).



3b

6-methoxy-3,3'-bipyridine (3b)[2]

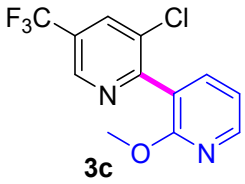
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 1.6 Hz, 1H), 8.60 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.38 – 7.29 (m, 1H), 6.86 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 4.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 148.6, 147.8, 145.1, 137.3, 133.8, 133.5, 126.8, 123.6, 111.2, 53.6.

Yield: 160 mg; 86 %

Physical appearance: High viscous oil.

Rf: 0.3 (10 % EtOAc in hexanes).



3c

3-chloro-2'-methoxy-5-(trifluoromethyl)-2,3'-bipyridine (3c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 2.0 Hz, 0.8 Hz, 1H), 8.69-8.68 (m, 1H), 8.05-8.03 (m, 2H), 6.86 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 4.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 148.2, 144.4 (dd, *J* = 79.0 Hz, *J* = 4.0 Hz), 139.6, 135.4 (q, *J* = 3.5 Hz), 130.0, 126.8 (d, *J* = 18.0 Hz), 126.2, 125.9 (q, *J* = 33.0 Hz), 122.6 (d, *J* = 271 Hz), 110.4, 53.7.

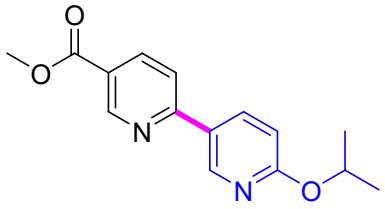
HRMS (ESI): *m/z* calculated for $C_{12}H_9ClF_3N_2O$: 289.0356; $[M+H]^+$ found: 289.0358.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.25

Yield: 205 mg; 72 %

Physical appearance: High viscous oil.

Rf: 0.3 (10 % EtOAc in hexanes).



3d

methyl 6'-isopropoxy-[2,3'-bipyridine]-5-carboxylate (3d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, *J* = 2.0 Hz, 1H), 8.80 (d, *J* = 2.0 Hz, 1H), 8.33 – 8.27 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.38 (m, 1H), 3.97 (s, 3H), 1.38 (d, *J* = 6.0 Hz, 6H).

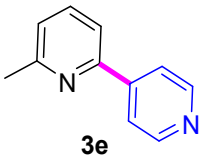
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 164.6, 158.7, 151.1, 146.4, 137.9, 137.5, 127.0, 123.9, 118.8, 111.7, 68.7, 52.4, 22.0.

HRMS (ESI): *m/z* calculated for $C_{15}H_{17}N_2O_3$: 273.1239; $[M+H]^+$ found: 273.1241.

Yield: 200 mg; 74 %

Physical appearance: High viscous oil.

Rf: 0.25 (10 % EtOAc in hexanes).



3e

6-methyl-2,4'-bipyridine (3e)[3]

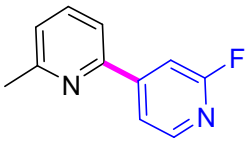
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 2H), 7.88 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 2.64 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.02, 154.0, 150.2, 146.7, 137.1, 123.3, 121.1, 117.9, 24.6.

Yield: 150 mg; 88 %

Physical appearance: High viscous oil.

Rf: 0.3 (85 % EtOAc in hexanes).



3f

2'-fluoro-6-methyl-2,4'-bipyridine (3f)[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.2 Hz, 1H), 7.77-7.75 (m, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 2.63 (s, 3H).

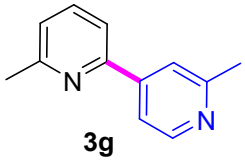
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (d, *J* = 236 Hz), 159.1, 152.6 (d, *J* = 3.7 Hz), 152.4 (d, *J* = 8.1 Hz), 148.0 (d, *J* = 15.0 Hz), 137.2, 123.9, 118.9 (d, *J* = 4.0 Hz), 118.0, 106.9 (d, *J* = 39.0 Hz), 24.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.08

Yield: 165 mg; 88 %

Physical appearance: High viscous oil.

Rf: 0.3 (10 % EtOAc in hexanes).



3g

2',6-dimethyl-2,4'-bipyridine (3g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.2 Hz, 1H), 7.77 (s, 1H), 7.69-7.64 (m, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.19-7.17 (m, 1H), 2.64 (s, 6H).

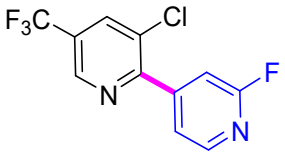
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.9, 154.3, 149.5, 147.1, 137.1, 123.2, 120.7, 118.3, 118.0, 24.6, 24.5.

HRMS (ESI): *m/z* calculated for $C_{12}H_{13}N_2$: 185.1079; $[M+H]^+$ found: 185.1102.

Yield: 168 mg; 92 %

Physical appearance: High viscous oil.

Rf: 0.3 (10 % EtOAc in hexanes).



3h

3-chloro-6'-fluoro-5-(trifluoromethyl)-2,3'-bipyridine (3h)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 1.2 Hz, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 1.2 Hz, 1H), 7.59 (dt, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.35 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d, *J* = 237.0 Hz), 155.9, 149.5 (d, *J* = 8.1 Hz), 147.9 (d, *J* = 15.1 Hz), 144.6 (q, *J* = 38.0 Hz), 135.8 (q, *J* = 36.0 Hz), 130.5, 127.7 (q, *J* = 34.0 Hz), 122.3 (q, *J* = 271 Hz), 121.5 (d, *J* = 4.3 Hz), 110.2 (d, *J* = 39.0 Hz).

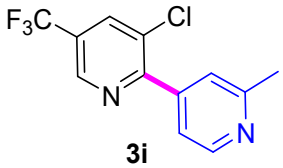
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.39, -66.71

HRMS (ESI): *m/z* calculated for $C_{11}H_6ClF_4N_2$: 277.0156; $[M+H]^+$ found: 277.0159.

Yield: 204 mg; 74 %

Physical appearance: High viscous oil.

Rf: 0.25 (10 % EtOAc in hexanes).



3i

3-chloro-6'-methyl-5-(trifluoromethyl)-2,3'-bipyridine (3i)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 - 8.86 (m, 1H), 8.65 (d, *J* = 5.2 Hz, 1H), 8.08 (d, *J* = 1.2 Hz, 1H), 7.51 (s, 1H), 7.47 (dd, *J* = 5.2 Hz, 1.2 Hz 1H), 2.66 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 157.6, 149.2, 144.6, 144.5 (q, *J* = 3.8 Hz), 135.5 (q, *J* = 3.5 Hz), 130.5, 127.1(q, *J* = 33.6 Hz), 123.1, 122.4 (q, *J* = 271 Hz), 120.7, 24.5.

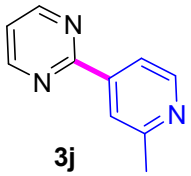
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.31

HRMS (ESI): *m/z* calculated for $C_{12}H_9ClF_3N_2$: 273.0406; [M+H]+ found: 273.0409.

Yield: 213 mg; 79 %

Physical appearance: High viscous oil.

Rf: 0.25 (10 % EtOAc in hexanes).



3j

2-(2-methylpyridin-4-yl)pyrimidine (3j)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 4.8 Hz, 2H), 8.66 (d, *J* = 5.2 Hz, 1H), 8.16 (d, *J* = 1.2 Hz, 1H), 8.09 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.31 (t, *J* = 4.8 Hz, 1H), 2.67 (s, 3H).

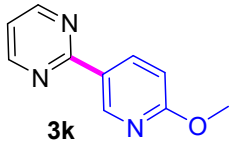
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 159.4, 157.5, 149.9, 145.1, 121.5, 120.5, 119.1, 24.6.

HRMS (ESI): *m/z* calculated for $C_{10}H_{10}N_3$: 172.0875; $[M+H]^+$ found: 172.0874.

Yield: 139 mg; 82 %

Physical appearance: High viscous oil.

Rf: 0.2 (10 % EtOAc in hexanes).



3k

5-(6-methoxypyridin-3-yl)pyrimidine (3k)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, *J* = 2.4 Hz, 1H), 8.76 (d, *J* = 4.8 Hz, 2H), 8.58 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.16 (t, *J* = 4.8 Hz, 1H), 6.83 (dd, *J* = 8.8 Hz, 0.4 Hz, 1H), 4.02 (s, 3H).

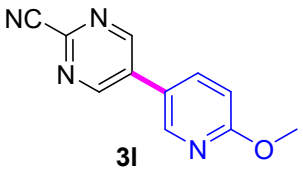
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 163.2, 157.2, 148.0, 138.2, 126.9, 118.9, 110.6, 53.8.

HRMS (ESI): *m/z* calculated for $C_{10}H_9N_3O$: 188.0824; $[M+H]^+$ found: 188.0822.

Yield: 165 mg; 88 %

Physical appearance: High viscous oil.

Rf: 0.2 (10 % EtOAc in hexanes).



3l

5-(6-methoxypyridin-3-yl)pyrimidine-2-carbonitrile (3l)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 2H), 8.45 (d, *J* = 2.8 Hz, 1H), 7.83 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.02 (s, 3H).

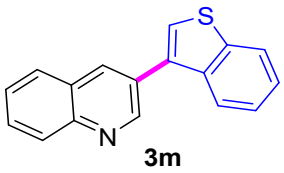
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 155.0, 145.8, 143.4, 136.9, 133.7, 123.6, 115.7, 112,3, 54.0.

HRMS (ESI): *m/z* calculated for $C_{11}H_9N_4O$: 213.0776; [M+H]+ found: 213.0776.

Yield: 143 mg; 68 %

Physical appearance: High viscous oil.

Rf: 0.15 (10 % EtOAc in hexanes).



3m

3-(benzo[b]thiophen-3-yl)quinoline (3m)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 2.0 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.98 – 7.88 (m, 3H), 7.78 – 7.74 (m, 1H), 7.63 – 7.60 (m, 2H), 7.57 – 7.41 (m, 2H).

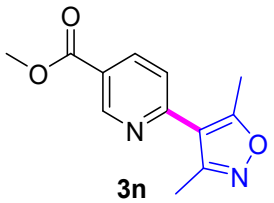
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 147.4, 140.7, 137.7, 34.8, 134.4, 129.6, 129.4, 128.0, 127.9, 127.7, 127.2, 125.1, 124.86, 124.82, 123.1, 122.4.

HRMS (ESI): *m/z* calculated for $C_{17}H_{12}NS$: 262.069; [M+H]+ found: 262.0693.

Yield: 199 mg; 76 %

Physical appearance: off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



3n

methyl 6-(3,5-dimethylisoxazol-4-yl)nicotinate (3n)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.33 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H), 7.42 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H), 3.98 (s, 3H), 2.63 (s, 3H), 2.47 (s, 3H).

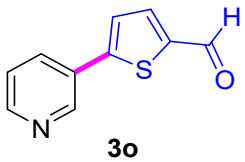
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 165.6, 158.6, 154.7, 151.0, 137.6, 123.7, 121.8, 115.5, 52.4, 12.8, 11.8.

HRMS (ESI): *m/z* calculated for $C_{12}H_{13}N_2O_3$: 233.0926; $[M+H]^+$ found: 233.0926.

Yield: 180 mg; 77 %

Physical appearance: off-white solid.

Rf: 0.25 (10 % EtOAc in hexanes).



3o

5-(pyridin-3-yl) thiophene-2-carbaldehyde (3o)[5]

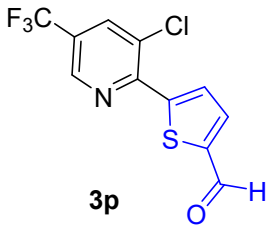
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.94 (d, *J* = 1.6 Hz, 1H), 8.62 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 7.95-7.92 (m, 1H), 7.79 (d, *J* = 4.0 Hz, 1H), 7.47 (d, *J* = 4.0 Hz, 1H), 7.40-7.36 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 150.2, 149.9, 147.2, 143.6, 137.2, 133.6, 129.1, 125.1, 123.8.

Yield: 156 mg; 84 %

Physical appearance: off-white solid.

Rf: 0.25 (10 % EtOAc in hexanes).



3p

5-(3-chloro-5-(trifluoromethyl)pyridine-2-yl)thiophene-2-carbaldehyde (3p)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.79 (d, *J* = 0.8 Hz, 1H), 8.25 (d, *J* = 4.0 Hz, 1H), 8.04 (d, *J* = 0.8 Hz, 1H), 7.80 (d, *J* = 4.0 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 151.1, 149.0, 145.9, 144.2 (q, *J* = 8.0 Hz), 136.3 (q, *J* = 7.0 Hz), 135.9, 130.8, 128.7, 126.3(q, *J* = 68.0 Hz), 122.4 (q, *J* = 542.0 Hz), 121.0**.**

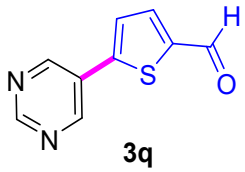
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.31.

HRMS (ESI): *m/z* calculated for $C_{11}H_6ClF_3NOS$: 291.9811; $[M+H]^+$ found: 291.9815.

Yield: 206 mg; 72 %

Physical appearance: Off-white semi-solid.

Rf: 0.2 (10 % EtOAc in hexanes).



3q

5-(pyrimidine-5-yl)thiophene-2-carbaldehyde (3q)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.23 (s, 1H), 9.03 (s, 2H), 7.83 (d, *J* = 4.0 Hz, 1H), 7.52 (d, *J* = 4.0 Hz, 1H).

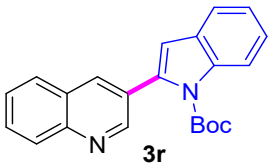
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 153.9, 149.2, 140.6, 135.9, 132.2, 122.8, 121.3.

HRMS (ESI): *m/z* calculated for $C_9H_7N_2OS$: 191.0279; [M+H]+ found: 191.0265.

Yield: 142 mg; 75 %

Physical appearance: Off-white solid.

Rf: 0.2 (10 % EtOAc in hexanes).



3r

tert-butyl 2-(quinolin-3-yl)-1H-indole-1-carboxylate (3r)[6]

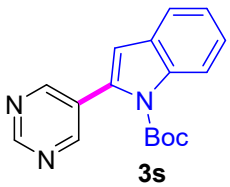
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.63 (m, 2H), 7.40 (m, 1H), 7.39 (m, 1H), 7.29 (m, 1H), 6.72 (m, 1H), 1.30 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 150.0, 146.9, 137.5, 136.9, 134.1, 129.6, 129.3, 129.1, 128.4, 127.8, 127.4, 127.1, 125.0, 123.3, 120.7, 115.7, 111.8, 84.2, 27.7.

Yield: 286 mg; 84 %

Physical appearance: White solid.

Rf: 0.2 (10 % EtOAc in hexanes).



3s

tert-butyl 2-(pyrimidin-5-yl)-1H-indole-1-carboxylate (3s)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.81 (s, 2H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.32 – 7.28 (m, 1H), 6.69 (s, 1H), 1.42 (s, 9H).

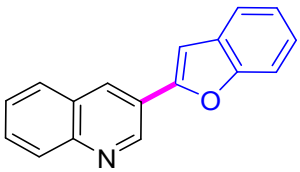
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 156.0, 149.7, 137.6, 132.9, 129.4, 128.8, 125.5, 123.5, 120.9, 115.8, 112.5, 84.7, 27.8.

HRMS (ESI): *m/z* calculated for $C_{17}H_{18}N_3O_2$: 296.1399; $[M+H]^+$ found: 296.1401.

Yield: 210 mg; 72 %

Physical appearance: High viscous oil.

Rf: 0.2 (10 % EtOAc in hexanes).



3t

3-(benzofuran-2-yl)quinoline (3t)[7]

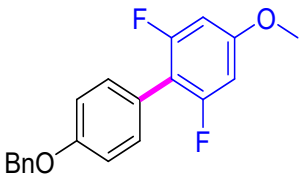
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, *J* = 2.4 Hz, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.88 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.72 – 7.69 (m, 1H), 7.65 – 7.61 (m, 1H), 7.57 – 7.47 (m, 2H), 7.35 – 7.25 (m, 2H), 7.24 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 153.2, 147.6, 147.5, 130.7, 129.8, 129.4, 128.9, 128.2, 127.7, 127.4, 125.0, 123.7, 123.3, 121.3, 111.3, 103.0,

Yield: 190 mg; 78 %

Physical appearance: Off-white solid.

Rf: 0.2 (20 % EtOAc in hexanes).



3u

4'-(benzyloxy)-2,6-difluoro-4-methoxy-1,1'-biphenyl (3u)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 7H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 5.10 (s, 2H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8 (d, *J* = 10.0 Hz), 158.5 (t, *J* = 14.1 Hz), 158.4, 157.3, 135.8, 130.4, 127.5, 126.9, 126.4, 120.6, 113.5, 109.5 (d, *J* = 19.4 Hz), 97.0 (d, *J* = 30.1 Hz), 97.0 (d, *J* = 11.9 Hz), 68.9, 54.7.

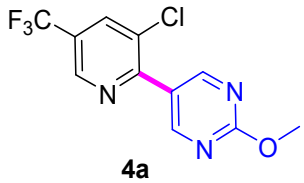
^{19}F NMR (376 MHz, $CDCl_3$) δ -113.79

HRMS (ESI): *m/z* calculated for $C_{20}H_{17}F_2O_2$: 327.1197; $[M+H]^+$ found: 327.1206.

Yield: 282 mg; 86 %

Physical appearance: off-white solid.

Rf: 0.2 (20 % EtOAc in hexanes).



4a

5-(3-chloro-5-(trifluoromethyl)pyridine-2-yl)-2-methoxy pyrimidine (4a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 2H), 8.87 (d, *J* = 1.6 Hz, 1H), 8.07 (d, *J* = 1.6 Hz), 4.11 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 160.0, 154.3, 144.7 (q, *J* = 8.0 Hz), 135.5 (q, *J* = 7.0 Hz), 130.2, 126.5 (q, *J* = 34.0 Hz), 124.7, 123.8, 55.4.

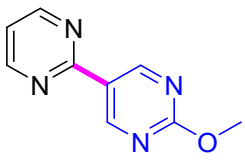
HRMS (ESI): *m/z* calculated for $C_{11}H_8ClF_3N_3O$: 290.0308; $[M+H]^+$ found: 290.0311.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.28

Yield: 206 mg; 72 %

Physical appearance: High viscous oil.

Rf: 0.3 (20 % EtOAc in hexanes).



4b

2'-methoxy-2,5'-bipyrimidine (4b)[8]

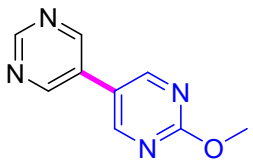
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 2H), 8.80 (d, *J* = 4.8 Hz, 2H), 7.24 (t, *J* = 4.8 Hz, 1H), 4.11 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 161.3, 159.6, 157.4, 125.2, 119.6, 55.3.

Yield: 144 mg; 77 %

Physical appearance: Off-white solid.

Rf: 0.3 (15 % EtOAc in hexanes).



4c

2-methoxy-5,5'-bipyrimidine (4c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.93 (s, 2H), 8.76 (s, 2H), 4.10 (s, 3H).

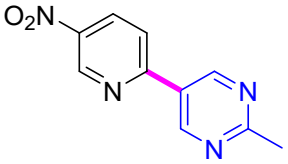
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.3, 157.4, 154.4, 128.6, 122.0, 55.3.

HRMS (ESI): *m/z* calculated for $C_9H_9N_4O$: 189.0776; $[M+H]^+$ found: 189.0771.

Yield: 152 mg; 81 %

Physical appearance: Semi-solid.

Rf: 0.3 (15 % EtOAc in hexanes).



4d

2-methyl-5-(5-nitropyridin-2-yl)pyrimidine (4d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 2.8 Hz, 1H), 9.33 (s, 2H), 8.62 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 2.85 (s, 3H).

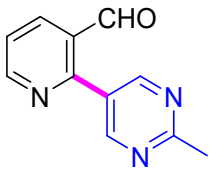
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 157.6, 155.8, 145.7, 143.5, 132.4, 127.4, 119.9, 26.1.

HRMS (ESI): *m/z* calculated for $C_{10}H_9N_4O_2$: 217.0726; $[M+H]^+$ found: 217.0726.

Yield: 157 mg; 74 %

Physical appearance: High viscous oil.

Rf: 0.3 (20 % EtOAc in hexanes).



4e

2-(2-methylpyrimidin-5-yl)nicotinaldehyde (4e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.94 (dd, *J* = 4.8 Hz, 1.6 H, 1H), 8.90 (s, 2H), / integrate in spectra/ Ravi) 8.37 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.55 (dd, *J* = 7.6 Hz, 0.8 Hz, 1H), 2.86 (s, 3H).

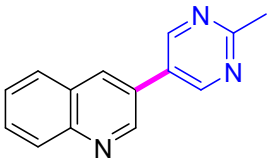
^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 168.9, 157.6, 155.9, 154.1, 137.1, 129.9, 127.9, 123.6, 26.0.

HRMS (ESI): *m/z* calculated for $C_{11}H_{10}N_3O$: 200.0824; $[M+H]^+$ found: 200.0823.

Yield: 125 mg; 63 %

Physical appearance: High viscous oil.

Rf: 0.3 (20 % EtOAc in hexanes).



4f

3-(2-methylpyrimidin-5-yl)quinoline (4f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 2.0 Hz, 1H), 8.99 (s, 2H), 8.34 (d, *J* = 2.0 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.79 (m, 1H), 7.64 (m, 1H), 2.85 (s, 3H).

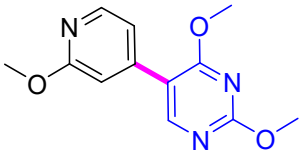
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 155.2, 148.6, 147.9, 133.6, 130.4, 129.4, 128.4, 128.0, 127.7, 127.6, 127.5, 25.8.

HRMS (ESI): *m/z* calculated for $C_{14}H_{11}N_3$: 222.1031; $[M+H]^+$ found: 222.1033.

Yield: 179 mg; 80 %

Physical appearance: Light brown color solid.

Rf: 0.3 (20 % EtOAc in hexanes).



4g

2,4-dimethoxy-5-(2-methoxypyridin-4-yl)pyrimidine (4g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 7.04 (dd, *J* = 5.6 Hz, 1.6 Hz, 1H), 6.92 (s, 1H), 4.05 (s, 6H), 3.98 (s, 3H).

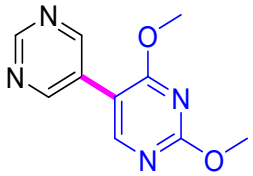
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 165.2, 164.5, 157.9, 146.9, 143.8, 116.6, 113.6, 110.2, 55.1, 54.3, 53.5.

HRMS (ESI): *m/z* calculated for $C_{12}H_{14}N_3O_3$: 248.1035; $[M+H]^+$ found: 248.1038

Yield: 185 mg; 75 %

Physical appearance: Light brown color solid.

Rf: 0.3 (20 % EtOAc in hexanes).



4h

2,4-dimethoxy-5,5'-bipyrimidine (4h)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.91 (s, 2H), 8.33 (s, 1H), 4.07 (s, 6H).

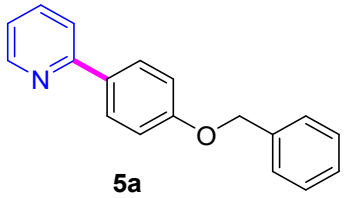
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 165.6, 157.6, 157.5, 156.0, 127.6, 109.6, 55.2, 54.5

HRMS (ESI): *m/z* calculated for $C_{10}H_{11}N_4O_2$: 219.0882; $[M+H]^+$ found: 219.0885.

Yield: 151 mg; 70 %

Physical appearance: off-white solid.

Rf: 0.3 (20 % EtOAc in hexanes).



5a

2-(4-(benzyloxy)phenyl)pyridine (5a)[9]

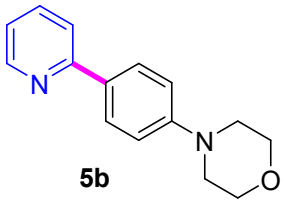
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.64 (m, 1H), 7.96 – 9.93 (m, 2H), 7.74 – 7.65 (m, 2H), 7.47 – 7.45 (m, 2H), 7.42 – 7.38 (m, 2H), 7.35 – 7.31 (m, 1H), 7.19 – 7.16 (m, 1H), 7.07 (d, *J* = 9.2 Hz, 2H), 5.14 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.0, 148.5, 135.8, 135.6, 131.2, 127.6, 127.1, 127.0, 126.5, 120.4, 118.8, 114.0, 69.0.

Yield: 185 mg; 71 %

Physical appearance: off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



5b

4-(4-(pyridine-2-yl)phenyl)morpholine (5b)[10]

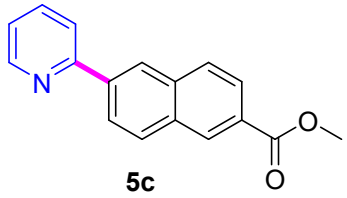
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.09 – 7.06 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.81 (t, *J* = 5.2 Hz, 4H), 3.17 (t, *J* = 5.2 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 150.7, 148.5, 135.6, 129.6, 126.7, 120.2, 118.5, 114.2, 65.8, 47.7.

Yield: 148 mg; 62 %

Physical appearance: off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



5c

methyl 6-(pyridin-2-yl)-2-naphthoate (5c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.69 (m, 1H), 8.57 (s, 1H), 8.45 (s, 1H), 8.14 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 8.07 – 7.91 (m, 2H), 7.98 – 7.91 (m, 1H), 7.84 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.25 – 7.22 (m, 1H), 3.93 (s, 3H).

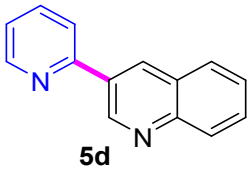
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 156.8, 149.9, 138.9, 136.9, 135.6, 132.6, 130.8,129.9, 128.9, 127.9, 126.1, 125.7, 125.4, 122.6, 121.0, 52.3.

HRMS (ESI): *m/z* calculated for $C_{17}H_{14}NO_2$: 264.1025; $[M+H]^+$ found: 264.1028.

Yield: 173 mg; 67 %

Physical appearance: Off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



5d

3-(pyridin-2-yl)quinoline (5d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J* = 2.0 Hz, 1H), 8.79 – 8.78 (m, 2H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.85 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.76 (td, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.60 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.36 – 7.34 (m, 1H).

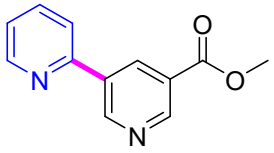
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 150.2, 149.3, 148.2, 137.1, 133.9, 131.9, 130.0, 129.2, 128.5, 127.9, 127.0, 122.8, 120.8.

HRMS (ESI): *m/z* calculated for $C_{14}H_{11}N_2$: 207.0922; $[M+H]^+$ found: 207.0922.

Yield: 124 mg; 60 %

Physical appearance: Semi-solid.

Rf: 0.3 (10 % EtOAc in hexanes).



5e

methyl [2,3'-bipyridine]-5'-carboxylate (5e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 9.27 (s, 1H), 8.90 (s, 1H), 8.76 (d, *J* = 4.4 Hz, 1H), 7.86 – 7.81 (m, 2H), 7.36 – 7.33 (m, 1H), 4.00 (s, 3H).

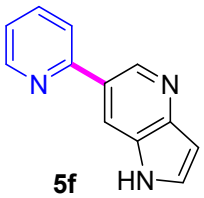
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 153.7, 151.8, 150.8, 150.2, 137.2, 135.2, 134.7, 126.1, 123.3, 120.8, 52.5.

HRMS (ESI): *m/z* calculated for $C_{12}H_{11}N_2O_2$: 215.0821; $[M+H]^+$ found: 215.0819.

Yield: 118 mg; 55 %

Physical appearance: off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



5f

6-(pyridin-2-yl)-1H-pyrrolo[3,2-b]pyridine (5f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (brs, 1H), 9.06 (brs, 1H), 8.69 – 8.67 (m, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.74 – 7.73 (m, 1H), 7.36 – 7.32 (m, 1H), 6.60 (s, 1H).

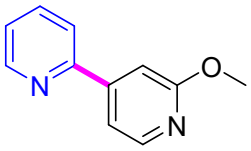
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 150.1, 147.3, 141.9, 137.7, 131.3, 129.4, 127.9, 122.6, 120.6, 116.6, 102.2.

HRMS (ESI): *m/z* calculated for $C_{12}H_{10}N_3$: 196.0875; $[M+H]^+$ found: 196.0873.

Yield: 114 mg; 59 %

Physical appearance: off-white Solid

Rf: 0.3 (10 % EtOAc in hexanes).



5g

2'-methoxy-2,4'-bipyridine

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.0 Hz, 1H), 8.26 (d, *J* = 5.2 H, 1H), 7.82 – 7.74 (m, 2H), 7.49 (dd, *J* = 5.2 Hz, 1.6 Hz, 1H), 7.34 – 7.31 (m, 2H), 3.99 (s, 3H).

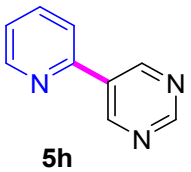
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 153.7, 148.9, 148.3, 146.4, 135.9, 122.7, 119.9, 113.6, 107.2, 52.6.

HRMS (ESI): *m/z* calculated for $C_{11}H_{11}N_2O$: 187.0871; [M+H]+ found: 187.0874.

Yield: 116 mg; 64 %

Physical appearance: Brown solid.

Rf: 0.3 (20 % EtOAc in hexanes).



5h

5-(pyridin-2-yl)pyrimidine[11]

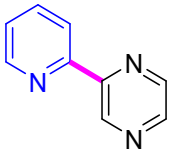
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 2H), 9.27 (s, 1H), 8.75 (m, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.01 – 7.97 (m, 1H), 7.53 – 7.48 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 155.3, 151.7, 150.6, 138.1, 132.2, 124.5, 121.5.

Yield: 102 mg; 65 %

Physical appearance: Colorless gummy.

Rf: 0.3 (10 % EtOAc in hexanes).



5i

2-(pyridin-2-yl)pyrazine[12]

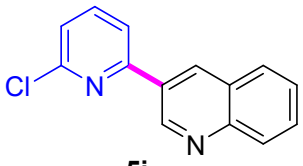
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 1.2 Hz, 1H), 8.73 (d, *J* = 4.4 Hz, 1H), 8.63 – 8.60 (m, 2H), 8.36 (d, *J* = 8.0 Hz, 1H), 7.88 -7.83 (m, 1H), 7.39 – 7.36 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 151.1, 149.5, 144.5, 143.6, 143.4, 137.1, 124.5, 121.5.

Yield: 95 mg; 62 %

Physical appearance: Off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



5j

3-(6-chloropyridin-2-yl)quinoline[13]

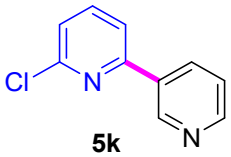
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, *J* = 2.0 Hz, 1H), 8.83 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.85 – 7.62 (m, 3H), 7.62 – 7.60 (m, 1H), 7.37 – 7.35 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 151.9, 148.8, 148.4, 139.6, 134.4, 130.4, 130.3, 129.3, 128.7, 127.7, 127.2, 123.4, 119.0.

Yield: 194 mg; 82 %

Physical appearance: Off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



5k

6-chloro-2,3'-bipyridine[14]

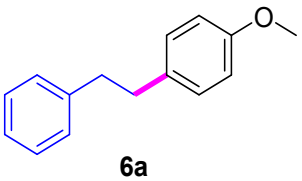
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.67 (d, *J* = 1.6 Hz, 1H), 8.36 – 8.33 (m, 1H), 7.79 – 7.68 (m, 2H), 7.42 – 7.40 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 151.8, 150.5, 148.1, 139.6, 143.6, 133.4, 123.7, 123.4, 118.8.

Yield: 138 mg; 74 %

Physical appearance: Off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



6a

10.1-methoxy-4-phenethylbenzene (5g)[15]

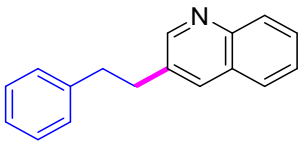
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.19-7.15 (m, 3H), 7.08 (d, *J* = 6.4 Hz, 2H), 6.81 (d, *J* = 6.4 Hz, 2H), 3.77 (s, 3H), 2.87-2.86 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 141.9, 133.9, 129.4, 128.5, 128.3, 125.9, 113.8, 55.2, 38.2, 37.0.

Yield: 164 mg; 78 %

Physical appearance: Off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



6b

3-phenethylquinoline (6b)[16]

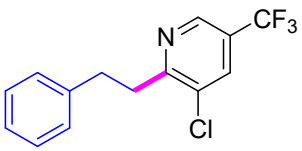
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.0 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.72 – 7.70 (m, 1H), 7.66 – 7.61 (m, 1H), 7.49 (m, 1H), 7.29 – 7.25 (m, 2H), 7.23- 7.19 (m, 3H), 3.10 -2.97 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 146.9, 140.8, 134.5, 134.2, 129.2, 128.7, 128.5, 128.5, 128.1, 127.4, 126.6, 126.3, 37.5, 35.1.

Yield: 195 mg; 84 %

Physical appearance: colorless gum.

Rf: 0.3 (10 % EtOAc in hexanes).



6c

3-chloro-2-phenethyl-5-(trifluoromethyl)pyridine

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 1.6 Hz, 1H), 7.88 (d, *J* = 1.6 Hz, 1H), 7.32 – 7.22 (m, 5H), 3.30 (t, *J* = 8.0 Hz, 2H), 3.08 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 143.9, 143.9 (q, *J* = 8.0 Hz), 140.9, 133.8 (q, *J* = 7.0 Hz), 131.3, 128.4 (d, *J* = 7.0 Hz), 126.8, 125.6 (q, *J* = 66.0 Hz), 122.8 (d, *J* = 272.0 Hz), 37.4, 33.8.

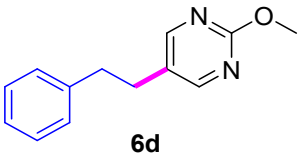
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.16

HRMS (ESI): *m/z* calculated for $C_{14}H_{11}ClF_3N$: 286.061; $[M+H]^+$ found: 286.0612.

Yield: 154 mg; 54 %

Physical appearance: Off-white solid.

Rf: 0.3 (10 % EtOAc in hexanes).



6d

2-methoxy-5-phenethylpyrimidine (6d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 2H), 7.28 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 2H), 3.97 (s, 3H), 2.89 (t, *J* = 5.6 Hz, 2H), 2.84 (t, *J* = 5.6 Hz, 2H).

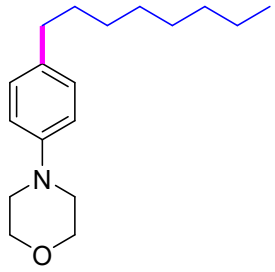
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 158.9, 140.1, 128.6, 128.5, 127.3, 126.4, 54.8, 37.3, 31.2.

HRMS (ESI): *m/z* calculated for $C_{13}H_{14}N_2O$: 215.1184; $[M+H]^+$ found: 215.1192.

Yield: 145 mg; 68 %

Physical appearance: Off-white solid

Rf: 0.3 (10 % EtOAc in hexanes).



6e

4-(4-octylphenyl)morpholine

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3,86 (t, *J* = 5.6 Hz, 4H), 3.12 (t, *J* = 5.6 Hz, 4H), 2,52 (t, *J* = 7.2 Hz, 2H), 1.60 – 1.55 (m, 2H), 1.29 – 1.21 (m, 10H), 0.88 (t, *J* = 4.4 Hz, 3H).

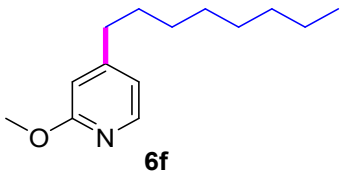
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 134.8, 129.1, 115.89, 67.0, 49.8, 35.0, 31.9, 31.7, 29.5, 29.35, 29.31, 22.7, 14.1.

HRMS (ESI): *m/z* calculated for $C_{18}H_{30}NO$: 276.2327; $[M+H]^+$ found: 276.2332.

Yield: 170 mg; 62 %

Physical appearance: High viscous oil Naveen.

Rf: 0.4 (10 % EtOAc in hexanes).



6f

2-methoxy-4-octylpyridine

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 5.2 Hz, 1H), 6.70 (dd, *J* = 5.2 Hz, 1.6 Hz, 1H), 6.55 (d, *J* = 1.6 Hz, 1H), 3.92 (s, 3H), 2,54 (t, *J* = 7.6 Hz, 2H), 1.63 – 1.55 (m, 2H), 1.29 – 1.24 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H).

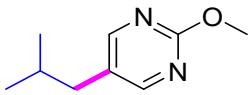
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 154.7, 146.4, 117.6, 110.2, 53.3, 35.2, 31.8, 30.2, 29.4, 29.2, 29.1, 22.6, 14.1.

HRMS (ESI): *m/z* calculated for $C_{14}H_{24}NO$: 222.1858; $[M+H]^+$ found: 222.1871.

Yield: 120 mg; 54 %

Physical appearance: colorless oil.

Rf: 0.4 (5 % EtOAc in hexanes).



6g

5-isobutyl-2-methoxy pyrimidine (6g)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 2H), 3.99 (s, 3H), 2.40 (d, *J* = 7.2 Hz, 2H), 1.83 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 159.3, 127.2, 54.7, 38.5, 29.8, 21.9.

HRMS (ESI): *m/z* calculated for $C_9H_{15}N_2O$: 167.1184; $[M+H]^+$ found: 167.1185.

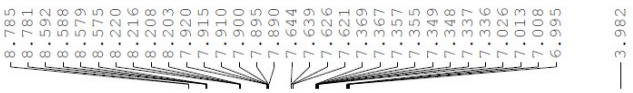
Yield: 75 mg; 45 %

Physical appearance: High viscous oil.

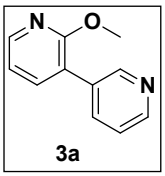
Rf: 0.3 (5 % EtOAc in hexanes).

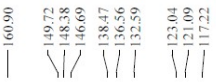
9. Scanned copy of spectra's (^{1}H, ^{13}C, and ^{19}F-NMR) of SMC products (3a – 3u, 4a – 4h, 5a – 5i, 6a – 6g)

^{1}H and ^{13}C NMR of Compound 3a

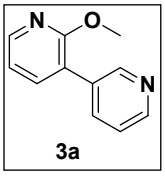


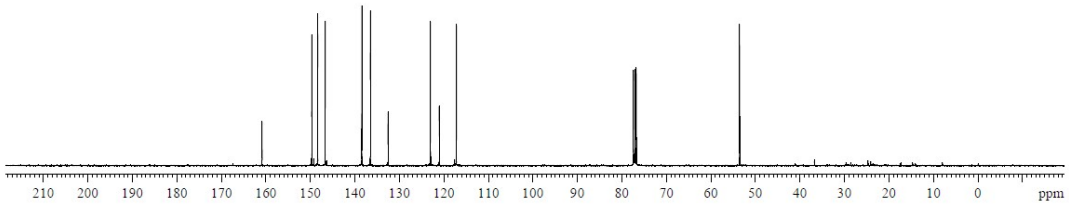
^{1}H NMR in $CDCl_3$ 400 MHz 3a



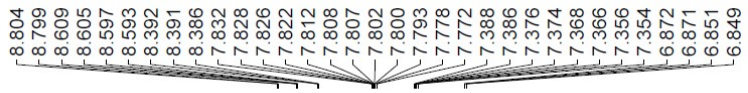


^{13}C NMR in $CDCl_3$ 100 MHz 3a

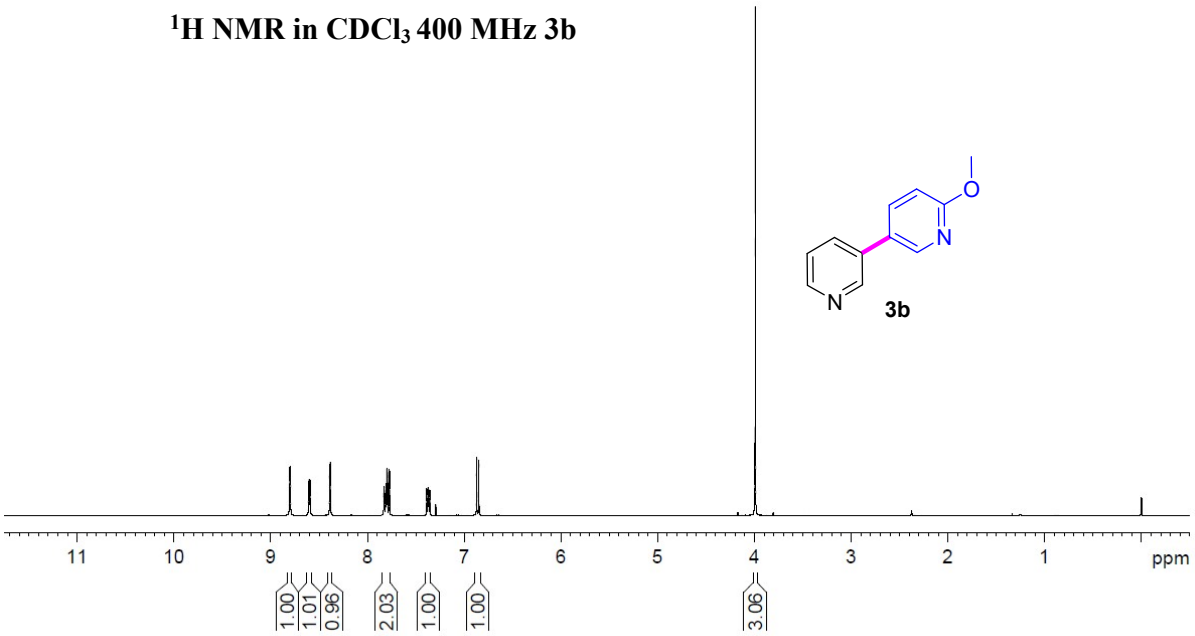




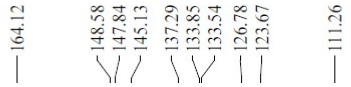
^{1}H and ^{13}C NMR of Compound 3b



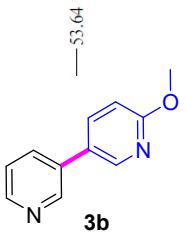
^{1}H NMR in $CDCl_3$ 400 MHz 3b



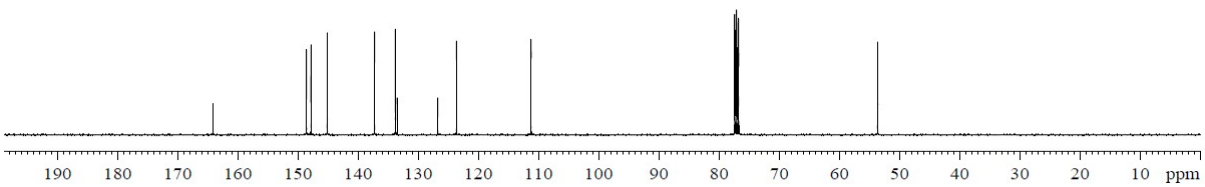
3b



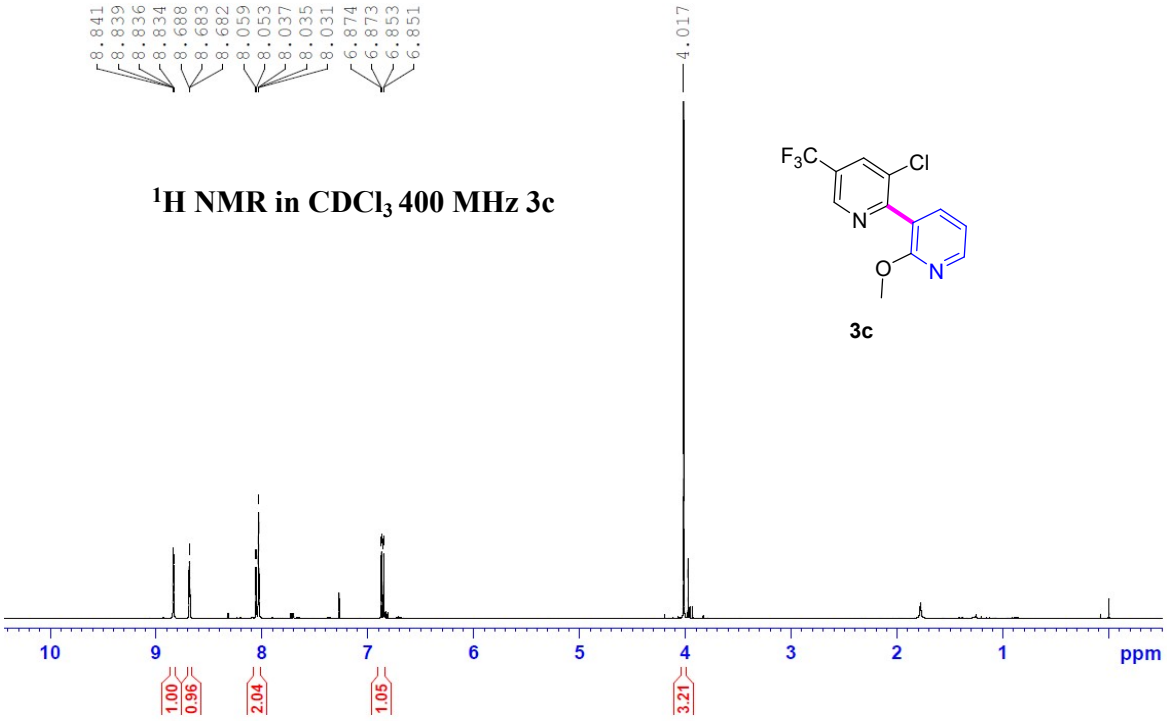
^{13}C NMR in $CDCl_3$ 100 MHz 3b



3b

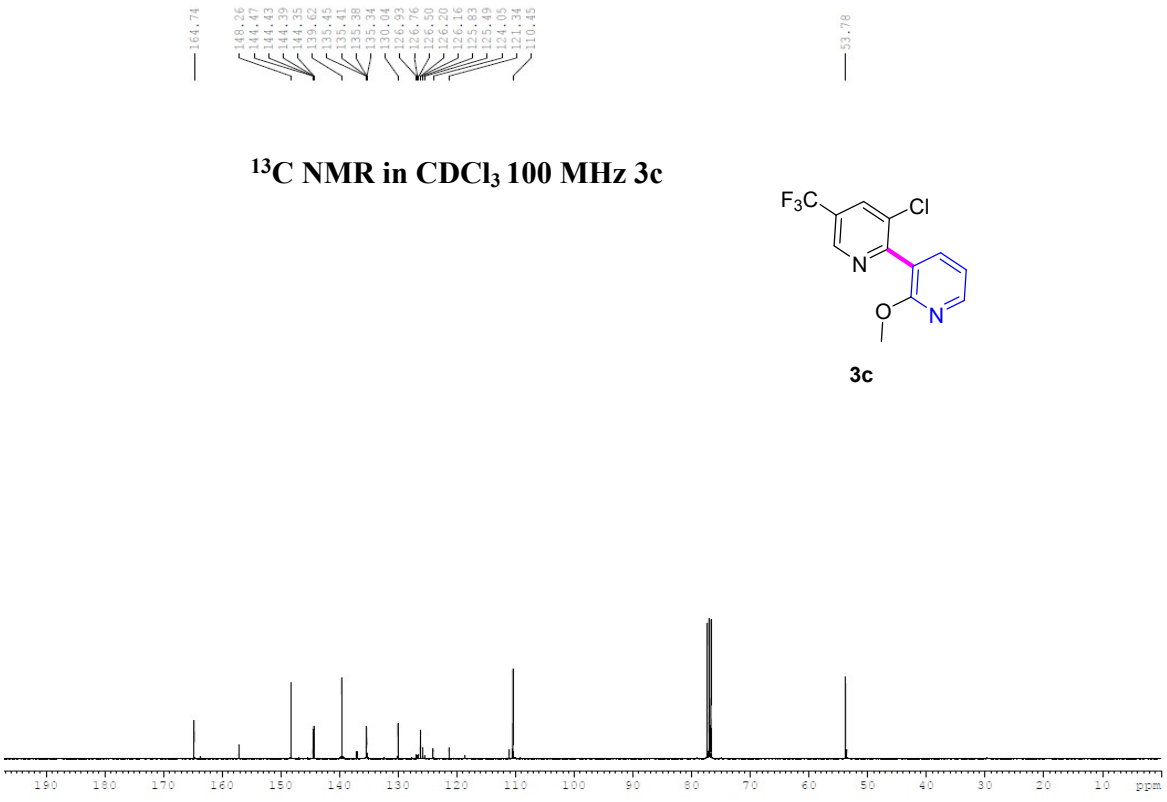


^{1}H, ^{13}C, and ^{19}F-NMR of Compound 3c



^{1}H NMR in $CDCl_3$ 400 MHz 3c

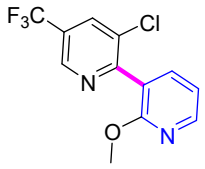
3c



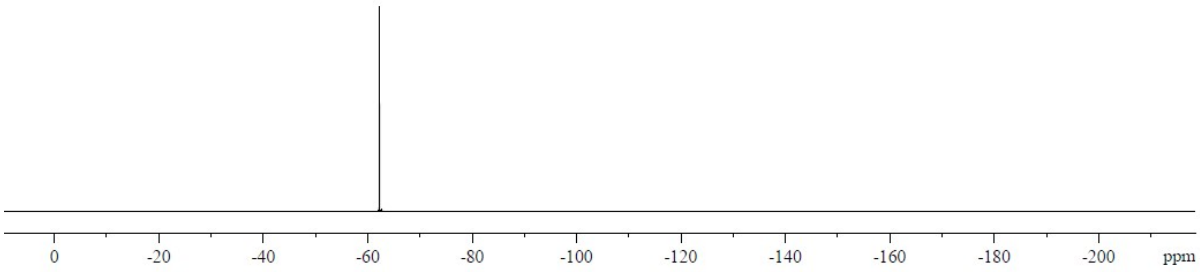
^{13}C NMR in $CDCl_3$ 100 MHz 3c

3c

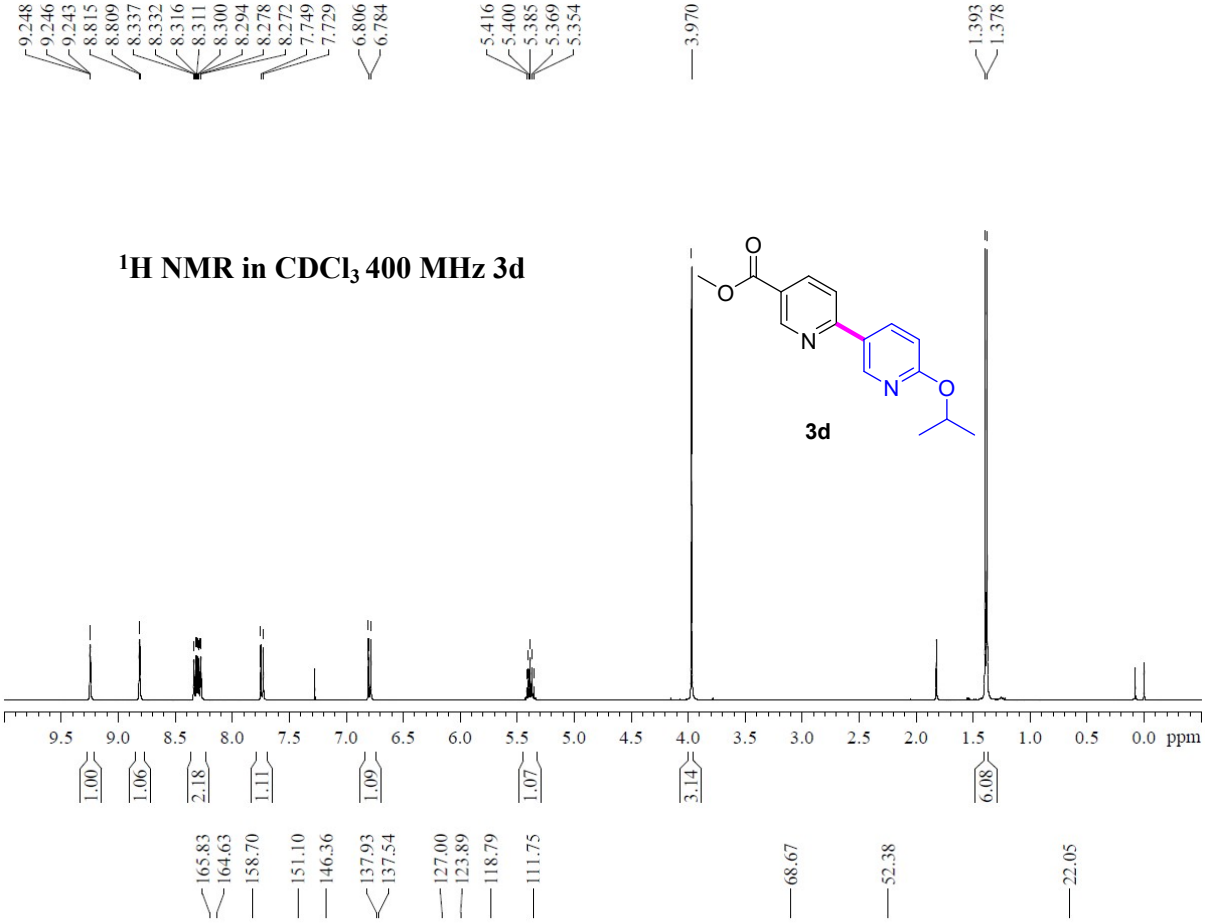
^{19}F NMR in $CDCl_3$ 376 MHz 3c



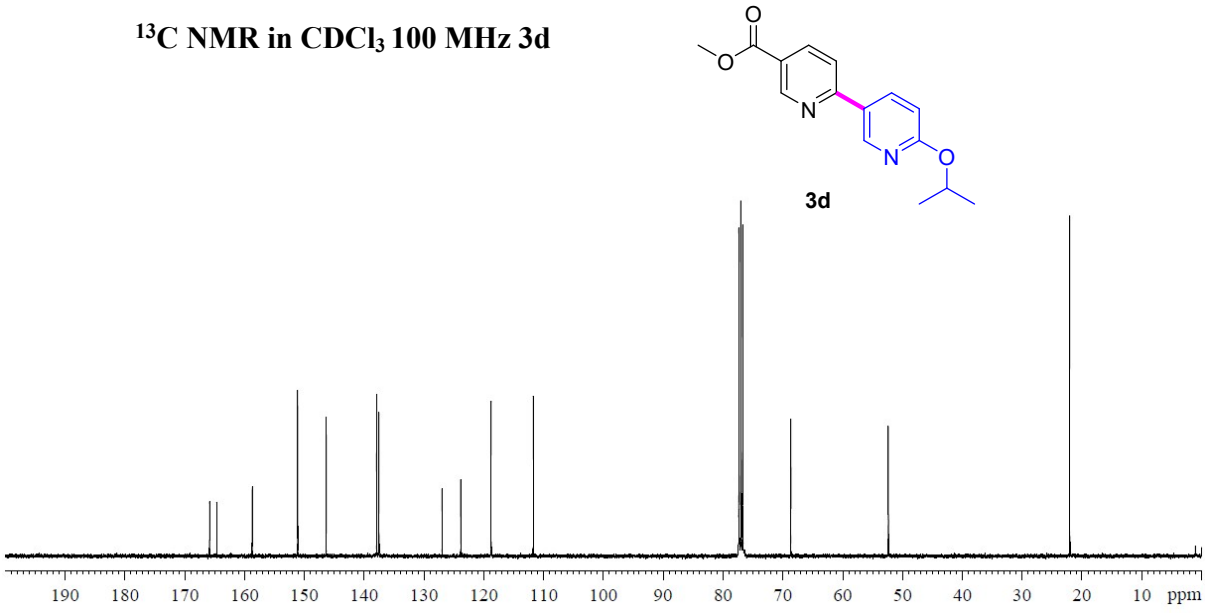
3c



^{1}H and ^{13}C NMR of Compound 3d

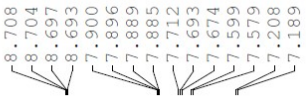


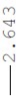
^{1}H NMR in $CDCl_3$ 400 MHz 3d



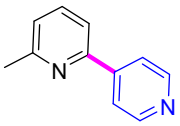
^{13}C NMR in $CDCl_3$ 100 MHz 3d

^{1}H and ^{13}C NMR of Compound 3e

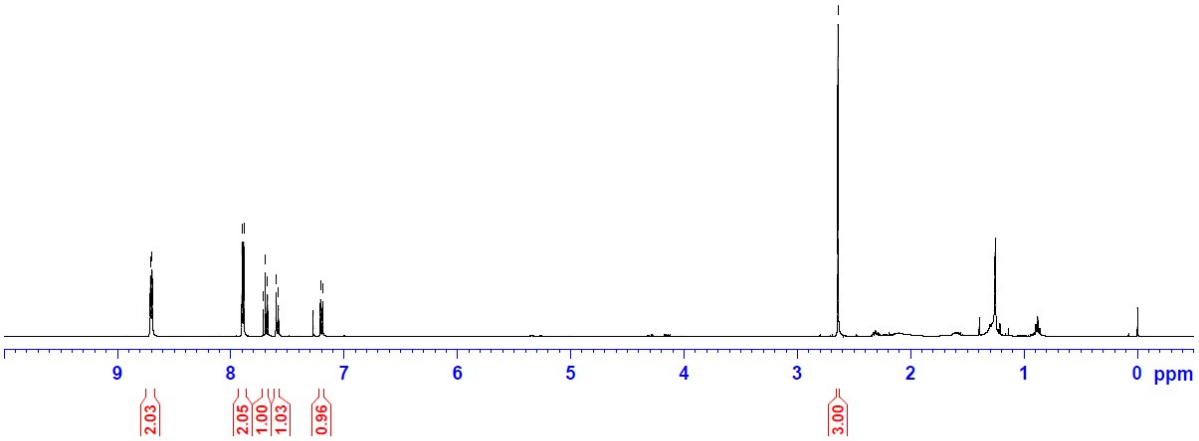




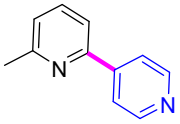
^{1}H NMR in $CDCl_3$ 400 MHz 3e



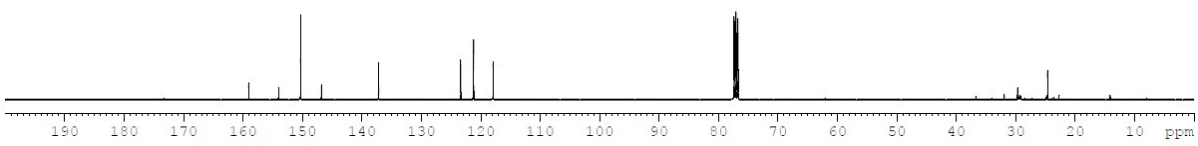
3e



^{13}C NMR in $CDCl_3$ 100 MHz 3e

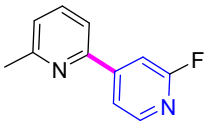


3e

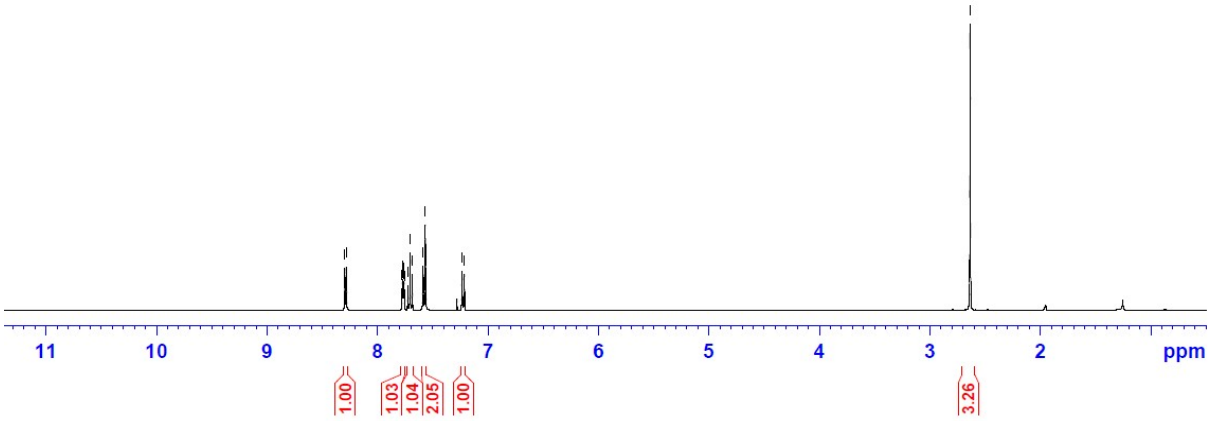


^{1}H, ^{13}C, and ^{19}F-NMR of Compound 3f

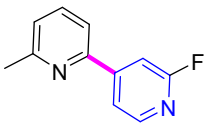
^{1}H NMR in $CDCl_3$ 400 MHz 3f



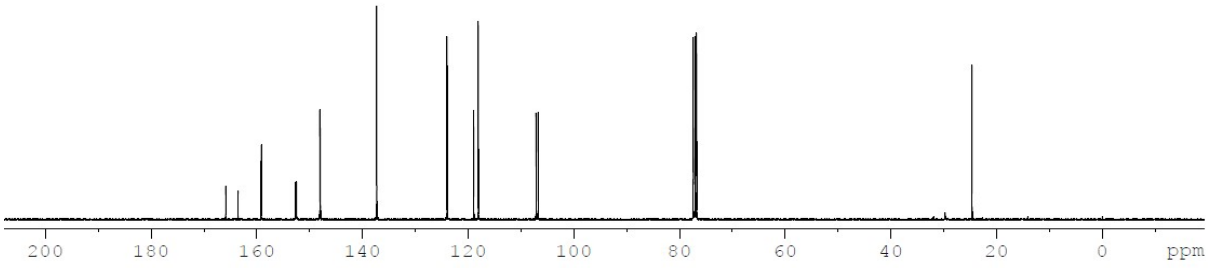
3f

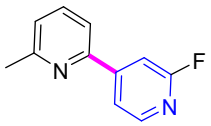


^{13}C NMR in $CDCl_3$ 100 MHz 3f



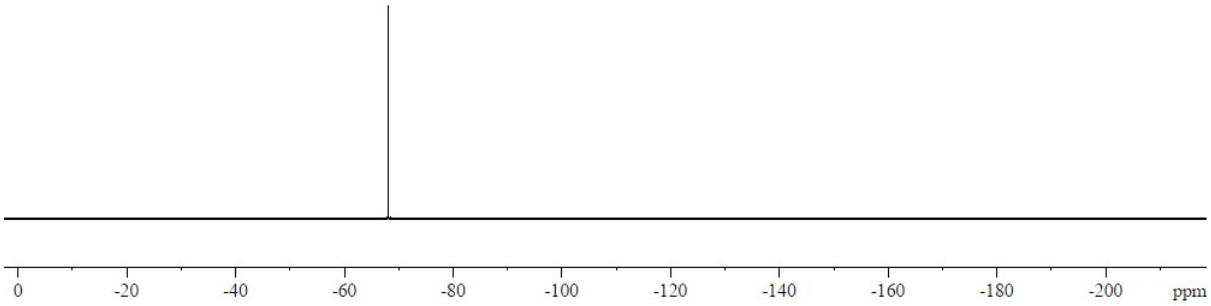
3f



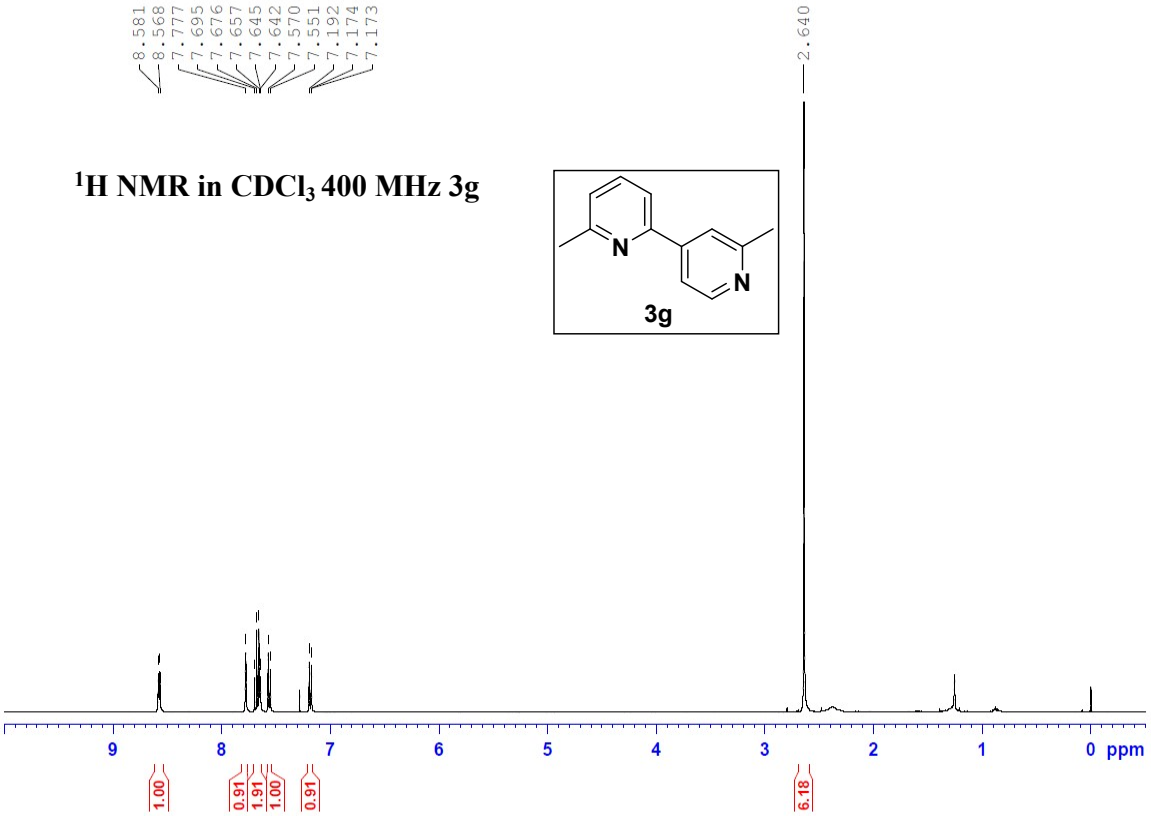


3f

^{19}F NMR in $CDCl_3$ 376 MHz 3f

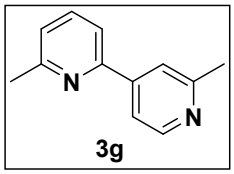


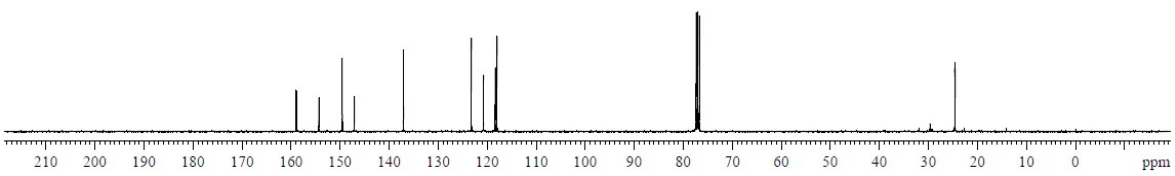
^{1}H and ^{13}C NMR of Compound 3g



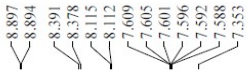
^{1}H NMR in $CDCl_3$ 400 MHz 3g

^{13}C NMR in $CDCl_3$ 100 MHz 3g

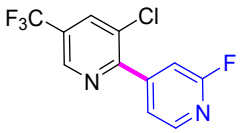




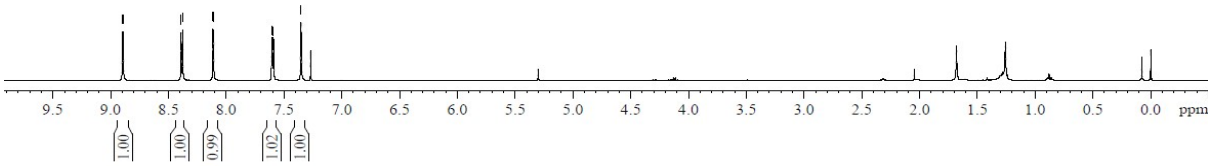
^{1}H, ^{13}C, and ^{19}F-NMR of Compound 3h

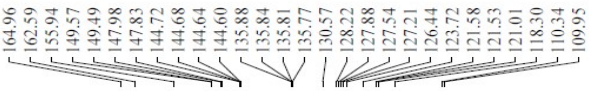


^{1}H NMR in $CDCl_3$ 400 MHz 3h

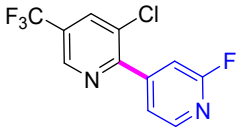


3h

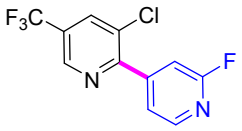




^{13}C NMR in $CDCl_3$ 100 MHz 3h

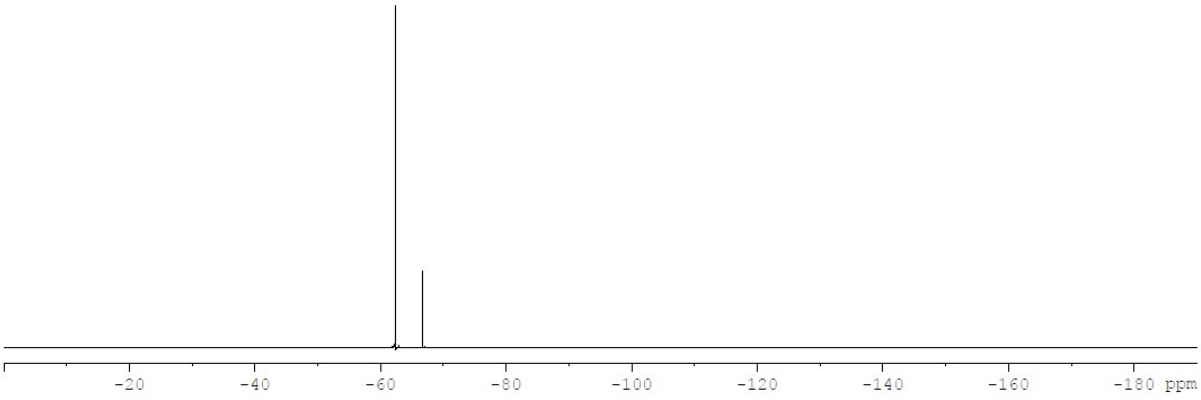


3h

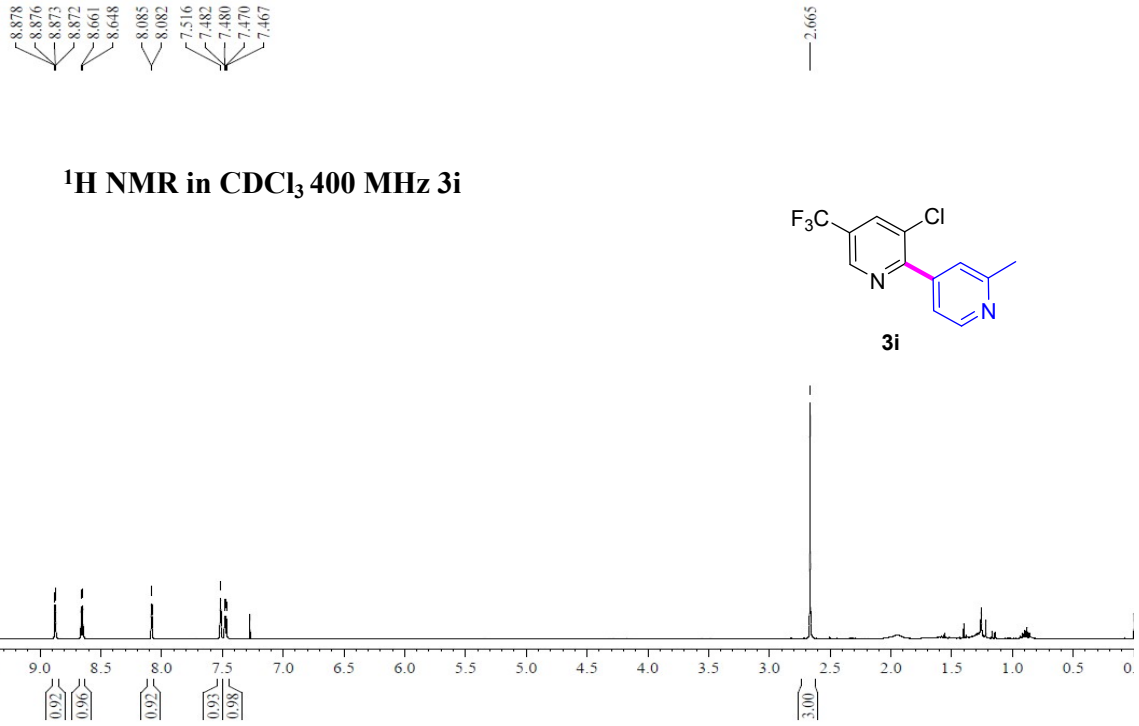


3h

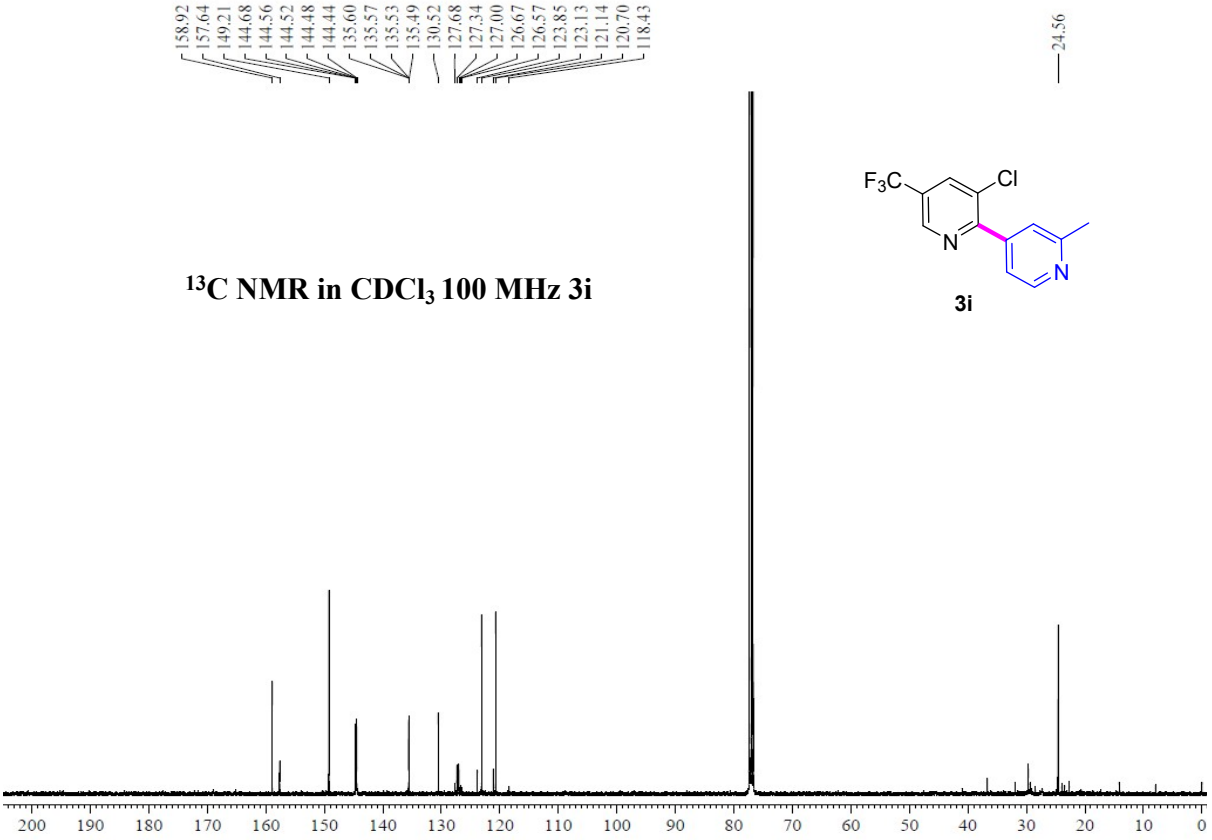
^{19}F NMR in $CDCl_3$ 376 MHz 3h



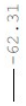
^{1}H, ^{13}C, and ^{19}F-NMR of Compound 3i



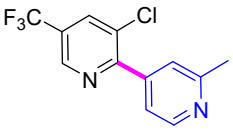
^{1}H NMR in $CDCl_3$ 400 MHz 3i



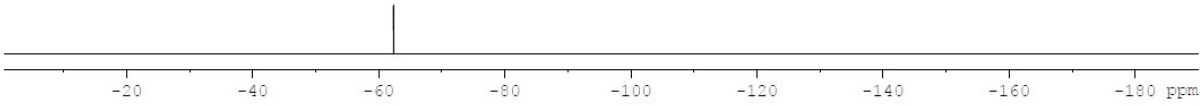
^{13}C NMR in $CDCl_3$ 100 MHz 3i



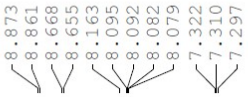
^{19}F NMR in $CDCl_3$ 376 MHz 3i



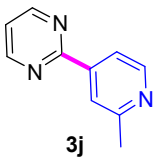
3i



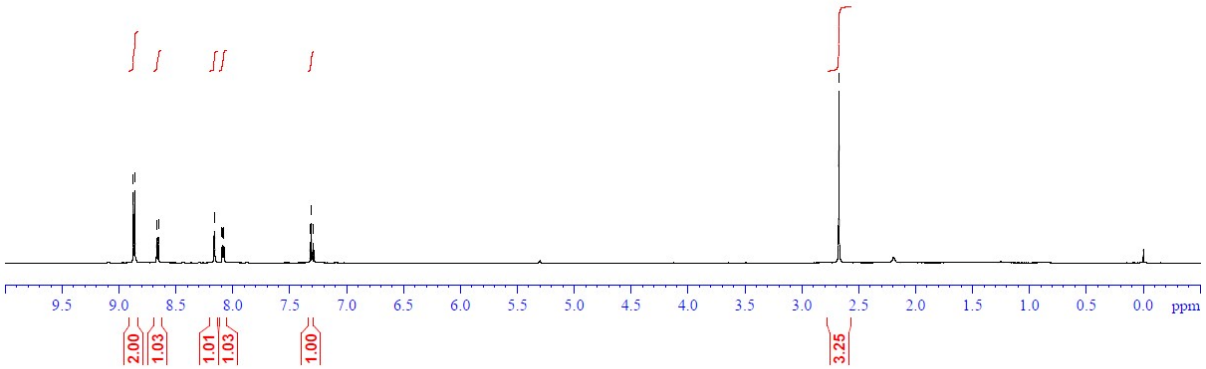
^{1}H and ^{13}C NMR of Compound 3j



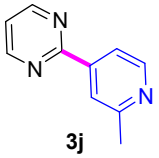
^{1}H NMR in $CDCl_3$ 400 MHz 3j



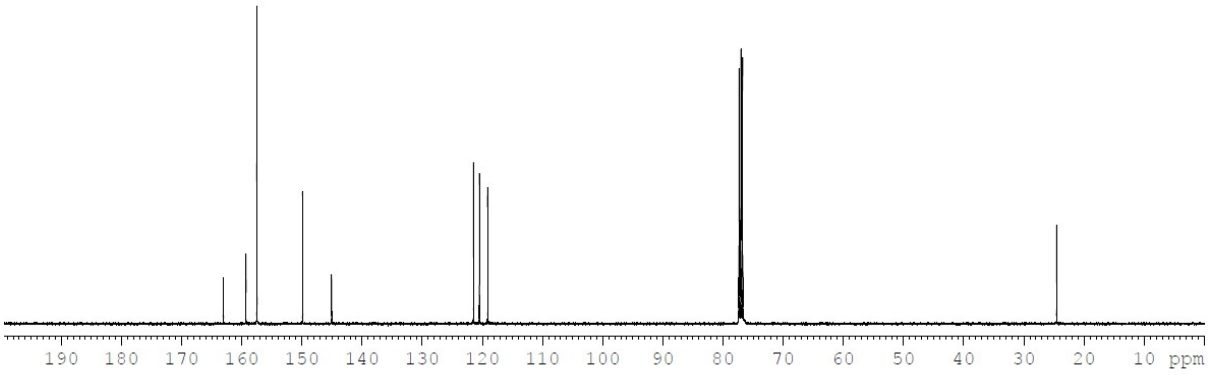
3j



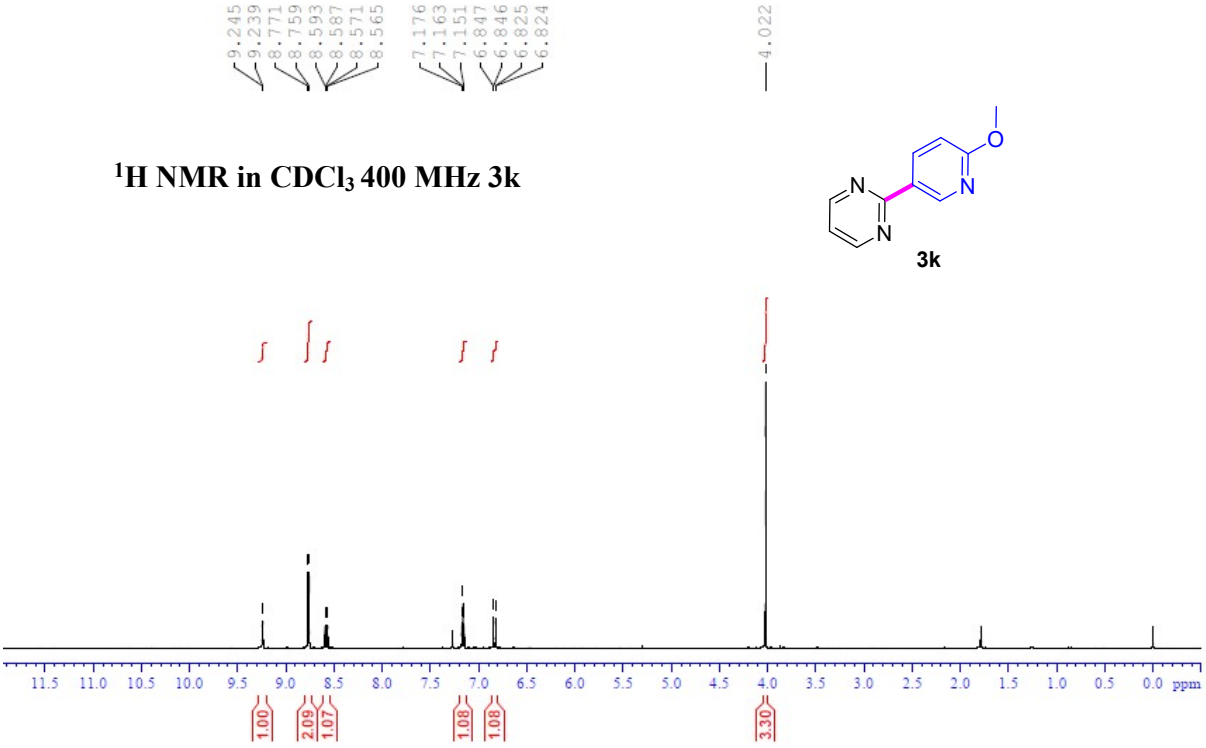
^{13}C NMR in $CDCl_3$ 100 MHz 3j



3j

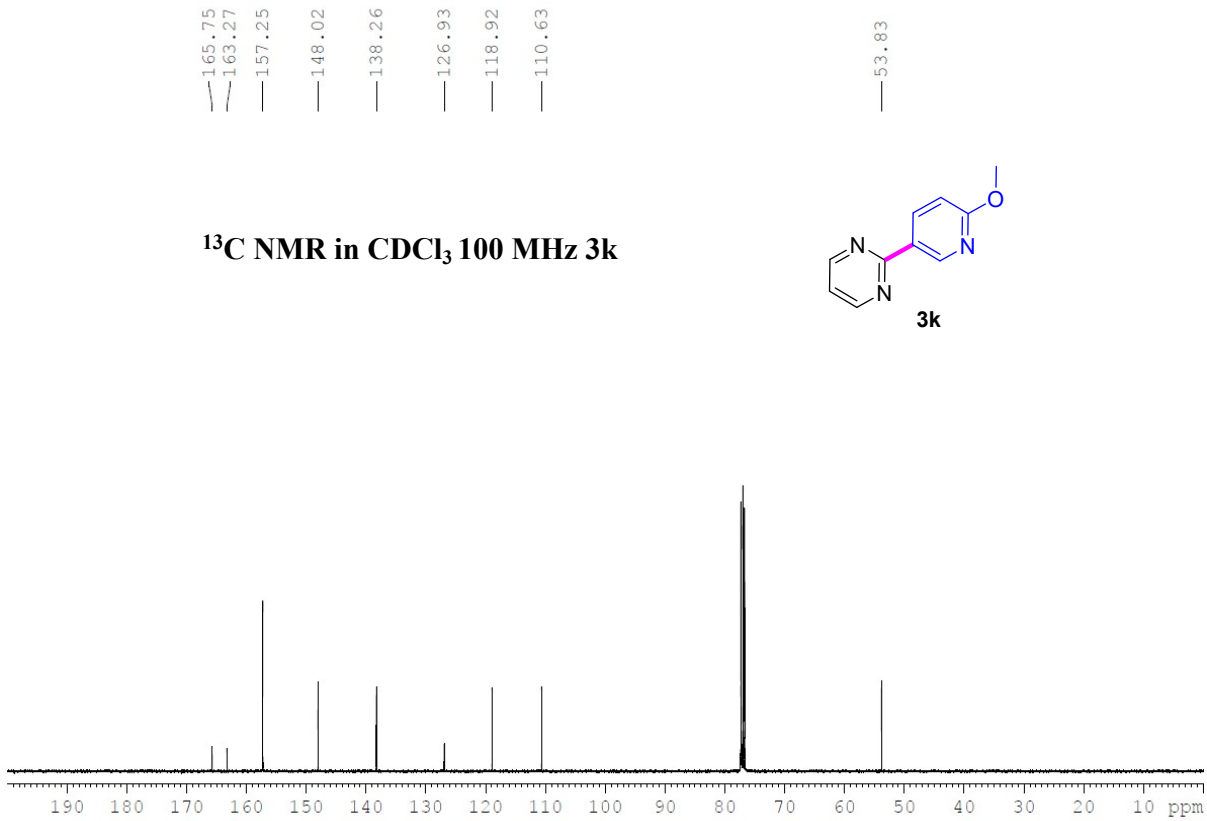


^{1}H and ^{13}C NMR of Compound 3k



^{1}H NMR in $CDCl_3$ 400 MHz 3k

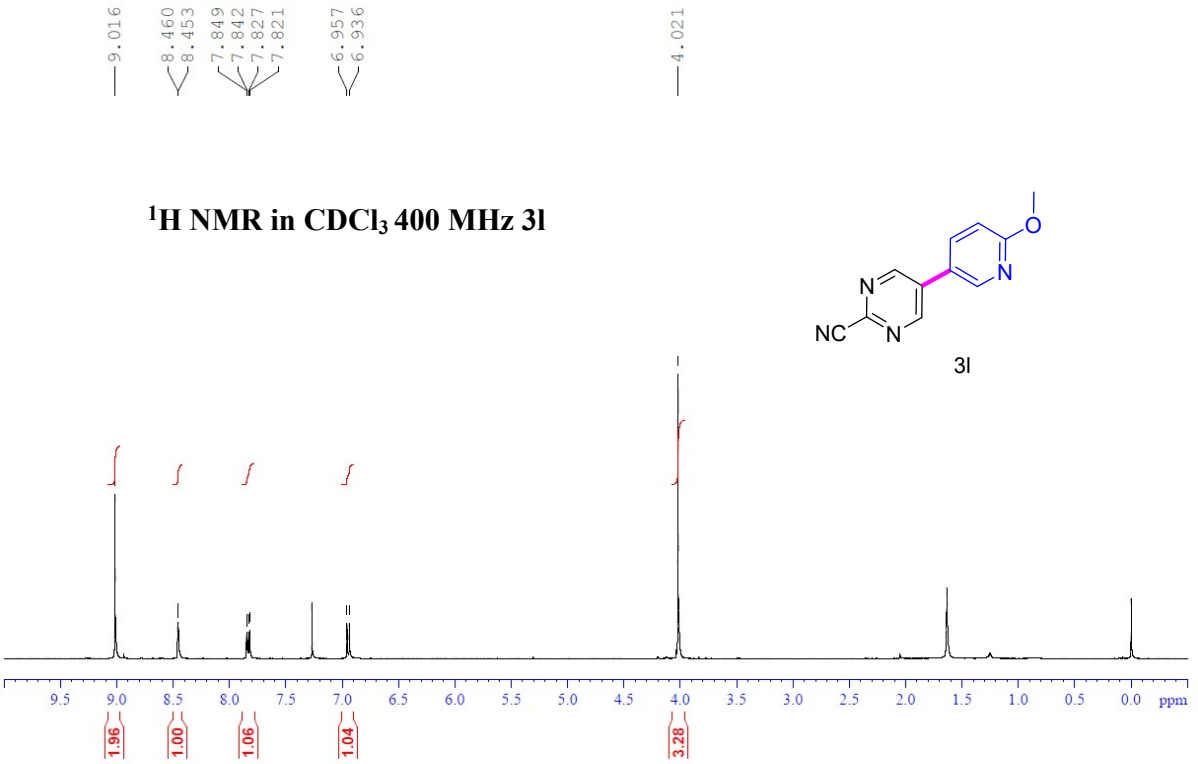
3k



^{13}C NMR in $CDCl_3$ 100 MHz 3k

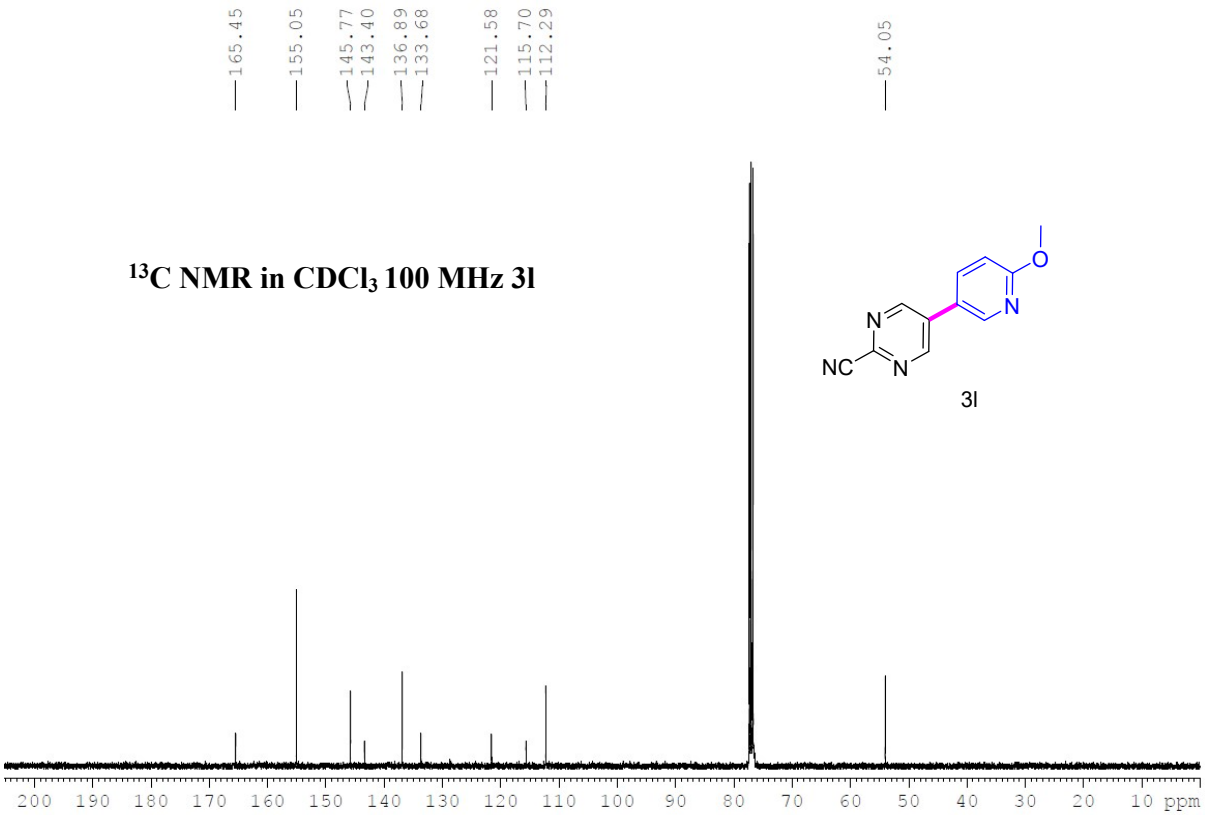
3k

^{1}H and ^{13}C NMR of Compound 3l



^{1}H NMR in $CDCl_3$ 400 MHz 3l

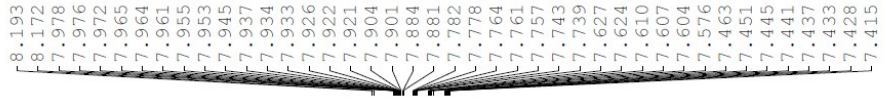
3l



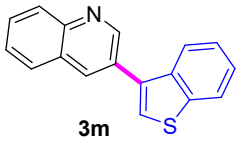
^{13}C NMR in $CDCl_3$ 100 MHz 3l

3l

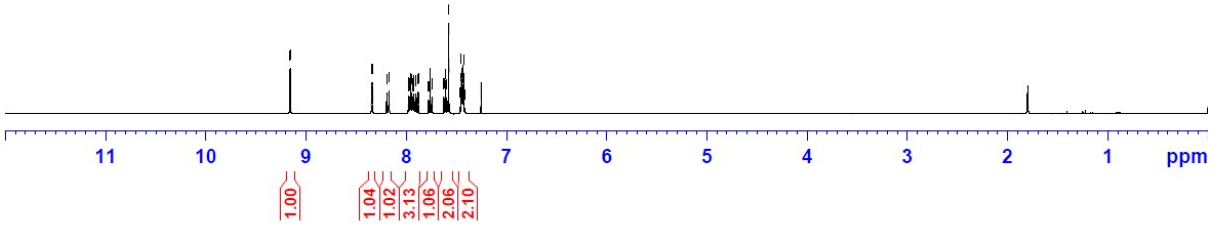
^{1}H and ^{13}C NMR of Compound 3m

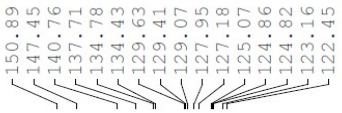


^{1}H NMR in $CDCl_3$ 400 MHz 3m

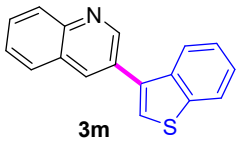


3m

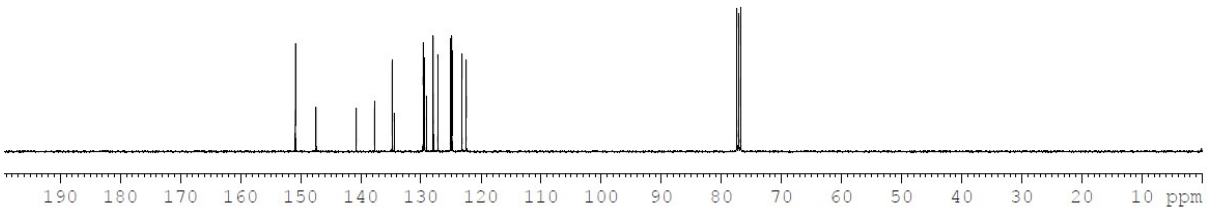




^{13}C NMR in $CDCl_3$ 100 MHz 3m

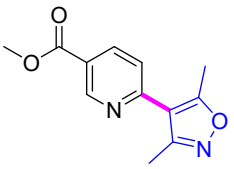


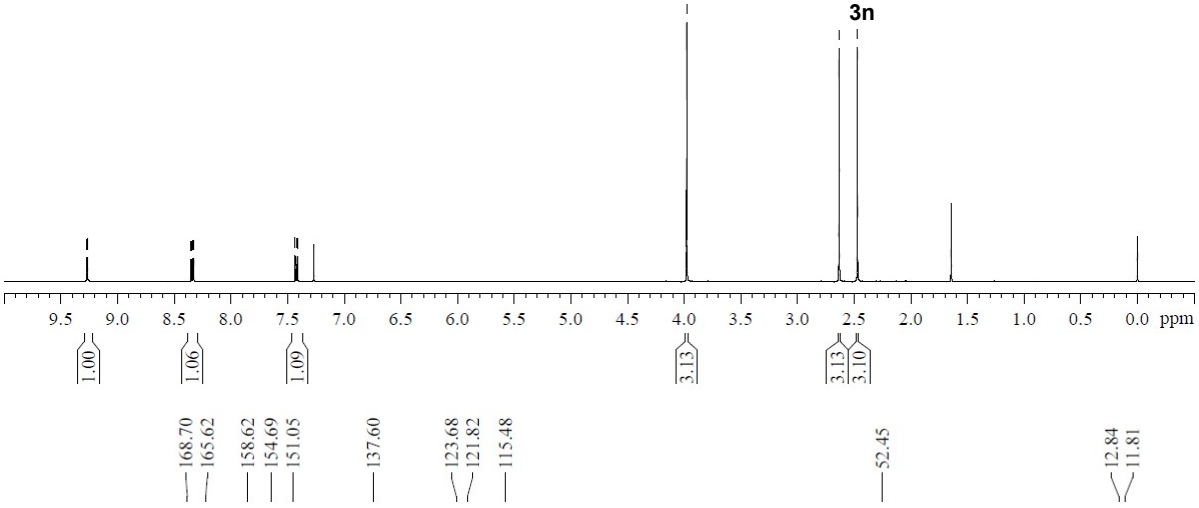
3m



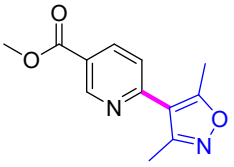
^{1}H and ^{13}C NMR of Compound 3n

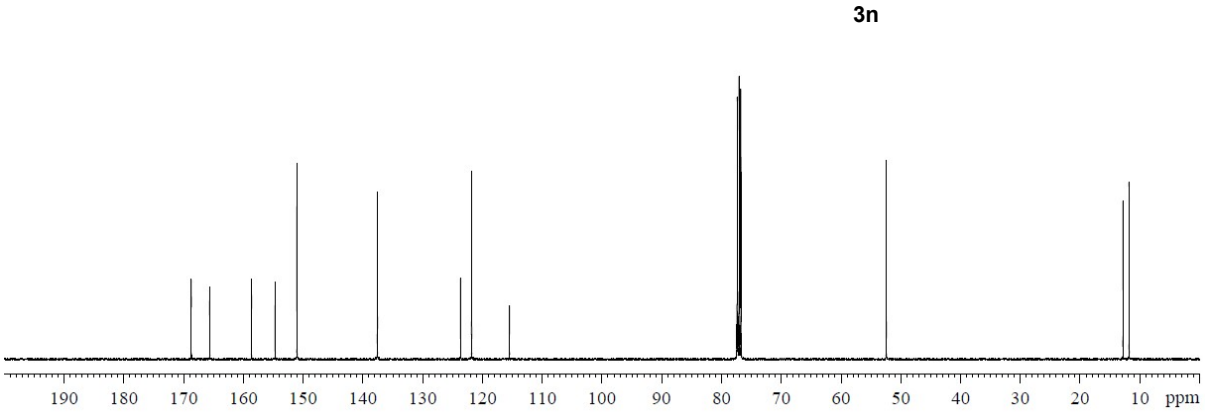
^{1}H NMR in $CDCl_3$ 400 MHz 3n



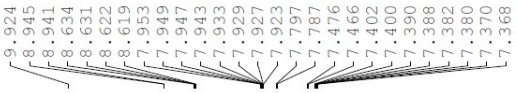


^{13}C NMR in $CDCl_3$ 100 MHz 3n

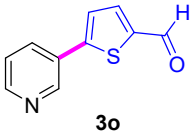




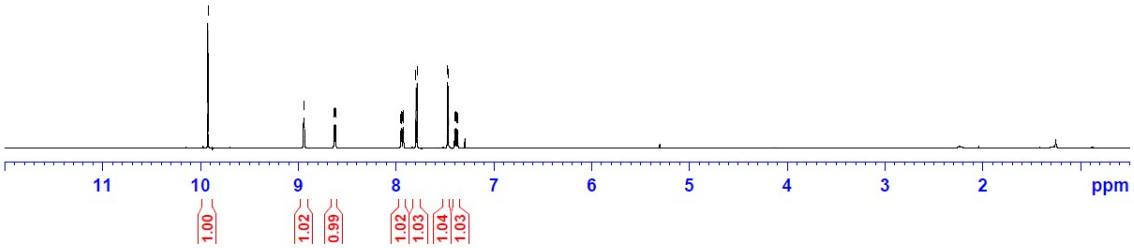
^{1}H and ^{13}C NMR of Compound 3o

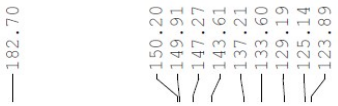


^{1}H NMR in $CDCl_3$ 400 MHz 3o

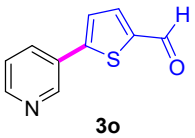


3o

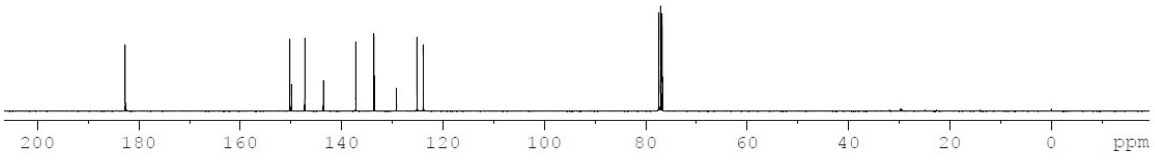




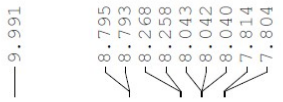
^{13}C NMR in $CDCl_3$ 100 MHz 3o



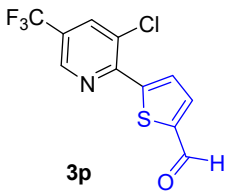
3o



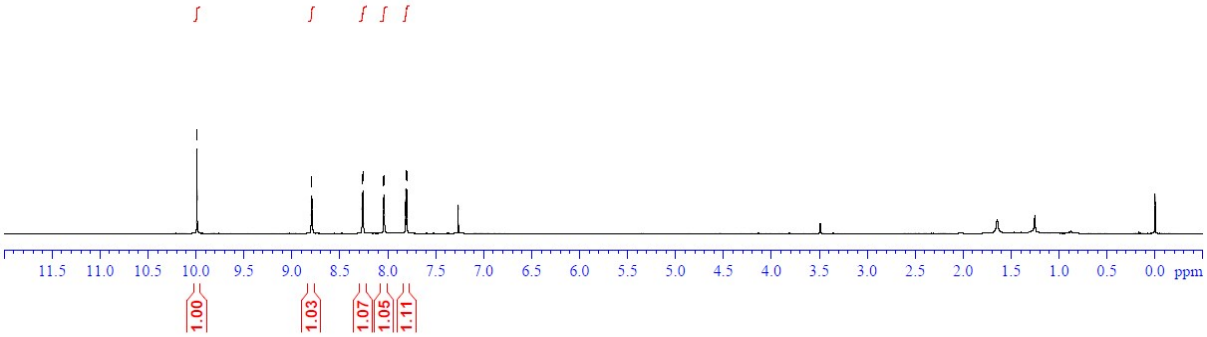
^{1}H, ^{13}C, and ^{19}F-NMR of Compound 3p

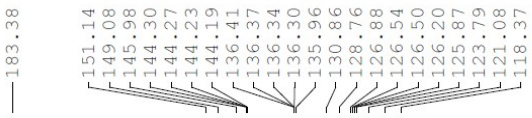


^{1}H NMR in $CDCl_3$ 400 MHz 3p

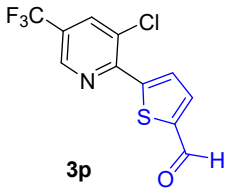


3p

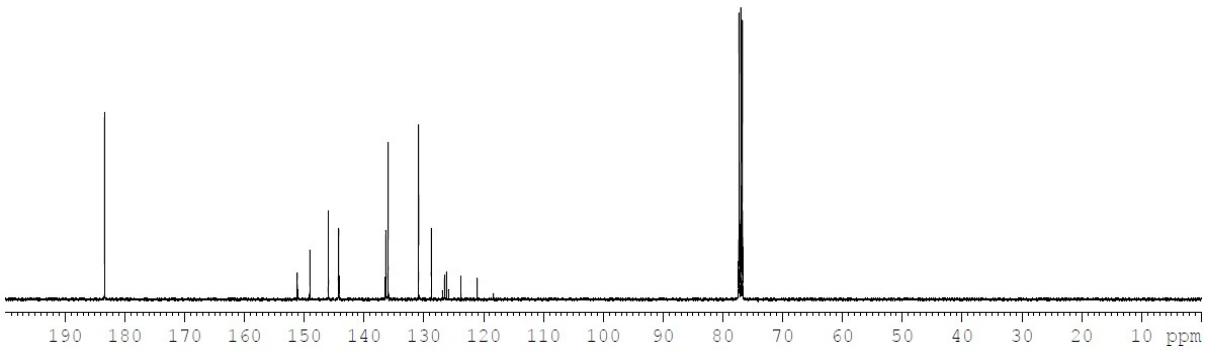


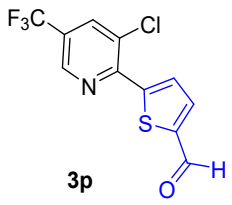


^{13}C NMR in $CDCl_3$ 100 MHz 3p



3p



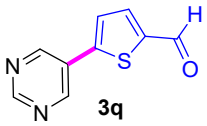


3p

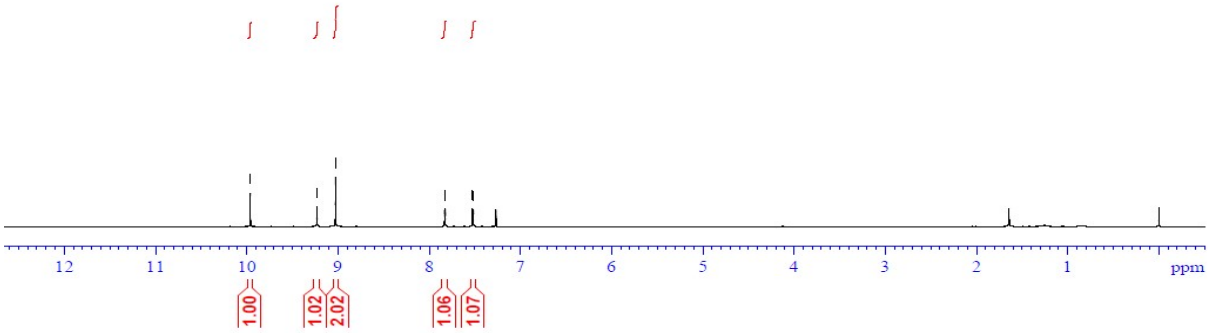
^{19}F NMR in $CDCl_3$ 376 MHz 3p

^{1}H and ^{13}C NMR of Compound 3q

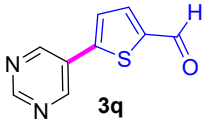
^{1}H NMR in $CDCl_3$ 400 MHz 3q



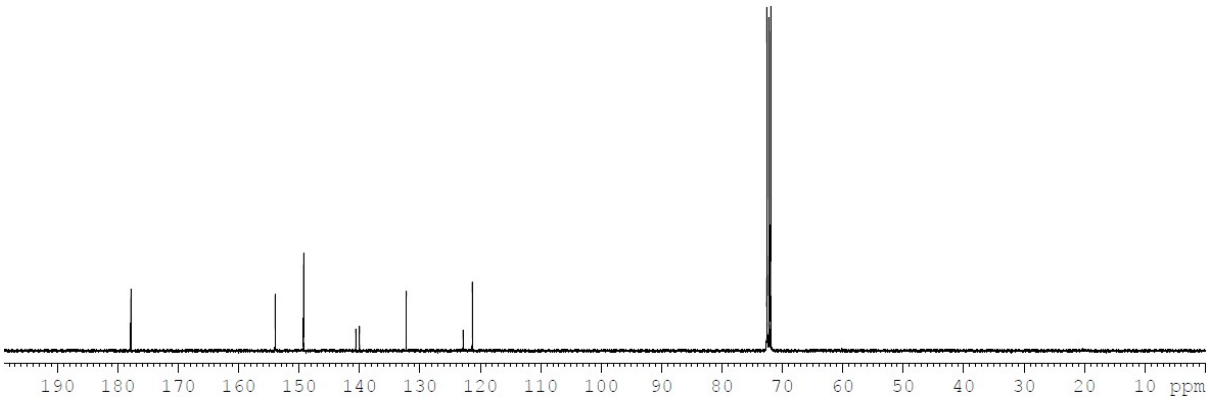
3q



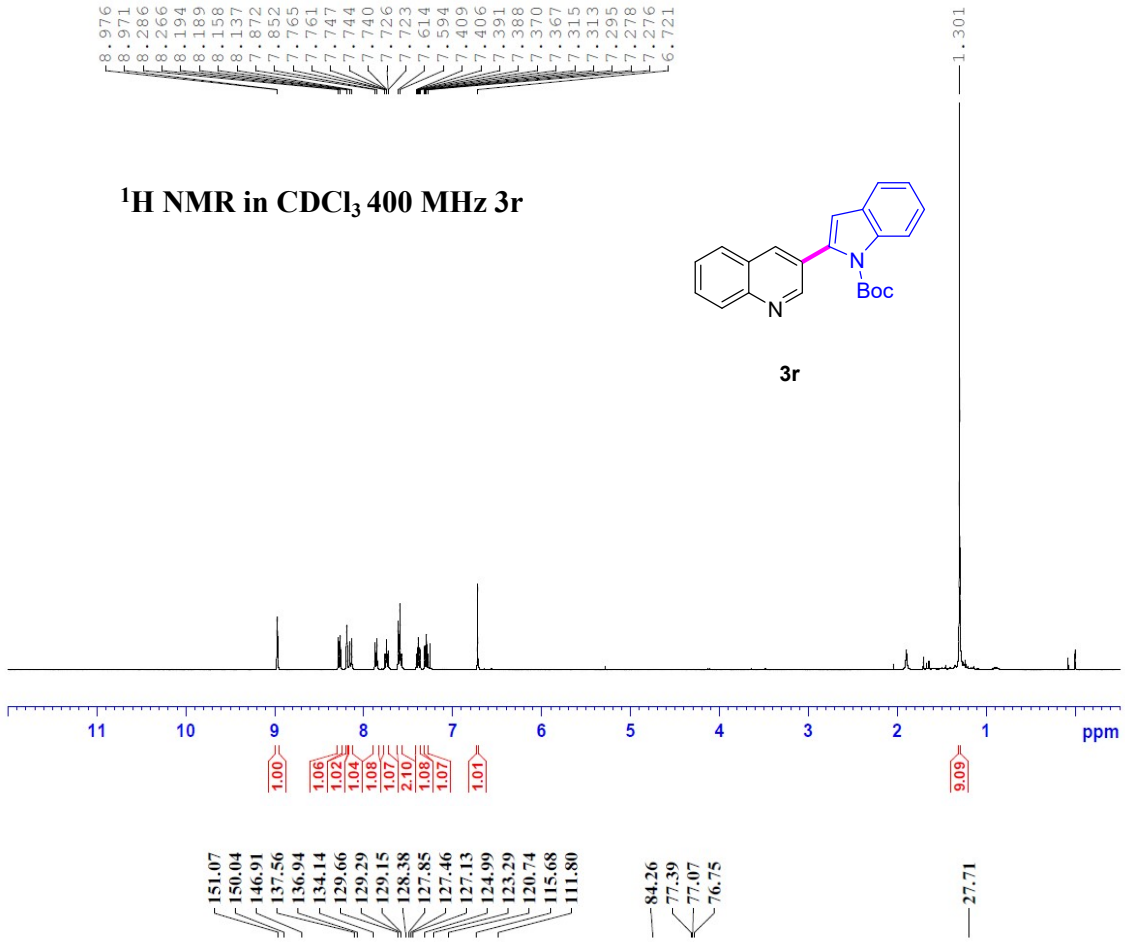
^{13}C NMR in $CDCl_3$ 100 MHz 3q



3q



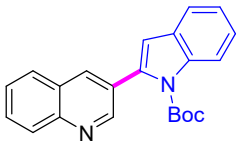
^{1}H and ^{13}C NMR of Compound 3r



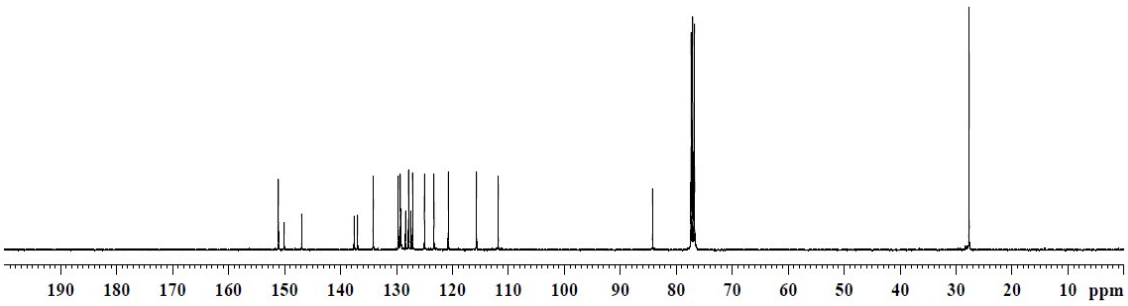
^{1}H NMR in $CDCl_3$ 400 MHz 3r

3r

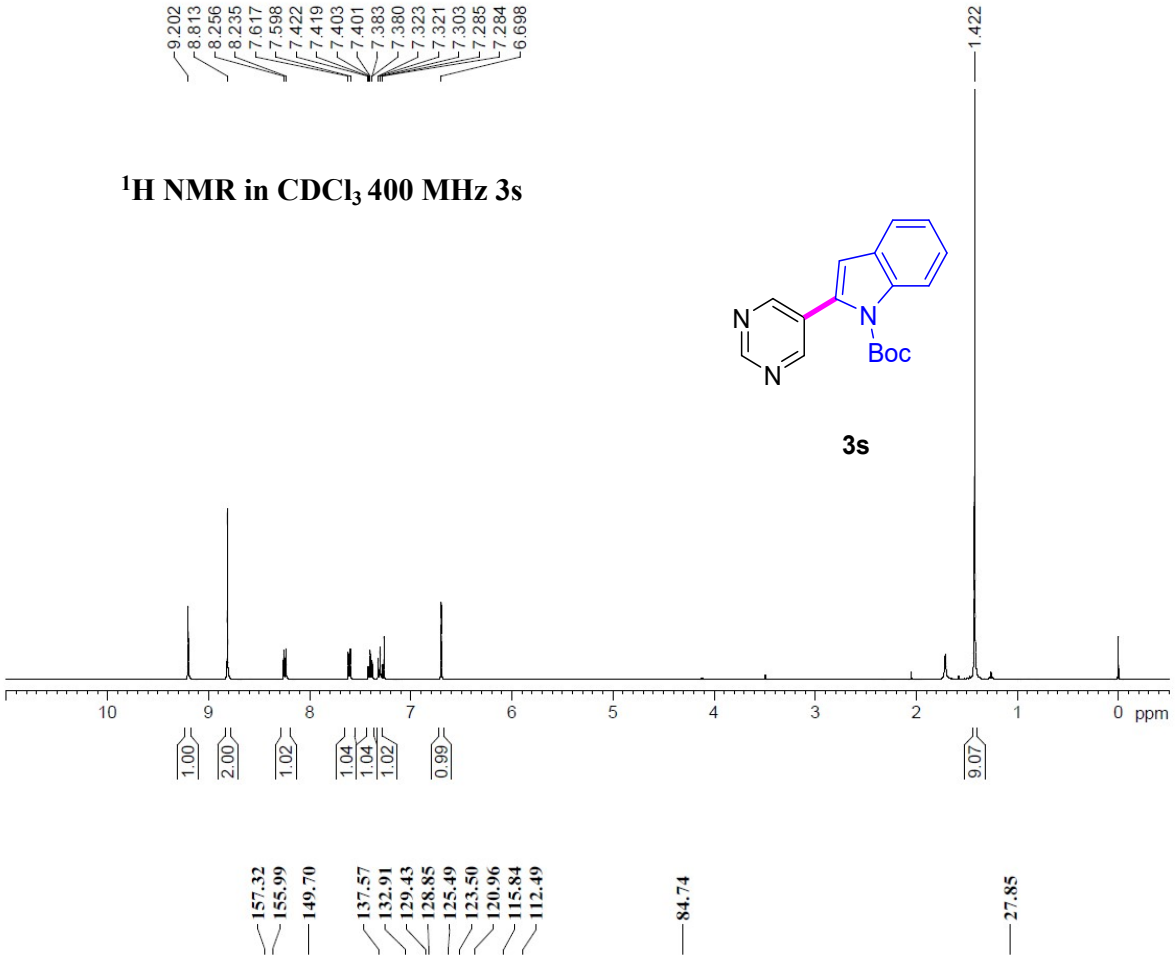
^{13}C NMR in $CDCl_3$ 100 MHz 3r



3r

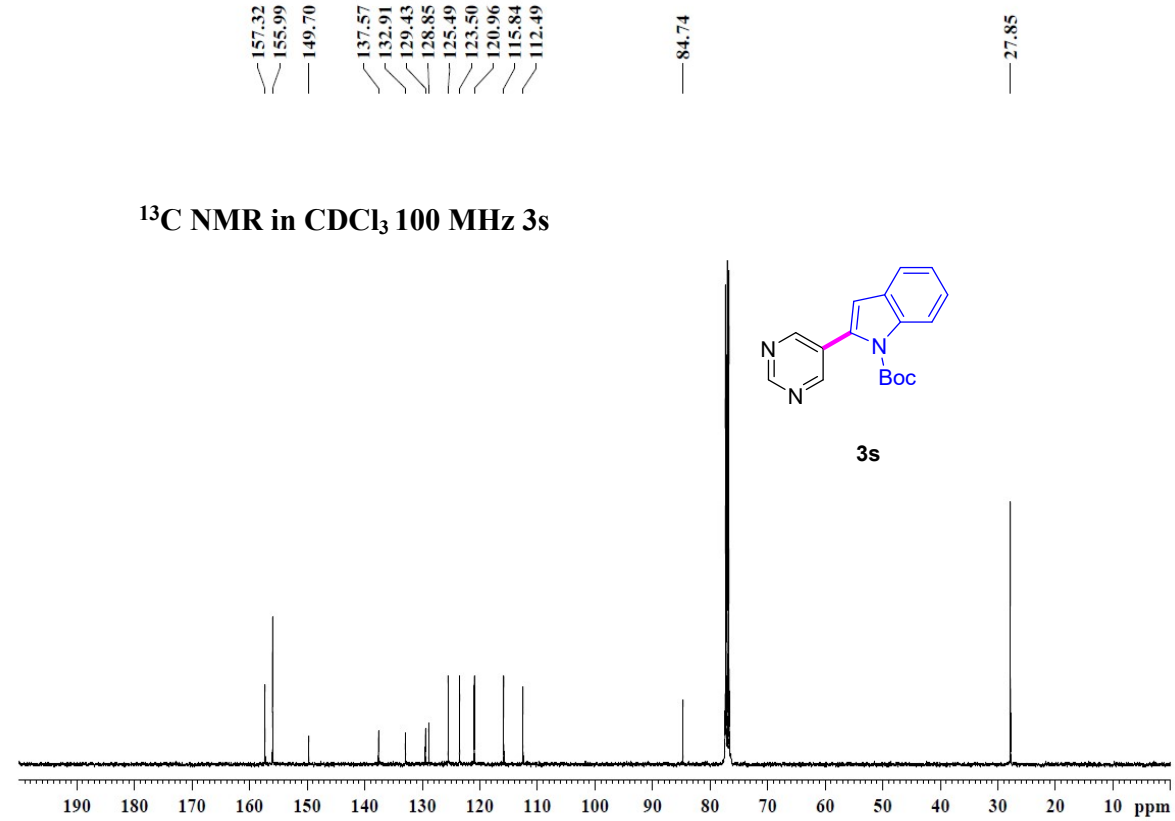


^{1}H and ^{13}C NMR of Compound 3s



^{1}H NMR in $CDCl_3$ 400 MHz 3s

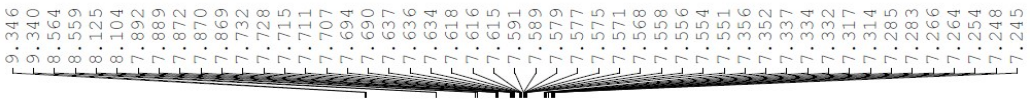
3s



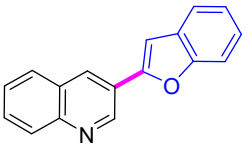
^{13}C NMR in $CDCl_3$ 100 MHz 3s

3s

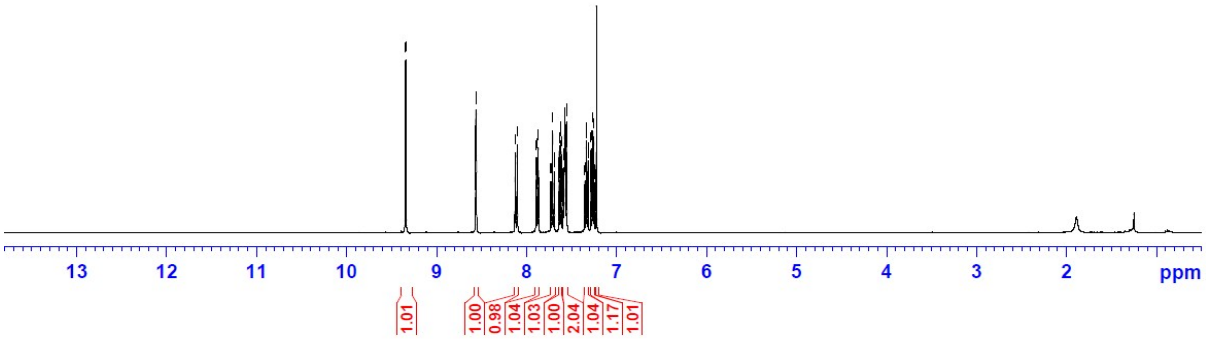
^{1}H and ^{13}C NMR of Compound 3t

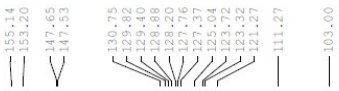


^{1}H NMR in $CDCl_3$ 400 MHz 3t

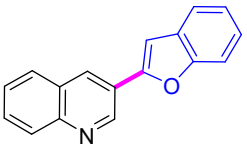


3t

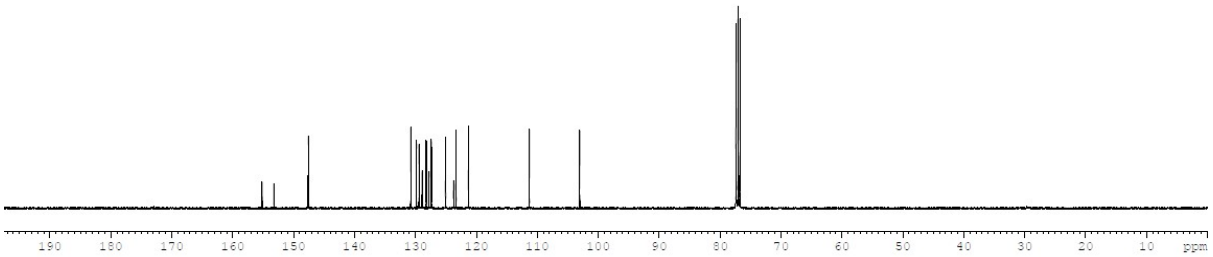




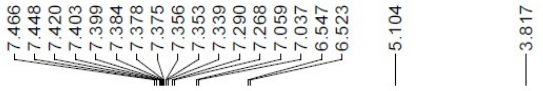
^{13}C NMR in $CDCl_3$ 100 MHz 3t



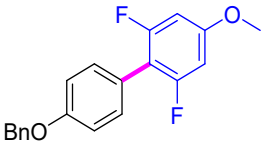
3t



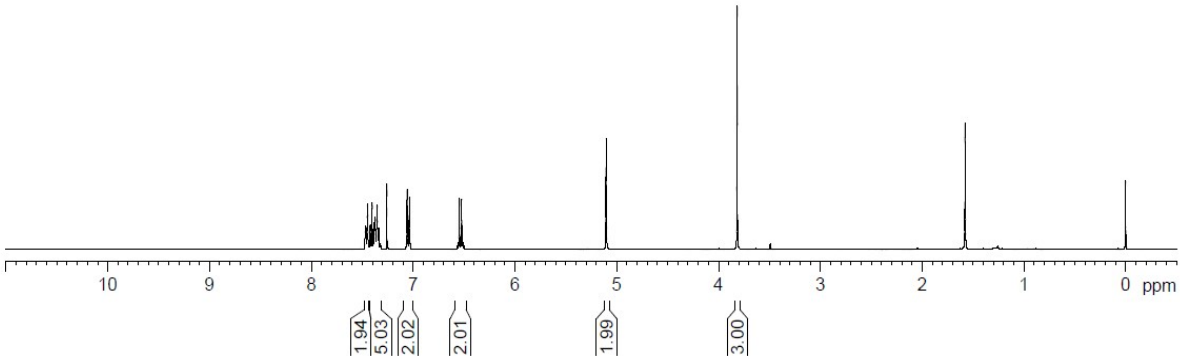
^{1}H, ^{13}C, and ^{19}F-NMR of Compound 3u

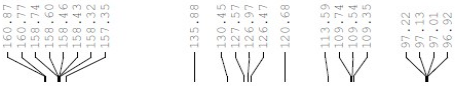


^{1}H NMR in $CDCl_3$ 400 MHz 3u

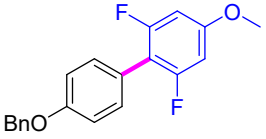


3u

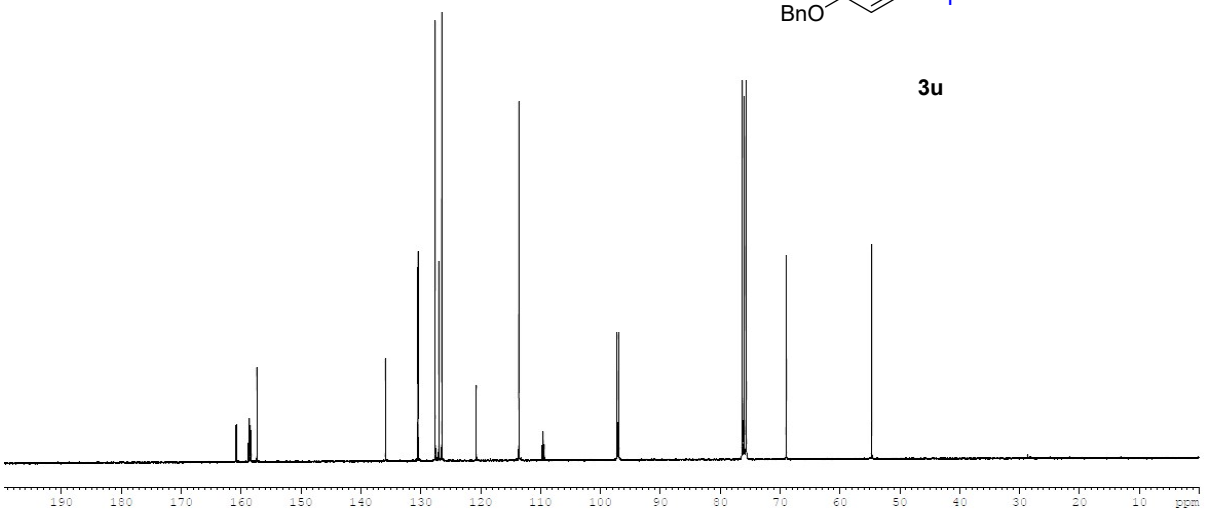




^{13}C NMR in $CDCl_3$ 100 MHz 3u



3u



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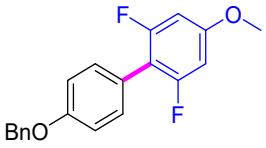
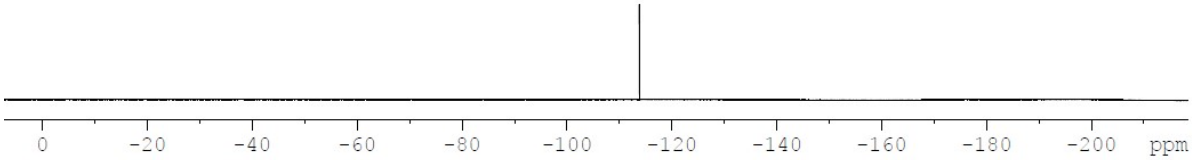
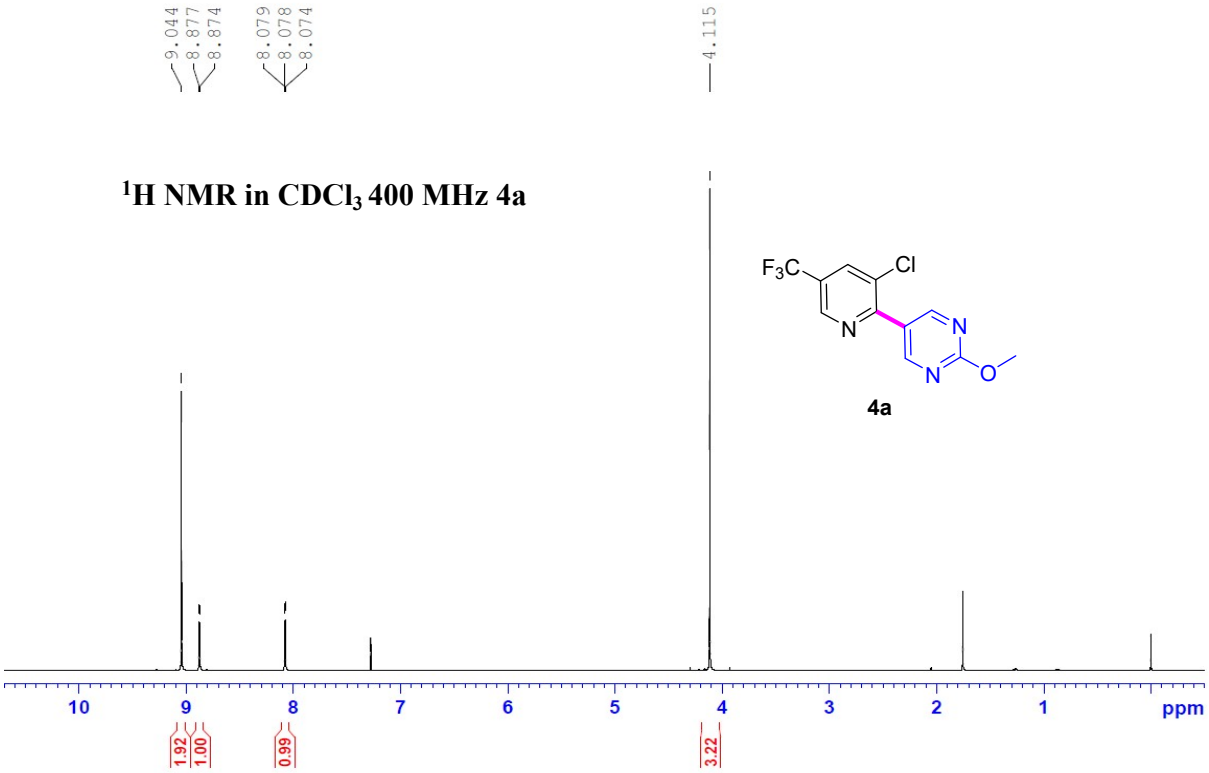


3u

^{19}F NMR in $CDCl_3$ 376 MHz 3u

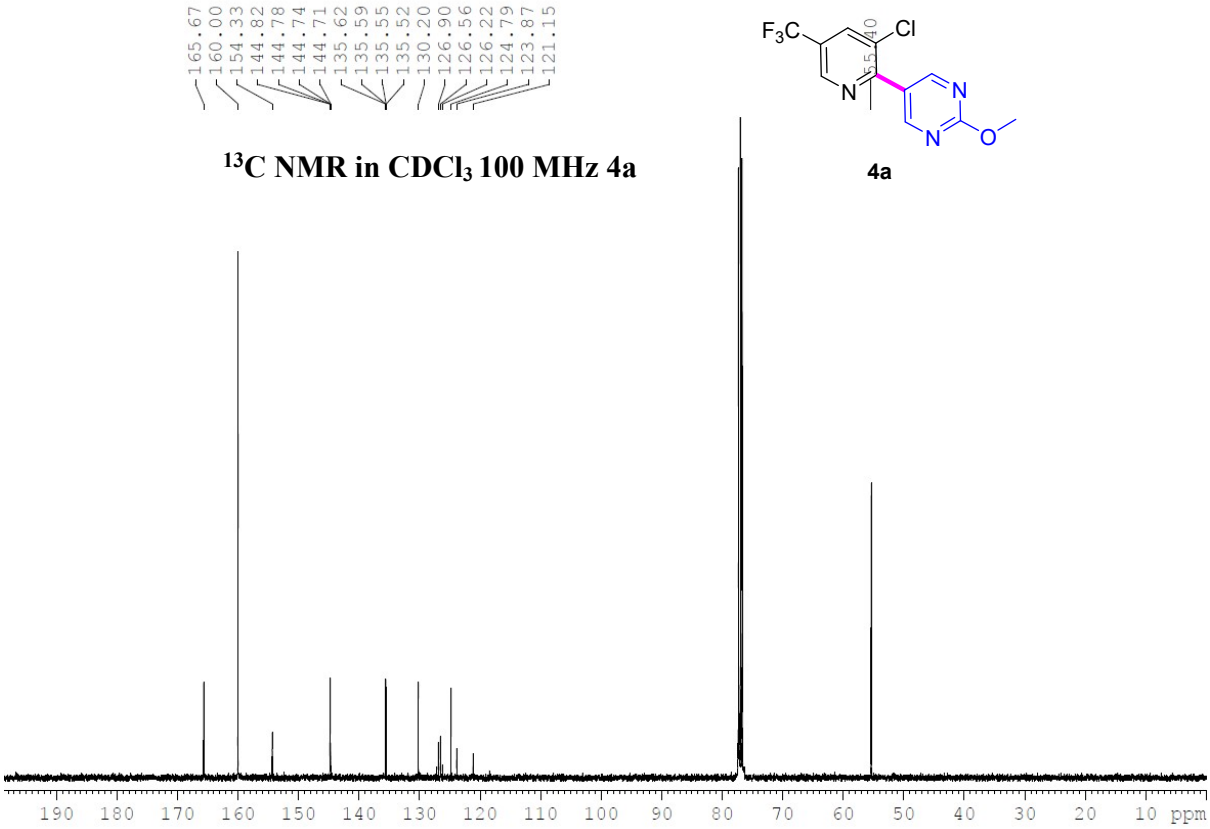


^{1}H, ^{13}C, and ^{19}F-NMR of Compound 4a



^{1}H NMR in $CDCl_3$ 400 MHz 4a

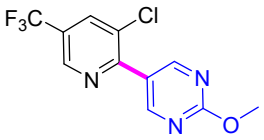
4a



^{13}C NMR in $CDCl_3$ 100 MHz 4a

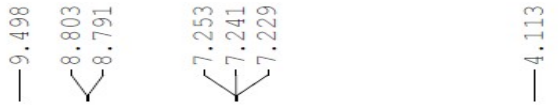
4a

^{19}F NMR in $CDCl_3$ 376 MHz 4a

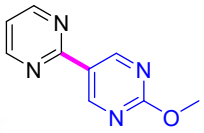


4a

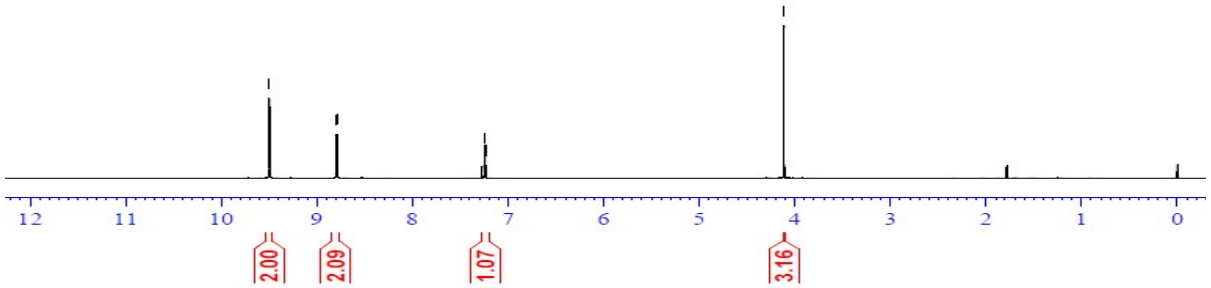
^{1}H and ^{13}C NMR of Compound 4b



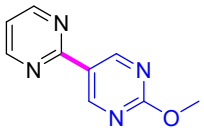
^{1}H NMR in $CDCl_3$ 400 MHz 4b



4b

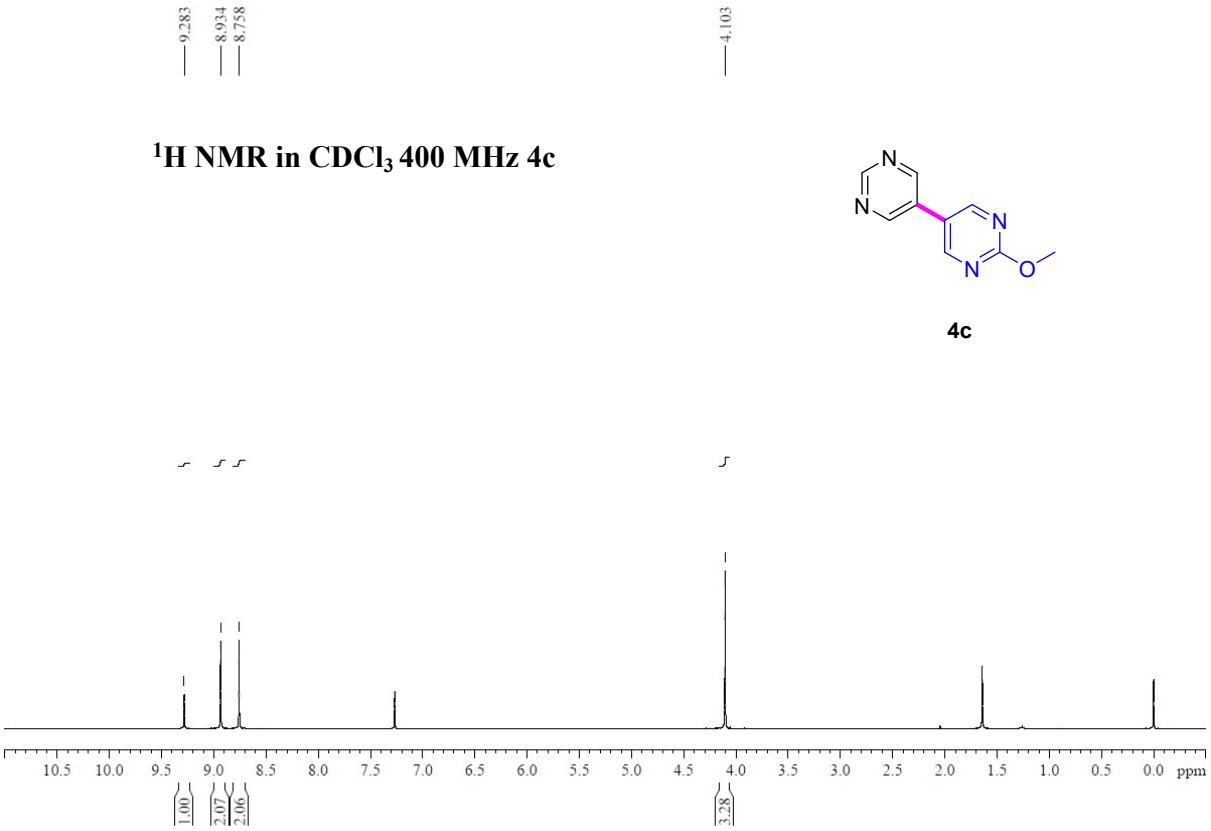


^{13}C NMR in $CDCl_3$ 100 MHz 4b



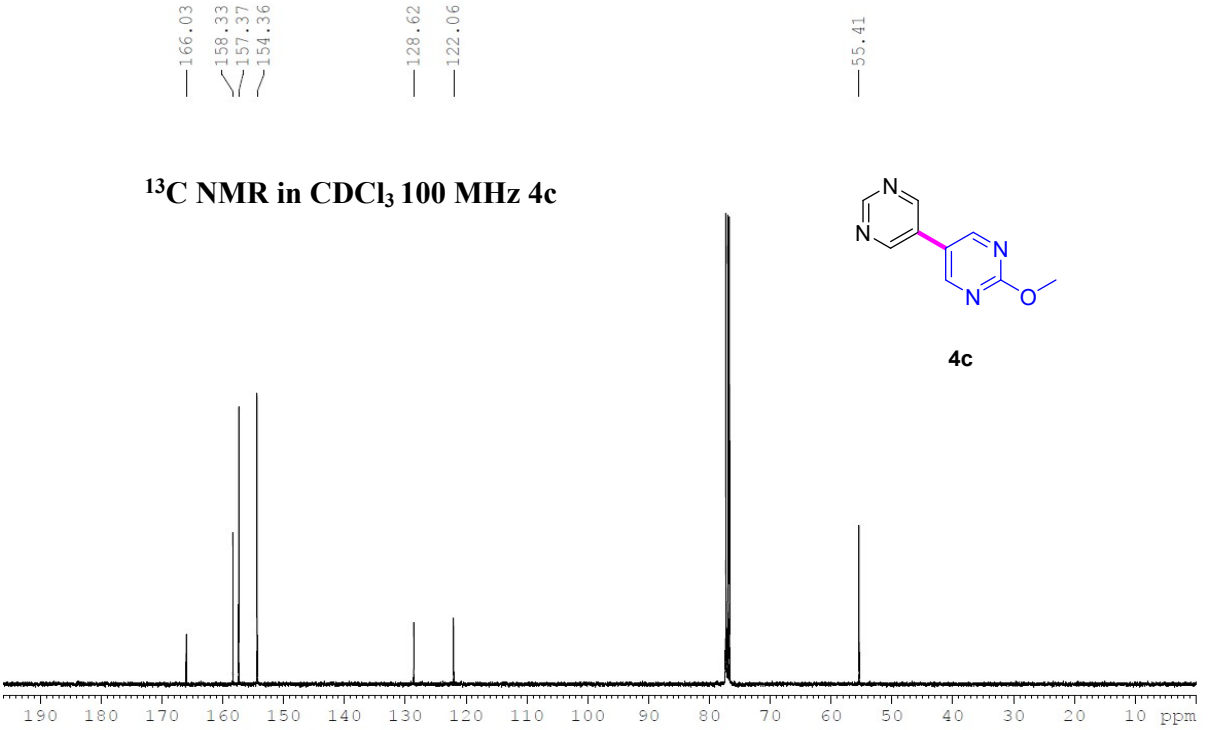
4b

^{1}H and ^{13}C NMR of Compound 4c



^{1}H NMR in $CDCl_3$ 400 MHz 4c

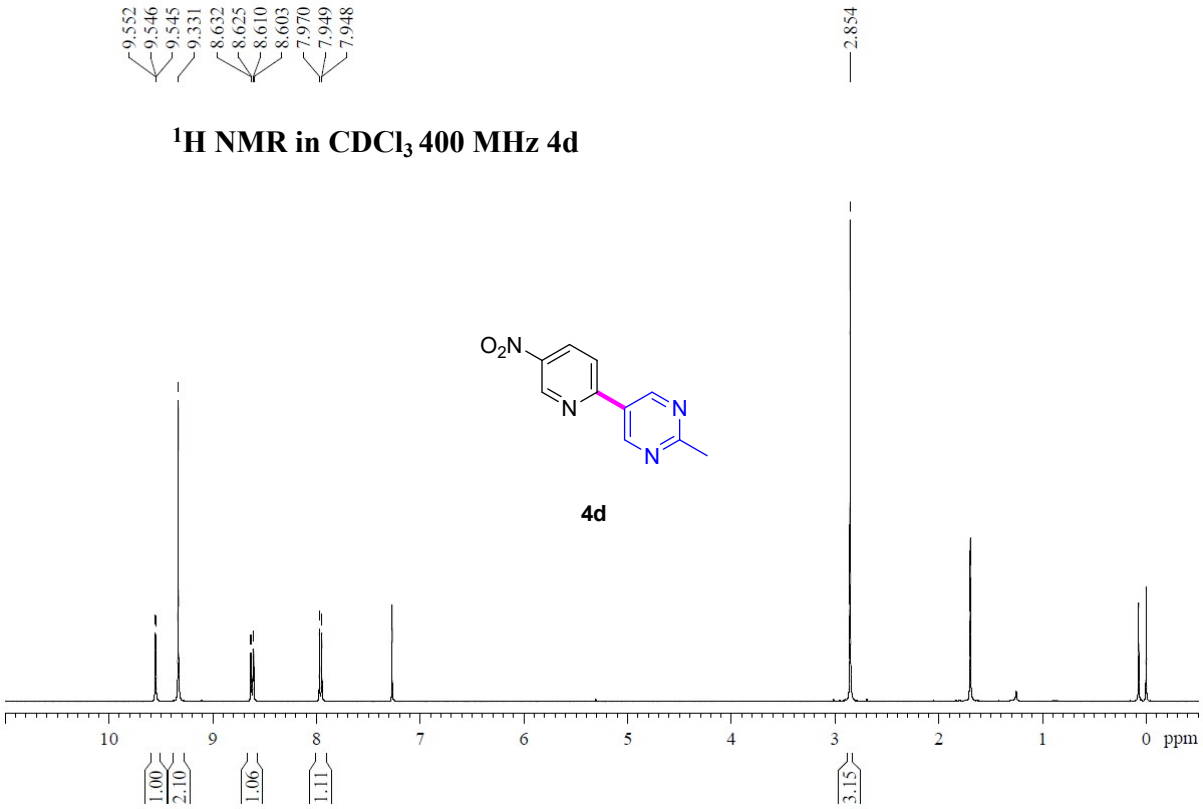
4c



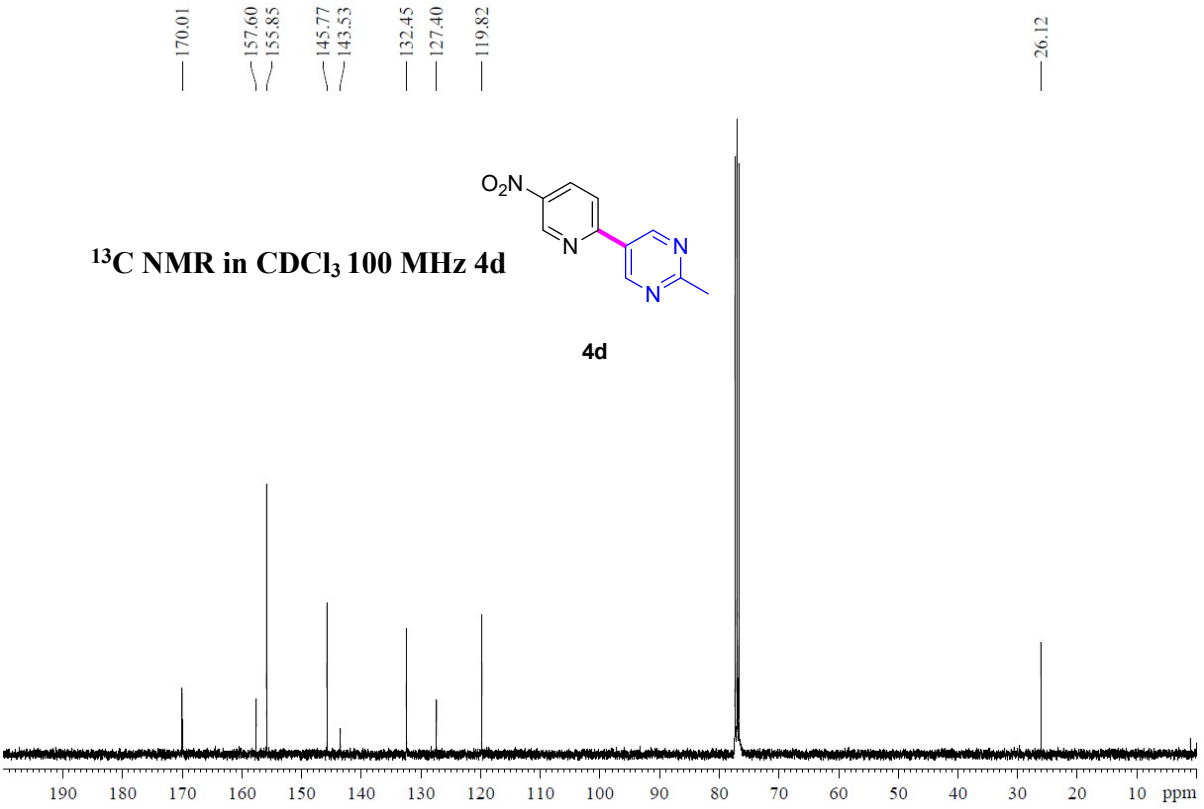
^{13}C NMR in $CDCl_3$ 100 MHz 4c

4c

^{1}H and ^{13}C NMR of Compound 4d

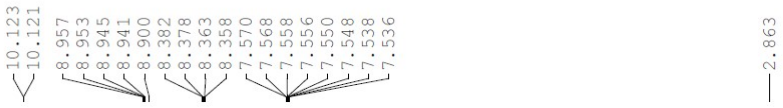


^{1}H NMR in $CDCl_3$ 400 MHz 4d

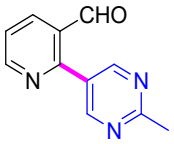


^{13}C NMR in $CDCl_3$ 100 MHz 4d

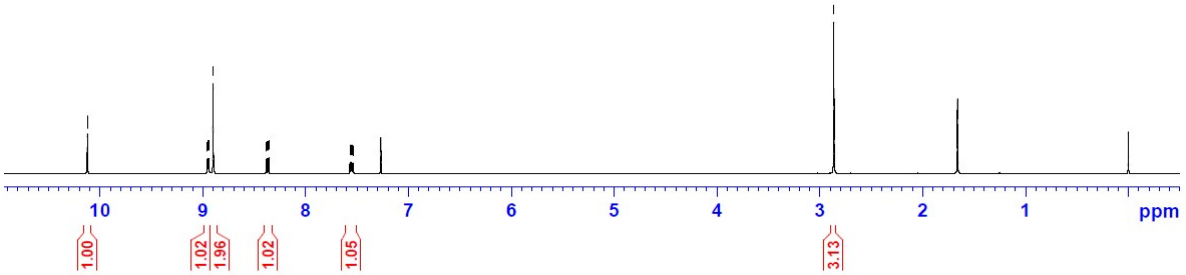
^{1}H and ^{13}C NMR of Compound 4e



^{1}H NMR in $CDCl_3$ 400 MHz 4e

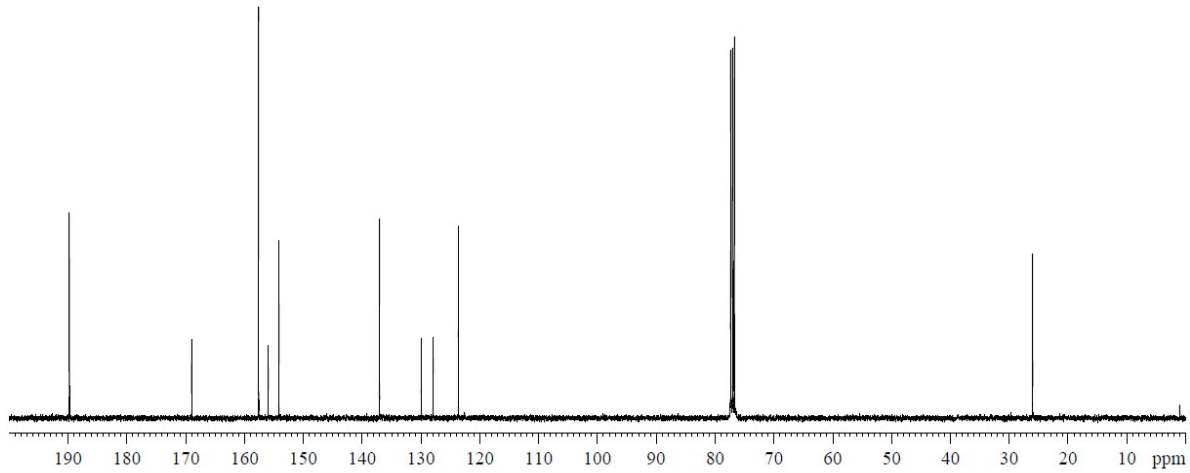


4e

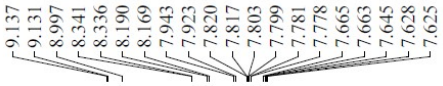


4e

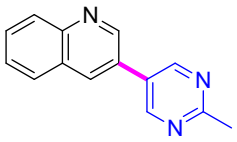
^{13}C NMR in $CDCl_3$ 100 MHz 4e



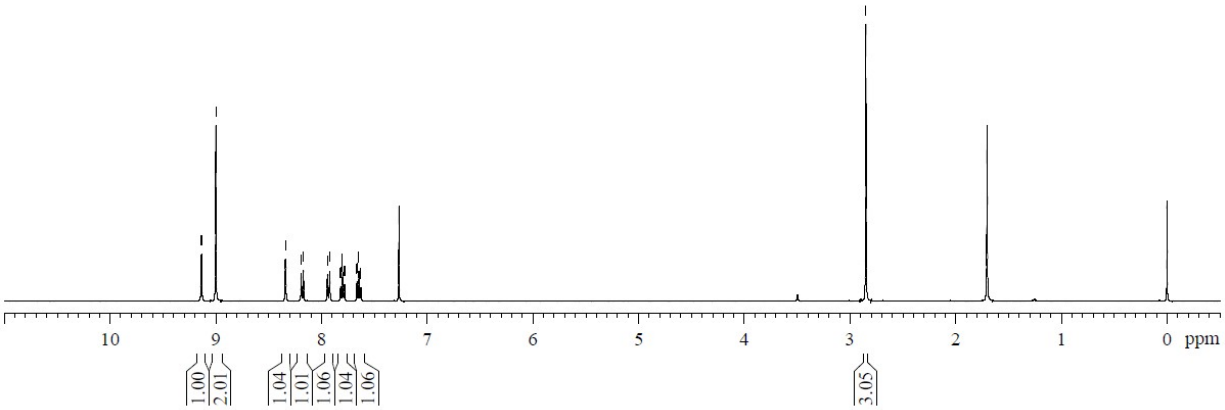
^{1}H and ^{13}C NMR of Compound 4f

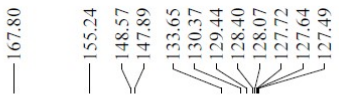


^{1}H NMR in $CDCl_3$ 400 MHz 4f

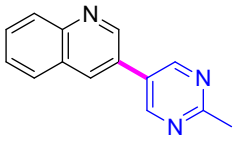


4f





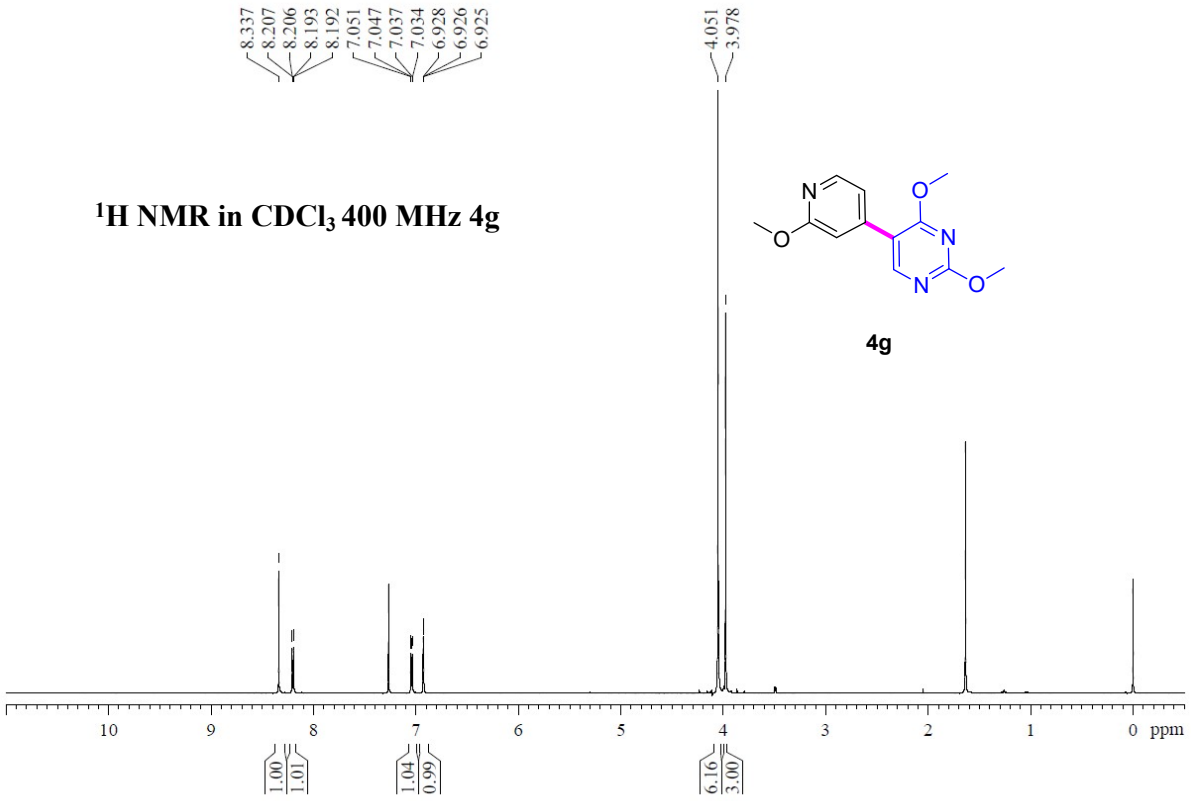
^{13}C NMR in $CDCl_3$ 100 MHz 4f



4f

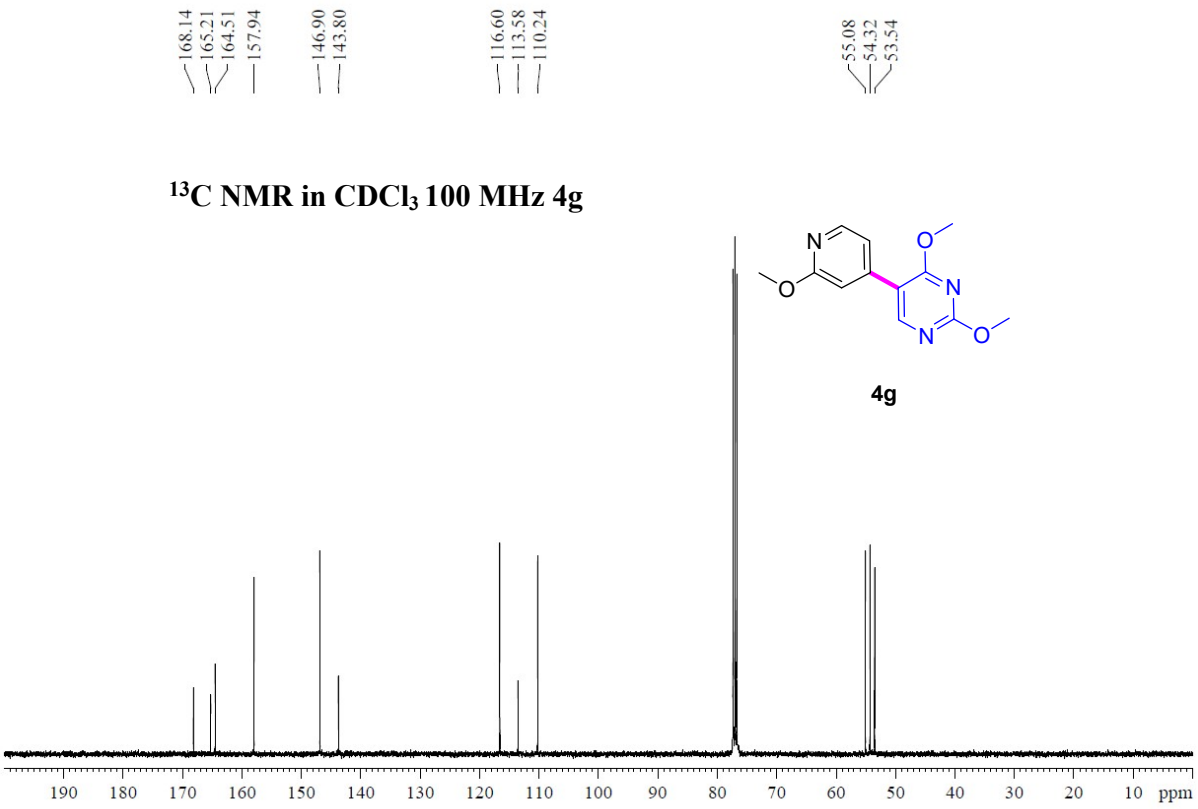
^{1}H and ^{13}C NMR of Compound 4g

^{1}H NMR in $CDCl_3$ 400 MHz 4g



4g

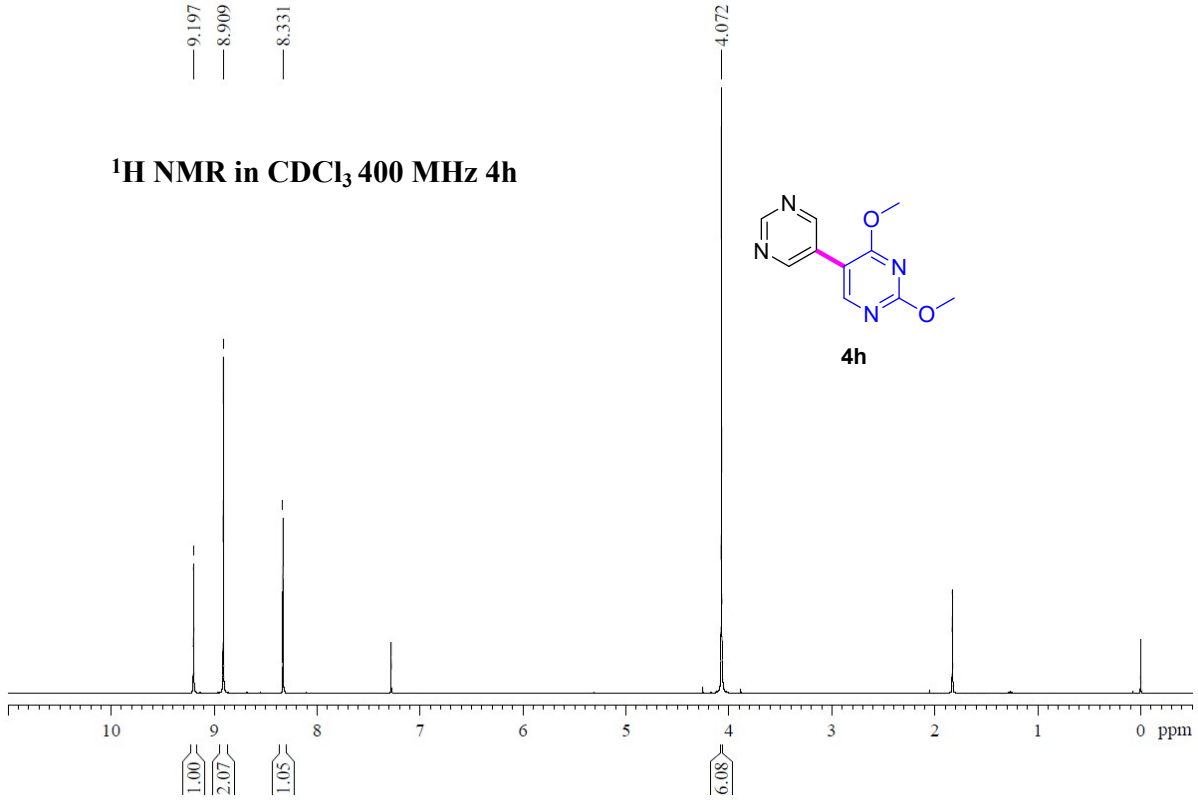
^{13}C NMR in $CDCl_3$ 100 MHz 4g



4g

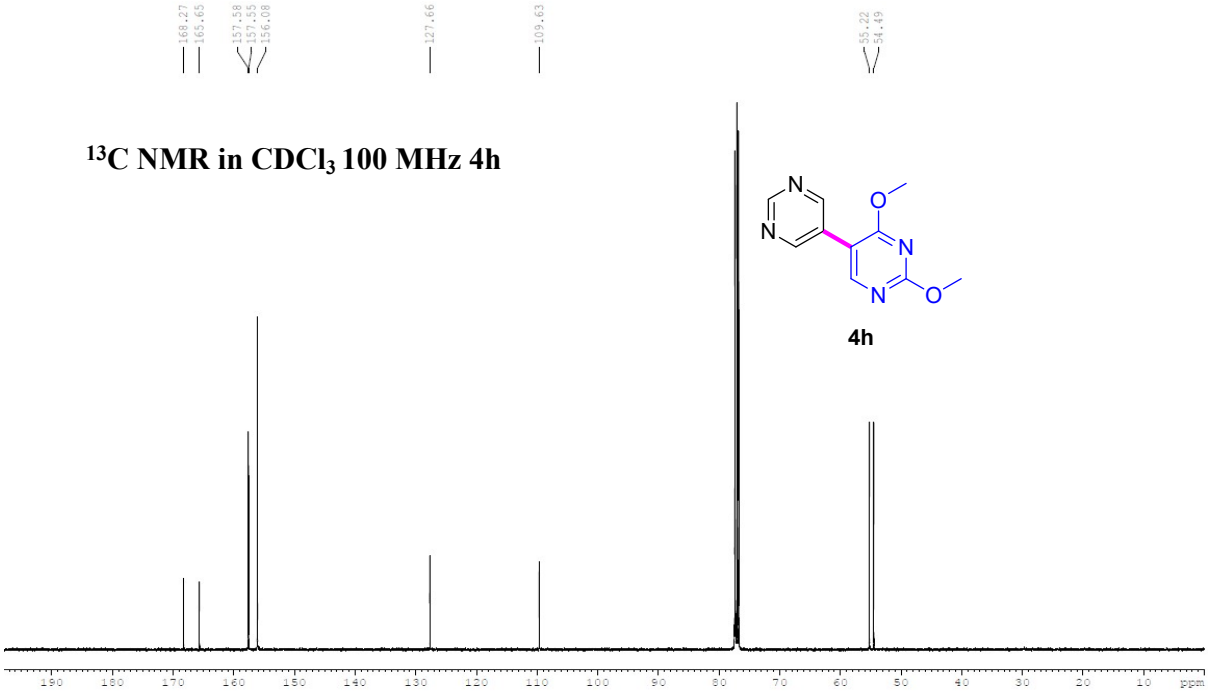
^{1}H and ^{13}C NMR of Compound 4h

^{1}H NMR in $CDCl_3$ 400 MHz 4h



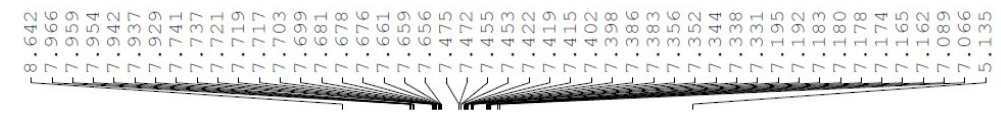
4h

^{13}C NMR in $CDCl_3$ 100 MHz 4h

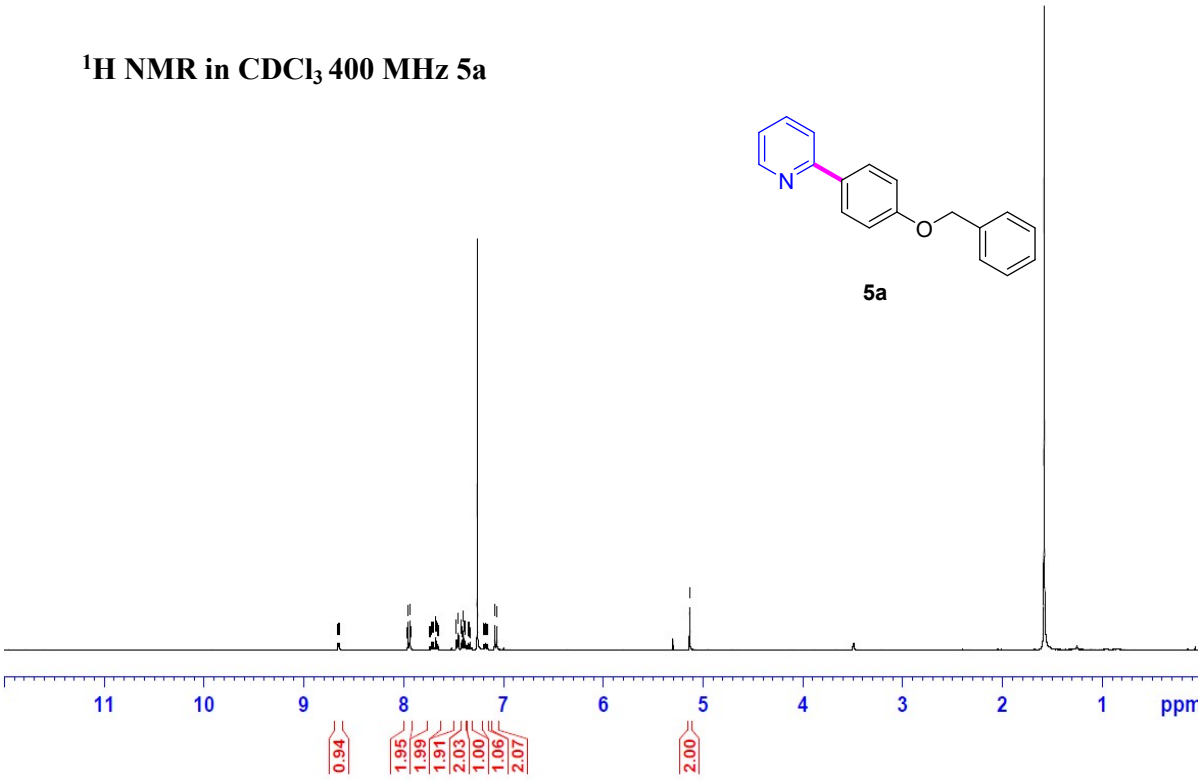


4h

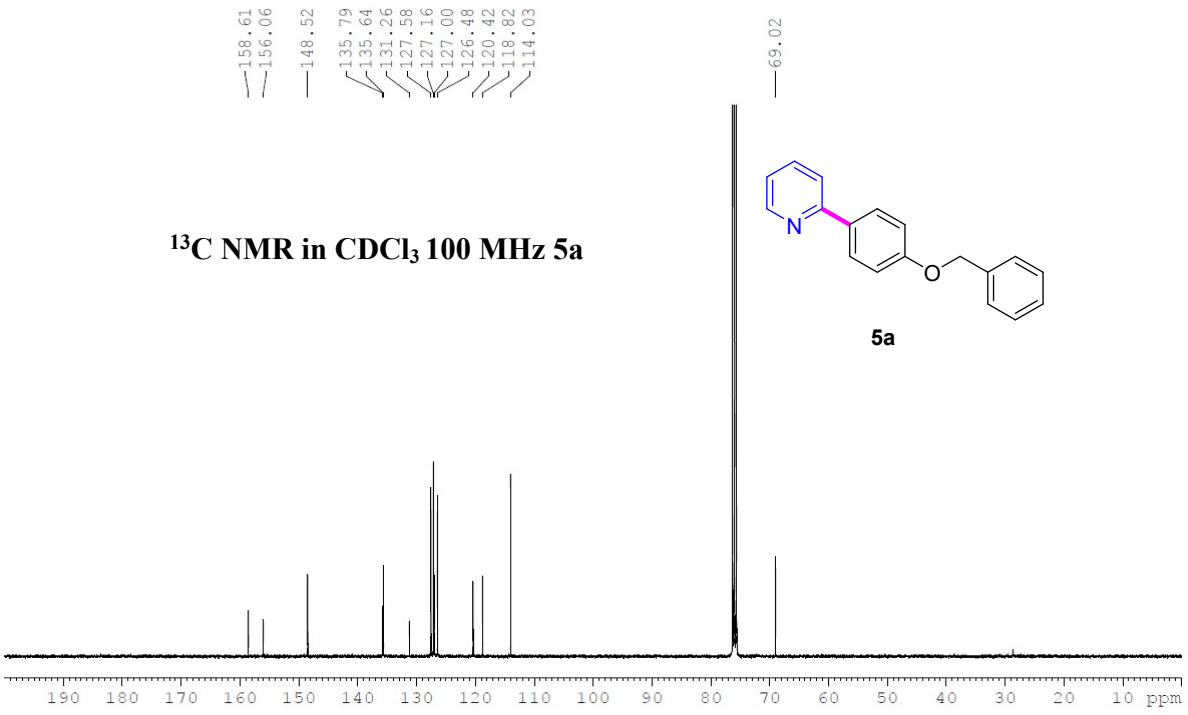
^{1}H and ^{13}C NMR of Compound 5a



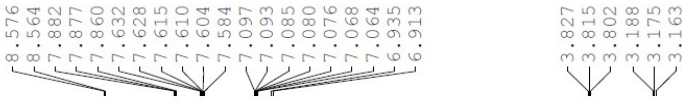
^{1}H NMR in $CDCl_3$ 400 MHz 5a



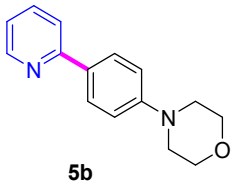
^{13}C NMR in $CDCl_3$ 100 MHz 5a



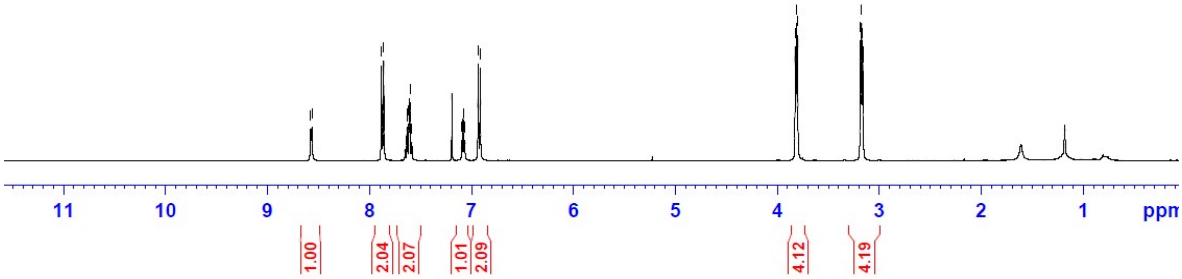
^{1}H and ^{13}C NMR of Compound 5b



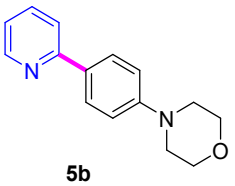
^{1}H NMR in $CDCl_3$ 400 MHz 5b



5b

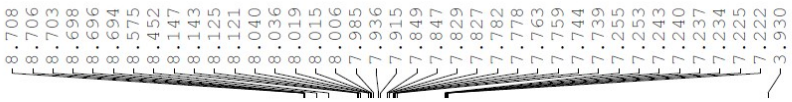


^{13}C NMR in $CDCl_3$ 100 MHz 5b

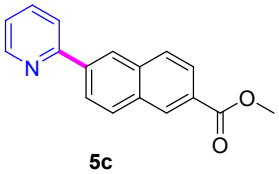


5b

^{1}H and ^{13}C NMR of Compound 5c



^{1}H NMR in $CDCl_3$ 400 MHz 5c



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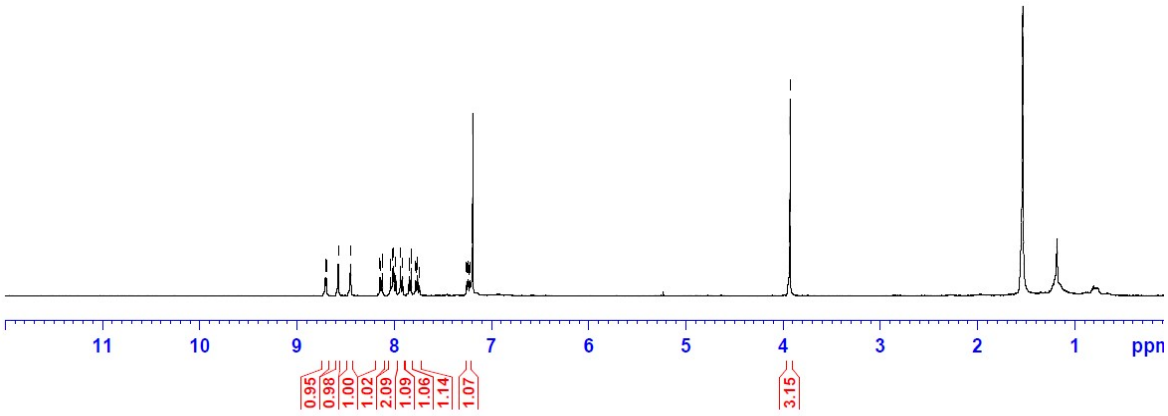
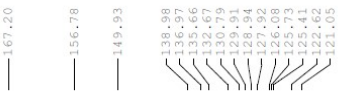
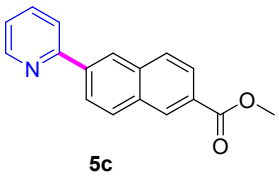
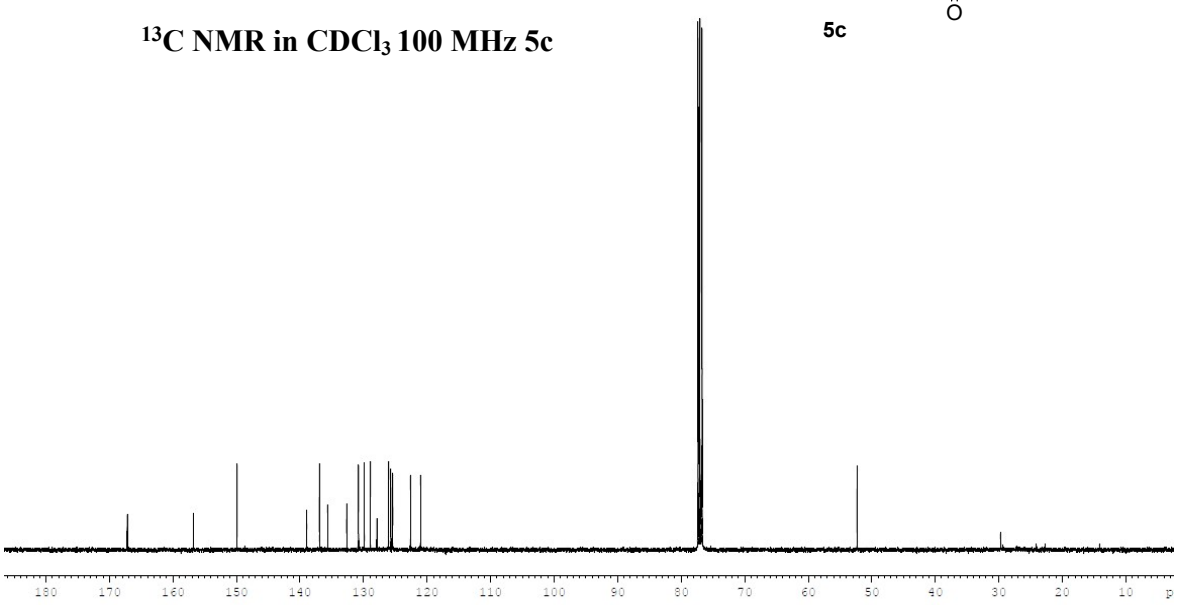




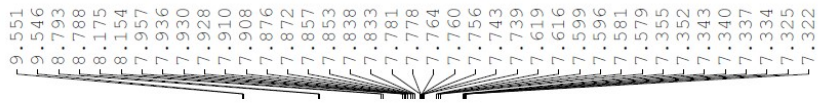


5c

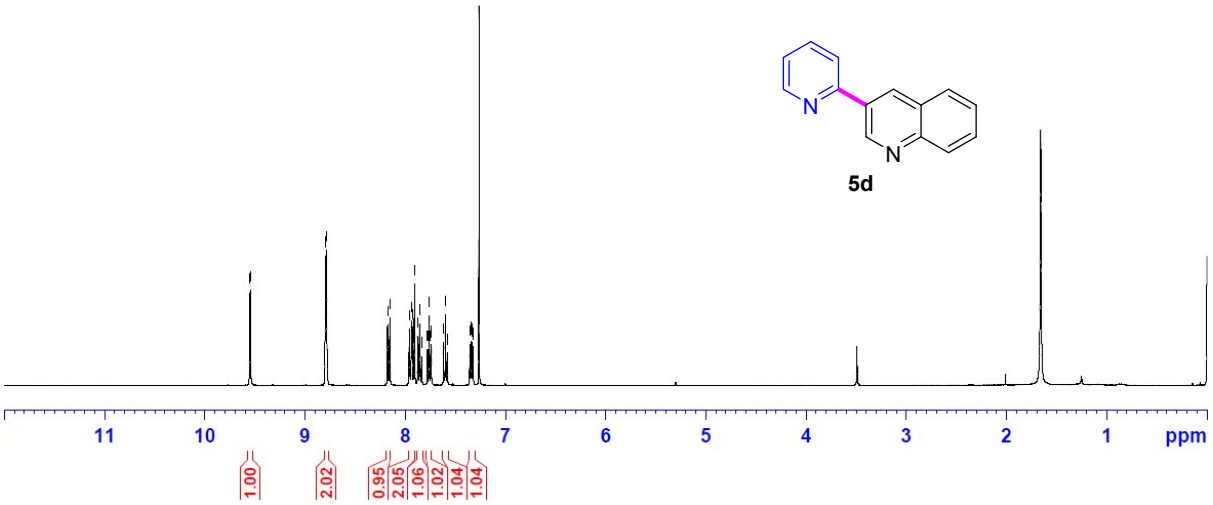
^{13}C NMR in $CDCl_3$ 100 MHz 5c

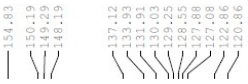


^{1}H and ^{13}C NMR of Compound 5d

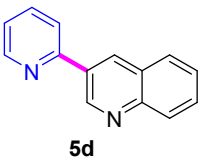


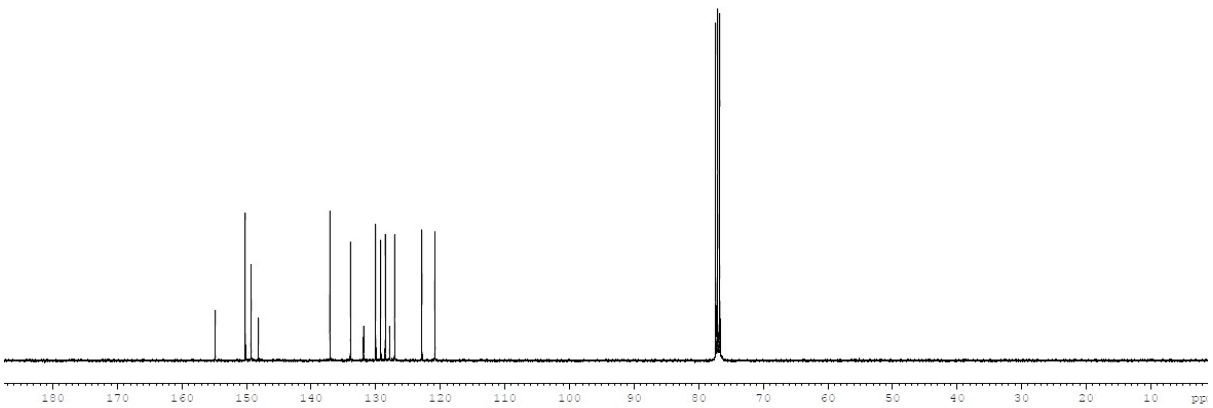
^{1}H NMR in $CDCl_3$ 400 MHz 5d



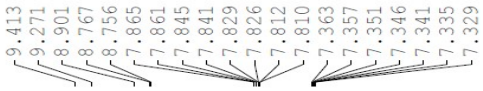


^{13}C NMR in $CDCl_3$ 100 MHz 5d

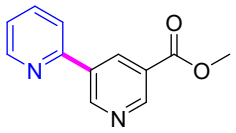




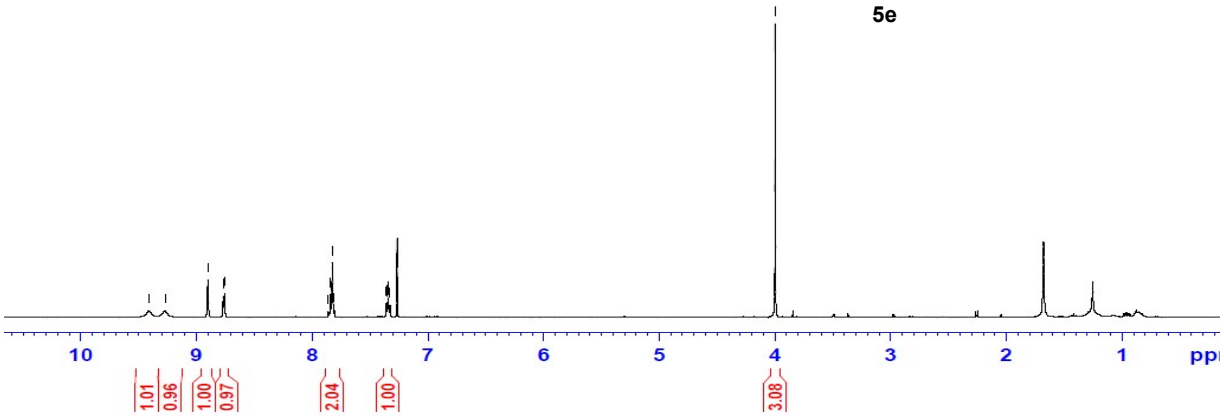
^{1}H and ^{13}C NMR of Compound 5e



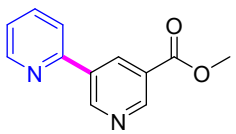
^{1}H NMR in $CDCl_3$ 400 MHz 5e



5e

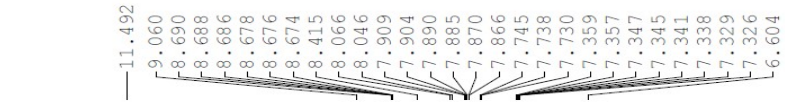


^{13}C NMR in $CDCl_3$ 100 MHz 5e

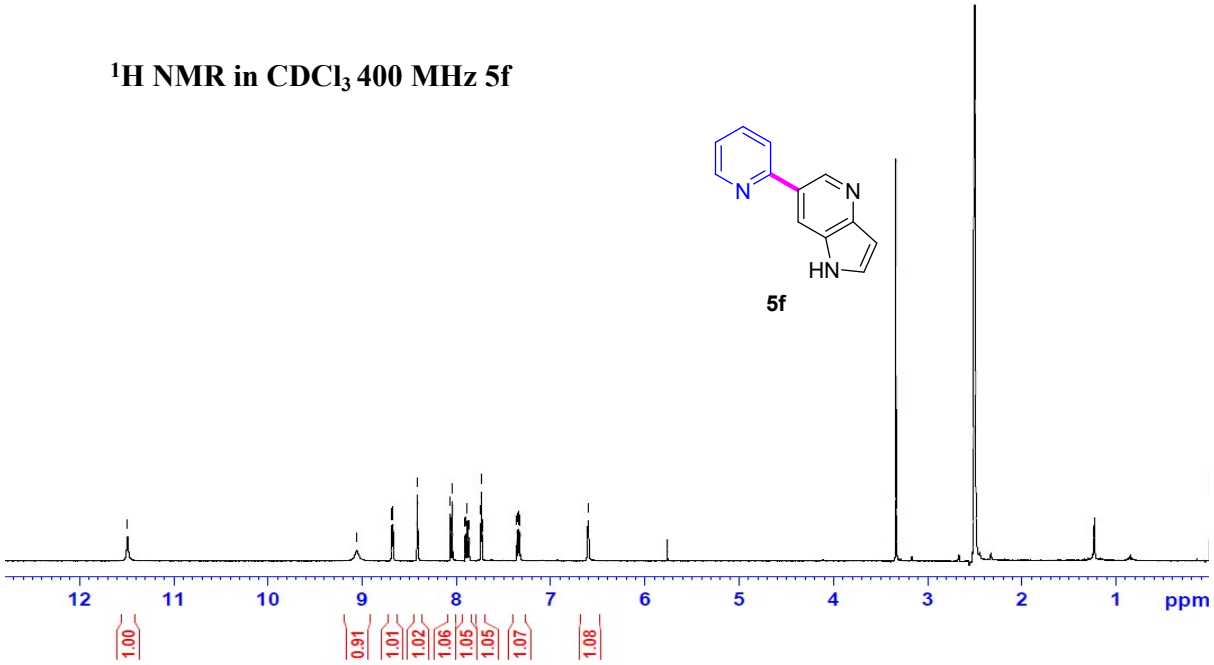


5e

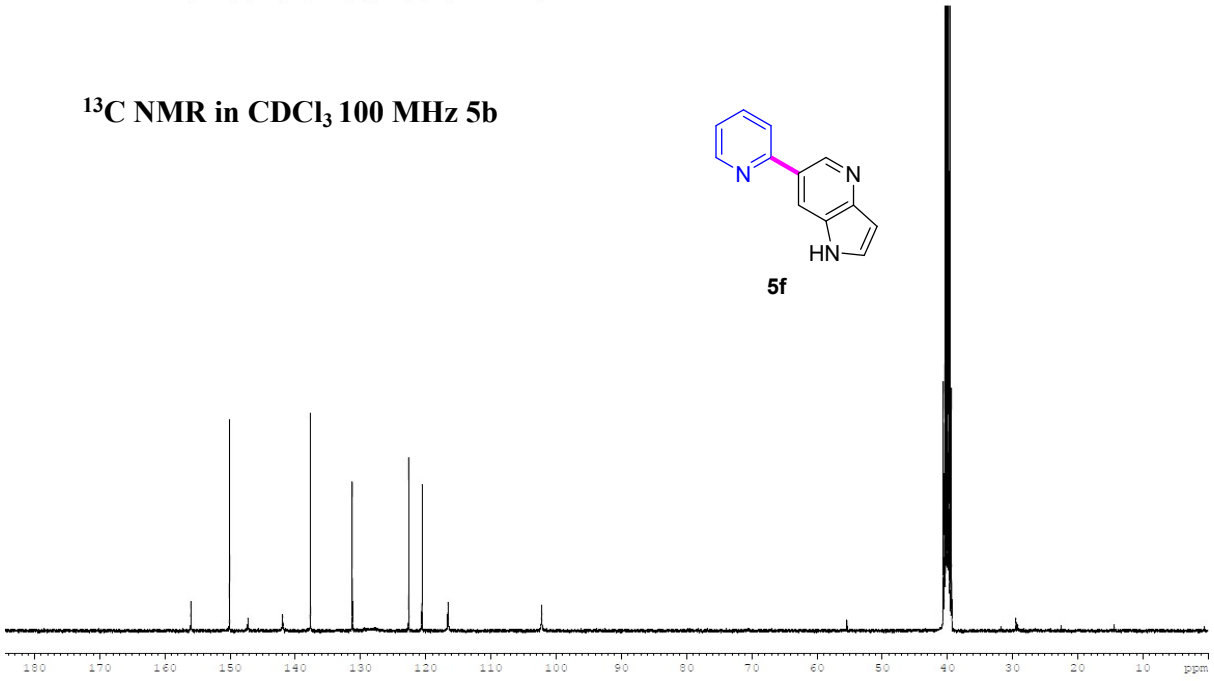
^{1}H and ^{13}C NMR of Compound 5f



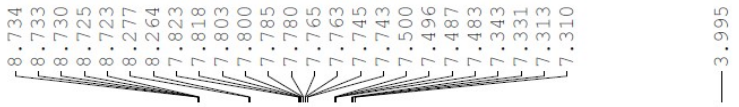
^{1}H NMR in $CDCl_3$ 400 MHz 5f



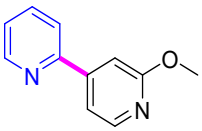
^{13}C NMR in $CDCl_3$ 100 MHz 5b



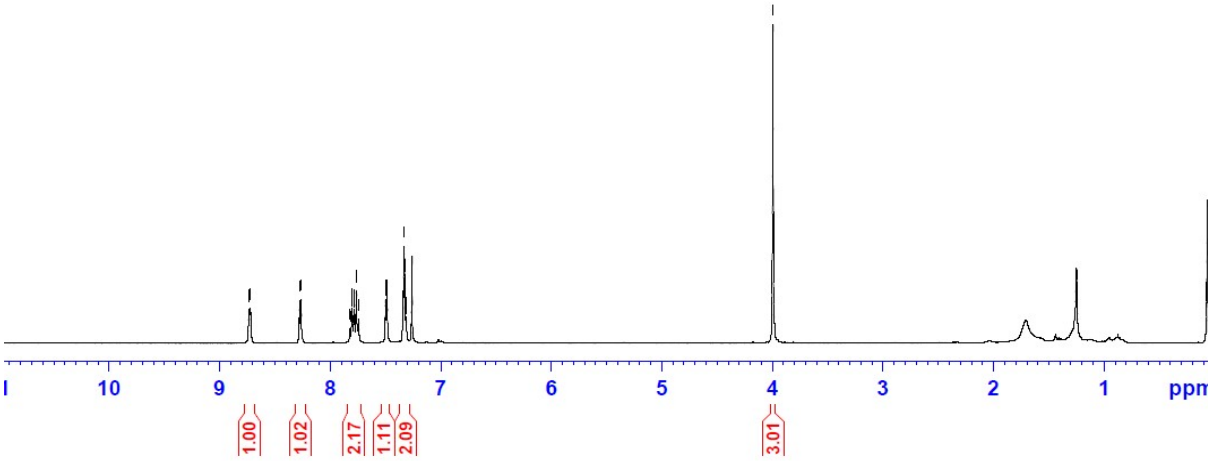
^{1}H and ^{13}C NMR of Compound 5g



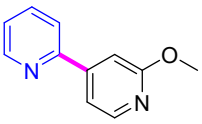
^{1}H NMR in $CDCl_3$ 400 MHz 5g



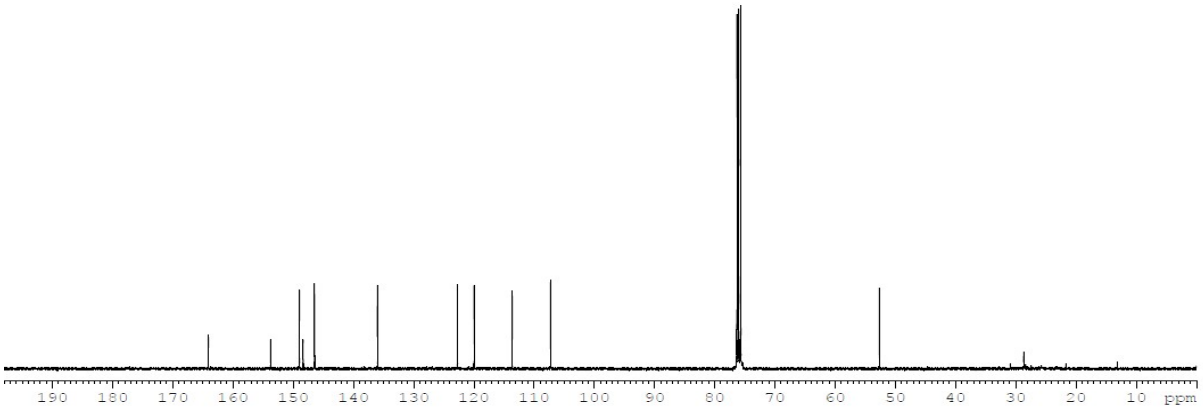
5g



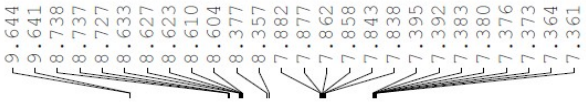
^{13}C NMR in $CDCl_3$ 100 MHz 5g



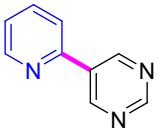
5g



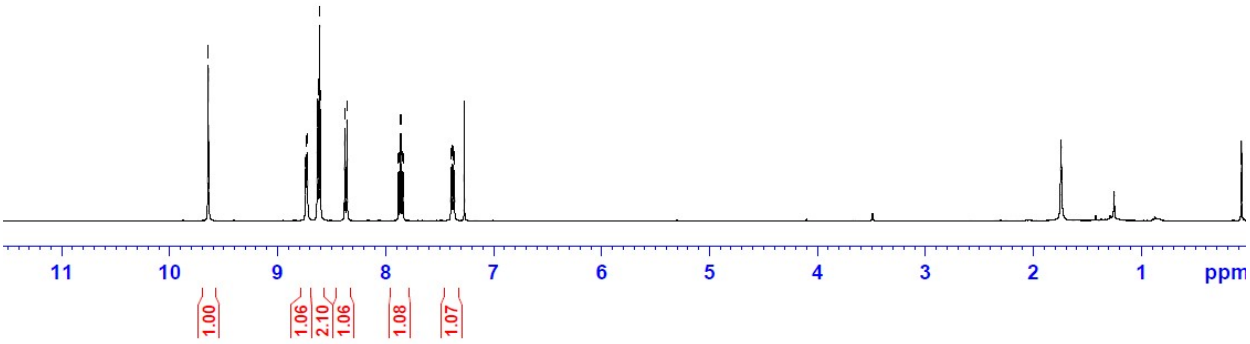
^{1}H and ^{13}C NMR of Compound 5h

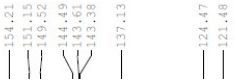


^{1}H NMR in $CDCl_3$ 400 MHz 5h

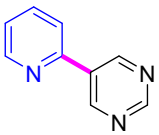


5h

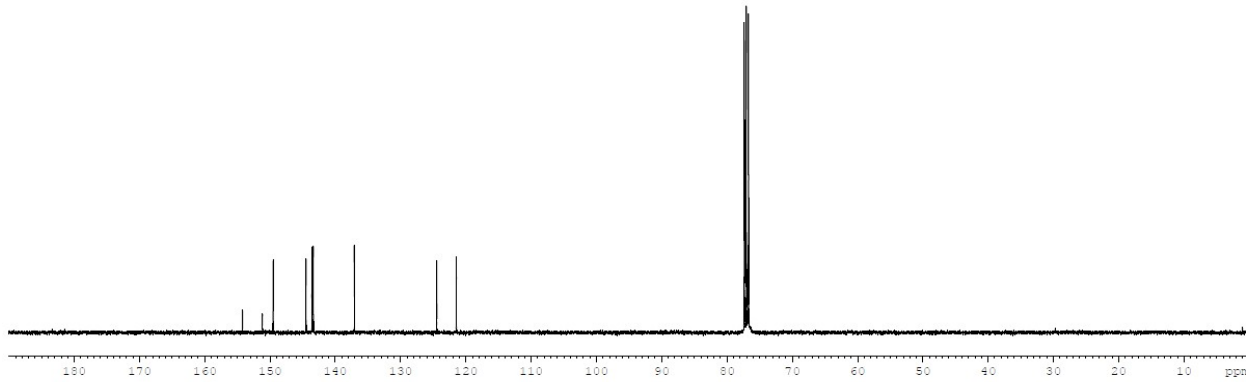




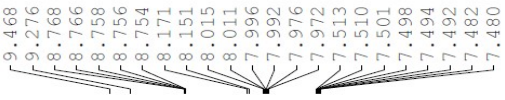
^{13}C NMR in $CDCl_3$ 100 MHz 5h



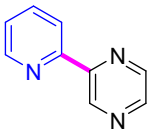
5h



^{1}H and ^{13}C NMR of Compound 5i

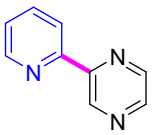


^{1}H NMR in $CDCl_3$ 400 MHz 5i



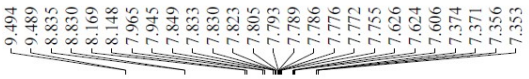
5i

^{13}C NMR in $CDCl_3$ 100 MHz 5i

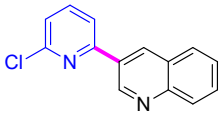


5i

^{1}H and ^{13}C NMR of Compound 5j



^{1}H NMR in $CDCl_3$ 400 MHz 5j



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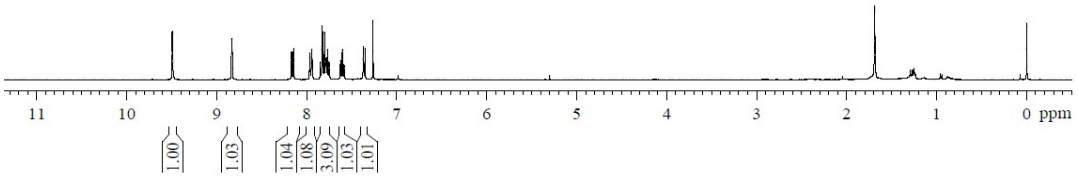
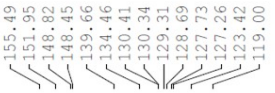
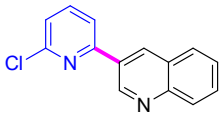


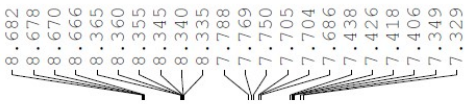




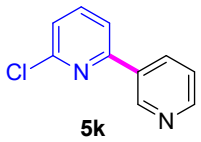
5j

^{13}C NMR in $CDCl_3$ 100 MHz 5j

^{1}H and ^{13}C NMR of Compound 5k



^{1}H NMR in $CDCl_3$ 400 MHz 5k



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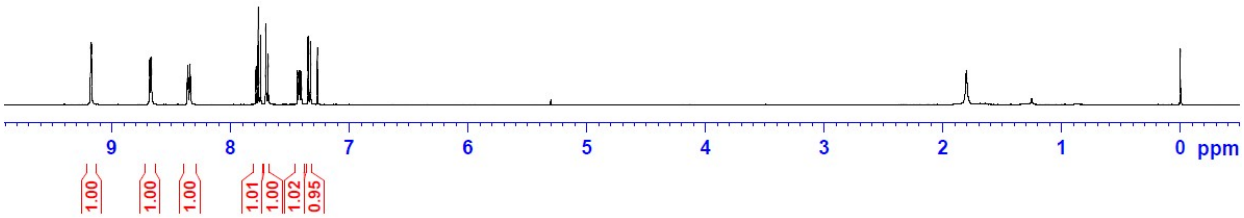
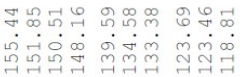
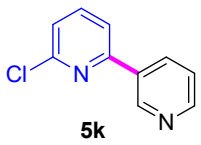


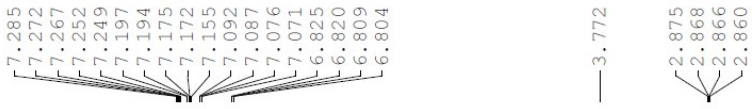


^{13}C NMR in $CDCl_3$ 100 MHz 5k

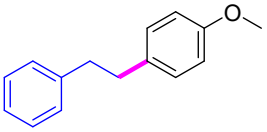


5k

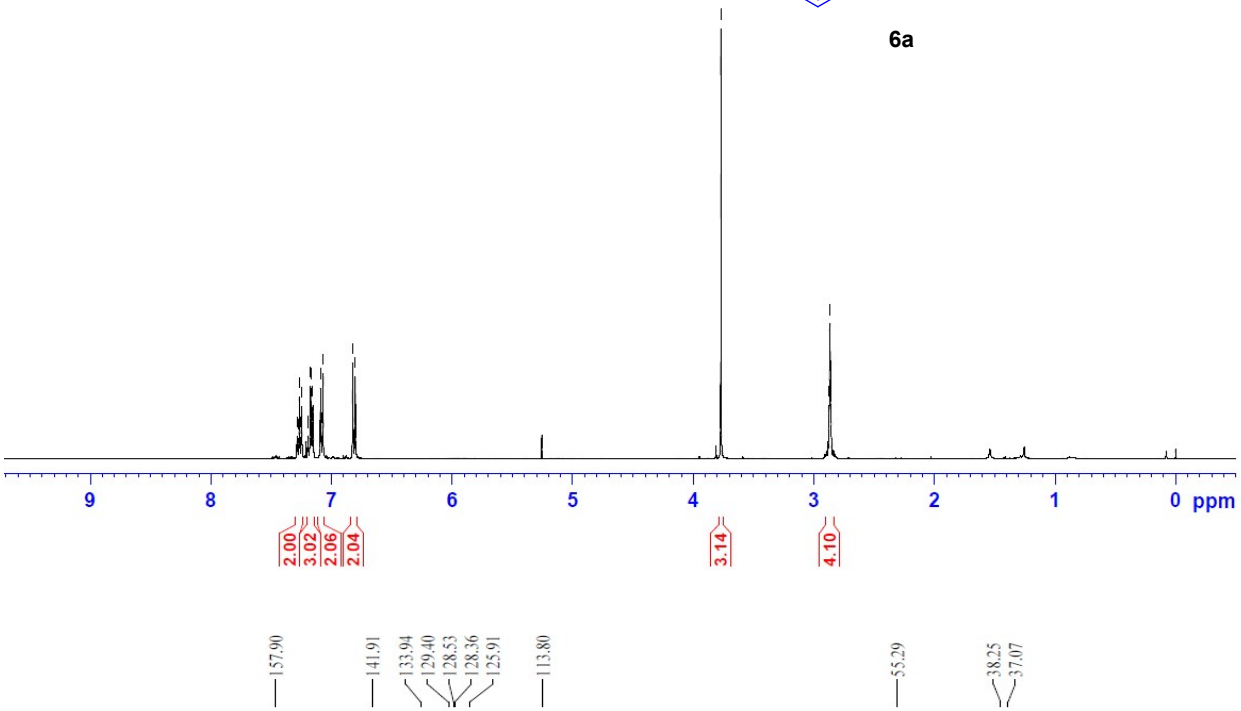
^{1}H and ^{13}C NMR of Compound 6a



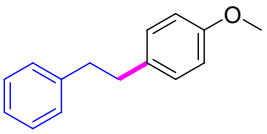
^{1}H NMR in $CDCl_3$ 400 MHz 6a



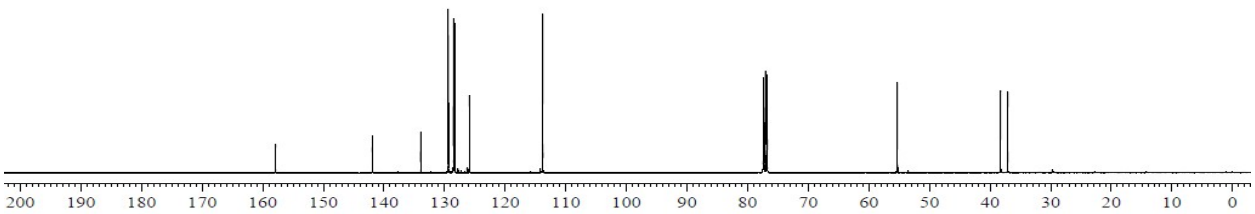
6a



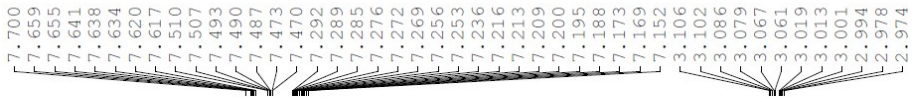
^{13}C NMR in $CDCl_3$ 100 MHz 6a



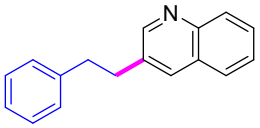
6a



^{1}H and ^{13}C NMR of Compound 6b



^{1}H NMR in $CDCl_3$ 400 MHz 6b



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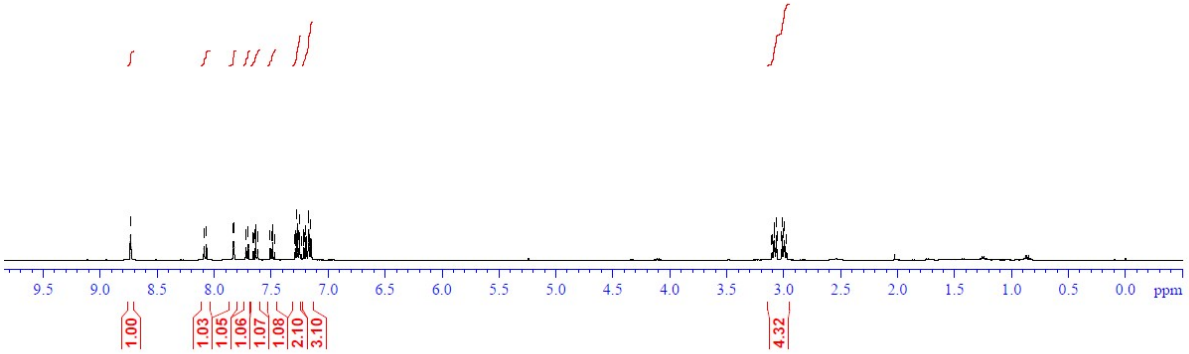
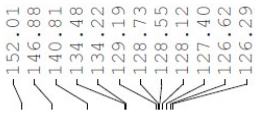
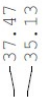
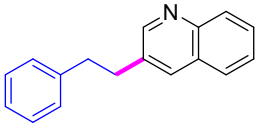






^{13}C NMR in $CDCl_3$ 100 MHz 6b



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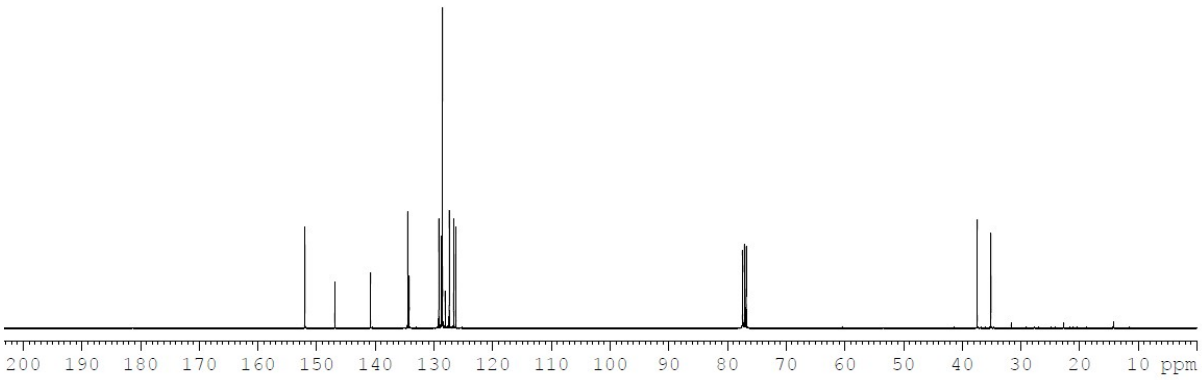
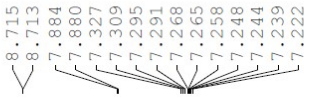
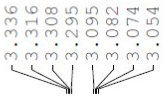
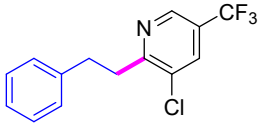


^{1}H, ^{13}C, and ^{19}F-NMR of Compound 6c





^{1}H NMR in $CDCl_3$ 400 MHz 6c



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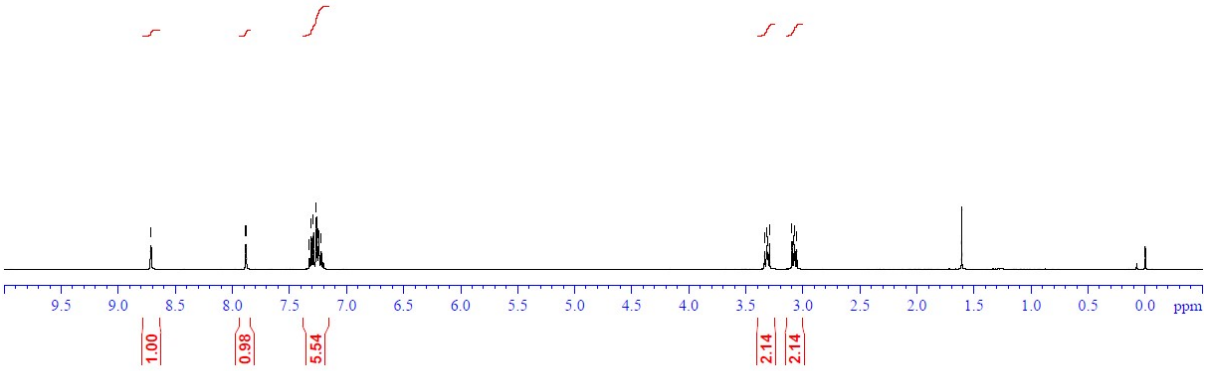
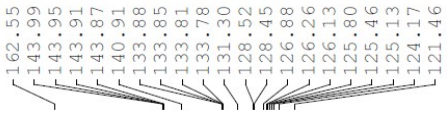
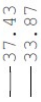
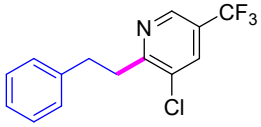




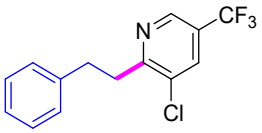


^{13}C NMR in $CDCl_3$ 100 MHz 6c



6c

^{19}F NMR in $CDCl_3$ 376 MHz 6c



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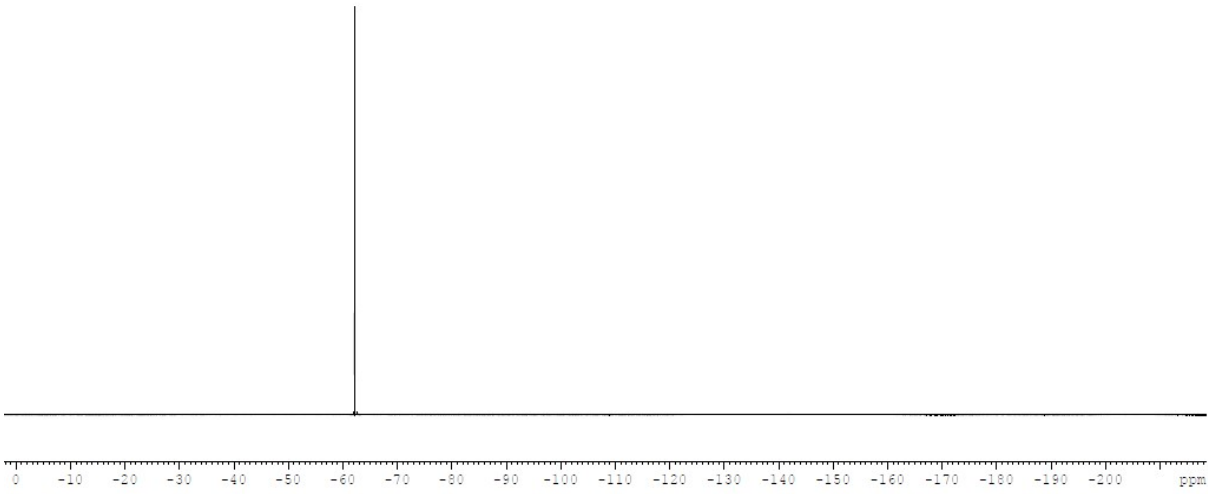
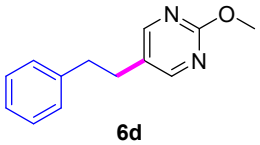


^{1}H and ^{13}C NMR of Compound 6d

^{1}H NMR in $CDCl_3$ 400 MHz 6d



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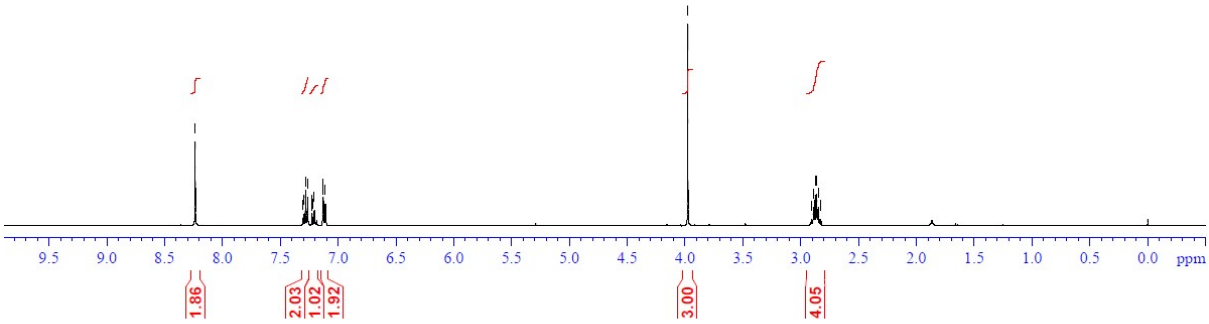
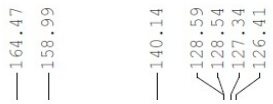
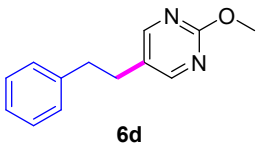
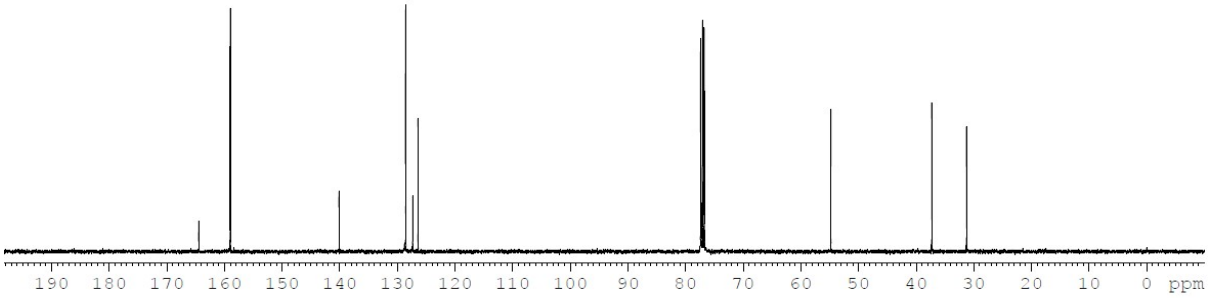




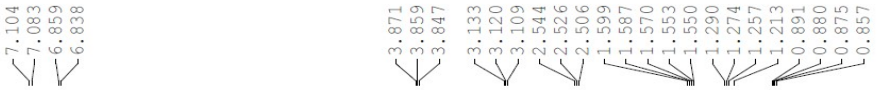
^{13}C NMR in $CDCl_3$ 100 MHz 6d



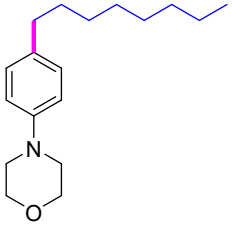
6d



^{1}H and ^{13}C NMR of Compound 6e



^{1}H NMR in $CDCl_3$ 400 MHz 6e



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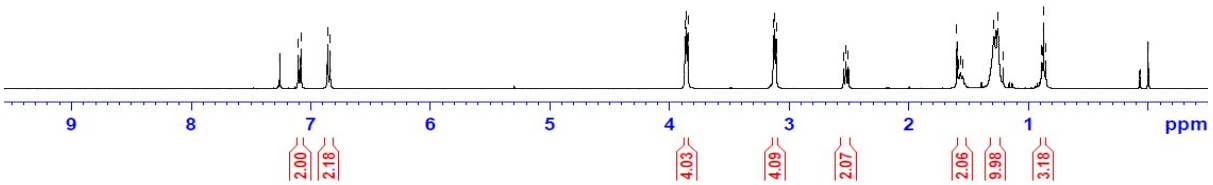
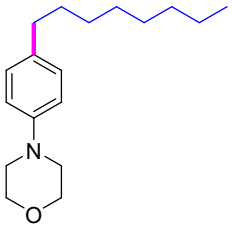


^{13}C NMR in $CDCl_3$ 100 MHz 6e



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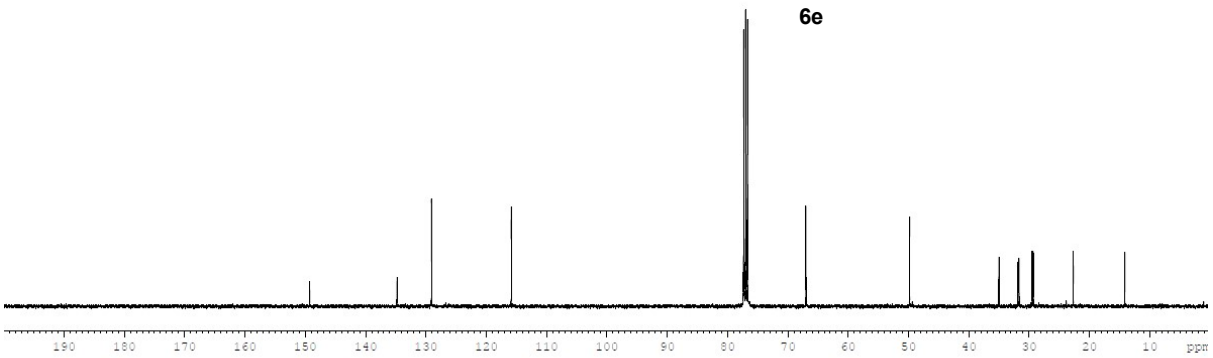
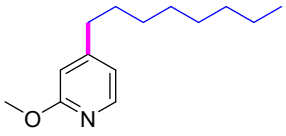


^{1}H and ^{13}C NMR of Compound 6f

^{1}H NMR in $CDCl_3$ 400 MHz 6f



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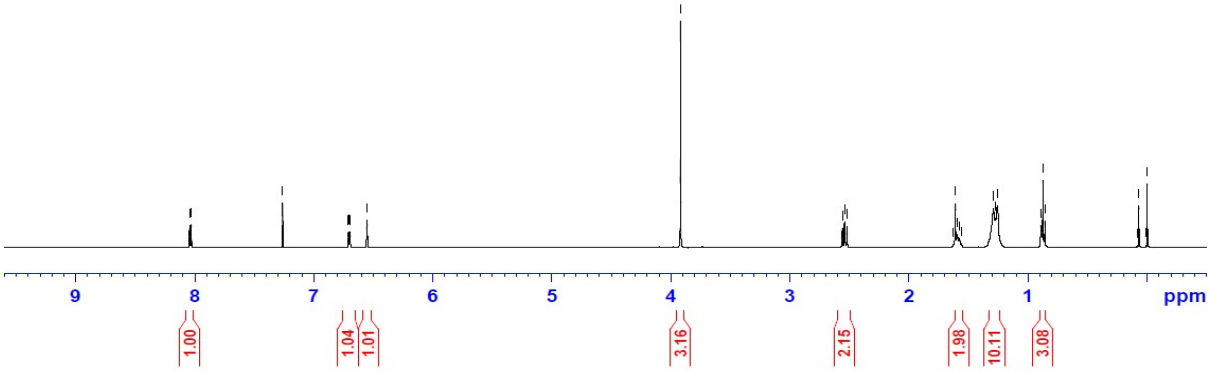
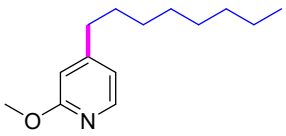


^{13}C NMR in $CDCl_3$ 100 MHz 6f



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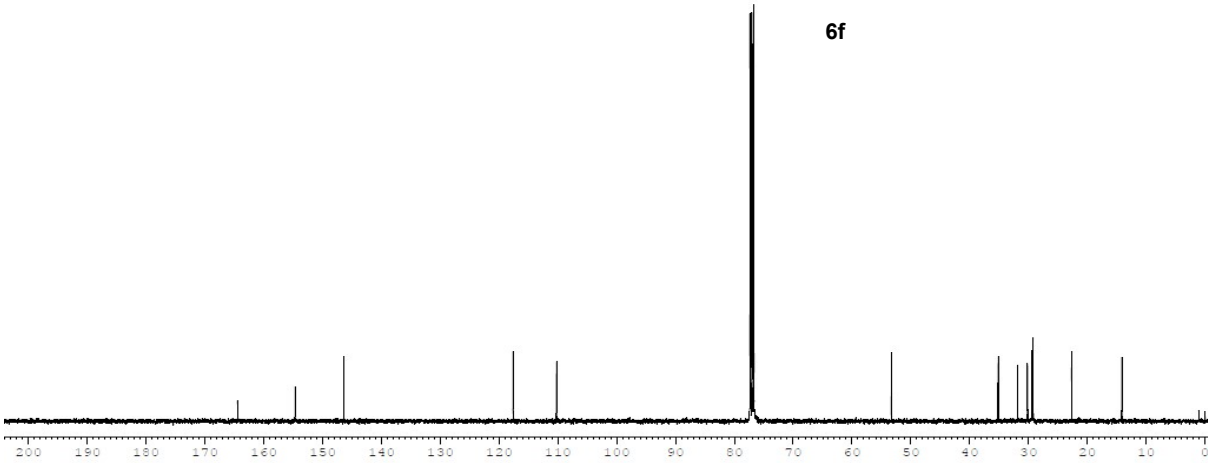
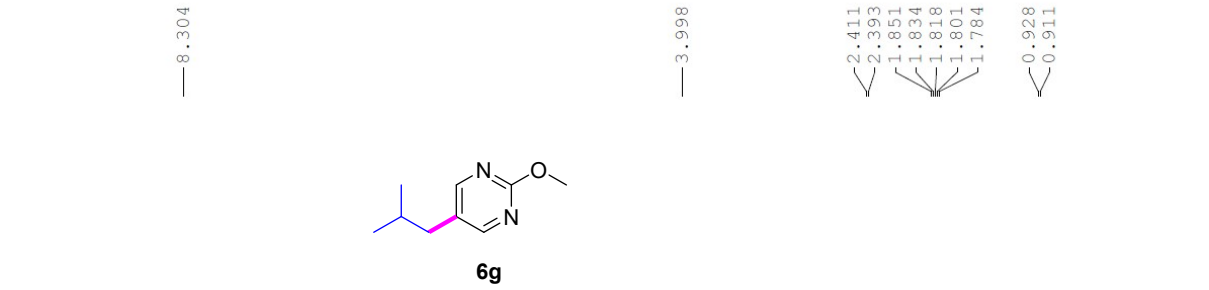
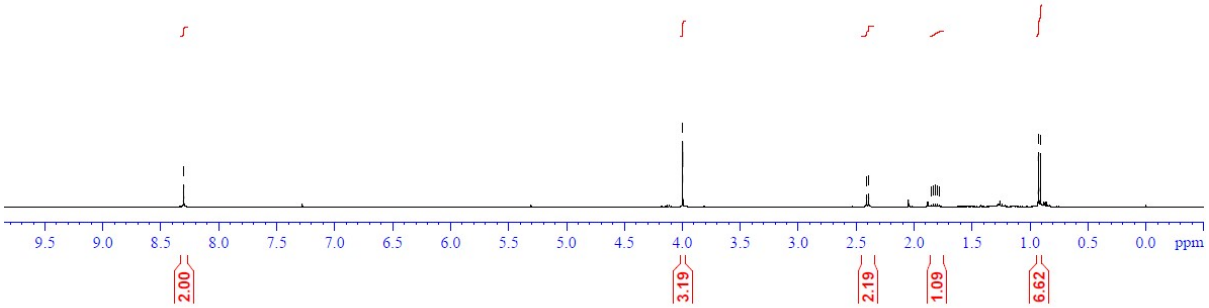


^{1}H and ^{13}C NMR of Compound 6g

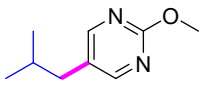


6g

^{1}H NMR in $CDCl_3$ 400 MHz 6g



^{13}C NMR in $CDCl_3$ 100 MHz 4g



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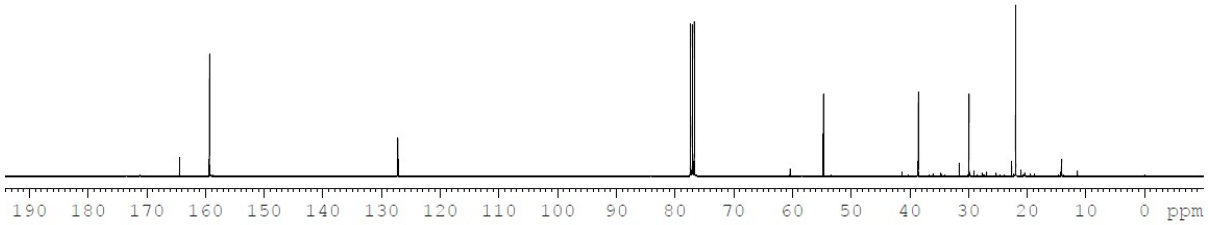


10. IPC-MS spectra for Pd-content:

IPC-MS spectra of compound-3m

FirstSource Laboratory Solutions LLP.
(Analytical Services)

TEST REPORT

REPORT NO: FSLS(AS)-5231523001	DATE OF ISSUANCE OF REPORT: 27/12/2023
JOB REGISTRATION NO: FSLS(AS)-5231523	SAMPLE ID: FSLS(AS)-5231523001

CUSTOMER DETAILS:	SAMPLE DETAILS:	
ISSUED TO: M/s Curia India Pvt.Ltd	NAME OF SAMPLE BRAND/ GRADE/ VARIETY BATCH NO/ LOT NO/ CODE DATE OF MANUFACTURING	: IN-BDS-G-32 : NA : IN-BDS-G-32 : NA
ADDRESS: Thurkapally, Shameerpet Genome valley,RR District Hyderabad- 500078.	DATE OF EXPIRY QUANTITY OF SAMPLE RECEIVED MODE OF PACKING SEAL DETAILS ANY OTHER INFORMATION	: NA : ~1.0 g x 1 No : Packed in sealed vial : Intact : NA

SAMPLE NOT DRAWN BY FSLS(AS)

TEST DETAILS AND RESULTS:

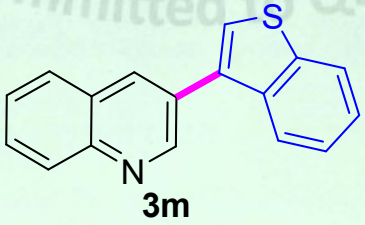
SAMPLE REGISTRATION DATE: 22/12/2023	ANALYSIS START DATE: 26/12/2023	ANALYSIS COMPLETED DATE: 26/12/2023

S No	TESTS	METHOD	UNIT	RESULT
1	Palladium as Pd	FSLS(AS)/DP-STP-044,VERSION:08	mg/kg (ppm)	12.01

Remarks:

1) Samples tested on Received Basis.
2) Instrument used: ICP-MS (Make: Agilent, Model: 7800).
3) ppm: parts per million, mg: milligram, kg: kilogram, NA: Not Applicable.
4) The above reported results are for R&D information purpose only and not for any regulatory submission or QC release.

***** End of Report ****



3m

For FirstSource Laboratory Solutions LLP.
(Analytical Services)

27/12/2023
V Raju
(Sr.Manager – Drugs & Pharma)
Authorized Signatory

ORIGINAL

Page 1 of 1

No: 658657

Note : This report is subject to the terms & conditions mentioned overleaf.

IPC-MS spectra of compound-4h

FirstSource Laboratory Solutions LLP.
(Analytical Services)

TEST REPORT

REPORT NO: FSLS(AS)-5231523002	DATE OF ISSUANCE OF REPORT: 27/12/2023
JOB REGISTRATION NO: FSLS(AS)-5231523	SAMPLE ID: FSLS(AS)-5231523002

CUSTOMER DETAILS:	SAMPLE DETAILS:	
ISSUED TO: M/S Curia India Pvt.Ltd	NAME OF SAMPLE BRAND/ GRADE/ VARIETY BATCH NO/ LOT NO/ CODE DATE OF MANUFACTURING DATE OF EXPIRY QUANTITY OF SAMPLE RECEIVED MODE OF PACKING SEAL DETAILS ANY OTHER INFORMATION	: IN-MRK-F-100-5 : NA : IN-MRK-F-100-5 : NA : NA : ~1.0 g x 1 No : Packed in sealed vial : Intact : NA
ADDRESS: Thurkapally, Shameerpet Genome valley,RR District Hyderabad- 500078.		

SAMPLE NOT DRAWN BY FSLS(AS)

TEST DETAILS AND RESULTS:

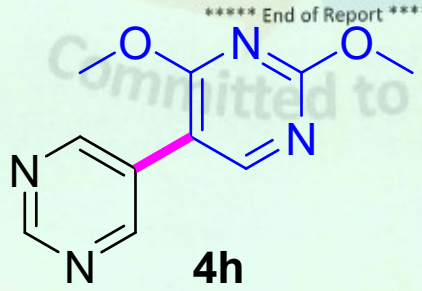
SAMPLE REGISTRATION DATE: 22/12/2023	ANALYSIS START DATE: 26/12/2023	ANALYSIS COMPLETED DATE: 26/12/2023

S No	TESTS	METHOD	UNIT	RESULT
1	Palladium as Pd	FSLS(AS)/DP-STP-044,VERSION:08	mg/kg (ppm)	41.20

Remarks:

1) Samples tested on Received Basis.
2) Instrument used: ICP-MS (Make: Agilent, Model: 7800).
3) ppm: parts per million, mg: milligram, kg: kilogram, NA: Not Applicable.
4) The above reported results are for R&D information purpose only and not for any regulatory submission or QC release.

***** End of Report ****



4h

For FirstSource Laboratory Solutions LLP.
(Analytical Services)

27/12/2023

V Raju
(Sr.Manager – Drugs & Pharma)
Authorized Signatory

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Page 1 of 1

No:

Note : This report is subject to the terms & conditions mentioned overleaf.

IPC-MS spectra of compound-5a

FirstSource Laboratory Solutions LLP.
(Analytical Services)

FirstSource Laboratory Solutions
Committed to Quality

TEST REPORT

REPORT NO: FSLS(AS)-5231523003	DATE OF ISSUANCE OF REPORT: 27/12/2023
JOB REGISTRATION NO: FSLS(AS)-5231523	SAMPLE ID: FSLS(AS)-5231523003

CUSTOMER DETAILS:	SAMPLE DETAILS:	
ISSUED TO: M/S Curia India Pvt.Ltd	NAME OF SAMPLE BRAND/ GRADE/ VARIETY BATCH NO/ LOT NO/ CODE DATE OF MANUFACTURING DATE OF EXPIRY QUANTITY OF SAMPLE RECEIVED MODE OF PACKING SEAL DETAILS ANY OTHER INFORMATION	: IN-MRK-G-116-1 : NA : IN-MRK-G-116-1 : NA : NA : ~1.0 g x 1 No : Packed in sealed vial : Intact : NA
ADDRESS: Thurkapally, Shameerpet Genome valley,RR District Hyderabad- 500078.		

SAMPLE NOT DRAWN BY FSLS(AS)

TEST DETAILS AND RESULTS:

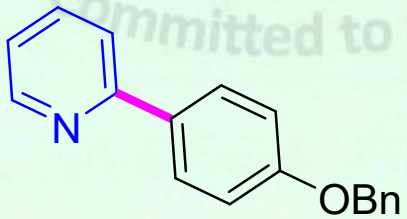
SAMPLE REGISTRATION DATE: 22/12/2023	ANALYSIS START DATE: 26/12/2023	ANALYSIS COMPLETED DATE: 26/12/2023

S No	TESTS	METHOD	UNIT	RESULT
1	Palladium as Pd	FSLS(AS)/DP-STP-044,VERSION:08	mg/kg (ppm)	1.88

Remarks:

1) Samples tested on Received Basis.
2) Instrument used: ICP-MS (Make: Agilent, Model: 7800).
3) ppm: parts per million, mg: milligram, kg: kilogram, NA: Not Applicable.
4) The above reported results are for R&D information purpose only and not for any regulatory submission or QC release.

***** End of Report ****



5a

For FirstSource Laboratory Solutions LLP.
(Analytical Services)

27/12/2023

V Raju
(Sr.Manager – Drugs & Pharma)
Authorized Signatory

ORIGINAL

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No:

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Note : This report is subject to the terms & conditions mentioned overleaf.

11. References:

1. Pena, M. A.; Perez Sestelo, J.; Sarandeses, L. A. Palladium-Catalyzed Aryl− Aryl Cross-Coupling Reaction Using Ortho-Substituted Arylindium Reagents. *J. Org. Chem*. **2007**, *72*, 1271.
2. Bhattacharjee, P.; Dewan, A.; Boruah, P. K.; Das, M. R.; Mahanta, S. P.; Thakur, A. J.; Bora, U. Bimetallic Pd–Ag nanoclusters decorated micro-cellulose bio-template towards efficient catalytic Suzuki–Miyaura coupling reaction of nitrogen-rich heterocycles. *Green Chem*. **2022**, *24*, 7208.
3. Chen, W.; Chen, W.; Liu, M.; Wu, H. Construction of heterobiaryl skeletons through Pd-catalyzed cross-coupling of nitroarenes and heterocyclic arylborononate esters with a sterically demanding NHC ligand. *Org. Lett*. **2022**, *24*, 6983.
4. Horan, A. M.; Duong, V. K.; McGarrigle, E. M. Synthesis of Bis-heteroaryls Using Grignard Reagents and Pyridylsulfonium Salts. *Org. Lett*. **2021**, 23, 9089.
5. Barder, T. E.; Buchwald, S. L. Efficient catalyst for the suzuki− miyaura coupling of potassium aryl trifluoroborates with aryl chlorides. *Org. Lett*. **2004**, *6*, 2649.
6. Pena, M. A.; Perez Sestelo, J.; Sarandeses, L. A. Palladium-Catalyzed Aryl− Aryl Cross-Coupling Reaction Using ortho-Substituted Arylindium Reagents. *J. Org. Chem.* **2007**, *72*, 1271.
7. Cervantes-Reyes, A.; Smith, A. C.; Chinigo, G. M.; Blakemore, D. C.; Szostak, M. Decarbonylative Pd-catalyzed Suzuki cross-coupling for the synthesis of structurally diverse heterobiaryls. *Org. Lett*. **2022**, *24*, 1678.
8. Saygili, N.; Batsanov, A. S.; Bryce, M. R. 5-Pyrimidylboronic acid and 2-methoxy-5-pyrimidylboronic acid: new heteroarylpyrimidine derivatives via Suzuki cross-coupling reactions. *Org. Biomol. Chem*. **2004**, *2*, 852.
9. Lai, B.; Ye, M.; Liu, P.; Li, M.; Bai, R.; Gu, Y. A novel and robust heterogeneous Cu catalyst using modified lignosulfonate as support for the synthesis of nitrogen-containing heterocycles. *Beilstein J. Org. Chem*. **2020**, *16*, 2888.
10. Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. Ni(0)/NHC-catalyzed amination of N-heteroaryl methyl ethers through the cleavage of carbon–oxygen bonds. *Tetrahedron*, **2012**, *68*, 5157.
11. Kudo, N.; Perseghini, M.; Fu, G. C. A versatile method for Suzuki cross-coupling reactions of nitrogen heterocycles. *Angew. Chem., Int. Ed*. **2006**, 45, 1282.

12. Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. Pyridine sulfinates as general nucleophilic coupling partners in palladium-catalyzed cross-coupling reactions with aryl halides. *Chem. Sci*. **2017**, *8*, 4437.
13. Choppin, S.; Gros, P.; Fort, Y. Unusual C-6 Lithiation of 2-Chloropyridine-Mediated by BuLi− Me_2N (CH2) 2OLi. New Access to 6-Functional-2-chloro pyridines and Chloro-bis-heterocycles. *Org. Lett,* **2000***, 2*, 803.
14. Guo, P.; Zhang, H.; Zhou, J.; Gallou, F.; Parmentier, M.; Wang, H. Micelle-Enabled Suzuki–Miyaura Cross-Coupling of Heteroaryl Boronate Esters. *J. Org. Chem*. **2018**, *83*, 7523.
15. Nguyen, J.; Chong, A.; Lalic, G. Nickel-catalyzed anti-Markovnikov hydroarylation of alkenes. *Chem. Sci*. **2019**, *10*, 3231.
16. Liao, J.; Basch, C. H.; Hoerrner, M. E.; Talley, M. R.; Boscoe, B. P.; Tucker, J. W.; Watson, M. P. Deaminative reductive cross-electrophile couplings of alkylpyridinium salts and aryl bromides. *Org. Lett*. **2019**, *21*, 2941.