Supporting Information for:

Cu/Base Co-catalyzed [3 + 3] Cycloaddition for the Synthesis of Highly Functionalized 4-Fluoropyridines

Jinhuan Dong,‡[a] Wanzhong Feng,‡[b] Lei Wang,[a] Mei Li,[a] Zhe Chen,*[b] and Xianxiu Xu*[a]

[a]College of Chemistry, Chemical Engineering and Materials Science, Collaborative Innovation Center of Functionalized Probes for Chemical Imaging in Universities of Shandong, Key Laboratory of Molecular and Nano Probes, Ministry of Education, Shandong Provincial Key Laboratory of Clean Production of Fine Chemicals, Shandong Normal University, Jinan, 250014, P. R. China.

[b]School of Science, Jilin Institute of Chemical Technology, Jilin 132022, PR China.

E-mail: chenzhecz999@163.com; xuxx677@sdnu.edu.cn.

table of contents

1. General Experimenta

Unless otherwise indicated, all reagents and solvents were commercial and used without further purification. Melting points of all compounds were measured with a micro melting point apparatus. Flash column chromatography was carried on 300-400 mesh silica gel. All reactions were monitored by thin layer chromatography (TLC), which was performed on silica gel 60 (F254). NMR spectra were determined at 25 ℃ on 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. All chemical shifts were quoted in ppm and 0.0 ppm for TMS as an internal standard. High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF II focus spectrometer (ESI).

2．Experimental Procedures

2.1 Synthesis of starting materials.

gem-Difluorocyclopropenes **1a**-**o**,[1-4] **1q**-**s**[1-4] and **1p**[5] were synthesized according to known literature procedure.

References

[1] F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang and J. Hu, *Chem. Commun.*, 2011, **47**, 2411–2413**.**

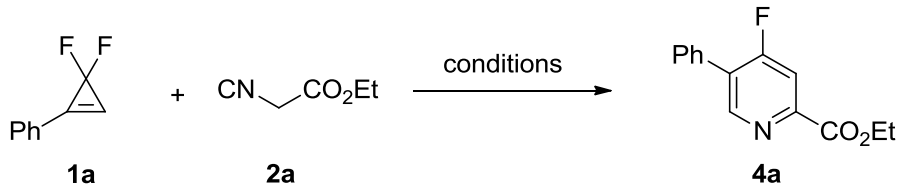
[2] K. Sekine, A. Ushiyama, Y. Endo and K. Mikami, *J. Org.Chem***.,** 2020, **85**, 7916–7924.

[3] X. Deng, J. Lin, J. Zheng and J. Xiao, *Chem. Commun*., 2015, **51**, 8805–8808

[4] F. Wang, T. Luo, J. Hu, Y. Wang, H. S. Krishnan, P. V. Jog, S. K. Ganesh, G. K. S. Prakash and G. A. Olah, *Angew. Chem. Int. Ed***.,** 2011, **50**, 7153–7157**.**

[5] K. Yamani, H. Pierre, A. Archambeau, C. Meyer and J. Cossy, *Angew. Chem. Int. Ed.*, 2020, **59**, 18505-18509.

2.2 Optimization of reaction conditions



1a **2a** **4a**

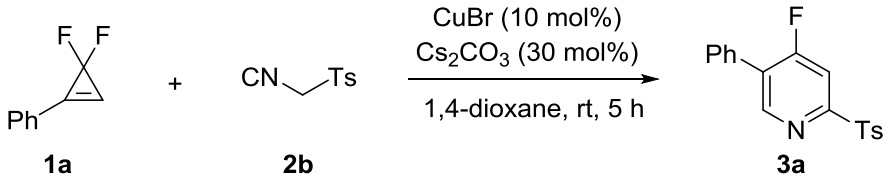
Entry	**1a**：**2a**	Catalyst	Base	Solvent	Temp. (^{o}C)	Time (h)	**4a** (%)[b]

1	1:2	-	DBU (30 mol%)	1,4-dioxane	25	12	NR
2	1:2	-	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	12	NR
3	1:2	Cu_2O (30 mol%)	-	1,4-dioxane	25	35	53
4	1:2	CuBr (30 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	5	73
5	1:2	Cu_2O (30 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	26	65
6	1:2	CuCl (30 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	7	55
7	1:2	$CuBr_2$ (30 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	48	28
8	1:2	CuI (30 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	22	64
9	1:2	Ag_2CO_3 (30 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	48	44
10	1:2	Ag_2O (30 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	48	51
11	***1:2***	***CuBr (10 mol%)***	***Cs_2CO_3 (30 mol%)***	***1,4-dioxane***	***25***	***6***	***79***
12	1:2	CuBr (5 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	24	32
13	1:2	CuBr (10 mol%)	Cs_2CO_3 (10 mol%)	1,4-dioxane	25	6	40
14	1:2	CuBr (10 mol%)	Cs_2CO_3 (50 mol%)	1,4-dioxane	25	6	55
15	1:1.5	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	6	66
16	1:2.5	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	24	68
17	1:2	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	60	6	63
18	1:2	CuBr (10 mol%)	K_2CO_3 (30 mol%)	1,4-dioxane	25	6	70
19[c]	1:2	CuBr (10 mol%)	*t*-BuOK (30 mol%)	1,4-dioxane	25	6	22
20[c]	1:2	CuBr (10 mol%)	DBU (30 mol%)	1,4-dioxane	25	6	44

21[c]	1:2	CuBr (10 mol%)	K_3PO_4 (30 mol%)	1,4-dioxane	25	6	50
22[c]	1:2	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	DCE	25	6	52
23[c]	1:2	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	CH_3CN	25	6	30
24[c]	1:2	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	EtOAc	25	6	61
25[c]	1:2	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	THF	25	6	44
26[d]	1:2	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	6	77
27[e]	1:2	CuBr (10 mol%)	Cs_2CO_3 (30 mol%)	1,4-dioxane	25	6	76

[a]Reaction conditions: **1a** (0.2 mmol), **2a**, base and catalyst, solvent (2.0 mL) in open air. [b]Isolated yields. [c]H NMR yield (using CH_2Br_2 as internal standard). [d]N_2 atmosphere. [e]O_2 atmosphere.

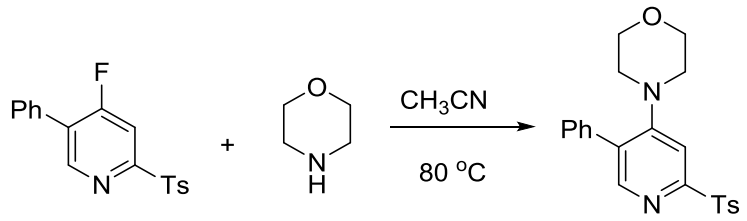
2.3 General procedure for the synthesis of 3-8 (3a as an example):



1a **2b** **3a**

(3,3-difluorocypropane-1-ene-1-yl) benzene **1a** (30.4 mg, 0.2 mmol), *p*-methylbenzene sulfonyl methyl isonitrile **2a** (78.1 mg, 0.4 mmol), CuBr (2.8 mg, 0.02 mmol), Cs_2CO_3 (19.5 mg, 0.06 mmol) and 1,4-dioxane (2 mL) were successively added into a 15 mL pressure tube. The reaction was carried out at 25 ^oC for 5 h, and TLC was used to monitor the reaction process. Cooled to room temperature, the reaction mixture was poured into 50 mL of saturated aqueous NH_4Cl and extracted with DCM (CH_2Cl_2, 20 mL×3). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **3a** (61 mg, 93% yield).

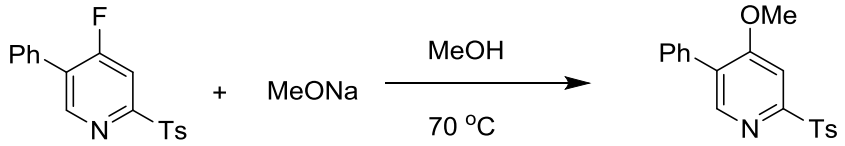
2.4 General procedure for the synthesis of 9



3a **9**

To a stirred solution of 4-fluoro-5-phenyl-2-tosylpyridine **3a** (65.4 mg, 0.2 mmol) in MeCN (0.2 mL) was added morpholine (0.136 mL, 0.8 mmol) and the reaction mixture was stirred at 80 ℃ for 9 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **9** (70 mg, 89% yield) as a white solid.

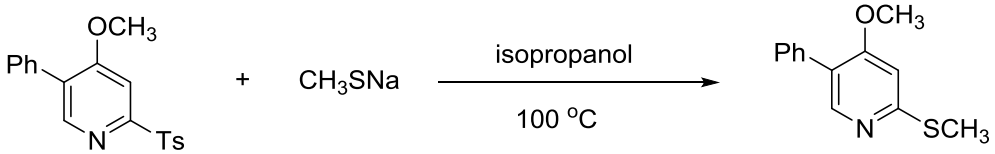
2.5 General procedure for the synthesis of 10



3a **10**

To a stirred solution of Na (0.4 mmol) in MeOH (2 mL) at 0 ℃. And was added 4-fluoro-5-phenyl-2-tosylpyridine **3a** (65.4 mg, 0.2 mmol) and the reaction mixture was stirred at 70 ℃ for 1 h. An aqueous saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with AcOEt (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **10** (64 mg, 94% yield) as a white solid.

2.6 General procedure for the synthesis of 11



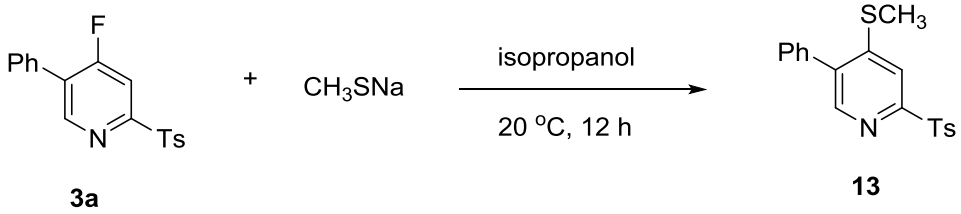
8 **11**

To a stirred solution of 4-methoxy-5-phenyl-2-tosylpyridine **8** (67.8 mg, 0.2 mmol) in isopropanol (2 mL) was added CH_3SNa (0.122 g, 1.6 mmol) and the reaction mixture was stirred at 100 ℃ for 12 h. An aqueous saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with DCM (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **11** (35 mg, 76% yield) as a colorless oil.

2.7 General procedure for the synthesis of 12

To a stirred solution of 4-fluoro-5-phenyl-2-tosylpyridine **3a** (65.4 mg, 0.2 mmol) in DMSO (2 mL) was added NaOH (0.016 g, 0.4 mmol) and the reaction mixture was stirred at 20 ℃ for 12 h. An aqueous saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with AcOEt (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **12** (47 mg, 71% yield) as a white solid.

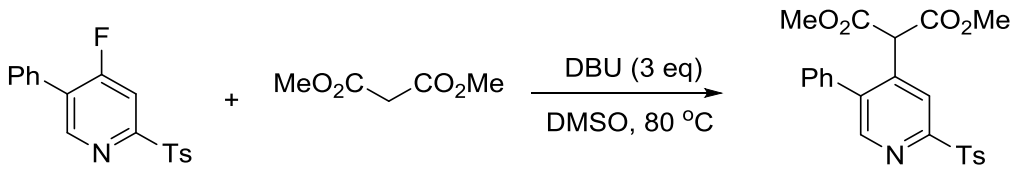
2.8 General procedure for the synthesis of 13



To a stirred solution of 4-fluoro-5-phenyl-2-tosylpyridine **3a** (65.4 mg, 0.2 mmol) in isopropanol (2 mL) was added CH_3SNa (0.084 g, 1.2 mmol) and the reaction mixture was stirred at 20 ℃ for 12 h. An aqueous saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with DCM (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **13** (69 mg, 97% yield)

as a white solid.

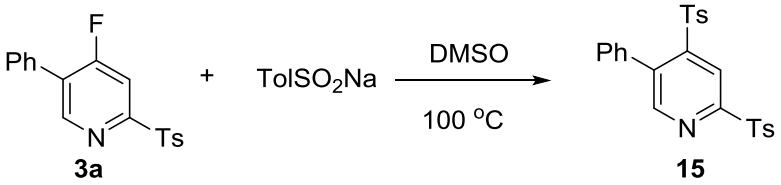
2.9 General procedure for the synthesis of 14



3a **14**

To a stirred solution of 4-fluoro-5-phenyl-2-tosylpyridine **3a** (65.4 mg, 0.2 mmol) in DMSO (0.5 mL) was added dimethyl malonate (0.071 mL, 0.6 mmol) and DBU (0.093 mL, 0.6 mmol) and the reaction mixture was stirred at 80 ℃ for 6 h. An aqueous saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with AcOEt (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **14** (60 mg, 68% yield) as a white solid.

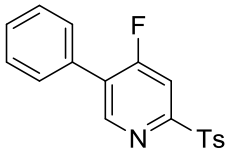
2.10 General procedure for the synthesis of 15



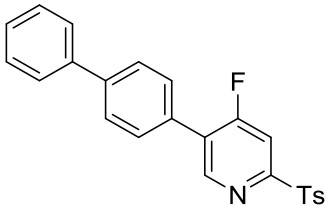
3a **15**

To a stirred solution of 4-fluoro-5-phenyl-2-tosylpyridine **3a** (65.4 mg, 0.2 mmol) in DMSO (2 mL) was $TolSO_2Na$ (54 mg, 0.3 mmol) and the reaction mixture was stirred at 100 ℃ for 3 h. An aqueous saturated NH_4Cl solution was added to the mixture and the aqueous phase was extracted with AcOEt (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc = 25:1 to 10:1, v/v) to afford the desired product **15** (83 mg, 90% yield) as a white solid.

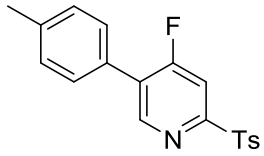
3. Analytical Data of Compounds



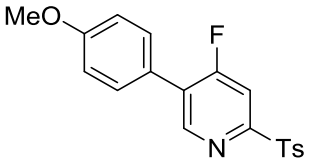
3a, **4-Fluoro-5-phenyl-2-tosylpyridine**: White solid, 93% yield, 61 mg, m.p. 145−146 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, J = 9.2 Hz, 1H), 8.02-7.98 (m, 3H), 7.52-7.41 (m, 5H), 7.36 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.2. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.7 (d, J = 268 Hz), 159.7 (d, J = 6 Hz), 152.7 (d, J = 4 Hz), 145.2, 135.2, 130.2, 129.8, 129.3, 128.9 (2C), 128.8 (d, J = 3 Hz), 128.3 (d, J = 9 Hz), 110.9 (d, J = 21 Hz), 21.5. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{14}FNO_2NaS^+$ ($[M+Na]^+$) 350.0621, found 350.0624.



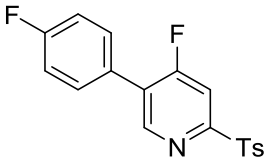
3b, **5-([1,1'-Biphenyl]-4-yl)-4-fluoro-2-tosylpyridine**: White solid, 68% yield, 54 mg, m.p. 140−142 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.77 (d, J = 9.2 Hz, 1H), 8.05-7.96 (m, 3H), 7.72 (d, J = 8.0 Hz, 2H), 7.62 (t, J = 8.0 Hz, 4H), 7.47 (t, J = 8.0 Hz, 2H), 7.41-7.36 (m, 3H), 2.44 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.0. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0 (d, J = 268 Hz), 159.9 (d, J = 6 Hz), 152.7 (d, J = 3 Hz), 145.3, 142.4, 139.9, 135.4, 129.9, 129.4 (d, J = 4 Hz), 129.2, 129.1, 128.9, 128.2 (d, J = 9.8 Hz), 127.9, 127.7, 127.1, 111.2 (d, J = 22 Hz), 21.7. **HRMS** (ESI-TOF) m/z calculated for $C_{24}H_{18}FNO_2NaS^+$ ($[M+Na]^+$) 426.0934, found 426.0931.



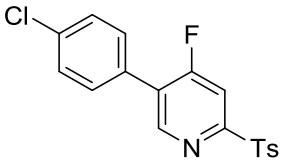
3c, **4-Fluoro-5-(*p*-tolyl)-2-tosylpyridine**: White solid,73% yield, 50 mg, m.p. 165−166 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (d, J = 9.2 Hz, 1H), 7.99-7.96 (m, 3H), 7.41 (dd, J = 8.0, 1.6 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H), 2.40 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.4. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8 (d, J = 268 Hz), 159.5 (d, J = 6 Hz), 152.6 (d, J = 4 Hz), 145.1, 139.7, 135.4, 129.8, 129.7, 128.9, 128.7 (d, J = 2.8 Hz), 128.4 (d, J = 10 Hz), 127.4, 110.9 (d, J = 22 Hz), 21.6, 21.2. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{16}FNO_2NaS^+$ ($[M+Na]^+$) 364.0778, found 364.0770.



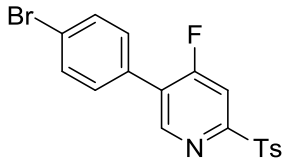
3d, **4-Fluoro-5-(4-methoxyphenyl)-2-tosylpyridine**: White solid, 81% yield, 58 mg, m.p.120−122 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 8.8 Hz, 3H), 7.46 (dd, J = 8.8, 1.6 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.42 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.7. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.6 (d, J = 267 Hz), 160.6, 159.0 (d, J = 6 Hz), 152.4 (d, J = 4 Hz), 145.1, 135.4, 130.2 (d, J = 3 Hz), 129.8, 128.9, 128.1 (d, J = 9 Hz), 122.5, 114.5, 111.0 (d, J = 22 Hz), 55.3, 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{16}FNO_3NaS^+$ ($[M+Na]^+$) 380.0727, found 380.0733.



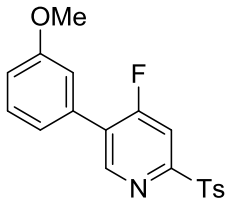
3e, 4-Fluoro-5-(4-fluorophenyl)-2-tosylpyridine: White solid, 96% yield, 66 mg, m.p. 163−164 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (d, J = 9.2 Hz, 1H), 8.03-7.95 (m, 3H), 7.52-7.48 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.18 (tt, J = 8.0 Hz, J = 2.0 Hz, 2H), 2.43 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.3, -110.9. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8 (d, J = 267 Hz), 163.3 (d, J = 249 Hz), 160.0 (d, J = 6 Hz), 152.5 (d, J = 4 Hz), 145.3, 135.2, 130.9 (d, J = 3 Hz), 130.8 (d, J = 3 Hz), 129.9, 129.1, 127.4 (d, J = 10 Hz), 126.3 (d, J = 4 Hz), 116.2 (d, J = 22 Hz), 111.0 (d, J = 22 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{13}F_2NO_2NaS^+$ ($[M+Na]^+$) 368.0527, found 368.0541.



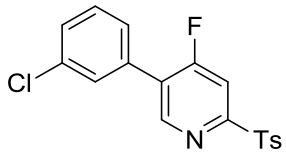
3f, **5-(4-Chlorophenyl)-4-fluoro-2-tosylpyridine**: White solid, 85% yield, 61 mg, m.p. 155−156 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.49-7.42 (m, 4H), 7.36 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.0. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9 (d, J = 268 Hz), 160.3 (d, J = 6 Hz), 152.5 (d, J = 4 Hz), 145.3, 135.8, 135.2, 130.2 (d, J = 3 Hz), 129.9, 129.3, 129.1, 128.8, 127.3 (d, J = 10 Hz), 111.1 (d, J = 22 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{13}ClFNO_2NaS^+$ ($[M+Na]^+$) 384.0232, found 384.0201.



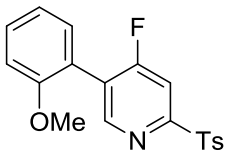
3g, **5-(4-Bromophenyl)-4-fluoro-2-tosylpyridine**: White solid, 89% yield, 72 mg, m.p. 193−195 ^{o}C . **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (d, J = 9.2 Hz, 1H), 8.02-7.96 (m, 3H), 7.63 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -102.9. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8 (d, J = 268 Hz), 160.4 (d, J = 6 Hz), 152.4 (d, J = 3 Hz), 145.3, 135.2, 132.3, 130.4 (d, J = 3 Hz), 129.9, 129.3, 129.1, 127.4 (d, J = 10 Hz), 124.2, 111.0 (d, J = 22 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{13}BrFNO_2NaS^+$ ($[M+Na]^+$) 427.9727, found 427.9702.



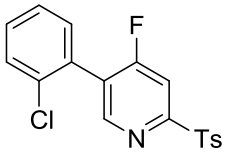
3h, **4-Fluoro-5-(3-methoxyphenyl)-2-tosylpyridine**: White solid, 76% yield, 54 mg, m.p. 125−126 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, J = 9.2 Hz, 1H), 8.01-7.96 (m, 3H), 7.41-7.33 (m, 3H), 7.07 (d, J = 9.2 Hz, 1H), 7.03-6.96 (m, 2H), 3.82 (s, 3H), 2.42 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.8. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8 (d, J = 268 Hz), 159.9 (d, J = 6 Hz), 159.8, 152.7 (d, J =4 Hz), 145.2, 135.3, 131.6, 130.1, 129.8, 129.0, 128.3 (d, J = 10 Hz), 121.2 (d, J = 3 Hz), 114.8, 114.7 (d, J = 3 Hz), 110.9 (d, J = 22 Hz), 55.3, 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{16}FNO_3NaS^+$ ($[M+Na]^+$) 380.0727, found 380.0733.



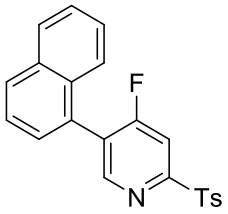
3i, **5-(3-Chlorophenyl)-4-fluoro-2-tosylpyridine**: White solid, 93% yield, 67 mg, m.p. 150−151 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.48 (s, 1H), 7.46-7.41 (m, 2H), 7.39-7.35 (m, 3H), 2.43 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -102.7. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8 (d, J = 268 Hz), 160.5 (d, J = 6 Hz), 152.5 (d, J = 3 Hz), 145.3, 135.1, 134.9, 132.0, 130.3, 129.9, 129.6, 129.1, 128.9 (d, J = 3 Hz), 127.1 (d, J = 3 Hz), 127.0, 111.0 (d, J = 22 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{13}ClFNO_2NaS^+$ ($[M+Na]^+$) 384.0232, found 384.0245.



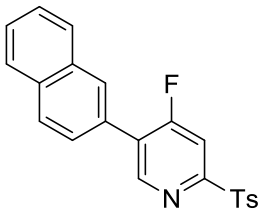
3j, **4-Fluoro-5-(2-methoxyphenyl)-2-tosylpyridine**: White solid, 60% yield, 43 mg, m.p. 123−125 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.8 Hz, 1H), 7.44 (td, J = 8.0, 2.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 6.4 Hz, 1H), 7.08-6.98 (m, 2H), 3.78 (s, 3H), 2.43 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -98.4. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.2 (d, J =268 Hz), 159.7 (d, J = 6 Hz), 156.8, 154.0 (d, J = 4 Hz), 145.1, 135.4, 131.1, 130.9 (d, J = 2 Hz), 129.8, 129.0, 126.1 (d, J = 12 Hz), 120.7, 119.4, 111.1, 110.6 (d, J = 22 Hz), 55.5, 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{16}FNO_3NaS^+$ ($[M+Na]^+$) 380.0727, found 380.0742.



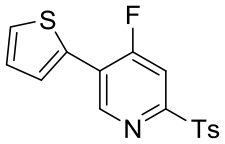
3k, **5-(2-Chlorophenyl)-4-fluoro-2-tosylpyridine**: White solid, 90% yield, 65 mg, m.p. 148−149 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (d, J = 8.8 Hz, 1H), 8.03-7.99 (m, 3H), 7.52 (dd, J = 8.0, 2.0 Hz, 1H), 7.46-7.34 (m, 4H), 7.29-7.25 (m, 1H), 2.44 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -97.9. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6 (d, J = 268 Hz), 161.0 (d, J = 6 Hz), 153.5 (d, J = 3 Hz), 145.3, 135.1, 133.6, 131.3, 130.8, 129.9, 129.8, 129.6, 129.2, 127.1, 126.7 (d, J = 12 Hz), 110.6 (d, J = 22 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{18}H_{13}ClFNO_2NaS^+$ ($[M+Na]^+$) 384.0232, found 384.0201.



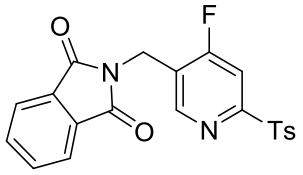
3l, **4-Fluoro-5-(naphthalen-1-yl)-2-tosylpyridine:** White solid, 86% yield, 65 mg, m.p. 165−166 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 8.01-7.92 (m, 2H), 7.59-7.52 (m, 2H), 7.48-7.47 (m, 2H), 7.41-7.38 (m, 3H), 2.46 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -98.1. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4 (d, J = 268 Hz), 160.7 (d, J = 5 Hz), 154.2 (d, J = 4 Hz), 145.4, 135.2, 133.5, 131.1, 130.0, 129.9, 129.2, 128.6, 128.2, 128.1, 127.9 (d, J = 12 Hz), 127.0, 126.4, 125.1, 124.6, 110.7 (d, J = 22 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{16}FNO_2NaS^+$ ($[M+Na]^+$) 400.0778, found 400.0791.



3m, **4-Fluoro-5-(naphthalen-2-yl)-2-tosylpyridine:** White solid, 93% yield, 70 mg, m.p. 160−162 ^{o}C . **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.83 (d, J = 9.2 Hz, 1H), 8.05 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 8.0 Hz, 3H), 7.95 (d, J = 8.0 Hz, 1H), 7.92-7.85 (m, 2H), 7.62-7.52 (m, 3H), 7.37 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.0. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.1 (d, J = 268 Hz), 159.9 (d, J = 6 Hz), 153.0 (d, J = 3 Hz), 145.2, 135.4, 133.3, 133.1, 129.9, 129.1, 128.9 (d, J = 3 Hz), 128.8, 128.5 (d, J = 10 Hz), 128.3, 127.7 (2C), 127.3, 126.9, 125.8 (d, J = 3 Hz), 111.1 (d, J = 22 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{16}FNO_2NaS^+$ ($[M+Na]^+$) 400.0778, found 400.0792.

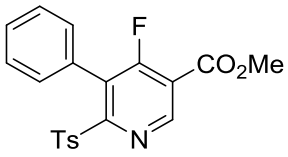


3n, **4-Fluoro-5-(thiophen-2-yl)-2-tosylpyridine**: White solid, 56% yield, 38 mg, m.p. 148−149^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (d, J = 9.2 Hz, 1H), 8.01-7.93 (m, 3H), 7.59 (d, J = 4.0 Hz, 1H), 7.52 (dd, J = 5.2, 0.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.18 (m, 1H), 2.42 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -100.2. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.4 (d, J = 269 Hz), 158.8 (d, J = 6 Hz), 150.6 (d, J = 4 Hz), 145.2, 135.3, 131.3 (d, J = 4 Hz), 129.9, 129.0, 128.9 (d, J = 6 Hz), 128.7 (d, J = 4 Hz), 128.3, 122.2 (d, J = 9 Hz), 111.1 (d, J = 22 Hz), 21.7. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{12}FNO_2NaS_2^+$ ($[M+Na]^+$) 356.0186 , found 356.0165.

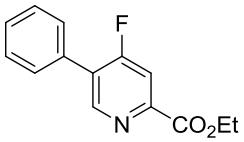


3o, **2-((4-Fluoro-6-tosylpyridin-3-yl)methyl)isoindoline-1,3-dione:** White solid, 65% yield, 53mg, m.p. 170−172^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 3H), 7.86-7.84 (m, 2H), 7.77-7.72 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.94 (s, 2H), 2.41 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -101.0. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.3, 167.1 (d, J = 269

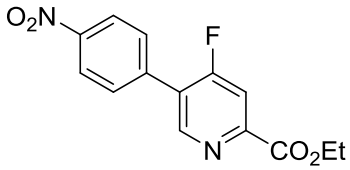
Hz), 161.2 (d, *J* = 6 Hz), 153.3 (d, *J* = 4 Hz), 145.3, 135.0, 134.4, 131.7, 129.9, 129.2, 123.7, 123.2 (d, *J* = 9 Hz), 110.4 (d, *J* = 22 Hz), 32.7 (d, *J* = 4 Hz), 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{21}H_{15}FN_2NaO_4S^+$ ($[M+Na]^+$) 433.0629, found 433.0628.



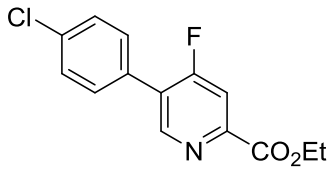
3p, **Methyl 4-fluoro-5-phenyl-6-tosylnicotinate**: White solid, 27% yield, 21 mg, m.p. 169−171 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.49-7.42 (m, 3H), 7.27-7.21 (m, 4H), 3.96 (s, 3H), 2.42 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -95.40. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}FNO_4NaS^+$ ($[M+Na]^+$) 408.0676, found 408.0686.



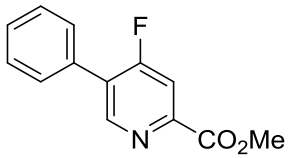
4a, **Ethyl 4-fluoro-5-phenylpicolinate**: yellow oil, 79% yield, 39 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 10.0 Hz, 1H), 7.93 (d, *J* = 10.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.52-7.42 (m, 3H), 4.49 (q, *J* = 7.2 Hz, 2H), 1.45 (d, *J* = 7.2 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -106.6. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8 (d, *J* = 263 Hz), 164.1 (d, *J* = 4 Hz), 152.1 (d, *J* = 4 Hz), 149.4 (d, *J* = 4 Hz), 131.1, 129.2, 129.0 (d, *J* = 4 Hz), 128.9, 128.3 (d, *J* = 10 Hz), 113.6 (d, *J* = 20 Hz), 62.3, 14.3. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{12}FNNaO_2^+$ ($[M+Na]^+$) 268.0744, found 268.0737



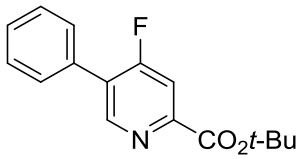
4b, **Ethyl 4-fluoro-5-(4-nitrophenyl)picolinate**: yellow oil, 62% yield, 36 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 9.6 Hz, 1H), 8.37 (d, *J* = 9.6 Hz, 2H), 8.00 (d, *J* = 9.6 Hz, 1H), 7.77 (dd, *J* = 8.8, 1.6 Hz, 2H), 4.53 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -105.5. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9 (d, *J* = 265 Hz), 163.7 (d, *J* = 4 Hz), 151.7 (d, *J* = 3 Hz), 151.1 (d, *J* = 8 Hz), 148.2, 137.5, 130.0 (d, *J* = 3 Hz), 126.2 (d, *J* = 10 Hz), 124.1, 113.7 (d, *J* = 20 Hz), 62.6, 14.3. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{11}FN_2NaO_4^+$ ($[M+Na]^+$) 313.0595, found 313.0585.



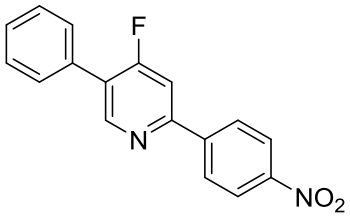
4c, **Ethyl 5-(4-chlorophenyl)-4-fluoropicolinate**. yellow oil, 75% yield, 42 mg. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.80 (d, J = 10.0 Hz, 1H), 7.96 (d, J = 10.0 Hz, 1H), 7.54-7.48 (m, 4H), 4.52 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H). ^{19}**F NMR** (376 MHz, $CDCl_3$) δ -106.4. ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 165.7 (d, J = 264 Hz), 163.8 (d, J = 3 Hz), 151.7 (d, J = 3 Hz), 149.8 (d, J = 7 Hz), 135.5, 130.2 (d, J = 3 Hz), 129.4, 129.2, 127.2 (d, J = 10 Hz), 113.5 (d, J = 20 Hz), 62.3, 14.2. **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{11}ClFNNaO_2^+$ ($[M+Na]^+$) 302.0355, found 302.0386.



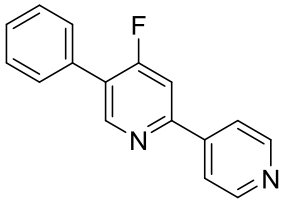
4d, **Methyl 4-fluoro-5-phenylpicolinate**: yellow oil, 70% yield, 32 mg. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.82 (d, J = 10.0 Hz, 1H), 7.96 (d, J = 10.0 Hz, 1H), 7.61-7.57 (m, 2H), 7.55-7.46 (m, 3H), 4.05 (s, 3H). ^{19}**F NMR** (376 MHz, $CDCl_3$) δ -106.4. ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 165.7 (d, J = 264 Hz), 164.4 (d, J = 4 Hz), 152.0 (d, J = 3 Hz), 149.1 (d, J = 7 Hz), 131.0, 129.2, 129.0 (d, J = 3 Hz), 128.9, 128.5 (d, J = 10 Hz), 113.6 (d, J = 22 Hz), 53.1. **HRMS** (ESI-TOF) m/z calculated for $C_{13}H_{10}FNaO_2^+$ ($[M+Na]^+$) 254.0588, found 254.0614.



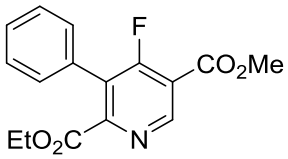
4e, **Tert-butyl 4-fluoro-5-phenylpicolinate**: yellow oil in, 70% yield, 39 mg. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.80 (d, J = 10.0 Hz, 1H), 7.85 (d, J = 10.4 Hz, 1H), 7.57-7.55 (m, 2H), 7.53-7.42 (m, 3H), 1.65 (s, 9H). ^{19}**F NMR** (376 MHz, $CDCl_3$) δ -107.2. ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 165.8 (d, J = 263 Hz), 162.9 (d, J = 4 Hz), 152.0 (d, J = 4 Hz), 150.9 (d, J = 7 Hz), 131.2, 129.1, 129.0 (d, J = 3 Hz), 128.9, 127.8 (d, J = 10 Hz), 113.2 (d, J = 20 Hz), 82.8, 28.0. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{16}FNNaO_2^+$ ($[M+Na]^+$) 296.1057, found 296.1073.



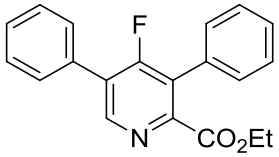
4f, **4-Fluoro-2-(4-nitrophenyl)-5-phenylpyridine**: yellow oil, 34% yield, 20 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.82 (d, J = 10.4 Hz, 1H), 8.35 (d, J = 6.8 Hz, 2H), 8.22 (d, J = 6.8 Hz, 2H), 7.66-7.59 (m, 3H), 7.55-7.50 (m, 2H), 7.50-7.44 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -107.3. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.2 (d, J = 262 Hz), 156.2 (d, J = 7 Hz), 152.2 (d, J = 4 Hz), 148.4, 143.7, 131.5, 128.9 (2C), 128.8, 127.6, 125.1 (d, J = 10 Hz), 124.1, 109.2 (d, J = 21 Hz). **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{11}FN_2NaO_2^+$ ($[M+Na]^+$) 317.0697, found 317.0687.



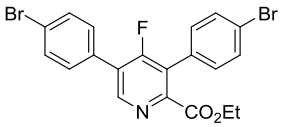
4g, **4-Fluoro-5-phenyl-2,4'-bipyridine**: White solid, 55% yield, 28 mg, m.p. 135–136 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (d, J = 9.2 Hz, 3H), 7.92 (d, J = 4.8 Hz, 2H), 7.68-7.58 (m, 3H), 7.56-7.42 (m, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -107.5. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.2 (d, J = 268 Hz), 156.1 (d, J = 8 Hz), 152.2 (d, J = 4 Hz), 150.6, 144.9 (d, J = 3 Hz), 131.6, 128.9, 128.8, 125.4 (d, J = 10 Hz), 120.9, 108.8 (d, J = 20 Hz). **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}FN_2Na^+$ ($[M+Na]^+$) 273.0798, found 273.0791.



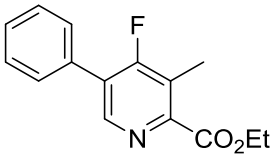
5, **2-Ethyl 5-methyl 4-fluoro-3-phenylpyridine-2,5-dicarboxylate**. yellow oil, 75% yield, 45 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (d, J = 8.4 Hz, 1H), 7.52-7.43 (m, 3H), 7.35-7.33 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -100.4. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.1 (d, J = 274 Hz), 165.0 (d, J = 3 Hz), 162.6 (d, J = 3 Hz), 155.0 (d, J = 4 Hz), 152.2, 129.9, 129.2, 128.9, 128.4, 126.3 (d, J = 15 Hz), 116.4 (d, J = 8 Hz), 62.1, 52.9, 13.5. **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{14}FNNaO_4^+$ ($[M+Na]^+$) 326.0799, found 326.0822.



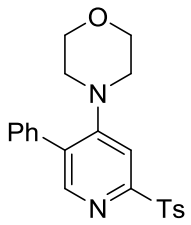
6, **Ethyl 4-fluoro-3,5-diphenylpicolinate**. yellow oil, 56% yield, 45 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (d, J = 9.2 Hz, 1H), 7.62-7.57 (m, 2H), 7.54-7.42 (m, 6H), 7.41-7.35 (m, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.9. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.5 (d, J = 4 Hz), 162.8 (d, J = 262 Hz), 150.4 (d, J = 4 Hz), 150.3 (d, J = 3 Hz), 131.3, 131.2, 129.3, 129.1 (d, J = 3 Hz), 129.0, 128.9, 128.6, 128.3, 127.1 (d, J = 10 Hz), 126.3 (d, J = 15 Hz), 61.8, 13.7. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{16}FNNaO_2^+$ ($[M+Na]^+$) 344.1057, found 344.1078.



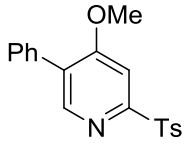
7, Ethyl 3,5-bis(4-bromophenyl)-4-fluoropicolinate: White solid, 82% yield, 78 mg. m.p. 125−126 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.72 (d, J = 9.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.48-7.43 (m, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.15 (t, J = 7.2 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.4. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.1 (d, J = 4 Hz), 162.4 (d, J = 262 Hz), 150.4 (d, J = 4 Hz), 150.3, 132.3, 131.6, 130.9, 130.6 (d, J = 3 Hz), 129.9 (d, J = 12 Hz), 126.2 (d, J = 12 Hz), 125.5 (d, J = 16 Hz), 123.8, 123.1, 62.1, 13.8. **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{14}Br_2FNO_2Na^+$ ($[M+Na]^+$) 499.9268, found 499.9285.



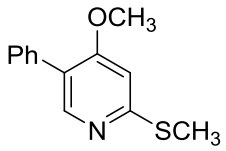
8, Ethyl 4-fluoro-3-methyl-5-phenylpicolinate: yellow oil, 34% yield, 18 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (d, J = 9.2 Hz, 1H), 7.59-7.43 (m, 5H), 4.49 (q, J = 7.2 Hz, 2H), 2.56 (d, J = 2.4 Hz, 3H), 1.47 (t, J = 7.2 Hz, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.7. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.6 (d, J = 37 Hz), 164.5 (d, J = 260 Hz), 149.0 (d, J = 14 Hz), 148.7 (d, J = 4 Hz), 131.6, 129.1 (d, J = 4 Hz), 128.9, 128.8, 126.9 (d, J = 12 Hz), 123.7 (d, J = 16 Hz), 61.9, 14.3, 10.7 (d, J = 6 Hz).



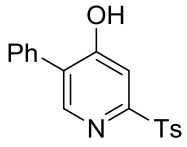
9, 4-(5-Phenyl-2-tosylpyridin-4-yl)morpholine: White solid, 89% yield, 70 mg. m.p. 178−179 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 7.51-7.41 (m, 4H), 7.39-7.33 (m, 3H), 3.67-3.59 (m, 4H), 3.06-2.96 (m, 4H), 2.42 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 157.0, 152.4, 144.6, 136.8, 135.9, 130.0, 129.6, 129.1, 128.8, 128.4, 127.8, 109.8, 66.0, 49.4, 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{22}H_{22}NO_3SNa^+$ ($[M+Na]^+$) 417.1243, found 417.1256.



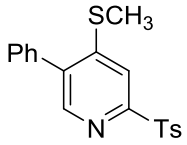
10, 4-Methoxy-5-phenyl-2-tosylpyridine: White solid, 94% yield, 64 mg, m.p. 128−130 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.82 (s, 1H), 7.46-7.40 (m, 5H), 7.35 (d, J = 8.0 Hz, 2H), 3.98 (s, 3H), 2.42 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.7, 159.4, 151.2, 144.8, 135.8, 133.1, 129.8, 129.3, 129.1, 128.9, 128.4, 128.4, 104.9, 56.2, 21.6. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{17}NaNO_3S^+$ ($[M+Na]^+$) 362.0821, found 362.0829.



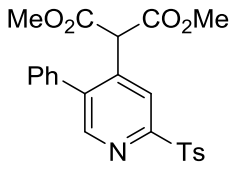
11, 4-Methoxy-2-(methylthio)-5-phenylpyridine: colorless oil, 76% yield, 35 mg. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.49-7.47 (m, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.37-7.31 (m, 1H), 6.77 (s, 1H), 3.82 (s, 3H), 2.61 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.3, 160.4, 149.8, 134.7, 129.3, 128.2, 127.4, 123.2, 103.5, 55.3, 13.3. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{13}NaNOS^+$ ($[M+H]^+$) 254.0610, found 254.0623.



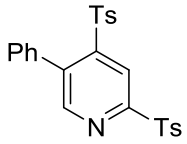
12, 5-Phenyl-2-tosylpyridin-4-ol: White solid, 71% yield, 47 mg, m.p. 230−232 °C. **^{1}H NMR** (400 MHz, DMSO) δ 11.86 (s, 1H), 8.43 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.74 (s, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.48-7.35 (m, 5H), 2.39 (s, 3H). **^{13}C NMR** (100 MHz, DMSO) δ 163.0, 158.4, 151.8, 145.2, 136.1, 133.9, 130.5, 129.7, 129.0, 128.8, 128.6, 127.6, 109.8, 21.6. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{16}NO_3S^+$ ($[M+H]^+$) 326.0845, found 326.0862.



13, **4-(Methylthio)-5-phenyl-2-tosylpyridine**: White solid, 97% yield, 69 mg, m.p. 127−129 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.00 (s, 2H), 7.98 (s, 1H), 7.48-7.44 (m, 3H), 7.39-7.33 (m, 4H), 2.52 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.8, 152.4, 149.1, 144.9, 137.8, 135.8, 135.2, 129.8, 129.1, 129.0, 128.9, 128.7, 115.7, 21.7, 14.6. **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{17}NaNO_2S_2^+$ ($[M+Na]^+$) 378.0593, found 378.0583.



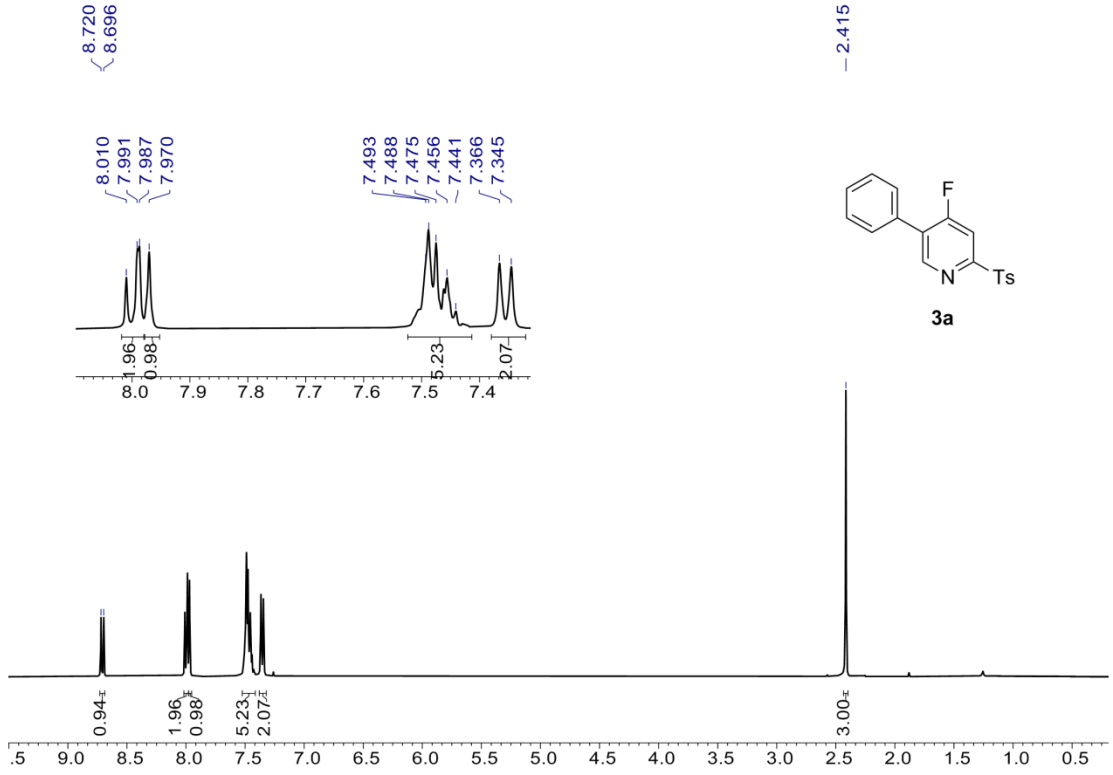
14, **Dimethyl 2-(5-phenyl-2-tosylpyridin-4-yl)malonate**: White solid, 68% yield, 60 mg, m.p. 180−181 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.46 (s, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.50-7.47 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.28-7.24 (m, 2H), 4.89 (s, 1H), 3.77 (s, 6H), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.8, 157.7, 151.4, 144.9, 141.1, 141.0, 135.8, 134.7, 129.8, 129.1, 129.0, 128.9, 122.6, 53.3, 21.6. **HRMS** (ESI-TOF) m/z calculated for $C_{23}H_{21}NO_6SNa^+$ ($[M+Na]^+$) 462.0982, found 462.0987.



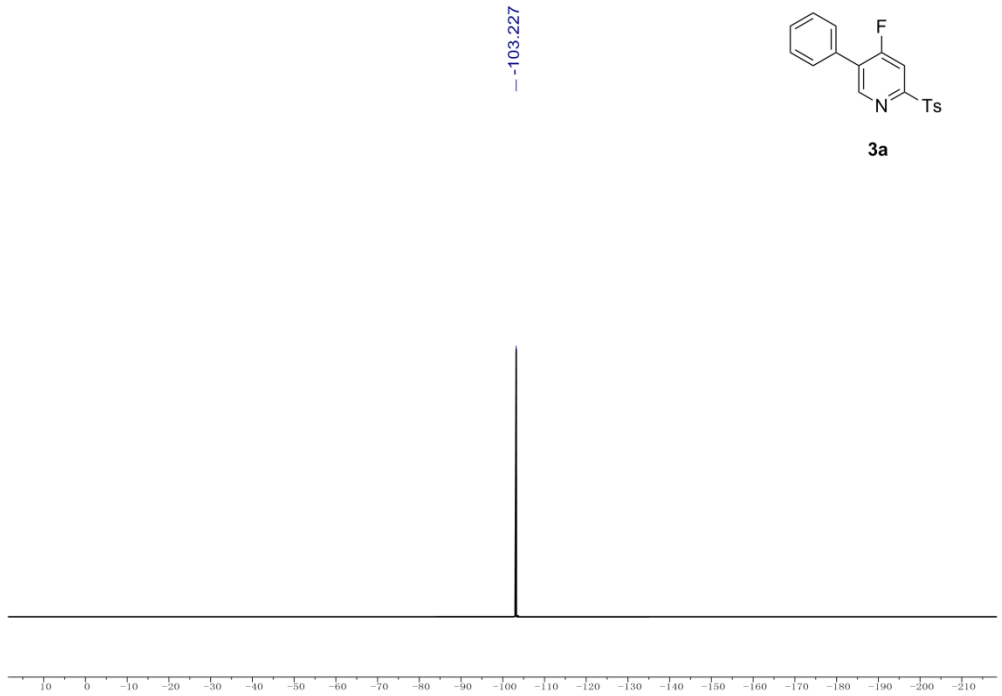
15, 5-Phenyl-2,4-ditosylpyridine: White solid, 90% yield, 83 mg, m.p. 170−172 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.51 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.41-7.38 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 7.01-6.97 (m, 2H), 2.45 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 153.8, 150.2, 145.5, 145.1, 138.9, 135.2, 135.1, 133.0, 130.0, 129.8, 129.4, 129.2, 129.1, 128.3, 127.8, 119.5, 21.7, 21.6. HRMS (ESI-TOF) m/z calculated for $C_{25}H_{21}NaNO_4S_2^+$ ($[M+Na]^+$) 486.0804, found 486.0799.

4.Copies of ^{1}H NMR , ^{19}F NMR and ^{13}C NMR spectra of compounds

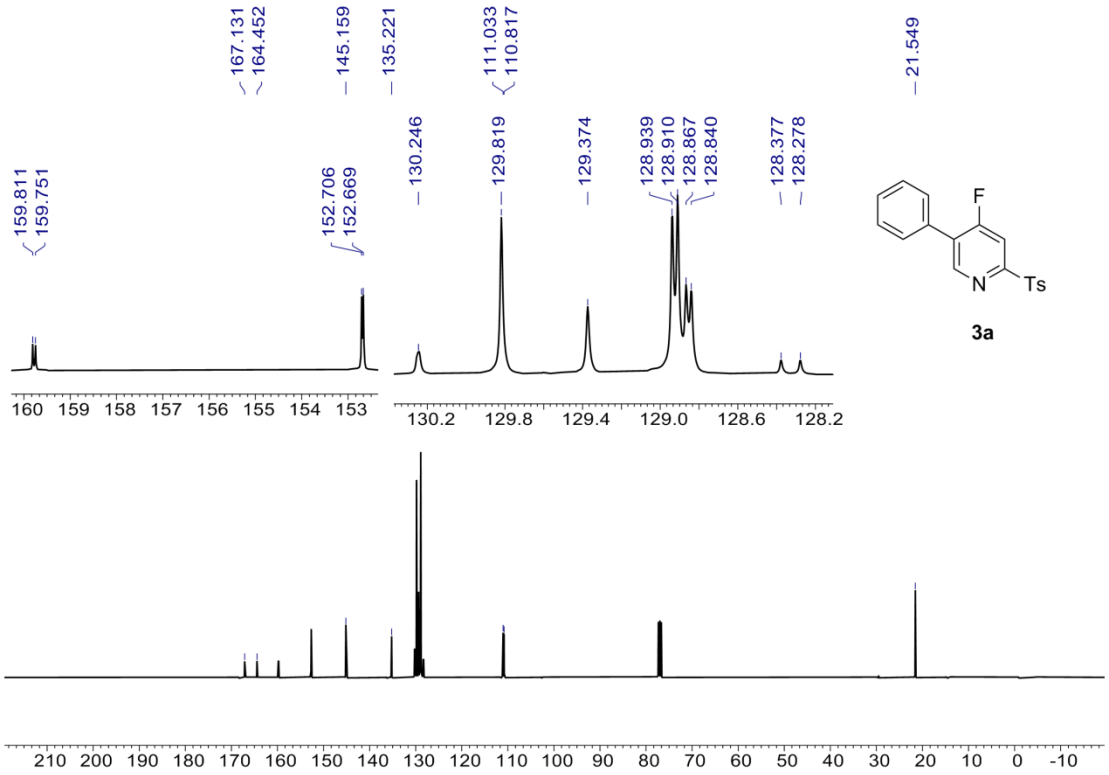
^{1}H NMR (400 MHz, $CDCl_3$) for **3a**



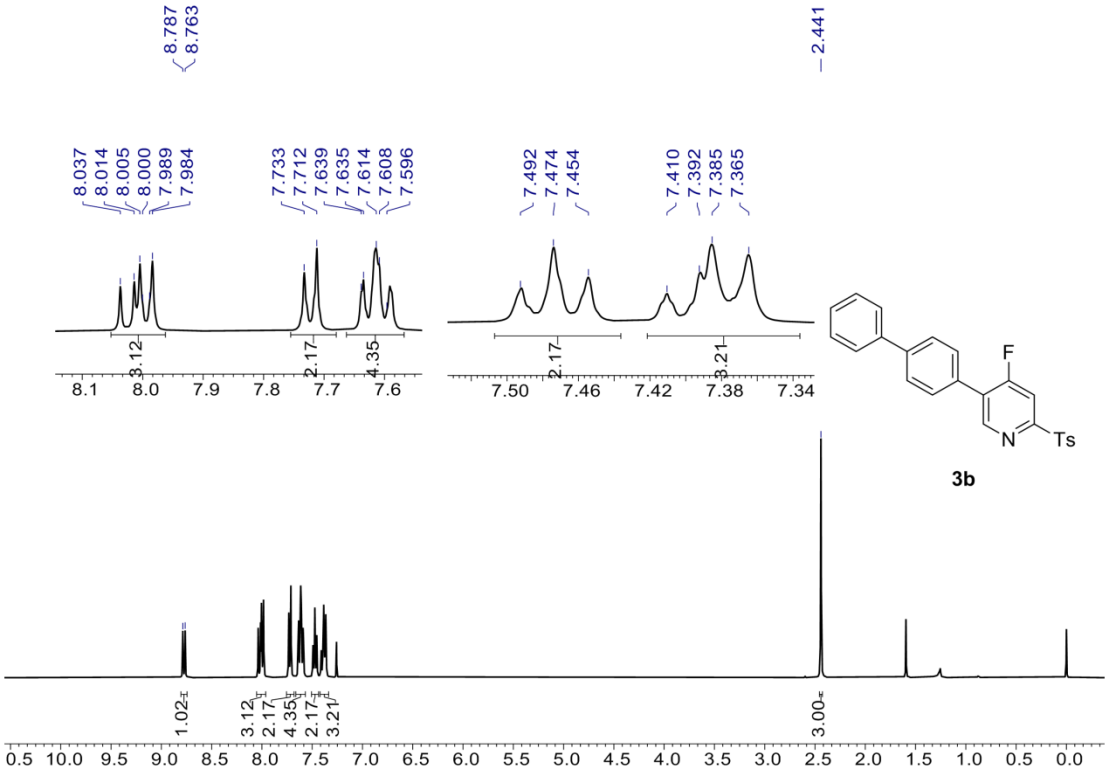
^{19}F NMR (376 MHz, $CDCl_3$) for **3a**



^{13}C NMR (400 MHz, $CDCl_3$) for **3a**

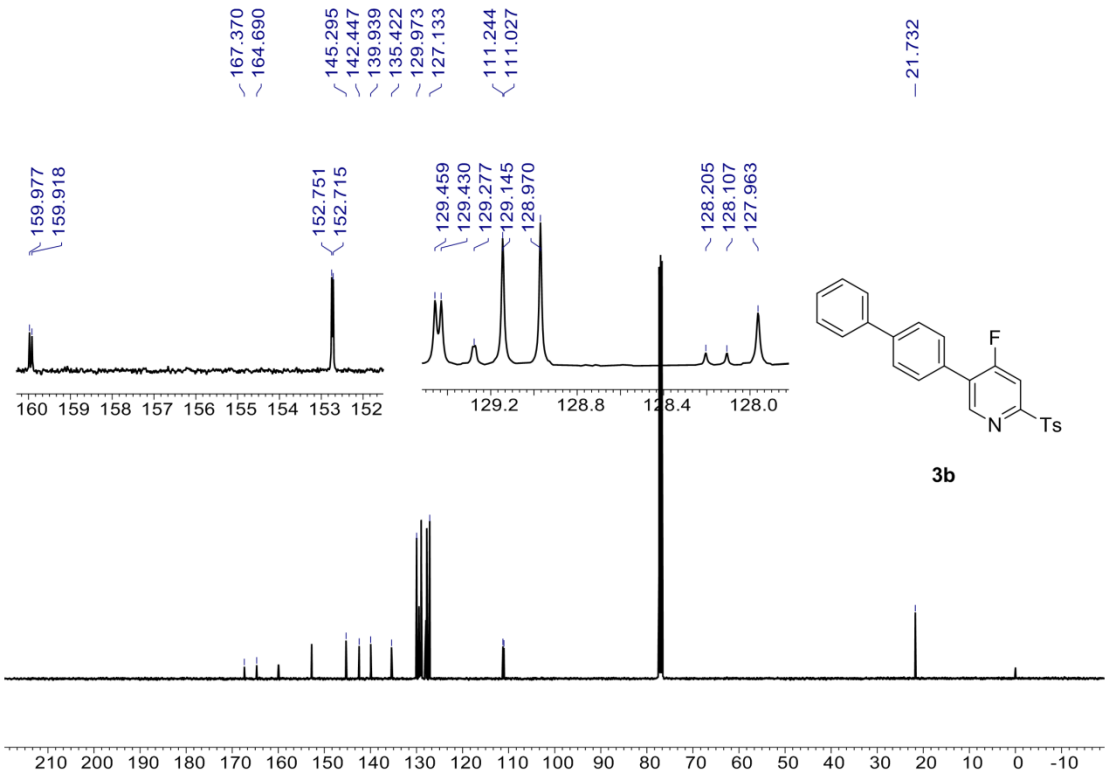


^{1}H NMR (400 MHz, $CDCl_3$) for **3b**

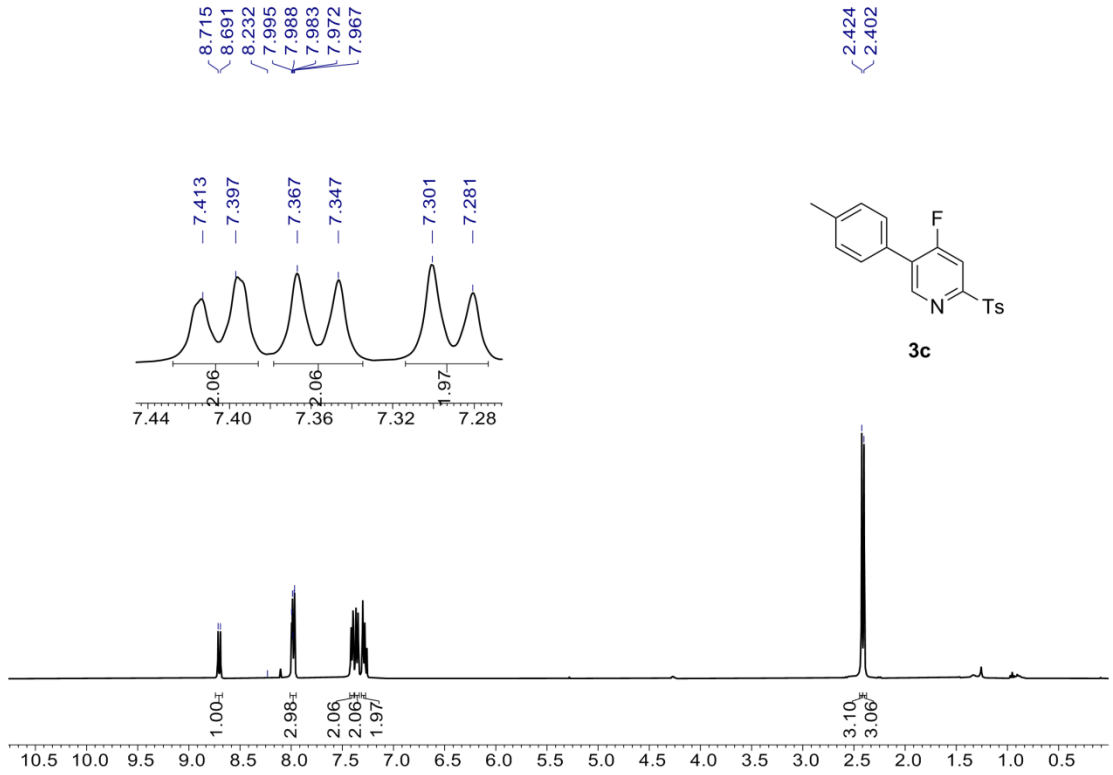


^{19}F NMR (376 MHz, $CDCl_3$) for **3b**

^{13}C NMR (400 MHz, $CDCl_3$) for **3b**

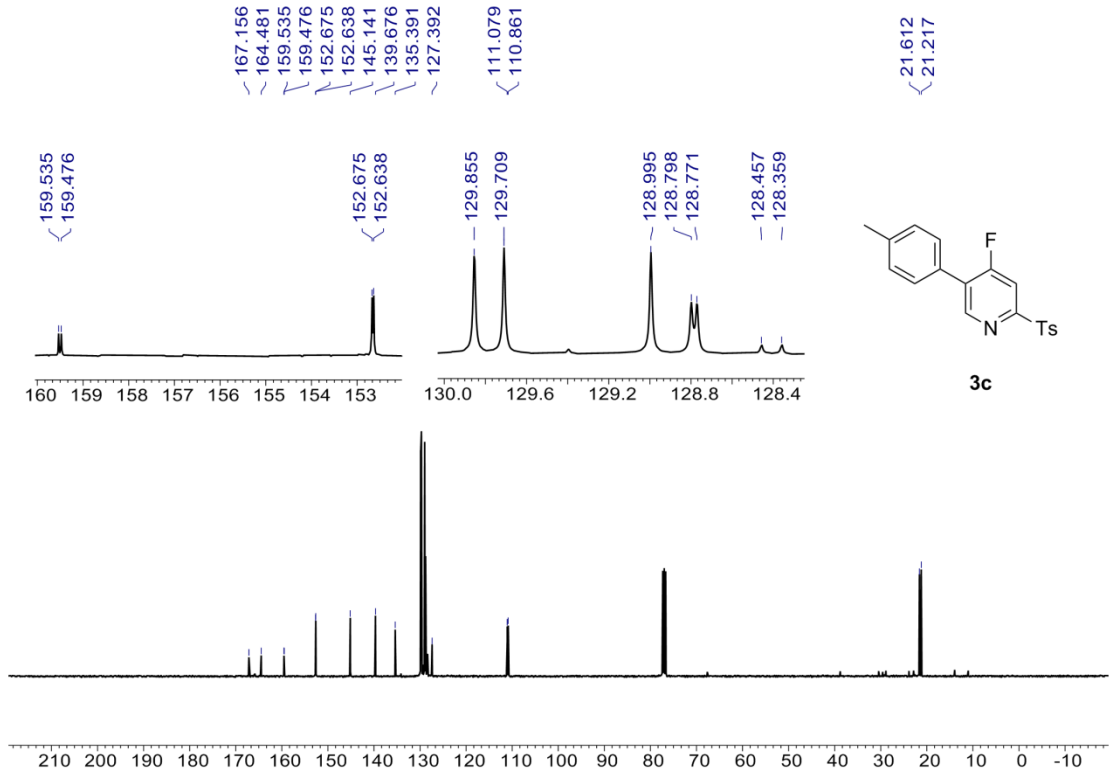


^{1}H NMR (400 MHz, $CDCl_3$) for **3c**

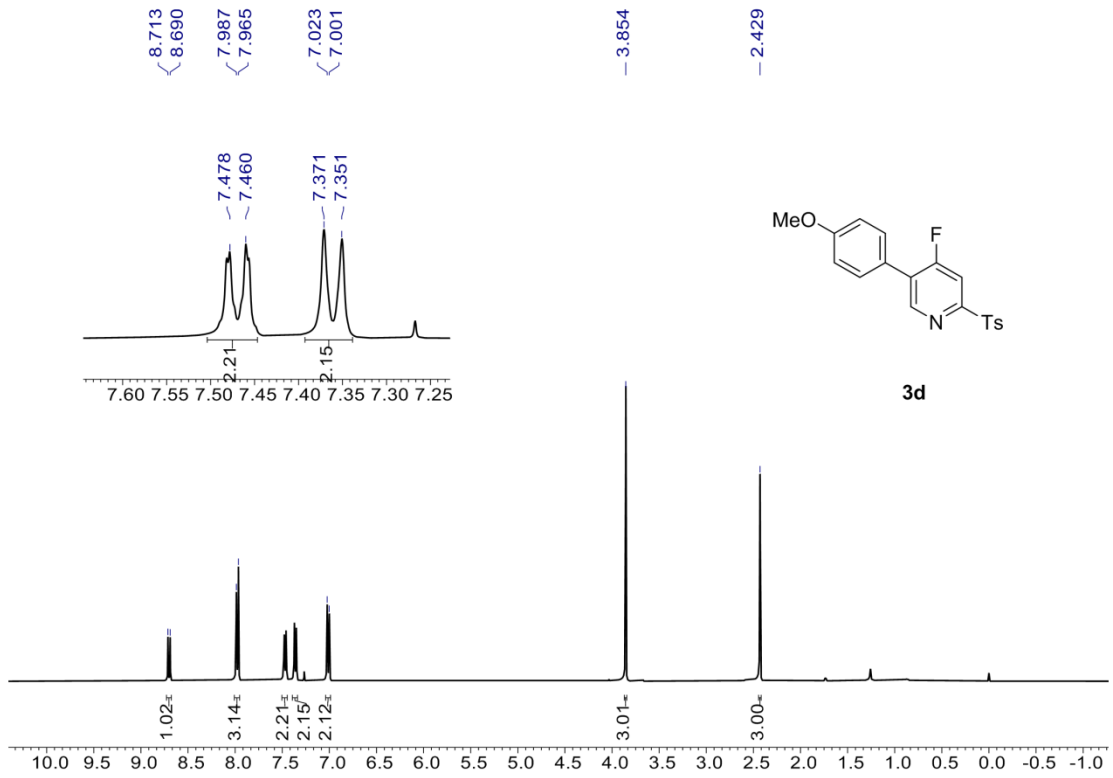


^{19}F NMR (376 MHz, $CDCl_3$) for **3c**

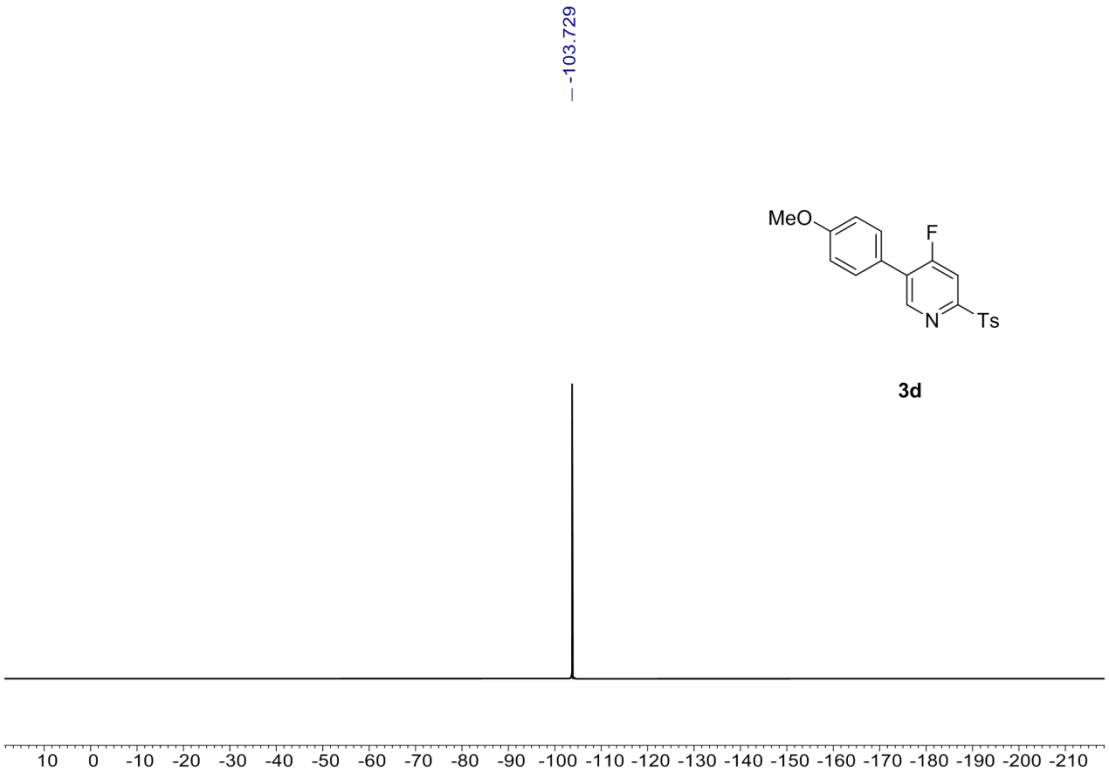
^{13}C NMR (100 MHz, $CDCl_3$) for **3c**



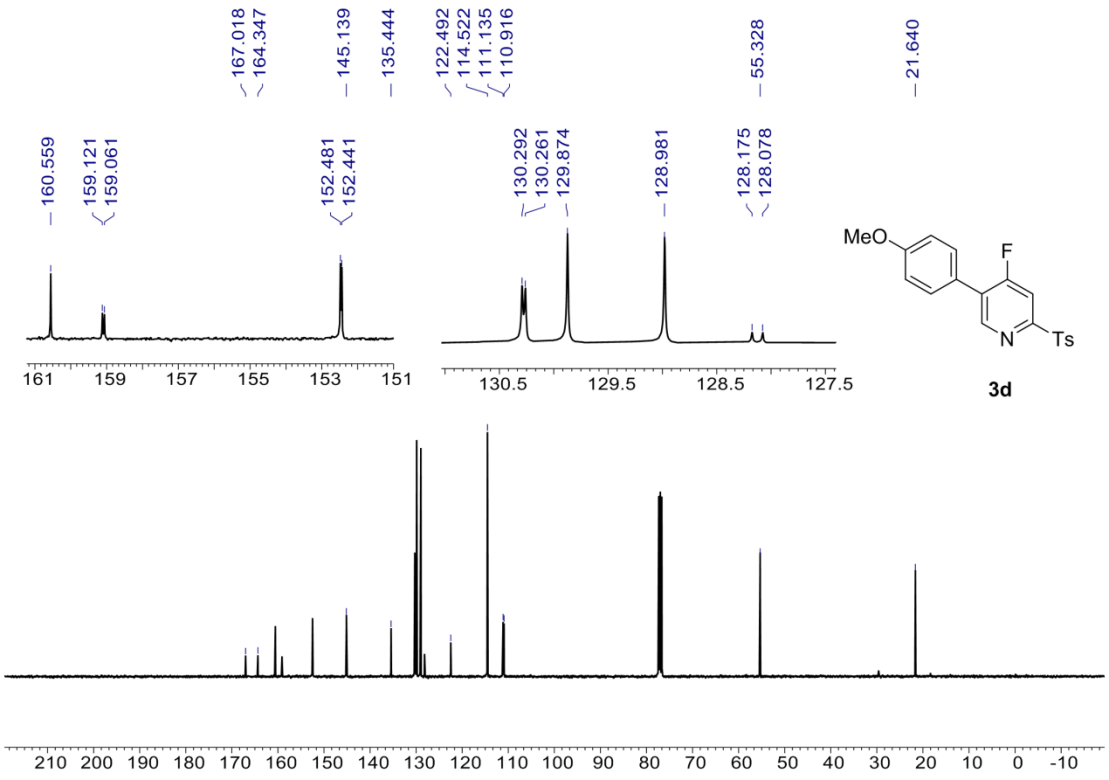
^{1}H NMR (400 MHz, $CDCl_3$) for **3d**



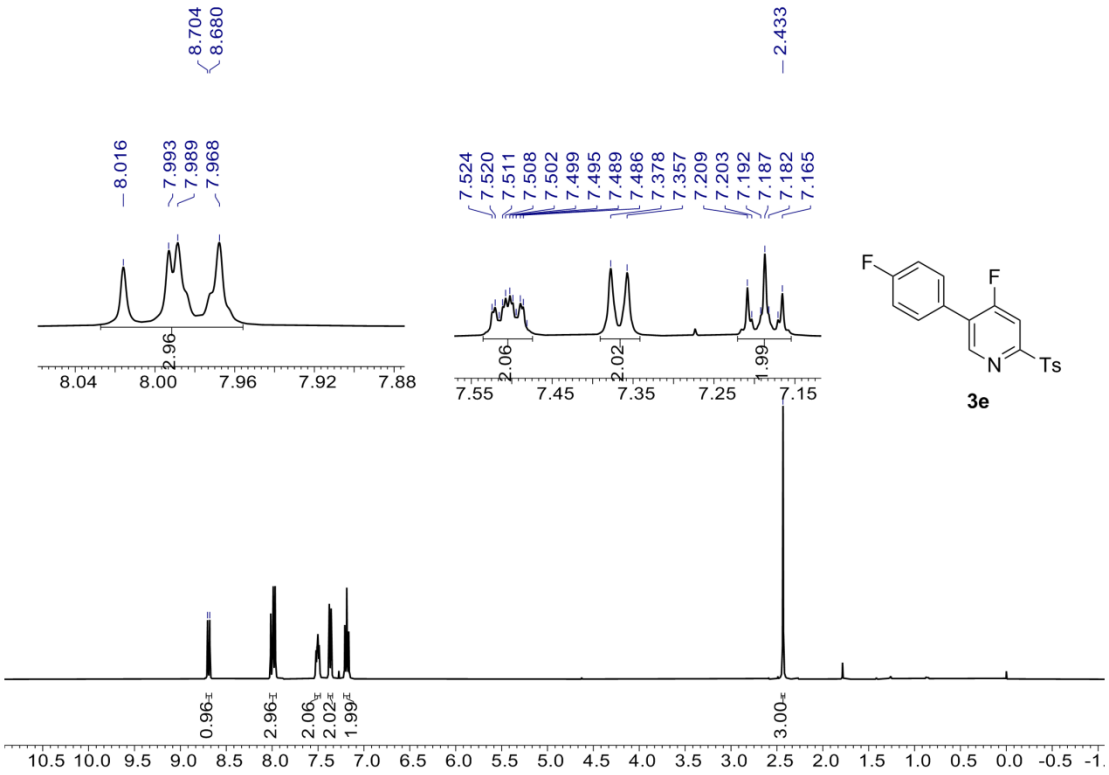
^{19}F NMR (376 MHz, $CDCl_3$) for **3d**



^{13}C NMR (100 MHz, $CDCl_3$) for **3d**

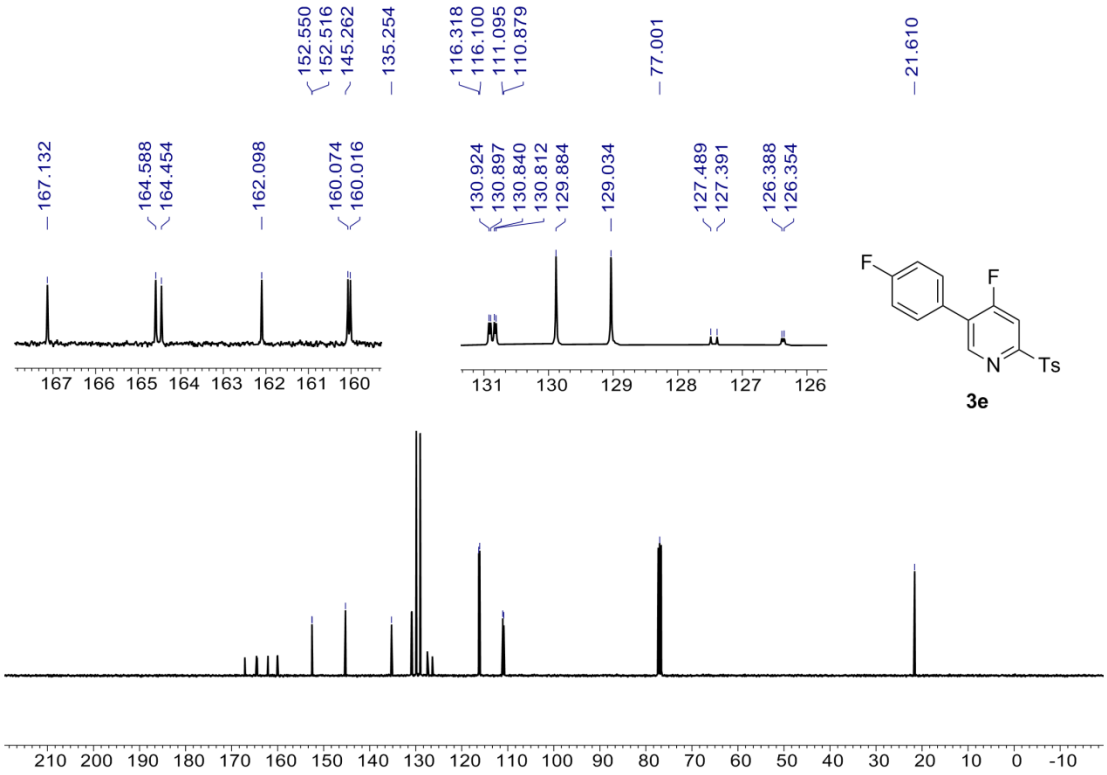


[1]H NMR (400 MHz, $CDCl_3$) for **3e**

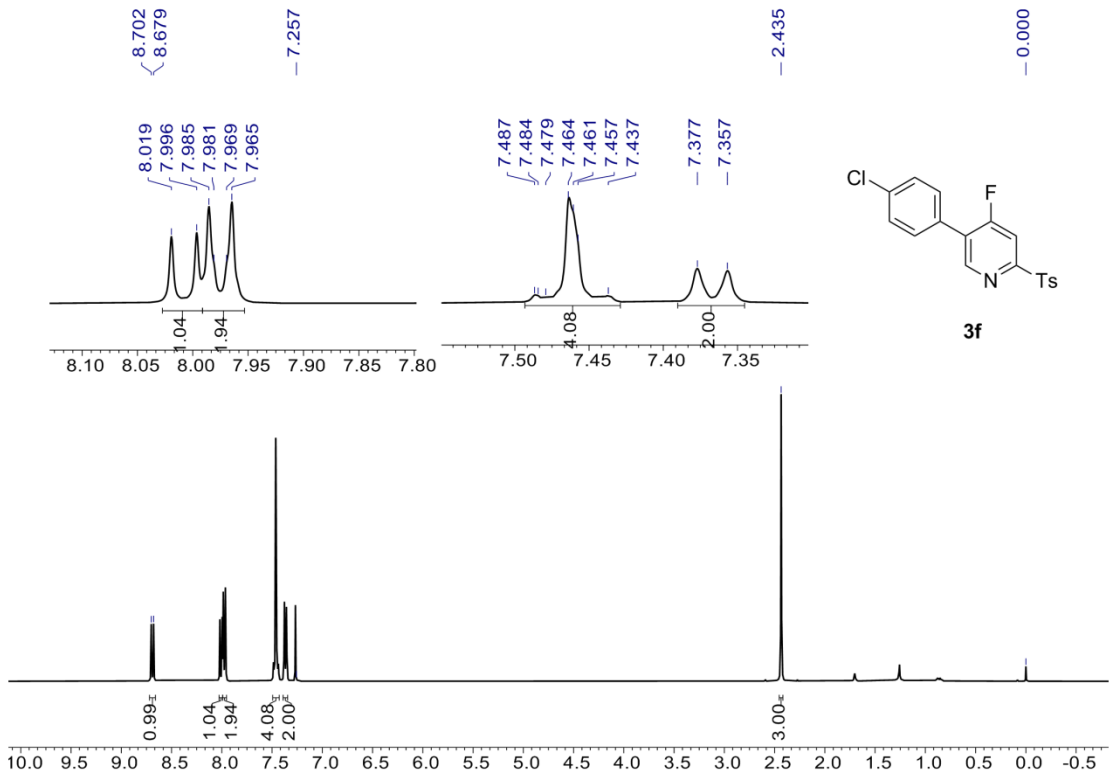


[19]F NMR (376 MHz, $CDCl_3$) for **3e**

^{13}C NMR (100 MHz, $CDCl_3$) for **3e**

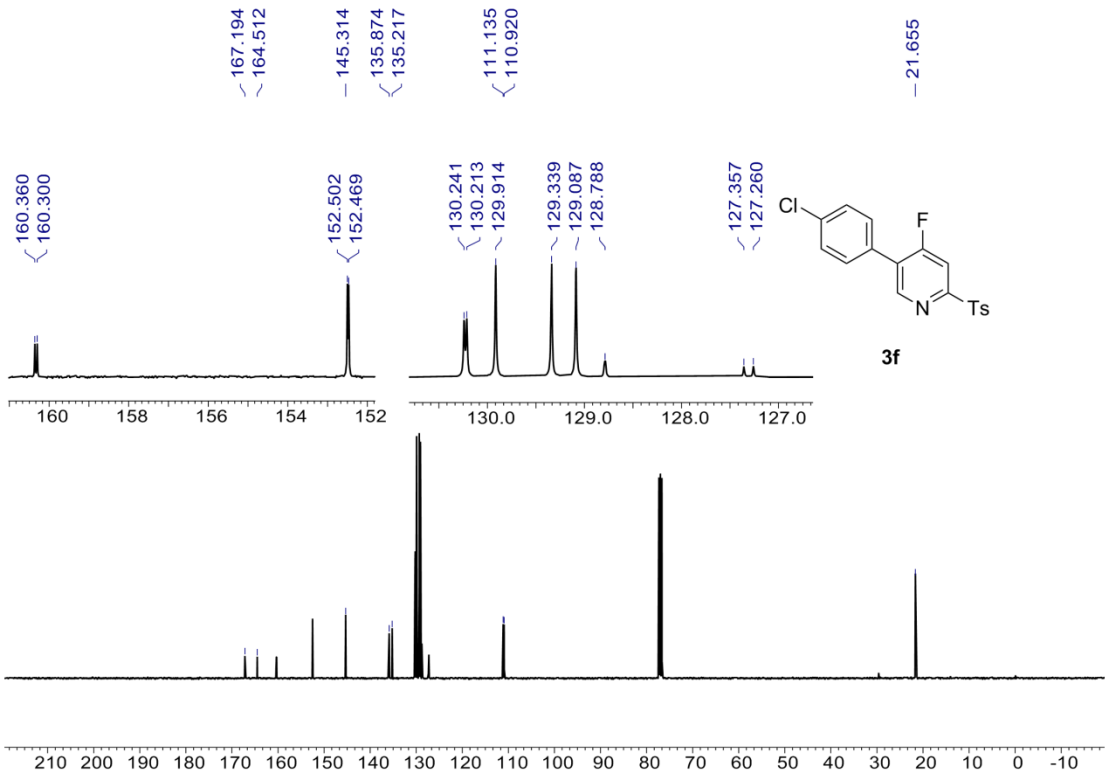


^{1}H NMR (400 MHz, $CDCl_3$) for **3f**

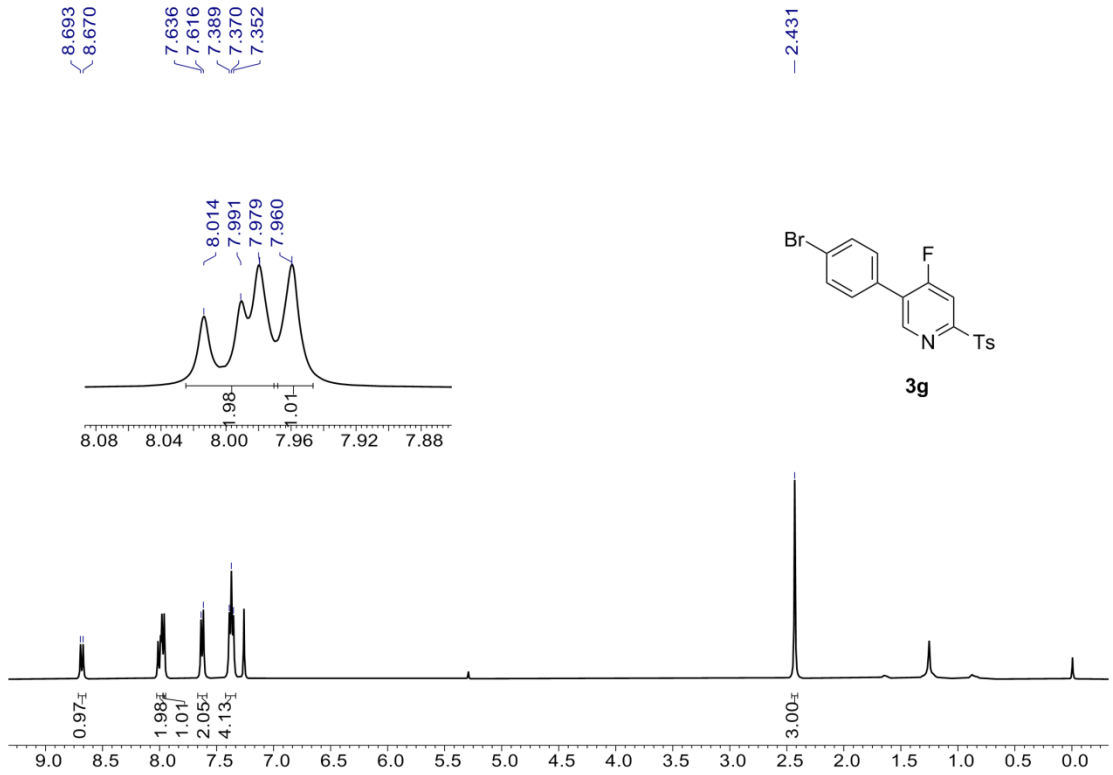


^{19}F NMR (376 MHz, $CDCl_3$) for **3f**

^{13}C NMR (100 MHz, $CDCl_3$) for **3f**

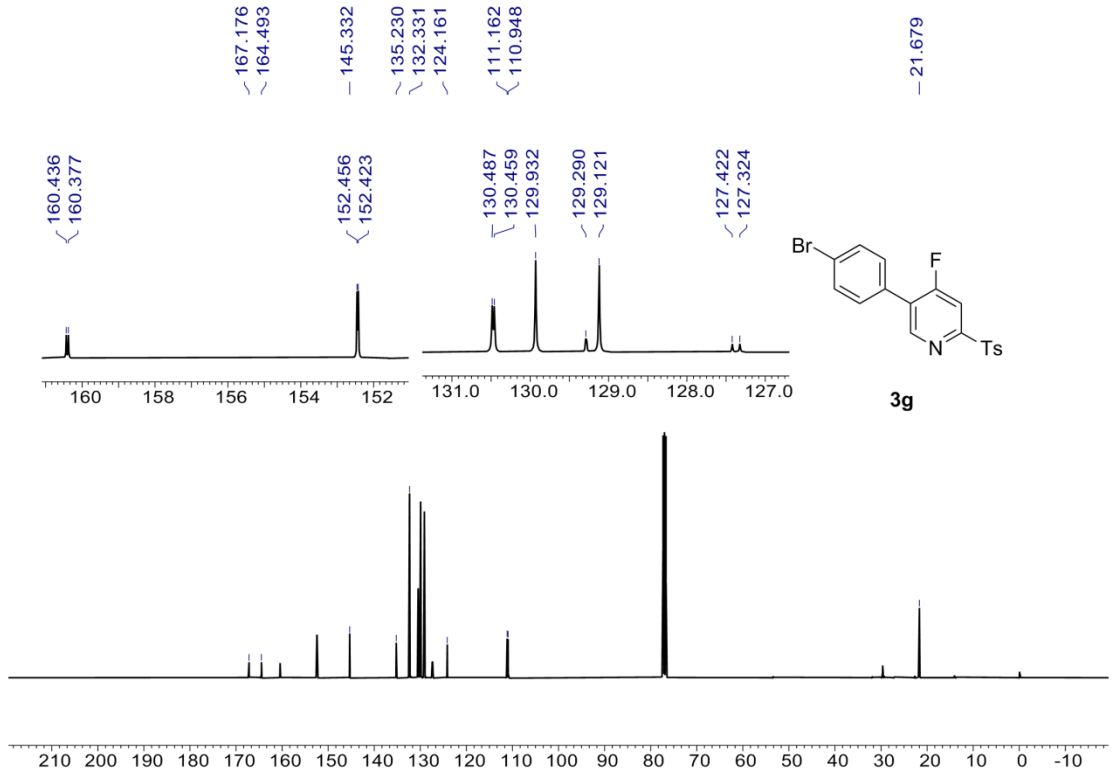


[1]H NMR (400 MHz, $CDCl_3$) for **3g**

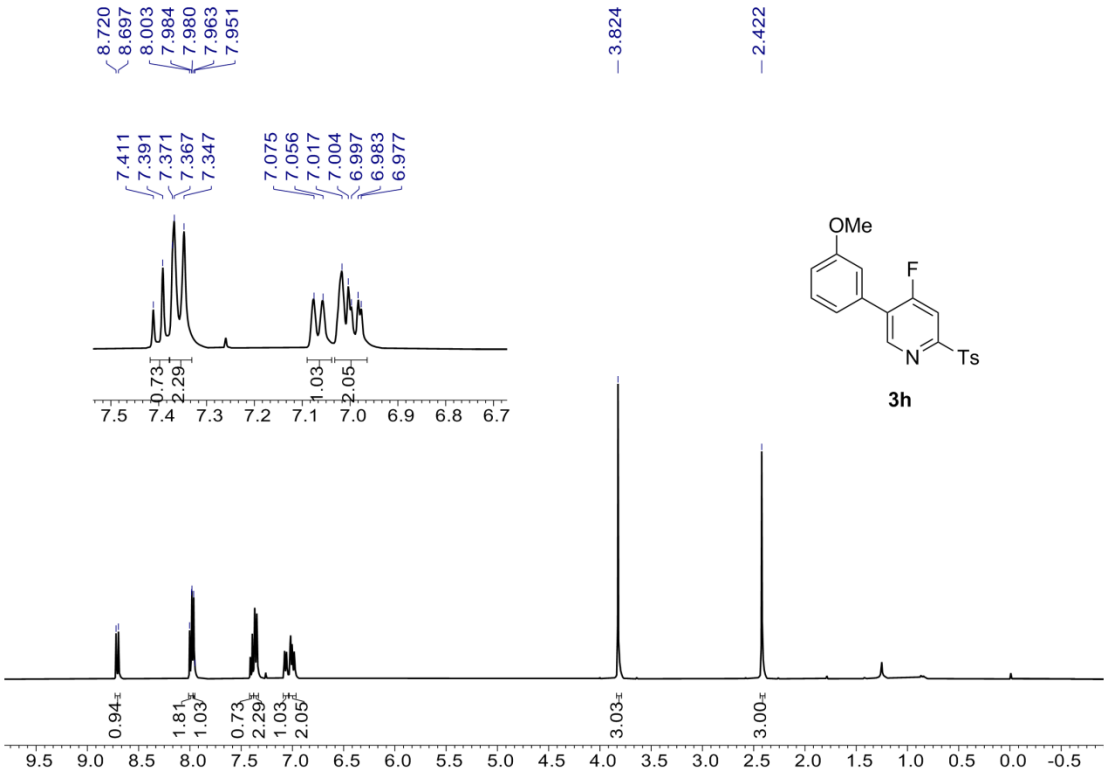


[19]F NMR (376 MHz, $CDCl_3$) for **3g**

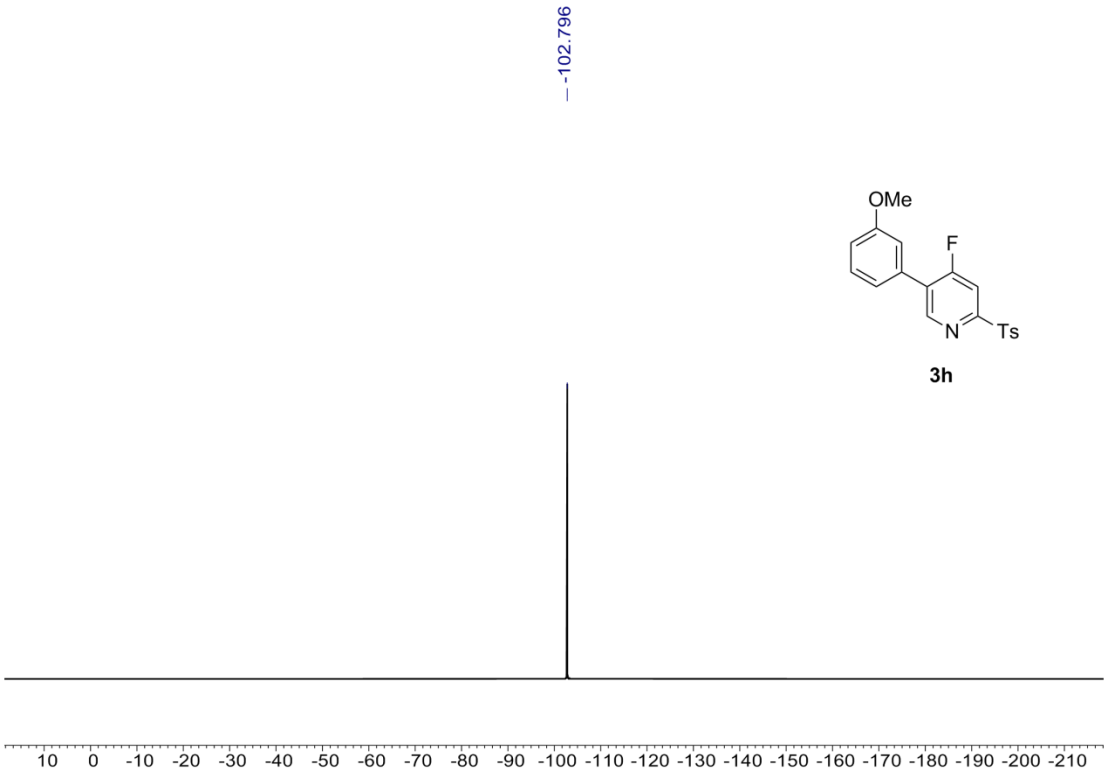
^{13}C NMR (100 MHz, $CDCl_3$) for **3g**



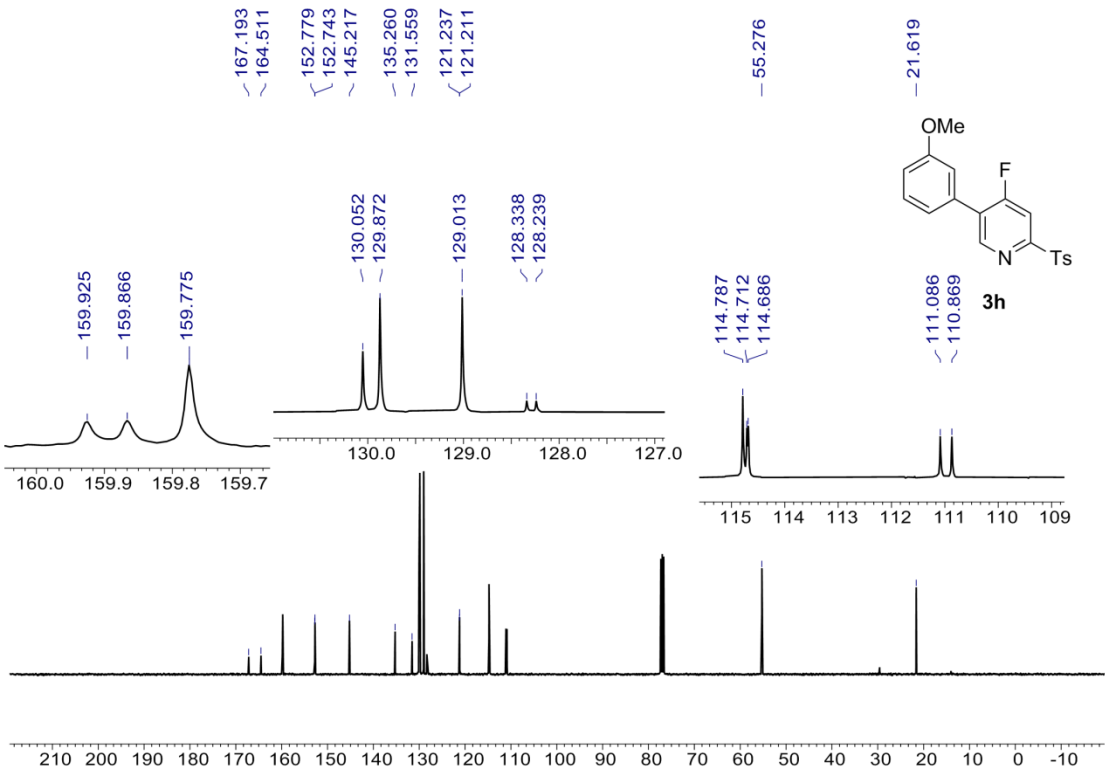
^{1}H NMR (400 MHz, $CDCl_3$) for **3h**



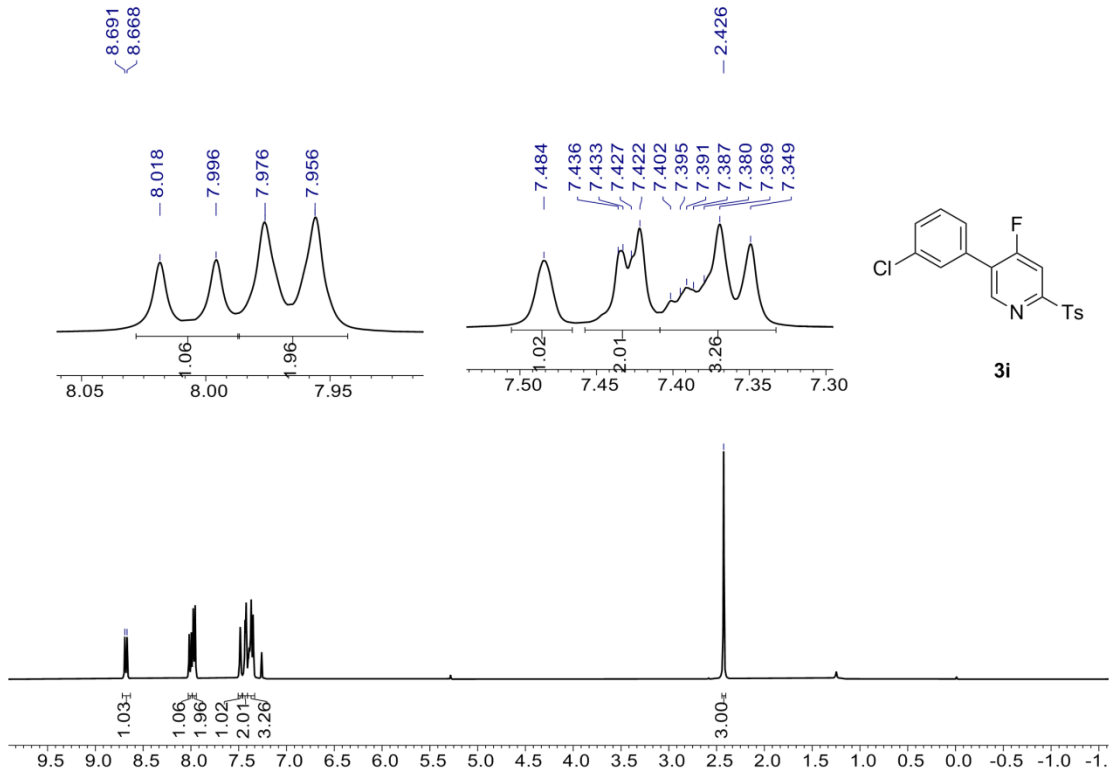
^{19}F NMR (376 MHz, $CDCl_3$) for **3h**



^{13}C NMR (100 MHz, $CDCl_3$) for **3h**

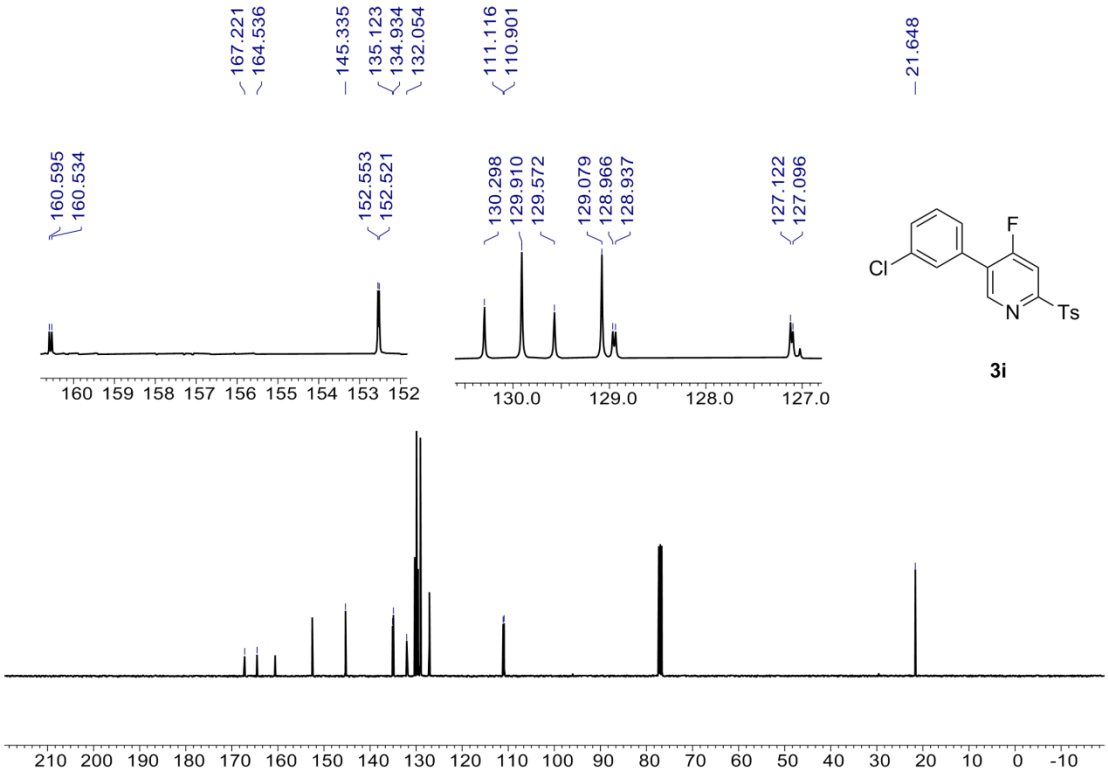


^{1}H NMR (400 MHz, $CDCl_3$) for **3i**

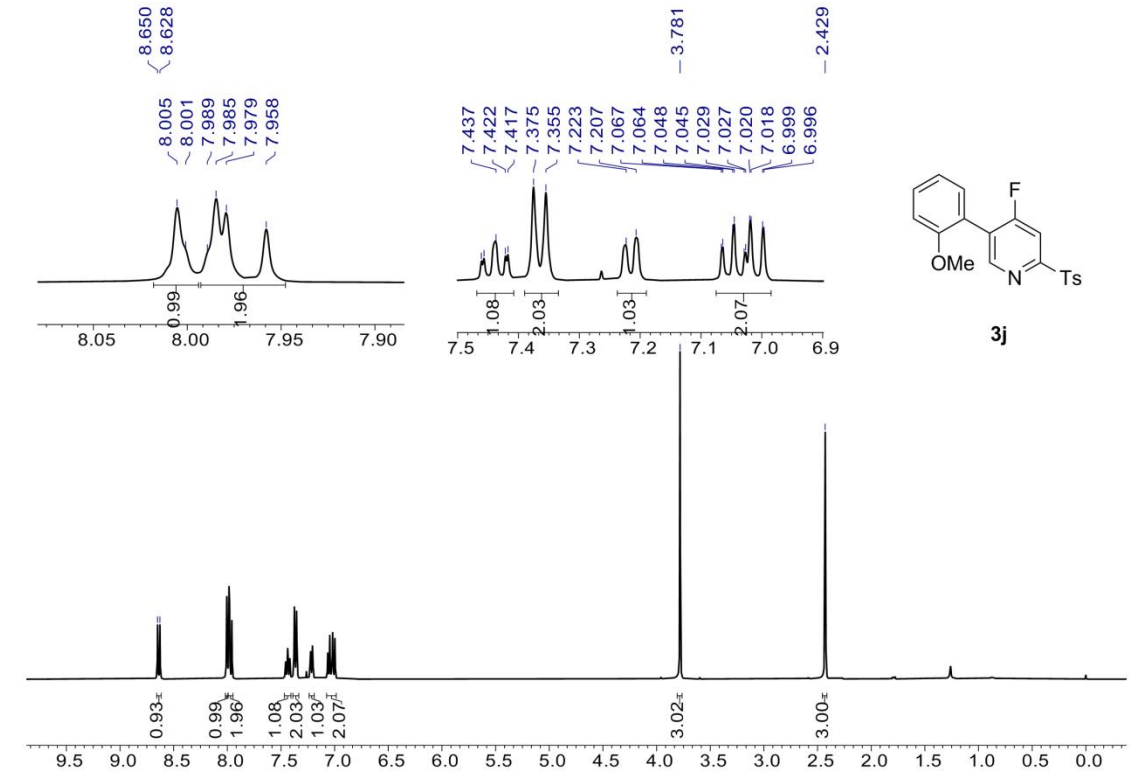


^{19}F NMR (376 MHz, $CDCl_3$) for **3i**

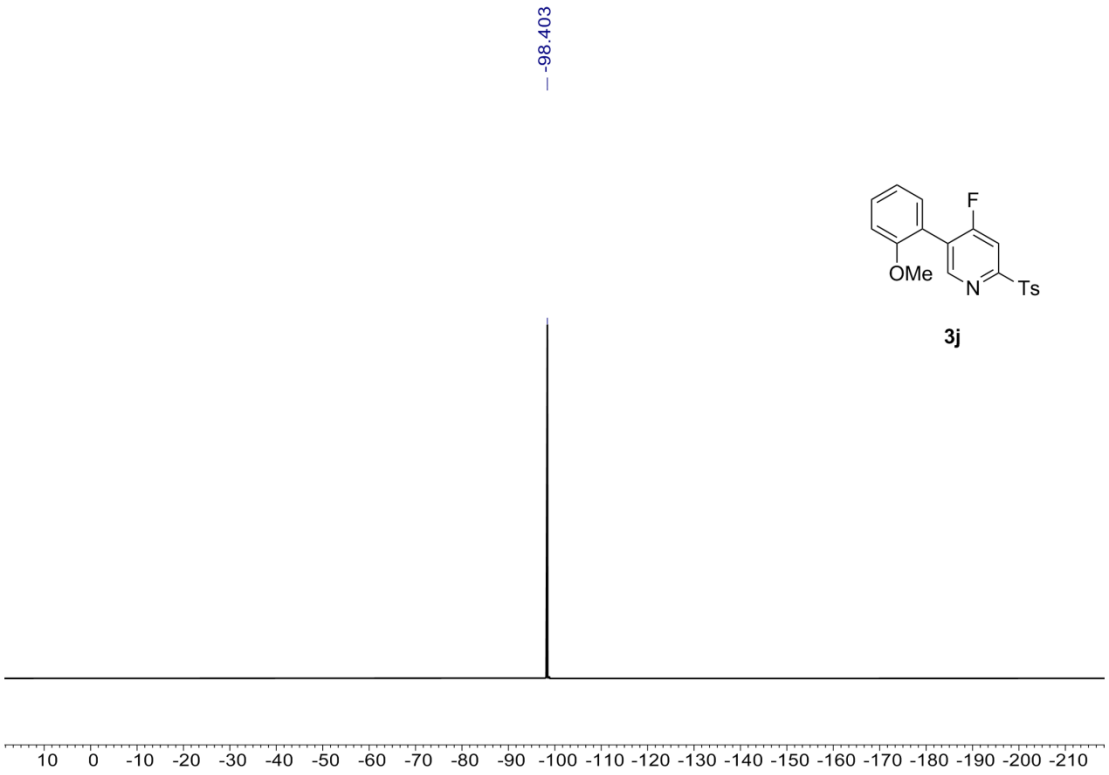
^{13}C NMR (100 MHz, $CDCl_3$) for **3i**



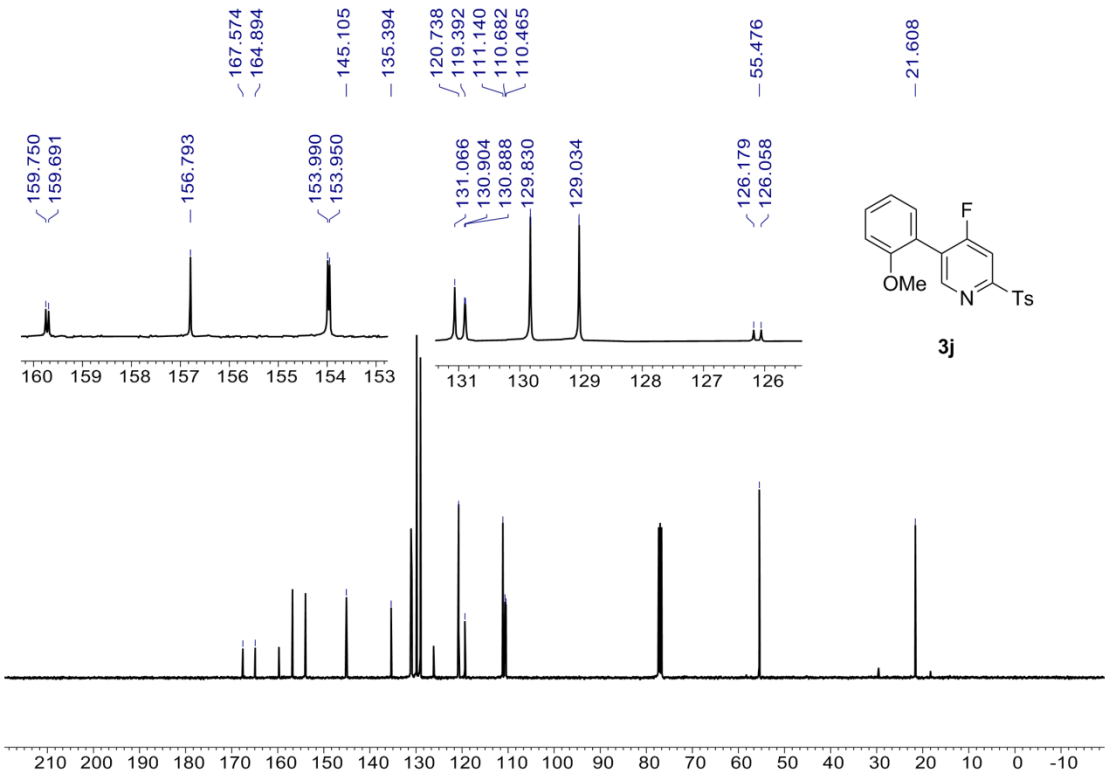
^{1}H NMR (400 MHz, $CDCl_3$) for **3j**



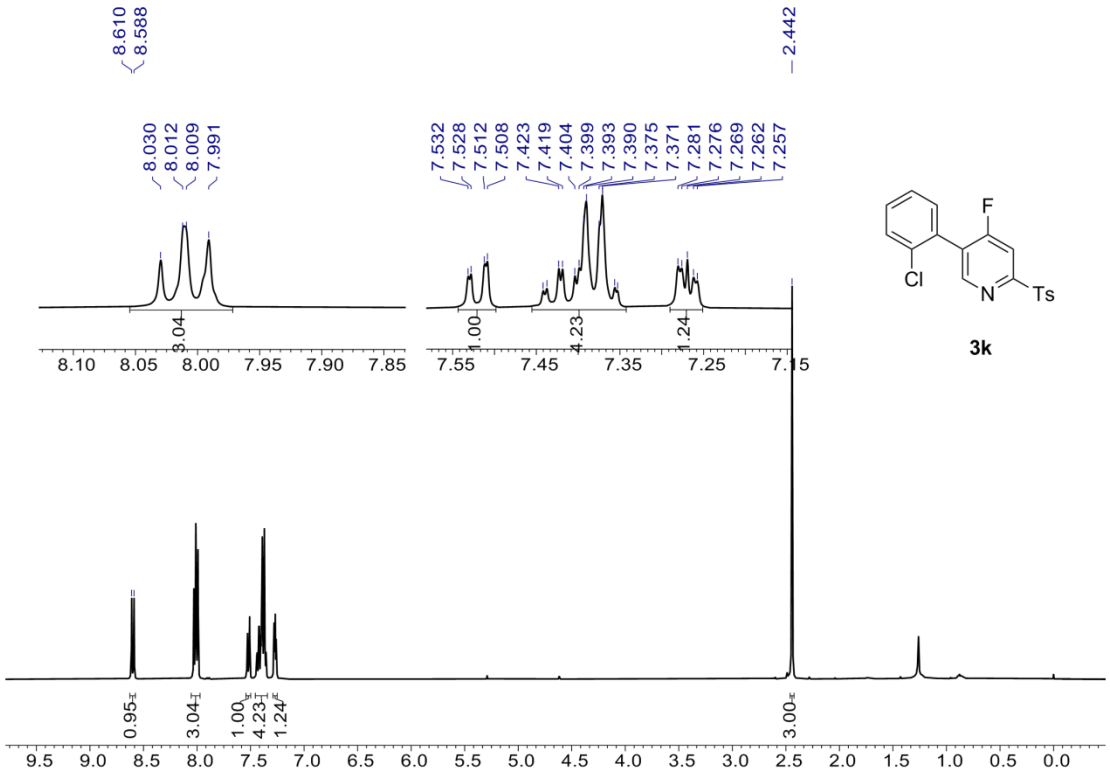
^{19}F NMR (376 MHz, $CDCl_3$) for **3j**



^{13}C NMR (100 MHz, $CDCl_3$) for **3j**

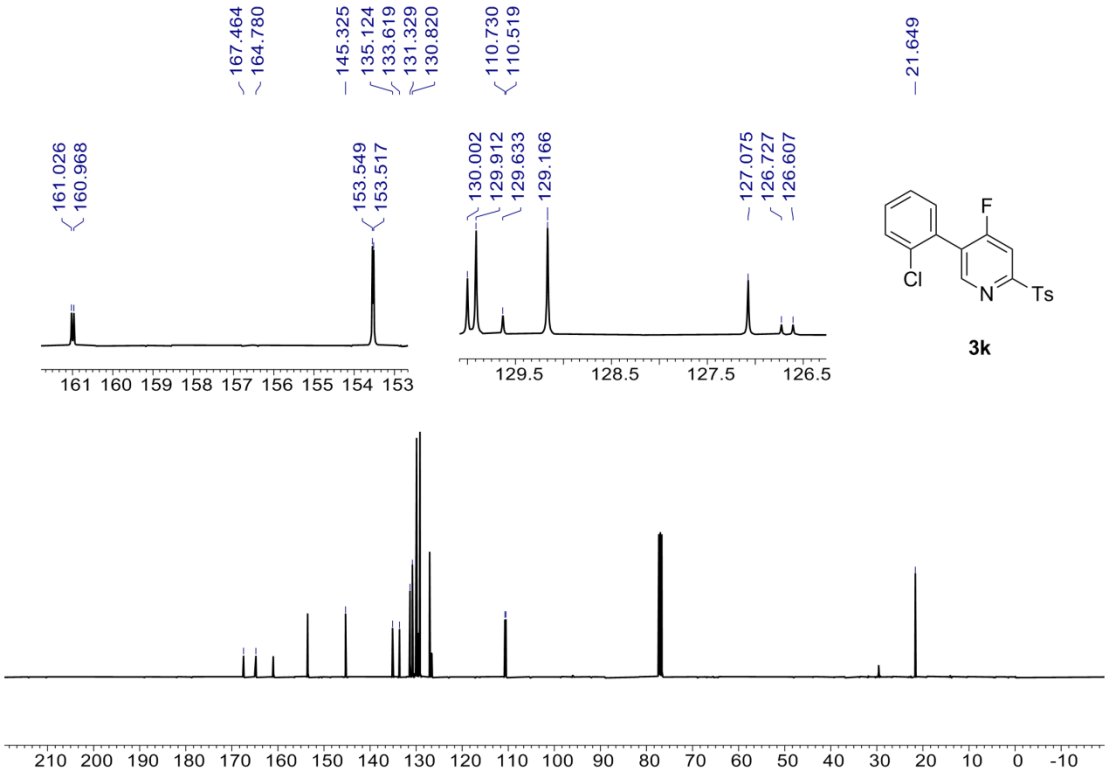


[1]H NMR (400 MHz, $CDCl_3$) for **3k**

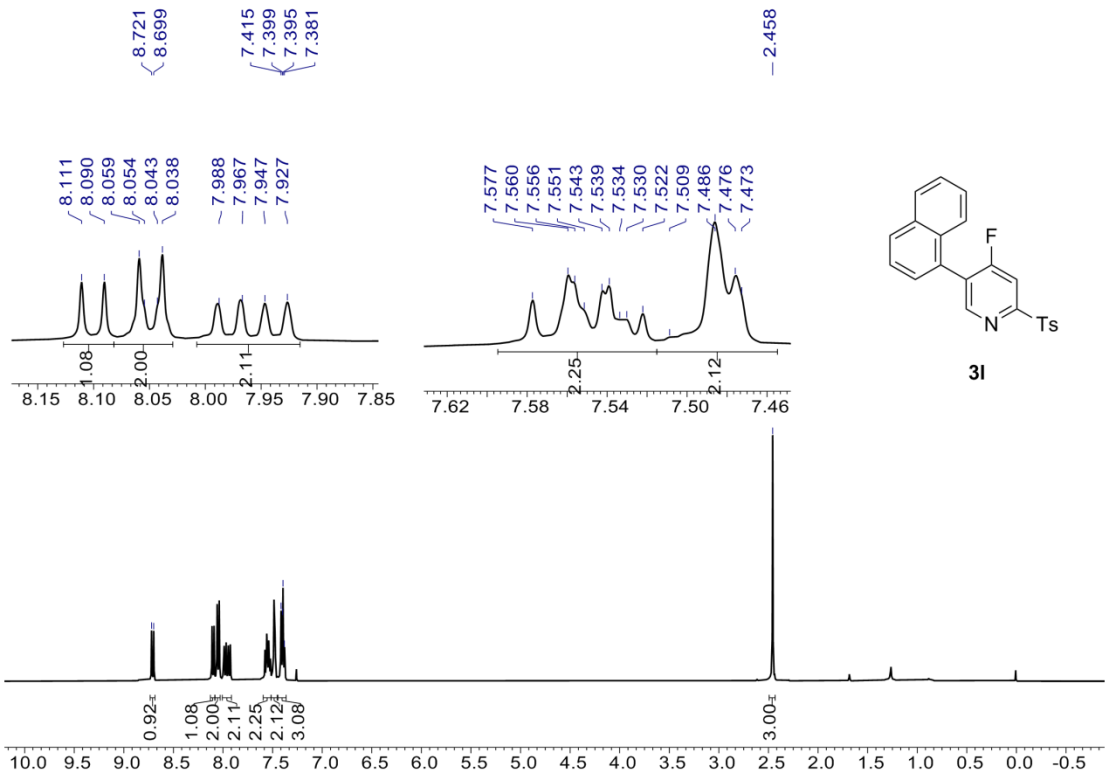


[19]F NMR (376 MHz, $CDCl_3$) for **3k**

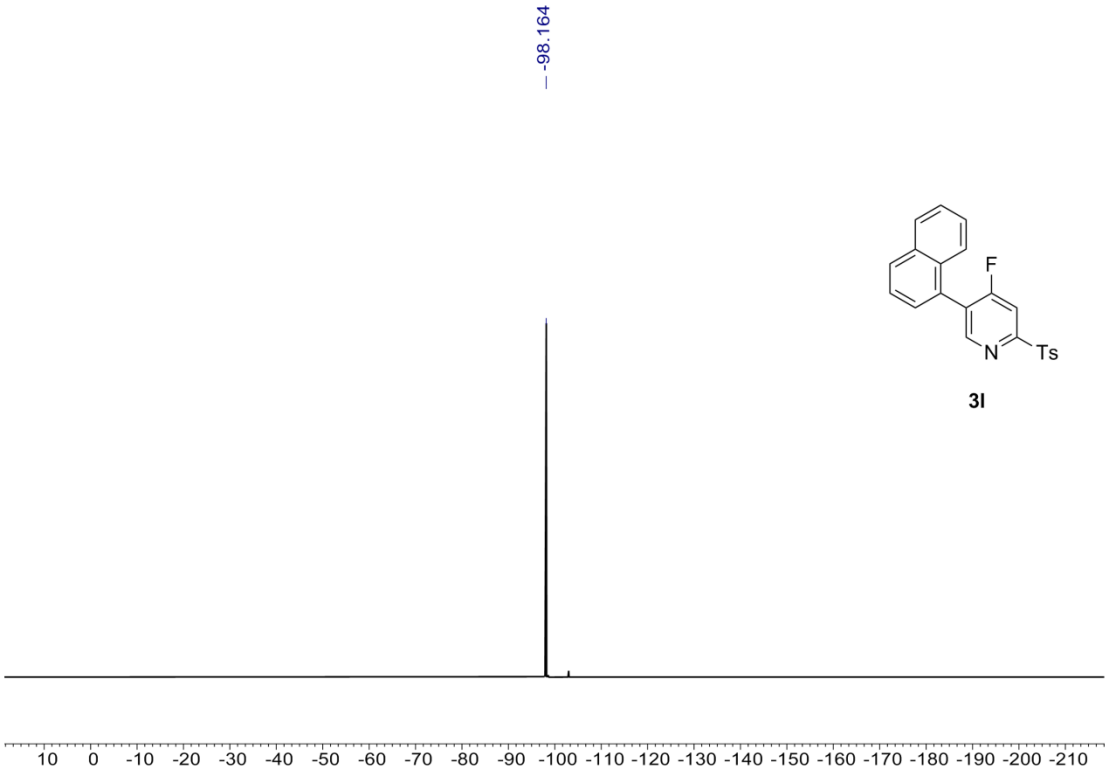
^{13}C NMR (100 MHz, $CDCl_3$) for **3k**



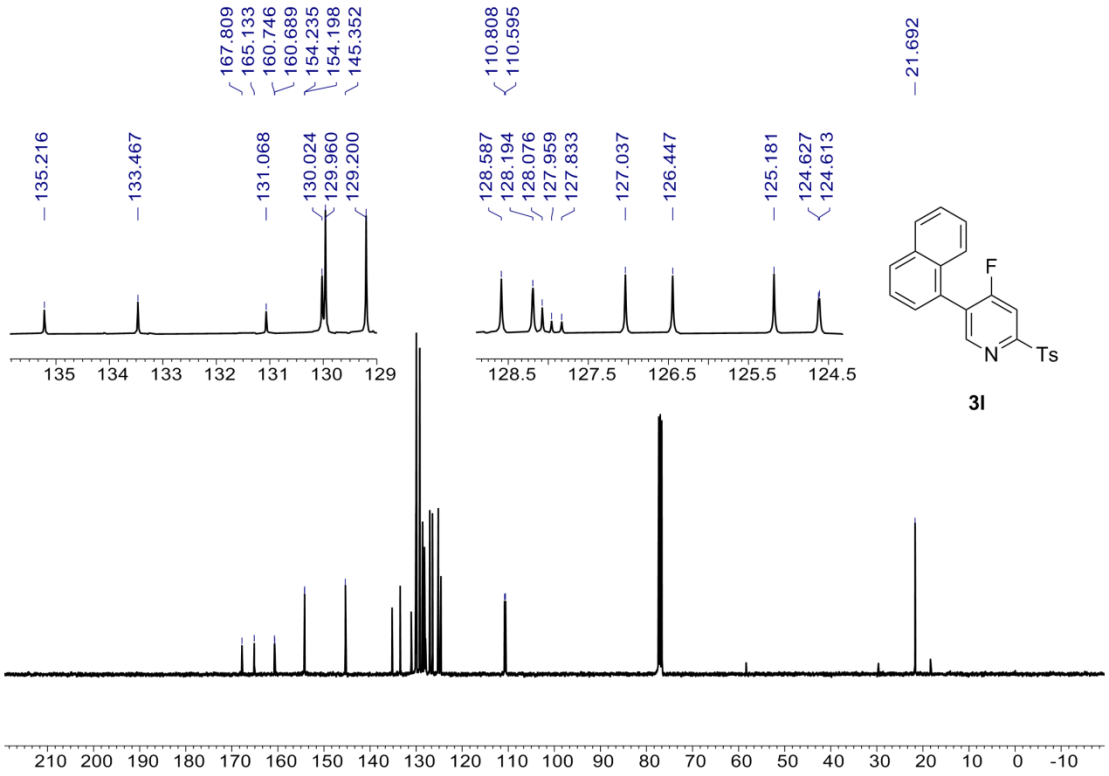
^{1}H NMR (400 MHz, $CDCl_3$) for **3l**



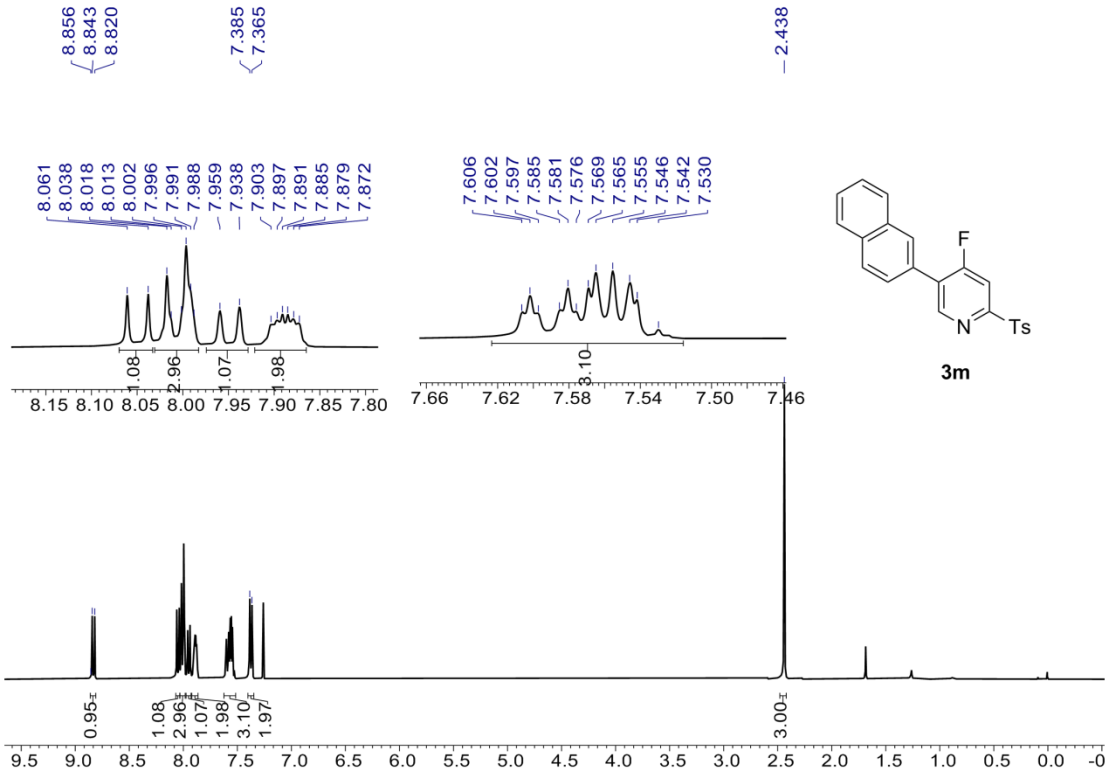
^{19}F NMR (376 MHz, $CDCl_3$) for **3l**



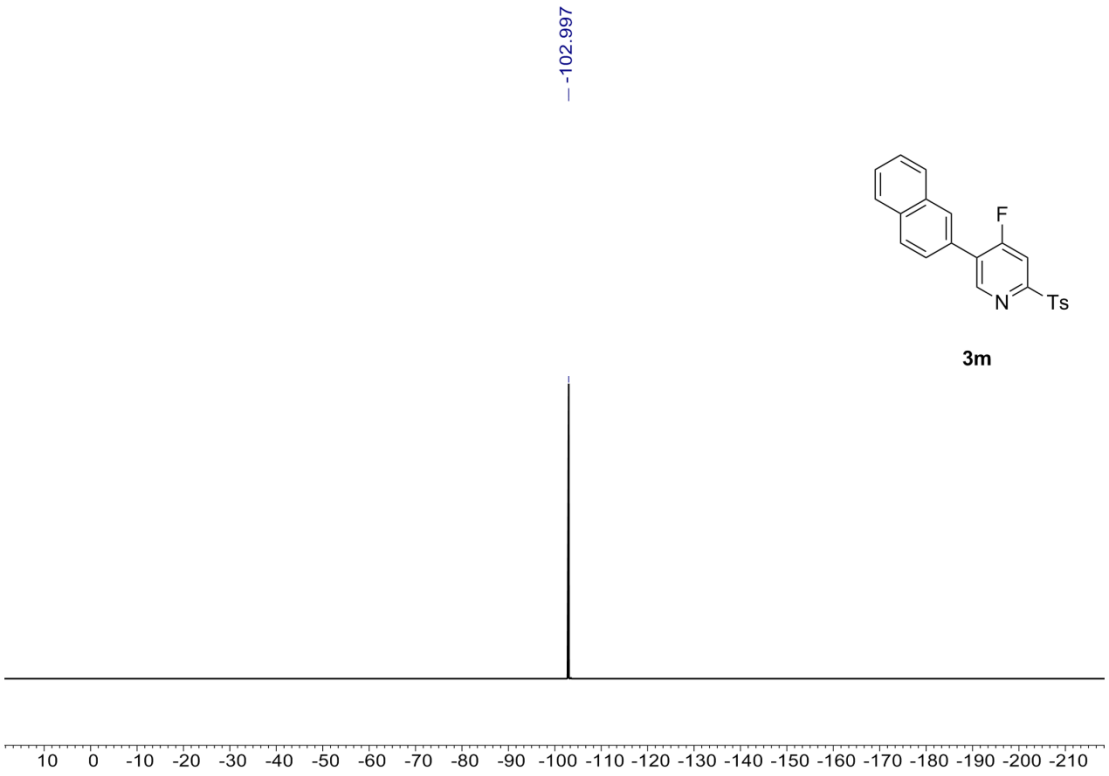
^{13}C NMR (100 MHz, $CDCl_3$) for **3l**



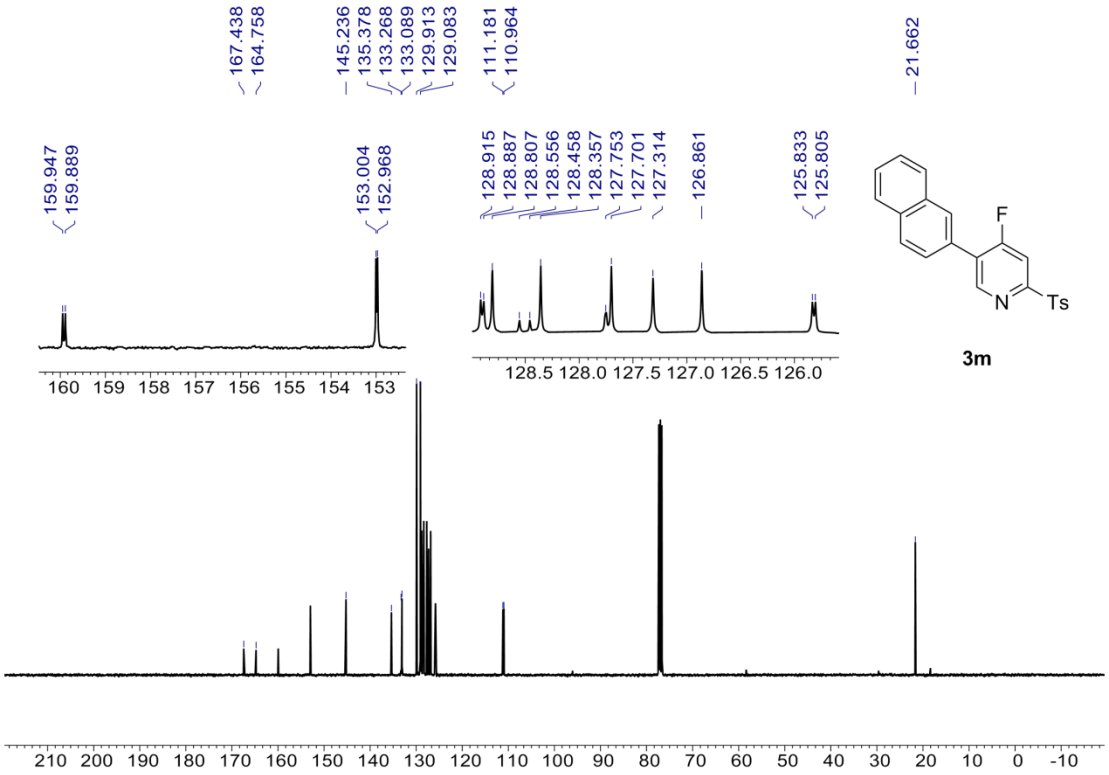
^{1}H NMR (400 MHz, $CDCl_3$) for **3m**



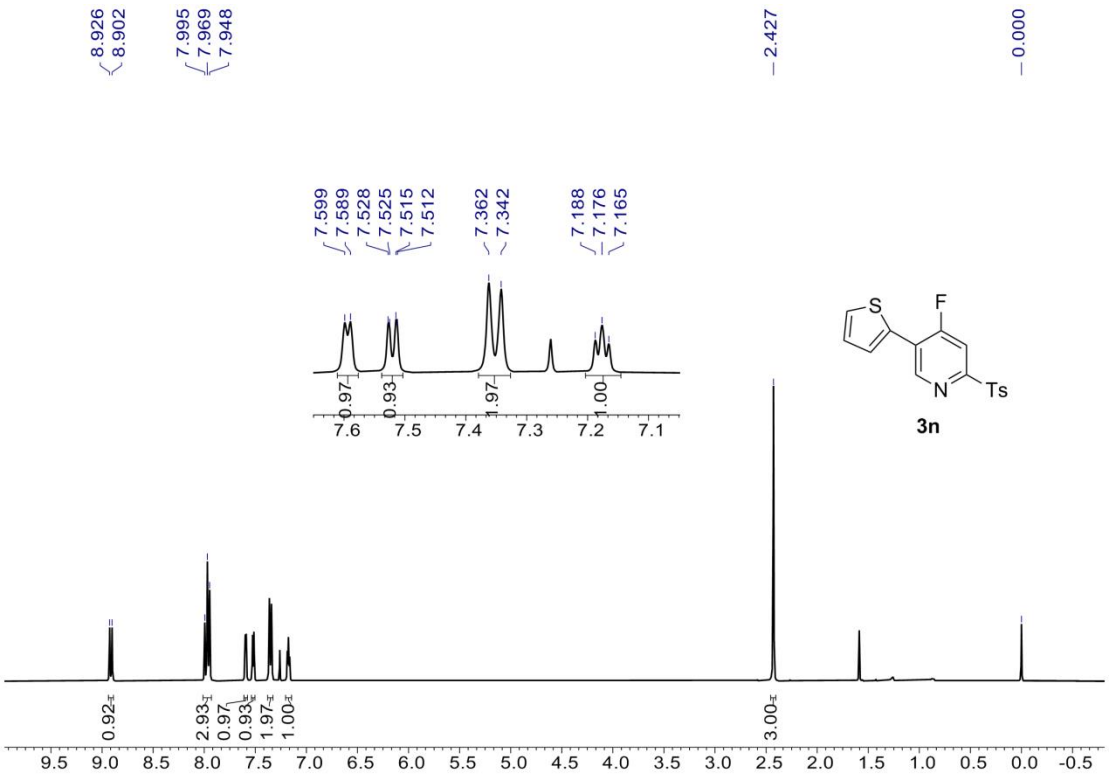
^{19}F NMR (376 MHz, $CDCl_3$) for **3m**



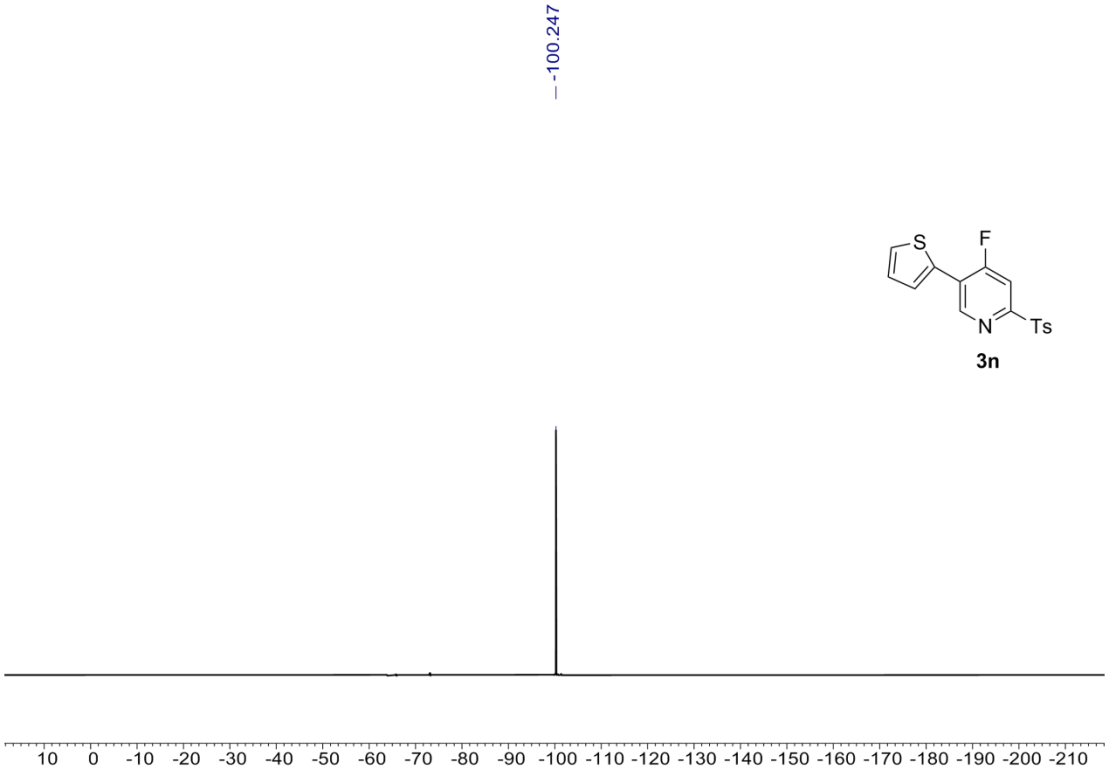
^{13}C NMR (100 MHz, $CDCl_3$) for **3m**



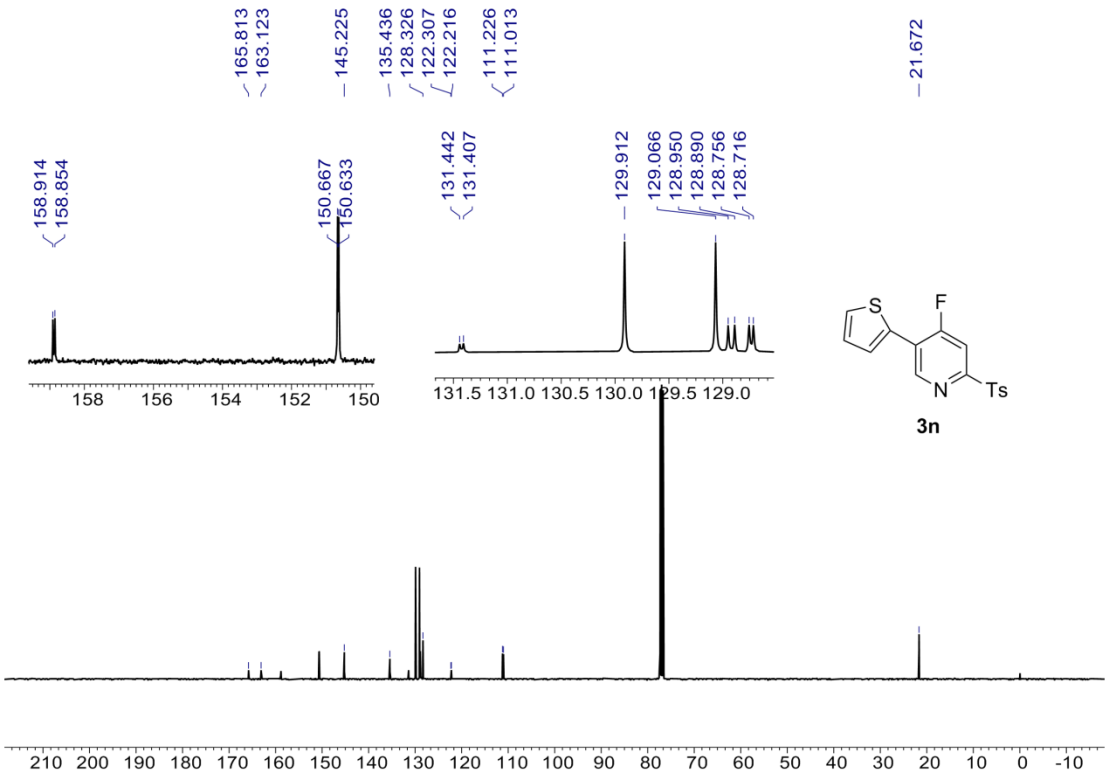
^{1}H NMR (400 MHz, $CDCl_3$) for **3n**



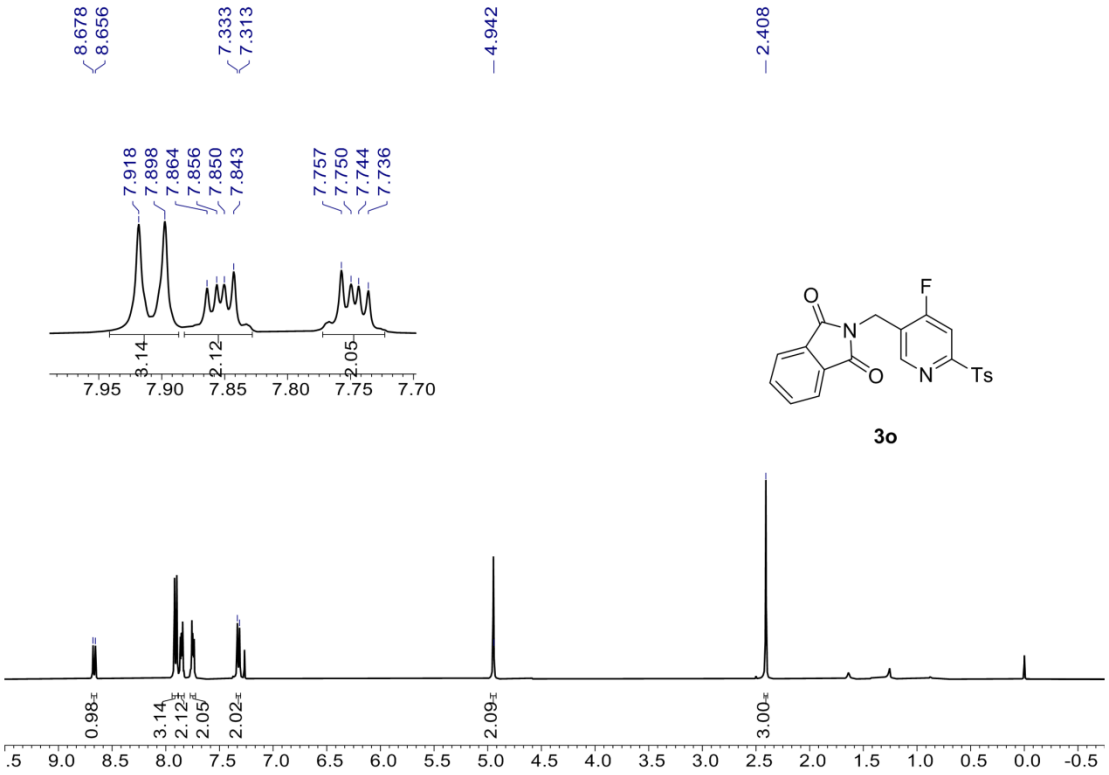
^{19}F NMR (376 MHz, $CDCl_3$) for **3n**



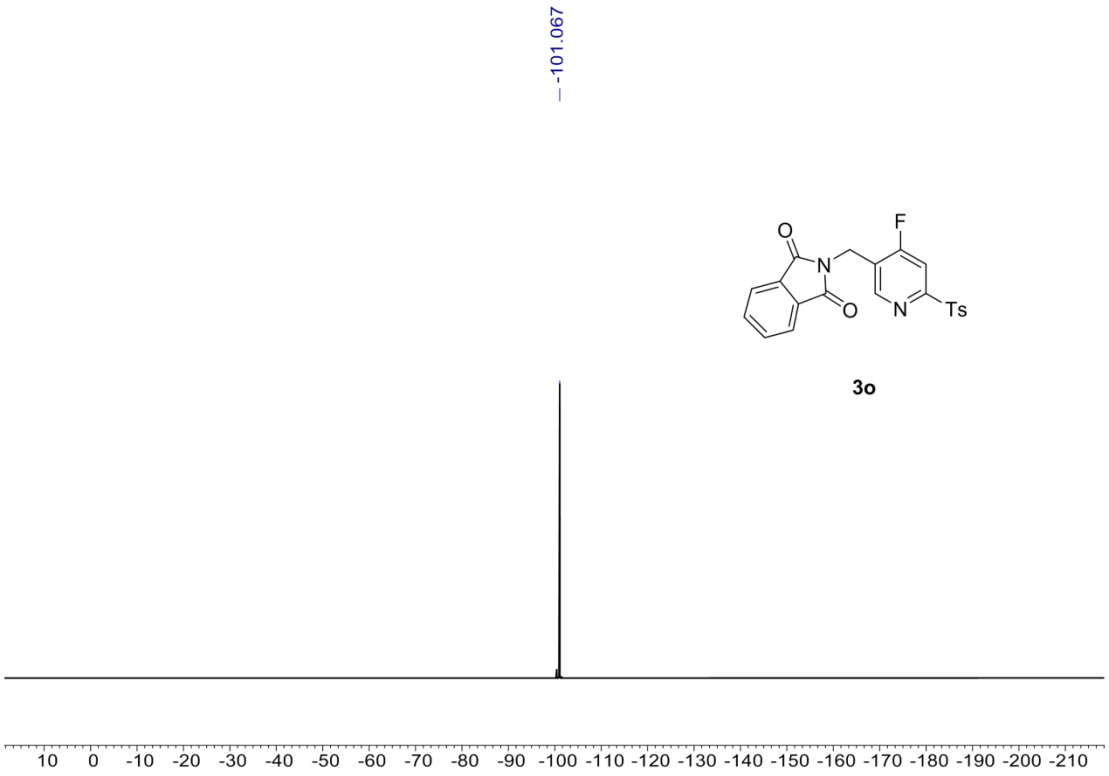
^{13}C NMR (100 MHz, $CDCl_3$) for **3n**



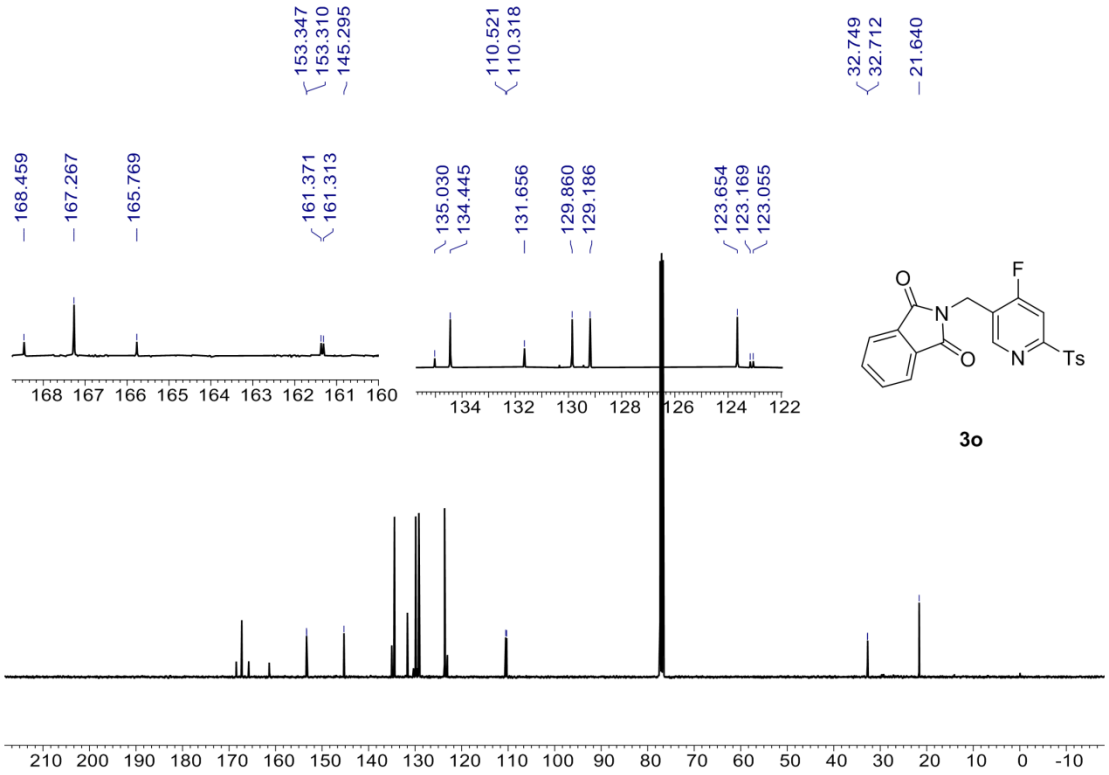
[1]H NMR (400 MHz, $CDCl_3$) for **3o**



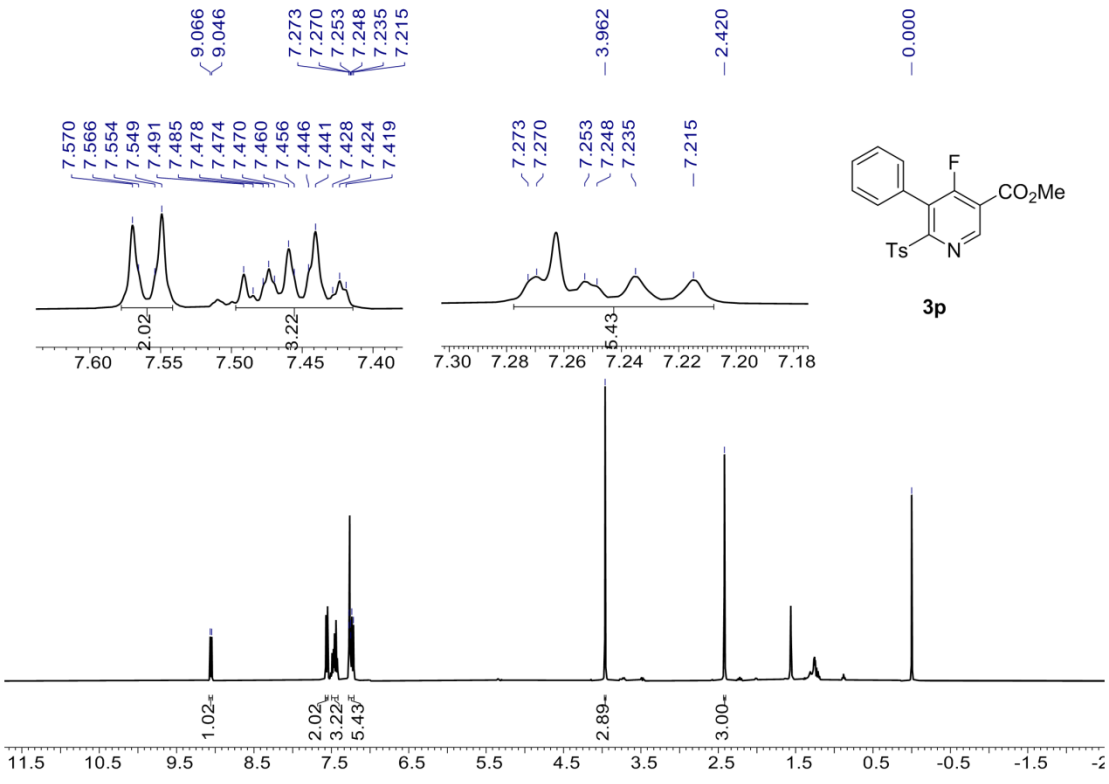
[19]F NMR (376 MHz, $CDCl_3$) for **3o**



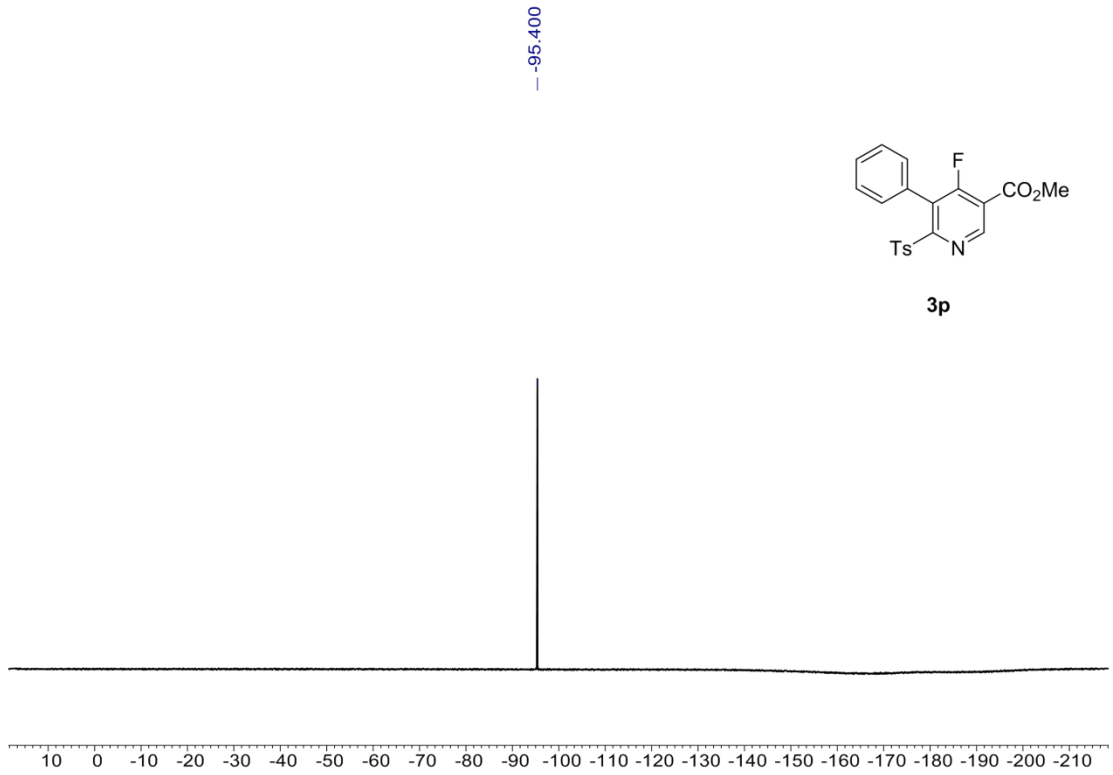
^{13}C NMR (100 MHz, $CDCl_3$) for **3o**



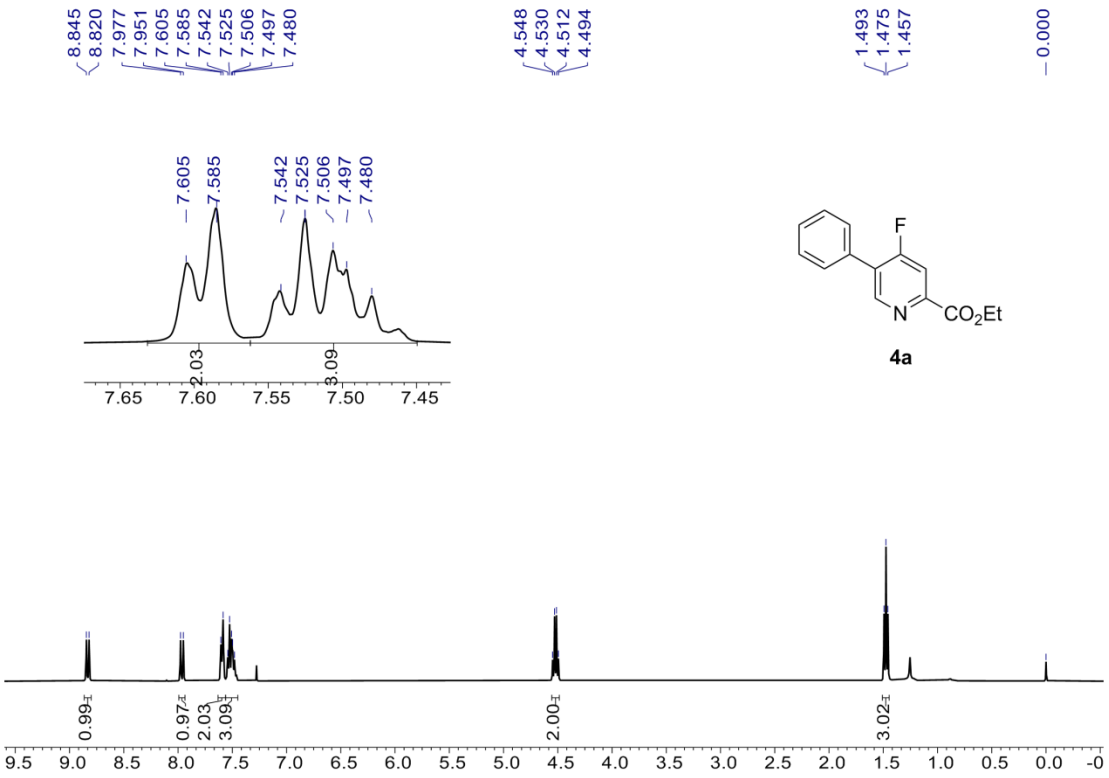
^{1}H NMR (400 MHz, $CDCl_3$) for **3p**



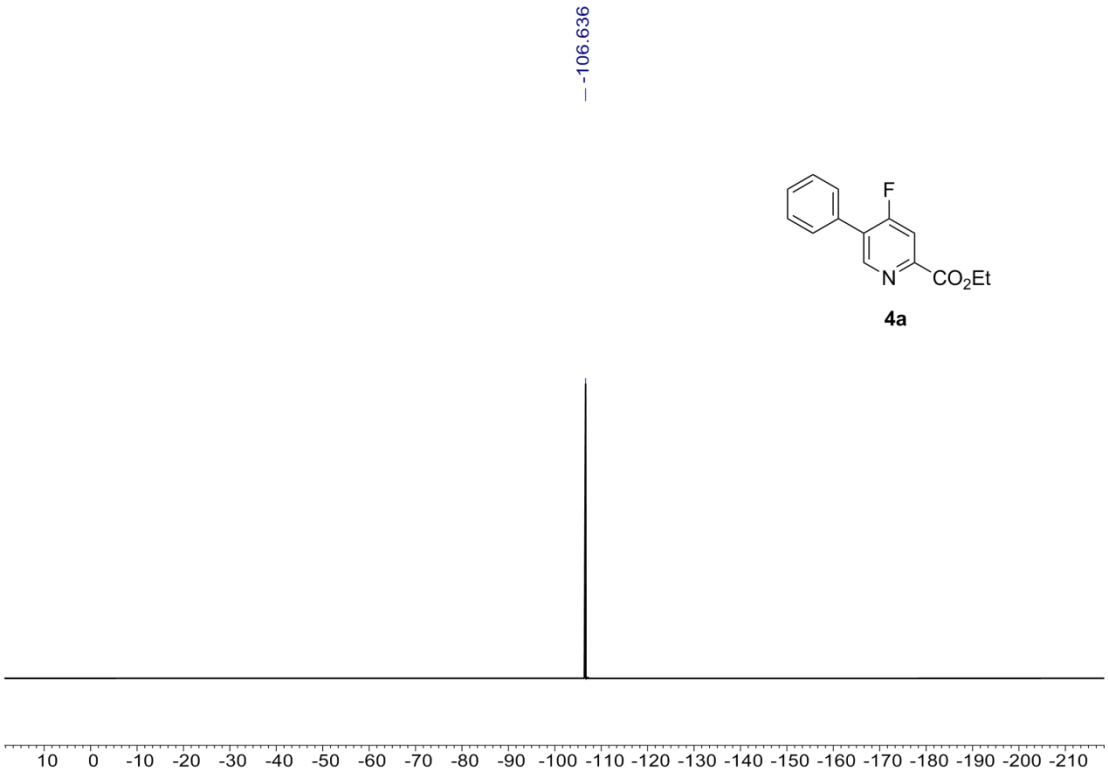
^{19}F NMR (376 MHz, $CDCl_3$) for **3p**



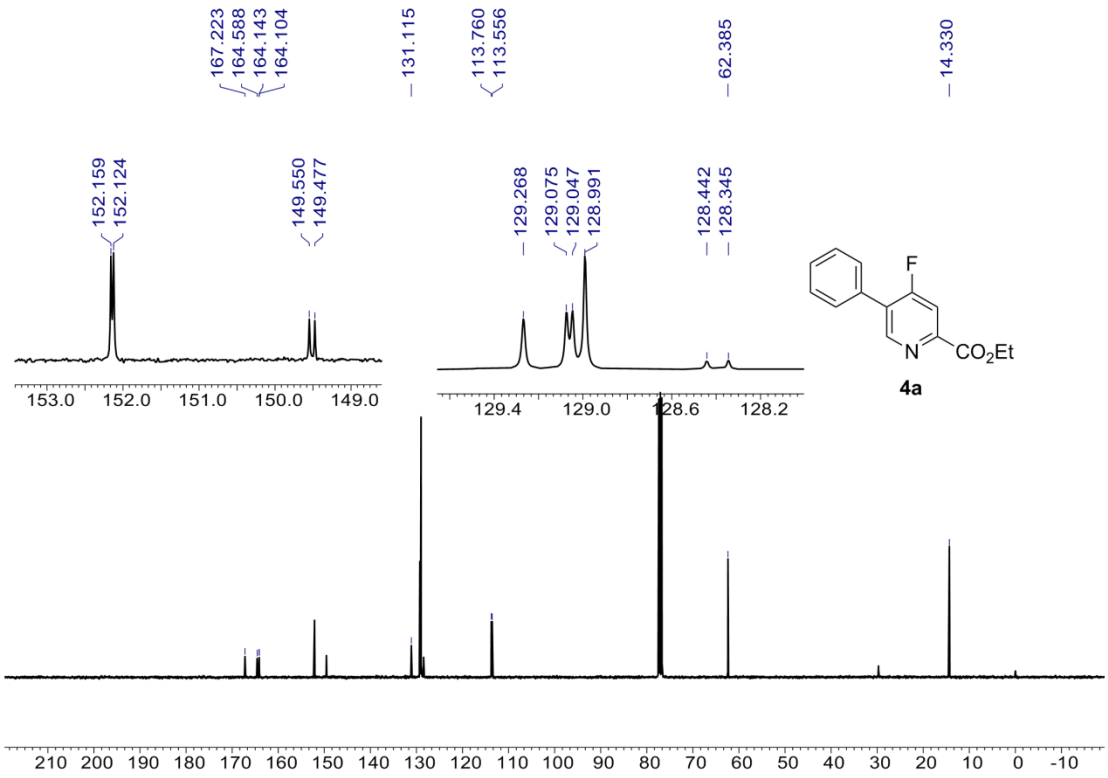
^{1}H NMR (400 MHz, $CDCl_3$) for **4a**



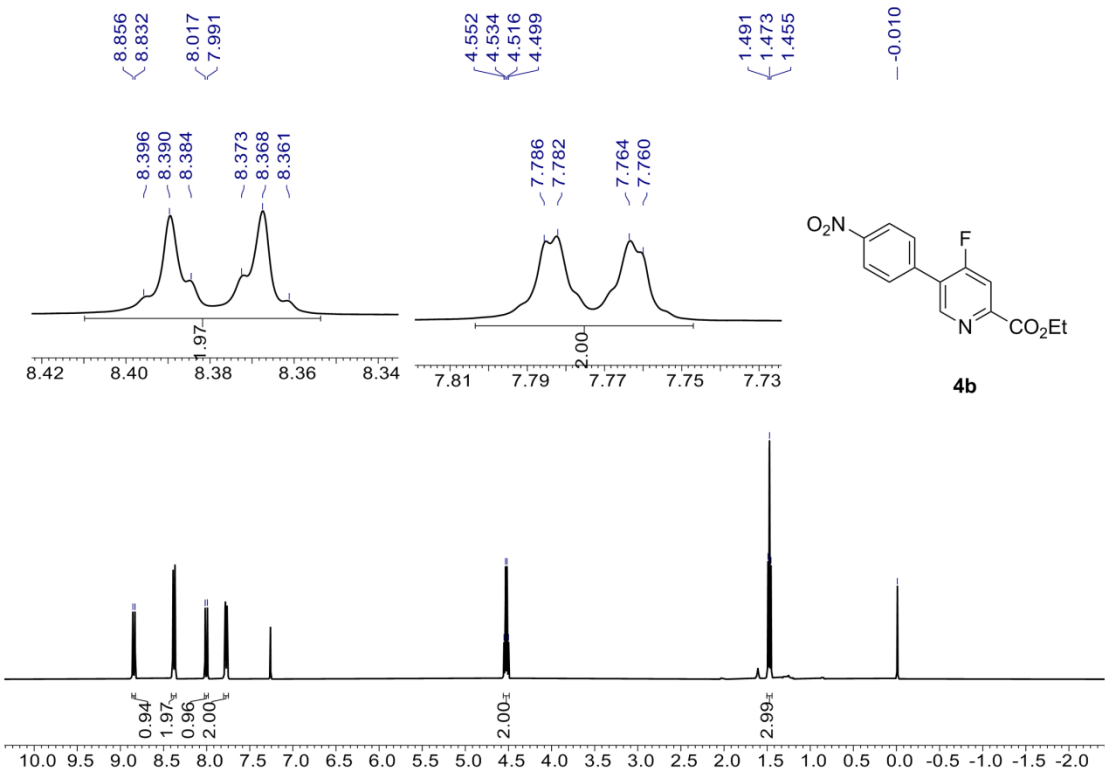
^{19}F NMR (376 MHz, $CDCl_3$) for **4a**



^{13}C NMR (100 MHz, $CDCl_3$) for **4a**

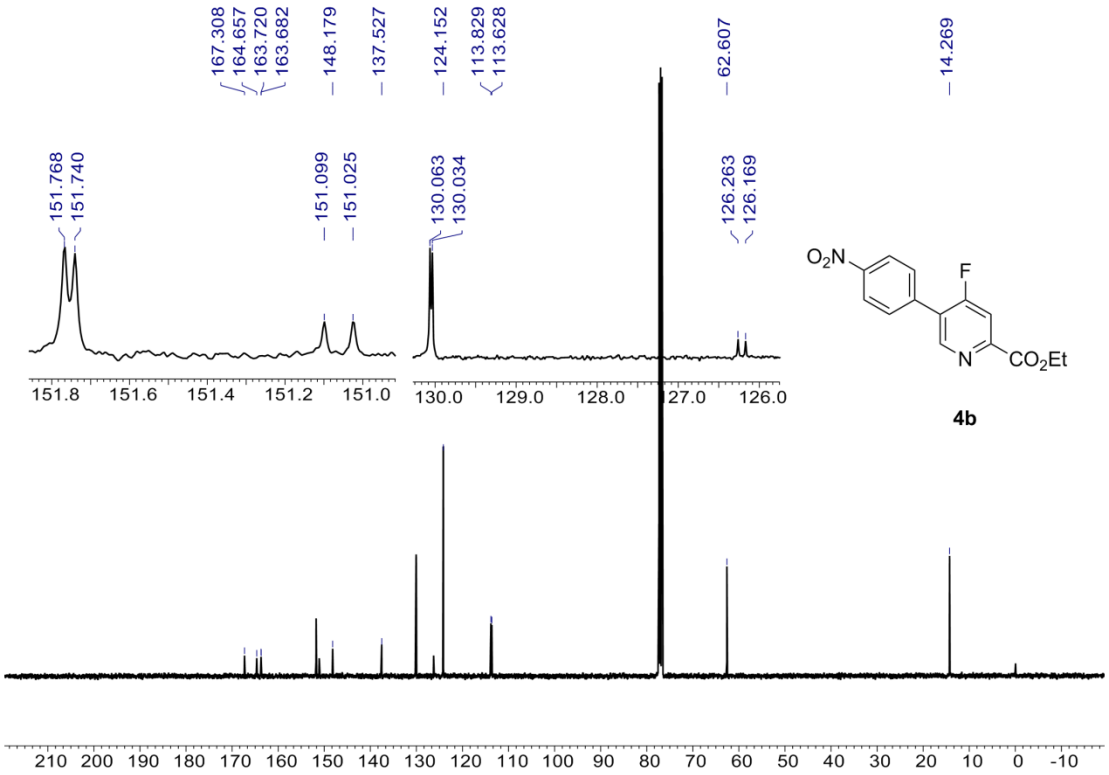


^{1}H NMR (400 MHz, $CDCl_3$) for **4b**

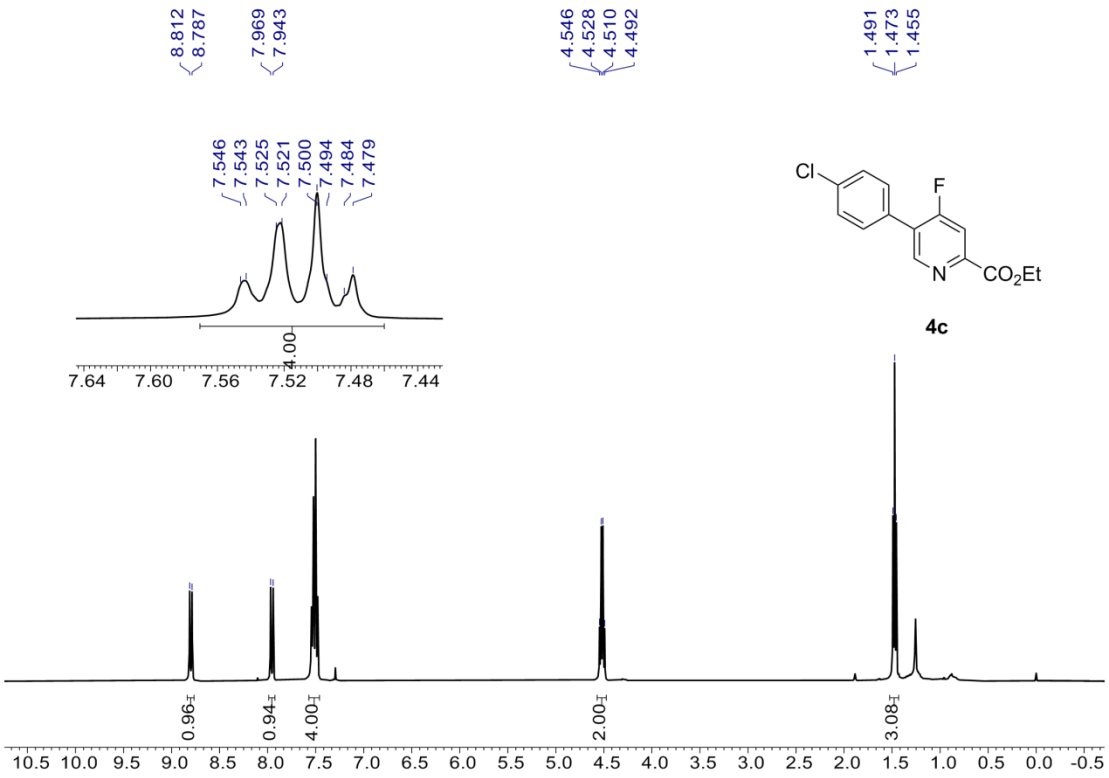


^{19}F NMR (376 MHz, $CDCl_3$) for **4b**

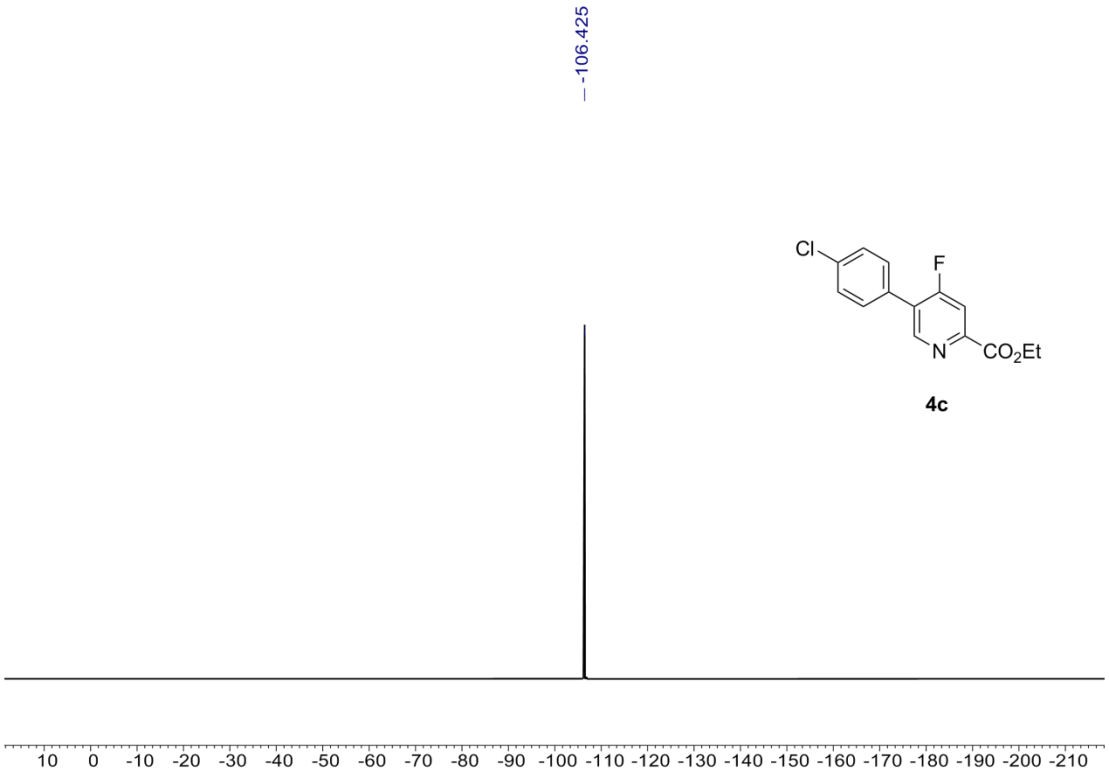
^{13}C NMR (100 MHz, $CDCl_3$) for **4b**



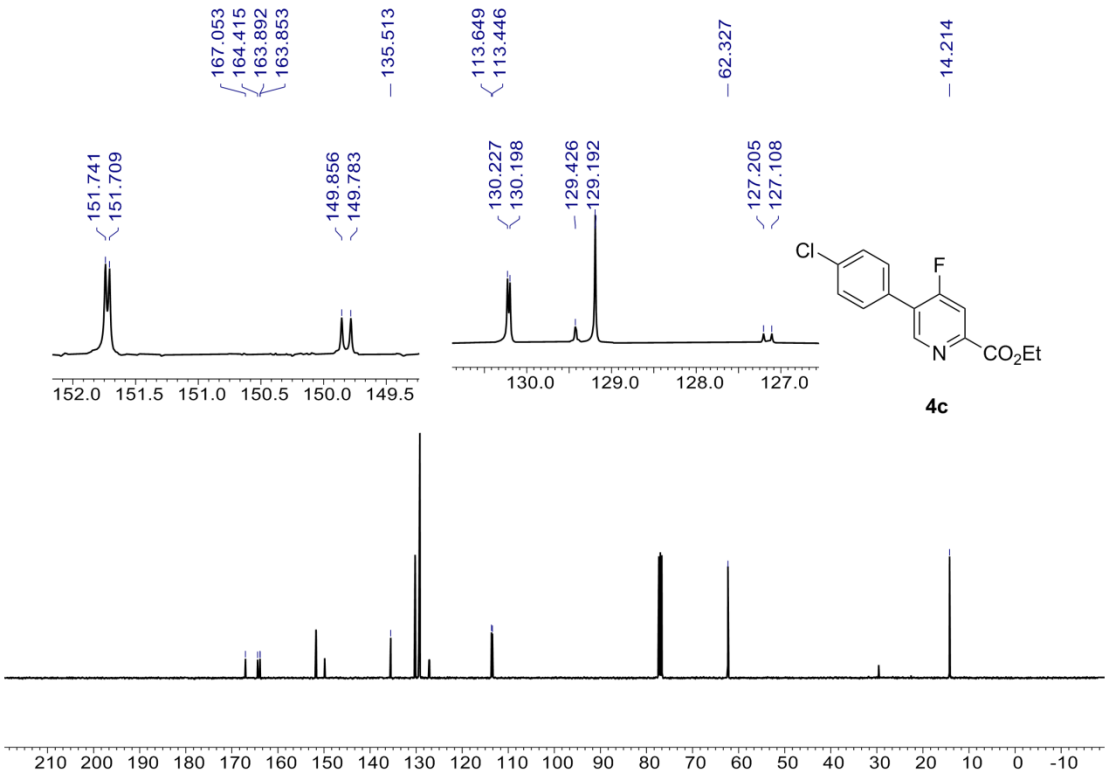
^{1}H NMR (400 MHz, $CDCl_3$) for **4c**



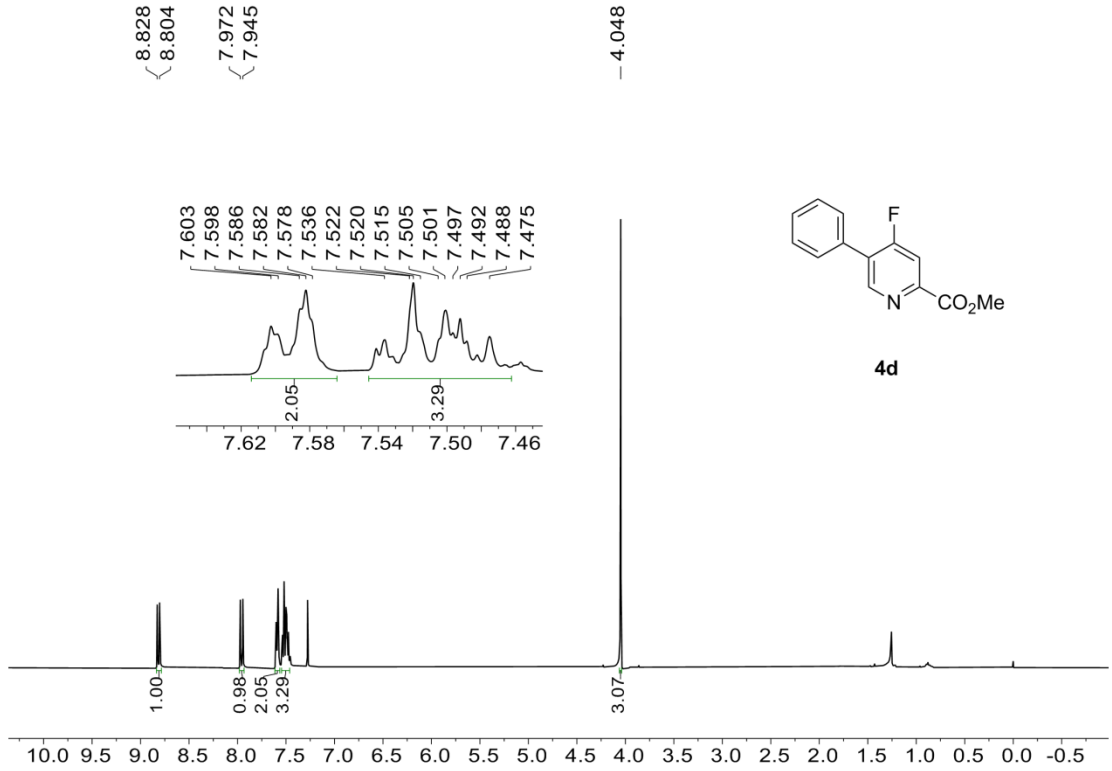
^{19}F NMR (376 MHz, $CDCl_3$) for **4c**



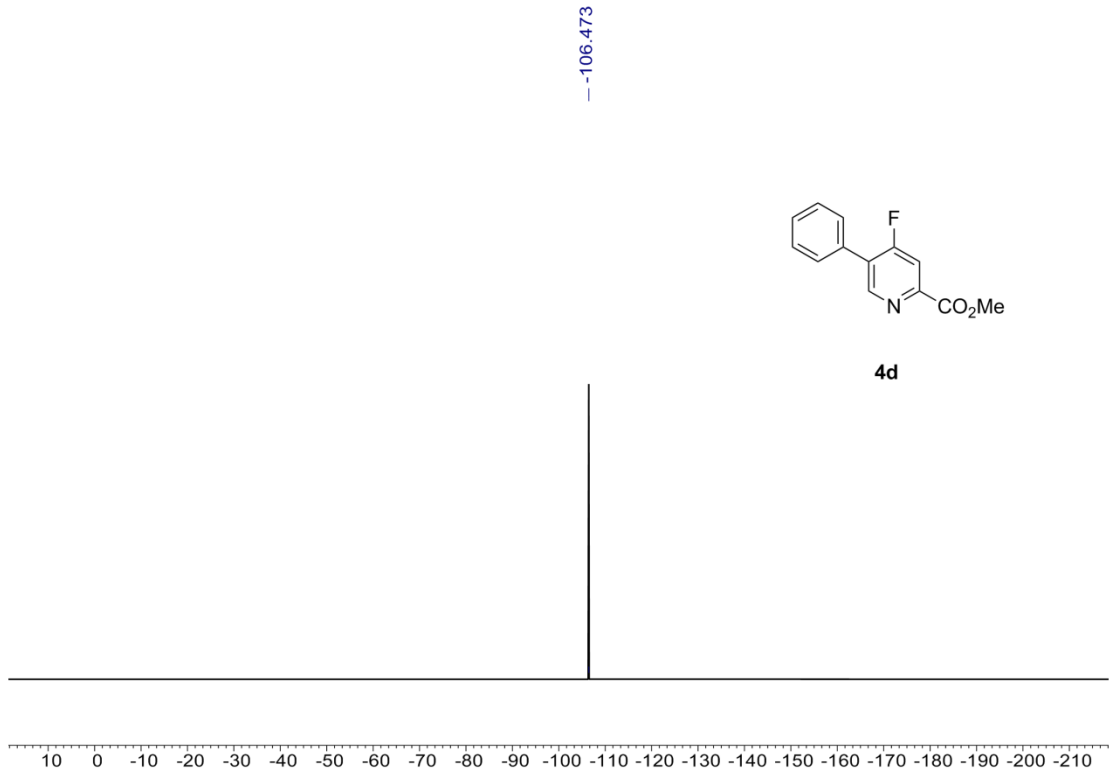
^{13}C NMR (100 MHz, $CDCl_3$) for **4c**



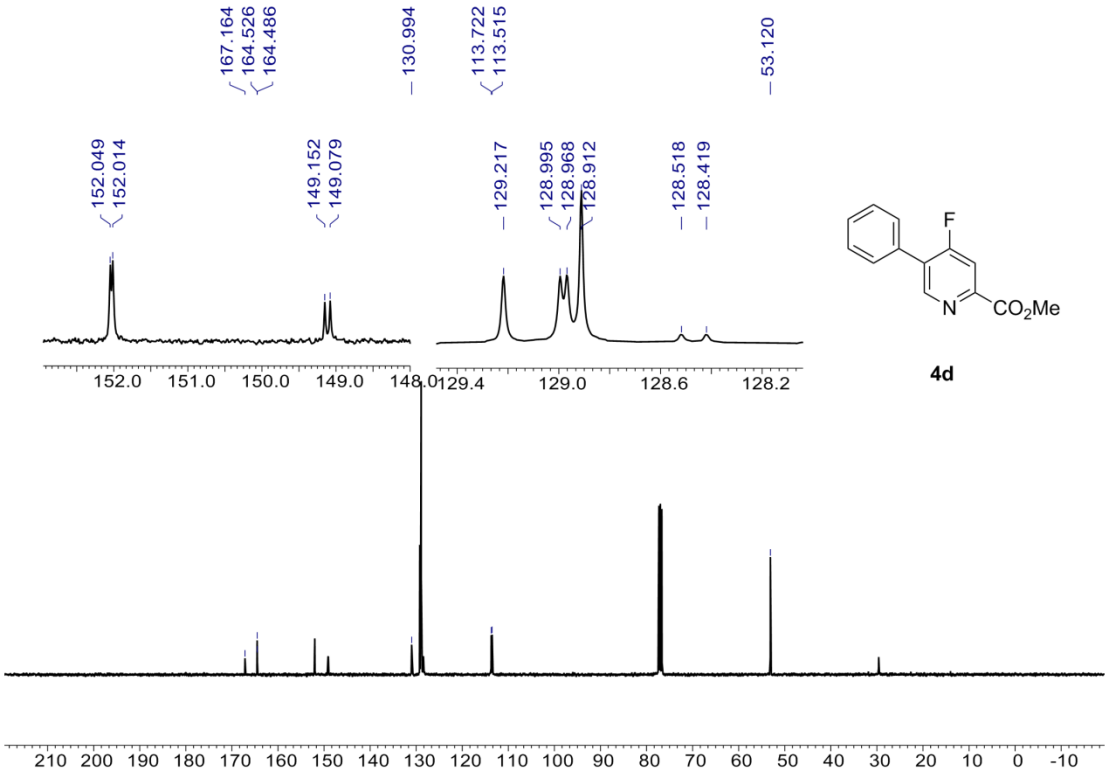
[1]H NMR (400 MHz, $CDCl_3$) for **4d**



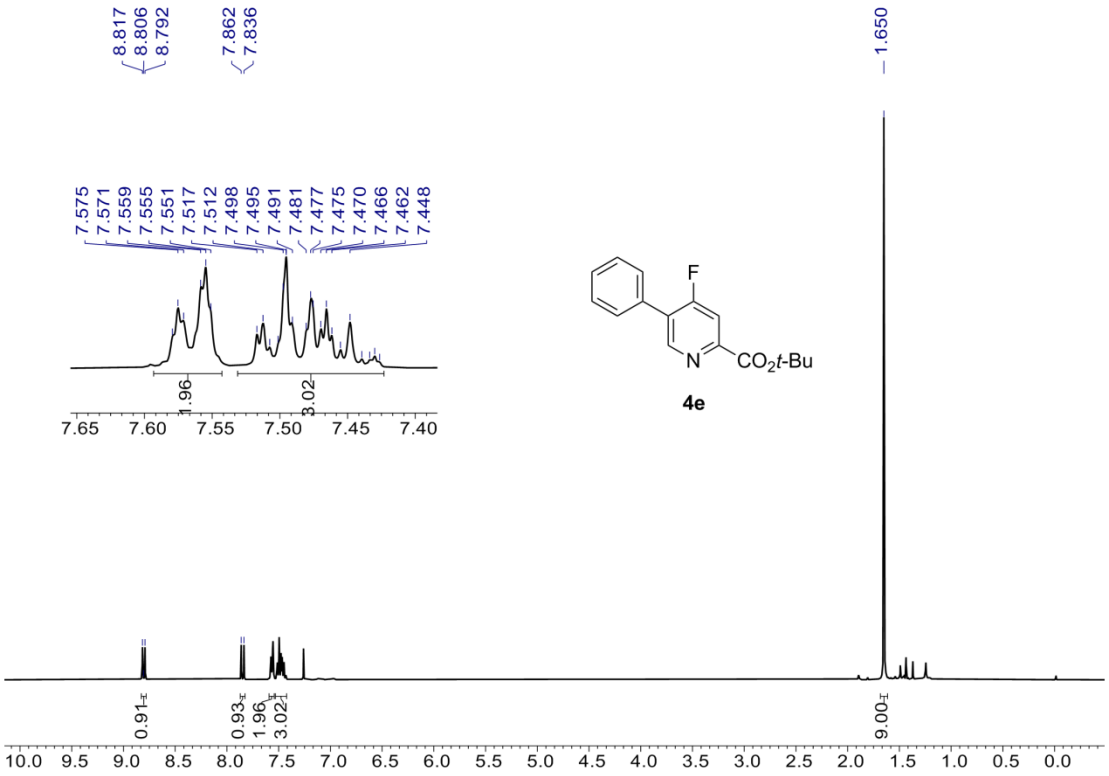
[19]F NMR (376 MHz, $CDCl_3$) for **4d**



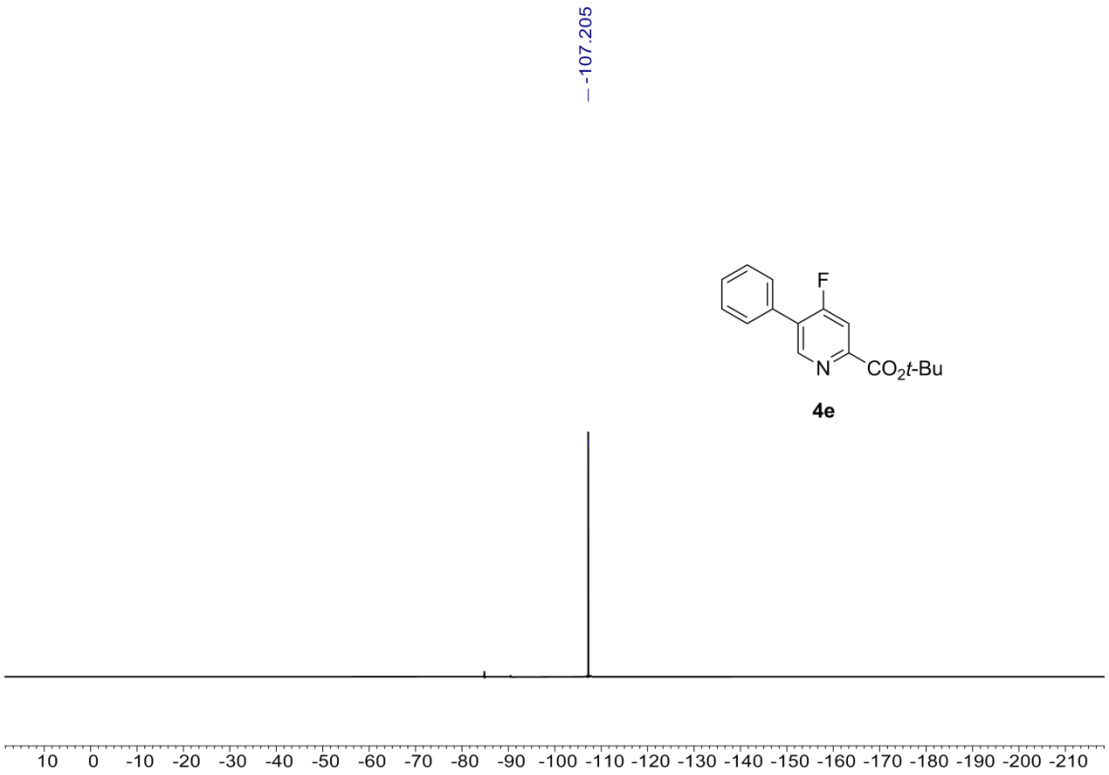
^{13}C NMR (100 MHz, $CDCl_3$) for **4d**



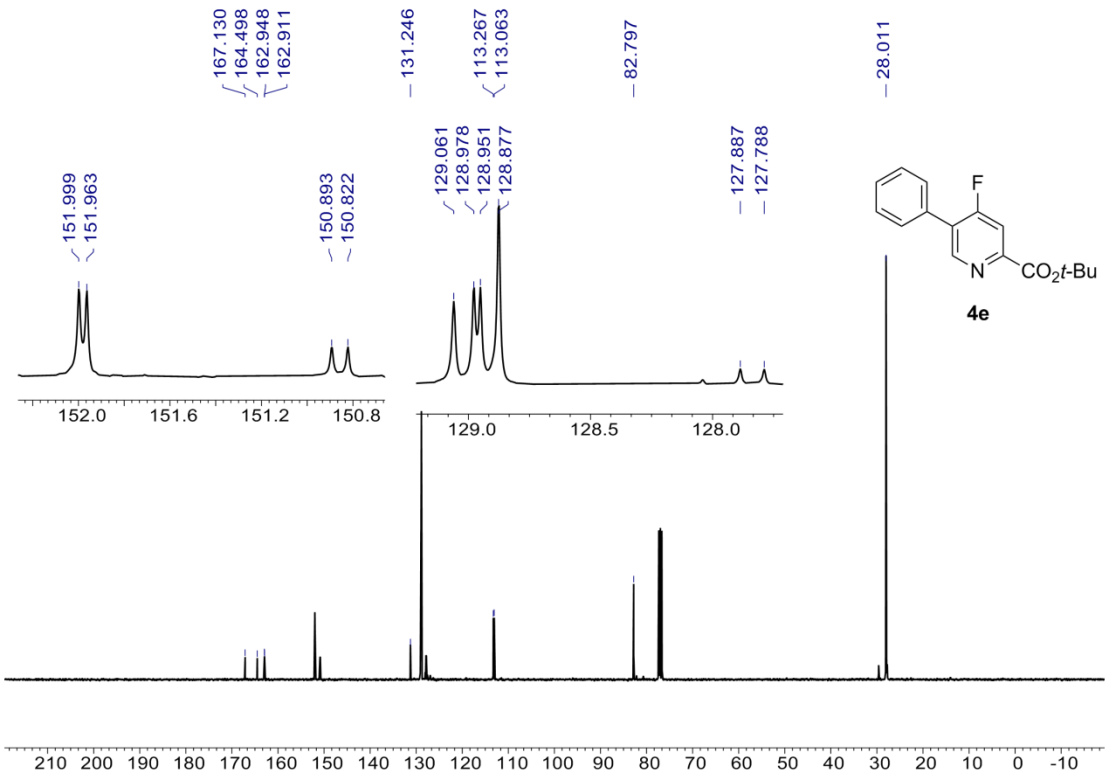
^{1}H NMR (400 MHz, $CDCl_3$) for **4e**



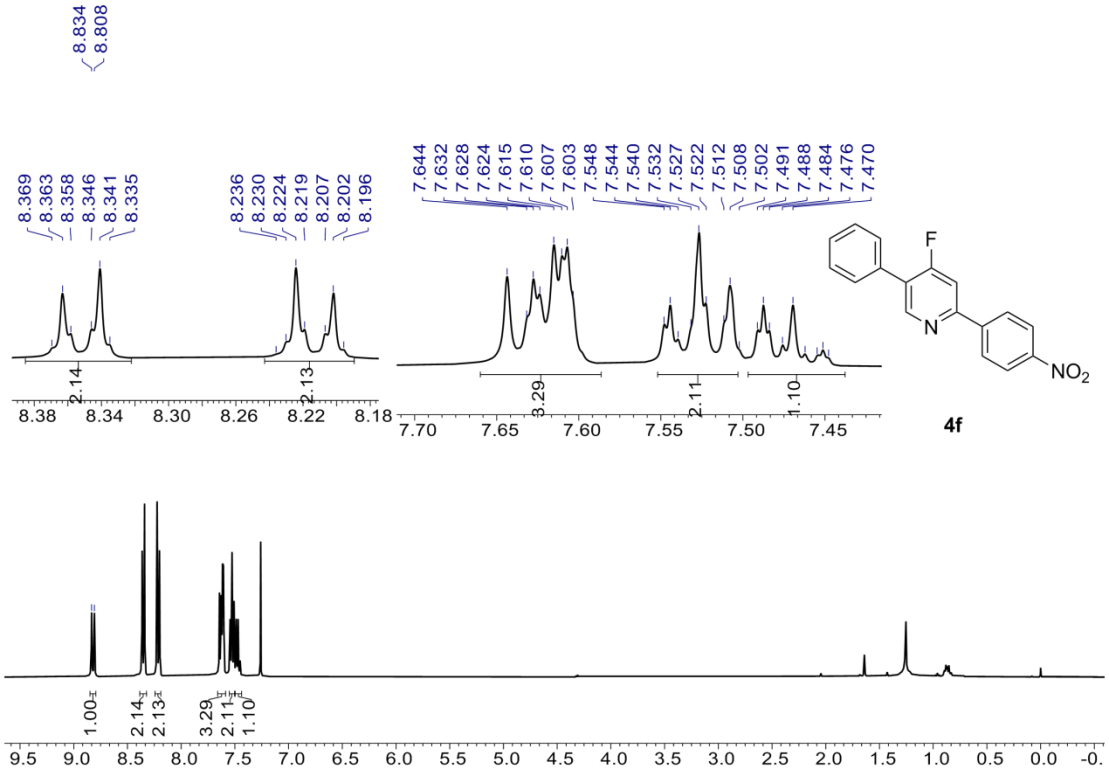
^{19}F NMR (376 MHz, $CDCl_3$) for **4e**



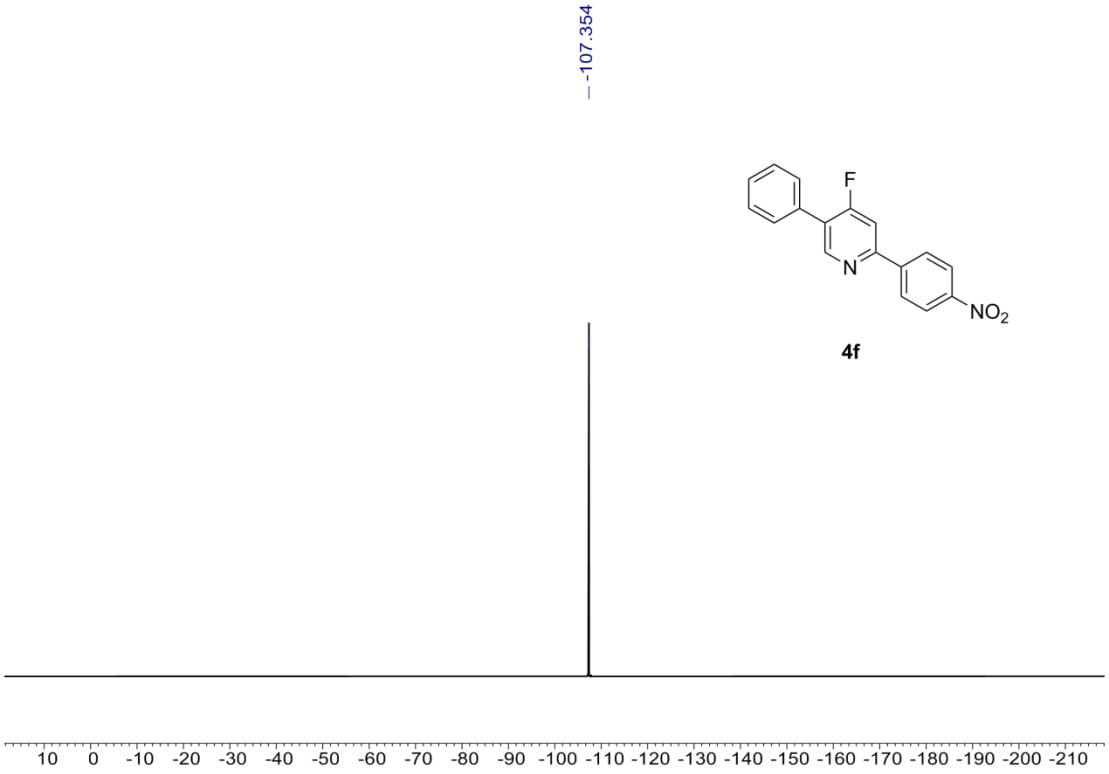
^{13}C NMR (100 MHz, $CDCl_3$) for **4e**



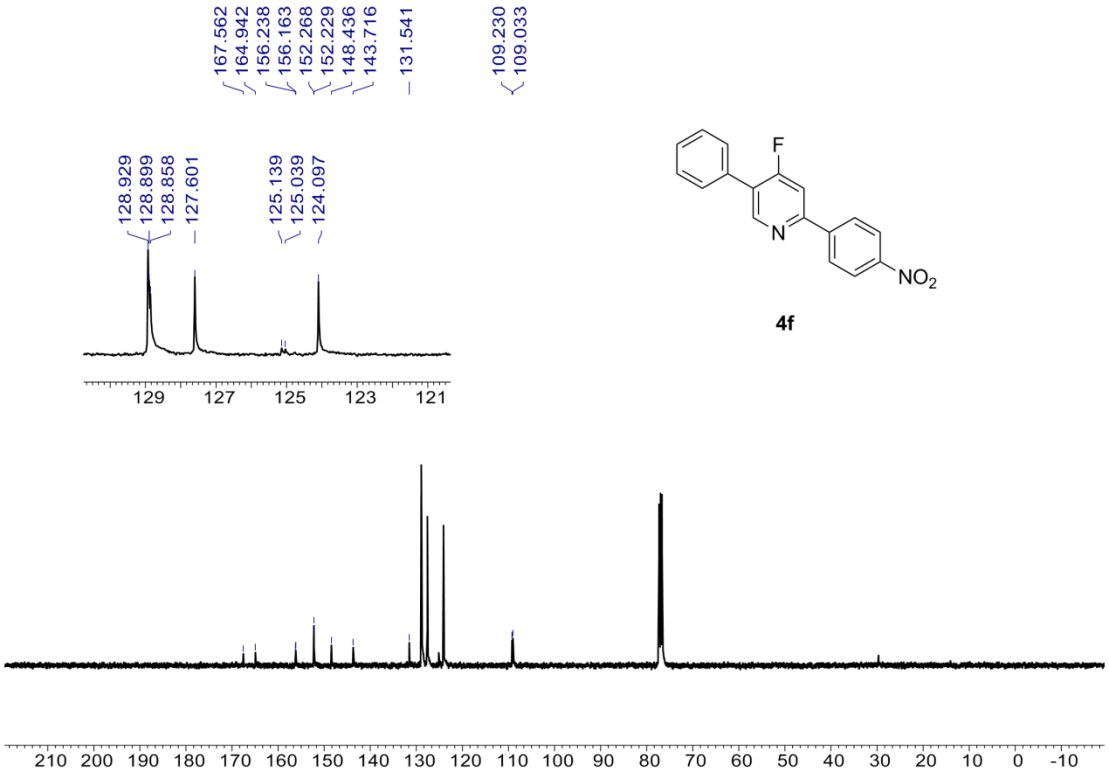
[1]H NMR (400 MHz, $CDCl_3$) for **4f**



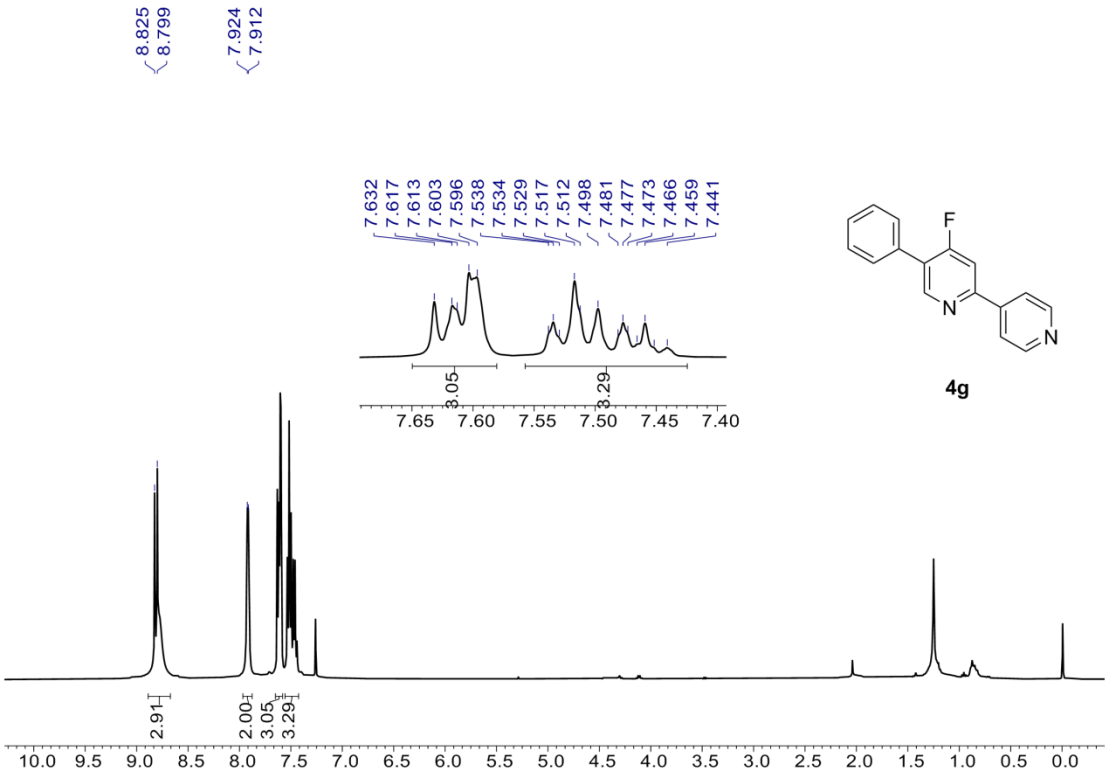
[19]F NMR (376 MHz, $CDCl_3$) for **4f**



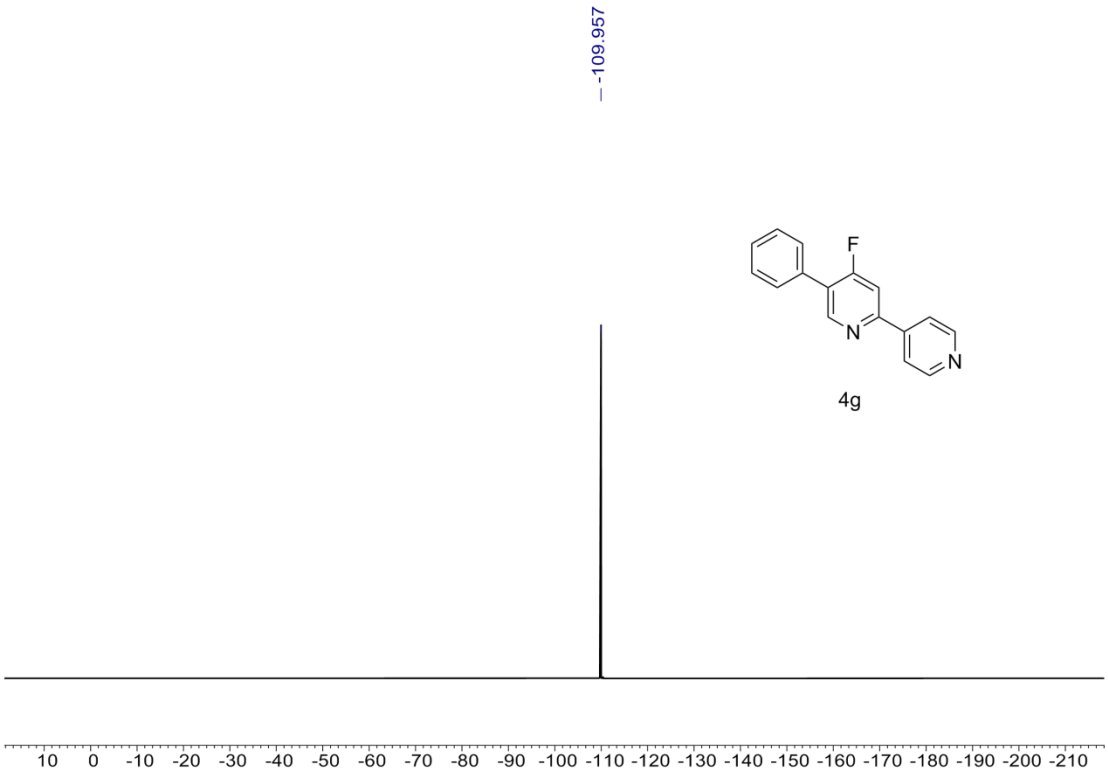
^{13}C NMR (100 MHz, $CDCl_3$) for **4f**



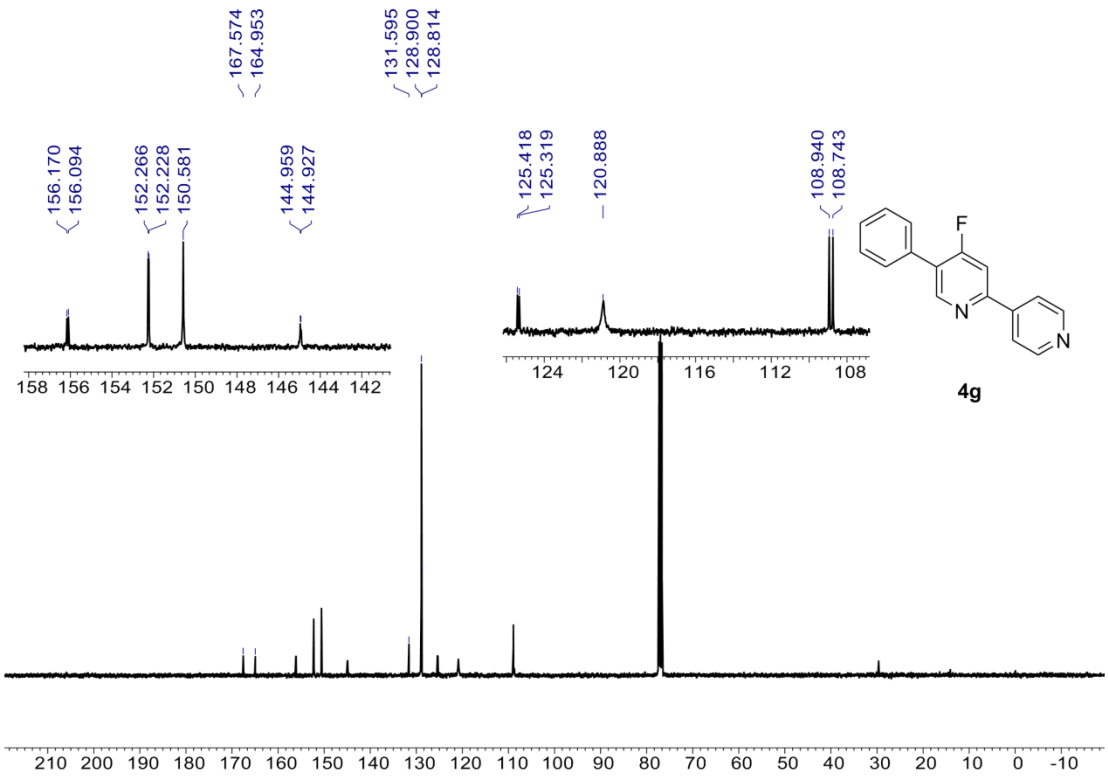
^{1}H NMR (400 MHz, $CDCl_3$) for **4g**



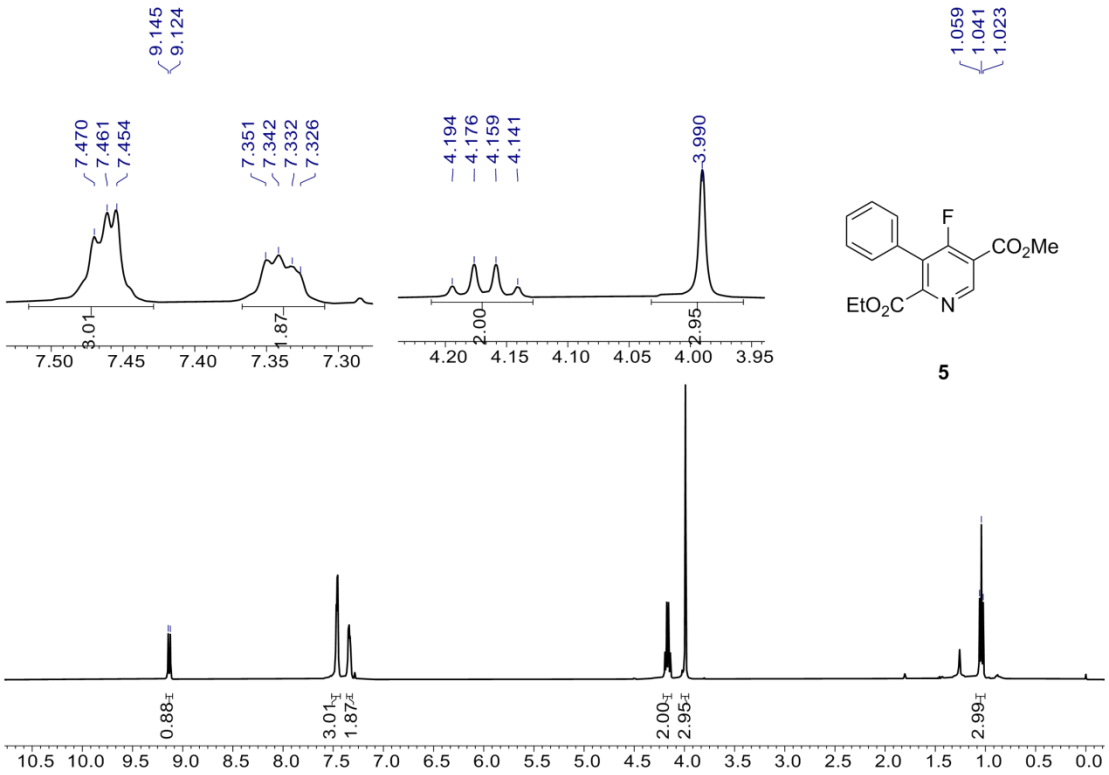
^{19}F NMR (376 MHz, $CDCl_3$) for **4g**



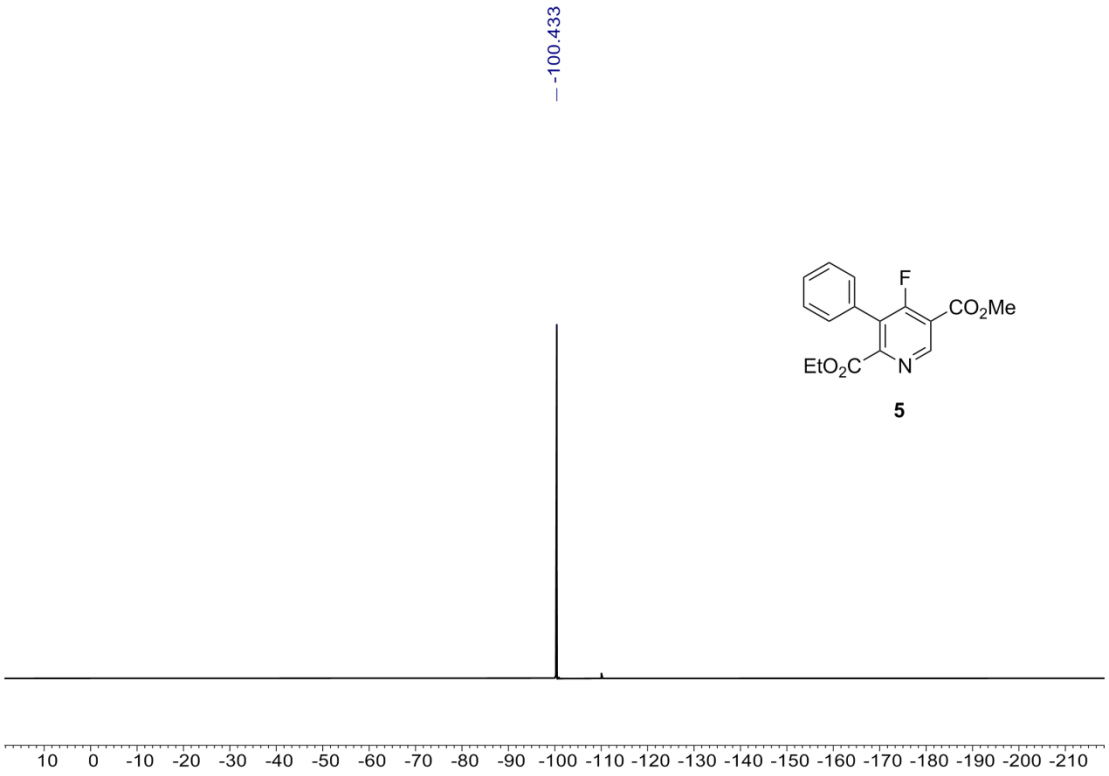
^{13}C NMR (100 MHz, $CDCl_3$) for **4g**



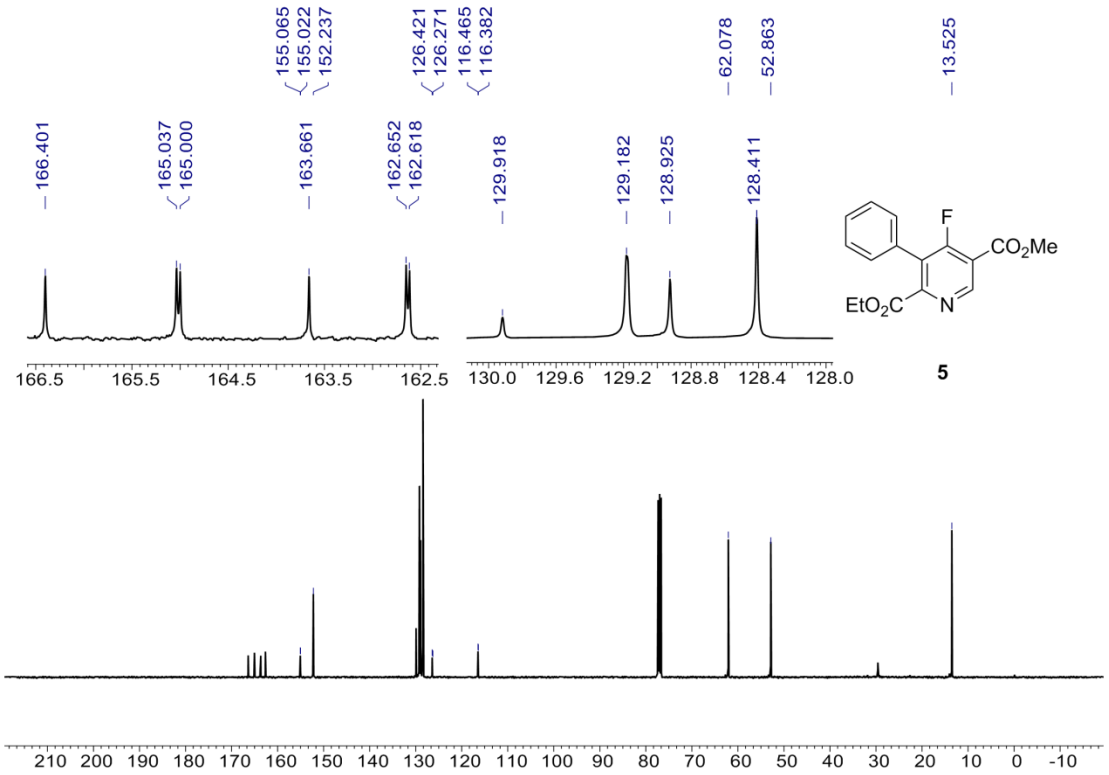
^{1}H NMR (400 MHz, $CDCl_3$) for **5**



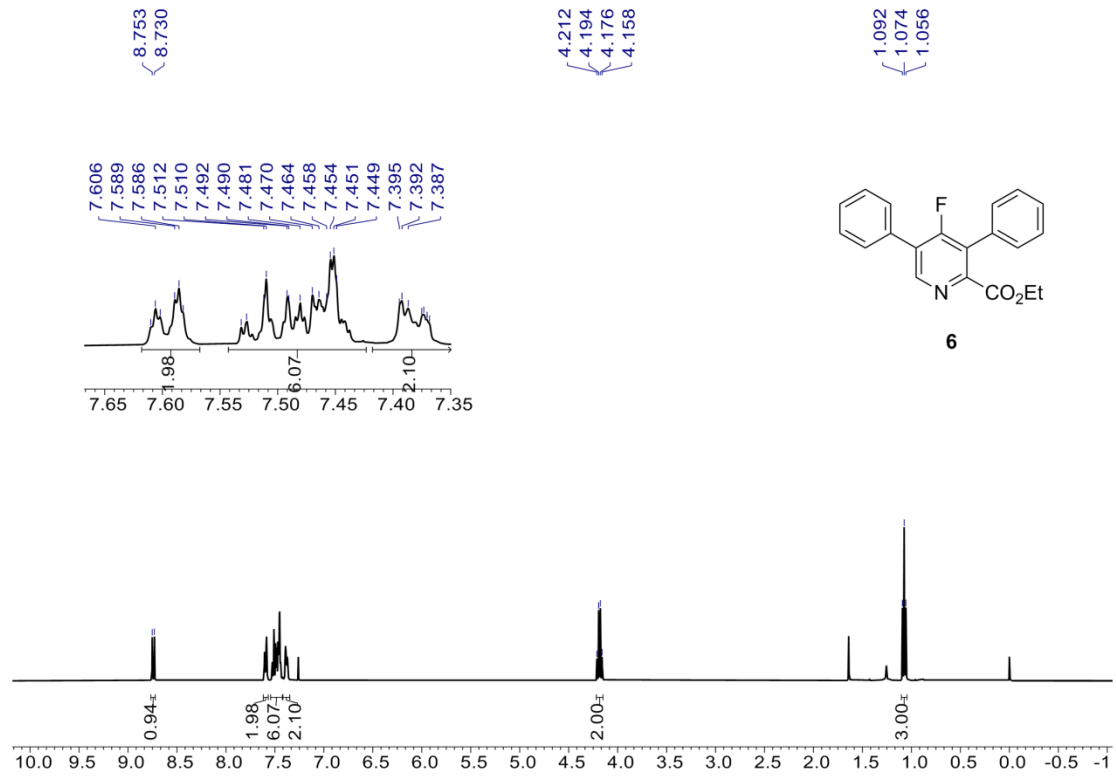
^{19}F NMR (376 MHz, $CDCl_3$) for **5**



^{13}C NMR (100 MHz, $CDCl_3$) for **5**

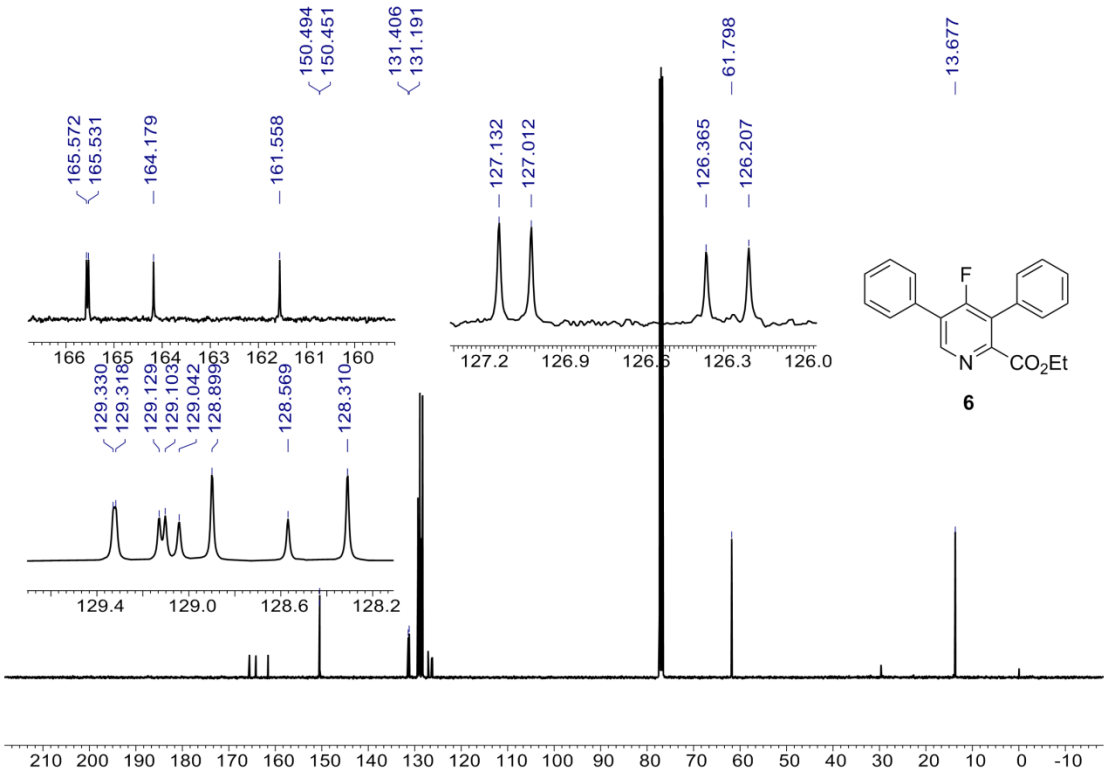


^{1}H NMR (400 MHz, $CDCl_3$) for **6**

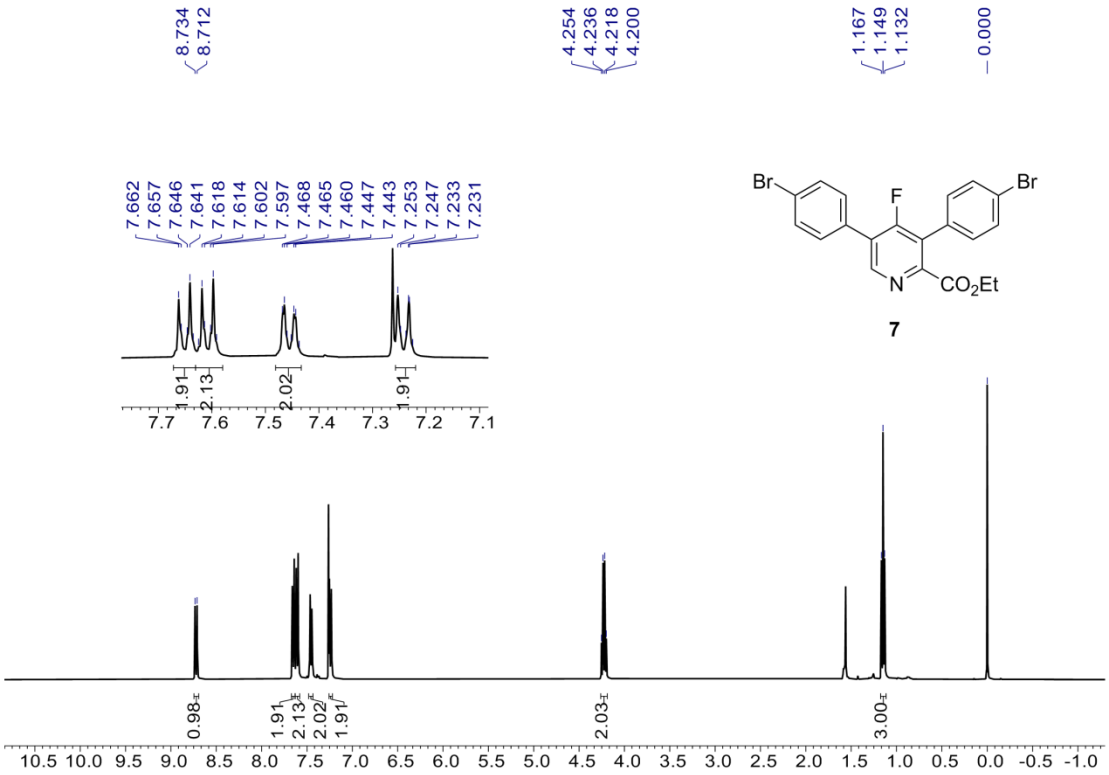


^{19}F NMR (376 MHz, $CDCl_3$) for **6**

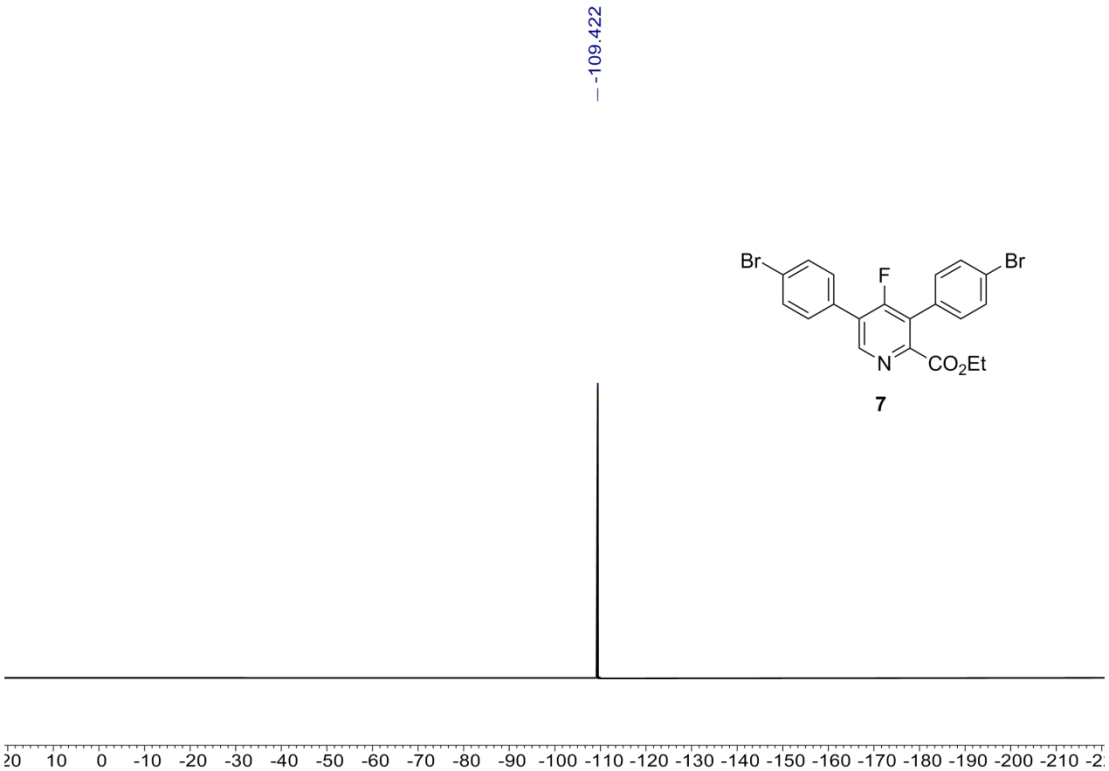
^{13}C NMR (100 MHz, $CDCl_3$) for **6**



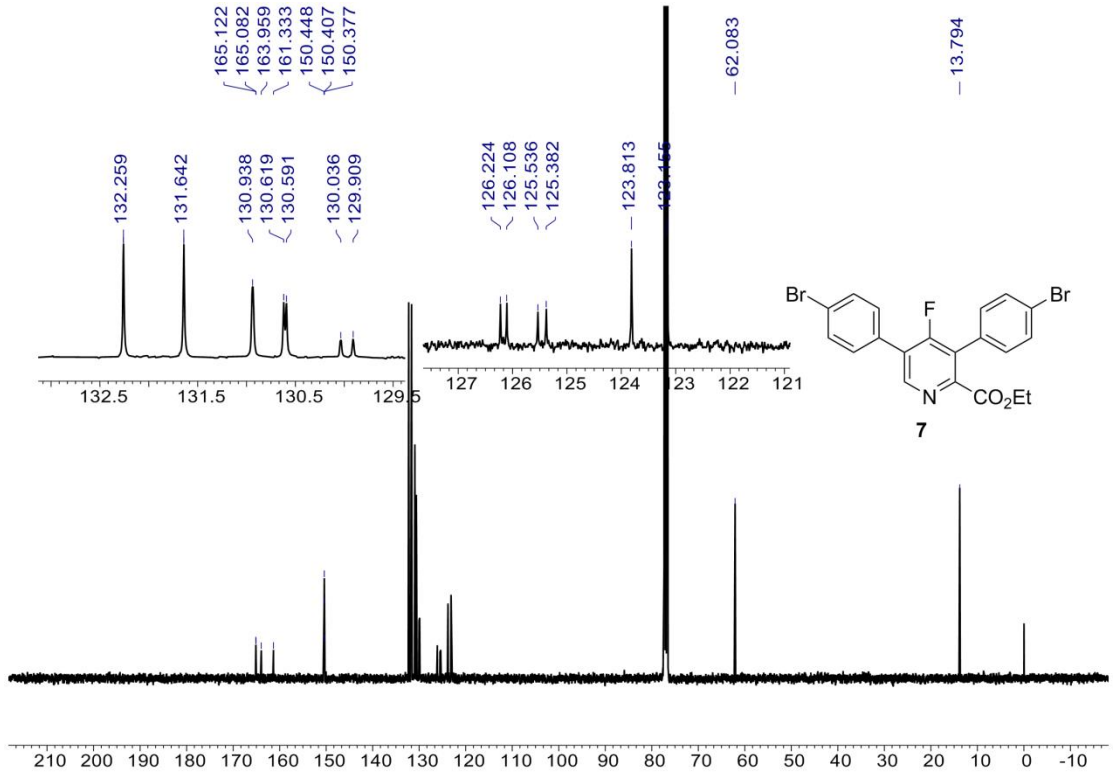
[1]H NMR (400 MHz, $CDCl_3$) for **7**



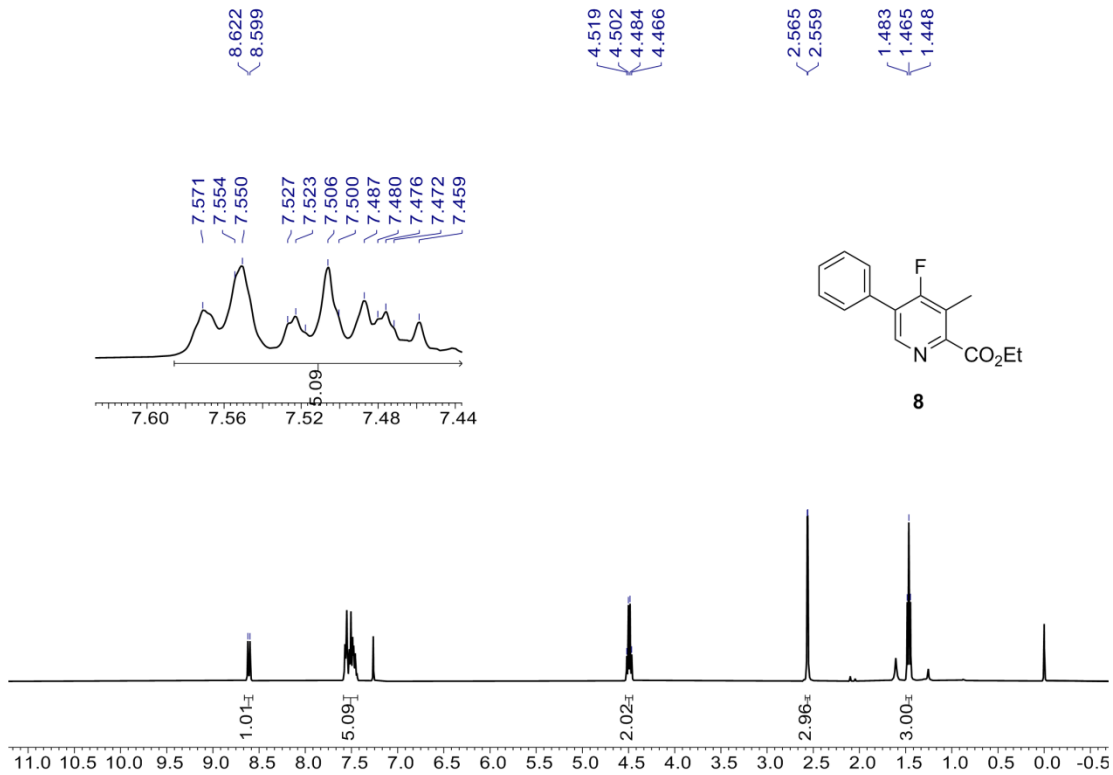
[19]F NMR (376 MHz, $CDCl_3$) for **7**



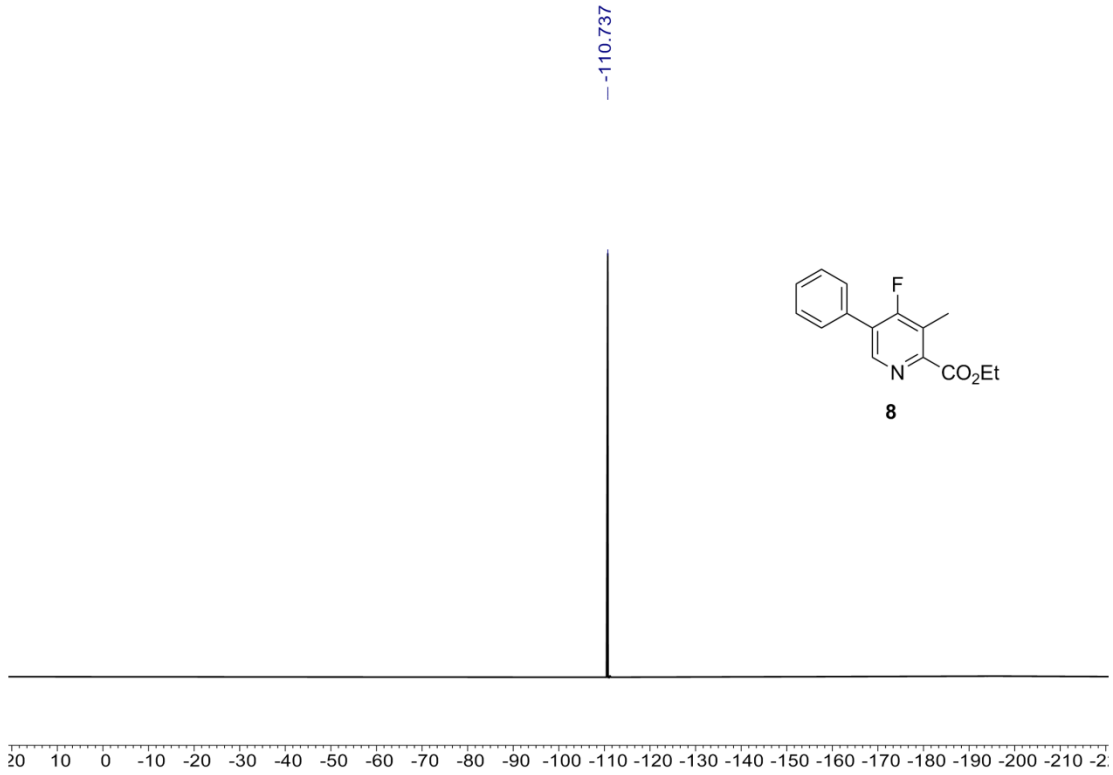
^{13}C NMR (100 MHz, $CDCl_3$) for **7**



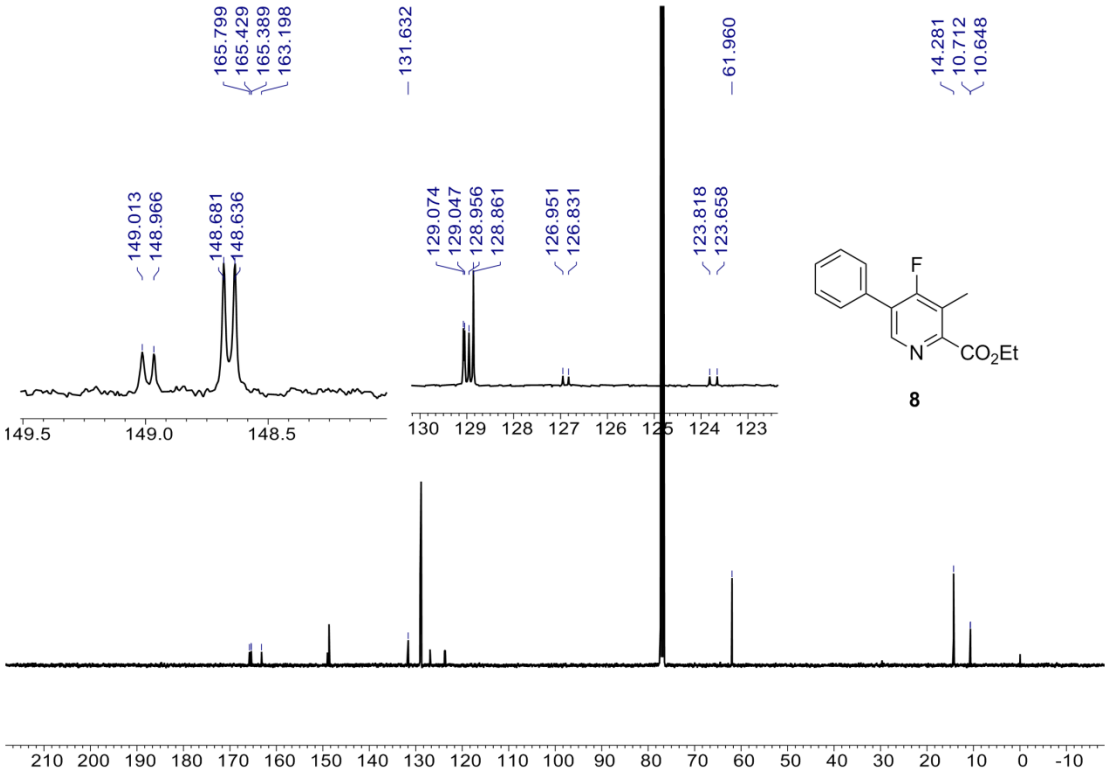
^{1}H NMR (400 MHz, $CDCl_3$) for **8**



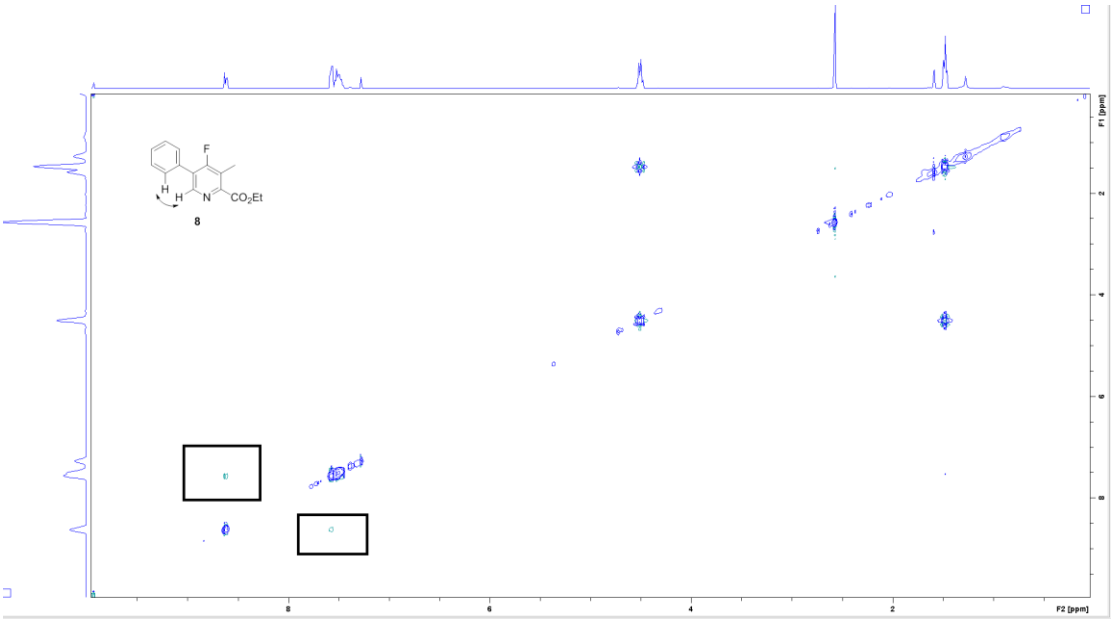
^{19}F NMR (376 MHz, $CDCl_3$) for **8**



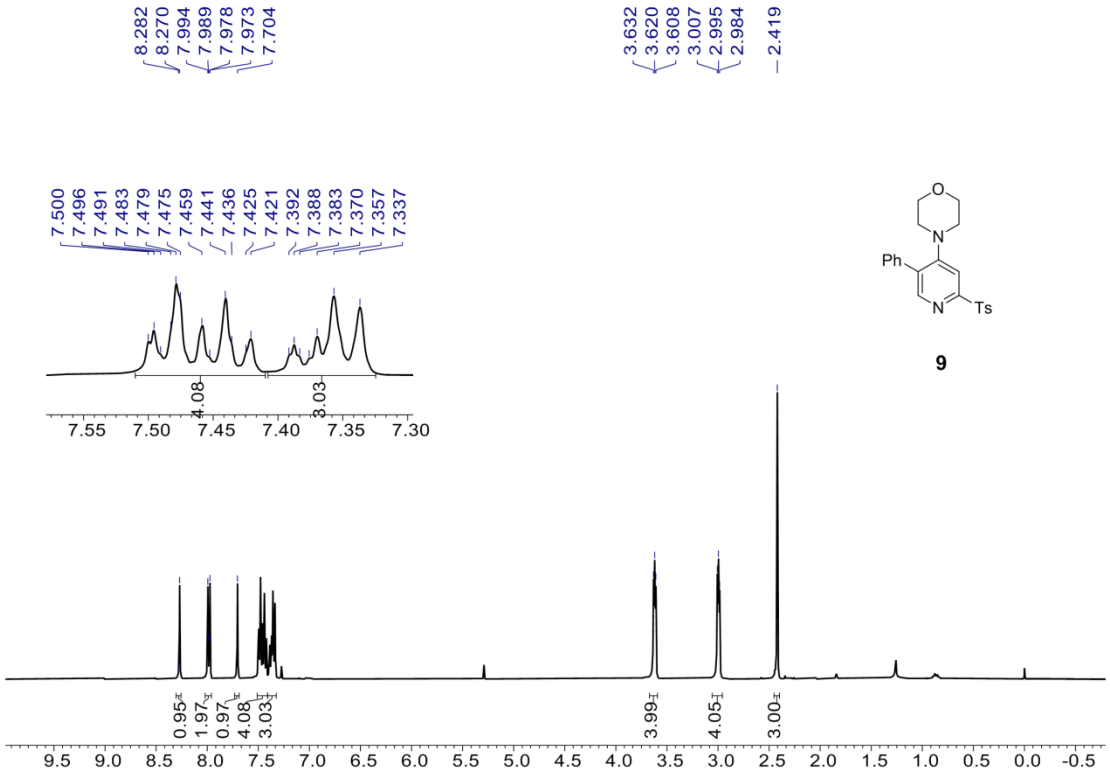
^{13}C NMR (100 MHz, $CDCl_3$) for **8**



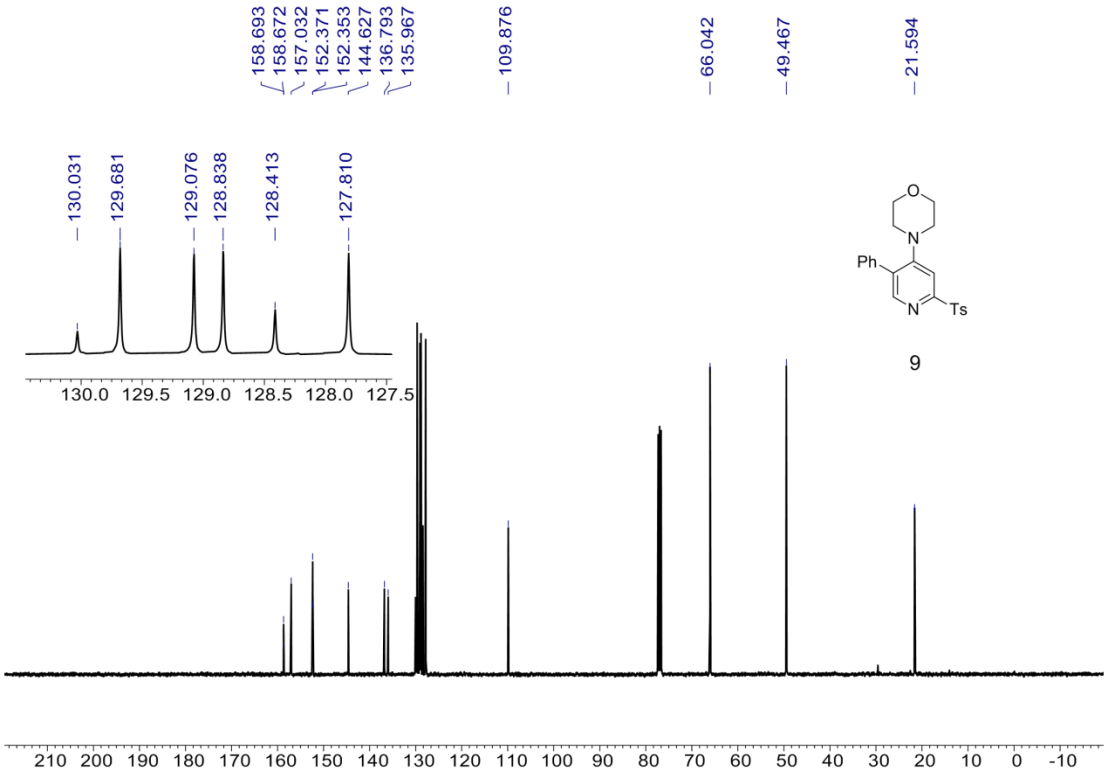
The NOESY spectrum of **8**



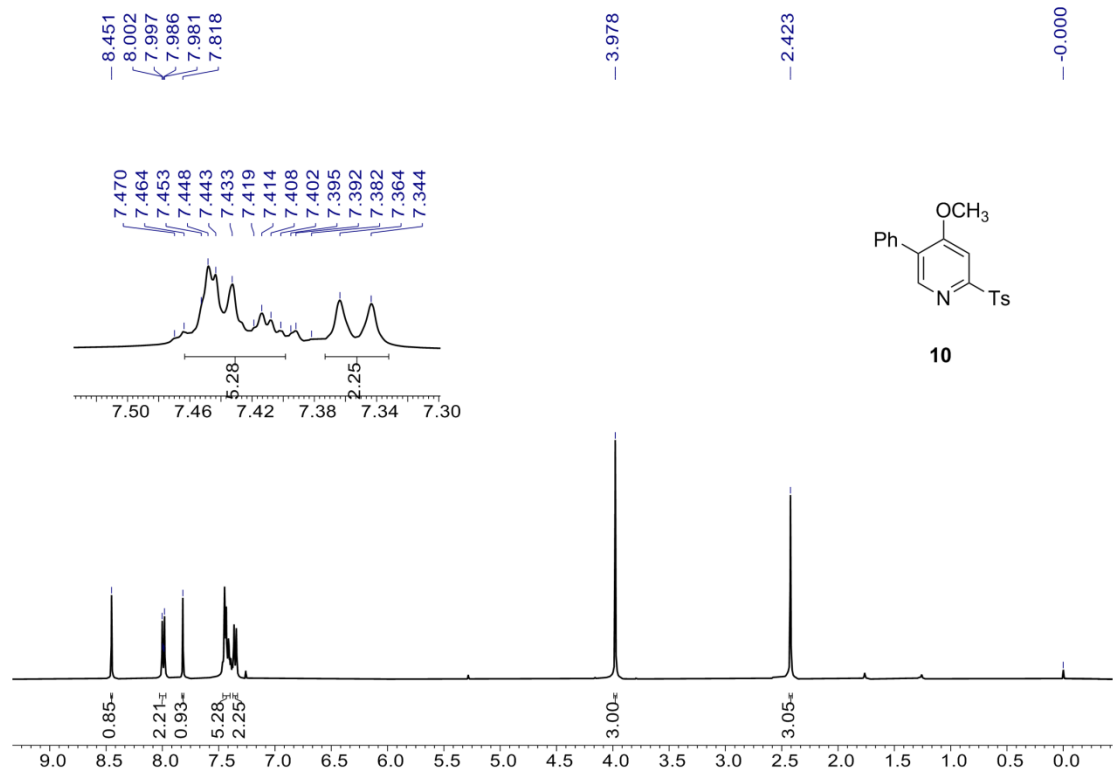
^{1}H NMR (400 MHz, $CDCl_3$) for **9**



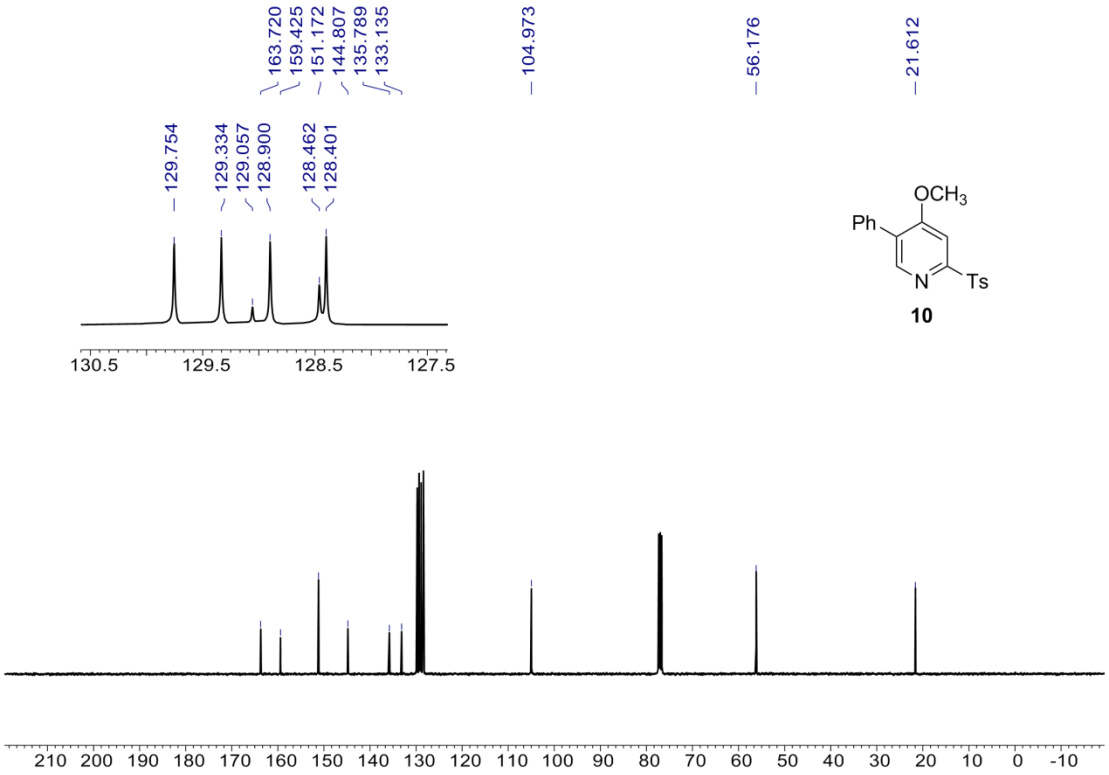
^{13}C NMR (100 MHz, $CDCl_3$) for **9**



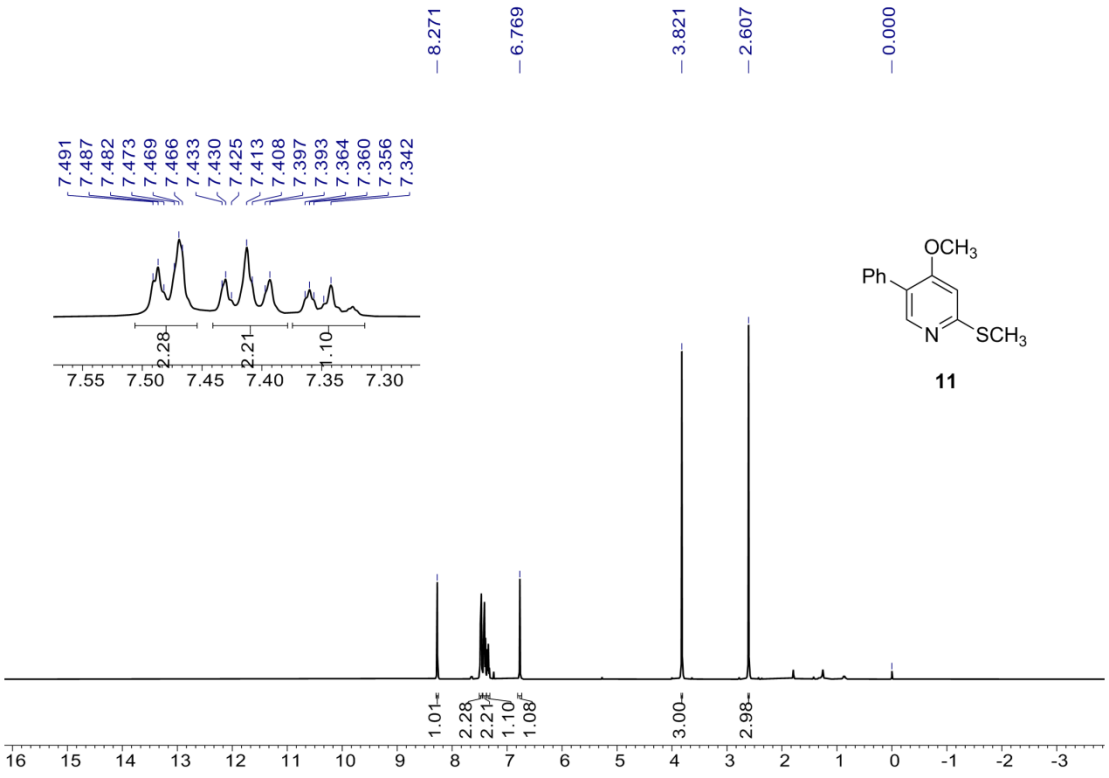
^{1}H NMR (400 MHz, $CDCl_3$) for **10**



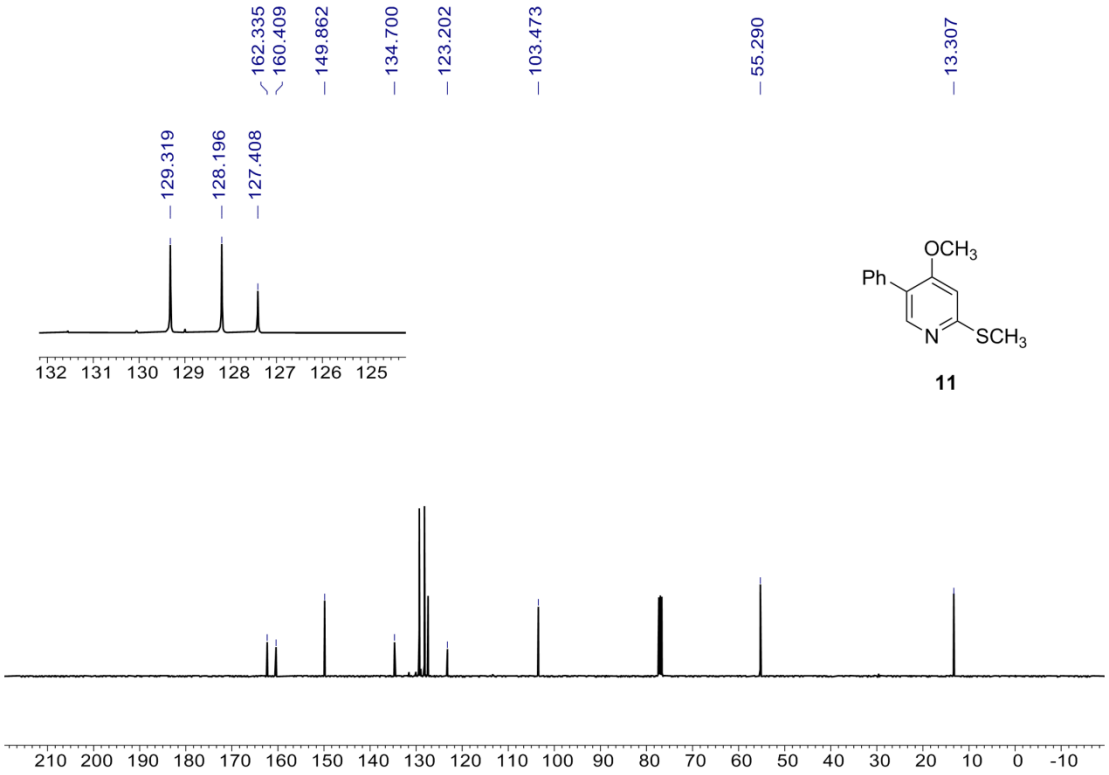
^{13}C NMR (100 MHz, $CDCl_3$) for **10**



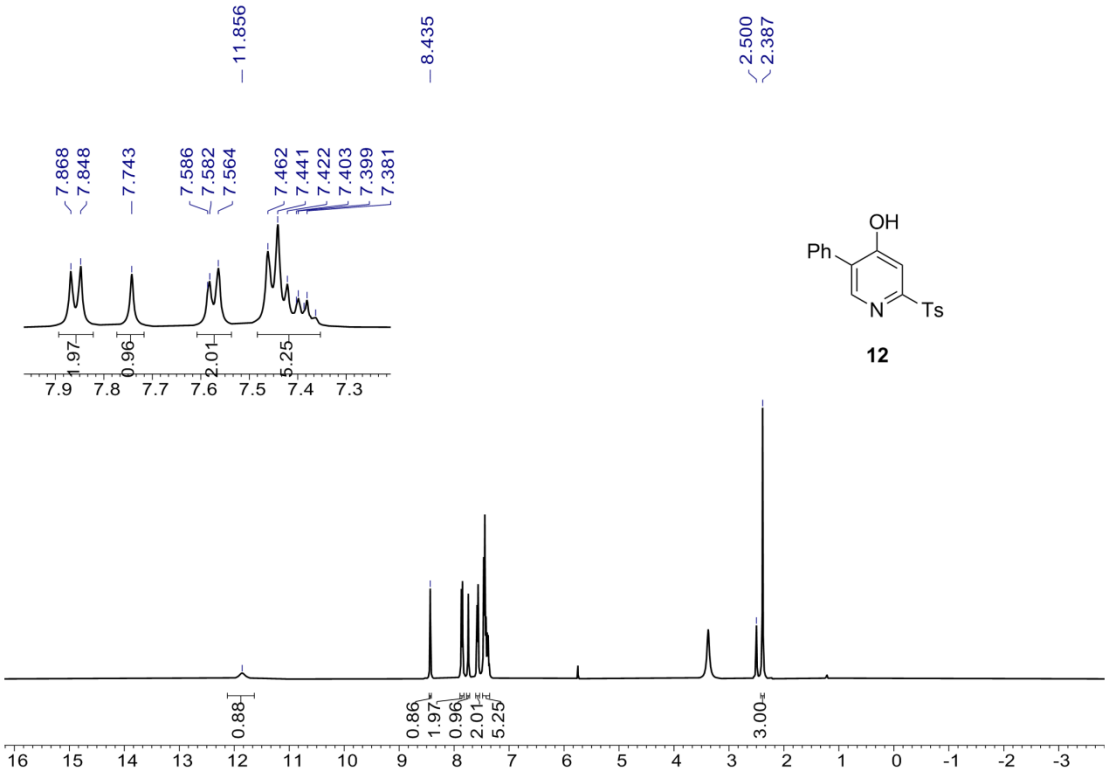
^{1}H NMR (400 MHz, $CDCl_3$) for **11**



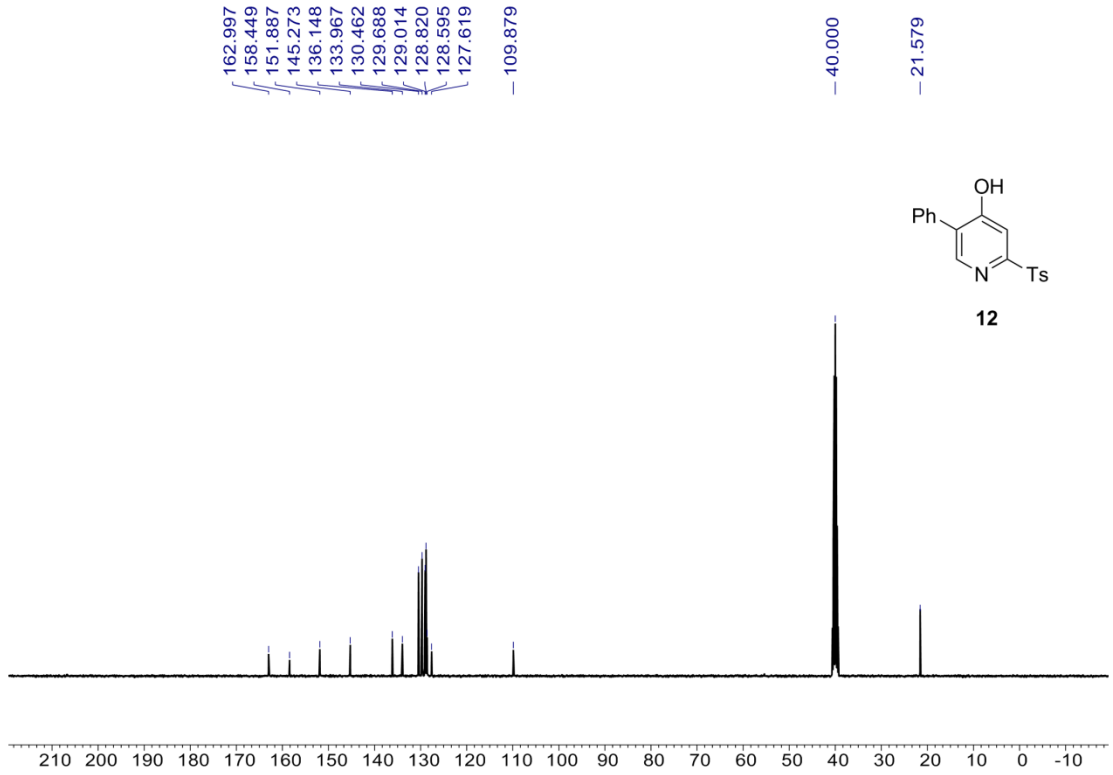
^{13}C NMR (100 MHz, $CDCl_3$) for **11**



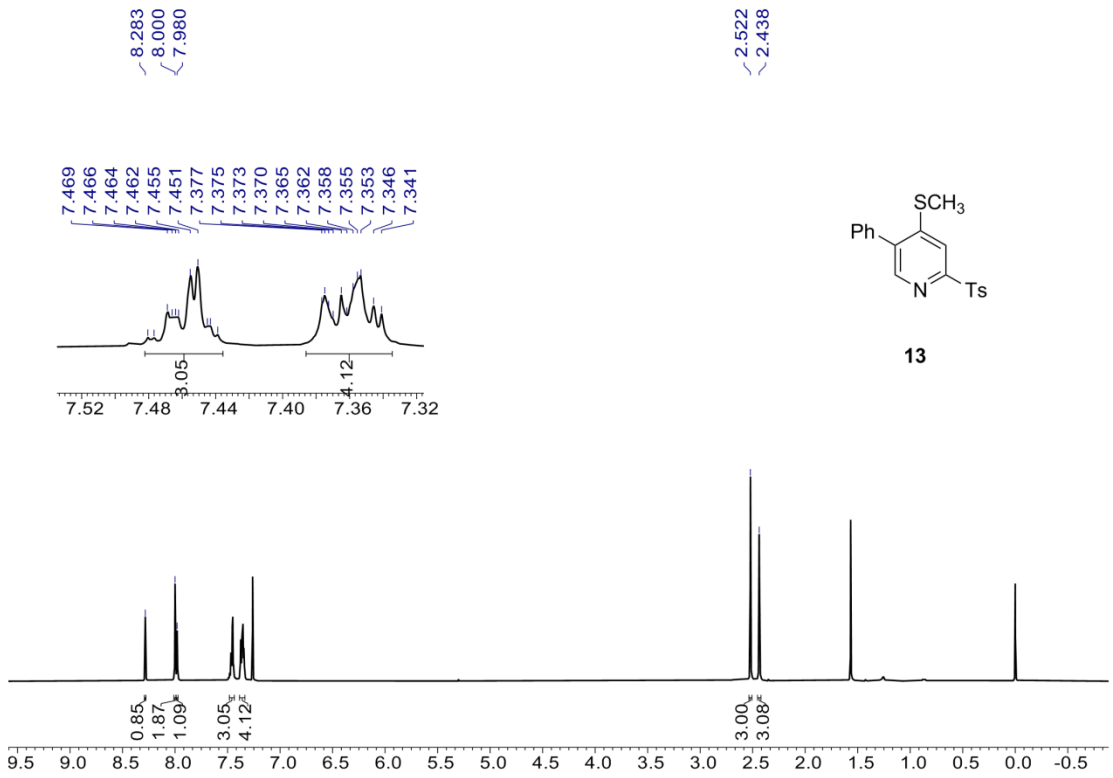
^{1}H NMR (400 MHz, DMSO-*d_6*) for **12**



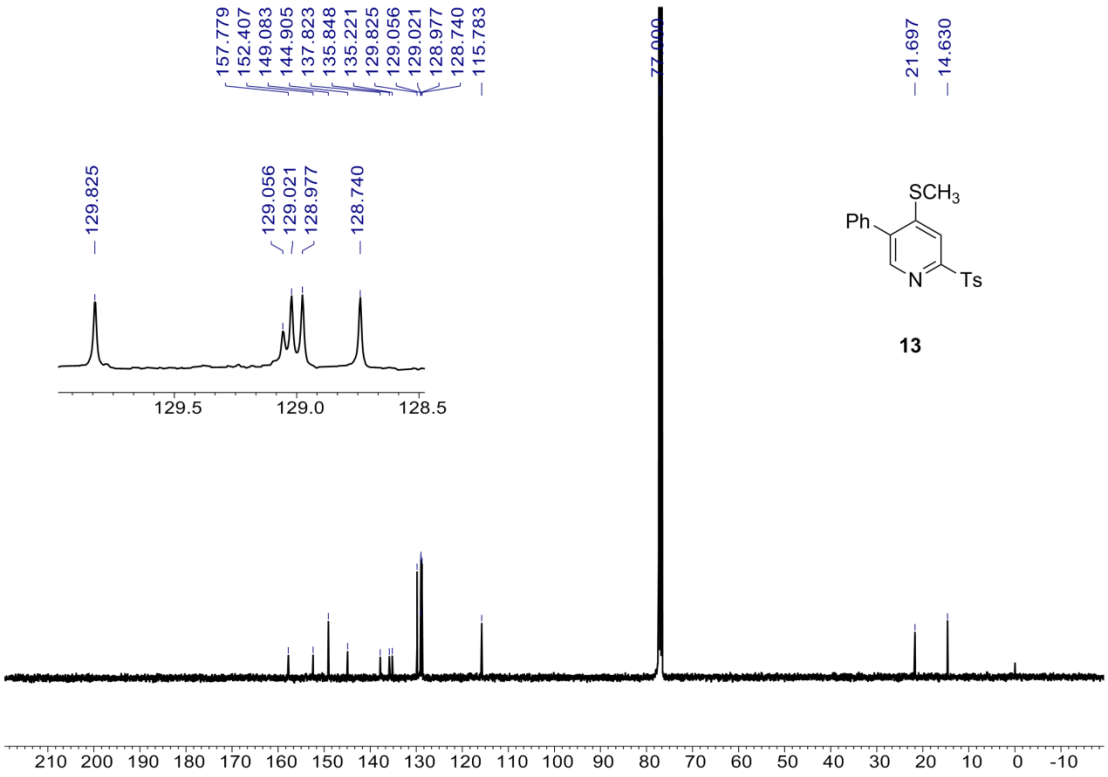
^{13}C NMR (100 MHz DMSO-d_6,) for 12



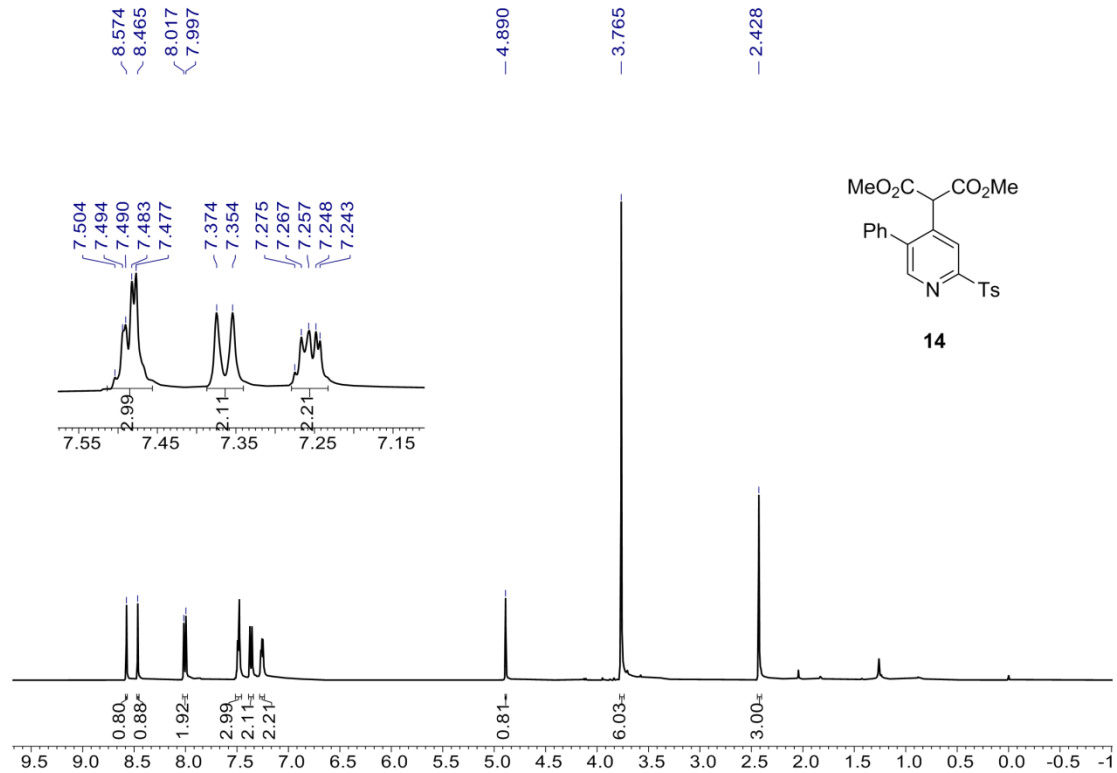
^{1}H NMR (100 MHz, $CDCl_3$**) for 13**



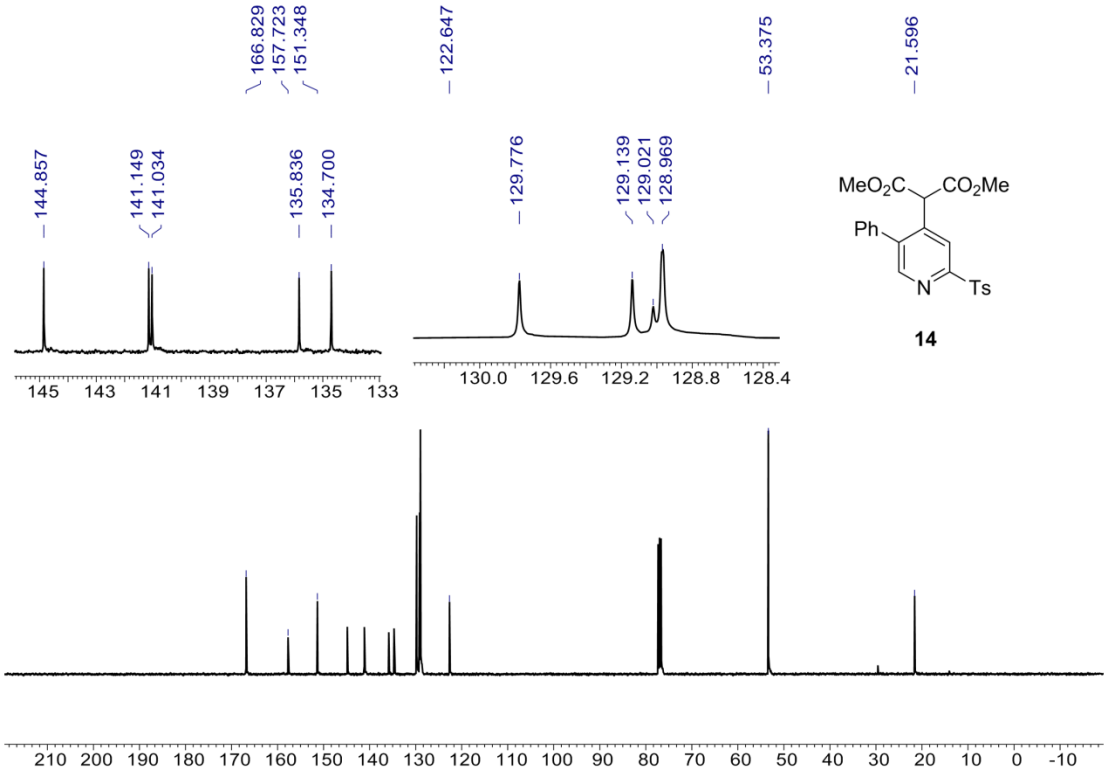
^{13}C NMR (100 MHz, $CDCl_3$**) for 13**



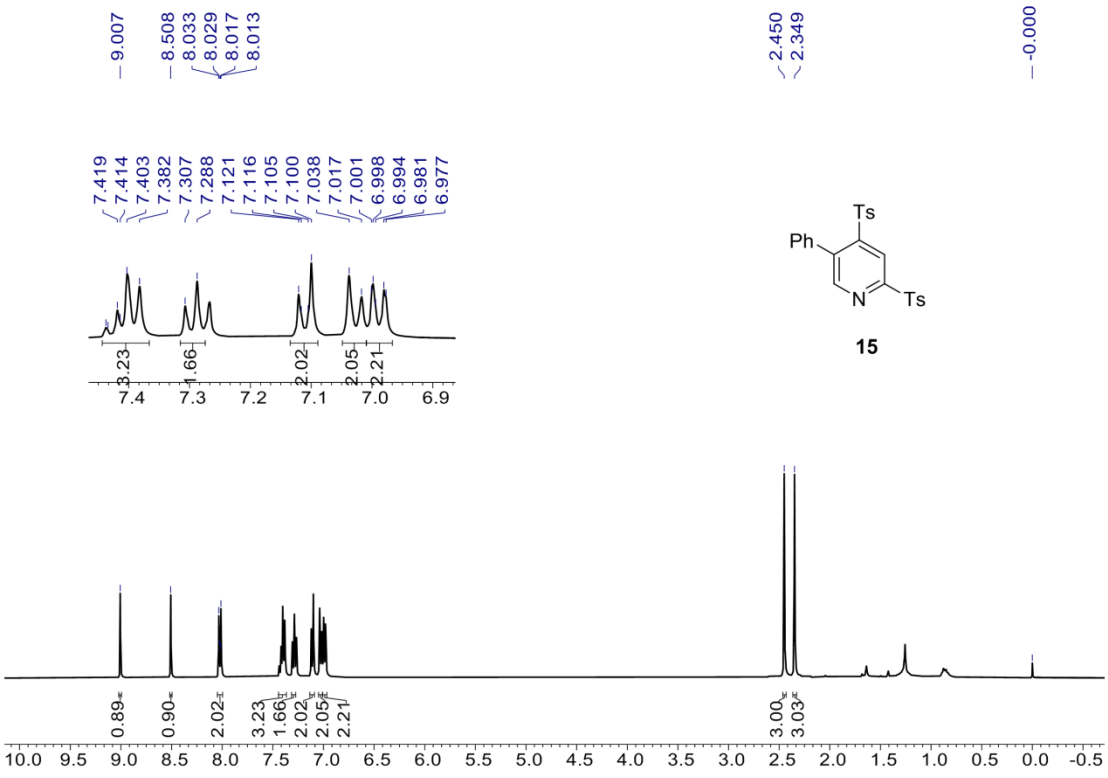
^{1}H NMR (100 MHz, $CDCl_3$**) for 14**



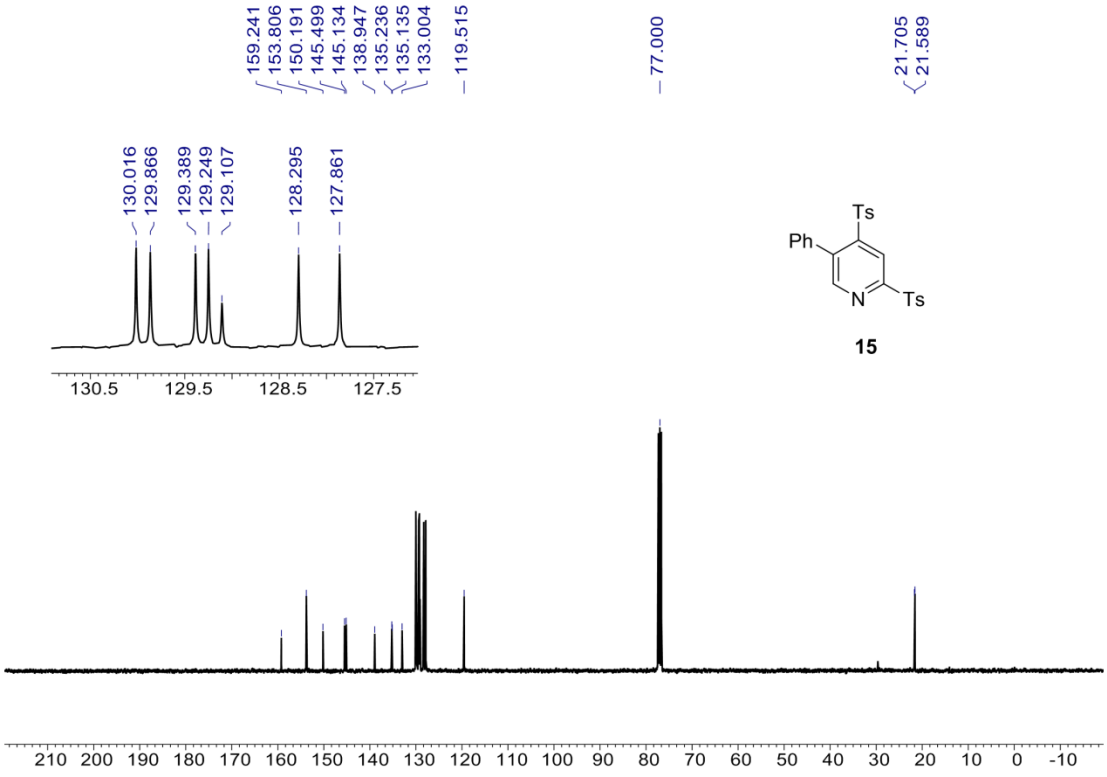
^{13}C NMR (100 MHz, $CDCl_3$**) for 14**



^{1}H NMR (100 MHz, $CDCl_3$**) for 15**

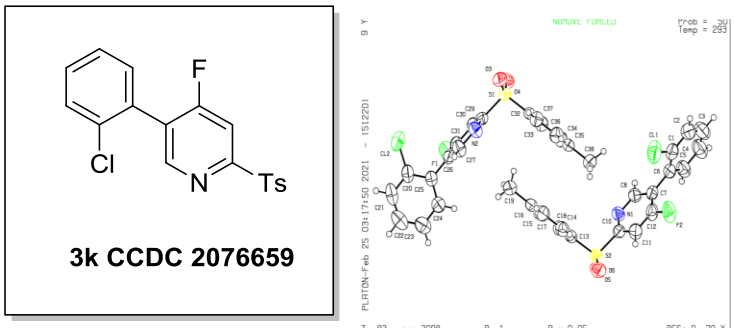


^{13}C NMR (100 MHz, $CDCl_3$**) for 15**



5.X-ray Crystallographic Data of compound 3k, 3p, 4c

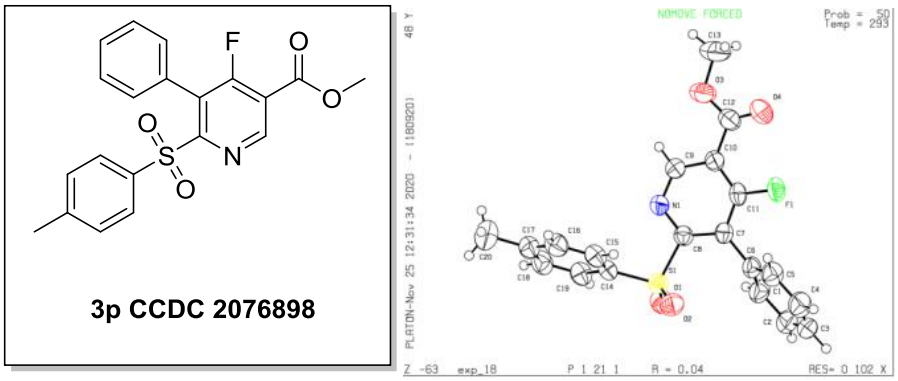
Single-crystal X-ray diffraction data was collected at room temperature on a Oxford Diffraction Gemini R Ultra diffractometer, the X-ray generator using Mo-Kα (λ = 0.71073 Å) radiation with a ω scan technique. The crystal structures were solved by direct method of SHELXS-97 and refined by full-matrix least-squares techniques using the SHELXL-97 program. Non-hydrogen atoms were refined anisotropic. CCDC deposition number: 2076659 (**3k**), 2076898 (**3p**), 2076661 (**4c**). Data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).



Crystal data and structure refinement for **3k**

Empirical formula	$C_{36}H_{26}O_4N_2F_2S_2Cl_2$
Formula weight	723.61
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.5995(5)
b/Å	11.0868(7)
c/Å	18.5904(14)
α/°	96.689(6)
β/°	101.847(6)
γ/°	99.853(5)
Volume/Å^3	1687.83(19)
Z	2
ρ_{calc}mg/mm^3	1.424

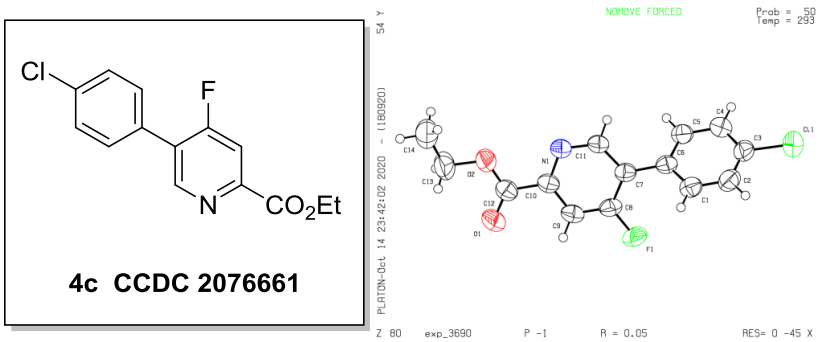
m/mm^{-1}	3.345
F(000)	744.0
Crystal size/mm^3	0.09 × 0.02 × 0.01
Index ranges	$-10 \le h \le 9$, $-13 \le k \le 13$, $-22 \le l \le 22$
Reflections collected	11108
Independent reflections	6014[R(int) = 0.0260]
Data/restraints/parameters	6014/0/433
Goodness-of-fit on F^2	1.034
Final R indexes [I>=2σ (I)]	R_1 = 0.0482, wR_2 = 0.1257
Final R indexes [all data]	R_1 = 0.0677, wR_2 = 0.1447
Largest diff. peak/hole / e Å^{-3}	0.24/-0.37



Crystal data and structure refinement for **3p**

Empirical formula	$C_{20}H_{16}NO_4SF$
Formula weight	385.40
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	6.0579(2)
b/Å	15.5439(5)
c/Å	9.8183(3)
α/°	90.00
β/°	92.620(3)

γ/°	90.00
Volume/Å^3	923.56(5)
Z	2
ρ_{calc}mg/mm^3	1.386
m/mm^{-1}	1.877
F(000)	400.0
Crystal size/mm^3	0.26 × 0.20 × 0.09
Index ranges	$-7 \le h \le 7$, $-13 \le k \le 18$, $-11 \le l \le 8$
Reflections collected	3793
Independent reflections	2576[R(int) = 0.0185]
Data/restraints/parameters	2576/1/244
Goodness-of-fit on F^2	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0350, wR_2 = 0.0918
Final R indexes [all data]	R_1 = 0.0365, wR_2 = 0.0935
Largest diff. peak/hole / e Å^{-3}	0.15/-0.24
Flack parameter	0.029(18)



Crystal data and structure refinement for **4c**

Empirical formula	$C_{14}H_{11}NO_2ClF$
Formula weight	279.69
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.3135(7)
b/Å	7.6484(6)

c/Å	12.3996(11)
α /°	103.627(7)
β /°	97.874(8)
γ /°	98.131(7)
Volume/$Å^3$	656.75(10)
Z	2
ρ_{calc}mg/mm^3	1.414
m/mm^{-1}	2.675
F(000)	288.0
Crystal size/mm^3	0.22 × 0.16 × 0.13
2Θ range for data collection	7.46 to 134.02°
Index ranges	-8 ≤ h ≤ 8, -9 ≤ k ≤ 6, -14 ≤ l ≤ 14
Reflections collected	3825
Independent reflections	2312[R(int) = 0.0210]
Data/restraints/parameters	2312/0/174
Goodness-of-fit on F^2	1.052
Final R indexes [I>=2σ (I)]	R_1 = 0.0507, wR_2 = 0.1399
Final R indexes [all data]	R_1 = 0.0603, wR_2 = 0.1547
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.21