Supporting Information

Generating Pd-catalyzed δ C–H chalcogenation of aliphatic picolinamides: systematically decreasing the bias

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Table of Contents

1. General Information

1.1. Reagent Information: Unless otherwise stated, all reactions were carried out under air atmosphere in screw cap reaction tubes. All solvents were bought from Aldrich in sure-seal bottle and were used as received. Disulfides and Diselenides were purchased from TCI, India. All the other chemicals were bought from Aldrich and Alfa Aesar. For column chromatography, silica gel (60-120 mesh or 100-200 mesh) obtained from SRL Co. was used. A gradient elution using petroleum ether and ethyl acetate was performed, based on Merck aluminum TLC sheets (silica gel $60F_{254}$).

1.2. Analytical Information. All isolated compounds were characterized by ^{1}H, ^{13}C spectroscopy and HR-MS. Copies of the ^{1}H NMR, ^{13}C NMR can be found in the supporting information. Unless otherwise stated, all Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz and 500 MHz instrument. All ^{1}H NMR experiments are reported in units of parts per million (ppm) and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent, unless otherwise stated. All ^{13}C NMR spectra were reported in ppm relative to $CDCl_3$ (77.16 ppm), unless otherwise stated, and all were obtained with ^{1}H decoupling. All HPLC analyses were performed on an Agilent 1260 Infinity U.S.A HPLC system with a DAD detector using a ZORBAX CN column (5 μm, 4.6*250 mm) utilizing acetophenone as the internal standard. High-resolution mass spectra (HRMS) were recorded on a micro-mass ESI TOF (time of flight) mass spectrometer.

2. General Procedures:

General Procedure A for Ester Protection:

To a 100 mL of round bottom flask was added amino acid (Leucine) (30.0 mmol), MeOH (2.0 eq) and H_2SO_4 (2 mL) at room temperature. The reaction was stirred at room temperature for 3 hours, followed by refluxing for 12hrs. Then the aqueous solution was slowly acidified with K_2CO_3 until pH = 6-7 at room temperature. The mixture was extracted with EtOAc (30 mL × 3). The combined organic layers was washed with brine, dried with $MgSO_4$, filtrated and concentrated affording the crude product which was purified by flash column chromatography (silica gel, petroleum ether/EtOAc 3/1 to 1/1).

General Procedure B for Preparation of ethyl picolinoylleucinate:[1]

In a clean oven dried 100 mL round-bottomed flask equipped with stir-bar, 2-picolinic acid (10 mmol, 1.17g) was taken and *N,N'*-Dicyclohexylcarbodiimide (DCC) (10 mmol, 2.05g) and Hydroxybenzotriazole (10 mmol, 1.33g) were added. Subsequently ester protected leucine (8 mmol, 1.33g) was introduced in the flask. Later dichloromethane was added. Subsequently *N*,*N*-Diisopropylethylamine (24 mmol, 4.27 mL) was added slowly *via* syringe and reaction mixture was cooled to 0 ℃ and then brought to room temperature. Reaction mixture was allowed to stirred for 12 h and upon completion of reaction it was quenched with saturated NH_4Cl and extracted in ethyl acetate thrice (3 X 50 mL). Organic layer was dried over Na_2SO_4 and solvent was removed under *vacuum* and purified with column chromatography by eluent as petroleum ether/ethyl acetate (80:20 v/v).

General Procedure C for Thioarylation of ethyl picolinoylleucinate:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with ethyl picolinoylleucinate (0.1 mmol, 26.4 mg), palladium(II) pivalate (10 mol%, 0.01 mmol, 3.12 mg) and 2-chloroquinoline (20 mol%, 0.02 mmol, 3.2 mg). Then, Ag_2O (3 eq., 0.3 mmol, 69.6 mg) and diphenyl disulfide (1.8 eq., 0.18 mmol, 39.4 mg) were introduced in this reaction mixture. The cap was fitted with a rubber septum. TFT (2 mL) was added to this mixture by syringe. The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 130 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 5 mL) followed by water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under *vacuum*. The crude reaction mixture was purified by column chromatography using silica gel (60-120/100-200 mesh size) and petroleum ether/ethyl acetate as the eluent (93:7) to give the desired thioarylated product.

General Procedure D for Selenoarylation of ethyl picolinoylleucinate:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with ethyl picolinoylleucinate (0.1 mmol, 26.4 mg), palladium(II) acetate (10 mol%, 0.01 mmol,

2.24 mg) and 2-chloroquinoline (20 mol%, 0.02 mmol, 3.2 mg). Then Ag_2O (3 eq., 0.3 mmol, 69.6 mg) and diphenyl diselenide (1.8 eq., 0.18 mmol, 39.4 mg) were introduced in this reaction mixture. The cap was fitted with a rubber septum. TFT (2 mL) was added to this mixture by syringe. The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 130 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 5 mL) followed by water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under *vacuum*. The crude reaction mixture was purified by column chromatography using silica gel (60-120/100-200 mesh size) and petroleum-ether/ethyl acetate as the eluent (92:8) to give the desired selenoarylated product.

General Procedure E for Thioarylation of N-(2,4,4-trimethylpentan-2-yl)picolinamide:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with ethyl picolinoylleucinate (0.1 mmol, 26.4 mg), palladium(II) acetate (10 mol%, 0.01 mmol, 3.12 mg) and 4-hydroxyquinoline (20 mol%, 0.02 mmol, 3.2 mg). Then Ag_2CO_3 (3 eq., 0.3 mmol, 69.6 mg) and diphenyl disulfide (1.0 eq., 0.18 mmol, 21.8 mg) were introduced in this reaction mixture. The cap was fitted with a rubber septum and filled with vacuum and oxygen thrice. MeOH (2 mL) was added to this mixture by syringe. The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 90 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 5 mL) followed by water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under *vacuum*. The crude reaction mixture was purified by column chromatography using silica gel (60-120/100-200 mesh size) and petroleum ether/ethyl acetate as the eluent (95:5) to give the desired thioarylated product.

General Procedure F for Heterodi functionalization:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with arylated picolanimide (0.1 mmol, 26.4 mg), palladium(II) acetate (10 mol%, 0.01 mmol, 2.24 mg) and 4-hydroxyquinoline (20 mol%, 0.02 mmol, 3.2 mg). Then Ag_2CO_3 (3 eq., 0.3 mmol, 81.8

mg) and diphenyl disulfide (1.0 eq., 0.18 mmol, 21.8 mg) were introduced in this reaction mixture in an oxygen atmosphere. MeOH (2 mL) was added to this mixture by syringe. The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 90 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 5 mL) followed by water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under *vacuum*. The crude reaction mixture was purified by column chromatography using silica gel (60-120/100-200 mesh size) and petroleum ether/ethyl acetate as the eluent (93:7) to give the desired thioarylated product.

General Procedure G for δ-Arylation:[2]

In a clean, oven–dried screw cap reaction tube containing magnetic stir-bar, ethyl picolinoylleucinate (0.1 mmol), iodoarene (3 eq., 0.3 mmol), $Pd(OPiv)_2$ (10 mol %, 0.01 mmol), Ag_2CO_3 (3 eq., 0.3 mmol), CF_3CO_2Na (2 eq., 0.2 mmol) and 4-benzyloxy-2-hydroxy pyridine (20 mol%, 0.02 mmol) were weighed. Then TBME (2.0 mL) was introduced in the reaction tube through a common laboratory syringe and the tube was tightly closed by screw cap fitted with rubber septum. Finally, the reaction tube was placed in a preheated oil bath at 130 °C to stir vigorously for 36 h. After completion, the reaction mixture was cooled to room temperature and filtered through celite with aid of ethyl acetate (15 mL). This filtrate was concentrated under reduced pressure and purified by column chromatography through silica gel using petroleum ether/ethyl acetate as eluent.

3. Optimization Details

3.1. Optimization details for δ-thioarylation of amino acids:

Table S1: Initial reaction conditions

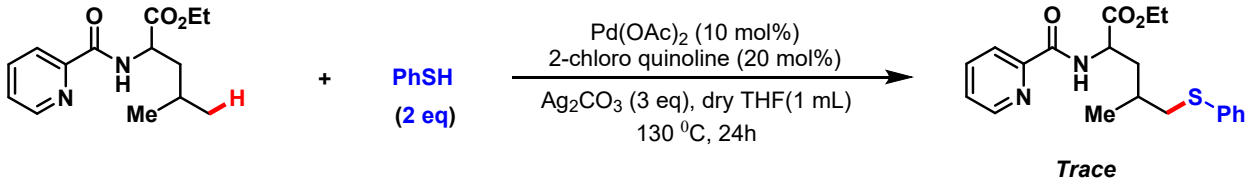

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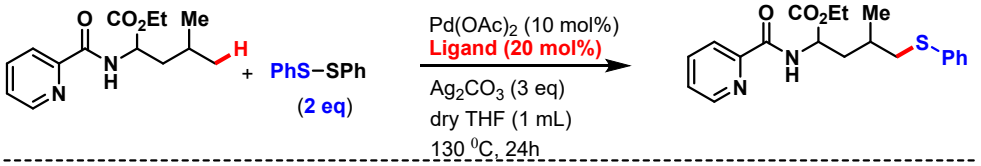
Table S2: Ligand optimization



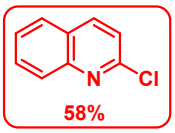
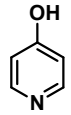
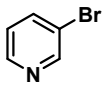
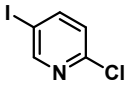
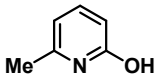
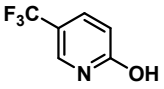
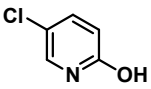
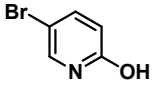
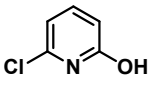
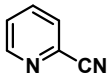
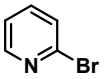
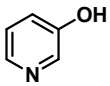
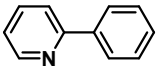
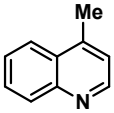
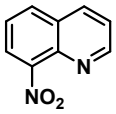
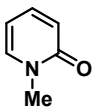
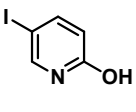
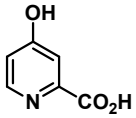
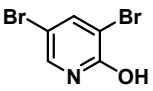
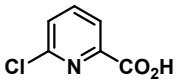
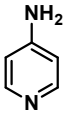
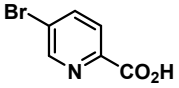
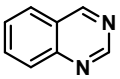
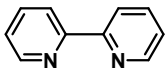
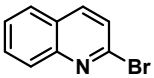
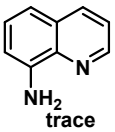
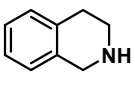
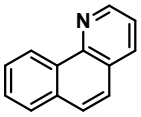
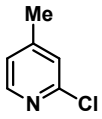
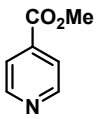
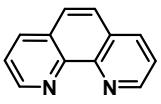
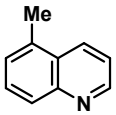
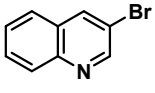
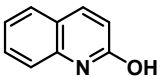
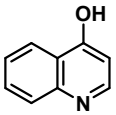
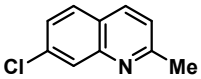
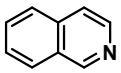
 58%	 8%	 41%	 40%	 53%
 5%	 20%	 43%	 35%	 45%
 10%	 50%	 25%	 56%	 40%
 51%	 56%	 46%	 16%	 35%
 38%	 51%	 20%	 trace	 53%
 40%	 55%	 trace	 54%	 46%
 49%	 trace	 45%	 50%	 42%
 trace	 trace	 55%	 30%	trace
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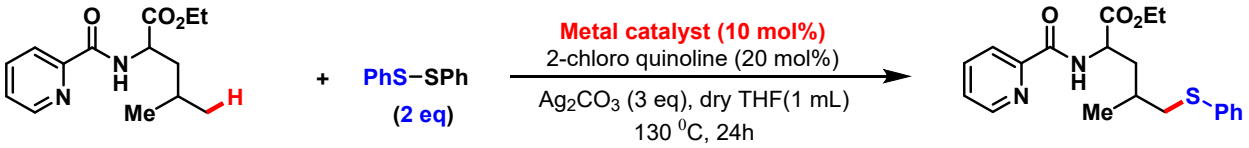
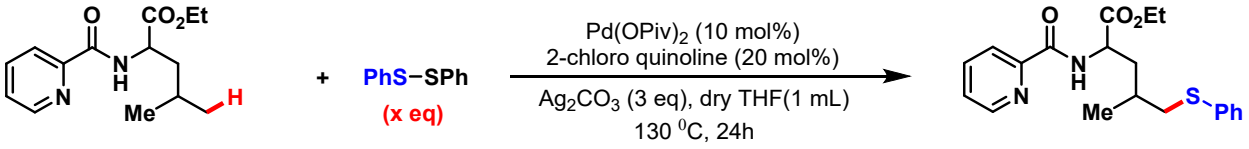
Table S3: Metal Catalyst Optimization



Entry	Catalyst	Yield (%)
1	$Pd(OAc)_2$	58
2	PdO	N.D.
3	$PdCl_2$	35
4	$PdCl_2(PPh_3)_2$	31
5	$Pd(acac)_2$	N.D.
6	$Pd(CH_3CN)_2Cl_2$	30
7	$Pd(PhCN)_2Cl_2$	19
8	$Pd(TFA)_2$	20
9	$Pd(PPh_3)_4$	33
10	**Palladium pivalate**	61
11	$Pd_2(dba)_3$	N.D

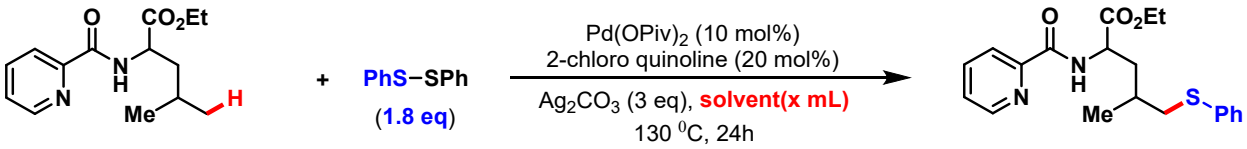
Table S4: Disulphide loading Optimization



Entry	Disulphide loading	Yield (%)
1	1.0 eq	26%
2	1.2 eq	42%
3	1.4 eq	56%

4	1.6 eq	59%
5	**1.8 eq**	**64%**
6	2.0 eq	61%

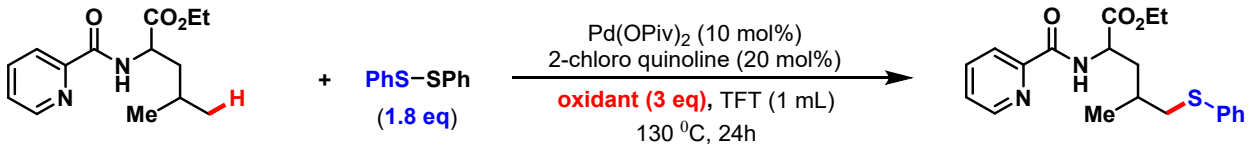
Table S5: Solvent Optimization



Entry	Solvent	Yield (%)
1	Dry THF	64
2	THF	25
3	DCM	50
4	Dry DCM	68
5	DCE	71
6	^{t}BuOH	N.D.
7	TBME	61
8	**TFT**	**78**
9	1,4-dioxane	20
10	Toluene	35
11	Chloroform	62
12	m-xylene	40
13	EtOH	N.D.
14	Chlorobenzene	N.D.
15	DMF	N.D.
16	MeCN	N.D.

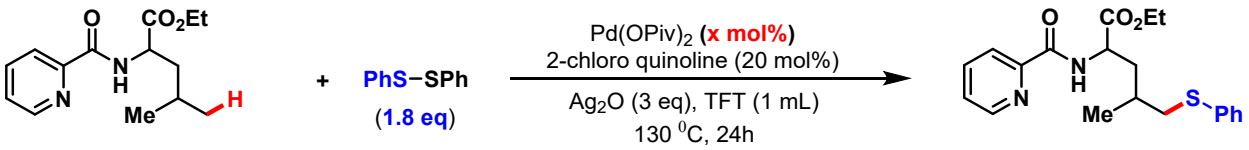
17	2-Me THF	20
18	Amyl alcohol	N.D.
19	Benzene	75
20	MeOH	N.D.
21	Acetone	N.D.
22	DMSO	N.D.
23	HFIP	20

Table S6: Oxidant Optimization



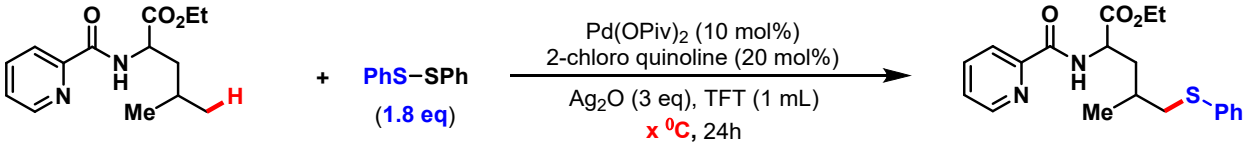
Entry	Oxidant	Yield (%)
1	$Cu(OAc)_2$	N.D.
2	AgOAc	70
3	Ag_2CO_3	78
4	$AgNO_2$	5
5	$AgNO_3$	20
6	AgCN	N.D.
7	AgBr	N.D.
8	AgTFA	60
9	O_2	25
10	$Ag_2CO_3 + O_2$	75
11	Ag_2SO_4	40
12	**Ag_2O**	**82**
13	Benzoquinone	31
14	No oxidant	15

Table S7: Metal Catalyst Loading Optimization



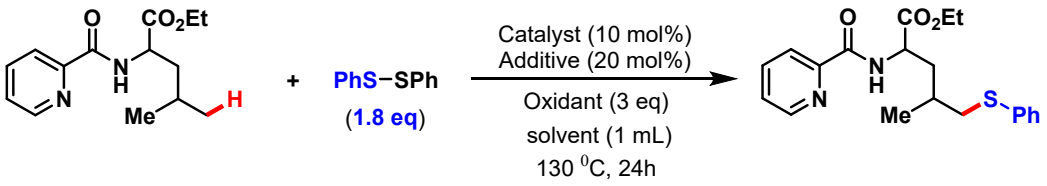
Entry	Metal catalyst loading	Yield (%)
1	2.0 mol%	10
2	4.0 mol%	25
3	6.0 mol%	33
4	8.0 mol%	58
5	**10 mol%**	**82**
6	12 mol%	76

Table S8: Temperature Optimization



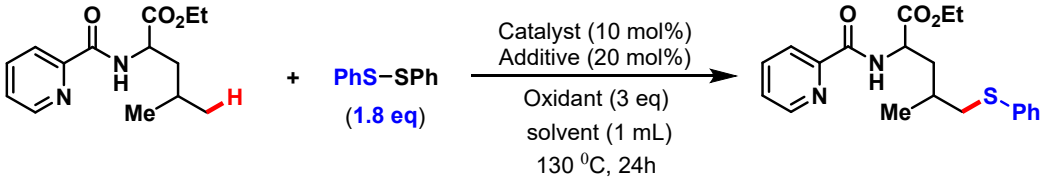
Entry	Temperature (℃)	Yield (%)
1	80	N.D.
2	90	40
3	100	62
4	110	71
5	120	75
6	**130**	**82**
7	140	76

Table S9: Catalyst Optimization



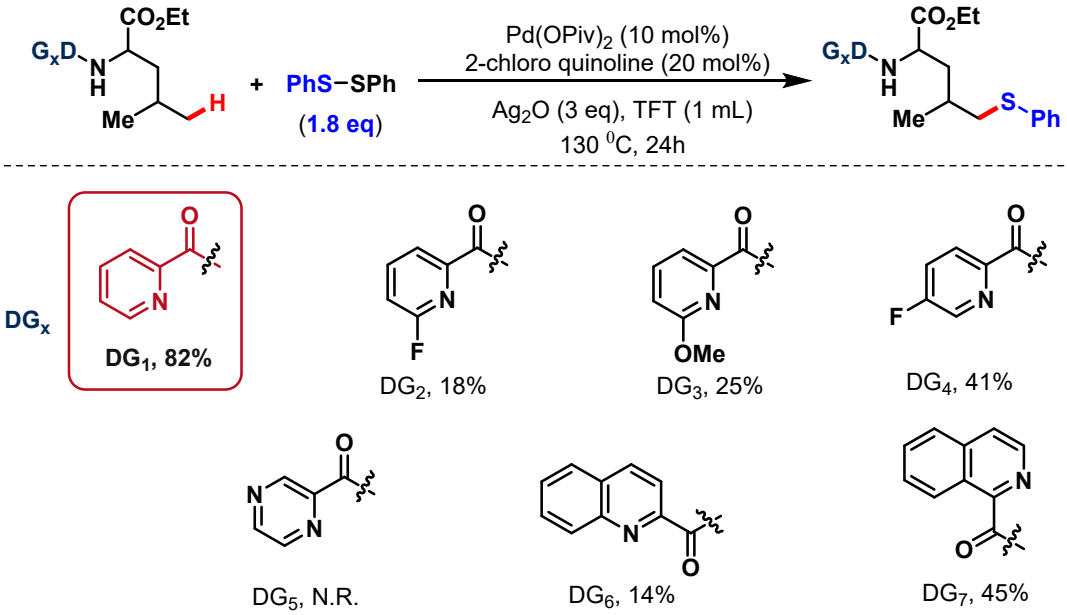
Entry	Metal catalyst variation	Yield (%)
1	**Standard conditions**	**82**
2	$NiCl_2$ + PPh_3 in DMF	N.D.
3	$Ni(OTf)_2$ + PPh_3 in DMF	N.D.
4	$Cu(OAc)_2.H_2O$ + 1,10-phen. in THF	N.D.
5	$Cu(OAc)_2.H_2O$ + 1,10-phen. + Ag_2O in THF	N.D.
6	$Co(OAc)_2.H_2O$ + 1,10-phen. in THF	N.D.
7	$Co(OAc)_2.H_2O$ + 1,10-phen. + Ag_2O in THF	N.D.

Table S10: Deviation from standard reaction conditions



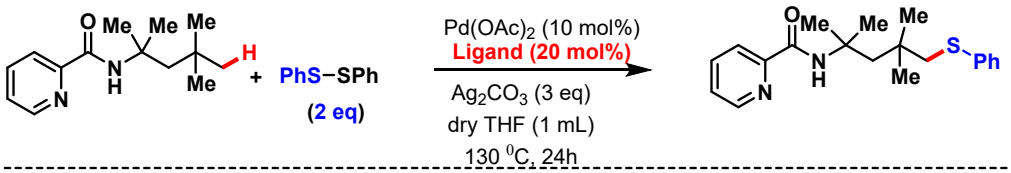
Entry	Deviation	Yield (%)
1	**Standard conditions**	**82**
2	No $Pd(OPiv)_2$	N.D.
3	No Ag_2O	15
4	Ag_2CO_3 instead of Ag_2O	74
5	Benzene instead of TFT	75
6	N_2 instead of air	57
7	O_2 instead of air	74

Table S11: Directing group optimization



3.2. Optimization details for δ-thioarylation of biased aliphatic amines:

Table S12: Ligand optimization


Me
Me
Me
H
Me
+ PhS–SPh
(2 eq)
Pd(OAc)2 (10 mol%)
Ligand (20 mol%)
Ag2CO3 (3 eq)
dry THF (1 mL)
130 0C, 24h
S
Ph

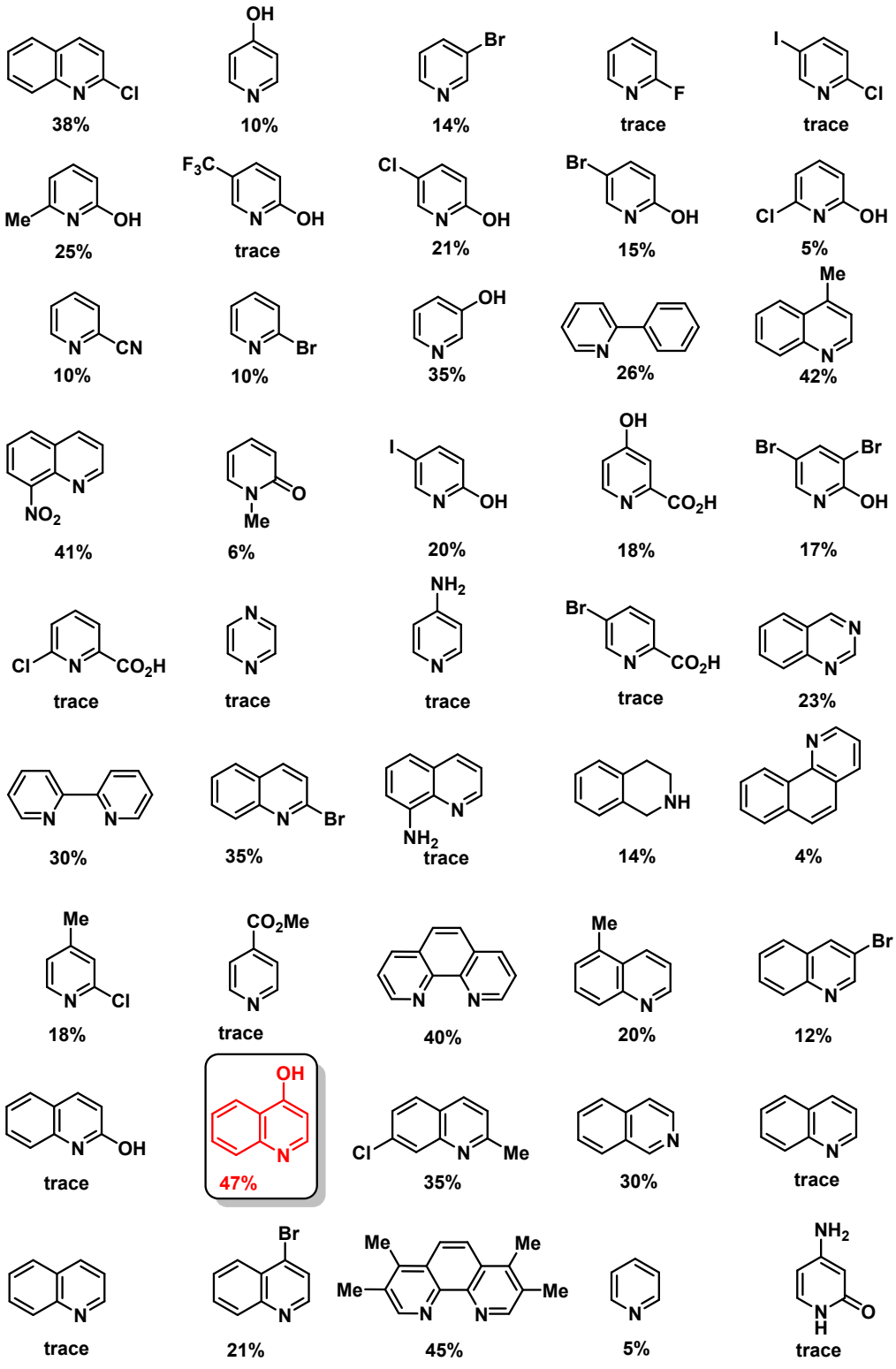
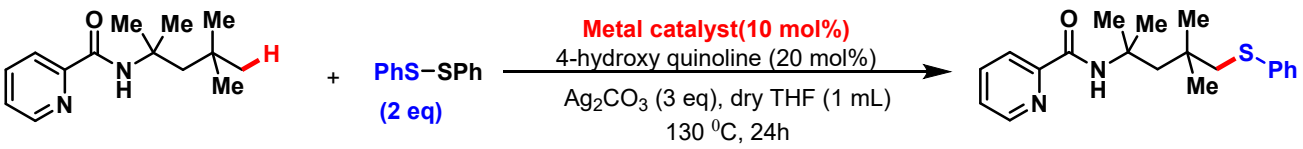
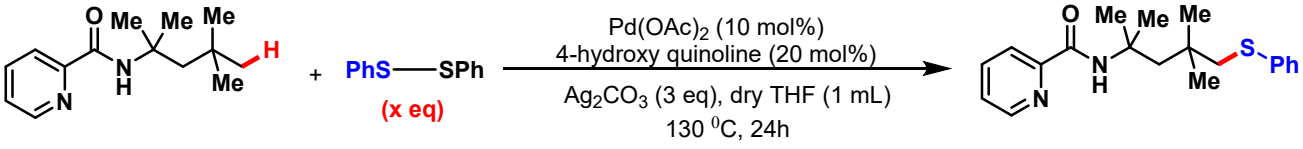

38%
10%
14%
trace
trace
25%
trace
21%
15%
5%
10%
10%
35%
26%
42%
41%
6%
20%
18%
17%
trace
trace
trace
trace
23%
30%
35%
trace
14%
4%
18%
trace
40%
20%
12%
trace
47%
35%
30%
trace
trace
21%
45%
5%
trace

Table S13: Metal catalyst optimization



Entry	Catalyst	Yield (%)
1	**$Pd(OAc)_2$**	**47**
2	PdO	N.D.
3	$PdCl_2$	ND
4	$PdCl_2(PPh_3)_2$	11
5	$Pd(acac)_2$	N.D.
6	$Pd(CH_3CN)_2Cl_2$	ND
7	$Pd(PhCN)_2Cl_2$	ND
8	$Pd(TFA)_2$	ND
9	$Pd(PPh_3)_4$	ND
10	Palladium pivalate	44
11	$Pd_2(dba)_3$	N.D.

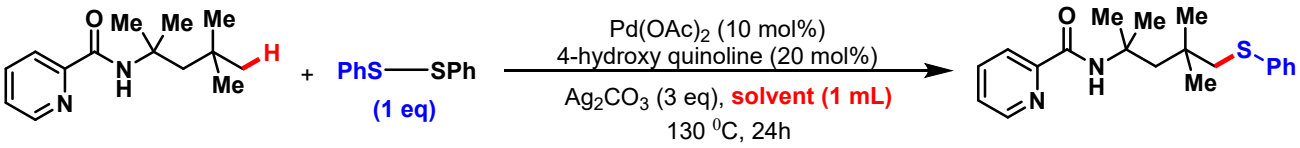
Table S14: Disulphide loading optimization



Entry	Disulphide loading	Yield (%)
1	**1.0 eq**	**56%**
2	1.2 eq	52%
3	1.4 eq	50%

4	1.6 eq	49%
5	1.8 eq	47%
6	2.0 eq	47%

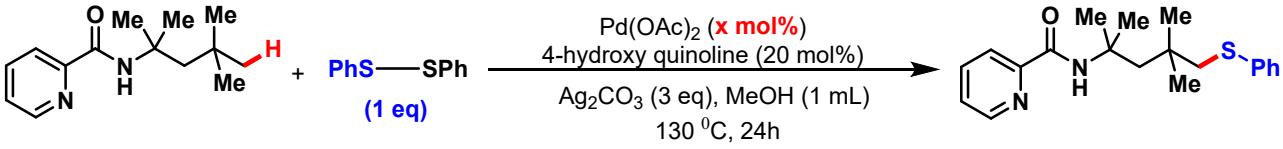
Table S15: Solvent optimization



Entry	Solvent	Yield (%)
1	Dry THF	56
2	THF	45
3	DCM	ND
4	Dry DCM	18
5	DCE	51
6	^{t}BuOH	52
7	TBME	31
8	TFT	34
9	1,4-dioxane	20
10	Toluene	ND
11	Chloroform	10
12	m-xylene	ND
13	EtOH	50
14	Chlorobenzene	41
15	DMF	N.D.
16	MeCN	N.D.

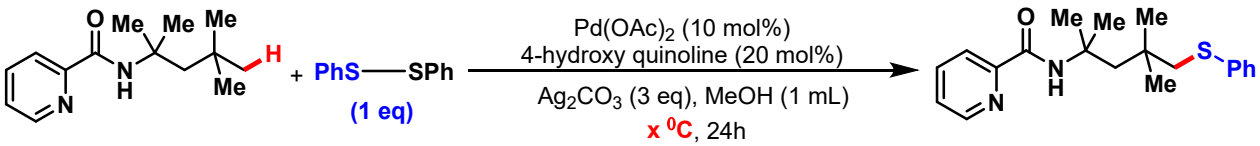
17	2-Me THF	20
18	Amyl alcohol	59
19	Benzene	49
20	**MeOH**	**60**
21	Acetone	N.D.
22	DMSO	37
23	HFIP	20

Table S16: Metal catalyst loading optimization



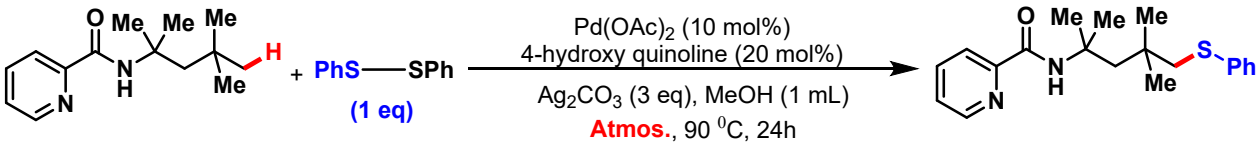
Entry	Metal catalyst loading	Yield (%)
1	2.0 mol%	10
2	4.0 mol%	15
3	6.0 mol%	36
4	8.0 mol%	58
5	**10 mol%**	**60**
6	12 mol%	59

Table S17: Temperature optimization



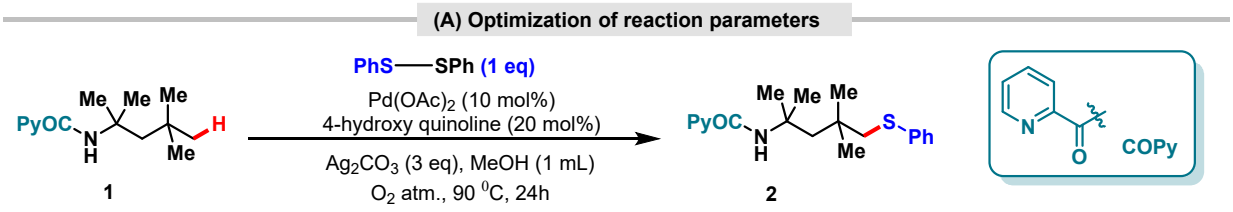
Entry	Temperature (℃)	Yield (%)
1	80	58
2	**90**	**68**
3	100	63
4	110	62
5	120	60
6	130	60

Table S18: Atmosphere optimization



Entry	Atmosphere	Yield (%)
1	air	68
2	N_2	51
3	**O_2**	**76**

Table S19: Standard reaction optimization

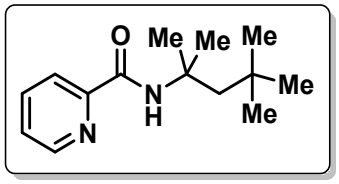


Entry	Temperature	Oxidant	Solvent	Yield
1	90℃	Ag_2CO_3	MeOH	68%[b]

2	110°C	Ag_2CO_3	MeOH	62%[b]
3	130°C	Ag_2CO_3	MeOH	60%[b]
4	90°C	Ag_2CO_3	TFT	34%[b]
5		No $Pd(OAc)_2$		No product
6		No Ag_2CO_3		20%[b]
7	N_2	instead of	air	51%
8	O_2	instead of	air	76%[a]

[a] **1** (0.05 mmol, 1 eq), Ph_2S_2 (1 eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (3 eq), 4-hydroxyquinoline (20 mol%) in MeOH (1 mL) under O_2 atmosphere at 90 C for 24h. [b] air instead of O_2. Yields determined by ^{1}HNMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

4. Characterization data:



***N*-(2,4,4-trimethylpentan-2-yl)picolinamide (Scheme 2, entry 1)** [2]

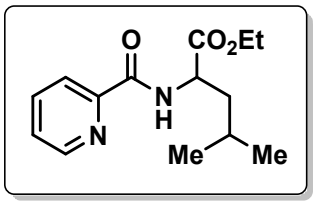
Yield: 81%

Nature: Yellow liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (m, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 8.07 (s, 1H), 7.80-7.72 (m, 1H), 7.32 (m, 1H), 1.81 (s, 2H), 1.50 (s, 6H), 0.92 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.20, 150.91, 147.84, 137.38, 126.10, 121.72, 55.25, 52.13, 32.31, 31.42, 29.13.

TLC: R_f = 0.1 (95:5 petroleum ether:EtOAc).

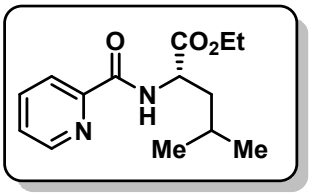


Ethyl picolinoylleucinate (Scheme 4, entry 1'a) [2]

Yield: 84%

Physical state: Yellow liquid.

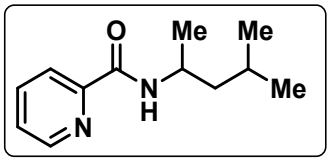
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.46 (m, 1H), 8.32 (d, J = 8.6 Hz, 1H), 8.08 (dd, J = 7.8, 0.9 Hz, 1H), 7.74 (td, J = 7.7, 1.6 Hz, 1H), 7.34 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 4.75 – 4.71 (m, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.73 – 1.61 (m, 3H), 1.19 (t, J = 7.1 Hz, 3H), 0.96 – 0.89 (m, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.42, 164.10, 149.39, 148.35, 137.38, 126.40, 122.41, 61.42, 50.79, 41.66, 25.01, 22.87, 21.66, 14.26.
TLC: R_f = 0.1 (90:10 petroleum ether:EtOAc).



Ethyl picolinoyl-L-leucinate (Scheme 4, entry 1'j)[2]

Yield: 80%

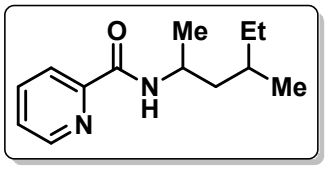
Nature: Orangish liquid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50-8.44 (m, 1H), 8.35 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.85 (td, J = 7.8, 1.6 Hz, 1H), 7.34 (ddd, J = 7.6, 4.8, 1.0 Hz, 1H), 4.81 (td, J = 8.8, 5.0 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 1.78 – 1.70 (m, 3H), 1.23 (t, J = 7.1 Hz, 3H), 0.99 – 0.95 (m, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.11, 164.50, 149.52, 148.39, 137.50, 126.54, 122.10, 60.84, 50.96, 41.95, 25.08, 23.05, 22.01, 13.78.
TLC: R_f = 0.12 (90:10 petroleum ether:EtOAc).



***N*-(4-methylpentan-2-yl)picolinamide (Scheme 4, entry 1'n)**[2]

Yield: 76%

Nature: Yellow liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 4.6 Hz, 1H), 8.19 (d, J = 7.7 Hz, 1H), 7.77 (td, J = 7.8, 1.3 Hz, 2H), 7.43 (dd, J = 7.4, 4.9 Hz, 1H), 4.35 – 4.25 (m, 1H), 1.71 – 1.63 (m, 1H), 1.43 (ddd, J = 14.2, 8.6, 6.2 Hz, 1H), 1.37 (ddd, J = 13.8, 8.0, 5.9 Hz, 1H), 1.25 (d, J = 6.5 Hz, 3H), 0.94 (t, J = 7.0 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.79, 150.41, 148.14, 137.50, 126.23, 122.22, 46.79, 43.50, 26.13, 23.67, 22.09, 21.33.
TLC: R_f = 0.08 (90:10 petroleum ether:EtOAc).

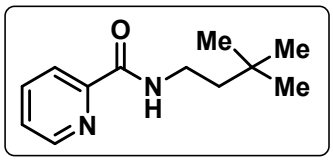


***N*N-(4-methylhexan-2-yl)picolinamide (Scheme 4, entry 1'p)**[2]

Yield: 82%

Nature: Yellow liquid**.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.562 (d, J = 4.3 Hz, 1H), 8.19 (dd, J = 7.8, 0.6 Hz, 1H), 7.84 (td, J = 7.7, 1.6 Hz, 2H), 7.43 – 7.39 (m, 1H), 4.37– 4.30 (m, 1H), 1.61-1.53 (m, 2H), 1.47 – 1.25 (m, 2H), 1.25 – 1.21 (m, 3H), 1.21 – 1.14 (m, 1H), 0.93 – 0.90 (m, 3H), 0.85 (td, J = 7.3, 5.3 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.68, 150.34, 148.10, 137.53, 126.15, 122.41, 44.50, 43.39, 31.52, 29.92, 22.14, 19.22, 11.38.
TLC: R_f = 0.12 (85:15 petroleum ether:EtOAc).

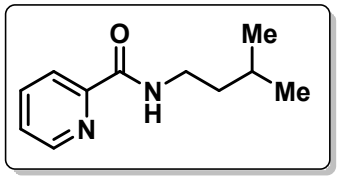


***N* -(3,3-dimethylbutyl)picolinamide (Scheme 4, entry 1't)**[6]

Yield: 70%

Nature: Yellow liquid**.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.7 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 – 7.40 (m, 1H), 3.59-3.47 (m, 2H), 1.87 – 1.79 (m, 2H), 0.94 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.13, 150.13, 148.31, 137.89, 126.14, 121.88, 47.00, 35.44, 27.17, 27.04.
TLC: R_f = 0.15 (85:15 petroleum ether:EtOAc).

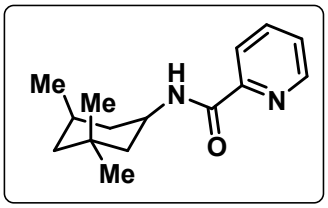


***N*-isopentylpicolinamide (Scheme 4, entry 1'v)**[6]

Yield: 78 %

Nature: Yellow liquid**.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.80 (td, *J* = 7.7, 1.5 Hz, 1H), 7.40-7.36 (m, 1H), 3.66 – 3.58 (m, 2H), 1.90 – 1.82 (m, 2H), 1.58 – 1.50 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.20, 150.08, 148.16, 137.48, 125.90, 122.33, 40.87, 36.24, 25.86, 24.59.
TLC: R_f = 0.12 (85:15 petroleum ether:EtOAc).

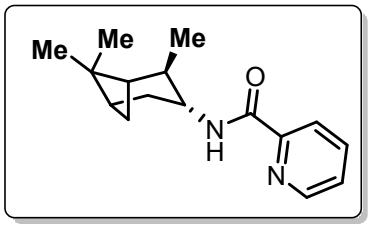


***N*-((5R)-3,3,5-trimethylcyclohexyl)picolinamide (Scheme 4, entry 1'z)**[2]

Yield: 69%

Nature: Yellow semi-solid

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (dd, J = 9.8, 4.8 Hz, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.82 (td, J = 7.7, 1.6 Hz, 1H), 7.41 – 7.37 (m, 1H), 4.38 – 4.31 (m, 1H), 1.89 – 1.83 (m, 2H), 1.74 (d, J = 14.2 Hz, 1H), 1.49 – 1.40 (m, 2H), 1.22 (ddd, J = 14.2, 12.6, 4.2 Hz, 1H), 1.07 (s, 3H), 0.93 (dd, J = 10.8, 7.0 Hz, 7H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.41, 150.39, 148.22, 137.42, 126.05, 122.12, 47.96, 45.64, 41.95, 38.78, 34.03, 30.95, 28.16, 24.13, 22.65.
TLC: R_f = 0.1 (85:15 petroleum ether:EtOAc).

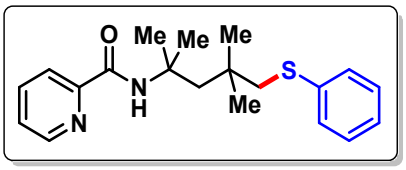


***N*-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)picolinamide (Scheme 4, entry 1'ad)**[2]

Yield: 60%

Nature: Brownish yellow liquid**.**

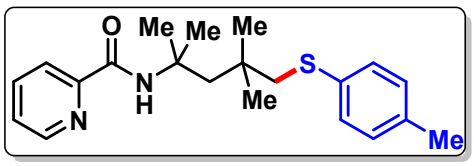
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 – 8.52 (m, 1H), 8.23 – 8.18 (m, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.83 (tdd, J = 4.7, 3.1, 1.6 Hz, 1H), 7.43 – 7.38 (m, 1H), 4.52 – 4.43 (m, 1H), 2.67 (ddd, J = 10.3, 6.1, 2.2 Hz, 1H), 2.48 – 2.41 (m, 1H), 1.98 (dd, J = 13.1, 7.6 Hz, 2H), 1.89 – 1.86 (m, 1H), 1.68 (ddd, J = 13.9, 6.0, 2.4 Hz, 1H), 1.24 (d, J = 2.3 Hz, 3H), 1.18 – 1.14 (m, 3H), 1.10 (d, J = 2.4 Hz, 3H), 0.99 (dd, J = 9.8, 1.8 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.82, 150.38, 148.14, 137.55, 126.18, 122.51, 48.02, 47.99, 46.36, 41.81, 38.68, 37.20, 35.42, 28.25, 23.62, 21.05.
TLC: R_f = 0.1 (85:15 petroleum ether:EtOAc).



***N*-(2,4,4-trimethyl-5-(phenylthio)pentan-2-yl)picolinamide (Scheme 2, entry 2a)**

Yield: 78%

Nature: Yellow liquid
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.1 Hz, 1H), 8.19 – 8.14 (m, 2H), 7.82 (td, *J* = 7.7, 1.6 Hz, 1H), 7.38 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.25 (s, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.11 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.03 (s, 2H), 2.06 (s, 2H), 1.58 (s, 6H), 1.16 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.40, 150.91, 147.95, 138.37, 137.48, 128.90, 128.86, 125.94, 125.55, 121.82, 54.65, 49.47, 48.62, 36.28, 29.45, 28.59.
HRMS (ESI): calcd. for $C_{20}H_{26}N_2OSNa$: 365.1861, found: 365.1862.
IR (cm^{-1}): 747.618 (S-S stretch), 819.311 (C-S stretch), 1519.493, 1590.620, 1590.620 (C-C stretch), 1678.175 (C=O stretch in amide), 2924.917, 2960.514 (C-H stretch), 3372.88 (N-H stretch)**.**
TLC: R_f = 0.12 (90:10 petroleum ether:EtOAc).

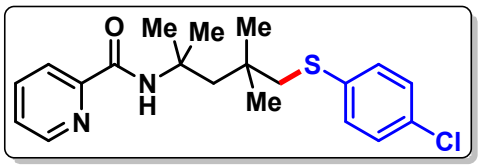


***N*-(2,4,4-trimethyl-5-(p-tolylthio)pentan-2-yl)picolinamide (Scheme 2, entry 2b)**

Yield: 74%

Nature: Colourless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.1 Hz, 1H), 8.19 – 8.14 (m, 2H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.39 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 2.99 (s, 2H), 2.28 (s, 3H), 2.05 (s, 2H), 1.57 (s, 8H), 1.14 (s, 6H).

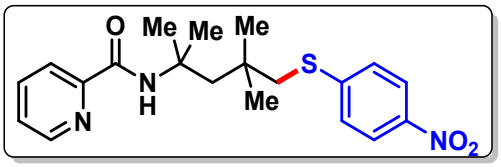
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.83, 150.49, 147.34, 138.15, 135.62, 134.65, 129.66, 129.62, 126.07, 122.32, 122.10, 121.90, 54.90, 49.51, 49.18, 36.34, 29.85, 29.43, 28.58, 28.52, 21.09.
HRMS (ESI): calcd. for $C_{21}H_{28}N_2OS$ 356.1961, found: 356.1963.
IR (cm^{-1}): 749.443 (S-S stretch), 805.716 (C-S stretch), 1521.742, 1570.245, 1591.794 (C-C stretch), 1681.801 (C=O stretch of amide), 2925.033, 2961.723 (C-H stretch), 3372.725 (N-H stretch).
TLC: R_f = 0.18 (90:10 petroleum ether:EtOAc).



***N*-(5-((4-chlorophenyl)thio)-2,4,4-trimethylpentan-2-yl)picolinamide (Scheme 2, entry 2c)**

Yield: 76%

Nature: Yellow liquid
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.1 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 2H), 7.85 (td, *J* = 7.7, 1.5 Hz, 1H), 7.41 (dd, *J* = 6.6, 4.8 Hz, 1H), 7.18 – 7.10 (m, 4H), 2.99 (s, 2H), 2.06 (s, 2H), 1.57 (s, 6H), 1.14 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.95, 150.47, 147.44, 138.08, 136.96, 131.35, 130.10, 128.92, 126.11, 122.24, 122.09, 54.79, 49.16, 48.73, 36.30, 29.83, 29.54, 28.65, 14.26.
HRMS (ESI): calcd. for $C_{20}H_{25}N_2OClS$ 376.1463, found: 376.1466.
IR (cm^{-1}): 750.086 (S-S stretch), 814.284 (C-S stretch), 1095.441 (C-Cl stretch), 1521.126, 1570.666 (C-C stretch), 1682.036 (C=O stretch of amide), 2854.614, 2927.440, 2963.217 (C-H stretch).
TLC: R_f = 0.16 (90:10 petroleum ether:EtOAc).

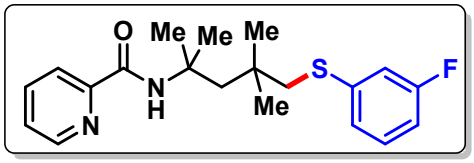


***N*-(2,4,4-trimethyl-5-((4-nitrophenyl)thio)pentan-2-yl)picolinamide (Scheme 2, entry 2d)**

Yield: 79%

Nature: Yellow Liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.1 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.11 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.84 (td, *J* = 7.7, 1.6 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.20 (d, *J* = 9.0 Hz, 2H), 3.10 (s, 2H), 2.12 (s, 2H), 1.58 (s, 6H), 1.20 (s, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.17, 150.48, 148.97, 147.61, 144.77, 137.99, 126.24, 126.20, 123.83, 122.15, 54.67, 49.19, 46.15, 36.04, 29.72, 28.84.

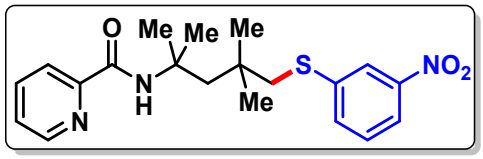
HRMS (ESI): calcd. for $C_{20}H_{25}N_3O_3S$ 387.1651, found: 387.1653.
IR (cm^{-1}): 742.521 (S-S stretch), 852.695 (C-S stretch), , 1335.459, 1510.885 (N-O stretch), 1578.333 (C-C stretch), 1677.052 (C=O stretch of amide), 2923.738, 2962.440 (C-H stretch), 3369.730 (N-H stretch).
TLC: R_f = 0.26 (90:10 petroleum ether:EtOAc).



***N*-(5-((3-fluorophenyl)thio)-2,4,4-trimethylpentan-2-yl)picolinamide (Scheme 2, entry 2e)**

Yield: 74%

Nature: Colourless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.4 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 2H), 7.86 (td, *J* = 7.7, 1.4 Hz, 1H), 7.41 (dd, *J* = 6.6, 5.0 Hz, 1H), 7.16 – 7.11 (m, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.93 – 6.88 (m, 1H), 6.77 (td, *J* = 8.3, 2.2 Hz, 1H), 3.02 (s, 2H), 2.07 (s, 2H), 1.58 (s, 6H), 1.16 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.12, 162.82, 161.66, 150.34, 147.28, 140.96, 138.27, 130.06, 129.98, 126.17, 123.83, 122.39, 115.02, 114.79, 112.32, 112.11, 54.86, 49.20, 47.74, 36.18, 29.55, 28.75.
^{19}F NMR (471 MHz, $CDCl_3$) δ -112.56.
HRMS (ESI): calcd. for $C_{20}H_{25}N_2OSFNa$: 383.1760, found: 383.1765.
IR (cm^{-1}): 749.768 (S-S stretch), 883.380 (C-S stretch), 1367.595 (C-F stretch), 1523.762, 1578.342 (C-C stretch), 1678.401 (C=O stretch in amide), 2927.690, 2964.531 (C-H stretch), 3375.439 (N-H stretch).
TLC: R_f = 0.15 (90:10 petroleum ether:EtOAc).

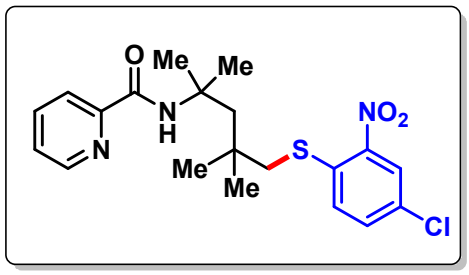


***N*-(2,4,4-trimethyl-5-((3-nitrophenyl)thio)pentan-2-yl)picolinamide (Scheme 2, entry 2f)**

Yield: 73%

Nature: Colourless liquid
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.1 Hz, 1H), 8.17 – 8.11 (m, 2H), 8.04 (t, *J* = 2.0 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.50 (dd, *J* = 4.8, 3.8 Hz, 1H), 7.40 – 7.29 (m, 2H), 3.07 (s, 2H), 2.10 (s, 2H), 1.58 (s, 6H), 1.18 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.50, 150.73, 147.93, 141.51, 137.54, 133.77, 129.40, 126.02, 122.30, 121.85, 120.08, 115.46, 54.57, 49.03, 47.86, 36.25, 32.07, 29.63, 28.72, 22.84, 14.26
HRMS (ESI): calcd. for $C_{20}H_{25}N_3O_3SNa$: 410.1511, found: 410.1509.

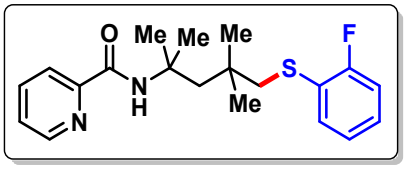
IR (cm^{-1}): 748.953 (S-S stretch), 799.253 (C-S stretch), 1348.632, 1526.987 (N-O stretch), 1676.055 (C=O stretch in amide), 2855.265, 2926.082 (C-H stretch).
TLC: R_f = 0.22 (90:10 petroleum ether:EtOAc).



N-(5-((4-chloro-2-nitrophenyl)thio)-2,4,4-trimethylpentan-2-yl)picolinamide (Scheme 2, entry 2g)

Yield: 76%

Nature: Colourless liquid
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.42 (m, 1H), 8.14 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.10 (d, *J* = 2.3 Hz, 2H), 7.84 (td, *J* = 7.5, 1.5 Hz, 1H), 7.40 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.24 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.00 (s, 2H), 2.14 (s, 2H), 1.58 (s, 6H), 1.24 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.43, 150.73, 147.94, 146.62, 137.61, 137.26, 133.27, 129.98, 128.15, 126.07, 125.87, 121.84, 54.62, 49.70, 46.51, 35.91, 29.73, 29.05.
HRMS (ESI): calcd. for $C_{20}H_{24}N_3O_3SCl$: 421.1232, found: 421.1235.
IR (cm^{-1}): 742.521 (S-S stretch), 852.695 (C-S stretch), 951.880 (C-Cl stretch), 1335.459, 1510.885 (N-O stretch), 1677.052 (C=O stretch in amide), 2923.738, 2962.440 (C-H stretch), 3369.730 (N-H stretch).
TLC: R_f = 0.22 (90:10 petroleum ether:EtOAc).

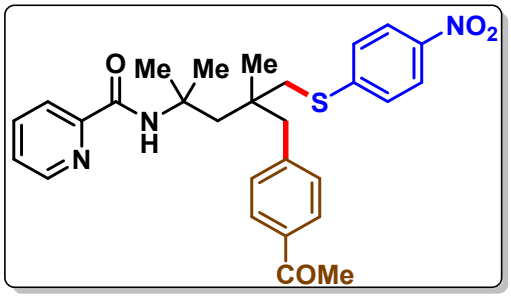


***N*-(5-((2-fluorophenyl)thio)-2,4,4-trimethylpentan-2-yl)picolinamide (Scheme 2, entry 2h)**

Yield: 74%

Nature: Yellow liquid
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.4 Hz, 1H), 8.18 – 8.08 (m, 2H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.30 – 7.26 (m, 1H), 7.13 (q, *J* = 6.4, 5.9 Hz, 1H), 6.98 (q, *J* = 7.6, 6.7 Hz, 2H), 2.99 (s, 2H), 2.07 (s, 2H), 1.57 (s, 6H), 1.16 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.41, 162.21, 160.26, 150.84, 147.93, 137.50, 131.47, 127.77, 127.70, 125.96, 125.21, 125.08, 124.47, 124.44, 121.82, 115.67, 115.49, 54.63, 49.23, 48.25, 36.27, 29.42, 28.39.

^{19}F NMR (471 MHz, $CDCl_3$) δ -109.54.
HRMS (ESI): calcd. for $C_{20}H_{25}N_2OSF$: 360.1672, found: 360.1675.
TLC: R_f = 0.12 (90:10 petroleum ether:EtOAc).

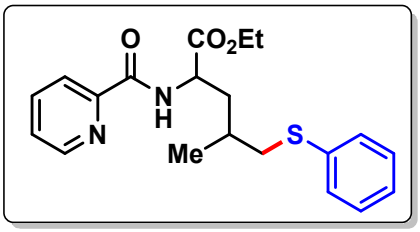


***N*-(4-(4-acetylbenzyl)-2,4-dimethyl-5-((4-nitrophenyl)thio)pentan-2-yl)picolinamide**

(Scheme 2, entry 2i)

Yield: 69%

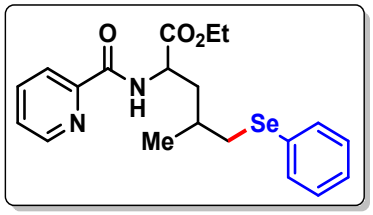
Nature: Yellow sticky liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 – 8.55 (m, 1H), 7.84 (d, *J* = 8.2 Hz, 4H), 7.78 (ddd, *J* = 7.7, 6.2, 1.7 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.31 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 4H), 3.69 (d, *J* = 11.4 Hz, 1H), 3.32 (d, *J* = 11.0 Hz, 1H), 2.79 (d, *J* = 13.0 Hz, 1H), 2.74 – 2.68 (m, 1H), 2.57 (s, 3H), 2.00 (d, *J* = 13.0 Hz, 1H), 1.75 (d, *J* = 5.9 Hz, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.01 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.00, 166.76, 156.22, 148.13, 147.13, 144.37, 144.08, 142.87, 137.08, 135.58, 130.49, 129.74, 128.27, 124.35, 123.04, 63.32, 61.08, 54.52, 46.28, 41.15, 28.28, 27.84, 26.69, 24.74.
HRMS (ESI): calcd. for $C_{28}H_{31}N_3NaO_4S$: 528.2034, found: 528.2037.
IR (cm^{-1}): 3315.473 (N-H stretch), 2929.424 (C-H stretch), 1736.154 (C=O stretch in ketones), 1680.960 (C=O stretch in amide), 1514.285, 1337.872 (N-O stretch), 803.925 (C-S stretch), 747.455 (S-S stretch).



Ethyl 4-methyl-5-(phenylthio)-2-(picolinamido)pentanoate (Scheme 4, entry 2'a)

Yield: 81%

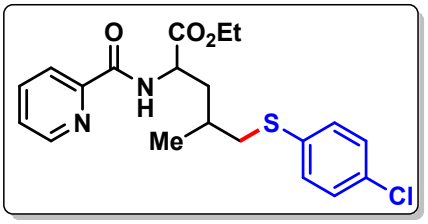
Physical state: Yellow liquid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.7 Hz, 1H), 8.43 (t, *J* = 9.8 Hz, 1H), 8.19 – 8.11 (m, 1H), 7.83 (td, *J* = 7.7, 1.4 Hz, 1H), 7.42 (dd, *J* = 6.9, 5.3 Hz, 1H), 7.28 (dd, *J* = 12.8, 6.0 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 7.0 Hz, 1H), 4.84 (p, *J* = 6.3 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.02 (dd, *J* = 12.9, 5.6 Hz, 1H), 2.84 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.17 (td, *J* = 13.3, 6.6 Hz, 1H), 1.92 (tt, *J* = 12.3, 6.2 Hz, 1H), 1.75 (dd, *J* = 14.3, 7.0 Hz, 1H), 1.23 – 1.18 (m, 3H), 1.13 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.36, 164.11, 149.39, 148.33, 137.38, 136.61, 129.45, 128.88, 126.47, 125.91, 122.39, 61.55, 50.63, 40.50, 38.90, 29.86, 19.62, 14.21.
HRMS (ESI): calcd. for $C_{20}H_{24}NaN_2O_3S$: 395.1401, found: 395.1400.
IR (cm^{-1}): 745.785 (S-S stretch), 818.652 (C-S stretch), 1677.530 (C=O stretch in amides), 1737.266 (C=O stretch of esters), 2925.128 (C-H stretch), 3059.492, 3381.789 (N-H stretch).
TLC: R_f = 0.13 (80:20 petroleum ether:EtOAc).



Ethyl 4-methyl-5-(phenylselanyl)-2-(picolinamido)pentanoate (Scheme 4, entry 2'b)

Yield: 82%

Nature: Yellowish liquid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.40 (dd, *J* = 15.5, 8.8 Hz, 1H), 8.21 – 8.10 (m, 1H), 7.85 (td, *J* = 7.7, 1.8 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.19 – 7.07 (m, 3H), 4.86 – 4.75 (m, 1H), 4.17 (pt, *J* = 7.7, 4.0 Hz, 2H), 3.04 (dd, *J* = 12.1, 5.3 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.15 (dt, *J* = 13.4, 6.5 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.83 – 1.69 (m, 1H), 1.25 (dt, *J* = 14.3, 7.1 Hz, 3H), 1.13 (dd, *J* = 6.5, 4.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.43, 164.11, 149.46, 148.36, 137.41, 132.80, 129.08, 129.05, 126.82, 126.49, 122.44, 61.58, 50.70, 39.58, 35.52, 30.58, 20.41, 14.28.
HRMS (ESI): calcd. for $C_{20}H_{24}NaN_2O_3Se$: 443.0848, found: 443.0845.
IR (cm^{-1}): 3365.542 (N-H stretch), 2810.012 (C-H stretch), 1736.305 (C=O stretch of ester), 1676.039 (C=O stretch in amide), 816.749 (C-Se stretch), 710.647 (Se-Se stretch).
TLC: R_f = 0.13 (80:20 petroleum ether:EtOAc).



Ethyl 5-((4-chlorophenyl)thio)-4-methyl-2-(picolinamido)pentanoate (Scheme 4, entry 2'c)

Yield: 71%

Nature: Yellowish semi solid.

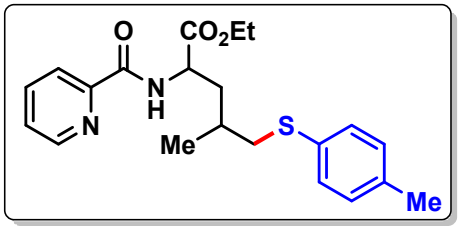
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.0 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 4.83 (dd, *J* = 14.6, 8.1 Hz, 1H), 4.24 – 4.14 (m, 2H), 3.08 – 3.01 (m, 1H), 2.85 – 2.77 (m, 1H), 2.18 – 2.11 (m, 1H), 1.89 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.77 (dd, *J* = 14.1, 7.3 Hz, 1H), 1.25 – 1.21 (m, 3H), 1.11 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.38, 164.16, 149.35, 148.40, 137.48, 135.11, 131.96, 130.98, 129.02, 126.58, 122.44, 61.66, 50.51, 40.67, 38.87, 29.70, 19.69, 14.25.

HRMS (ESI): calcd. for $C_{20}H_{23}ClN_2NaO_3S$: 429.1010, found: 429.1011.

IR (cm^{-1}): 750.079 (S-S stretch), 816.779 (C-S stretch), 873.106 (C-Cl stretch), 1678.016 (C=O stretch of amide), 1738.328 (C=O stretch of ester), 2927.051, 2960.057 (C-H stretch), 3379.676 (N-H stretch).

TLC: R_f = 0.12 (80:20 petroleum ether:EtOAc).



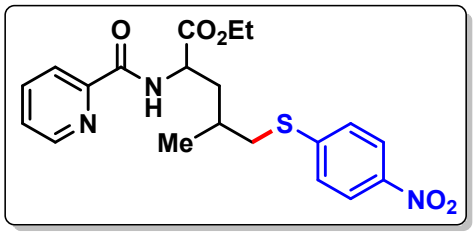
Ethyl 4-methyl-2-(picolinamido)-5-(p-tolylthio)pentanoate (Scheme 4, entry 2'd)

Yield: 77%

Nature: Yellow semi solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dt, *J* = 4.9, 1.2 Hz, 1H), 8.42 (d, *J* = 8.9 Hz, 1H), 8.16 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.84 (td, *J* = 7.7, 1.8 Hz, 1H), 7.43 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H), 7.23 – 7.17 (m, 2H), 6.98 (d, *J* = 7.9 Hz, 2H), 4.81 (td, *J* = 8.2, 6.5 Hz, 1H), 4.16 (qd, *J* = 7.1, 2.5 Hz, 2H), 2.97 (dd, *J* = 13.0, 5.6 Hz, 1H), 2.79 (dd, *J* = 12.9, 7.3 Hz, 1H), 2.23 (s, 3H), 2.22 – 2.12 (m, 1H), 1.88 (p, *J* = 6.7 Hz, 1H), 1.74 (dt, *J* = 13.7, 7.7 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H).

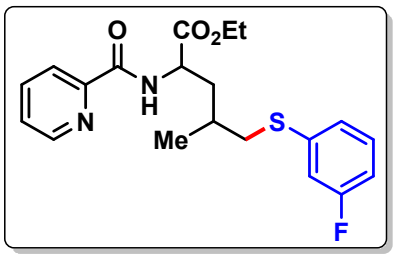
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.40, 164.05, 149.40, 148.31, 137.36, 136.05, 132.71, 130.60, 130.31, 129.66, 129.64, 126.43, 122.37, 61.53, 50.61, 41.26, 38.83, 29.84, 21.06, 19.58, 14.21.
HRMS (ESI): calcd. for $C_{21}H_{26}N_2O_3S$: 387.1737, found: 387.1737.
IR (cm^{-1}): 750.047 (S-S stretch), 805.238 (C-S stretch), 1677.698 (C=O stretch of amide), 1738.032 (C=O stretch of esters), 2855.561, 2925.887, 2959.631 (C-H stretch), 3383.448 (N-H stretch).
TLC: R_f = 0.12 (80:20 petroleum ether:EtOAc).



Ethyl 4-methyl-5-((4-nitrophenyl)thio)-2-(picolinamido)pentanoate (Scheme 4, entry 2'e)

Yield: 67%

Nature: Sticky yellow liquid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.4 Hz, 1H), 8.48 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.87 (td, *J* = 7.7, 1.2 Hz, 1H), 7.45 (dd, *J* = 6.7, 5.0 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 4.90 (tt, *J* = 13.4, 6.8 Hz, 1H), 4.20 (tt, *J* = 18.0, 9.0 Hz, 2H), 3.22 (dd, *J* = 12.9, 5.0 Hz, 1H), 2.90 (dd, *J* = 12.9, 7.9 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.03 (dt, *J* = 12.5, 5.4 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.28 – 1.25 (m, 3H), 1.15 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.22, 164.31, 149.23, 148.44, 147.47, 145.09, 137.61, 126.83, 126.73, 123.97, 122.48, 61.83, 50.40, 39.09, 38.46, 29.83, 29.39, 19.94, 14.29.
HRMS (ESI): calcd. for $C_{20}H_{23}N_3O_5S$: 418.1431, found: 417.1437.
IR (cm^{-1}): 3379.824 (N-H stretch), 2925.794 (C-H stretch), 1737.498 (C=O stretch of ester), 1676.674 (C=O stretch in amide), 1510.416, 1336.603 (N-O stretch), 853.235 (C-S stretch), 743.085 (S-S stretch).
TLC: R_f = 0.28 (80:20 petroleum ether:EtOAc).



Ethyl 5-((3-fluorophenyl)thio)-4-methyl-2-(picolinamido)pentanoate (Scheme 4, entry 2'f)

Yield: 83%

Nature: Colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (qd, *J* = 3.6, 0.9 Hz, 1H), 8.46 (d, *J* = 8.3 Hz, 1H), 8.17 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.46 – 7.42 (m, 1H), 7.13 (tt, *J* = 5.8, 4.4 Hz, 1H), 7.07 – 7.04 (m, 1H), 7.01 – 6.98 (m, 1H), 6.80 – 6.76 (m, 1H), 4.85 (dq, *J* = 8.3, 6.3 Hz, 1H), 4.25 – 4.17 (m, 2H), 3.04 (dt, *J* = 13.1, 6.6 Hz, 1H), 2.87 (dt, *J* = 12.9, 6.3 Hz, 1H), 2.22 – 2.15 (m, 1H), 2.02 – 1.91 (m, 1H), 1.77 (ddd, *J* = 14.0, 8.0, 7.1 Hz, 1H), 1.27 – 1.21 (m, 3H), 1.14 (t, *J* = 6.9 Hz, 3H).

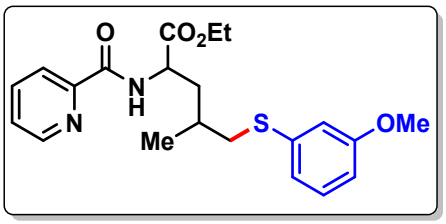
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.35, 164.18, 163.88, 161.91, 149.40, 148.38, 139.34, 139.28, 137.44, 130.18, 130.11, 126.53, 124.46, 124.44, 122.46, 115.77, 115.58, 112.80, 112.63, 61.66, 50.59, 40.05, 39.03, 29.81, 19.72, 14.26.

^{19}F NMR (471 MHz, $CDCl_3$) δ -112.46.

HRMS (ESI): calcd. for $C_{20}H_{23}N_2O_3SF$: 391.1483, found: 391.1486.

IR (cm^{-1}): 750.465 (S-S stretch), 819.145 (C-S stretch), 1349.945 (C-F stretch), 1677.948 (C=O stretch of amide), 1738.236 (C=O stretch of esters), 2926.900, 2961.562 (C-H stretch), 3385.895 (N-H stretch).

TLC: R_f = 0.08 (80:20 petroleum ether:EtOAc).



Ethyl 5-((3-methoxyphenyl)thio)-4-methyl-2-(picolinamido)pentanoate (Scheme 4, entry 2'g)

Yield: 75%

Nature: Yellow liquid

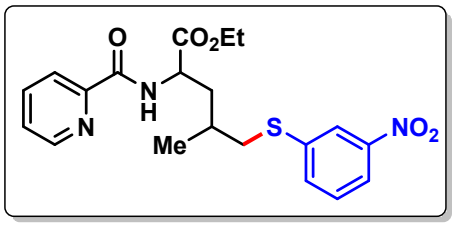
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.5 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 8.15 (dd, *J* = 14.1, 7.8 Hz, 1H), 7.84 (ddd, *J* = 7.7, 5.9, 1.6 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.11 – 7.06 (m, 1H), 6.86 (ddd, *J* = 9.8, 9.1, 4.8 Hz, 2H), 6.64 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.83 (dt, *J* = 15.0, 7.2 Hz, 1H), 4.17 (ddt, *J* = 14.1, 7.0, 3.6 Hz, 2H), 3.76 (s, 3H), 3.01 (dd, *J* = 12.9, 5.7 Hz, 1H), 2.90 – 2.84 (m, 1H), 2.21 – 2.15 (m, 1H), 1.96 (dt, *J* = 12.1, 6.2 Hz, 1H), 1.76 (dt, *J* = 14.0, 7.6 Hz, 1H), 1.23 (d, *J*= 7.1 Hz, 3H), 1.15 – 1.13 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.40, 164.13, 159.85, 149.43, 148.36, 138.02, 137.40, 129.73, 126.48, 122.42, 121.47, 114.68, 111.81, 61.60, 55.32, 50.66, 40.43, 38.98, 29.96, 19.66, 14.25.

HRMS (ESI): calcd. for $C_{21}H_{26}N_2O_4S$: 441.1245, found: 441.1244.

IR (cm^{-1}): 750.139 (S-S stretch), 819.138 (C-S stretch), 1677.707 (C=O stretch of amide), 1737.689 (C=O stretch of ester), 2854.880 (C-O stretch of methoxy group), 2926.899 (C-H stretch), 3377.320 (N-H stretch).

TLC: R_f = 0.2 (80:20 petroleum ether:EtOAc).



Ethyl 4-methyl-5-((3-nitrophenyl)thio)-2-(picolinamido)pentanoate (Scheme 4, entry 2'h)

Yield: 73%

Nature: Sticky yellow liquid

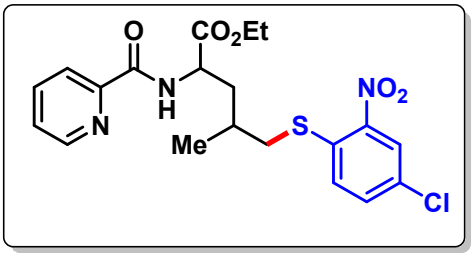
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.2 Hz, 1H), 8.46 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.10 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.85 (td, *J* = 7.8, 1.3 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 6.7, 5.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 4.86 (dt, *J* = 10.6, 4.2 Hz, 1H), 4.20 (tt, *J* = 6.1, 3.2 Hz, 2H), 3.15 (dd, *J* = 12.5, 5.1 Hz, 1H), 2.98 – 2.92 (m, 1H), 2.20 – 2.12 (m, 1H), 2.02 – 1.96 (m, 1H), 1.81 (dd, *J* = 14.2, 7.9 Hz, 1H), 1.26 – 1.24 (m, 3H), 1.16 (t, *J* = 7.7 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.25, 164.21, 149.30, 148.56, 148.40, 140.02, 137.49, 134.34, 129.57, 126.60, 123.08, 122.44, 120.49, 61.76, 50.50, 39.93, 39.01, 29.78, 19.84, 14.28.

HRMS (ESI): calcd. for $C_{20}H_{23}N_3O_5S$: 418.1431, found: 418.1431.

IR (cm^{-1}): 748.761 (S-S stretch), 801.499 (C-S stretch), 1348.133, 1521.264 (N-O stretch), 1676.024 (C=O stretch of amide), 1737.206 (C=O stretch of esters), 2926.411, 2961.990 (C-H stretch), 3375.699 (N-H stretch).

TLC: R_f = 0.26 (80:20 petroleum ether:EtOAc).



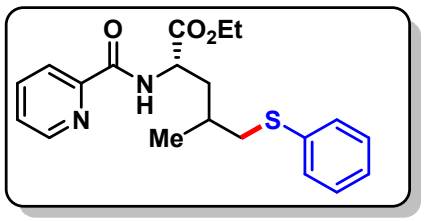
Ethyl 5-((5-chloro-2-nitrophenyl)thio)-4-methyl-2-(picolinamido)pentanoate (Scheme 4, entry 2'i)

Yield: 67%

Nature: Yellowish liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 8.50 (d, *J* = 8.9 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.12 (d, *J* = 1.8 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (dd, *J* = 7.6, 4.8 Hz, 1H),

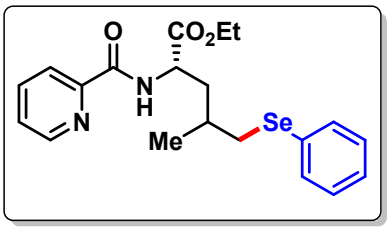
7.37 (d, J = 2.0 Hz, 2H), 4.90 (td, J = 8.9, 5.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.18 (dd, J = 12.3, 4.7 Hz, 1H), 2.84 (dd, J = 12.3, 8.0 Hz, 1H), 2.17 (ddd, J = 13.6, 7.6, 5.2 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.87 (ddd, J = 14.2, 8.9, 5.7 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.16, 164.30, 149.21, 148.46, 146.66, 137.57, 136.25, 133.60, 130.33, 128.41, 126.69, 125.94, 122.44, 61.89, 50.34, 39.45, 38.77, 29.07, 20.12, 14.32.
HRMS (ESI): calcd. for $C_{20}H_{23}ClN_3O_5S$: 452.1041, found: 452.1038.
TLC: R_f = 0.18 (80:20 petroleum ether:EtOAc).



Ethyl (2S)-4-methyl-5-(phenylthio)-2-(picolinamido)pentanoate (Scheme 4, entry 2'j)

Yield: 84%

Nature: Orangish liquid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (pdd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.42 (dd, J = 24.2, 9.4 Hz, 1H), 8.18 – 8.11 (m, 1H), 7.84 (tdd, J = 7.6, 4.0, 1.6 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.32 – 7.27 (m, 2H), 7.19 – 7.13 (m, 2H), 7.11 – 7.06 (m, 1H), 4.87 – 4.78 (m, 1H), 4.21 – 4.11 (m, 2H), 3.07 – 3.00 (m, 1H), 2.86 (ddd, J = 18.3, 10.7, 6.8 Hz, 1H), 2.22 – 2.16 (m, 1H), 1.94 (dd, J = 13.2, 6.5 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.23 (dd, J = 8.7, 5.6 Hz, 3H), 1.14 – 1.13 (m, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.39, 164.12, 149.41, 148.35, 137.40, 136.63, 129.47, 128.90, 126.48, 125.94, 122.42, 61.59, 50.64, 40.53, 38.94, 29.88, 19.66, 14.25.
HRMS (ESI): calcd. for $C_{20}H_{24}NaN_2O_3S$: 395.1401, found: 395.1407.
IR (cm^{-1}): 742.431 (S-S stretch), 819.143 (C-S stretch), 1676.915 (C=O stretch in amides), 1736.812 (C=O stretch of esters), 2925.524, 2959.313 (C-H stretch), 3058.772, 3379.311 (N-H stretch).
TLC: R_f = 0.16 (80:20 petroleum ether:EtOAc).

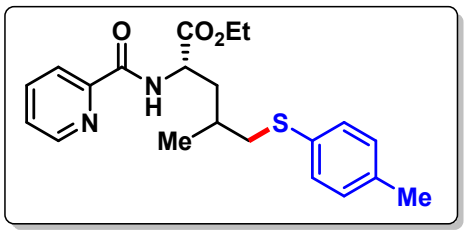


Ethyl (2S)-4-methyl-5-(phenylselanyl)-2-(picolinamido)pentanoate (Scheme 4, entry 2'k)

Yield: 76%

Nature: Yellow liquid.

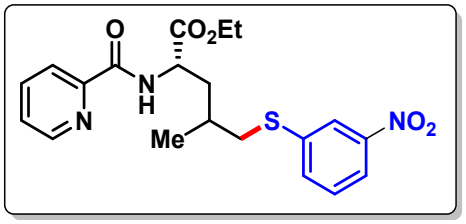
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 6.8, 4.7, 2.5 Hz, 1H), 8.40 (t, *J* = 12.3 Hz, 1H), 8.15 (dd, *J* = 12.7, 7.8 Hz, 1H), 7.85 (ddd, *J* = 7.4, 4.6, 1.5 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.17 – 7.11 (m, 3H), 4.84 – 4.76 (m, 1H), 4.22 – 4.15 (m, 2H), 3.04 (dd, *J* = 12.1, 5.3 Hz, 1H), 2.91 – 2.85 (m, 1H), 2.15 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.97 – 1.90 (m, 1H), 1.80 – 1.73 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.13 – 1.11 (m, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.45, 164.14, 149.47, 148.37, 137.43, 132.81, 130.52, 129.09, 126.83, 126.50, 122.46, 61.59, 50.71, 39.57, 35.52, 30.58, 20.40, 14.27.
HRMS (ESI): calcd. for $C_{20}H_{24}NaN_2O_3Se$: 443.0848, found: 443.0851.
IR (cm^{-1}) 737.051 (Se-Se stretch), 818.844 (C-Se stretch), 1677.162 (C=O stretch in amide), 1737.243 (C=O stretch of ester), 2927.452, 2960.027 (C-H stretch), 3381.717 (N-H stretch).
TLC: R_f = 0.15 (80:20 petroleum ether:EtOAc).



Ethyl (2S)-4-methyl-2-(picolinamido)-5-(p-tolylthio)pentanoate (Scheme 4, entry 2'l)

Yield: 73%

Nature: Yellow sticky liquid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 9.3 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.16 (dd, *J* = 15.8, 6.7 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.44 (dd, *J* = 6.6, 4.9 Hz, 1H), 7.22 (dd, *J* = 6.9, 4.9 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 4.82 (dd, *J* = 15.1, 8.1 Hz, 1H), 4.22 – 4.15 (m, 2H), 2.97 (dd, *J* = 12.9, 5.7 Hz, 1H), 2.80 (dd, *J* = 13.0, 7.3 Hz, 1H), 2.25 (s, 3H), 1.90 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.45, 164.18, 149.44, 148.38, 137.43, 130.39, 129.71, 126.49, 122.46, 120.54, 115.47, 61.60, 50.72, 41.39, 38.88, 29.94, 21.08, 19.60, 14.23.
HRMS (ESI): calcd. for $C_{21}H_{26}NaN_2O_3S$: 410.1786, found: 410.1787.
IR (cm^{-1}): 748.903 (S-S stretch), 804.001 (C-S stretch), 1677.835 (C=O stretch in amide), 1736.996 (C=O stretch of esters), 2909.504, 2982.025 (C-H stretch), 3383.235 (N-H stretch).
TLC: R_f = 0.15 (80:20 petroleum ether:EtOAc).



Ethyl (2S)-4-methyl-5-((3-nitrophenyl)thio)-2-(picolinamido)pentanoate (Scheme 4, entry 2'm)

Yield: 79%

Nature: Yellow liquid.

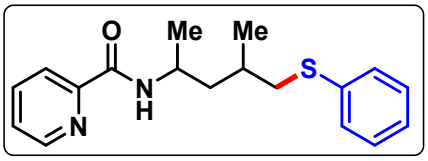
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.1 Hz, 1H), 8.43 (dd, *J* = 31.5, 8.3 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 17.1 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 22.7, 7.7 Hz, 1H), 7.43 (dd, *J* = 6.6, 5.2 Hz, 1H), 7.33 (dd, *J* = 14.1, 6.1 Hz, 1H), 4.85 (dd, *J* = 14.4, 8.4 Hz, 1H), 4.20 (dd, *J* = 14.4, 7.2 Hz, 2H), 3.15 (dd, *J* = 12.7, 5.3 Hz, 1H), 2.99 – 2.93 (m, 1H), 2.21 – 2.15 (m, 1H), 2.00 (dt, *J* = 12.3, 6.2 Hz, 1H), 1.85 – 1.78 (m, 1H), 1.25 (dd, *J* = 8.6, 5.2 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.25, 164.22, 149.32, 148.58, 148.40, 140.03, 137.50, 134.36, 129.57, 126.60, 123.10, 122.45, 120.49, 61.75, 50.52, 39.96, 39.02, 29.80, 19.84, 14.28.

HRMS (ESI): calcd. for $C_{20}H_{23}N_3O_5S$: 418.1431, found: 418.1436.

IR (cm^{-1}): 749.242 (S-S stretch), 800.889 (C-S stretch), 1347.761, 1524.225 (N-O stretch), 1676.674 (C=O stretch in amide), 1736.872 (C=O stretch of esters), 2927.357, 2961.162 (C-H stretch), 3375.860 (N-H stretch).

TLC: R_f = 0.1 (70:30 petroleum ether:EtOAc).



N-(4-methyl-5-(phenylthio)pentan-2-yl)picolinamide (Scheme 4, entry 2'n)

Yield: 78%

Nature: Orangish liquid**.**

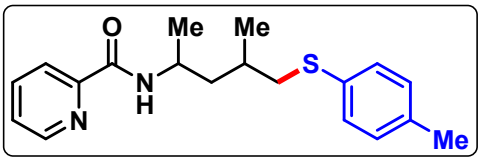
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 4.7, 0.7 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.85 (ddd, *J* = 7.7, 6.0, 3.8 Hz, 2H), 7.42 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.19 (dd, *J* = 10.5, 4.8 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.33 – 4.25 (m, 1H), 3.02 (dd, *J* = 12.8, 5.6 Hz, 1H), 2.90 – 2.84 (m, 1H), 1.88 (td, *J* = 13.4, 6.8 Hz, 1H), 1.74 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.61 – 1.55 (m, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.11, 149.79, 147.62, 138.06, 137.08, 129.22, 128.92, 126.34, 125.80, 122.74, 43.43, 43.26, 40.80, 30.25, 21.23, 19.74.

HRMS (ESI): calcd. for $C_{18}H_{22}N_2OSK$: 353.1077, found: 353.1074.

IR (cm^{-1}): 748.035 (S-S stretch), 805.137 (C-S stretch), 1570.703 (C-C stretch), 1676.407 (C=O stretch in amide), 2926.442, 3059.776 (C-H stretch), 3388.172 (N-H stretch).

TLC: R_f = 0.12 (80:20 petroleum ether:EtOAc).



N-(4-methyl-5-(phenylthio)pentan-2-yl)picolinamide (Scheme 4, entry 2'o)

Yield: 71%

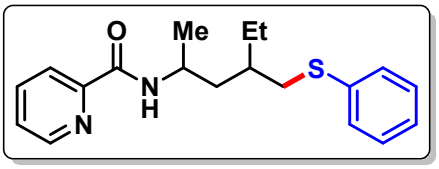
Nature: Orangish liquid**.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.7 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.44 – 7.39 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 4.31 – 4.22 (m, 1H), 2.96 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.80 (dd, *J* = 12.8, 7.1 Hz, 1H), 2.25 (s, 3H), 1.83 (td, *J* = 13.2, 6.6 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.59 – 1.50 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.43, 150.04, 148.00, 137.48, 135.88, 133.12, 129.99, 129.66, 126.15, 122.32, 43.23, 43.18, 41.50, 30.19, 21.20, 21.05, 19.65.

IR (cm^{-1}): 737.051 (S-S stretch), 803.018 (C-S stretch), 1513.107, 1578.977 (C-C stretch), 1677.162 (C=O stretch in amide), 2927.452, 2960.027 (C-H stretch), 3381.717 (N-H stretch).

TLC: R_f = 0.12 (80:20 petroleum ether:EtOAc).



***N*-(4-((phenylthio)methyl)hexan-2-yl)picolinamide (Scheme 4, entry 2'p)**

Yield: 85%

Nature: Yellow liquid**.**

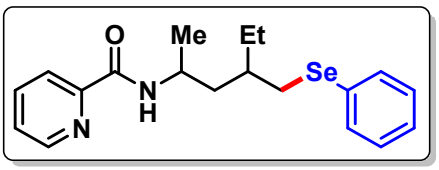
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.96 – 7.72 (m, 2H), 7.40 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 4.28 (dh, *J* = 14.1, 6.8 Hz, 1H), 3.06 (dd, *J* = 12.6, 5.3 Hz, 1H), 2.99 (dd, *J* = 12.6, 5.2 Hz, 1H), 1.75 – 1.59 (m, 3H), 1.51 (dp, *J* = 14.0, 7.0 Hz, 2H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.59, 150.11, 148.06, 137.44, 137.23, 129.21, 128.88, 126.14, 125.74, 122.31, 43.11, 40.33, 37.63, 36.09, 25.85, 21.63, 10.80.

LRMS (ESI): calcd. for $C_{19}H_{25}N_2OS$: 329.1643, found: 329.1888.

IR (cm^{-1}): 743.241 (S-S stretch), 818.582 (C-S stretch), 1518.460, 1570.774, 1591.090 (C-C stretch), 1670.872 (C=O stretch in amide), 2926.445, 2962.615 (C-H stretch), 3375.578 (N-H stretch).

TLC: R_f = 0.11 (70:30 petroleum ether:EtOAc).



***N*-(4-((phenylselanyl)methyl)hexan-2-yl)picolinamide (Scheme 4, entry 2'q)**

Yield: 87%

Nature: Orangish liquid**.**

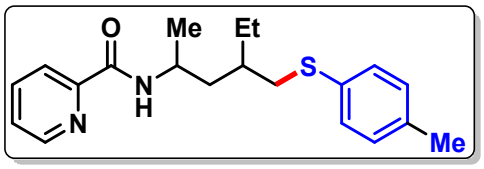
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.50 (m, 1H), 8.17 (dd, *J* = 11.9, 7.2 Hz, 1H), 7.83 (ddd, *J* = 7.7, 2.9, 1.1 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.42 – 7.39 (m, 1H), 7.21 – 7.10 (m, 3H), 4.29 – 4.20 (m, 1H), 3.11 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.06 – 3.01 (m, 1H), 1.71 – 1.62 (m, 2H), 1.48 (tt, *J* = 13.5, 6.9 Hz, 2H), 1.20 (d, *J* = 22.7, 6.5 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.60, 150.15, 148.08, 137.44, 132.74, 130.89, 129.06, 126.71, 126.14, 122.33, 43.12, 41.08, 36.76, 33.24, 26.64, 21.62, 10.87.

LRMS (ESI): calcd. for $C_{19}H_{25}N_2OSe$: 377.1054, found: 377.0717.

IR (cm^{-1}): 735.675 (Se-Se stretch), 818.684 (C-Se stretch), 1516.818, 1570.195 (C-C stretch), 1670.603 (C=O stretch of amide), 2874.339, 2925.739, 2964.234 (C-H stretch), 3374.347 (N-H stretch).

TLC: R_f = 0.11 (70:30 petroleum ether:EtOAc).



***N*-(4-((p-tolylthio)methyl)hexan-2-yl)picolinamide (Scheme 4, entry 2'r)**

Yield: 86%

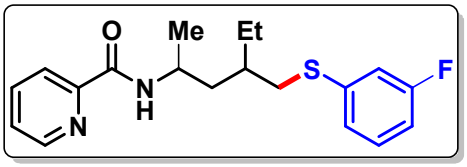
Nature: Yellow liquid**.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.5 Hz, 1H), 8.23 (dd, *J* = 14.7, 7.8 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.50 – 7.44 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.32 (dt, *J* = 14.2, 4.3 Hz, 1H), 3.13 – 3.06 (m, 1H), 3.04 – 2.97 (m, 1H), 2.32 (s, 3H), 1.78 – 1.68 (m, 3H), 1.64 – 1.55 (m, 2H), 1.27 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.58, 150.16, 148.07, 137.41, 135.84, 133.37, 130.01, 129.67, 126.11, 122.30, 43.13, 40.26, 38.40, 36.12, 25.77, 21.59, 21.06, 10.75.

LRMS (ESI): calcd. for $C_{20}H_{27}N_2OS$: 343.1799, found: 343.1738.

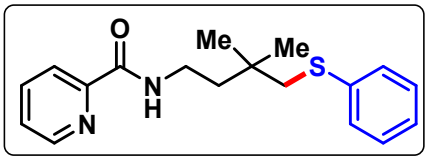
IR (cm^{-1}): 749.339 (S-S stretch), 802.442 (C-S stretch), 1516.425, 1569.833, 1591.522 (C-C stretch), 1672.439 (C=O stretch of amide), 2923.821, 2963.791 (C-H stretch), 3377.296 (N-H stretch).
TLC: R_f = 0.1 (70:30 petroleum ether:EtOAc).



***N*-(4-(((3-fluorophenyl)thio)methyl)hexan-2-yl)picolinamide (Scheme 4, entry 2's)**

Yield: 82%

Nature: Yellow liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.6 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.85 (dt, *J* = 7.8, 6.0 Hz, 2H), 7.43 – 7.39 (m, 1H), 7.15 (dt, *J* = 7.1, 5.7 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.03 – 6.99 (m, 1H), 6.80 – 6.75 (m, 1H), 4.30 (dt, J = 15.0, 7.3 Hz, 1H), 3.03 (tt, *J* = 12.4, 6.4 Hz, 2H), 1.75 (dt, *J* = 11.9, 6.1 Hz, 1H), 1.70 – 1.65 (m, 1H), 1.51 (tt, *J* = 13.9, 7.1 Hz, 2H), 1.23 (dd, *J* = 9.8, 6.7 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.14, 163.67, 161.68, 150.09, 148.10, 139.94, 139.87, 137.47, 130.15, 130.06, 126.19, 124.15, 124.12, 122.37, 115.48, 115.25, 112.58, 112.37, 43.03, 40.42, 37.19, 35.97, 25.92, 21.70, 10.82.
^{19}F NMR (471 MHz, $CDCl_3$) δ -112.55.
LRMS (ESI): calcd. for $C_{19}H_{24}N_2OFS$: 347.1549, found: 347.1472.
IR (cm^{-1}): 748.903 (S-S stretch), 804.001 (C-S stretch), 1374.489 (C-F stretch), 1511.905, 1570.618, 1592.366, 1677.835 (C=O stretch of amide), 2909.504, 2982.025 (C-H stretch), 3383.235 (N-H stretch).
TLC: R_f = 0.1 (70:30 petroleum ether:EtOAc).

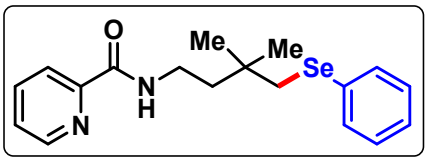


***N*-(3,3-dimethyl-4-(phenylthio)butyl)picolinamide (Scheme 4, entry 2't)**

Yield: 74%

Nature: Orangish liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.7 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.00 (s, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.35 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 3.53 – 3.45 (m, 2H), 2.96 (s, 2H), 1.78 – 1.71 (m, 2H), 1.11 (s, 6H).

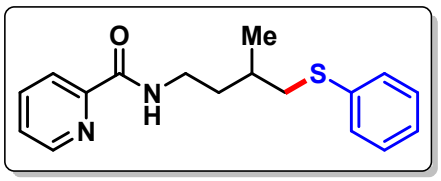
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.36, 150.09, 148.16, 137.96, 137.48, 129.40, 128.98, 126.20, 125.91, 122.28, 47.10, 40.45, 35.77, 34.65, 27.17, 14.26.
HRMS (ESI): calcd. for $C_{18}H_{22}N_2OSK$: 353.1076, found: 353.1084.
IR (cm^{-1}): 748.035 (S-S stretch), 805.137 (C-S stretch), 1527.205, 1570.703 (C-C stretch), 1676.407 (C=O stretch of amide), 2855.020, 2926.442 (C-H stretch), 3388.172 (N-H stretch).
TLC: R_f = 0.12 (70:30 petroleum ether:EtOAc).



***N*-(3,3-dimethyl-4-(phenylselanyl)butyl)picolinamide (Scheme 4, entry 2'u)**

Yield: 76%

Nature: Orangish liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.47 (m, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.96 (s, 1H), 7.83 (td, *J* = 7.7, 1.8 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.41 (ddd, *J* = 7.7, 4.8, 1.3 Hz, 1H), 7.21 (td, *J* = 7.1, 6.5, 3.4 Hz, 2H), 3.51 – 3.38 (m, 2H), 2.99 (s, 2H), 1.76 – 1.65 (m, 2H), 1.09 (s, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.28, 150.03, 148.12, 137.45, 132.84, 131.53, 129.13, 126.84, 126.18, 122.24, 43.06, 40.96, 35.83, 34.62, 27.46.
HRMS (ESI): calcd. for $C_{18}H_{22}N_2OSeK$: 401.0531, found: 401.0561.
IR (cm^{-1}): 735.312 (Se-Se stretch), 818.177 (C-Se stretch), 1523.829, 1578.584 (C-C stretch), 1672.528 (C=O stretch of amide), 2925.369, 2958.594 (C-H stretch), 3388.100 (N-H stretch).
TLC: R_f = 0.12 (70:30 petroleum ether:EtOAc).

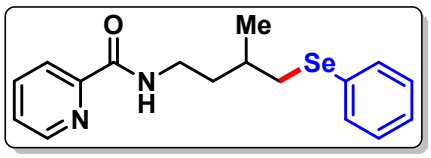


***N*-(3-methyl-4-(phenylthio)butyl)picolinamide (Scheme 4, entry 2'v)**

Yield: 86 %

Nature: Orange liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.5 Hz, 1H), 7.42 (dd, *J* = 6.5, 4.8 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 2H), 7.22 (dd, *J* = 10.5, 4.8 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 3.58 – 3.47 (m, 2H), 2.95 (dd, *J* = 12.7, 5.9 Hz, 1H), 2.84 (dd, *J* = 12.7, 6.9 Hz, 1H), 1.94 – 1.85 (m, 2H), 1.62 – 1.54 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.42, 149.92, 148.10, 137.54, 136.96, 129.34, 128.97, 125.95, 122.34, 115.52, 41.17, 37.40, 35.80, 30.93, 19.48.

HRMS (ESI): calcd. for $C_{17}H_{20}N_2OSNa$: 323.1187, found: 323.1189.
IR (cm^{-1}): 745.859 (S-S stretch), 818.085 (C-S stretch), 1527.392, 1591.346 (C-C stretch), 1666.693 (C=O stretch of amide), 2925.968, 2957.992 (C-H stretch), 3380.873 (N-H stretch).
TLC: R_f = 0.13 (80:20 petroleum ether:EtOAc).

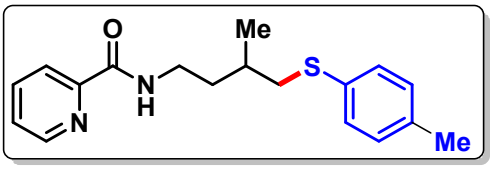


***N*-(3-methyl-4-(phenylselanyl)butyl)picolinamide (Scheme 4, entry 2'w)**

Yield: 81 %

Nature: Brownish liquid**.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (t, *J* = 4.8 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 52.5 Hz, 1H), 7.84 (td, *J* = 7.7, 1.6 Hz, 1H), 7.47 (ddd, *J* = 8.9, 5.6, 2.3 Hz, 2H), 7.43 – 7.40 (m, 1H), 7.22 – 7.17 (m, 3H), 3.57 – 3.44 (m, 2H), 3.00 – 2.95 (m, 1H), 2.87 (dd, *J* = 12.0, 6.8 Hz, 1H), 1.92 – 1.83 (m, 2H), 1.60 – 1.55 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.38, 150.01, 148.12, 137.48, 132.74, 130.77, 129.13, 126.84, 126.22, 122.31, 37.41, 36.40, 36.21, 31.61, 20.14.
HRMS (ESI): calcd. for $C_{17}H_{20}N_2OSeNa$: 371.0626, found: 371.0634.
IR (cm^{-1}): 735.987 (Se-Se stretch), 819.034 (C-Se stretch), 1524.381, 1569.340 (C-C stretch), 1670.167 (C=O stretch of amide), 2871.430, 2925.836 (C-H stretch), 3388.197 (N-H stretch).
TLC: R_f = 0.14 (80:20 petroleum ether:EtOAc).

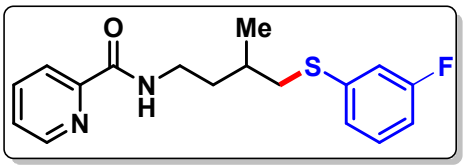


***N*-(3-methyl-4-(p-tolylthio)butyl)picolinamide (Scheme 4, entry 2'x)**

Yield: 78%

Nature: Yellow liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.52 (m, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.03 (s, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 3.56 – 3.44 (m, 2H), 2.91 (dd, *J* = 12.8, 6.2 Hz, 1H), 2.80 (dd, *J* = 12.8, 7.0 Hz, 1H), 2.28 (s, 3H), 1.94 – 1.80 (m, 2H), 1.55 (tdd, *J* = 12.9, 7.6, 5.7 Hz, 1H), 1.09 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.37, 150.06, 148.12, 137.46, 136.14, 133.11, 130.25, 129.77, 126.20, 122.30, 41.99, 37.38, 35.77, 30.95, 21.11, 19.47.

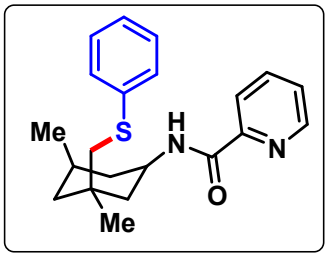
HRMS (ESI): calcd. for $C_{18}H_{22}N_2OSNa$: 337.1344, found: 337.1345.
IR (cm^{-1}): 748.786 (S-S stretch), 802.787 (C-S stretch), 1523.592, 1569.124, 1591.098 (C-C stretch), 1671.395 (C=O stretch of amide), 2924.345, 2957.497 (C-H stretch), 3055.979, 3384.755 (N-H stretch).
TLC: R_f = 0.12 (80:20 petroleum ether:EtOAc).



***N*-(4-((3-fluorophenyl)thio)-3-methylbutyl)picolinamide (Scheme 4, entry 2'y)**

Yield: 76 %

Nature: Orange liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.3 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 23.6 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 7.18 (td, *J* = 8.0, 6.1 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.80 (td, *J* = 8.3, 2.0 Hz, 1H), 3.60 – 3.48 (m, 2H), 2.96 (dd, *J* = 12.7, 5.8 Hz, 1H), 2.86 (dd, *J* = 12.1, 6.2 Hz, 1H), 1.94 – 1.85 (m, 2H), 1.63 – 1.53 (m, 1H), 1.12 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.43, 163.94, 161.97, 149.99, 148.16, 139.67, 139.60, 137.49, 130.23, 130.16, 126.25, 124.24, 124.22, 122.31, 115.53, 115.35, 112.76, 112.59, 40.68, 37.31, 35.89, 30.84, 19.51.
^{19}F NMR (471 MHz, $CDCl_3$) δ -112.41.
HRMS (ESI): calcd. for $C_{17}H_{19}N_2OFSNa$: 341.1100, found: 341.1105.
IR (cm^{-1}): 749.034 (S-S stretch), 818.861 (C-S stretch), 1378.250 (C-F stretch), 1524.915, 1577.671 (C-C stretch), 1672.427 (C=O stretch of amide), 2926.440, 3059.292 (C-H stretch), 3385.984 (N-H stretch).
TLC: R_f = 0.1 (80:20 petroleum ether:EtOAc).



***N*-((3S,5R)-3,5-dimethyl-3-((phenylthio)methyl)cyclohexyl)picolinamide (Scheme 4, entry 2'z)**

Yield: 73%

Nature: Yellow semi-solid

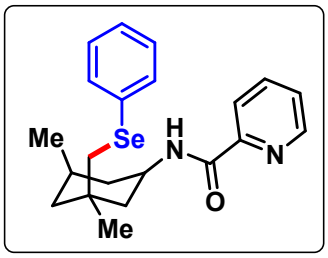
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 6.0 Hz, 1H), 8.18 (d, *J* = 4.9 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.77 (td, *J* = 7.7, 1.8 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.12 – 7.06 (m, 1H), 4.31 (dt, *J* = 7.4, 3.8 Hz, 1H), 3.26 – 3.01 (m, 2H), 2.23 – 2.08 (m, 1H), 2.03 – 1.91 (m, 1H), 1.87 – 1.70 (m, 1H), 1.45 (dd, *J* = 14.7, 4.5 Hz, 1H), 1.26 (ddd, *J* = 13.6, 11.6, 4.2 Hz, 1H), 1.09 (s, 3H), 0.99 (dd, *J* = 13.6, 11.4 Hz, 1H), 0.93 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.75, 150.17, 148.01, 138.03, 137.28, 128.69, 128.54, 125.94, 125.33, 121.93, 46.03, 45.52, 44.62, 39.12, 38.29, 35.05, 30.62, 23.81, 22.39.

HRMS (ESI): calcd. for $C_{21}H_{26}NaN_2OS$: 377.1658, found: 377.1662.

IR (cm^{-1}): 749.568 (S-S stretch), 819.057 (C-S stretch), 1515.908, 1591.402, 1591.402 (C-C stretch), 1676.491 (C=O stretch in amide), 2924.632, 2954.483 (C-H stretch), 3388.920 (N-H stretch).

TLC: R_f = 0.11 (70:30 petroleum ether:EtOAc).



***N*-((3S,5R)-3,5-dimethyl-3-((phenylselanyl)methyl)cyclohexyl)picolinamide (Scheme 4, entry 2'aa)**

Yield: 76%

Nature: yellow liquid**.**

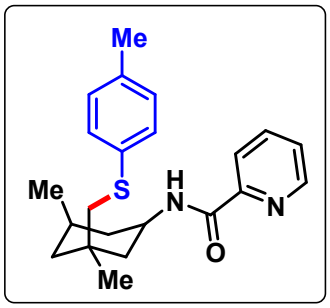
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.7 Hz, 1H), 8.30 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.81 (td, *J* = 7.7, 0.6 Hz, 1H), 7.42 – 7.39 (m, 2H), 7.38 – 7.35 (m, 1H), 7.16 – 7.13 (m, 3H), 4.32 (td, *J* = 7.4, 3.7 Hz, 1H), 3.21 – 3.12 (m, 2H), 2.11 (d, *J* = 14.6 Hz, 1H), 1.87 (d, *J* = 13.8 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.50 (dd, *J* = 14.4, 4.2 Hz, 1H), 1.34 – 1.26 (m, 1H), 1.06 (s, 3H), 0.99 (dd, *J* = 13.1, 11.4 Hz, 1H), 0.89 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.65, 150.22, 148.09, 137.39, 132.34, 131.74, 128.92, 126.45, 126.05, 122.07, 45.86, 45.40, 41.19, 40.08, 38.47, 35.35, 31.26, 23.94, 22.35.

HRMS (ESI): calcd. for $C_{21}H_{26}N_2OSeNa$: 425.1107, found: 425.1104.

IR (cm^{-1}): 735.977 (Se-Se stretch), 818.686 (C-Se stretch), 1512.614, 1578.861 (C-C stretch), 1676.528 (C=O stretch of amide), 2922.533, 2952.259 (C-H stretch), 3057.088, 3392.287 (N-H stretch).

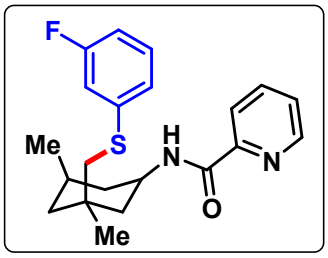
TLC: R_f = 0.12 (70:30 petroleum ether:EtOAc).



***N*-((3S,5R)-3,5-dimethyl-3-((p-tolylthio)methyl)cyclohexyl)picolinamide (Scheme 4, entry 2'ab)**

Yield: 82 %

Nature: Sticky yellow liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.6 Hz, 1H), 8.28 (d, *J* = 4.5 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.79 (td, *J* = 7.7, 1.1 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 4.32 (dd, *J* = 6.9, 3.3 Hz, 1H), 3.14 (d, *J* = 11.8 Hz, 1H), 3.07 (d, *J* = 11.8 Hz, 1H), 2.28 (s, 3H), 2.16 (d, *J* = 14.5 Hz, 1H), 1.94 (d, *J* = 13.7 Hz, 1H), 1.78 (d, *J* = 14.8 Hz, 1H), 1.44 (dd, *J* = 14.6, 4.4 Hz, 1H), 1.30 – 1.25 (m, 2H), 1.08 (s, 3H), 0.98 (dd, *J* = 12.9, 11.0 Hz, 1H), 0.92 (d, *J* = 6.4 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.84, 150.13, 148.05, 137.36, 135.41, 134.28, 129.49, 125.97, 122.03, 115.58, 45.95, 45.63, 45.53, 39.10, 38.32, 35.15, 30.54, 23.82, 22.38, 21.06.
HRMS (ESI): calcd. for $C_{22}H_{28}N_2OSNa$: 391.1814, found: 391.1815.
IR (cm^{-1}): 750.303 (S-S stretch), 805.046 (C-S stretch), 1462.775, 1515.479 (C-C stretch), 1678.018 (C=O stretch in amide), 2924.844, 3058.138 (C-H stretch), 3394.263 (N-H stretch).
TLC: R_f = 0.13 (70:30 petroleum ether:EtOAc).



***N*-((3S,5R)-3-(((3-fluorophenyl)thio)methyl)-3,5-dimethylcyclohexyl)picolinamide (Scheme 4, entry 2'ac)**

Yield: 79 %

Nature: Sticky yellow liquid**.**
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.24 (s, 1H), 8.16 – 8.14 (m, 1H), 7.83 – 7.69 (m, 1H), 7.34 – 7.30 (m, 1H), 7.12 – 7.07 (m, 1H), 6.97 – 6.94 (m, 1H), 6.89 (d, *J* = 9.7 Hz, 1H), 6.75 (s, 1H), 4.32 (d, *J*= 2.9 Hz, 1H), 3.19 – 3.07 (m, 2H), 2.21 (d, *J* = 14.5 Hz, 1H), 1.95 (d, *J* = 13.4

Hz, 1H), 1.80 (d, *J* = 13.8 Hz, 1H), 1.44 (d, *J* = 14.6 Hz, 1H), 1.29 (d, *J* = 17.4 Hz, 2H), 1.08 (d, *J* = 3.4 Hz, 3H), 1.02 (d, *J* = 13.9 Hz, 1H), 0.98 – 0.92 (m, 3H).

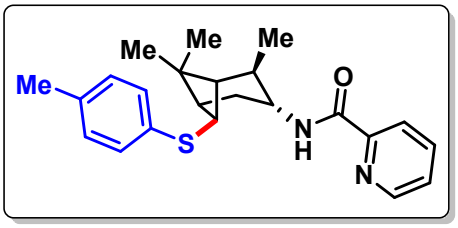
^{13}C NMR (126 MHz, $CDCl_3$) δ 163.76, 161.69, 150.07, 148.07, 140.64, 137.33, 129.84, 129.77, 126.05, 123.75, 121.97, 114.80, 114.62, 112.13, 111.97, 46.08, 45.50, 44.19, 38.98, 38.26, 34.96, 32.03, 30.64, 23.81, 22.42.

^{19}F NMR (471 MHz, $CDCl_3$) δ -112.58.

HRMS (ESI): calcd. for $C_{21}H_{25}N_2OFNaS$: 395.1564, found: 395.1564.

IR (cm^{-1}): 749.279 (S-S stretch), 819.006 (C-S stretch), 1378.381 (C-F stretch), 1514.064, 1578.124 (C-C stretch), 1677.769 (C=O stretch of amide), 2853.308, 2924.038 (C-H stretch), 3387.748 (N-H stretch).

TLC: R_f = 0.12 (70:30 petroleum ether:EtOAc).



***N*-((1R,2R,3R,5S)-2,6,6-trimethyl-7-(p-tolylthio)bicyclo[3.1.1]heptan-3-yl)picolinamide**

(Scheme 4, entry 2'ad)

Yield: 72 %

Nature: Brownish liquid**.**

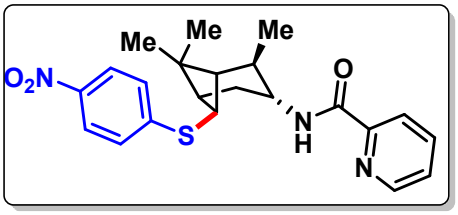
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 9.4 Hz, 1H), 8.62 (d, *J* = 4.1 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.28 (d, *J* = 5.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.50 (tt, *J* = 10.2, 6.2 Hz, 1H), 4.21 (t, *J* = 5.2 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.34 (s, 3H), 2.33 – 2.29 (m, 2H), 2.21 (td, *J* = 5.5, 1.6 Hz, 1H), 1.93 (ddd, *J* = 14.7, 5.7, 2.3 Hz, 1H), 1.36 (s, 3H), 1.25 (s, 3H), 1.21 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.89, 150.47, 148.38, 137.30, 136.09, 133.07, 129.89, 129.81, 126.00, 122.44, 52.05, 49.25, 46.51, 45.97, 40.27, 38.51, 32.42, 27.53, 23.77, 21.15, 20.45.

HRMS (ESI): calcd. for $C_{23}H_{28}N_2OSK$: 419.1549, found: 419.1554.

IR (cm^{-1}): 749.109 (S-S stretch), 803.252 (C-S stretch), 1514.217, 1569.450, 1591.368 (C-C stretch), 1673.307 (C=O stretch of amide), 2925.364 (C-H stretch), 3375.055 (N-H stretch).

TLC: R_f = 0.13 (70:30 petroleum ether:EtOAc).



***N*-((1R,2R,3R,5S)-2,6,6-trimethyl-7-((4-nitrophenyl)thio)bicyclo[3.1.1]heptan-3-yl)picolinamide (Scheme 4, entry 2'ae)**

Yield: 71 %

Nature: Brownish liquid**.**

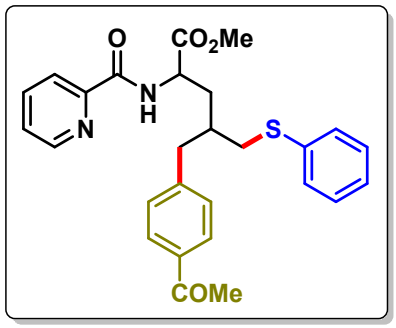
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.2 Hz, 1H), 8.55 (d, *J* = 7.9 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 2H), 7.85 (td, *J* = 7.7, 1.6 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.37 (d, *J* = 8.9 Hz, 2H), 4.50 (ddd, *J* = 12.0, 7.8, 4.6 Hz, 1H), 4.34 (t, *J* = 5.4 Hz, 1H), 2.69 – 2.62 (m, 1H), 2.46 – 2.43 (m, 1H), 2.31 (td, *J* = 5.6, 1.7 Hz, 1H), 2.19 (dd, *J* = 12.8, 5.7 Hz, 1H), 1.43 (s, 3H), 1.28 (s, 3H), 1.21 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.86, 150.29, 148.29, 147.60, 145.36, 137.48, 127.19, 126.18, 124.19, 122.56, 52.04, 47.49, 46.49, 45.85, 40.34, 39.17, 32.47, 27.60, 23.76, 20.38.

HRMS (ESI): calcd. for $C_{22}H_{25}N_3O_3SNa$: 434.1502, found: 434.1509.

IR (cm^{-1}): 744.981 (S-S stretch), 819.532 (C-S stretch), 1379.654, 1515.306 (N-O stretch), 1674.210 (C=O stretch of amide), 2925.821 (C-H stretch).

TLC: R_f = 0.13 (60:40 petroleum ether:EtOAc).



Methyl 4-(4-acetylbenzyl)-5-(phenylthio)-2-(picolinamido)pentanoate (Scheme 4, entry 2'af)

Yield: 68%

Nature: Orangish liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.57 (m, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.89 – 7.80 (m, 4H), 7.45 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 4H), 7.06 – 6.77 (m, 1H), 4.96 (td, *J* = 8.6, 5.6 Hz, 1H), 3.77 (d, *J* = 8.9 Hz, 3H), 2.92 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.56 (s, 3H), 2.43 (dd, *J* = 13.2, 8.3 Hz, 1H), 1.94 (dd, *J* = 19.1, 9.9 Hz, 2H), 1.72 (dt, *J* = 12.8, 7.4 Hz, 2H), 0.92 (d, *J* = 6.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.04, 172.98, 164.22, 149.43, 148.41, 146.52, 137.53, 137.42, 135.25, 130.63, 129.70, 129.60, 128.56, 128.50, 126.60, 122.51, 52.56, 50.63, 42.60, 40.11, 31.81, 26.67, 19.75.

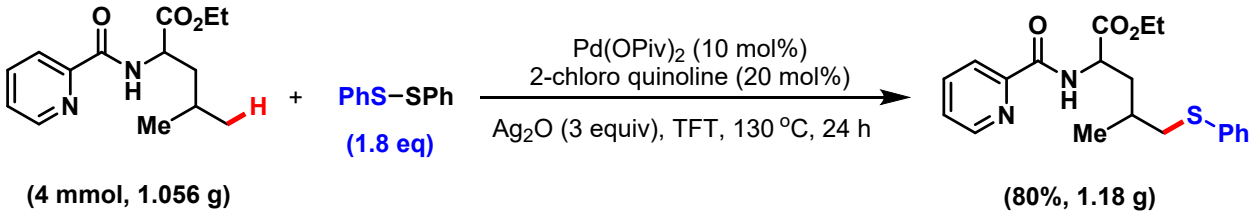
HRMS (ESI): calcd. for $C_{29}H_{32}N_2O_4S$: 504.2083, found: 504.2079.

IR (cm^{-1}): 748.754 (S-S stretch), 802.018 (C-S stretch), 1606.311 (C=O stretch in ester), 1678.225 (C=O stretch in amides), 1743.113 (C=O stretch in ketones), 2956.923 (C-H stretch), 3015.447 (C-H stretch), 3377.276 (N-H stretch).

5. Synthetic applications of δ-thioarylation of amines

Gram scale synthesis:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with ethyl picolinoylleucinate (4 mmol, 1.056 g), palladium(II) pivalate (10 mol%, 0.4 mmol, 123.5 mg) and 2-chloroquinoline (20 mol%, 0.8 mmol, 130.9 mg). Then Ag_2O (3 eq., 12 mmol, 2.8 g) and diphenyl disulfide (1.8 eq., 7.2 mmol, 1.57 g) were introduced in this reaction mixture. The cap was fitted with a rubber septum. TFT (10 mL) was added to this mixture by syringe. The reaction mixture was vigorously stirred for 24 h in a preheated oil bath at 130 °C. After the stipulated time, the reaction mixture was cooled to room temperature and filtered through a celite bed using ethyl acetate as the eluent (30 mL). The diluted ethyl acetate solution of the reaction mixture was subsequently washed with saturated brine solution (2 x 5 mL) followed by water (2 x 5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under *vacuum*. The crude reaction mixture was purified by column chromatography using silica gel (60-120/100-200 mesh size) and petroleum ether/ethyl acetate as the eluent (93:7) to give the desired thioarylated product in gram scale (80%, 1.18 g).



(4 mmol, 1.056 g) **(80%, 1.18 g)**

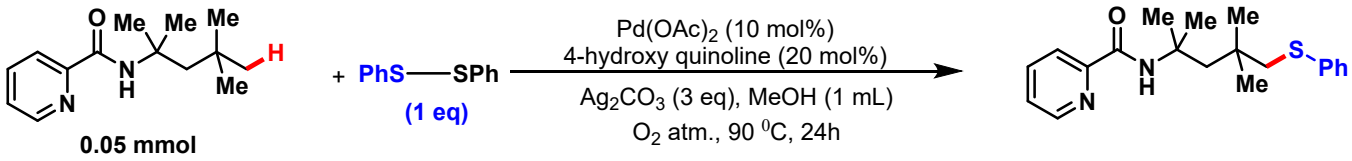
6. Mechanistic investigations

6.1. Order determination studies: To probe more about the mechanistic insight and to get a full proof idea about the components involved in the rate-determining step of the reaction, we carried out

the order determination studies using amide as substrate with respect to substrate and disulphide for both substrate 1 and 1'a. The results are as follows-

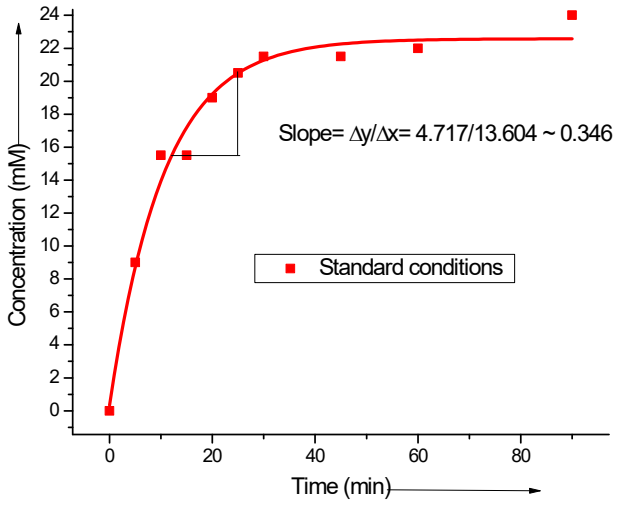
Order Determination studies with respect to 2,4,4-trimethylpentan-2-amine:

Run 1: Reaction was carried out with 0.05 mmol of amide and yield was monitored



Amide	Disulphide	$Pd(OAc)_2$	4-hydroxyquinoline	Ag_2CO_3	MeOH
0.05 mmol	0.05 mmol	0.005 mmol	0.01 mmol	0.15 mmol	1 mL

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	9
3	10	15.5
4	15	15.5
5	20	19
6	25	20.5
7	30	21.5
8	45	21.5
9	60	22
10	90	24



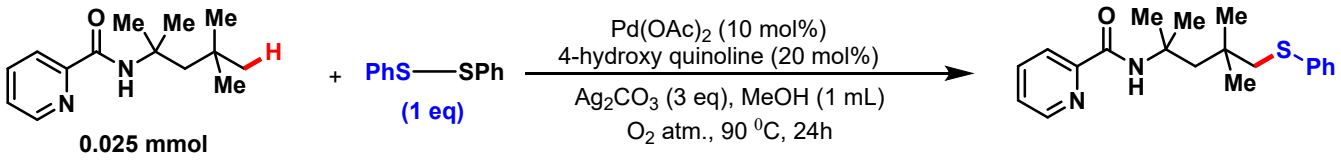
Slope of the curve= $(y_2-y_1)/(x_2-x_1) = \Delta y/\Delta x$

$= (20.370-15.653)/(26.613-13.009)$

$= 4.717/13.604$

~ 0.346

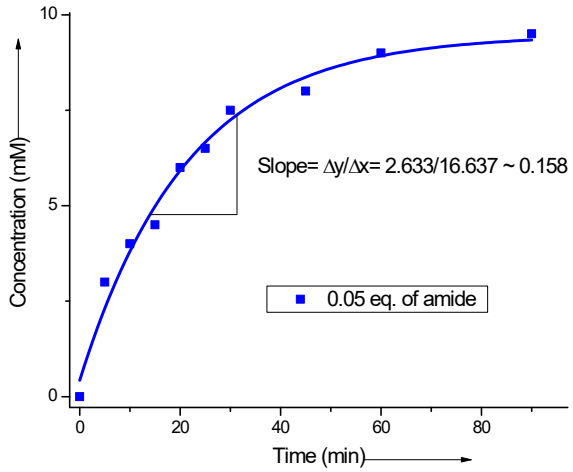
Run 2: Reaction was carried out with 0.025 mmol of amide and yield was monitored



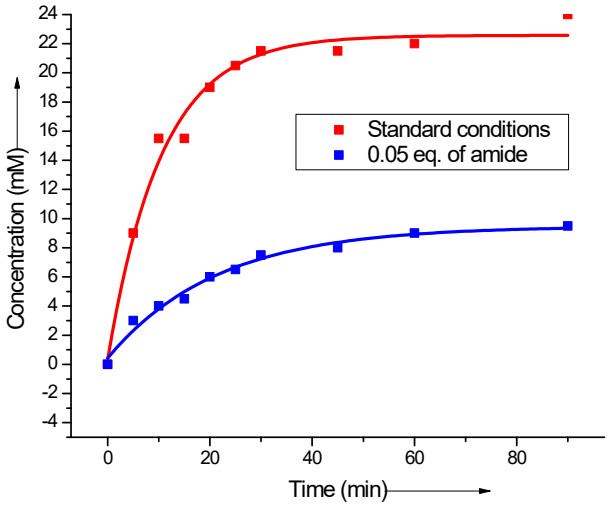
Amide	Disulphide	$Pd(OAc)_2$	4-hydroxyquinoline	Ag_2CO_3	MeOH
0.025 mmol	0.05 mmol	0.005 mmol	0.01 mmol	0.15 mmol	1 mL

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	3
3	10	4
4	15	4.5
5	20	6
6	25	6.5

7	30	7.5
8	45	8
9	60	9
10	90	9.5



Slope of the curve= $(y_2-y_1)/(x_2-x_1) = \Delta y/\Delta x$
= (7.426-4.793)/(31.229-14.592)
= 2.633/16.637
~ 0.158



From the equation (1) we got, Rate = k. $[Amide]^x$ $[SR]^y$

For run 1, initial rate = Rate 1

So, Rate 1 = k. $[Amide]^x$ $[SR]^y$

or, 0.346 $(mmol^{-1}.min^{-1})$ = k . $[0.05]^x$ $[0.05]^y$ ……(2)

For run 2, initial rate = Rate 2

So, Rate 2 = k. $[Amide]^x$ $[SR]^y$

or, 0.158 $(mmol^{-1}.min^{-1})$ = k . $[0.025]^x$ $[0.05]^y$ ……(3)

Hence from equation (2) and (3)

We get, [Rate 1/ Rate 2] = $[0.05/ 0.025]^x$

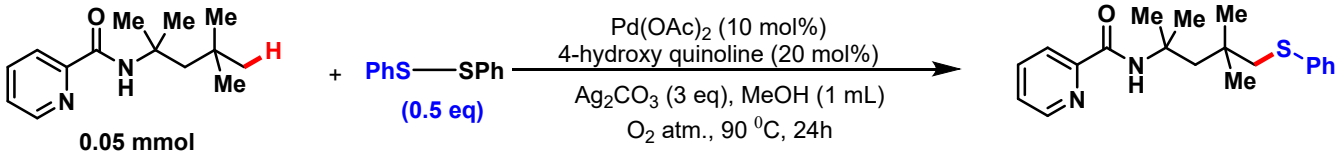
or, x = [log (Rate 1) – log (Rate 2)] / [log (0.05) – log (0.025)]

or, x = [log (0.346) – log (0.158)] / [log (0.05) – log (0.025)]

or, x = 1.13

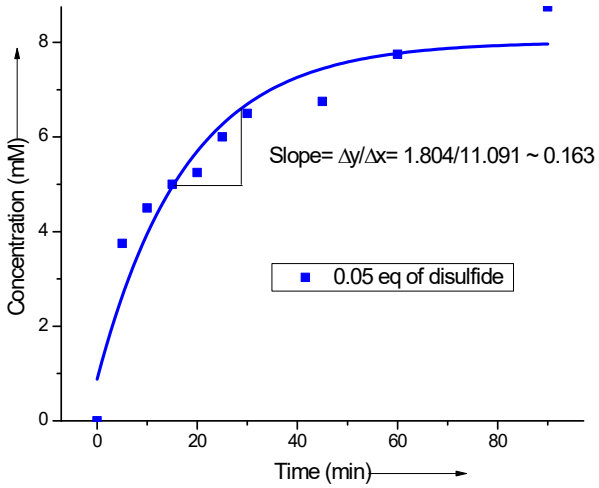
So, order with respect to amide derivative is ~ 1

Run 3: Reaction was carried out with 0.05 mmol of amide and 0.025 mmol of disulphide and yield was monitored

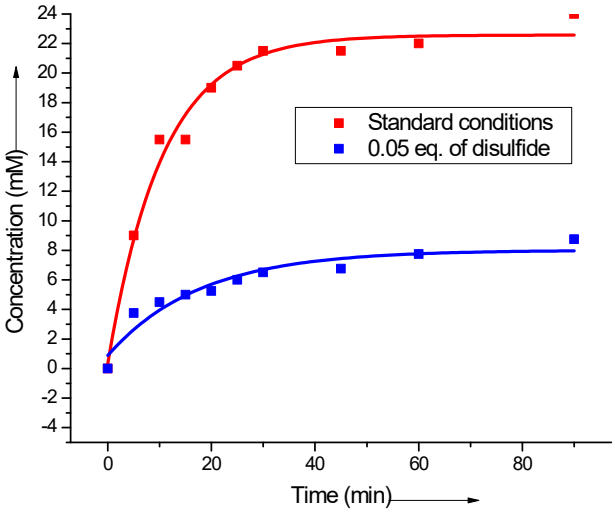


Amide	Disulphide	$Pd(OAc)_2$	4-hydroxyquinoline	Ag_2CO_3	MeOH
0.05 mmol	0.025 mmol	0.005 mmol	0.01 mmol	0.15 mmol	1 mL

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	3.75
3	10	4.5
4	15	5
5	20	5.25
6	25	6
7	30	6.5
8	45	6.75
9	60	7.75
10	90	8.75



Slope of the curve= $(y_2-y_1)/(x_2-x_1) = \Delta y/\Delta x$
= (6.730-4.926)/(27.549-16.458)
= 1.804/11.091
~ 0.163



From the equation (1) we got, Rate = k. $[Amide]^x$ $[SR]^y$
For run 1, initial rate = Rate 1
So, Rate 1 = k. $[Amide]^x$ $[SR]^y$
or, 0.346 ($mmol^{-1}.min^{-1}$) = k . $[0.05]^x$ $[0.05]^y$ ……(2)

For run 2, initial rate = Rate 2

So, Rate 2 = k. $[Amide]^x$ $[SR]^y$

or, 0.163 ($mmol^{-1}.min^{-1}$) = k . $[0.05]^x$ $[0.025]^y$ ……(3)

Hence from equation (2) and (3)

We get, [Rate 1/ Rate 2] = $[0.05/ 0.025]^y$

or, x = [log (Rate 1) – log (Rate 2)] / [log (0.05) – log (0.025)]

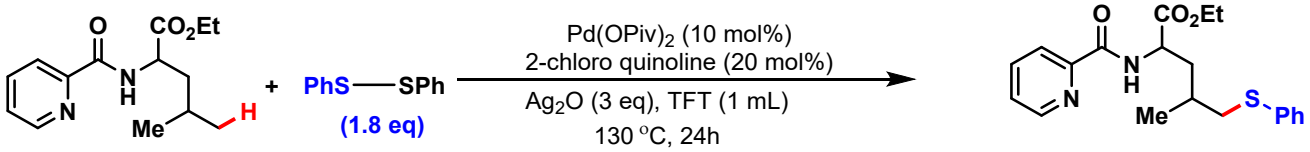
or, x = [log (0.346) – log (0.163)] / [log (0.05) – log (0.025)]

or, x = 1.086

So, order with respect to disulphide is ~ 1

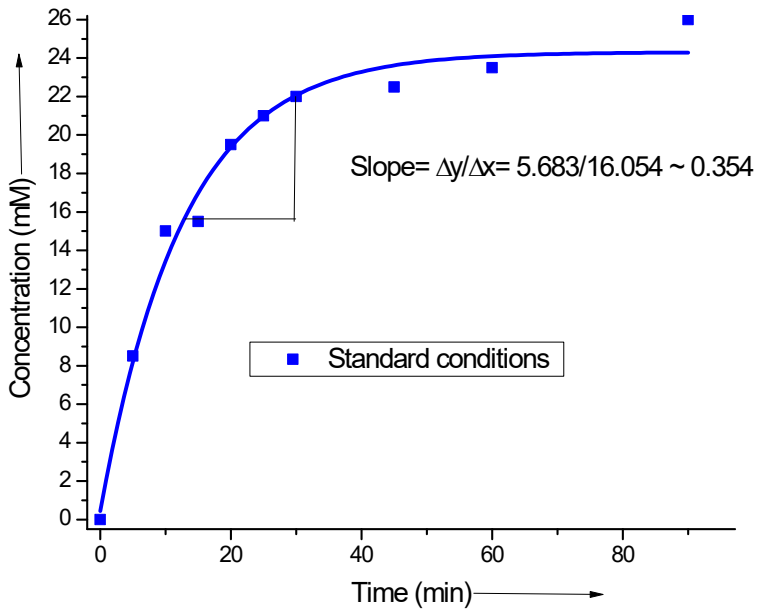
6.2. Order Determination studies of leucine:

Run 4: Reaction was carried out with 0.05 mmol of amide and yield was monitored



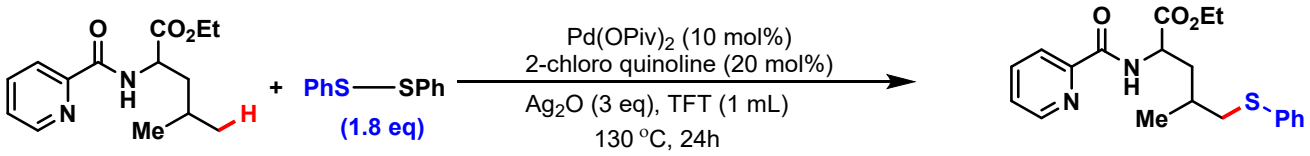
Amide	Disulphide	$Pd(OPiv)_2$	2-chloroquinoline	Ag_2O	TFT
0.05 mmol	0.09 mmol	0.005 mmol	0.01 mmol	0.15 mmol	1 mL

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	8.5
3	10	15
4	15	15.5
5	20	19.5
6	25	21
7	30	22
8	45	22.5
9	60	23.5
10	90	26



Slope of the curve= $(y_2-y_1)/(x_2-x_1) = \Delta y/\Delta x$
= (21.667-15.984)/(29.60-13.546)
= 5.683/16.054
~ 0.354

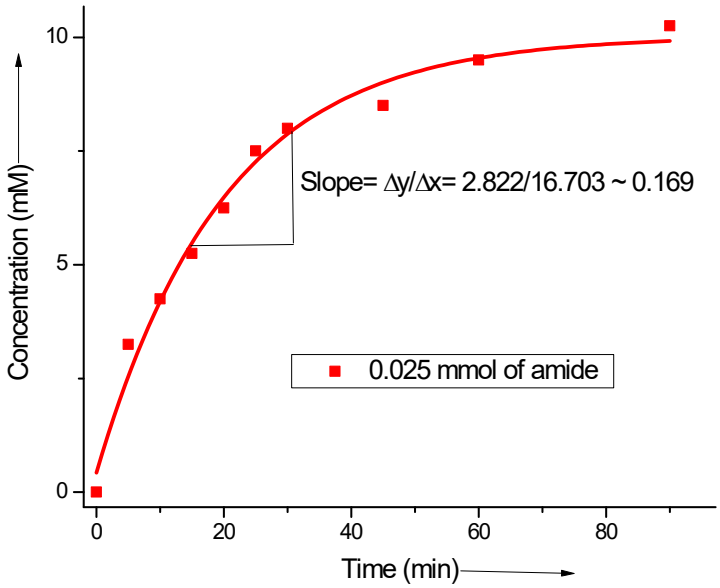
Run 5: Reaction was carried out with 0.025 mmol of amide and yield was monitored



Amide	Disulphide	$Pd(OPiv)_2$	2-chloroquinoline	Ag_2O	TFT
0.025 mmol	0.09 mmol	0.005 mmol	0.01 mmol	0.15 mmol	1 mL

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	3.25
3	10	4.25
4	15	5.25
5	20	6.25

6	25	7.5
7	30	8
8	45	8.5
9	60	9.5
10	90	10.25

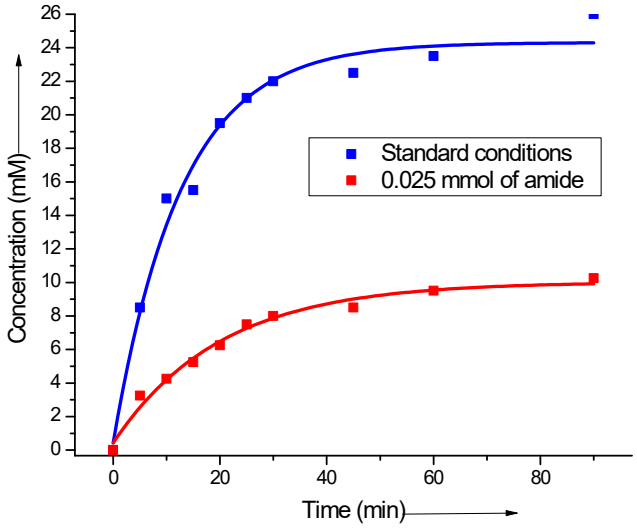


Slope of the curve= $(y_2-y_1)/(x_2-x_1) = \Delta y/\Delta x$

$= (8.211-5.389)/(31.110-14.407)$

$= 2.822/16.703$

~ 0.169



From the equation (1) we got, Rate = k. $[Amide]^x$ $[SR]^y$
For run 4, initial rate = Rate 1

So, Rate 1 = k. $[Amide]^x$ $[SR]^y$

or, 0.354 ($mmol^{-1}.min^{-1}$) = k . $[0.05]^x$ $[0.09]^y$ ……(2)

For run 5, initial rate = Rate 2

So, Rate 2 = k. $[Amide]^x$ $[SR]^y$

or, 0.169 ($mmol^{-1}.min^{-1}$) = k . $[0.025]^x$ $[0.09]^y$ ……(3)

Hence from equation (2) and (3)

We get, [Rate 1/ Rate 2] = $[0.05/ 0.025]^x$

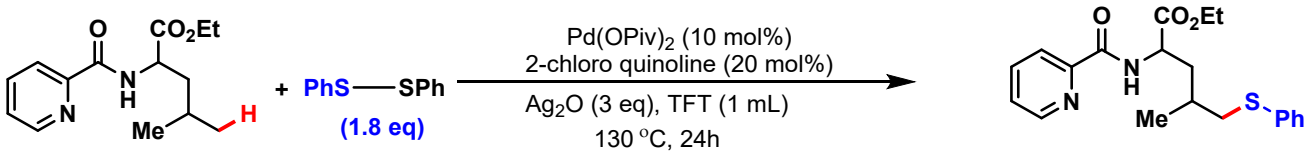
or, x = [log (Rate 1) – log (Rate 2)] / [log (0.05) – log (0.025)]

or, x = [log (0.354) – log (0.169)] / [log (0.05) – log (0.025)]

or, x = 1.07

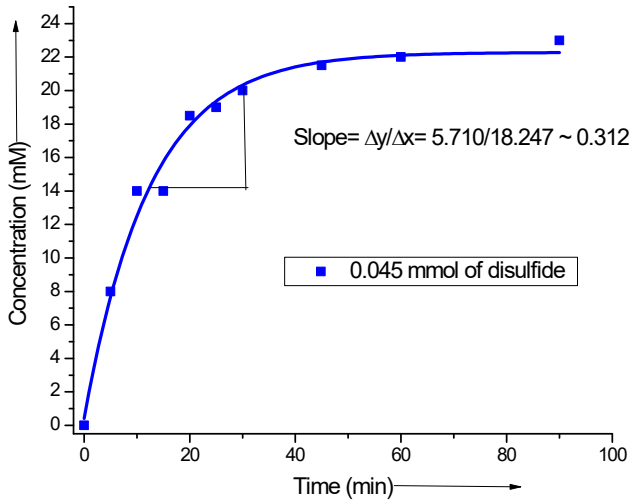
So, order with respect to amide derivative is ~ 1

Run 6: Reaction was carried out with 0.05 mmol of amide and 0.025 mmol of disulphide and yield was monitored



Amide	Disulphide	$Pd(OPiv)_2$	2-chloroquinoline	Ag_2O	TFT
0.05 mmol	0.045 mmol	0.005 mmol	0.01 mmol	0.15 mmol	1 mL

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	8
3	10	14
4	15	14
5	20	18.5
6	25	19
7	30	20
8	45	21.5
9	60	22
10	90	23

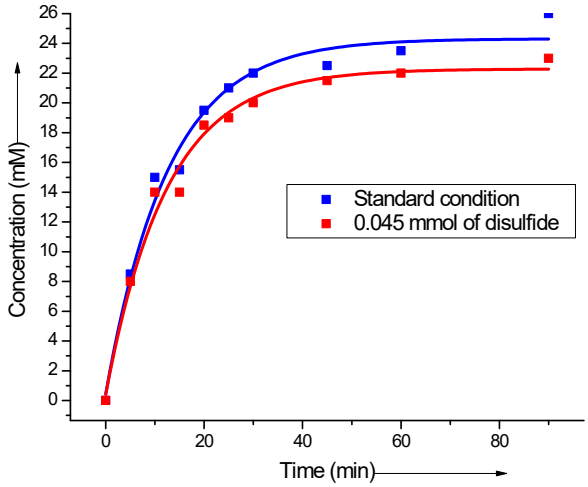


Slope of the curve= $(y_2-y_1)/(x_2-x_1) = \Delta y/\Delta x$

= (19.770-14.060)/(29.460-12.313)

= 5.710/18.247

~ 0.312



From the equation (1) we got, Rate = k. $[Amide]^x$ $[SR]^y$
For run 4, initial rate = Rate 1
So, Rate 1 = k. $[Amide]^x$ $[SR]^y$
or, 0.354 ($mmol^{-1}.min^{-1}$) = k . $[0.05]^x$ $[0.09]^y$ ……(2)

For run 6, initial rate = Rate 2
So, Rate 2 = k. $[Amide]^x$ $[SR]^y$
or, 0.312 ($mmol^{-1}.min^{-1}$) = k . $[0.05]^x$ $[0.045]^y$ ……(3)

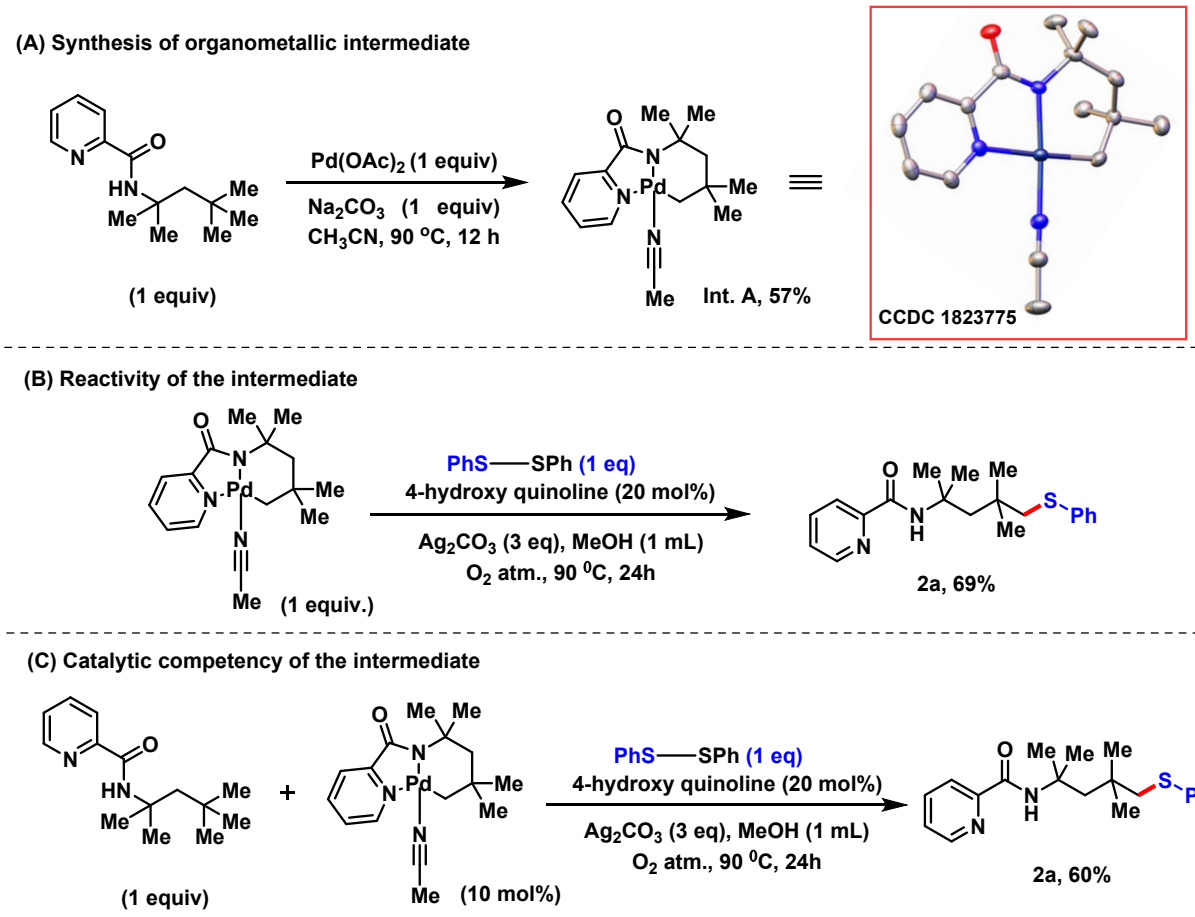
Hence from equation (2) and (3)
We get, [Rate 1/ Rate 2] = $[0.09/ 0.045]^y$
or, x = [log (Rate 1) – log (Rate 2)] / [log (0.09) – log (0.045)]
or, x = [log (0.354) – log (0.312)] / [log (0.09) – log (0.045)]
or, x = 0.18

So, order with respect to disulphide is ~ 0

6.3. Synthesis, Reactivity and Catalytic Competency of Organometallic Intermediate:

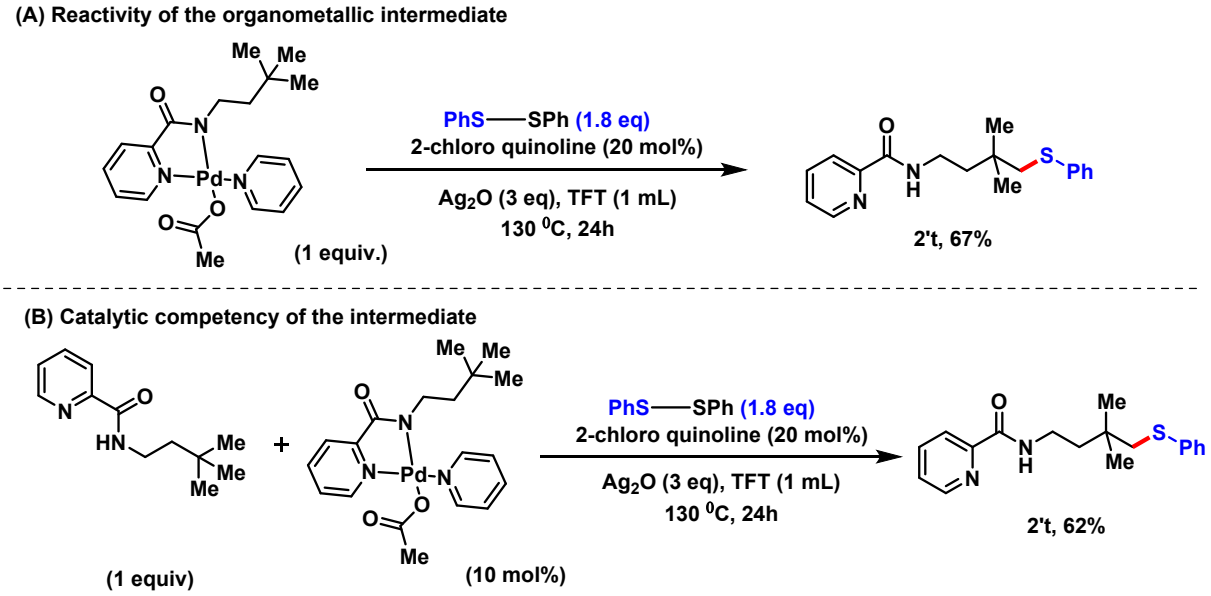
6.3.1. Mechanistic insights with Int. A: To obtain a thorough understanding about the mechanistic cycle that might be involved, we embarked on the synthesis of the C–H activated organopalladium complex that might be involved in this transformation.[3] The MeCN-coordinated [5,6]-fused C–H activated intermediate (**Int. A**) was isolated and characterized crystallographically. To prove the viability of Int. A in the plausible mechanistic cycle, standard conditions were undertaken using 1 equiv. of intermediate. The protocol was obtained to be suitably compatible in synthesizing the δ-thioarylated product, clearly demonstrating the

involvement of **Int. A** in the plausible mechanistic cycle. Additionally, employment of standard reaction conditions utilizing **Int. A** replacing $Pd(OAc)_2$ provided 60% of the desired δ-thioarylated product. This demonstrates that **Int. A** is not only a useful reaction intermediate in our plausible mechanistic cycle but also catalytically competent.



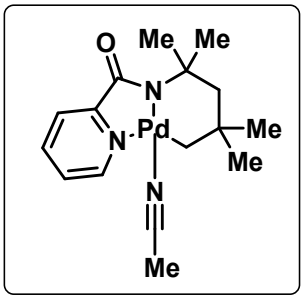
6.3.2. Mechanistic insights with Int. C: Once we had a concrete understanding on the nature and role of the C−H activated intermediate (**Int. A**), we delved into synthesizing and deciphering the role and nature of pre-C−H activated intermediates (**Int. C**).[4] The pyridine-bound pre-C−H activated intermediate was isolated using the standard procedures and characterized crystallographically. The nature of this intermediate was determined. Even though it is not a C–H activated intermediate, it was found to be reactive towards our developed reaction protocol as well as catalytically competent to the reaction methodology, similar to **Int. A**. Consequently, this pre-

C−H activated intermediate (**Int. C**) is a crucial component in the overall plausible mechanistic cycle.



Spectral characterization data of Int. A[3]:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir–bar was charged with palladium acetate (0.1 mmol, 1 equiv) suspension in MeCN. N-(2,4,4- trimethylpentan-2-yl)picolinamide (0.1 mmol, 1 equiv) and sodium carbonate (0.1 mmol, 1 equiv) was added. The cap was fitted with a rubber septum and the reaction the reaction mixture was vigorously stirred for 12 h in a preheated oil bath at 90 °C. The reaction mixture was then cooled to room temperature and filtered through cotton plug. The filtrate was concentrated under vacuum and extracted with diethyl ether (3 x 30 mL). The resulting solution was concentrated and crystallized from diethyl ether.



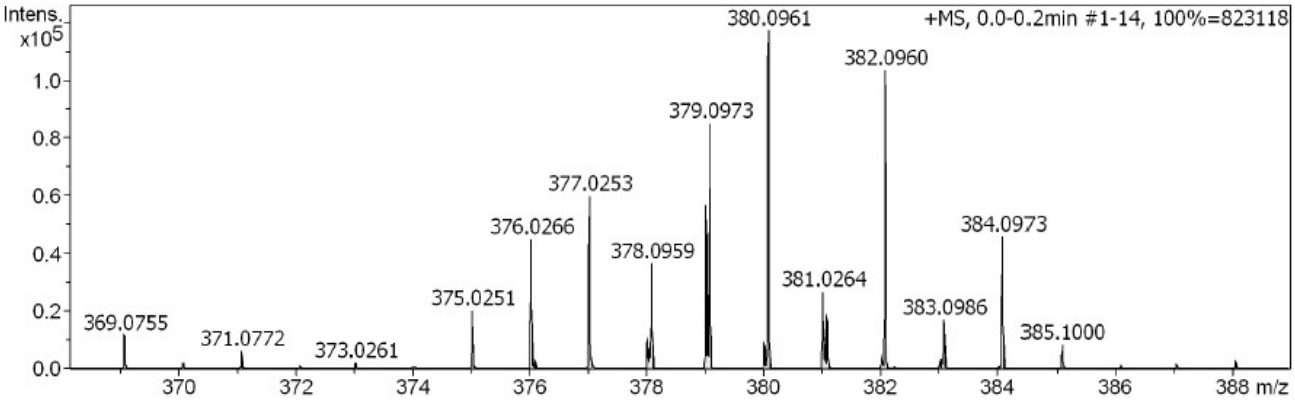
C–H activated organometallic complex (Int. A)

Nature: Brownish solid

Yield: 57%

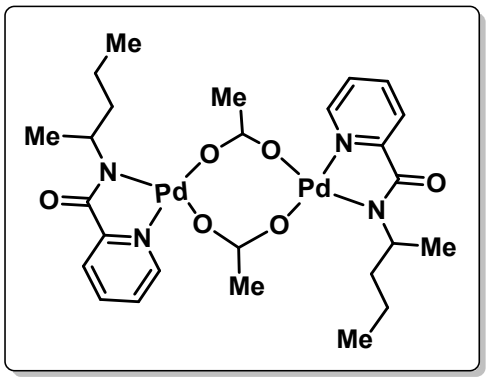
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (1H), 8.44 (1H), 8.16 (1H), 7.88 – 7.82 (1H), 2.13 (3H), 1.86 (2H), 1.50 (2H), 1.49 (6H), 1.06 (6H).

LRMS: Calculated for $C_{16}H_{24}N_3OPd$ 380.0876 and found m/z 380.0961.



Spectral characterization data of Int. B[4]:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir–bar was charged with palladium acetate (0.1 mmol, 1 equiv) suspension in MeCN. substrate (0.1 mmol, 1 equiv) was added in dropwise manner. The cap was fitted with a rubber septum and the reaction mixture was vigorously stirred overnight in a preheated oil bath at 90 °C. The reaction mixture was then cooled to room temperature and filtered through cotton plug. The filtrate was concentrated under vacuum and extracted with hexane (10 mL) followed by diethyl ether (3 x 30 mL). The resulting solution was concentrated and crystallized from diethyl ether.



Pre-C–H activated organometallic complex (Int. B)

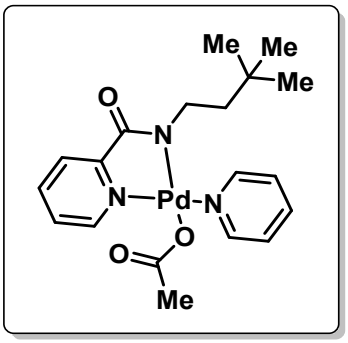
Nature: Yellow solid

Yield: 66%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.67 (m, 1H), 7.33 (m, 1H), 2.14 (t, 2H), S31
1.64 (s, 3H), 0.98 (d, 2H), 0.93 (m, 3H), 0.86 (t, 3H), 0.75 (m, 1H).

Spectral characterization data of Int. C[4]:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir–bar was charged with palladium acetate (0.1 mmol, 1 equiv) suspension in MeCN. substrate (0.1 mmol, 1 equiv) was added in dropwise manner while stirring. This mixture was stirred for 1 h at room temperature followed by addition of pyridine solution in MeCN (1 equiv). The cap was fitted with a rubber septum and the reaction mixture was vigorously stirred overnight in a preheated oil bath at 70 °C. The reaction mixture was then cooled to room temperature and filtered through cotton plug. The filtrate was concentrated under vacuum and extracted with hexane (10 mL) followed by diethyl ether (3 x 30 mL). The resulting solution was concentrated and crystallized from diethyl ether.



Pre-C–H activated organometallic complex (Int. C)

Nature: Yellow solid

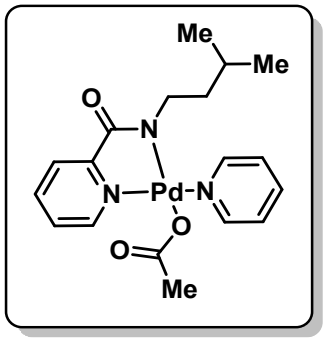
Yield: 62%

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (d, 2H), 8.15 (d, 1H), 7.97 (t, 1H), 7.90 (d, 2H), 7.48 (t, 2H), 7.35 (t, 1H), 2.71 (dd, 2H), 1.21 (dd, 2H), 0.57 (s, 9H).

Spectral characterization data of Int. D[4]:

A clean, oven-dried screw cap reaction tube with previously placed magnetic stir–bar was charged with palladium acetate (0.1 mmol, 1 equiv) suspension in MeCN. substrate (0.1 mmol, 1 equiv) was added in dropwise manner while stirring. This mixture was stirred for 1 h at room temperature followed by addition of pyridine solution in MeCN (1 equiv). The cap was fitted with a rubber septum and the reaction mixture was vigorously stirred overnight in a preheated oil bath at 70 °C.

The reaction mixture was then cooled to room temperature and filtered through cotton plug. The filtrate was concentrated under vacuum and extracted with hexane (10 mL) followed by diethyl ether (3 x 30 mL). The resulting solution was concentrated and crystallized from diethyl ether.



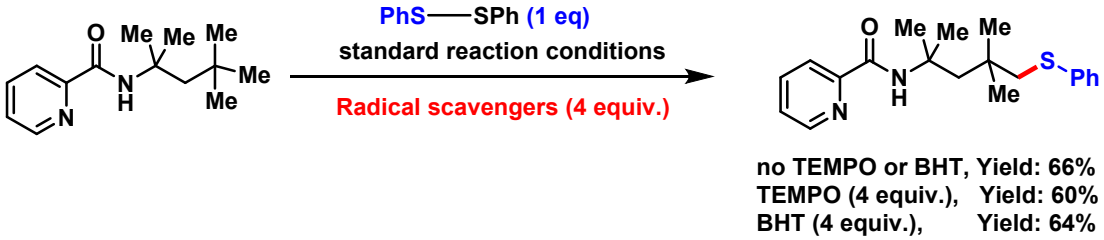
Pre-C–H activated organometallic complex (Int. D)

Nature: Yellow solid

Yield: 69%

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, 2H), 8.15 (d, 1H), 7.96 (t, 1H), 7.90 (d, 2H), 7.47 (t, 2H), 7.39 (t, 1H), 2.67 (dd, 2H), 1.17 (m, 3H), 0.57 (d, 6H).

6.4. Probing the existence of radical mechanism: To gain evidence about whether the reaction is proceeding *via* a radical mechanism or not, standard reactions were carried out with upto 4 equiv. of radical scavengers such as TEMPO and BHT.[5] The reaction yield remained practically unaltered, clearly depicting that the protocol does not proceed through a radical mechanism.

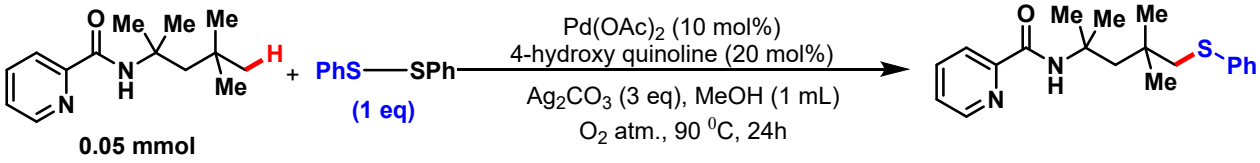


no TEMPO or BHT, Yield: 66%
TEMPO (4 equiv.), Yield: 60%
BHT (4 equiv.), Yield: 64%

6.5. Role of individual components

6.5.1. Role of individual components for 2,4,4-trimethylpentan-2-amine: To determine the role of ligand and oxidant in the reaction mechanism, we have carried out our methodology in different combinations of ligand and oxidant. One case involves the standard reaction condition, the second

case involves the absence of ligand, the third case involves the absence of oxidant while the last case involve the reaction in absence of both ligand and oxidant. Following their results, we have tried to plot the role each component plays.



The results are as follows-

Run 1- Under standard conditions

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	9
3	10	15.5
4	15	15.5
5	20	19
6	25	20.5
7	30	21.5
8	45	21.5
9	60	22
10	90	24

Run 2- In the absence of ligand (4-hydroxy quinoline)

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	3.5
3	10	4.5
4	15	5
5	20	5.5
6	25	6

7	30	6.5
8	45	7
9	60	7.5
10	90	9

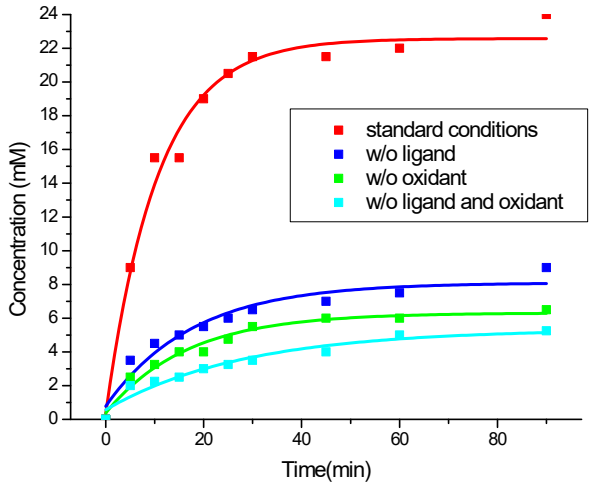
Run 3- In the absence of oxidant (Ag_2CO_3)

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	2.5
3	10	3.25
4	15	4
5	20	4
6	25	4.75
7	30	5.5
8	45	6
9	60	6
10	90	6.5

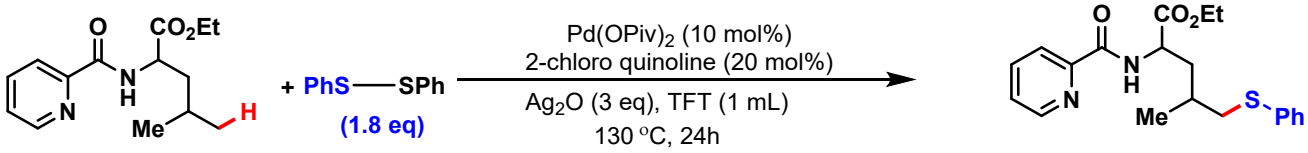
Run 4- In the absence of both ligand and oxidant (4-hydroxy quinoline and Ag_2CO_3)

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	2
3	10	2.25
4	15	2.5
5	20	3
6	25	3.25
7	30	3.5
8	45	4

9	60	5
10	90	5.25



6.5.2. Role of individual components for leucine: We have also determined the role of different components for substrate 1'a. The results are as follows:



Run 1- Under standard conditions

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	8.5
3	10	15
4	15	15.5
5	20	19.5
6	25	21
7	30	22

8	45	22.5
9	60	23.5
10	90	26

Run 2- In the absence of ligand

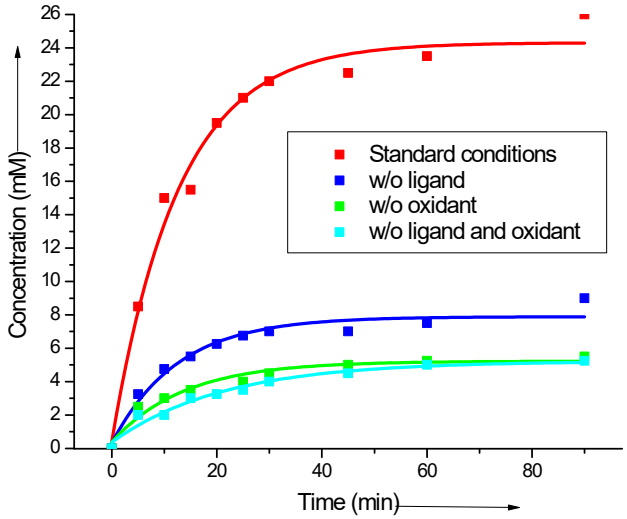
Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	3.25
3	10	4.75
4	15	5.5
5	20	6.25
6	25	6.75
7	30	7
8	45	7
9	60	7.5
10	90	9

Run 3- In the absence of oxidant (Ag_2CO_3)

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	2.5
3	10	3
4	15	3.5
5	20	-
6	25	4
7	30	4.5
8	45	5
9	60	5.25
10	90	5.5

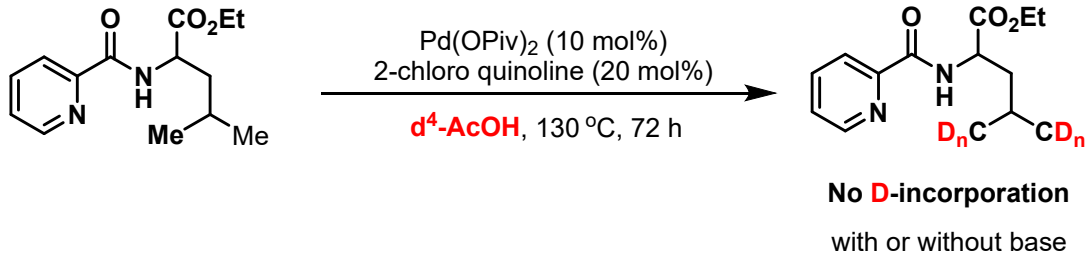
Run 4- In the absence of both ligand and oxidant (2-chloro quinoline and Ag_2CO_3)

Sl. No.	Time (min)	Concentration (mM)
1	0	0
2	5	2
3	10	2
4	15	3
5	20	3.25
6	25	3.5
7	30	4
8	45	4.5
9	60	5
10	90	5.25



6.6. Reversibility experiment: To investigate whether C–H activation is the rate-determining step of the overall reaction protocol, reversibility experiments were undertaken using Ethyl picolinoylleucinate (1'a) as substrate. Deuterium incorporation studies were carried out with d^4-AcOH in the presence of metal catalyst and ligand at high temperatures (130 ℃). However, even

after letting the reaction run for 72 h, no deuterium incorporation was observed in the substrate, suggesting that C–H activation, in all probability might be the rate-determining step of the methodology.



7. References

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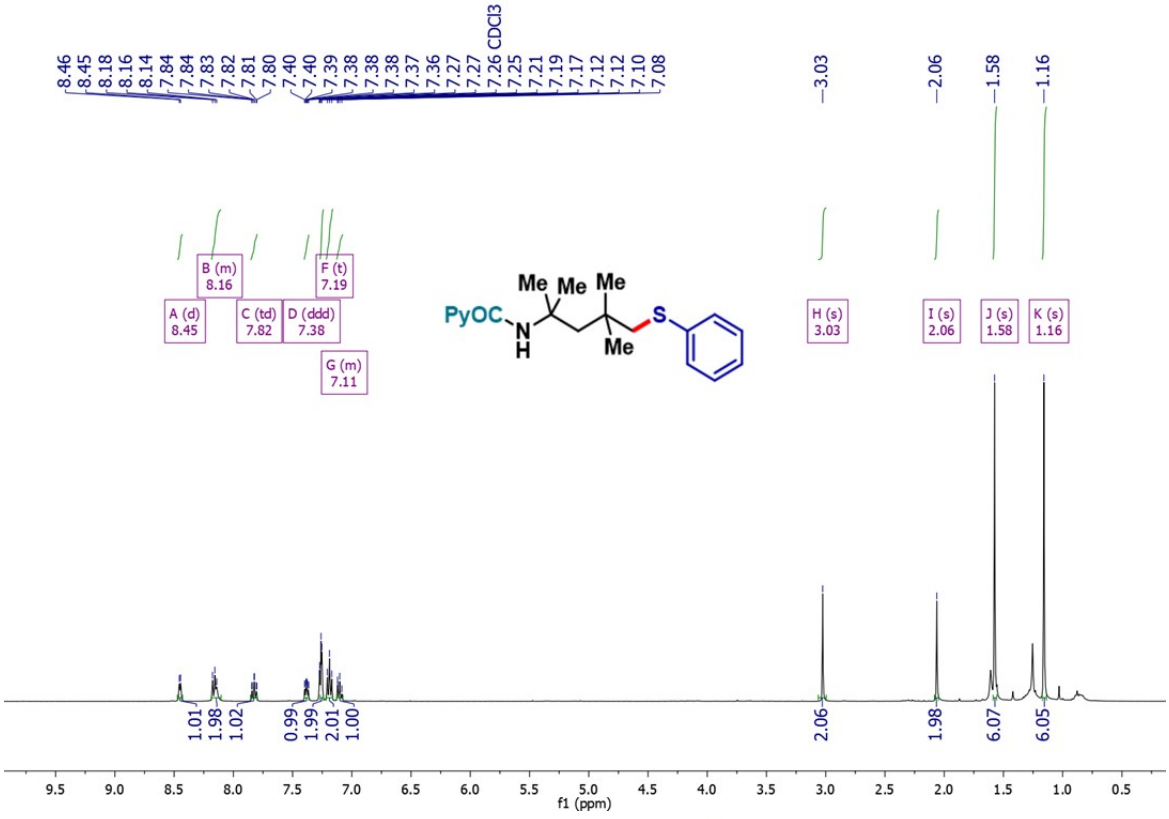
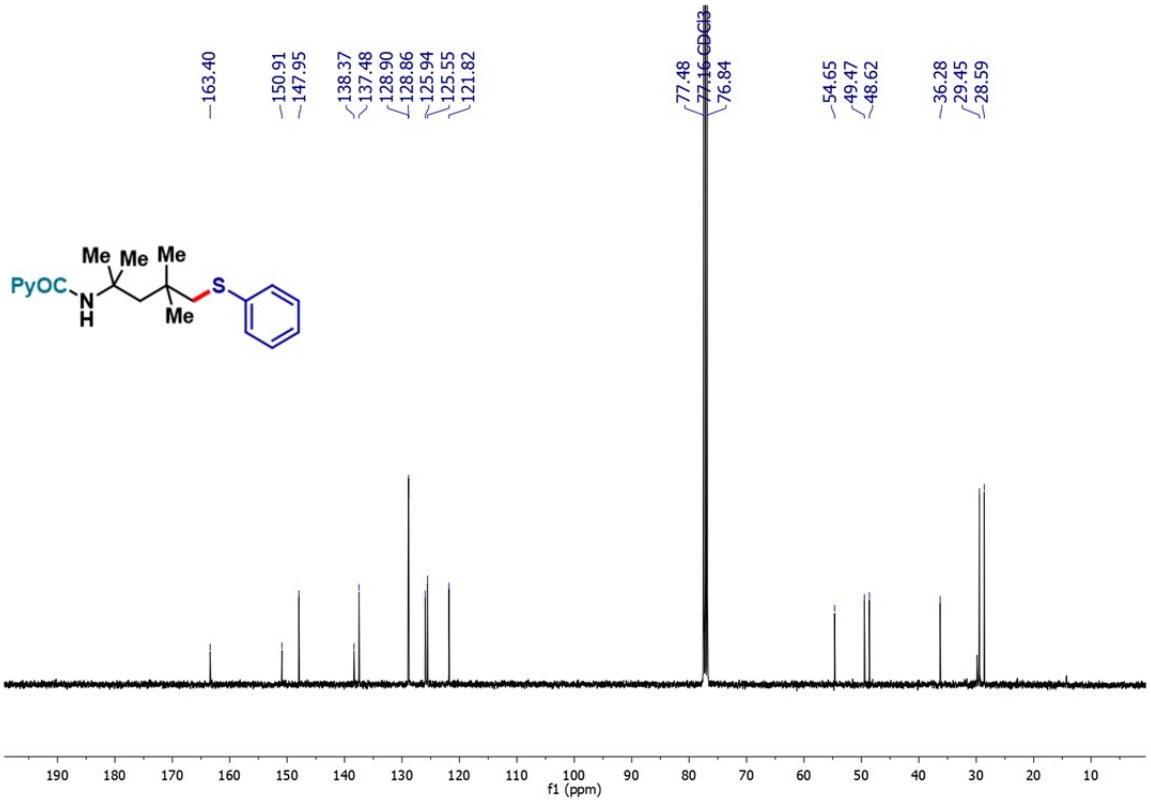
6. E. M. Dauncey, T. D. Sheppard, P. D. Smith and R. H. Munday, *Org. Lett.* 2024, **26**, 10441–10446.

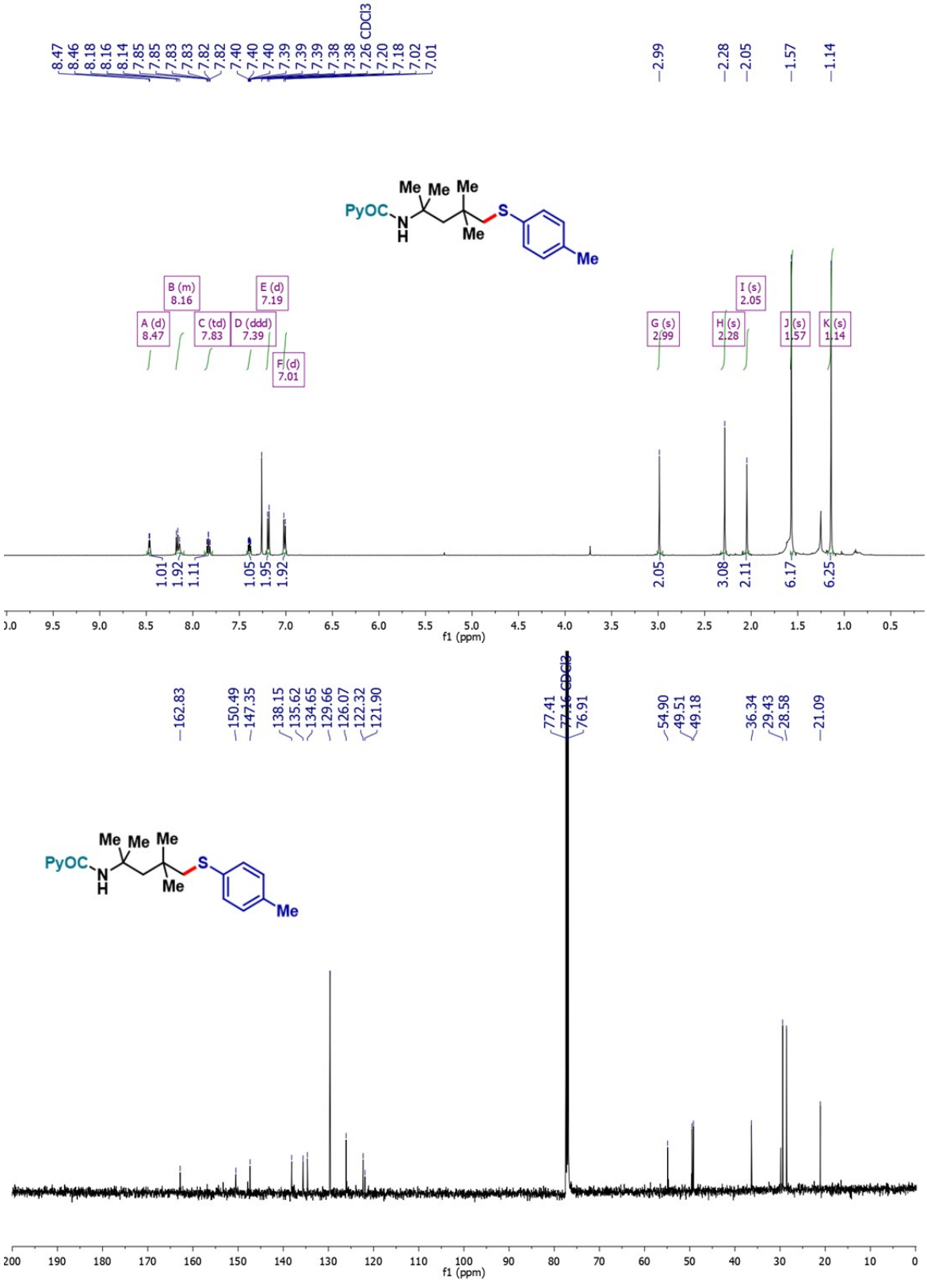
NMR Spectra

Scheme 2, entry 2a

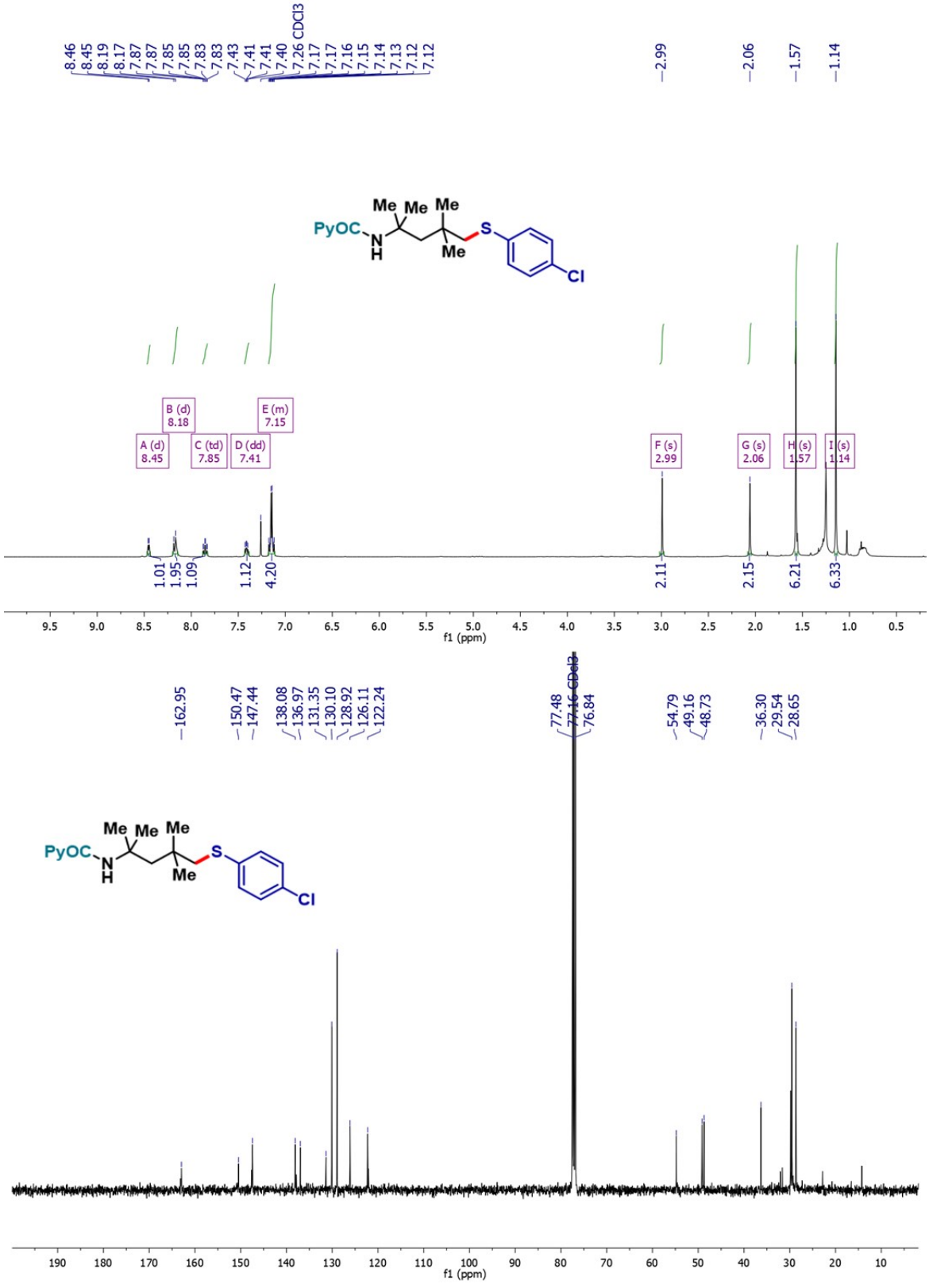




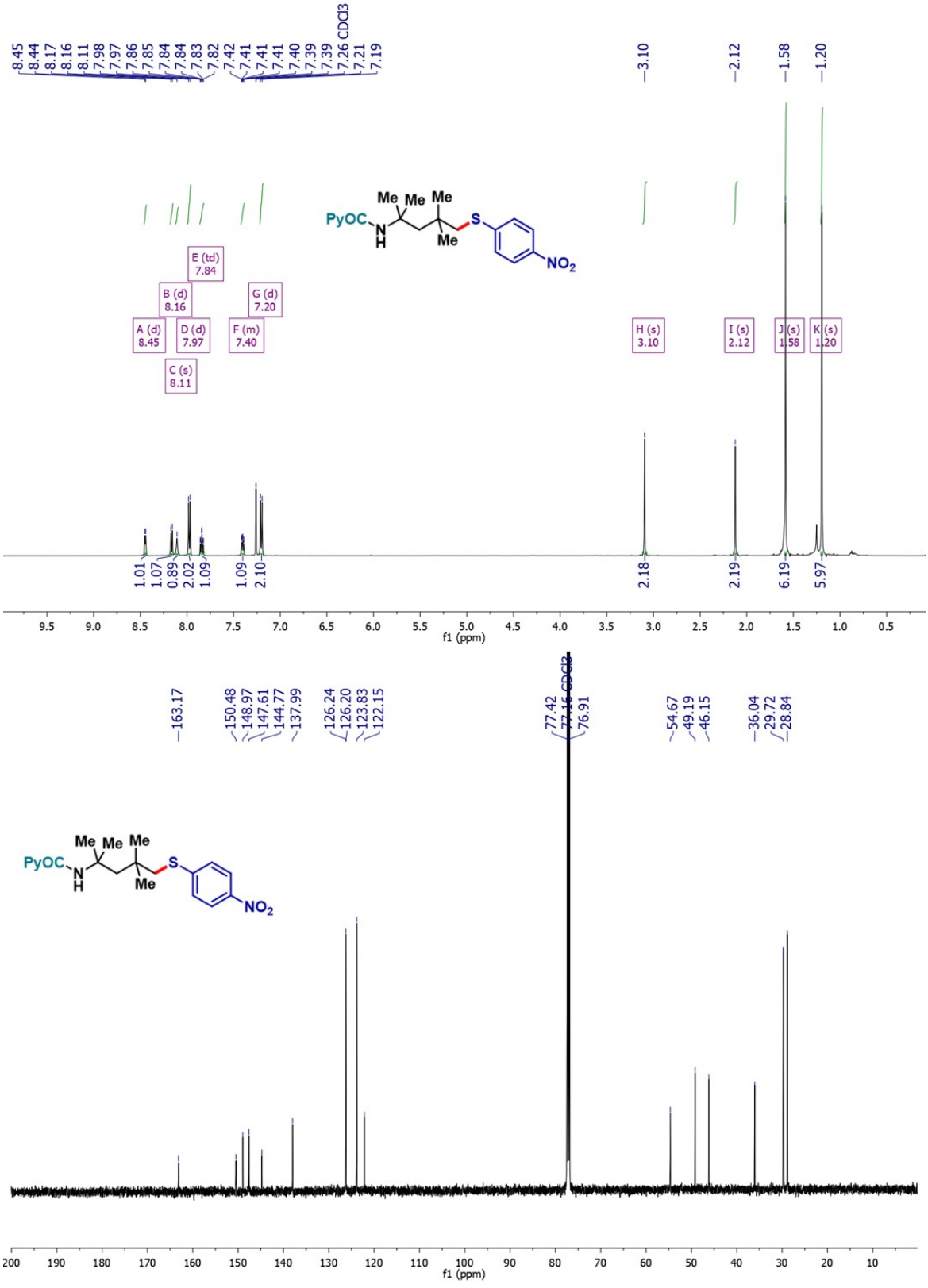
Scheme 2, entry 2b



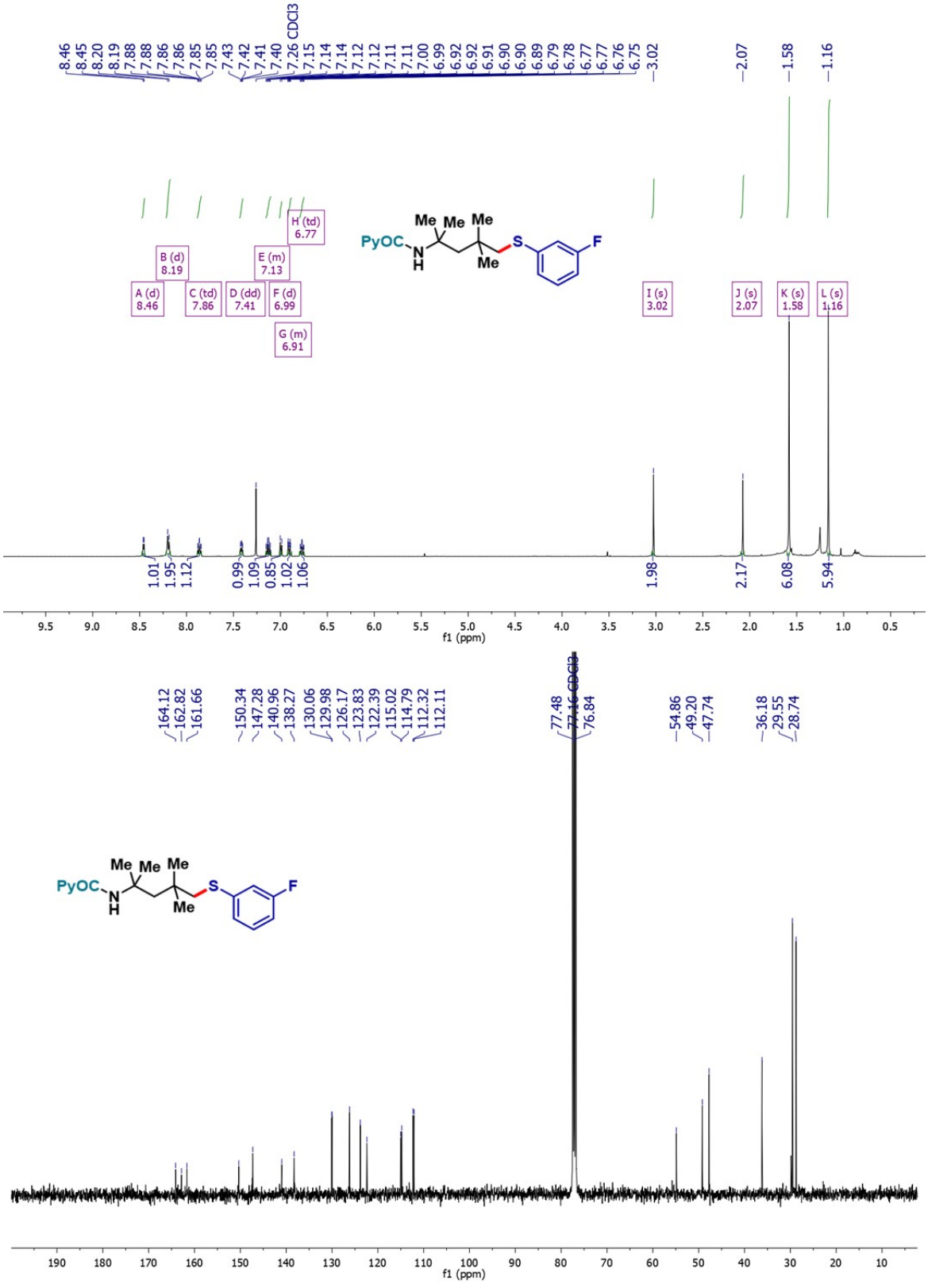
Scheme 2, entry 2c

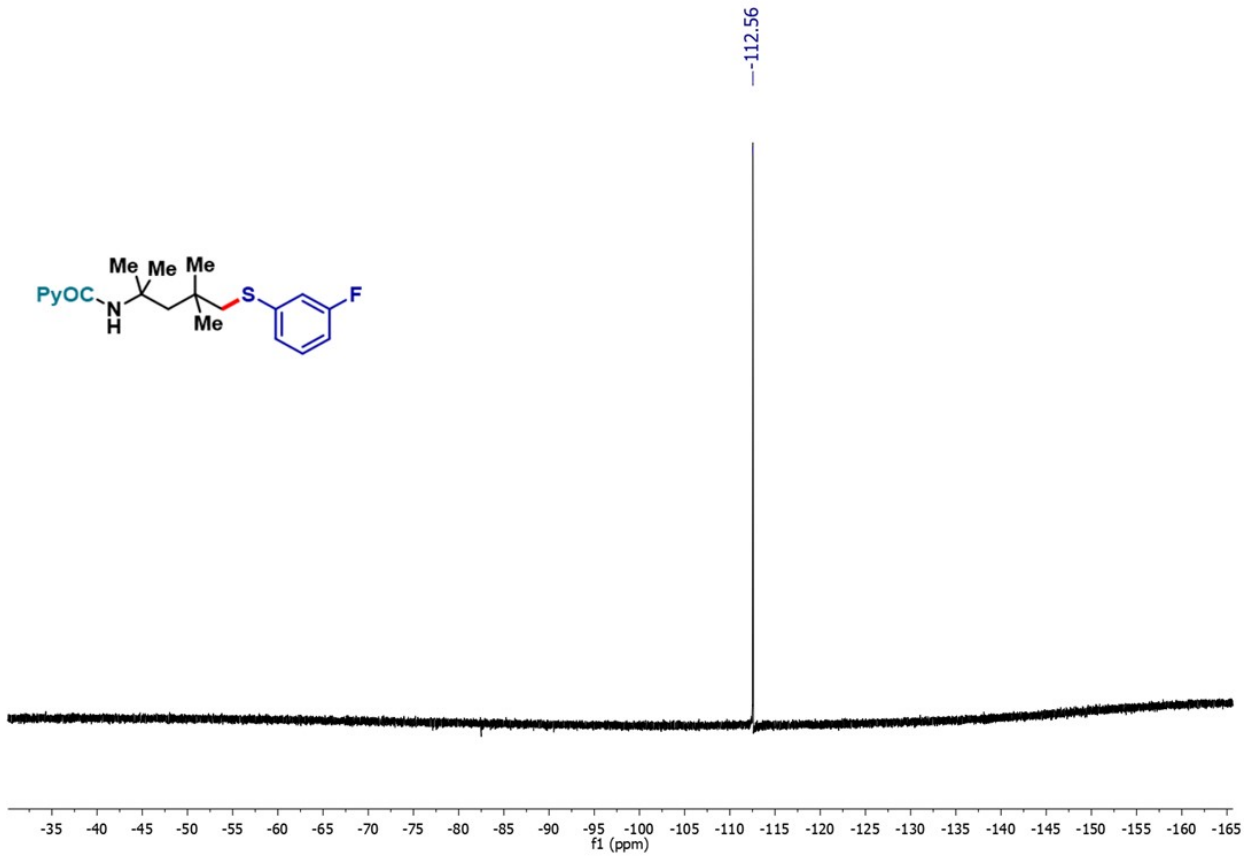


Scheme 2, entry 2d



Scheme 2, entry 2e

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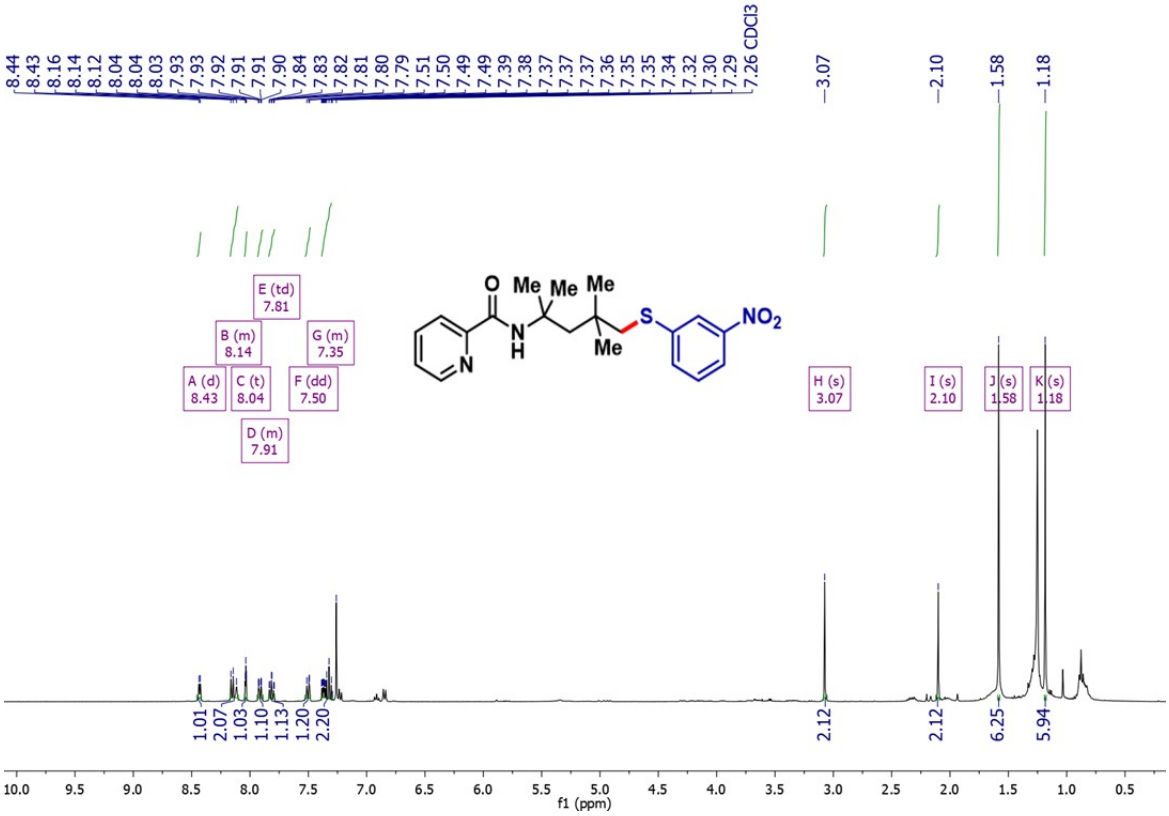
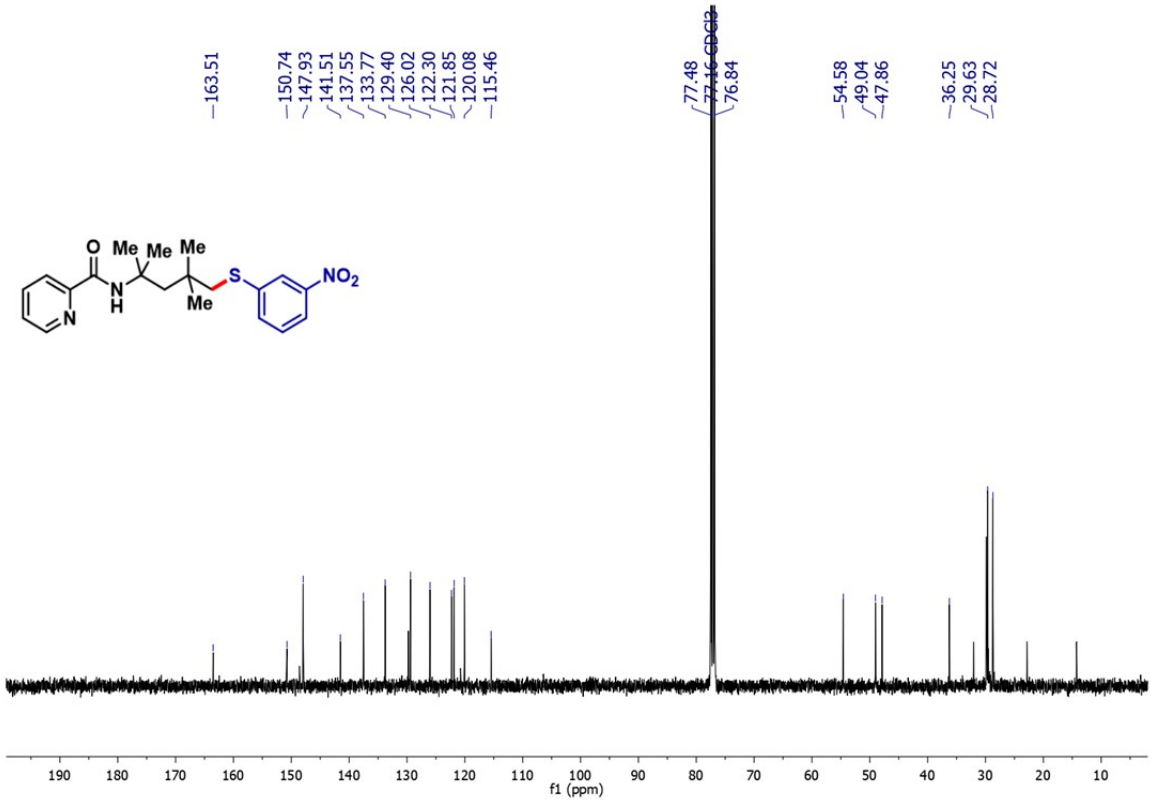
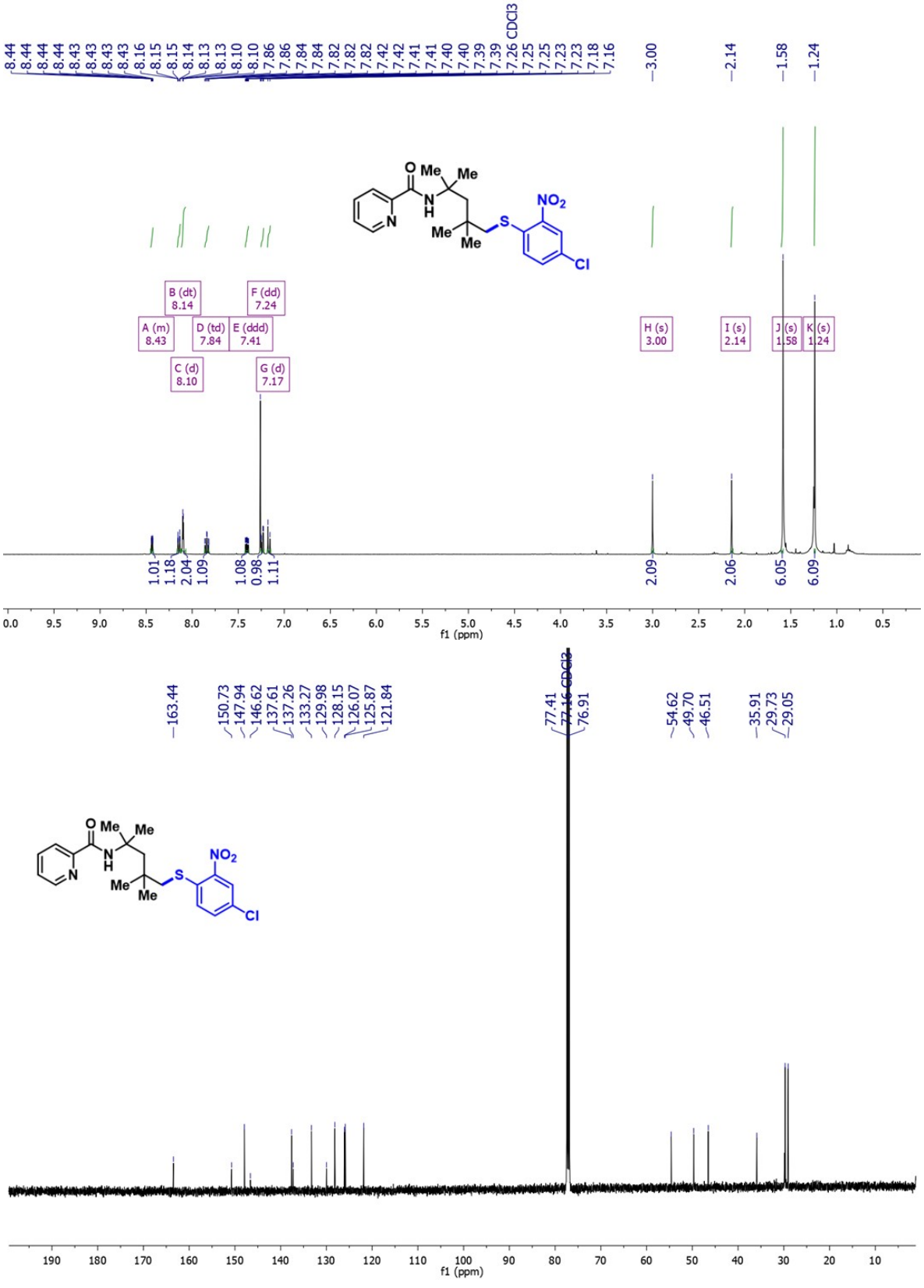
f1 (ppm)

Scheme 2, entry 2f

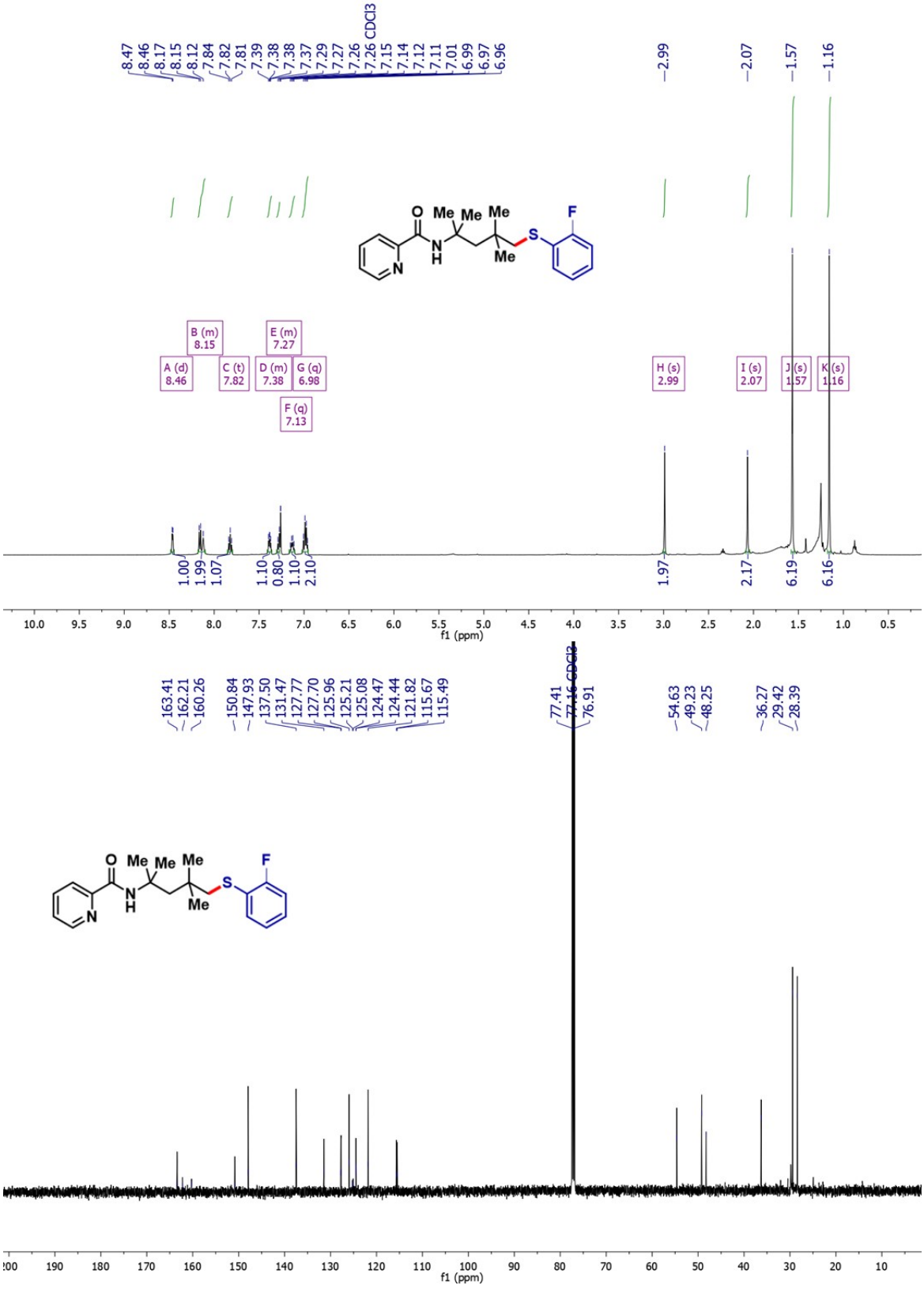


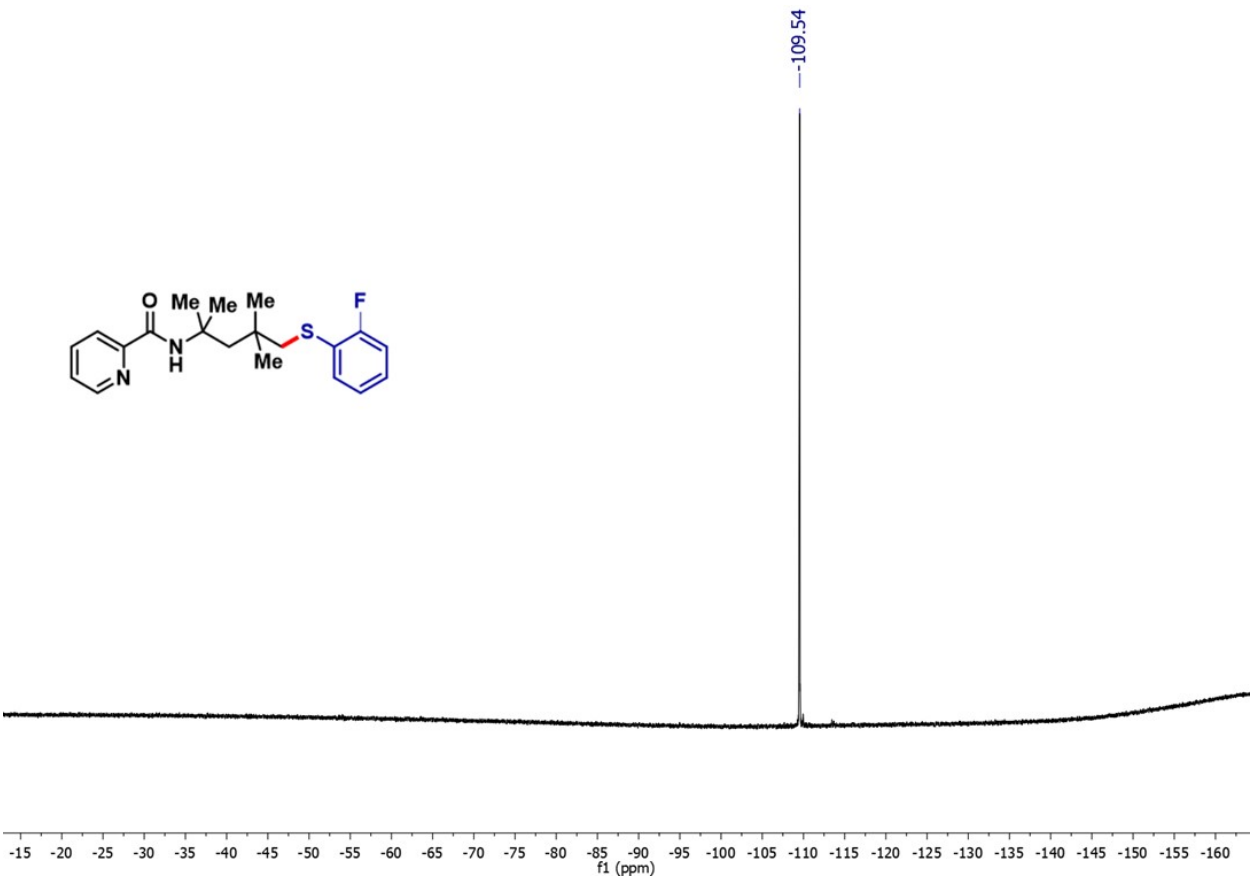


Scheme 2, entry 2g



Scheme 2, entry 2h

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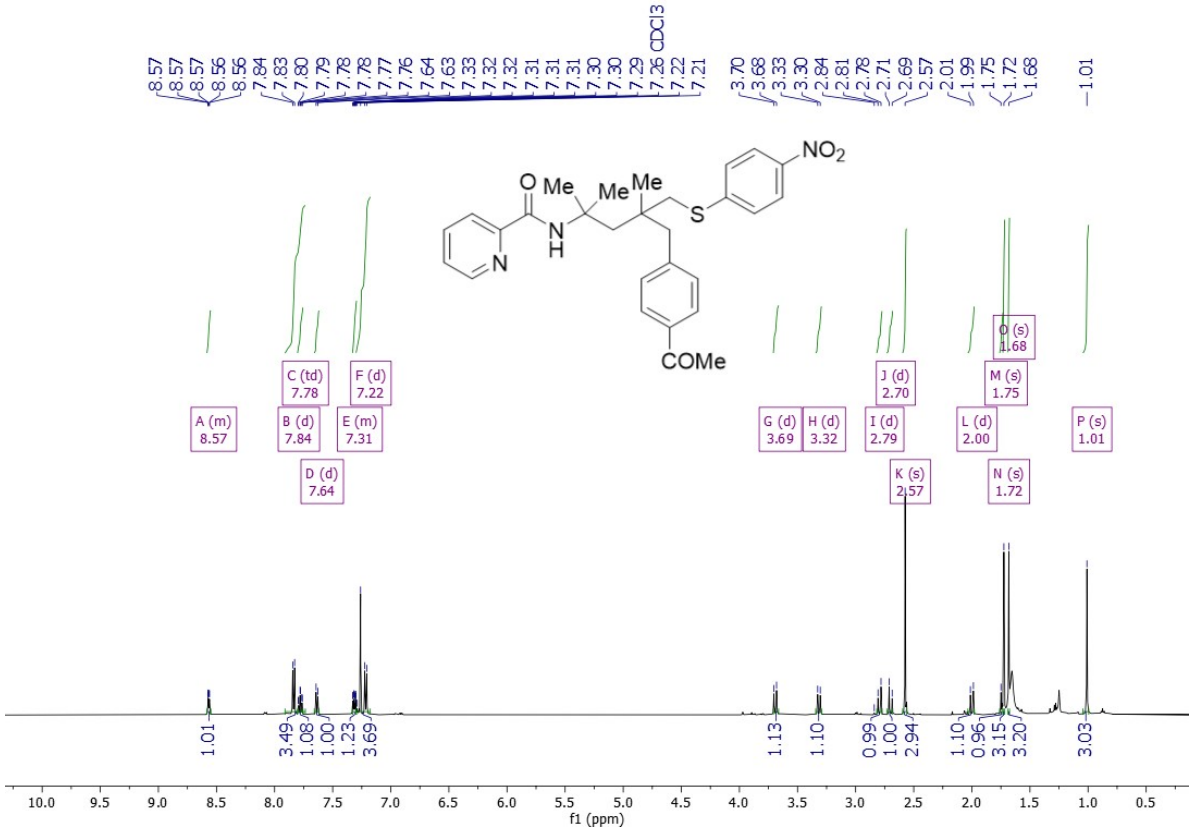
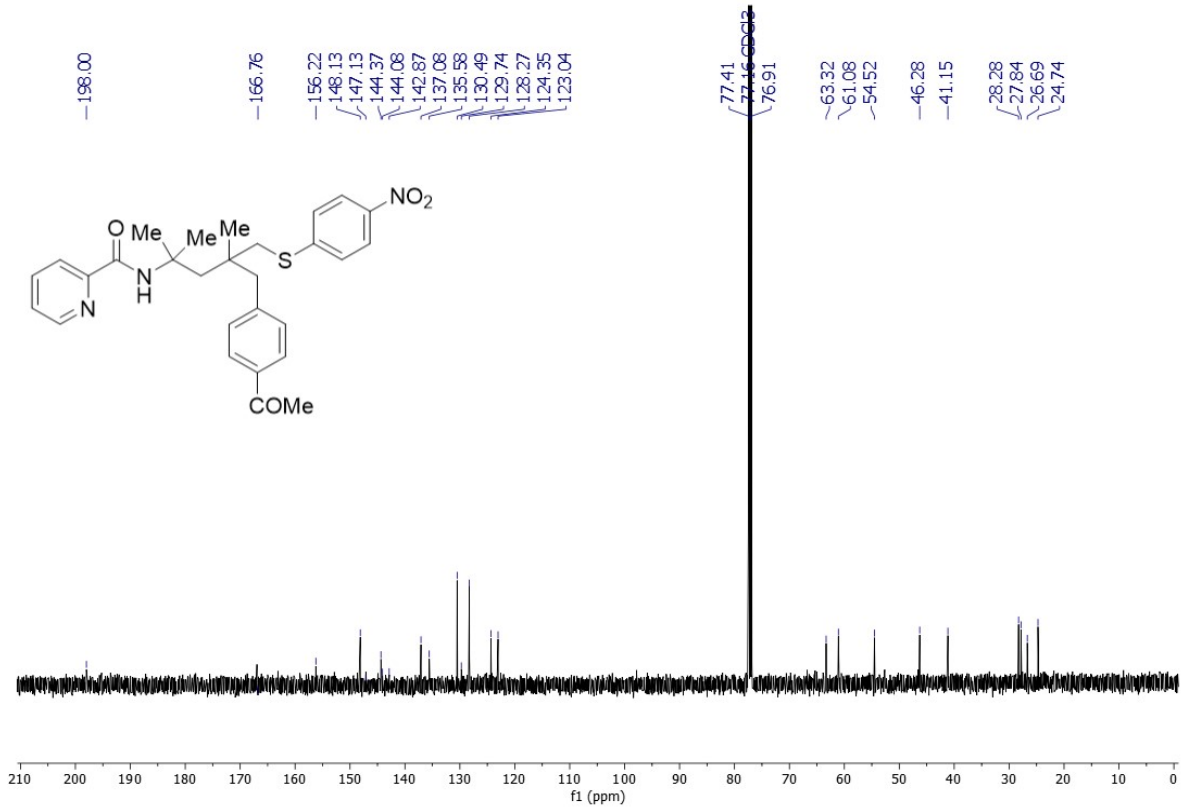
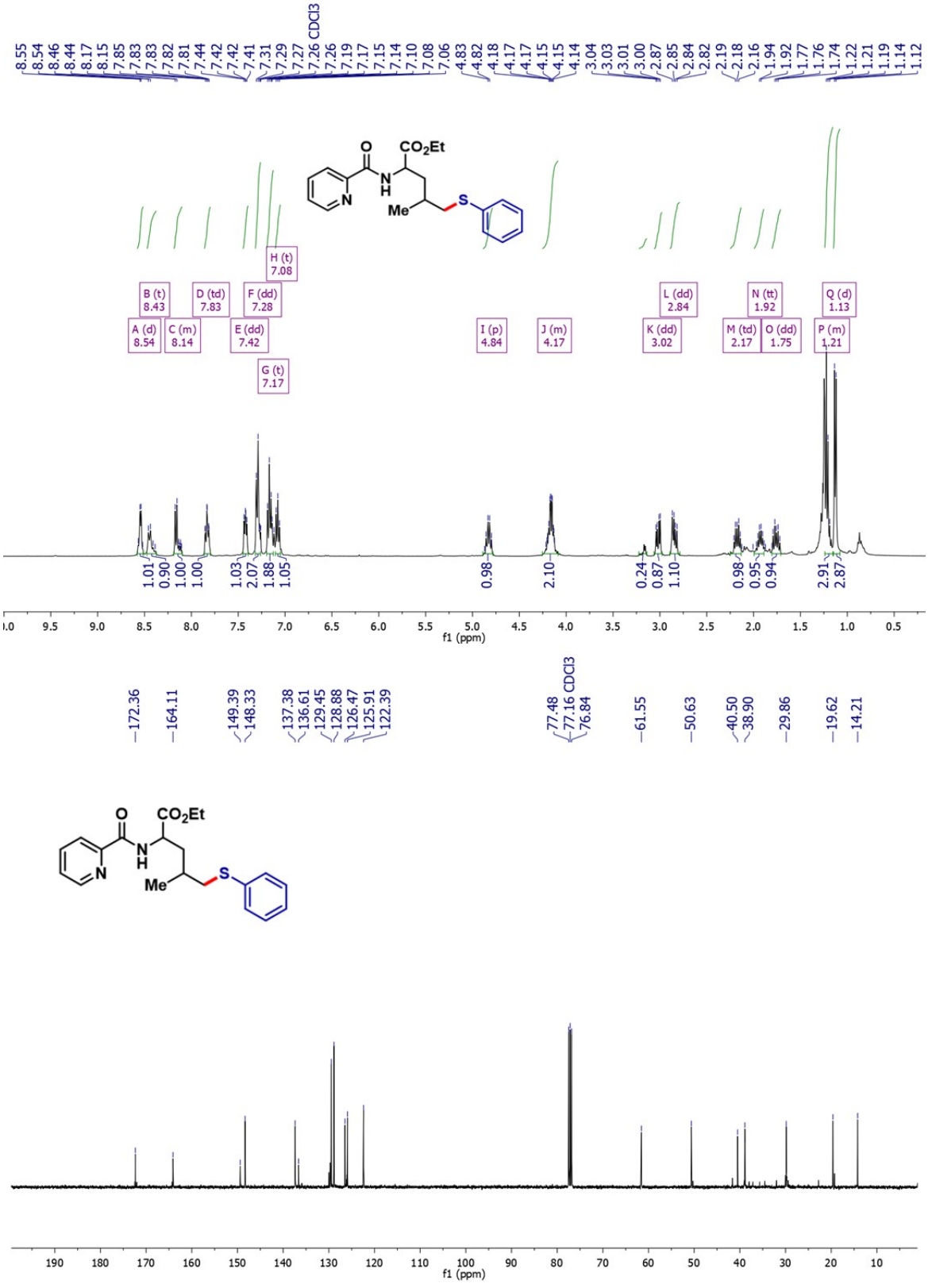
f1 (ppm)

Scheme 2, entry 2i

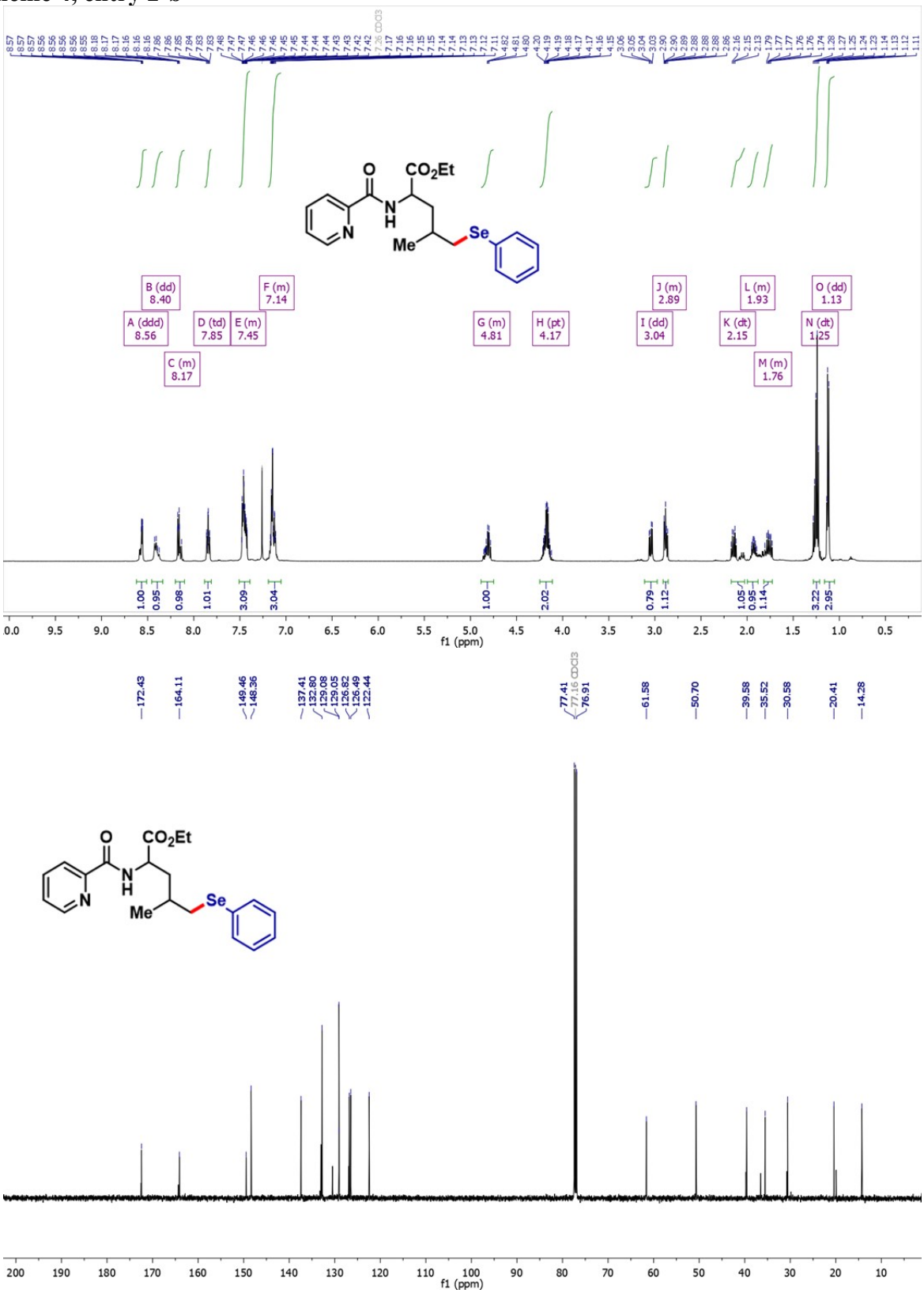




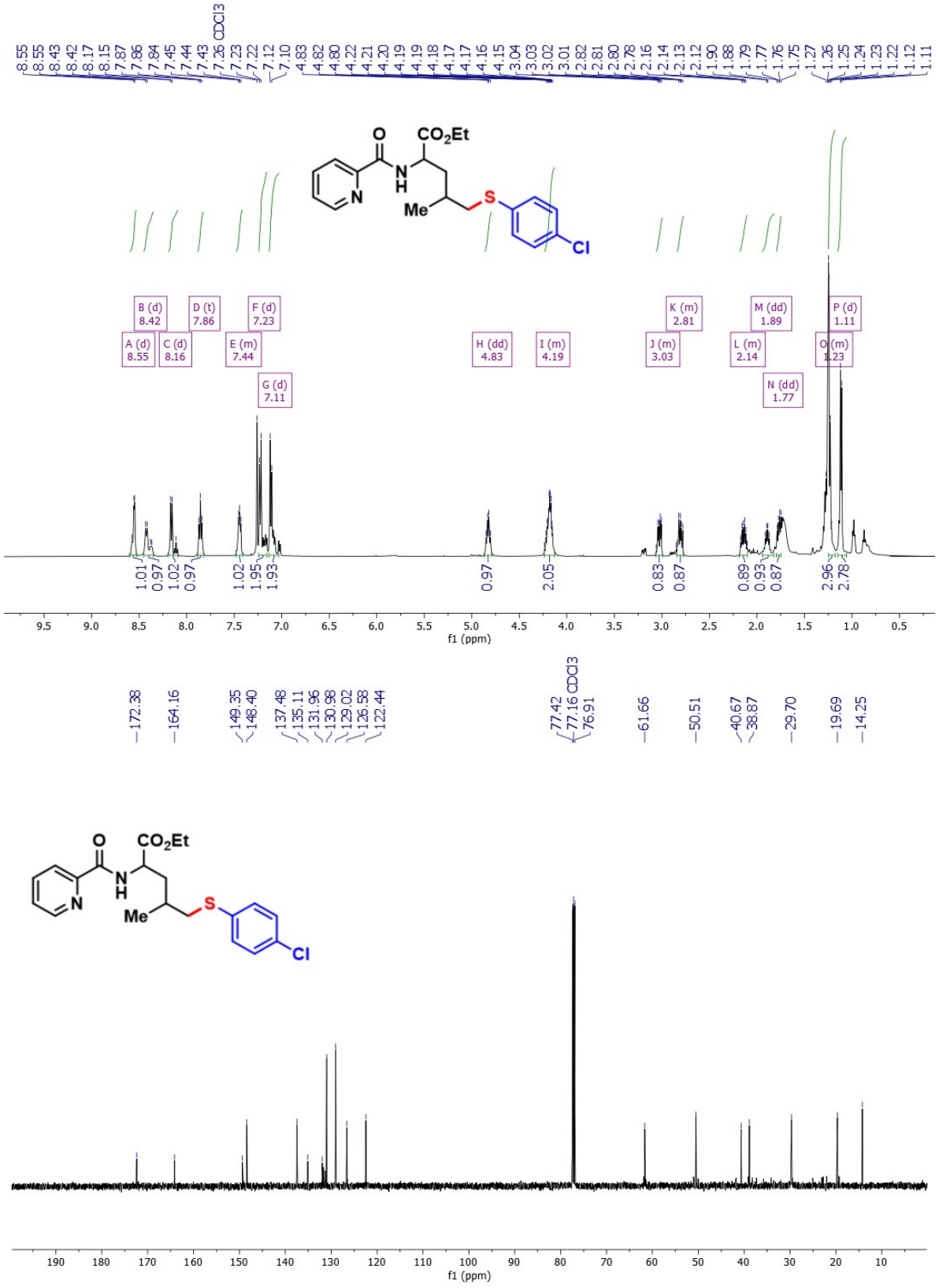
Scheme 4, entry 2'a



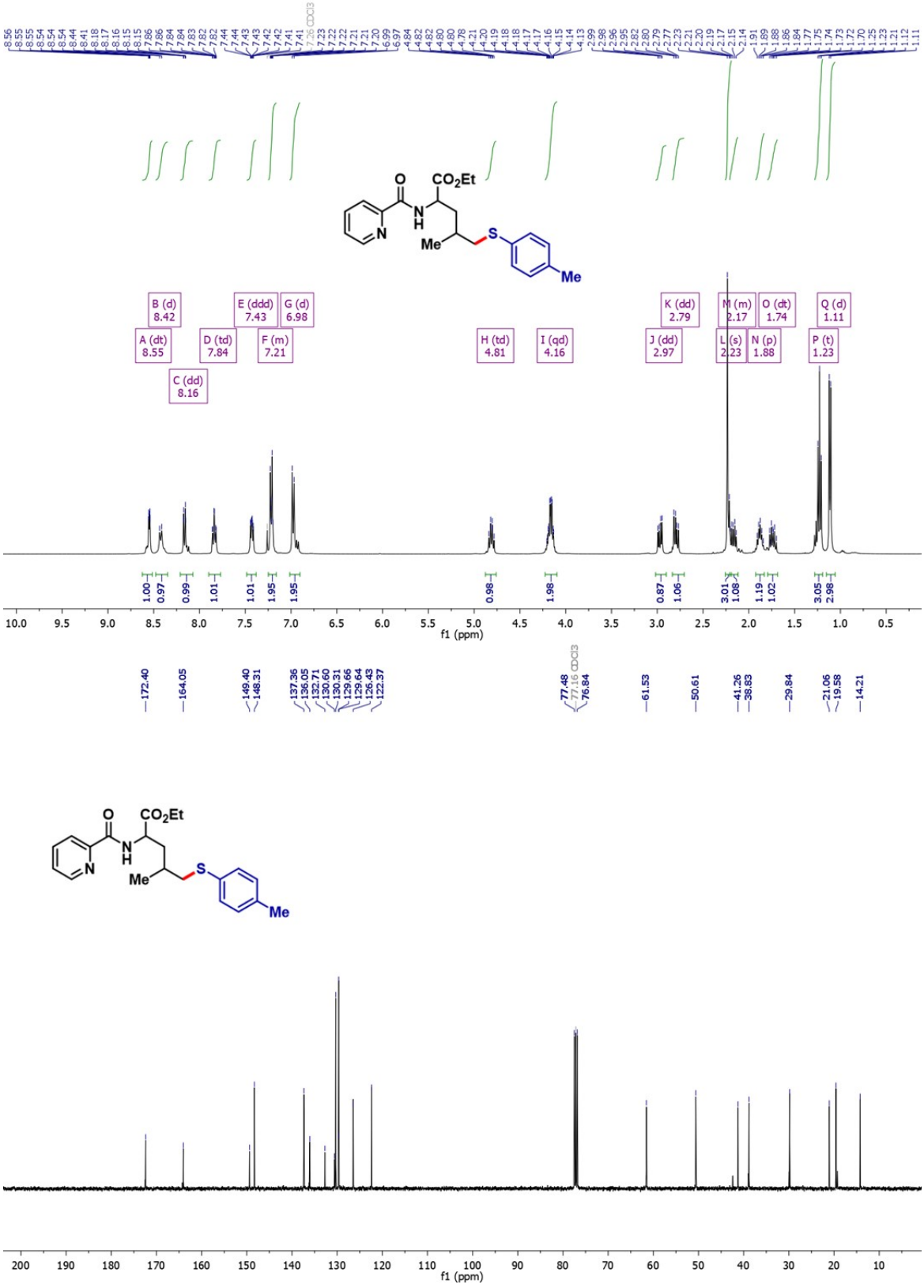
Scheme 4, entry 2'b



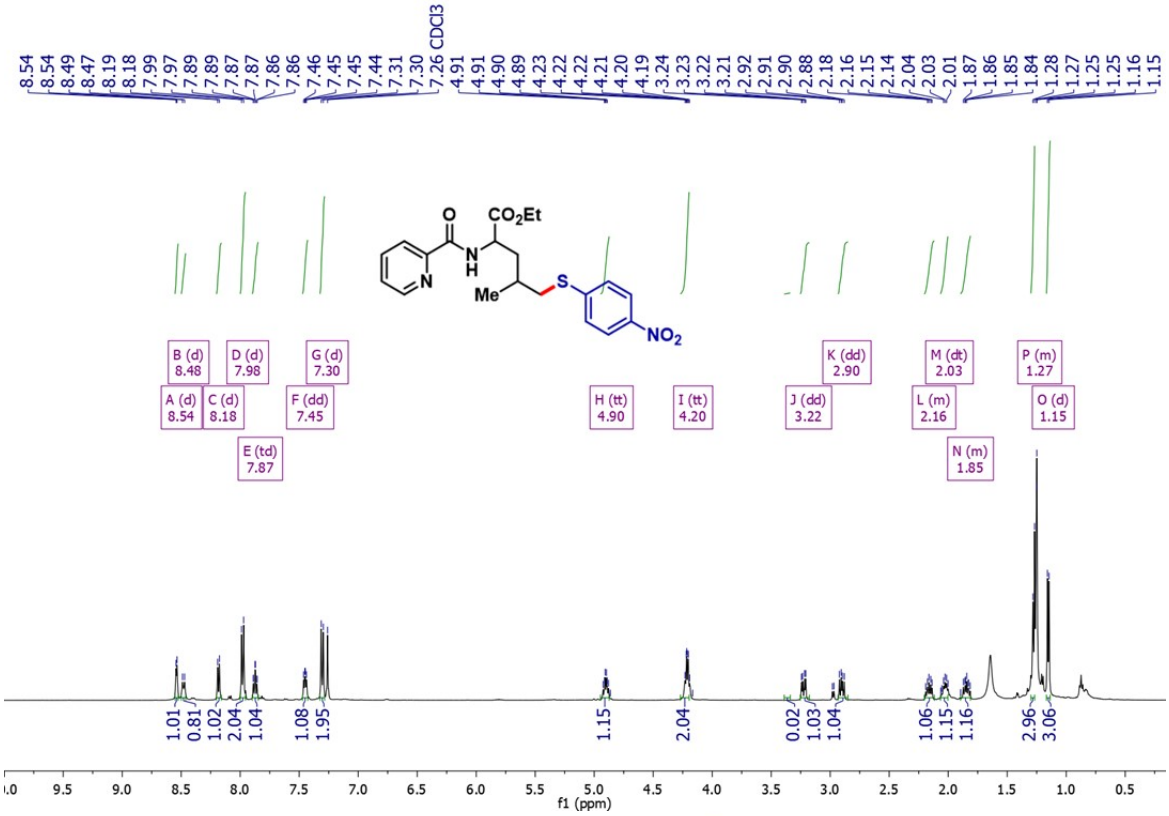
Scheme 4, entry 2'c

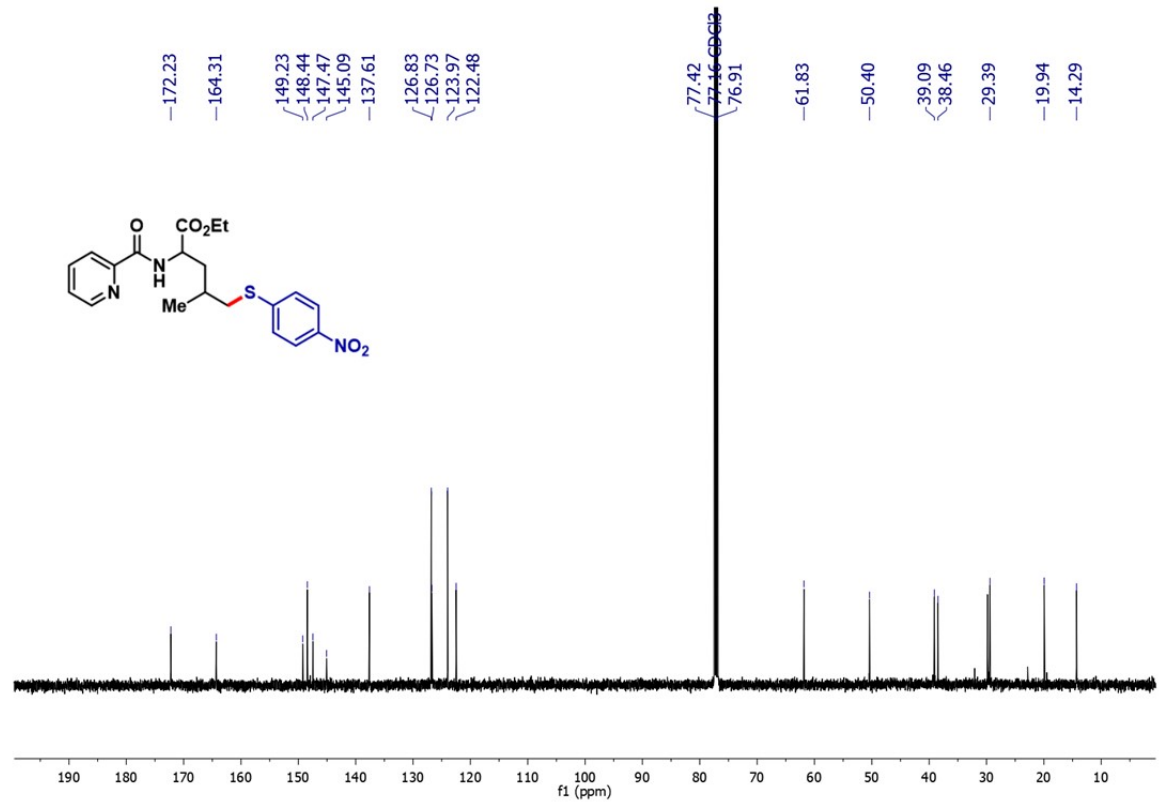


Scheme 4, entry 2'd

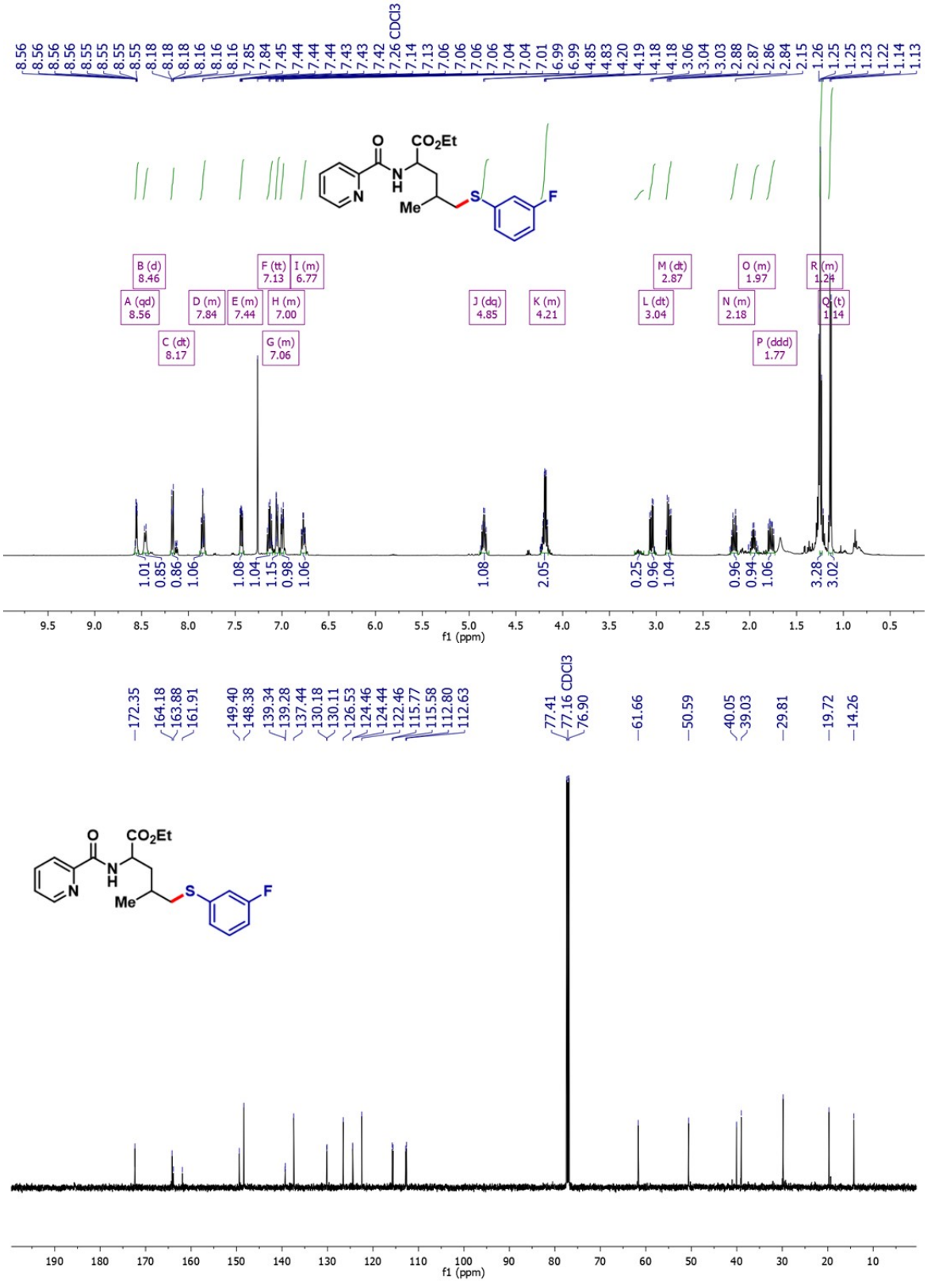


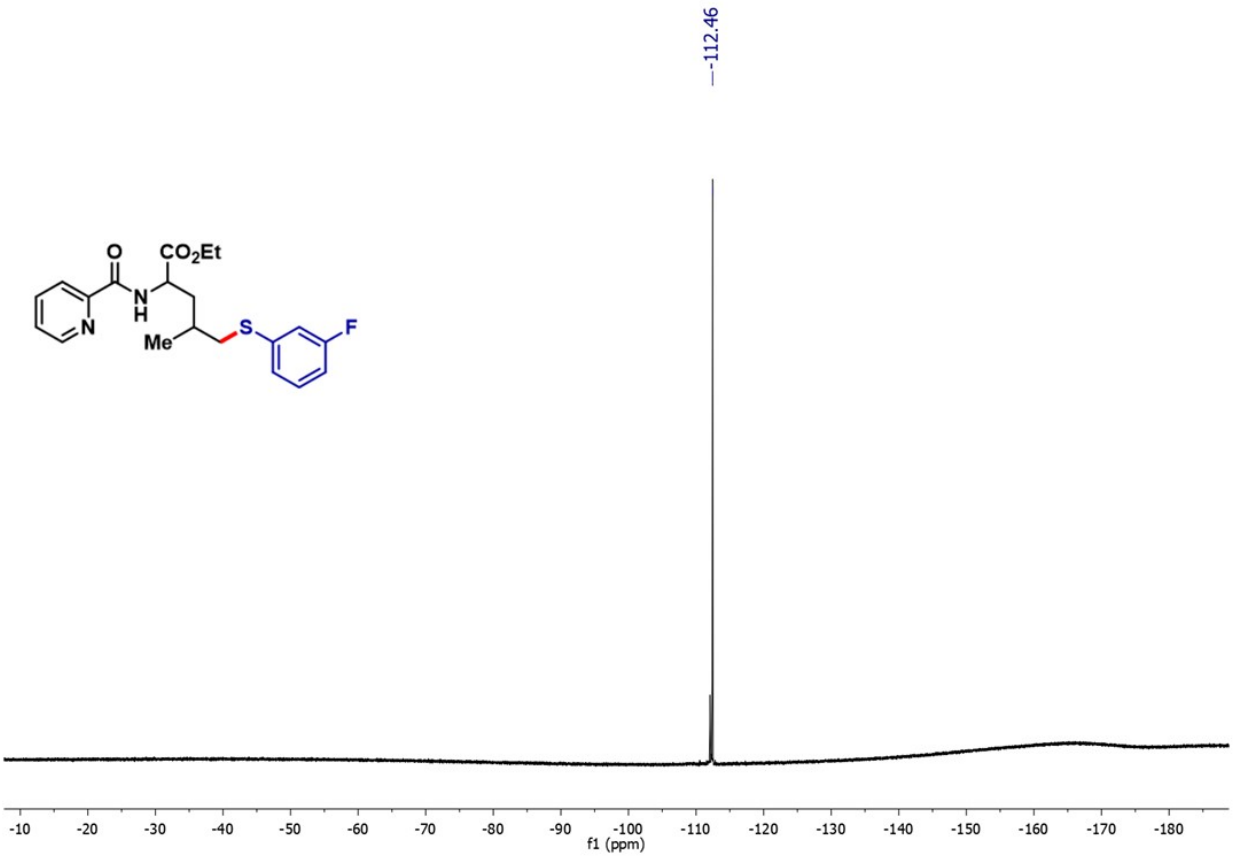
Scheme 4, entry 2'e





Scheme 4, entry 2'f

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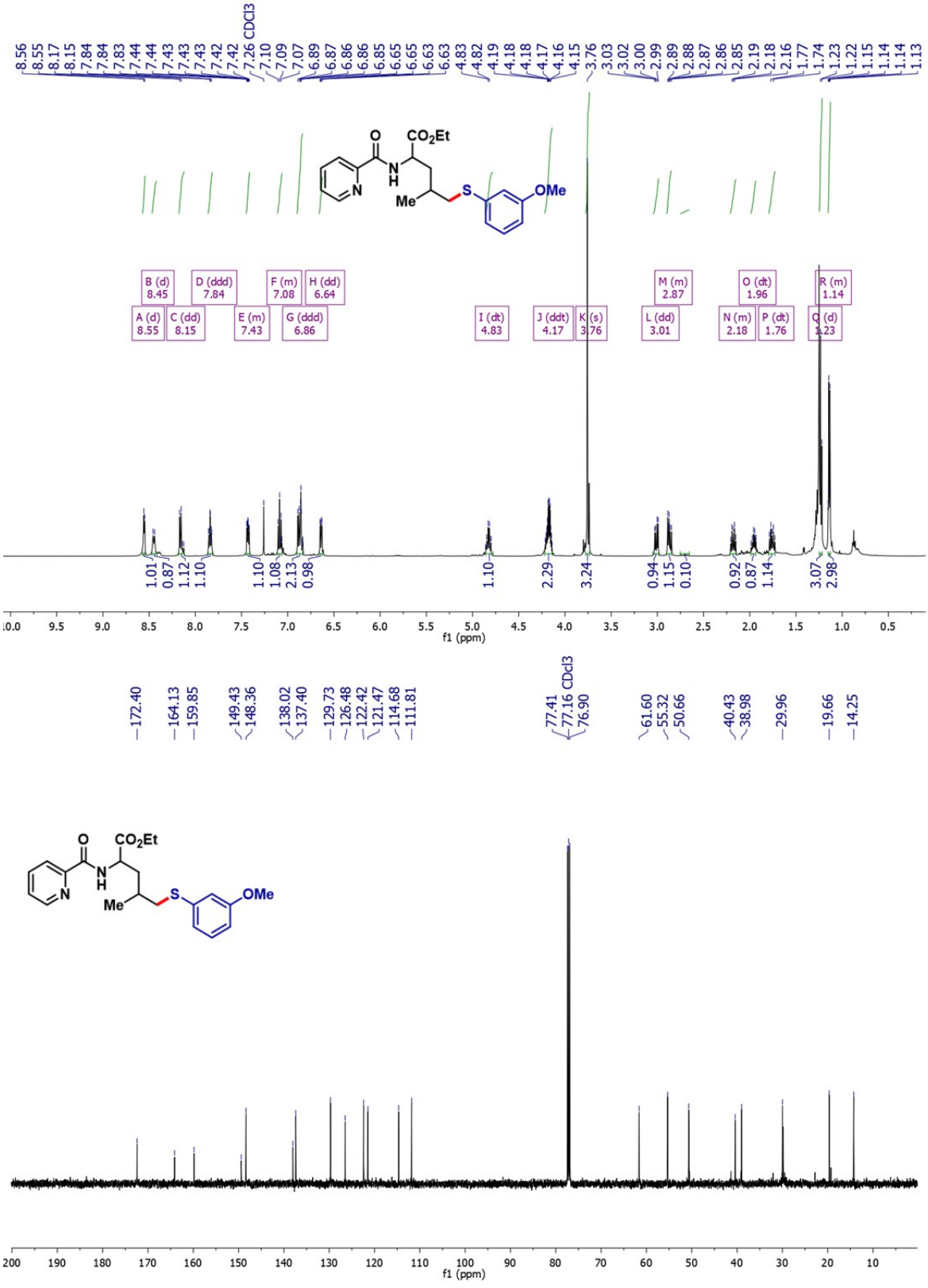
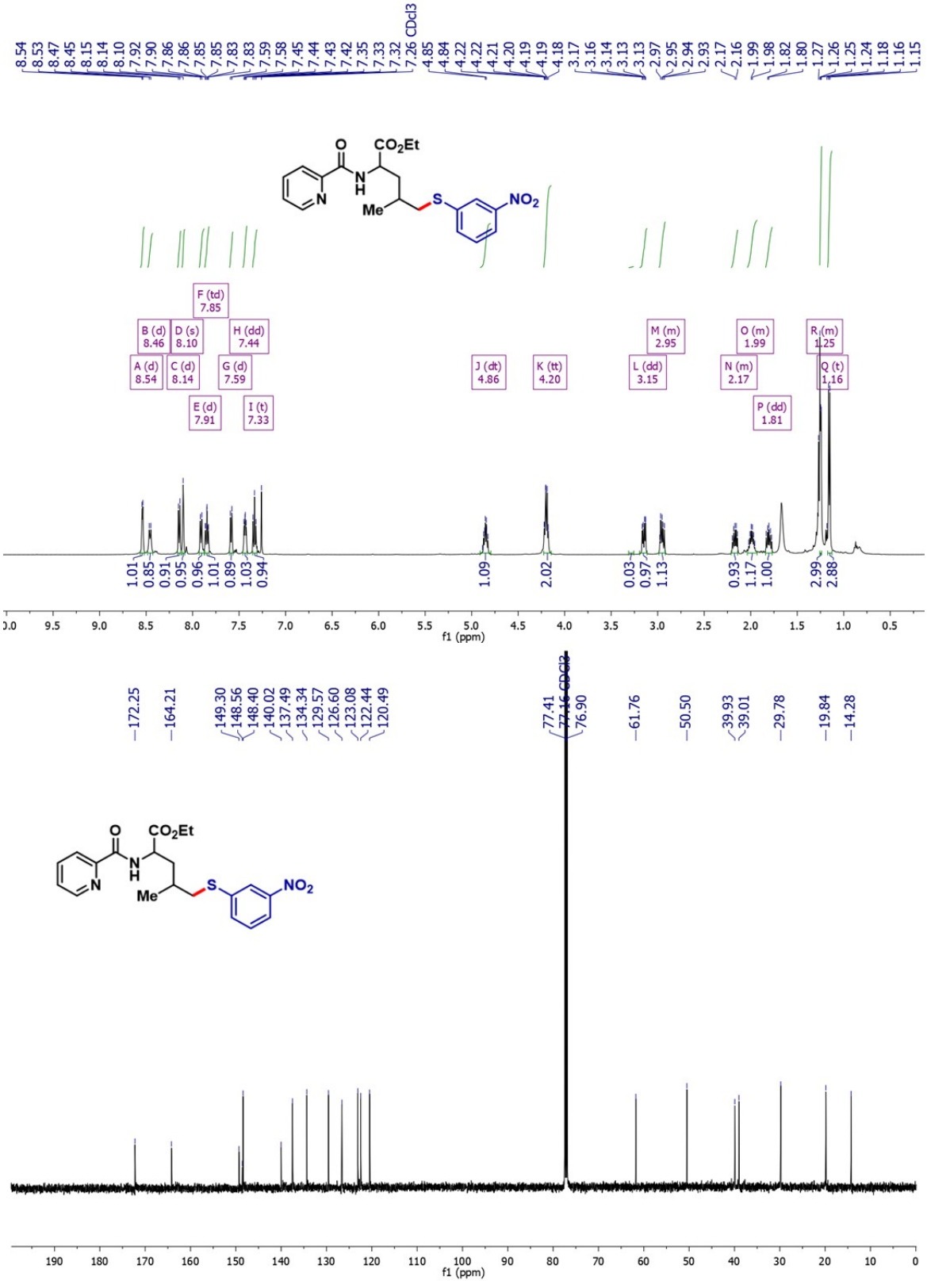
-170
-180
f1 (ppm)

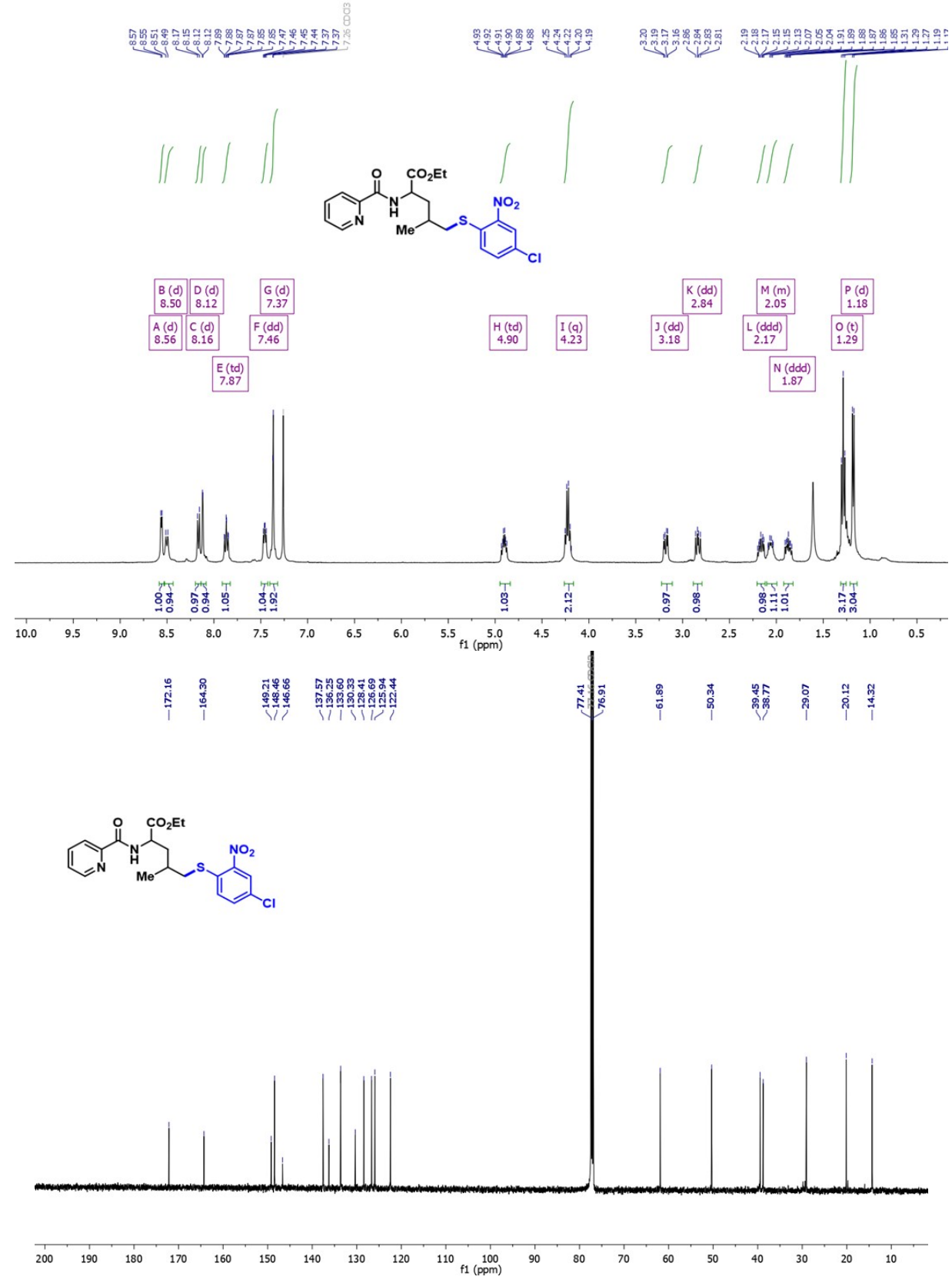
Scheme 4, entry 2'g



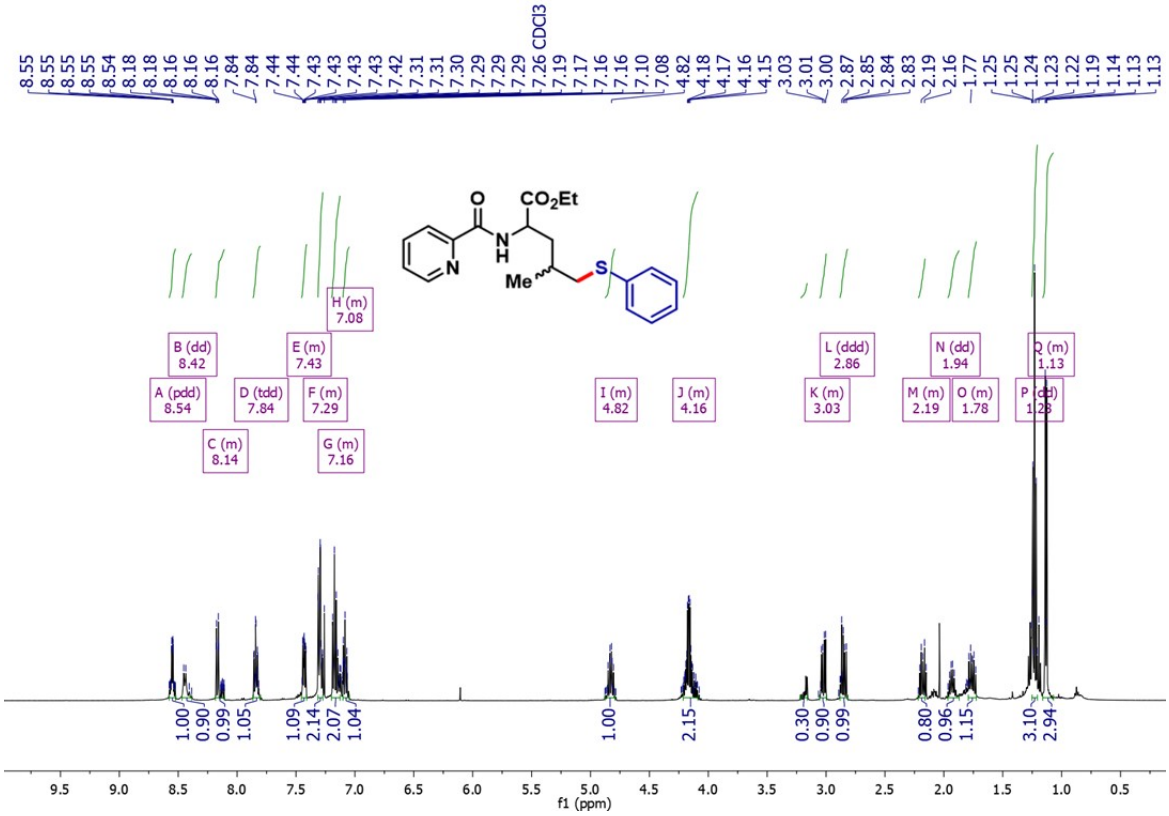
Scheme 4, entry 2'h

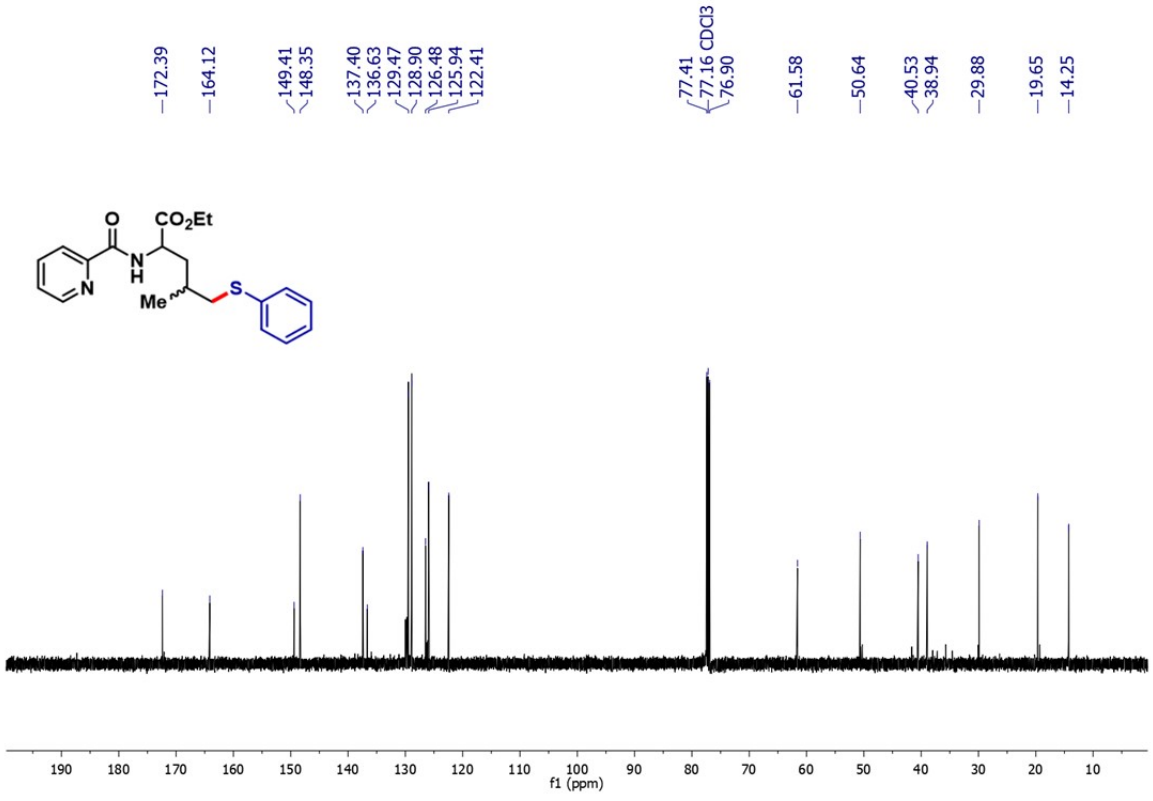


Scheme 4, entry 2'i

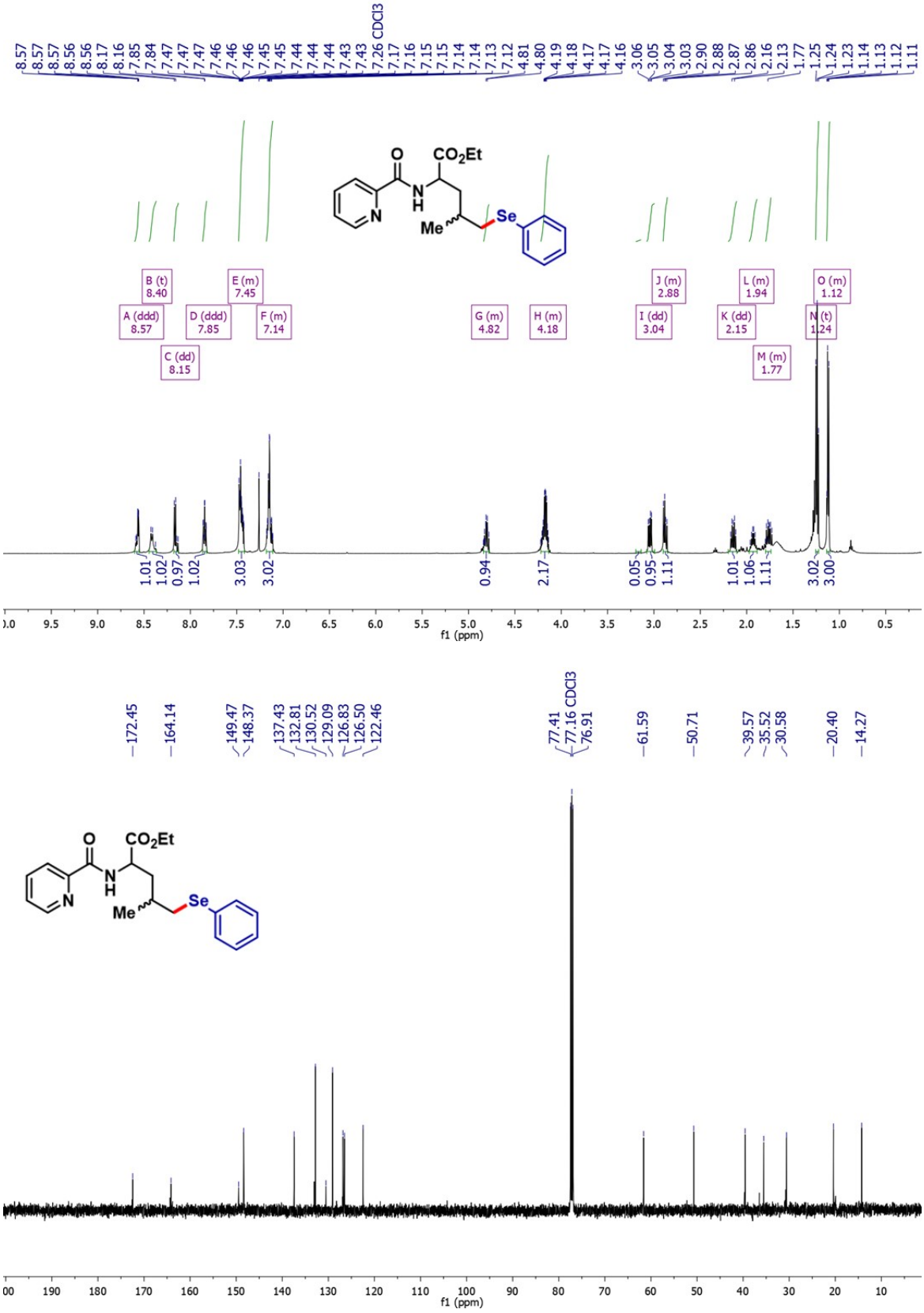


Scheme 4, entry 2'j

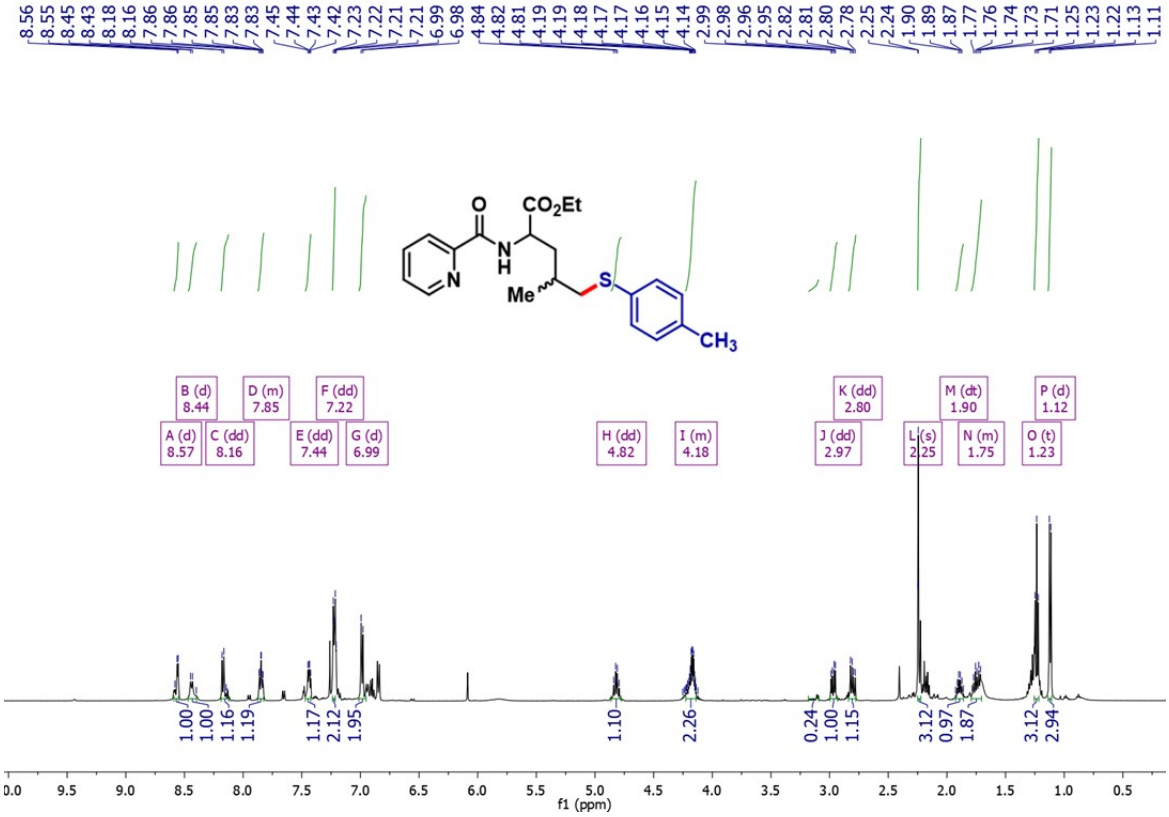


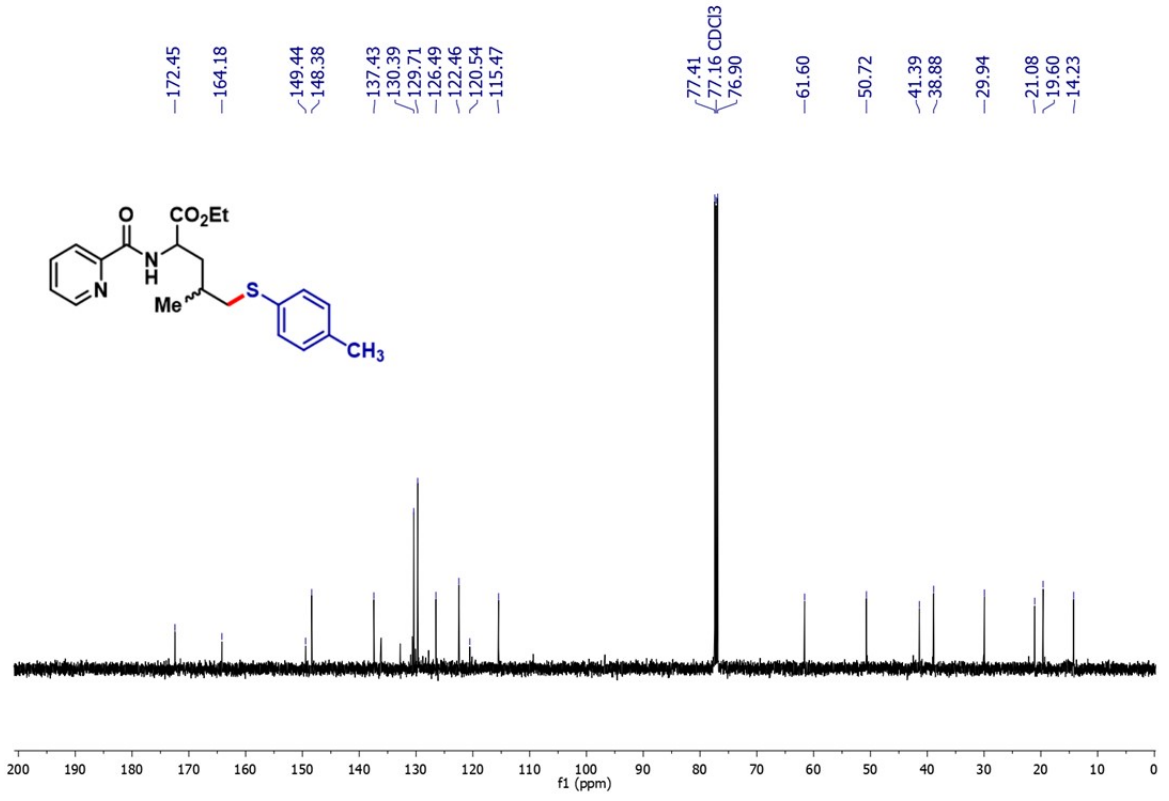


Scheme 4, entry 2'k

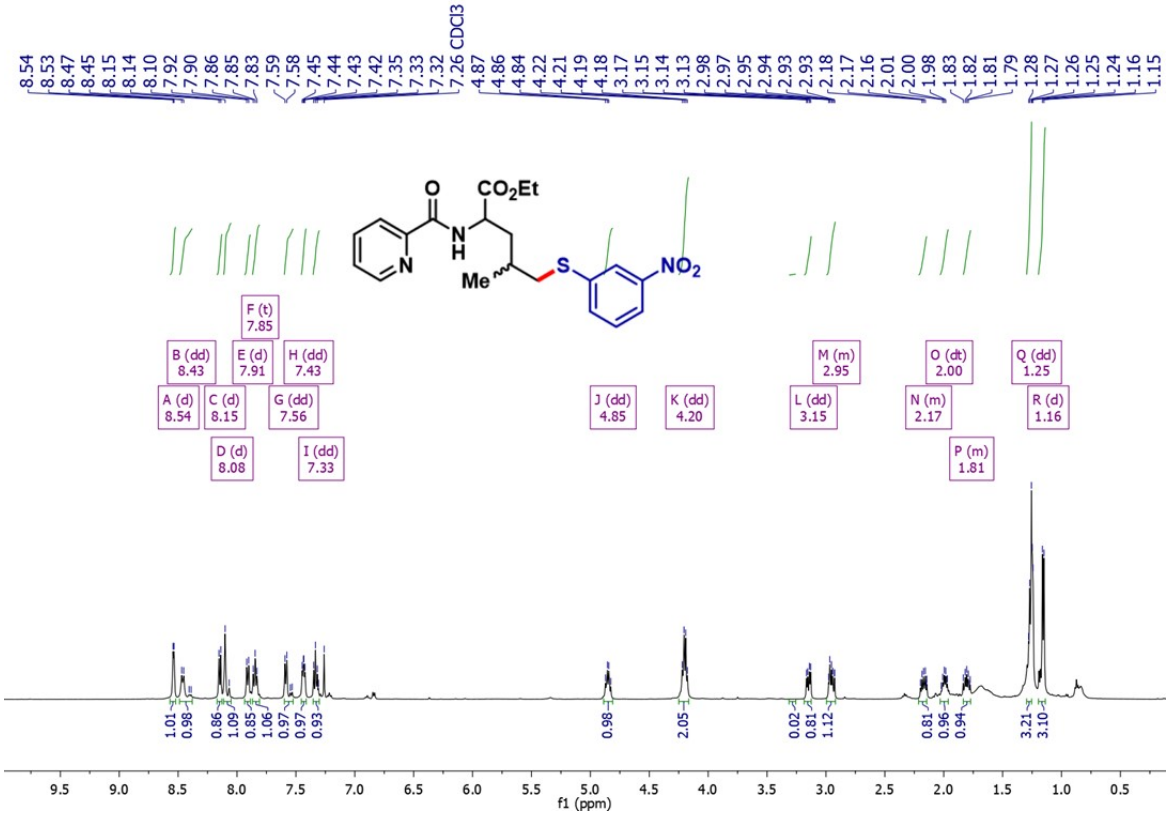


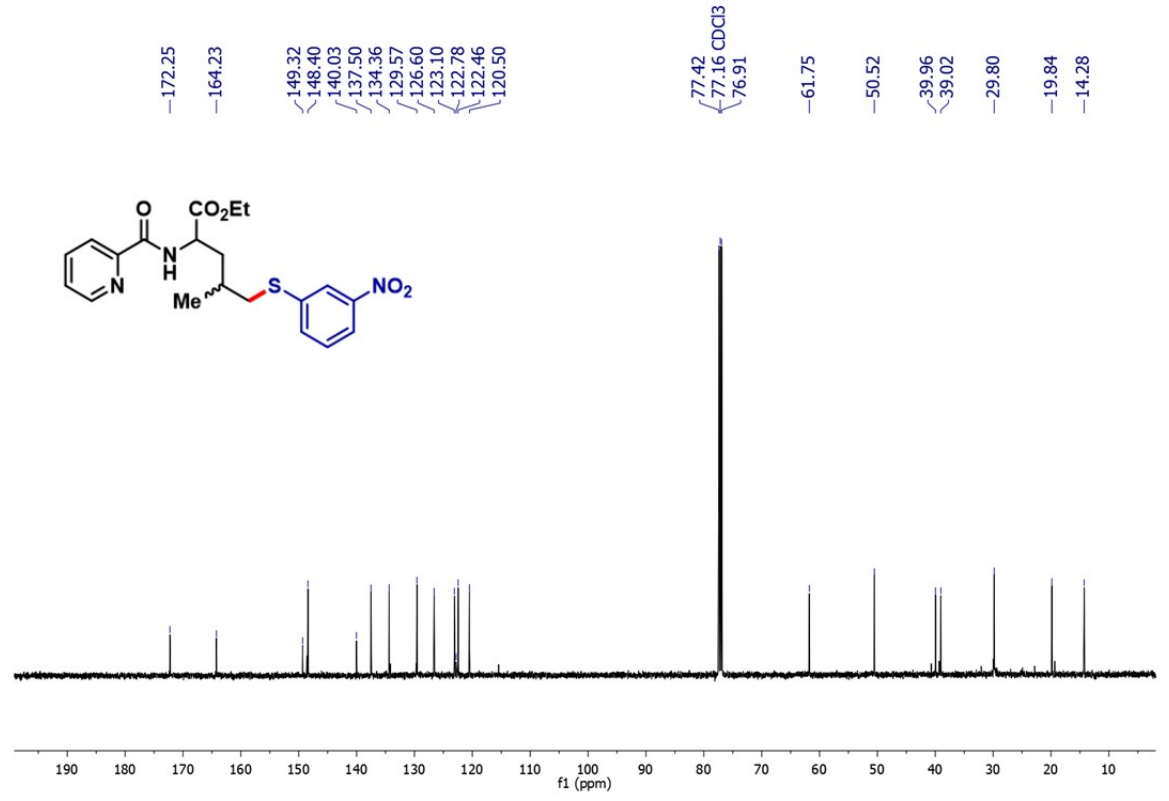
Scheme 4, entry 2'l



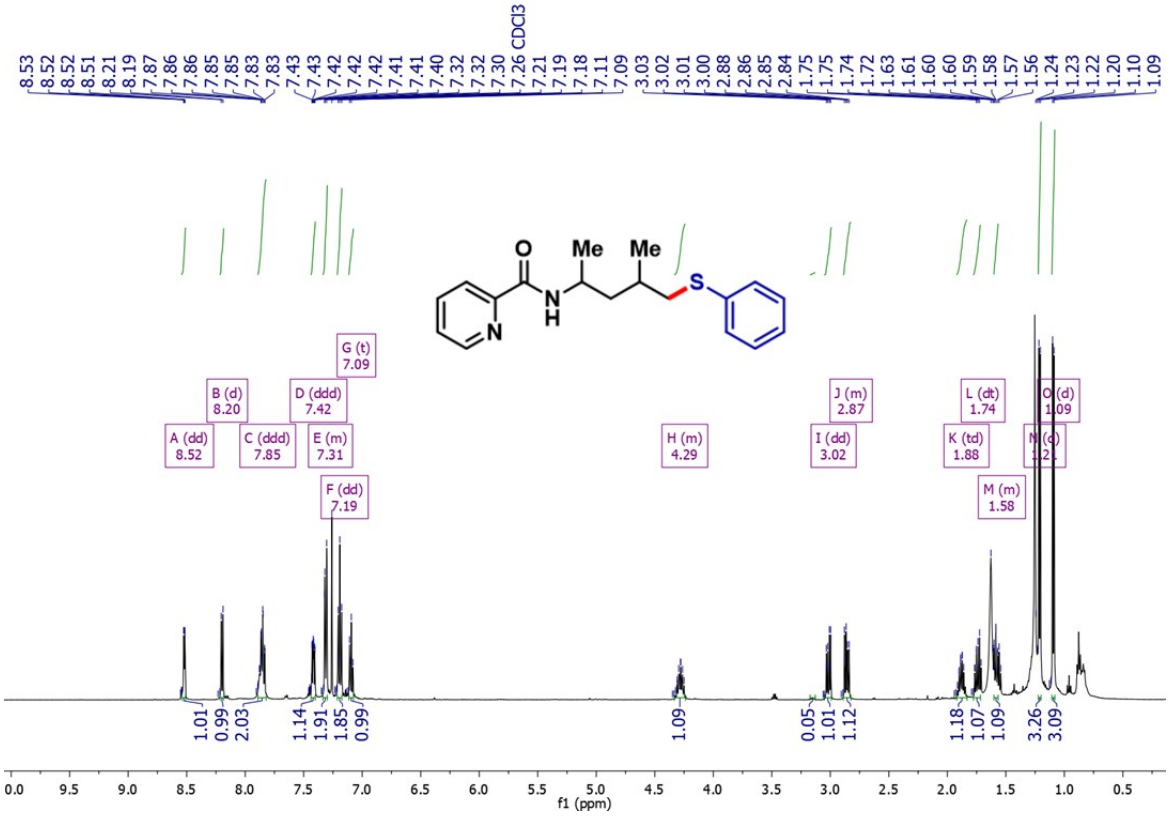


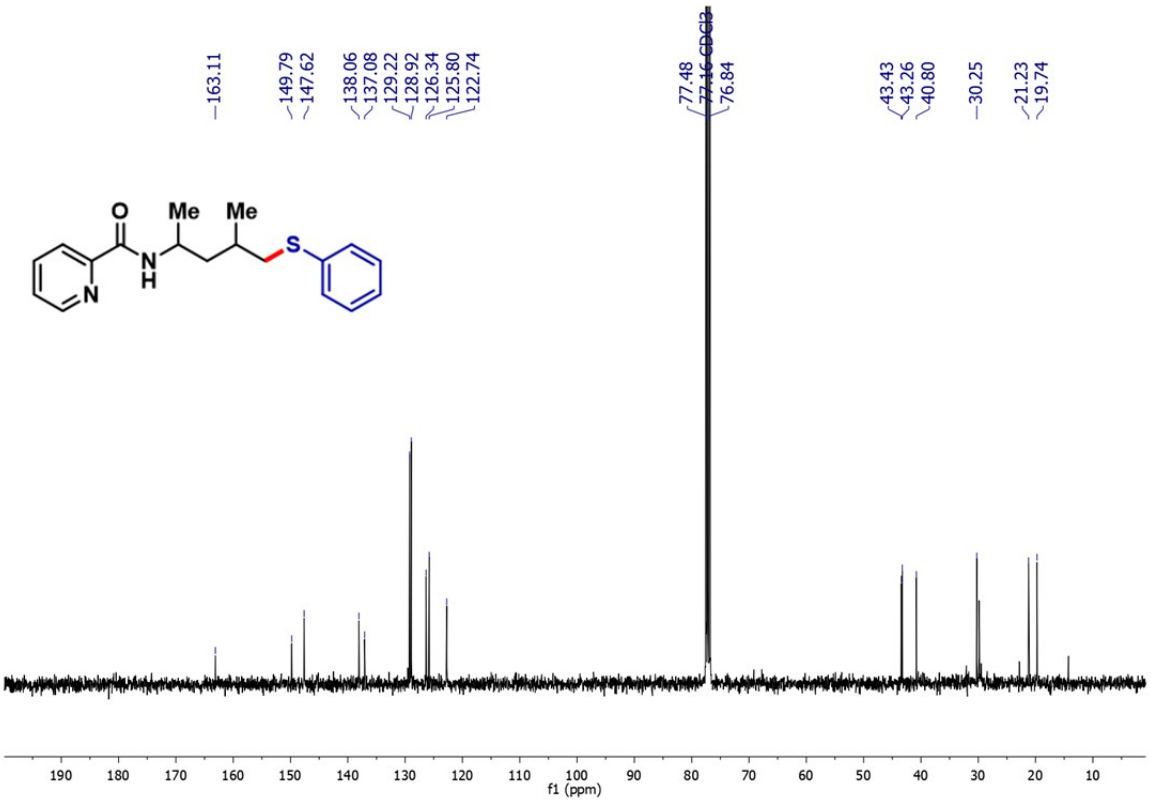
Scheme 4, entry 2'm



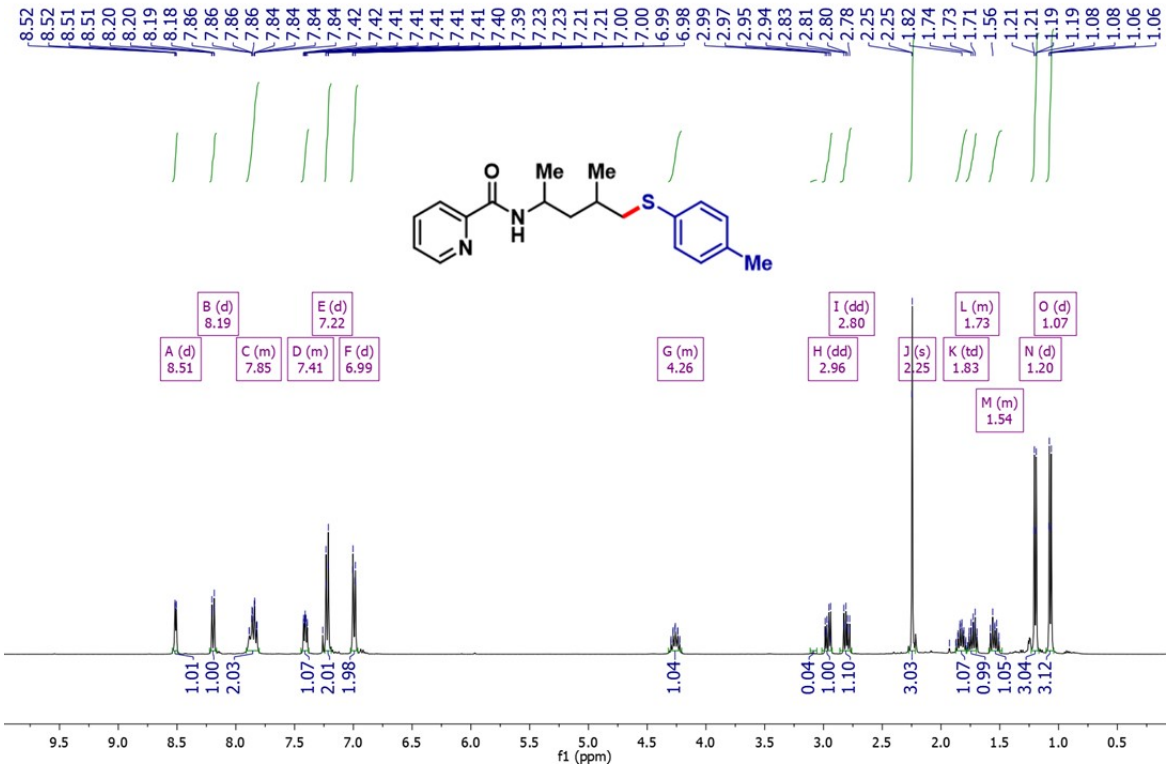


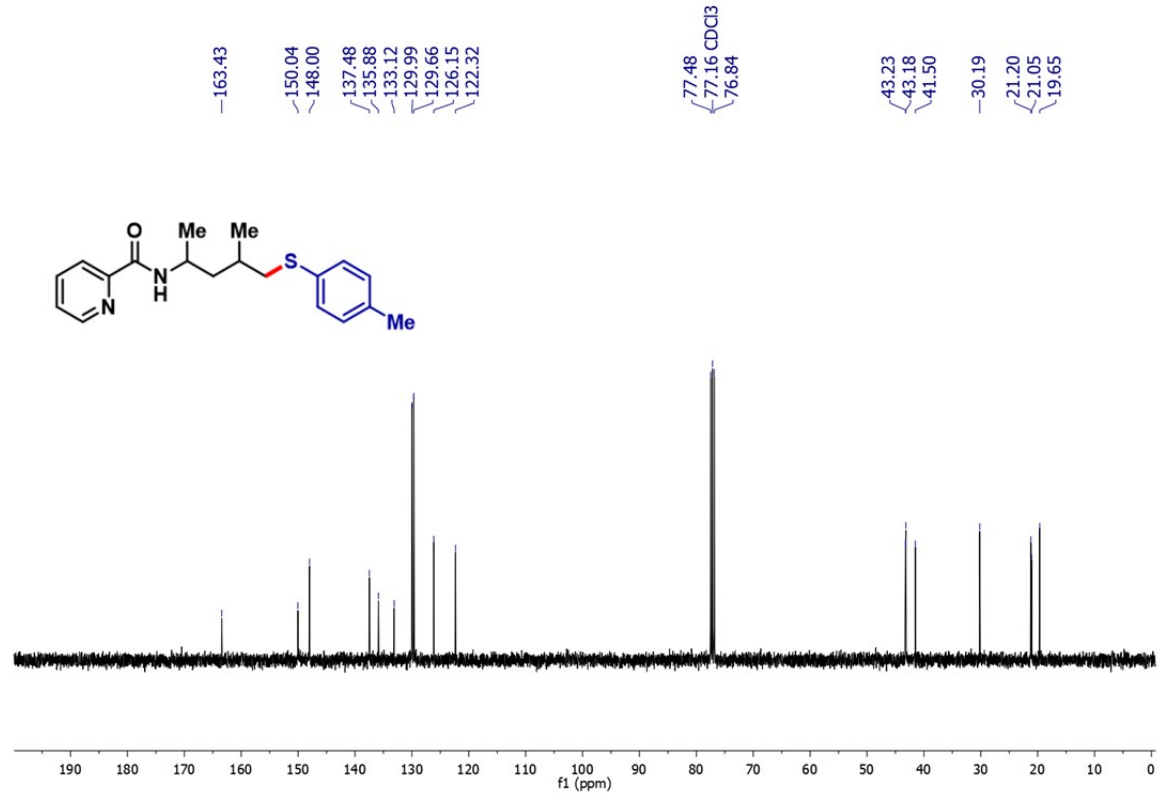
Scheme 4, entry 2'n



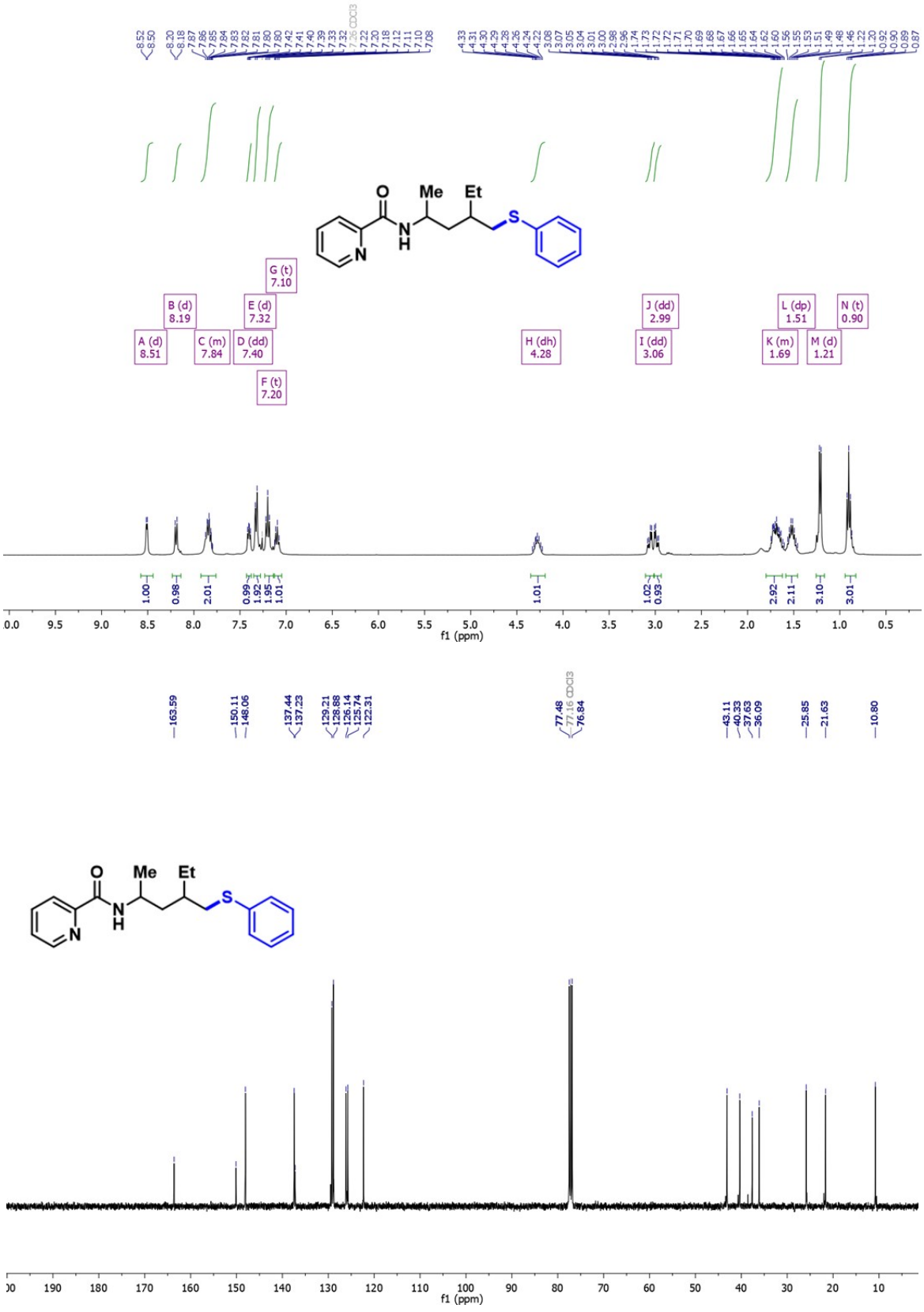


Scheme 4, entry 2'o

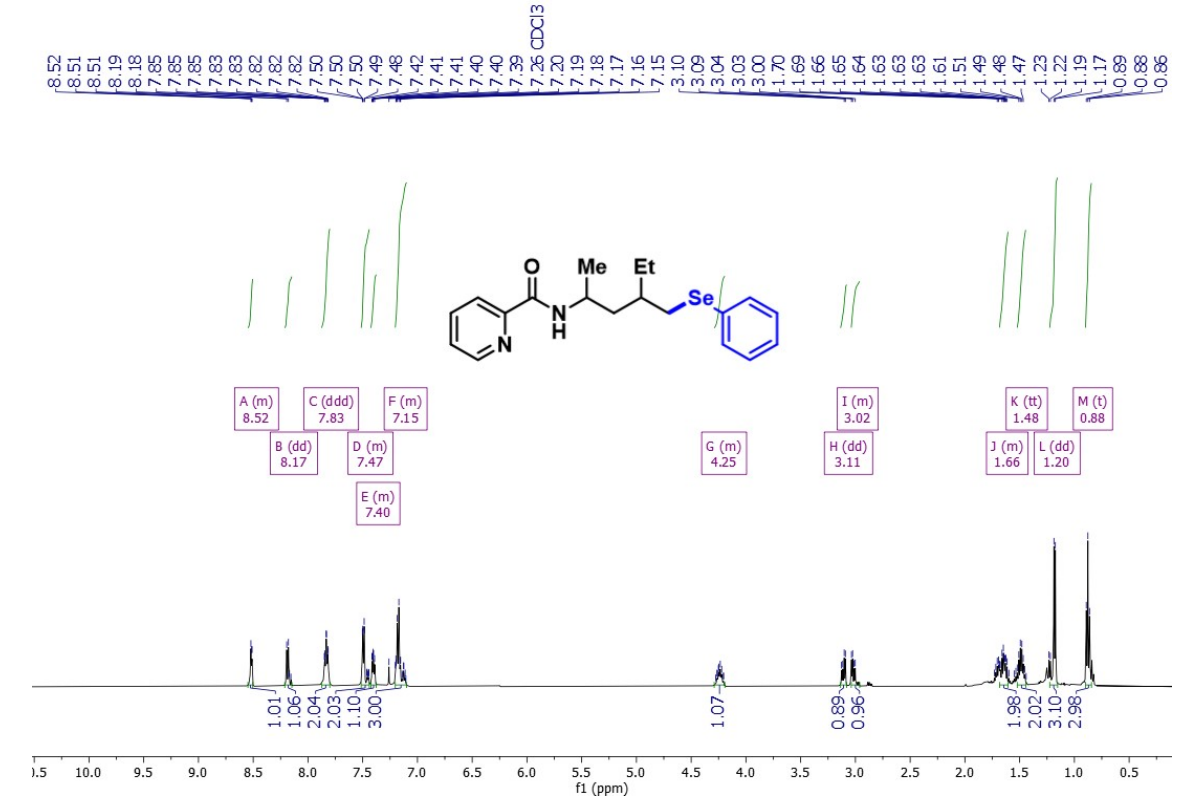


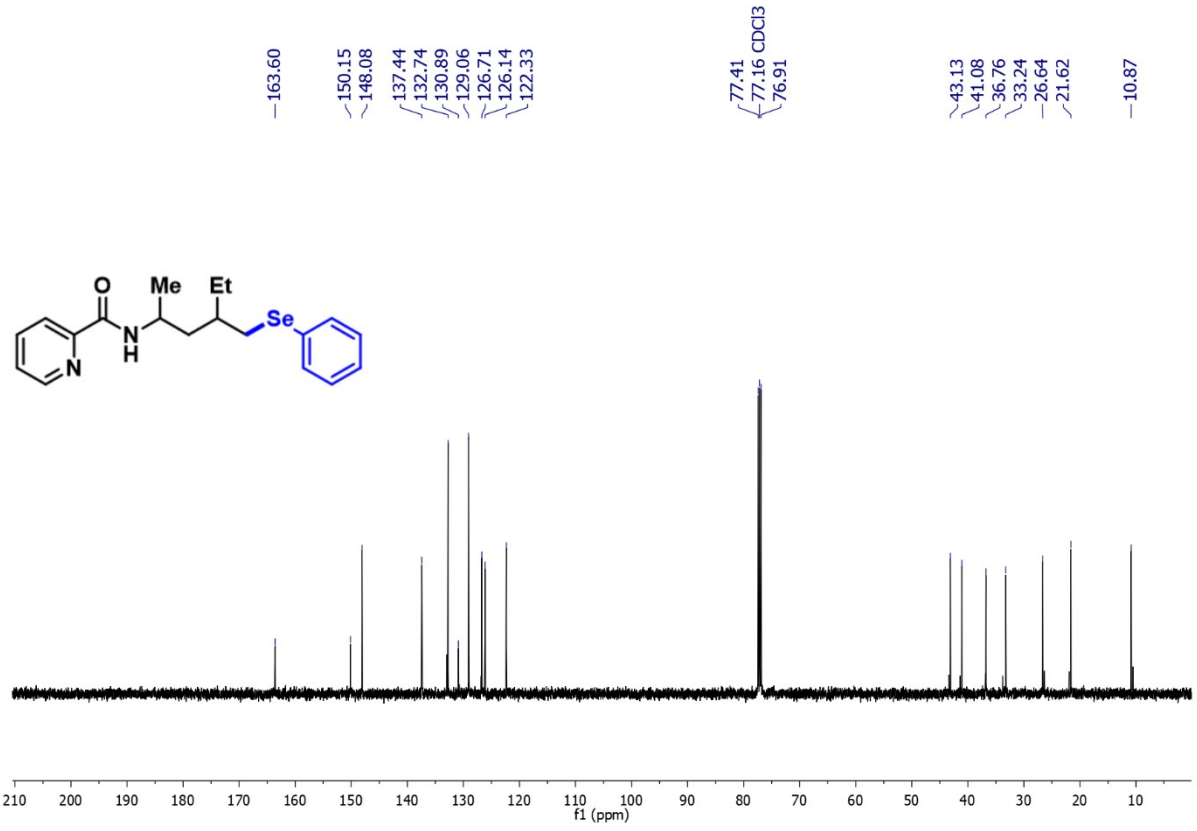


Scheme 4, entry 2'p

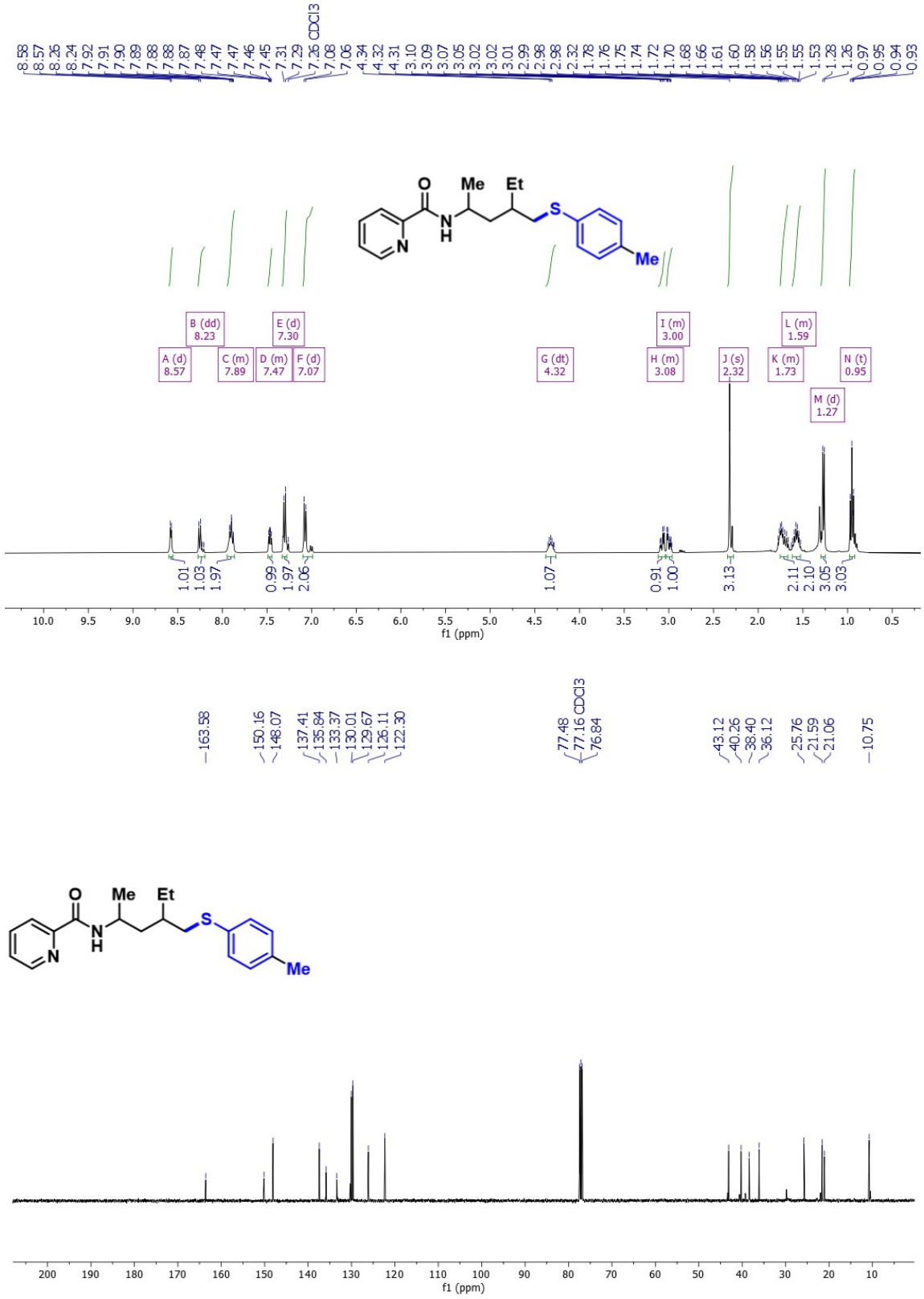


Scheme 4, entry 2'q

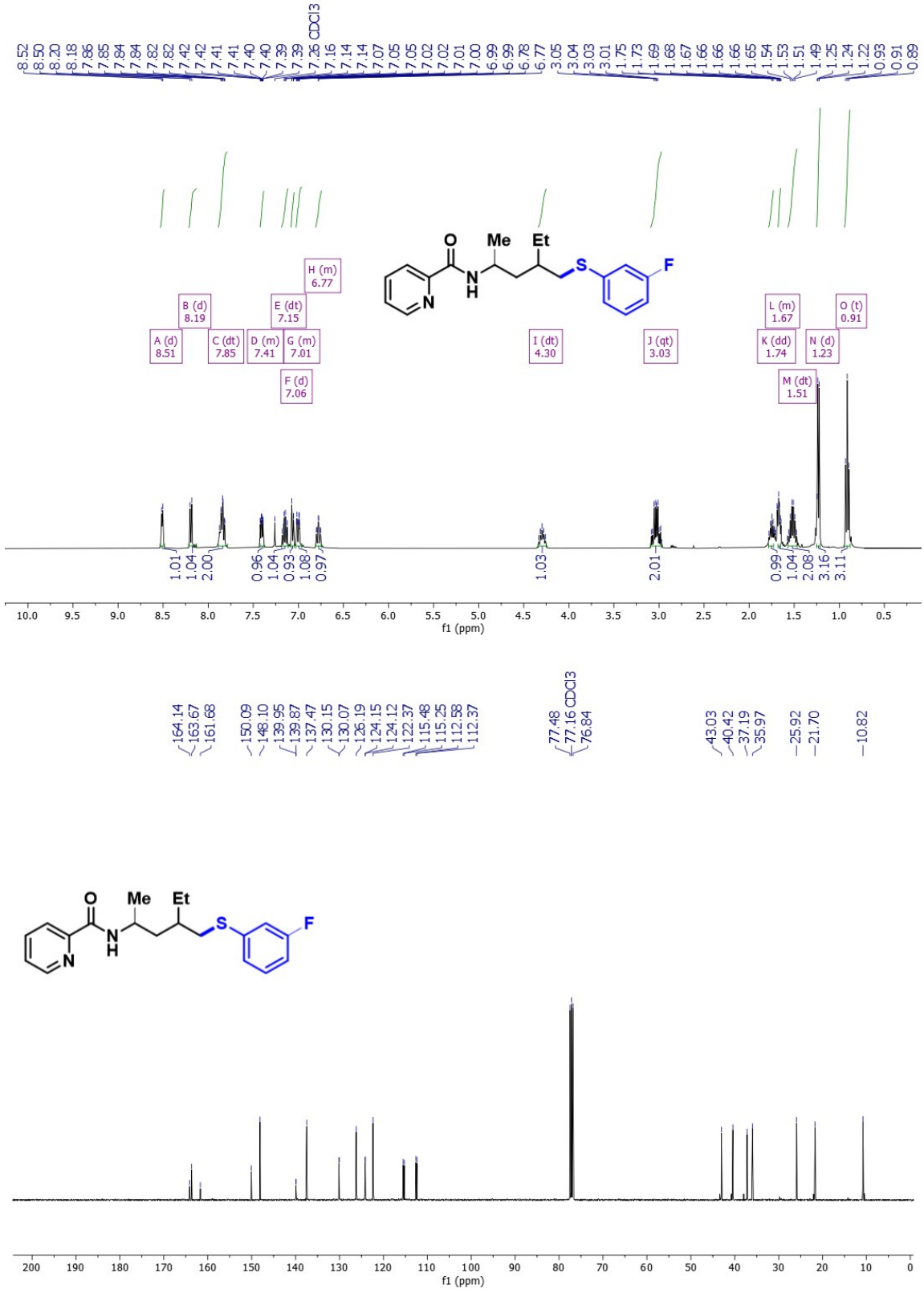


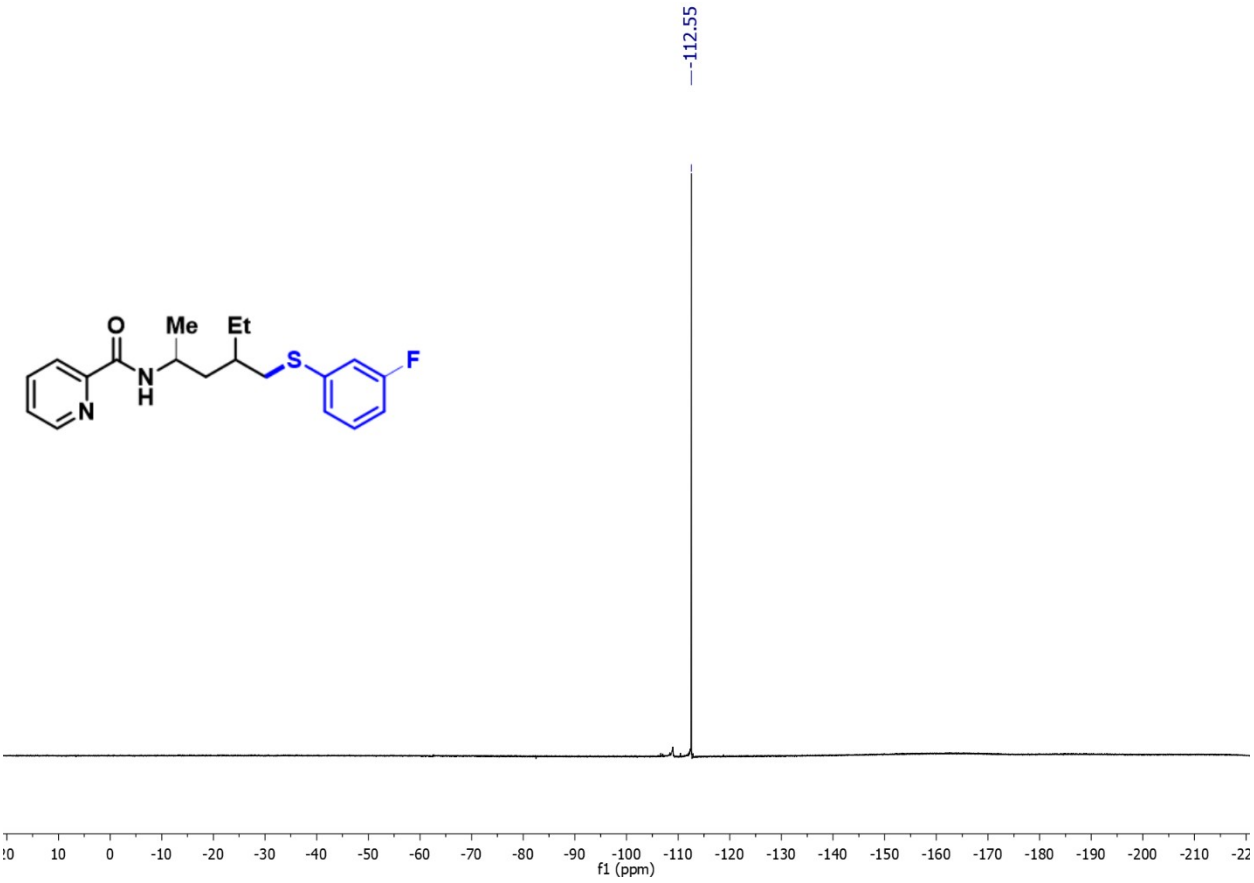


Scheme 4, entry 2'r



Scheme 4, entry 2's

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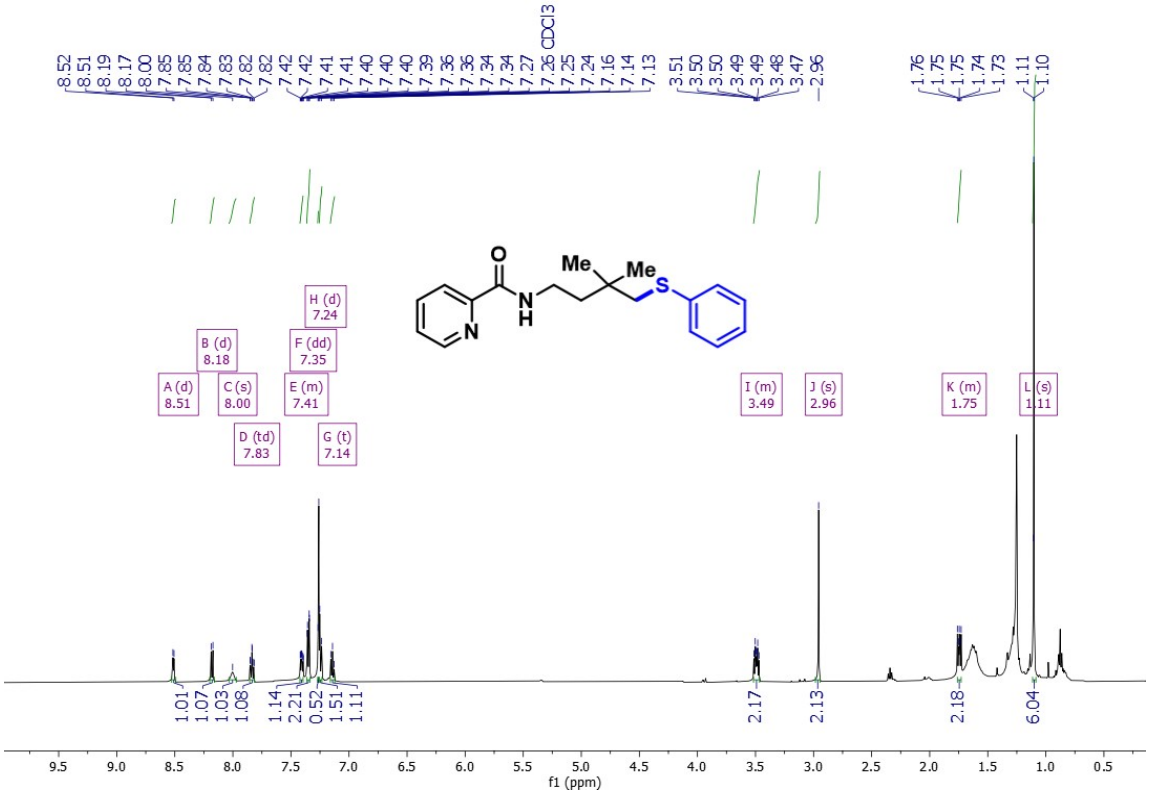
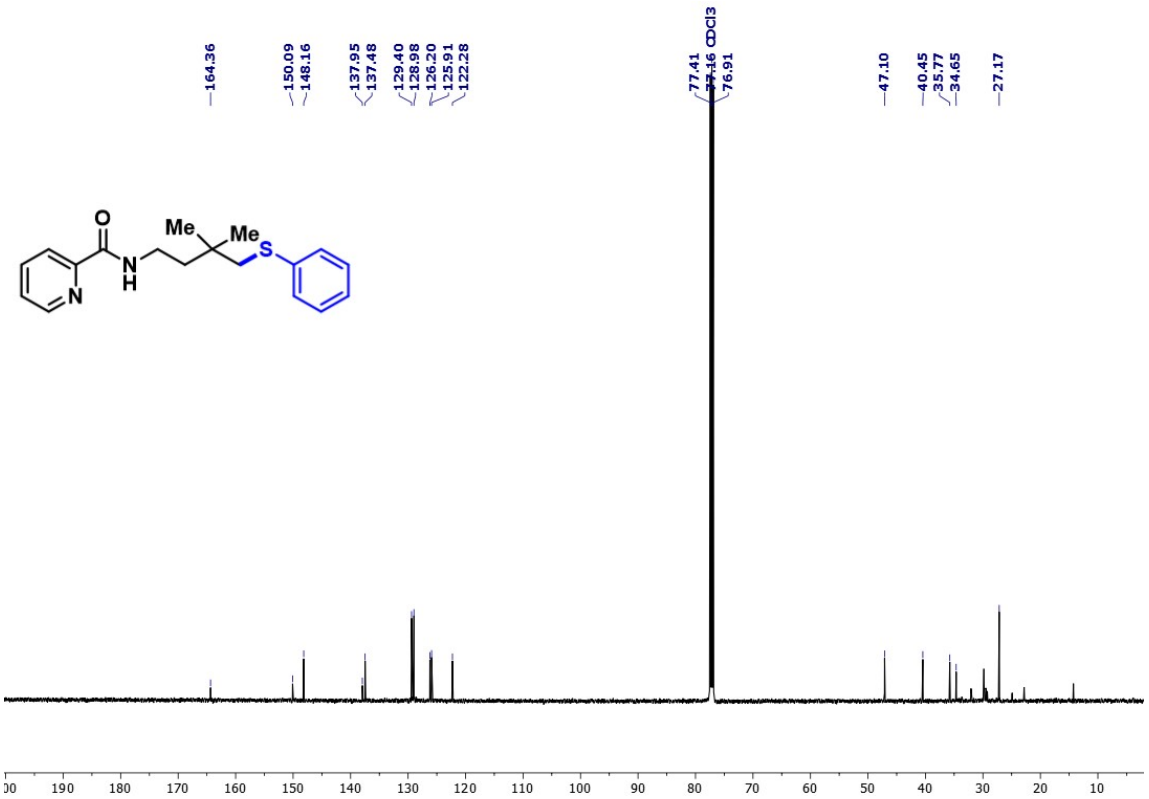
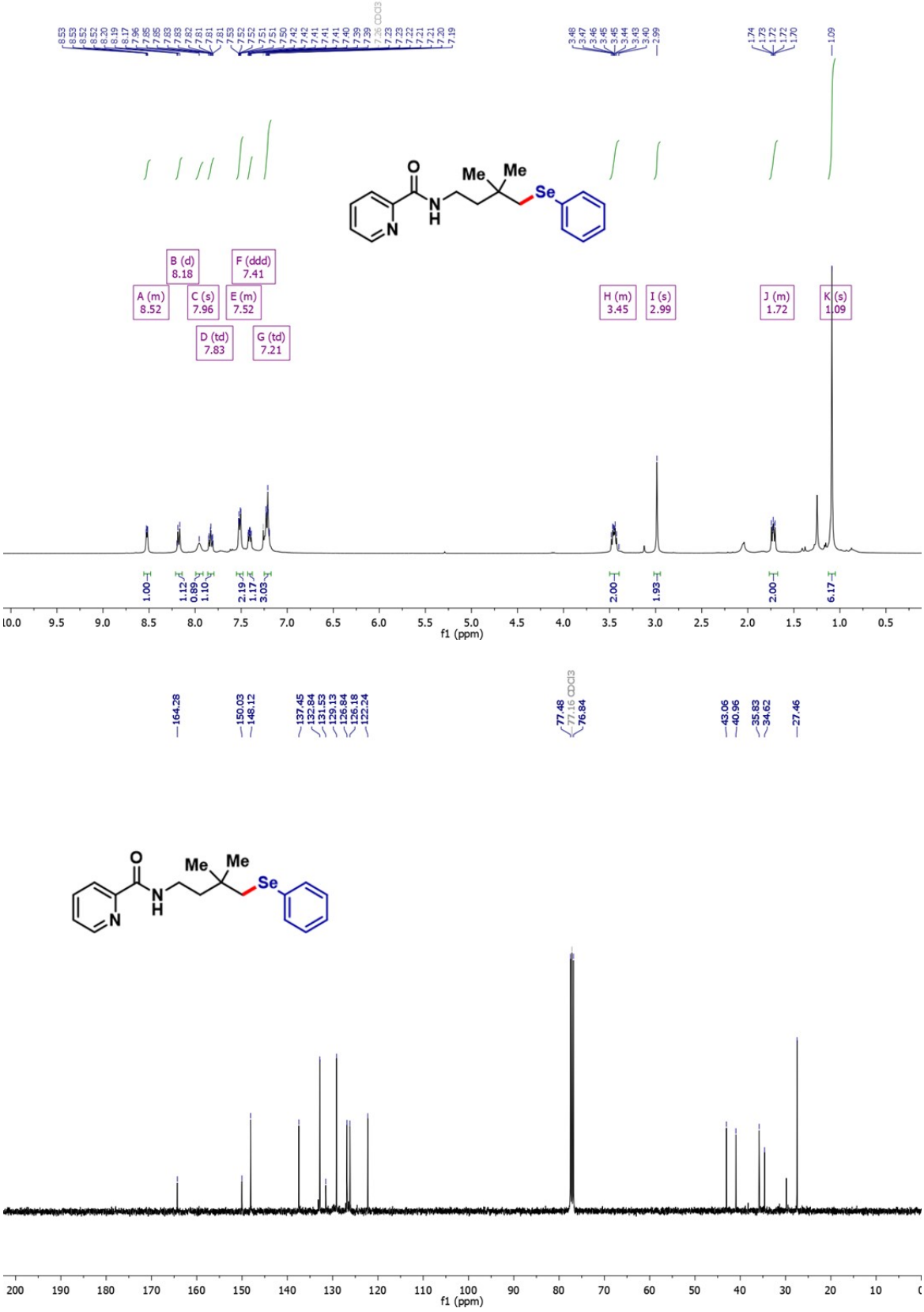
f1 (ppm)

Scheme 4, entry 2't

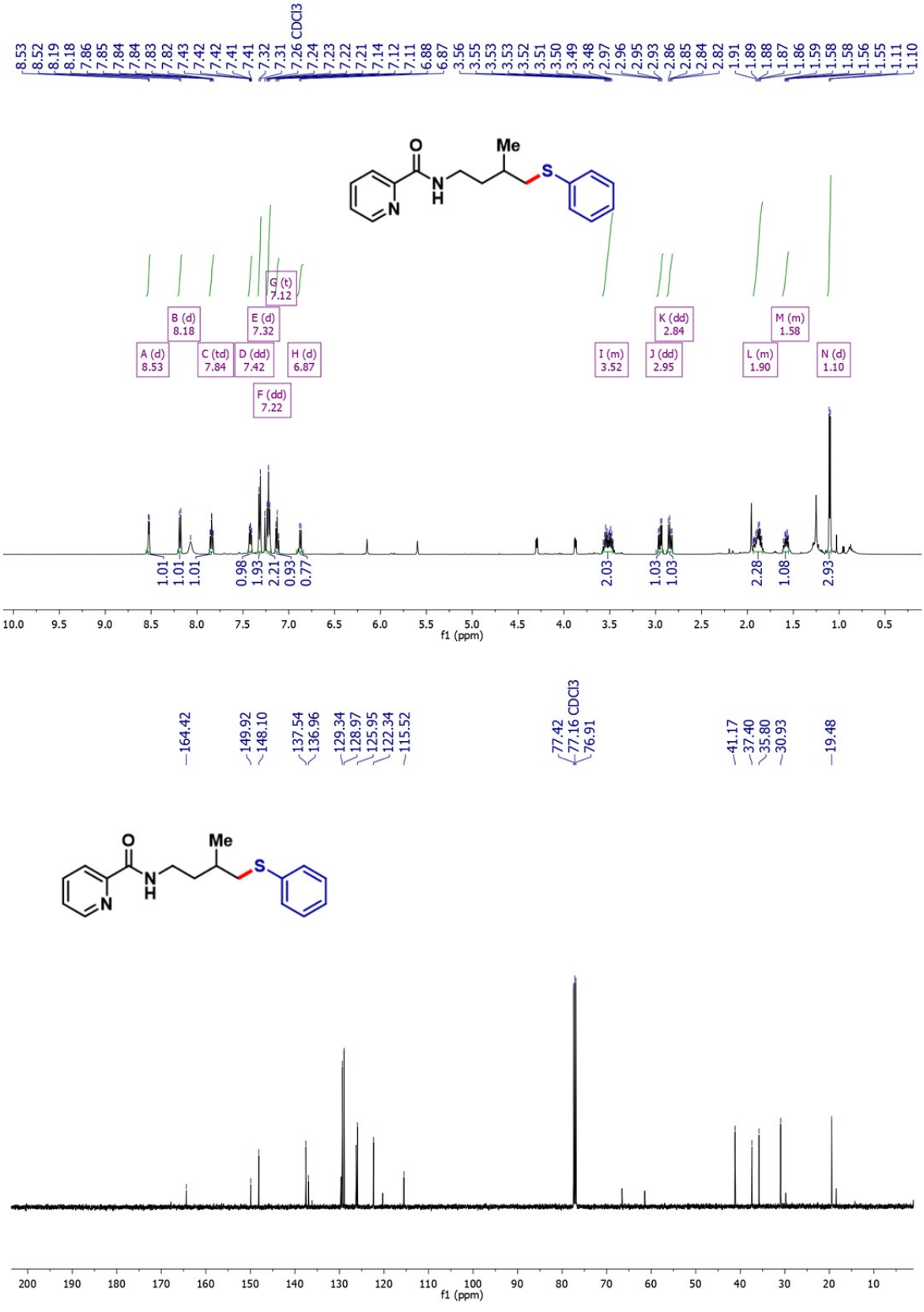




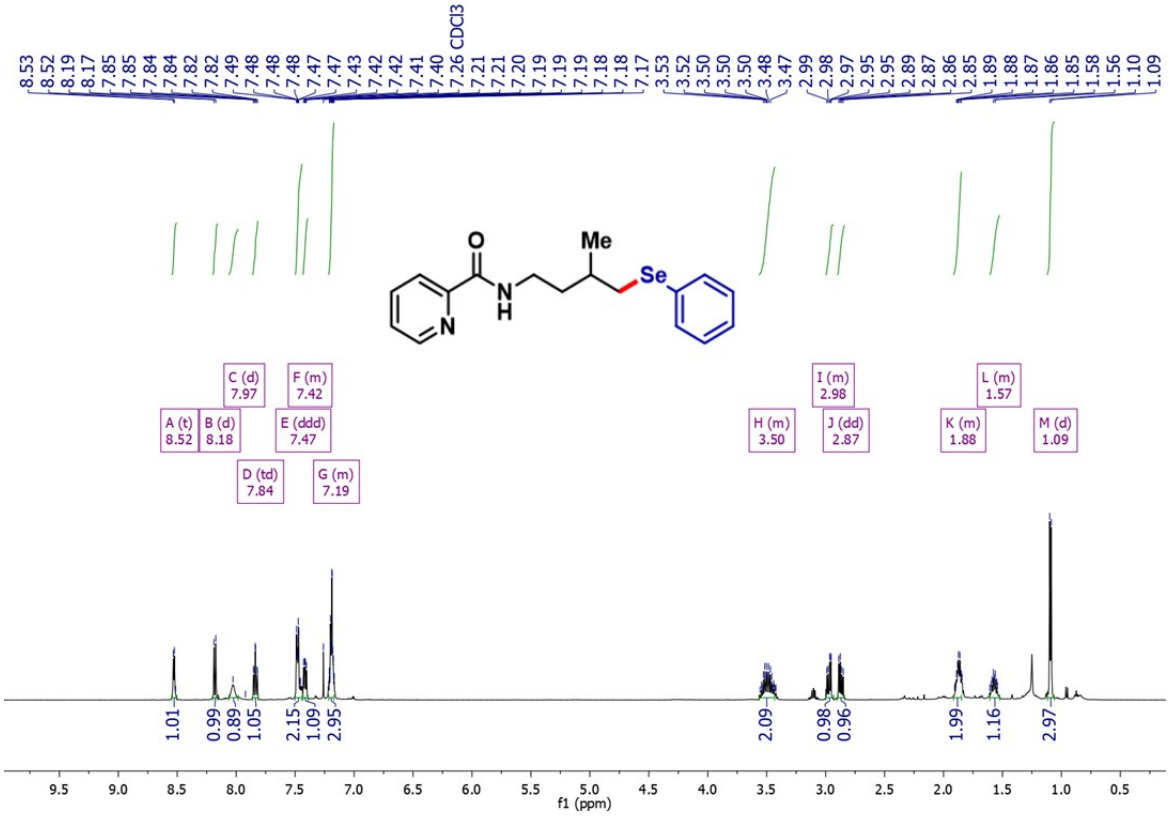
Scheme 4, entry 2'u

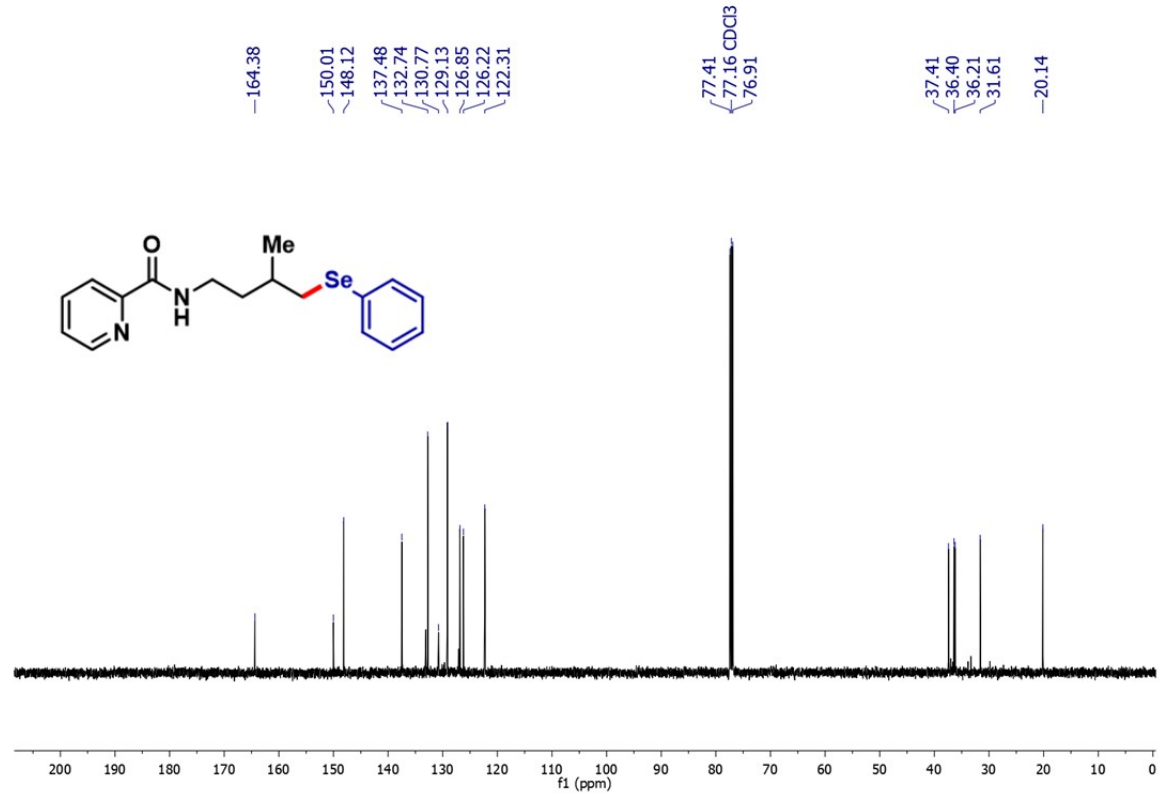


Scheme 4, entry 2'v

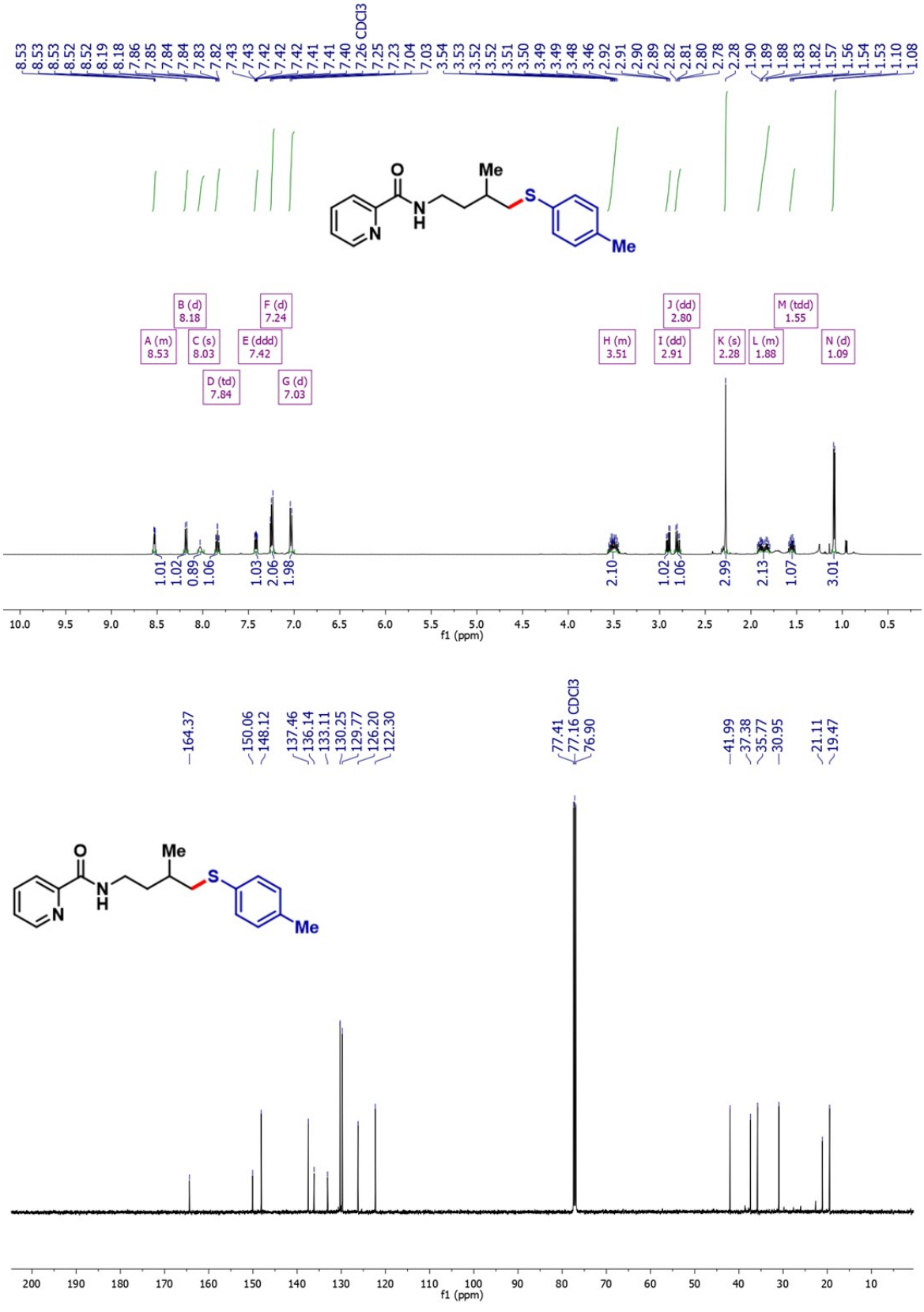


Scheme 4, entry 2'w

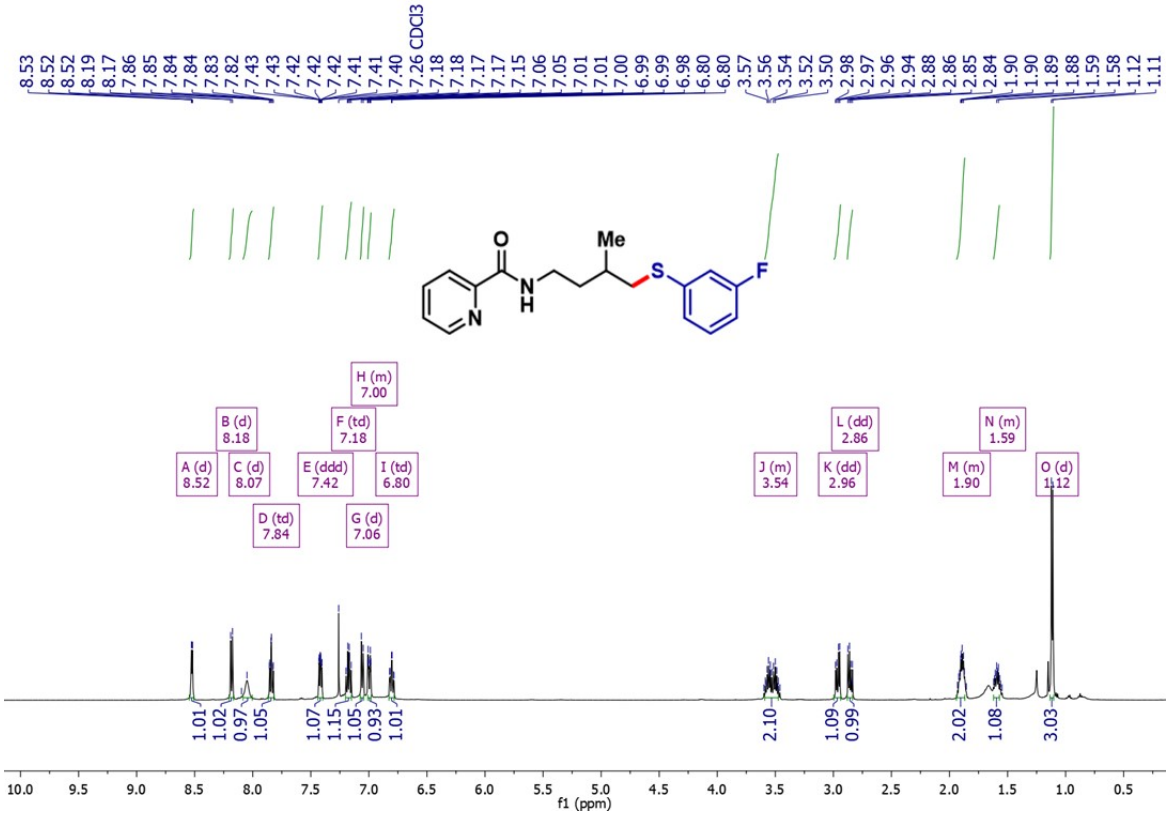


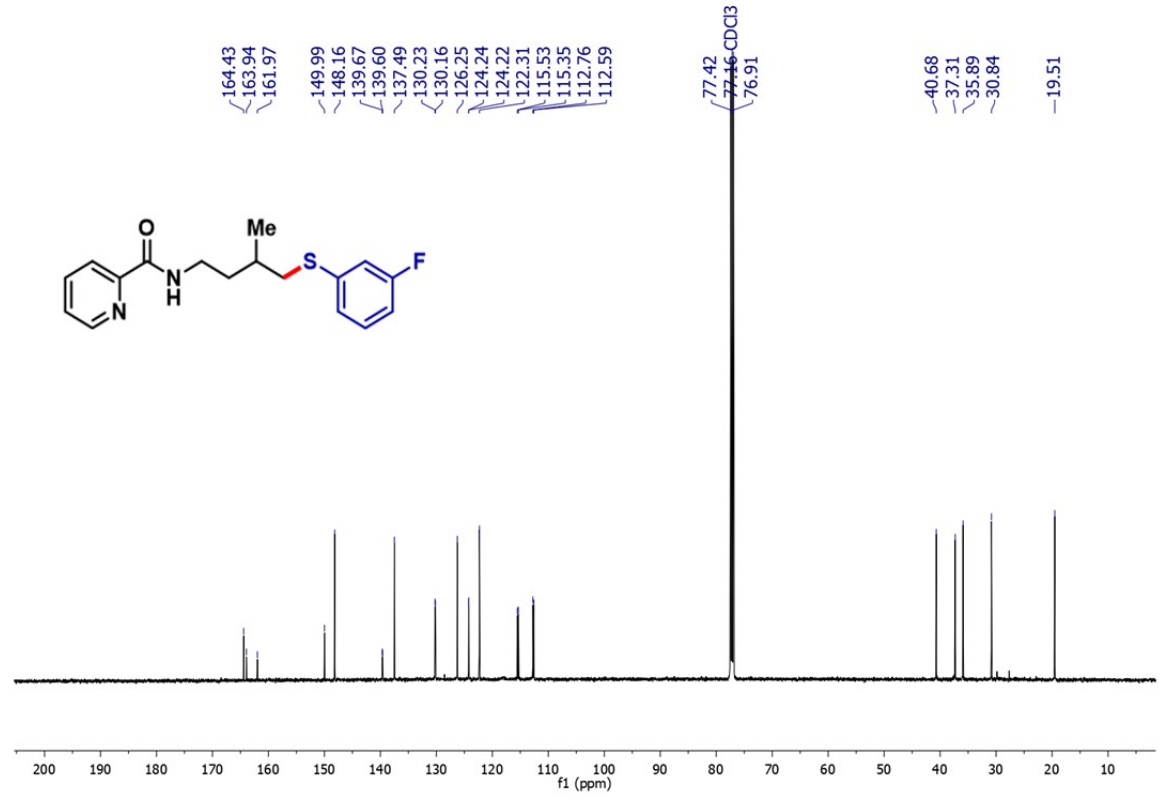


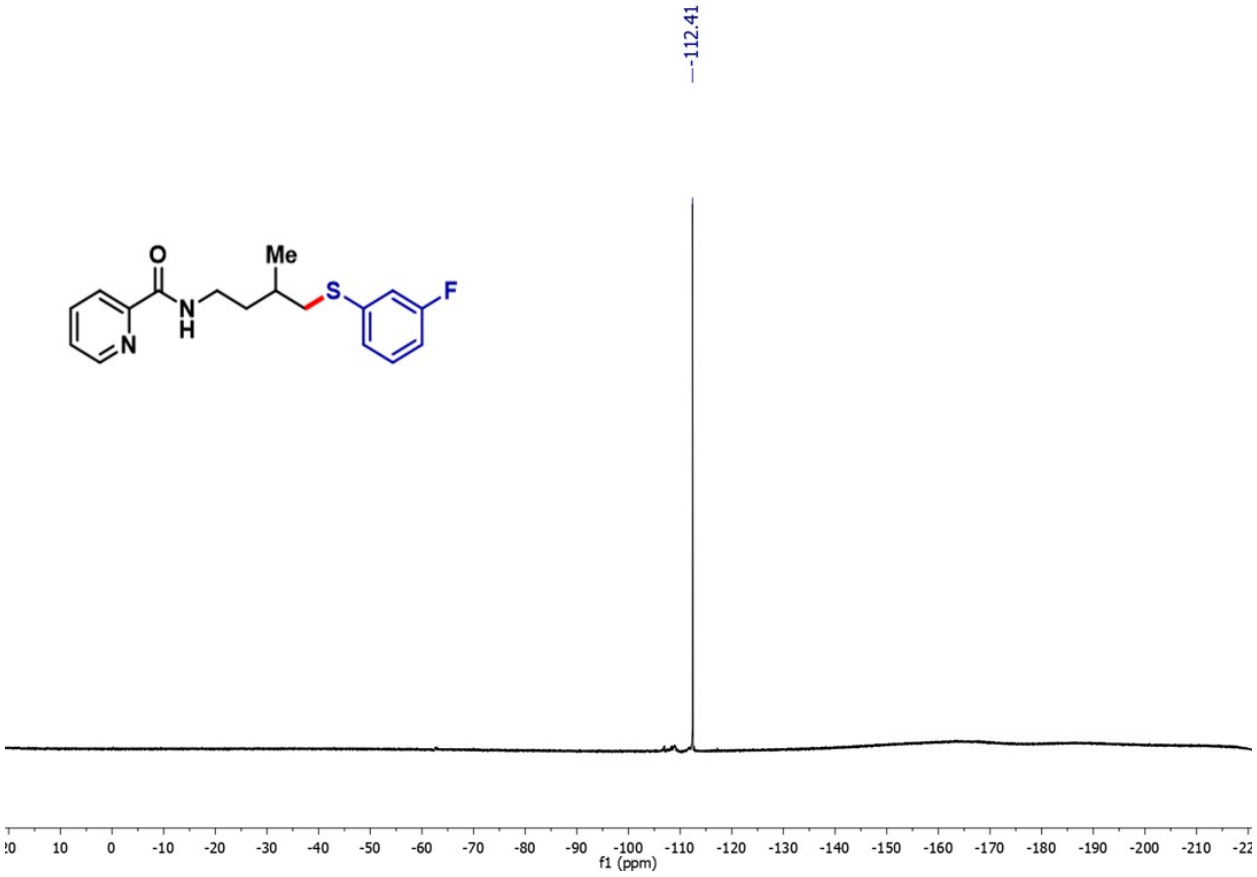
Scheme 4, entry 2'x



Scheme 4, entry 2'y



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-180
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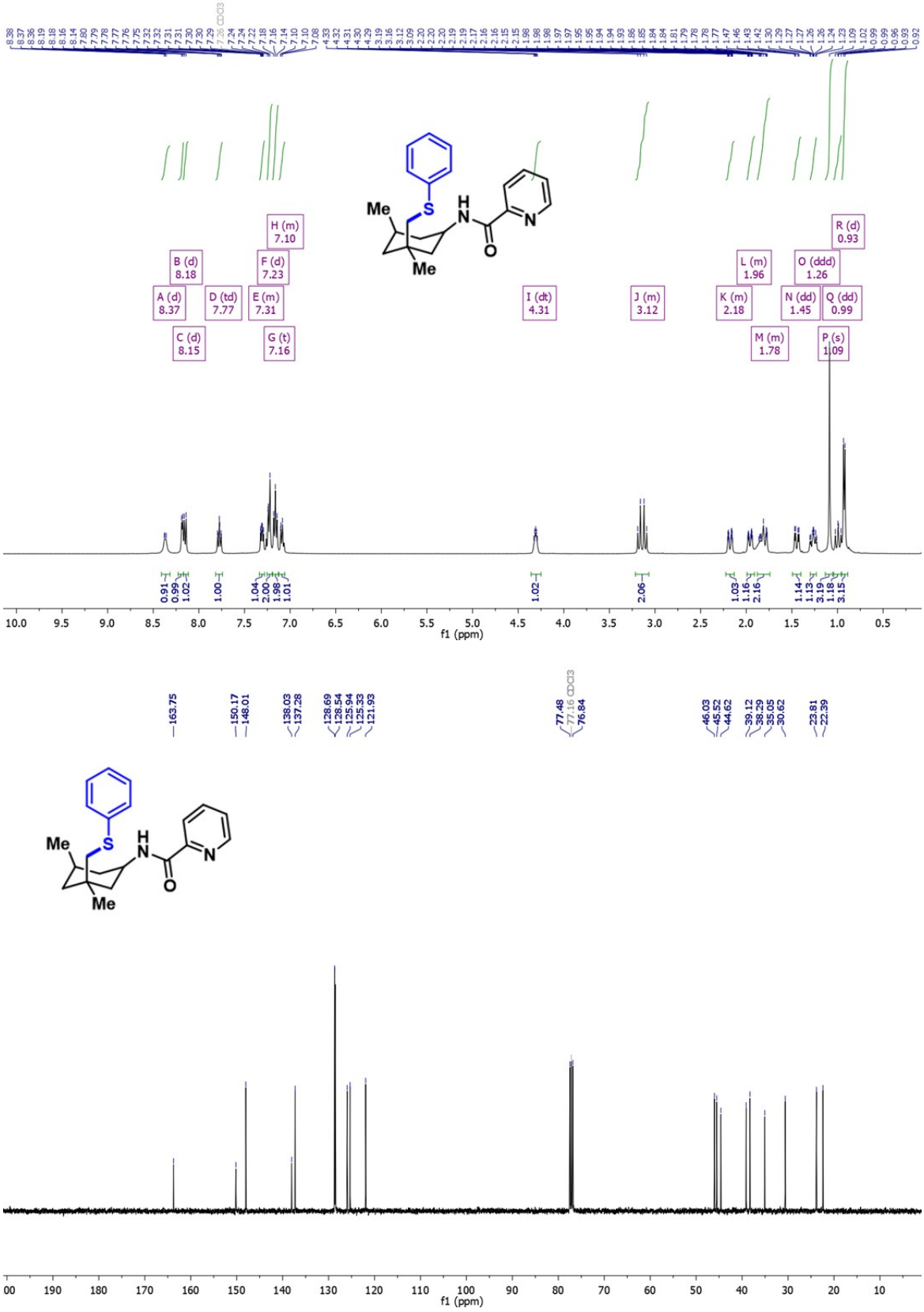
-200
-210
f1 (ppm)

Scheme 4, entry 2'z



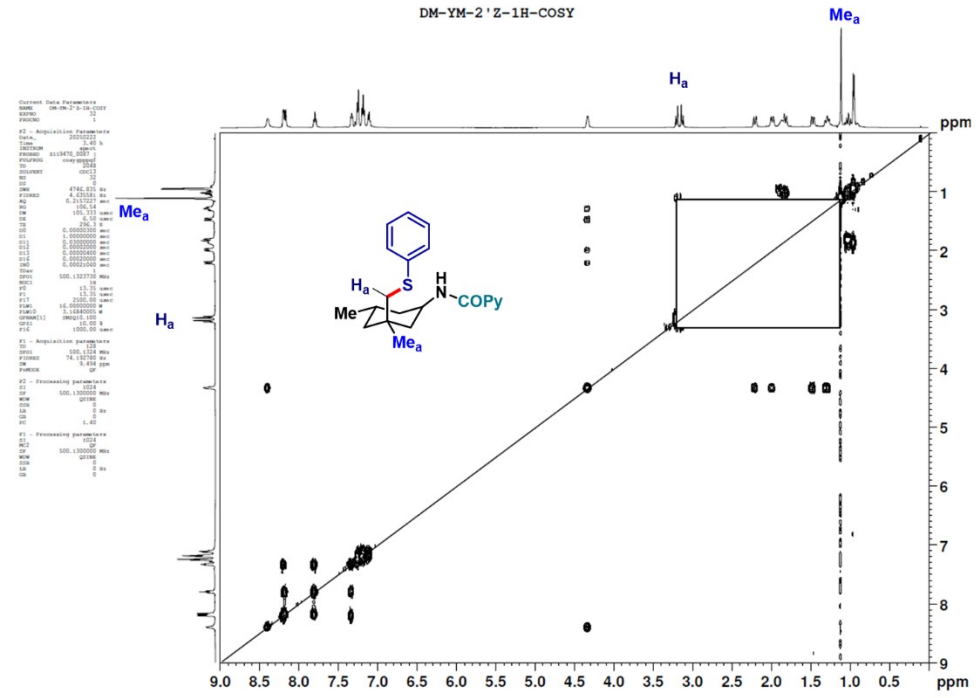


Figure 1: 2D COSY NMR of 2'z

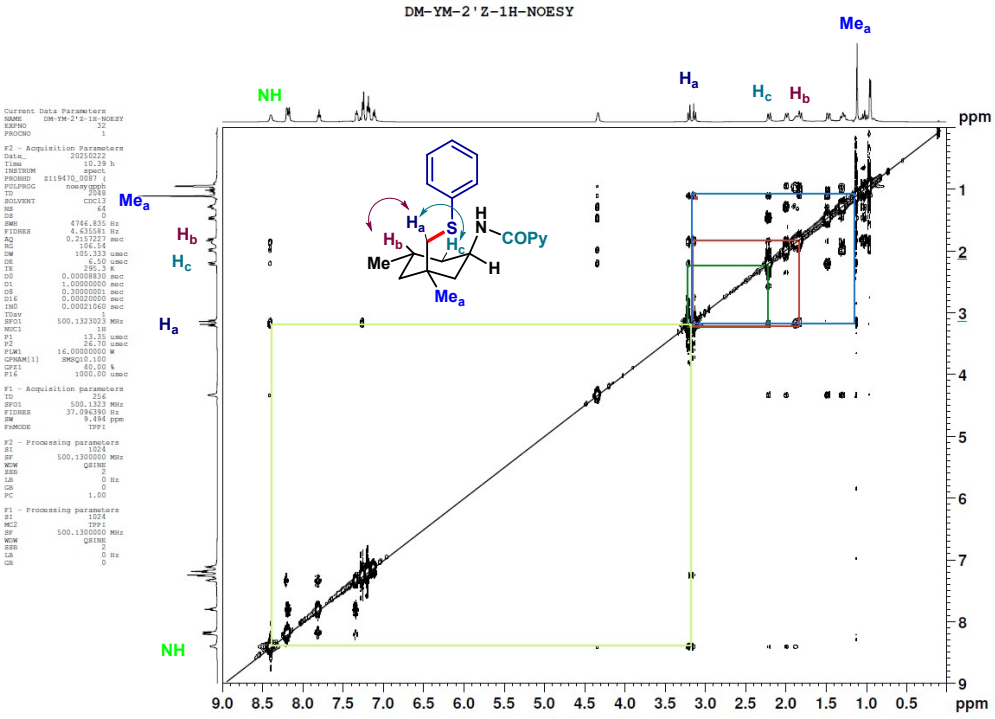
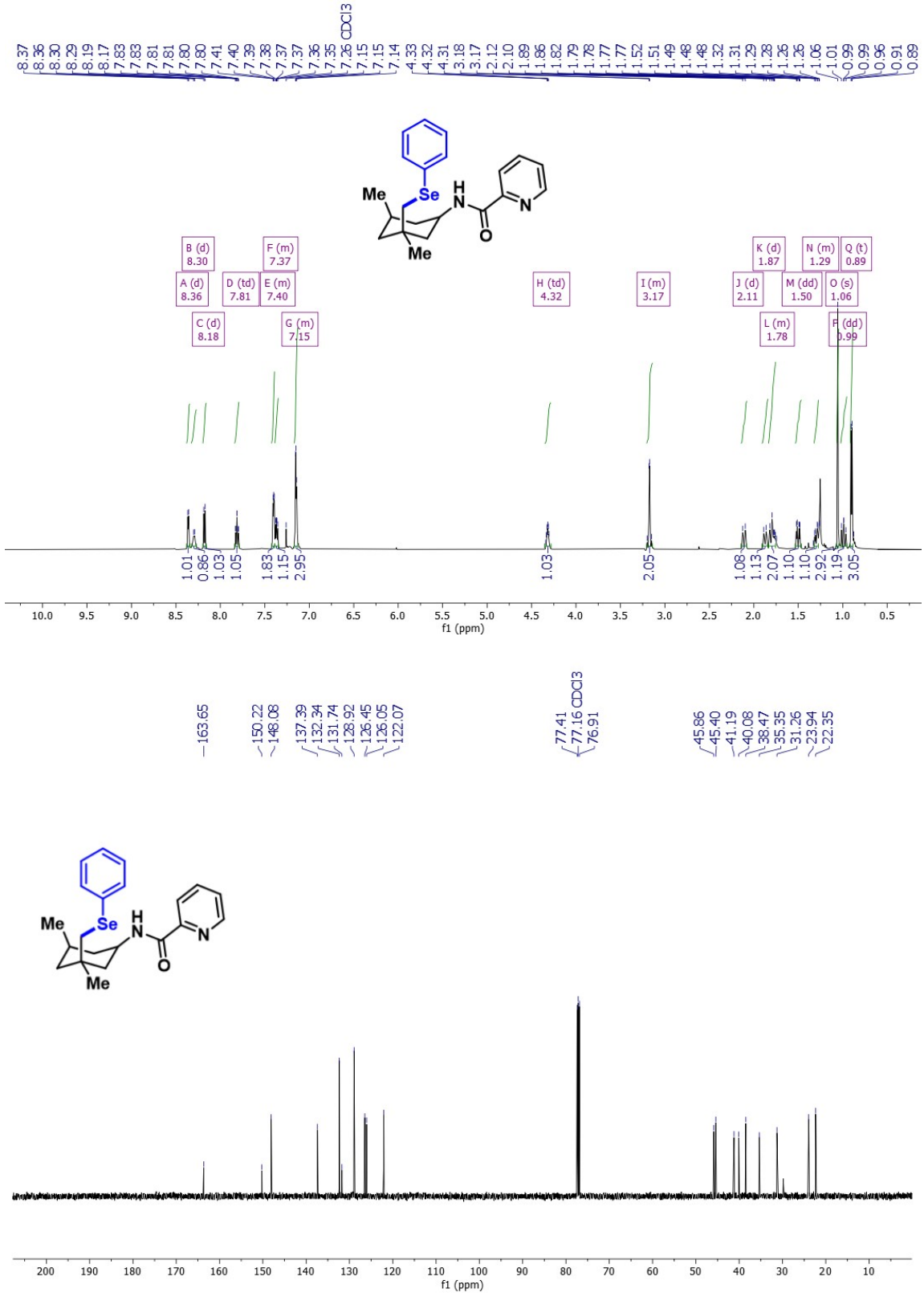


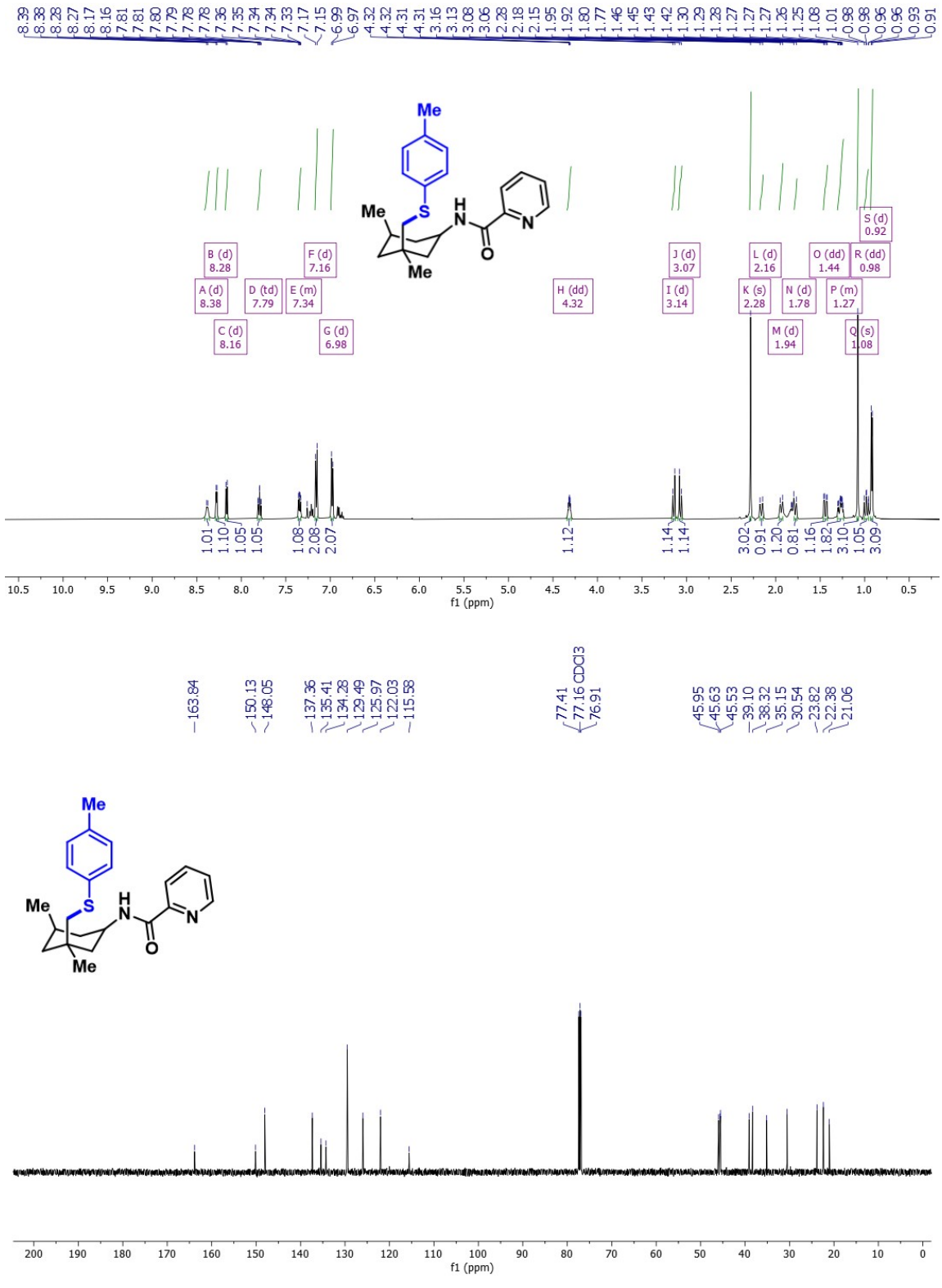
Figure 2: 2D NOESY NMR of 2'z

H_a is found to correlate with H_b, H_c, NH and Me_a in the 2D NOESY spectrum, which confirms the structure of the product.

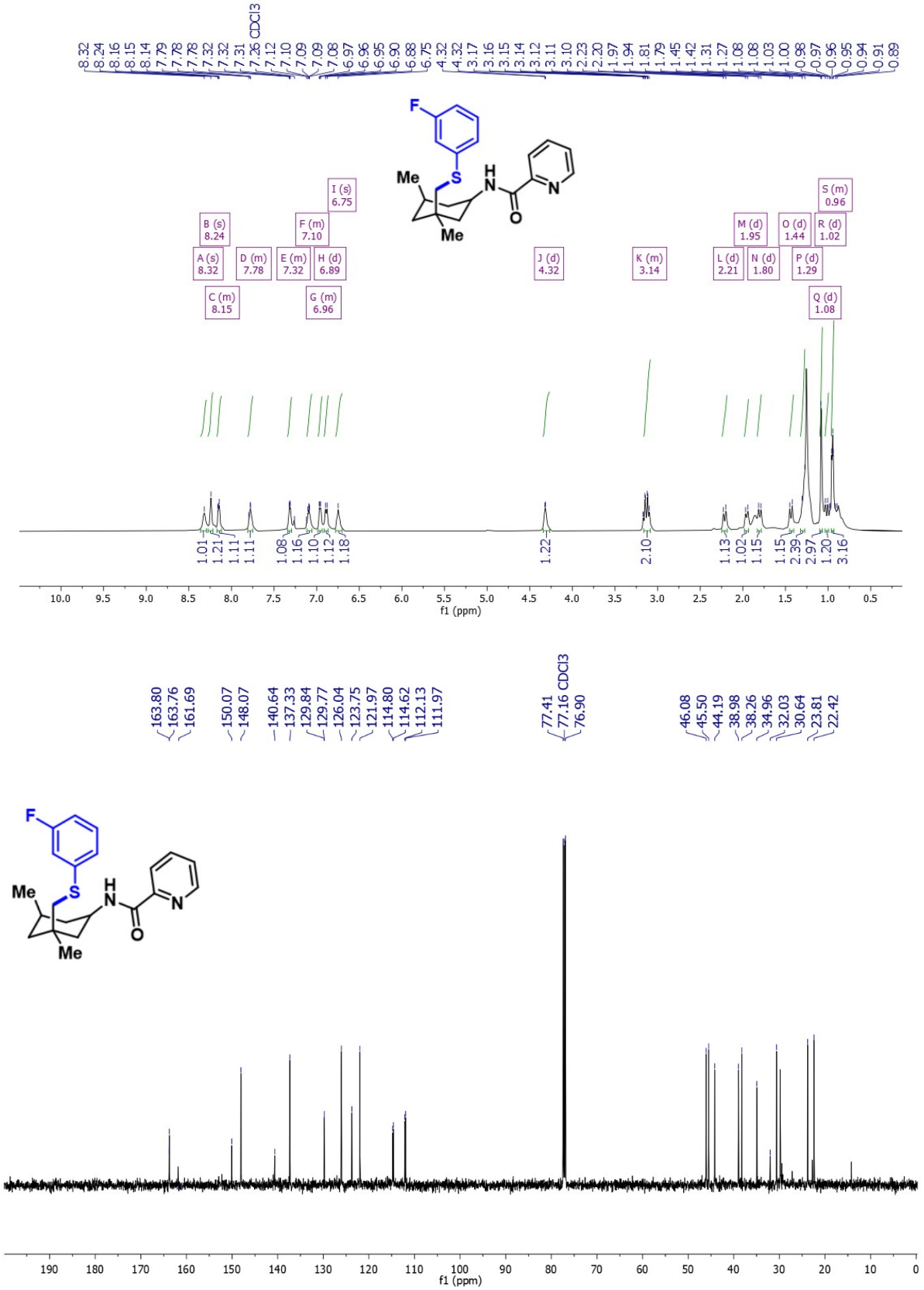
Scheme 4, entry 2'aa

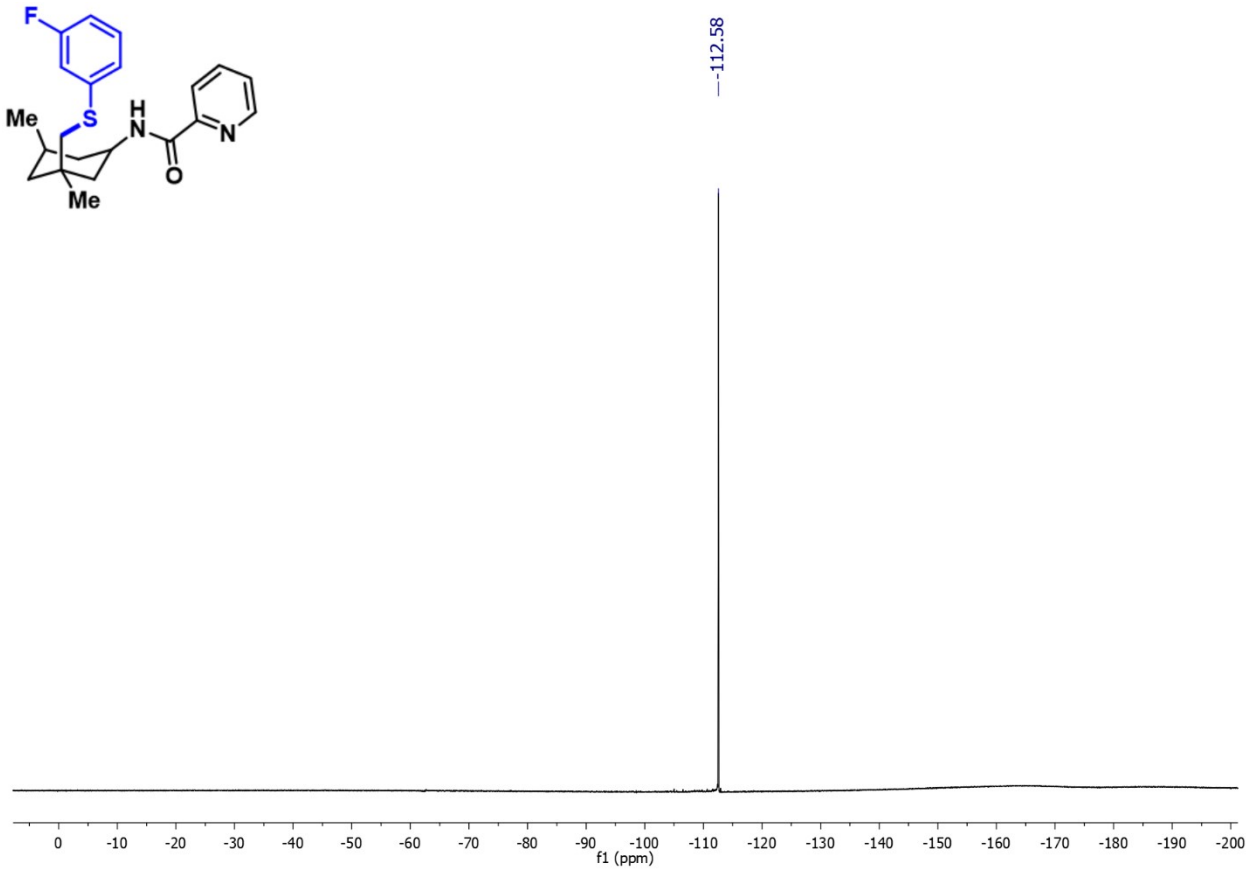


Scheme 4, entry 2'ab

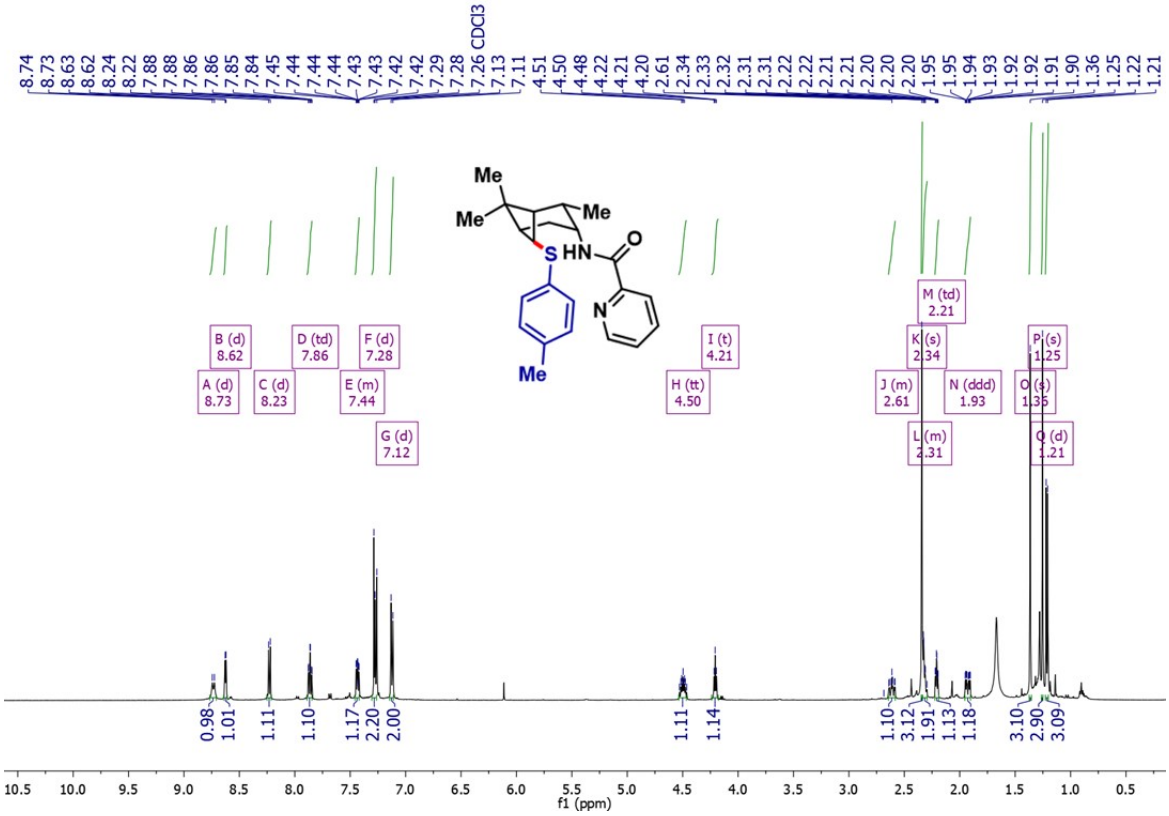


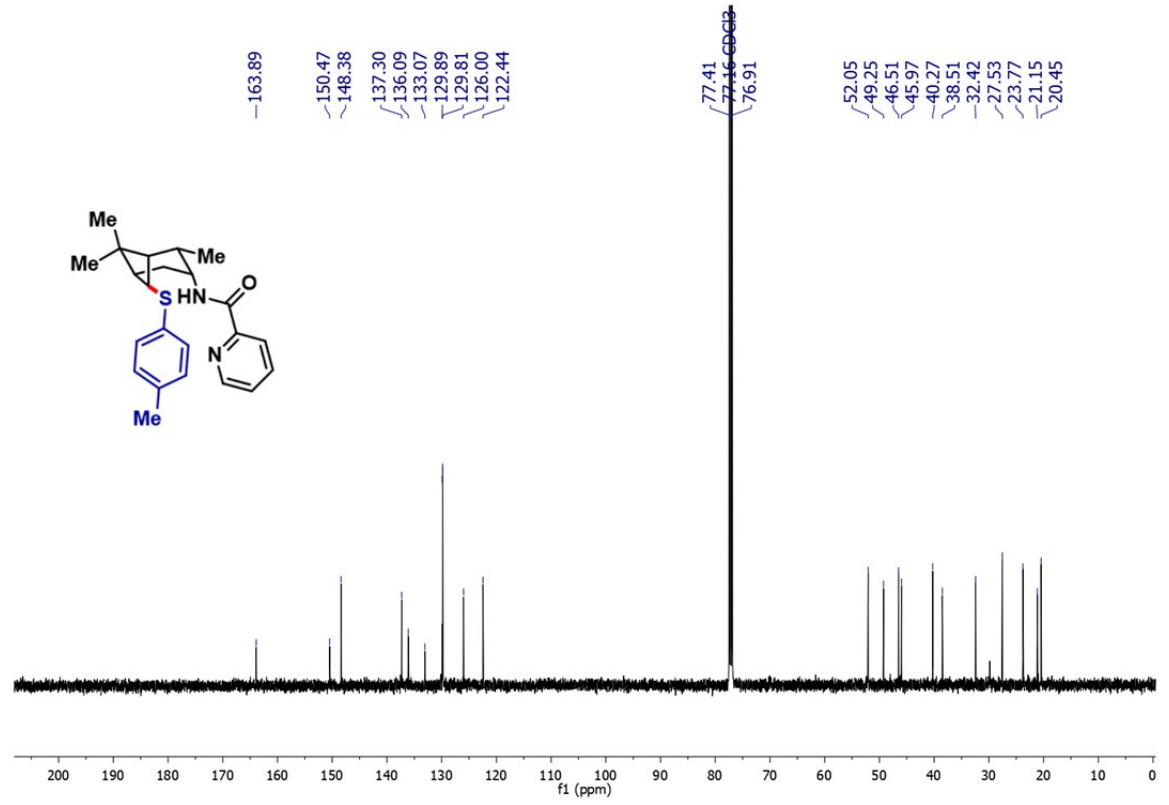
Scheme 4, entry 2'ac



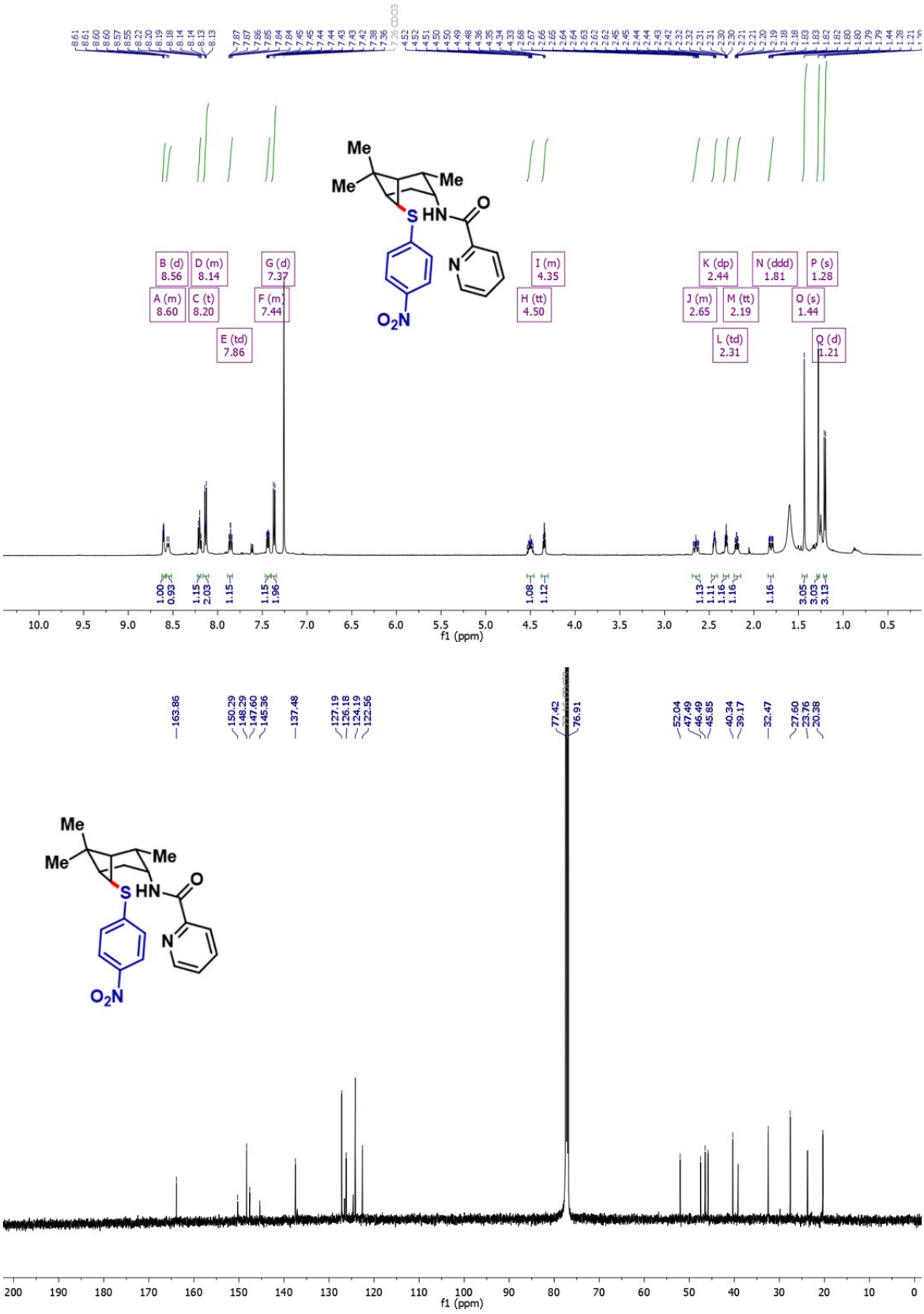

F
S
Me
Me
H
N
O
N
-112.58
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

Scheme 4, entry 2'ad





Scheme 4, entry 2'ae



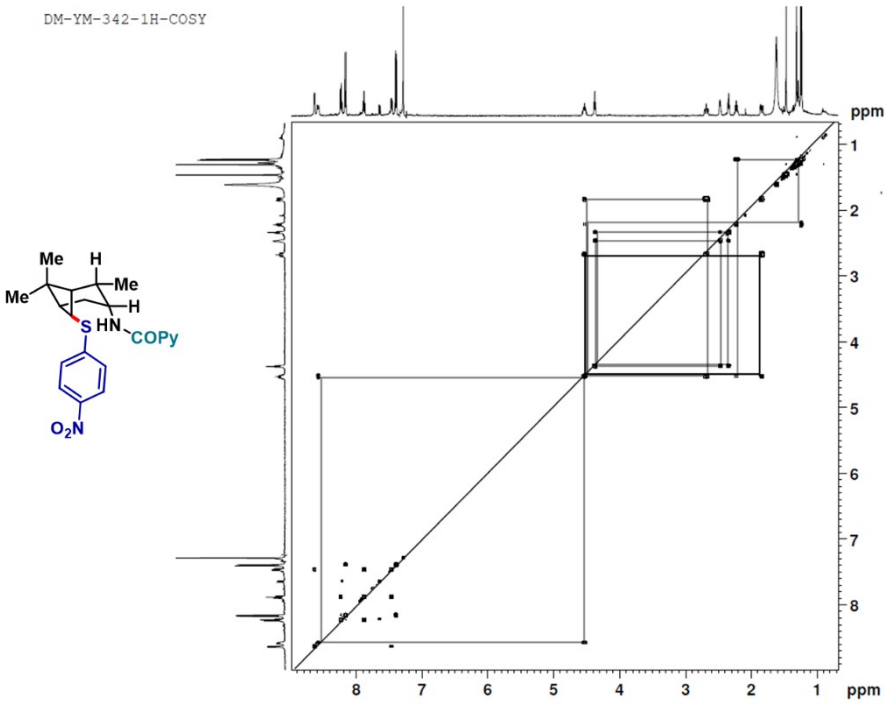


Figure 3: 2D COSY NMR of 2'ae

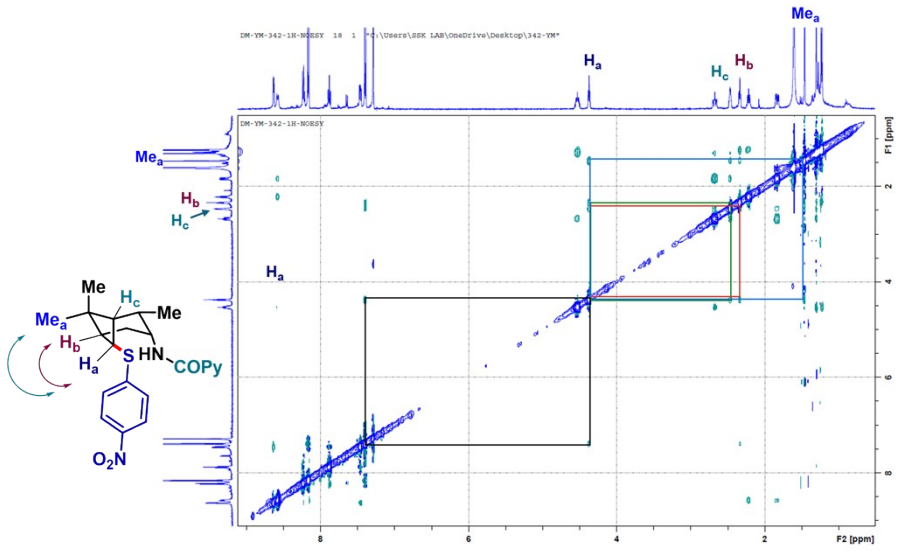


Figure 4a: 2D NOESY NMR of 2'ae

In Figure 4a, for compound 2'ae, NOESY NMR indicates H_a is found to correlate with only H_b, H_c, Me_a, which confirms that the thioaryl group is pointing towards the picolinamide directing group.

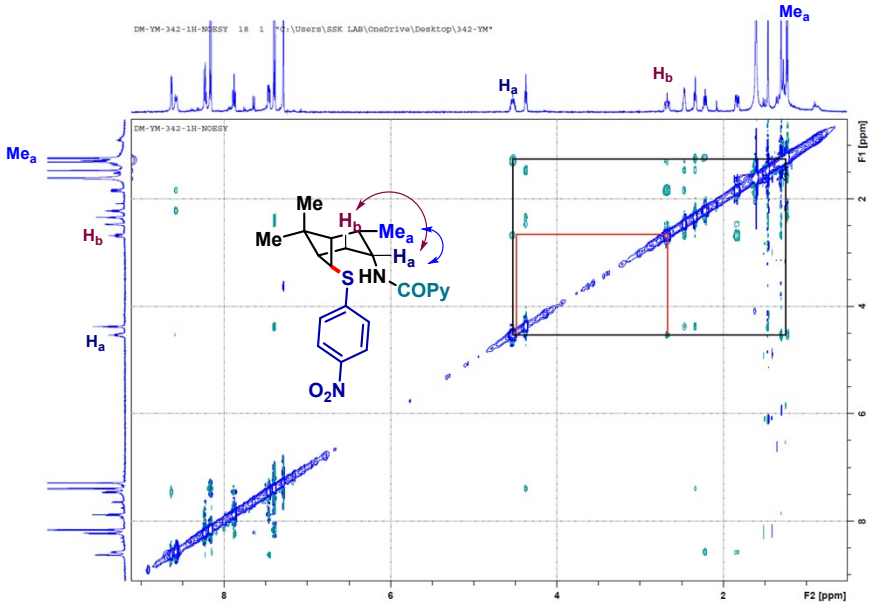


Figure 4b: Second 2D NOESY NMR of 2'ae

In Figure 4b, for compound 2'ae, NOESY NMR indicates the H_a depicted here correlates with only H_b and the Me_a present in the 2-position with respect to the directing group.

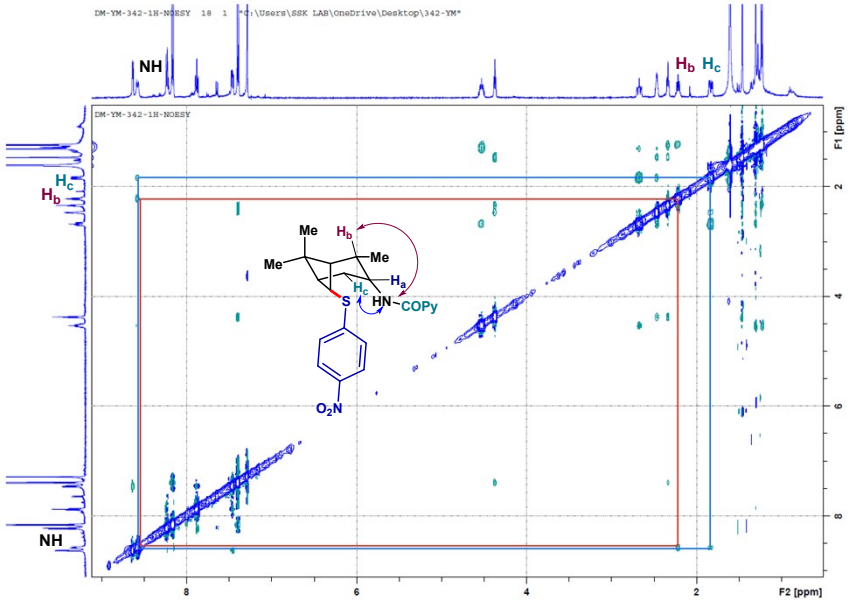


Figure 4c: Third 2D NOESY NMR of 2'ae

In Figure 4c, for compound 2'ae, NOESY NMR shows that the NH correlates with the H_b at the 2-axial position and H_c. This confirms that the picolinamide directing group is axial and the thioaryl group is facing towards the directing group.

Scheme 4, entry 2'af