

Transition Metal-Free Decarboxylative Photoredox Coupling of Carboxylic Acids and Alcohols with Aromatic Nitriles

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Supporting Information

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I. Light Sources and Reaction Setup for Irradiations

Light sources:

400 W medium pressure metal halide lamp: Cleo-HPA 400/30 S (Philips). Case: Upper body solarium type 912 from Efbe-Schott. The clock timer and the UV-cut off glass filter were removed manually.

25 W energy-saving UV/Vis-CFL bulb: Reptile UVB 200 from Exo-Terra.
(http://www.exo-terra.com/en/products/reptile_uv200.php).

400 W UV-A spotlight: Black light gun from *Eurolite* with an UV-A lamp from *Omnilux* (<http://eshop.steinigke.de/de/mpn89514005-omnilux-uv-lampe-400w-e-40.html>).

25 W energy-saving UV-A lamp: UV-A spotlight from *Eurolite* with an UV-A lamp by *Omnilux* with $\lambda_{\text{max}} = 368 \text{ nm}$ (<http://eshop.steinigke.de/de/mpn51100700-eurolite-uv-strahler-mit-uv-es-lampe-25w.html>).

Reaction setup for irradiations:

The 400 W medium pressure metal halide lamp or the 25 W energy-saving lamps were placed in a distance of 50 cm or 5 cm from the reaction vessel. No further cooling was necessary to maintain ambient temperature. When the 400 W UV-A spotlight was used, the reaction vessel was placed inside a cooled water bath to maintain a temperature of 23 °C. The distance between the lamp and the reaction vessel was approximately 10 cm.

Irradiations with sunlight were performed by placing the reaction vessel outside (April 2016, Mainz, Germany, 49°59'27.9"N) from morning to evening. The samples were kept in a fridge at -24 °C overnight. This procedure was repeated until full consumption of the starting nitrile was achieved as judged by TLC (30 h).

II. Optimization Studies and Control Experiments

II.1 Coupling of Carboxylic Acids with Aromatic Nitriles

Table S1: Base screening for the coupling of carboxylic acids with aromatic nitriles.

$\text{BocHN-CH(CH}_3\text{)-CO}_2\text{H}$ (31, 3.0 equiv.) + $\text{CN-C}_5\text{H}_4\text{N}$ (32, 1.0 equiv.) $\xrightarrow[\text{UV-light, rt, 12 h}]{\text{phenanthrene (5 mol\%), base (3.0 equiv.), MeCN/H}_2\text{O}}$ $\text{H}_3\text{C-CH(CH}_3\text{)-NH-Boc-C}_5\text{H}_4\text{N}$ (±)-1

Entry	Base	MeCN/H ₂ O	Yield (%) ^a
1	KHCO ₃	23:10	7
2	KH ₂ PO ₄	23:10	9
3	Cs ₂ CO ₃	9:1	23
4	CsF	9:1	27

Procedure: The reactions were performed in a glass vial according to the General Procedure A using Boc-L-valine (**31**, 104 mg, 480 μmol), 4-Cyanopyridine (**32**, 16.7 mg, 160 μmol), phenanthrene (**24**, 1.43 mg, 8 μmol) and the indicated base (480 μmol). While the total volume was 8 mL for all reactions, the ratio of acetonitrile and water was varied depending on the solubility of the base. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S2: Influence of the acid and base concentration on the coupling of carboxylic acids with aromatic nitriles.

$\text{BocHN-CH(CH}_3\text{)-CO}_2\text{H}$ (31, X equiv.) + $\text{CN-C}_5\text{H}_4\text{N}$ (32, 1.0 equiv.) $\xrightarrow[\text{UV-light, rt, 12 h}]{\text{phenanthrene (5 mol\%), CsF (Y equiv.), MeCN/H}_2\text{O 9:1}}$ $\text{H}_3\text{C-CH(CH}_3\text{)-NH-Boc-C}_5\text{H}_4\text{N}$ (±)-1

Entry	X (equiv.)	Y (equiv.)	Yield (%) ^a
1	1.0	1.0	17
2	2.0	2.0	20
3	3.0	3.0	27
4	5.0	5.0	29
5	3.0	5.0	23

Procedure: The reactions were performed as described for Table S1. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S3: Solvent screening for the coupling of carboxylic acids with aromatic nitriles.

$\text{H}_3\text{C}-\text{CH}(\text{CO}_2\text{H})-\text{CH}_2\text{NHBoc} + \text{4-CN-pyridine} \xrightarrow[\text{UV-light, rt, 12 h}]{\text{phenanthrene (5 mol\%), CsF (3.0 equiv.), MeCN/H}_2\text{O}}$
 $\text{H}_3\text{C}-\text{CH}(\text{CO}_2\text{NHBoc})-\text{CH}_2\text{NHBoc}$

31 (3.0 equiv.) **32** (1.0 equiv.) **(±)-1**

Entry	Solvent	Yield (%) ^a
1	dry MeCN	26
2	undried MeCN	26
3	MeCN/H₂O 9:1	27
4	MeCN/H ₂ O 7:3	7
5	MeCN/H ₂ O 1:1	4
6	MeCN/H ₂ O 3:7	3
7	H ₂ O	1

Procedure: The reactions were performed as described for Table S1. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S4: Influence of the phenanthrene loading on the coupling of carboxylic acids with aromatic nitriles.

$\text{H}_3\text{C}-\text{CH}(\text{CO}_2\text{H})-\text{CH}_2\text{NHBoc} + \text{4-CN-pyridine} \xrightarrow[\text{UV-light, rt, 18 h}]{\text{phenanthrene (X mol\%), CsF (3.0 equiv.), MeCN/H}_2\text{O 9:1}}$
 $\text{H}_3\text{C}-\text{CH}(\text{CO}_2\text{NHBoc})-\text{CH}_2\text{NHBoc}$

31 (3.0 equiv.) **32** (1.0 equiv.) **(±)-1**

Entry	X (mol%)	Yield (%) ^a
1	5	27
2	10	40
3	15	59
4	20	64
5	25	65
6	30	68
7	50	71
8	75	77
9	100	72

Procedure: The reactions were performed as described for Table S1. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S5: Control experiments for the coupling of carboxylic acids with aromatic nitriles.

$\text{H}_3\text{C}-\text{CH}_2-\text{CH}(\text{NH}-\text{Boc})-\text{CO}_2\text{H}$ (31, 3.0 equiv.) + CN phenanthrene (75 mol%),
 CsF (3.0 equiv.), $\text{MeCN}/\text{H}_2\text{O}$ 9:1
 $\xrightarrow{\text{UV-light, rt, 18 h}}$ $\text{H}_3\text{C}-\text{CH}_2-\text{CH}(\text{NH}-\text{Boc})-\text{C}_5\text{H}_4\text{N}$ (±)-1

Entry	Conditions	Yield (%) ^a
1	normal	77
2	no phenanthrene	6
3	exclusion of light	0

Procedure: The reactions were performed as described for Table S1. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

II.2 Coupling of Alcohols Activated as Oxalates with Aromatic Nitriles

Table S6: Base screening for the coupling of cesium oxalates with aromatic nitriles.

$\text{CsO}-\text{C}(=\text{O})-\text{O}-\text{C}(\text{CH}_3)(\text{C}_6\text{H}_{11})-\text{C}(=\text{O})-\text{O}-\text{Cs}$ (33, 3.0 equiv.) + CN phenanthrene (1.0 equiv.),
 base (1.0 equiv.), $\text{MeCN}/\text{H}_2\text{O}$ 9:1
 $\xrightarrow{\text{UV-light, rt, 24 h}}$ $\text{C}_6\text{H}_4(\text{CN})-\text{C}(\text{CH}_3)(\text{C}_6\text{H}_{11})$ 10

Entry	Base	Yield (%) ^a
1	CsF	22
2	CsOH	5
3	Bu ₄ NOH	14
4	none	31

Procedure: The reactions were performed according to the General Procedure B using cesium oxalate **33** (153 mg, 480 μmol), 4-Cyanopyridine (**32**, 16.7 mg, 160 μmol), phenanthrene (**24**, 28.5 mg, 160 μmol) and the indicated base (160 μmol). The total volume was 8 mL for all reactions. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethyl-silyl)benzene as internal standard.

Table S7: Solvent screening for the coupling of cesium oxalates with aromatic nitriles.

33 (3.0 equiv.) + 32 (1.0 equiv.) $\xrightarrow[\text{UV-light, rt, 24 h}]{\text{phenanthrene (1.0 equiv.), solvent}}$ 10

Entry	Solvent	Yield (%) ^a
1	MeCN	28
2	MeCN/H ₂ O 9:1	31
3	MeCN/H ₂ O 7:3	7
4	DMF	28
5	DMF/H ₂ O 9:1	36
6	DMSO	37
7	DMSO/H ₂ O 9:1	26
8	DME	1
9	DME/H ₂ O 9:1	24
10	DME/DMF 3:1	10
11	DME/DMSO 3:1	24
12	DMSO/DMF 1:1	42
13	DMSO/DME 1:1	41

Procedure: The reactions were performed as described for Table S6. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S8: Influence of the reactant concentrations on the coupling of cesium oxalates with aromatic nitriles.

33 (3.0 equiv.) + 32 (1.0 equiv.) $\xrightarrow[\text{UV-light, rt, 24 h}]{\text{phenanthrene (1.0 equiv.), DMSO/DMF 1:1}}$ 10

Entry	[27] (mmol/L)	Yield (%) ^a
1	10	37
2	13	46
3	20	42
4	27	31
5	40	29

Procedure: The reactions were performed as described for Table S6. Different reactant concentrations were obtained by altering the total volume of the solvent mixture. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S9: Influence of the ratio of nitrile to oxalate on the coupling of cesium oxalates with aromatic nitriles.

CsO=C(C(=O)OC1CCCCC1C)C(=O)OC1CCCCC1C + N#Cc1cccnc1
 $\xrightarrow[\text{UV-light, rt, 24 h}]{\text{phenanthrene (1.0 equiv.), DMSO/DMF 1:1}}$
CC1(CCCCC1)c2cccnc2

33 (X equiv.) **32** (Y equiv.) **10**

Entry	X (equiv.)	Y (equiv.)	Yield (%) ^a
1	1.0	1.0	23
2	2.0	1.0	33
3	3.0	1.0	46
4	5.0	1.0	45
5	1.0	3.0	17

Procedure: The reactions were performed as described for Table S6. One equivalent equals 160 μmol . ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S10: Influence of the phenanthrene loading on the coupling of cesium oxalates with aromatic nitriles.

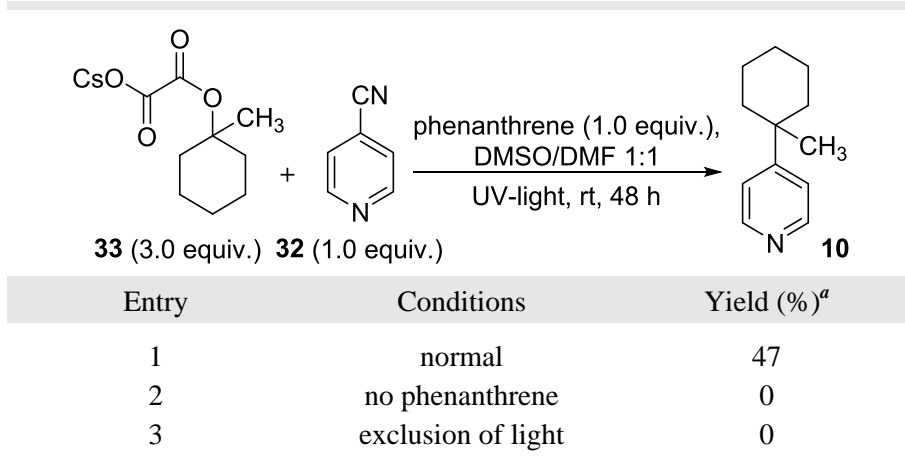
CsO=C(C(=O)OC1CCCCC1C)C(=O)OC1CCCCC1C + N#Cc1cccnc1
 $\xrightarrow[\text{UV-light, rt, 48 h}]{\text{phenanthrene (X mol%), DMSO/DMF 1:1}}$
CC1(CCCCC1)c2cccnc2

33 (3.0 equiv.) **32** (1.0 equiv.) **10**

Entry	X (mol%)	Yield (%) ^a
1	10	7
2	25	16
3	50	22
4	75	34
5	100	47
6	125	55
7	150	55
8	175	53

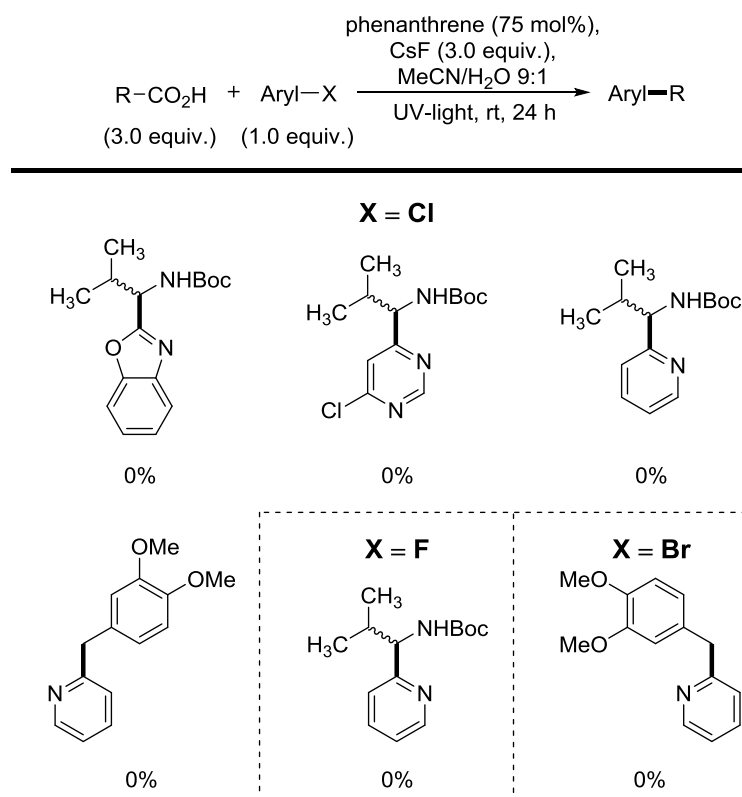
Procedure: The reactions were performed as described for Table S9. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

Table S11: Control experiments for the coupling of cesium oxalates with aromatic nitriles.



Procedure: The reactions were performed as described for Table S9. ^aYields were determined by ¹H NMR spectroscopy of the reaction mixture after extraction using 1,4-bis(trimethylsilyl)benzene as internal standard.

III. Experiments Concerning Halides as Potential Leaving Groups



Scheme S1: Experiments concerning halides as leaving groups for the phenanthrene-catalyzed decarboxylative coupling. All reactions were performed according to the General Procedure A using the indicated aromatic halide instead of an aromatic nitrile.

The experiments summarized in Scheme S1 show that halides do not represent suitable groups for the decarboxylative coupling reported herein.

IV. Recovery of Excess Radical Precursor

All reaction mixtures were irradiated for 24 h. After this time, TLC confirmed complete consumption of the aromatic nitrile. However, when carboxylic acids were used, it was possible to recover some of the excess radical source by a simple extraction procedure:

The alkaline aqueous phase obtained during the extraction of the reaction mixture was acidified under ice-cooling by careful addition of dilute hydrochloric acid. If the radical precursor contained an acid-sensitive group (e.g. Boc- or Cbz-protecting group), citric acid was used instead. Hydrogen cyanide was removed by intense nitrogen sparging for 30 min (**Caution: Hydrogen cyanide is extremely toxic and must not be inhaled**). The acidified aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to afford the pure acid.

Since the radical precursors employed in the coupling reaction reported herein are inexpensive and mostly readily available, they were typically not recovered. However, in exemplary experiments, homoveratric acid was recovered after the alkylation of 4-cyanopyridine (entry 9 in Scheme 1) in a yield of 48%. Boc-L-phenylalanine was recovered after the alkylation of 4-cyanopyridine (entry 3 in Scheme 1) in 40% yield.

The incomplete recovery of the excess carboxylic acid is at least partly attributed to side reactions. Although these reactions have not been studied in detail, reductive decarboxylation of the carboxylic acids yielding the respective hydrocarbons occurred to some extent. Cesium oxalates could not be recovered after successful alkylations.

V. UV-Vis-Spectroscopy Data and Information about Glassware

All reactions on a preparative scale (Scheme 1, Table 1) were performed in round bottom flasks made of DURAN[®] and all reactions in Tables S1–S11 were performed in vials made of AR-GLAS[®]. The manufacturer of these glasses claims no significant transmission of light with wavelengths of less than about 300 nm (For technical information about the used glasses, the reader is directed to the homepage of SCHOTT: http://www.schott.com/tubing/english/product_selector/#!/region--all/lang--english/filter--list). Figure S1 shows the absorption spectra of phenanthrene in both solvent mixtures used for the coupling reactions. Taking the considerations about the used glassware into account, excitation of phenanthrene should mainly be attributed to light with wavelengths of about 300–350 nm (Figure S1).

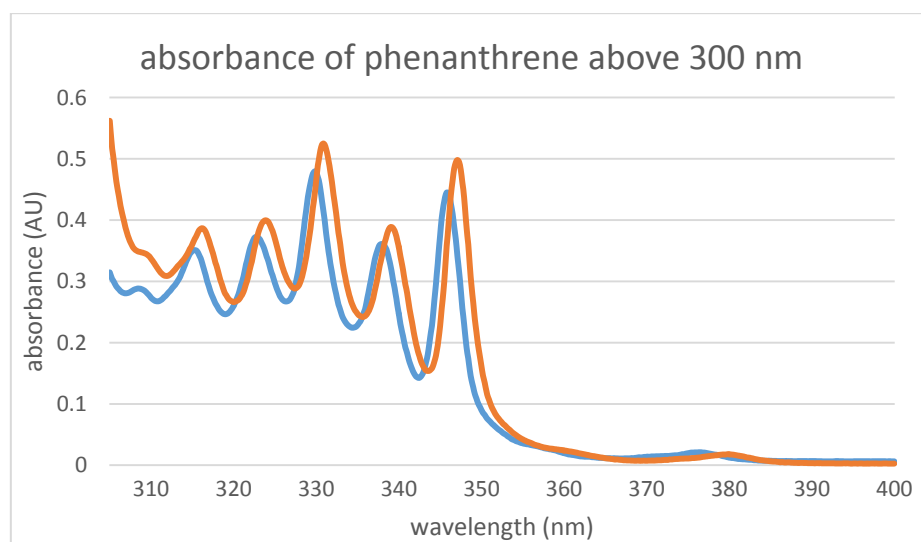
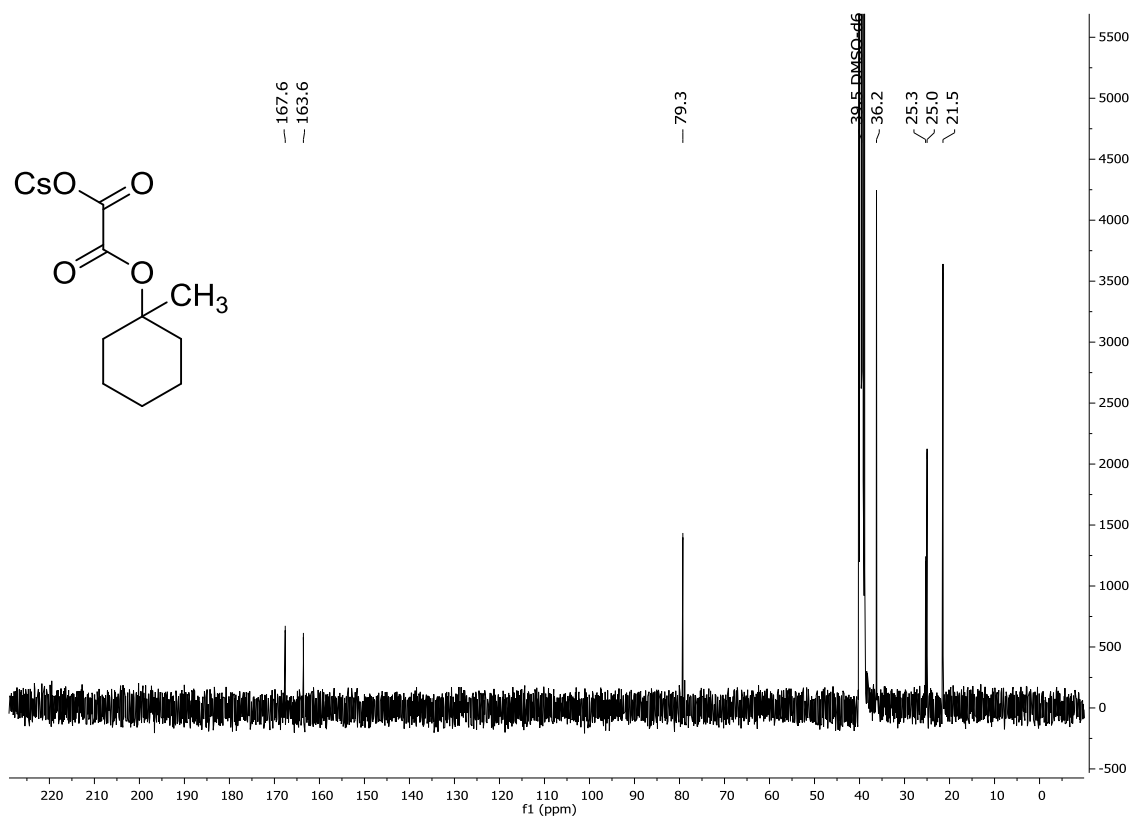
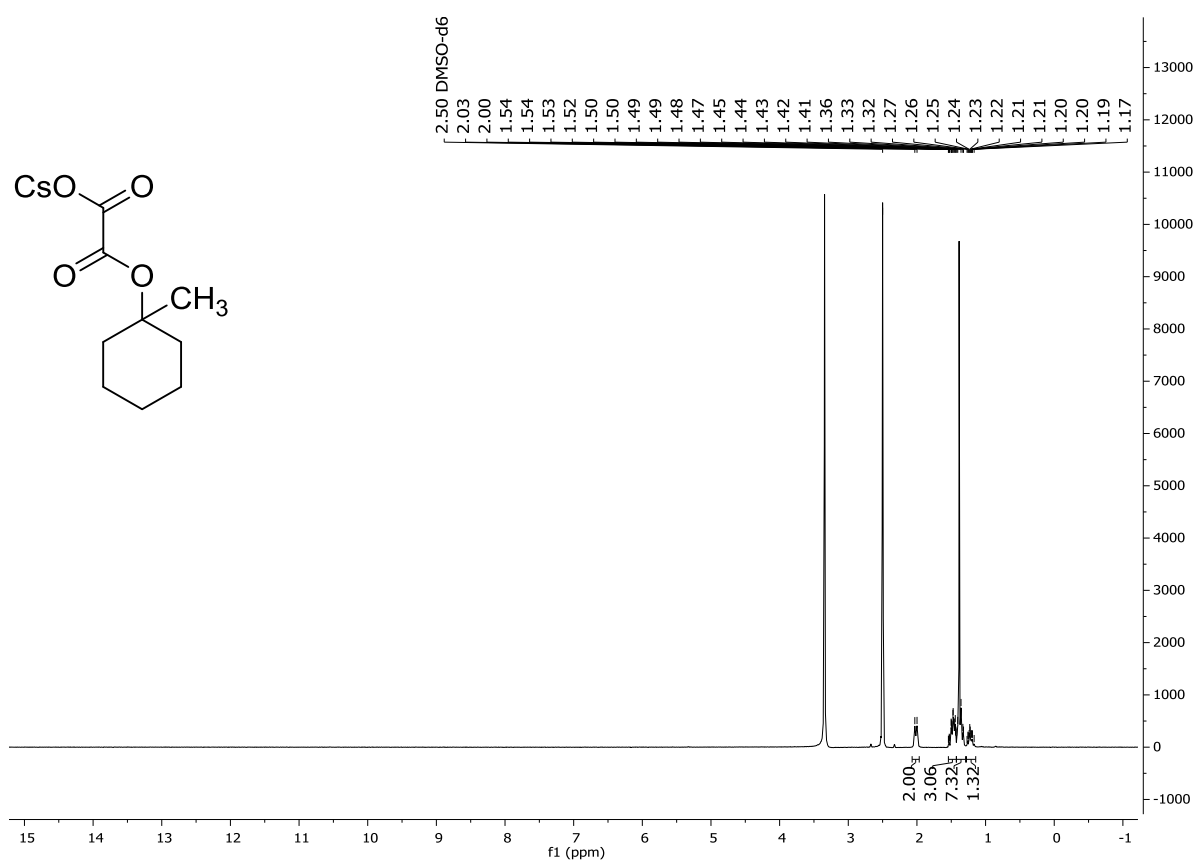
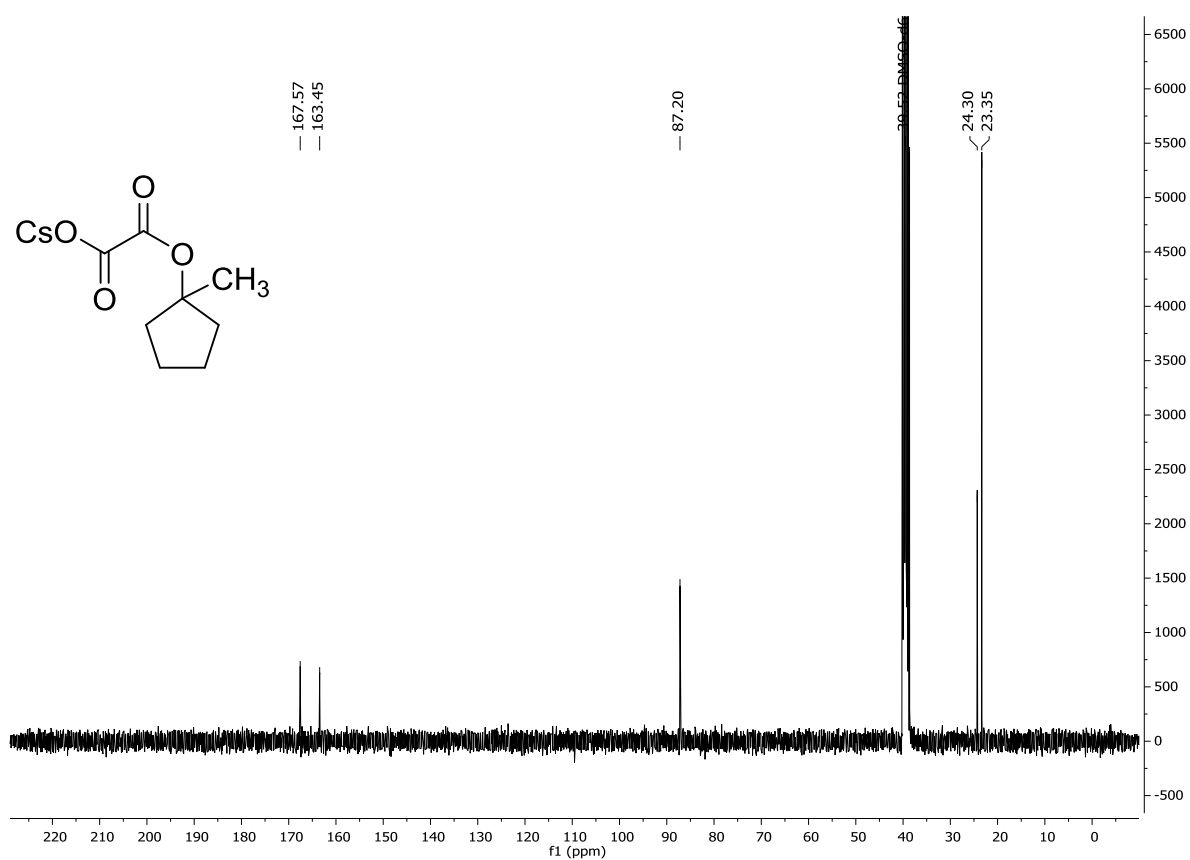
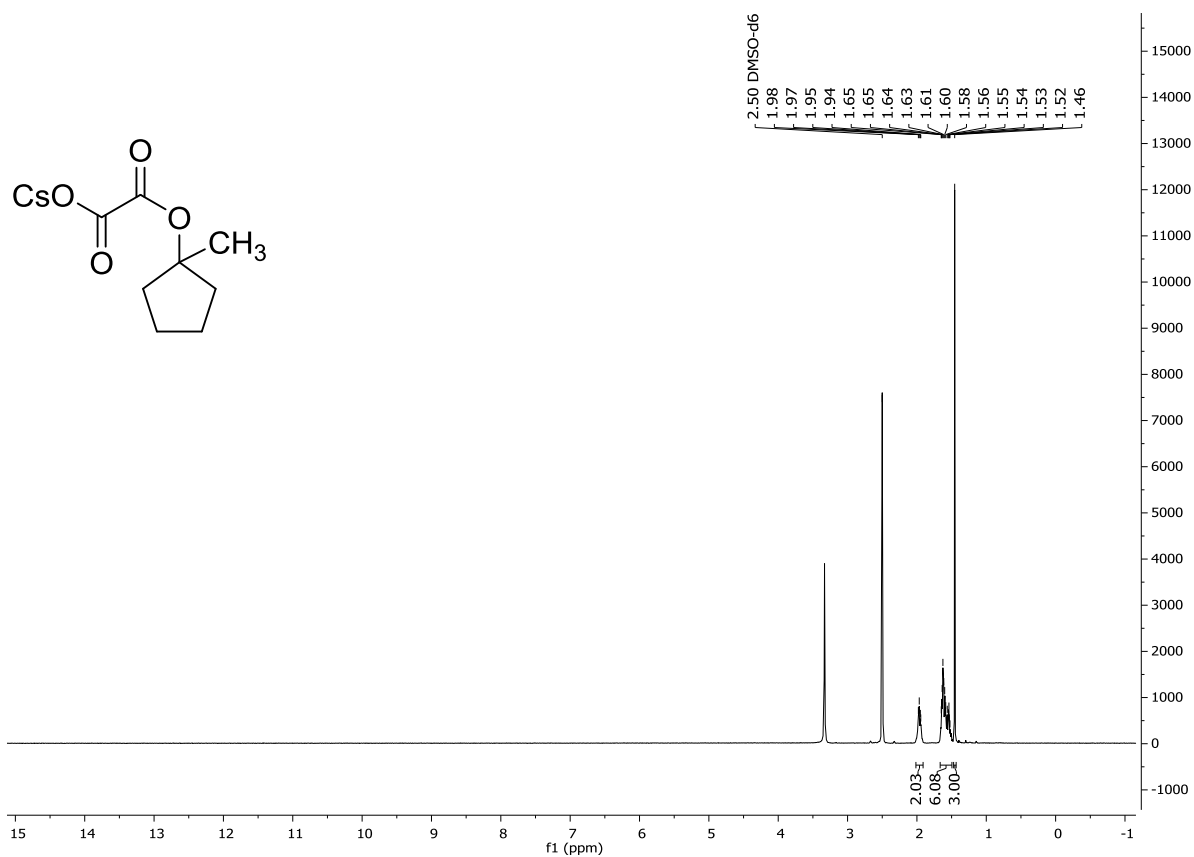
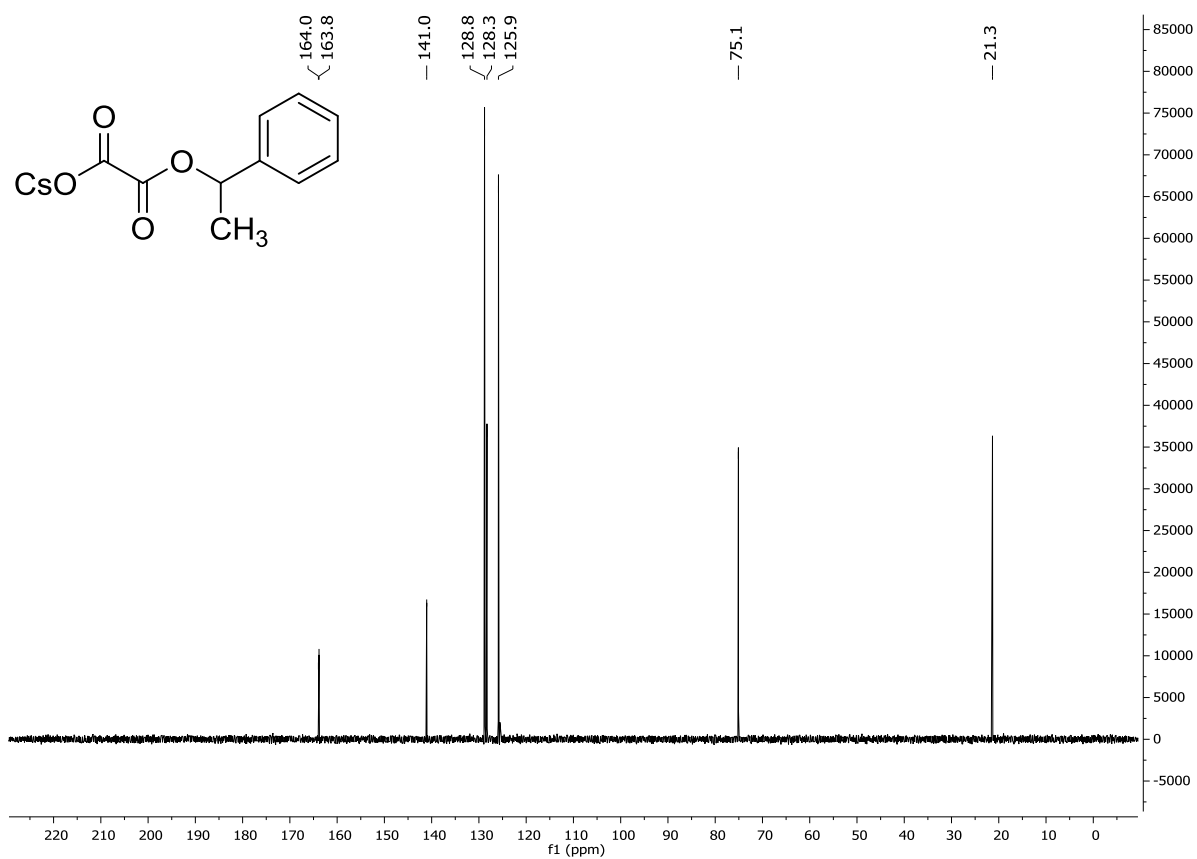
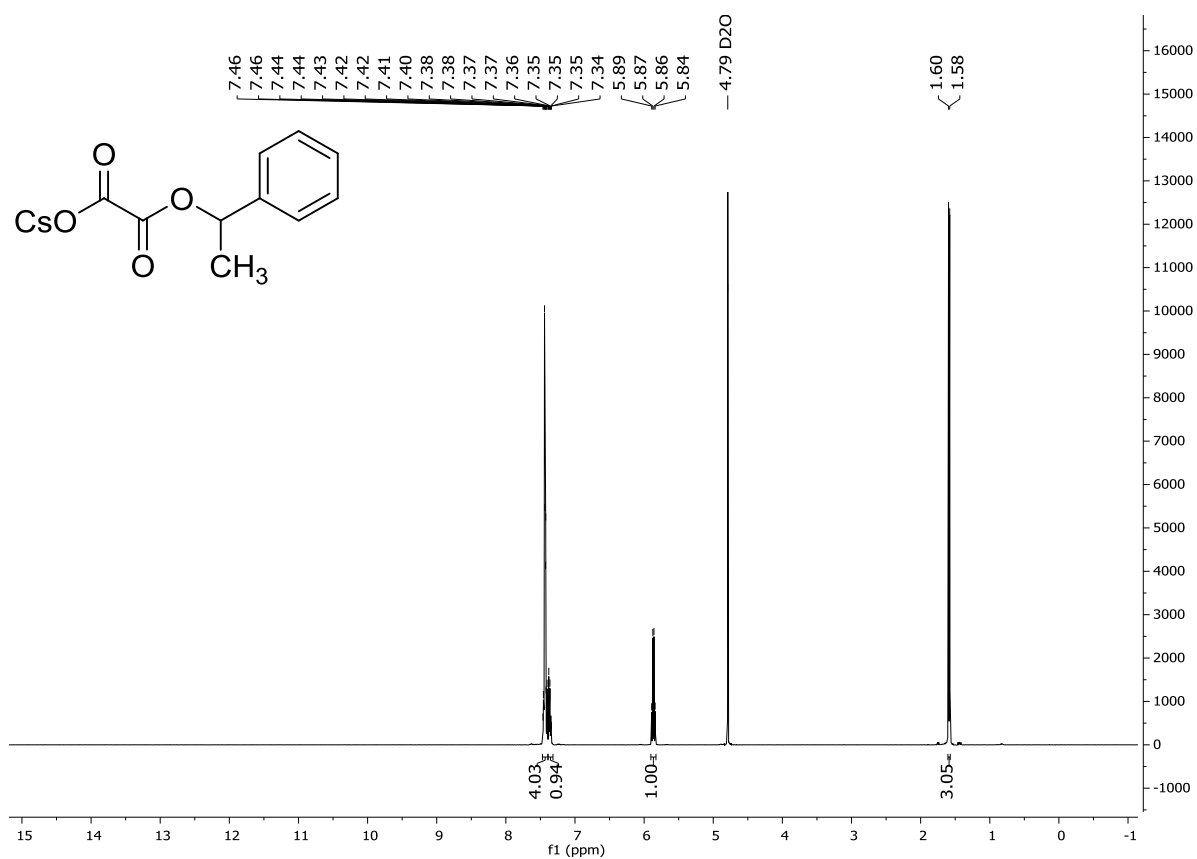


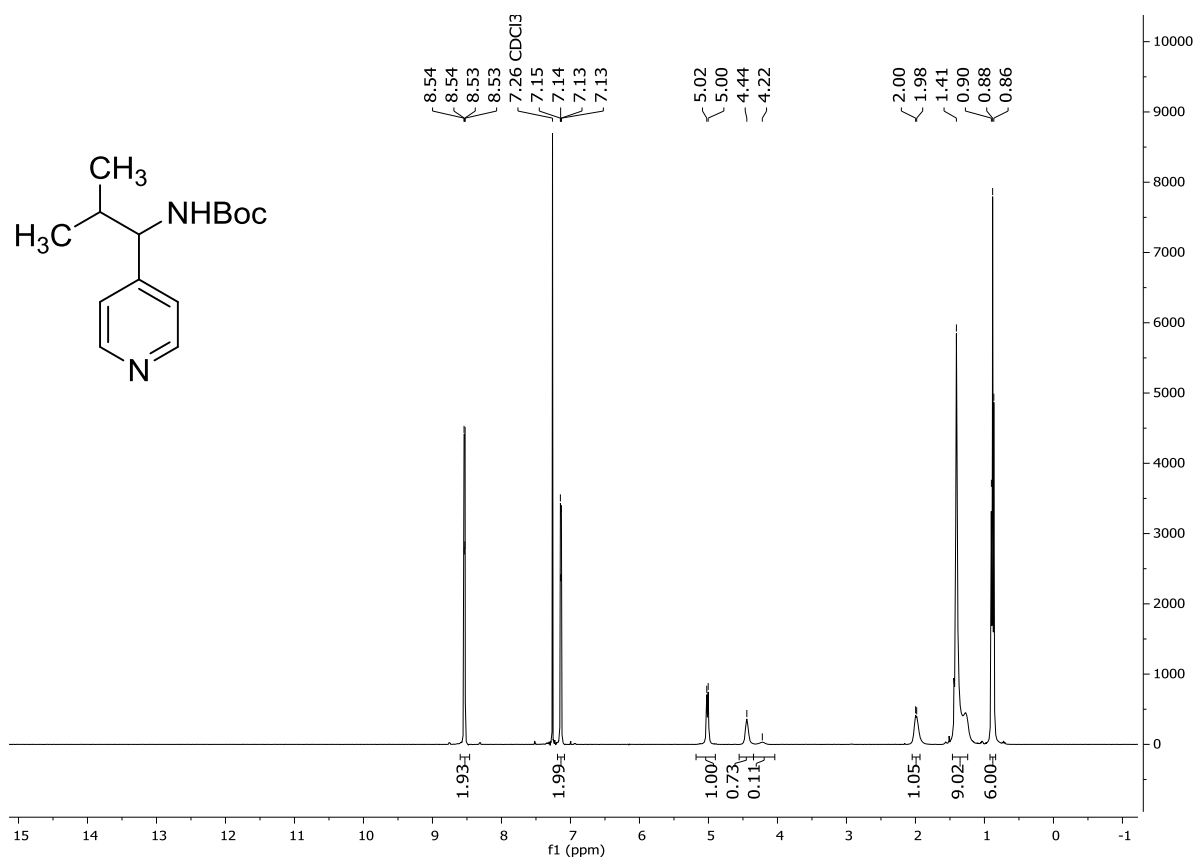
Figure S1: Absorbance of phenanthrene (0.266 mg/mL) in both reaction solvents over the range from 300 nm to 400 nm. blue: MeCN/H₂O 9:1, orange: DMSO/DMF 1:1.

VI. NMR Spectra

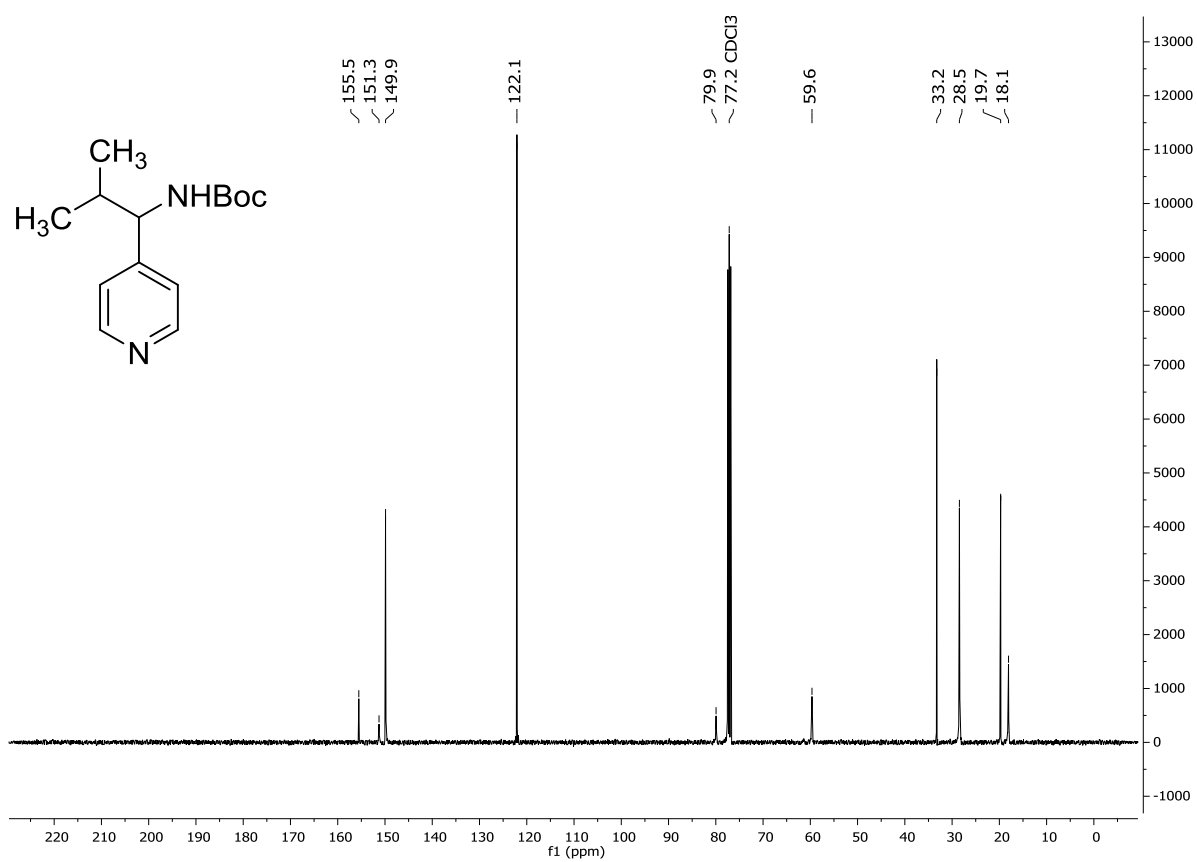




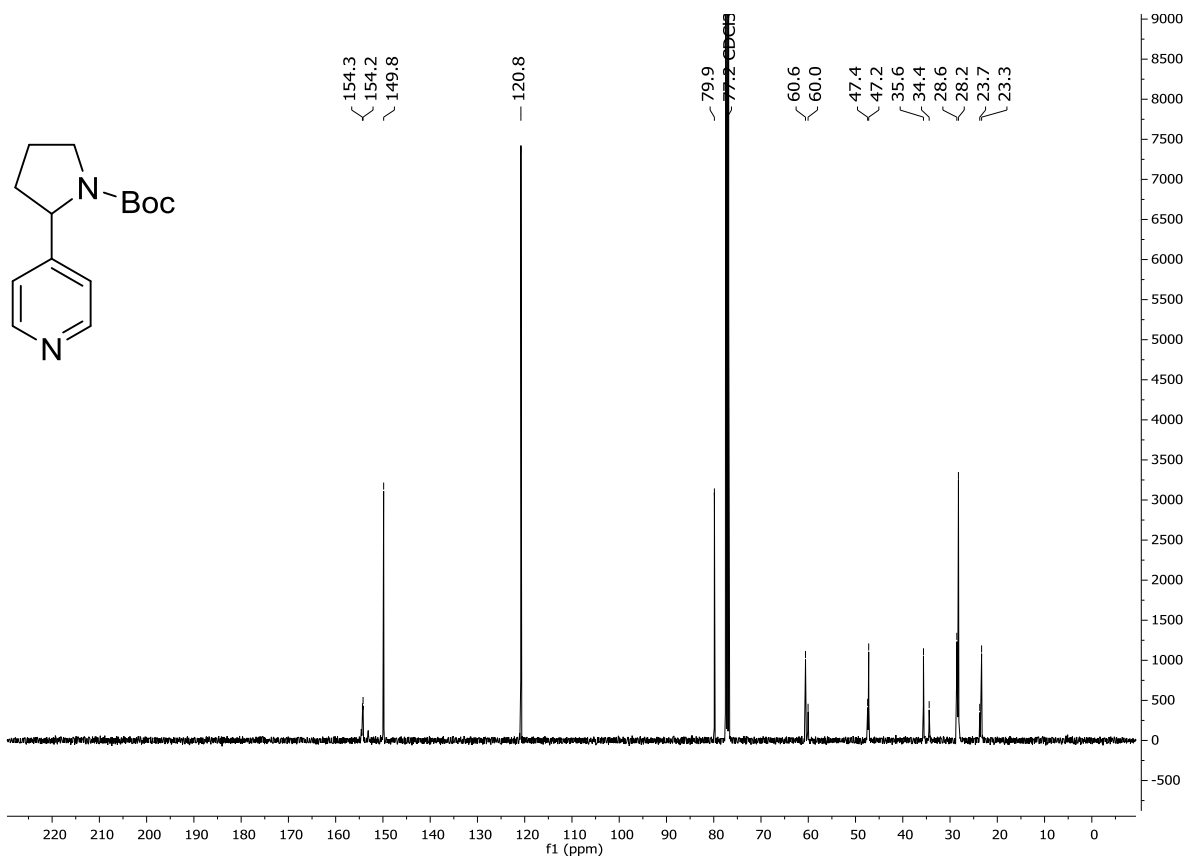
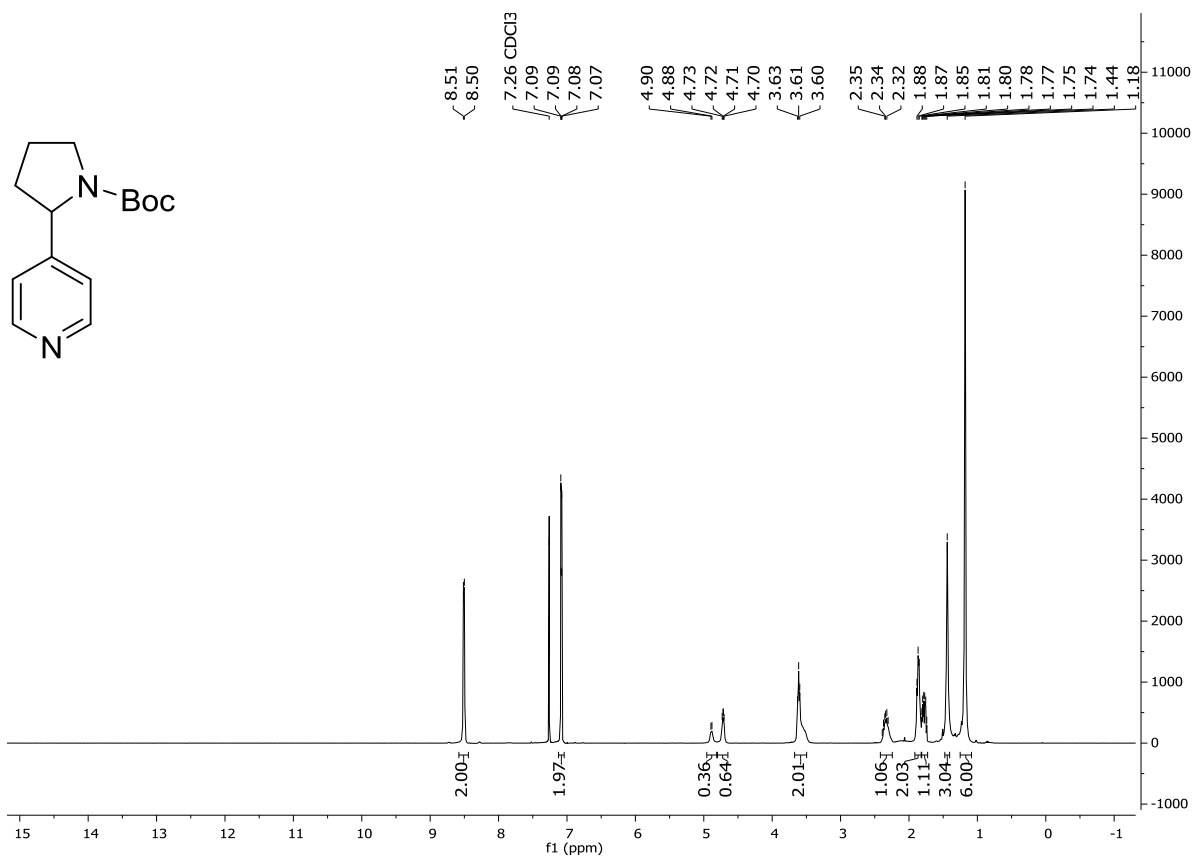


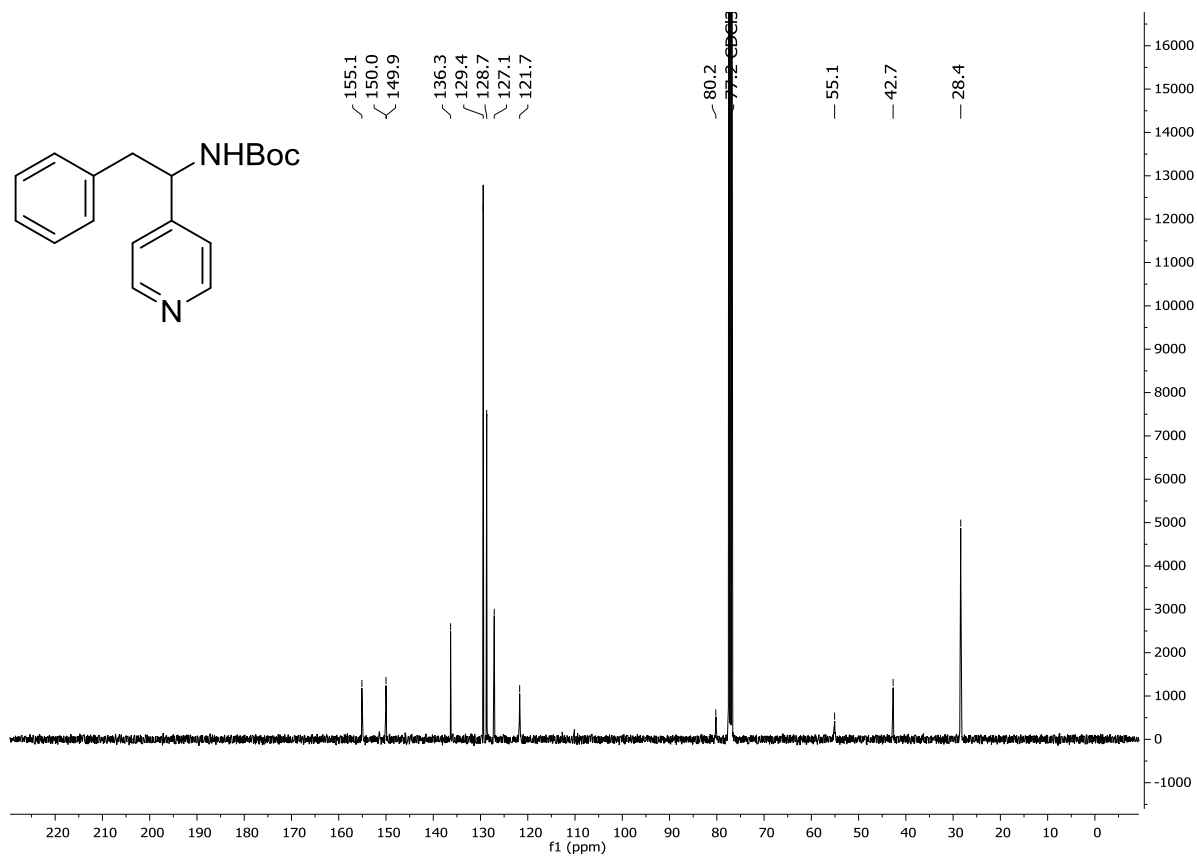
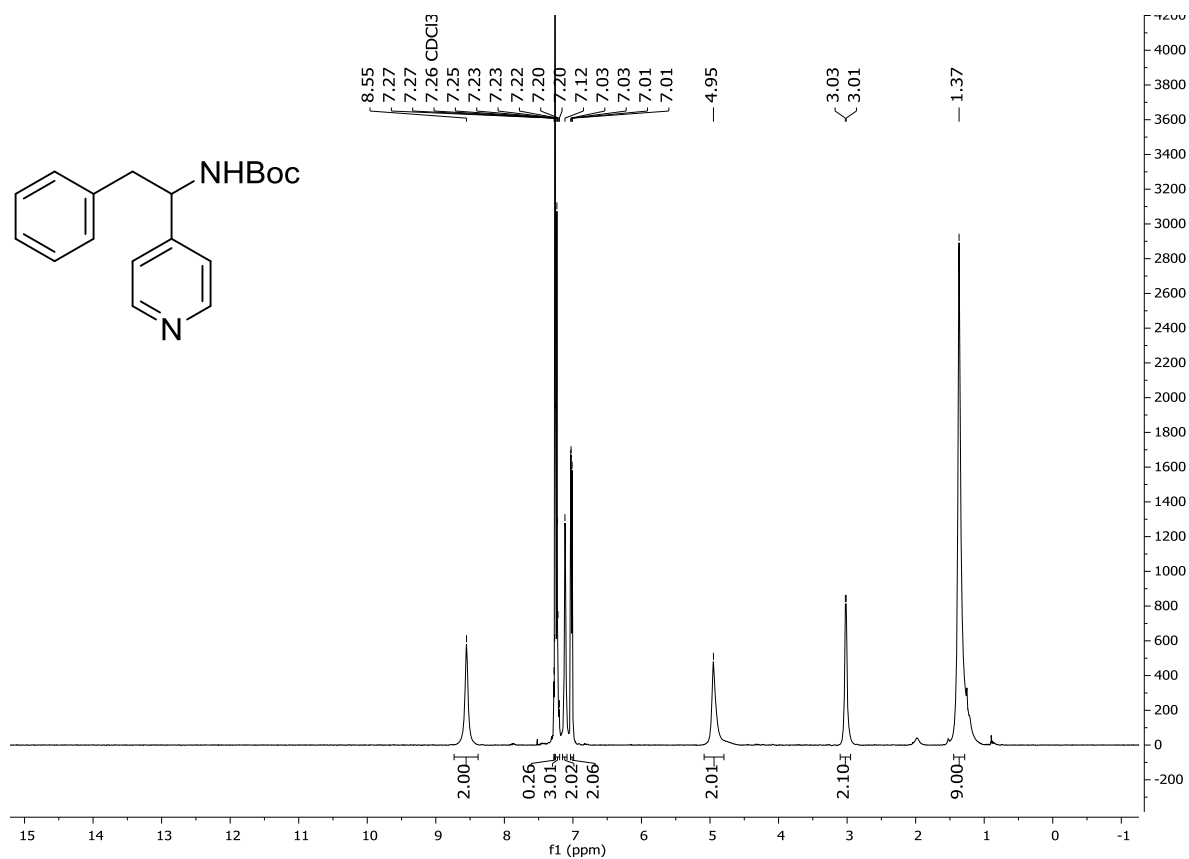


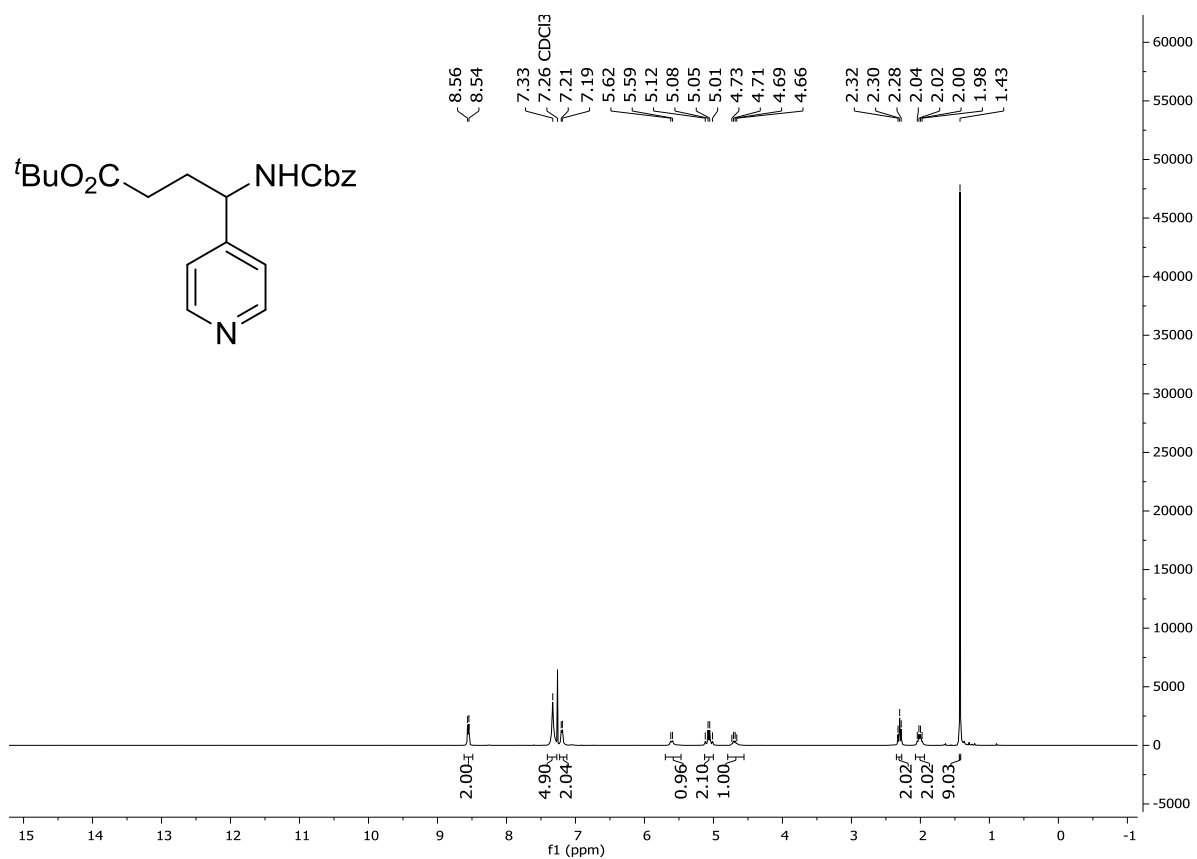
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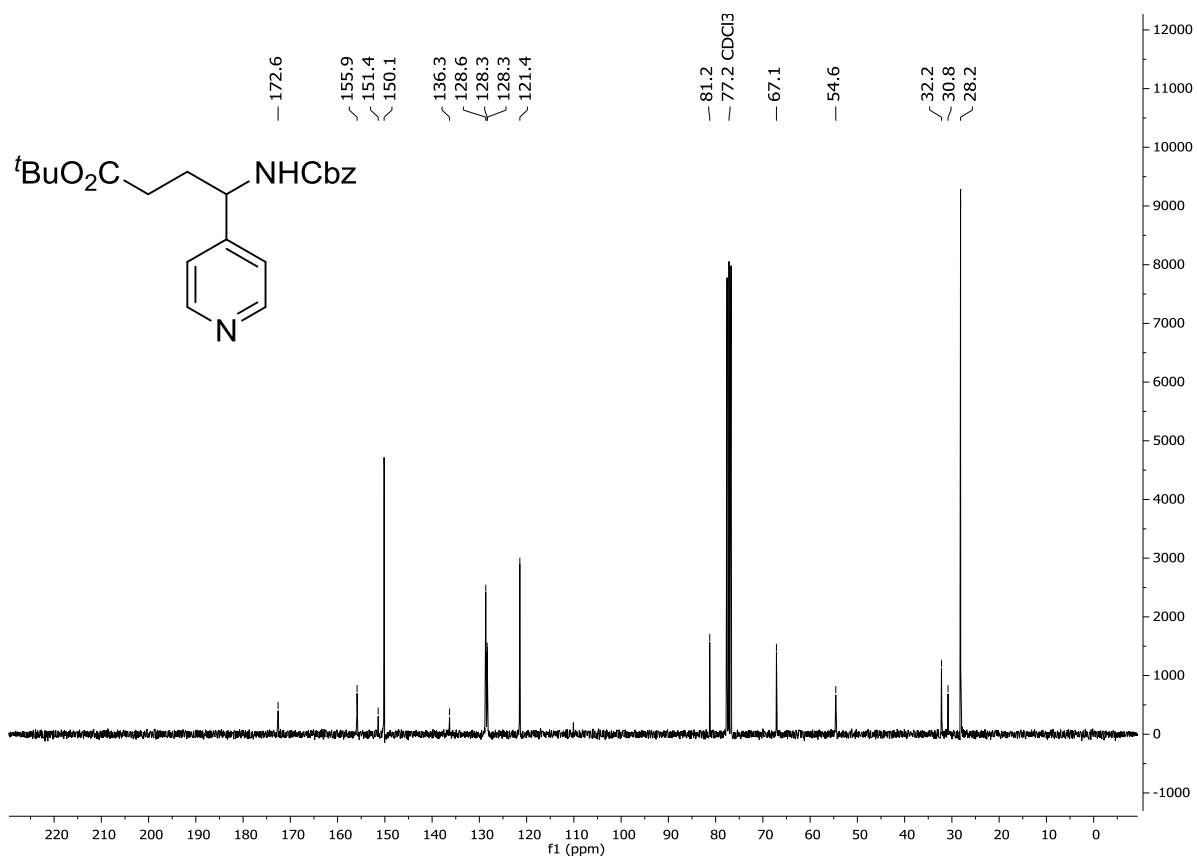
¹³C NMR (100.6 MHz, CDCl₃): Compound **1**



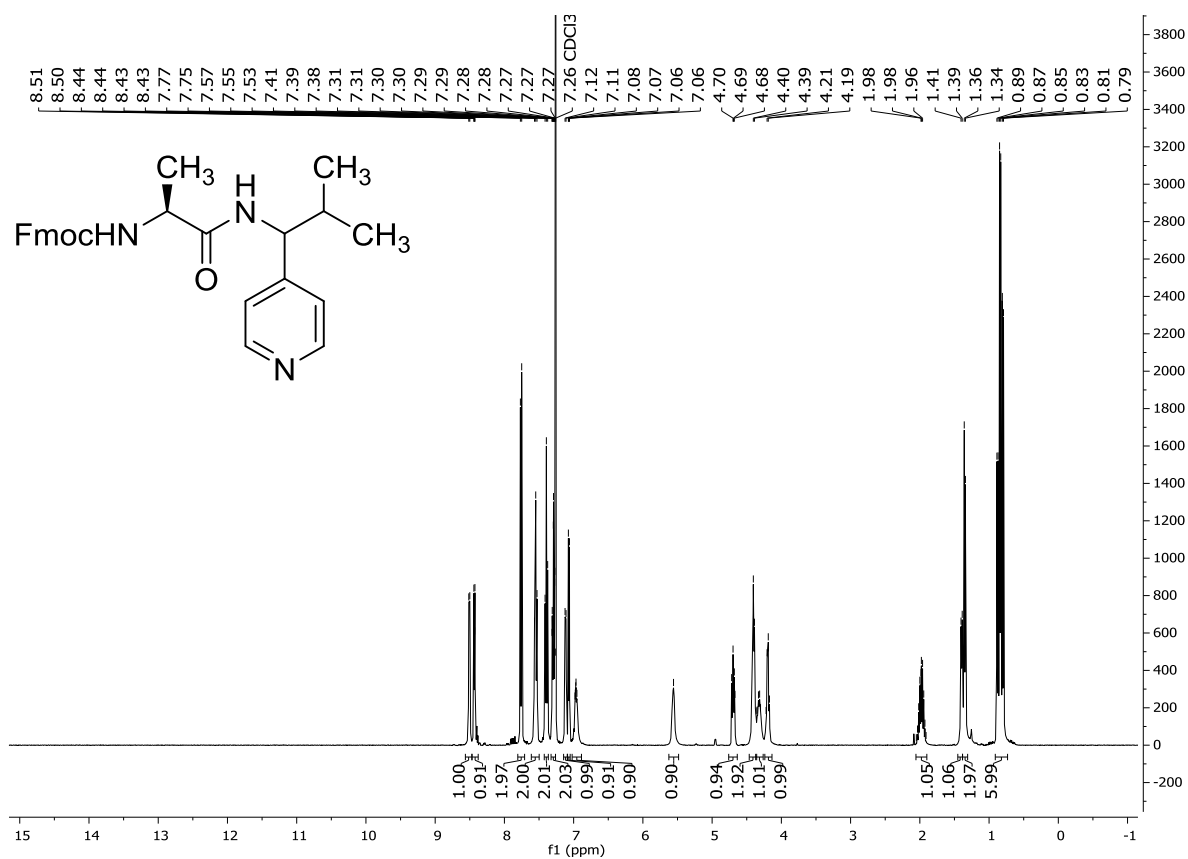




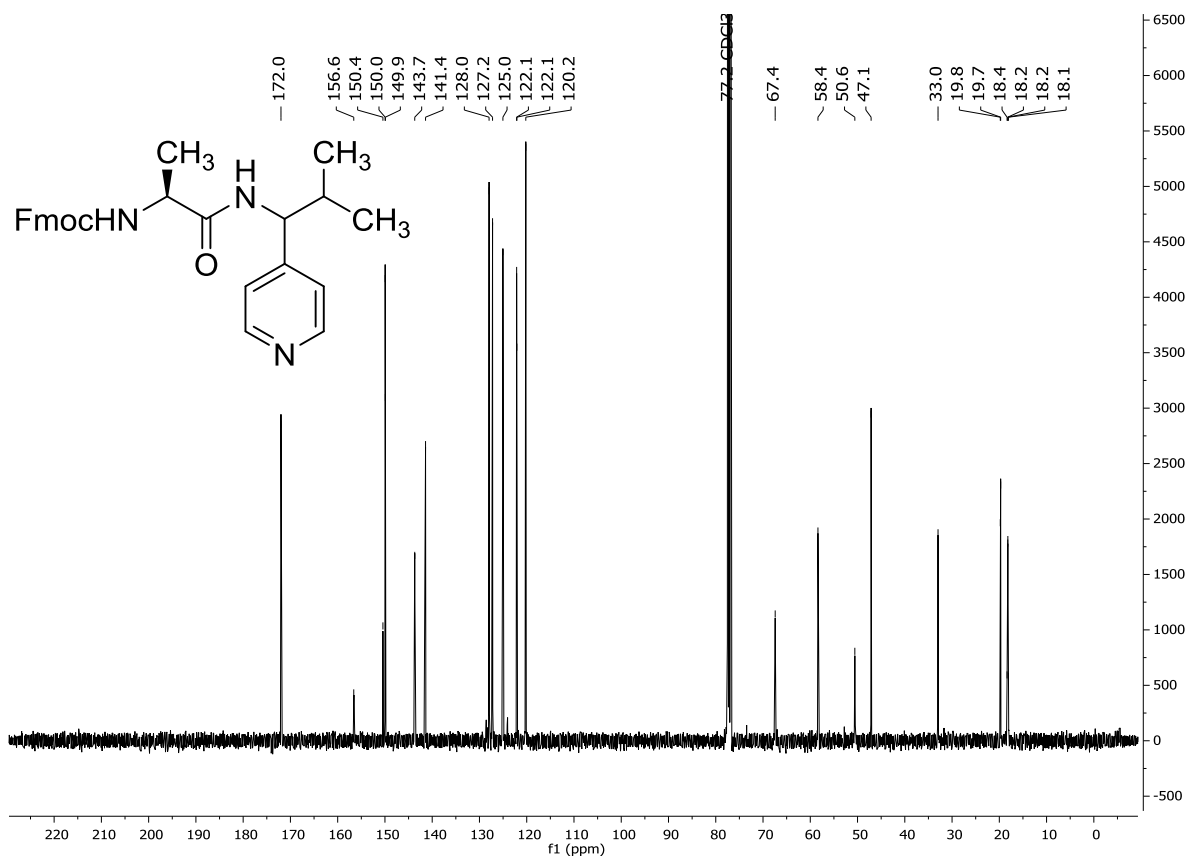
¹H NMR (300 MHz, CDCl₃): Compound **4**



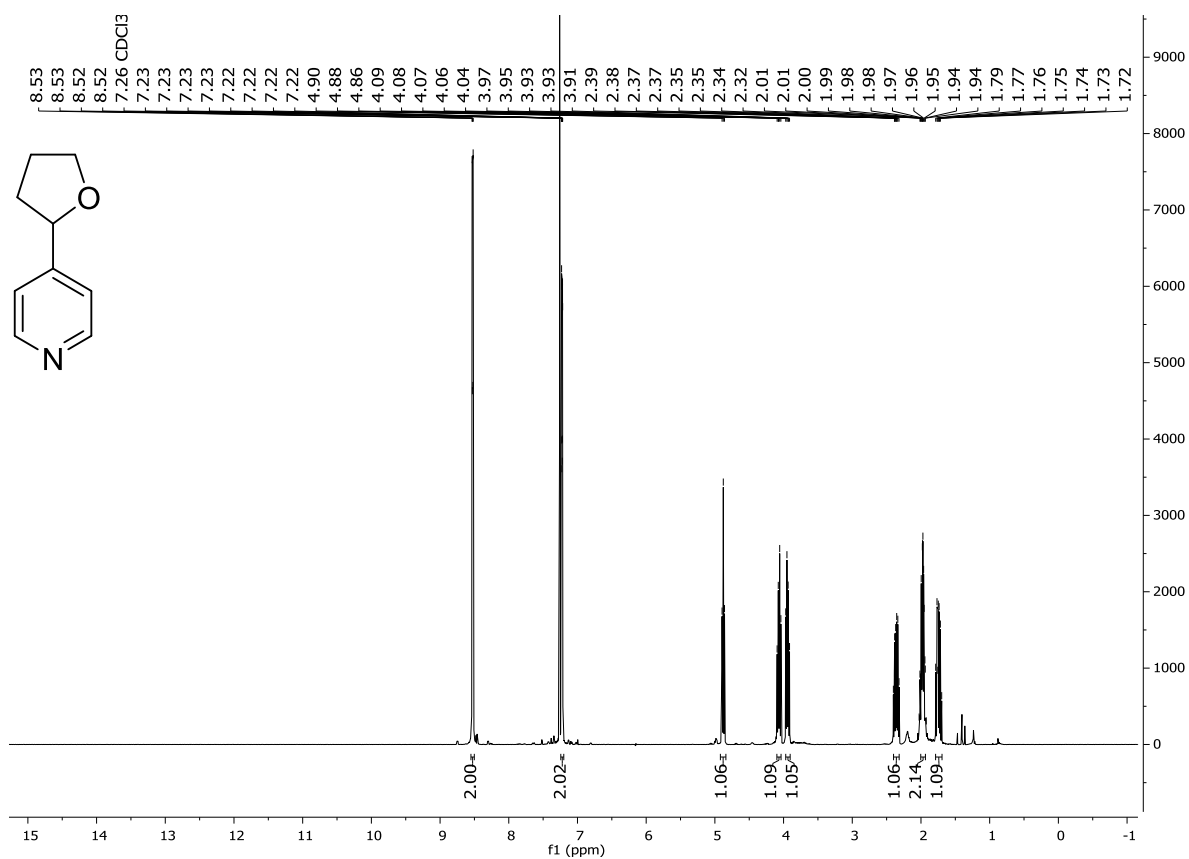
¹³C NMR (75 MHz, CDCl₃): Compound **4**



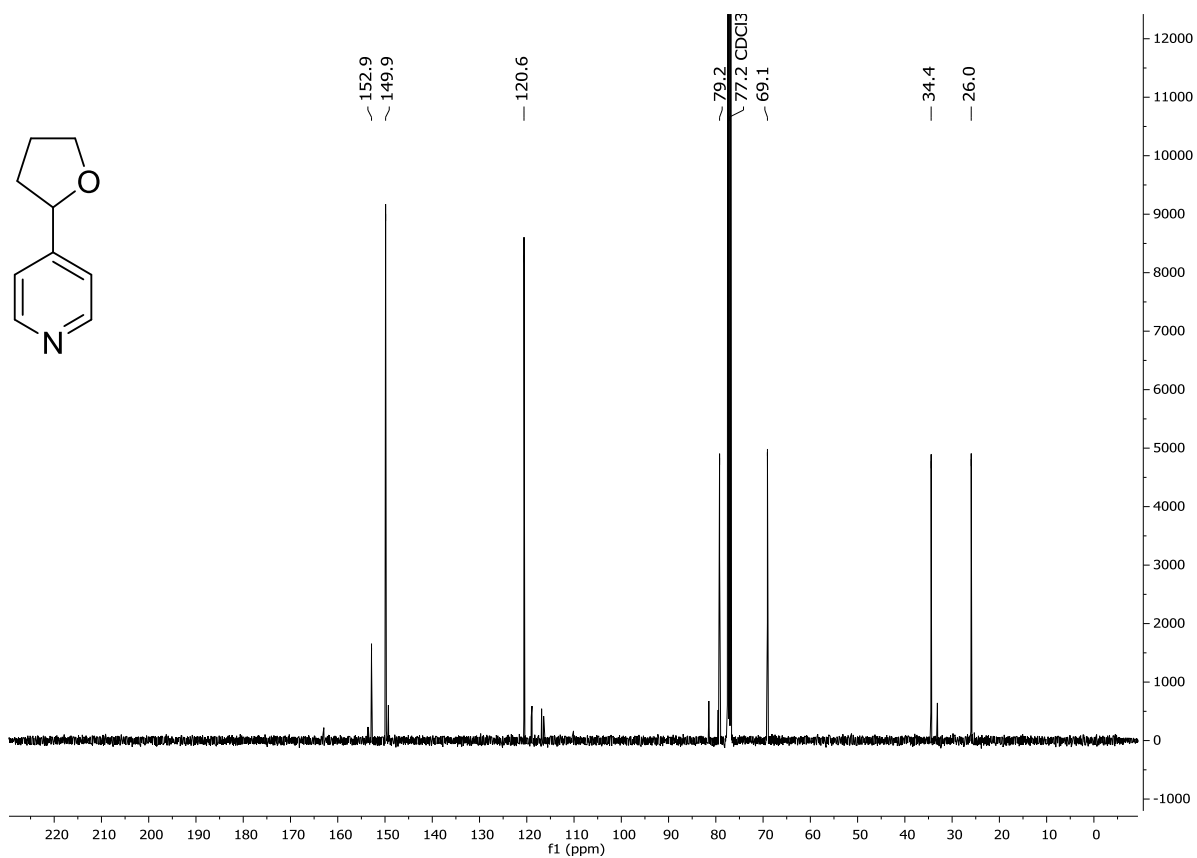
¹H NMR (400 MHz, CDCl₃): Compound **5**



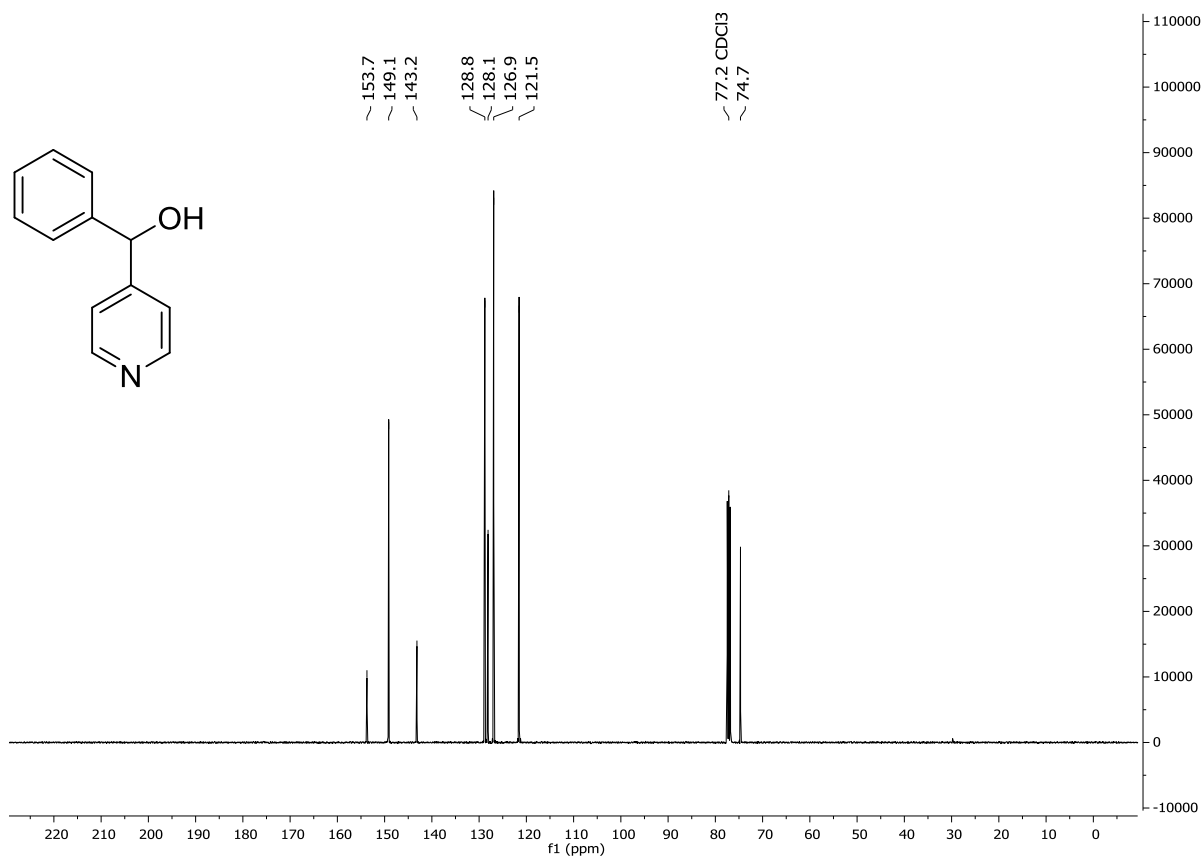
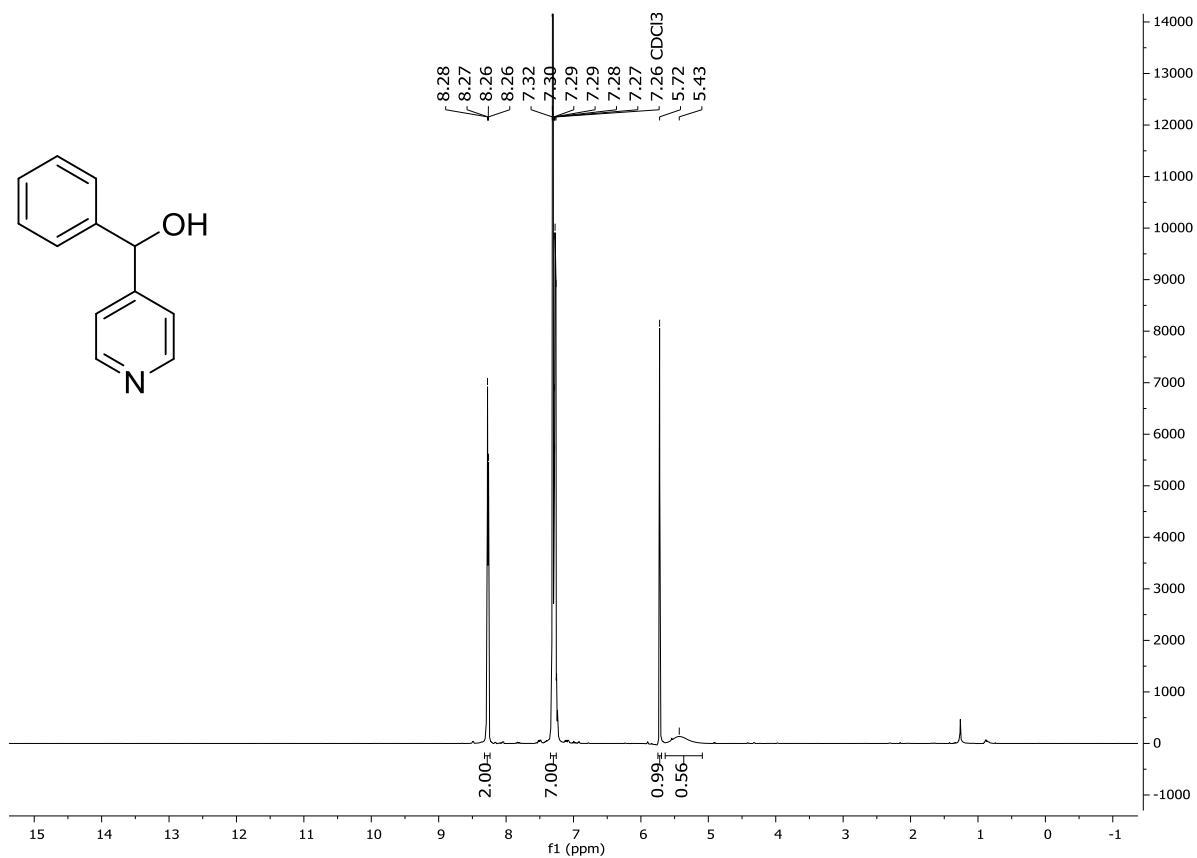
¹³C NMR (100.6 MHz, CDCl₃): Compound **5**

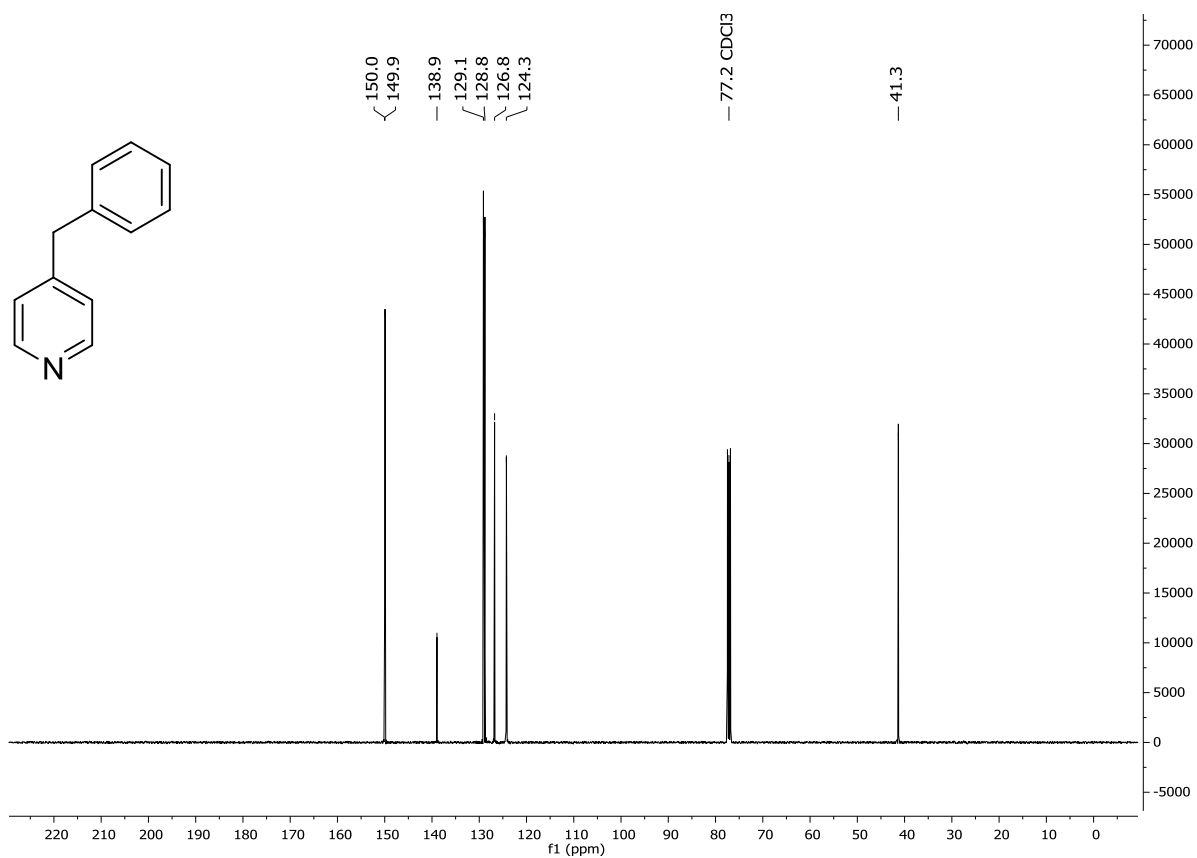
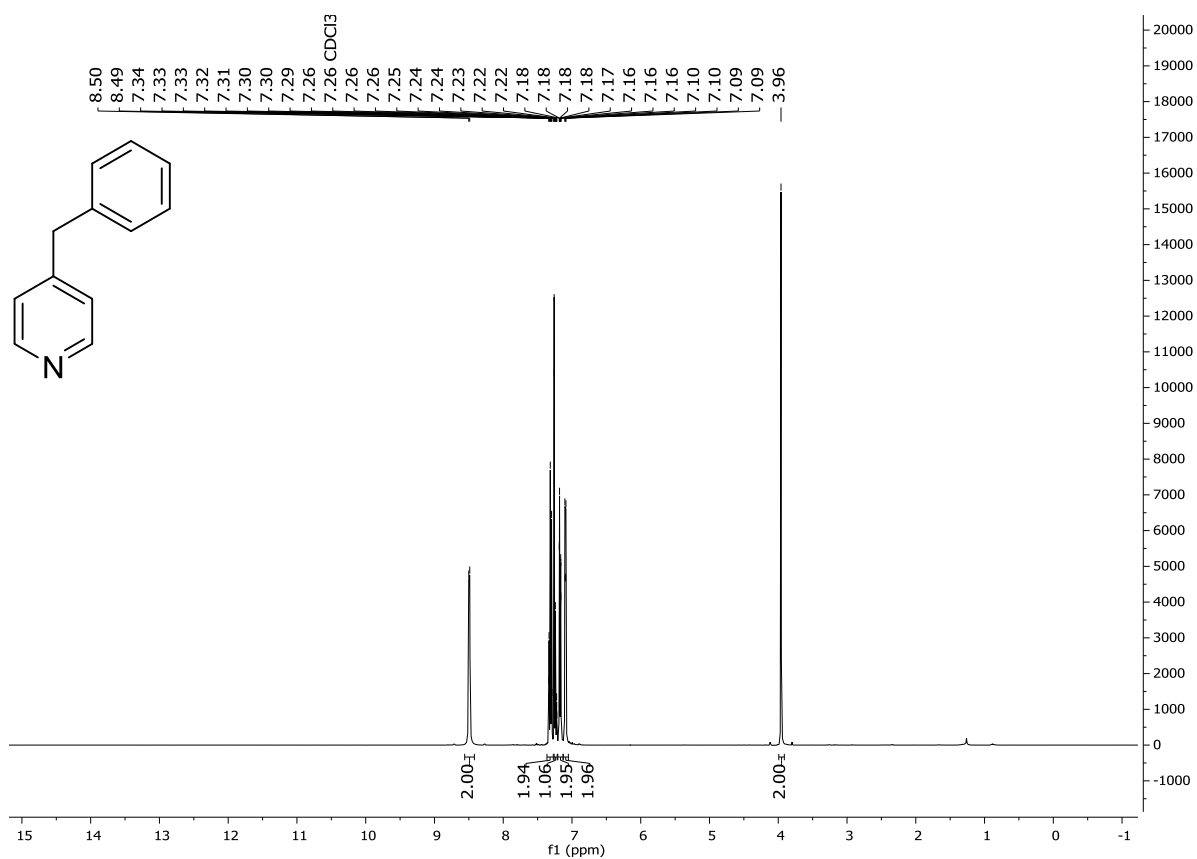


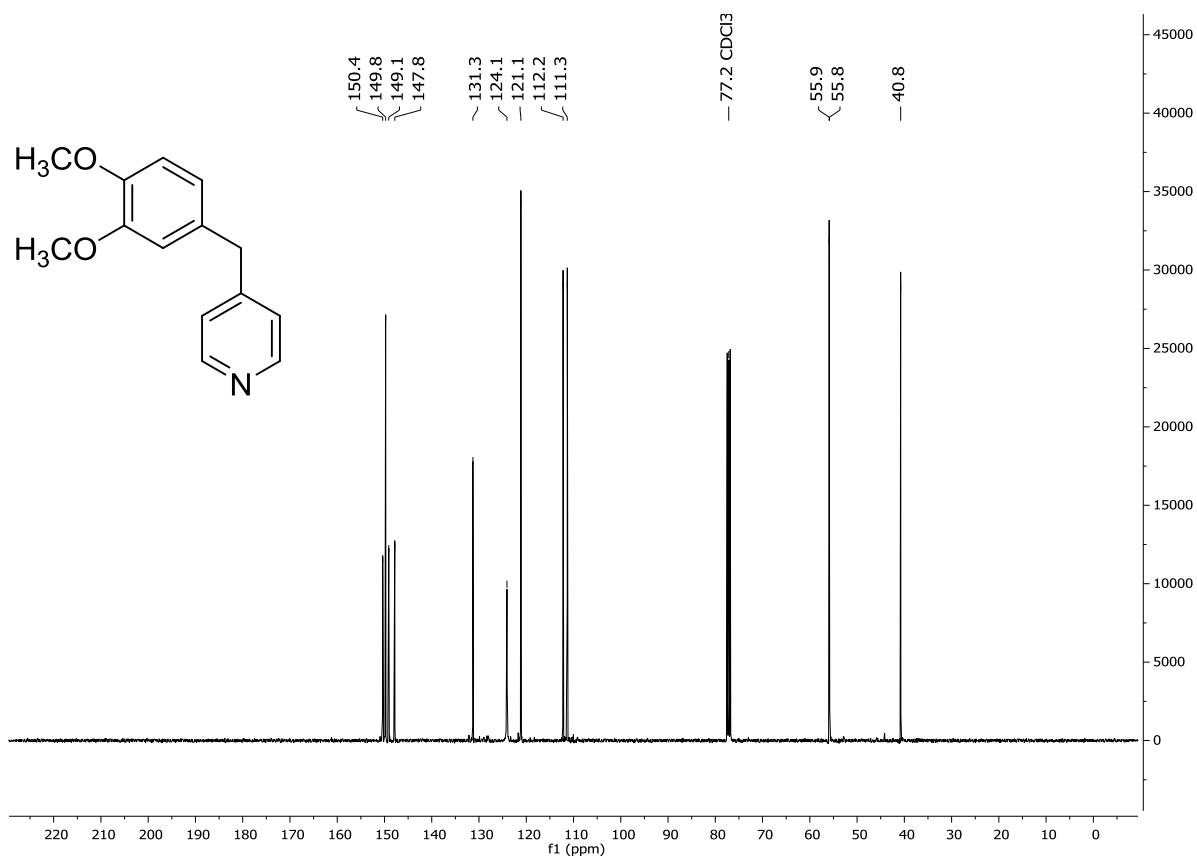
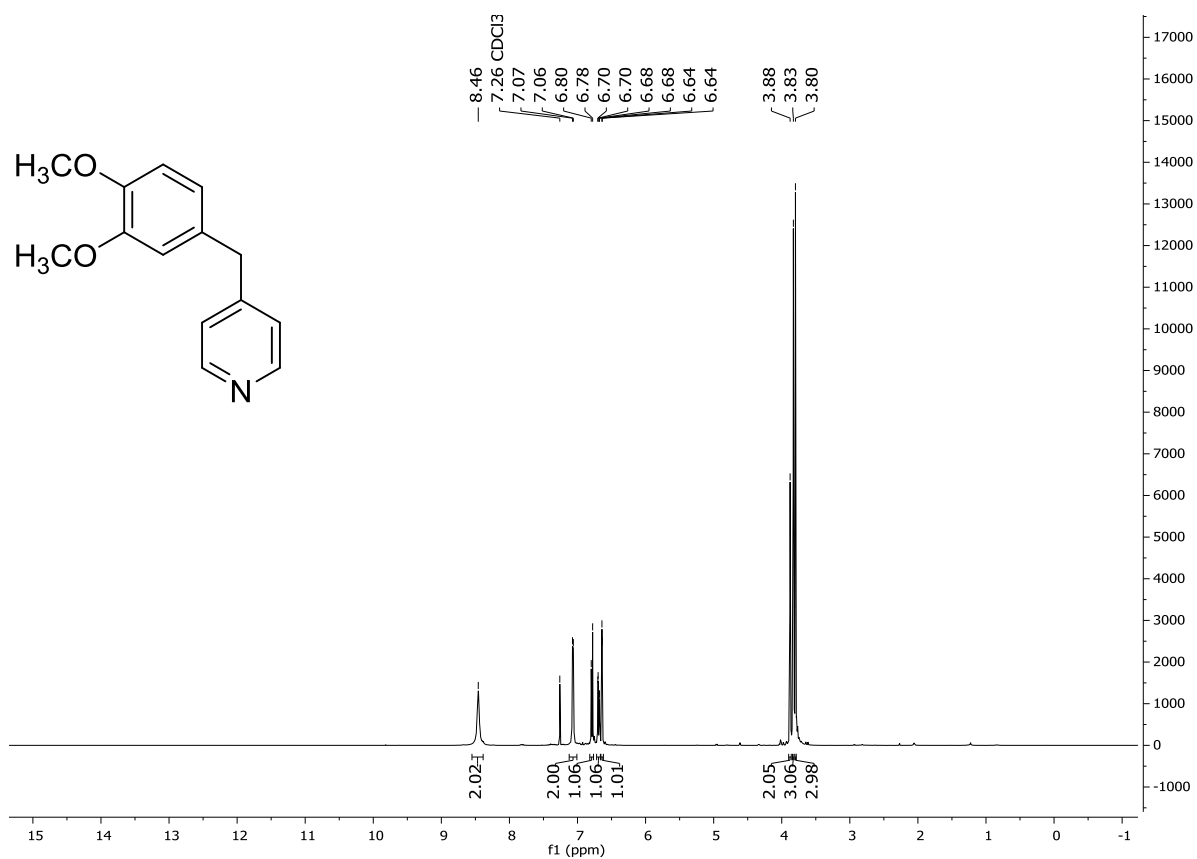
¹H NMR (400 MHz, CDCl₃): Compound 6

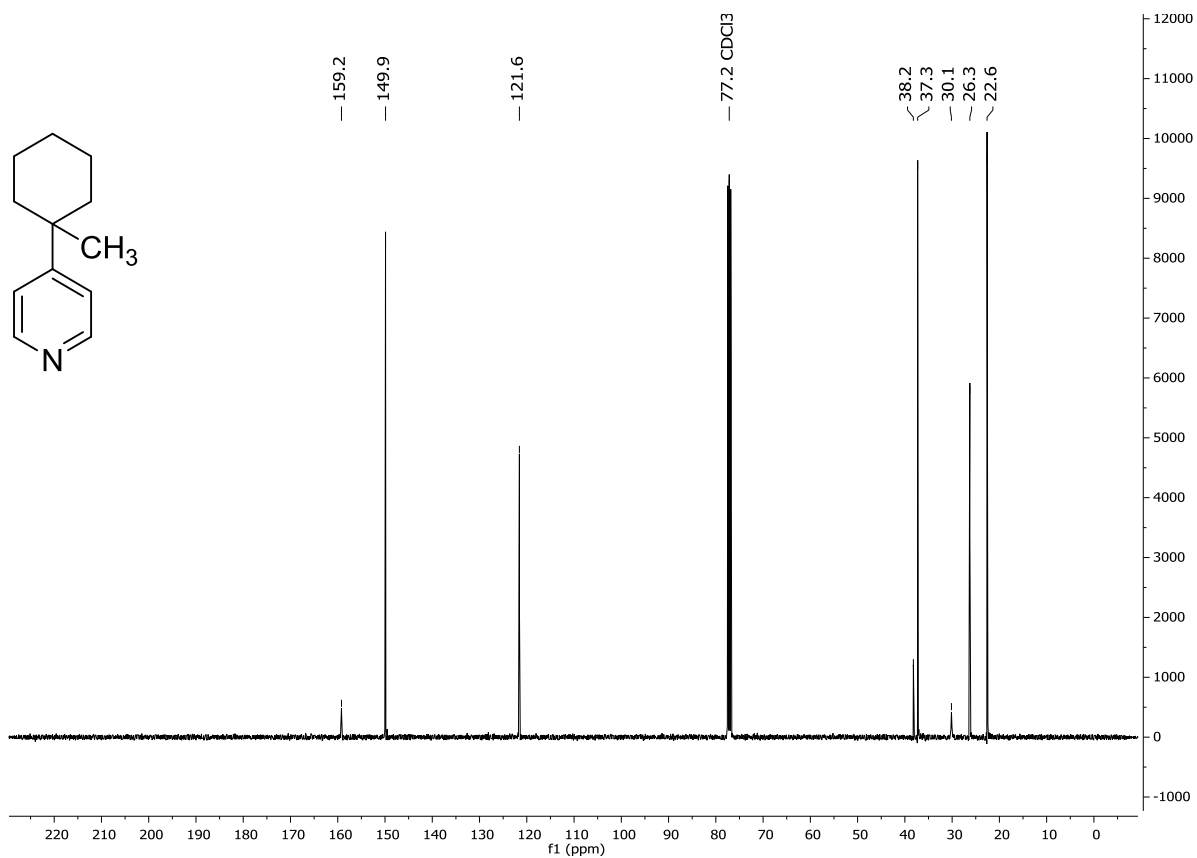
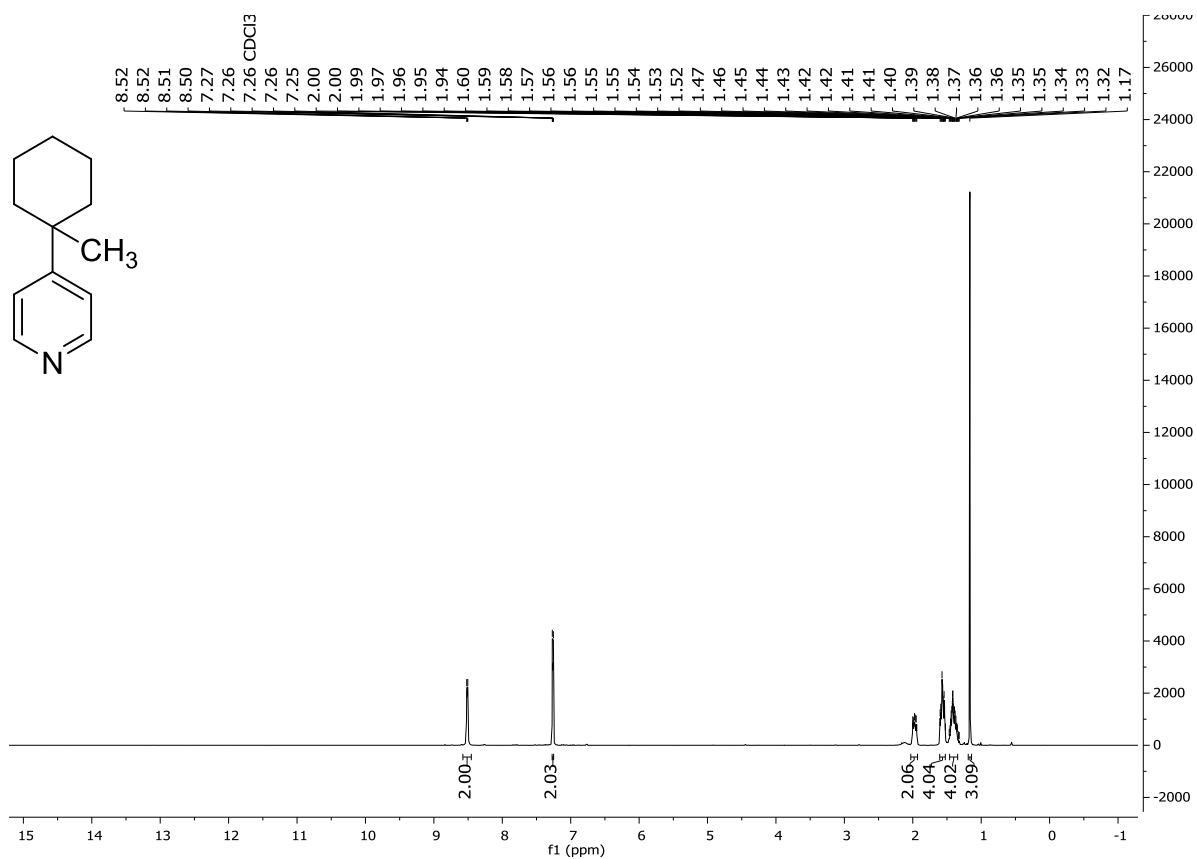


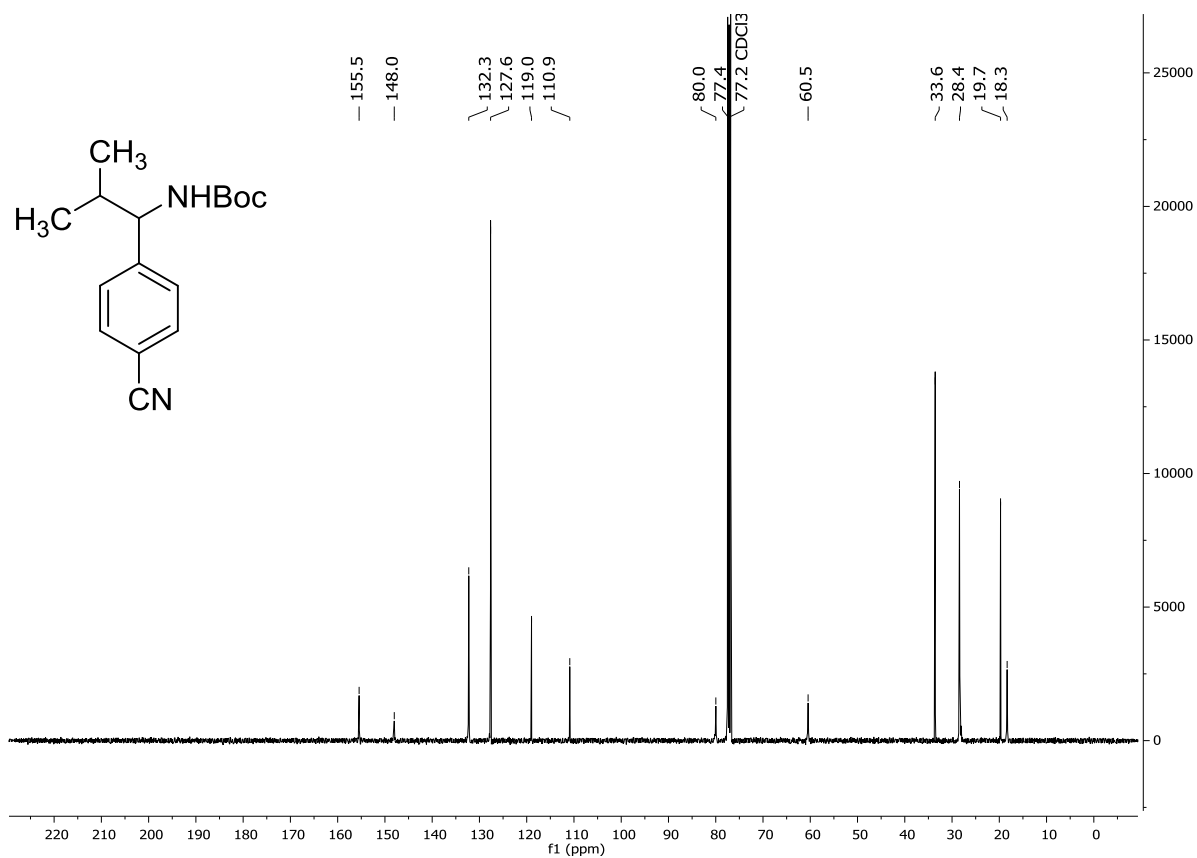
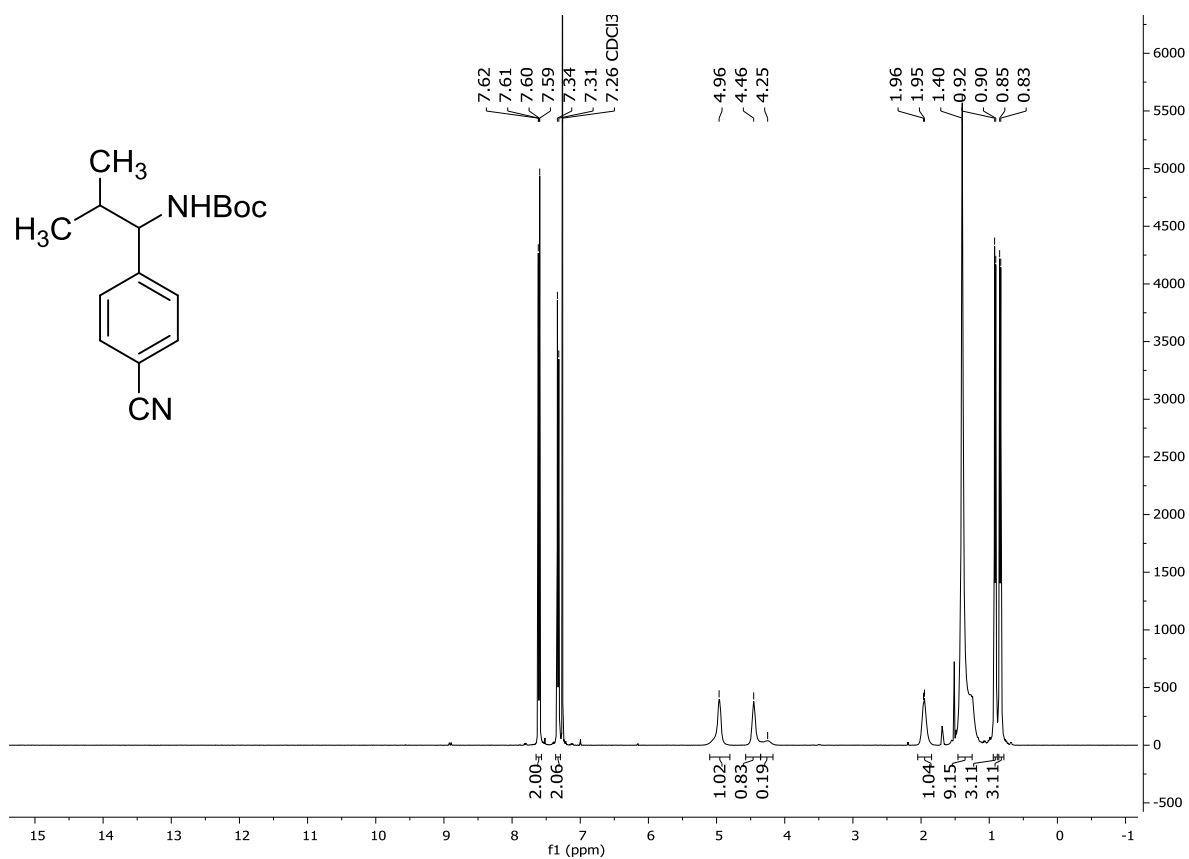
¹³C NMR (100.6 MHz, CDCl₃): Compound 6. In contrast to the ¹H NMR spectrum, beginning decomposition of the sample can be observed.

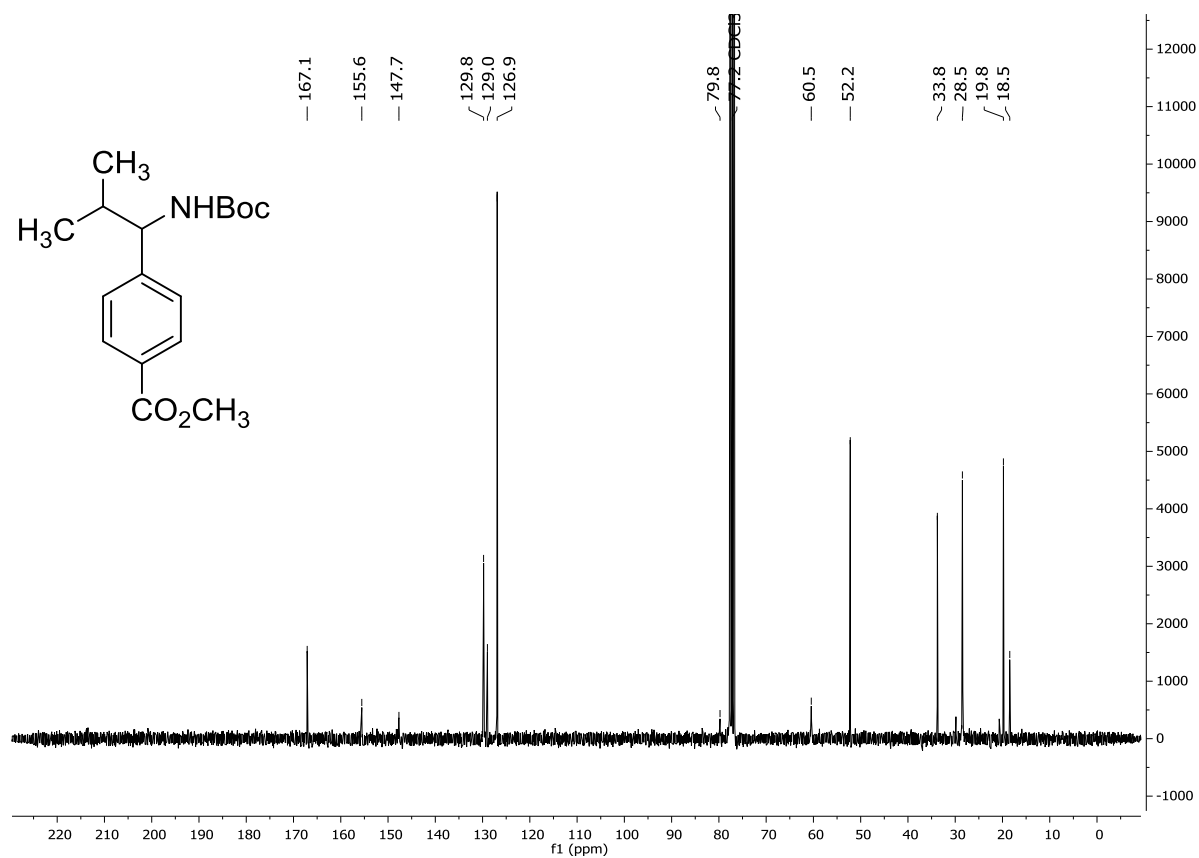
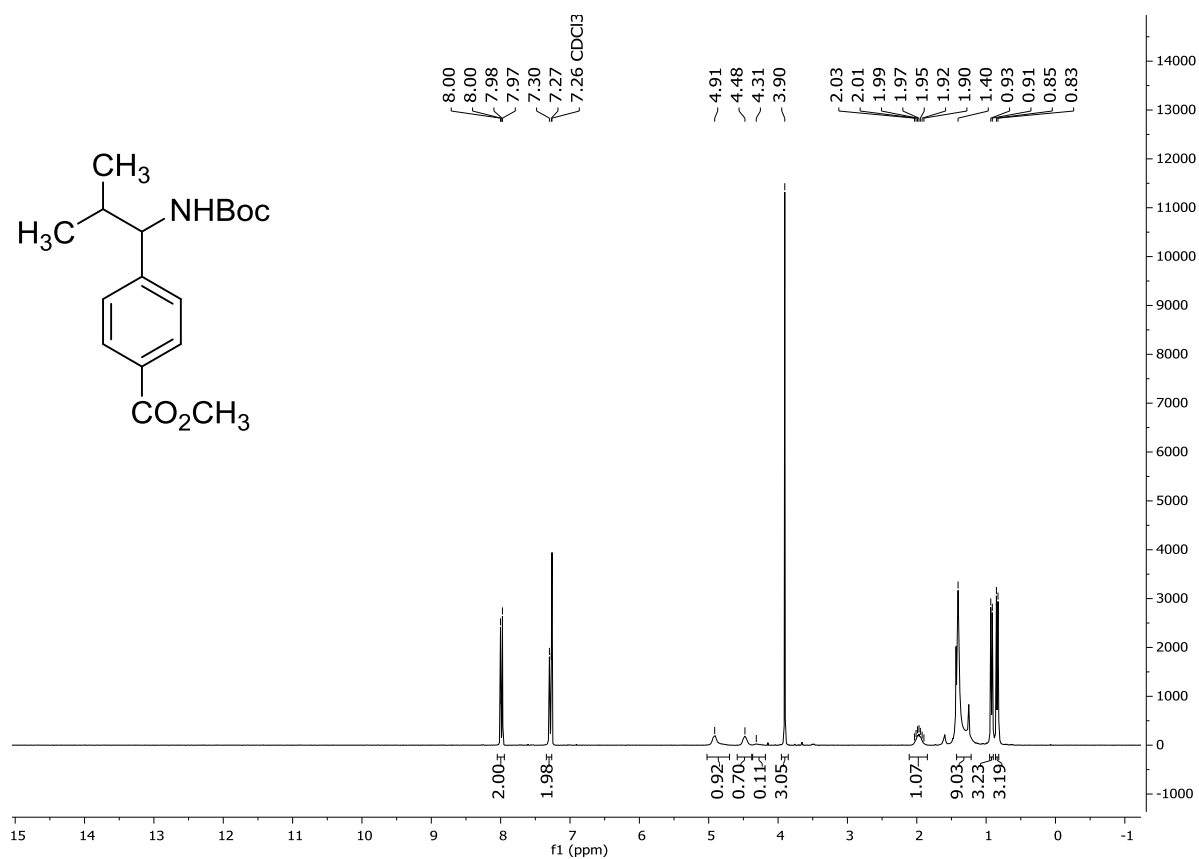


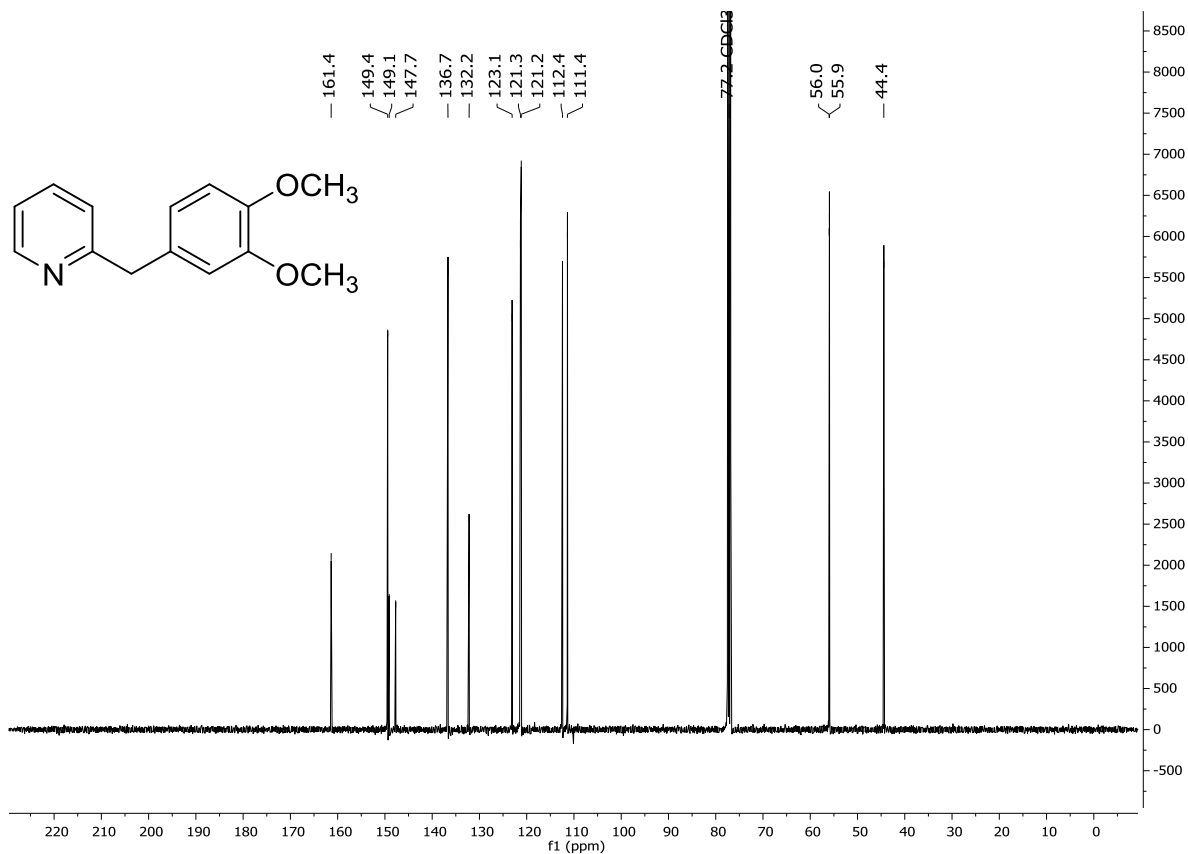
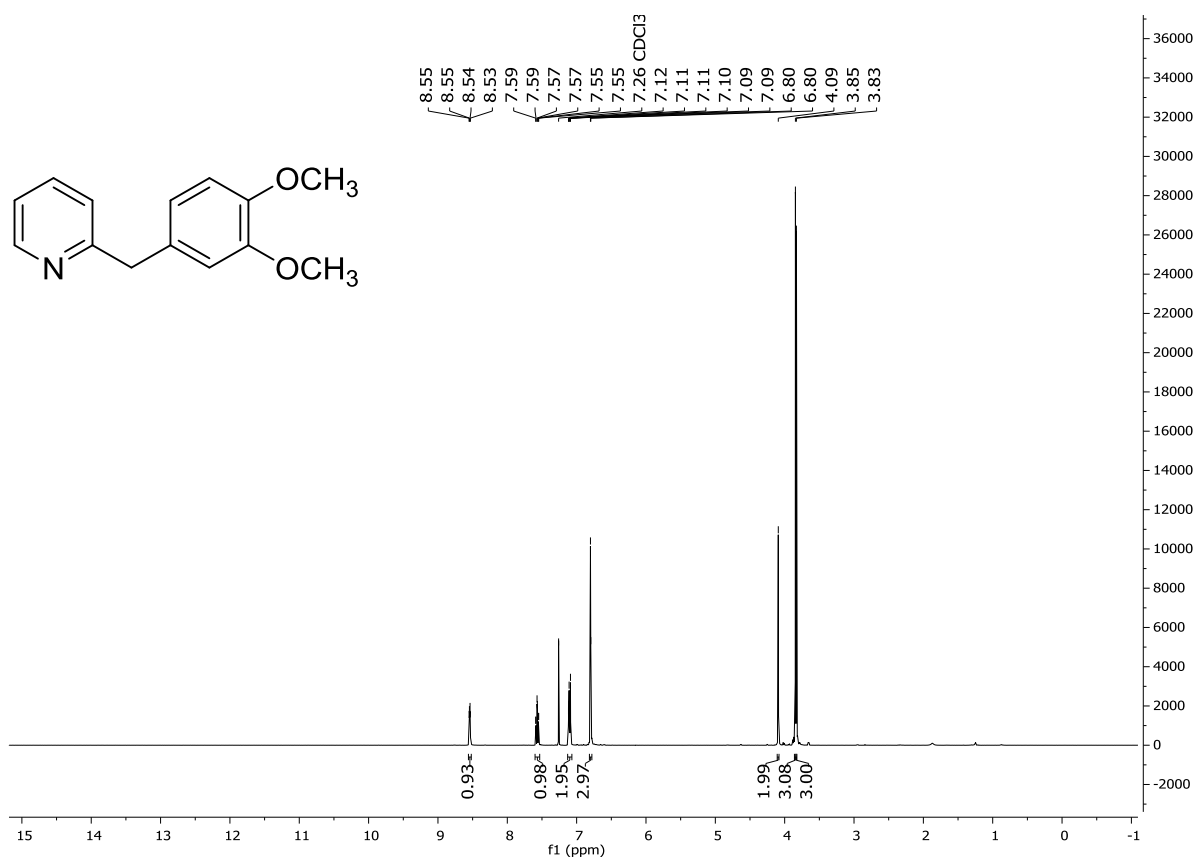


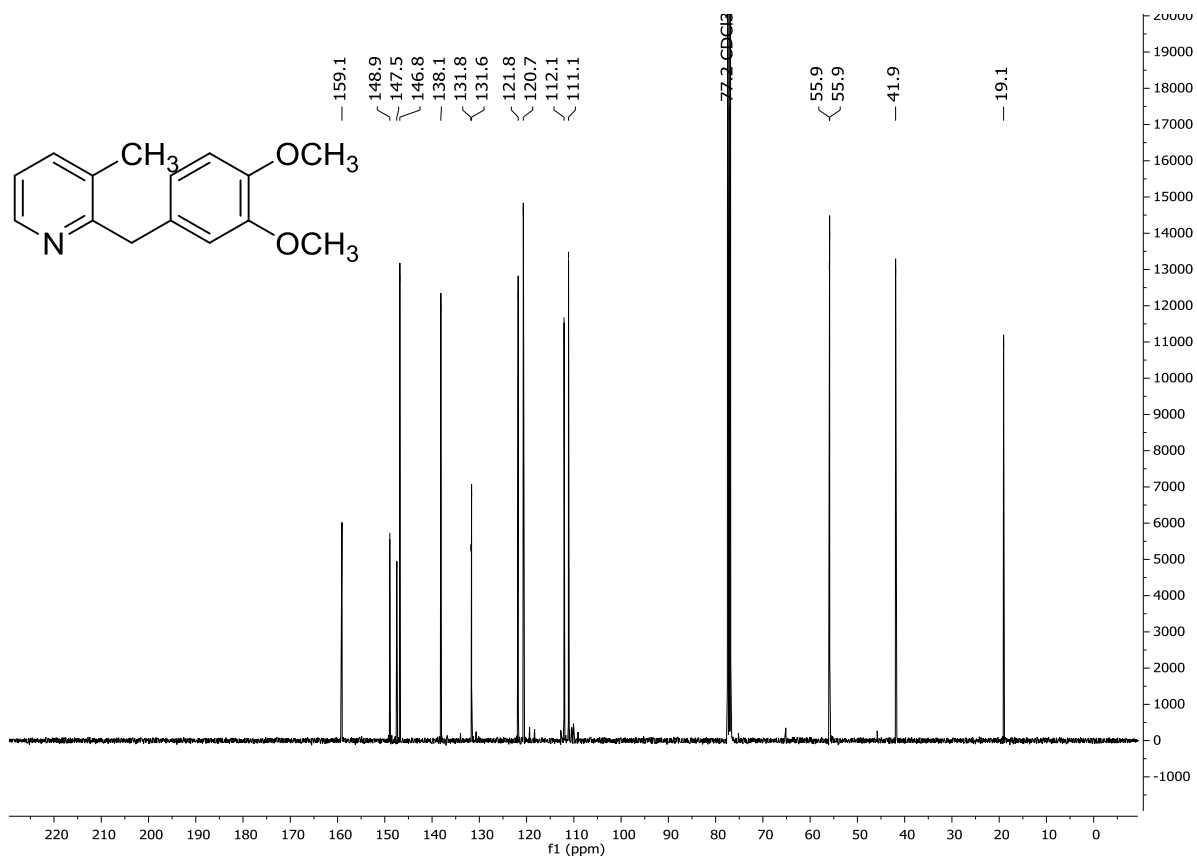
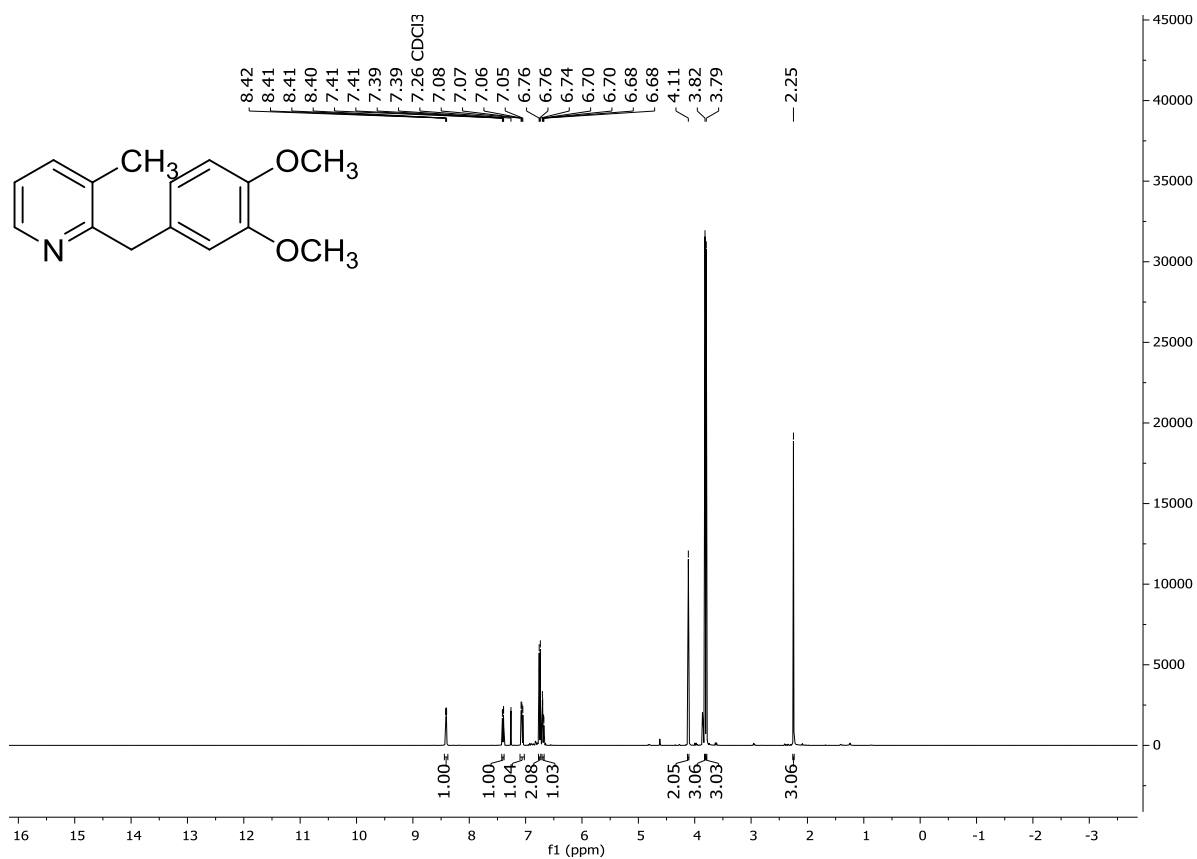


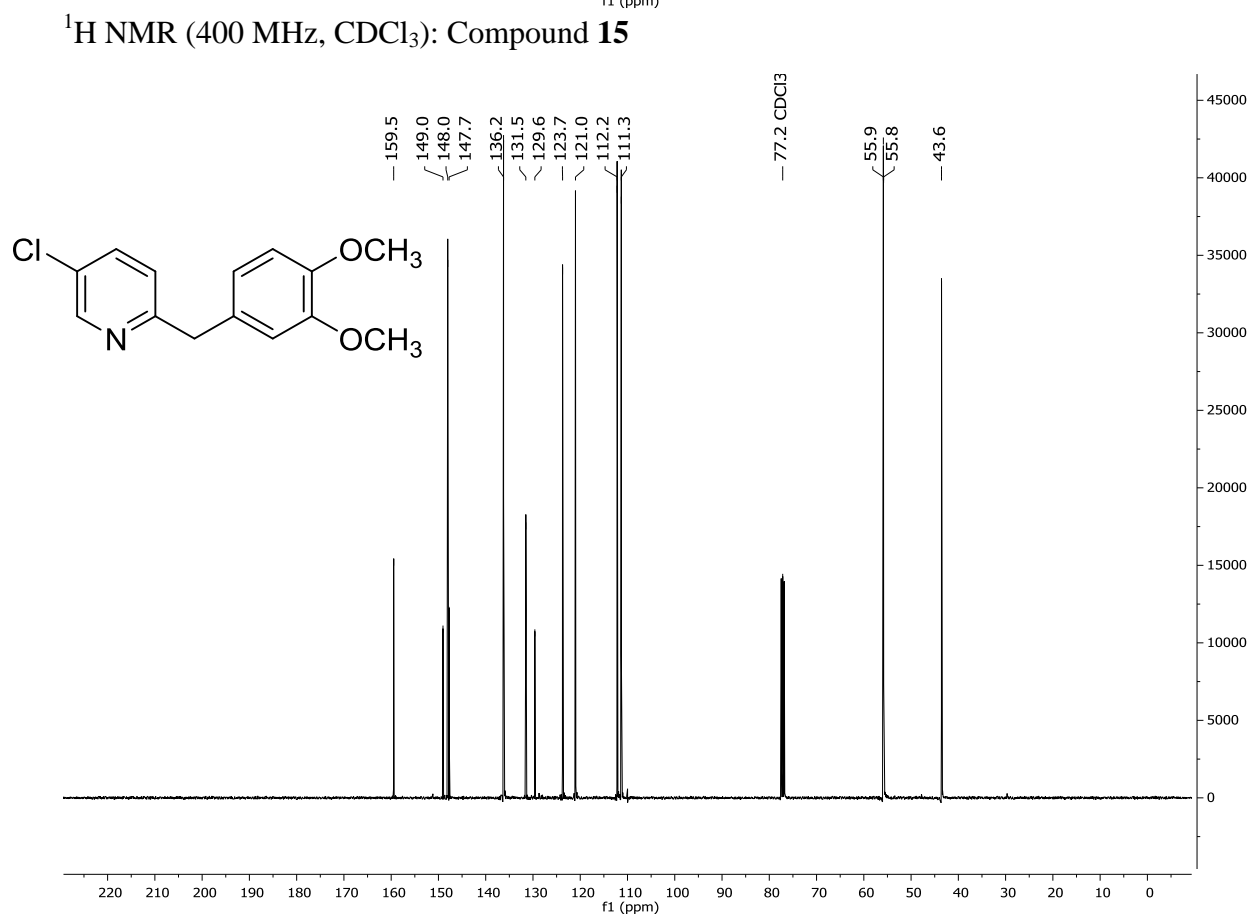
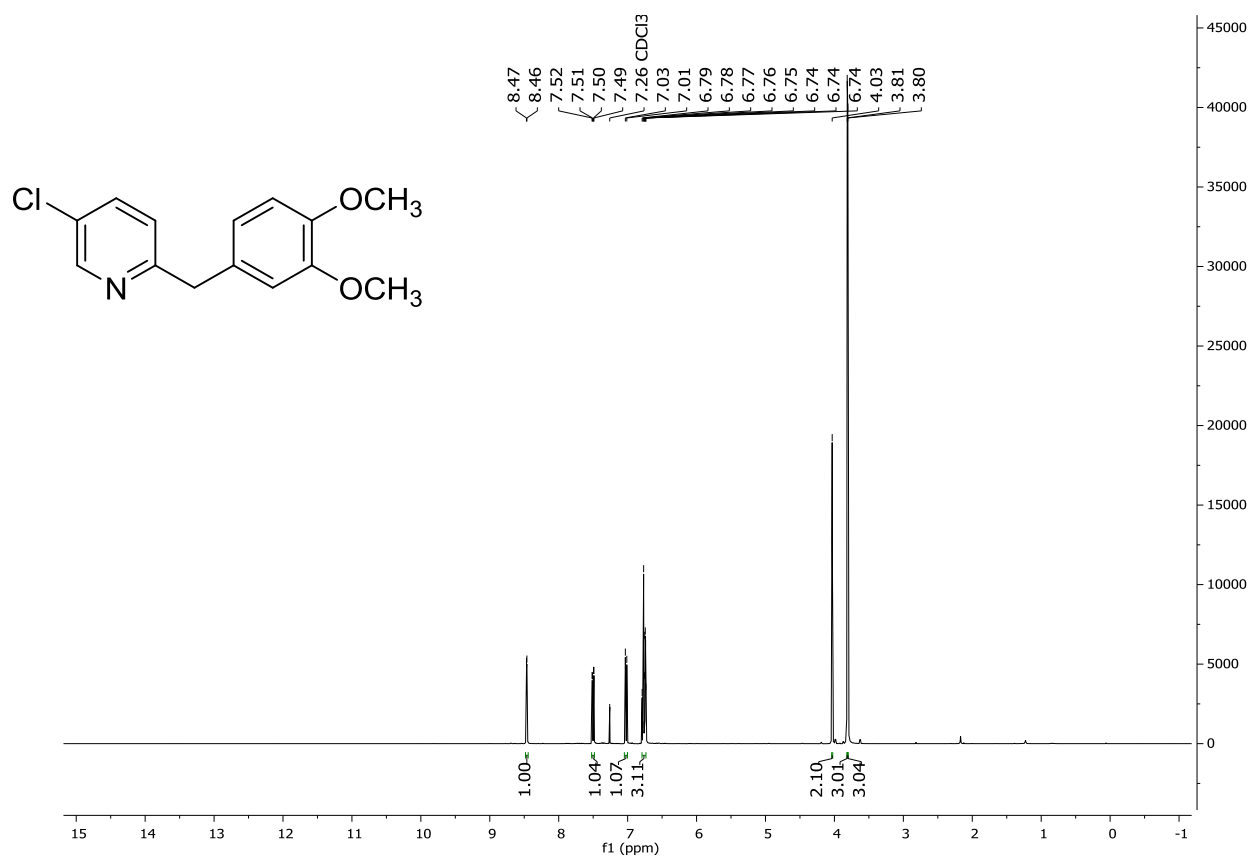


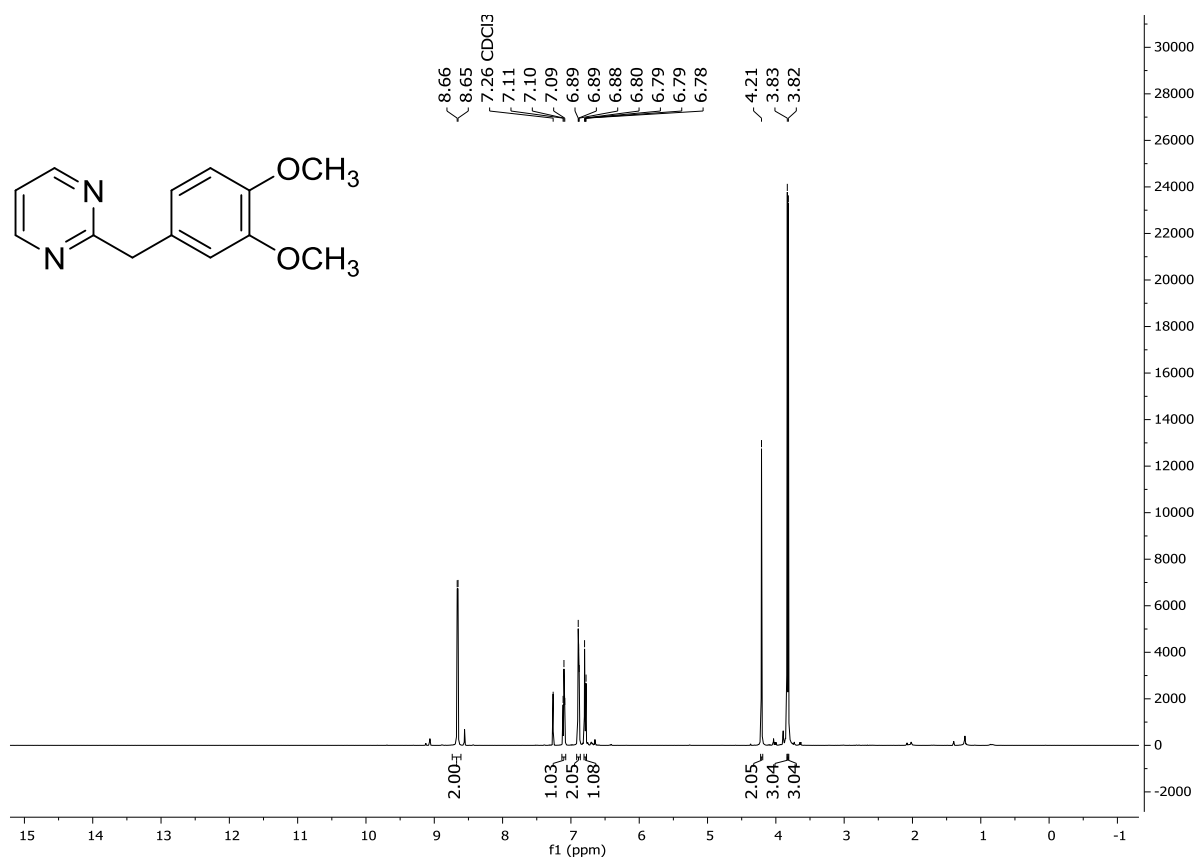




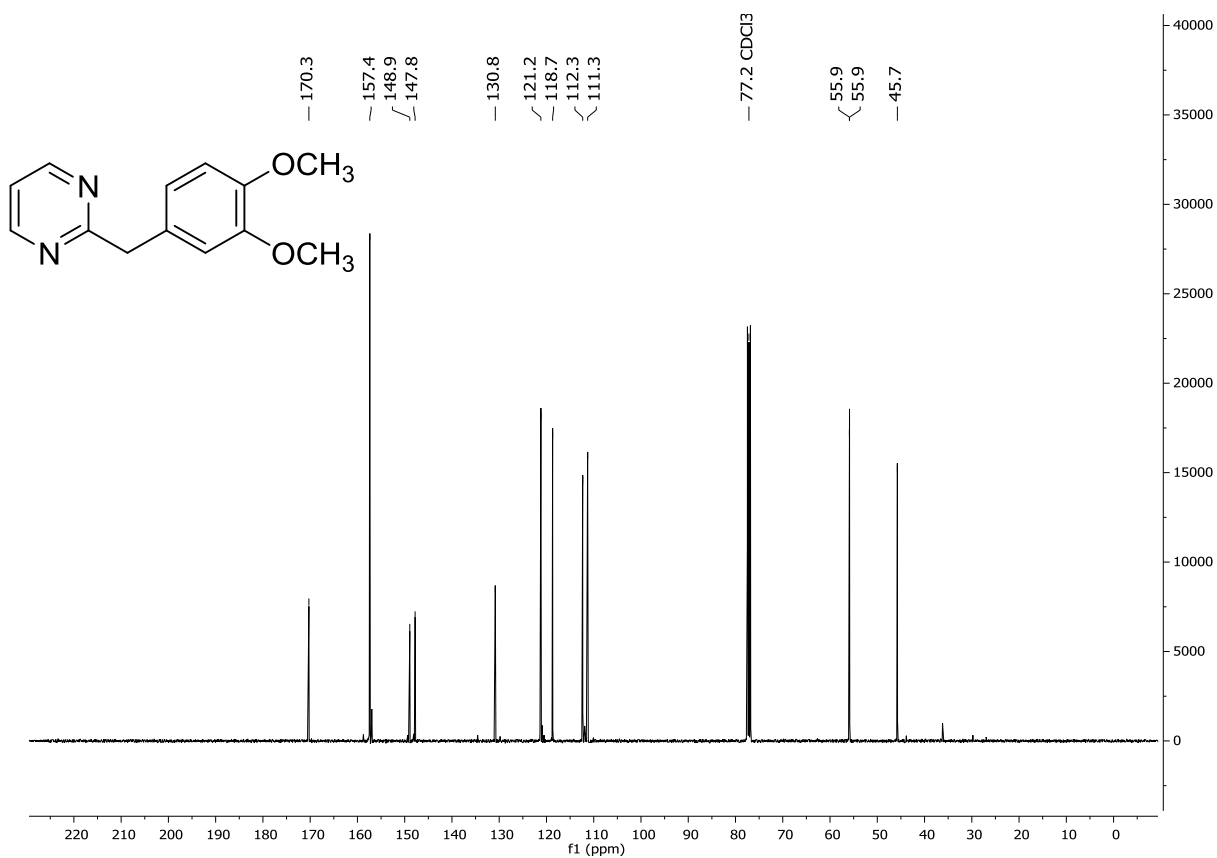




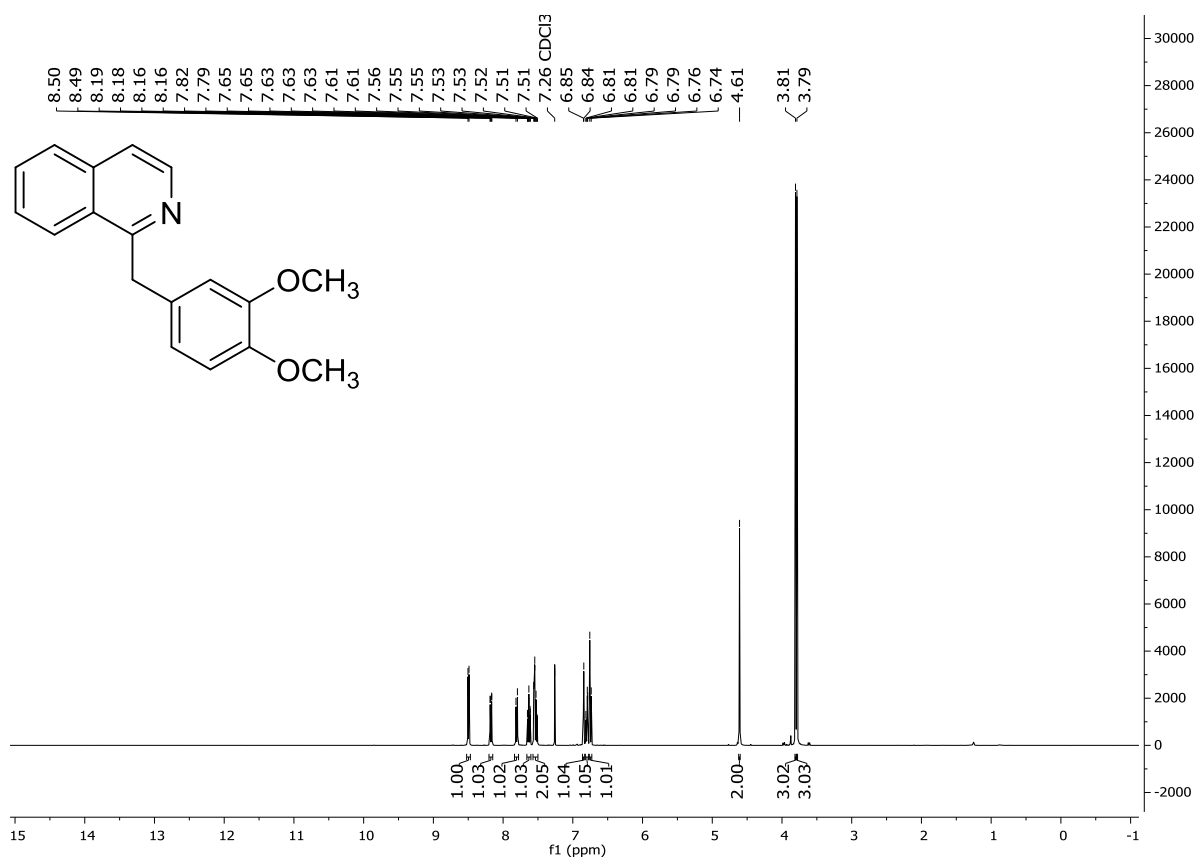




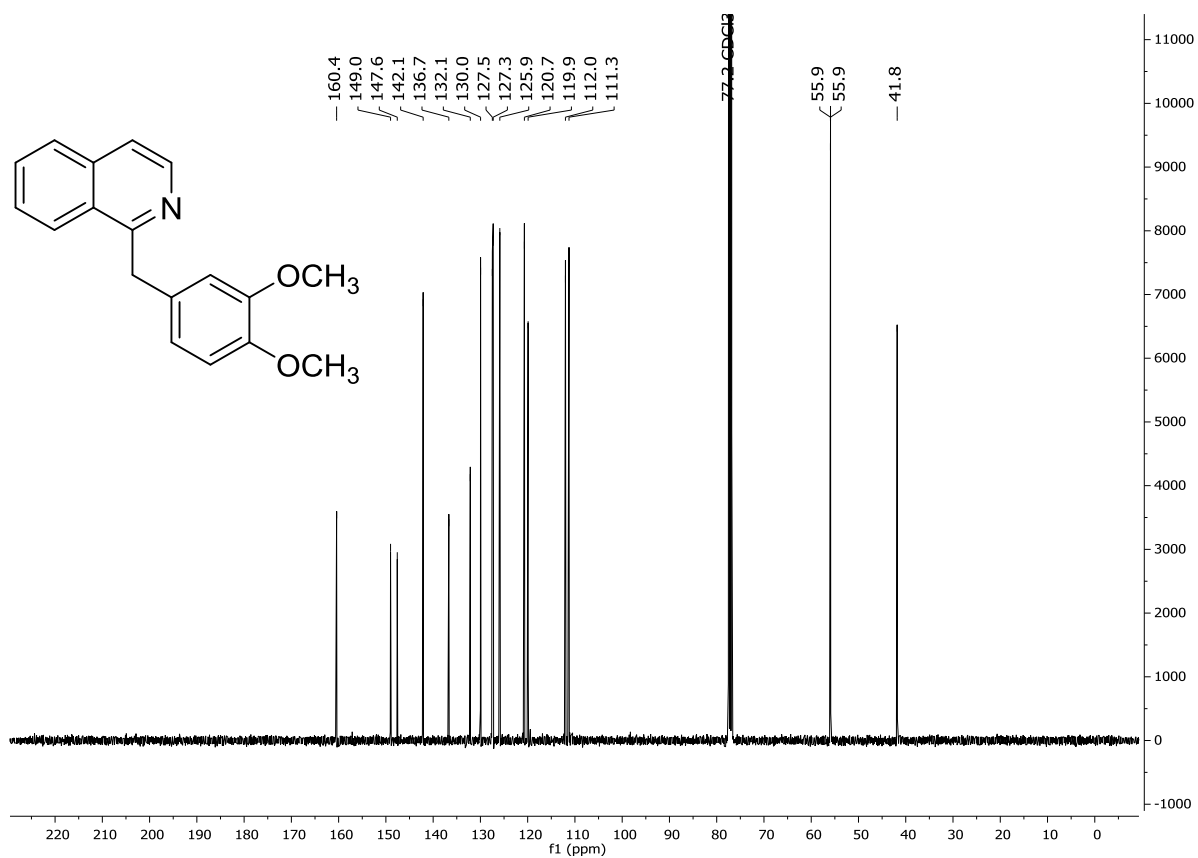
¹H NMR (400 MHz, CDCl₃): Compound **16**



¹³C NMR (100.6 MHz, CDCl₃): Compound **16**



¹H NMR (400 MHz, CDCl₃): Compound 17



¹³C NMR (100.6 MHz, CDCl₃): Compound 17

