

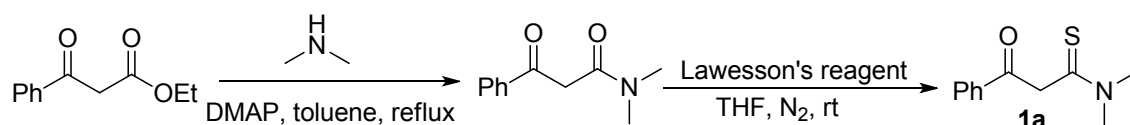
Supporting Information

Direct Synthesis of Polysubstituted 2-Aminothiophenes through Cu(II)-Catalyzed Addition/Oxidative Cyclization of Alkynoates with Thioamides

Li-Shi Ge, Zheng-Lin Wang, Xing-Lan An, Xiaoyan Luo,* and Wei-Ping Deng*

1. General procedure for the preparation of thioamides.

1a. Procedure for the preparation of 1a~1e, 1m and 1l.¹⁻²



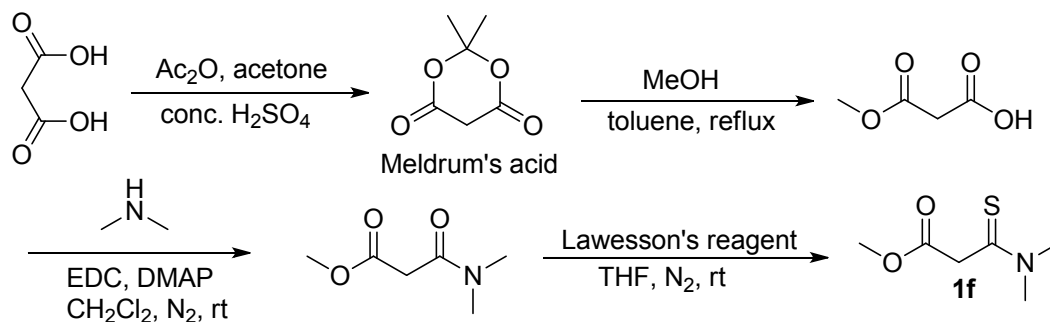
Ethyl 3-oxo-3-phenylpropanoate (1.74 mL, 10 mmol, 1 equiv), dimethylammonium chloride (1.63 g, 20 mmol, 2 equiv) and DMAP (5.62 g, 4.6 mmol, 0.46 equiv) were dissolved in 20 mL of toluene. The mixture was stirred sufficiently under reflux until the reaction was completed as judged by TLC. After cooling to room temperature, the solvent was quenched with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, and dried over anhydrous Na₂SO₄. After the solvent was evaporated in vacuo, the residue was purified by column chromatography on 100–200 mesh silica gel to afford pure *N,N*-dimethyl-3-oxo-3-phenylpropanamide.

N,N-dimethyl-3-oxo-3-phenylpropanamide (765 mg, 4 mmol, 1.0 equiv) and Lawesson's reagent (889 mg, 2.2 mmol, 0.55 equiv) were suspended in 20 mL of anhydrous THF under an atmosphere of N₂. The mixture was stirred sufficiently at ambient temperature until the reaction was completed as judged by TLC. The reaction was concentrated in vacuo, the residue was purified by column chromatography on 100–200 mesh silica gel to afford pure *N,N*-dimethyl-3-oxo-3-phenylpropanethioamide **1a**.

For the spectral analysis of **1a**, see; L. K. Ransborg, L. Albrecht, C. F. Weise, J. R. Bak and K. A. Jørgensen, *Org. Lett.*, 2012, **14**, 724;

1b~1e, **1m** and **1l** were all synthesized using this general procedure.

2a. Procedure for the preparation of 1f~1k, 1n~1p.²⁻⁵



To a mixture of malonic acid (52 g, 499.7 mmol, 1 equiv) and acetic anhydride (62 mL, 639.6 mmol, 1.3 equiv) were added concentrated sulfuric acid (3 mL, 40.0 mmol, 0.08 equiv) with constant stirring in an ice-water bath. After 30 min, most of the malonic acid dissolved during cooling. Acetone (50.8 mL, 699.6 mmol, 1.4 equiv) was added slowly, and the reaction mixture was stirred sufficiently at ambient temperature until the reaction was completed as judged by TLC. After cooling in the refrigerator, the resulting crystals were filtered and washed with ice water to give a flaky white solid, which was dried in a vacuum desiccator.

Meldrum's acid (10 g, 69.4 mmol, 1 equiv) and methyl alcohol (4.4 mL, 104.1 mmol, 1.5 equiv) were dissolved in 20 mL of toluene. The reaction mixture was heated under reflux until the reaction was completed as judged by TLC. After cooling to room temperature, the reaction was concentrated in vacuo. The residue was purified by column chromatography on 100–200 mesh silica gel to afford pure 3-methoxy-3-oxopropanoic acid.

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 3.82 g, 20 mmol, 2 equiv), 4-dimethylaminopyridine (DMAP, 489 mg, 4 mmol, 0.2 equiv) and dimethylammonium chloride (1.63 mg, 20.0 mmol, 1 equiv) were added to a solution of 3-methoxy-3-oxopropanoic acid (2.36 g, 20.0 mmol, 1 equiv) in 30 mL of anhydrous CH_2Cl_2 under argon atmosphere. The reaction mixture was stirred sufficiently at ambient temperature until the reaction was completed as judged by TLC. The solvent was diluted with water and extracted with CH_2Cl_2 . The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 . After the solvent was evaporated in vacuo, the residue was purified by column chromatography on 100–200 mesh silica gel to afford pure methyl 3-(dimethylamino)-3-oxopropanoate.

Methyl 3-(dimethylamino)-3-oxopropanoate (726 mg, 5 mmol, 1 equiv) and Lawesson's reagent (1.1 g, 2.75 mmol, 0.55 equiv) were suspended in 40 mL of anhydrous THF under an atmosphere of N_2 . The mixture was stirred sufficiently at ambient temperature until the reaction was completed as judged by TLC. The reaction was concentrated in vacuo, the residue was purified by column chromatography on 100–200 mesh silica gel to afford pure methyl 3-(dimethylamino)-3-thioxopropanoate **1f**.

For the spectral analysis of **1f**, see; L. K. Ransborg, Ł. Albrecht, C. F. Weise, J. R. Bak and K. A. Jørgensen, *Org. Lett.*, 2012, **14**, 724;

1h~1k, **1n~1p** were all synthesized using this general procedure.

2. General procedure for the preparation of polysubstituted 2-aminothiophenes **3**.

Thioamide compounds **1** (0.2 mmol) and **2** (0.24 mmol) were added to a solution of $\text{Cu}(\text{OAc})_2$ (0.02 mmol) in dry DMA (2 mL) under air atmosphere. The resulting mixture was stirred at 80 °C until the

reaction was completed as judged by TLC. After cooling to room temperature, the solvent was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, and dried over anhydrous Na₂SO₄. After the solvent was evaporated in vacuo, the residue was purified by column chromatography on 100–200 mesh silica gel to afford pure 2-aminothiophene compounds **3**.

References:

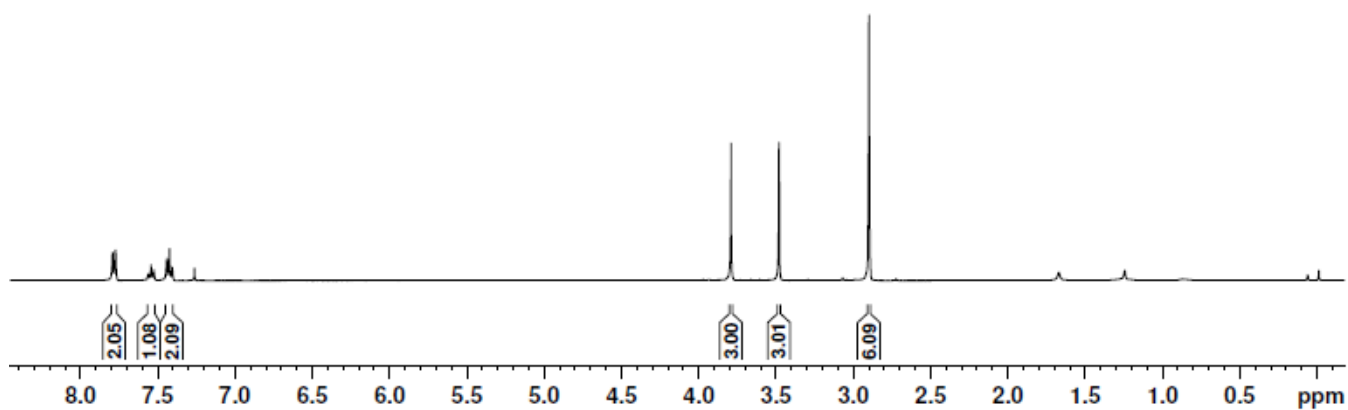
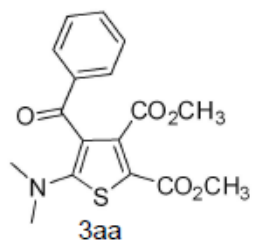
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1392.5325

1159.5368



190.80

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138.46

132.98

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128.35

117.04

111.69

77.37

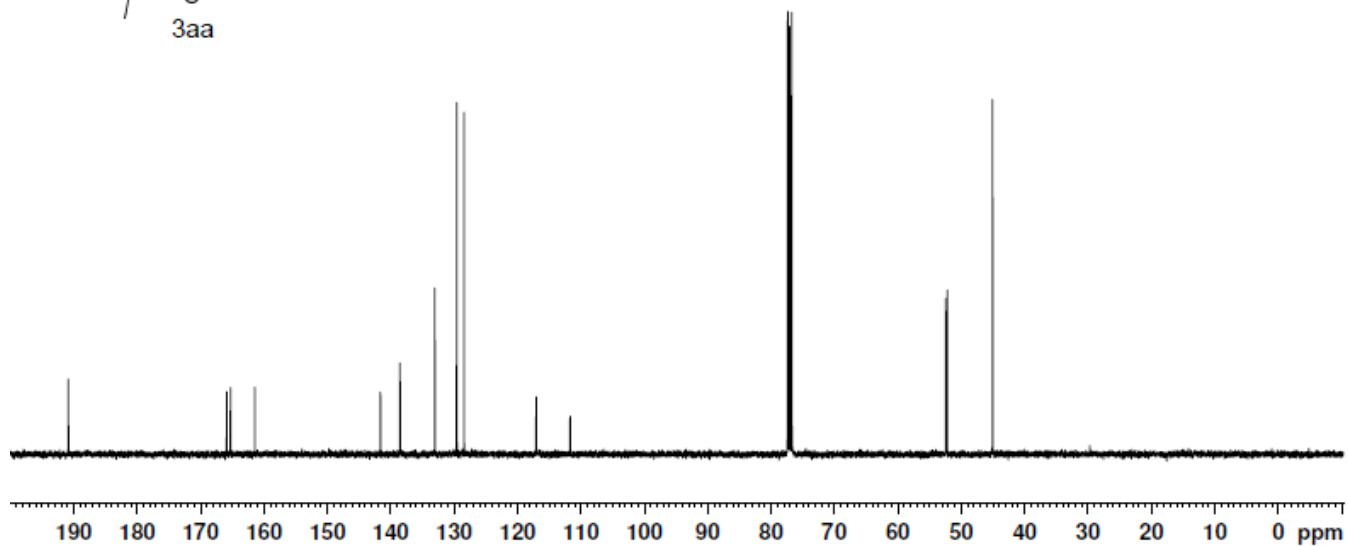
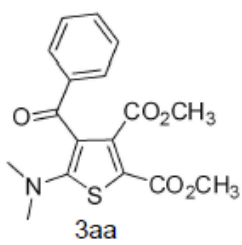
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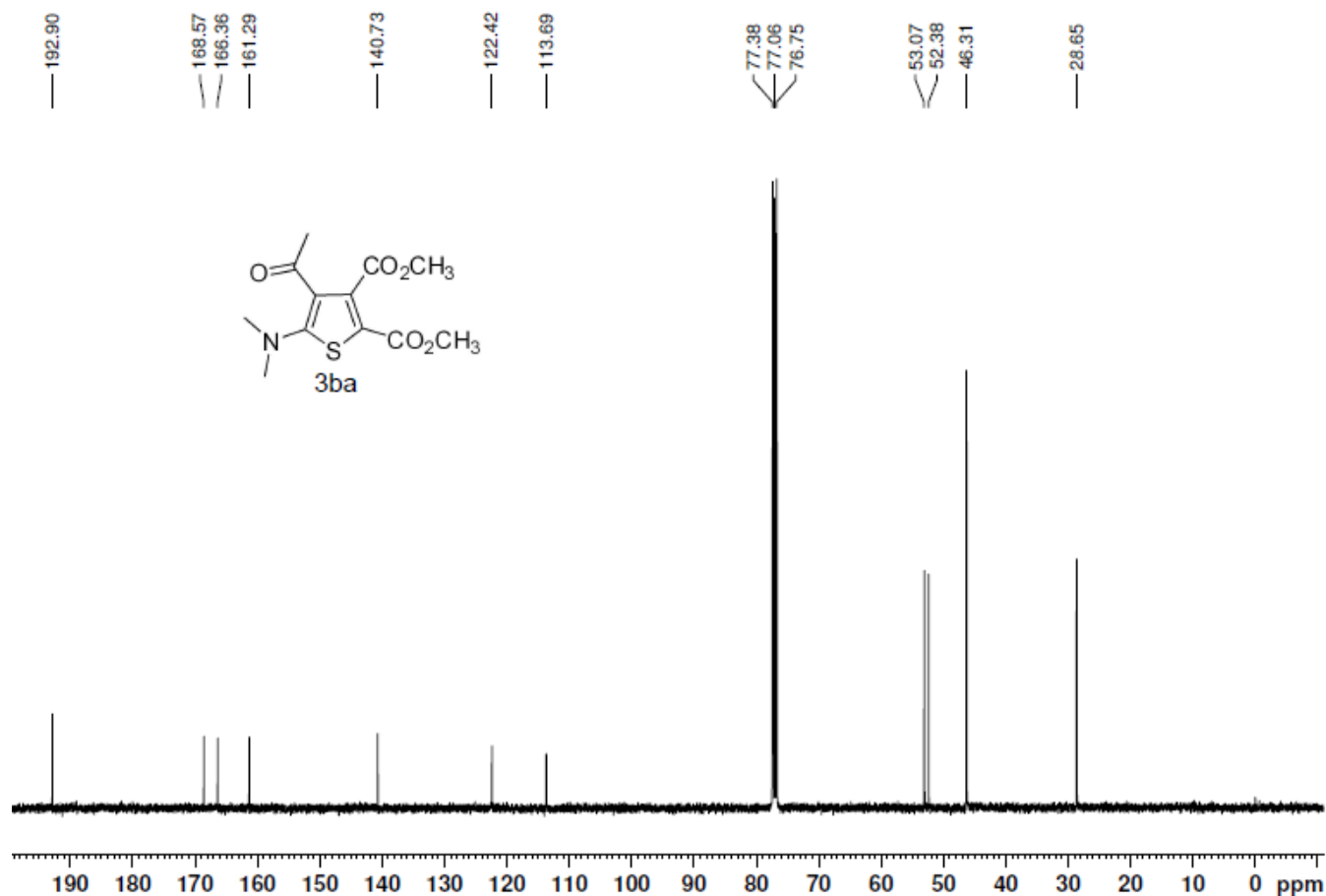
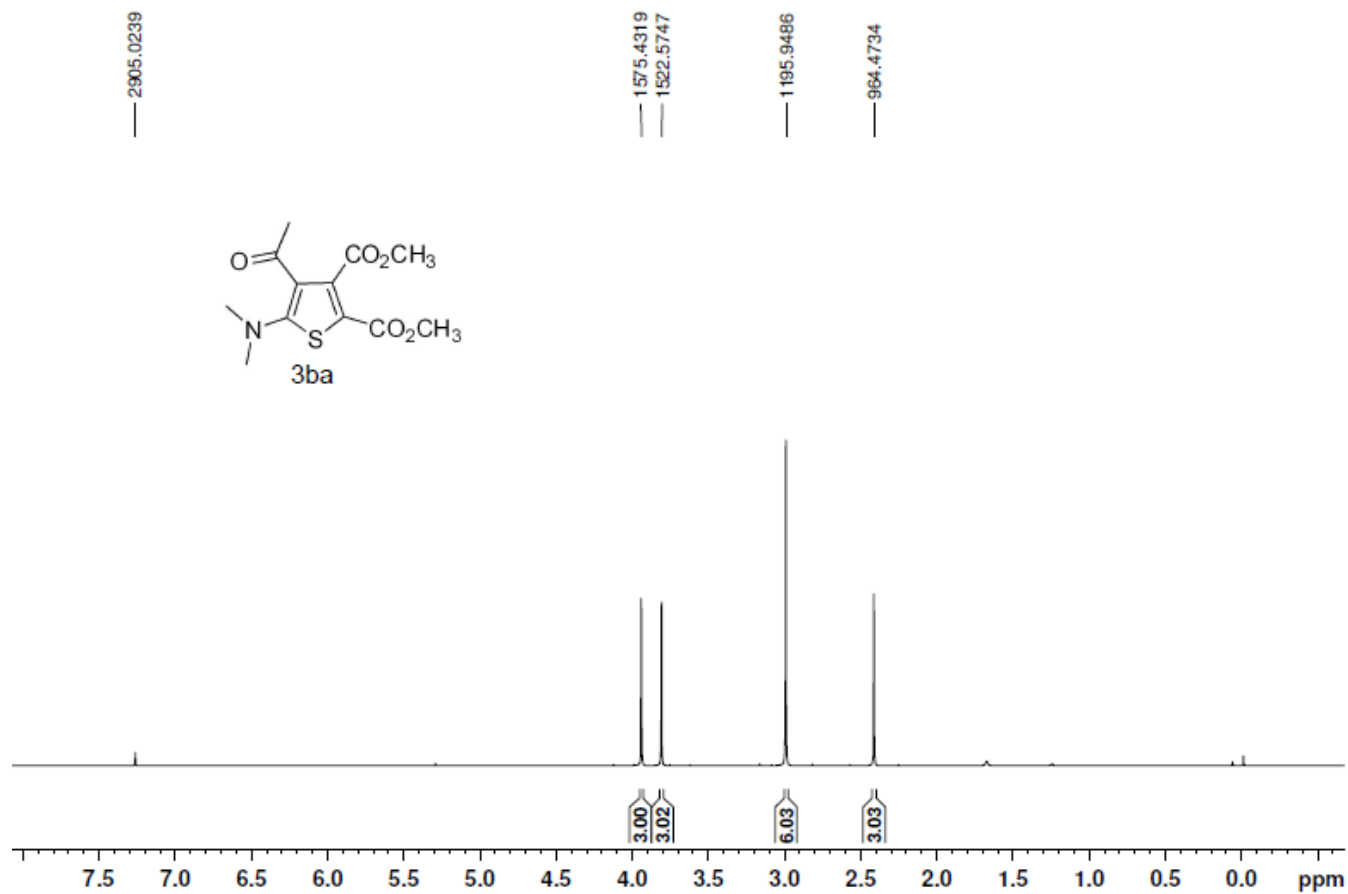
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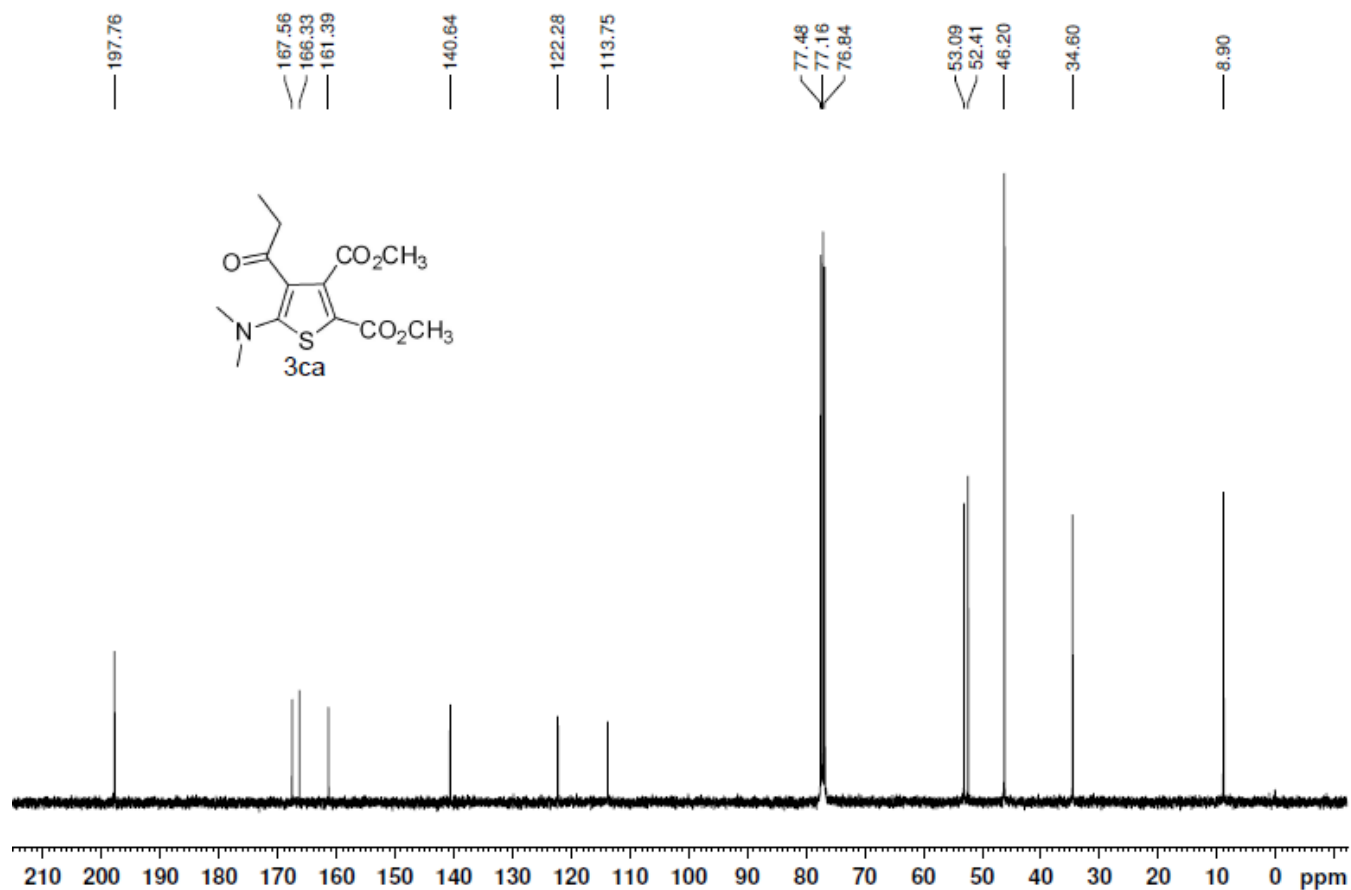
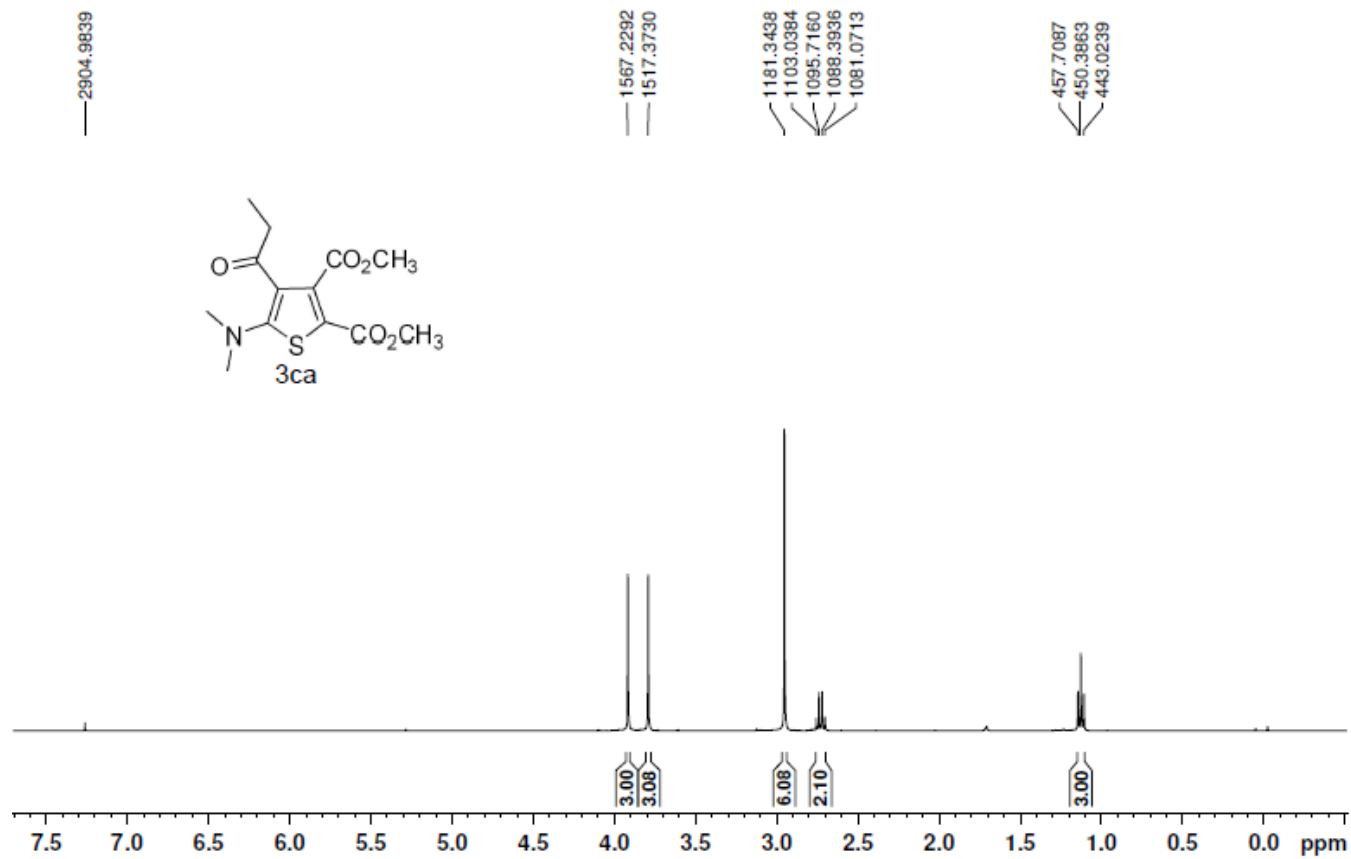
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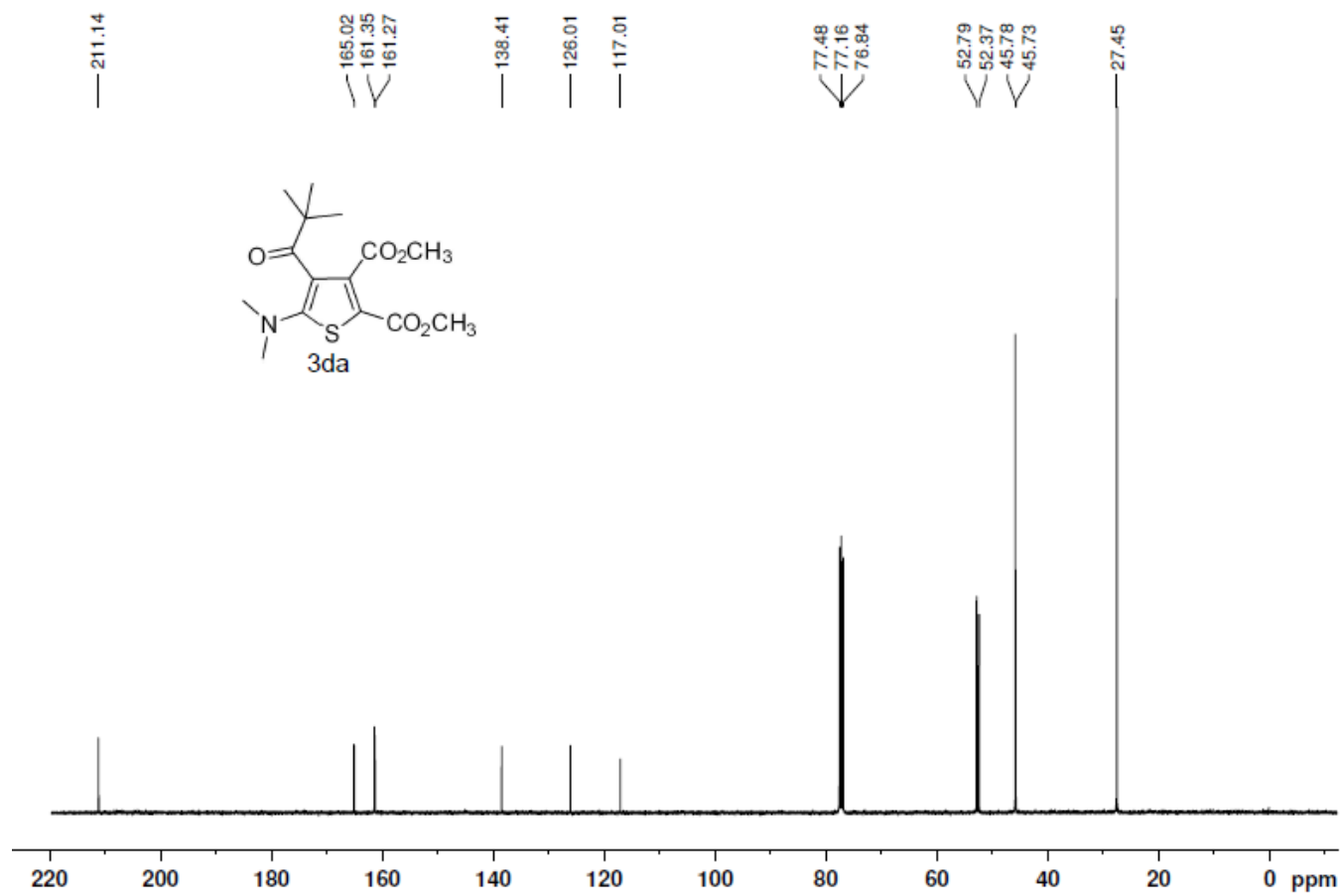
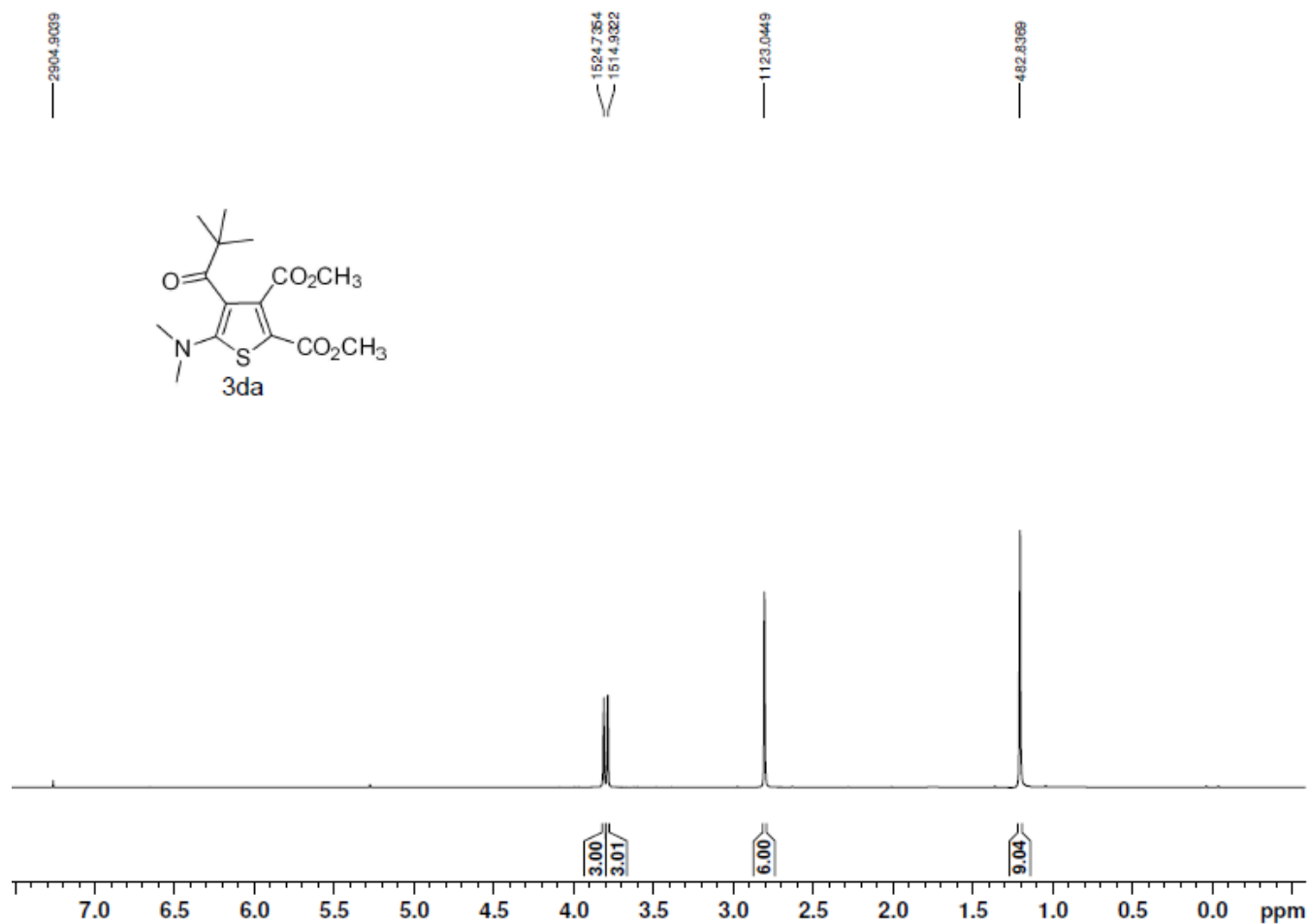
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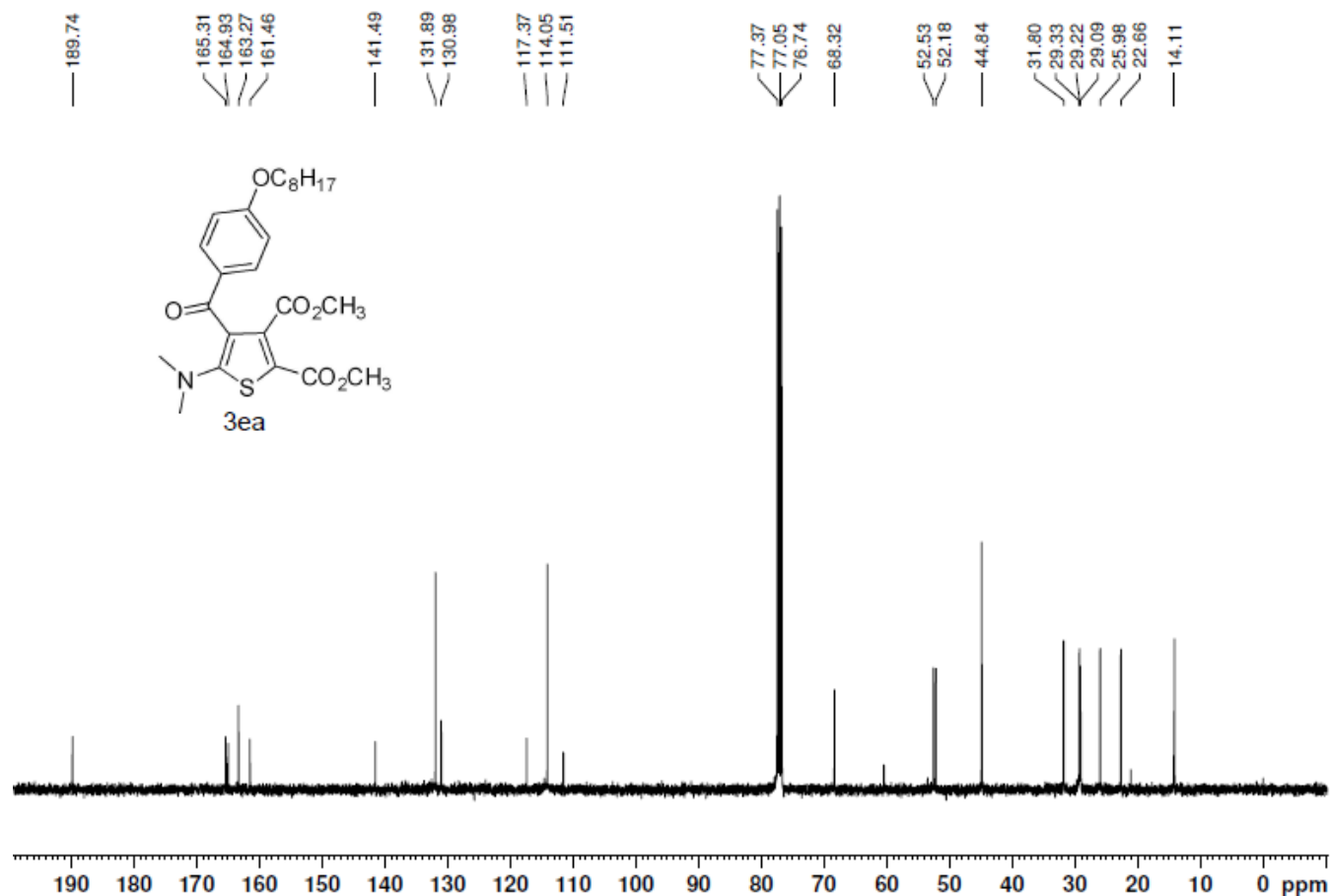
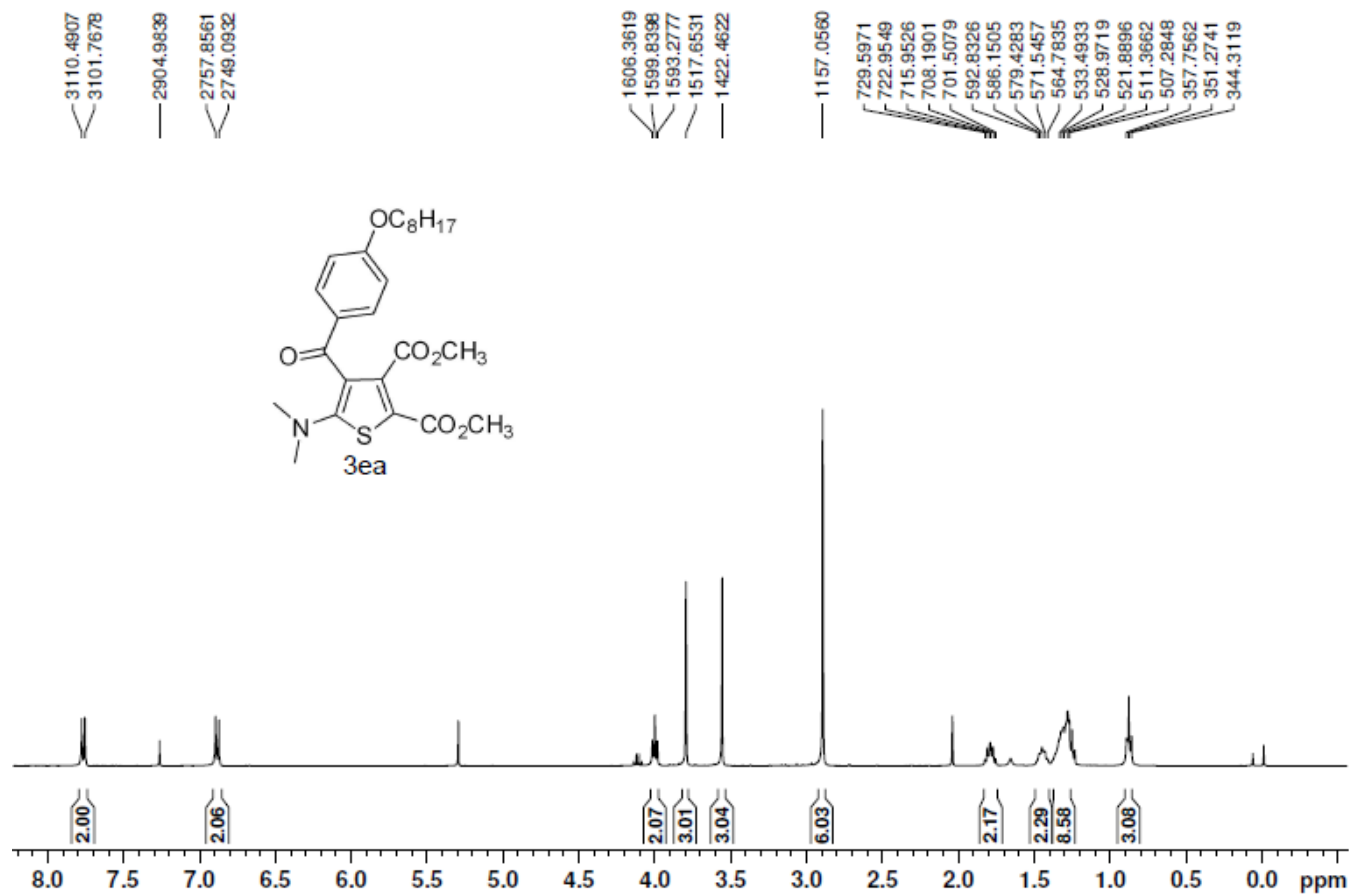
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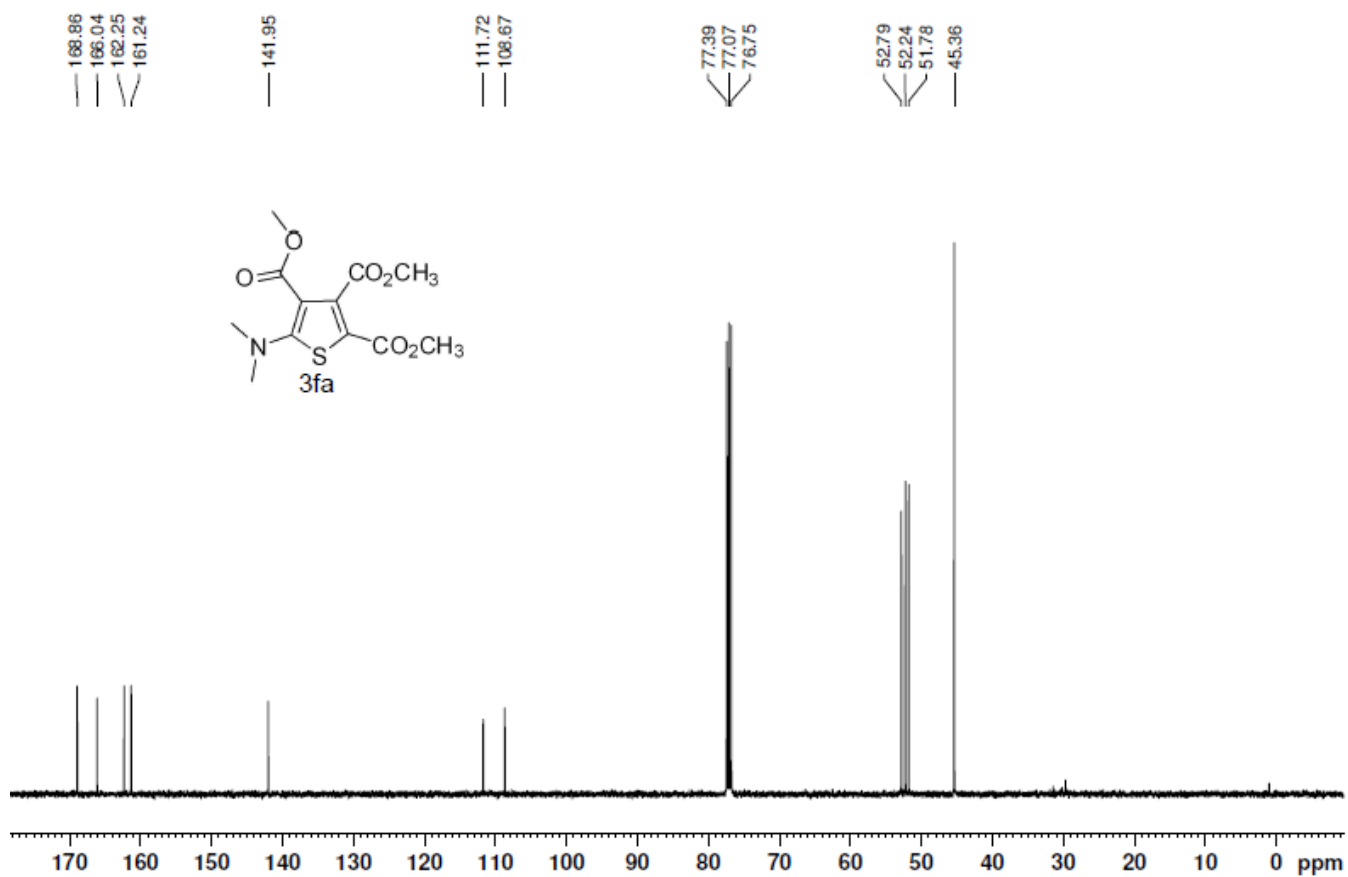
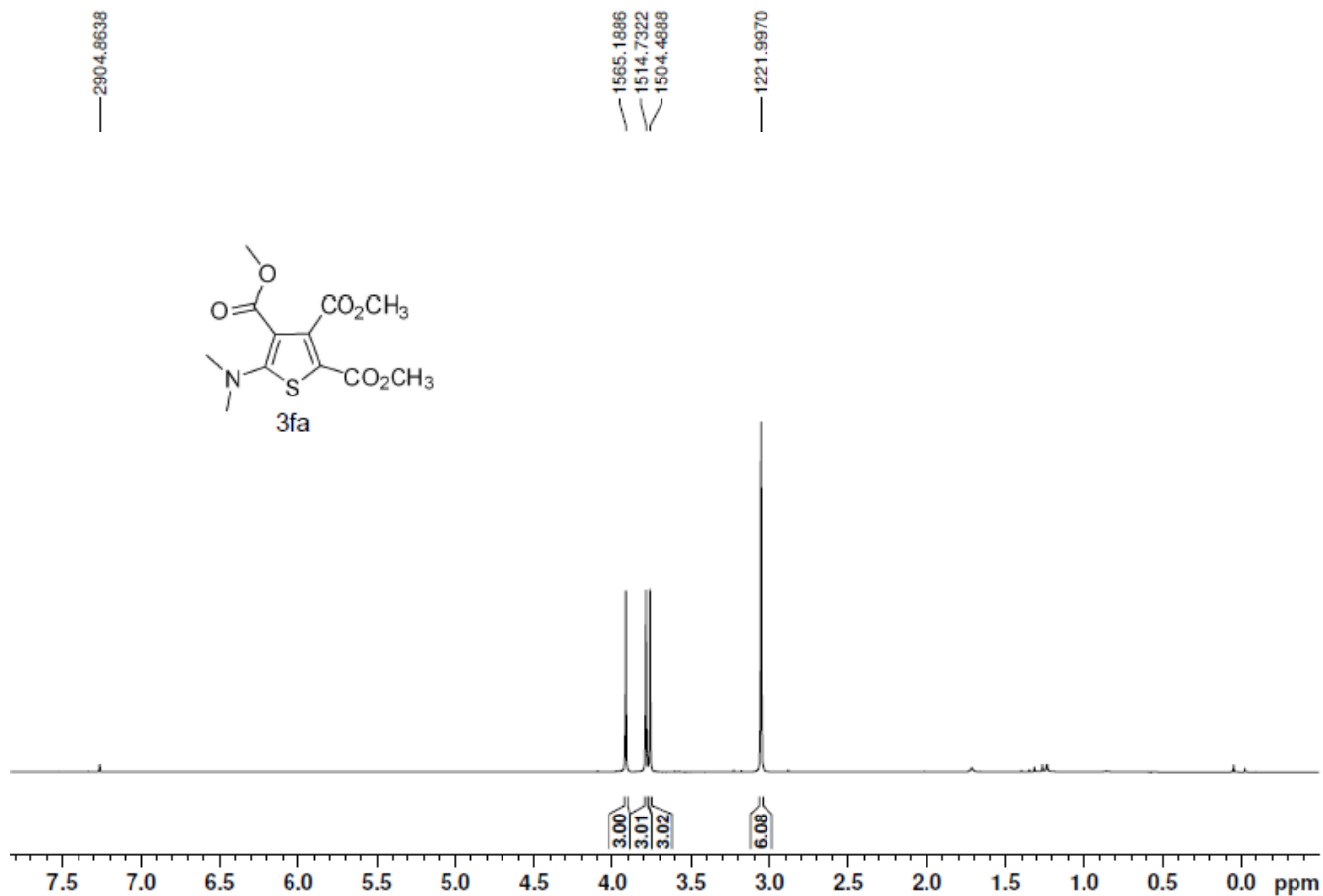


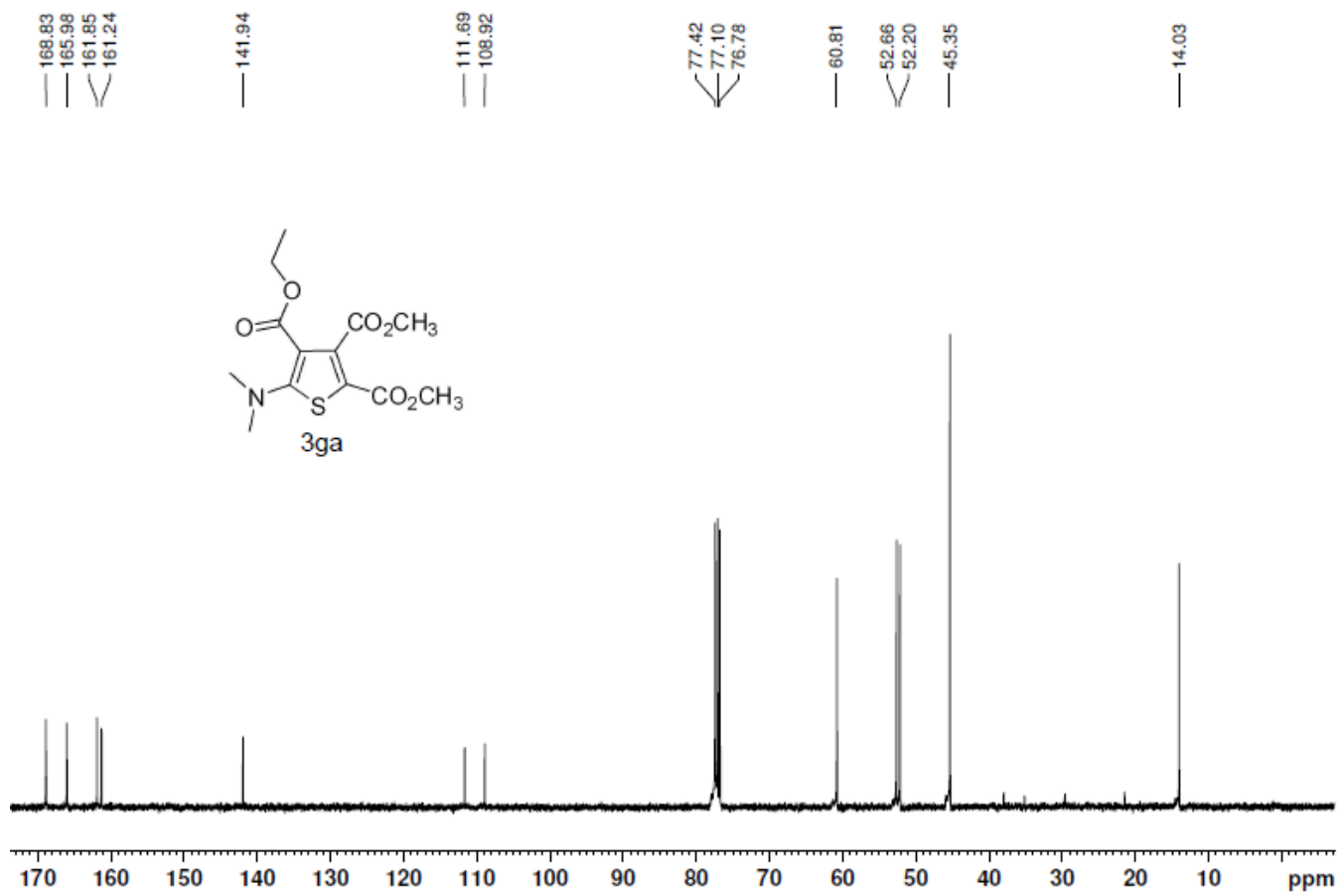
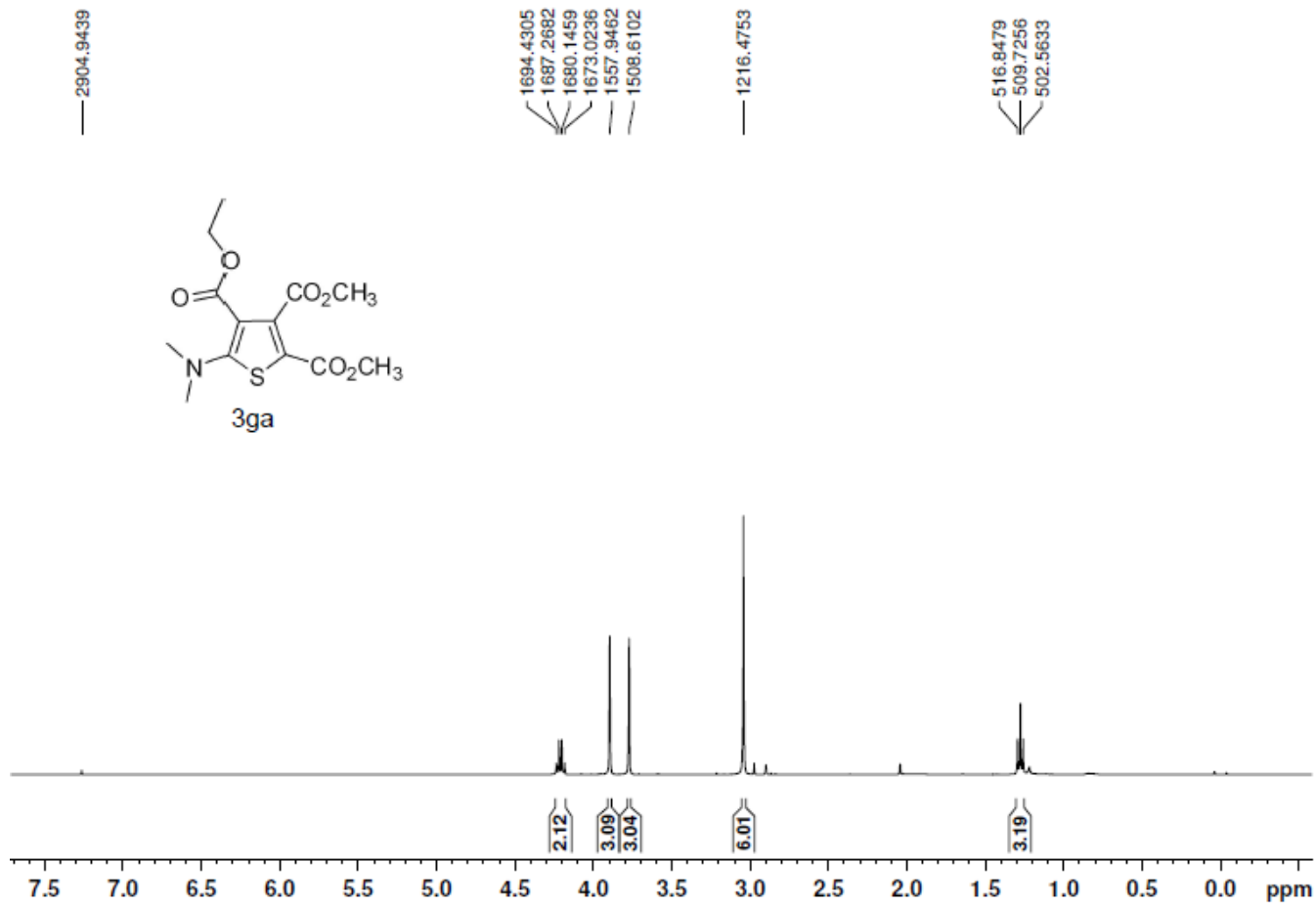


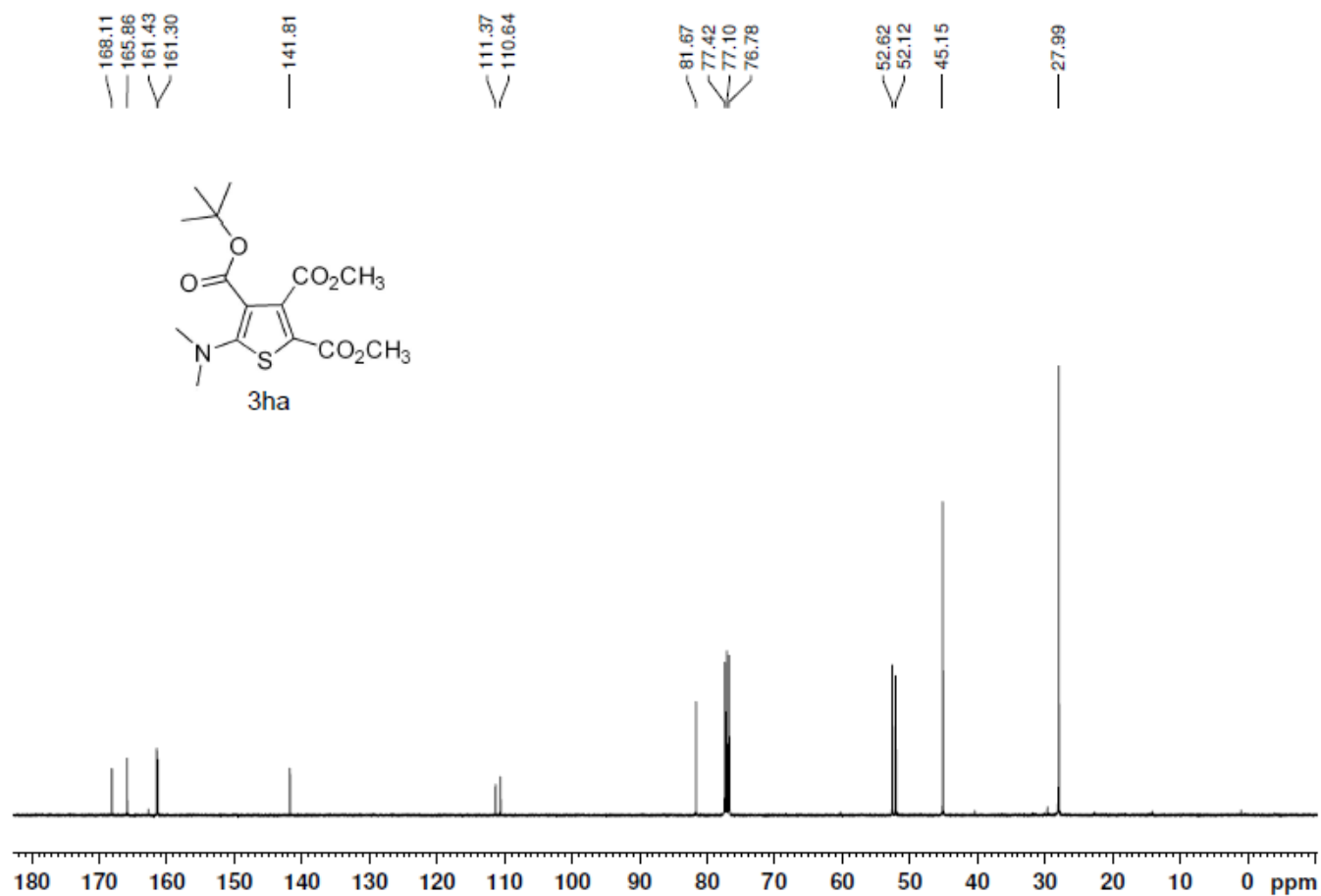
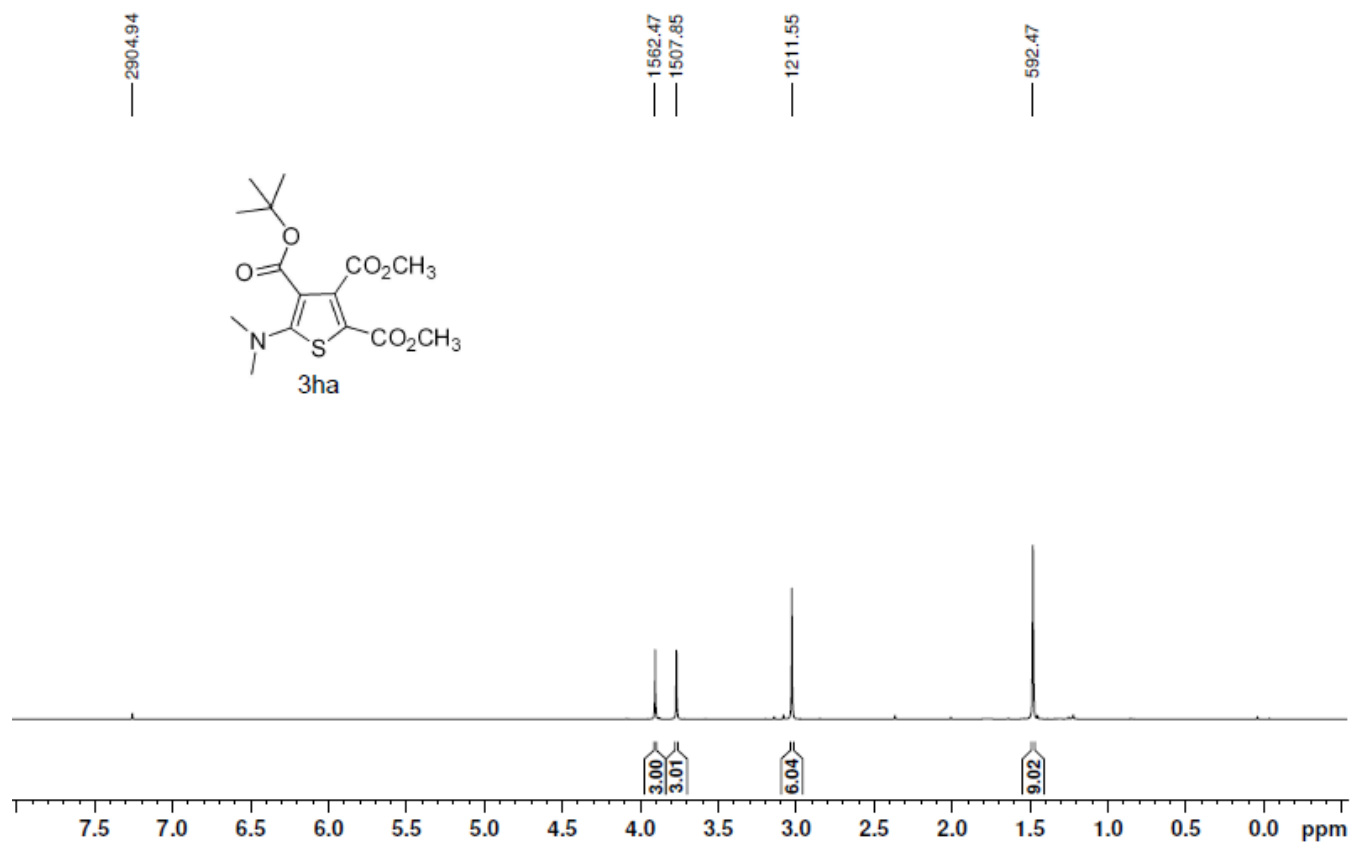


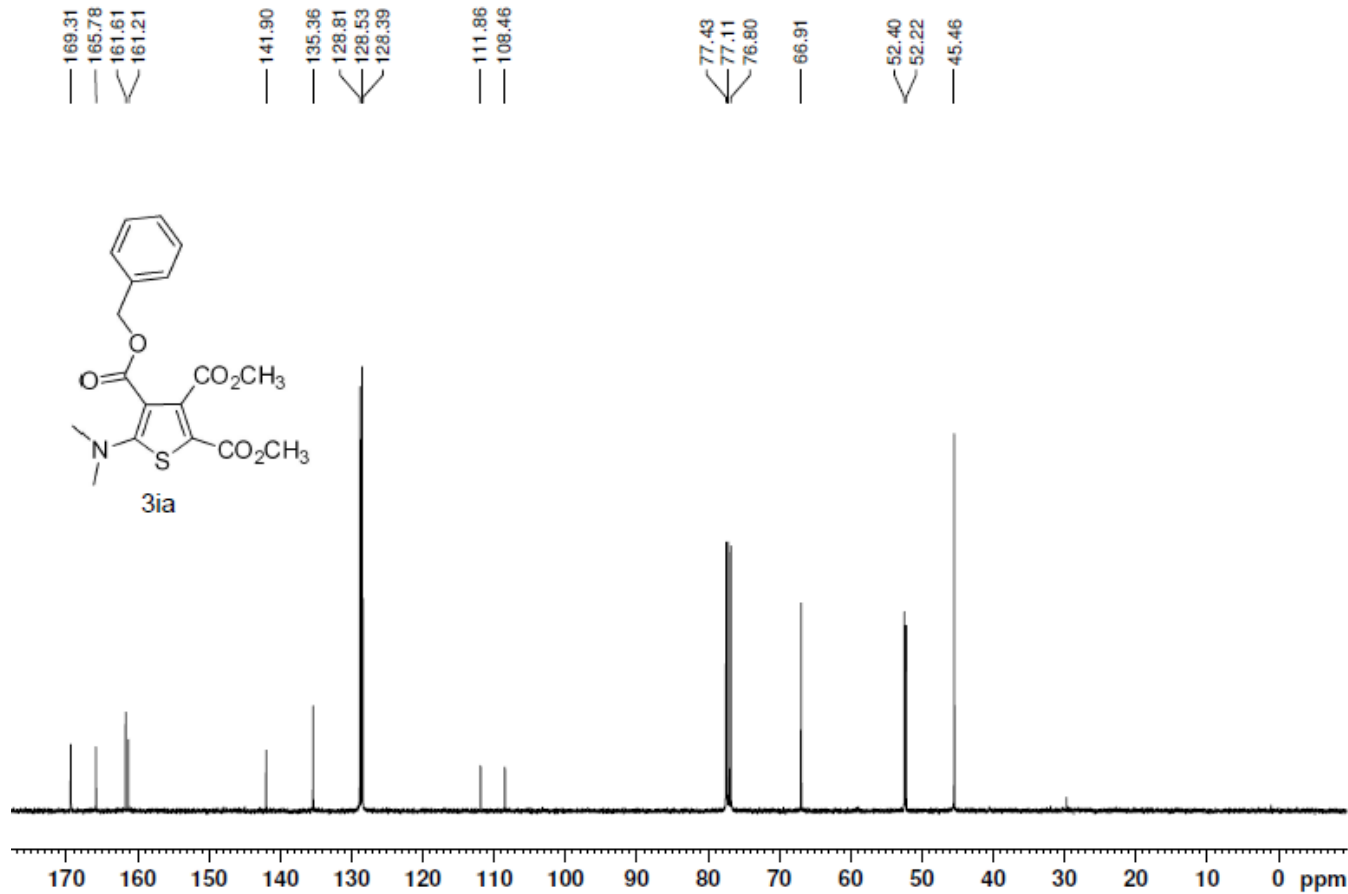
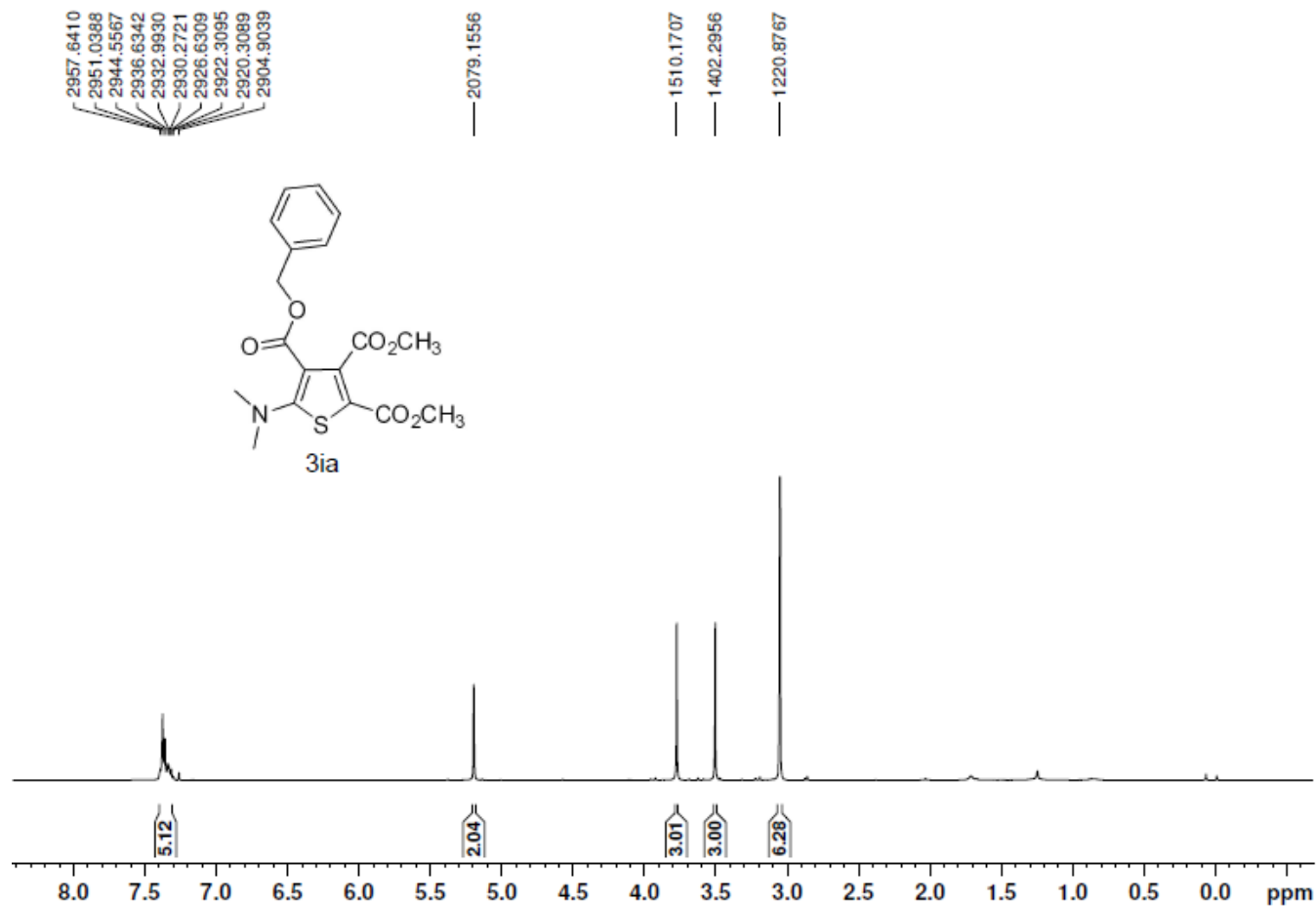


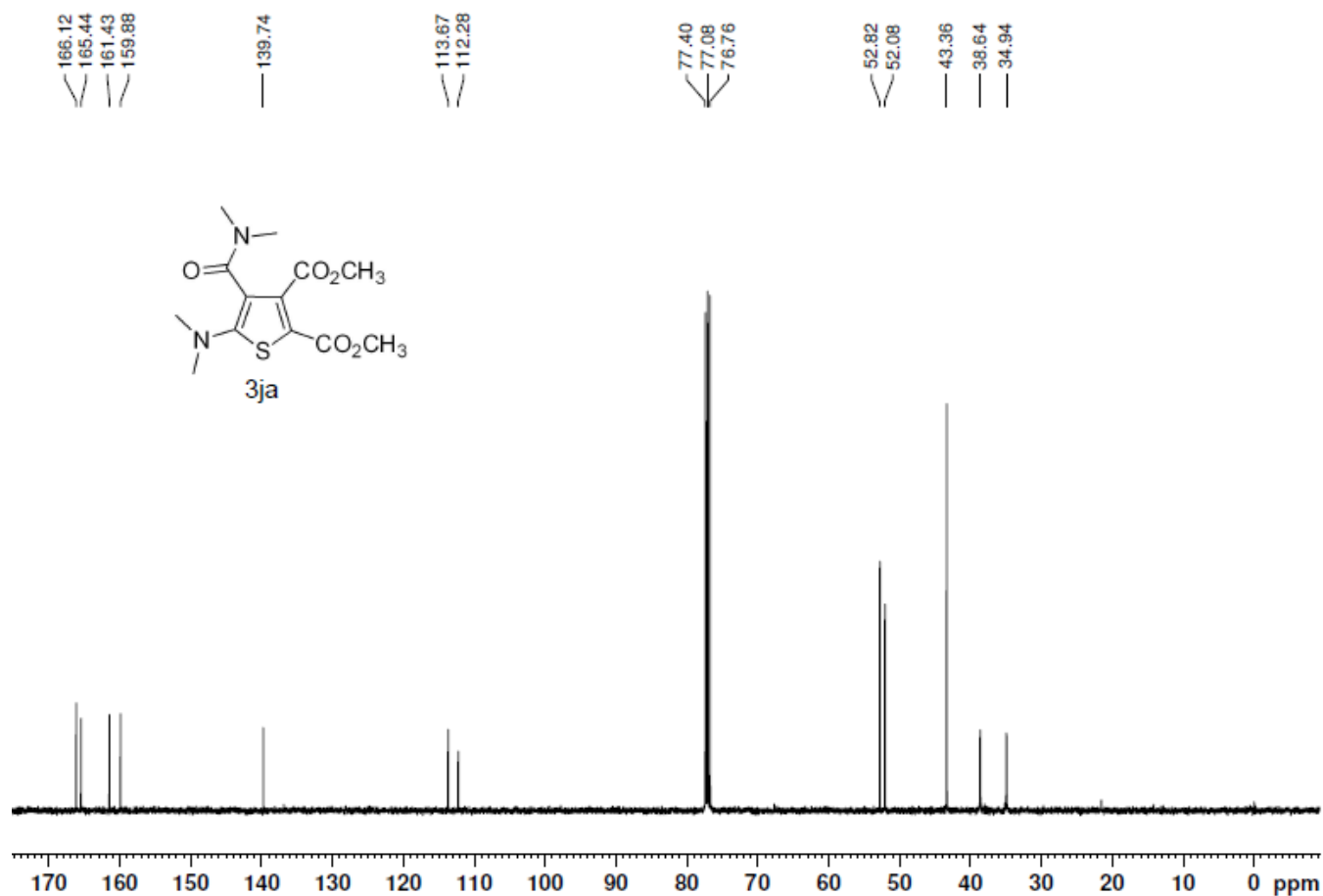
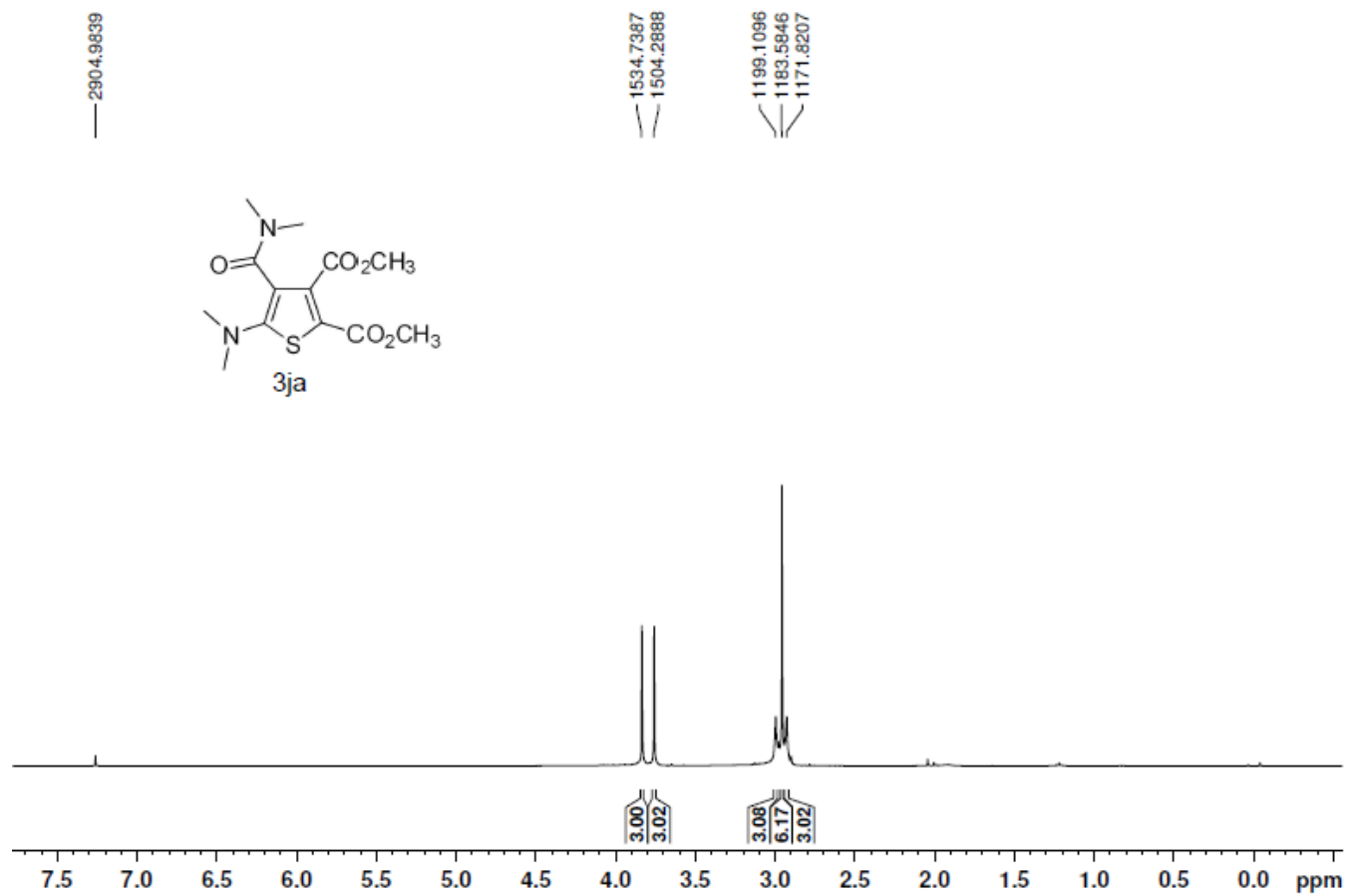






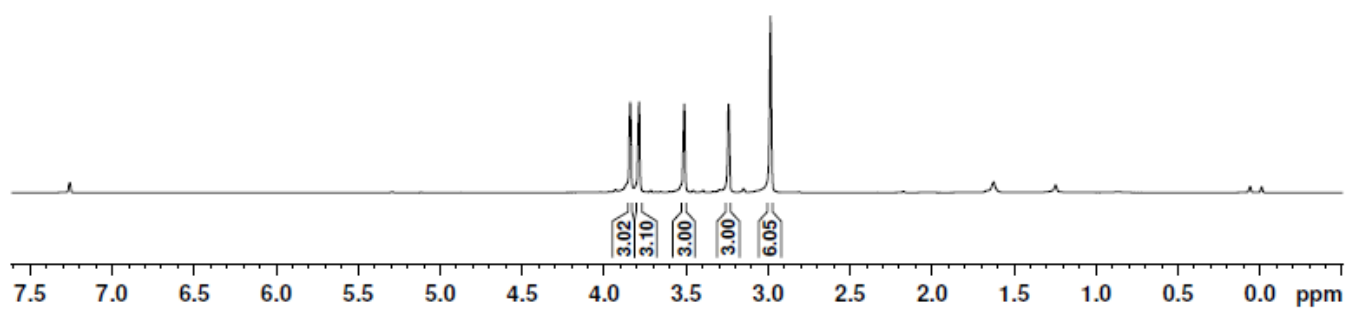
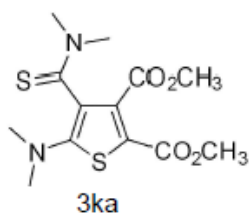






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— 193.52

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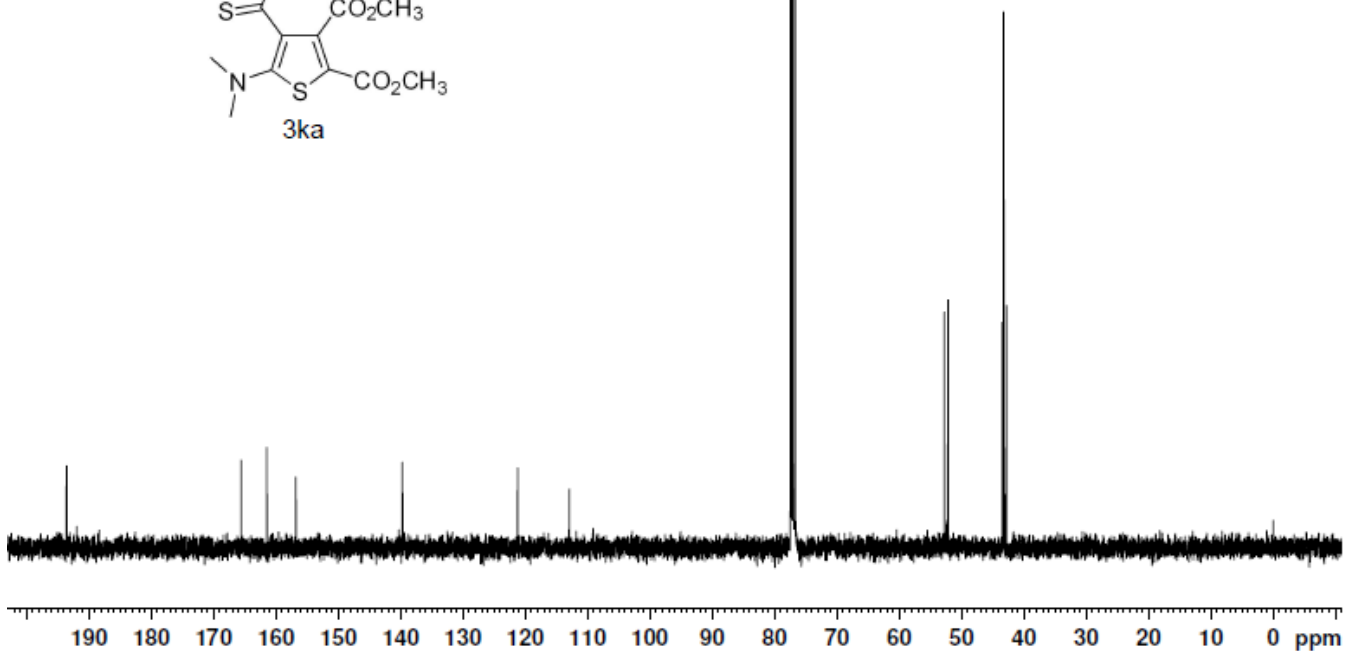
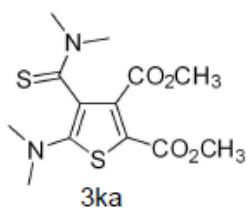
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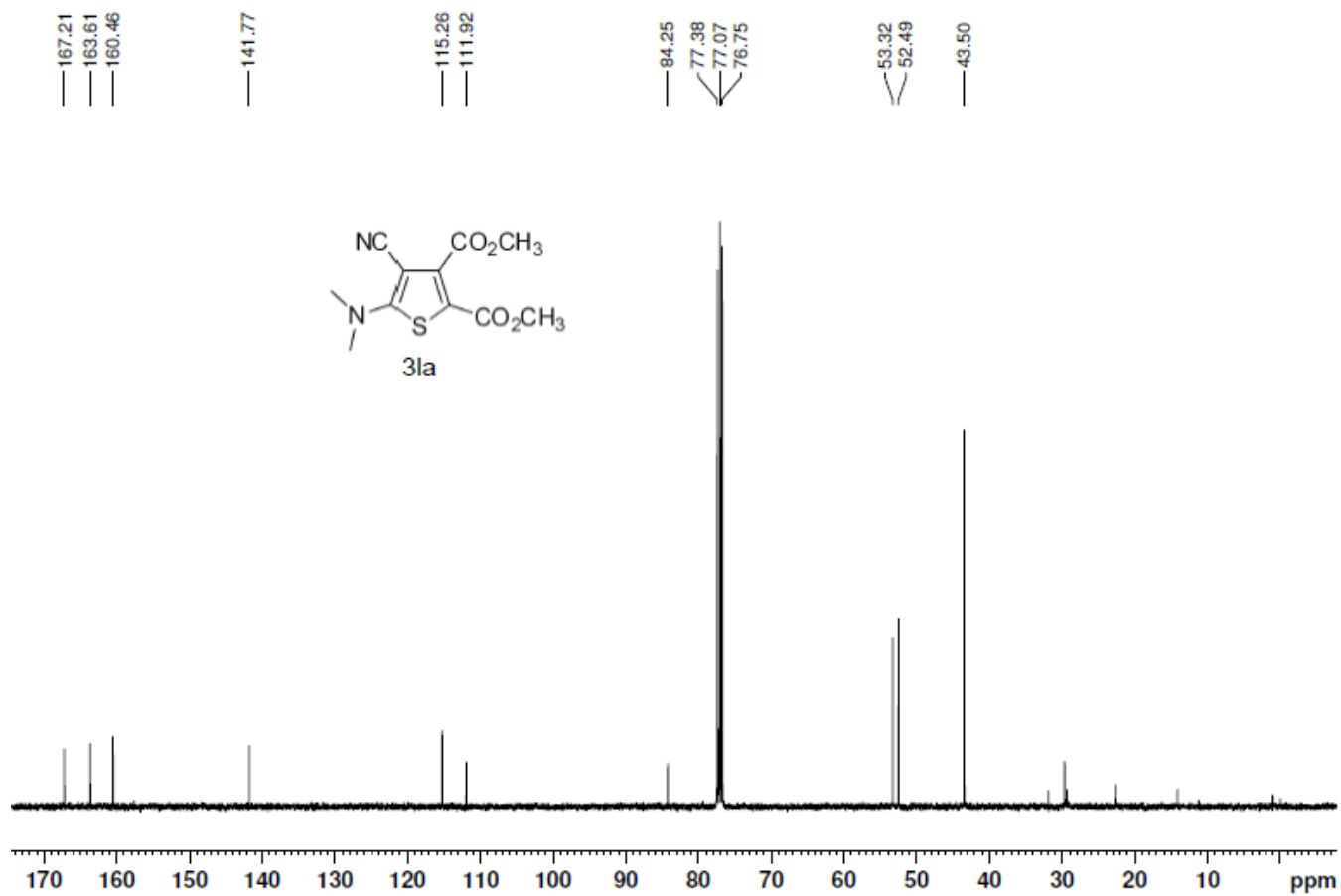
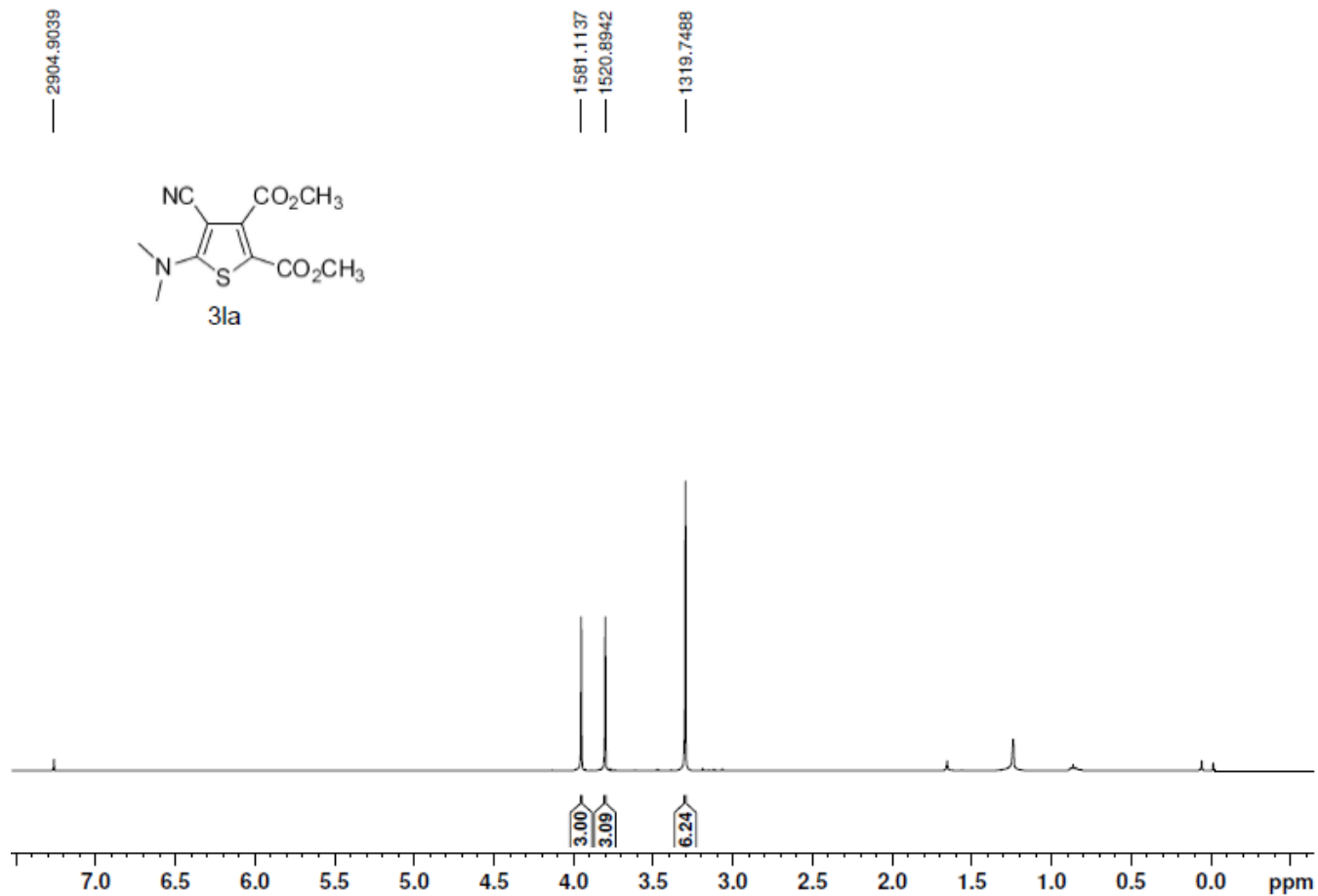
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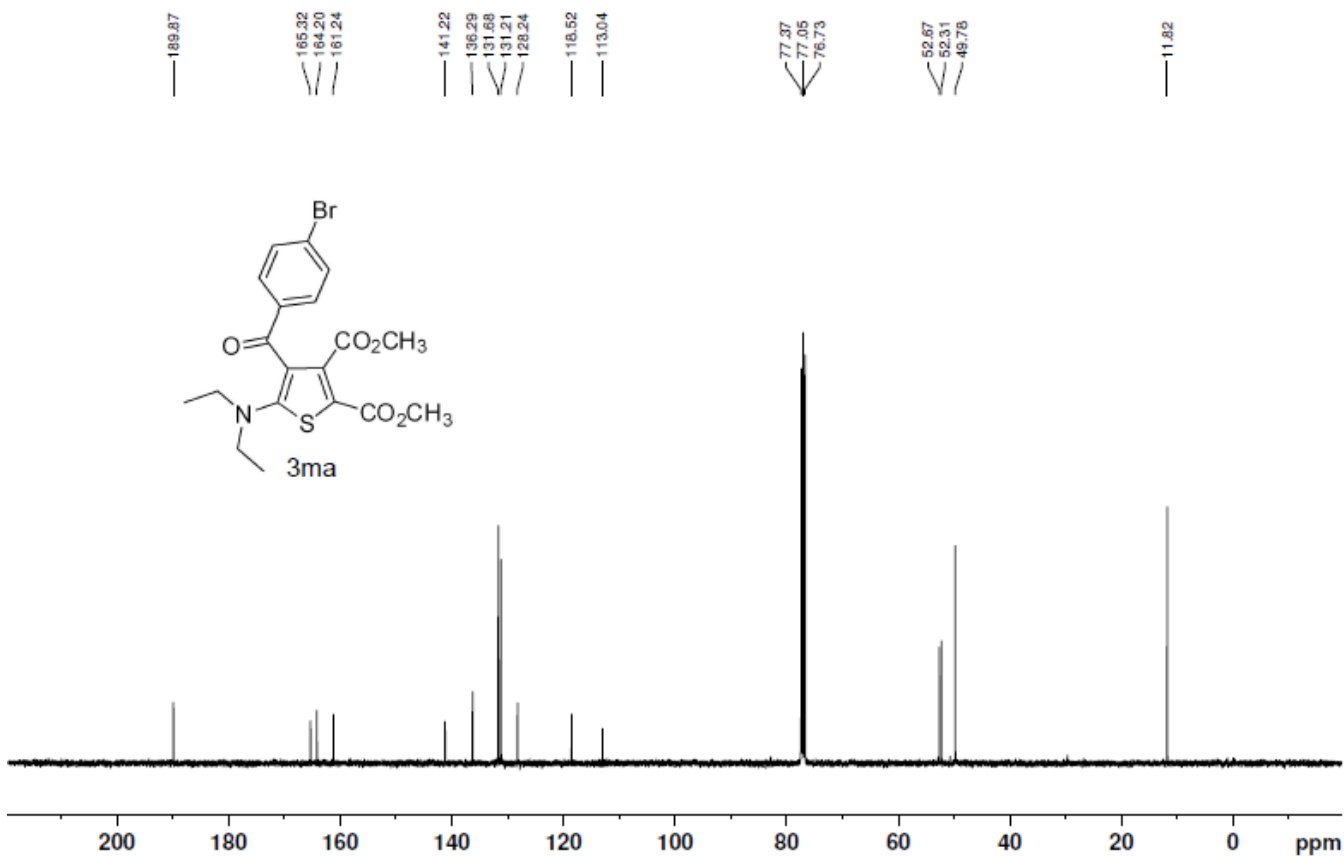
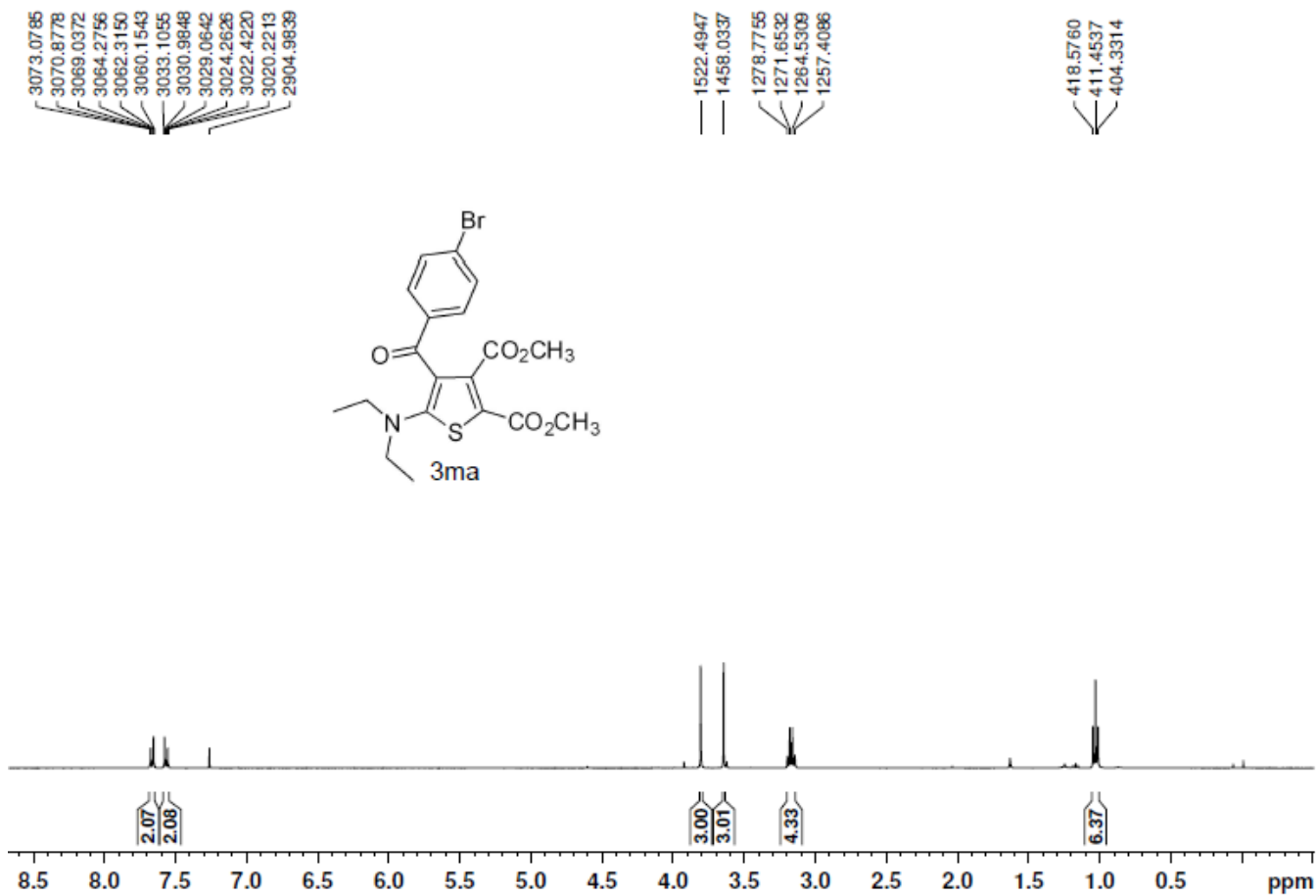
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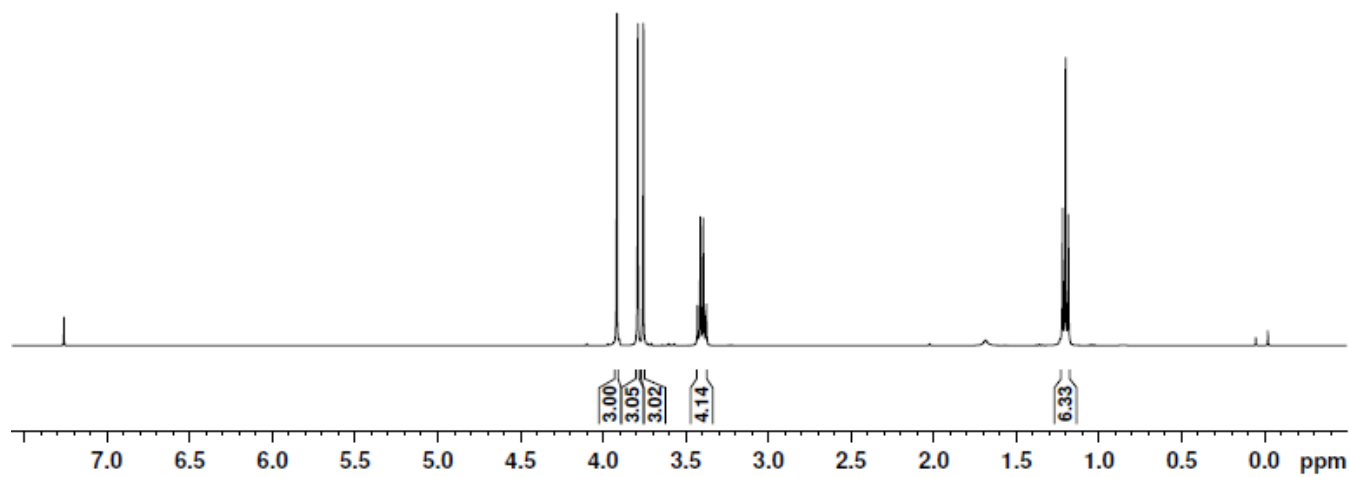
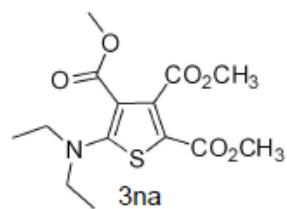




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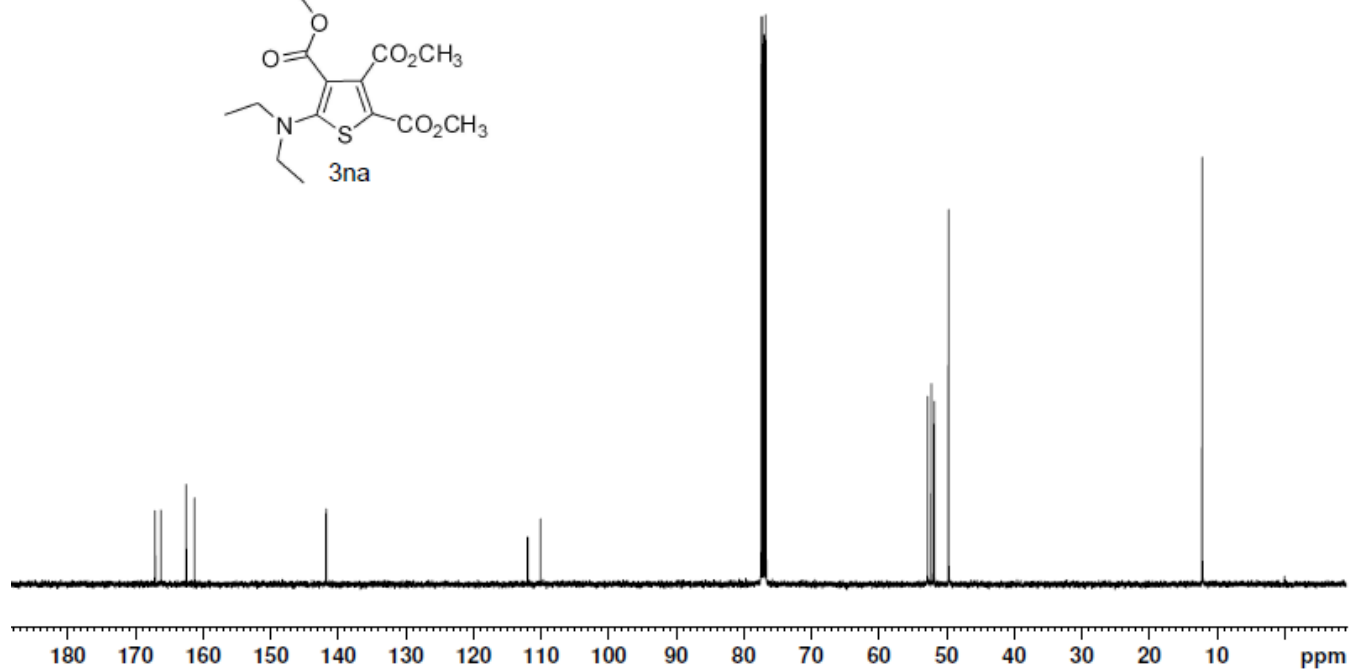
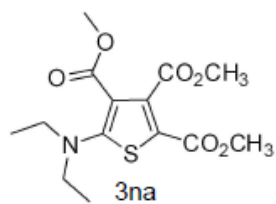
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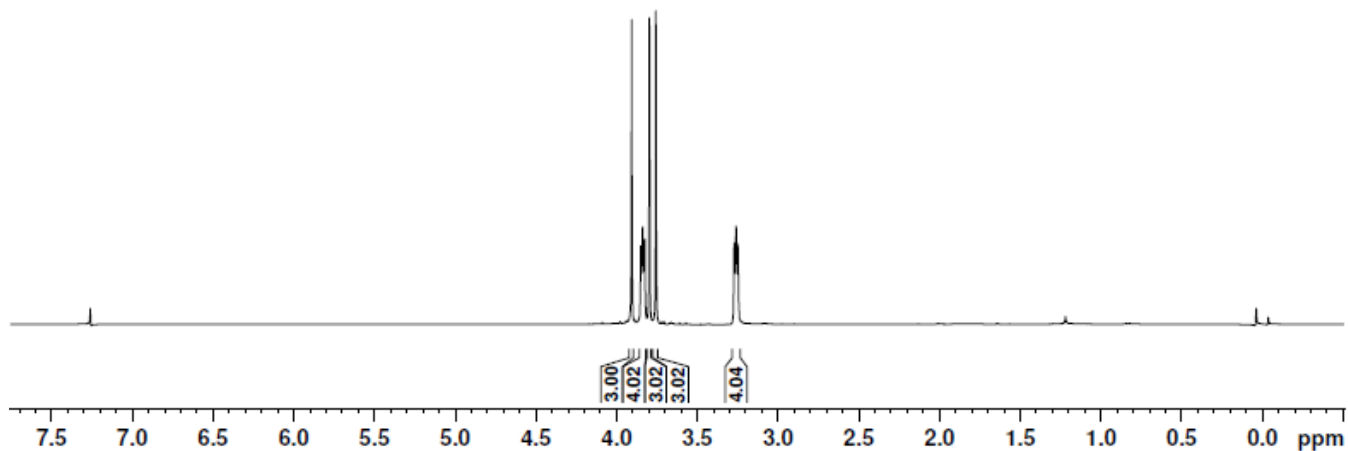
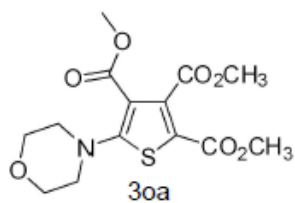
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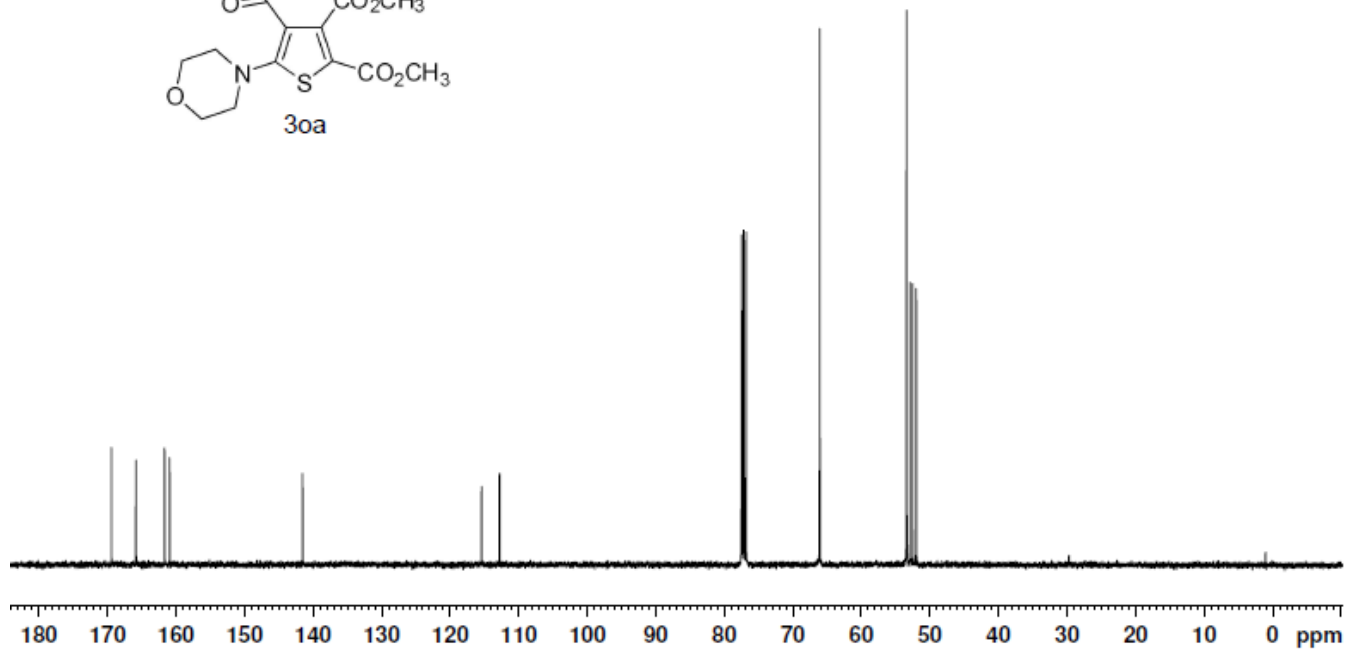
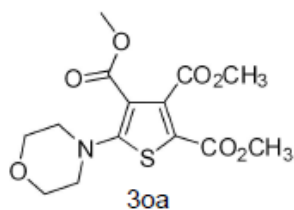


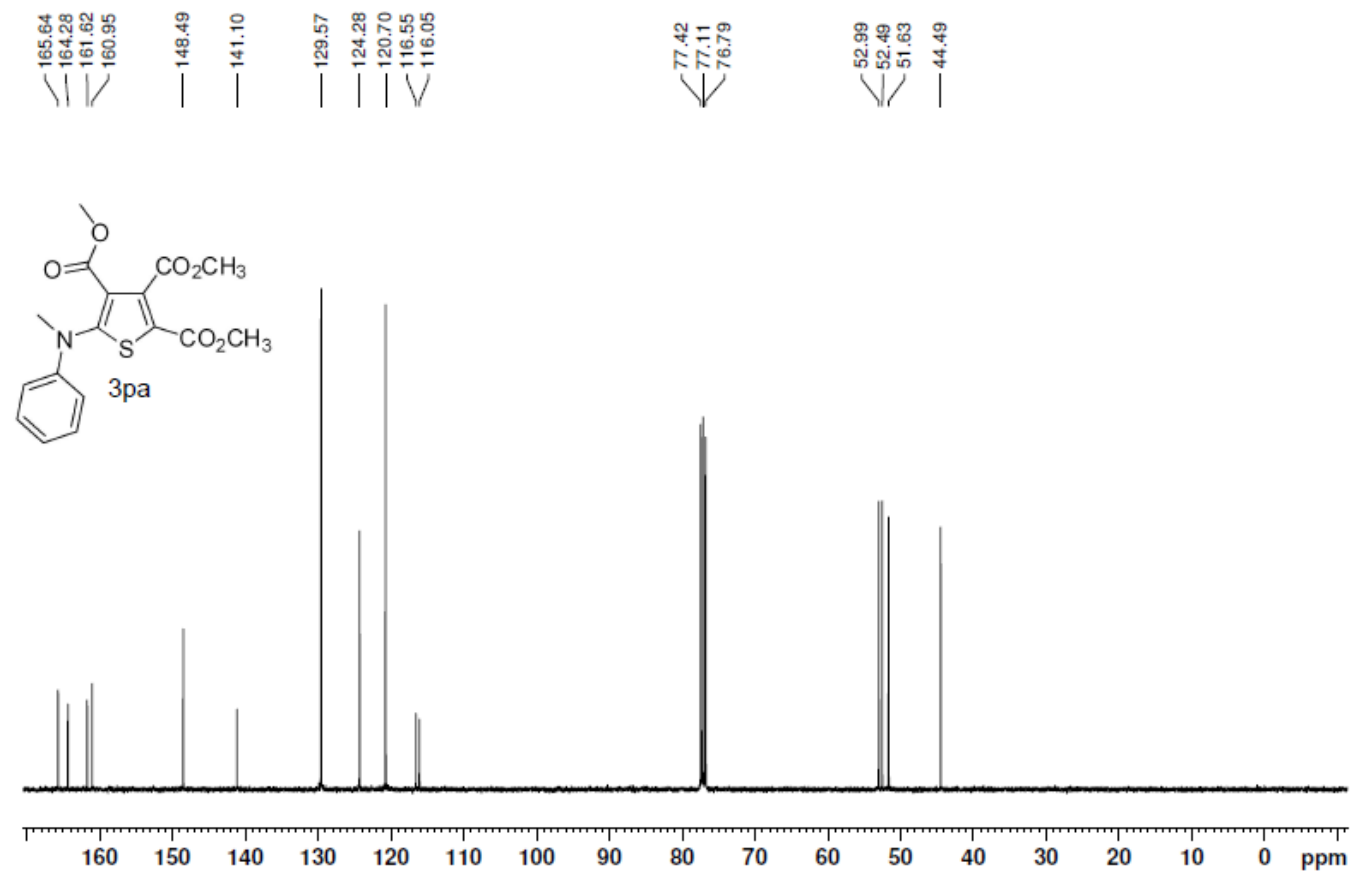
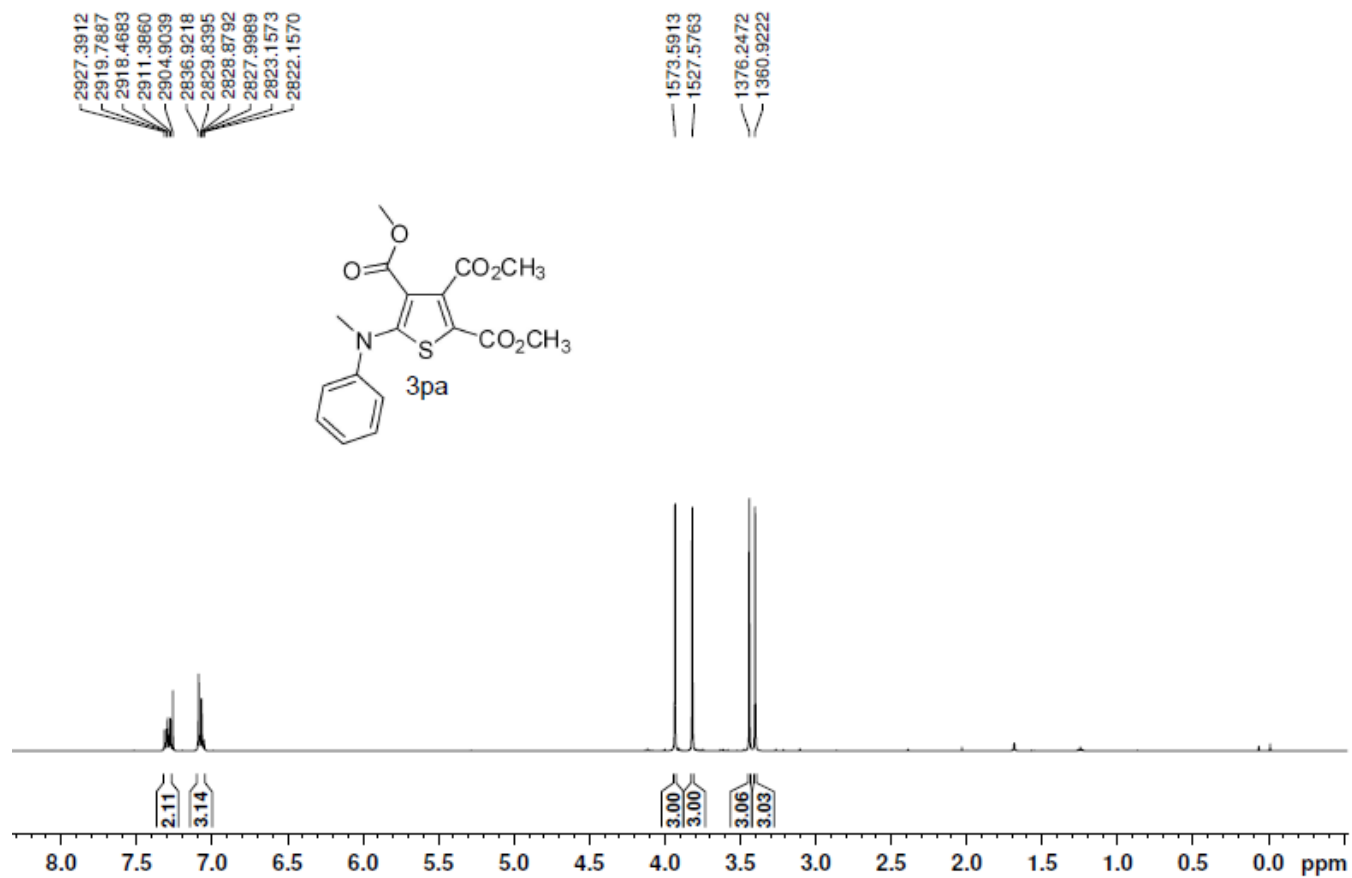
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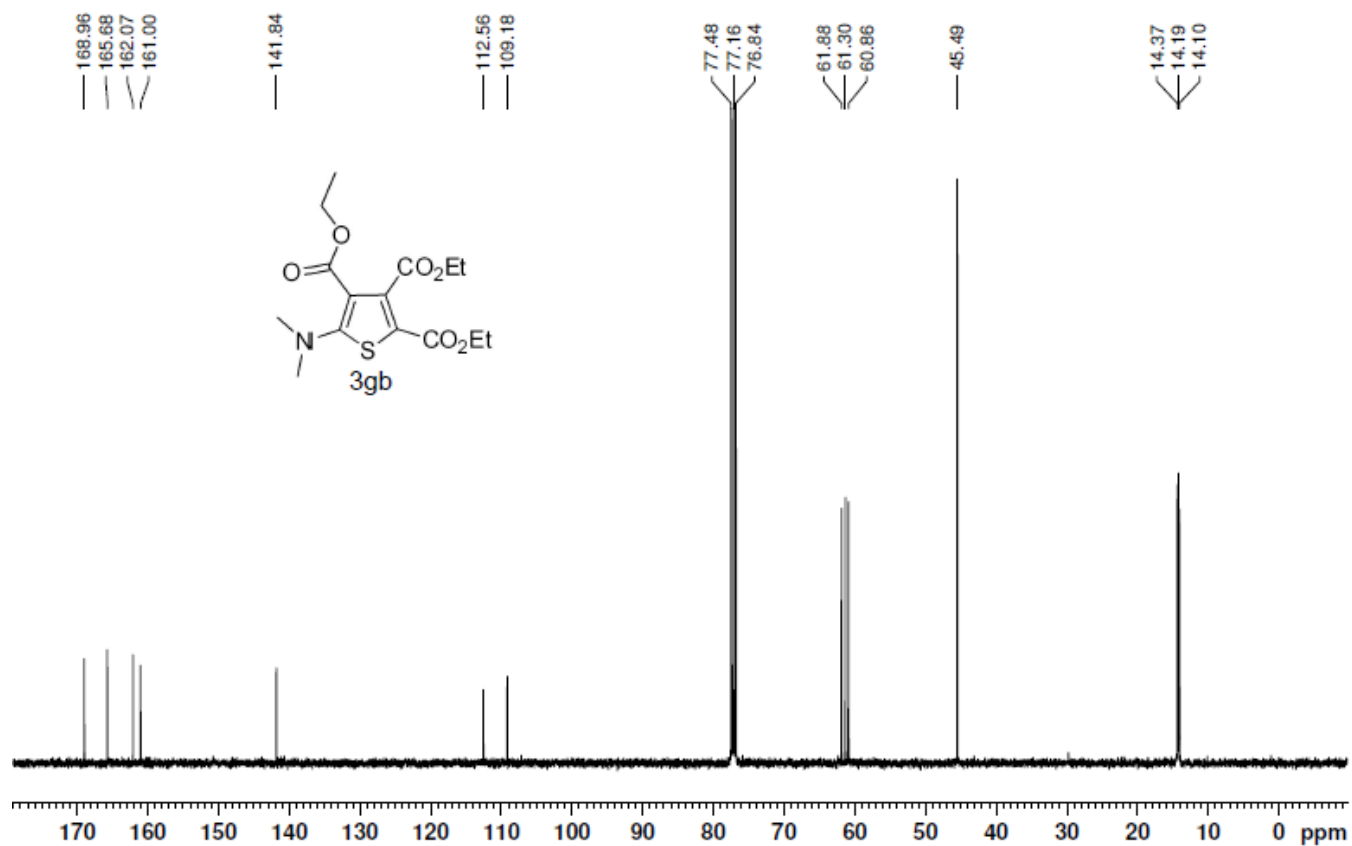
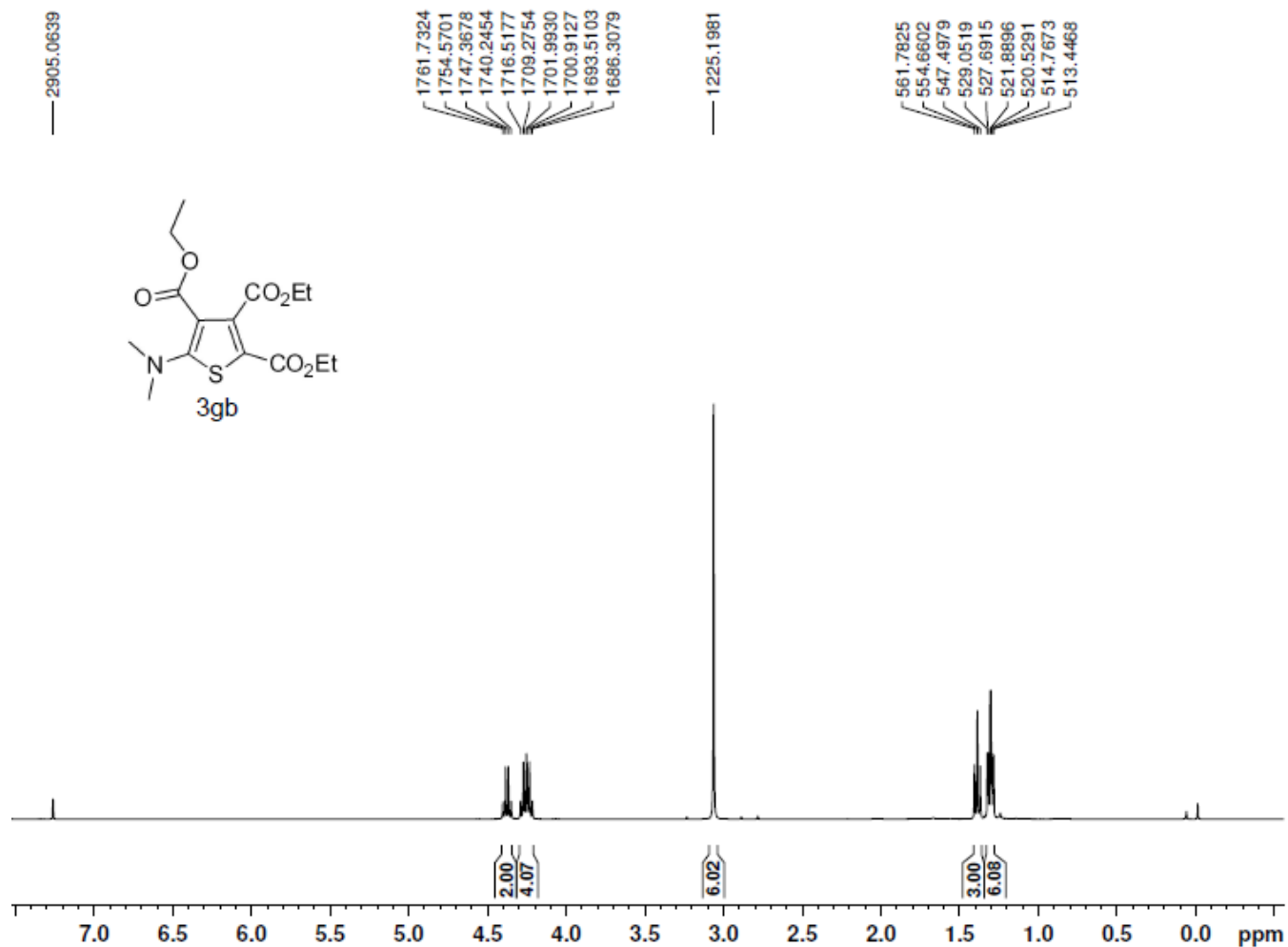
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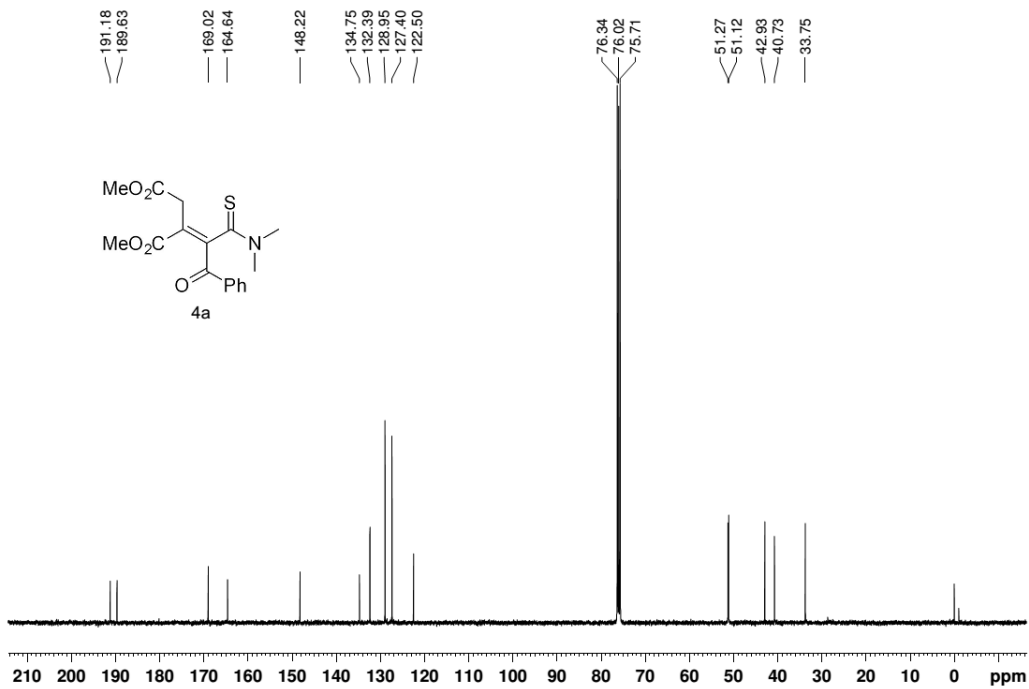
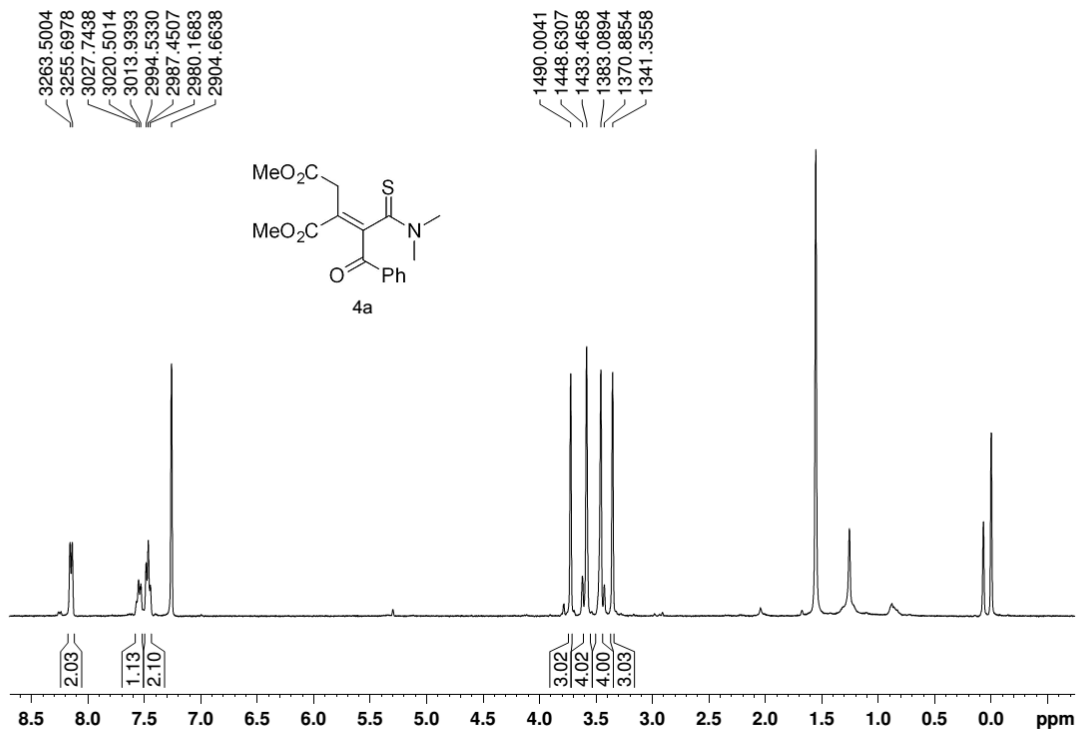


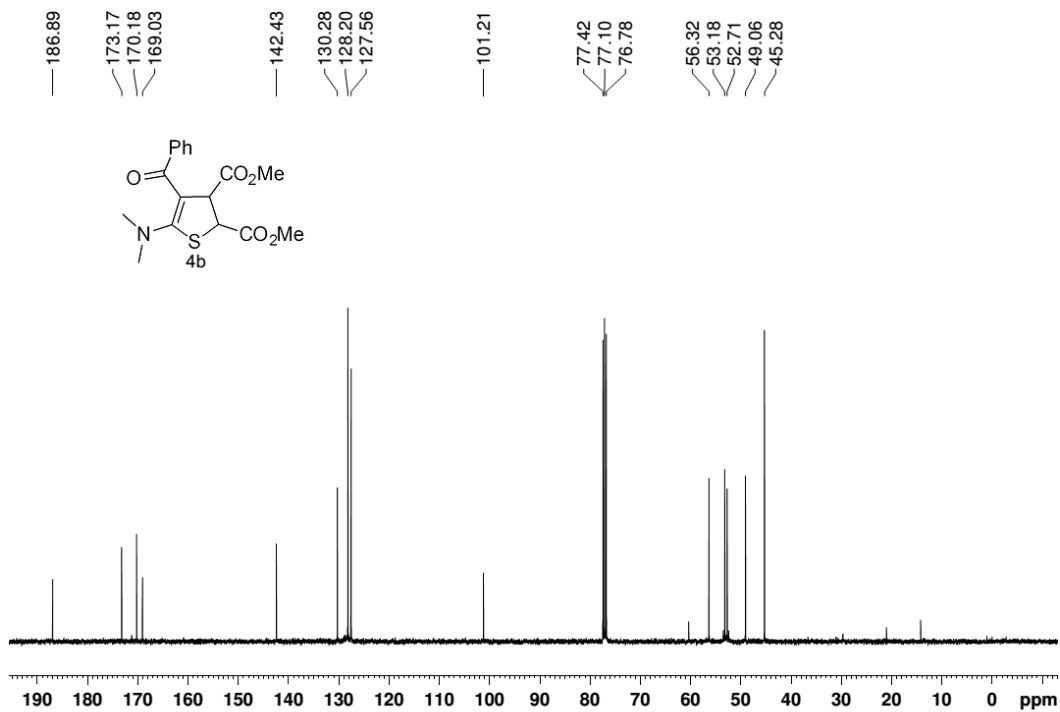
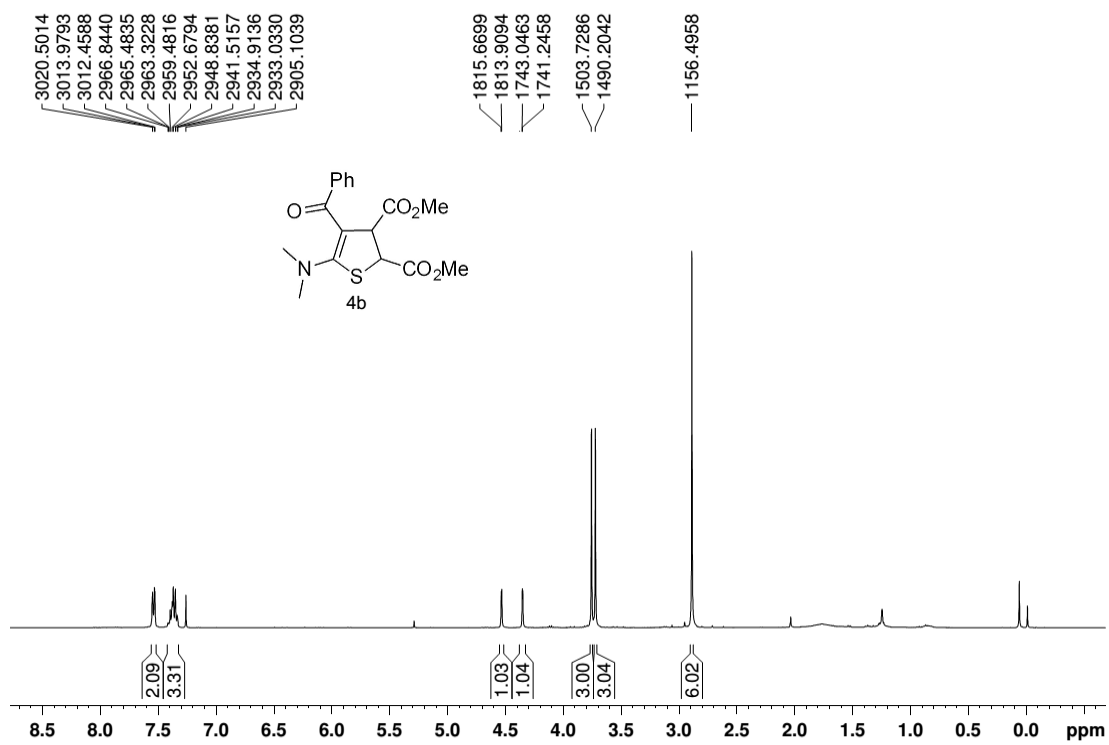
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3. Crystal data and structure refinement for 3aa.

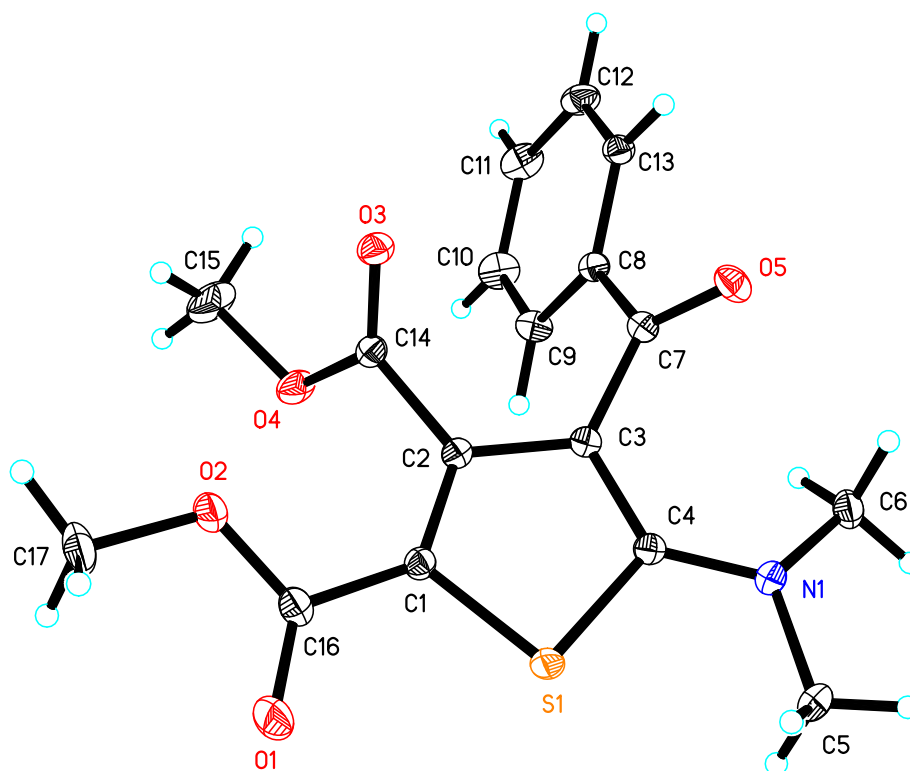


Figure S1. X-ray crystal structure of **3aa**. Displacement ellipsoids are drawn at the 30% probability level.

The X-ray crystallography data of **3aa** are listed below: a yellowish monoclinic crystal from n-hexane/dichloroform (1:3) was slowly exposed to graphite-monochromated Mo K α irradiation. The structures were solved by direct methods and refined on F^2 using all the reflections.

Empirical formula	C ₁₇ H ₁₇ NO ₅ S	
Formula weight	347.37	
Temperature	140(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.7645(9) Å	$\alpha = 90^\circ$.
	b = 7.4690(7) Å	$\beta = 95.351(2)^\circ$.
	c = 11.4907(11) Å	$\gamma = 90^\circ$.
Volume	834.38(14) Å ³	
Z	2	
Density (calculated)	1.383 Mg/m ³	

Absorption coefficient	0.221 mm ⁻¹
F(000)	364
Crystal size	0.450 x 0.350 x 0.320 mm ³
Theta range for data collection	2.095 to 30.550°.
Index ranges	-11<=h<=13, -10<=k<=10, -16<=l<=16
Reflections collected	8491
Independent reflections	5018 [R(int) = 0.0173]
Completeness to theta = 25.242°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7461 and 0.6644
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5018 / 1 / 221
Goodness-of-fit on F ²	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0333, wR2 = 0.0841
R indices (all data)	R1 = 0.0362, wR2 = 0.0866
Absolute structure parameter	0.02(2)
Extinction coefficient	n / a
Largest diff. peak and hole	0.266 and -0.295 e.Å ⁻³