Supporting information

Synthesis of ^{11}C-labelled ureas by palladium (II)-mediated oxidative carbonylation

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Table of contents

Calculations and definitions

[^{11}C]CO was transferred to the capped reaction vial and the radioactivity was measured to determine the starting amount of [^{11}C]CO (A_1). The reaction was heated during the specified reaction time. When finished, the radioactivity was measured (A_2) before venting the reaction vial and purging with N_2 to remove unreacted [^{11}C]CO and, possibly, volatile ^{11}C-labelled compounds formed during the reaction. A third radioactivity measurement (A_3) was performed before either preparation of a sample for determination of product selectivity or semi-preparative HPLC purification. After isolation and a final radioactivity measurement (A_4) of the ^{11}C-labelled product, an aliquot was analyzed to determine radiochemical purity and the identity of the ^{11}C-labelled product was confirmed using the isotopically unmodified product as reference. Activities were decay corrected to the same time point before used in calculations.

Conversion

The conversion, the measurement of [^{11}C]CO incorporated into non-volatile ^{11}C-labelled compounds, was based on the radioactivity measurements A_3 and A_2.

$$\text{Conversion (\%)} = \frac{\text{A3 (d. c.)}}{A2} \times 100$$

Product selectivity

Percentage of ^{11}C-labelled product formed, based on HPLC analysis of crude reaction mixture.

Radiochemical yield in optimization tables 1 and 3

An estimate of the radiochemical yield (RCY) of the non-isolated ^{11}C-labelled product based on the [^{11}C]CO-conversion and the ^{11}C-labelled product selectivity.

$$RCY\ (\%) = Conversion \times Product\ selectivity$$

Radiochemical yield

Based on the activity of the isolated ^{11}C-labelled product (A_4) and the starting amount of [^{11}C]CO, transferred to the reaction vial (A_1).

$$RCY\ (\%) = \frac{A4\ (d.c.)}{A1} \times 100$$

Radiochemical purity

Based on the HPLC analysis of an aliquot from the isolated ^{11}C-labelled product fraction.

Identity of synthesized ^{11}C-labelled compound

The identity of a labelled compound was confirmed by adding isotopically unmodified compound (UV-active) to an aliquot of the isolated ^{11}C-labelled product and comparing the retention times of the UV-peak and radio-peak on analytical HPLC.

Molar activity calculations

A calibration curve for *N*-(2,4-dichlorobenzyl)-4-phenoxypiperidine-1-carboxamide (**19**) was prepared using five concentrations; 0.25, 0.5, 1.0, 2.0 and 5.0 μg/mL. 50 μL was injected, starting from the lowest concentration, and analyzed at 221 nm to construct a calibration curve (Figure S1). A blank sample consisting of acetonitrile was injected between every run to avoid carry-over.

The molar activity for **19** was determined in two experiments and calculated from the activity of the isolated product (A_4) and the volume and concentration of the product fraction (Table S1).

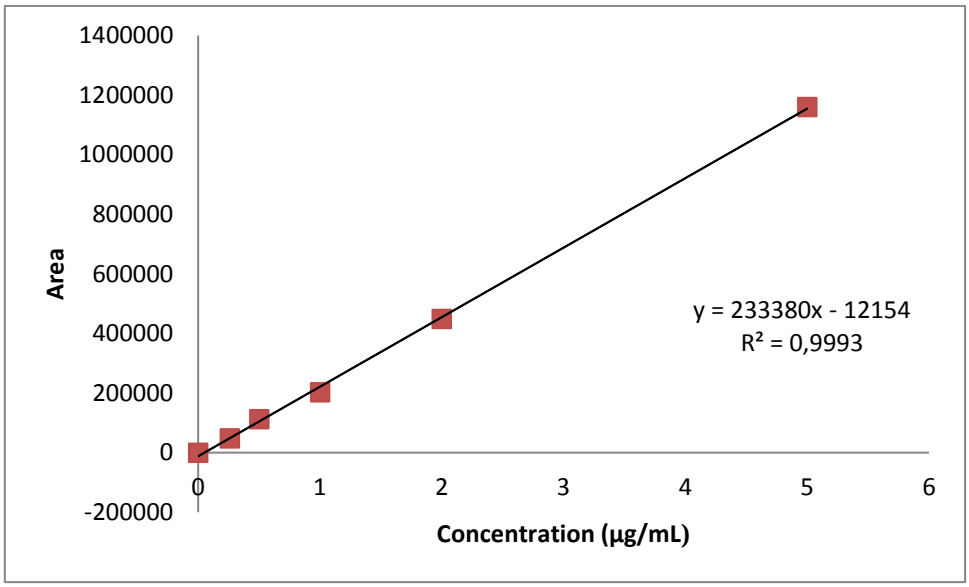


Figure S1. Calibration curve for *N*-(2,4-dichlorobenzyl)-4-phenoxypiperidine-1-carboxamide (**19**).

Table S1. Determination of molar activity.

Experiment	Area	Concentration (μg/mL)	Volume (mL)	Mass (μg)	Amount (μmol)	Activity (GBq)	Molar activity (GBq/μmol)
1	114169	0.599	5.12	2.86	0.00754	1.86	247
2	31211	0.186	13.5	2.51	0.00662	2.11	319

3D-structures from Scheme 2

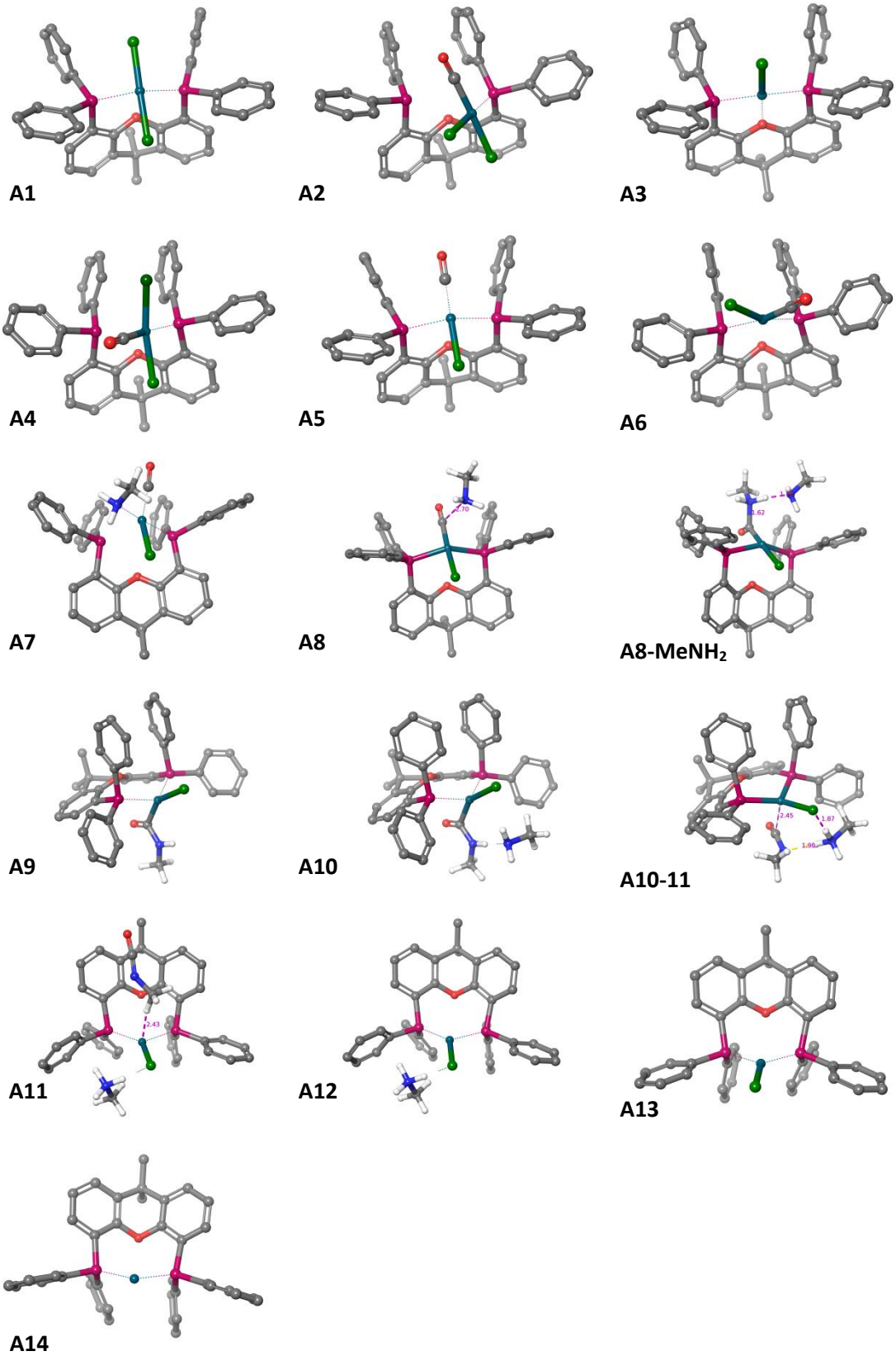
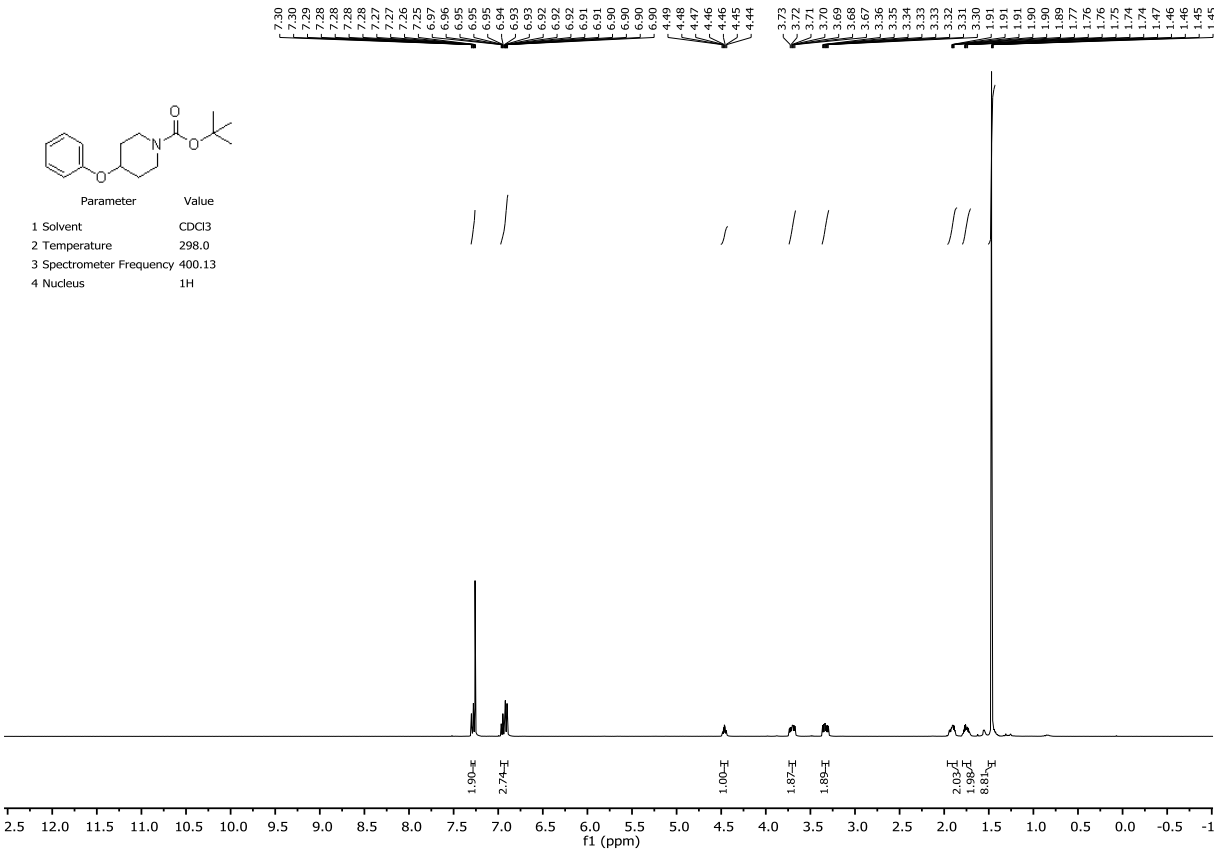


Figure S2. Optimized structures of intermediates and one transition state shown in Scheme 2.

NMR spectra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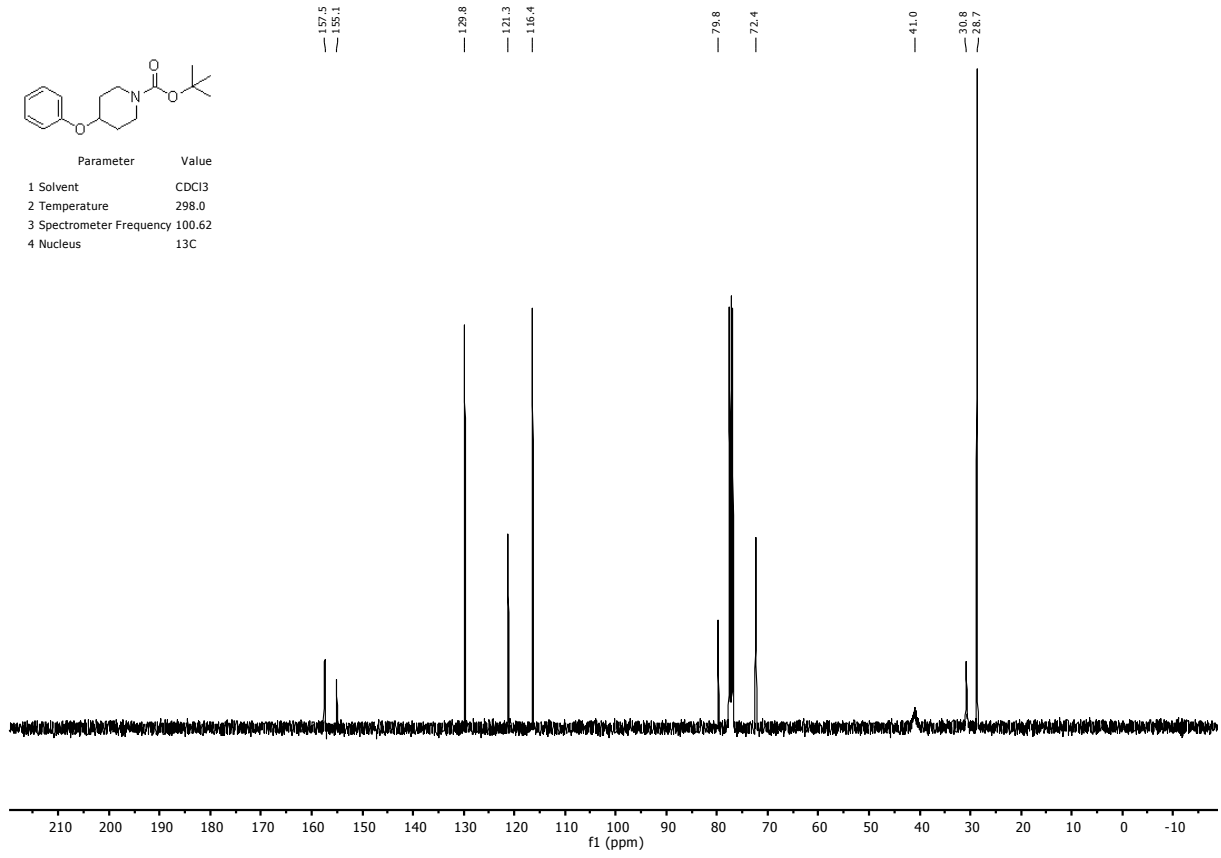
4 Nucleus 1H
f1 (ppm)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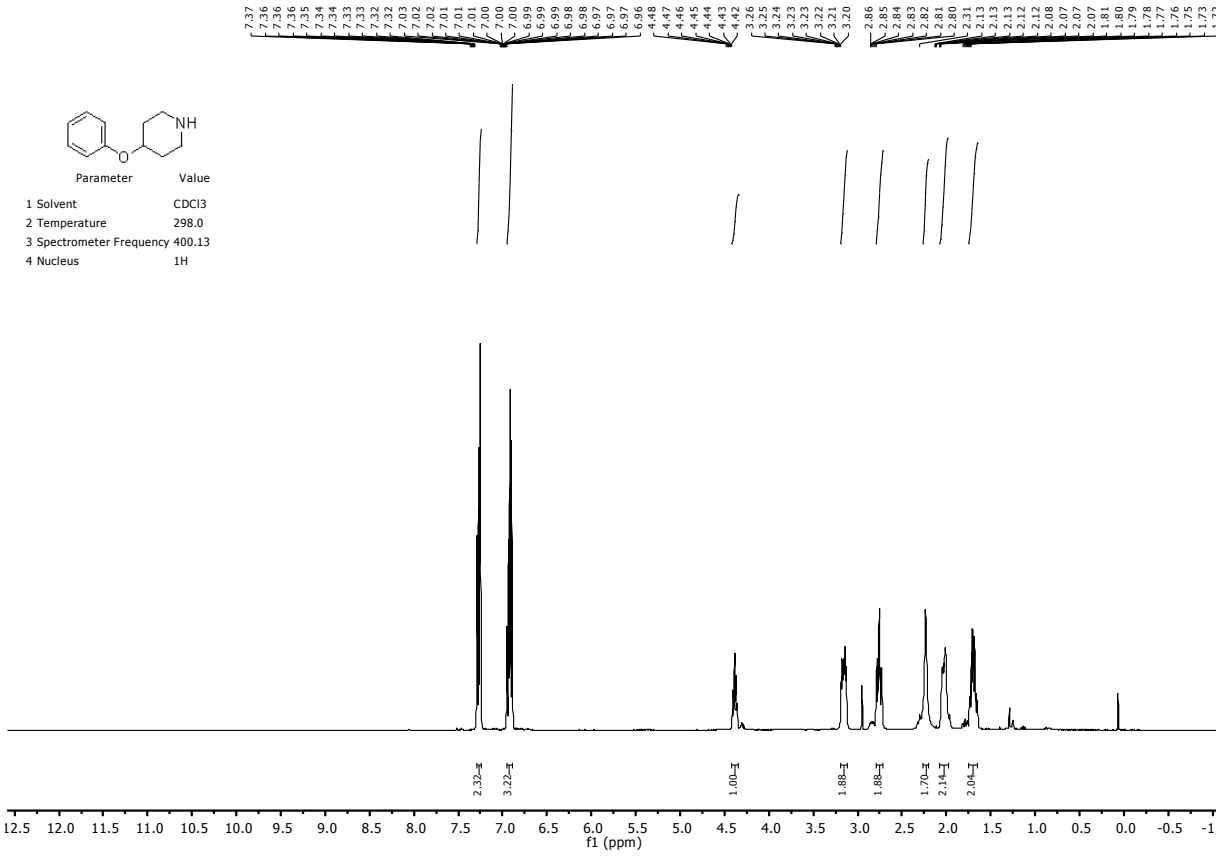
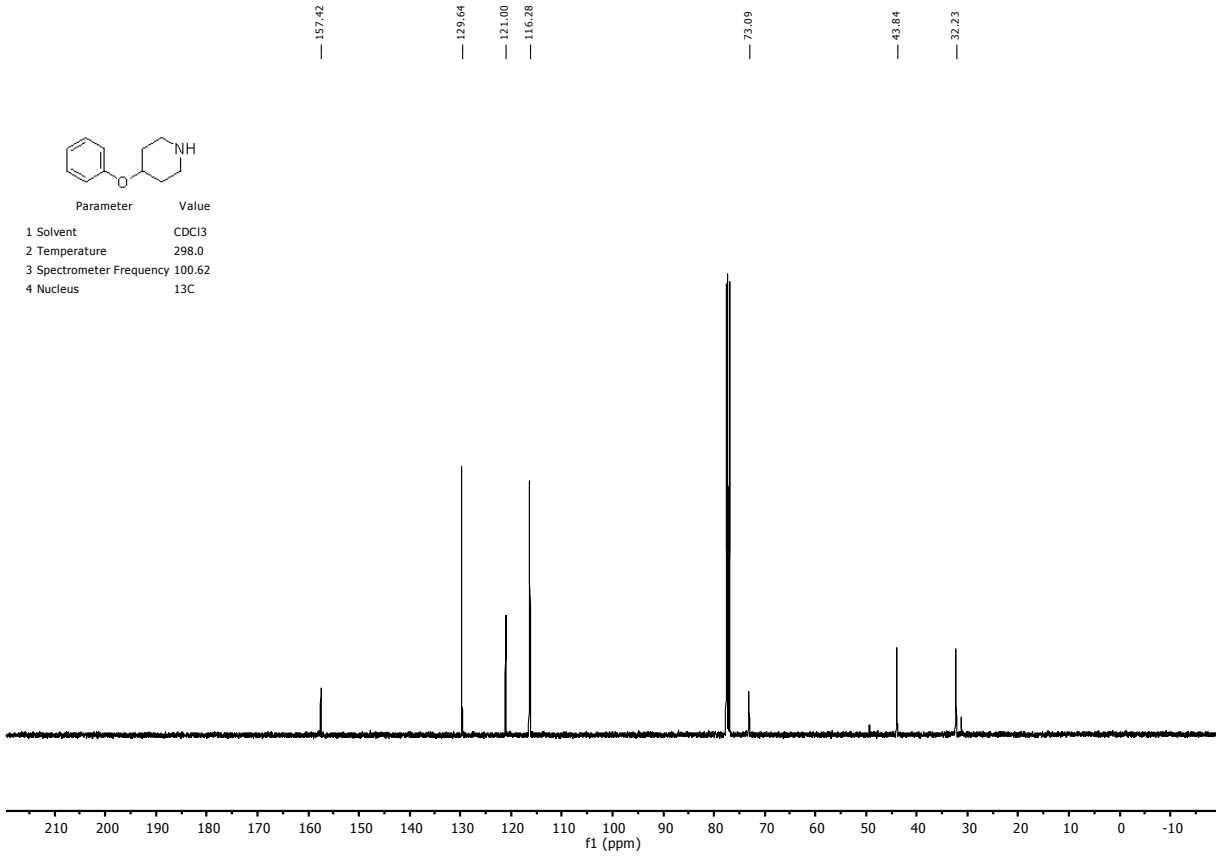
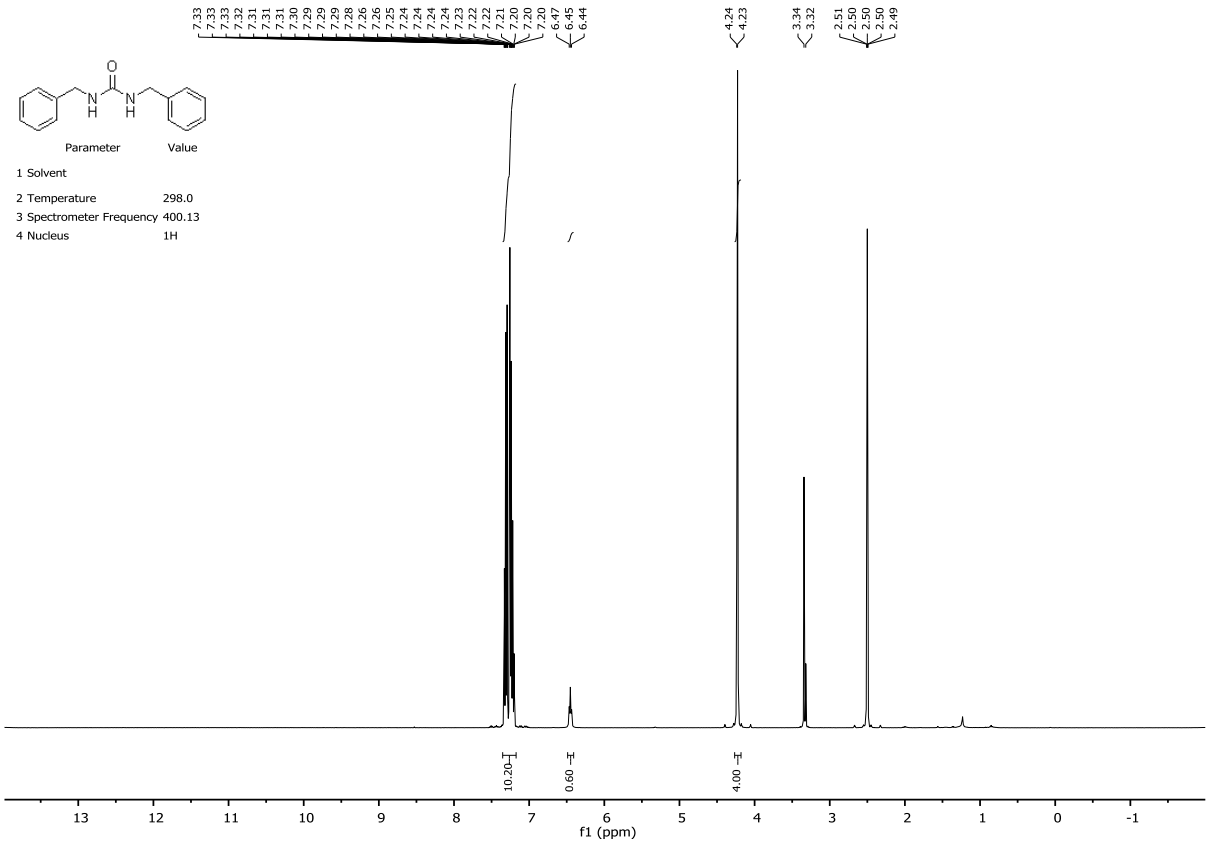
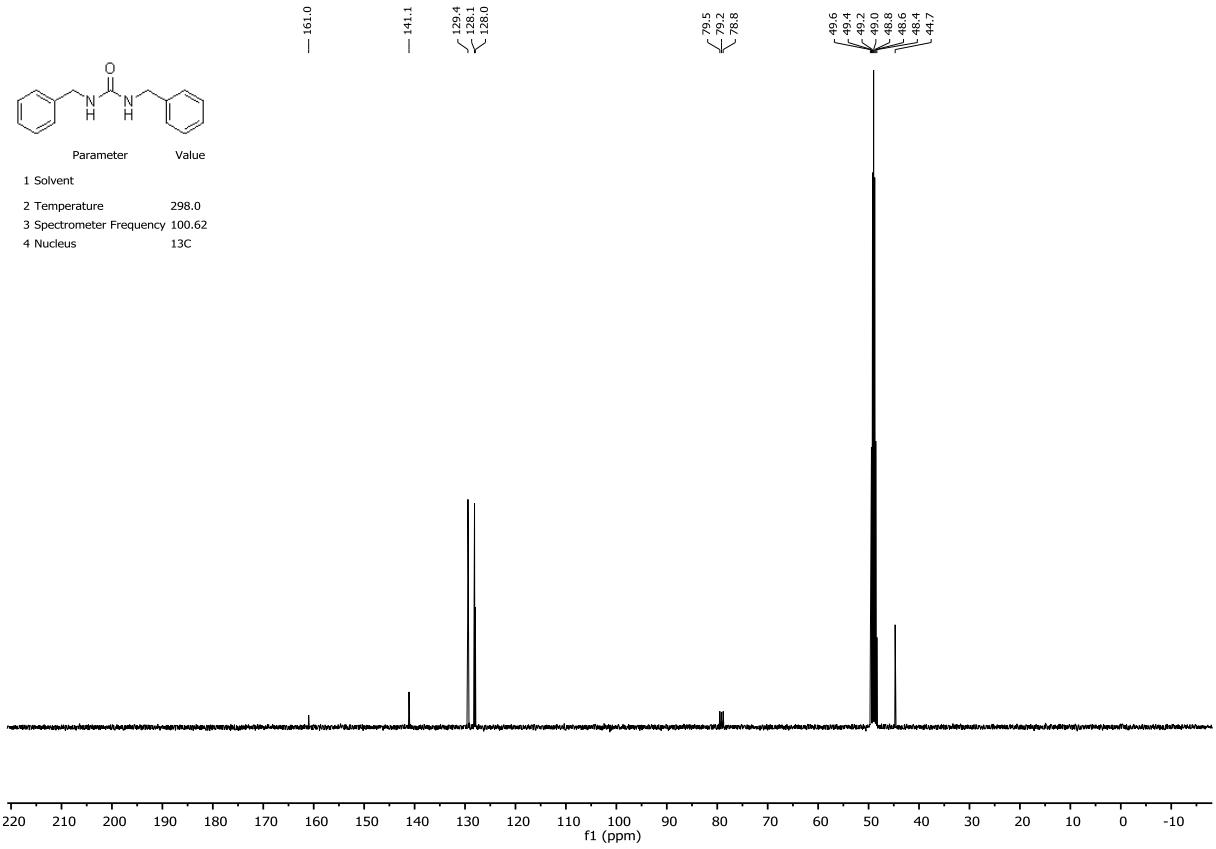


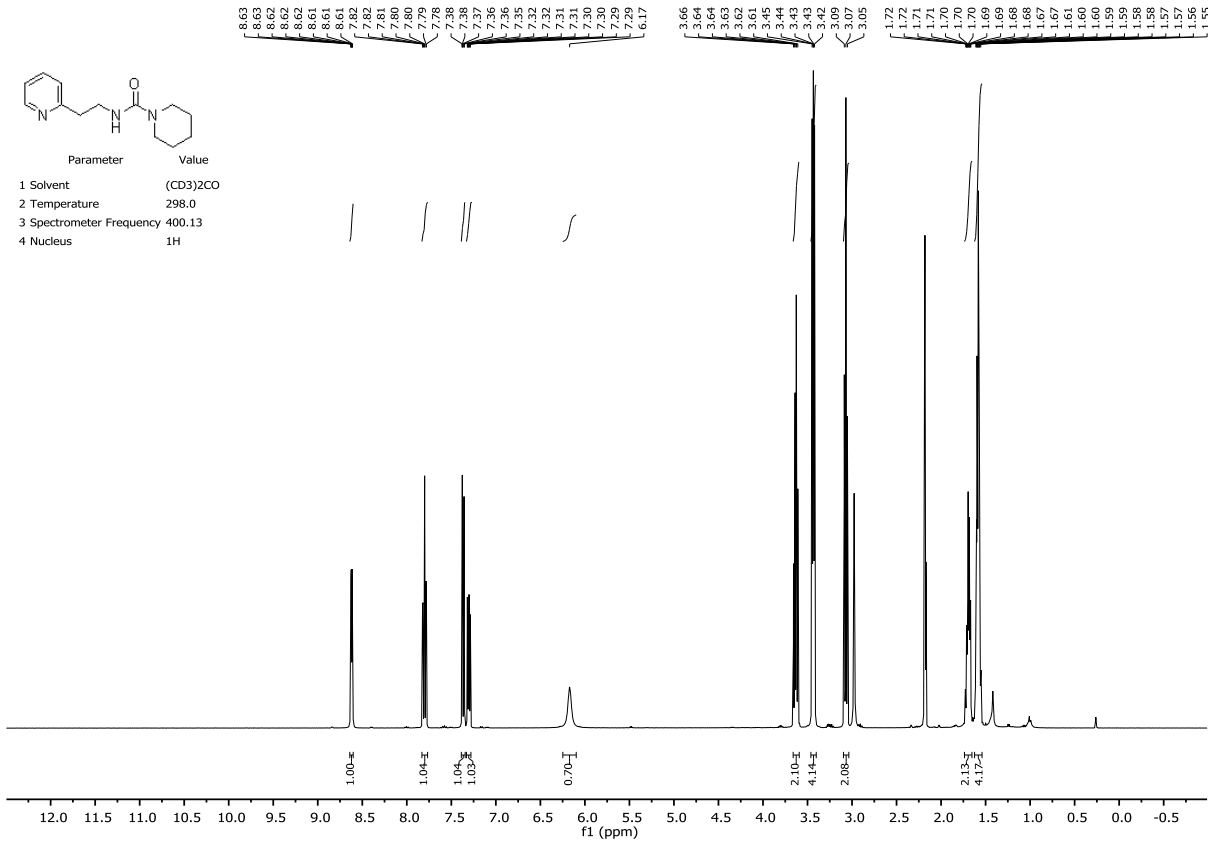


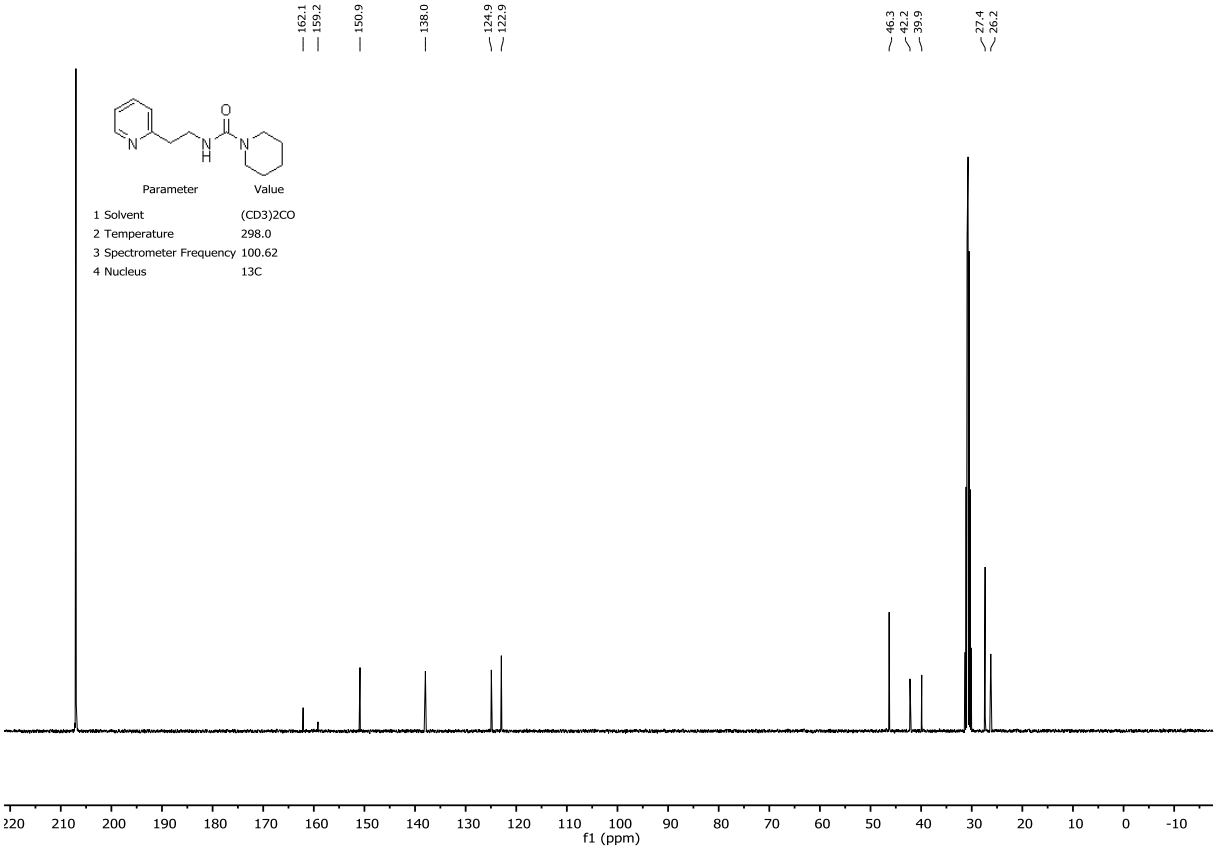
4-Phenoxypiperidine [1] CAS: 3202-33-3





1,3-Dibenzylurea [2] CAS: 1466-67-7





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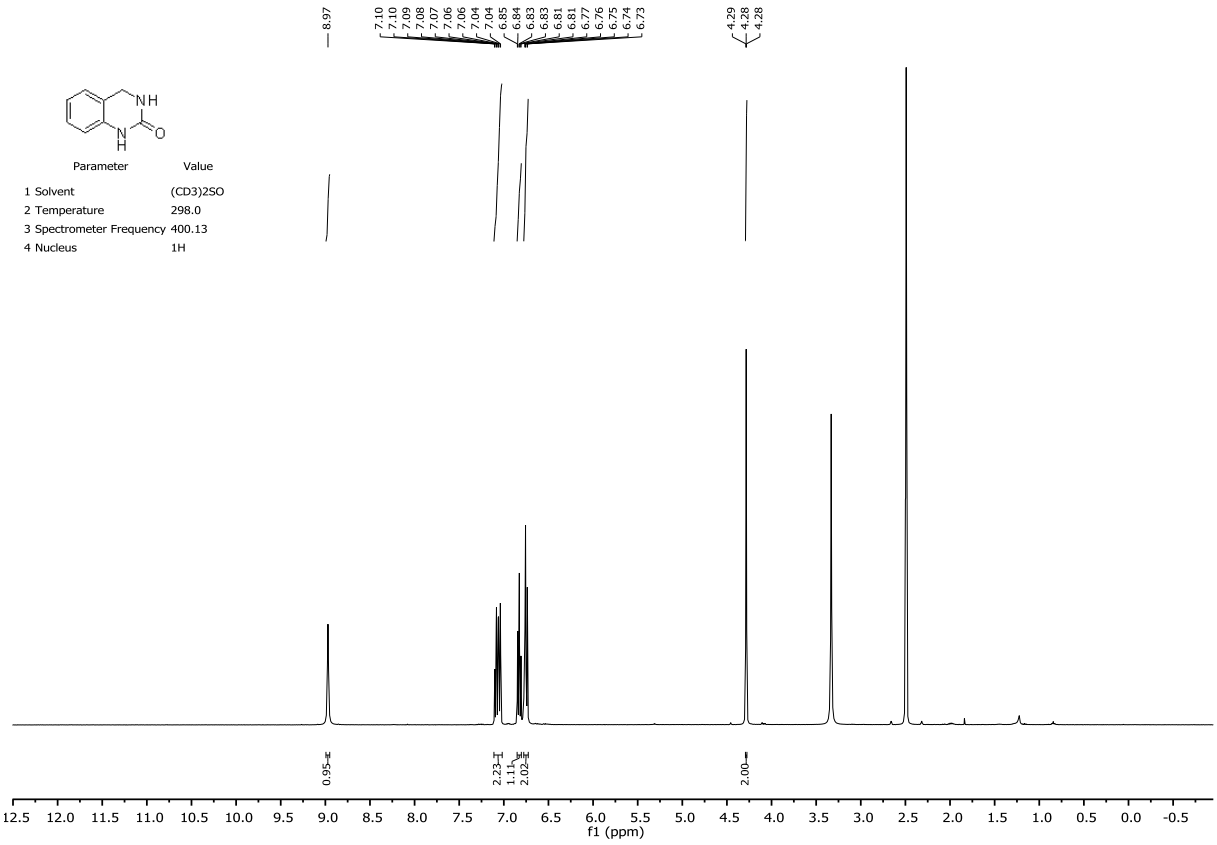

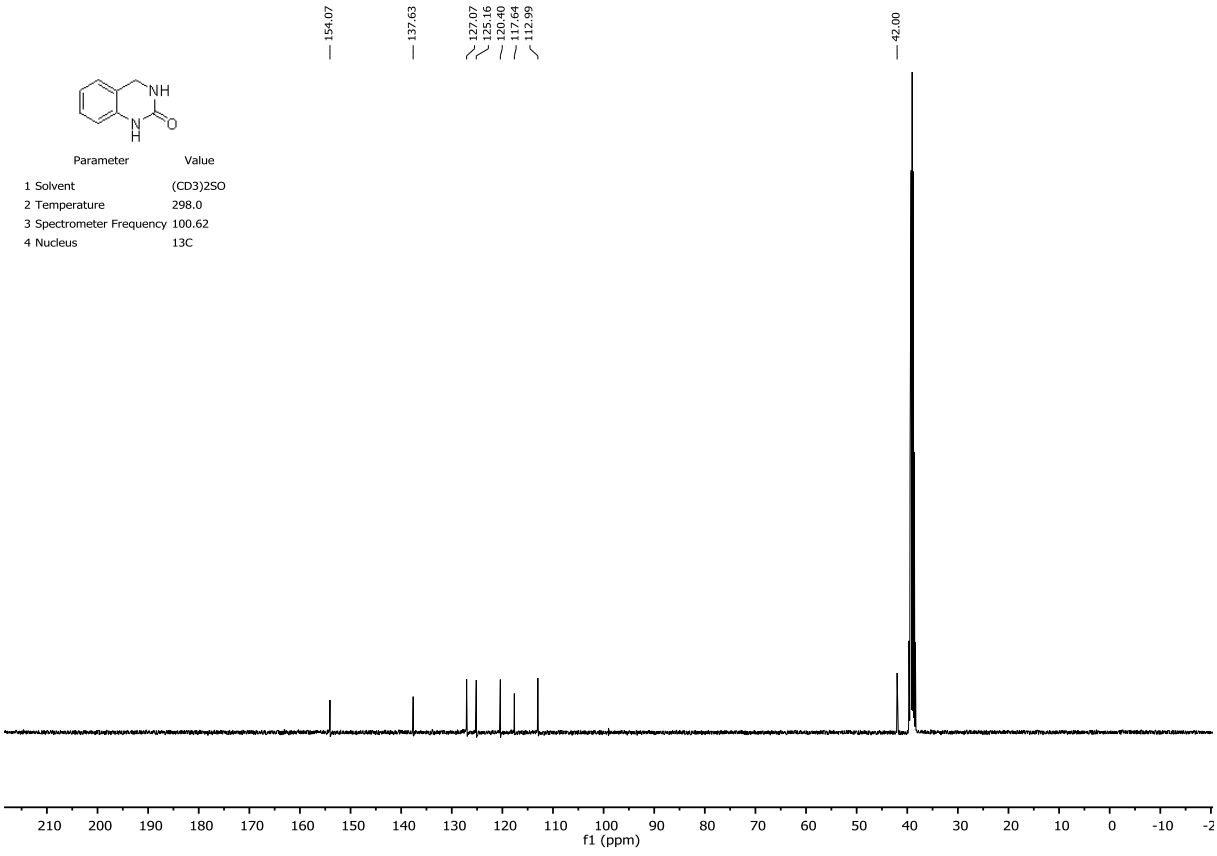

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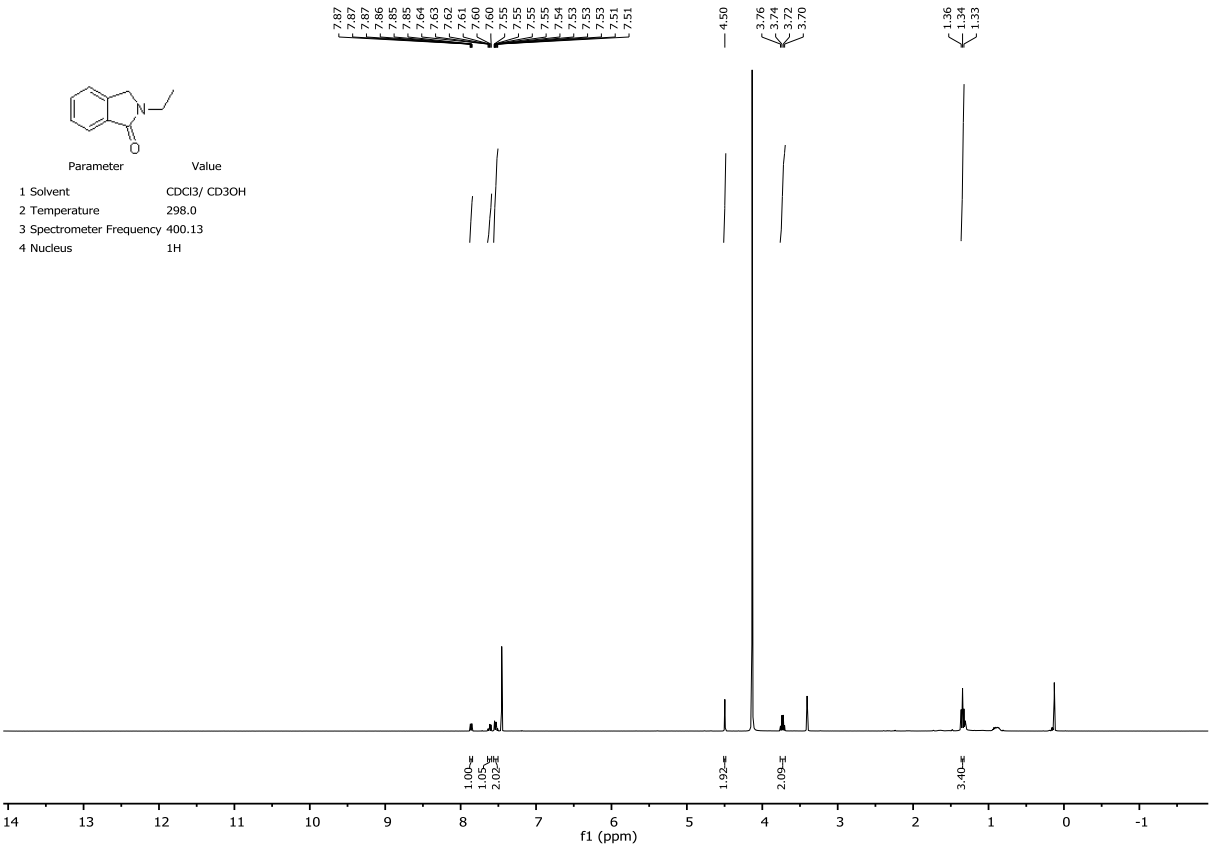
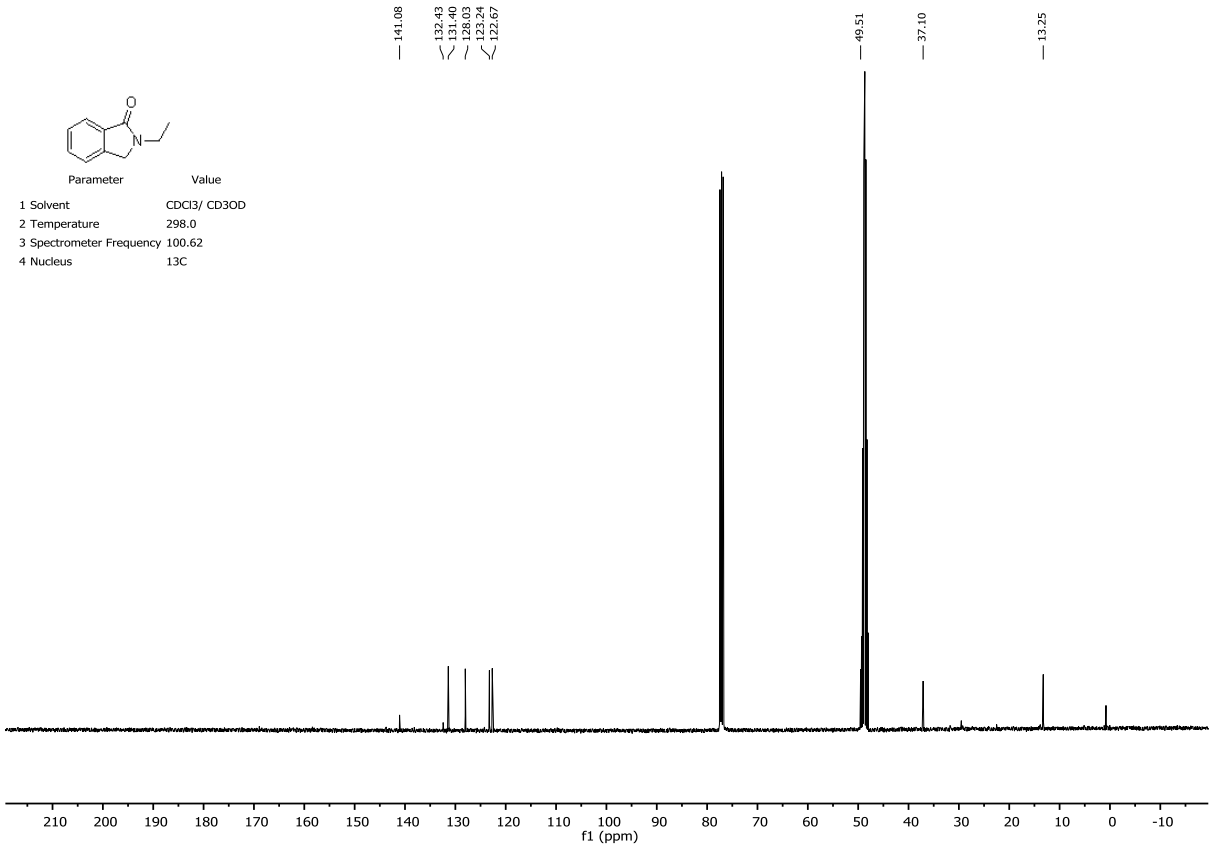
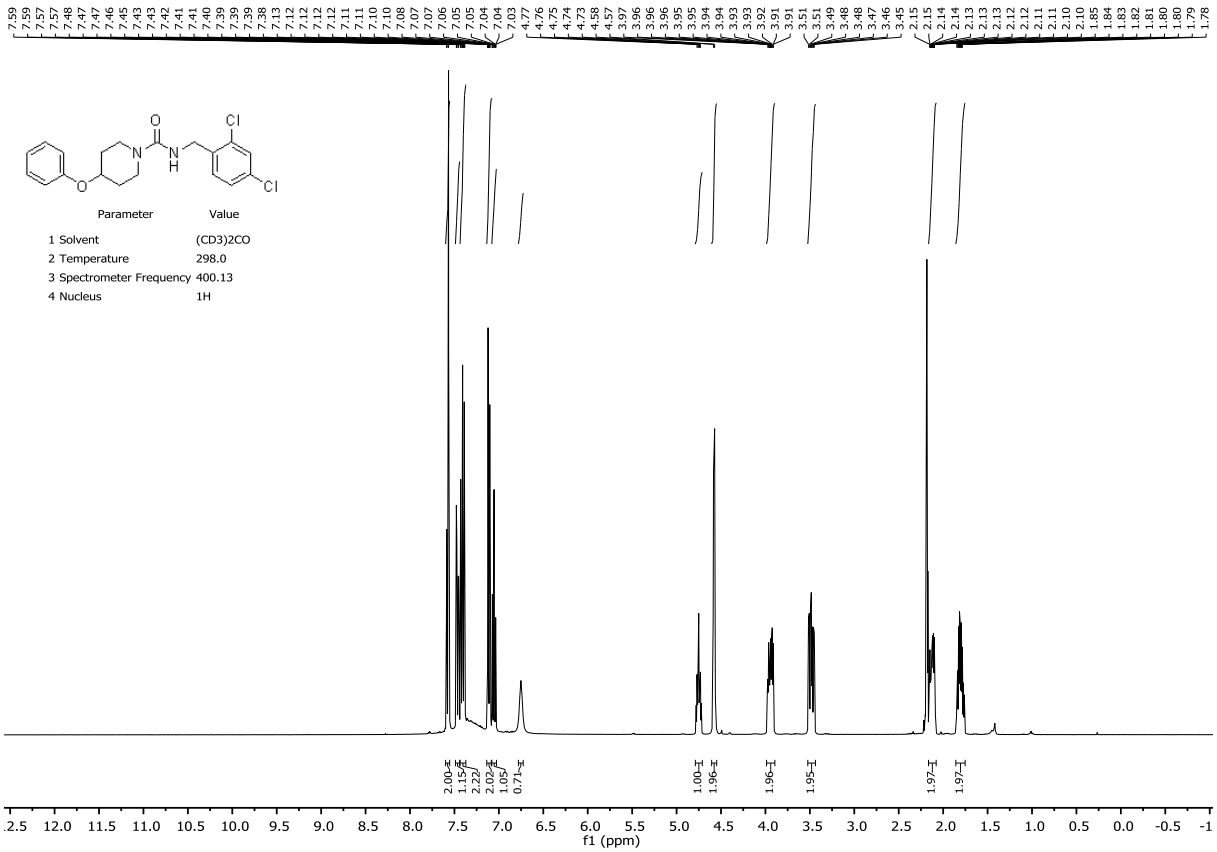
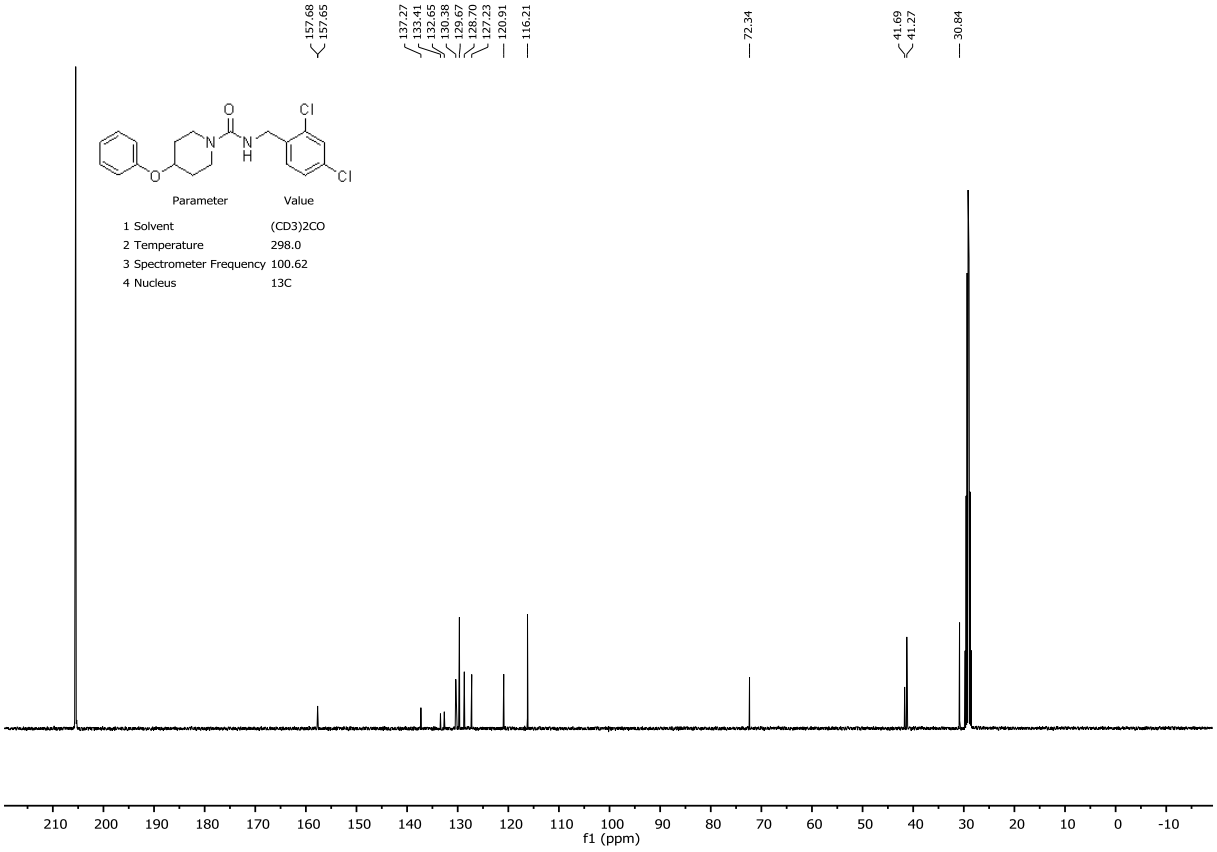


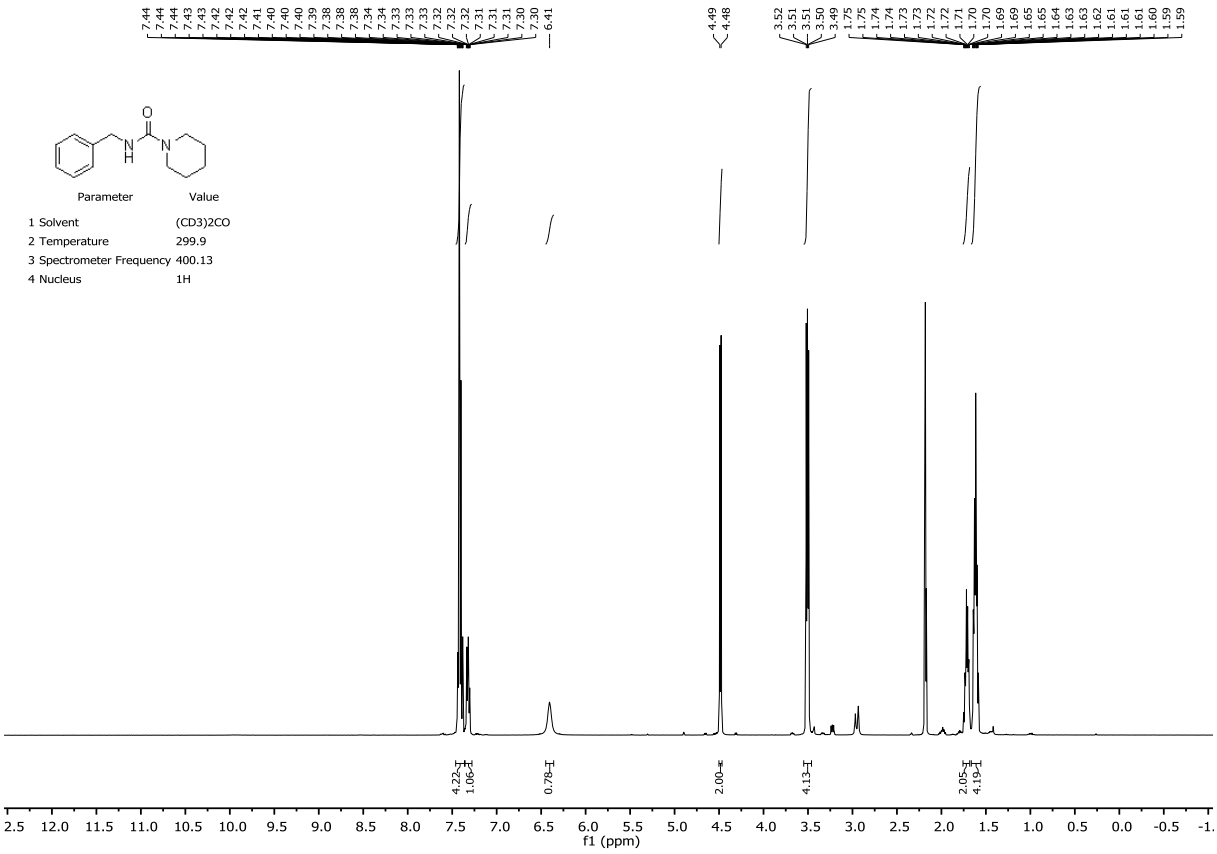


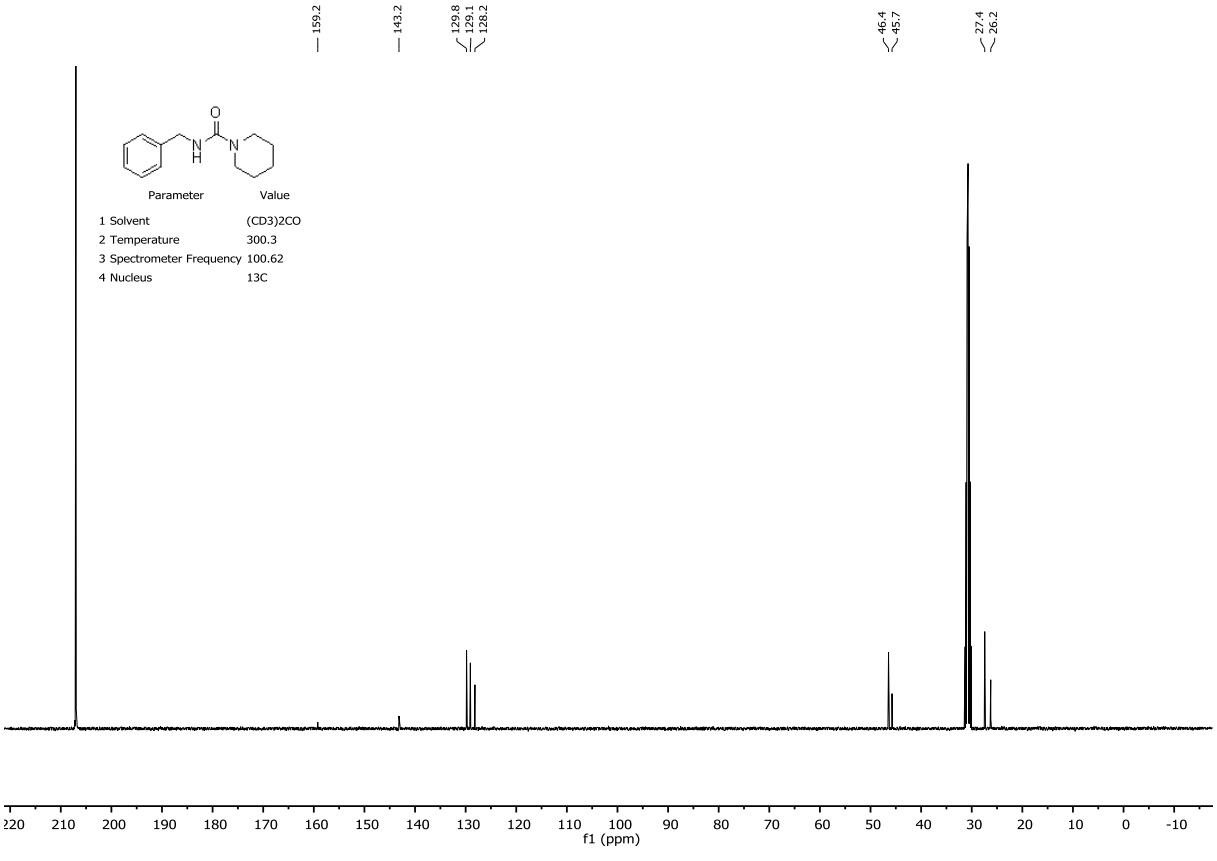
2-Ethylisoindolin-1-one [4] CAS: 23967-95-5





N-(2,4-Dichlorobenzyl)-4-phenoxypiperidine-1-carboxamide CAS: 950645-62-2





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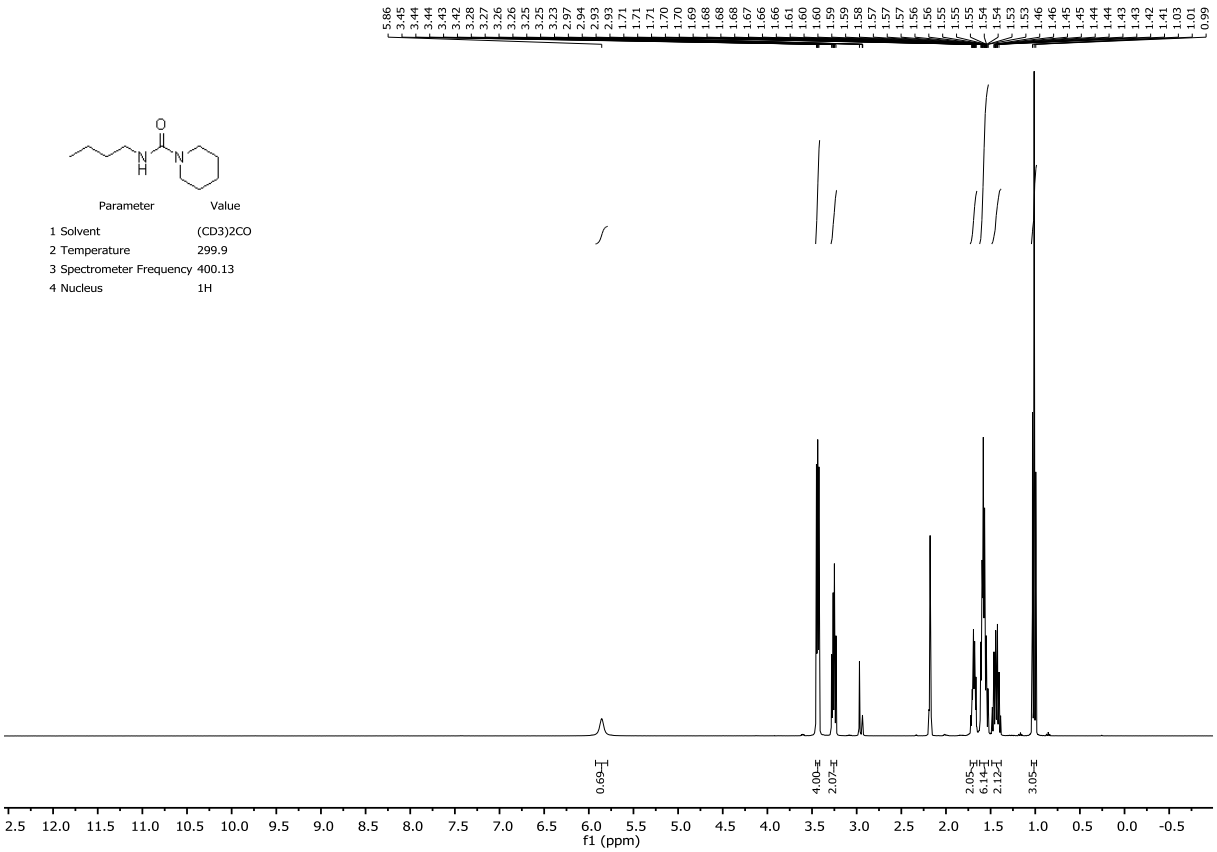

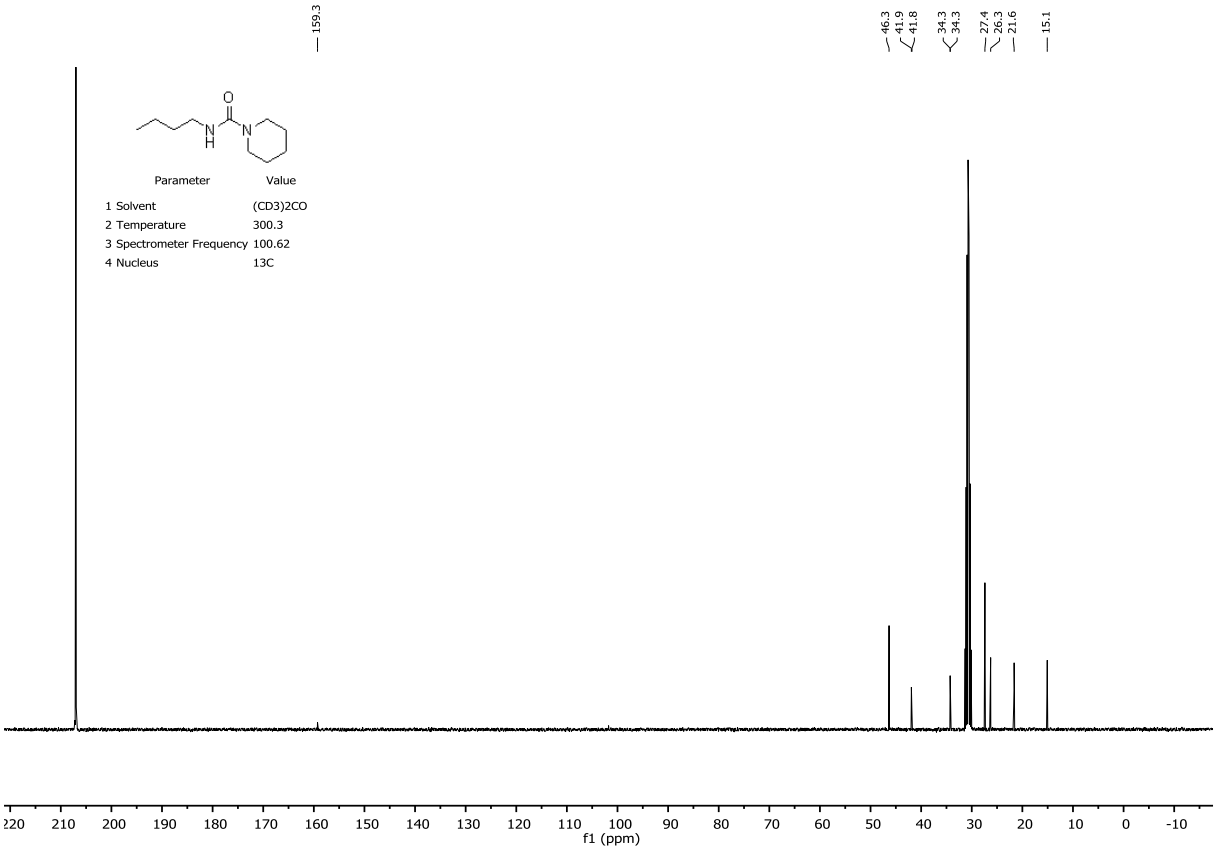

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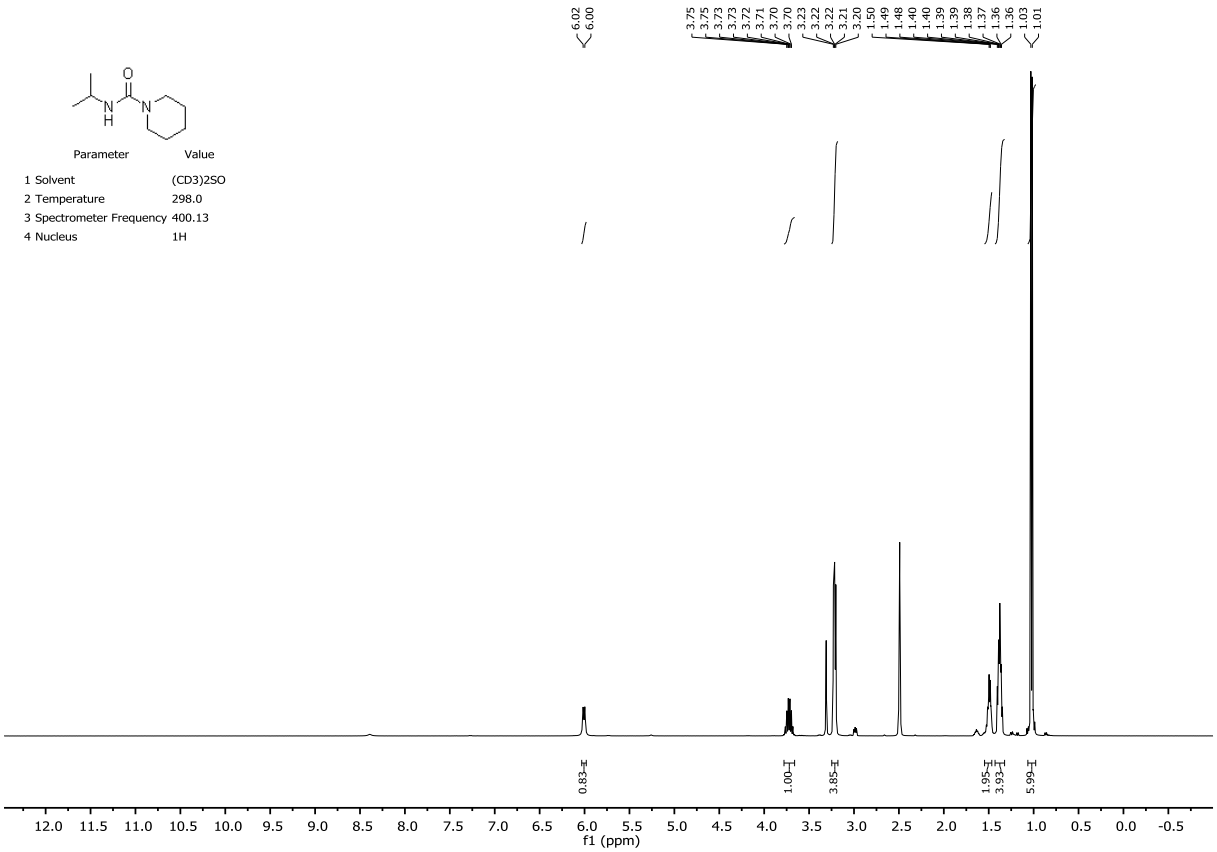

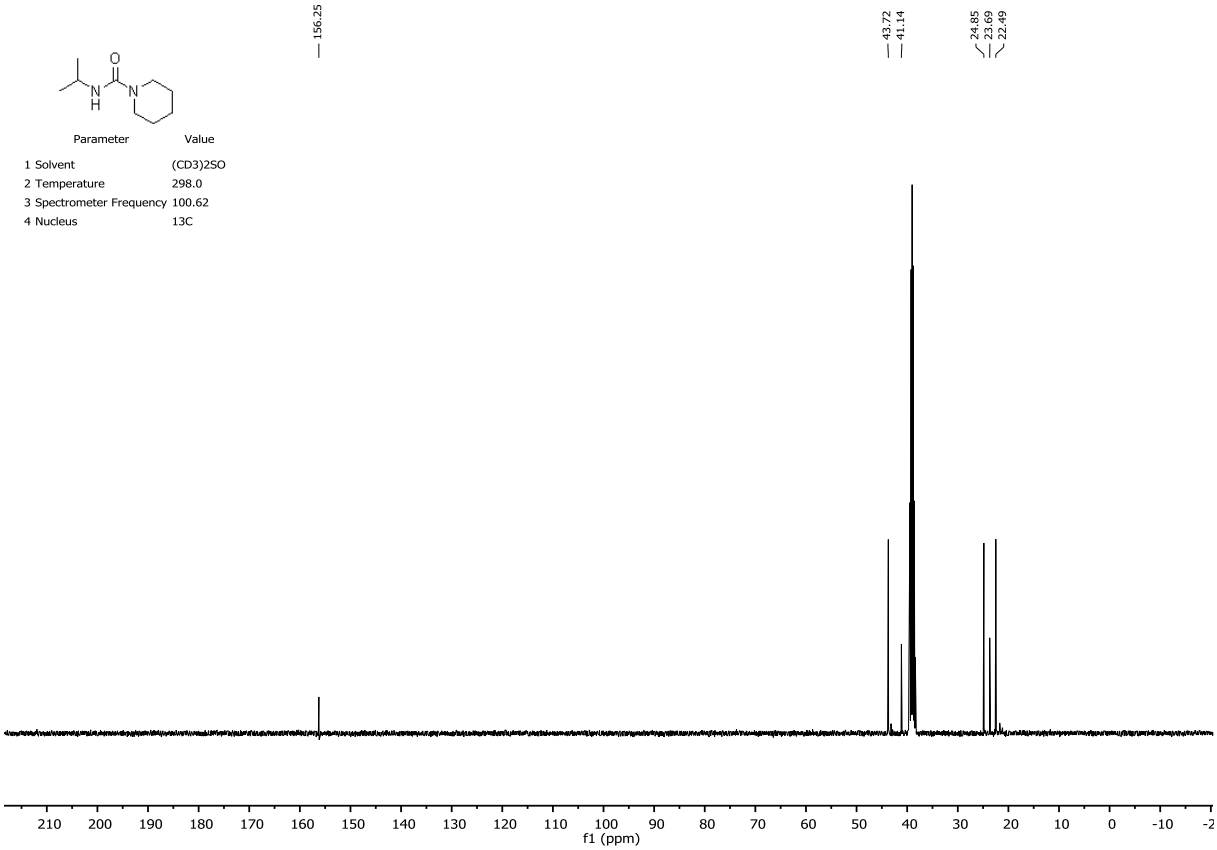

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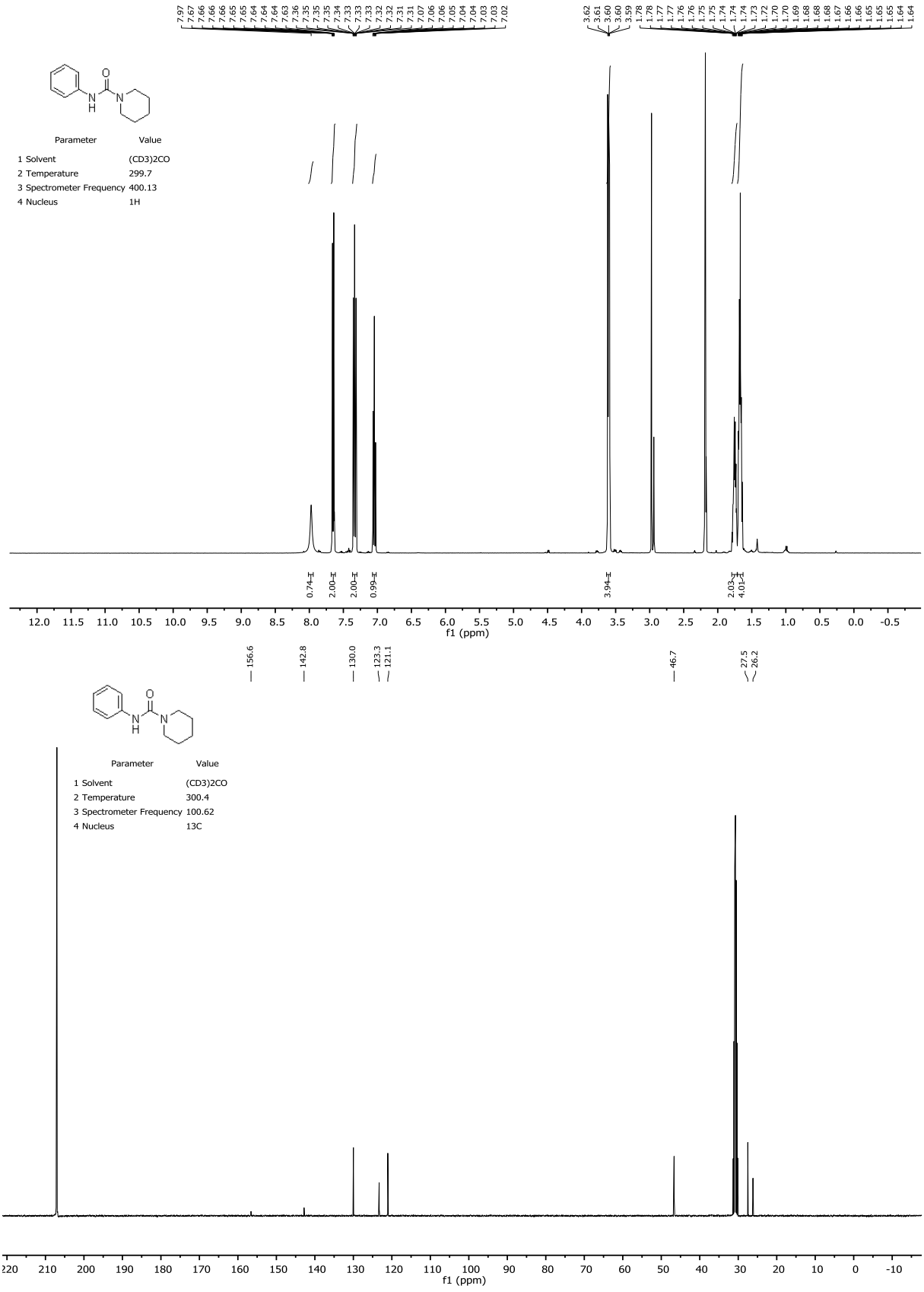
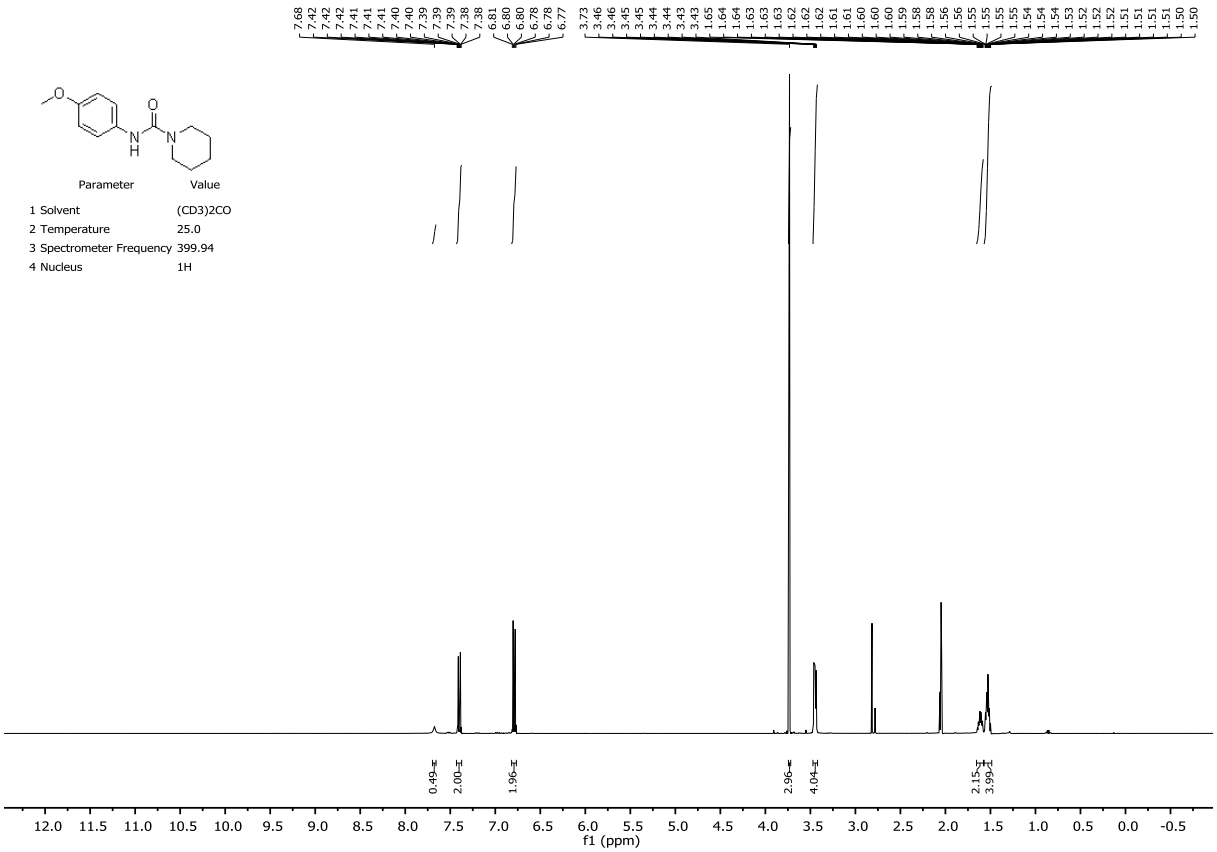
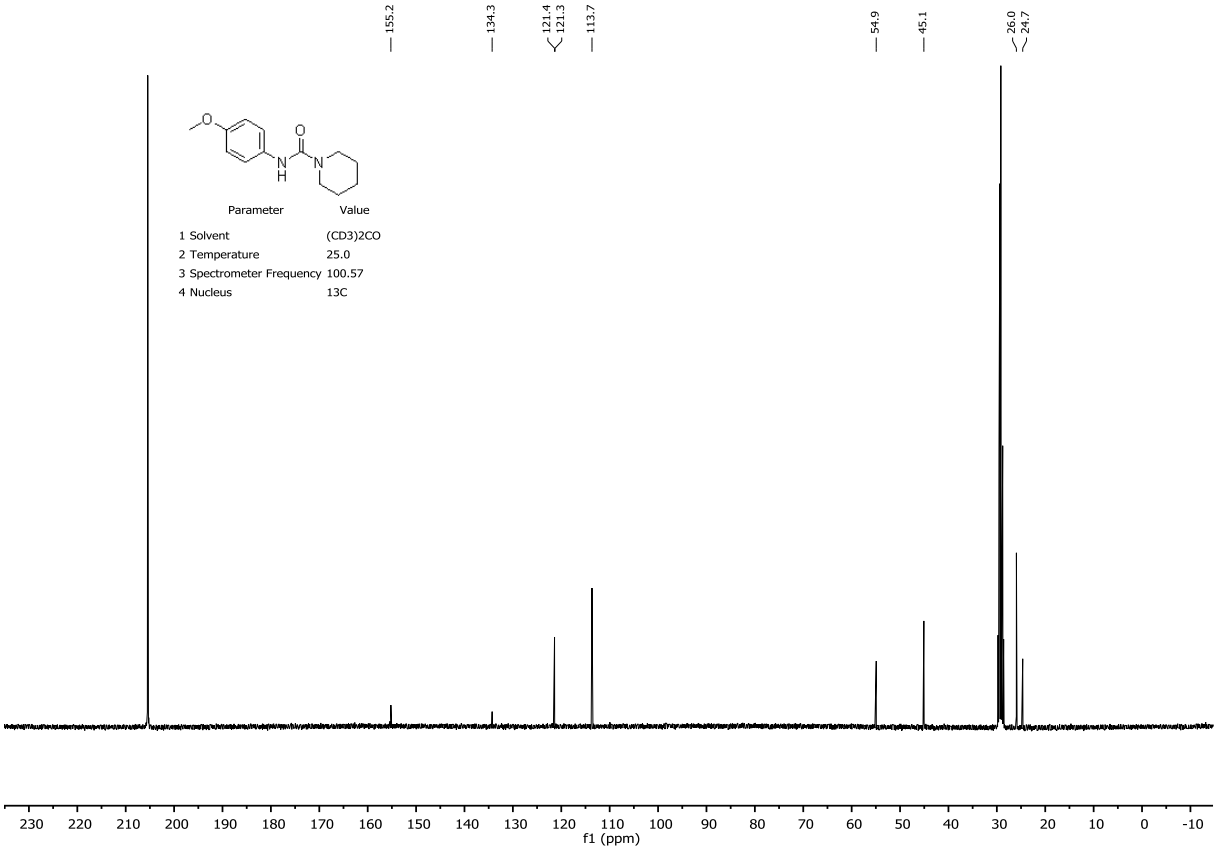


N-Phenylpiperidine-1-carboxamide [5] CAS: 2645-36-5





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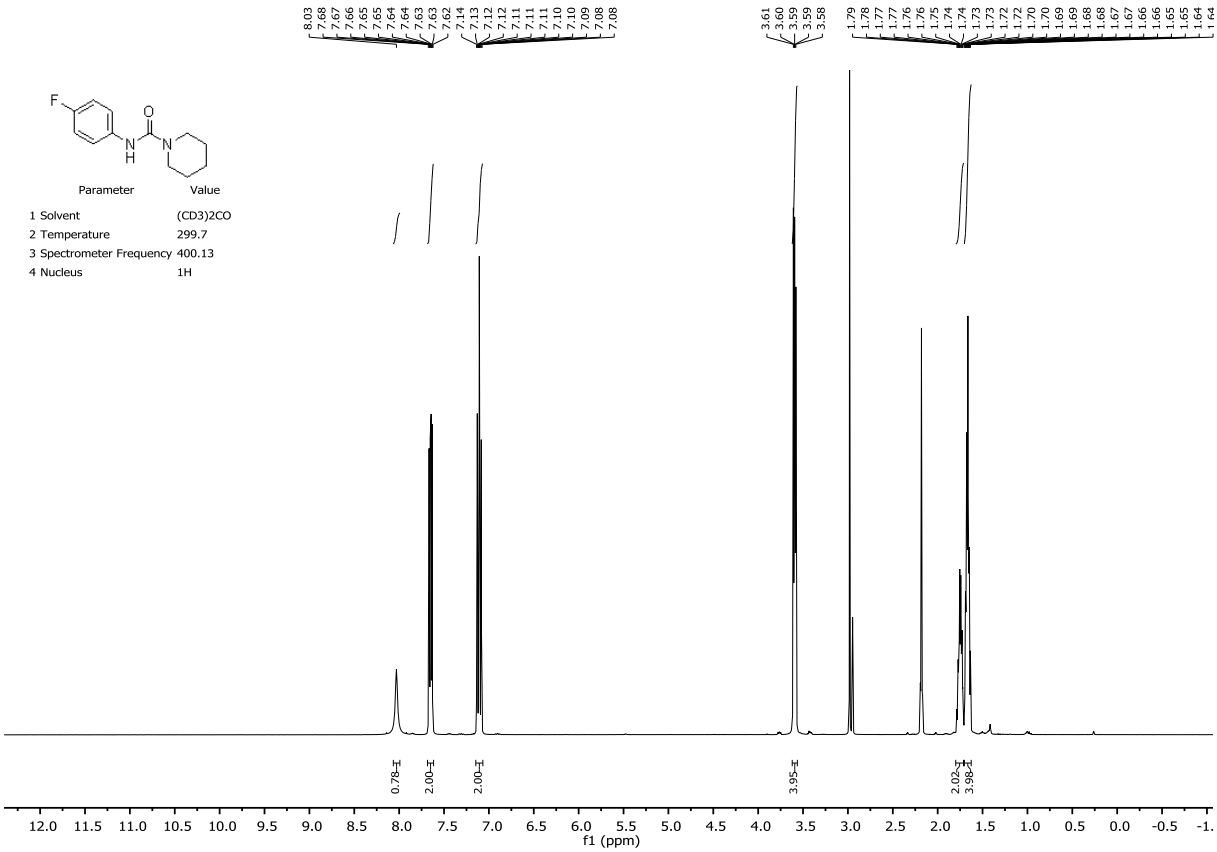

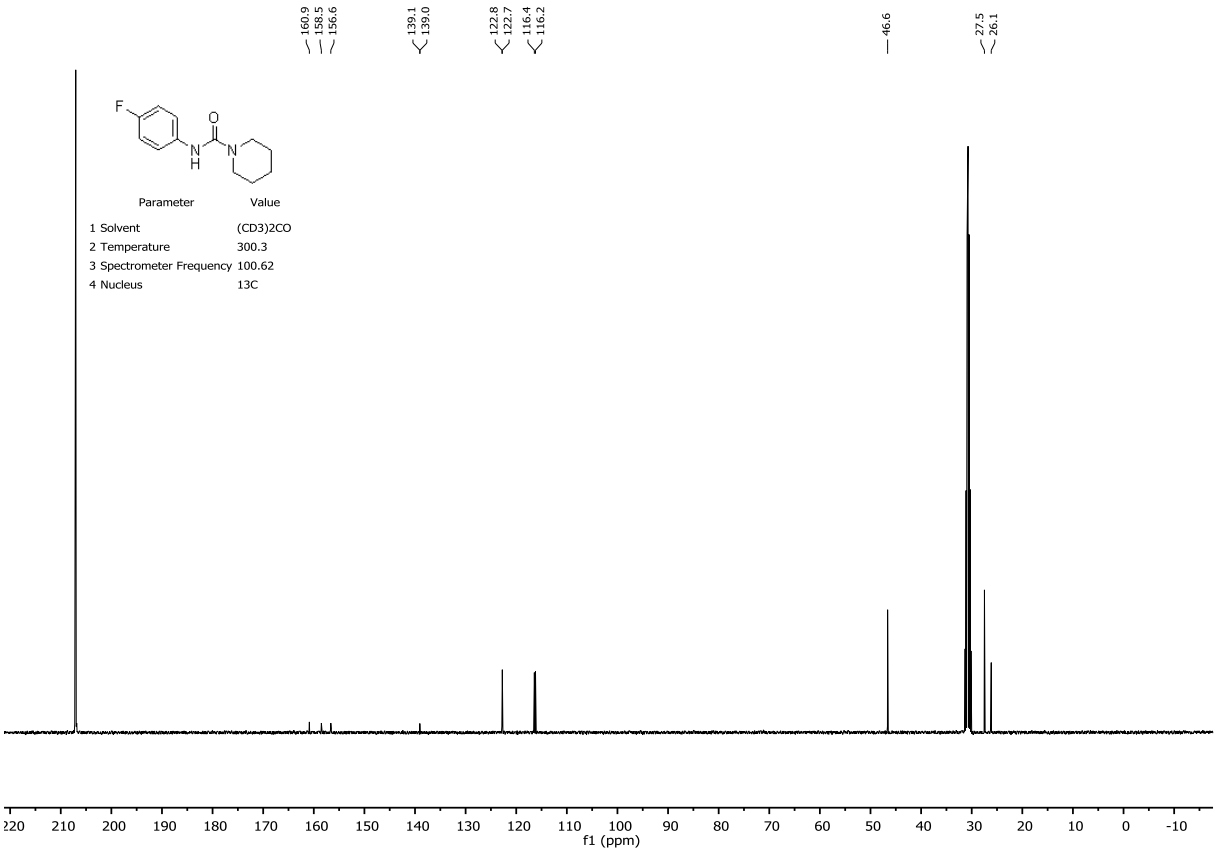

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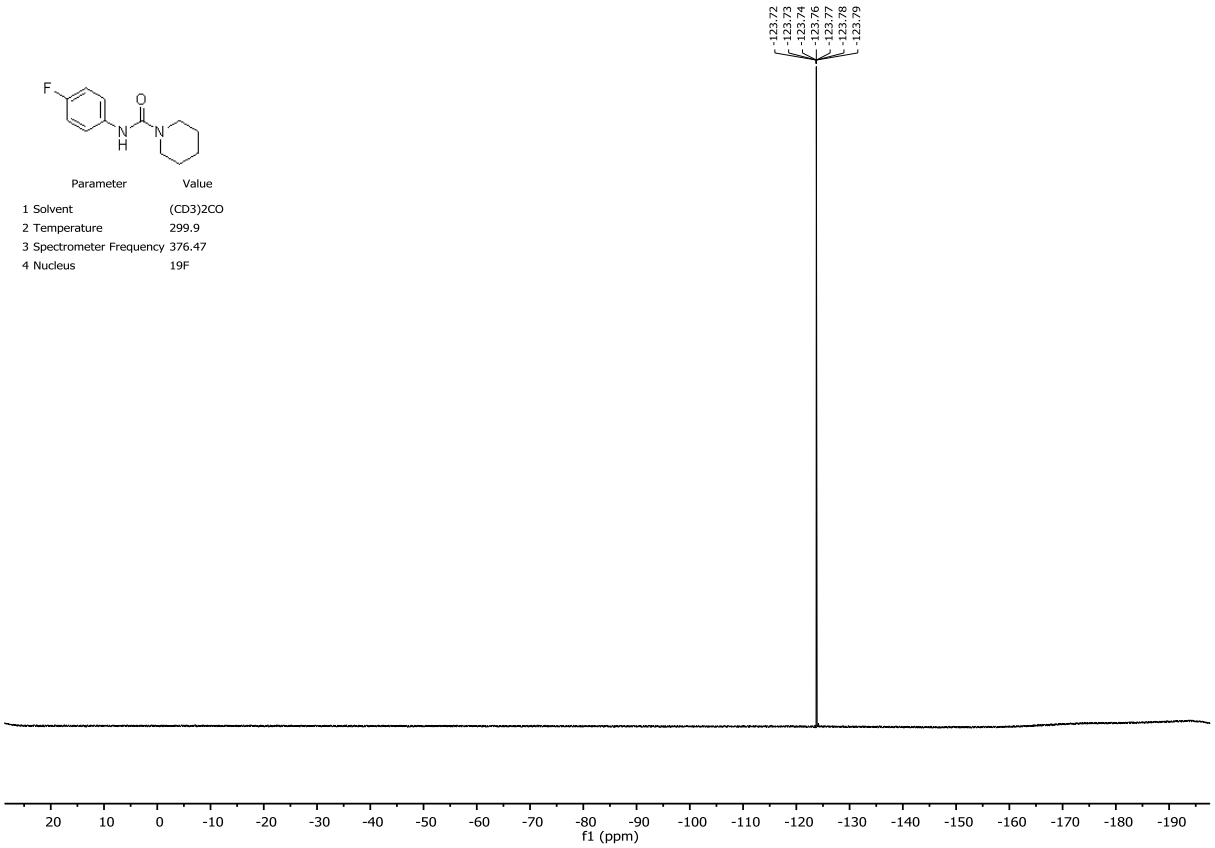

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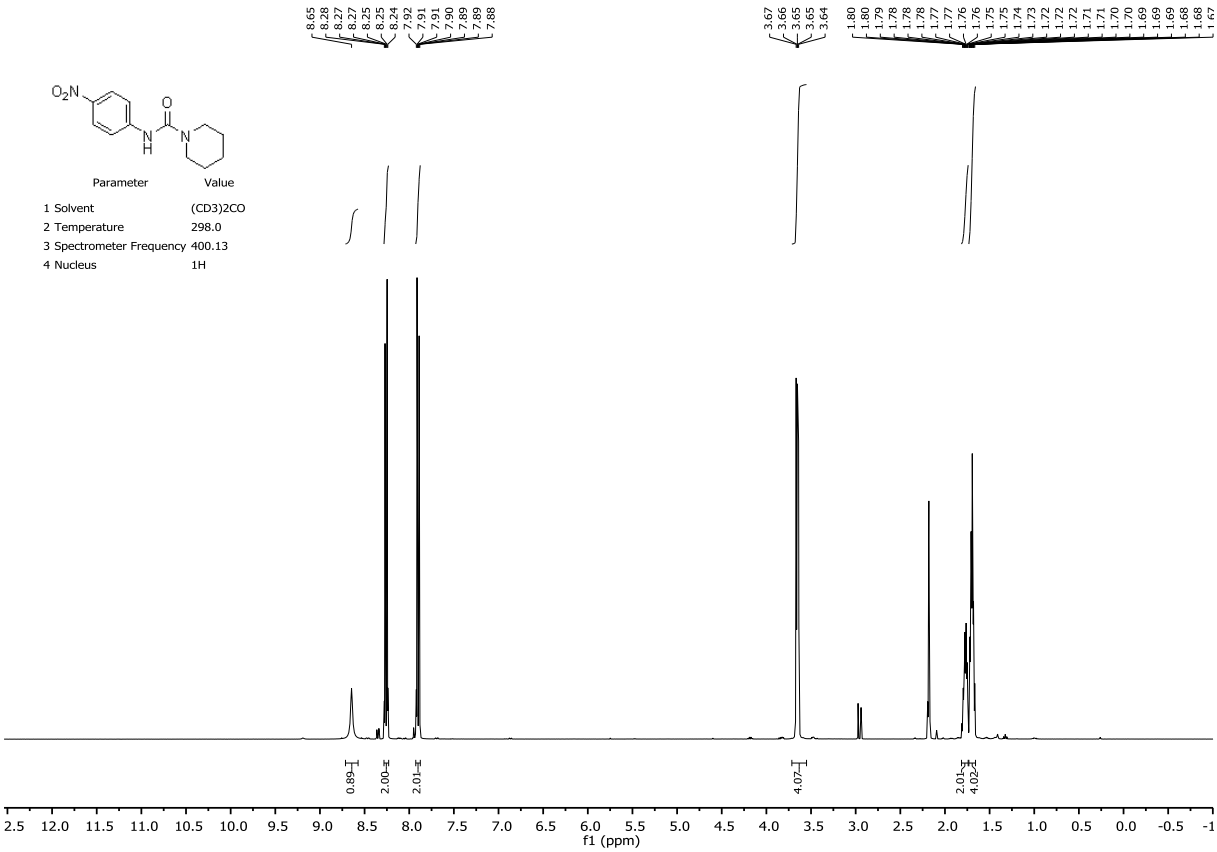

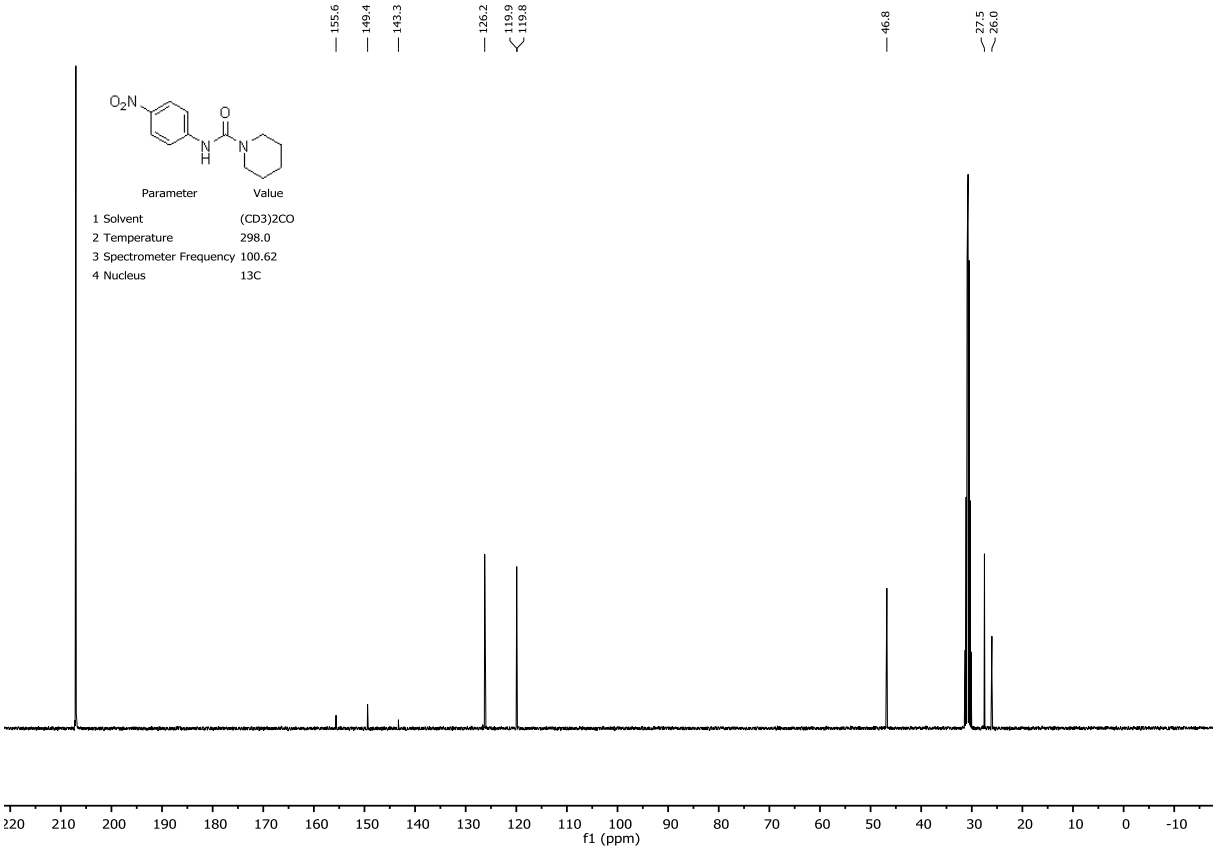

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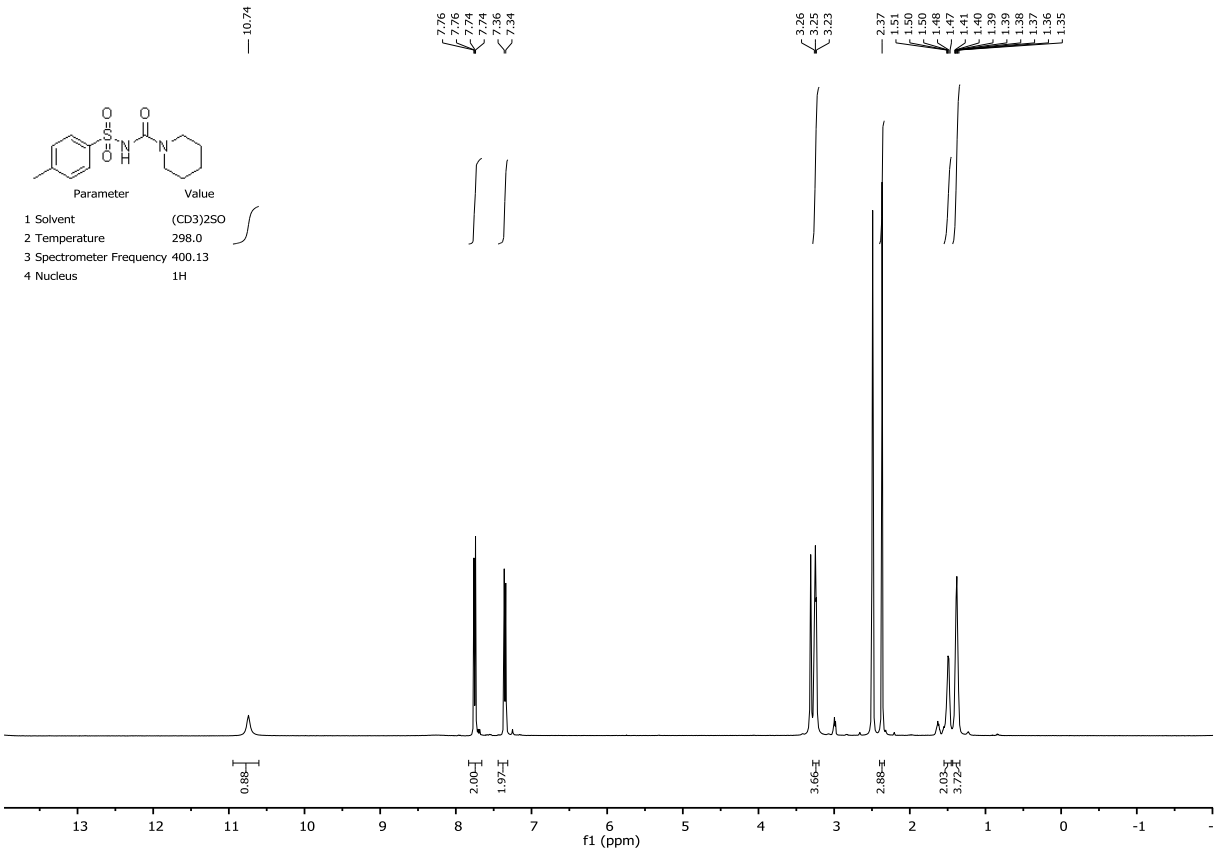
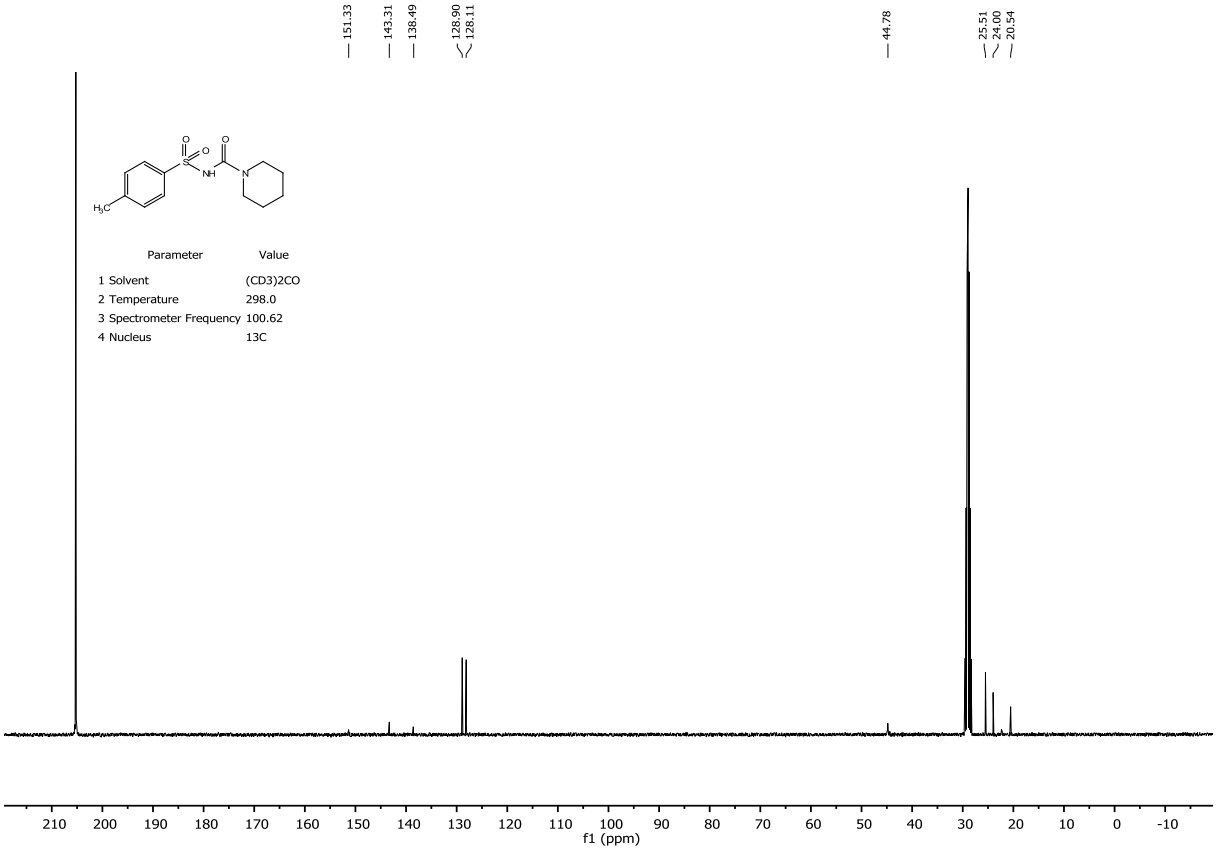
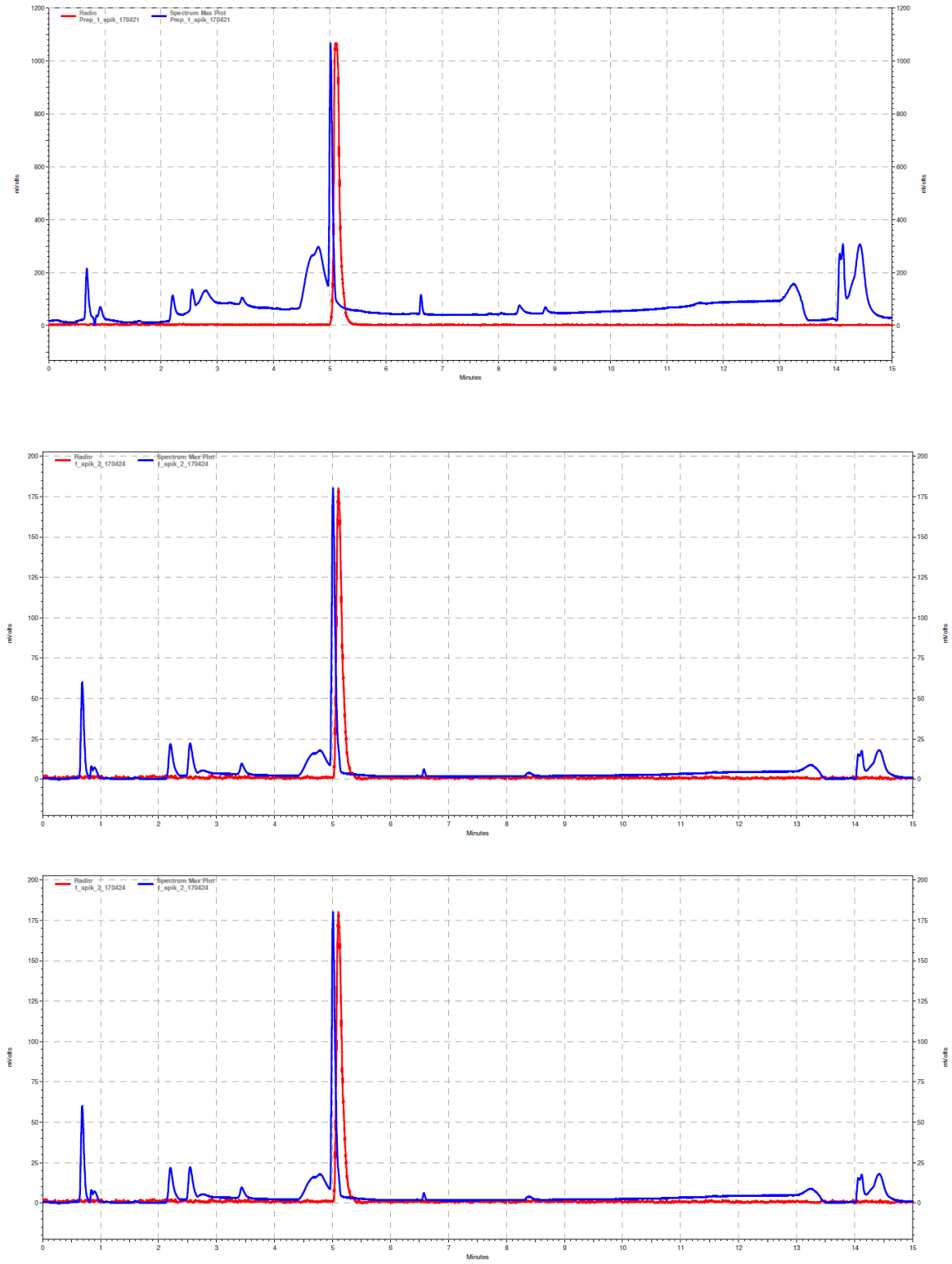




N-Tosylpiperidine-1-carboxamide CAS: 23730-08-7

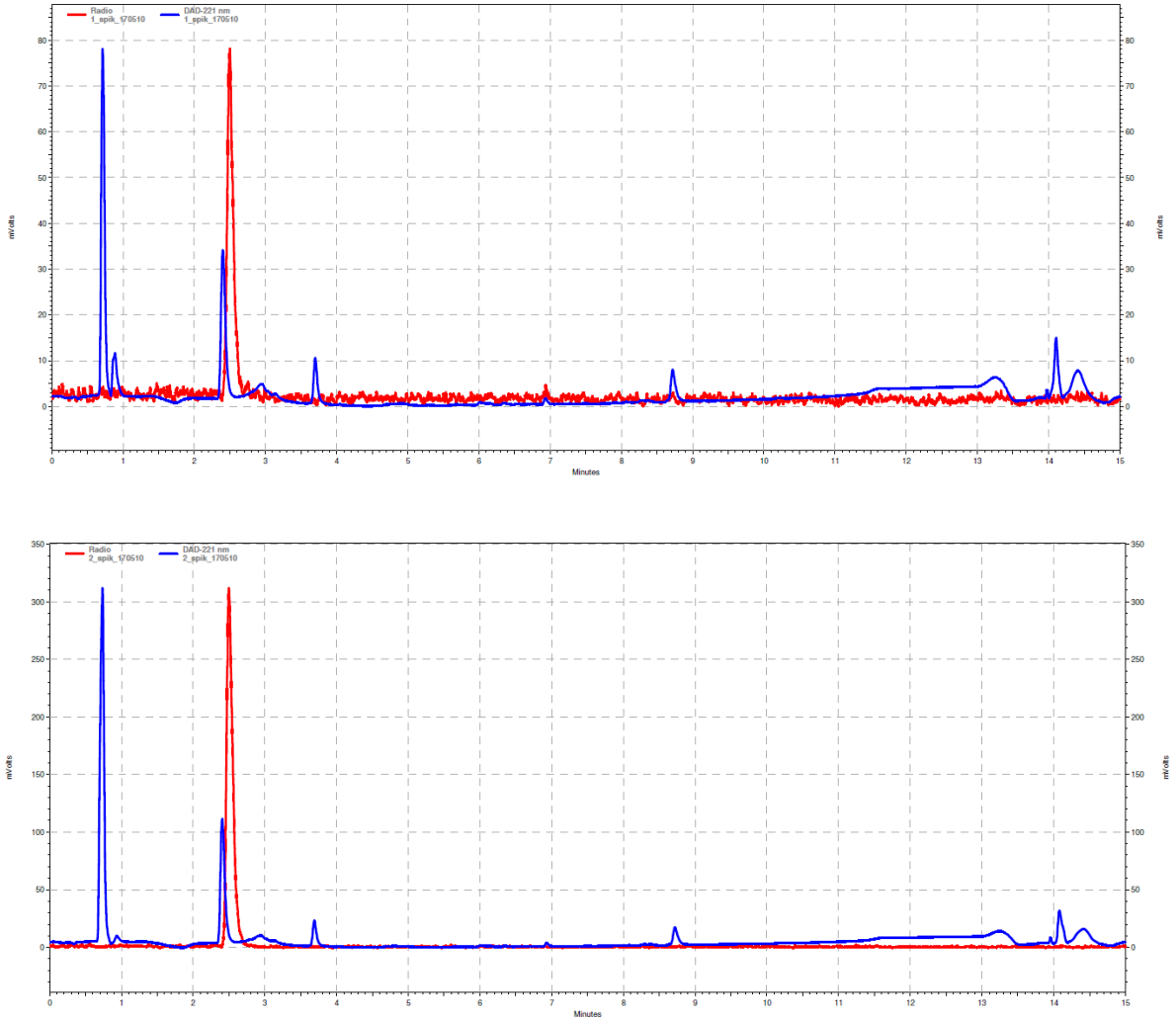
HPLC Chromatogram

[carbonyl-^{11}C]N,N-dibenzylurea **2**



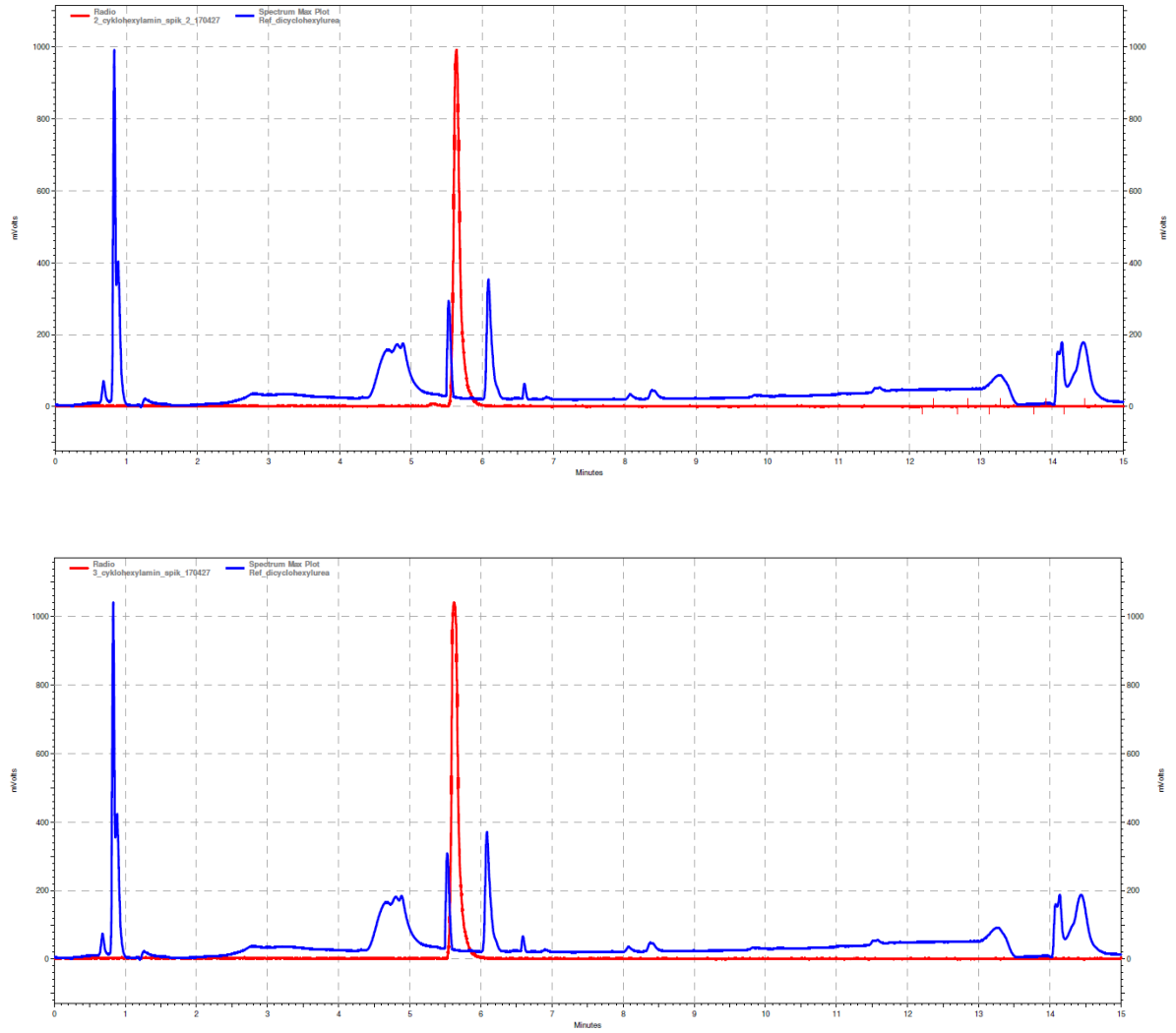
Analysis of isolated fraction containing isotopically unmodified *N,N*-dibenzylurea. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.

[carbonyl-^{11}C]N,N-dipropylurea ***3***



Analysis of isolated fraction containing isotopically unmodified *N,N*-dipropylurea. Top: experiment 1; Bottom: experiment 2.

[carbonyl-^{11}C]N,N-dicyclohexylurea ***4***



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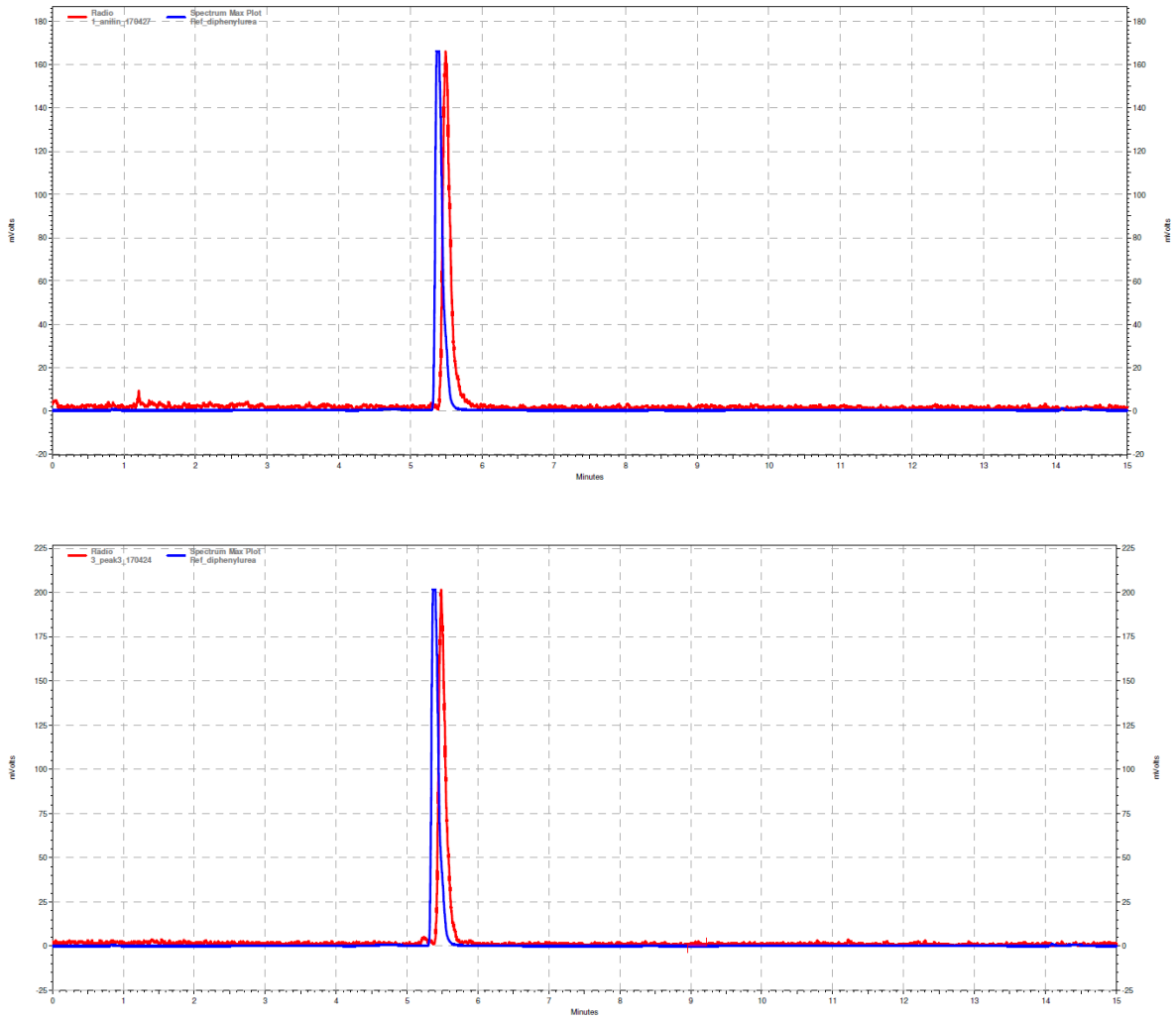
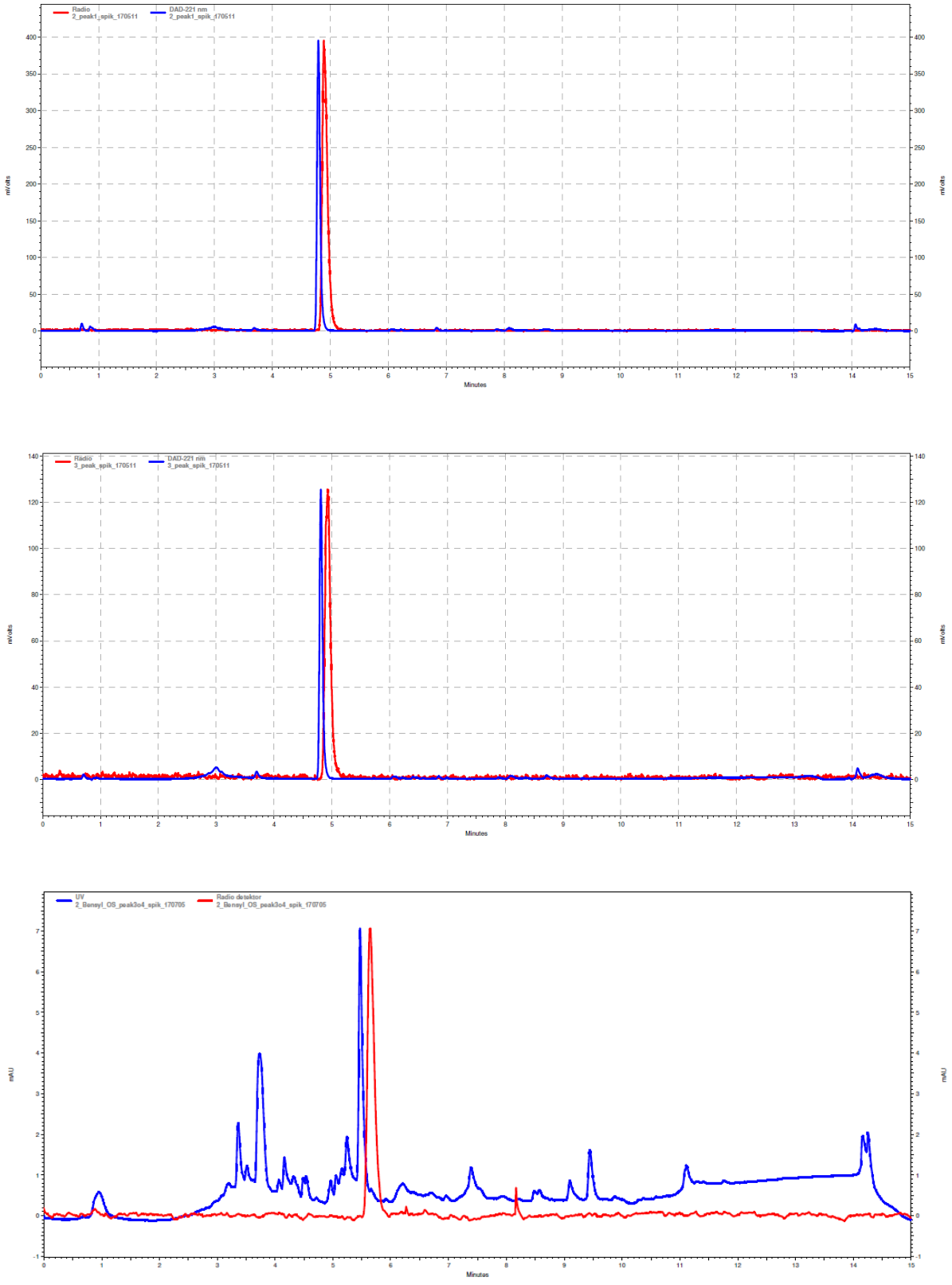
[carbonyl-^{11}C]N,N-diphenylurea ***5***

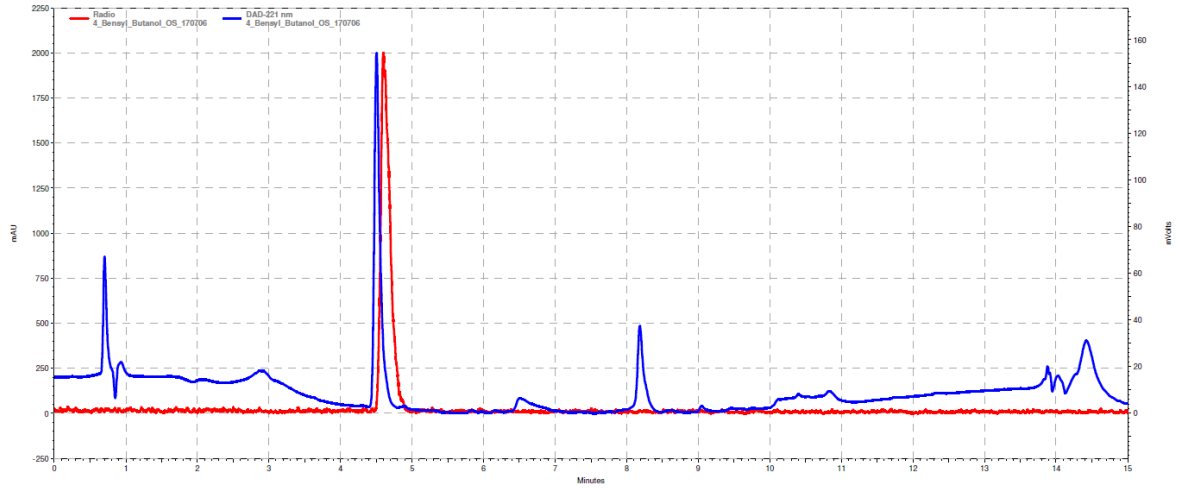


Analysis of isolated fraction containing isotopically unmodified *N,N*-diphenylurea. Top: experiment 1; Bottom: experiment 2.

[carbonyl-^{11}C]N-benzylpiperidine-1-carboxamide **7**

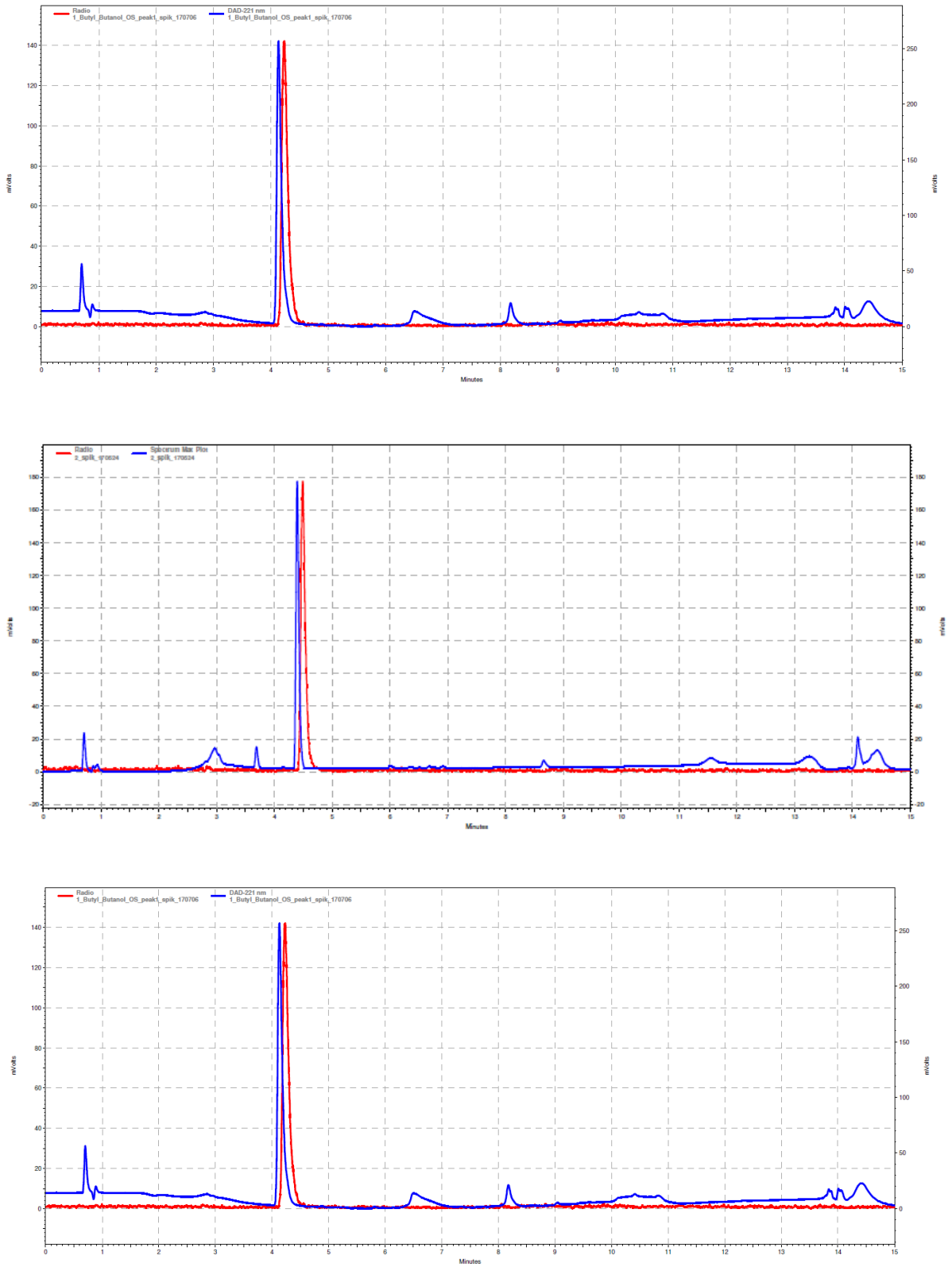


Analysis of isolated fraction containing isotopically unmodified *N*-benzylpiperidine-1-carboxamide. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.



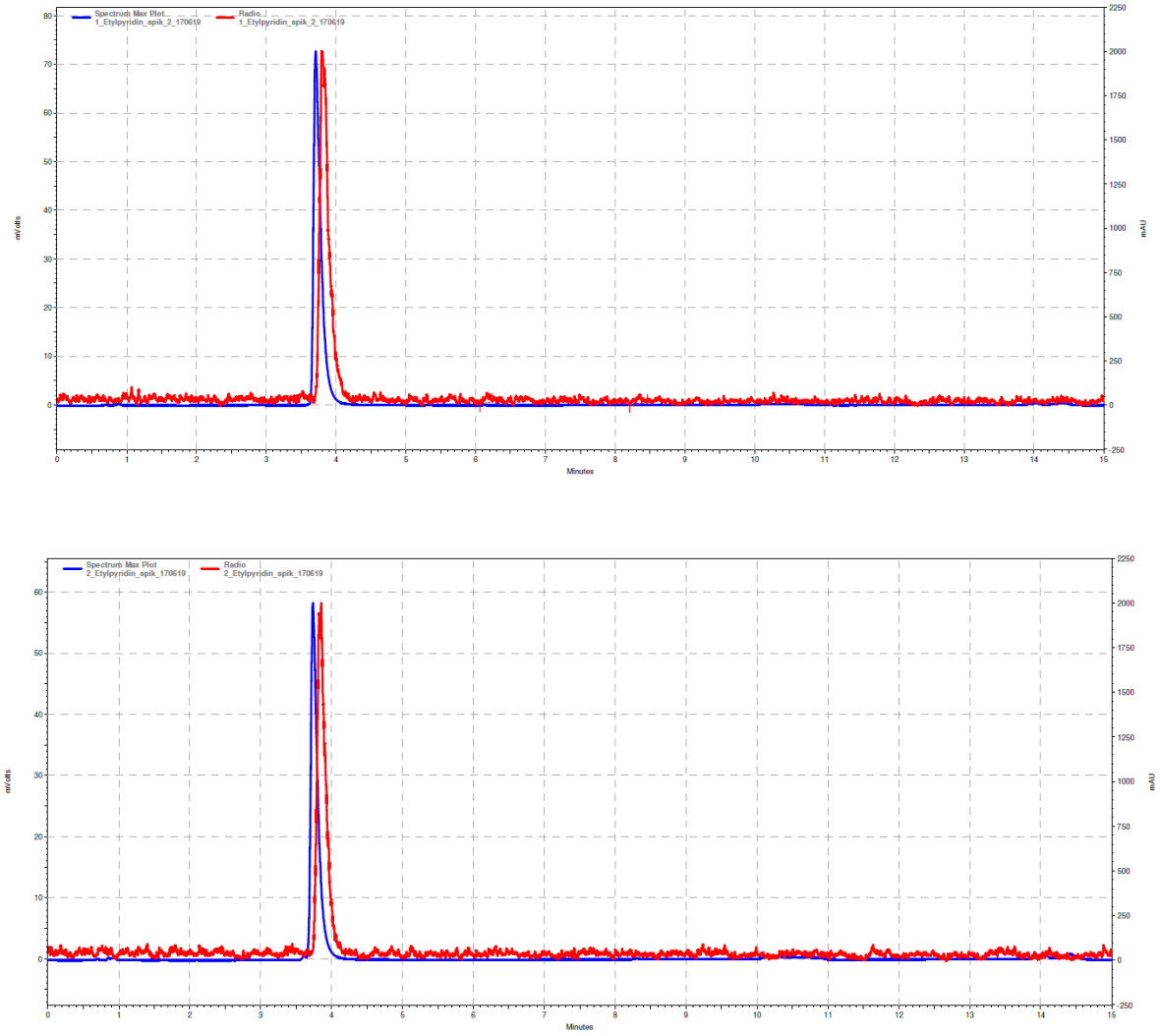
Analysis of isolated fraction containing isotopically unmodified *N*-benzylpiperidine-1-carboxamide. Bottom: experiment 4.

[carbonyl-^{11}C]N-butylpiperidine-1-carboxamide ***8***



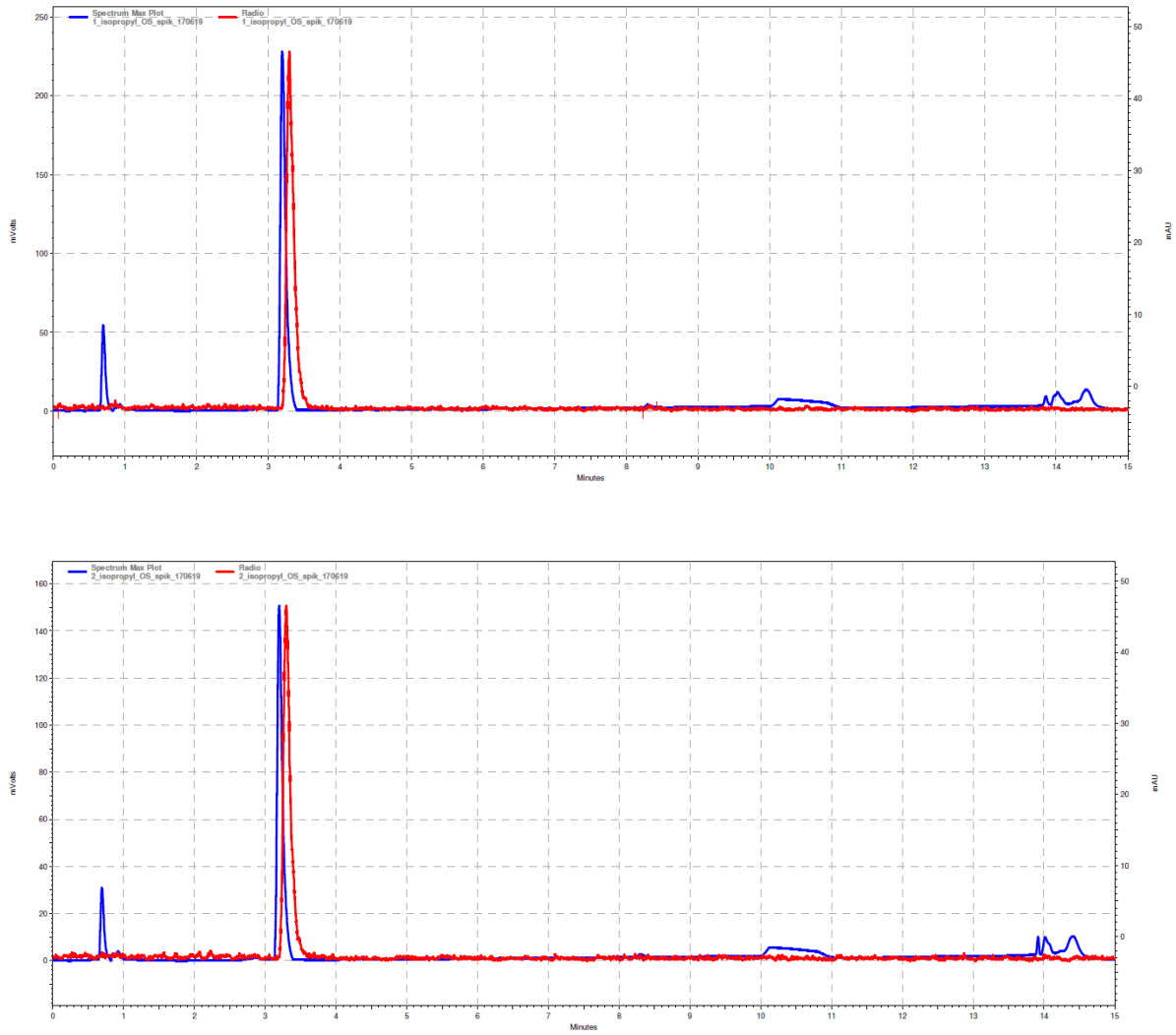
Analysis of isolated fraction containing isotopically unmodified *N*-butylpiperidine-1-carboxamide. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.

[carbonyl-^{11}C]N-(2-(pyridin-2-yl)ethyl)piperidine-1-carboxamide ***9***



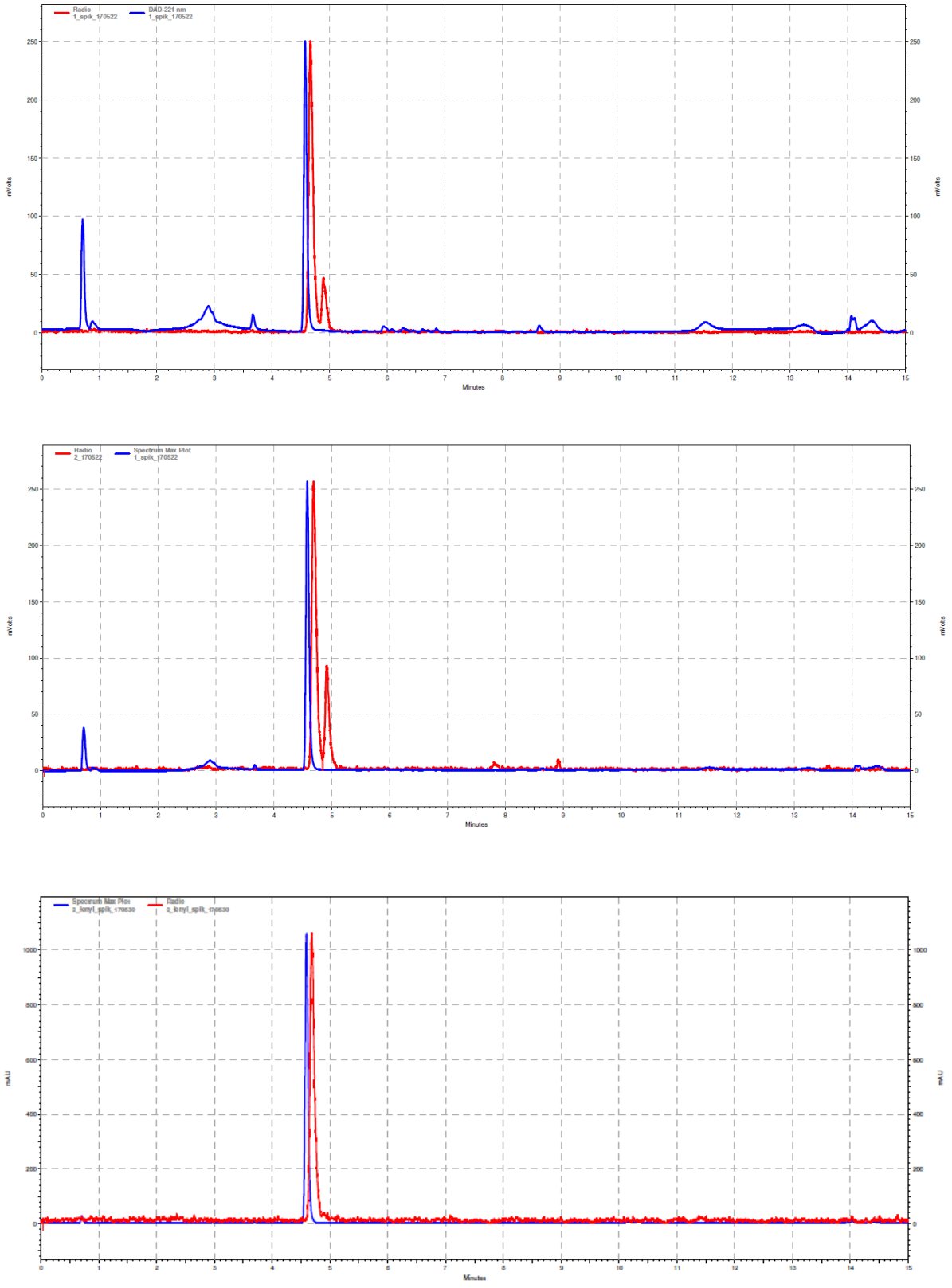
Analysis of isolated fraction containing isotopically unmodified *N*-(2-(pyridin-2-yl)ethyl)piperidine-1-carboxamide. Top: experiment 1; Bottom: experiment 2.

[carbonyl-^{11}C]N-isopropylpiperidine-1-carboxamide ***10***

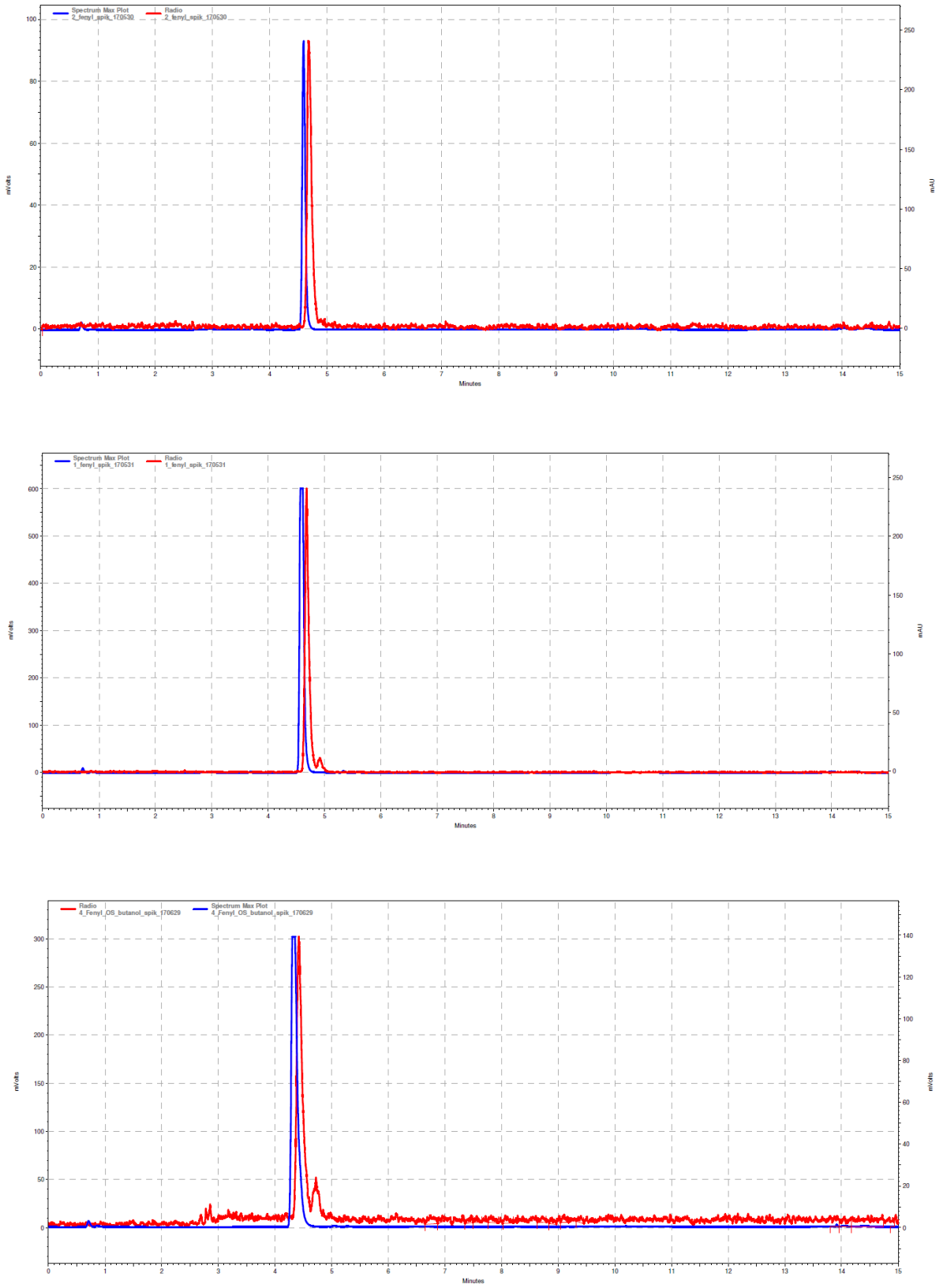


Analysis of isolated fraction containing isotopically unmodified *N*-isopropylpiperidine-1-carboxamide. Top: experiment 1; Bottom: experiment 2.

[carbonyl-^{11}C]N-phenylpiperidine-1-carboxamide ***11***

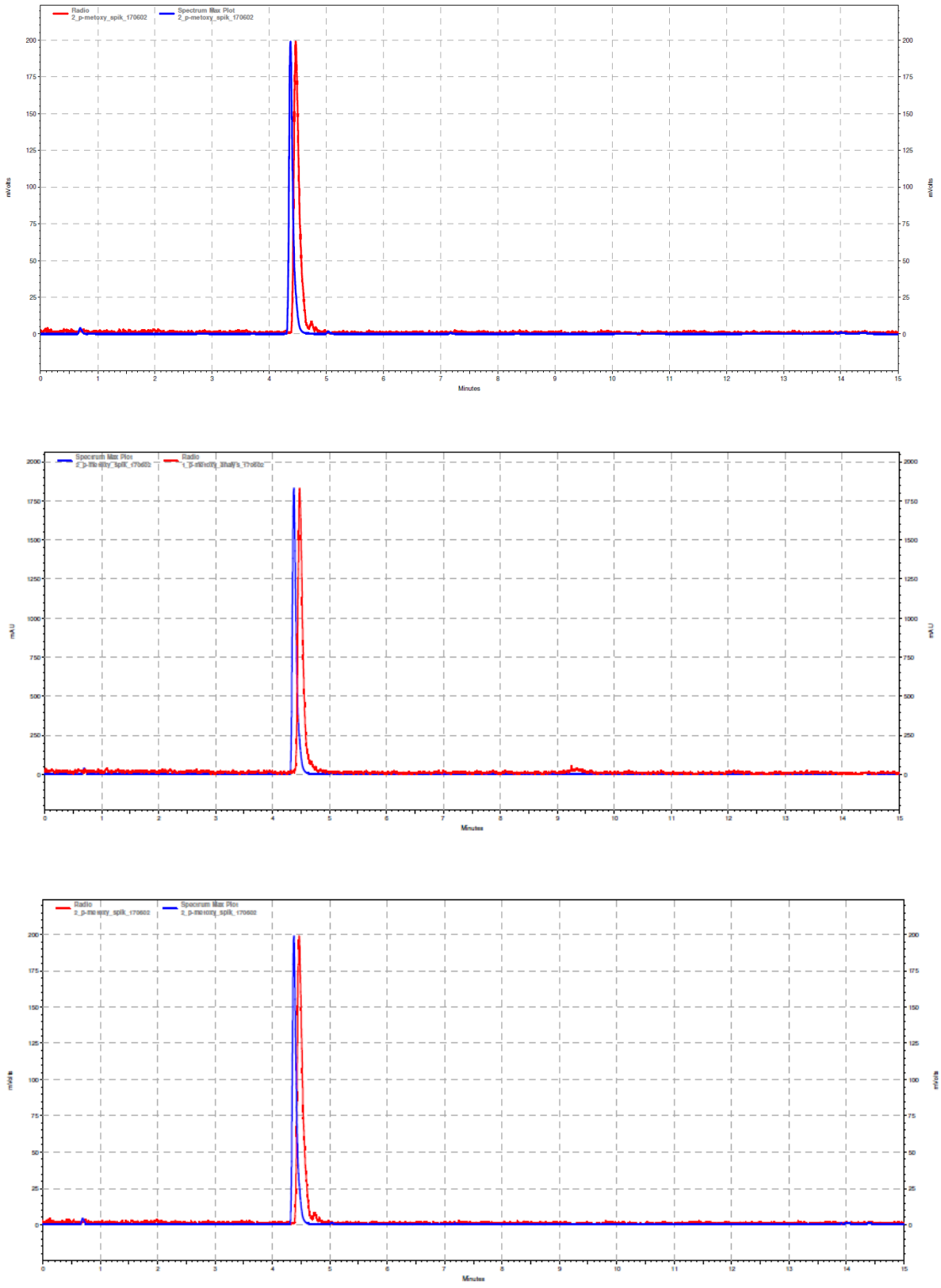


Analysis of isolated fraction containing isotopically unmodified *N*-phenylpiperidine-1-carboxamide. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.



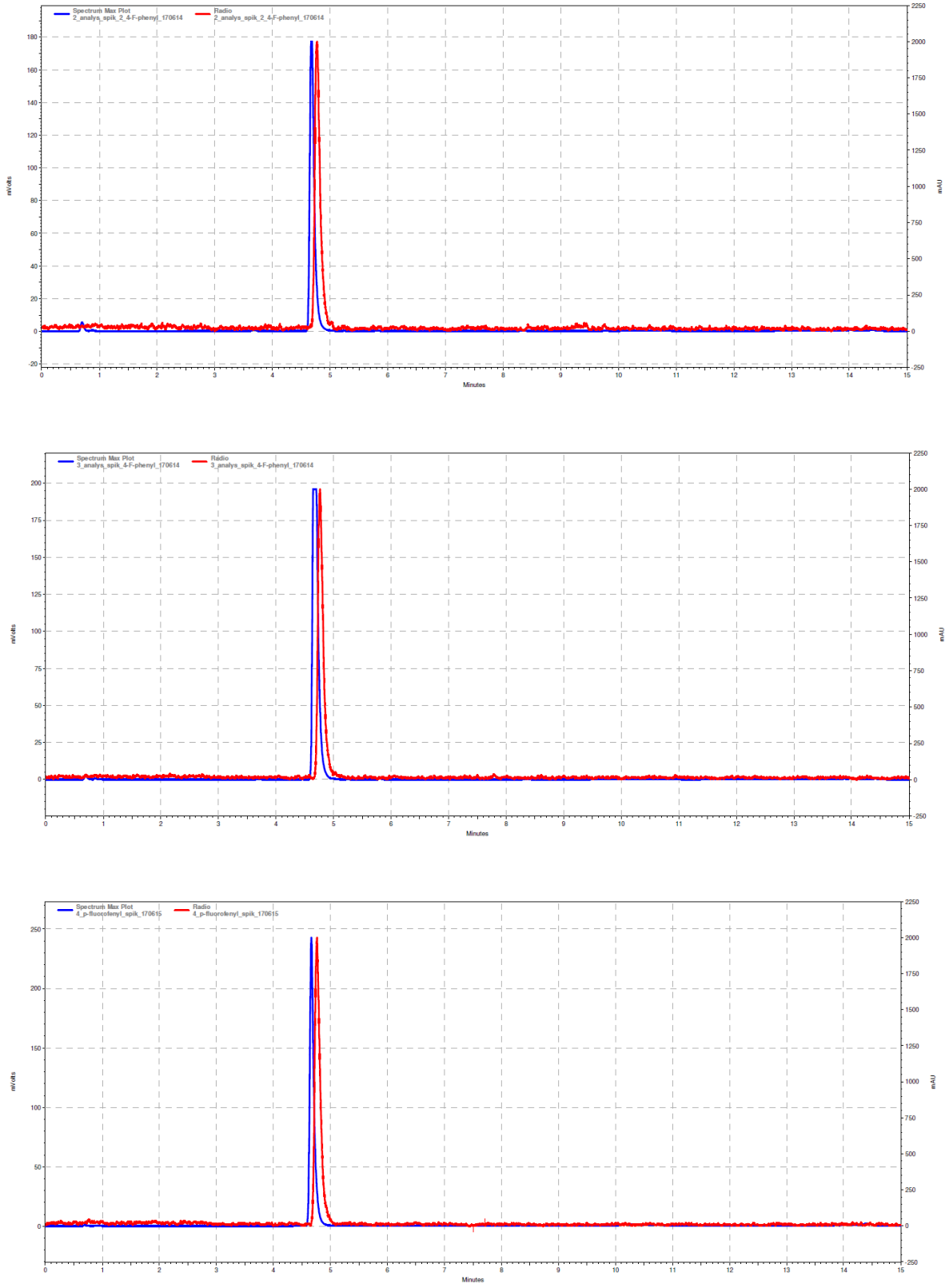
Analysis of isolated fraction containing isotopically unmodified *N*-phenylpiperidine-1-carboxamide. Top: experiment 4; Middle: experiment 5; Bottom: experiment 6.

[carbonyl-^{11}C]N-(4-methoxyphenyl)piperidine-1-carboxamide ***12***

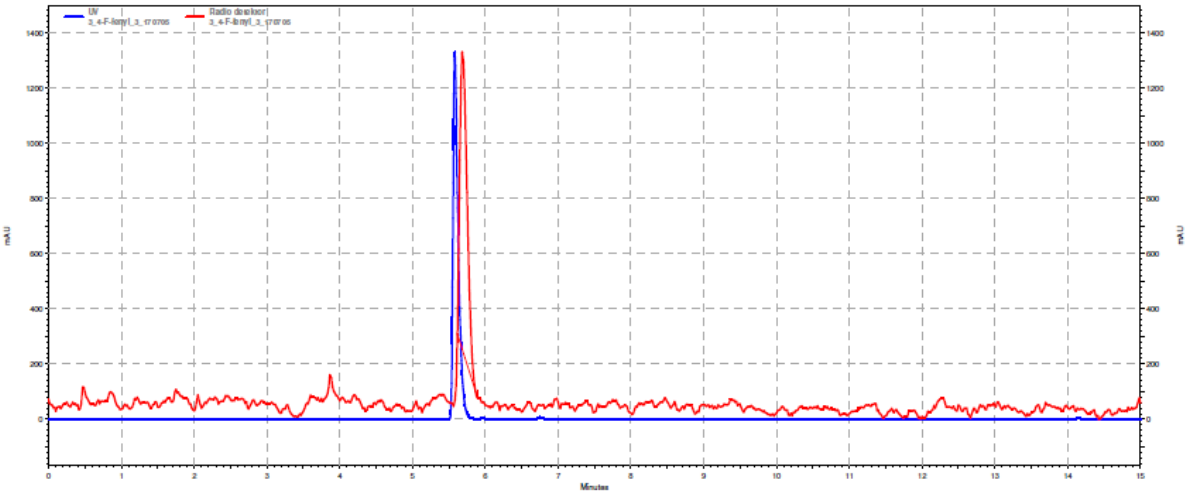


Analysis of isolated fraction containing isotopically unmodified *N*-(4-methoxyphenyl)piperidine-1-carboxamide. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.

[carbonyl-^{11}C]N-(4-fluorophenyl)piperidine-1-carboxamide ***13***

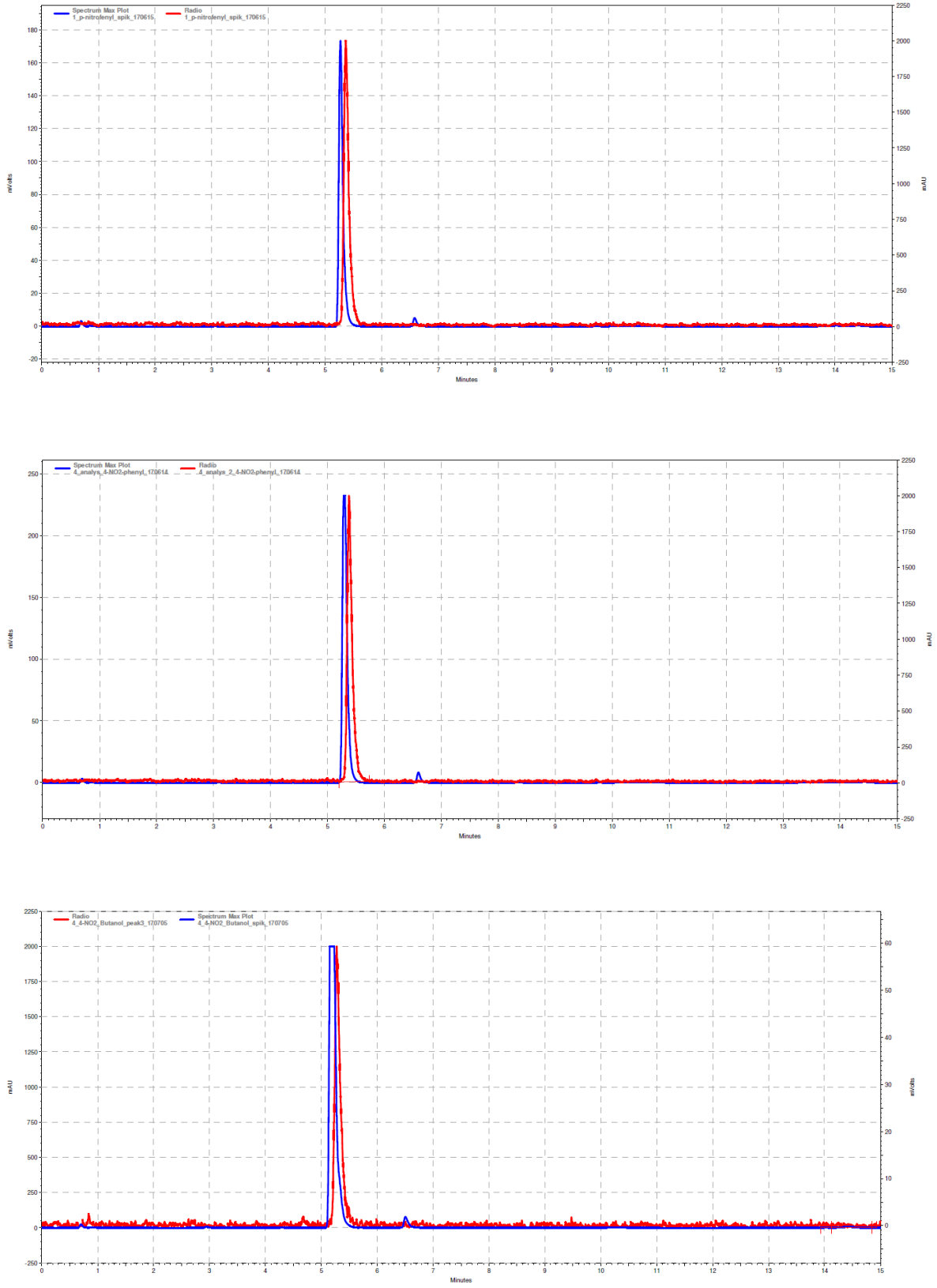


Analysis of isolated fraction containing isotopically unmodified *N*-(4-fluorophenyl)-piperidine-1-carboxamide. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.



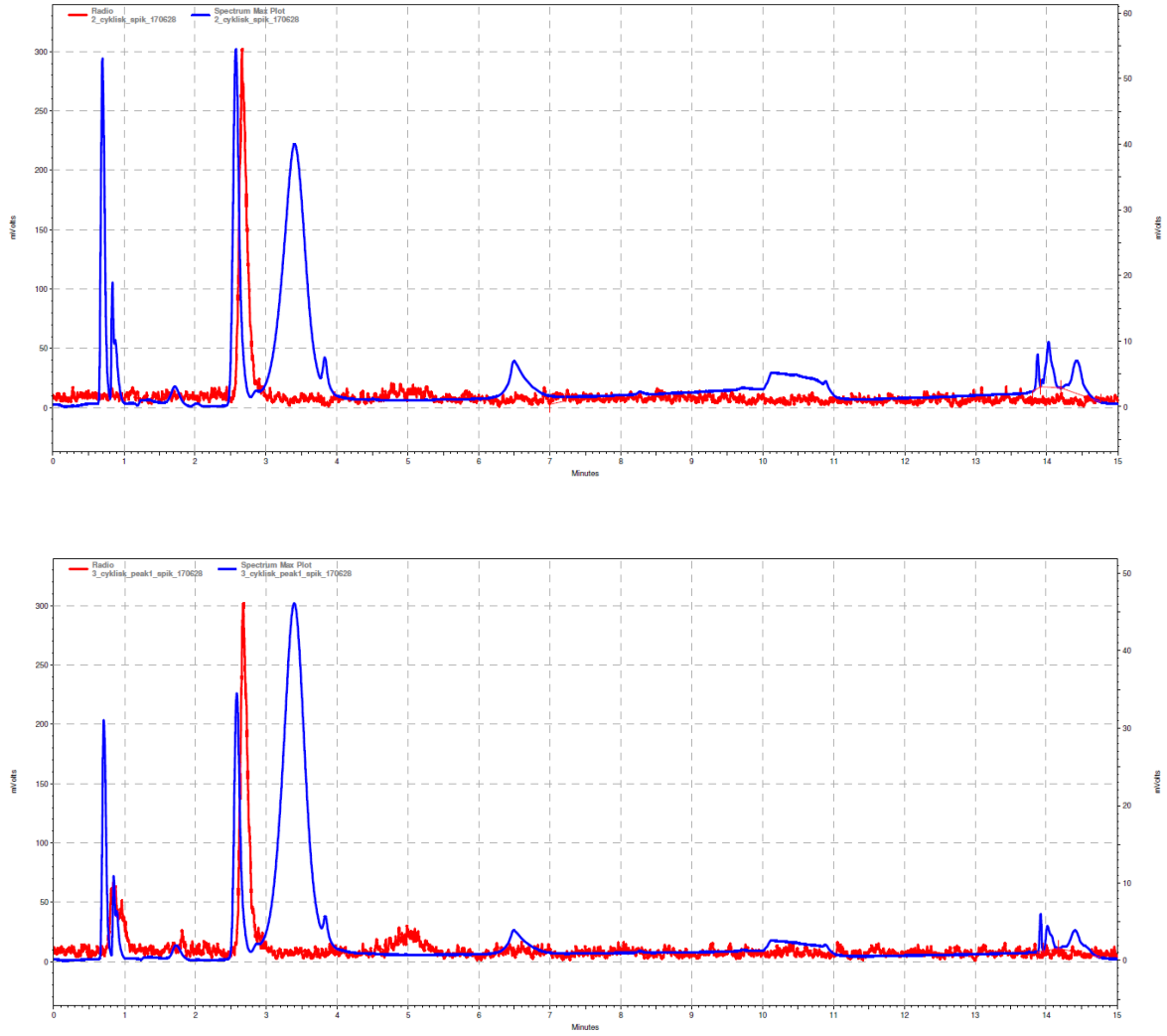
Analysis of isolated fraction containing isotopically unmodified *N*-(4-fluorophenyl)piperidine-1-carboxamide. Experiment 4.

[carbonyl-^{11}C]N-(4-nitrophenyl)piperidine-1-carboxamide ***14***



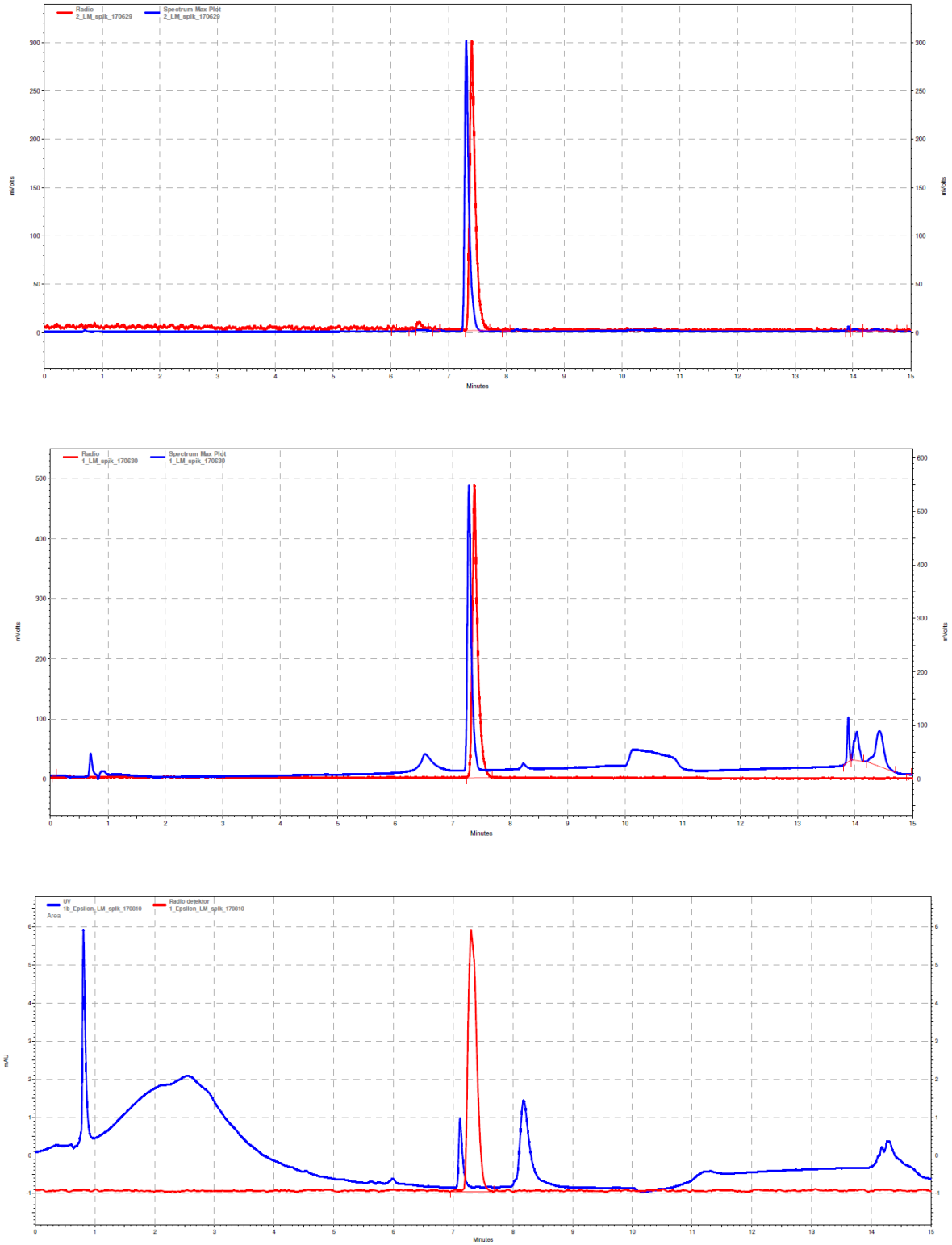
Analysis of isolated fraction containing isotopically unmodified *N*-(4-nitrophenyl)piperidine-1-carboxamide. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.

[carbonyl-^{11}C]3,4-dihydroquinazolin-2(1H)-one ***15***



Analysis of isolated fraction containing isotopically unmodified 3,4-dihydroquinazolin-2(1H)-one. Top: experiment 1; Bottom: experiment 2.

[carbonyl-^{11}C]N-(2,4-dichlorobenzyl)-4-phenoxypiperidine-1-carboxamide ***19***



Analysis of isolated fraction containing isotopically unmodified *N*-(2,4-dichlorobenzyl)-4-phenoxypiperidine-1-carboxamide. Top: experiment 1; Middle: experiment 2; Bottom: experiment 3.

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