Supporting information

Catalytic Utilization of Converter Gas – An industrial Waste for the Synthesis of Pharmaceuticals

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General information

Unless otherwise stated, all substrates and reagents were purchased from commercial suppliers and used without further purification. THF was distilled over sodium/benzophenone. Rh and Ru precursors (>99% purity) were purchased in Shanghai Aopudishi Chemical Technology Co.,Ltd.

^{1}H spectra were recorded in $CDCl_3$, DMSO-d_6 and D_2O on Bruker Avance 300 and Bruker Avance 400 and Varian Inova-400 spectrometers. ^{13}C spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker Avance 400 and Varian Inova-400 spectrometers at 101 MHz or on Bruker Avance 300 at 75 MHz. Chemical shifts are reported in parts per million relative to $CHCl_3$ (7.26 and 77.16 ppm for ^{1}H and ^{13}C respectively) or DMSO (2.50 and 39.52 ppm for ^{1}H and ^{13}C respectively). Chemical shifts δ are reported in ppm relative to the solvents resonance signal as an internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad; coupling constants are given in Hertz (Hz).

High-resolution mass spectra (HRMS) were obtained from a Bruker Daltonics micrOTOF-Q II hybrid quadrupole time-of-flight mass spectrometer using electrospray ionization (ESI) and measurements were done in positive ion mode. The voltage on the capillary was 4500 V; range of scanned masses, m/z 50-3000; external calibration (Electrospray Calibrant Solution; Fluka, Germany); nebulizer pressure: 0.4 bar; flow rate: 3 μl/min; nitrogen as dry gas (6 l/min); interface temperature: 180 °C.

Analytical gas chromatography (GC) was performed using a Chromatec Crystal 5000.2 Gas Chromatograph fitted with a flame ionization detector (He was used as the carrier gas, 37 mL/min) and MS detector. Injections were made on a Chromatec CR-5 and Chromatec CR-5MS (30 meters) capillary column.

GC settings for the qualitative analysis using MS detector: Column CR5-MS. The injector temperature 250 °C, the FID temperature 250°C, transfer line temperature 230°C, ion source temperature 200°C,. Split ratio 75:1 at the moment of injection. Temperature program. 60°C for 4 min, 60°C → 250°C at 30°C/min, 250°C for 12 min. Flow rate 1 mL/min. Retention times (t_R) and integrated ratios were obtained using Chromatec Analytic Software.

All catalytic reactions were carried out using 10 mL or 100 mL autoclaves. Reactions were carried out either in glass vials by placing them into the stainless-steel autoclave or directly in the titanium autoclave. For the reactions directly in an autoclave, the blank experiments were performed without the catalyst to confirm that no unspecific reactions occurred.

Preparation of converter gas: The converter gas was prepared in a 40-liter gas cylinder at room temperature. The gas cylinder was filled with 29 bar of carbon monoxide, followed by 10 bar of carbon dioxide and 11 bar of nitrogen. Industrial converter gas could contain different admixtures including sulfur-containing products, so we carried out additional test with addition of thiophene to the reaction mixture. In did not influence the results (see table S7).

General procedure for a 10 mL autoclaves

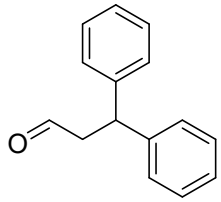
A glass vial in a 10 mL stainless steel or titanium autoclave was charged with the catalyst, the corresponding solvent and reactants. The autoclave was sealed, flushed three times with 10 atmosphere of converter gas, and then charged with the indicated pressure of converter gas. The reactor was placed into a preheated oil bath. After the indicated time, the reactor was cooled to the room temperature and depressurized. Its content was analyzed using NMR or GC, and the product was isolated using chromatography (preparative TLC, column chromatography on silica gel or using flash chromatograph InterChim PuriFlash).

General procedure for catalytic reactions in a bolted-closure 100 mL Parr autoclave

A glass vial was charged with the catalyst, the corresponding solvent, reactants and magnetic stir bar. The vial was placed in a 100 mL stainless steel, bolted-closure autoclave with a removable top section fitted with an inlet and outlet needle valves, thermocouple and a pressure gauge. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with the indicated pressure of converter gas. The autoclave was placed on a hot plate and reaction was allowed to progress for a desired time under stirred condition. After the indicated time, the autoclave was cooled to the room temperature and depressurized. The residue was purified using flash chromatograph InterChim PuriFlash.

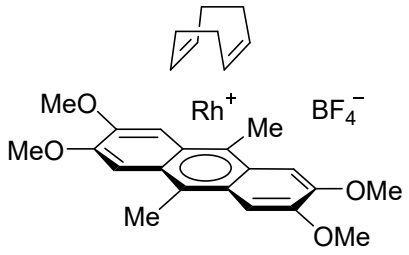
Synthesis of starting materials

3,3-diphenylpropanal



3,3-diphenylpropanal was synthesized according to the literature procedure [1] To a Schlenk tube, phenylboronic acid (366 mg, 3.0 mmol), cynnamaldehyde (126 μL, 1.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), bipyridine (31.2 mg, 0.20 mmol), HOAc (1 mL), THF (0.5 mL), and H_2O (0.3 mL) were added under argon. The mixture was stirred and heated at 40 °C for 3 days. The reaction mixture was neutralized with saturated $NaHCO_3$ and then extracted with Et_2O. The combined ether solution was dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (EtOAc/hexane) to give 3,3-diphenylpropanal in 40% yield as a colorless oil.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (t, *J* = 1.9 Hz, 1H), 7.35 – 7.18 (m, 10H), 4.64 (t, *J* = 7.8 Hz, 1H), 3.18 (dd, *J* = 7.8, 1.9 Hz, 2H).

Central-ring isomer [(η^4-cyclooctadiene)Rh(η^6-2,3,6,7-tetramethoxy-9,10-dimethylanthracene)]BF_4, Rh1



Rh1 was synthesized according to the procedure. [2] A mixture of [(η-4-cyclooctadiene)RhCl]$_2$ (50 mg, 0.1 mmol) and $AgBF_4$.3dioxane (92 mg, 0.2 mmol) was dissolved in degassed $MeNO_2$ (4 ml) and stirred for 1 h. Then 2,3,6,7-tetramethoxy-9,10-dimethylanthracene (82 mg, 0.25 mmol) was added and the color of the solution was immediately changed from orange to dark-red. Then the mixture was stirred for additional 2 h, opened to air and evaporated to dryness. The residue was washed with Et_2O (10 ml) and then dissolved in a mixture of CH_2Cl_2 (6 ml) and $MeNO_2$ (0.2 ml). The precipitate of AgCl was centrifuged off, and the product was precipitated from the solution by addition of Et_2O (50 ml). Yield 68 mg (54%). Further purification was achieved by crystallization (slow diffusion of Et_2O vapors into solution of the product in CH_2Cl_2/$MeNO_2$).
^{1}H NMR (400 MHz, CD_3NO_2): 1.74 (m, 8H), 2.52 (s, 6H), 3.80 (br. s, 4H), 4.10 (s, 12H) 7.27 (s, 4H).

Optimization of reaction conditions

General procedure

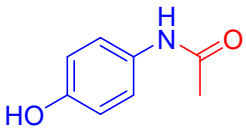
Synthesis of N-(4-hydroxyphenyl)acetamide (Paracetamol, **3a**) from 4-nitrophenol **1a** and acetic acid **2a** was used as a model reaction. A glass vial in a 10 mL stainless steel autoclave was charged with prescribed quantity of the catalysts, 4-nitrophenol (28 mg, 100 mol %, 0.20 mmol), acetic acid (29 - 114 µL, 250-1000 mol%, 0.50 - 2.00 mmol) and mesitylene (23 µL, 0.17 mmol) as internal standard and 0.2 mL of the corresponding solvent. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with the indicated pressure of converter gas. The reactor was placed into a preheated oil bath and the reaction was allowed to progress for the desired time under stirred condition. After 22 hour, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and diluted with 4.5 mL methanol, then it was injected into CR-5 GC column (30 m, 0.32 mm ID). The column oven temperature program was as follows: 140 °C for 3 minutes, 140 °C to 260 °C at 20 °C/min, then 260 °C for 9 minutes.

GC response factors were established by the following equation using 4-nitrophenol (**1a**), N-(4-hydroxyphenyl)acetamide (**3a**).

$$Response\ factor = \frac{(mmols\ of\ compound)}{(area\ of\ compound)} \times \frac{(area\ of\ mesitylene)}{(mmols\ of\ mesitylene)}$$

Four samples of different concentration containing a known amount of the desired compound and mesitylene were prepared and dissolved in methanol. An aliquot of each sample was injected three times into GC. The final response factor for N-(4-hydroxyphenyl)acetamide (**3a**) was calculated as an average of all response factors for each GC analysis, relative standard deviation is 6.63%.

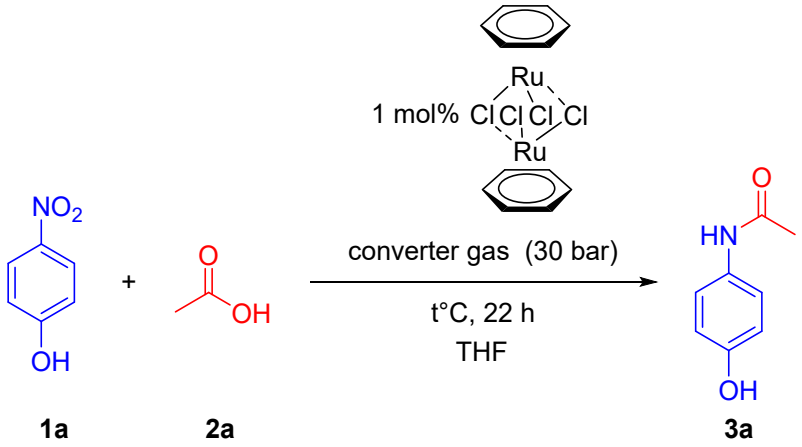
Table S1. GC calibration factors for N-(4-hydroxyphenyl)acetamide (Paracetamol, 3a)



Concertation of the compound g/L	Concentration of mesitylene g/L	t_R (min) of the compound	Response factor	An average response factor	Relative standard deviation
8.60	27.60	8.30	1.52	1.48	6.63
8.60	27.60		1.48		
8.60	27.60		1.44		
14.13	11.53		1.33		

14.13	11.53	1.36
14.13	11.53	1.43
14.33	22.60	1.23
14.33	22.60	1.31
14.33	22.60	1.37
22.06	24.13	1.29
22.06	24.13	1.31
22.06	24.13	1.26

Table S2. Investigations on the effect of temperature for the synthesis of Paracetamol

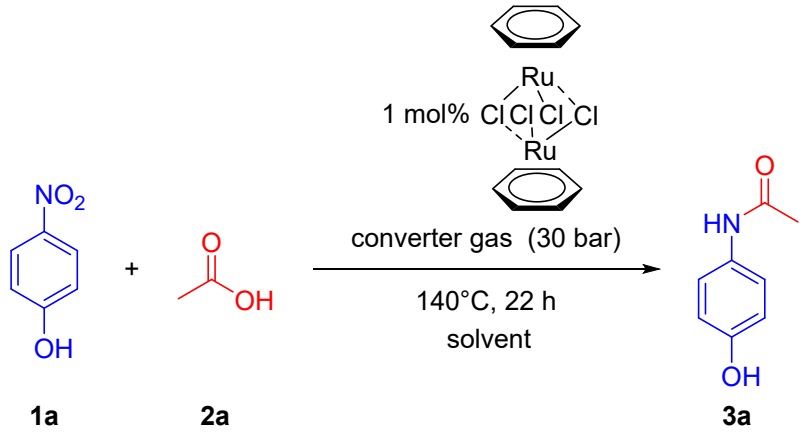


1a **2a** **3a**

Entry[a]	Temperature (°C)	Yield (%)[b]
1	120	7
2	130	56
3	140	99
4	150	77
5	160	78

Reaction conditions: [a]Catalyst $[(C_6H_6)RuCl_2]_2$ (1 mg, 1 mol %, 0.002 mmol), THF (0.2 mL), 4-nitrophenol **1a** (28 mg, 100 mol %, 0.20 mmol), acetic acid **2a** (114 µL, 1000 mol%, 2.00 mmol) and mesitylene (23 µL, 0.17 mmol) as GC internal standard. [b] Yields were determined by GC

Table S3. Investigations on the influence of solvents for the synthesis of Paracetamol

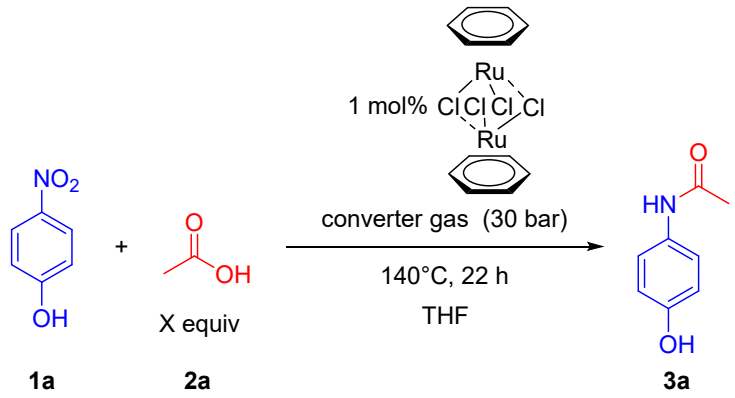


1a **2a** **3a**

Entry[a]	Solvent	Yield (%)[b]
1	THF	99
2	H_2O	85
3	MeOH	73
4	Toluene	56
6	EtOAc	44
7	Neat	40
8	MeCN	10
9	DCM	9

Reaction conditions: [a]Catalyst $[(C_6H_6)RuCl_2]_2$ (1 mg, 1 mol %, 0.002 mmol), solvent (0.2 mL), 4-nitrophenol **1a** (28 mg, 100 mol %, 0.20 mmol), acetic acid **2a** (114 µL, 1000 mol%, 2.00 mmol) and mesitylene (23 µL, 0.17 mmol) as an GC internal standard. [b] Yields were determined by GC

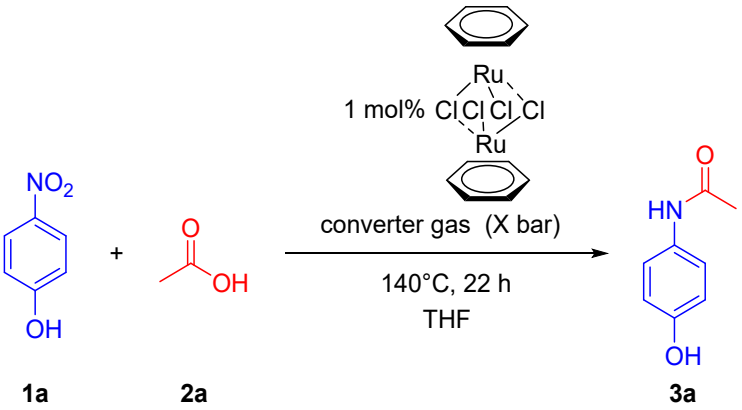
Table S4. Investigations on the influence of amount of acetic acid for the synthesis of Paracetamol



Entry[a]	Acetic acid (Equiv.)	Yield, %[b]
1	10	99
2	5	97
3	2.5	92
4	1.25	68

Reaction conditions: [a]Catalyst $[(C_6H_6)RuCl_2]_2$ (1 mg, 1 mol %, 0.002 mmol), THF (0.2 mL), 4-nitrophenol **1a** (28 mg, 100 mol %, 0.20 mmol), acetic acid **2a** (29 - 114 µL, 125-1000 mol%, 0.50 - 2.00 mmol) and mesitylene (23 µL, 0.17 mmol) as GC internal standard. [b] Yields were determined by GC.

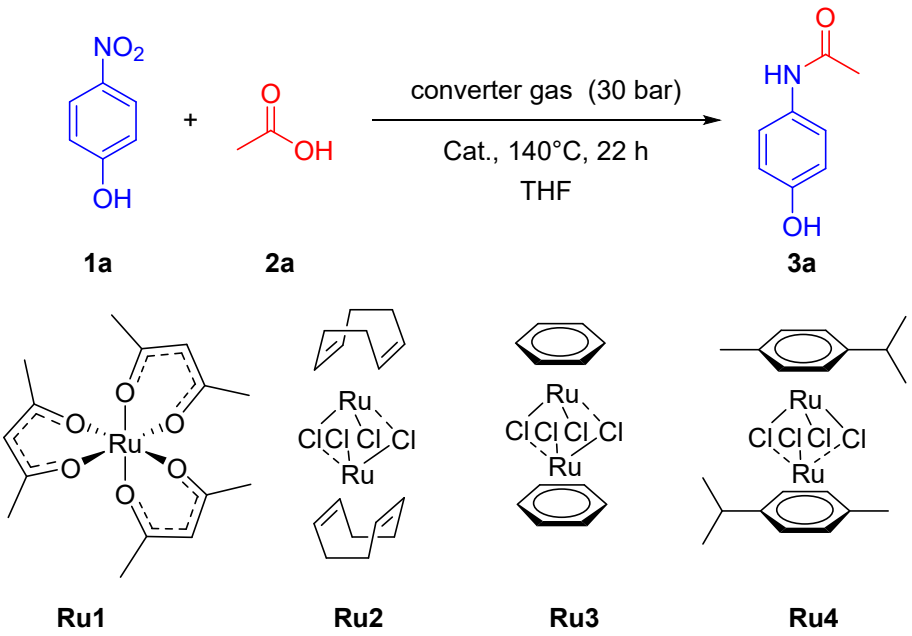
Table S5. Investigations on the effect of pressure of converter gas for the synthesis of Paracetamol



Entry[a]	Pressure, bar	Yield, %[b]
1	30	99
2	20	47

Reaction conditions: [a]Catalyst $[(C_6H_6)RuCl_2]_2$ (1 mg, 1 mol %, 0.002 mmol), THF (0.2 mL), 4-nitrophenol **1a** (28 mg, 100 mol %, 0.20 mmol), acetic acid **2a** (114 µL, 1000 mol%, 2.00 mmol) and mesitylene (23 µL, 0.17 mmol) as an GC internal standard were used. [b] Yields were determined by GC

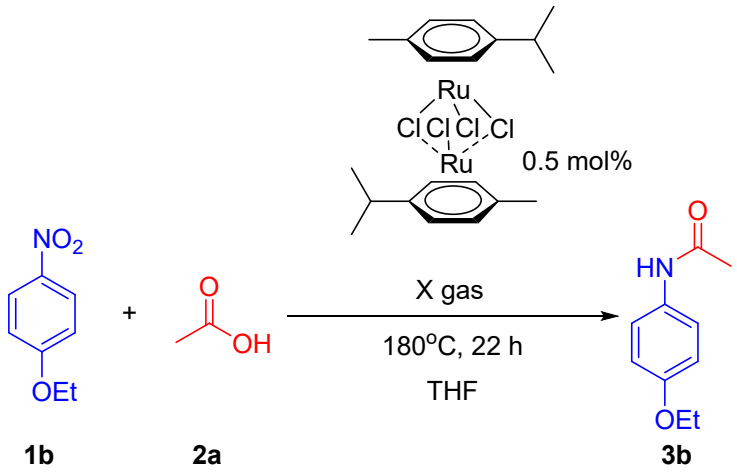
Table S6. Comparison of catalytic activities of different ruthenium complexes: synthesis of Paracetamol



Entry	Catalyst	Catalyst loading (mol% Ru)	Yield of 3a (%)
1[a]	**Ru4**	2	99
1[b]	**Ru3**	2	99
2[b]	**Ru3**	1	87
3[b]	**Ru3**	0.5	83
4[b]	**Ru2**	2	89
5[b]	**Ru1**	2	84
5[b]	$RuCl_3$	2	31
7[b]	No catalyst	0	traces

Reaction conditions: [a]1 Catalyst (1 mol %), THF (0.6 mL), 4-nitrophenol **1a** (77.7 mg, 100 mol %, 0.56 mmol), acetic acid **2a** (319 µL, 1000 mol%, 5.59 mmol), yields were determined by NMR. [b]Catalyst (0 – 2 mol %), THF (0.2 mL), 4-nitrophenol **1a** (28 mg, 100 mol %, 0.20 mmol), acetic acid **2a** (114 µL, 1000 mol%, 2.00 mmol) and mesitylene (23 µL, 0.17 mmol) as GC internal standard, yields were determined by GC.

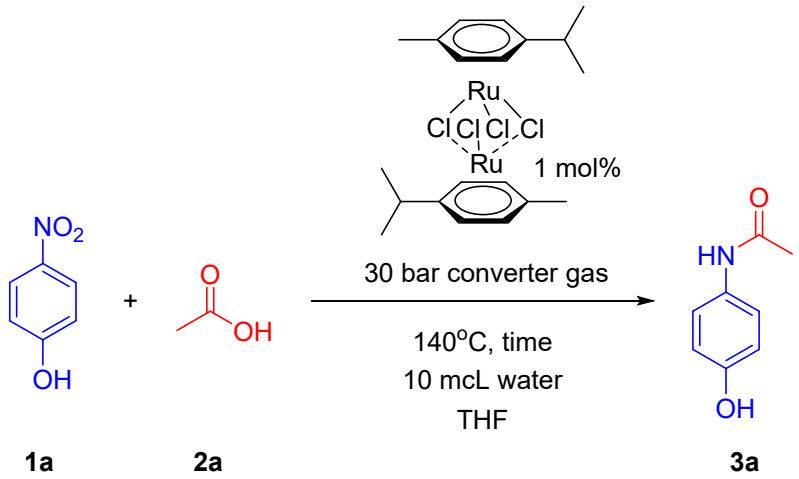
Table S7. Investigations the effect of different types of gas on the synthesis of Phenacetin



Entry[a]	Types of gas	Yield, %[b]
1	converter gas, 50 bar	85
2	CO, 50 bar	62
3	CO_2, 50 bar	0
4	CO, 28 bar	64
5	CO, 28 bar + N_2, 22 bar	63
6	CO, 28 bar + CO_2, 22 bar	88
7	converter gas, 50 bar + 1 mcl of thiophene[c]	86

Reaction conditions: [a]Catalyst $[(p\text{-Cymene})RuCl_2]_2$ (1.3 mg, 0.5 mol %, 0.002 mmol), THF (0.45 mL), 1-ethoxy-4-nitrobenzene **1b** (70.2 mg, 100 mol %, 0.42 mmol), acetic acid **2a** (240 µL, 1000 mol %, 4.2 mmol). [b] Yields were determined by NMR as average of 2 experiments. [c] 1 mcl of thiophene was added to the reaction mixture to test the possible influence of the S-containing admixtures.

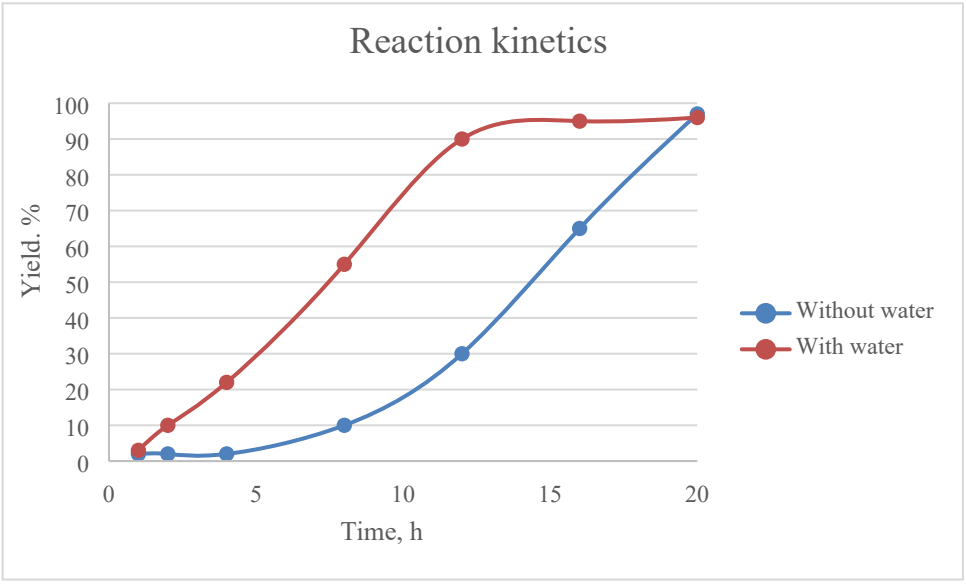
Table S8. Investigation of the water influence



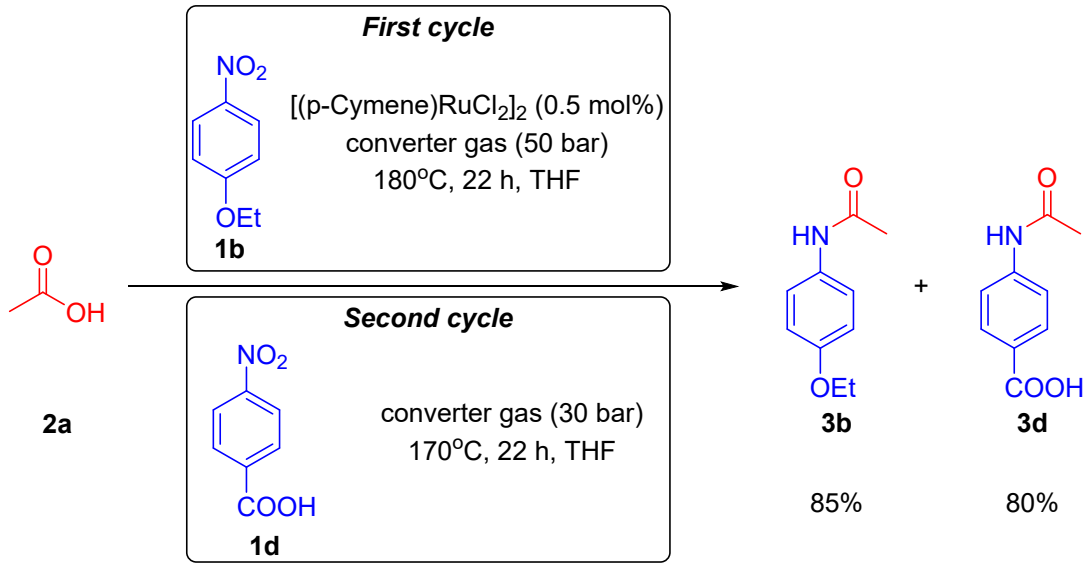
1a **2a** **3a**

Entry[a]	Time, h	Yield/conversion with water addition, %	Yield/conversion without water addition, %
1	1	3/13	0/10
2	2	10/22	0/10
3	4	22/35	0/13
4	8	55/64	15/28
5	12	90/95	30/41
6	16	95/99	65/73
7	20	96/99	97/100

Reaction conditions: [a]Catalyst $[(p\text{-Cymene})RuCl_2]_2$ (1 mg, 1 mol %, 0.0015 mmol), THF (0.2 mL), 4-nitrophenol **1a** (22.7 mg, 100 mol %, 0.16 mmol), acetic acid **2a** (94 µL, 1000 mol %, 1.6 mmol) and 10 µL (0.55 mmol, 350 mol%) of water (if required). Yields were determined by NMR.



Scheme S1. Recycle of the catalyst



Ruthenium catalyst [(p-Cymene)$RuCl_2]_2$ (1.3 mg, 0.5 mol %, 2.1 µmol) was placed into a titanium autoclave as an aliquot in dichloromethane, after evaporation of DCM 1-ethoxy-4-nitrobenzene **1b** (70.2 mg, 100 mol %, 0.42 mmol), acetic acid **2a** (240 µL, 1000 mol %, 4.2 mmol), 450 µL of THF, and magnetic stirring bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 50 bar of converter gas. The reactor was placed into an oil bath preheated to 180 °C. After 20 h of heating, the reactor was cooled to the room temperature and depressurized. 4-nitrobenzoic acid **1d** (70.1 mg, 100 mol %, 0.42 mmol) was added as a solution in 600 µL of THF *via* the autoclave valve. The autoclave was charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 170 °C. After 20 h of heating, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR to give 85% yield of **3b** and 80% yield of **3d**.

Mechanistic considerations

Despite the detailed investigations of catalytic reductions using CO by many authors,[3–5] the exact mechanisms such reactions are not fully clear to us. Herein we give only tentative explanations, which do not exclude other possibilities.

We assume that the formation of amides involves two principal steps: 1) the ruthenium-catalyzed reduction of nitro group by carbon monoxide into isocyanate or aniline, and 2) the reaction of isocyanate or aniline with carboxylic acid to give amide. The crucial component of the converter gas is the reducing carbon monoxide, while the carbon dioxide promotes reaction either by changing the acidity of the media or by changing the solubility of the gases.

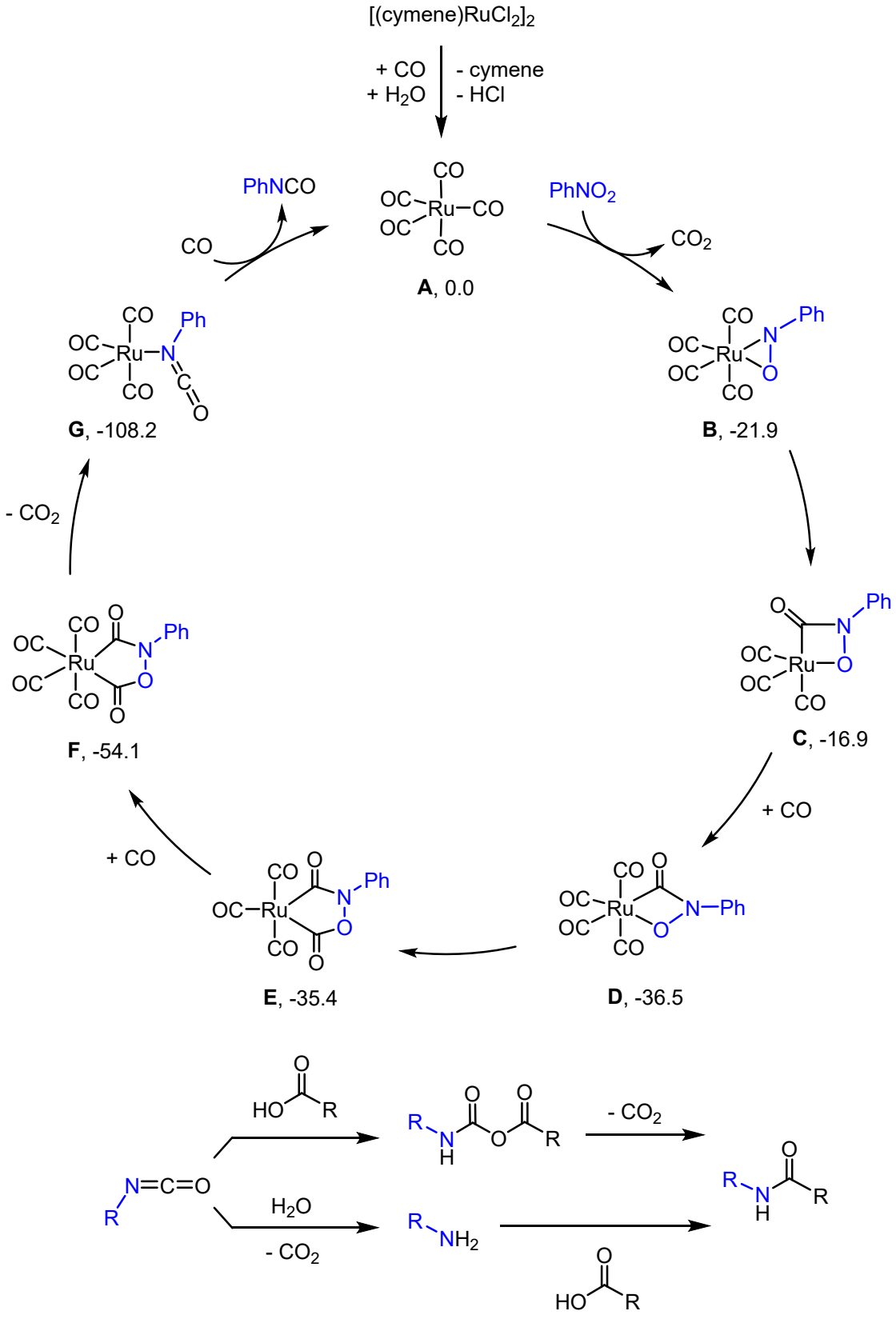
Initially pre-catalyst $[(p\text{-cymene})RuCl_2]_2$ can react with carbon monoxide and traces of water to give carbonyl species, which we depicted below as $Ru(CO)_5$ (**A**; Scheme S2). The exact nature of these species is difficult to clarify, because ruthenium chlorides are known to give a number interconverting complexes under similar conditions.[6] However, we assume than Ru^0 complexes are the active species under the reducing conditions of CO.

Next, these $Ru(CO)_5$ species presumably reduce nitroarenes to give CO_2 and nitroso complex **B** via electron-transfer processes. This electron-transfer reduction is consistent with the experimental observation that aromatic nitro compounds, which are strong electron acceptors, are much more reactive substrates than their aliphatic congeners. The experimental conformation of such reaction was provided for a very similar ruthenium complex $(dppe)Ru(CO)_3$, for which the nitroso compound $(dppe)Ru(CO)_2(\eta^2\text{-ON-Ar})$ has been isolated and characterized by X-ray diffraction analysis.[7]

The insertion of CO into Ru−N bond in complex **B** gives the metallacycle **C**, which then coordinates an additional CO molecule in order to compensate electron deficiency to give **D**. This step has been again confirmed experimentally for the analogous complex $(dppe)Ru(CO)_2(CONO\text{-}Ar)$[8] This complex has been shown to reacts further with MeOH and CO to give aniline and CO_2. However, the mechanism of N−O bond dissociation and formation of CO_2 has remained unclear. One can assume that complex **D** undergoes insertion of CO into Ru−O bond with formation of the five-membered metallacycles **E** and **F**, similar to the one described experimentally for the palladium complex.[9] Further extrusion of CO_2 from **F** produces the isocyanate complex **G**, which can either exchange isocyanate ArNCO for CO and regenerate $Ru(CO)_5$. It should be noted however, that Gargulak and Cladfelter observed the formation aniline from $(dppe)Ru(CO)_2(CON(Ar)O)$ *before* the formation of isocyanate.[10]

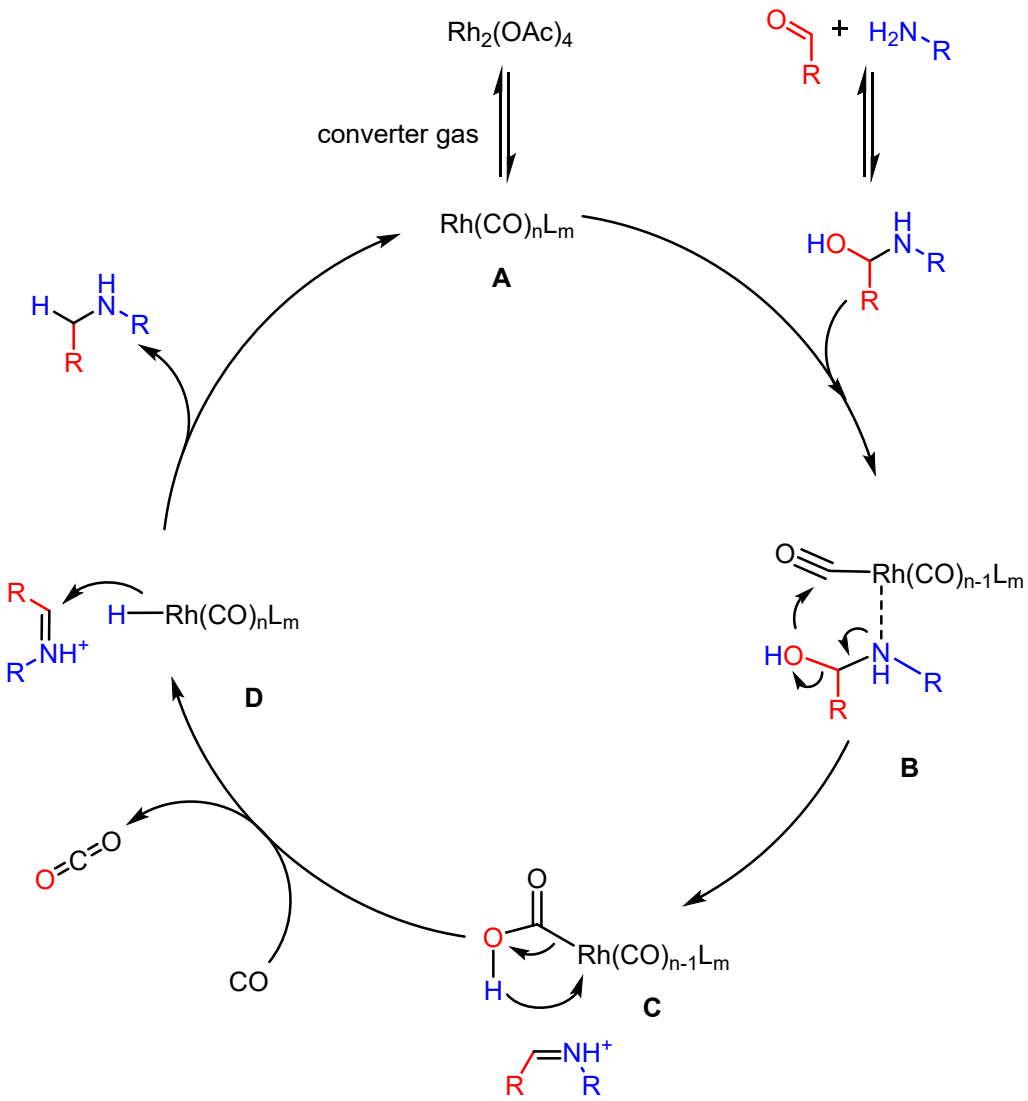
Finally, the isocyanate can either react with carboxylic acid directly,[11] or undergo hydrolysis to give amine, which reacts with carboxylic acid to give the target amide. Possibly, the amine reacts faster than isocyanate, which would additionally explain the acceleration effect of added water.

Scheme S2. Possible catalytic transformation of nitro compounds into isocyanates.
The numbers bellow the formulas correspond to free energies (at 298 K) relative to $Ru(CO)_5$ calculated at B97-3c level[12] with CPCM solvent correction for THF using Orca 4.2 software. The Cartesian coordinates for the calculated structures are given in the next pages.



In the case of the rhodium-catalyzed reductive amination we assume that the major reaction pathway is the previously established reductive amination without an external hydrogen source.[13] [14] Similar to ruthenium, rhodium acetate forms some carbonyl rhodium complexes **A**, that could reduce the hemiaminal formed from amine and carbonyl compound **B** (Scheme S3). However, as the reaction of amine and aldehyde could give water, an alternative reduction pathway involving the water-gas shift reaction[4,15,16] is possible.

Scheme S3. Possible mechanism for reductive amination by CO in the presence of a rhodium catalyst.



Cartesian coordinates for the optimized structures given in Scheme S2.

CO

Gibbs free energy -113.24713040 Hartree,

Lowest frequency = 2147.07 cm^{-1}.

6	-0.499813000	-0.266426000	0.001924000
8	0.499813000	0.266426000	-0.001924000

CO_2

Gibbs free energy -188.52341740 Hartree,

Lowest frequency = 648.70 cm^{-1}.

6	0.000000000	0.000000000	0.000000000
8	0.543276000	-0.119891000	1.023476000
8	-0.556344000	0.132840000	-1.014821000

$PhNO_2$

Gibbs free energy -436.50923632 Hartree,

Lowest frequency = 30.07 cm^{-1}.

6	-0.213619000	-0.481213000	-0.942426000
6	-0.974150000	0.637769000	-0.632850000
6	0.736698000	-0.988439000	-0.067353000
6	-0.772573000	1.261334000	0.586899000
6	0.925528000	-0.354258000	1.149025000
6	0.173955000	0.767901000	1.476946000
1	-1.704400000	1.007845000	-1.334472000
1	1.311803000	-1.859717000	-0.337015000
1	-1.356326000	2.134144000	0.841902000
1	1.660825000	-0.737882000	1.841718000
1	0.325969000	1.258526000	2.428281000
7	-0.420279000	-1.147961000	-2.234775000
8	0.274196000	-2.129978000	-2.497763000
8	-1.277931000	-0.691887000	-2.991305000

A

Gibbs free energy -661.68786913 Hartree,

Lowest frequency = 31.3 cm^{-1}.

44	0.000695000	-0.000184000	0.001354000
6	-1.708146000	-0.894459000	0.158606000
6	0.295516000	-0.226260000	1.899253000
8	-2.719190000	-1.422478000	0.249566000
8	0.471503000	-0.361721000	3.027644000
6	-0.890641000	1.584505000	-0.656690000
8	-1.423276000	2.525052000	-1.049563000
6	0.596983000	-1.357988000	-1.239166000
6	1.709367000	0.895028000	-0.158062000
8	2.719413000	1.423819000	-0.253481000
8	0.947777000	-2.165315000	-1.979462000

B

Gibbs free energy -909.70853550 Hartree,

Lowest frequency = 6.39 cm^{-1}.

44	0.114479000	-0.501530000	-2.102977000
6	-1.096809000	-1.423669000	-0.879686000
8	-1.835609000	-1.965215000	-0.201427000
7	1.332779000	0.159080000	-0.471613000
8	1.682662000	-1.099559000	-0.802654000
6	0.693478000	0.271113000	0.789468000
6	0.025411000	1.465400000	1.073880000
6	0.795284000	-0.718152000	1.767812000
6	-0.552477000	1.654772000	2.314063000
6	0.211549000	-0.516051000	3.010490000
6	-0.464382000	0.663507000	3.290618000
1	-0.047790000	2.224263000	0.305240000
1	1.331001000	-1.628751000	1.545810000
1	-1.078306000	2.576627000	2.523977000
1	0.293576000	-1.285210000	3.767254000
1	-0.916026000	0.815692000	4.261452000
6	-1.240432000	0.752861000	-2.550488000
8	-2.095833000	1.468658000	-2.825970000
6	-0.215737000	-1.825216000	-3.462106000
6	1.384450000	0.451779000	-3.218011000
8	2.137850000	1.036504000	-3.842734000
8	-0.459119000	-2.576903000	-4.292397000

C

Gibbs free energy -909.70066245 Hartree,

Lowest frequency = 12.38 cm^{-1}.

44	0.085842000	-0.834752000	-2.909759000
6	-0.999404000	-0.571081000	-4.427726000
8	-1.722085000	-0.371512000	-5.298507000
7	-0.098713000	0.113577000	-0.529238000
8	0.549205000	-1.067922000	-0.979440000
6	-0.064894000	0.432023000	0.828675000
6	-0.719625000	1.569180000	1.311694000
6	0.630696000	-0.402627000	1.704643000
6	-0.666446000	1.856690000	2.665313000
6	0.668560000	-0.094885000	3.055676000
6	0.024222000	1.032488000	3.545915000
1	-1.259935000	2.213287000	0.637172000
1	1.133042000	-1.278263000	1.325301000
1	-1.174102000	2.738429000	3.032517000
1	1.210150000	-0.746949000	3.727561000
1	0.057654000	1.266590000	4.601010000

6	-0.639041000	0.695114000	-1.623108000
8	-1.333486000	1.686219000	-1.704095000
6	0.955625000	-2.475602000	-3.638632000
6	1.222898000	0.424020000	-3.568634000
8	1.981078000	1.194479000	-3.967445000
8	1.581010000	-3.314287000	-4.096069000

D

Gibbs free energy -1023.00138566 Hartree,

Lowest frequency = 13.64 cm^{-1}.

44	-0.070227000	-0.926284000	-2.968710000
6	-0.915951000	-0.425751000	-4.584827000
8	-1.461241000	-0.069771000	-5.528447000
7	-0.140183000	0.049232000	-0.559069000
8	0.600963000	-1.071639000	-0.983433000
6	-0.072306000	0.414481000	0.789725000
6	-0.773591000	1.522428000	1.274881000
6	0.714177000	-0.349937000	1.652786000
6	-0.679493000	1.848823000	2.617502000
6	0.793612000	-0.004071000	2.992834000
6	0.100641000	1.093245000	3.484980000
1	-1.380904000	2.115082000	0.610765000
1	1.252056000	-1.202931000	1.271012000
1	-1.224627000	2.707237000	2.986272000
1	1.405157000	-0.602435000	3.654716000
1	0.166230000	1.357491000	4.531488000
6	-0.825082000	0.556794000	-1.597791000
8	-1.576448000	1.507405000	-1.663747000
6	0.900018000	-2.466605000	-3.730815000
6	1.348248000	0.382918000	-3.237836000
8	2.170254000	1.161797000	-3.364665000
8	1.480089000	-3.367864000	-4.122875000
6	-1.639779000	-1.928011000	-2.392913000
8	-2.557271000	-2.496236000	-2.027286000

E

Gibbs free energy -1022.99962634 Hartree,

Lowest frequency = 14.50 cm^{-1}.

44	-0.474832000	-0.593337000	-2.903641000
6	-1.641824000	-1.982839000	-2.220633000
8	-2.320391000	-2.791708000	-1.784194000
7	0.084976000	0.105257000	-0.162488000
8	1.072059000	-0.858598000	-0.502166000
6	0.090753000	0.441599000	1.208807000
6	-0.234402000	1.742436000	1.583661000
6	0.400543000	-0.517026000	2.170491000
6	-0.272934000	2.070295000	2.930047000
6	0.382115000	-0.165142000	3.510601000
6	0.038621000	1.123926000	3.897076000
1	-0.455804000	2.484462000	0.833253000
1	0.658592000	-1.522213000	1.873981000
1	-0.530827000	3.079668000	3.219614000
1	0.629816000	-0.909047000	4.255191000
1	0.019442000	1.390393000	4.944858000
6	-0.833365000	0.401160000	-1.122998000
8	-1.775183000	1.162489000	-0.964372000
6	1.003915000	-1.356488000	-1.791094000
6	0.686915000	0.890337000	-3.351379000
8	1.377028000	1.772018000	-3.579264000
8	1.829416000	-2.172537000	-2.095124000
6	-0.052204000	-1.579557000	-4.535770000
8	0.317575000	-2.215548000	-5.414456000

F

Gibbs free energy -1136.29904038 Hartree,

Lowest frequency = 10.83 cm^{-1}.

44	-0.186771000	-0.483703000	-2.700758000
6	-1.980168000	-1.096864000	-2.286986000
6	0.465646000	-1.924631000	-1.319744000
8	-3.027319000	-1.452881000	-2.005539000
8	0.854699000	-3.047702000	-1.494919000
7	-0.043271000	-0.166101000	0.194007000
8	0.426867000	-1.495169000	-0.006347000
6	0.060593000	0.237824000	1.548345000
6	-1.020499000	0.870363000	2.151252000
6	1.235780000	0.006692000	2.256502000
6	-0.912481000	1.291903000	3.467609000
6	1.321840000	0.411663000	3.579086000
6	0.253379000	1.060276000	4.185738000
1	-1.930647000	1.030954000	1.593944000
1	2.067983000	-0.489375000	1.778955000
1	-1.750700000	1.788280000	3.936741000
1	2.232120000	0.228254000	4.132953000
1	0.328045000	1.380363000	5.215942000
6	-0.827991000	1.054338000	-3.744954000
8	-1.202779000	1.992158000	-4.274785000
6	-0.362422000	0.613164000	-0.879139000
8	-0.698905000	1.776978000	-0.759545000
6	0.071302000	-1.728343000	-4.204821000
6	1.650156000	0.142989000	-2.695875000
8	2.729077000	0.512316000	-2.654078000
8	0.246465000	-2.513747000	-5.013583000

G

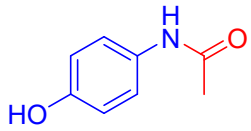
Gibbs free energy -947.86189170 Hartree,

Lowest frequency = 24.51 cm^{-1}.

44	-0.485185000	-1.184964000	-1.969789000
6	-1.955224000	-1.936538000	-0.972381000
8	-2.815161000	-2.357559000	-0.340710000
7	0.603028000	-0.811924000	0.073500000
6	1.309445000	-1.806318000	0.185163000
6	0.441947000	0.286132000	0.955887000
6	-0.459423000	1.284199000	0.618310000
6	1.172120000	0.361059000	2.139480000
6	-0.632576000	2.365362000	1.469492000
6	0.990558000	1.445455000	2.981450000
6	0.089093000	2.450662000	2.651603000
1	-1.013803000	1.207987000	-0.306365000
1	1.876575000	-0.417364000	2.401272000
1	-1.336697000	3.141090000	1.202724000
1	1.558228000	1.502603000	3.899776000
1	-0.048553000	3.294405000	3.313382000
6	-1.667049000	0.037787000	-2.772895000
8	-2.410562000	0.672163000	-3.395301000
6	-0.103017000	-2.848913000	-2.793530000
6	0.996803000	-0.324929000	-2.856344000
8	1.889104000	0.206288000	-3.343585000
8	0.017642000	-3.810481000	-3.423439000
8	1.982707000	-2.756202000	0.282302000

Synthetic procedures and characterization of products

Paracetamol, N-(4-hydroxyphenyl)acetamide (3a)



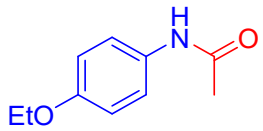
Ruthenium catalyst $[(p\text{-Cymene})RuCl_2]_2$ (3.4 mg, 1.0 mol %, 5.5 µmol) was placed into a stainless-steel autoclave as an aliquot in dichloromethane, after evaporation of the DCM, 4-nitrophenol **2a** (77.7 mg, 100 mol %, 0.56 mmol), acetic acid (319 µL, 1000 mol %, 5.59 mmol), 600 µL of THF and magnetic stir bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The autoclave was placed into an oil bath preheated to 140 °C. After 20 h of reaction time, the autoclave was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 99 % yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.5 in 10:1 DCM:MeOH) to afford 82.7 mg (98%) of the product as white crystals.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 – 9.63 (broad s, 1H), 9.14 (s, 1H), 7.33 (d, J = 8.9 Hz, 2H), 6.66 (d, J = 8.9 Hz, 2H), 1.97 (s, 3H)

^{13}C NMR (101 MHz, DMSO-d_6) δ 167.6, 153.2, 131.1, 120.8, 115.0, 23.8.

NMR spectra are in agreement with the literature data.[17]

Phenacetin, 4-methoxy-*N*-(4-methylbenzyl)aniline (3b)



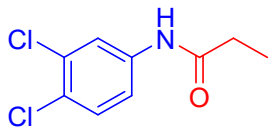
Ruthenium catalyst [(p-Cymene)$RuCl_2]_2$ (1.3 mg, 0.5 mol %, 2.1 µmol) was placed into a titanium autoclave as an aliquot in dichloromethane, after evaporation of DCM 1-ethoxy-4-nitrobenzene **1b** (70.2 mg, 100 mol %, 0.42 mmol), acetic acid **2a** (240 µL, 1000 mol %, 4.2 mmol), 450 µL of THF, and magnetic stir bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 50 bar of converter gas. The reactor was placed into an oil bath preheated to 180 °C. After 20 h of heating, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 85% yield by NMR (average of three experiments). The residue was purified by flash chromatograph InterChim PuriFlash in Hexane – DCM binary system (isocratic 50% Hexane and 50% DCM or 3 min then gradient to 100% DCM for 7 min and then isocratic 100% DCM for 10 min, Rf 0.3 in DCM) to afford 57.8 mg (77 %) of the product as yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (broad s, 1H), 7.36 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 3.98 (q, J = 7.0 Hz, 2H), 2.12 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 155.9, 131.0, 122.1, 114.8, 63.8, 24.4, 15.0.

NMR spectra are in agreement with the literature data.[18]

Propanil, N-(3,4-dichlorophenyl)propionamide (3c)



Ruthenium catalyst [(p-Cymene)$RuCl_2]_2$ (1.2 mg, 0.5 mol %, 2.0 µmol) was placed into a titanium autoclave as an aliquot in dichloromethane, after evaporation of DCM 1,2-dichloro-4-nitrobenzene **1c** (70.2 mg, 100 mol %, 0.42 mmol), propionic acid **2b** (300 µL, 1000 mol %, 4.0 mmol), 400 µL of THF, and magnetic stir bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 160 °C. After 20 h of heating, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 86% yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in Hexane – DCM binary system (isocratic 50% Hexane and 50% DCM or 3 min then gradient to 100% DCM for 7 min and then isocratic 100% DCM for 10 min, Rf 0.3 in DCM) to afford 75 mg (86 %) of the product as yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.14 (broad s, 1H), 7.75 (s, 1H), 7.33 – 7.27 (m appears as s, 2H), 2.38 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 137.6, 132.6, 130.4, 127.4, 121.8, 119.4, 30.7, 9.7.

NMR spectra are in agreement with the literature data.[19]

Acedoben, 4-acetamidobenzoic acid (3d)

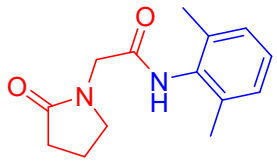
Ruthenium catalyst [(p-Cymene)$RuCl_2]_2$ (1.2 mg, 0.5 mol %, 2.0 µmol) was placed into a titanium autoclave as an aliquot in dichloromethane, after evaporation of DCM 4-nitrobenzoic acid **1d** (66.8 mg, 100 mol %, 0.40 mmol), acetic acid **2a** (228 µL, 1000 mol %, 4.0 mmol), 400 µL of THF, and magnetic stir bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 170 °C. After 20 h of heating, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 85% yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.3 in 10:1 DCM:MeOH) to afford 60.0 mg (83%) of the product as white crystals.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 – 10.24 (broad s, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 2.07 (s, 3H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 168.9, 167.1, 143.3, 130.5, 125.2, 118.2, 24.2.

NMR spectra are in agreement with the literature data.[20]

Nefiracetam, N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide (3e)



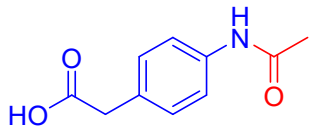
Ruthenium catalyst [(p-Cymene)$RuCl_2]_2$ (1.2 mg, 0.5 mol %, 2.0 µmol) was placed into a titanium autoclave as an aliquot in dichloromethane, after evaporation of DCM 1,3-dimethyl-2-nitrobenzene **1e** (30.8 mg, 100 mol %, 0.20 mmol), 2-(2-oxopyrrolidin-1-yl)acetic acid **2c** (145.8 mg, 500 mol %, 1.0 mmol), 400 µL of THF, and magnetic stir bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 170 °C. After 20 h of heating, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 67% yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 98% DCM and 2% MeOH to 93% DCM and 7% MeOH for 25 min, isocratic 93% DCM and 7% MeOH for 6 min, Rf 0.5 in 20:1 DCM:MeOH) to afford 33.0 mg (67 %) of the product as yellow crystals.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.82 (broad s, 1H), 7.30-7.05 (m, 3H), 4.07 (s, 2H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 7.9 Hz, 2H), 2.18 (s, 6H), 2.10 (tt appear as q, *J* = 8.1 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 167.0, 135.3, 133.4, 128.3, 127.5, 48.7, 47.7, 30.5, 18.5, 18.2.

NMR spectra are in agreement with the literature data.[21]

Actarit, 2-(4-acetamidophenyl)acetic acid (3f)



Ruthenium catalyst [(p-Cymene)$RuCl_2]_2$ (1.9 mg, 0.75 mol %, 3.2 µmol) was placed into a titanium autoclave as an aliquot in dichloromethane, after evaporation of DCM 2-(4-nitrophenyl)acetic acid **1f** (76.2 mg, 100 mol %, 0.42 mmol), acetic acid **2a** (228 µL, 1000 mol %, 4.0 mmol), 400 µL of THF, and magnetic stir bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 140 °C. After 40 h, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 65% yield by NMR. The product was isolated by flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (isocratic 98% DCM and 2% MeOH for 10 min, gradient to 95% DCM and 5% MeOH for 2 min, isocratic 95% DCM and 5% MeOH for 7 min, gradient to 100% MeOH for 8 min, Rf 0.2 in 20:1 DCM:MeOH (spot with a long tail)) to afford 52.0 mg (64%) of the product as yellow crystals.

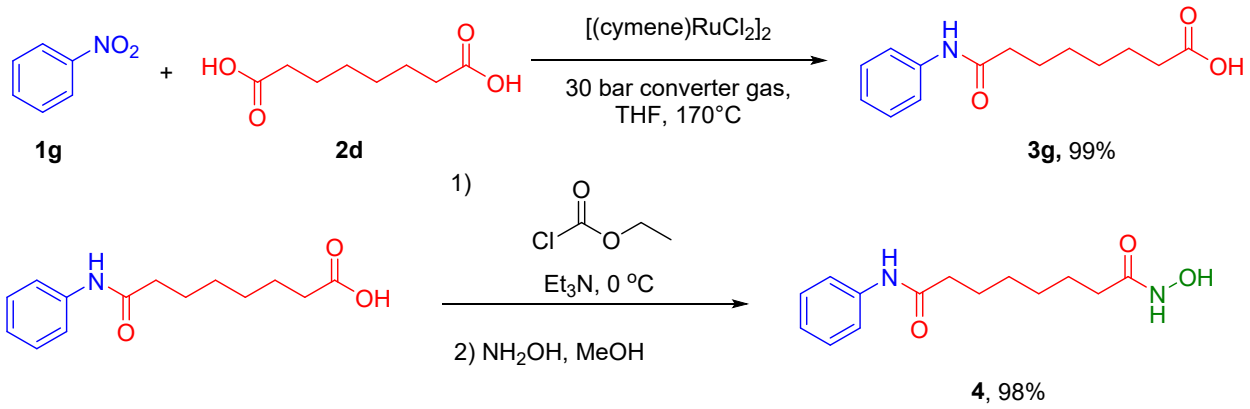
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.49 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 3.56 (s, 2H), 2.11 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 173.0, 168.4, 138.0, 129.70, 129.66, 119.0, 40.2, 24.1.

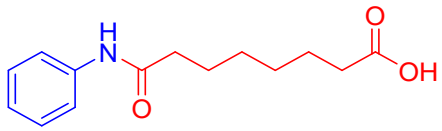
NMR spectra are in agreement with the literature data.[22]

Vorinostat, N^1-hydroxy-N^8-phenyloctanediamide (4)

Vorinostat **4** was prepared in two steps via Suberanilic acid **3g**.



Suberanilic acid, 8-oxo-8-(phenylamino)octanoic acid (3g)



Ruthenium catalyst [(p-Cymene)$RuCl_2]_2$ (0.9 mg, 0.75 mol %, 1.5 µmol) was placed into a titanium autoclave as an aliquot in dichloromethane, after evaporation of DCM nitrobenzene **2g** (20.7 µL, 100 mol %, 0.20 mmol), octanedioic acid **1d** (164 mg, 500 mol %, 1.0 mmol), 200 µL of THF, and magnetic stir bar were added. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar converter gas. The reactor was placed into an oil bath preheated to 170 °C. After 20 h, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 99% yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.5 in 10:1 DCM:MeOH) to afford 49.3 mg (99 %) of the product as white crystals.

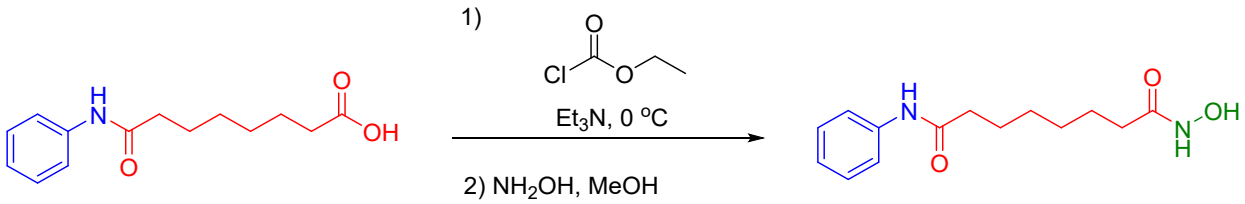
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 – 11.61 (broad s, 1H), 9.86 (s, 1H), 7.58 (d, J = 7.9 Hz, 2H), 7.27 (dd appears as t, J = 7.9 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 2.28 (t, J = 7.4 Hz, 2H), 2.19 (t, J = 7.3 Hz, 2H), 1.62 – 1.42 (m, 4H), 1.39 – 1.18 (m, 4H).

^{13}C NMR (75 MHz, DMSO-d_6) δ 174.6, 171.3, 139.4, 128.7, 123.0, 119.0, 36.4, 33.7, 28.5, 28.4, 25.0, 24.4.

NMR spectra are in agreement with the literature data.[23,24]

Vorinostat (4)

Next step was carried out according to the published procedure [25]:



The reactions were conducted in a flame-dried Schlenk flask under an inert atmosphere. To a solution of suberanilic acid **3g** (90 mg, 100 mol%, 0.36 mmol) in anhydrous tetrahydrofuran (2 mL), ethyl chloroformate (90 µL, 200 mol%, 0.70 mmol) and triethylamine (72 µL, 270 mol%, 0.98 mmol) were added, and the mixture was stirred for 20 min. The generated solid was filtered off and the filtrate was added to freshly prepared hydroxylamine solution (40 mg, 40 mol%, 1.23 mmol) in methanol. The resulting mixture was stirred at room temperature for 20 min, then was evaporated and the residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – i-PrOH binary system (isocratic 95% DCM to 5% i-PrOH for 10 min, gradient to 87% DCM and 13% i-PrOH for 16 min, isocratic 87% DCM and 13% i-PrOH for 10 min, Rf 0.3 in 10:1 DCM:i-PrOH (spot with a long tail)) to afford 94.0 mg (98%) of the product as white crystals.

Solution of hydroxylamine in methanol was prepared according to the following procedure:

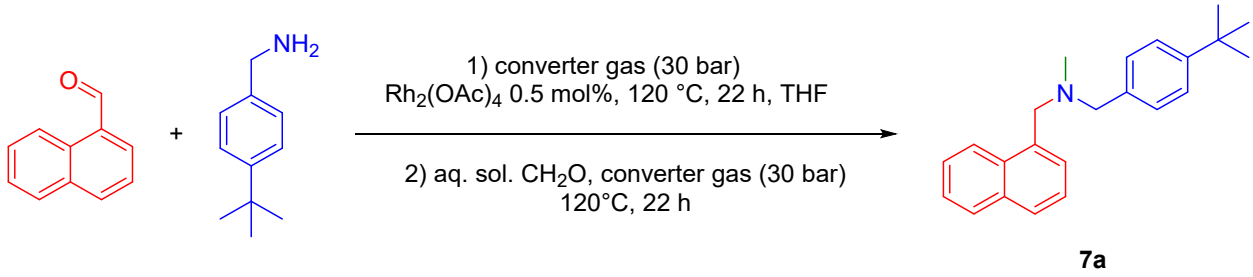
A solution of hydroxylamine hydrochloride (86 mg, 100 mol%, 1.23 mmol) in methanol (2 mL) was added to a stirred solution of potassium hydroxide (69 mg, 100 mol%, 1.23 mmol) in methanol (2 mL). After stirring for 15 min, the precipitate was removed and the filtrate was used as such.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 – 10.33 (br s, 1H), 9.91 – 9.83 (br s, 1H), 8.72 – 8.66 (br s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.27 (dd appears as t, J = 7.8 Hz, 2H), 7.01 (t, J = 7.4 Hz, 1H), 2.28 (t, J = 7.4 Hz, 2H), 1.93 (t, J = 7.3 Hz, 2H), 1.56 (t, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 2H), 1.29 – 1.24 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 169.1, 139.4, 128.7, 123.0, 119.0, 36.4, 32.3, 28.49, 28.47, 25.1 (2C).

NMR spectra are in agreement with the literature data [26]

Butenafine, N-(4-(tert-butyl)benzyl)-N-methyl-1-(naphthalen-1-yl)methanamine (7a)



7a

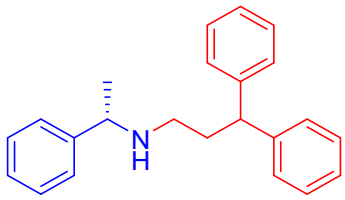
Rhodium(II) acetate dimer (0.53 mg, 0.5 mol%, 1.20 μmol), 235 μL of THF, (4-(tert-butyl)phenyl)methanamine (63 μL, 150 mol%, 0.36 mmol) and 1-naphthaldehyde (32.4 μL, 100 mol%, 0.24 mmol) were charged in glass vial and placed in a stainless-steel autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 120 °C. After 22 h the reactor was cooled to the room temperature and depressurized. 40 % aq. solution of formalin (40 μL, 220 mol%, 0.53 mmol) was added to the reaction mixture. The autoclave was sealed and then charged with 30 bar converter gas (it can be flushed one time with 5 bar of converter gas). The reactor was placed into an oil bath preheated to 120 °C. After 22 h of reaction time, the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 72% yield by NMR. The residue was purified by column chromatography (eluent: ethyl acetate:hexane:triethylamine = 0.10:6.00:0.01; Rf=0.2) to afford 47.1 mg (62%) of the product as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.19 (m, 1H), 7.88 – 7.81 (m, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.52 – 7.45 (m, 3H), 7.45 – 7.36 (m appears as t, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.93 (s, 2H), 3.59 (s, 2H), 2.21 (s, 3H), 1.32 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 136.4, 135.2, 134.0, 132.7, 128.9, 128.5, 128.0 (2C), 127.5, 125.8, 125.7, 125.2, 125.0, 62.2, 60.6, 42.5, 34.6, 31.6.

NMR spectra are in agreement with the literature data. [27,28]

(-)-Fendiline, (S)-3,3-diphenyl-N-(1-phenylethyl)propan-1-amine (7b)



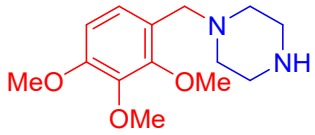
Rhodium(II) acetate dimer (0.51 mg, 0.5 mol%, 1.2 µmol), 3,3-diphenylpropanal (48.2 mg, 100 mol%, 0.23 mmol) dissolved in 412 µL of THF, and (S)-1-phenylethan-1-amine (32 µL, 109 mol%, 0.25 mmol) were added to the glass vial and placed into a stainless-steel autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 140 °C. After 22 h the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2 x 1 mL), solvents were removed on a rotary evaporator, and the residue was analyzed by NMR. 83% yield by NMR. The residue was purified by preparative column chromatography (eluent: ethyl acetate:hexane:triethylamine = 1.00:5.00:0.05; Rf=0.2) to afford 58.5 mg (80%) of the product as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 15H), 4.03 (t, *J* = 7.7 Hz, 1H), 3.72 (q, *J* = 6.6 Hz, 1H), 2.60 – 2.37 (m, 2H), 2.37 – 2.13 (m, 2H), 1.34 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 145.1, 144.8, 128.5, 128.5, 128.0, 127.8, 126.9, 126.6, 126.2, 58.2, 49.1, 46.1, 36.2, 24.5.

NMR spectra are in agreement with the literature data.[29]

Trimetazidine, 1-(2,3,4-trimethoxybenzyl)piperazine (7c)



Rhodium catalyst **Rh1** (1.1 mg, 1 mol%, 1.76 μmol), 2,3,4-trimethoxybenzaldehyde (35.2 mg, 100 mol%, 0.18 mmol), piperazine (158 mg, 1020 mol%, 1.84 mmol) and 2 mL of tBuOH were added to the glass vial and placed into a stainless steel autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar converter gas. The reactor was placed into an oil bath preheated to 120 °C. After 22 h, the autocalve was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2x1mL), the combined solution was passed through a short layer of silica gel, solvents and excess of piperazine were removed on a rotary evaporator, the residue was analyzed by NMR. 83% yield by NMR as an average of two experiments. The residue was purified by preparative column chromatography (eluent: methanol : dichloromethane : triethylamine = 0.20:3.00:0.02; Rf=0.3) to afford 37.2 mg (78%) of the product as yellow viscous oil with tendency to crystallization.

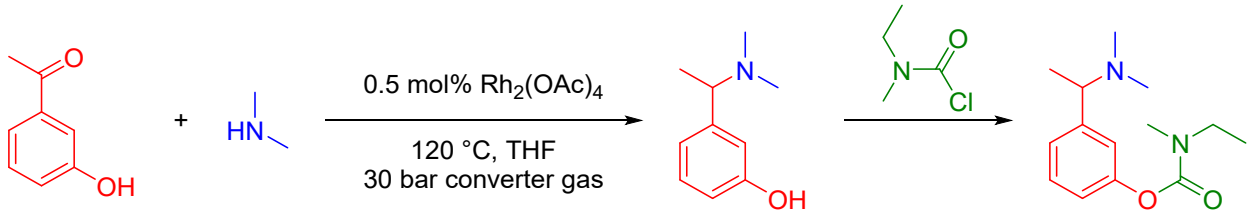
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 4.01 – 3.69 (m, 9H), 3.46 (s, 2H), 2.93 (t, J = 4.9 Hz, 4H), 2.56 – 2.44 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 152.7, 142.4, 125.2, 123.5, 107.0, 61.3, 60.9, 56.9, 56.1, 52.7, 45.3.

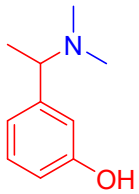
HRMS: Calculated for $C_{14}H_{23}N_2O_3$ ($[M+H]^+$): 267.1703; Found: 267.1704

Rivastigmine, 3-(1-(dimethylamino)ethyl)phenyl ethyl(methyl)carbamate (7d)

Rivastigmine (**7d**) was prepared in two steps via intermediate synthesis of 3-(1-(dimethylamino)ethyl)phenol.



3-(1-(dimethylamino)ethyl)phenol



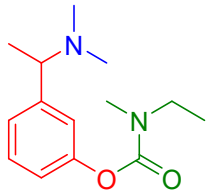
Rhodium(II) acetate dimer (0.57 mg, 0.54 mol%, 1.3 µmol), 1-(3-hydroxyphenyl)ethane-1-one (32.1 mg, 0.24 mmol, 100 mol%), 247 µL THF, and dimethylamine solution (680 µL, 1.24 mmol, 5.25 eq., 1.82 M solution in THF) were added to the glass vial and placed into a 10 ml stainless steel autoclave. The autoclave was sealed and without flushing it with converter gas was charged with 30 bar of converter gas. The reactor was placed into an oil bath preheated to 120°C. After 48 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2 × 1 mL), the solution was passed through a short layer of silica gel, solvents were removed on a rotary evaporator, the residue was analyzed by NMR. 77% yield by NMR (average of two experiments). The residue was purified by preparative column chromatography (eluent: MeOH: CH_2Cl_2: Et_3N = 5:50:0.2; Rf = 0.2) to afford 27.5 mg (71%) of the product as an yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.84 – 6.70 (m, 3H), 3.33 (q, *J* = 6.7 Hz, 1H), 2.24 (s, 6H), 1.41 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 143.6, 129.5, 119.8, 115.5, 115.3, 66.1, 43.0, 19.4.

NMR spectra are in agreement with the literature data.[30]

Rivastigmine, 3-(1-(dimethylamino)ethyl)phenyl ethyl(methyl)carbamate (7d)



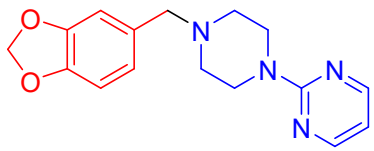
This step was performed according to the literature procedure. [30] NaH (60% suspension in oil) (18.0 mg, 0.45 mmol, 2 equiv.) was suspended in 7 mL of dry THF, (S)-3-(1-(dimethylamino)ethyl)phenol (36.8 mg, 0.22 mmol, 1 equiv.) was added and the suspension was stirred for 60 min at room temperature. A solution of ethyl(methyl)carbamic chloride (53.8 mg, 0.44 mmol, 2 equiv.) in 3 mL of dry THF was added dropwise and the mixture was stirred for 5 h at room temperature. Distilled H_2O was added followed by saturated solution of K_2CO_3 until basic pH. The resulting mixture was extracted with EtOAc, the organic layers were combined, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. 96% NMR yield. Purification: flash column chromatography, eluent DCM/MeOH/NH_3OH=94:6:0.5. Isolated as an yellowish oil 92% (49.7 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.08 – 7.04 (m, 1H), 7.03 – 6.96 (m, 1H), 3.52 – 3.33 (m, 2H, 2 rotamers), 3.23 (q, *J* = 6.7 Hz, 1H), 3.05 (s, 1.5H, rotamer 1), 2.98 (s, 1.5H, rotamer 1), 2.19 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 3H), 1.28 – 1.13 (m, 3H, 2 rotamers).

^{13}C NMR (101 MHz, $CDCl_3$) (two rotamers) δ 154.7, 154.5, 151.6, 145.7, 145.6, 129.0, 124.4, 120.9, 120.8, 120.4, 65.7, 44.1, 43.3, 34.3, 33.9, 20.1, 13.3, 12.6.

NMR spectra are in agreement with the literature data. [30]

Piribedil, 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidine (7e)



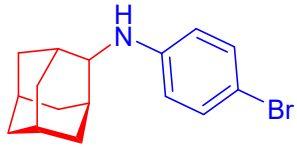
Rhodium(II) acetate dimer (0.50 mg, 0.5 mol%, 1.1 µmol), piperonal (34.0 mg, 100 mol%, 0.23 mmol), 2-(piperazin-1-yl)pyrimidine (37.2 mg, 100 mol%, 0.23 mmol) and 100 µL THF were added to the glass vial and placed into a 10 ml stainless steel autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar converter gas. The reactor was placed into an oil bath preheated to 120 °C. After 22 h the reactor was cooled to the room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2x1mL), solvents were removed on a rotary evaporator, the residue was analyzed by NMR. 90% yield by NMR. The residue was purified by preparative column chromatography (eluent: ethyl acetate:hexane:triethylamine = 1.00:4.00:0.05; Rf=0.3) to afford 57 mg (85%) of the product as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 4.8 Hz, 2H), 6.87 (s, 1H), 6.74 (d, J = 1.1 Hz, 2H), 6.44 (t, J = 4.7 Hz, 1H), 5.92 (s, 2H), 3.80 (dd appears as t, J = 5.1 Hz, 4H), 3.43 (s, 2 H), 2.46 (dd appears as t, J = 5.1 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 157.8, 147.7, 146.7, 131.9, 122.3, 109.8, 109.6, 108.0, 101.0, 62.9, 52.9, 43.7.

NMR spectra are in agreement with the literature data[28,31]

Bromantane, N-(4-bromophenyl)adamantan-2-amine (7f)



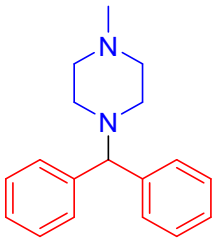
Rhodium(II) acetate dimer (0.62 mg, 0.5 mol%, 1.4 μmol), 2-adamantanone (86.6 mg, 0.58 mmol, 200 mol%), 4-bromoaniline (49.8 mg, 0.29 mmol, 100 mol%), and 186 μL of tBuOH were added to the glass vial and placed into 10 ml stainless steel autoclave. The autoclave was sealed, flushed two times with 10 bar of converter gas, and then charged with 42 bar of converter gas. The reactor was placed into an oil bath preheated to 120°C. After 20 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2 × 1 mL), the solution was passed through a short layer of silica gel, solvents were removed on a rotary evaporator, the residue was analyzed by NMR. 85% yield by NMR (average of two experiments). The residue was purified by preparative column chromatography (eluent: toluene:ethyl acetate = 20:1; Rf = 0.95) to afford 76.1 mg (85%) of the product as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.01 (br s, 1H), 3.49 (s, 1H), 2.01 (s, 2H), 1.95 – 1.71 (m, 10H), 1.60 (d, *J* = 12.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 132.0, 114.7, 108.1, 56.9, 37.7, 37.4, 31.6, 31.5, 27.5, 27.3.

NMR spectra are in agreement with the literature data.[32]

Cyclizine, 1-benzhydryl-4-methylpiperazine (7g)



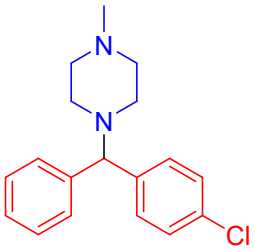
Rhodium(II) acetate dimer (2 mg, 2 mol%, 4.5 µmol), N-methylpiperazine (125 µL, 500 mol%, 1.13 mmol), benzophenone (41 mg, 100 mol%, 0.23 mmol) were added to the 10 ml titanium autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 45 bar of converter gas. The reactor was placed into an oil bath preheated to 130 °C. After 48 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2x1mL), solvents were removed on a rotary evaporator. 76% yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.4 in 10:1 DCM:MeOH) to afford 45 mg (73%) of the product as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 6.7 Hz, 4H), 7.18 (t, J = 7.5 Hz, 4H), 7.08 (t, J = 7.3 Hz, 2H), 4.12 (s, 1H), 2.67 – 2.11 (br s, 8H), 2.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 128.6, 128.0, 127.0, 76.4, 55.5, 52.1, 46.1.

NMR spectra are in agreement with the literature data.[33]

Chlorocyclizine, 1-((4-chlorophenyl)(phenyl)methyl)-4-methylpiperazine (7h)



Rhodium(II) acetate dimer (2 mg, 2 mol%, 4.5 µmol), N-methylpiperazine (125 µL, 500 mol%, 1.13 mmol), (4-chlorophenyl)(phenyl)methanone (49 mg, 100 mol%, 0.23 mmol) were added to the 10 ml titanium autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 45 bar of converter gas. The reactor was placed into an oil bath preheated to 130 °C. After 48 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was washed with dichloromethane (2x1mL), solvents were removed on a rotary evaporator. 72% yield by NMR. The residue was purified using preparative flash chromatograph InterChim PuriFlash in DCM – MeOH binary system (gradient 100% DCM to 10% MeOH in DCM for 30 min, Rf 0.4 in 10:1 DCM:MeOH) to afford 45 mg (65%) of the product as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.29 – 7.22 (m, 4H), 7.21 – 7.16 (m, 1H), 4.19 (s, 1H), 2.74 – 2.04 (m appears as br s, 8H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 141.6, 132.6, 129.3, 128.8, 128.7, 127.9, 127.3, 75.6, 55.5, 52.0, 46.1.

NMR spectra are in agreement with the literature data.[34]

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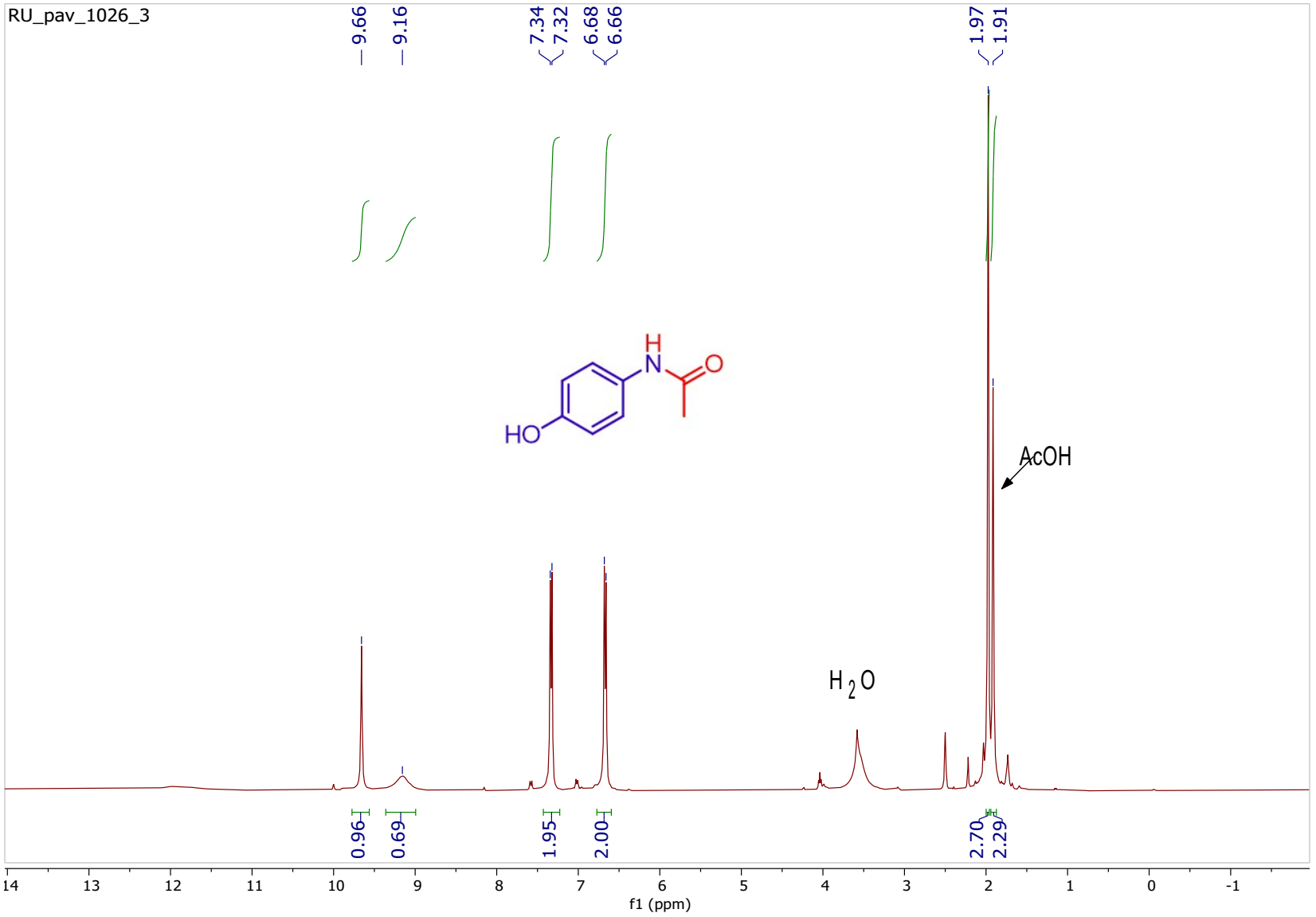
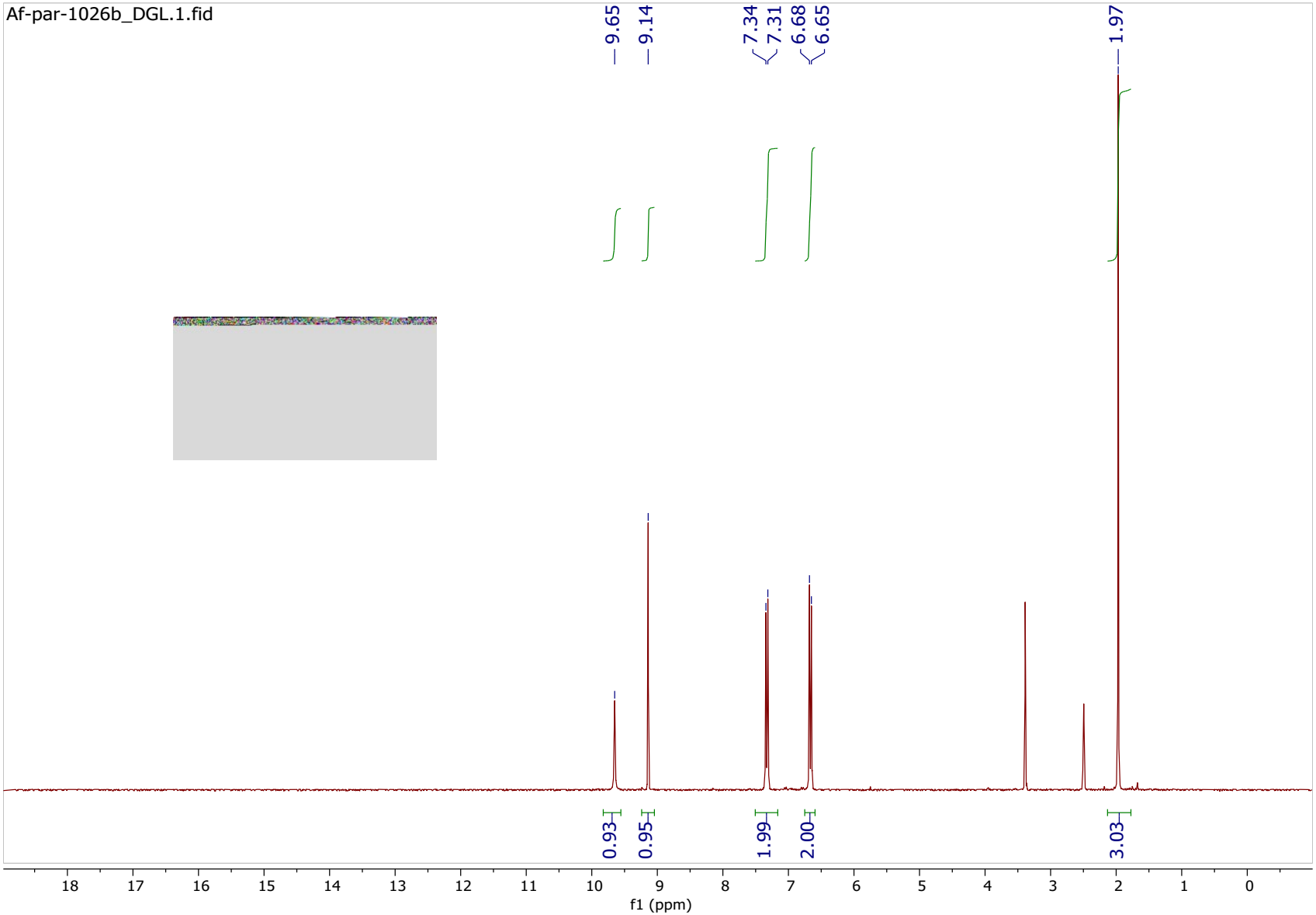
^{1}H and ^{13}C NMR, and mass spectra of products

Paracetamol, N-(4-hydroxyphenyl)acetamide reaction mixture (3a) (^{1}H NMR, DMSO-d6, 400 MHz)

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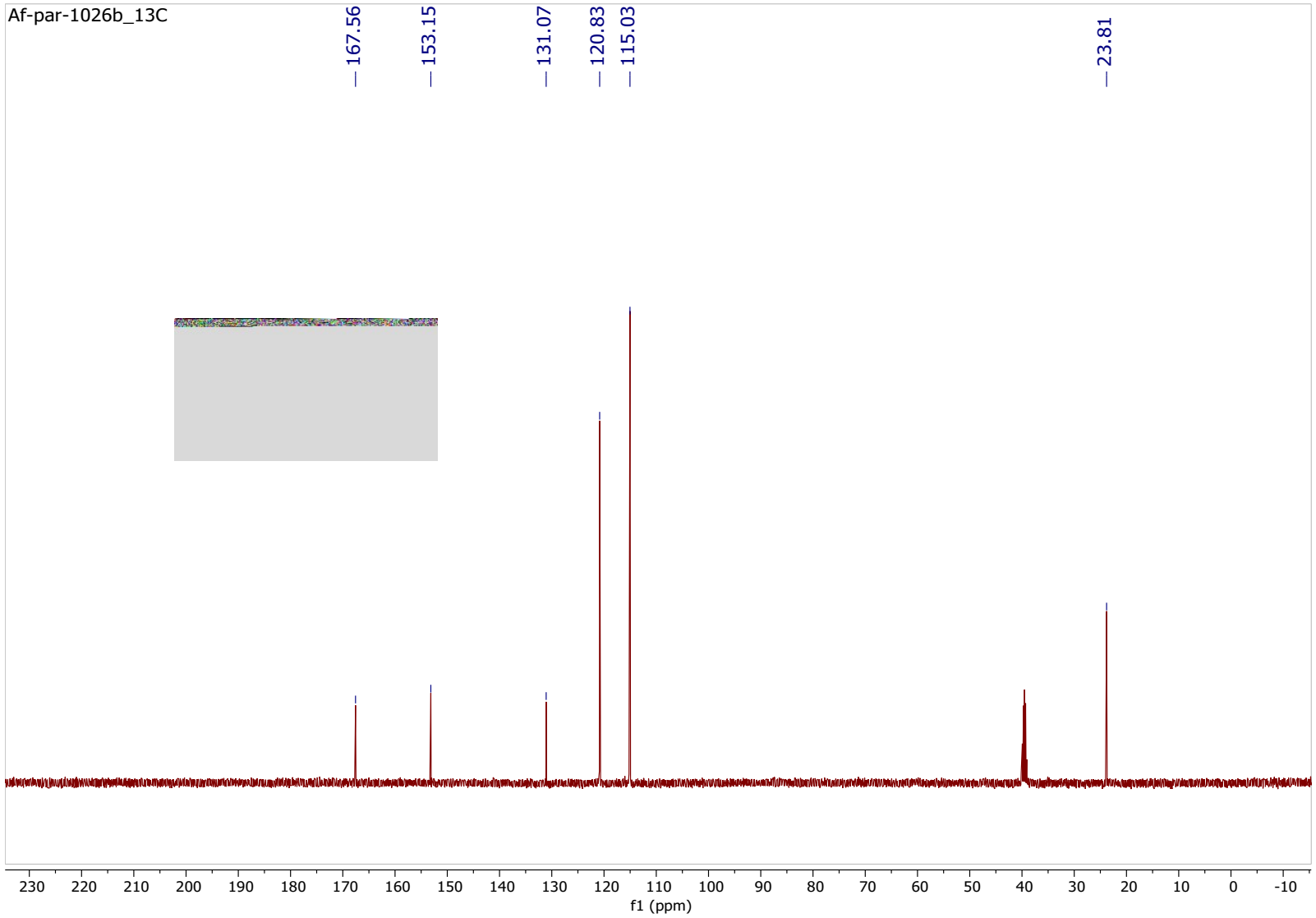
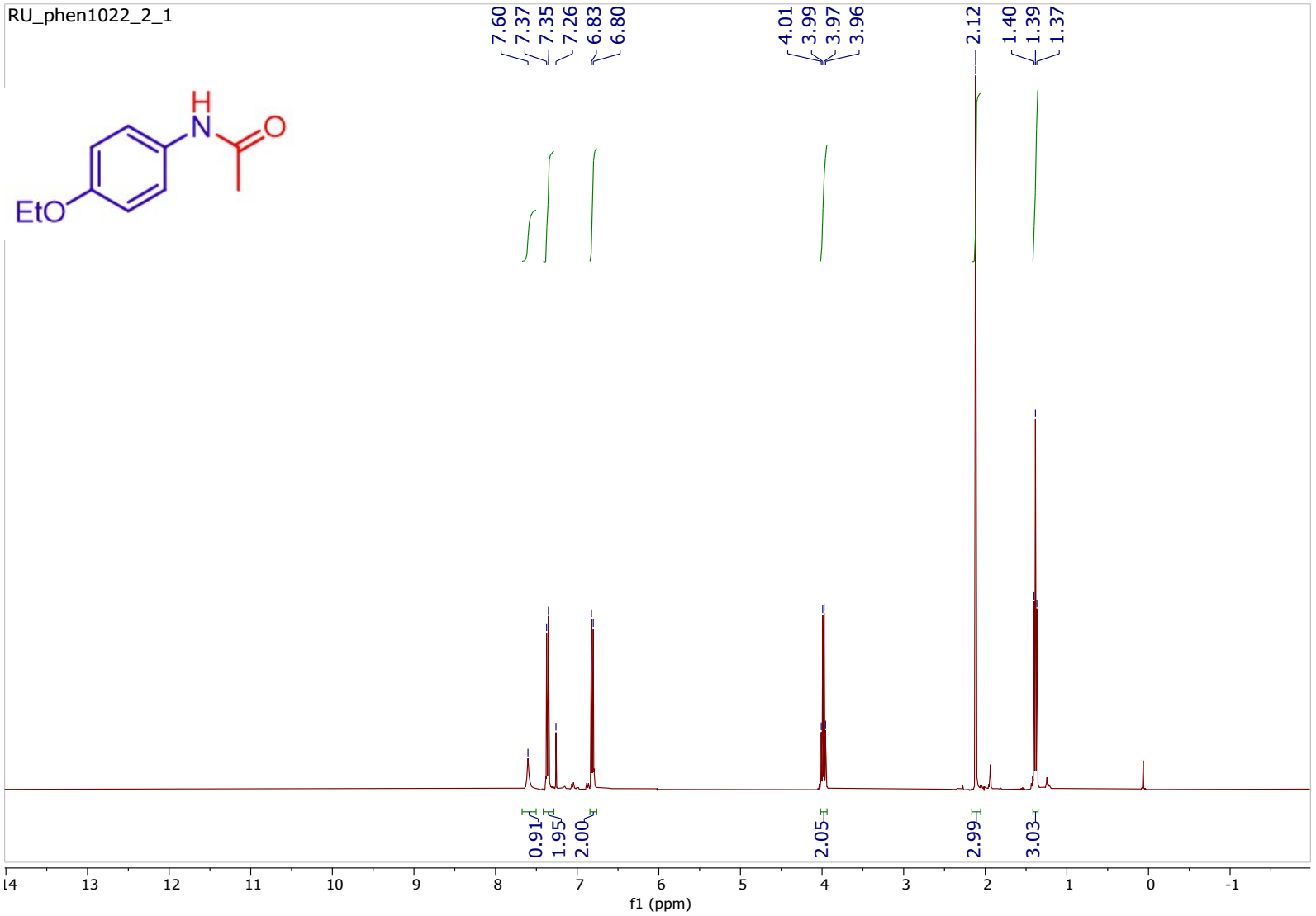
9.65
9.14
7.34
7.31
6.68
6.65
1.97
0.93
0.95
1.99
2.00
3.03
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

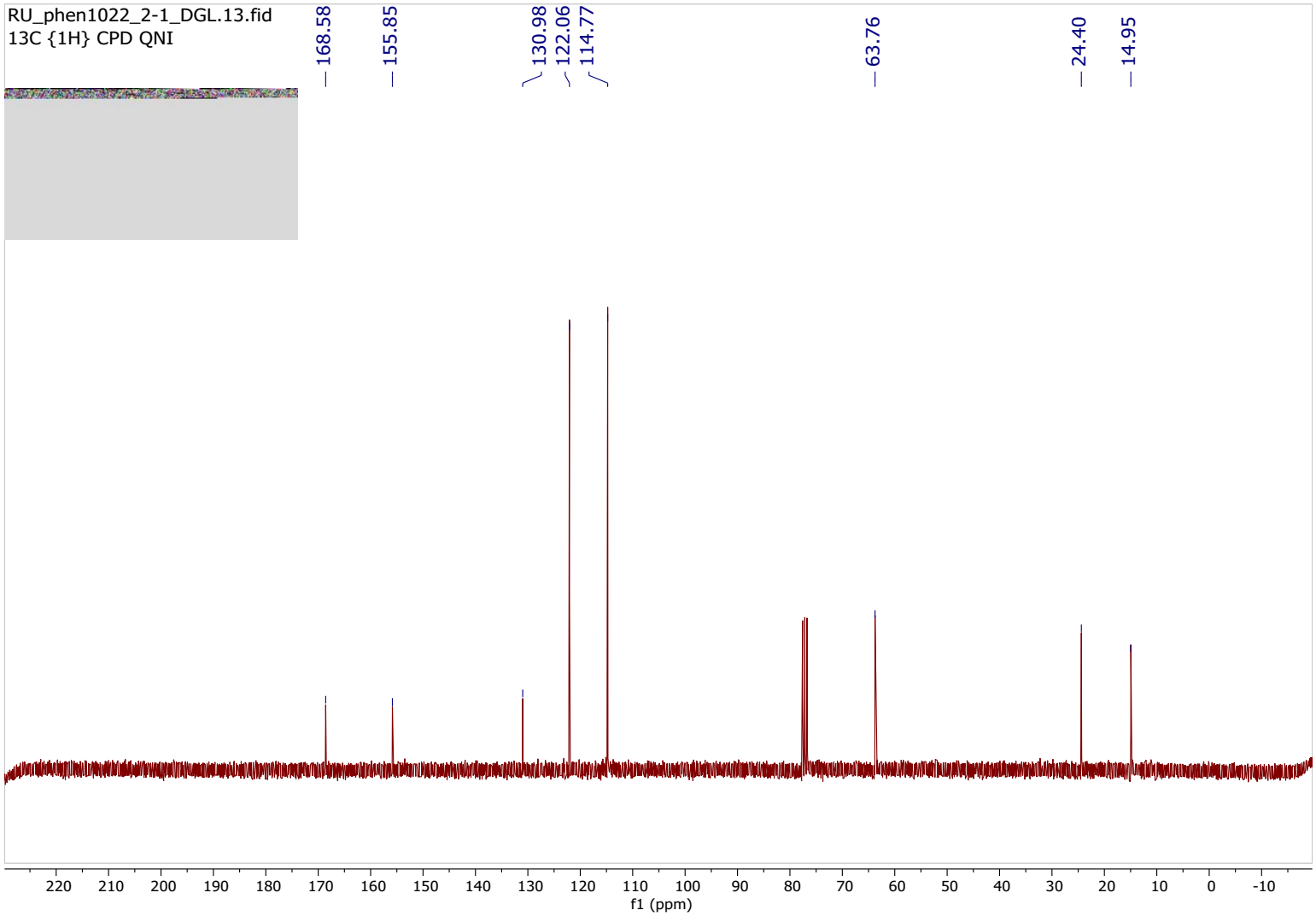
Paracetamol, N-(4-hydroxyphenyl)acetamide (3a) (^{13}C NMR, DMSO-d6, 101 MHz)



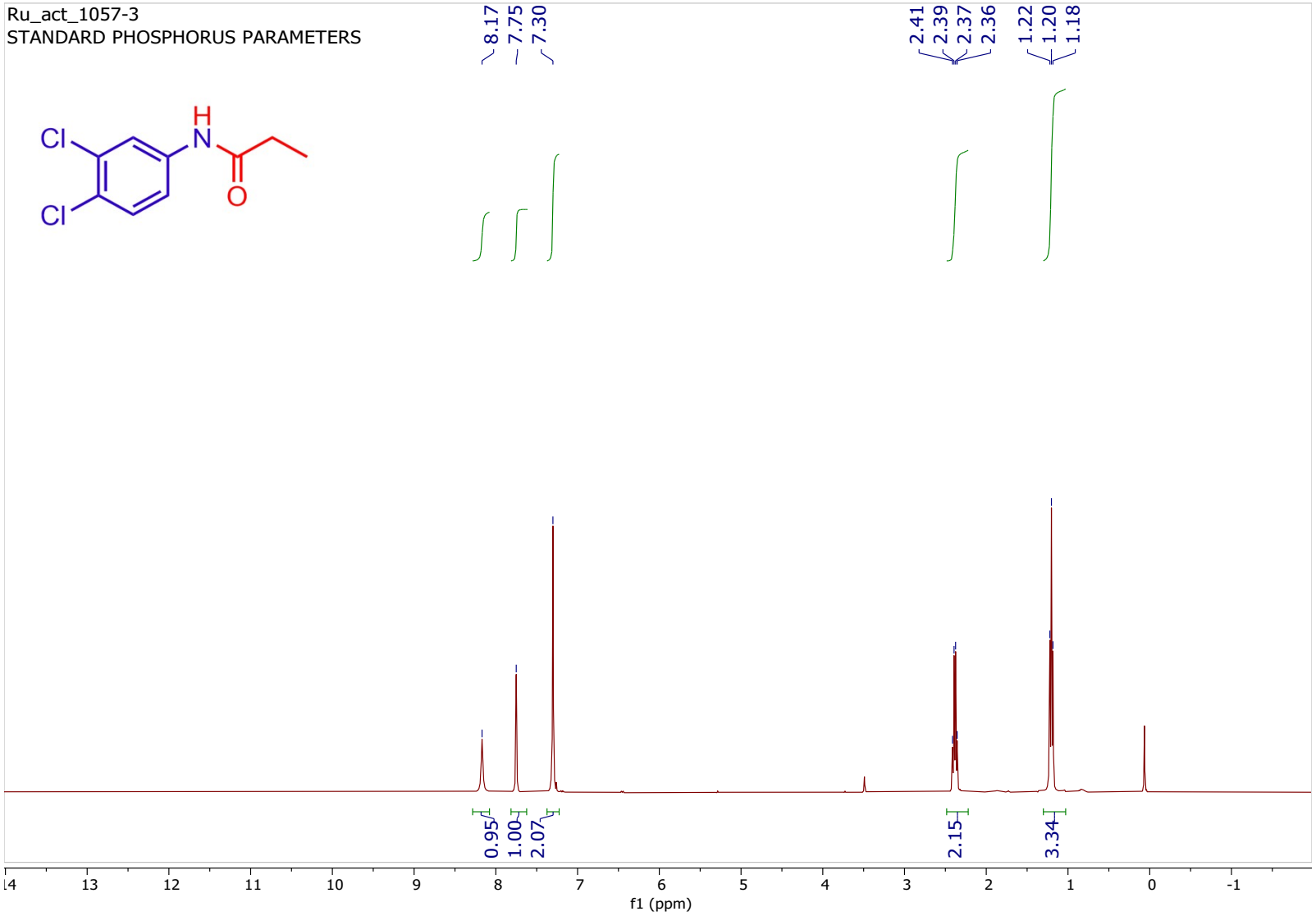
Phenacetin, 4-methoxy-*N*-(4-methylbenzyl)aniline (3b) (^{1}H NMR, $CDCl_3$, 400 MHz)



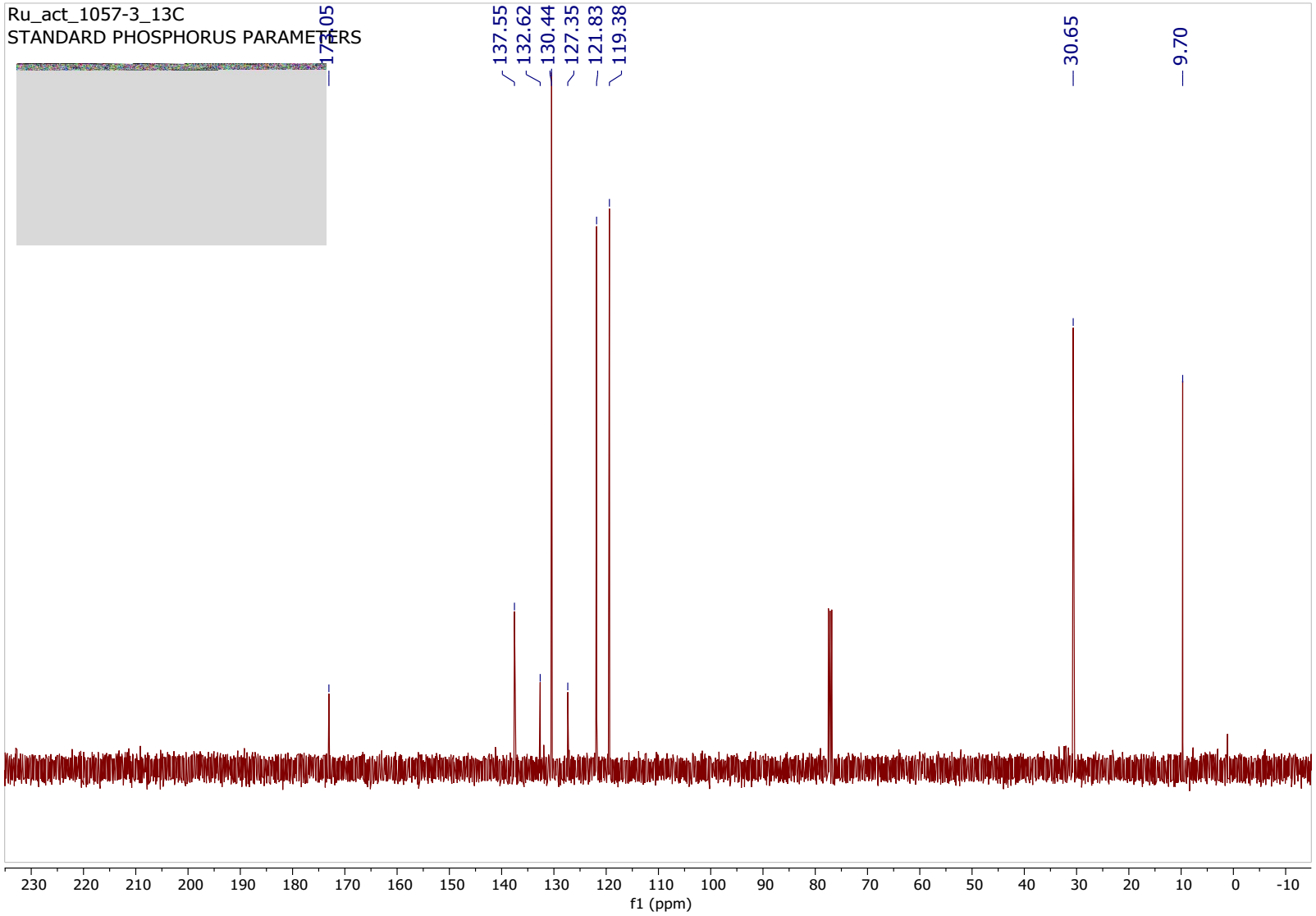
Phenacetin, 4-methoxy-*N*-(4-methylbenzyl)aniline (3b) (^{13}C NMR, $CDCl_3$, 75 MHz)



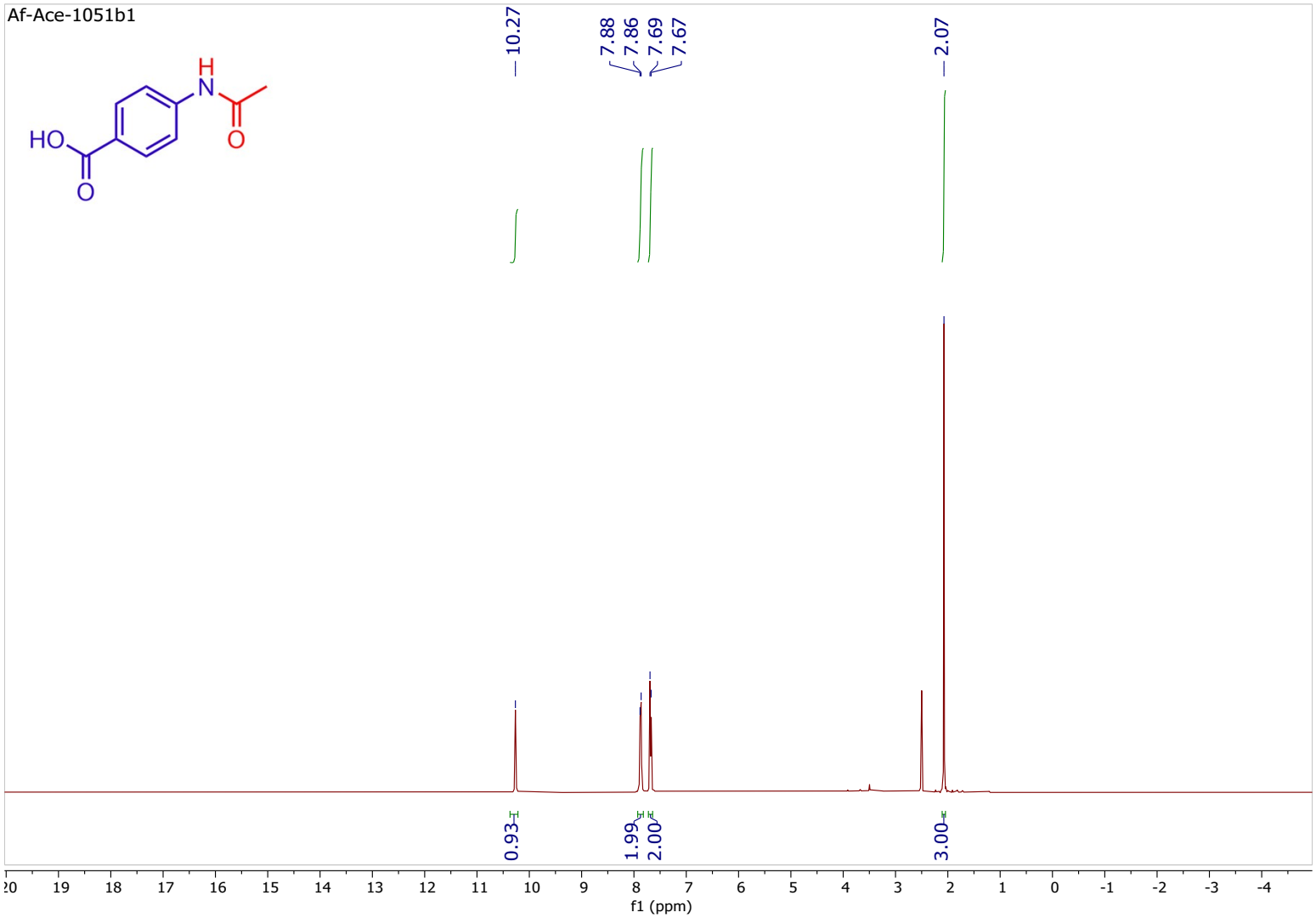
Propanil, N-(3,4-dichlorophenyl)propionamide (3c) (^{1}H NMR, $CDCl_3$, 400 MHz)



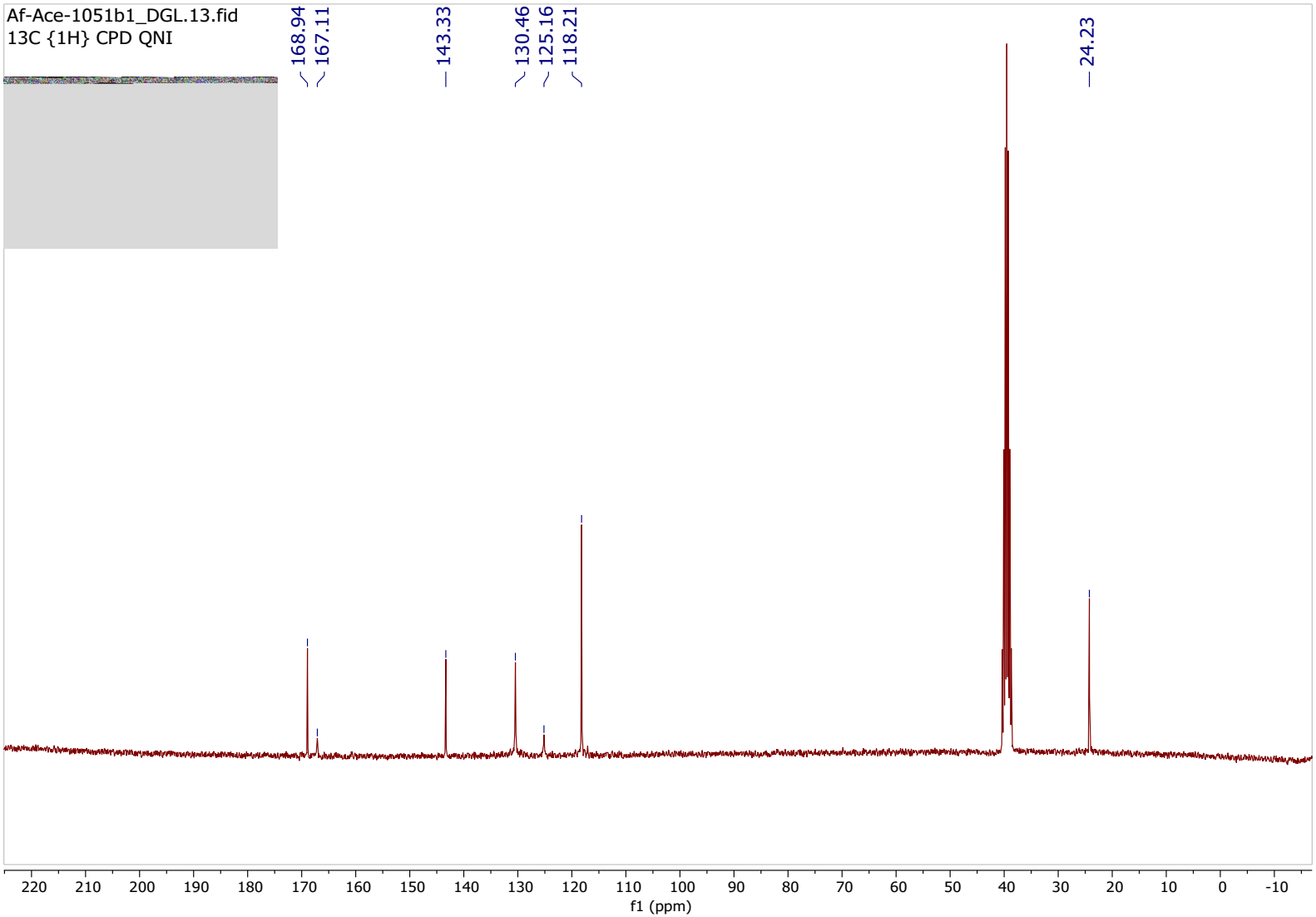
Propanil, N-(3,4-dichlorophenyl)propionamide (3c) (^{13}C NMR, $CDCl_3$, 101 MHz)



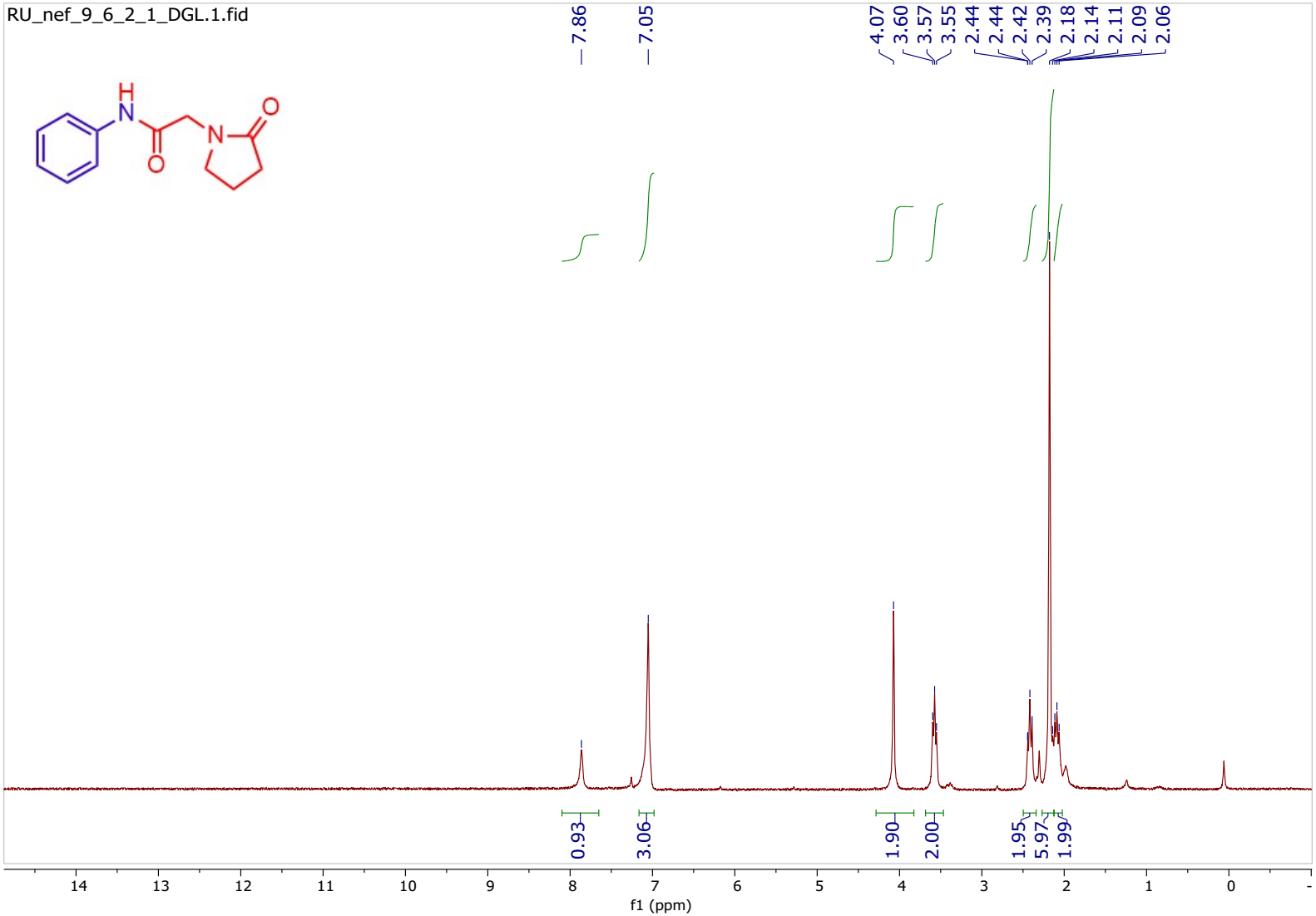
Acedoben, 4-acetamidobenzoic acid (3d) (^{1}H NMR, DMSO-d_6, 300 MHz)



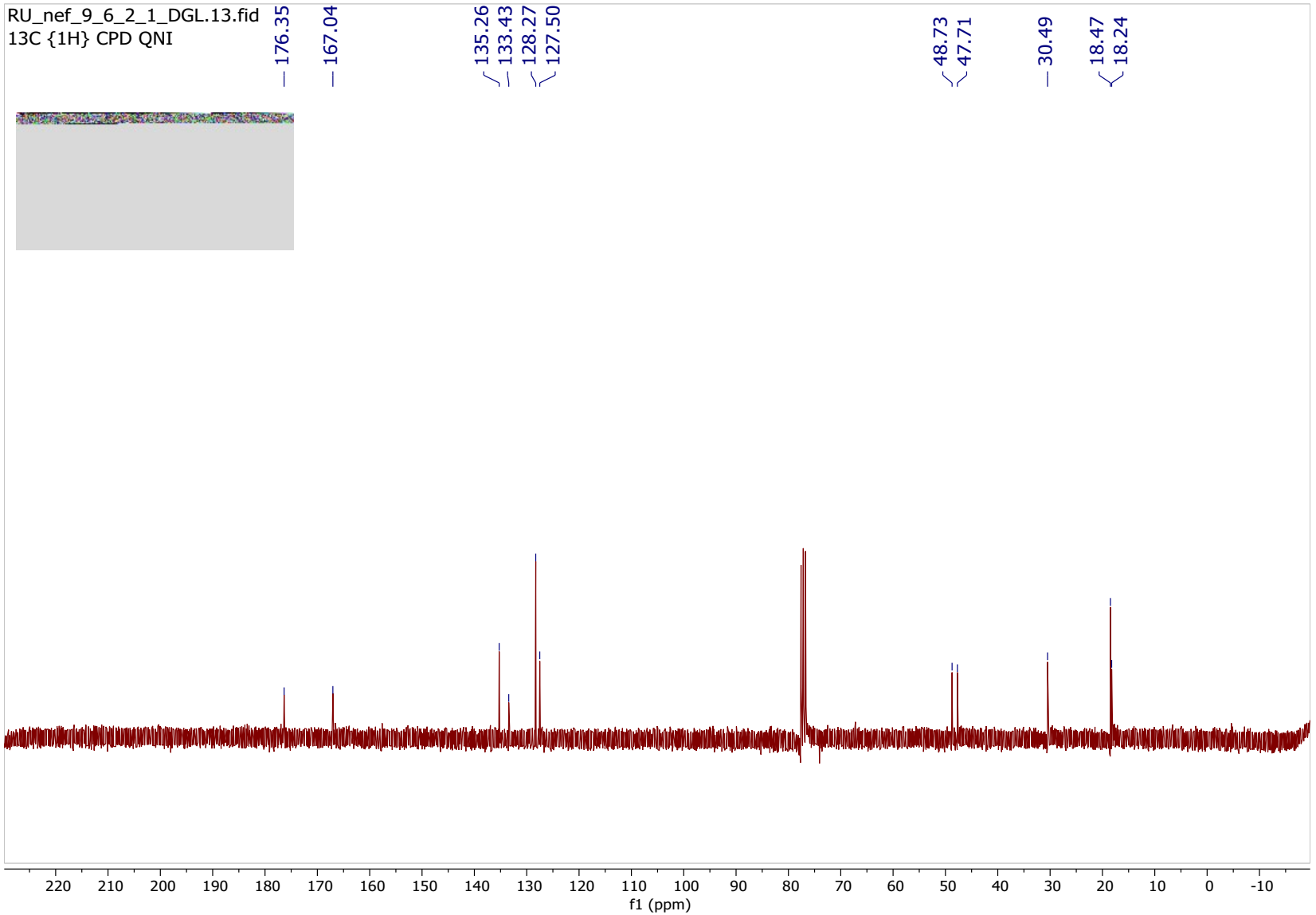
Acedoben, 4-acetamidobenzoic acid (3d) (^{13}C NMR, DMSO-d_6, 75 MHz)



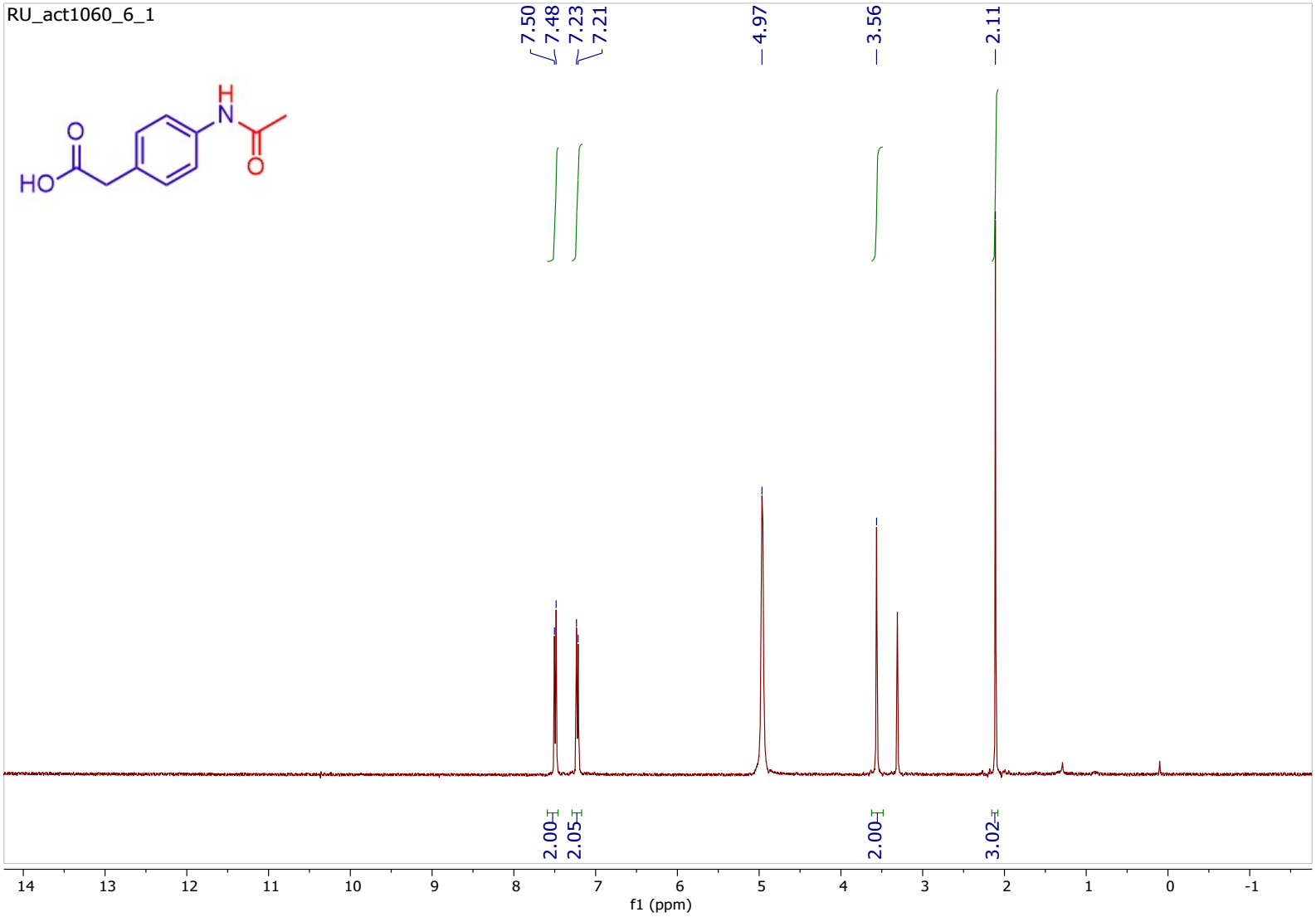
Nefiracetam, N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide (3e) (^{1}H NMR, $CDCl_3$, 300 MHz)



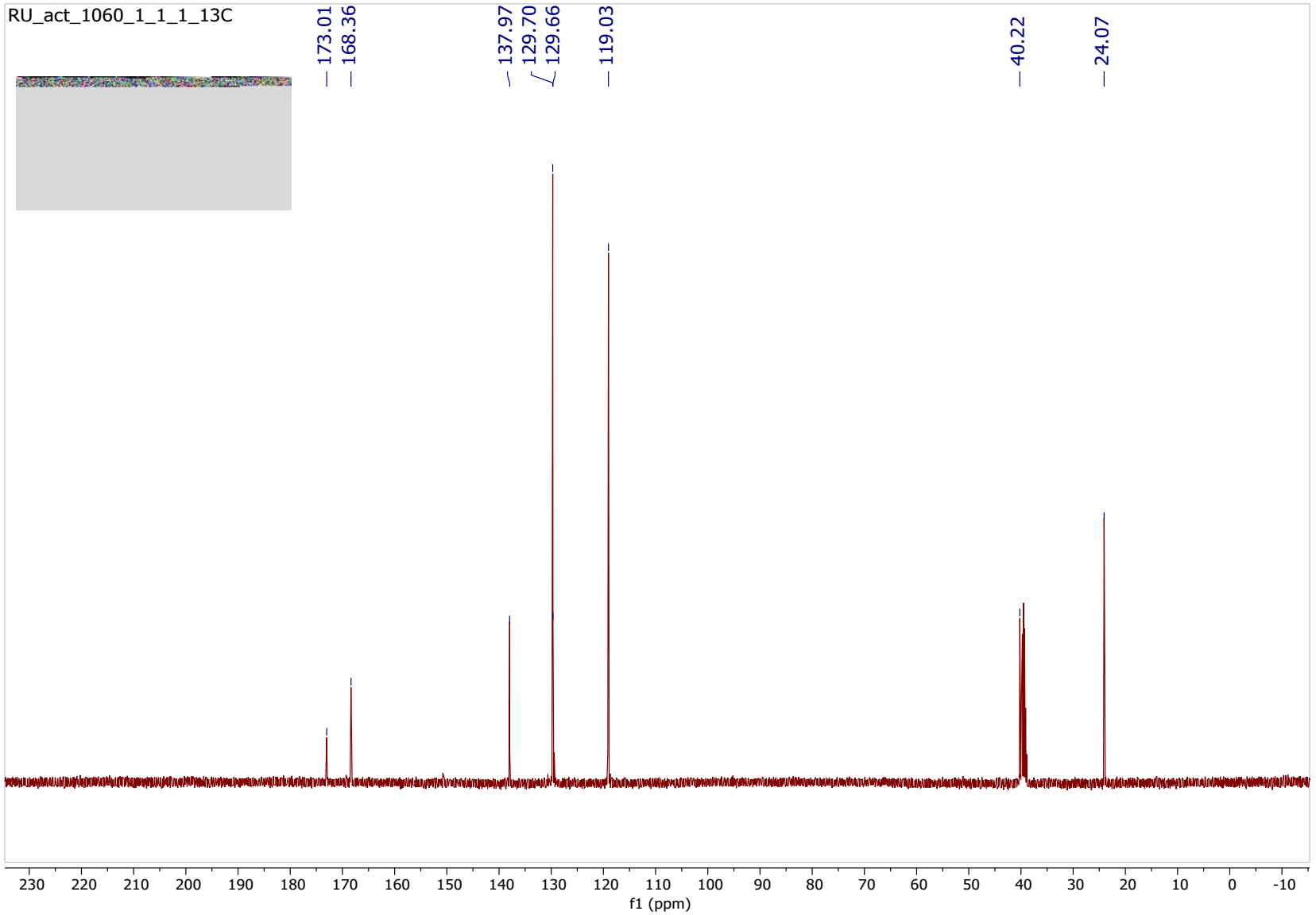
Nefiracetam, N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide (3e) (^{13}C NMR, $CDCl_3$, 75 MHz)



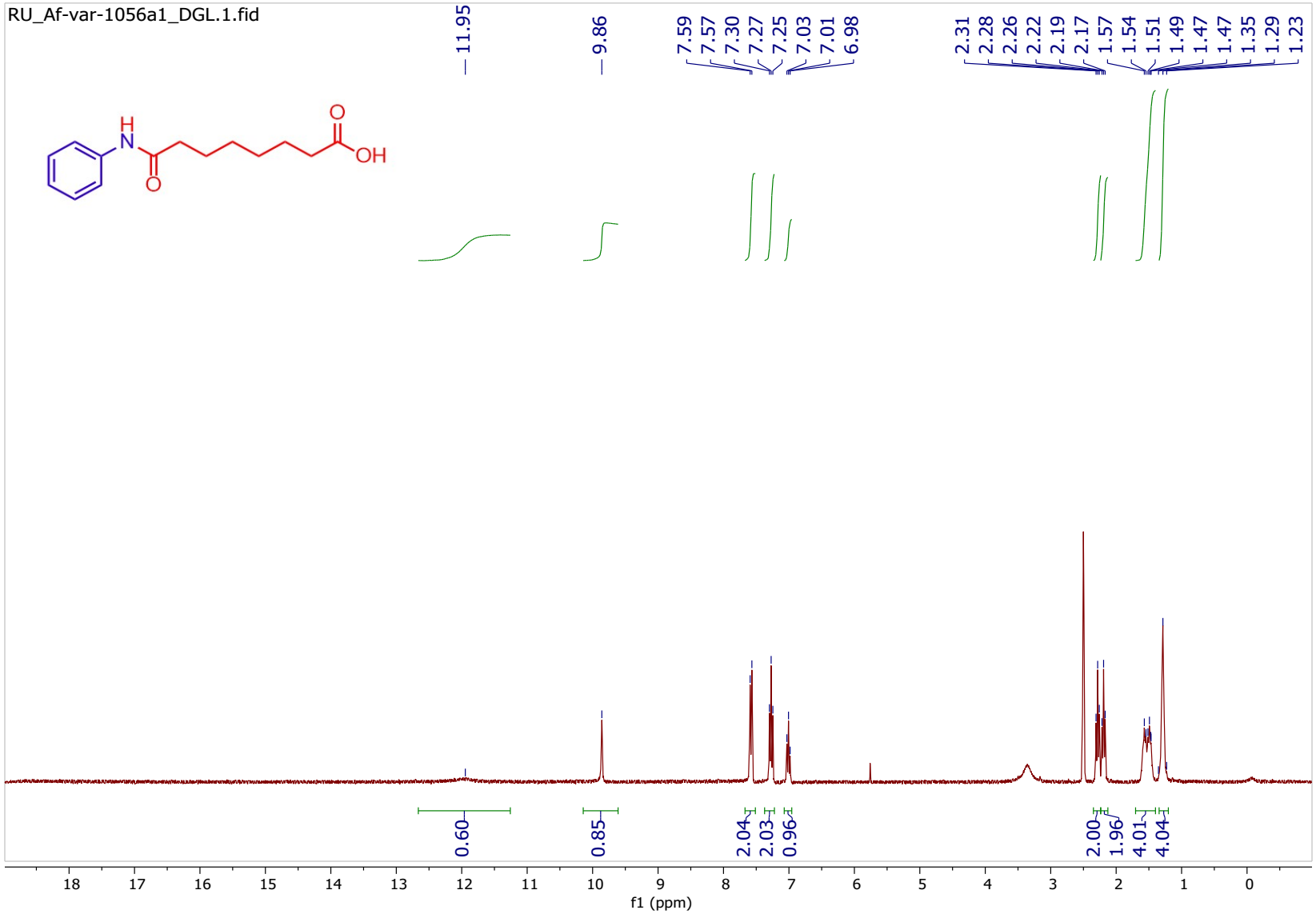
Actarit, 2-(4-acetamidophenyl)acetic acid (3f) (^{1}H NMR, Methanol-d_4, 400 MHz)



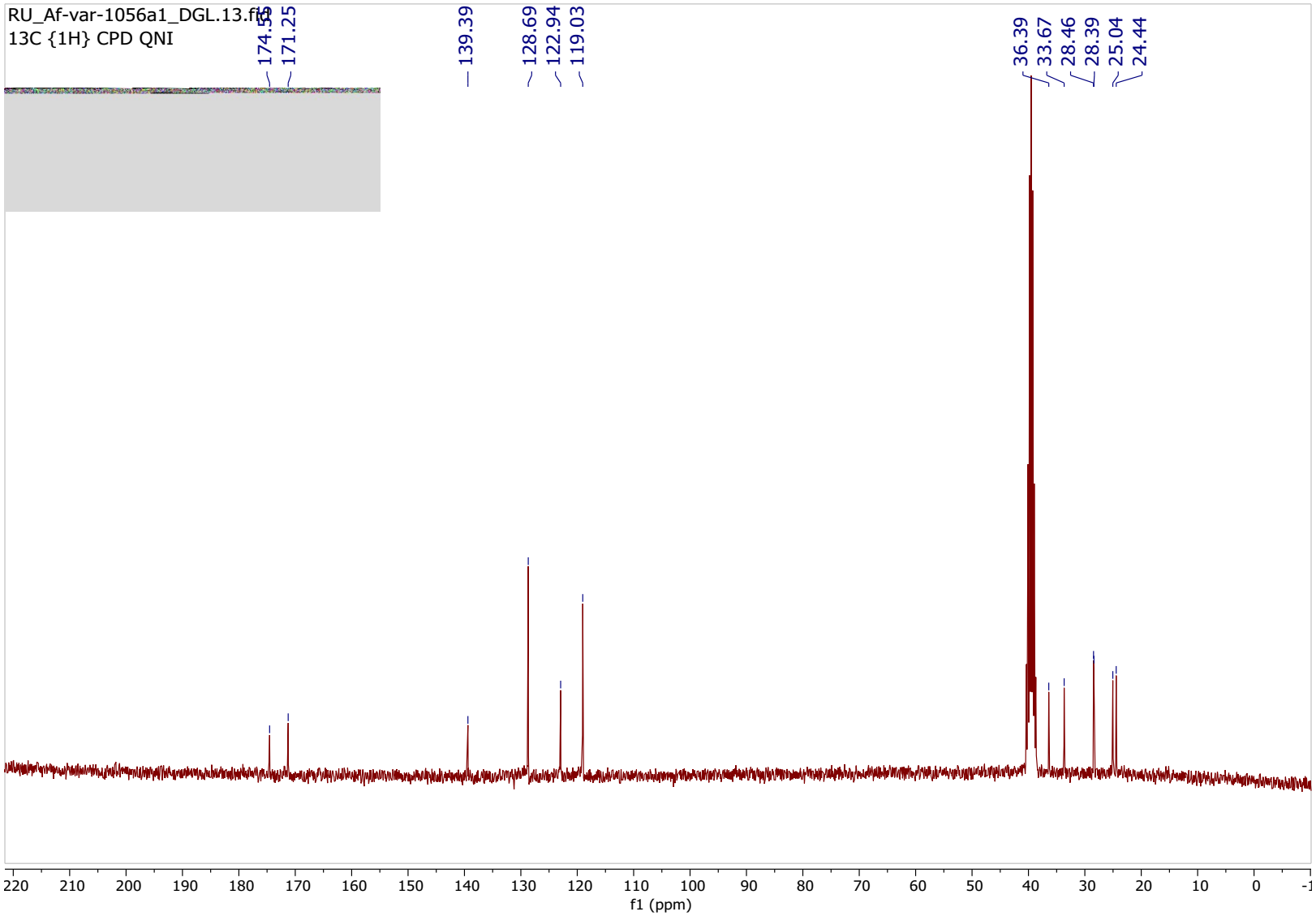
Actarit, 2-(4-acetamidophenyl)acetic acid (3f) (^{13}C NMR, DMSO-d$_6$, 101 MHz)



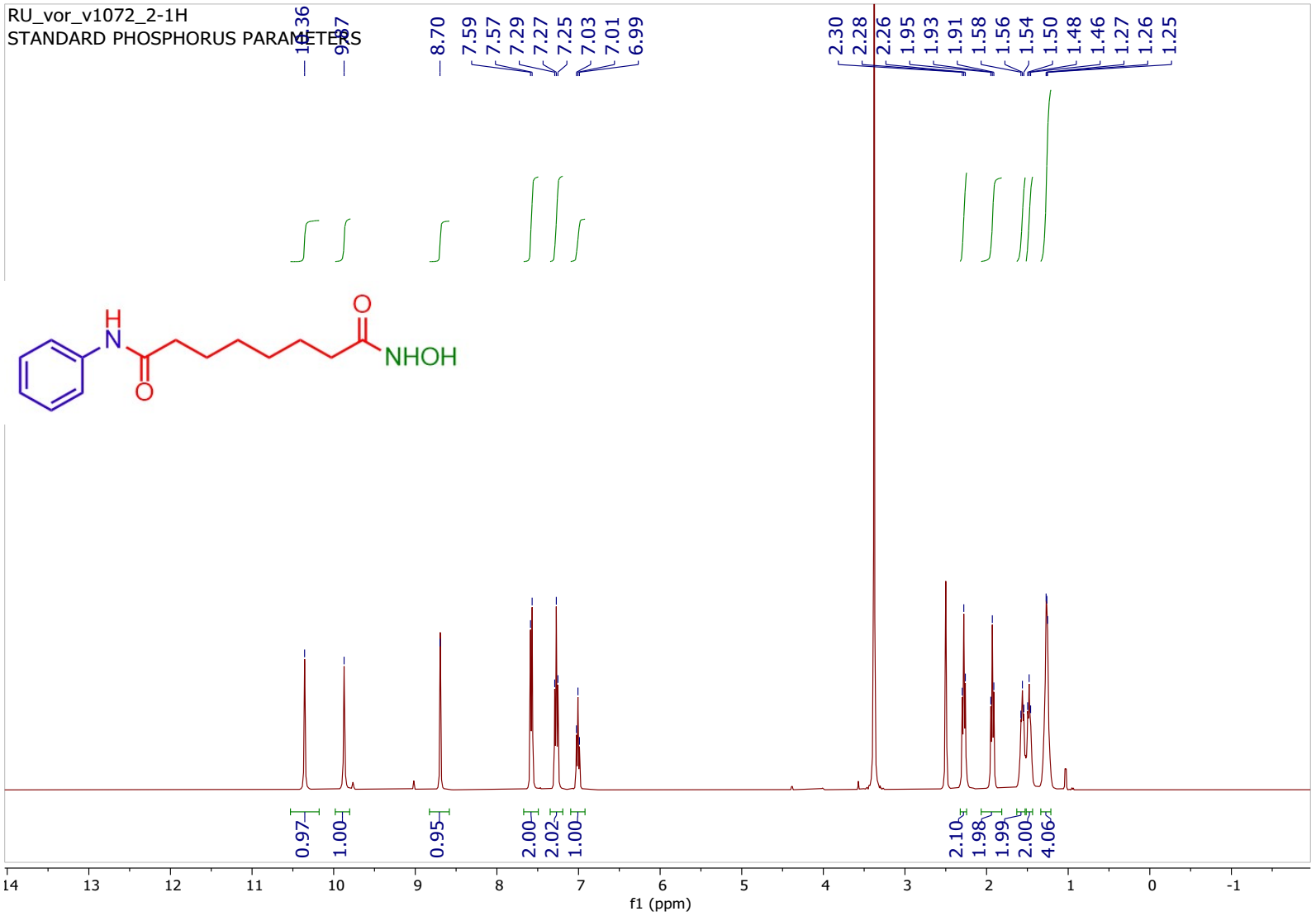
Suberanilic acid, 8-oxo-8-(phenylamino)octanoic acid (3g) (^{1}H NMR, DMSO-d_6, 300 MHz)



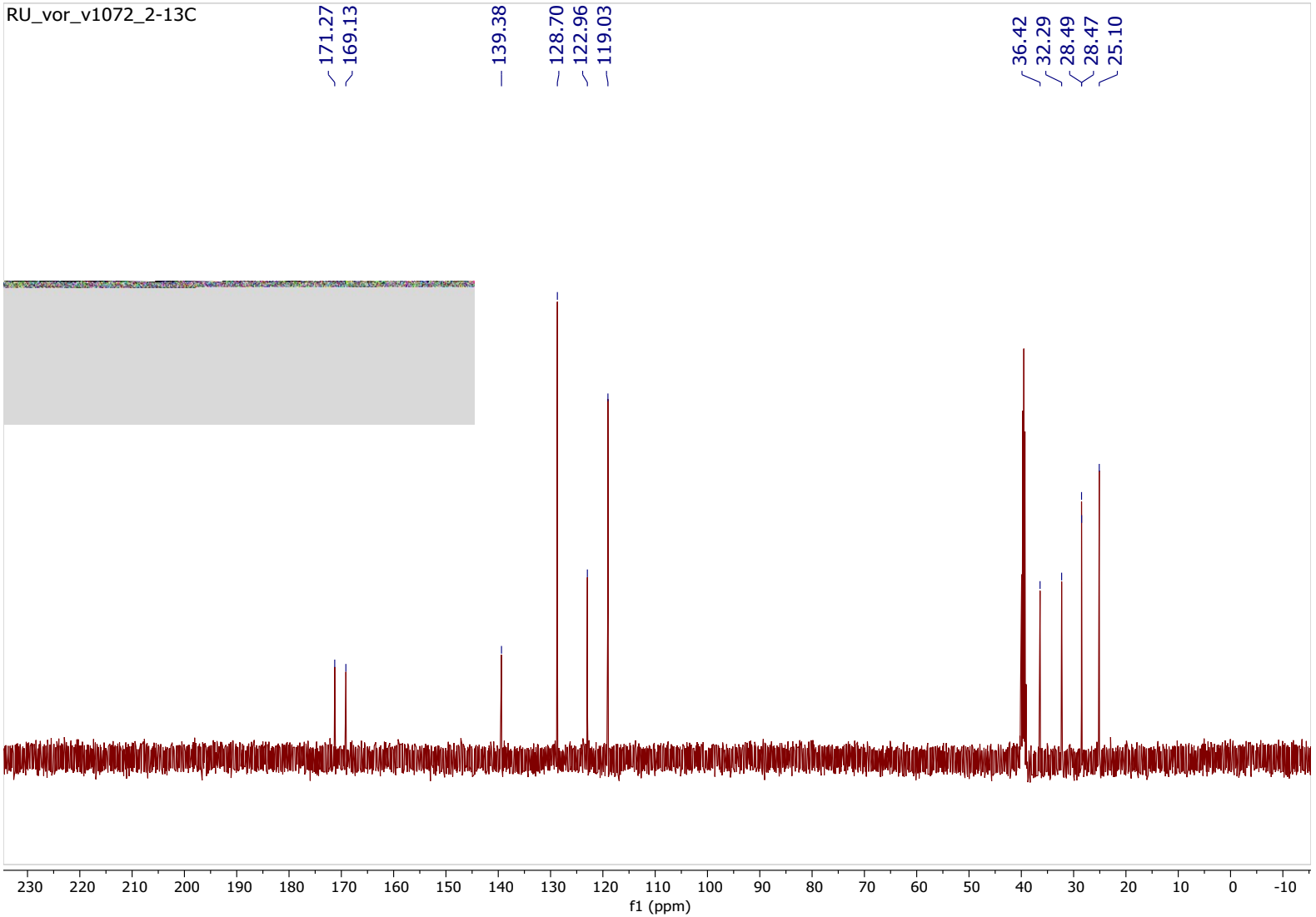
Suberanilic acid, 8-oxo-8-(phenylamino)octanoic acid (3g) (^{13}C NMR, DMSO-d$_6$, 75 MHz)



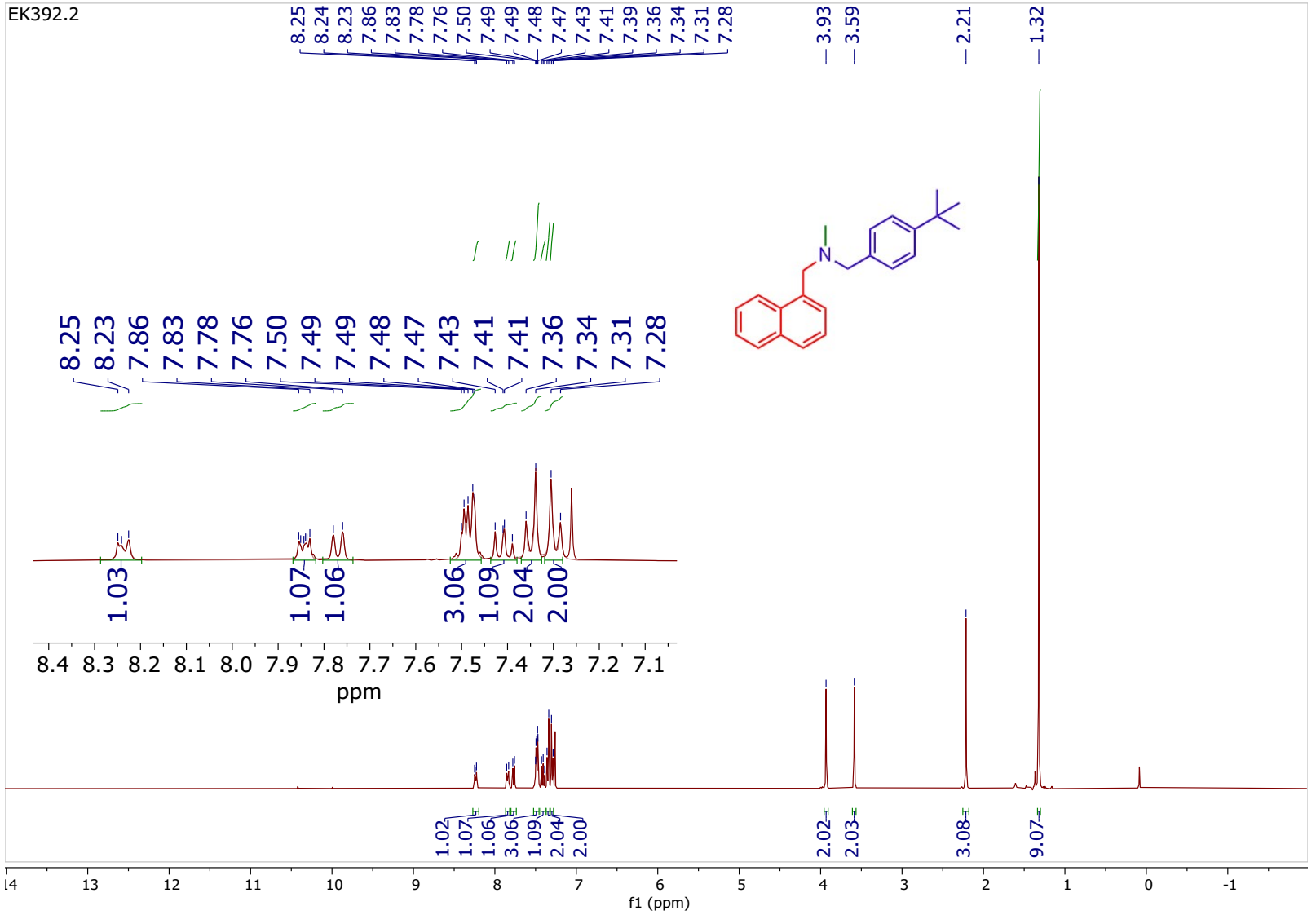
Vorinostat, N1-hydroxy-N8-phenyloctanediamide (4) (^{1}H NMR, DMSO-d_6, 400 MHz)



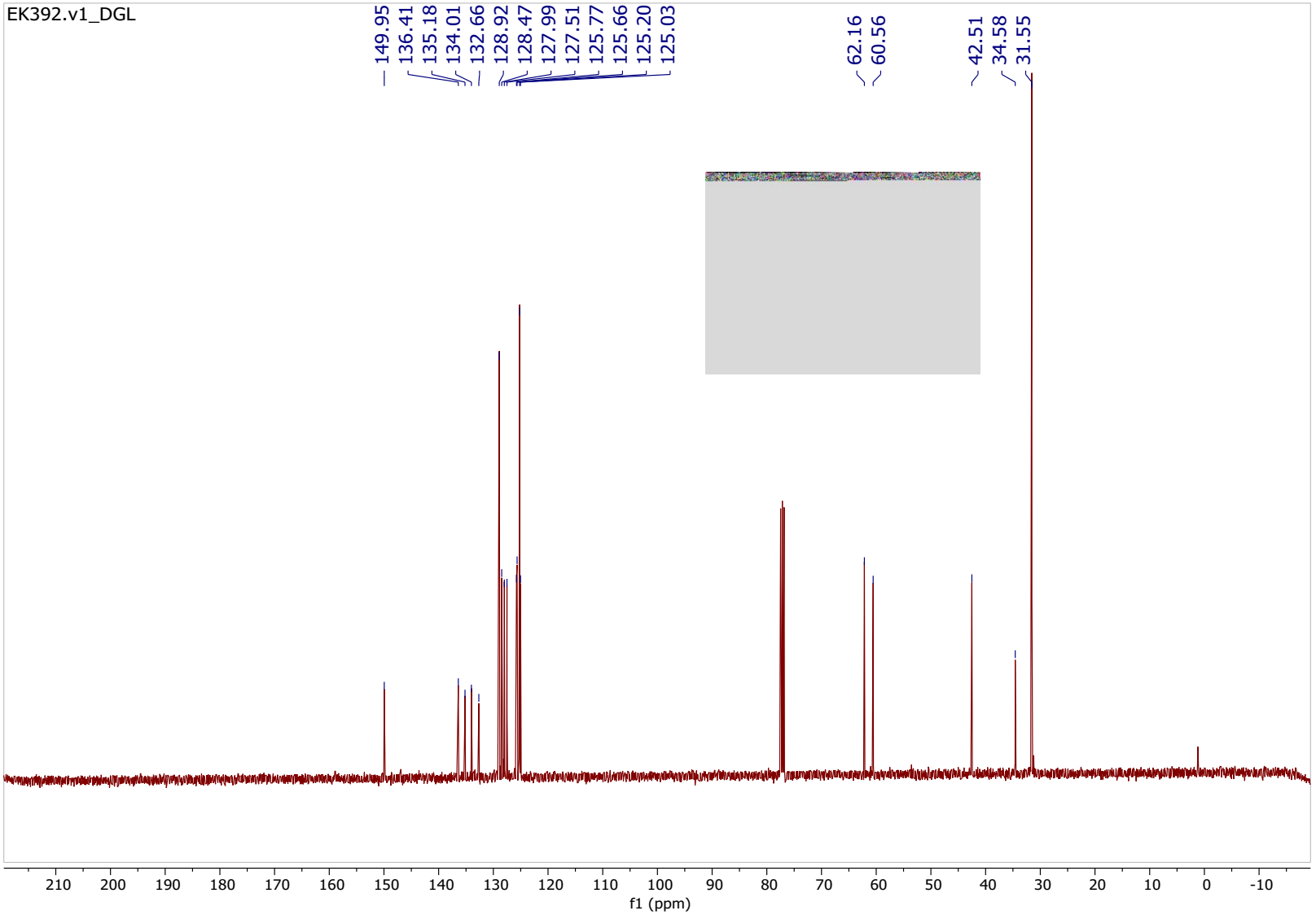
Vorinostat, N1-hydroxy-N8-phenyloctanediamide (4) (^{13}C NMR, DMSO-d_6, 101 MHz)



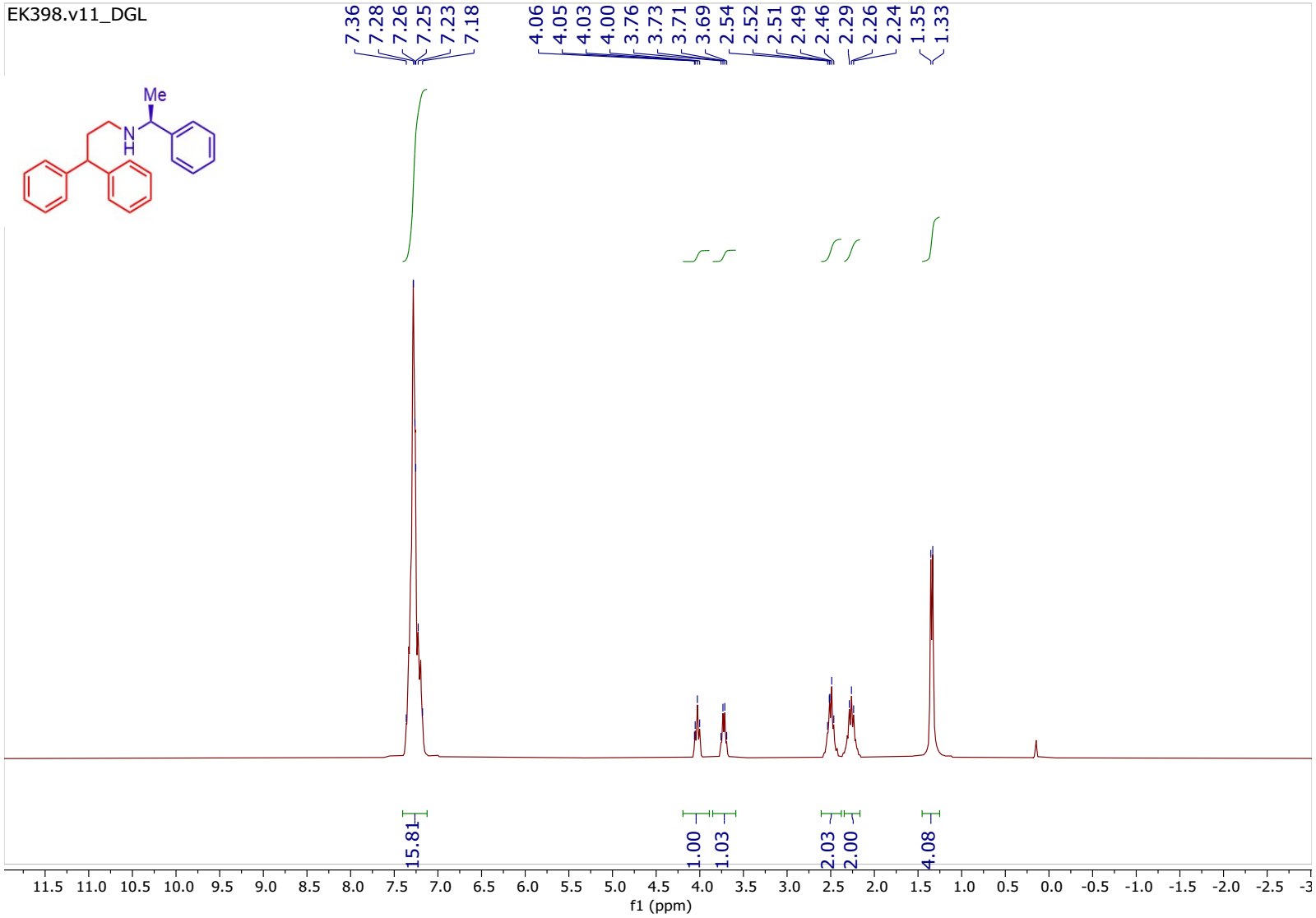
Butenafine, N-(4-(tert-butyl)benzyl)-N-methyl-1-(naphthalen-1-yl)methanamine (7a) (^{1}H NMR, $CDCl_3$, 400 MHz)



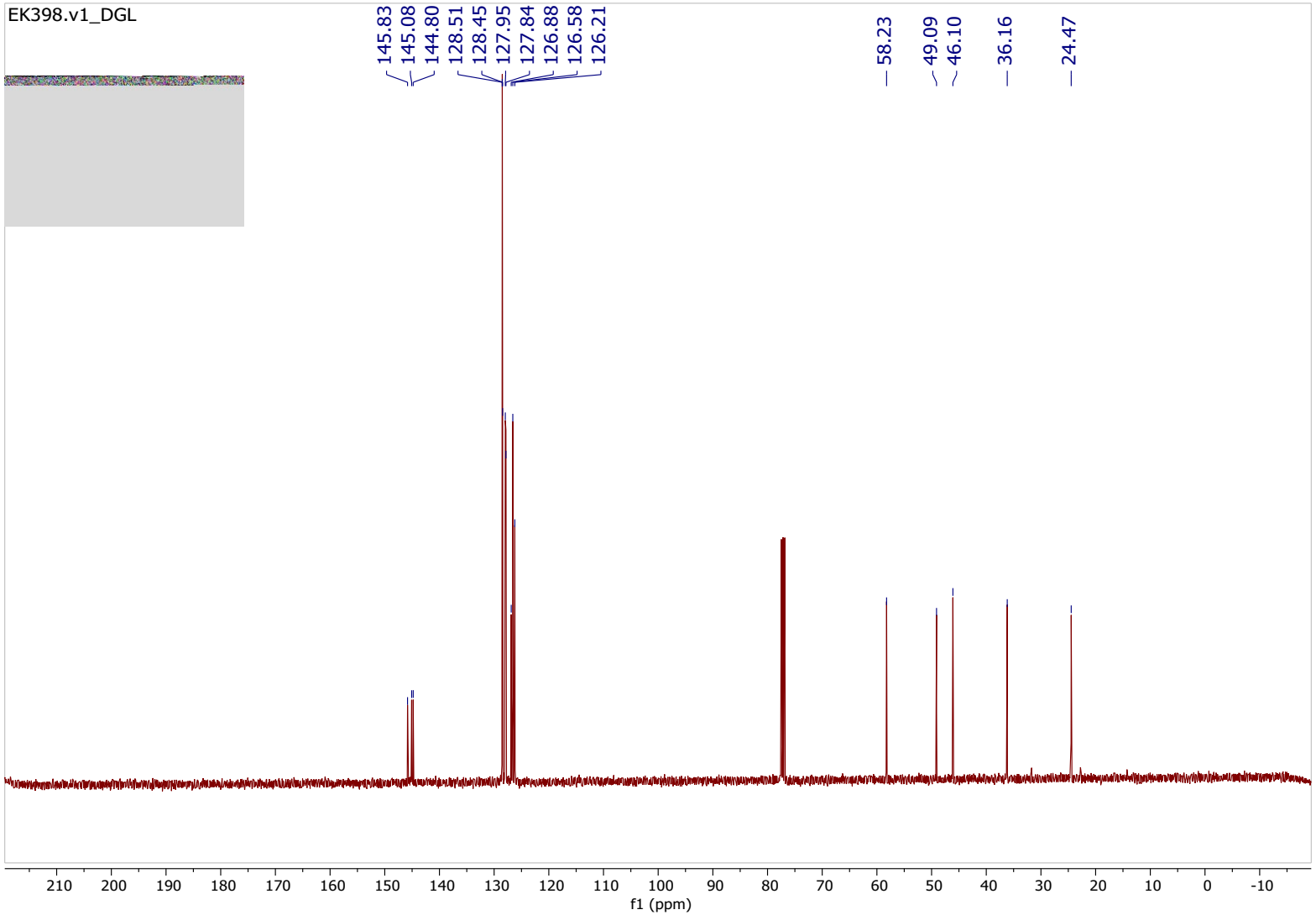
Butenafine, N-(4-(tert-butyl)benzyl)-N-methyl-1-(naphthalen-1-yl)methanamine (7a) (^{13}C NMR, $CDCl_3$, 101 MHz)



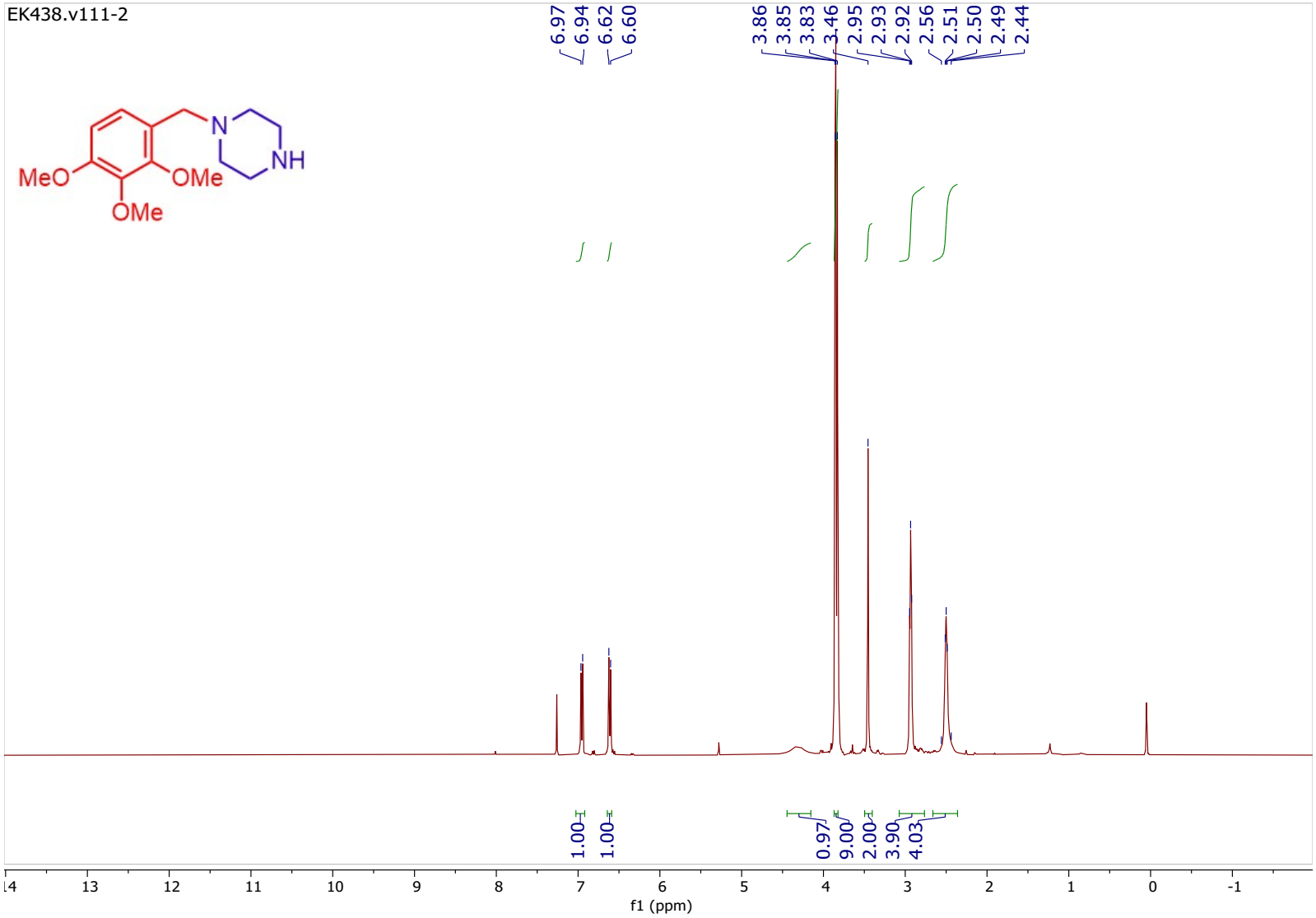
(-)-Fendiline, (S)-3,3-diphenyl-N-(1-phenylethyl)propan-1-amine (7b) (^{1}H NMR, $CDCl_3$, 300 MHz)



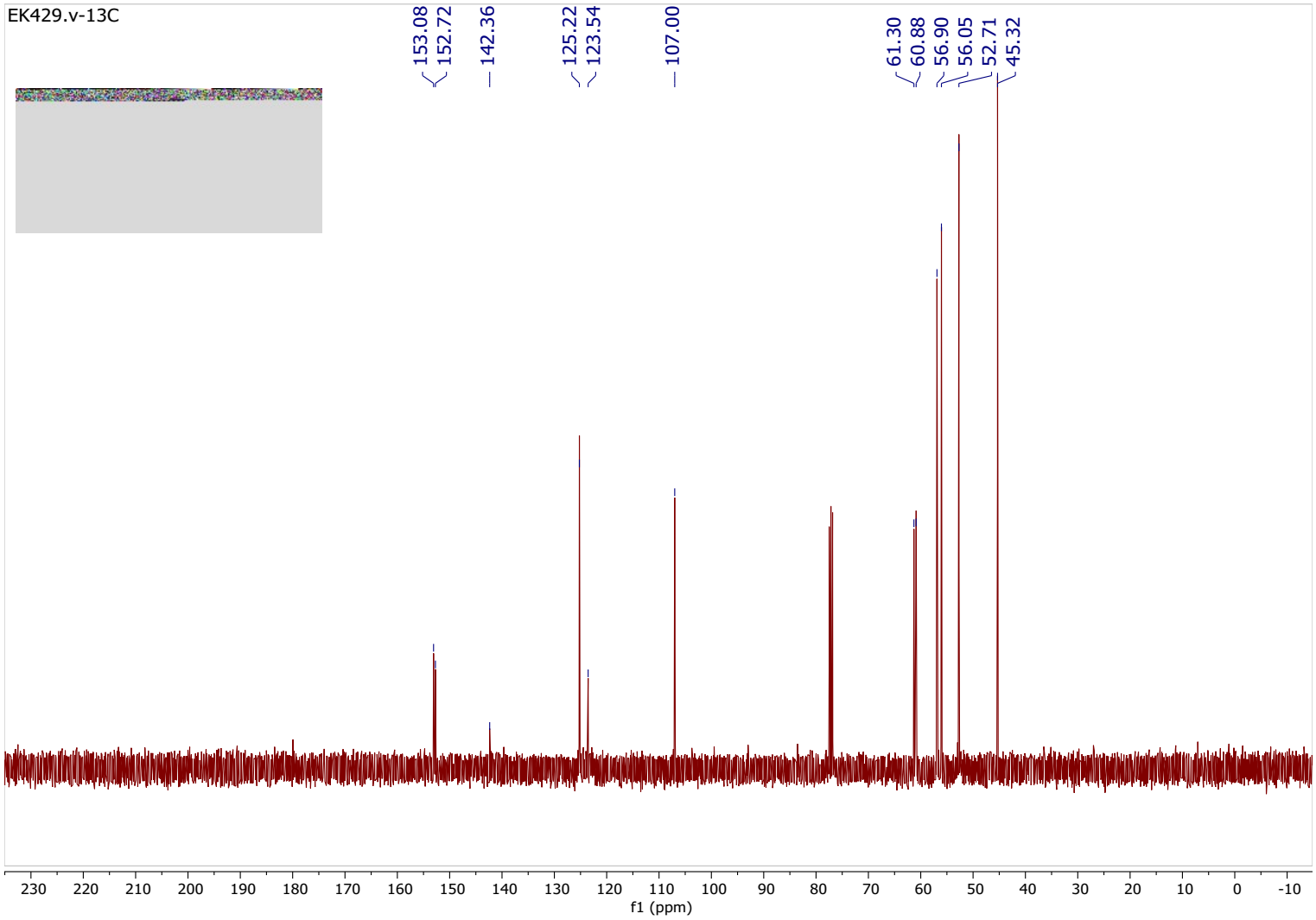
(-)-Fendiline, (S)-3,3-diphenyl-N-(1-phenylethyl)propan-1-amine (7b) (^{13}C NMR, $CDCl_3$, 101 MHz)



Trimetazidine, 1-(2,3,4-trimethoxybenzyl)piperazine (7c) (^{1}H NMR, $CDCl_3$, 400 MHz)



Trimetazidine 1-(2,3,4-trimethoxybenzyl)piperazine (7c) (^{13}C NMR, $CDCl_3$, 101 MHz)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123.54
107.00
61.30
60.88
56.90
56.05
52.71
45.32
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Trimetazidine 1-(2,3,4-trimethoxybenzyl)piperazine (7c) (HRMS)

Display Report

Analysis Info

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Method	la_2.2_small.m	Operator	BDAL@DE
Sample Name	DCh-24 (trim)	Instrument	compact 8255754.20088
Comment			

Acquisition Parameter

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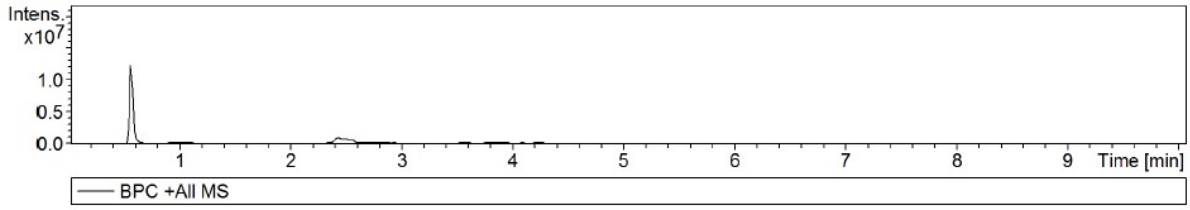
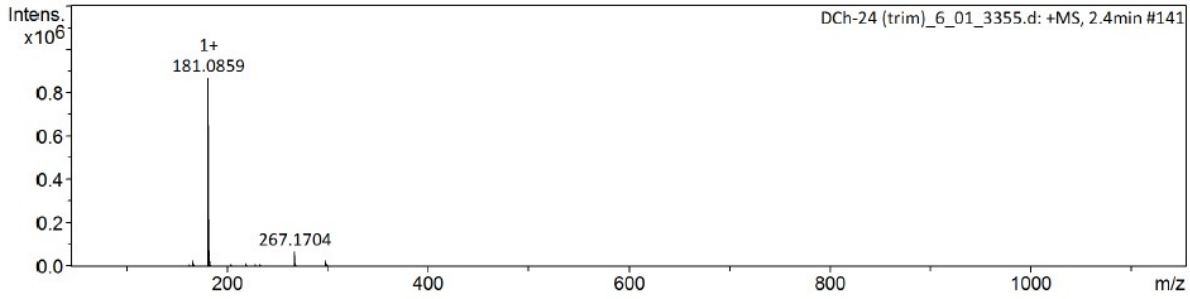
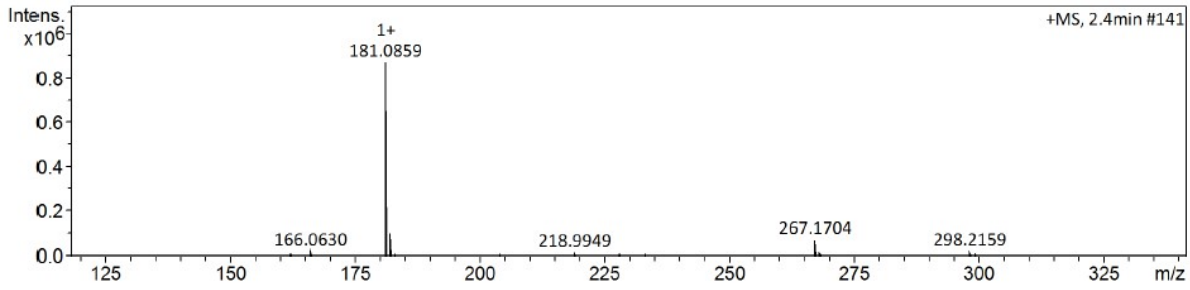
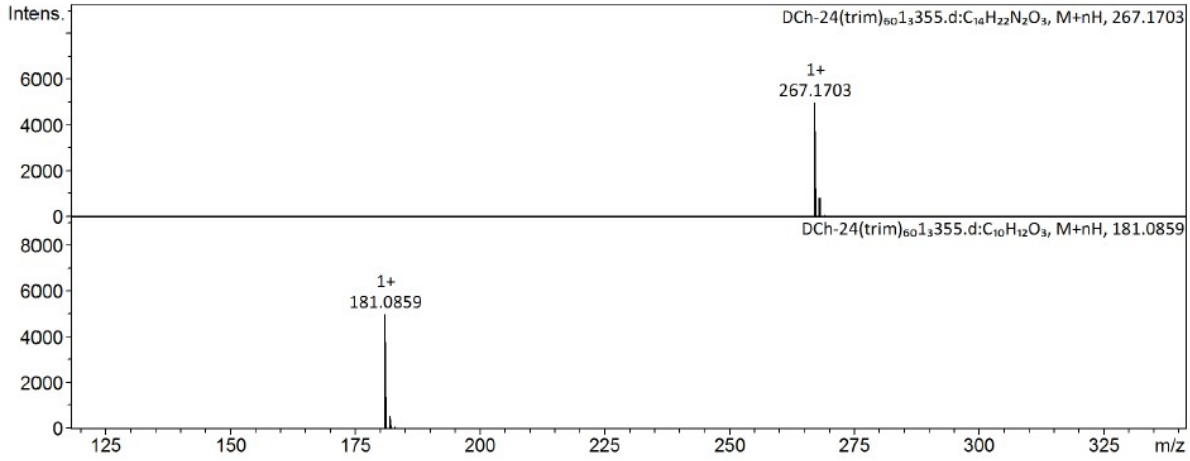
Scan End	3000 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C





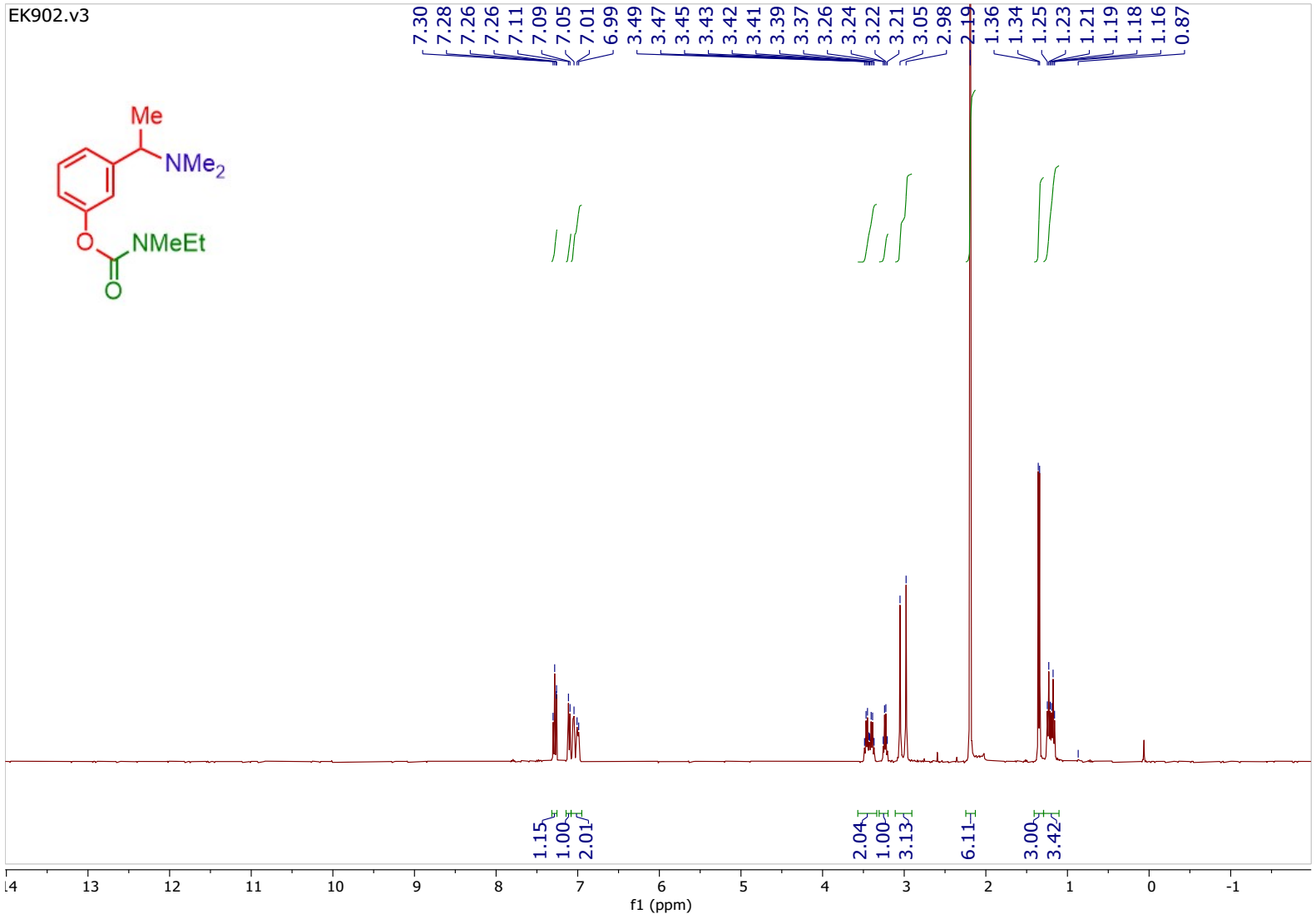




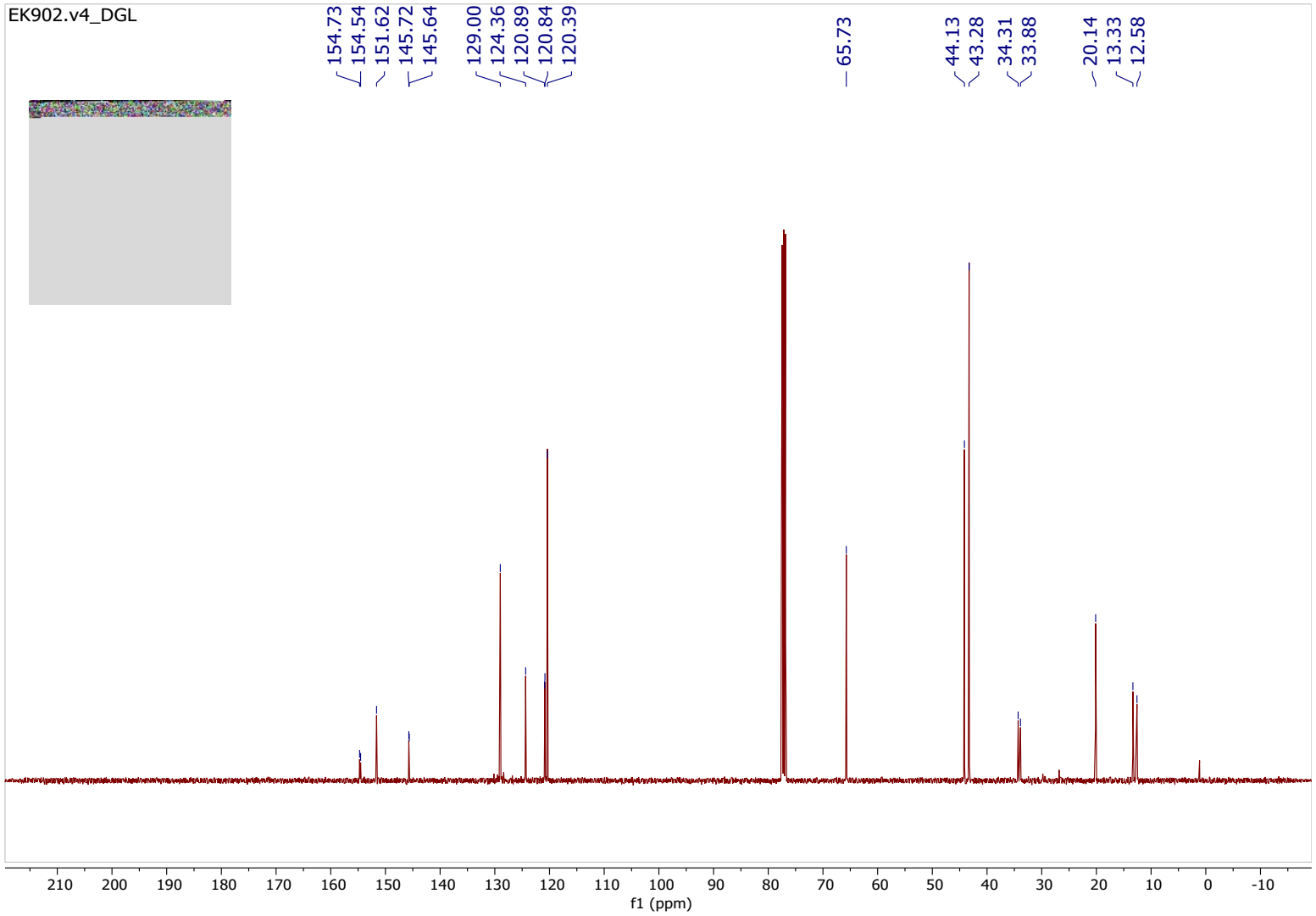
DCh-24 (trim)_6_01_3355.d

Bruker Compass DataAnalysis 4.3 printed: 6/23/2020 10:32:04 PM by: BDAL@DE Page 1 of 1

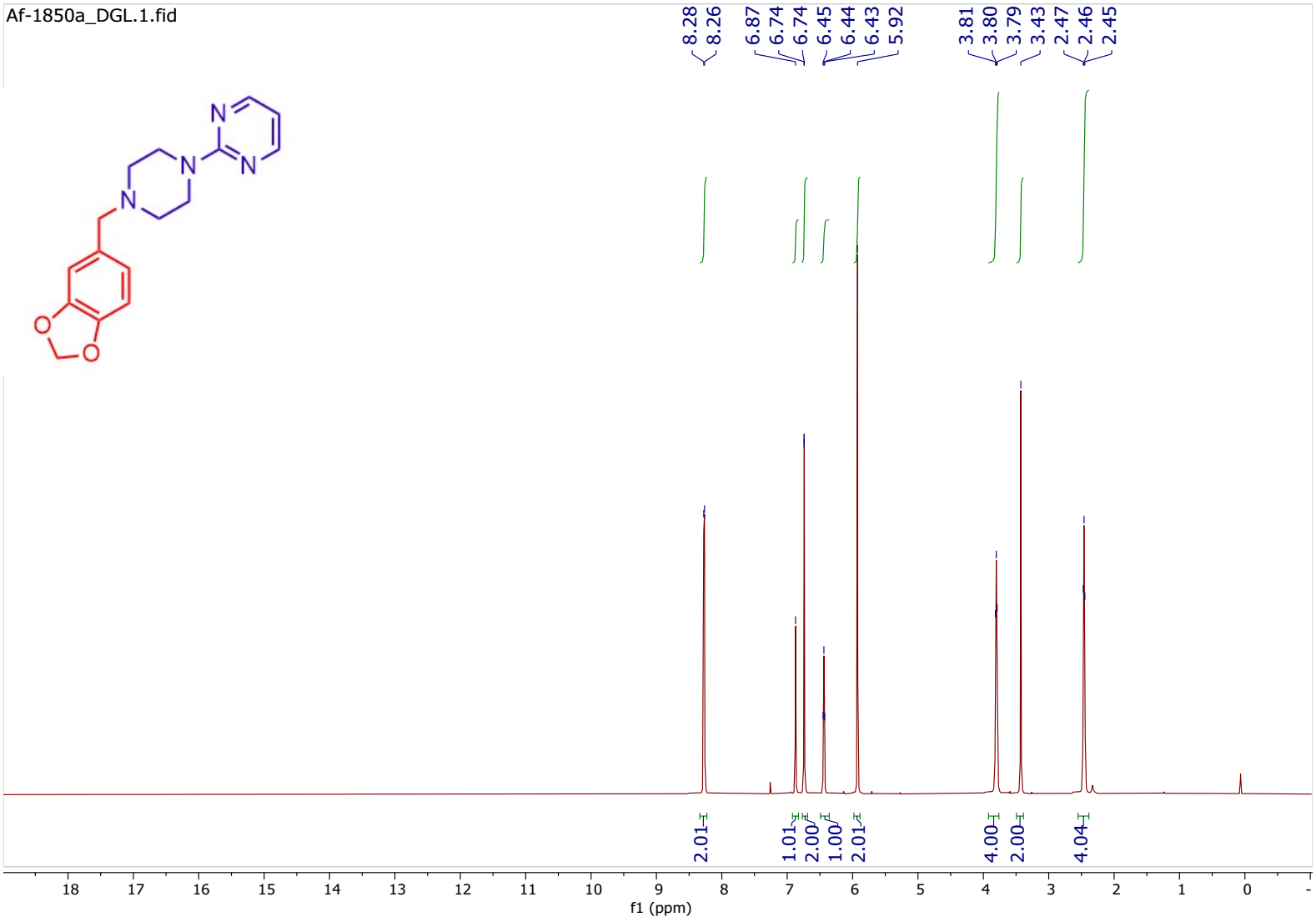
Rivastigmine, 3-(1-(dimethylamino)ethyl)phenyl ethyl(methyl)carbamate (7d) (^{1}H NMR, $CDCl_3$, 400 MHz)



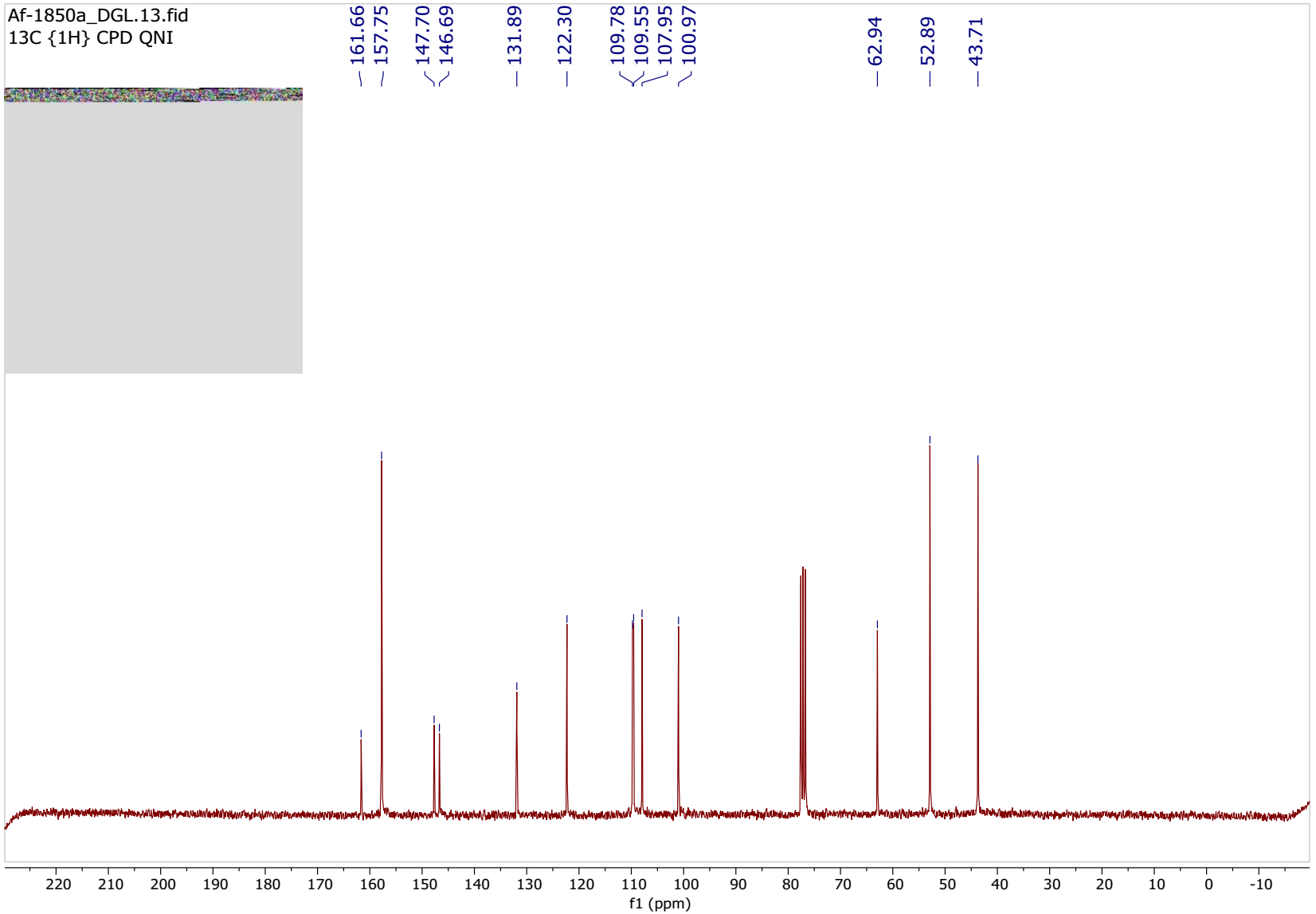
Rivastigmine, 3-(1-(dimethylamino)ethyl)phenyl ethyl(methyl)carbamate (7d) (^{13}C NMR, $CDCl_3$, 101 MHz)



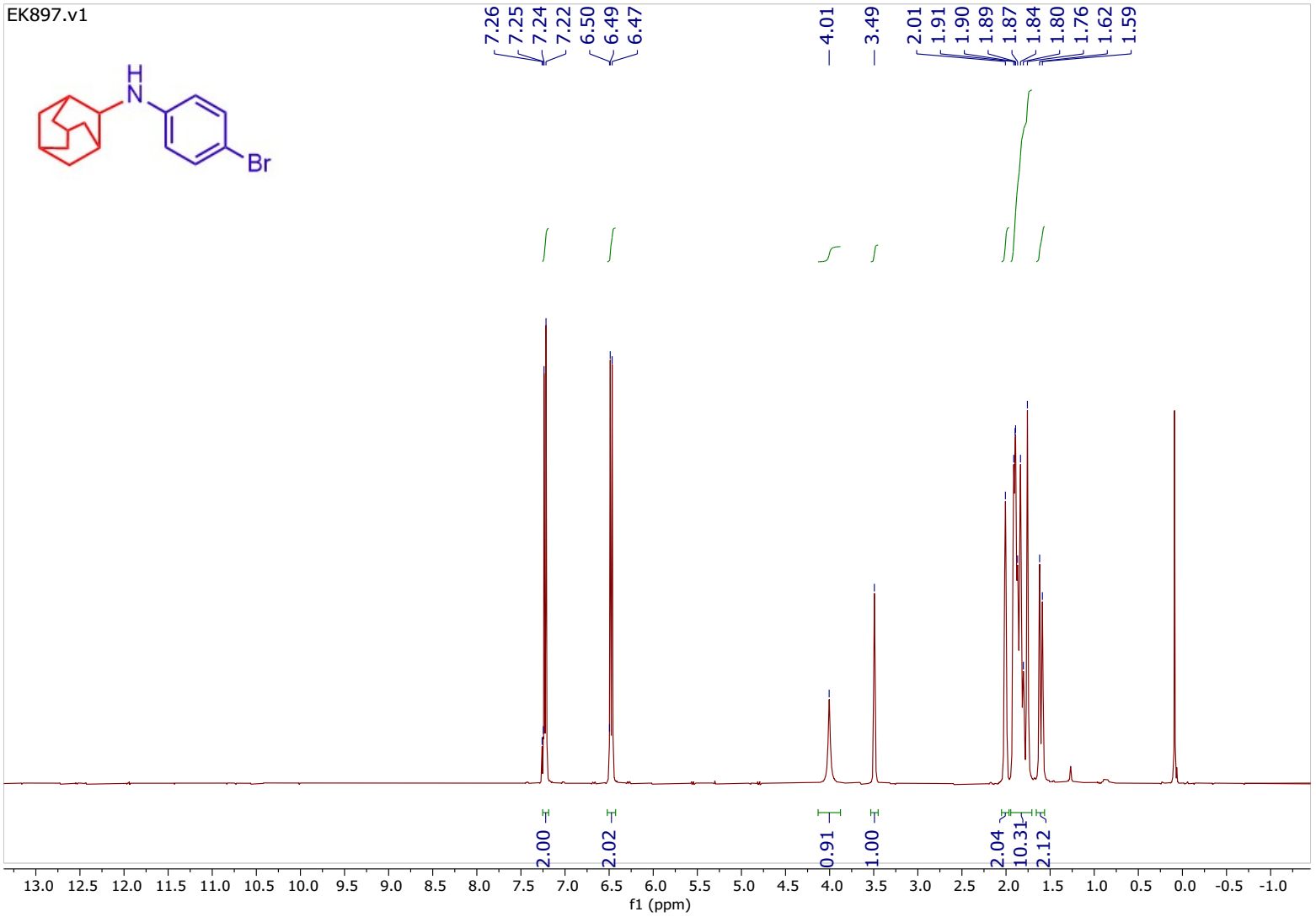
Piribedil, 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidine (7e) (^{1}H NMR, $CDCl_3$, 400 MHz)



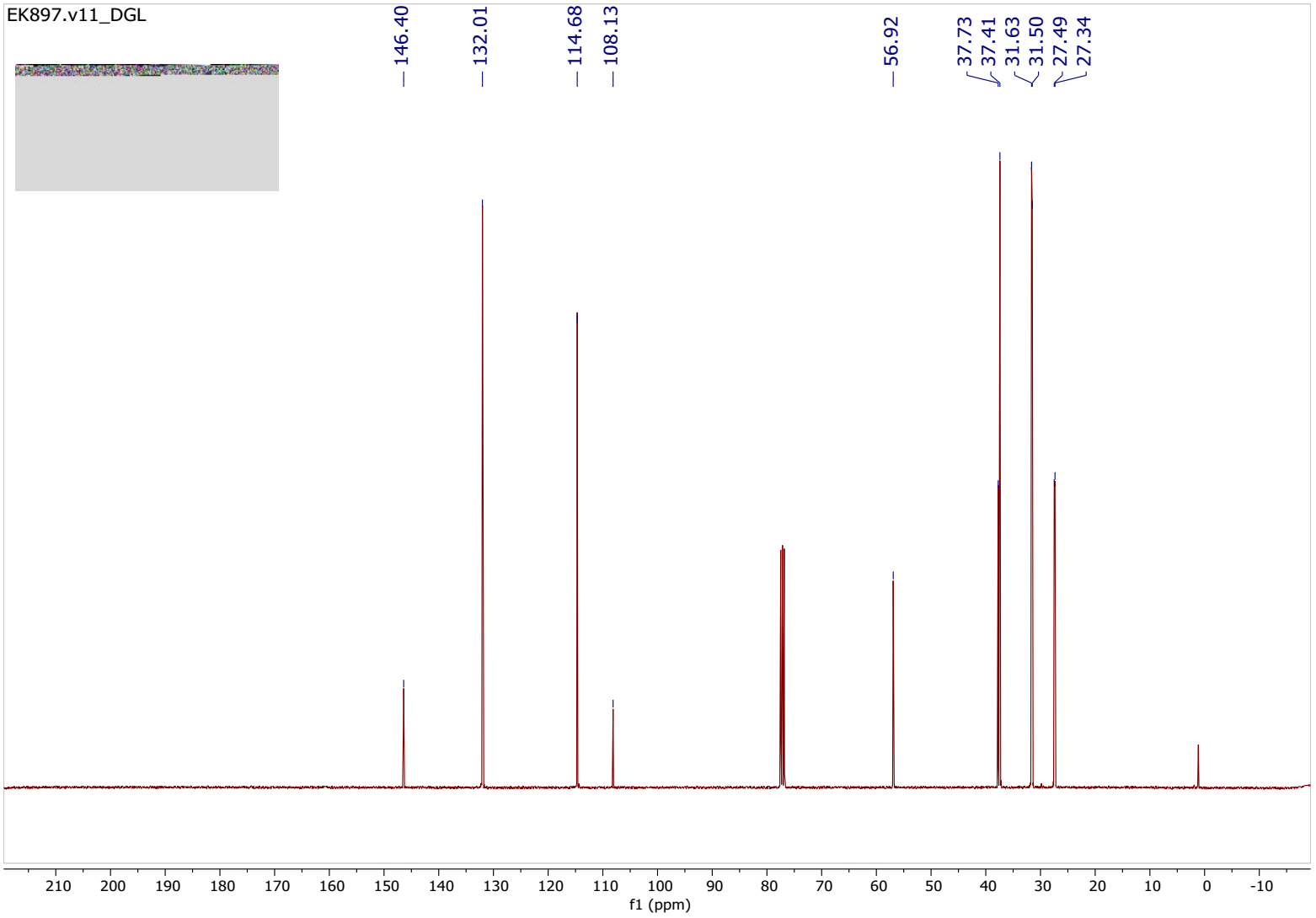
Piribedil, 2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidine (7e) (^{13}C NMR, $CDCl_3$, 101 MHz)



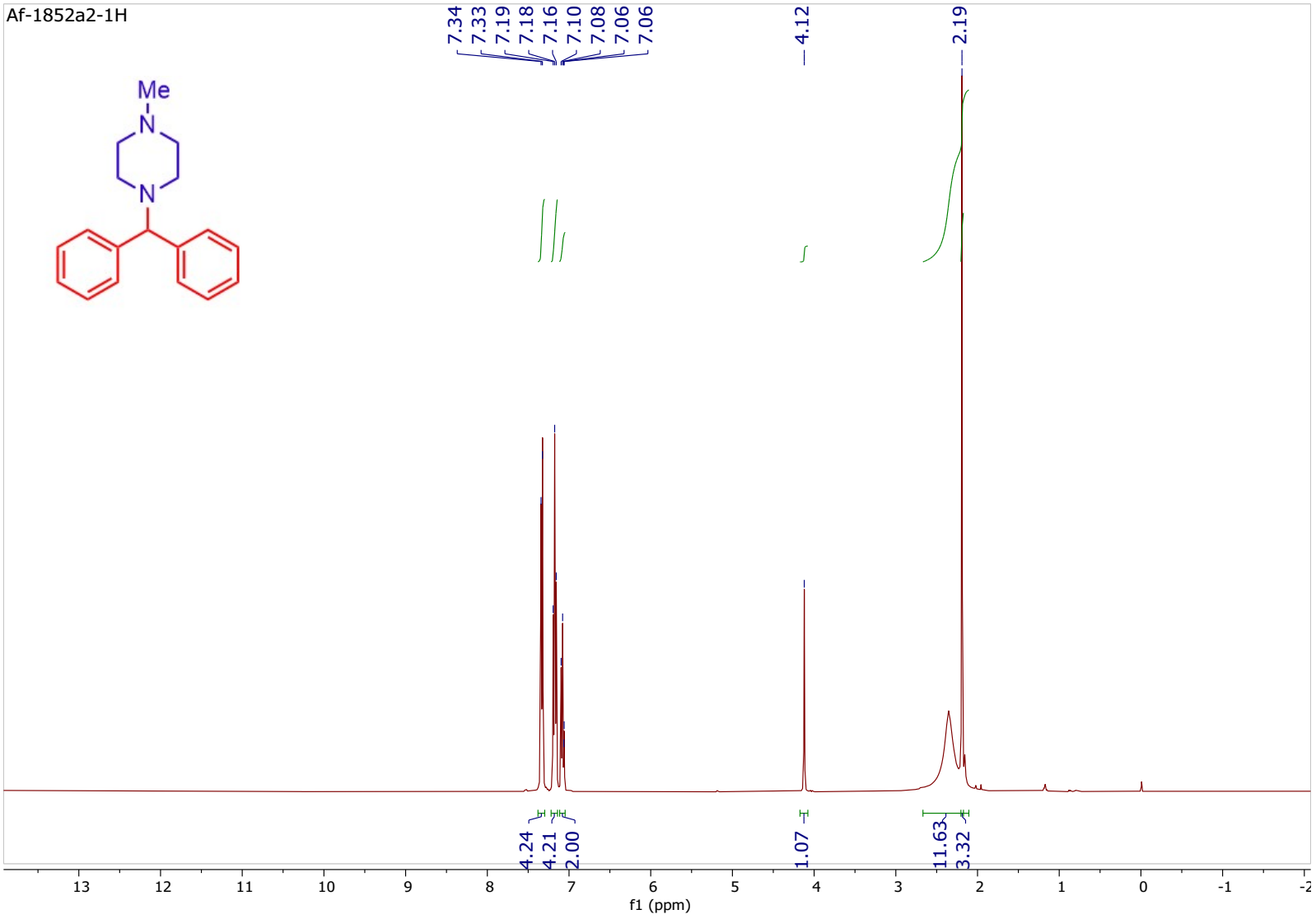
Bromantane, N-(4-bromophenyl)adamantan-2-amine, (7f) (^{1}H NMR, $CDCl_3$, 400 MHz)



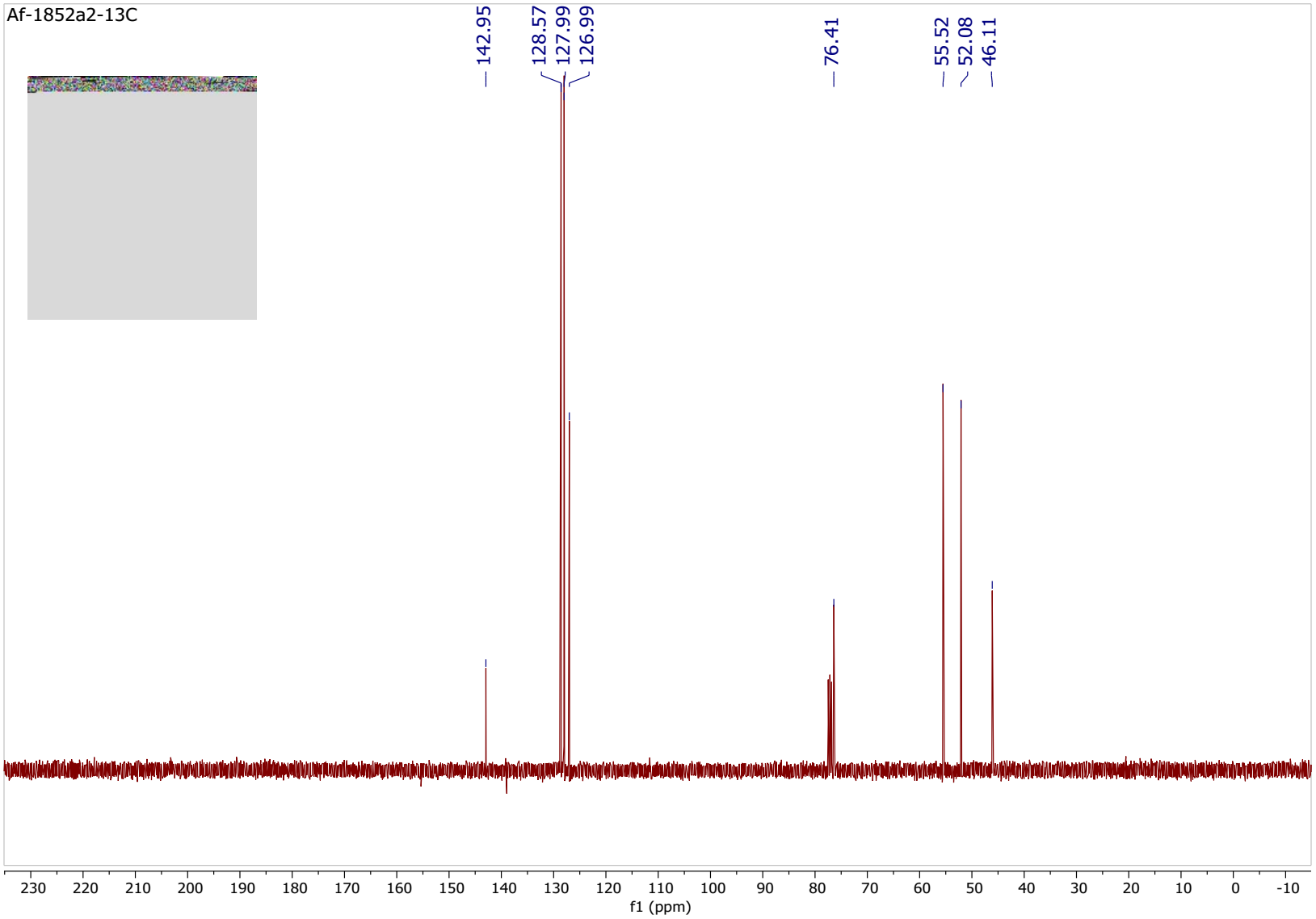
Bromantane, N-(4-bromophenyl)adamantan-2-amine, (7f) (^{13}C NMR, $CDCl_3$, 101 MHz)



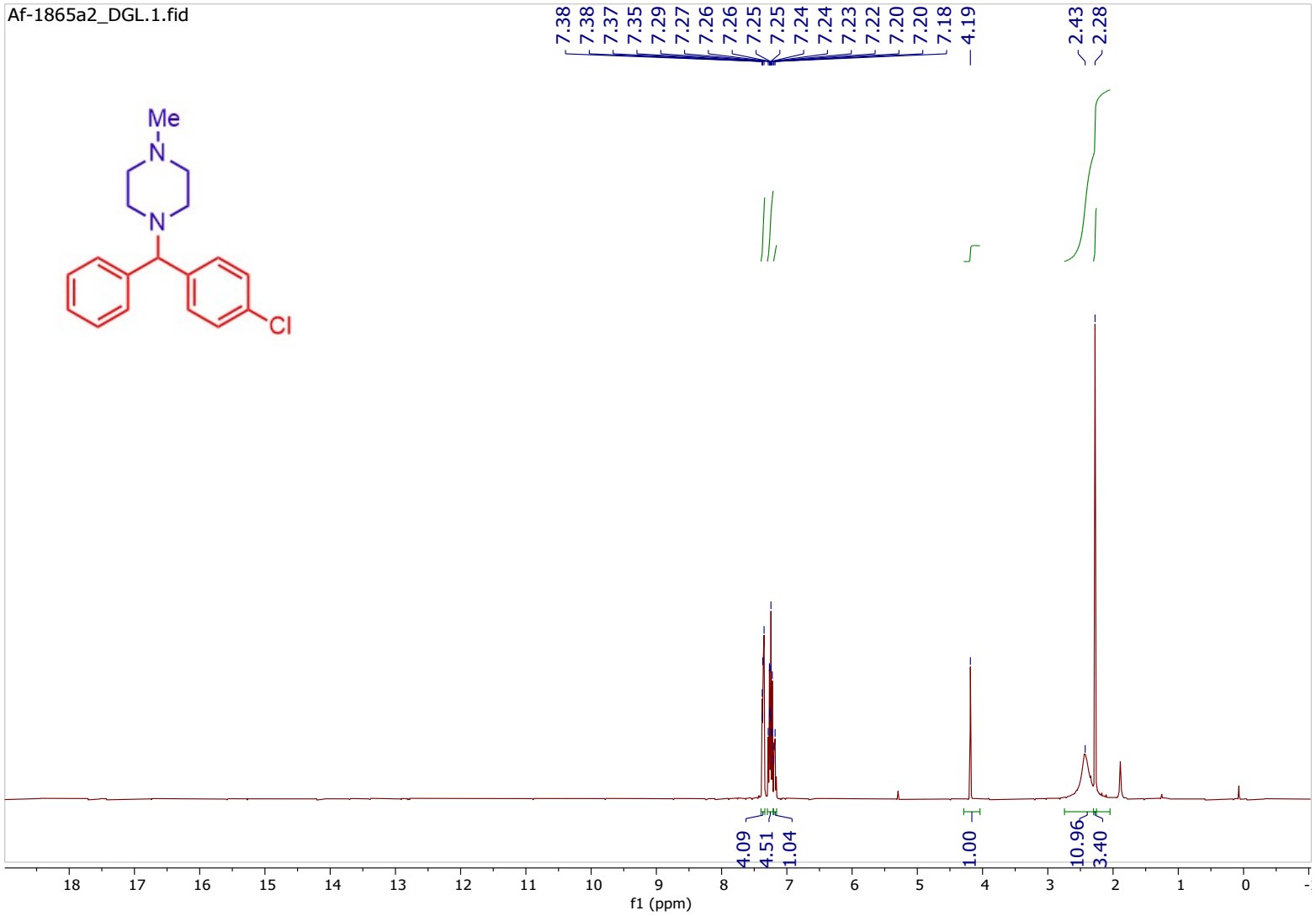
Cyclizine, 1-benzhydryl-4-methylpiperazine (7g) (^{1}H NMR, $CDCl_3$, 400 MHz)



Cyclizine, 1-benzhydryl-4-methylpiperazine (7g) (^{13}C NMR, $CDCl_3$, 101 MHz)



Chlorcyclizine, 1-((4-chlorophenyl)(phenyl)methyl)-4-methylpiperazine (7h) (^{1}H NMR, $CDCl_3$, 400 MHz)



Chlorcyclizine, 1-((4-chlorophenyl)(phenyl)methyl)-4-methylpiperazine (7h) (^{13}C NMR, $CDCl_3$, 400 MHz)