Electronic Supplementary Information (ESI)

Vegetable oil as a highly effective 100% bio-based alternative solvent for the one-pot multicomponent Biginelli reaction

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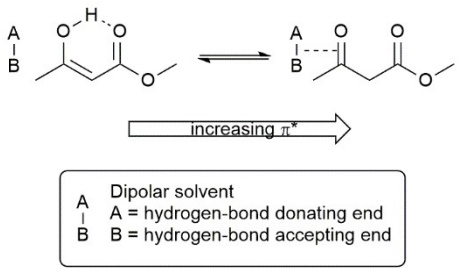
Table S1. Full yields for the synthesis of **4** and the tautomerisation equilibrium constants of **3**.

Solvent	ln(K_T)	Yield	ln(**4**/**1**)
Castor oil	-1.98[†]	27%	-1.02
CPME	-1.48[†]	49%	-0.02
Cyclohexane	-0.09	73%	1.02
DMF	-2.91	31%	-0.82
Jojoba oil	-1.30[†]	53%	0.12
Linseed oil	-1.43[†]	44%	-0.26
Need oil	n/a	45%	-0.22
n-Heptane	0.12[†]	68%	0.78
Palm oil	-0.79[†]	74%	1.02
Soybean oil	-0.90[†]	65%	0.61
TMO	-1.23[†]	51%	0.05
Waste palm oil	-1.37[†]	57%	0.28
Waste soybean oil	-1.82[†]	46%	-0.18

[†]Predicted from equation of previous report[1]



Scheme S1 Solvent stabilization and the resulting tautomerization equilibrium of β-keto-ester[1]

Table S2. Fatty acid composition of palm, palm kernel, soybean, castor, linseed, jojoba, neem oils.

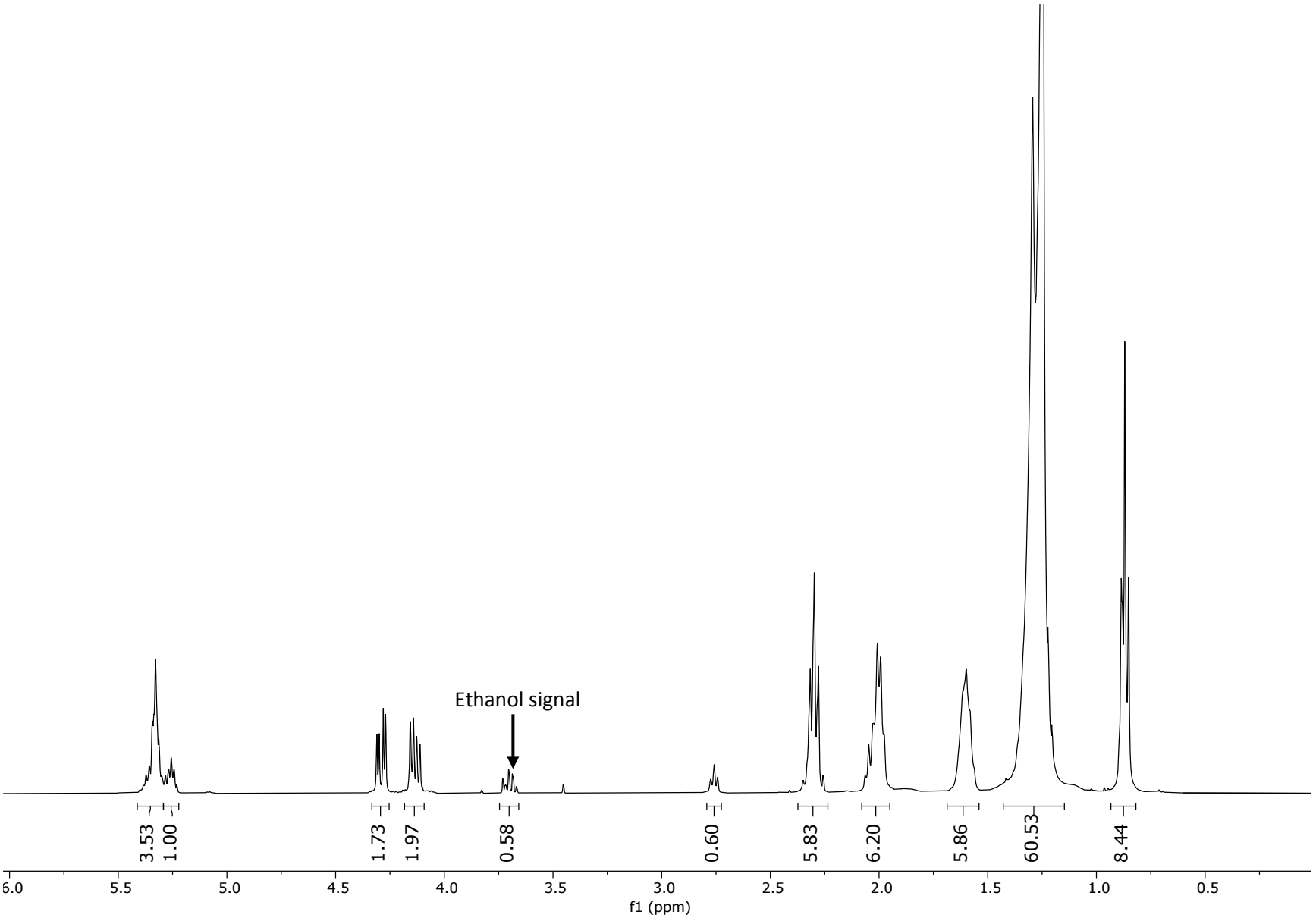
Fatty acid	Palm oil	Palm kernel oil	Soybean oil	Castor oil	Linseed oil	Jojoba oil	Neem oil
Caproic acid (C6:0)	-	0.2	-	-	-	-	-
Caprylic acid (C8:0)	-	3.3	-	-	-	-	-
Capric acid (C10:0)	-	3.5	-	-	-	-	-
Lauric acid (C12:0)	0.2	47.8	-	-	0.08	-	-
Myristic acid (C14:0)	1.1	16.3	-	-	0.08	-	-
Palmitic acid (C16:0)	44.0	8.5	14.7	1.0	5.6	1.6	18.1
Palmitoleic acid (C16:1)	-	-	-	-	0.1	0.1	-
Stearic acid (C18:0)	4.5	2.4	5.4	1.1	4.0	0.1	18.1
Oleic acid (C18:1)	39.2	15.4	26.8	3.3	19.3	11.2	44.5
Ricinoleic acid (C18:1-OH)	-	-	-	89.1	-	-	-
Linoleic acid (C18:2)	10.1	2.4	44.4	4.6	17.2	-	18.3
Linolenic acid (C18:3)	0.4	-	8.0	0.5	48.8	-	0.2
Arachidic acid (C20:0)	0.1	0.1	0.4	-	0.2	0.2	0.8
Eicosenoic acid (C20:1)	-	-	-	0.3	0.1	70.7	-
Behenic acid (C22:0)	-	-	0.33	-	-	0.3	-
Erucic acid (C22:1)						14.1	
Lignoceric acid (C24:0)						0.02	
Nervonic acid (C24:1)						1.6	
Reference	2	2	3	4	5	6	7

Table S3. Effect of addition of impurity and degradation products in palm oil on reaction yield.

Impurity/degradation product	Mole of addition	Yield
Ethanol	0.5 mmol	41.2%
Glycerol	0.5 mmol	43.1%
Palmitic acid	0.5 mmol	37.5%
Acrylamide	0.5 mmol	37.5%

Table S4. Kamlet-Taft parameters,[8-10] recovery and reaction yields of consecutive runs with recovered palm oil.

Solvent	α	β	π*	recovery	Yield
Native	-0.12	1.22	0.21	98%	70%
1st recovered	-0.11	1.23	0.20	98%	67%
2nd recovered	-0.11	1.23	0.20	97%	57%
3rd recovered	-0.12	1.21	0.22	96%	57%
4th recovered	-0.11	1.23	0.20	92%	58%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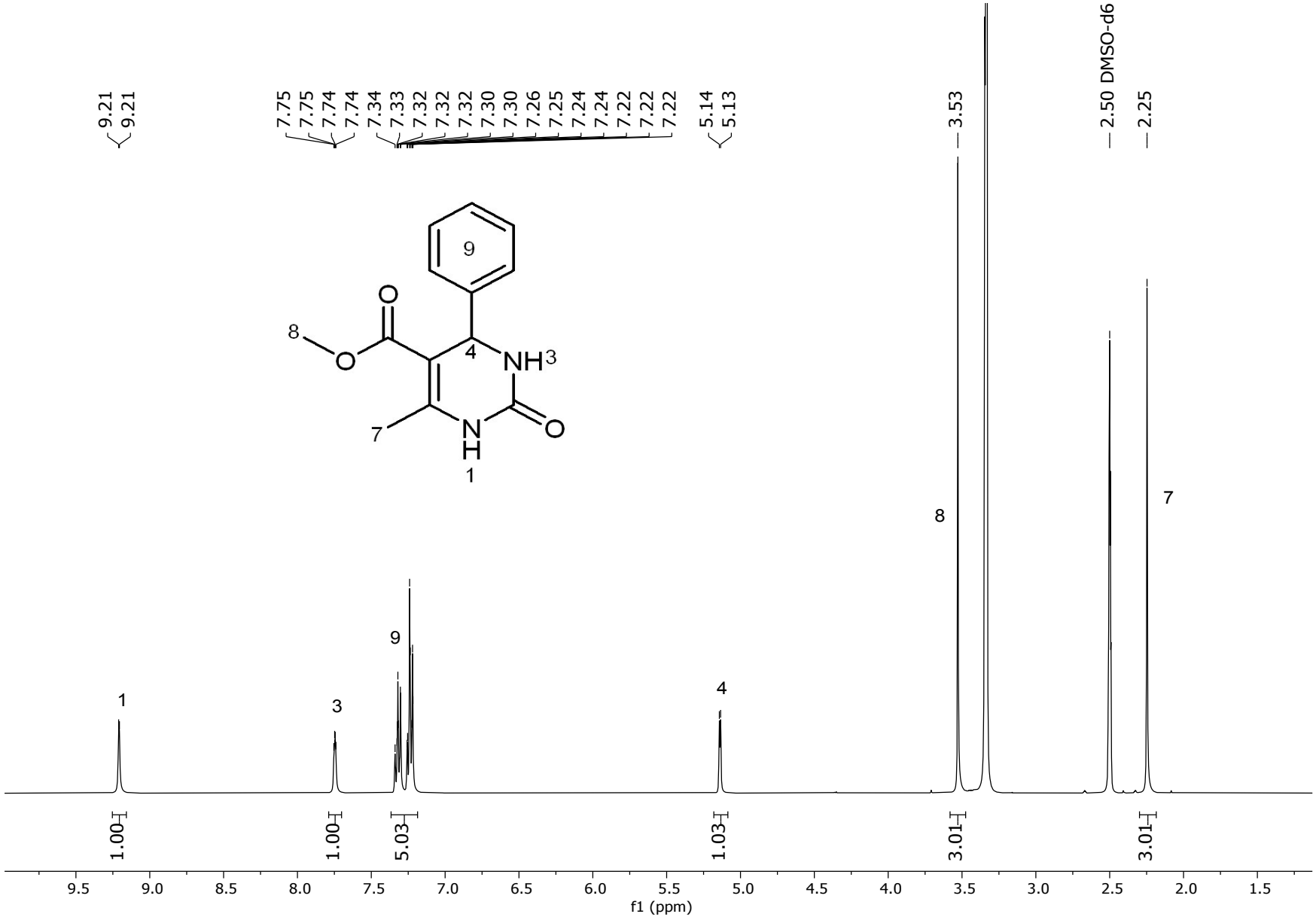
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7.25
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7.22
7.22
7.22
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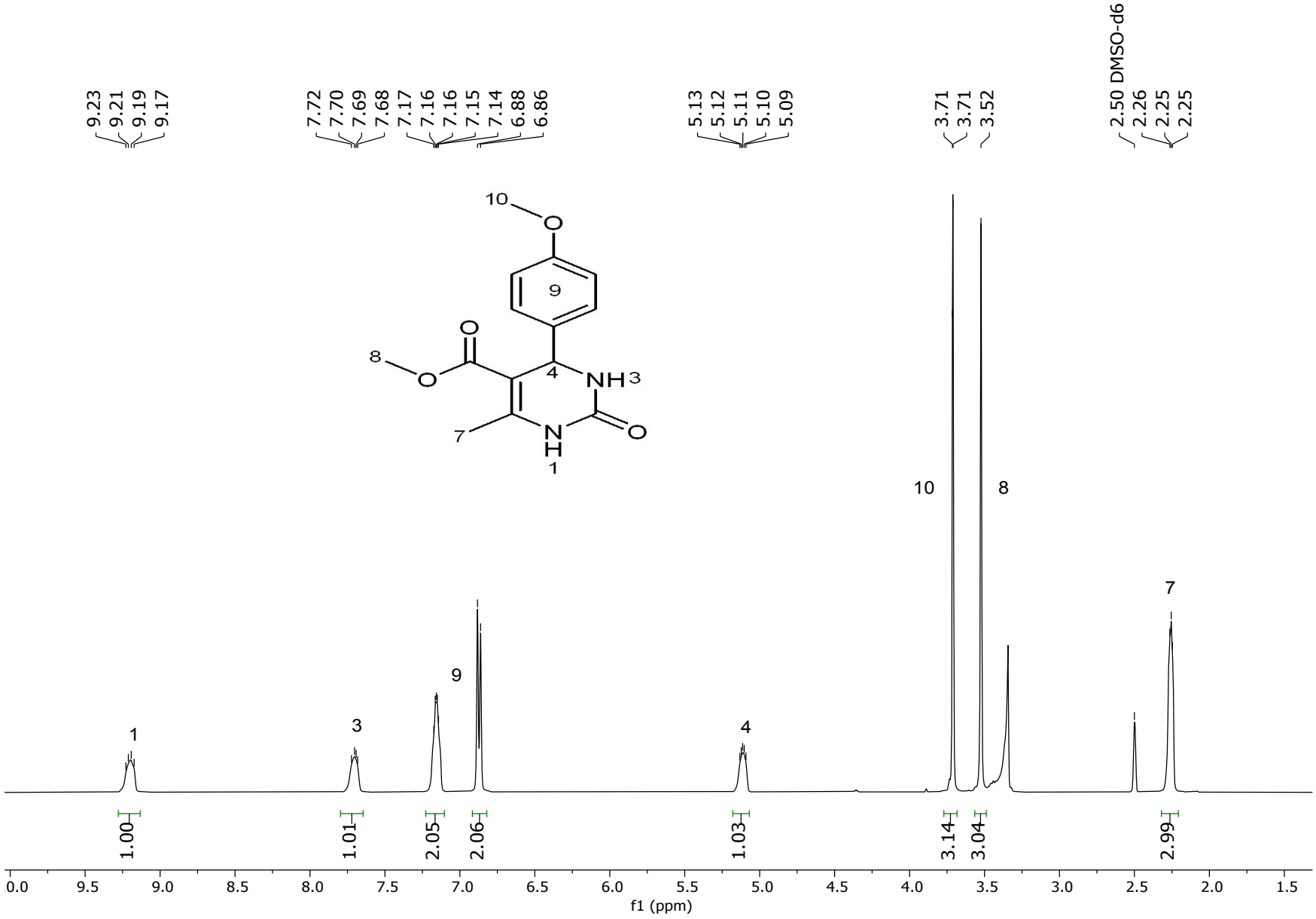
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5.12
5.11
5.10
5.09
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3.71
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2.25
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O
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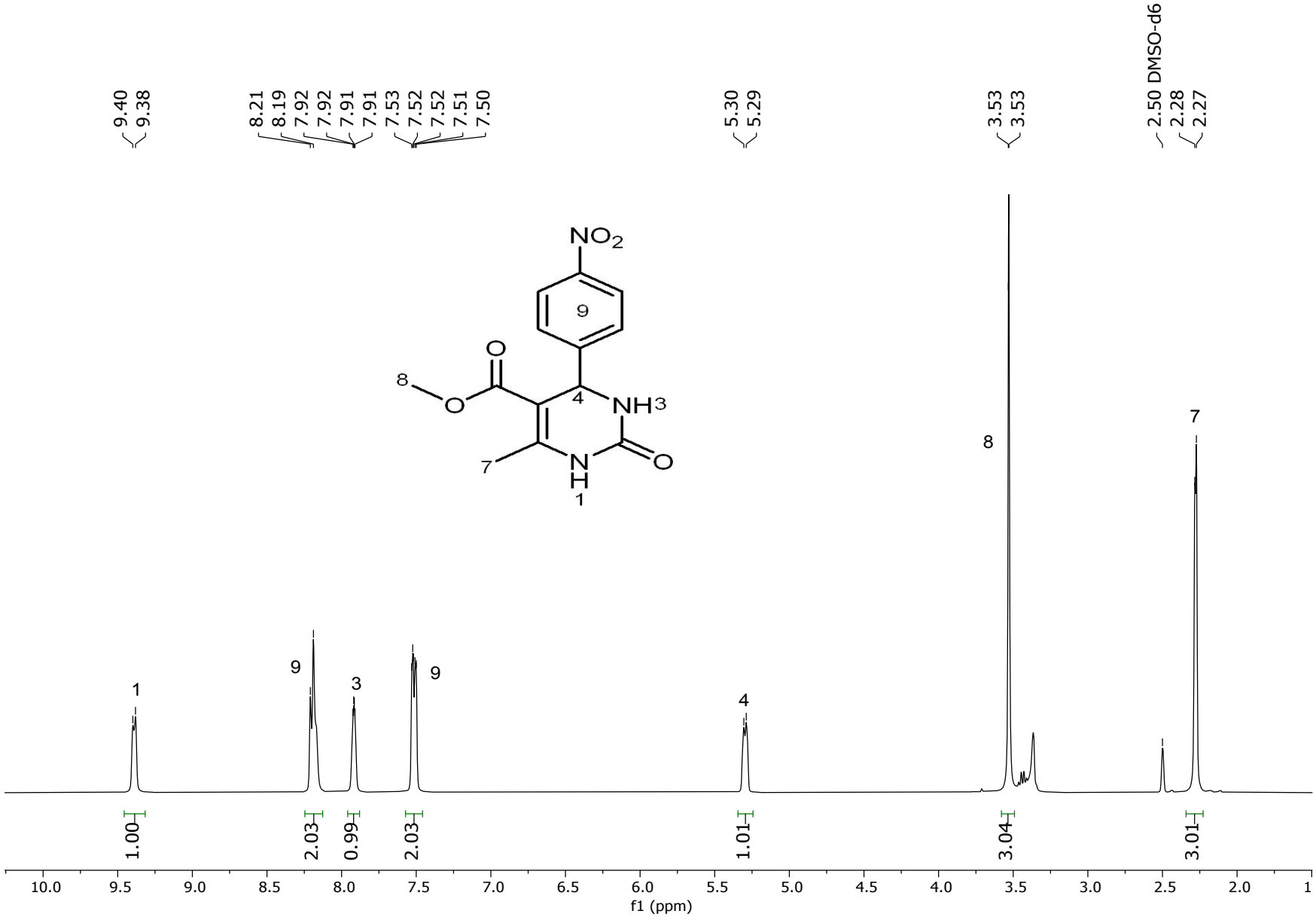
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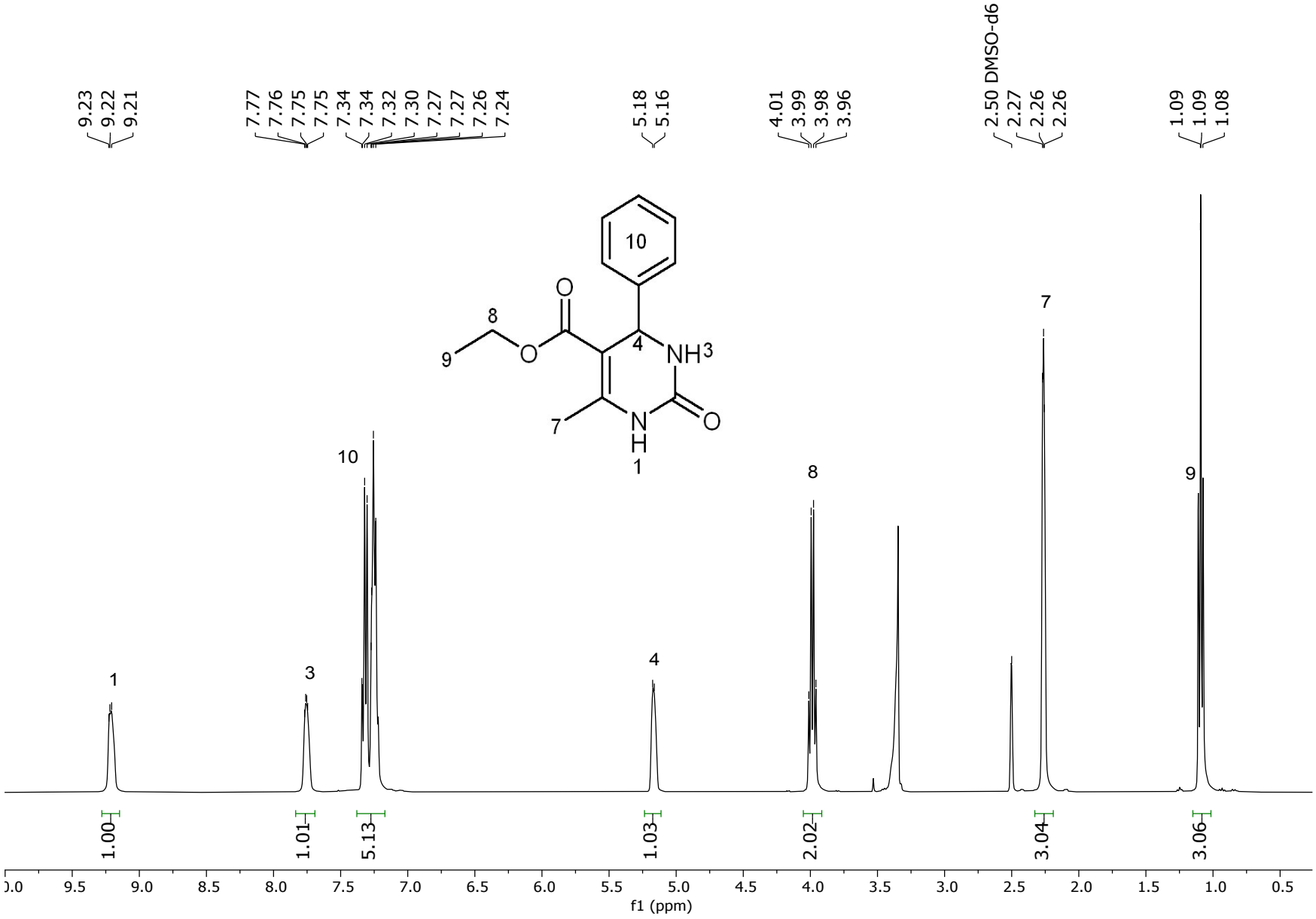
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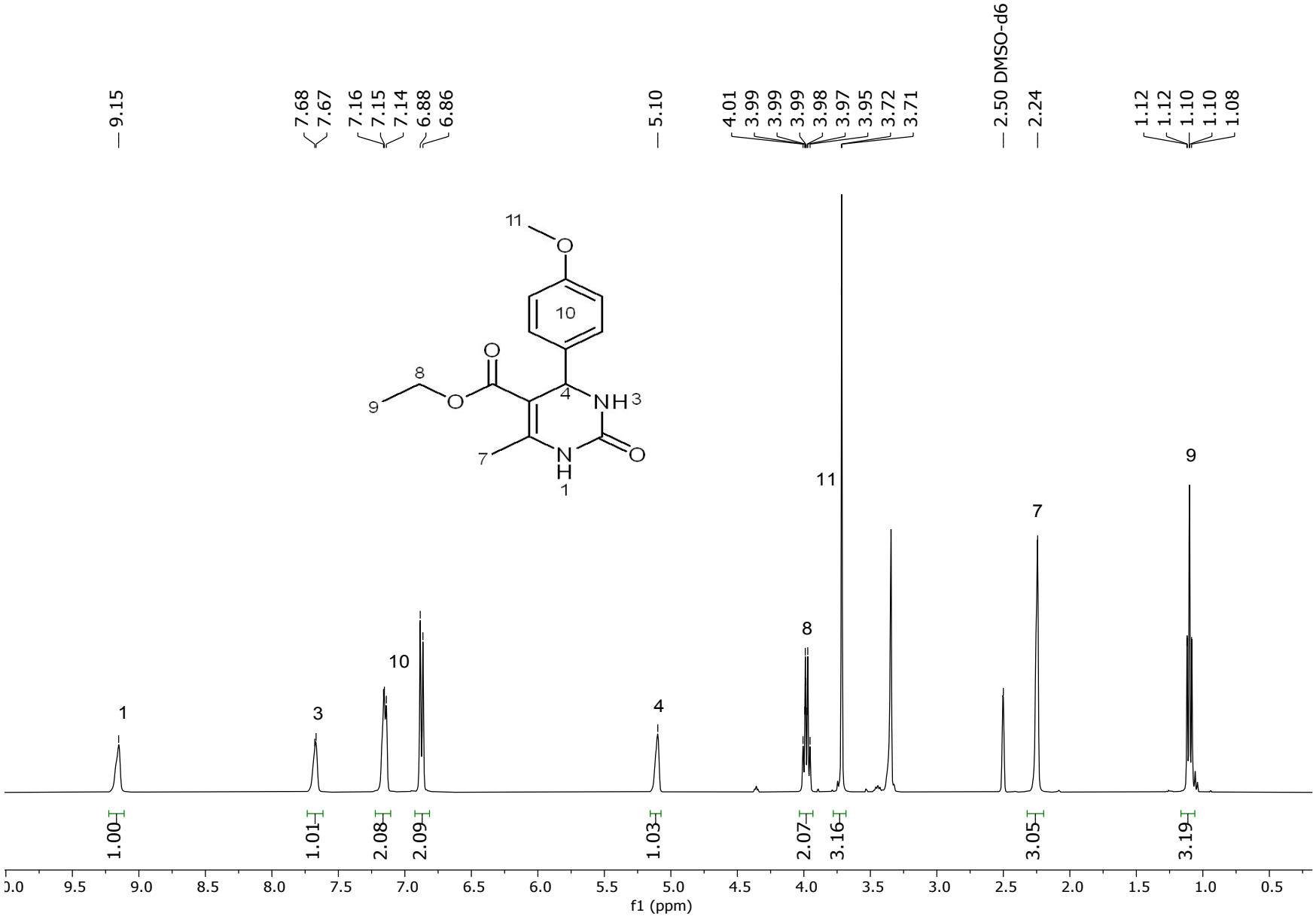
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1.10
1.10
1.08
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O
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O
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3
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4
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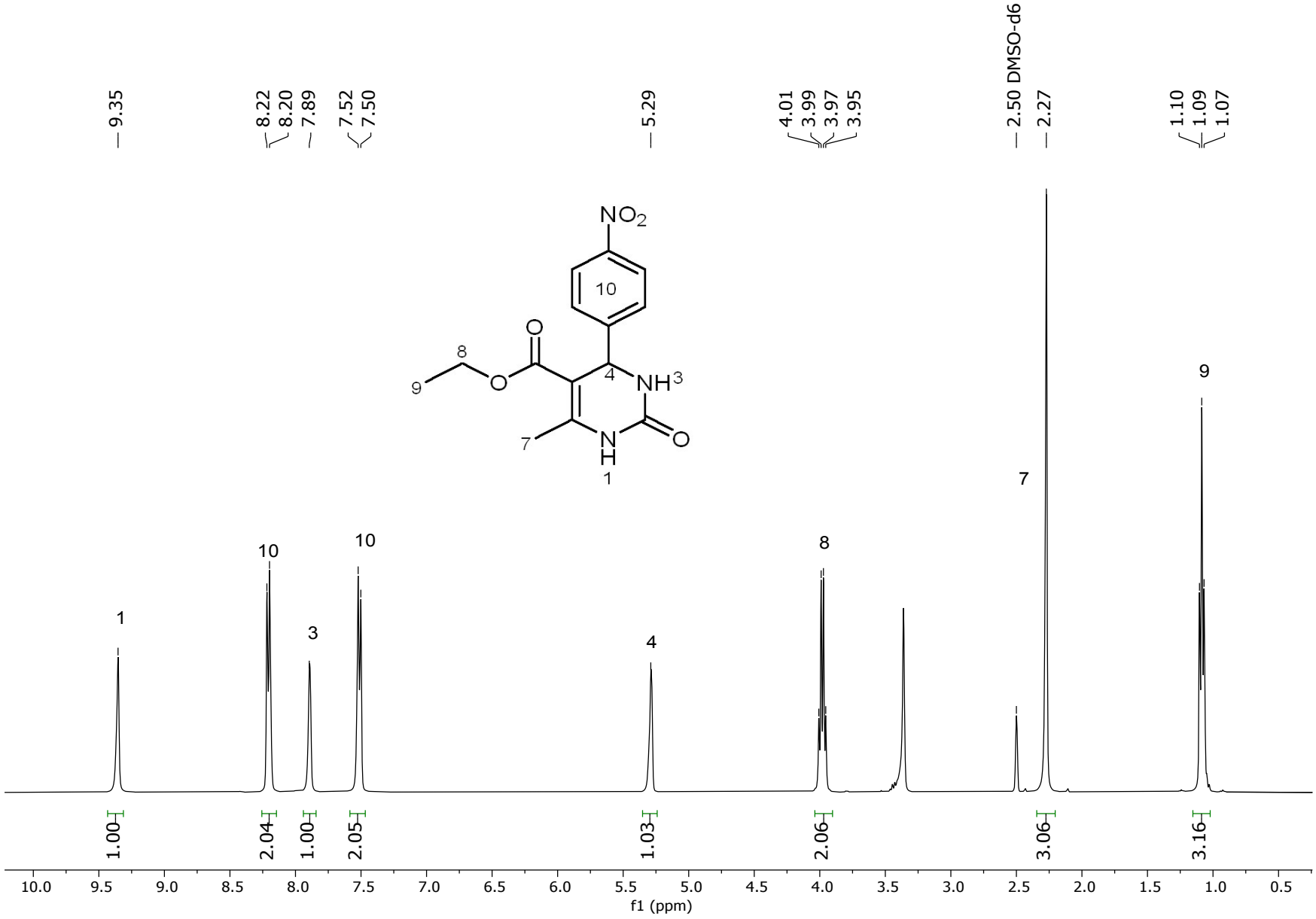
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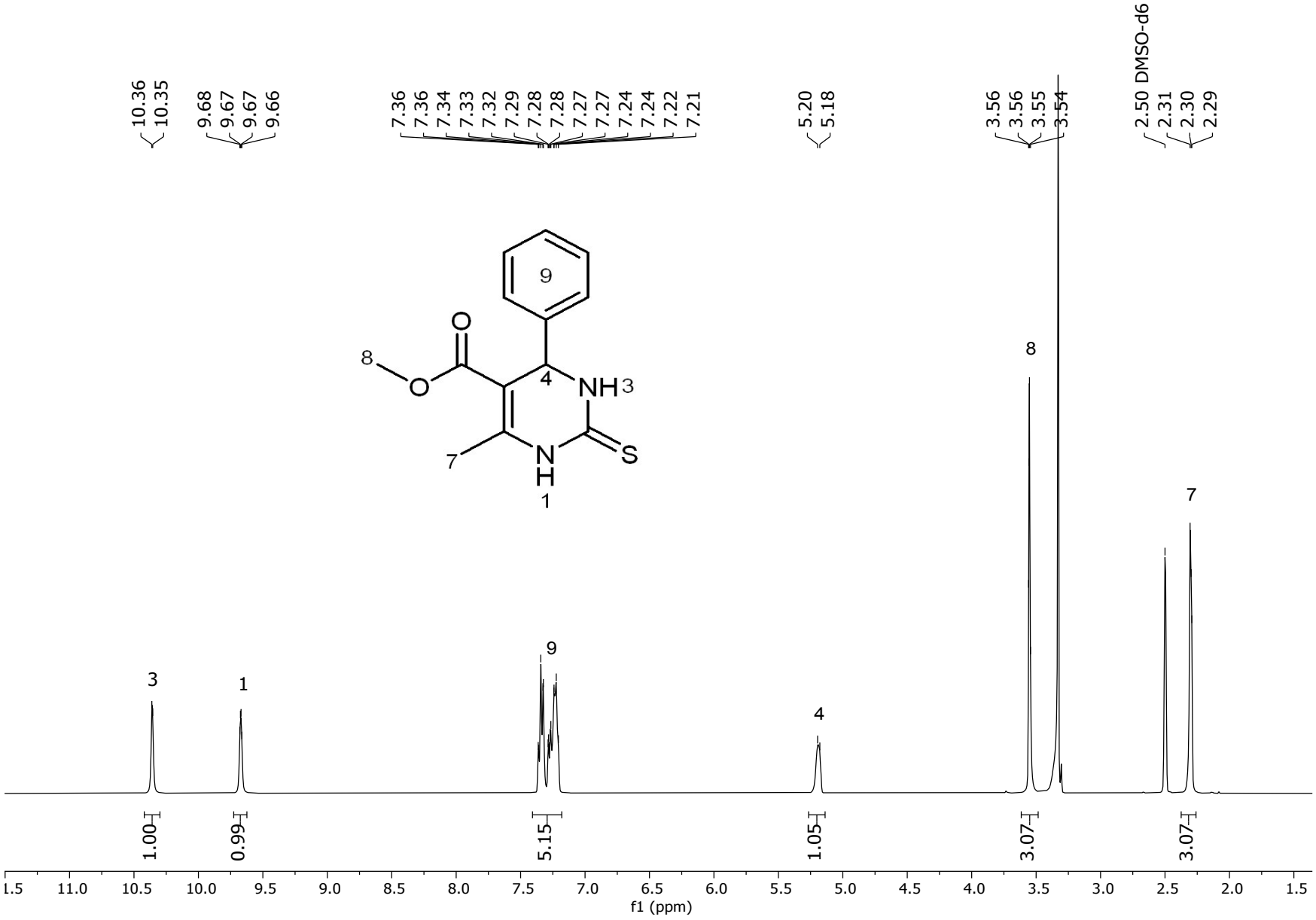
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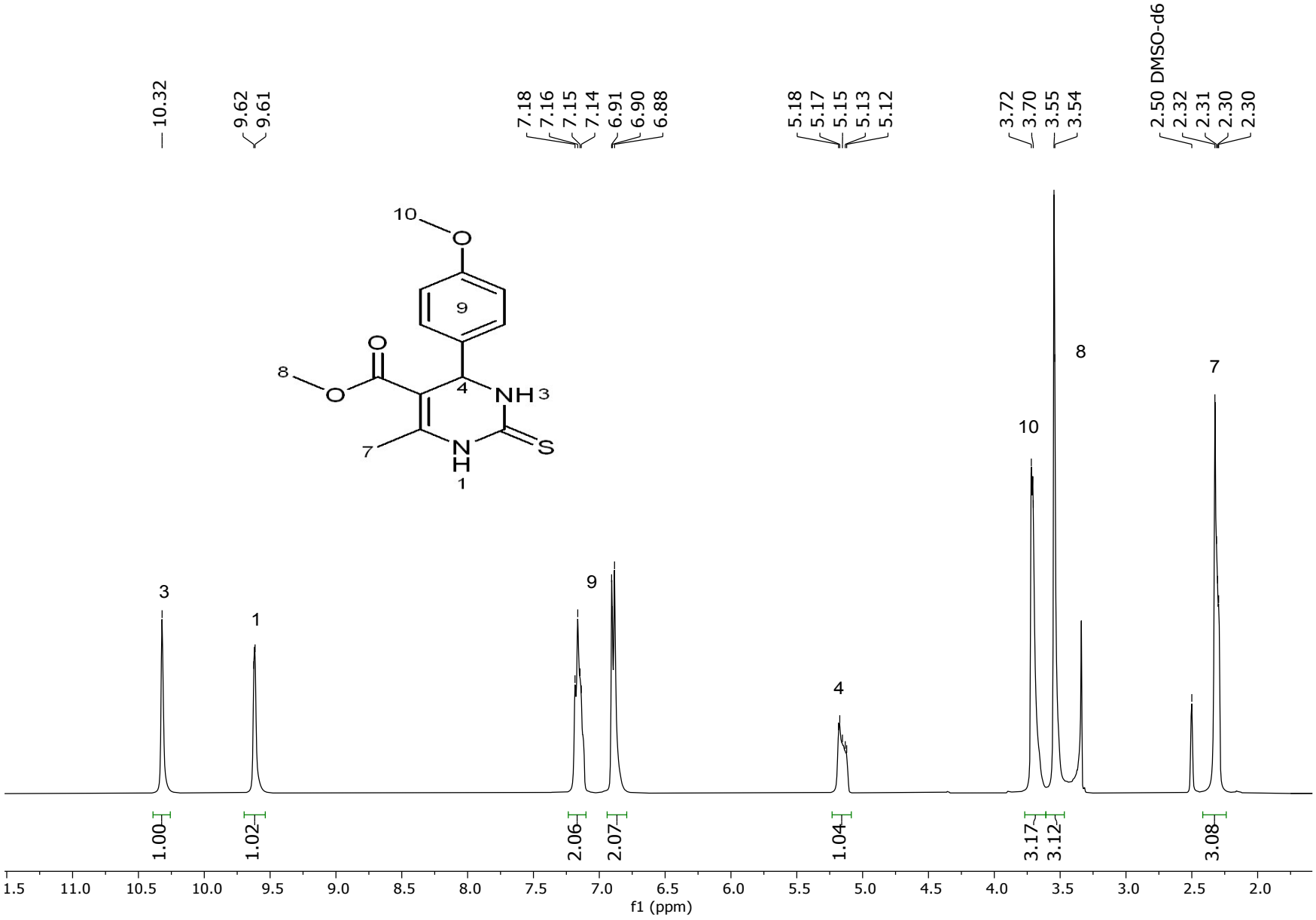
f1 (ppm)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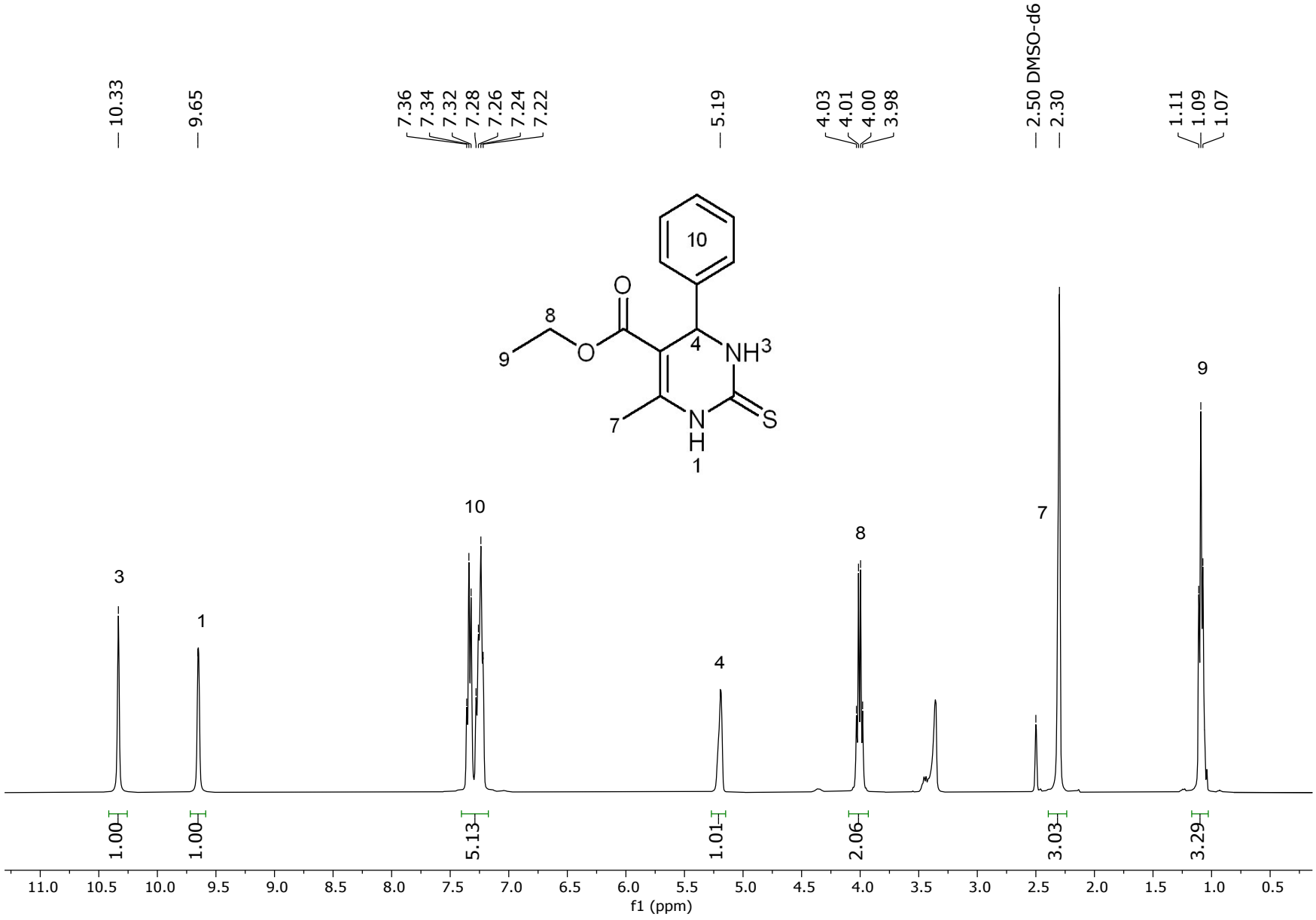
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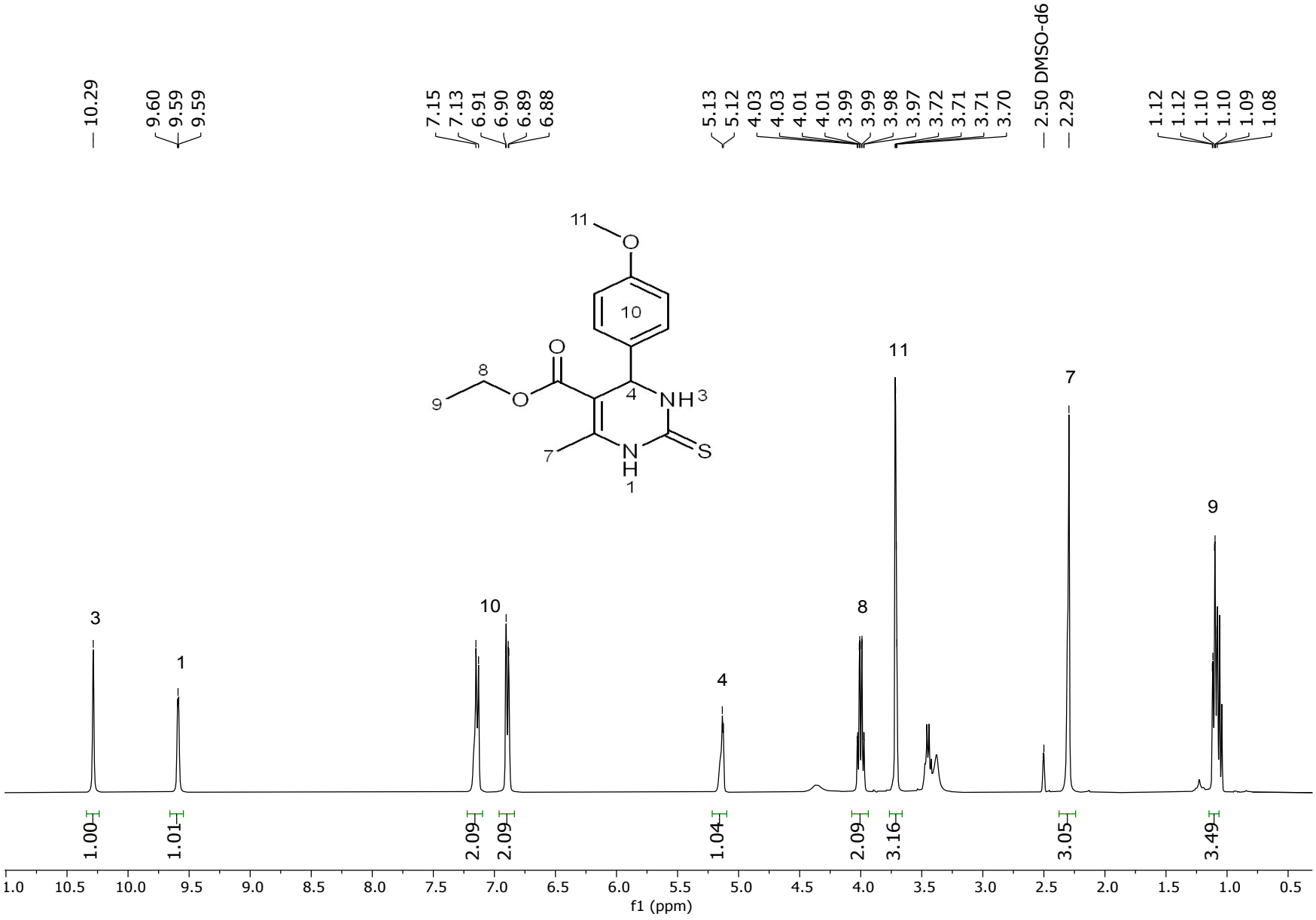
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3.0
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2.0
1.5
1.0
0.5
f1 (ppm)

Green chemistry metrics analysis

The following formulae were used for calculating Process Mass Intensity (PMI), E-factor, Solvent and Water Intensity (SI and WI).[11-22]

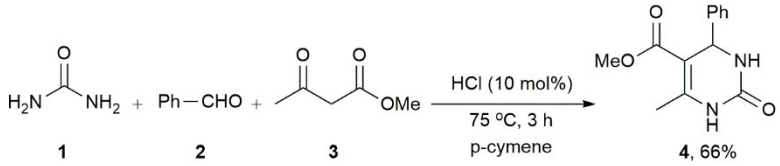
$$\text{PMI} = \frac{\text{Total mass of input material in the whole process}}{\text{Mass of product}}$$

$$\text{E Factor} = \text{PMI} - 1$$

$$\text{SI} = \frac{\text{Total mass of solvents excl. water in the whole process}}{\text{Mass of product}}$$

$$\text{WI} = \frac{\text{Total mass of water used in the whole process}}{\text{Mass of product}}$$

Previous report, Process A (using p-cymene as reaction medium)[1]



Reported procedures for process A do not always contain all the required information; therefore, some realistic assumptions were used where appropriate and are italicized in the calculations given below.

Experimental procedures: urea **1** (0.30 g, 5.00 mmol) and p-cymene (4 mL) were heated to 75 °C. upon reaching thermal equilibrium, benzaldehyde **2** (0.51 mL, 5.00 mmol), methyl 3-oxobutanoate **3** (0.81 mL, 7.50 mmol) and finally concentrated hydrochloric acid (10 mol%) were added to the mixture. The reaction was stirred at 300 rpm for a duration of 3 h. Upon completion of the reaction, the mixture was allowed to cool to ambient temperature. The resultant solid was separated from the reaction mixture by filtration, washed with 50% aqueous ethanol (*15 mL*) and recrystalised from ethanol (*20 mL*) to give a white crystalline solid **4** (0.81 g, 66%).

Materials used for metrics calculations: urea **1** (0.30 g, 5.00 mmol), benzaldehyde **2** (0.53 g, 5.00 mmol), methyl 3-oxobutanoate **3** (0.87 g, 7.50 mmol), HCl (0.02 g, 0.05 mmol), p-cymene (4 mL, 3.43 g) EtOH (27.5 mL, 22.0 g), H_2O (7.5 mL, 7.5 g), compound **4** (0.81 g, 3.23 mmol).

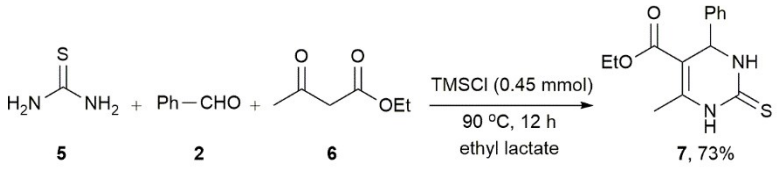
$$\textbf{PMI (4)} = \frac{0.30 + 0.53 + 0.87 + 0.02 + 22.0 + 3.43 + 7.5}{0.81} = 43$$

E Factor (4) = 43 – 1 = 42

$$\textbf{SI (4)} = \frac{22.0 + 3.43}{0.81} = 31$$

$$\textbf{WI (4)} = \frac{7.5}{0.81} = 9$$

Previous report, Process B (using ethyl lactate as reaction medium)[23]



Reported procedures for process B do not always contain all the required information; therefore, some realistic assumptions were used where appropriate and are italicized in the calculations given below. Drying agents, when used, were not included in the calculations.

Experimental procedures: thiourea **5** (0.45 mmol), benzaldehyde **2** (0.30 mmol), ethyl acetoacetate **6** (0.30 mmol), TMSCl (0.45 mmol) and ethyl lactate (2 mL) were heated at 90 °C. The reaction was stirred for a duration of 12 h. Upon completion of the reaction, the mixture was allowed to cool to room temperature. Water (10 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic phases were combined and dried over anhydrous Na_2SO_4. The solid was filtered out and the solution was subjected to vacuum evaporation to remove solvent. Finally, the residue was subjected to silica column chromatography (PE /EtOAc = 3:1, *total 85 mL*) to give compound **7** (0.061, 73%).

Materials used for metrics calculations: thiourea **5** (0.034 g, 0.45 mmol), benzaldehyde **2** (0.032 g, 0.30 mmol), methyl 3-oxobutanoate **6** (0.039 g, 0.30 mmol), TMSCl (0.049 g, 0.45 mmol), ethyl lactate (2 mL, 2.06 g) EtOAc (30 mL, 27 g), H_2O (10 mL, 10 g), PE:EtOAc (85 mL, 68 g), compound **7** (0.061 g, 0.22 mmol).

PMI (4) $= \dfrac{0.034 + 0.032 + 0.039 + 0.049 + 2.06 + 27 + 10 + 68}{\mathbf{0.061}} =$

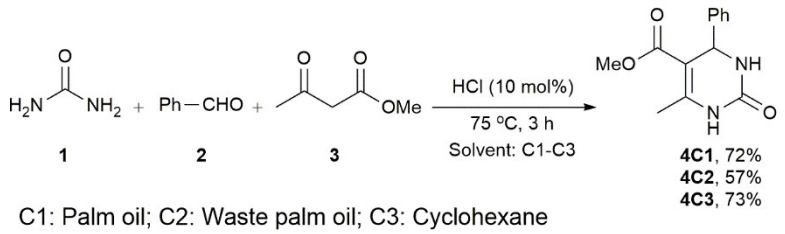
1,758

E Factor (4) = 1,758 – 1 = 1,757

SI (4) $= \dfrac{2.06 + 27 + 68}{\mathbf{0.061}} =$ **1,591**

WI (4) = $\frac{10}{0.061}$ = **164**

Current work, Process C1-C3 (This work)



C1: Palm oil; C2: Waste palm oil; C3: Cyclohexane

Experimental procedures: urea **1** (0.30 g, 5.00 mmol) and solvent (C1 or C2 or C3) (4 mL) were heated to 75 °C. upon reaching thermal equilibrium, benzaldehyde **2** (0.51 mL, 5.00 mmol), methyl 3-oxobutanoate **3** (0.81 mL, 7.50 mmol) and finally concentrated hydrochloric acid (10 mol%) were added to the mixture. The reaction was stirred at 300 rpm for a duration of 3 h. Upon completion of the reaction, the mixture was allowed to cool to ambient temperature. The resultant solid was separated from the reaction mixture by filtration, washed with 50% aqueous ethanol (15 mL) and recrystalised from ethanol (20 mL) to give a white crystalline solid **4** (0.91 g, 74%). Palm oil and waste palm oil can be recovered and reused. Preparative scale reaction was effectively accomplished using 40 mL of C1 (10-fold) leading to provide 8.8 g (72%) of product.

Materials used for metrics calculations: urea **1** (0.30 g, 5.00 mmol), benzaldehyde **2** (0.53 g, 5.00 mmol), methyl 3-oxobutanoate **3** (0.87 g, 7.50 mmol), HCl (0.02 g, 0.05 mmol), EtOH (17.5 mL, 13.80 g), H_2O (2.5 mL, 2.5 g), cyclohexane C3 (4 mL, 3.12 g), compound **4C1** (0.91 g, 3.68 mmol), **4C2** (0.70, 2.83 mmol), **4C3** (0.91 g, 3.68 mmol). Palm oil and waste palm oil were not included in the calculations.[11,15]

Palm oil (4C1, 10-fold)

PMI (4C1) = $\frac{3.0 + 5.3 + 8.7 + 0.2 + 220 + 75}{8.8}$ = **35**

E Factor (4C1) = 35 – 1 = 34

SI (4C1) = $\frac{220}{8.8}$ **= 25**

WI (4C1) = $\frac{7.5}{8.8}$ **= 9**

Waste palm oil (4C2)

PMI (4C2) = $\frac{0.30 + 0.53 + 0.87 + 0.02 + 22.0 + 7.5}{0.70}$ **= 45**

E Factor (4C2) = 45 – 1 = 44

SI (4C2) = $\frac{22.0}{0.70}$ **= 31**

WI (4C2) = $\frac{7.5}{0.70}$ **= 11**

Cyclohexane (4C3)

PMI (4C3) = $\frac{0.30 + 0.53 + 0.87 + 0.02 + 22.0 + 7.5 + 3.12}{0.91}$ **= 38**

E Factor (4C3) = 38 – 1 = 37

$$\text{SI (4C3)} = \frac{22.0 + 3.12}{0.91} = 28$$

$$\text{WI (4C3)} = \frac{7.5}{0.91} = 8$$

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