Electronic Supplementary Material (ESI) for RSC Advances.

Regioselective microwave synthesis and derivatization of 1,5-diaryl-3-amine-1,2,4-triazoles and a study of their cholinesterase inhibition properties.

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Supporting Information

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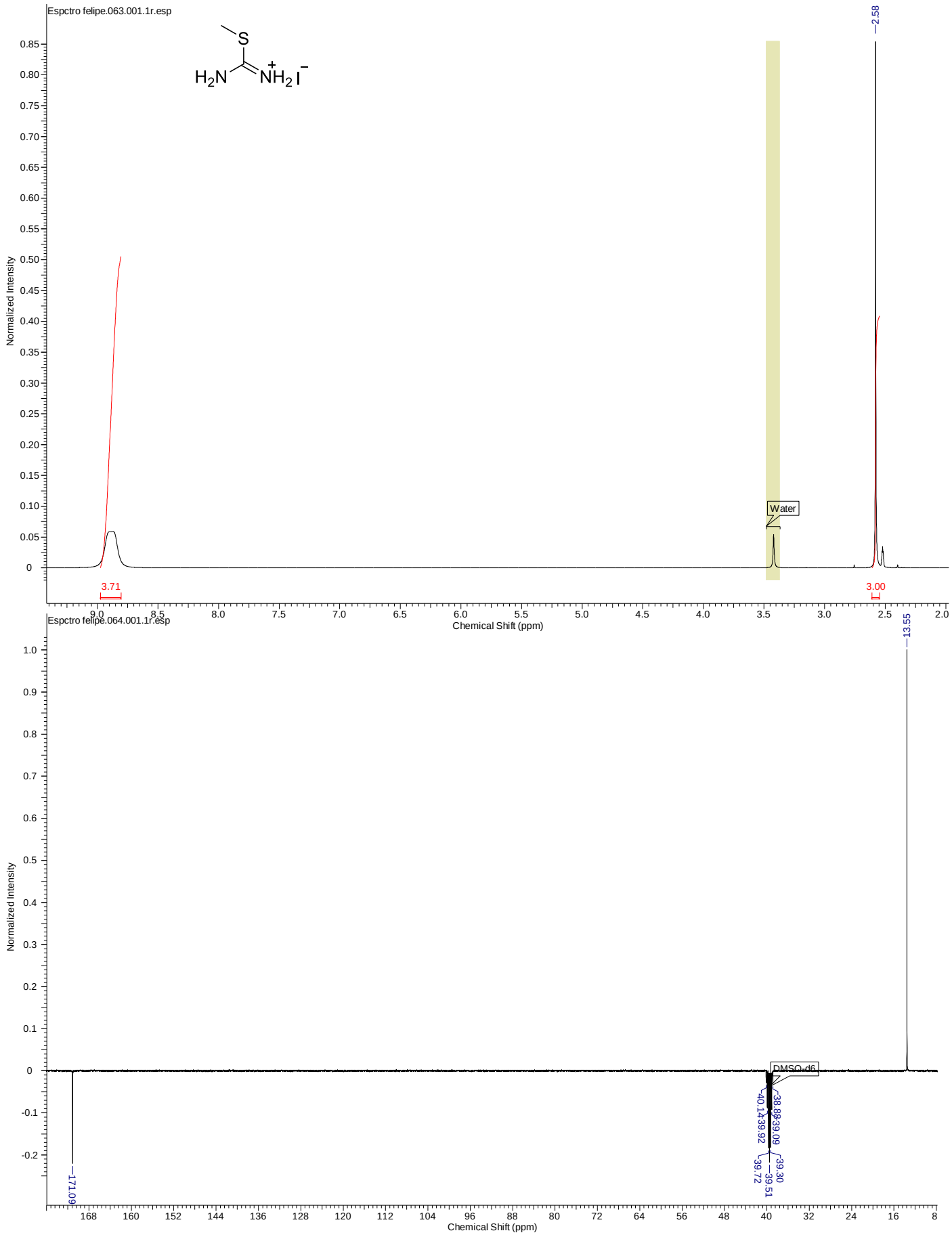
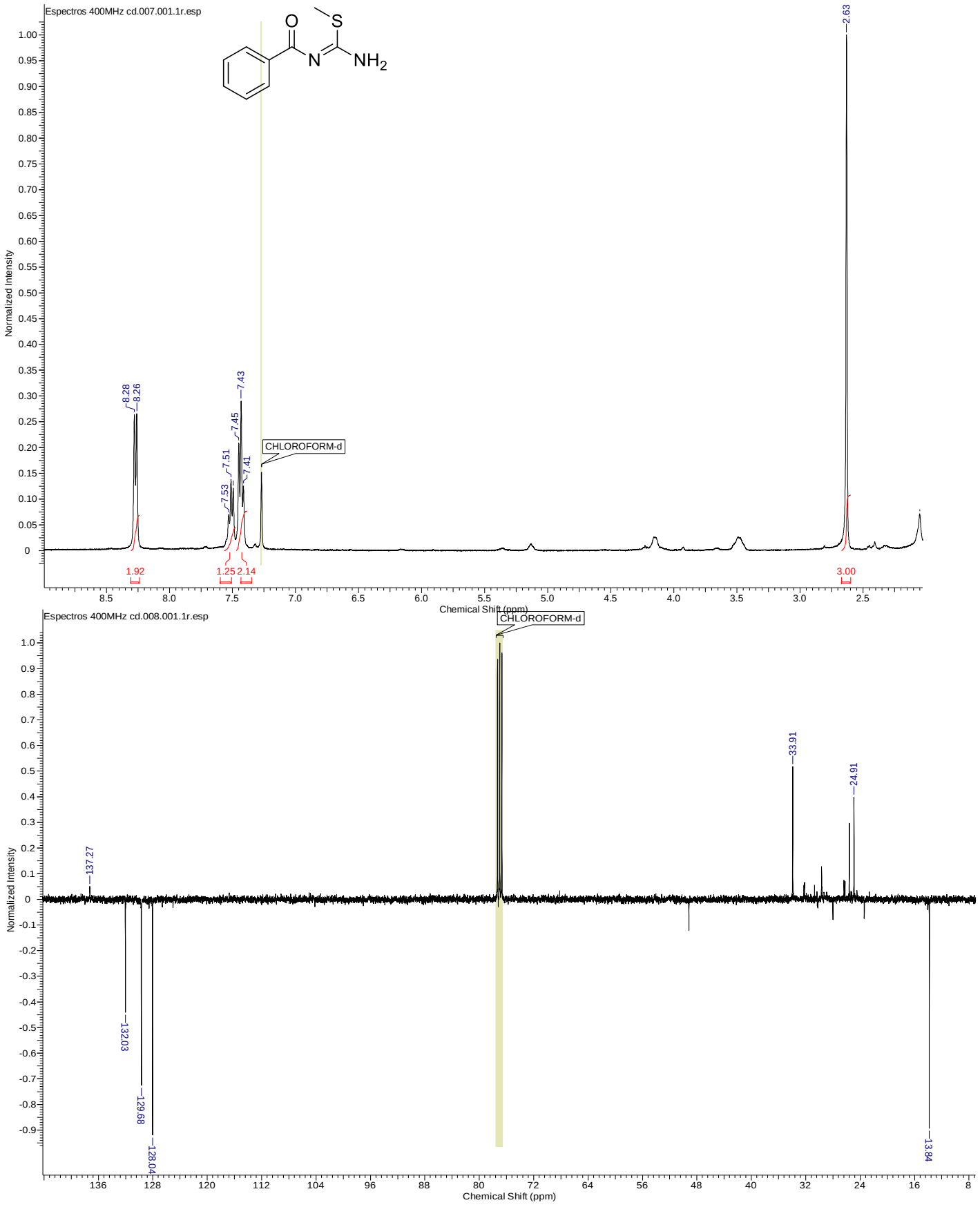


Fig. S1. ^{1}H NMR (500 MHz), DEPT-Q (125 MHz) spectra of 1 in DMSO-*d6*.



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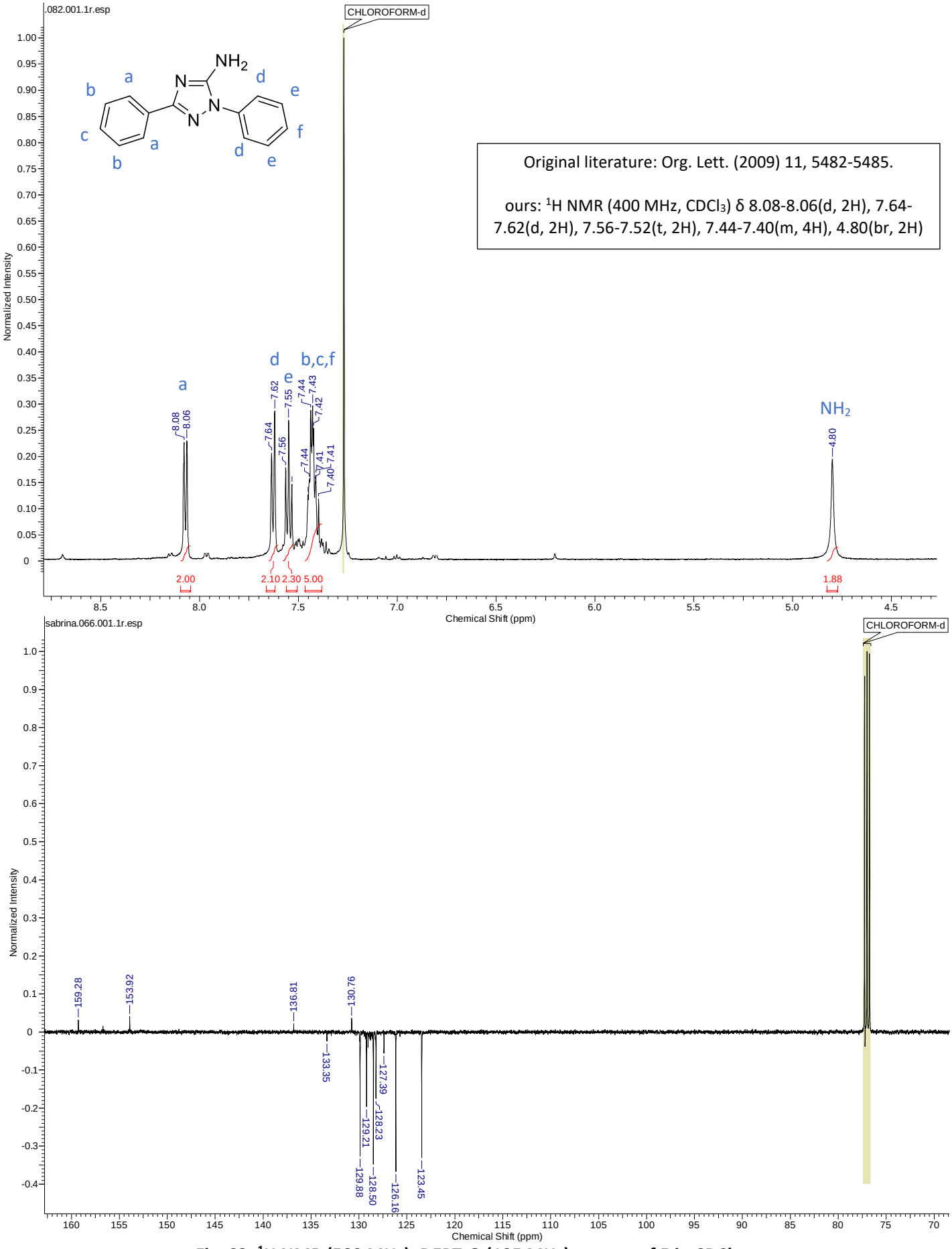

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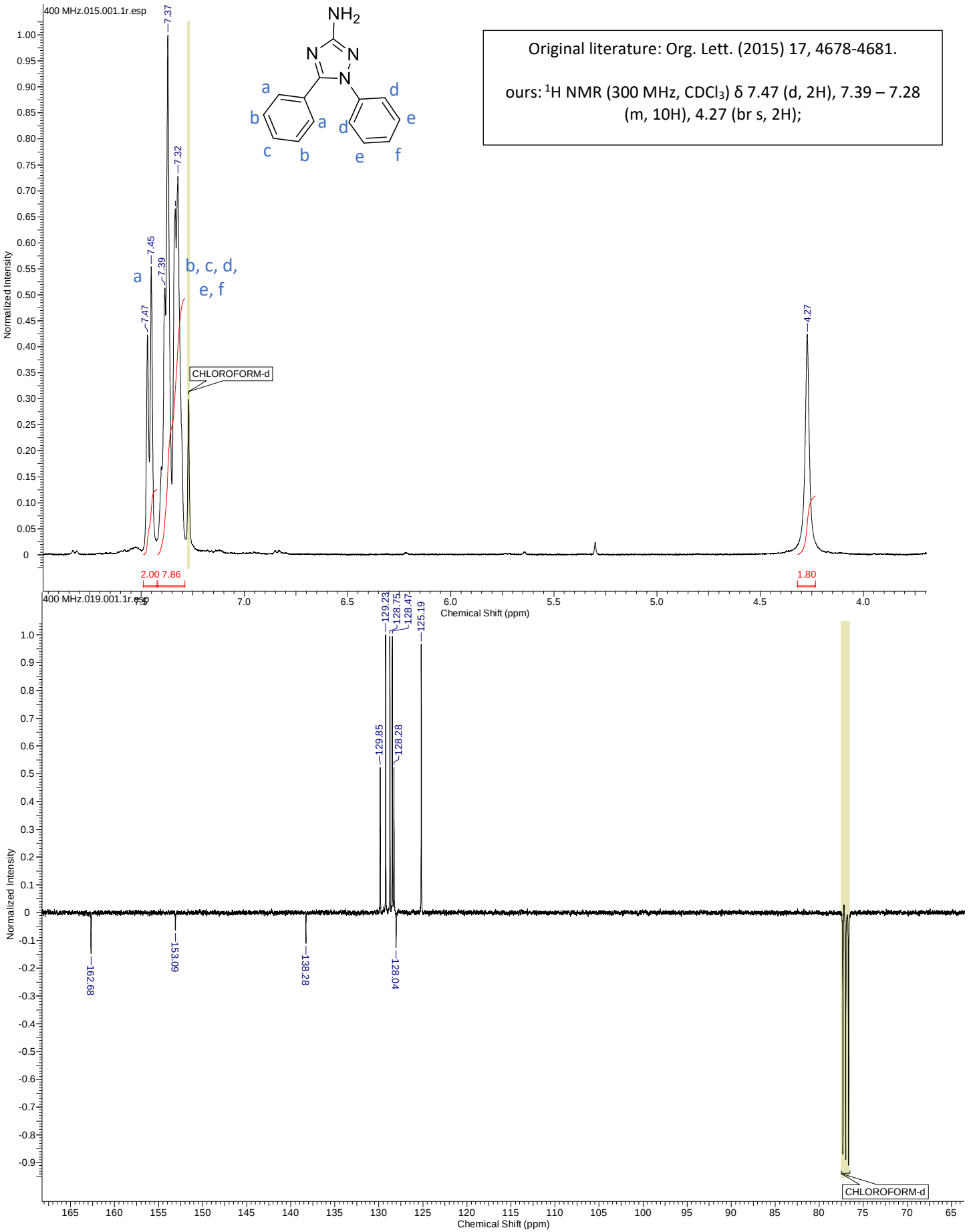

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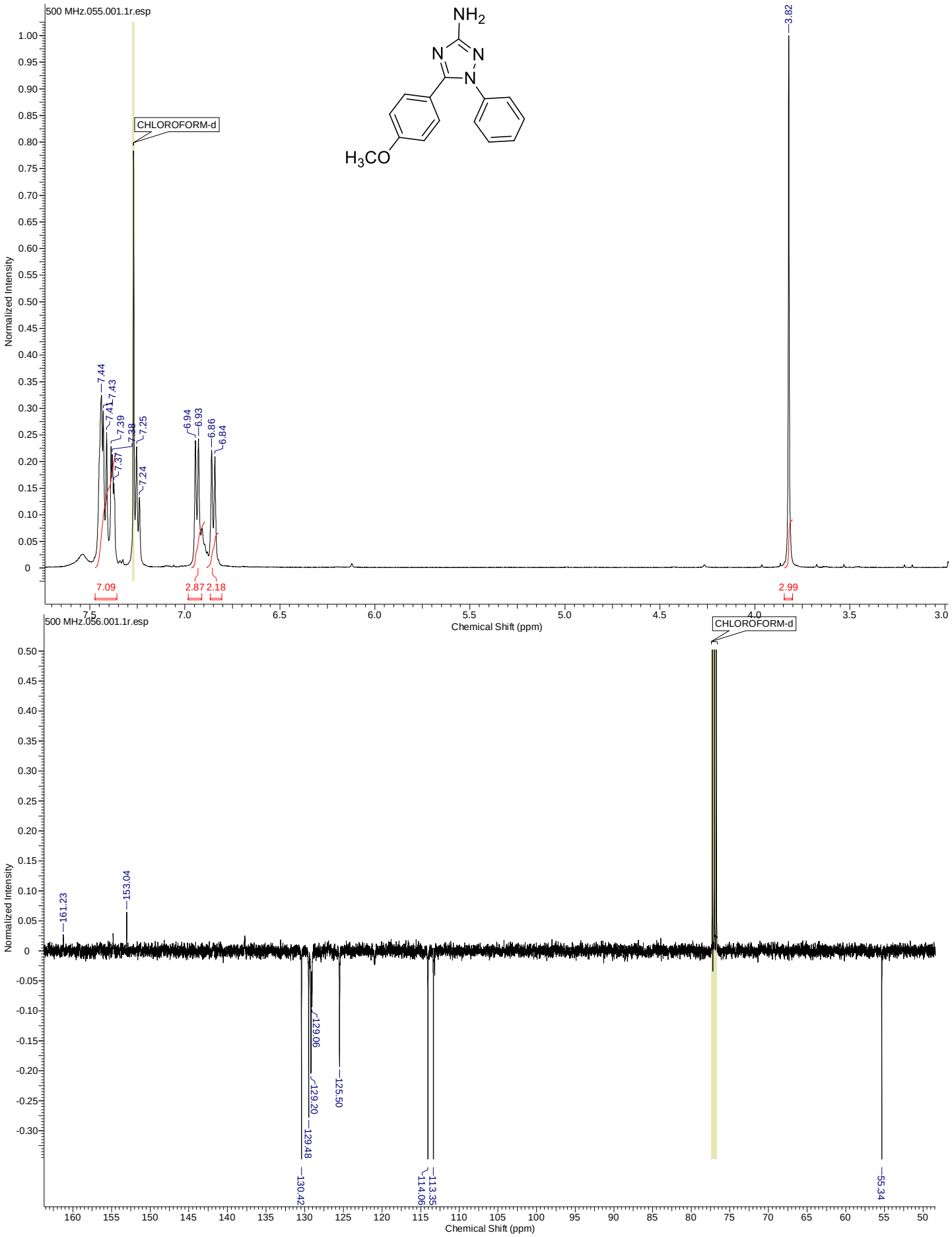

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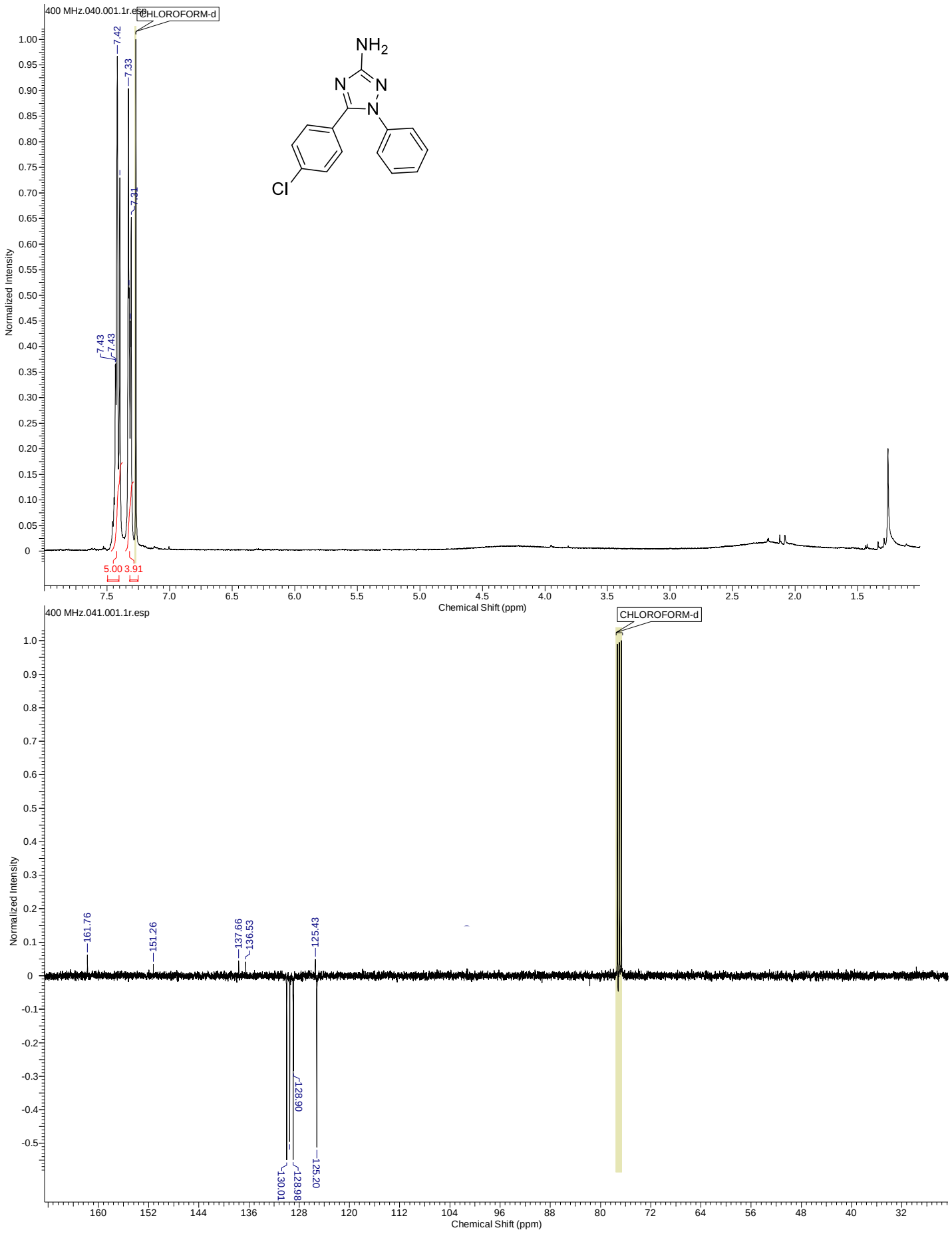

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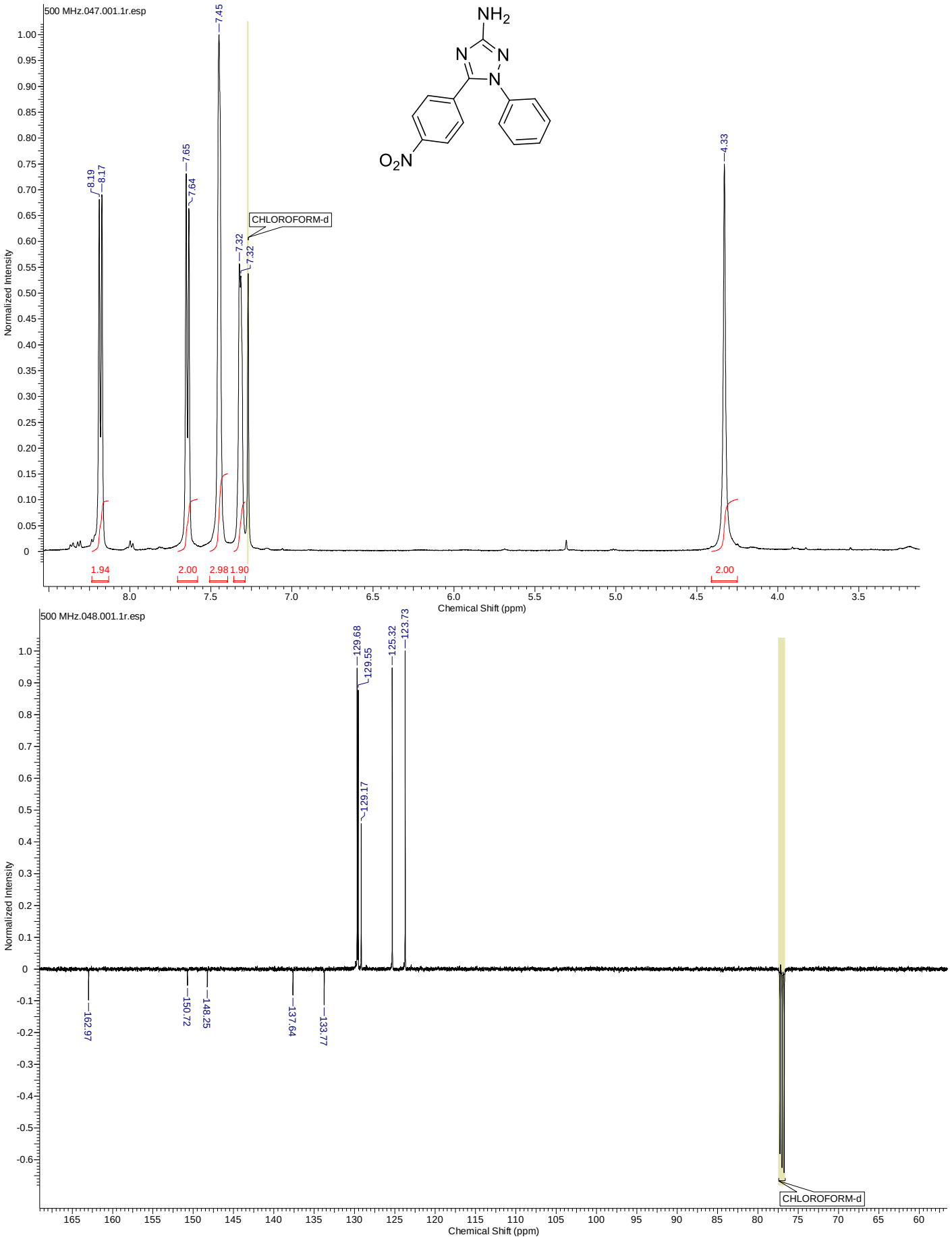

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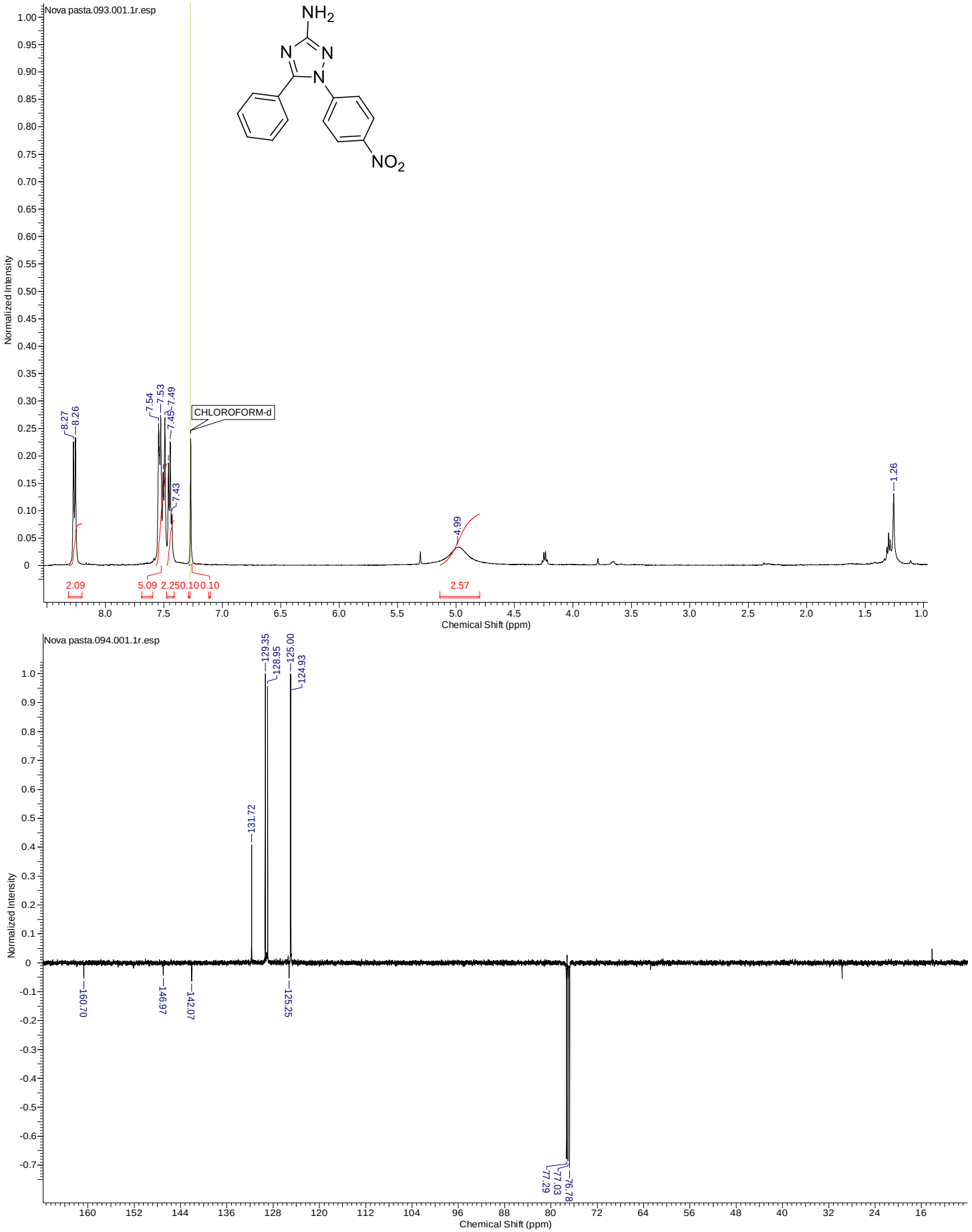

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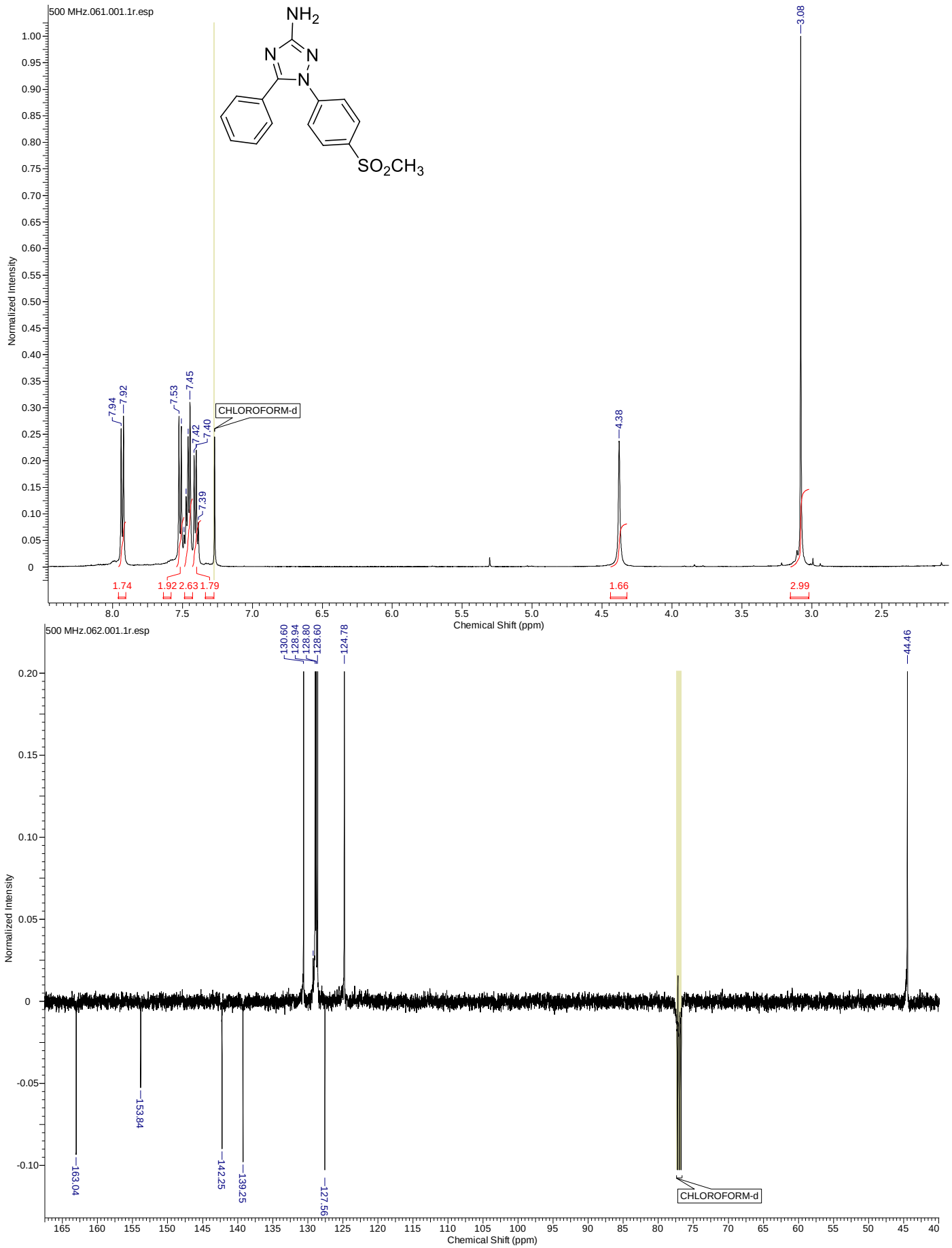

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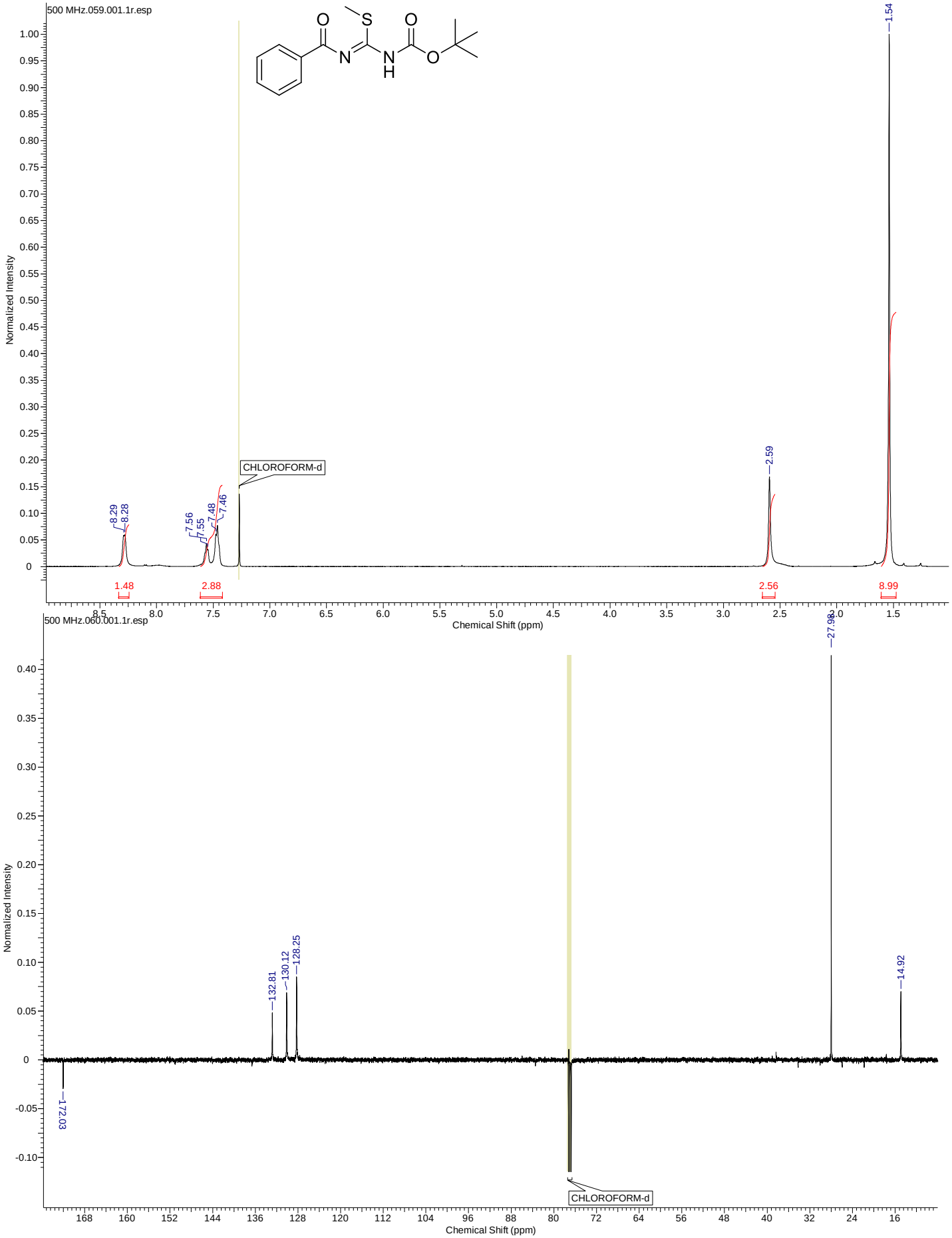

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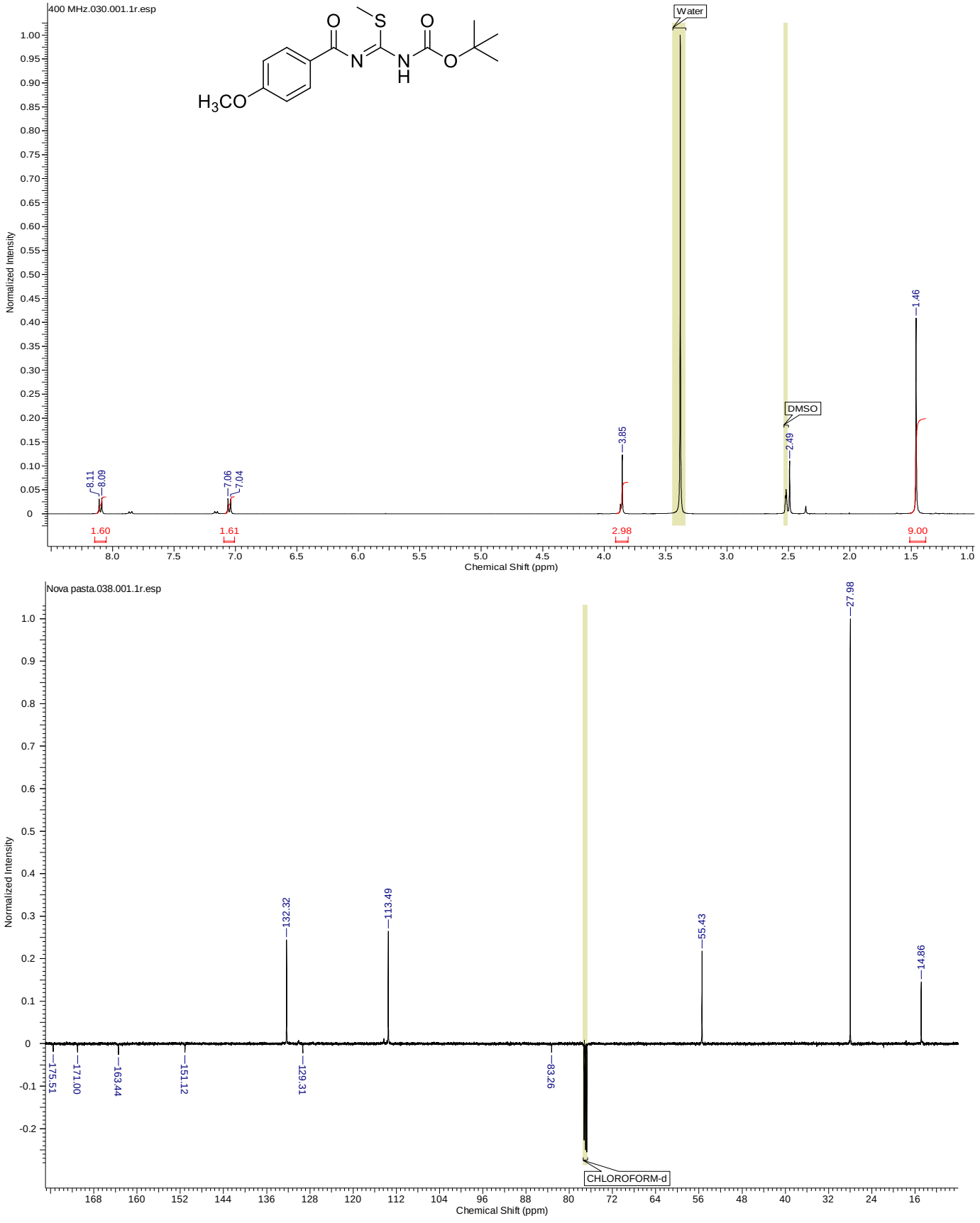

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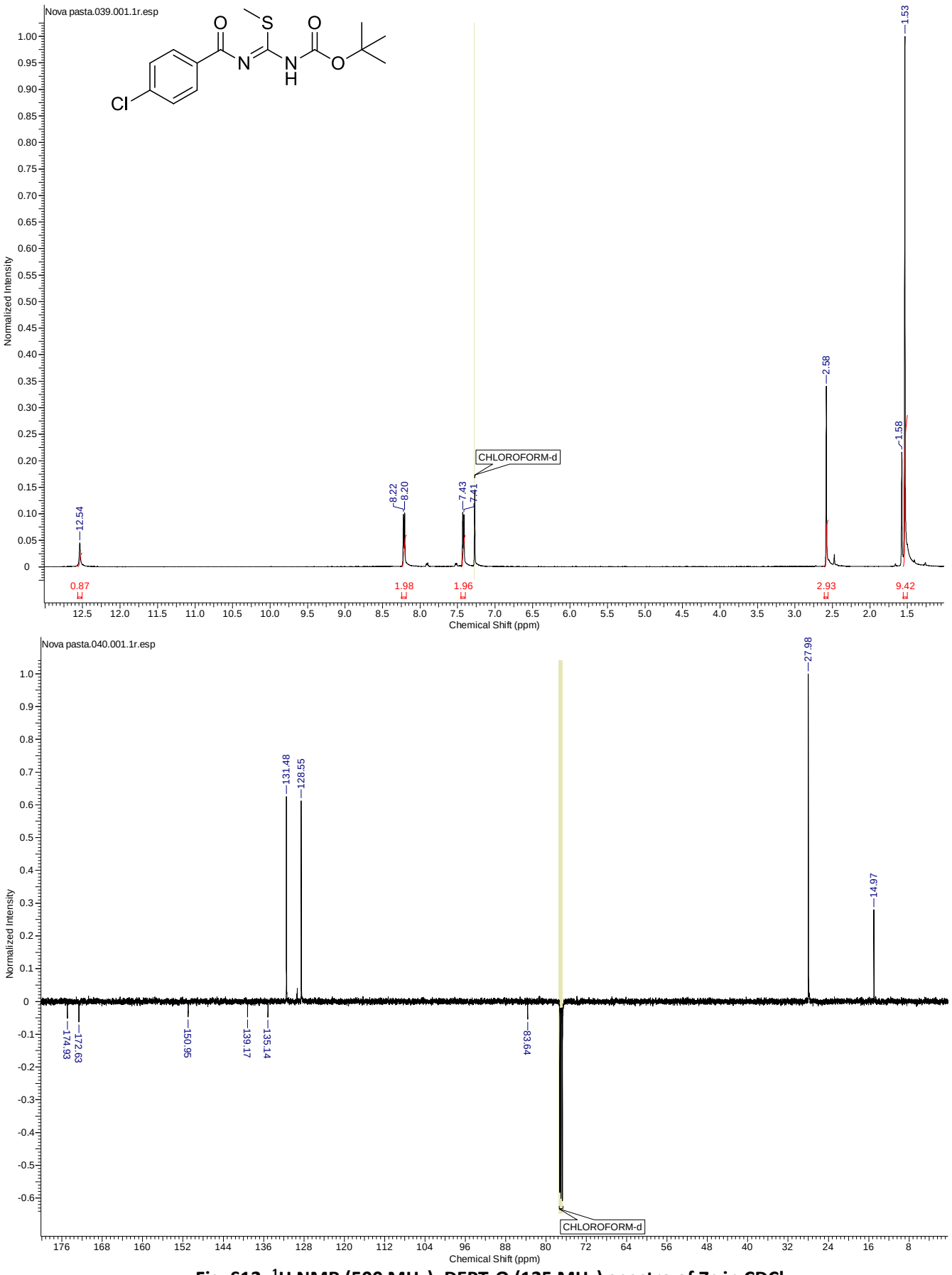

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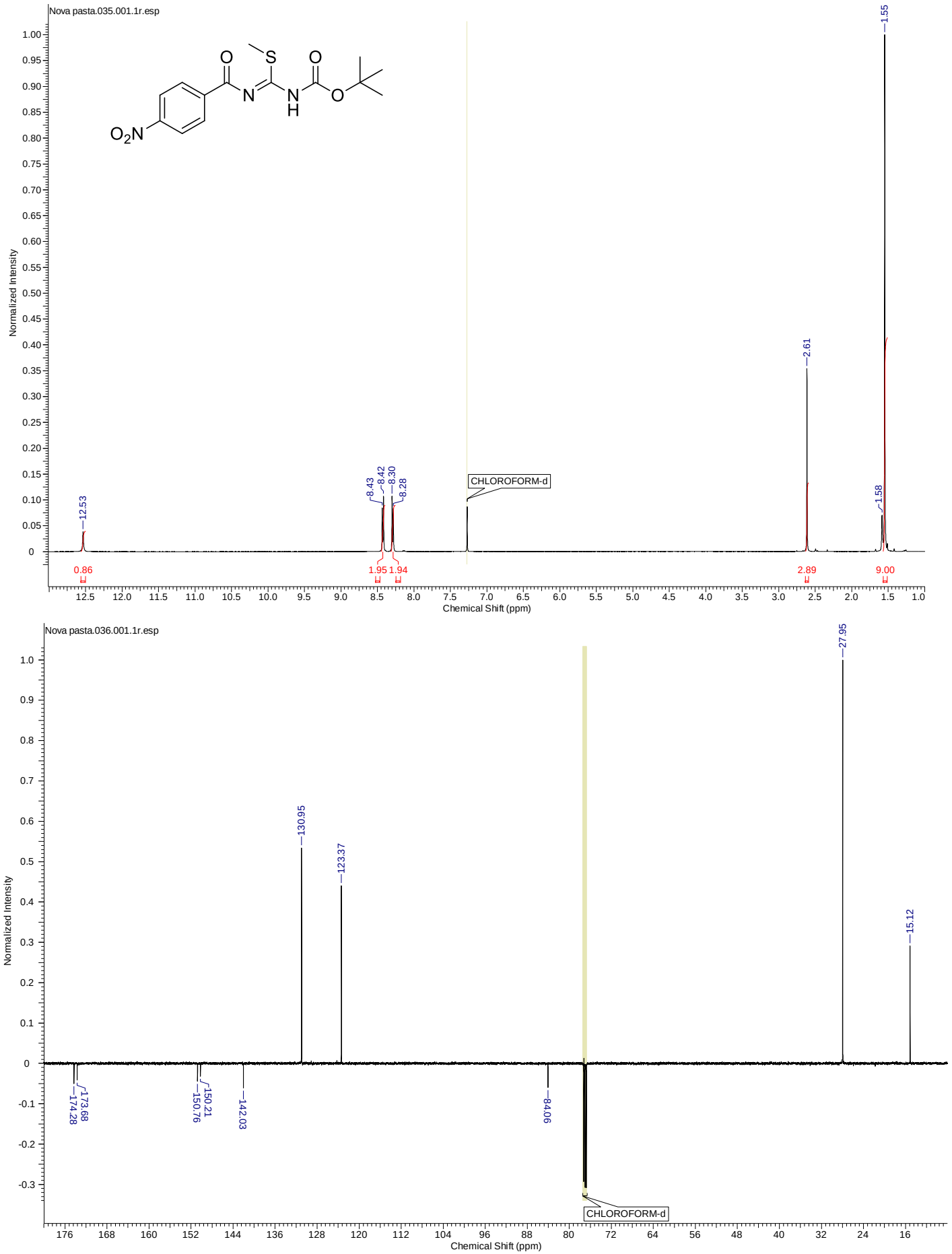

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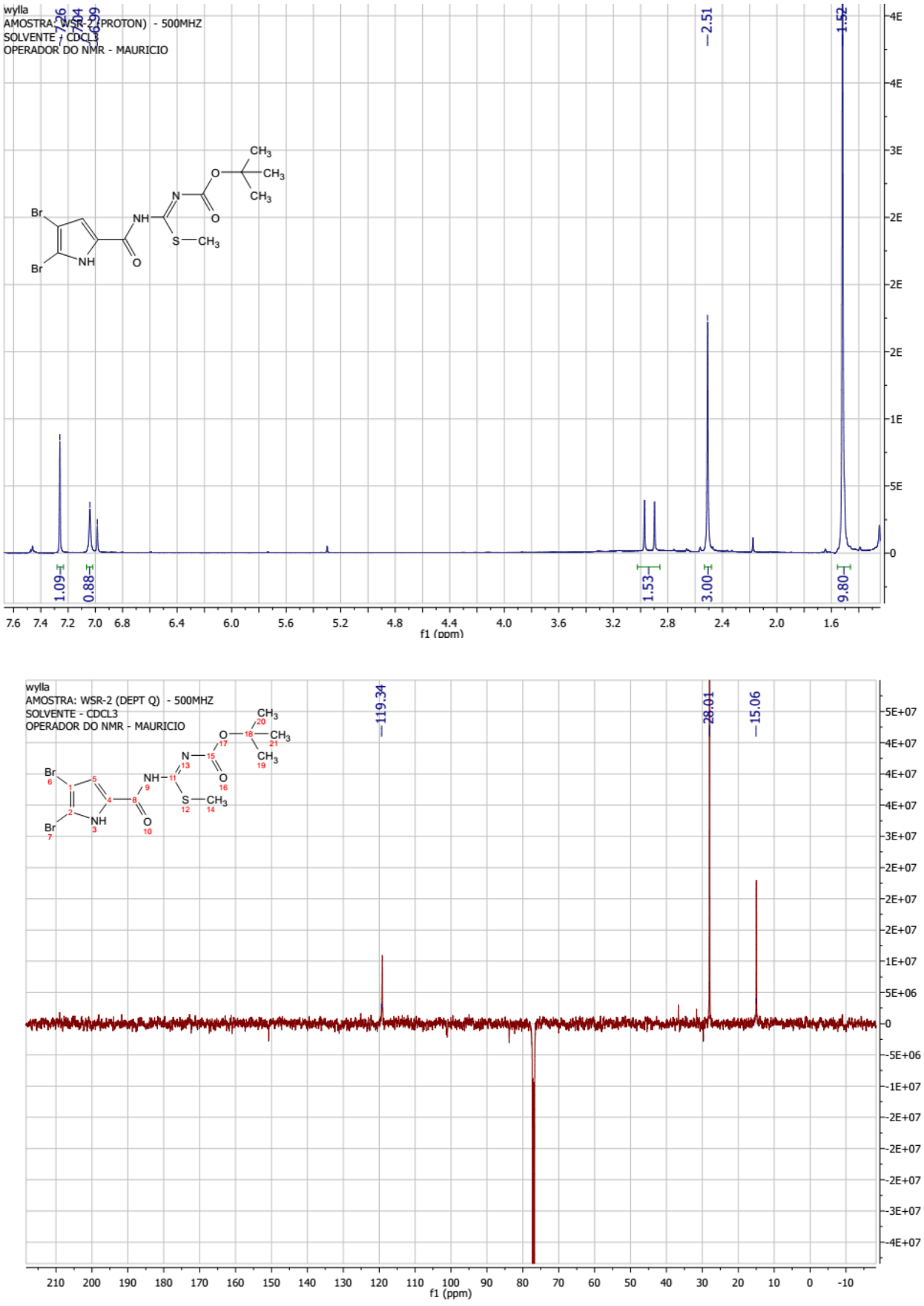

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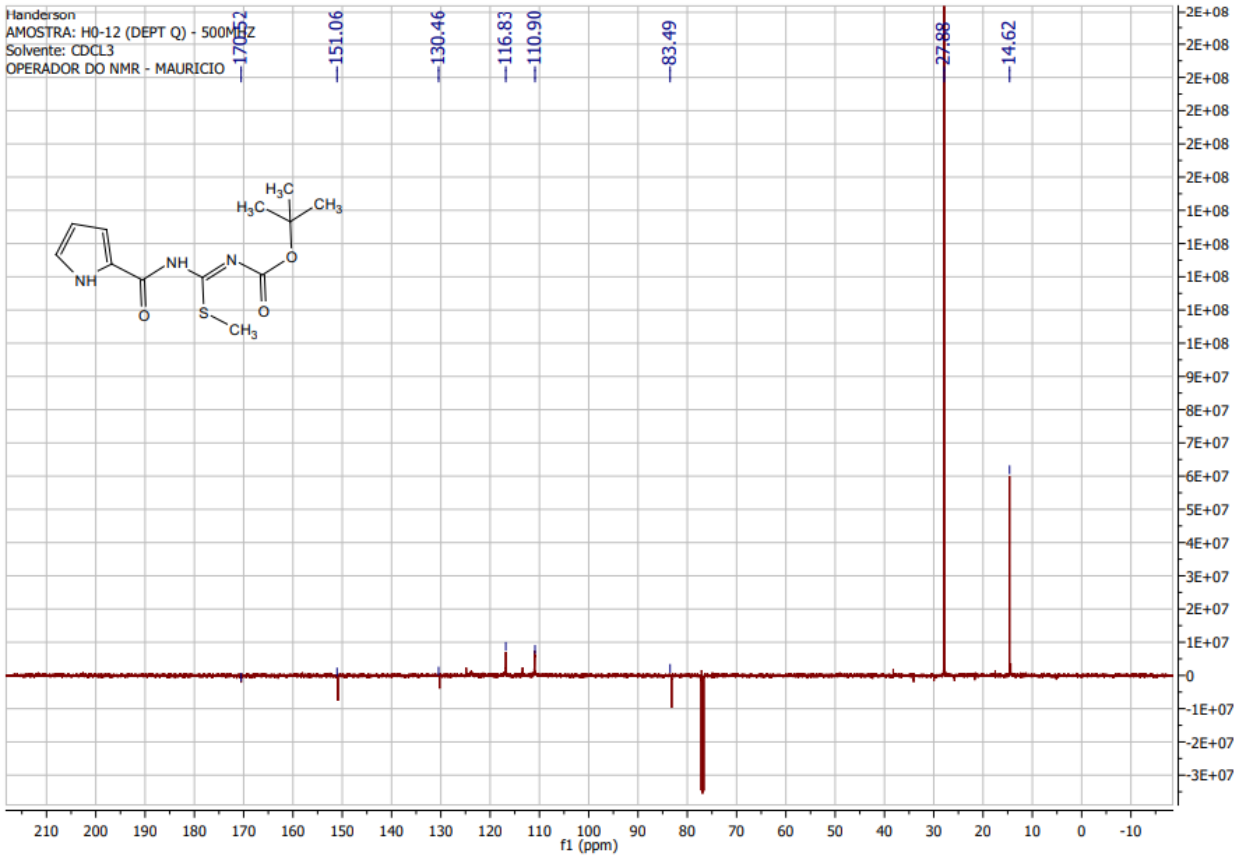

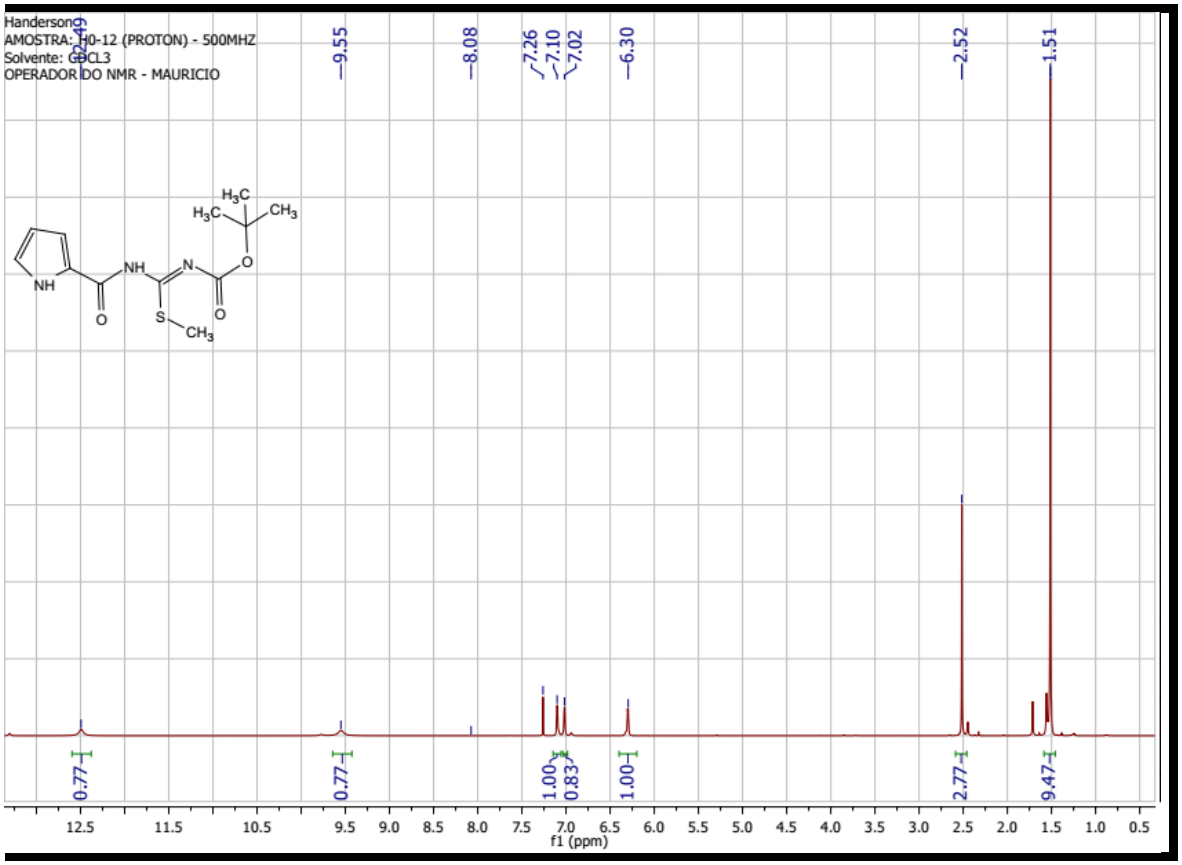

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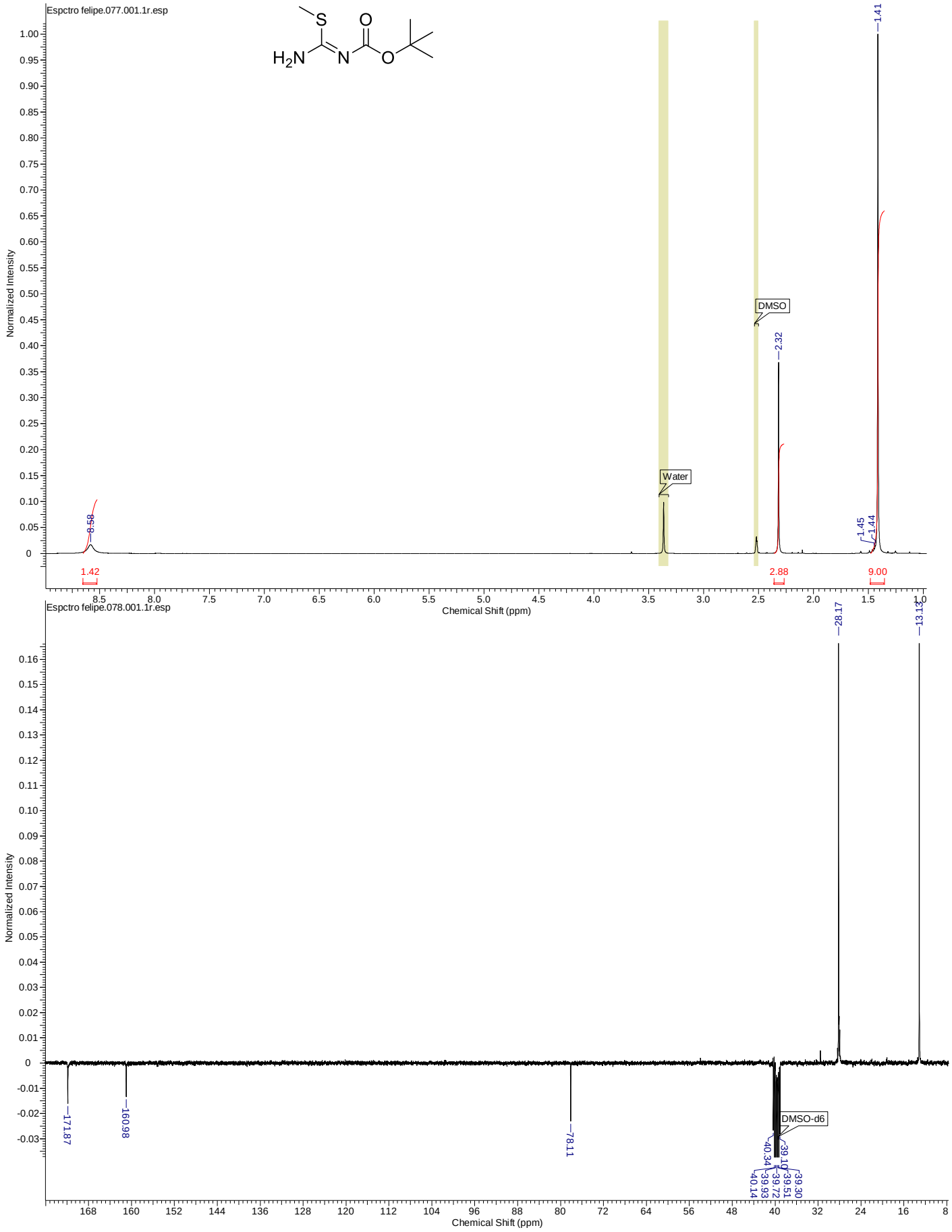

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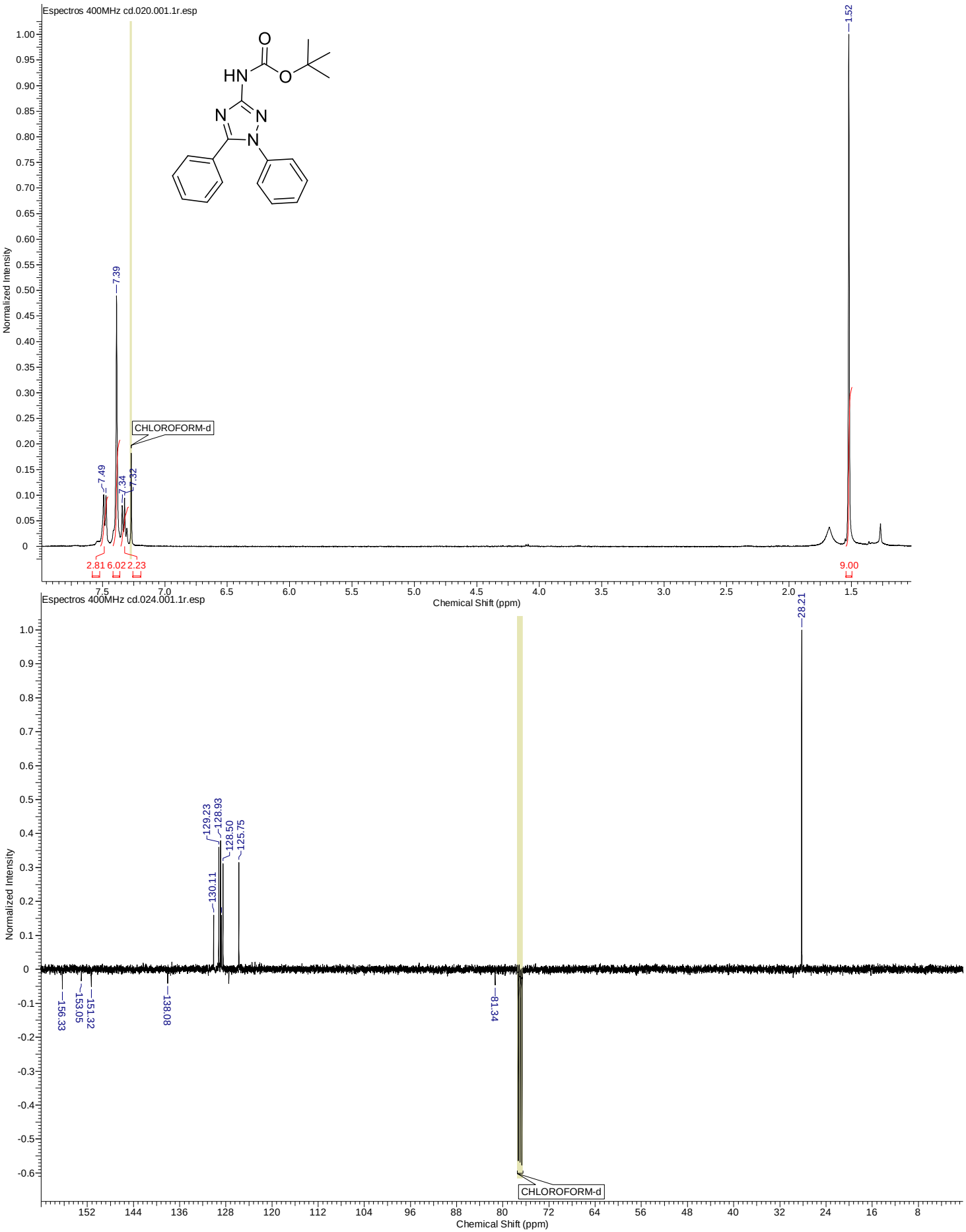

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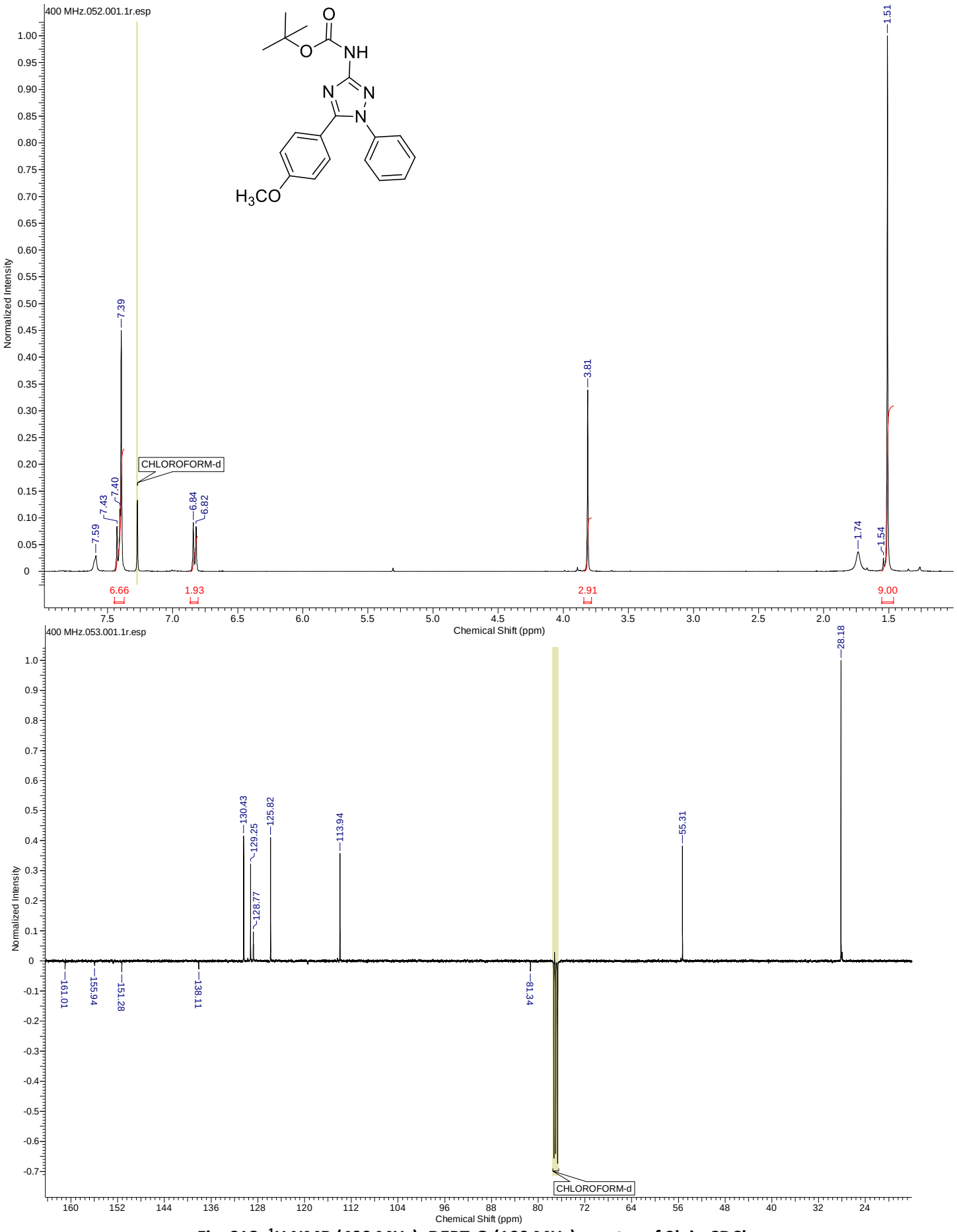

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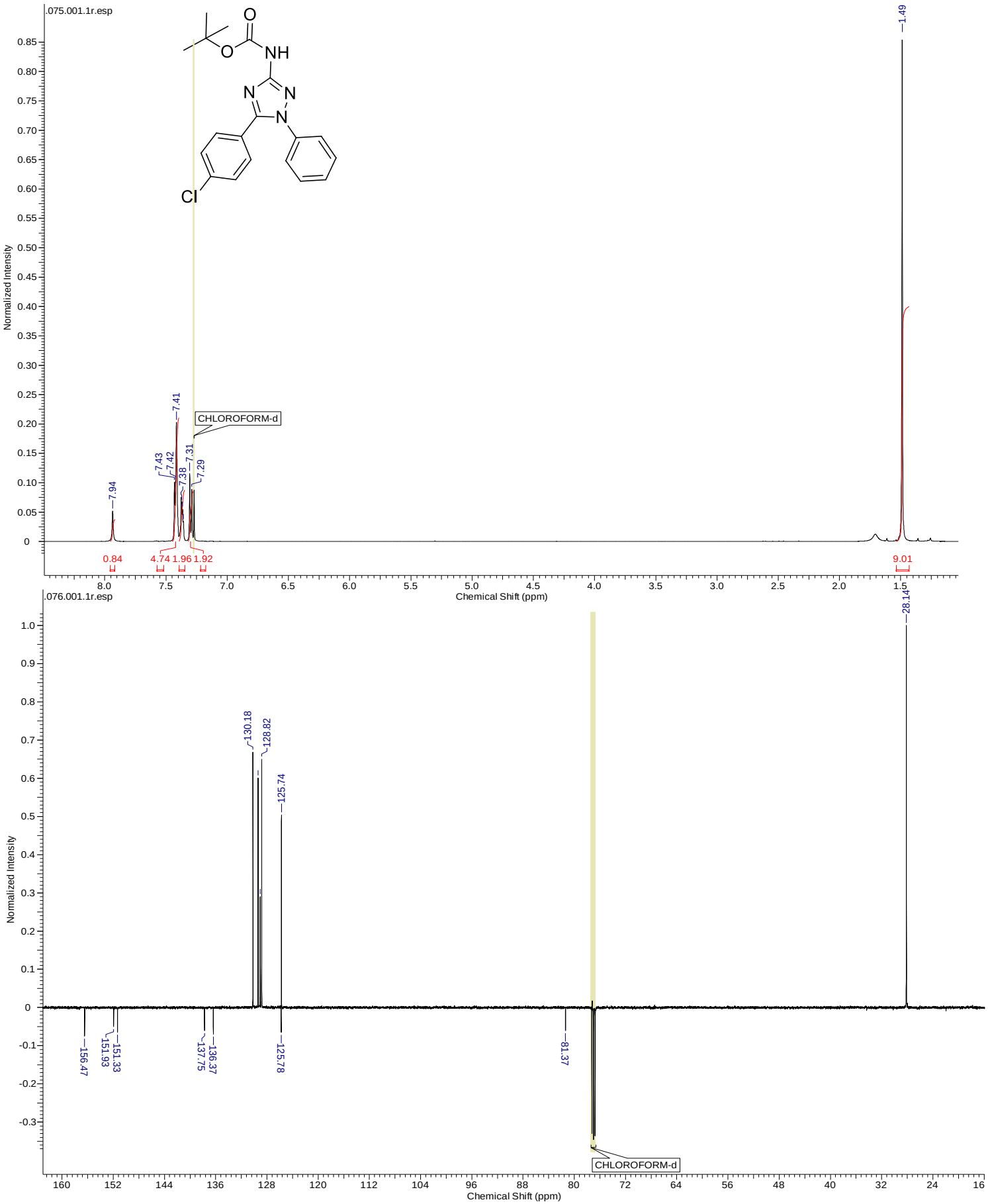

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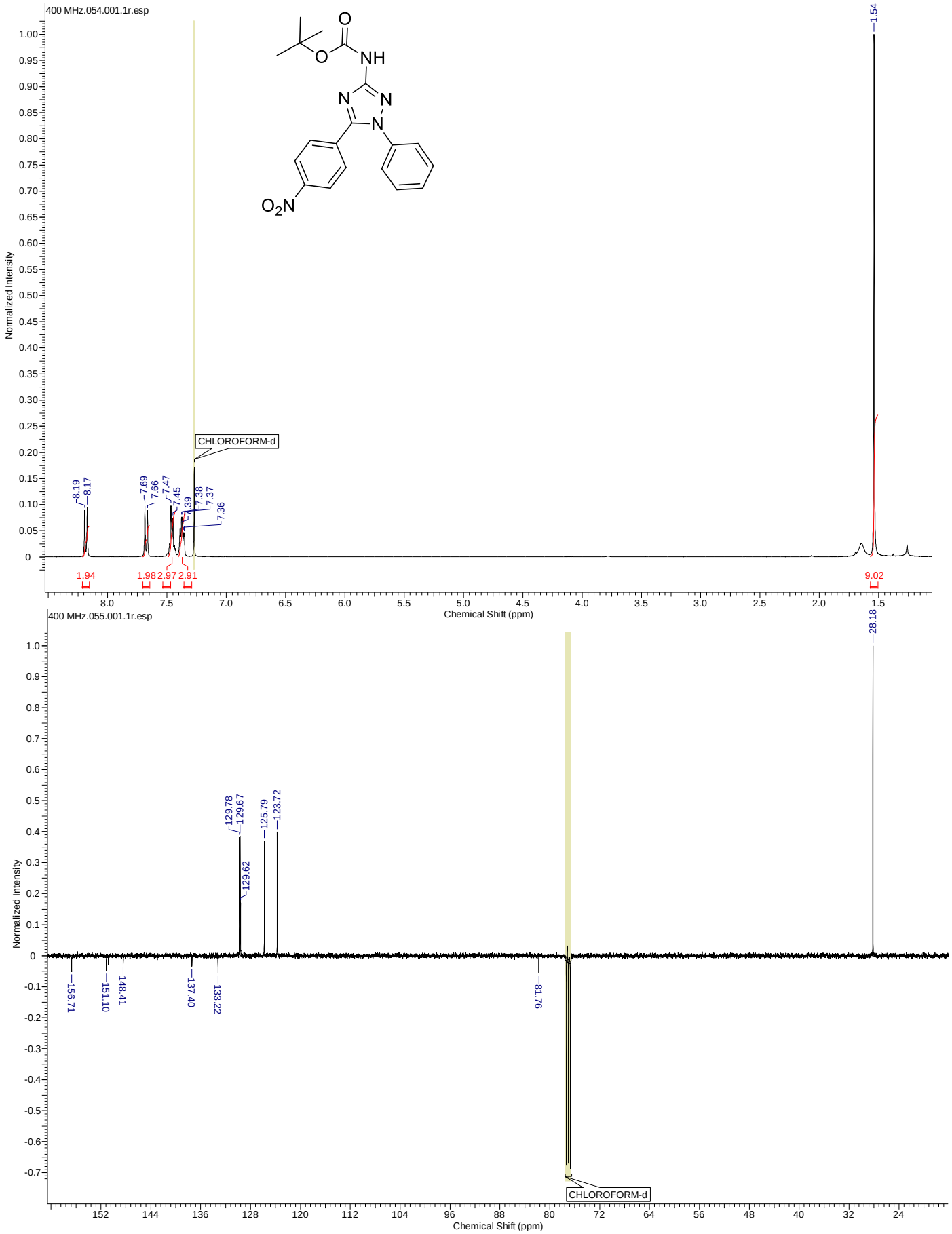

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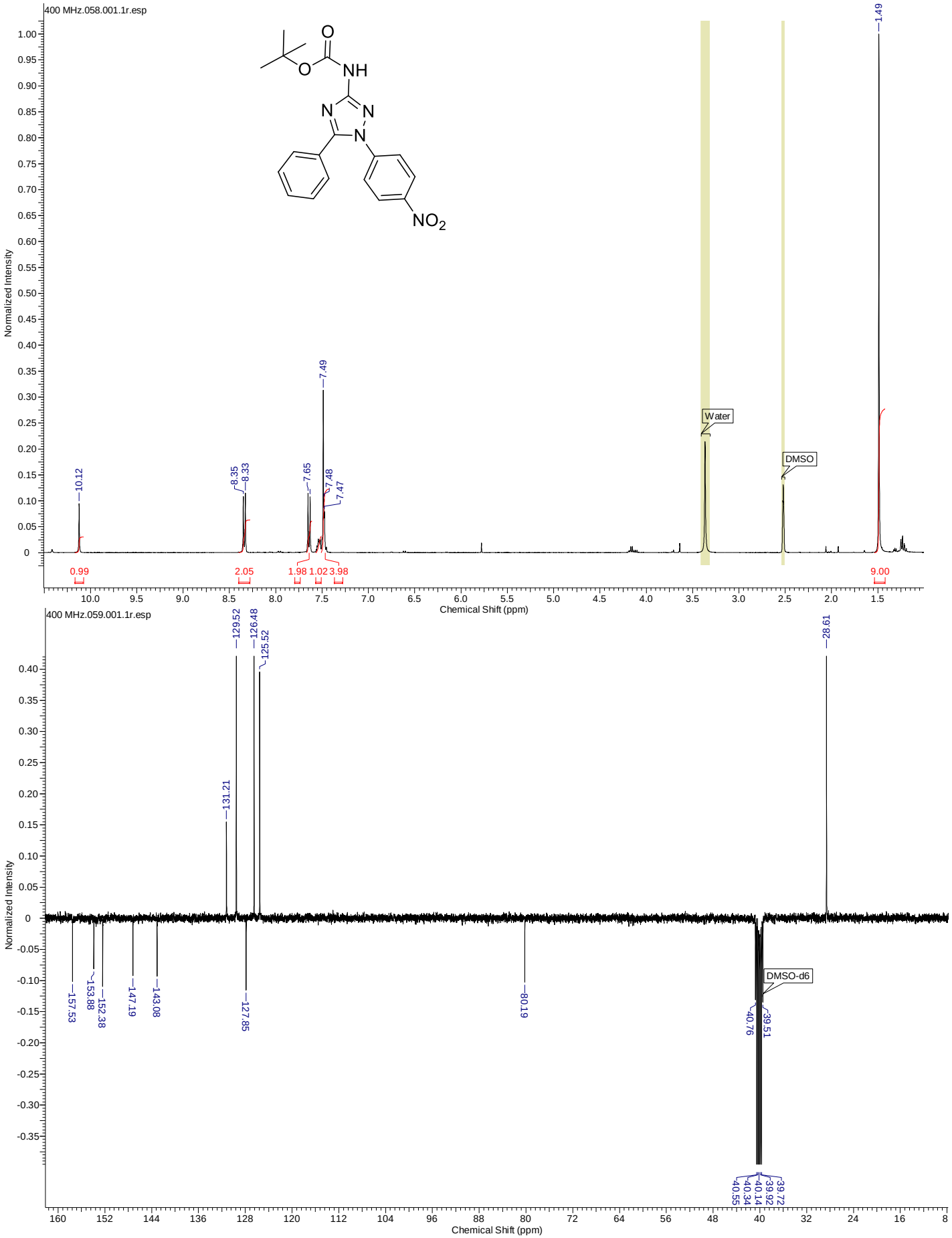

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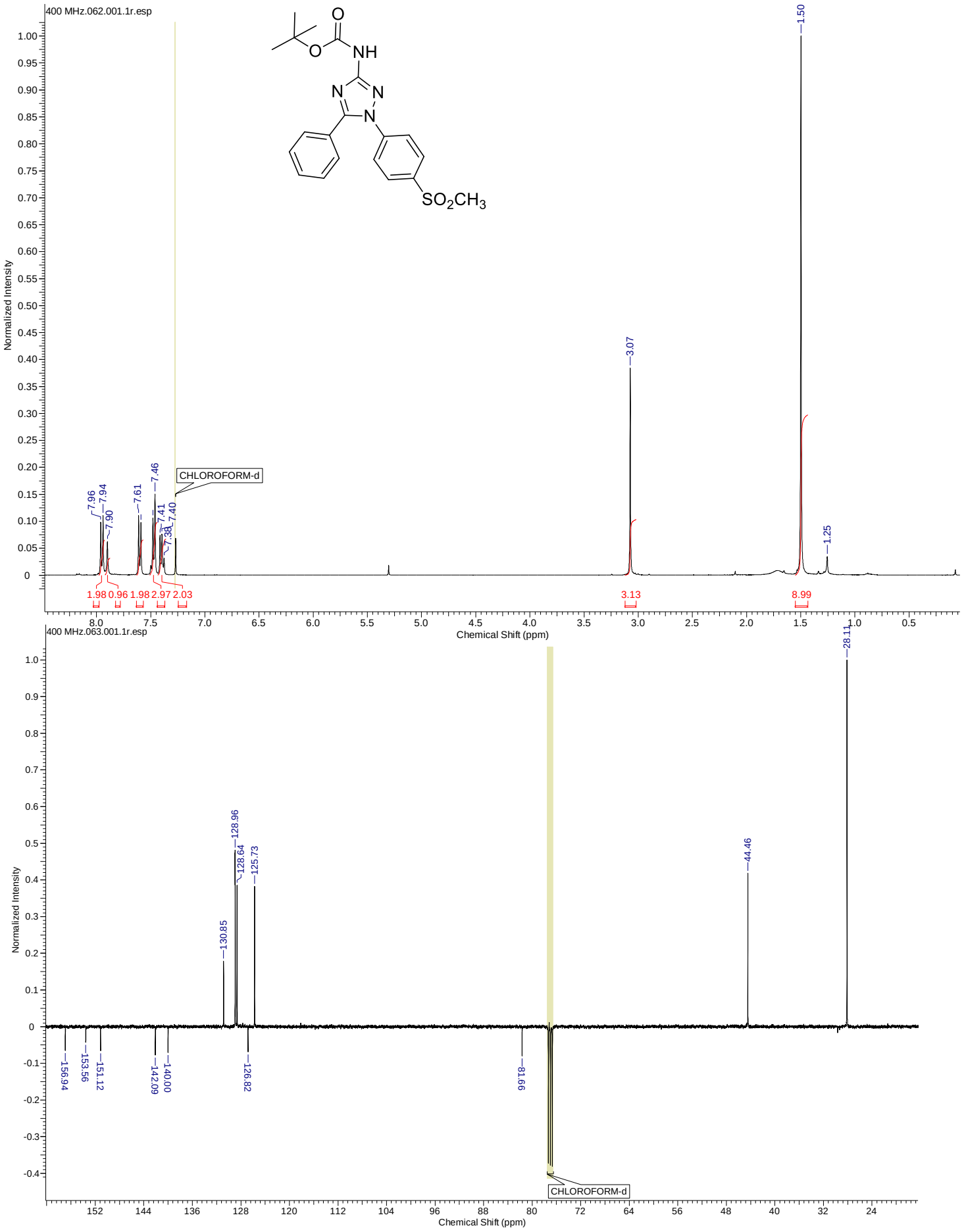

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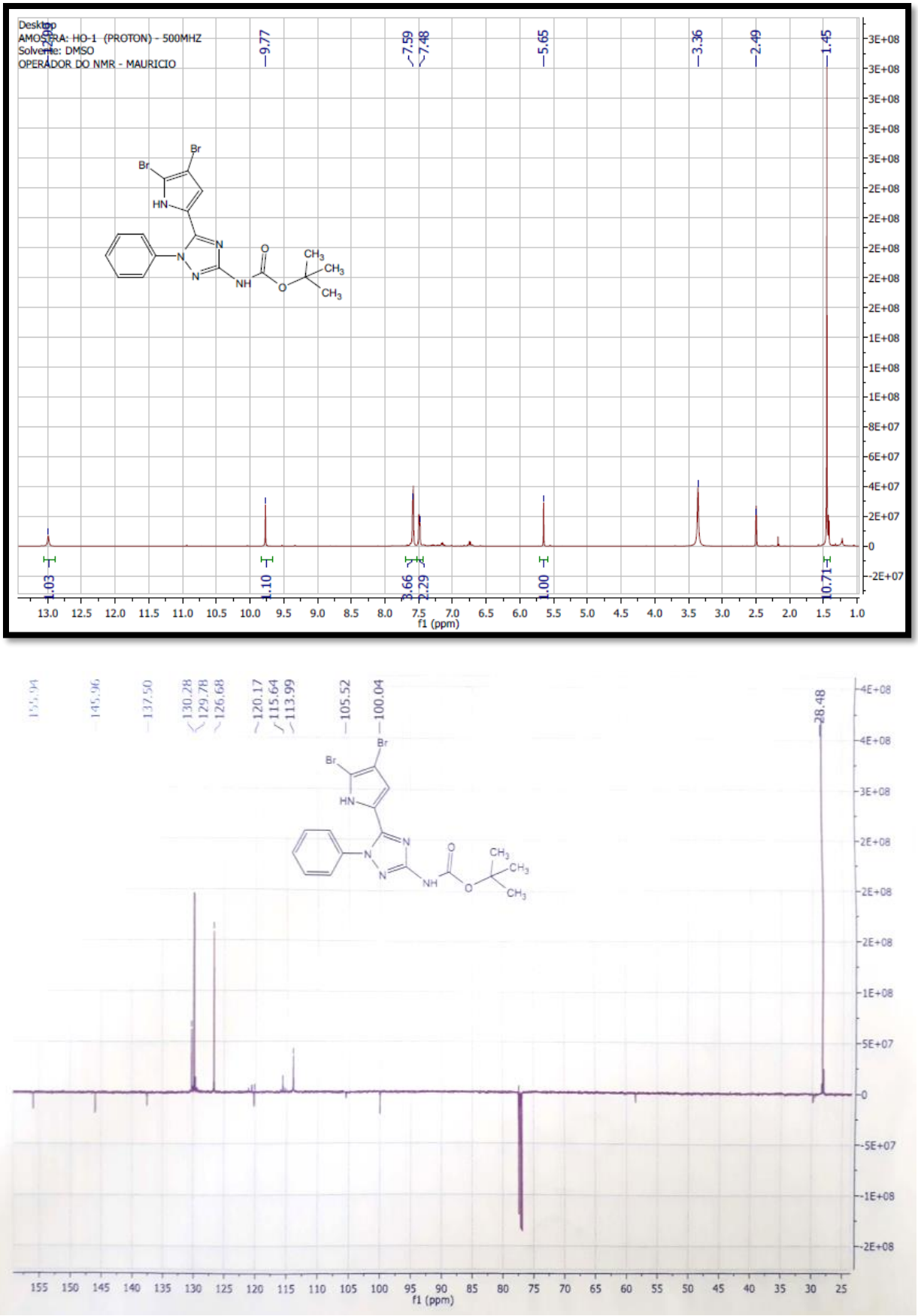

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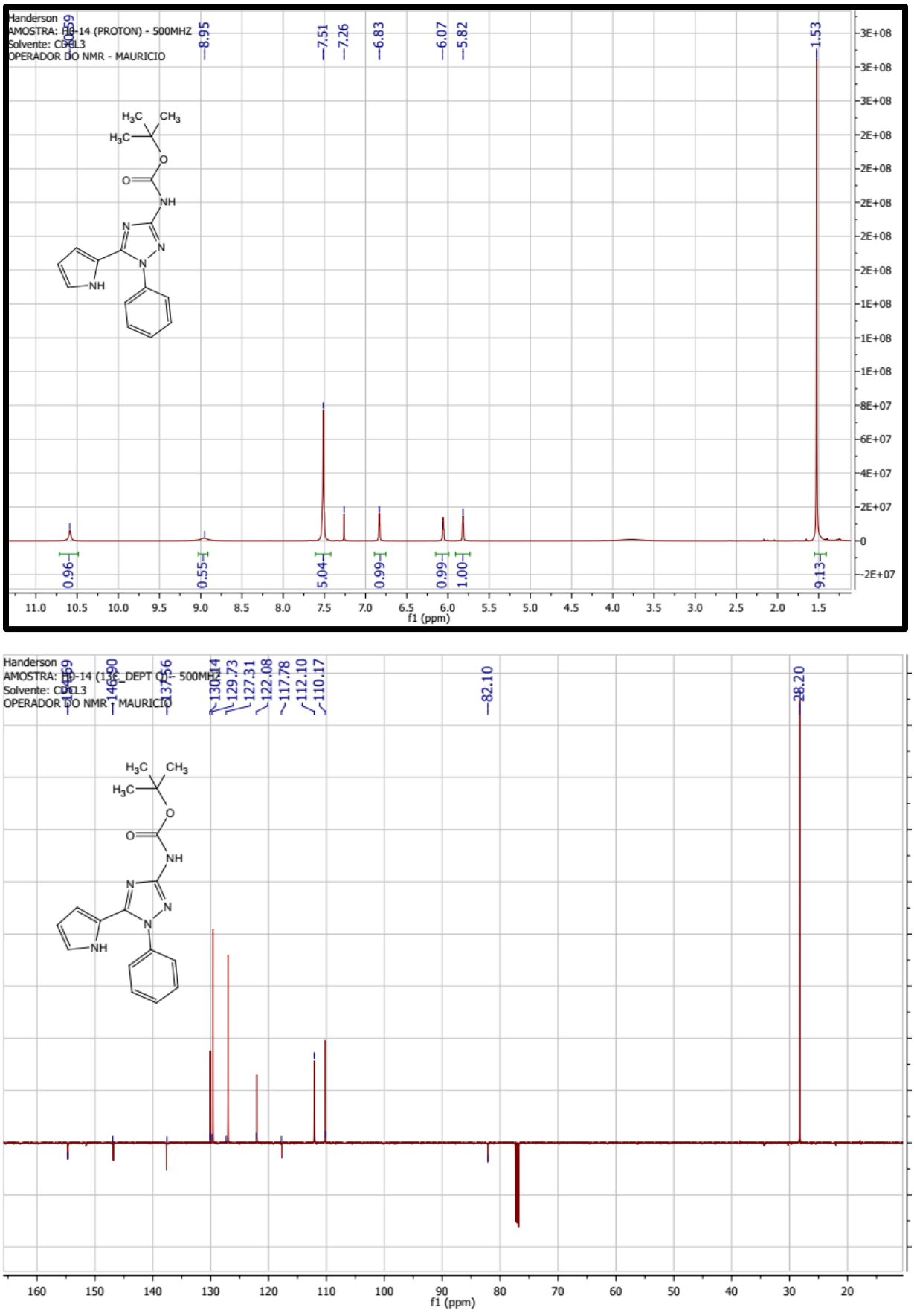

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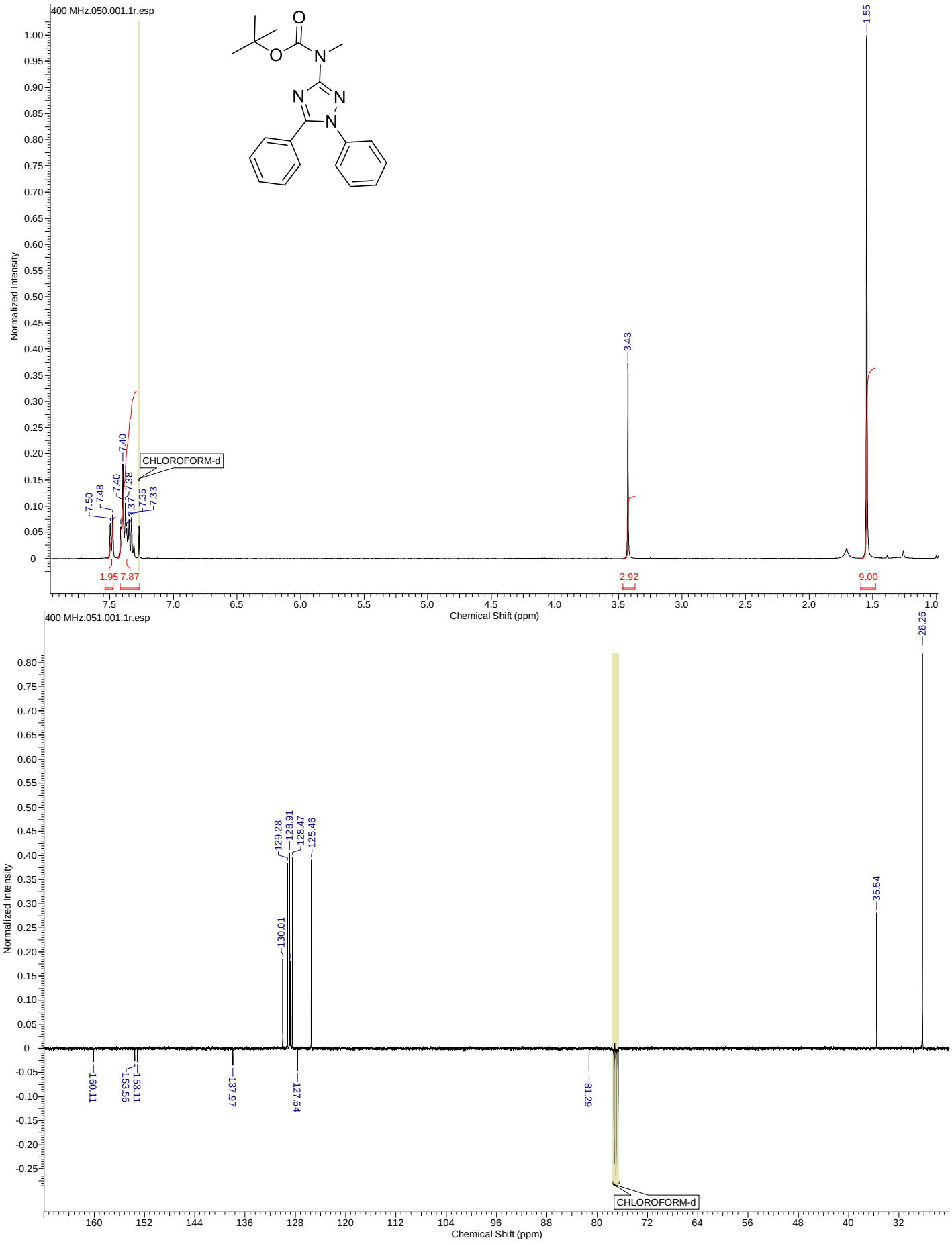

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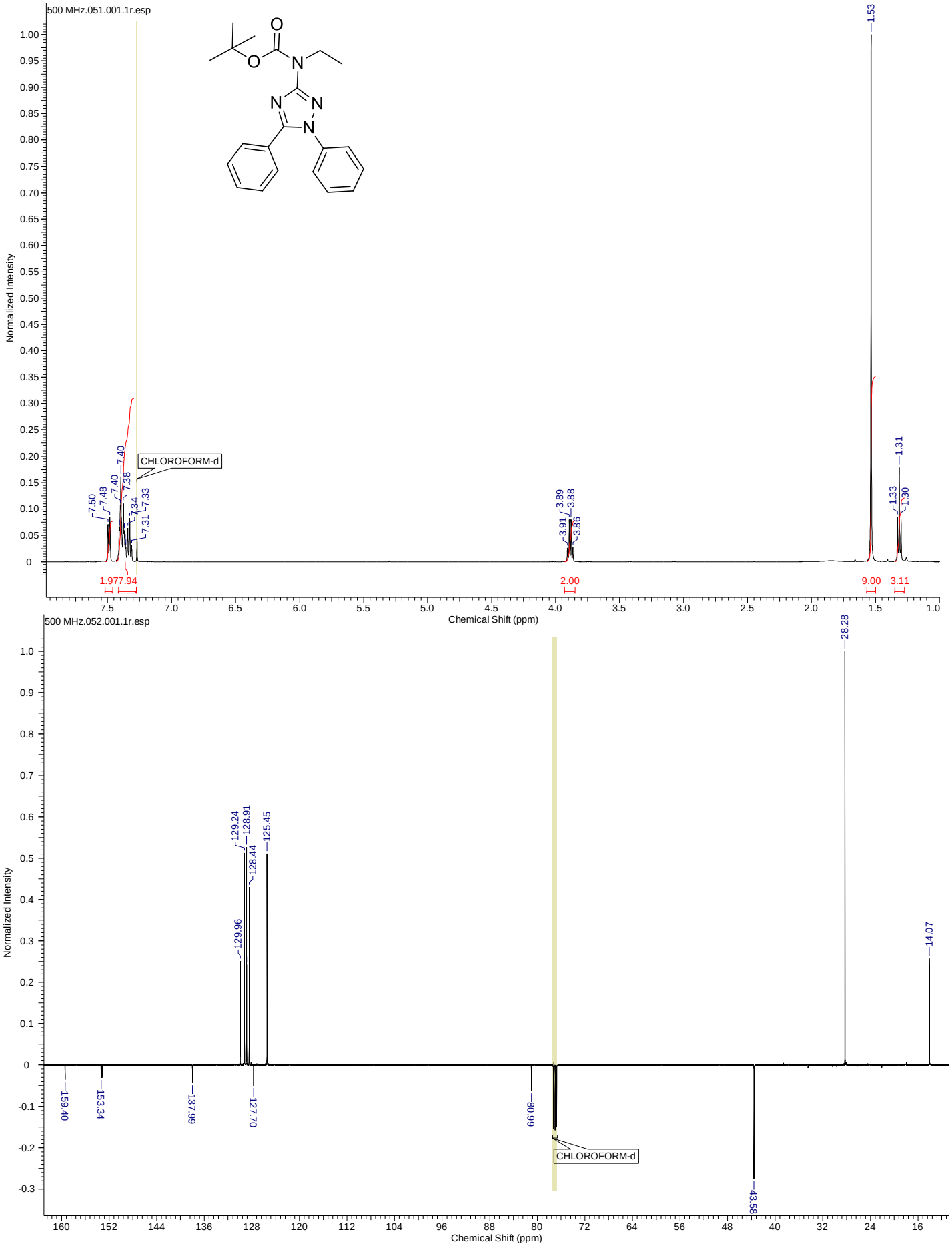

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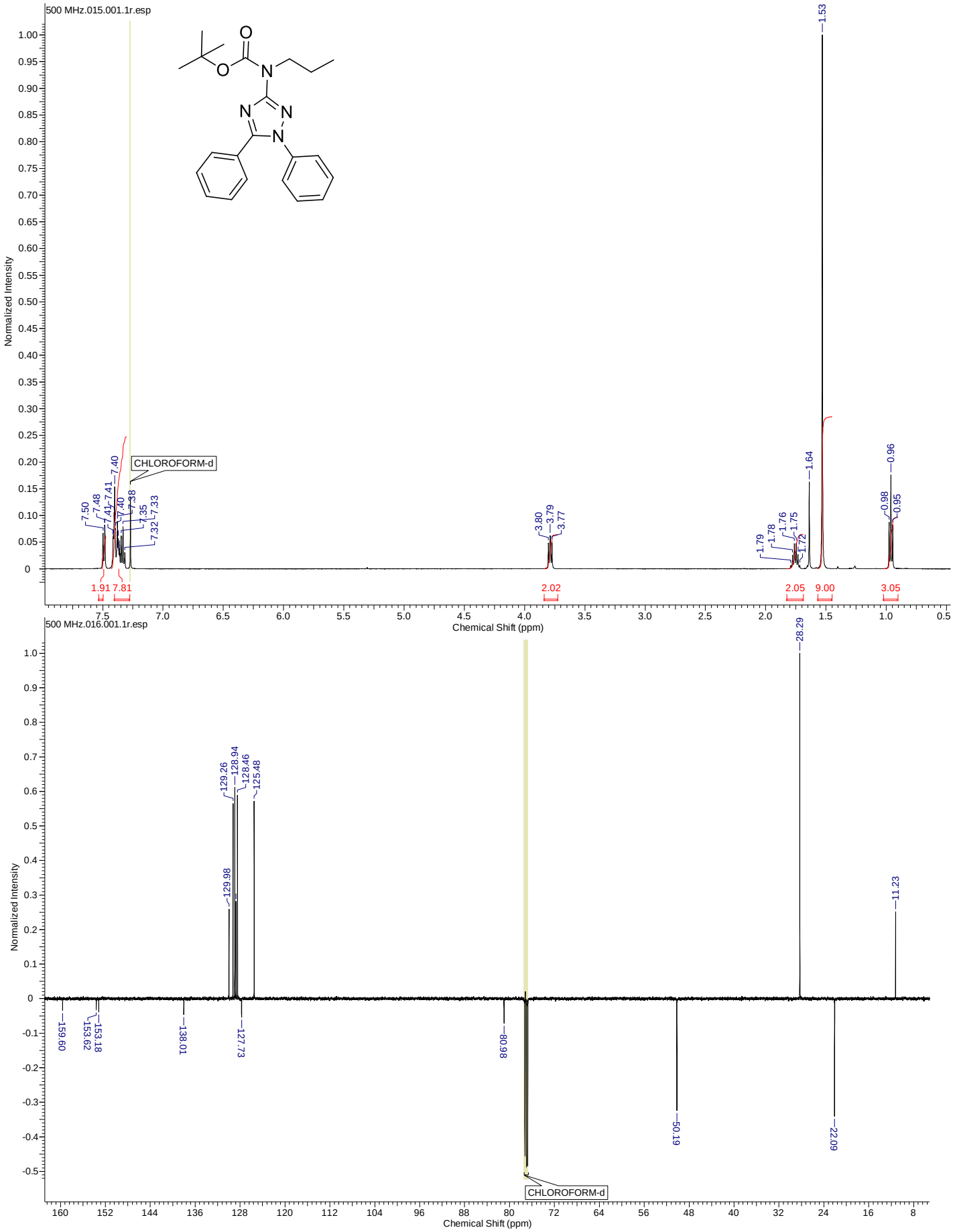

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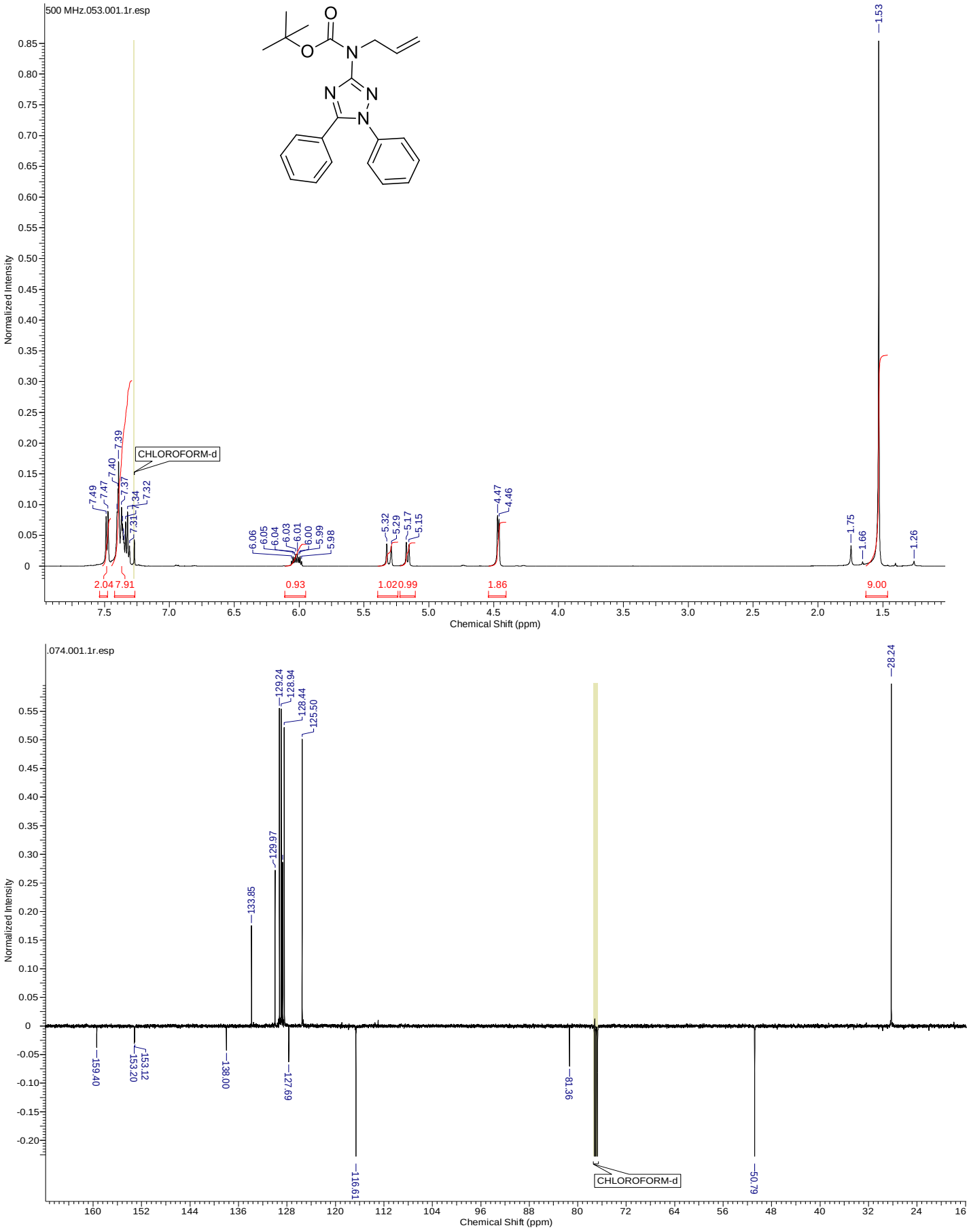

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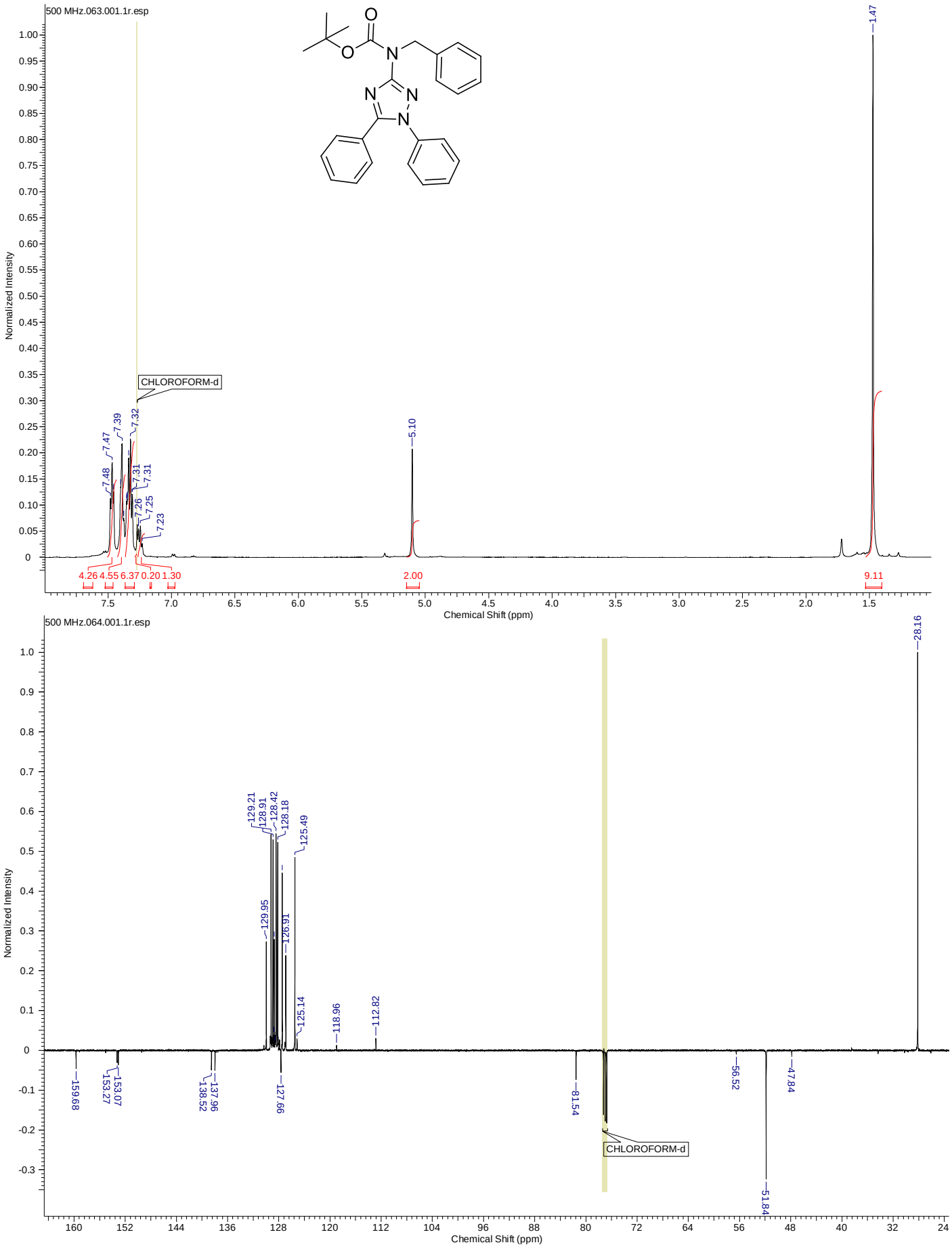

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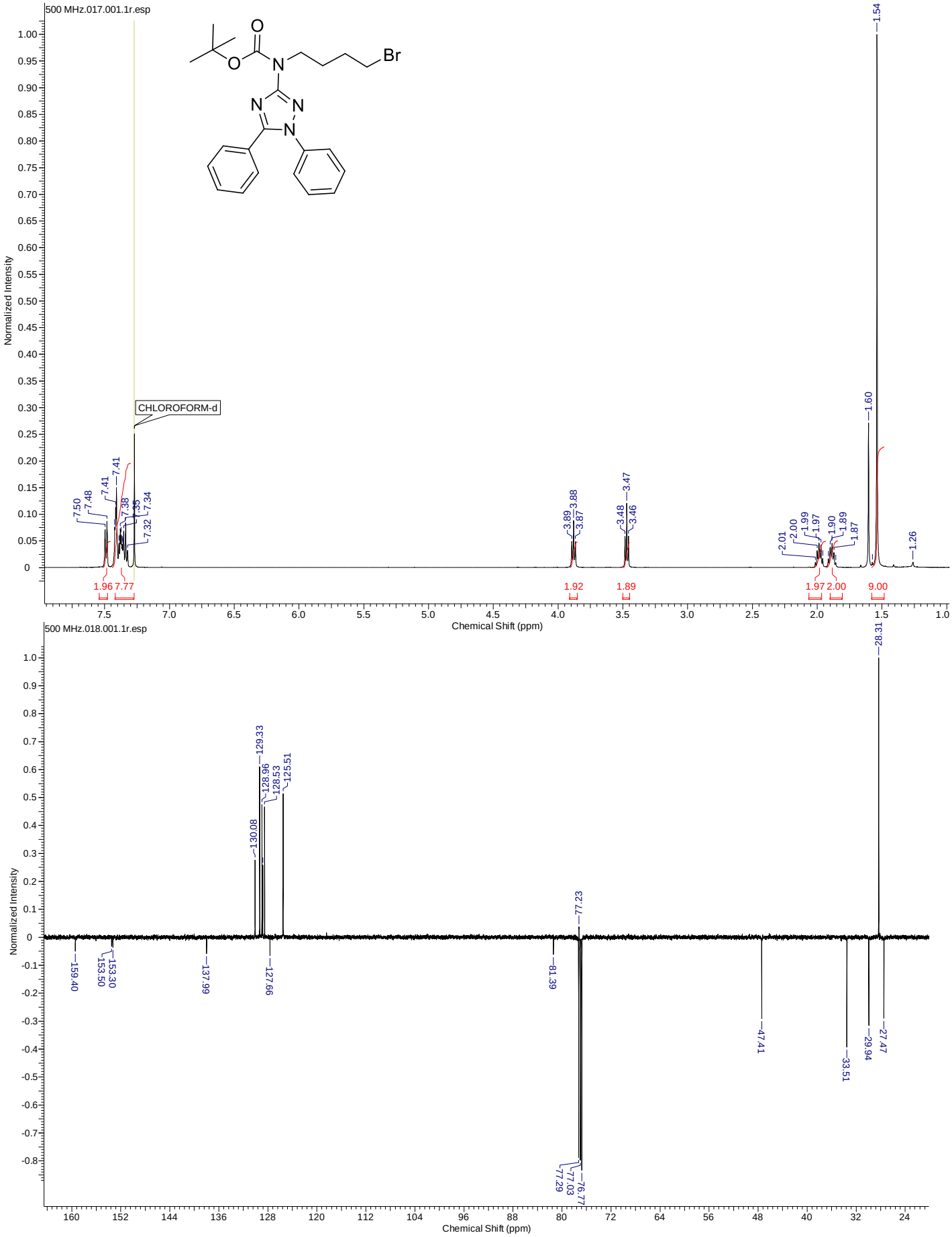

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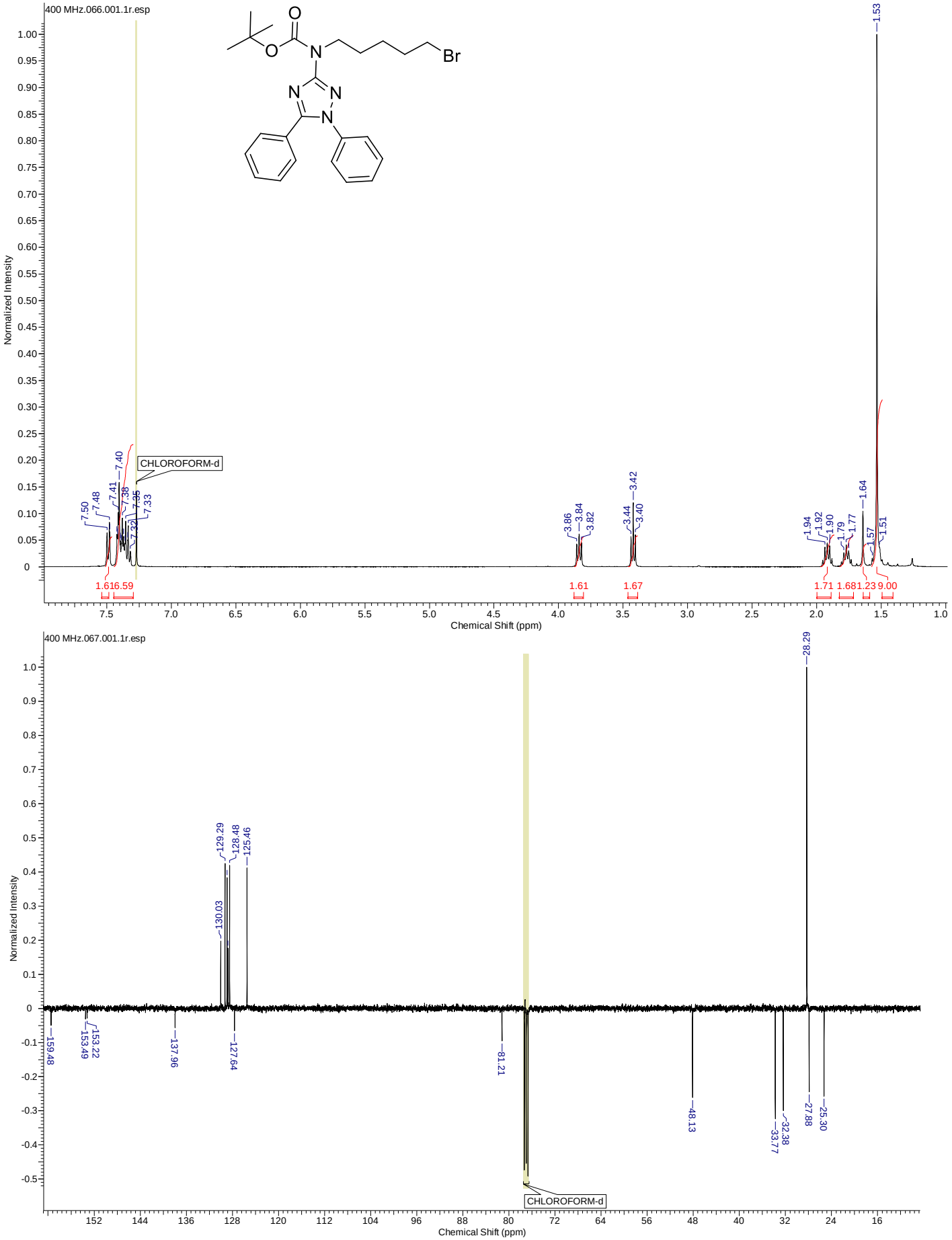

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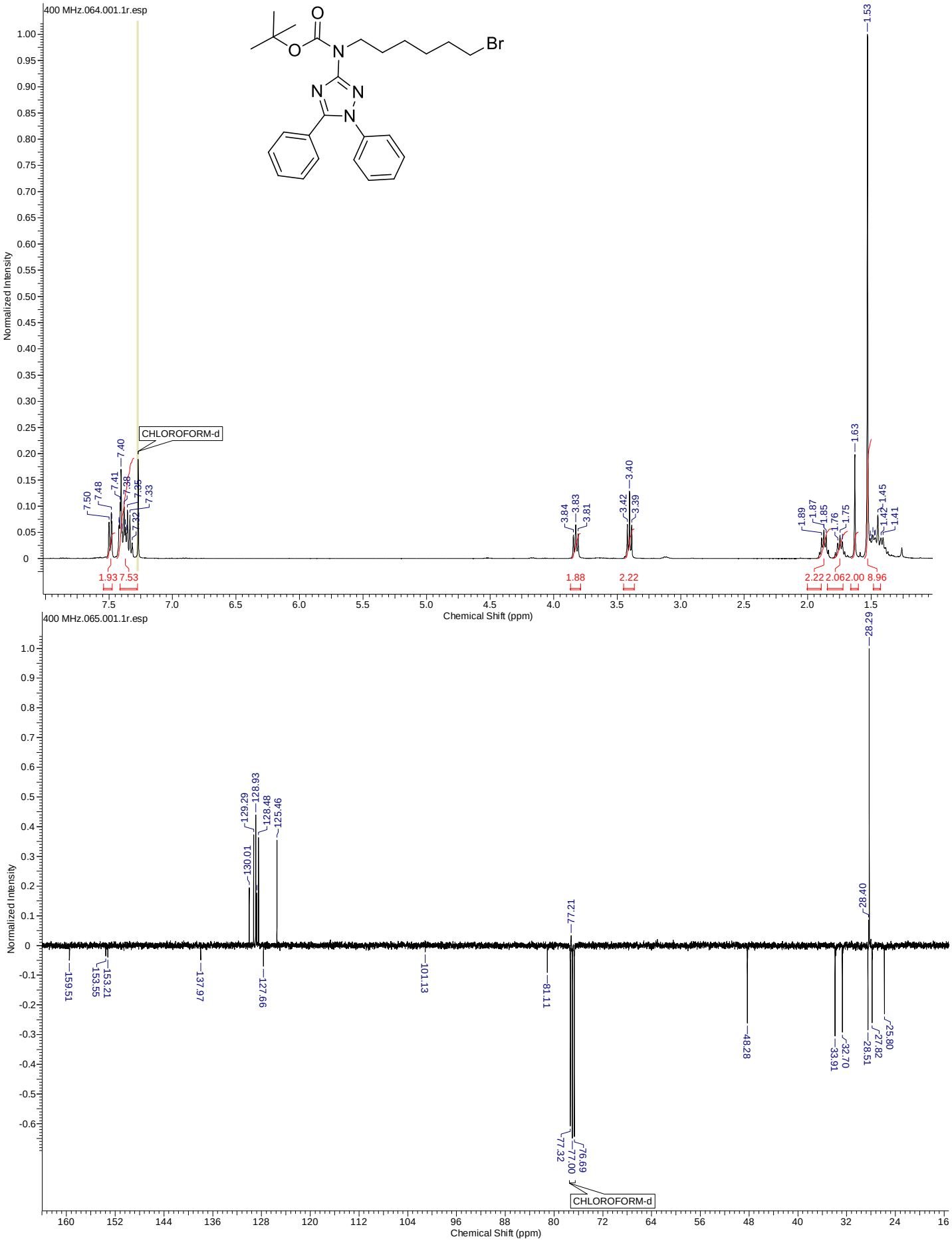

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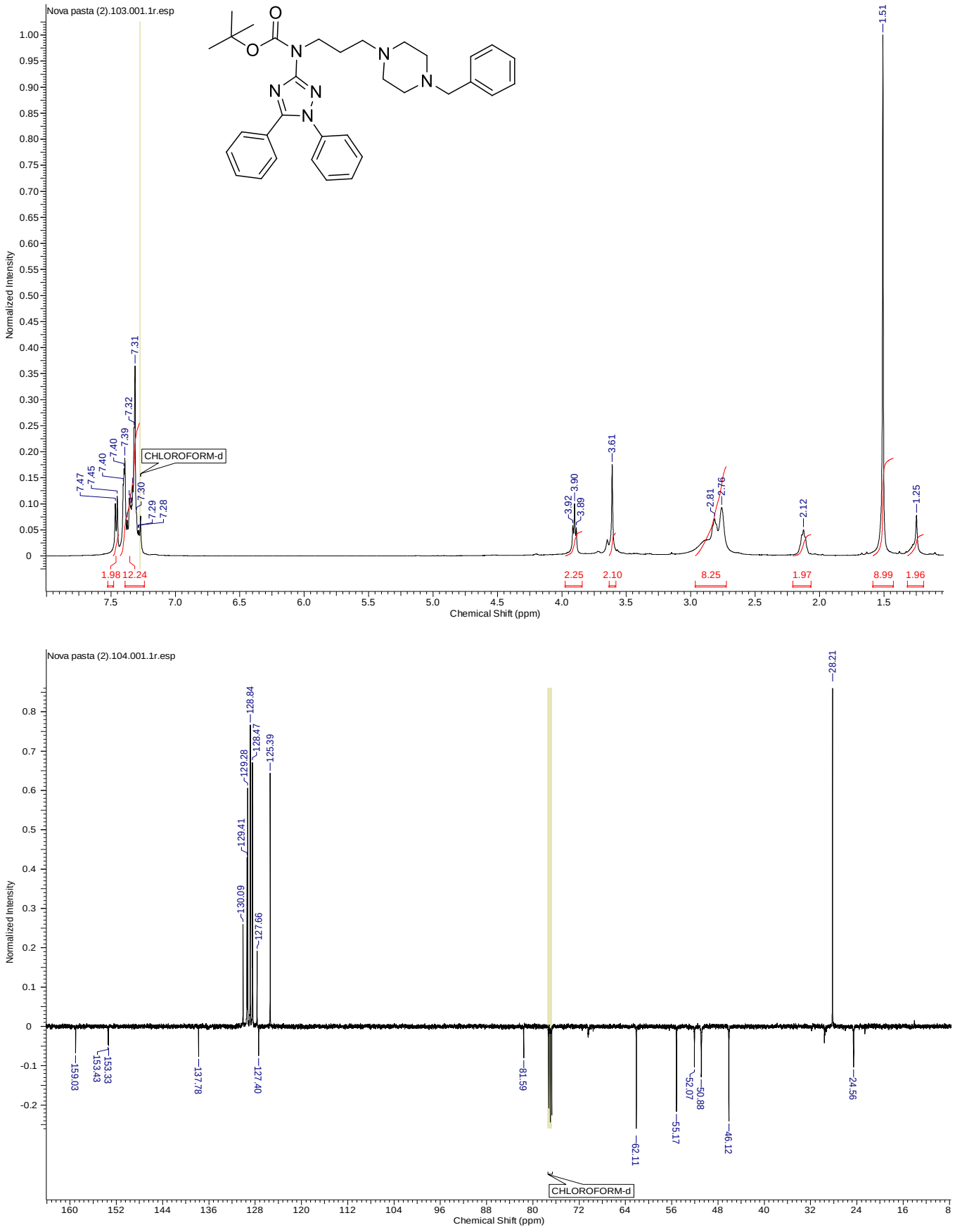

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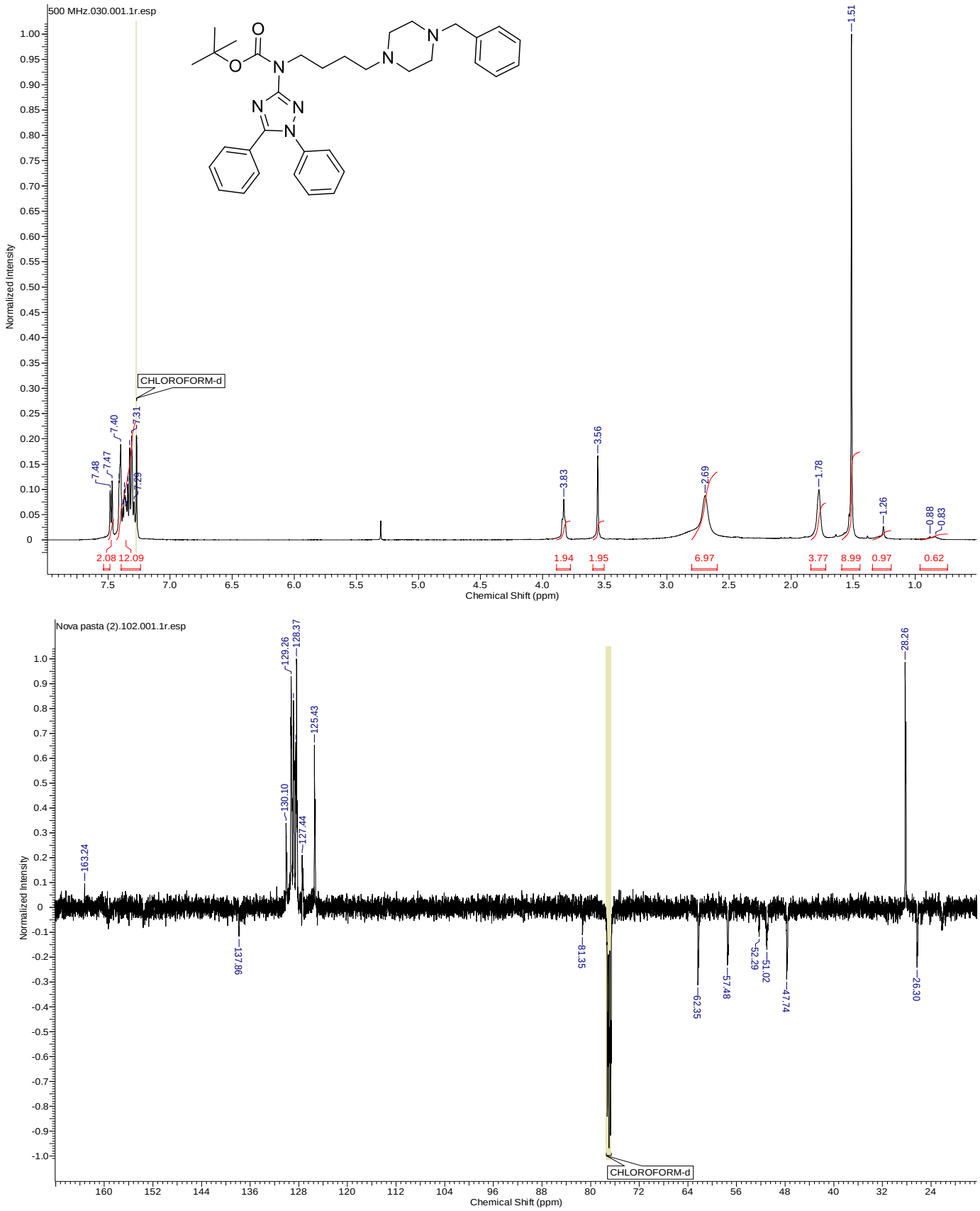

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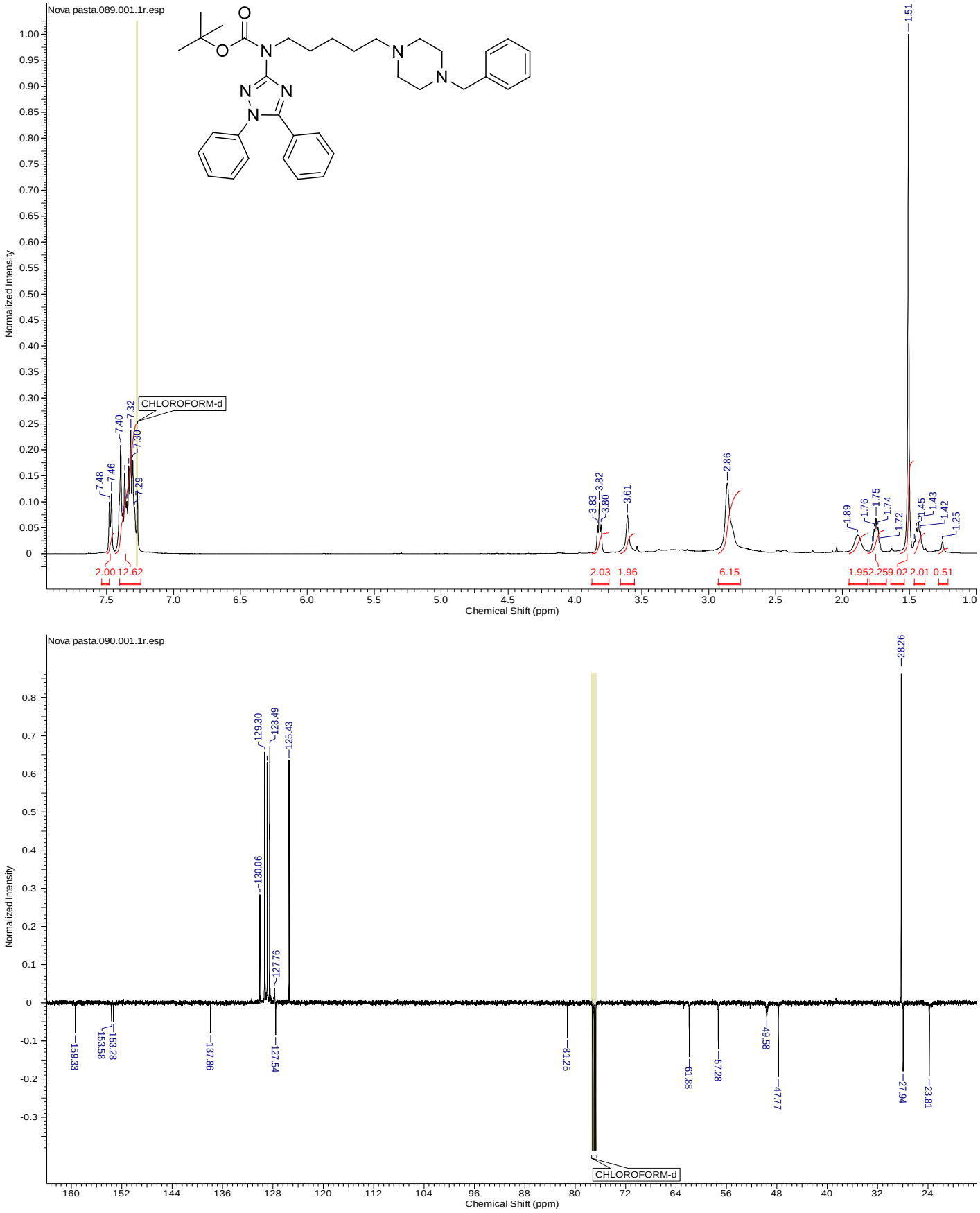

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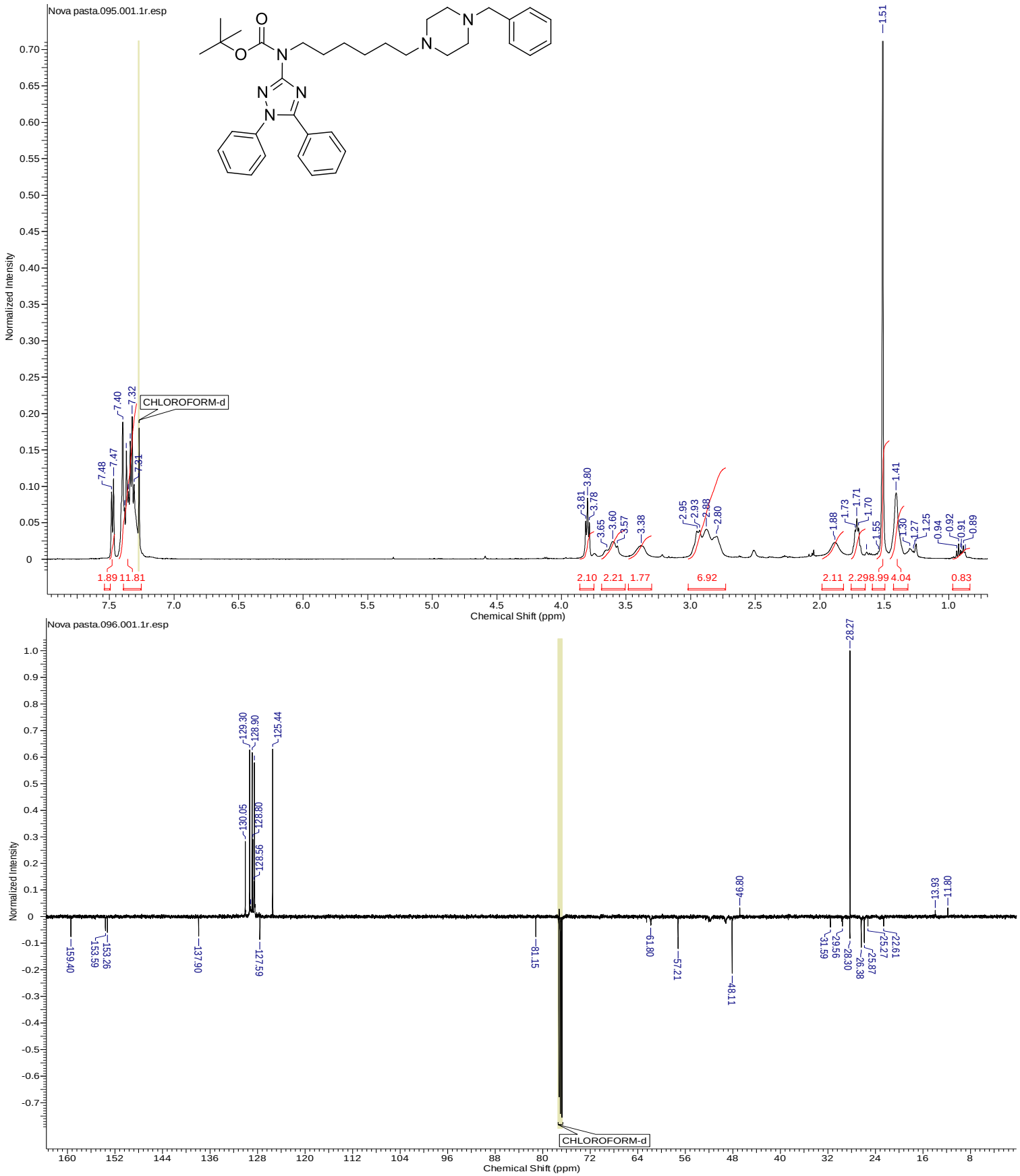

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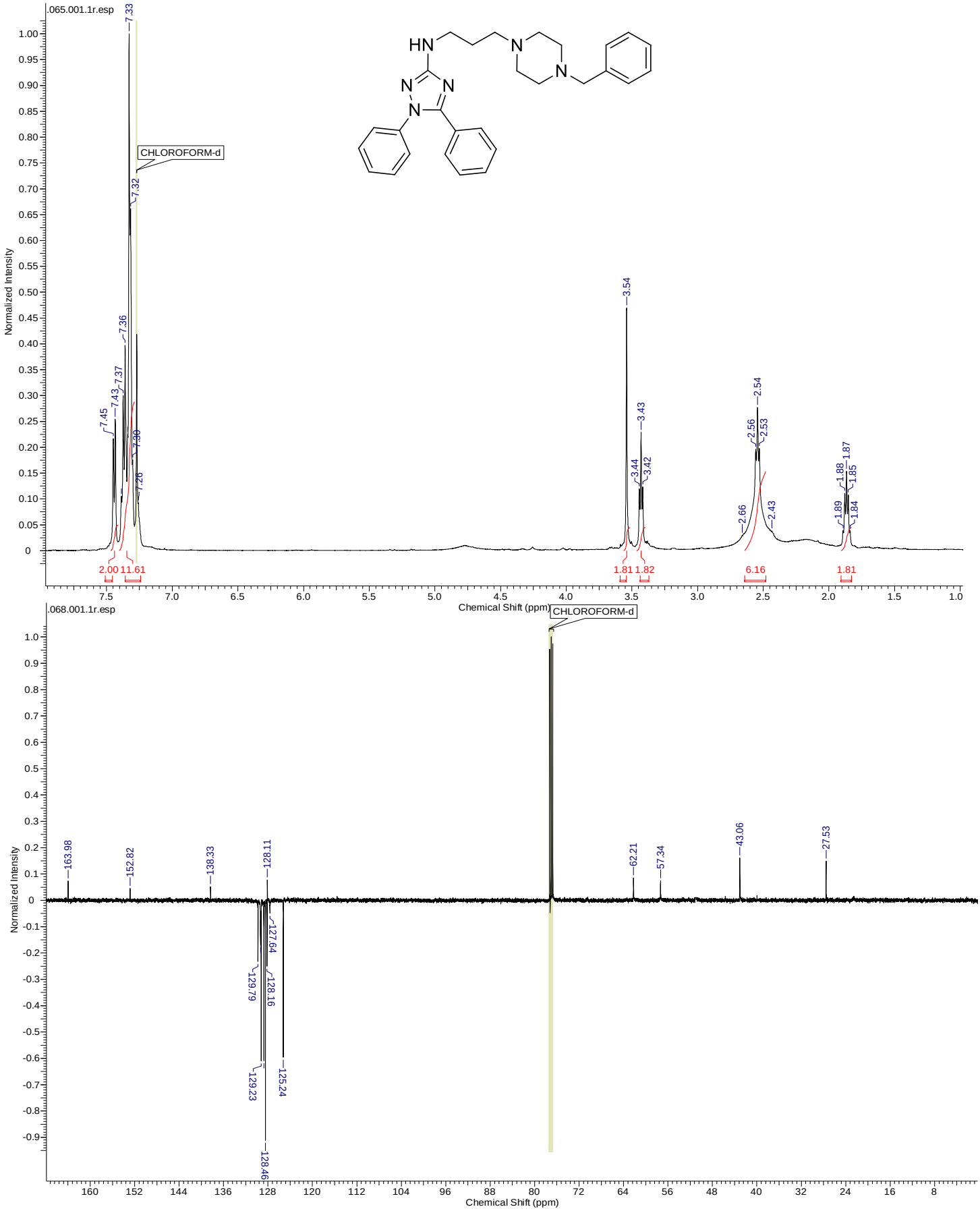

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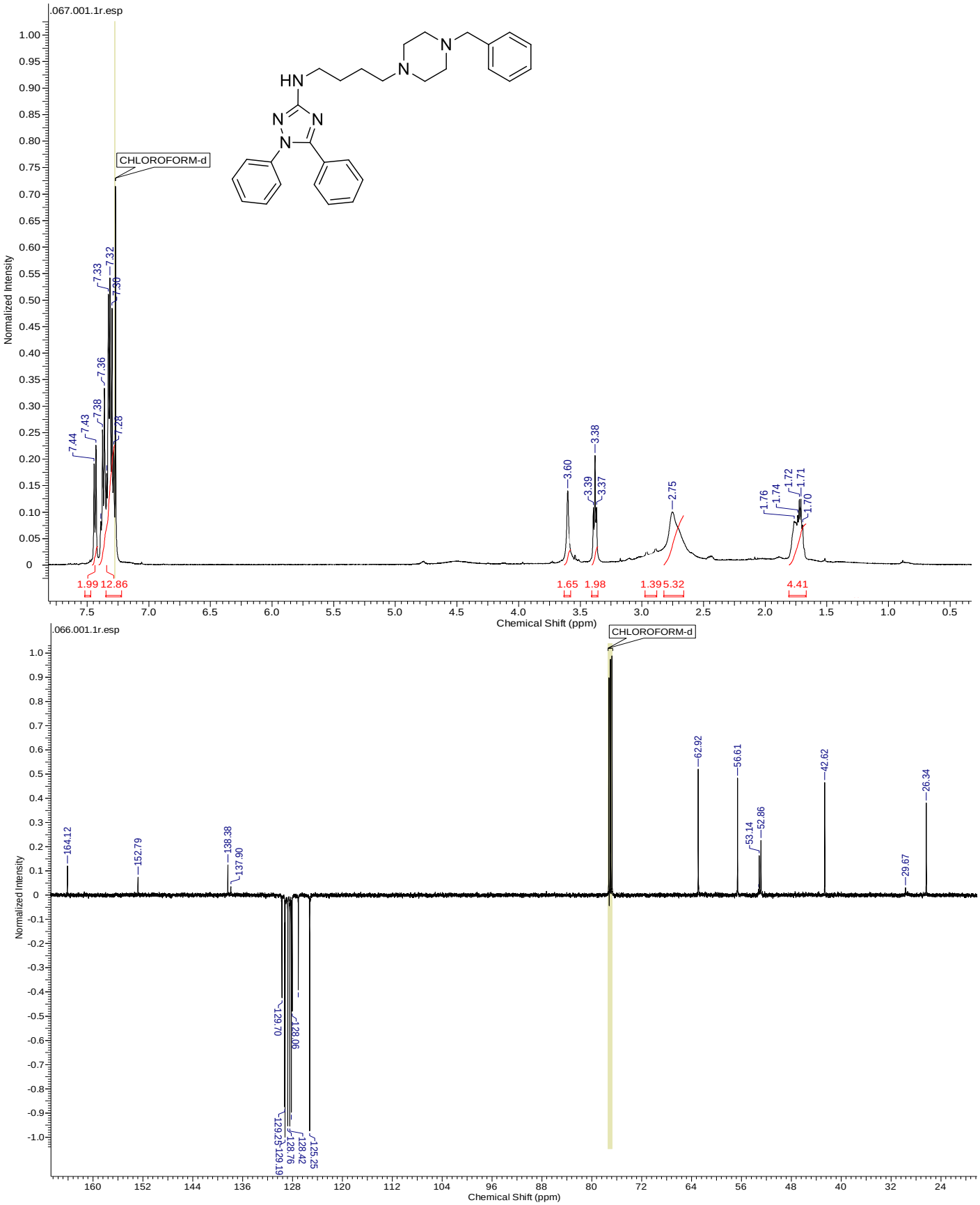

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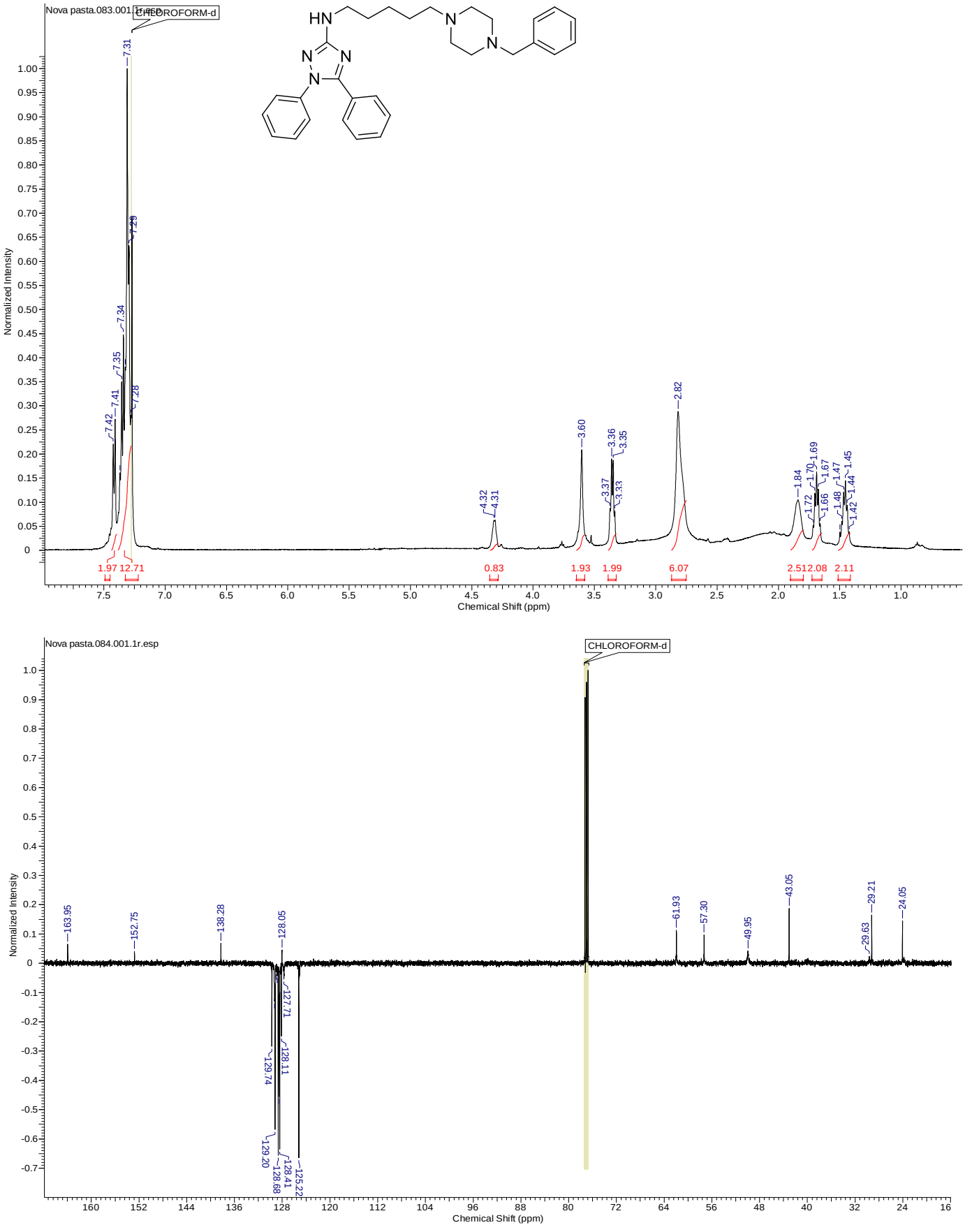


Fig. S39. ^{1}H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 13c in $CDCl_3$

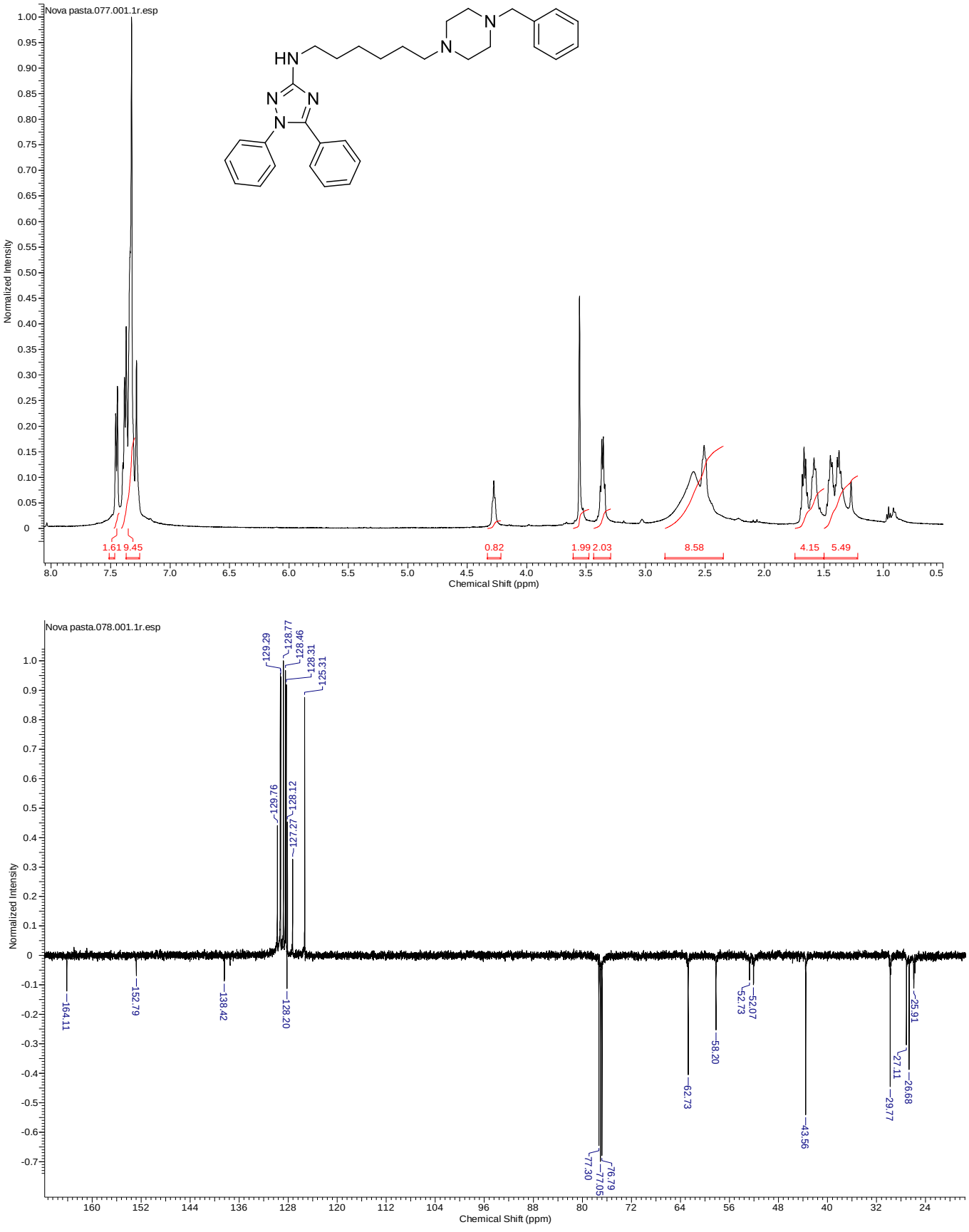
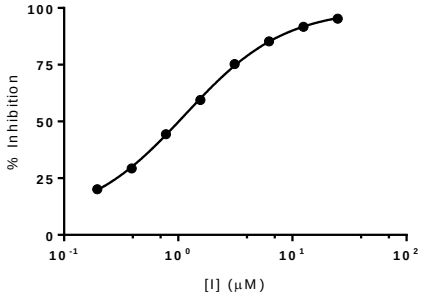


Fig. S40. ^{1}H NMR (400 MHz), DEPT-Q (100 MHz) spectra of 13d in $CDCl_3$

Biological Results



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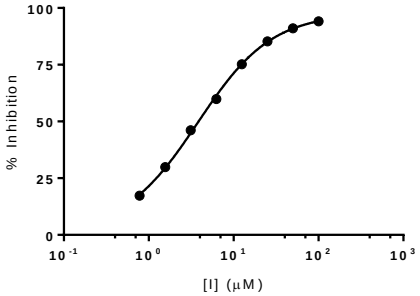

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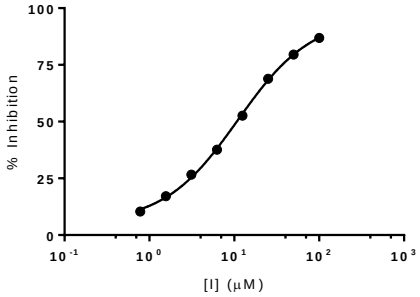

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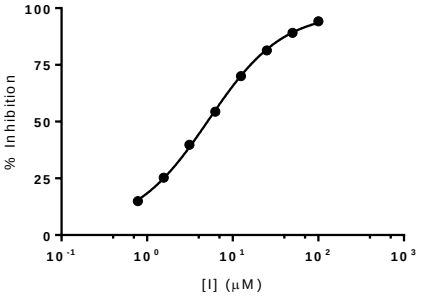
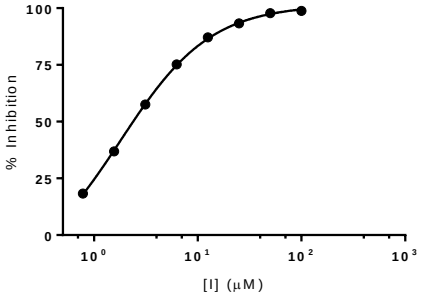


13d

Fig S41. Graphs of AChE inhibition percentage vs. inhibitor concentration



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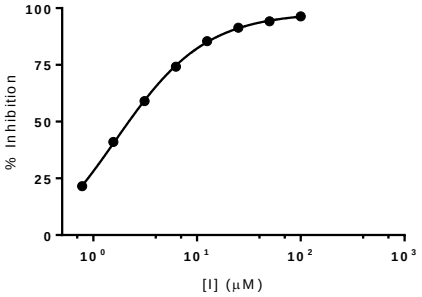

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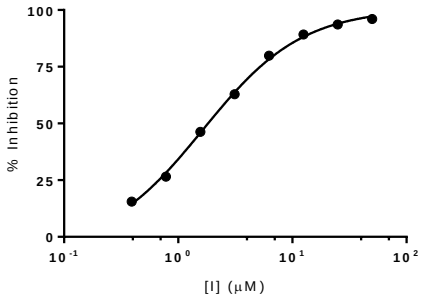
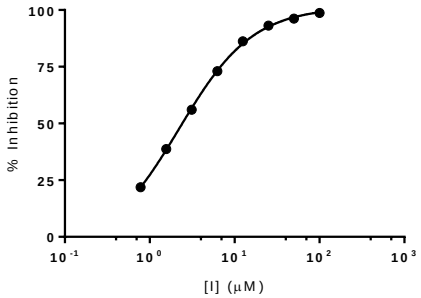


13c



13d

Fig S42. Graphs of BuChE inhibition percentage vs. inhibitor concentration

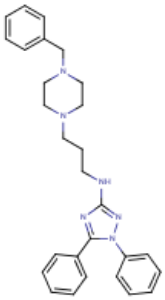
Table 1. Kinetic evaluations data for compound 13a

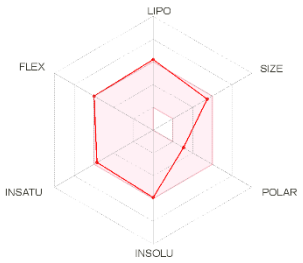
Concentração (μM)	$V_{máx}$ ± DP (μM/min)	K_m ± DP (μM)	K_i (μM) ± DP[a]	$K_{i'}$ (μM) ± DP[b]
		13a (AChE)		
0	13,24 ± 0,628	51,60 ± 2,843		
3	5,12 ± 0,234	106,17 ± 3,828	0,36 ± 0,008	1,29 ± 0,031
6	3,20 ± 0,273	121,05 ± 4,313		
		13a (BuChE)		
0	11,51 ± 0,169	70,12 ± 0,042		
1	9,92 ± 0,411	116,25 ± 3,606	0,62 ± 0,013	2,00 ± 0,033
3	6,27 ± 0,438	180,60 ± 2,404		

[a] inhibitory constant for competitive inhibition; [b] inhibitory constant for non-competitive inhibition; Data obtained ± standard deviation (SD) of triplicates from independent assays.

ADMET previsions[23-27]

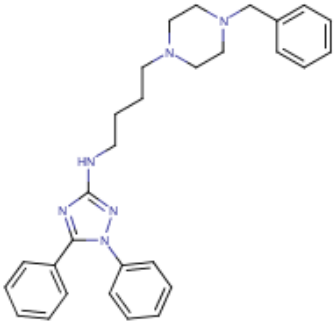
Molecule 13a

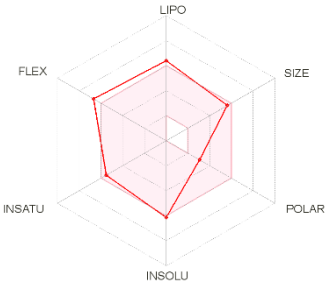




Physicochemical Properties	
Molecular weight	452.59 g/mol
Fraction Csp3	0.29
Num. rotatable bonds	9
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	145.74
TPSA	49.22 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.65
Log $P_{o/w}$ (XLOGP3)	5.34
Log $P_{o/w}$ (WLOGP)	3.45
Log $P_{o/w}$ (MLOGP)	4.19
Log $P_{o/w}$ (SILICOS-IT)	3.71
Consensus Log $P_{o/w}$	4.27
Water Solubility	
Log *S* (ESOL)	-5.92
Solubility	5.48e-04 mg/ml ; 1.21e-06 mol/l
Class	Moderately soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Veber	Yes
Egan	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.72

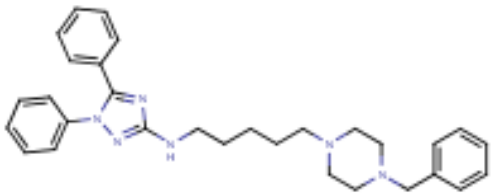
Molecule 13b

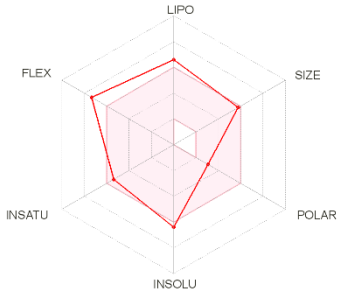




Physicochemical Properties	
Molecular weight	466.62 g/mol
Fraction Csp3	0.31
Num. rotatable bonds	10
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	150.55
TPSA	49.22 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	4.93
Log $P_{o/w}$ (XLOGP3)	5.70
Log $P_{o/w}$ (WLOGP)	3.84
Log $P_{o/w}$ (MLOGP)	4.39
Log $P_{o/w}$ (SILICOS-IT)	4.10
Consensus Log $P_{o/w}$	4.59
Water Solubility	
Log *S* (ESOL)	-6.15
Solubility	3.30e-04 mg/ml ; 7.07e-07 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Veber	Yes
Egan	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.79

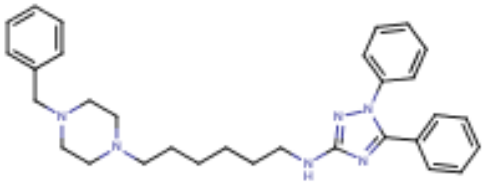
Molecule 13c

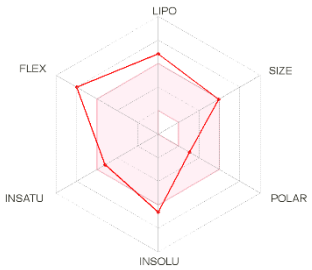




Physicochemical Properties	
Molecular weight	480.65 g/mol
Fraction Csp3	0.33
Num. rotatable bonds	11
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	155.36
TPSA	49.22 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	5.13
Log $P_{o/w}$ (XLOGP3)	6.06
Log $P_{o/w}$ (WLOGP)	4.23
Log $P_{o/w}$ (MLOGP)	4.58
Log $P_{o/w}$ (SILICOS-IT)	4.50
Consensus Log $P_{o/w}$	4.90
Water Solubility	
Log *S* (ESOL)	-6.38
Solubility	1.98e-04 mg/ml ; 4.12e-07 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Veber	No; 1 violation: Rotors>10
Egan	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.88

Molecule 13d





Physicochemical Properties	
Molecular weight	494.67 g/mol
Fraction Csp3	0.35
Num. rotatable bonds	12
Num. H-bond acceptors	4
Num. H-bond donors	1
Molar Refractivity	160.17
TPSA	49.22 Å²
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	5.21
Log $P_{o/w}$ (XLOGP3)	6.41
Log $P_{o/w}$ (WLOGP)	4.62
Log $P_{o/w}$ (MLOGP)	4.77
Log $P_{o/w}$ (SILICOS-IT)	4.90
Consensus Log $P_{o/w}$	5.18
Water Solubility	
Log *S* (ESOL)	-6.61
Solubility	1.21e-04 mg/ml ; 2.44e-07 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Druglikeness	
Lipinski	Yes; 1 violation: MLOGP>4.15
Veber	No; 1 violation: Rotors>10
Egan	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5
Synthetic accessibility	4.00