

Supporting information

A Sequential Reaction of Picolinamide with Benzaldehydes Promoted by Pd(TFA)₂: Rapid Access to 4,5-Disubstituted 2-(Pyridin-2-yl)oxazoles in *n*-Octane

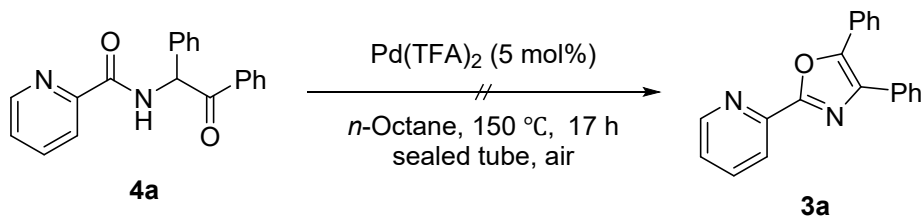
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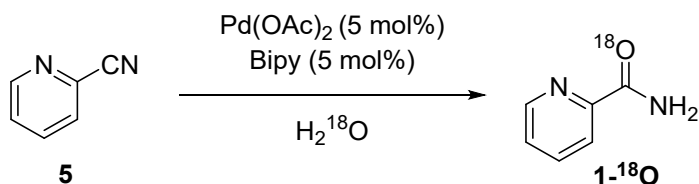
Experimental Section

Synthesis of oxazole 3a from 4a



A mixture of compound **4a** (316 mg, 1 mmol) and Pd(TFA)₂ (17 mg, 0.05 mmol) in octane (4 mL) was heated at 150 °C for 17 h in a sealed tube under air. After cooling, 1,3,5-trimethoxybenzene (168 mg, 1 mmol, internal standard) was added. The sample was dissolved in CDCl₃, which was analyzed by ¹H-NMR spectroscopy.

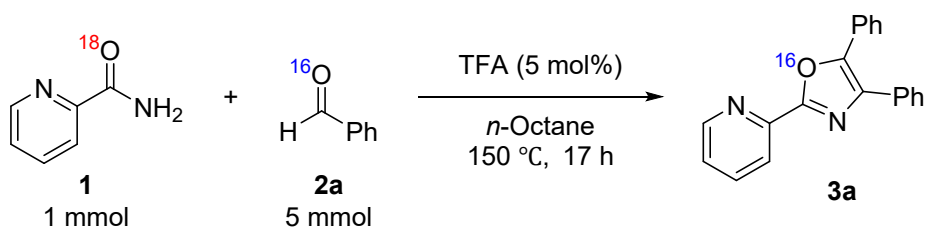
Preparation of ¹⁸O-picolinamide¹



A mixture of 2-cyanopyridine (1.043 g, 10 mmol), palladium(II) acetate (112 mg, 0.5 mmol), 2,2'-bipyridyl (79 mg, 0.5 mmol) in H₂¹⁸O (1 mL) was heated at 120 °C for 20 h in a sealed tube under air. After cooling, the reaction mixture was poured into water and extracted with CHCl₃. The organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc) to give desired product ¹⁸O-picolinamide (879 mg, 71%) as a white solid.

mp: 106-107 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.59 (ddd, *J* = 7.3, 4.8, 1.4 Hz, 1H), 7.65 (brs, 1H), 7.98 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 8.02-8.05 (m, 1H), 8.12 (brs, 1H), 8.63 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 121.9, 126.5, 137.6, 148.5, 150.3, 166.0; FT-IR (KBr, cm⁻¹): 3419, 3182, 1603; HRMS (FAB): *m/z* [M+H]⁺ calcd for [M+H]⁺ = C₆H₆N₂¹⁸O: 125.0601; found: 125.0601.

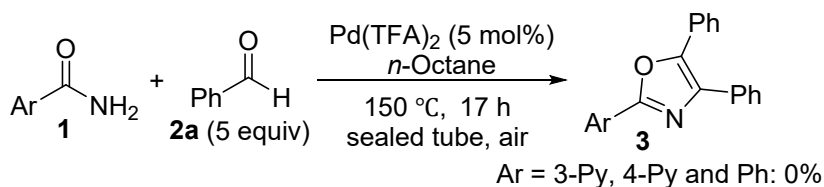
Reaction using ¹⁸O-labeled picolinamide²



Prepared according to the general procedure by using ¹⁸O-2-picolinamide (124 mg, 1 mmol), Pd(TFA)₂ (17 mg, 5 mol %) and benzaldehyde (505 μL, 5 mmol) in octane (4 mL) at 150 °C for 17 h. The desired product 3a was obtained in 50% yield (150 mg) as a light yellow solid.

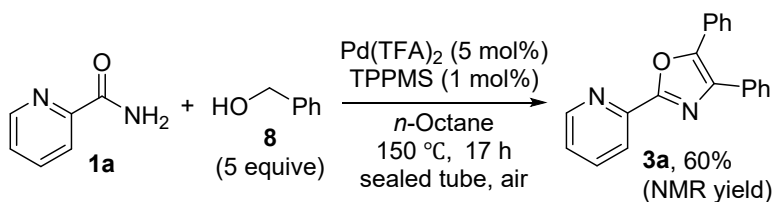
HRMS (EI): *m/z* [M]⁺ calcd for [M]⁺ = C₂₀H₁₄N₂O: 298.1106; found:298.1106.

The reaction of nicotinamide, isonicotinamide and benzamide.³



Prepared according to the general procedure by using nicotinamide (122 mg, 1 mmol) or isonicotinamide (122 mg, 1 mmol) or benzamide (121 mg, 1 mmol), Pd(TFA)₂ (17 mg, 5 mol %) and benzaldehyde (505 μL, 5 mmol) in octane (4 mL) at 150 °C for 17 h. After a cooling, 1,3,5-trimethoxybenzene (1 mmol) was added as an internal standard. The desired product was not be confirmed using ¹H NMR spectrometry.

Direct use of benzyl alcohol 8 for construction of the oxazole 3a



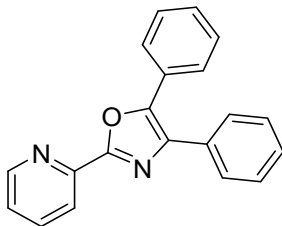
A mixture of picolinamide 1a (122 mg, 1 mmol), Pd(OAc)₂ (17 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 4 mg, 0.01 mmol), and benzyl alcohol 2a (515 μL, 5 mmol), in octane (4 mL) was heated at 150 °C for 17 h in a sealed tube under air. After the reaction mixture was cooled, 1,3,5-trimethoxybenzene (168 mg, 1 mmol, internal standard) and CHCl₃ were added to the reaction mixture. The solution was concentrated in vacuo. The residue was analyzed by ¹H-NMR spectroscopy.

References

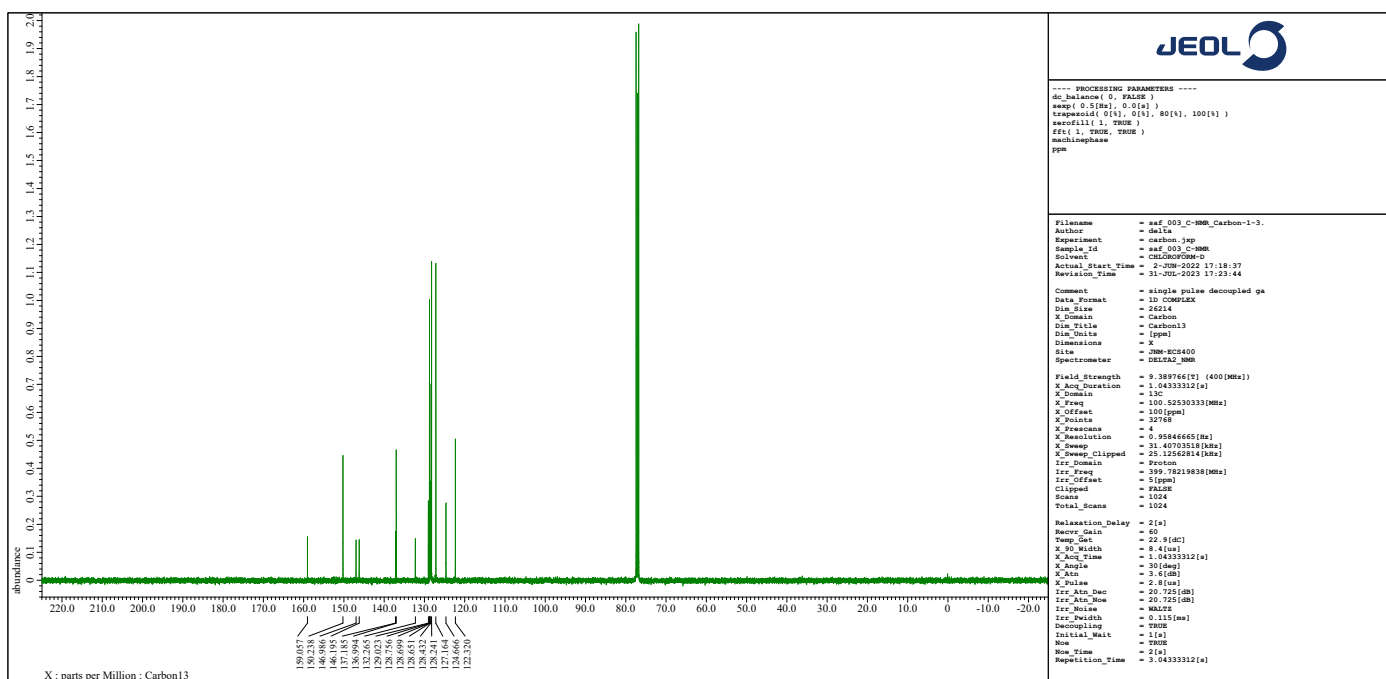
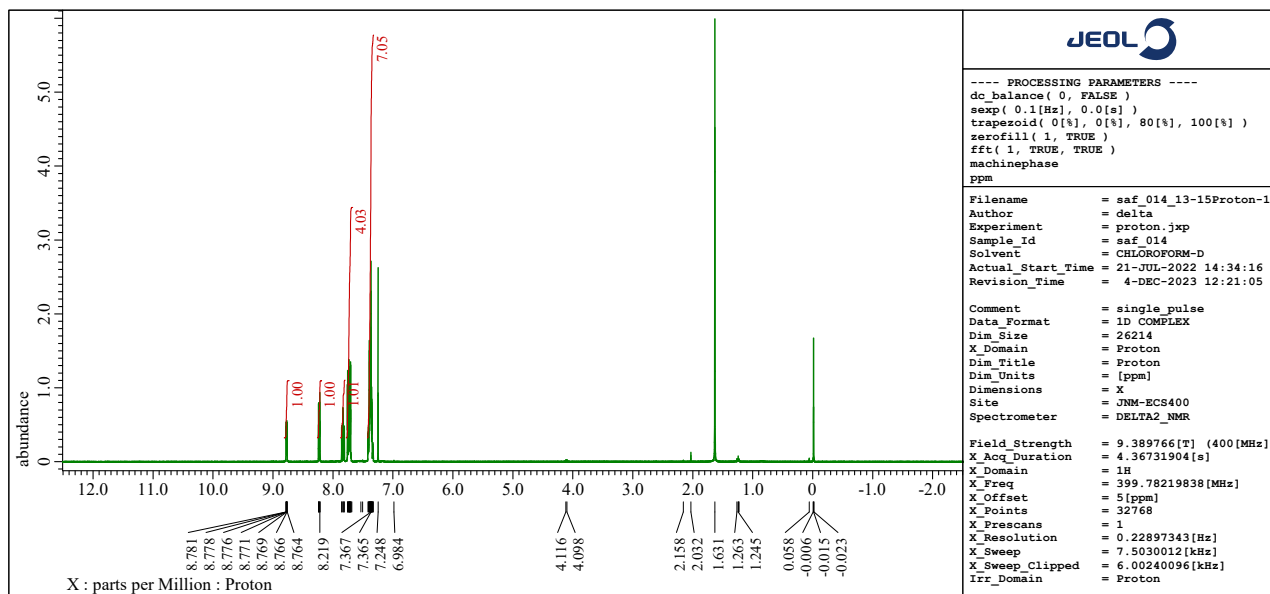
- 1) Sharley, Daniel D. Sanz; Jonathan MJ Williams. *Tetrahedron Letters*, **2017**, 58, 43, 4090-4093.
- 2) Wasserman, H. H.; Vinick, F. J. *The Journal of Organic Chemistry*, **1973**, 38, 13, 2407-2408.
- 3) Banerji, B.; Adhikary, S.; Majumder, L.; Ghosh, S. *Asian Journal of Organic Chemistry*, **2019**, 8, 4, 514-525.

¹H- and ¹³C-NMR

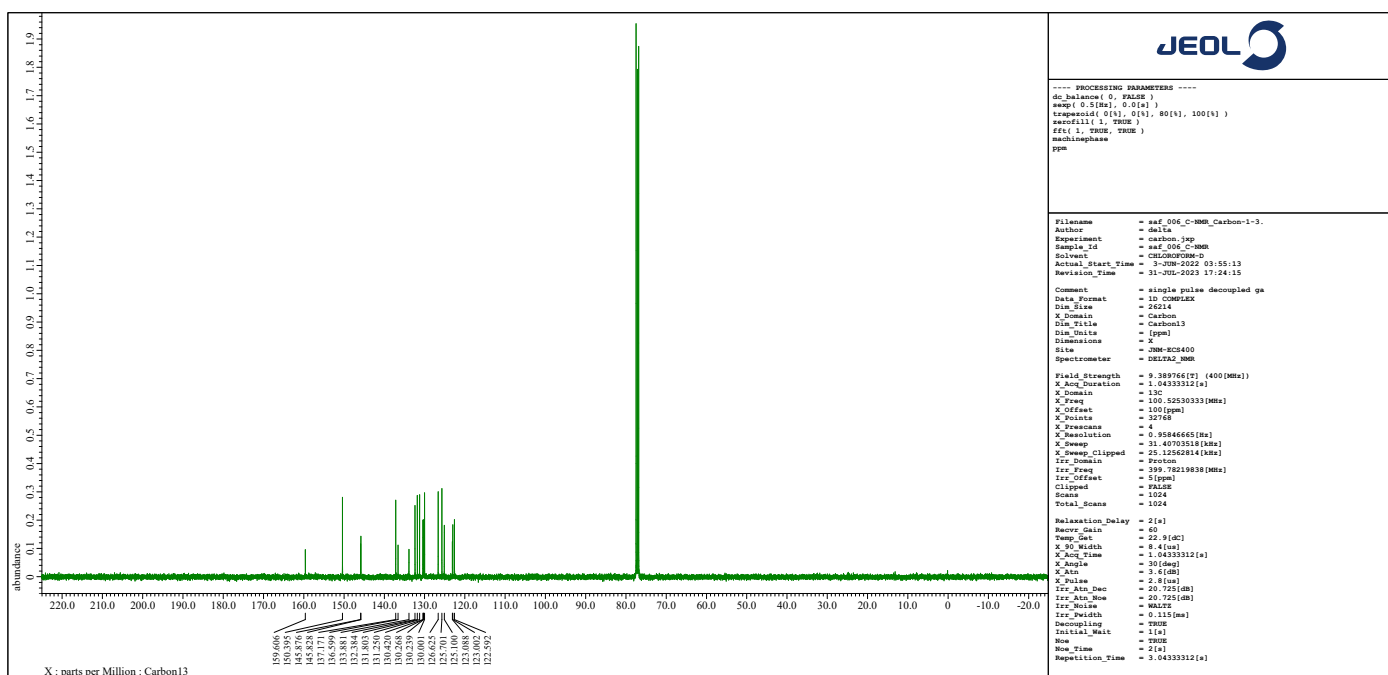
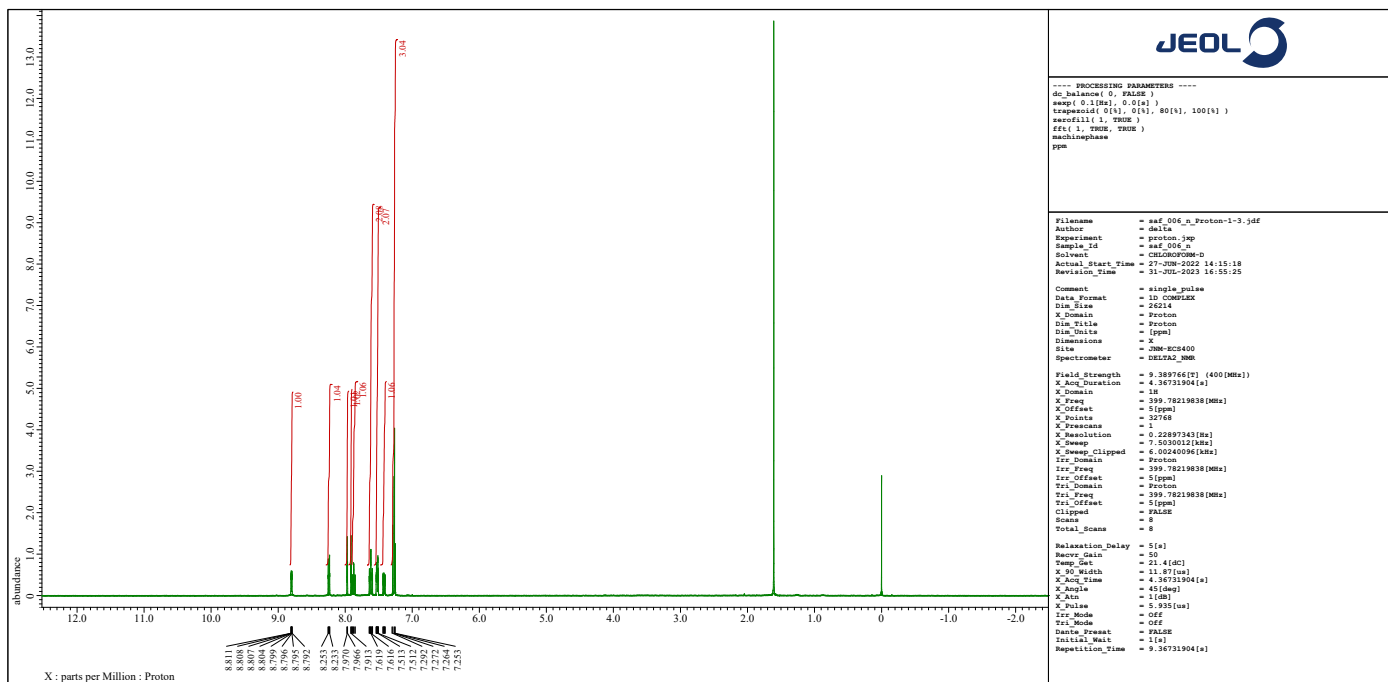
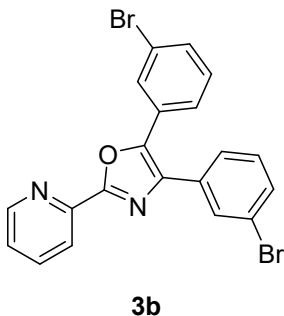
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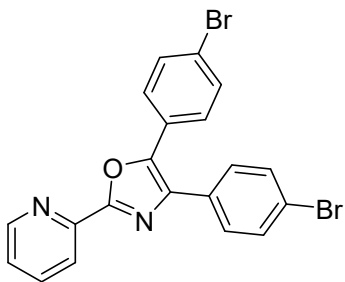
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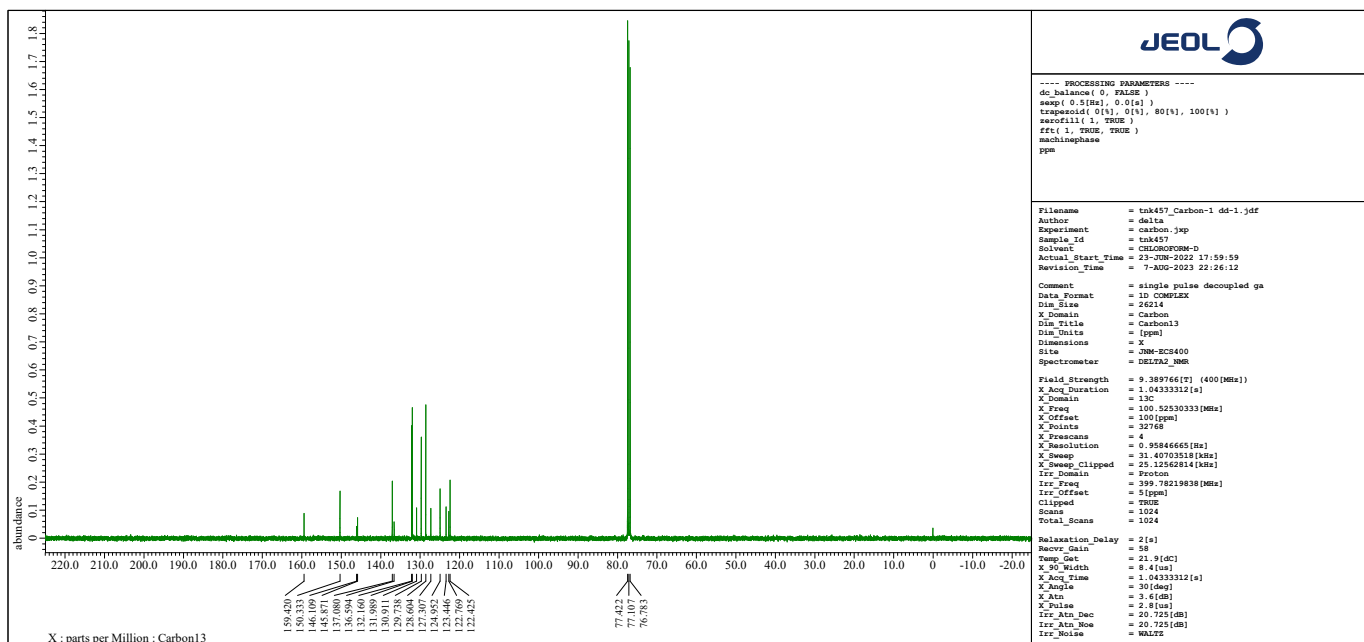
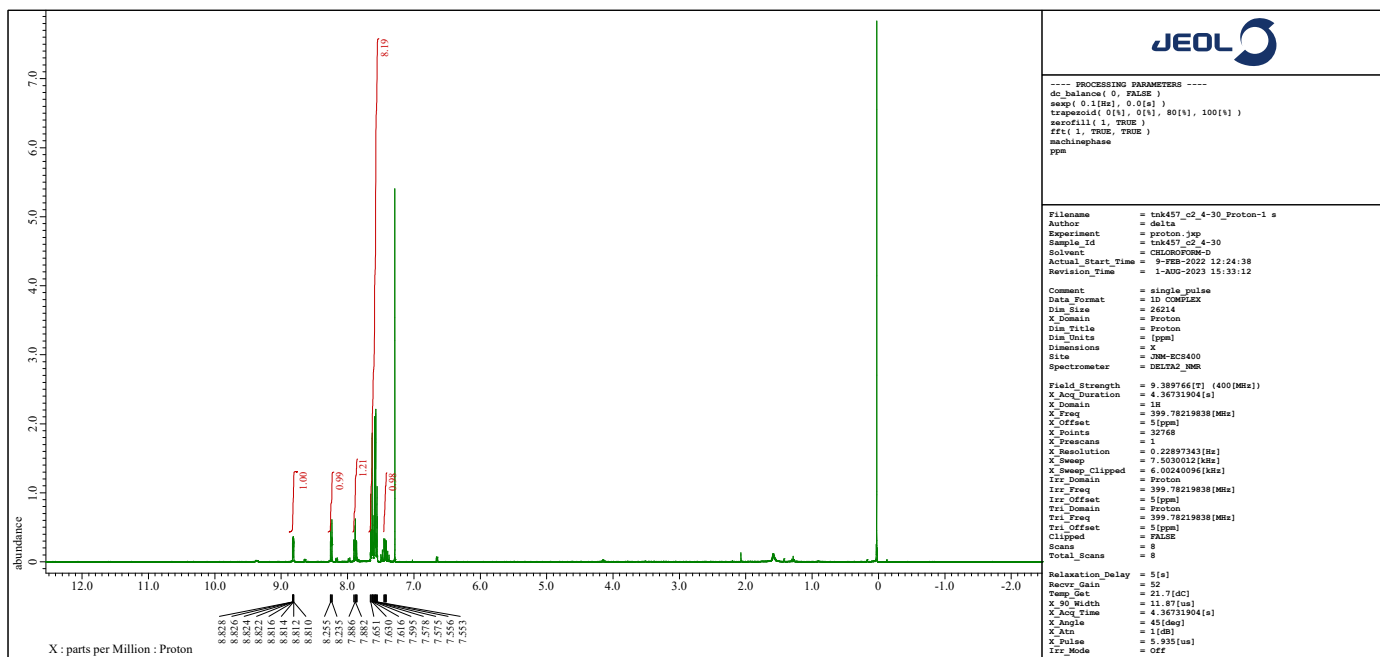
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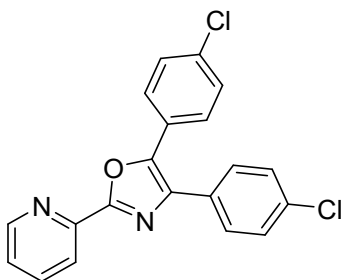
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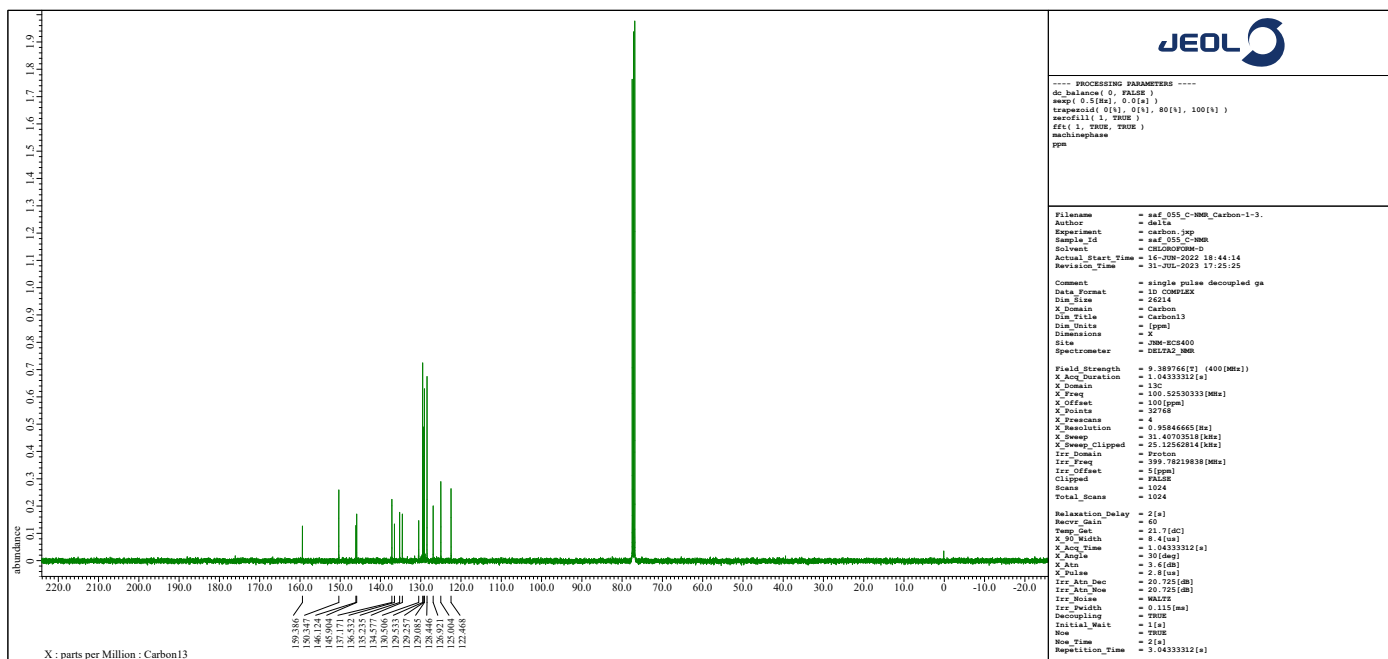
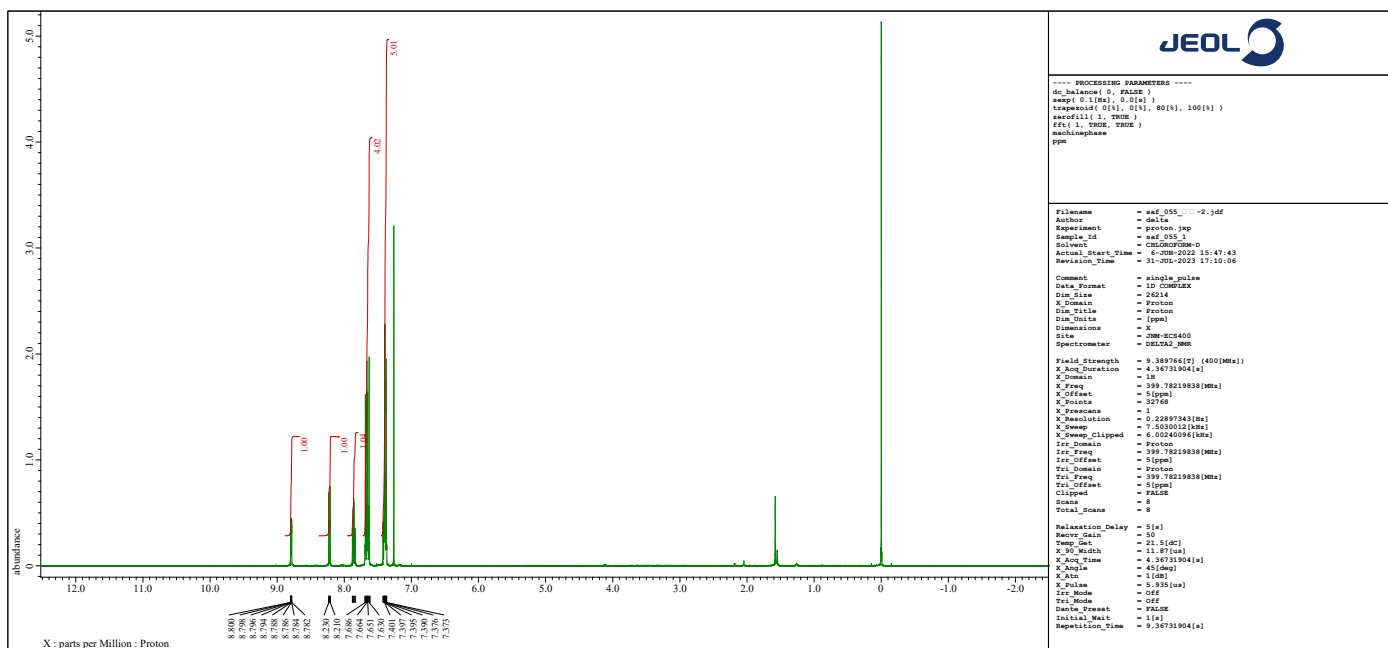
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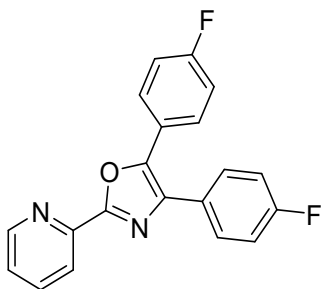
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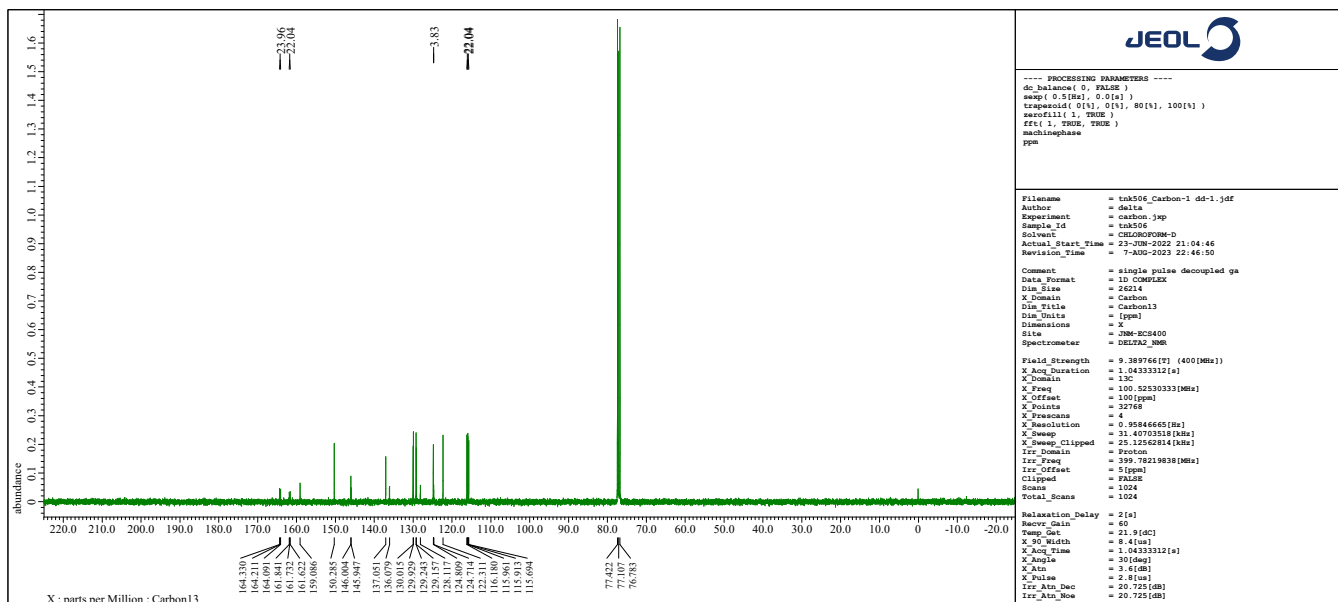
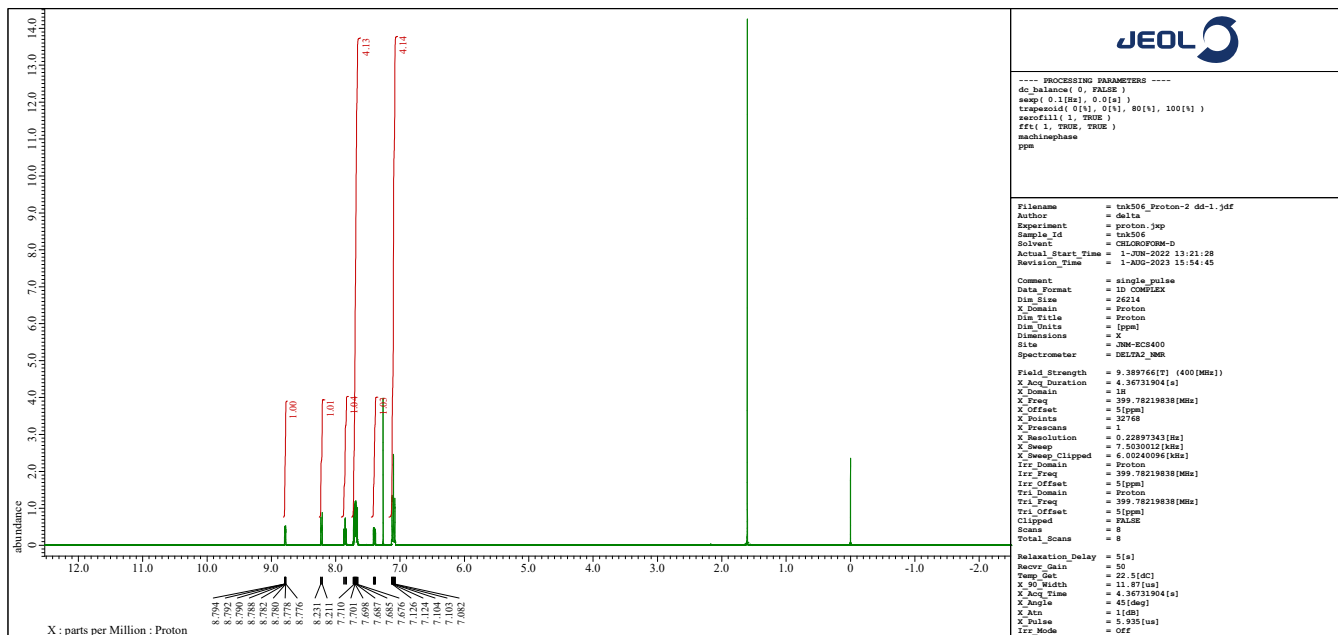
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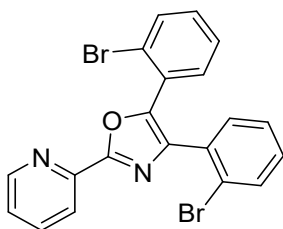
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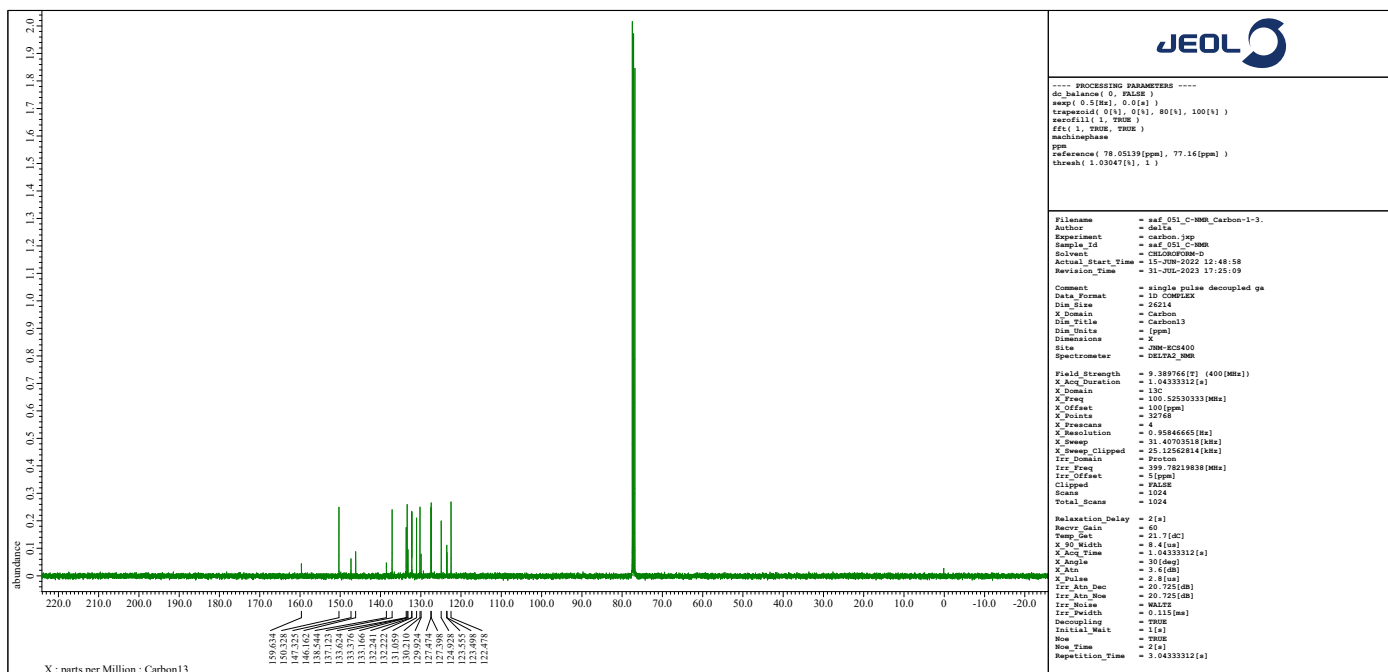
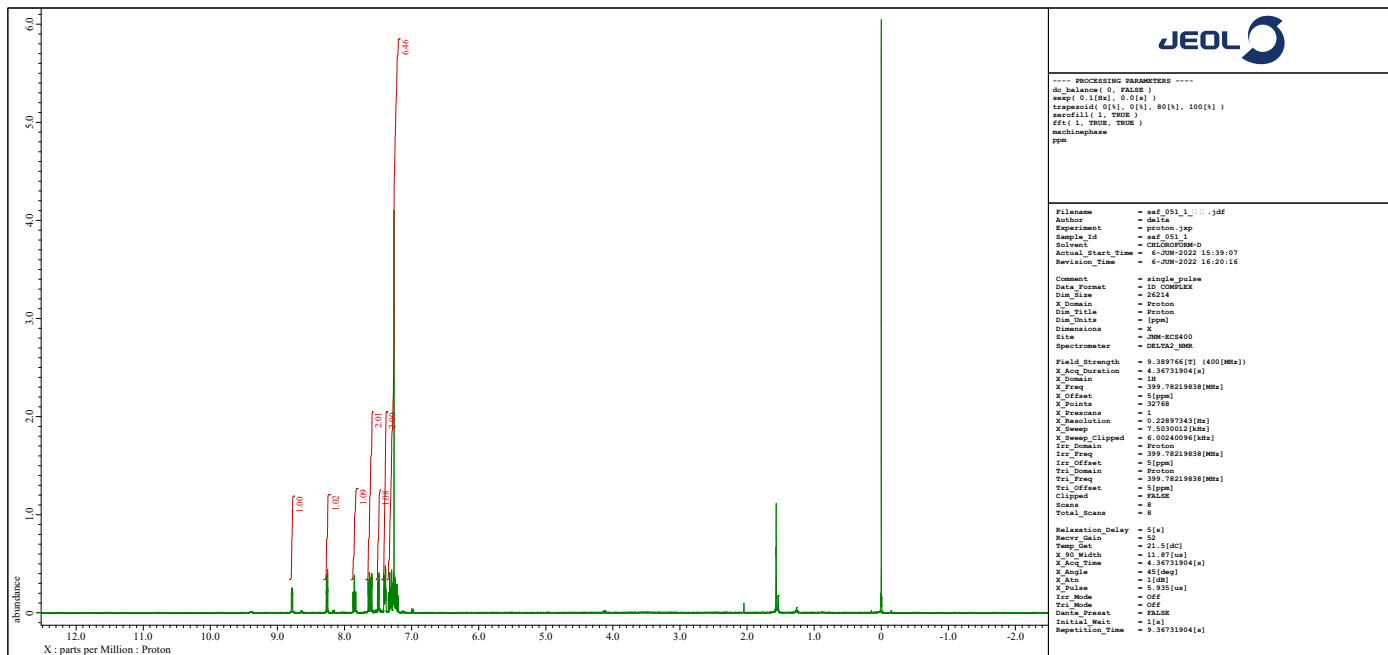
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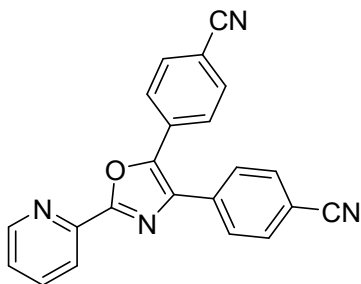
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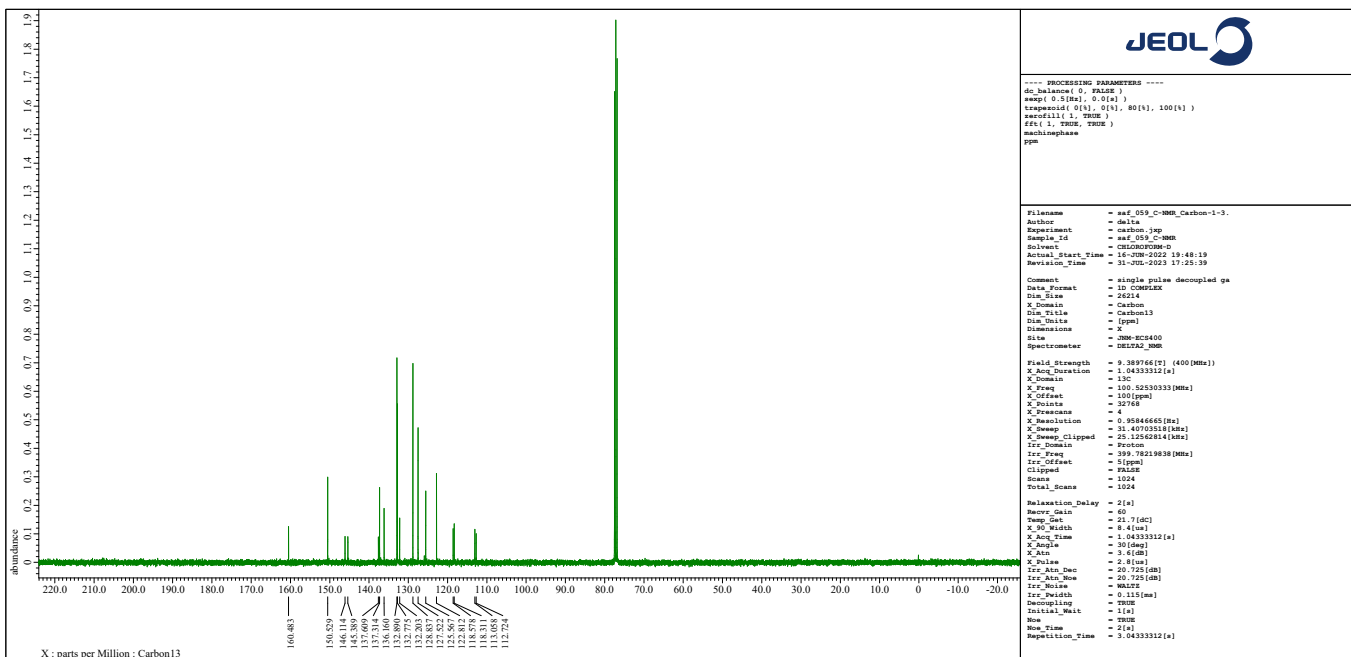
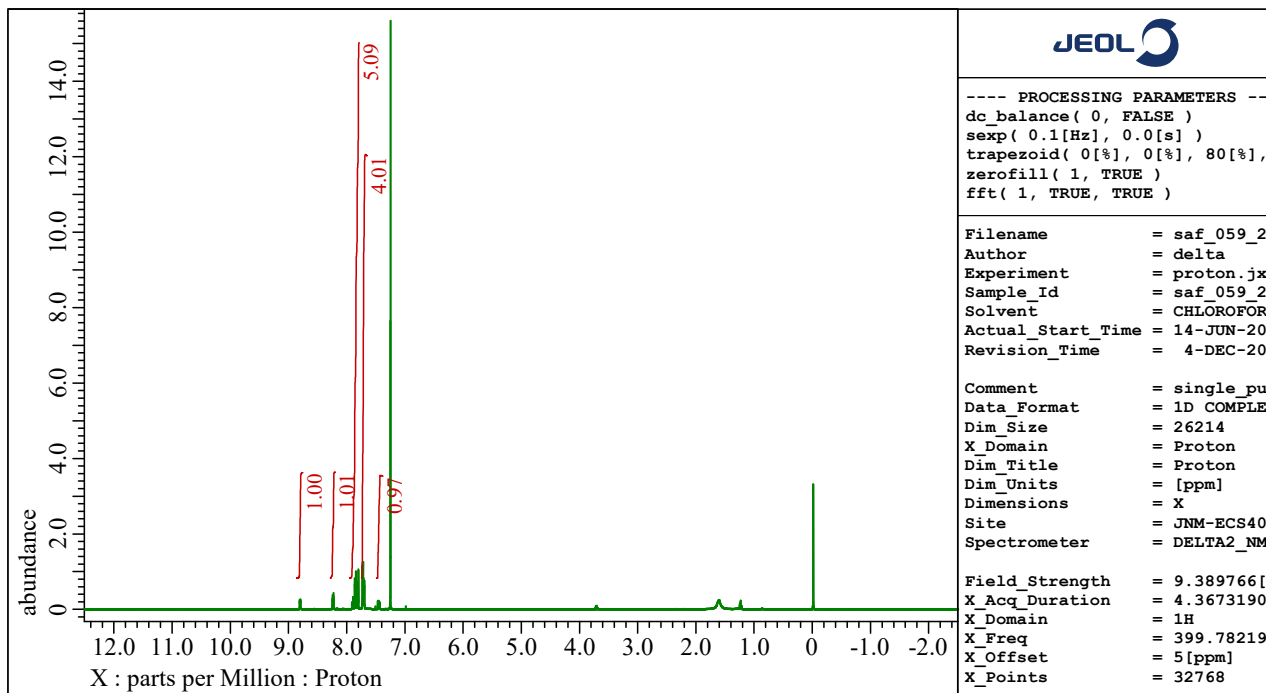
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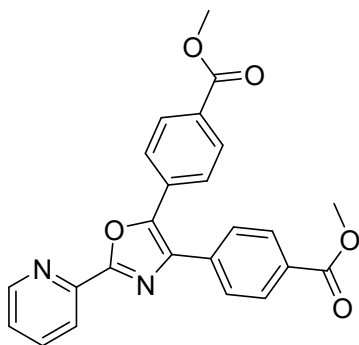
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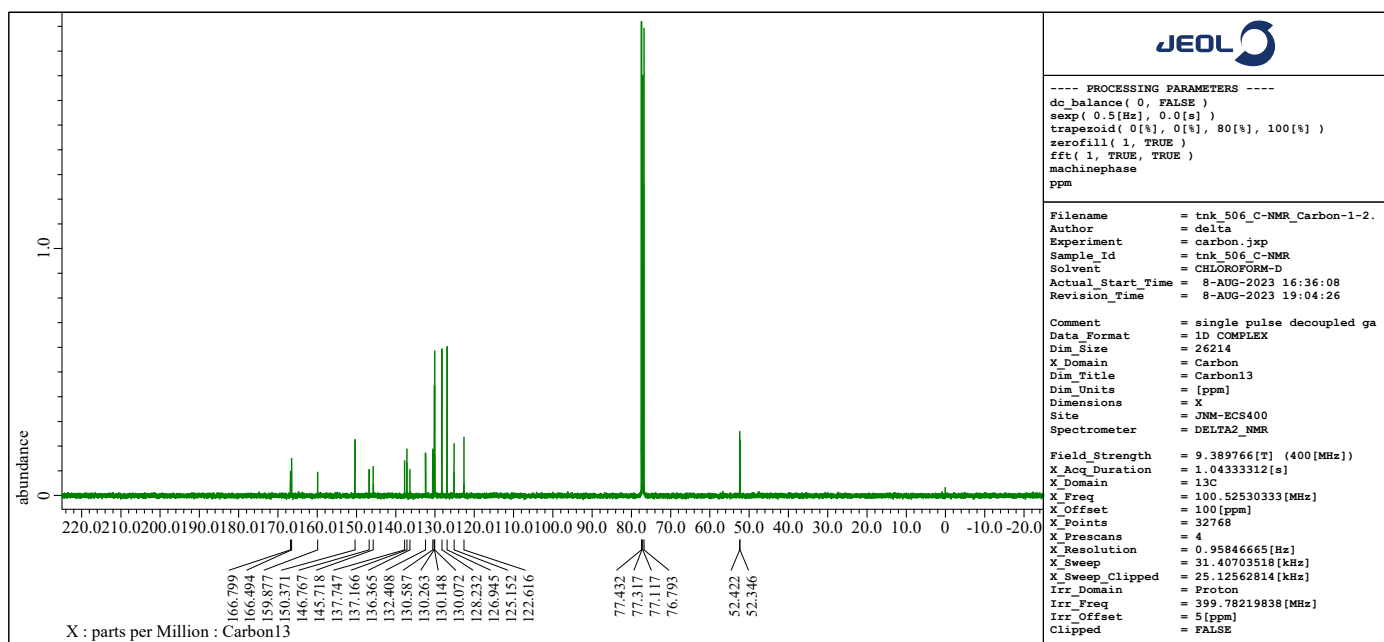
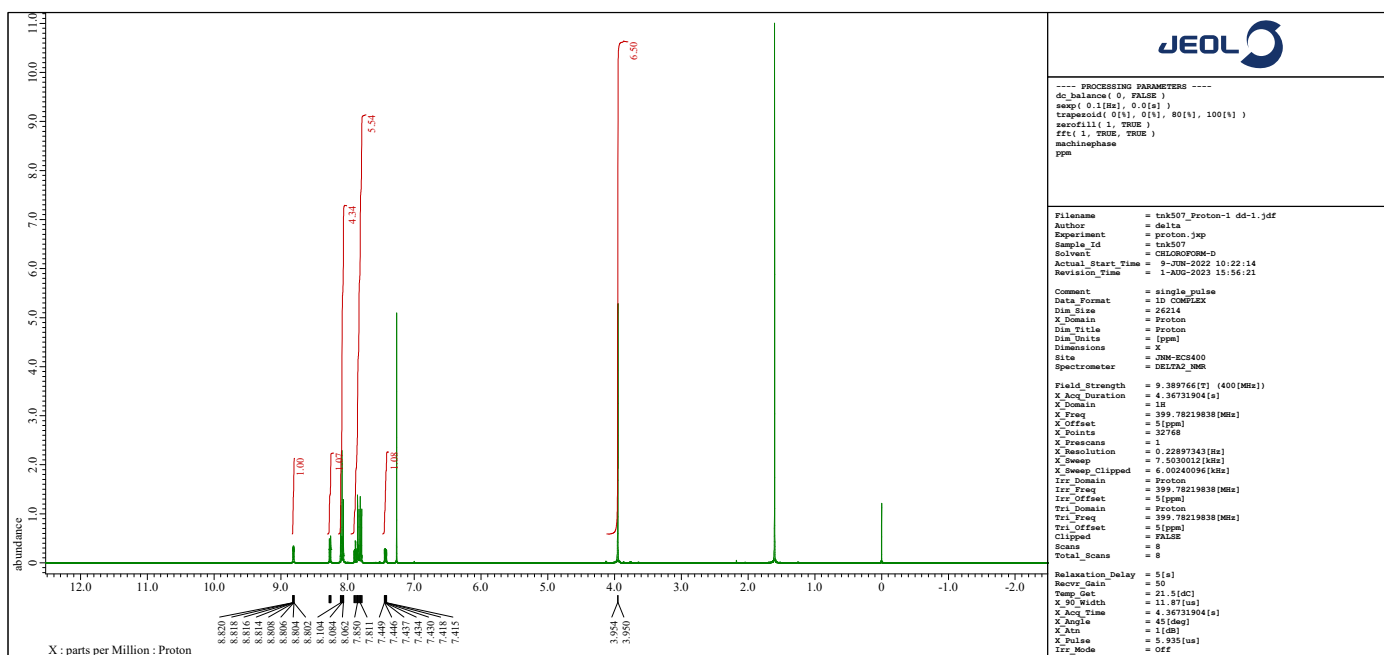
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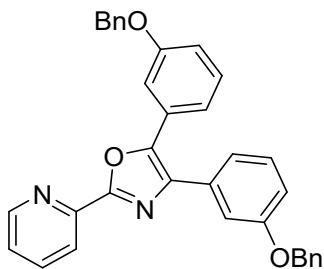
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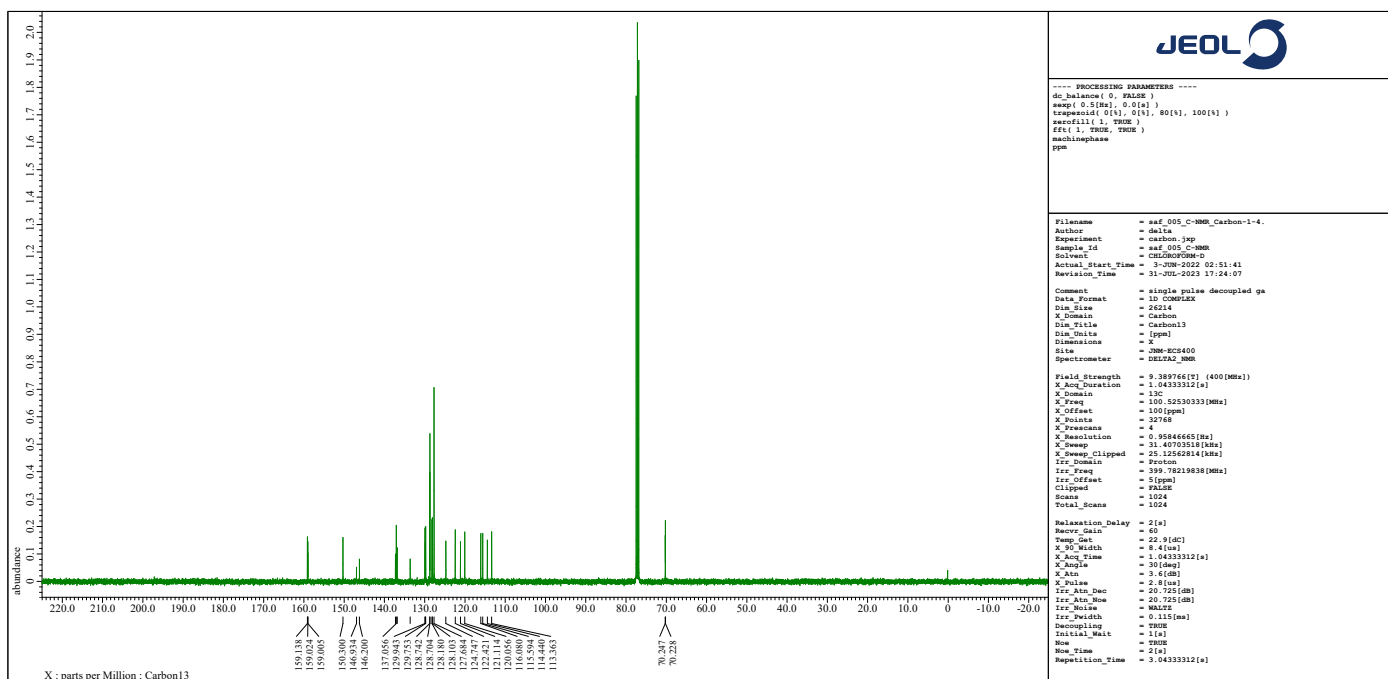
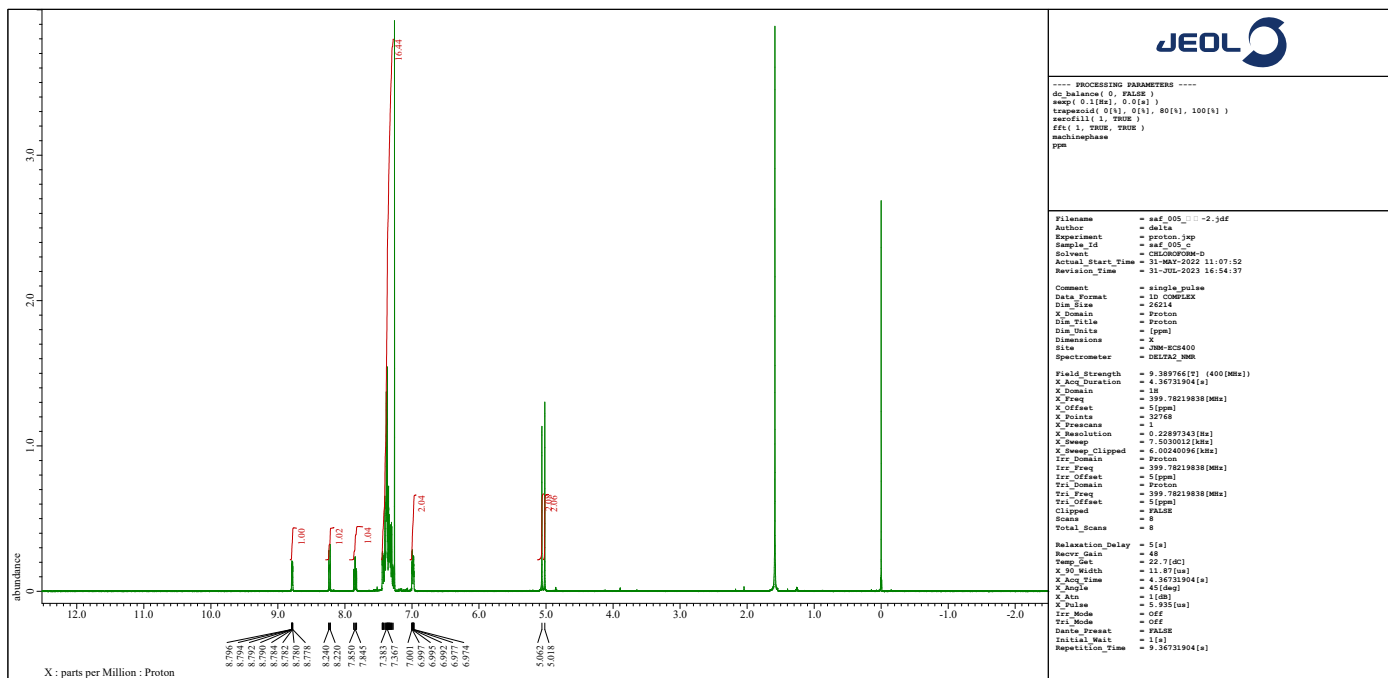
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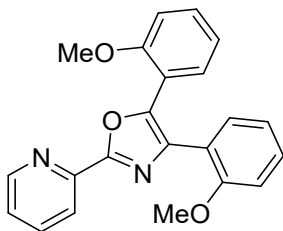
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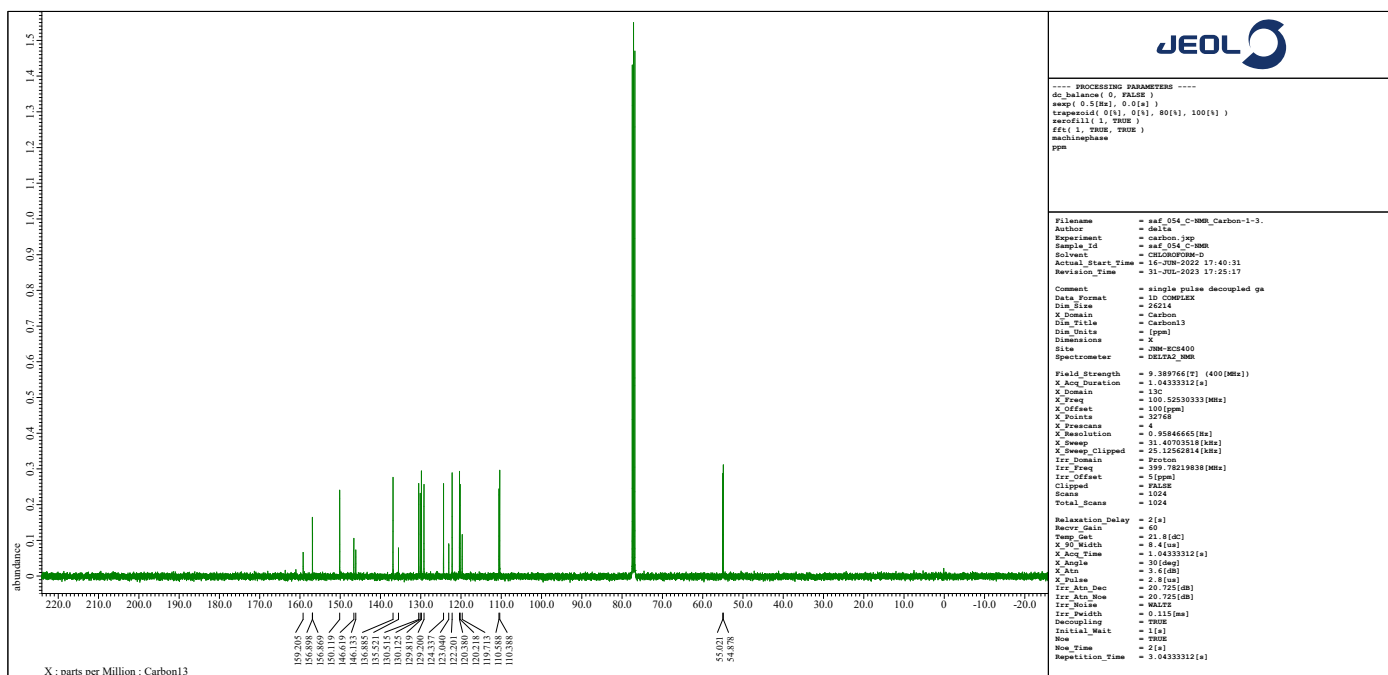
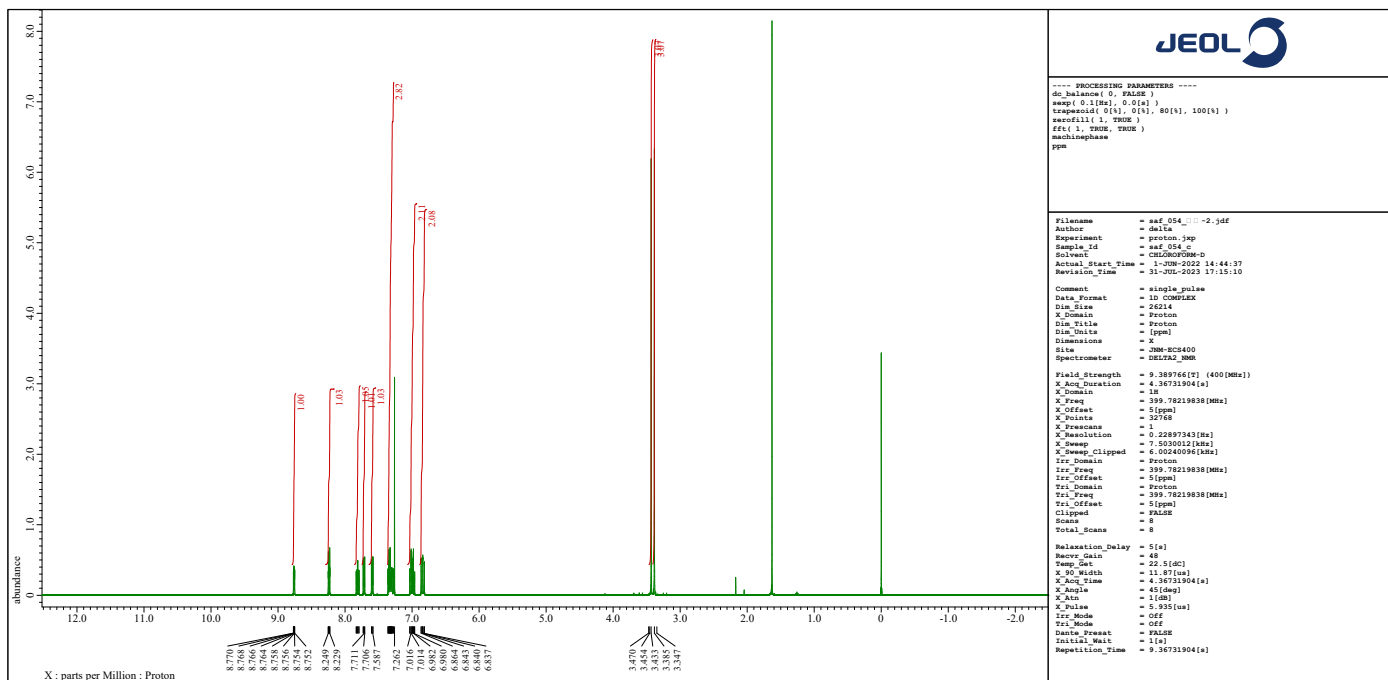
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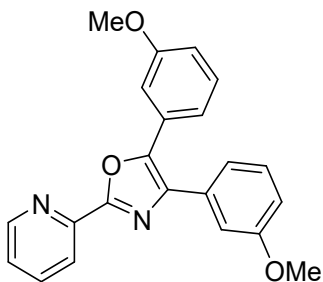
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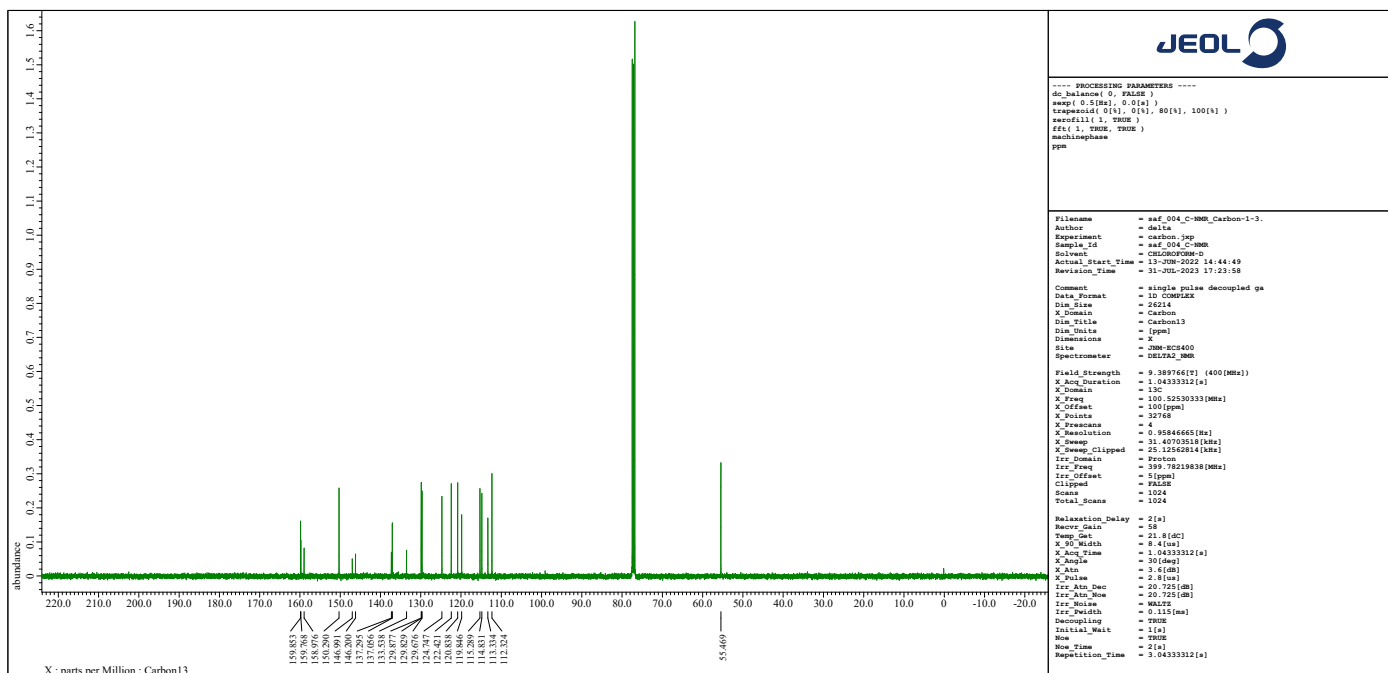
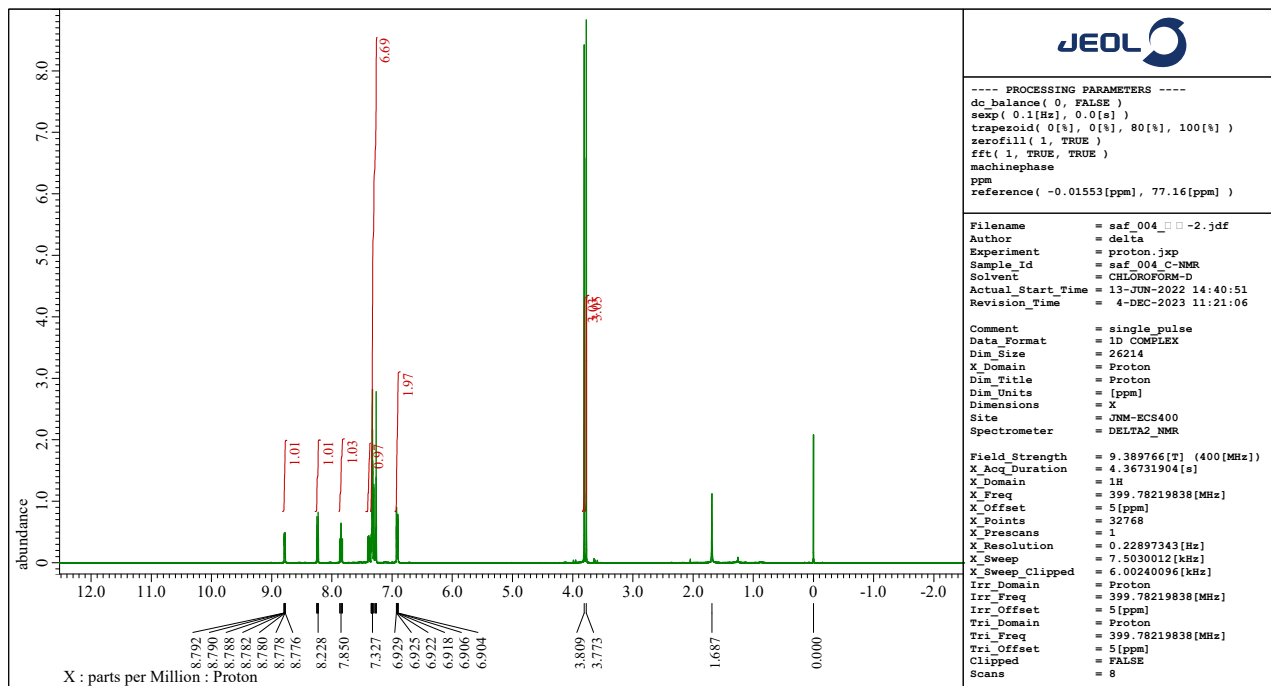
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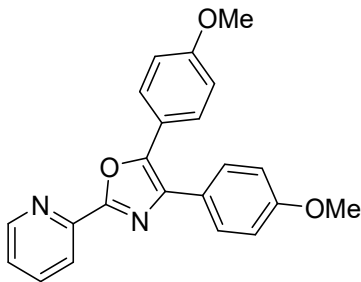
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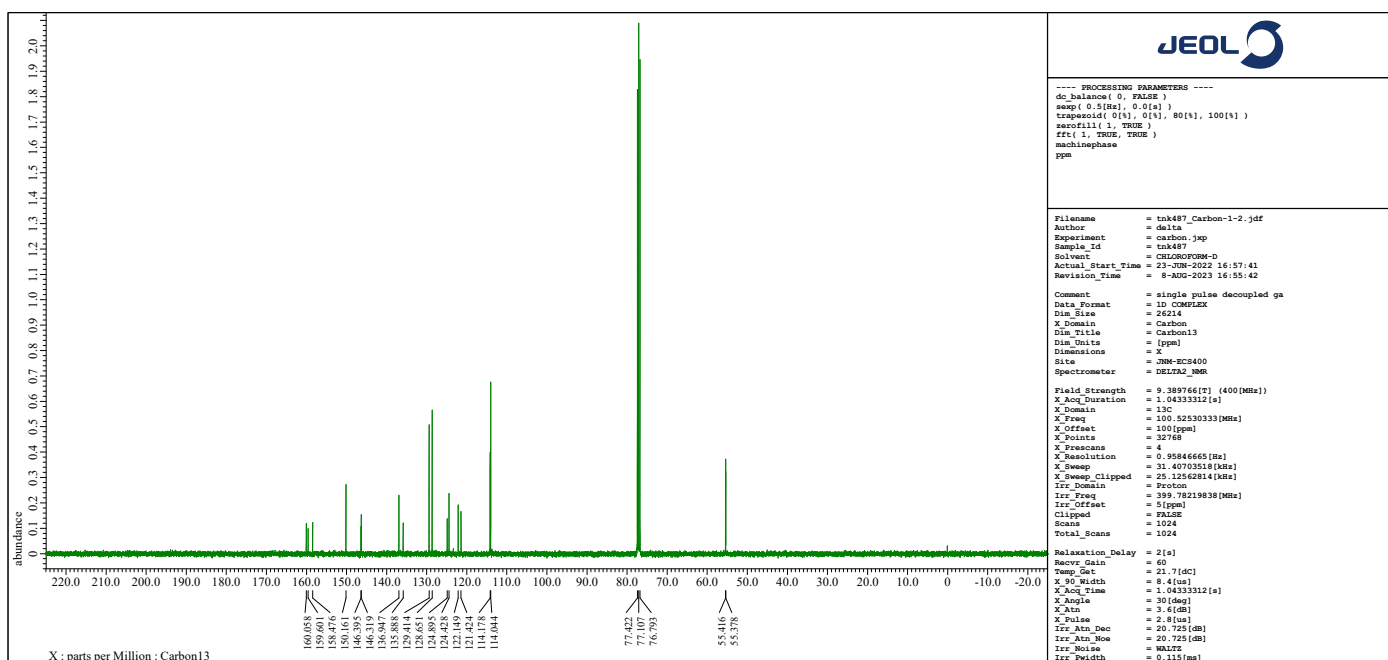
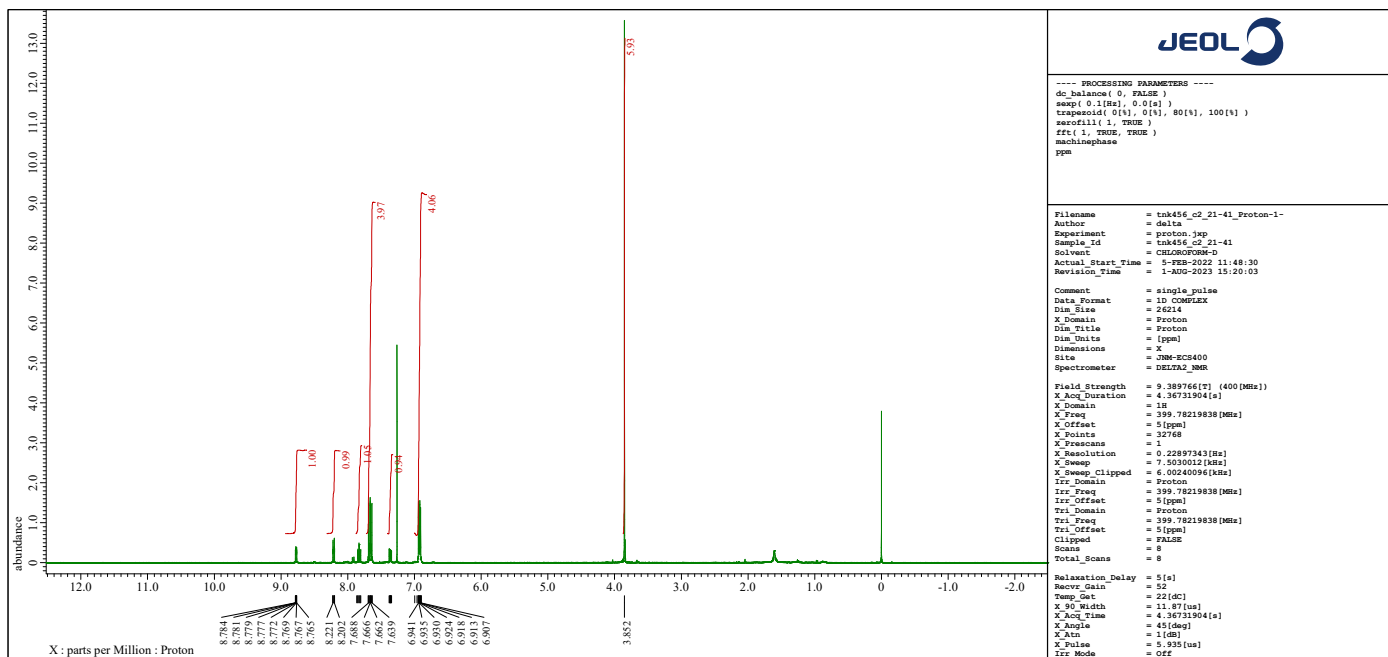
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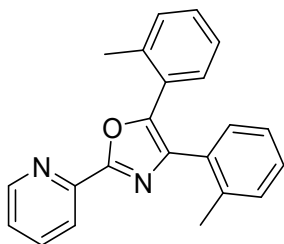
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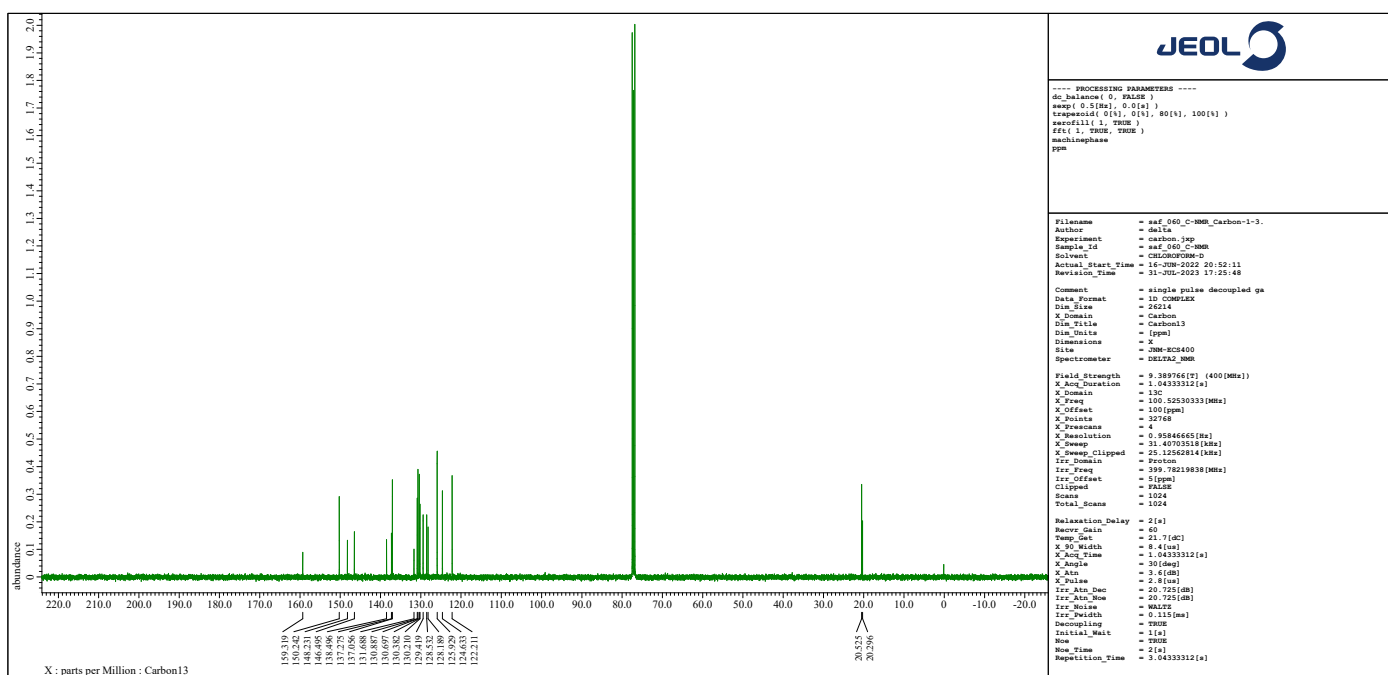
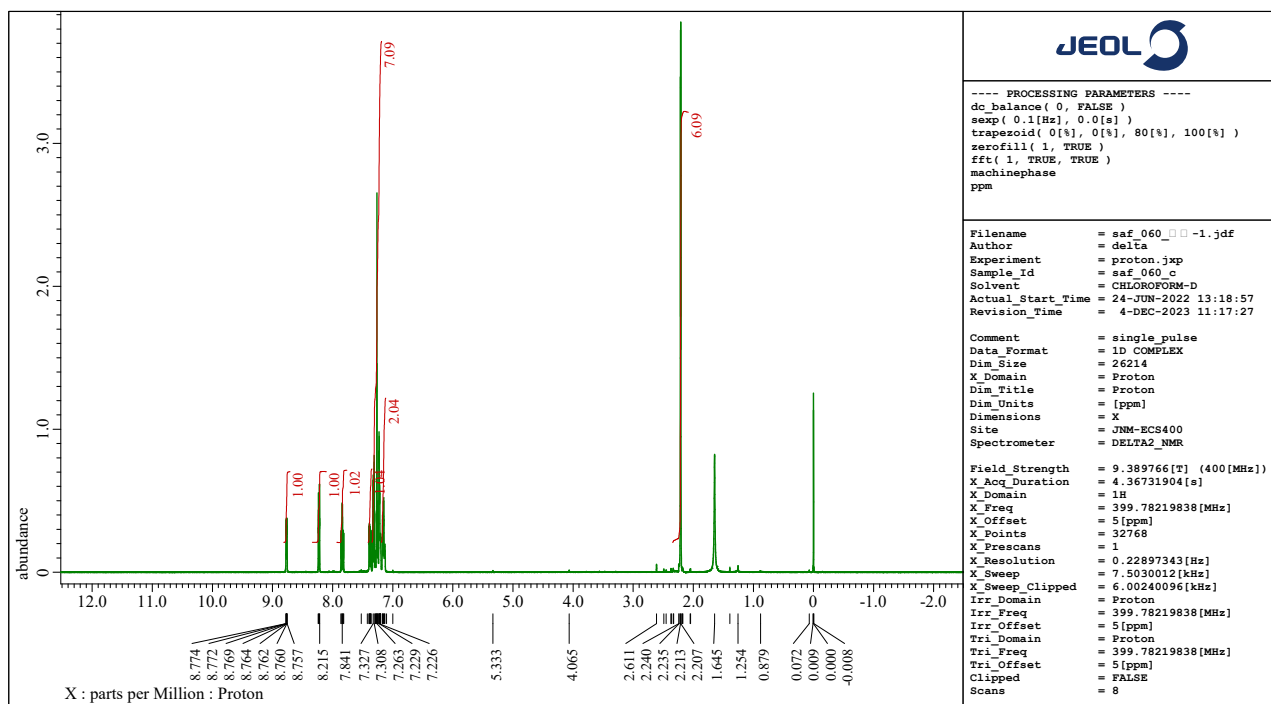
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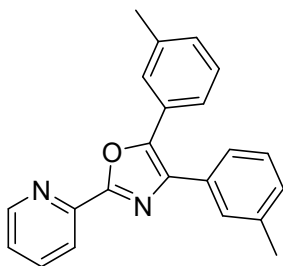
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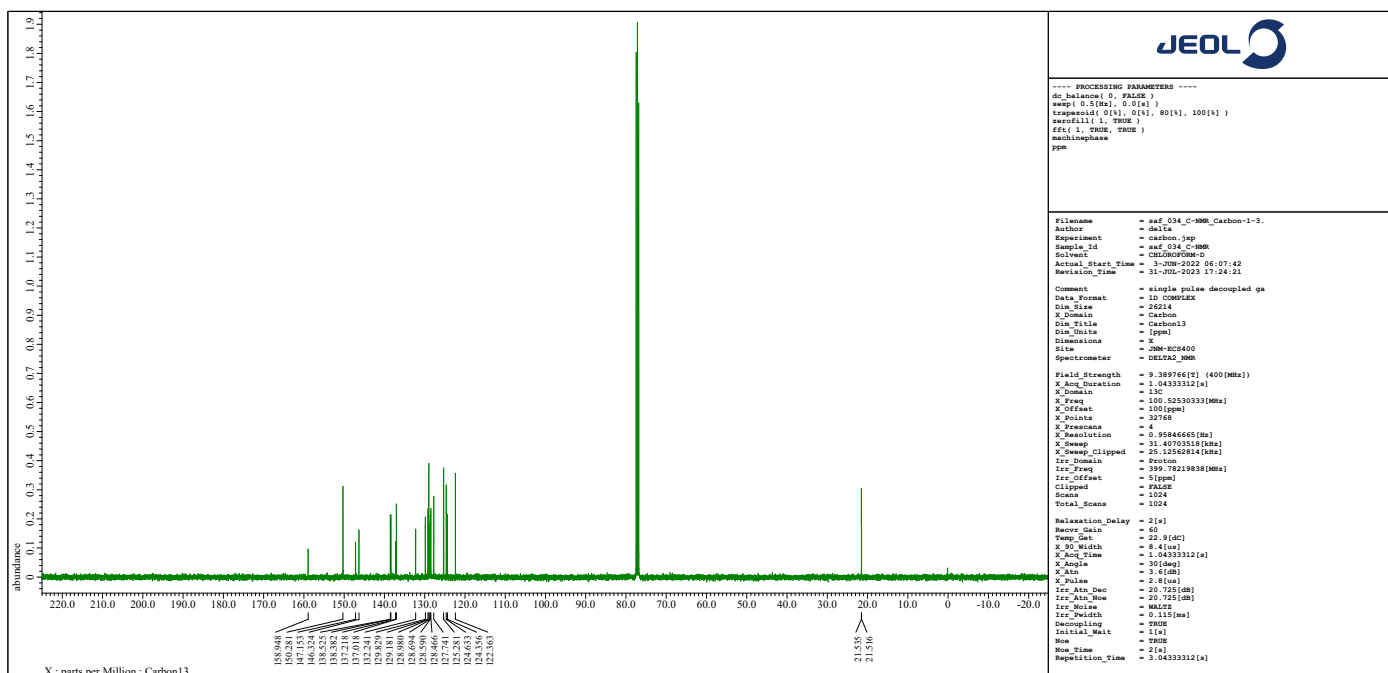
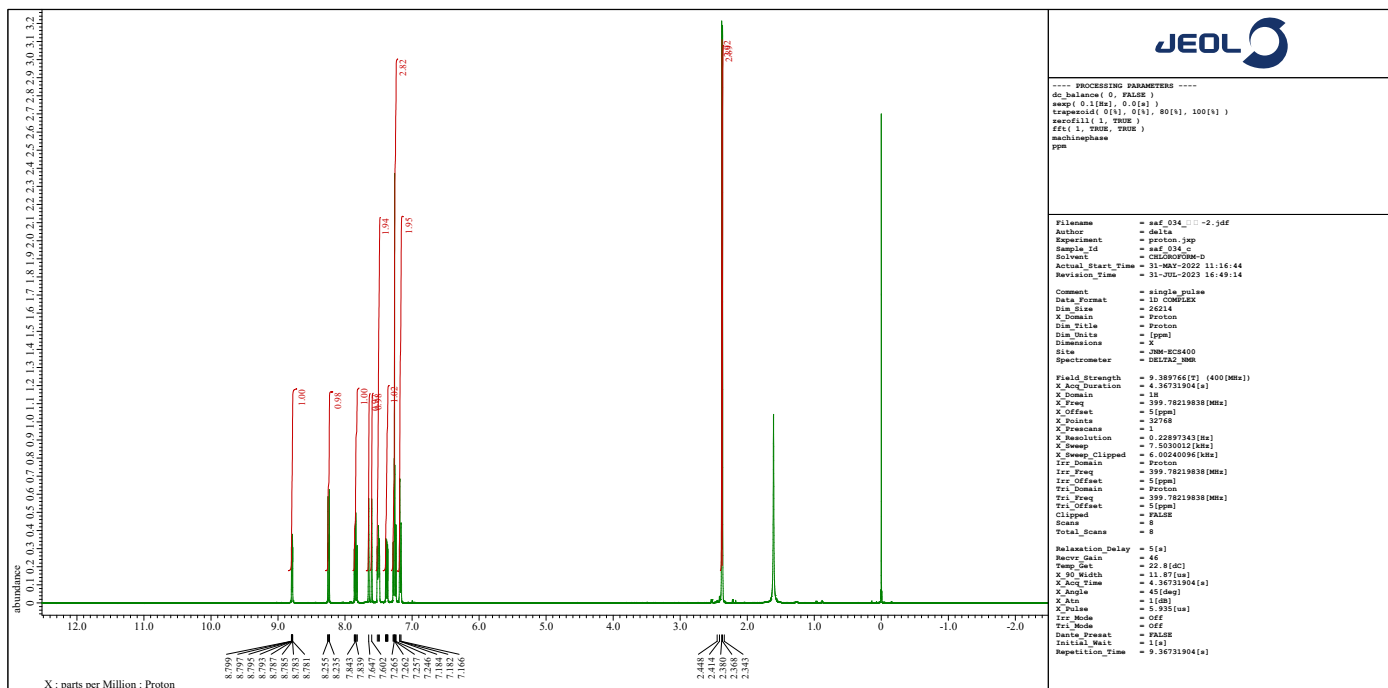
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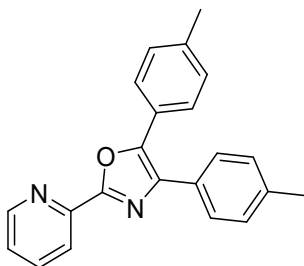
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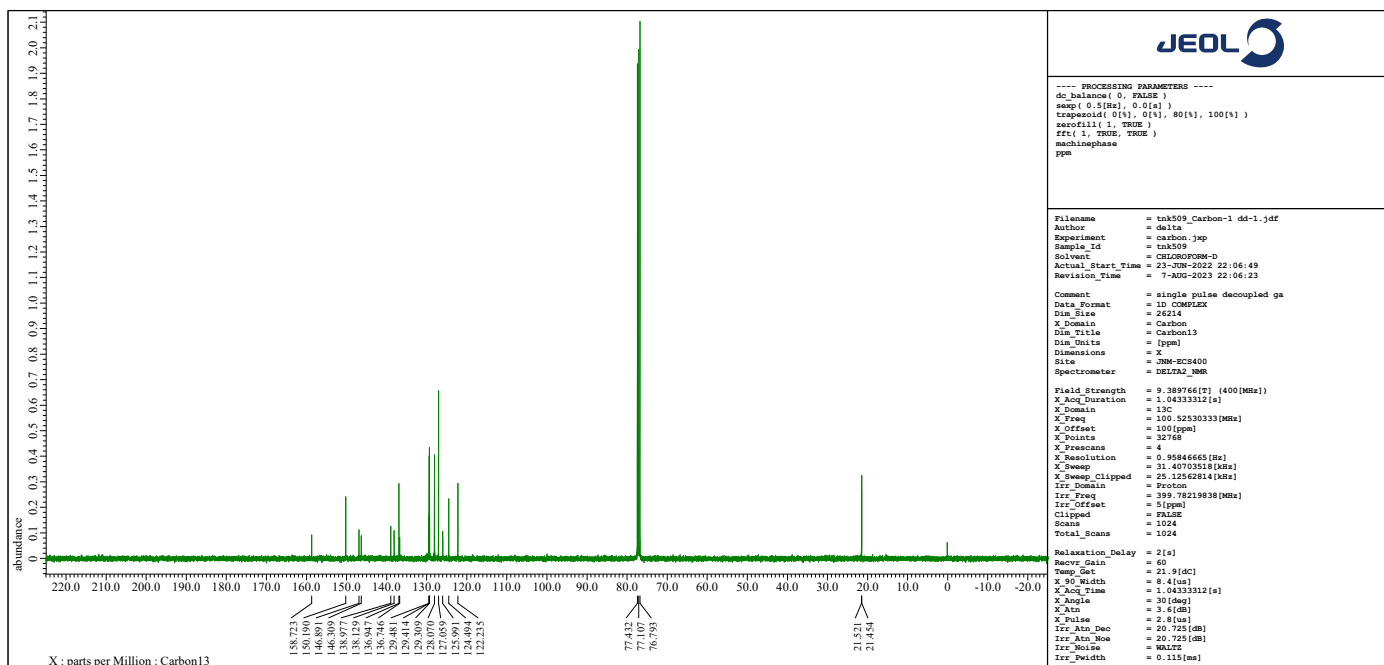
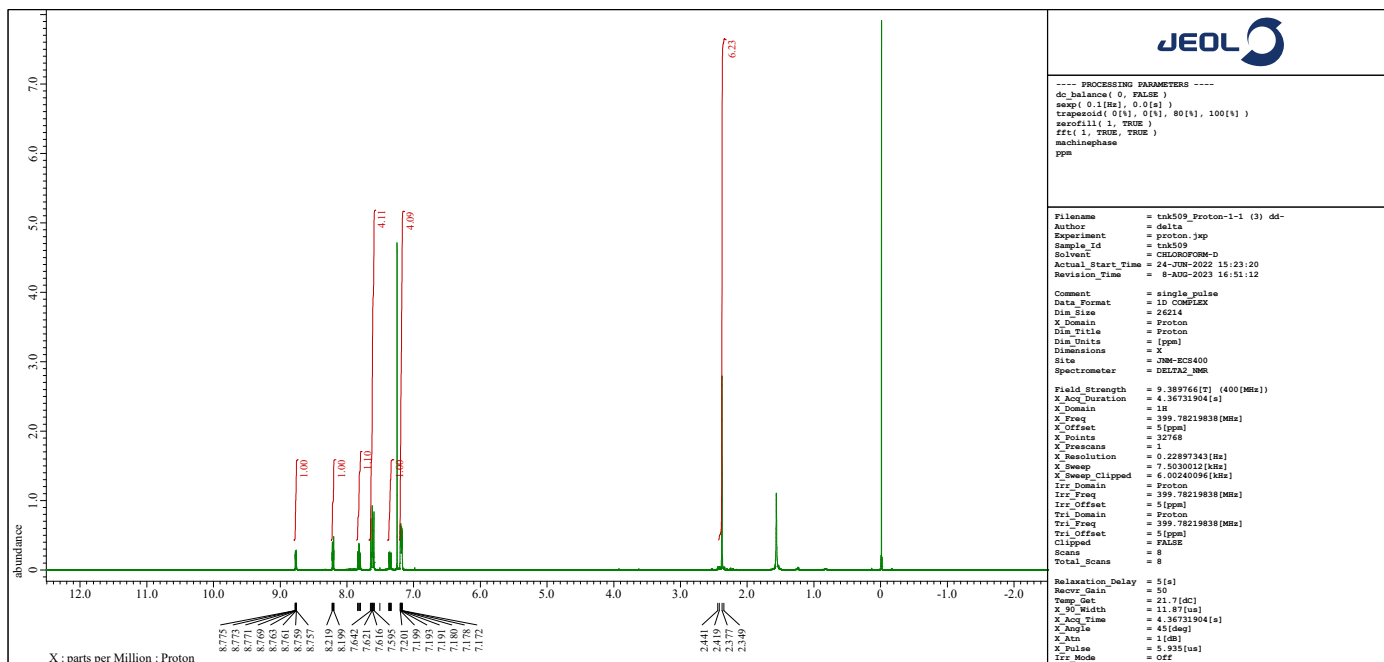
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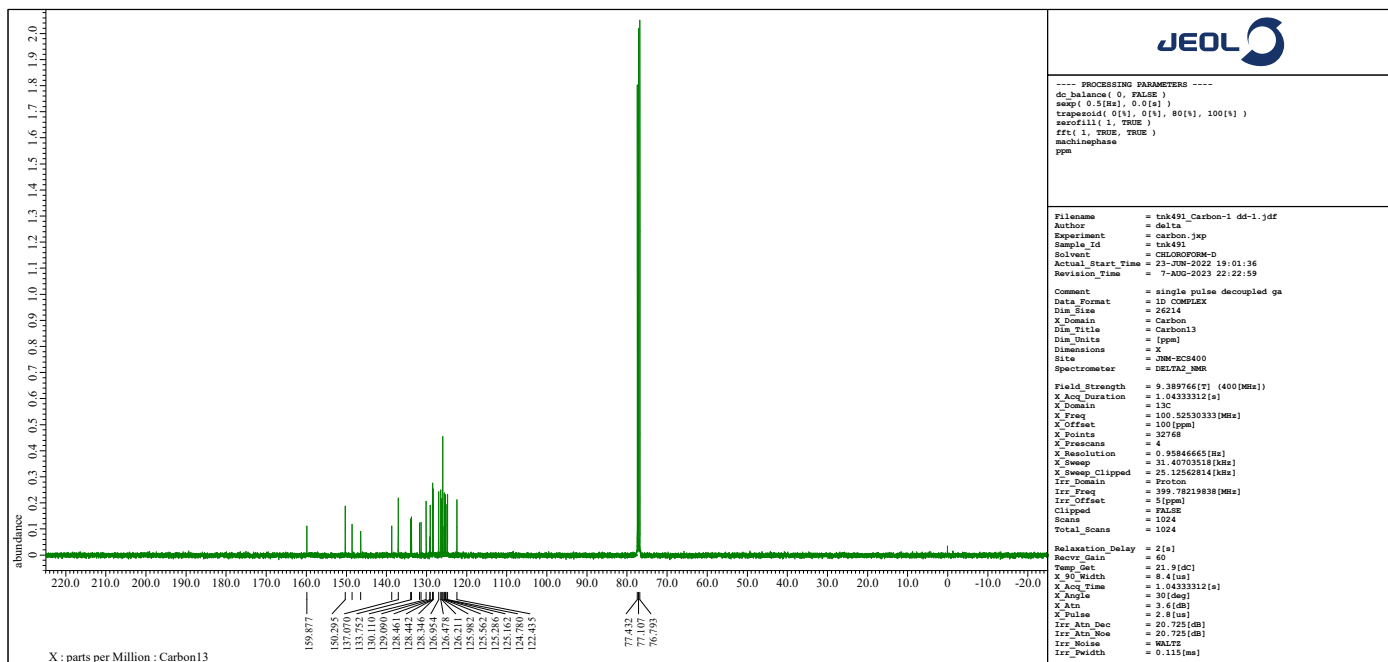
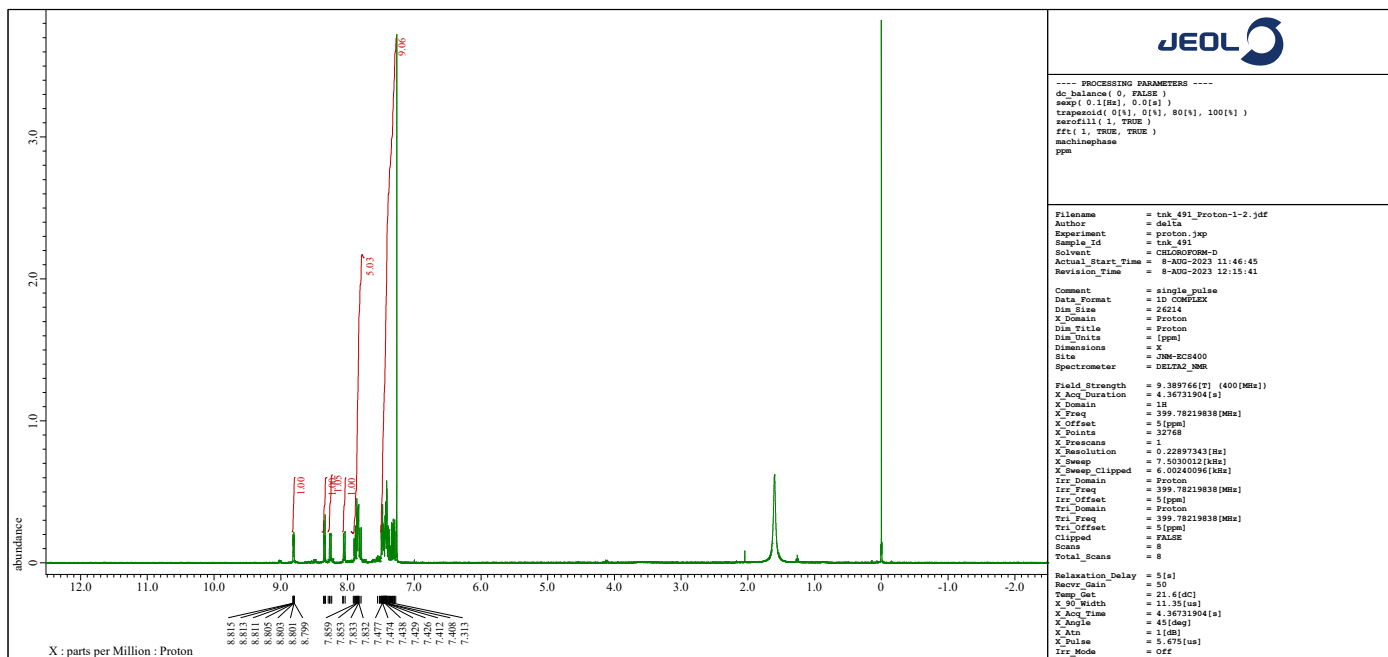
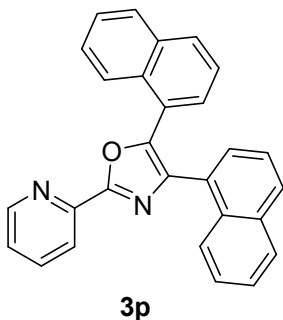
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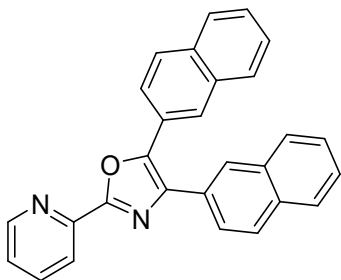
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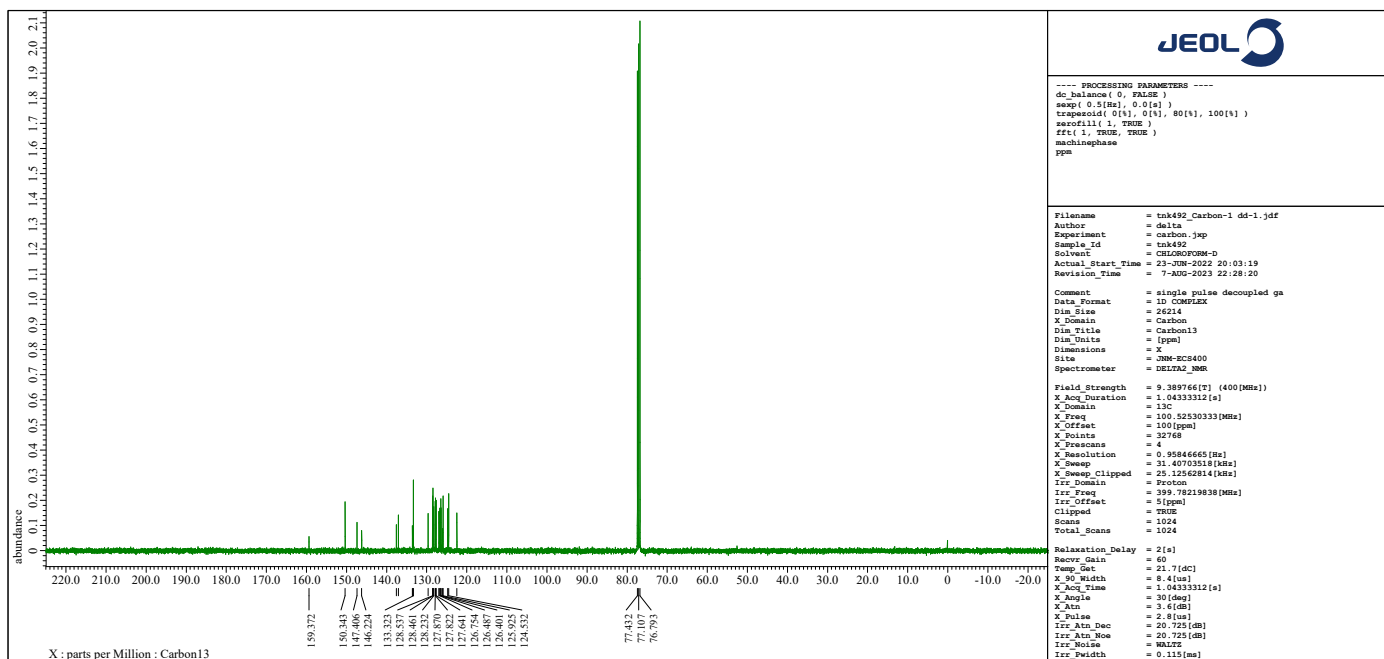
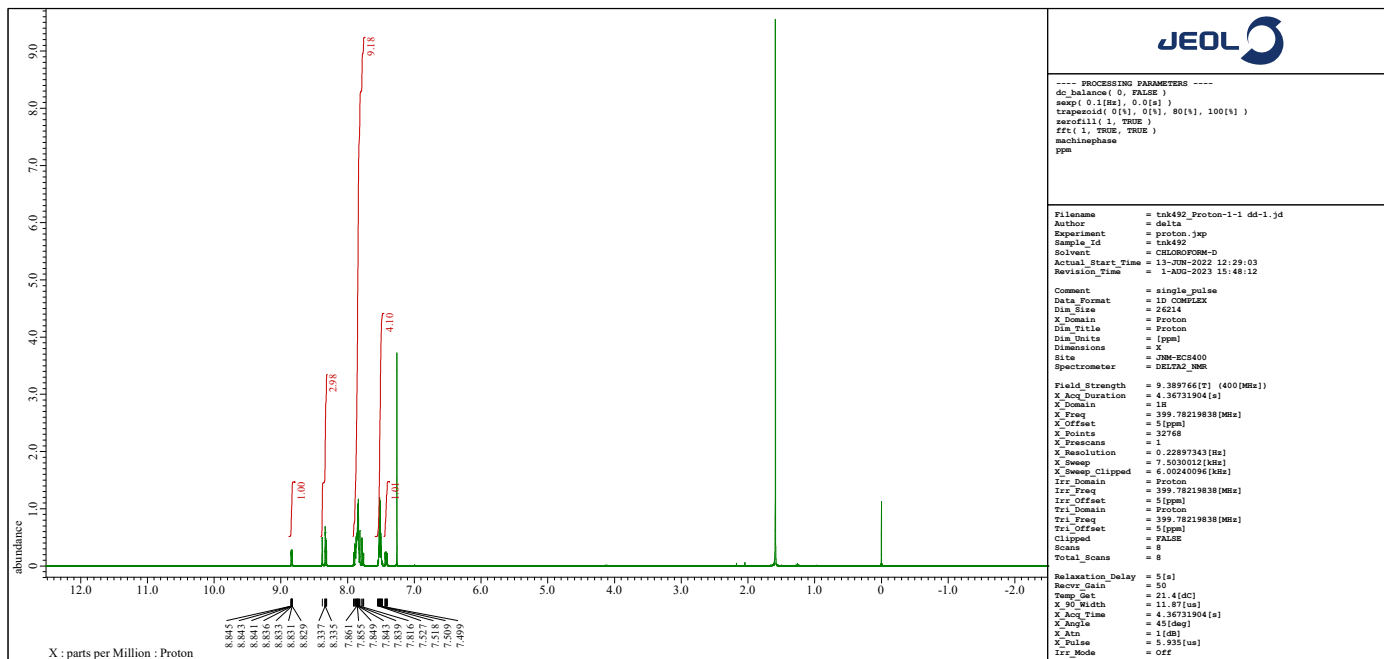
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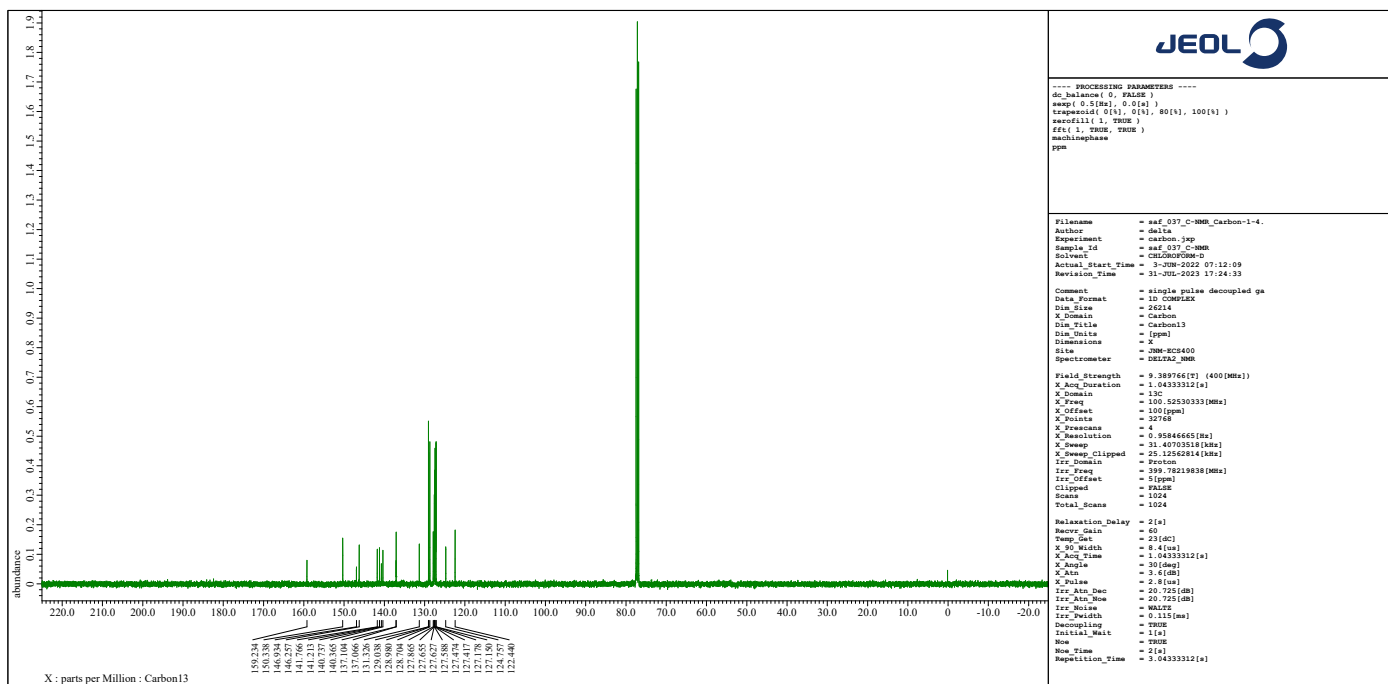
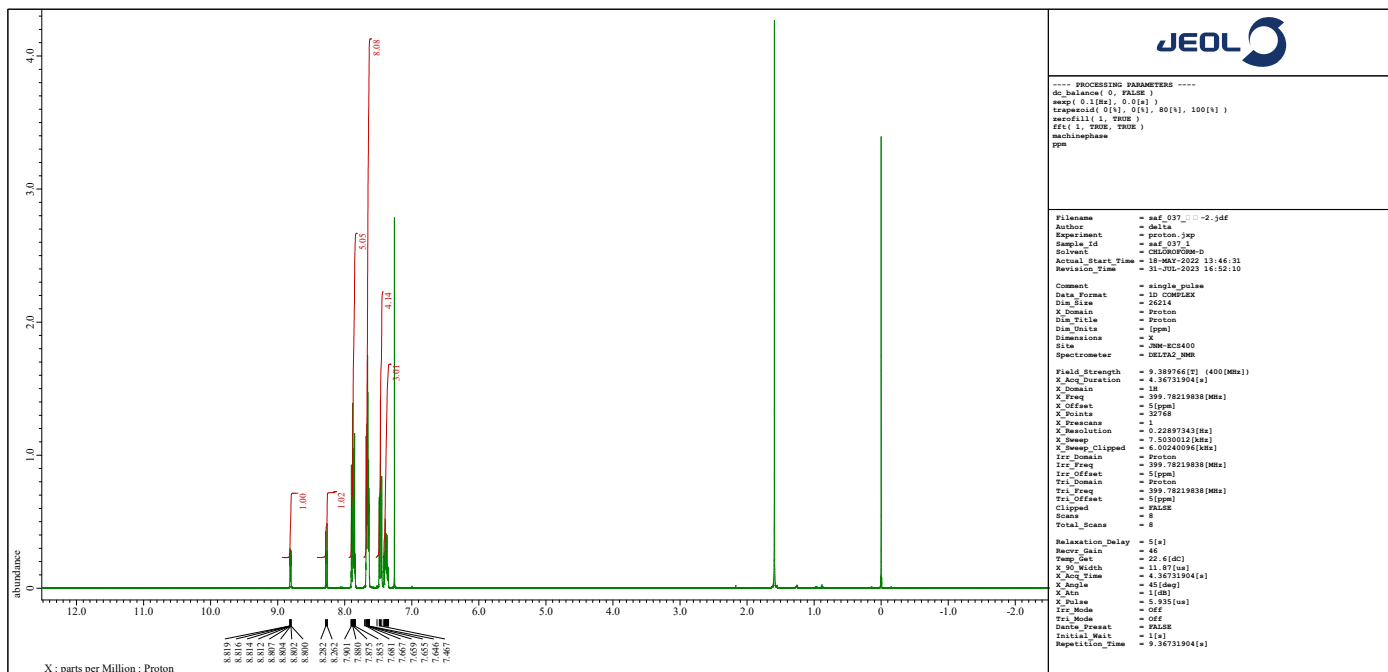
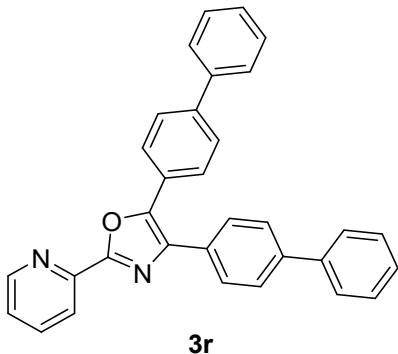
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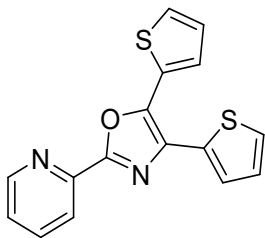
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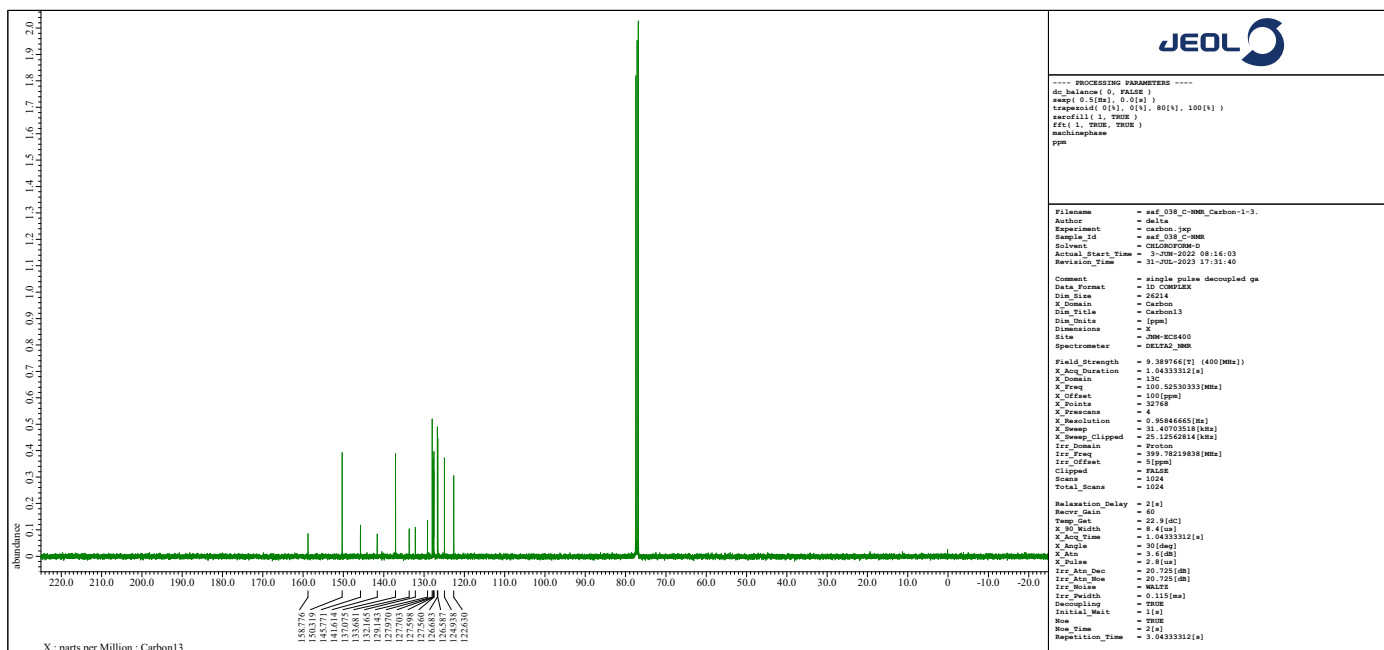
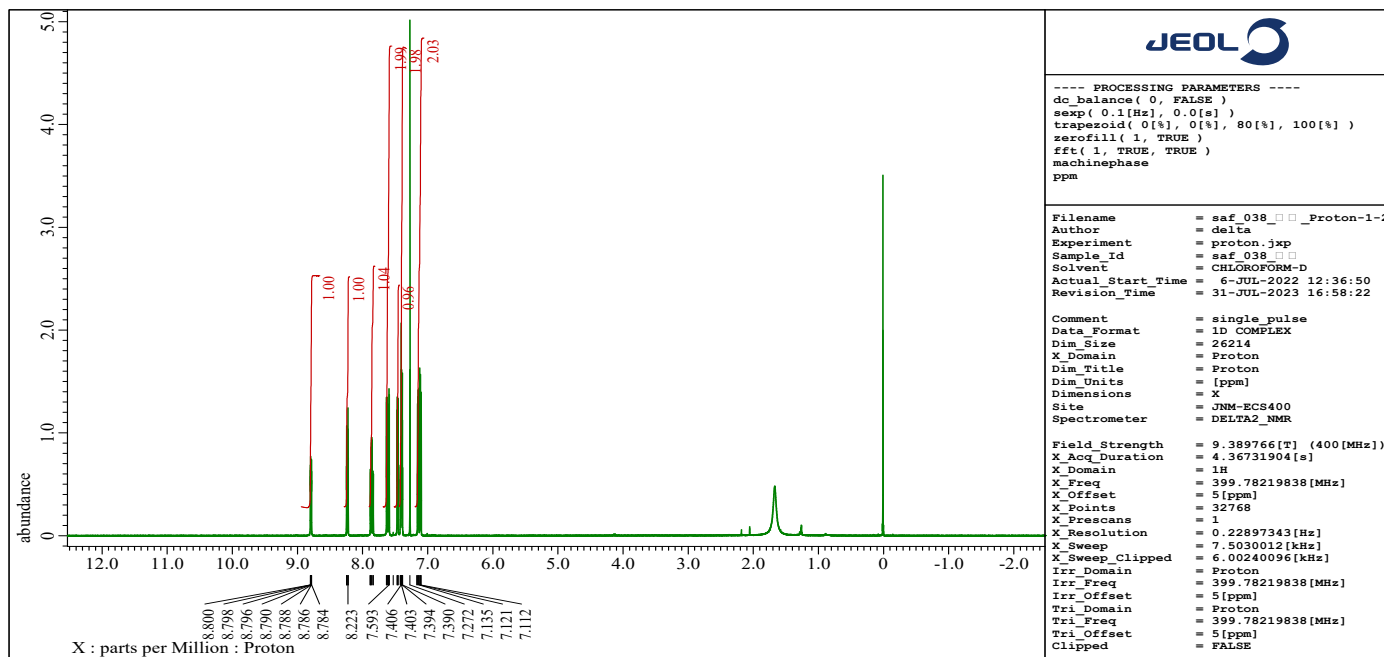
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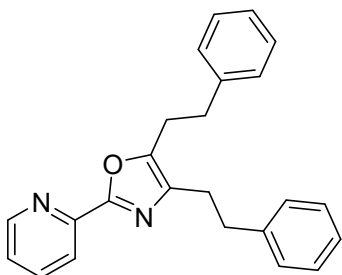
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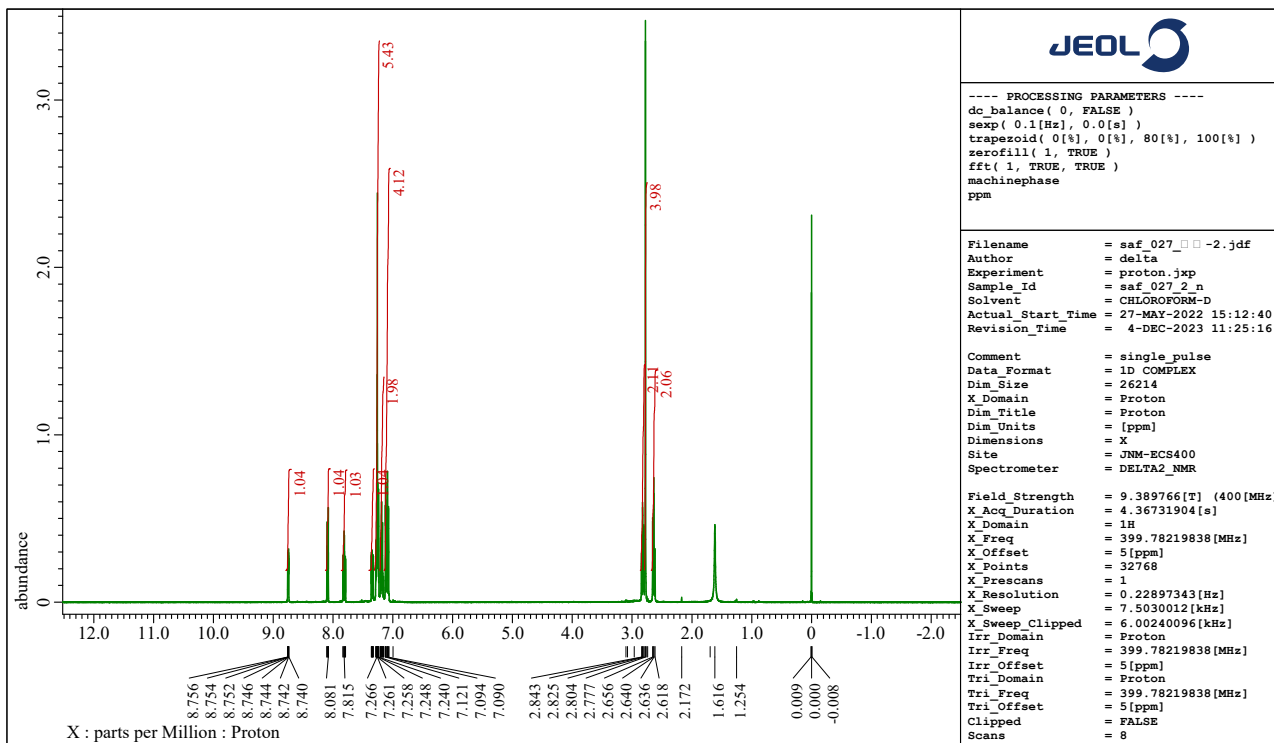
3s



4,5-Diphenethyl-2-(pyridin-2-yl)oxazole (3t)



3t



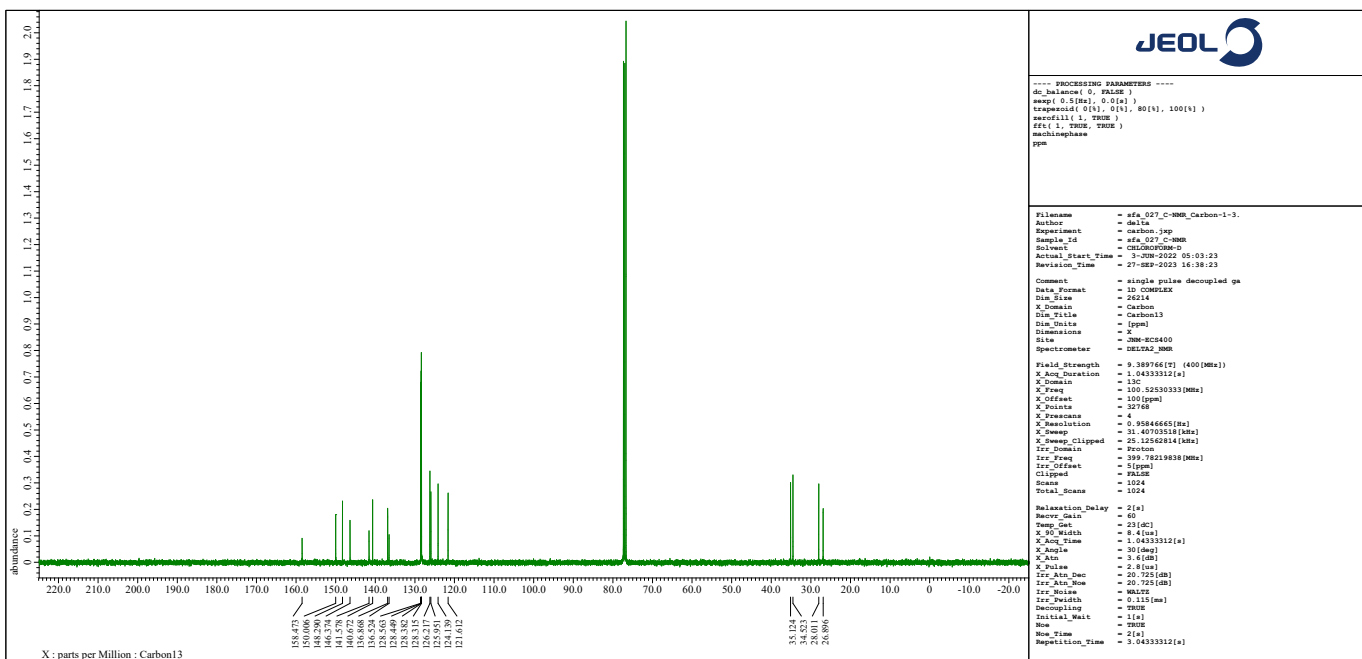
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machinephase
ppm

Filename      = saf_027_C-NMR_Carbon-1-3
Author       = delta
Experiment   = carbon.jxp
Sample_Id    = saf_027_C-NMR
Solvent      = CHLOROFORM-D
Actual_Start_Time = 3-JUN-2022 05:03:23
Revision_Time   = 27-SEP-2023 16:38:23

Comment      = single pulse decoupled ga
Data_Format  = 1D COMPLEX
Dim_Size     = 26214
X_Domain    = Carbon
Dim_Title    = Carbon13
Dim_Units    = [ppm]
Dimensions   = X
Site        = JNM-ECS400
Spectrometer = DELTA2_NMR

Field_Strength = 9.389766[T] (400[MHz])
X_Acq_Duration = 1.0433312[s]
X_Domain      = 13C
X_Freq       = 100.52530333[MHz]
X_Offset     = 100[ppm]
X_Points     = 32768
X_Prescans   = 4
X_Resolution = 0.98846665[Hz]
X_Sweep     = 31.40753333[kHz]
X_Sweep_Clipped = 25.12562884[kHz]
Irr_Domain   = Proton
Irr_Freq     = 399.78219838[MHz]
Irr_Offset   = 5[ppm]
Clipped     = FALSE
Scans       = 1024
Total_Scans = 1024

Relaxation_Delay = 2[s]
Recvr_Gain      = 60
Temp_Set       = 23[deg]
X_90_Width    = 8.4[us]
X_Acq_Time    = 1.0433312[s]
X_Amp        = 30[deg]
X_Ain        = 3[us]
X_Pulse      = 2.8[us]
Irr_Ain_Dec  = 20.725[db]
Irr_Ain_90  = 20.725[db]
Irr_Width    = 0.115[us]
Decoupling    = WALTZ
Initial_Wait = 1[s]
Hsu         = 2[us]
Hsu_Time     = 2[s]
Repetition_Time = 3.0433312[s]
    
```


¹⁸O-Picolinamide ([¹⁸O]-1a)

