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SUPPLEMENTARY INFORMATION

Water-Assisted Cascade Synthesis of CF_3-tethered Nevirapine Analogues: *In vitro* and *In silico* Antibacterial Studies

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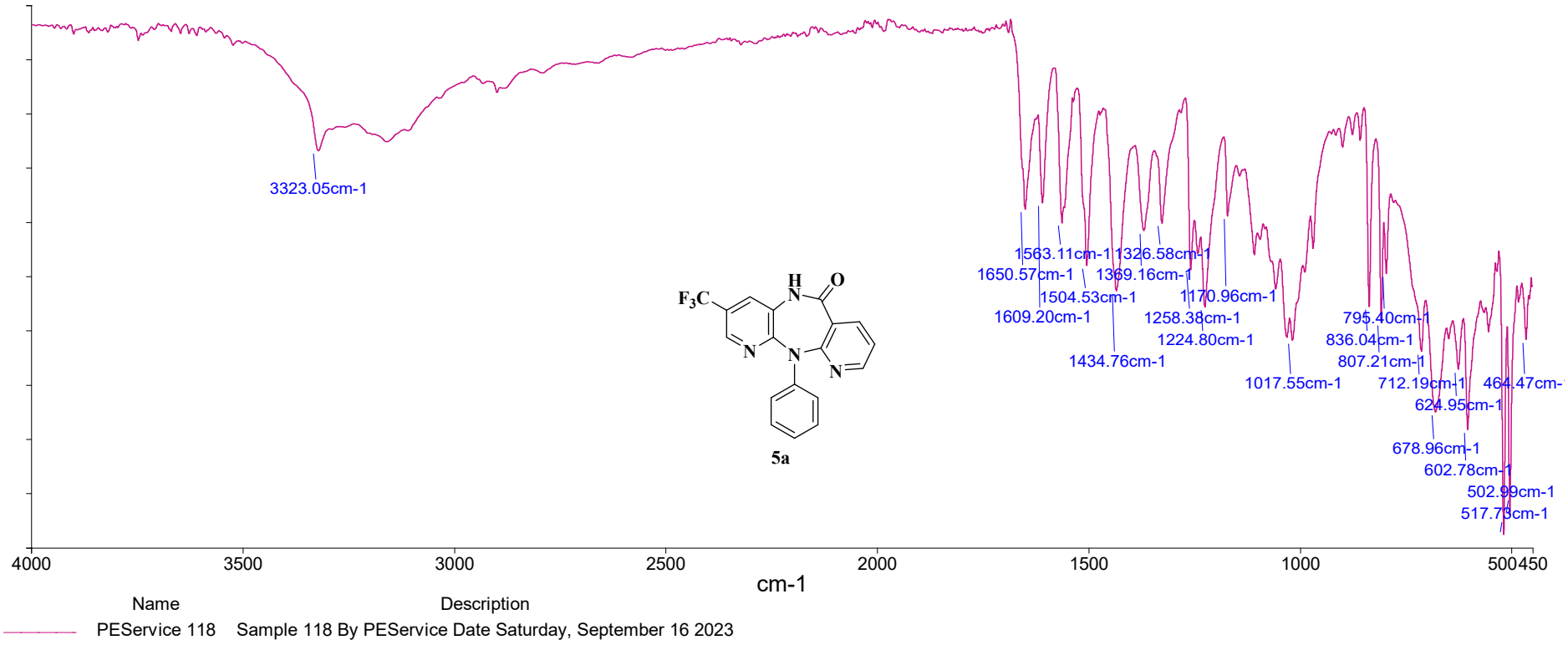
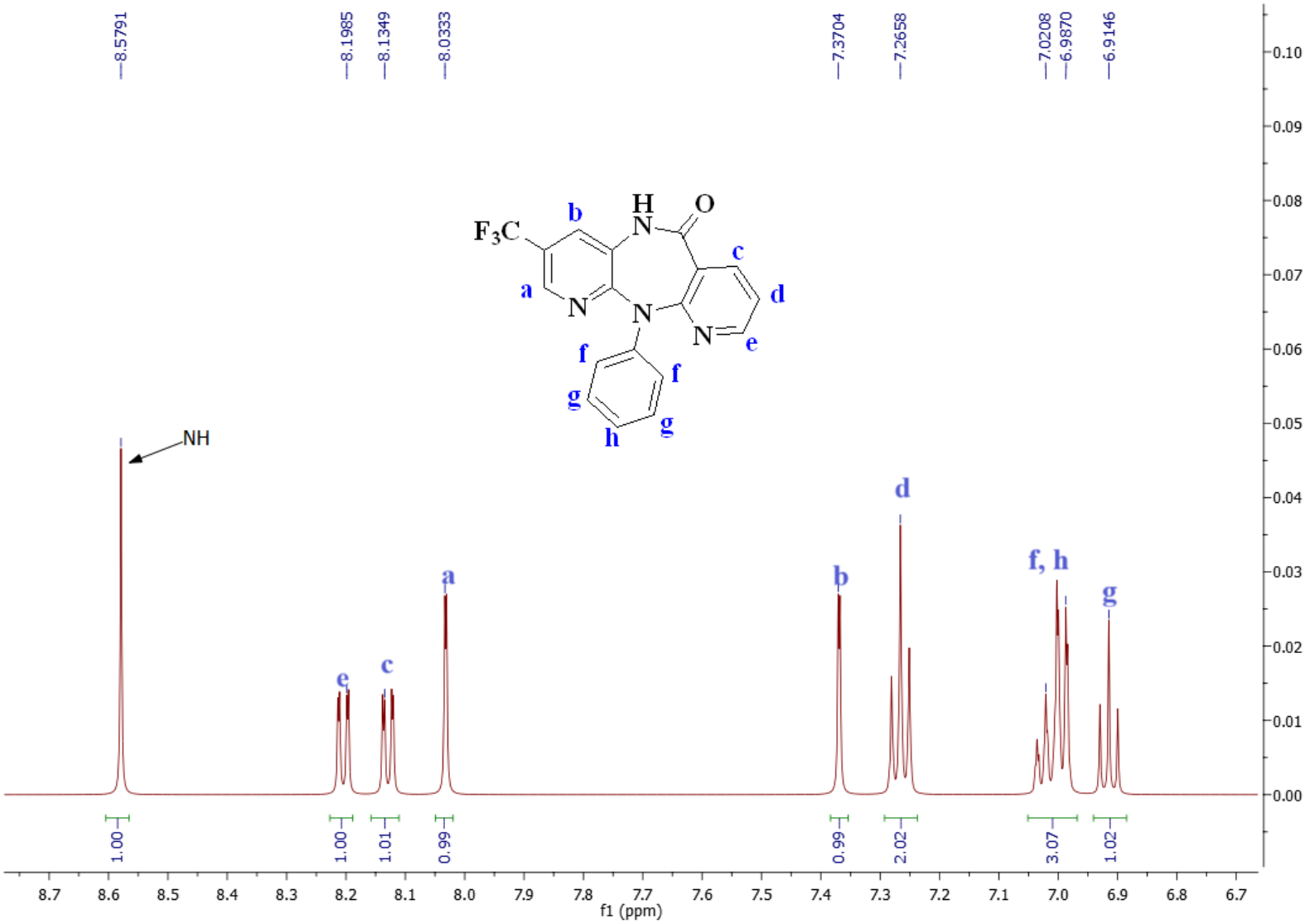
Contents

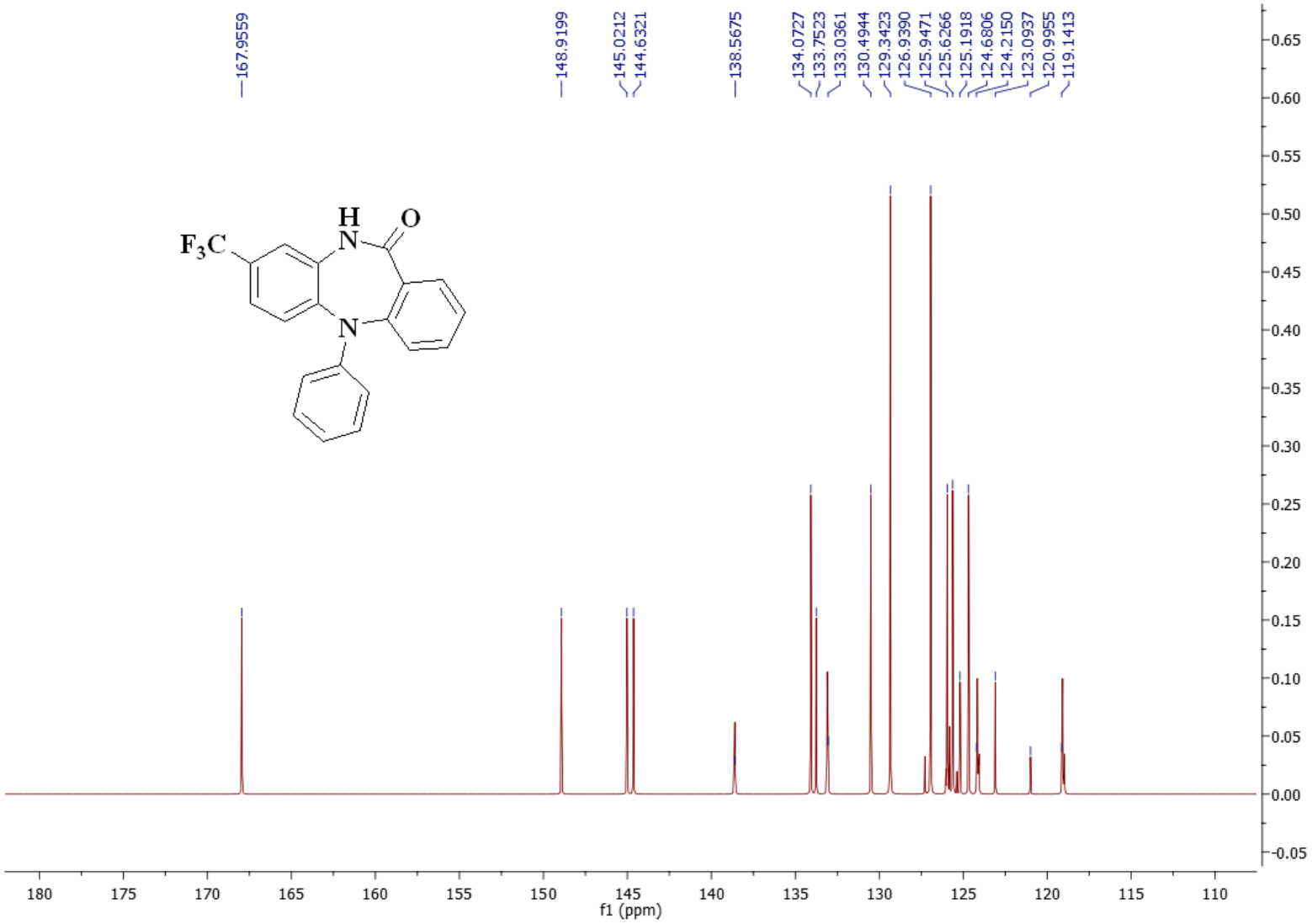
1. Spectral graph of synthesized compounds (5a-5k)



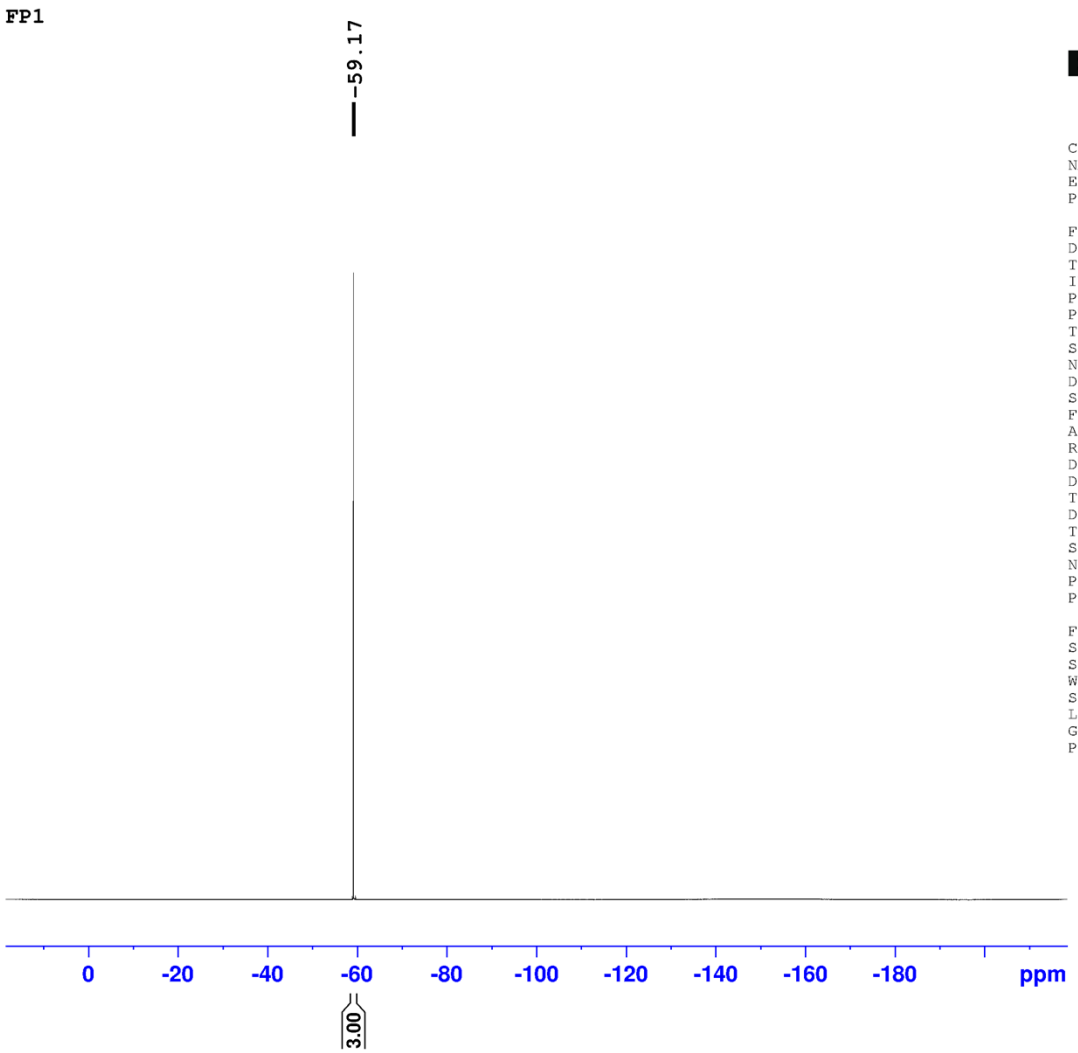
S1: IR spectrum of **5a**



S2: ^{1}H NMR of **5a**



S3: ^{13}C NMR of **5a**



BRUKER

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TE                298.0 K
D1           1.00000000 sec
TD0                   1
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NUC1                 19F
P1                15.00 usec
PLW1        17.00000000 W

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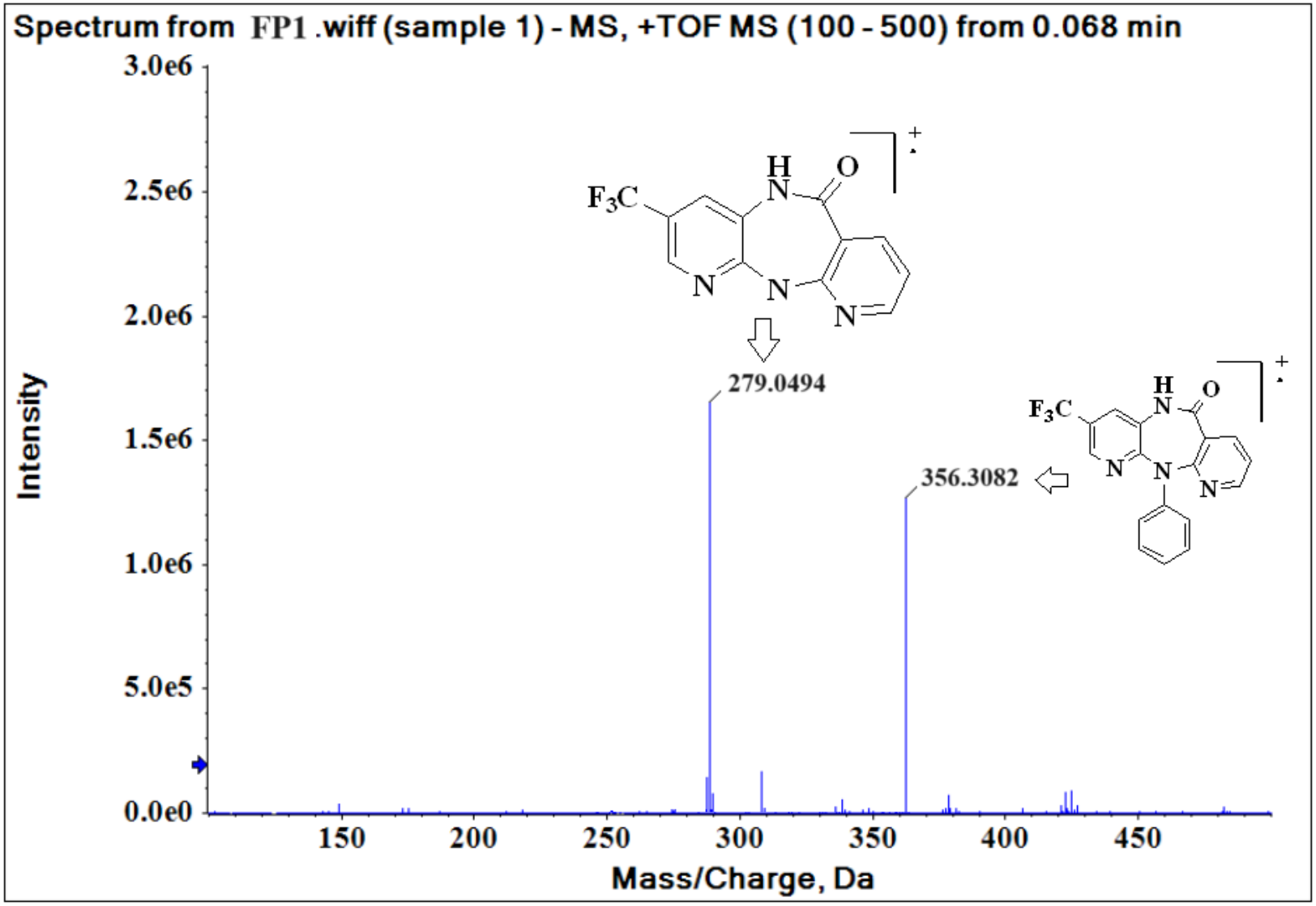

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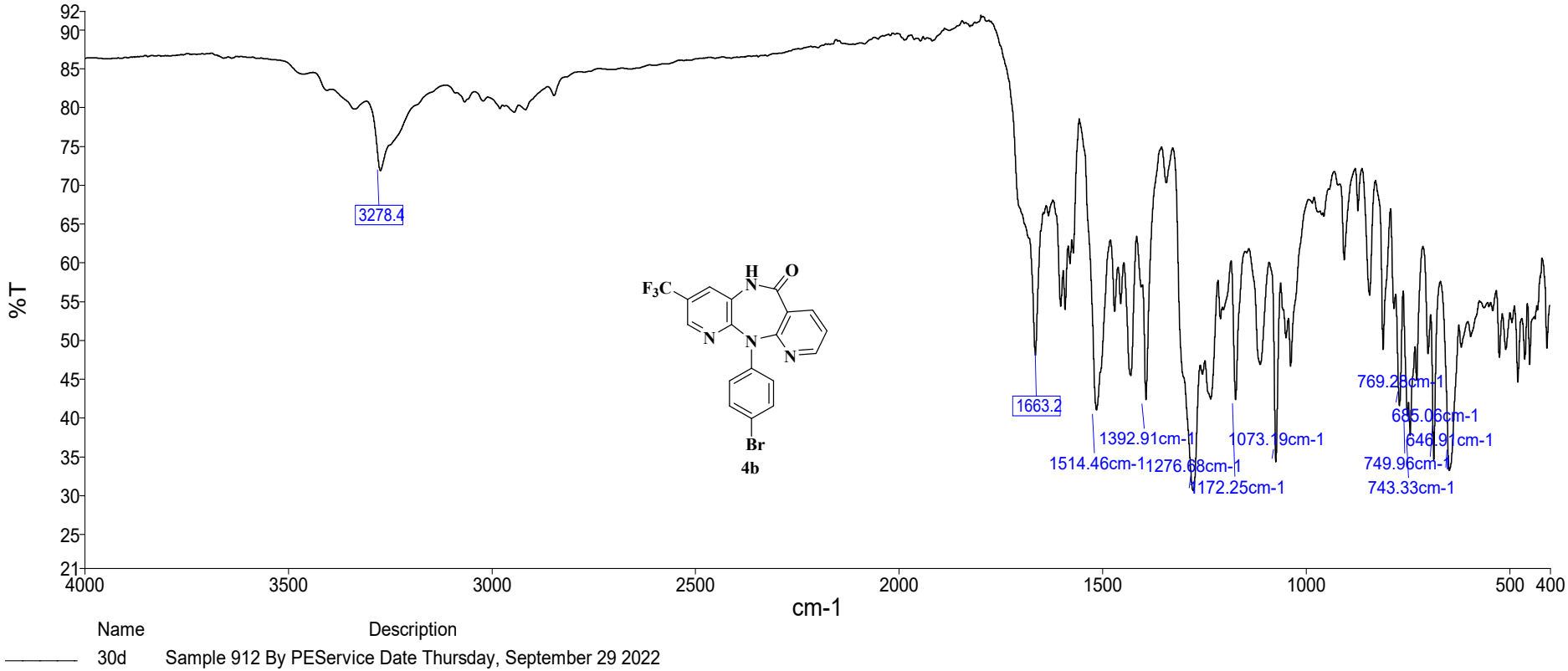

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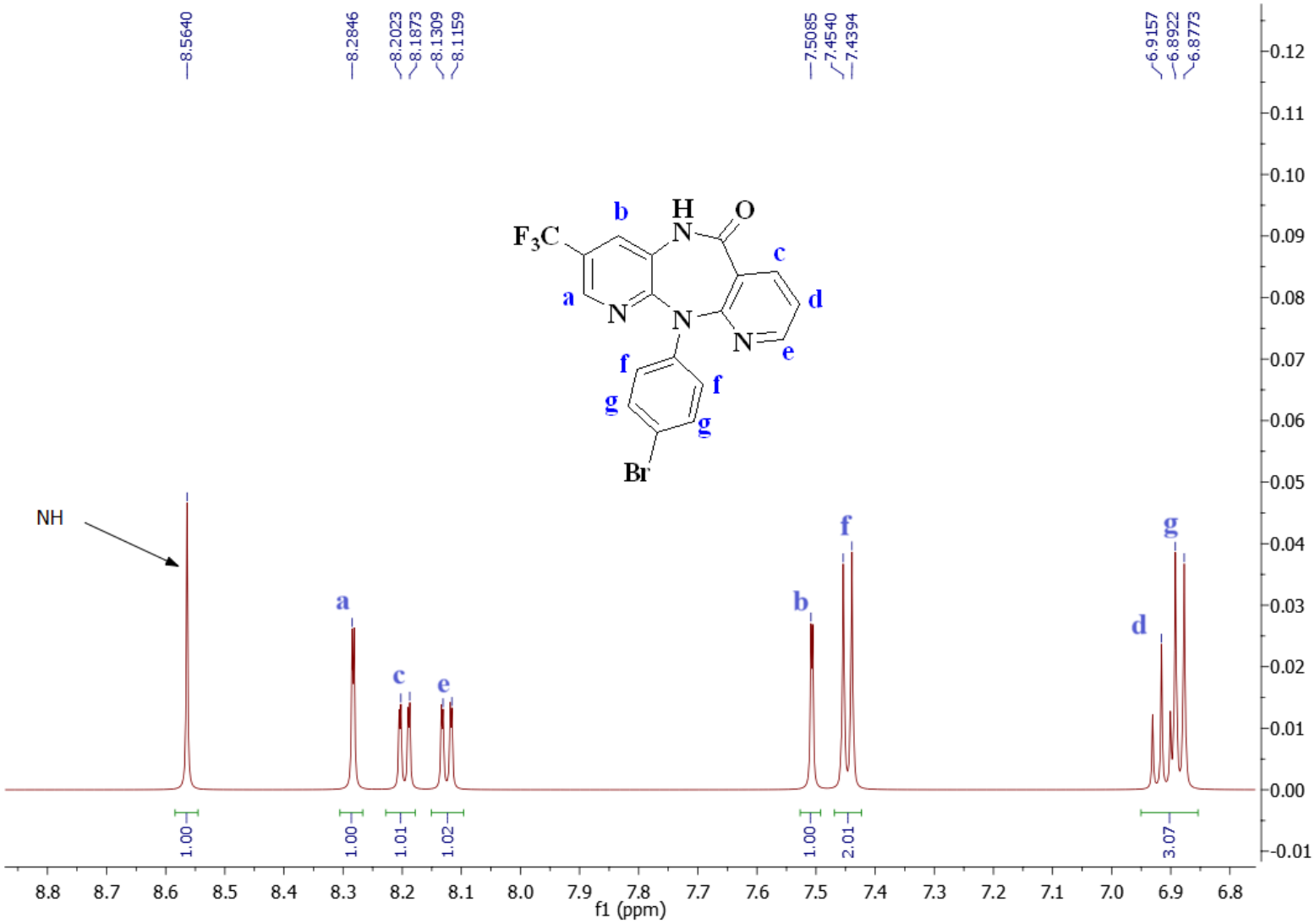

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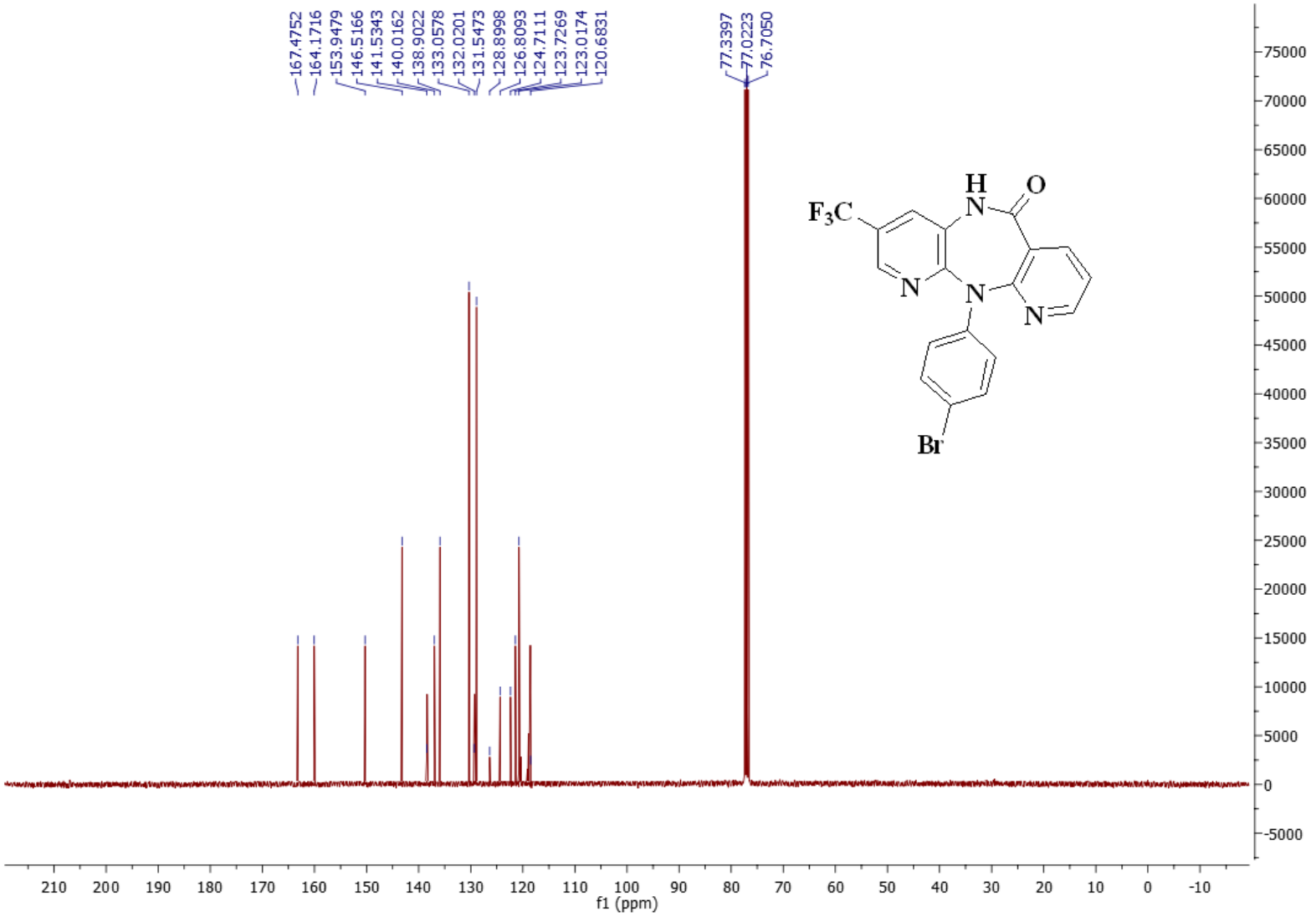

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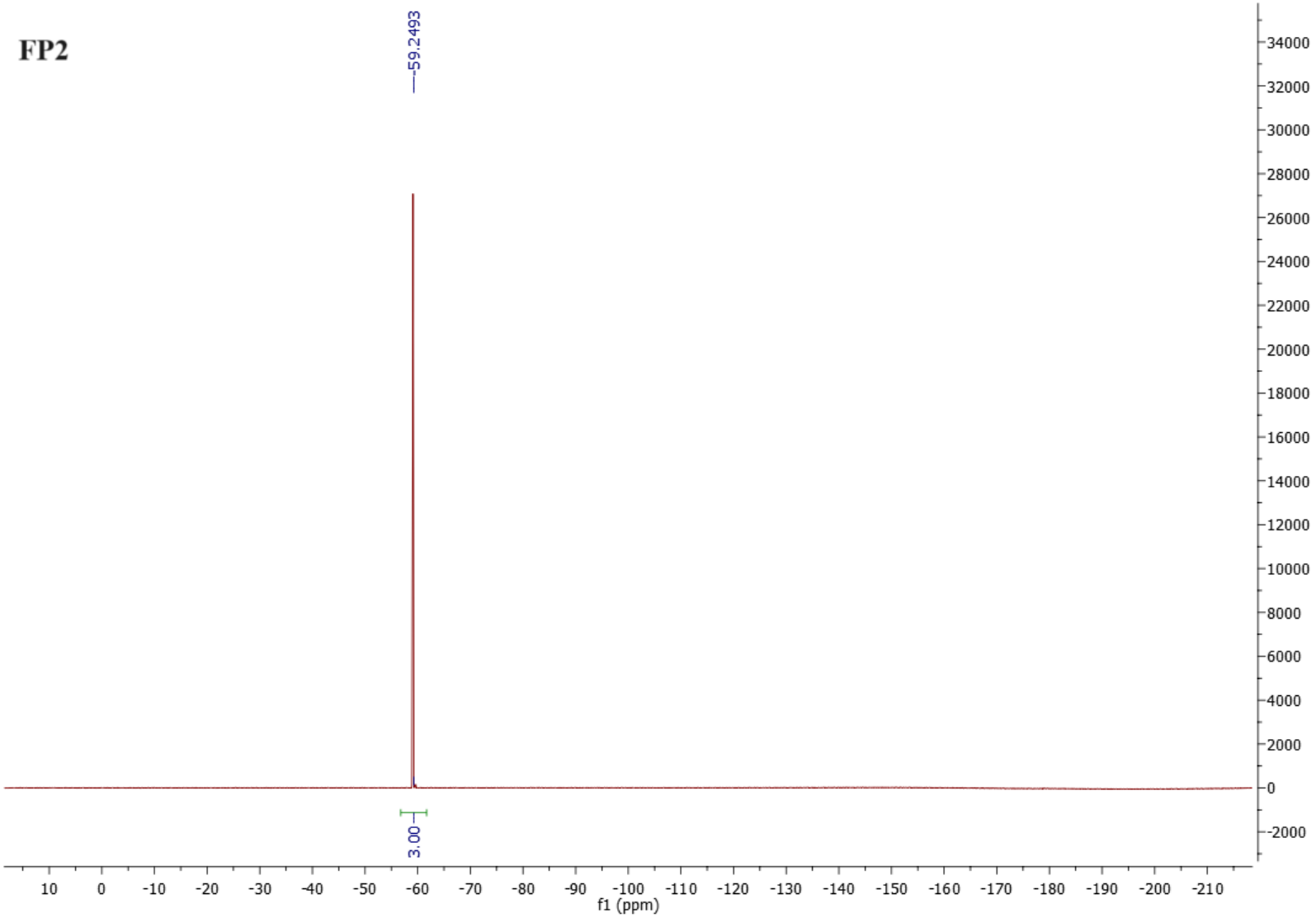

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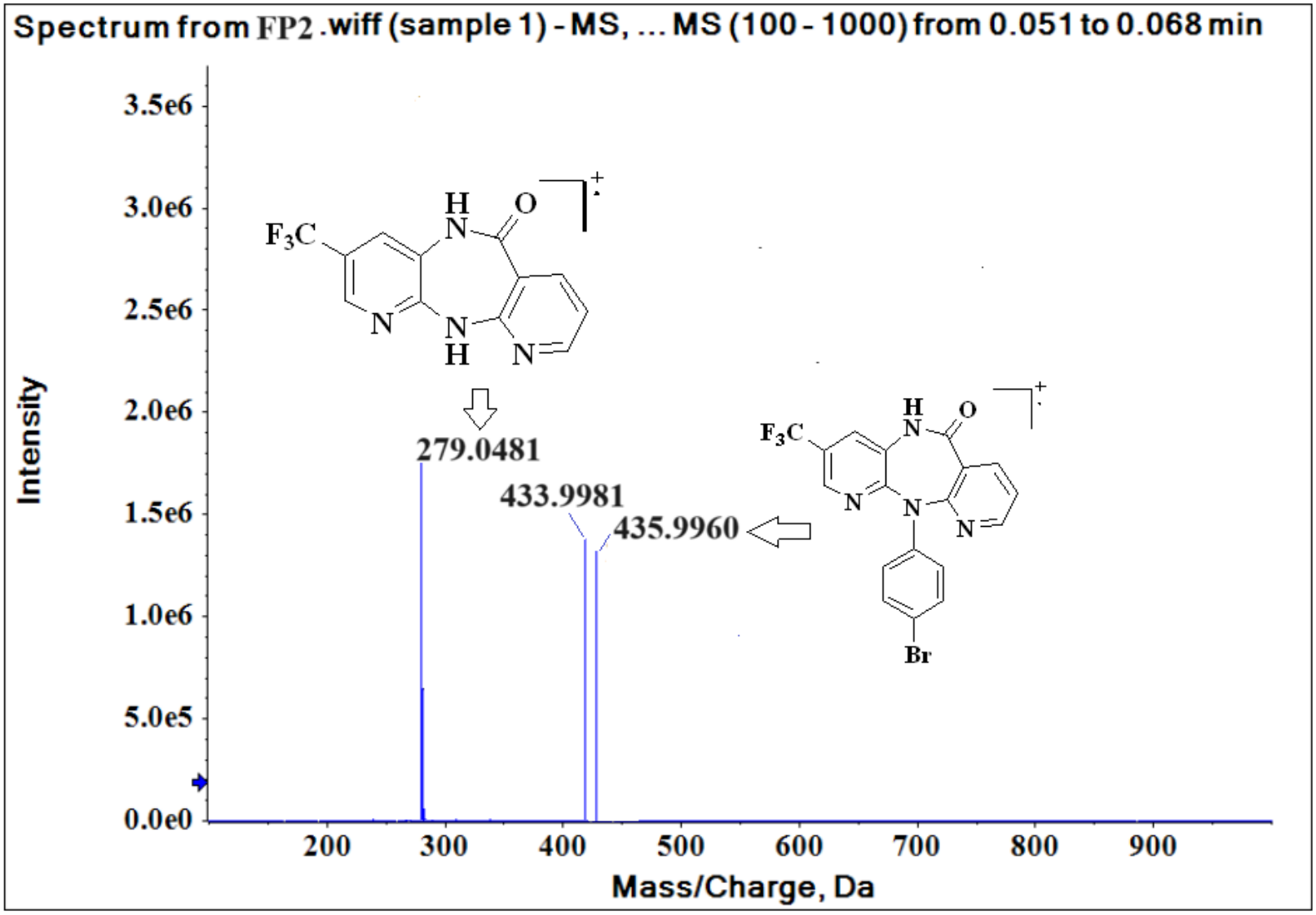

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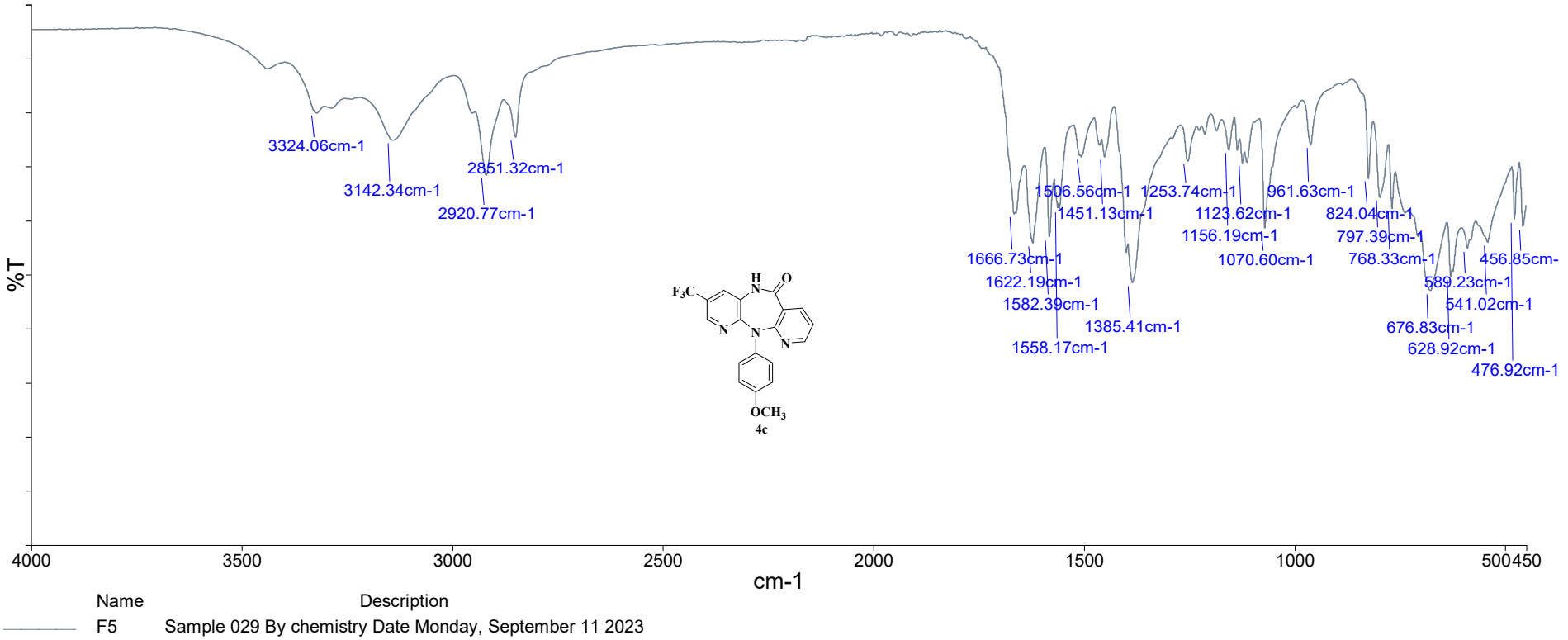
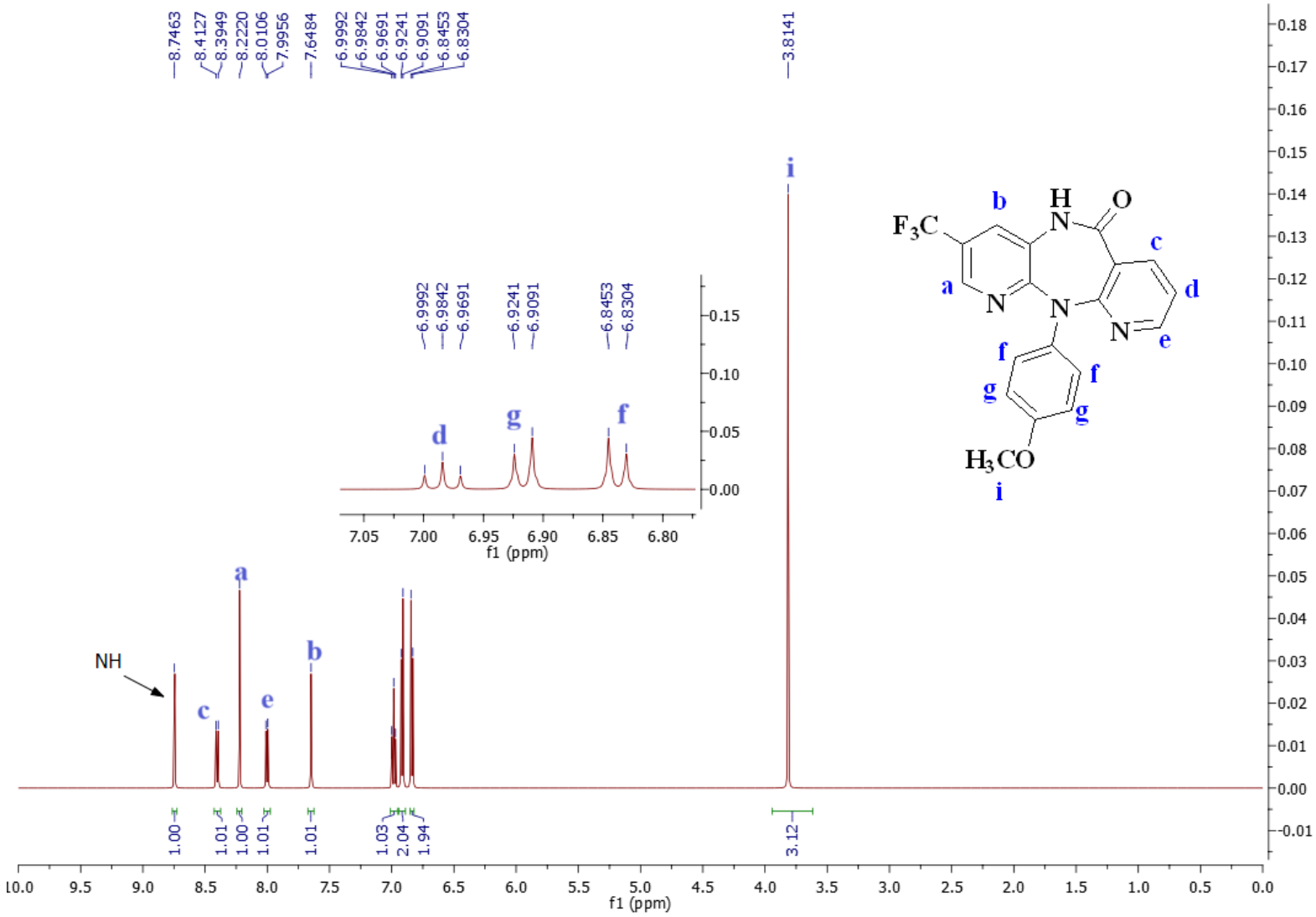


4c

S11: IR spectrum of **5c**



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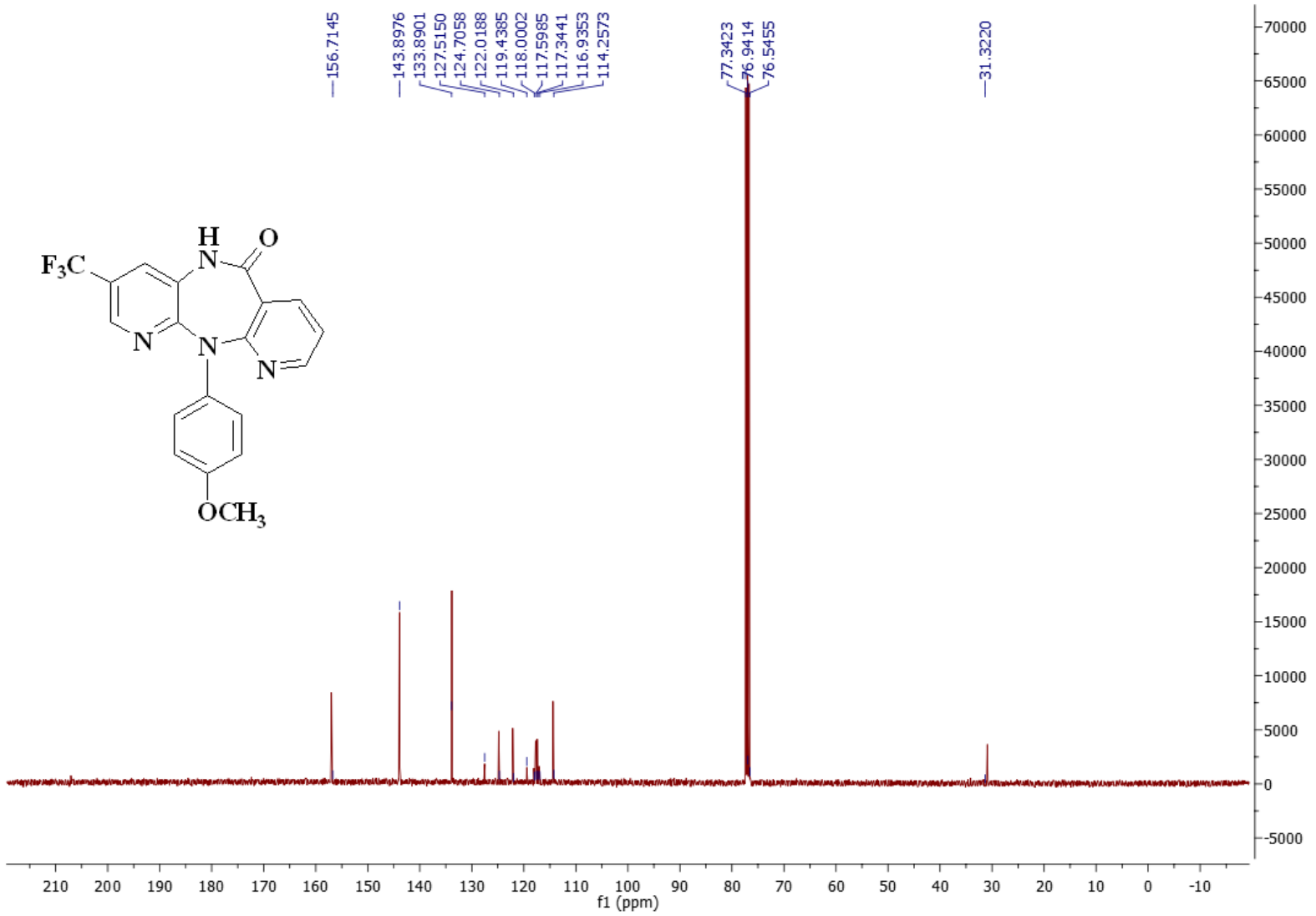

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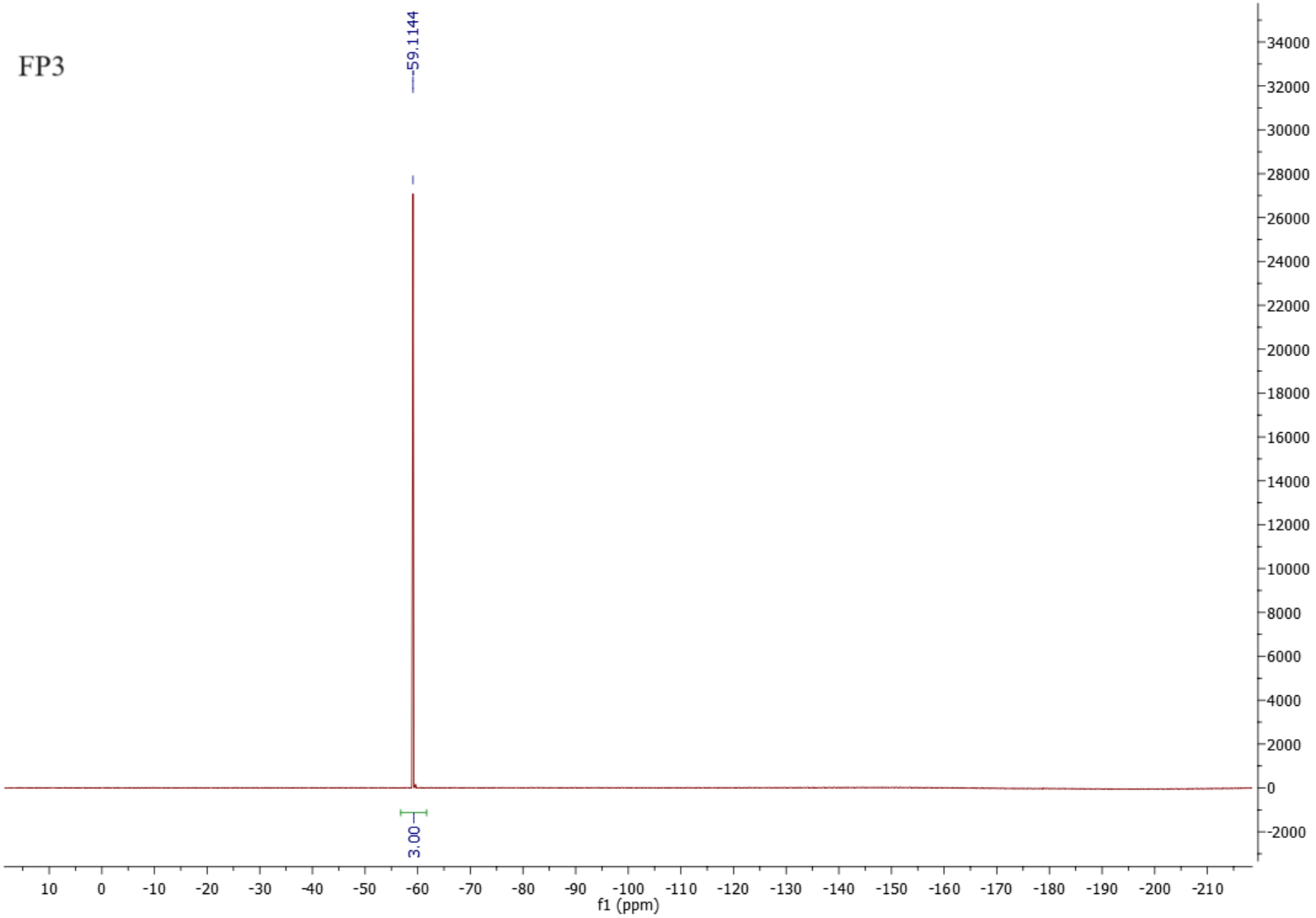

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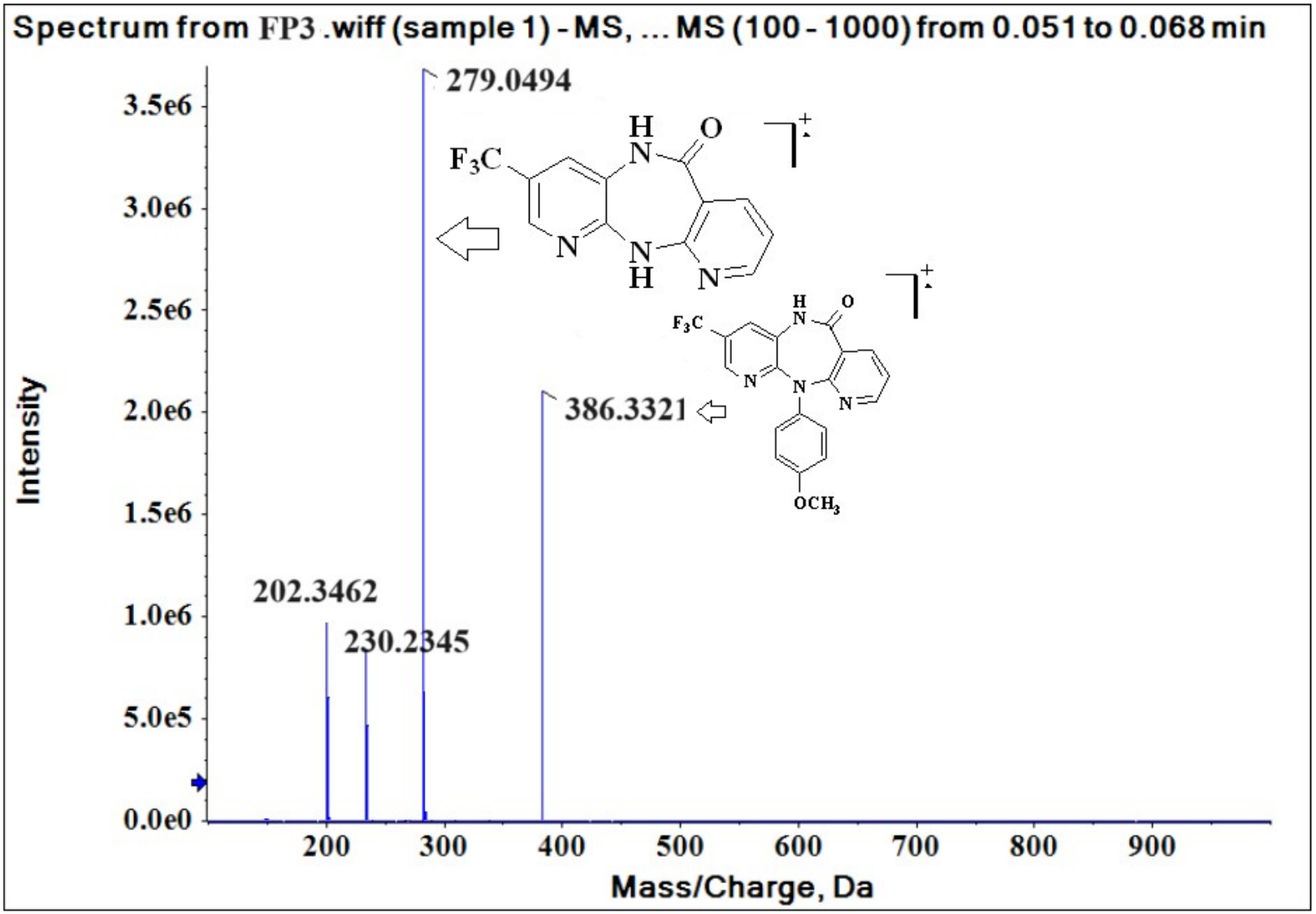

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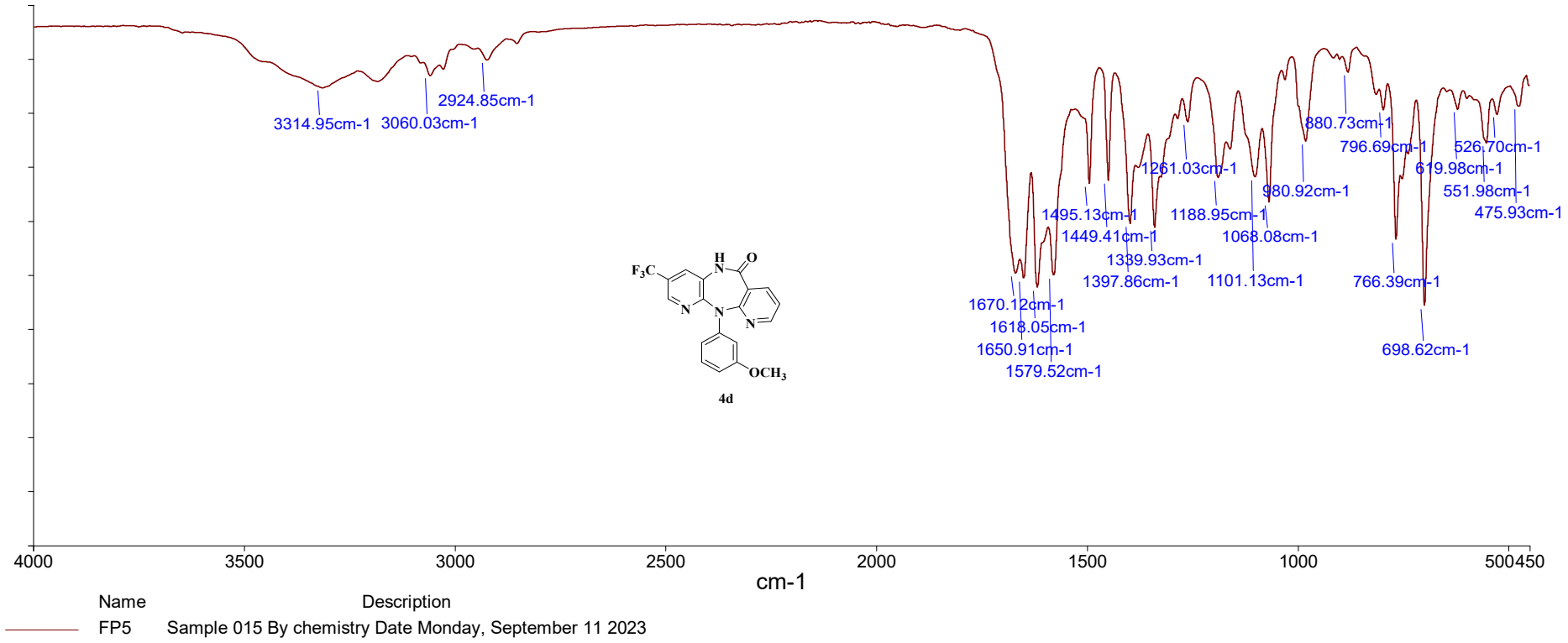

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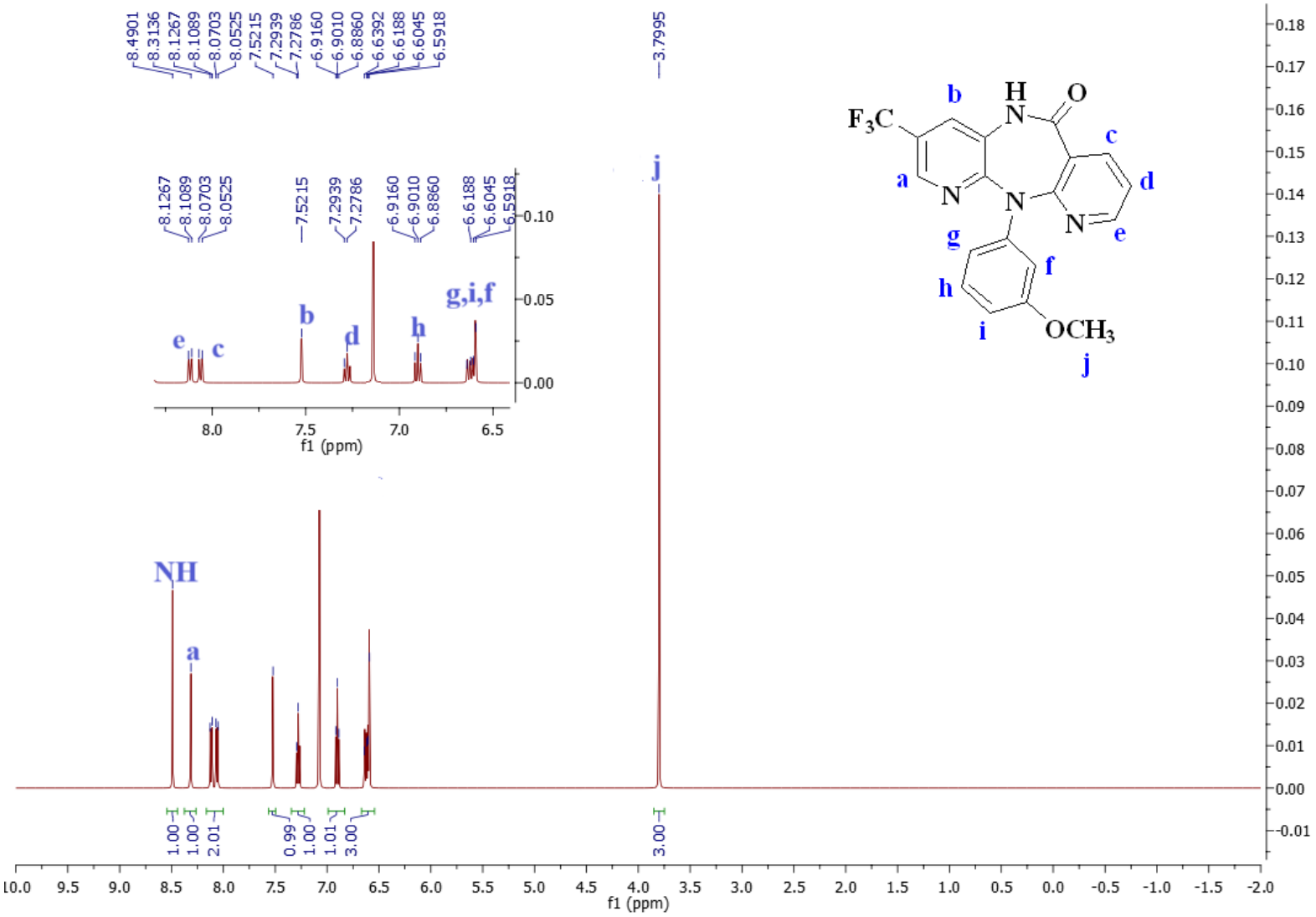

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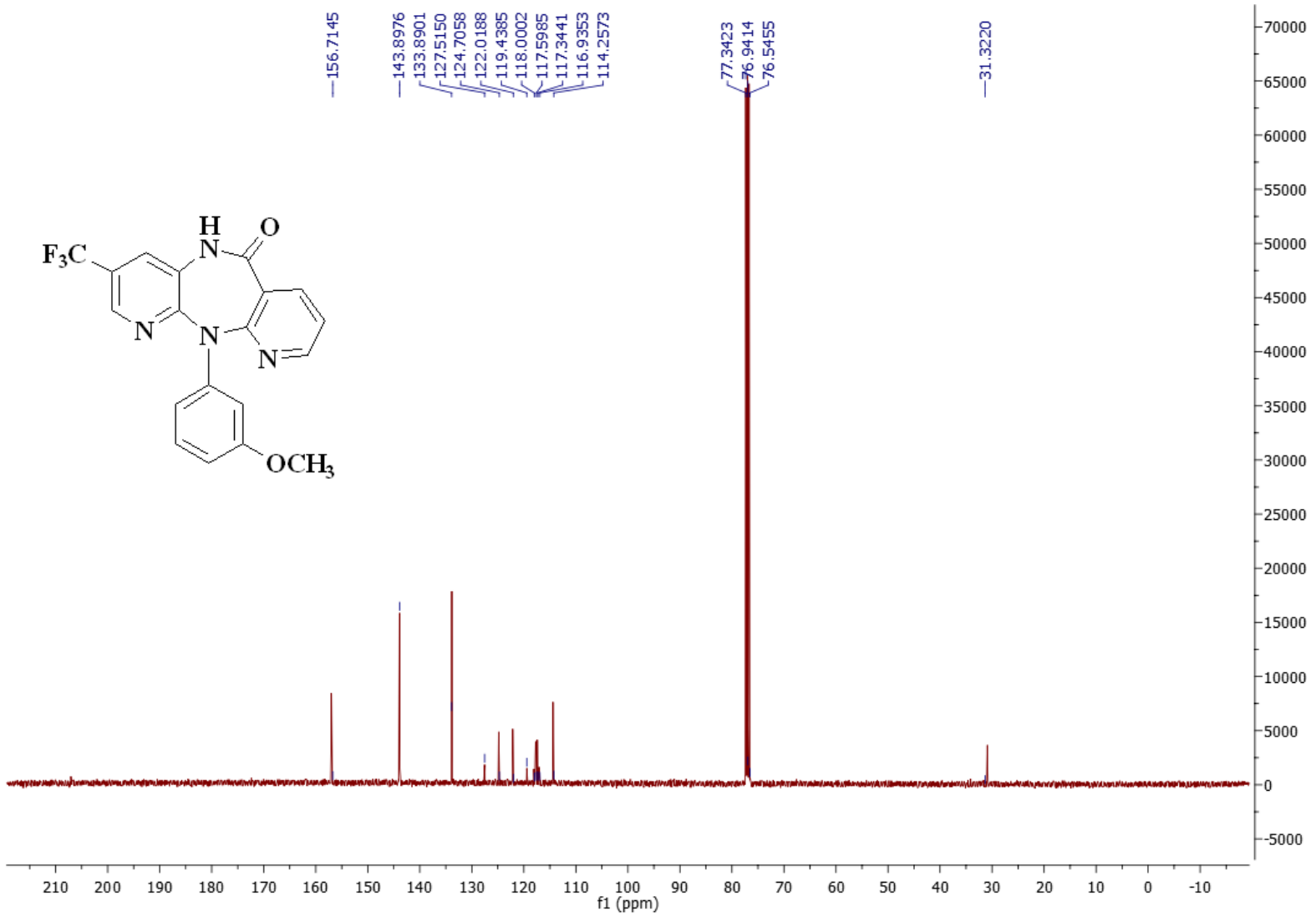

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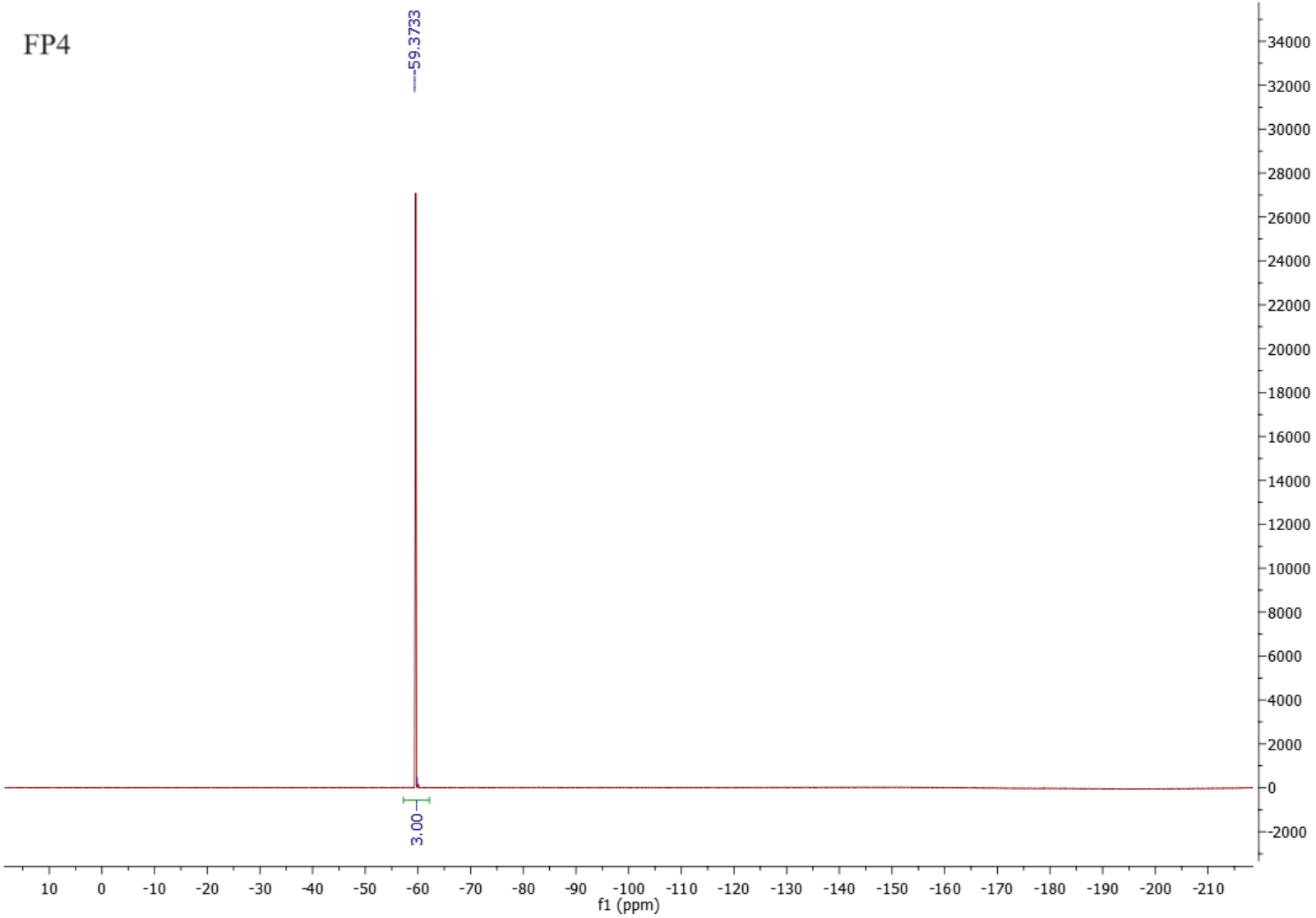

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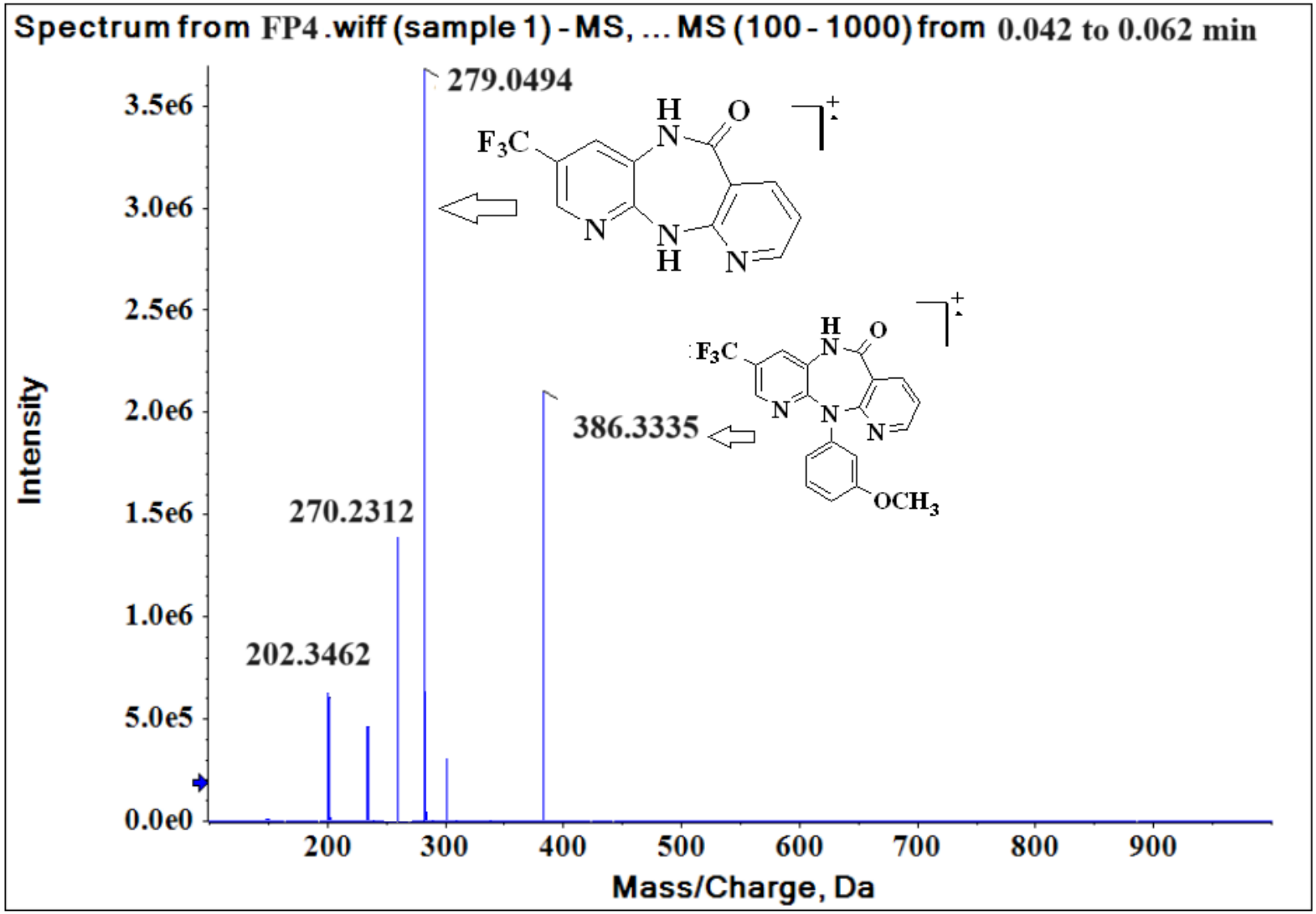

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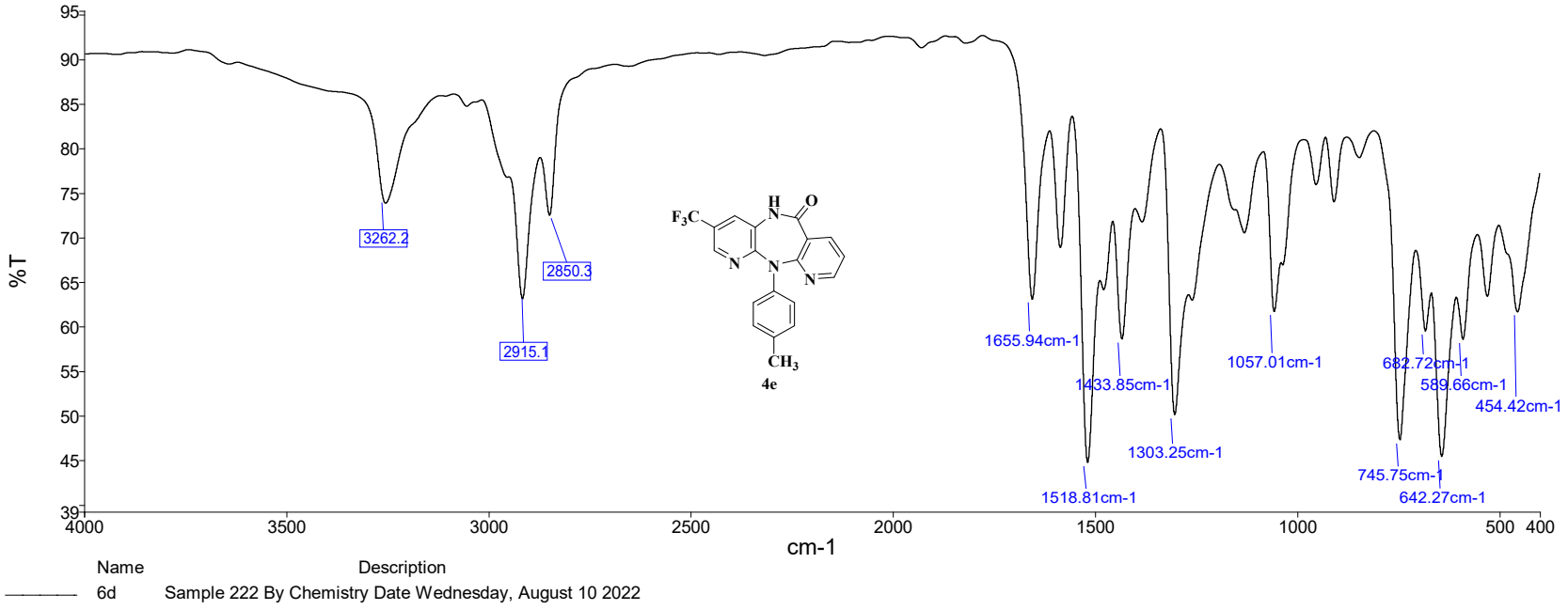

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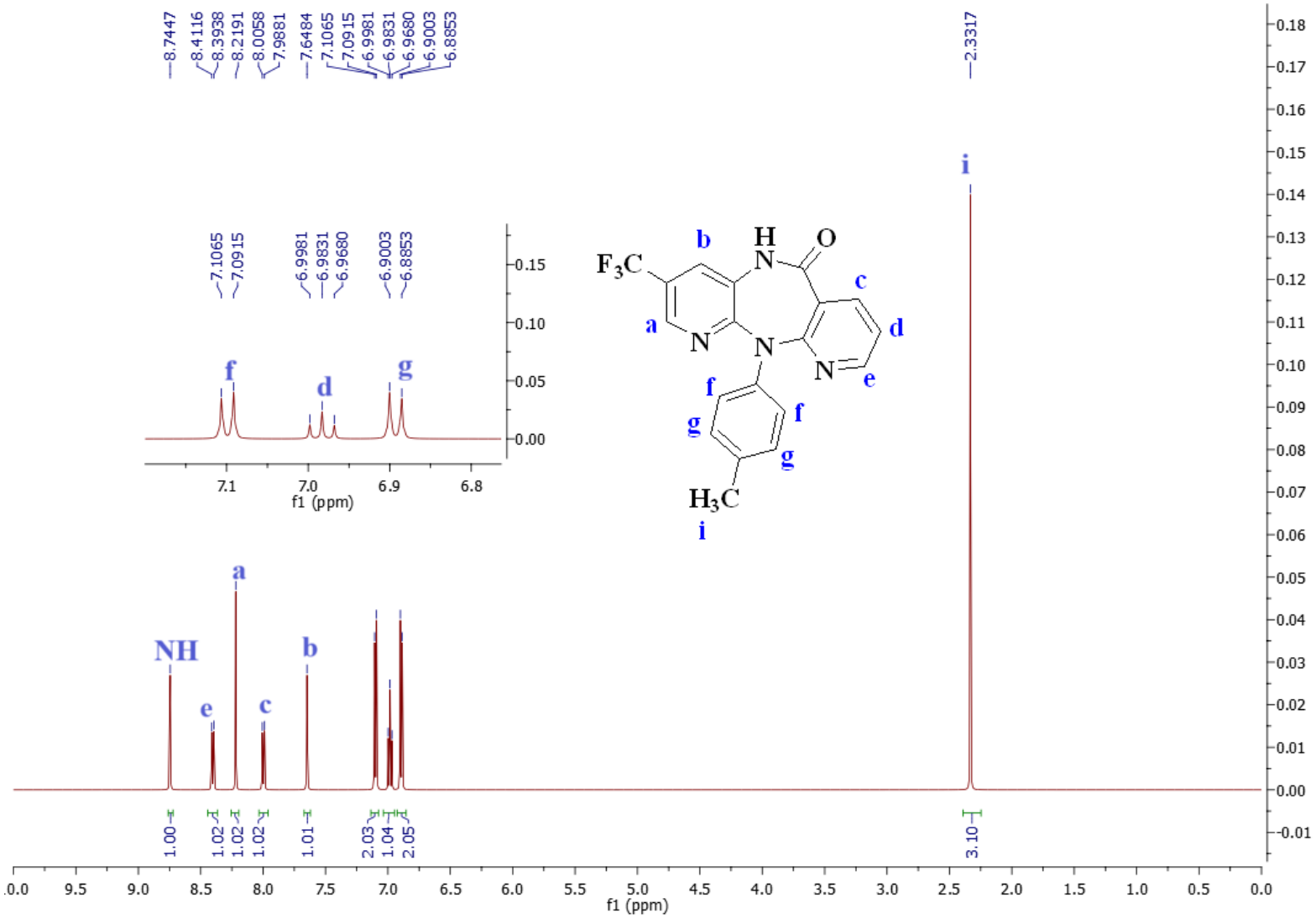

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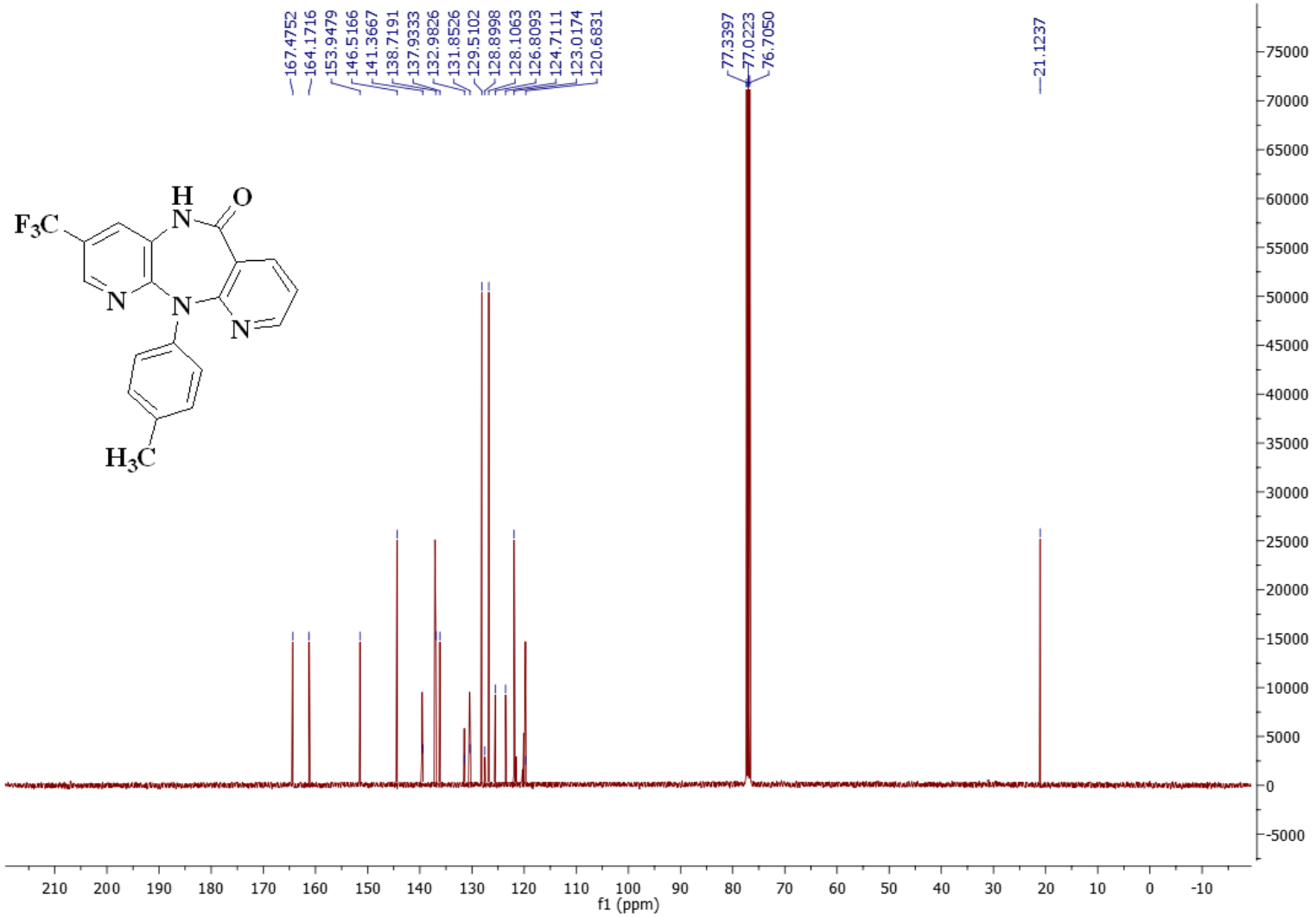

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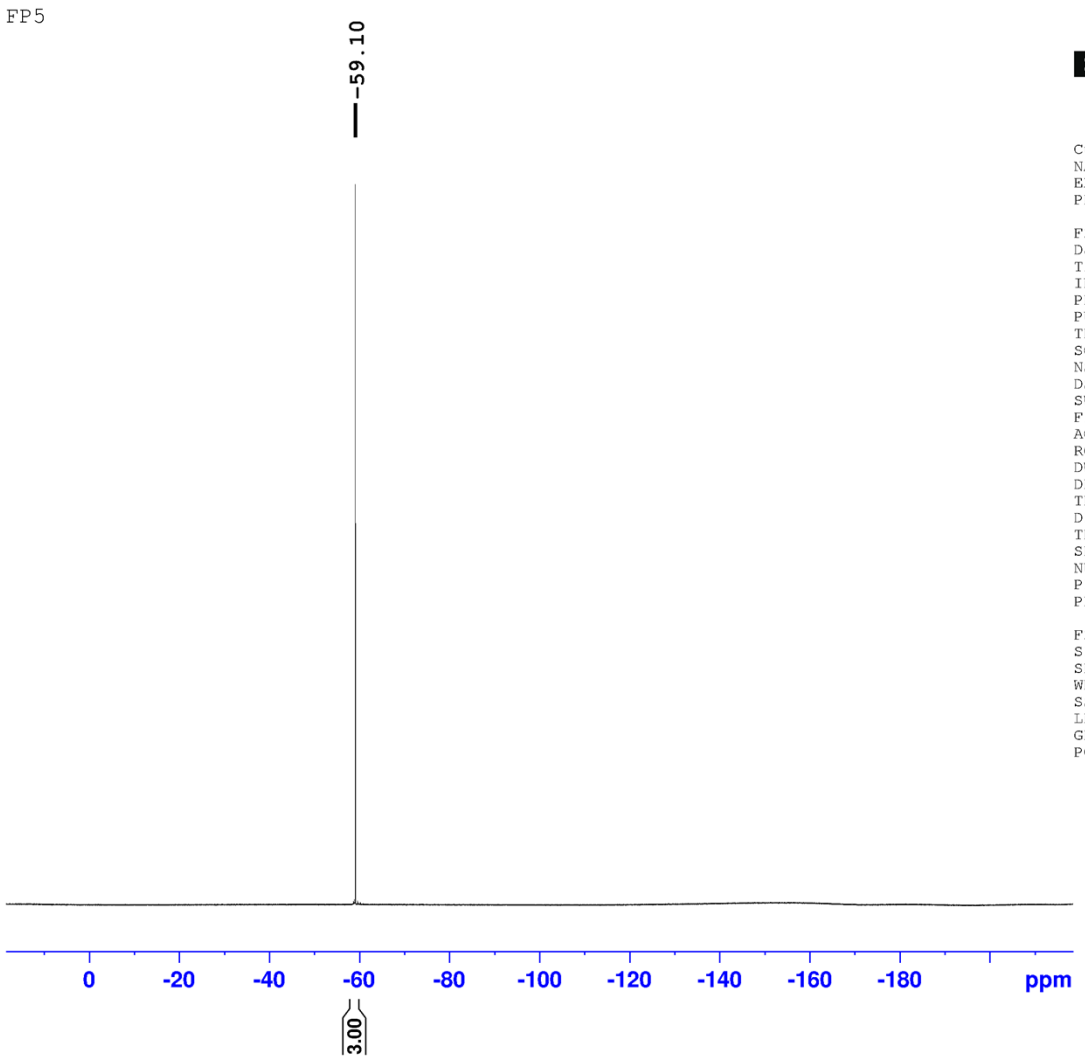


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DE                 6.50 usec
TE                298.0 K
D1             1.00000000 sec
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NUC1                 19F
P1                15.00 usec
PLW1         17.00000000 W

F2 - Processing parameters
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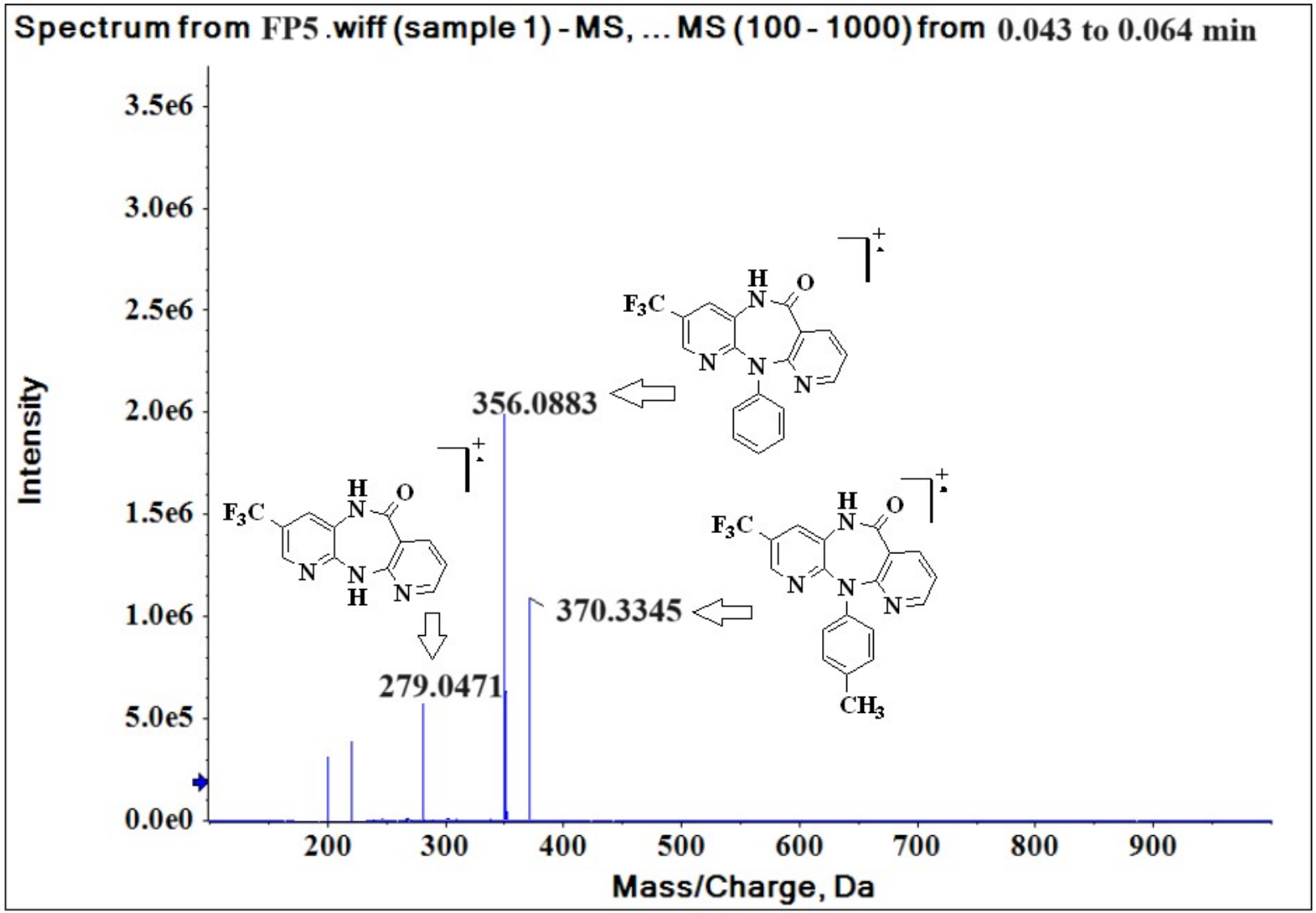

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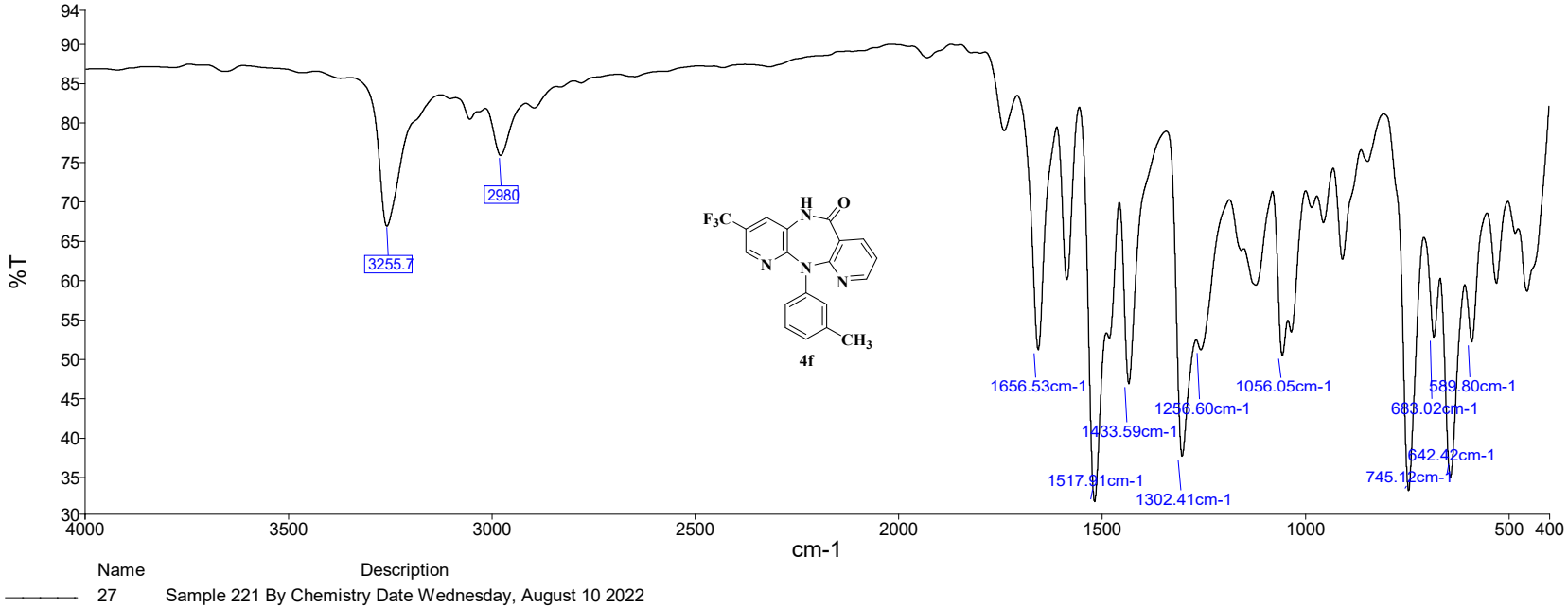

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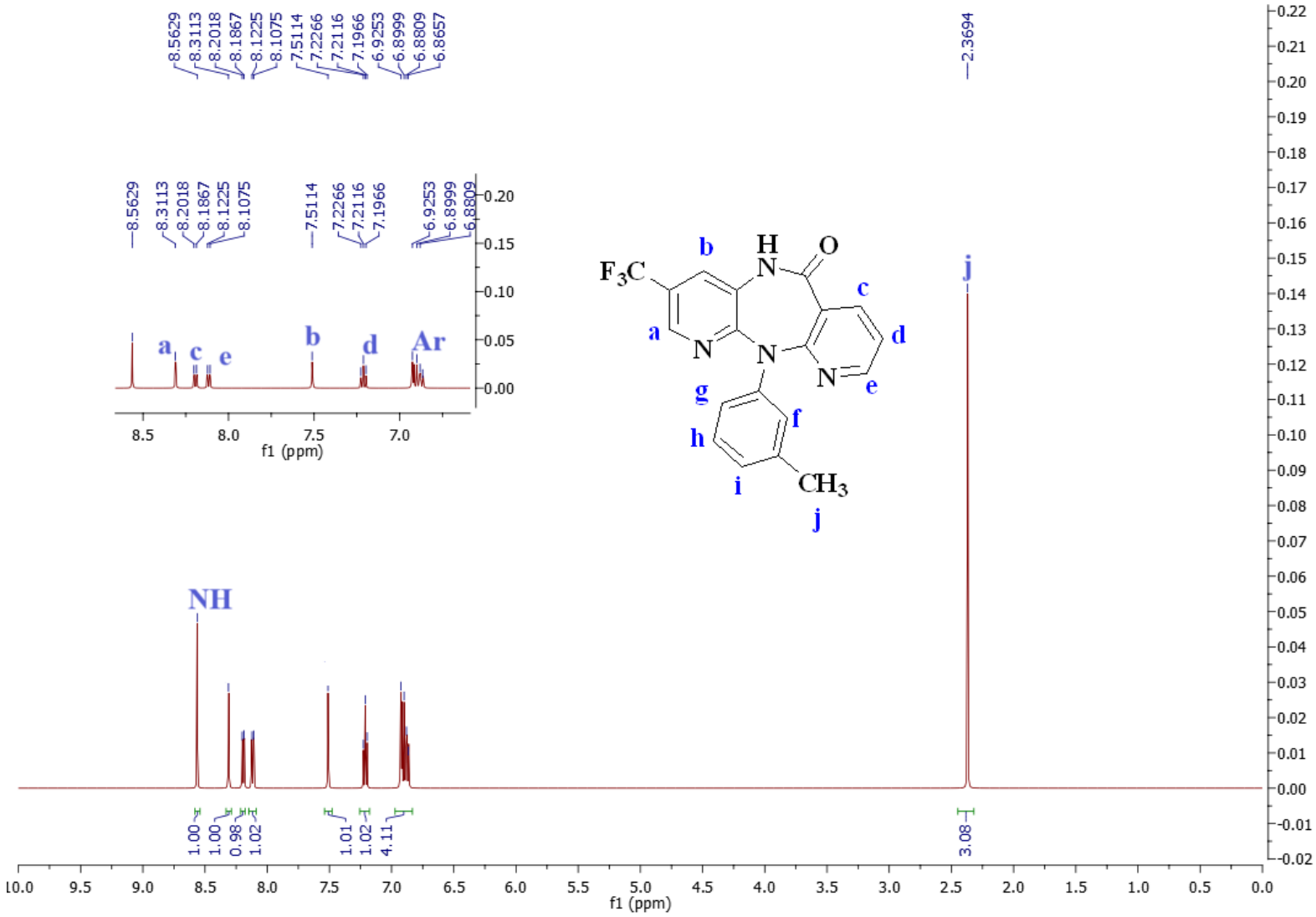

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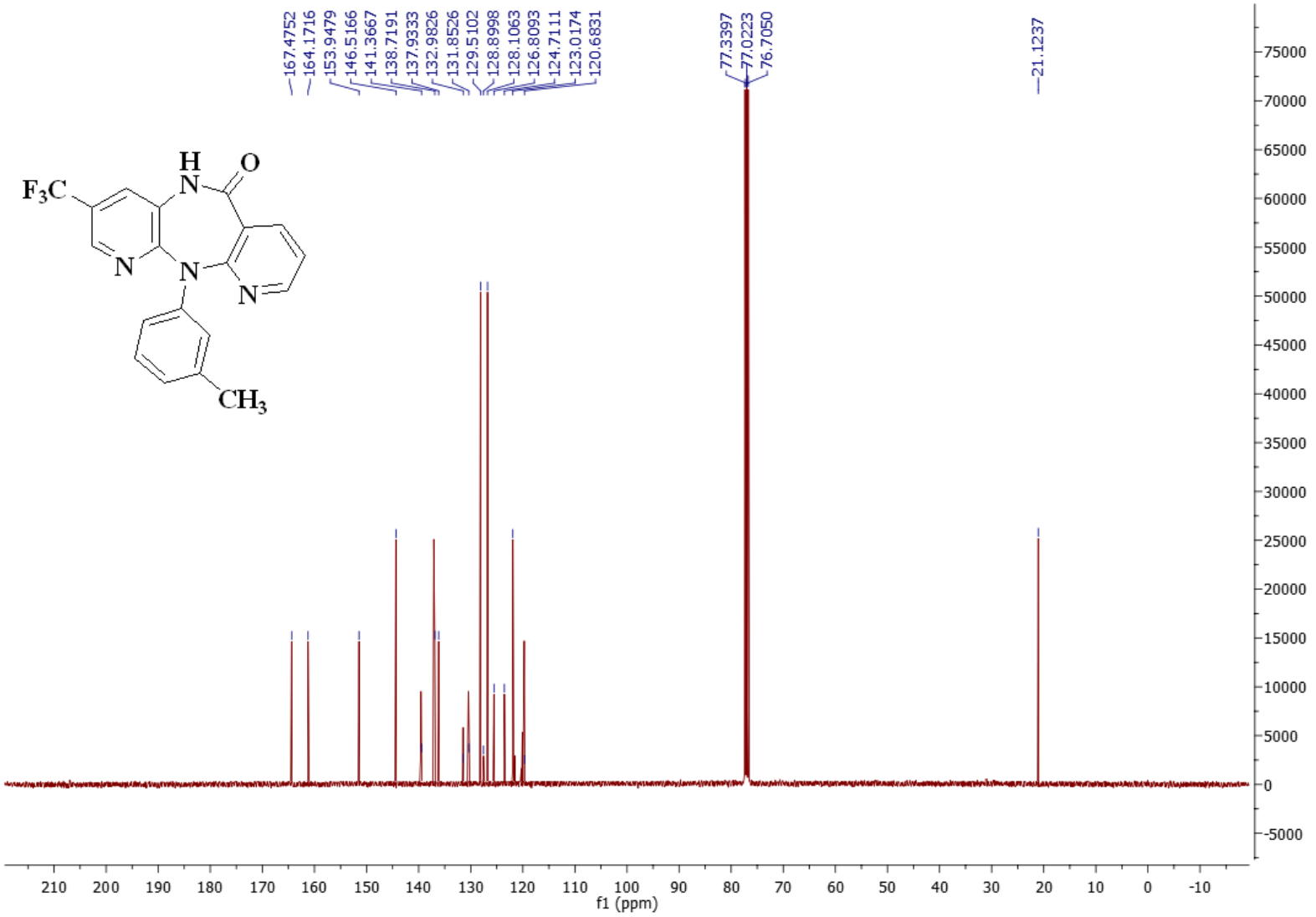

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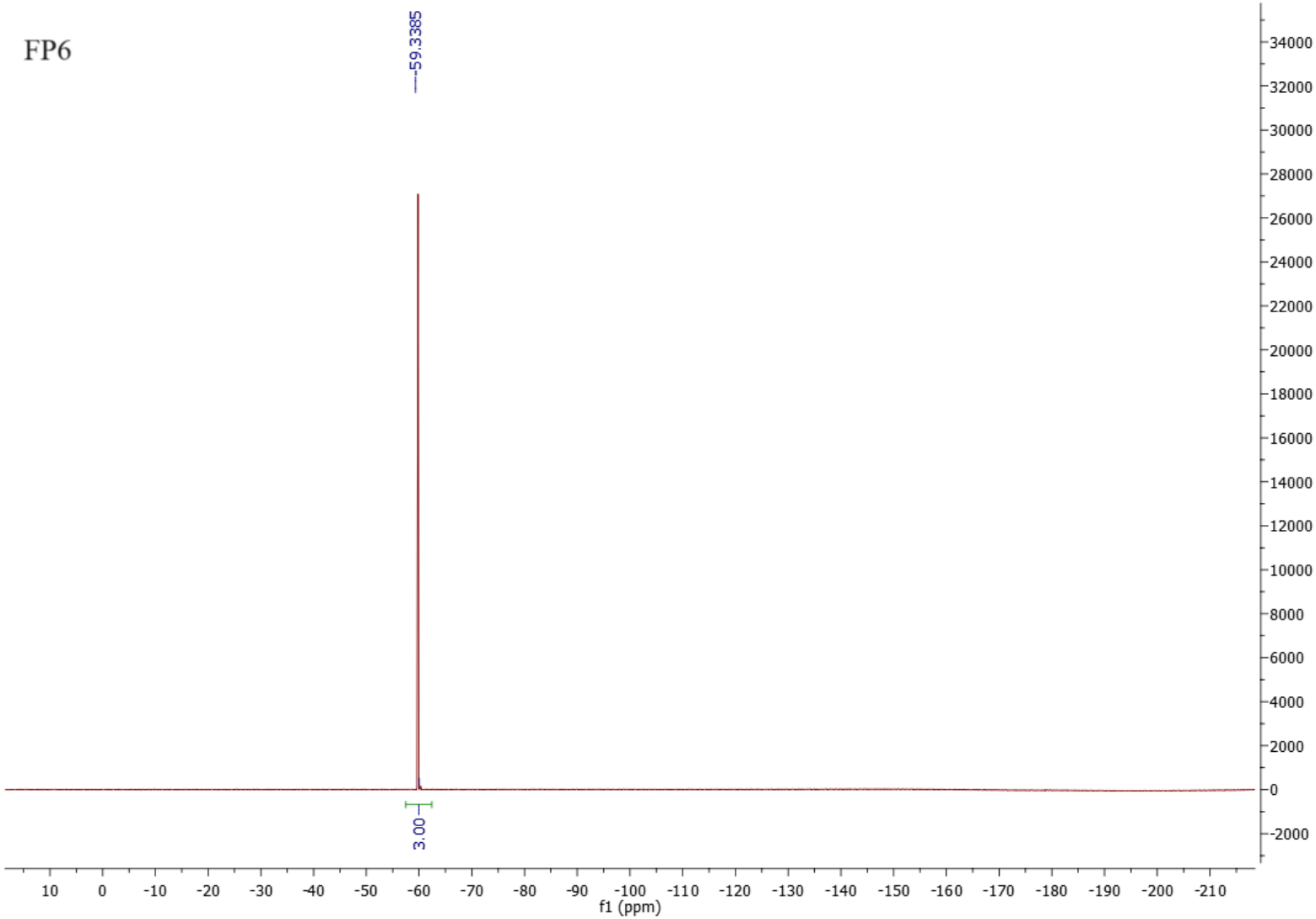

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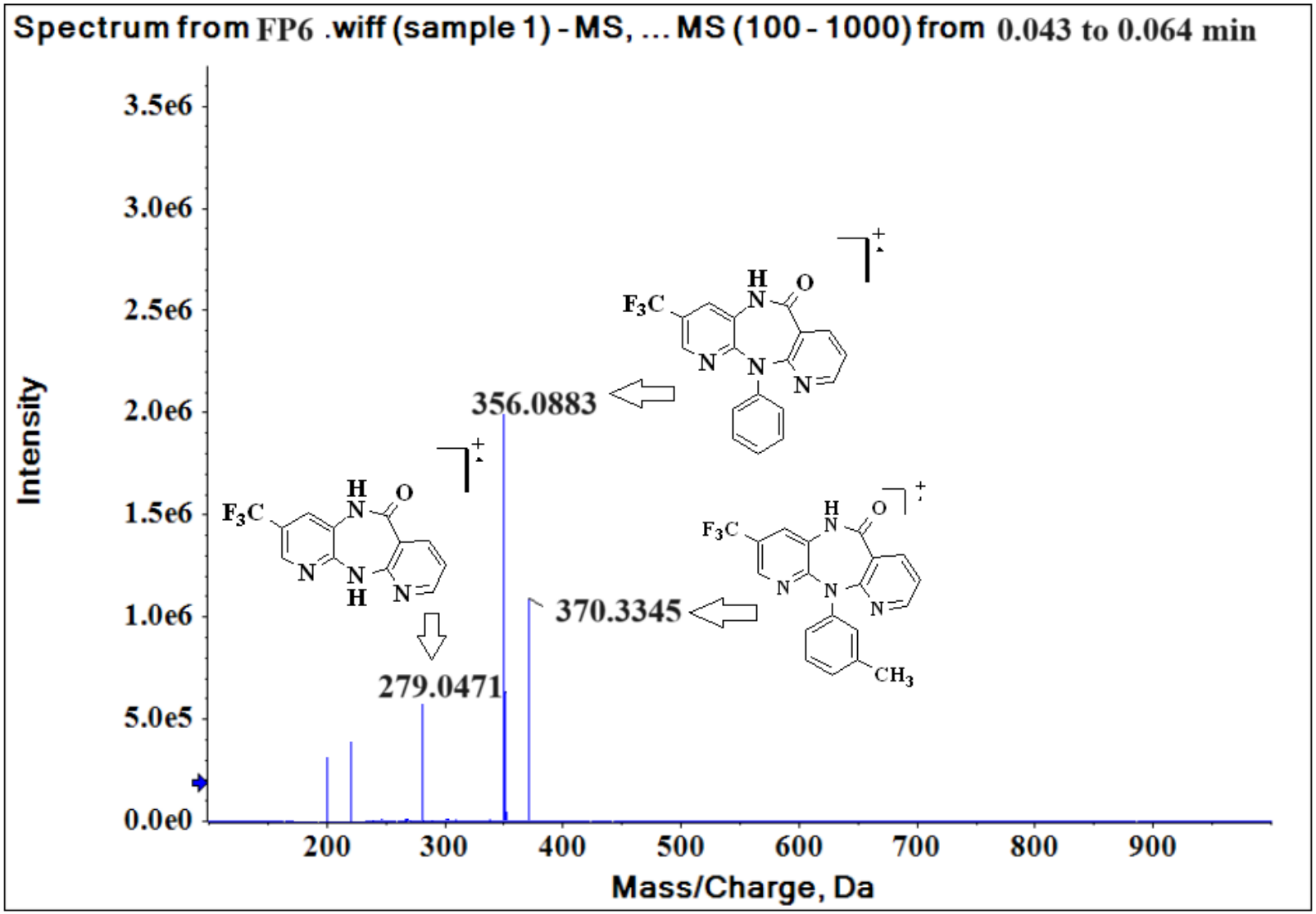

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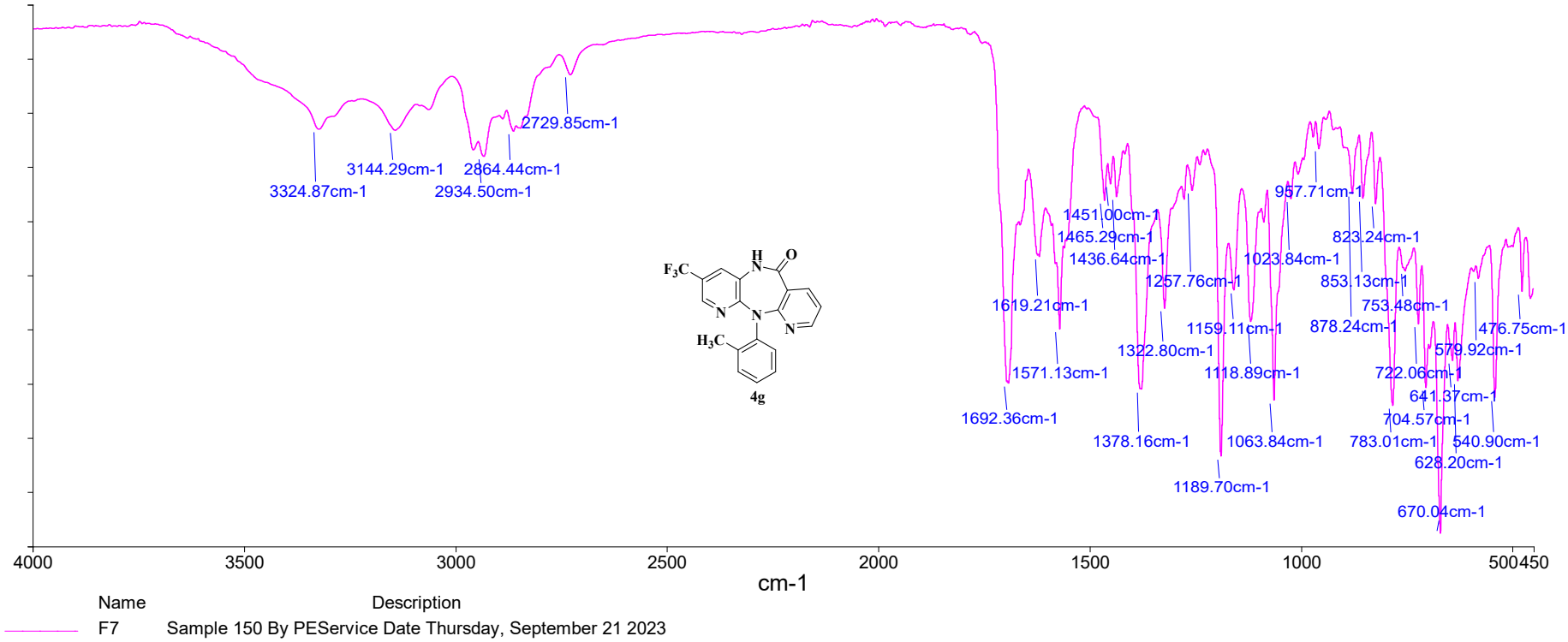

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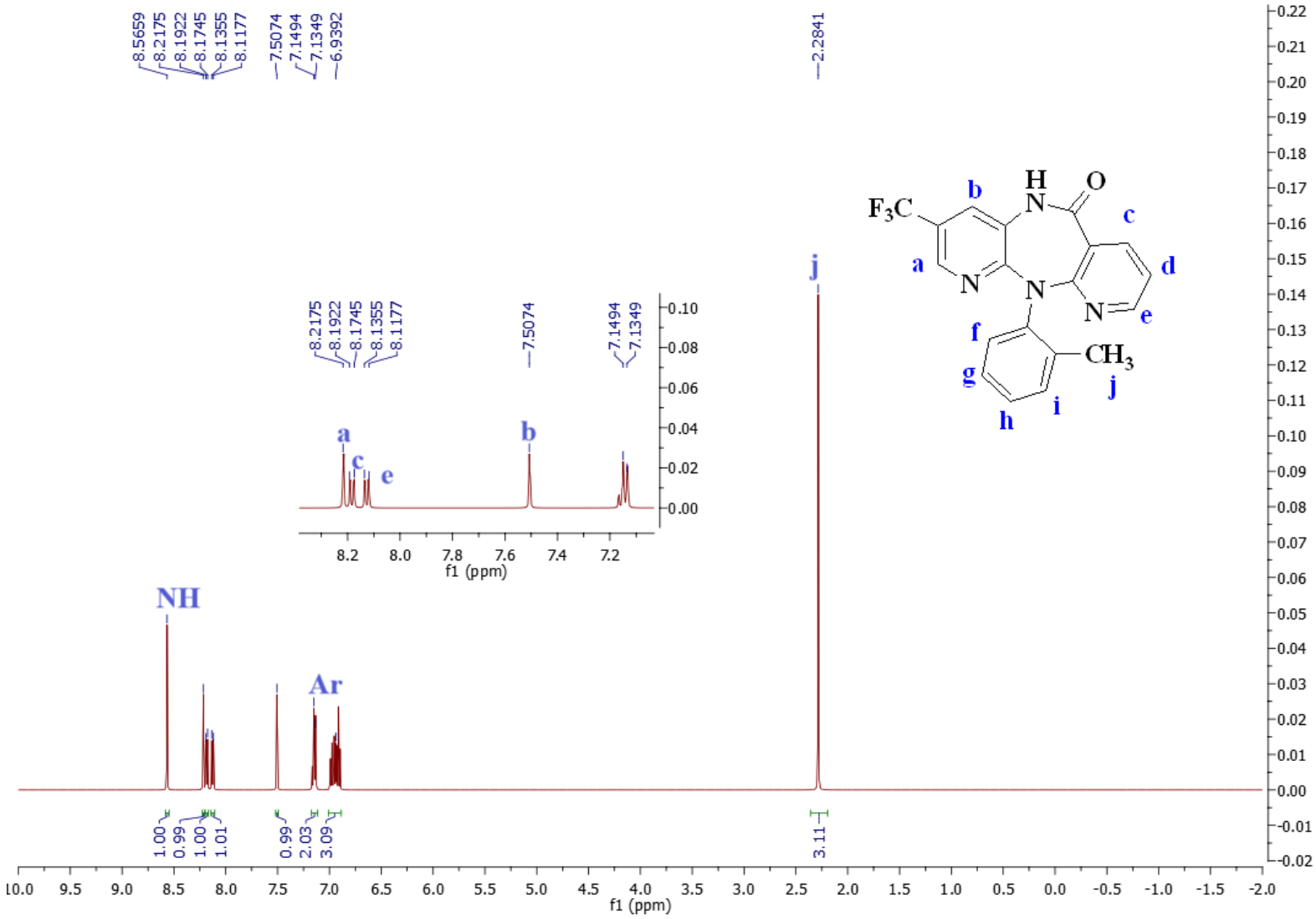

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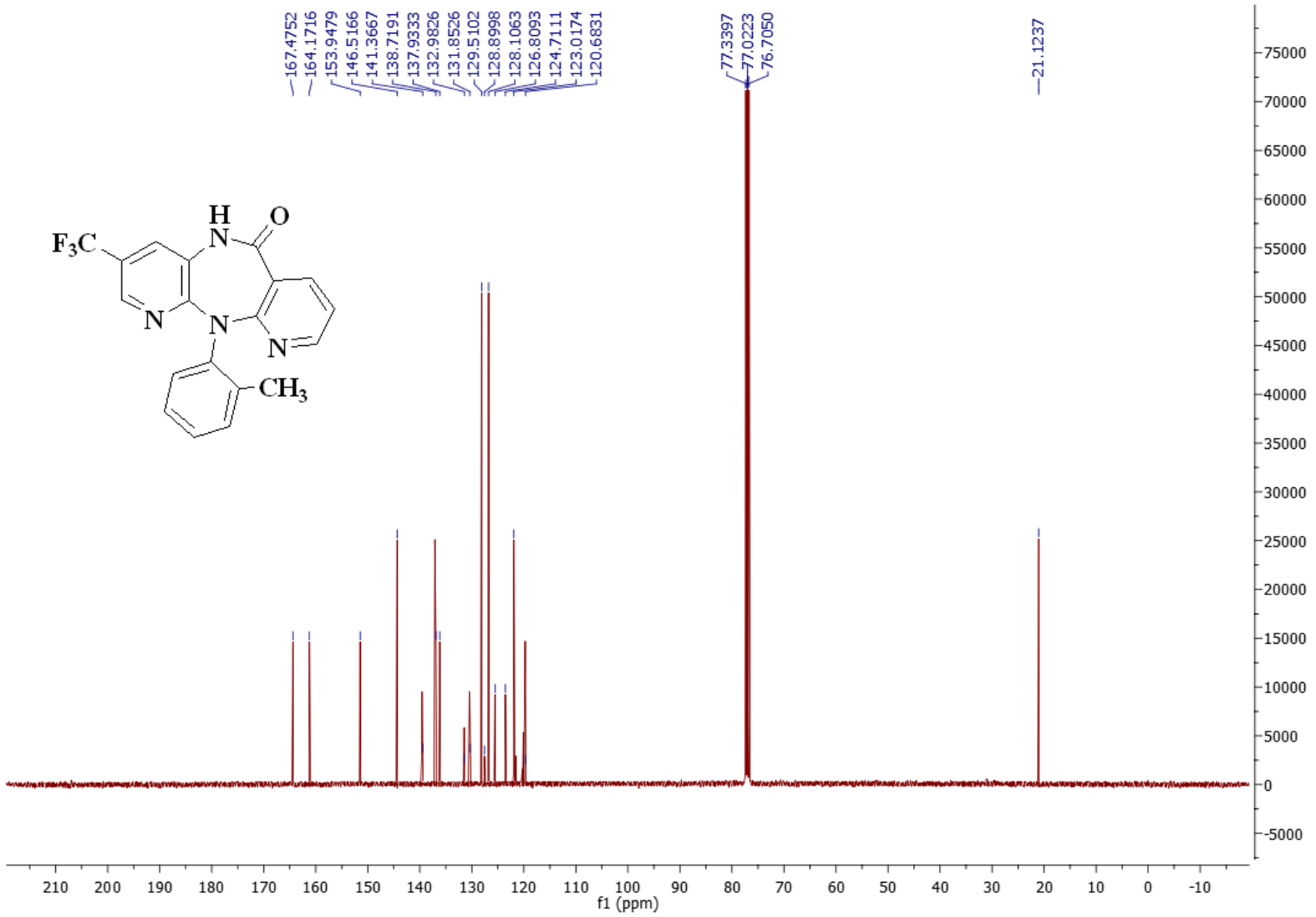

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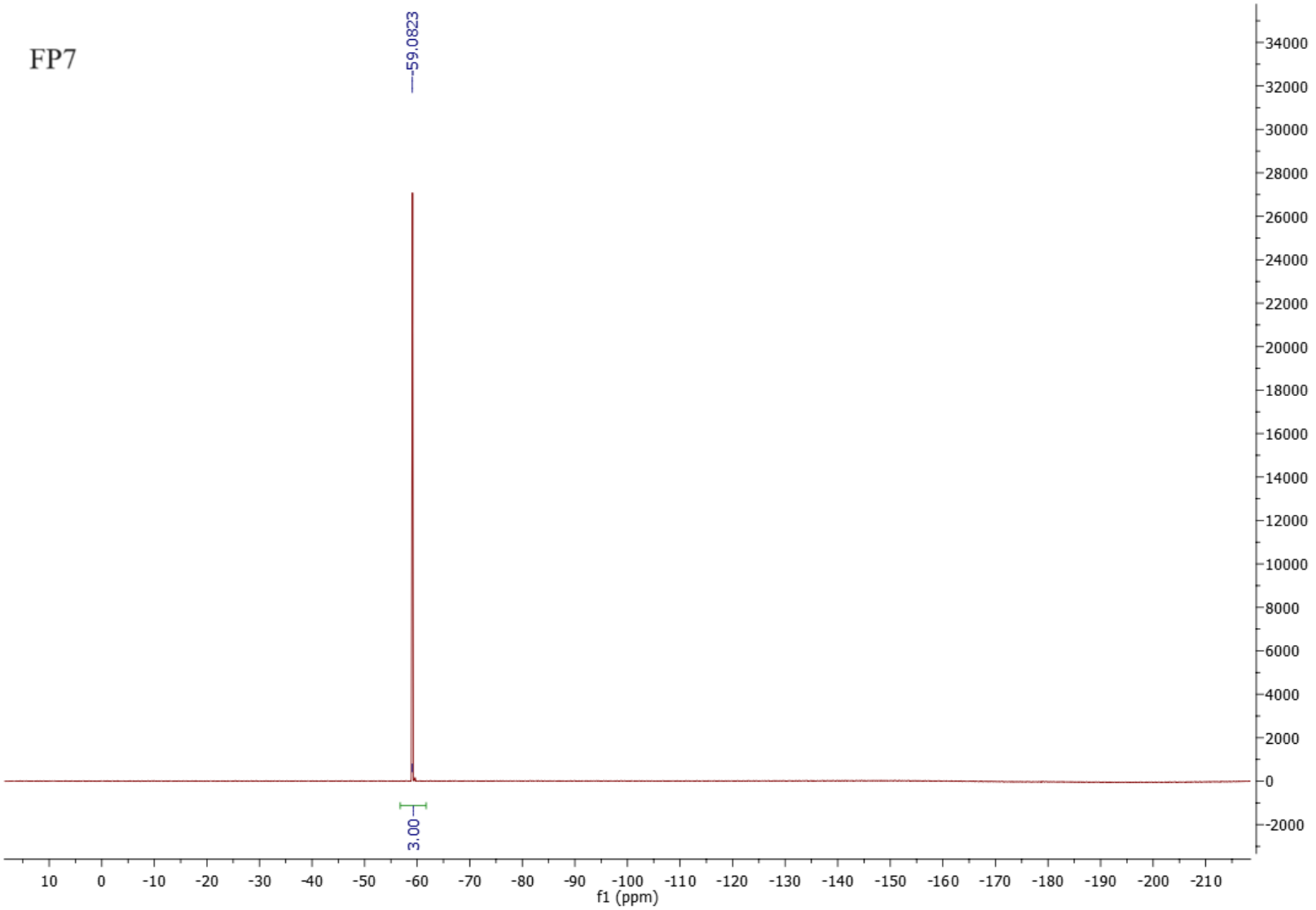

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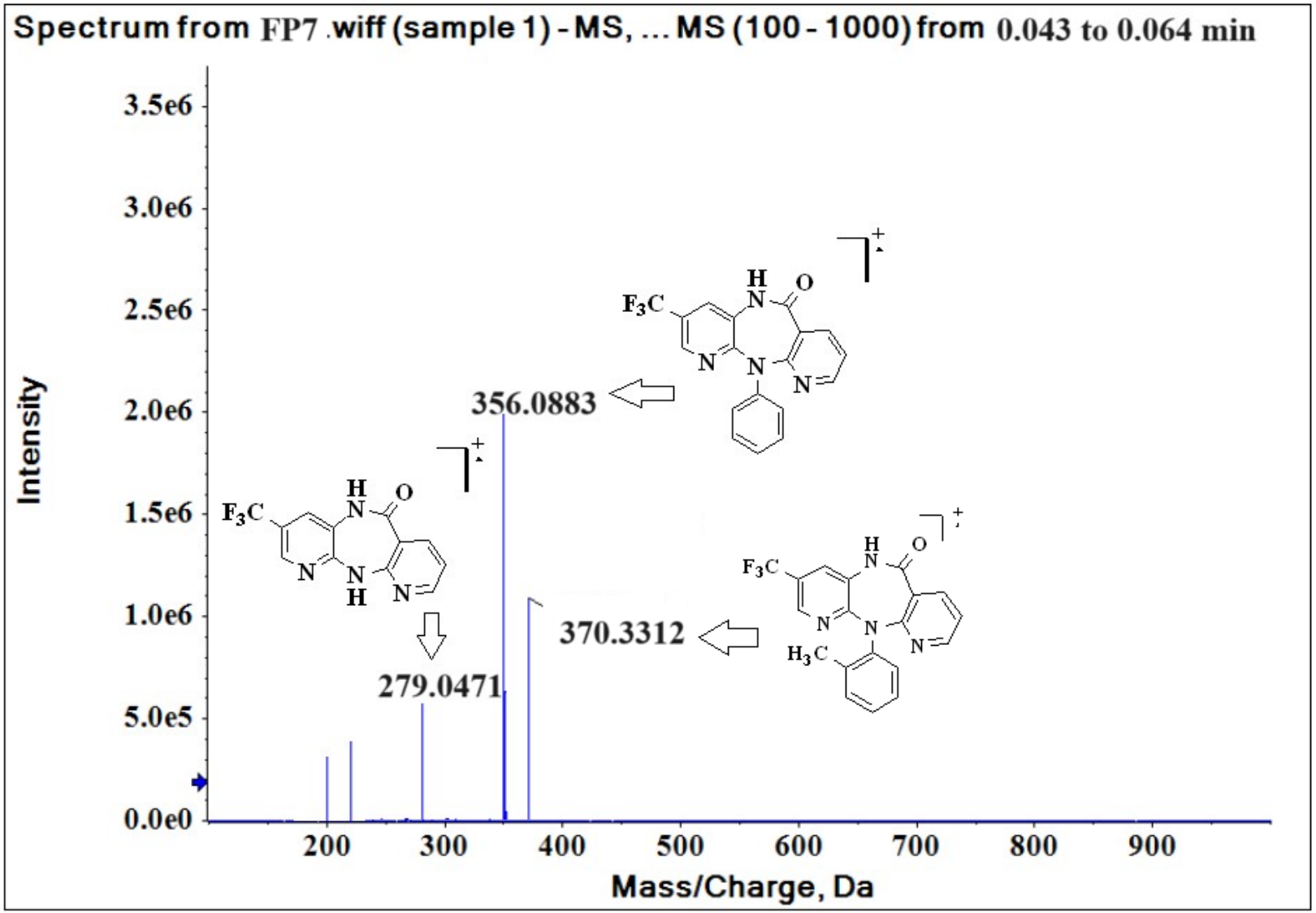

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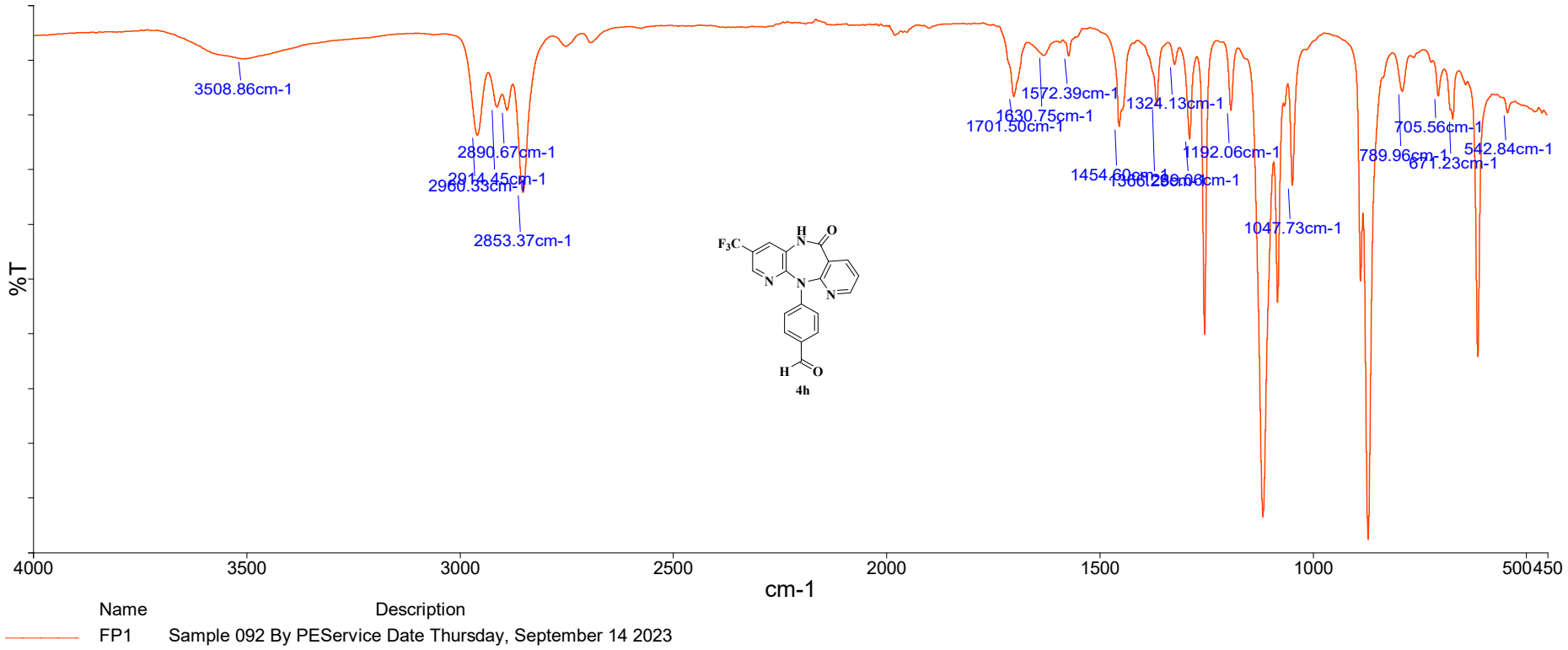

4h

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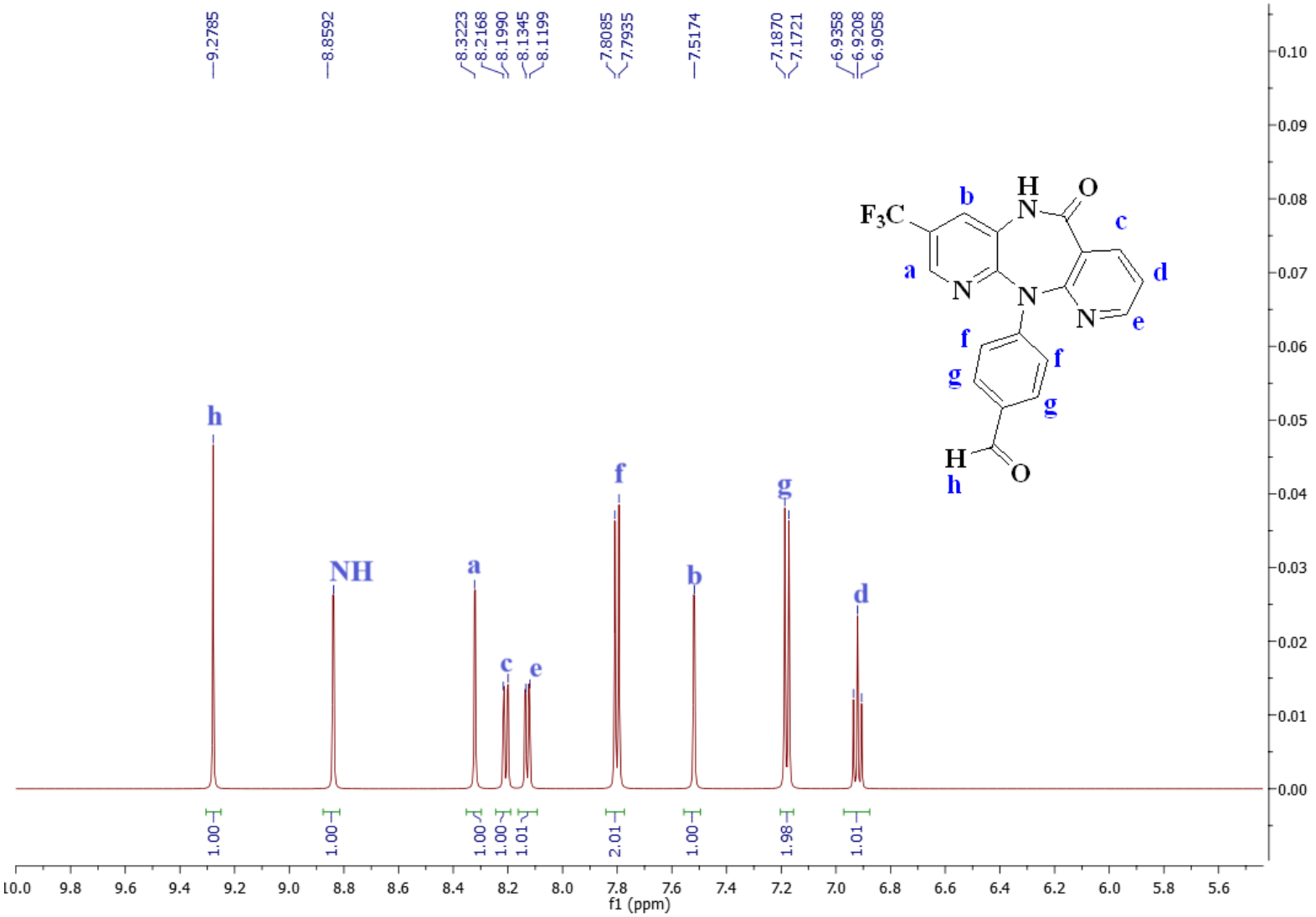
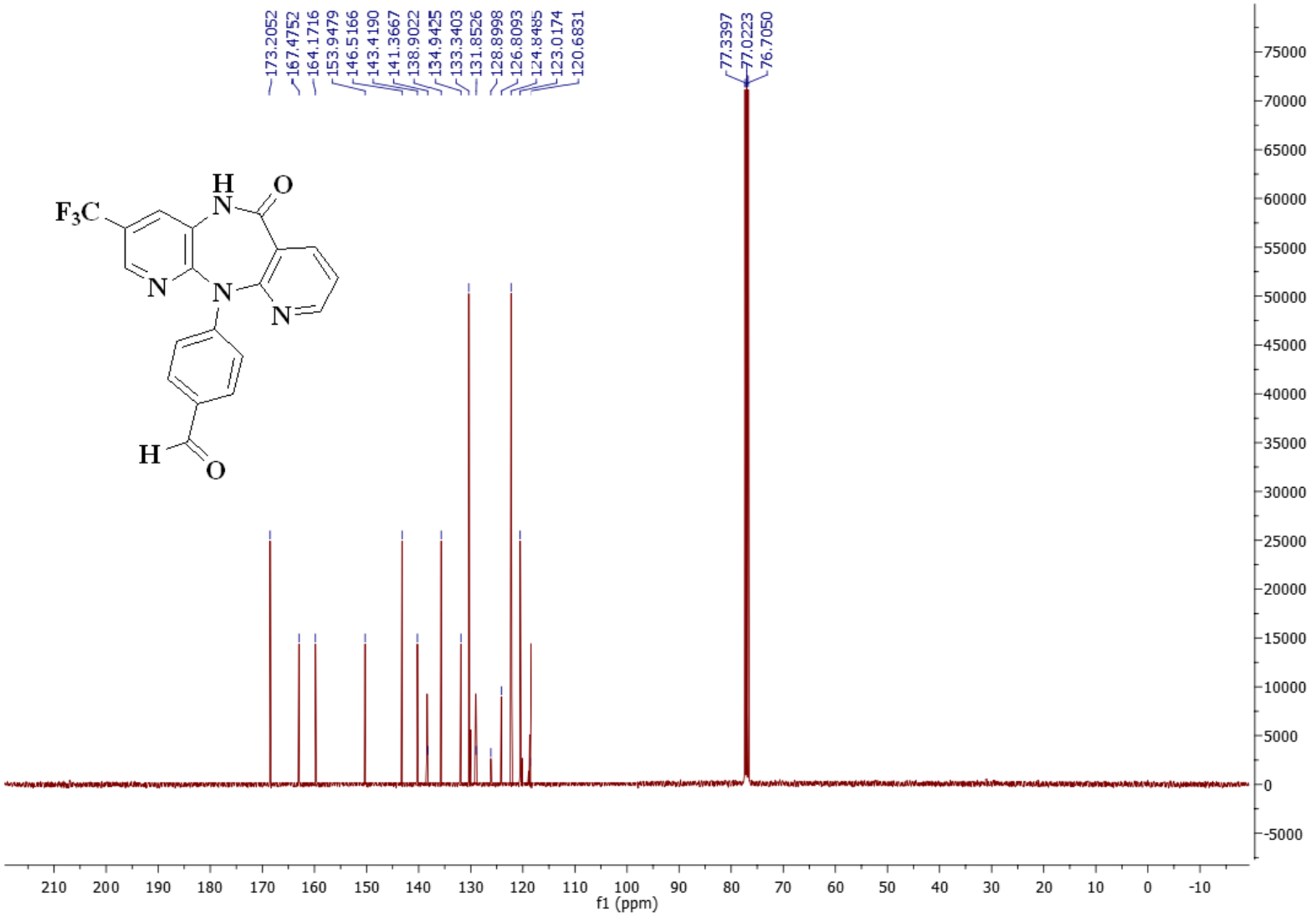


S37: ^{1}H NMR of **5h**



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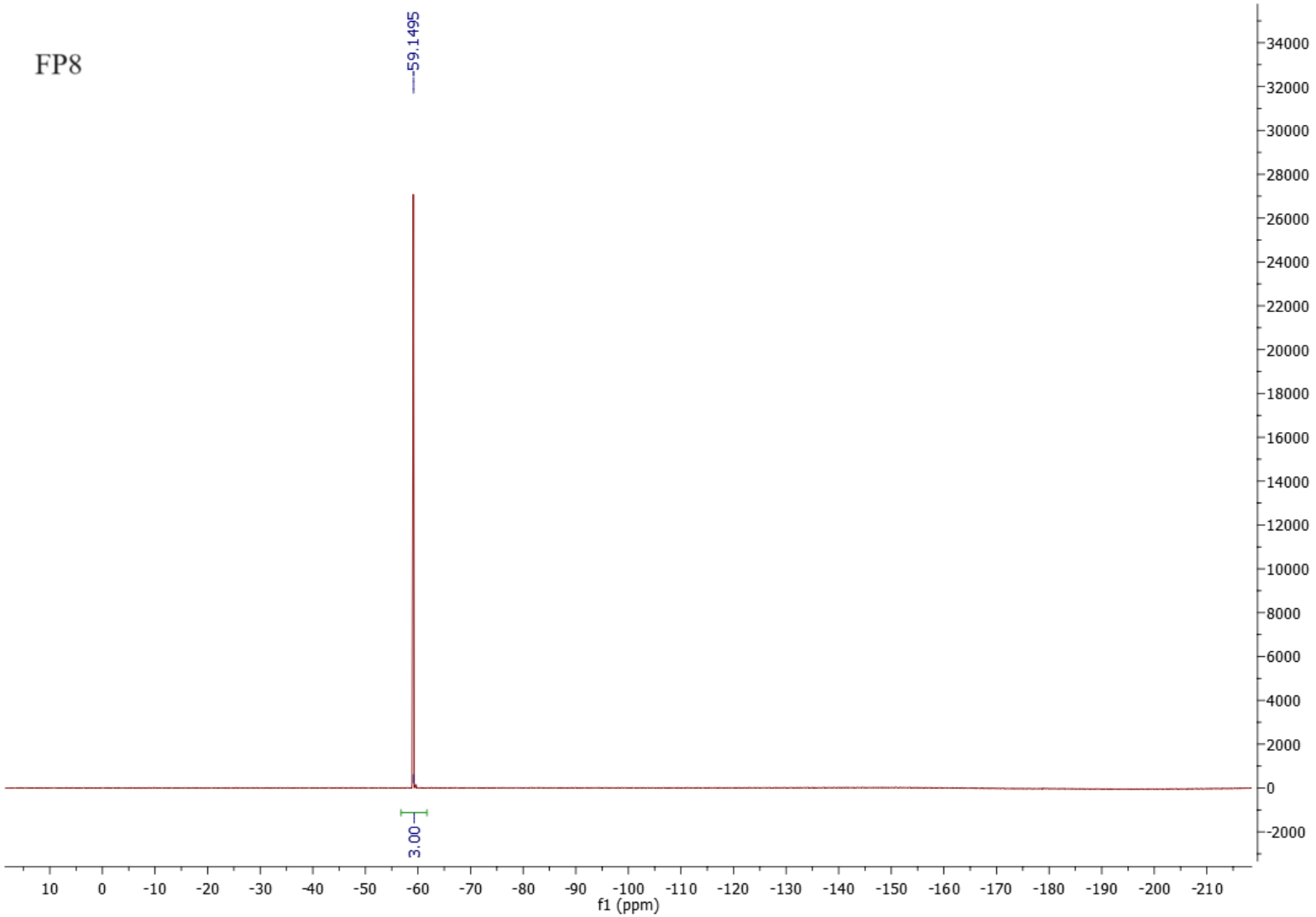

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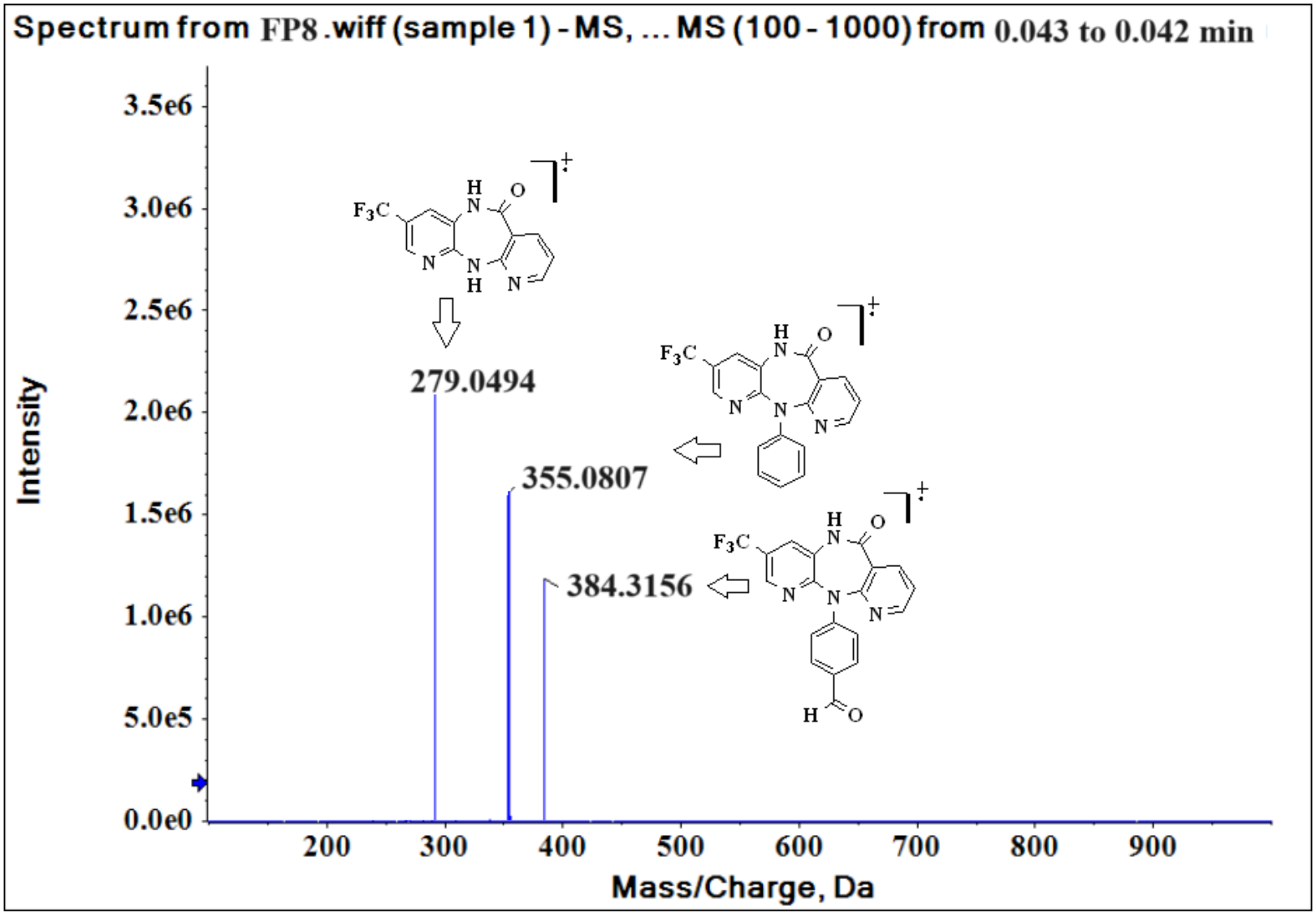

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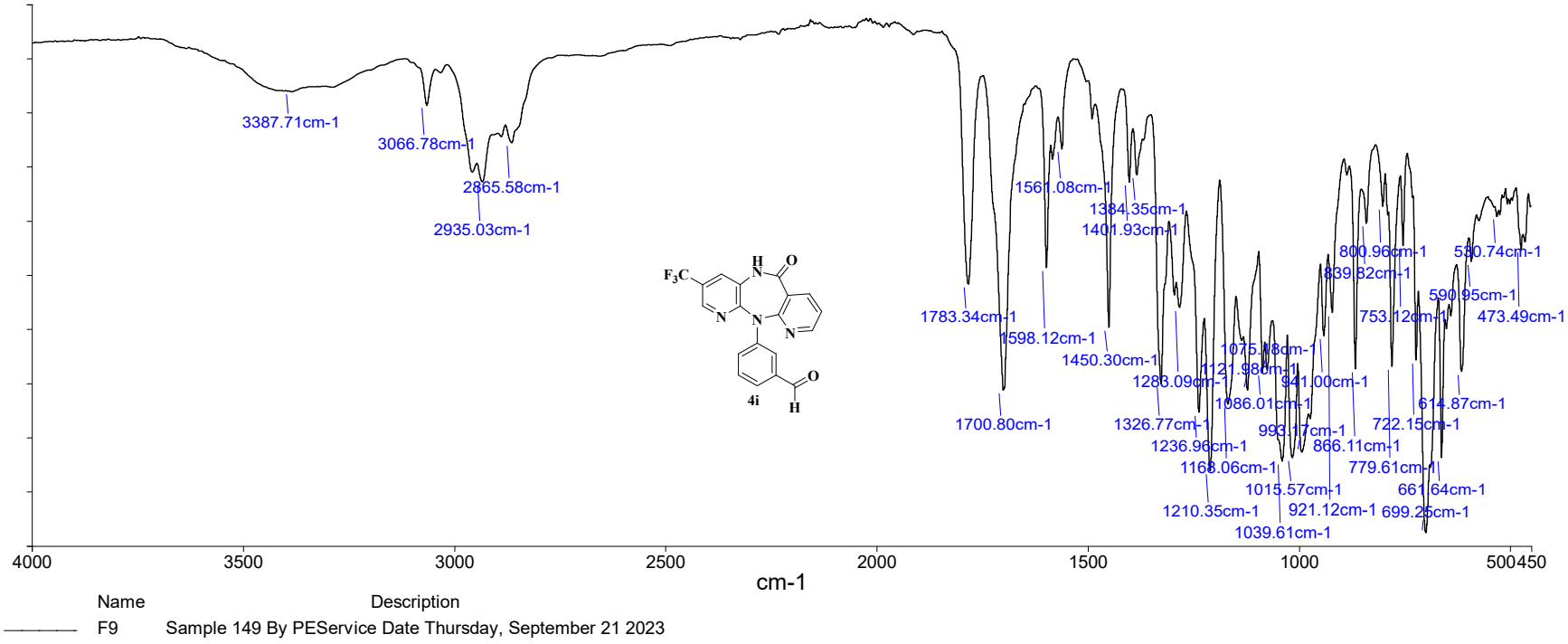

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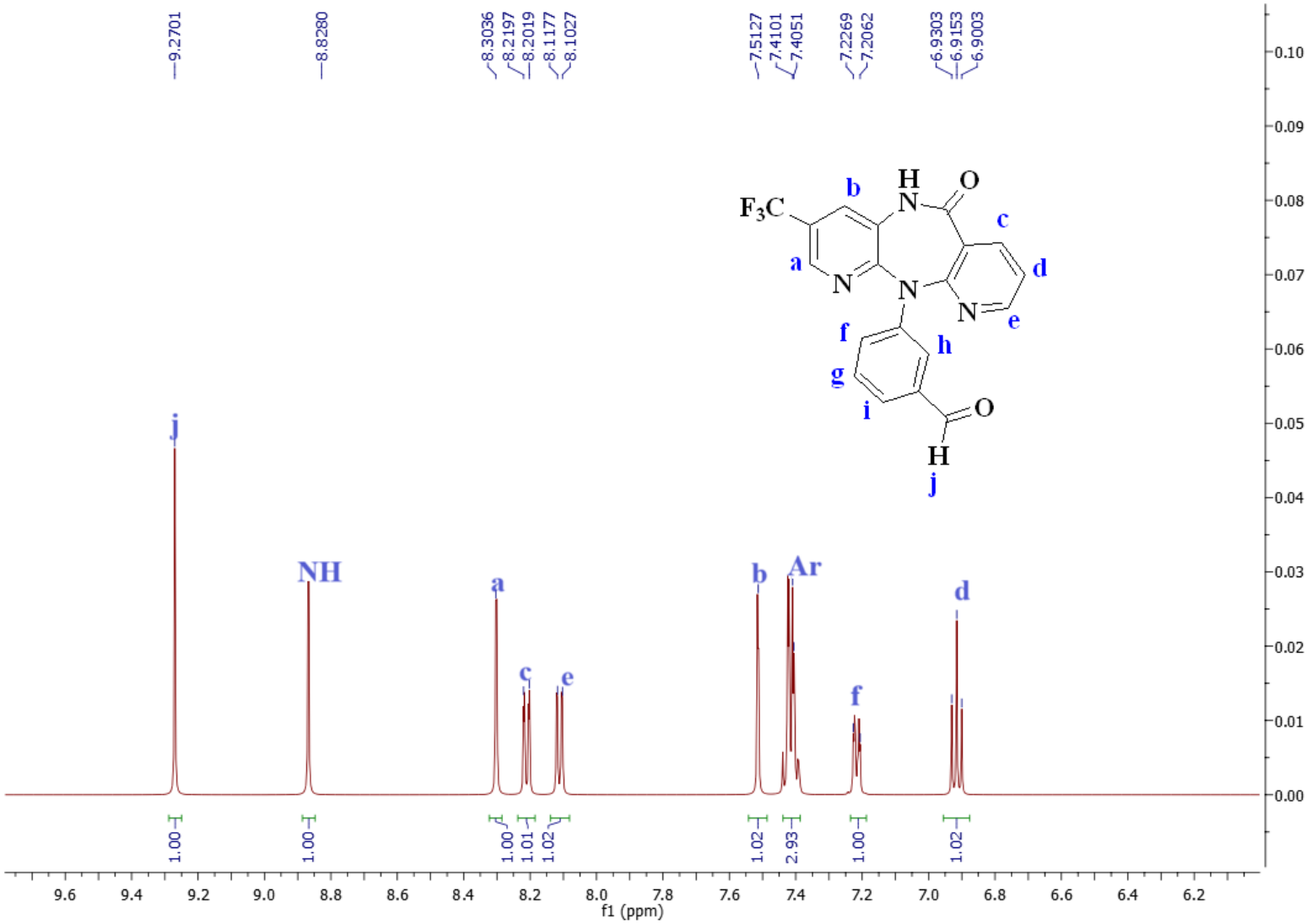

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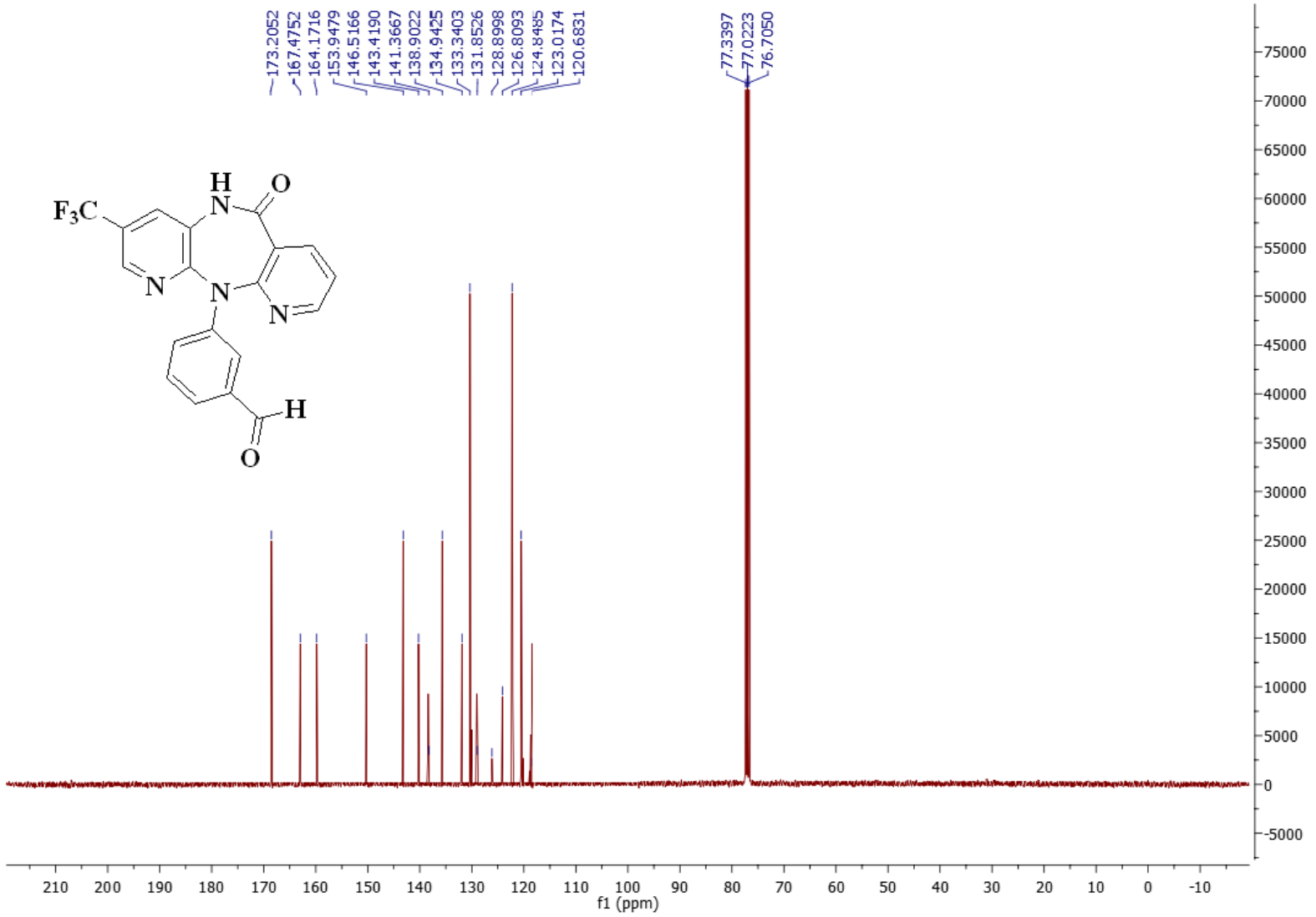

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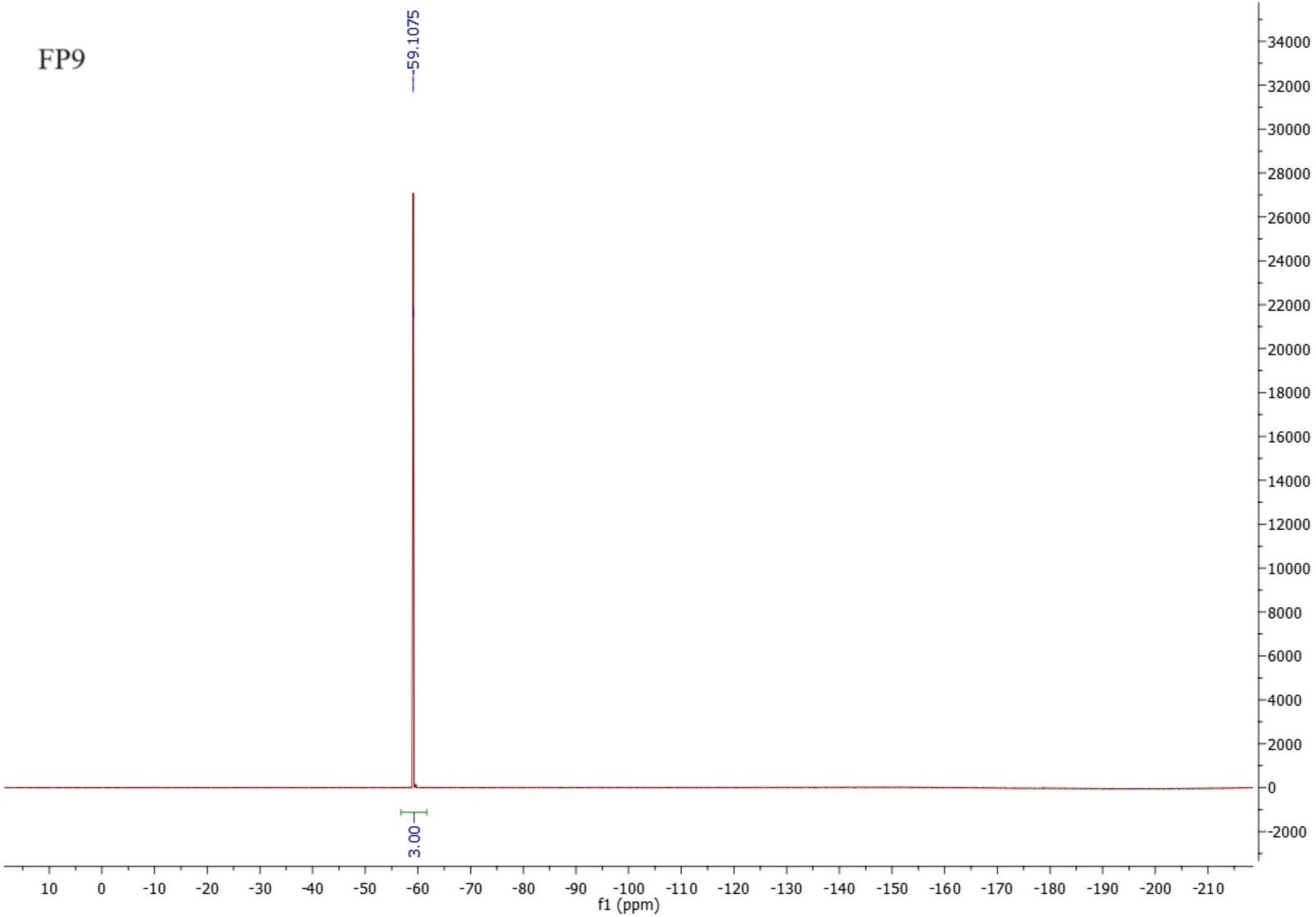

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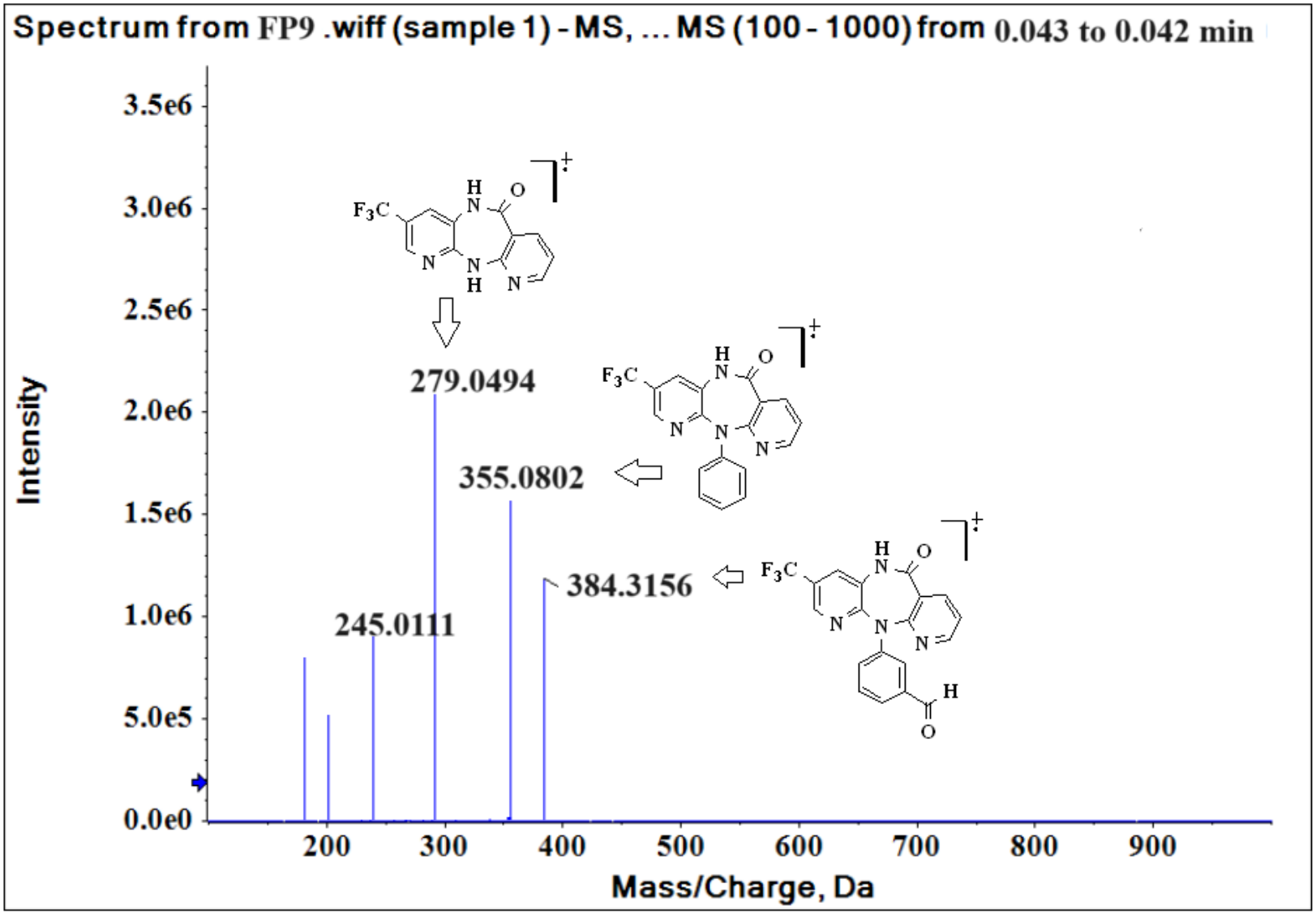

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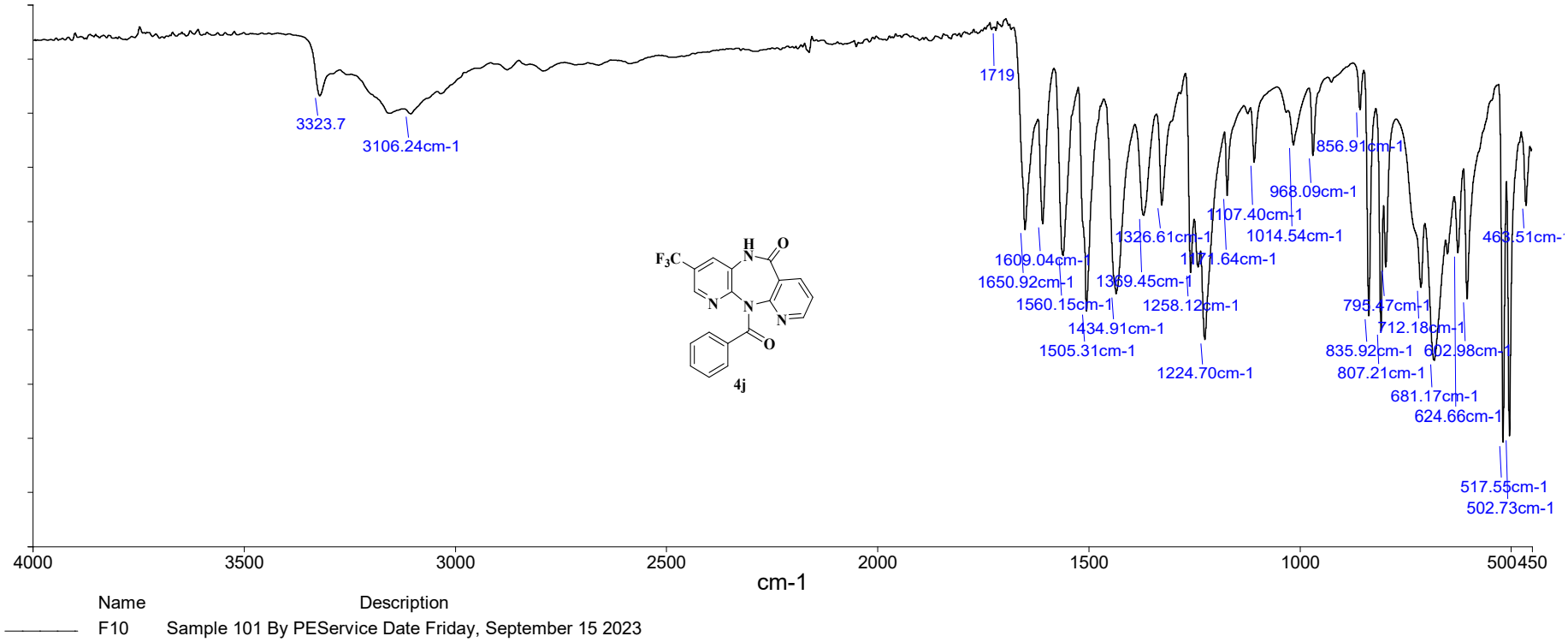
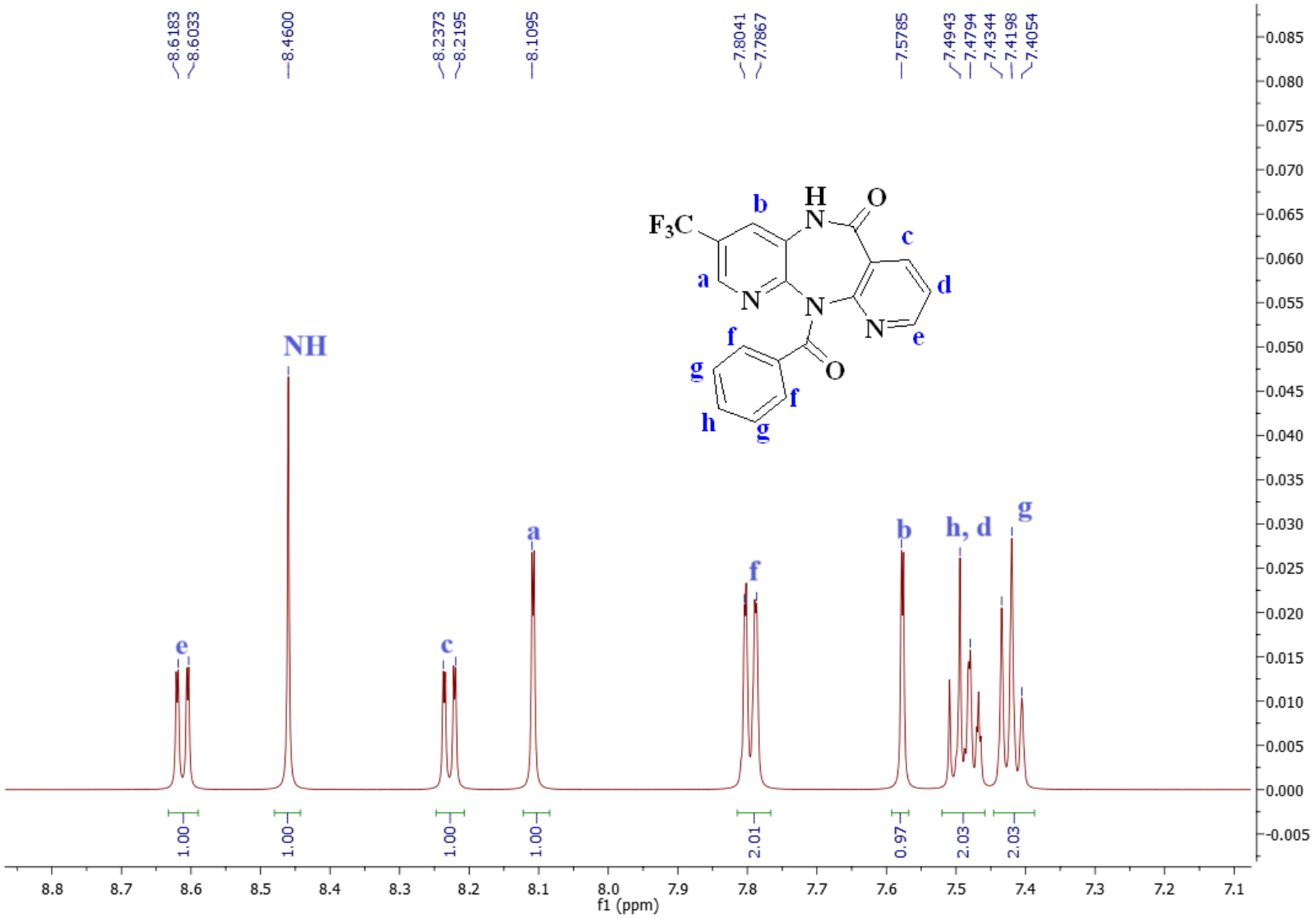
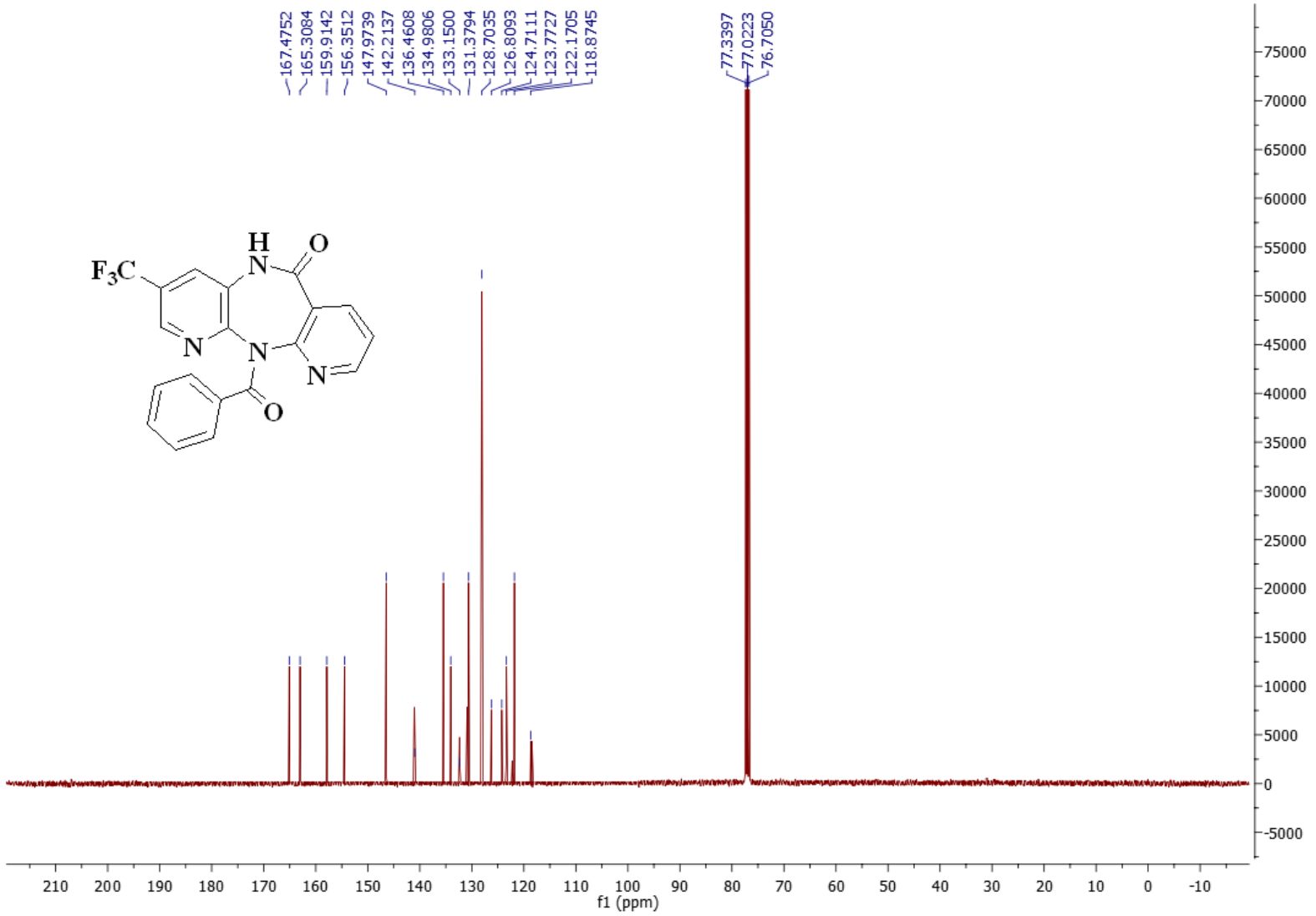


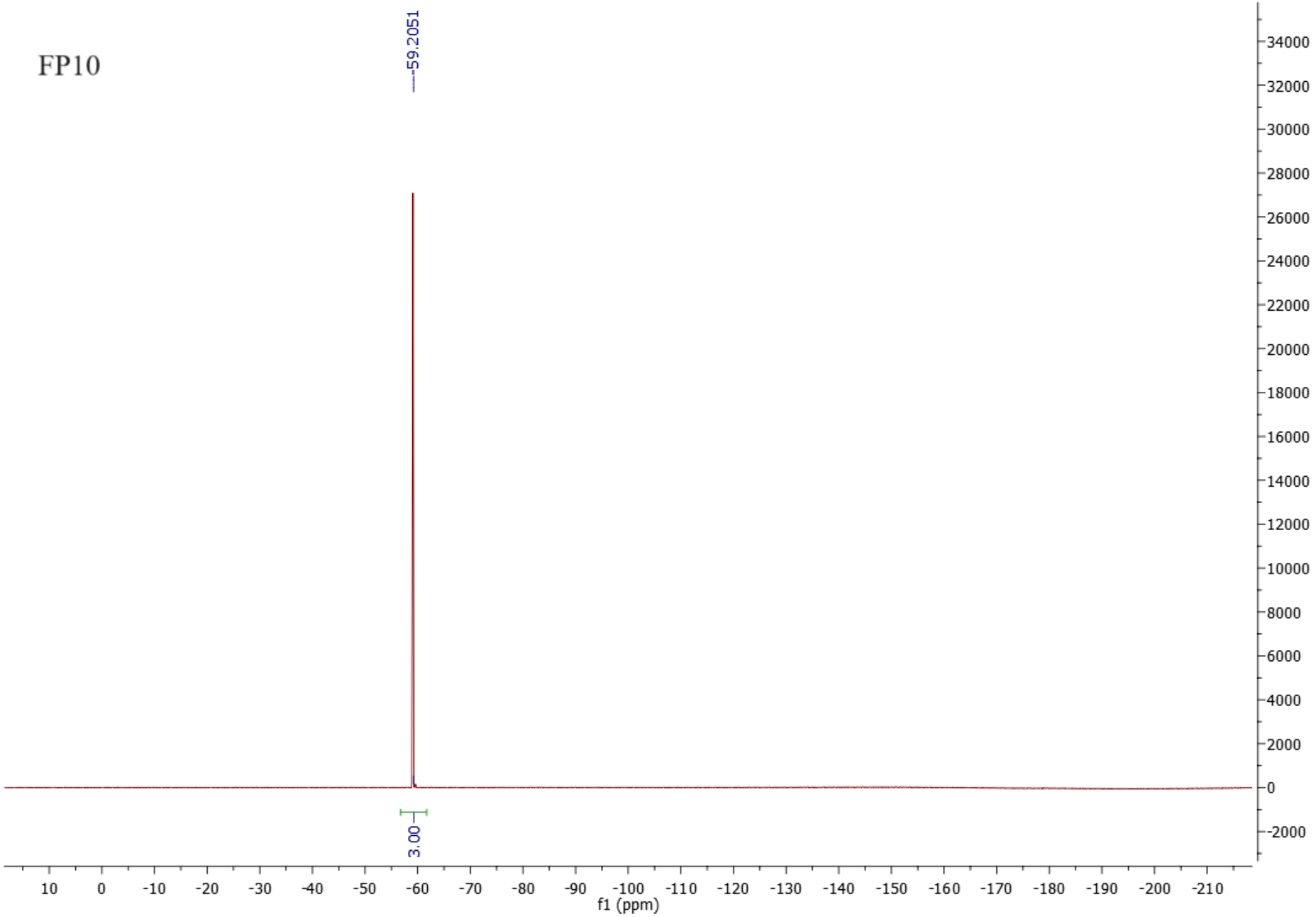
S46: IR spectrum of **5j**



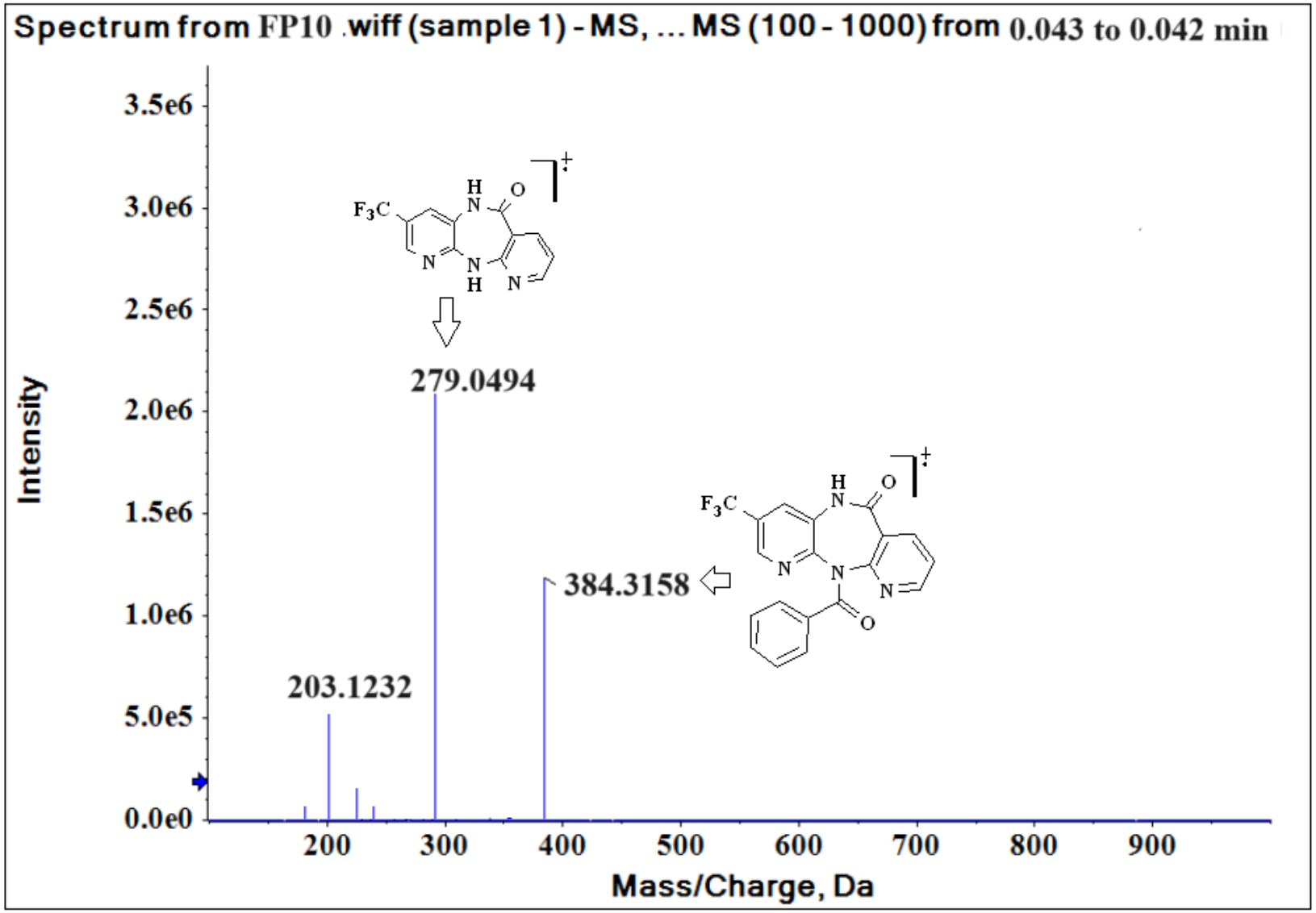
S47: ^{1}H NMR of **5j**



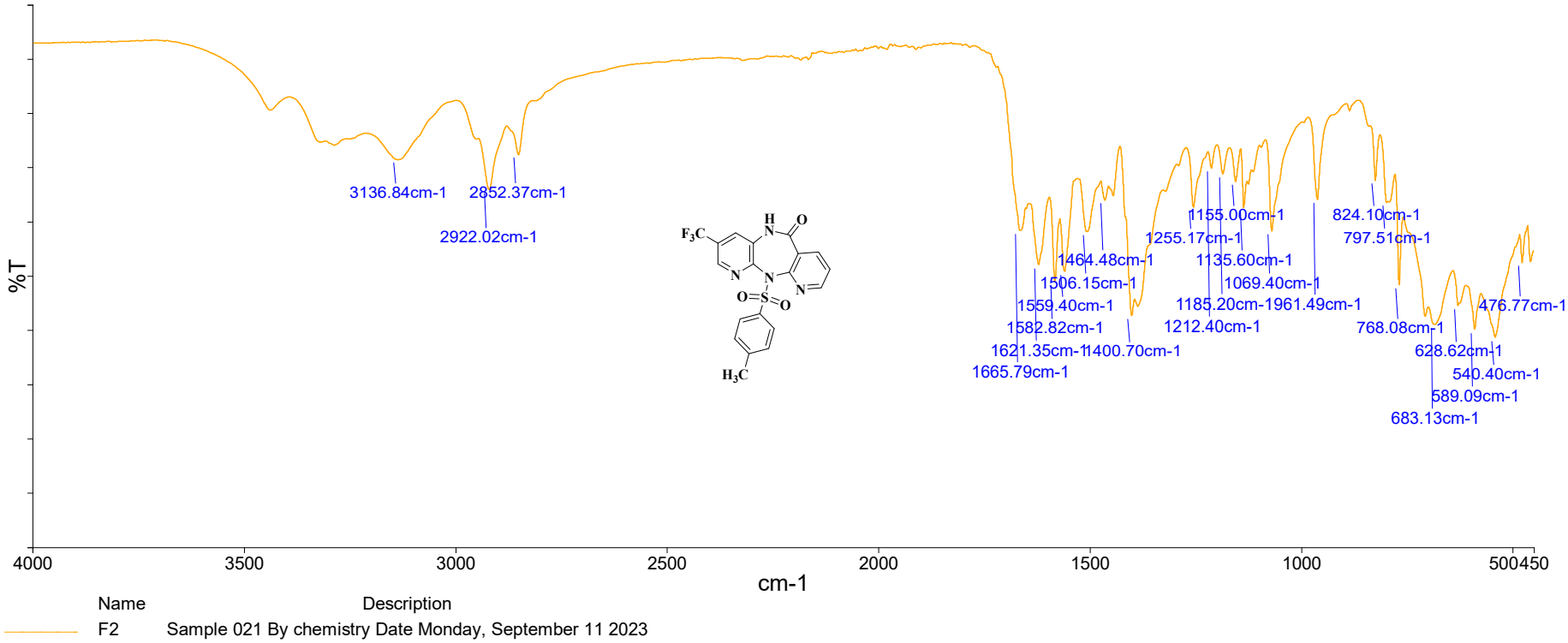
S48: ^{13}C NMR of **5j**



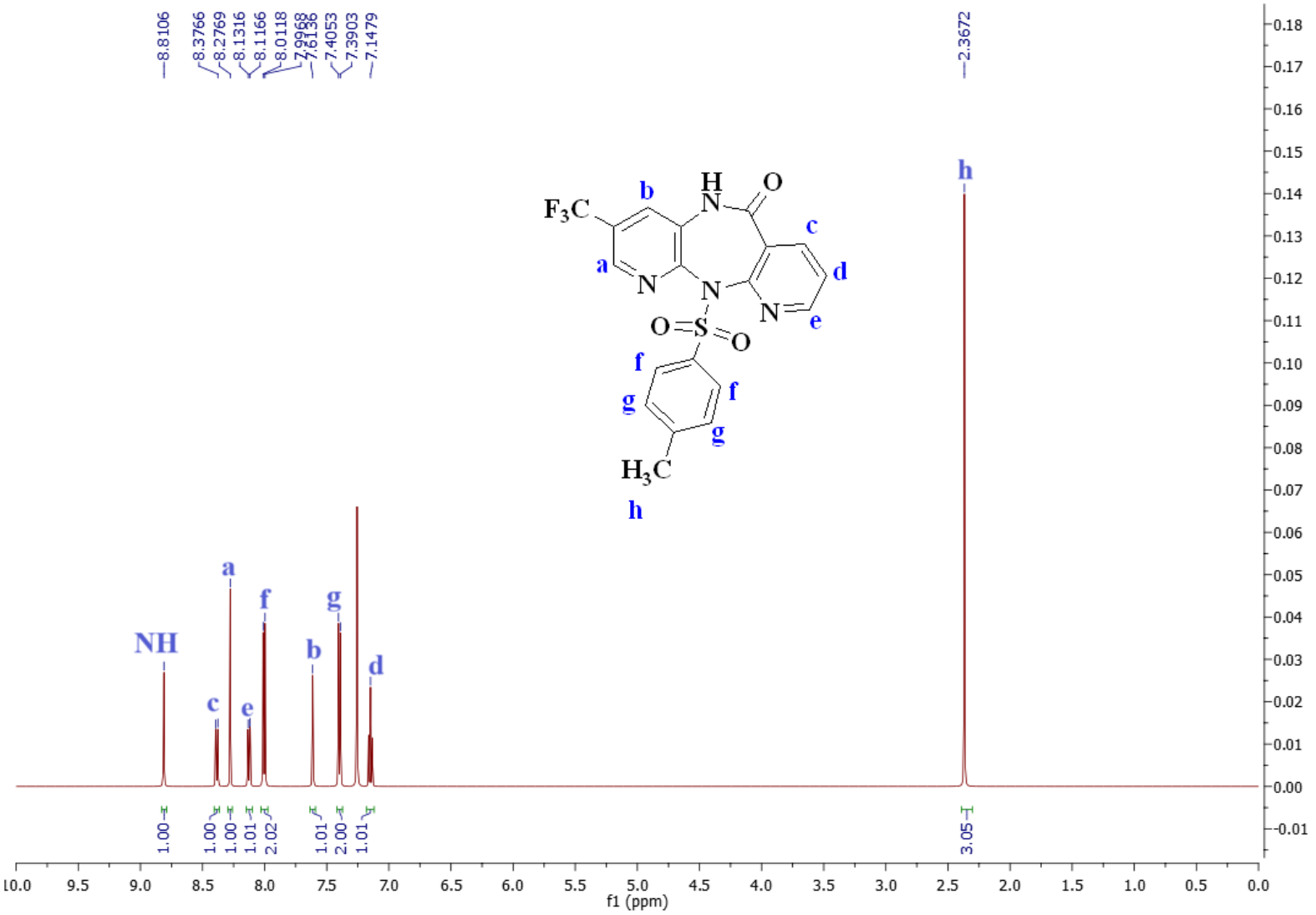
S49: ^{19}F NMR of **5j**



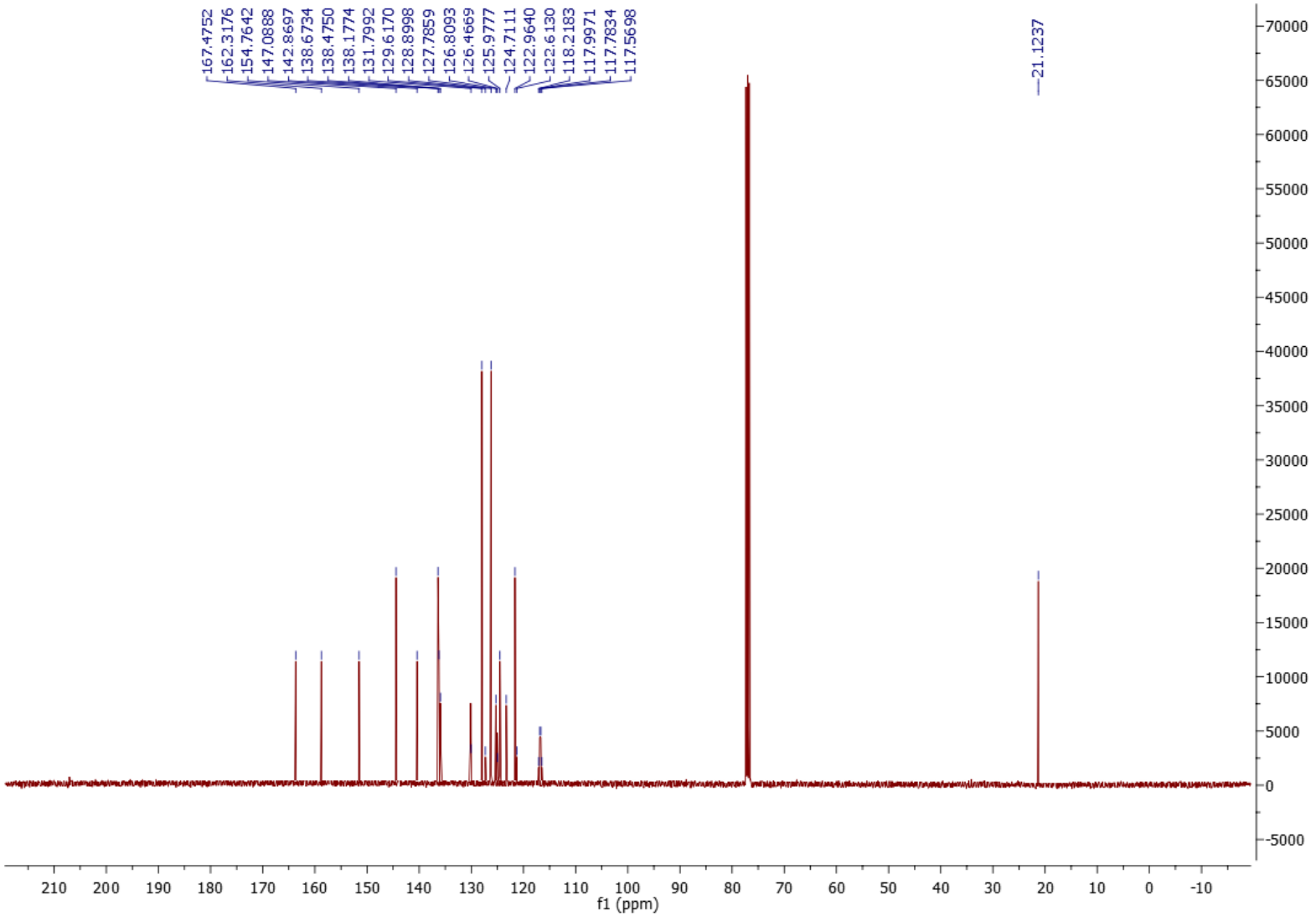
S50: Mass spectrum of **5j**



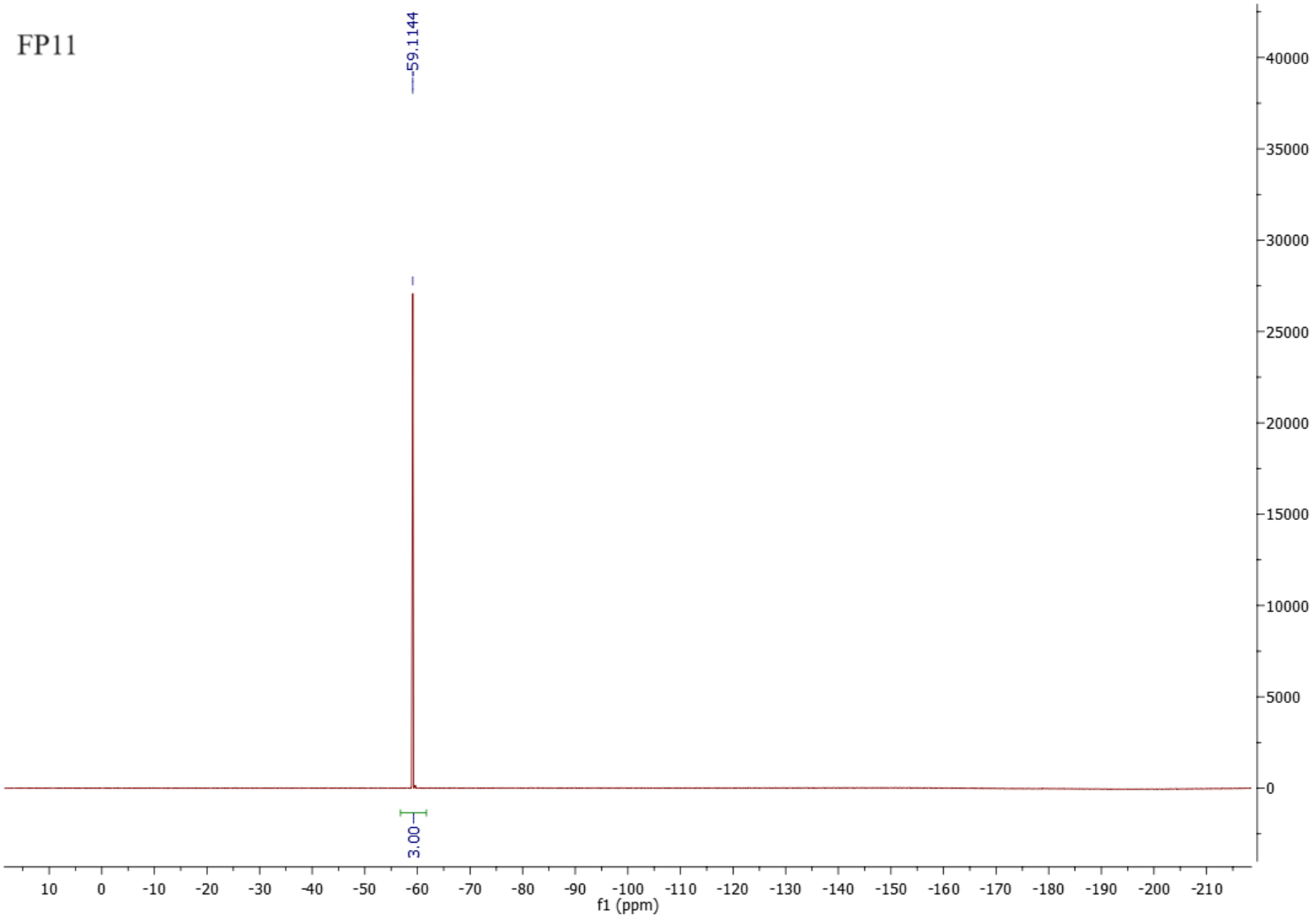
S51: IR spectrum of **5k**



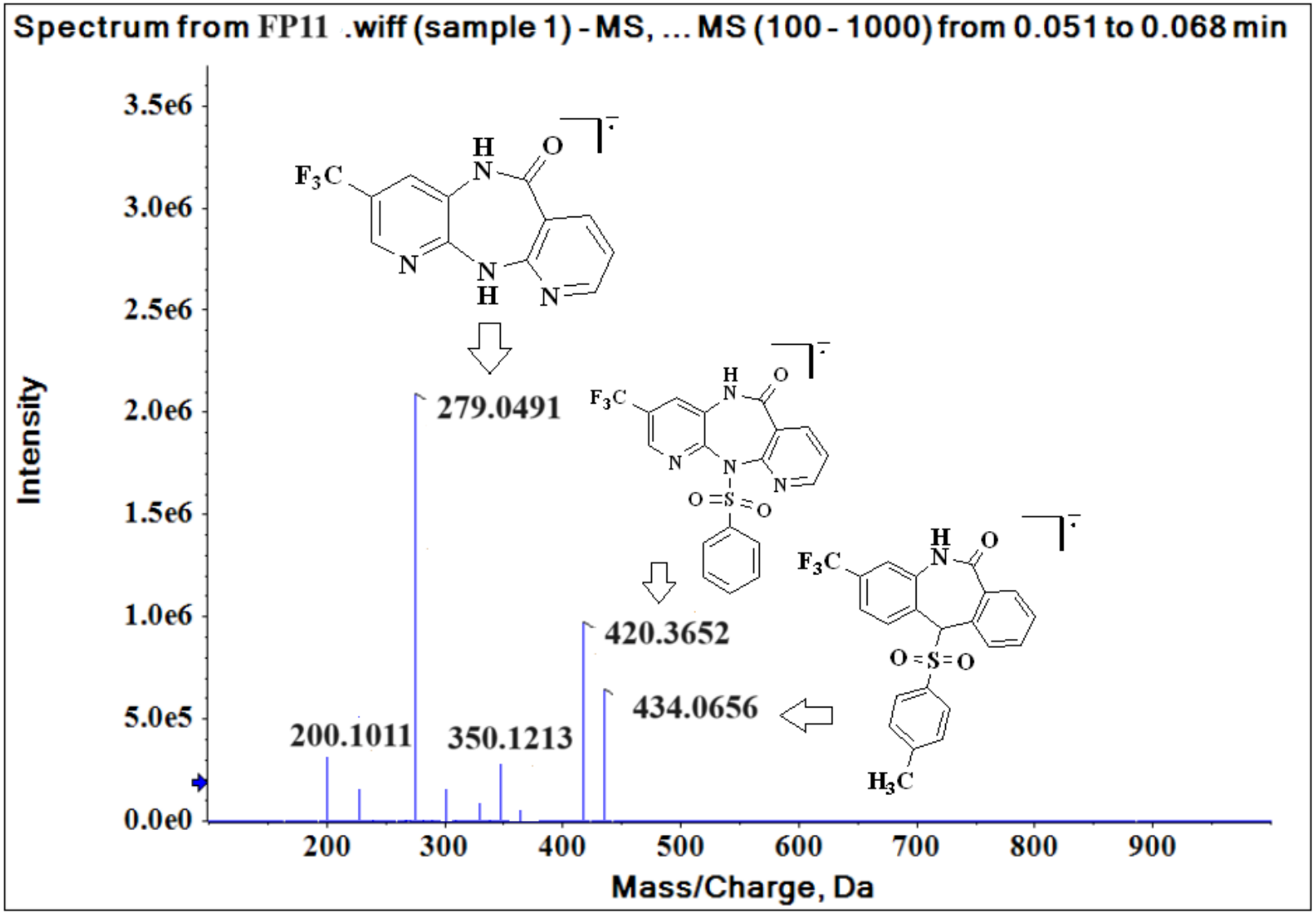
S52: ^{1}H NMR of **5k**



S53: ^{13}C NMR of **5k**

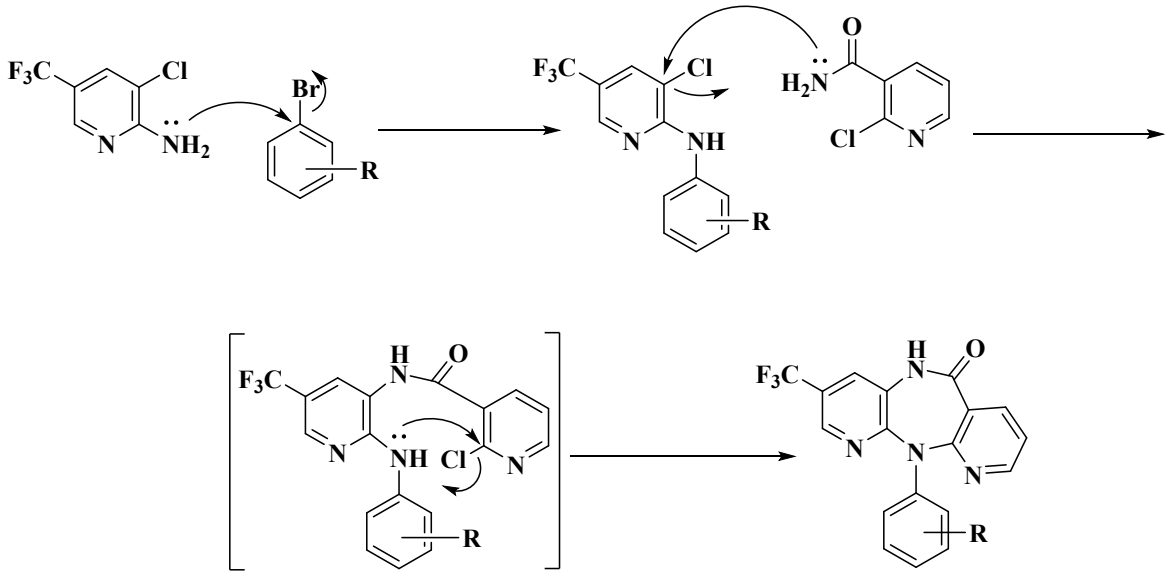


S54: ^{19}F NMR of **5k**



S55: Mass spectrum of **5k**

2. Plausible Mechanism



Scheme S1: Plausible mechanism

3. Documentation of calculation of green metrics of one representative Entry 5a

$$AE = \frac{\textbf{Molecular weight of product}}{\textbf{Total molecular weight of reactant}} \textbf{ x 100}$$

$$\frac{356.30802}{196.55+156.56+157.0100} \text{ x } 100 = 69.84\%$$

$$RME = \frac{\textbf{Mass of isolated product}}{\textbf{Total mass of reactant}} \textbf{ x 100}$$

$$= \frac{0.35}{0.6} \text{ x } 100 = 58.33\%$$

$$OE = \frac{\textbf{RME}}{\textbf{AE}} \textbf{ x 100} = \frac{58.33}{69.84} \text{ x } 100 = 83.51\%$$

$$\text{E-factor} = \frac{\textbf{Total mass of wastes}}{\textbf{Mass of product}} = \frac{0.35-0.21}{0.21} = 0.6 \text{ (g/g)}$$

Table S1: Calculated Green Metrics (AE, RME, OE and E-factor)

Compounds	MW	%yield	AE	RME	OE	E-factor
5a	356.30	79%	69.84%	58.33%	83.51%	0.7
5b	435.20	92%	73.32%	63.54%	86.66%	0.4
5c	386.33	75%	71.54%	61.23%	85.58%	0.5
5d	386.33	87%	71.33%	61.24%	85.85%	0.4
5e	370.33	85%	70.22%	60.21%	85.74%	0.3
5f	370.33	92%	70.88%	60.56%	85.44%	0.4
5g	370.33	82%	70.54%	60.44%	85.68%	0.5
5h	384.31	88%	71.23%	61.24%	85.97%	0.6
5i	384.31	80%	71.65%	61.25%	85.48%	0.6
5j	384.31	91%	71.25%	61.45%	86.24%	0.6
5k	434.39	94%	79.80%	69.81%	87.48%	0.5

4. Molecular docking

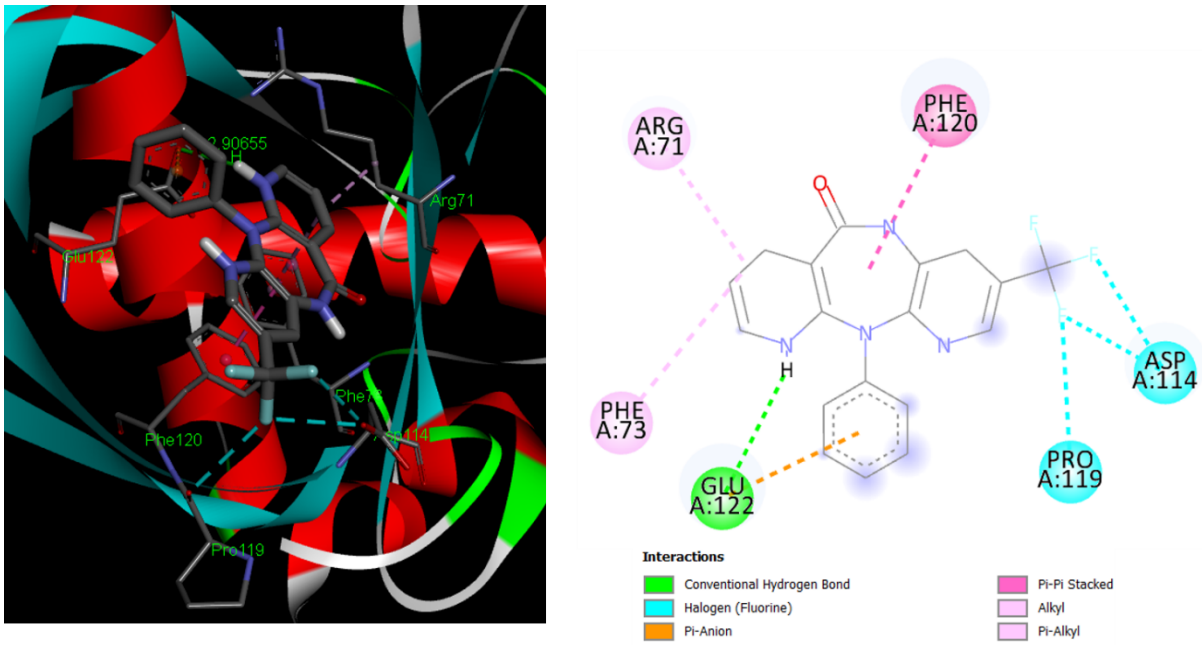


Fig. S1: Molecular interaction of compound 5a with peptide deformylase enzyme

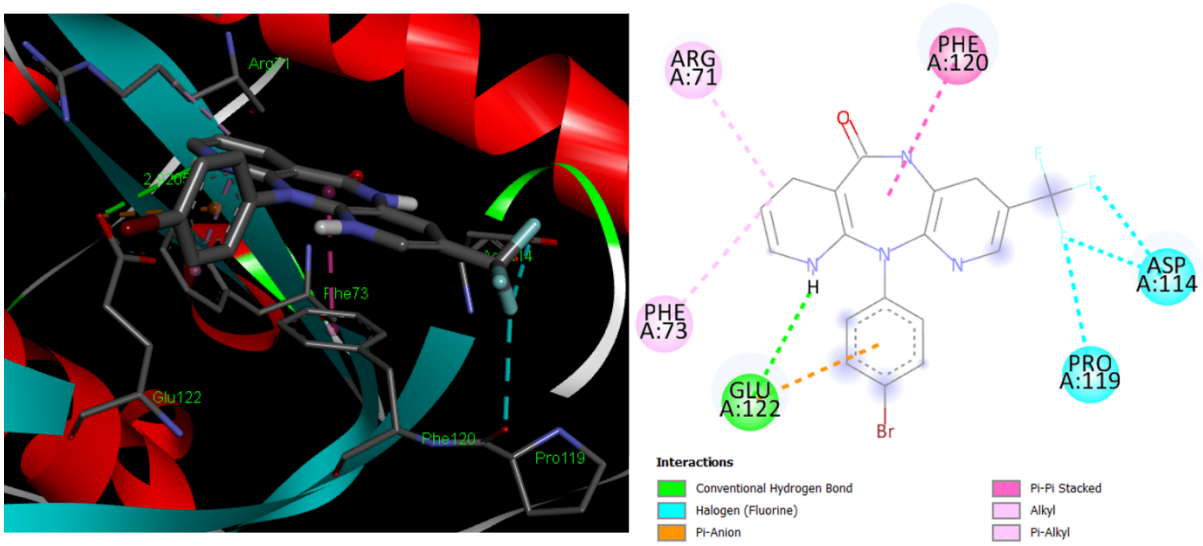


Fig. S2: Molecular interaction of compound 5b with peptide deformylase enzyme

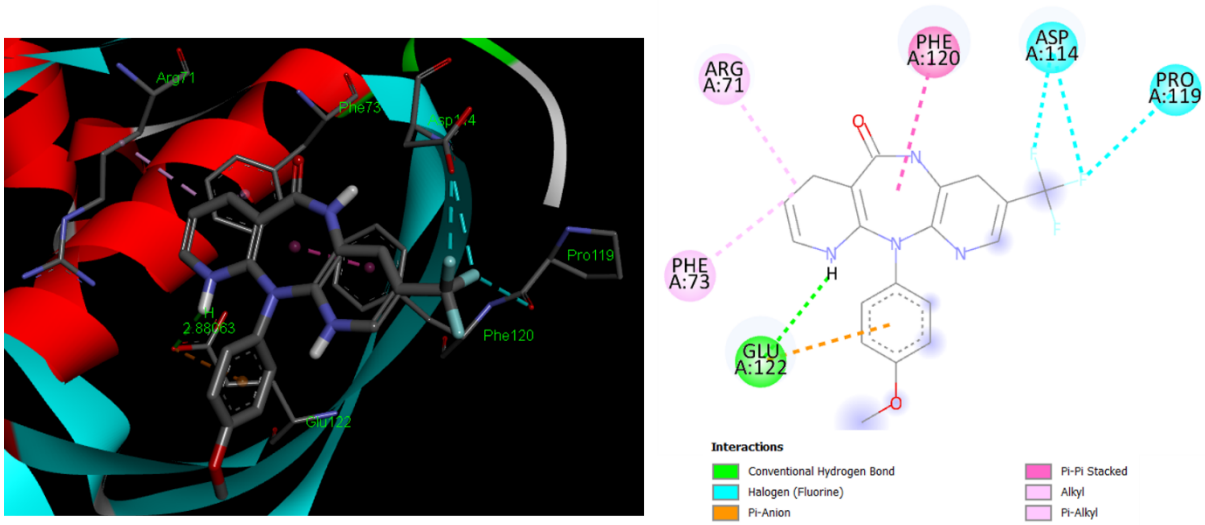


Fig. S3: Molecular interaction of compound 5c with peptide deformylase enzyme

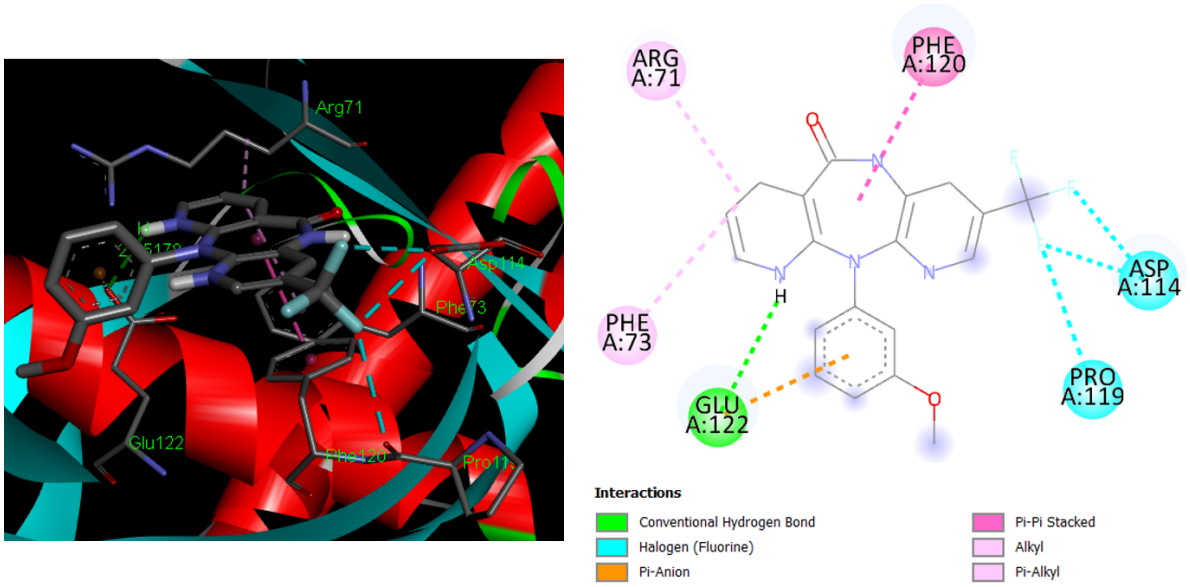


Fig. S4: Molecular interaction of compound 5d with peptide deformylase enzyme

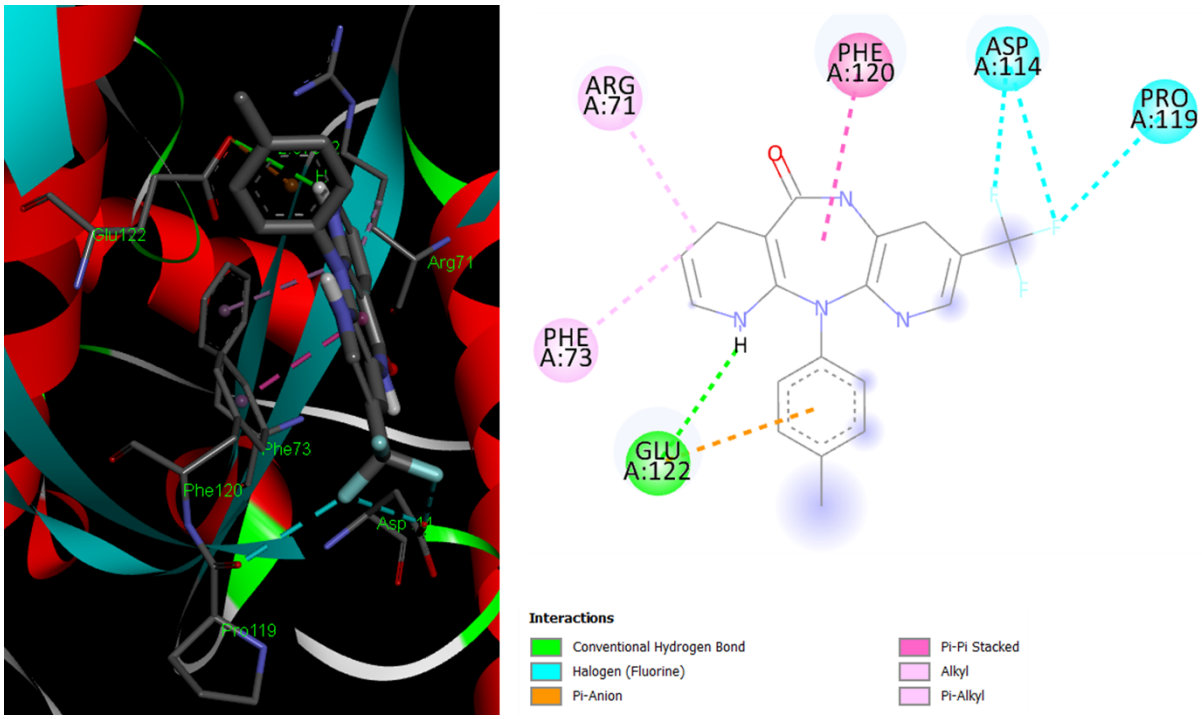


Fig. S5: Molecular interaction of compound 5e with peptide deformylase enzyme

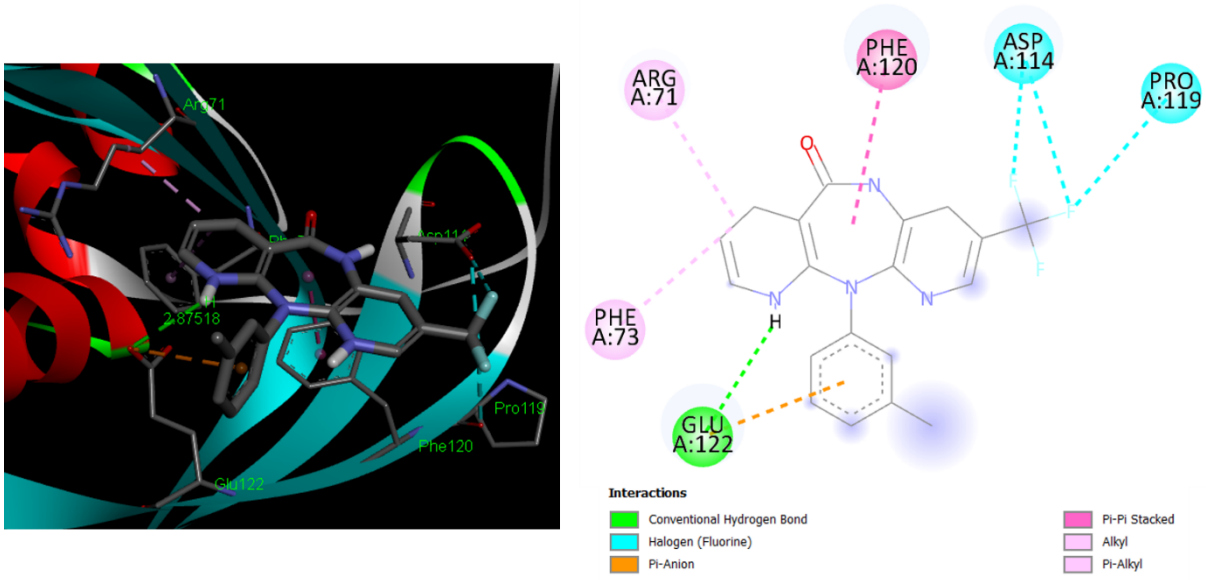


Fig. S6: Molecular interaction of compound 5f with peptide deformylase enzyme

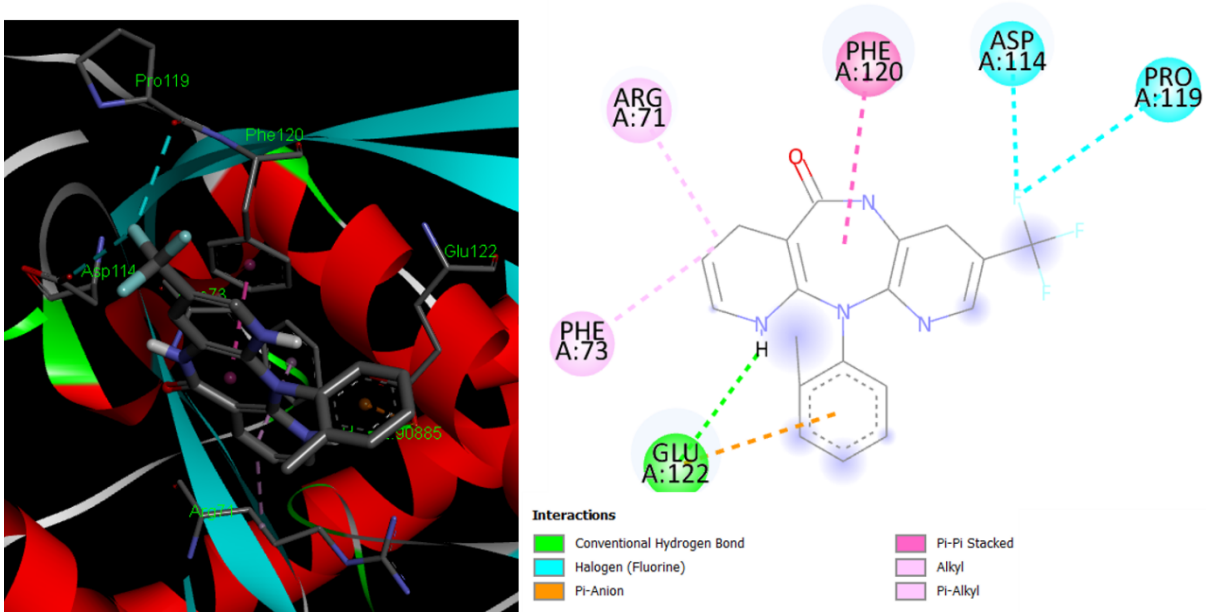


Fig. S7: Molecular interaction of compound 5g with peptide deformylase enzyme

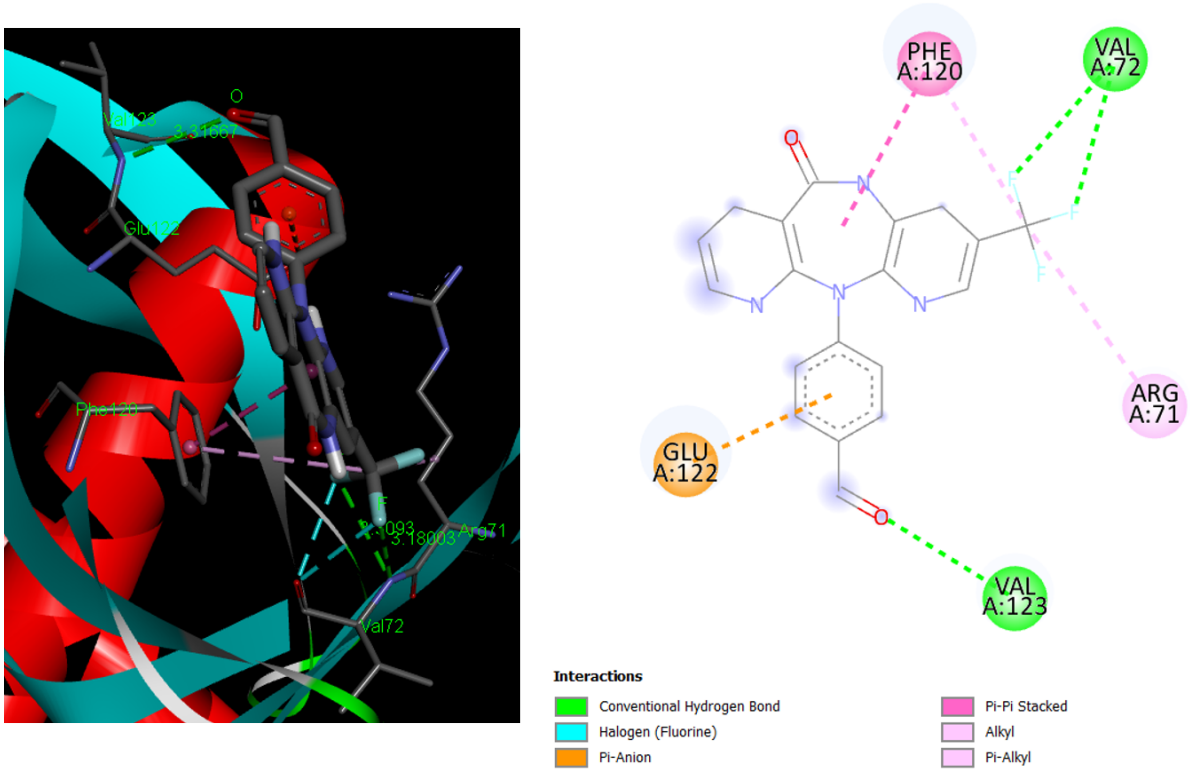


Fig. S8: Molecular interaction of compound 5h with peptide deformylase enzyme

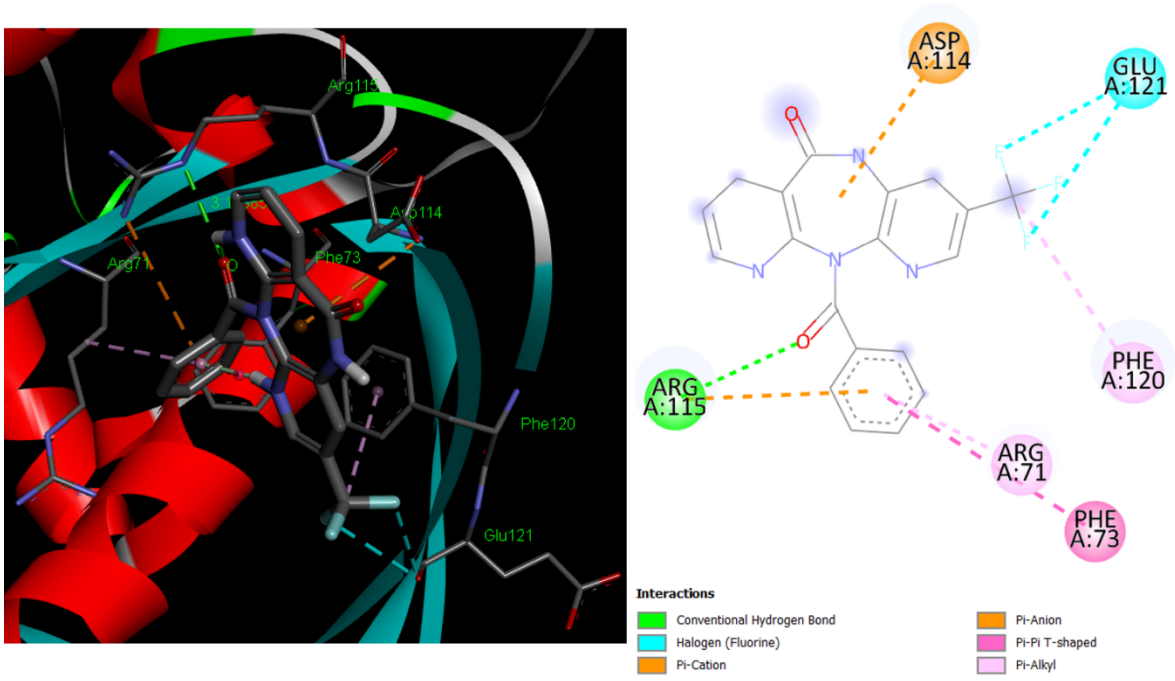


Fig. S9: Molecular interaction of compound 5j with peptide deformylase enzyme

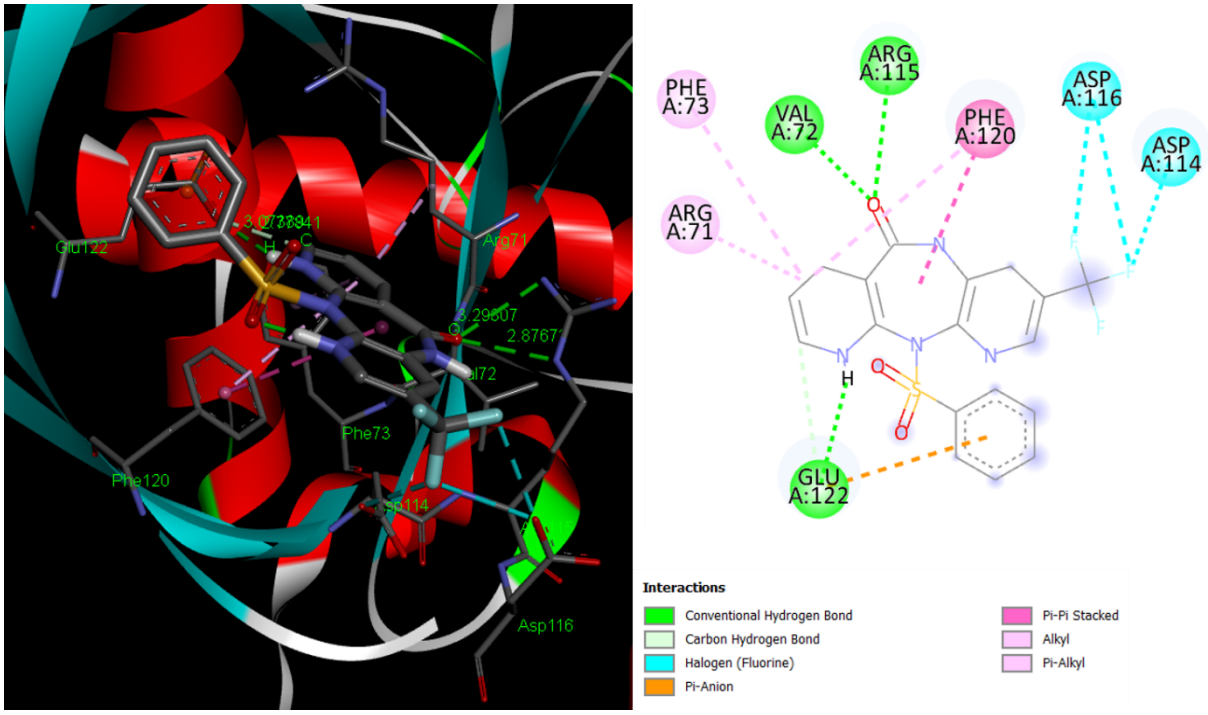


Fig. S10: Molecular interaction of compound 5k with peptide deformylase enzyme

5. SAR

SAR of synthesized compound was proposed on the basis of in vitro, in silico and molecular modelling results **Fig. S11**. The eleven derivatives of dipyridodiazepinone were synthesized and examined for inhibitory effect against peptide deformylase enzyme. SAR analysis inferred that *m*-substituted carbonyl bearing benzene ring showed highest activity compared to other derivatives and involve in H-bond interaction, pi-interaction, and hydrophobic interaction. Interestingly, *para*-substituted bromo and methyl group is preferred and retain the activity whereas *meta*-methoxy **(5d)** and *meta*-methyl substituent **(5f)** showed lower activity. Hence, the finding of docking and in vitro results revealed that electron donating substituent at *para*-position of benzene ring showed higher activity in comparison to *meta*-substituted electron donating group. Interestingly, electron withdrawing group at *meta*-position (CO) group in compound **5i** was responsible to retain the highest activity and found to very active compared to the *p*ara-carbonyl in compound **5h**. Molecular docking studies also inferred that CF_3 and carbonyl group involve in the hydrogen bond interaction and pyridine ring involve in the hydrophobic interaction.

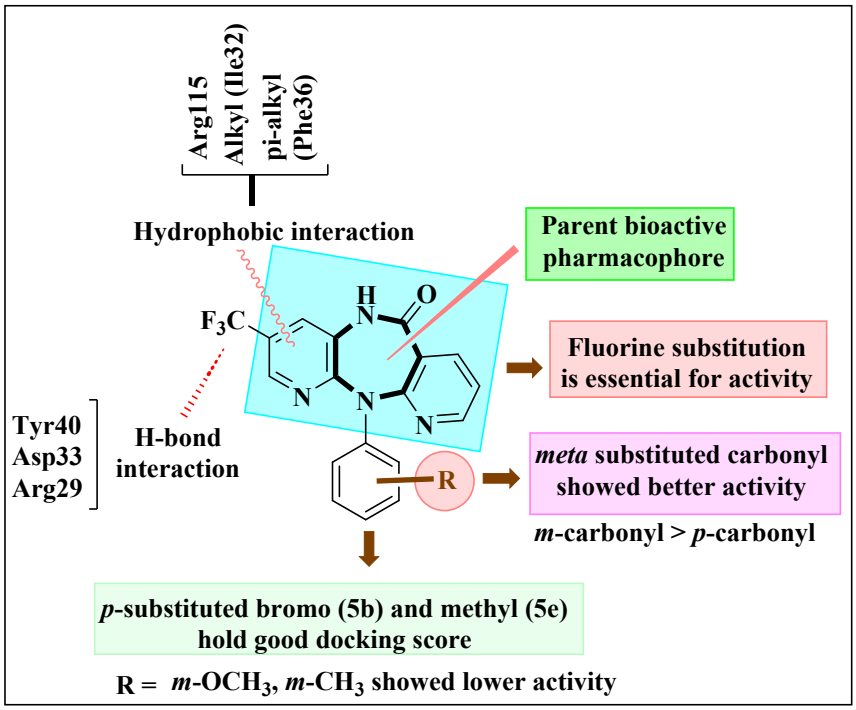


Fig. S11. SAR of dipyridodiazepinone derivatives.