Supporting information

Pd-catalysed [3+2]-Cycloaddition towards the generation of bioactive bisheterocycles/Identification of COX-2 inhibitors via *in silico* analysis

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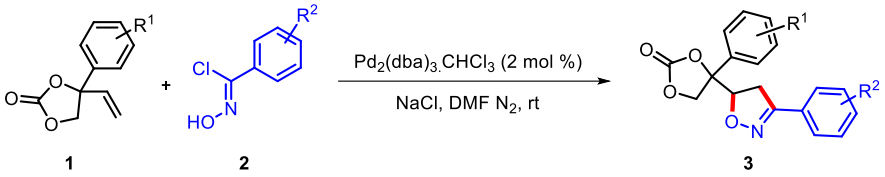
1. General considerations:

All the reactions were carried out in flame or oven dried glassware using anhydrous solvents unless otherwise indicated. All the reagents and some solvents such as anhyd. CH_3CN, anhyd. DMF were commercially procured from Aldrich, TCI and Alfa Aesar and used without further purification. Other solvents like THF and Toluene were freshly dried and distilled over Na/benzophenone and kept under an inert atmosphere and dichloromethane (DCM) (over P_2O_5) was freshly distilled before use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 (400 MHz) spectrophotometer operating at 400 MHz for ^{1}H and 101 MHz for ^{13}C experiments as solutions in $CDCl_3$; Spectra were recorded at 295 K in $CDCl_3$. Chemical shifts were calibrated to the residual proton and carbon resonance of the solvent, $CDCl_3$ (^{1}H δ 7.269; ^{13}C δ 77.0). Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), sept (septet) and m (multiplet). Peaks at 1.26 ppm and 1.56 ppm in ^{1}H NMR spectra correspond to grease and moisture respectively whereas peak at 29.67 ppm in ^{13}C NMR spectra corresponds to grease. Coupling constant (*J*) values are reported in hertz (Hz). Analytical TLC was performed using 2 x 4 cm plate coated with a 0.25 mm thickness of silica gel ($60_{F\text{-}254}$ Merck), and visualization was accomplished with UV light or staining the plates with ethanolic p-anisaldehyde solution/ phosphomolybdic acid solution/ ninhydrin solution and heating to 120 °C. Mass spectra were recorded on Water Q-ToF-Micro Micromass. Vinyl ethylene carbonates[1] and *N*-hydroxymoyl chloride[2] were prepared according to reported literature.

2. Experimental Section:

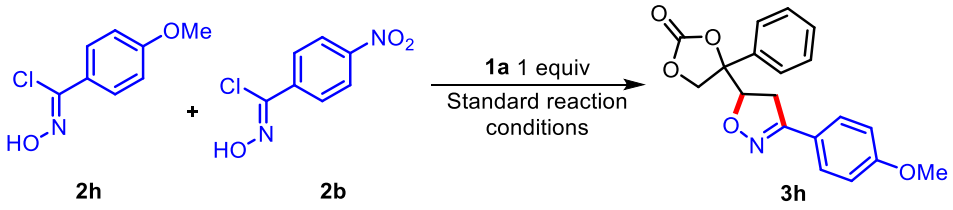
2.1. General procedure for the [3+2] cycloaddition of Vinyl ethylene carbonate and *N*-hydroxymoyl chloride for the synthesis of the 3,5-substituted isoxazoles:



Vinyl ethylene carbonate (0.2 mmol) and *N*-hydroxymoyl chloride (0.24 mmol) were added into a clean oven dried reaction vial, dissolved in DMF and the mixture of contents was purged with nitrogen gas for 5 min. NaCl and $Pd_2(dba)_3.CHCl_3$ were added after 5 min and stirred at room temperature under inert atmosphere. Reaction progress was monitored on TLC. The reaction mixture was extracted with (3 X 50 ml) ethyl acetate and aqueous NH_4Cl solution further the organic layer was washed with cold water (50 ml) for three times. The organic layer was concentrated under reduced pressure and purified by passing through column.

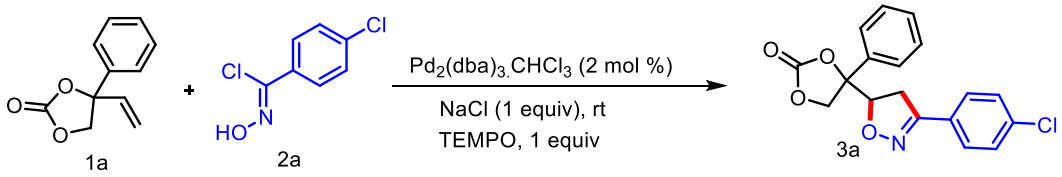
2.2. Competitive experiment:

Competitive experiment was carried between electron donating methoxy substituted *N*-hydroxymoyl chlorides and electron withdrawing nitro substituted *N*-hydroxymoyl chlorides under standard reaction conditions with 1 equivalents of vinyl ethylene carbonate.



2.3. Radical trap experiment:

Radical trap experiment was carried by reacting (0.2 mmol) of vinyl ethylene carbonate **1a** and (0.24 mmol) of *N*-hydroxymoyl chloride under standard reaction conditions in presence of TEMPO.



3. Crystallographic data:

The shining crystal was obtained by the slow evaporation of the DCM and petroleum ether solvent. A suitable crystal was selected and examined in the instrument called Rigaku oxford diffractometer. The diffraction data were collected and solved by using Olex21. The structure was solved on olex22 with the method of charge flipping and refined with the ShelX3 refinement package using least-squares minimization. The crystal data confirms the molecular formula $C_{18}H_{14}ClNO_4$ and is solved using triclinic space group P1.

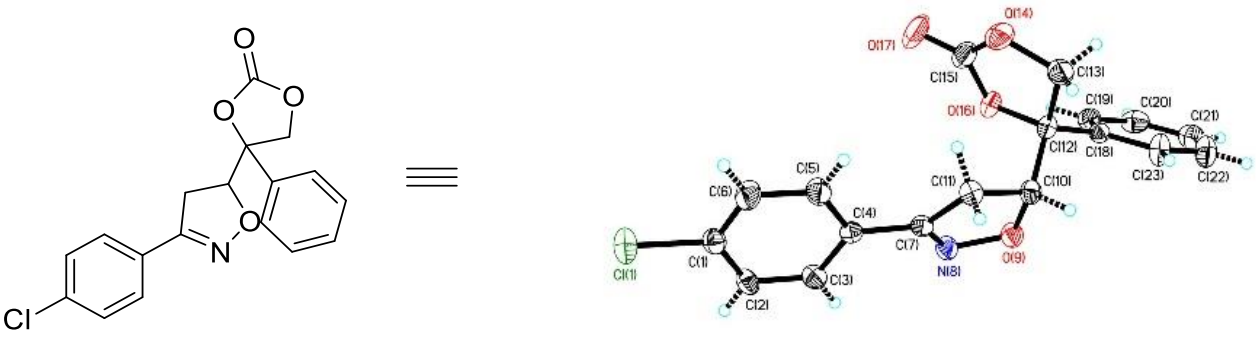


Figure S1. ORTEP diagram with 30% ellipsoidal plot presenting the X-ray crystal structure of compound 3a.

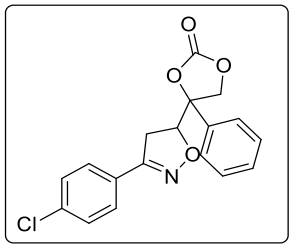
Table 1. Crystal data and structure refinement for 3a

Identification code	CCDC No 2151147	
Empirical formula	$C_{18}H_{14}ClNO_4$	
Formula weight	343.75	
Temperature	293 K	
Wavelength	0.71073	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.777 (4)	α = 110.956 (10)
	B = 9.470 (4)	β = 90.069 (10)
	C = 10.205 (4)	γ = 90.054 (10)
Volume	792.1 (6)	
Z	2	
Density (calculated)	1.441 g/cm^3	
Absorption coefficient	0.263 mm^{-1}	
F (000)	356	
Crystal size	0.2 X 0.2 X 0.3 mm^3	
Theta range for data collection	2.52 to 26.41°	
Index ranges	-10<=h<=10, -11<=k<=11,	
	12<=l<= 12	
Reflections collected	18576	
Independent reflections	4755 [R(int) = 0.0486]	
Completeness to theta	25.24°	
Absorption correction	Multi scan	
Max. and min. transmission	1.000 and 0.999	
Refinement method	ShelXL	
Data / restraints / parameters	6086/3/434	
Goodness-of-fit on F^2	1.128	

Final R indices [I>2sigma(I)]	0.0486
R indices (all data)	0.0758
Extinction coefficient	0.0155 (19)
Largest diff. peak and hole	0.213 and -0.180

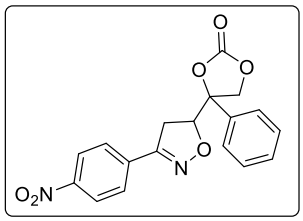
4. Spectral data of synthesized compounds:

(3a) 4-(3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl)-4-phenyl-1,3-dioxolan-2-one:



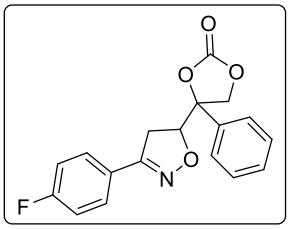
The general procedure was followed. White solid (70%), R_f = 0.3 (EtOAc/Hexane: 15/75)**. 1H NMR (500 MHz, $CDCl_3$) δ** 7.44 (dt, *J* = 6.9, 1.6 Hz, 2H), 7.39 (dt, *J* = 5.6, 1.2 Hz, 2H), 7.38 – 7.33 (m, 3H), 7.31 (dt, *J* = 8.7, 2.0 Hz, 2H), 5.19 (dd, *J* = 11.0, 6.8 Hz, 1H), 5.05 (d, *J* = 8.7 Hz, 1H), 4.68 (d, *J* = 8.7 Hz, 1H), 3.43 (dd, *J* = 17.3, 11.0 Hz, 1H), 3.12 (dd, *J* = 17.3, 6.8 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 156.0, 153.4, 136.6, 134.6, 129.5, 129.0, 128.8, 127.8, 126.6, 125.5, 84.1, 83.3, 73.2, 36.7. **HRMS-ESI (m/z):** Calculated for $C_{18}H_{14}ClNO_4$ $[M+H]^+$: 344.0684, found: 344.0690.

(3b) 4-(3-(4-nitrophenyl)-4,5-dihydroisoxazol-5-yl)-4-phenyl-1,3-dioxolan-2-one:



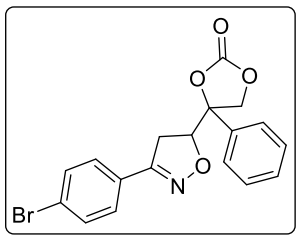
The general procedure was followed. White solid (68%), R_f = 0.4 (EtOAc/Hexane: 30/70) **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.19 (dt, *J* = 8.9, 2.0 Hz, 2H), 7.58 (dt, *J* = 8.9, 2.0 Hz, 2H), 7.44 (dt, *J* = 6.6, 1.8 Hz, 2H), 7.40 – 7.33 (m, 3H), 5.27 (dd, *J* = 11.1, 6.7 Hz, 1H), 5.07 (d, *J* = 8.8 Hz, 1H), 4.69 (d, *J* = 8.8 Hz, 1H), 3.50 (dd, *J* = 17.4, 11.1 Hz, 1H), 3.19 (dd, *J* = 17.4, 6.7 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.5, 153.2, 148.8, 134.4, 134.1, 129.6, 128.9, 127.4, 125.5, 123.9, 83.9, 83.8, 73.2, 36.4. **HRMS-ESI (m/z):** Calculated for $C_{18}H_{14}N_2O_6$ $[M+H]^+$: 355.0925, found: 355.0916.

(3c) 4-(3-(4-fluorophenyl)-4,5-dihydroisoxazol-5-yl)-4-phenyl-1,3-dioxolan-2-one:



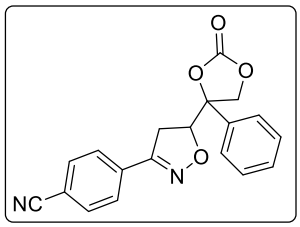
The general procedure was followed. White solid (65%), R_f = 0.5 (EtOAc/Hexane: 10/80). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.52 – 7.28 (m, 7H), 7.01 (t, *J* = 8.6 Hz, 2H), 5.16 (dd, *J* = 11.0, 6.9 Hz, 1H), 5.03 (d, *J* = 8.7 Hz, 1H), 4.66 (d, *J* = 8.7 Hz, 1H), 3.42 (dd, *J* = 17.3, 11.0 Hz, 1H), 3.11 (dd, *J* = 17.3, 6.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.9, 153.4, 134.8, 129.4, 128.8, 128.7, 128.6, 125.5, 124.4, 116.1, 115.8, 84.1, 83.3, 73.17, 36.9. **^{19}F NMR (471 MHz, $CDCl_3$) δ** -108.89 (s). **HRMS-ESI (m/z):** Calculated for $C_{18}H_{14}FNO_4$ $[M+H]^+$: 328.0980, found: 328.0984.

(3d) 4-(3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl)-4-phenyl-1,3-dioxolan-2-one:



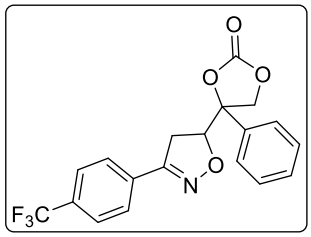
The general procedure was followed. White solid (64%), R_f = 0.5 (EtOAc/Hexane: 15/75). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.47-7.41 (m, 4H), 7.41 – 7.33 (m, 3H), 7.29 (dt, *J* = 8.7, 1.9 Hz, 2H), 5.18 (dd, *J* = 11.0, 6.9 Hz, 1H), 5.02 (d, *J* = 8.8 Hz, 1H), 4.67 (d, *J* = 8.8 Hz, 1H), 3.42 (dd, *J* = 17.4, 11.0 Hz, 1H), 3.11 (dd, *J* = 17.4, 6.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 156.1, 153.4, 134.8, 131.9, 129.4, 128.8, 128.0, 127.1, 125.5, 124.9, 84.2, 83.4, 73.0, 36.6. **HRMS-ESI (m/z):** Calculated for $C_{18}H_{15}BrNO_4^+$ $[M+H]^+$: 388.0179, **found**: 388.0186.

(3e) 4-(5-(2-oxo-4-phenyl-1,3-dioxolan-4-yl)-4,5-dihydroisoxazol-3-yl)benzonitrile:



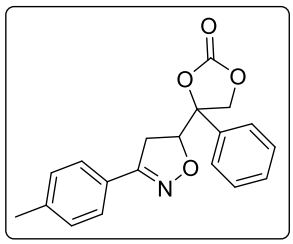
The general procedure was followed. White solid (62%), R_f = 0.5 (EtOAc/hexane: 20/80). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.61 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 7.1 Hz, 2H), 7.35 (dt, *J* = 20.8, 7.1 Hz, 3H), 5.23 (dd, *J* = 11.0, 6.7 Hz, 1H), 5.04 (d, *J* = 8.8 Hz, 1H), 4.67 (d, *J* = 8.8 Hz, 1H), 3.45 (dd, *J* = 17.4, 11.1 Hz, 1H), 3.13 (dd, *J* = 17.4, 6.8 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.8, 153.3, 134.6, 132.5, 132.4, 129.5, 128.9, 127.1, 125.5, 118.1, 113.9, 84.1, 83.9, 72.9, 36.2. **HRMS-ESI (m/z):** Calculated for $C_{19}H_{14}N_2O_4^+$ $[M+H]^+$: 335.1026, **found**: 335.1030.

(3f) 4-phenyl-4-(3-(4-(trifluoromethyl)phenyl)-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one:



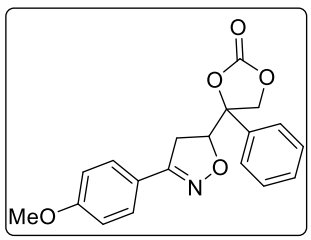
The general procedure was followed. White solid (62%), R_f = 0.4 (EtOAc/hexane: 15/85). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.58 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 1H), 5.22 (dd, *J* = 10.9, 6.8 Hz, 1H), 5.04 (d, *J* = 8.7 Hz, 1H), 4.67 (d, *J* = 8.7 Hz, 1H), 3.46 (dd, *J* = 17.4, 11.0 Hz, 1H), 3.15 (dd, *J* = 17.4, 6.8 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 155.9, 153.3, 134.6, 129.5, 128.8, 126.9, 125.7, 125.7, 125.7, 125.6, 125.5, 84.0, 83.6, 73.1, 36.6. **^{19}F NMR (471 MHz, $CDCl_3$) δ** -63.09 (s). **HRMS-ESI (m/z):** Calculated for $C_{19}H_{14}F_3NO_4^+$ $[M+H]^+$: 378.0948, **found**: 378.0952.

(3g) 4-phenyl-4-(3-(p-tolyl)-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one:



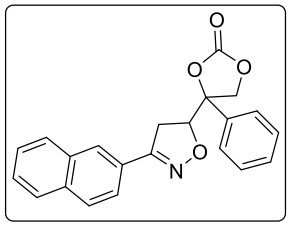
The general procedure was followed. White solid (70%), R_f = 0.5 (EtOAc/Hexane: 10/90). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.44 (d, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 8.1 Hz, 3H), 7.13 (d, *J* = 7.8 Hz, 2H), 5.14 (dd, *J* = 10.9, 7.1 Hz, 1H), 5.02 (d, *J* = 8.7 Hz, 1H), 4.65 (d, *J* = 8.7 Hz, 1H), 3.42 (dd, *J* = 17.3, 10.9 Hz, 1H), 3.10 (dd, *J* = 17.3, 7.1 Hz, 1H), 2.34 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 156.9, 153.6, 140.9, 137.7, 129.5, 129.4, 129.3, 126.8, 125.7, 124.3, 85.4, 83.6, 73.0, 36.2, 21.5. **HRMS-ESI (m/z):** Calculated for $C_{19}H_{17}NO_4^+$ $[M+H]^+$: 324.1230, **found**: 324.1236.

(3h) 4-(3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-yl)-4-phenyl-1,3-dioxolan-2-one:



The general procedure was followed. White solid (72%), R_f = 0.5 (EtOAc/Hexane: 30/70). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.52 – 7.30 (m, 7H), 6.84 (d, *J* = 7.6 Hz, 2H), 5.14 (dd, *J* = 11.0, 7.0 Hz, 1H), 5.03 (d, *J* = 8.4 Hz, 1H), 4.66 (d, *J* = 8.2 Hz, 1H), 3.81 (s, 3H), 3.42 (dd, *J* = 16.7, 11.1 Hz, 1H), 3.10 (dd, *J* = 17.0, 6.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 161.4, 156.4, 153.5, 134.9, 129.3, 128.8, 128.2, 125.6, 120.6, 114.1, 84.4, 82.9, 73.1, 55.3, 37.1. **HRMS-ESI (m/z):** Calculated for $C_{19}H_{17}NO_5^+$ $[M+H]^+$: 340.1179, **found**: 340.1185.

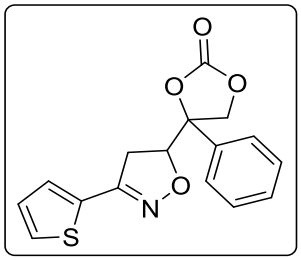
(3i) 4-(3-(naphthalen-2-yl)-4,5-dihydroisoxazol-5-yl)-4-phenyl-1,3-dioxolan-2-one:



The general procedure was followed. White solid (68%), R_f = 0.5 (EtOAc/Hexane: 15/75). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.85 – 7.80 (m, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.71 (dd, *J* = 10.2, 1.6 Hz, 2H), 7.57 – 7.51 (m, 2H), 7.51 – 7.45 (m, 2H), 7.38 (t, *J* = 7.1 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 5.23 (dd, *J* = 11.0, 7.0 Hz, 1H), 5.07 (d, *J* = 8.7 Hz, 1H), 4.69 (d, *J* = 8.7 Hz,

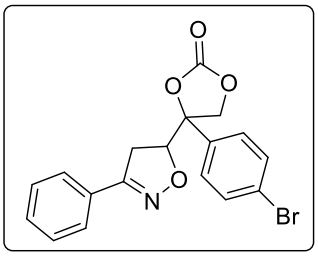
1H), 3.57 (dd, *J* = 17.3, 11.0 Hz, 1H), 3.27 (dd, *J* = 17.3, 7.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 157.0, 153.5, 134.9, 134.1, 132.7, 129.4, 128.8, 128.6, 128.4, 127.8, 127.4, 127.1, 126.8, 125.7, 125.6, 123.2, 84.3, 83.4, 73.1, 36.8. **HRMS-ESI (m/z):** Calculated for $C_{22}H_{17}NO_4^+$ $[M+H]^+$: 360.1230, **found**: 360.1234.

(3j) 4-phenyl-4-(3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one:



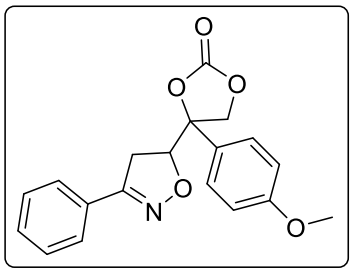
The general procedure was followed. White solid (63%), R_f = 0.5 (EtOAc/Hexane: 15/85). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.51 – 7.30 (m, 5H), 7.01 (d, *J* = 19.8 Hz, 2H), 5.16 (dd, *J* = 10.2, 7.4 Hz, 1H), 5.03 (d, *J* = 8.5 Hz, 1H), 4.66 (d, *J* = 8.3 Hz, 1H), 3.66 (s, 1H), 3.46 (dd, *J* = 16.8, 11.0 Hz, 1H), 3.14 (dd, *J* = 17.2, 7.2 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 153.4, 152.5, 134.75, 130.3, 129.6, 129.4, 128.9, 128.9, 127.3, 125.6, 84.2, 83.3, 73.2, 37.6. **HRMS-ESI (m/z):** Calculated for $C_{16}H_{13}NO_4S^+$ $[M+H]^+$: 316.0638, **found**: 316.0644.

(3k) 4-(4-bromophenyl)-4-(3-phenyl-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one:



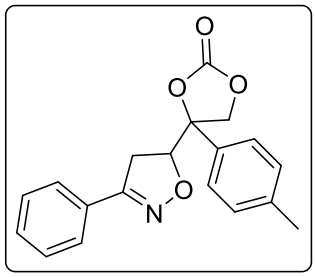
The general procedure was followed. White solid (70%), R_f = 0.5 (EtOAc/Hexane: 10/90). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.51 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 7.0 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 4H), 5.14 (dd, *J* = 10.9, 7.2 Hz, 1H), 5.01 (d, *J* = 8.8 Hz, 1H), 4.59 (d, *J* = 8.7 Hz, 1H), 3.48 (dd, *J* = 17.4, 11.0 Hz, 1H), 3.08 (dd, *J* = 17.4, 7.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 157.0, 153.2, 134.0, 132.1, 130.8, 128.8, 127.9, 127.3, 126.6, 123.8, 83.8, 82.9, 73.2, 36.9. **HRMS-ESI (m/z):** Calculated for $C_{18}H_{14}BrNO_4^+$ $[M+H]^+$: 388.0179, **found**: 388.0175.

(3l) 4-(4-methoxyphenyl)-4-(3-phenyl-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one:



The general procedure was followed. White solid (68%), R_f = 0.5 (EtOAc/Hexane: 20/80). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.47 – 7.43 (d, *J* = 6.9 Hz, 2H), 7.35 (m, 5H), 6.9 (d, *J* = 8.9 Hz, 2H), 5.14 (dd, *J* = 11.0, 7.3 Hz, 1H), 4.98 (d, *J* = 8.7 Hz, 1H), 4.62 (d, *J* = 8.7 Hz, 1H), 3.76 (s, 3H), 3.43 (dd, *J* = 17.3, 11.0 Hz, 1H), 3.11 (dd, *J* = 17.3, 7.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 160.2, 156.9, 153.6, 130.6, 128.7, 128.2, 126.9, 126.8, 126.7, 114.3, 84.3, 83.3, 73.2, 55.3, 36.9. **HRMS-ESI (m/z):** Calculated for $C_{19}H_{17}NO_5^+$ $[M+H]^+$: 340.1179, **found**: 340.1185.

(3m) 4-(3-phenyl-4,5-dihydroisoxazol-5-yl)-4-(p-tolyl)-1,3-dioxolan-2-one:



The general procedure was followed. White solid (70%), R_f = 0.5 (EtOAc/Hexane: 20/80). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.44 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.40 – 7.29 (m, 5H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.14 (dd, *J* = 11.0, 7.0 Hz, 1H), 5.03 (d, *J* = 8.7 Hz, 1H), 4.65 (d, *J* = 8.7 Hz, 1H), 3.42 (dd, *J* = 17.3, 11.0 Hz, 1H), 3.11 (dd, *J* = 17.3, 7.0 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 156.9, 153.6, 139.3, 132.0, 130.5, 129.5, 128.7, 128.3, 126.7, 125.4, 84.5, 83.4, 72.9, 36.8, 21.1. **HRMS-ESI (m/z):** Calculated for $C_{19}H_{17}NO_4^+$ $[M+H]^+$: 324.1230, **found**: 324.1236.

5. Molecular docking results

We revisited our synthetic **3j** and generated all the 4 enantiomers using LigPrep and thereafter performed the docking of all the generated enantiomers using the COX-2 receptor (PDB ID: 3LN1). The analysis results are represented in **Table S1**. The analysis reveals the enantiomeric binds with COX-2 with marginally distinct docking scores. The enantiomeric state (**I**) was found to possess highest binding affinity towards COX-2 receptor. So, considering this we do agree that enantiomeric form and chirality in general plays a major role in the drug discovery process. The individual binding pattern of other enantiomeric states (I - **IV**) is illustrated in **Figure S2**.

Table S1. Docking scores of generated enantiomers of **3j**

Enantiomeric state	Docking score (Kcal/mol)	Docking Pose
(S)-4-phenyl-4-((R)-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one **(I)**	-9.97	**Figure S2A**
(R)-4-phenyl-4-((S)-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one **(II)**	-9.51	**Figure S2B**
(S)-4-phenyl-4-((S)-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one **(III)**	-9.42	**Figure S2C**
(R)-4-phenyl-4-((R)-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-yl)-1,3-dioxolan-2-one **(IV)**	-9.31	**Figure S3D**

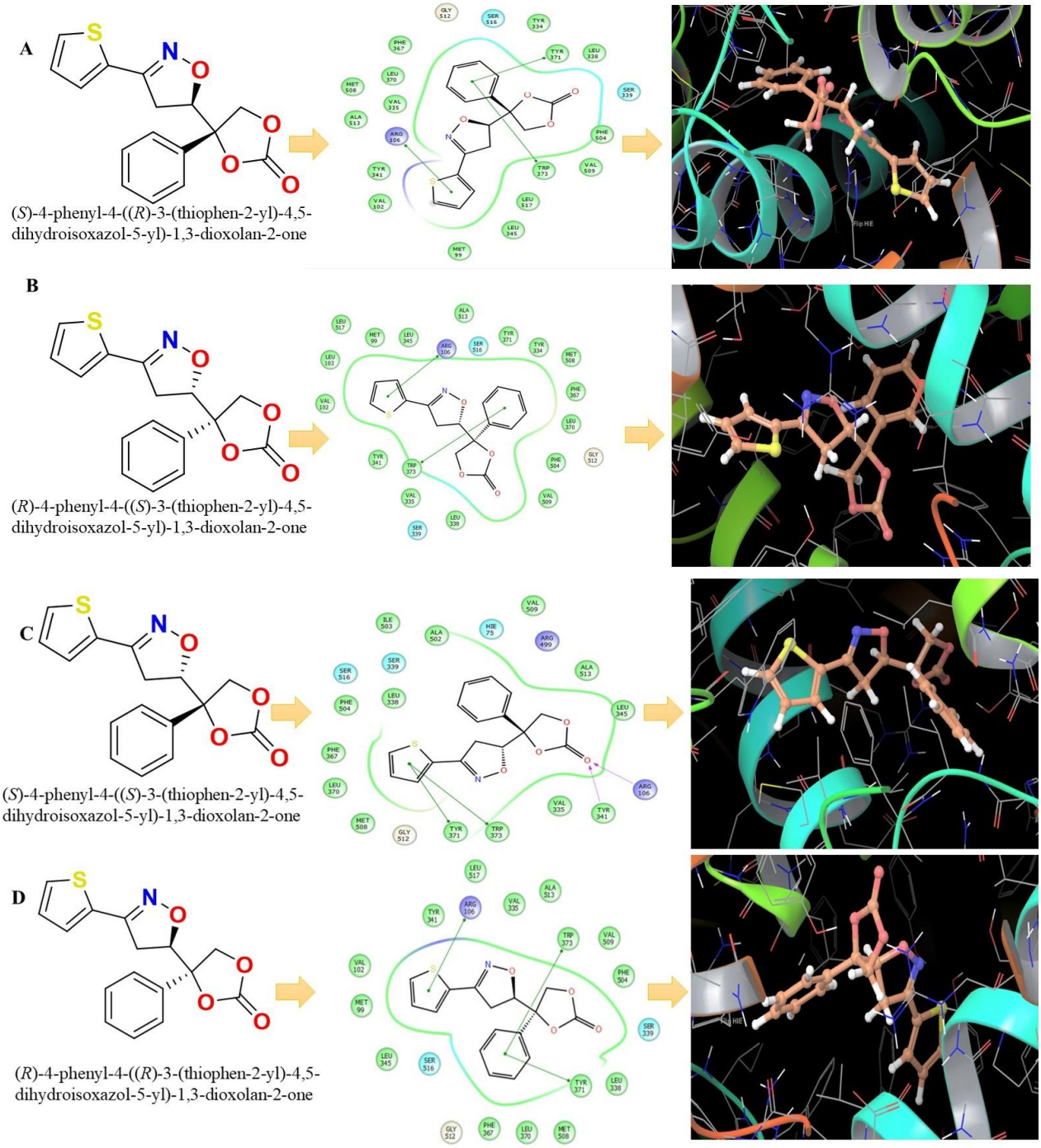


Figure S2 (A-D). Illustration of generated enantiomeric state of **3j** and their interaction with residual amino acids within the active domain of COX-2

Table S2. MMGBSA parameters to deduce binding affinity of **3j** in comparison to celecoxib for COX-2 active site (energy is provided in kcal/mol)

Code	MMGBSA Bind	MMGBSA Coulomb	MMGBSA Covalent	MMGBSA Lipo	MMGBSA Packing
3j	-97.0419	21.20379	2.32556	-38.7804	-0.65907
Celecoxib	-60.1937	4.254314	8.648821	-46.9426	-0.74567

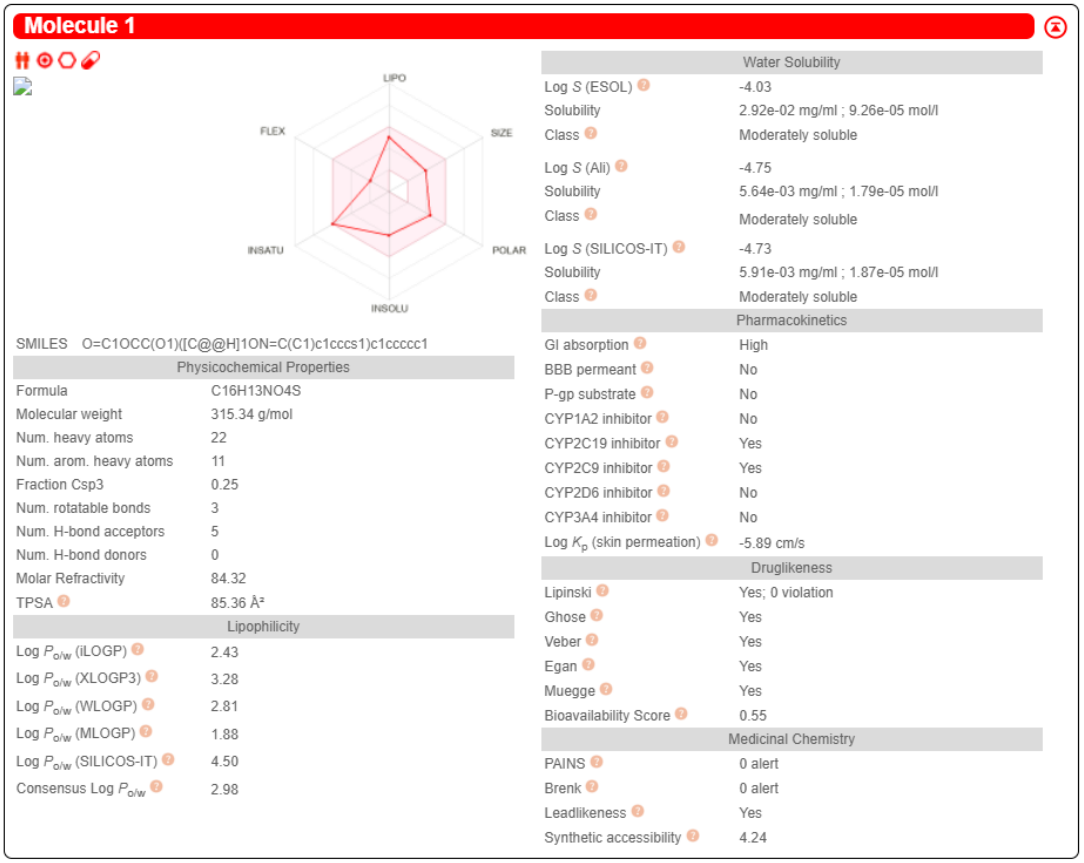
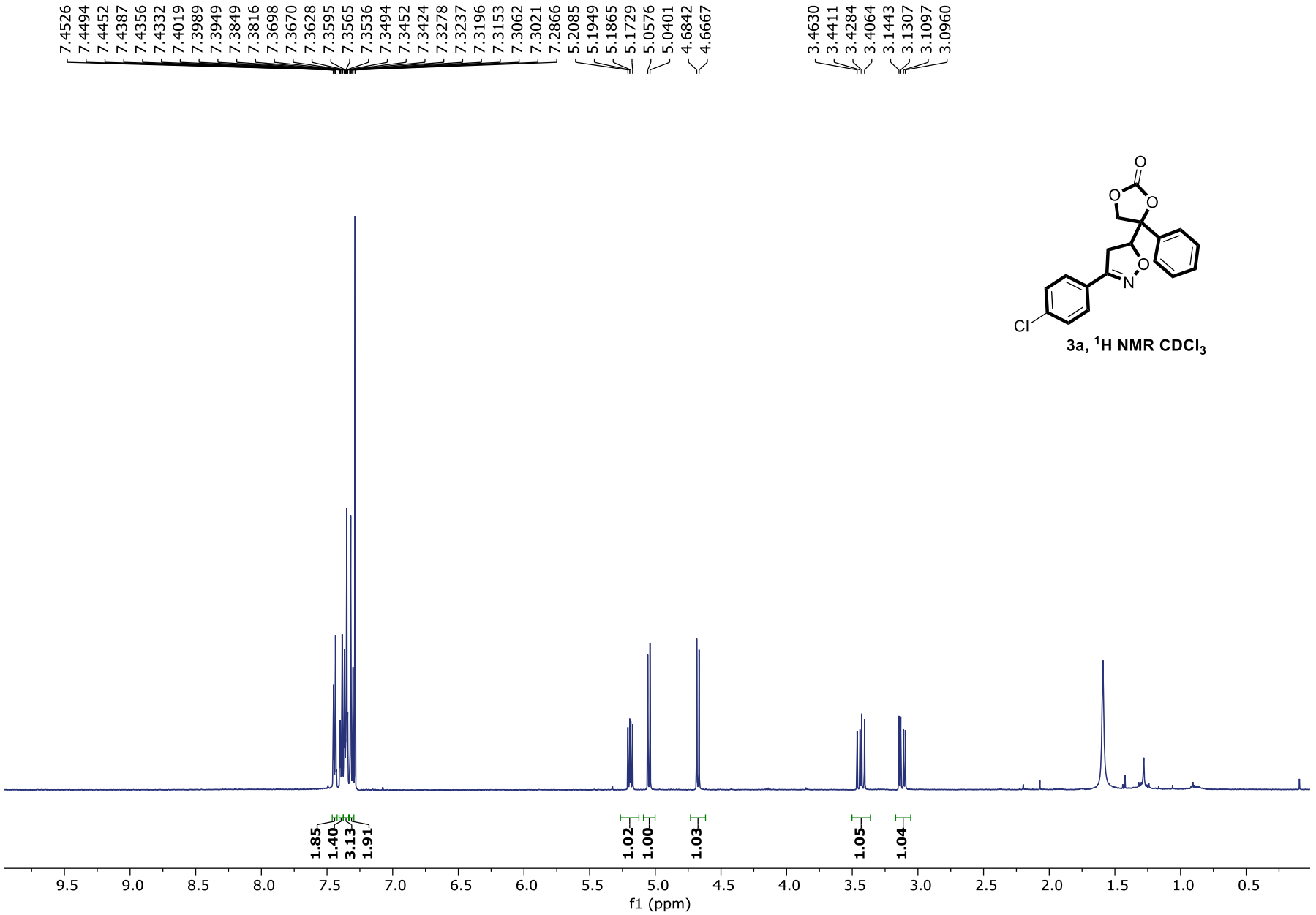


Figure S3. Illustration of physicochemical descriptors, ADME parameters, pharmacokinetic properties, druglike nature and medicinal chemistry friendliness of compound **3j**. The analysis was done using SwissADME online server

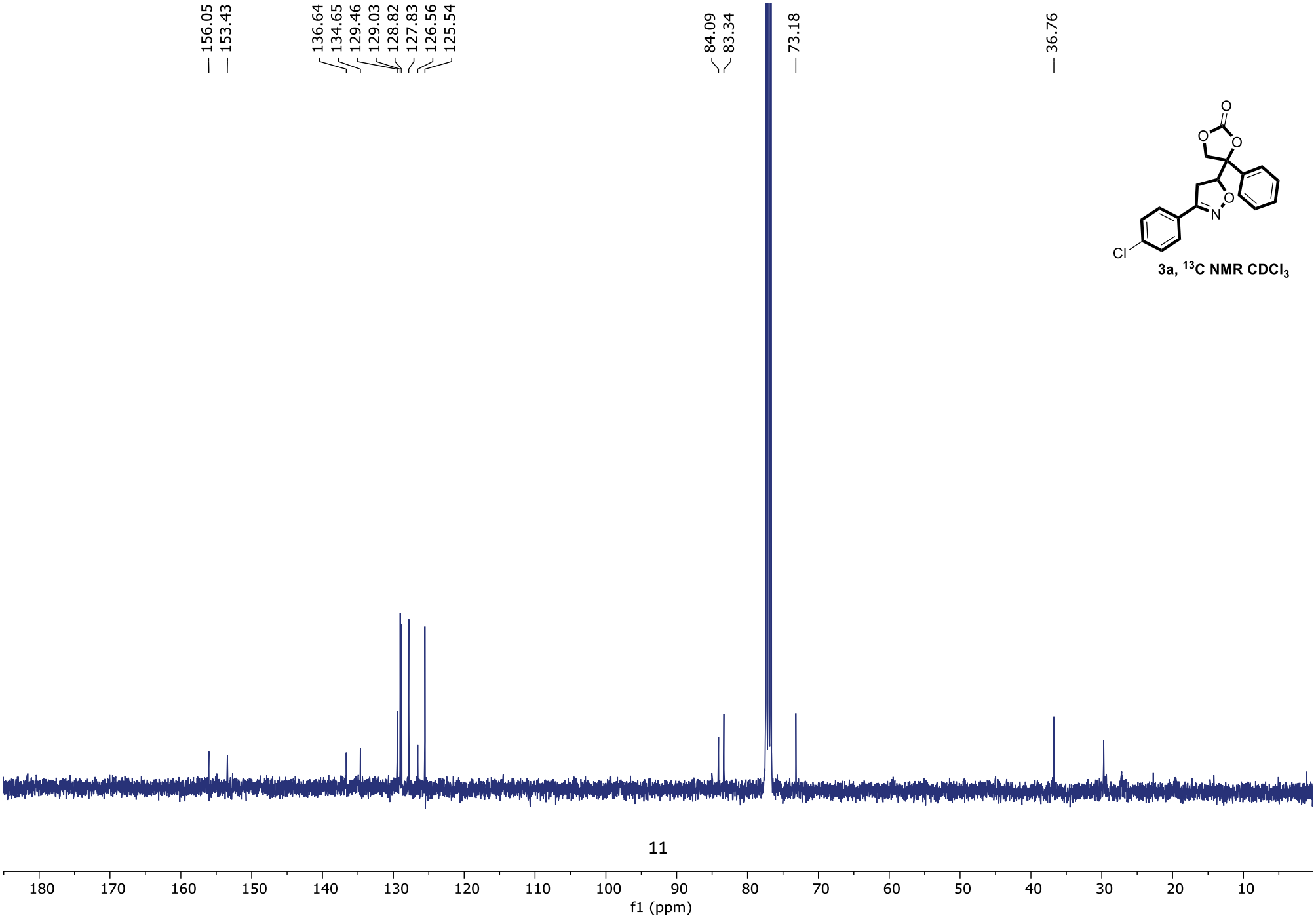
6. References:

1. Khan, A.; Zheng, R.; Kan, Y.; Ye, J.; Xing, J.; Zhang, Y. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6439-6442.
2. Jiang, K. M.; Luesakul, U.; Zhao, S. Y.; An, K.; Muangsin, N.; Neamati, N.; Jin, Y.; Lin, J. *ACS Omega.* **2017**, *2*, 3123−31.

7. ^{1}H, ^{13}C NMR and HRMS spectra of all compounds



3a, ^{1}H NMR $CDCl_3$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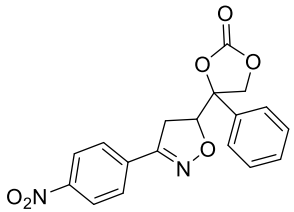
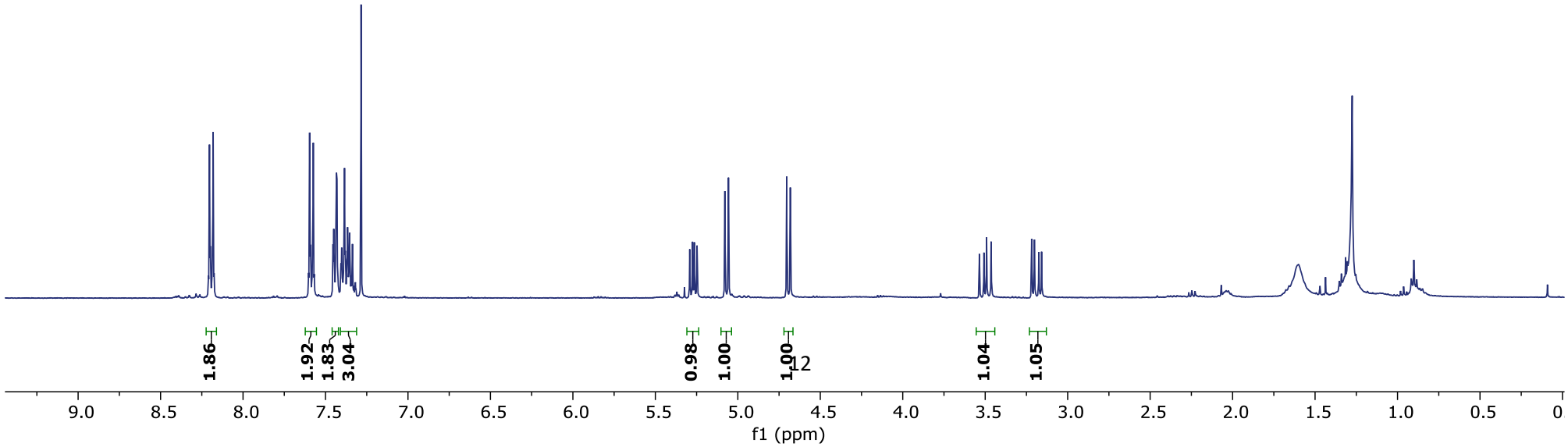
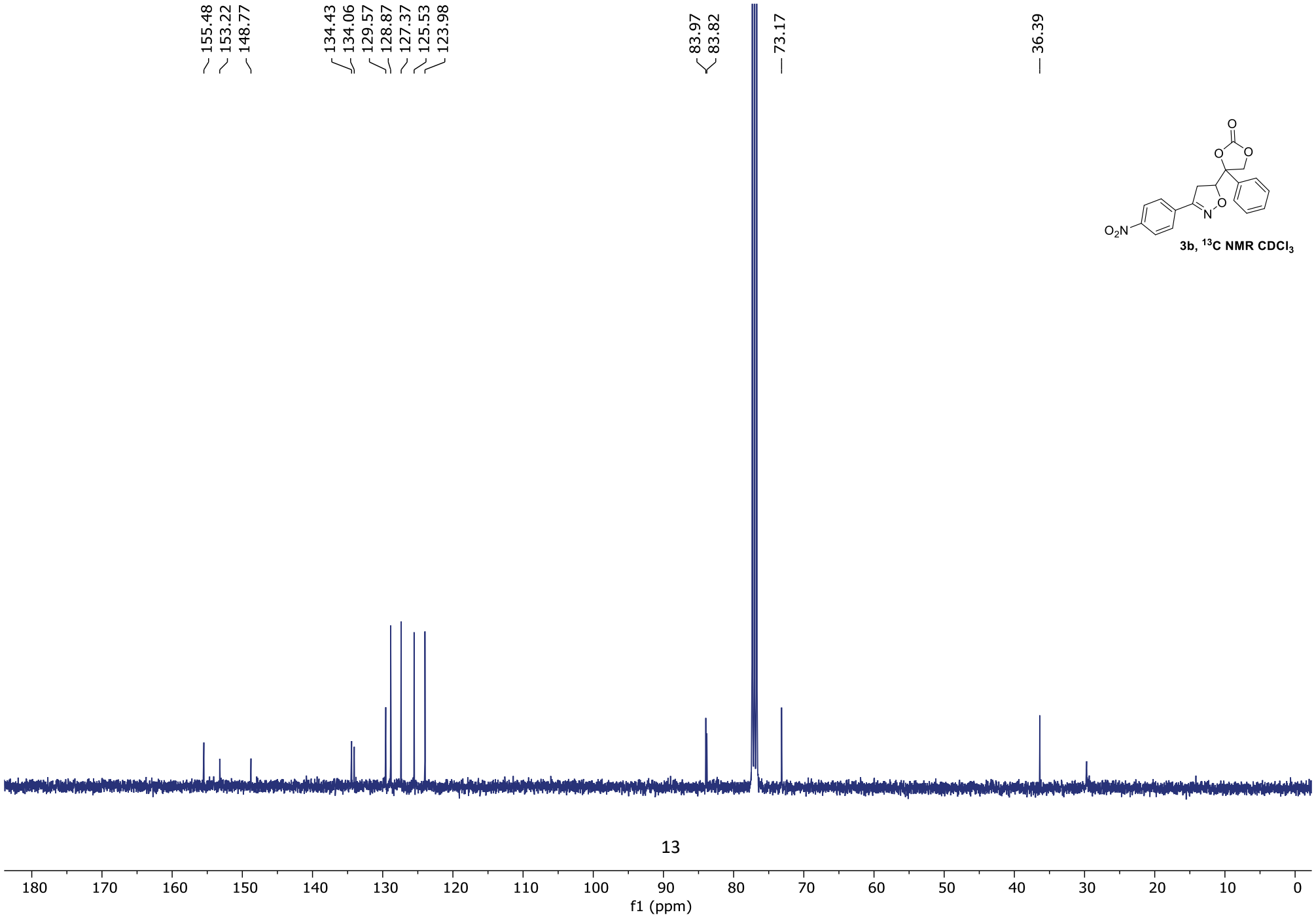
153.43
136.64
134.65
129.46
129.03
128.82
127.83
126.56
125.54
84.09
83.34
73.18
36.76
O
O
O
O
N
Cl
3a, ^{13}C NMR CDCl$_3$
11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



3b, ^{1}H NMR $CDCl_3$

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134.06
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127.37
125.53
123.98
83.97
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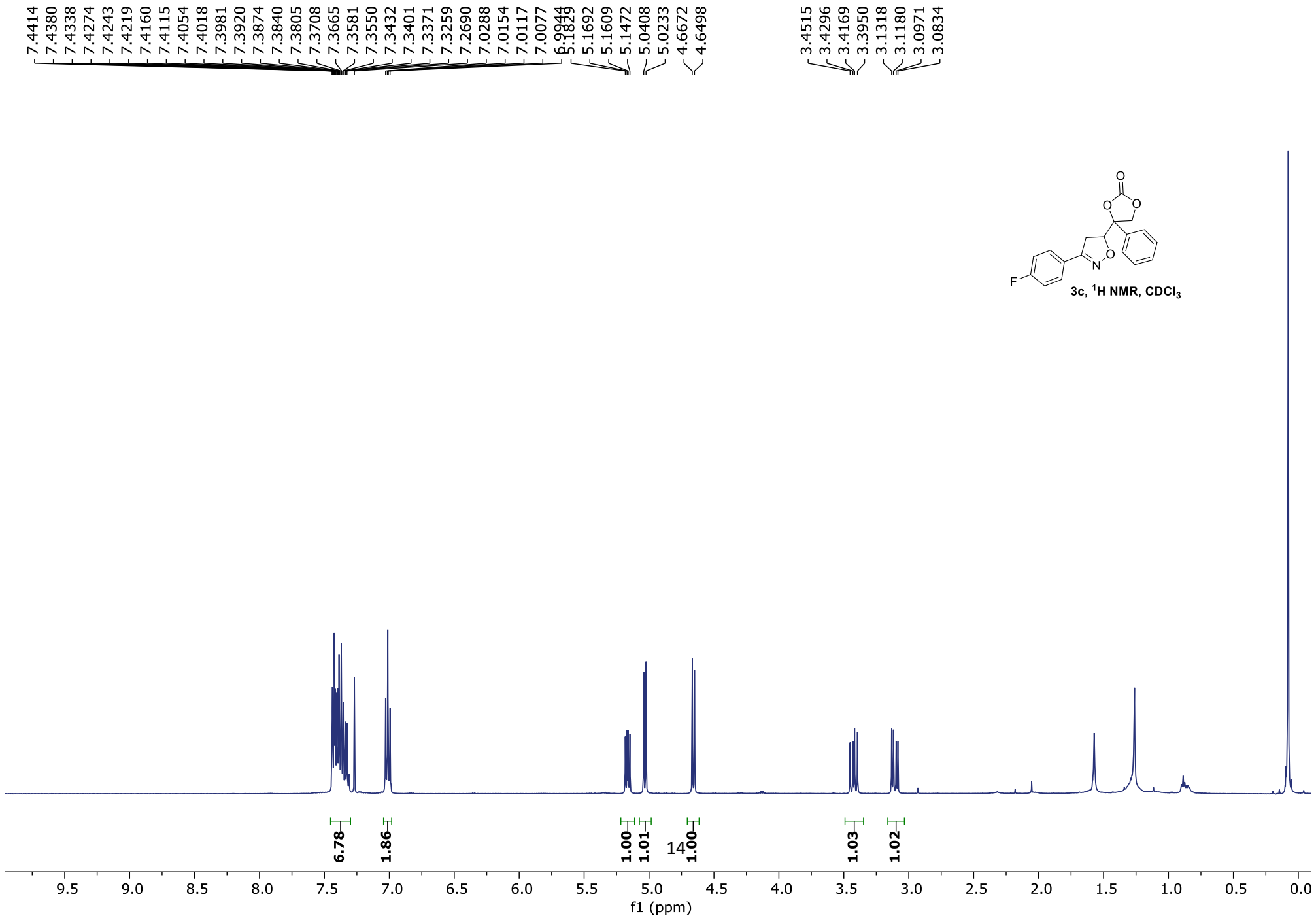
73.17
36.39
O
O
O
N
O
O_2N
3b, ^{13}C NMR $CDCl_3$
13
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.4274
7.4243
7.4219
7.4160
7.4115
7.4054
7.4018
7.3981
7.3920
7.3874
7.3840
7.3805
7.3708
7.3665
7.3581
7.3550
7.3432
7.3401
7.3371
7.3259
7.2690
7.0288
7.0154
7.0117
7.0077
6.9944
5.1829
5.1692
5.1609
5.1472
5.0408
5.0233
4.6672
4.6498
3.4515
3.4296
3.4169
3.3950
3.1318
3.1180
3.0971
3.0834
O
O
O
N
O
F
3c, ^{1}H NMR, CDCl$_3$
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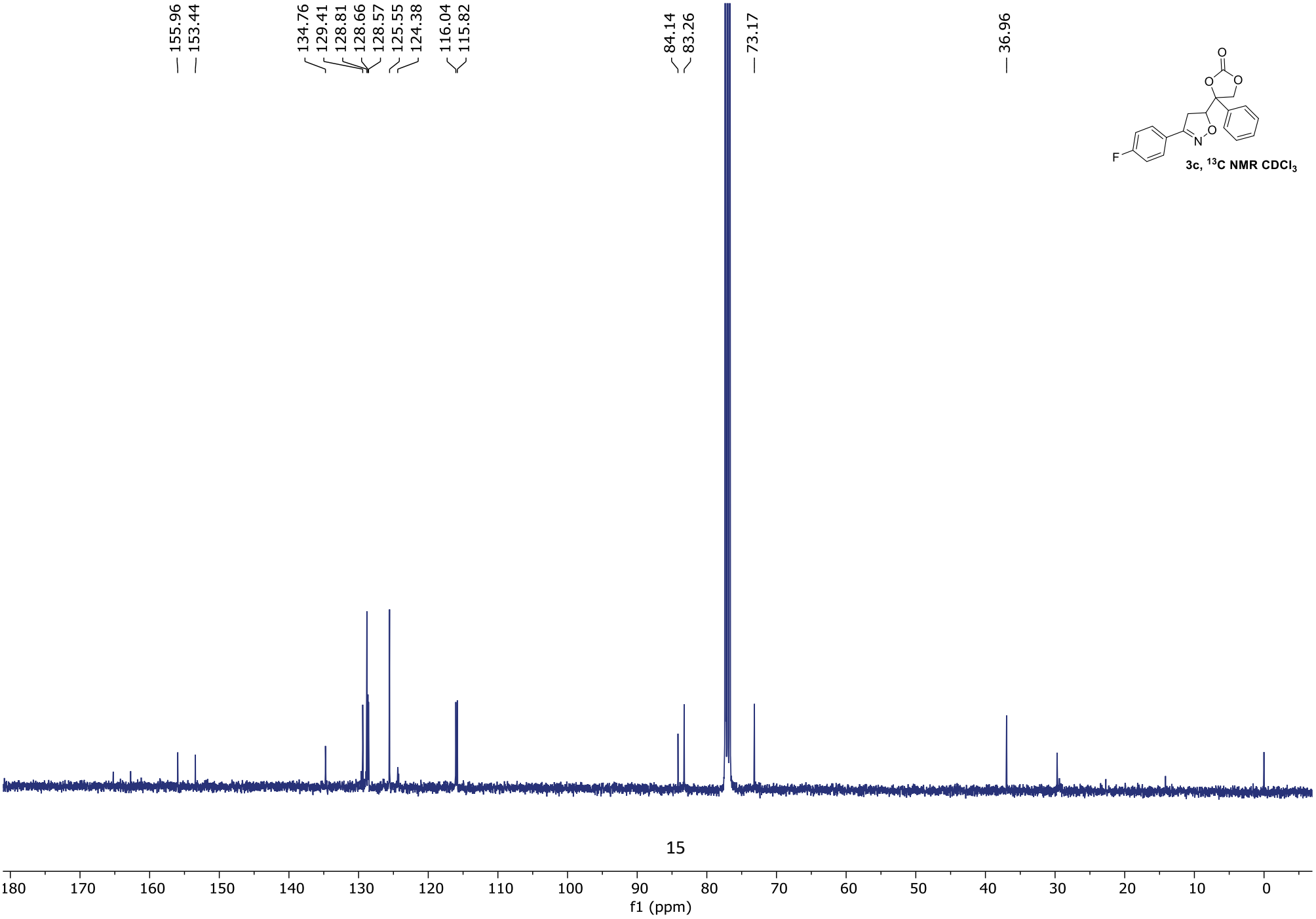
1.86
1.00
1.01
1.00
1.03
1.02
f1 (ppm)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115.82
84.14
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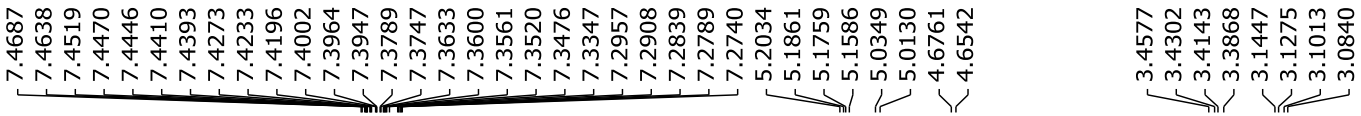
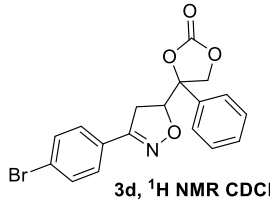
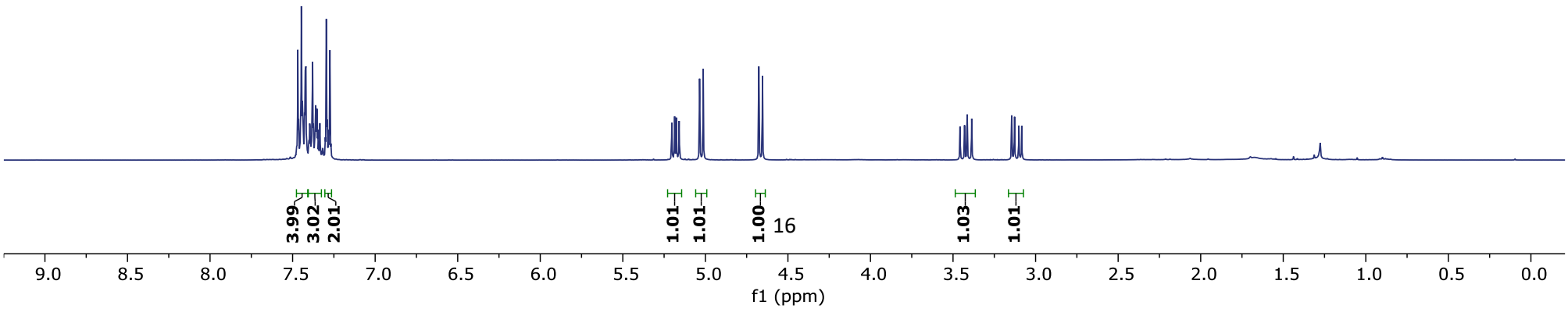
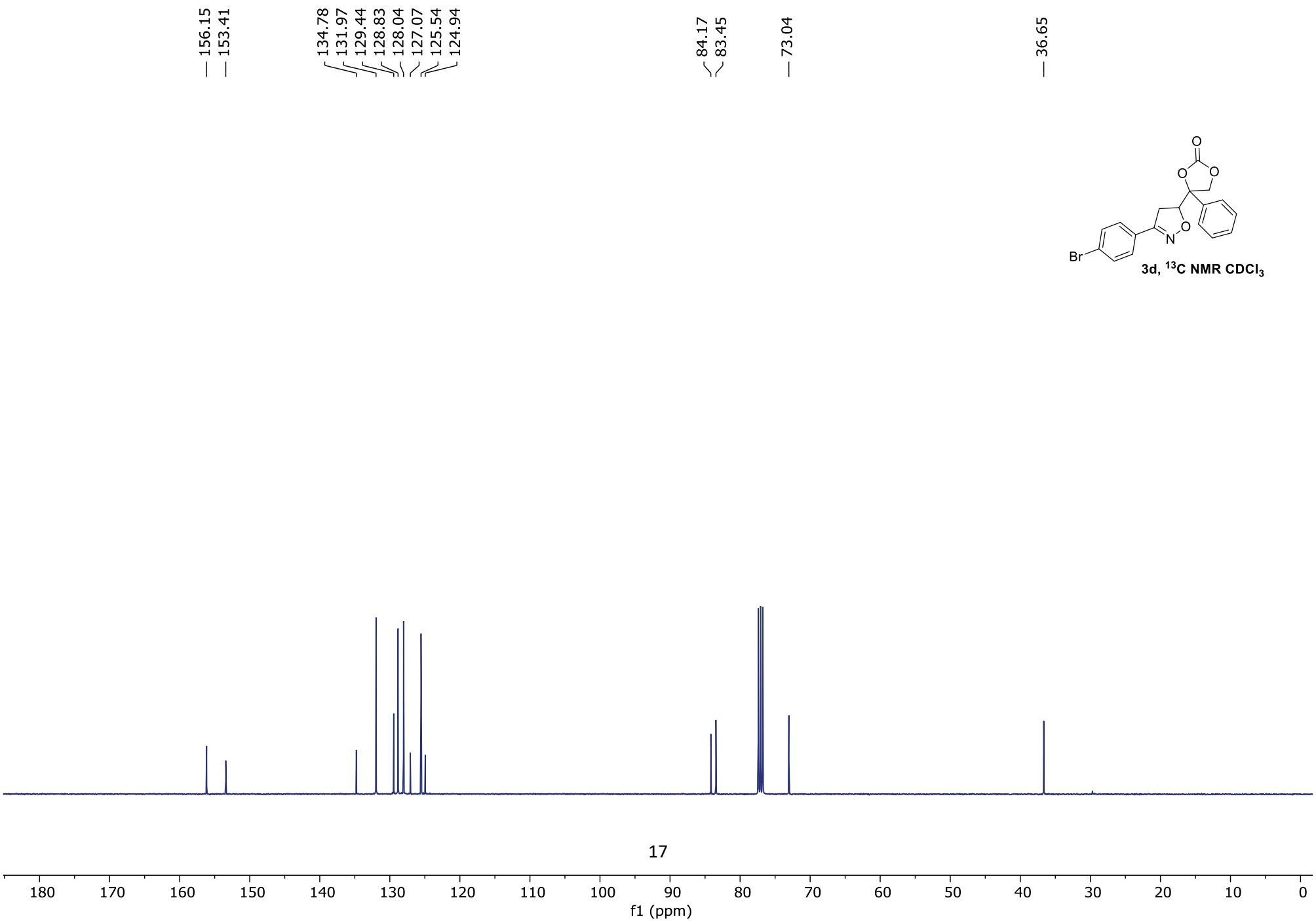
73.17
36.96
O
O
O
O
N
F
3c, ^{13}C NMR CDCl$_3$
15
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)





3d, ^{1}H NMR $CDCl_3$

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127.07
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124.94
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83.45
73.04
36.65
O
O
O
O
N
Br
3d, ^{13}C NMR CDCl$_3$
17
180
170
160
150
140
130
120
110
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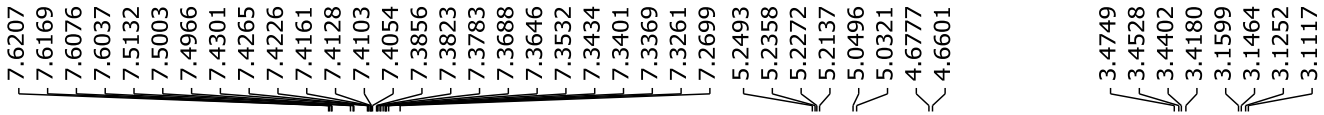
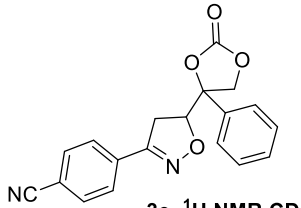
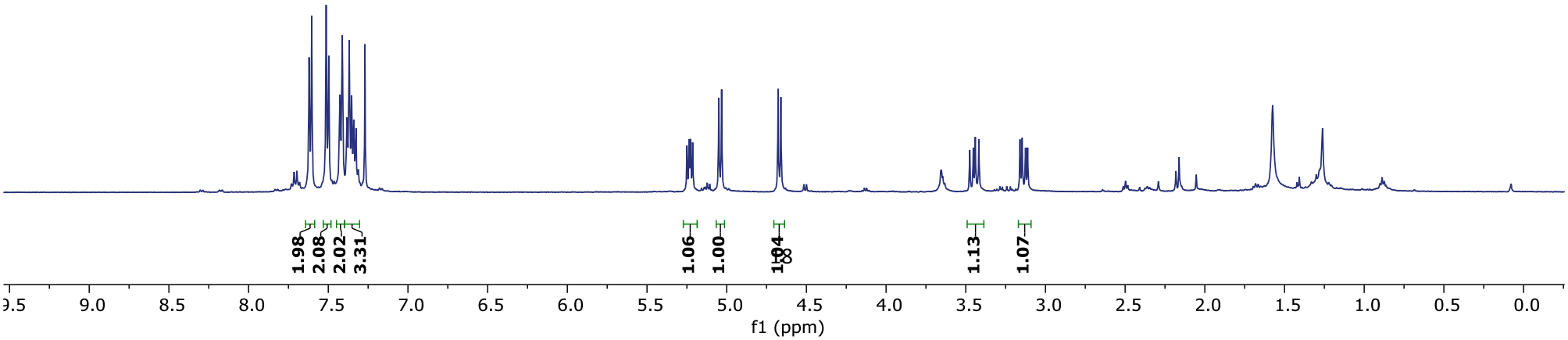
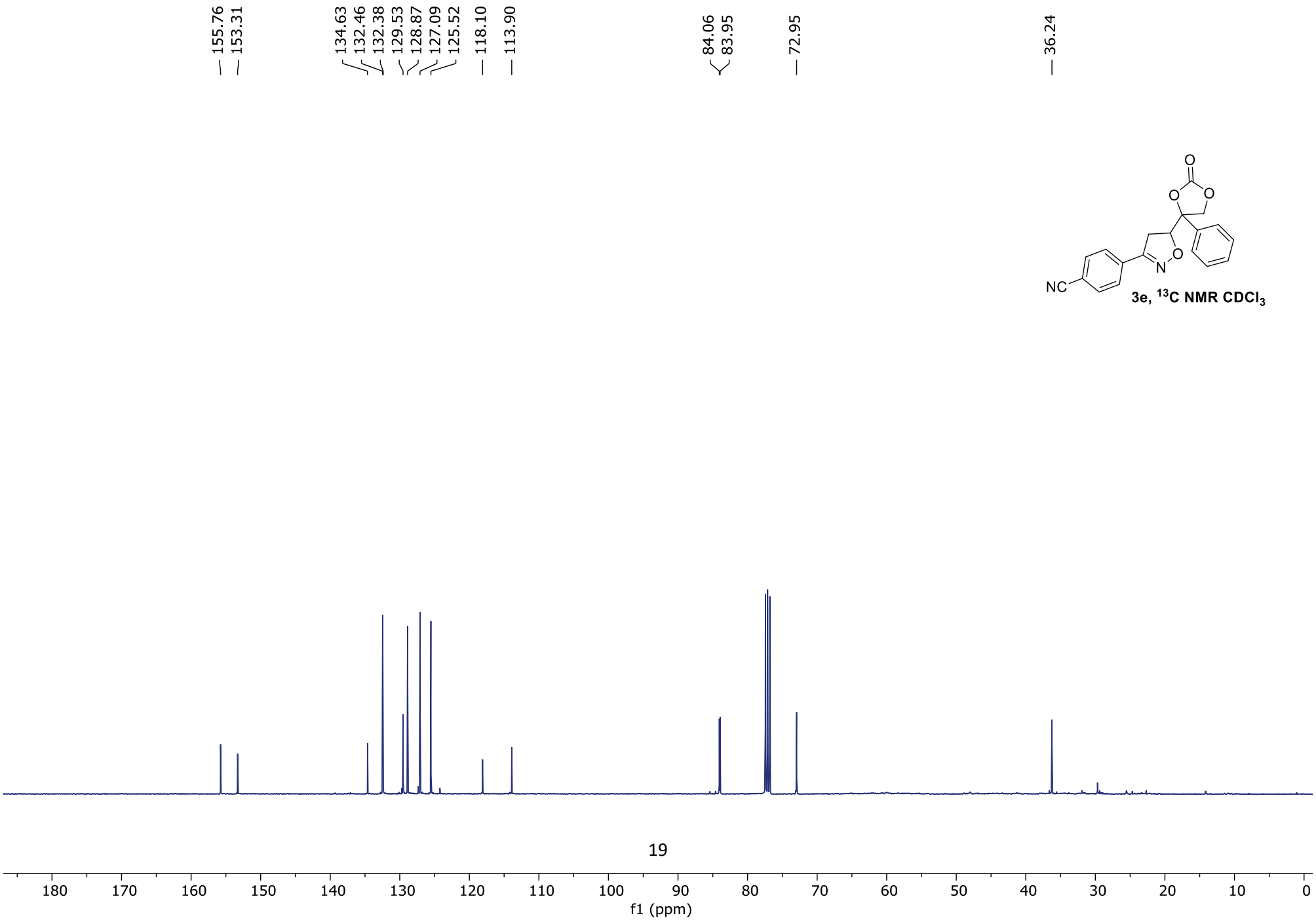
90
80
70
60
50
40
30
20
10
0
f1 (ppm)





3e, ^{1}H NMR $CDCl_3$

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72.95
36.24
O
O
O
N
O
NC
3e, ^{13}C NMR CDCl$_3$
19
180
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120
110
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90
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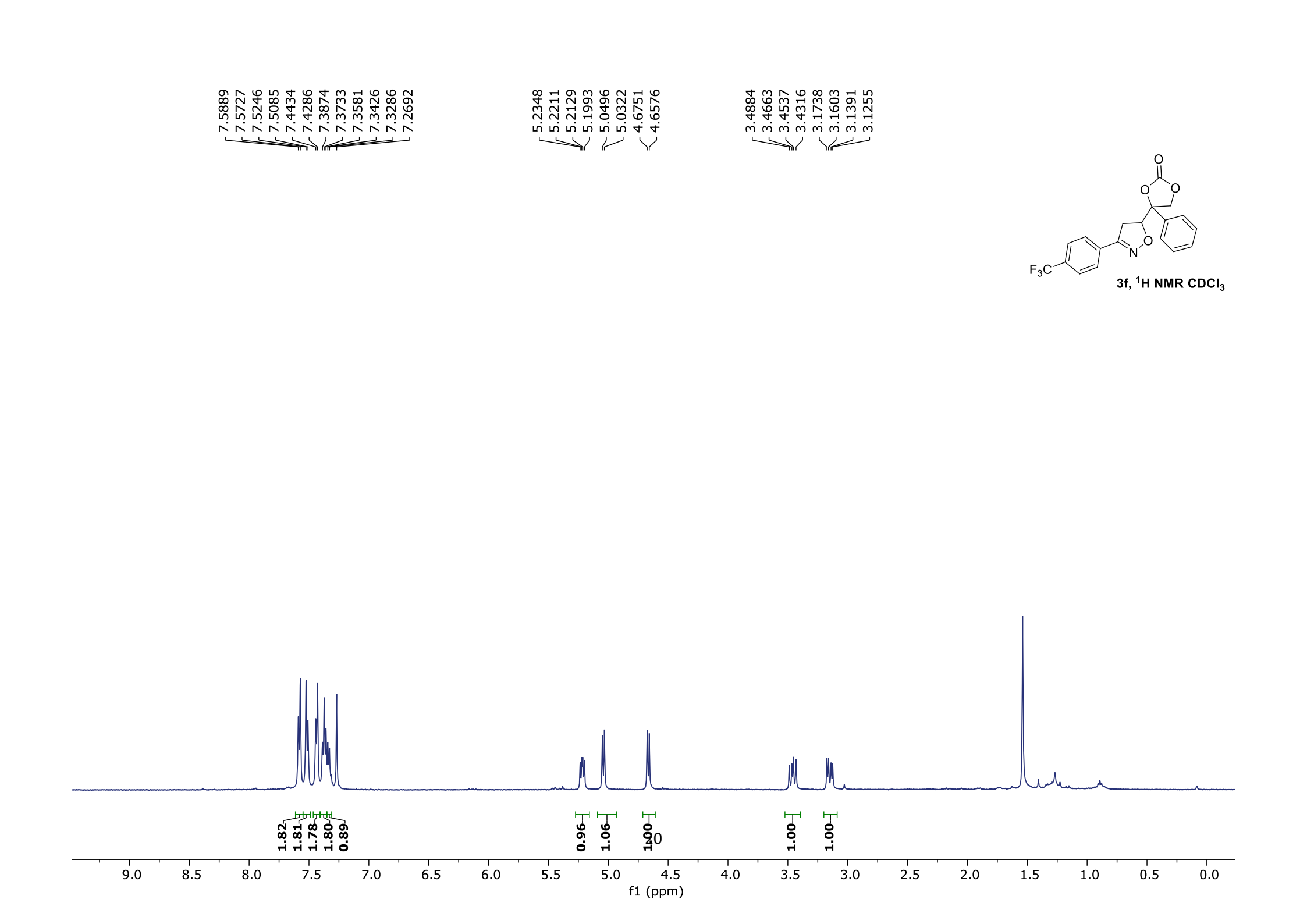
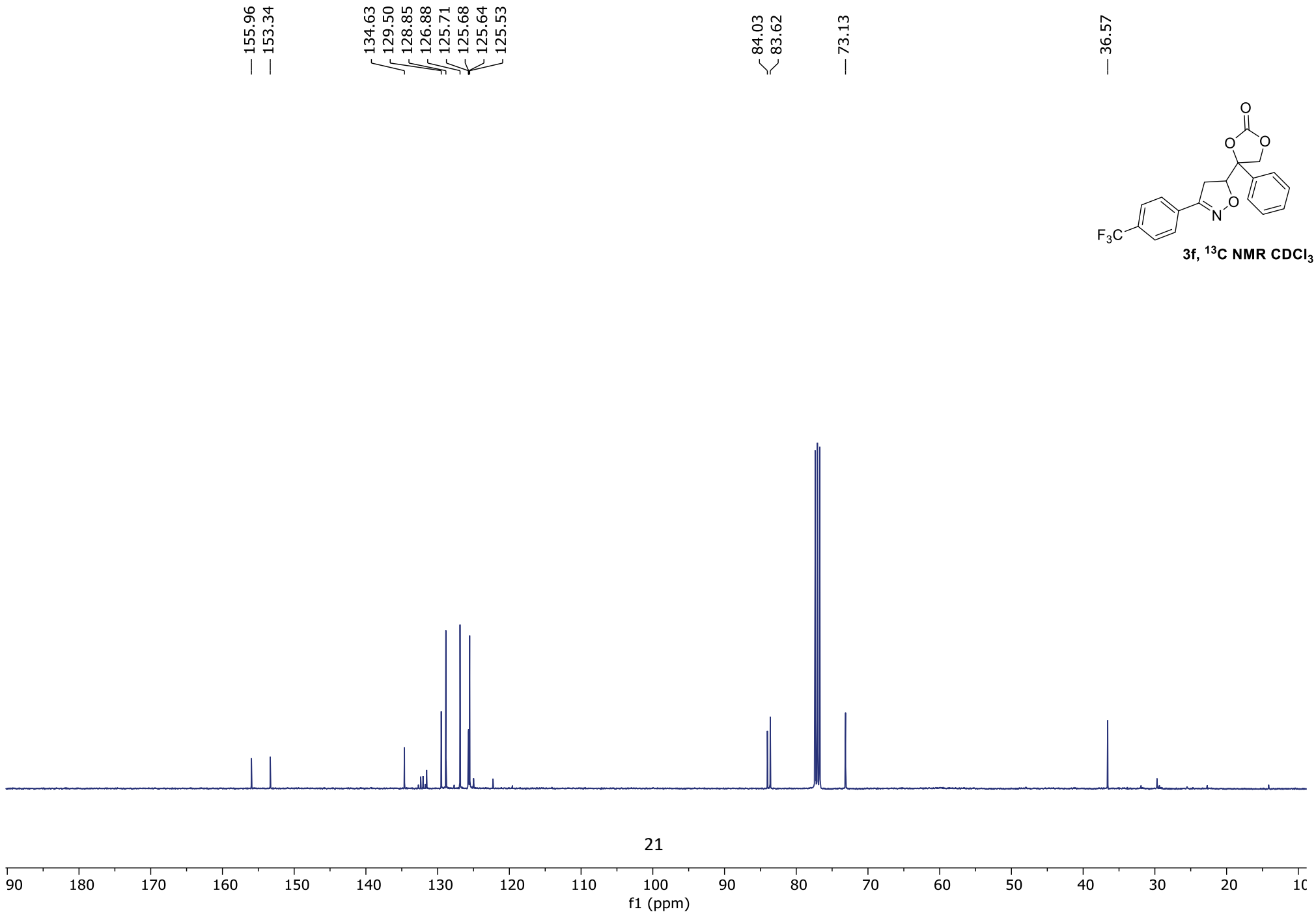
50
40
30
20
10
0
f1 (ppm)



3f, ^{1}H NMR $CDCl_3$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129.50
128.85
126.88
125.71
125.68
125.64
125.53
84.03
83.62
73.13
36.57
O
O
O
O
N
F3C
3f, 13C NMR CDCl3
21
90
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140
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80
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60
50
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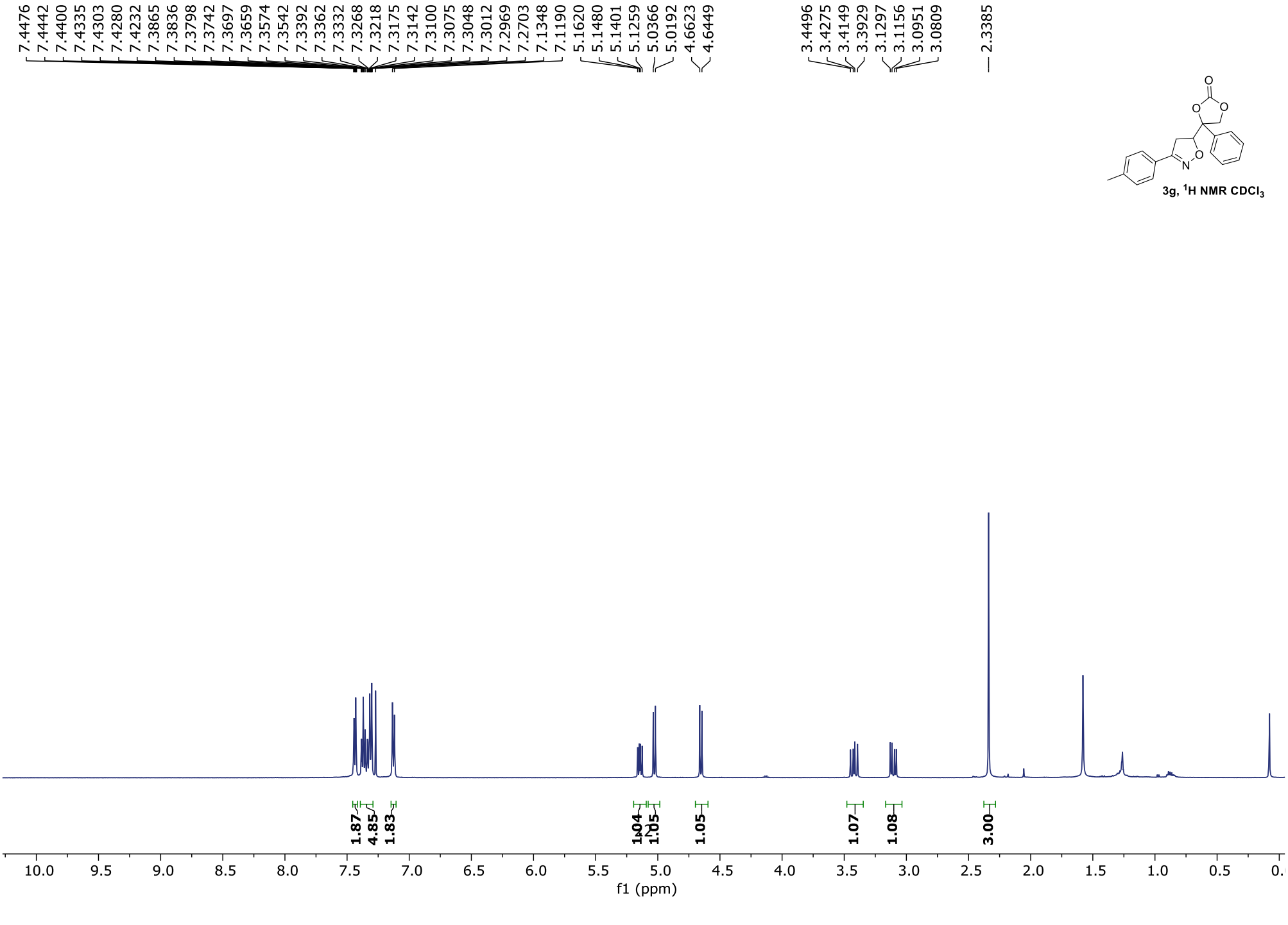
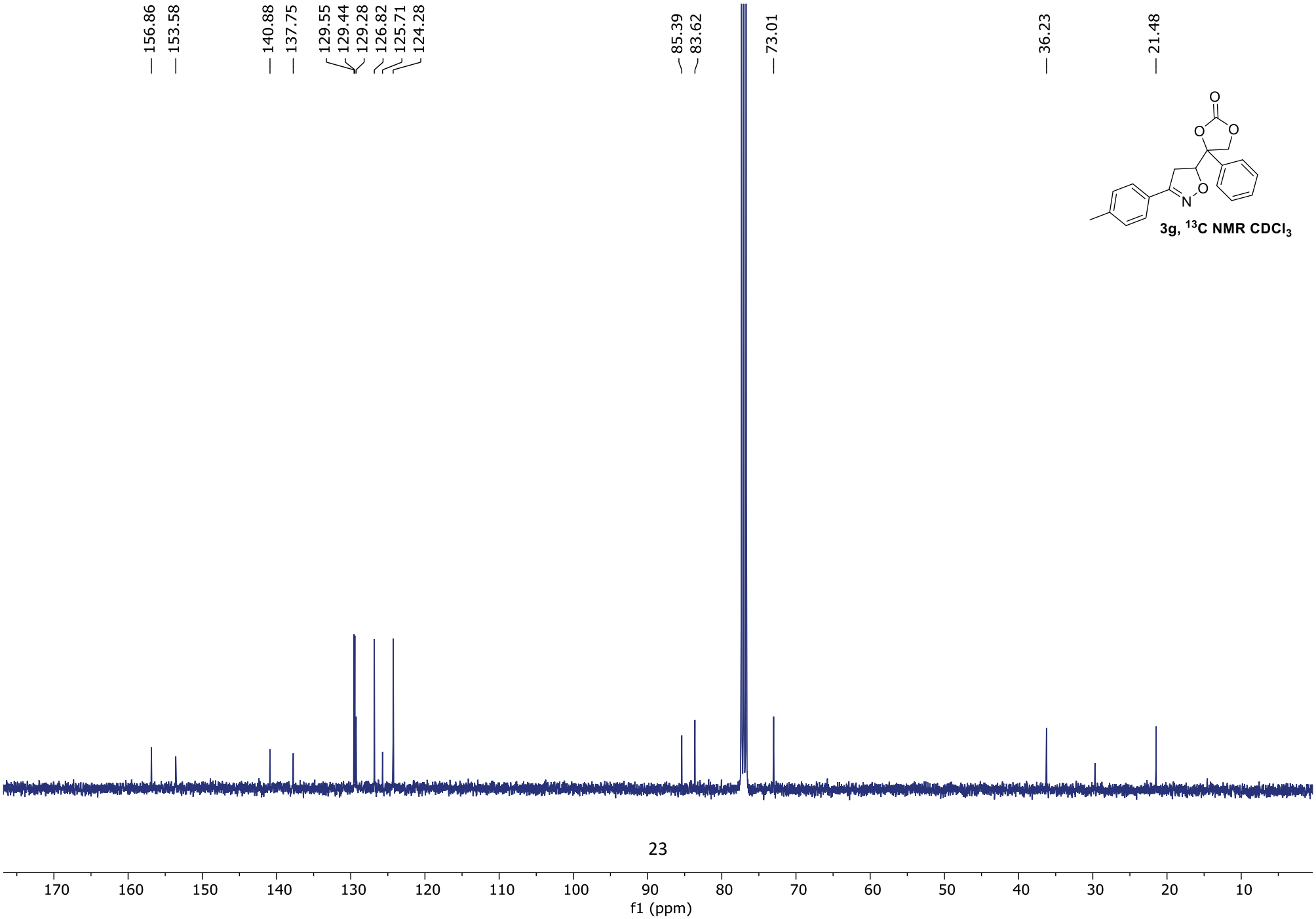
30
20
10
f1 (ppm)



3g, ^{1}H NMR $CDCl_3$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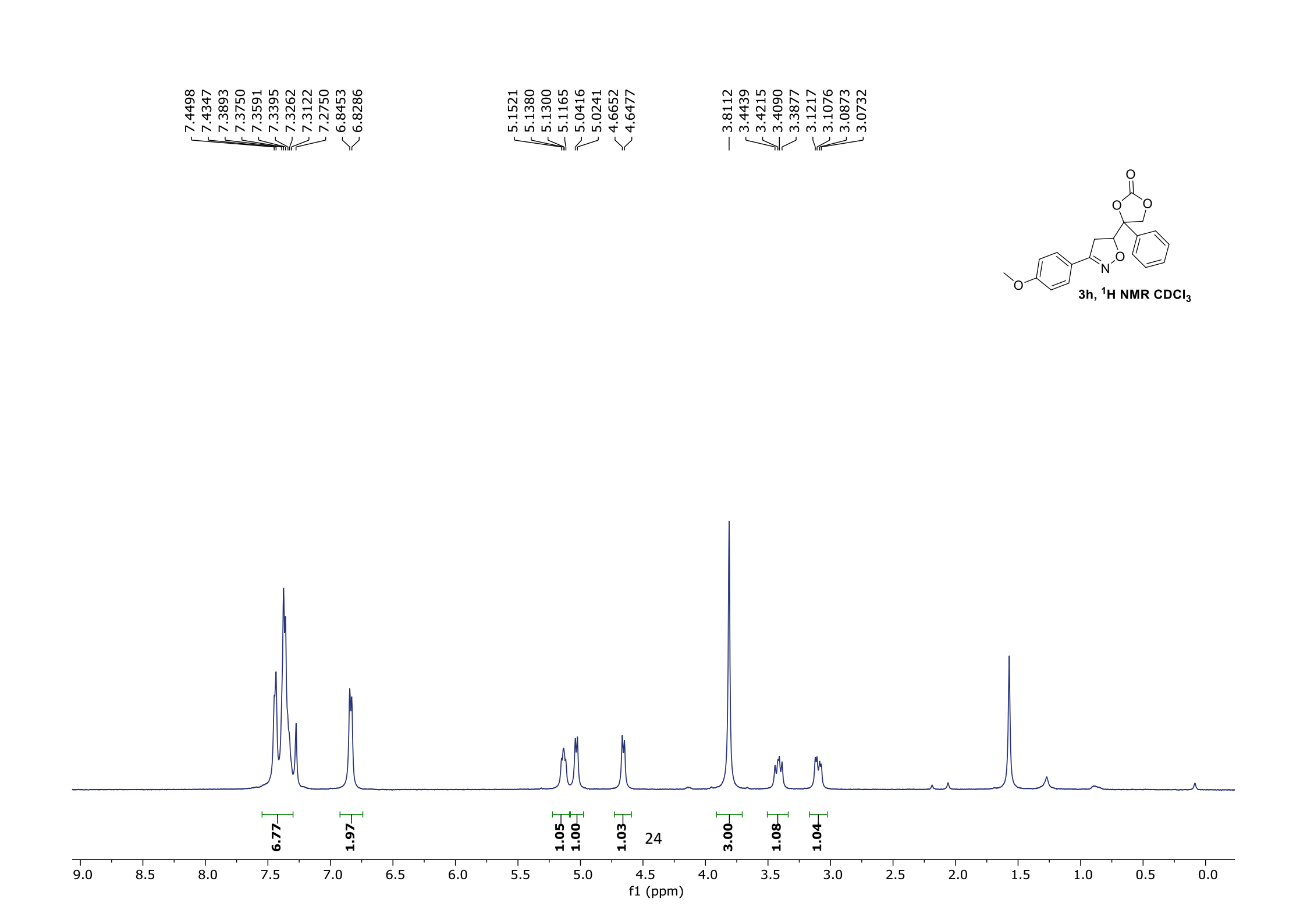
36.23
21.48
O
O
O
N
O
3g, ^{13}C NMR CDCl$_3$
23
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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3.4215
3.4090
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O
O
O
O
N
O
3h, ^{1}H NMR CDCl$_3$
6.77
1.97
1.05
1.00
1.03
24
3.00
1.08
1.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
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1.5
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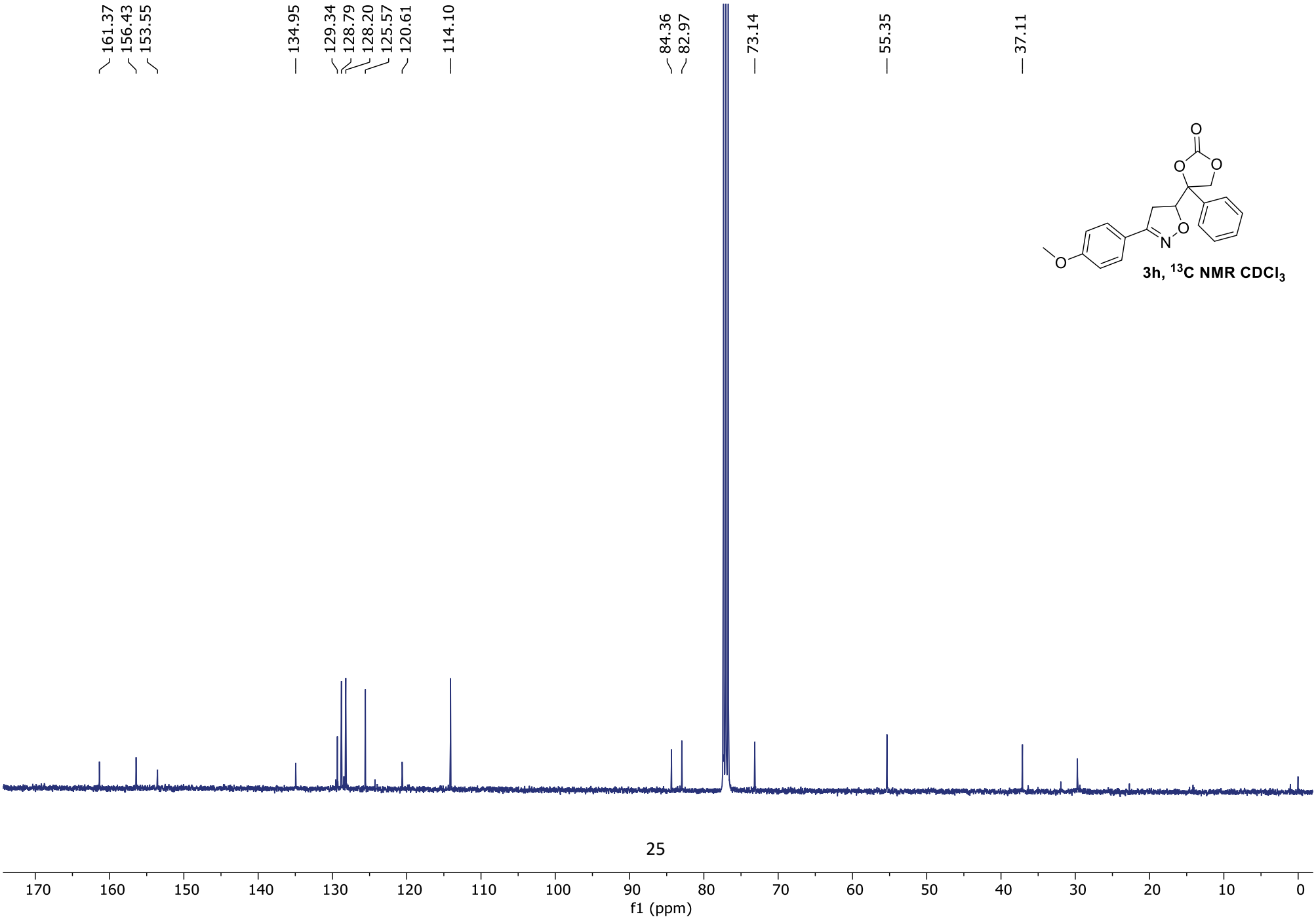
0.5
0.0
f1 (ppm)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129.34
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125.57
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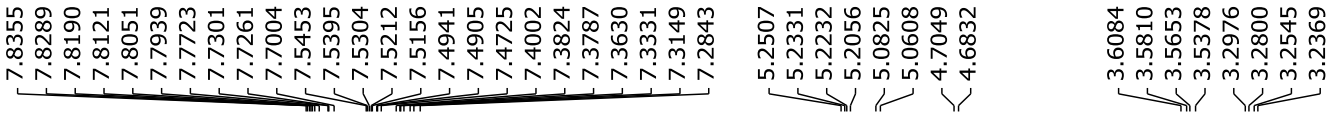
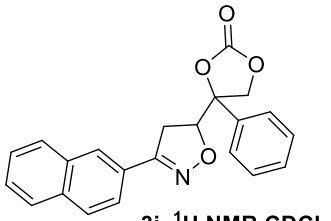
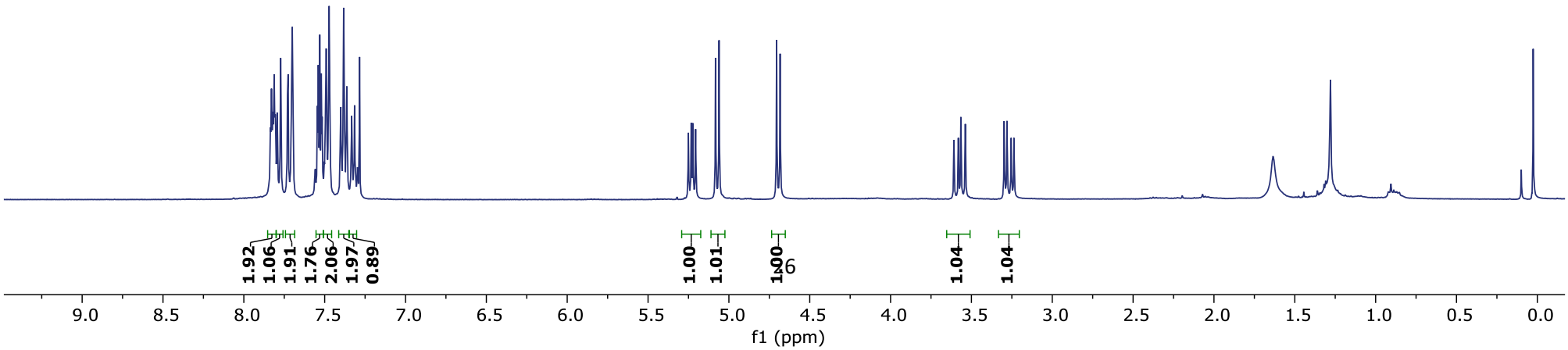
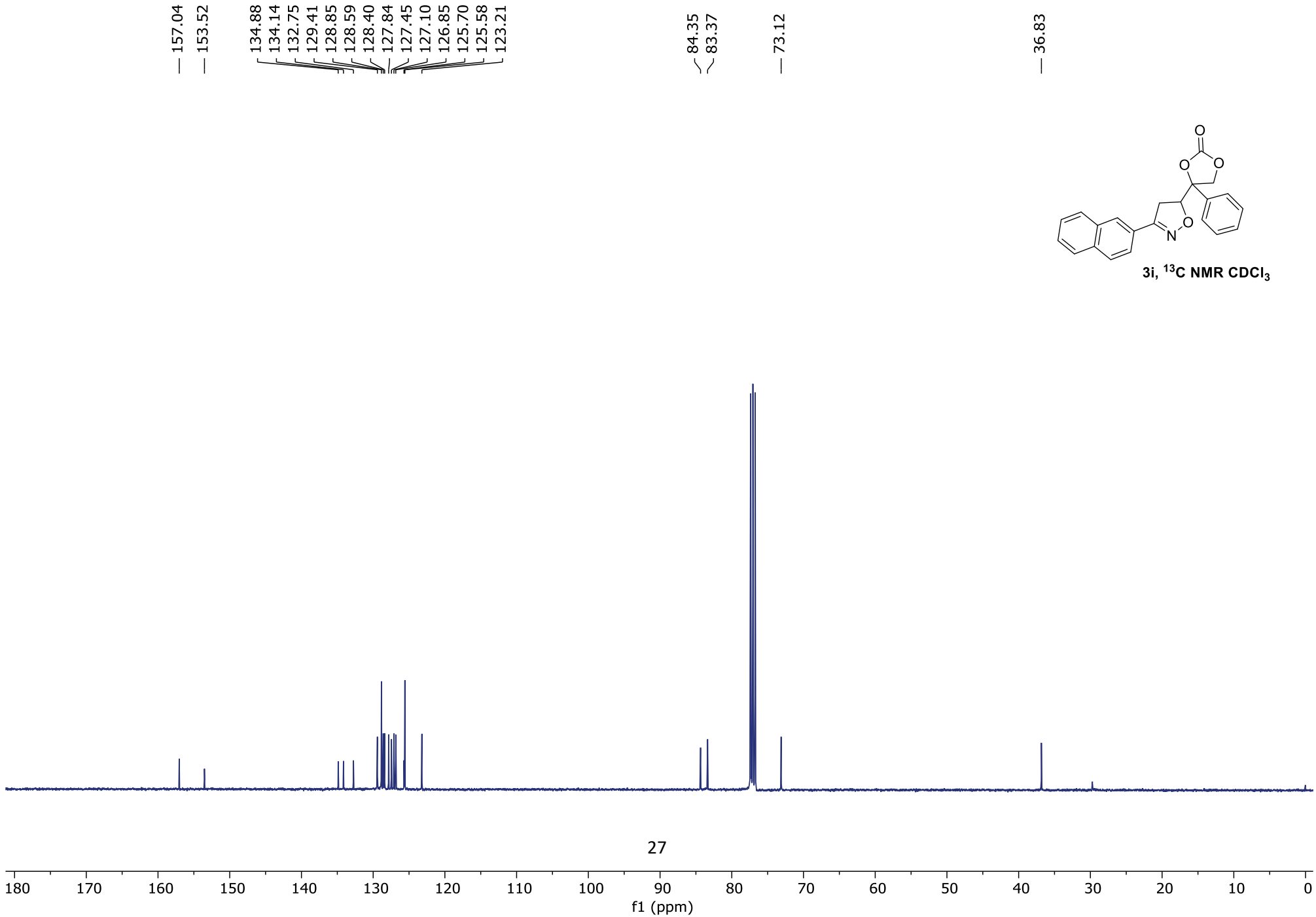
114.10
84.36
82.97
73.14
55.35
37.11
O
O
O
O
N
O
O
3h, ^{13}C NMR CDCl$_3$
25
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)





3i, ^{1}H NMR $CDCl_3$

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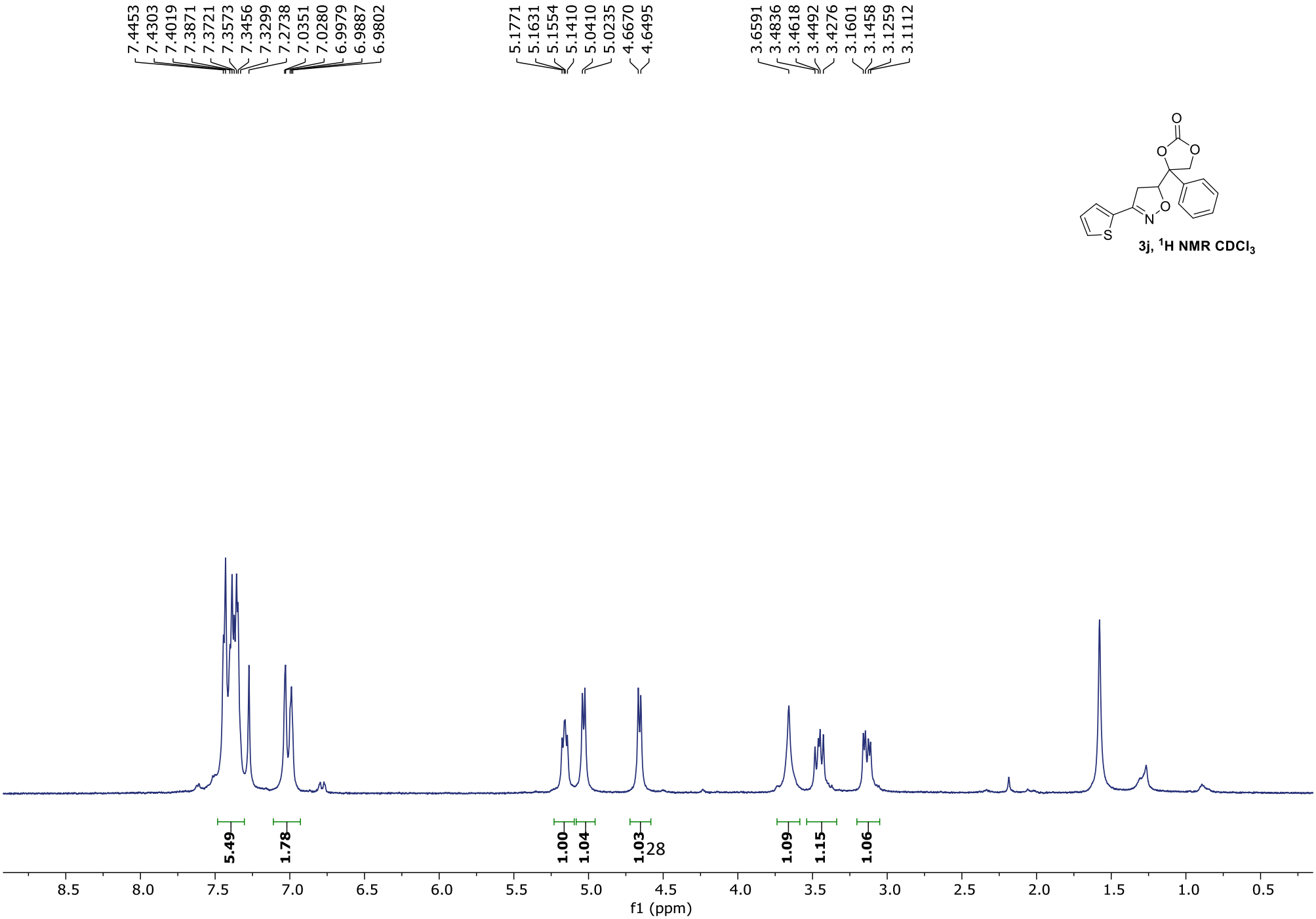
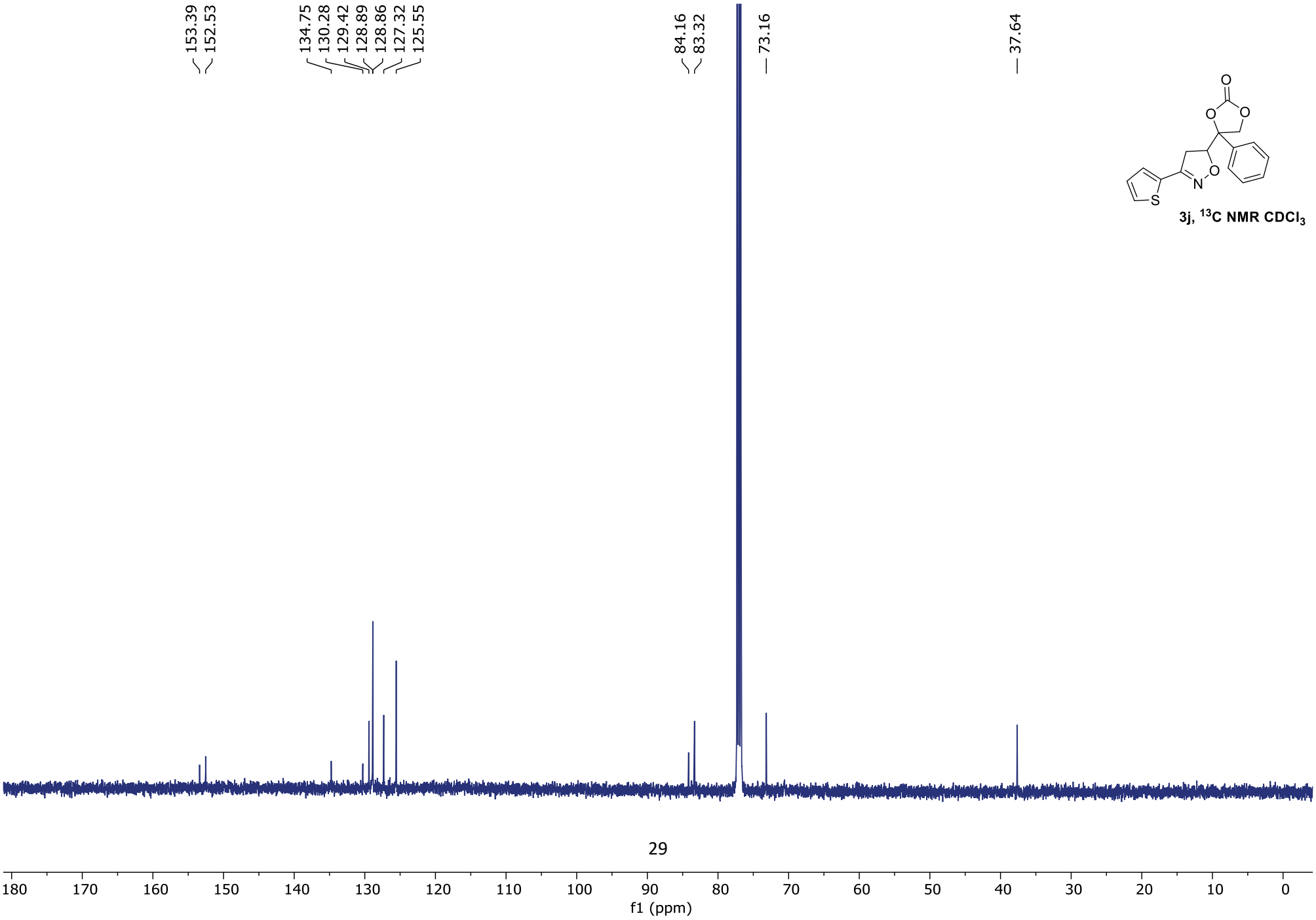
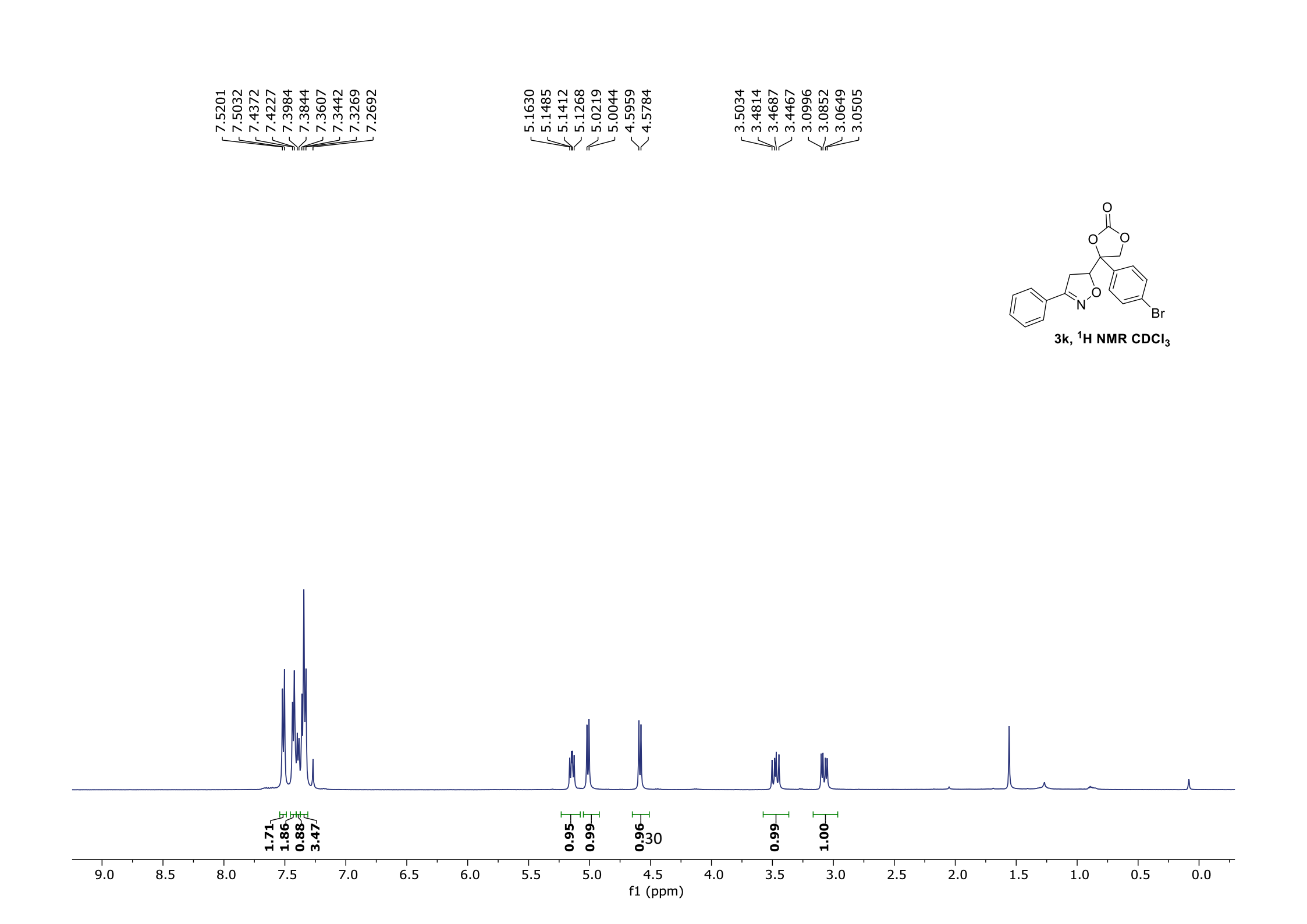
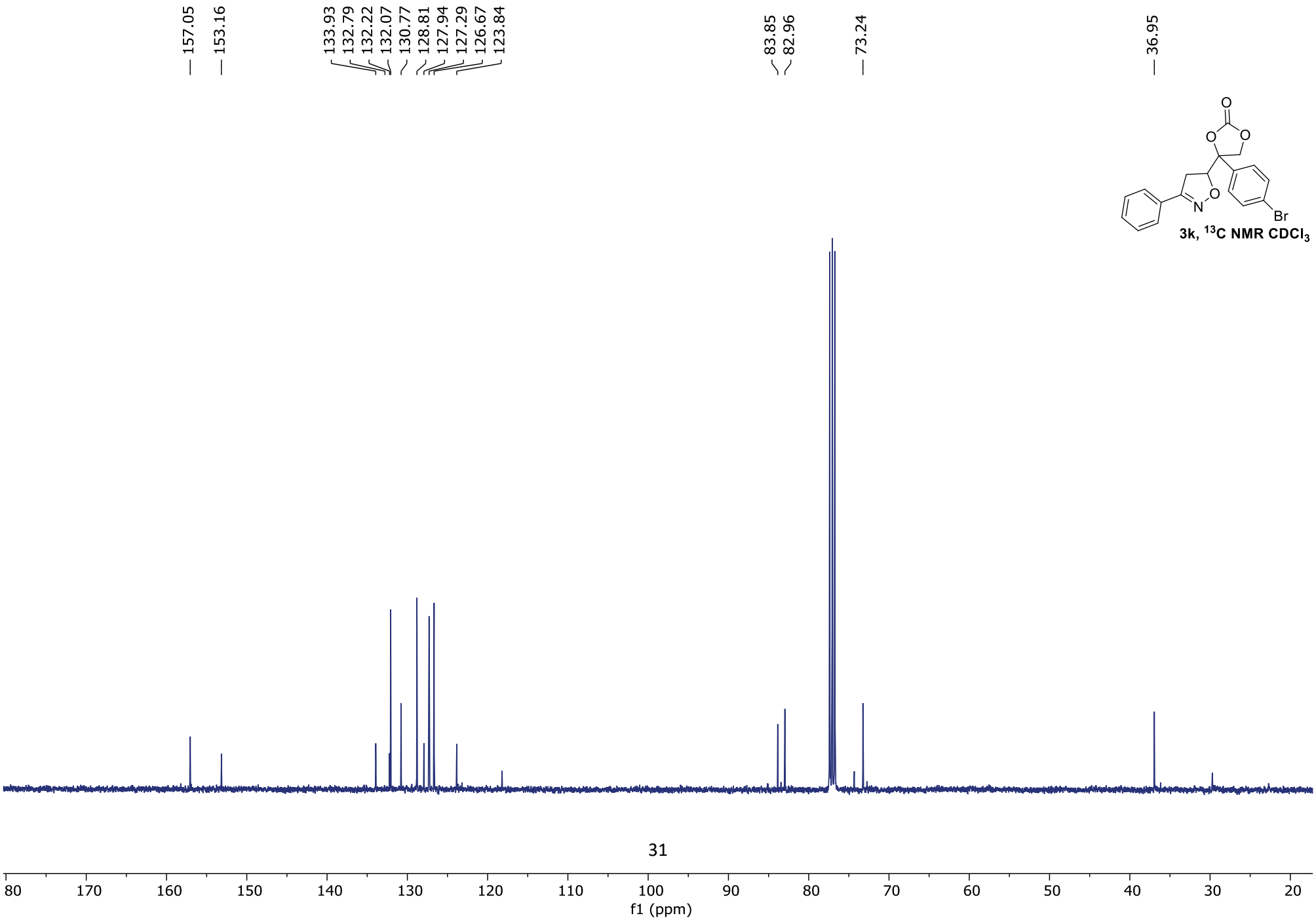
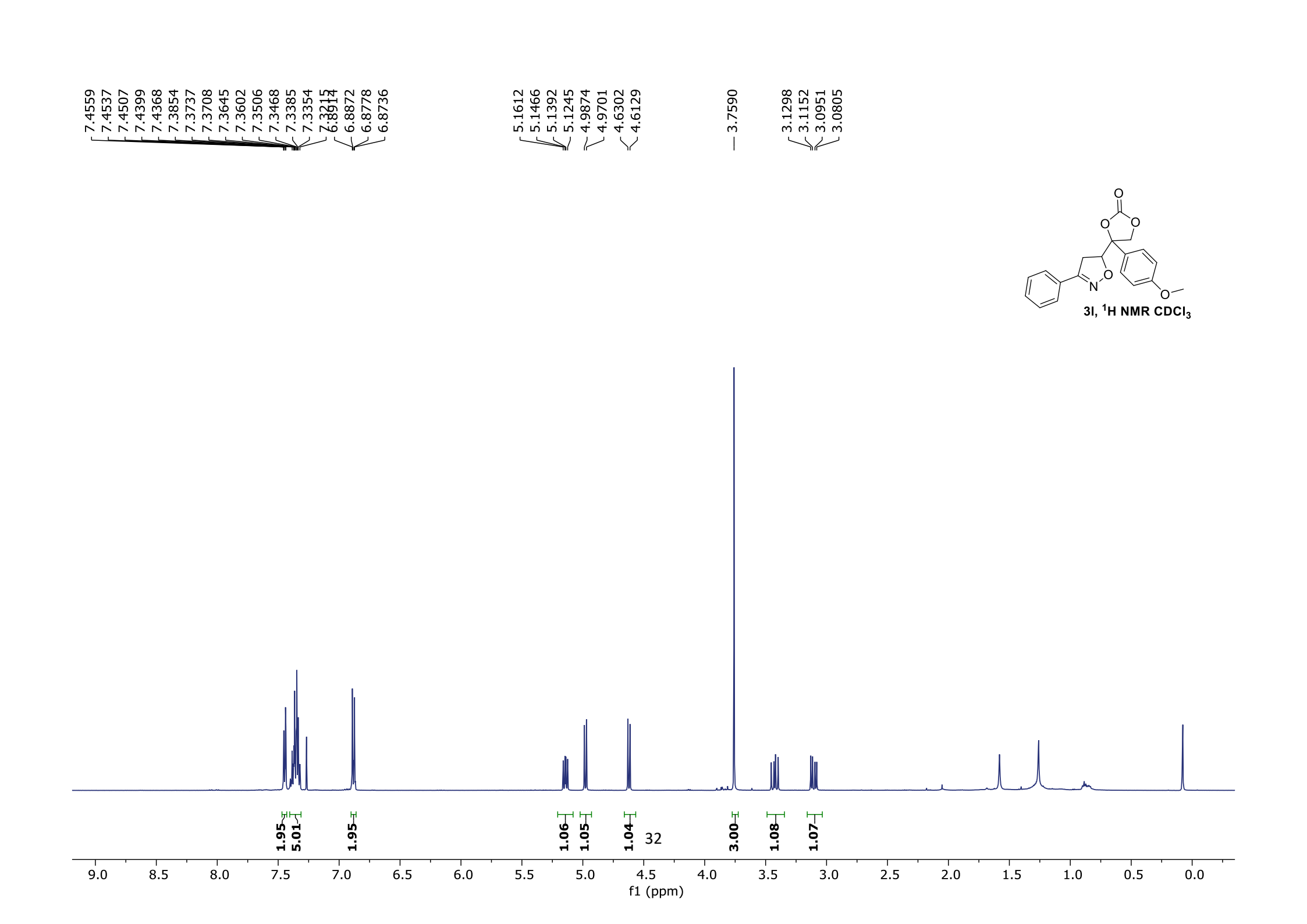
126.85
125.70
125.58
123.21
84.35
83.37
73.12
36.83
O
O
O
O
N
3i, ^{13}C NMR CDCl$_3$
27
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

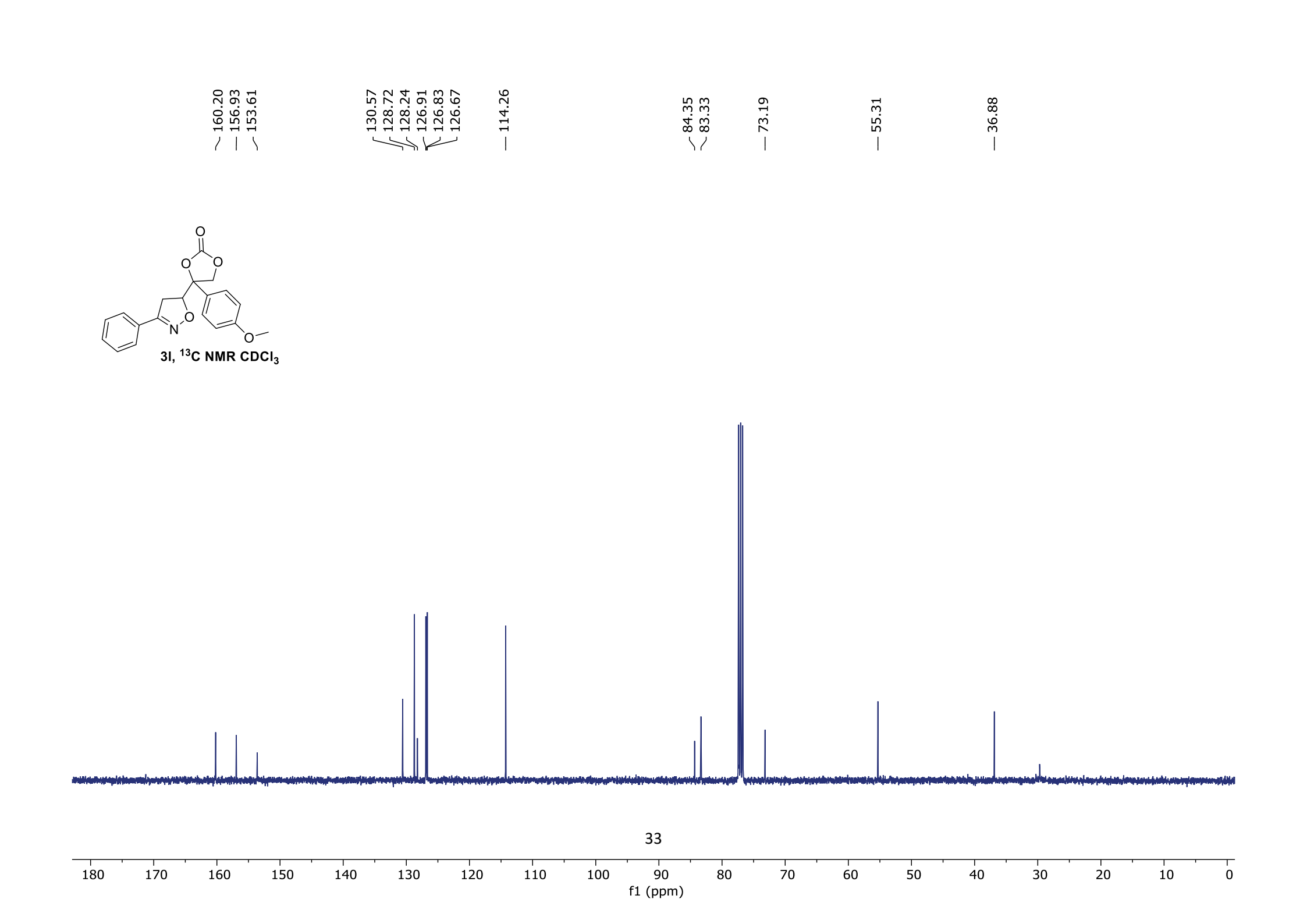

7.4453
7.4303
7.4019
7.3871
7.3721
7.3573
7.3456
7.3299
7.2738
7.0351
7.0280
6.9979
6.9887
6.9802
5.1771
5.1631
5.1554
5.1410
5.0410
5.0235
4.6670
4.6495
3.6591
3.4836
3.4618
3.4492
3.4276
3.1601
3.1458
3.1259
3.1112
O
O
O
O
N
S
3j, ^{1}H NMR CDCl$_3$
5.49
1.78
1.00
1.04
1.03
1.09
1.15
1.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

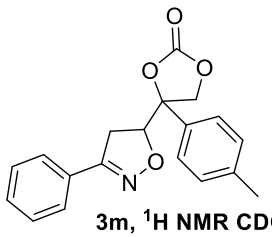

153.39
152.53
134.75
130.28
129.42
128.89
128.86
127.32
125.55
84.16
83.32
73.16
37.64
O
O
O
N
O
S
3j, ^{13}C NMR CDCl$_3$
29
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.5201
7.5032
7.4372
7.4227
7.3984
7.3844
7.3607
7.3442
7.3269
7.2692
5.1630
5.1485
5.1412
5.1268
5.0219
5.0044
4.5959
4.5784
3.5034
3.4814
3.4687
3.4467
3.0996
3.0852
3.0649
3.0505
O
O
O
N
O
Br
3k, ^{1}H NMR CDCl$_3$
1.71
1.86
0.88
3.47
0.95
0.99
0.96
0.99
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

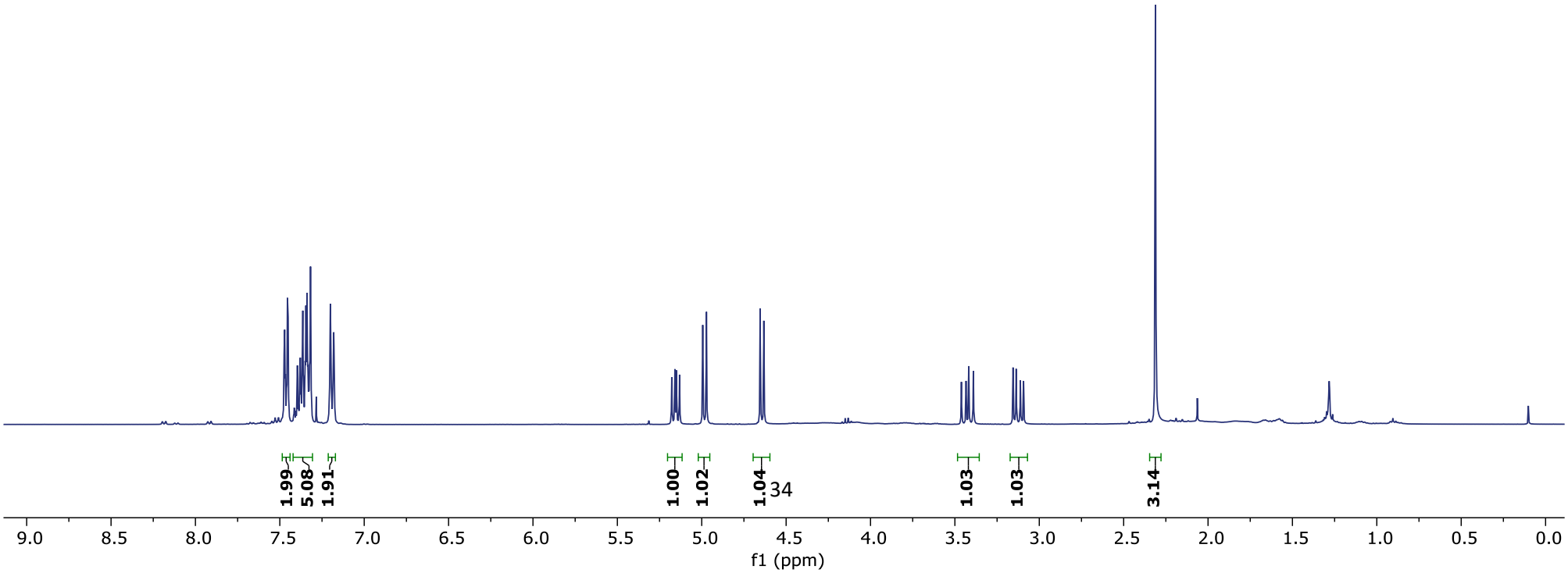

157.05
153.16
133.93
132.79
132.22
132.07
130.77
128.81
127.94
127.29
126.67
123.84
83.85
82.96
73.24
36.95
O
O
O
O
N
Br
3k, ^{13}C NMR CDCl$_3$
31
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

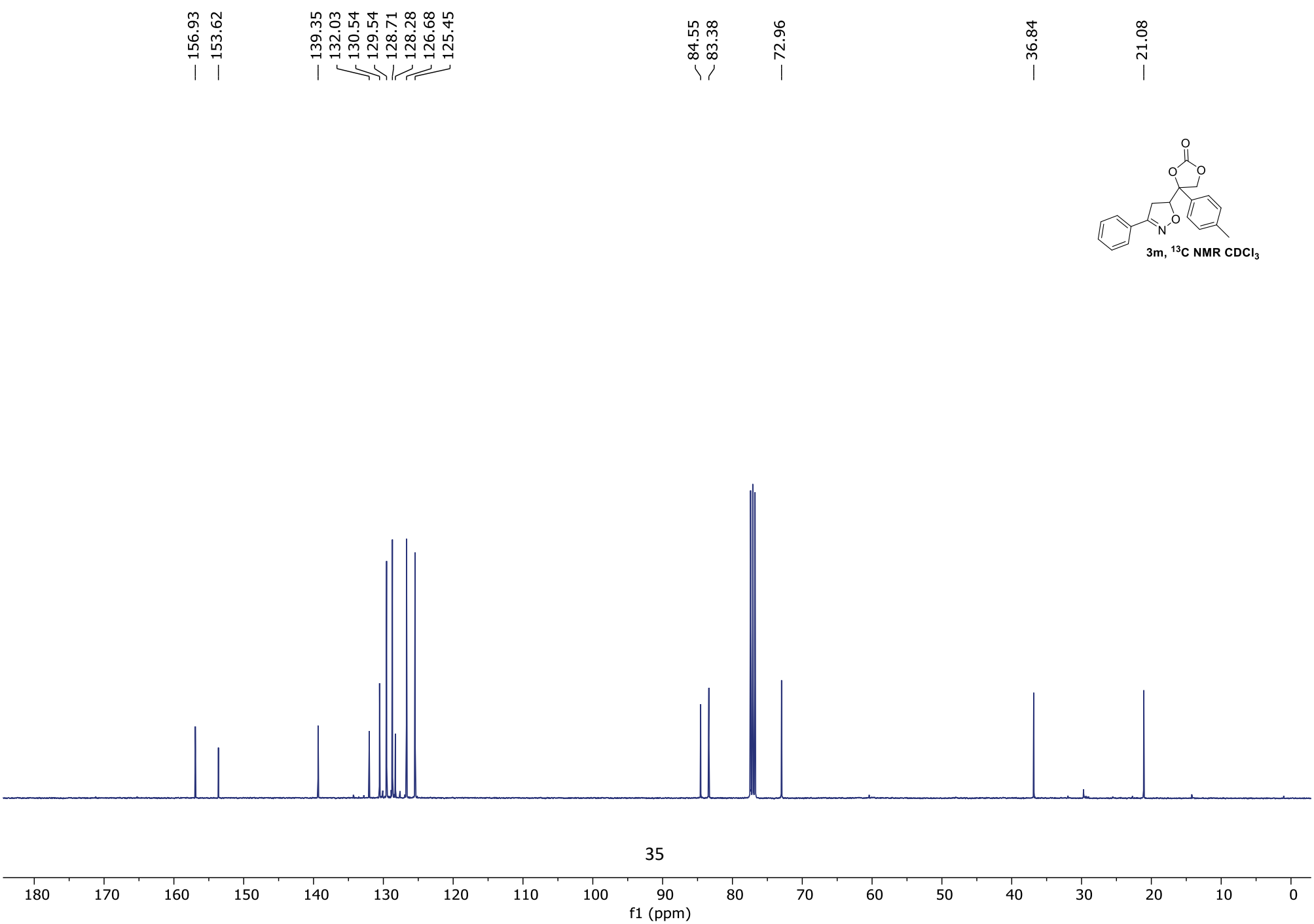

7.4559
7.4537
7.4507
7.4399
7.4368
7.3854
7.3737
7.3708
7.3645
7.3602
7.3506
7.3468
7.3385
7.3354
7.3215
6.8814
6.8872
6.8778
6.8736
5.1612
5.1466
5.1392
5.1245
4.9874
4.9701
4.6302
4.6129
3.7590
3.1298
3.1152
3.0951
3.0805
3l, ^{1}H NMR CDCl$_3$
1.95
5.01
1.95
1.06
1.05
1.04
32
3.00
1.08
1.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


160.20
156.93
153.61
130.57
128.72
128.24
126.91
126.83
126.67
114.26
84.35
83.33
73.19
55.31
36.88
O
O
O
N
O
O
3l, ^{13}C NMR CDCl$_3$
33
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



3m, ^{1}H NMR $CDCl_3$




156.93
153.62
139.35
132.03
130.54
129.54
128.71
128.28
126.68
125.45
84.55
83.38
72.96
36.84
21.08
O
O
O
O
N
3m, ^{13}C NMR CDCl$_3$
35
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

HRMS Spectra

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions

1007 formula(e) evaluated with 11 results within limits (up to 1 closest results for each mass)

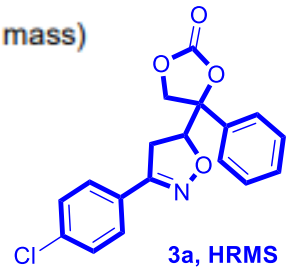
Elements Used:

C: 0-40 H: 0-100 N: 0-10 O: 0-10 S: 0-2 Cl: 1-1

Sample Name : DMS_ES_02_035_A IITRPR

Test Name :

030522_DMS_ES_02_035_A 8 (0.186)

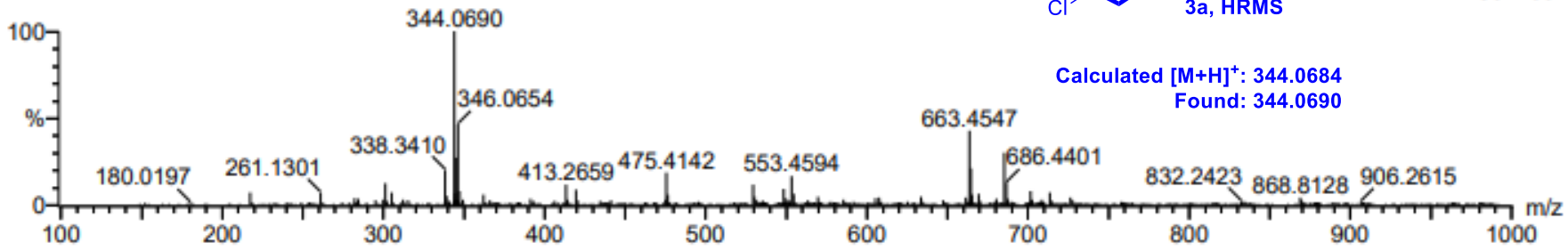


3a, HRMS

XEVO G2-XS QTOF

1: TOF MS ES+
1.80e+007

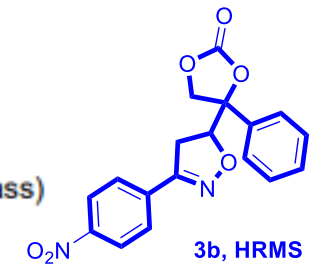
Calculated $[M+H]^+$: 344.0684
Found: 344.0690



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
344.0690	344.0690	0.0	0.0	11.5	1876.0	n/a	n/a	C18 H15 N O4 Cl

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5



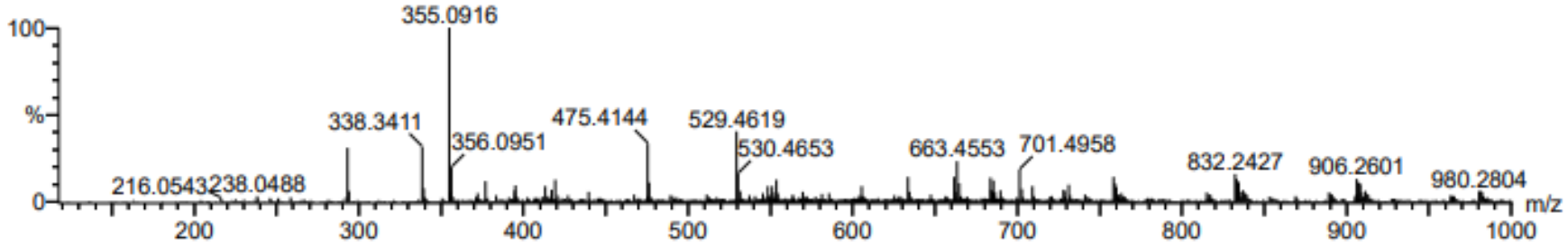
3b, HRMS

Monoisotopic Mass, Even Electron Ions
139 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10

Sample Name : DMS_ES_02_046
Test Name :
030522_DMS_ES_02_046 9 (0.203)

IITRPR

XEVO G2-XS QTOF
Calculated $[M+H]^+$: 355.0925
Found: 355.0916
1: TOF MS ES+
5.56e+006



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
355.0916	355.0930	-1.4	-3.9	12.5	423.5	n/a	n/a	C18 H15 N2 O6

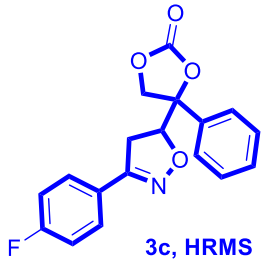
Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
453 formula(e) evaluated with 4 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3

Sample Name : DMS_ES_02_045_A
Test Name :
030522_DMS_ES_02_045_A 8 (0.186)

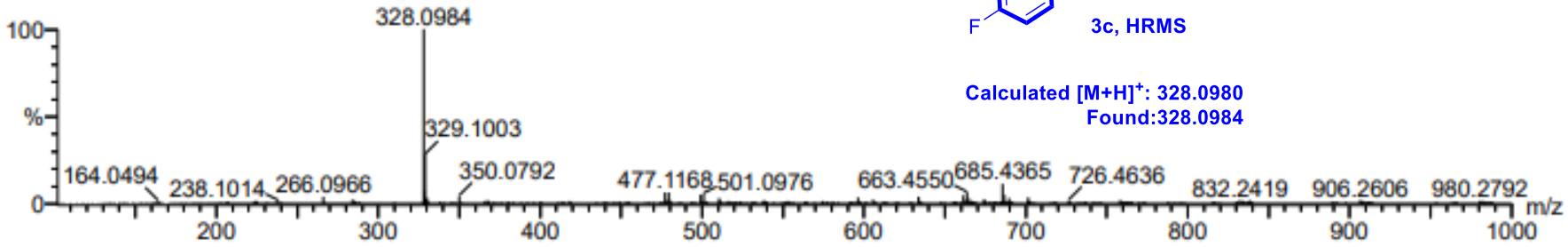
IITRPR



3c, HRMS

XEVO G2-XS QTOF

1: TOF MS ES+
6.41e+007



Calculated $[M+H]^+$: 328.0980
Found:328.0984

Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
328.0984	328.0985	-0.1	-0.3	11.5	1349.4	n/a	n/a	C18 H15 N O4 F

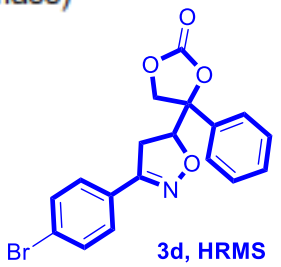
Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
198 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 Br: 1-2

Sample Name : DMS_ES_02_023_A
Test Name :
030522_DMS_ES_02_023_A 7 (0.169)

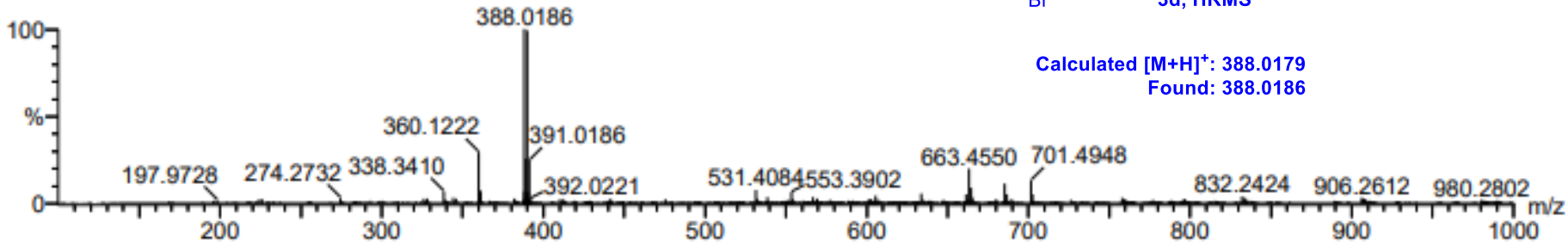
IITRPR



3d, HRMS

XEVO G2-XS QTOF

1: TOF MS ES+
5.36e+007



Calculated $[M+H]^+$: 388.0179
Found: 388.0186

Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
388.0186	388.0184	0.2	0.5	11.5	1715.6	n/a	n/a	C18 H15 N O4 Br

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

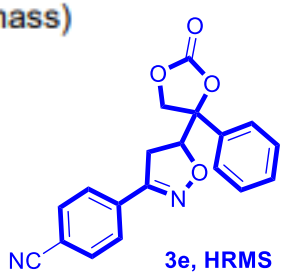
Monoisotopic Mass, Even Electron Ions
134 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10

Sample Name : DMS_ES_02_044_A
Test Name :
030522_DMS_ES_02_044_A 40 (0.854)

IITRPR

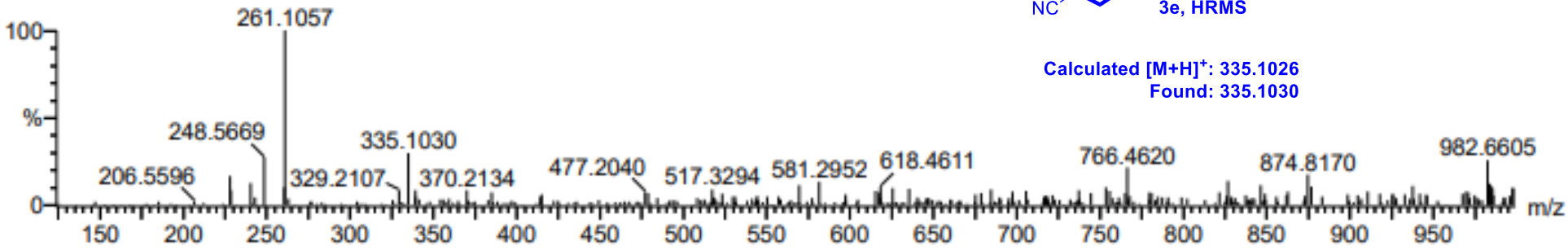
XEVO G2-XS QTOF

1: TOF MS ES+
2.46e+004



3e, HRMS

Calculated $[M+H]^+$: 335.1026
Found: 335.1030



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
335.1030	335.1032	-0.2	-0.6	13.5	61.4	n/a	n/a	C19 H15 N2 O4

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

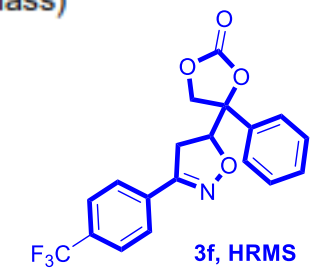
Monoisotopic Mass, Even Electron Ions
533 formula(e) evaluated with 6 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3

Sample Name : DMS_ES_02_027_A
Test Name :
030522_DMS_ES_02_027_A 6 (0.141)

IITRPR

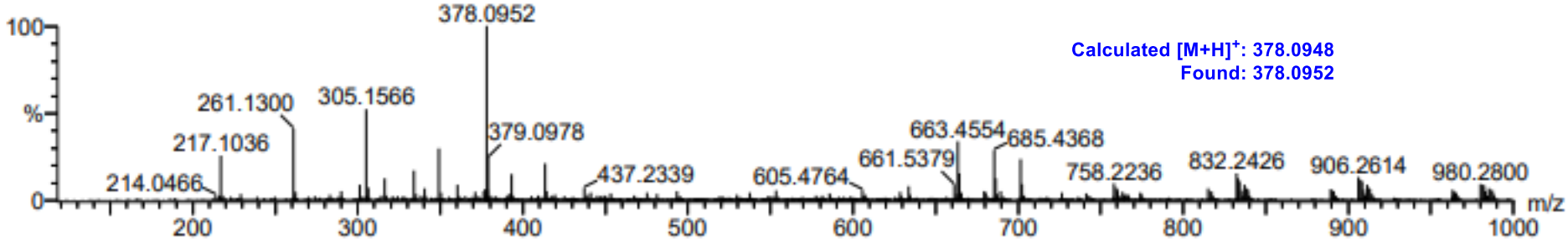
XEVO G2-XS QTOF

1: TOF MS ES+
3.64e+007



3f, HRMS

Calculated $[M+H]^+$: 378.0948
Found: 378.0952



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
378.0952	378.0953	-0.1	-0.3	11.5	1369.2	n/a	n/a	C19 H15 N O4 F3

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

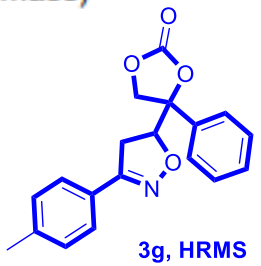
Monoisotopic Mass, Even Electron Ions
446 formula(e) evaluated with 4 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3

Sample Name : DMS_ES_02_033_A
Test Name :
030522_DMS_ES_02_033_A 10 (0.232)

IITRPR

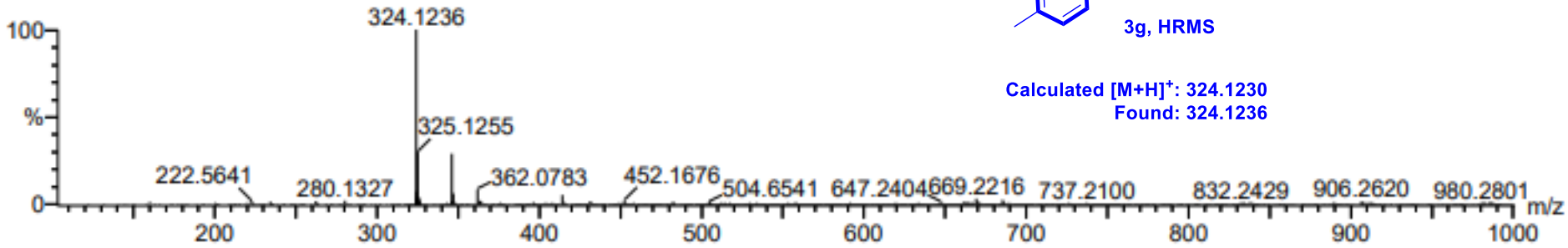
XEVO G2-XS QTOF

1: TOF MS ES+
4.49e+007



3g, HRMS

Calculated $[M+H]^+$: 324.1230
Found: 324.1236



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
324.1236	324.1236	0.0	0.0	11.5	1062.4	n/a	n/a	C19 H18 N O4

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

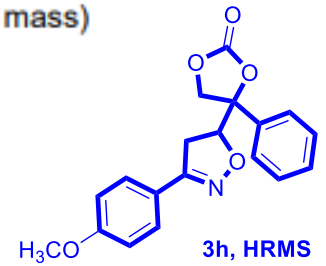
Monoisotopic Mass, Even Electron Ions
471 formula(e) evaluated with 4 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3

Sample Name : DMS_ES_02_055_A
Test Name :
030522_DMS_ES_02_055_A 7 (0.169)

IITRPR

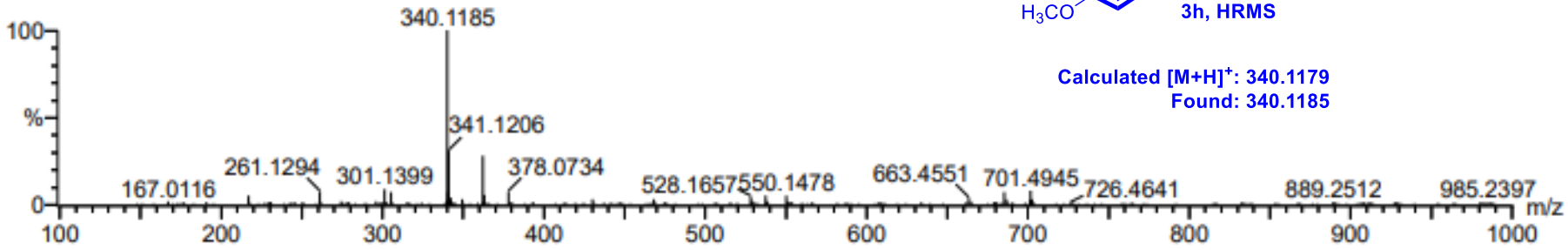
XEVO G2-XS QTOF

1: TOF MS ES+
1.01e+008



3h, HRMS

Calculated $[M+H]^+$: 340.1179
Found: 340.1185



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
340.1185	340.1185	0.0	0.0	11.5	2233.4	n/a	n/a	C19 H18 N O5

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

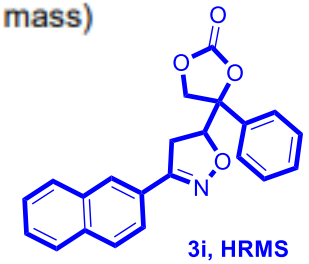
Monoisotopic Mass, Even Electron Ions
505 formula(e) evaluated with 5 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3

Sample Name : DMS_ES_02_020_A
Test Name :
030522_DMS_ES_02_020_A 12 (0.265)

IITRPR

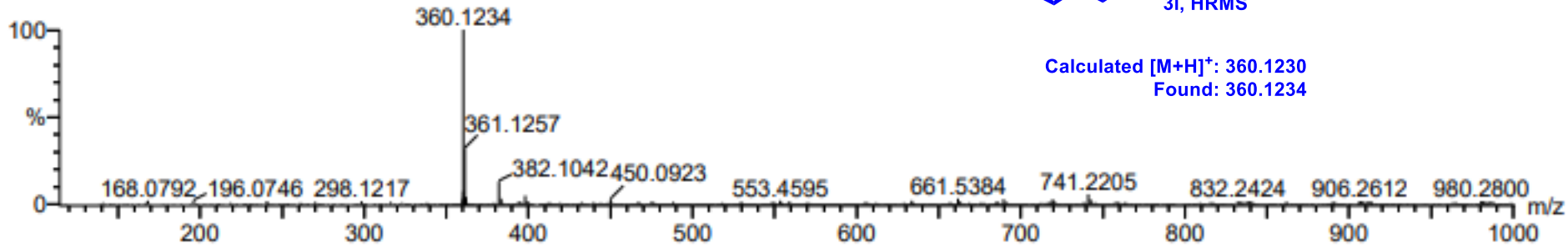
XEVO G2-XS QTOF

1: TOF MS ES+
6.18e+007



3i, HRMS

Calculated $[M+H]^+$: 360.1230
Found: 360.1234



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
360.1234	360.1236	-0.2	-0.6	14.5	988.6	n/a	n/a	C22 H18 N O4

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

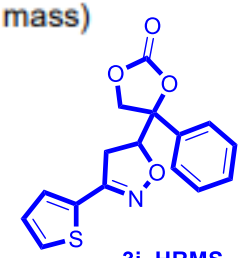
Monoisotopic Mass, Even Electron Ions
1150 formula(e) evaluated with 11 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3 S: 0-2

Sample Name : DMS_ES_02_047_A
Test Name :
030522_DMS_ES_02_047_A 7 (0.169)

IITRPR

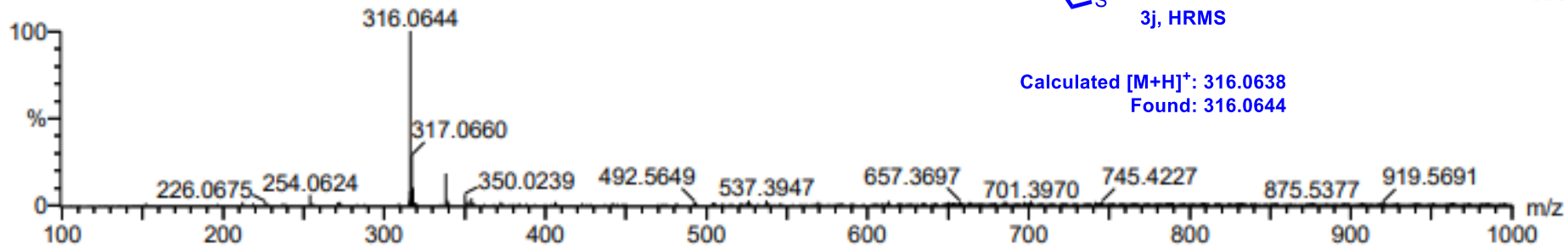
XEVO G2-XS QTOF

1: TOF MS ES+
1.12e+008

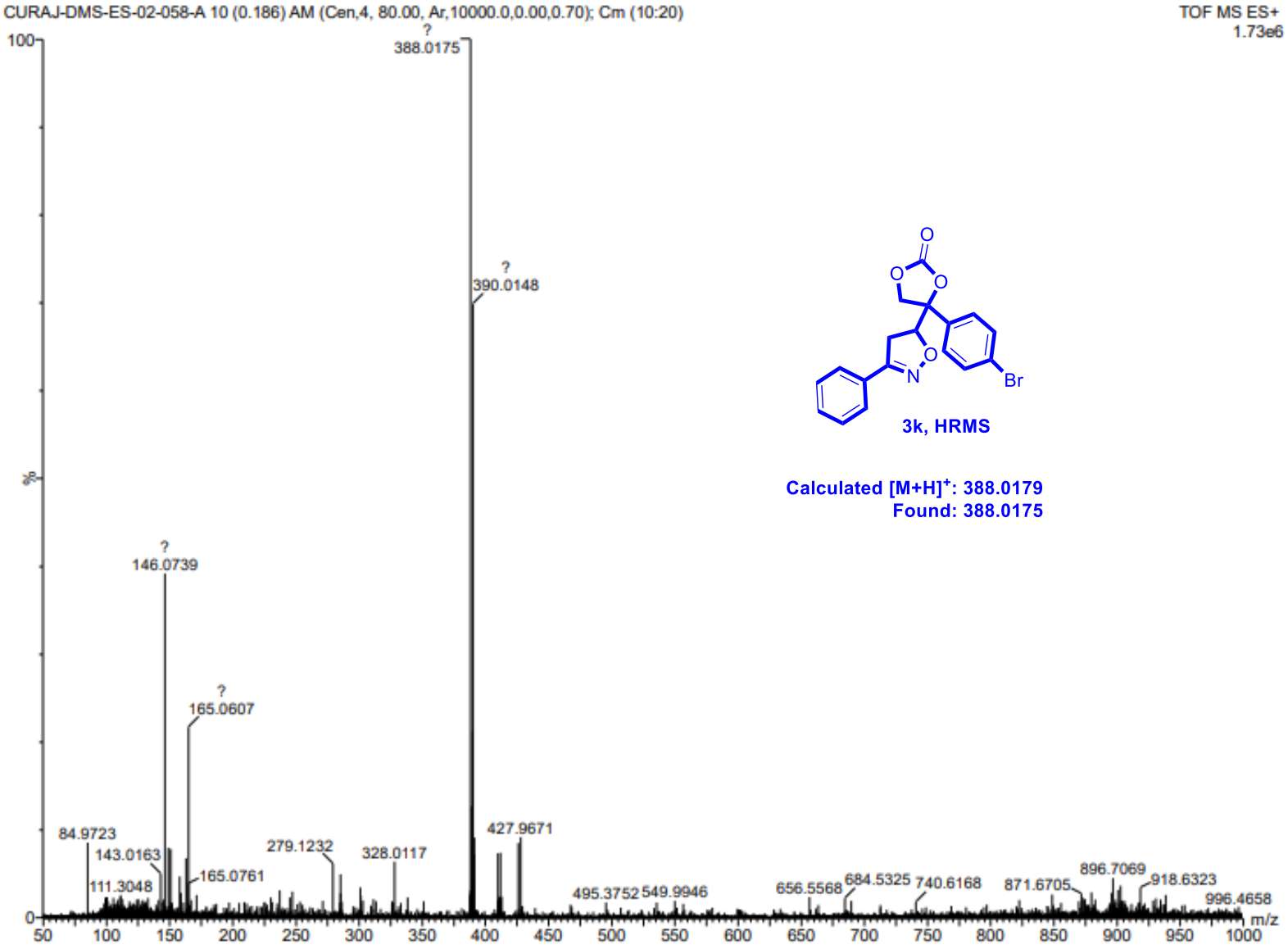


3j, HRMS

Calculated $[M+H]^+$: 316.0638
Found: 316.0644



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
316.0644	316.0644	0.0	0.0	10.5	1655.8	n/a	n/a	C16 H14 N O4 S



3k, HRMS

Calculated $[M+H]^+$: 388.0179
Found: 388.0175

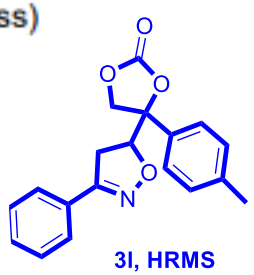
Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
446 formula(e) evaluated with 4 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3

Sample Name : DMS_ES_02_050_A
Test Name :
030522_DMS_ES_02_050_A 9 (0.203)

IITRPR

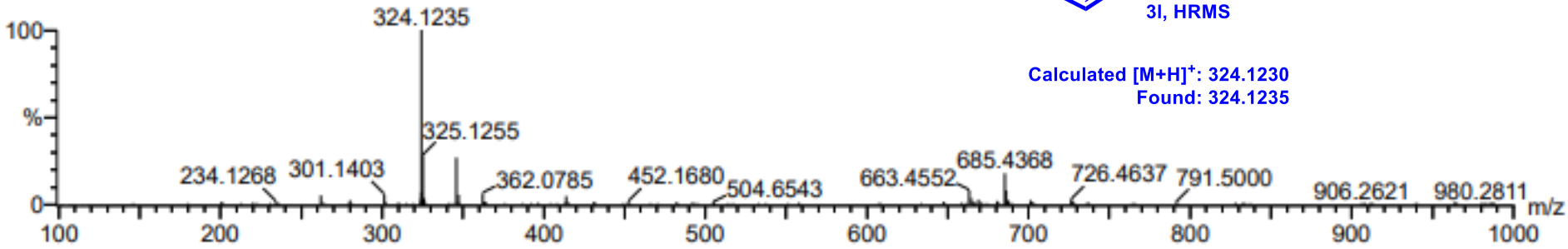


3l, HRMS

XEVO G2-XS QTOF

1: TOF MS ES+
1.10e+008

Calculated $[M+H]^+$: 324.1230
Found: 324.1235



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
324.1235	324.1236	-0.1	-0.3	11.5	1653.9	n/a	n/a	C19 H18 N O4

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

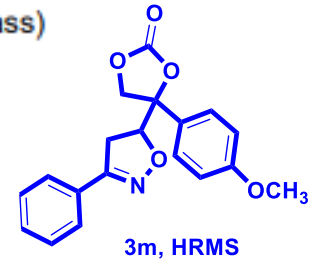
Monoisotopic Mass, Even Electron Ions
471 formula(e) evaluated with 4 results within limits (up to 1 closest results for each mass)
Elements Used:
C: 0-40 H: 0-100 N: 0-2 O: 0-10 F: 0-3

Sample Name : DMS_ES_02_055_A
Test Name :
030522_DMS_ES_02_055_A 7 (0.169)

IITRPR

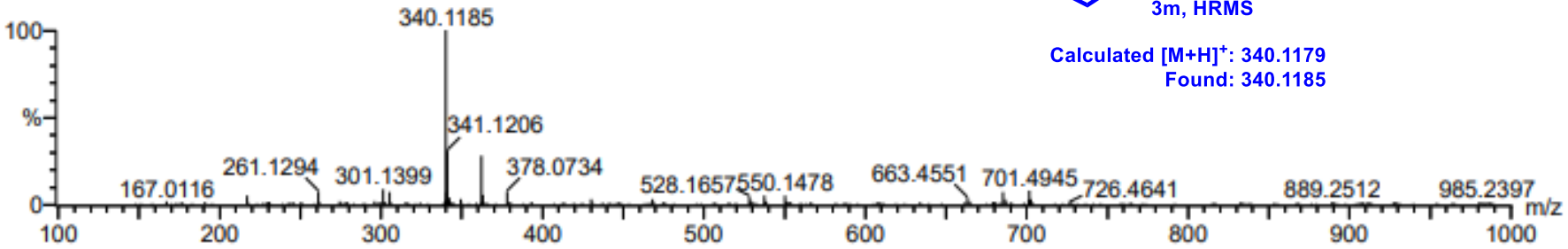
XEVO G2-XS QTOF

1: TOF MS ES+
1.01e+008



3m, HRMS

Calculated $[M+H]^+$: 340.1179
Found: 340.1185



Minimum:				-1.5				
Maximum:		2.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
340.1185	340.1185	0.0	0.0	11.5	2233.4	n/a	n/a	C19 H18 N O5