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Accounts and Rapid Communications in Chemical Synthesis

Supporting Information

for DOI: 10.1055/s-0042-1751378

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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Design, synthesis and biological evaluation of 2-phenylquinazolin-4-yl 4-methylbenzenesulfonate derivatives as anticancer agents via tubulin inhibition

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^{1}H, ^{13}C NMR, & HRMS Spectra of Representative Compounds

Content

1. Experimental

1.1. Chemistry

General Procedure for the synthesis of 2

The ice-cold solution o different substituted aldehydes (5 mmol) in glacial acetic acid were taken in a 100 mL round bottom flask, followed by dropwise addition of HNO_3:H_2SO_4 (6:1, 10 ml) mixture over a period of 5 min. The reaction mixture was allowed to come to room temperature and ut for stirring for 30 min to 1 hour. The completion of the reaction was monitored through TLC. On completion, crushed ice was added to the reaction mixture, which resulted in the precipitation of desired product (**2**). The precipitates were filtered under vacuum, washed with cold water, and dried to get the dried desired 2- nitrobenzaldehyde (**2**). The product was used further without any purification.

General Procedure for the synthesis of 3

The suspension of substituted 2-nitrobenzaldehyde (**2**) in methanol (4 mmol) was put on at room temperature, stirring, followed by the addition of iron (6 mmol) and NH_4Cl (8 mmol). The resulting mixture was put on reflux for 5 to 6 hours, and the progress of the reaction was monitored through TLC. After completion, the reaction was allowed to cool, filtered through a celite bed, and vacuum dried to evaporate methanol to get solid crude residues. The solid obtained was further extracted using ethyl acetate (30 × 3) from an aqueous solution, and the organic layer was combined, washed with brine, and dried over a rotary evaporator to get desired product (**3**) in good yield and used without further purification.

General Procedure for the synthesis of 4

A solution of **3** (2 mmol) and iodine (2.5 mmol) in ammonia water (15 mL of 28% solution) and THF (2 mL) was stirred at room temperature for 1 h. The solution became colorless over time which indicates the end of the reaction. At the end of the reaction, aqueous H_2O_2 (3 mL of 35% solution) solution was added dropwise and stirred for 2-4 h and followed by extraction with chloroform. The organic layer was combined and washed with brine, followed by vacuum drying to get crude **4**. The residue was rinsed with hexane/ethyl acetate (1:3) to give a pure amide product **4** in moderate to good yield.

General Procedure for the synthesis of 5

In a clean and dried 100 mL round bottom flask, **5** (2 mmol) and appropriately substituted benzaldehyde (2 mmol) was taken in ethanol. The reaction mixture was stirred at room temperature, and iodine (2 mmol) was added. After the addition of iodine, the reaction mixture was refluxed at 80˚ C for 4 to 5 hours. The reaction progress was monitored through TLC. Upon completion of the reaction, ethanol was concentrated under a vacuum, and a saturated aqueous solution of sodium thiosulphate was added to quench the remaining iodine, which resulted in the precipitation of desired cyclized product (**5**). The obtained product was filtered, washed, dried, and used in the next step without further purification.

General Procedure for the synthesis of 6a-6j

The quinazolinone (**5**) derivative (2 mmol) and triethylamine (2.2 mmol) in THF (5 mL) were stirred at room temperature for 10 min. After 10 min, *p*- toluenesulfonyl chloride (2.0 mmol) was added, and the reaction mixture was kept on stirring for 8 to 9 hours. On completion of the reaction, the reaction mixture was concentrated under a vacuum and diluted with a saturated solution of sodium bicarbonate, and extracted with EtOAc (10 * 2 ml). The final organic layer was washed with brine and passed through anhydrous sodium sulphate. The EtOAc layer was concentrated under vacuum to get the crude product (**6a-6j**) which was purified with column chromatography (15% EtOAc in Hexane).

2-(*p*-tolyl)quinazolin-4-yl 4-methylbenzenesulfonate(6a)

Colour: Pink, solid; mp: 176-178 ˚C; Yield: 64%; **^{1}H NMR (DMSO, 400 MHz, δ with TMS = 0):** 7.76 (1H, d, *J* = 8Hz), 7.61-7.58 (3H, m), 7.49-7.45 (1H, m), 7.29-7.23 (3H, m), 7.14 (2H, d, *J* = 8Hz), 7.00 (2H, d, *J* = 8 Hz), 2.02 (6H, s) **^{13}C NMR (DMSO, 100 MHz, δ with TMS = 0) δ**: 164.63, 161.28, 155.27, 140.94, 140.89, 137.45, 135.52, 133.83, 129.32, 129.18, 128.92, 128.46, 126.74, 124.47, 112.84. 20.72. HRMS (TOF-ESI) Calcd for $C_{22}H_{18}N_2O_3S$: 390.1038 $[M]^+$, observed: 391.2117 $[M + H]^+$.

2-(4-methoxyphenyl)quinazolin-4-yl 4-methylbenzenesulfonate (6b)

Colour: Pale Brown; solid; mp: 177-179 ˚C; Yield: 65%; **^{1}H NMR ($CDCl_3$, 400 MHz, δ with TMS = 0):** 8.19 (1H, d, *J* = 8Hz), 8.06 (1H, d, *J*= 8Hz), 7.99 (2H, d, *J* = 8Hz), 7.95-7.91 (1H, m), 7.80 (2H, d, *J* = 8Hz), 7.74-7.70 (1H, m), 7.60 (2H, d, *J* = 8 Hz), 7.32 (2H, d, *J* = 8Hz) 4.0 (3H, s), 2.43 (3H, s). **^{13}C NMR ($CDCl_3$, 100 MHz, δ with TMS = 0) δ**: 163.03, 163.00, 161.68, 155.67, 141.34, 137.85, 134.25, 131.51, 130.56, 129.72, 129.58, 128.86, 127.14, 124.67,

113.91, 113.24, 56.03, 21.12. Calcd for $C_{22}H_{18}N_2O_4S$: 406.0987 $[M]^+$, observed: 407.1806 $[M + H]^+$.

2-(4-chlorophenyl)quinazolin-4-yl 4-methylbenzenesulfonate (6c)

Colour: Light Brown; solid; mp: 193-195 ˚C; Yield: 70%; **^{1}H NMR (DMSO, 400 MHz, δ with TMS = 0):** 7.85 (1H, d, *J* = 8Hz), 7.71-7.68 (3H, m), 7.56 (1H, t, *J* = 4 Hz), 7.38-7.35 (3H, m), 7.24 (4H, d, *J* = 8Hz), 2.12 (3H, d, *J* = 8 Hz) **^{13}C NMR (DMSO, 100 MHz, δ with TMS = 0) δ**: 164.73, 161.38, 155.37, 141.04, 137.70, 137.55, 134.38, 133.93, 129.42, 129.36, 129.28, 128.56, 126.84, 124.57, 112.94. 20.82. Calcd for $C_{21}H_{15}ClN_2O_3S$: 410.0492 $[M]^+$, observed: 411.0411 $[M + H]^+$.

2-(2-fluorophenyl)quinazolin-4-yl 4-methylbenzenesulfonate (6d)

Colour: Greenish yellow; solid; mp: 151-153 ˚C; Yield: 73%; **^{1}H NMR (DMSO, 400 MHz, δ with TMS = 0):** 7.67 (1H, d, *J* = 8Hz), 7.51-7.48 (3H, m), 7.36 (1H, dd, *J* = 4 Hz), 7.23-7.15 (2H, m), 7.04 (2H, d, *J* = 8Hz), 6.95-6.93 (1H, m), 6.81-6.74 (2H, m) 1.91 (3H, s) **^{13}C NMR (DMSO, 100 MHz, δ with TMS = 0) δ**: 163.18, 161.80, 160.55, 160.44, 160.36, 155.74, 141.14, 137.65, 134.03, 129.52, 129.38, 128.66, 127.55, 126.94, 125.62, 125.59, 124.67, 115.42, 112.69, 20.92. Calcd for $C_{21}H_{15}FN_2O_3S$: 394.0787 [M]+, observed: 395.0717 $[M + H]^+$.

2-(4-hydroxyphenyl)quinazolin-4-yl 4-methylbenzenesulfonate (6e)

Colour: Light Yellow; solid; mp: 201-203 ˚C; Yield: 59%; **^{1}H NMR ($CDCl_3$, 400 MHz, δ with TMS = 0):** 8.12 (1H, d, *J* = 8Hz), 8.01 (1H,dd, *J*= 4Hz), 7.93 (2H, d, *J* = 8Hz), 7.89-7.85 (1H, m), 7.68-7.64 (1H, m), 7.60 (2H, d, *J* = 4 Hz), 7.54 (2H, d, *J* = 8Hz), 7.14 (2H, d, *J* = 8Hz) 2.38 (3H, s): **^{13}C NMR ($CDCl_3$, 100 MHz, δ with TMS = 0) δ**: 165.43, 162.08, 161.95, 156.07, 141.74, 138.25, 134.63, 131.21, 130.12, 129.98, 129.26, 127.54, 126.95, 116.19, 113.64, 21.52. Calcd for $C_{21}H_{16}N_2O_4S$: 392.0831 [M]+, observed: 393.1095 $[M + H]^+$.

2-(4-(prop-2-yn-1-yloxy)phenyl)quinazolin-4-yl 4-methylbenzenesulfonate (6f)

Colour: Pale yellow; solid; mp: 186-188 ˚C; Yield: 75%; **^{1}H NMR (DMSO, 400 MHz, δ with TMS = 0):** 8.14 (1H, d, *J* = 8Hz), 8.00-7.95 (3H, m), 7.89-7.87 (3H, m), 7.58 (1H, d, *J* = 4Hz), 7.36 (1H, d, *J* = 4 Hz), 7.10 (1H, d, *J* = 4 Hz), 4.85 (2H, s), 2.55 (1H, s), 2.44 (3H, s): **^{13}C NMR (DMSO, 100 MHz, δ with TMS = 0) δ**: 164.03, 160.68, 154.67, 140.34, 136.85, 133.23, 132.43, 128.79, 126.14, 123.87, 114.86, 112.24, 79.00, 77.89, 57.85, 20.12. Calcd for $C_{24}H_{18}N_2O_4S$: 430.0987 [M]+, observed: 431.0205 $[M + H]^+$.

7-methoxy-2-(4-(prop-2-yn-1-yloxy)phenyl)quinazolin-4-yl 4-methylbenzenesulfonate (6g)

Colour: Yellow orange; solid; mp: 183-185 ˚C; Yield: 61%; **^{1}H NMR (DMSO, 400 MHz, δ with TMS = 0):** 8.14 (1H, d, *J* = 8Hz), 8.08 (2H, d, *J* = 4 Hz), 8.03-8.00 (2H, m), 7.97-7.95 (1H, m), 7.88 (1H, m), 7.59-7.56 (1H, m), 7.36 (1H, d, *J* = 4Hz), 7.10 (1H, d, *J* = 8 Hz), 4.85 (2H, s), 4.01 (3H, s) 2.55 (1H, s), 2.44 (3H, s): **^{13}C NMR (DMSO, 100 MHz, δ with TMS = 0) δ**: 162.07, 162.05, 159.31, 159.30, 153.54, 149.67, 149.58, 149.55, 145.81, 145.79, 134.89, 129.89, 128.97, 127.64, 123.45, 122.18, 122.16, 114.61, 113.41, 111.86, 111.84, 56.74, 56.16, 21.81. Calcd for $C_{25}H_{20}N_2O_5S$: 460.1093 [M]+, observed: 461.1148 $[M + H]^+$.

2-(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)quinazolin-4-yl 4-methylbenzenesulfonate (6h)

Colour: Light yellow; solid; mp: 205-207 ˚C; Yield: 73%; **^{1}H NMR (DMSO, 400 MHz, δ with TMS = 0):** 8.04 (1H, d, *J* = 4Hz), 8.00 (2H, d, *J* = 4 Hz), 7.93-7.86 (3H, m), 7.78-7.75 (1H, m), 7.48 (1H, t, *J* = 4 Hz), 7.29 (2H, d, *J* = 4Hz) 7.01 (1H, d, *J* = 4Hz), 4.76 (2H, s), 3.91 (3H, s) 2.45 (1H, s), 2.34 (3H, s): **^{13}C NMR (DMSO, 100 MHz, δ with TMS = 0) δ**: 166.00, 161.54,161.48, 158.46, 155.18, 141.34, 137.85, 133.43, 129.79, 129.72, 128.86, 126.16, 115.86, 114.14, 112.15, 110.35, 80.00, 78.77, 58.85, 56.03, 21.12. Calcd for $C_{25}H_{20}N_2O_5S$: 460.1093 $[M]^+$, observed: 461.1004 $[M + H]^+$.

6,7,8-trimethoxy-2-(4-(prop-2-yn-1-yloxy)phenyl)quinazolin-4-yl4-methylbenzenesulfonate (6i)

Colour: Pale Brown; solid; mp: 191-193 ˚C; Yield: 65%; **^{1}H NMR (DMSO, 400 MHz, δ with TMS = 0):** 7.95 (2H, d, *J* = 8Hz), 7.71 (2H, d, *J* = 8 Hz), 7.64 (1H, s), 7.51 (2H, m), 7.21 (2H, d, *J* = 8 Hz), 5.01 (2H, s), 3.95 (3H, s), 3.93 (6H, s), 2.43(3H, s), 2.36 (1H, s): **^{13}C NMR (DMSO, 100 MHz, δ with TMS = 0) δ**: 164.38, 161.34, 157.26, 150.65, 147.06, 145.46, 144.94, 141.14, 137.65, 133.23, 129.59, 129.52, 128.66, 115.66, 110.94, 101.81, 79.80, 78.59, 60.65, 60.45, 58.65, 56.58, 20.92. Calcd for $C_{27}H_{24}N_2O_7S$: 520.1304 [M]+, observed: 521.2657 $[M + H]^+$.

2-(4-hydroxyphenyl)-6,7,8-trimethoxyquinazolin-4-yl 4-methylbenzenesulfonate (6j)

Colour: Yellow orange; solid; mp: 185-187 ˚C; Yield: 58%; **^{1}H NMR ($CDCl_3$, 400 MHz, δ with TMS = 0):** 8.05 (2H, d, *J* = 8Hz), 7.69-7.67 (3H, m), 7.61 (2H, d, *J* = 8 Hz), 7.20 (2H, d, *J* = 8 Hz), 4.06 (3H, s), 3.97 (6H, s), 2.49 (3H, s): **^{13}C NMR (DMSO, 100 MHz, δ with TMS**

= 0) δ: 164.18, 161.05, 156.96, 150.35, 146.76, 145.16, 144.64, 140.80, 137.35, 130.31, 129.22, 128.36, 126.05, 115.29, 110.64, 101.51, 60.35, 60.15, 56.28, 20.62. Calcd for $C_{24}H_{22}N_2O_7S$: 482.1148 [M]+, observed: 483.3080 $[M + H]^+$.

1.2. Biological Studies

1.2.1. Cytotoxic studies

To evaluate the cytotoxic activity of the synthesized compounds, the conventional MTT assay method was used. This method measures the metabolic activities of the cells on the basis of the potential of NADPH-dependent cellular oxidoreductase enzymes to carry out the reduction of MTT dye to formazan (insoluble form) having a purple color. The cytotoxicity produced by the new quinazoline derivatives was evaluated against four cancer cell lines; two breast cancer cell lines (MCF-7 and MDA-MB-2321) and lung cancer cell lines (A549), and colon cancer cell lines (HCT-116). Colchicine was used as a standard drug to compare cytotoxicity. The cells were incorporated into 96-well plates at a concentration of 1×10^4 cells per well and kept overnight. Each treatment was replicated into five replicates and cultured for 2 to 3 days. Then 20 μL of MTT dye solution (5mg/mL) was added to all the wells and allowed to culture for 4 hours. The supernatant was discarded, and 150 μL DMSO was added to the wells. The incubation was carried out for another 30 minutes at 37°C, followed by swirling for 10 minutes. The absorbance was recorded at 570 nm, and the experiments were repeated thrice.[1-5]

1.2.2. Free radical scavenging assay (DPPH assay)

Free radicals arise from a variety of metabolic pathways of the body and are responsible for the progression of several diseases, including cancer [6]. Therefore, the title compounds were tested for free radical scavenging potentials. The traditional DPPH (1,1-diphenyl-2-picrylhydrazyl) assay was used to evaluate the antioxidant potential of the synthesized compounds. Ascorbic acid is used as a reference as per the standard protocols. 3.94 mg of DPPH was dissolved in 100 mL of methanol to give a concentration of 0.1 mM and was kept in the dark place for 2 hours. Further, the free radical scavenging potentials were evaluated by mixing 2 mL of this DPPH solution with 2 mL solution of the test compounds prepared in different concentrations (0.01-1 mM), followed by incubation at room temperature for 30 minutes. Then the absorbance of the resulting mixture was recorded using a UV-visible spectroscope at a 517 nm wavelength [7]. The same procedure was repeated thrice, and mean

± SD was calculated. The percentage of free radical scavenging activity was determined by the following equation:

Percentage radical scavenging = (A-B)/A×100

Where A = absorbance of the control (DPPH); B = absorbance of the sample

1.2.3. PI vs Annexin V assay

In order to evaluate the mode of cell death induced in the MDA-MB-231 cell line upon treatment with **6a** and **6f** with respect to control, we performed a PI vs. Annexin V assay. The analysis was performed at a 5 µM concentration of investigational compounds. Briefly, 1 X 10^4 cells were cultured as described previously. Upon confluency, cells were treated with the investigational compounds and were incubated further for 48 h. Thereafter cells were washed, the media (containing debris) was collected, and adhered cells were trypsinized and collected together. The cells were centrifuged and washed thoroughly with 1X PBS. After washing, cells were collected and further incubated with PI and annexin V dye for 30 min at dark. After a stipulated time, interval, cells were analyzed using flow cytometry. [1-5]

1.2.4. Cell cycle study

A similar procedure as discussed above was followed for cell cycle analysis using propidium iodide (PI). The only difference made was that cells were fixed before incubation with PI in the dark. The analysis was done using flow cytometry.

1.2.5. Tubulin polymerization inhibitory assay

Tubulin polymerization assay of the bovine tubulin was performed as per protocol reported earlier elsewhere by Beyer *et al.* [8]. The target compounds (**6a** and **6f**) and colchicine (Positive control) were added to the wells of 96 well plates in triplicate. Tubulin obtained as Bovine tubulin (1.8 mg/mL; Sigma) was mixed with ice-cold polymerization buffer (PEM: 80 mM PIPES, 0.5 mM EGTA, 2 mM $MgCl_2$, 10% glycerol, and 1mM GTP) and put for centrifugation at 4 °C for 5 minutes. The resulting supernatant obtained was immediately transferred to the wells (100 uL/well) of the 96-well plate already containing the test compounds or positive control colchicine (DMSO in control wells). The addition of tubulin was followed by transfer of the plate immediately to a spectrophotometer, maintained at 37 °C, for recording absorbance at 340 nm by every 10 min for 2.5 hours. The studies were performed in triplicate, and the results were represented as the mean of these values.

1.3 *In silico* Studies

1.3.1 Docking Studies

Docking studies were performed to investigate the possible interaction modes of potent compounds with the receptor along with the binding energies. Molecular docking was carried out on tubulin (PDB: 1SA0) utilizing Autodock software. Chemdraw Ultra 15.0 was used to generate 2D structures of compounds, and all input files were prepared by Autodock tools version 4.2.6. Chem 3D ultra was utilized for energy minimization and generation of files in PDB format. The input file of tubulin was created by following a sequence of steps, including the amalgamation of non-polar hydrogens and calculation of partial atomic charge by the Kollman method. The generated file was saved in the. pdbqt file format. Further, a grid map was created using Autodock tools with grid box dimensions of 34 x 24 x 24Å points with a grid center of 0.375Å. Finally, the docking was performed in Autodock vina 1.1.2 version by superimposing the ligands onto the grid box. To visualize and analyze the interaction poses, Discovery Studio visualizer version 17.222 and PyMol Tcl version 1.1 were utilized. The docking protocol was validated by re-docking the internal ligand on the co-crystalized ligand, and the RMSD value was calculated [9]. Potent tubulin inhibitor drug colchicine was used as a reference drug to compare the results.

1.3.2 Drug likeliness, ADME, and Toxicity Prediction

Drug likeliness studies predict whether the prepared compounds will behave like a drug or not. These studies are also helpful in predicting the bio-availability and pharmacokinetics (ADME) properties of a compound on the basis of structural properties. If a compound follows Lipinski's Rule of Five, then it is considered to behave as "drug-like". These predictions were carried out using an online tool, SwissADME. Similarly, the toxicity prediction studies were carried out using PreADME software. Toxicity prediction studies are significant in estimating the toxic effects of synthesized compounds on normal tissues and cells. These *in silico* studies may be proven to be time-saving economic and can reduce the number of experimental animals. PreADME predicts the toxicity against the Human Ether Related Gene factor (hERG). The hERG is an indicator of severe cardiotoxicity.[1-5]

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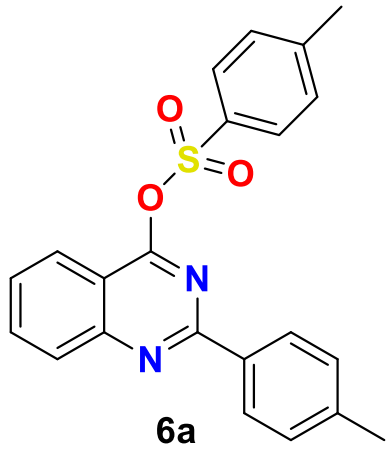
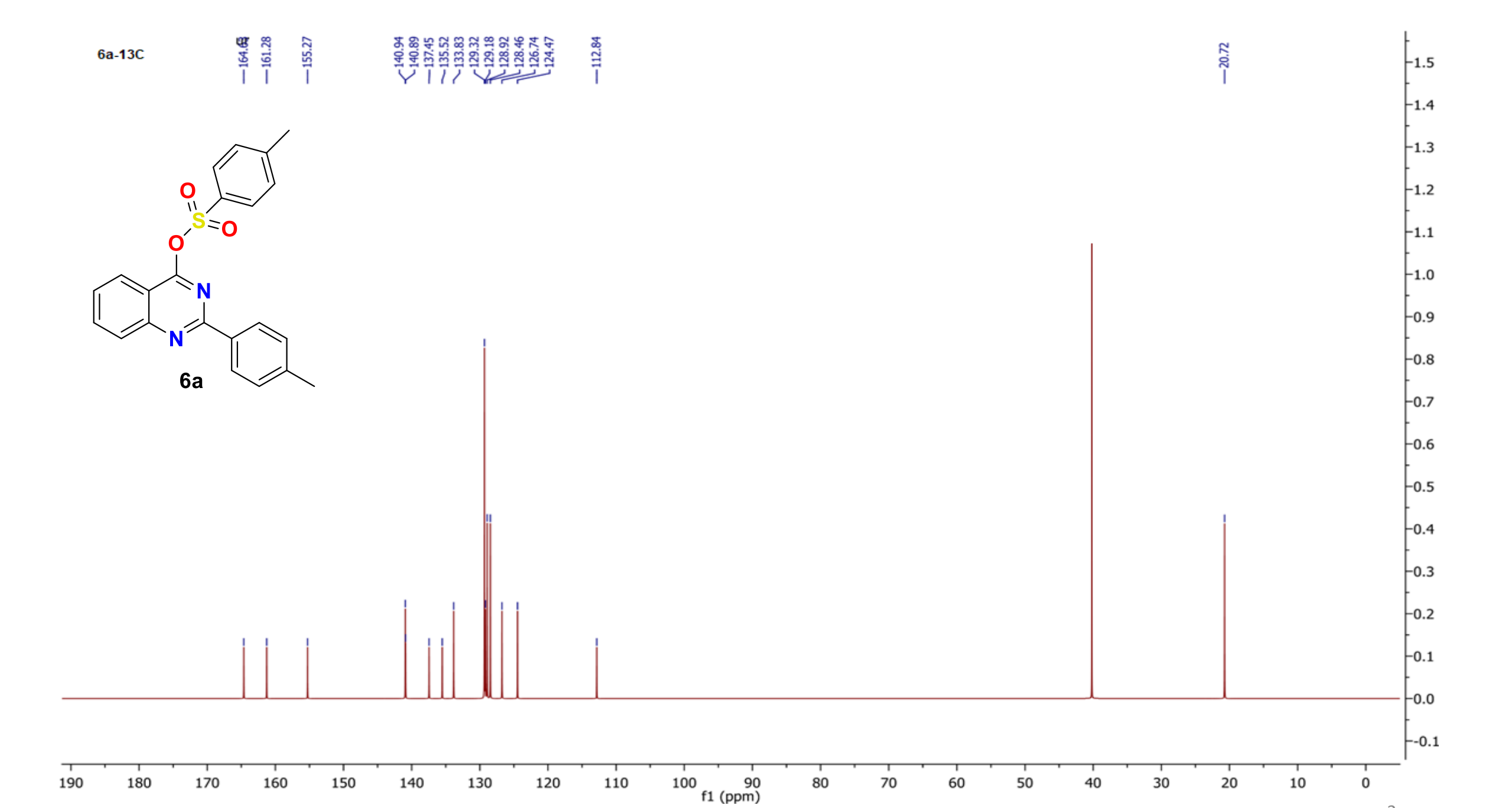
6a-1H DMSO



6a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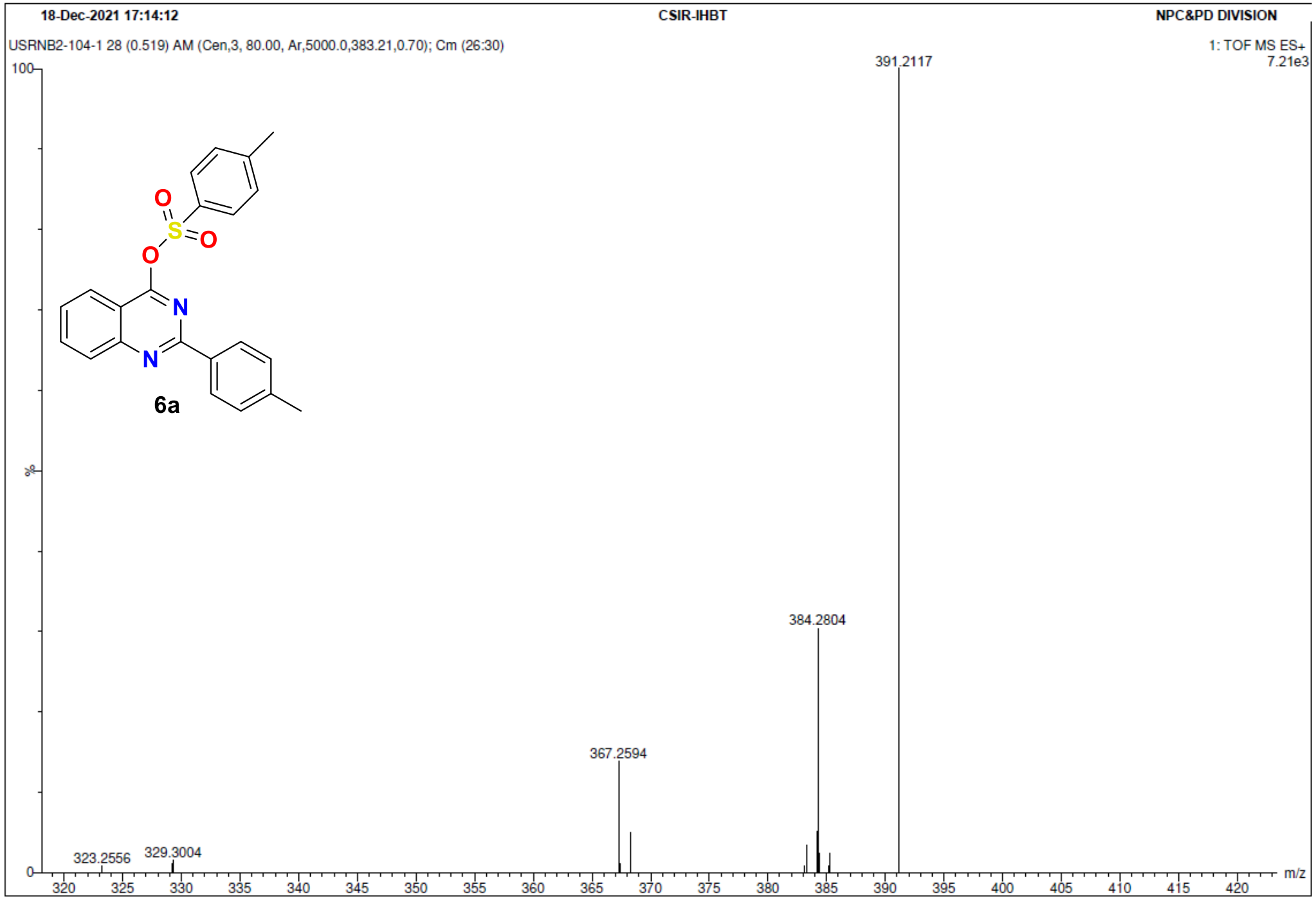
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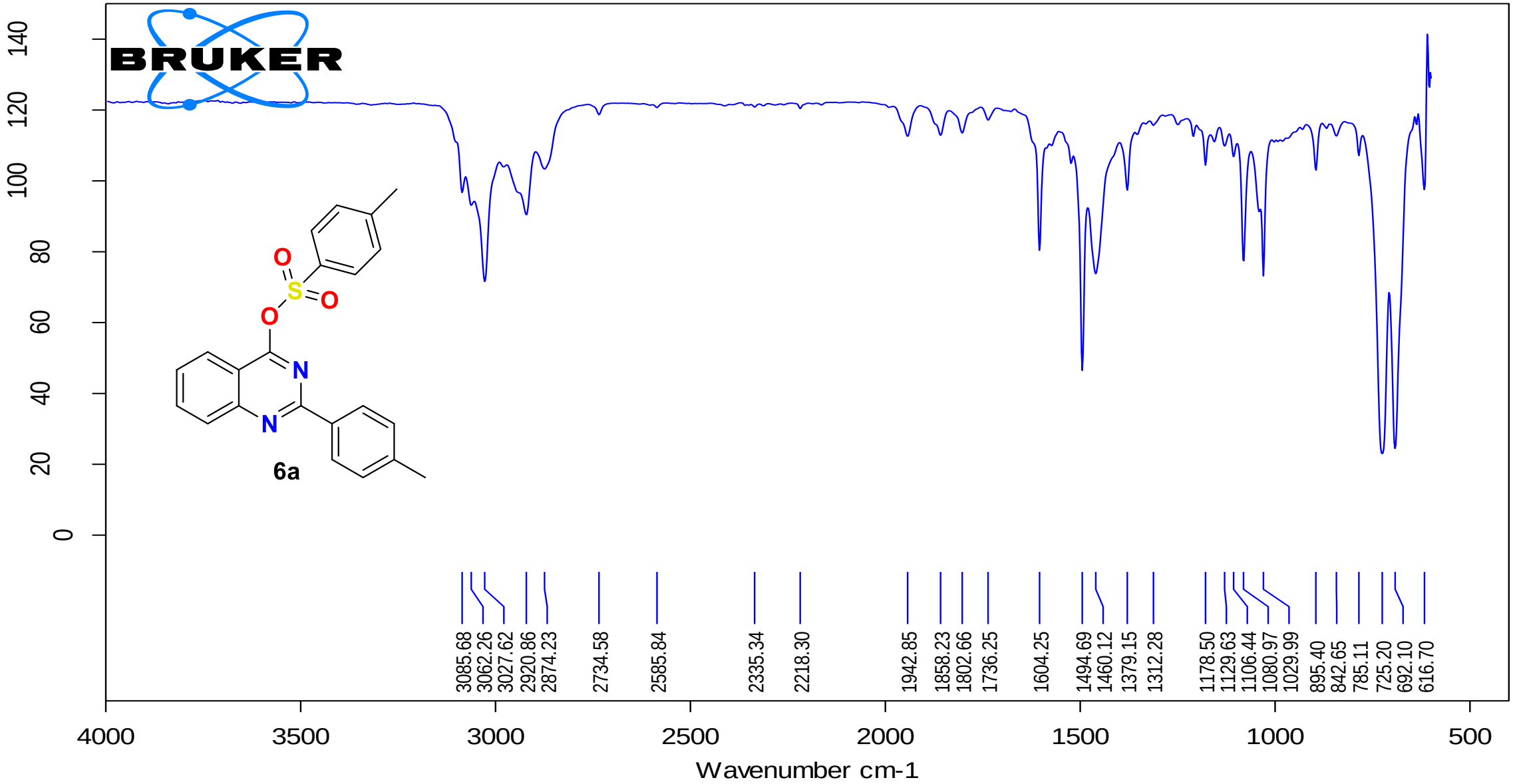
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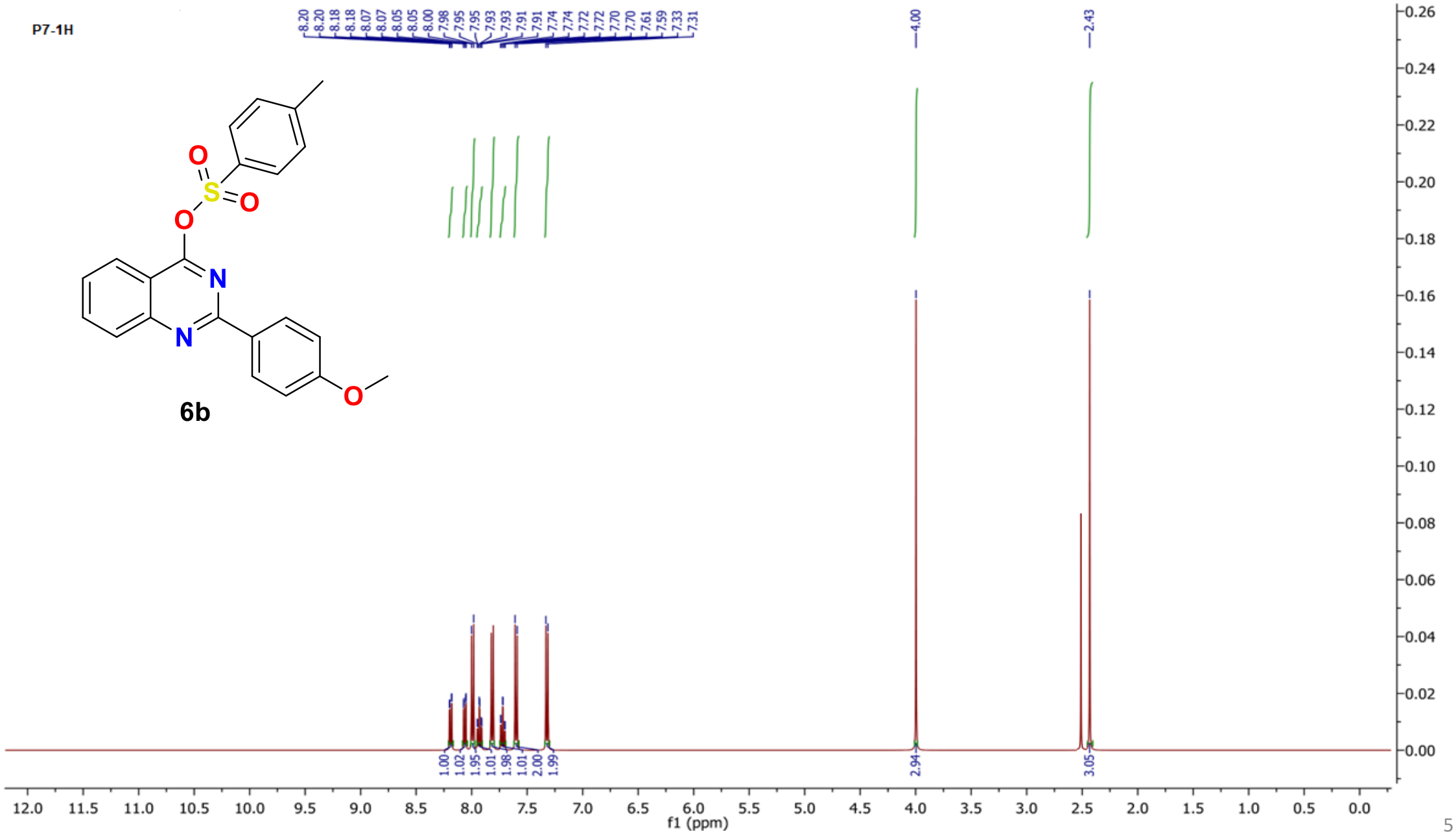
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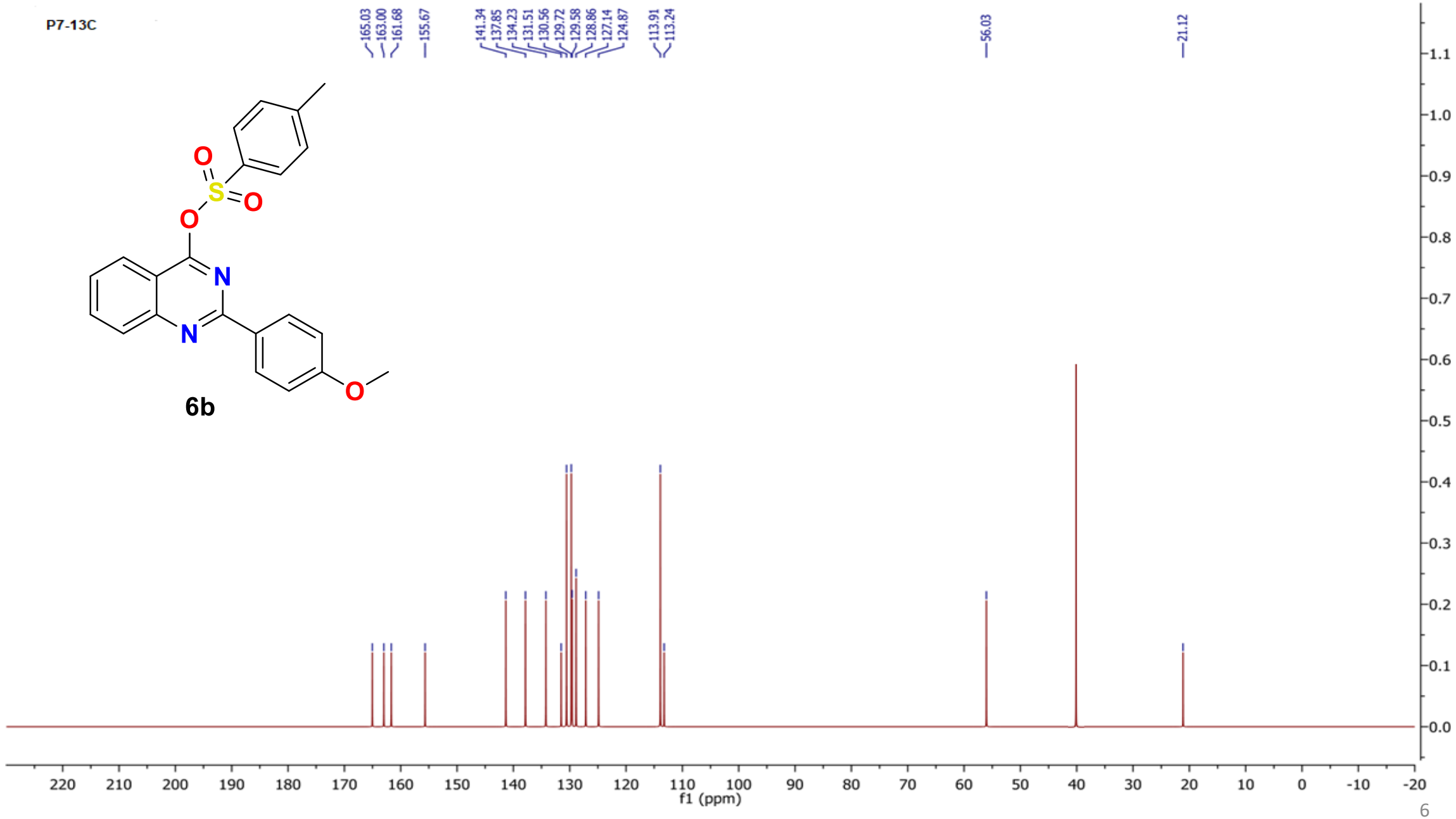
8.18
8.18
8.07
8.07
8.05
8.05
8.00
7.98
7.95
7.95
7.93
7.93
7.91
7.91
7.74
7.74
7.72
7.72
7.70
7.70
7.61
7.59
7.33
7.31
4.00
2.43
O
S
O
O
N
N
O
6b
1.00
1.02
1.95
1.01
1.98
1.01
2.00
1.99
2.94
3.05
f1 (ppm)


P7-13C
165.03
163.00
161.68
155.67
141.34
137.85
134.23
131.51
130.56
129.72
129.58
128.86
127.14
124.87
113.91
113.24
56.03
21.12
O
S
O
O
N
N
O
6b
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

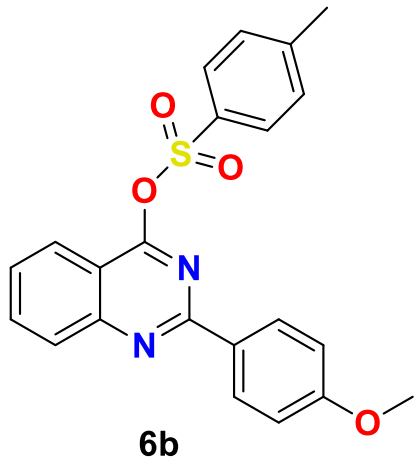
INDIAN INSTITUTE OF TECHNOLOGY
ROPAR

XEVO G2-XS QTOF

Test Name : HRMS-1

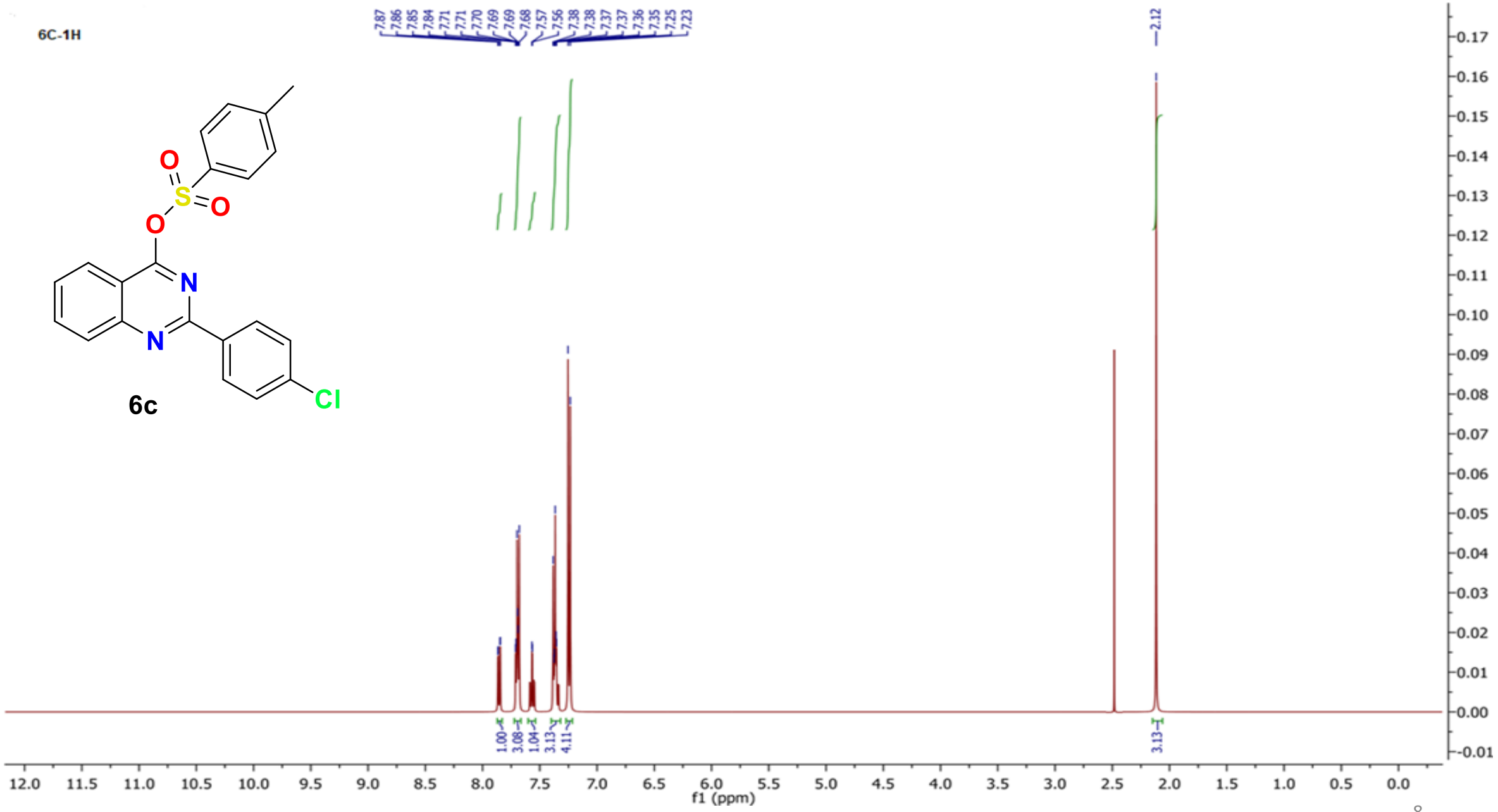
300817 16 (0.177) AM2 (Ar,18000.0,0.00,0.00); Cm (16:22)

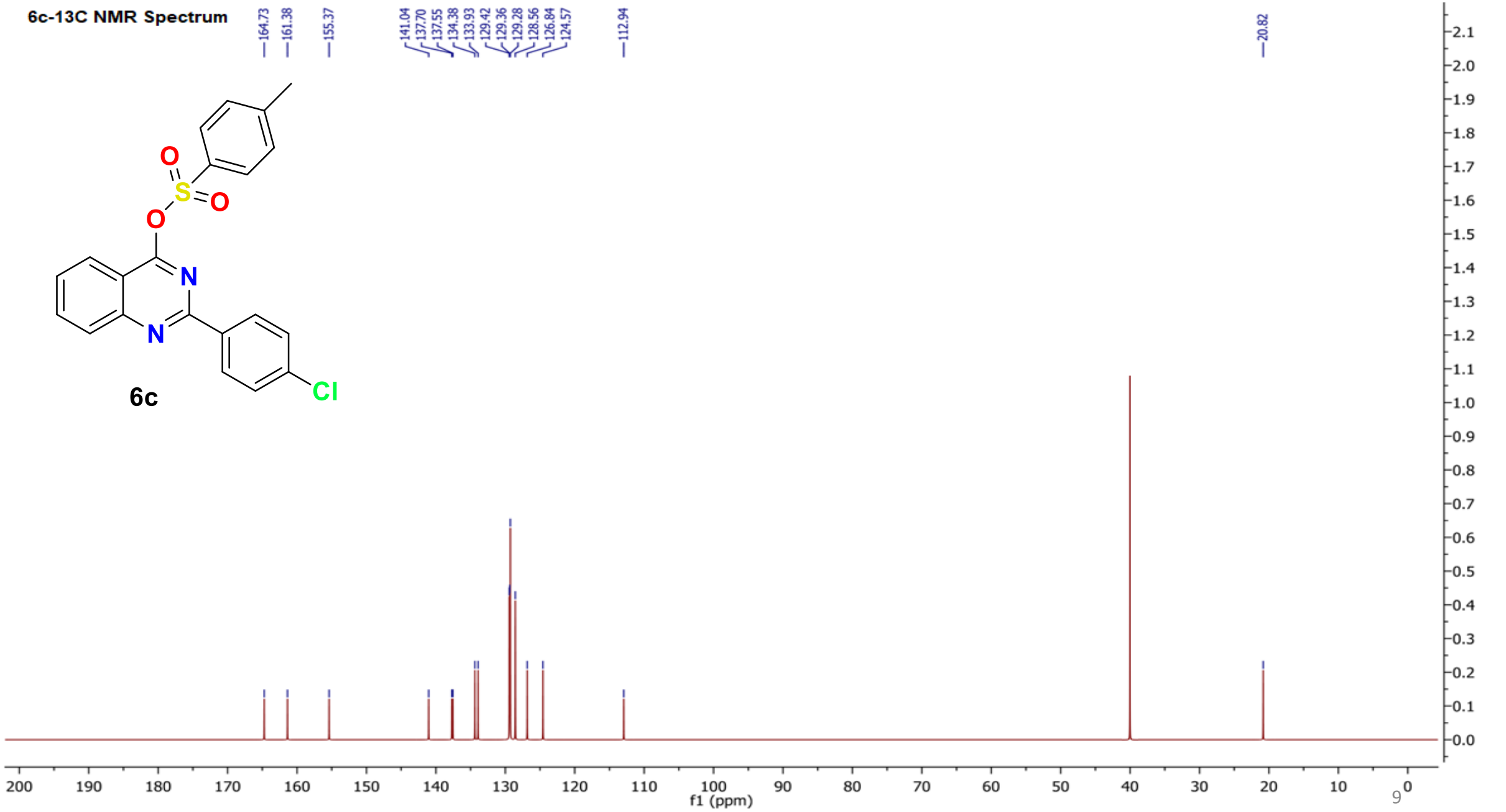
1: TOF MS ES+
1.21e7

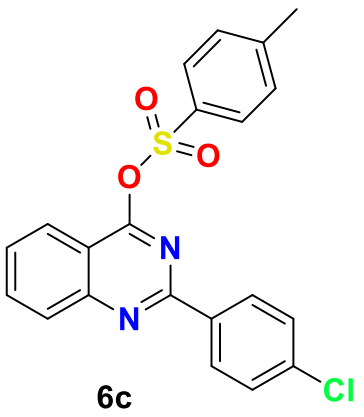


6b

Exact Mass: 406.0987


6C-1H
7.87
7.86
7.85
7.84
7.71
7.71
7.70
7.69
7.69
7.68
7.57
7.56
7.38
7.38
7.37
7.37
7.36
7.35
7.25
7.23
2.12
O
S
O
O
N
N
Cl
6c
1.00
3.08
1.04
3.13
4.11
3.13
f1 (ppm)


6c-13C NMR Spectrum
164.73
161.38
155.37
141.04
137.70
137.55
134.38
133.93
129.42
129.36
129.28
128.56
126.84
124.57
112.94
20.82
O
S
O
O
N
N
Cl
6c
f1 (ppm)



6c

Exact Mass: 410.0492

INDIAN INSTITUTE OF TECHNOLOGY
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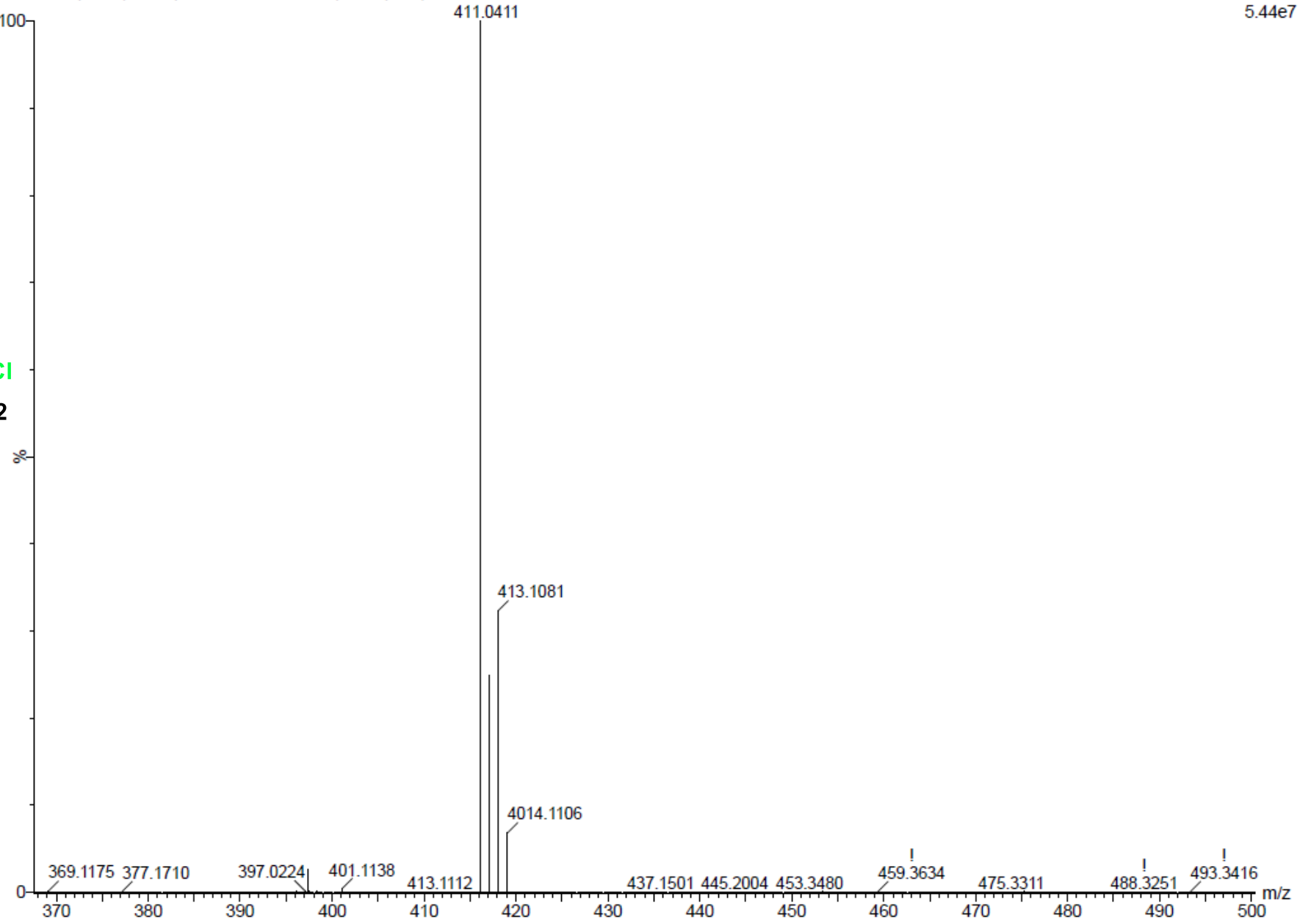
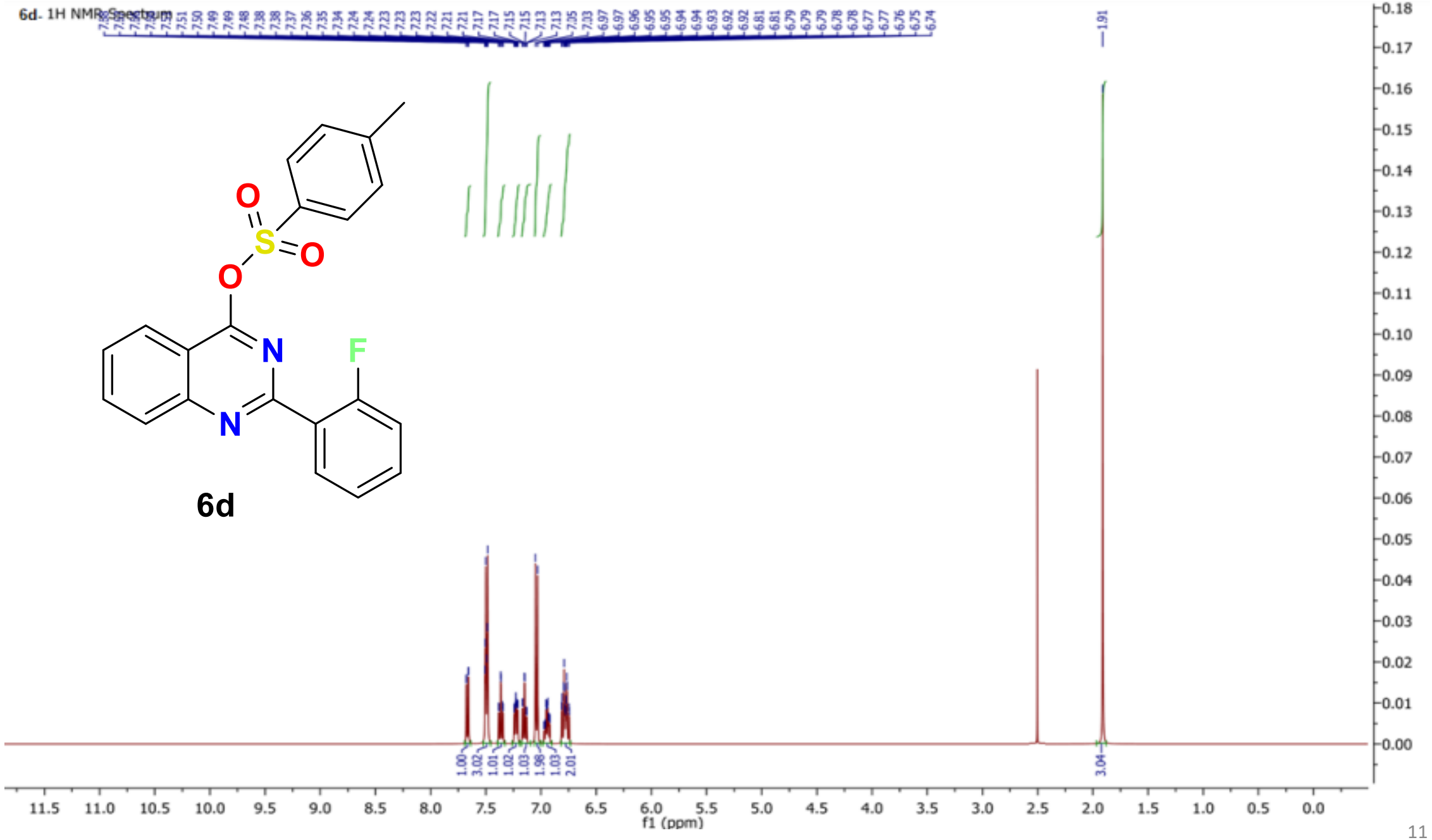
XEVO G2-XS QTOF

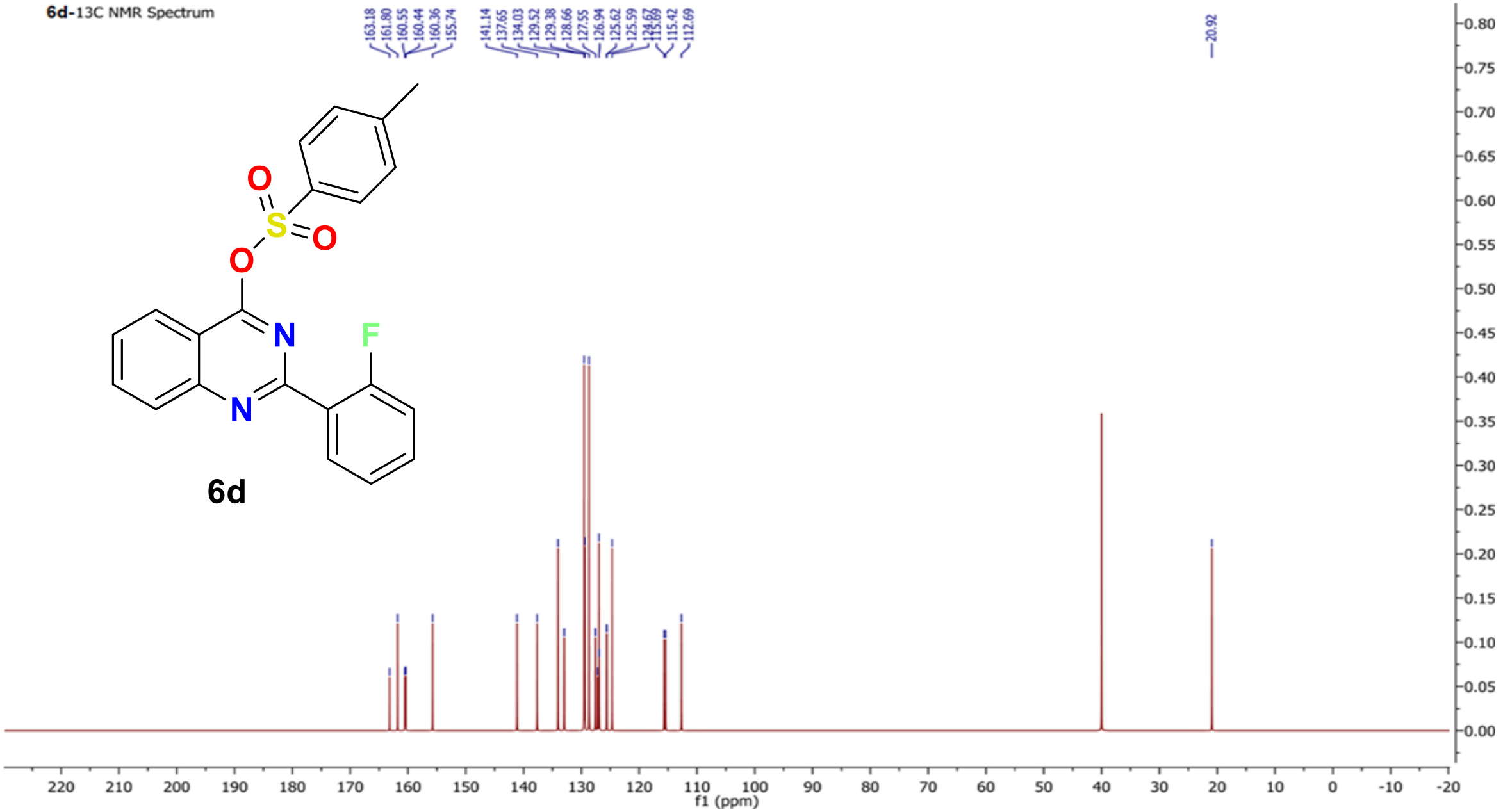
Test Name : HRMS-1
300817- 9 (0.117) AM2 (Ar,18000.0,0.00,0.00); Cm (5:19)

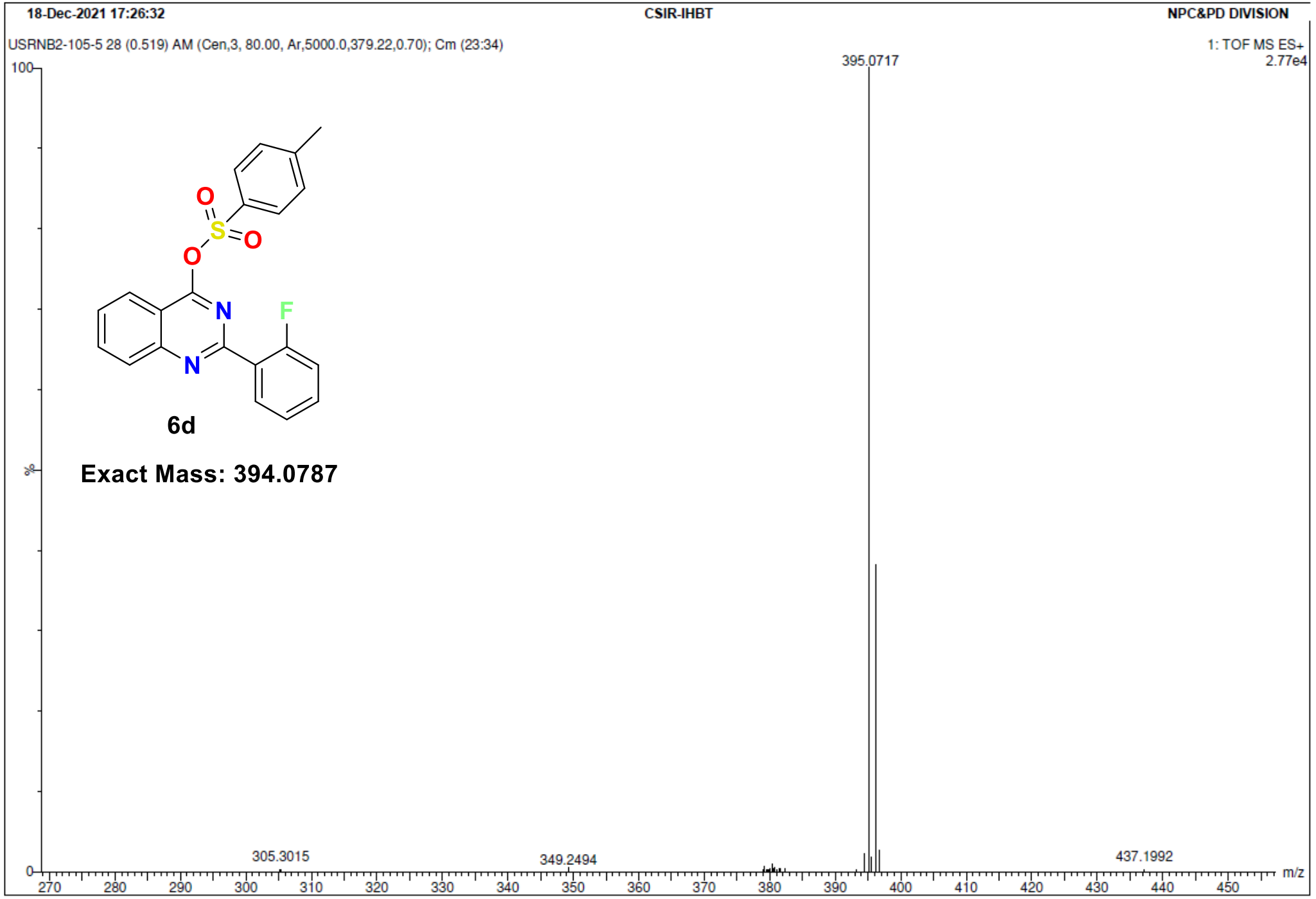
1: TOF MS ES+
5.44e7



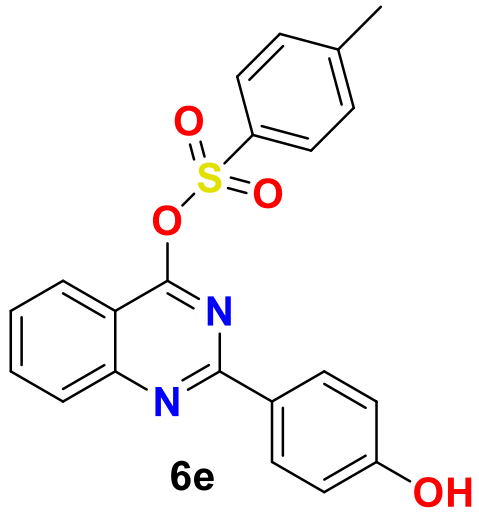

6d- 1H NMR Spectrum
O
S
O
O
N
F
N
6d
1.91
1.00
3.02
1.01
1.02
1.03
1.98
1.03
2.01
3.04
f1 (ppm)

6d-13C NMR Spectrum



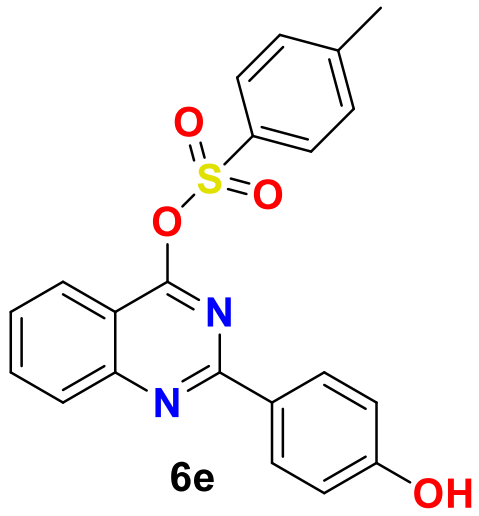

18-Dec-2021 17:26:32
CSIR-IHBT
NPC&PD DIVISION
USRNB2-105-5 28 (0.519) AM (Cen,3, 80.00, Ar,5000.0,379.22,0.70); Cm (23:34)
1: TOF MS ES+
2.77e4
395.0717
100
%
0
O
S
O
O
N
F
N
6d
Exact Mass: 394.0787
305.3015
349.2494
437.1992
m/z
270
280
290
300
310
320
330
340
350
360
370
380
390
400
410
420
430
440
450

6e- 1H NMR Spectrum



6e

6e- 13C NMR Spectrum



6e

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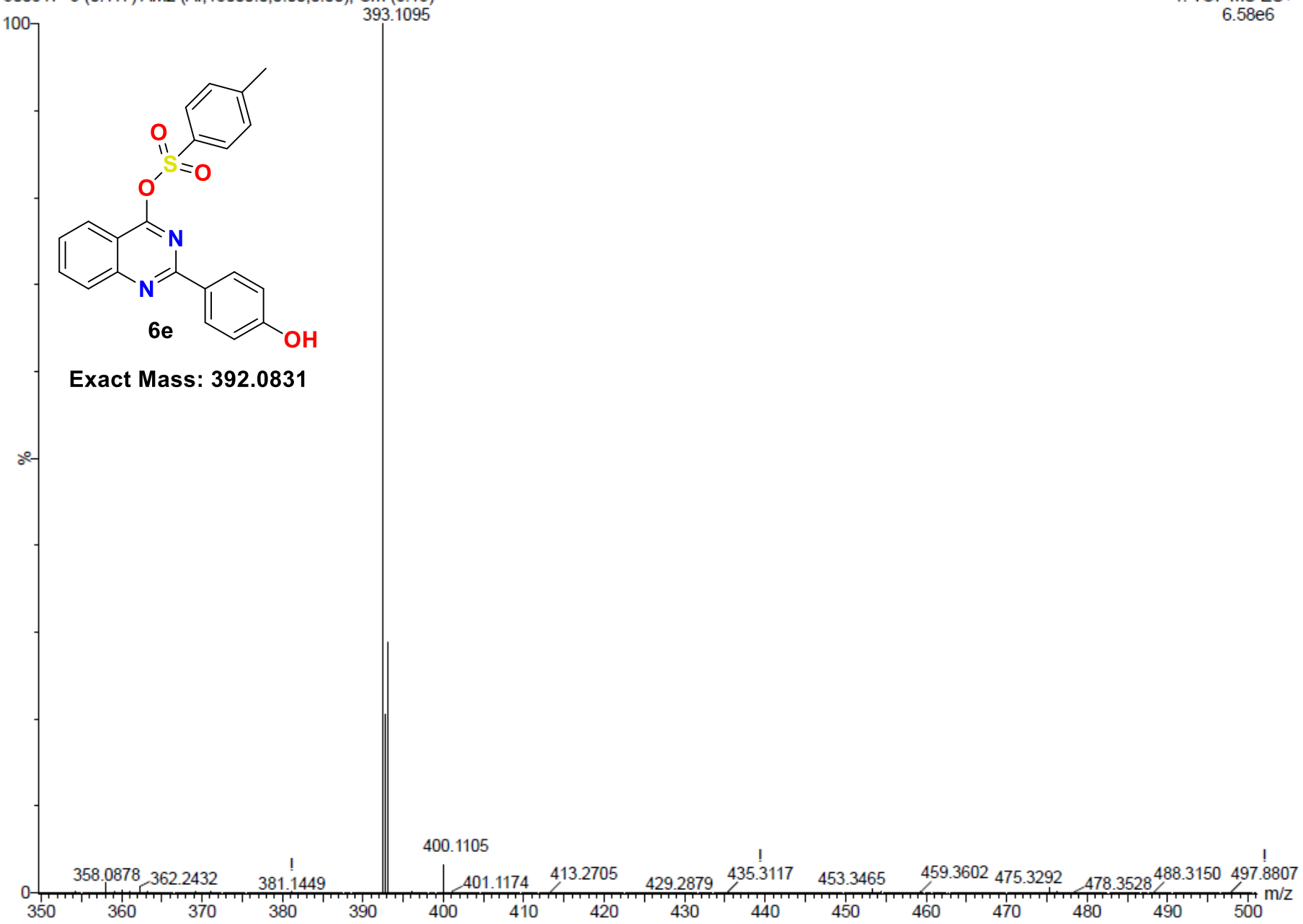
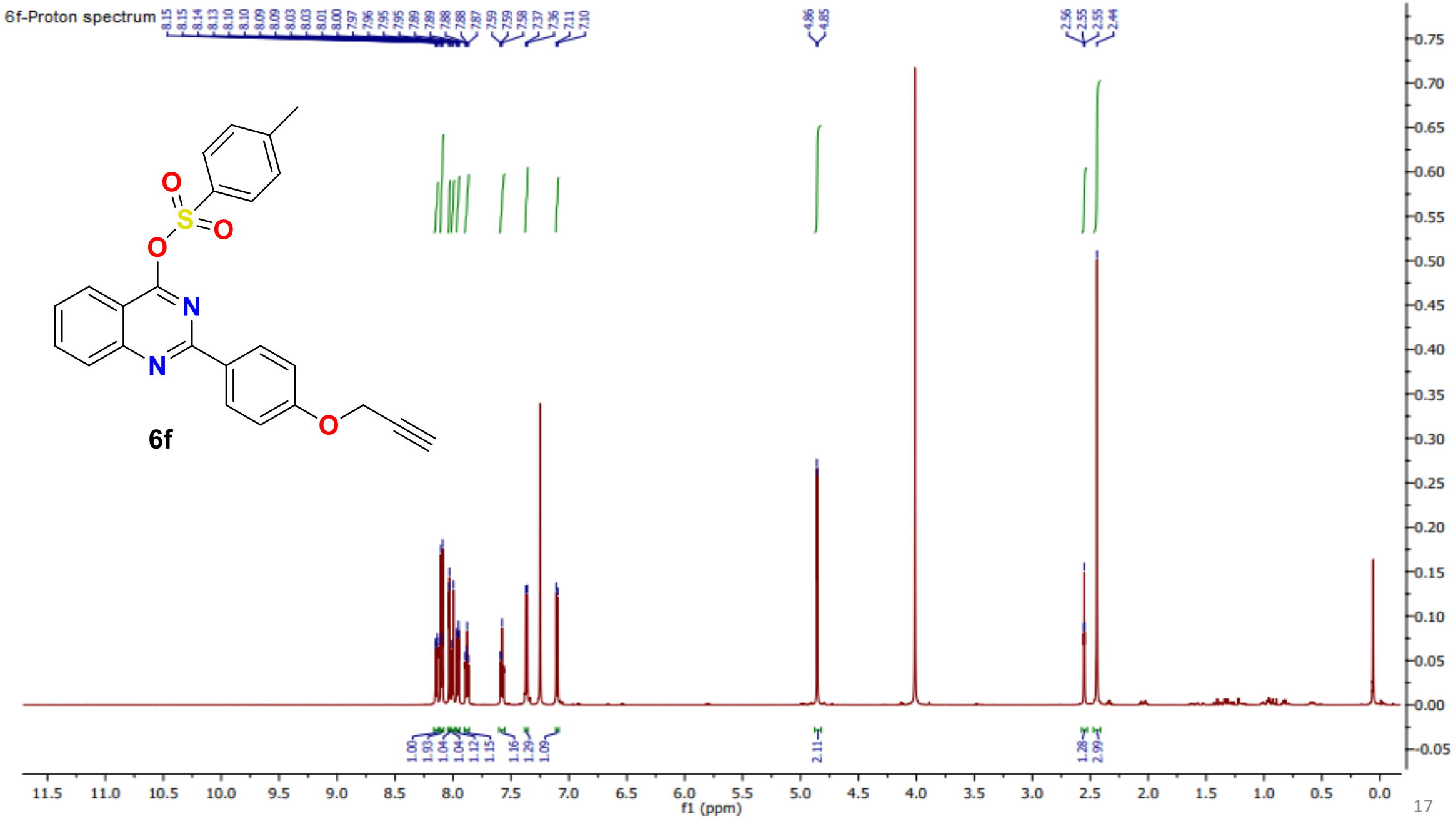
XEVO G2-XS QTOF

Test Name : HRMS-1

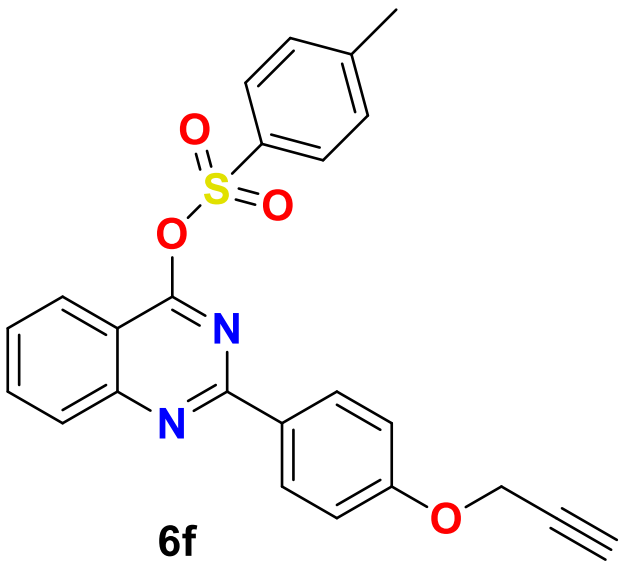
300817- 9 (0.117) AM2 (Ar,18000.0,0.00,0.00); Cm (8:19)

1: TOF MS ES+
6.58e6




6f-Proton spectrum
6f
f1 (ppm)

6f- 13C NMR Spectrum



6f

INDIAN INSTITUTE OF TECHNOLOGY
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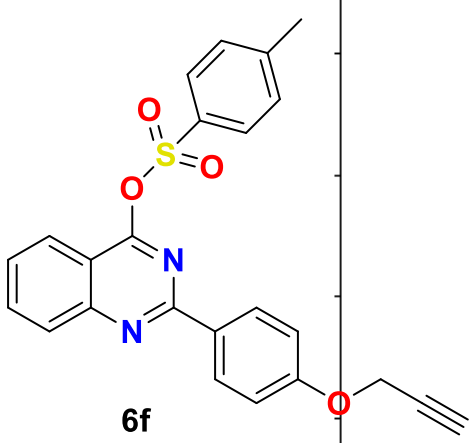
XEVO G2-XS QTOF

Test Name : HRMS-1

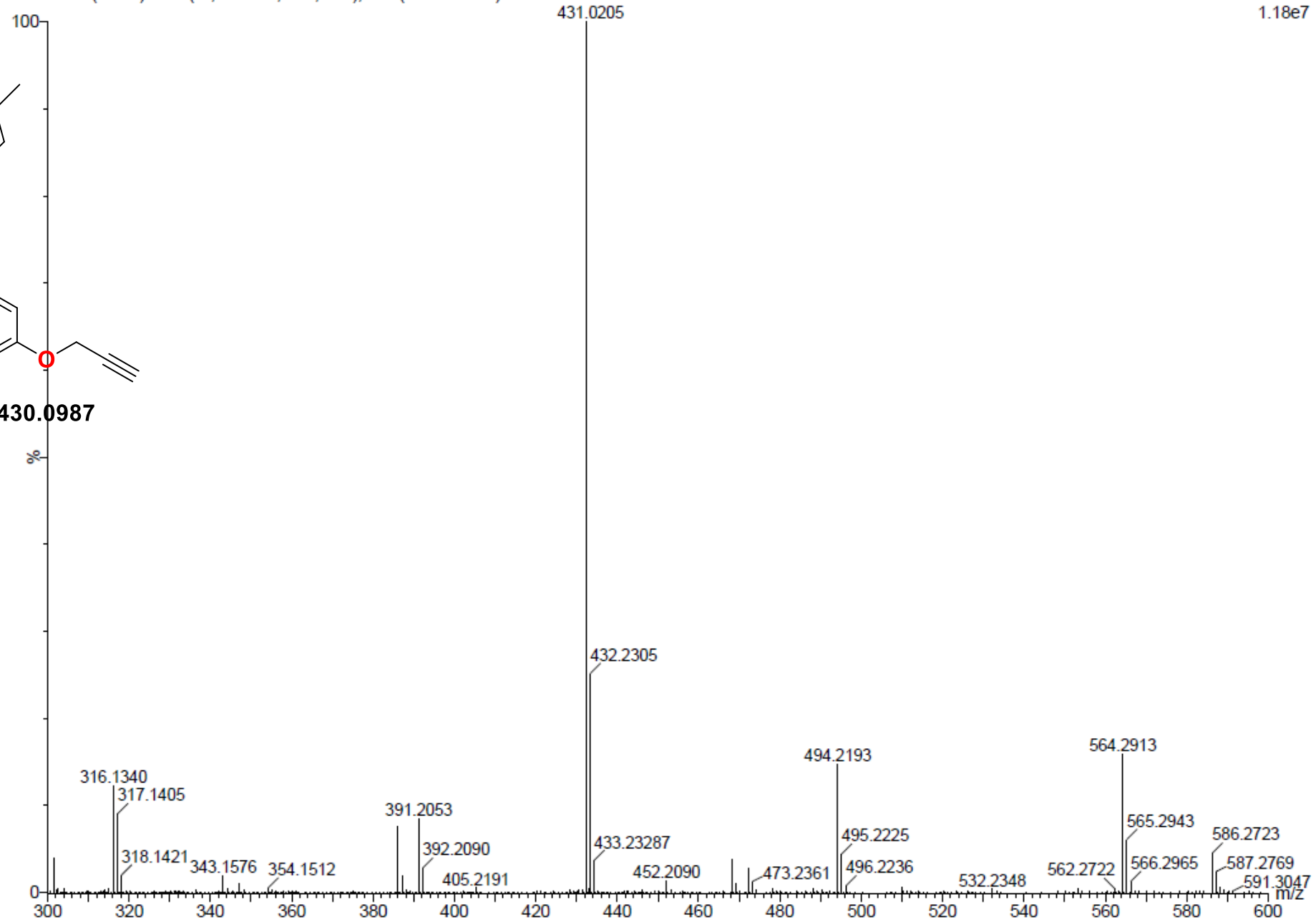
161117-14 (0.160) AM2 (Ar,15000.0,0.00,0.00); Cm (14:16-21:45)

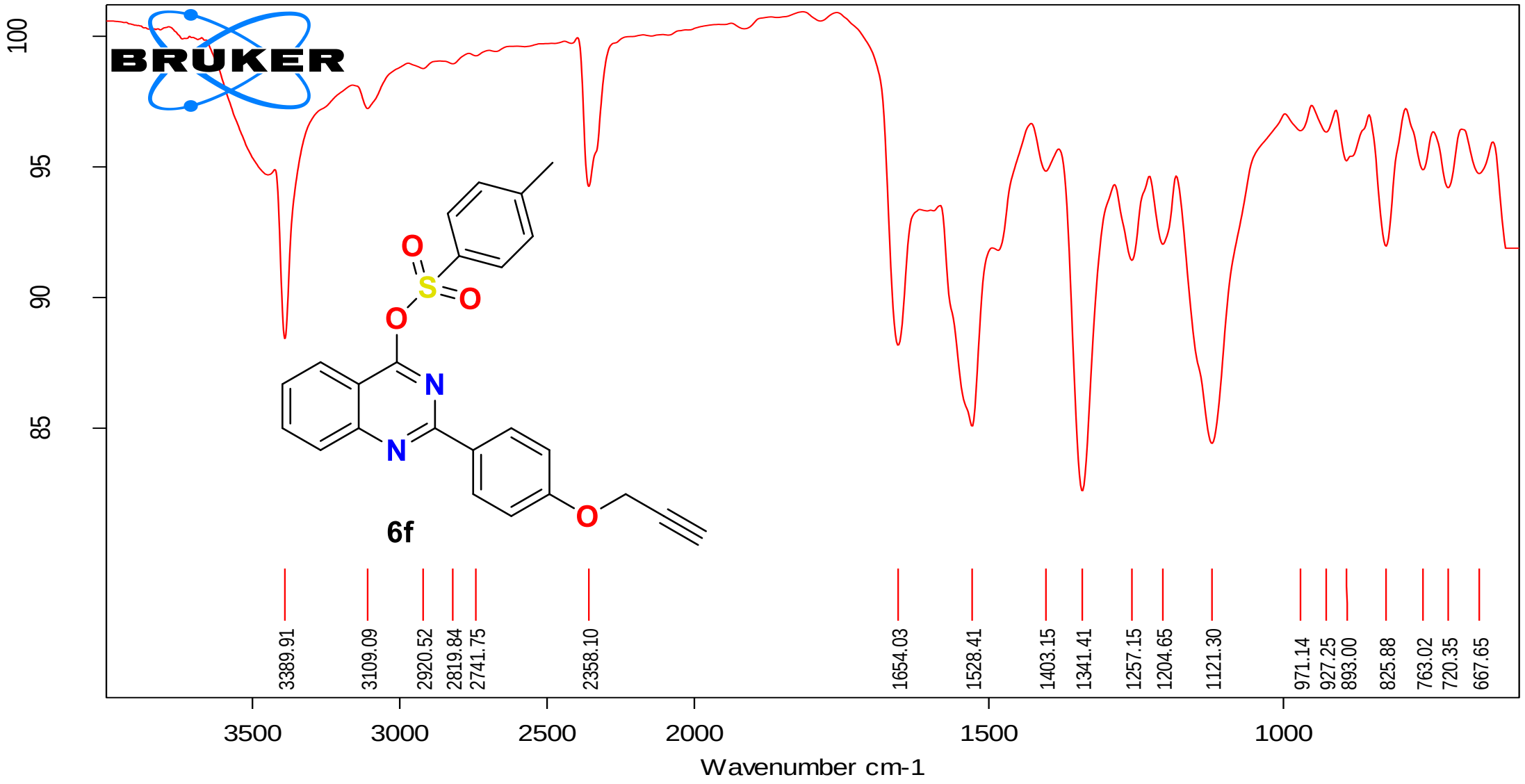
1: TOF MS ES+
1.18e7

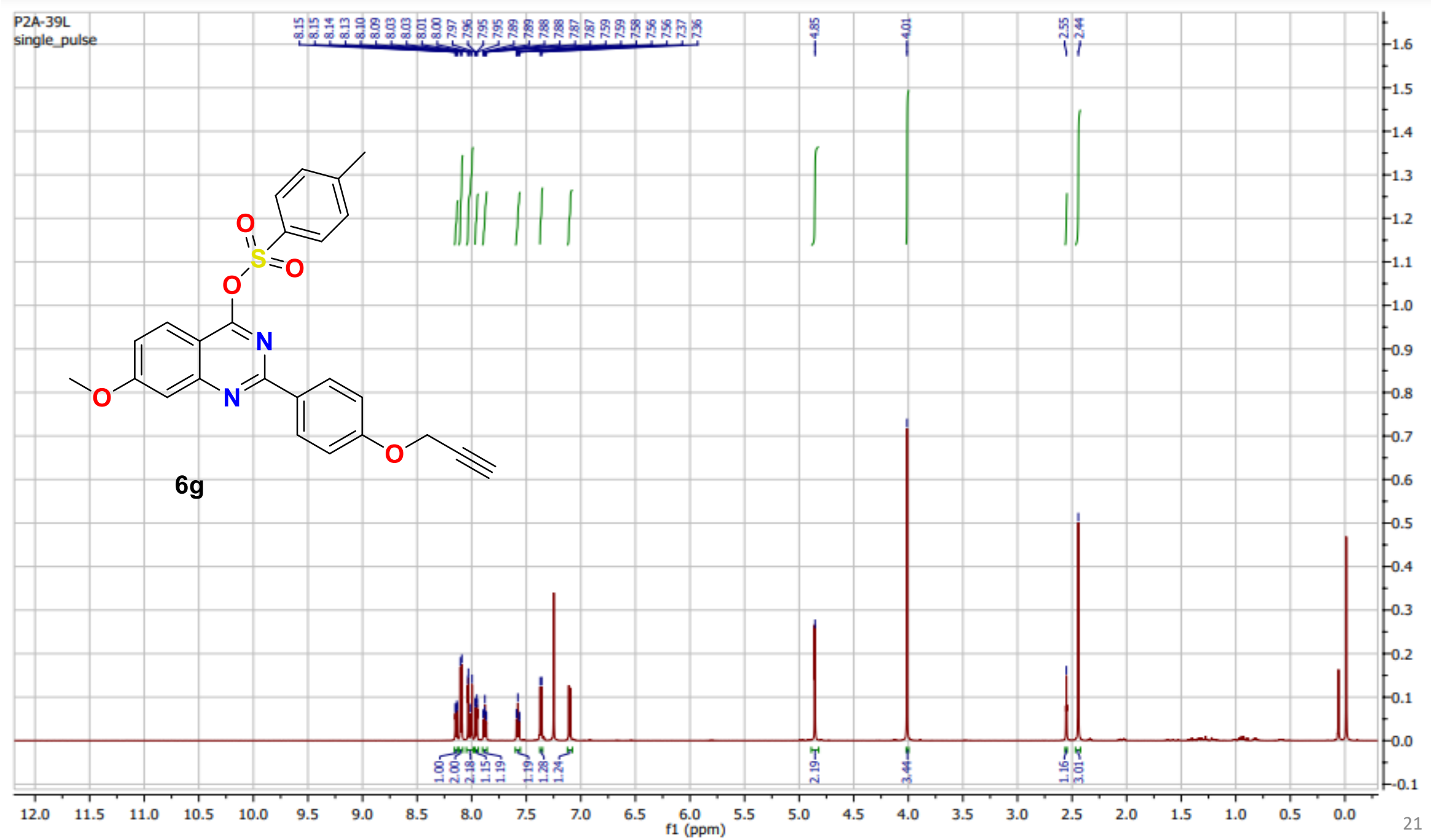


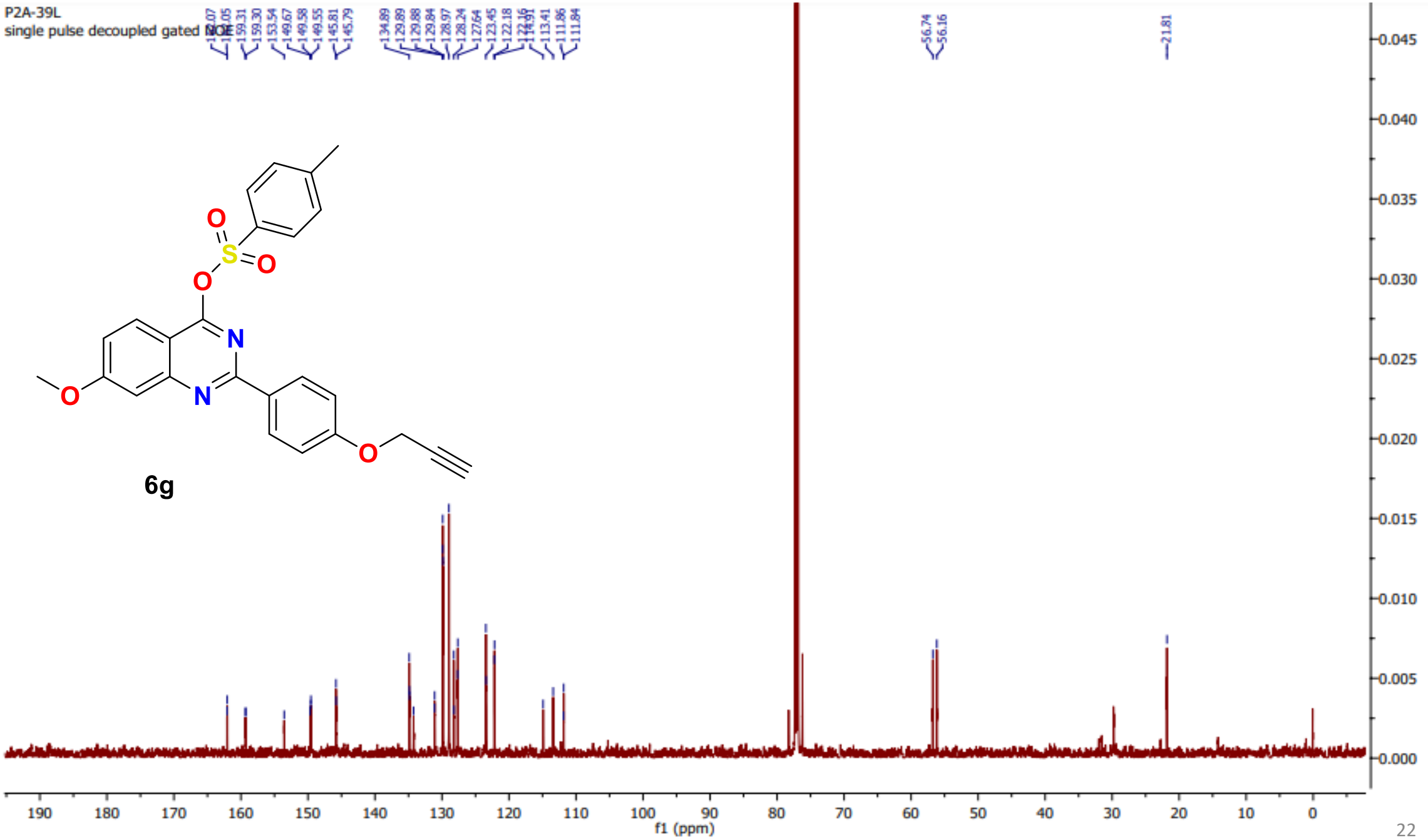
6f

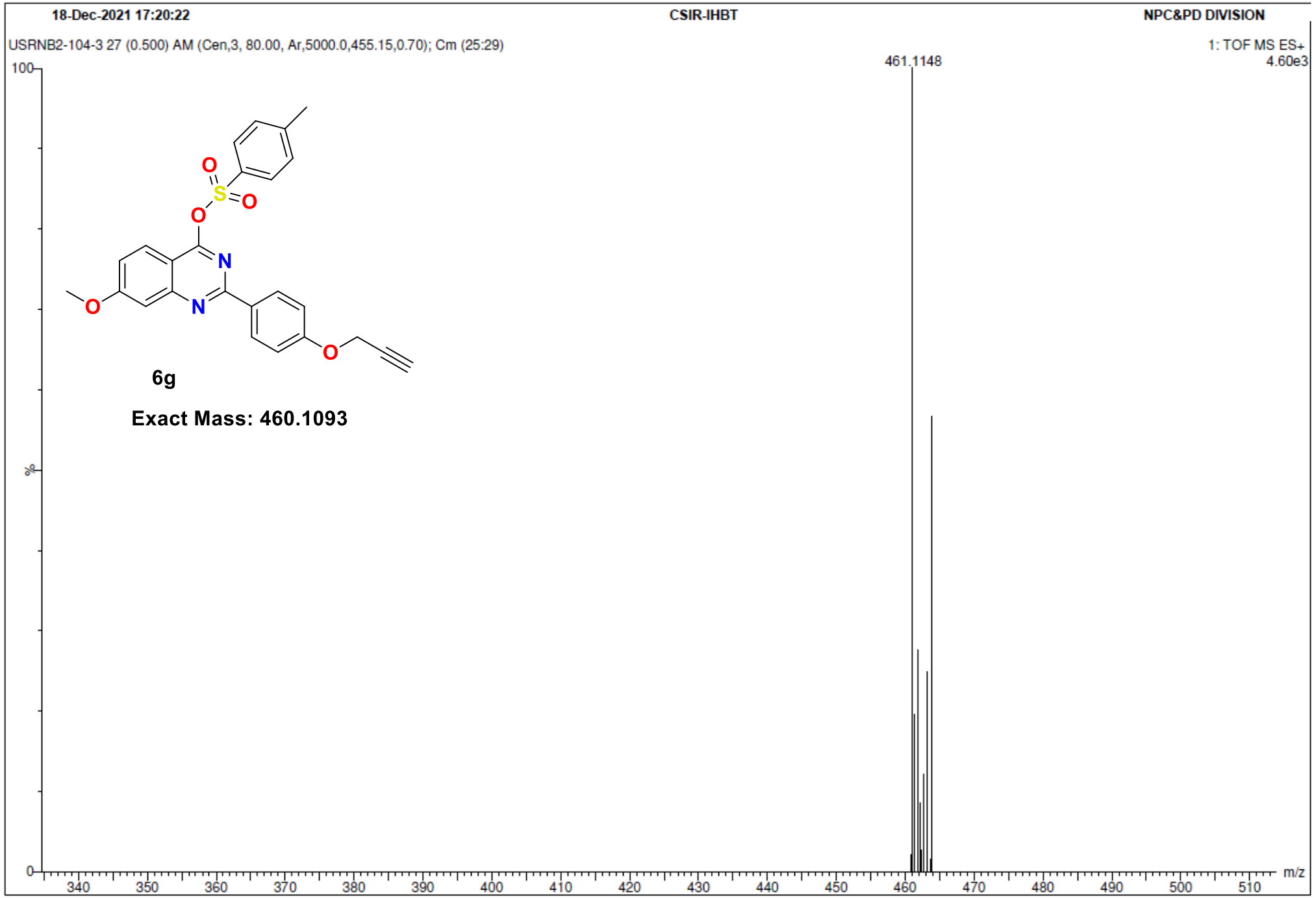
Exact Mass: 430.0987

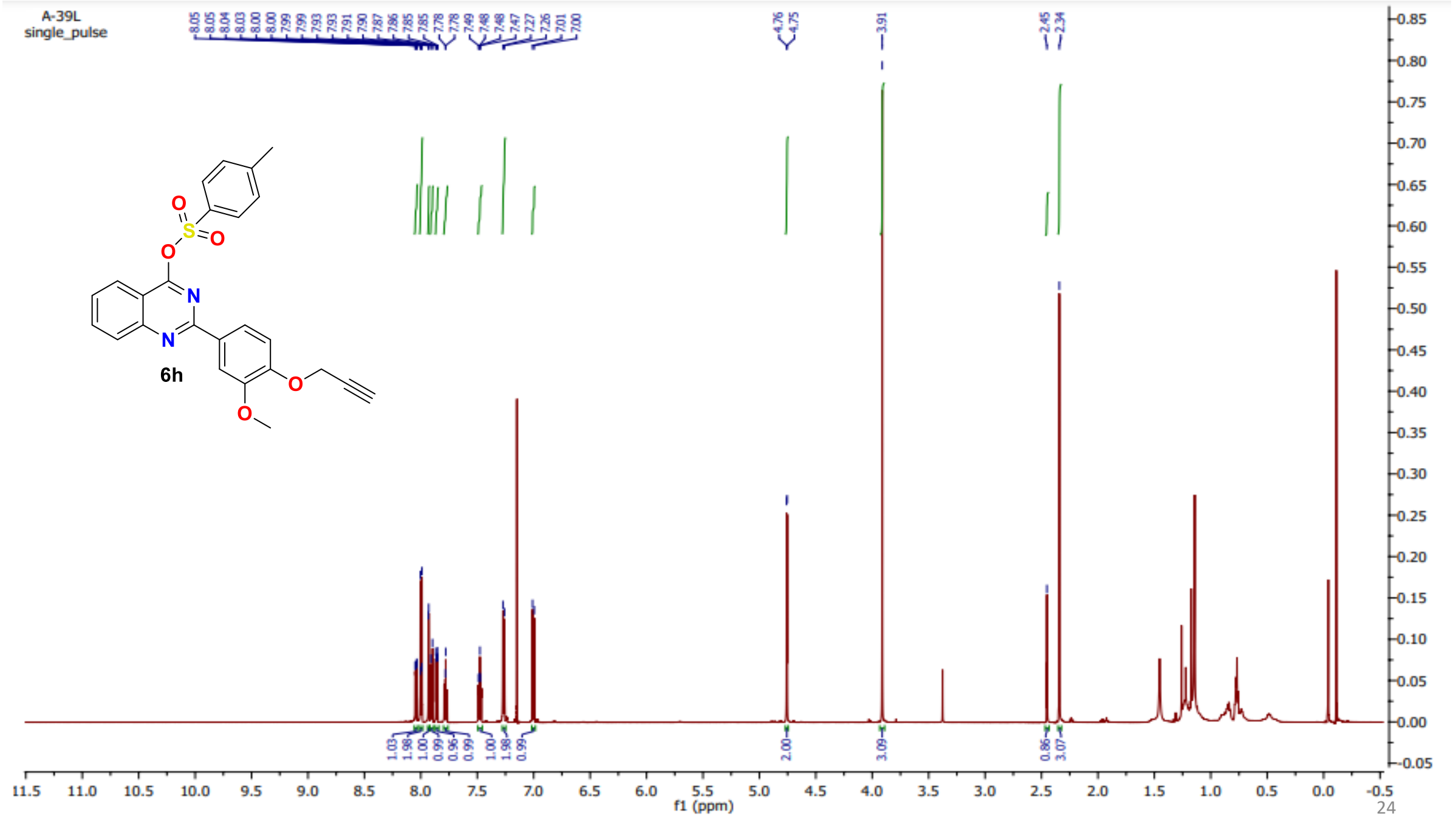


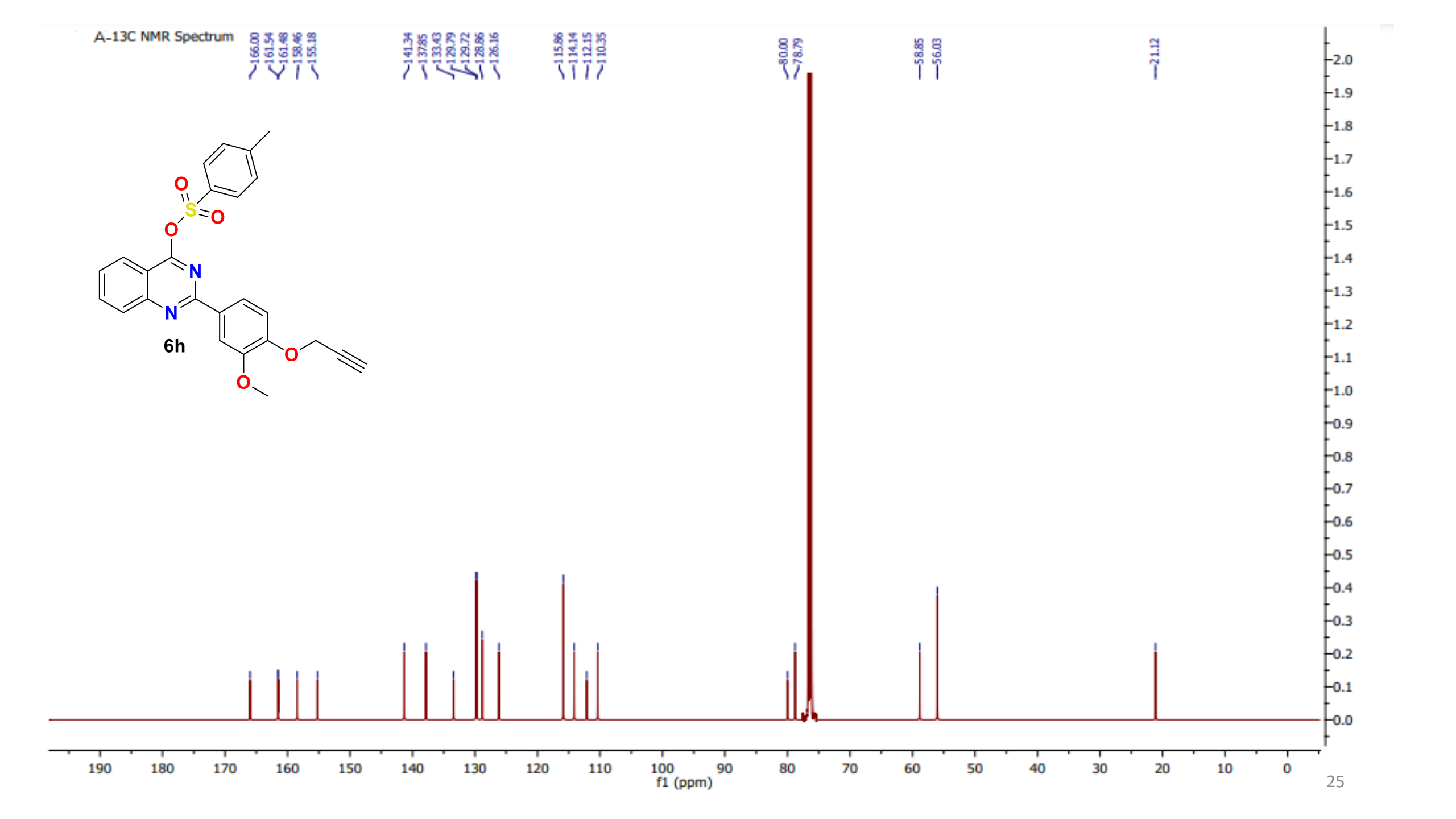

BRUKER
100
95
90
85
O
S
O
O
N
N
O
6f
3389.91
3109.09
2920.52
2819.84
2741.75
2358.10
1654.03
1528.41
1403.15
1341.41
1257.15
1204.65
1121.30
971.14
927.25
893.00
825.88
763.02
720.35
667.65
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

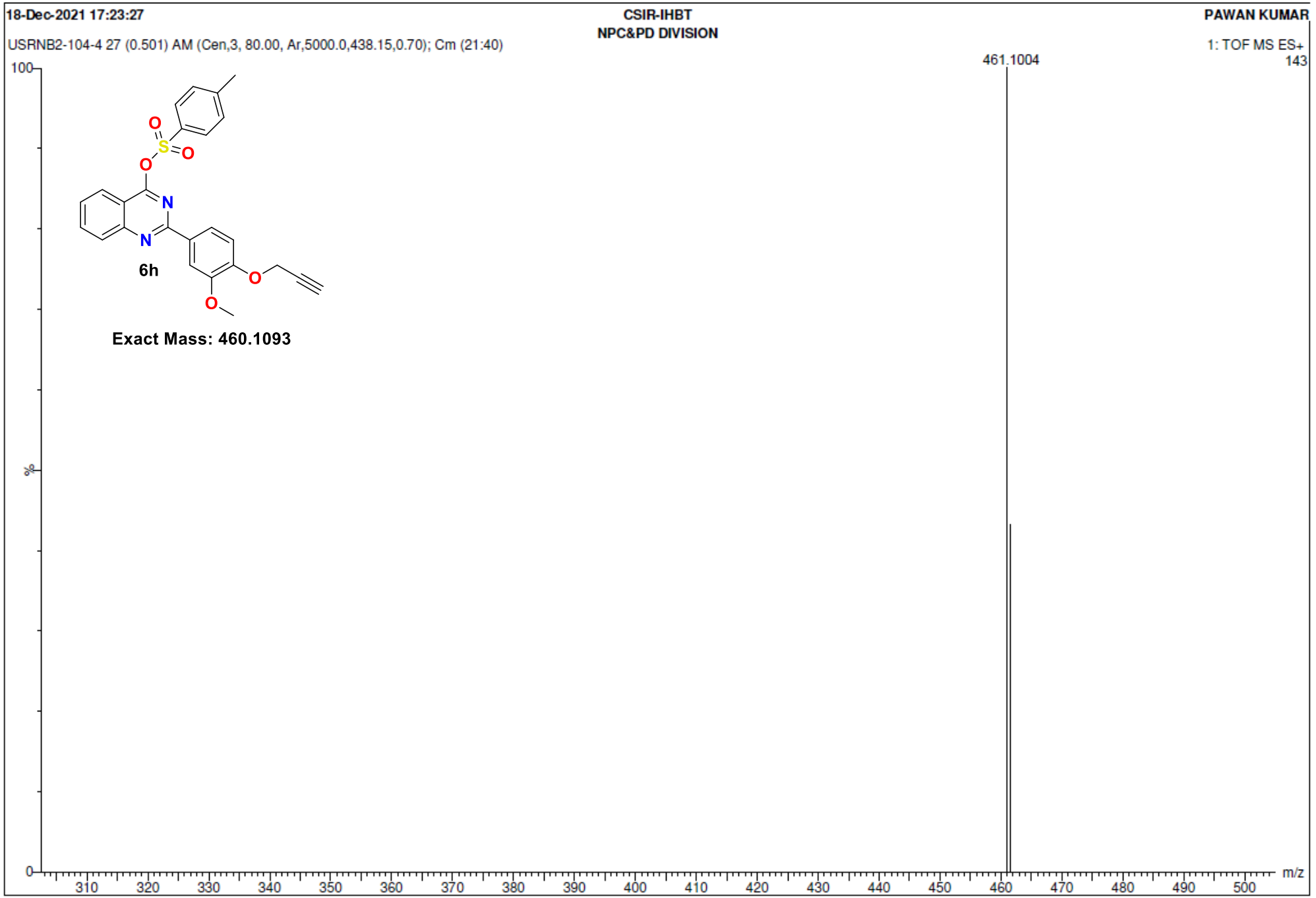

P2A-39L
single_pulse
8.15
8.15
8.14
8.13
8.10
8.09
8.03
8.03
8.01
8.00
7.97
7.96
7.95
7.95
7.89
7.89
7.88
7.88
7.87
7.87
7.59
7.59
7.58
7.56
7.56
7.37
7.36
4.85
4.01
2.55
2.44
O
S
O
O
N
N
O
O
6g
1.00
2.00
2.18
1.15
1.19
1.19
1.28
1.24
2.19
3.44
1.16
3.01
f1 (ppm)

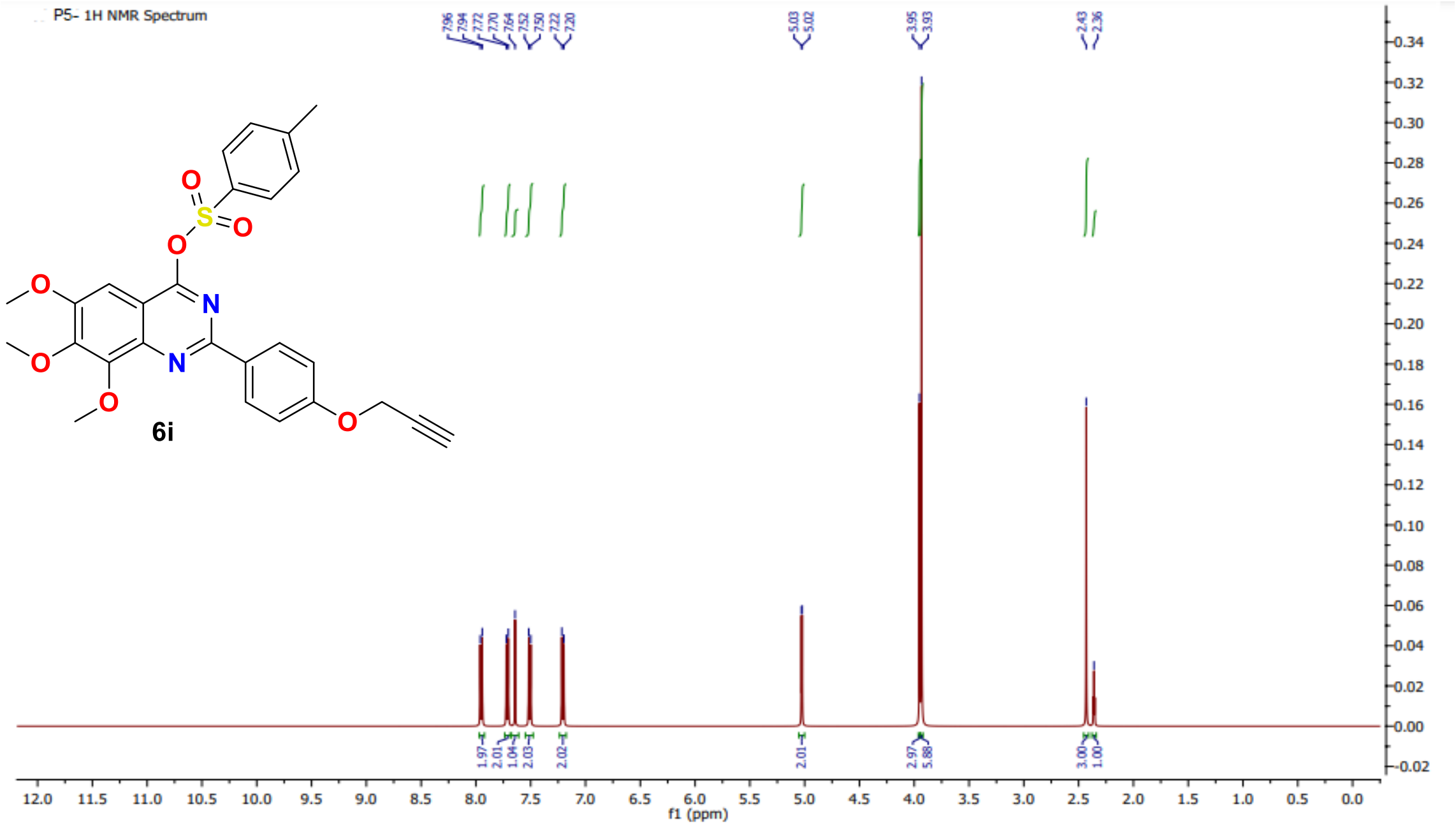

P2A-39L
single pulse decoupled gated NOE
159.31
153.54
149.67
149.58
149.55
145.81
145.79
134.89
129.89
129.88
129.84
128.97
128.24
127.64
123.45
122.18
113.41
111.86
111.84
56.74
56.16
21.81
O
S
O
O
N
N
O
O
6g
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

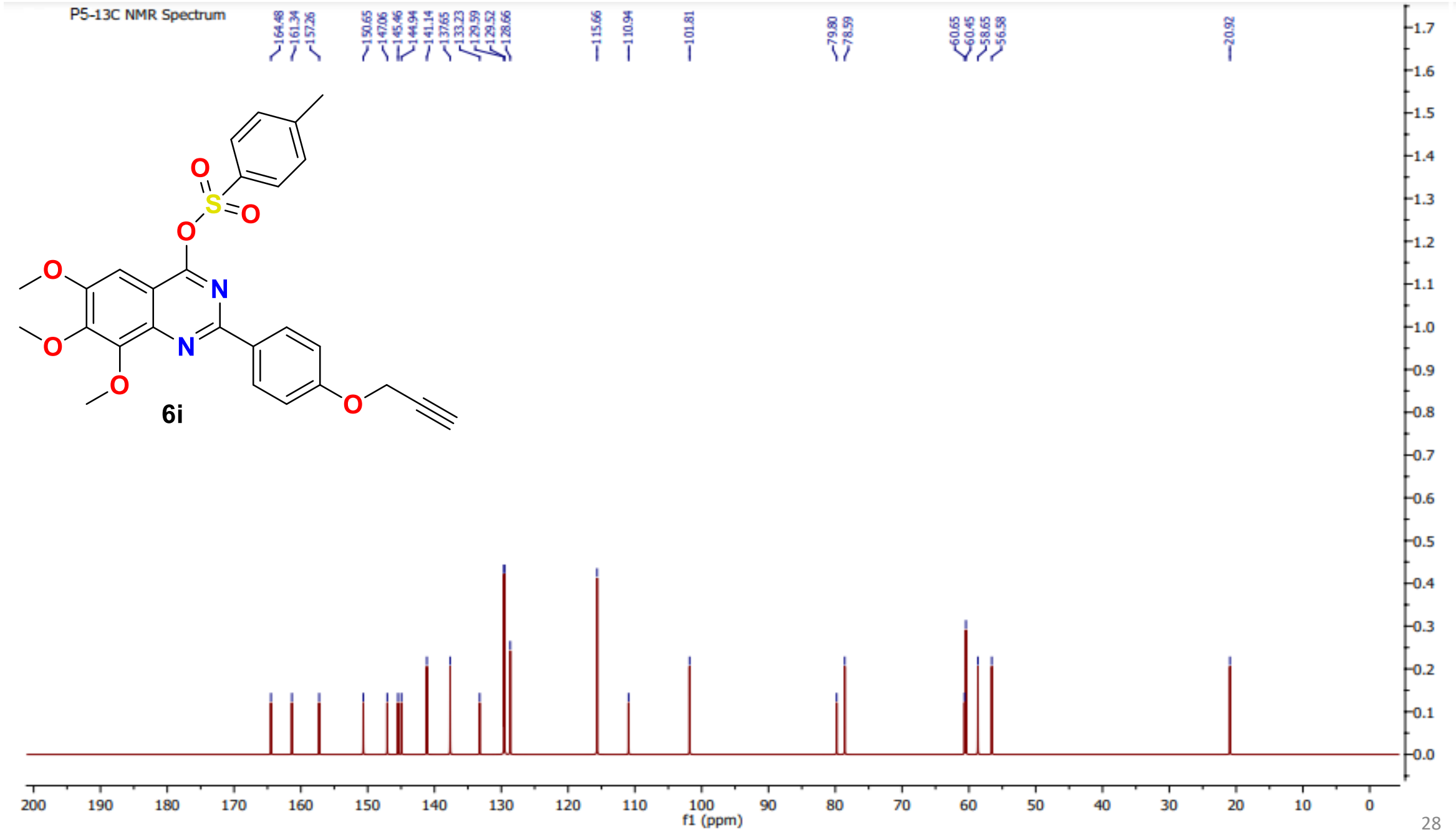

18-Dec-2021 17:20:22
CSIR-IHBT
NPC&PD DIVISION
USRNB2-104-3 27 (0.500) AM (Cen,3, 80.00, Ar,5000.0,455.15,0.70); Cm (25:29)
1: TOF MS ES+
4.60e3
461.1148
100
%
0
340
350
360
370
380
390
400
410
420
430
440
450
460
470
480
490
500
510
m/z
O
S
O
O
N
N
O
O
6g
Exact Mass: 460.1093


A-39L
single_pulse
6h
f1 (ppm)


A-13C NMR Spectrum
166.00
161.54
161.48
158.46
155.18
141.34
137.85
133.43
129.79
129.72
128.86
126.16
115.86
114.14
112.15
110.35
80.00
78.79
58.85
56.03
21.12
6h
f1 (ppm)


18-Dec-2021 17:23:27
CSIR-IHBT
NPC&PD DIVISION
PAWAN KUMAR
USRNB2-104-4 27 (0.501) AM (Cen,3, 80.00, Ar,5000.0,438.15,0.70); Cm (21:40)
1: TOF MS ES+
143
461.1004
100
%
0
6h
Exact Mass: 460.1093
310 320 330 340 350 360 370 380 390 400 410 420 430 440 450 460 470 480 490 500
m/z


P5- 1H NMR Spectrum
7.96
7.94
7.72
7.70
7.64
7.52
7.50
7.22
7.20
5.03
5.02
3.95
3.93
2.43
2.36
O
S
O
O
O
O
N
N
O
O
6i
1.97
2.01
1.04
2.03
2.02
2.01
2.97
5.88
3.00
1.00
0.34
0.32
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
12.0
11.5
11.0
10.5
10.0
9.5
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)


P5-13C NMR Spectrum
164.48
161.34
157.26
150.65
147.06
145.46
144.94
141.14
137.65
133.23
129.59
129.52
128.66
115.66
110.94
101.81
79.80
78.59
60.65
60.45
58.65
56.58
20.92
6i
f1 (ppm)

INDIAN INSTITUTE OF TECHNOLOGY
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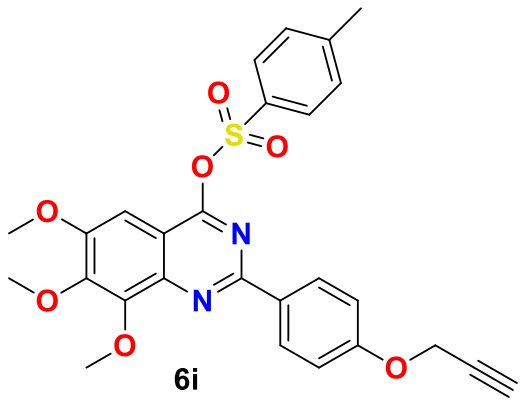
XEVO G2-XS QTOF

Test Name : HRMS-1

301017- 14 (0.160) AM2 (Ar,13000.0,0.00,0.00); Cm (14:16)

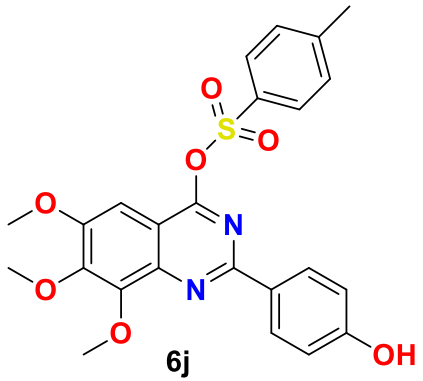
1: TOF MS ES+



6i

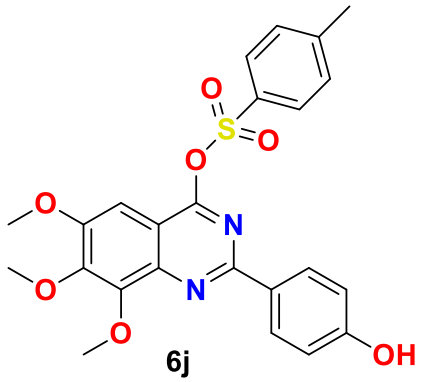
Exact Mass: 520.1304

6j-proton NMR



6j

6J-13C


O
S
O
O
O
O
N
O
N
O
OH

6j

164.18
161.05
156.96
150.35
146.76
145.16
144.64
140.84
137.35
130.31
129.22
128.36
126.05
115.29
110.64
101.51
60.35
60.15
56.28
20.62
f1 (ppm)

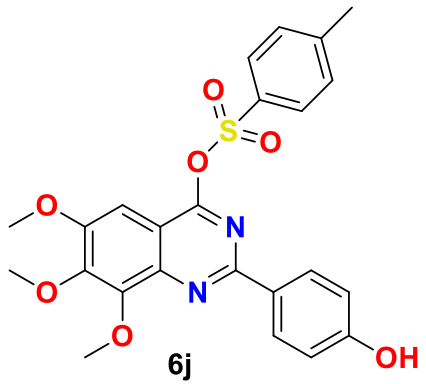
INDIAN INSTITUTE OF TECHNOLOGY
ROPAR

XEVO G2-XS QTOF

Test Name : HRMS-1

161117- 16 (0.177) AM2 (Ar,15000.0,0.00,0.00); Cm (16:19-24:50)

1: TOF MS ES+
4.49e6



6j

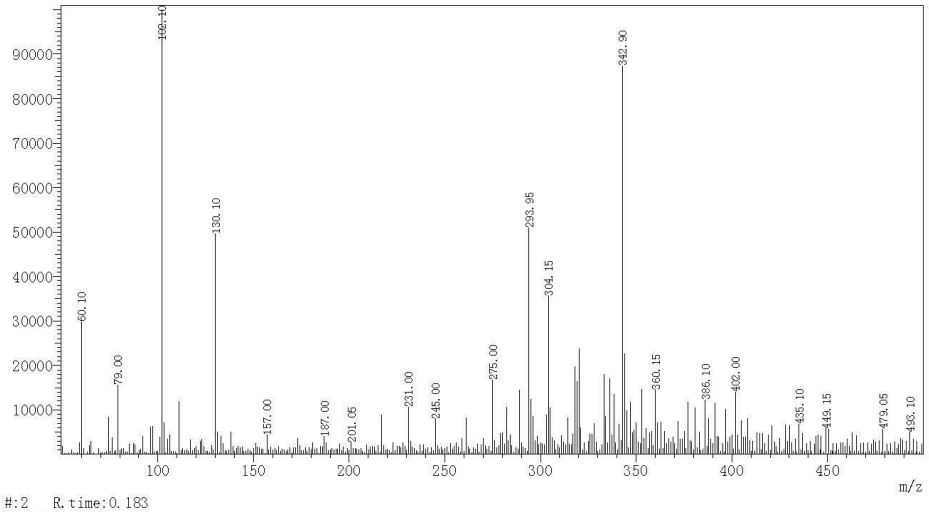
Exact Mass: 482.1148

TPPT: exact mass = 342.0

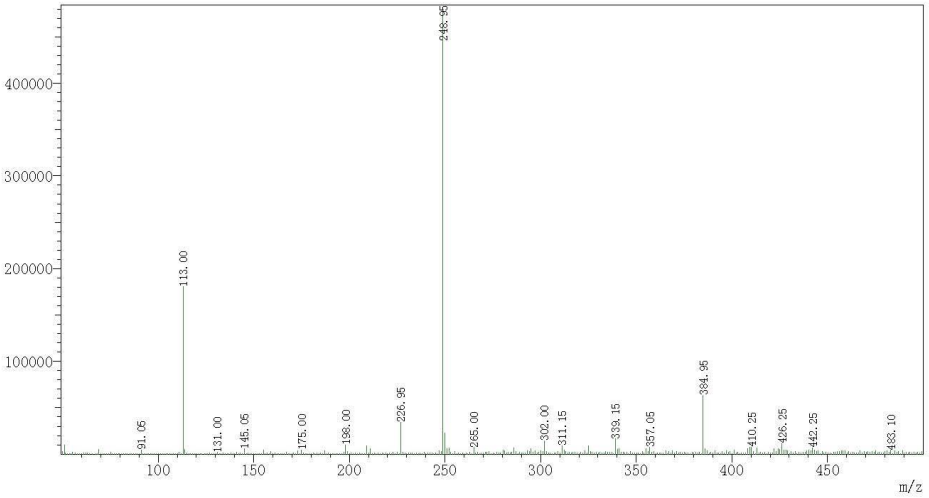
Produce for synthesizing TMTM and TPPT simultaneously
(TMTD/triphenyl phosphite = 1/1.2, 80℃, 10h, in Acetonitrile)
MS Data Report

〈Spectrum〉

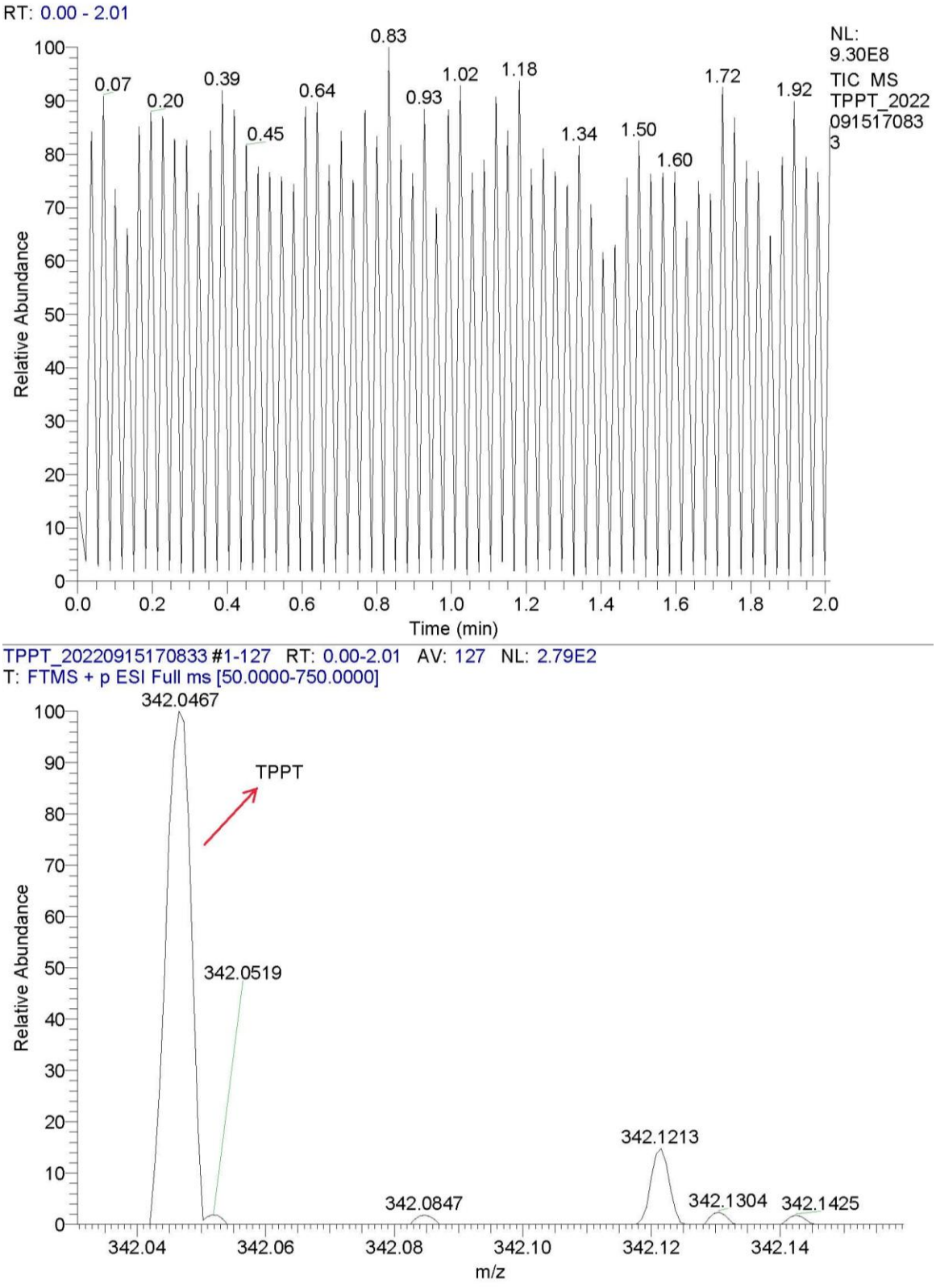
#:1 R.time:0.167
MassPeaks:450
BasePeak:102.10(99948)



#:2 R.time:0.183
MassPeaks:449
BasePeak:248.95



TPPT HRMS


RT: 0.00 - 2.01
NL:
9.30E8
TIC MS
TPPT_2022
091517083
3
Relative Abundance
Time (min)
0.07
0.20
0.39
0.45
0.64
0.83
0.93
1.02
1.18
1.34
1.50
1.60
1.72
1.92
TPPT_20220915170833 #1-127 RT: 0.00-2.01 AV: 127 NL: 2.79E2
T: FTMS + p ESI Full ms [50.0000-750.0000]
342.0467
TPPT
342.0519
342.0847
342.1213
342.1304
342.1425
m/z