Supporting Information

AN IMPROVED AND PRACTICAL SYNTHESIS OF RIVAROXABAN

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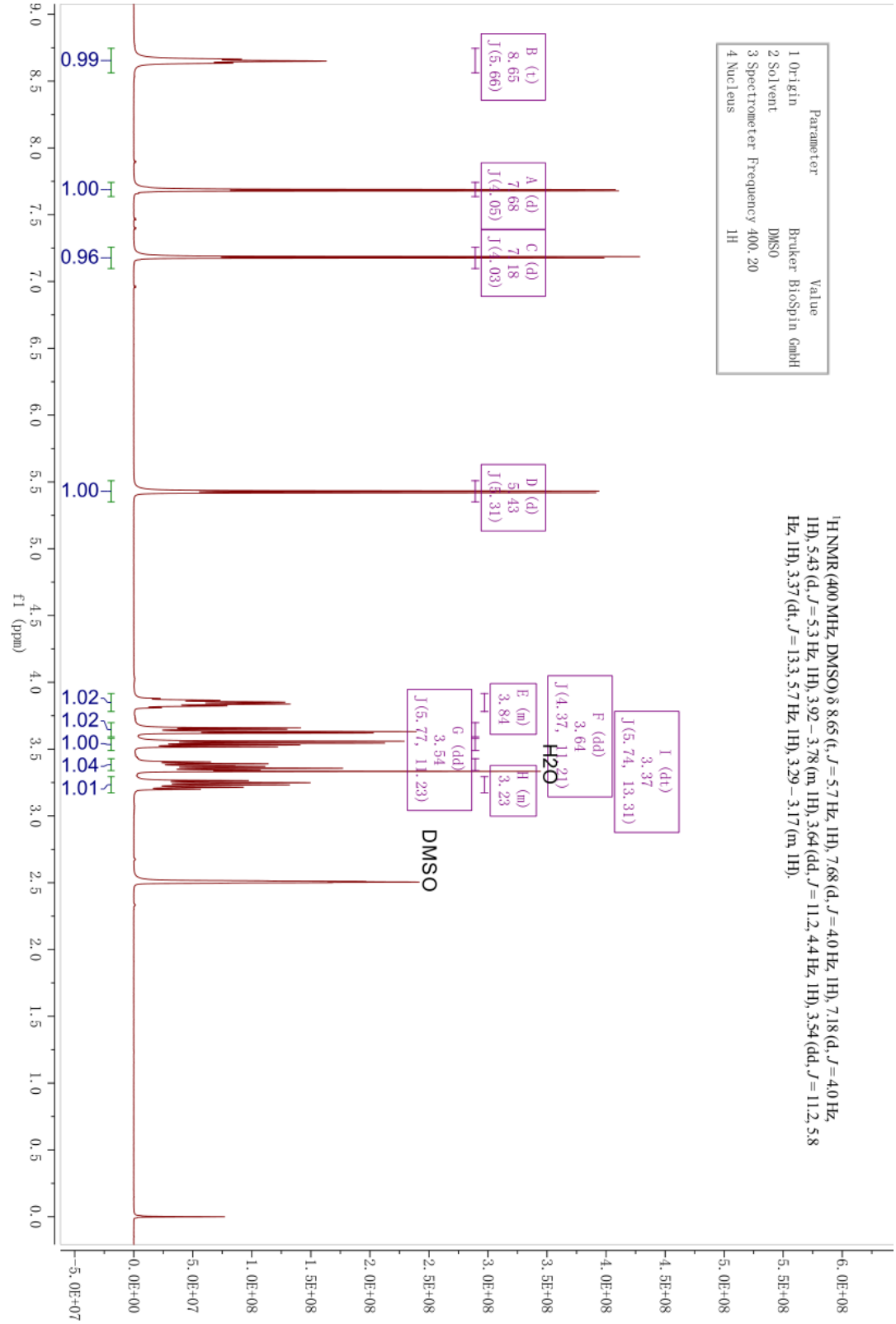
Contents

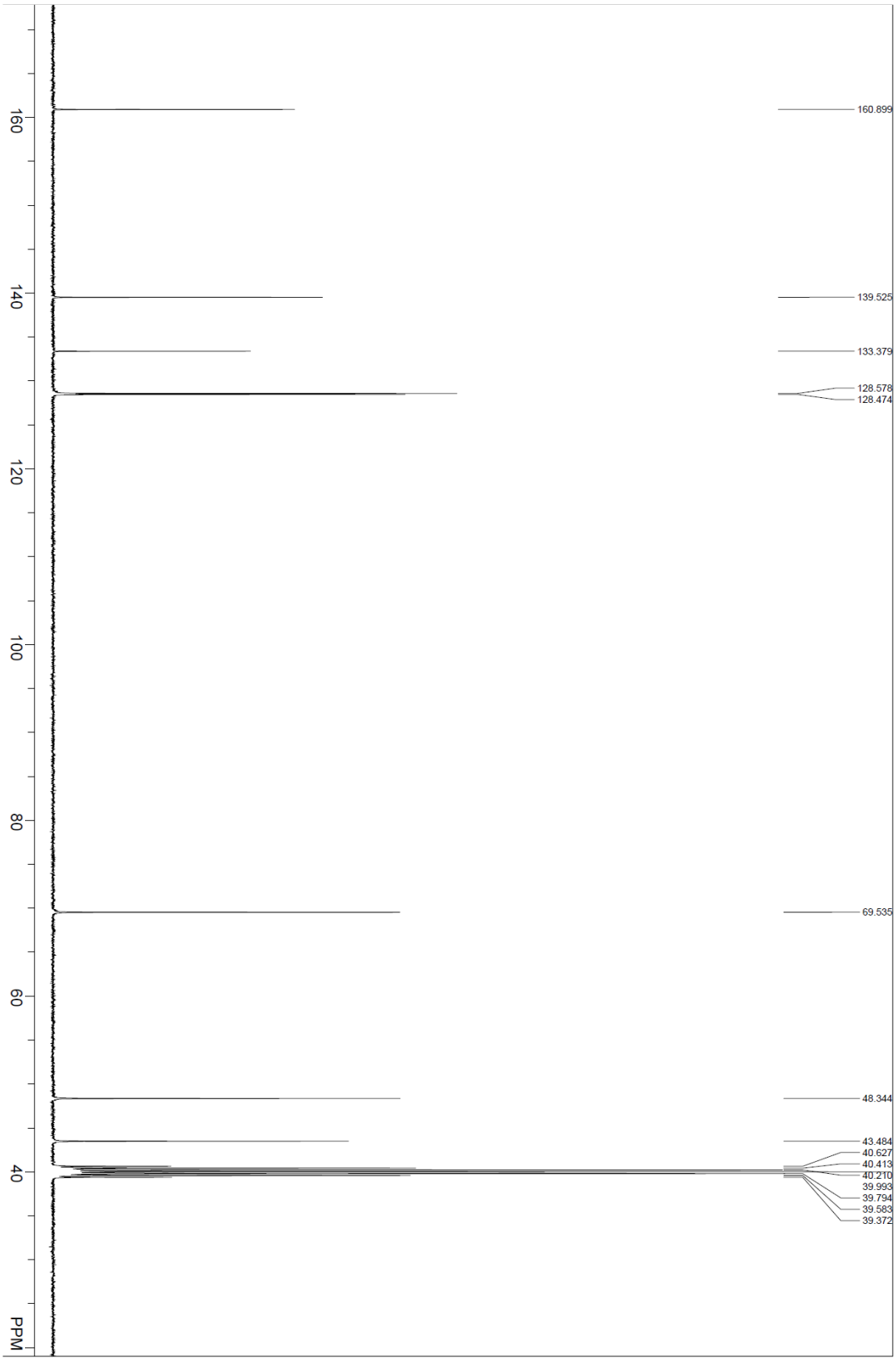
1. **Compound 15**

H NMR (*d*$_6$-DMSO, 400 M Hz)



^{1}H NMR (400 MHz, DMSO) δ 8.65 (t, *J* = 5.7 Hz, 1H), 7.68 (d, *J* = 4.0 Hz, 1H), 7.18 (d, *J* = 4.0 Hz, 1H), 5.43 (d, *J* = 5.3 Hz, 1H), 3.92 – 3.78 (m, 1H), 3.64 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.54 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.37 (dt, *J* = 13.3, 5.7 Hz, 1H), 3.29 – 3.17 (m, 1H).

^{13}C NMR (d_6-DMSO, 100 MHz)



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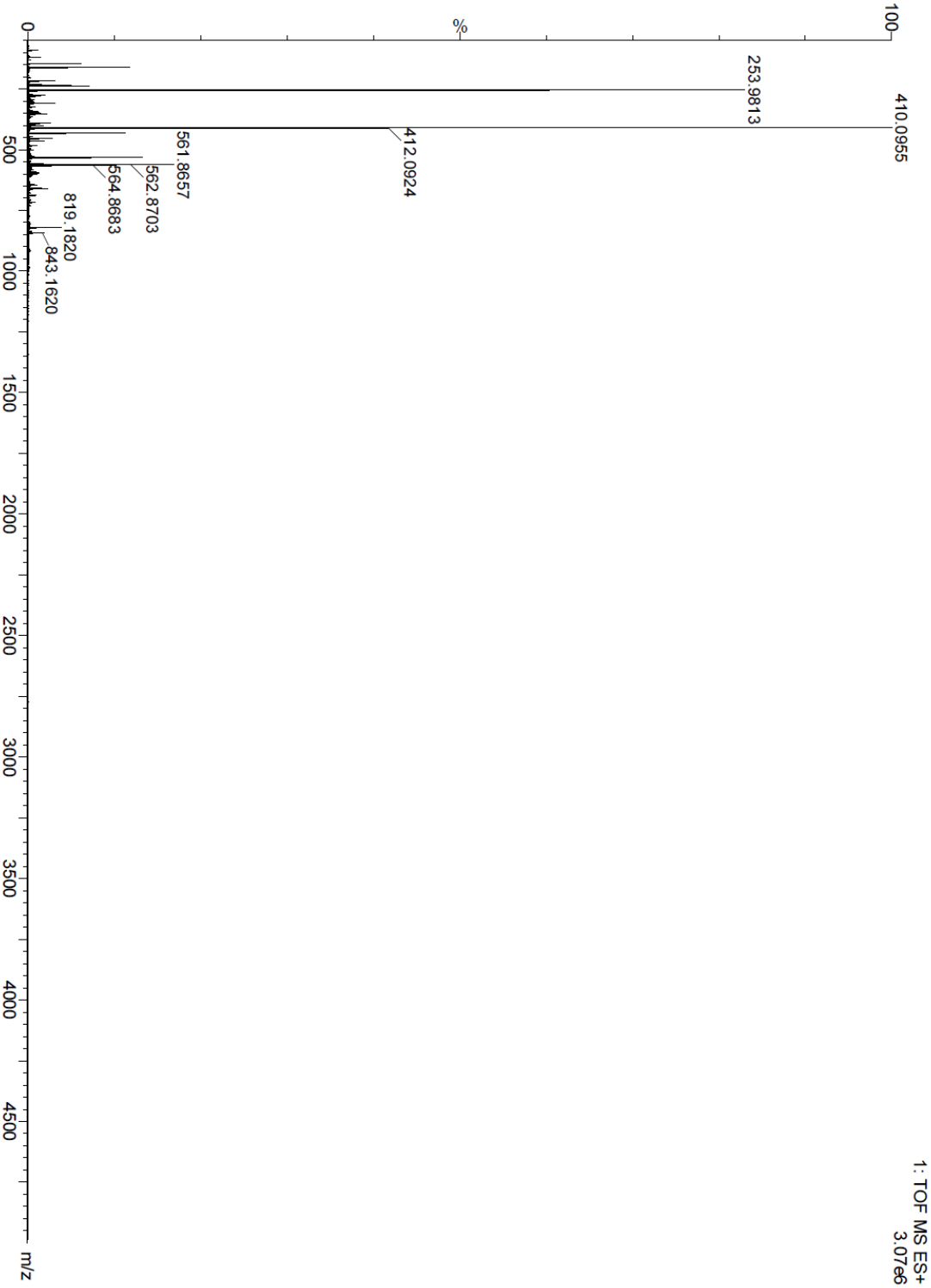
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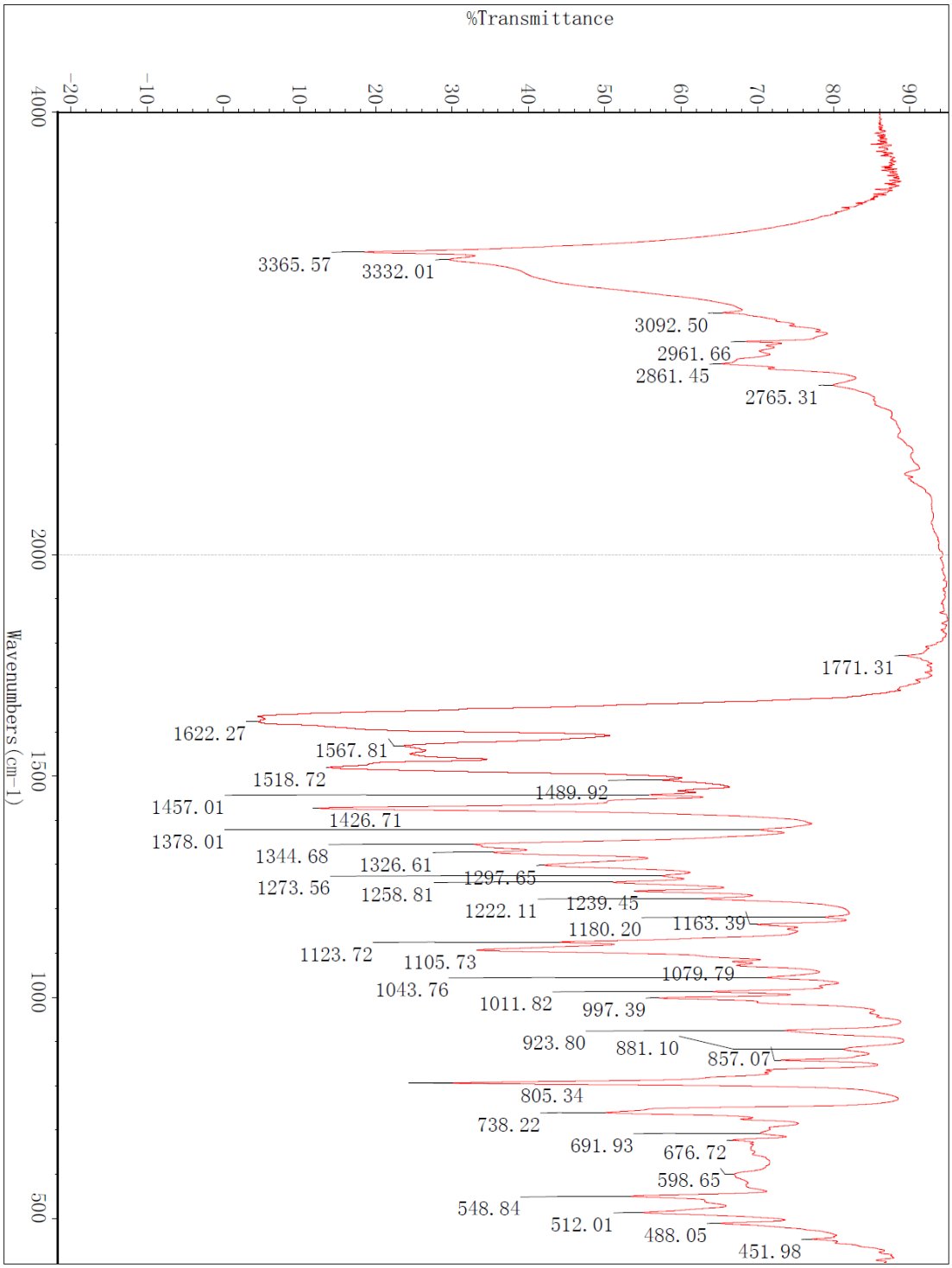
m/z
1: TOF MS ES+
3.07e6

IR: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Wavenumbers(cm-1)
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2861.45
2765.31
1771.31
1622.27
1567.81
1518.72
1489.92
1457.01
1426.71
1378.01
1344.68
1326.61
1297.65
1273.56
1258.81
1222.11
1239.45
1180.20
1163.39
1123.72
1105.73
1079.79
1043.76
1011.82
997.39
923.80
881.10
857.07
805.34
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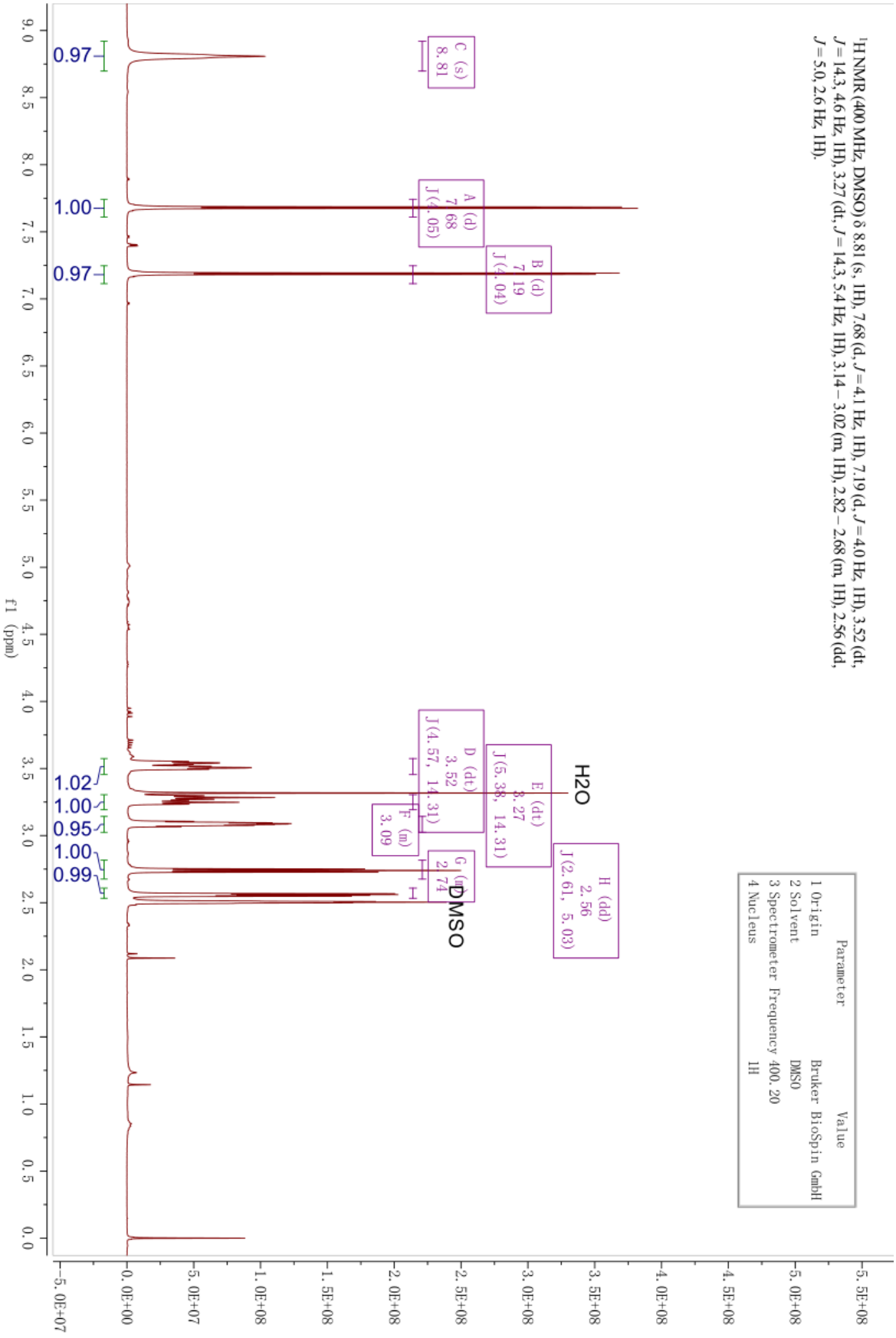
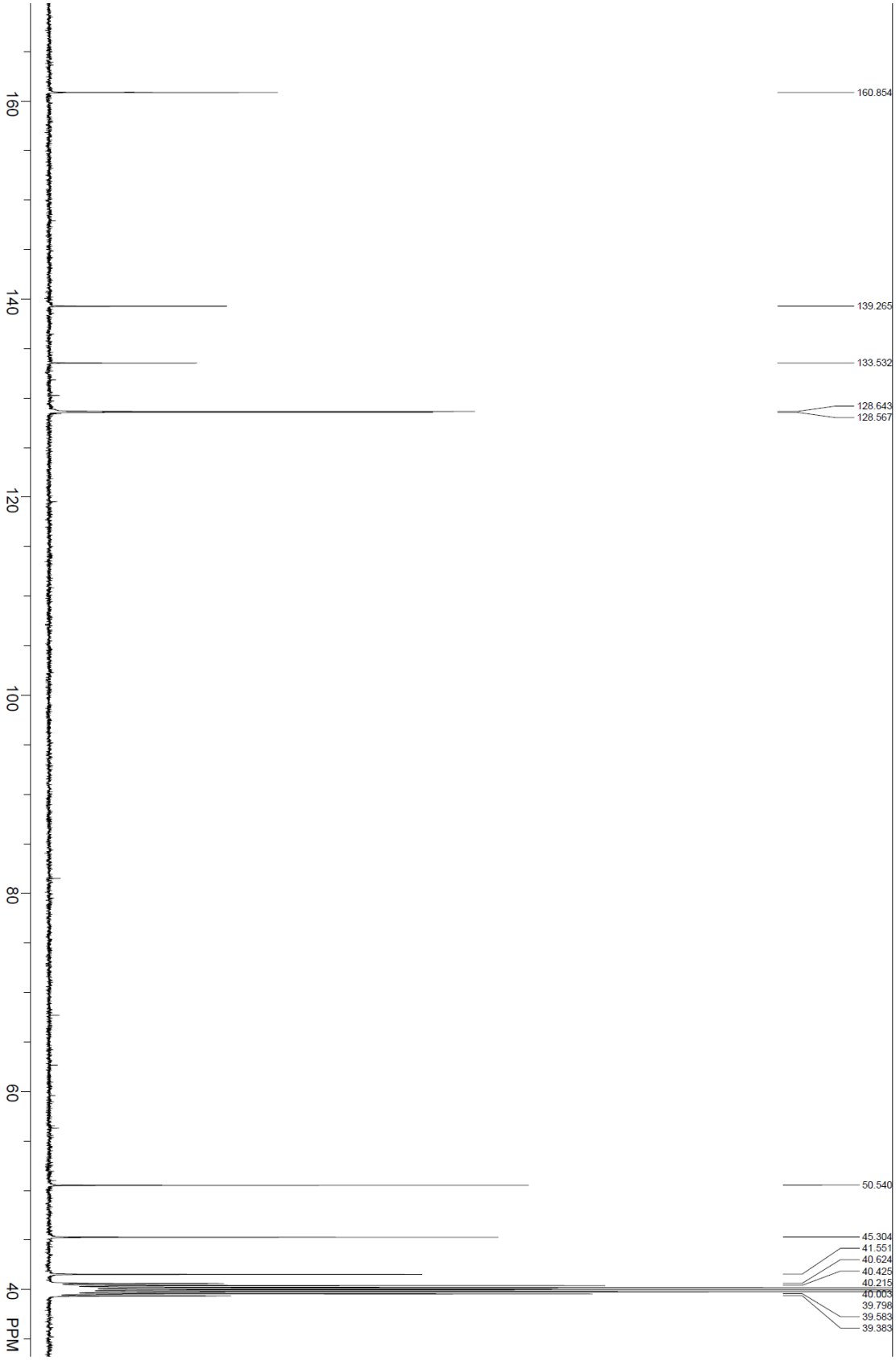
598.65
548.84
512.01
488.05
451.98

2. Compound 12

H NMR (d_6-DMSO, 400 MHz)



^{13}C NMR (d_6-DMSO, 100 MHz)



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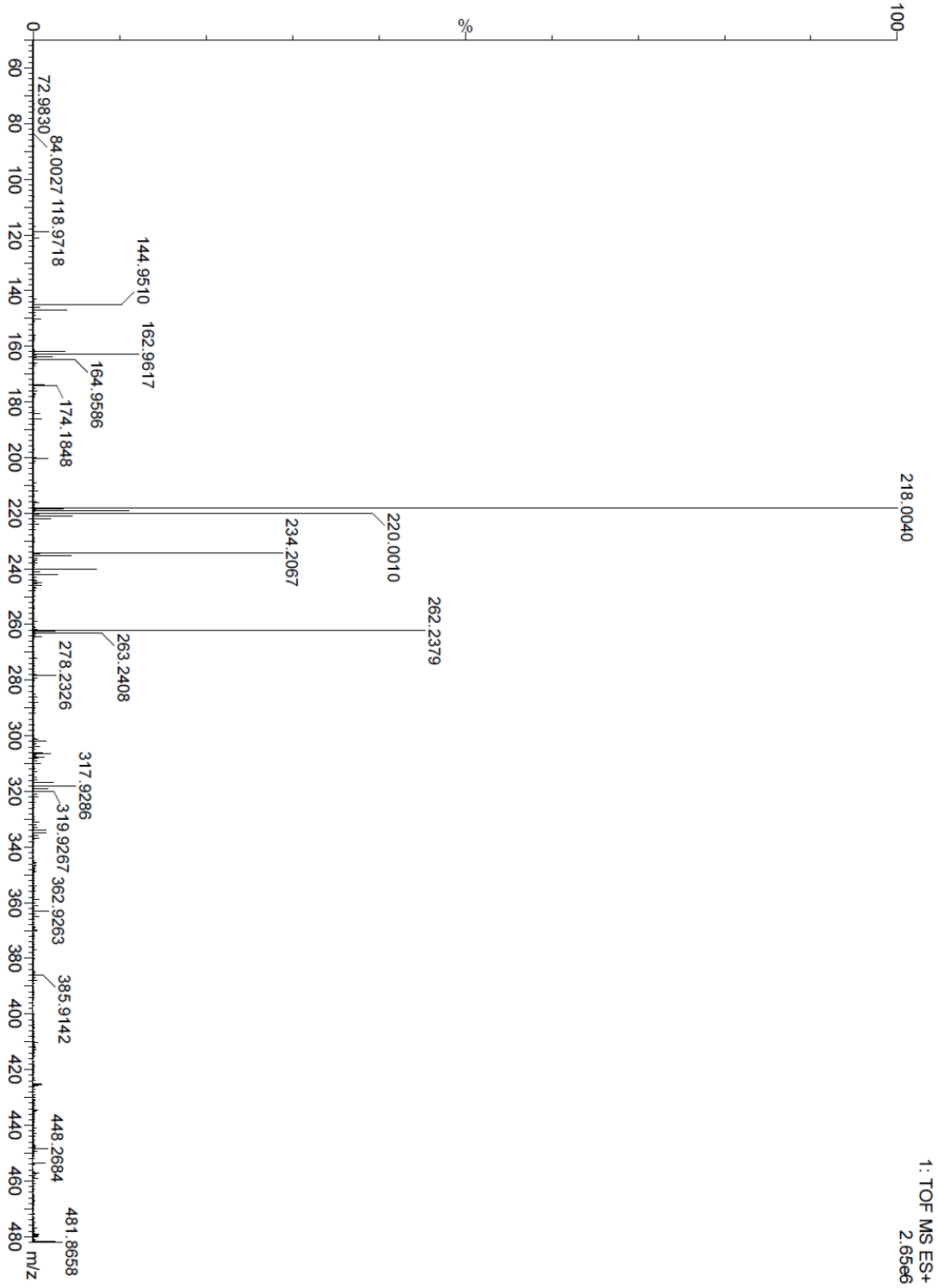
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440
460
480
m/z
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118.9718
144.9510
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164.9586
174.1848
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220.0010
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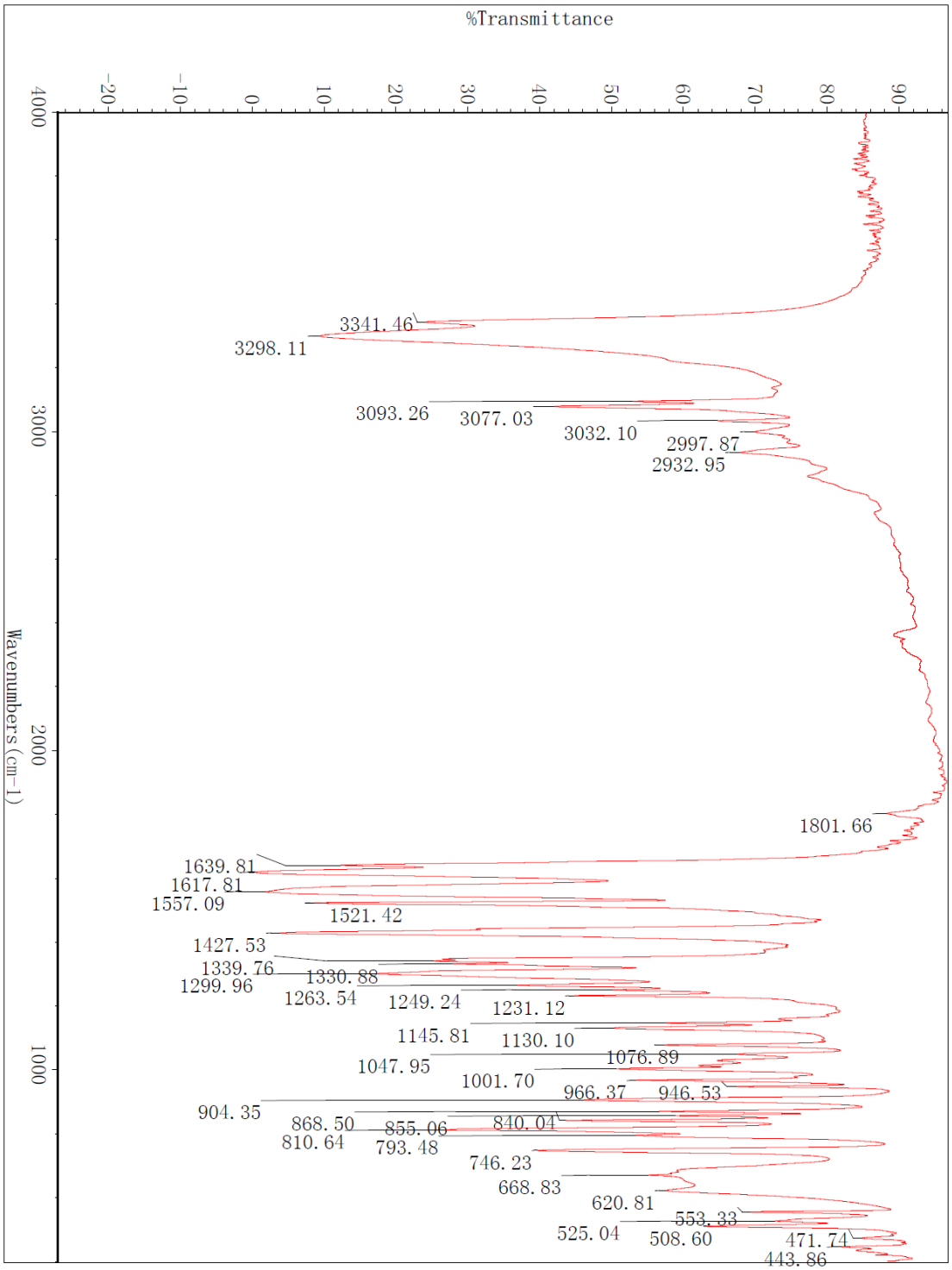
1: TOF MS ES+
2.65e6

IR: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1617.81
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1521.42
1427.53
1339.76
1330.88
1299.96
1263.54
1249.24
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1001.70
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946.53
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868.50
855.06
840.04
810.64
793.48
746.23
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553.33
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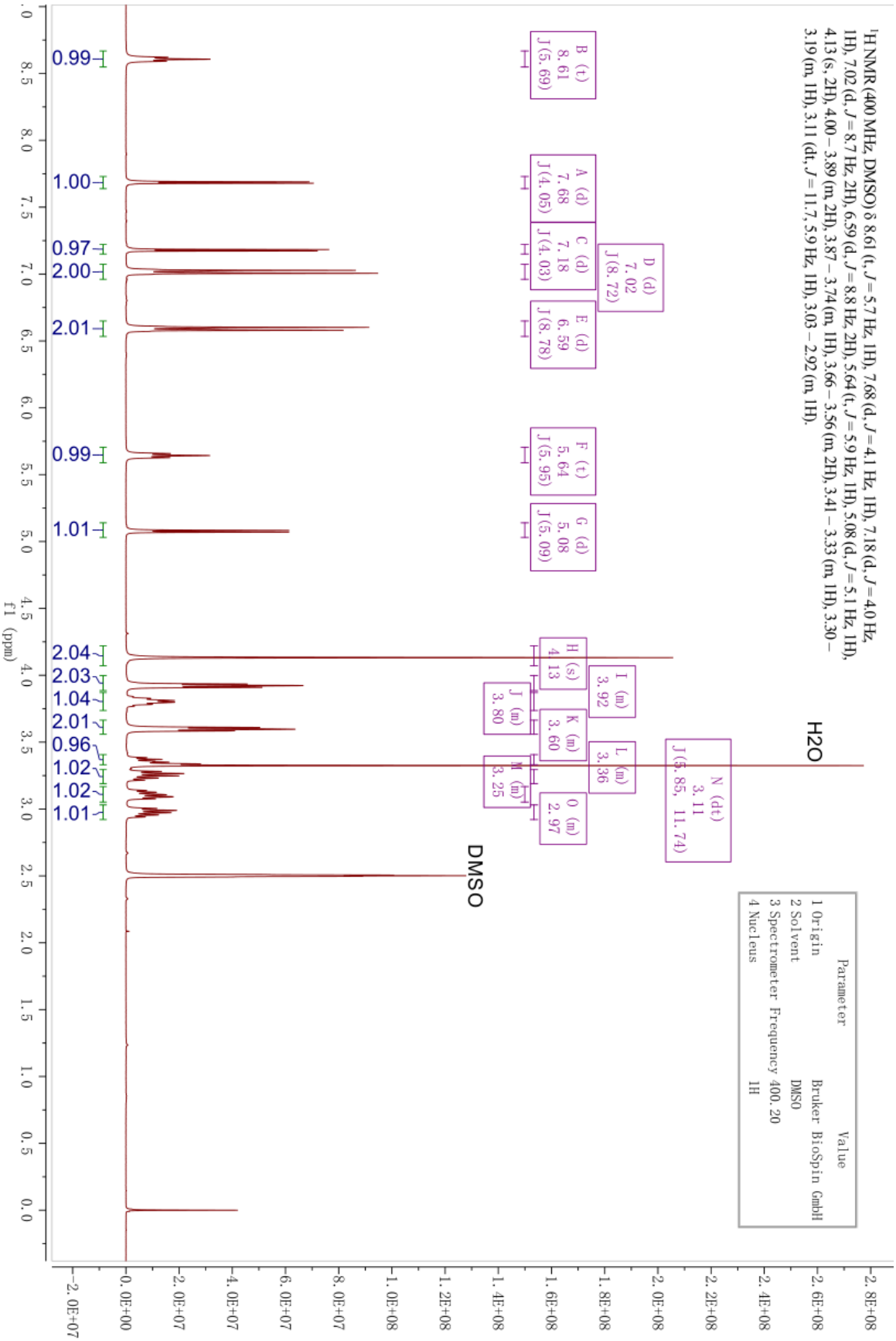
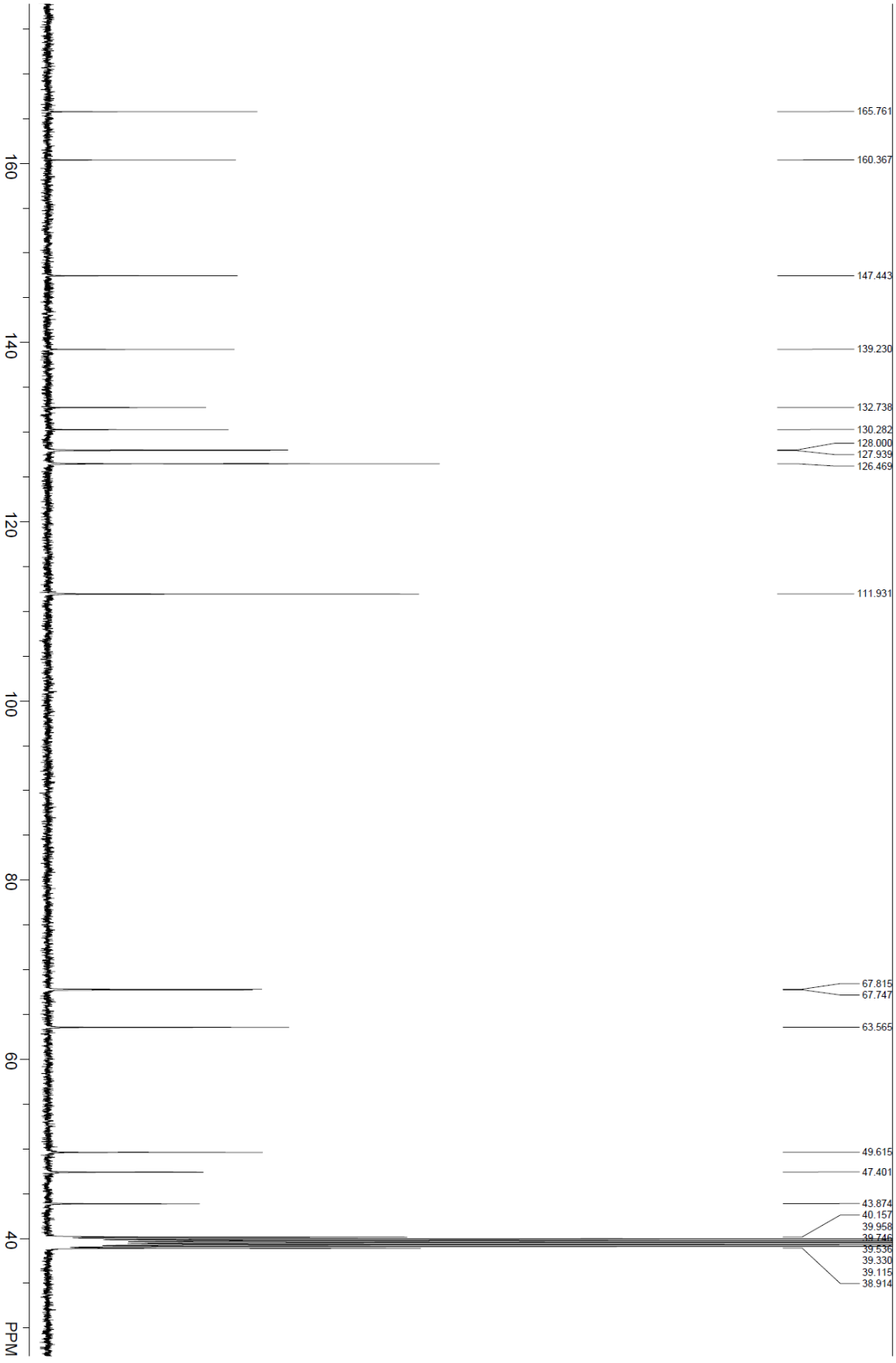
508.60
471.74
443.86

3. Compound 13

H NMR (d_6-DMSO, 400 MHz)



^{13}C NMR (d_6-DMSO, 100 MHz)



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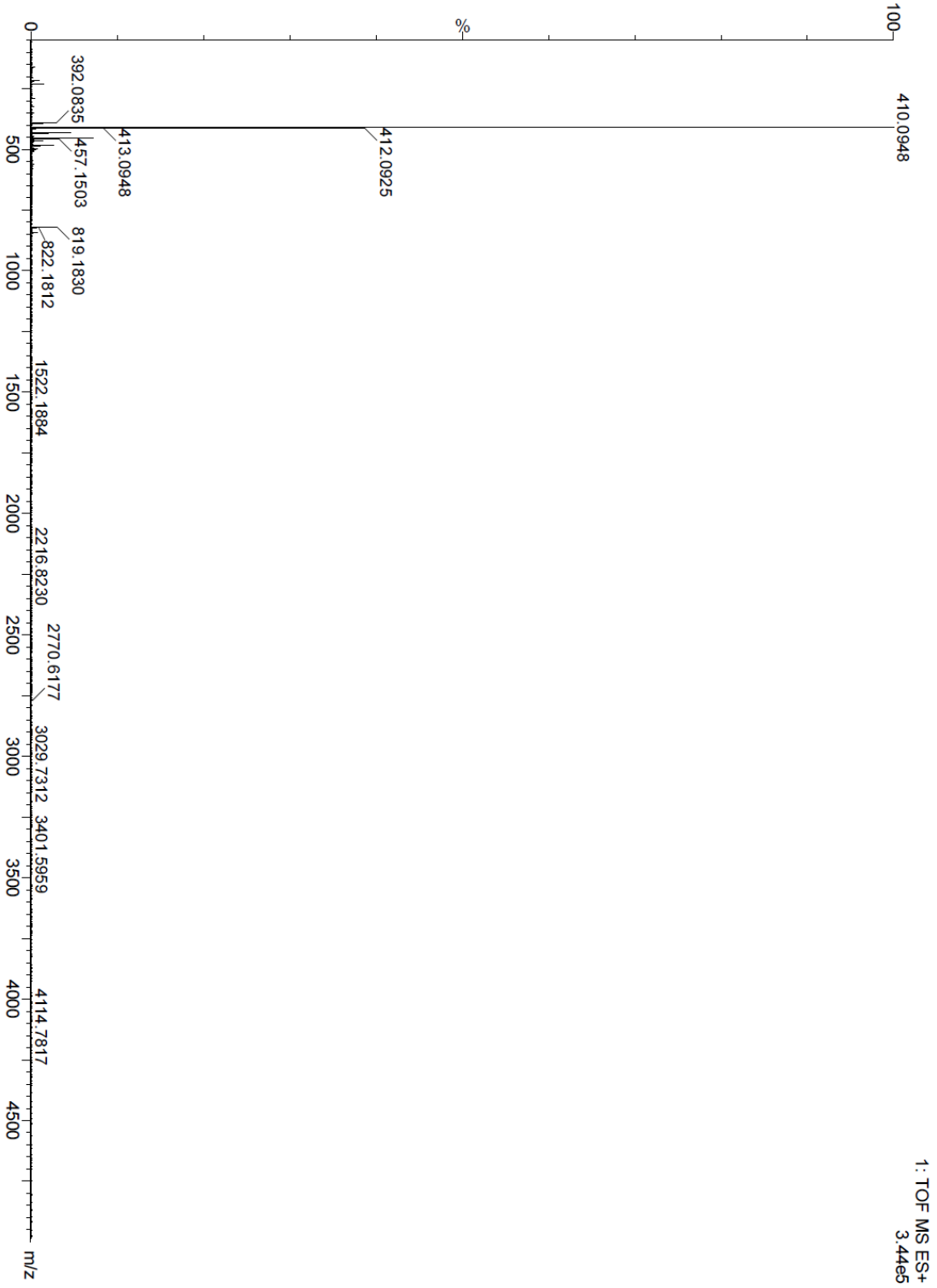
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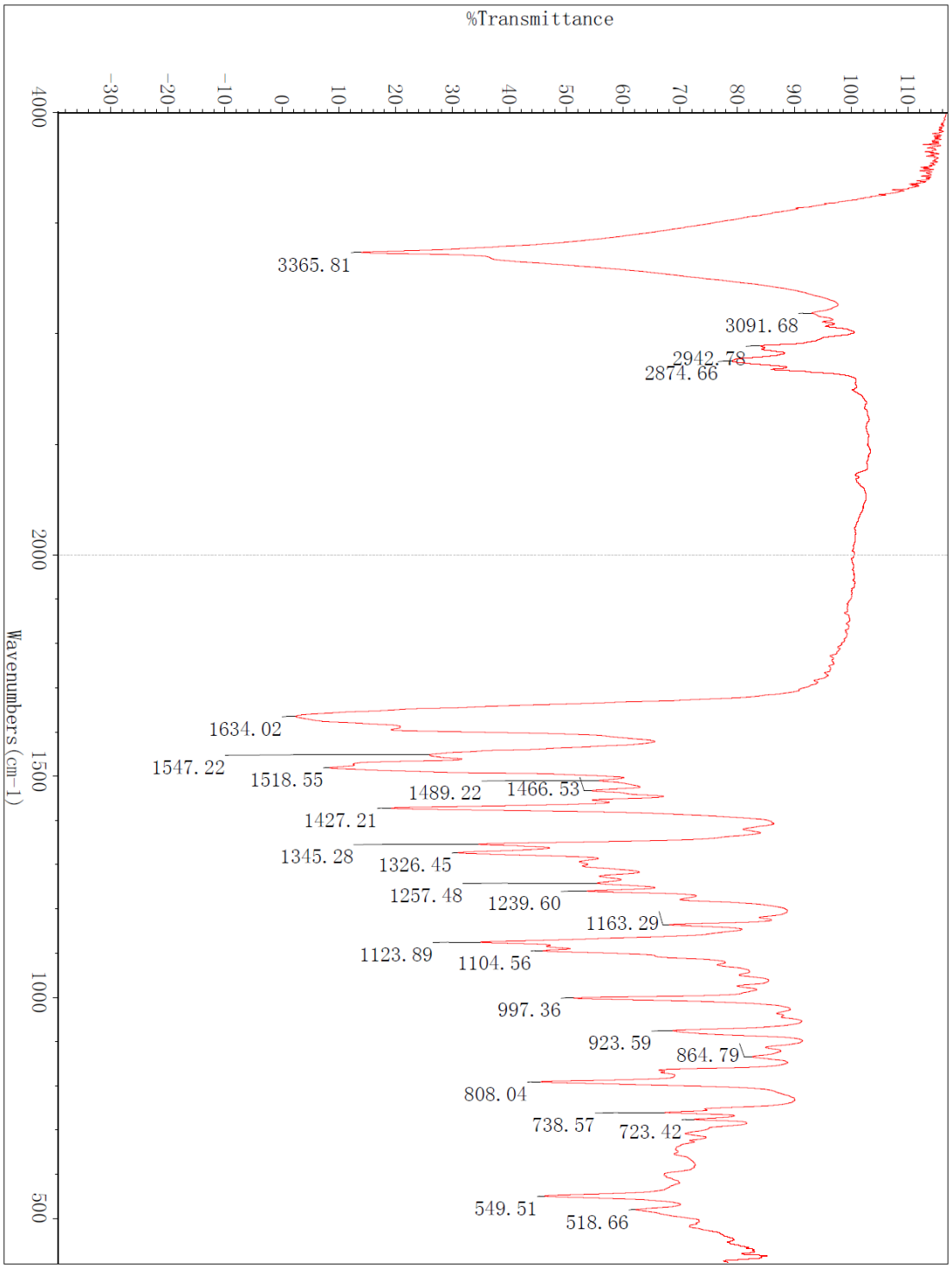
3.44e5

IR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1466.53
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1326.45
1257.48
1239.60
1163.29
1123.89
1104.56
997.36
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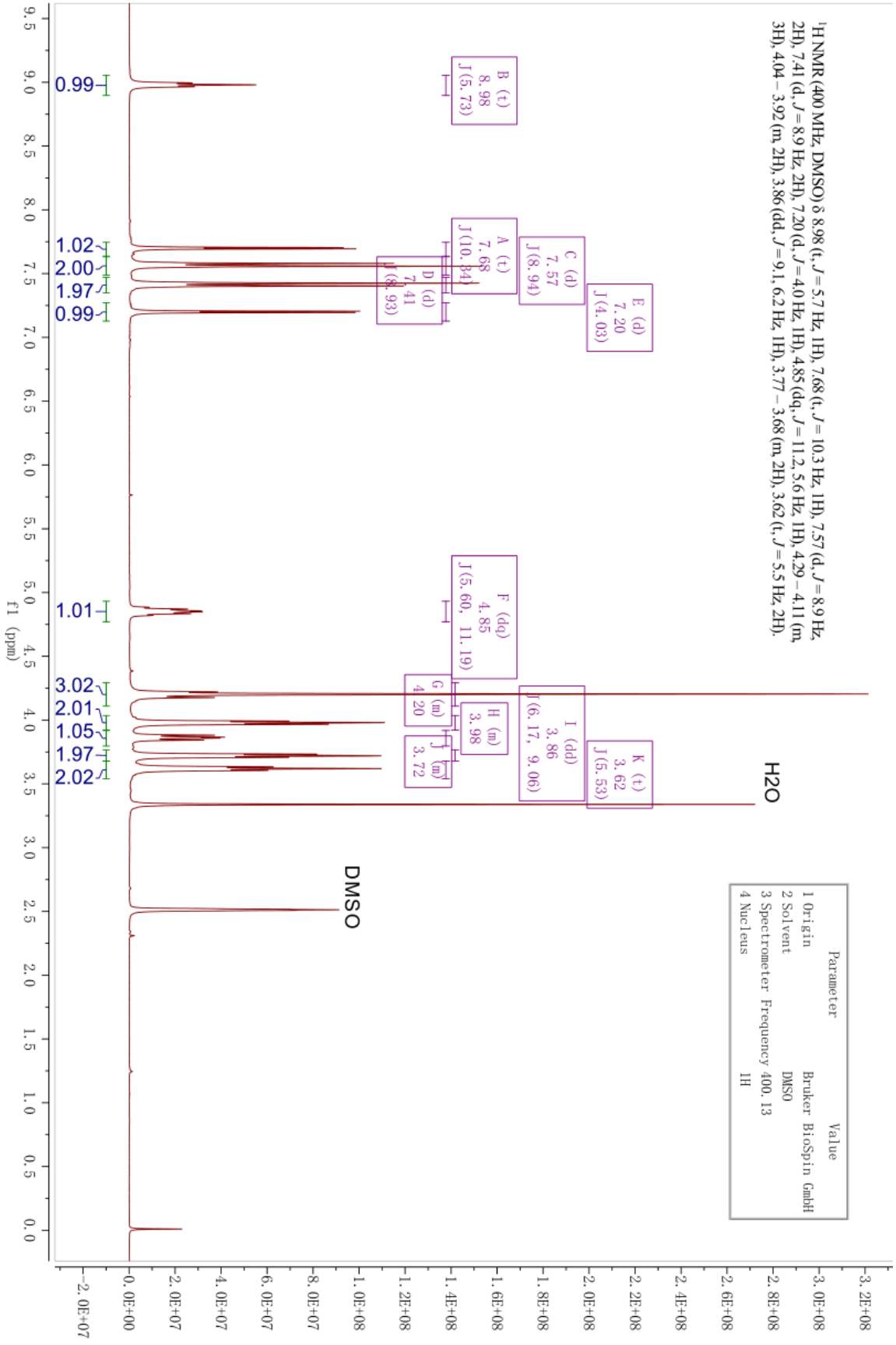
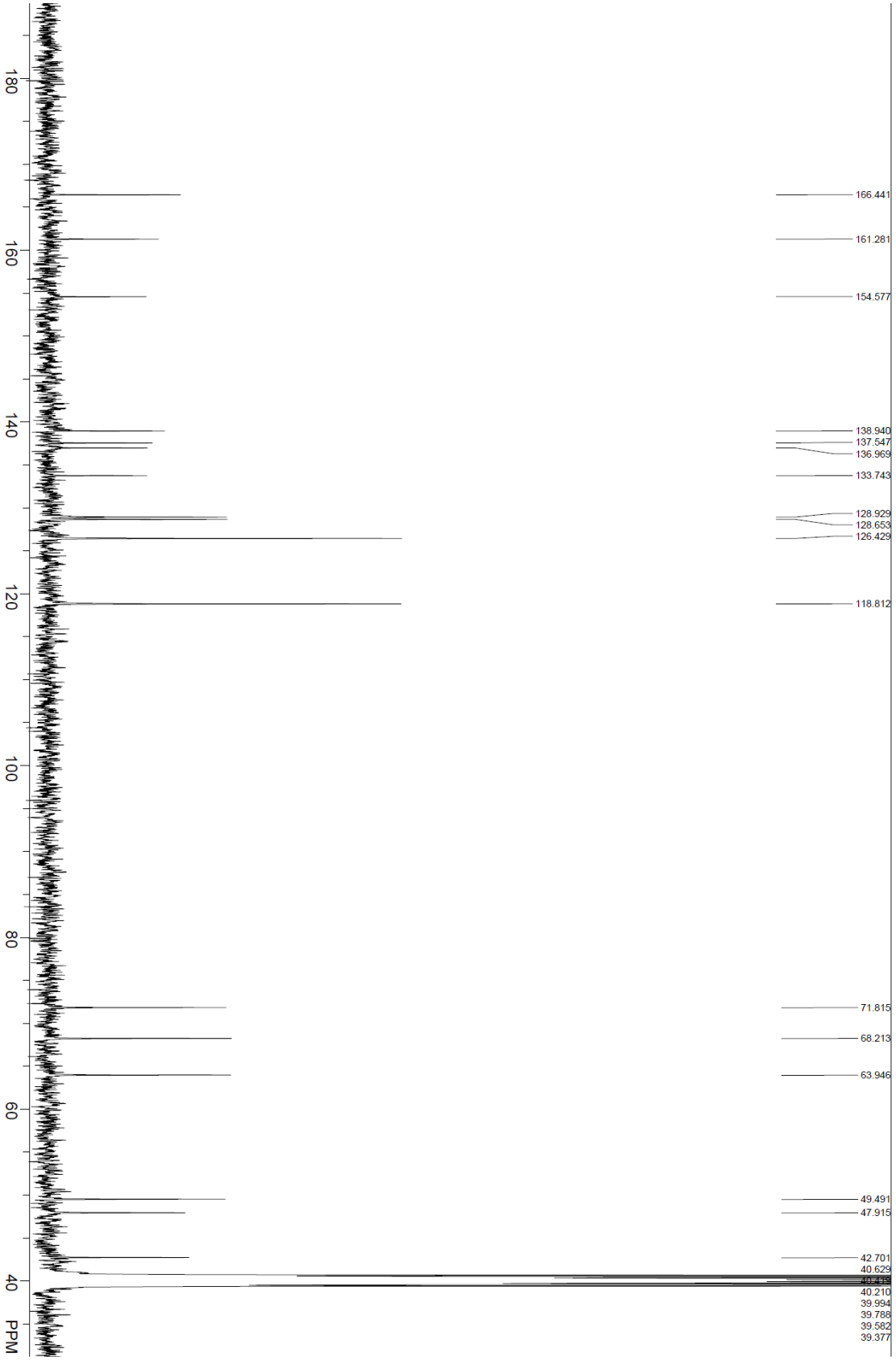
723.42
549.51
518.66

4. Rivaroxaban

H NMR (d_6-DMSO, 400 MHz)



^{13}C NMR (d_6-DMSO, 100 MHz)



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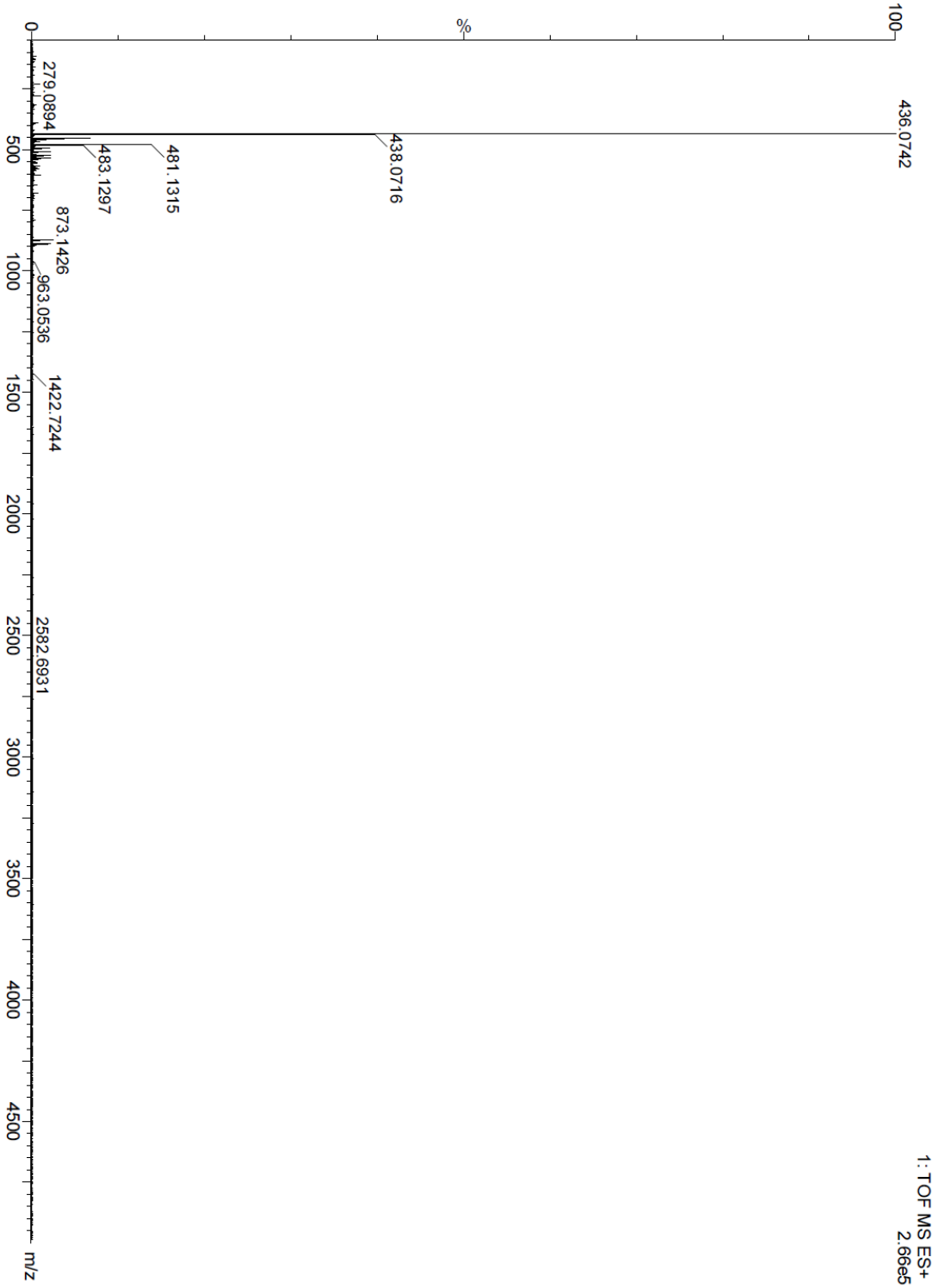
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1500
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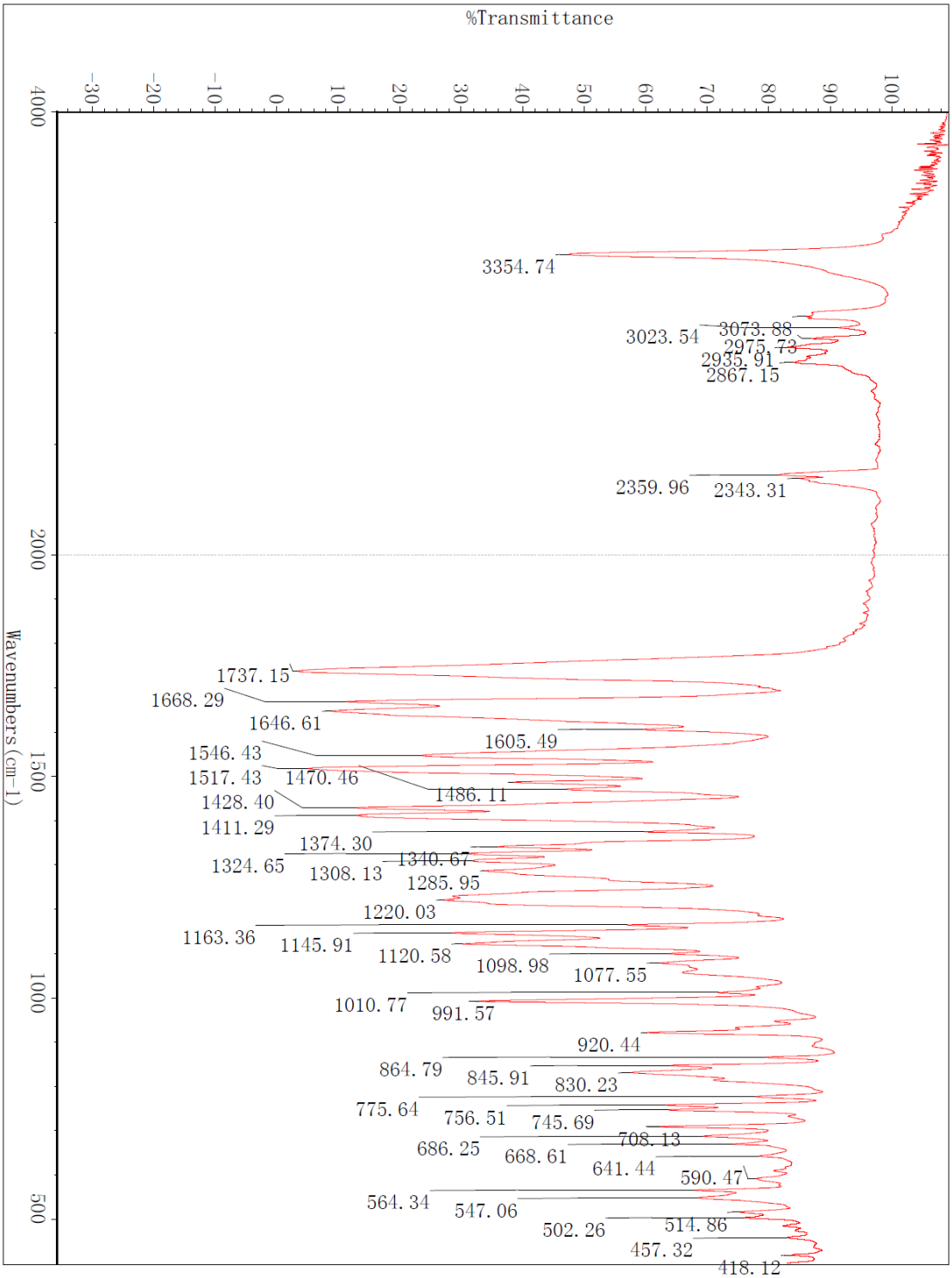
m/z
1: TOF MS ES+
2.66e5

IR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Wavenumbers (cm-1)
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1285.95
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1120.58
1098.98
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920.44
864.79
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775.64
756.51
745.69
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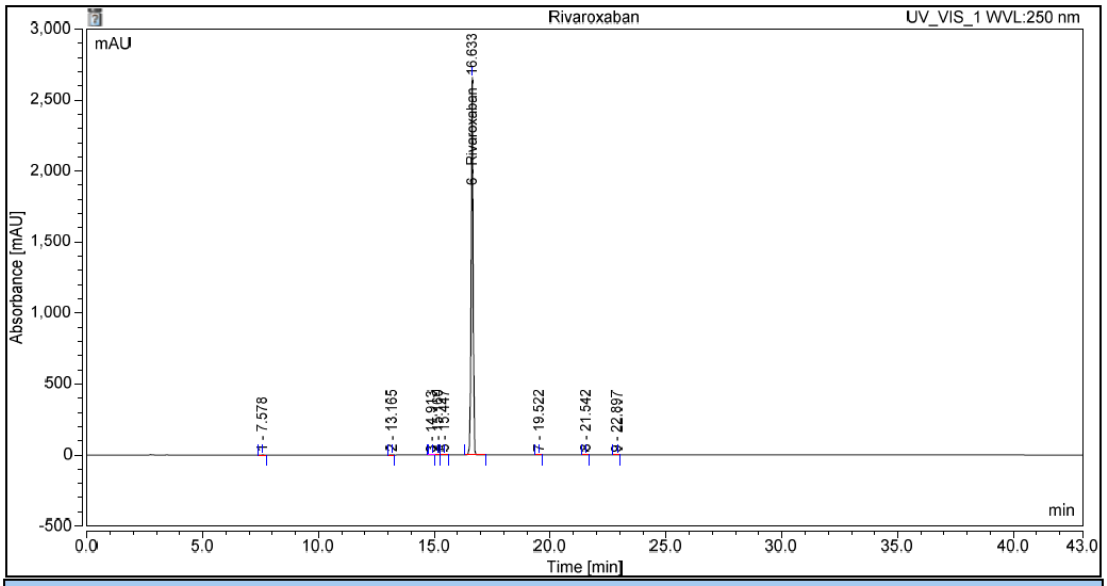
418.12

The HPLC Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*s	Height mAU	Relative Area %	Asymmetry (EP)	Resolution (EP)
1		7.578	3.93410	0.479	0.0267	0.98	32.26
2		13.165	5.22299	1.028	0.0355	0.93	15.15
3		14.913	1.75555	0.313	0.0119	n.a.	n.a.
4		15.160	2.34239	0.418	0.0159	0.83	1.87
5		15.447	12.07348	1.837	0.0820	0.94	7.52
6	Rivaroxaban	16.633	14687.54141	2660.119	99.7405	0.90	19.71
7		19.522	5.74767	0.959	0.0390	0.97	12.58
8		21.542	5.42145	0.799	0.0368	0.87	6.45
9		22.897	1.71674	0.189	0.0117	0.79	n.a.

HPLC method:

HPLC¨ ThermoFisher U3000

Column¨ Phenomenex Gemini C18 4.6 ×250 mm, 5 μm

Mobile phase A: 0.02 mol/L Potassium dihydrogen phosphate(pH 4.0) (weigh 2.72g of Potassium dihydrogen phosphate, dissolve in 950 mL of water, adjust the pH to 4.0 with phosphoric acid, dilute to 1000 mL with water, filter with 0.45 μm membrane, and degas to get mobile phase A).

Mobile Phase B: Acetonitrile

Time	A%	B%
0	80	20
3	80	20
25	30	70
35	30	70
35.1	80	20
43	80	20
Flow rate:	1.0 mL/min.	
Detection wavelength:	250 nm	
Column T:	30℃	
Injection:	5 μL	
Diluent	Water: Acetonitrile = 50:50 (V/V)	

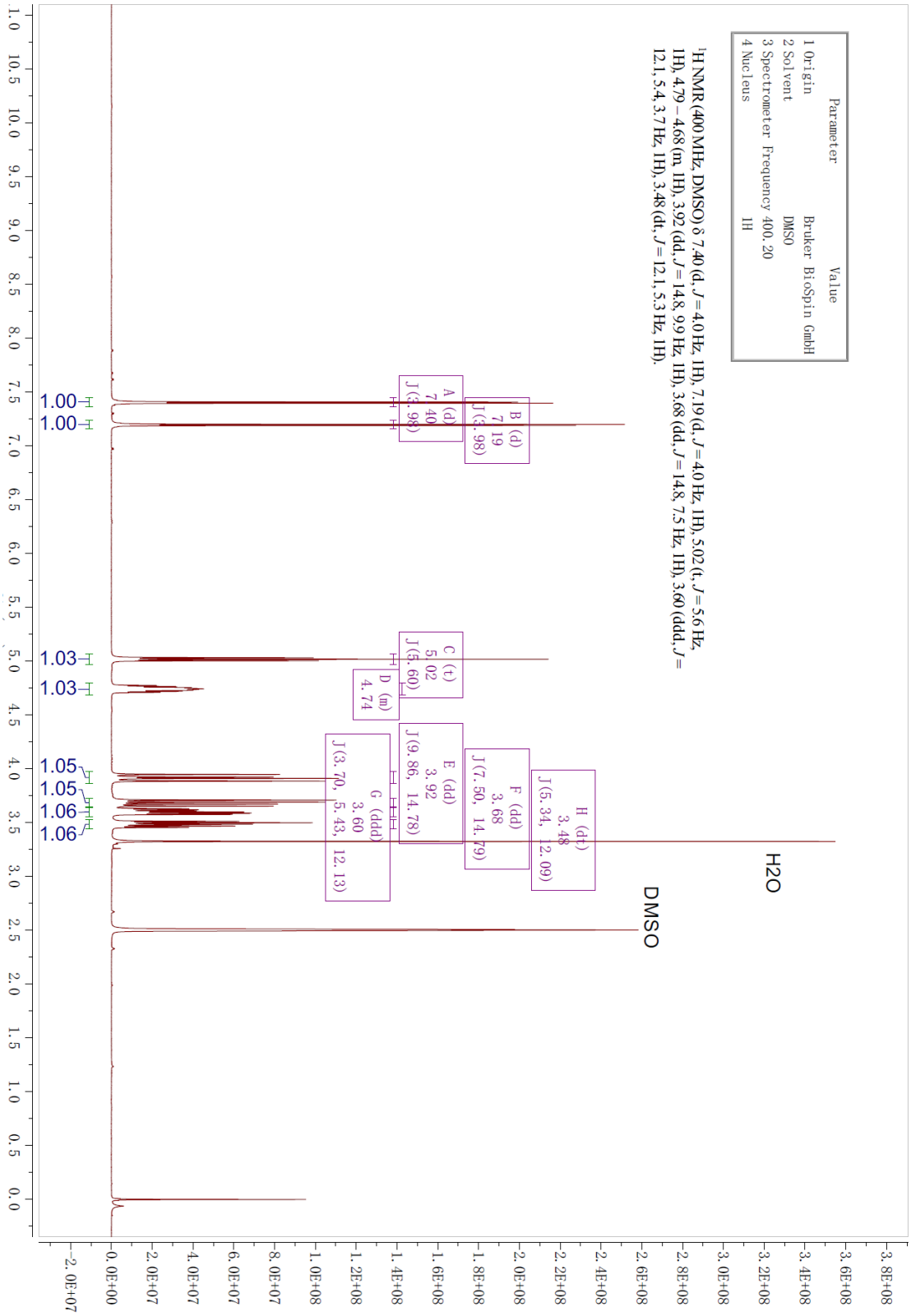
Blank: diluent

Sample solution¨

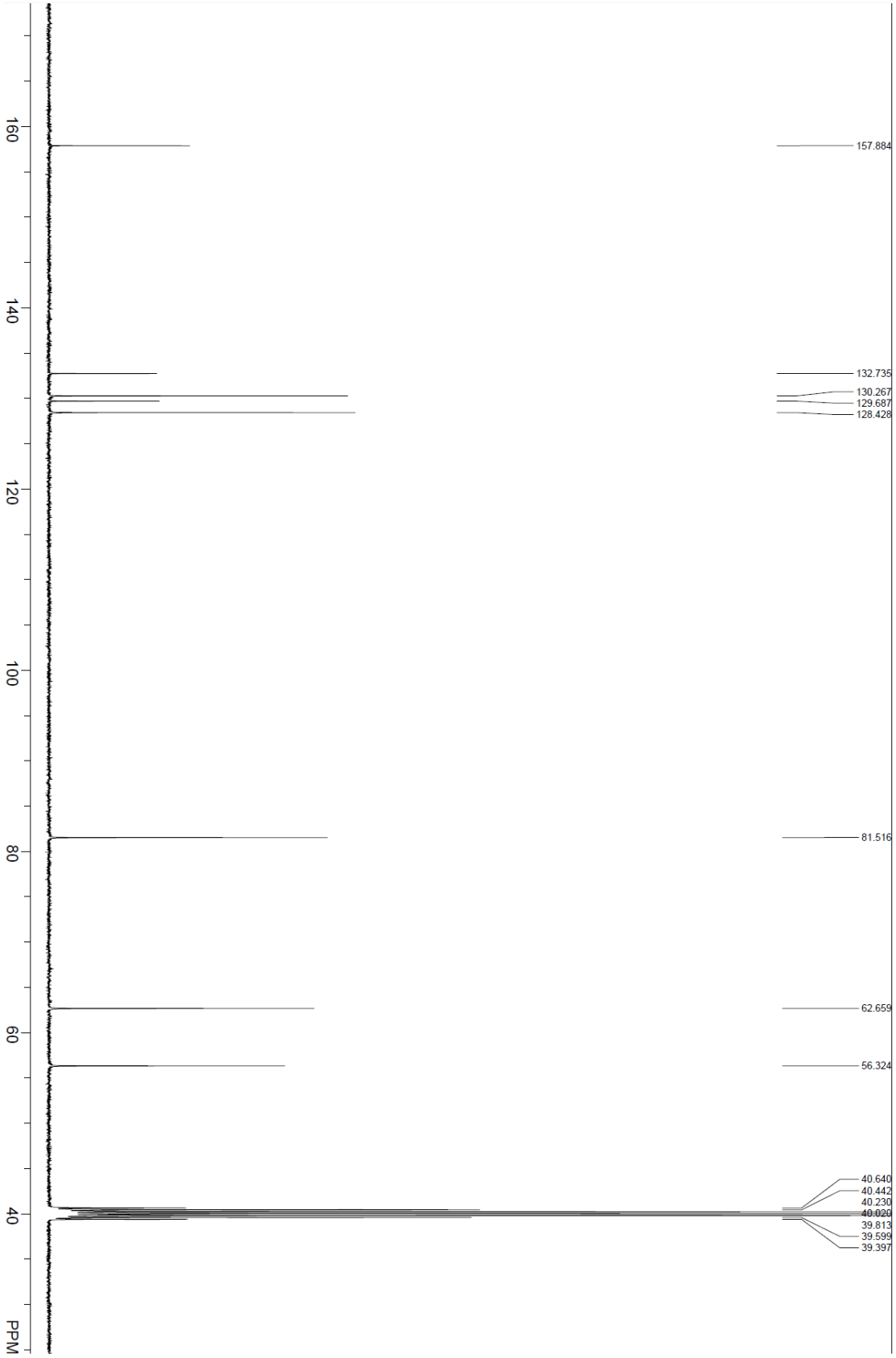
Add DMSO of the same volume into the reaction solution(about 0.1g/mL Rivaroxaban), shake evenly, then take 0.2ml, put it into a 10mL volumetric flask, add diluent to dissolve, dilute to the volume, and mix well(about 1mg/mL Rivaroxaban).

5. Compound 16

H NMR (d_6-DMSO, 400 MHz)



^{13}C NMR (d_6-DMSO, 100 MHz)



ESI-HRMS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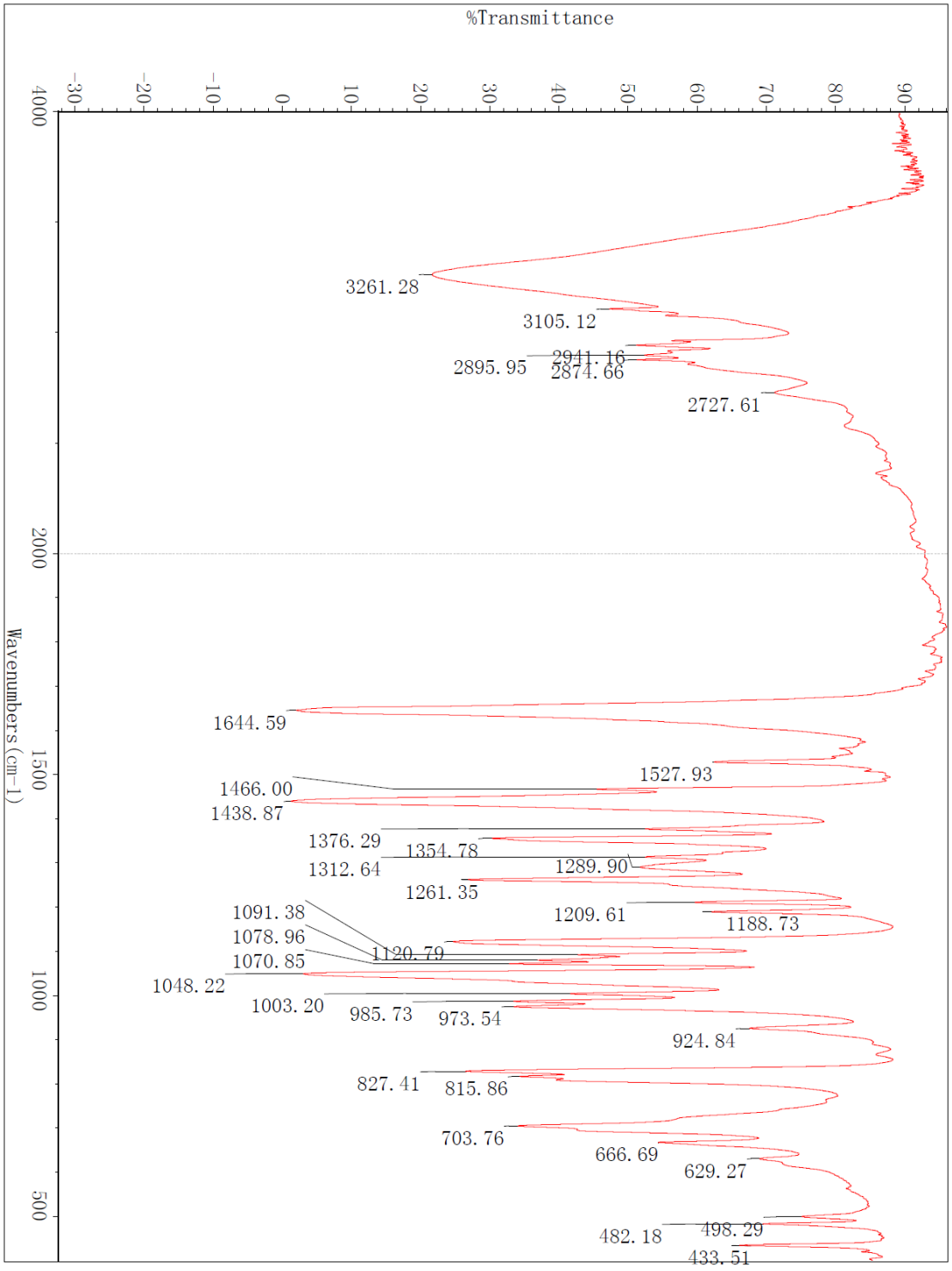
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Wavenumbers (cm-1)
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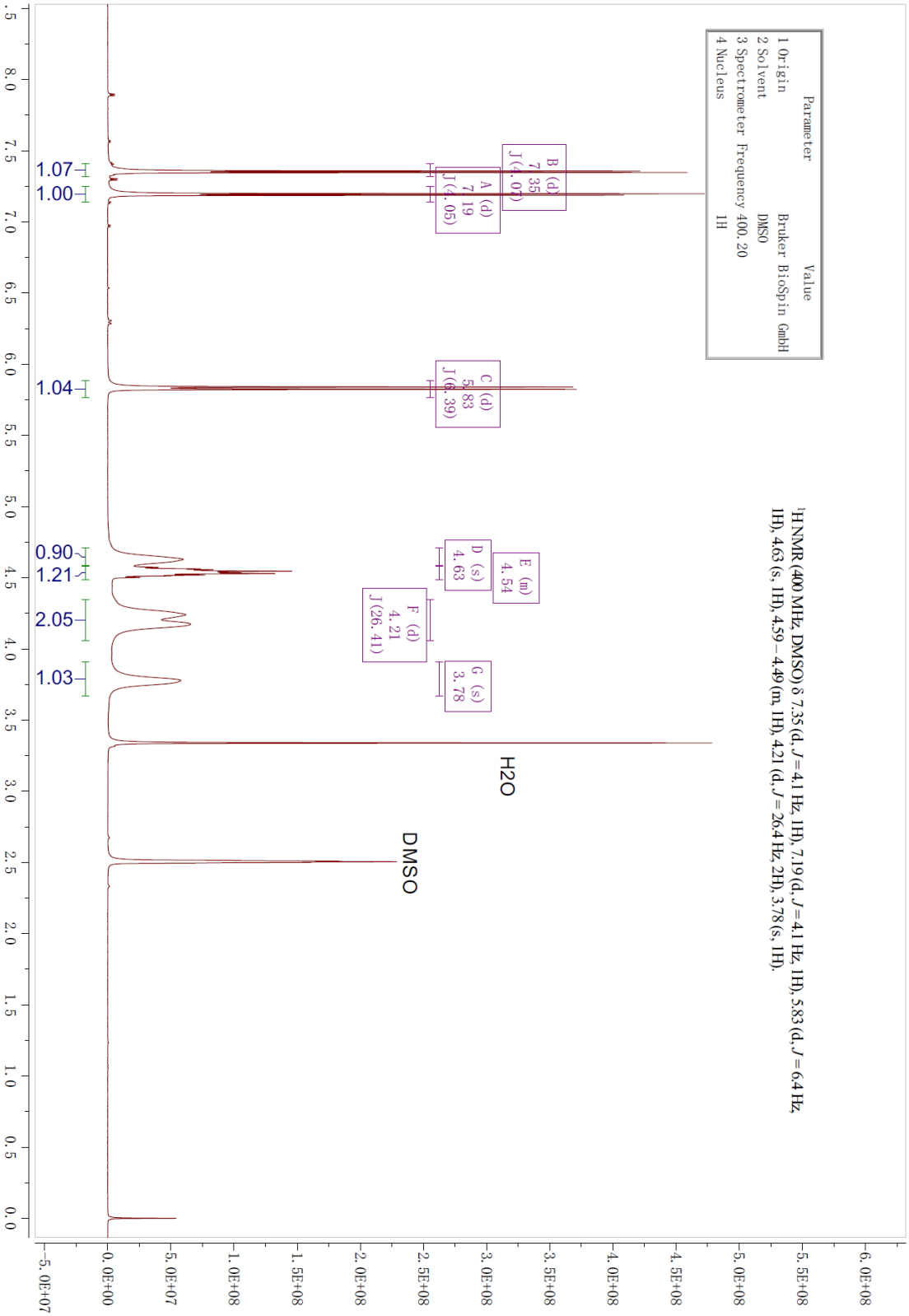
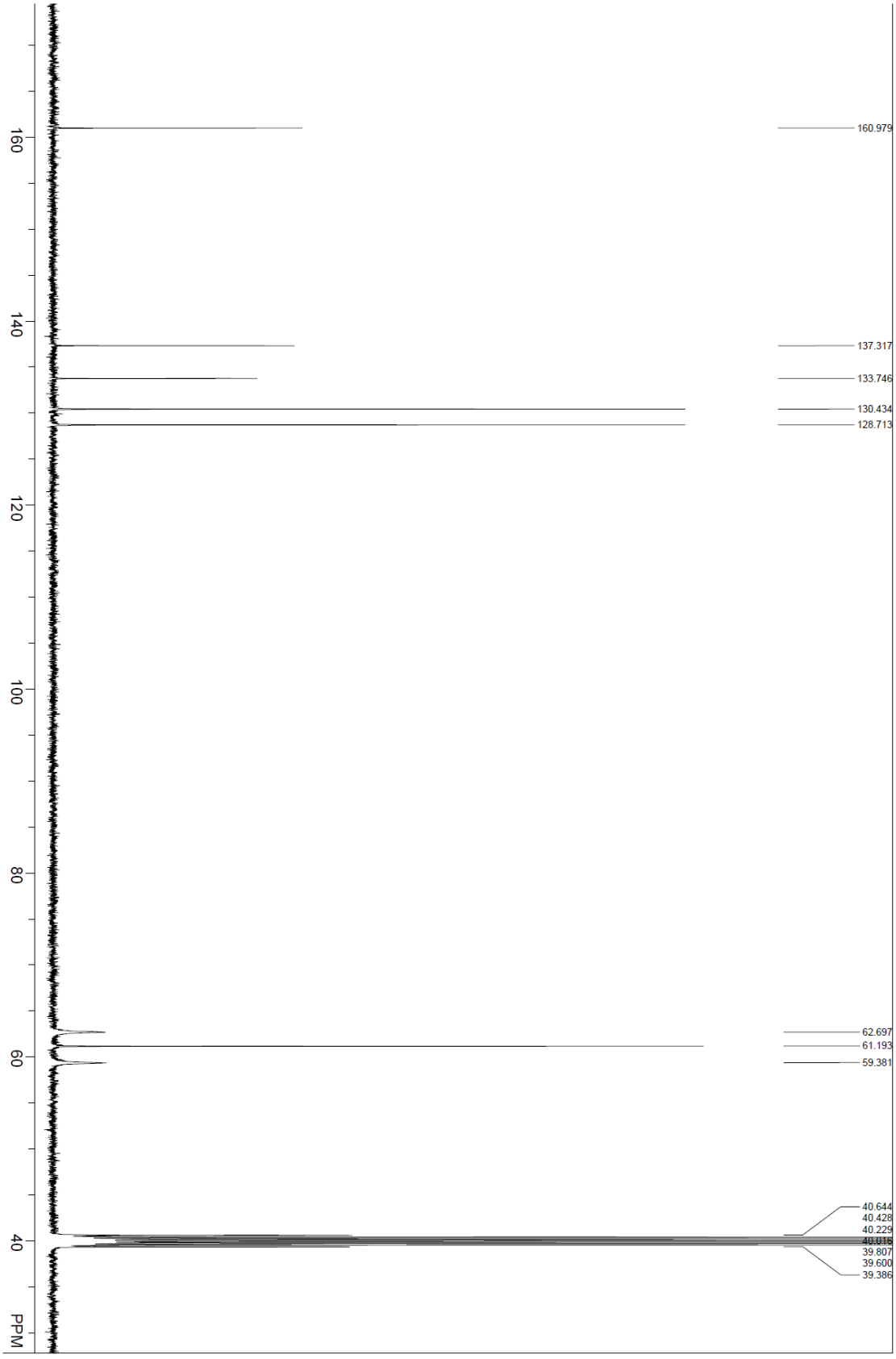
6. Compound 17

H NMR (d_6-DMSO, 400 MHz)



^{13}C NMR (d_6-DMSO, 100 MHz)



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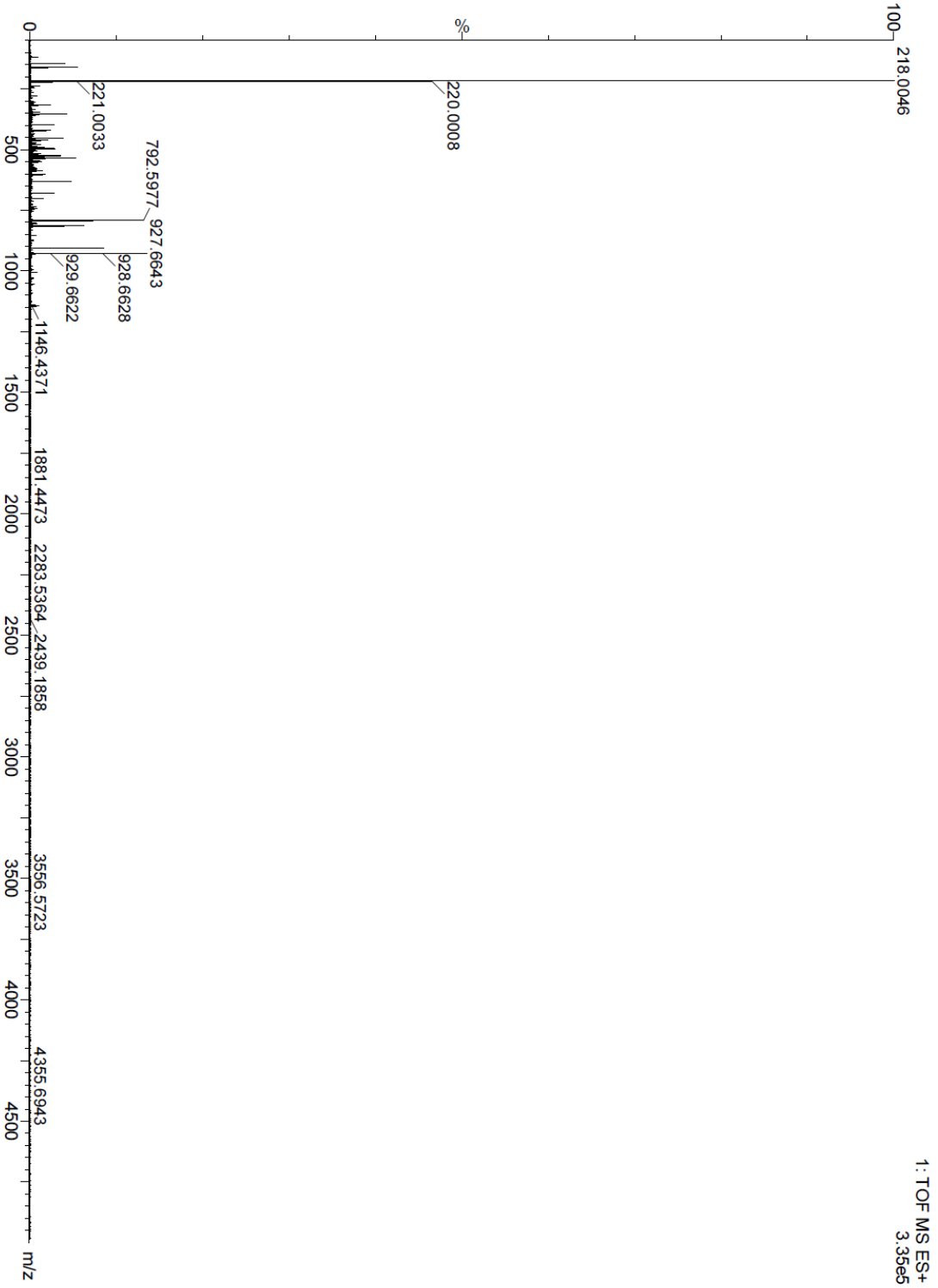
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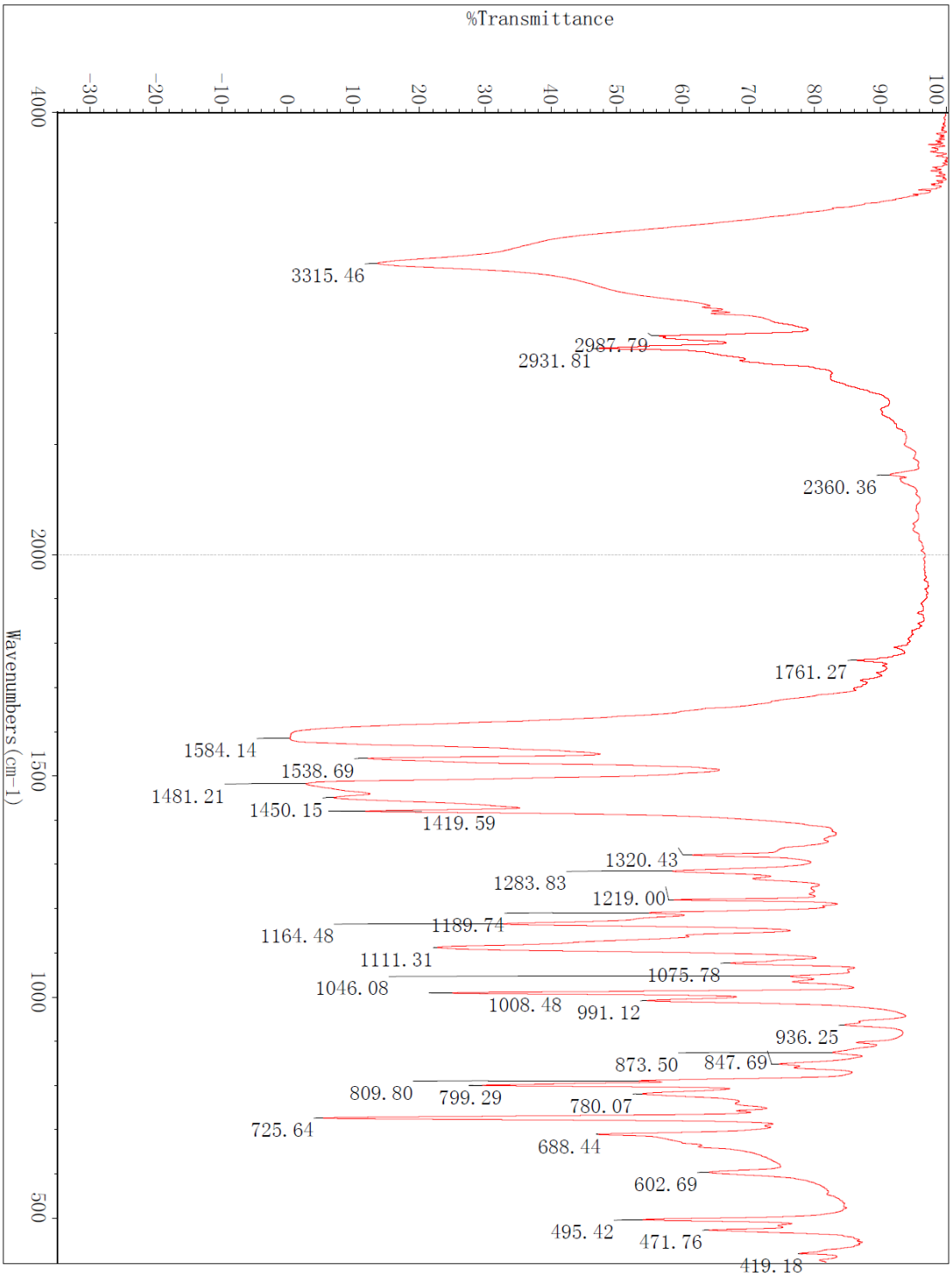
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Wavenumbers (cm-1)
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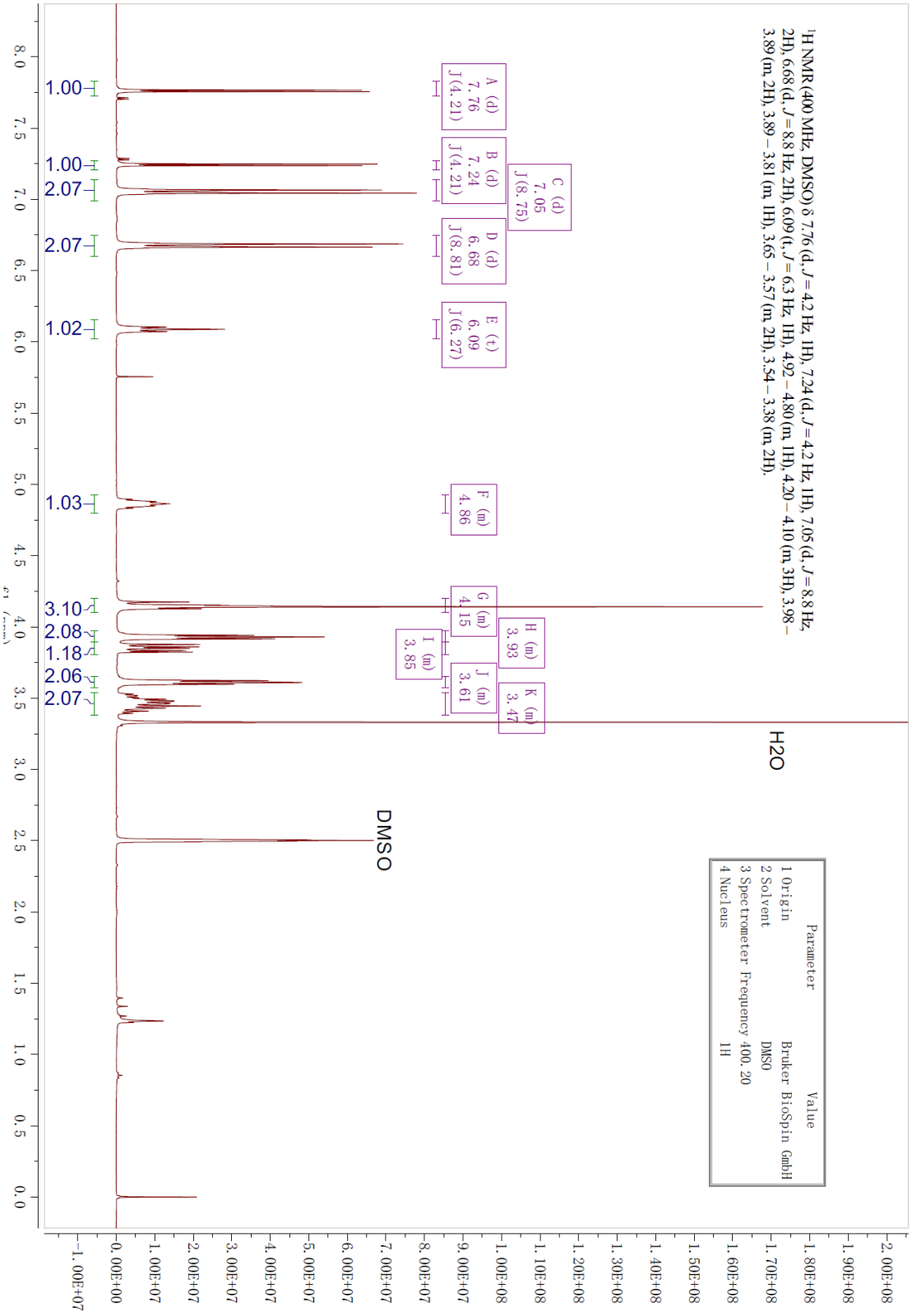
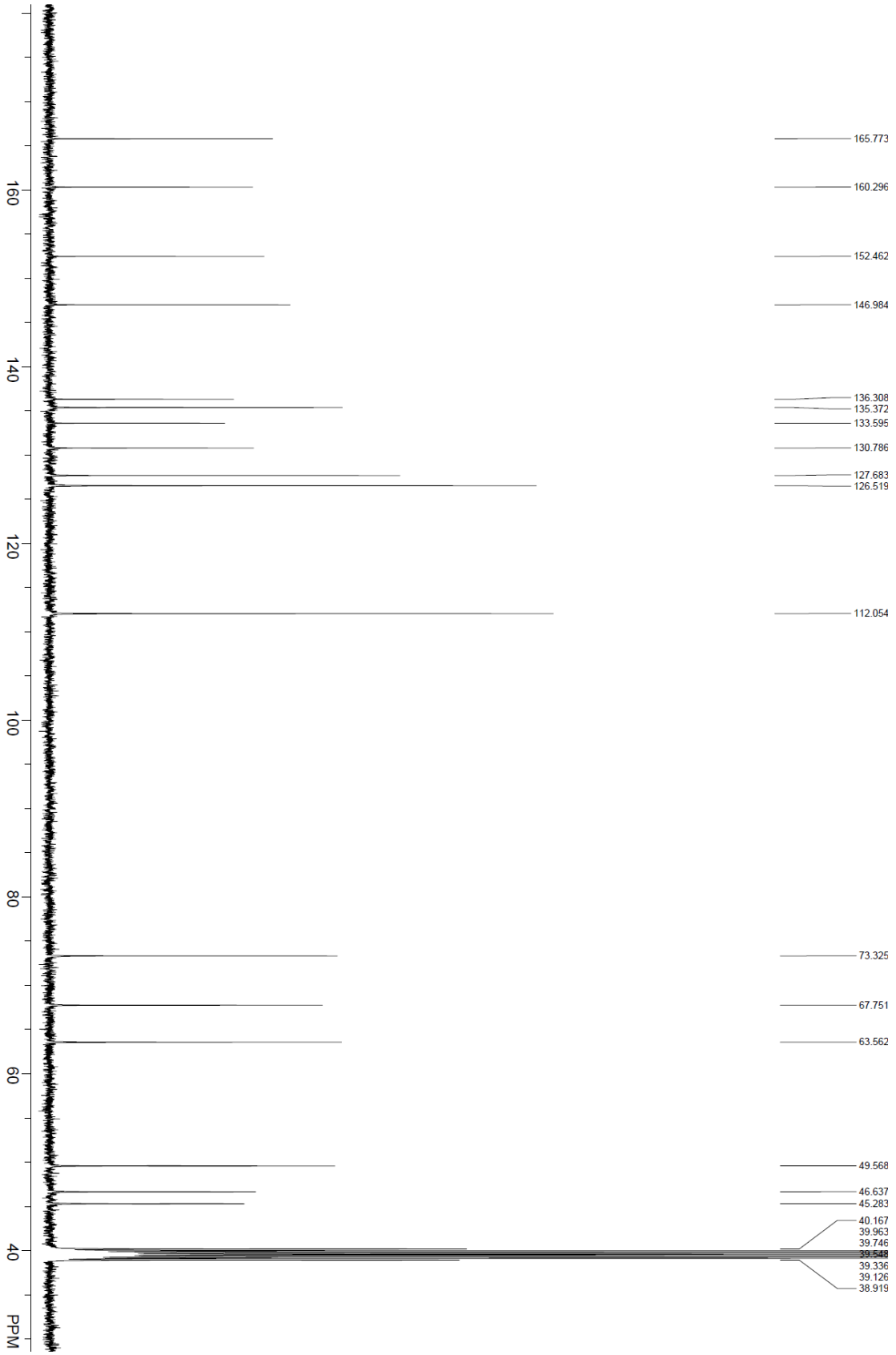
419.18

7. Compound 20

1H NMR (d_6-DMSO, 400 MHz)



^{13}C NMR (d_6-DMSO, 100 MHz)



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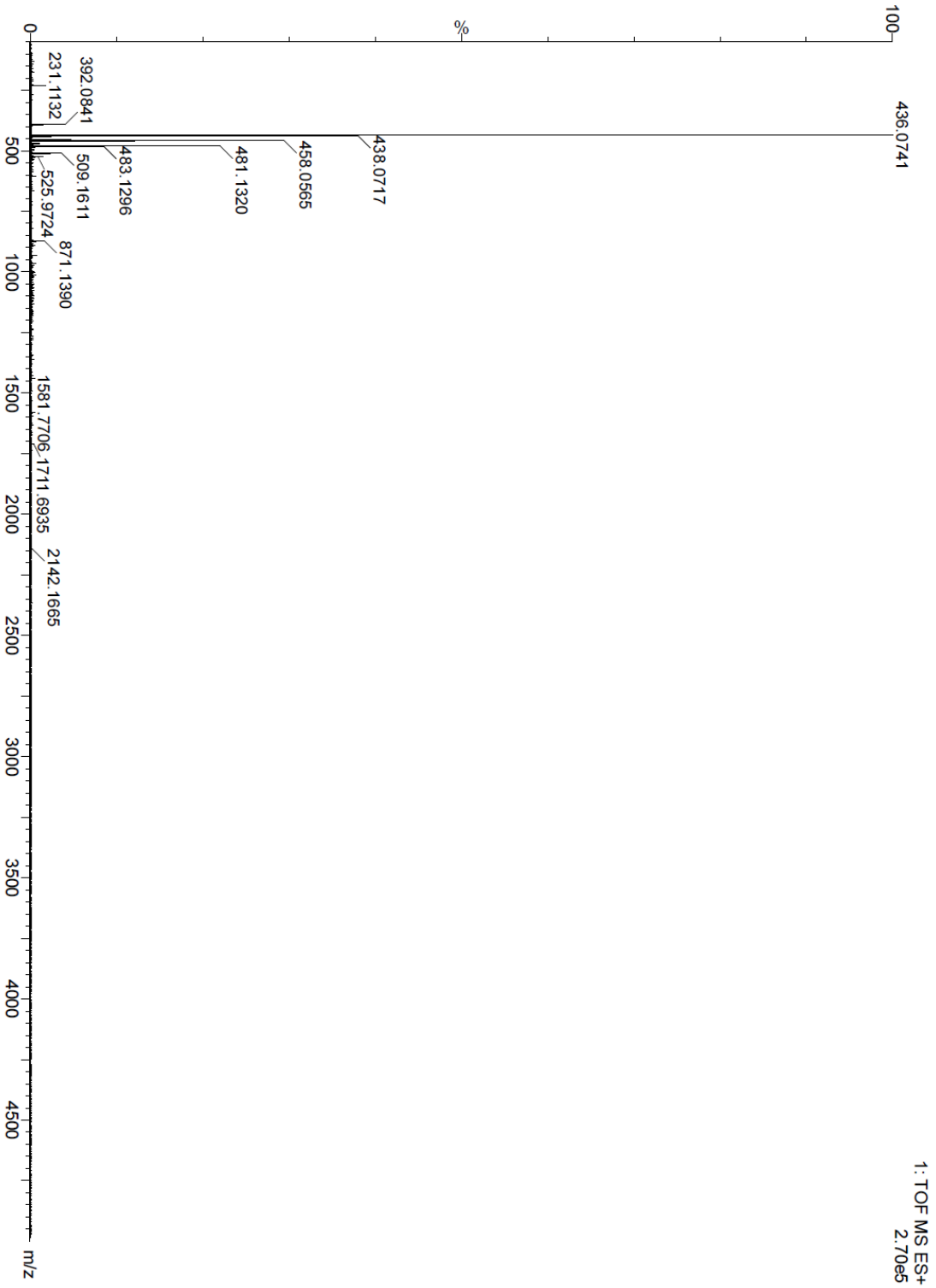
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m/z
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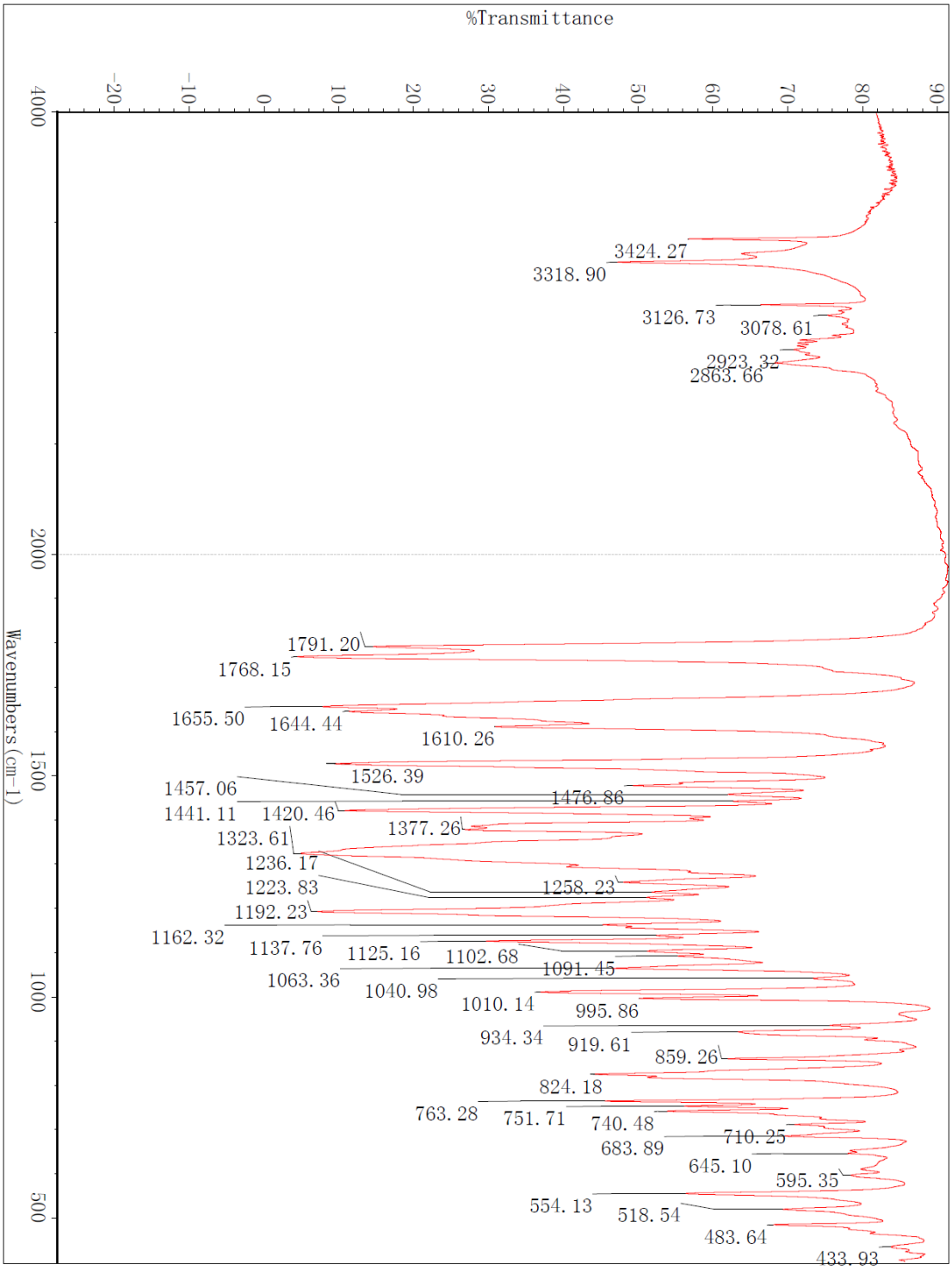
IR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Wavenumbers(cm-1)
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1323.61
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1223.83
1258.23
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1162.32
1137.76
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1102.68
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1063.36
1040.98
1010.14
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934.34
919.61
859.26
824.18
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751.71
740.48
710.25
683.89
645.10
595.35
554.13
518.54
483.64
433.93

TLC procedure for Table 1

Method: Thin Layer Chromatography, semi-quantitative analysis, limit test

Instrument: TLC, Silica gel (60) F254 plate, layer thickness 0.25 mm, Merck, development tank, hot air source (hairdryer), UV camera.

Reagent for preparation of reference solution:

5-chlorothiophene-2-carboxylic acid (Acid 6)**,** HPLC≥ 99 %

Solvents and reagents:

1. Ethyl acetate, CH3COOC2H5, for liquid chromatography
2. Methanol, CH3OH, for liquid chromatography
3. Acetic acid, CH3COOH, for liquid chromatography
4. Mobile phase: Ethyl acetate: Methanol : Acetic acid = 50:5:1 (V/V/V). Into 50 ml bottle with measuring cylinder measure 50 ml of Ethyl acetate´ 5 ml of Methanol ´ 1ml of Acetic acid and mix well;
5. Solvent: Methanol, CH3OH

Chromatographic conditions:

Plate: TLC, Silica gel (60) F254 plate, layer thickness 0.25 mm, size 10 x 10 cm, Merck.

Mobile phase: Ethyl acetate: Methanol : Acetic acid = 50:5:1 (V/V/V).

Chromatographic tank: saturated with mobile phase for 20 min.

Application: 2 µl, by hand, on spot.

Note: Values of weights and volumes can be properly adjusted.

Solution preparation:

Note: Ensure target concentrations of standard and sample solutions by corresponding adjustment of weights and volumes.

Standard solution (SS)

(1) Accurately weigh about 0.05 g of Acid 6 reagent into a 50 ml volumetric flask, dissolve in solvent, and dilute with solvent to the volume (SS). Mix well.
(SS: approx. 1 mg Acid 6 /ml, 1% of working concentration).

(2) Accurately weigh about 0.25 g of Acid 6 reagent into a 50 ml volumetric flask, dissolve in solvent, and dilute with solvent to the volume (SS). Mix well.
(SS: approx. 5 mg Acid 6 /ml, 5% of working concentration).

(3) Accurately weigh about 0.5 g of Acid 6 reagent into a 50 ml volumetric flask, dissolve in solvent, and dilute with solvent to the volume (SS). Mix well.
(SS: approx. 10 mg Acid 6 /ml, 10% of working concentration).

(4) Accurately weigh about 1.0 g of Acid 6 reagent into a 50 ml volumetric flask, dissolve in solvent, and dilute with solvent to the volume (SS). Mix well.
(SS: approx. 20 mg Acid 6 /ml, 20% of working concentration).

(5) Accurately weigh about 1.5 g of Acid 6 reagent into a 50 ml volumetric flask, dissolve in solvent, and dilute with solvent to the volume (SS). Mix well.

(SS: approx. 30 mg Acid 6 /ml, 30% of working concentration).

(6) Accurately weigh about 2.0 g of Acid 6 reagent into a 50 ml volumetric flask, dissolve in solvent, and dilute with solvent to the volume (SS). Mix well.
(SS: approx. 40 mg Acid 6 /ml, 40% of working concentration).

(7) Accurately weigh about 2.5 g of Acid 6 reagent into a 50 ml volumetric flask, dissolve in solvent, and dilute with solvent to the volume (SS). Mix well.
(SS: approx. 50 mg Acid 6 /ml, 50% of working concentration).

Sample solution (SaS)

Reaction mixture (0.5 mL) was quenched into the cold methylamine solution in ethanol （30%w/w,0.5ml） with shaking for 5 min (SaS).

Procedure:

Application:

Apply 4 μl of the sample solution (SaS) 10 mm from the lower edge and 20 mm from the left side edge of the plate, then separately in spots another 2 μl of standard solution (SS) allowing an interval of at least 10 mm, and then into the third spot another 2 μl of SS and 4 μl SaS (spike).

Development:

About 8 cm vertically in chromatographic tank. After development dry the plate in warm air.

Detection:

Evaluate under UV lamp at 254 nm, the plate is photographed without reduction of noise and with automatic time of lightening.

Assessment:

Intensity of Acid 6 spot in the sample should be lower than the intensity of Acid 6 spot in the standard solution (SS).

The conversion by TLC in the Tables 2-4 adopt the similar to that in Table 1