

Indole-2-carboxamide as an effective scaffold for the design of new TRPV1 agonists

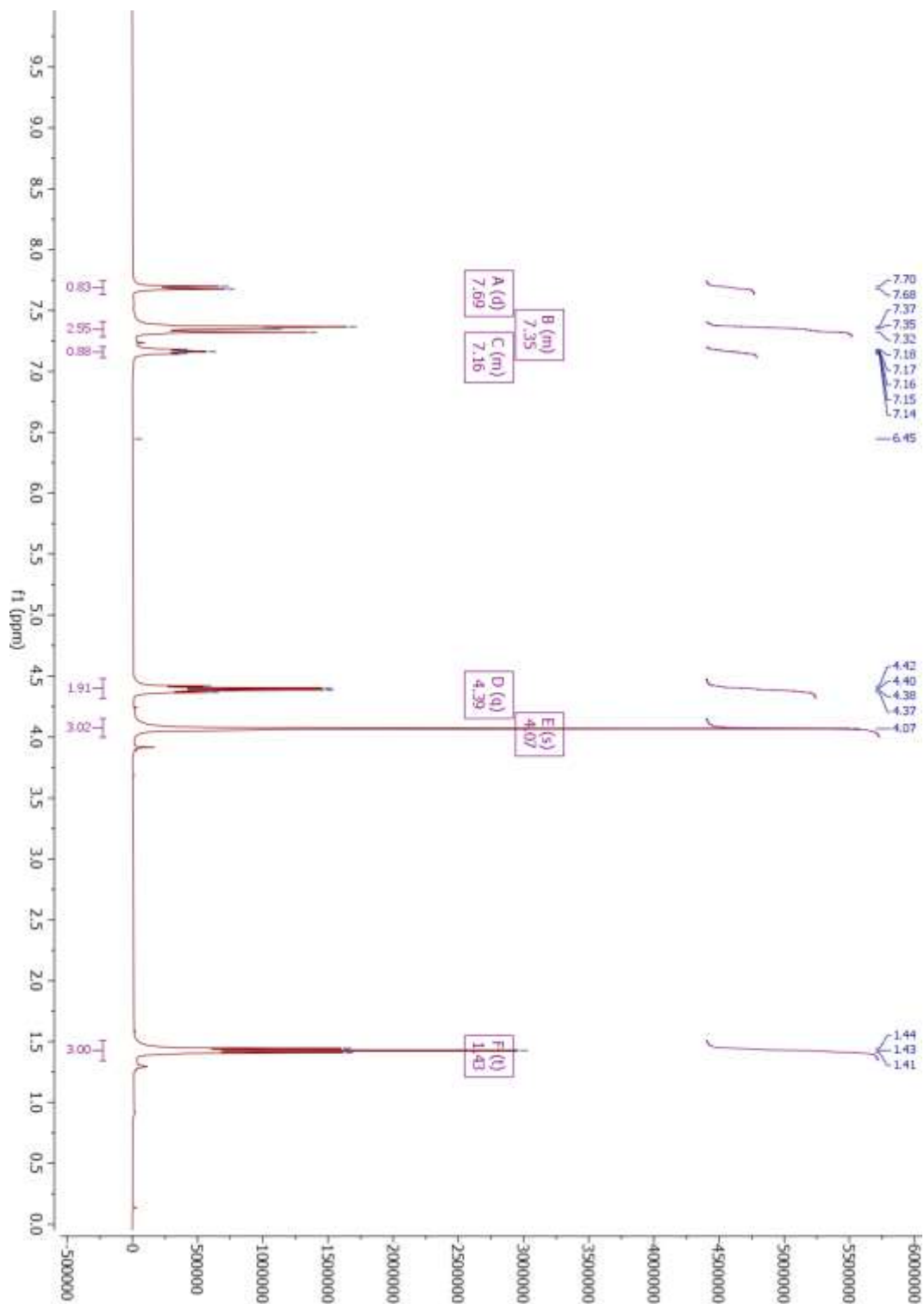
Samuele Maramai ^{1,*}, Claudia Mugnaini ¹, Marco Paolino ¹, Aniello Schiano Moriello ², Luciano De Petrocellis ², Federico Corelli ¹, Francesca Aiello ^{3,†} and Antonella Brizzi ^{1,†,*}

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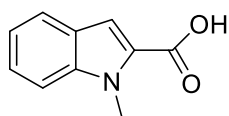
S2	¹ H-NMR of ethyl 1-methyl-1 <i>H</i> -indole-2-carboxylate.
S3	¹ H-NMR of 1-methyl-1 <i>H</i> -indole-2-carboxylic acid 9 .
S4-36	¹ H-NMR, ¹³ C-NMR and UPLC- or HPLC-MS of 1 <i>H</i> -indole-2-carboxyamides 5a-i .
S37-73	¹ H-NMR, ¹³ C-NMR and UPLC- or HPLC-MS of 1 <i>H</i> -indole-2-carboxyamides 6a-j .

CCOC(=O)c1c[nH]c2ccccc12

MW 203.24

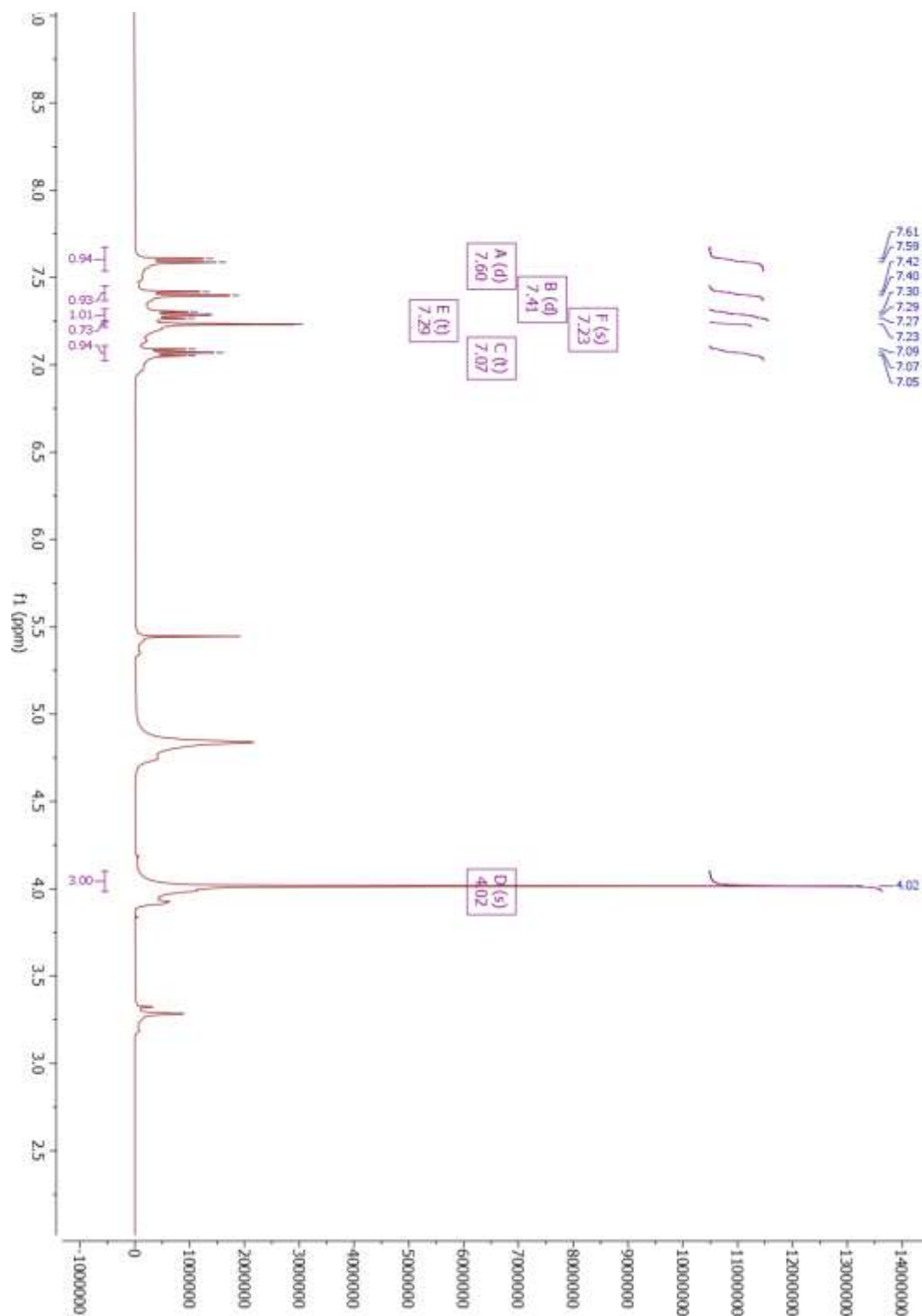


1-Methyl-1*H*-indole-2-carboxylic acid (9)

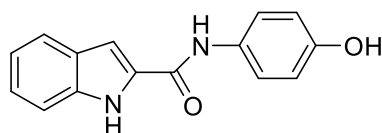


C₁₀H₉NO₂

MW 175.19

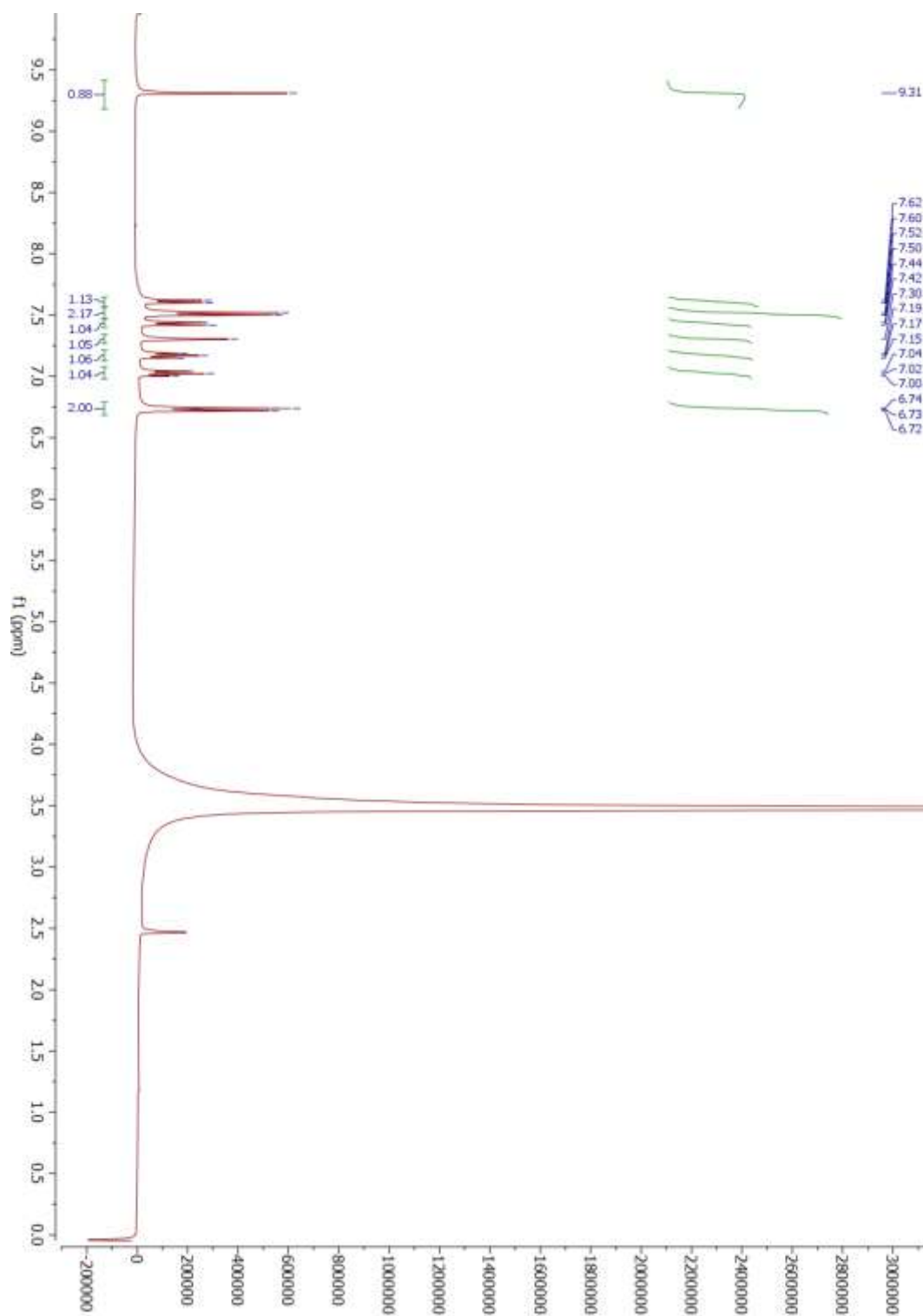


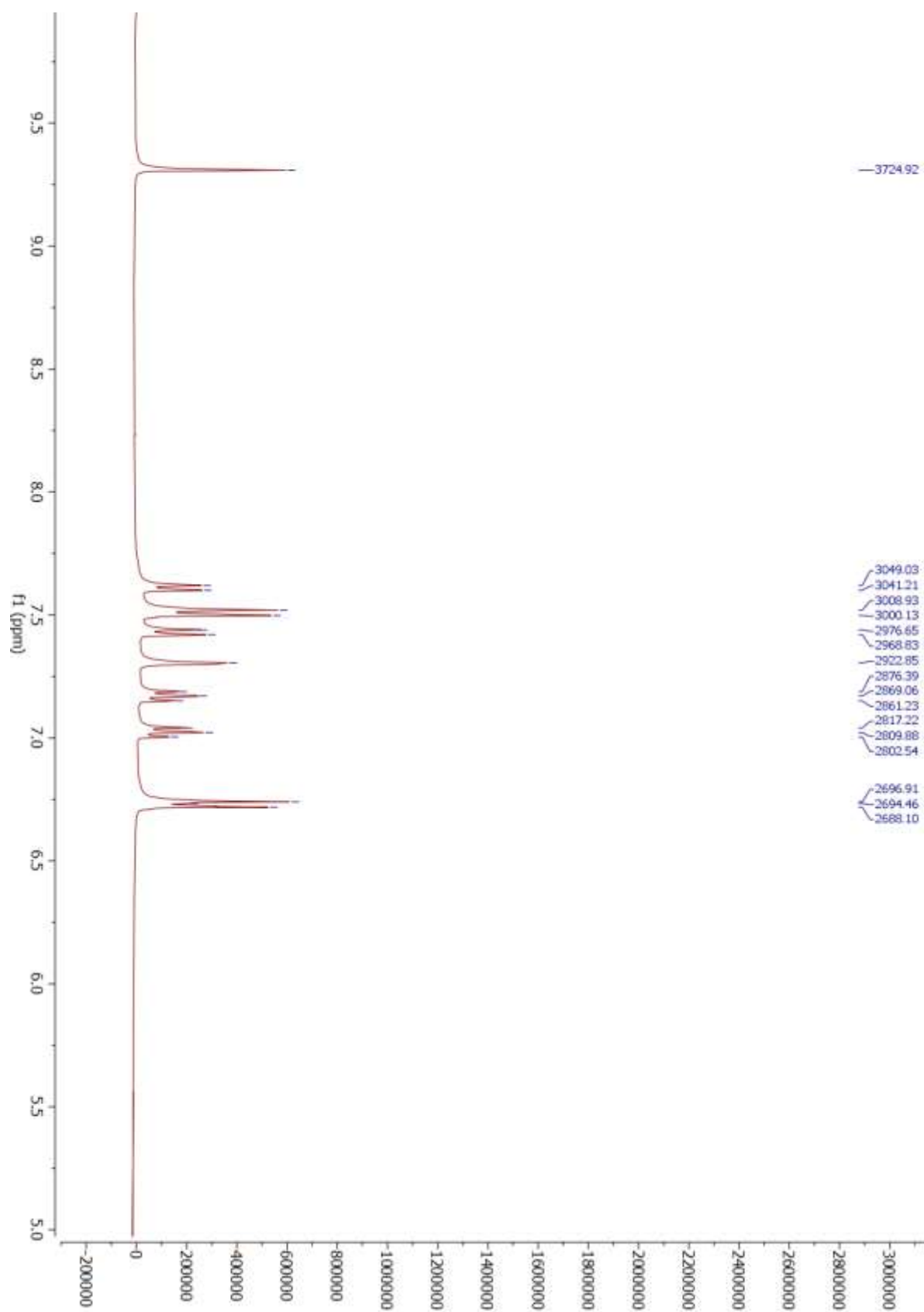
***N*-(4-Hydroxyphenyl)-1*H*-indole-2-carboxamide (5a)**

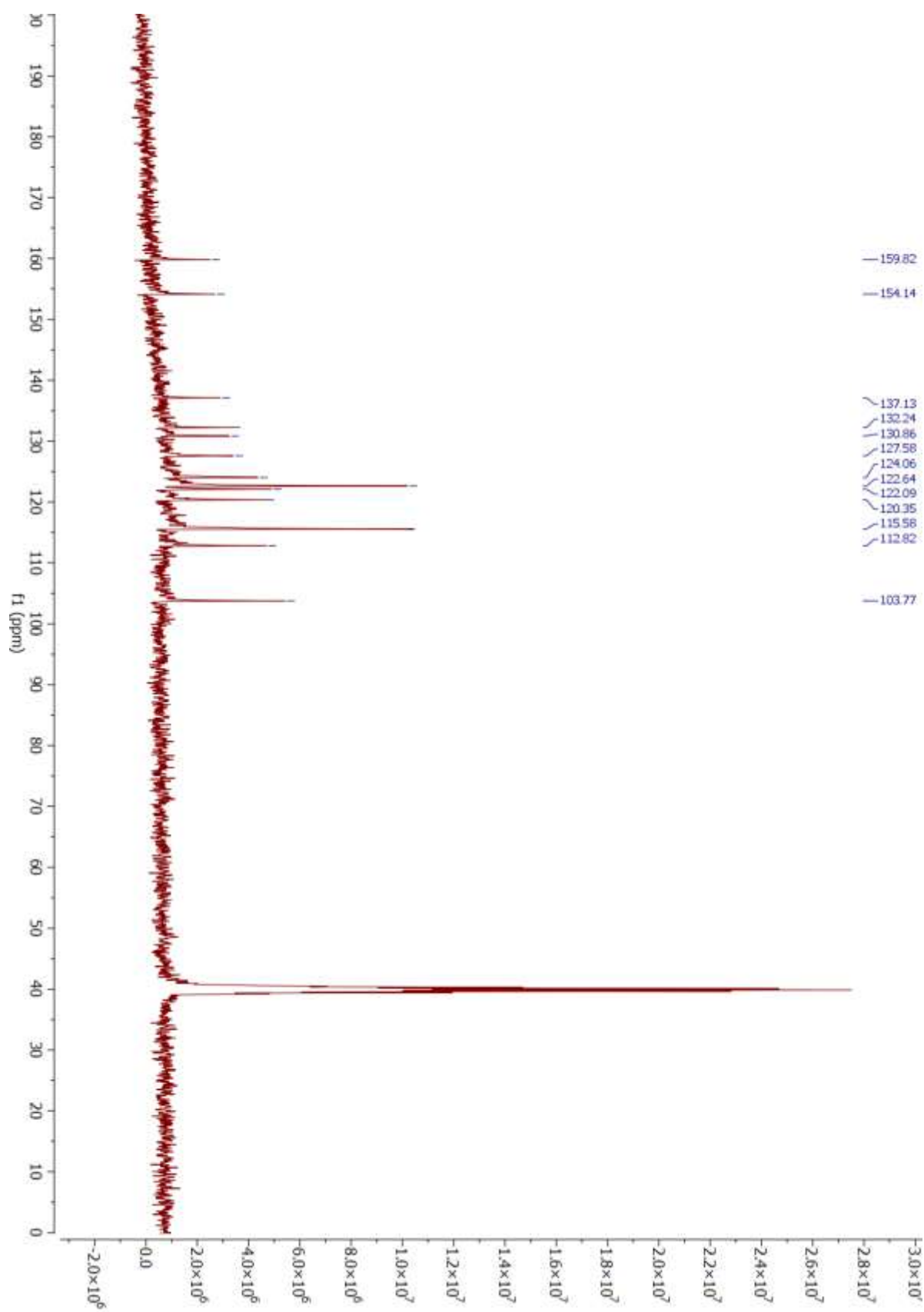


C₁₅H₁₂N₂O₂

MW 252.27







Openlynx Report -

Sample: 52
Date: 29-Aug-2018

Vial: 1:F,3
Time: 16:45:42

File: I-0416615-001

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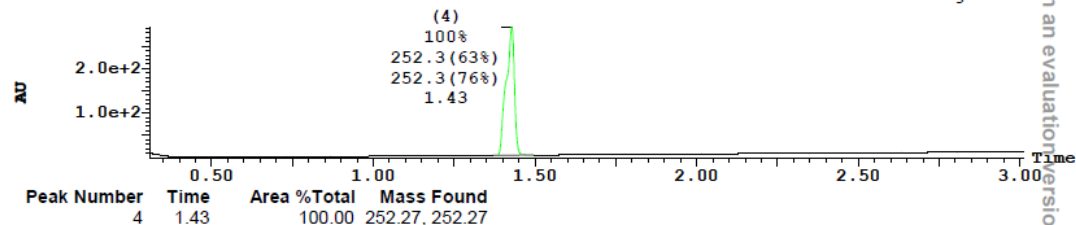
Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

Sample 52 Vial 1:F,3 ID File I-0416615-001 Date 29-Aug-2018 Time 16:45:42 Description Met Gen

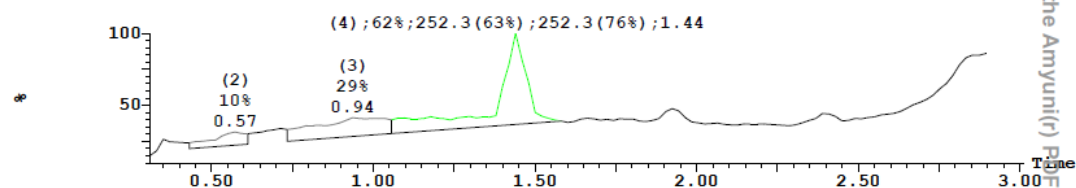
3: UV Detector: TIC

2.92e+2
Range: 2.92e+2



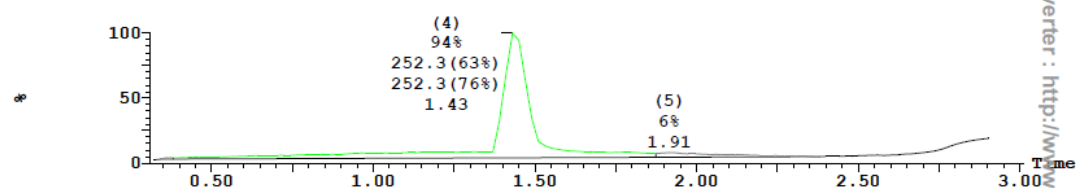
1: MS ES+ :TIC

6.3e+008



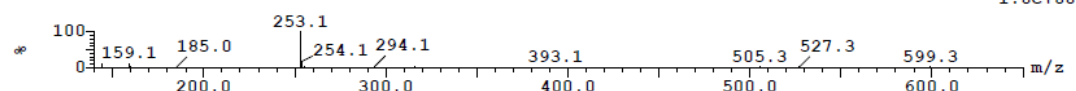
2: MS ES- :TIC

3.3e+008



Peak ID Time Mass Found
4 1.44 253.27
4: (Time: 1.43)

1: MS ES+
1.0e+007



Openlynx Report -

Sample: 52
Date: 29-Aug-2018

Vial: 1:F,3
Time: 16:45:42

File: I-0416615-001

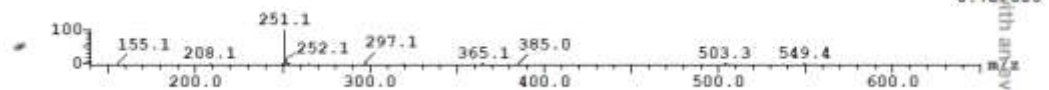
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Printed: Thu Aug 30 10:30:57 2018

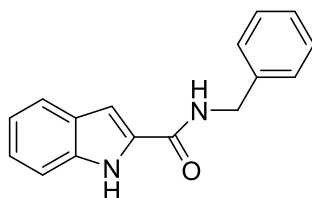
Sample Report (continued):

Peak ID Time Mass Found
4 1.44 251.27
4: (Time: 1.43)

2: MS ES-
8.7e+006

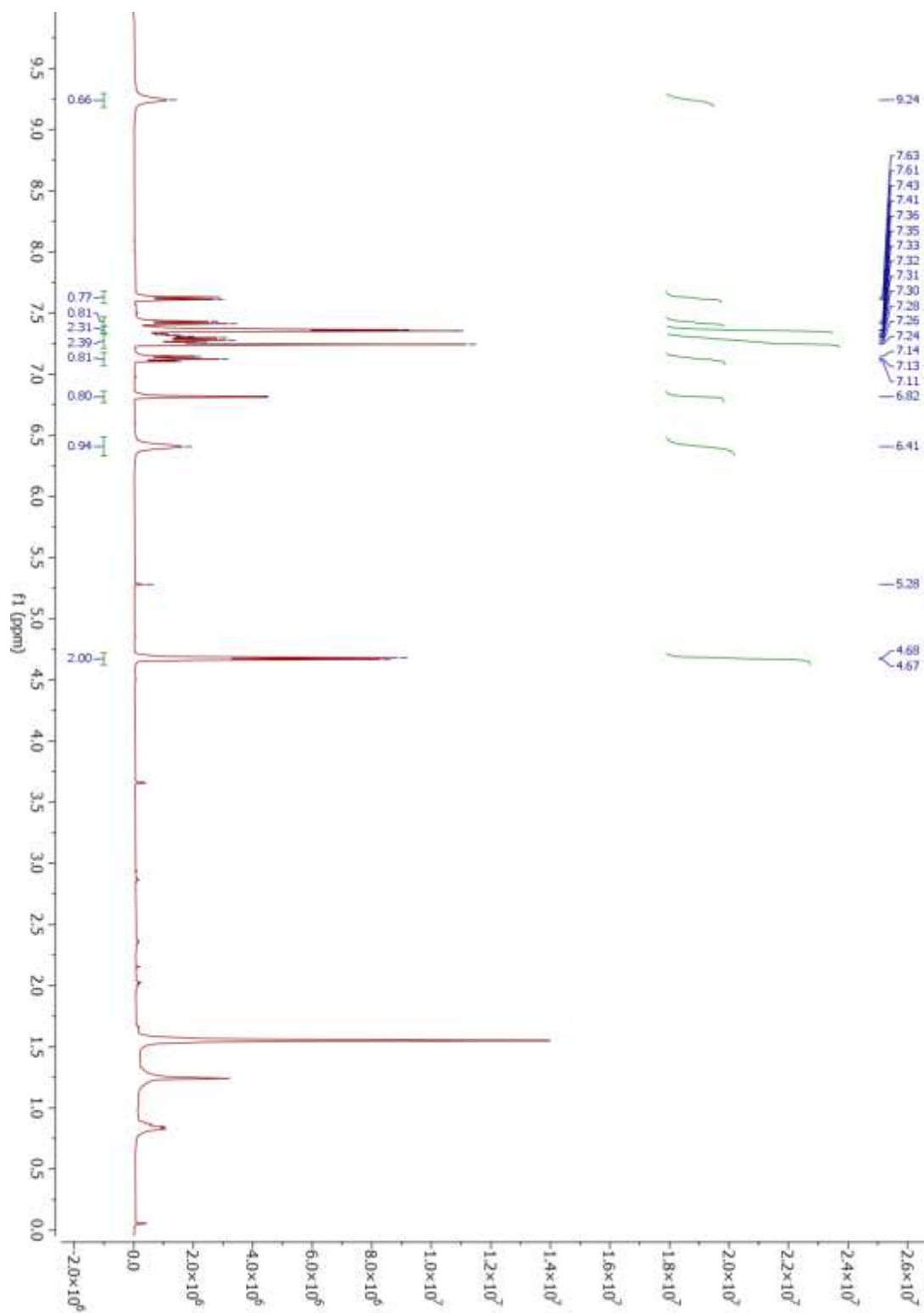


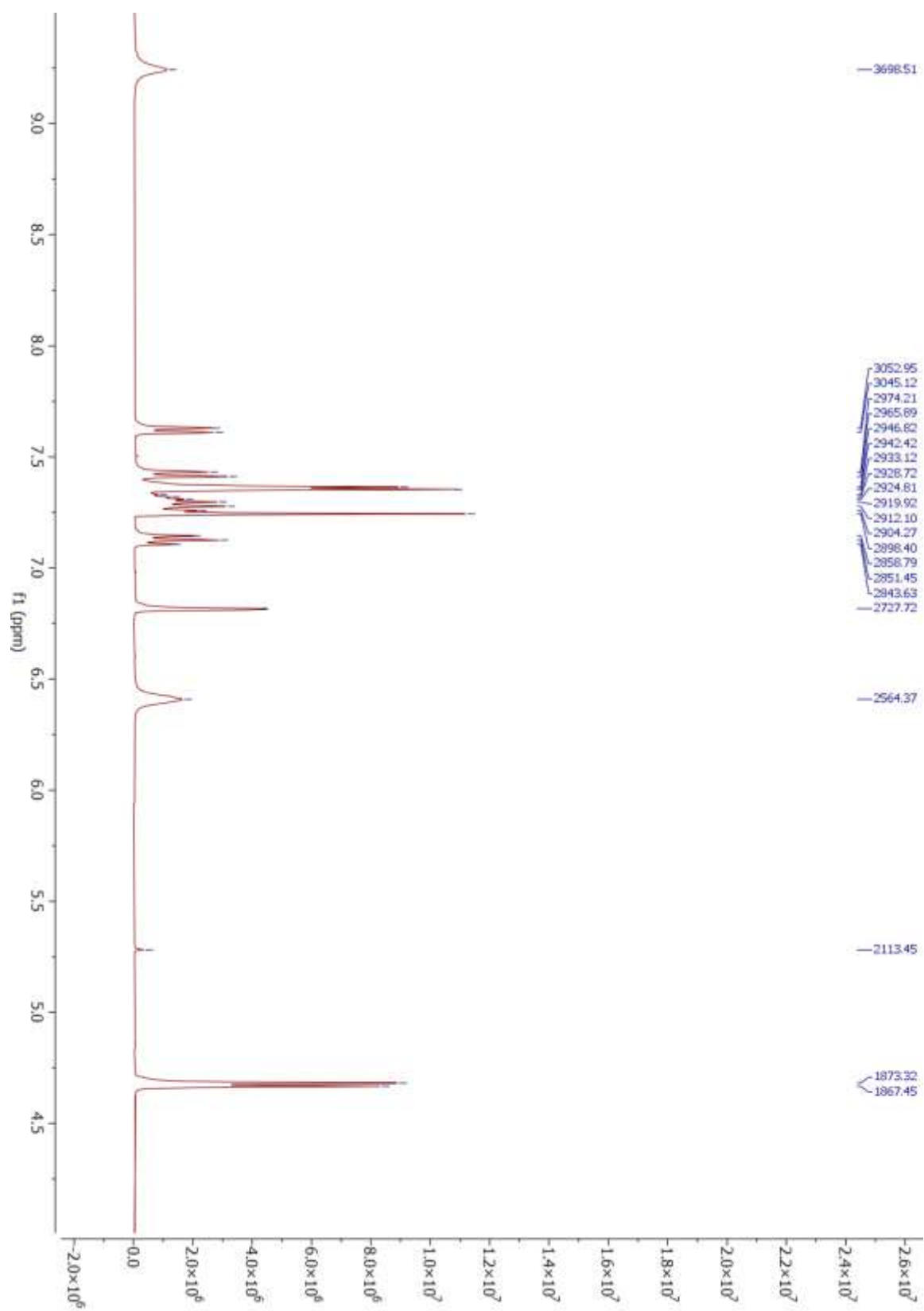
***N*-Benzyl-1*H*-indole-2-carboxamide (5b)**

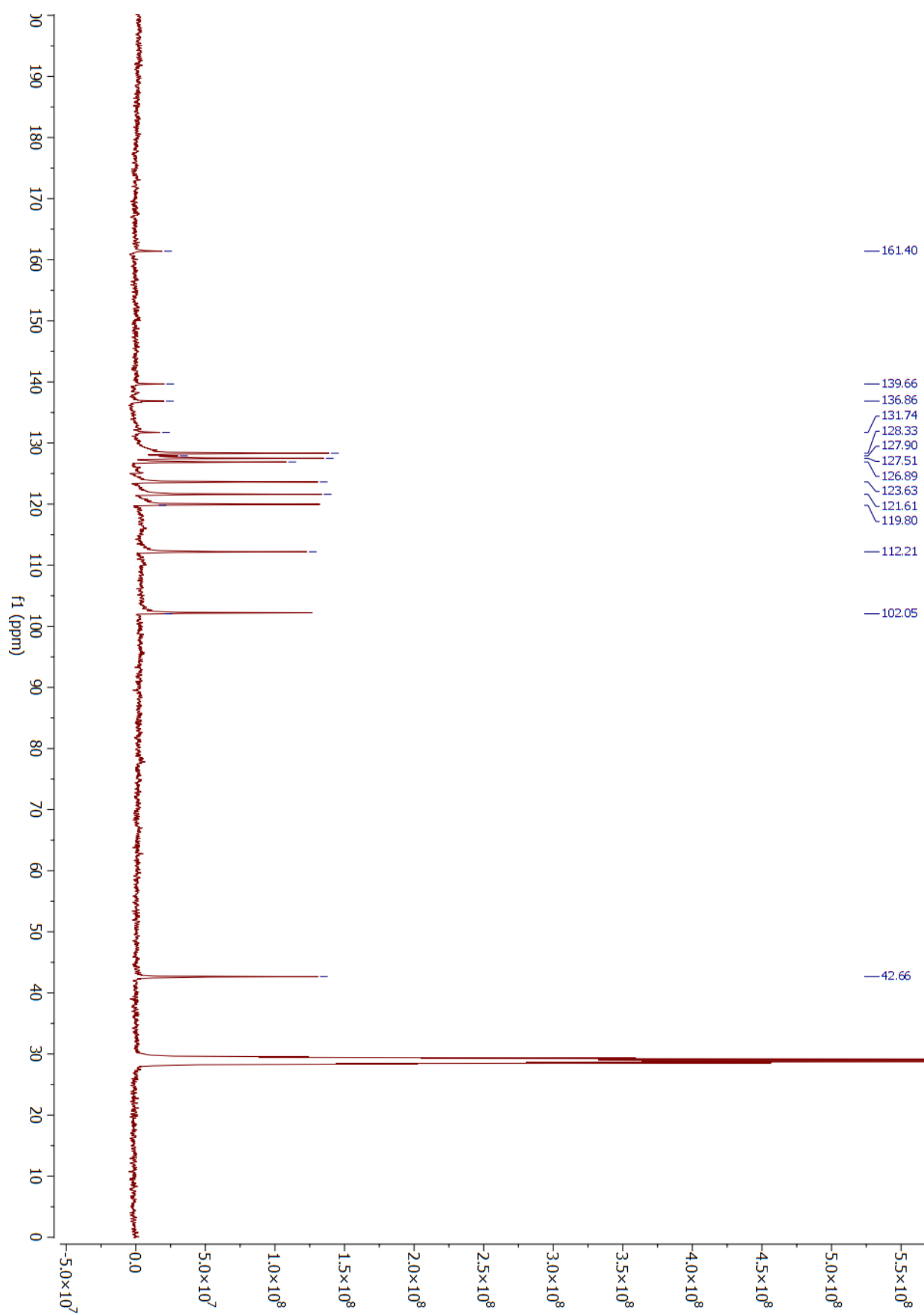


C₁₆H₁₄N₂O

MW 250.30







Openlynx Report -

Sample: 62
Date:29-Aug-2018

Vial:1;G,3
Time:17:30:00

File:I-0254678-002

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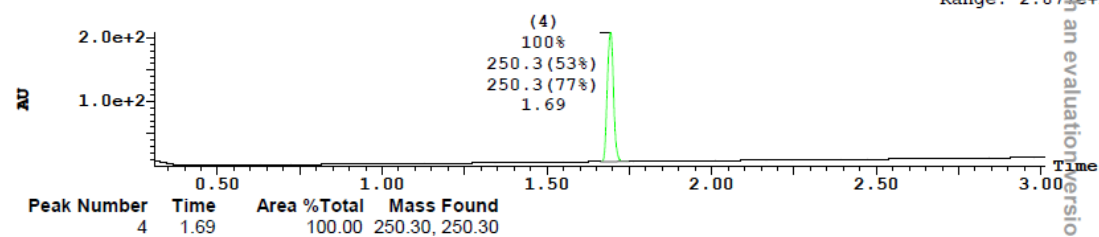
Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

Sample 62 Vial 1:G,3 ID File I-0254678-002 Date 29-Aug-2018 Time 17:30:00 Description Met Gen

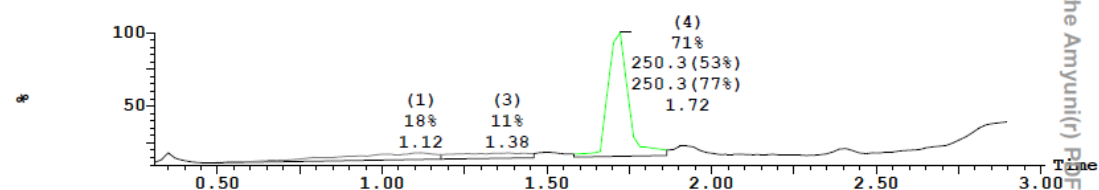
3: UV Detector: TIC

2.08e+2
Range: 2.07e+2



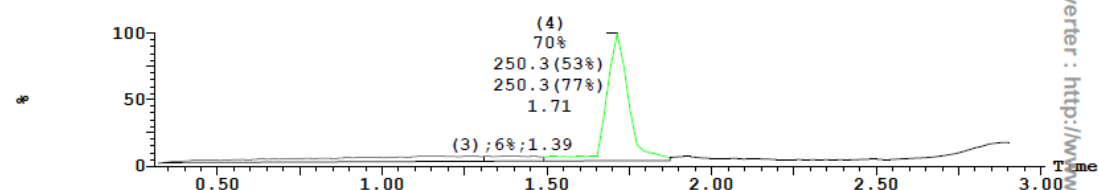
1: MS ES+ :TIC

1.2e+009



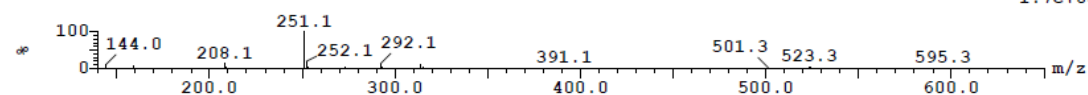
2: MS ES- :TIC

3.4e+008



Peak ID Time Mass Found
4 1.72 251.30
4: (Time: 1.69)

1:MS ES+
1.7e+007



Openlynx Report -

Sample: 62
Date:29-Aug-2018

Vial:1;G,3
Time:17:30:00

File:I-0254678-002

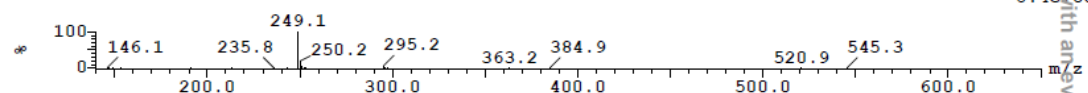
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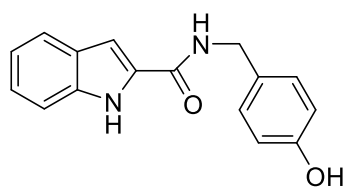
Sample Report (continued):

Peak ID Time Mass Found
4 1.72 249.30
4: (Time: 1.69)

2:MS ES-
8.4e+006

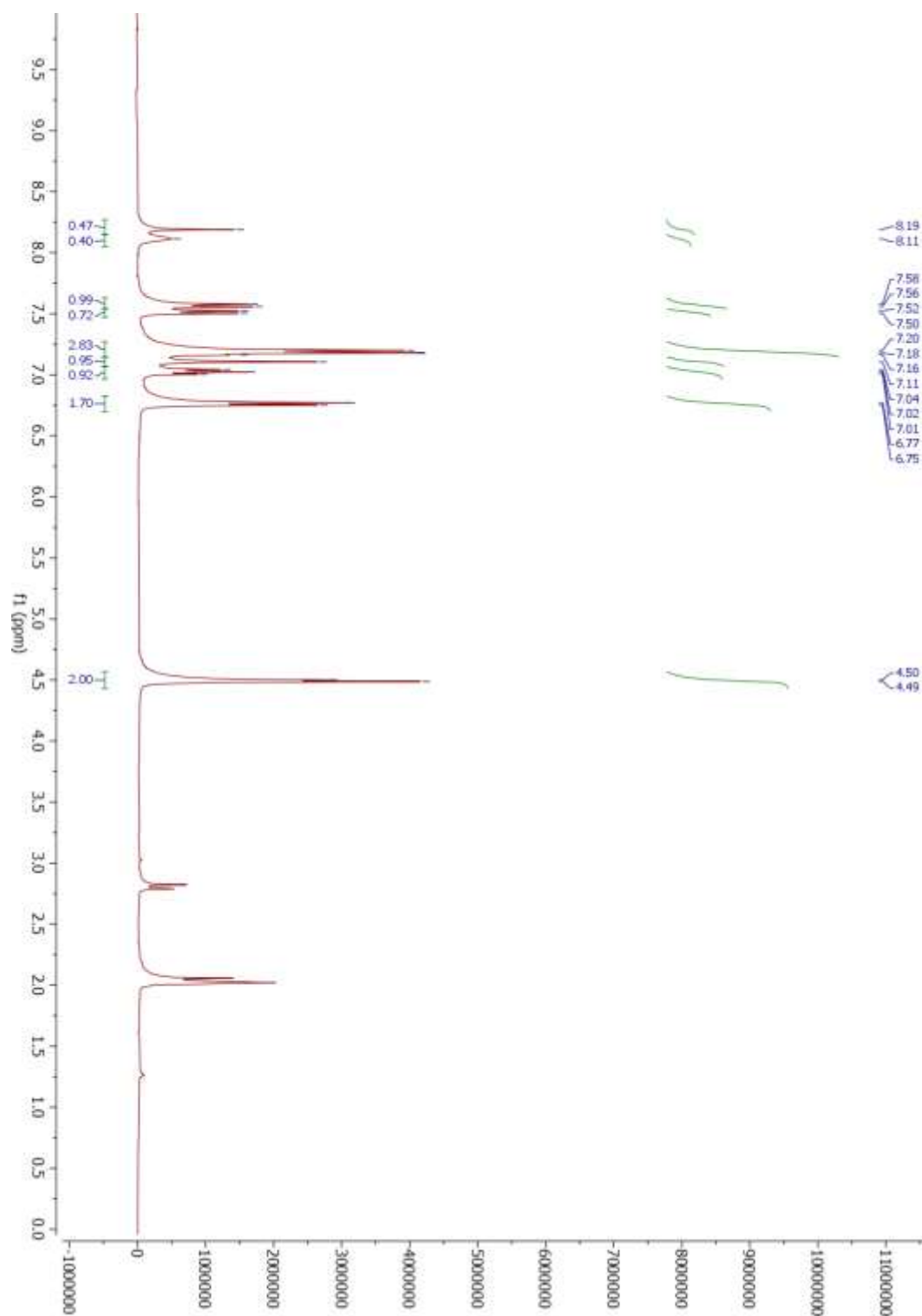


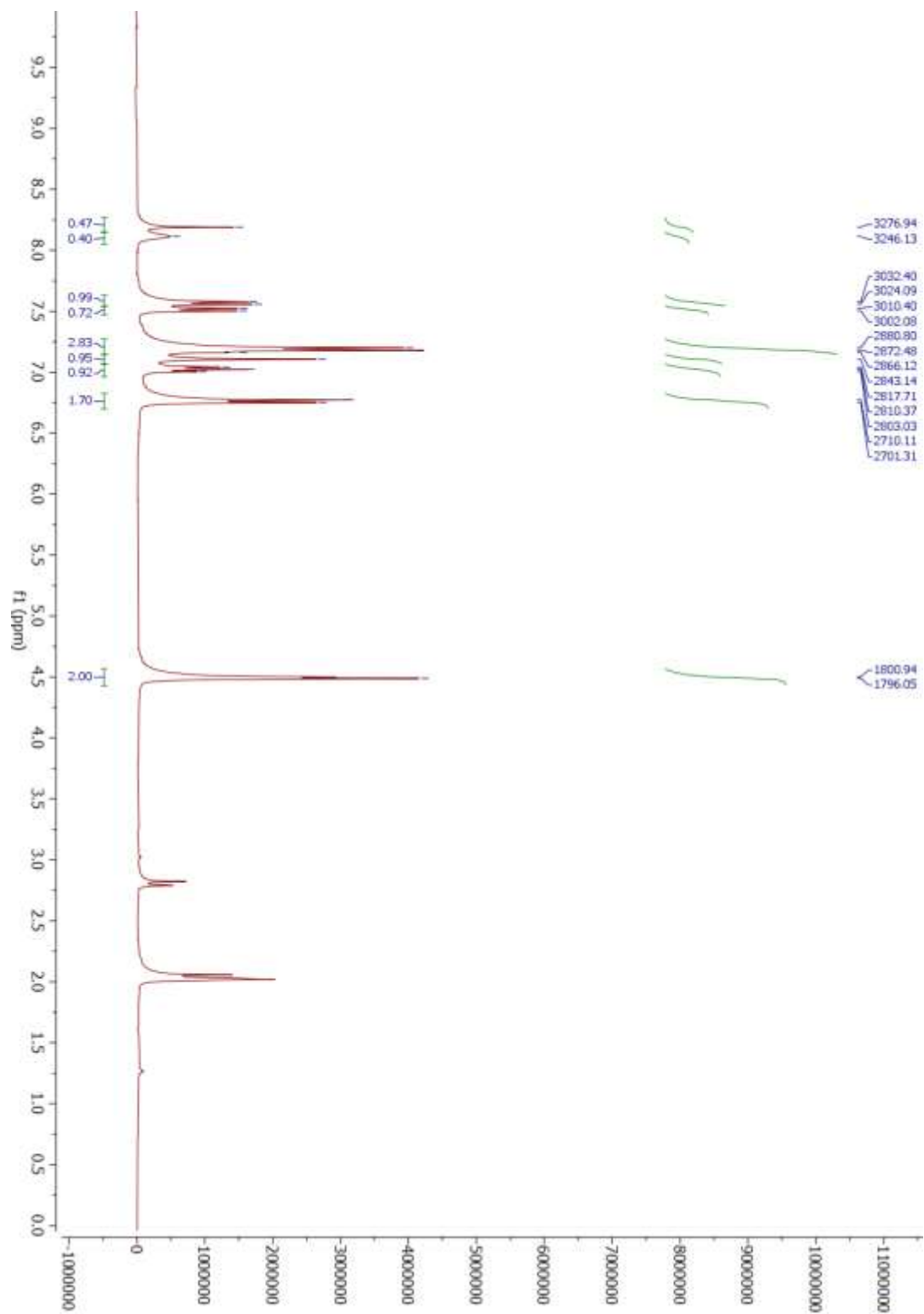
***N*-(4-Hydroxybenzyl)-1*H*-indole-2-carboxamide (5c)**

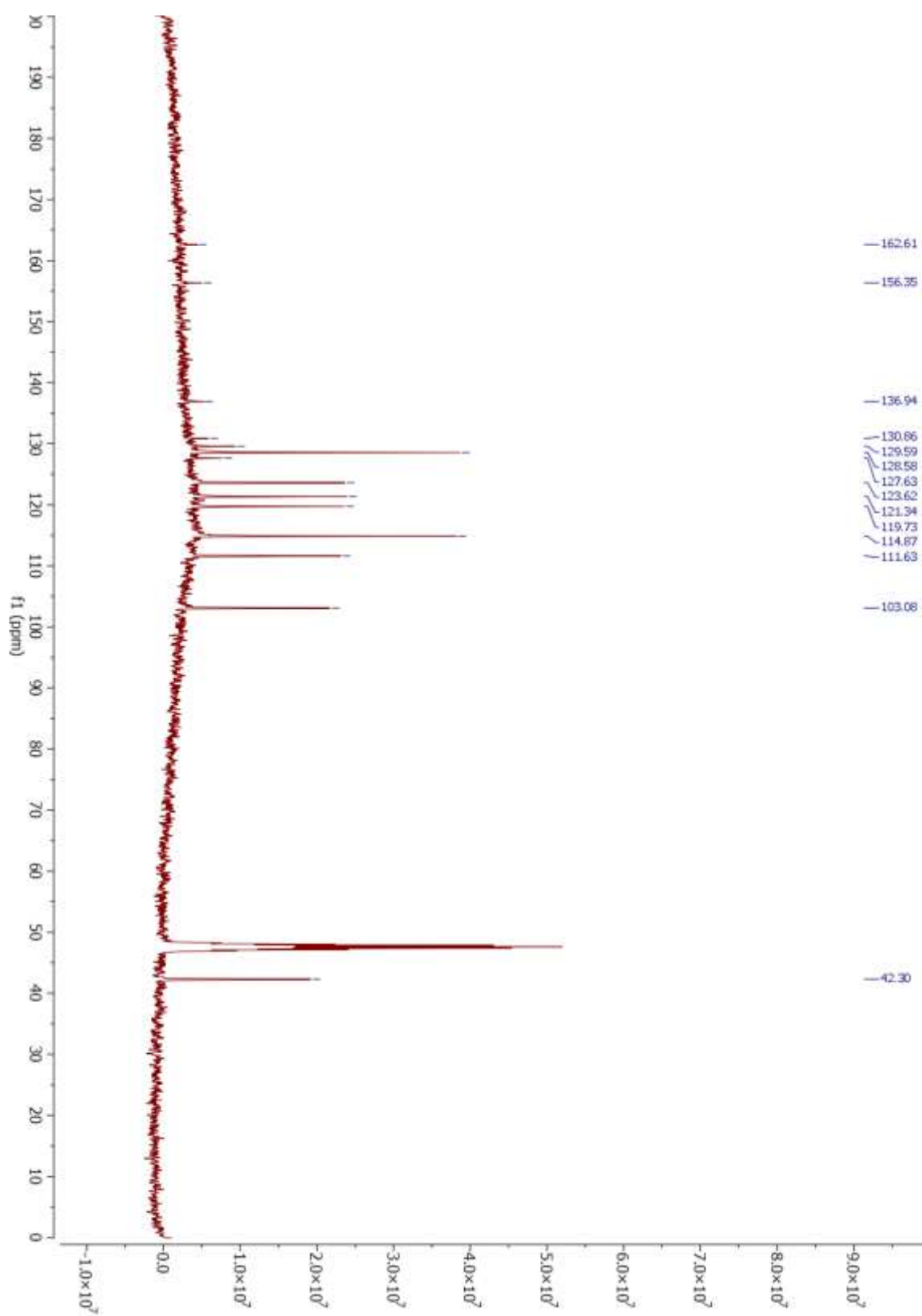


C₁₆H₁₄N₂O₂

MW 266.30







Openlynx Report -

Sample: 50
Date: 29-Aug-2018

Vial: 1:E,11
Time: 16:36:51

File: I-0416614-001

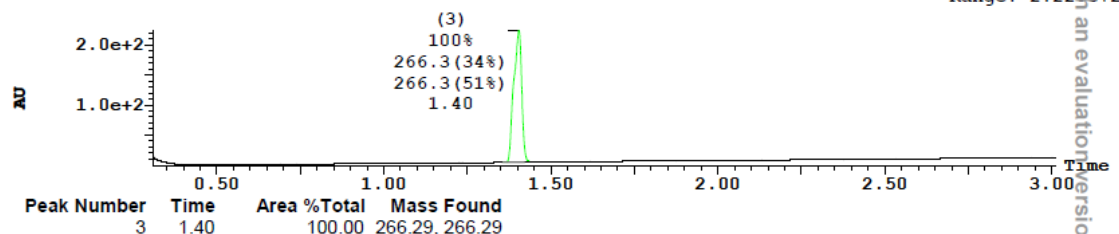
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Printed: Thu Aug 30 10:30:57 2018

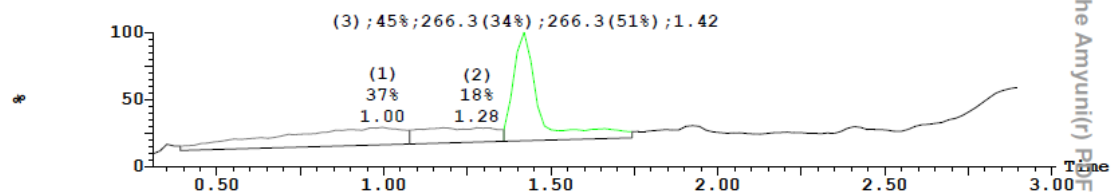
Sample Report (continued):

Sample 50 Vial 1:E,11 ID File I-0416614-001 Date 29-Aug-2018 Time 16:36:51 Description Met Gen

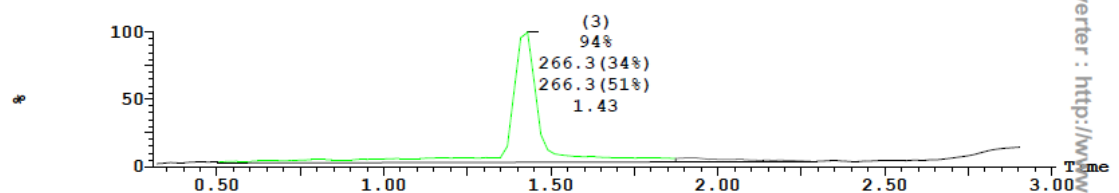
3: UV Detector: TIC



1: MS ES+ :TIC

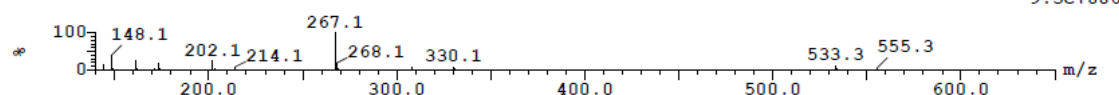


2: MS ES- :TIC



Peak ID Time Mass Found
3 1.42 267.29

3: (Time: 1.40)



Openlynx Report -

Sample: 50
Date: 29-Aug-2018

Vial: 1:E,11
Time: 16:36:51

File: I-0416614-001

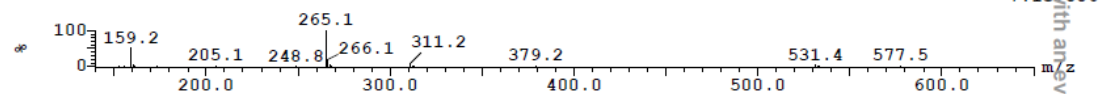
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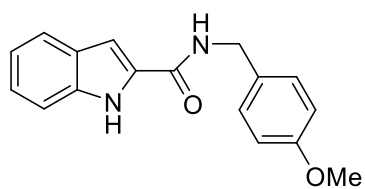
Sample Report (continued):

Peak ID Time Mass Found
3 1.42 265.29

3: (Time: 1.40)

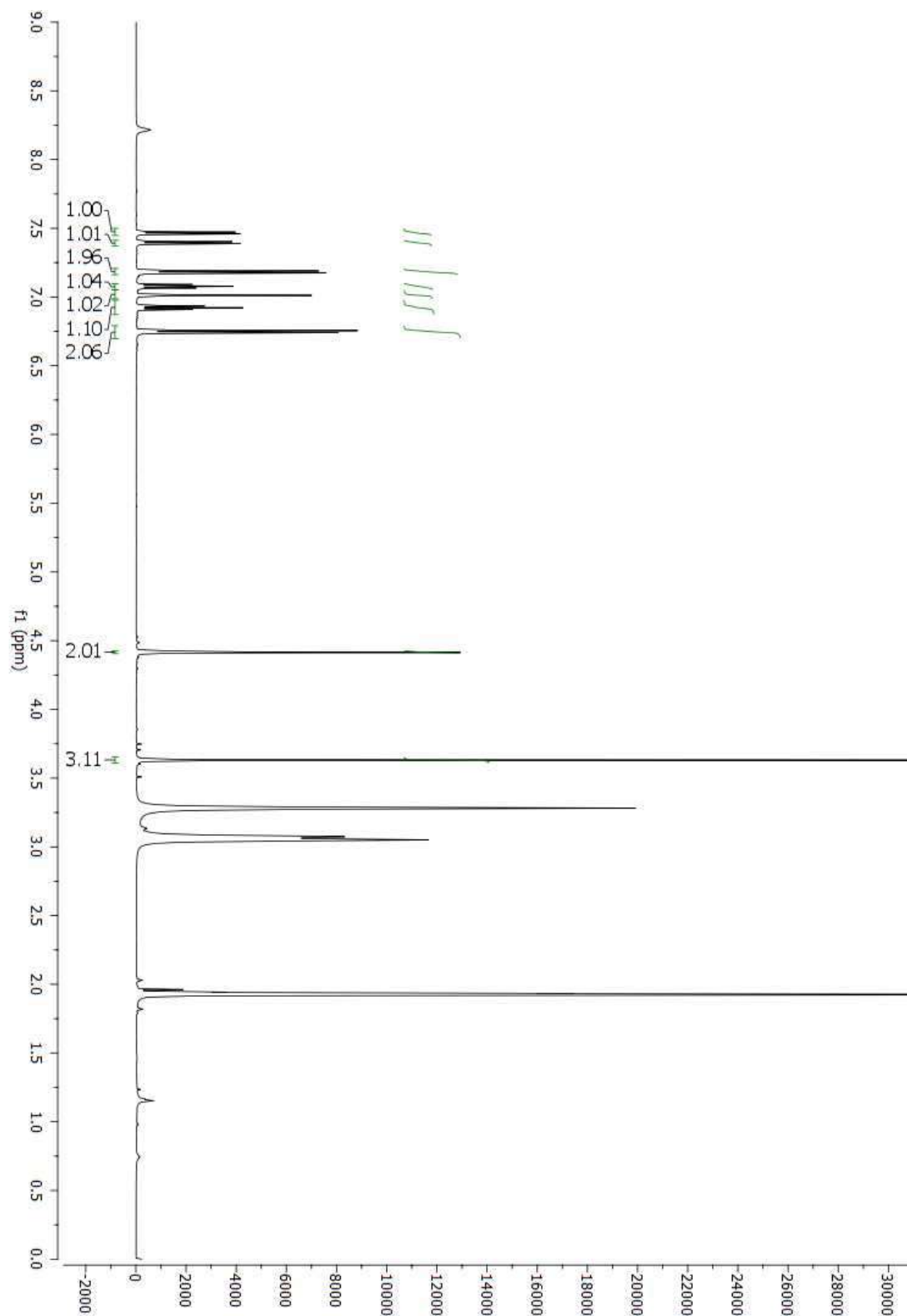


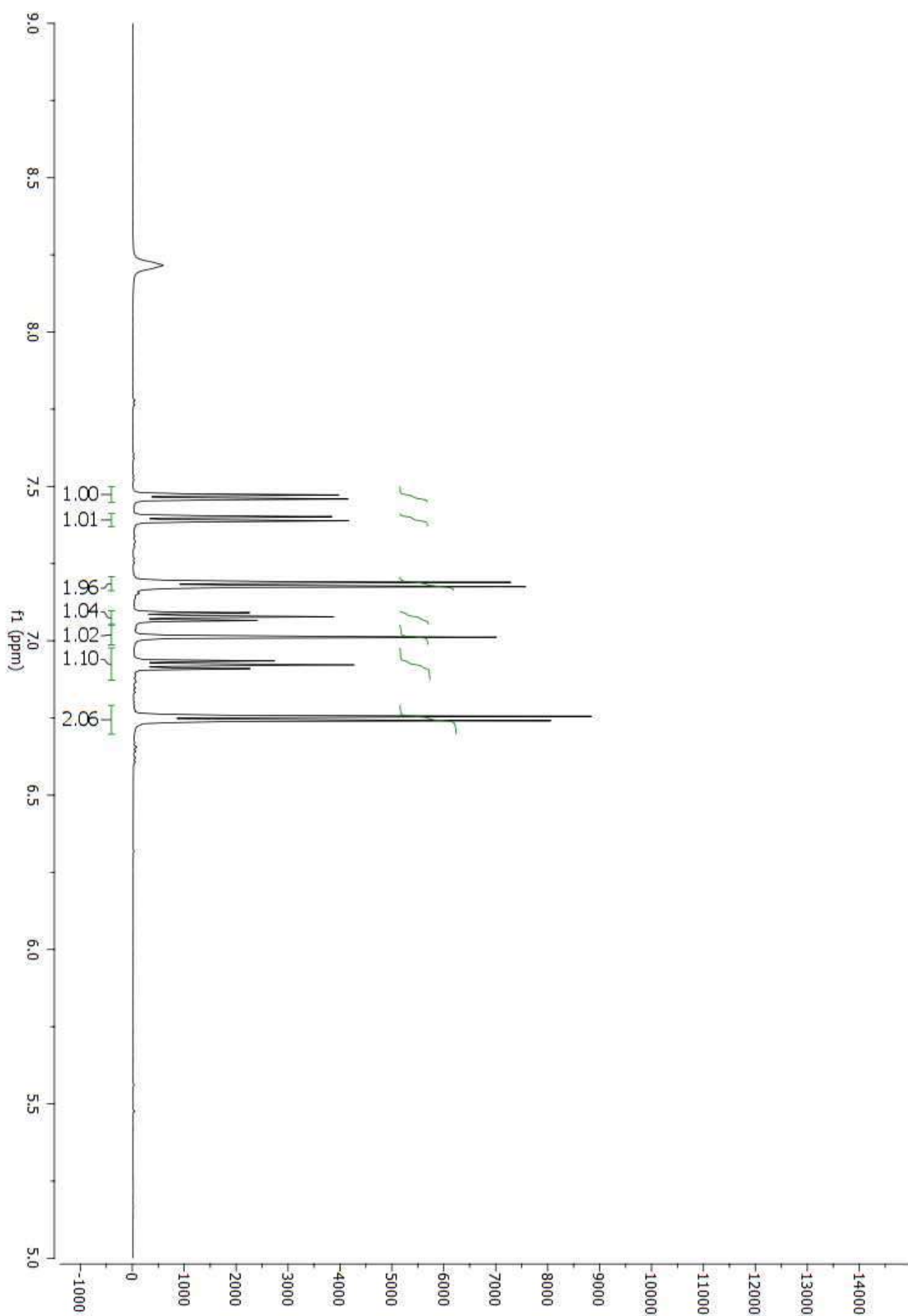
***N*-(4-Methoxybenzyl)-1*H*-indole-2-carboxamide (5d)**

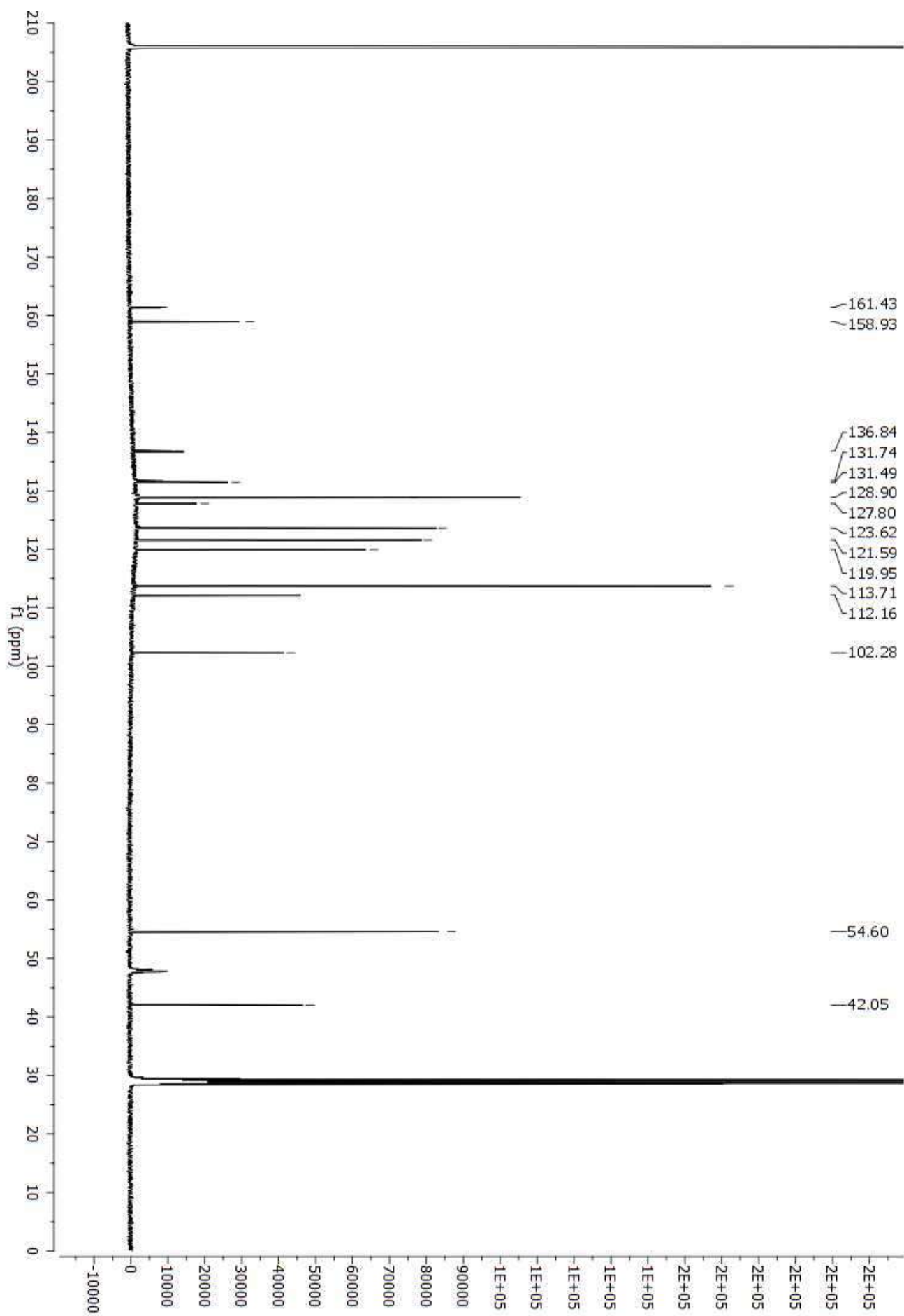


C₁₇H₁₆N₂O₂

MW 280.33





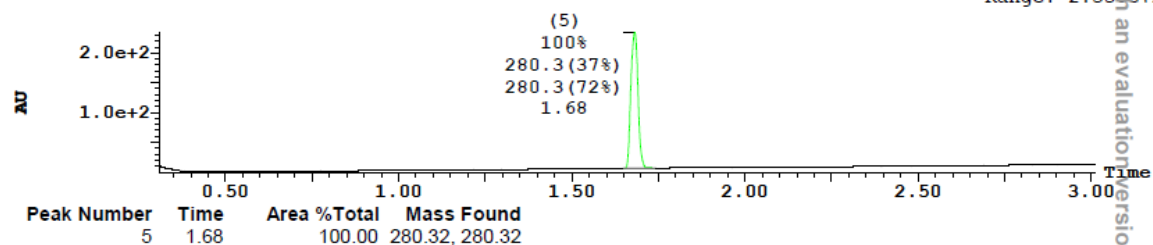


Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

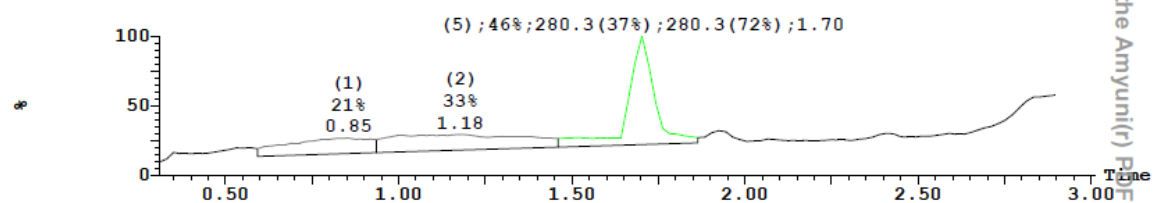
Sample 51 Vial 1:F,2 ID File I-0254881-002 Date 29-Aug-2018 Time 16:41:18 Description Met Gen

3: UV Detector: TIC

2.34e+2
Range: 2.33e+2

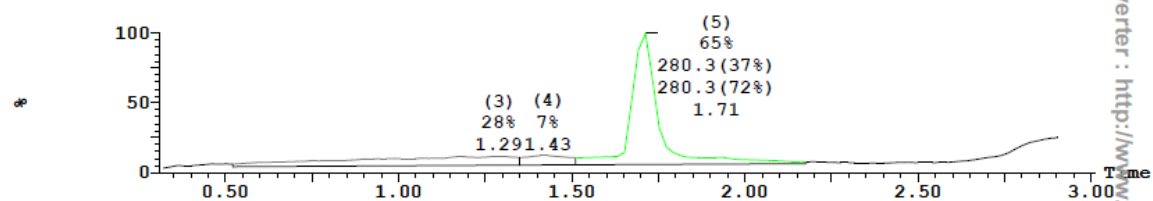
1: MS ES+ :TIC

9.9e+008



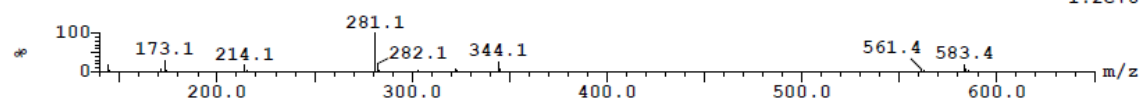
2: MS ES- :TIC

2.4e+008



Peak ID	Time	Mass Found
5	1.70	281.32

5: (Time: 1.68)

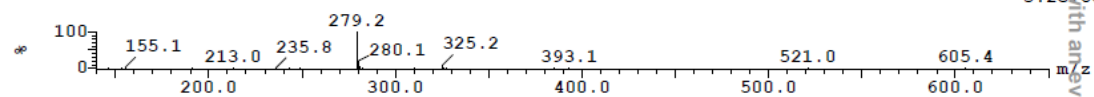
1: MS ES+
1.2e+007

Printed: Thu Aug 30 10:30:57 2018

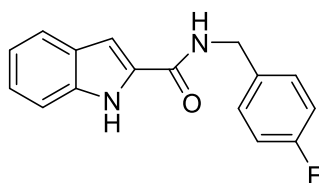
Sample Report (continued):

Peak ID	Time	Mass Found
5	1.70	279.32

5: (Time: 1.68)

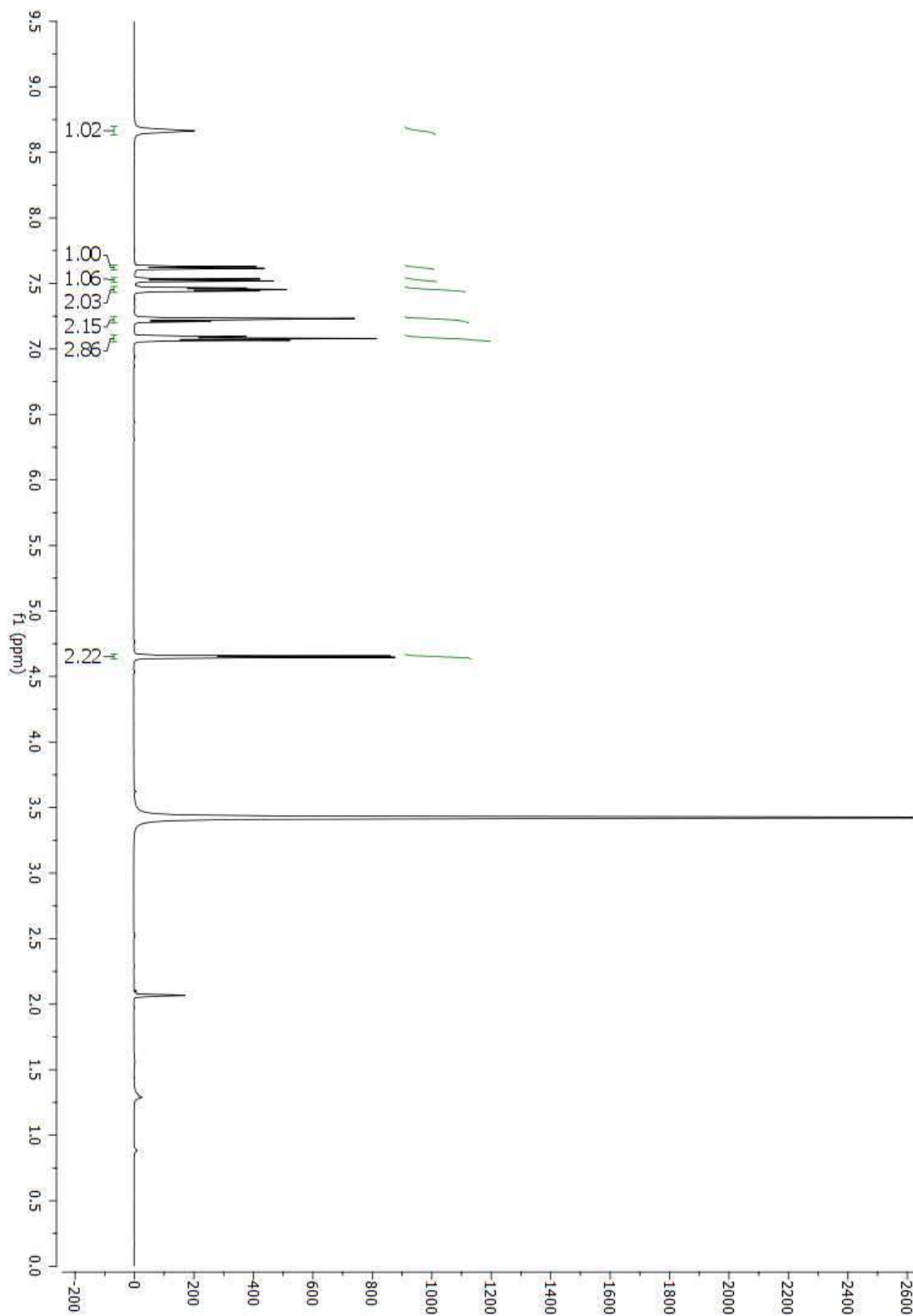
2: MS ES-
5.2e+006

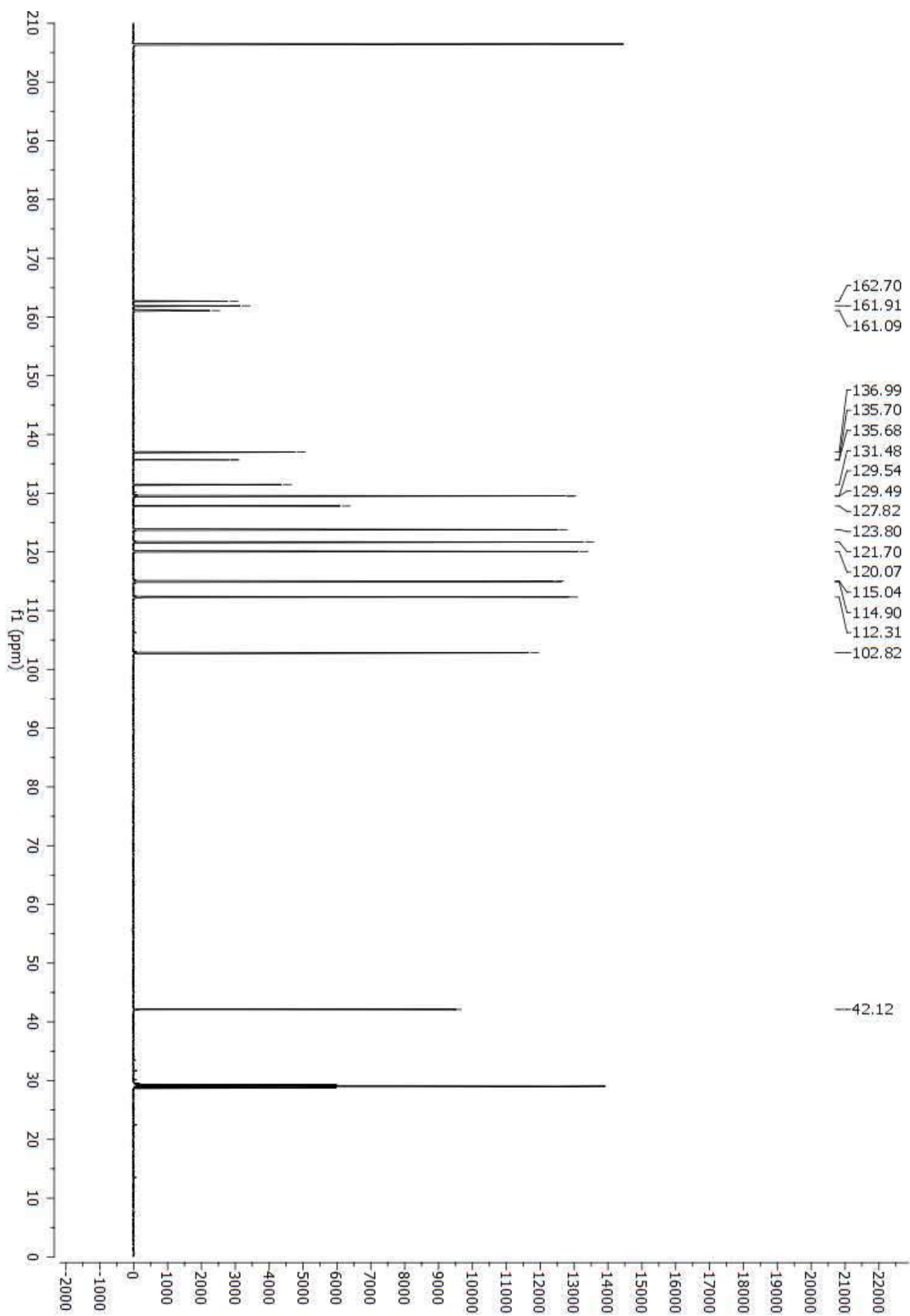
***N*-(4-Fluorobenzyl)-1*H*-indole-2-carboxamide (5e)**



C₁₆H₁₃FN₂O

MW 268.29



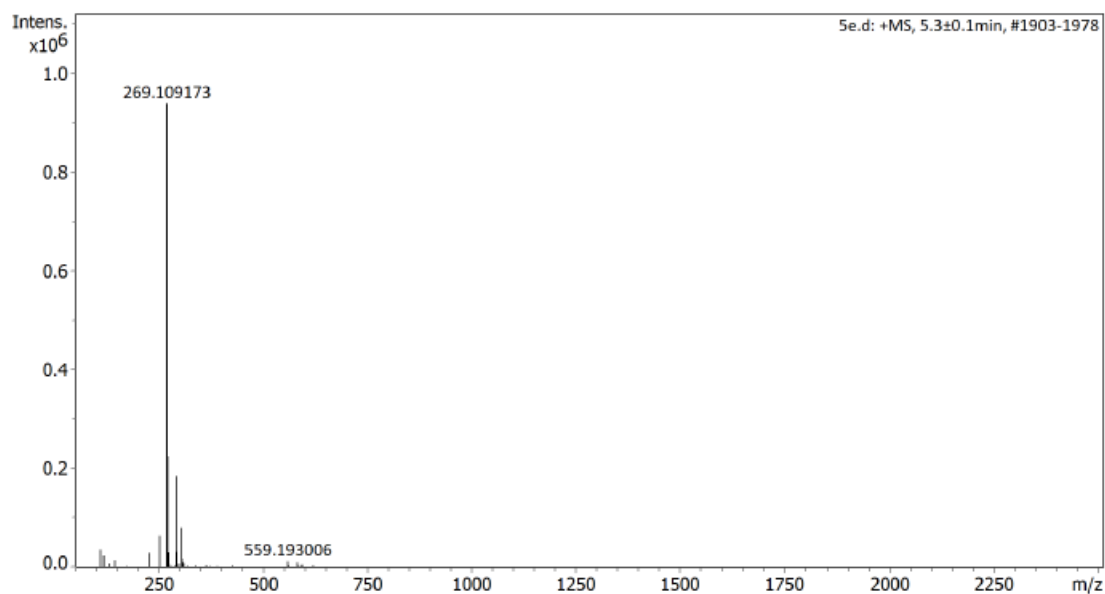
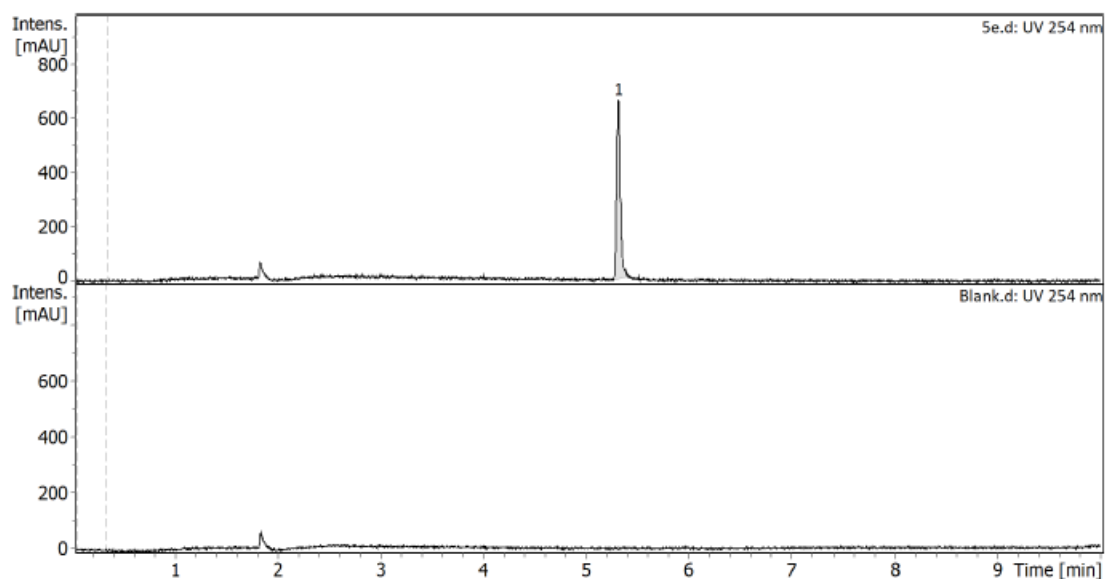


Analysis Info

Method MS_LC_POS_TimsOFF.m
Sample Name MSP137

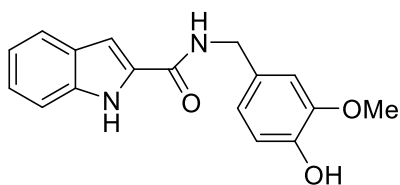
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



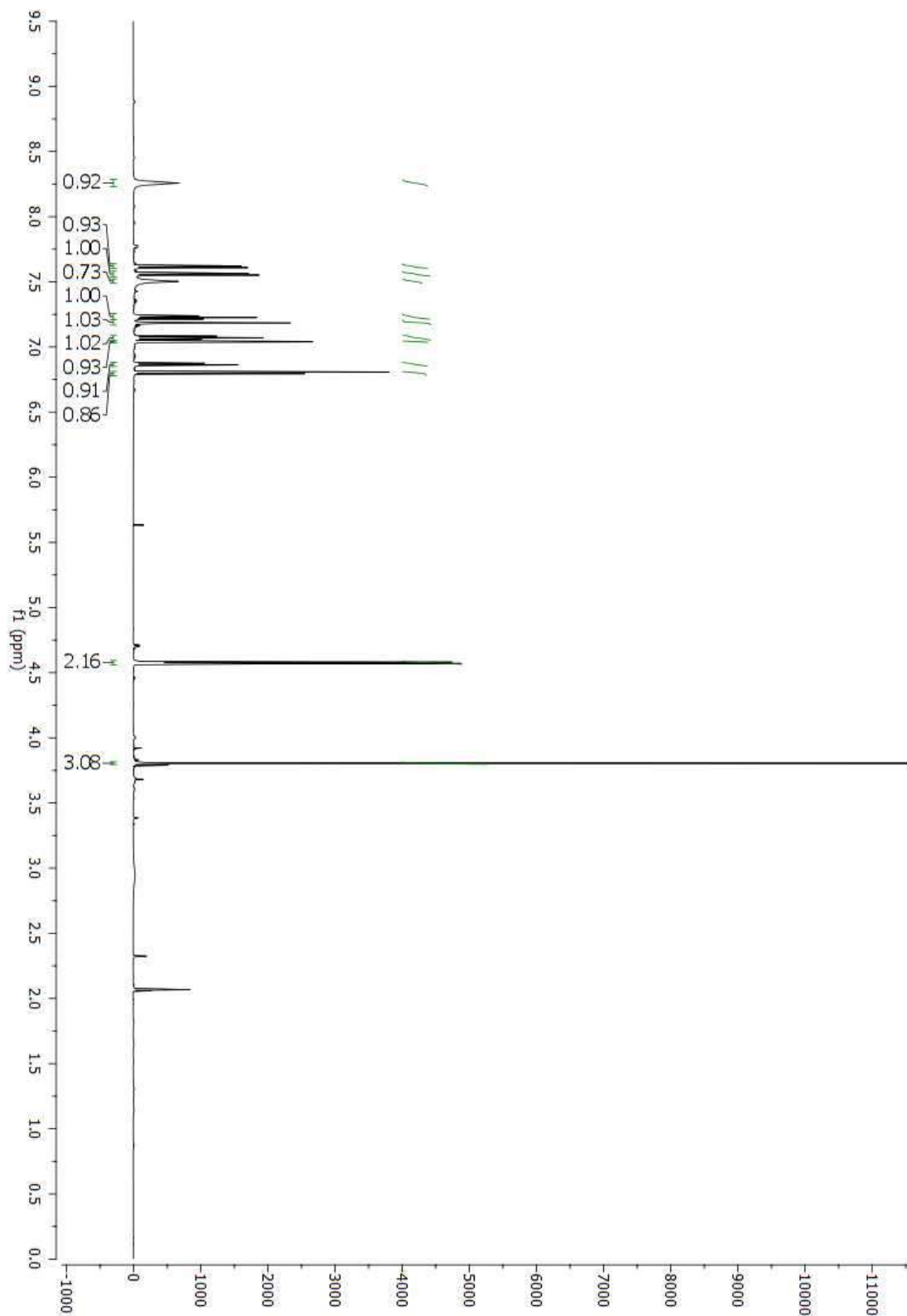
#	RT [min]	Area	Area Frac. %	I	S/N
1	5.3	1719.6	100.00	666	148.0

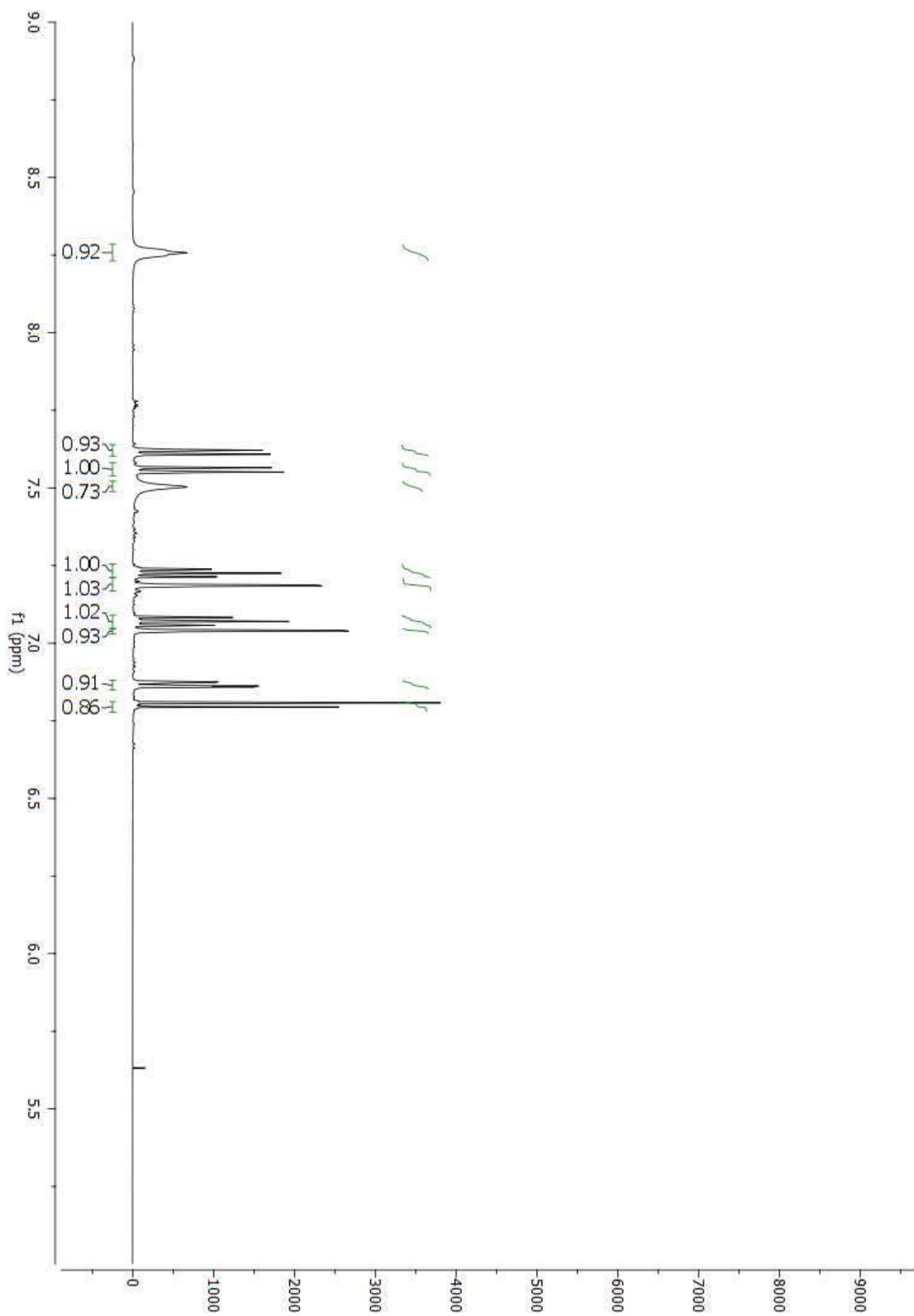
***N*-(4-Hydroxy-3-methoxybenzyl)-1*H*-indole-2-carboxamide (5f)**

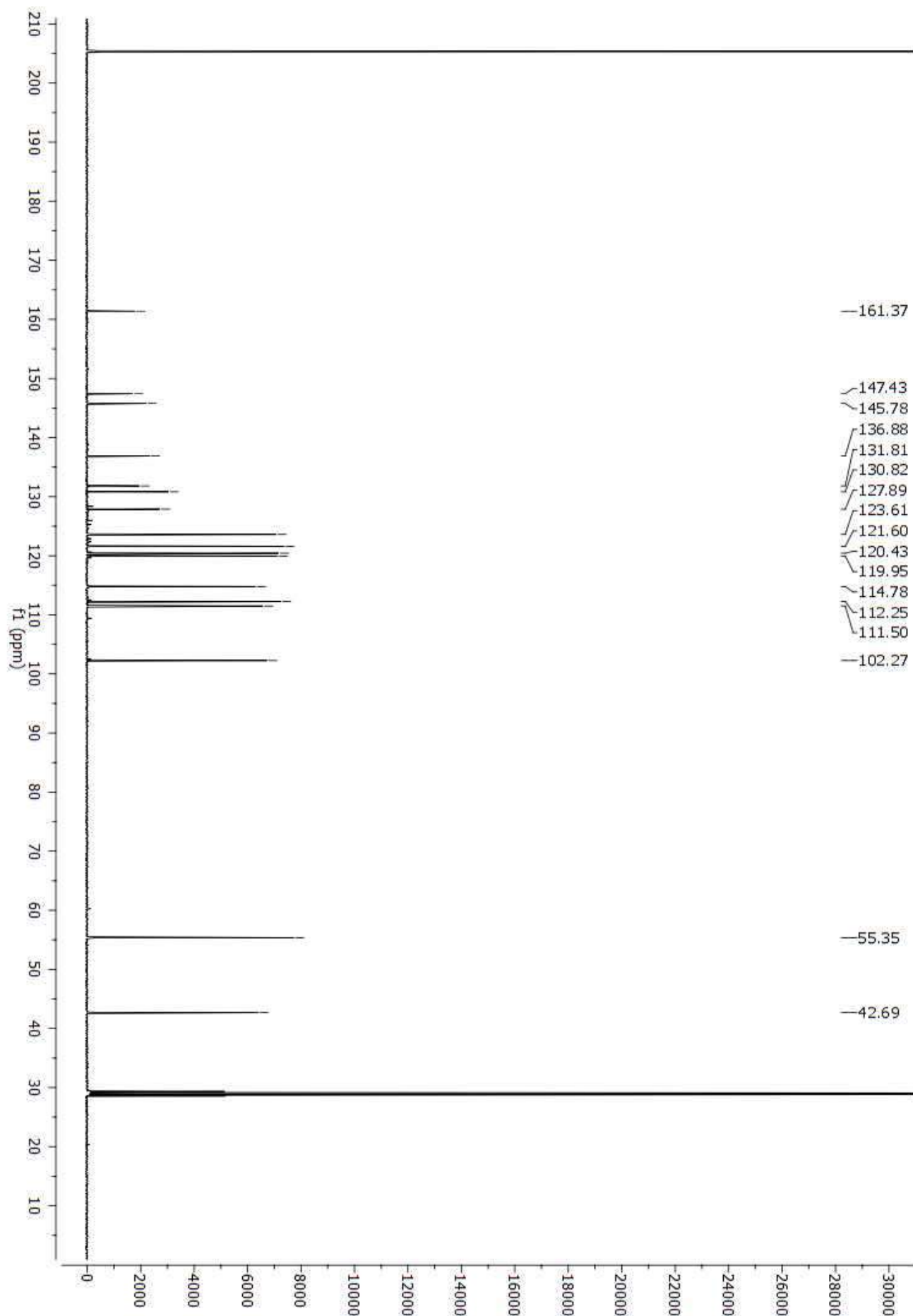


C₁₇H₁₆N₂O₃

MW 296.33





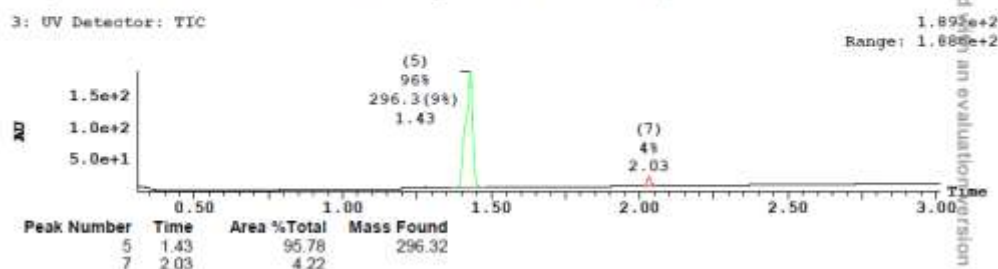


Printed: Thu Aug 30 10:30:57 2018

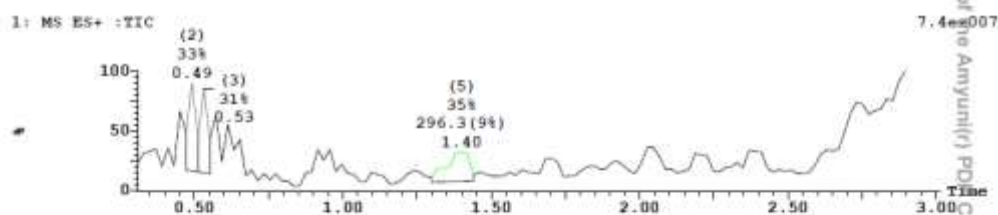
Sample Report (continued):

Sample 8 Vial 1:A.9 ID File I-0416572-001 Date 29-Aug-2018 Time 13:30:57 Description Met Gen

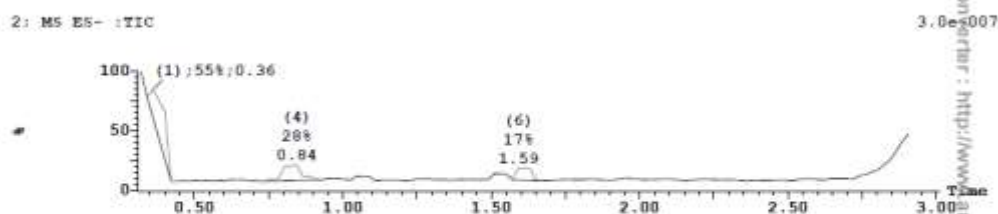
3: UV Detector: TIC



1: MS ES+ :TIC



2: MS ES- :TIC



Peak ID Time Mass Found

5: (Time: 1.43)

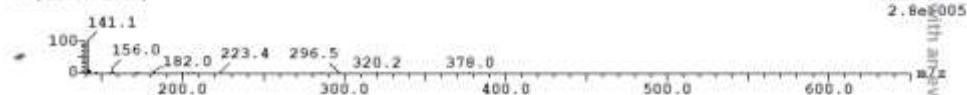


Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

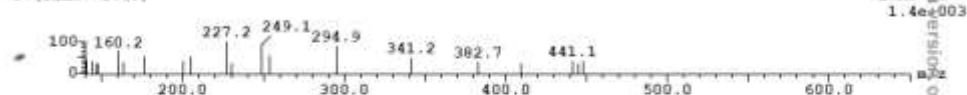
Peak ID Time Mass Found

7: (Time: 2.03)



Peak ID Time Mass Found

5: (Time: 1.43)

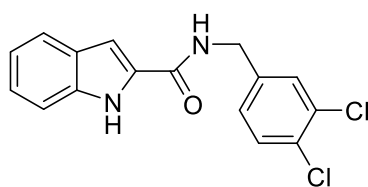


Peak ID Time Mass Found

7: (Time: 2.03)

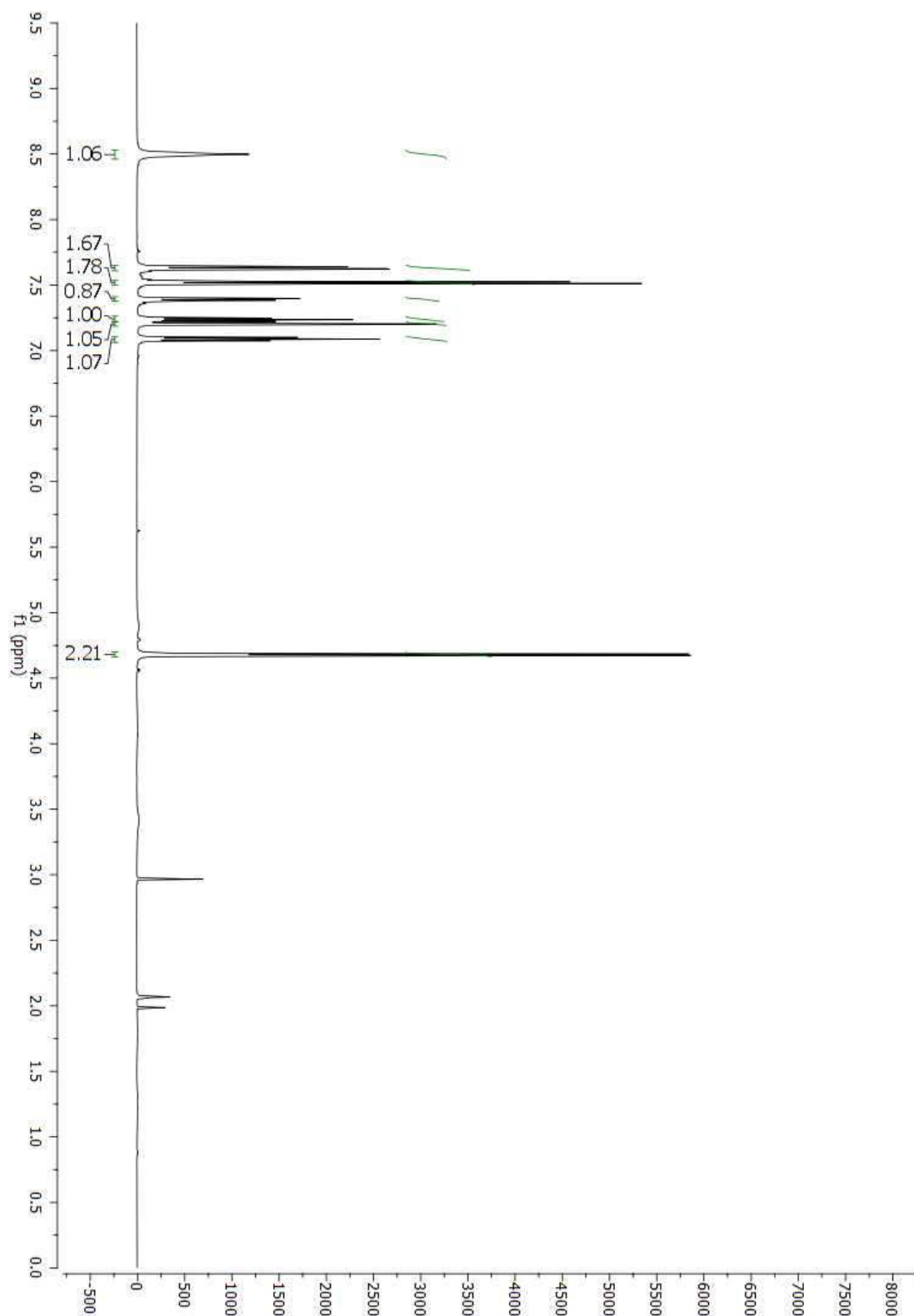


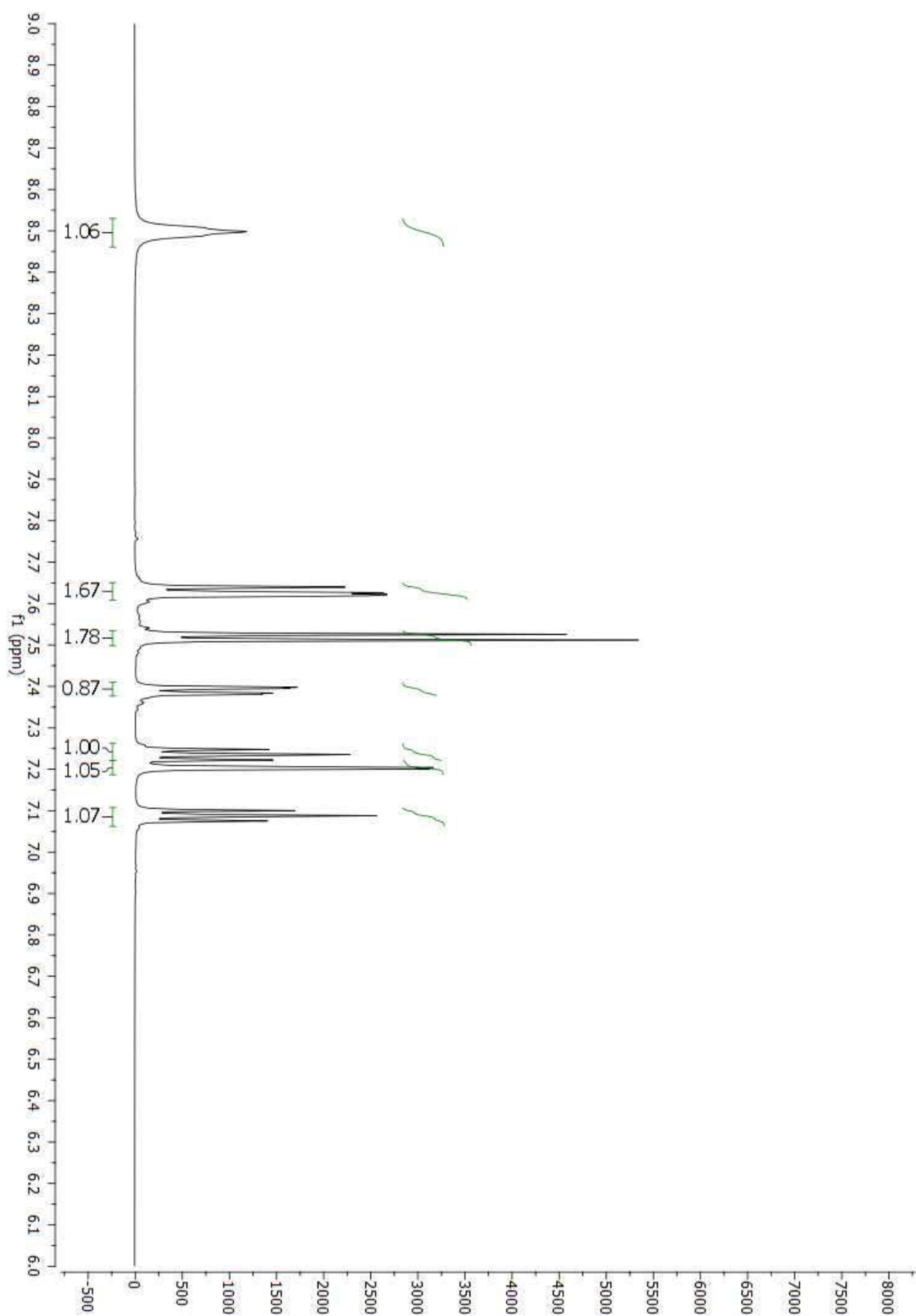
N-(3,4-Dichlorobenzyl)-1H-indole-2-carboxamide (5g)

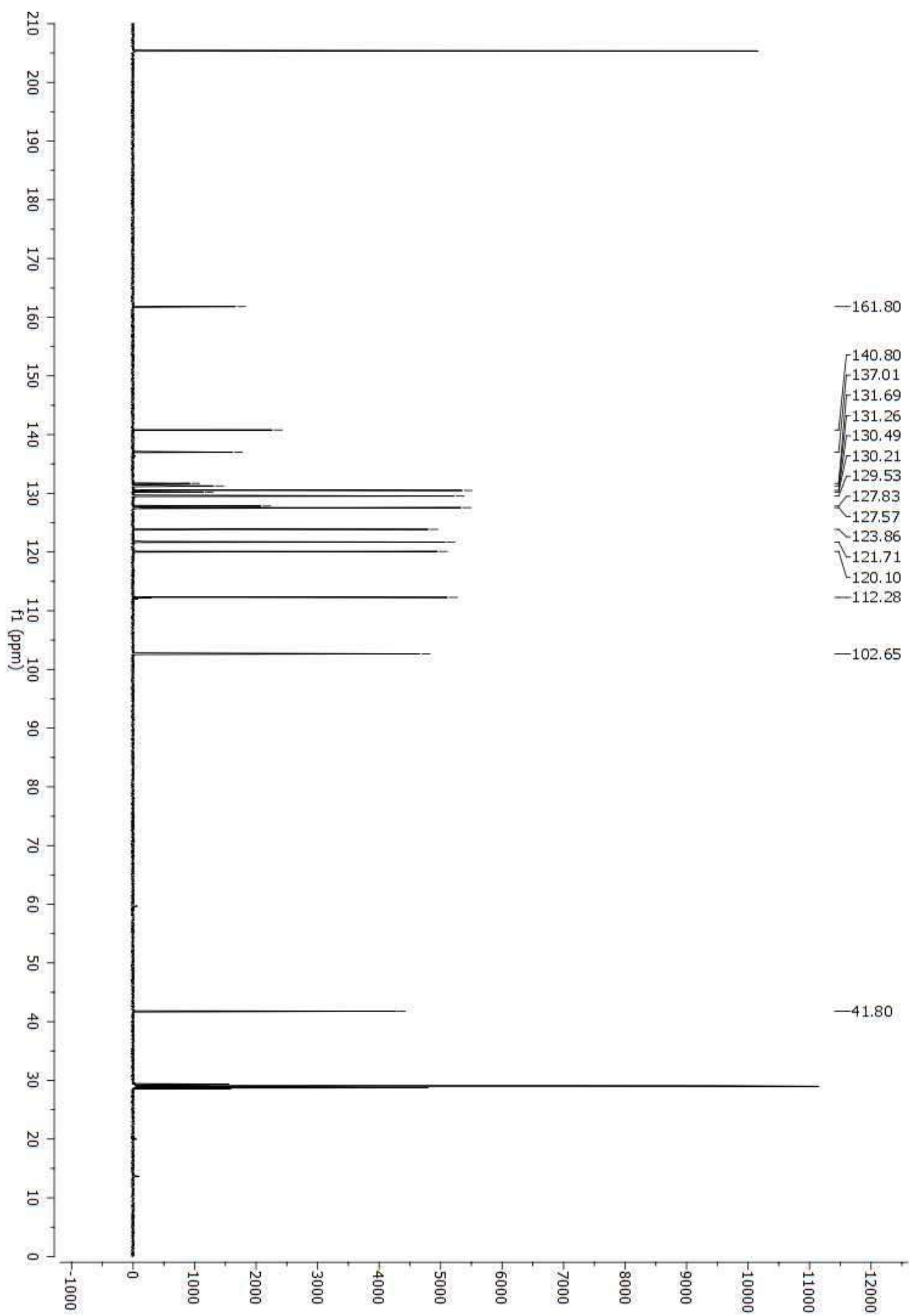


$C_{16}H_{12}Cl_2N_2O$

MW 319.18





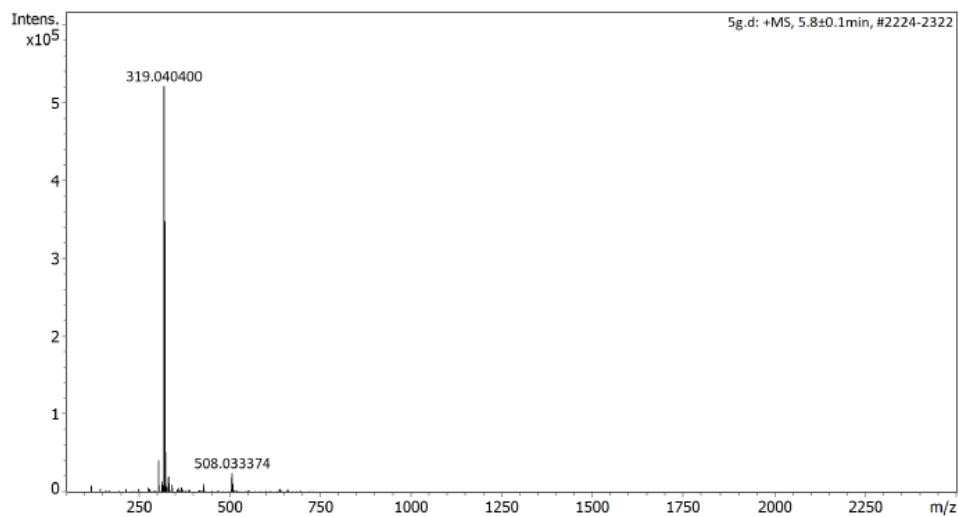
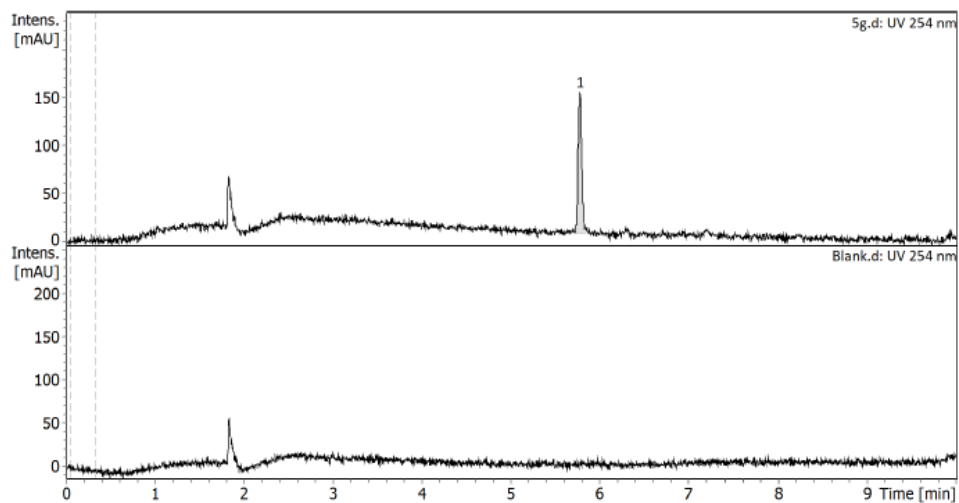


Analysis Info

Method MS_LC_POS_TimsOFF.m
Sample Name MSP26

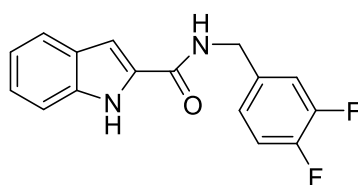
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



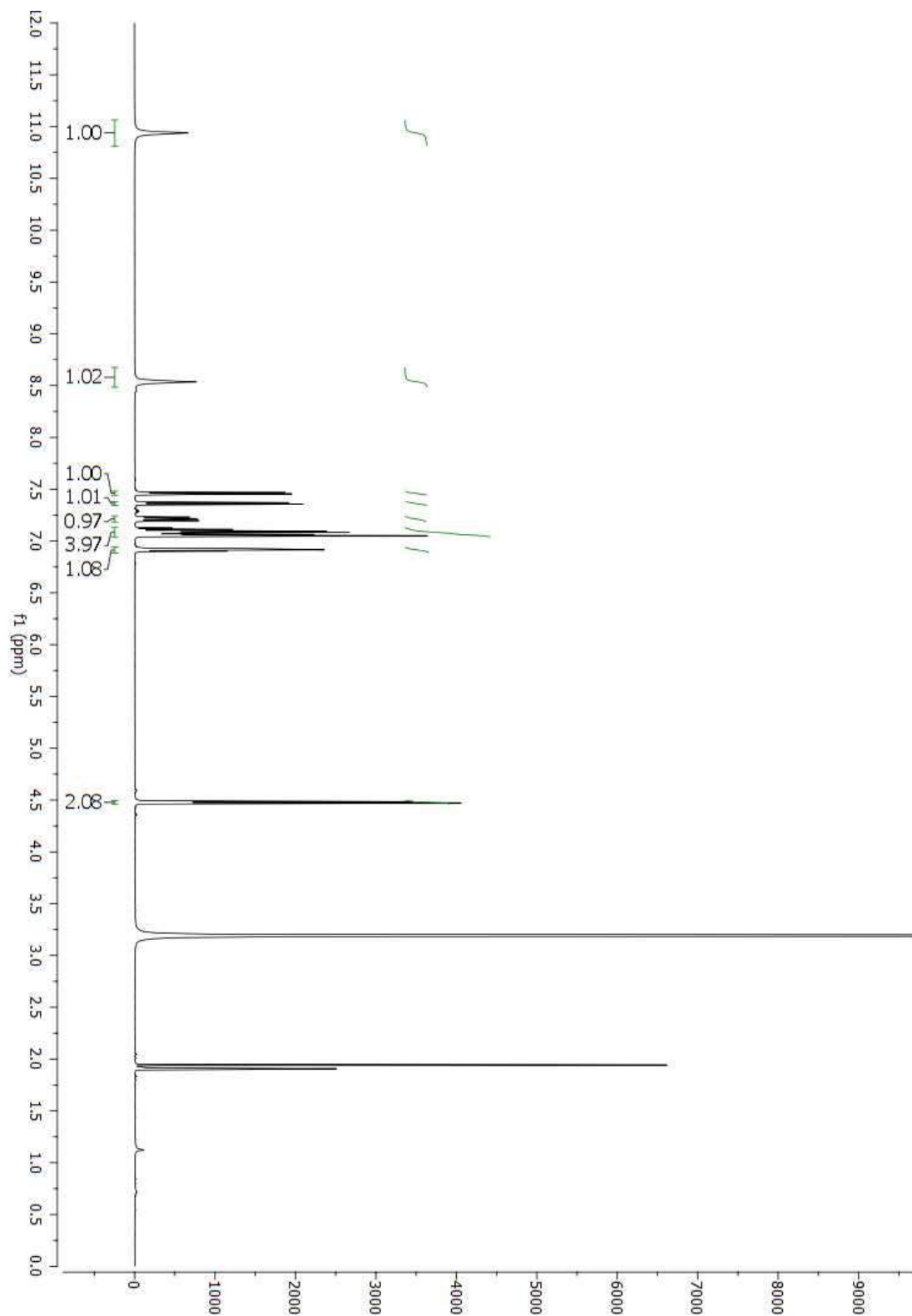
#	RT [min]	Area	Area Frac. %	I	S/N
1	5.8	400.50	100.00	156	63.6

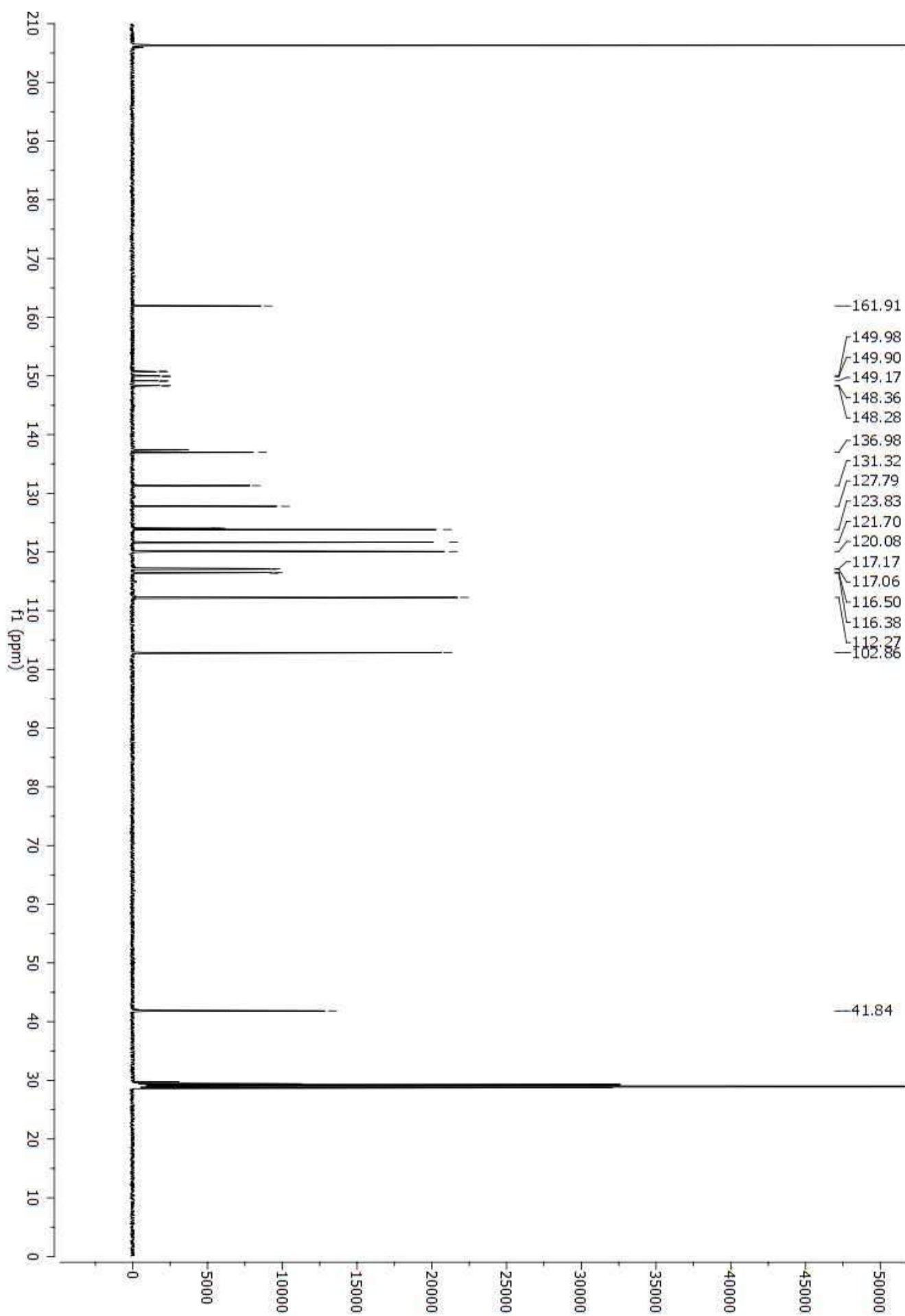
***N*-(3,4-Difluorobenzyl)-1*H*-indole-2-carboxamide (5h)**



C₁₆H₁₂F₂N₂O

MW 286.28



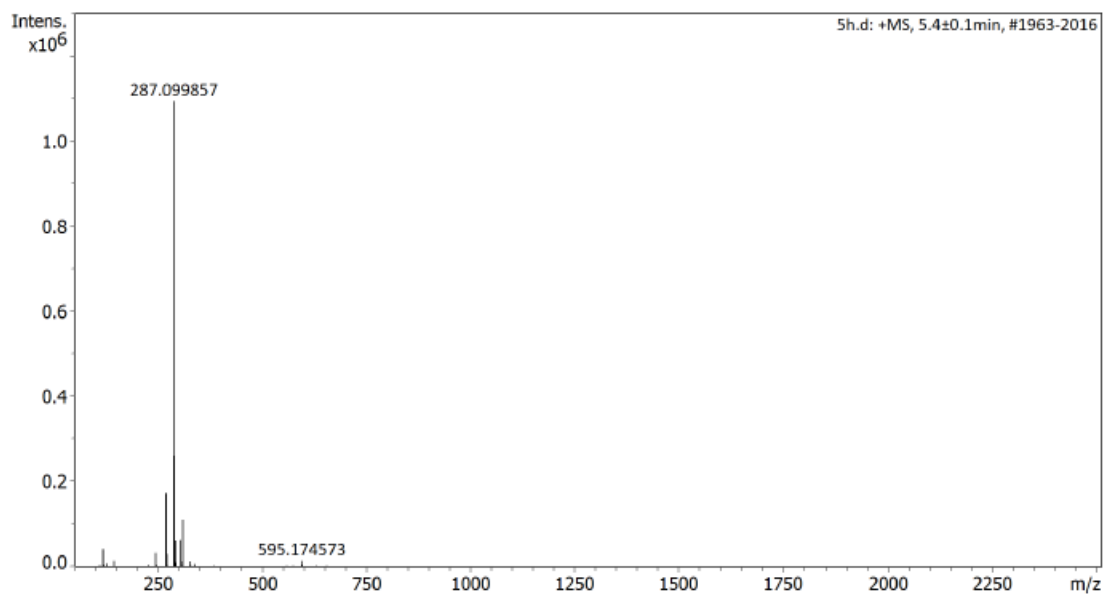
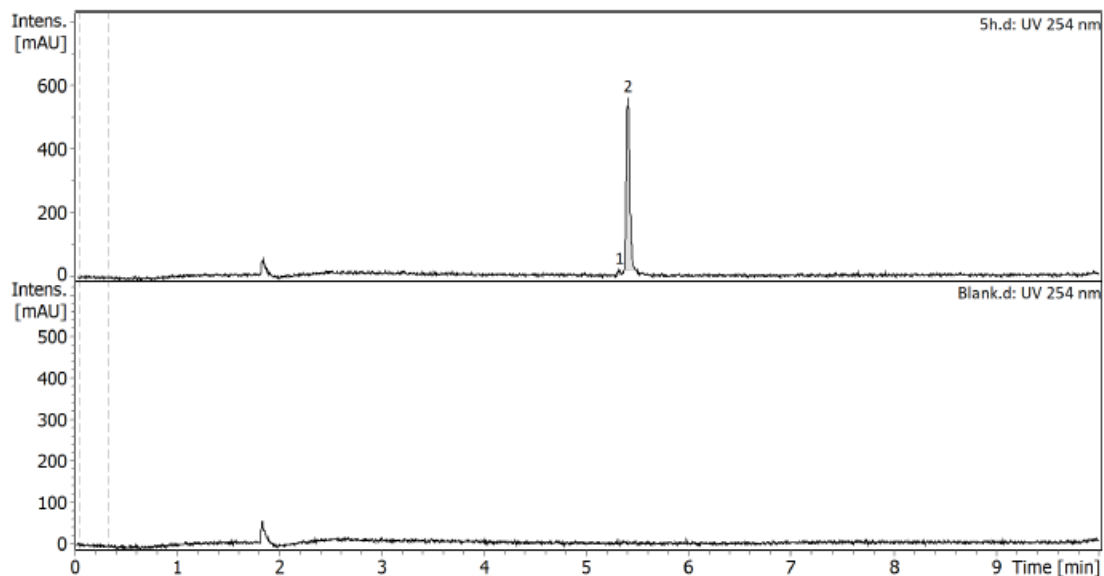


Analysis Info

Method MS_LC_POS_TimsOFF.m
Sample Name MSP138

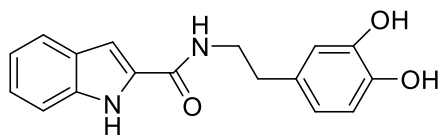
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



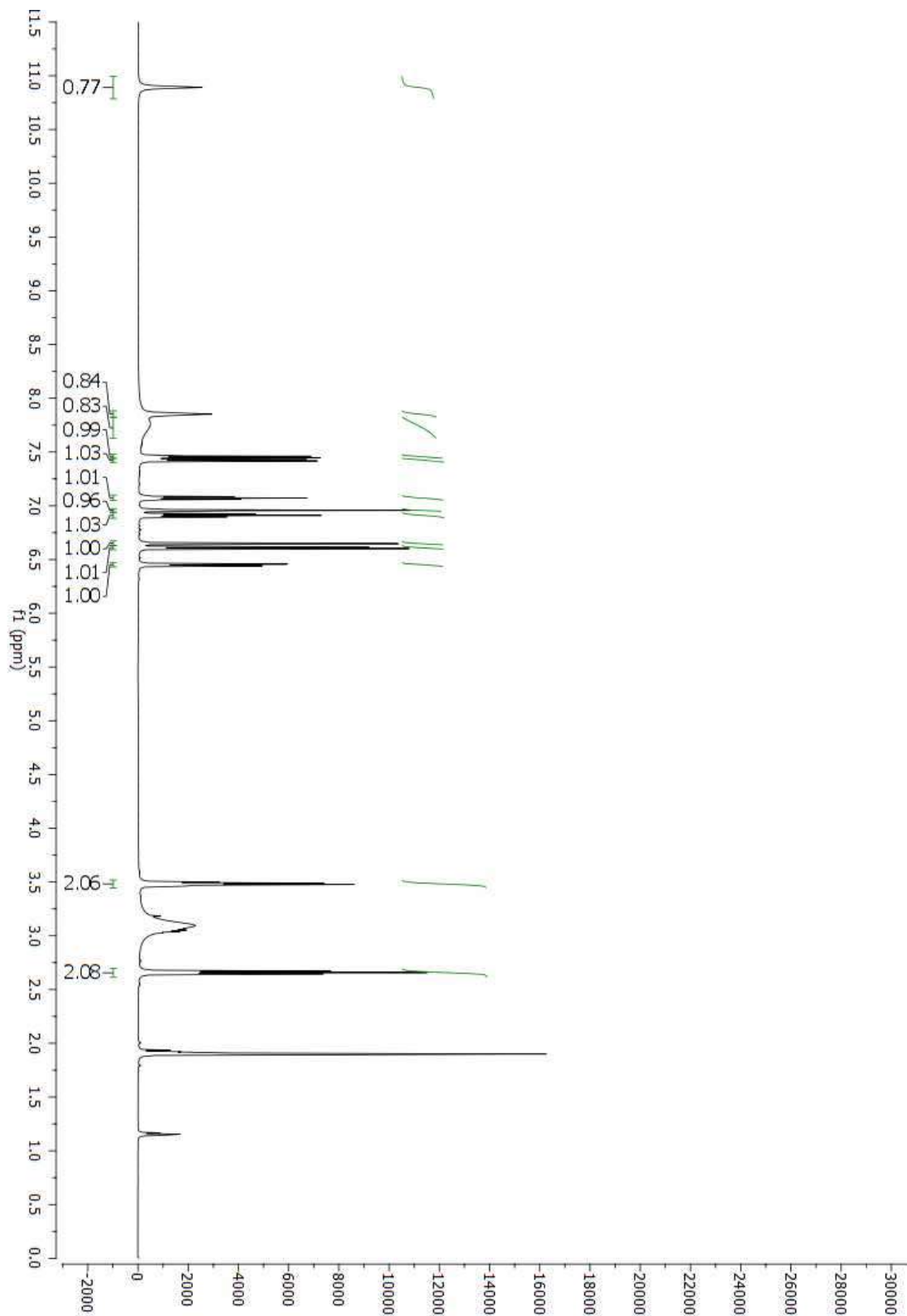
#	RT [min]	Area	Area Frac. %	I	S/N
1	5.3	24.080	1.79	23	5.3
2	5.4	1322.066	98.21	563	180.8

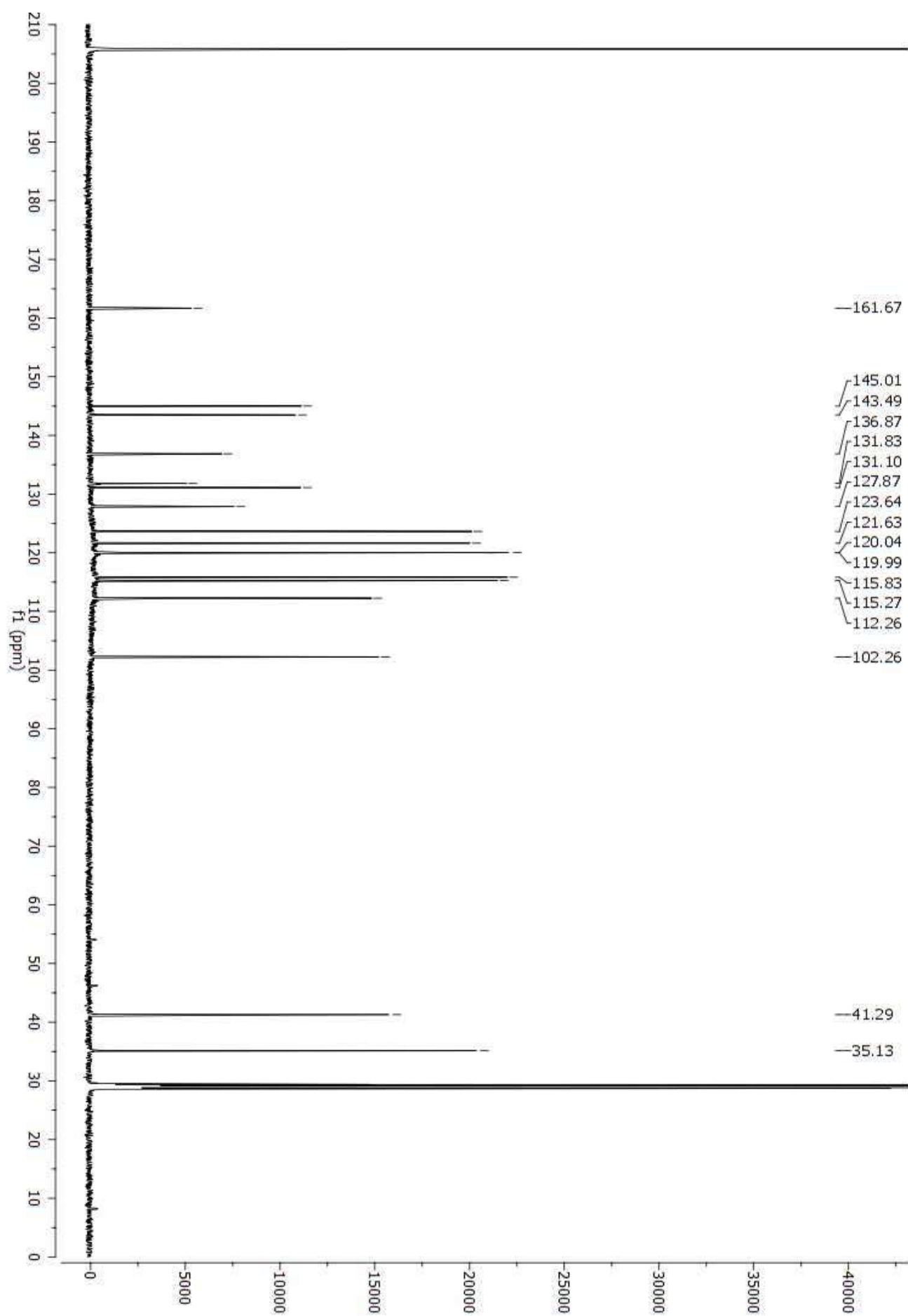
***N*-(3,4-Dihydroxyphenethyl)-1*H*-indole-2-carboxamide (5i)**



C₁₇H₁₆N₂O₃

MW 296.33



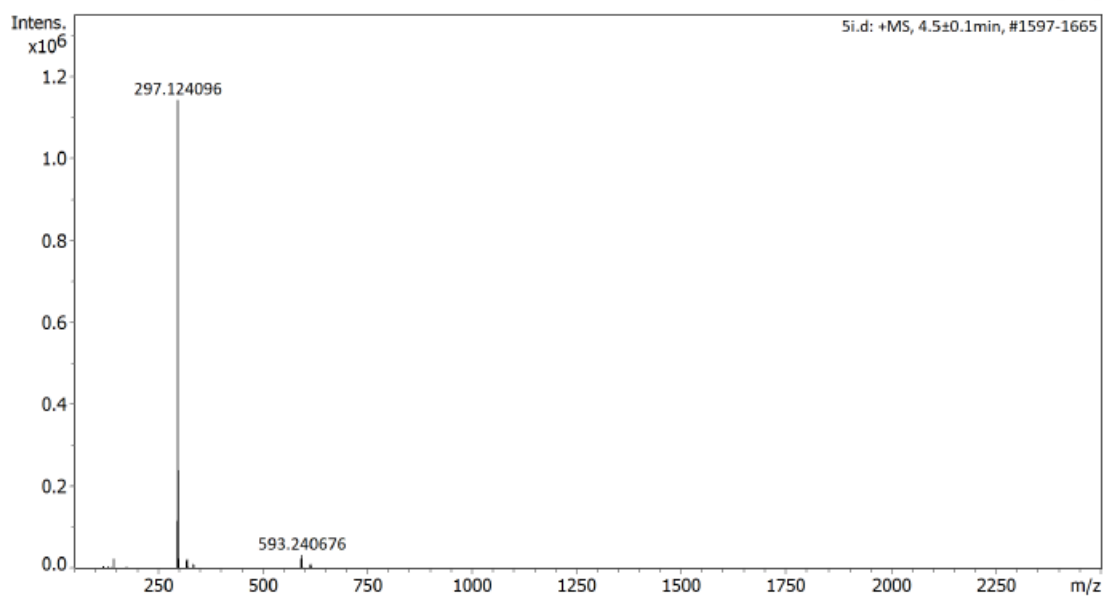
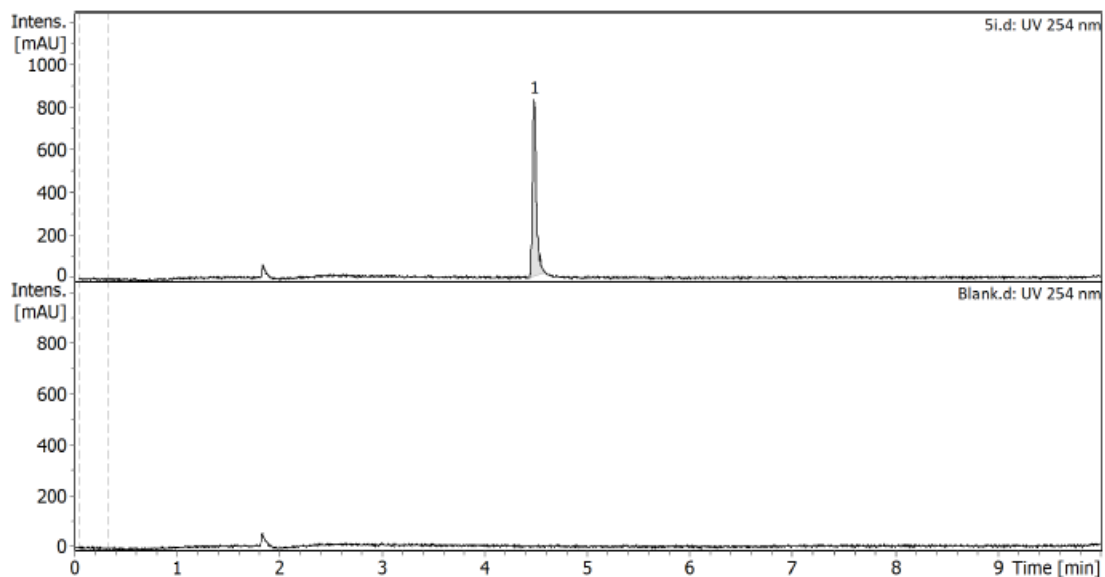


Analysis Info

Method MS_LC_POS_TimsOFF.m
Sample Name MSP28

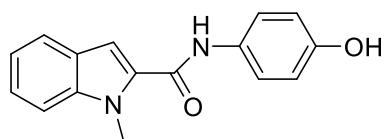
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



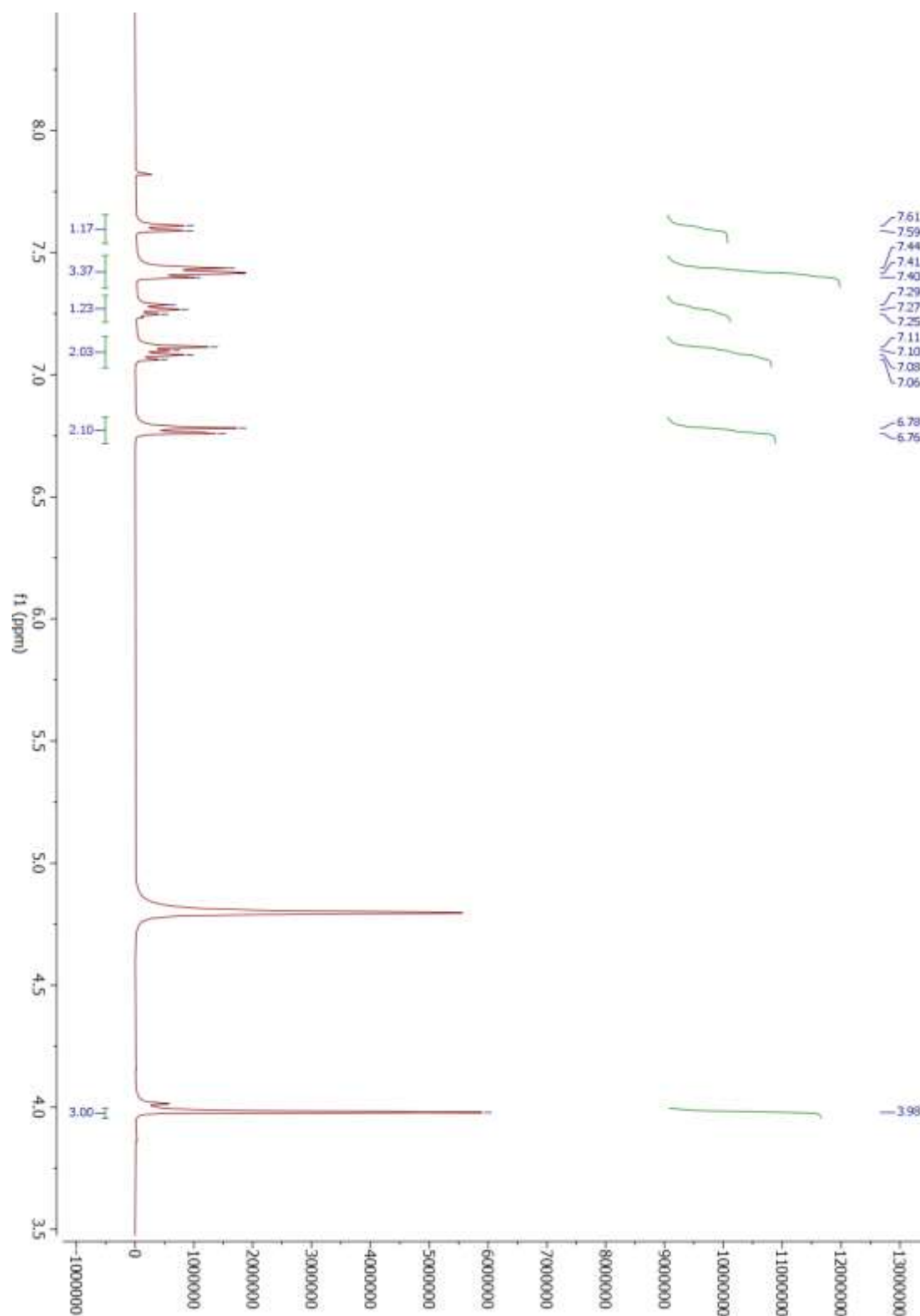
#	RT [min]	Area	Area Frac. %	I	S/N
1	4.5	2220.1	100.00	840	277.2

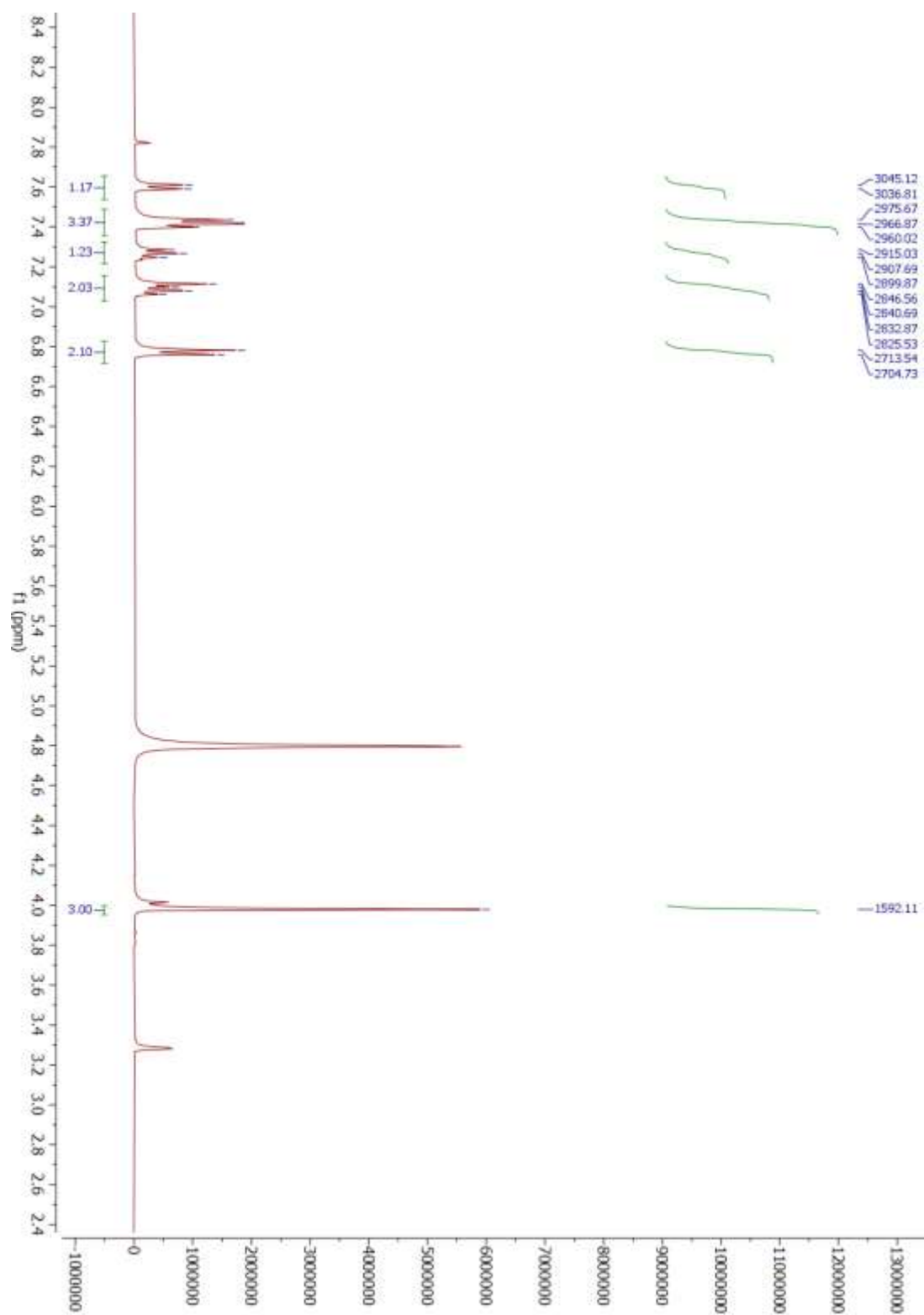
***N*-(4-Hydroxyphenyl)-1-methyl-1*H*-indole-2-carboxamide (6a)**

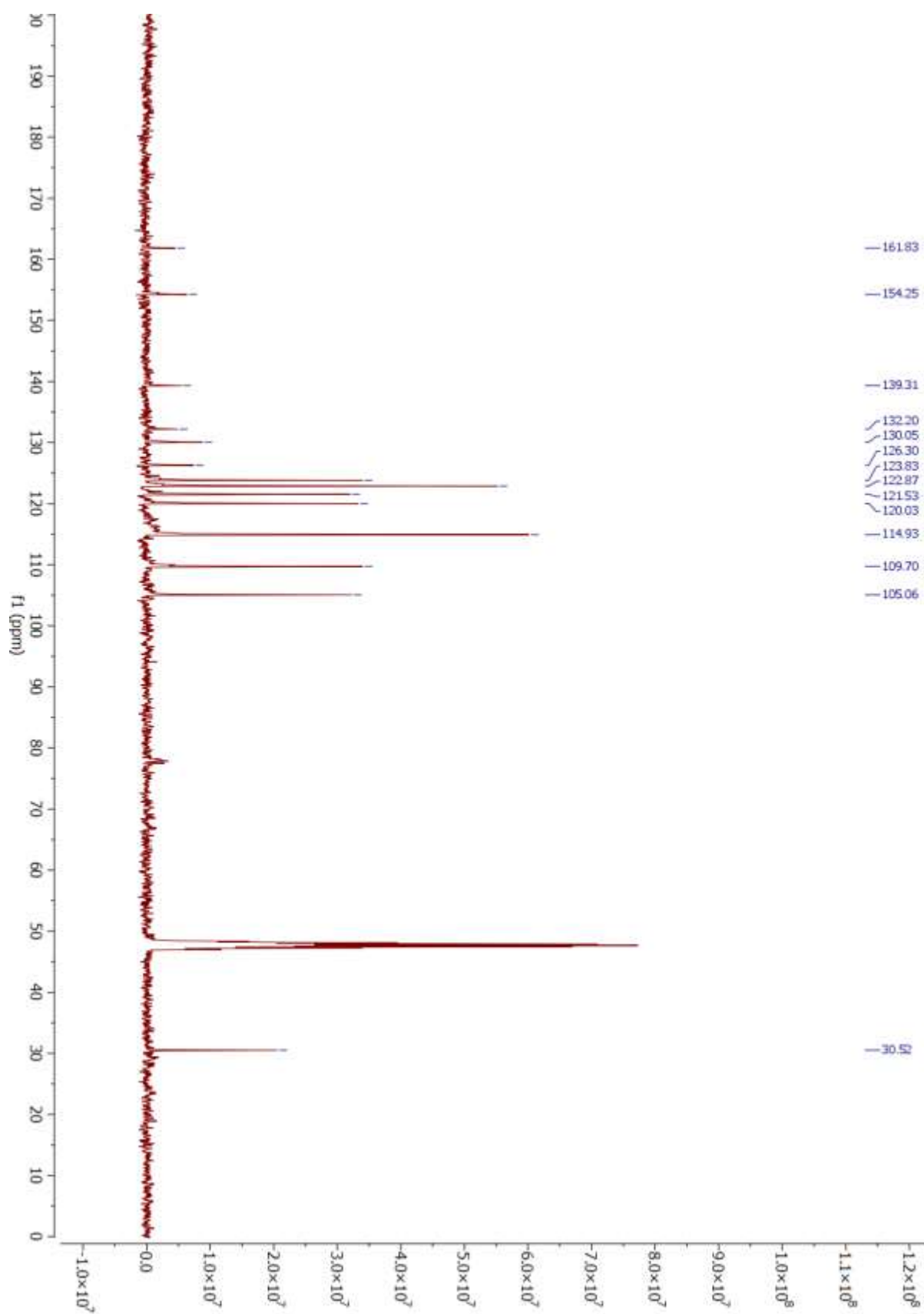


C₁₆H₁₄N₂O₂

MW 266.30





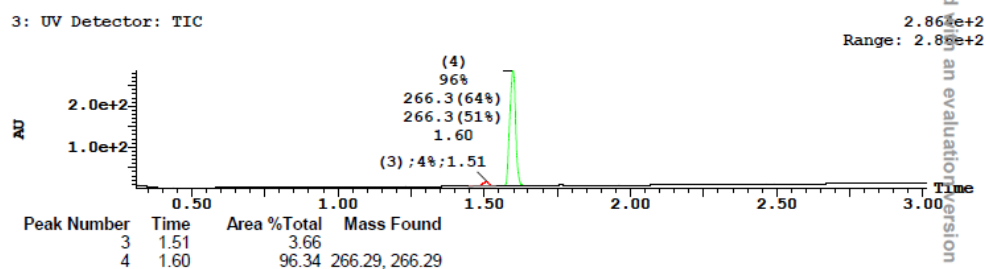


Printed: Thu Aug 30 10:30:57 2018

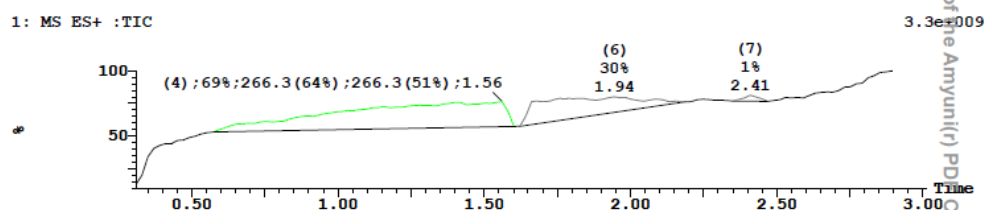
Sample Report (continued):

Sample 28 Vial 1:C,9 ID File I-0416592-001 Date 29-Aug-2018 Time 14:59:16 Description Met Gen

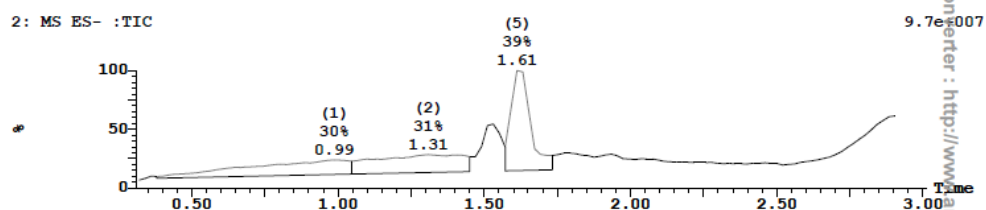
3: UV Detector: TIC



1: MS ES+ :TIC



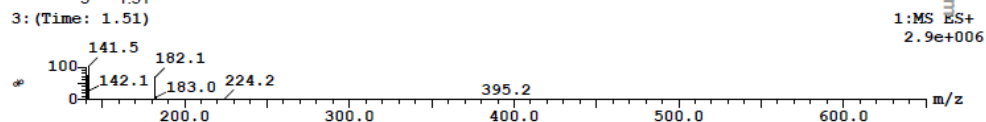
2: MS ES- :TIC



Peak ID Time Mass Found

Peak ID	Time	Mass Found
3	1.51	

3: (Time: 1.51)



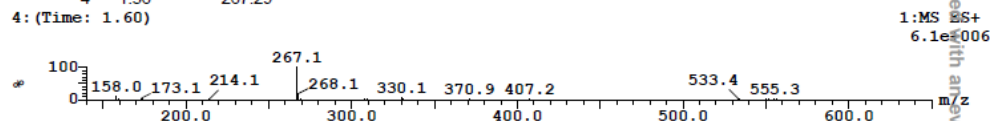
Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

Peak ID Time Mass Found

Peak ID	Time	Mass Found
4	1.56	267.29

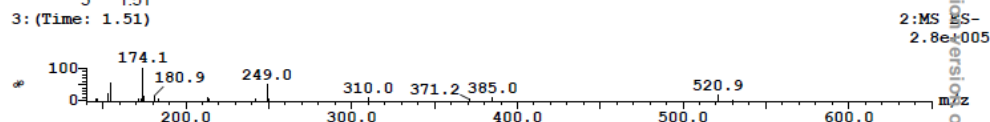
4: (Time: 1.60)



Peak ID Time Mass Found

Peak ID	Time	Mass Found
3	1.51	

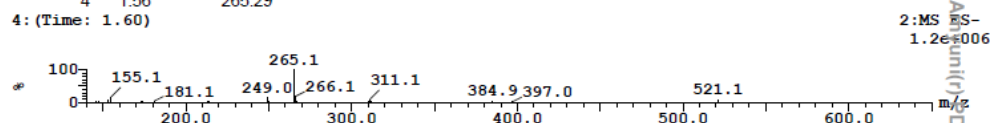
3: (Time: 1.51)



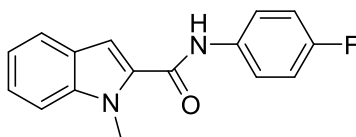
Peak ID Time Mass Found

Peak ID	Time	Mass Found
4	1.56	265.29

4: (Time: 1.60)

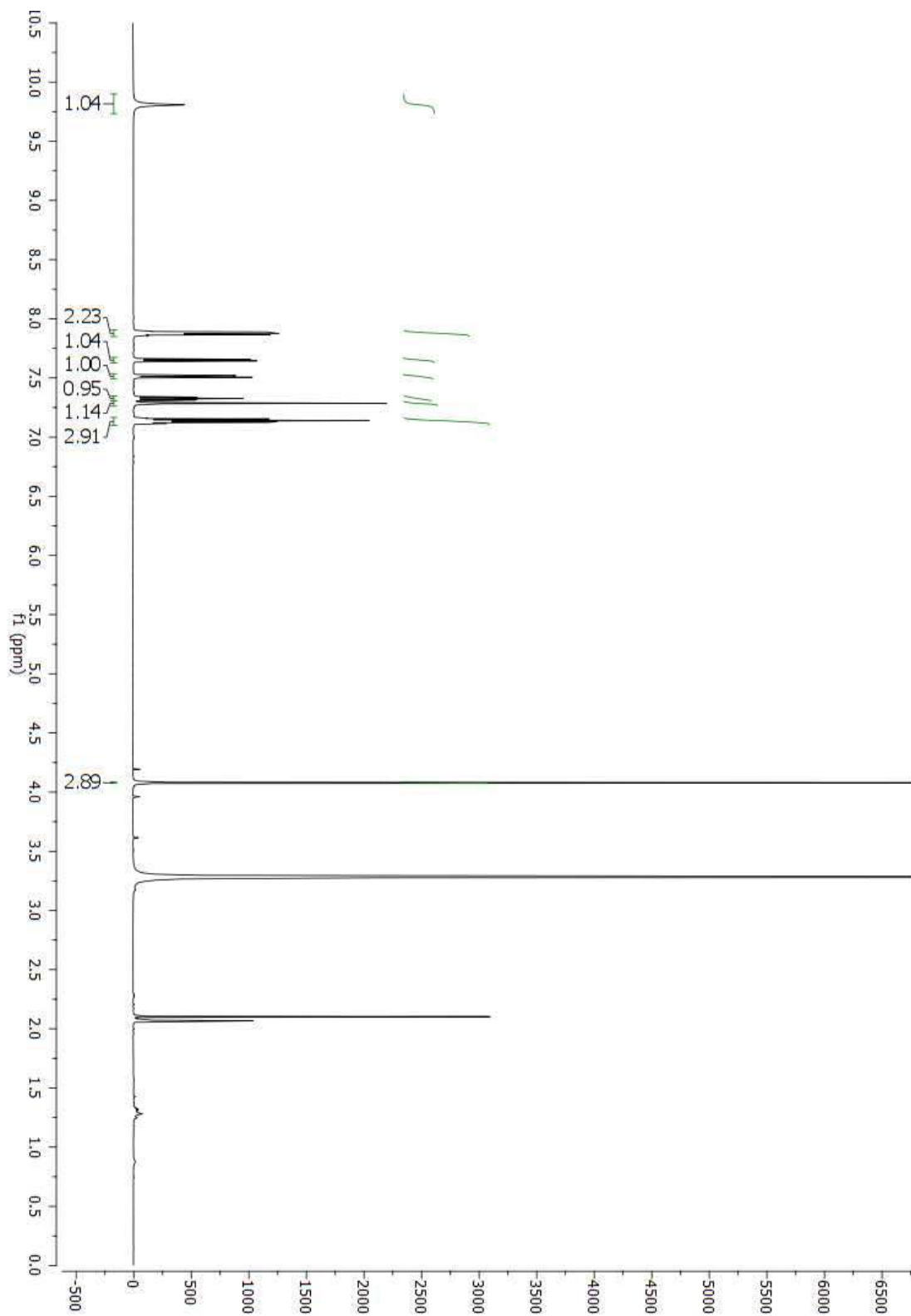


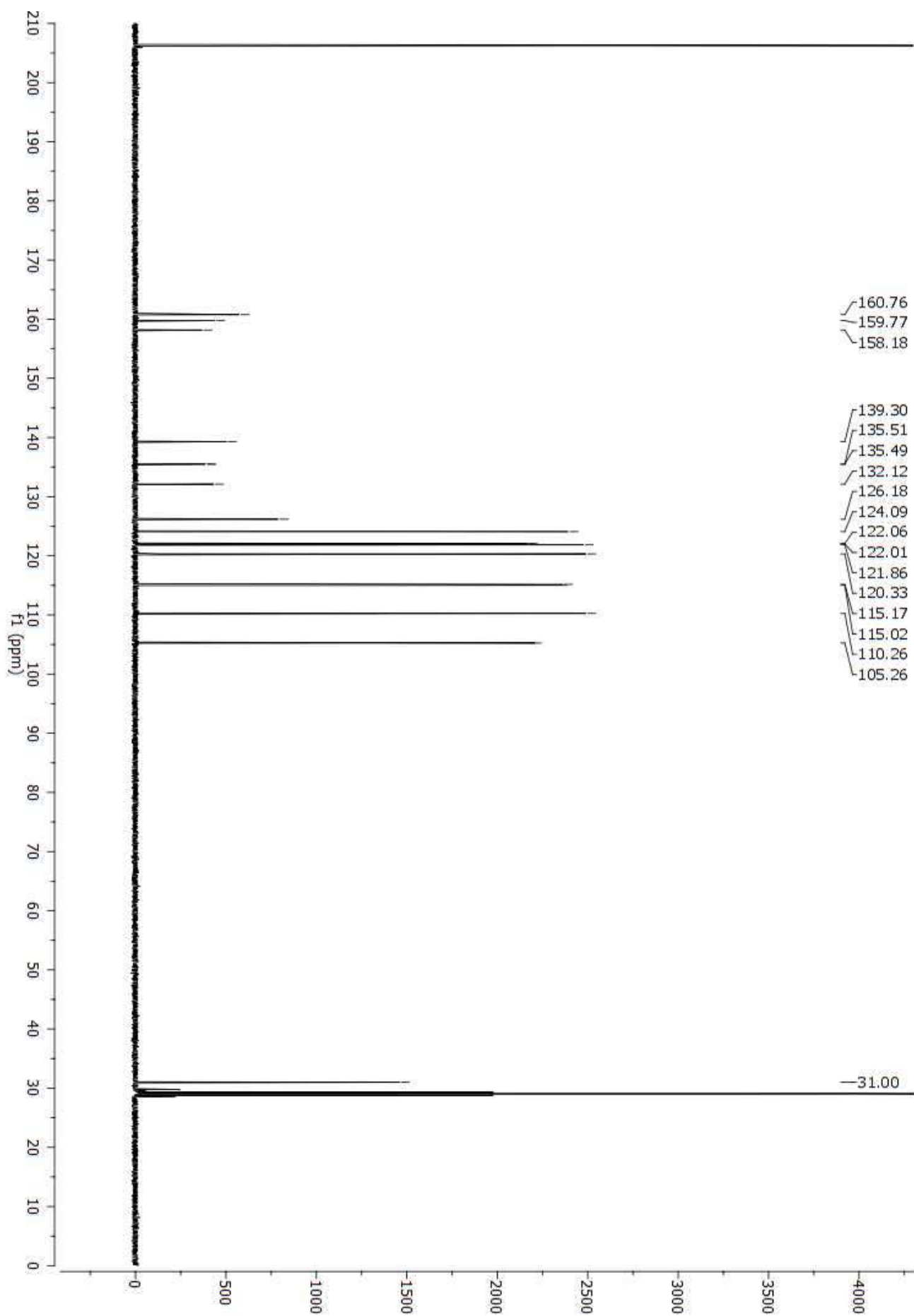
***N*-(4-Fluorophenyl)-1-methyl-1*H*-indole-2-carboxamide (6b)**



C₁₆H₁₃FN₂O

MW 268.29





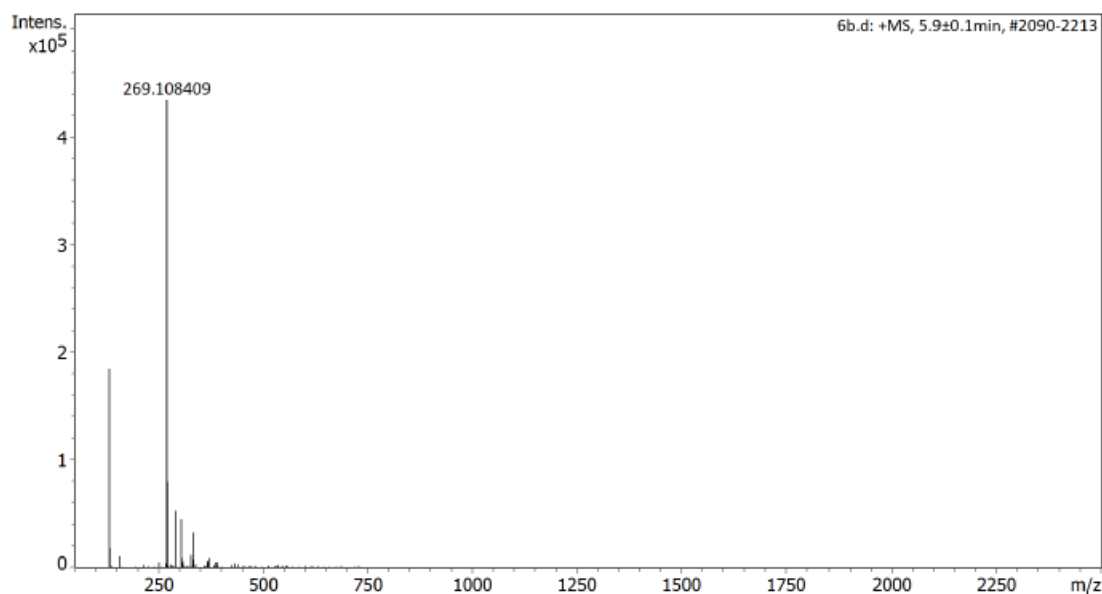
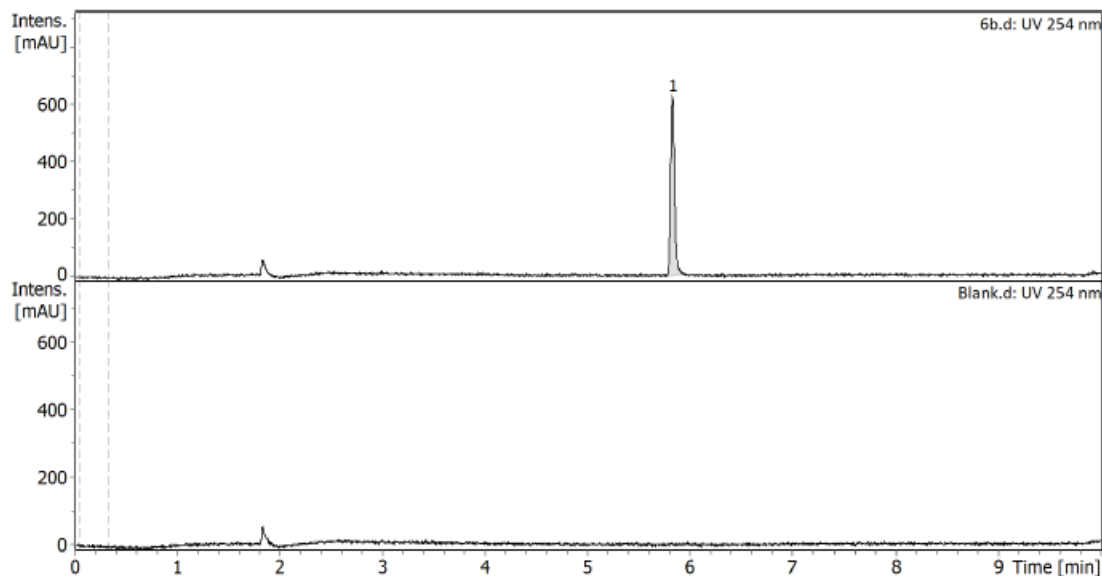
Analysis Info

Method MS_LC_POS_TimsOFF.m

Sample Name MSP141

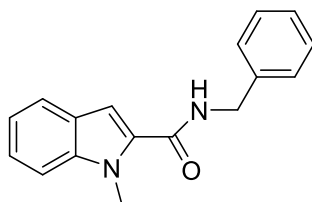
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



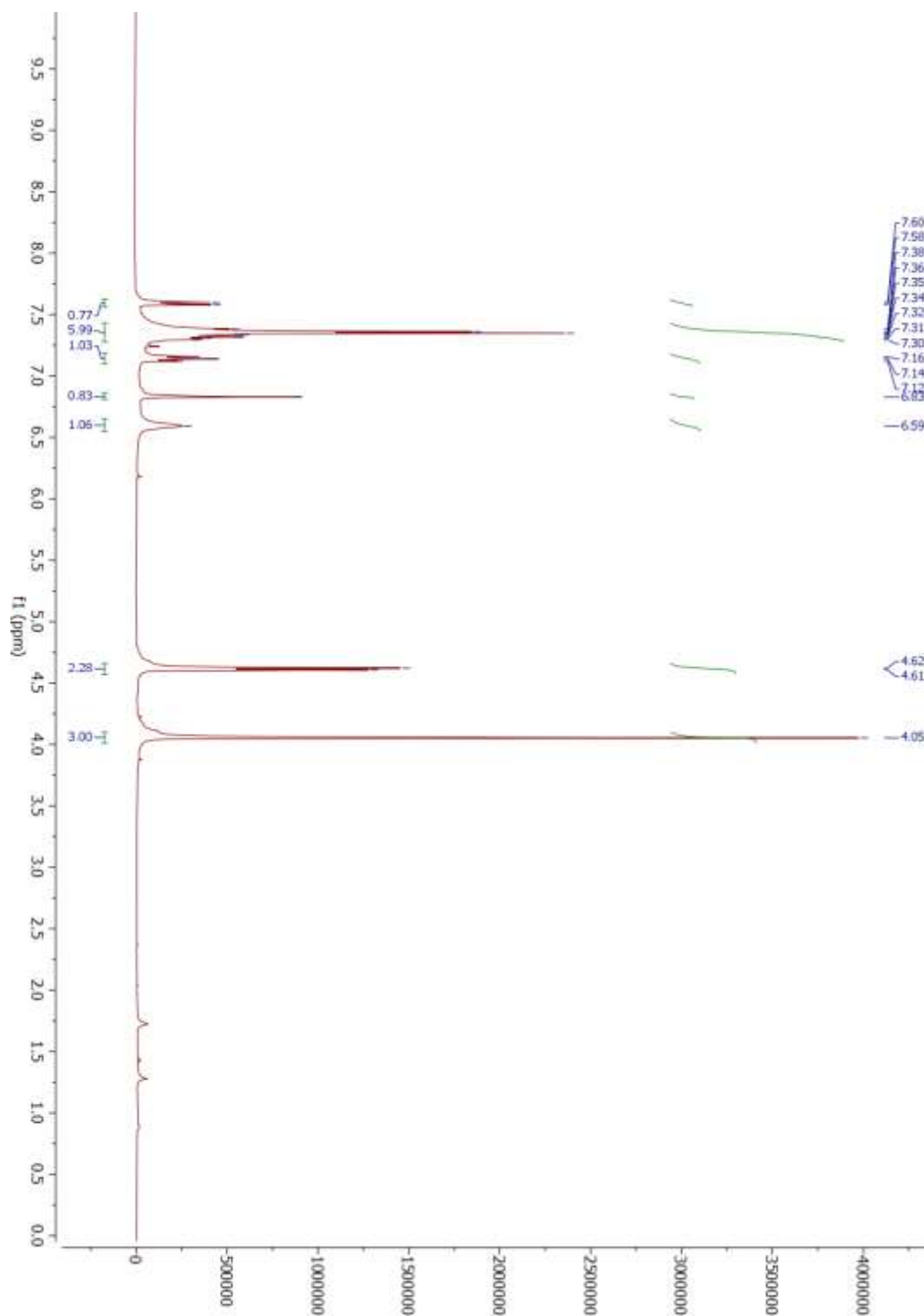
#	RT [min]	Area	Area Frac. %	I	S/N
1	5.8	1734.0	100.00	626	264.9

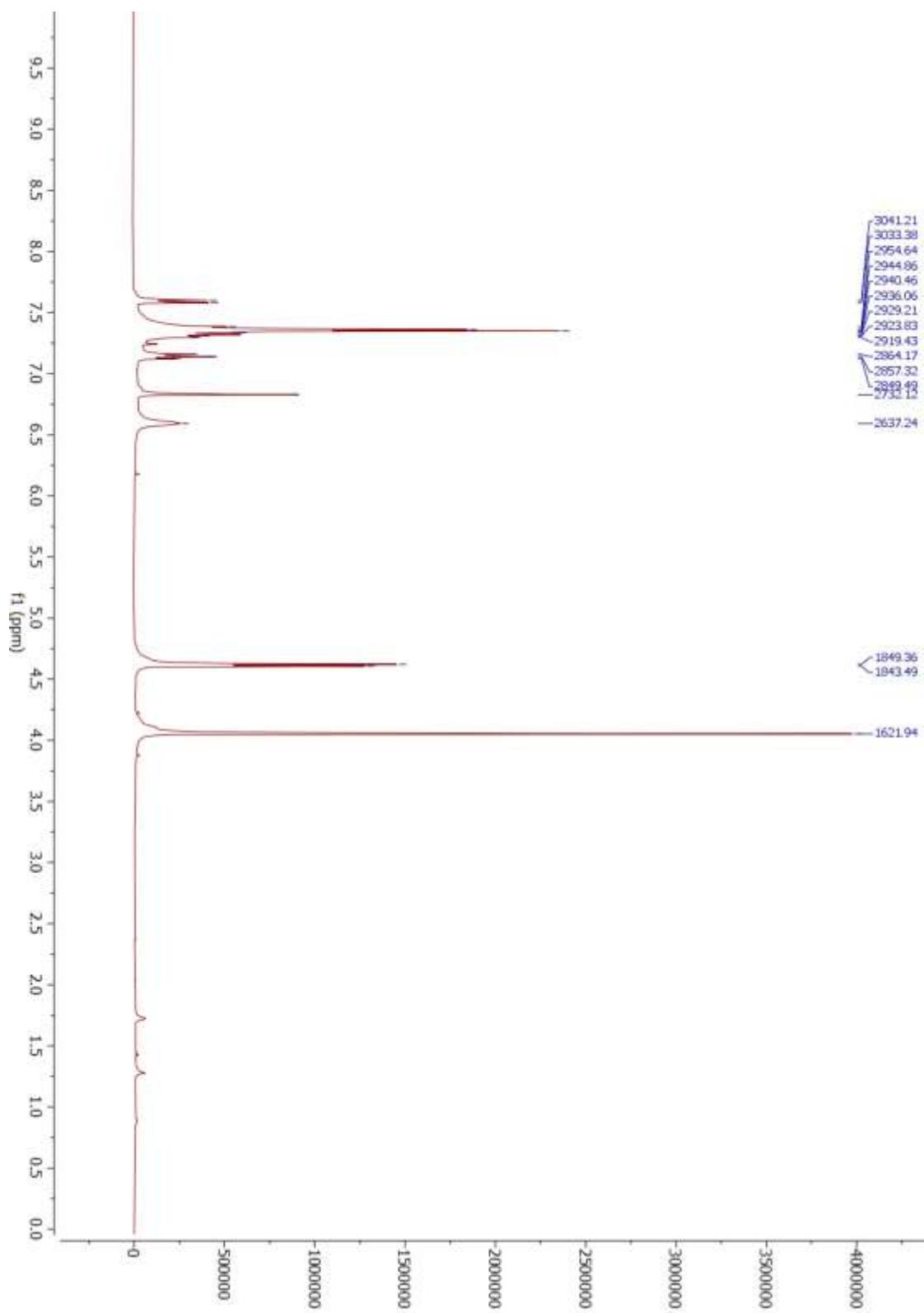
***N*-Benzyl-1-methyl-1*H*-indole-2-carboxamide (6c)**

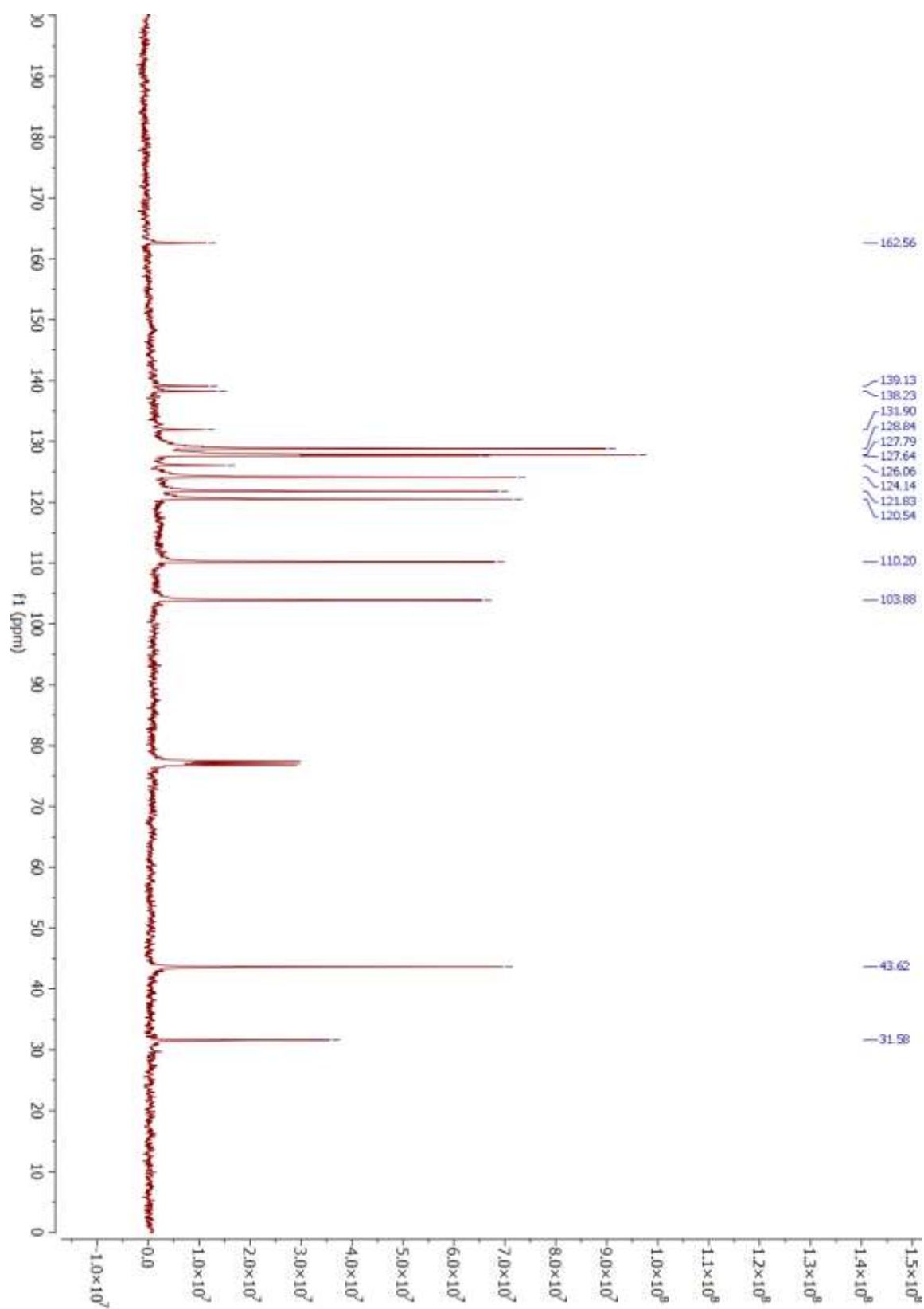


C₁₇H₁₆N₂O

MW 264.33







Openlynx Report -

Sample: 65
Date:29-Aug-2018

Vial:1:G,6
Time:17:43:20

File:I-0416627-001

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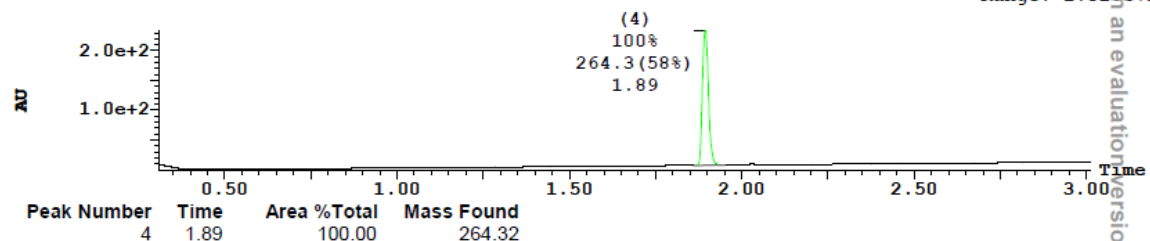
Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

Sample 65 Vial 1:G,6 ID File I-0416627-001 Date 29-Aug-2018 Time 17:43:20 Description Met Gen

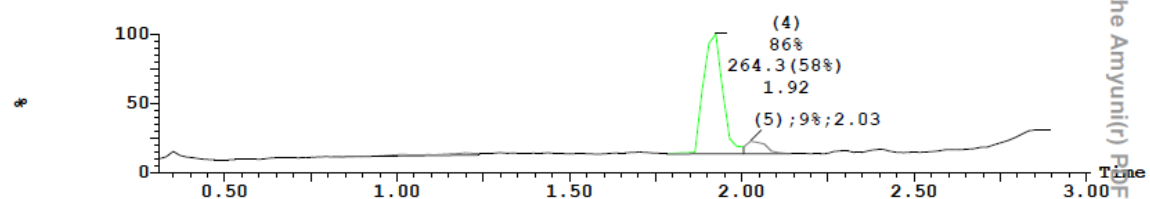
3: UV Detector: TIC

2.33e+2
Range: 2.32e+2



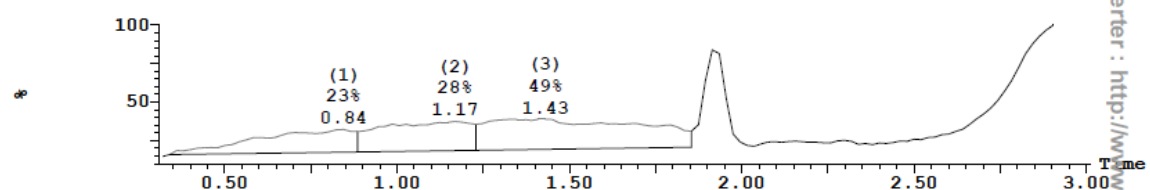
1: MS ES+ :TIC

1.5e+009



2: MS ES- :TIC

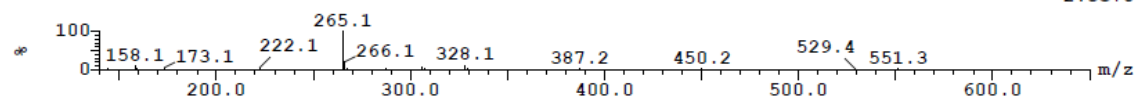
6.2e+007



Peak ID Time Mass Found
4 1.92 265.32

4: (Time: 1.89)

1:MS ES+
2.3e+007



Openlynx Report -

Sample: 65
Date:29-Aug-2018

Vial:1:G,6
Time:17:43:20

File:I-0416627-001

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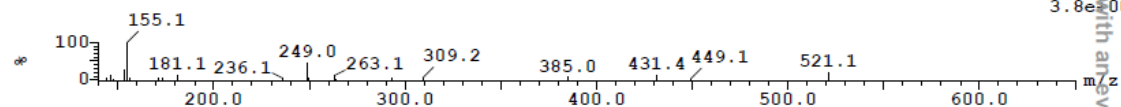
Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

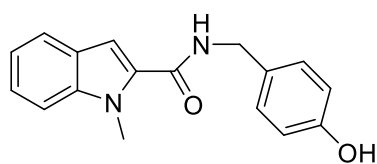
Peak ID Time Mass Found

4: (Time: 1.89)

2:MS ES-
3.8e+005

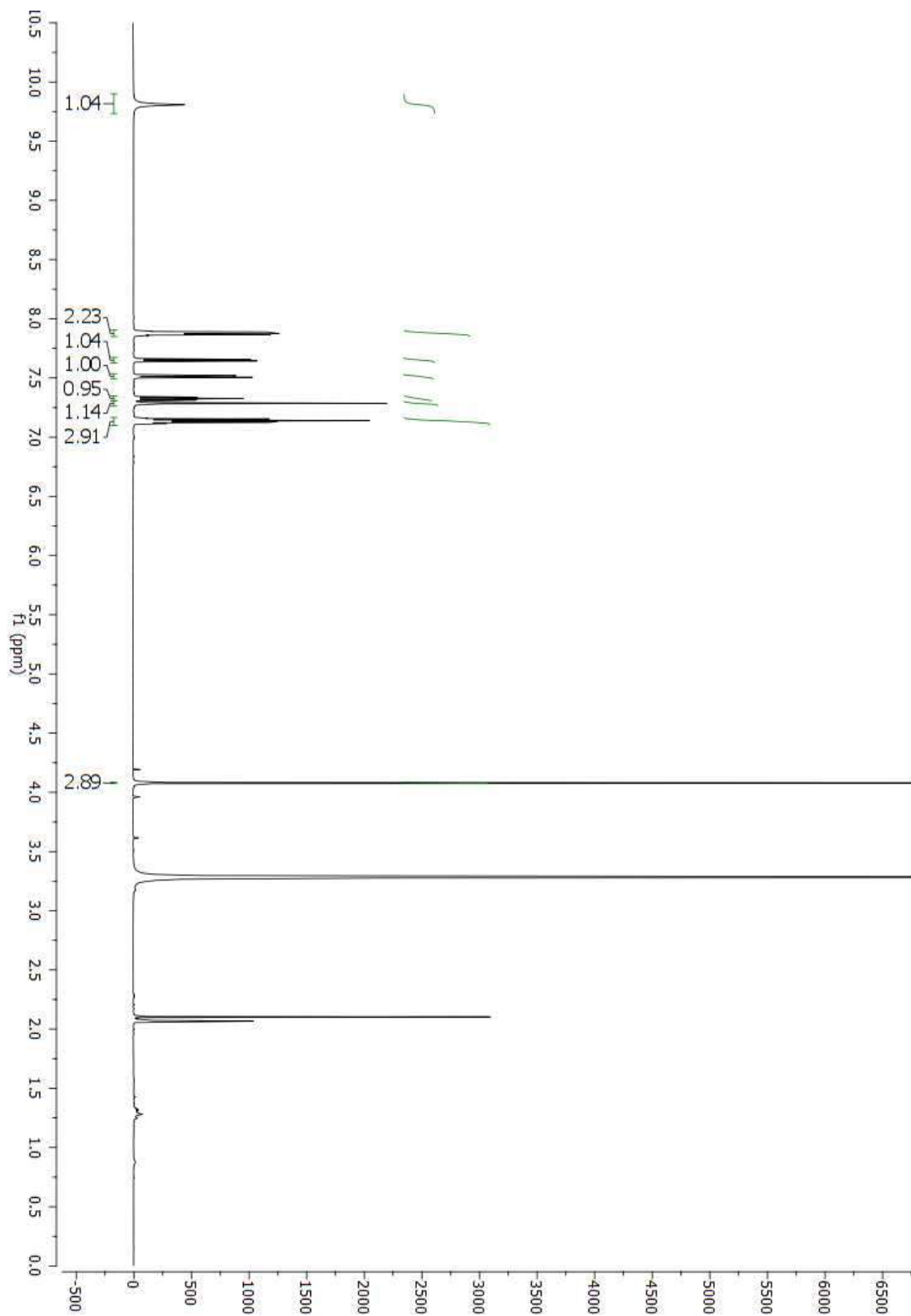


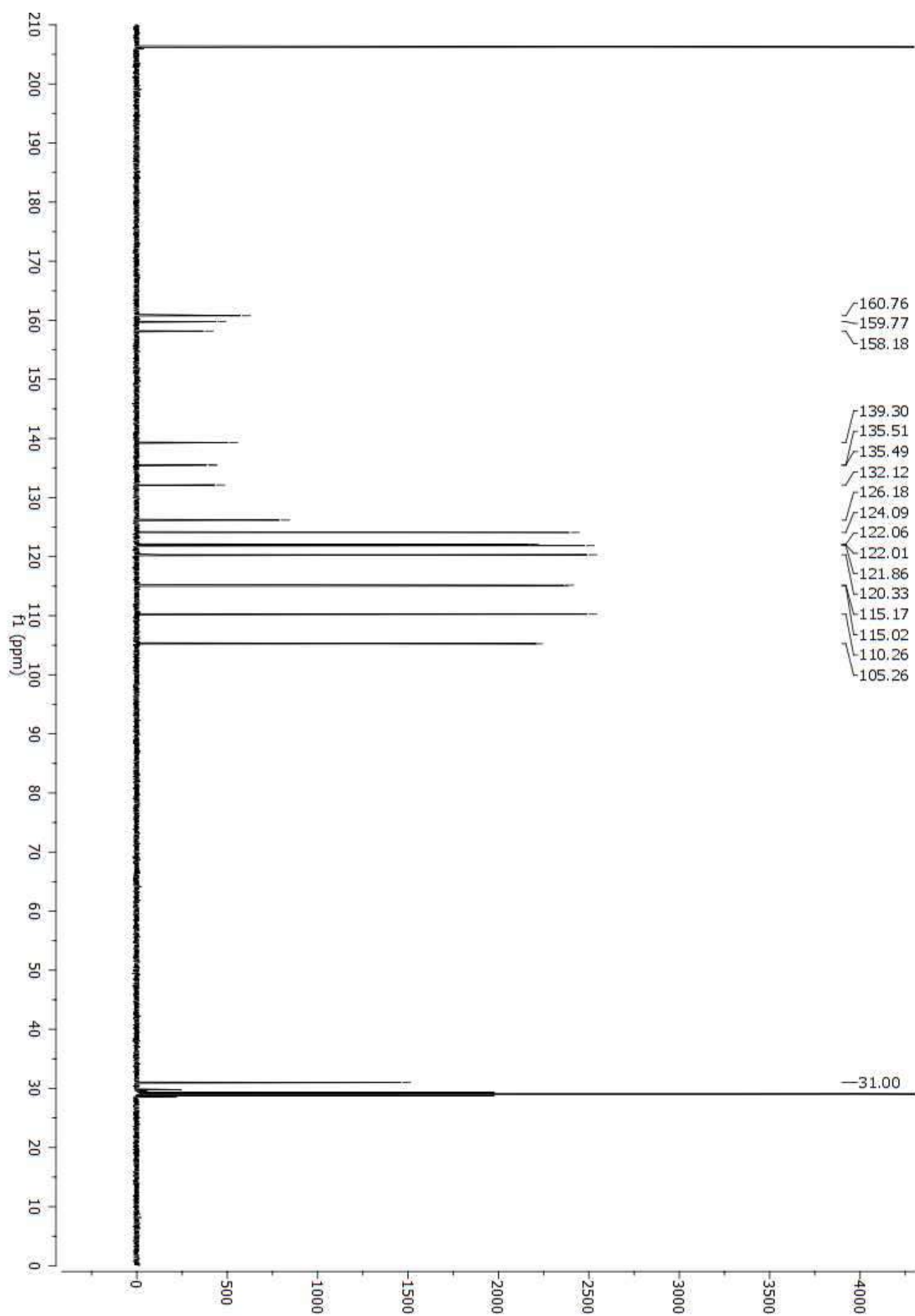
***N*-(4-Hydroxybenzyl)-1-methyl-1*H*-indole-2-carboxamide (6d)**



C₁₇H₁₆N₂O₂

MW 280.33





Openlynx Report -

Sample: 58
Date:29-Aug-2018

Vial:1:F,9
Time:17:12:14

File:I-0416621-001

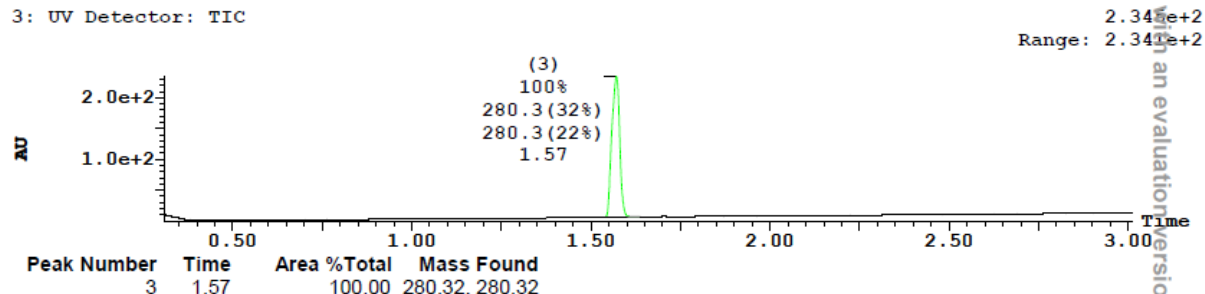
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Printed: Thu Aug 30 10:30:57 2018

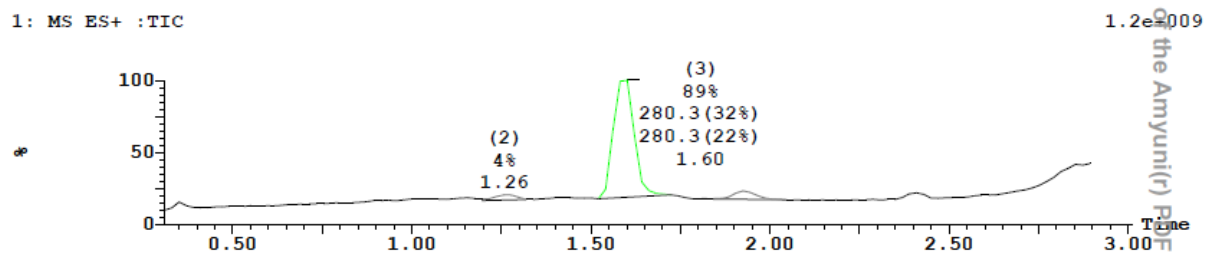
Sample Report (continued):

Sample 58 Vial 1:F,9 ID File I-0416621-001 Date 29-Aug-2018 Time 17:12:14 Description Met Gen

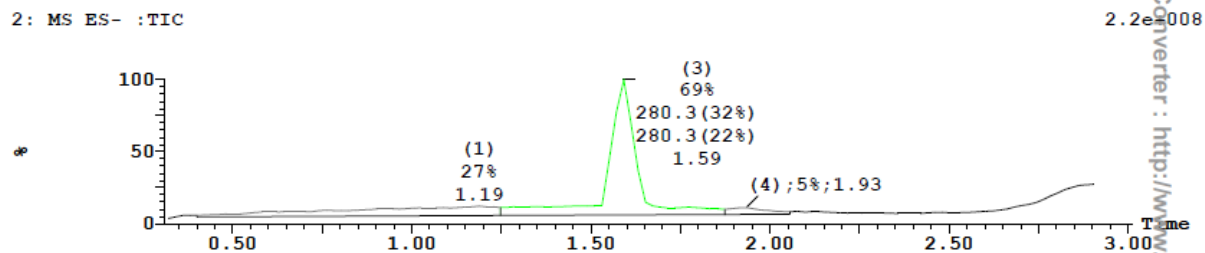
3: UV Detector: TIC



1: MS ES+ :TIC

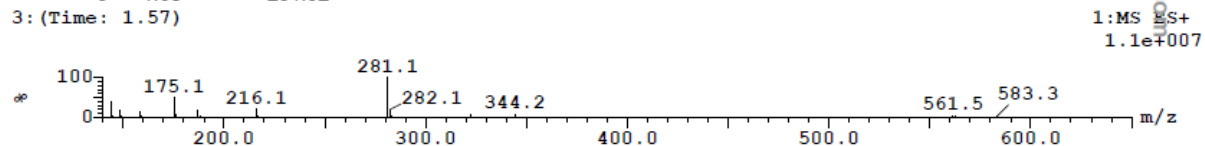


2: MS ES- :TIC



Peak ID Time Mass Found
3 1.60 281.32

3: (Time: 1.57)



Openlynx Report -

Sample: 58
Date:29-Aug-2018

Vial:1:F,9
Time:17:12:14

File:I-0416621-001

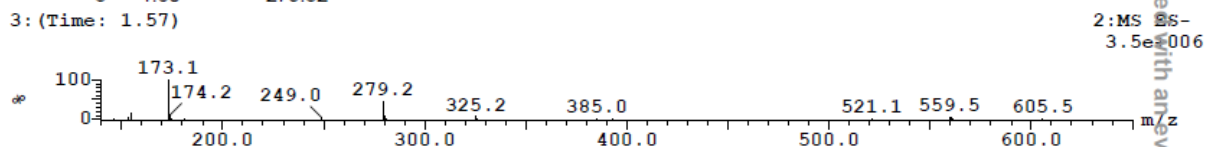
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Printed: Thu Aug 30 10:30:57 2018

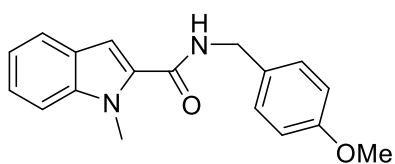
Sample Report (continued):

Peak ID Time Mass Found
3 1.60 279.32

3: (Time: 1.57)

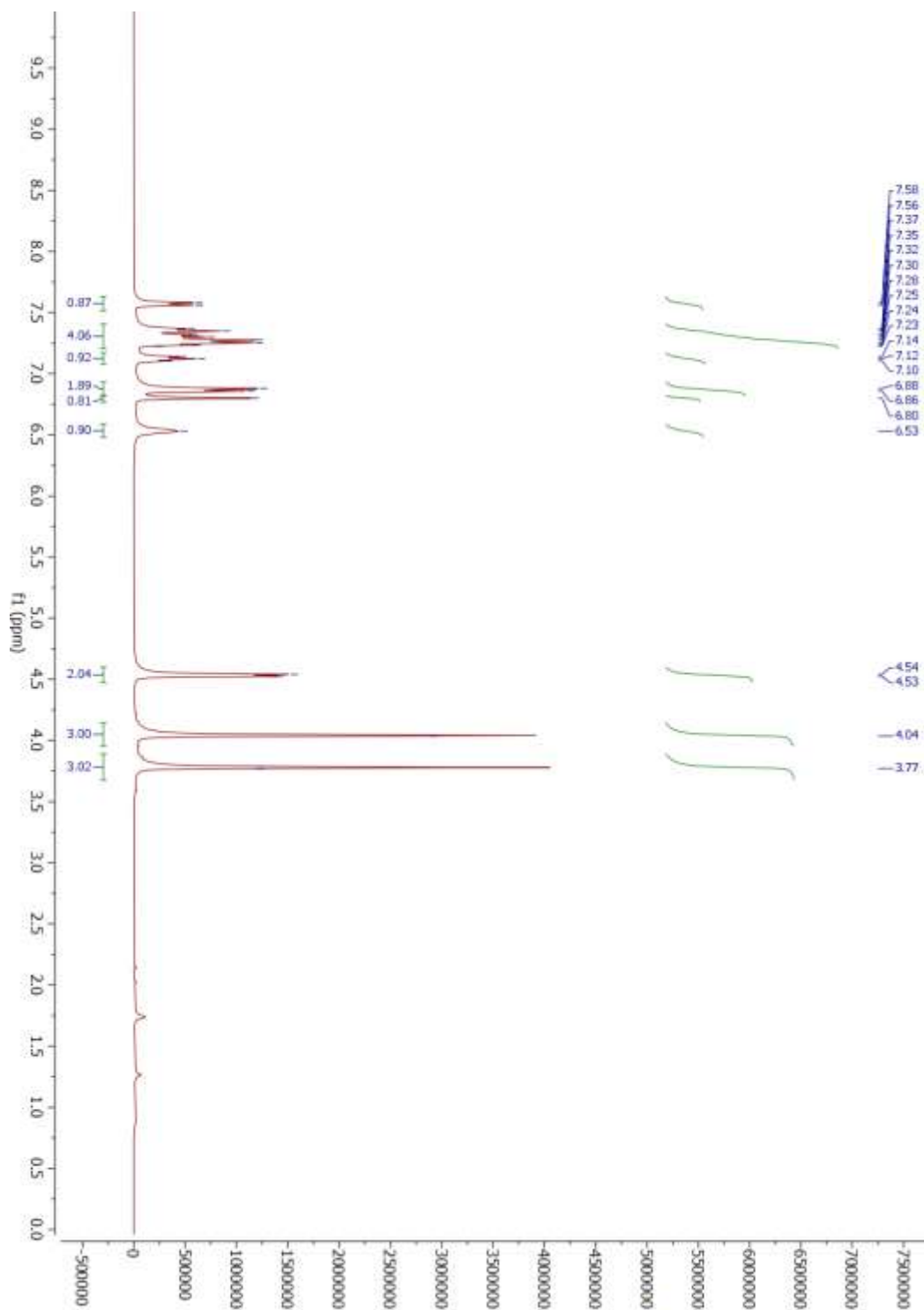


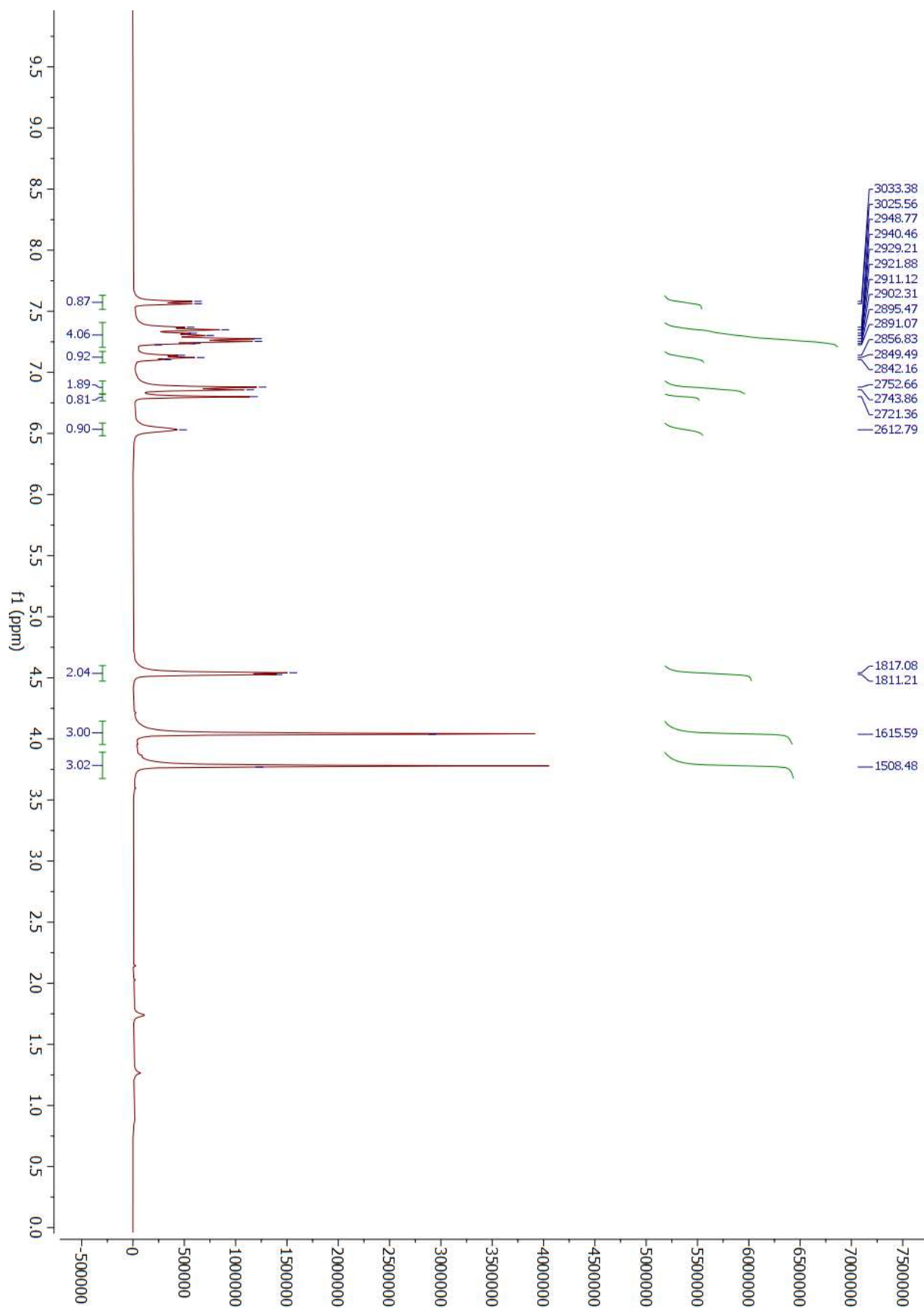
***N*-(4-Methoxybenzyl)-1-methyl-1*H*-indole-2-carboxamide (6e)**

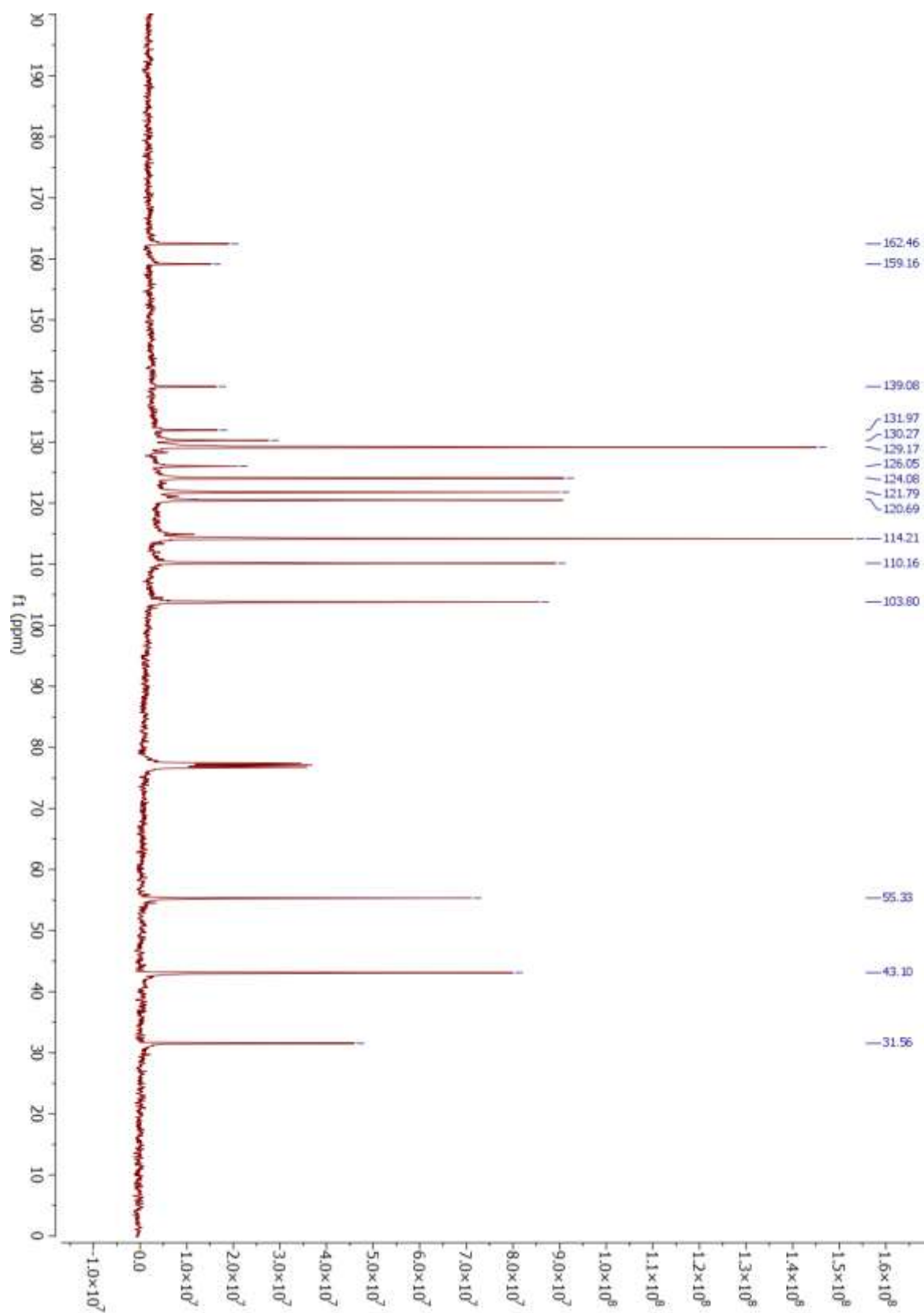


C₁₈H₁₈N₂O₂

MW 294.35







Openlynx Report -

Sample: 29
Date:29-Aug-2018

Vial:1:C,10
Time:15:03:44

File:I-0416593-001

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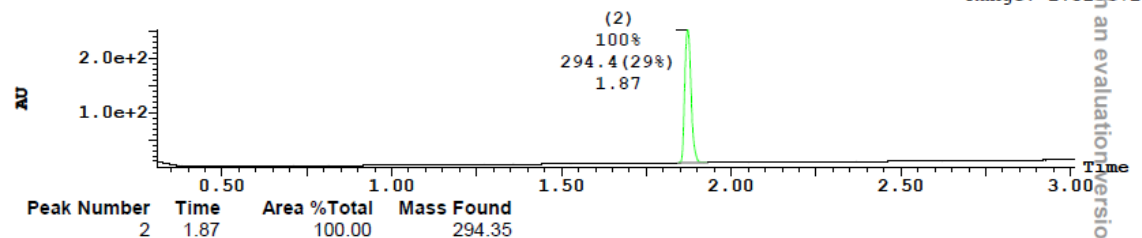
Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

Sample 29 Vial 1:C,10 ID File I-0416593-001 Date 29-Aug-2018 Time 15:03:44 Description Met Gen

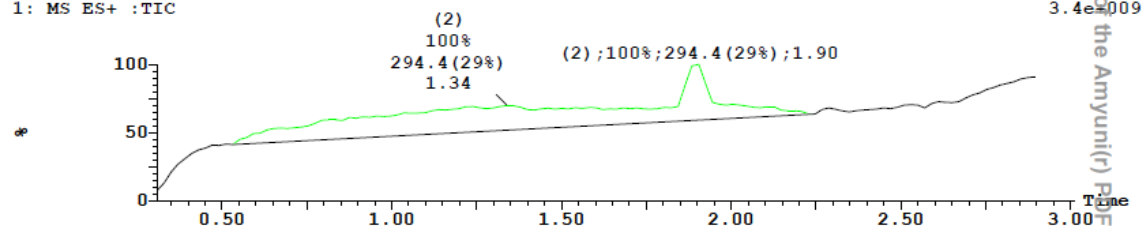
3: UV Detector: TIC

2.52e+2
Range: 2.52e+2



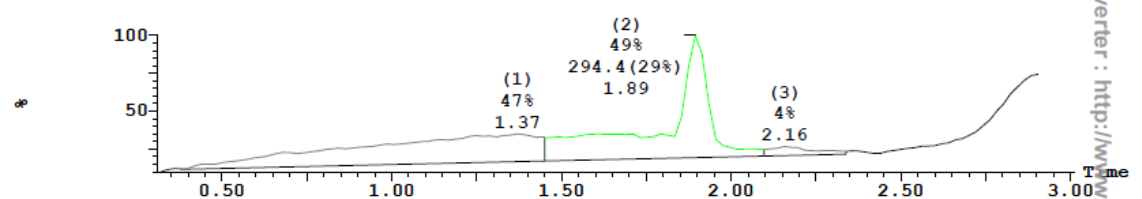
1: MS ES+ :TIC

3.4e+009



2: MS ES- :TIC

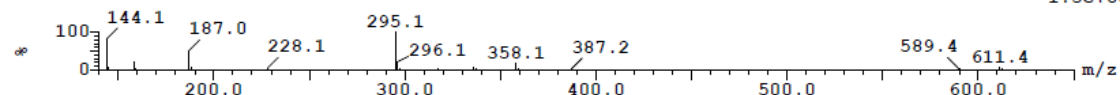
7.8e+007



Peak ID Time Mass Found
2 1.90 295.35

2: (Time: 1.87)

1: MS ES+
1.5e+007



Openlynx Report -

Sample: 29
Date:29-Aug-2018

Vial:1:C,10
Time:15:03:44

File:I-0416593-001

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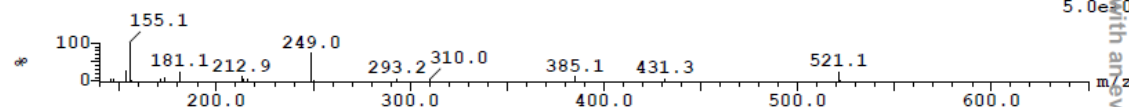
Printed: Thu Aug 30 10:30:57 2018

Sample Report (continued):

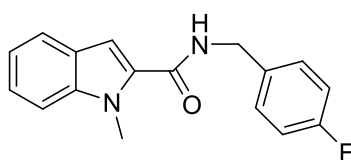
Peak ID Time Mass Found
2 1.90

2: (Time: 1.87)

2: MS ES-
5.0e+005

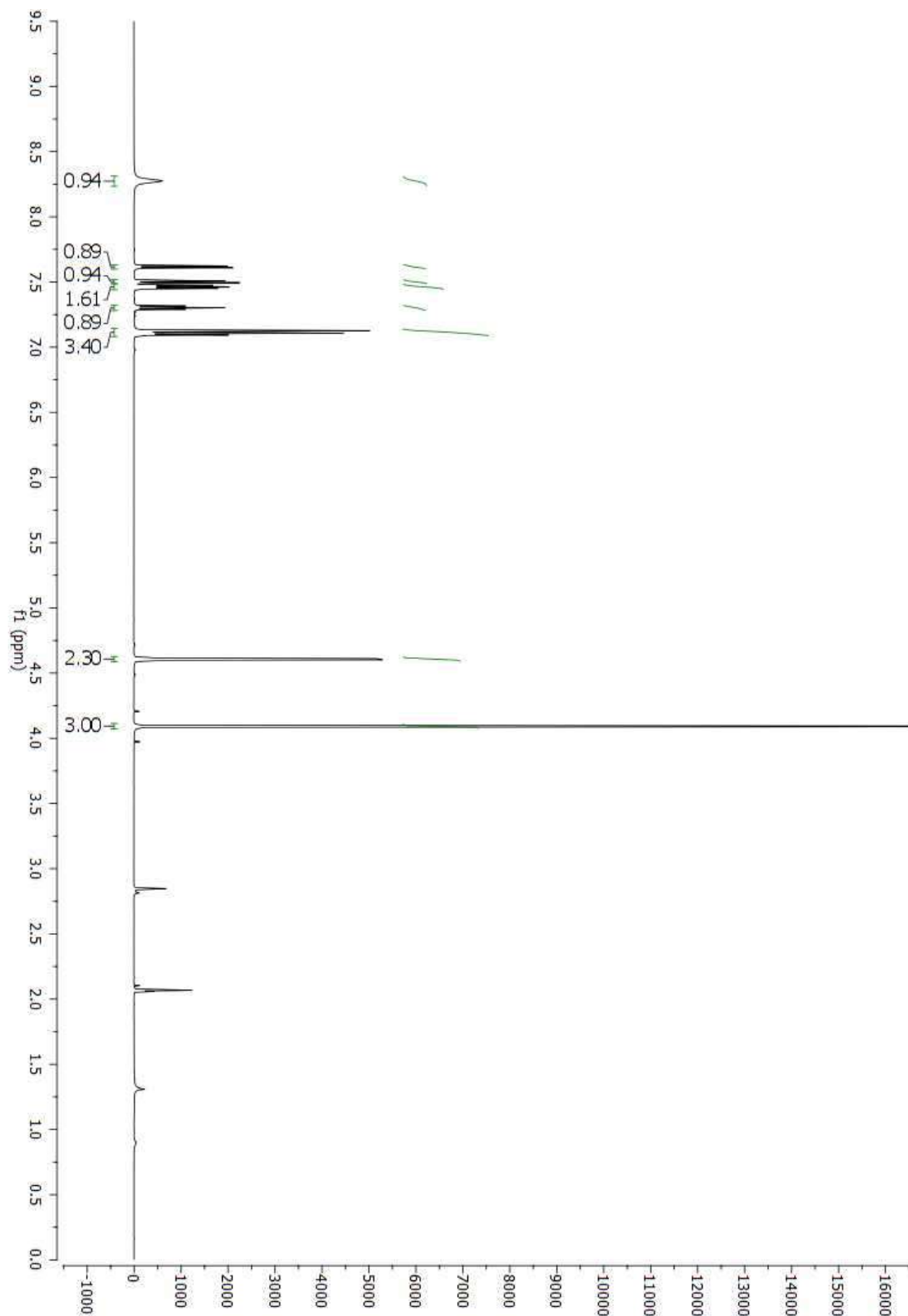


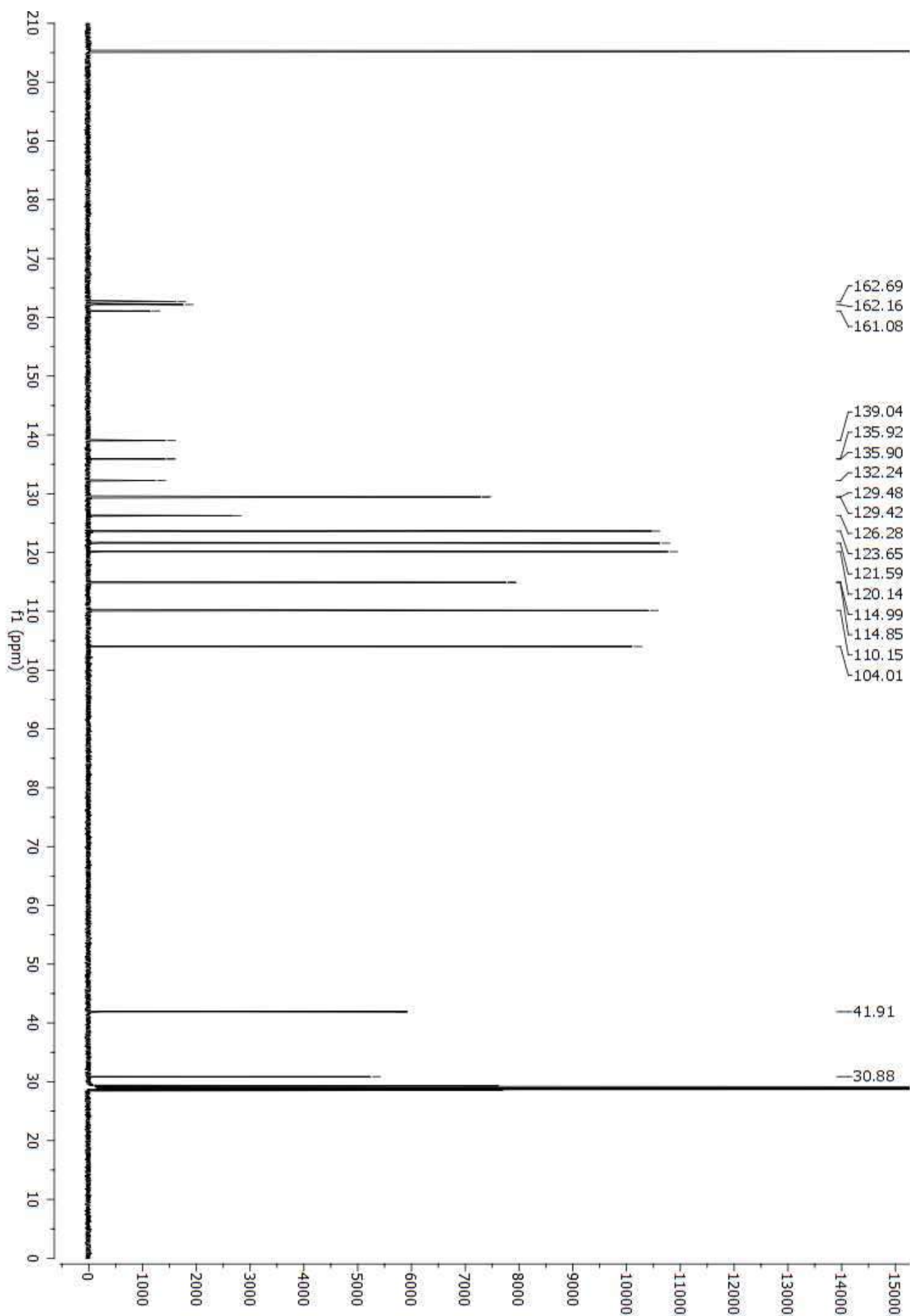
***N*-(4-Fluorobenzyl)-1-methyl-1*H*-indole-2-carboxamide (6f)**



C₁₇H₁₅FN₂O

MW 282.32



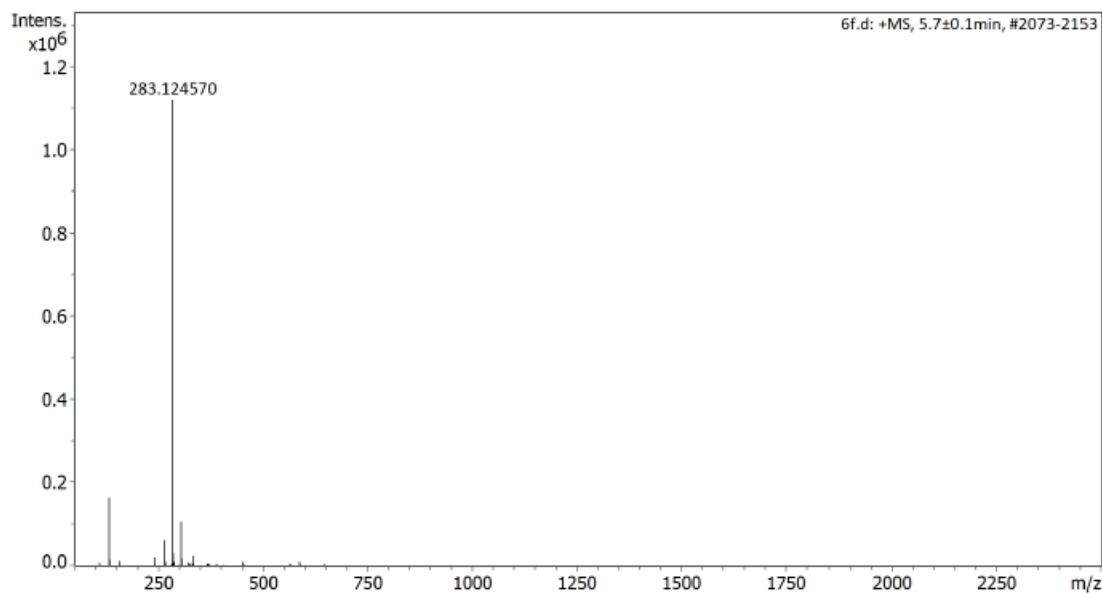
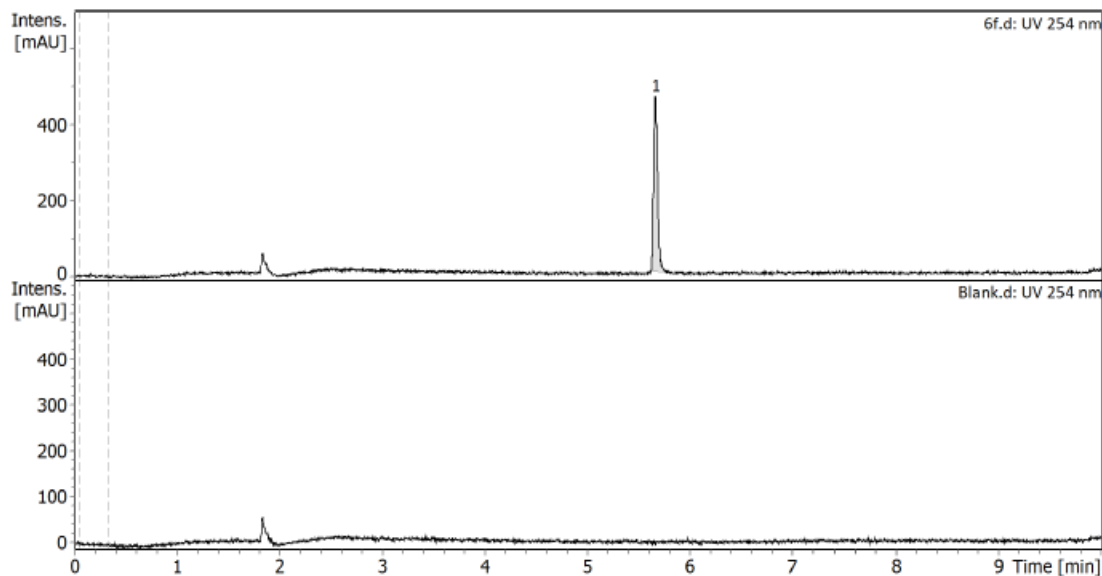


Analysis Info

Method MS_LC_POS_TimsOFF.m
Sample Name MSP139

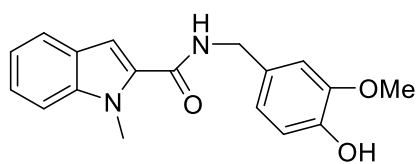
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



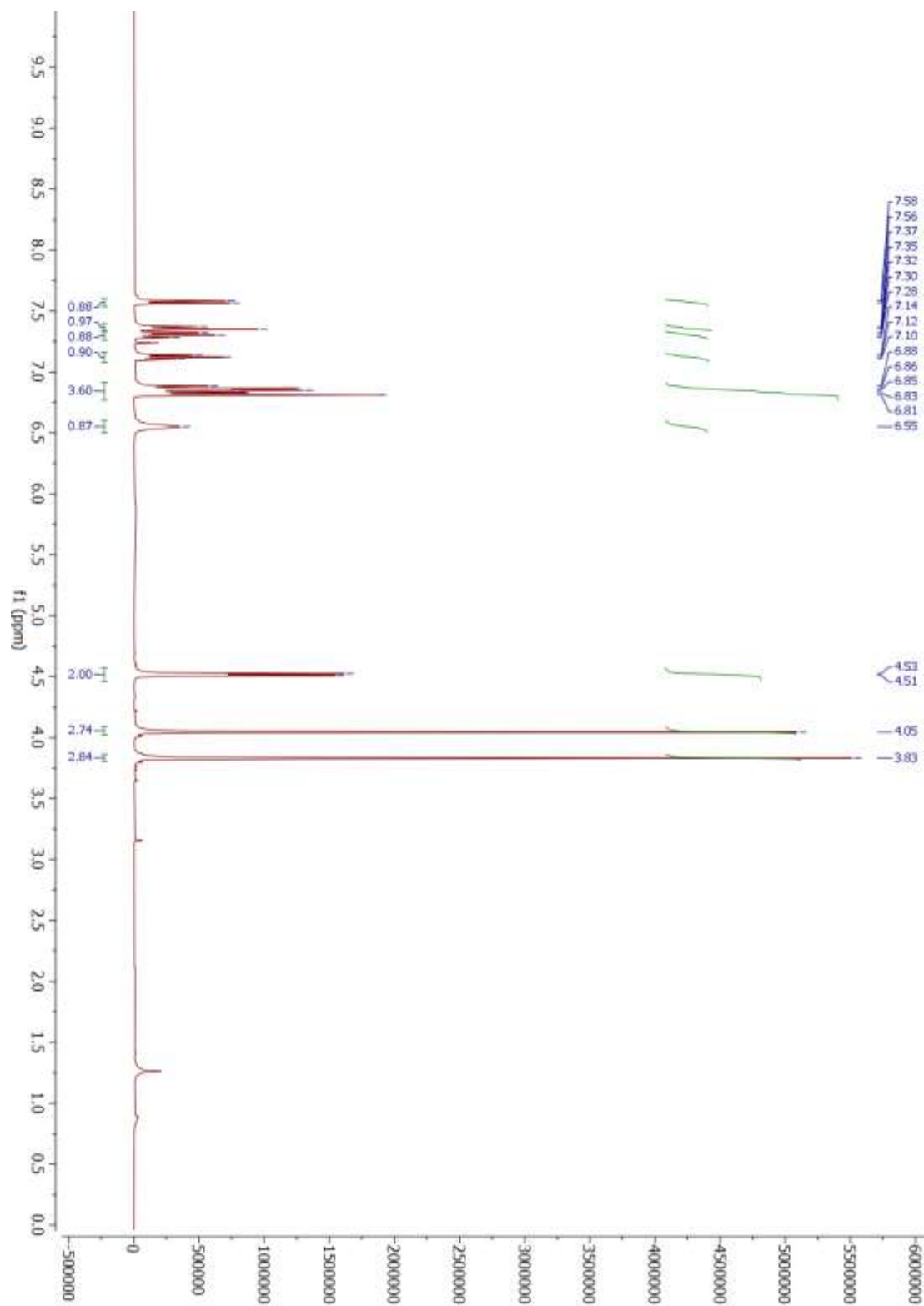
#	RT [min]	Area	Area Frac. %	I	S/N
1	5.7	1265.4	100.00	473	196.6

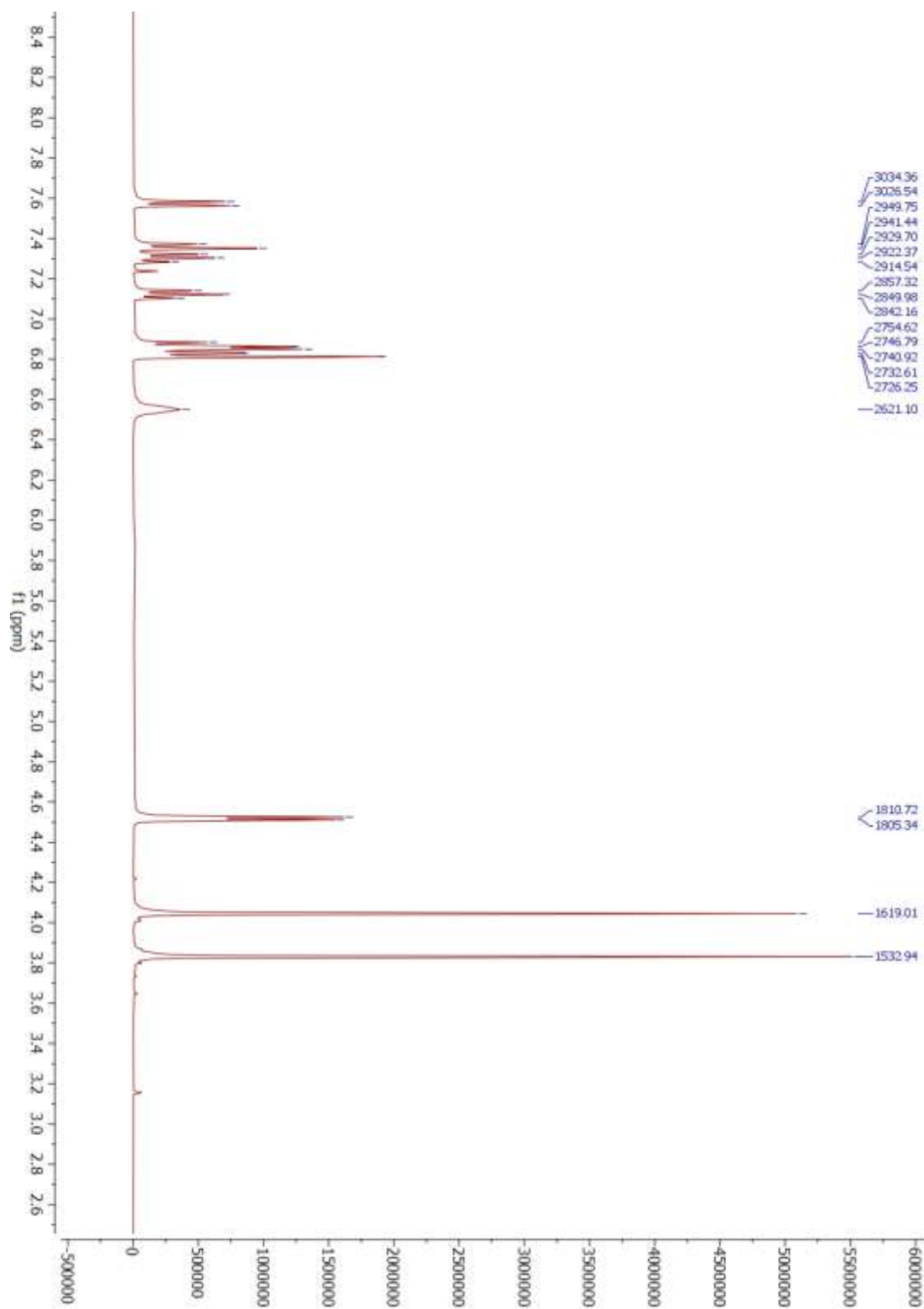
***N*-(4-Hydroxy-3-methoxybenzyl)-1-methyl-1*H*-indole-2-carboxamide (6g)**

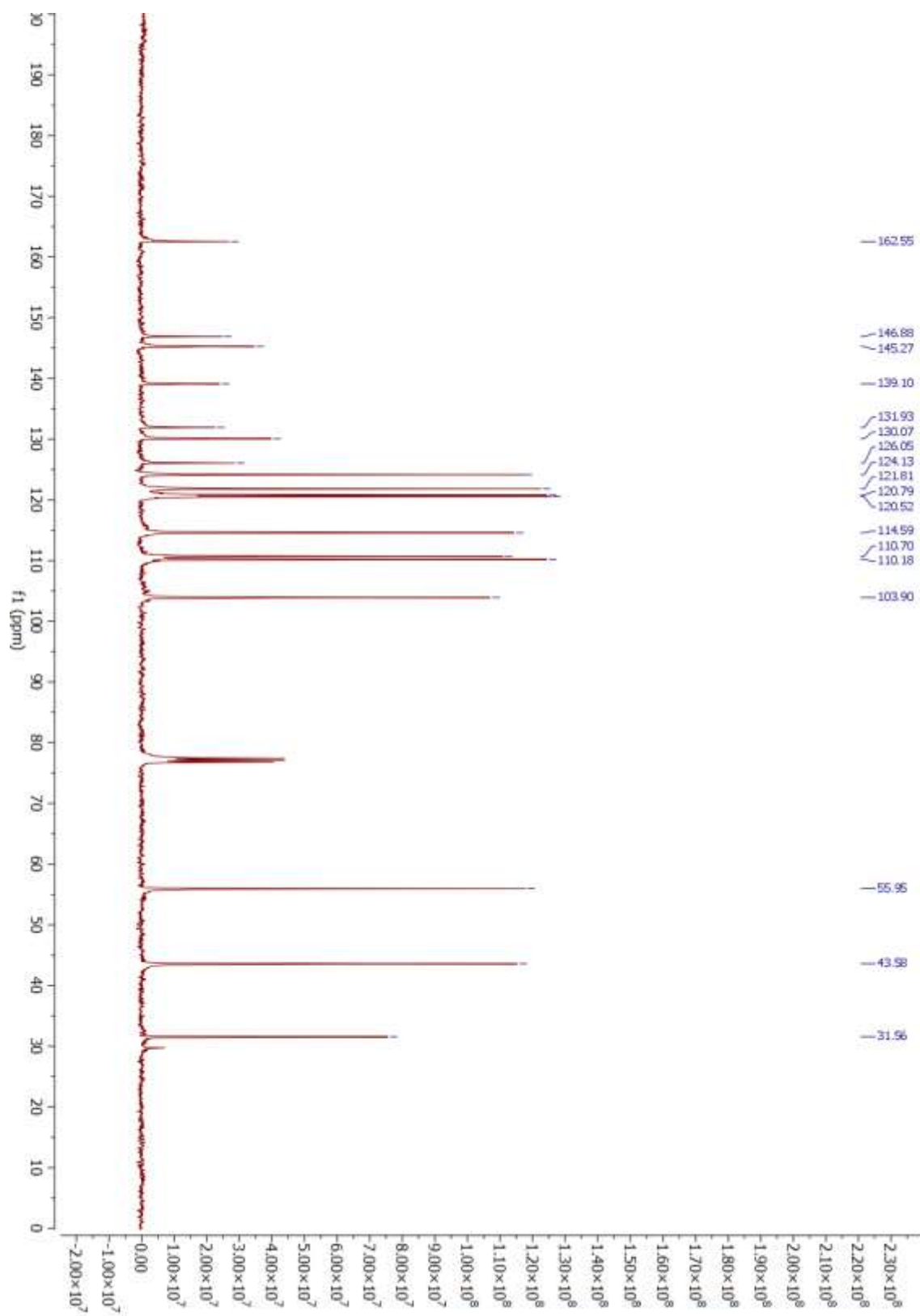


C₁₈H₁₈N₂O₃

MW 310.35







Printed: Thu Aug 30 10:30:57 2018

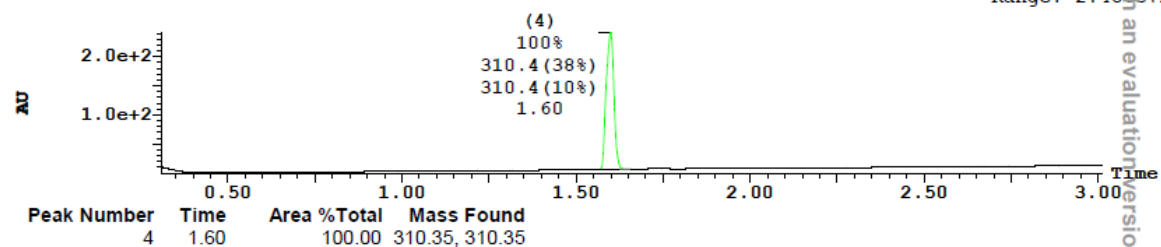
Sample Report (continued):

Sample 27 Vial 1:C,8 ID File I-0416591-001 Date 29-Aug-2018 Time 14:54:50 Description Met Gen

3: UV Detector: TIC

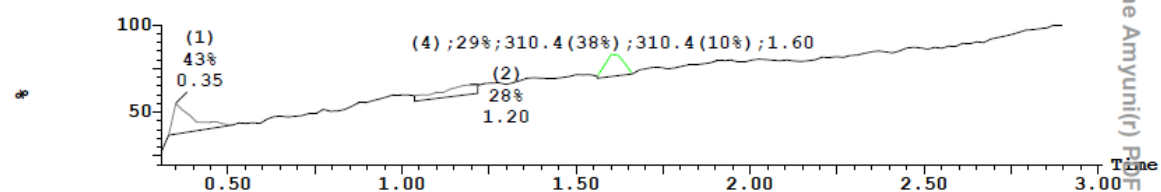
2.41e+2

Range: 2.40e+2



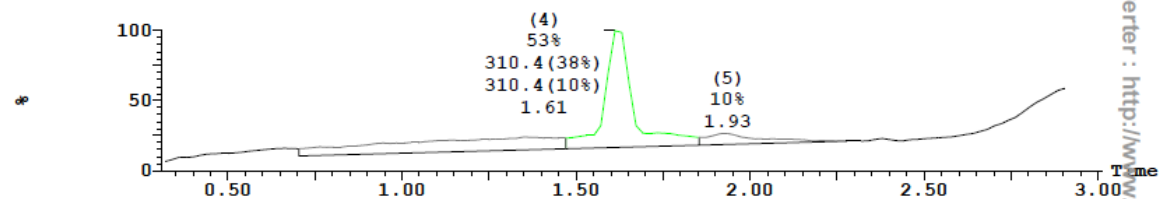
1: MS ES+ :TIC

3.6e+009



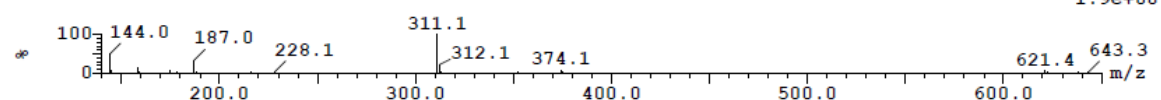
2: MS ES- :TIC

1.1e+008



Peak ID	Time	Mass Found
4	1.60	311.35

4: (Time: 1.60)

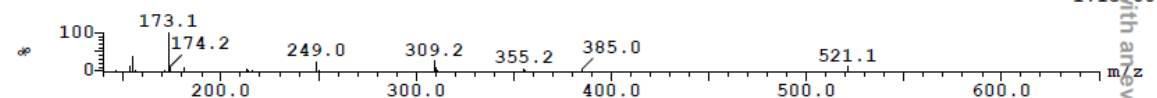
1:MS ES+
1.9e+007

Printed: Thu Aug 30 10:30:57 2018

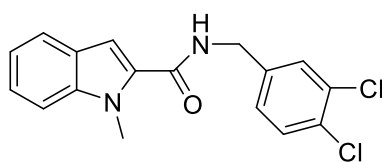
Sample Report (continued):

Peak ID	Time	Mass Found
4	1.60	309.35

4: (Time: 1.60)

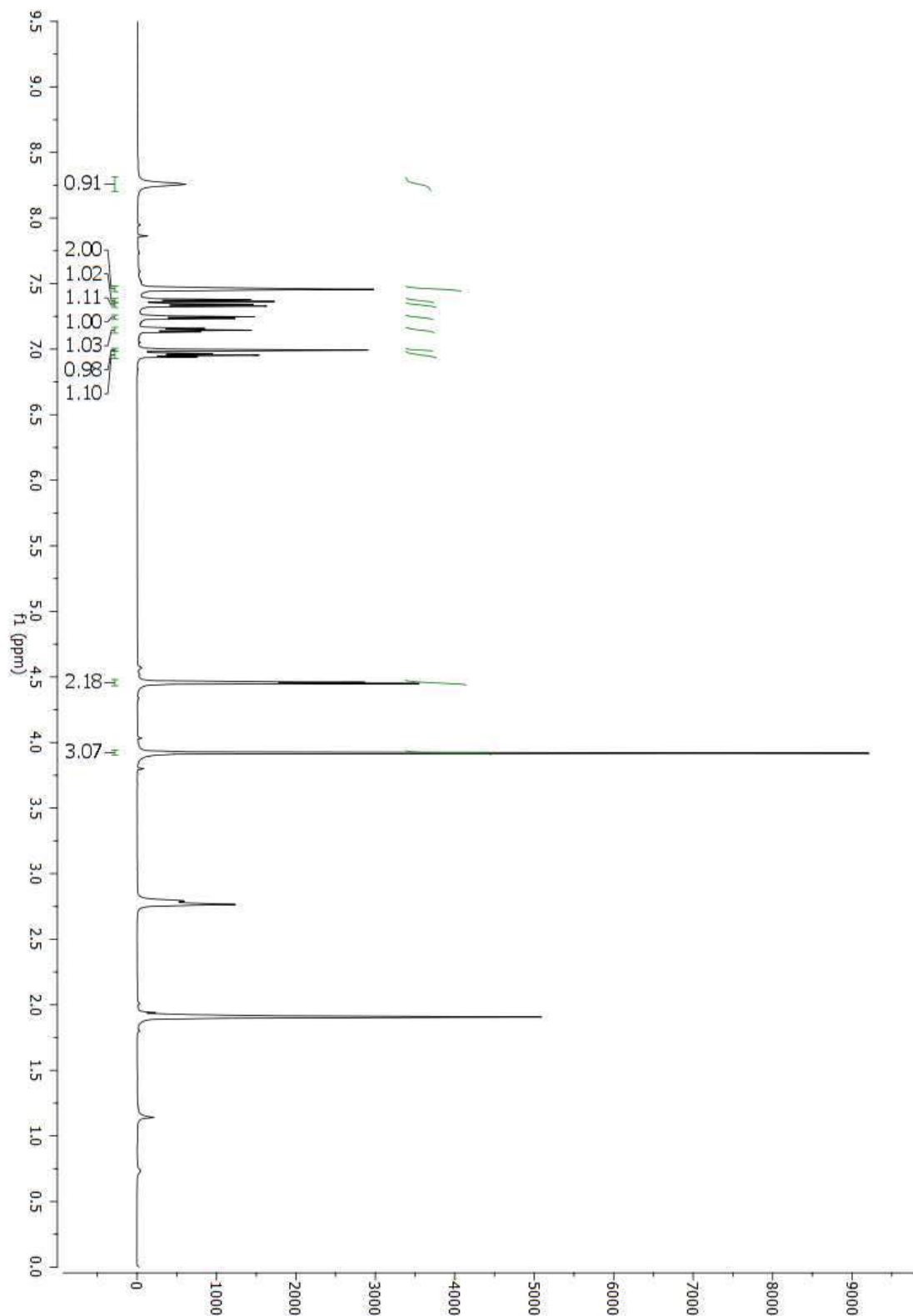
2:MS ES-
1.1e+006

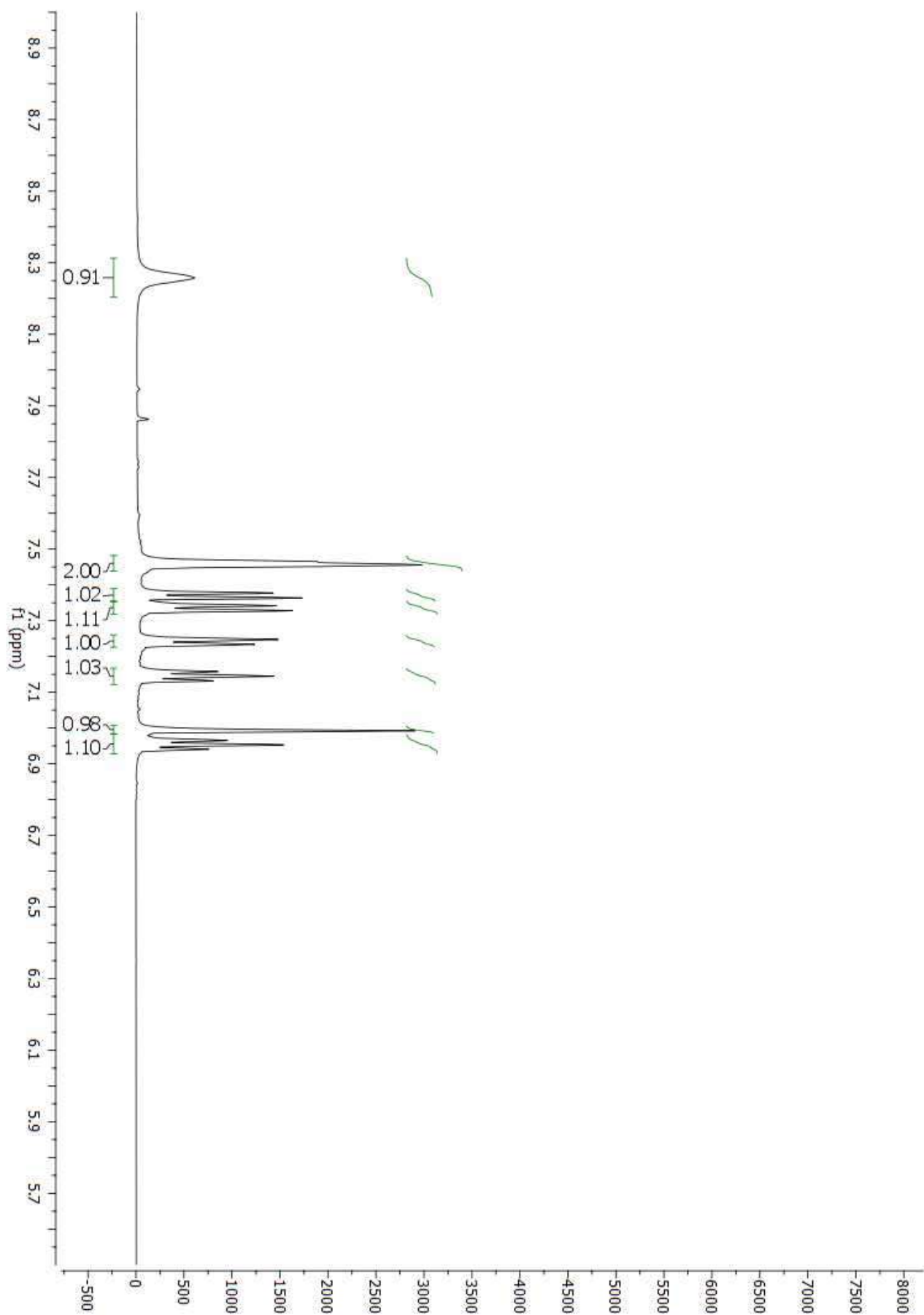
***N*-(3,4-Dichlorobenzyl)-1-methyl-1*H*-indole-2-carboxamide (6h)**

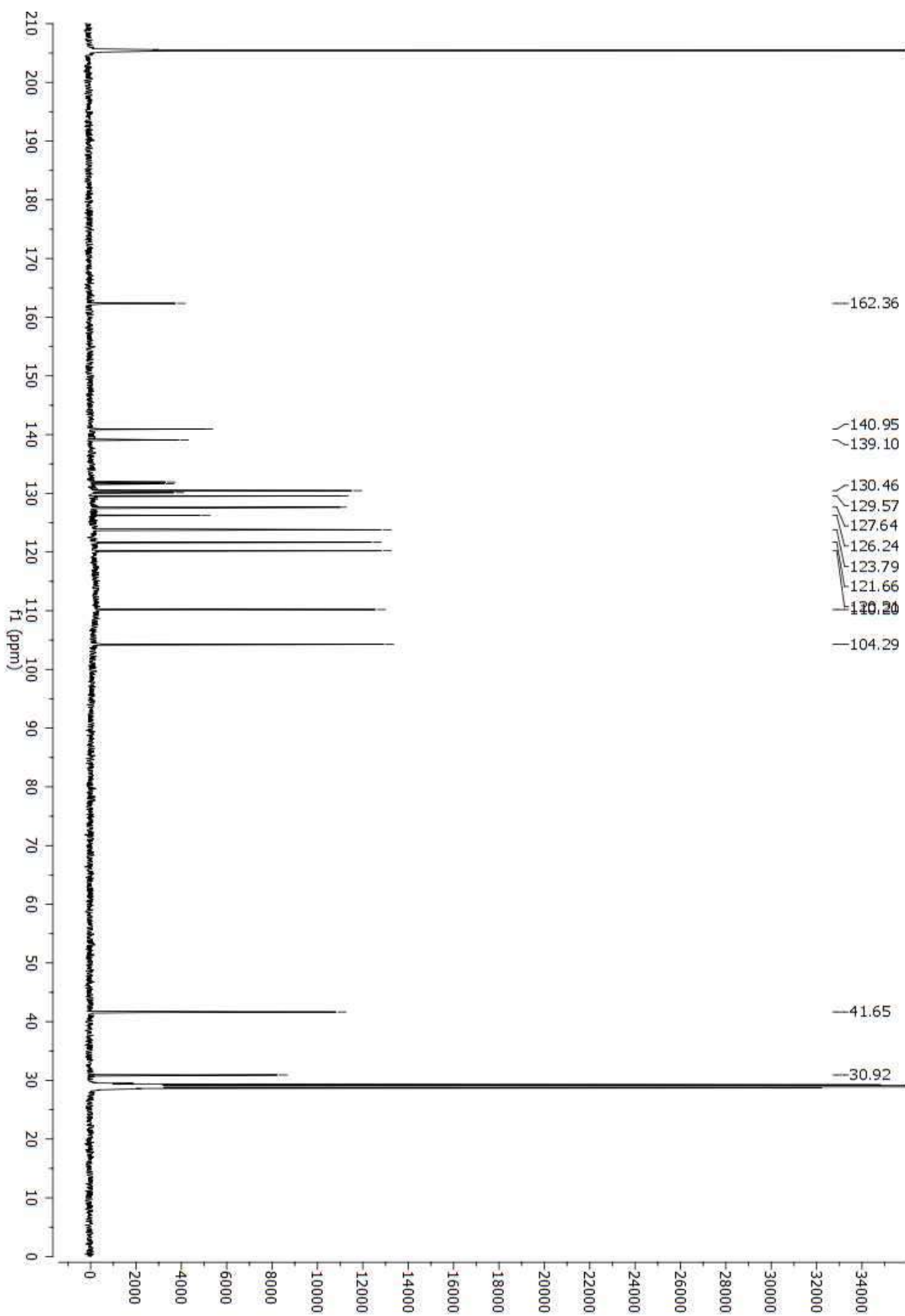


C₁₇H₁₄Cl₂N₂O

MW 333.21







Openlynx Report -

Sample: 26
Date:29-Aug-2018

Vial:1:C,7
Time:14:50:24

File:I-0416590-001

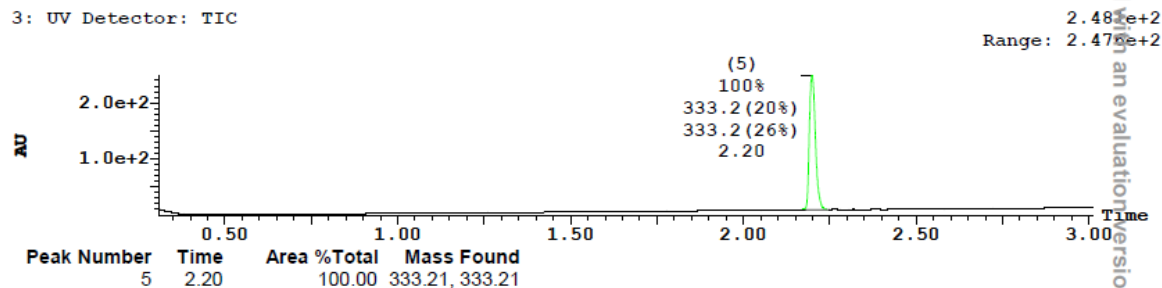
Page 53

Printed: Thu Aug 30 10:30:57 2018

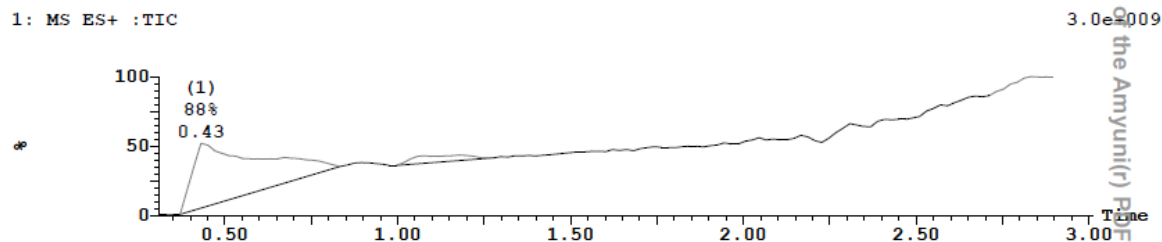
Sample Report (continued):

Sample 26 Vial 1:C,7 ID File I-0416590-001 Date 29-Aug-2018 Time 14:50:24 Description Met Gen

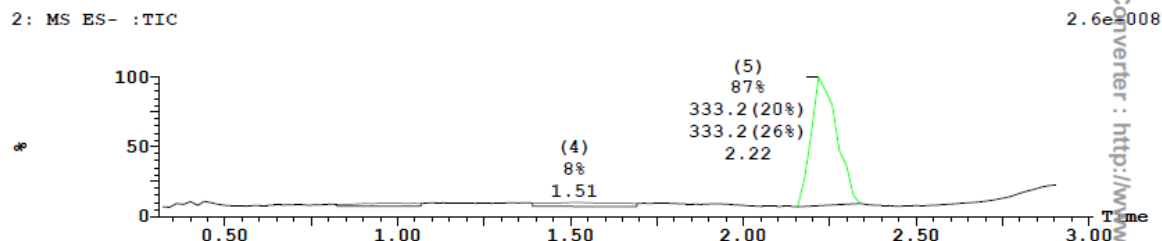
3: UV Detector: TIC



1: MS ES+ :TIC

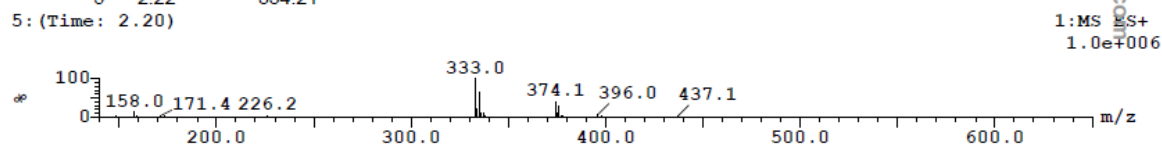


2: MS ES- :TIC



Peak ID	Time	Mass Found
5	2.22	334.21

5: (Time: 2.20)



Openlynx Report -

Sample: 26
Date:29-Aug-2018

Vial:1:C,7
Time:14:50:24

File:I-0416590-001

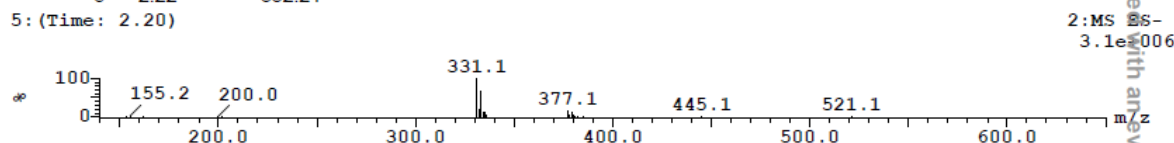
Page 54

Printed: Thu Aug 30 10:30:57 2018

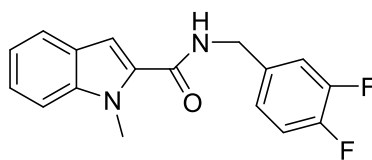
Sample Report (continued):

Peak ID	Time	Mass Found
5	2.22	332.21

5: (Time: 2.20)

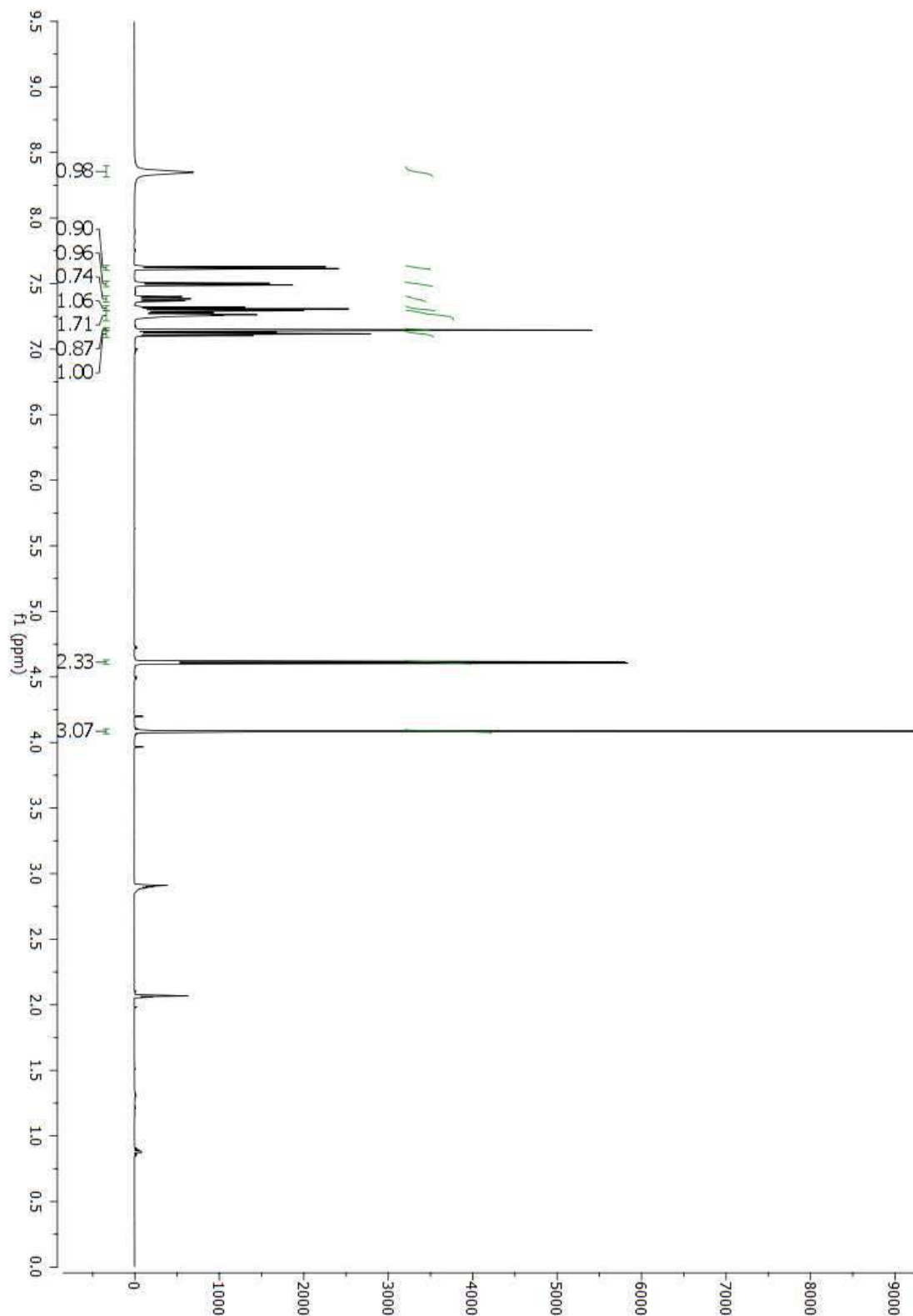


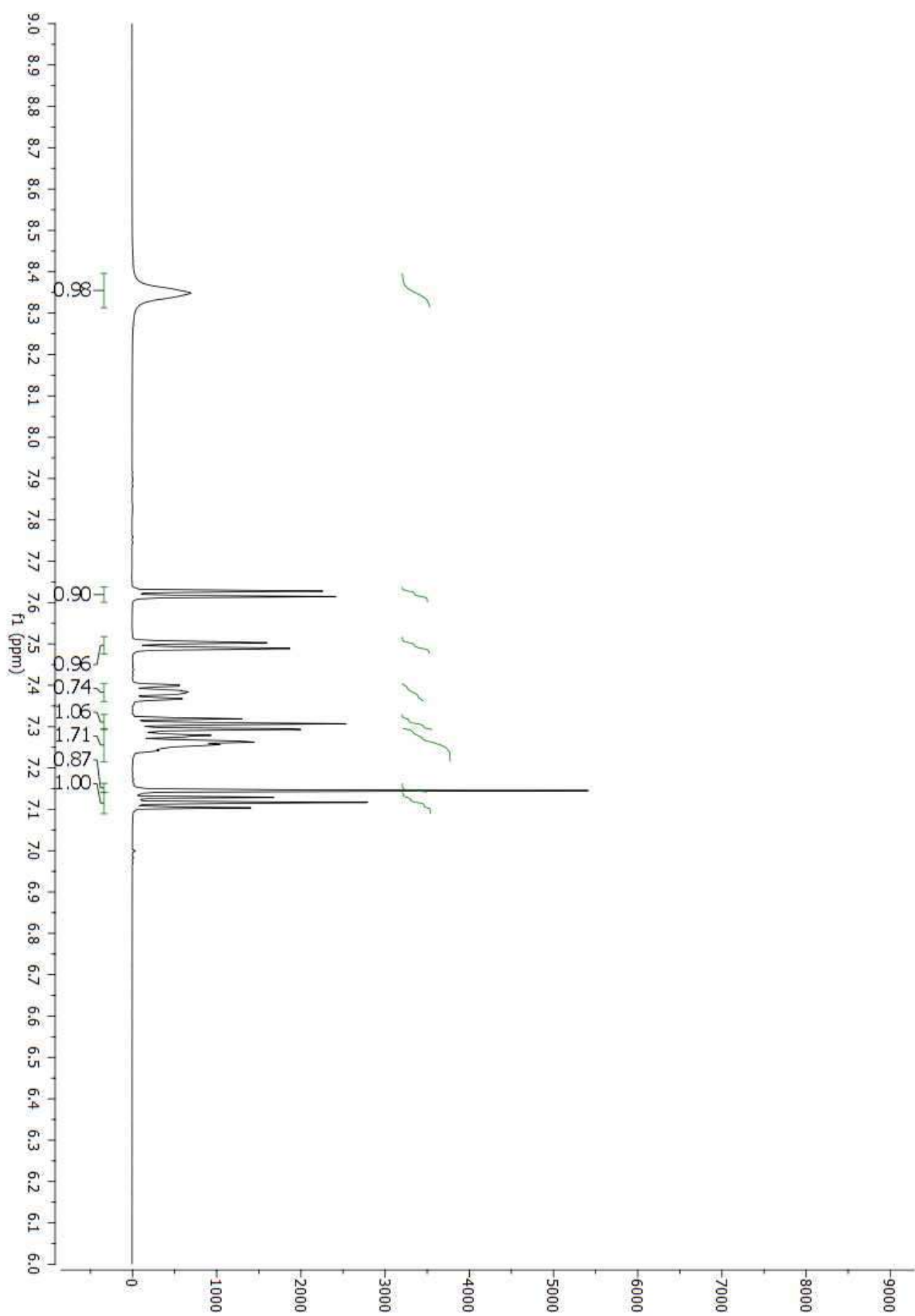
***N*-(3,4-Difluorobenzyl)-1-methyl-1*H*-indole-2-carboxamide (6i)**

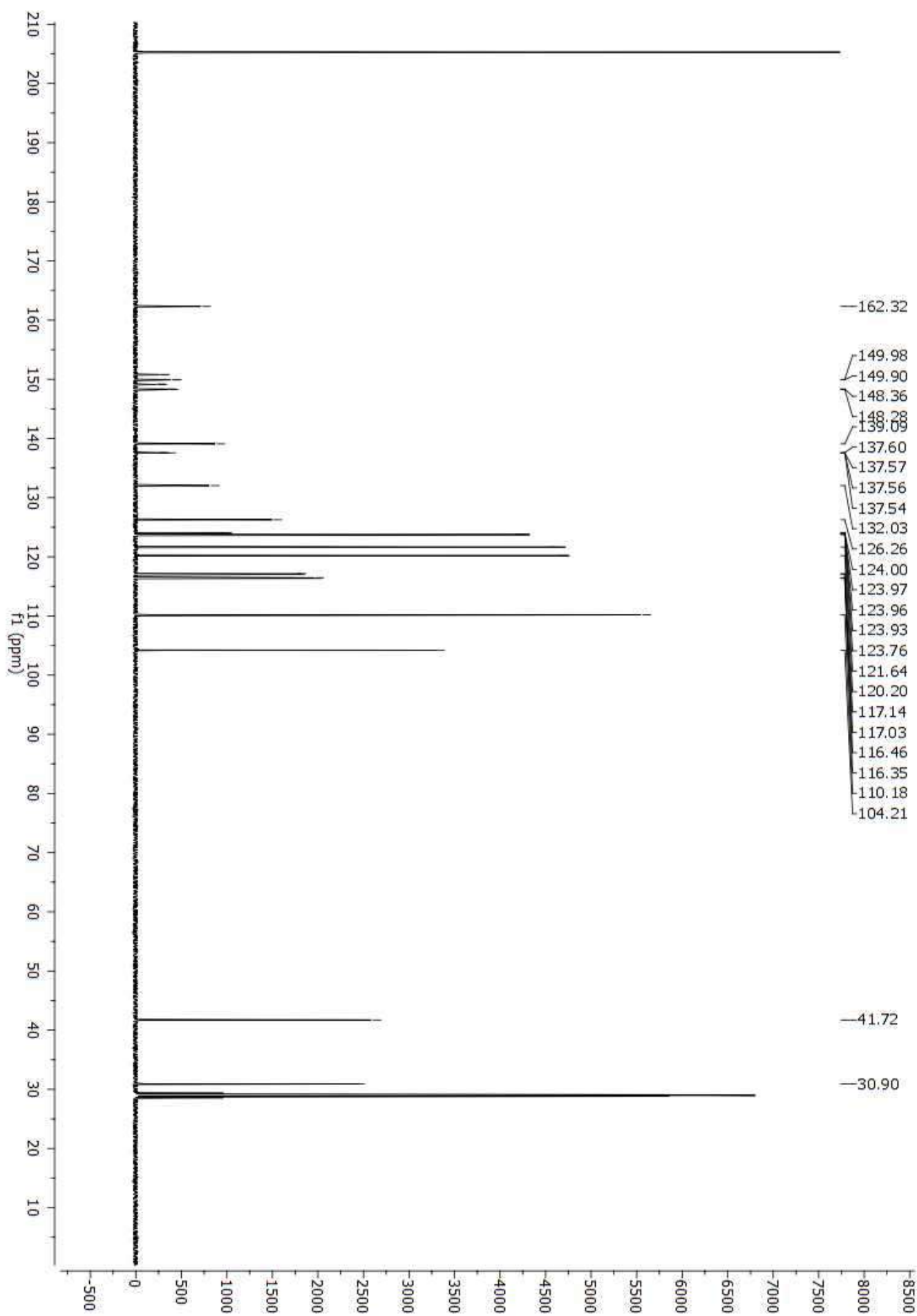


C₁₇H₁₄F₂N₂O

MW 300.31





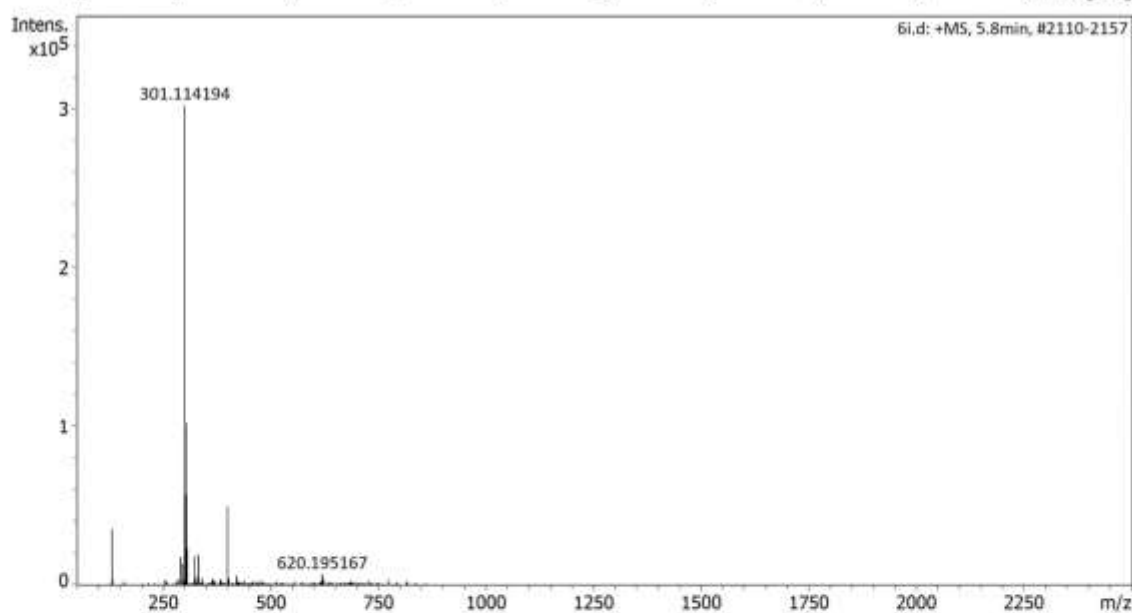
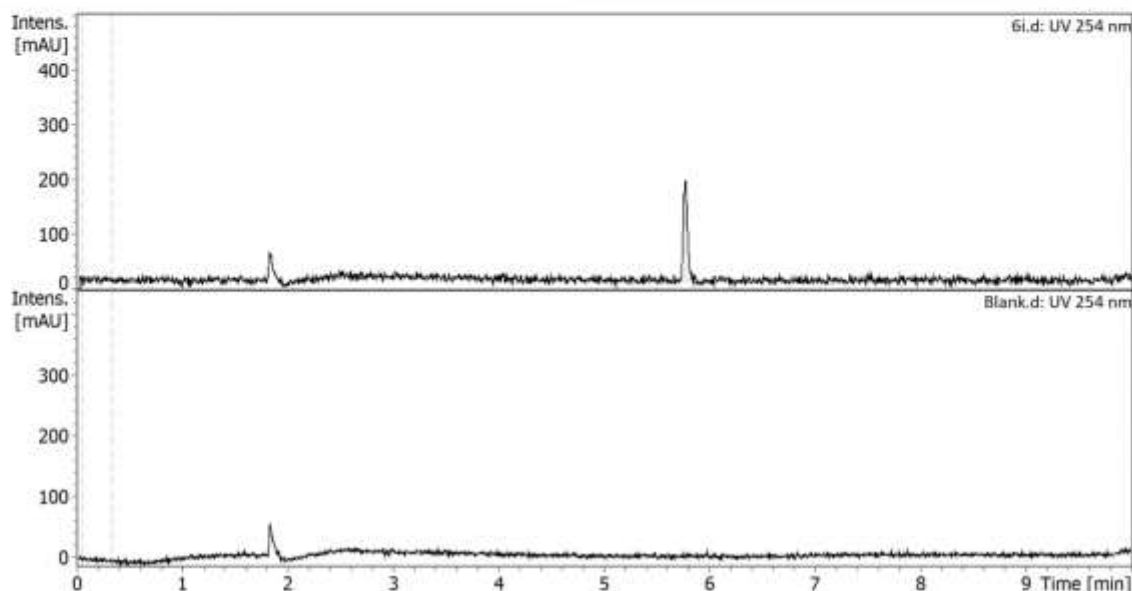


Analysis Info

Method MS_LC_POS_TimsOFF.m
Sample Name MSP140

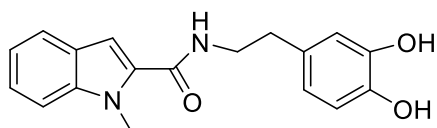
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



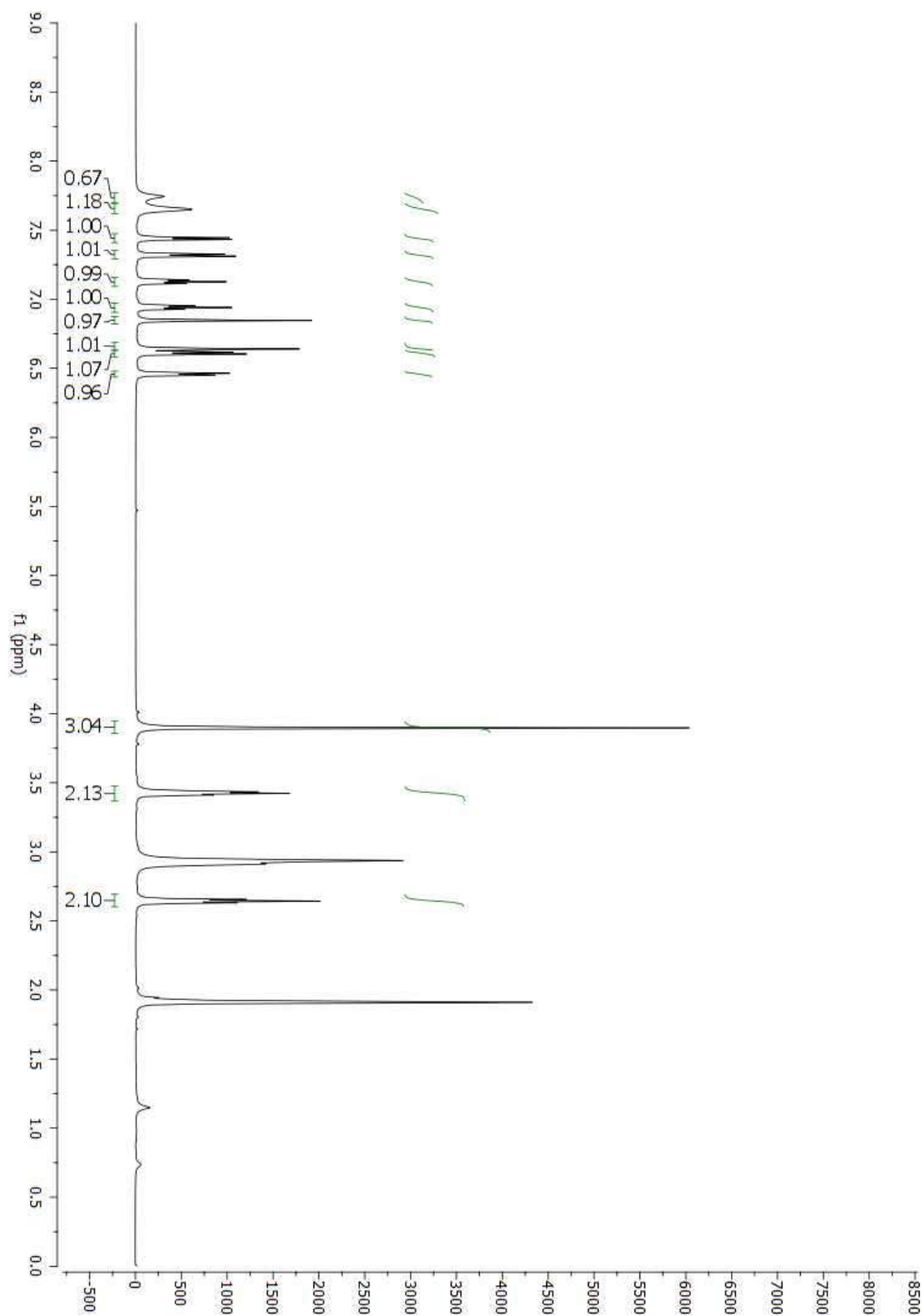
#	RT [min]	Area	Area Frac. %	I	S/N
2	5.8	508.34	100.00	199	24.7

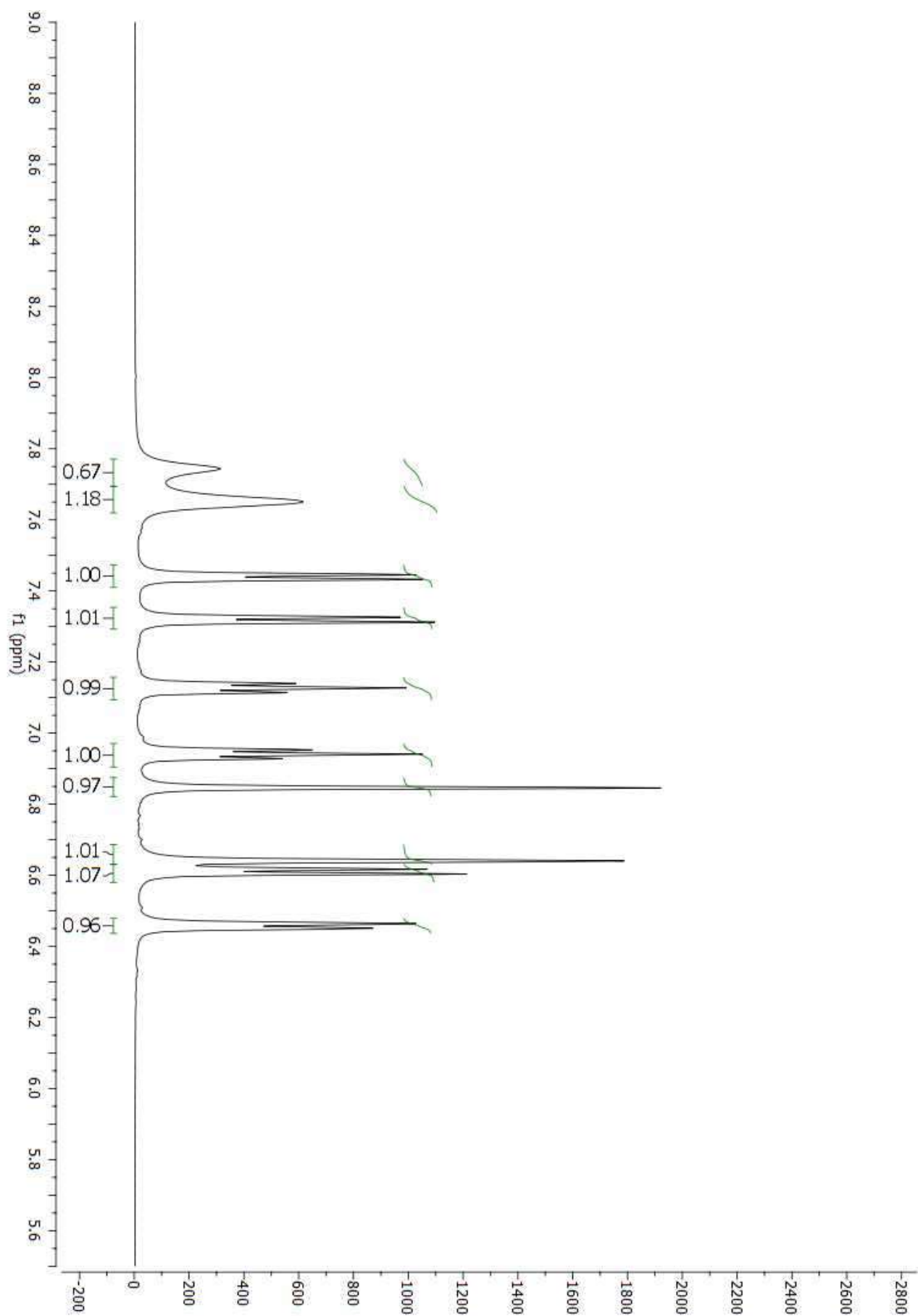
***N*-(3,4-Dihydroxyphenethyl)-1-methyl-1*H*-indole-2-carboxamide (6j)**

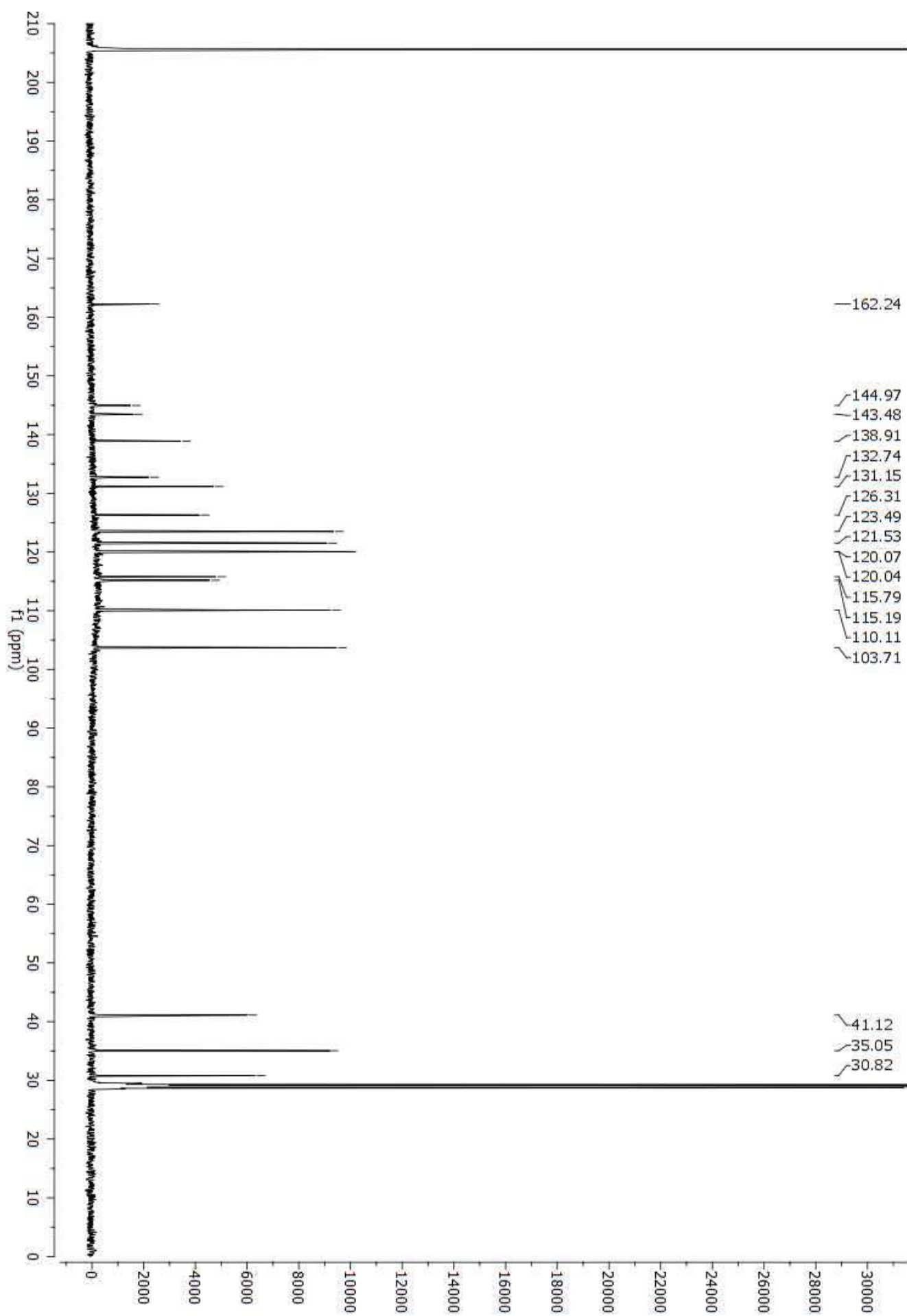


C₁₈H₁₈N₂O₃

MW 310.35





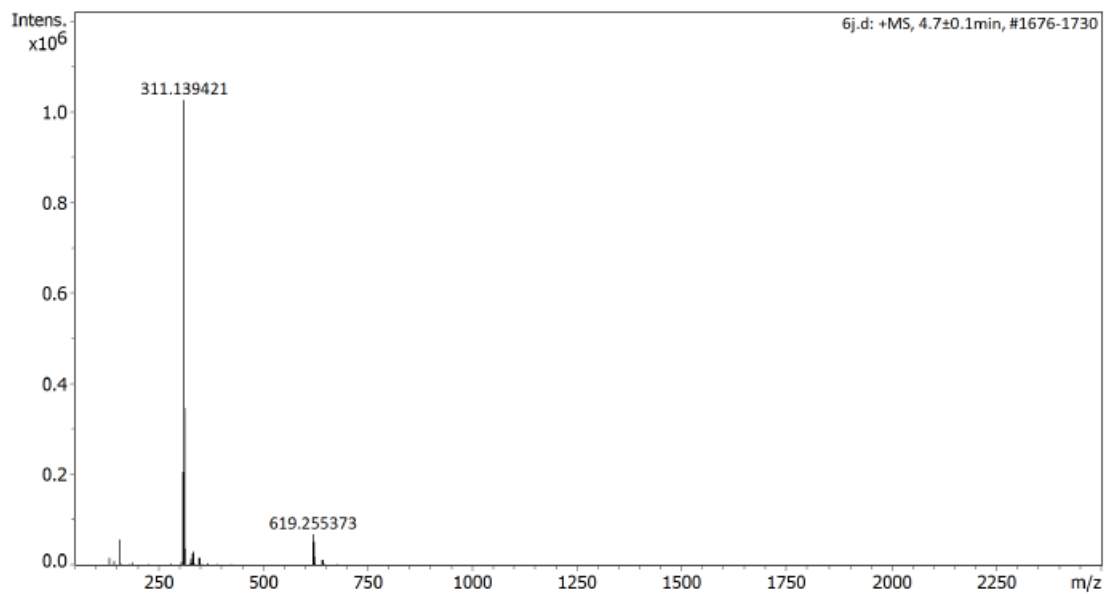
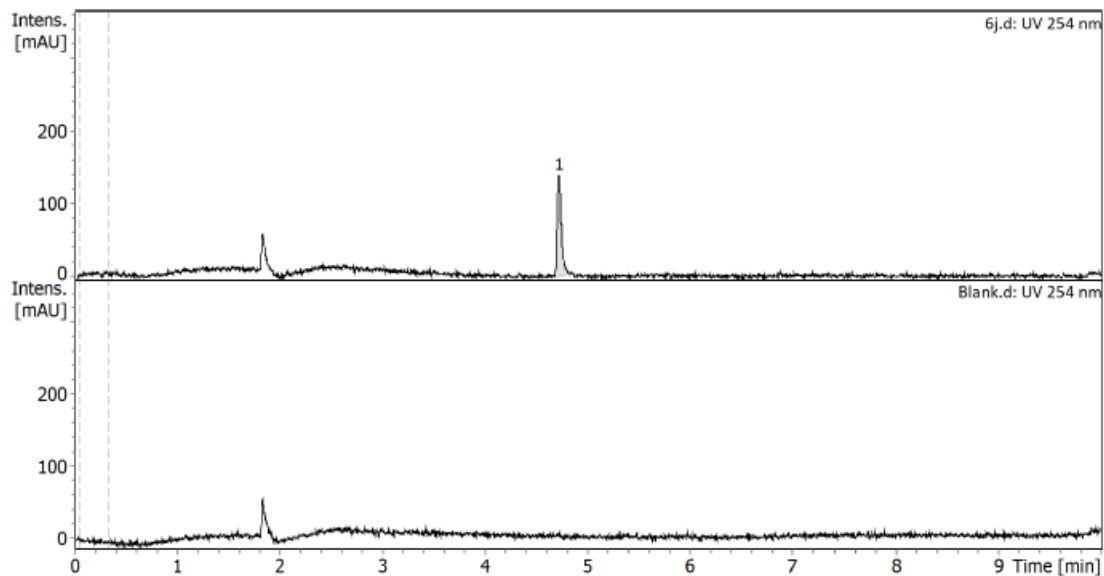


Analysis Info

Method MS_LC_POS_TimsOFF.m
Sample Name MSP68 sol.madre

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	2.2 Bar
Focus	Active	Set Capillary	4000 V	Set Dry Heater	220 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	10.0 l/min
Scan End	2500 m/z	Set Collision Cell RF	1800.0 Vpp	Set Divert Valve	Waste



#	RT [min]	Area	Area Frac. %	I	S/N
1	4.7	394.59	100.00	139	57.2