Scale-up and optimization of the synthesis of dual CBP/BRD4 inhibitor ISOX-DUAL

Anthony K. Edmonds,[a] Catherine S. Oakes,[b] Storm Hassell-Hart,[a] Didier Bruyère,[b] Graham J. Tizzard,[c] Simon J. Coles,[c] Robert Felix,[b] Hannah J. Maple,[b] Graham P. Marsh,[b] and John Spencer*[a,d]

[a] Chemistry Department, School of Life Sciences, University of Sussex, Falmer, Brighton, BN1 9QJ, UK.

[b] Bio-Techne (Tocris), The Watkins Building, Atlantic Road, Bristol, BS11 9QD, UK.

[c] National Crystallography Service, School of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK.

[d] Sussex Drug Discovery Centre, School of Life Sciences, University of Sussex, Falmer, Brighton, BN1 9QJ, UK.

X-Ray Crystallography

MIDA ester

Experimental. Single colourless block-shaped crystals were recrystallised from a mixture of DMF and hexane by solvent layering. A suitable crystal (0.15×0.08×0.05) mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku FRE+ diffractometer equipped with Arc)Sec VHF Varimax confocal mirrors and an AFC12 goniometer and HyPix 6000HE hybrid pixel array detector. The crystal was kept at T = 100(2) K during data collection. The structure was solved in the space group P-1 (# 2) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2018/3 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model. The model was refined as a two-component non-merohedral twin (0.5165(9):0.4835(9)) with the second component rotated by 179.9943° around [0.58 0.58 0.58] (reciprocal) or [0.61 0.55 0.57] (direct) lattice vectors. There are six independent molecules in the asymmetric unit (Z' = 6) an in each of the independent molecules the N and O atoms of the isoxoazole moieties are disordered in varying ratios of major to minor component ranging from approx. 0.53:0.47 to 0.68.0.32

Crystal Data. $C_{10}H_{13}BN_2O_5$, M_r = 252.03, triclinic, P-1 (No. 2), a = 14.4149(4) Å, b = 15.3357(4) Å, c = 17.4957(5) Å, α = 88.708(2)°, β = 85.627(2)°, γ = 64.579(3)°, V = 3482.78(18) Å^3, T = 100(2) K, Z = 12, Z' = 6, μ(MoK$_\alpha$) = 0.114, 26438 reflections measured, 26438 unique (R_{int} = .) which were used in all

calculations. The final wR_2 was 0.1838 (all data) and R_1 was 0.0675 (I > 2(I)). CCDC deposition number: 2110084

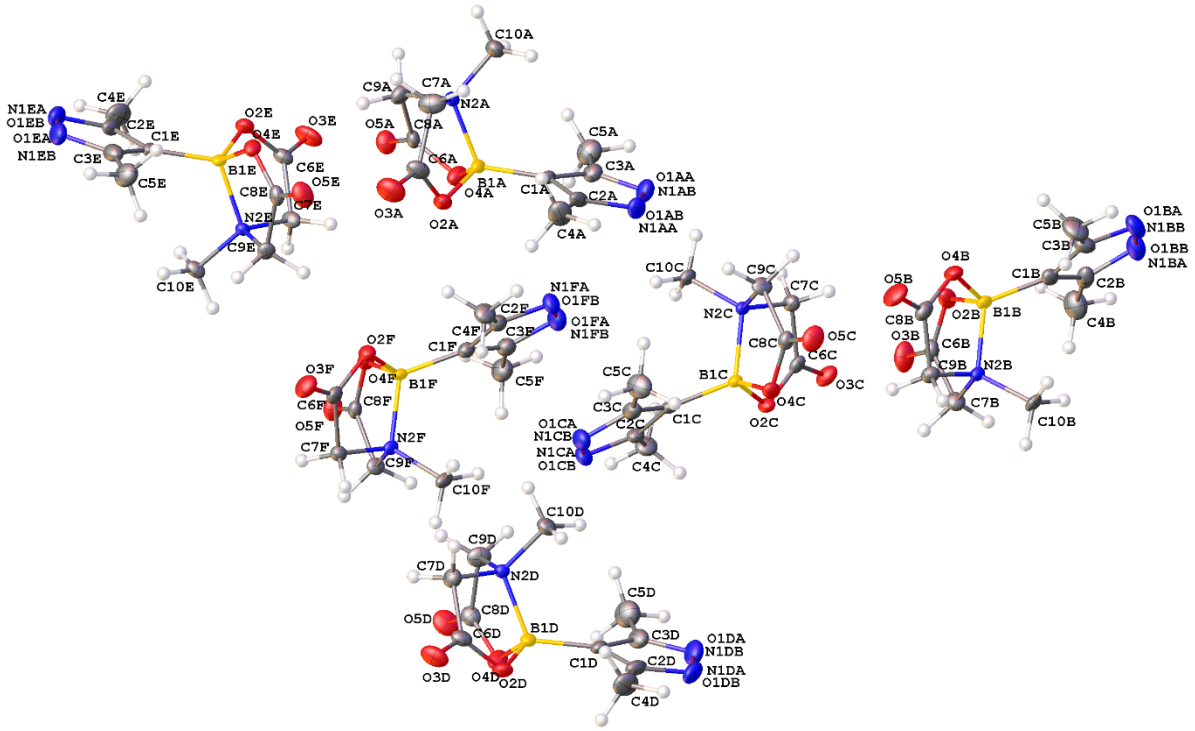


Fig S1. Crystal structure of ester with ADP ellipsoids displayed at 50% occupancy

10

Experimental. Single red plate-shaped crystals were recrystallised from DCM by slow evaporation. A suitable crystal (0.18×0.16×0.01) mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku FRE+ diffractometer equipped with HF Varimax confocal mirrors and an AFC12 goniometer and HG Saturn 724+ CCD detector. The crystal was kept at T = 100(2) K during data collection. The structure was solved in the space group $P2_1/c$ (# 14) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2017/1 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model except for H2 bonded to N2 which was located in the difference map and refined with the riding model.

Crystal Data. $C_{16}H_{21}N_5O_3$, M_r = 331.38, monoclinic, $P2_1/c$ (No. 14), a = 19.378(2) Å, b = 4.9594(2) Å, c = 18.3832(15) Å, β = 116.058(12)°, α = γ = 90°, V = 1587.1(3) Å^3, T = 100(2) K, Z = 4, Z' = 1, μ(MoK_α) = 0.099, 20280 reflections measured, 3640 unique (R_{int} = 0.0585) which were used in all calculations. The final wR_2 was 0.1447 (all data) and R_1 was 0.0542 (I > 2(I)). CCDC deposition number: 2110085

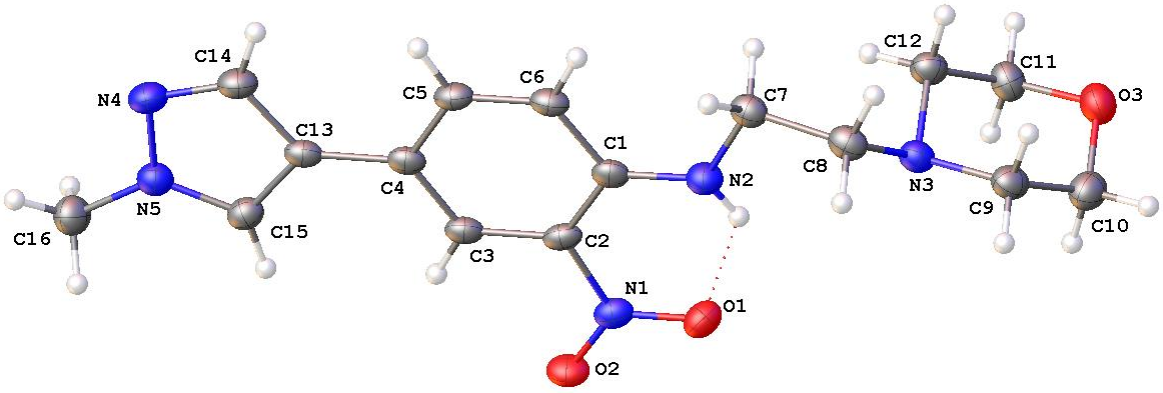


Fig S2. Crystal structure of **10** with ADP ellipsoids displayed at 50% occupancy

11

Experimental. Single red block-shaped crystals of were recrystallised from a mixture of DCM and hexane by slow evaporation. A suitable crystal 0.20×0.09×0.07 mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on an Rigaku 007HF diffractometer equipped with HF Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000HE hybrid pixel array detector. The crystal was kept at a steady T = 100(2) K during data collection. The structure was solved in the space group P-1 (# 2) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2018/3 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model except for H-atoms bonded to N-atoms which have been located in the difference map and refined with a riding model. The thiophene moieties of both independent molecules are disordered (ca. 69:31 and 90:10) and the disorder components were refined with thermal and geometrical restraints.

Crystal Data. $C_{16}H_{19}N_3O_3S$, M_r = 333.40, triclinic, P-1 (No. 2), a = 7.2068(2) Å, b = 15.1888(3) Å, c = 15.2406(2) Å, α = 74.263(2)°, β = 85.817(2)°, γ = 76.699(2)°, V = 1562.57(6) Å^3, T = 100(2) K, Z = 4, Z' = 2, μ(CuK$_\alpha$) = 2.010, 28801 reflections measured, 5671 unique (R_{int} = 0.0411) which were used in all calculations. The final wR_2 was 0.1054 (all data) and R_1 was 0.0362 (I > 2(I)). CCDC deposition number: 2110086

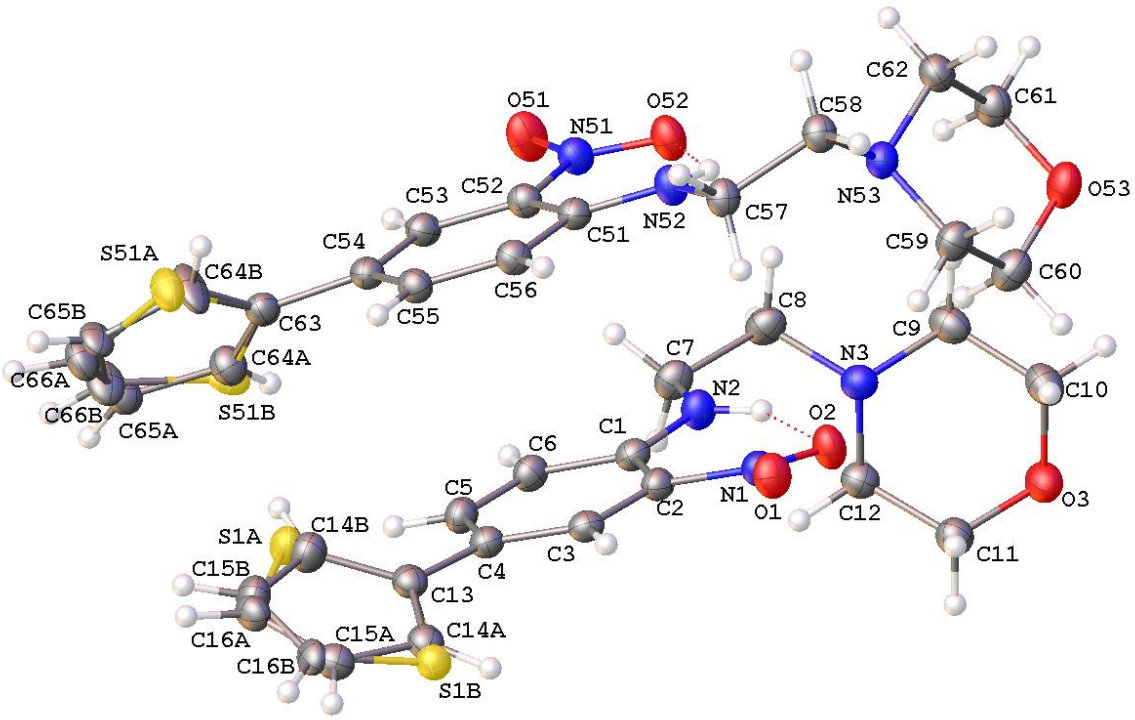


Fig S3. Crystal structure of **11** with ADP ellipsoids displayed at 50% occupancy

12

Experimental. Single red lath-shaped crystals were recrystallised from DCM by slow evaporation. A suitable crystal 0.30×0.07×0.01 mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku 007HF diffractometer equipped with HF Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000HE hybrid pixel array detector. The crystal was kept at a steady T = 100(2) K during data collection. The structure was solved in the space group $P2_12_12_1$ (# 19) by intrinsic phasing methods using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2018/3 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model except for H-atoms bonded to N-atoms which have been located in the difference map and refined with a riding model.

Crystal Data. $C_{17}H_{21}N_3O_4$, M_r = 331.37, orthorhombic, $P2_12_12_1$ (No. 19), a = 7.10820(10) Å, b = 14.5273(2) Å, c = 31.5780(5) Å, $\alpha = \beta = \gamma = 90°$, V = 3260.84(8) Å^3, T = 100(2) K, Z = 8, Z' = 2, μ(CuK$_\alpha$) = 0.804 mm^{-1}, 30636 reflections measured, 6152 unique (R_{int} = 0.0668) which were used in all calculations. The final wR_2 was 0.1309 (all data) and R_1 was 0.0533 (I > 2(I)). CCDC deposition number: 2110087

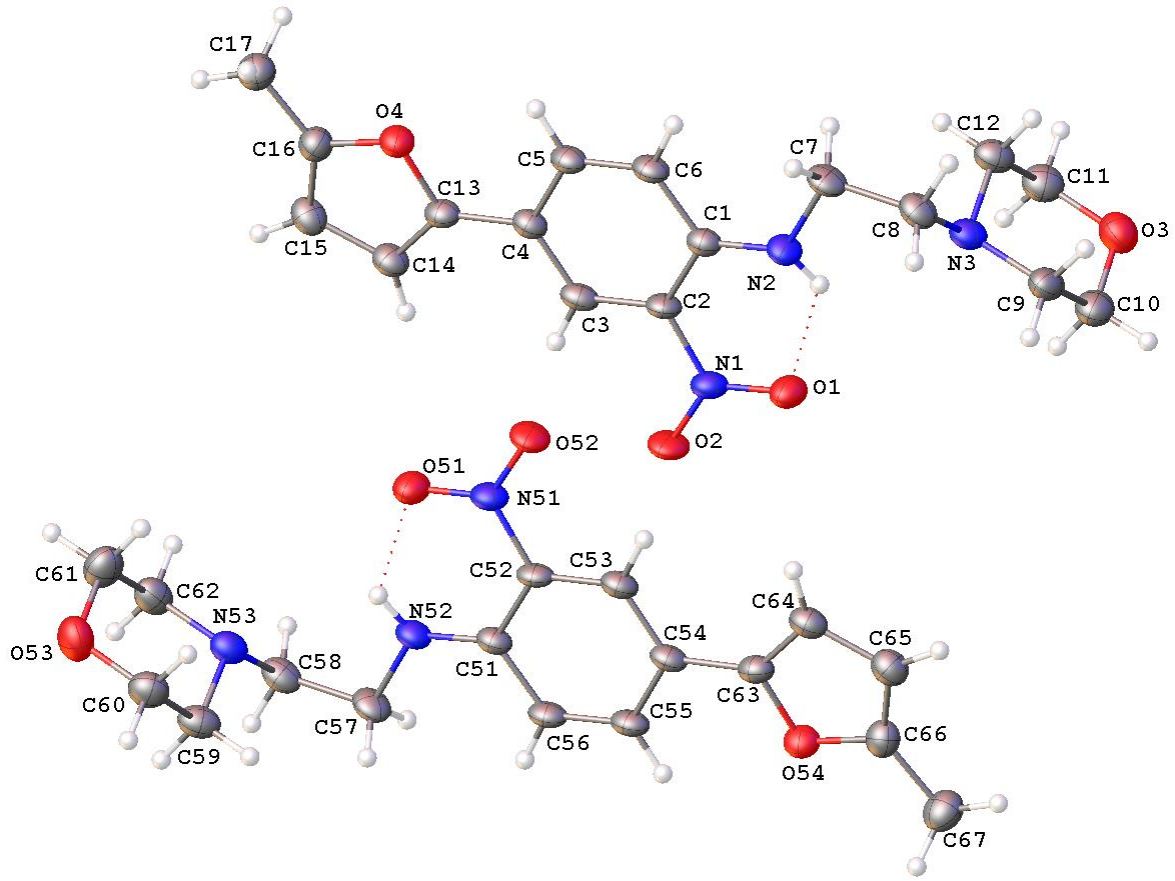


Fig S4. Crystal structure of **12** with ADP ellipsoids displayed at 50% occupancy

13

Experimental. Single orange block-shaped crystals were recrystallised from a mixture of DCM and hexane by slow evaporation. A suitable crystal (0.08×0.07×0.07) mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku FRE+ diffractometer equipped with Arc)Sec VHF Varimax confocal mirrors and an AFC12 goniometer and HyPix 6000HE hybrid pixel array detector. The crystal was kept at T = 100(2) K during data collection. The structure was solved in the space group Pccn (# 56) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2018/3 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model except H3 bonded to N3 which was located in the difference map and refined with the riding model.

Crystal Data. $C_{17}H_{19}N_4O_3Cl$, M_r = 362.81, orthorhombic, Pccn (No. 56), a = 31.8053(5) Å, b = 14.6164(3) Å, c = 7.25740(10) Å, $\alpha = \beta = \gamma = 90°$, V = 3373.81(10) Å^3, T = 100(2) K, Z = 8, Z' = 1, μ(MoK$_\alpha$) = 0.252, 42045 reflections measured, 4341 unique (R_{int} = 0.0372) which were used in all calculations. The final wR_2 was 0.0895 (all data) and R_1 was 0.0340 (I > 2(I)). CCDC deposition number: 2110088

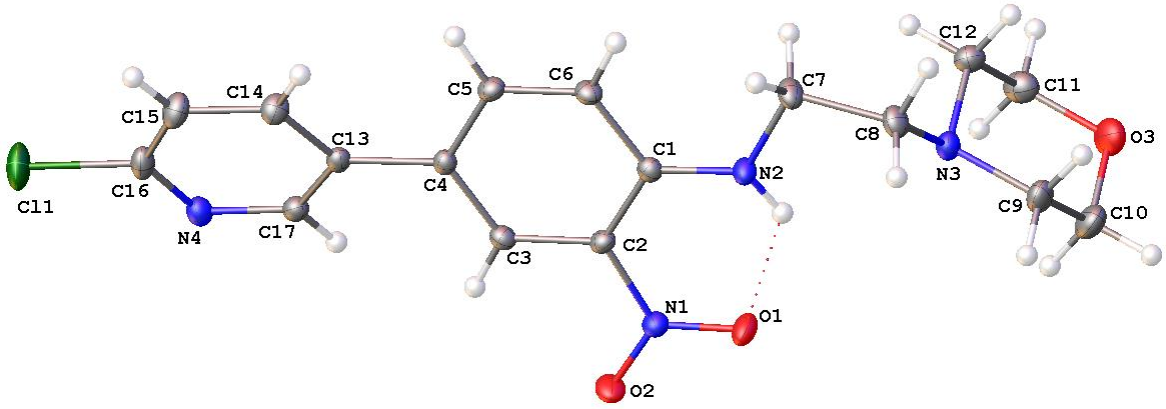


Fig S5. Crystal structure of **13** with ADP ellipsoids displayed at 50% occupancy

14

Experimental. Single orange plate-shaped crystals were recrystallised from DCM by slow evaporation. A suitable crystal 0.12×0.10×0.02 mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku 007HF diffractometer equipped with HF Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000HE hybrid pixel array detector. The crystal was kept at a steady T = 100(2) K during data collection. The structure was solved in the space group $P2_1/n$ (# 14) by intrinsic phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2018/3 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model except for H-atoms bonded to N-atoms which have been located in the difference map and refined with a riding model.

Crystal Data. $C_{17}H_{19}FN_4O_3$, M_r = 346.36, monoclinic, $P2_1/n$ (No. 14), a = 14.59320(10) Å, b = 7.25830(10) Å, c = 31.5918(4) Å, β = 102.7490(10)°, $\alpha = \gamma$ = 90°, V = 3263.76(7) Å^3, T = 100(2) K, Z = 8, Z' = 2, μ(CuK$_\alpha$) = 0.893 mm^{-1}, 33171 reflections measured, 6140 unique (R_{int} = 0.0296) which were used in all calculations. The final wR_2 was 0.1054 (all data) and R_1 was 0.0424 (I > 2(I)). CCDC deposition number: 2110089

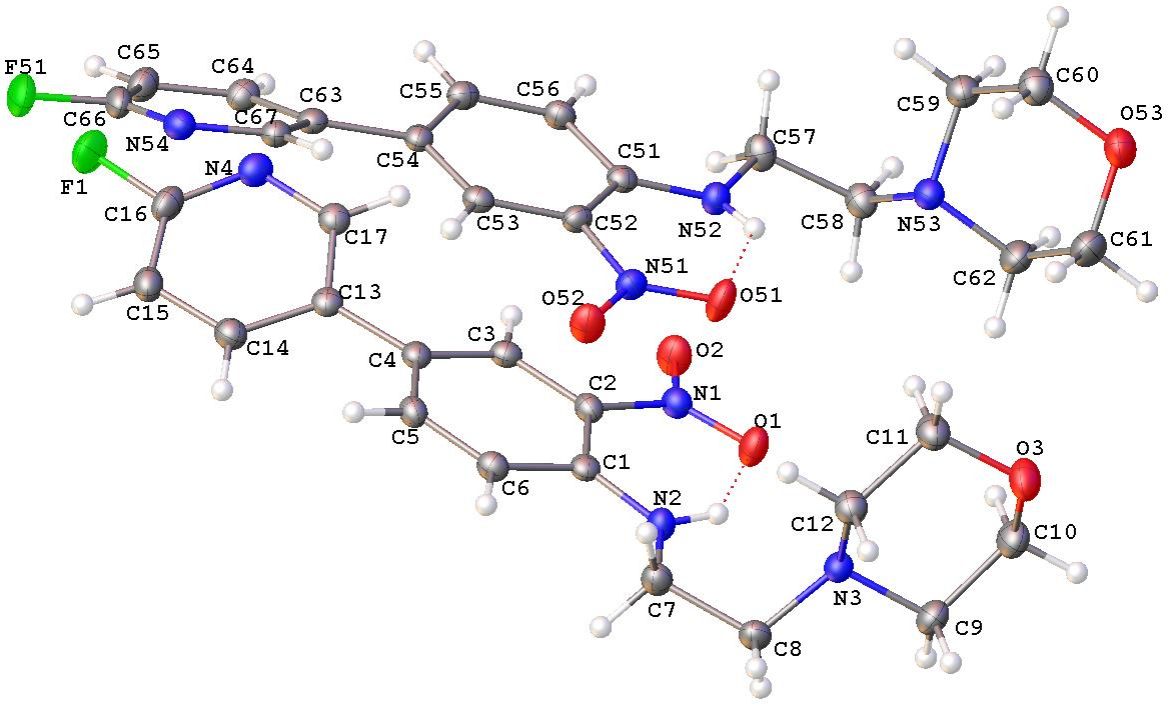


Fig S6. Crystal structure of **14** with ADP ellipsoids displayed at 50% occupancy

15

Experimental. Single colourless block-shaped crystals were recrystallised from a mixture of DCM and hexane by slow evaporation. A suitable crystal 0.36×0.35×0.15 mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on an Rigaku FRE+ diffractometer equipped with Arc)Sec VHF Varimax confocal mirrors and an AFC12 goniometer and HyPix 6000HE hybrid pixel array detector. The crystal was kept at a steady T = 100(2) K during data collection. The structure was solved in the space group $P2_1/c$ (# 14) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2018/3 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Most hydrogen atom positions were calculated geometrically and refined using the riding model except H-atoms bonded to O-atoms were located in the difference map and refined with the riding model. The H-atom bonded to O3/O4 is disordered over two positions (ca. 43:57 respectively).

Crystal Data. $C_{26}H_{31}N_3O_4$, M_r = 449.54, monoclinic, $P2_1/c$ (No. 14), a = 13.0873(2) Å, b = 12.4610(2) Å, c = 14.1989(2) Å, β = 95.111(2)°, $\alpha = \gamma$ = 90°, V = 2306.36(6) Å^3, T = 100(2) K, Z = 4, Z' = 1, μ(MoK$_\alpha$) = 0.088, 36365 reflections measured, 7030 unique (R_{int} = 0.0328) which were used in all calculations. The final wR_2 was 0.1390 (all data) and R_1 was 0.0496 (I > 2(I)). CCDC deposition number: 2110090

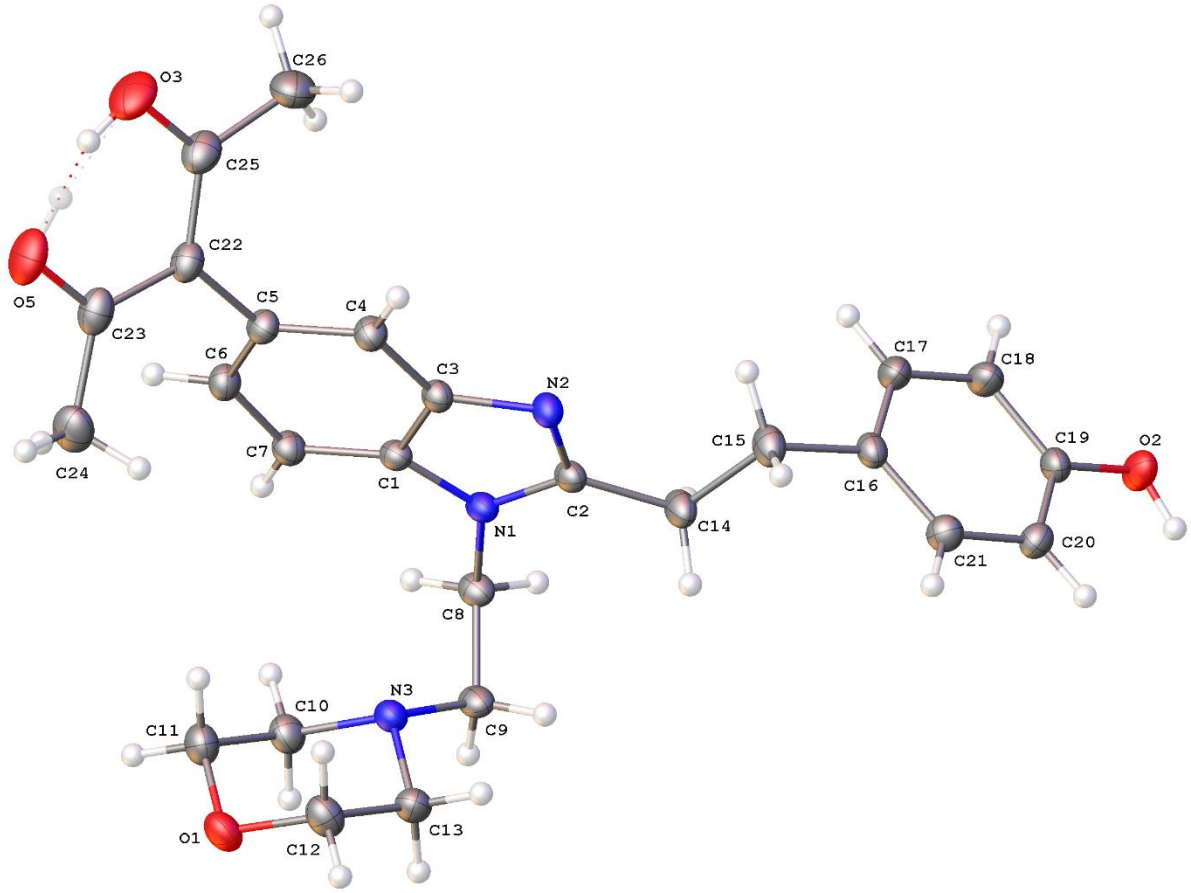
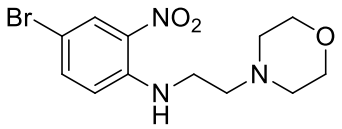


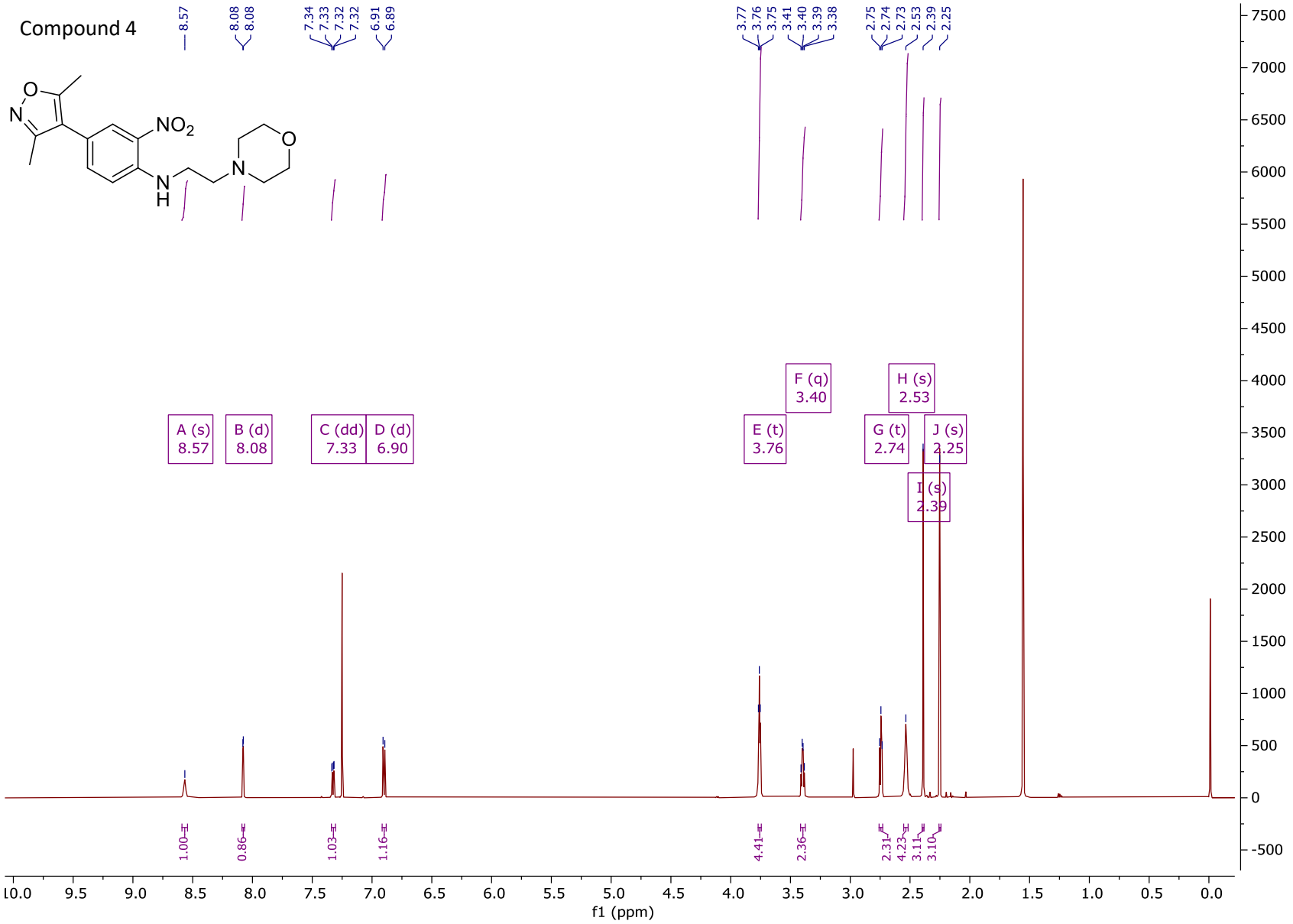
Fig S7. Crystal structure of **15** with ADP ellipsoids displayed at 50% occupancy

Contains Scans of spectra for final compounds

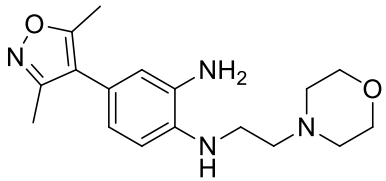
Compound **3**


Br
NO2
N
H
O
N

8.53
8.33
8.32
7.50
7.50
7.48
7.48
7.26 CDCl3
6.74
6.72
3.76
3.36
3.35
3.33
3.32
2.73
2.72
2.71
2.52
0.95
0.94
1.00
1.07
4.31
2.23
2.23
4.08
f1 (ppm)

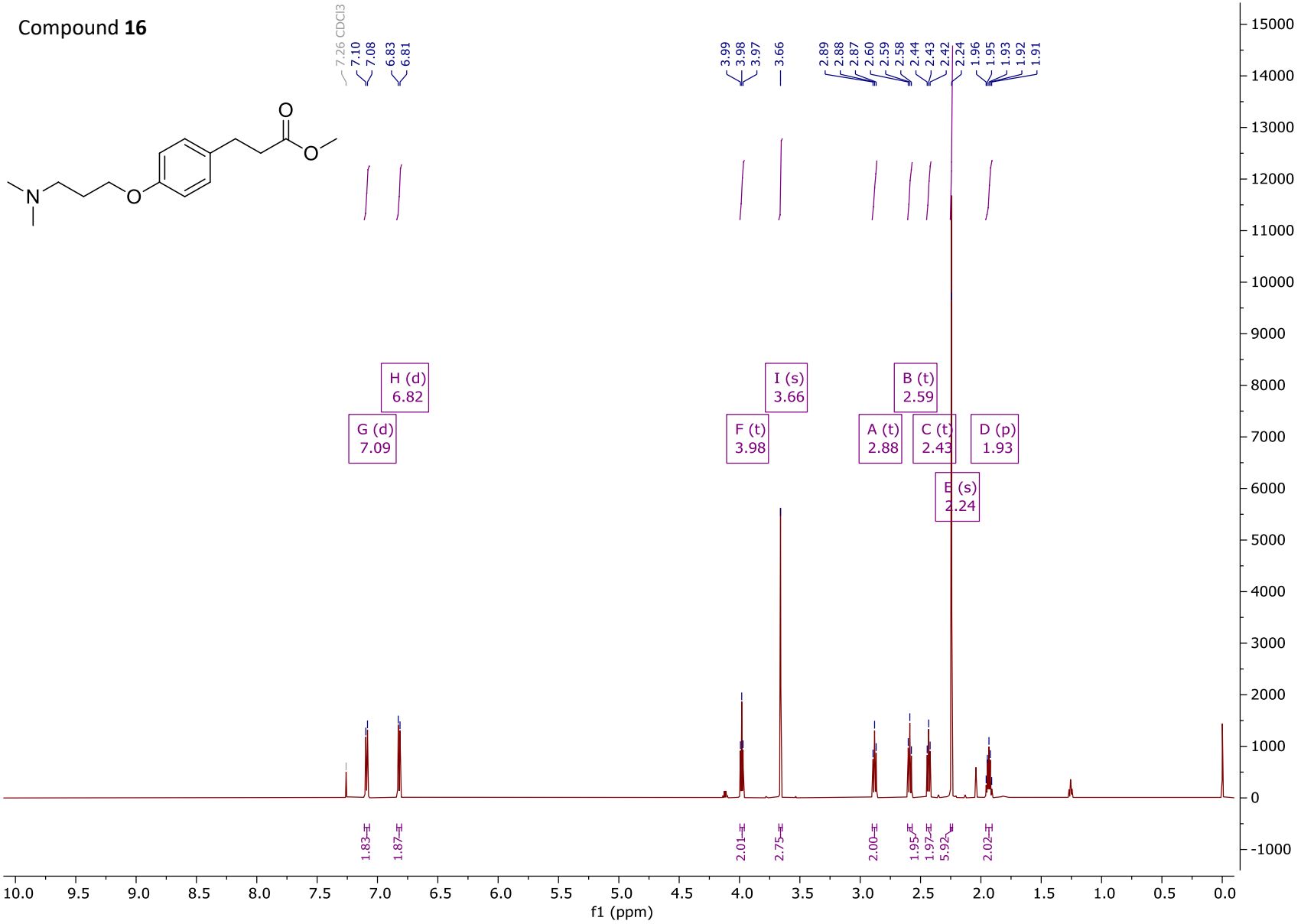

Compound 4
8.57
8.08
8.08
7.34
7.33
7.32
7.32
6.91
6.89
3.77
3.76
3.75
3.41
3.40
3.39
3.38
2.75
2.74
2.73
2.53
2.39
2.25
A (s) 8.57
B (d) 8.08
C (dd) 7.33
D (d) 6.90
E (t) 3.76
F (q) 3.40
G (t) 2.74
H (s) 2.53
I (s) 2.39
J (s) 2.25
1.00
0.86
1.03
1.16
4.41
2.36
2.31
4.23
3.11
3.10
f1 (ppm)

Compound **8**

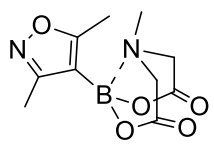

O
N
NH2
N
H
N
O

7.26 CDCl3
6.68
6.59
3.73
3.47
3.21
3.20
3.19
2.72
2.71
2.70
2.50
2.38
2.25
B (s) 6.59
A (s) 6.68
I (s) 3.47
C (s) 3.73
D (t) 3.20
F (s) 2.50
E (t) 2.71
H (s) 2.25
G (s) 2.38
2.00
0.94
4.06
1.86
2.32
2.40
4.36
3.14
3.02
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
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)

Compound **16**

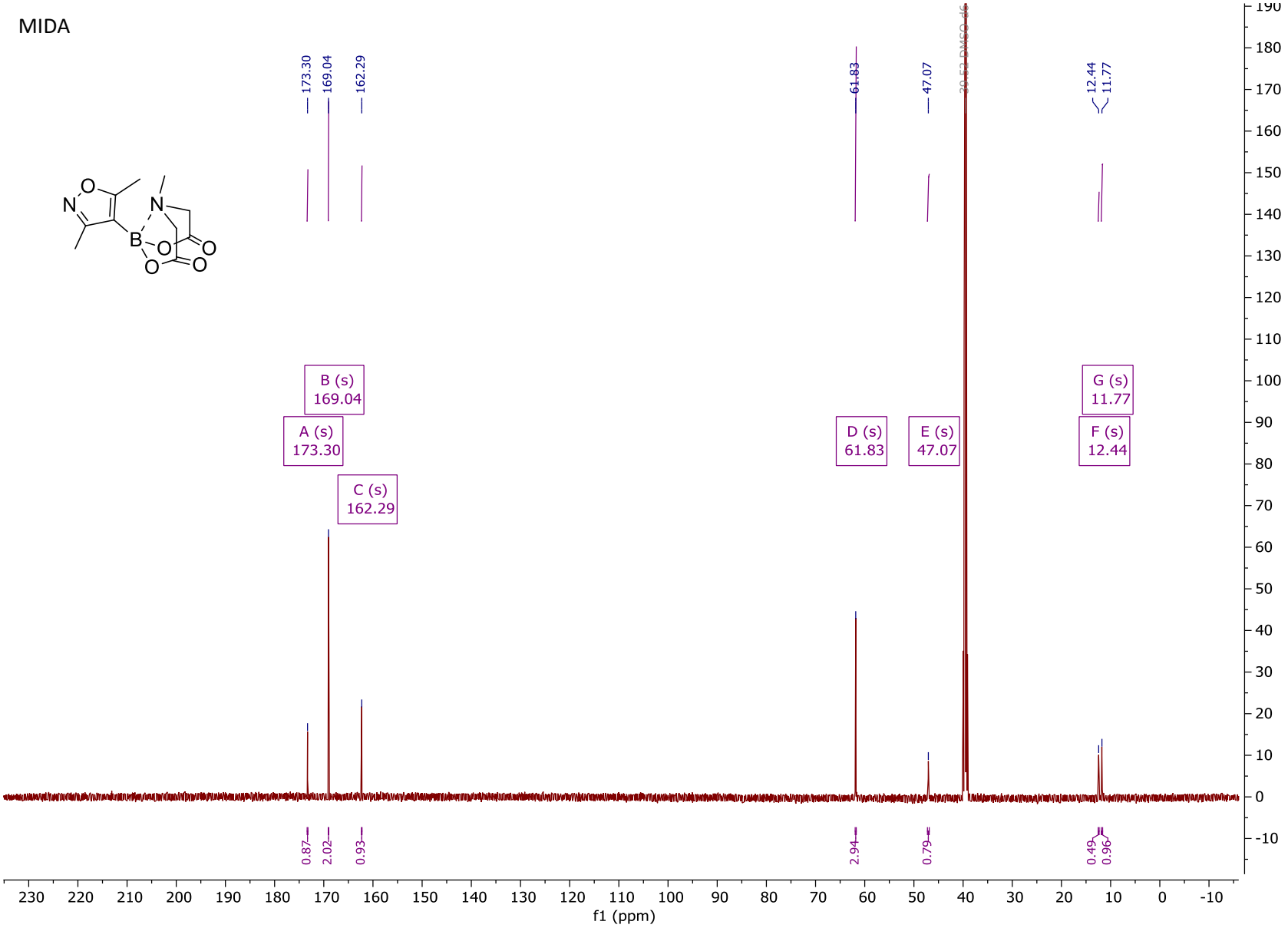

7.26 CDCl3
7.10
7.08
6.83
6.81
3.99
3.98
3.97
3.66
2.89
2.88
2.87
2.60
2.59
2.58
2.44
2.43
2.42
2.24
1.96
1.95
1.93
1.92
1.91
H (d) 6.82
G (d) 7.09
I (s) 3.66
F (t) 3.98
B (t) 2.59
A (t) 2.88
C (t) 2.43
D (p) 1.93
E (s) 2.24
1.83
1.87
2.01
2.75
2.00
1.95
1.97
5.92
2.02
f1 (ppm)

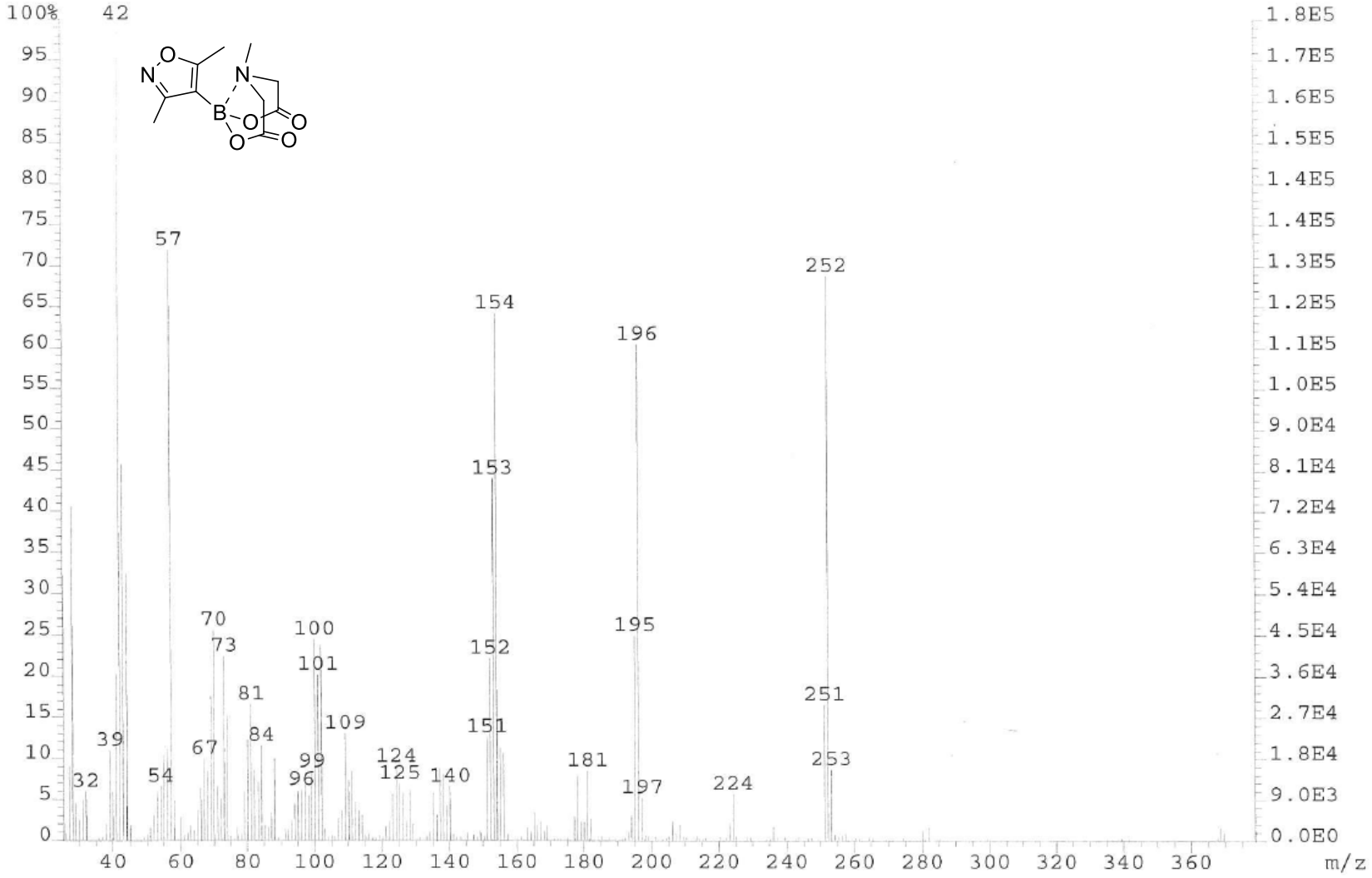
MIDA ester


O
N
N
B
O
O
O
O

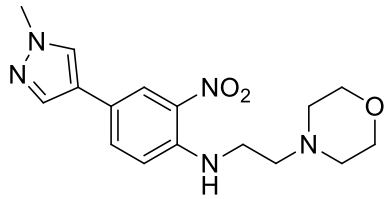
4.36
4.33
4.15
4.12
2.50 DMSO-d6
2.32
2.13
2.00
2.09
3.05
2.96
3.05
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

MIDA


173.30
169.04
162.29
61.83
47.07
39.52 DMSO-d6
12.44
11.77
B (s)
169.04
A (s)
173.30
C (s)
162.29
D (s)
61.83
E (s)
47.07
G (s)
11.77
F (s)
12.44
0.87
2.02
0.93
2.94
0.79
0.49
0.96
f1 (ppm)

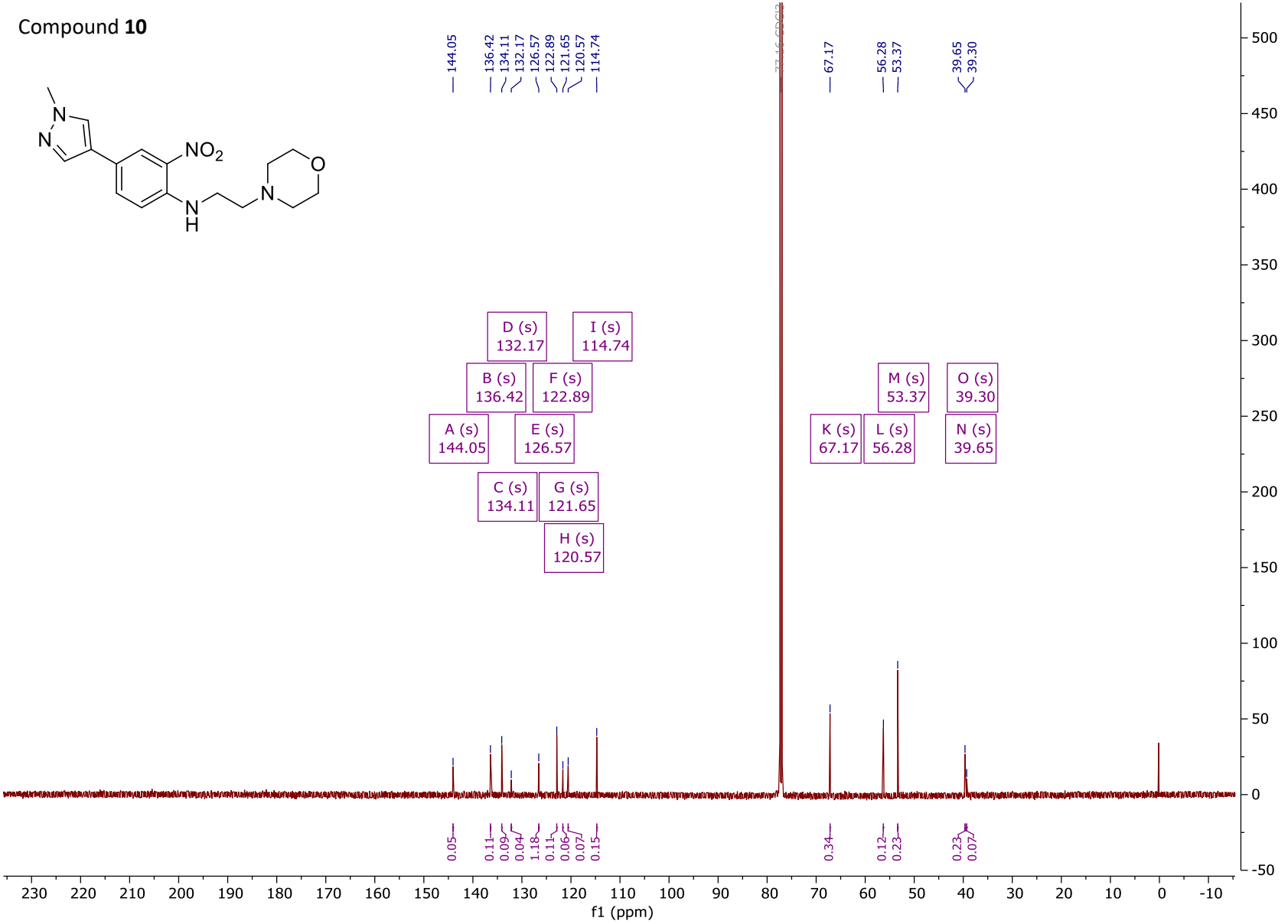

File:ANTHONY9133 Ident:18 Acq:15-JAN-2018 17:39:07 +0:54 Cal:LO
AutoSpecE EI+ Magnet BpI:181021 TIC:2434993 Flags:HALL
File Text:AKE-006B-3
100%
42
57
252
154
196
153
195
152
251
151
253
181
197
224
70
73
100
101
81
109
84
39
67
124
125
140
99
96
54
32
m/z

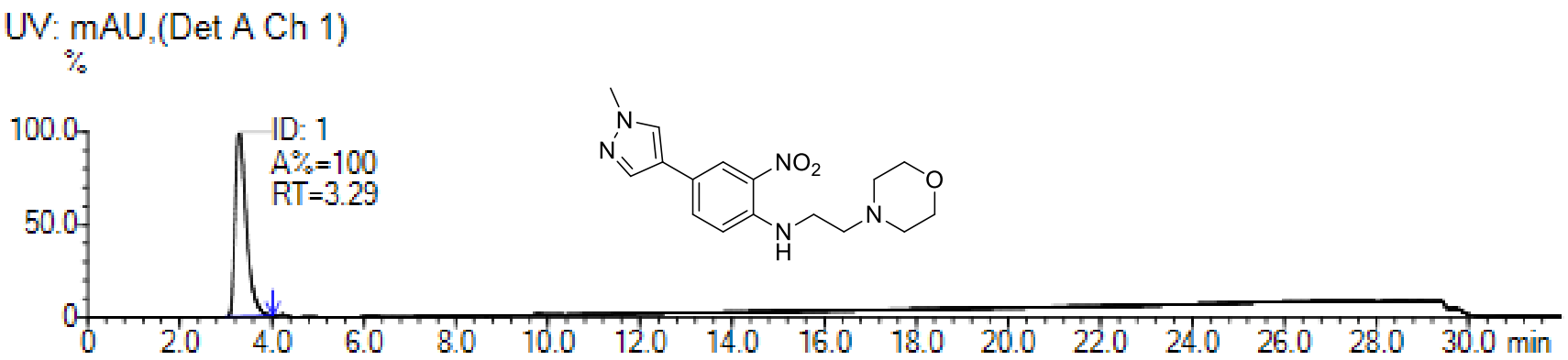
Compound **10**


N
N
NO2
O
N
N
H

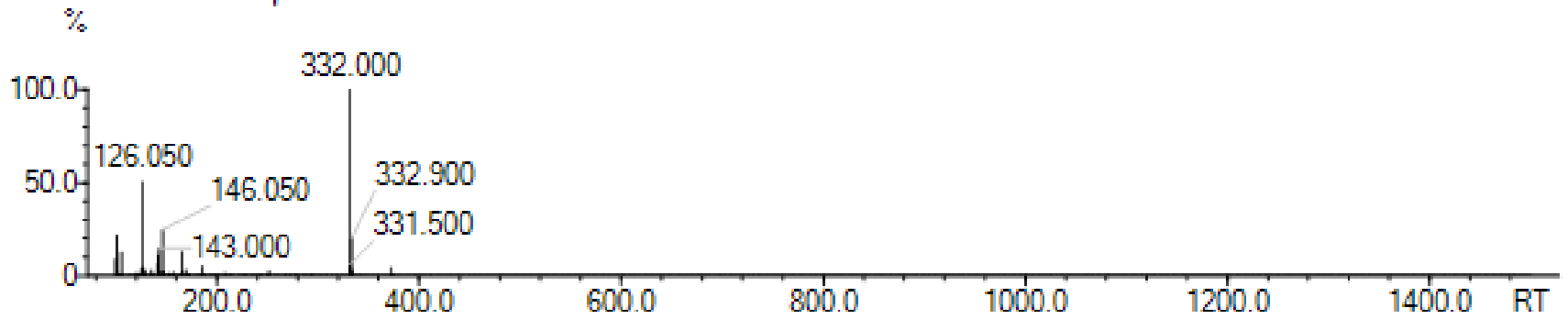
8.50
8.27
8.27
7.71
7.58
7.57
7.57
7.56
7.56
6.86
6.85
3.94
3.77
3.76
3.76
3.41
3.40
3.39
3.38
2.75
2.74
2.73
2.53
G (d) 8.27
I (s) 7.58
B (m) 3.76
E (s) 2.53
F (s) 8.50
H (s) 7.71
J (d) 6.85
A (s) 3.94
D (t) 2.74
K (dd) 7.57
C (q) 3.40
1.00
0.93
0.94
0.96
1.04
1.08
3.00
4.14
2.17
2.12
3.98
f1 (ppm)

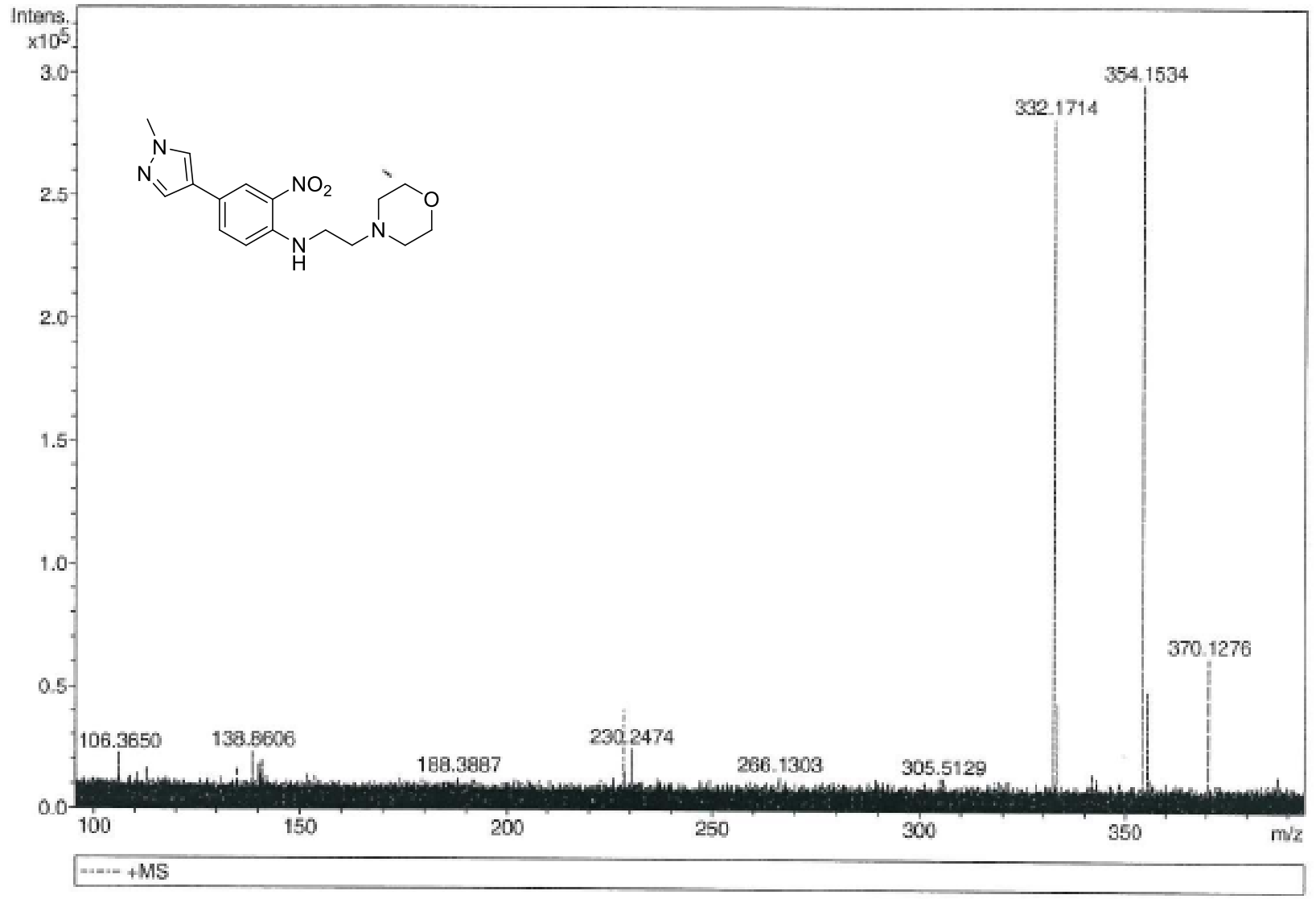
Compound **10**


144.05
136.42
134.11
132.17
126.57
122.89
121.65
120.57
114.74
77.16 CDCl3
67.17
56.28
53.37
39.65
39.30
D (s) 132.17
I (s) 114.74
B (s) 136.42
F (s) 122.89
M (s) 53.37
O (s) 39.30
A (s) 144.05
E (s) 126.57
K (s) 67.17
L (s) 56.28
N (s) 39.65
C (s) 134.11
G (s) 121.65
H (s) 120.57
0.05
0.11
0.09
0.04
1.18
0.11
0.06
0.07
0.15
0.34
0.12
0.23
0.23
0.07
f1 (ppm)

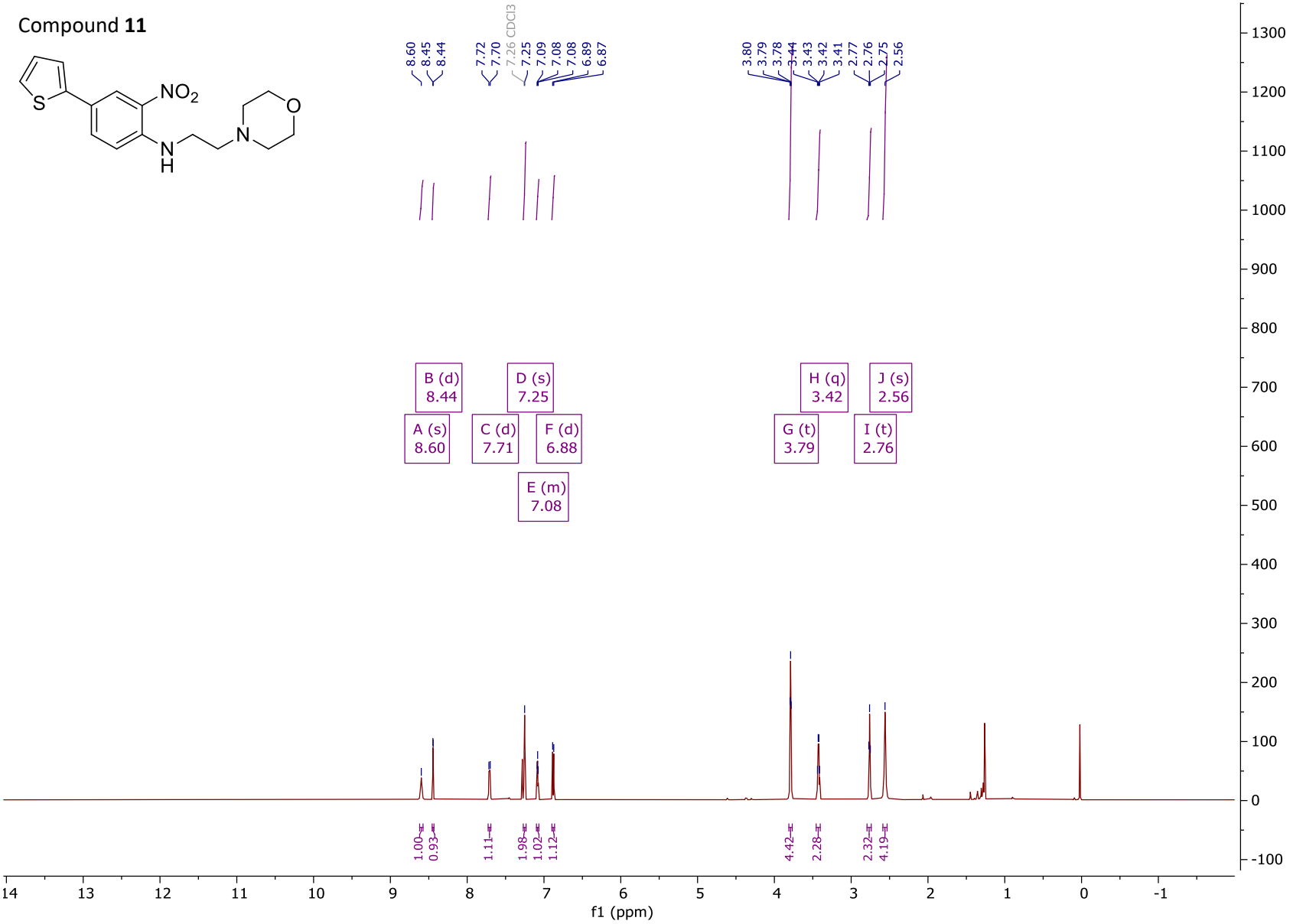


Peak ID	RT (min)	Channel	Area (%)
1	3.29	1	100

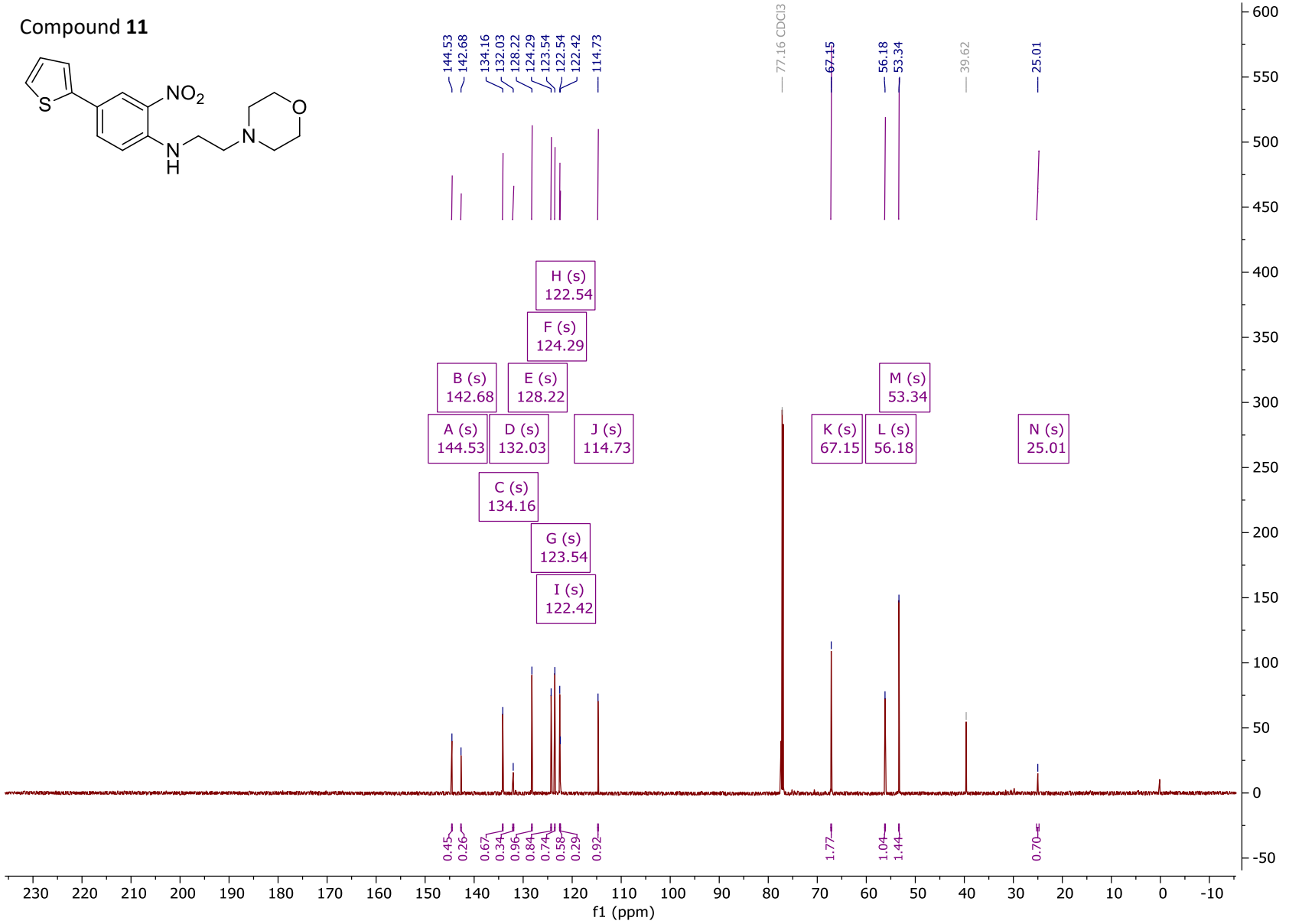


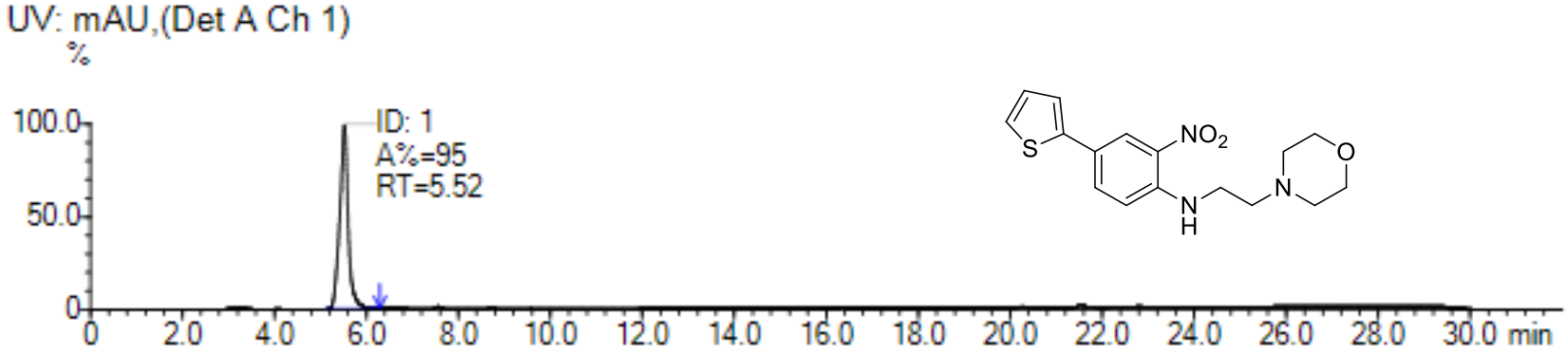

Intens.
x10^5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
354.1534
332.1714
370.1276
106.3650
138.9606
188.3887
230.2474
266.1303
305.5129
100
150
200
250
300
350
m/z
+MS

Compound **11**

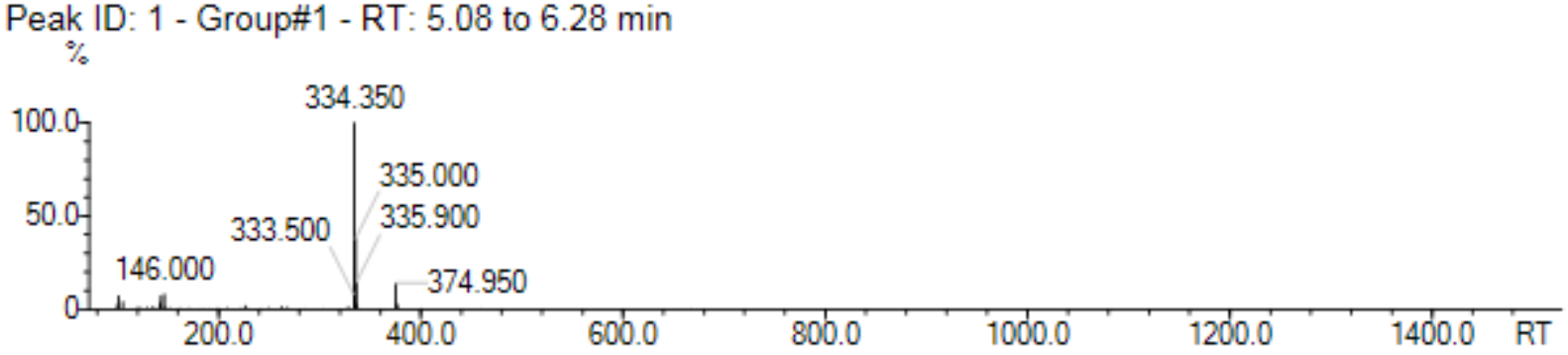

NO2
S
N
H
O
N
8.60
8.45
8.44
7.72
7.70
7.26 CDCl3
7.25
7.09
7.08
7.08
6.89
6.87
3.80
3.79
3.78
3.44
3.43
3.42
3.41
2.77
2.76
2.75
2.56
B (d) 8.44
D (s) 7.25
H (q) 3.42
J (s) 2.56
A (s) 8.60
C (d) 7.71
F (d) 6.88
G (t) 3.79
I (t) 2.76
E (m) 7.08
1.00
0.93
1.11
1.98
1.02
1.12
4.42
2.28
2.32
4.19
f1 (ppm)

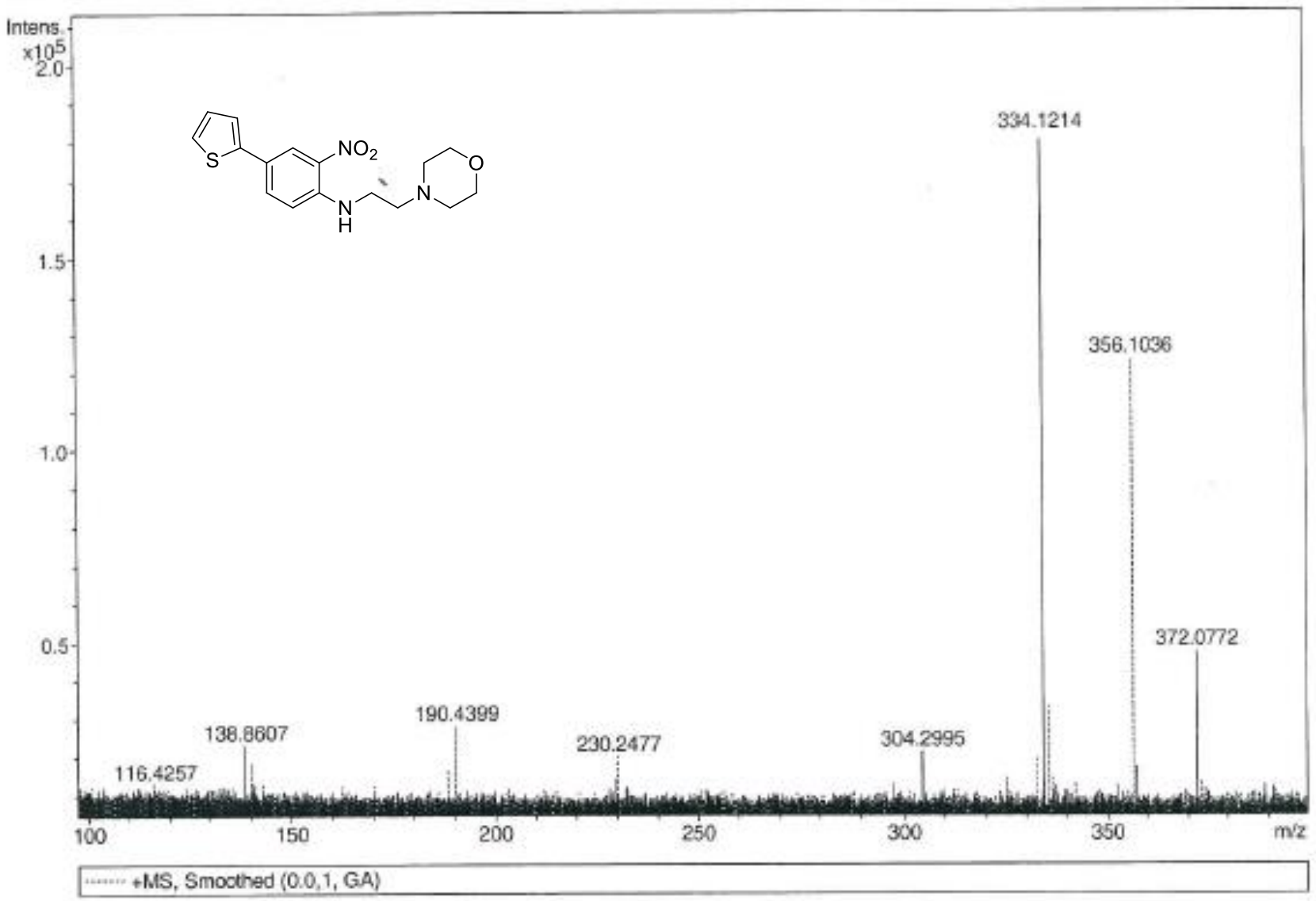
Compound **11**


144.53
142.68
134.16
132.03
128.22
124.29
123.54
122.54
122.42
114.73
77.16 CDCl3
67.15
56.18
53.34
39.62
25.01
H (s) 122.54
F (s) 124.29
B (s) 142.68
E (s) 128.22
M (s) 53.34
A (s) 144.53
D (s) 132.03
J (s) 114.73
K (s) 67.15
L (s) 56.18
N (s) 25.01
C (s) 134.16
G (s) 123.54
I (s) 122.42
0.45
0.26
0.67
0.34
0.96
0.84
0.74
0.58
0.29
0.92
1.77
1.04
1.44
0.70
f1 (ppm)

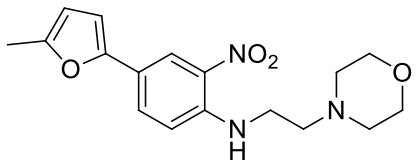


Peak ID	RT (min)	Channel	Area (%)
1	5.52	1	95.0



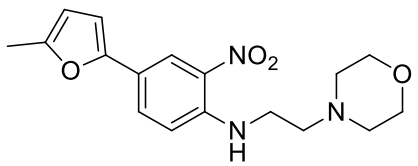

Intens.
x10^5
2.0
1.5
1.0
0.5
NO2
S
O
N
N
H
334.1214
356.1036
372.0772
190.4399
138.8607
230.2477
304.2995
116.4257
100
150
200
250
300
350
m/z
+MS, Smoothed (0.0,1, GA)

Compound **12**

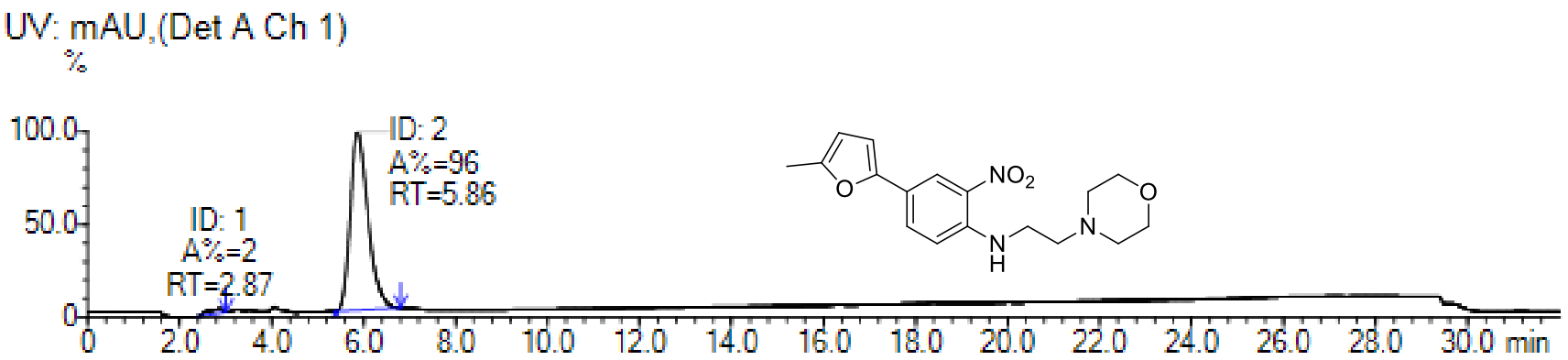

NO2
O
N
H
N
O

8.56
8.42
7.70
7.68
7.26 CDCl3
6.84
6.83
6.42
6.41
6.03
3.76
3.41
3.40
3.39
3.38
2.74
2.73
2.72
2.53
2.36
K (s) 8.42
C (s) 6.42
F (q) 3.39
H (s) 2.53
J (s) 8.56
A (d) 7.69
B (d) 6.83
D (s) 6.03
E (s) 3.76
G (t) 2.73
I (s) 2.36
1.06
0.91
1.02
1.07
1.00
0.97
4.04
2.07
2.11
4.08
3.00
f1 (ppm)

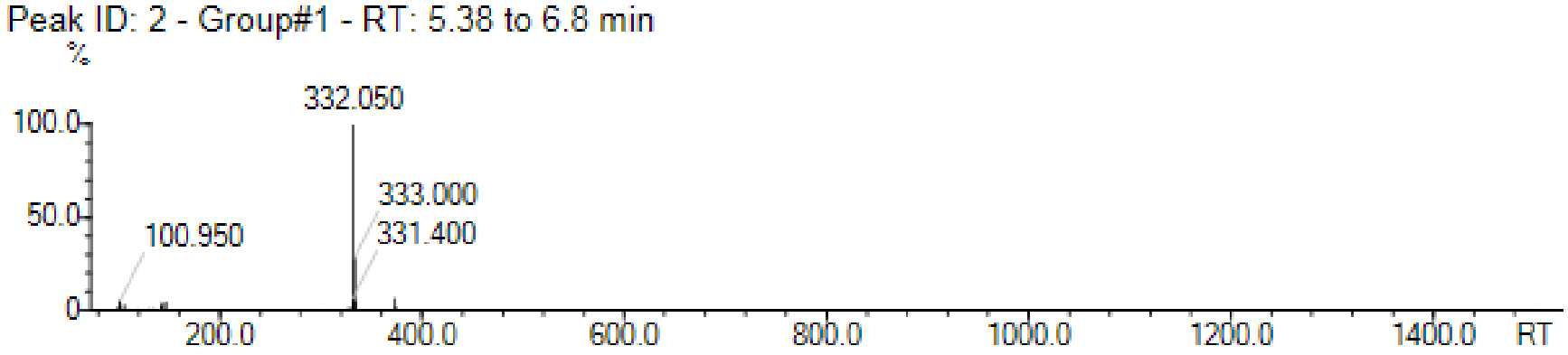
Compound **12**

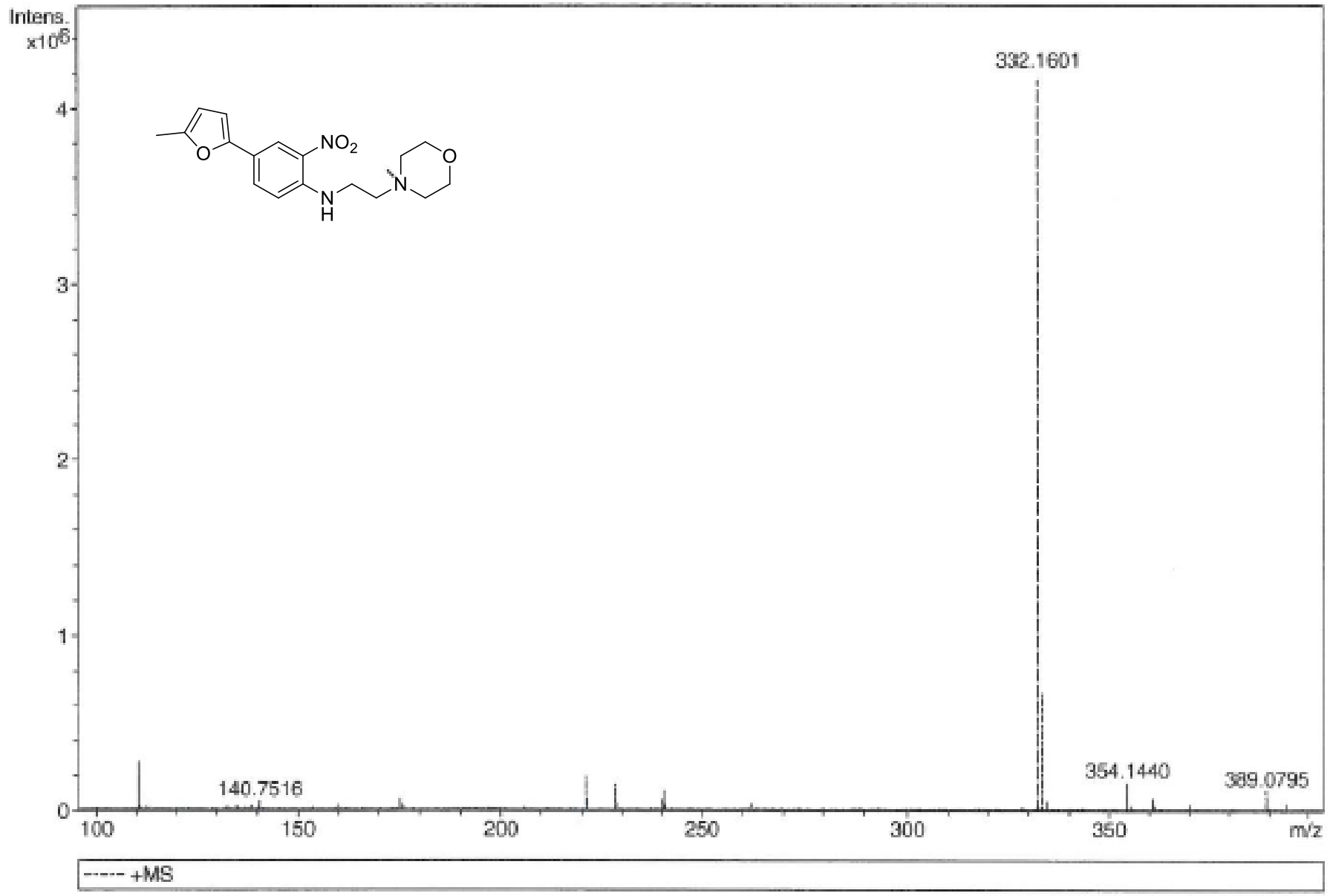

NO2
O
N
H
N
O

151.80
150.74
144.18
132.03
131.88
121.02
119.62
114.52
107.77
104.89
77.16 CDCl3
67.14
56.22
53.34
39.60
13.82
B (s) 150.74
E (s) 131.88
H (s) 114.52
N (s) 53.34
A (s) 151.80
D (s) 132.03
G (s) 119.62
J (s) 104.89
L (s) 67.14
M (s) 56.22
O (s) 39.60
P (s) 13.82
C (s) 144.18
F (s) 121.02
I (s) 107.77
0.08
0.18
0.11
0.09
0.17
0.18
0.09
1.03
0.18
0.18
0.75
0.25
0.49
0.25
0.14
f1 (ppm)

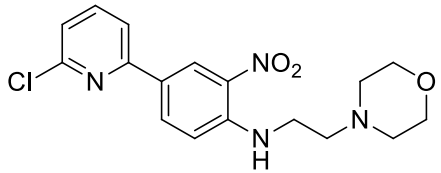


Peak ID	RT (min)	Channel	Area (%)
1	2.87	1	2.2
2	5.86	1	96.4



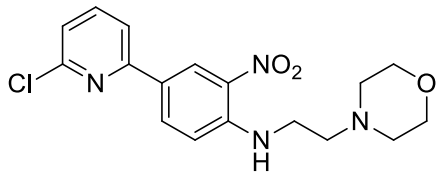

Intens.
x10^6
4
3
2
1
0
332.1601
354.1440
389.0795
140.7516
100
150
200
250
300
350
m/z
----- +MS

Compound **13**

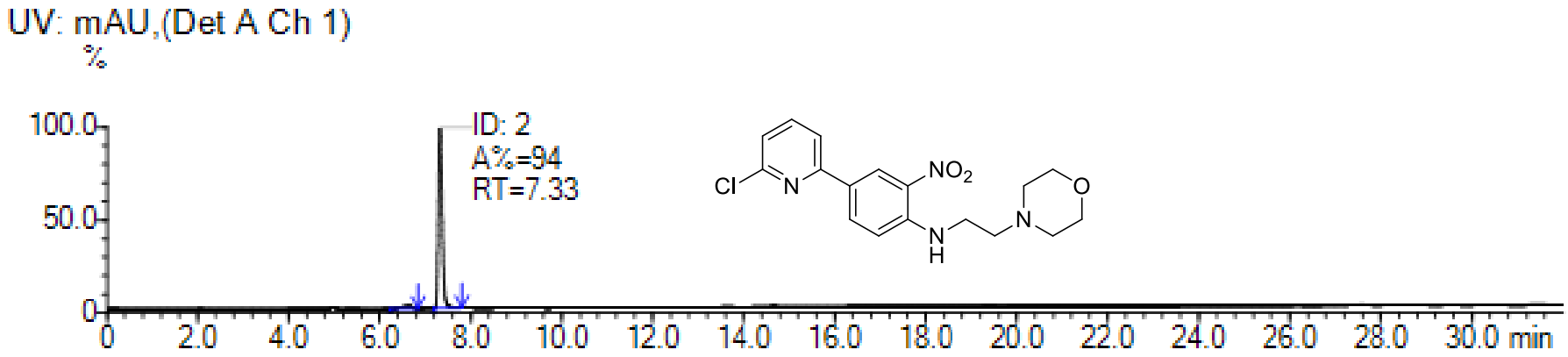

Cl
N
NO2
N
H
N
O

8.65
8.64
8.63
8.57
8.41
8.40
7.82
7.81
7.80
7.67
7.67
7.66
7.65
7.39
7.37
7.26 cddl3
7.26 CDCl3
6.96
6.94
3.78
3.77
3.76
3.44
3.43
3.42
3.41
2.76
2.75
2.74
2.54
1.67 H2O
B (d) 8.57
E (dd) 7.66
I (q) 3.42
K (s) 2.54
A (t) 8.64
D (dd) 7.81
G (d) 6.95
H (t) 3.77
J (t) 2.75
C (d) 8.41
F (d) 7.38
1.01
0.93
0.91
1.04
1.09
0.97
1.06
3.97
2.03
2.05
4.01
f1 (ppm)

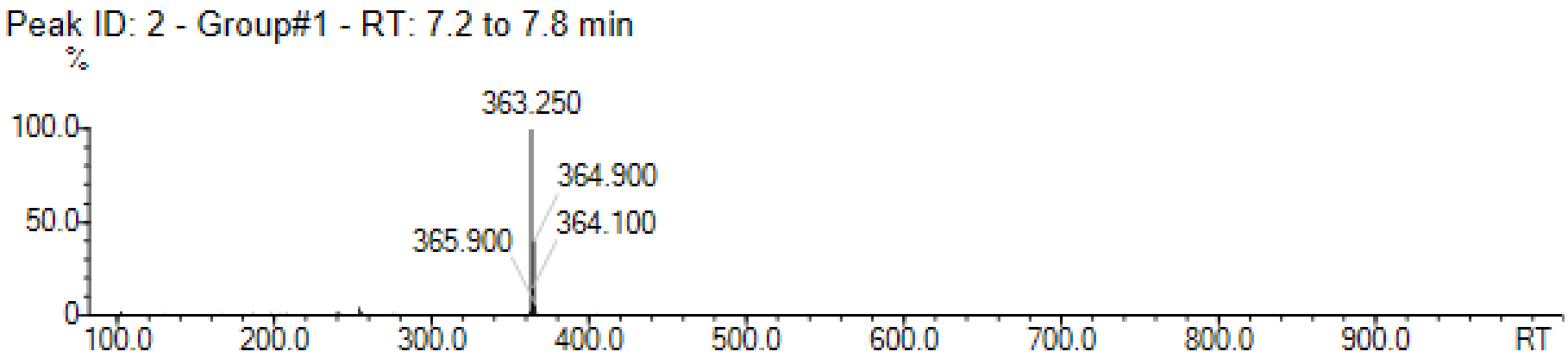
Compound **13**

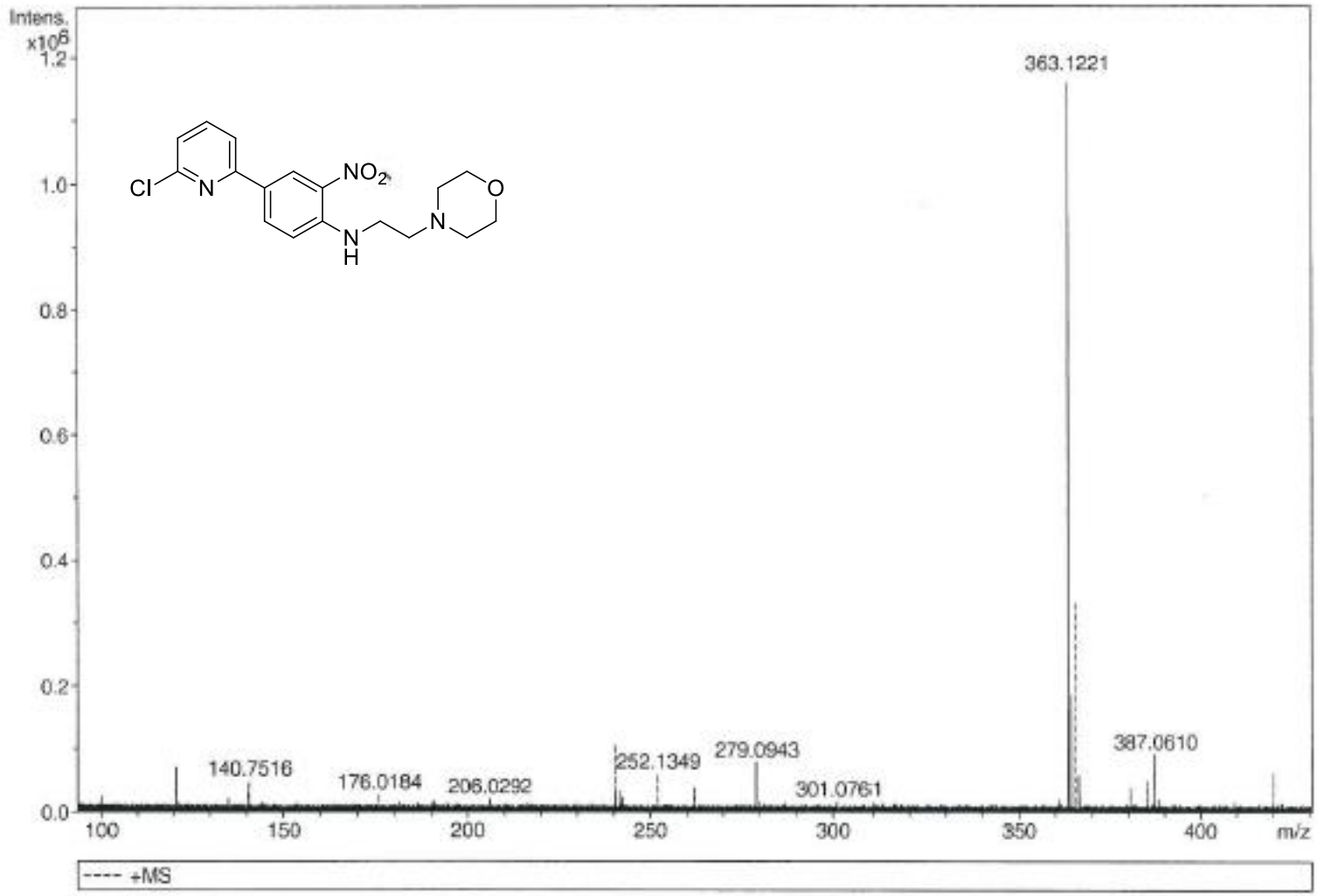

Cl
N
NO2
N
H
N
O

150.19
147.22
145.08
136.32
134.40
133.70
132.41
125.04
124.47
123.49
115.32
77.16 CDCl3
67.14
56.08
53.32
39.60
I (s) 124.47
F (s) 133.70
B (s) 147.22
E (s) 134.40
K (s) 115.32
O (s) 53.32
A (s) 150.19
D (s) 136.32
J (s) 123.49
M (s) 67.14
N (s) 56.08
P (s) 39.60
C (s) 145.08
G (s) 132.41
H (s) 125.04
0.18
0.23
0.14
0.40
0.22
0.28
0.11
0.31
0.21
0.13
0.30
0.97
0.43
0.60
1.28
f1 (ppm)

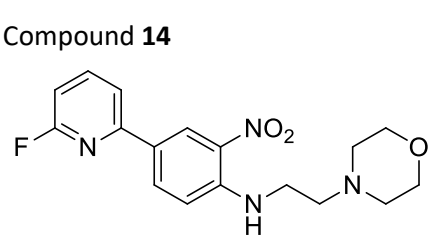


Peak ID	RT (min)	Channel	Area (%)
1	6.66	1	3.5
2	7.33	1	93.8



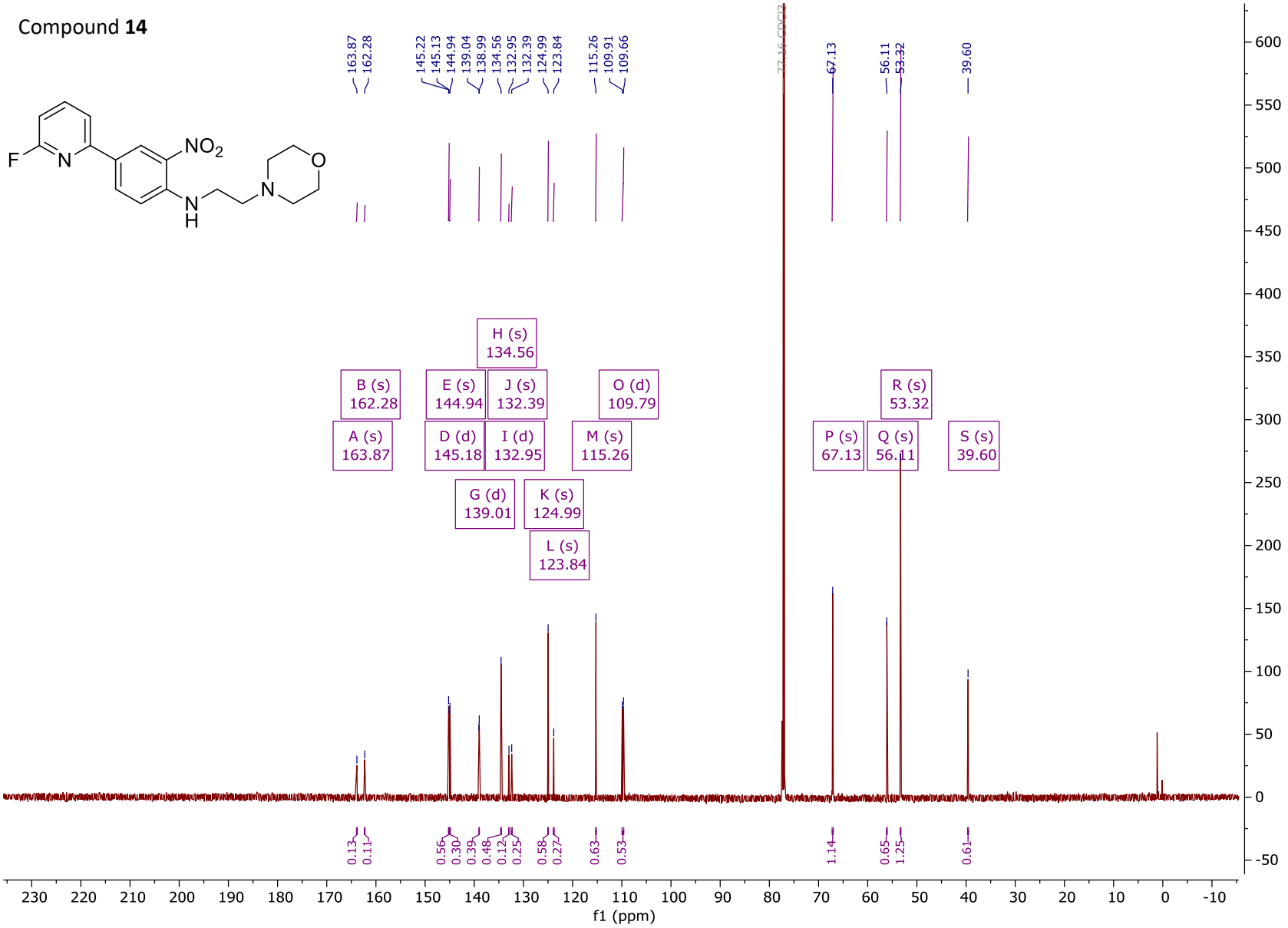

Intens.
x10^6
1.2
1.0
0.8
0.6
0.4
0.2
0.0
363.1221
387.0610
279.0943
252.1349
140.7516
176.0184
206.0292
301.0761
100
150
200
250
300
350
400
m/z
---- +MS
Cl
N
NO2
N
H
N
O

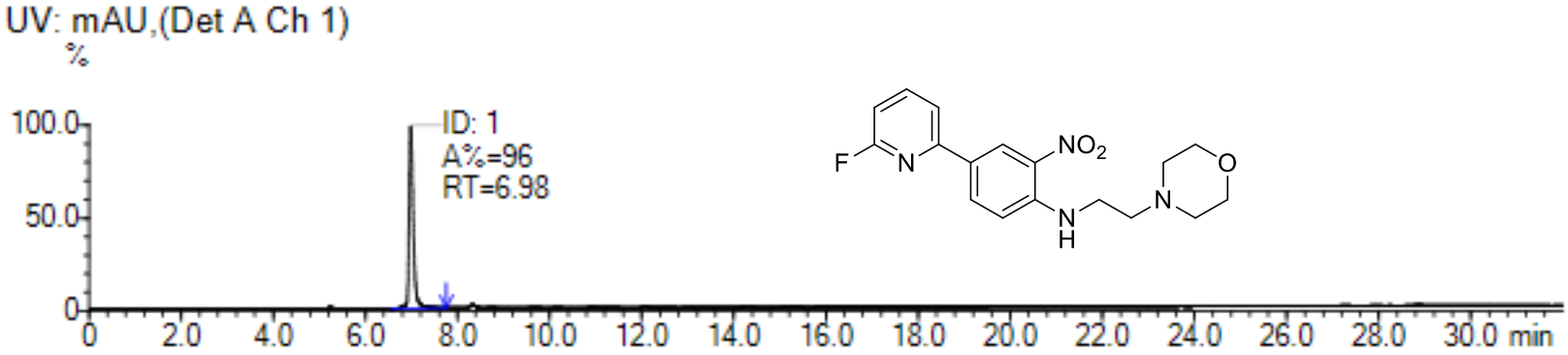
Compound **14**


F
N
NO2
N
H
N
O

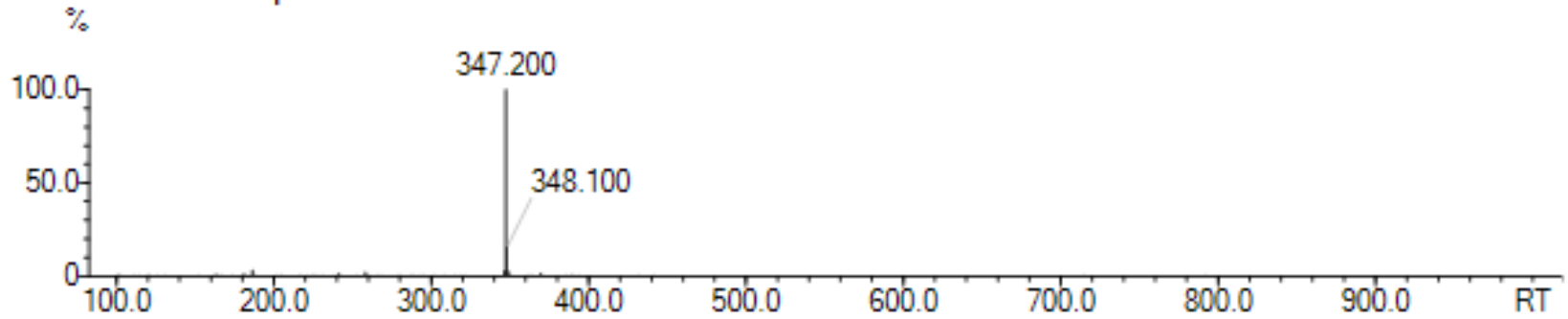
8.61
8.39
7.96
7.96
7.95
7.94
7.93
7.93
7.66
7.64
7.26 CDCl3
7.01
7.01
7.00
6.99
6.96
6.94
3.78
3.77
3.76
3.44
3.43
3.42
3.41
2.77
2.76
2.75
2.55
B (s) 8.39
D (d) 7.65
F (d) 6.95
H (q) 3.43
J (s) 2.55
A (s) 8.61
C (td) 7.94
E (dd) 7.00
G (t) 3.77
I (t) 2.76
0.91
1.74
1.00
1.02
0.97
1.05
4.15
2.18
2.13
3.95
f1 (ppm)

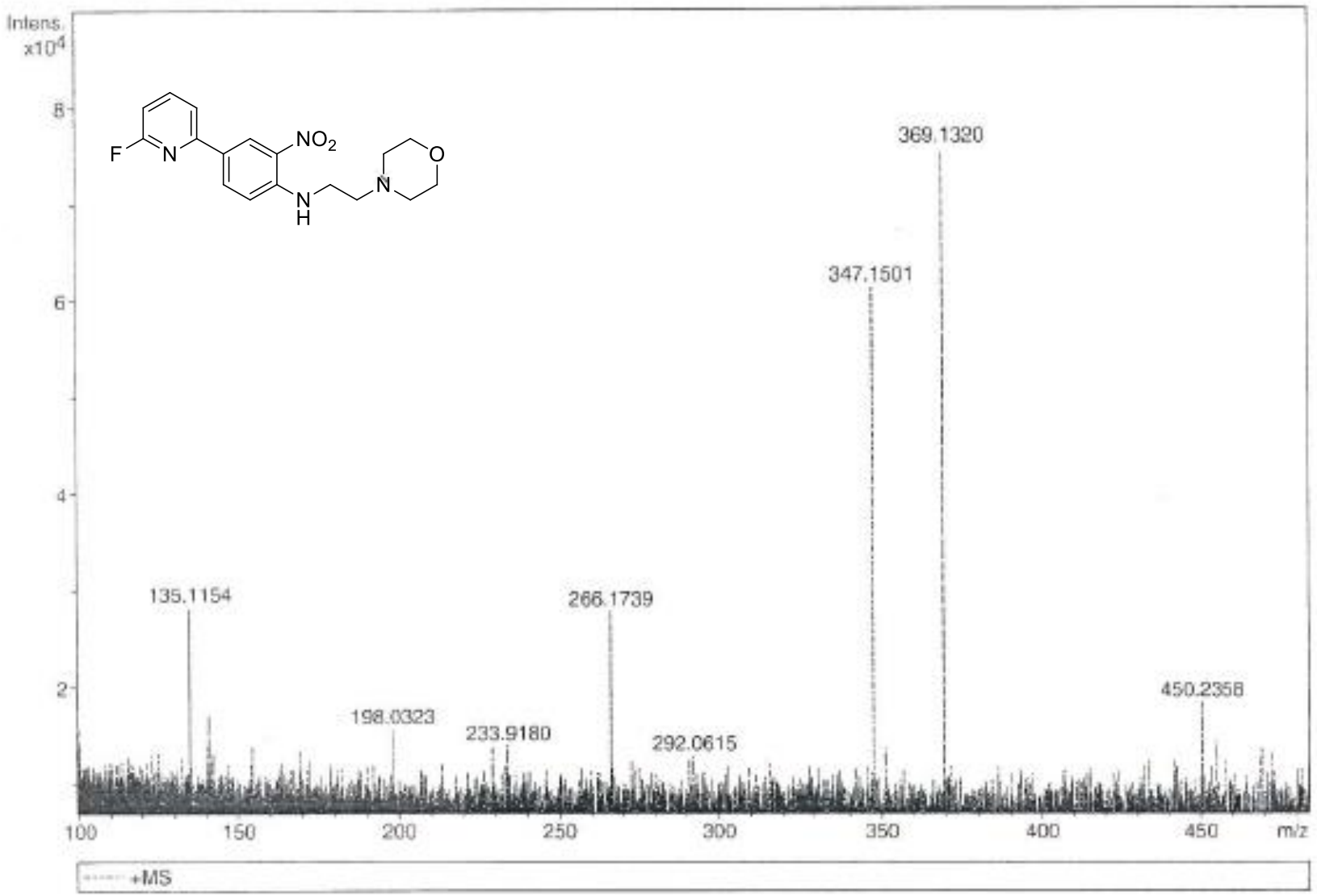
Compound **14**


F
N
NO2
N
H
N
O
163.87
162.28
145.22
145.13
144.94
139.04
138.99
134.56
132.95
132.39
124.99
123.84
115.26
109.91
109.66
77.16 CDCl3
67.13
56.11
53.32
39.60
H (s) 134.56
B (s) 162.28
E (s) 144.94
J (s) 132.39
O (d) 109.79
R (s) 53.32
A (s) 163.87
D (d) 145.18
I (d) 132.95
M (s) 115.26
P (s) 67.13
Q (s) 56.11
S (s) 39.60
G (d) 139.01
K (s) 124.99
L (s) 123.84
0.13
0.11
0.56
0.30
0.39
0.48
0.12
0.25
0.58
0.27
0.63
0.53
1.14
0.65
1.25
0.61
f1 (ppm)



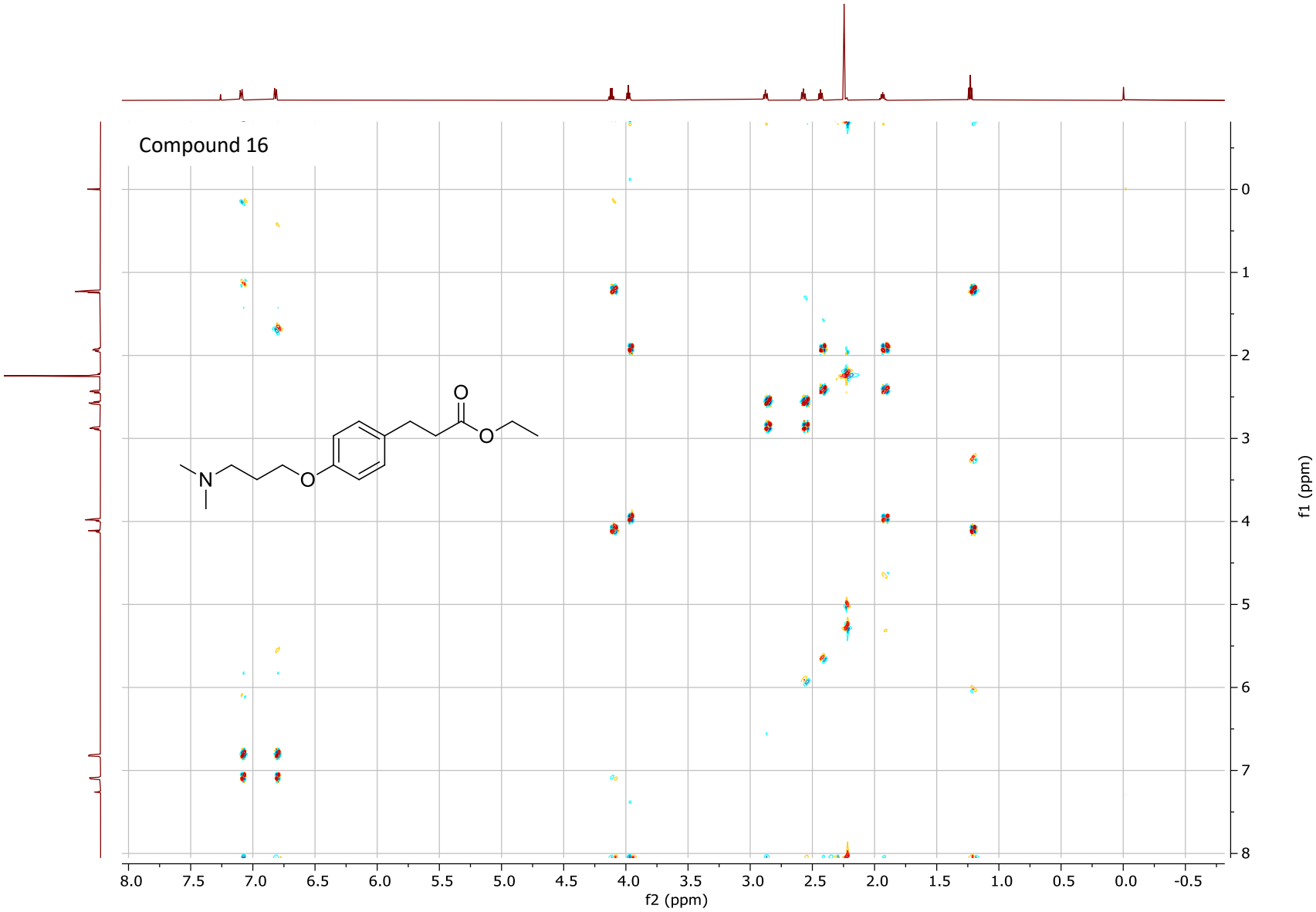
Peak ID	RT (min)	Channel	Area (%)
1	6.98	1	96.2



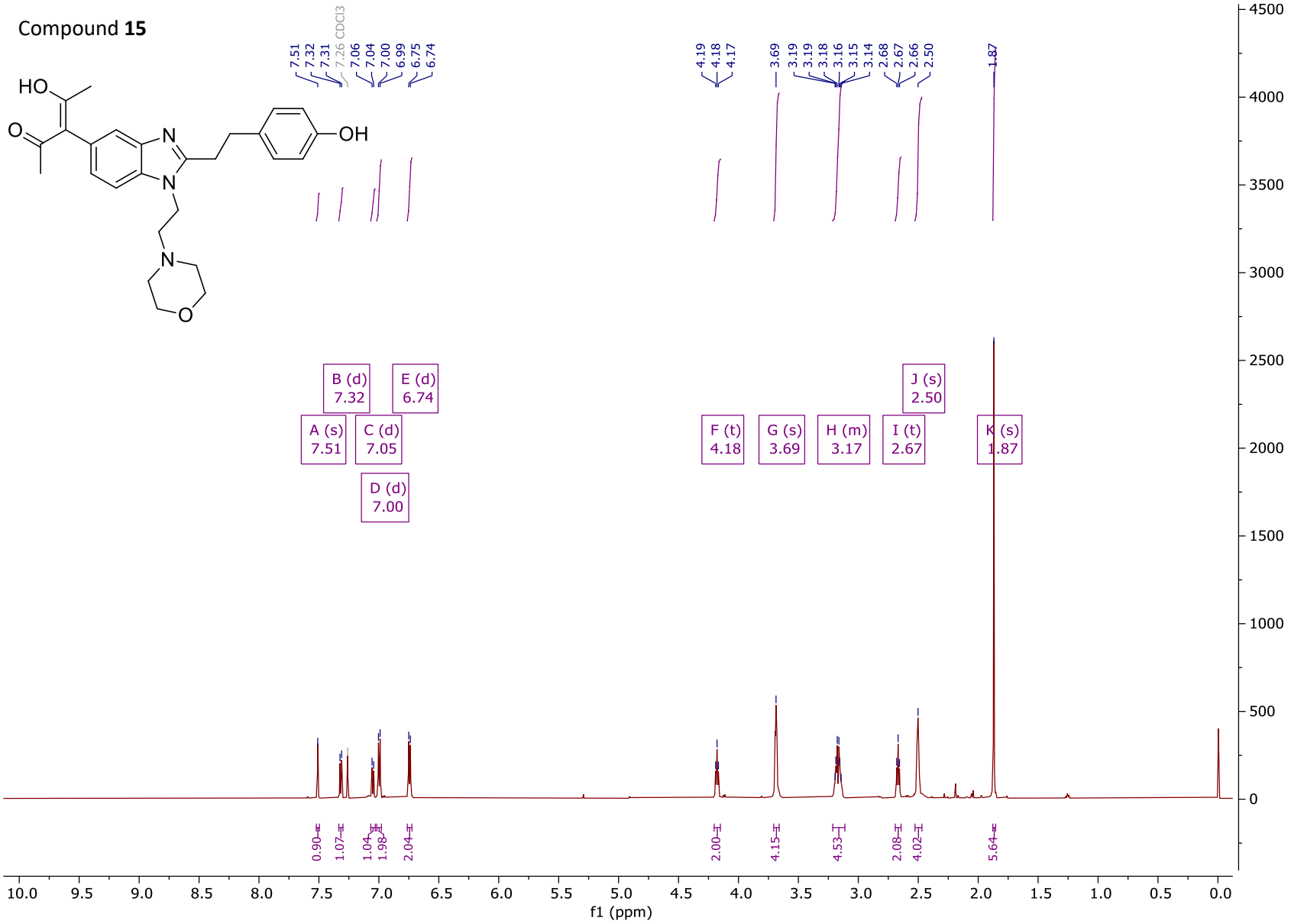

Intens.
x10^4
8
6
4
2
F
N
NO2
N
H
N
O
369.1320
347.1501
135.1154
266.1739
198.0323
233.9180
292.0615
450.2358
100
150
200
250
300
350
400
450
m/z
+MS

Compound **16**

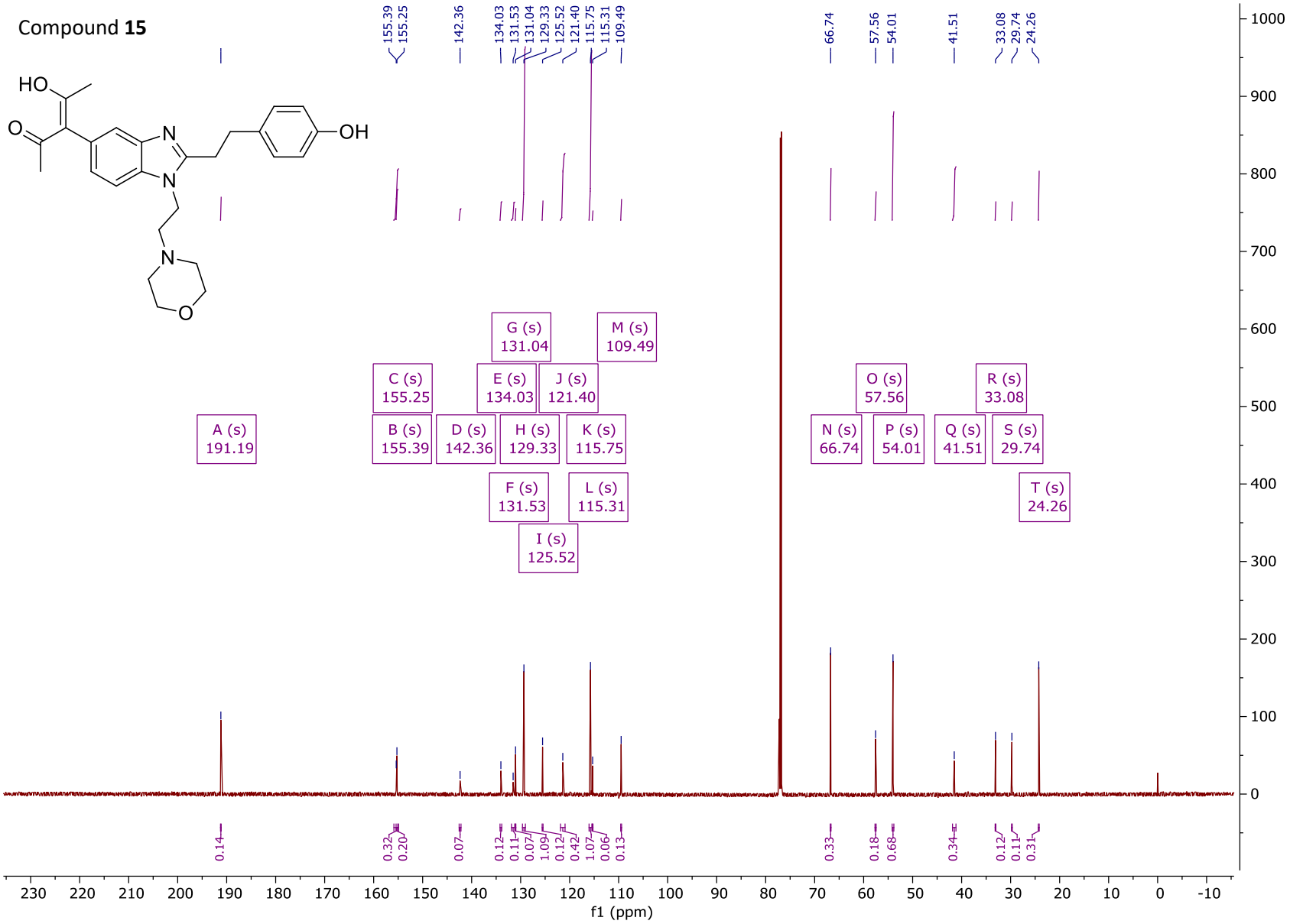

7.26 CDCl3
7.10
7.09
6.83
6.81
4.13
4.12
4.11
4.10
3.99
3.98
3.97
2.89
2.88
2.86
2.59
2.57
2.56
2.45
2.44
2.42
2.25
1.96
1.95
1.93
1.92
1.91
1.24
1.23
1.22
B (d)
6.82
D (t)
3.98
F (t)
2.57
A (d)
7.09
C (q)
4.12
E (t)
2.88
G (t)
2.44
H (p)
1.93
I (t)
1.23
2.00
2.08
2.16
2.19
2.29
2.28
2.15
2.24
3.21
f1 (ppm)

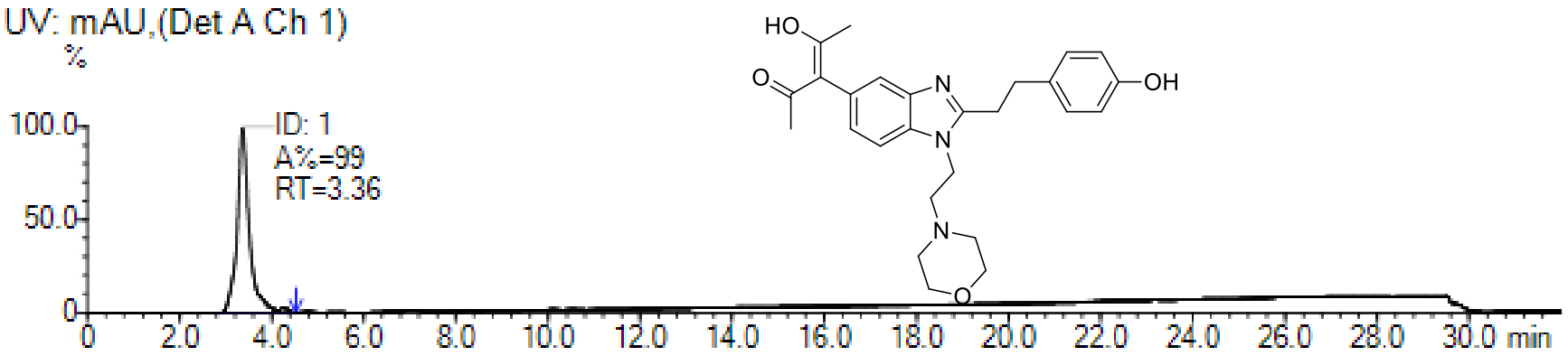

Compound 16
O
O
N
O
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
0
1
2
3
4
5
6
7
8
f1 (ppm)

Compound **15**

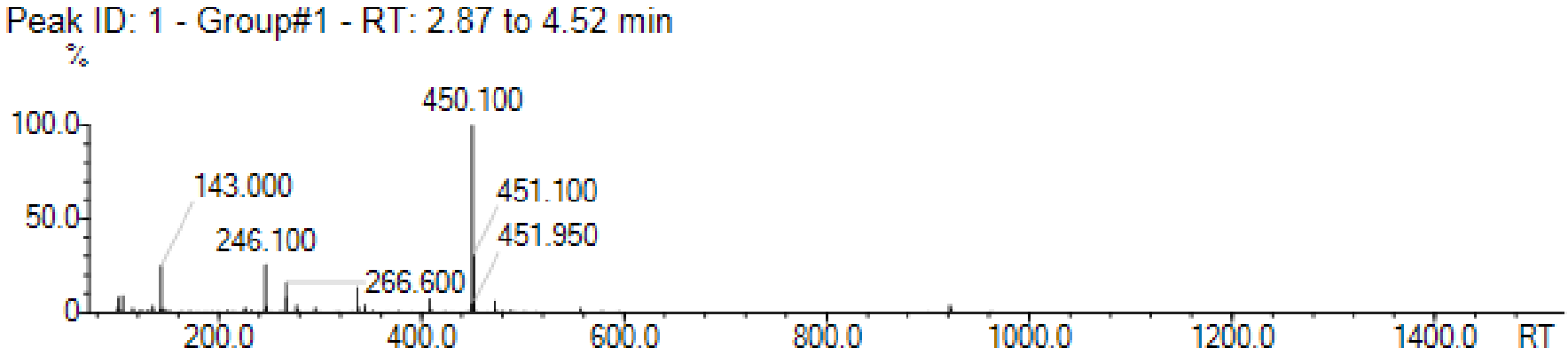

HO
O
N
N
OH
N
O
7.51
7.32
7.31
7.26 CDCl3
7.06
7.04
7.00
6.99
6.75
6.74
4.19
4.18
4.17
3.69
3.19
3.19
3.18
3.16
3.15
3.14
2.68
2.67
2.66
2.50
1.87
B (d) 7.32
E (d) 6.74
A (s) 7.51
C (d) 7.05
D (d) 7.00
F (t) 4.18
G (s) 3.69
H (m) 3.17
I (t) 2.67
J (s) 2.50
K (s) 1.87
0.90
1.07
1.04
1.98
2.04
2.00
4.15
4.53
2.08
4.02
5.64
f1 (ppm)

Compound **15**


HO
O
N
N
OH
N
O
155.39
155.25
142.36
134.03
131.53
131.04
129.33
125.52
121.40
115.75
115.31
109.49
66.74
57.56
54.01
41.51
33.08
29.74
24.26
A (s) 191.19
B (s) 155.39
C (s) 155.25
D (s) 142.36
E (s) 134.03
F (s) 131.53
G (s) 131.04
H (s) 129.33
I (s) 125.52
J (s) 121.40
K (s) 115.75
L (s) 115.31
M (s) 109.49
N (s) 66.74
O (s) 57.56
P (s) 54.01
Q (s) 41.51
R (s) 33.08
S (s) 29.74
T (s) 24.26
0.14
0.32
0.20
0.07
0.12
0.11
0.07
1.09
0.12
0.42
1.07
0.06
0.13
0.33
0.18
0.68
0.34
0.12
0.11
0.31
f1 (ppm)

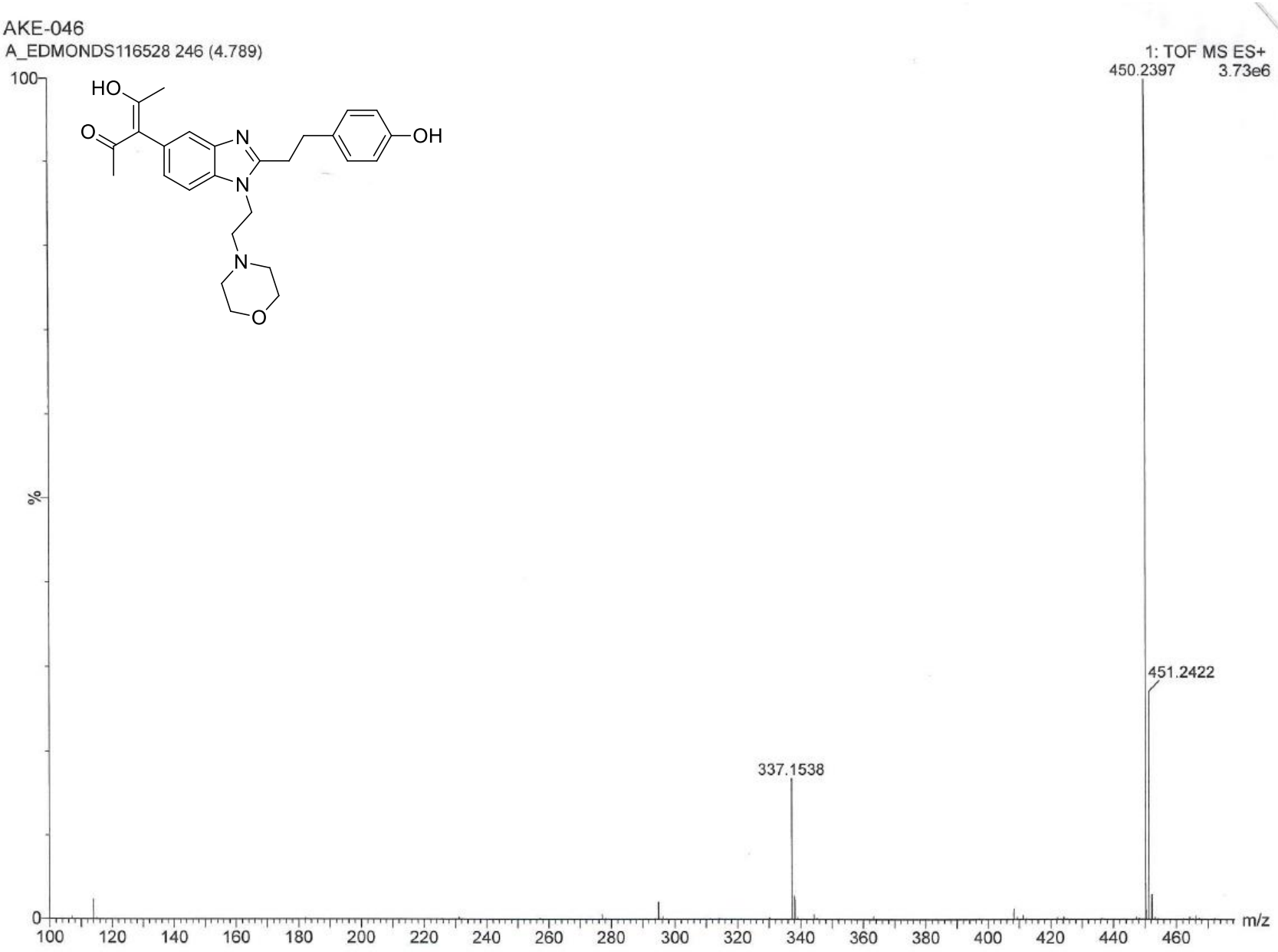


Peak ID	RT (min)	Channel	Area (%)
1	3.36	1	99.1

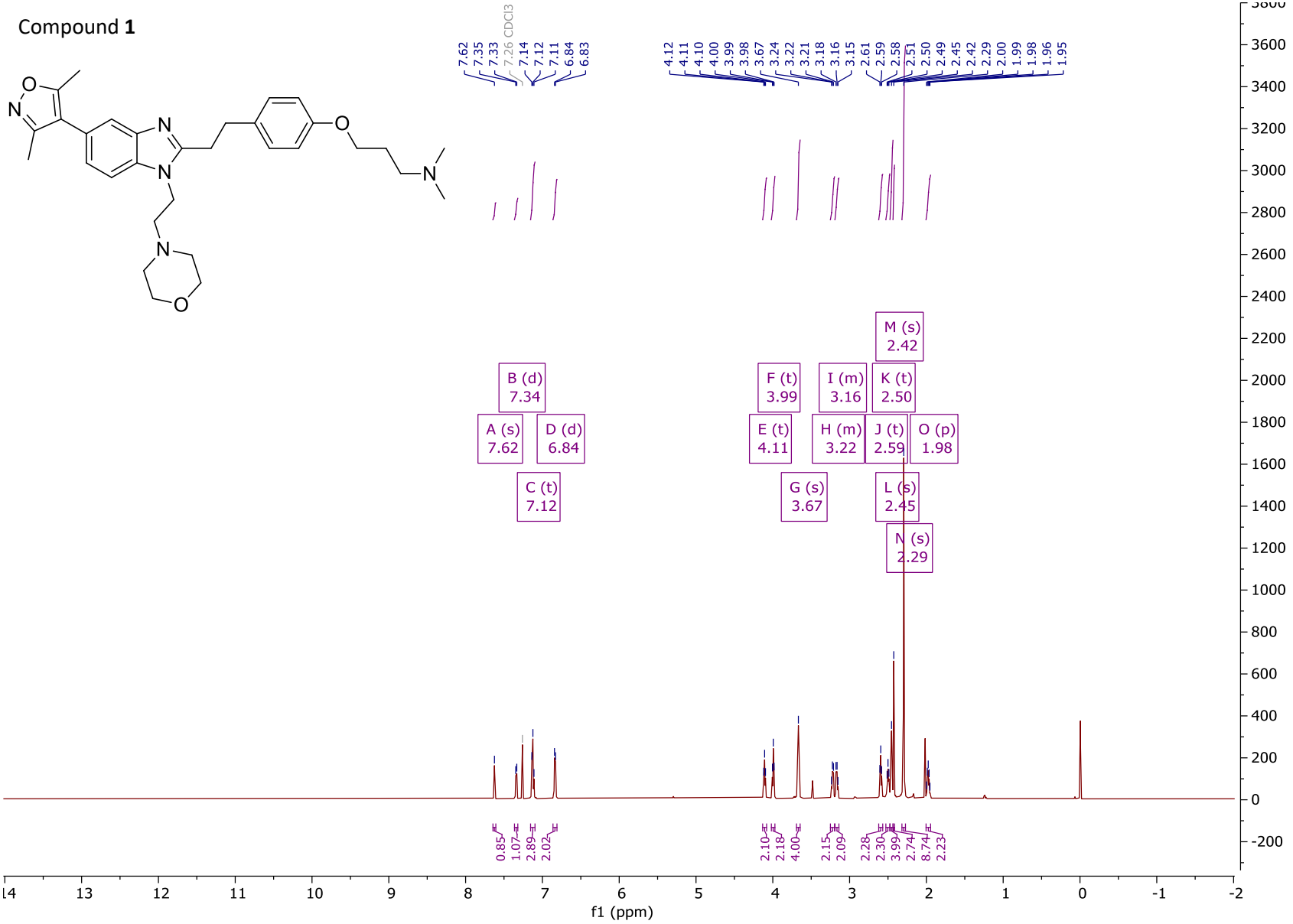


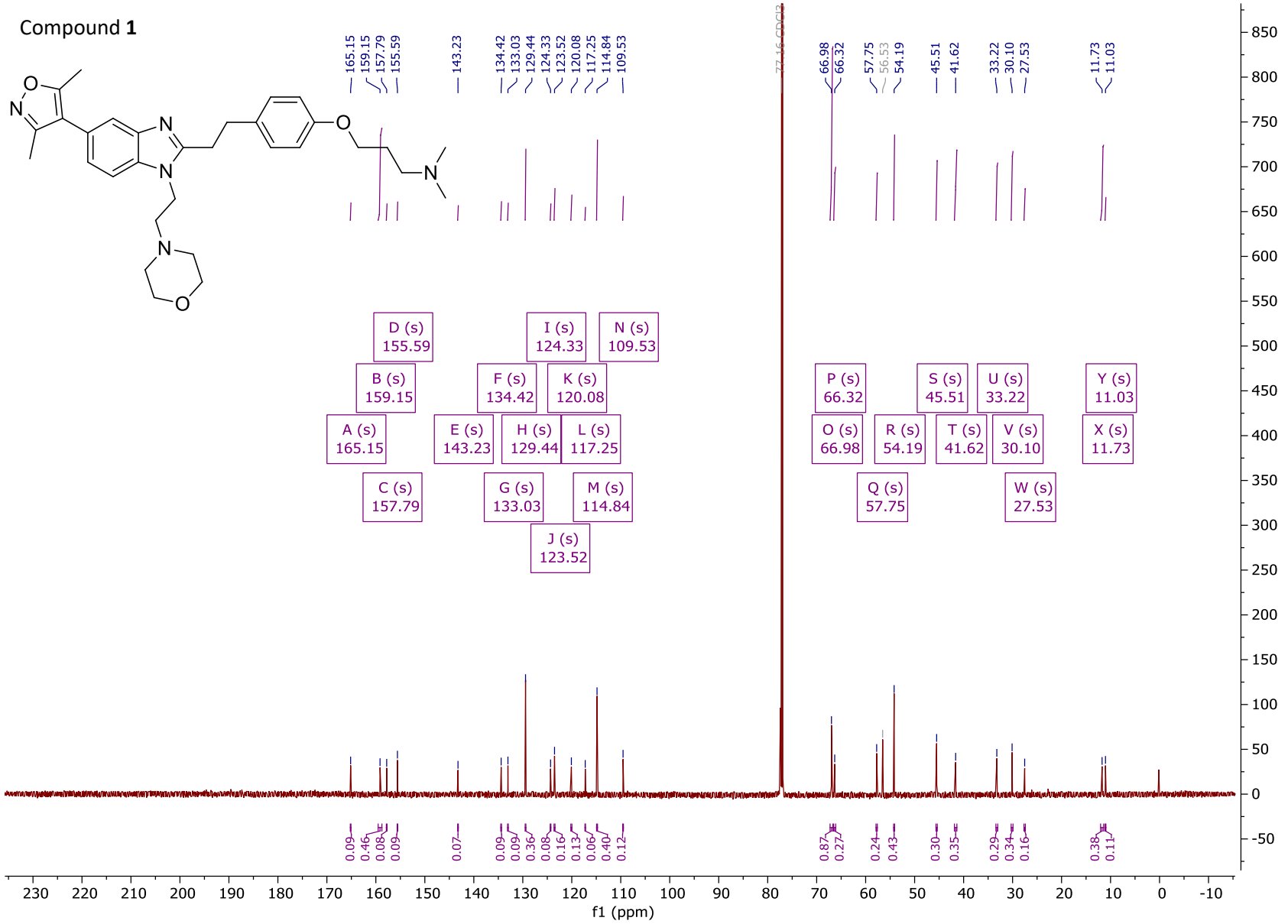
AKE-046

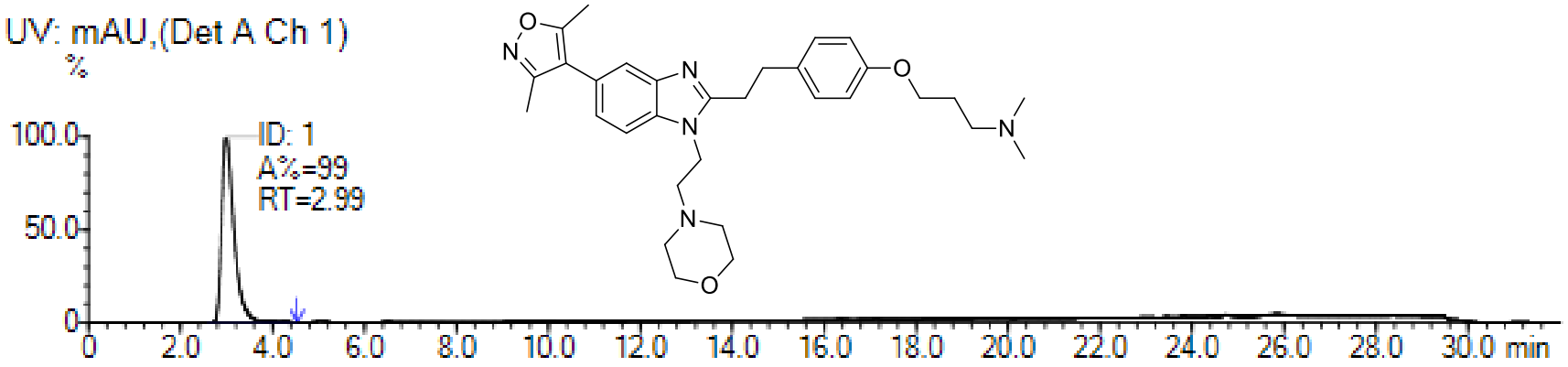
A_EDMONDS116528 246 (4.789)



Compound **1**


7.62
7.35
7.33
7.26 CDCl3
7.14
7.12
7.11
6.84
6.83
4.12
4.11
4.10
4.00
3.99
3.98
3.67
3.24
3.22
3.21
3.18
3.16
3.15
2.61
2.59
2.58
2.51
2.50
2.49
2.45
2.42
2.29
2.00
1.99
1.98
1.96
1.95
M (s) 2.42
B (d) 7.34
F (t) 3.99
I (m) 3.16
K (t) 2.50
A (s) 7.62
D (d) 6.84
E (t) 4.11
H (m) 3.22
J (t) 2.59
O (p) 1.98
C (t) 7.12
G (s) 3.67
L (s) 2.45
N (s) 2.29
0.85
1.07
2.89
2.02
2.10
2.18
4.00
2.15
2.09
2.28
2.30
3.99
2.74
8.74
2.23
f1 (ppm)


Compound 1
165.15
159.15
157.79
155.59
143.23
134.42
133.03
129.44
124.33
123.52
120.08
117.25
114.84
109.53
77.16 CDCl3
66.98
66.32
57.75
56.53
54.19
45.51
41.62
33.22
30.10
27.53
11.73
11.03
D (s) 155.59
I (s) 124.33
N (s) 109.53
B (s) 159.15
F (s) 134.42
K (s) 120.08
A (s) 165.15
E (s) 143.23
H (s) 129.44
L (s) 117.25
C (s) 157.79
G (s) 133.03
M (s) 114.84
J (s) 123.52
P (s) 66.32
S (s) 45.51
U (s) 33.22
Y (s) 11.03
O (s) 66.98
R (s) 54.19
T (s) 41.62
V (s) 30.10
X (s) 11.73
Q (s) 57.75
W (s) 27.53
0.09
0.46
0.08
0.09
0.07
0.09
0.09
0.36
0.08
0.16
0.13
0.06
0.40
0.12
0.87
0.27
0.24
0.43
0.30
0.35
0.29
0.34
0.16
0.38
0.11
f1 (ppm)



Peak ID	RT (min)	Channel	Area (%)
1	2.99	1	98.7