SUPPLEMENTARY INFORMATION

Mechanochemistry for "no solvent, no base" preparation of Hydantoin-based Active Pharmaceutical Ingredients: Nitrofurantoin and Dantrolene.

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Experimental part.

General remarks and experimental procedures

All reagents were commercially available. NMR spectra were recorded at room temperature with the appropriate deuterated solvent ($CDCl_3$ or d_6-DMSO). Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR spectra are reported in ppm relative to residual solvent signals (DMSO in DMSO-d_6: δ = 2.50 ppm for ^{1}H and DMSO-d_6: δ = 39.52 ppm for ^{13}C NMR); *J* values are given in *Hz*. ^{1}H and ^{13}C NMR spectra were registered at 300 MHz or 400 MHz, the samples were prepared by dissolving 10 mg of hydantoin in 0.7 mL of deuterated solvent. ^{1}H and ^{13}C NMR were recorded using 32 and 4096 scans respectively. The identity of analytically pure final product

Dantrolene **8** and **14** were assessed by comparison of its spectral data previously described in the literature and by their fragmentation in LC/MS. Compounds **9** and **12** have a CAS number but no spectral data and characterizations are available in the literature. Compounds **10**, **11**, **15** and **16** are still unknown; compound **13** has a CAS number but no references are associated to this compound. HRMS measurements were performed on a TOF mass analyzer. Analytical high performance liquid chromatography (HPLC) was performed with a UV-detector at 214 nm using a CHROMOLITH RP18 column (50 x 4.6 mm), flow 5 mL/min, linear gradient CH_3CN in water 0-100% (+ 0.1% TFA) in 3 min. LC-MS analyses were performed by HPLC, column Onyx C_{18}, (25 x 4.6 mm), flow 3 mL/min linear gradient CH_3CN in water 0-100% (+ 0.1% HCO_2H) in 2.5 min. Melting points were measured on a Büchi Melting Point 510 apparatus and are uncorrected. The ball-milling experiments were performed in a MM400 vibrational ball mill (Retsch GmbH, Haan, Germany) using 5 mL stainless steel jar (2 stainless steel balls, 5 mm Ø), a Pulverisette P7 (Fritsch, Idar-Oberstein, Germany) using a 12 mL agate or zirconium oxide jars (8 agate balls 8 mm Ø, 25 zirconium oxide balls 5 mm Ø) or in a SPEX 8000 mill using a 50 mL zirconium oxide jar (2 zirconium oxide balls 12 mm Ø).

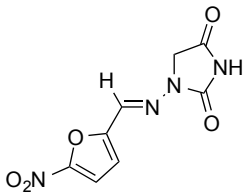
General procedure for the preparation of compounds 7-16.

1-aminohydantoin hydrochloride (1.0 equiv) and the aldehyde (1.0 equiv) were ground according to Method A, B or C as specified for each compound. The final product was recovered just scratching out the powder from the jar without further treatment (compounds **7-11** and **14**) or by precipitation in water and filtration (compounds **7**, **8**, **12**, **13**, **15**, and **16**). The crude was always dried *in vacuo* over P_2O_5 overnight.

METHOD A - Vibrating ball mill (VBM) *(only for compound 7 and **9**)*: 5 mL stainless steel jars, 2 stainless steel balls (5 mm Ø, 0.507 g for each ball) at 30 Hz for 30 min or 2 h;

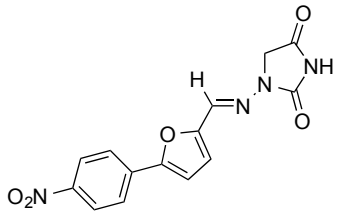
METHOD B - Planetary ball mill (PBM) (*for compounds 7, **8**, **10-16***): 12 mL zirconium oxide jars, 25 zirconium oxide balls (5 mm Ø, 0.391 g for each ball) at 600 rpm for 2 h except when differently stated for each compound;

METHOD C – SPEX *(only for compounds 7 and **8**)*: 50 mL zirconium oxide jars, 2 zirconium oxide balls (12 mm Ø, 3.3 g for each ball) for 15 min (in the case of nitrofurantoin **7**) or for 2 h (in the case of dantrolene **8**).



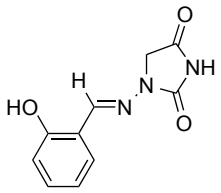
7

(*E*)-*N*-(5-nitro-2-furfurylidene)-1-aminohydantoin or Nitrofurantoin (7) CAS [67-20-9]. For *Method A* (30 min reaction): the reaction scale was 0.84 mmol (169 mg, 85%); for *Method B*: the reaction scale was 13.2 mmol (2.73 g, 87%). For *Method A and B* : The final product was recovered by precipitation in water. For *Method C*: the reaction scale was 6.6 mmol (1.49 g, 95%). The product was scratched out from the jar without any further work-up. Pale yellow powder; m.p. 269 - 272 °C (lit. 270-272°C with decomposition);[1] **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.46 (s, CH=N, 1H), 7.79 (s, CH and NH, 2H), 7.14 (s, 1H, CH), 4.35 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 168.7, 153.2, 151.9, 151.7, 131.1, 114.7, 114.5, 49.1; **ESI-(+)** *m/z :* 261.2 $[M+Na]^+$, 256.2 $[M+H+H_2O]^+$, 239.1 $[M+H]^+$, 191.3, 170.1, 141.0, 131.2, 100.5 ; **HRMS ESI-(+)** calcd for $C_8H_7N_4O_5$ $[M+H]^+$ 239.0416, found 239.0415.



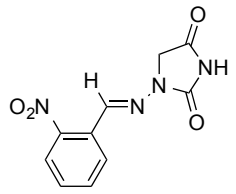
8

(*E*)-1-{[5-(4-nitrophenyl)-2-furyl]methylideneamino}-imidazolidine-2,4-dione or Dantrolene (8) CAS [7261-97-4]. The reaction scale was 6.6 mmol. For *Method B*: the final product was recovered by precipitation in water (1.84 g, 89%). For *Method C*: the product was scratched out from the jar without any further work-up (1.87 g, 90%). Deep orange powder; m.p. 262.7 - 264.7 °C (lit. 258-260 °C);[2] **^{1}H NMR** (300 MHz, DMSO-d_6)[3] δ (ppm): 11.37 (s, CH=N, 1H), 8.35 (dd, J = 6.9 and 1.8 *Hz*, CH_{Ar}, 2H), 8.06 (dd, J = 6.9 and 1.9 *Hz*, CH_{Ar}, 2H), 7.80 (s, 1H, NH), 7.49 (d, J = 3.7 *Hz*, 1H, CH), 7.09 (d, J = 3.7 *Hz*, 1H, CH), 4.40 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6)[4] δ (ppm): 169.8, 154.2, 153.1, 151.0, 147.2, 136.1, 133.6, 125.5, 125.4, 116.5, 113.4, 49.9; **ESI-(+)** *m/z :* 337.1 $[M+Na]^+$, 315.1 $[M+H]^+$, 130.2 ; **HRMS ESI-(+)** calcd for $C_{14}H_{11}N_4O_5$ $[M+H]^+$ 315.0729, found 315.0731.



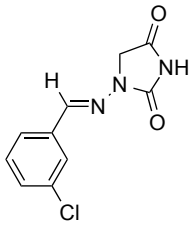
9

(*E*)-1-((2-hydroxybenzylidene)amino)imidazolidine-2,4-dione (9) CAS [1443299-56-6].[5] The reaction scale was 1.32 mmol (*Method A*, 2 h reaction). The product was scratched out from the jar without any further work-up (284 mg, 98%). Black powder; m.p. 244.0 - 247.4 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.35 (s, CH=N, 1H), 10.66 (s, 1H, OH), 8.02 (s, 1H, CH_{Ar}), 7.59 (s, 1H, NH), 7.30 (d, 1H, CH_{Ar}), 6.95 (s, 2H, CH_{Ar}), 4.40 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.8, 157.5, 154.5, 154.2, 143.5, 131.9, 129.4, 120.3, 119.8, 117.2, 49.4; **ESI-(+)** *m/z :* 220.0 $[M+H]^+$, 148.9, 130.2; **HRMS ESI-(+)** calcd for $C_{10}H_{10}N_3O_3$ $[M+H]^+$ 220.0722, found 220.0721.



10

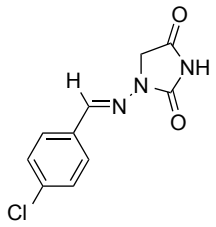
(*E*)-1-((2-nitrobenzylidene)amino)imidazolidine-2,4-dione (10). The reaction scale was 1.98 mmol (*Method B*). The product was scratched out from the jar without any further work-up (443 mg, 90%). White powder; m.p. 219.6 - 221.5 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.41 (s, CH=N, 1H), 8.08 (dd, J = 9.0 and 3.0 Hz, 3H, NH and 2 x CH_{Ar}), 7.85 (dt, J = 9.0 and 3.0 Hz, 1H, CH_{Ar}), 7.71 (dt, J = 9.0 and 3.0 Hz, 1H, CH_{Ar}), 4.40 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.7, 154.4, 149.0, 139.12, 134.7, 131.5, 129.3, 129.1, 125.7, 49.8; **ESI-(+)** *m/z* : 271.1 $[M+Na]^+$, 249.1 $[M+H]^+$, 134.0, 114.0; **HRMS ESI-(+)** calcd for $C_{10}H_9N_4O_4$ $[M+H]^+$ 249.0624, found 249.0624.



11

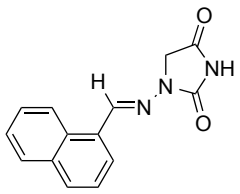
(*E*)-1-((3-chlorobenzylidene)amino)imidazolidine-2,4-dione (11) The reaction scale was 1.98 mmol (*Method B)*. The product was scratched out from the jar without any further work-up (453 mg, 96%). White powder; m.p. 256.4 - 257.4 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.34 (s, CH=N, 1H), 7.84 (s, 1H), 7.77 (m, 1H, CH_{Ar}), 7.71-7.67 (m, 1H), 7.53-7.51 (m, 2H), 4.34 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm):

169.8, 154.3, 142.3, 137.5, 134.6, 131.9, 130.5, 126.9, 126.5, 49.8; **ESI-(+)** *m/z* : 240.1 / 238.1 $[M+H]^+$, 167.0, 129.9, 114.0; **HRMS ESI-(+)** calcd for $C_{10}H_9N_3O_2Cl$ $[M+H]^+$ 238.0383, found 238.0385.



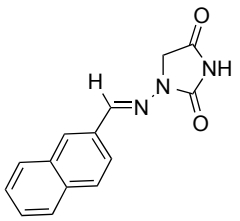
12

(*E*)-1-((4-chlorobenzylidene)amino)imidazolidine-2,4-dione (12) CAS [49548-85-8].[5-6] The reaction scale was 1.98 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (439 mg, 93%). White powder; m.p. 240.2 (darkening), 258.7 - 260.7 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.31 (s, CH=N, 1H), 7.84 (s, 1H, NH), 7.75 (d, J = 9 *Hz*, 2H, CH_{Ar}), 7.55 (d, J = 9 *Hz*, 2H, CH_{Ar}), 4.39 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.9, 154.3, 142.6, 135.1, 134.2, 129.9, 129.4, 49.8; **ESI-(+)** *m/z* : 240.1 / 238.1 $[M+H]^+$, 114.0 ; **HRMS ESI-(+)** calcd for $C_{10}H_9N_3O_2Cl$ $[M+H]^+$ 238.0383, found 238.0382.



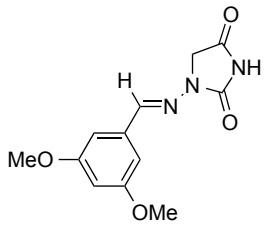
13

(*E*)-1-((naphthalen-1-ylmethylene)amino)imidazolidine-2,4-dione (13) CAS [1099292-03-1]. The reaction scale was 1.98 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (466 mg, 93%). White powder; m.p. 250.8 – 253.9 °C (darkening); **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.35 (s, CH=N, 1H), 8.93 (dd, J = 8.4 and 1.5 *Hz*, 1H) 8.42 (s, 1H, NH), 8.06-7.98 (m, 3H), 7.71-7.60 (m, 3H), 4.57 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 170.1, 154.5, 143.3, 134.5, 131.2, 131.1, 130.7, 129.7, 128.1, 127.2, 126.5, 125.4, 49.9; **ESI-(+)** *m/z* : 276.0 $[M+Na]^+$, 254.1 $[M+H]^+$, 154.1, 114.3 ; **HRMS ESI-(+)** calcd for $C_{14}H_{12}N_3O_2$ 254.0930, found 254.0931.



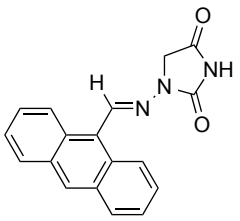
14

(*E*)-2-((naphthalen-2-ylmethylene)amino)imidazolidine-2,4-dione (14)[7] CAS [1062414-94-1].The reaction scale was 1.98 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The product was scratched out from the jar without any further work-up (477 mg, 95%). White powder; m.p. 251.84 °C (darkening) (lit. 262-264°C);[7] **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.33 (s, CH=N, 1H), 8.17 (m, 1H), 8.04-7.95 (m, 5H), 7.63-7.58 (m, 2H), 4.46 (s, 2H, CH_2); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.7, 154.4, 149.1, 139.1, 134.7, 131.5, 129.3, 129.1, 125.7, 49.8; **ESI-(+)** *m/z* : 276.0 $[M+Na]^+$, 254.1 $[M+H]^+$, 113.9 ; **HRMS ESI-(+)** calcd for $C_{14}H_{12}N_3O_2$ 254.0930, found 254.0932.



15

(*E*)-1-((3,5-dimethoxybenzylidene)amino)imidazolidine-2,4-dione (15) The reaction scale was 1.98 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (453 mg, 87%). Pale lila powder; m.p. 244.4 – 245.7 °C; **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.31 (s, CH=N, 1H), 7.77 (s, 1H), 6.90 (d, J = 3.0 Hz, 2H), 6.59 (t, J = 3.0 *Hz*, 1H), 4.38 (s, 2H, CH_2), 3.82 (s, 6H, CH_3); **^{13}C{1H} NMR** (75 MHz, DMSO-d_6) δ (ppm): 169.9, 161.6, 154.4, 143.9, 137.3, 105.6, 102.9, 56.3, 49.9; **ESI-(+)** *m/z* : 327.1 $[M+Na+ACN]^+$, 286.1 $[M+Na]^+$, 264.1 $[M+H]^+$, 114.0; **HRMS ESI-(+)** calcd for $C_{12}H_{14}N_3O_4$ 264.0984, found 264.0984.



16

(*E*)-1-((anthracen-9-ylmethylene)amino)imidazolidine-2,4-dione (16) The reaction scale was 1.32 mmol (*Method B*, 3 cycles of 2h each, with 5 minutes pause in between). The final product was recovered by precipitation in water (380 mg, 95%). Yellow powder; m.p. 274.8 – 282.7 °C (darkening); **^{1}H NMR** (300 MHz, DMSO-d_6) δ (ppm): 11.38 (s, CH=N, 1H), 8.75 (s, 1H), 8.69 (s, 1H), 8.62 (d, J = 9.0 Hz, 2H), 8.13 (d, J = 6.0 *Hz*, 2H), 7.70-7.51 (m, 5H), 4.70 (s, 2H, CH_2); **^{13}C{1H} NMR** (75

MHz, DMSO-d_6) δ (ppm): 170.2, 142.2, 142.2, 131.8, 130.4, 129.9, 129.7, 127.7, 126.7, 126.5, 126.2, 49.9; **ESI-(+)** *m/z* : 629.1 $[2M+Na]^+$, 367.1 $[M+Na+ACN]^+$, 326.1 $[M+Na]^+$, 304.1 $[M+H]^+$, 205.1, 130.2 ; **HRMS ESI-(+)** calcd for $C_{18}H_{14}N_3O_2$ $[M+H]^+$ 304.1086, found 304.1084.

PXDR Analyses of Nitrofurantoin 7.

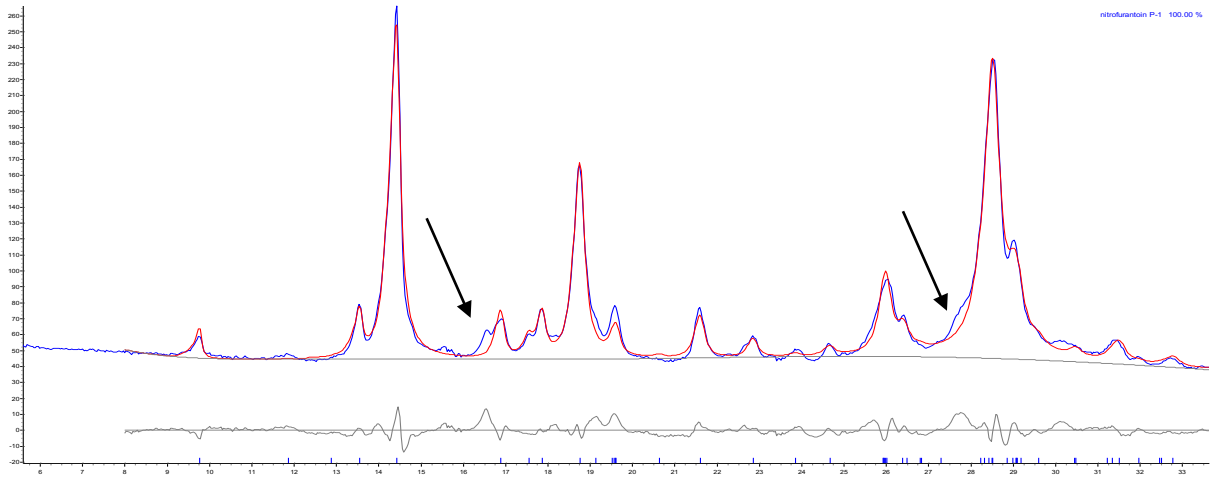


Figure S1. XRD pattern of Nitrofurantoin **7** obtained by *Method B* and recovered by precipitation in water. Rietveld fit modelled with slight preferred orientation. The sample is the triclinic polymorph of nitrofurantoine (CSD refcode LABJON01). Two impurity peaks are marked with arrows. The intensity is shown as their square root. Difference curve between measured and calculated is given below in grey.

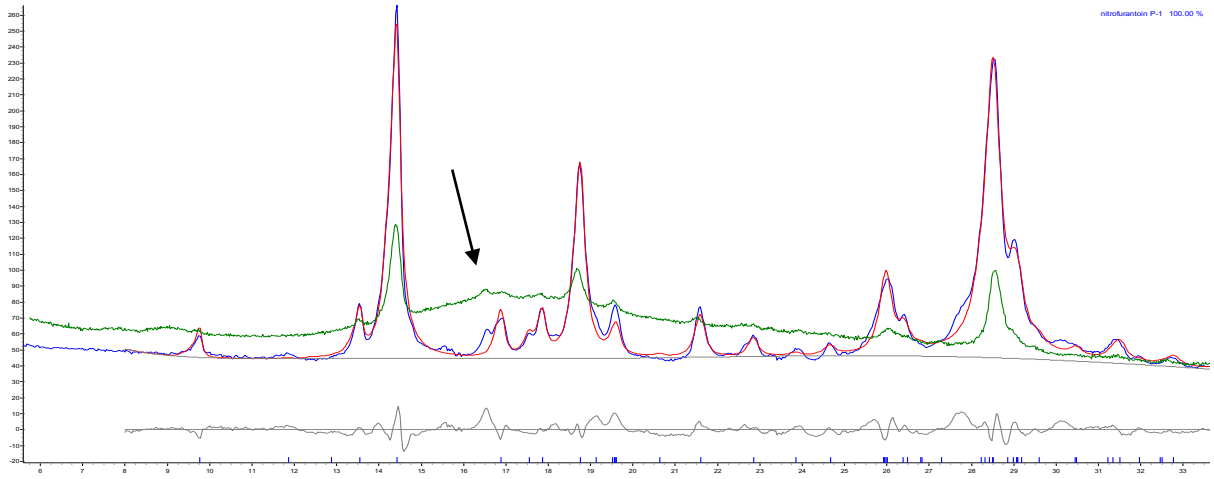
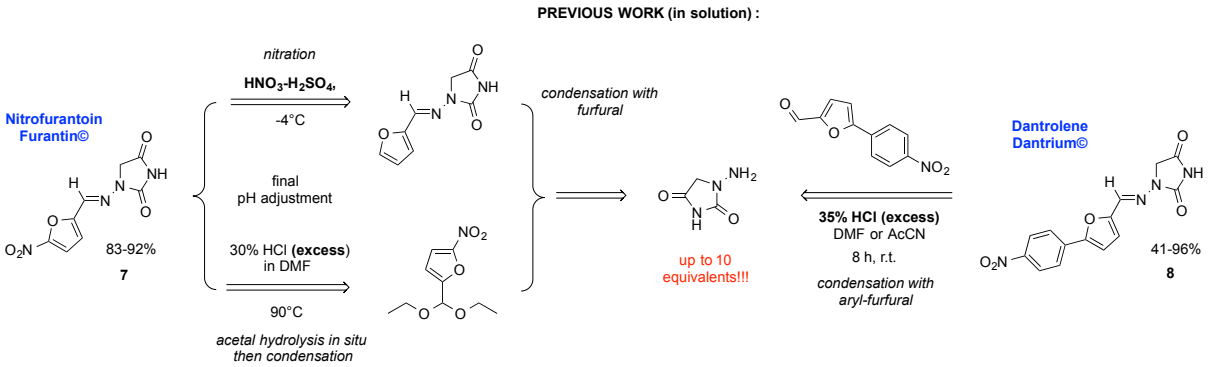


Figure S2. XRD pattern of Nitrofurantoin **7** obtained by *Method C* and directly recovered as a powder from the jar without post-synthetic treatment. **Green pattern** (overlaid with the pattern form given in Figure S1): the sample is the same polymorph of nitrofurantoin **7** as is visible from the three strongest peaks. The sample is very amorphous as evident from this big broad hump centered at *ca.* 18 degrees in 2θ. The intensity is shown as their square root.



Scheme S1. Retrosynthetic pathways leading to Nitrofurantoin **7** and Dantrolene **8** in solution.

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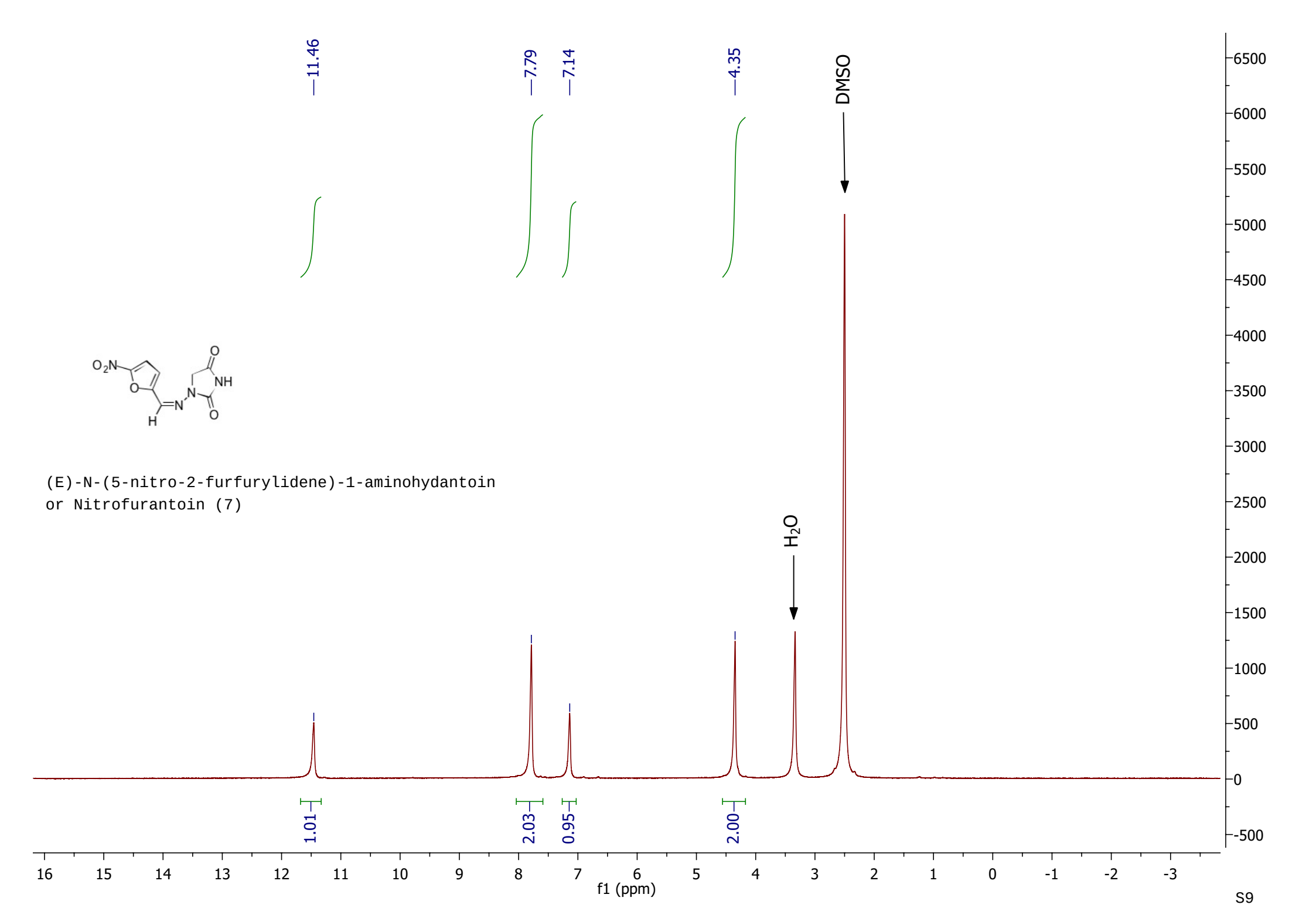
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7.79
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4.35
DMSO
H2O
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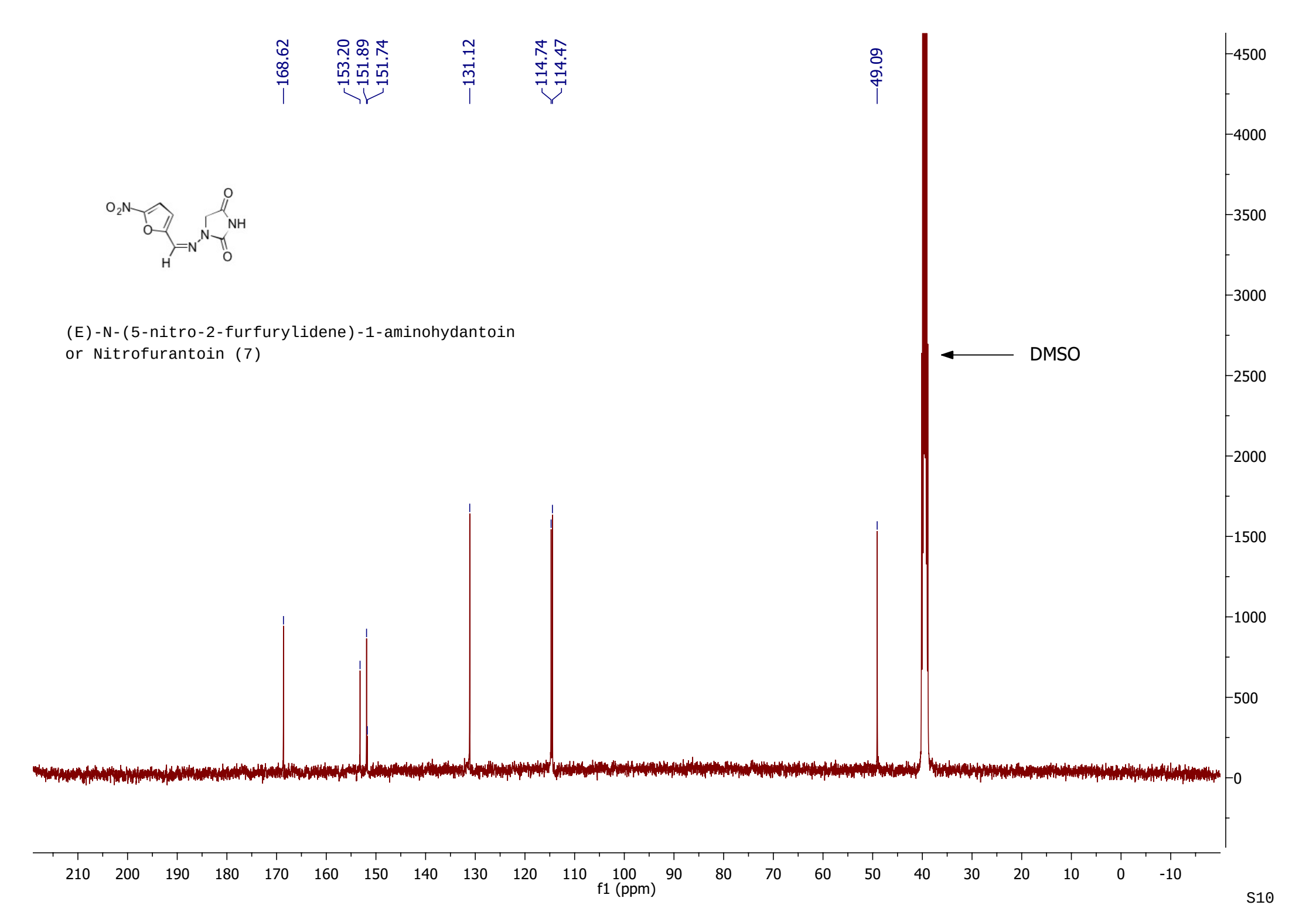
2.03
0.95
2.00
f1 (ppm)
(E)-N-(5-nitro-2-furfurylidene)-1-aminohydantoin
or Nitrofurantoin (7)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151.74
131.12
114.74
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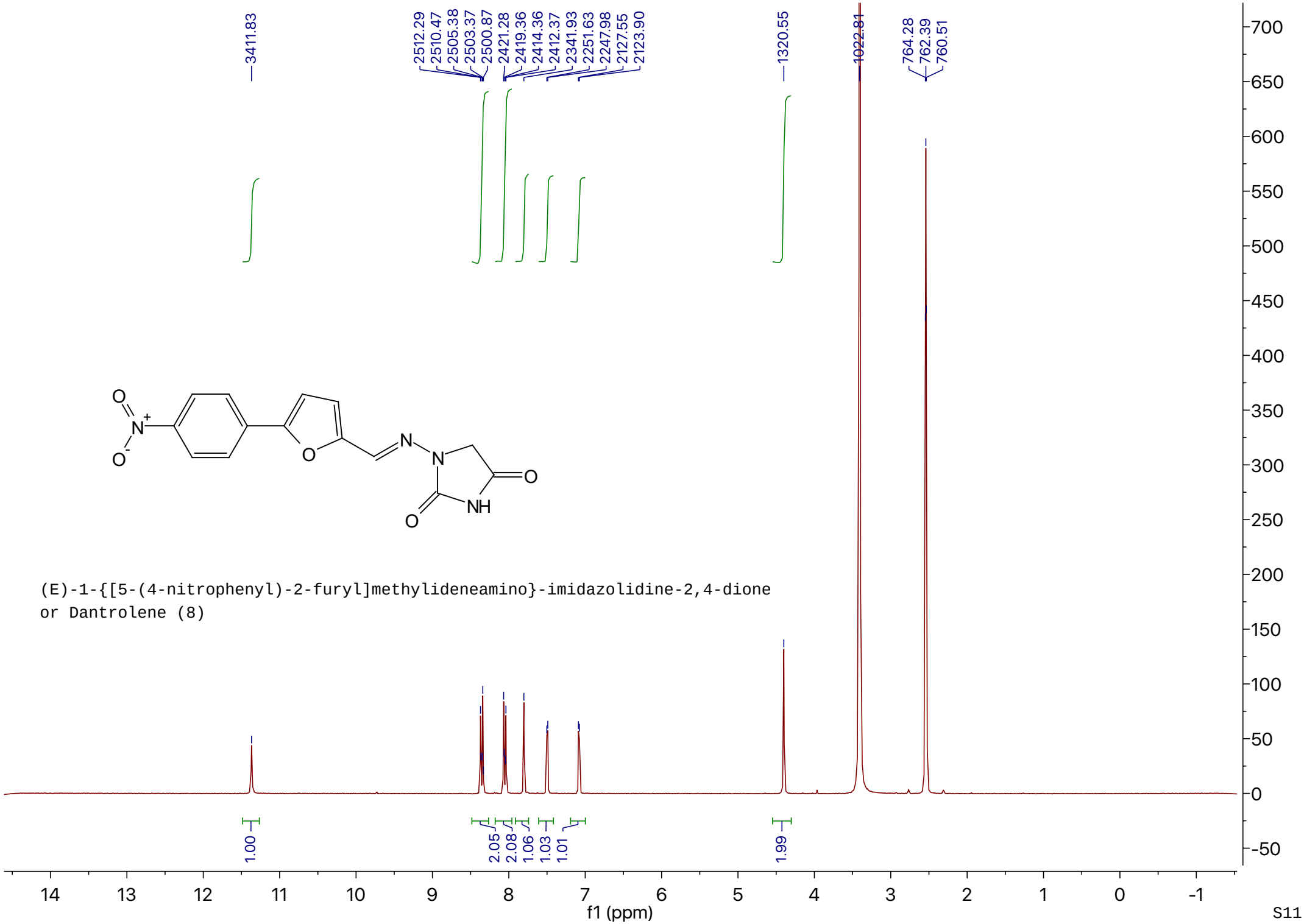
DMSO
(E)-N-(5-nitro-2-furfurylidene)-1-aminohydantoin
or Nitrofurantoin (7)
f1 (ppm)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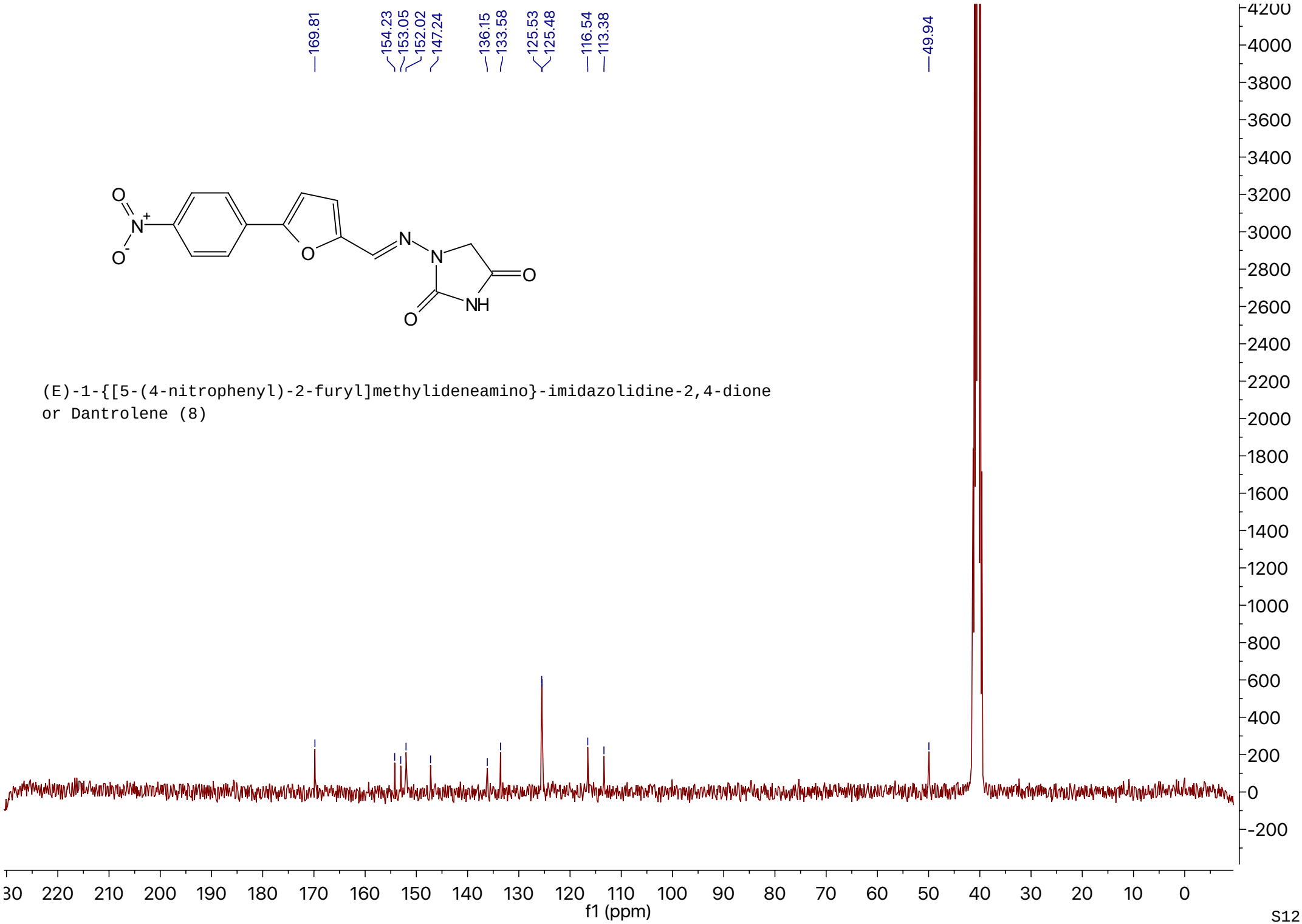
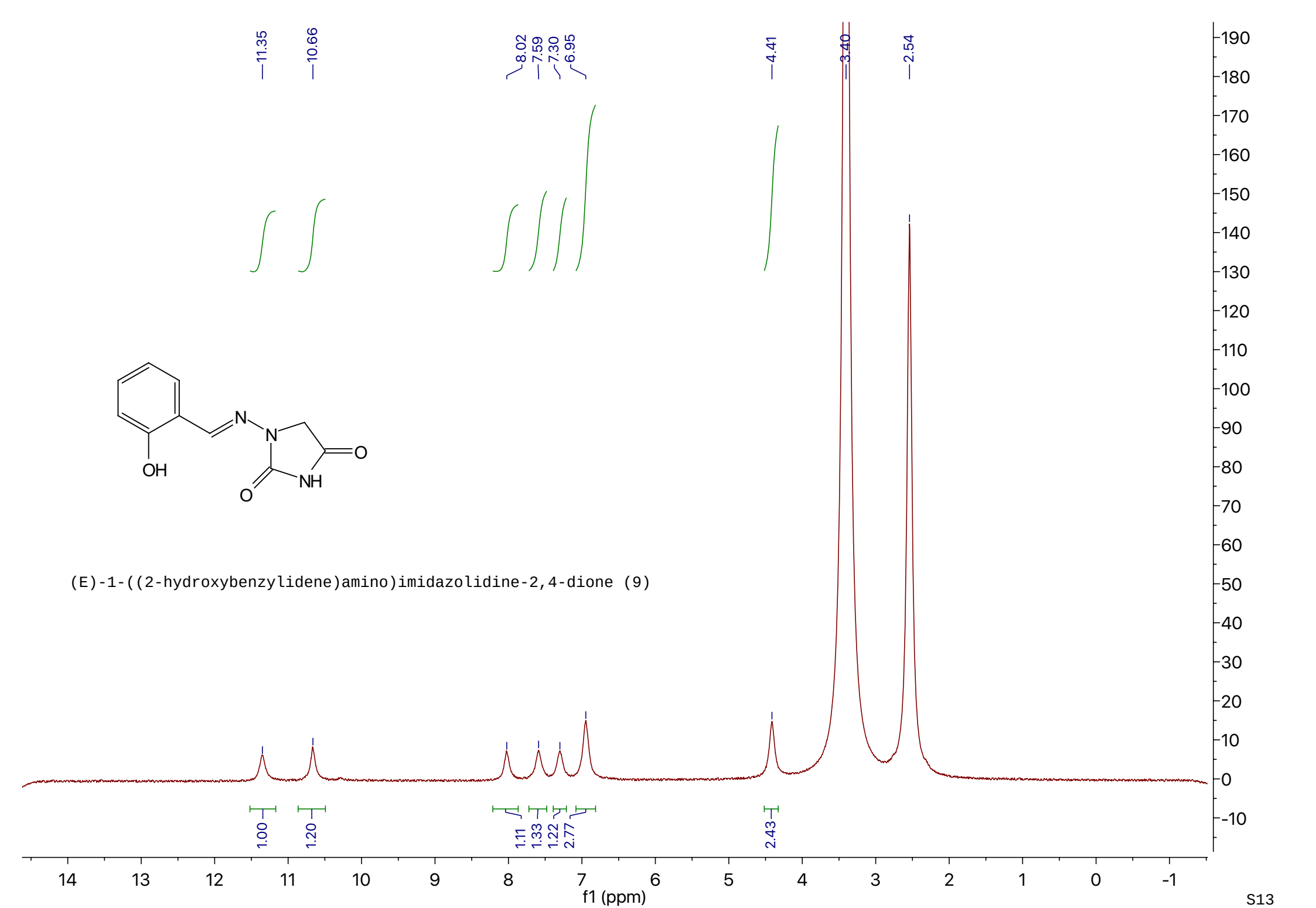
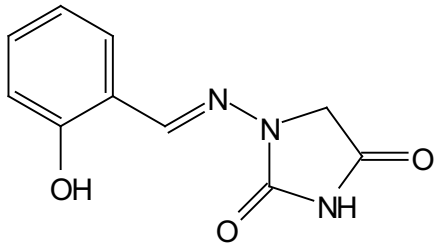
2247.98
2127.55
2123.90
1320.55
1022.81
764.28
762.39
760.51
O
N+
O-
O
N
N
O
NH
O
(E)-1-{[5-(4-nitrophenyl)-2-furyl]methylideneamino}-imidazolidine-2,4-dione
or Dantrolene (8)
1.00
2.05
2.08
1.06
1.03
1.01
1.99
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50

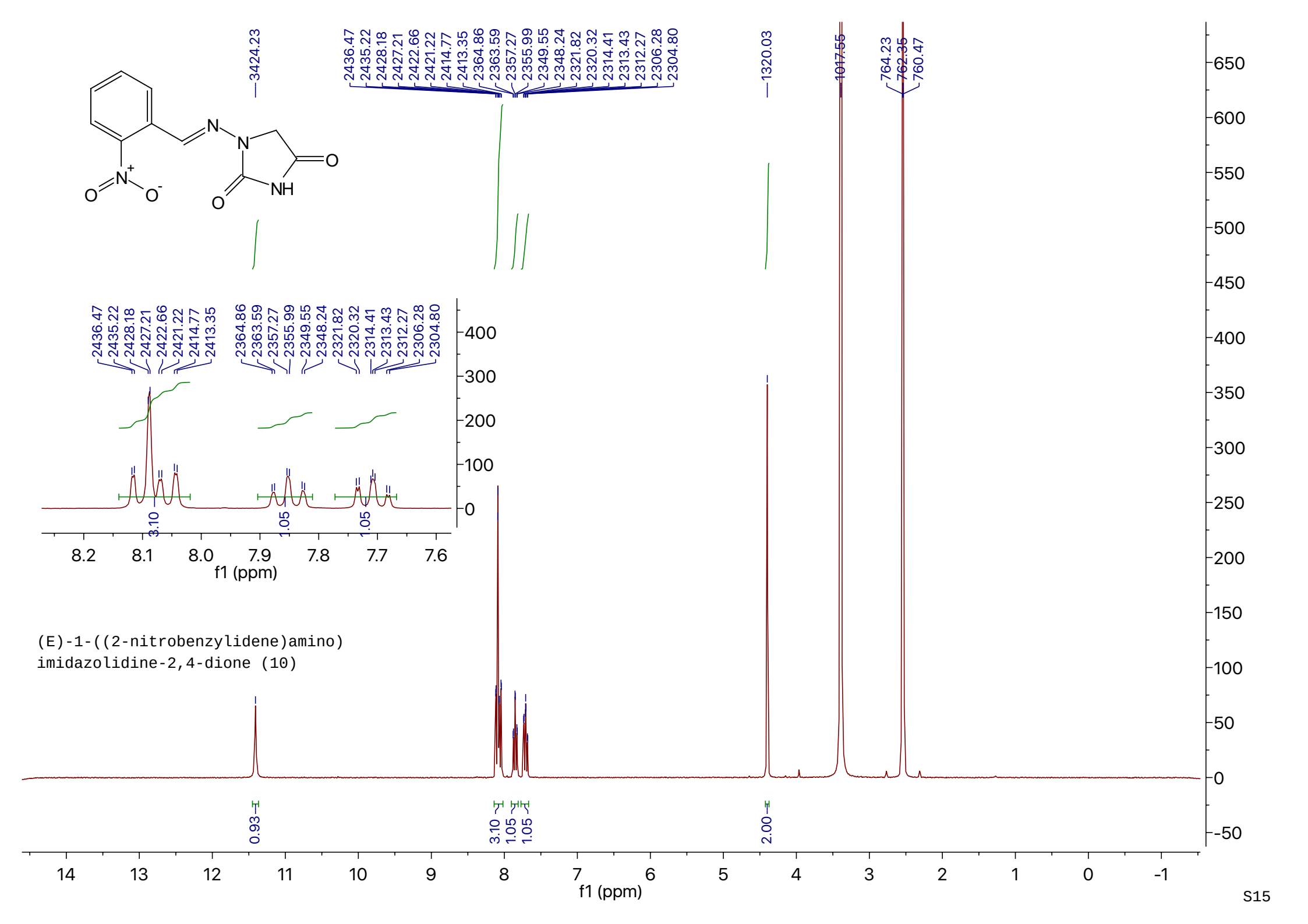

169.81
154.23
153.05
152.02
147.24
136.15
133.58
125.53
125.48
116.54
113.38
49.94
O
N+
O-
O
N
N
O
O
NH
(E)-1-{[5-(4-nitrophenyl)-2-furyl]methylideneamino}-imidazolidine-2,4-dione
or Dantrolene (8)
4200
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

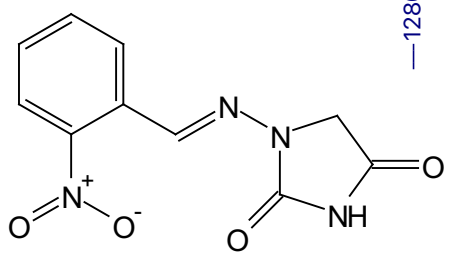


(E)-1-((2-hydroxybenzylidene)amino)imidazolidine-2,4-dione (9)

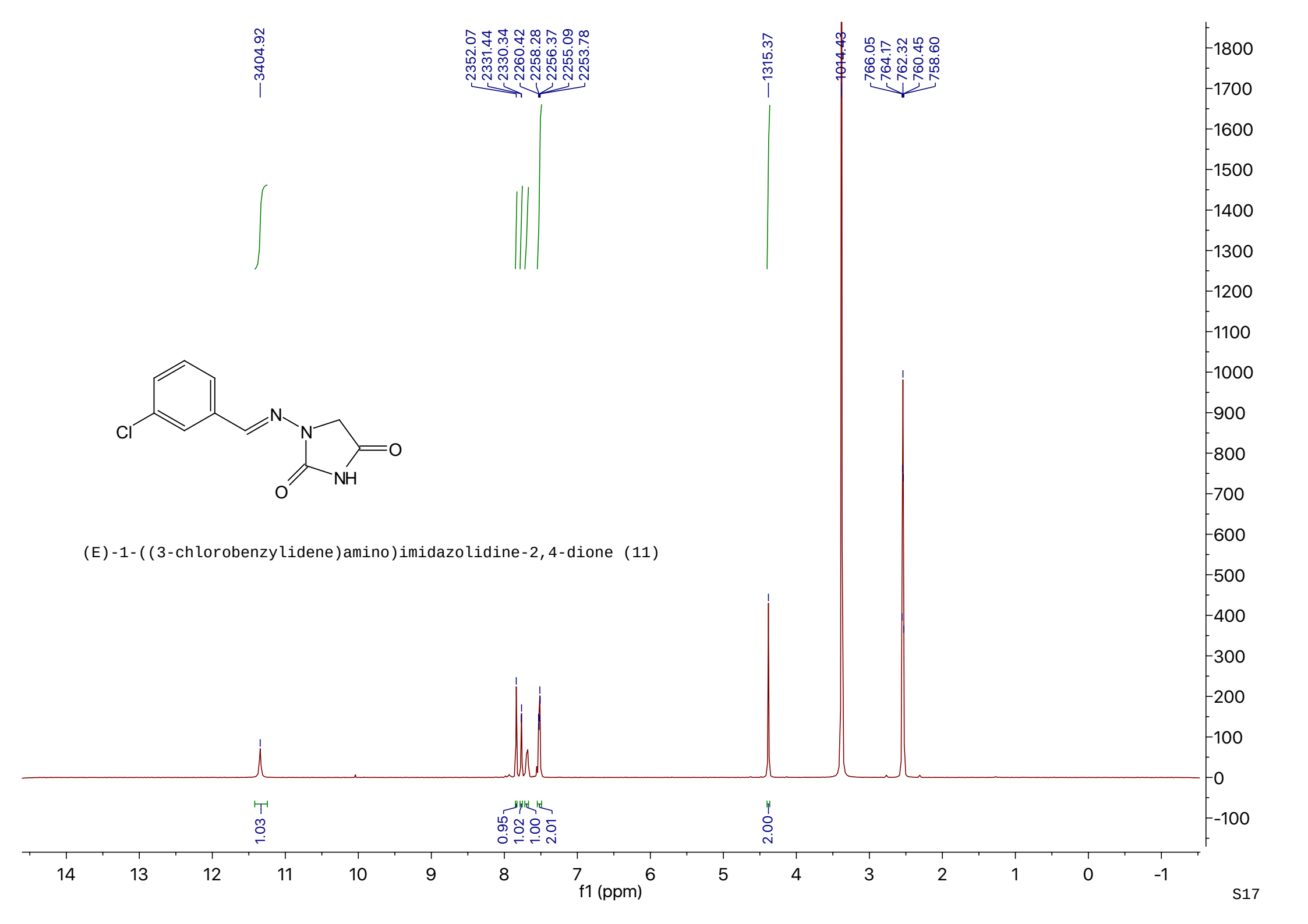


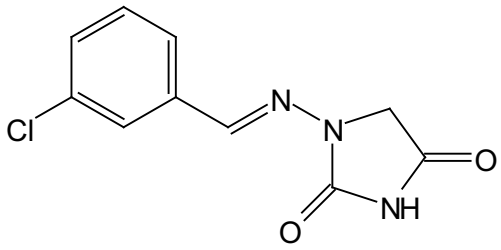
(E)-1-((2-hydroxybenzylidene)amino)imidazolidine-2,4-dione (9)


3424.23
2436.47
2435.22
2428.18
2427.21
2422.66
2421.22
2414.77
2413.35
2364.86
2363.59
2357.27
2355.99
2349.55
2348.24
2321.82
2320.32
2314.41
2313.43
2312.27
2306.28
2304.80
1320.03
1017.55
764.23
762.35
760.47
O
N
N
O
O
N+
O-
NH
O
(E)-1-((2-nitrobenzylidene)amino)
imidazolidine-2,4-dione (10)
0.93
3.10
1.05
1.05
2.00
f1 (ppm)
3.10
1.05
1.05
f1 (ppm)

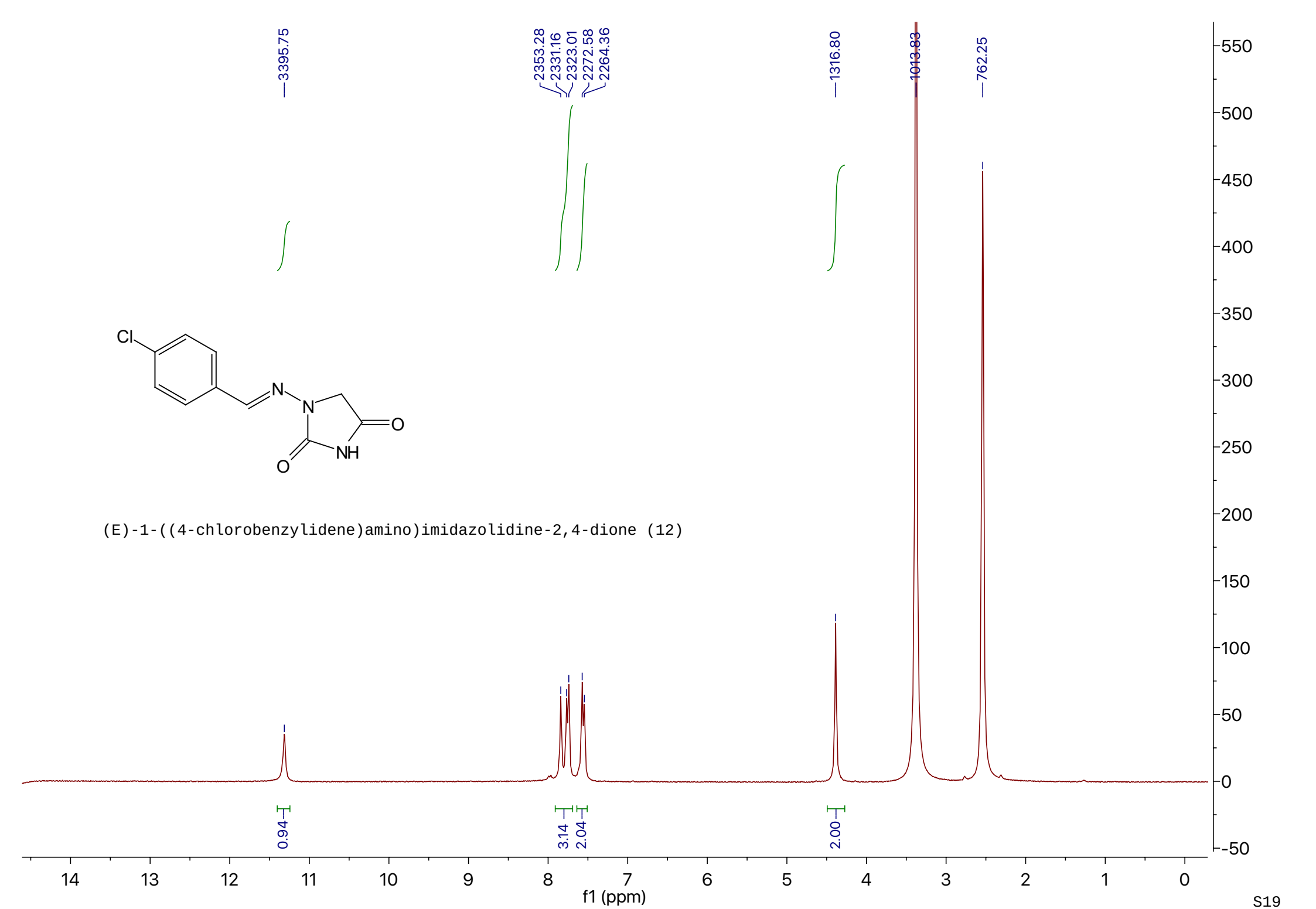


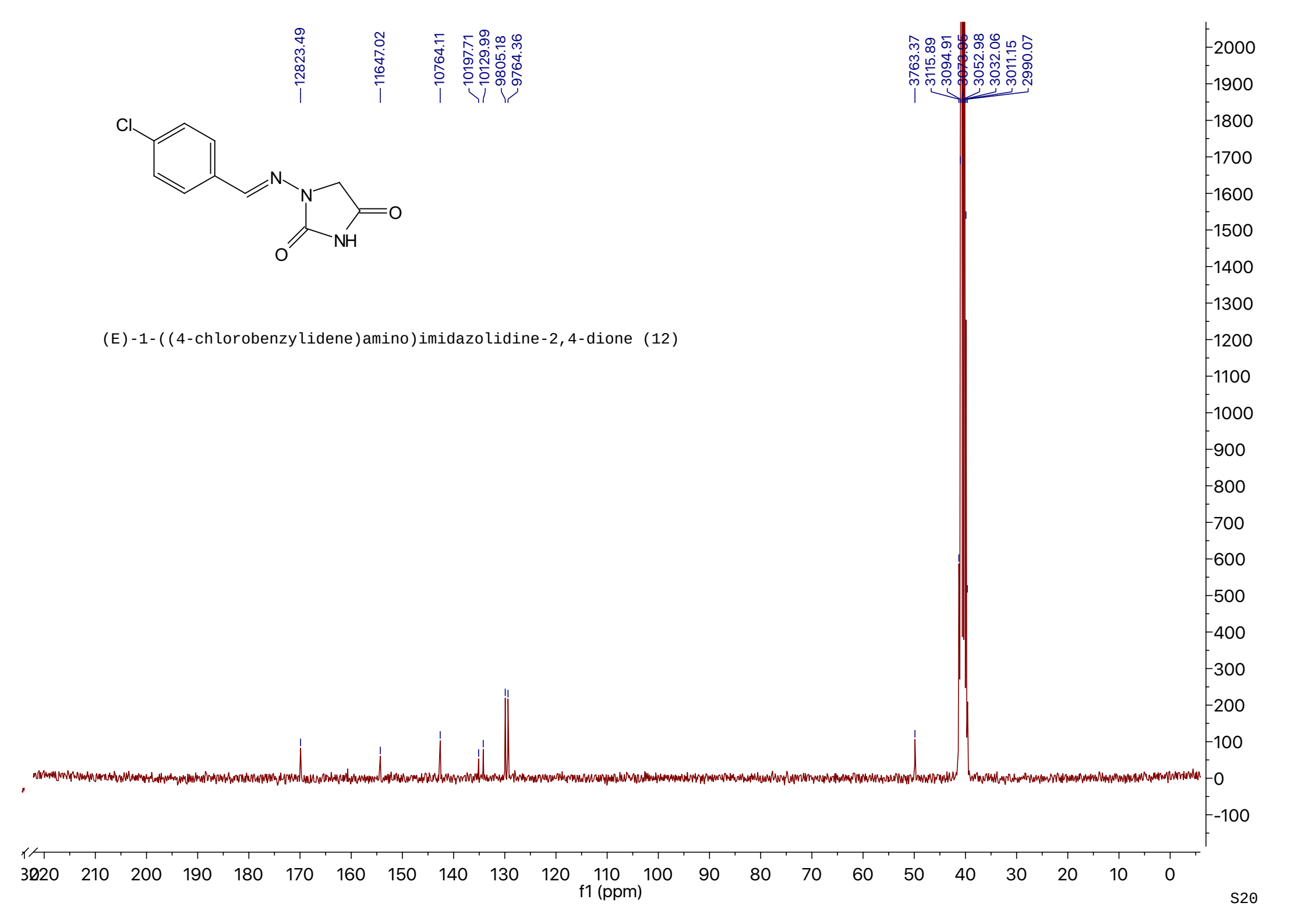
(E)-1-((2-nitrobenzylidene)amino)imidazolidine-2,4-dione (10)

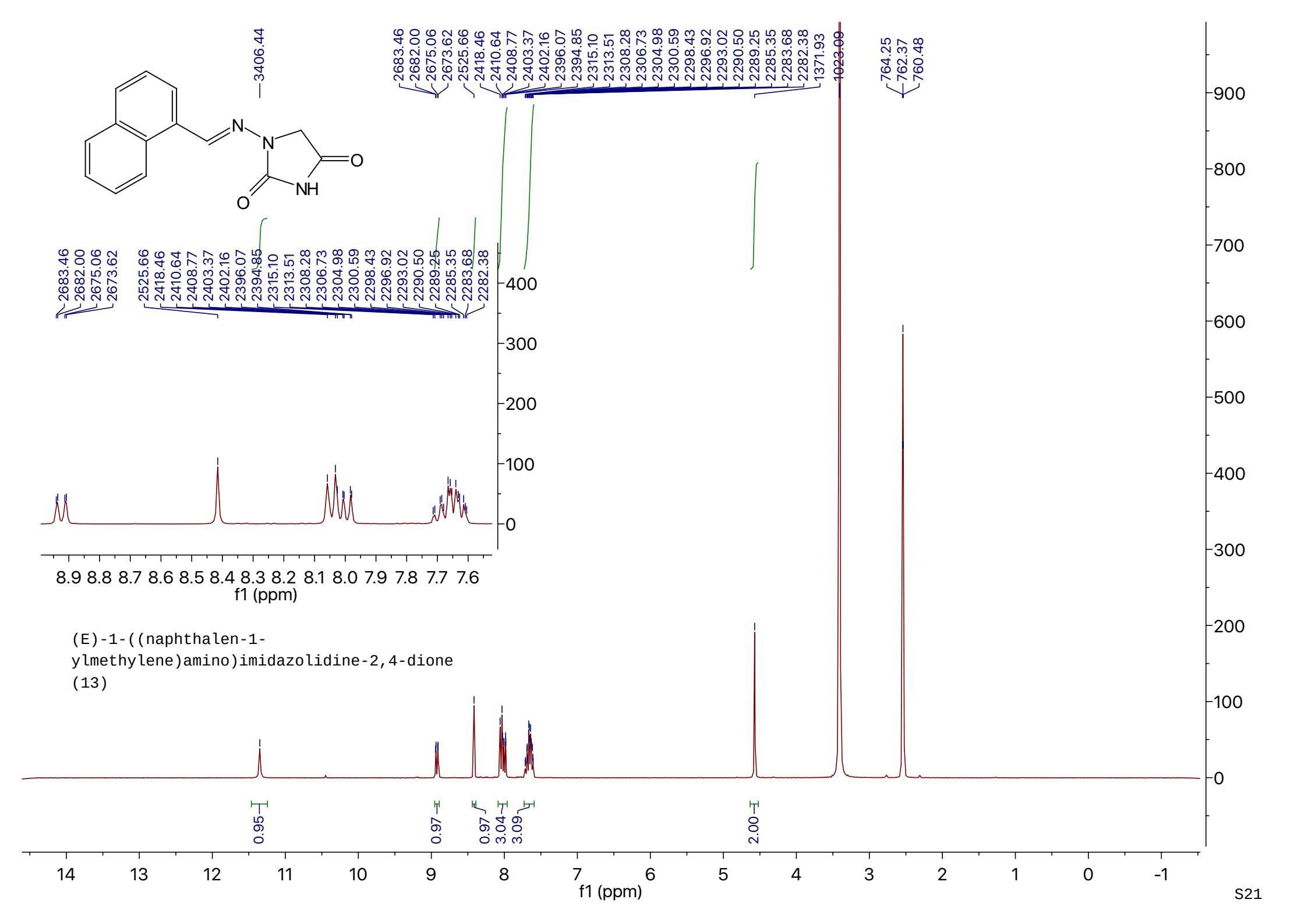

3404.92
2352.07
2331.44
2330.34
2260.42
2258.28
2256.37
2255.09
2253.78
1315.37
1014.43
766.05
764.17
762.32
760.45
758.60
Cl
N
N
O
NH
O
(E)-1-((3-chlorobenzylidene)amino)imidazolidine-2,4-dione (11)
1.03
0.95
1.02
1.00
2.01
2.00
f1 (ppm)

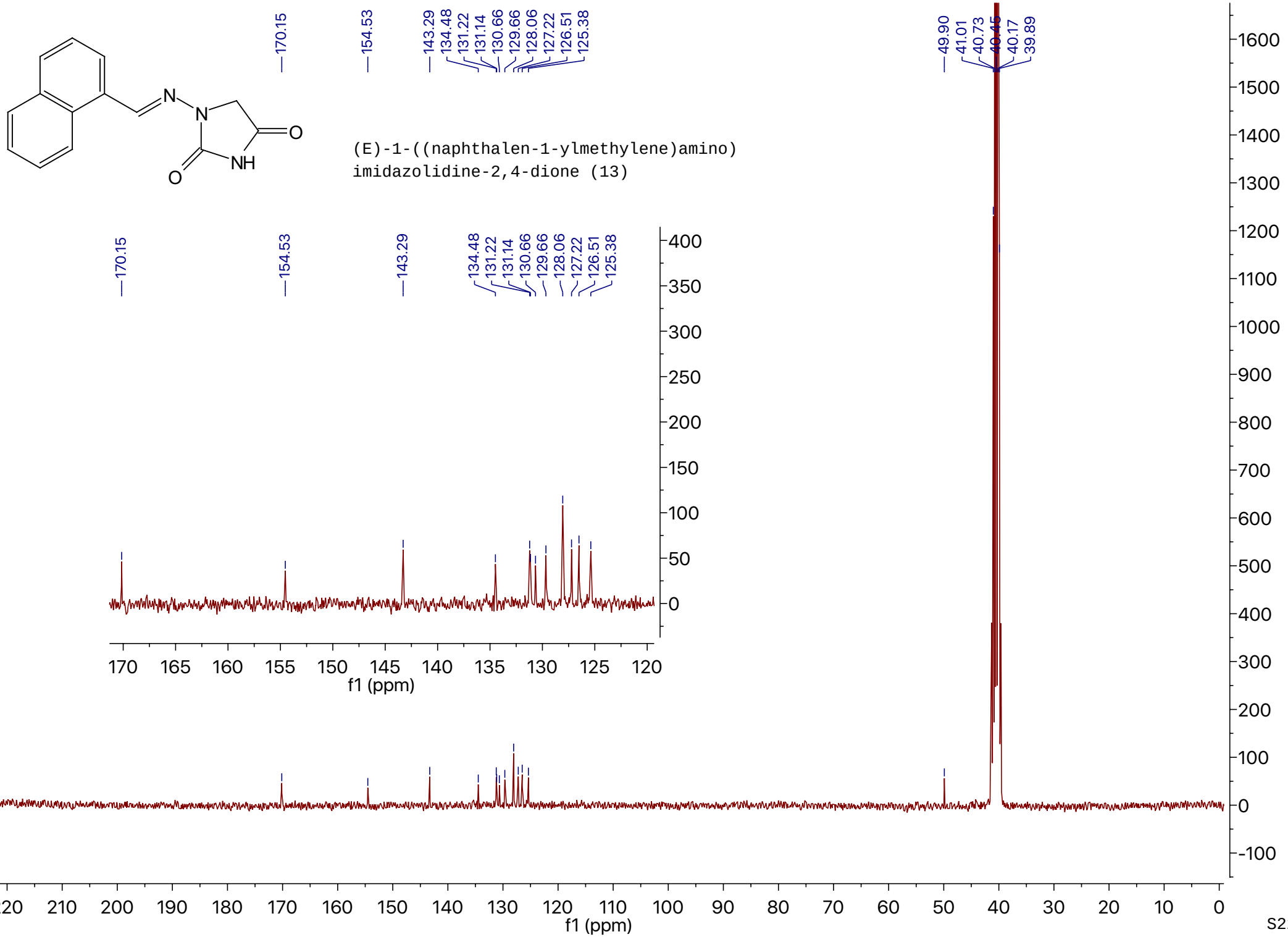


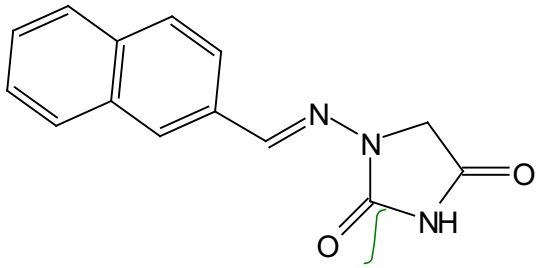
(E)-1-((3-chlorobenzylidene)amino)imidazolidine-2,4-dione (11)


3395.75
2353.28
2331.16
2323.01
2272.58
2264.36
1316.80
1013.93
762.25
Cl
N
N
O
NH
O
(E)-1-((4-chlorobenzylidene)amino)imidazolidine-2,4-dione (12)
0.94
3.14
2.04
2.00
f1 (ppm)

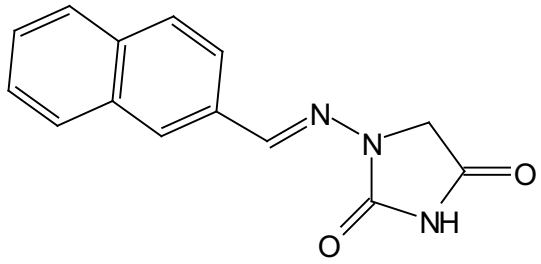

12823.49
11647.02
10764.11
10197.71
10129.99
9805.18
9764.36
3763.37
3115.89
3094.91
3073.05
3052.98
3032.06
3011.15
2990.07
Cl
N
N
O
NH
O
(E)-1-((4-chlorobenzylidene)amino)imidazolidine-2,4-dione (12)
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


3406.44
2683.46
2682.00
2675.06
2673.62
2525.66
2418.46
2410.64
2408.77
2403.37
2402.16
2396.07
2394.85
2315.10
2313.51
2308.28
2306.73
2304.98
2300.59
2298.43
2296.92
2293.02
2290.50
2289.25
2285.35
2283.68
2282.38
1371.93
1023.09
764.25
762.37
760.48
N
N
O
NH
O
8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6
f1 (ppm)
(E)-1-((naphthalen-1-
ylmethylene)amino)imidazolidine-2,4-dione
(13)
0.95
0.97
0.97
3.04
3.09
2.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

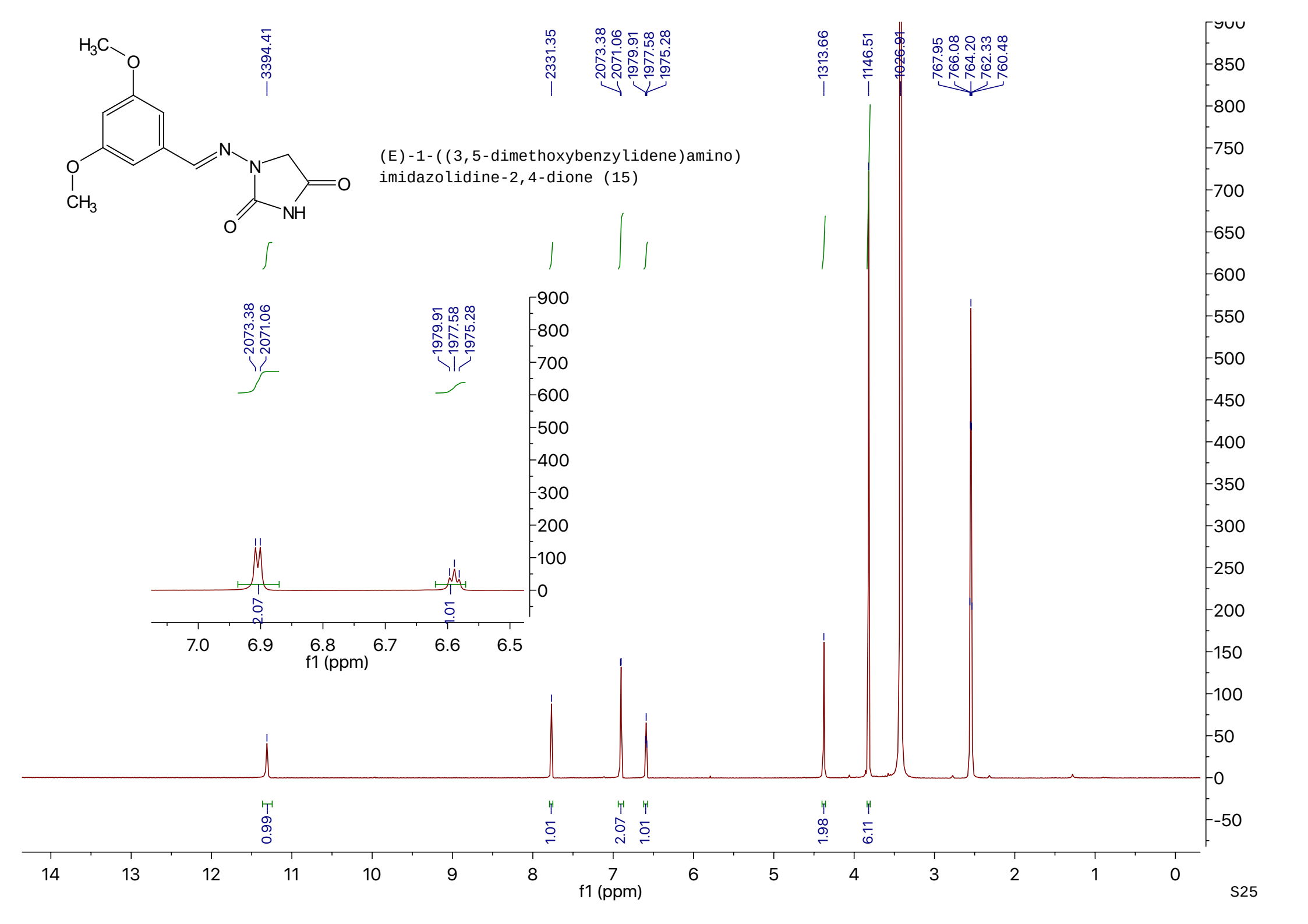

170.15
154.53
143.29
134.48
131.22
131.14
130.66
129.66
128.06
127.22
126.51
125.38
49.90
41.01
40.73
40.45
40.17
39.89
N
N
O
NH
O
(E)-1-((naphthalen-1-ylmethylene)amino)
imidazolidine-2,4-dione (13)
f1 (ppm)
f1 (ppm)

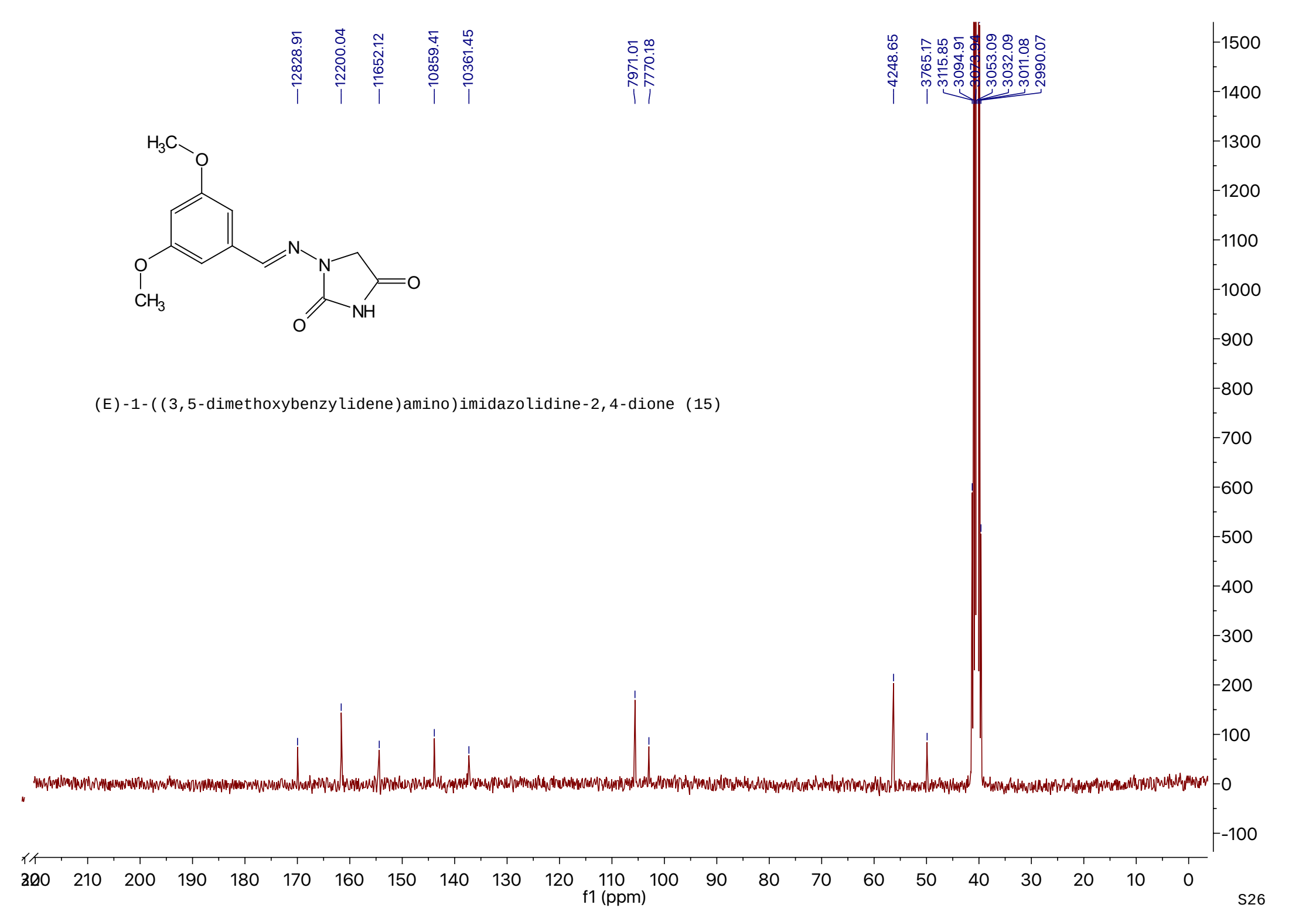


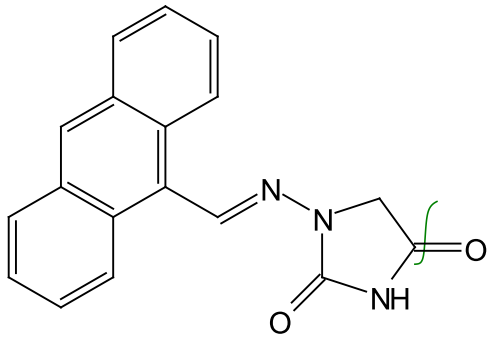
(E)-2-((naphthalen-2-ylmethylene)amino)
imidazolidine-2,4-dione (14)



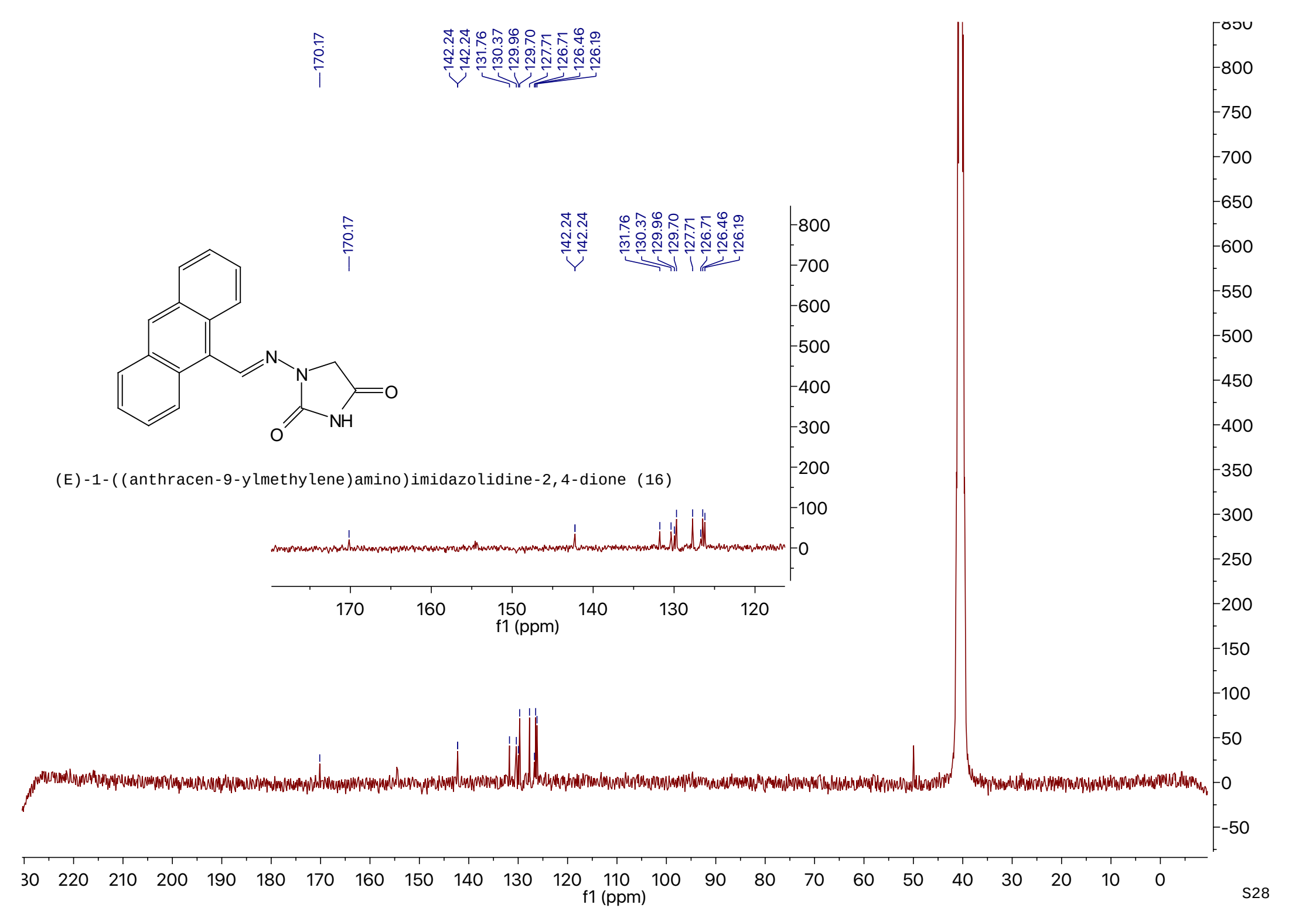
(E)-2-((naphthalen-2-ylmethylene)amino)
imidazolidine-2,4-dione (14)


(E)-1-((3,5-dimethoxybenzylidene)amino)
imidazolidine-2,4-dione (15)
3394.41
2331.35
2073.38
2071.06
1979.91
1977.58
1975.28
1313.66
1146.51
1026.91
767.95
766.08
764.20
762.33
760.48
0.99
1.01
2.07
1.01
1.98
6.11
f1 (ppm)


12828.91
12200.04
11652.12
10859.41
10361.45
7971.01
7770.18
4248.65
3765.17
3115.85
3094.91
3073.94
3053.09
3032.09
3011.08
2990.07
H3C
O
O
CH3
N
N
O
NH
O
(E)-1-((3,5-dimethoxybenzylidene)amino)imidazolidine-2,4-dione (15)
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



(E)-1-((anthracen-9-ylmethylene)amino)imidazolidine-2,4-dione (16)


170.17
142.24
142.24
131.76
130.37
129.96
129.70
127.71
126.71
126.46
126.19
N
N
O
NH
O
(E)-1-((anthracen-9-ylmethylene)amino)imidazolidine-2,4-dione (16)
f1 (ppm)
f1 (ppm)