

Design and Synthesis of New 4-(2-Nitrophenoxy) Benzamide Derivatives as Potential Antiviral Agents: Molecular Modeling and *In Vitro* Antiviral Screening

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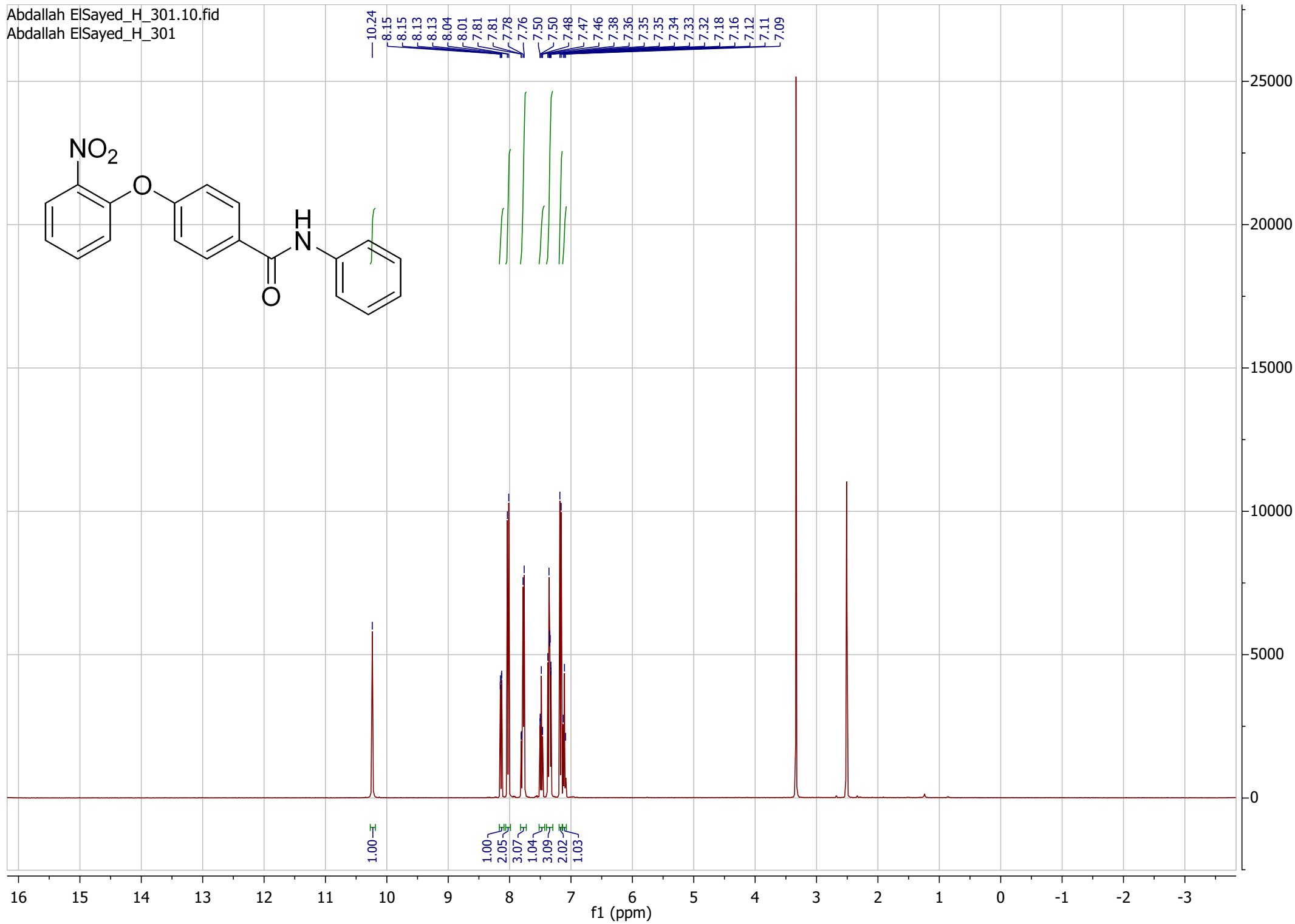
* **Corresponding authors:**

Abdallah E. Abdallah: Email: Abdulla_emara@azhar.edu.eg

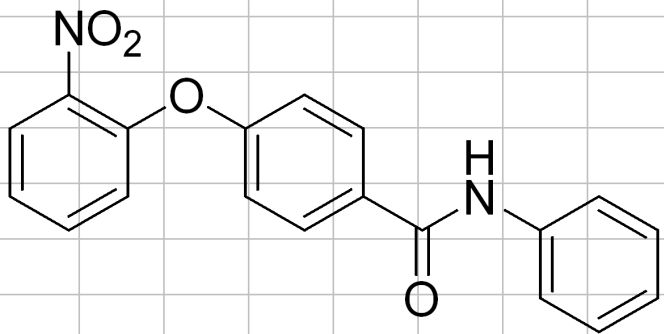
Hazem Elkady: Email: Hazemelkady@azhar.edu.eg

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Abdallah ElSayed_H_301.10.fid
Abdallah ElSayed_H_301



Abdallah ElSayed_C_301.10.fid
Abdallah ElSayed_C_301



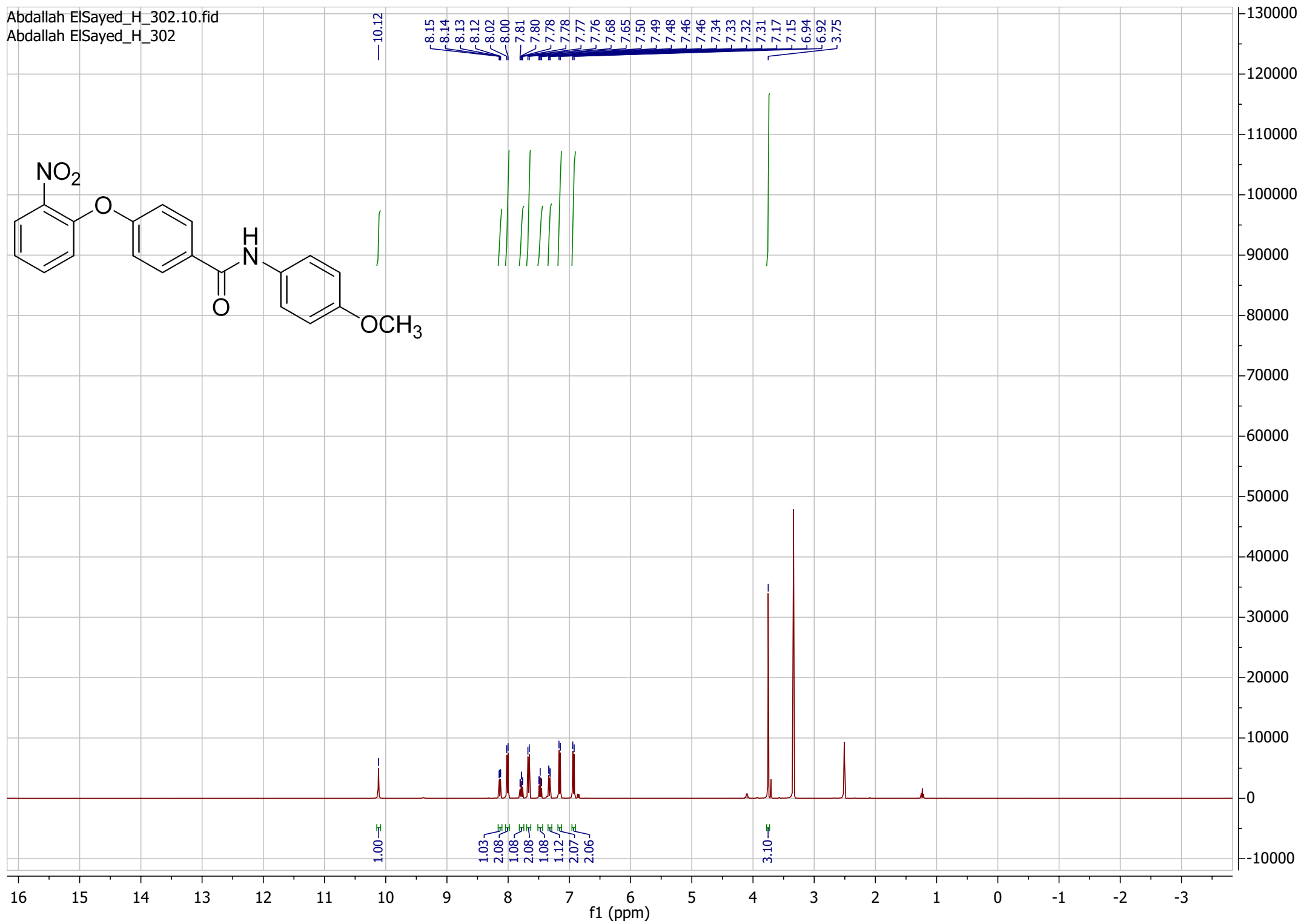
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139.58
135.86
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130.54
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126.34
125.90
124.15
122.91
120.86
117.78

40.56 DMSO
40.35 DMSO
40.14 DMSO
39.93 DMSO
39.72 DMSO
39.51 DMSO
39.31 DMSO

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

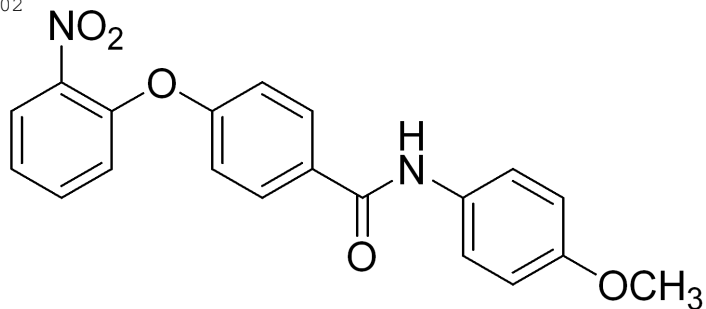
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4000
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2000
1000
0
-1000
-2000





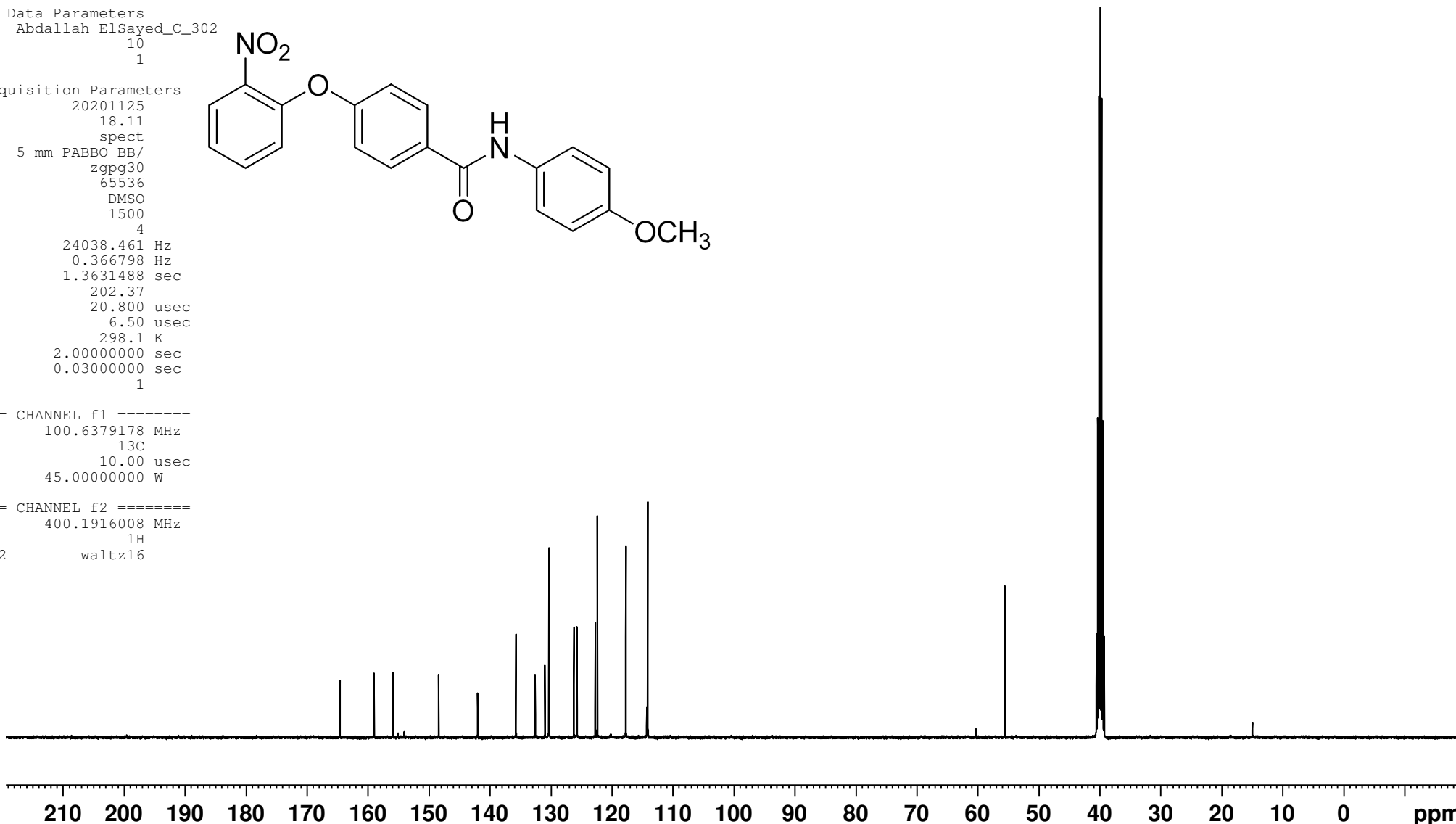
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 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 1500
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.366798 Hz
 AQ 1.3631488 sec
 RG 202.37
 DW 20.800 usec
 DE 6.50 usec
 TE 298.1 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1



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 NUC1 13C
 P1 10.00 usec
 PLW1 45.00000000 W

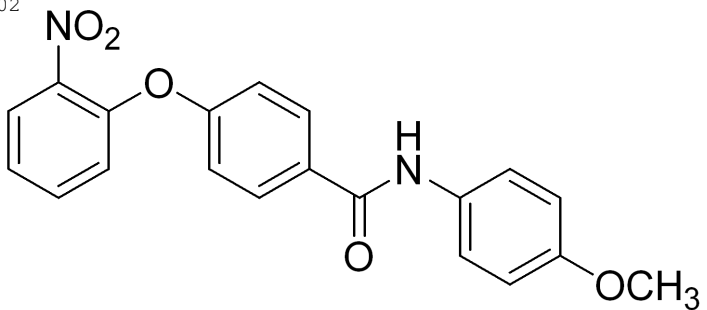
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 CPDPRG[2] waltz16





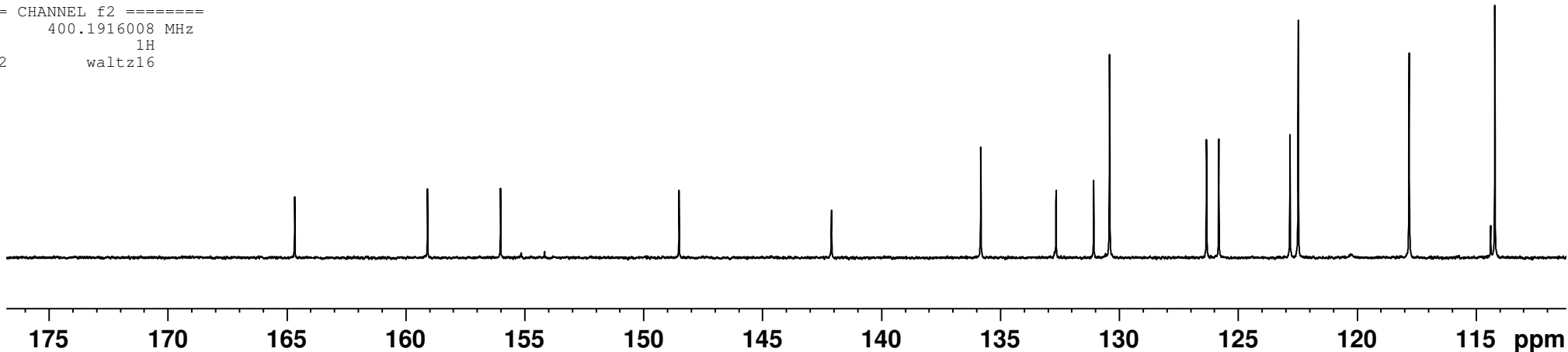
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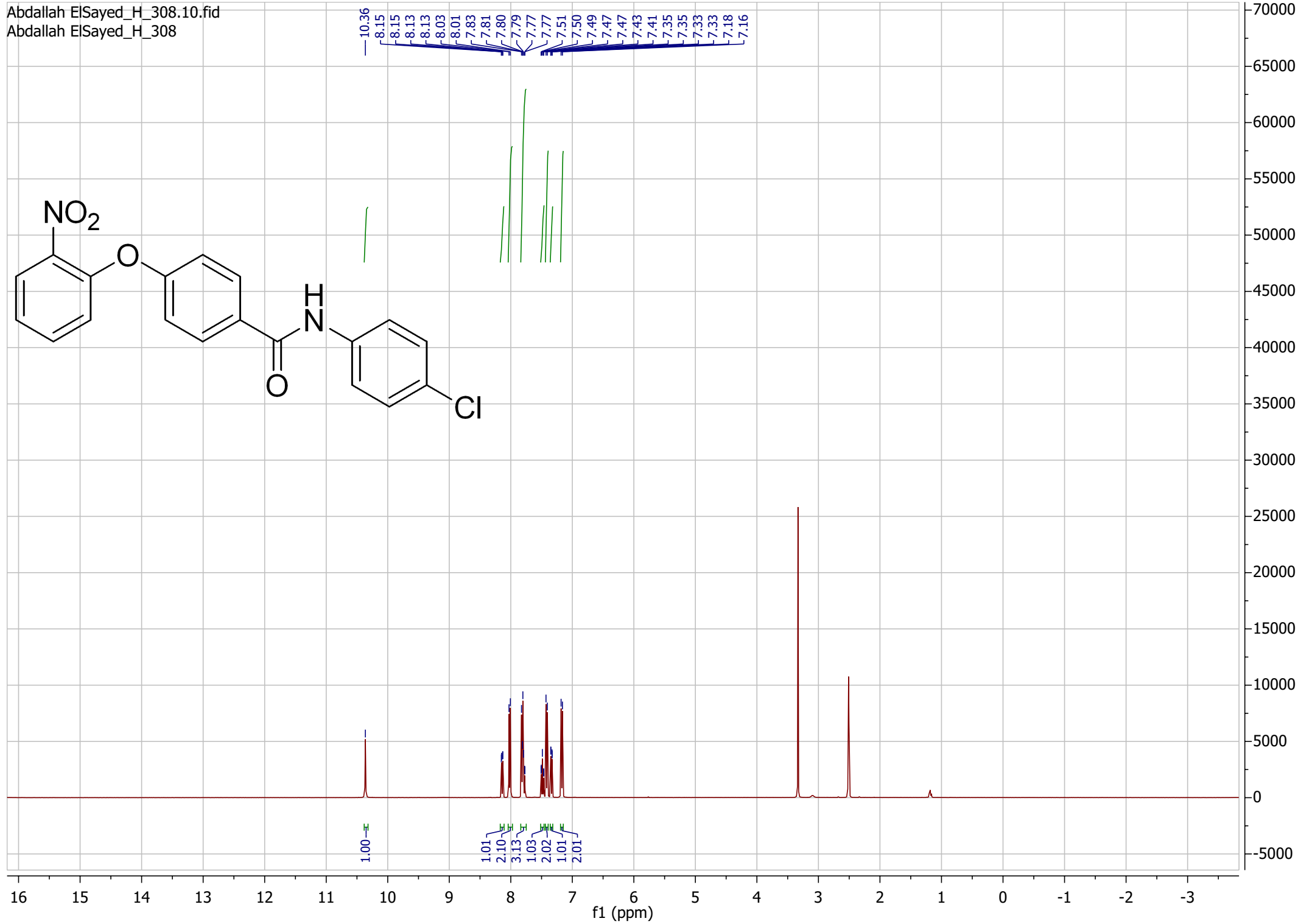
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 FIDRES 0.366798 Hz
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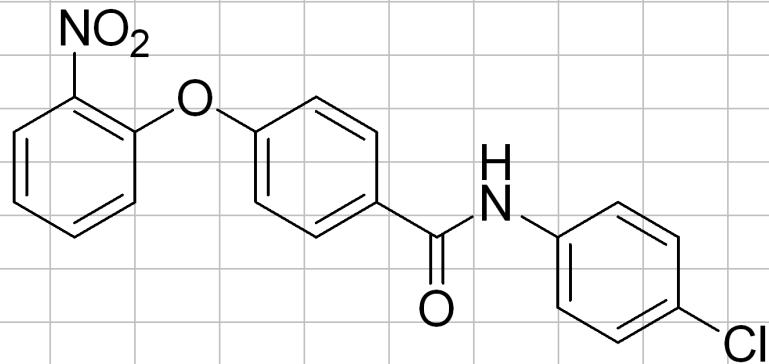


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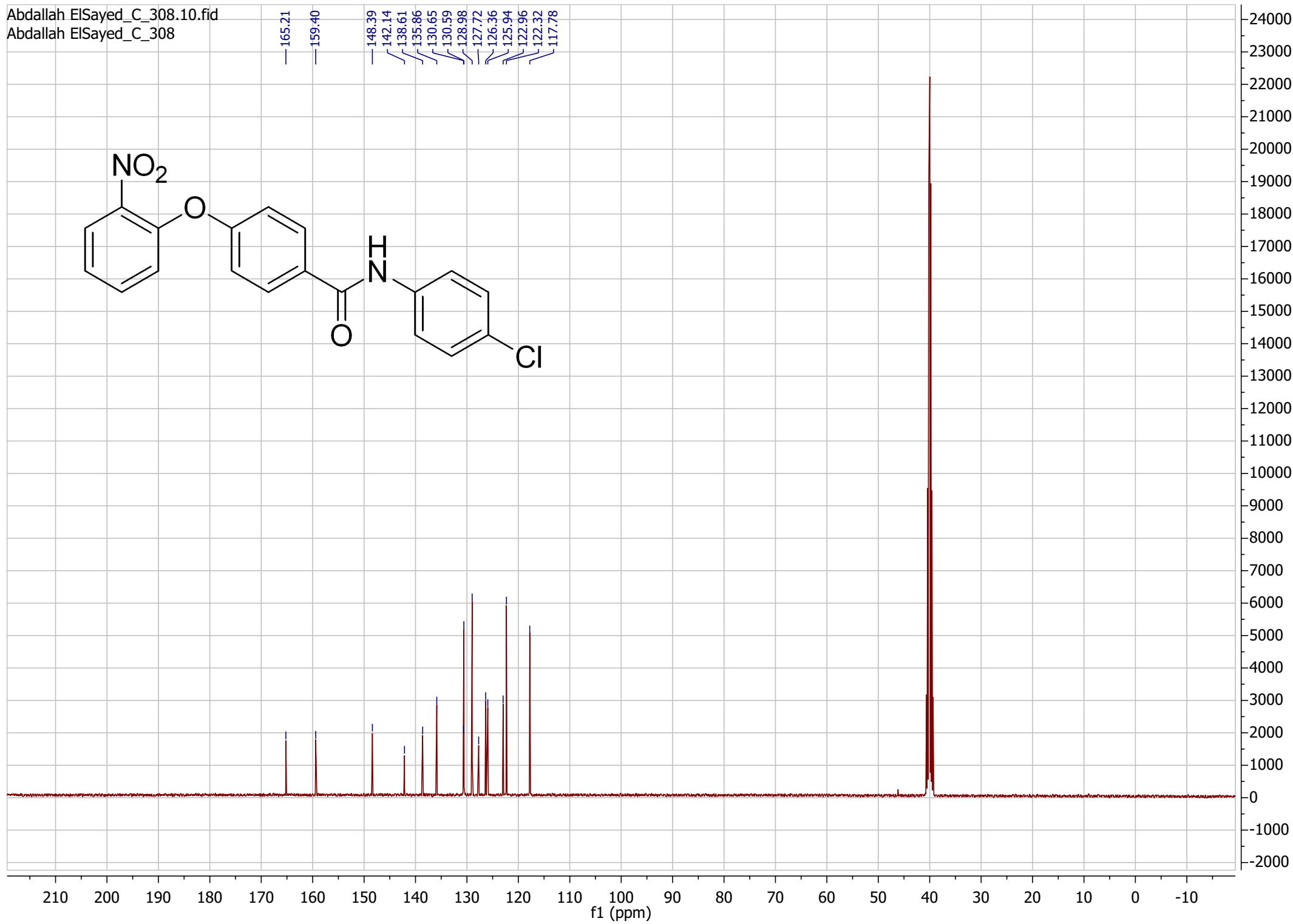
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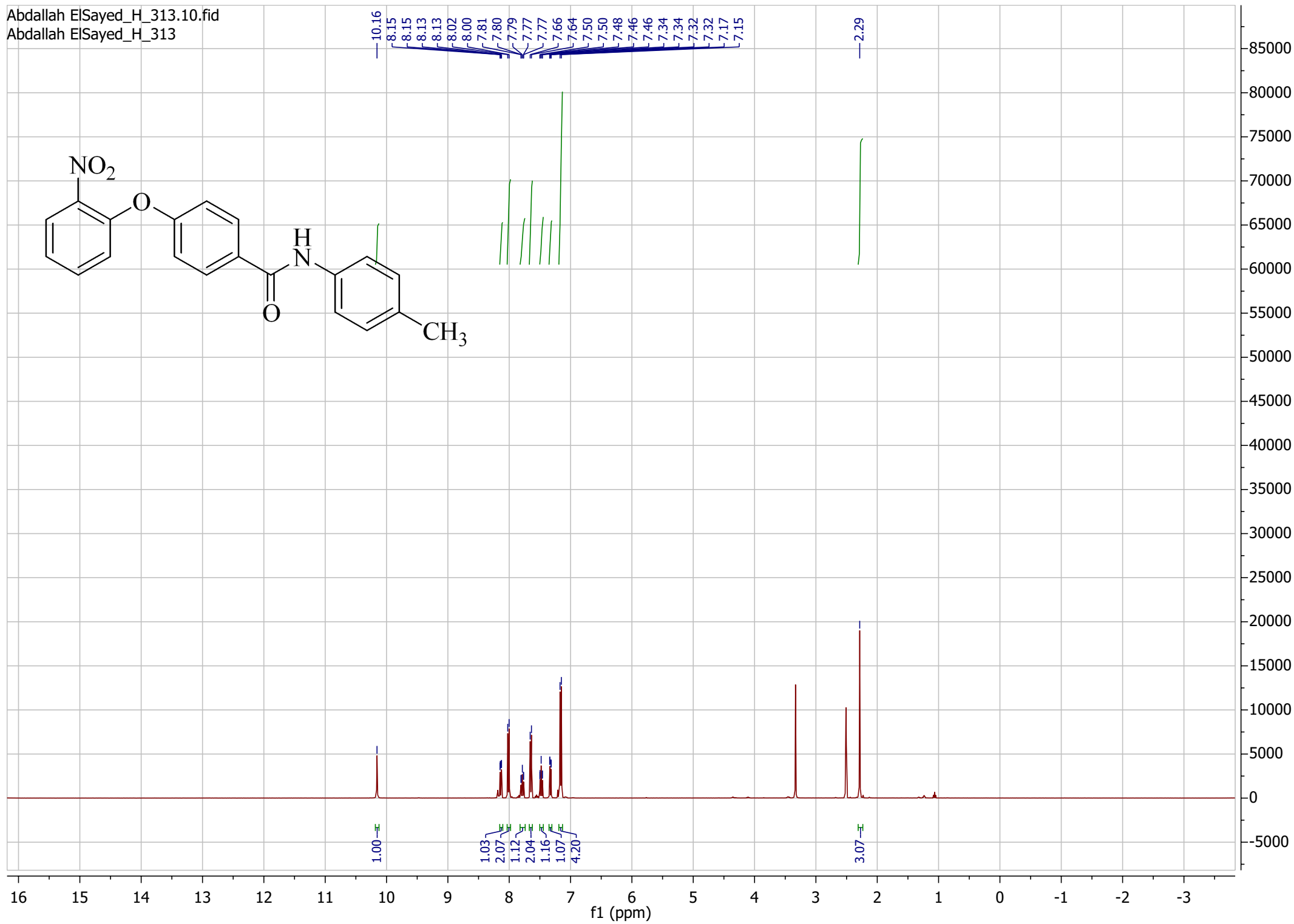


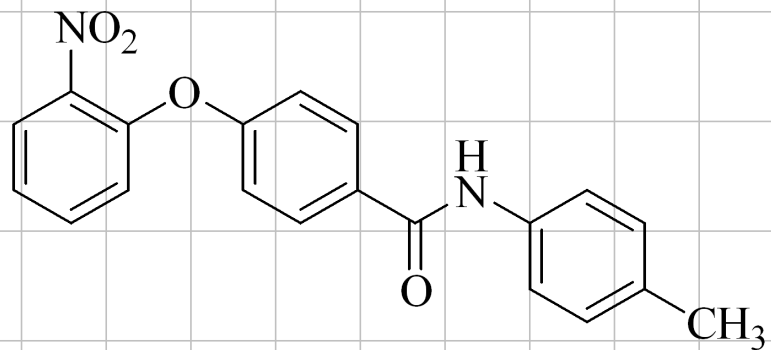




- 165.21
- 159.40
- 148.39
- 142.14
- 138.61
- 135.86
- 130.65
- 130.59
- 128.98
- 127.72
- 126.36
- 125.94
- 122.96
- 122.32
- 117.78

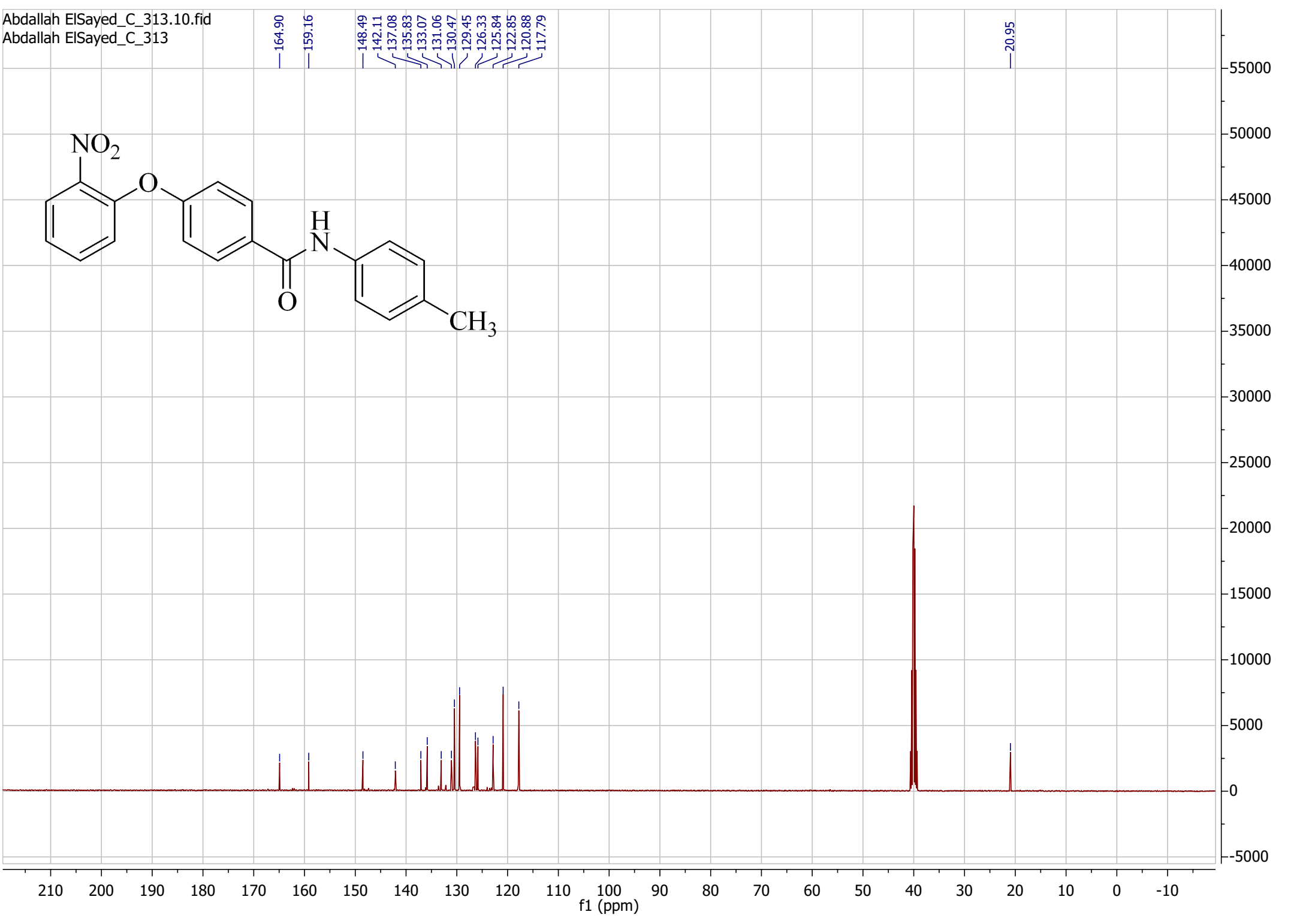


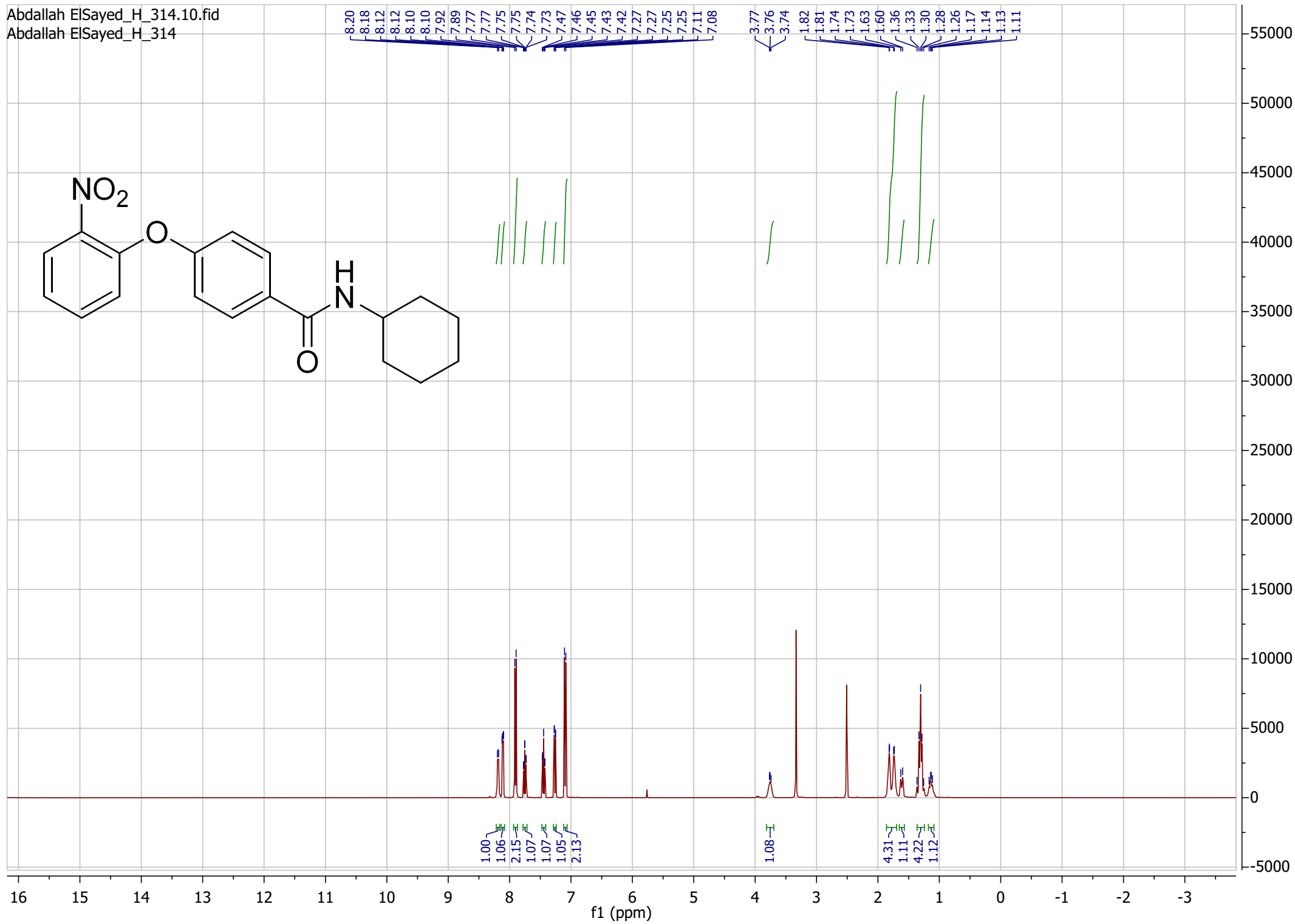
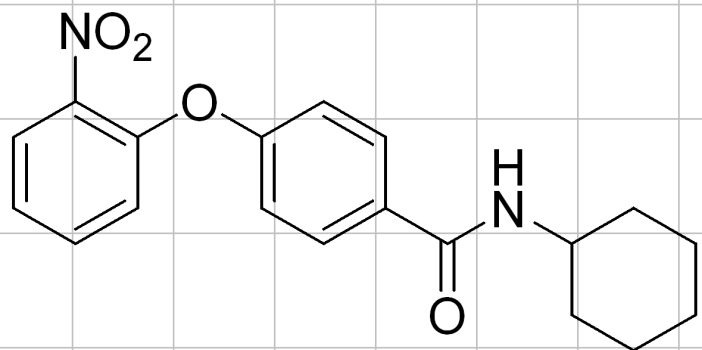


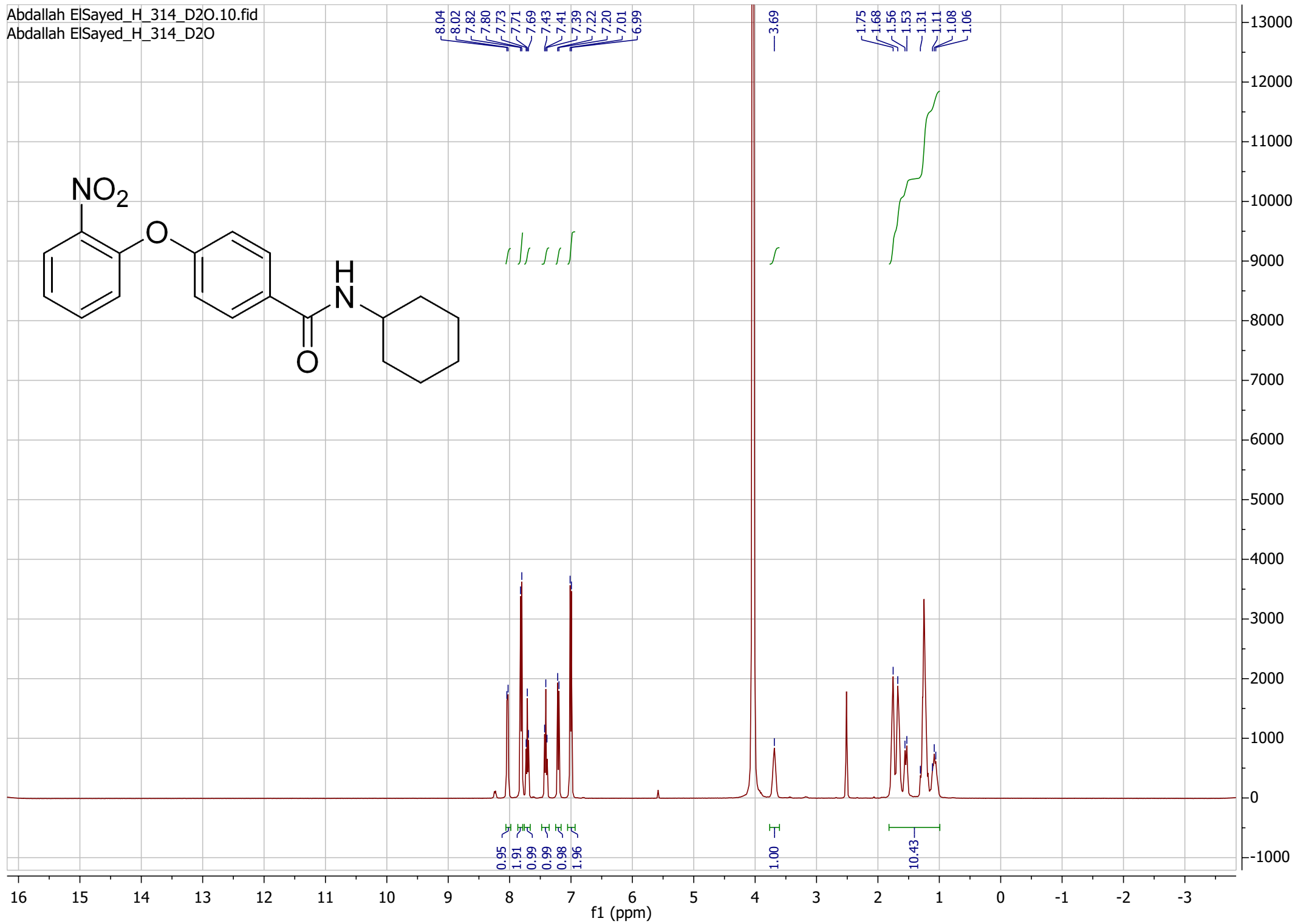
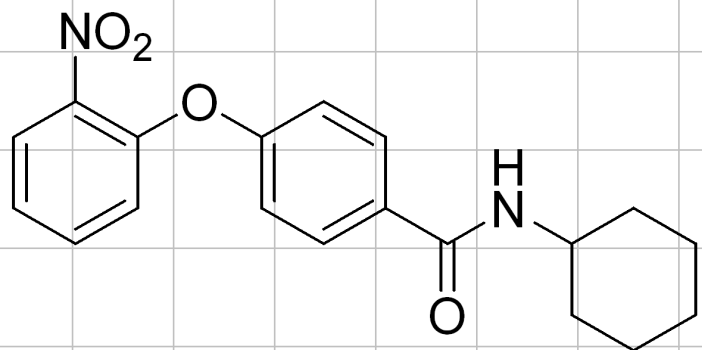


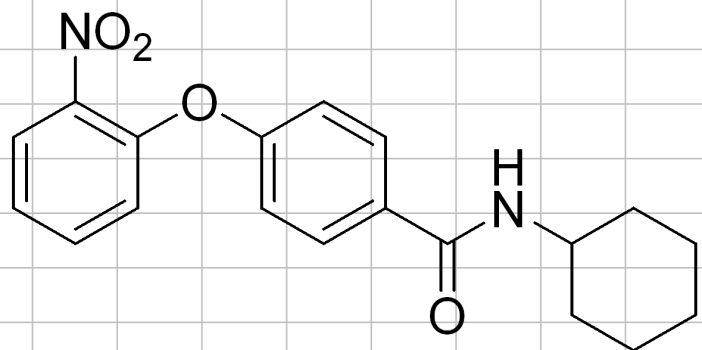
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159.16
148.49
142.11
137.08
135.83
133.07
131.06
130.47
129.45
126.33
125.84
122.85
120.88
117.79

20.95



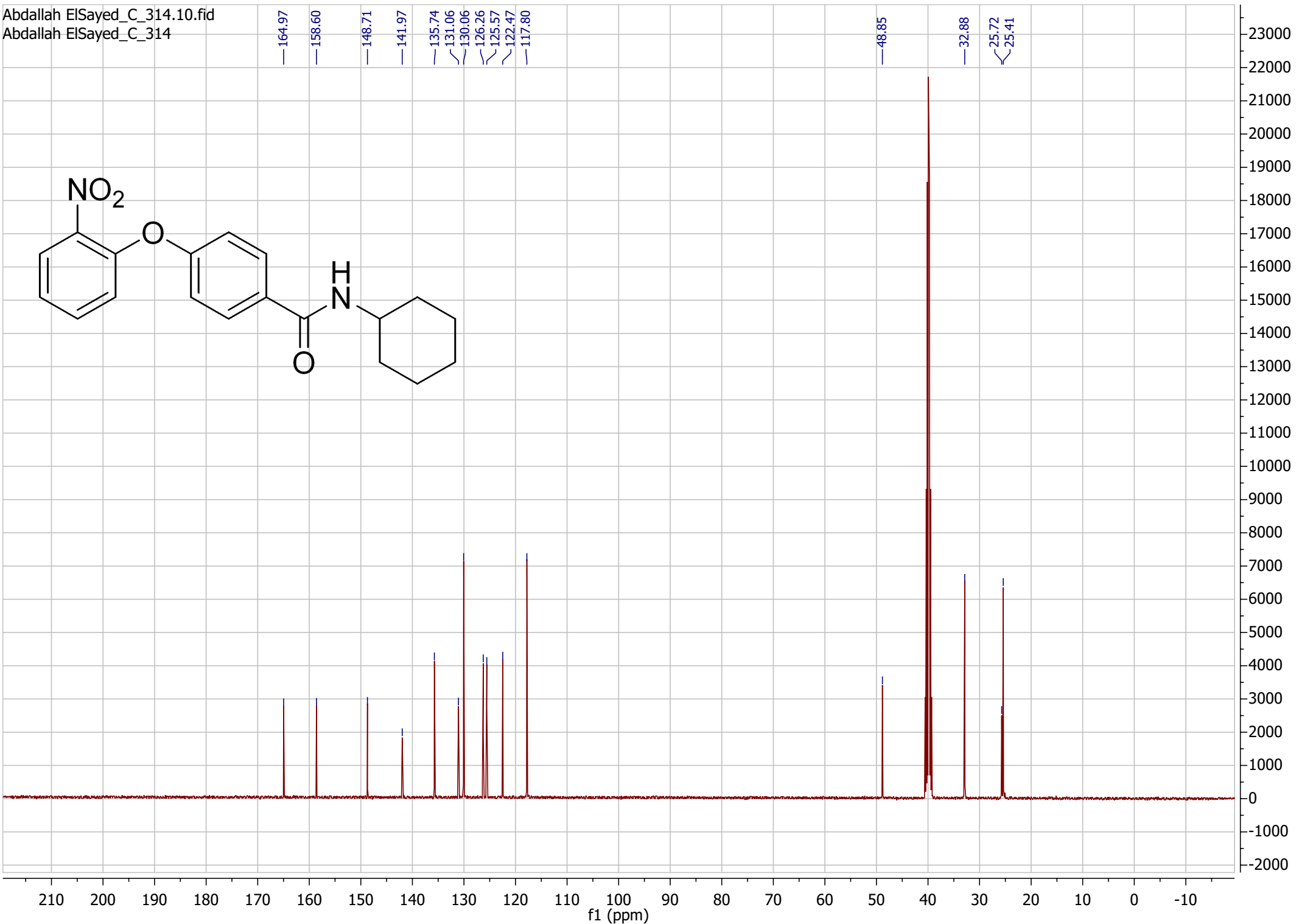


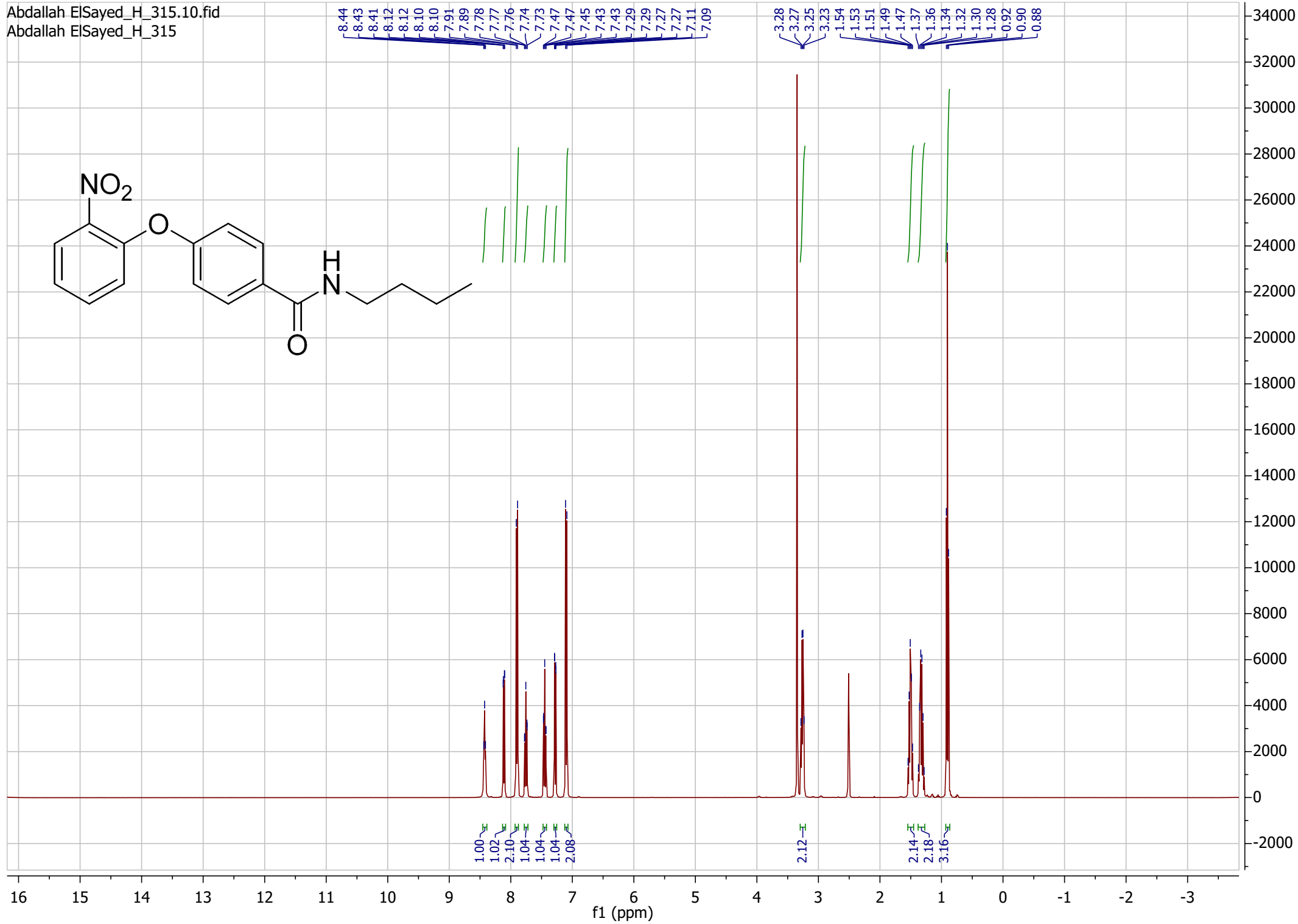
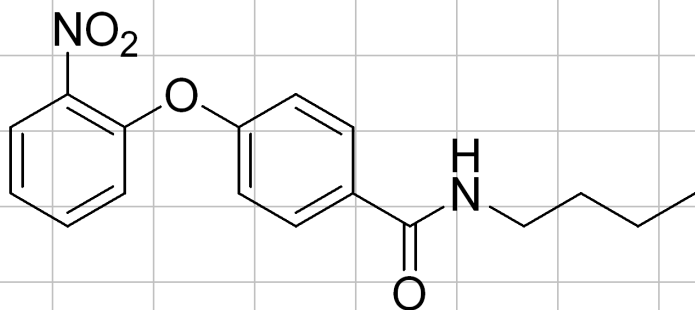




164.97
158.60
148.71
141.97
135.74
131.06
130.06
126.26
125.57
122.47
117.80

48.85
32.88
25.72
25.41





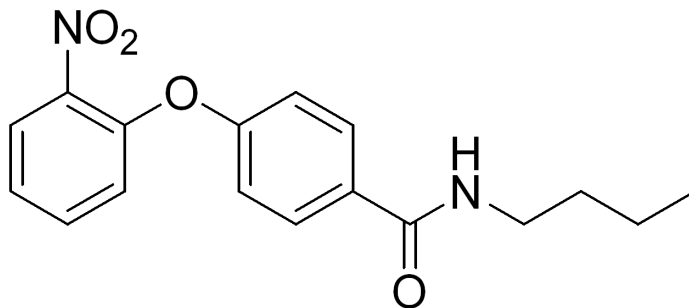


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8.4618
8.4479
8.0510
8.0480
8.0306
8.0277
7.8373
7.8155
7.7345
7.7313
7.7133
7.6952
7.6920
7.4298
7.4108
7.3917
7.2246
7.2043
7.0270
7.0053

3.9398
3.2486
3.2323
3.2191
3.2025
2.5111
1.4925
1.4749
1.4570
1.4386
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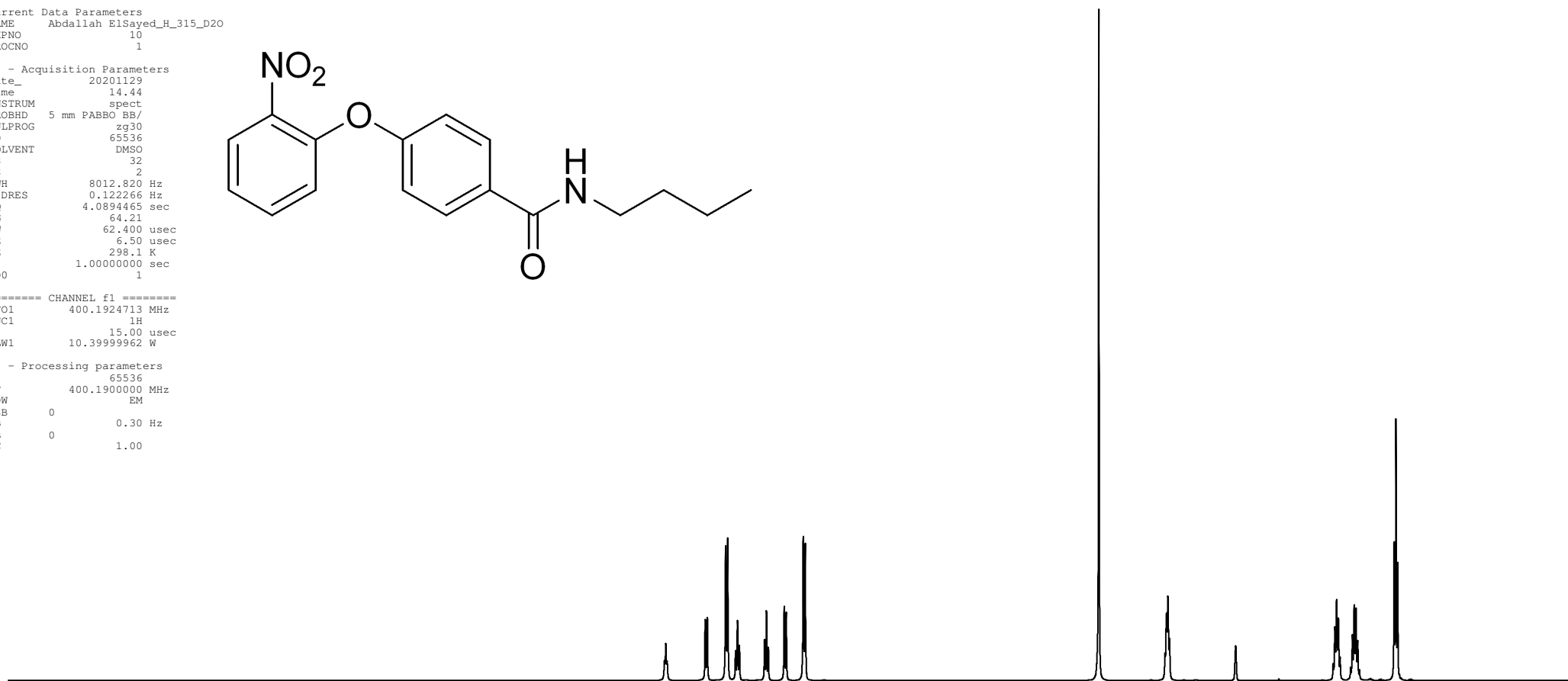
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 SOLVENT DMSO
 NS 32
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 64.21
 DW 62.400 usec
 DE 6.50 usec
 TE 298.1 K
 D1 1.0000000 sec
 TD0 1



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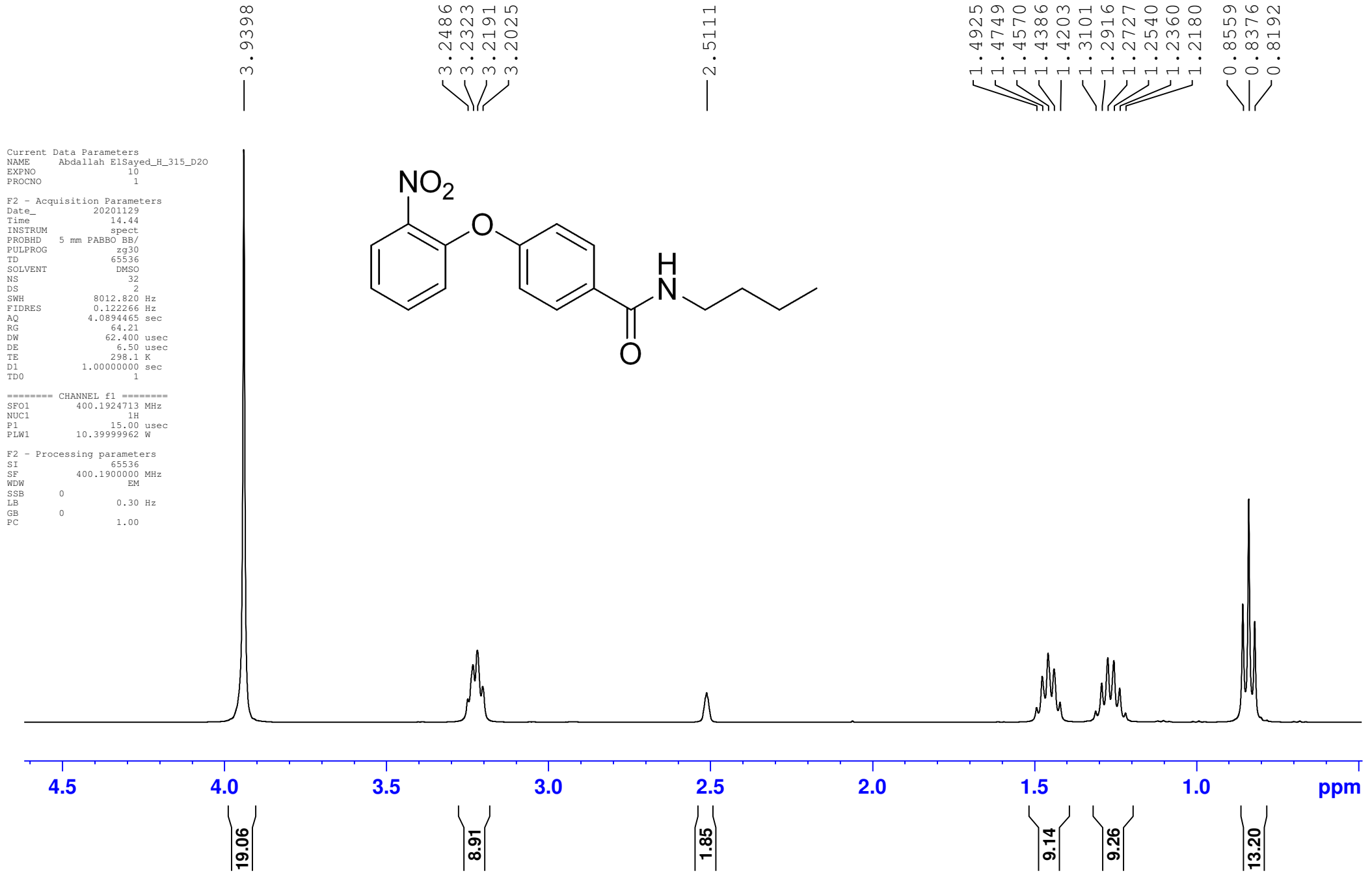
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 WDW EM
 SSB 0
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 GB 0
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15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

2.89
4.49
8.73
4.50
4.53
4.48
8.96

19.06
8.91
1.85
9.14
9.26
13.20





8.4754
 8.4618
 8.4479

8.0510
 8.0480
 8.0306
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 7.7313
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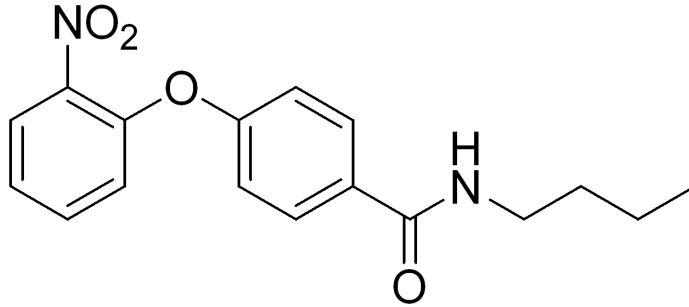
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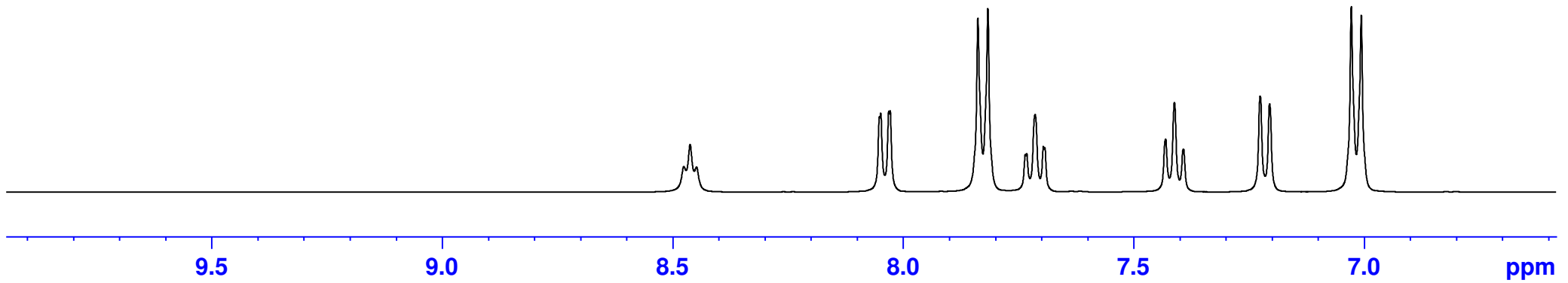
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 PULPROG zg30
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 SOLVENT DMSO
 NS 32
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.122266 Hz
 AQ 4.0894465 sec
 RG 64.21
 DW 62.400 usec
 DE 6.50 usec
 TE 298.1 K
 D1 1.00000000 sec
 TD0 1



===== CHANNEL f1 =====
 SF01 400.1924713 MHz
 NUC1 1H
 P1 15.00 usec
 PLW1 10.39999962 W

F2 - Processing parameters
 SI 65536
 SF 400.1900000 MHz
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 SSB 0
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 GB 0
 PC 1.00



2.89

4.49

8.73

4.50

4.53

4.48

8.96

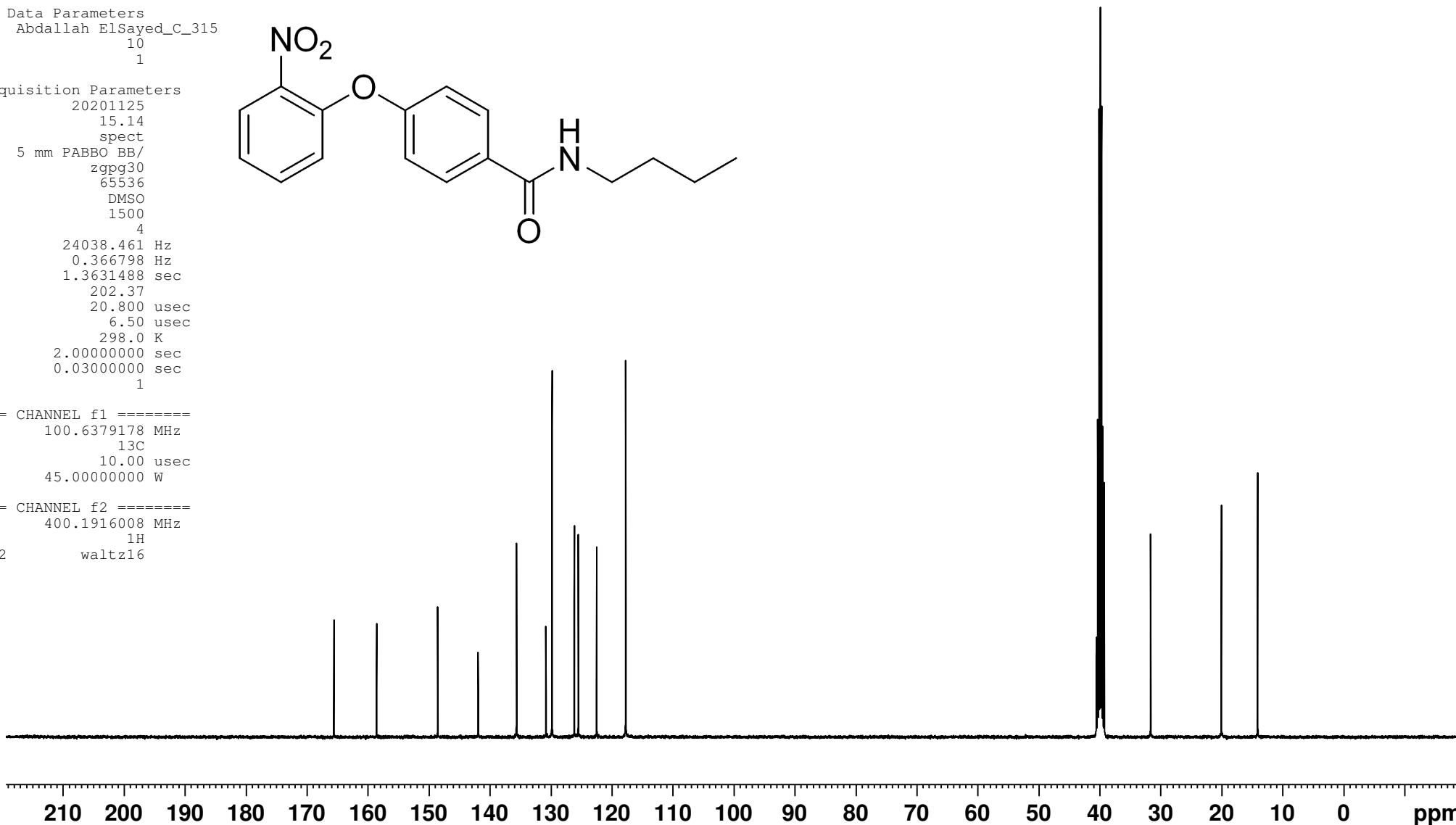
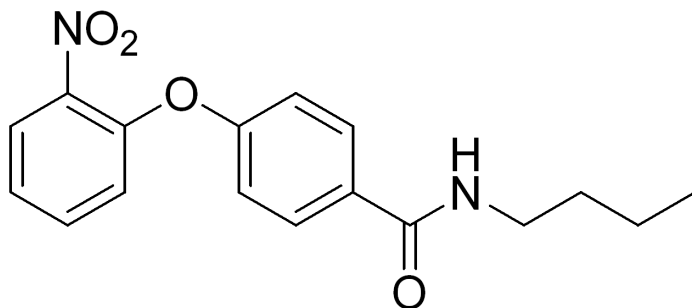


— 165.67
 — 158.68
 — 148.67
 — 142.02
 — 135.73
 — 130.91
 — 129.91
 — 126.25
 — 125.60
 — 122.58
 — 117.82

40.60
 40.40
 40.19
 39.98
 39.77
 39.56
 39.34
 31.73
 — 20.12
 — 14.17

Current Data Parameters
 NAME Abdallah ElSayed_C_315
 EXPNO 10
 PROCNO 1

F2 - Acquisition Parameters
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 PULPROG zgpg30
 TD 65536
 SOLVENT DMSO
 NS 1500
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.366798 Hz
 AQ 1.3631488 sec
 RG 202.37
 DW 20.800 usec
 DE 6.50 usec
 TE 298.0 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1



==== CHANNEL f1 =====
 SFO1 100.6379178 MHz
 NUC1 13C
 P1 10.00 usec
 PLW1 45.00000000 W

==== CHANNEL f2 =====
 SFO2 400.1916008 MHz
 NUC2 1H
 CPDPRG[2] waltz16

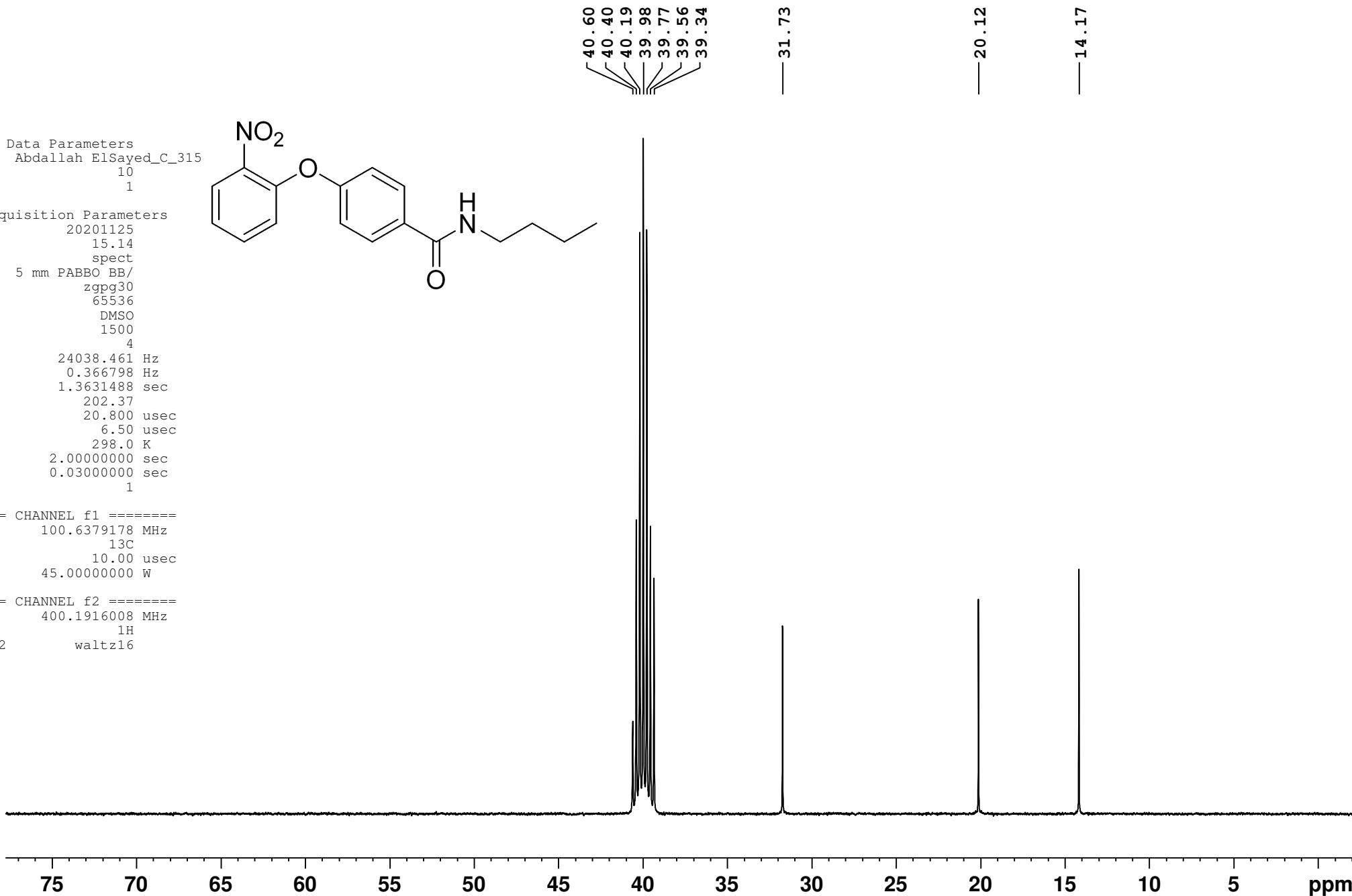
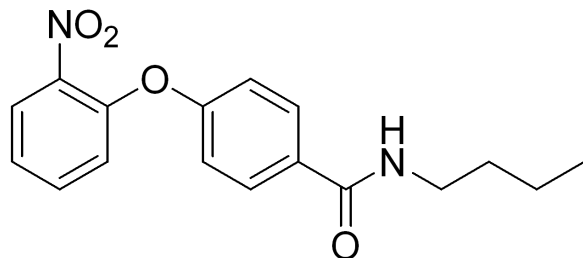


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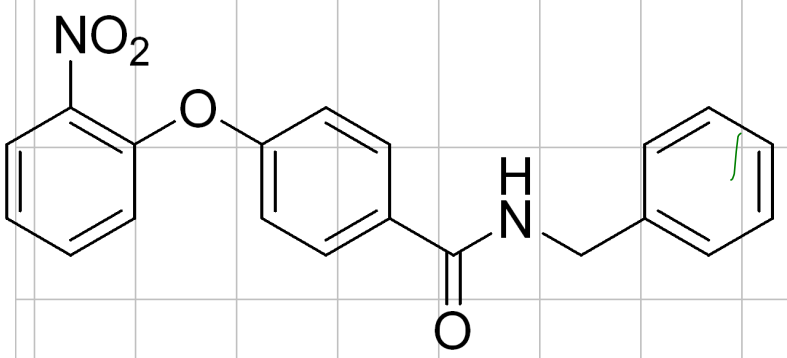
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SOLVENT DMSO
NS 1500
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 202.37
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1

==== CHANNEL f1 =====
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NUC1 13C
P1 10.00 usec
PLW1 45.00000000 W

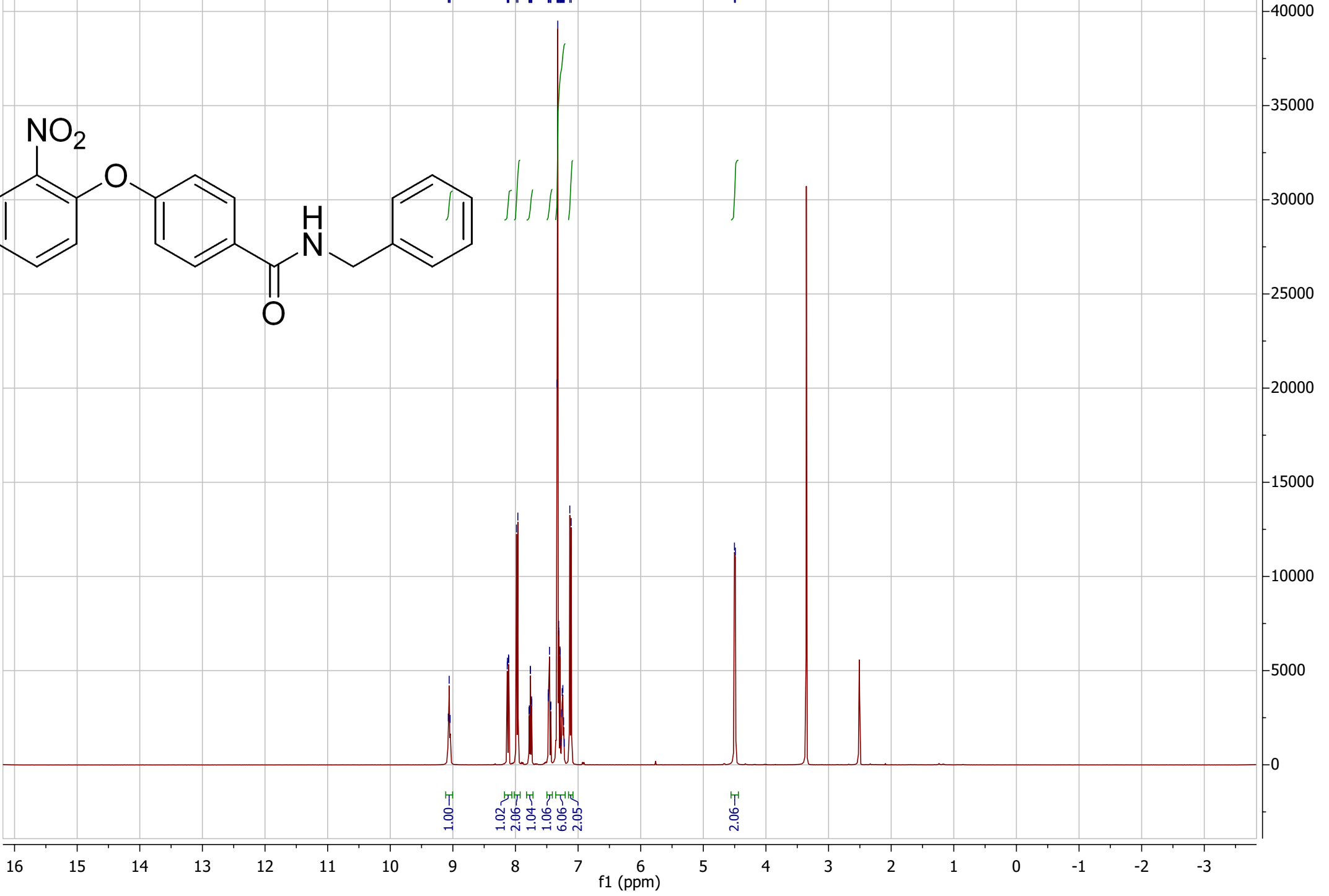
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NUC2 1H
CPDPRG[2] waltz16



Abdallah ElSayed_H_312.1051
Abdallah ElSayed_H_312



9.08
9.04
8.13
8.13
8.11
8.11
7.98
7.96
7.78
7.78
7.76
7.76
7.74
7.74
7.48
7.47
7.46
7.44
7.44
7.34
7.32
7.31
7.31
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7.22
7.13
7.11
4.50
4.49



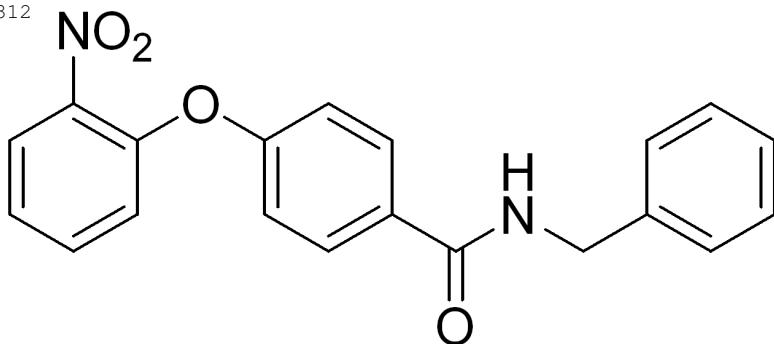


165.82
 158.96
 148.58
 142.06
 140.15
 135.77
 130.45
 130.08
 128.74
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 127.19
 126.28
 125.70
 122.73
 117.85

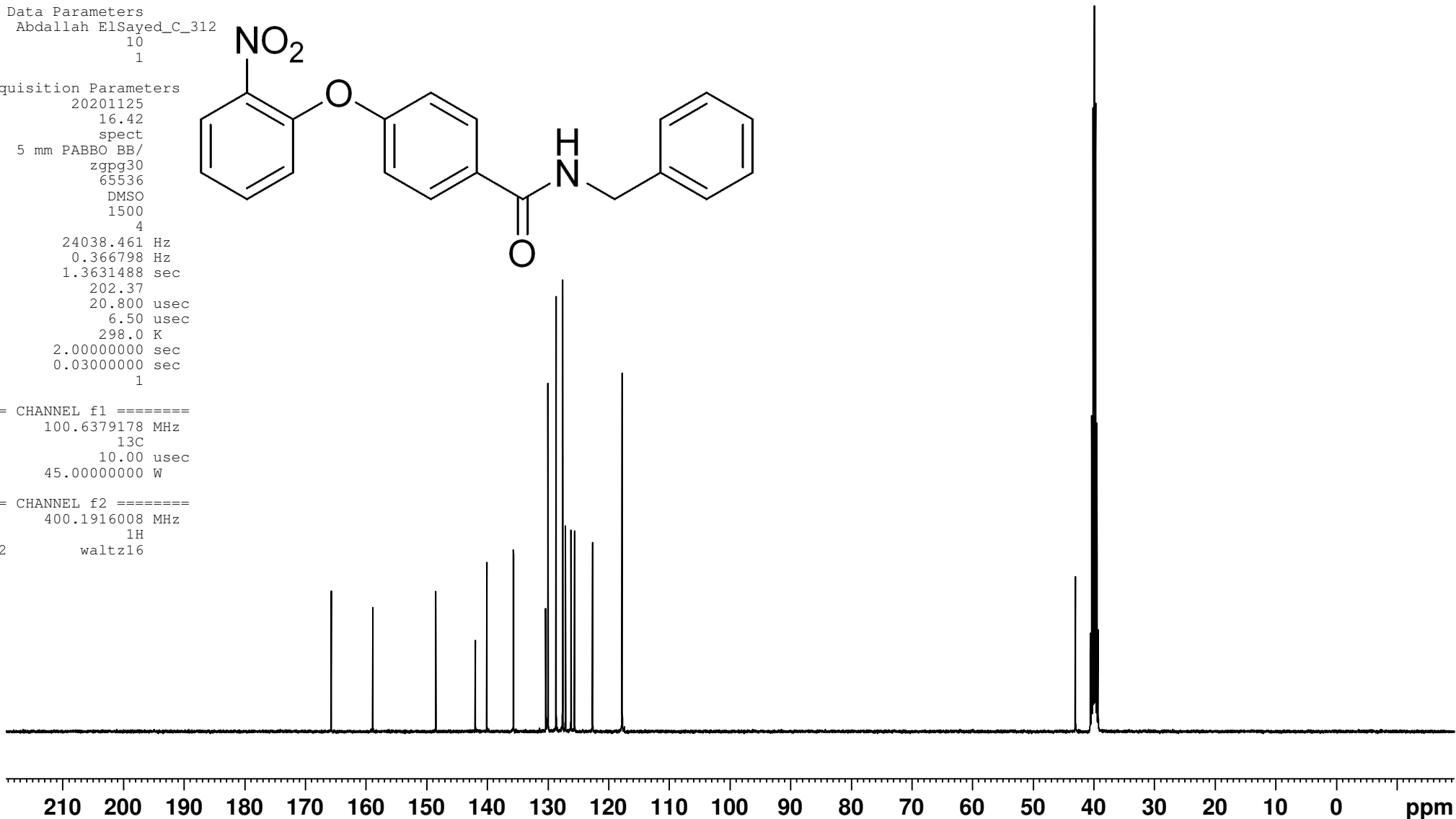
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 40.60
 40.40
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 39.77
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 39.35

Current Data Parameters
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 EXPNO 10
 PROCNO 1

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 PULPROG zgpg30
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 SOLVENT DMSO
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 FIDRES 0.366798 Hz
 AQ 1.3631488 sec
 RG 202.37
 DW 20.800 usec
 DE 6.50 usec
 TE 298.0 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1



==== CHANNEL f1 =====
 SFO1 100.6379178 MHz
 NUC1 13C
 P1 10.00 usec
 PLW1 45.00000000 W
 ===== CHANNEL f2 =====
 SFO2 400.1916008 MHz
 NUC2 1H
 CPDPRG[2] waltz16





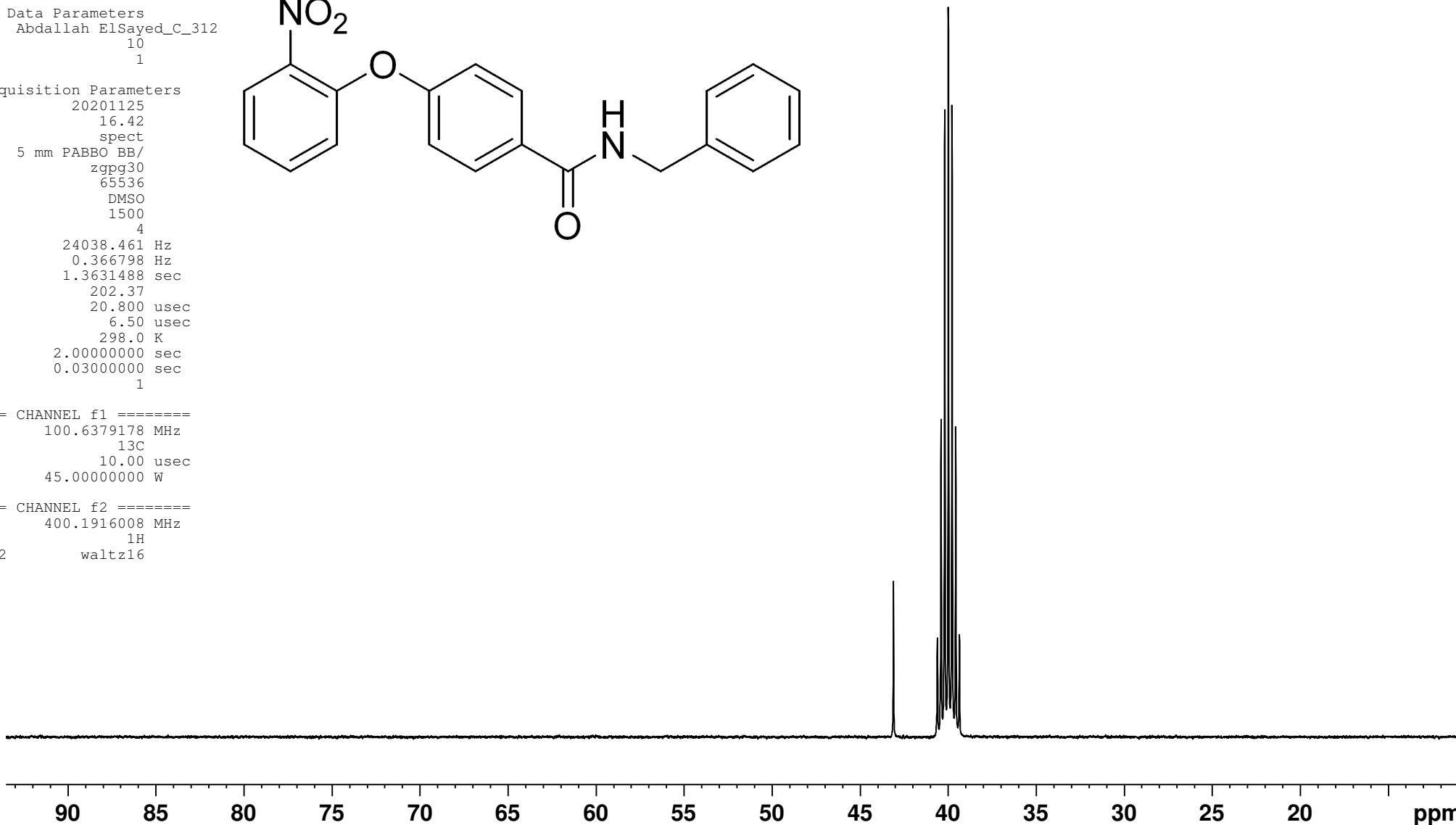
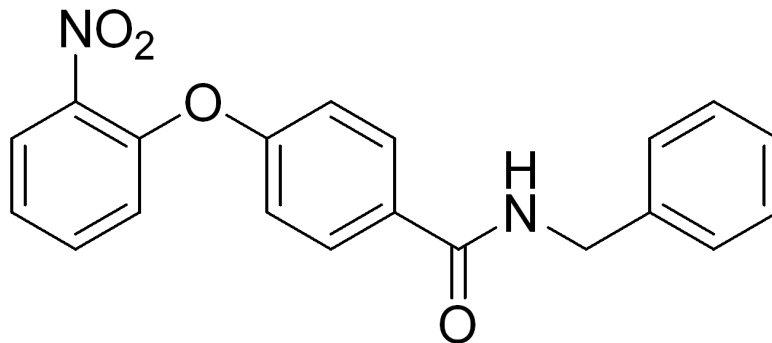
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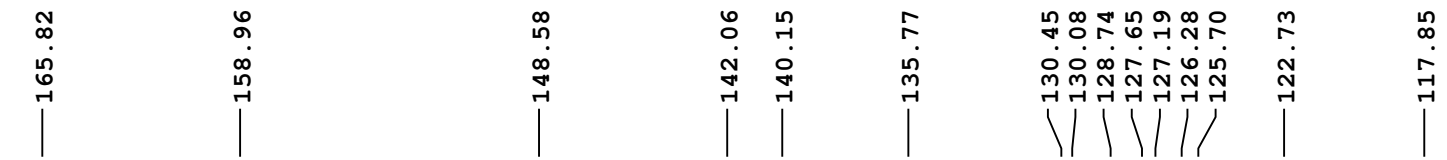
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 D11 0.03000000 sec
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==== CHANNEL f1 =====
 SFO1 100.6379178 MHz
 NUC1 13C
 P1 10.00 usec
 PLW1 45.00000000 W

==== CHANNEL f2 =====
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 NUC2 1H
 CPDPRG[2] waltz16



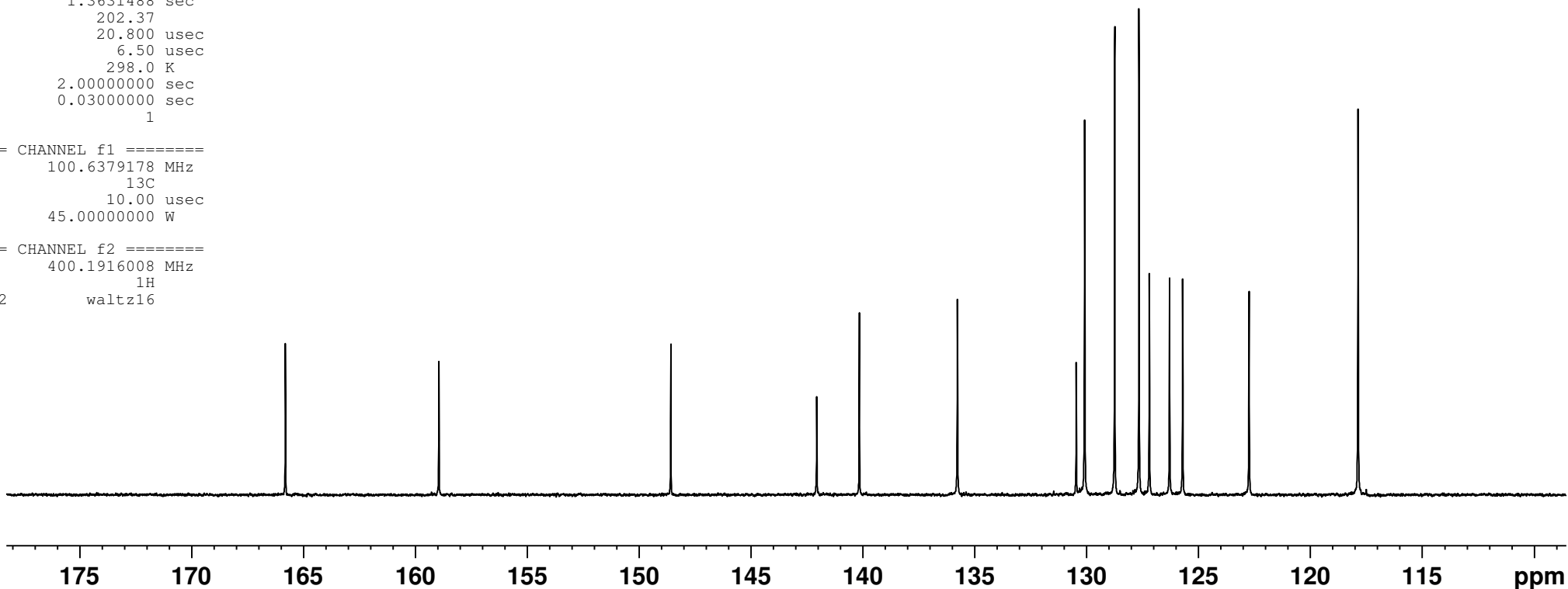


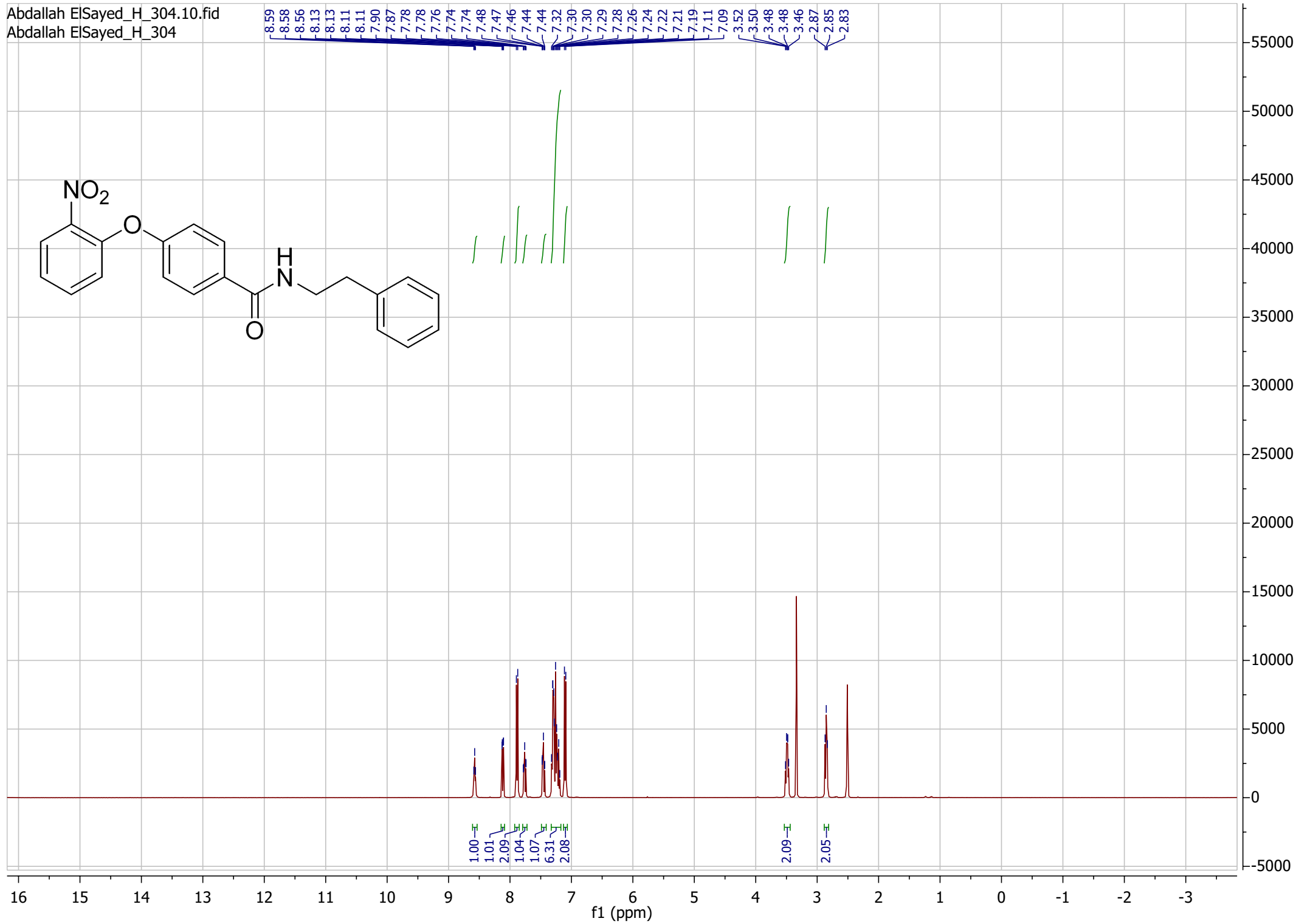
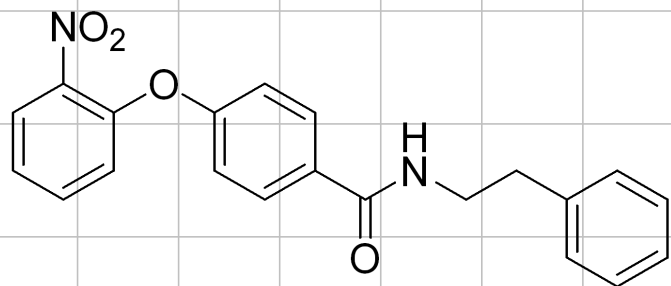
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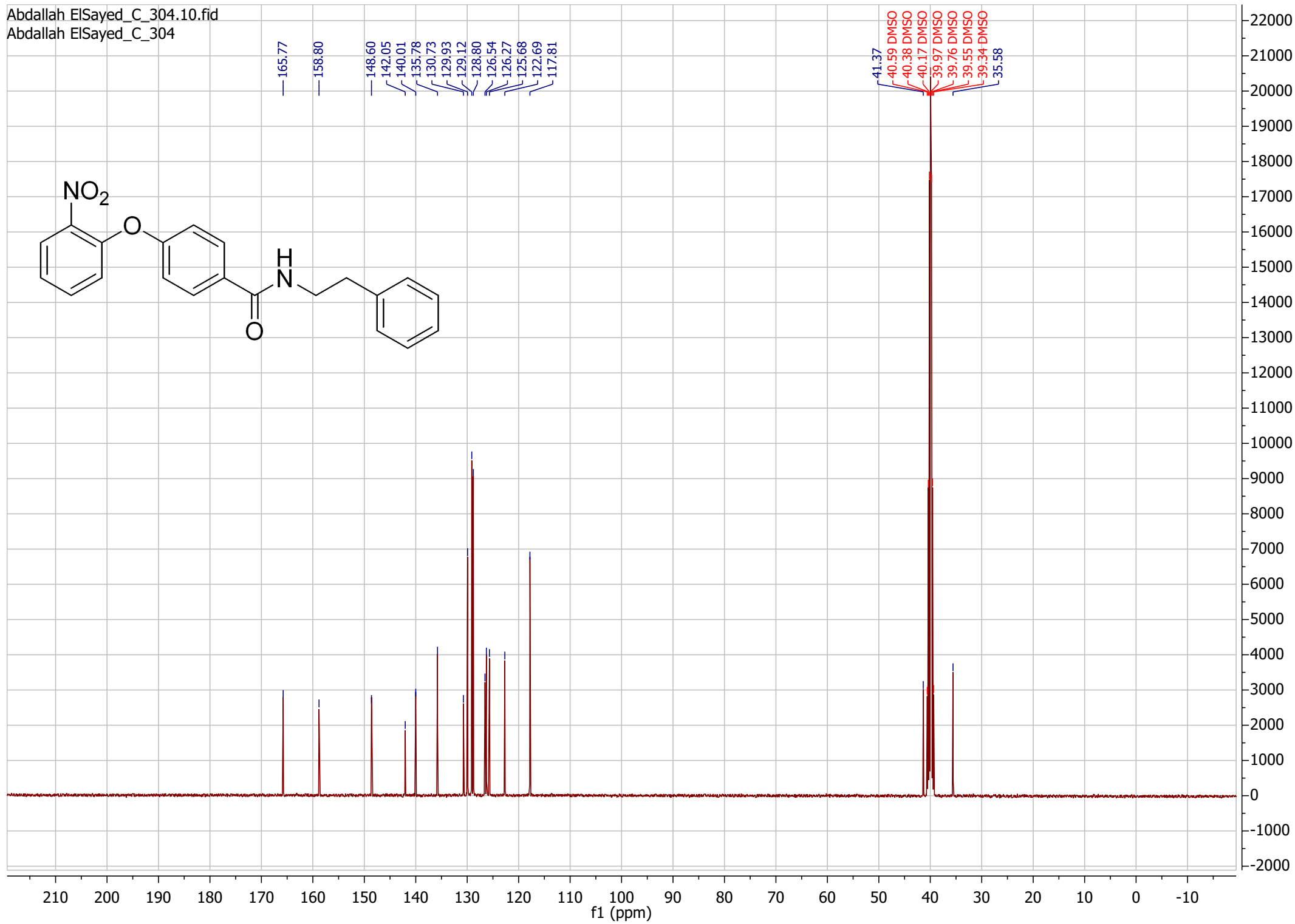
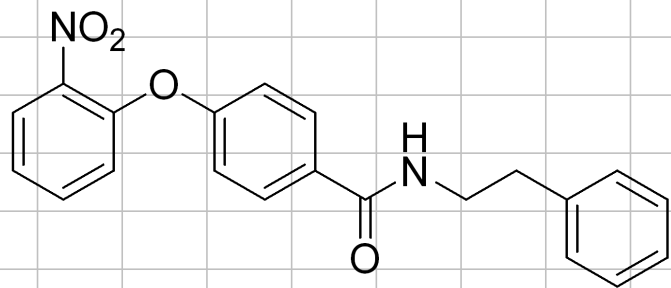
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 SOLVENT DMSO
 NS 1500
 DS 4
 SWH 24038.461 Hz
 FIDRES 0.366798 Hz
 AQ 1.3631488 sec
 RG 202.37
 DW 20.800 usec
 DE 6.50 usec
 TE 298.0 K
 D1 2.00000000 sec
 D11 0.03000000 sec
 TD0 1

==== CHANNEL f1 =====
 SFO1 100.6379178 MHz
 NUC1 13C
 P1 10.00 usec
 PLW1 45.00000000 W

==== CHANNEL f2 =====
 SFO2 400.1916008 MHz
 NUC2 1H
 CPDPRG[2] waltz16

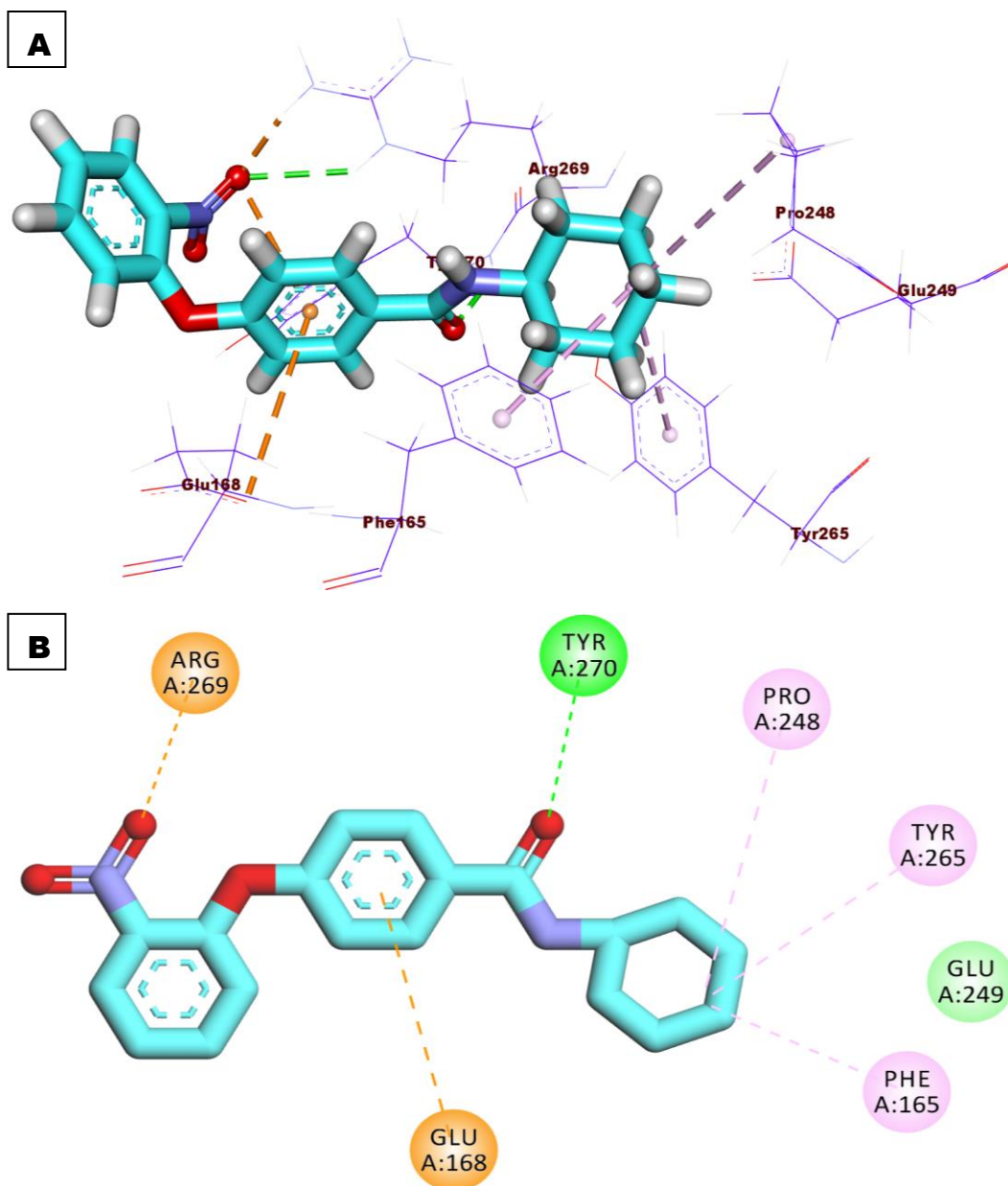




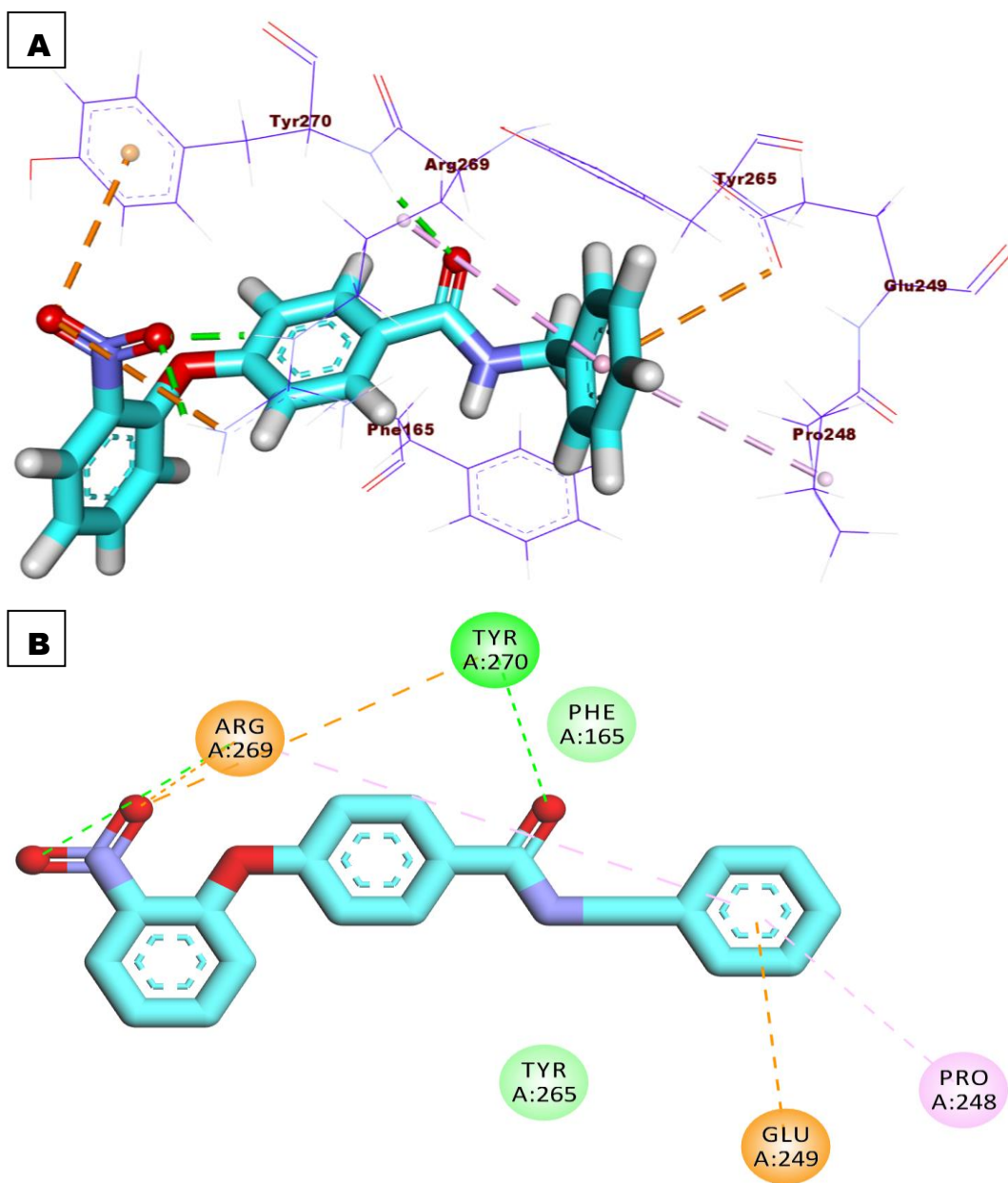


Mutation at four sites

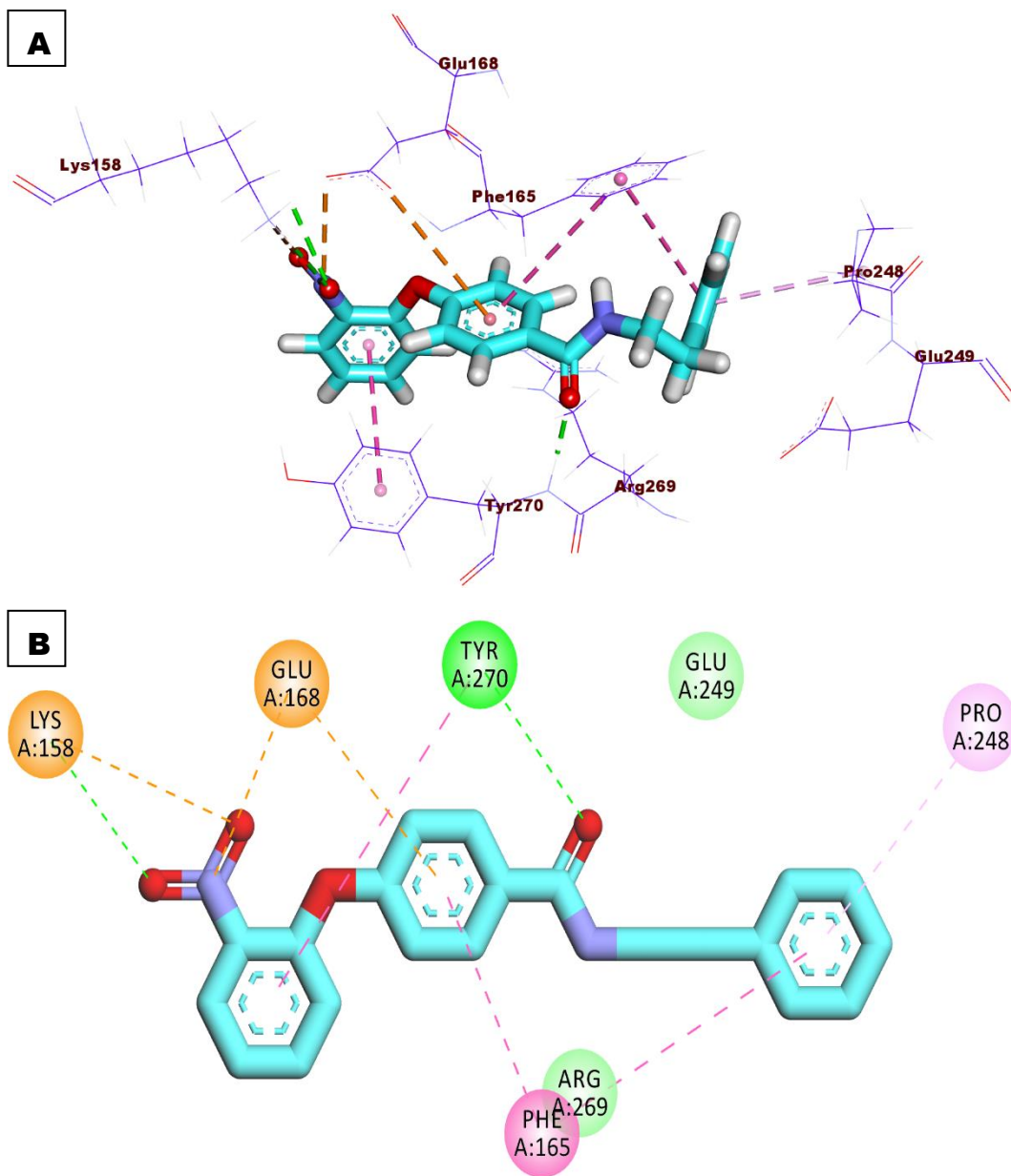
(Gln270 to Tyr270, Asp165 to Phe165, Pro249 to Glu249, and Tyr269 to Arg269)



SI 1: A) 3D binding mode of compound **9_a** into mutant PLpro active site. B) 2D binding mode of compound **9_a** into mutant PLpro active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).



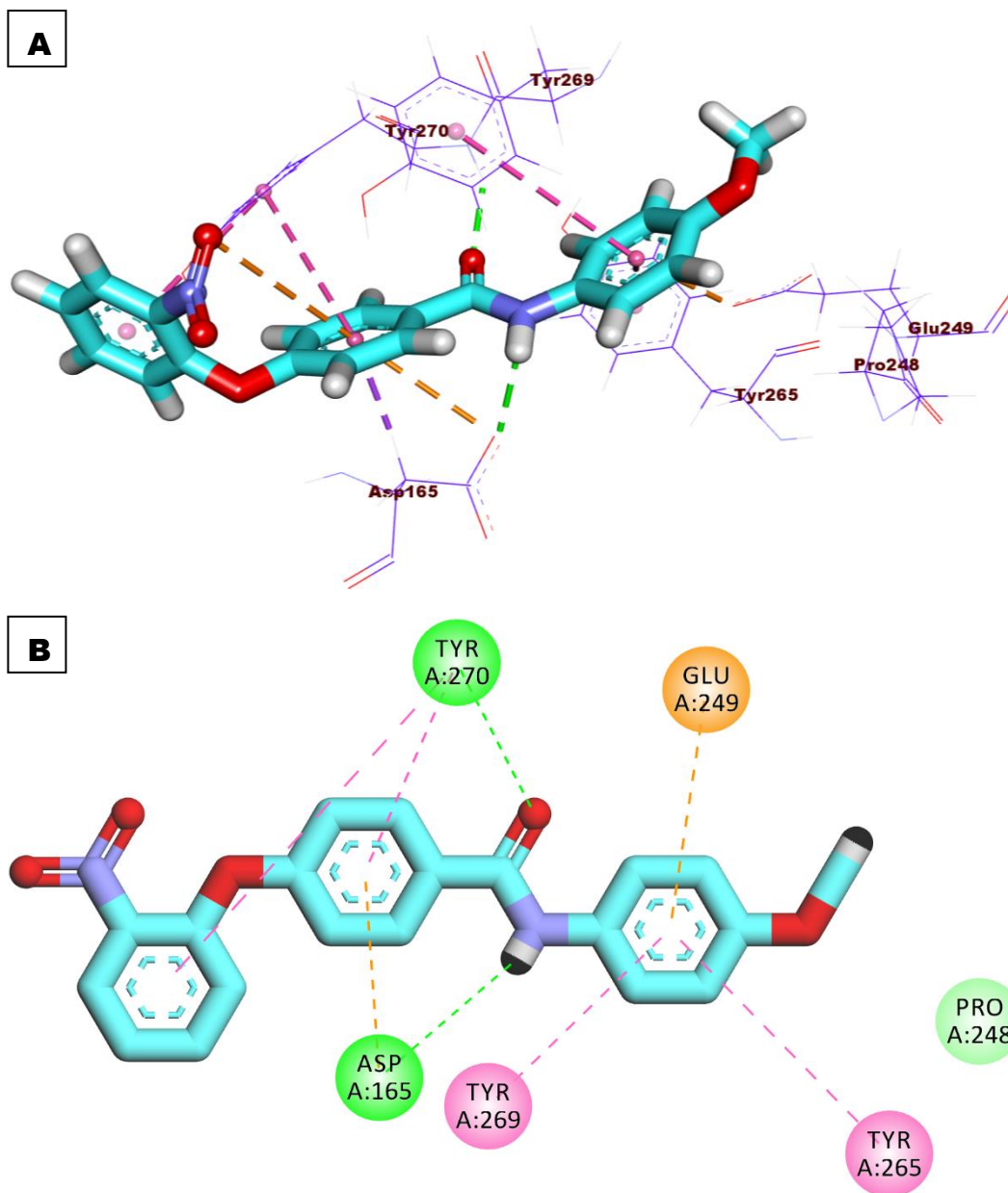
SI 2: A) 3D binding mode of compound **10_a** into mutant PLpro active site. B) 2D binding mode of compound **10_a** into mutant PLpro active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).



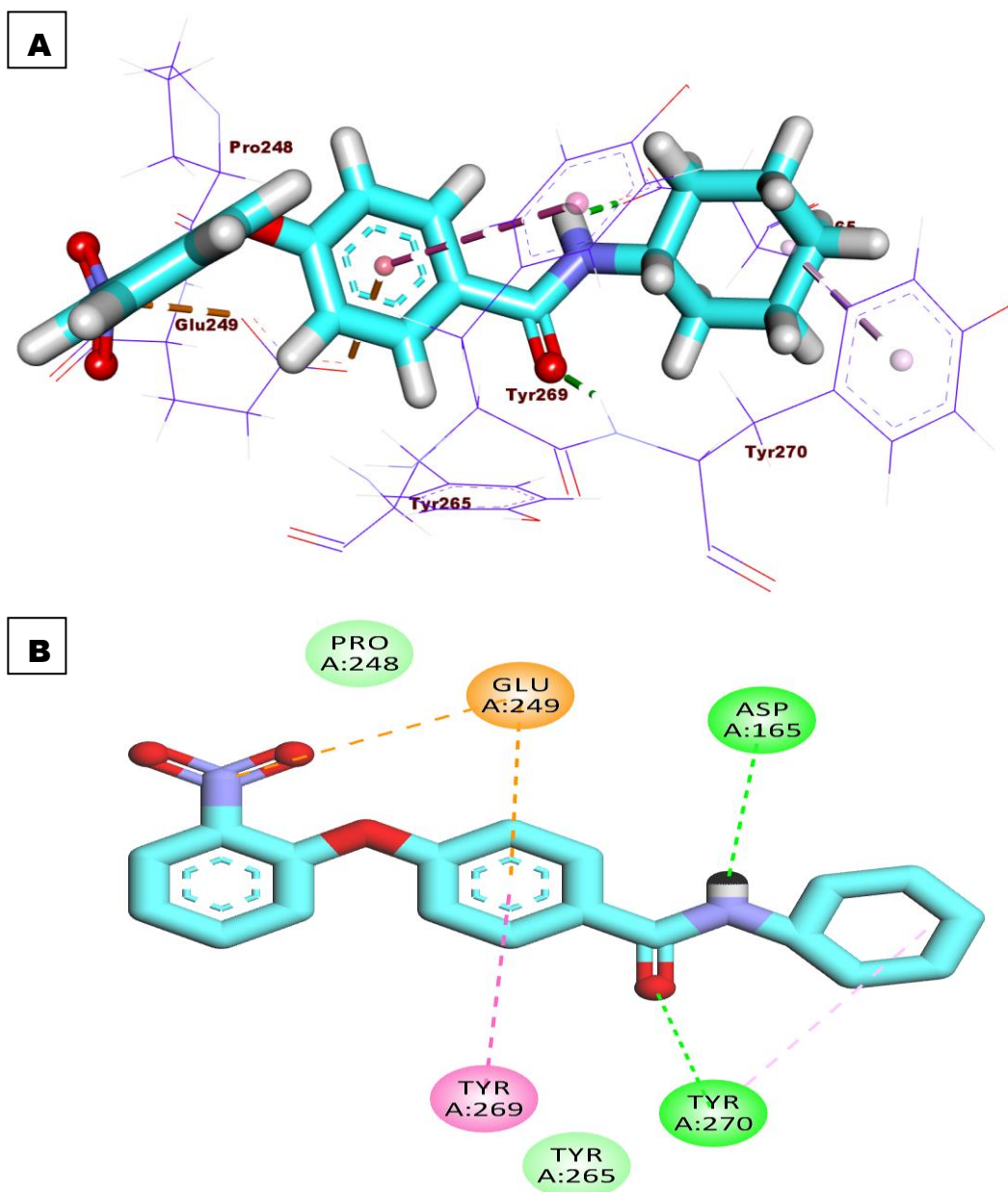
SI 3: A) 3D binding mode of compound **10b** into mutant PLpro active site. B) 2D binding mode of compound **10b** into mutant PLpro active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).

Mutation at two sites

(Gln270 to Tyr270 & Pro249 to Glu249)

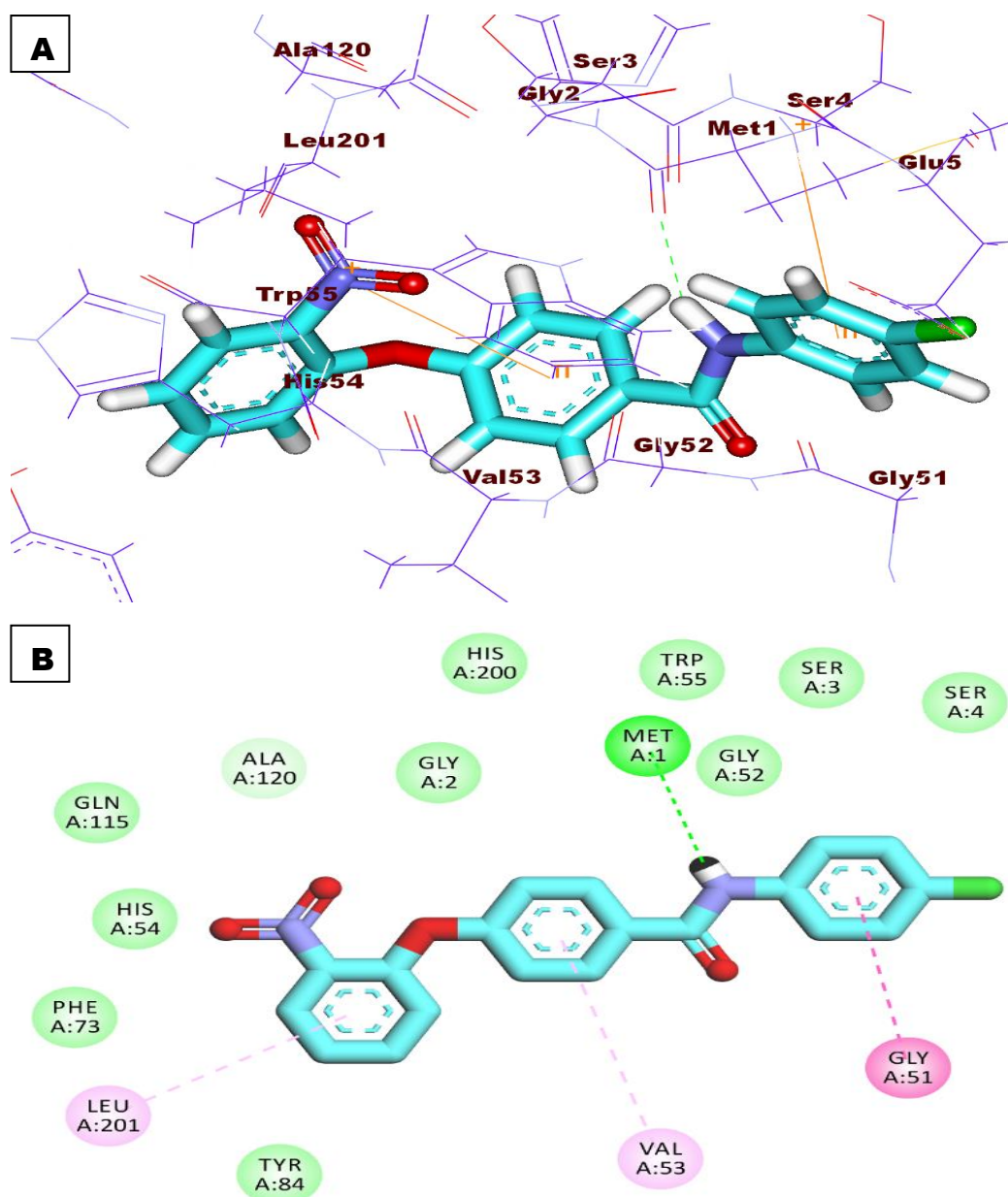


SI 4: A) 3D binding mode of compound **8b** into mutant PLpro active site. B) 2D binding mode of compound **8b** into mutant PLpro active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).

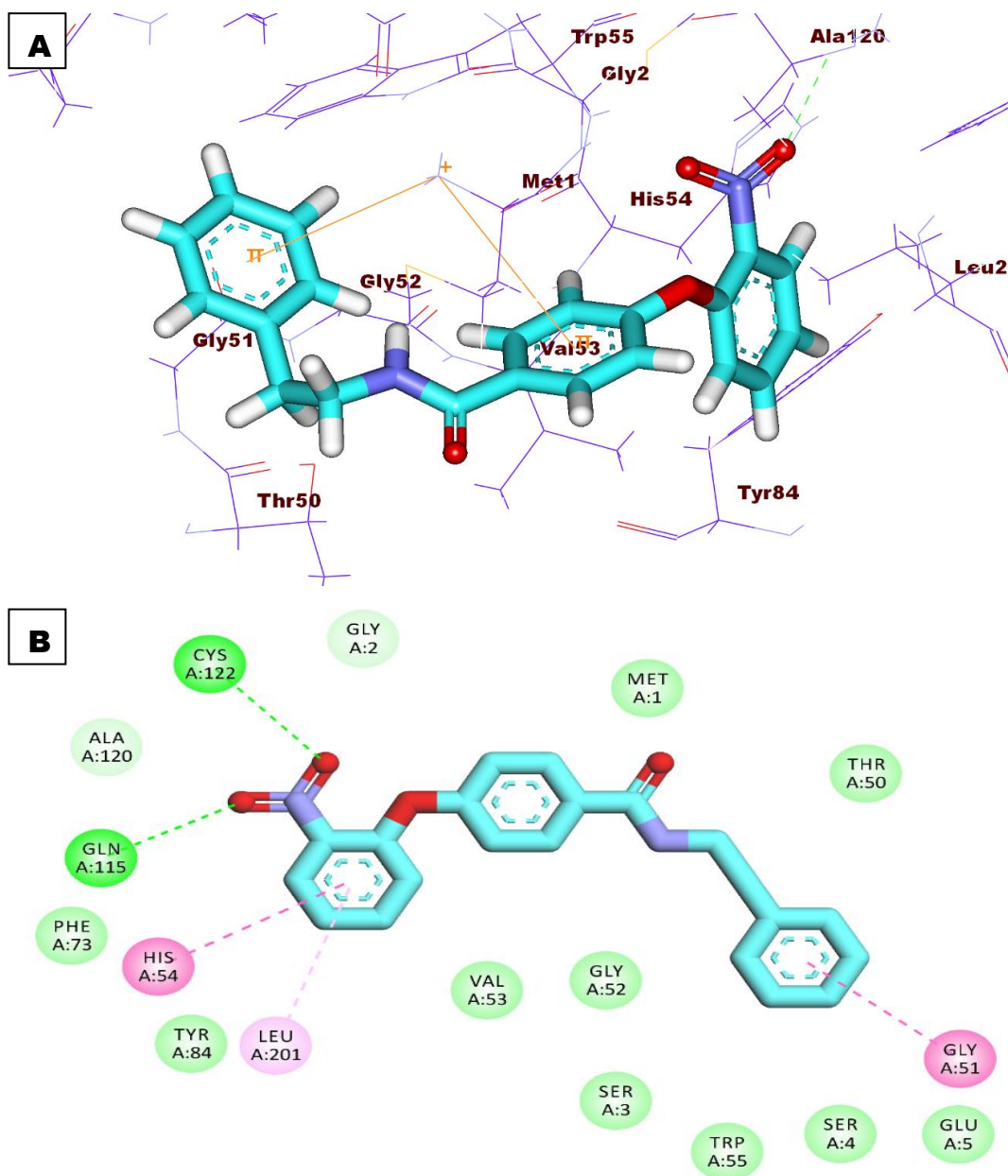


SI 5: A) 3D binding mode of compound **9_a** into mutant PLpro active site. B) 2D binding mode of compound **9_a** into mutant PLpro active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).

Docking against adenovirus



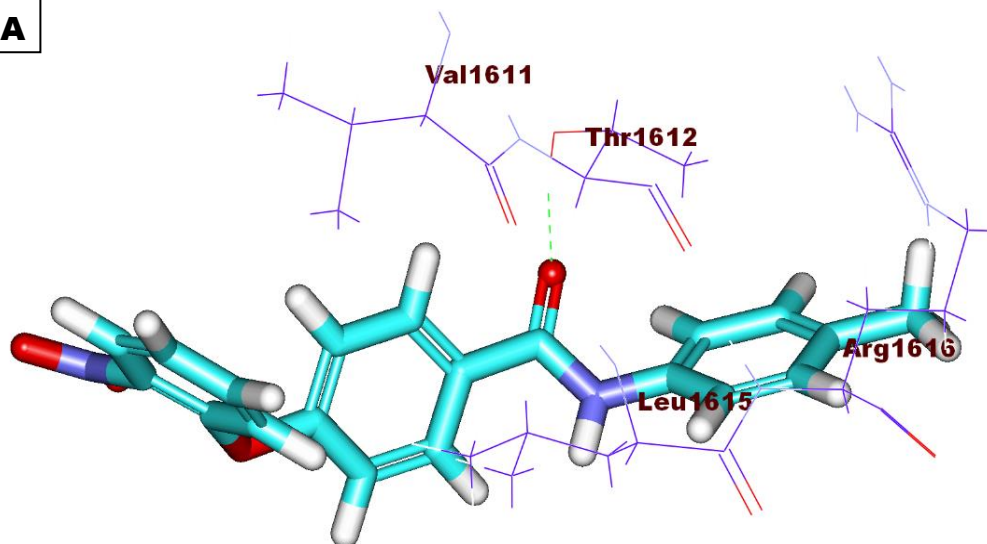
SI 6: A) 3D binding mode of compound **8c** into adenovirus active site. B) 2D binding mode of compound **8c** into adenovirus active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).



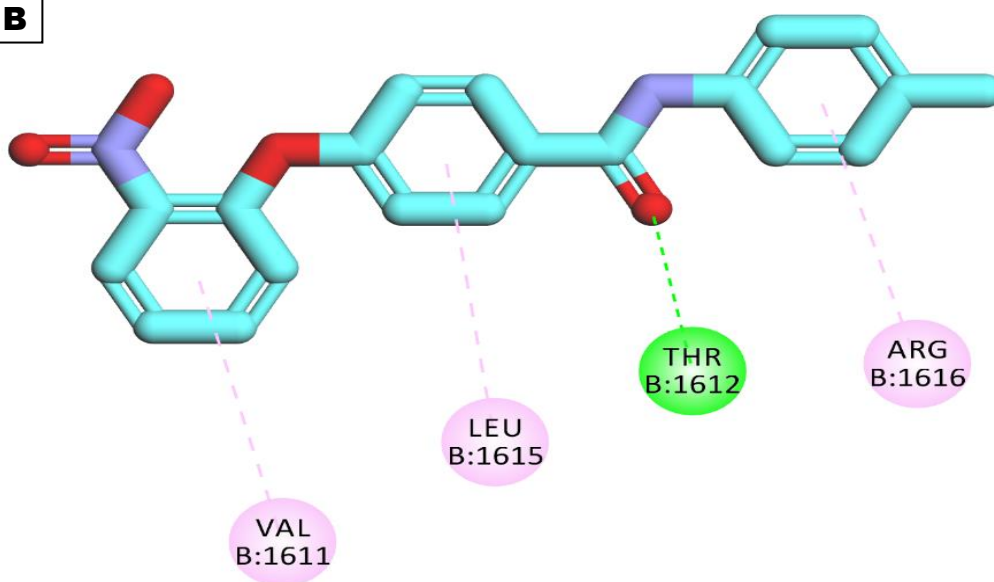
SI 7: A) 3D binding mode of compound **10b** into adenovirus active site. B) 2D binding mode of compound **10b** into adenovirus active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).

Docking against HSV-1

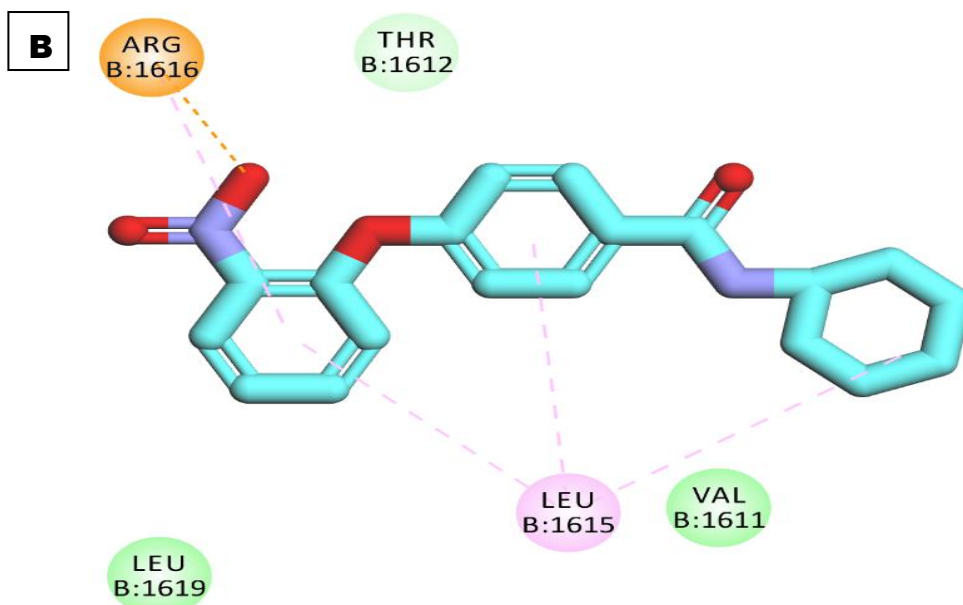
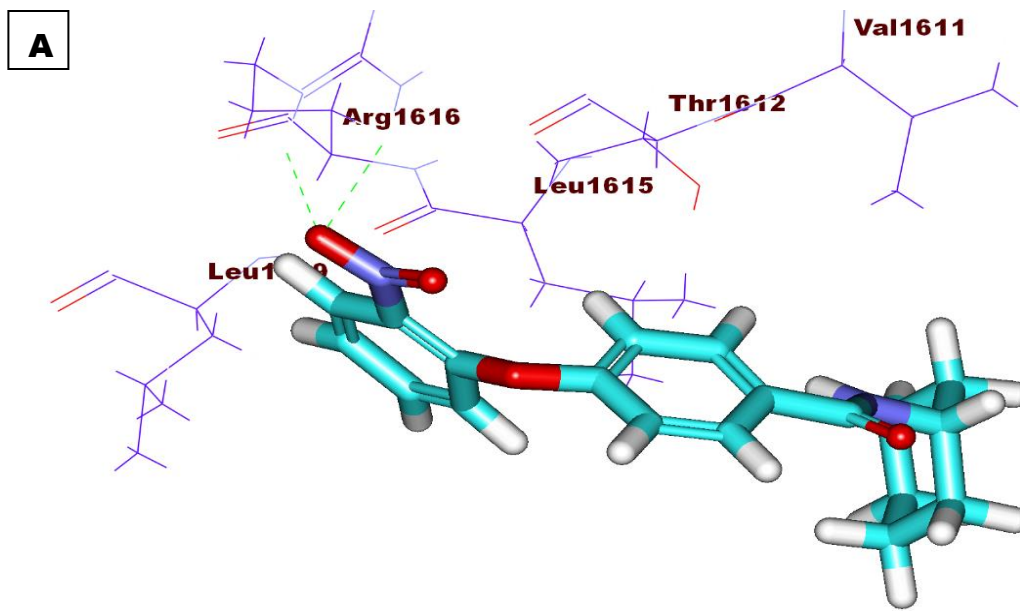
A



B

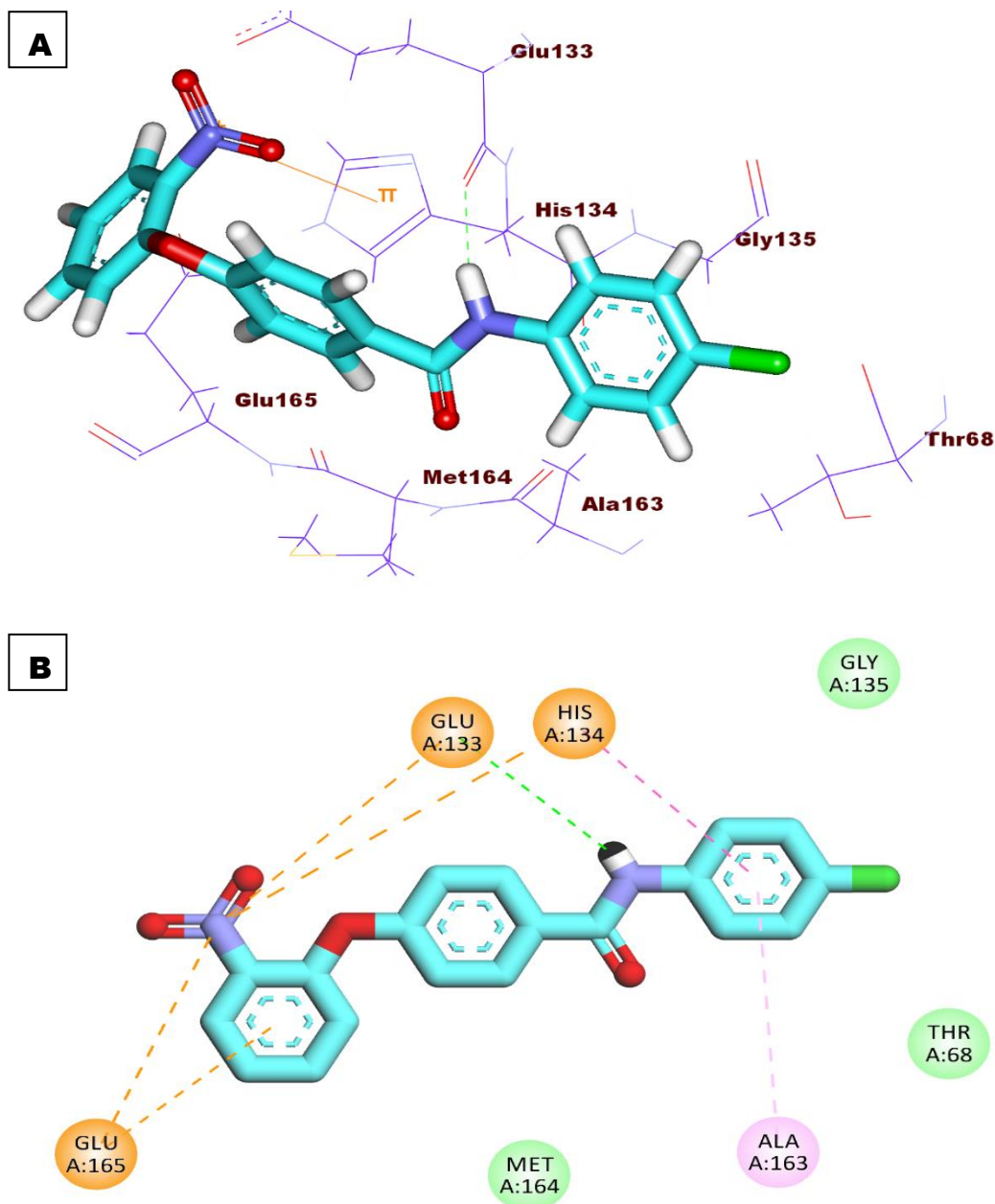


SI 8: A) 3D binding mode of compound **8a** into HSV-1 active site. B) 2D binding mode of compound **8a** into HSV-1 active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).

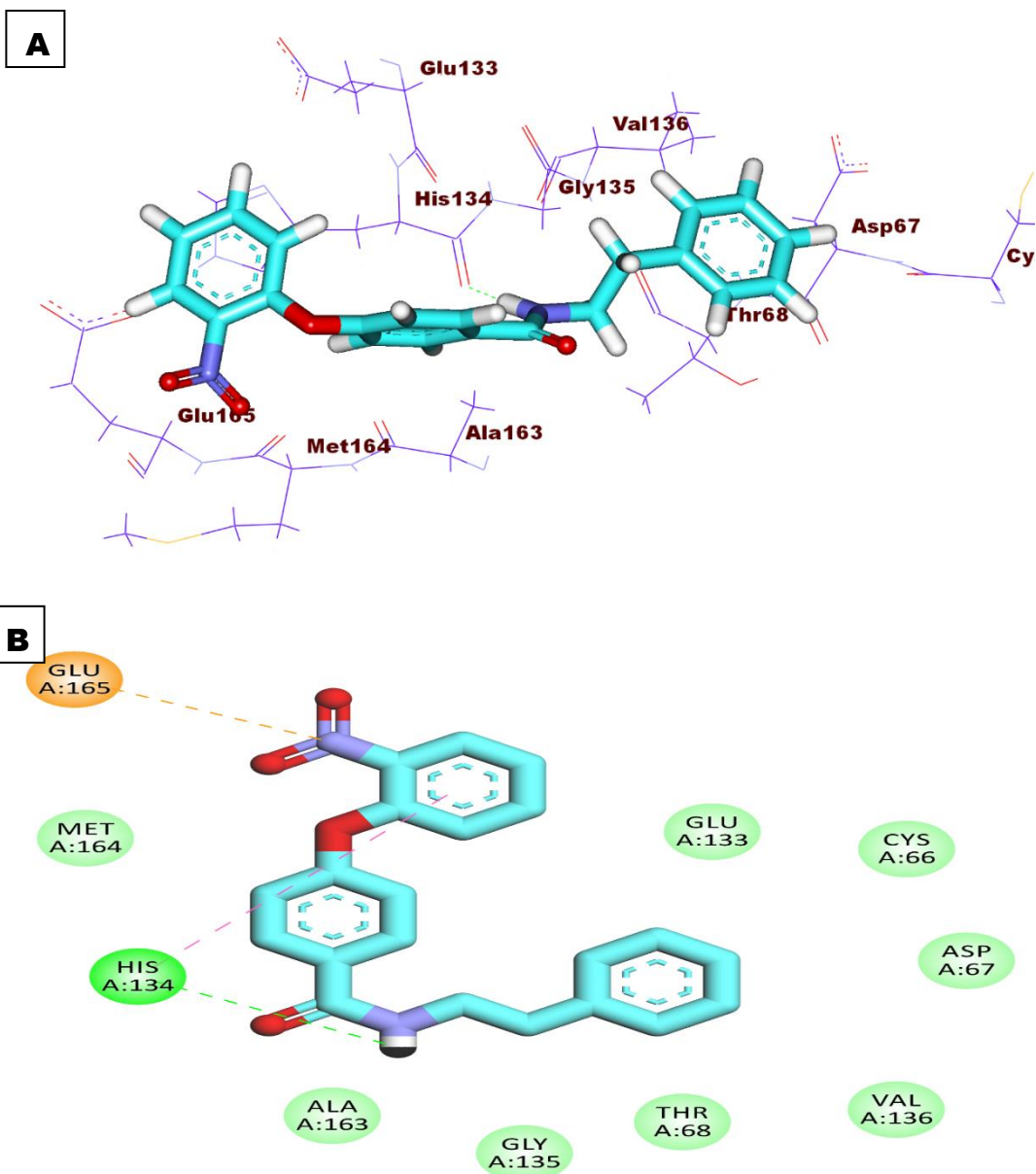


SI 9: A) 3D binding mode of compound **9a** into HSV-1 active site. B) 2D binding mode of compound **9a** into HSV-1 active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).

Docking against coxsackie virus



SI 10: A) 3D binding mode of compound **8c** into coxsackievirus active site. B) 2D binding mode of compound **8c** into coxsackievirus active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).



SI 11: A) 3D binding mode of compound **10a** into coxsacivirus active site. B) 2D binding mode of compound **10a** into coxsacivirus active site (hydrogen bonds = green dashed lines, electrostatic interactions = orange dashed lines, pi-pi interactions = deep pink dashed lines, and pi-alkyl interactions = light pink dashed lines).