Supplementary data

Novel wild type and mutate HIV-1 Protease inhibitors containing heteroaryl carboxamides in P2: synthesis, biological and ADME evaluations.

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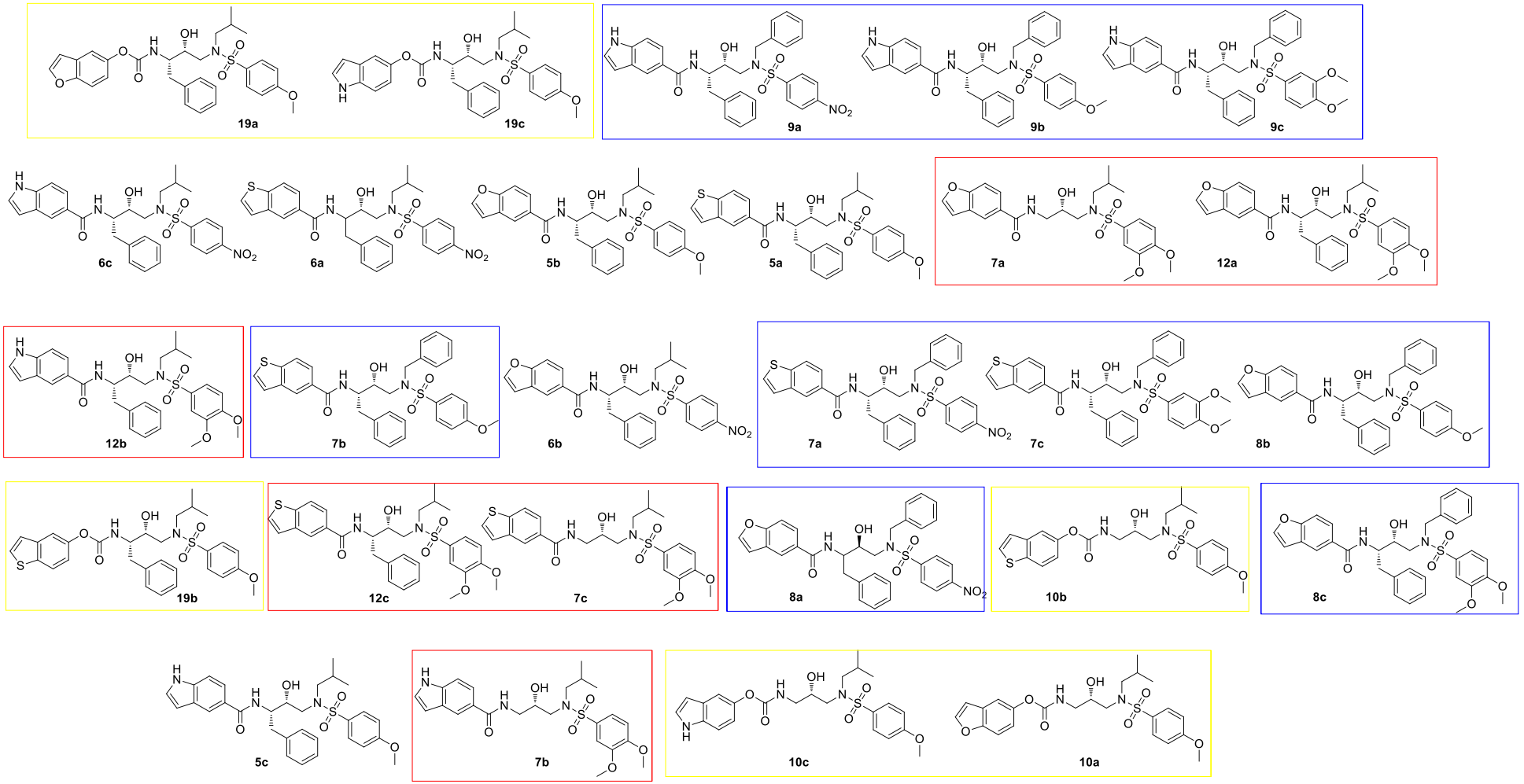
Table of contents:

Figure S1: Structures of the inhibitors used in the analysis of ADME properties



1. Compounds **10a-c** and **19a-c** in the yellow box were reported in *Bioorg. Med. Chem.* **2019**, *27*, 1863-1870.
2. Compounds **7a-c, 8a-c** and **9a-c** in the blu box were reported in *Biomolecules*, **2021**, *11*, 1584.
3. Compounds **7a-c** and **12a-c** in the red box were reported in *Bioorg. Med. Chem.* **2017**, *25*, 4715-4722.
4. Compounds **5a-c** and **6a-c** without colored box were described in this work.

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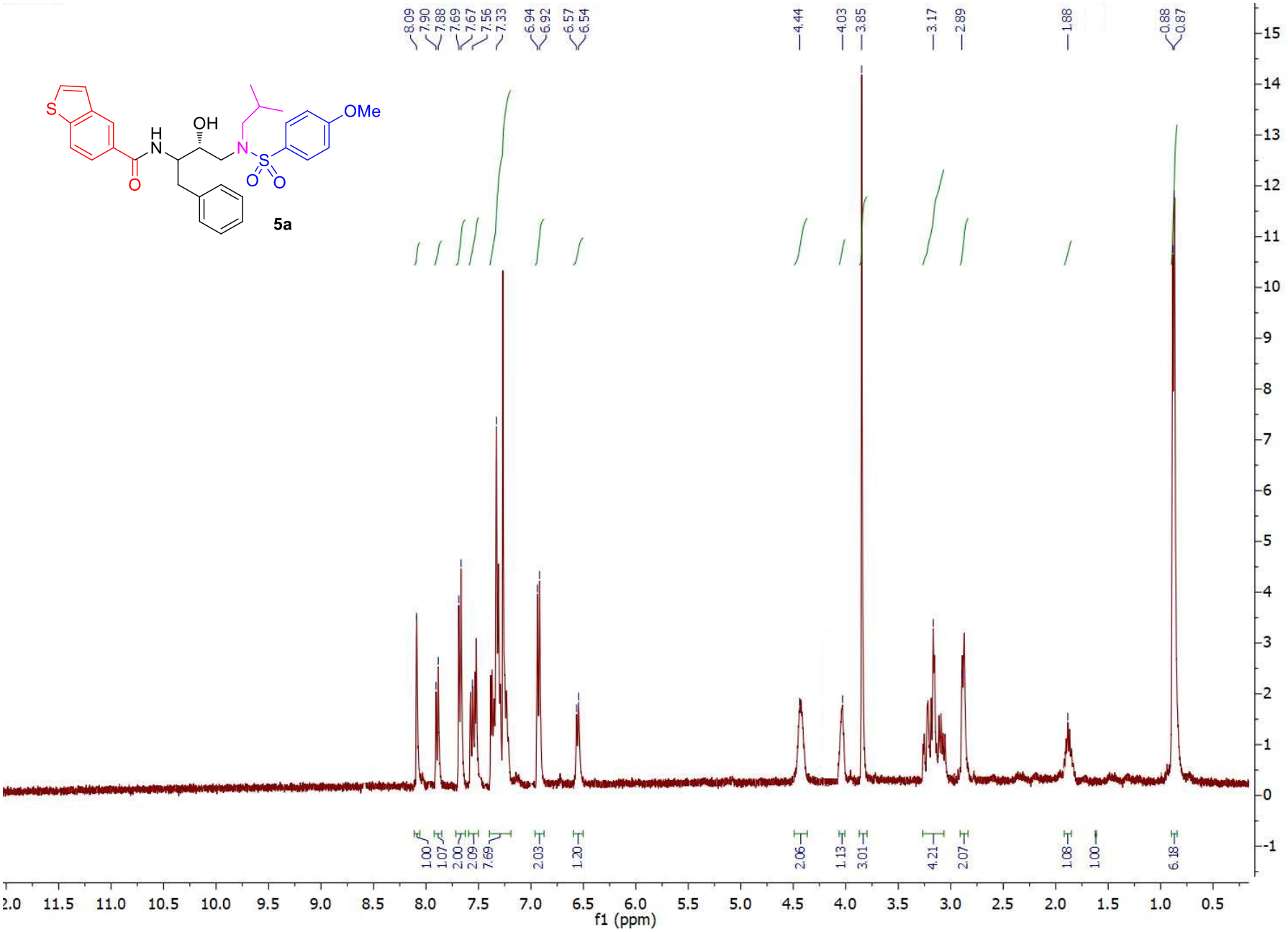
Comp.	IC_{50}	mol. Refract.	TPSA	logP	logS	logKp
19a [1]	6.00E-10	152.2	126.69	4.31	-7.88	-5.88
19c [1]	6.00E-10	154.29	129.34	4.14	-7.64	-6.07
9a [2]	6.00E-10	164.99	156.6	3.69	-7.93	-6.47
9b [2]	6.00E-10	162.66	120.11	3.85	-7.3	-6.28
9c [2]	6.00E-10	169.15	129.34	3.86	-7.47	-6.49
6c, [4]	6.00E-10	154.93	156.7	3.36	-7.75	-6.39
6a, [4]	6.00E-10	158.45	169.15	4.29	-8.95	-5.85
5b, [4]	6.00E-10	150.51	117.46	4.24	-7.36	-6
5a, [4]	6.00E-10	156.12	132.56	5.03	-8.32	-5.66
Average values for the better inhibitors		158.14	137.55	4.08	-7.84	-6.12
7a [3]	1.00E-09	127.71	126.69	2.77	-6.66	-7.09
12a [3]	1.10E-09	157	126.69	4.34	-7.52	-6.21
12b [3]	2.00E-09	159.09	129.34	4.19	-7.3	-6.39
7b [2]	2.30E-09	166.19	132.56	5.12	-8.49	-5.75
6b, [4]	4.00E-09	152.84	154.05	3.67	-7.99	-6.19
7a [2]	4.20E-09	168.52	169.15	4.4	-9.11	-5.94
7c [2]	6.20E-09	172.68	141.79	5.16	-8.65	-5.96
8b [2]	9.60E-09	160.58	117.46	4.52	-7.54	-6.09
19b [1]	1.08E-08	157.82	141.79	4.86	-8.83	-5.54
12c [3]	1.30E-08	162.61	141.79	4.97	-8.49	-5.86
7c [3]	1.50E-08	133.32	141.79	3.41	-6.39	-6.75
8a [2]	4.70E-08	162.91	154.05	3.81	-8.15	-6.29
10b[1]	4.90E-08	125	129.34	2.64	-5.55	-6.96
8c [2]	8.20E-08	167.07	126.69	4.15	-7.7	-6.29
5c, [4]	9.50E-08	152.6	120.11	4.23	-7.14	-6.19
7b [3]	4.00E-06	129.79	129.34	2.65	-5.2	-5.28
10c [1]	1.34E-05	125	129.34	2.64	-5.55	-6.96
10a [1]	1.54E-05	122.91	126.69	2.84	-5.77	-6.77

Table S1: Collection of molecular descriptors for the set of inhibitors. The value of IC_{50} for the better inhibitors (green set) has been arbitrarily set to 0.6 nM, and an average value of the descriptors has been used.

Compound	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations
Darunavir	1	3	2	1	0
19a [1]	1	4	1	1	1
19c [1]	1	3	1	0	0
9a [2]	1	3	2	1	1
9b [2]	1	4	1	0	1
9c [2]	1	4	1	0	2
6c, [4]	1	3	2	1	1
6a, [4]	1	4	2	2	2
5b, [4]	1	3	1	0	1
5a, [4]	1	4	1	2	1
7a [3]	0	1	1	0	0
12a [3]	1	3	1	0	1
12b [3]	1	3	1	0	0
7b [2]	1	4	1	2	2
6b, [4]	1	3	2	1	2
7a [2]	1	4	2	2	3
7c [2]	1	4	2	2	2
8b [2]	1	4	1	1	1
19b [1]	1	4	2	2	1
12c [3]	1	4	2	2	1
7c [3]	1	2	2	1	0
8a [2]	1	4	2	1	2
10b[1]	0	0	1	0	0
8c [2]	1	4	1	1	2
5c, [4]	1	3	1	0	0
7b [3]	0	1	1	0	0
10c [1]	0	0	1	0	0
10a [1]	0	0	1	0	0

Table S2: ADME predictions. Green background: equal or better than darunavir; red background: worse than darunavir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7.69
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7.33
6.94
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6.57
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4.03
3.85
3.17
2.89
1.88
0.88
0.87
OMe
OH
H
N
S
O
5a
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1.07
2.00
2.09
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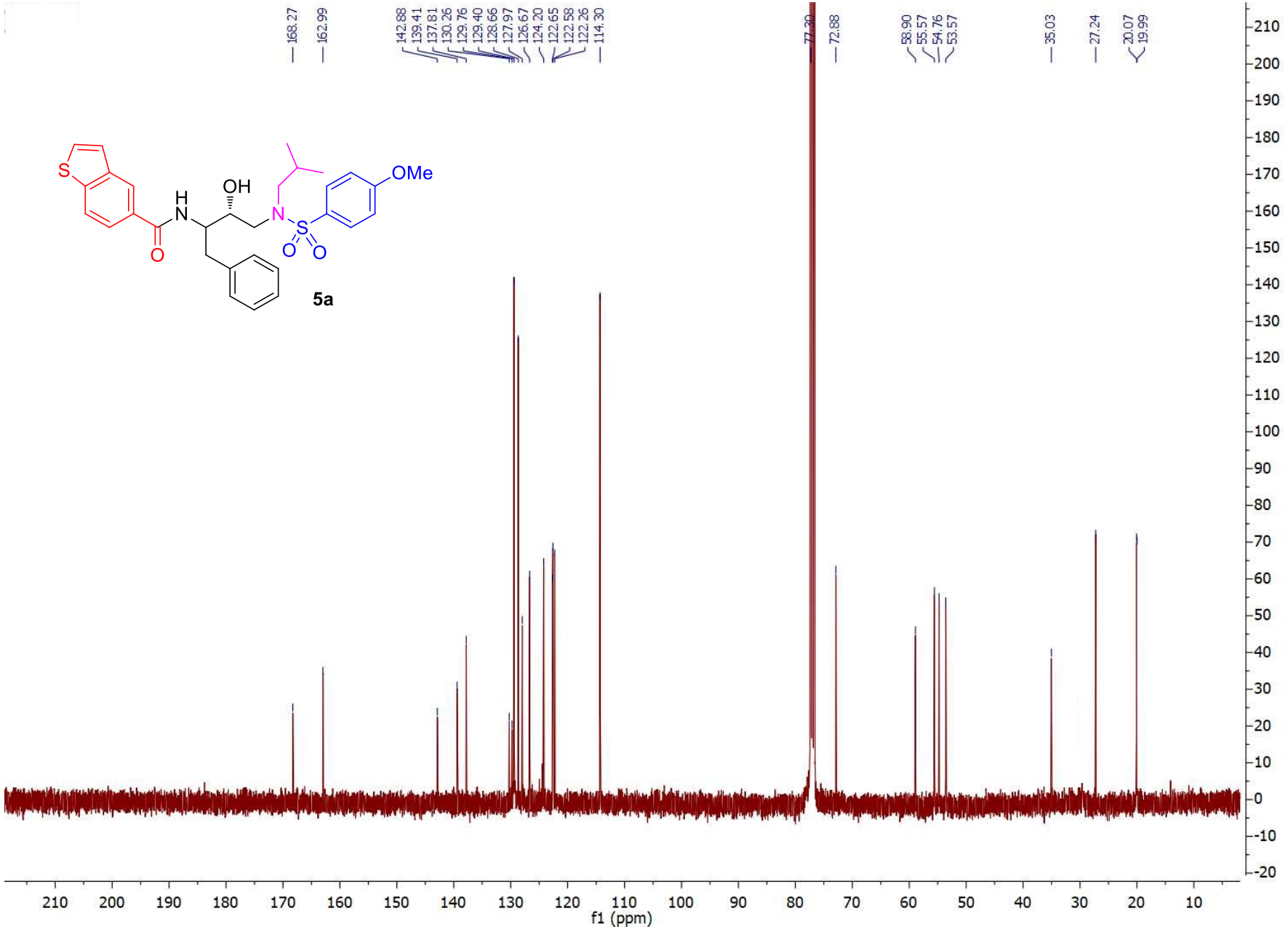
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122.58
122.26
114.30
77.30
72.88
58.90
55.57
54.76
53.57
35.03
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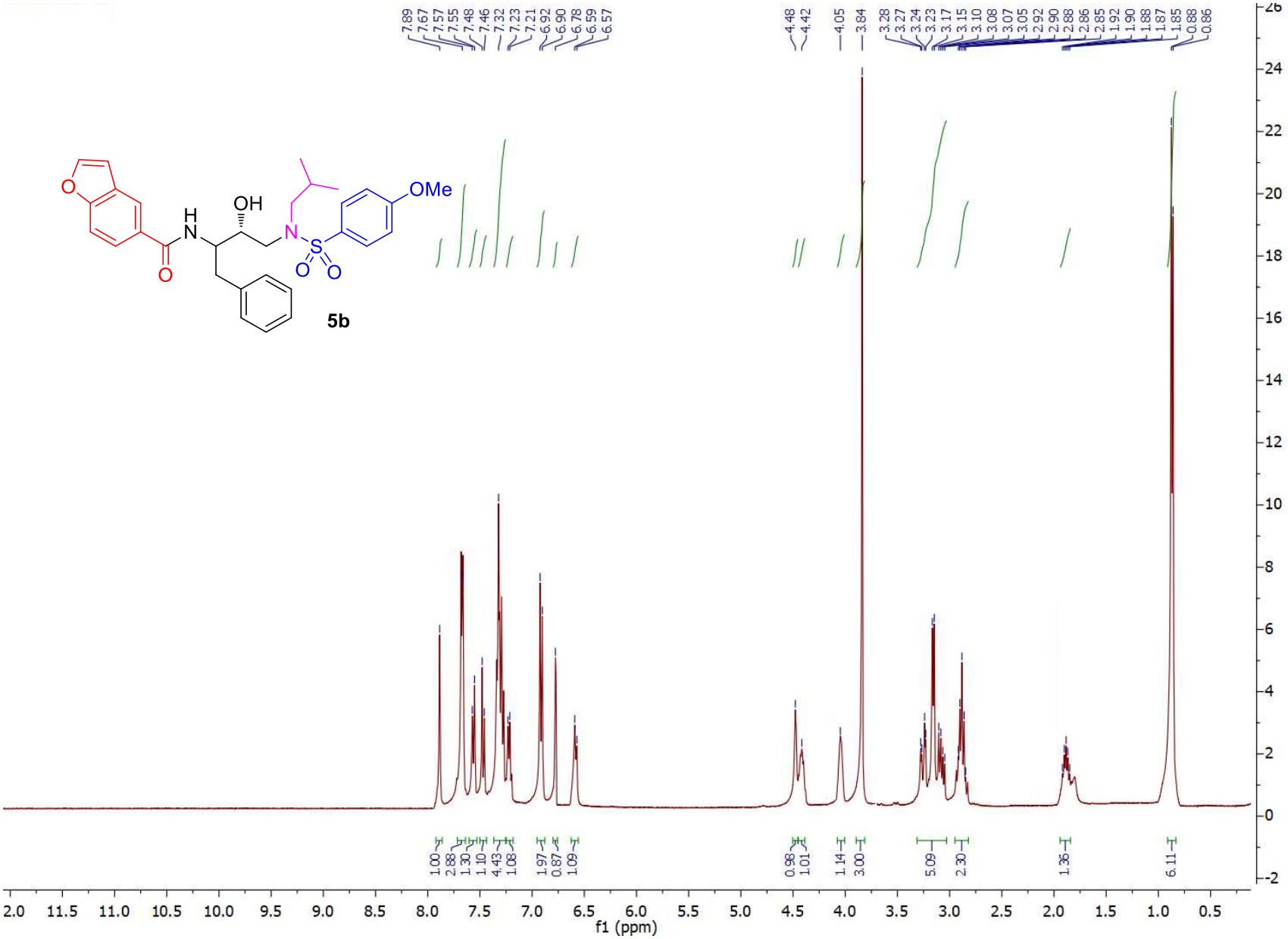
20.07
19.99
S
H
N
OH
N
S
O
O
O
OMe
5a
f1 (ppm)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4.05
3.84
3.28
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3.24
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3.10
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2.90
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2.85
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1.87
1.85
0.88
0.86
OMe
OH
H
N
O
S
O
O
O
5b
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1.10
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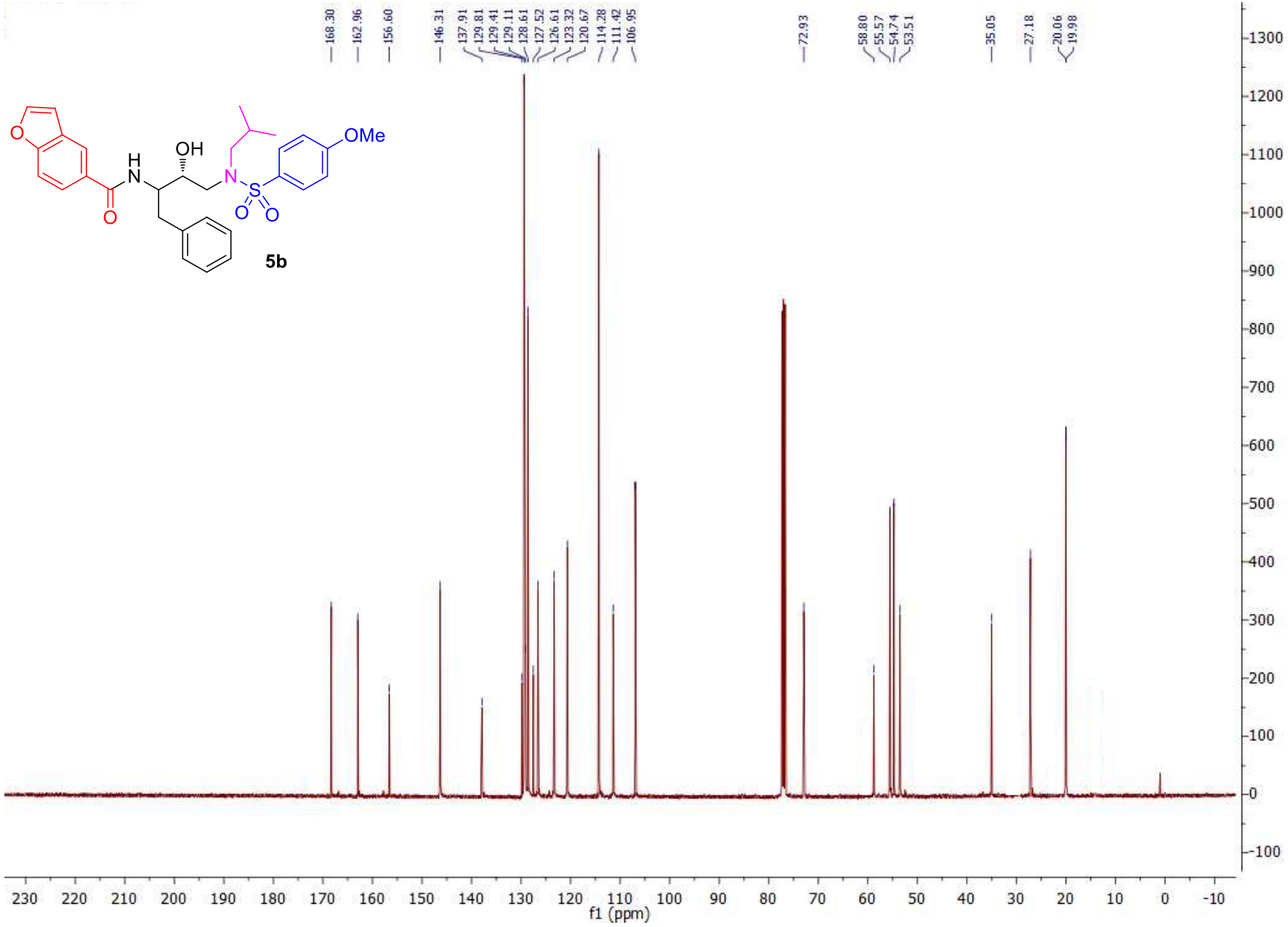
f1 (ppm)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114.28
111.42
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72.93
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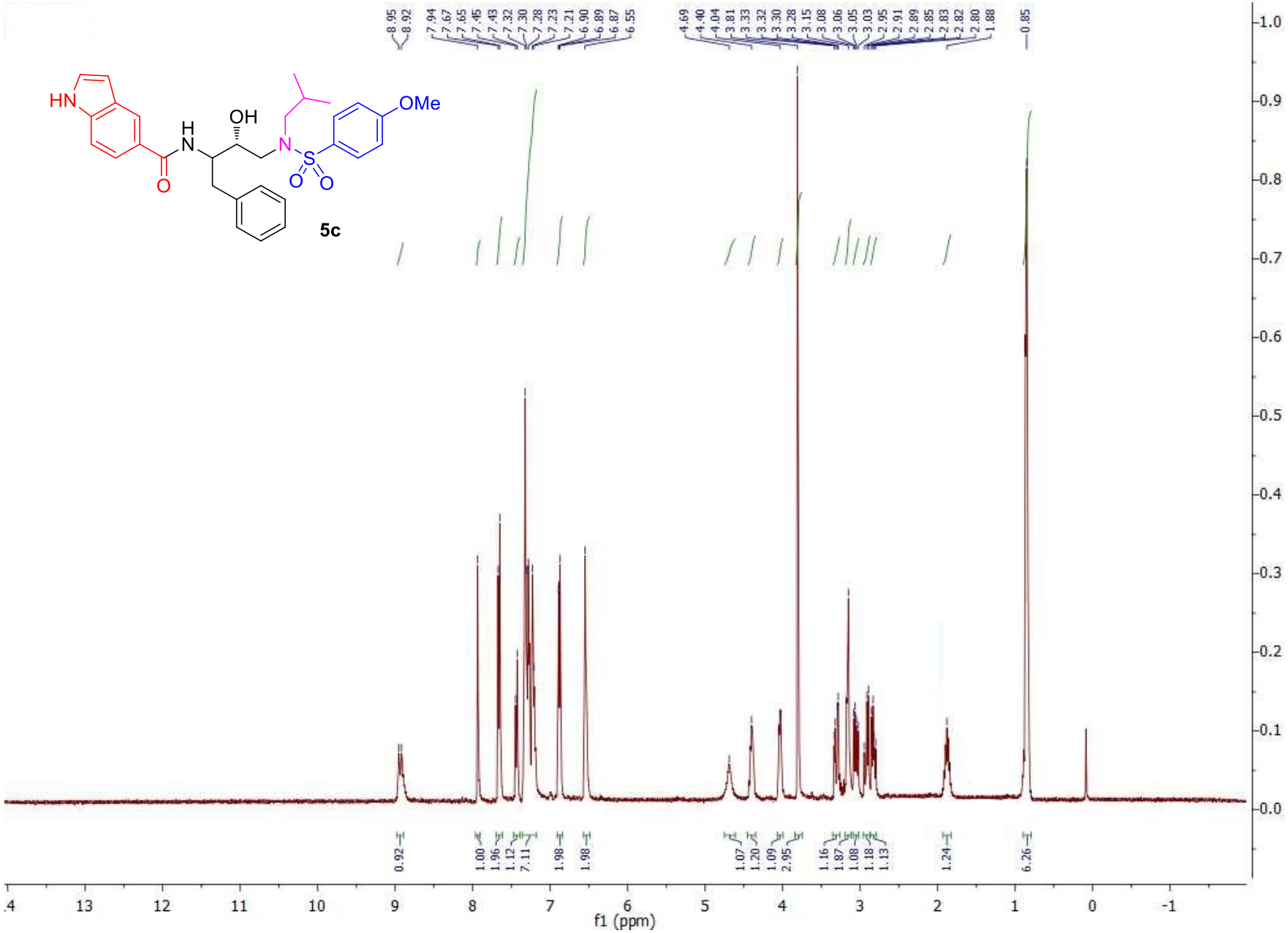
S
5b
f1 (ppm)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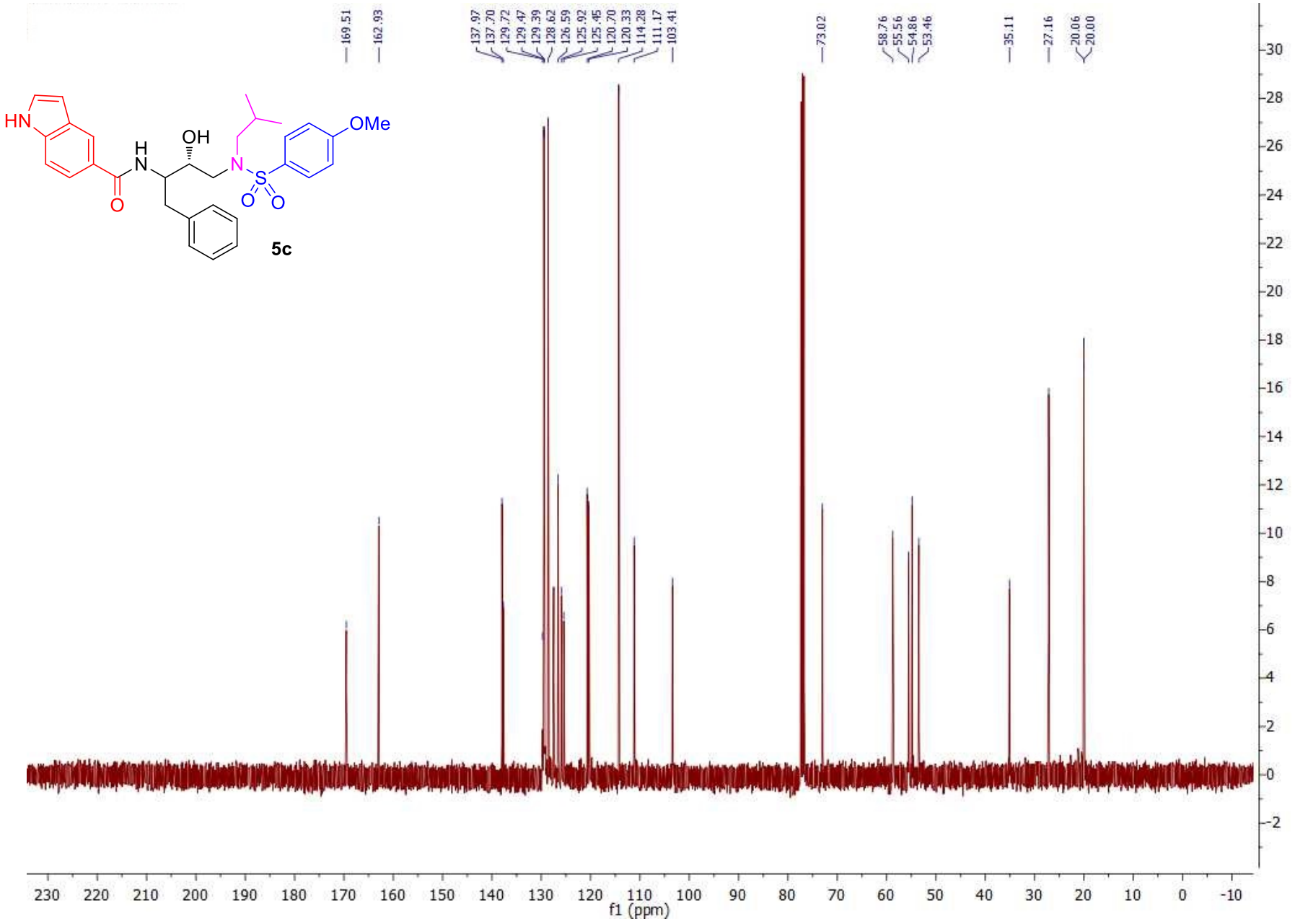
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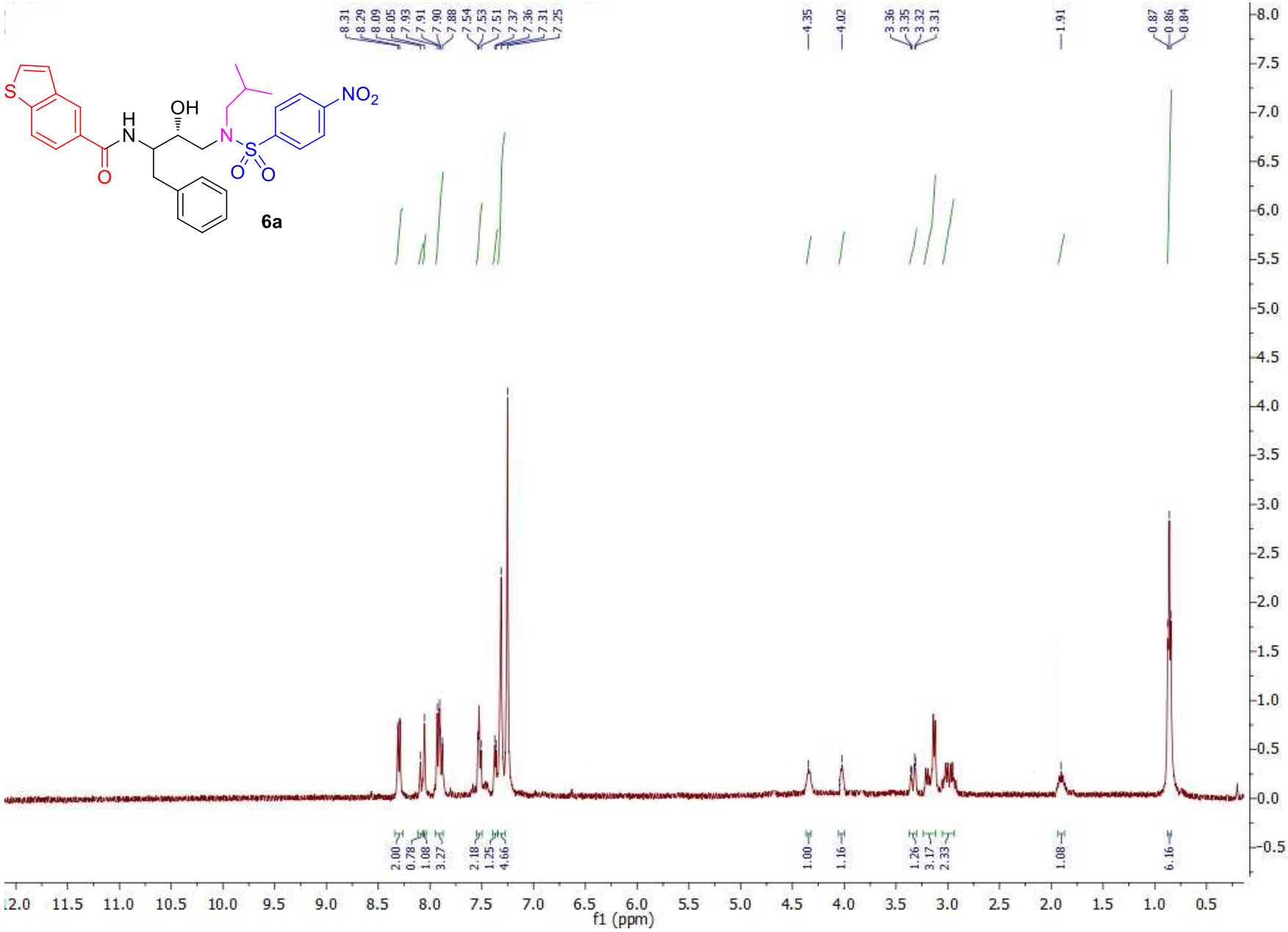
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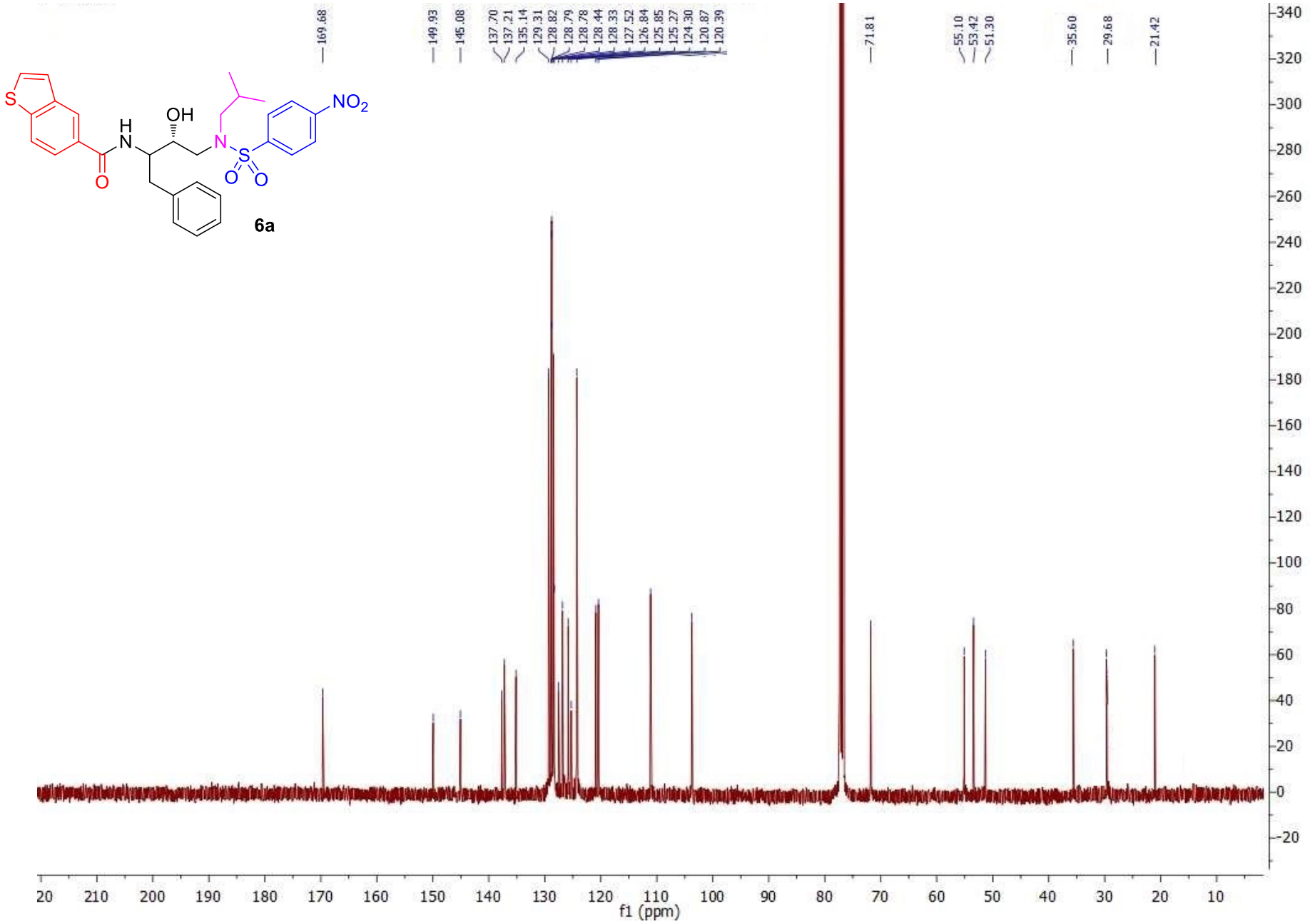
f1 (ppm)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125.85
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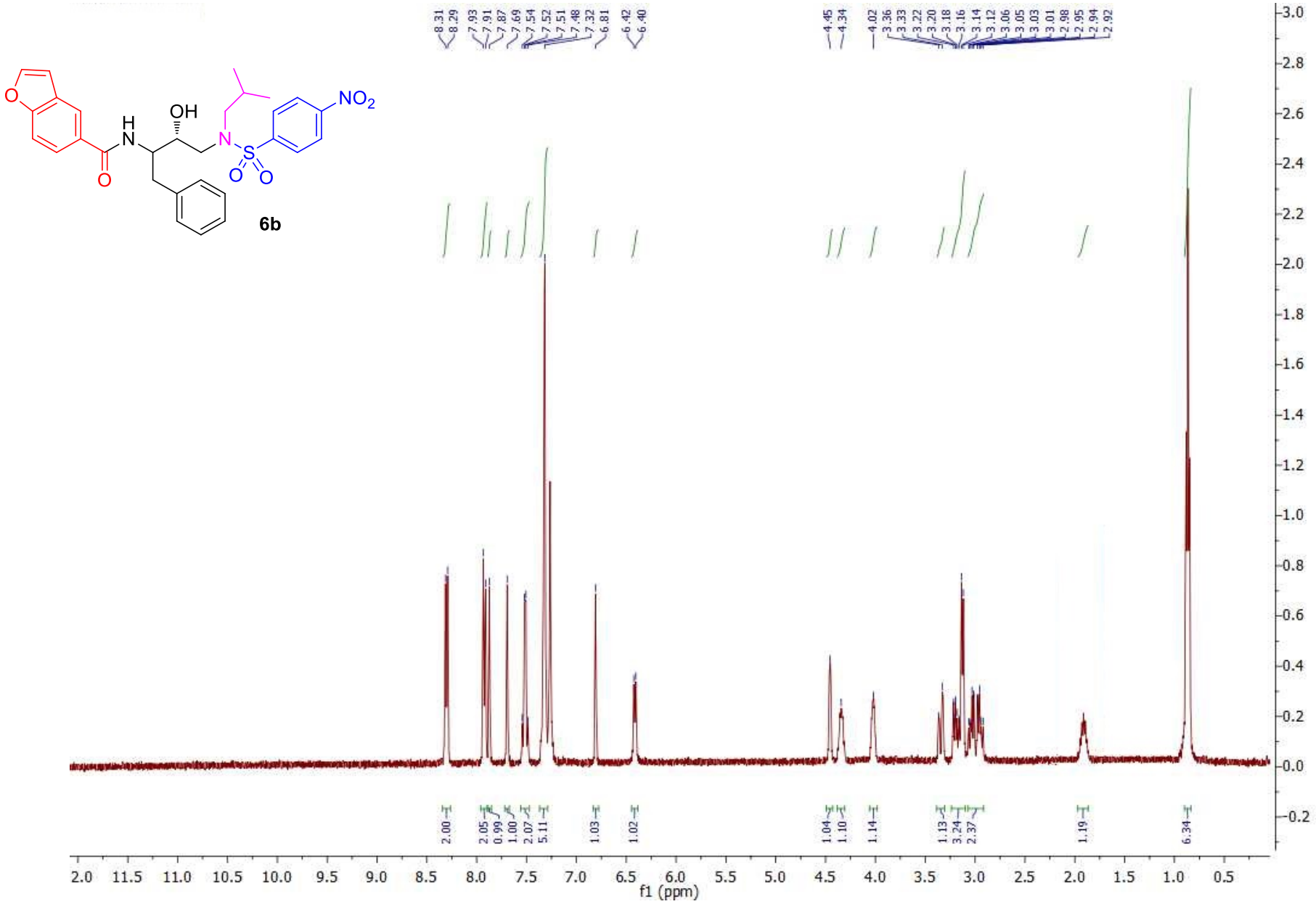
f1 (ppm)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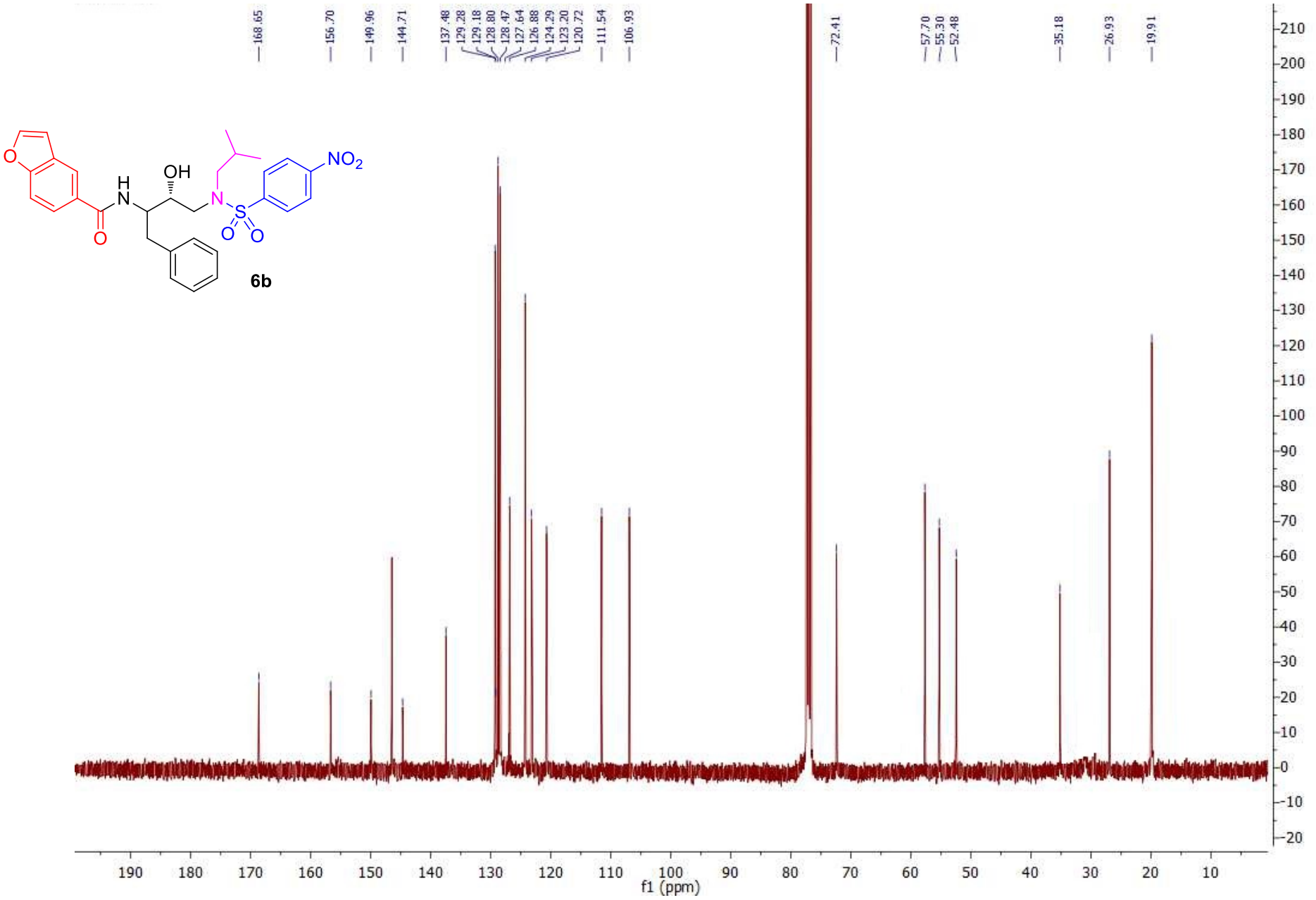
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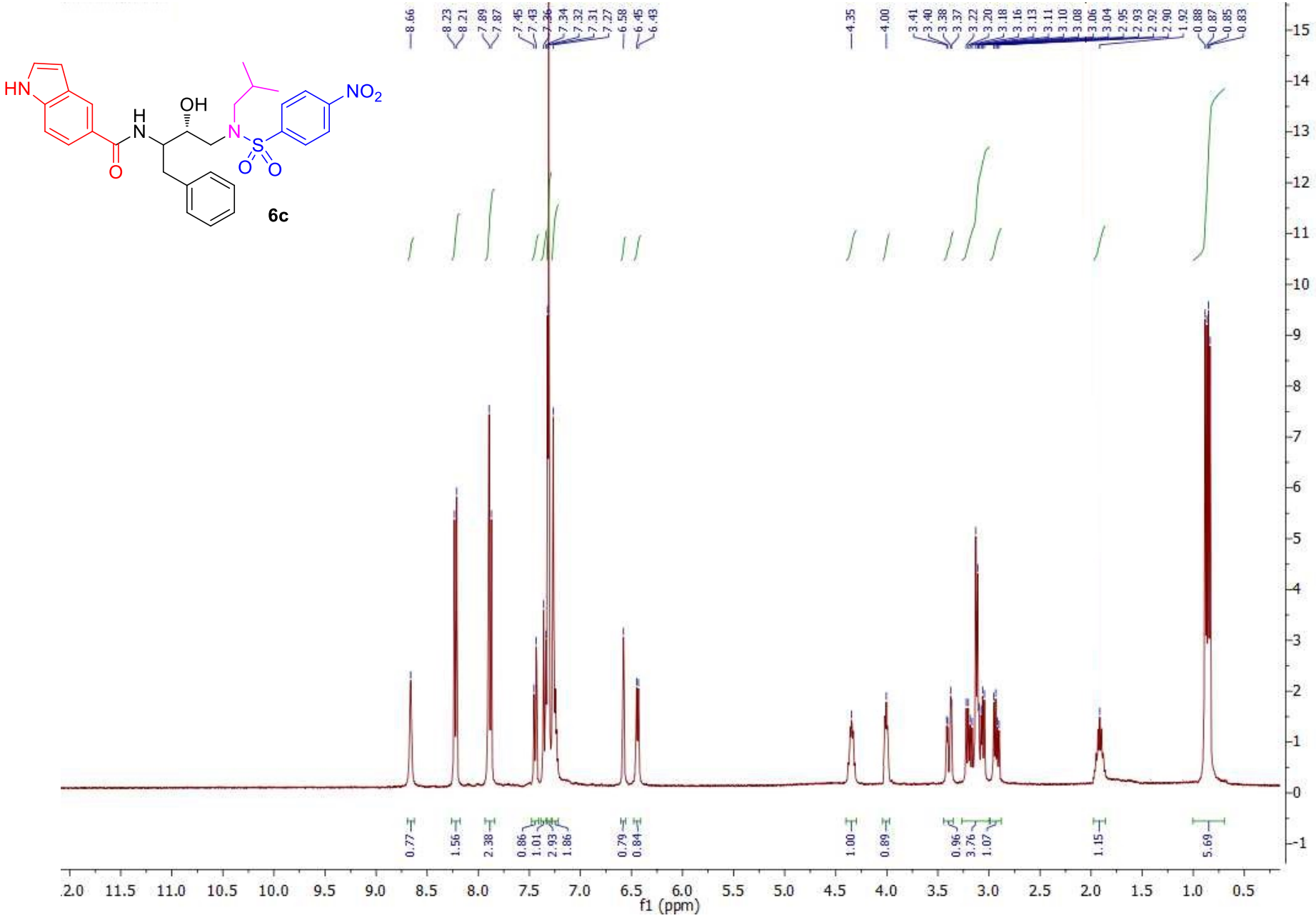
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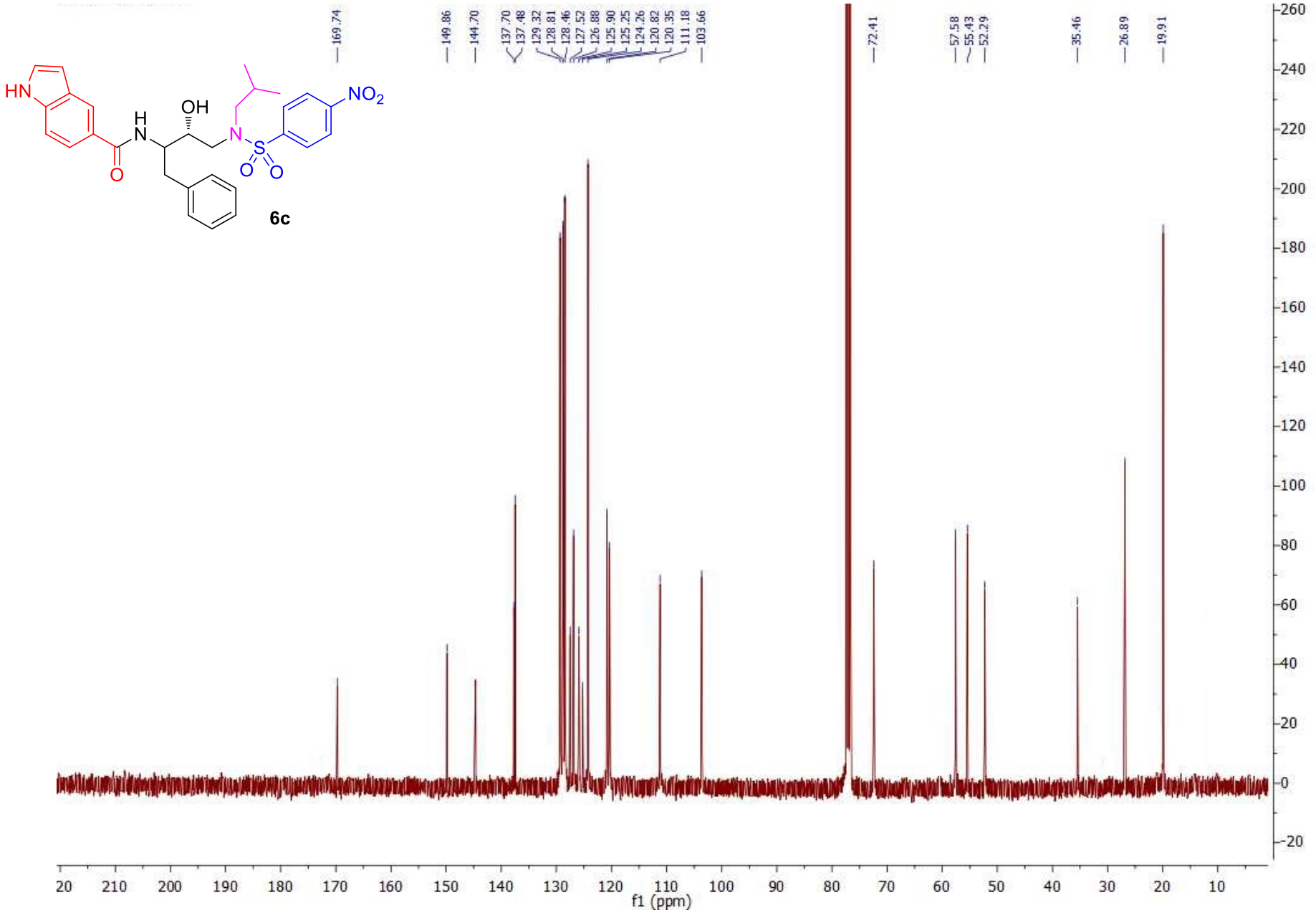
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