Supporting information

Synthesis of Boscalid via a Three-step Telescoped Continuous Flow Process Implemented on a MJOD Reactor Platform

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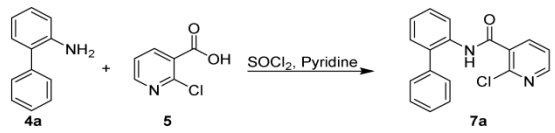
Optimization of the reaction step ③ - the amidation reaction.

Dichloromethane was used as reaction medium during the initial discovery of the reaction path. This solvent was unsuitable for our application due to the environmental profile of the solvent. Another factor is that chlorinated solvents can cause swelling of some of the polymer components in the MJOD continuous flow milli-scale plant. We performed a series of screening design experiments in order to identify an alternative to dichloromethane and appropriate reaction conditions with 2-amino-1,1´-biphenyl **4a** as starting material (Table 1). However, when the method was performed in our continuous flow reactor the yield varied. In order to improve the robustness of the method further design experiments was conducted that investigating the importance of the ratio between thionyl chloride and pyridine (Table 2). The resulting models (Table 2) were used to calculate the response surface for the different reaction products $\hat{y}_1$ unconverted staring material **4a**, $\hat{y}_2$ iminosulfanone **8a**, $\hat{y}_3$ unidentified side-product, and $\hat{y}_4$ compound **7a**. The three response surface maps were then combined into a single *iso*-contour projection describing the variable space (Figure 1). The response surface was then used to calibrate the experimental settings for the continuous flow reaction.

Table 1: Screening design



4a 5 7a

Variable	-1	+1
x_1 :Temp (°C)	35	70
x_2 :Time (min)	30	60
x_3 :Solvent	EtOAc	CH_3CN

#	x_1	x_2	x_3	Response Yield (%)
1	-1	-1	1	0
2	1	-1	-1	99
3	-1	1	-1	6
4	1	1	1	13

$$\hat{y} = 29.5 + 26.5x_1 - 20x_2 - 23x_3$$

Figure 1: Iso-contour projection of the variable space

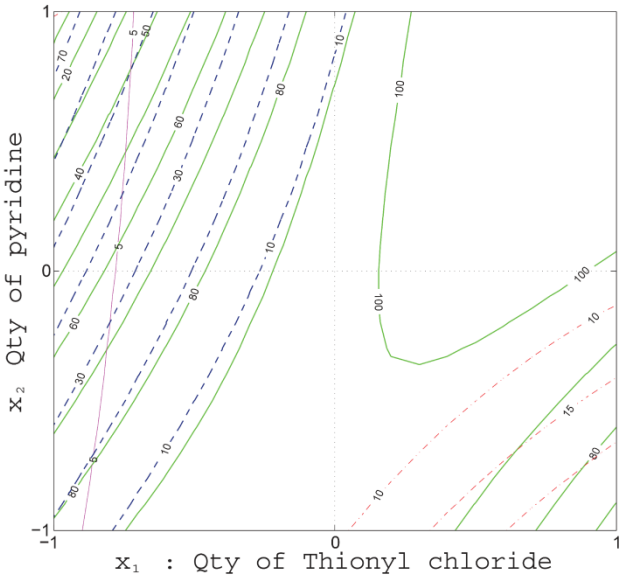
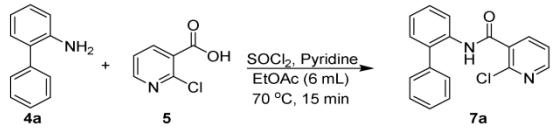


Table 2: Experimental design.



4a 5 7a

x_k	Experimental variables	Experimental levels -1.5	-1	0	+1	+1.5
x_1	Quantity of $SOCl_2$ (µl)	37.5	50	75	100	115.5
x_1	Quantity of Pyridine (µl)	52	70	105	140	152.5

#[b]	Experimental variables x_1	x_2	Responses[a] y_1[c] (%)	y_2[d] (%)	y_3[e] (%)	y_4[f] (%)
1	-1	-1	4.4	6.5	2.5	86.7
2	+1	-1	0	0	46.8	53.2
3	-1	+1	7.0	88.7	2.9	1.4
4	+1	+1	0	1.0	0	99.0
5	0	0	1.2	3.6	0	95.2
6	0	0	1.0	0	0	99.0
7	0	0	0	0	2.2	97.8
8	0	0	0	1.7	0	98.3
9	-1.5	0	13.2	86.6	0	0
10	+1.5	0	0	0	0	100
11	0	-1.5	0.6	2.7	0.6	96.1
12	0	+1.5	0	0.4	10.1	89.4

[a] Results from GC–MS of crude reaction mixture. [b] Experiments are given in standard order. [c] unconverted starting material. [d] N-sulfinyl intermediate. [e] unidentified sideproduct. [f] target product.

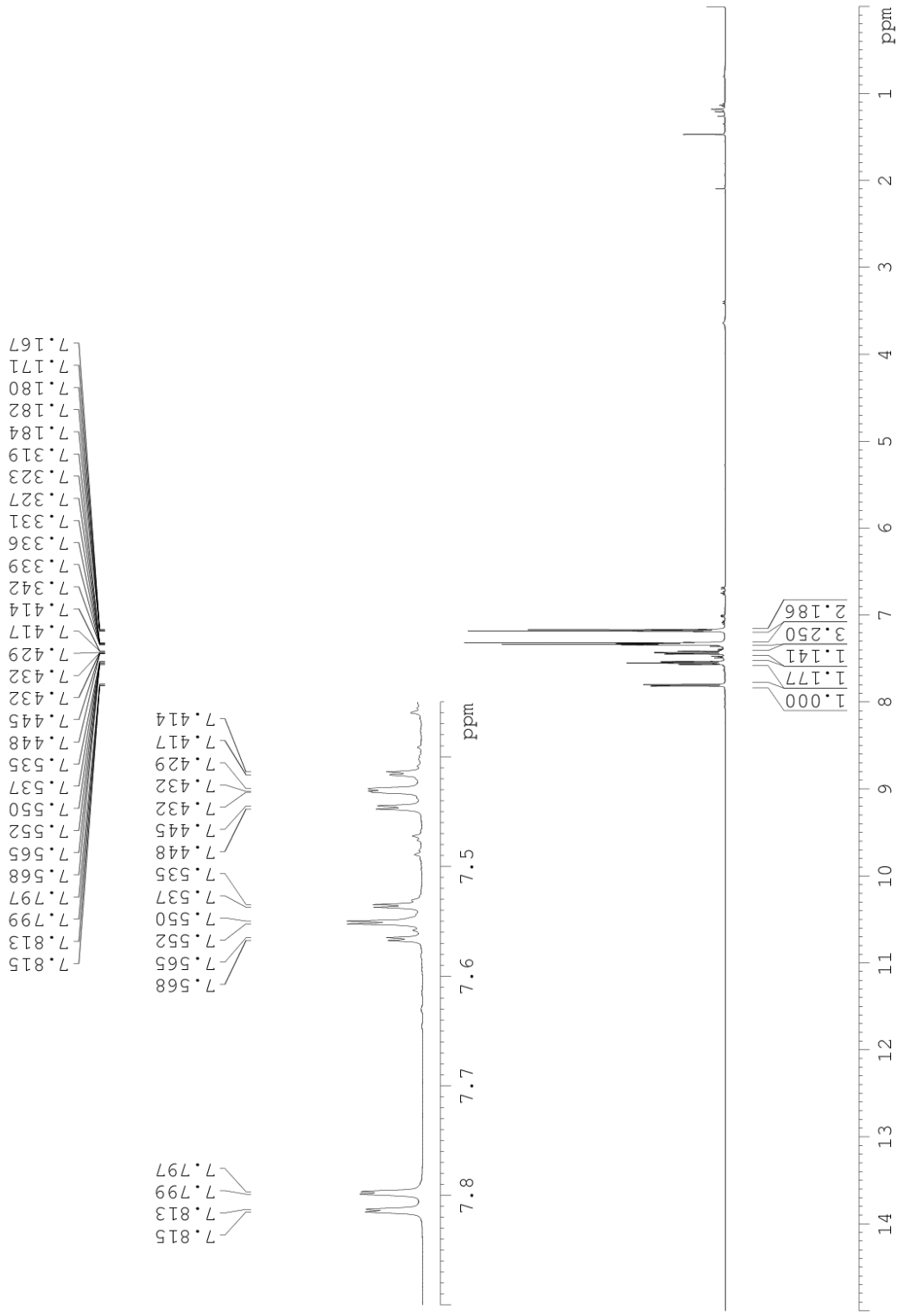
$$\hat{y}_1 = 0.65 - 3.75x_1 + 0.2x_2 - 0.65x_1x_2 + 2.57{x_1}^2 - 0.34{x_2}^2$$

$$\hat{y}_2 = 2.76 - 26.53x_1 + 9.38x_2 - 20.30x_1x_2 + 19.06{x_1}^2 - 0.57{x_2}^2$$

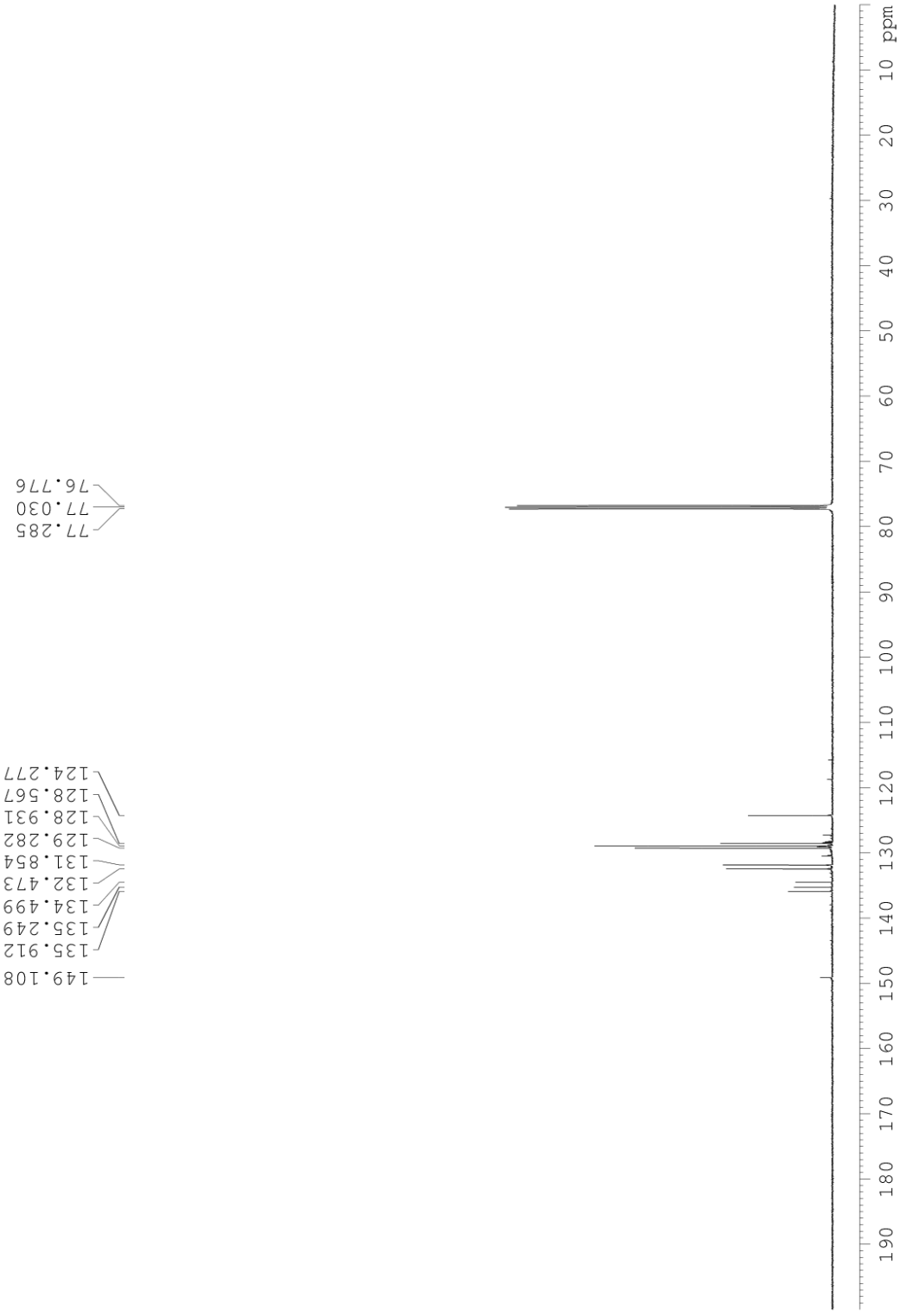
$$\hat{y}_3 = 4.27 + 5.06x_1 - 3.78x_2 - 11.80x_1x_2 + 1.01{x_1}^2 + 0.81{x_2}^2$$

$$\hat{y}_4 = 92.32 - 25.21x_1 - 5.83x_2 + 32.78x_1x_2 - 22.63{x_1}^2 + 0.09{x_2}^2$$

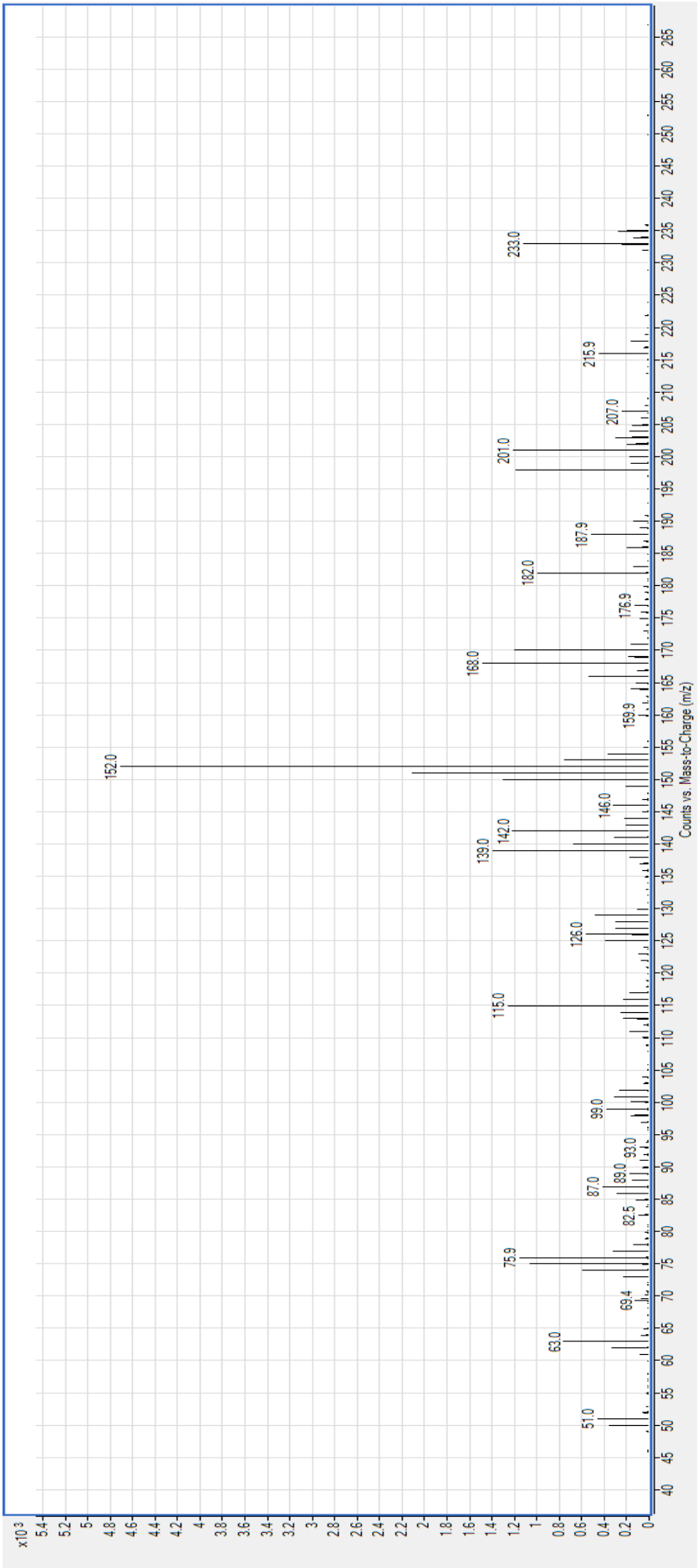
^{1}H-NMR of 4’-chloro-2-nitro-1,1'-biphenyl (3) in $CDCl_3$



^{13}C-NMR of 4’-chloro-2-nitro-1,1'-biphenyl (3) in $CDCl_3$



HR-MS (EI) of 4’-chloro-2-nitro-1,1'-biphenyl (3)



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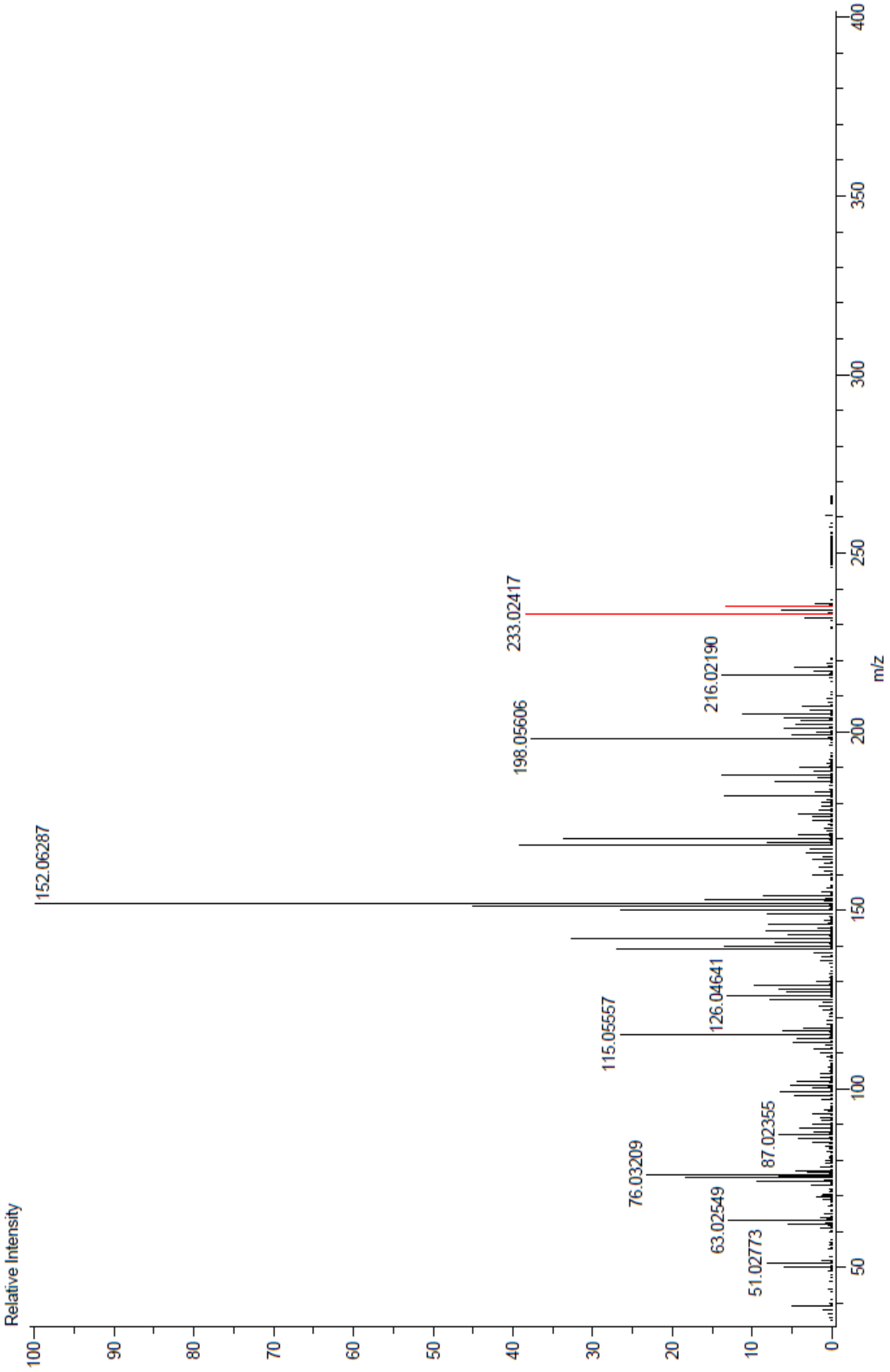
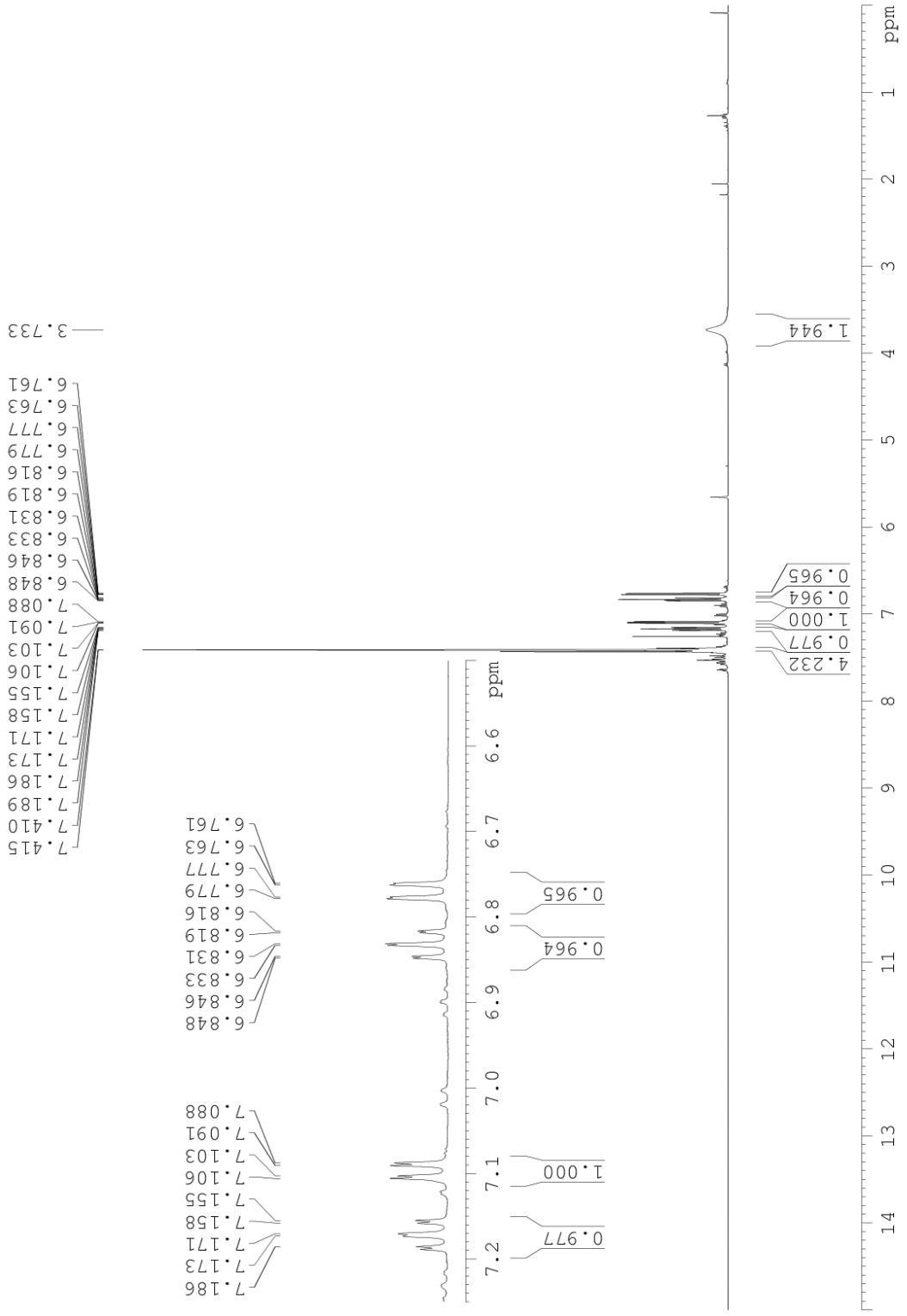
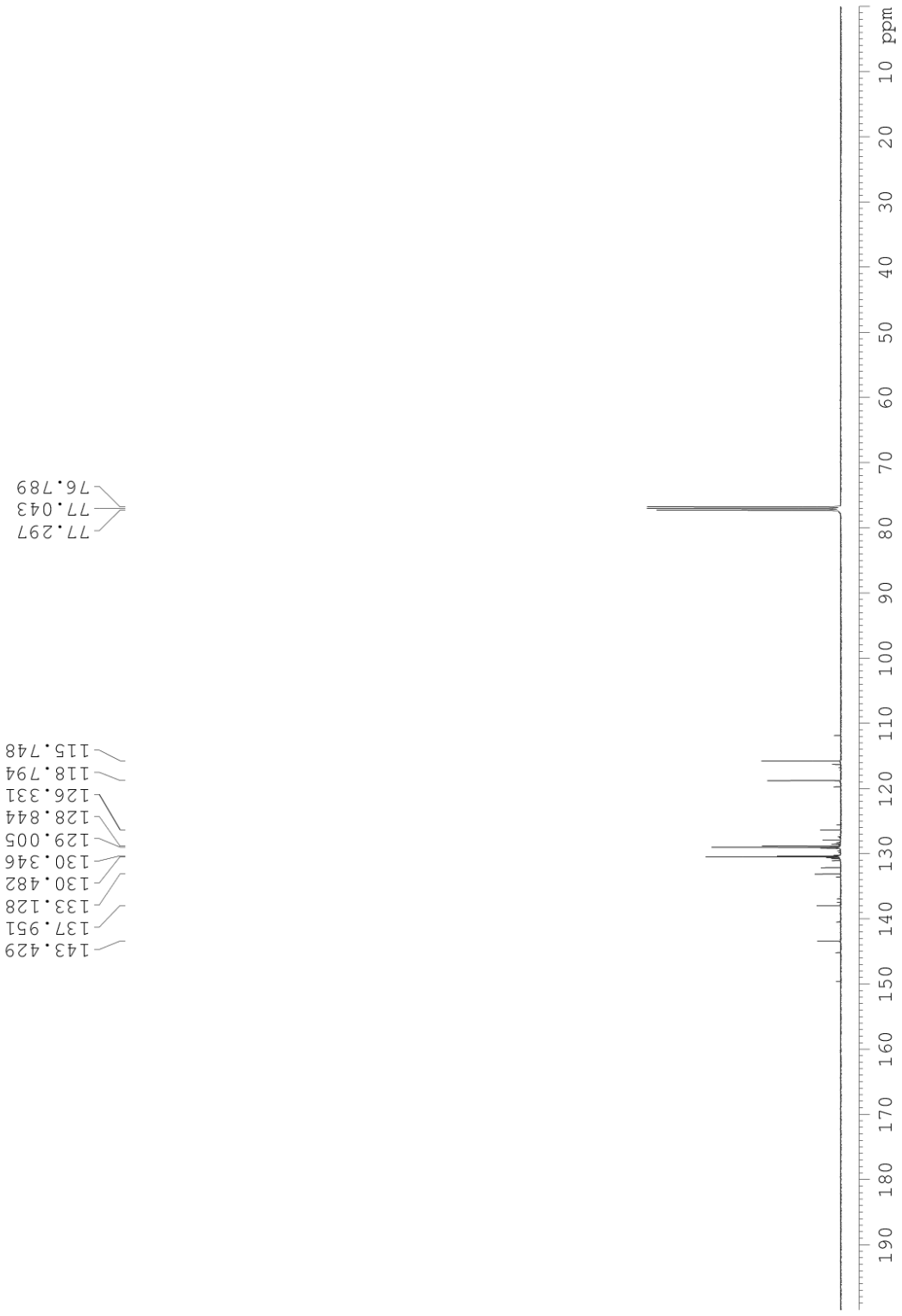


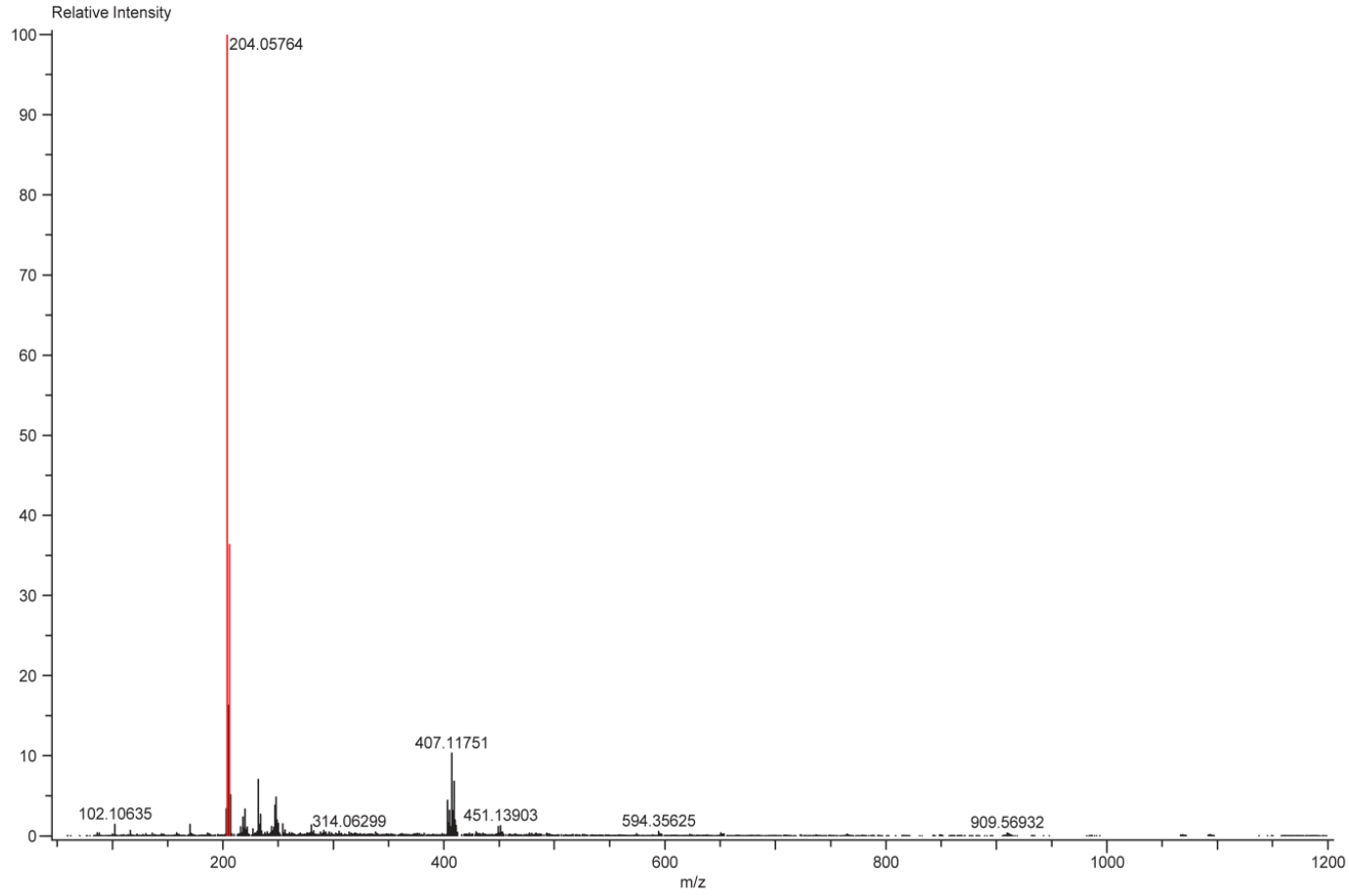
^{1}H-NMR of 4'-chloro-[1,1'-biphenyl]-2-amine (4) in $CDCl_3$



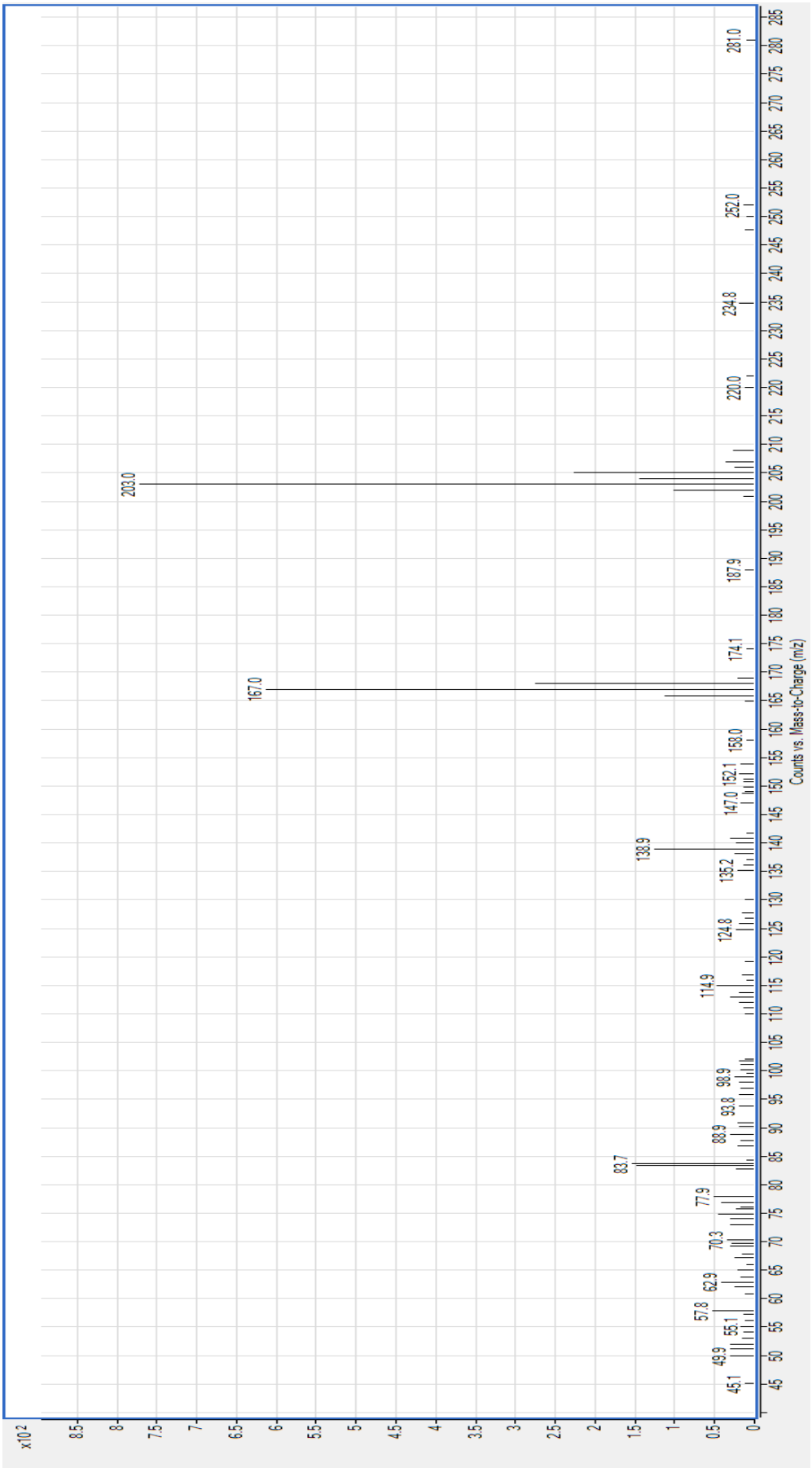
^{13}C-NMR of 4'-chloro-[1,1'-biphenyl]-2-amine (4) in $CDCl_3$



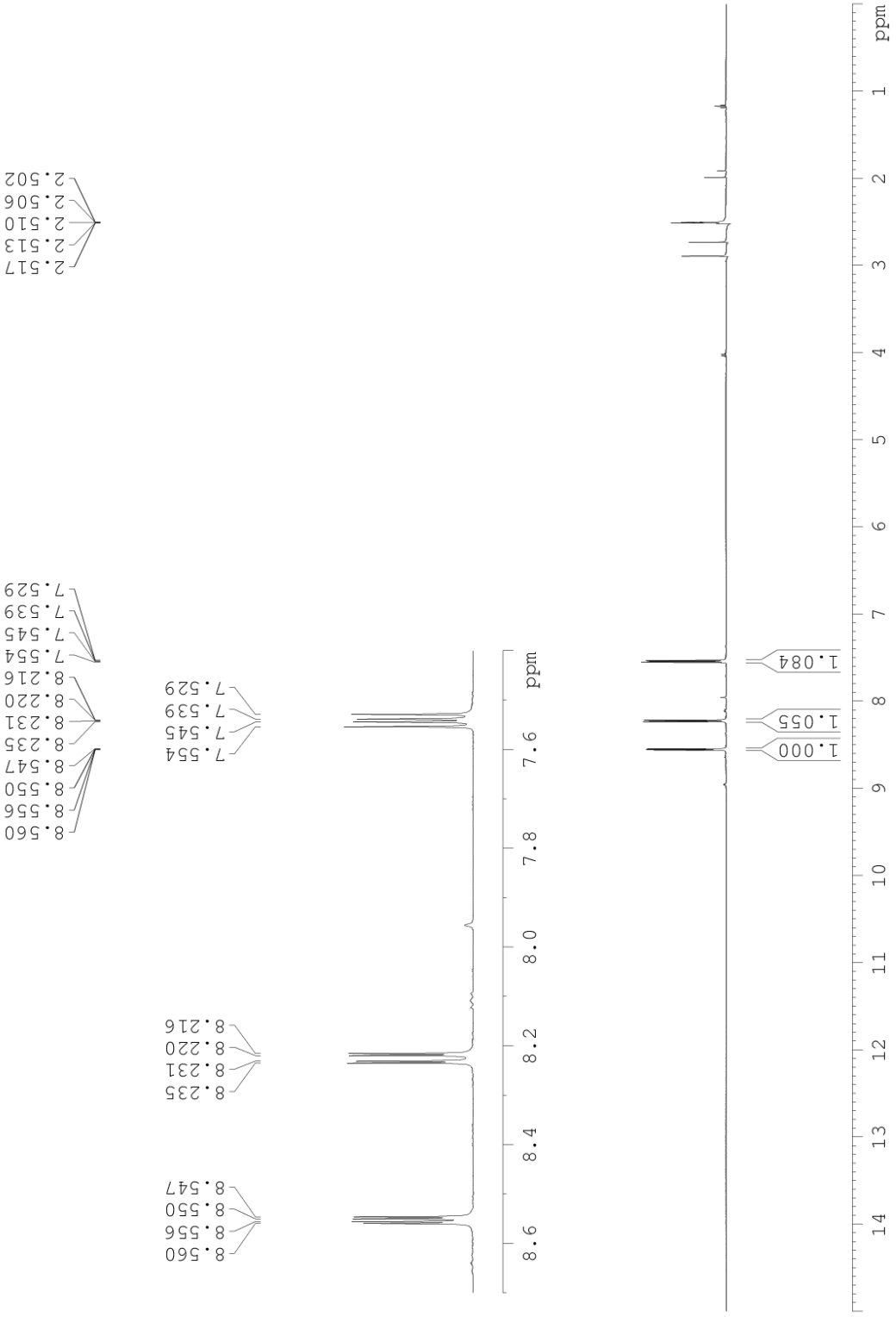
HR-MS (DART+) of 4'-chloro-[1,1'-biphenyl]-2-amine (4)



MS (EI) of 4'-chloro-[1,1'-biphenyl]-2-amine (4)



^{1}H-NMR of 2-chloronicotinoyl chloride (6) in DMSO-d_6



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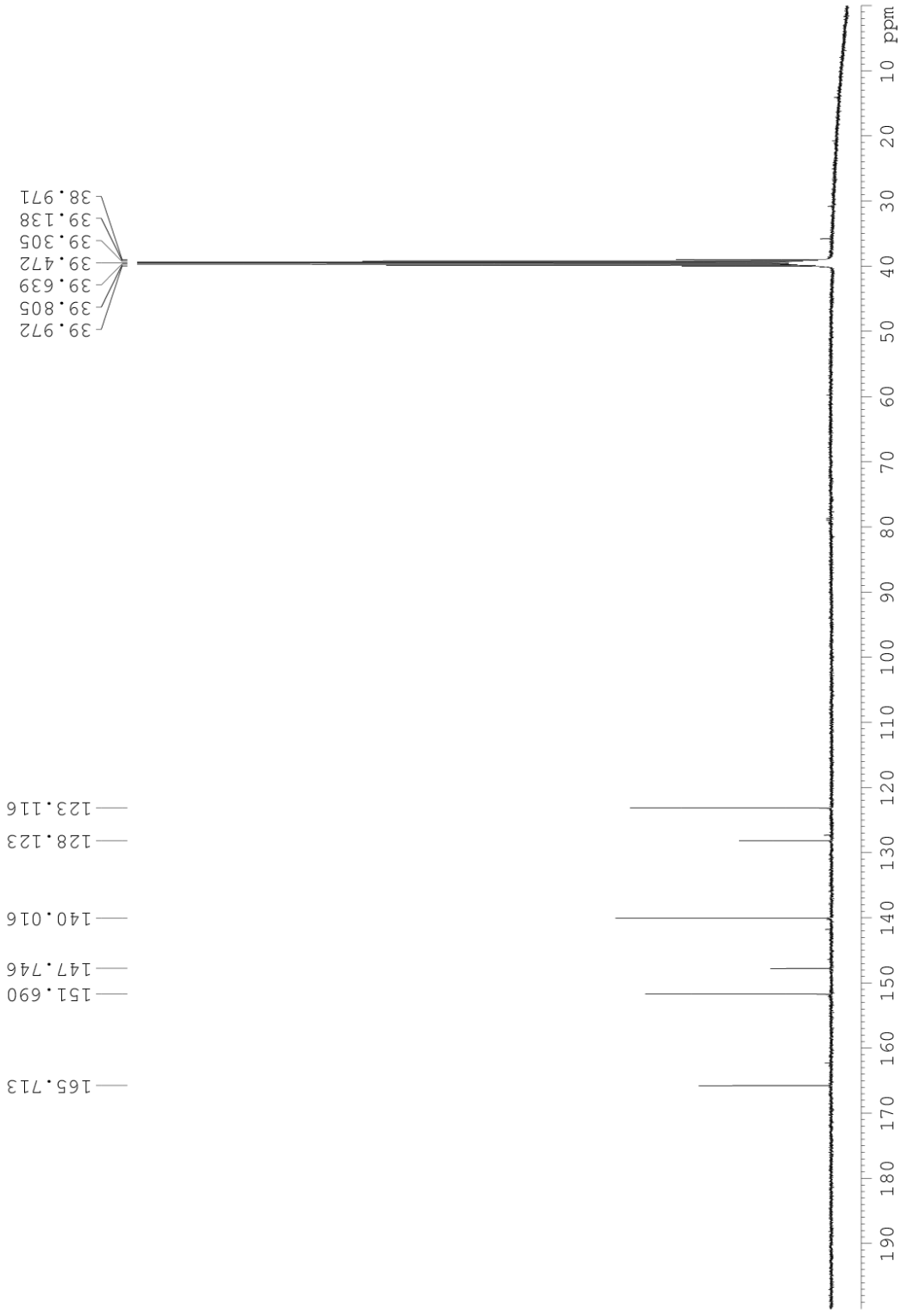
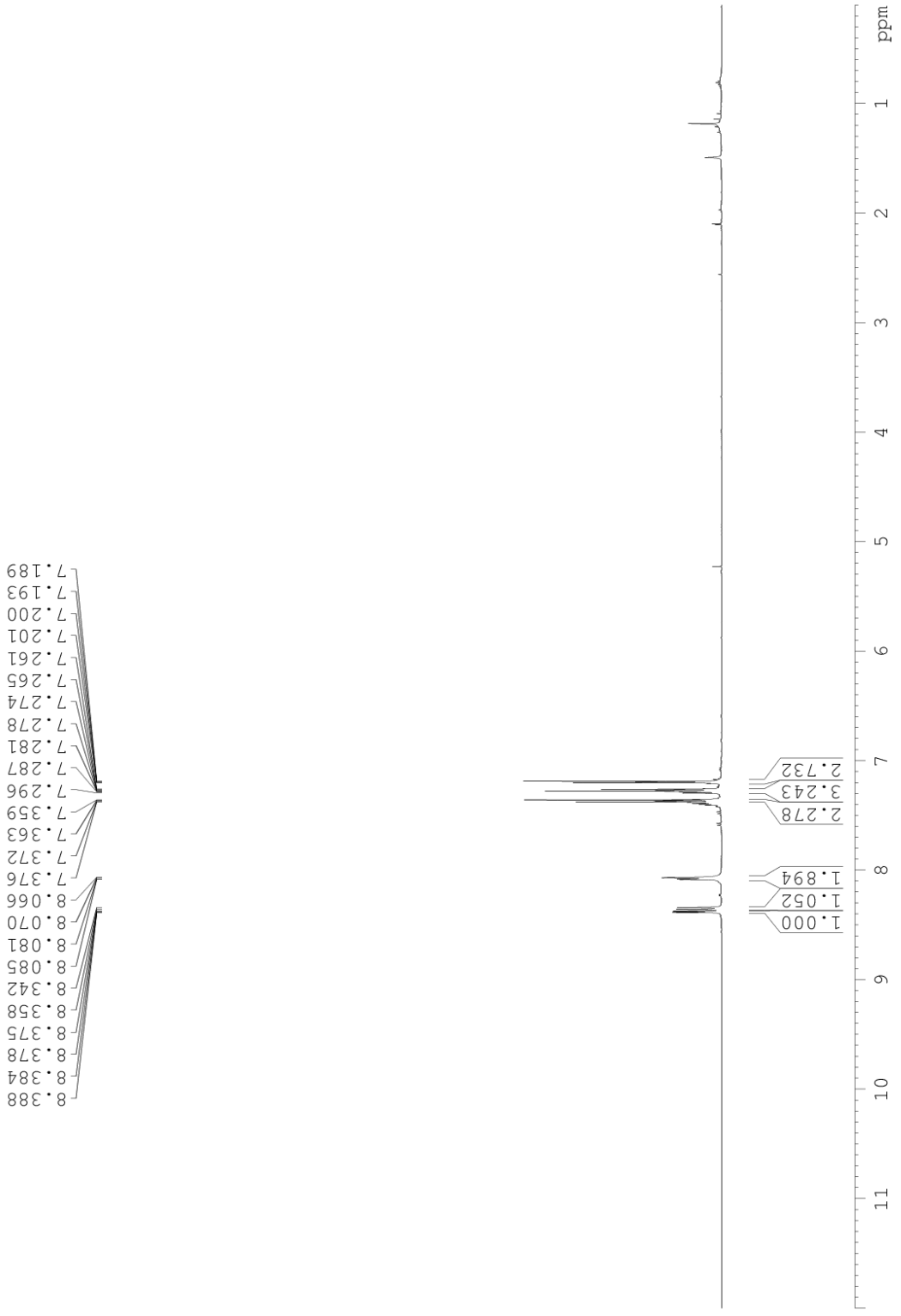


^{1}H-NMR of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) in $CDCl_3$ (method 1)



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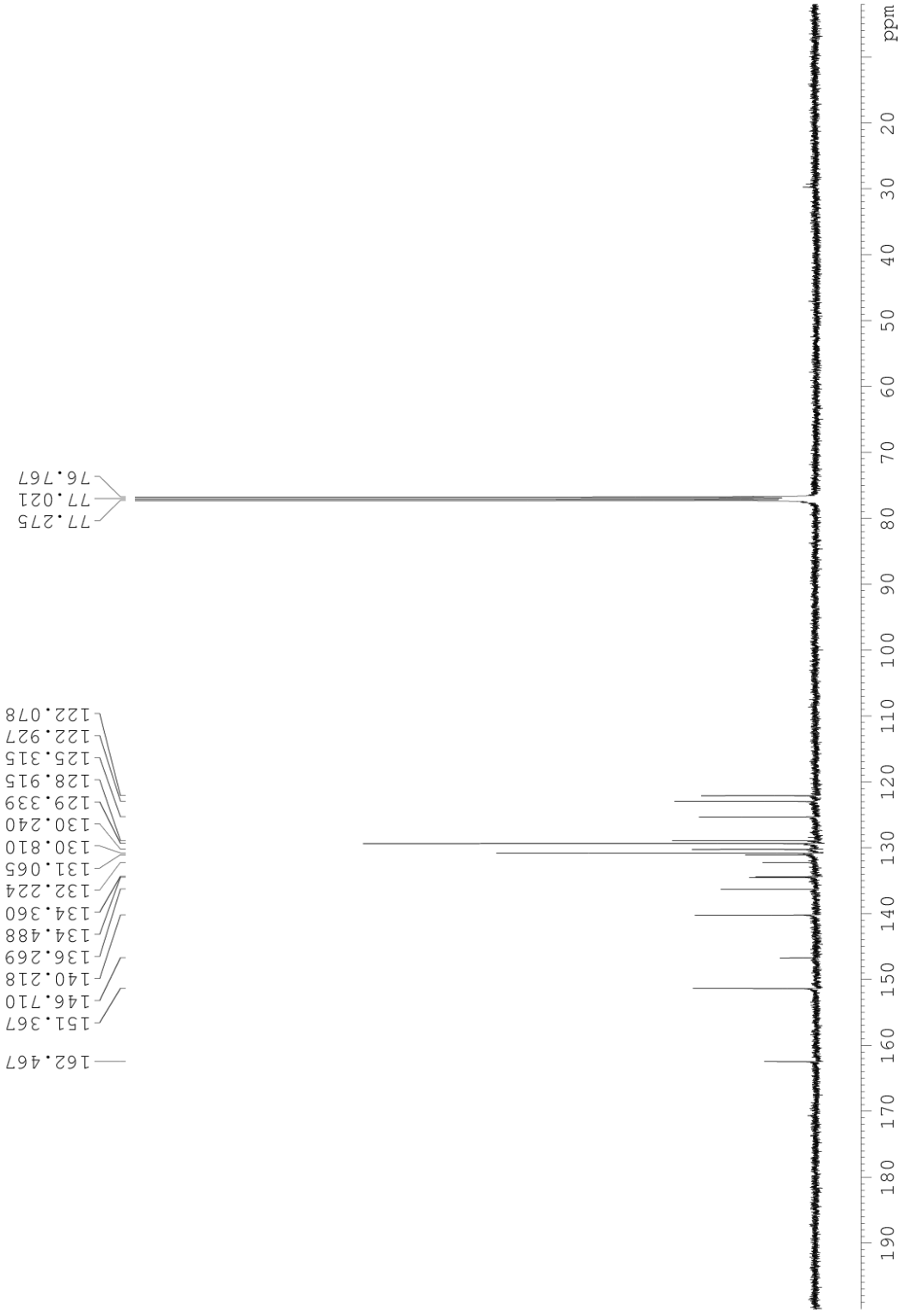
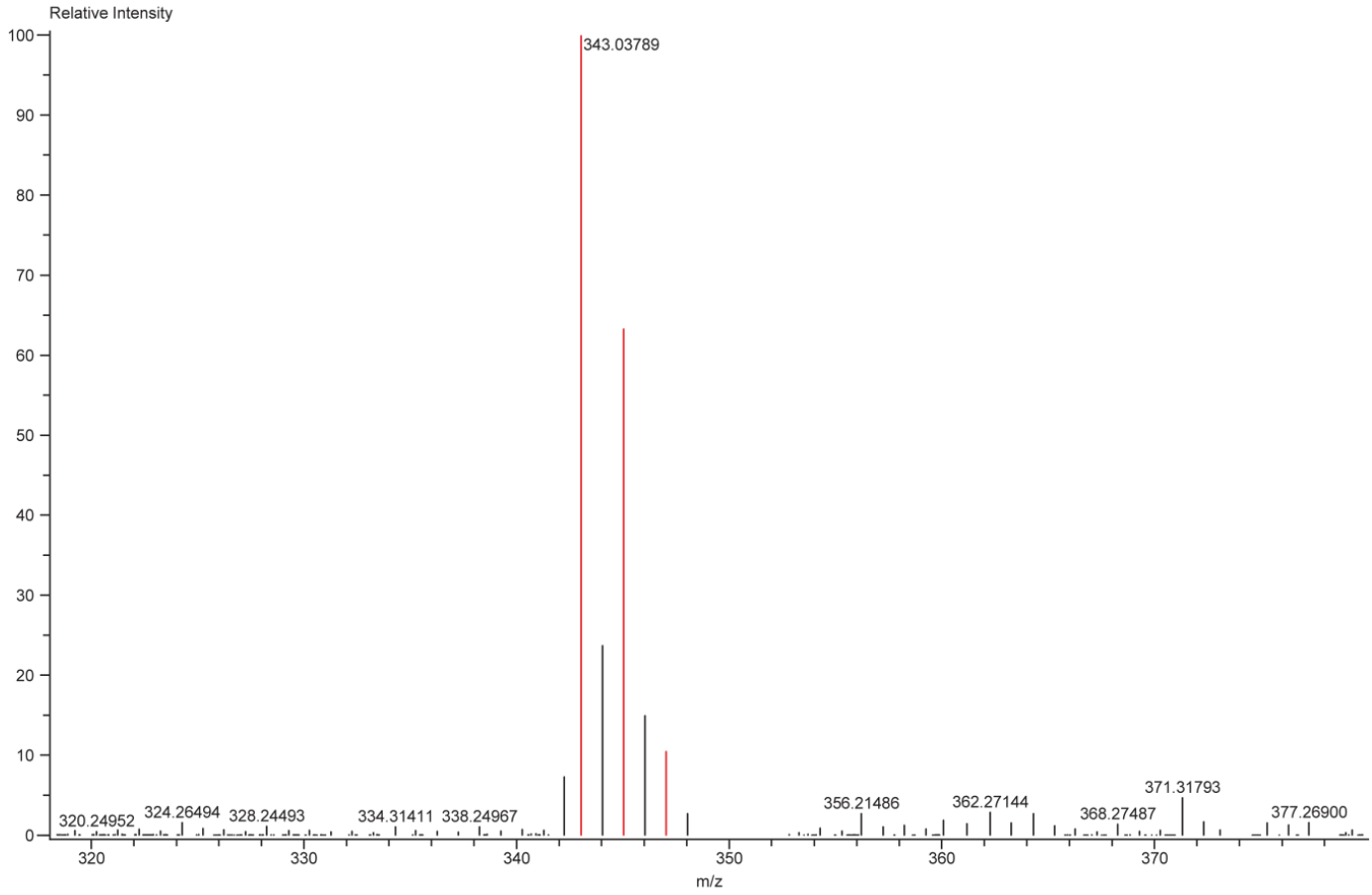
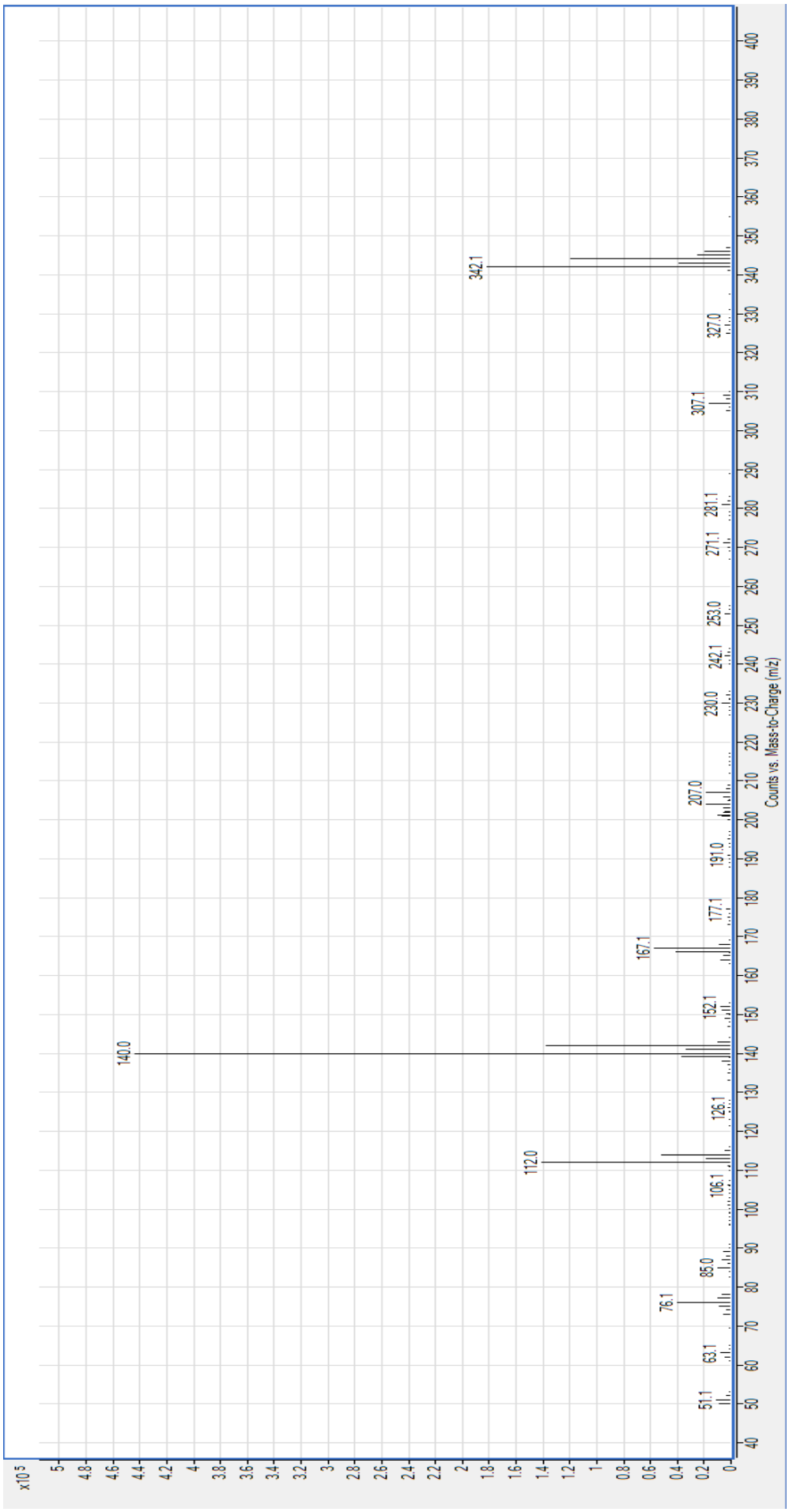


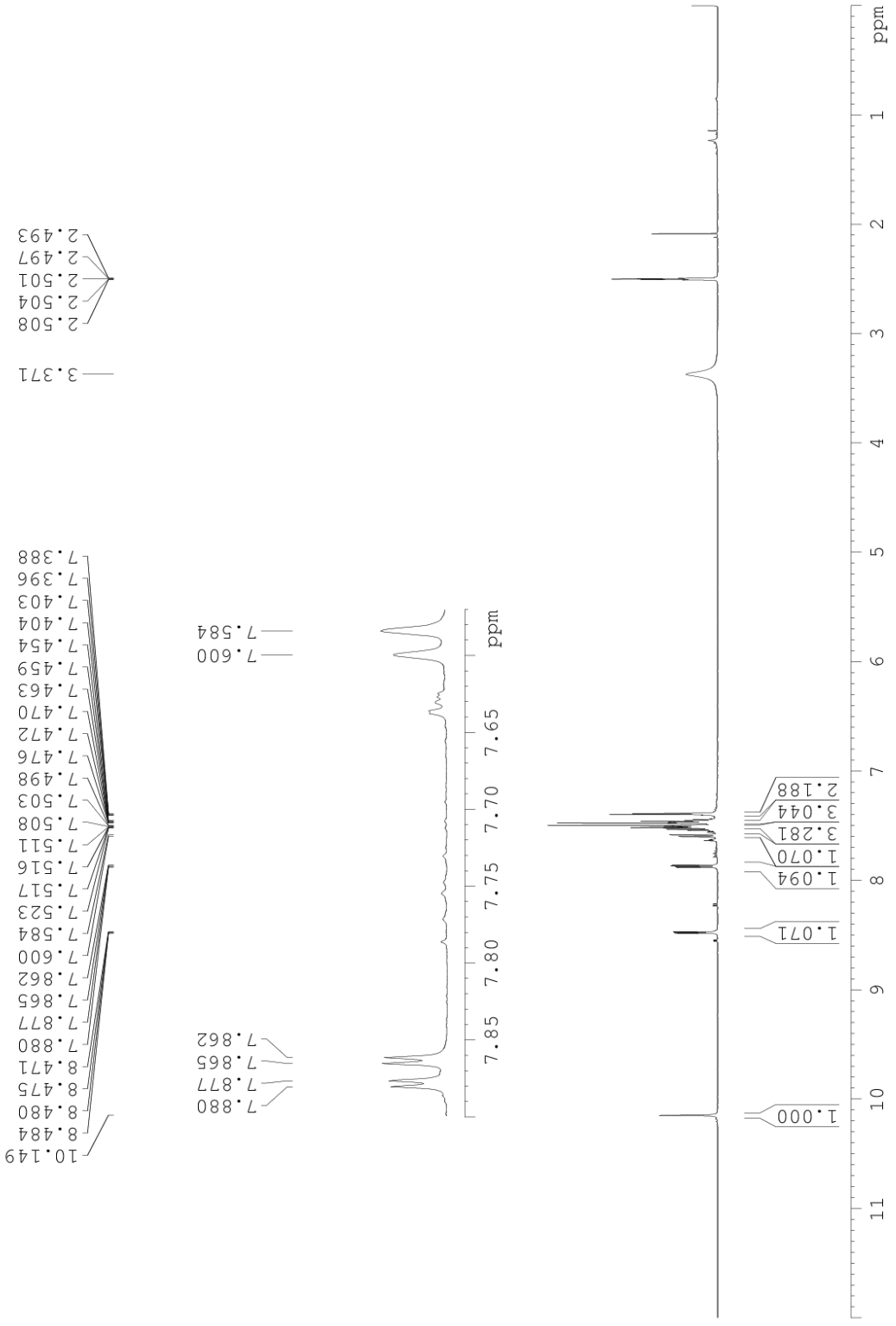
HR-MS (DART+) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) (method 1)



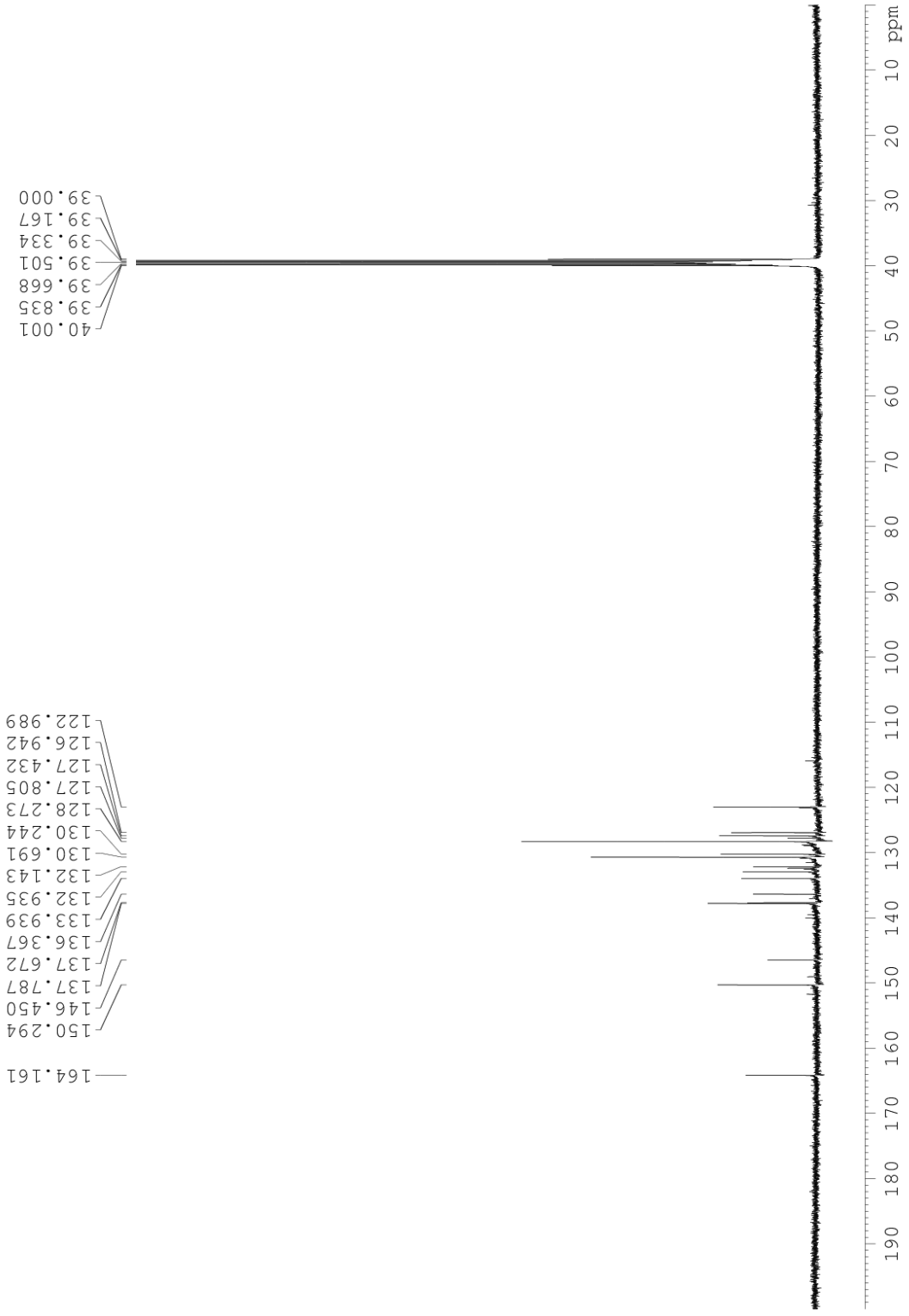
MS (EI) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) (method 1)



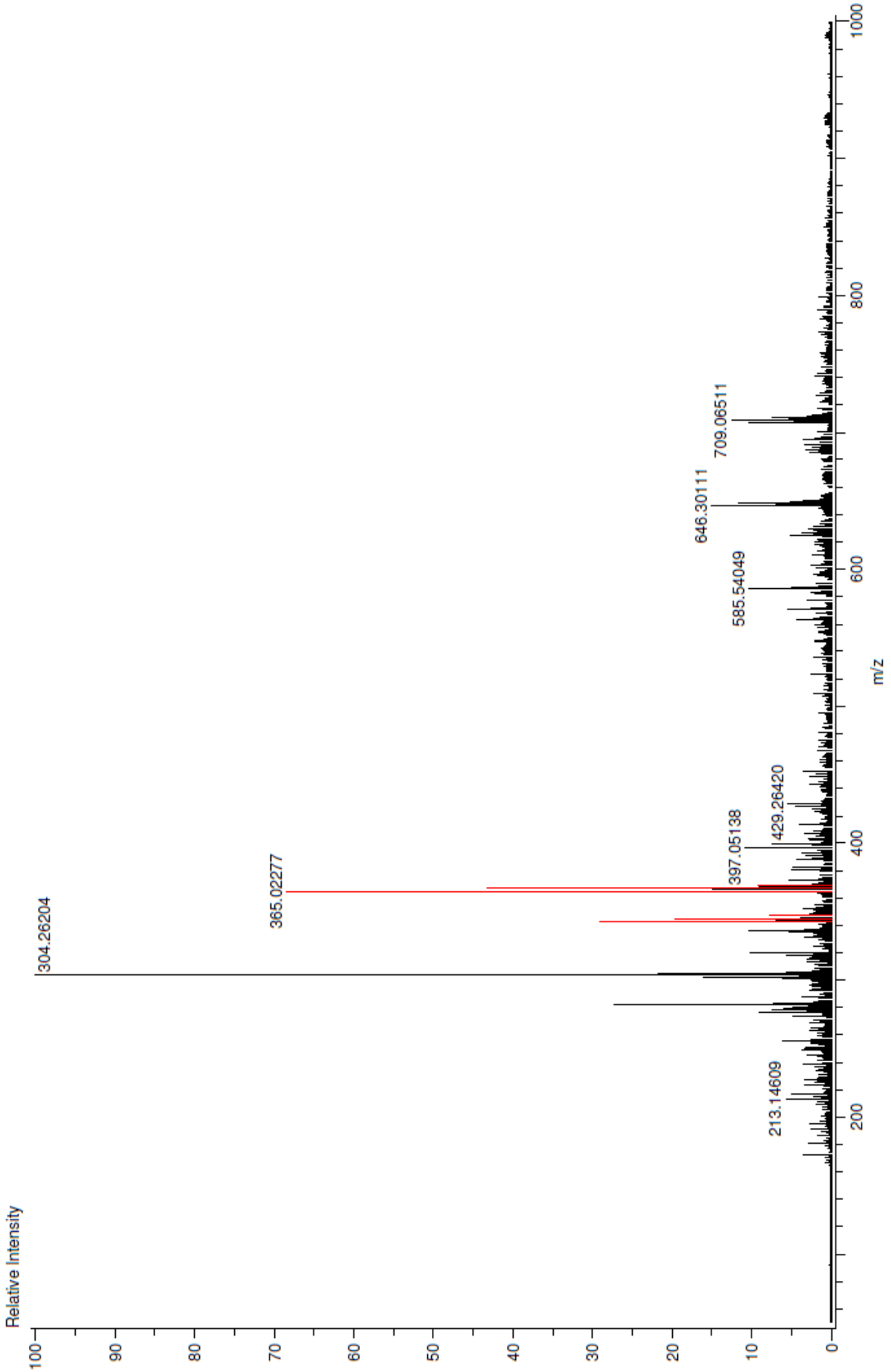
[1]H-NMR of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) in DMSO-d_6 (method 2)



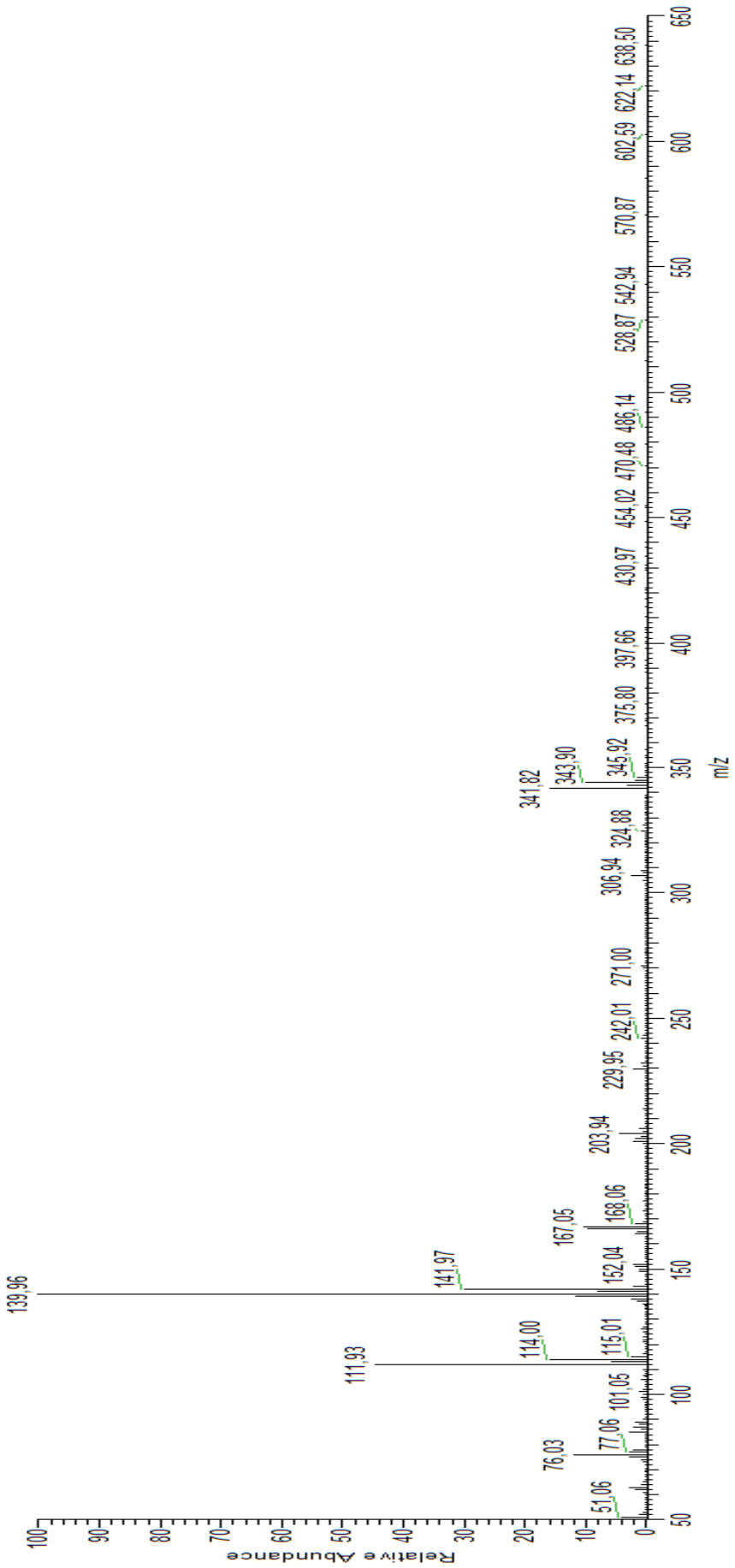
^{13}C-NMR of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) in DMSO-d_6 (method 2)



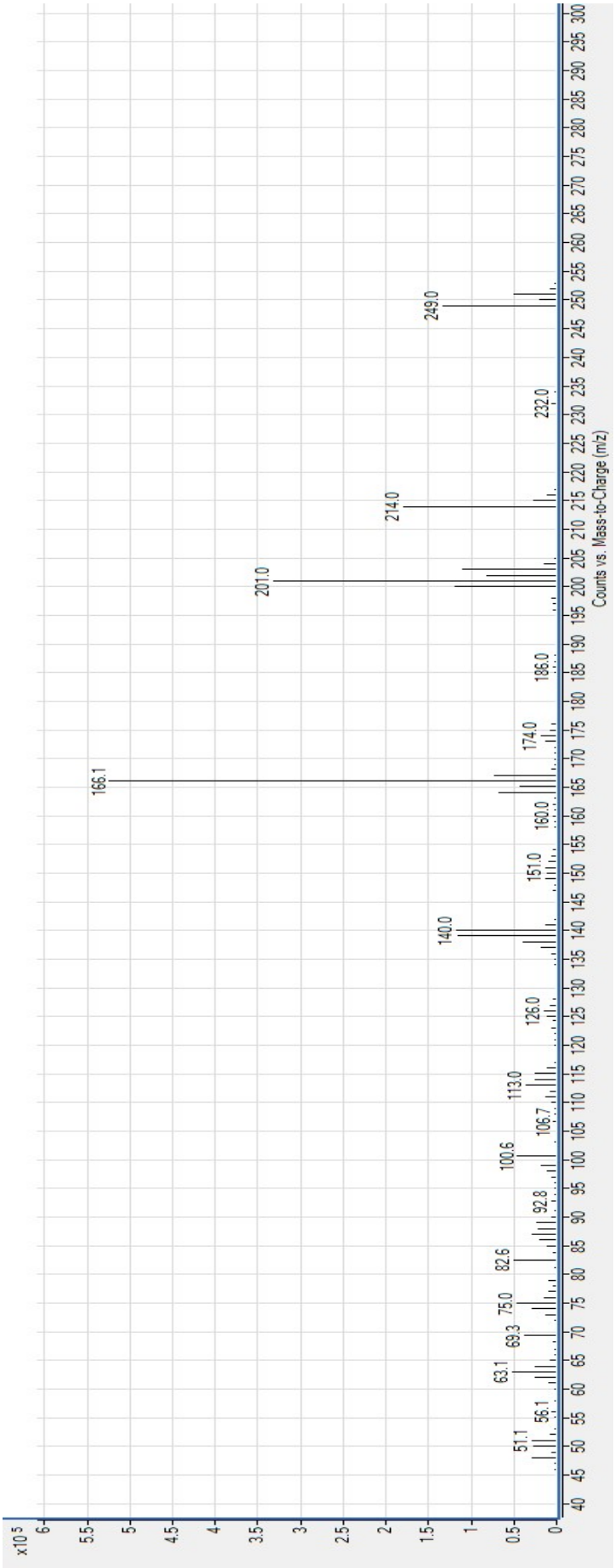
HR-MS (ESI+DI) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) (method 2)



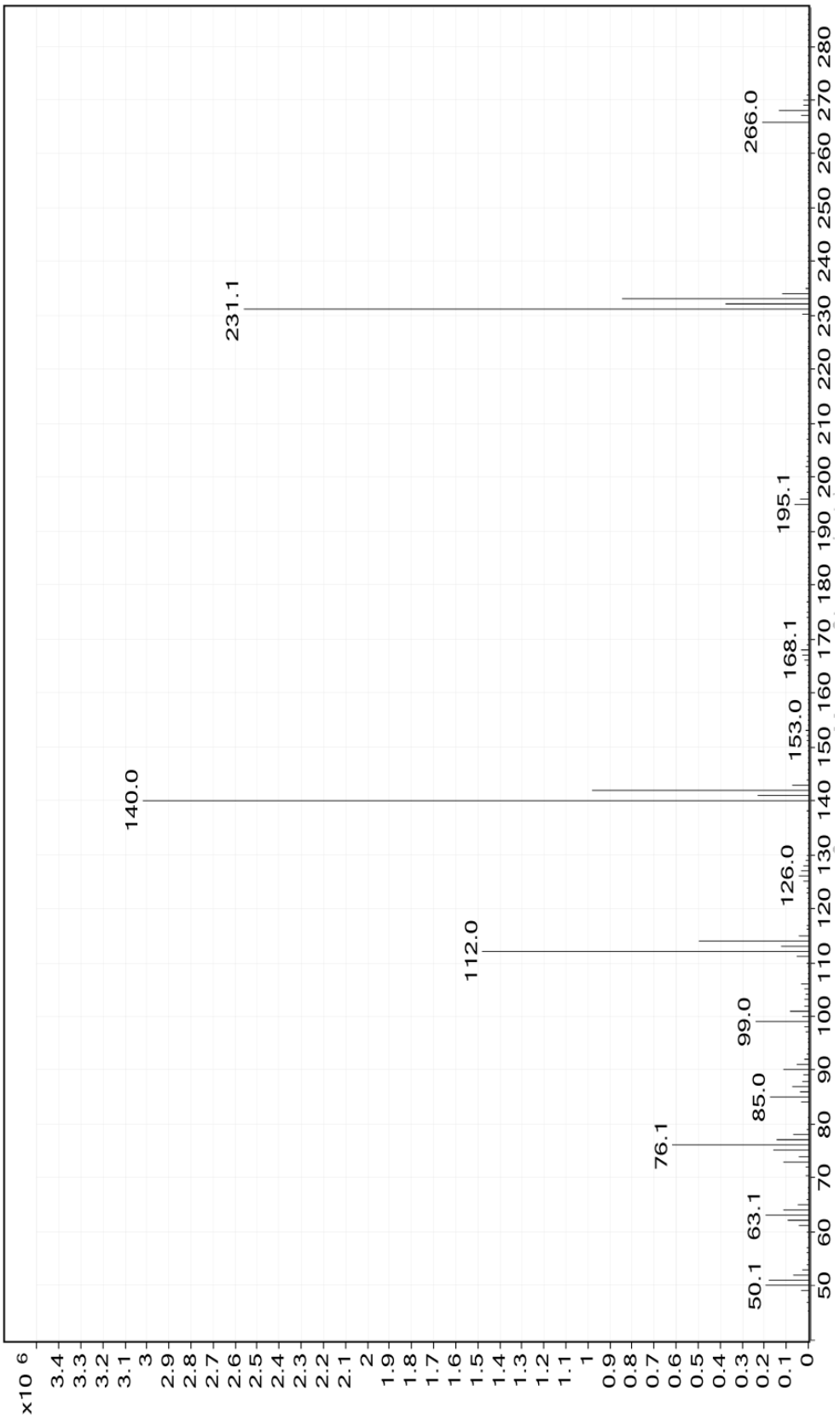
MS (EI) of 2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (7) (method 2)



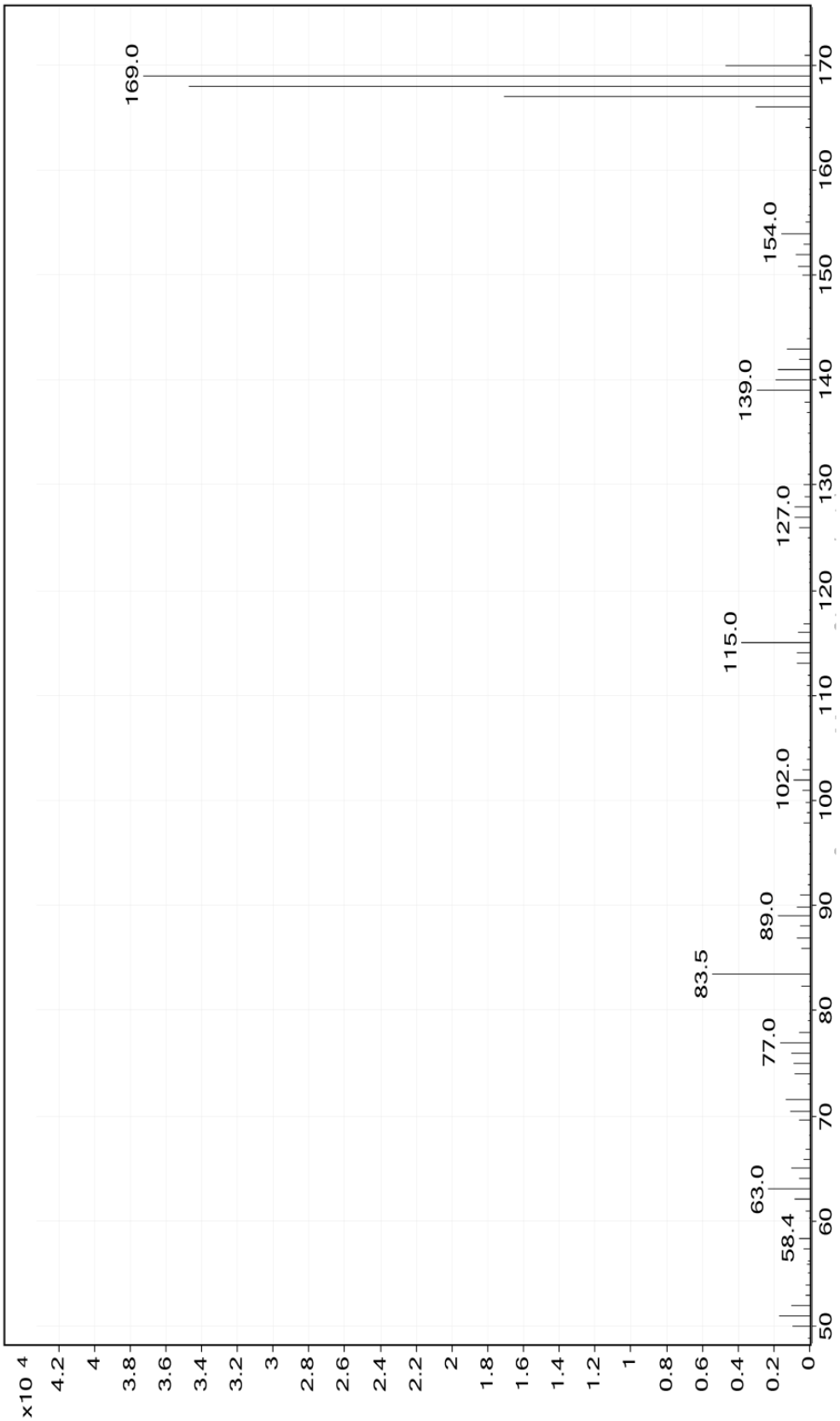
MS (EI) of ((4'-chloro-[1,1'-biphenyl]-4-yl)imino)-sulfanone (8)



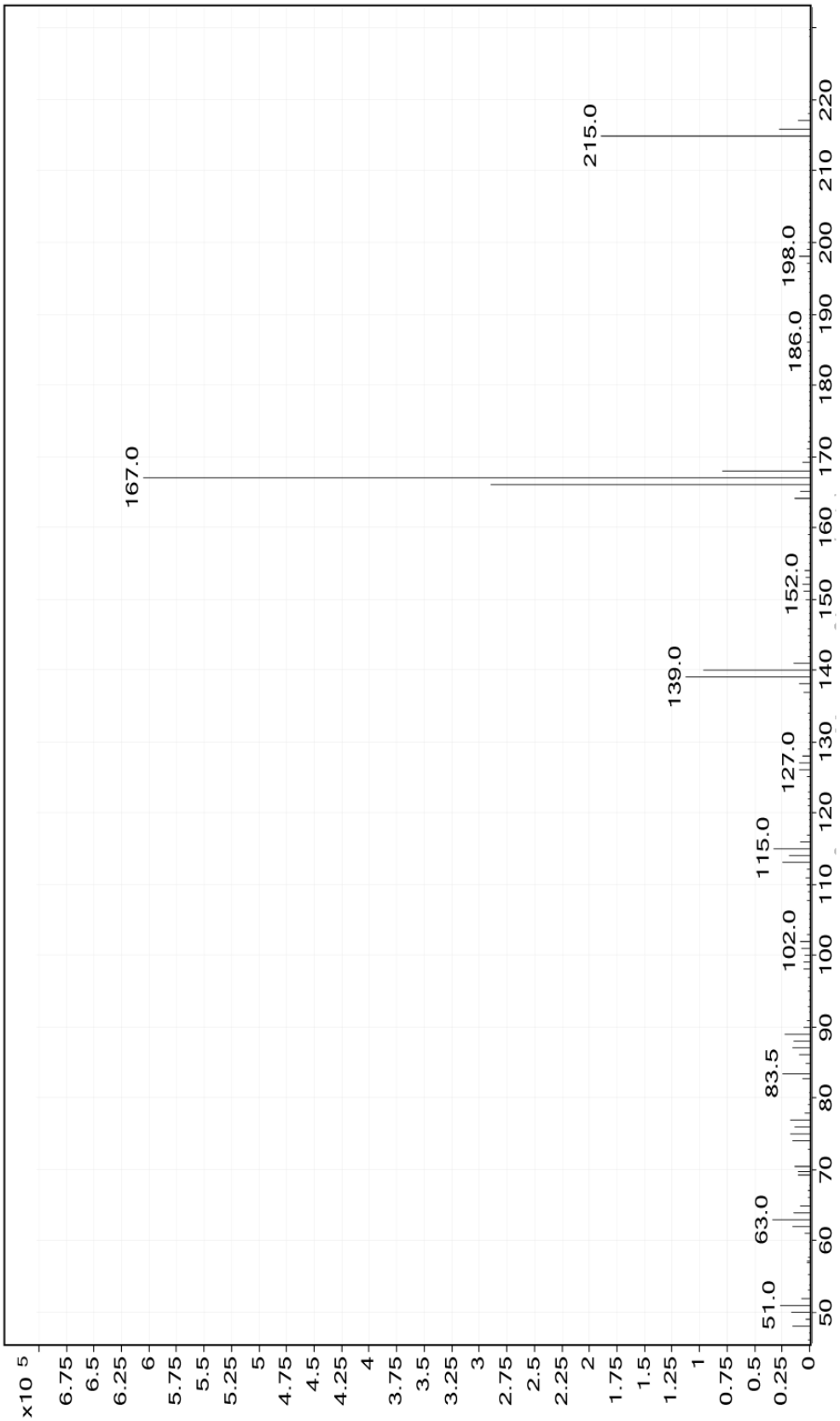
MS (EI) of 2-chloro-*N*-(2-chlorophenyl)nicotinamide (side product from the Flow process)



MS (EI) of [1,1'-biphenyl]-2-amine (4a) (y_1) (Design experiments)



MS (EI) of ([1,1'-biphenyl]-2-imino)-4-sulfanone (8a) (y_2) (Design of experiments)



MS (EI) of N-([1,1'-biphenyl]-2-yl)-2-chloronicotinamide (y_4) (7a) (Design of Experiments)