Supplementary materials

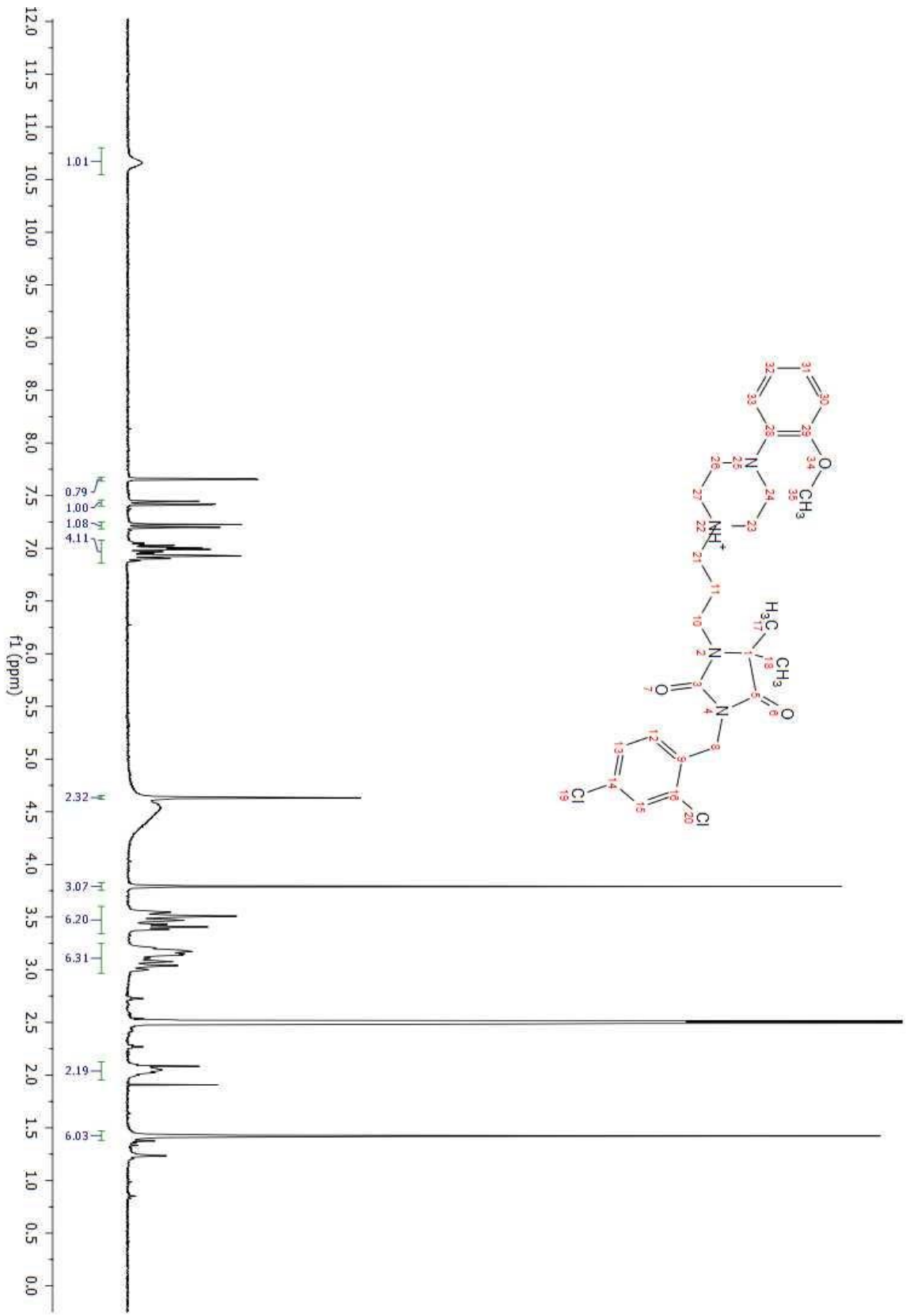
The subtype selectivity in search of potent hypotensive agents among 5,5-dimethylhydantoin derived α1-adrenoceptors antagonists

Aneta Kaczor [1†], Joanna Knutelska [2†], Katarzyna Kucwaj-Brysz [1], Małgorzata Zygmunt [2], Ewa Żesławska [3], Agata Siwek [4], Marek Bednarski [2], Sabina Podlewska [5], Magdalena Jastrzębska-Więsek [6], Wojciech Nitek [7], Jacek Sapa [2] and Jadwiga Handzlik [1,*]

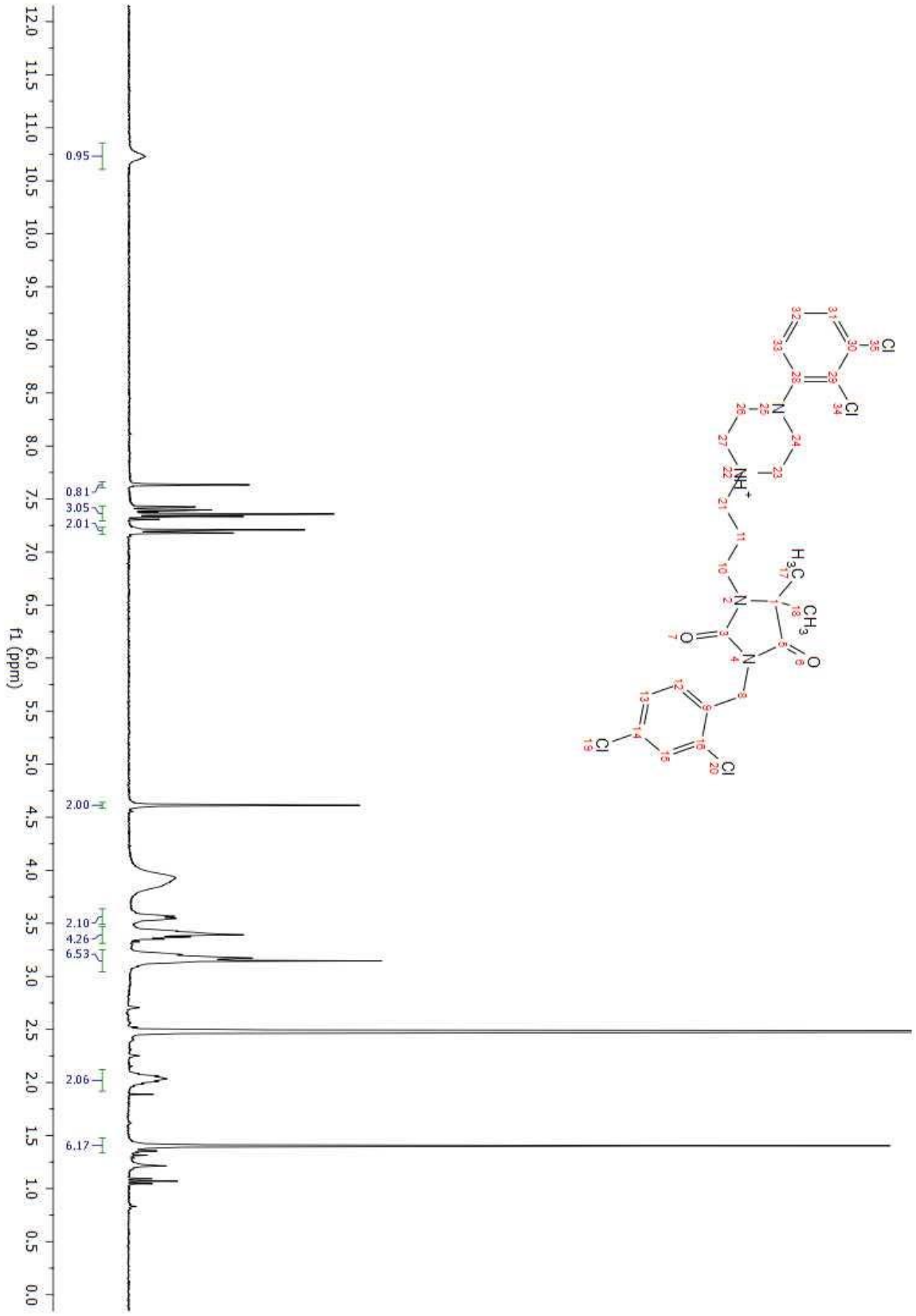
^{1}HNMRs

for final products obtained within the studies

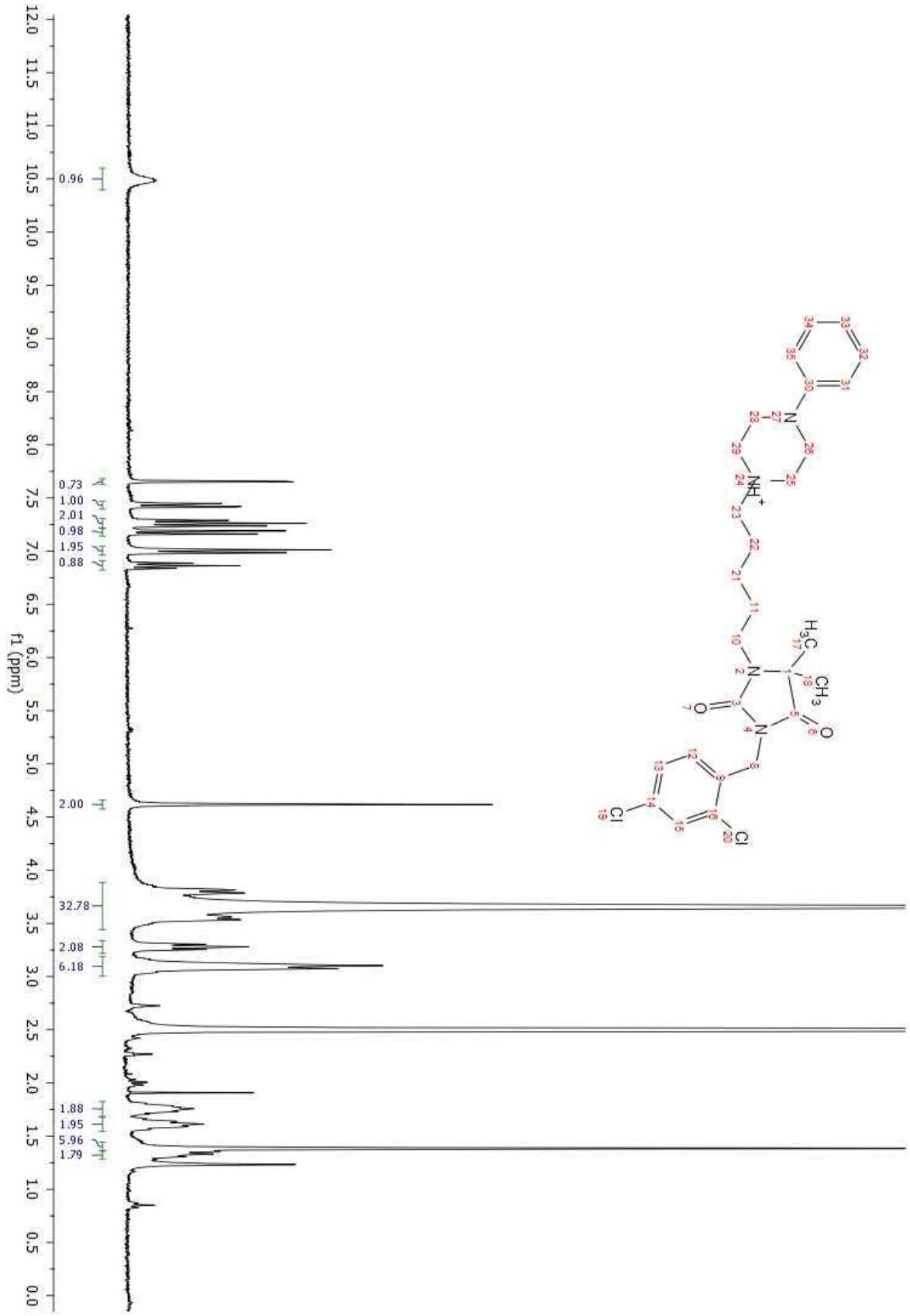
Compound 1



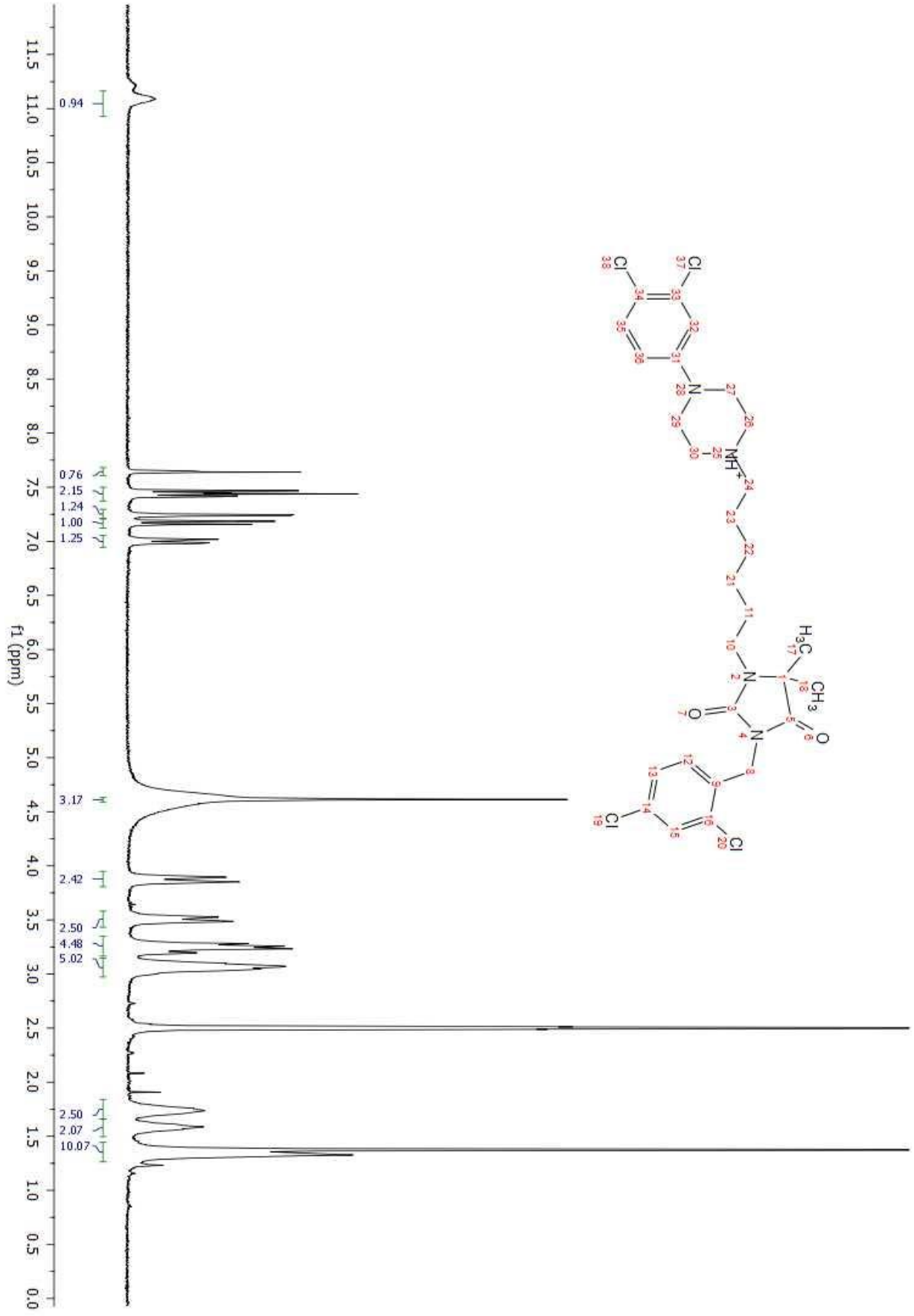
Compound 2



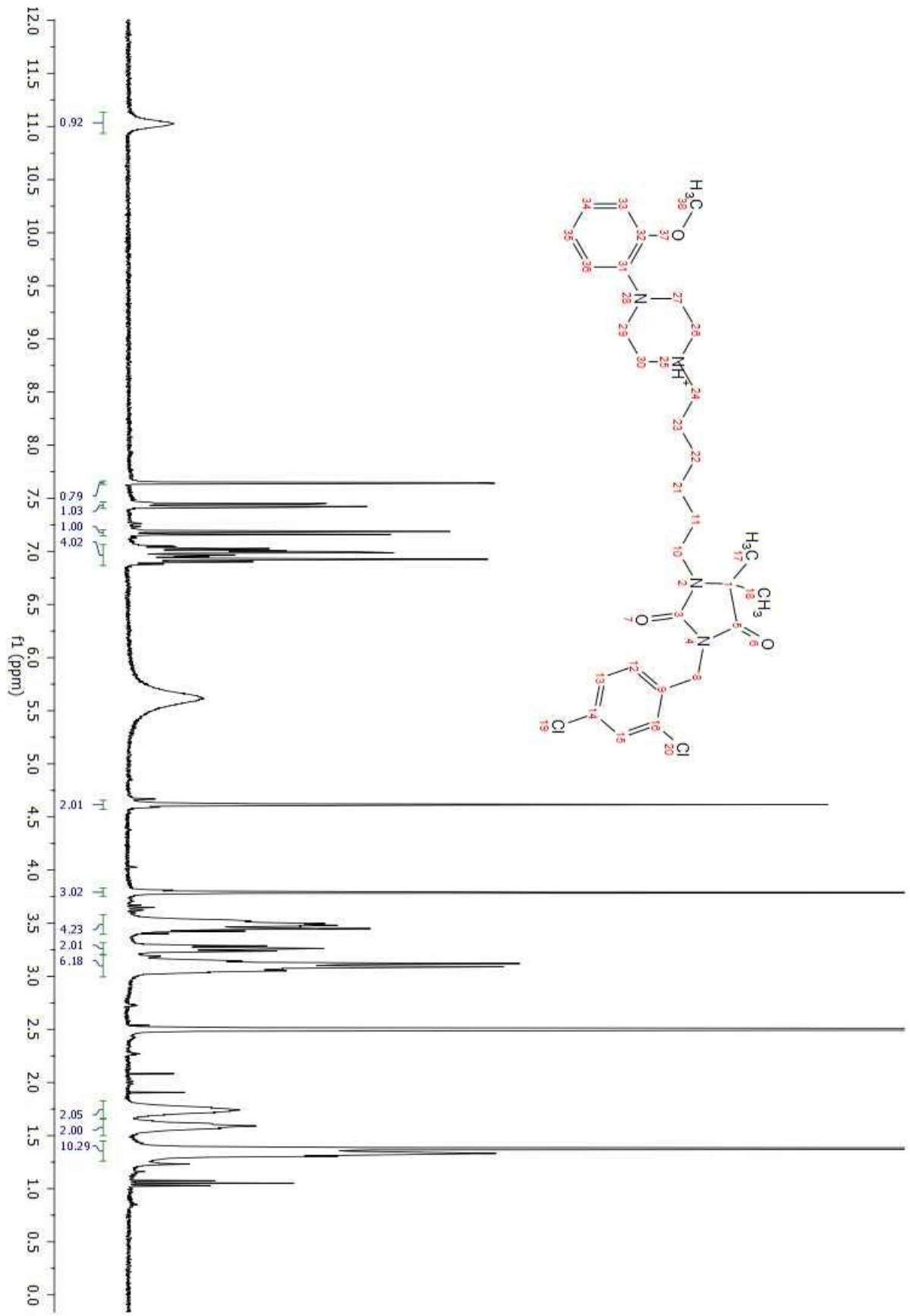
Compound 3


f1 (ppm)
0.96
0.73
1.00
2.01
0.98
1.95
0.88
2.00
32.78
2.08
6.18
1.88
1.95
5.96
1.79
H3C
CH3
O
O
Cl
Cl
NH+

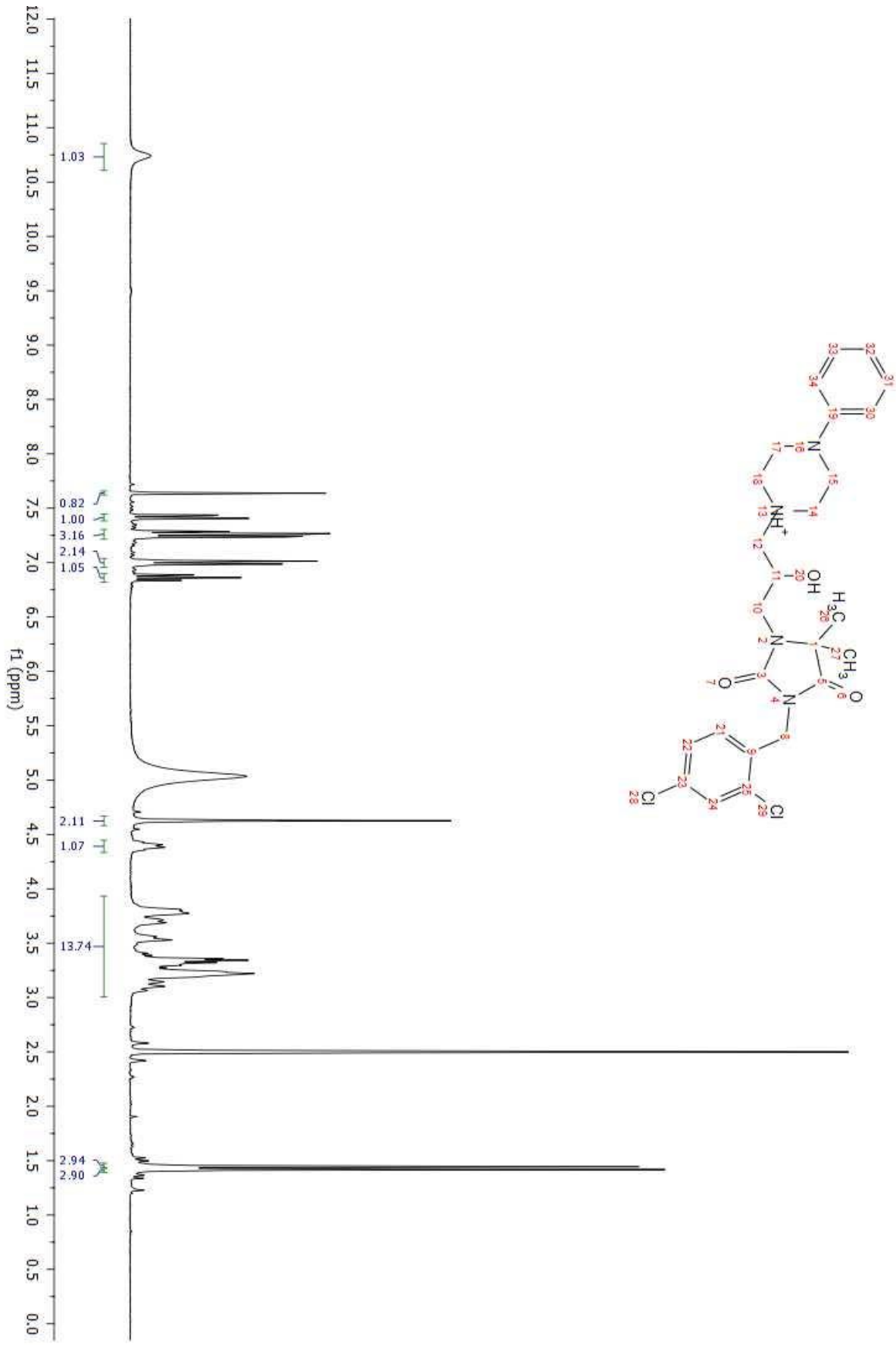
Compound 4


f1 (ppm)
0.94
0.76
2.15
1.24
1.00
1.25
3.17
2.42
2.50
4.48
5.02
2.50
2.07
10.07
MH+
Cl
Cl
Cl
Cl
O
O
N
N
N
CH3
H3C

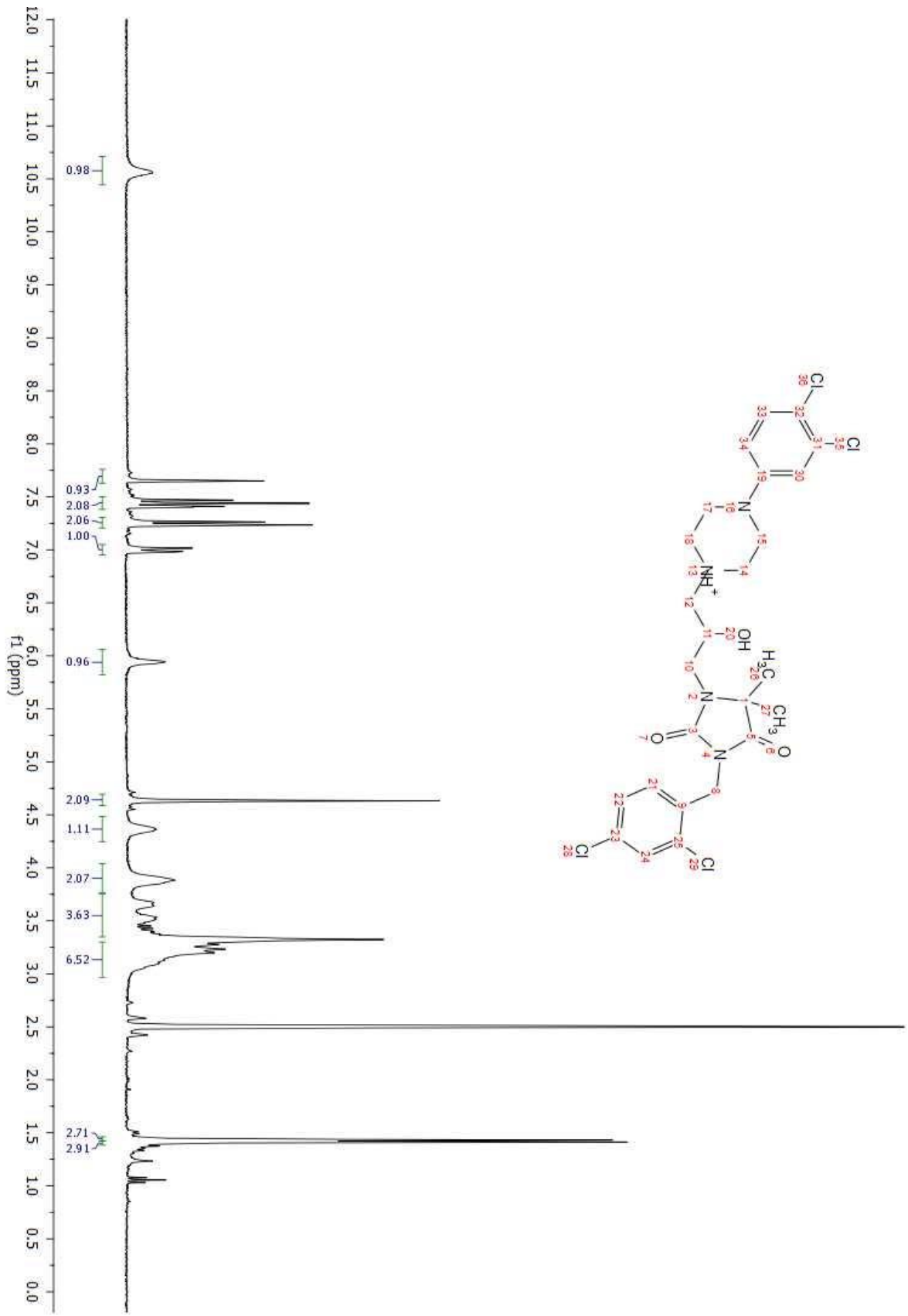
Compound 5



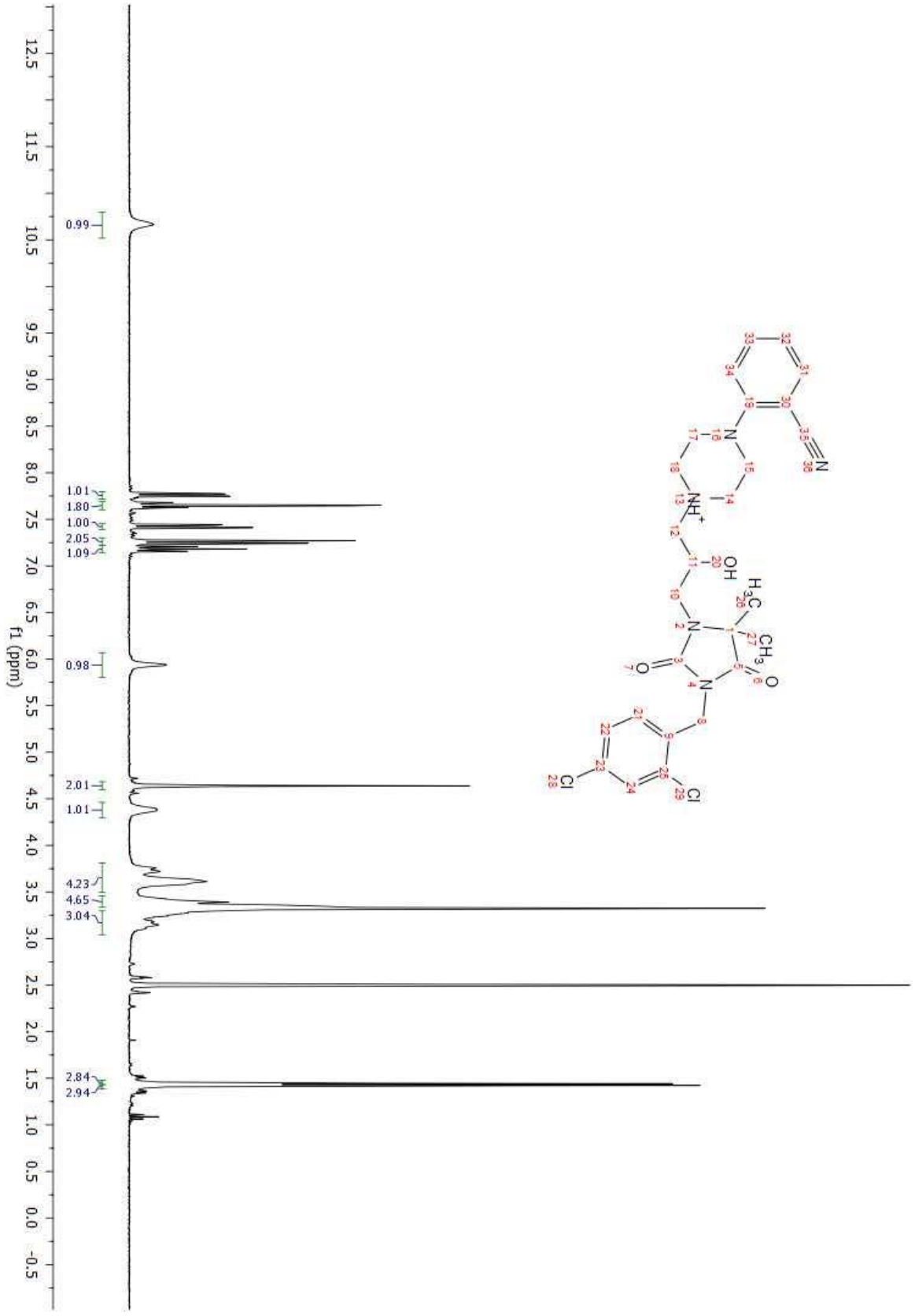
Compound 6



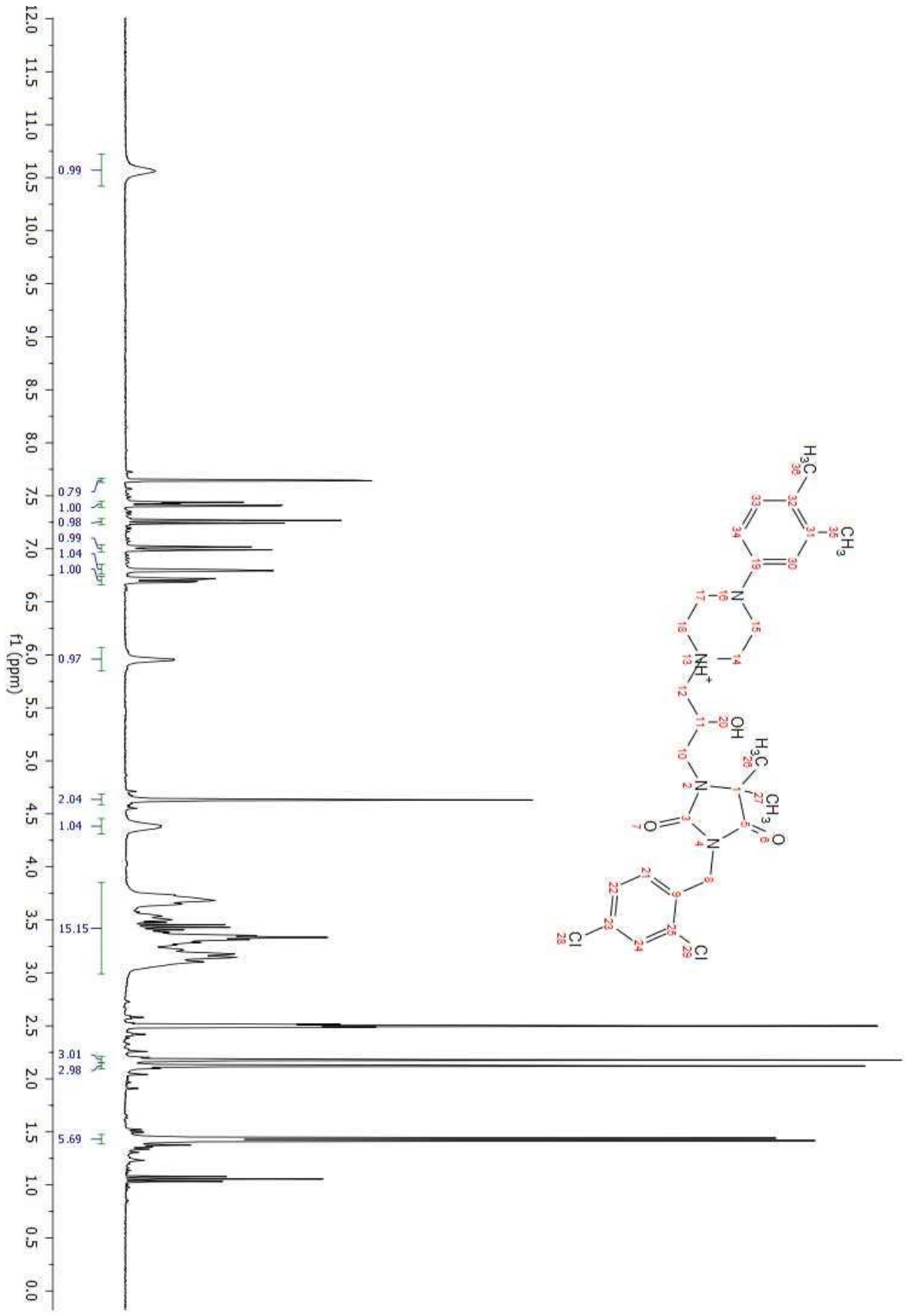
Compound 10



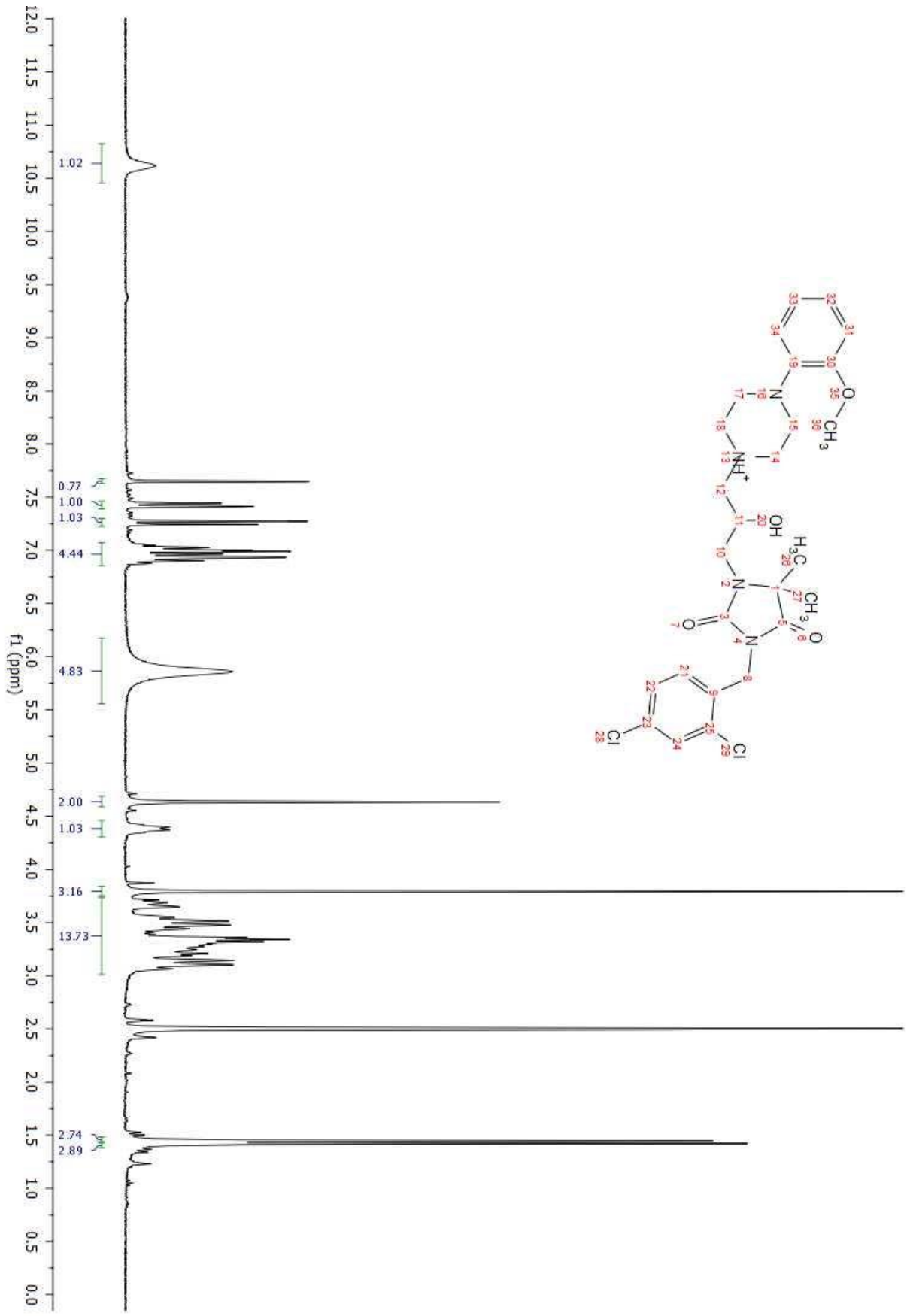
Compound 11



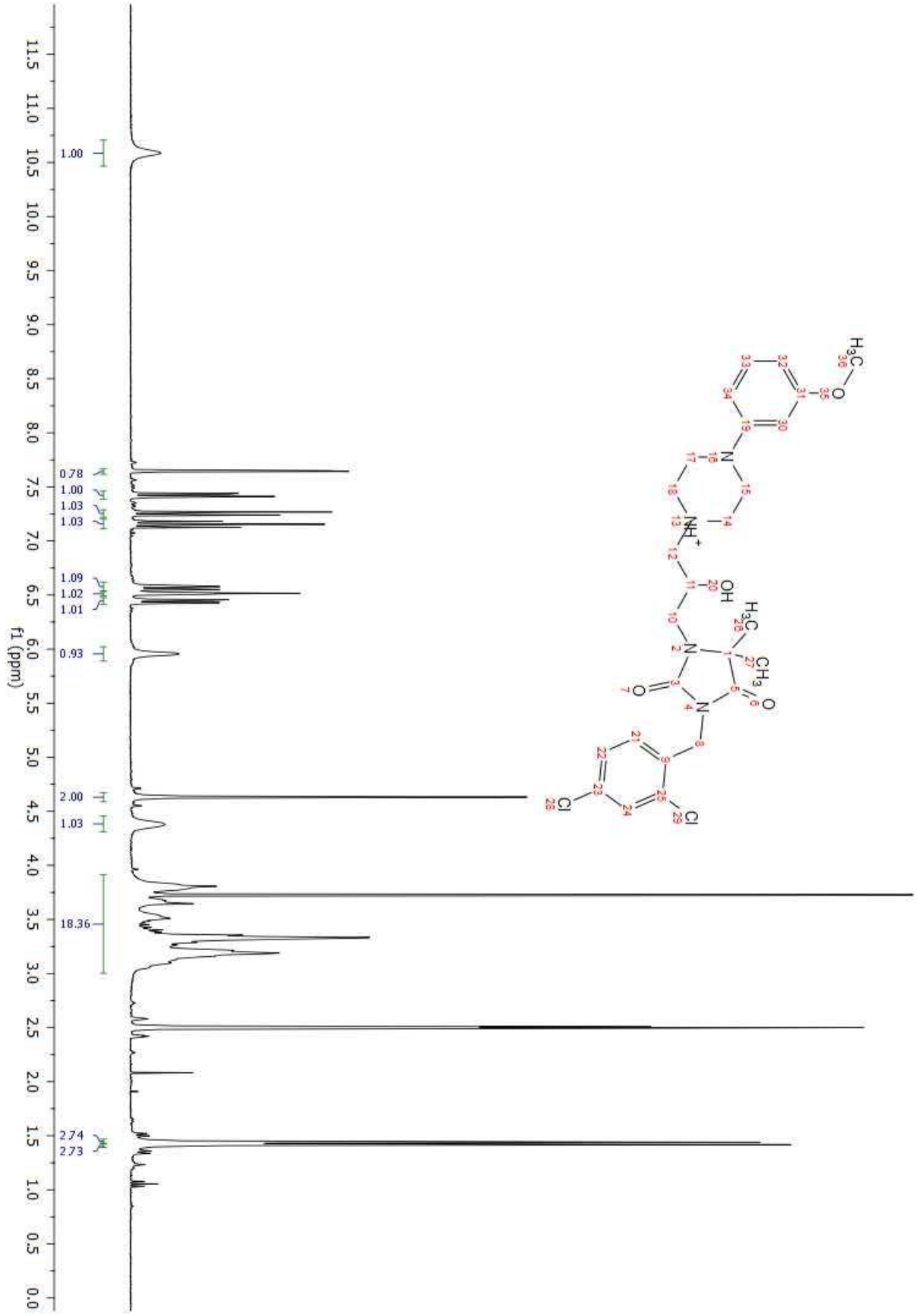
Compound 12


f1 (ppm)
0.99
0.79
1.00
0.98
0.99
1.04
1.00
0.97
2.04
1.04
15.15
3.01
2.98
5.69
OH
NH+
Cl
Cl

Compound 13



Compound 14


f1 (ppm)
11.5
11.0
10.5
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
1.00
0.78
1.00
1.03
1.03
1.09
1.02
1.01
0.93
2.00
1.03
18.36
2.74
2.73
OH
NH+
Cl
Cl
CH3
O
N

The synthetic procedure for intermediate 17

3-(2,4-dichlorobenzyl)-5,5-dimethylimidazolidine-2,4-dione (**16**) (40 mmol, 11.48 g), potassium carbonate (11.58 mmol, 16.0 g), TEBA (5.27 mmol, 1.2 g) and acetone (80 ml) was stirred for 30 min. Then, 1,3-dibromopropan (60 mmol, 12.11 g) in acetone (40 ml) was added. It was stirred for 4 days. Filtration was carried out and filtrate was evaporated. To the residue, dichloromethane was added and mixture was washed three times with 1% sodium hydroxide and twice with water. Organic fractions were dried, then filtrated and evaporated. Crude product was purified from reaction mixture using column chromatography in dichloromethane:acetone (10:1). As these reaction has been well established in our team using analogous starting materials [1,2], the resulted white solid, pure according to TLC control was directly used for synthesis of final compounds.

1. Handzlik, J.; Bojarski, A. J.; Satała, G.; Kubacka, M.; Sadek, B.; Ashoor, A.; Siwek, A.; Więcek, M.; Kucwaj, K.; Filipek, B.; Kieć-Kononowicz, K. SAR-studies on the importance of aromatic ring topologies in search for selective 5-HT(7) receptor ligands among phenylpiperazine hydantoin derivatives. *Eur J Med Chem.* **2014**, *78*, 324–339. doi: 10.1016/j.ejmech.2014.01.065.
2. Kononowicz, K.; Handzlik, J. Phenylpiperazine 5,5-Dimethylhydantoin Derivatives as First Synthetic Inhibitors of Msr(A) Efflux Pump in Staphylococcus epidermidis. *Molecules.* **2020**, *25*, 3788. doi: 10.3390/molecules25173788.

The influence on blood pressure in rats

Table S1. Influence on blood pressure for vehicle, tested compounds (**1**-**3**, **5**-**9**, **11**-**14**), and urapidil.

Cpd	Dose (mg/kg)	Blood pressure	Time of observation (min)							
			0	5	10	20	30	40	50	60
Vehicle	–	Systolic	133.2 ± 3.5	133.8 ± 3.1	130.3 ± 3.0	131.0 ± 3.2	130.3 ± 3.0	129.7 ± 3.5	132.2 ± 4.1	132.3 ± 3.5
		Diastolic	98.3 ± 3.3	98.0 ± 2.9	94.8 ± 2.5	95.7 ± 3.2	95.2 ± 3.0	95.2 ± 2.9	96.0 ± 3.6	96.3 ± 3.0
1	2.0	Systolic	133.3 ± 4.5	120.3 ± 3.1	113.0 ± 3.1**	112.2 ± 3.6**	114.2 ± 3.7*	114.7 ± 3.9*	116.0 ± 3.8*	117.5 ± 4.3*
		Diastolic	101.0 ± 3.1	88.3 ± 2.3	82.3 ± 3.3*	82.2 ± 4.2*	81.3 ± 3.9*	80.8 ± 3.1*	81.7 ± 2.3*	83.3 ± 2.1*
2	2.0	Systolic	129.3 ± 5.8	126.7 ± 5.6	124.2 ± 5.3	121.7 ± 6.3	121.2 ± 5.6	120.2 ± 5.7	120.3 ± 4.7	119.3 ± 5.1
		Diastolic	100.7 ± 4.3	98.5 ± 4.4	96.8 ± 4.0	92.8 ± 3.8	90.3 ± 3.9	89.3 ± 3.6	88.0 ± 3.1	88.0 ± 2.7
3	2.0	Systolic	132.2 ± 1.6	123.3 ± 1.7	113.7 ± 1.3***	113.0 ± 2.2***	116.3 ± 2.2**	116.3 ± 1.9**	120.3 ± 1.7*	119.7 ± 2.4*
		Diastolic	93.7 ± 2.5	90.3 ± 2.0	81.2 ± 2.3**	81.7 ± 2.6**	83.2 ± 2.4*	82.7 ± 2.1*	84.2 ± 2.6*	83.8 ± 3.3*
5	0.0625	Systolic	128.8 ± 2.0	121.0 ± 3.0*	116.8 ± 2.6**	114.2 ± 2.3***	113.3 ± 2.0***	114.7 ± 1.4**	116.8 ± 0.6**	116.3 ± 1.2***
		Diastolic	92.0 ± 1.9	87.7 ± 1.6*	84.2 ± 1.6*	81.7 ± 1.8**	82.7 ± 1.5**	81.7 ± 2.2**	81.8 ± 1.6**	83.3 ± 2.3**
6	2.0	Systolic	134.2 ± 2.8	124.2 ± 4.2	125.2 ± 3.7	126.3 ± 3.6	125.0 ± 4.0	126.7 ± 3.9	125.5 ± 4.4	125.8 ± 3.6
		Diastolic	98.2 ± 3.5	87.2 ± 4.8	90.3 ± 4.7	89.7 ± 4.4	89.0 ± 4.7	89.0 ± 4.5	89.2 ± 5.1	88.7 ± 4.6
7	2.0	Systolic	137.8 ± 5.5	125.3 ± 5.7	124.3 ± 5.9	121.8 ± 5.6	123.8 ± 6.0	123.7 ± 5.7	122.7 ± 6.0	121.5 ± 6.5
		Diastolic	103.2 ± 2.5	91.5 ± 4.2	91.0 ± 4.4	93.0 ± 4.6	92.0 ± 3.9	94.3 ± 4.7	93.2 ± 5.2	91.3 ± 4.2
8	2.0	Systolic	129.2 ± 6.9	121.5 ± 5.7	120.5 ± 6.3	120.0 ± 6.7	120.2 ± 6.7	119.5 ± 6.1	120.0 ± 6.5	119.0 ± 6.1
		Diastolic	96.7 ± 5.9	87.8 ± 6.5	89.0 ± 6.6	88.2 ± 5.9	86.5 ± 5.5	84.7 ± 5.2	85.5 ± 4.2	84.3 ± 4.6
9	2.0	Systolic	135.2 ± 8.0	133.3 ± 5.5	127.0 ± 6.5	125.0 ± 7.2	128.2 ± 7.0	128.2 ± 5.5	127.2 ± 5.0	122.0 ± 5.3
		Diastolic	100.3 ± 6.1	98.2 ± 4.4	93.5 ± 3.3	90.8 ± 4.0	93.2 ± 5.0	92.0 ± 4.9	90.3 ± 5.1	87.3 ± 3.8
11	2.0	Systolic	128.5 ± 5.2	117.0 ± 3.8	112.8 ± 5.1	113.0 ± 5.6	112.5 ± 5.9	113.8 ± 5.8	116.3 ± 6.0	118.2 ± 6.4
		Diastolic	91.7 ± 4.0	84.0 ± 4.4	80.7 ± 5.3	79.7 ± 5.6	79.8 ± 5.9	82.0 ± 5.9	82.3 ± 5.7	81.7 ± 6.1
12	2.0	Systolic	139.0	134.7	134.5	132.0	131.0	129.0	130.0	128. 0

			± 2.3	± 2.4	± 2.2	± 3.1	± 3.3	± 3.7	± 3.9	± 3.7
		Diastolic	104.2 ± 1.2	98.2 ± 1.9	99.5 ± 2.1	97.8 ± 1.8	96.7 ± 2.1	97.0 ± 2.0	96.8 ± 2.4	97.3 ± 2.0
13	2.0	Systolic	130.7 ± 4.6	102.8 ± 3.4****	107.7 ± 2.5****	109.3 ± 2.7***	112.7 ± 3.8**	113.3 ± 3.0*	117.2 ± 4.5*	118.0 ± 3.3*
		Diastolic	98.0 ± 3.2	61.2 ± 2.5****	70.8 ± 1.9****	77.3 ± 2.5***	82.2 ± 3.3*	82.8 ± 3.0*	82.2 ± 3.2*	83.7 ± 3.2*
		Systolic	132.5 ± 4.0	132.3 ± 3.9	132.0 ± 4.2	129.3 ± 4.4	127.7 ± 3.8	125.8 ± 4.6	124.5 ± 4.5	124.3 ± 4.1
14	2.0	Diastolic	100.8 ± 4.6	100.3 ± 4.3	100.7 ± 4.6	96.0 ± 4.0	96.0 ± 5.1	97.3 ± 4.7	94.3 ± 4.7	92.0 ± 4.7
		Systolic	127.3 ± 2.9	111.3 ± 3.6***	109.5 ± 3.9***	110.2 ± 4.7***	112.2 ± 3.7**	112.7 ± 3.2**	114.0 ± 3.2**	115.0 ± 2.4**
Urapidil	1.0	Diastolic	93.0 ± 2.7	77.5 ± 4.9***	75.5 ± 3.9***	76.0 ± 3.8***	78.8 ± 3.5**	79.2 ± 2.9**	80.8 ± 2.8*	81.2 ± 2.3*

Data represent the mean ± SEM (n = 6 rats per each group). Statistical analysis: two-way ANOVA and Sidak's multiple comparisons test. Statistically significant: *p < 0.05, **p < 0.02, ***p < 0.01, *****p< 0.001 vs. control group (vehicle treatment).