SUPPORTING INFORMATION

Tryptamine-based derivatives as Transient Receptor Potential Melastatin type-8 (TRPM8) channels modulators

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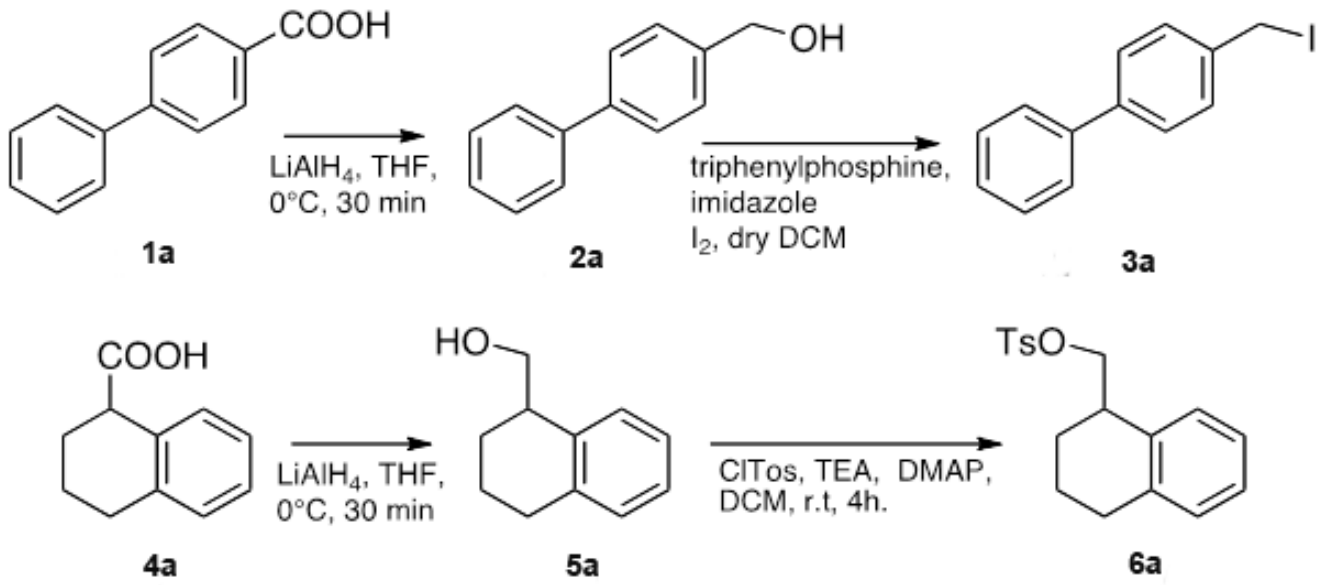


Scheme S1: Synthesis of intermediates 4-phenylbenzyl iodide (**3a**) and 1,2,3,4-tetrahydronaphthalen-4-yl)methyl 4-methylbenzenesulfonate (**6a**)

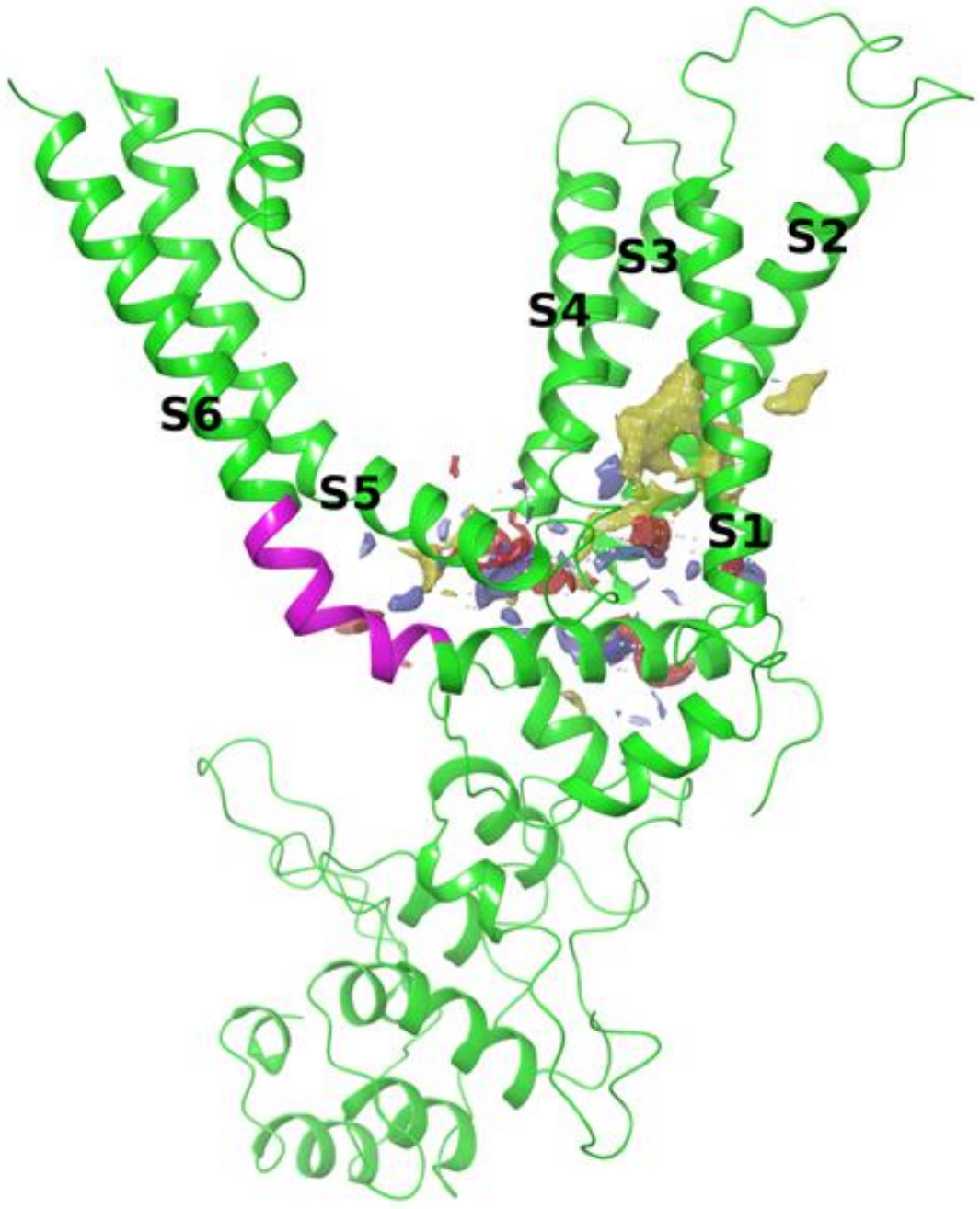


Figure S1: Sitemap graphical output for BP1. Hydrophobic surfaces are depicted in yellow, HB donors locations as blue surfaces, HB acceptors locations as red surfaces. The 980-990 region is highlighed in magenta

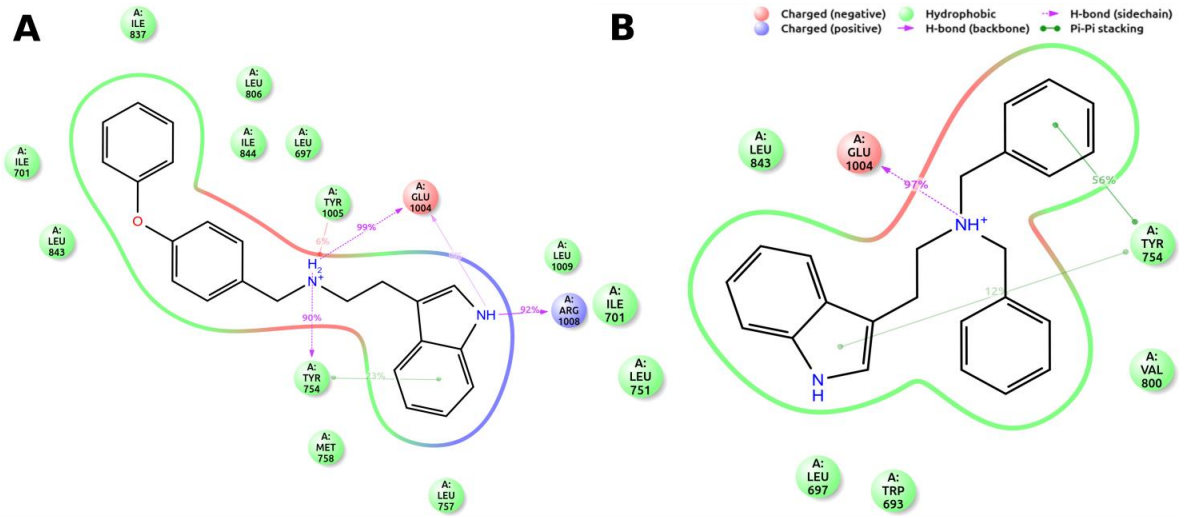


Figure S2 Protein-Ligand contacts for 21 (panel A) and 12 (panel B), recorded during 12 ns long MD trajectories.

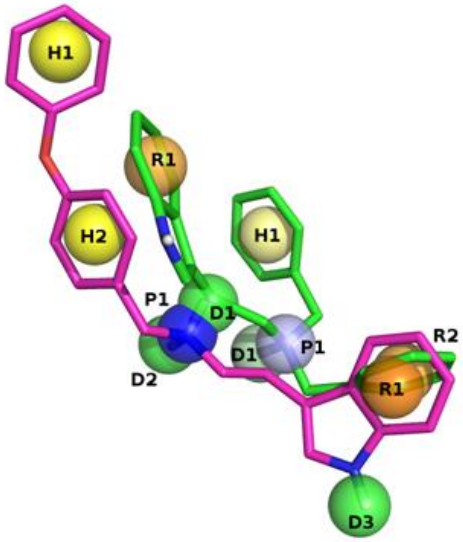
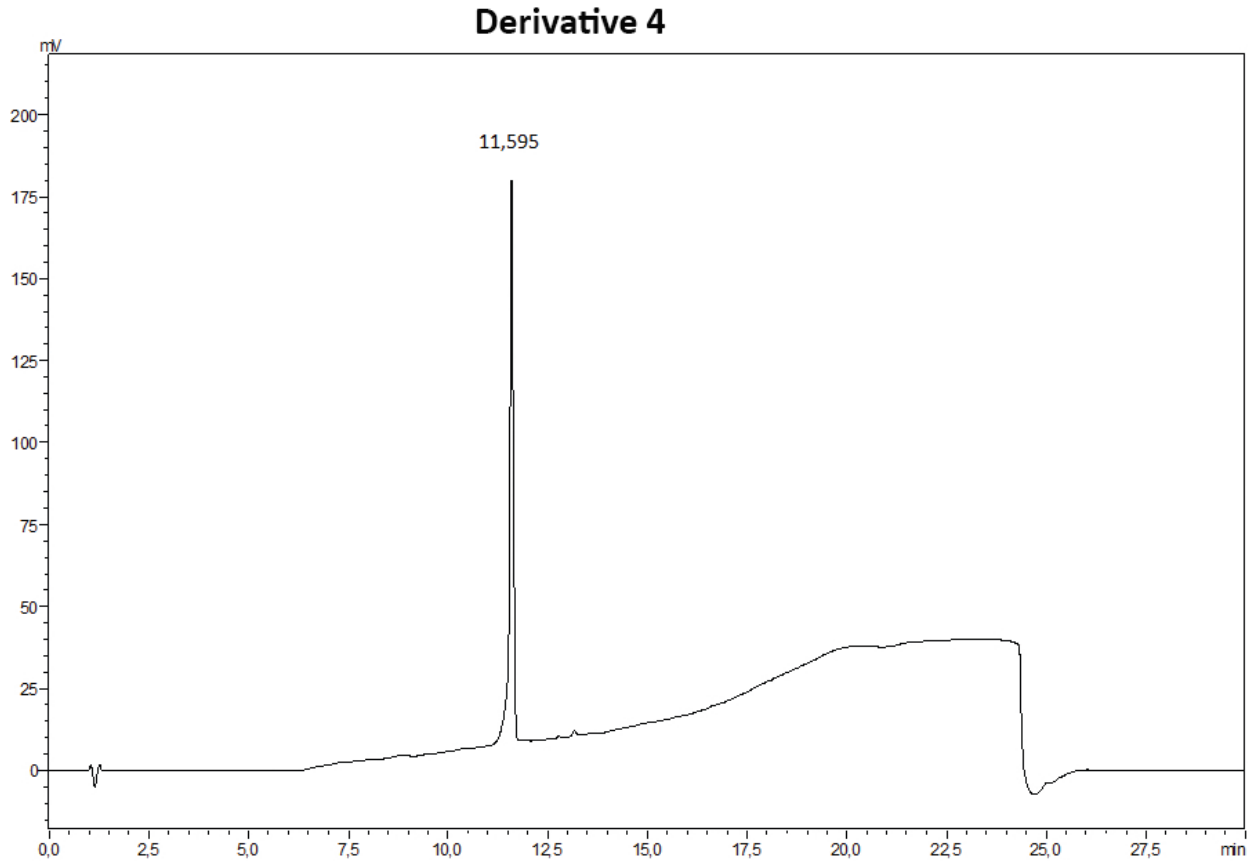


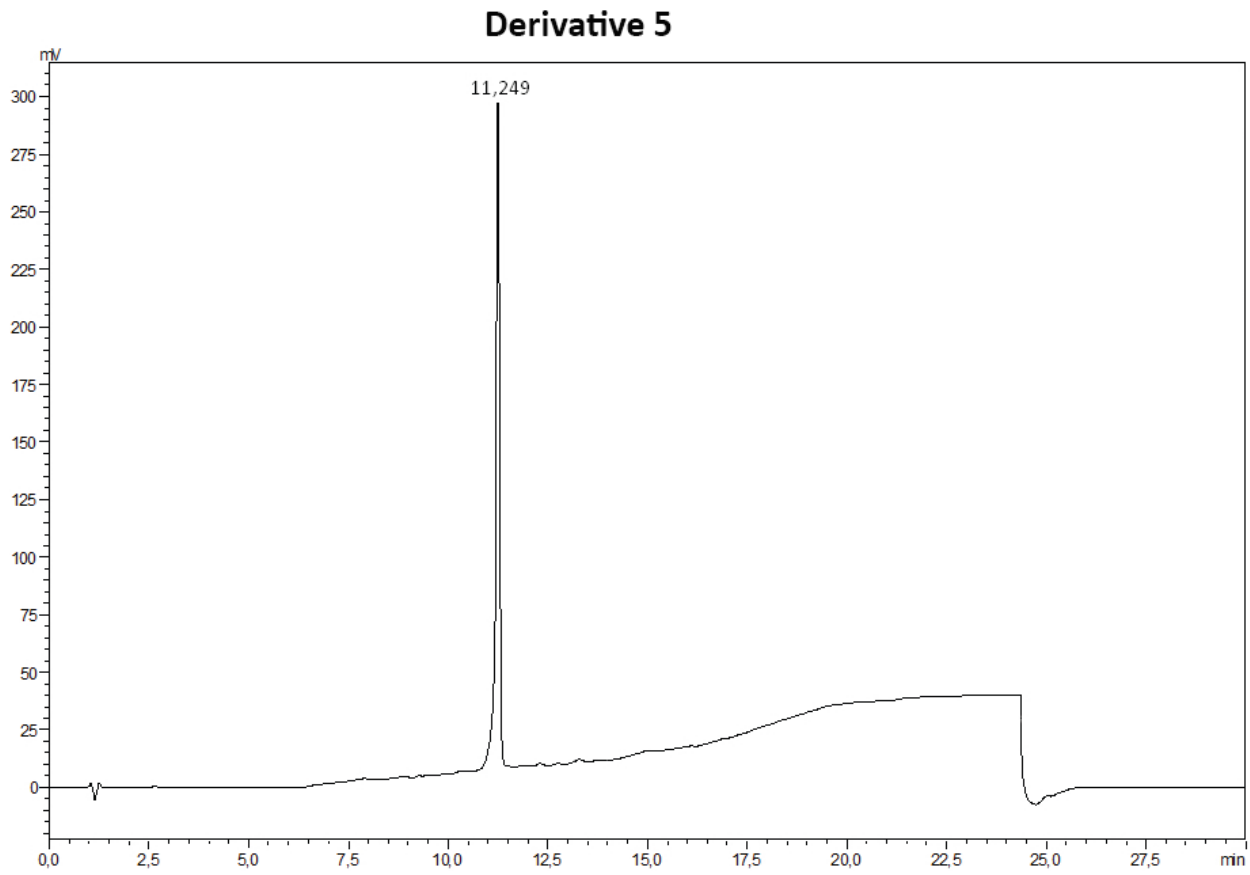
Figure S3: Pharmacophore models for tryptamine-based TRPM8 agonists and antagonists. Chemical features are depicted as spheres and color-coded as follows: yellow, H = hydrophobic; blue, P = positive charge; green, D = HB donor; orange, R= aromatic ring. Chemical features of the antagonist model are depicted in paler colors. **21** (magenta sticks) and **12** (green sticks) are represented as references.

Comp.	Agonist Model							Antagonist Model				
	H1	H2	R1	P1	D1	D2	D3	H1	R1	R2	P1	D1
	I^{701}	I^{844}	Y^{754} M^{758}	E^{1004}	Y^{754}	E^{1004}	R^{1008}	V^{800}	Y^{754}	R^{1008} Y^{754}	E^{1004}	E^{1004}
4	O	X	X	X	X	X			X	X	X	X
5		X	X	X	X	X	\		X	X	X	X
6	\	X	O	X	X	X			X	X	X	X
7		X	X	X	X	X			O	O	O	O
12			X	X		X	X	X	X	X	X	X
15		X	X	X	X	X	X		X	X	X	X
16		X	X	X	X	X	X		X	O	X	X
18		X	X	X	X	X	X		X	X	X	X
21	X	X	X	X	X	X	X		X	X	X	X
22s	O		O	X	O			X		O	X	X
22r	O		O	X		X	X	X	X	X	X	X

Table S1: Fittings of the tryptamine-based agonists and antagonists on the respective pharmacophore models. (X=good fit, O=partial fit, /=misfit, e.g. polar group on a hydrophobic location)

2. Qualitative HPLC runs for derivatives 4-12 and 14- 22

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300
275
250
225
200
175
150
125
100
75
50
25
0
0,0
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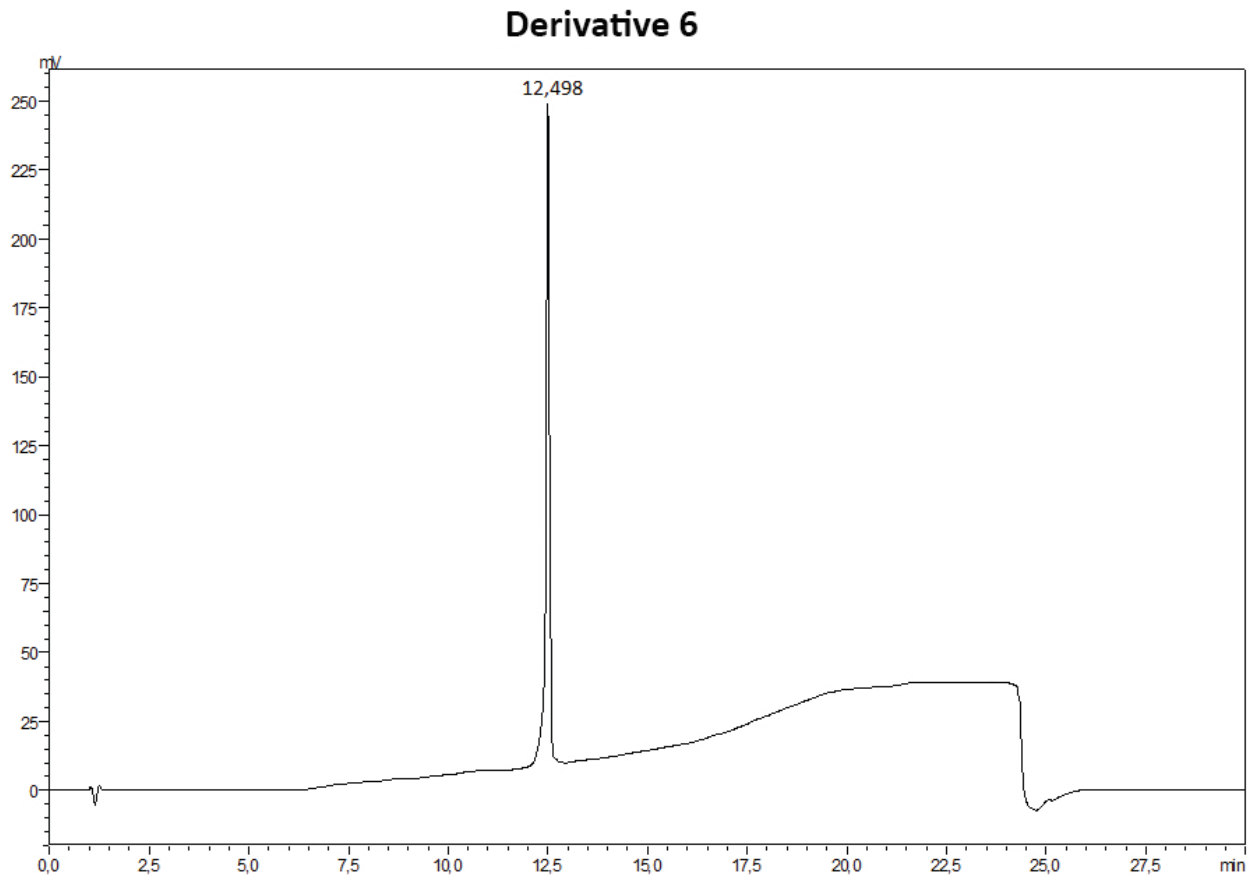
7,5
10,0
12,5
15,0
17,5
20,0
22,5
25,0
27,5
min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150
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100
75
50
25
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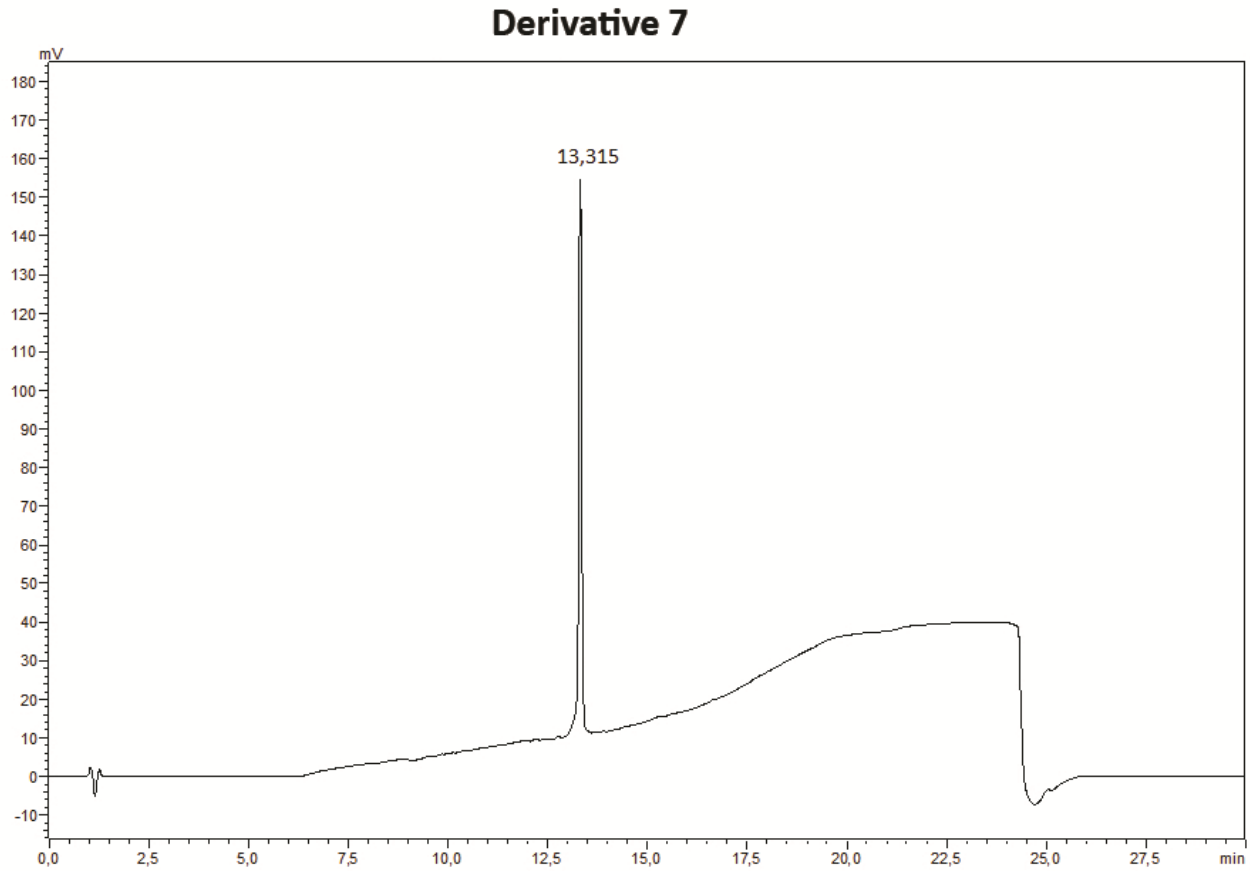
17,5
20,0
22,5
25,0
27,5
min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170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13,315
0,0
2,5
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7,5
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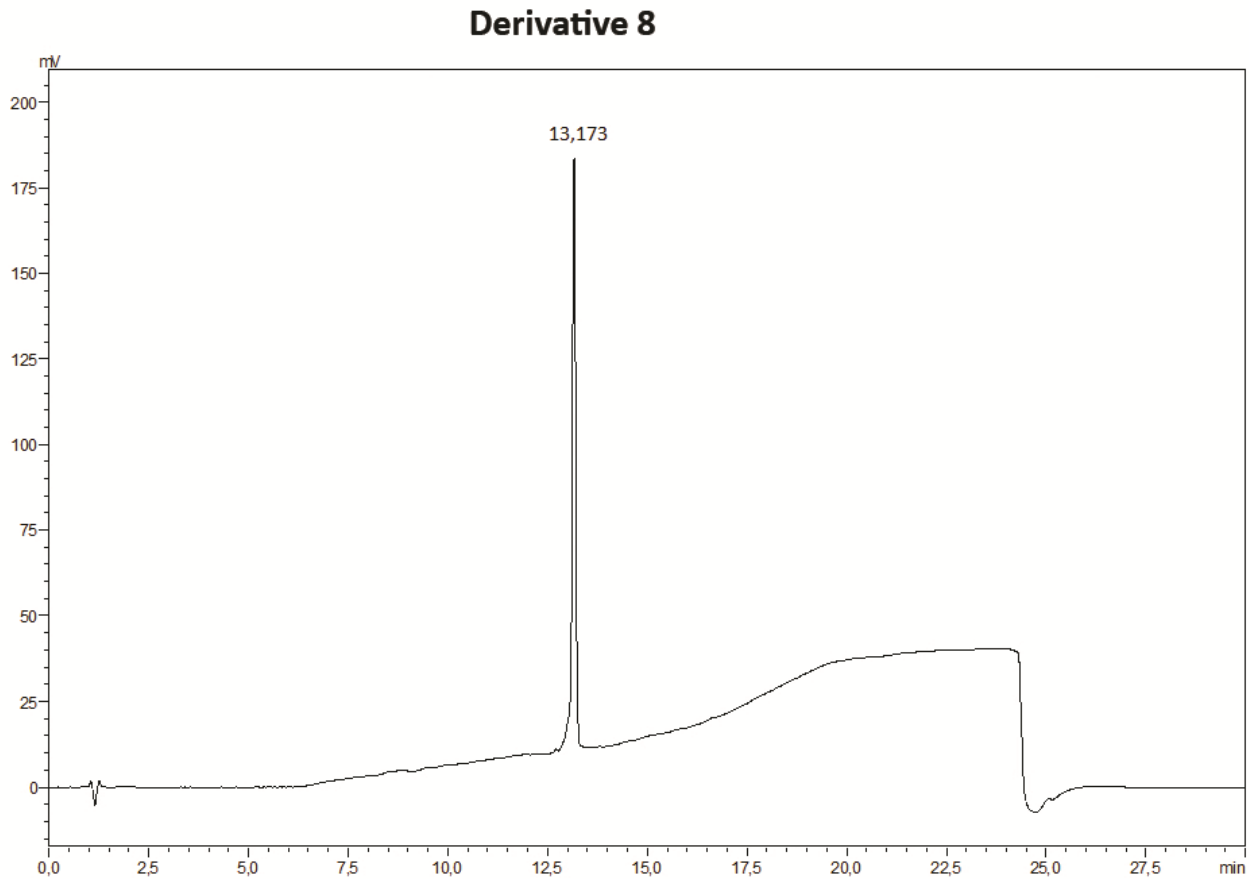
12,5
15,0
17,5
20,0
22,5
25,0
27,5
min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150
125
100
75
50
25
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13,173
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20,0
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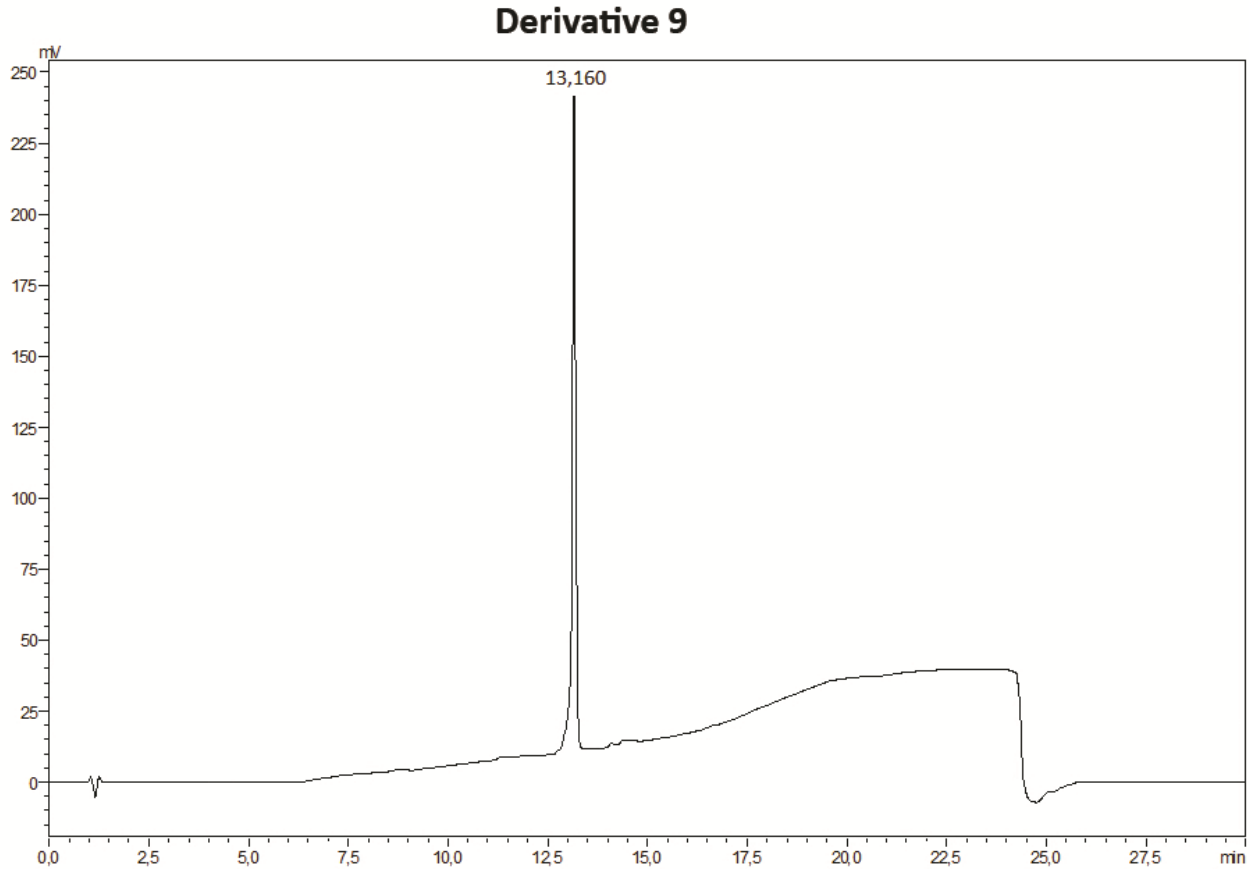
25,0
27,5
min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225
200
175
150
125
100
75
50
25
0
13,160
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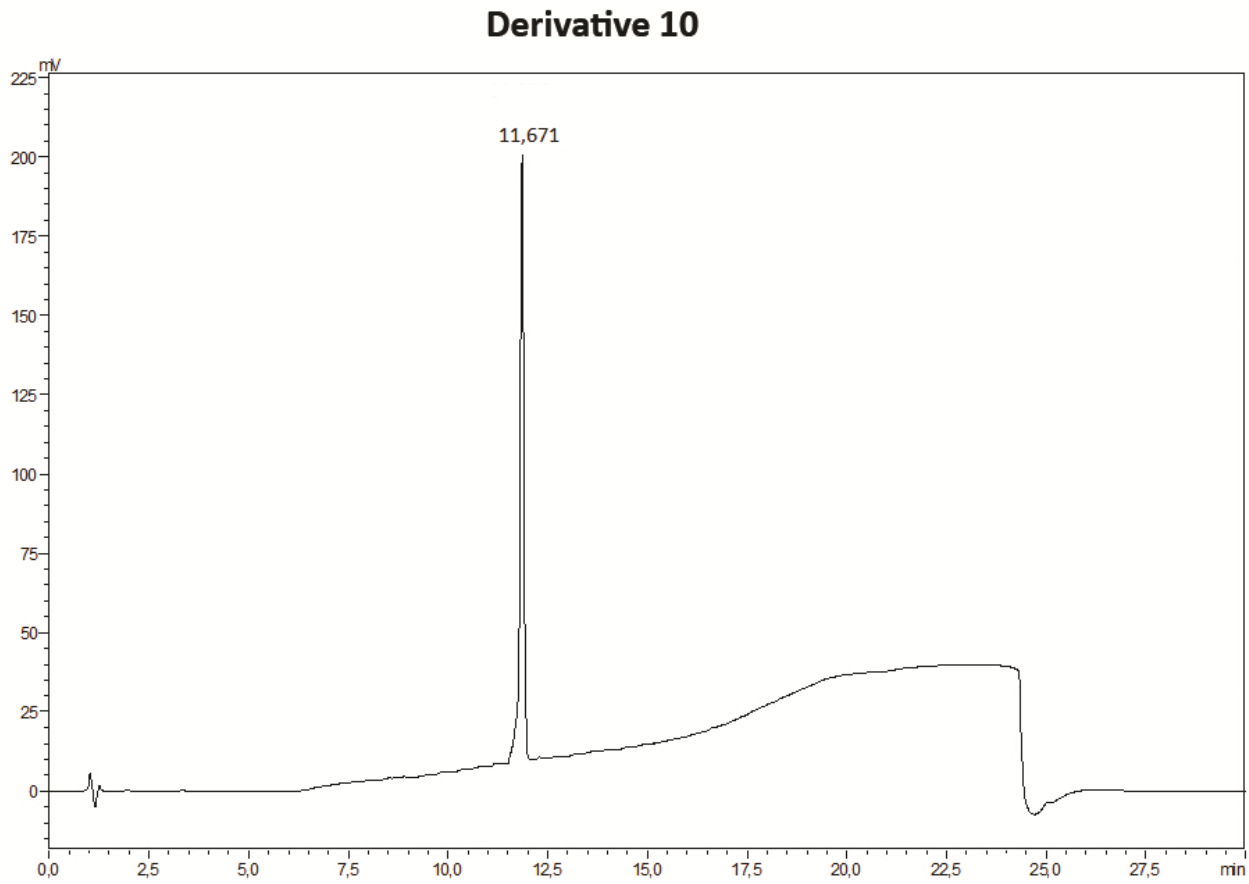
25,0
27,5
min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200
175
150
125
100
75
50
25
0
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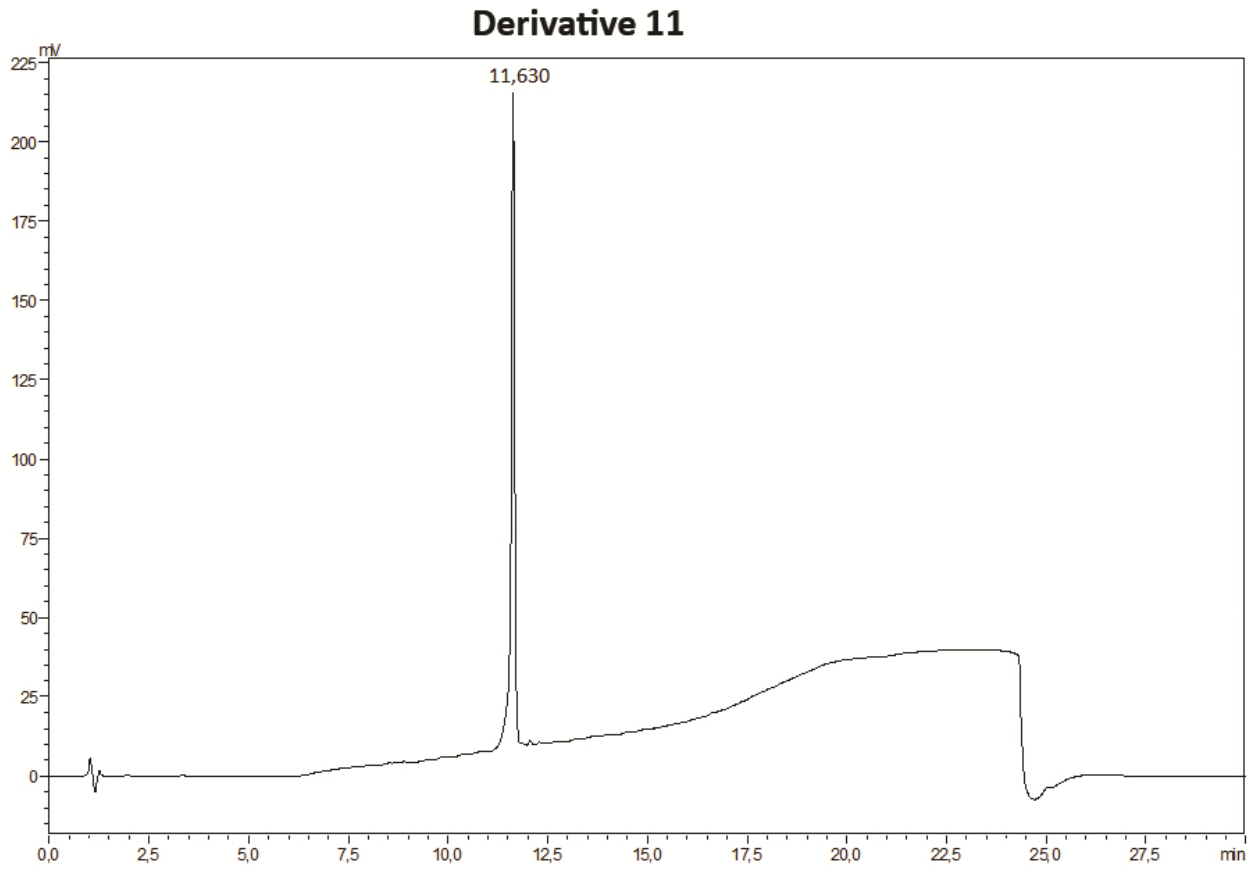
25,0
27,5
min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200
175
150
125
100
75
50
25
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11,630
0,0
2,5
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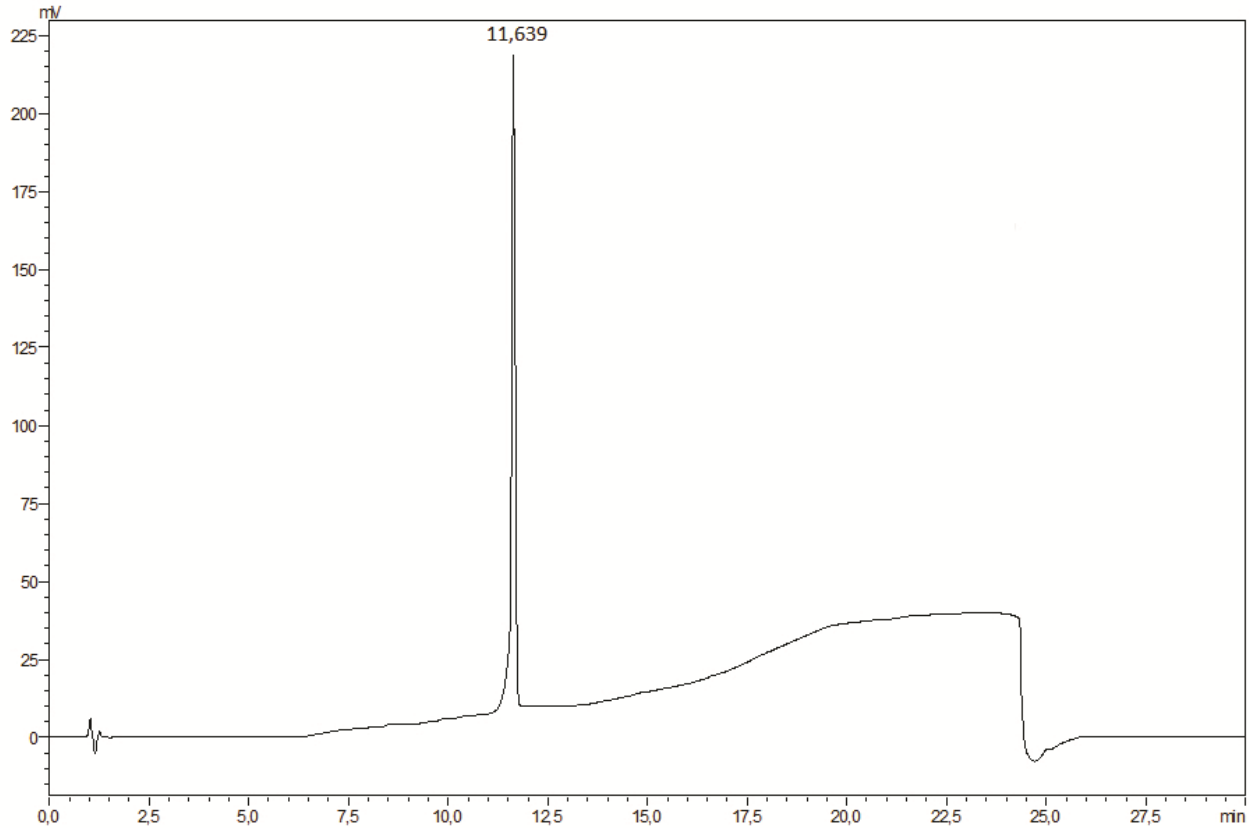
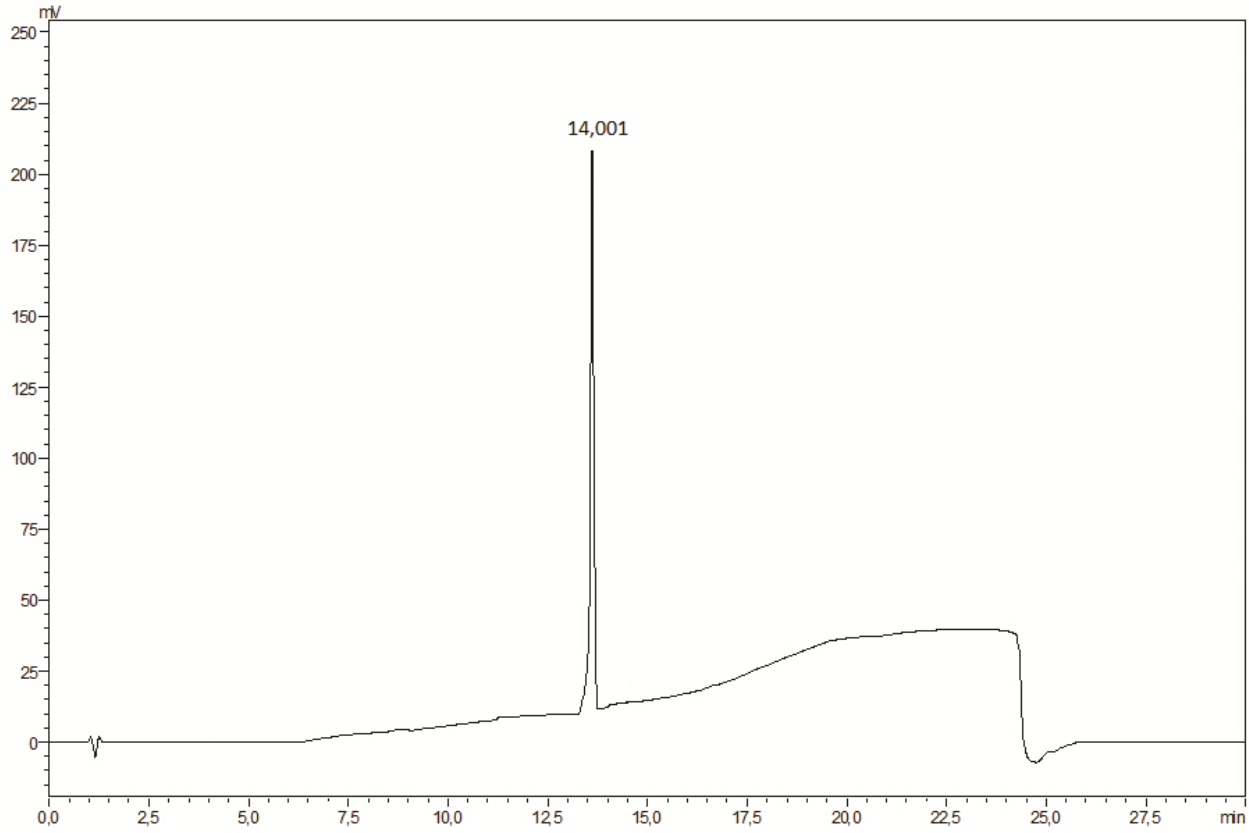
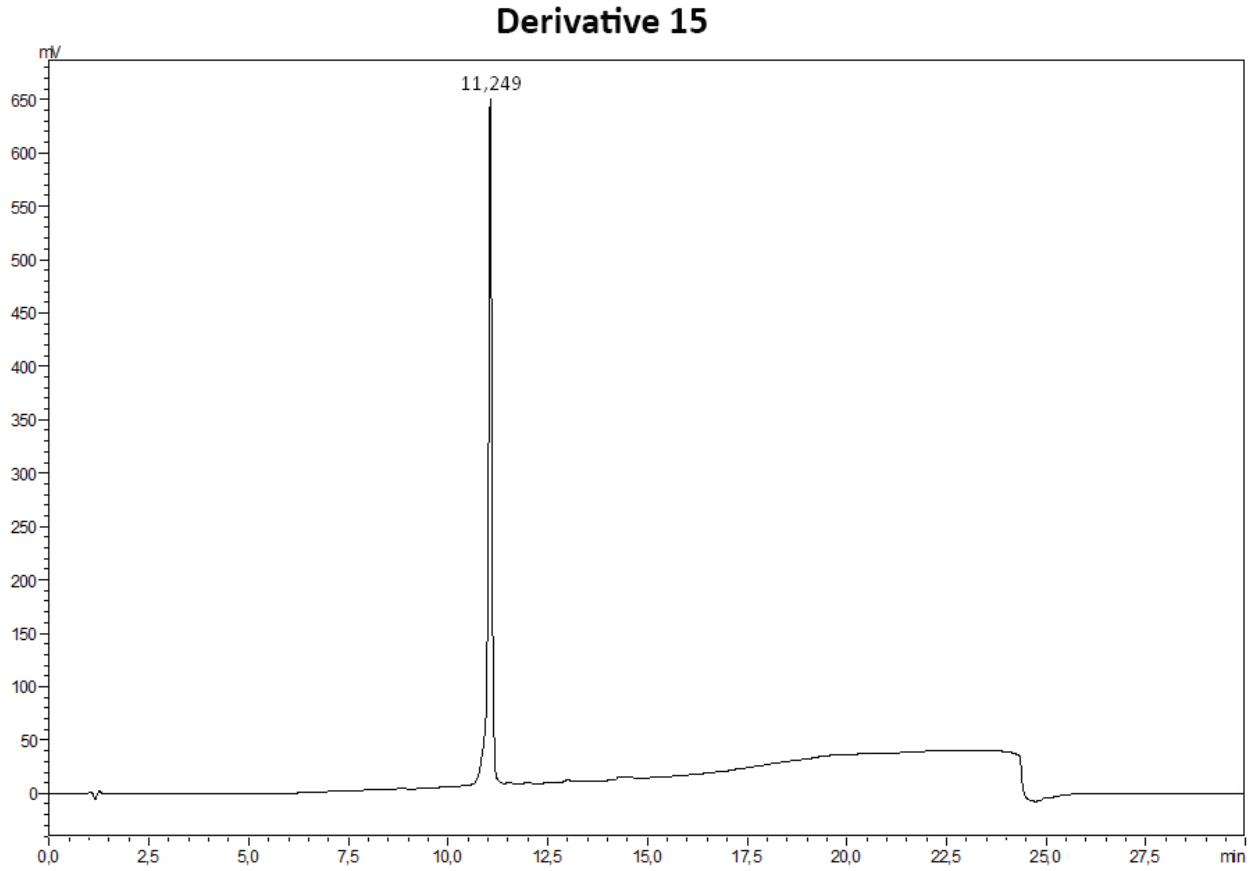
10,0
12,5
15,0
17,5
20,0
22,5
25,0
27,5
min

Derivative 12



Derivative 14




Derivative 15
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650
600
550
500
450
400
350
300
250
200
150
100
50
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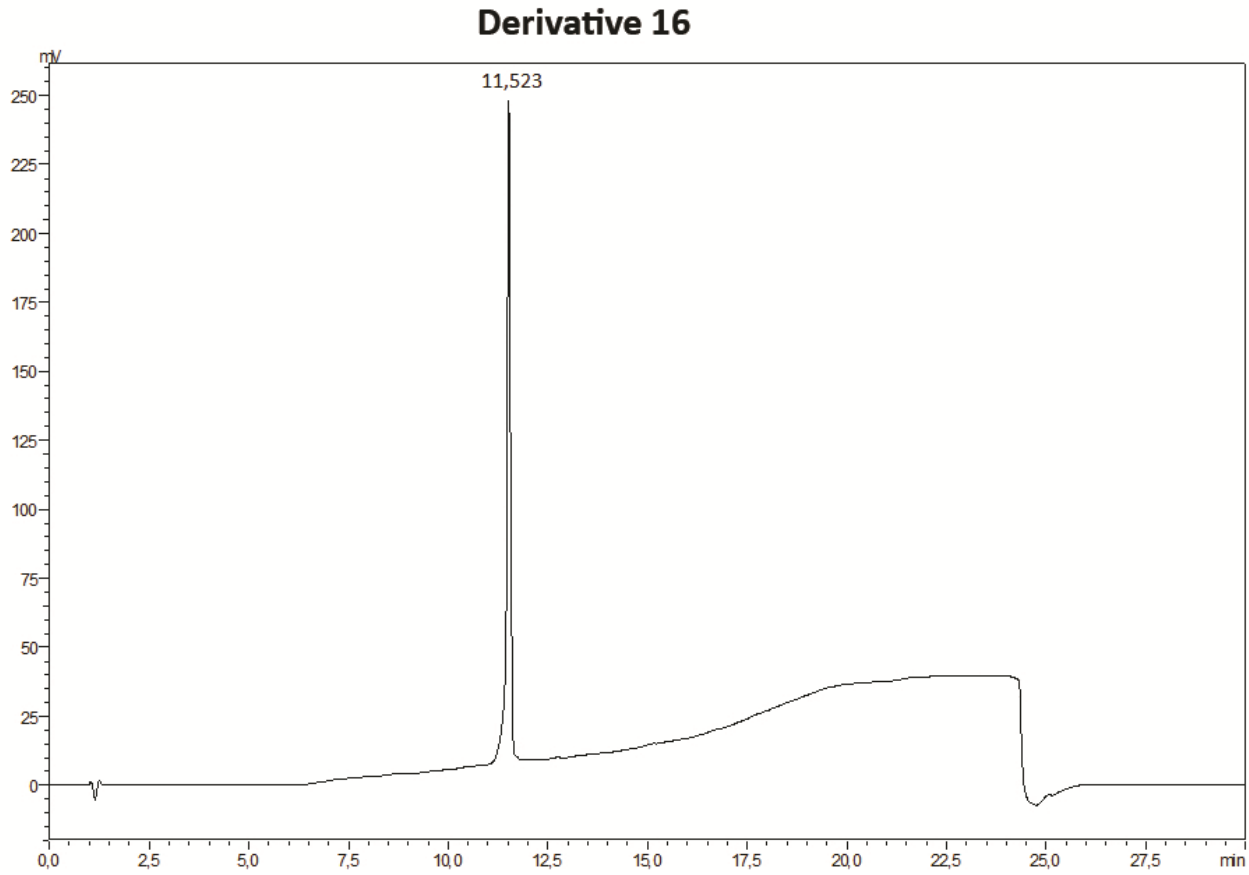
15,0
17,5
20,0
22,5
25,0
27,5
min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150
125
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75
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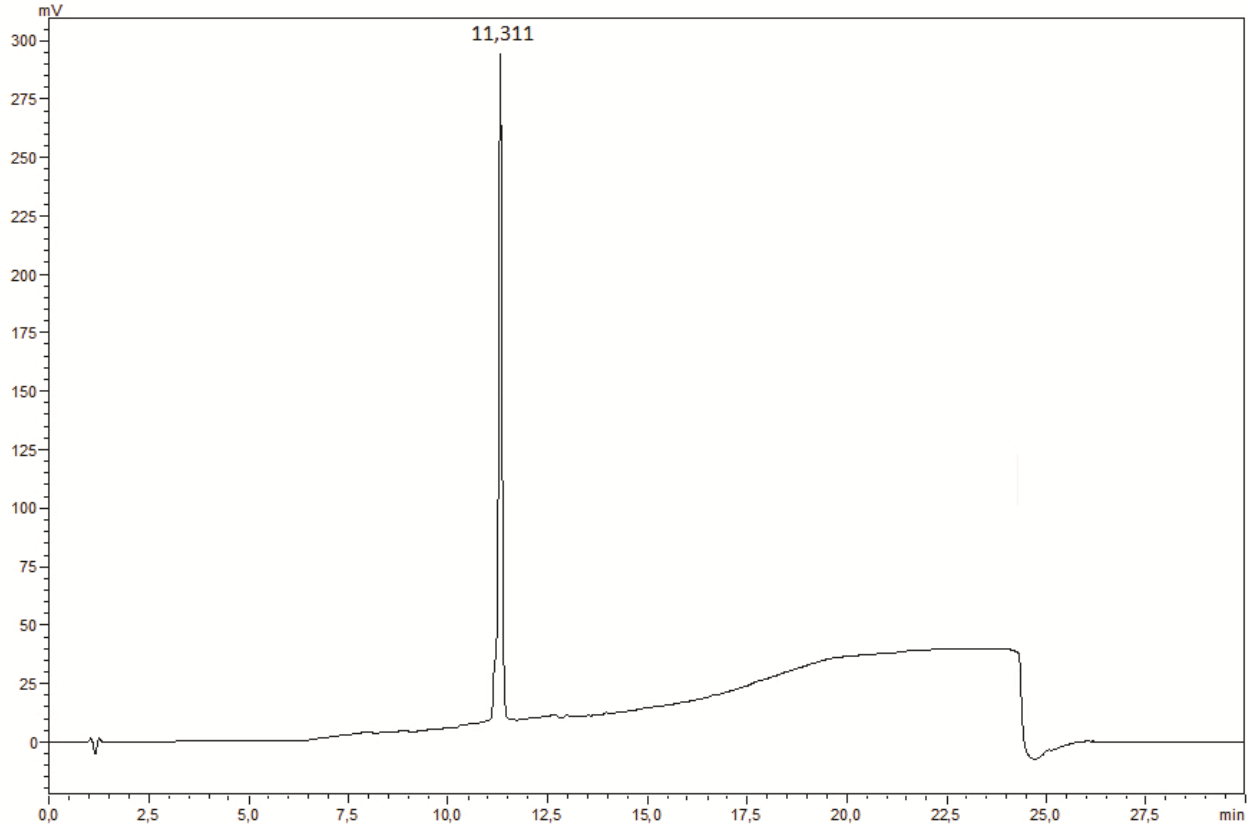
27,5
min

Derivative 17



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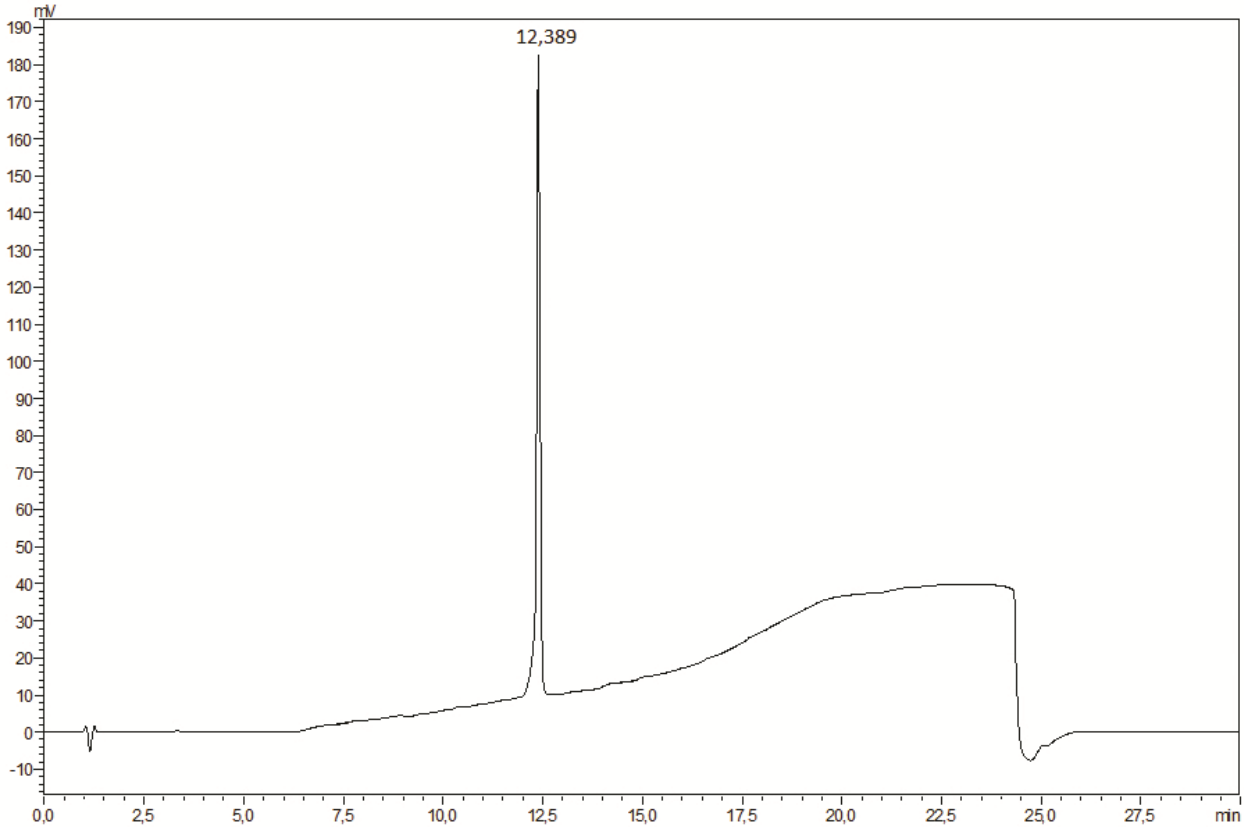
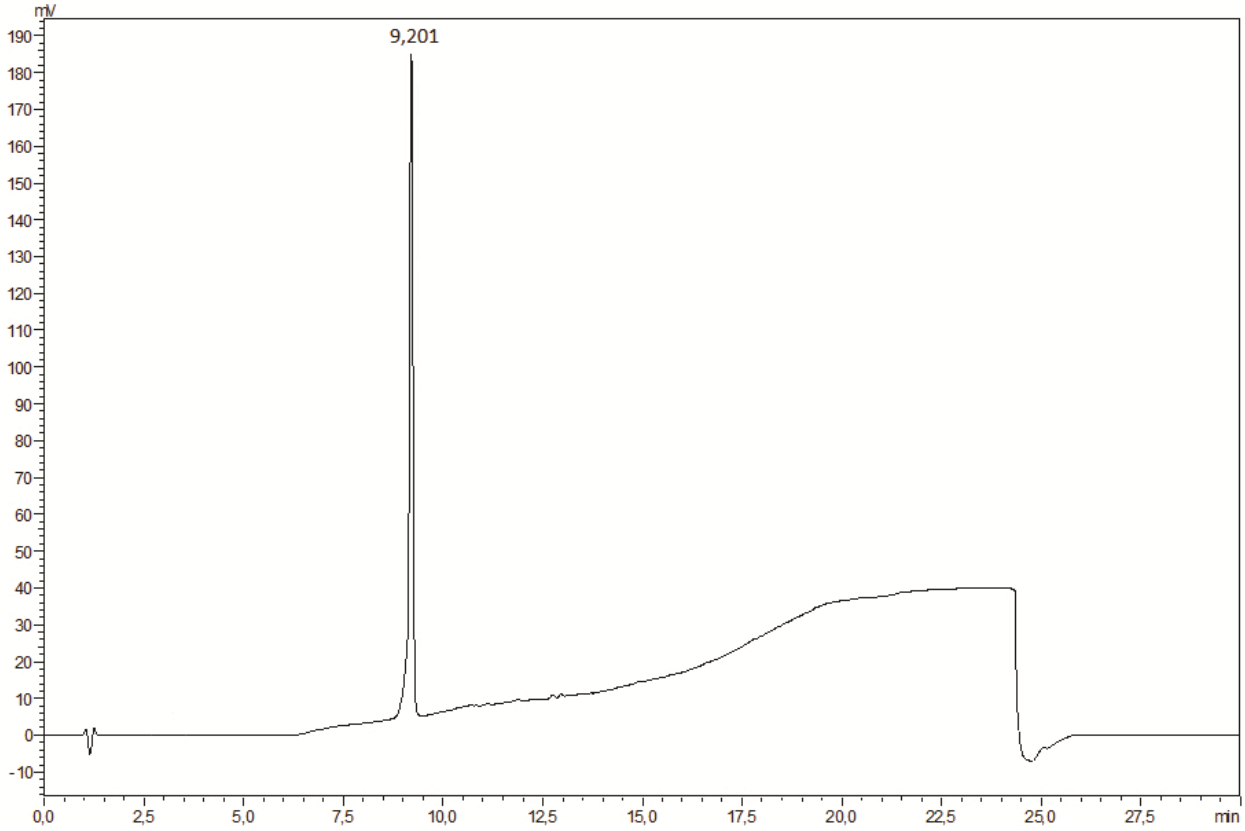
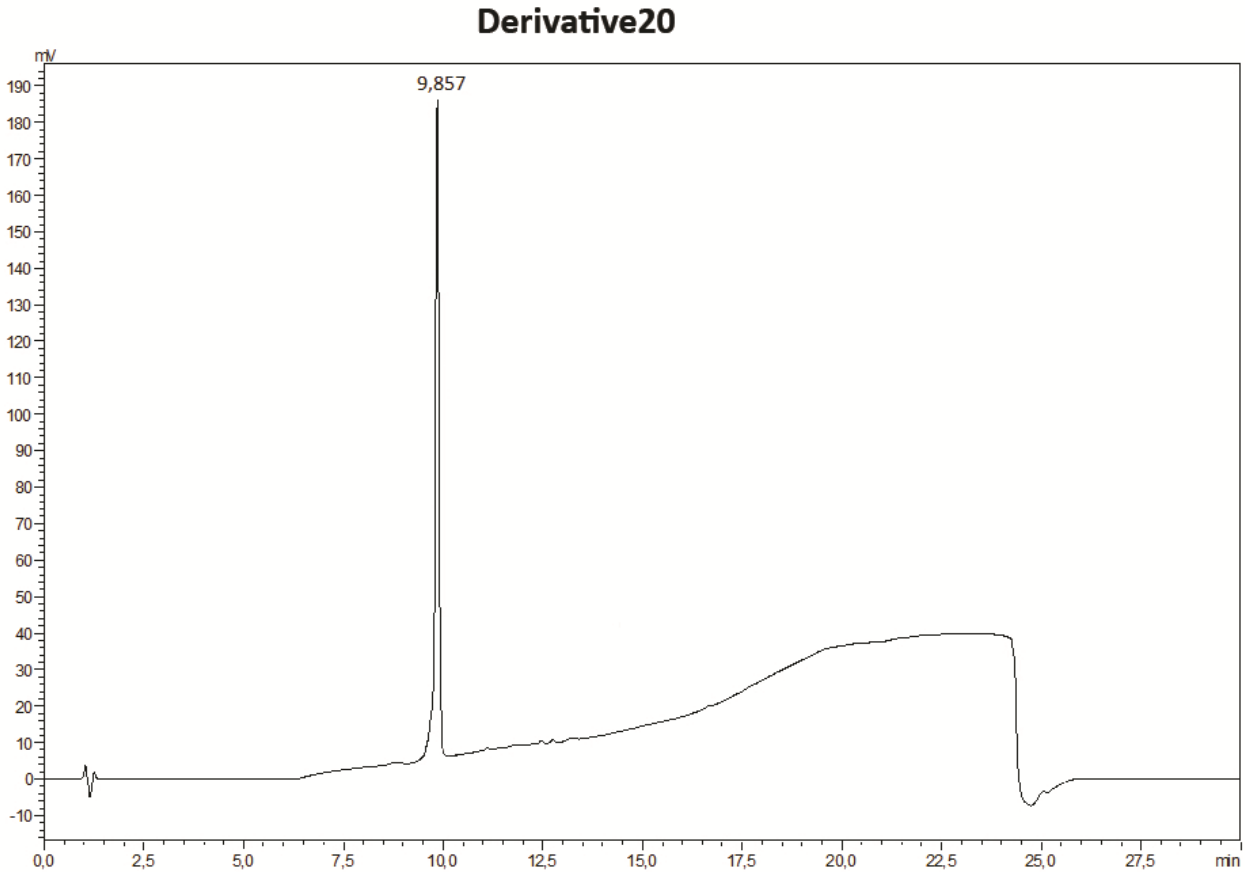


Derivative 19




Derivative20
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40
30
20
10
0
-10
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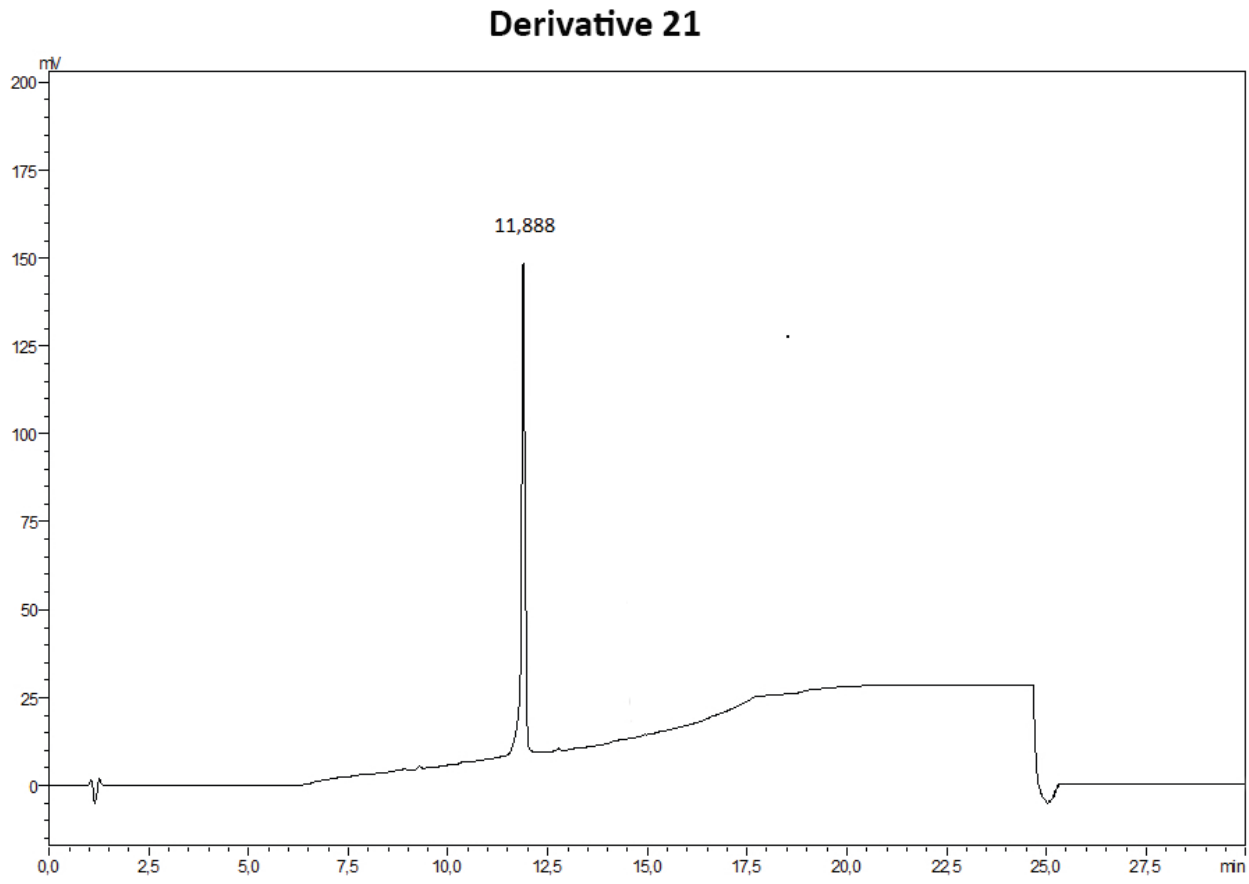
27,5
min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10,0
12,5
15,0
17,5
20,0
22,5
25,0
27,5
min

Derivative 22