Supplementary Material

Design, synthesis and biological evaluation of biscarbamates as potential selective butyrylcholinesetrase inhibitors for the treatment of Alzheimer`s disease

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Biscarbamates were synthesized starting from 3,5-dihroxyacethophenone using slightly modified protocol as previously described in the Wu et all, 2017. For the synthesis two methods were applied: Method 1 without hydrochloride formation and Method 2 which includs hydrochloride formation.

Method 1: A mixture of 3,5-dihydroxyacetophenone (2 g, 16 mmol), triethylamine (4.5 mL) and 4-dimethylamino pyridine (0.25 g, 2 mmol) with R-carbamoyl chloride (3.8 g, 32 mmol) in 1,2- dichloroethane (40 mL) were stirred at 60 ˚C in an argon atmosphere for 24 h. The reaction mixture was cooled down to room temperature, dichloromethane (50 mL) was added, and the layers separated. The organic phase was washed twice with water and with 1M hydrochloric acid (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the product A, which was used in the next step without further purification.

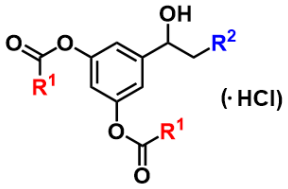
$CuBr_2$ (4.6 g; 20 mmol) was mixed with A (10 mmol) in an argon atmosphere in ethyl acetate (40 mL) and chloroform (40 mL) and stirred at 65 ˚C for 4.5 h. After cooling down, the mixture was filtered and washed with ethyl-acetate. Organic phase was washed twice with water, dried over Na_2SO_4 and filtered. The filtrate was evaporated and the crude product purified over a flash silica gel column as the stationary phase and dichloromethane /methanol mixtures as eluent system and concentrated to give intermediate B.

The compound B (1.25 mmol) was dissolved in methanol at room temperature and $NaBH_4$ (0.12 g, 3.12 mmol) was added to the solution. Dichloromethane (10 mL) was added to the suspension and the mixture was stirred for 2.5 hours at room temperature. The mixture was concentrated, redissolved in dichloromethane, and washed with the saturated solution of ammonium chloride. The organic phase was dried over Na_2SO_4, filtered and concentrated to produce oil C. The oil C was used in the next step of synthesis without further purification.

The oil C (1 mmol) was mixed with amine (2 mmol) in isopropanol. The mixture was stirred for 24 hours at 60-80˚C. After cooling down to room temperature, the resulting solution was evaporated to dryness. The oil product D was purified over a flash silica gel column chromatography (DCM:MeOH= 90:1 to 9:1) and concentrated to give a pure product.

Method 2: The oil D was dissolved in isopropanol and the pH of the solution was adjusted to 1 using hydrochloric acid in isopropanol. The mixture was concentrated

until it precipitated to produce final product E. The product E was purified over a flash silica gel column chromatography (DCM:MeOH= 90:1 to 9:1) and concentrated to give a pure product.



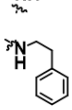
Compound	R¹	R²	Compound	R¹	R²	Compound	R¹	R²	Compound	R¹	R²	Compound	R¹	R²
1			4			8			12			15		
2			5			9			13			16		
3			6			10			14			17		
			7			11						18		

Figure S1. Structures of synthesized biscarbamates

Table S1. Decarbamylation rate constants (k_{decarb}) for BChE and AChE.

Compound	k_{decarb} [h^{-1}]	
	BChE	AChE
1	0.162 ± 0.006	0.174 ± 0.018
2	0.132 ± 0.012	0.180±0.018
3	0.150 ± 0.012	0.138 ± 0.012
4	0.0960 ± 0.006	0.180 ± 0.018
5	0.192 ± 0.018	0.174 ± 0.012
6	0.0960 ± 0.0060	0.150 ± 0.012
7	0.126 ± 0.006	0.150 ± 0.012
8	0.0720 ±0.006	0.216 ± 0.018
9	0.0720 ± 0.006	0.180 ± 0.018
10	0.114 ± 0.006	0.222 ± 0.018
11	0.126 ± 0.018	0.204 ± 0.012
12	0.174 ± 0.006	0.204 ± 0.06
13	0.108 ± 0.006	0.180 ±0.012
14	0.102 ± 0.006	0.174 ± 0.024
15	0.162 ± 0.012	0.210 ± 0.018
16	0.126 ± 0.018	0.168 ± 0.012
17	0.168 ± 0.012	0.156 ± 0.012
18	0.120 ± 0.012	0.162 ± 0.018

Table S2. Physiochemical properties (molecular weight, MW; lipophilicity coefficient, logP; number of hydrogen bond donors, HBD, and acceptors, HBA; rotable bonds, RB; polar surface area, PSA) of biscarbamates

Compound	MW/100	logP	HBD	HBA	RB	PSA/10
1	4.299	2.143	2	4	8	9.134
2	4.159	1.577	1	4	7	8.255
3	4.820	2.435	2	4	8	9.134
4	4.580	2.856	2	4	10	9.134
5	4.460	2.633	2	4	11	9.134
6	5.107	3.148	2	4	10	9.134
7	4.800	3.070	2	4	12	9.134
8	4.740	3.347	2	4	13	9.134
9	5.381	3.862	2	4	12	9.134
10	5.081	3.912	2	4	13	9.134
11	5.081	3.784	2	4	14	9.134
12	4,820	2.954	2	4	8	9.134
13	4.701	2.731	2	4	9	9.134
14	5.341	3.246	2	4	8	9.134
15	5.101	3.843	2	4	8	9.134
16	4.961	3.278	1	4	7	8.255
17	5.622	4.136	2	4	8	9.134
18	5.541	5.459	2	6	10	9.134
Bambuterol	4.039	1.397	2	4	8	9.134
Rivastigmine	2.500	2.400	0	2	5	3.270
Recommended values	5	5	5	10	10	9

1

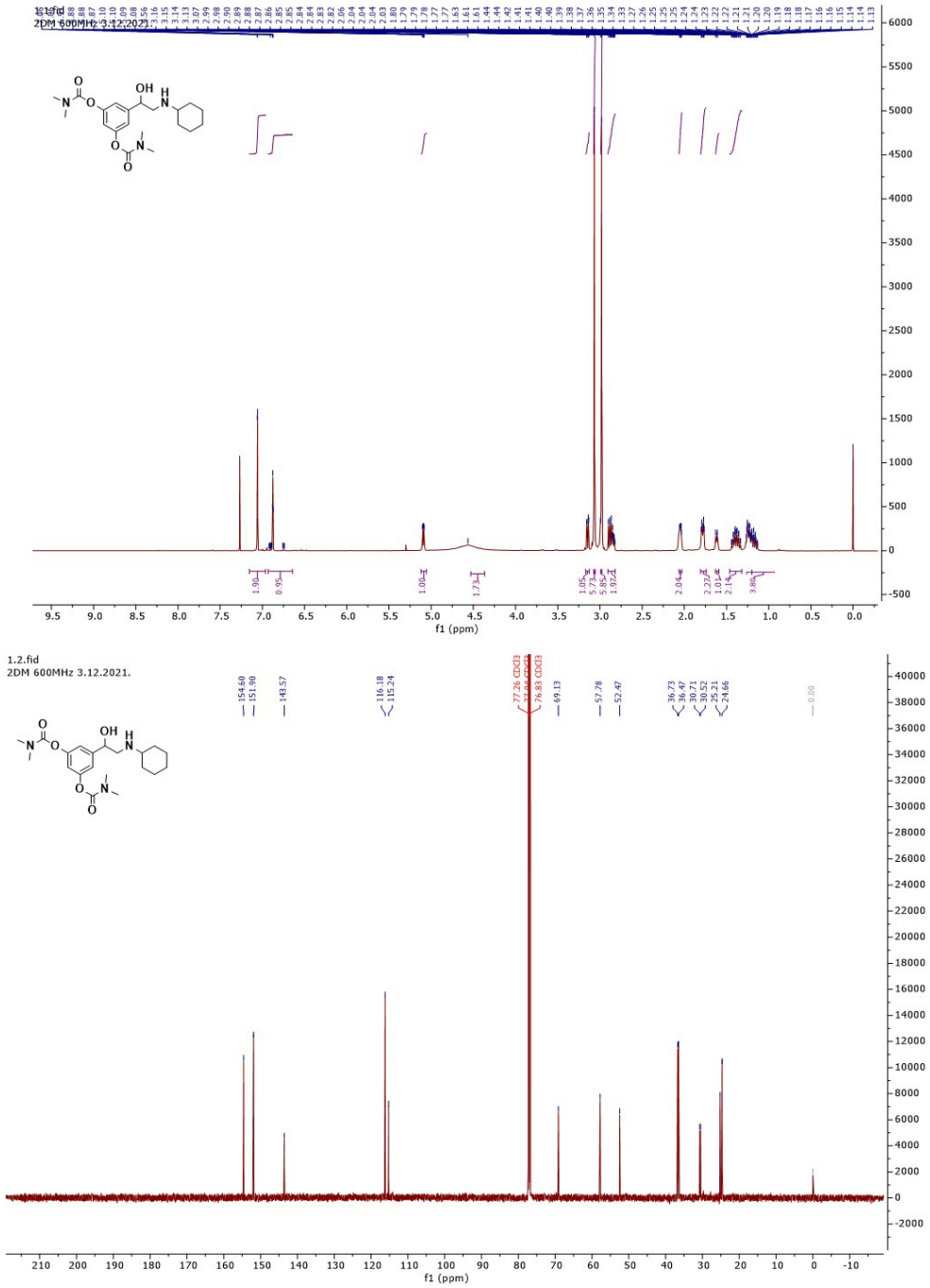


Figure S2. ^{1}H and ^{13}C spectra of the compound **1**

2

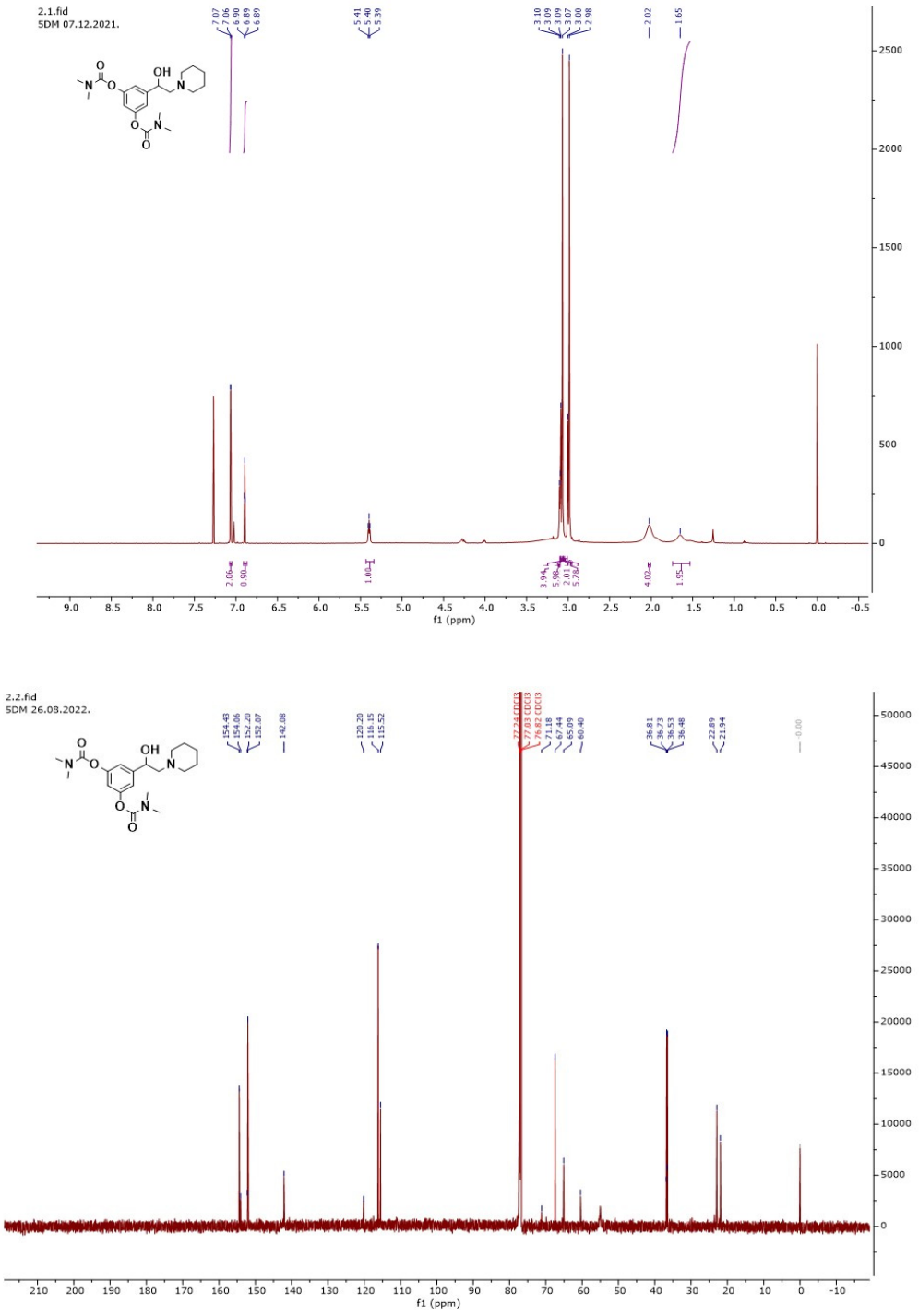


Figure S3. ^{1}H and ^{13}C spectra of the compound **2**

3

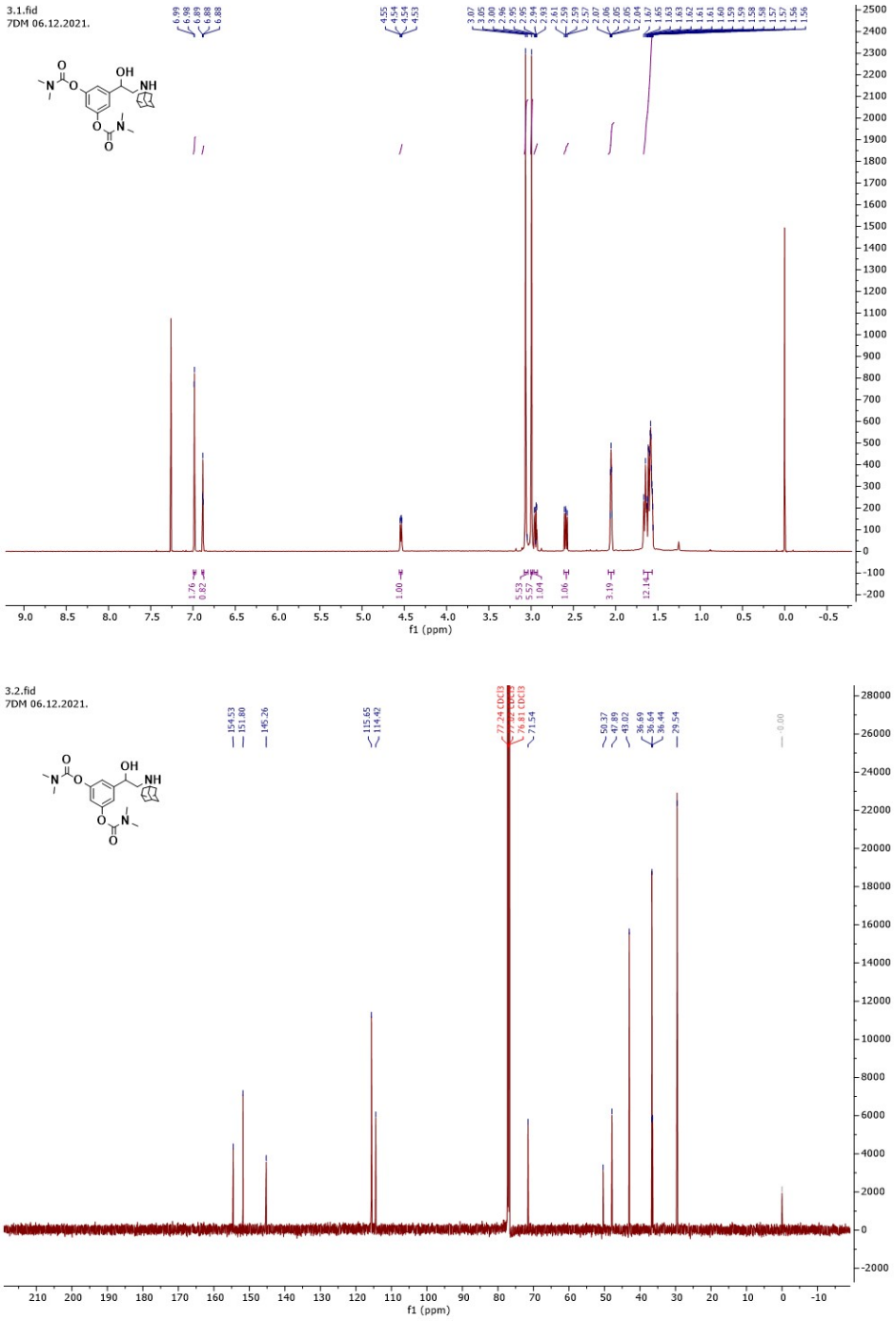


Figure S4. ^{1}H and ^{13}C spectra of the compound **3**

4

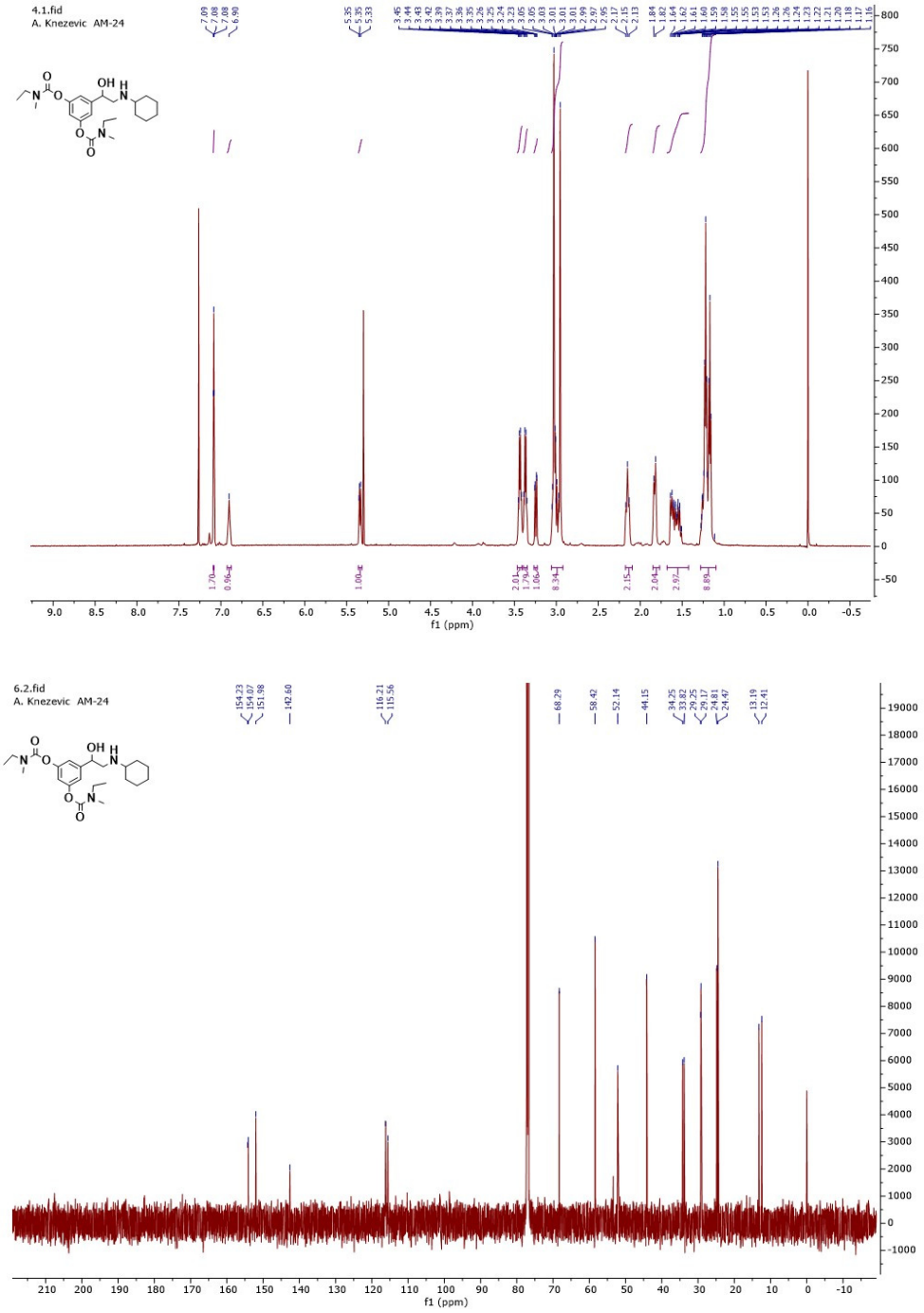


Figure S5. ^{1}H and ^{13}C spectra of the compound **4**

5

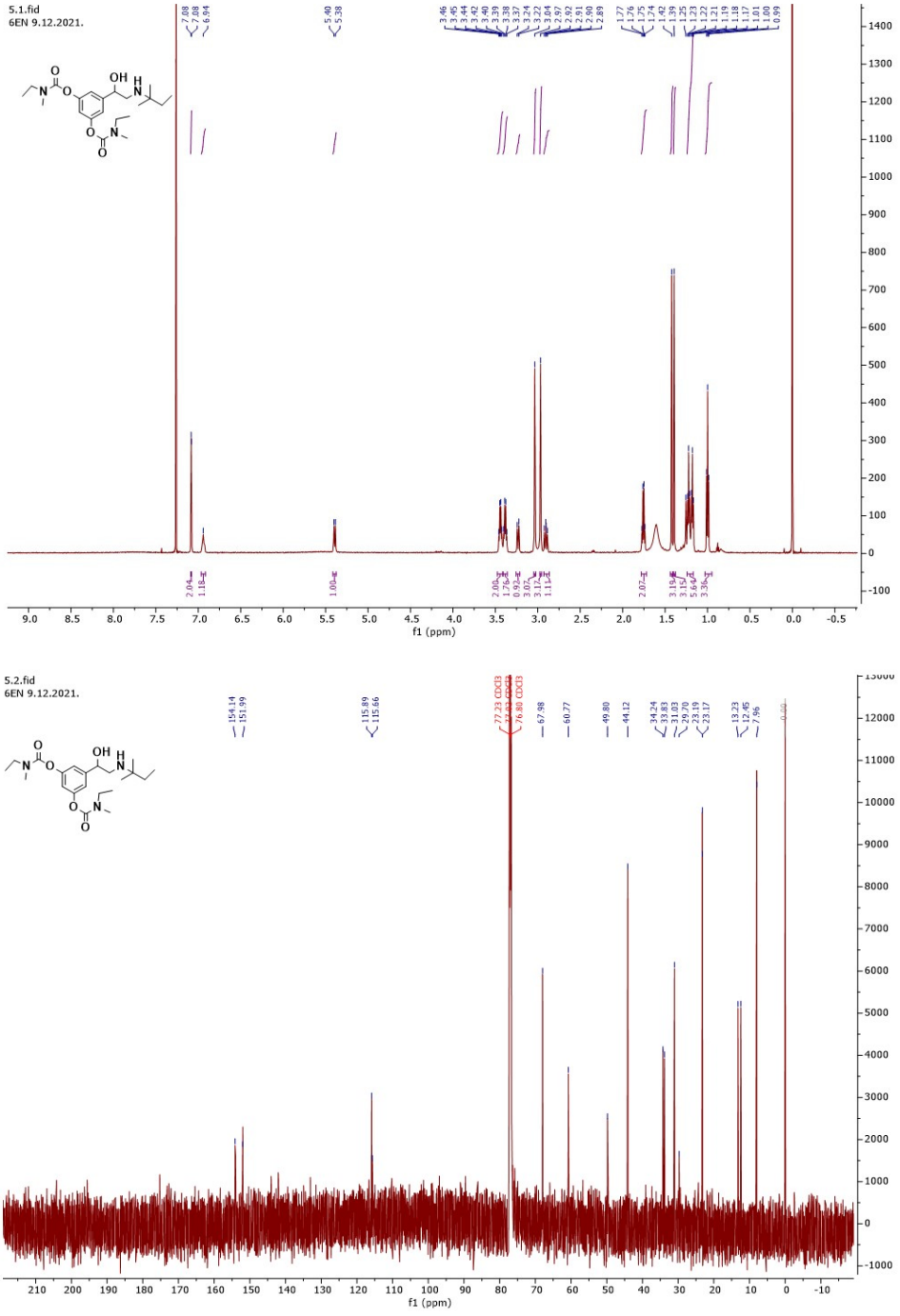


Figure S6. ^{1}H and ^{13}C spectra of the compound **5**

6

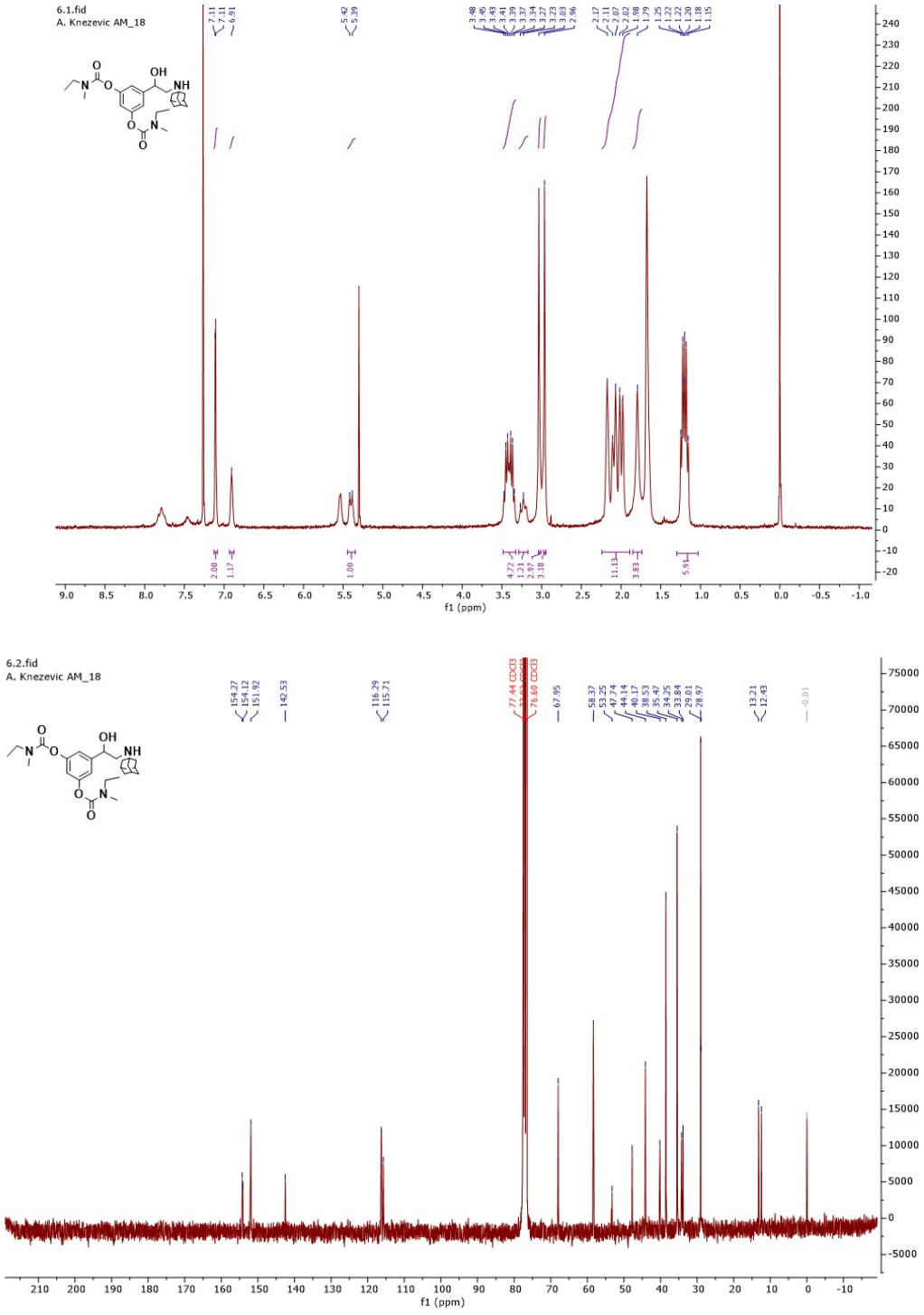


Figure S7. ^{1}H and ^{13}C spectra of the compound **6**

7

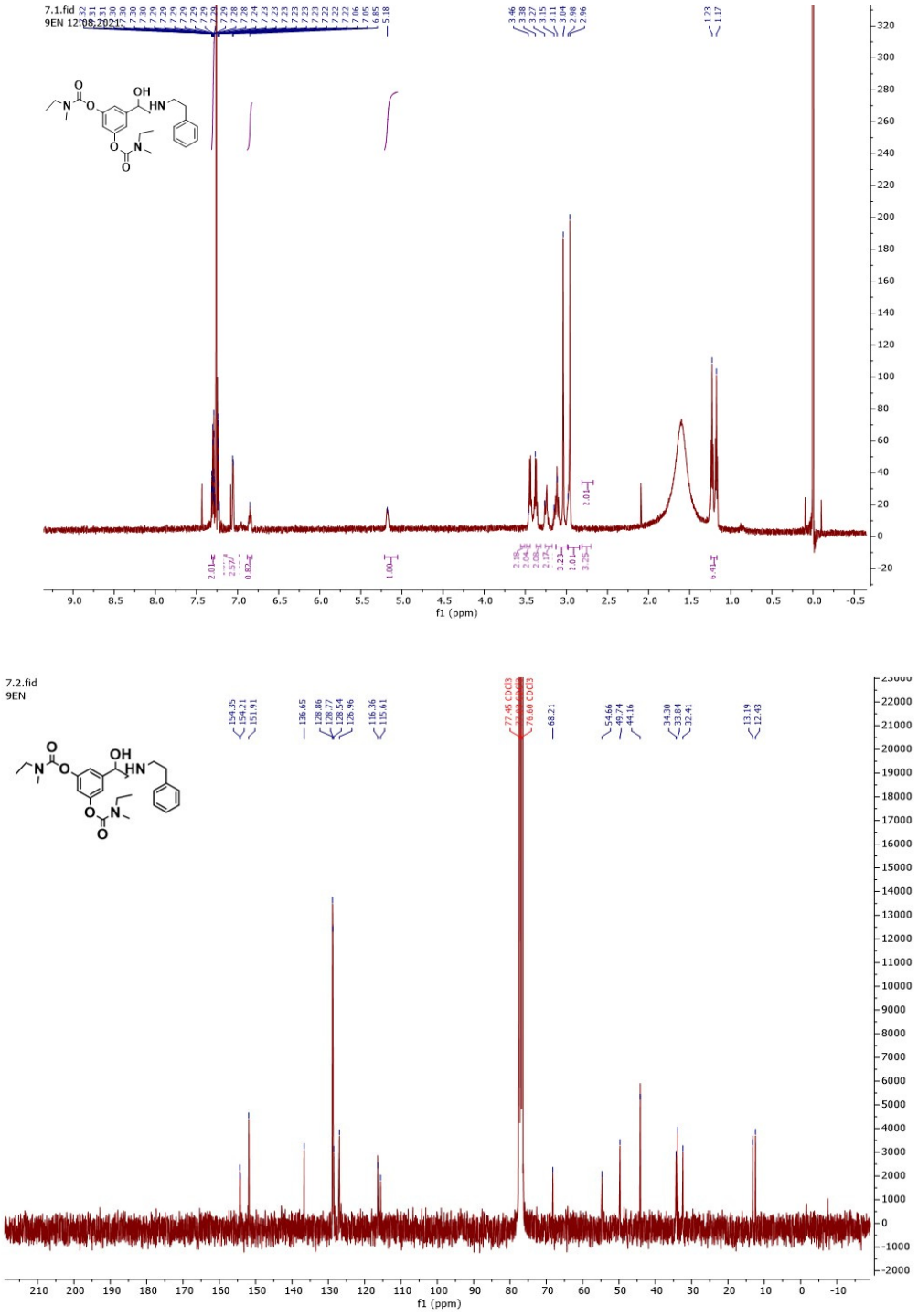


Figure S8. ^{1}H and ^{13}C spectra of the compound **7**

8

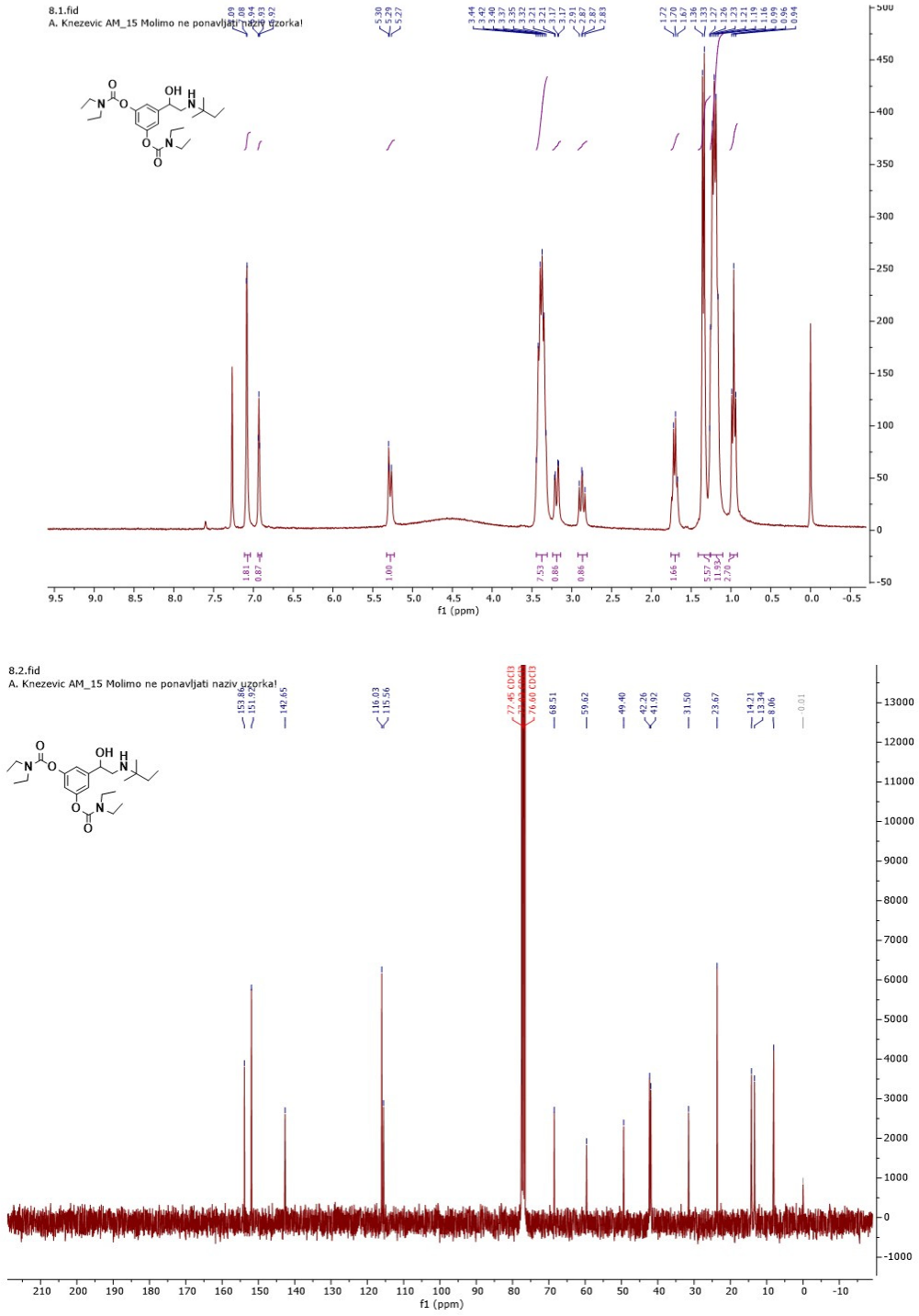


Figure S9. ^{1}H and ^{13}C spectra of the compound **8**

9

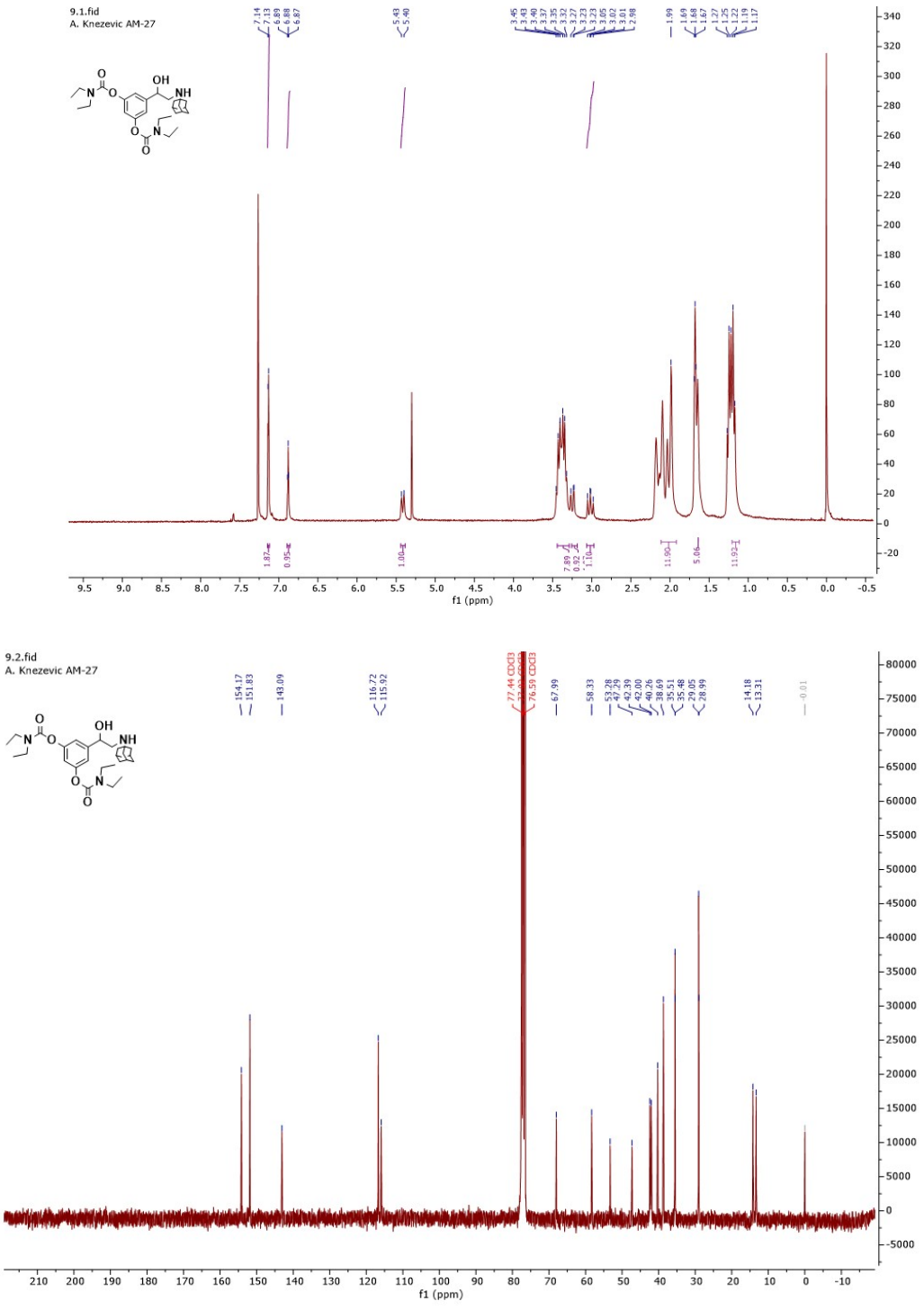


Figure S10. ^{1}H and ^{13}C spectra of the compound **9**

10

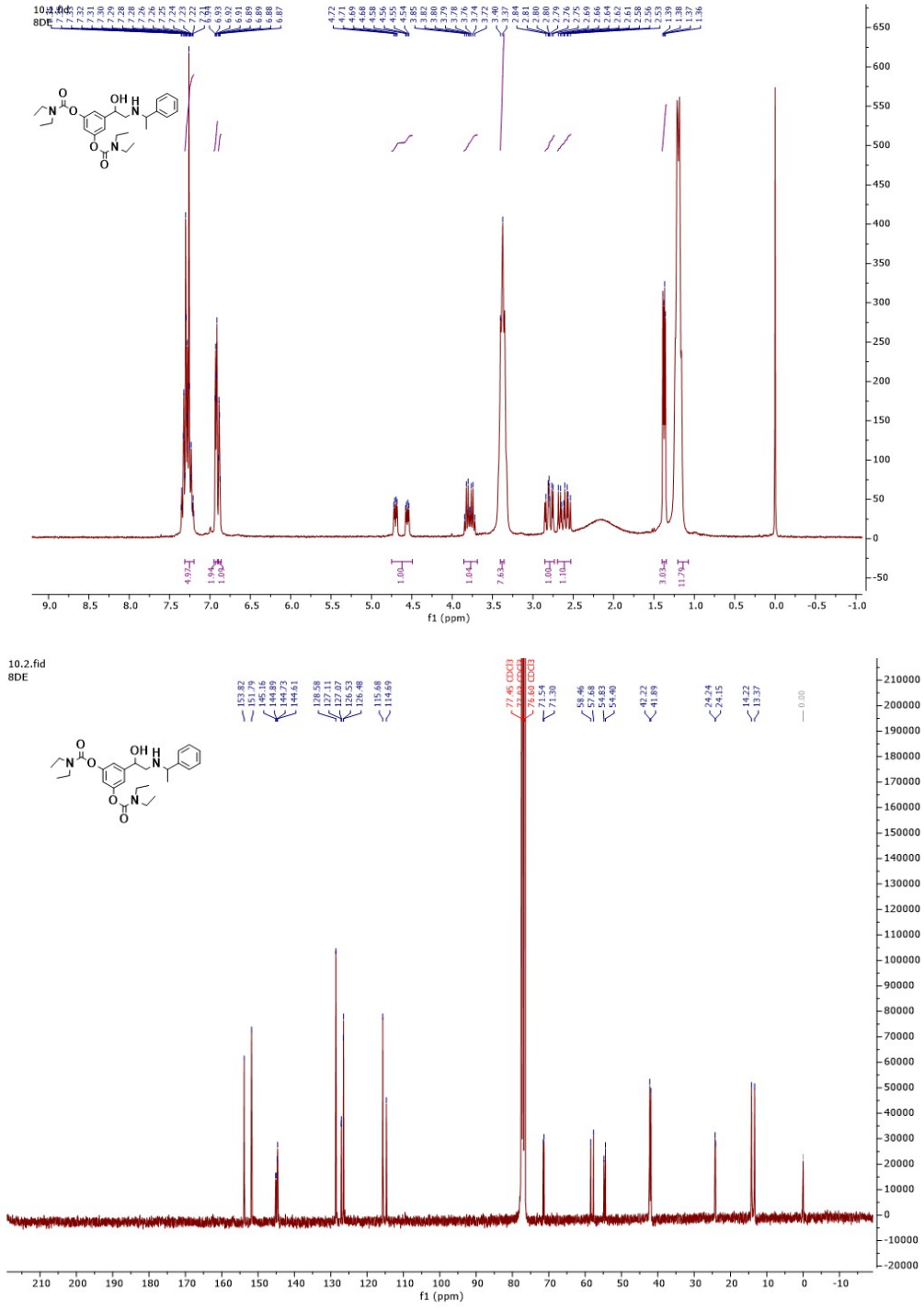


Figure S11. ^{1}H and ^{13}C spectra of the compound **10**

11

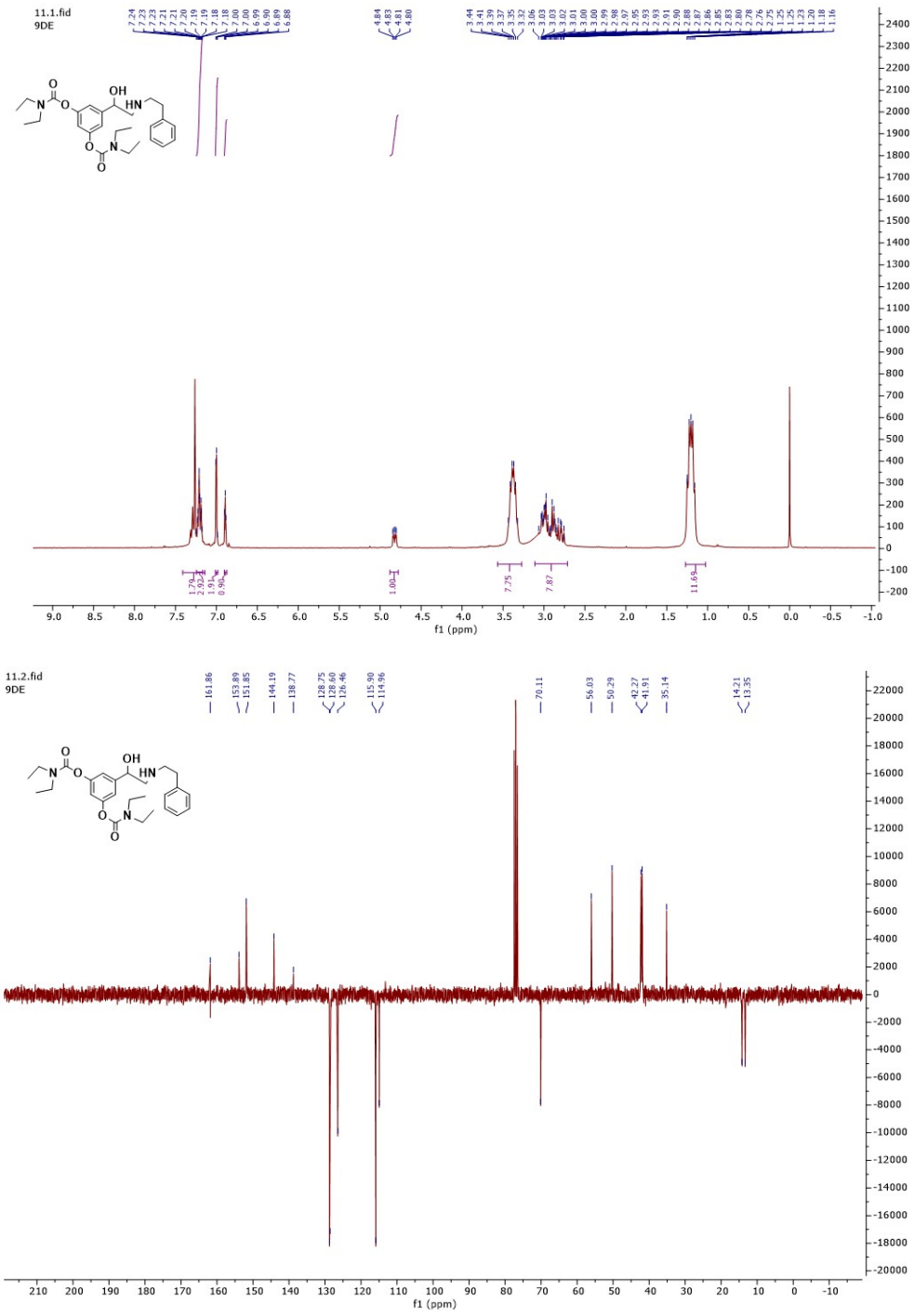


Figure S12. ^{1}H and ^{13}C spectra of the compound **11**

12

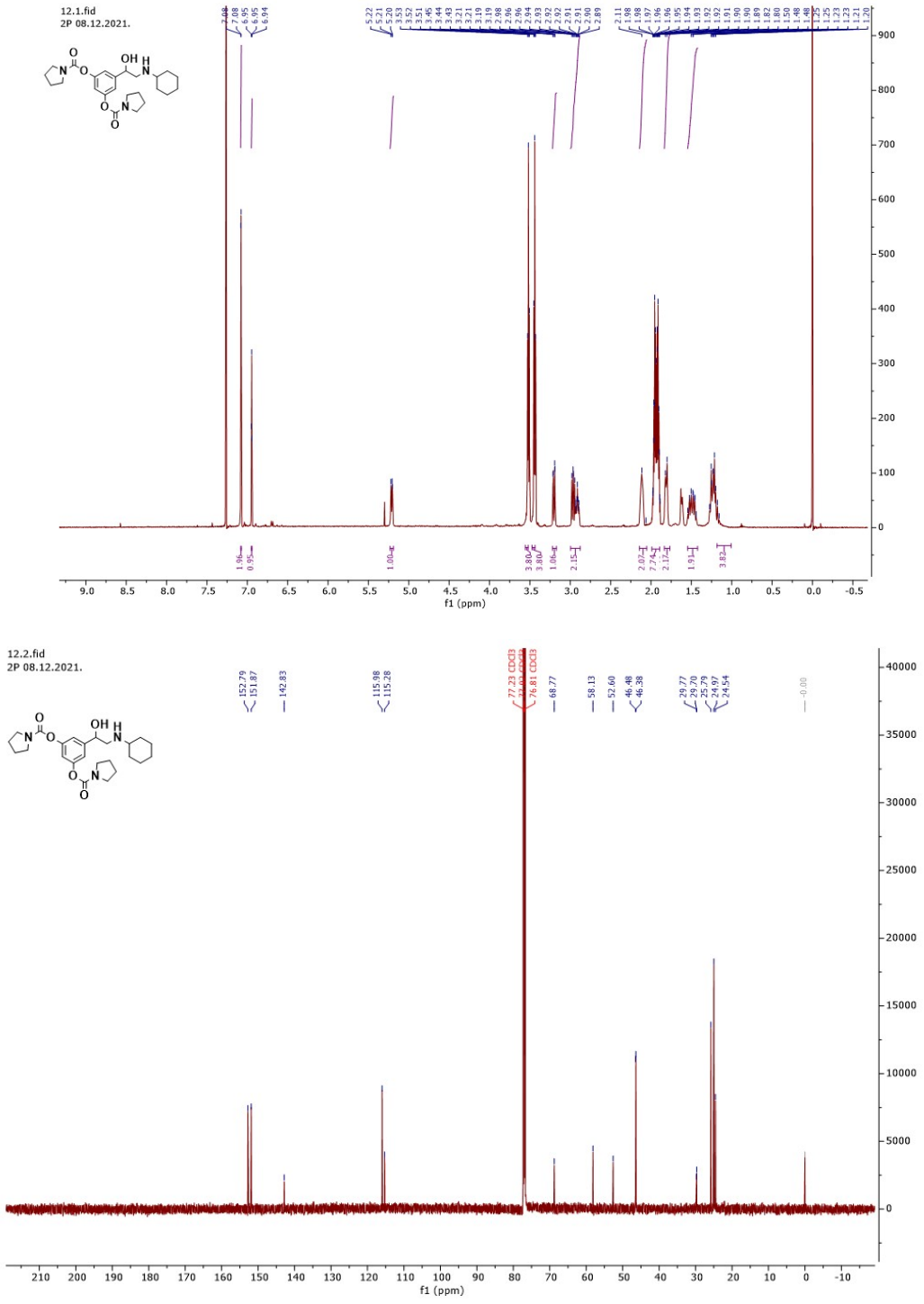


Figure S13. ^{1}H and ^{13}C spectra of the compound **12**

13

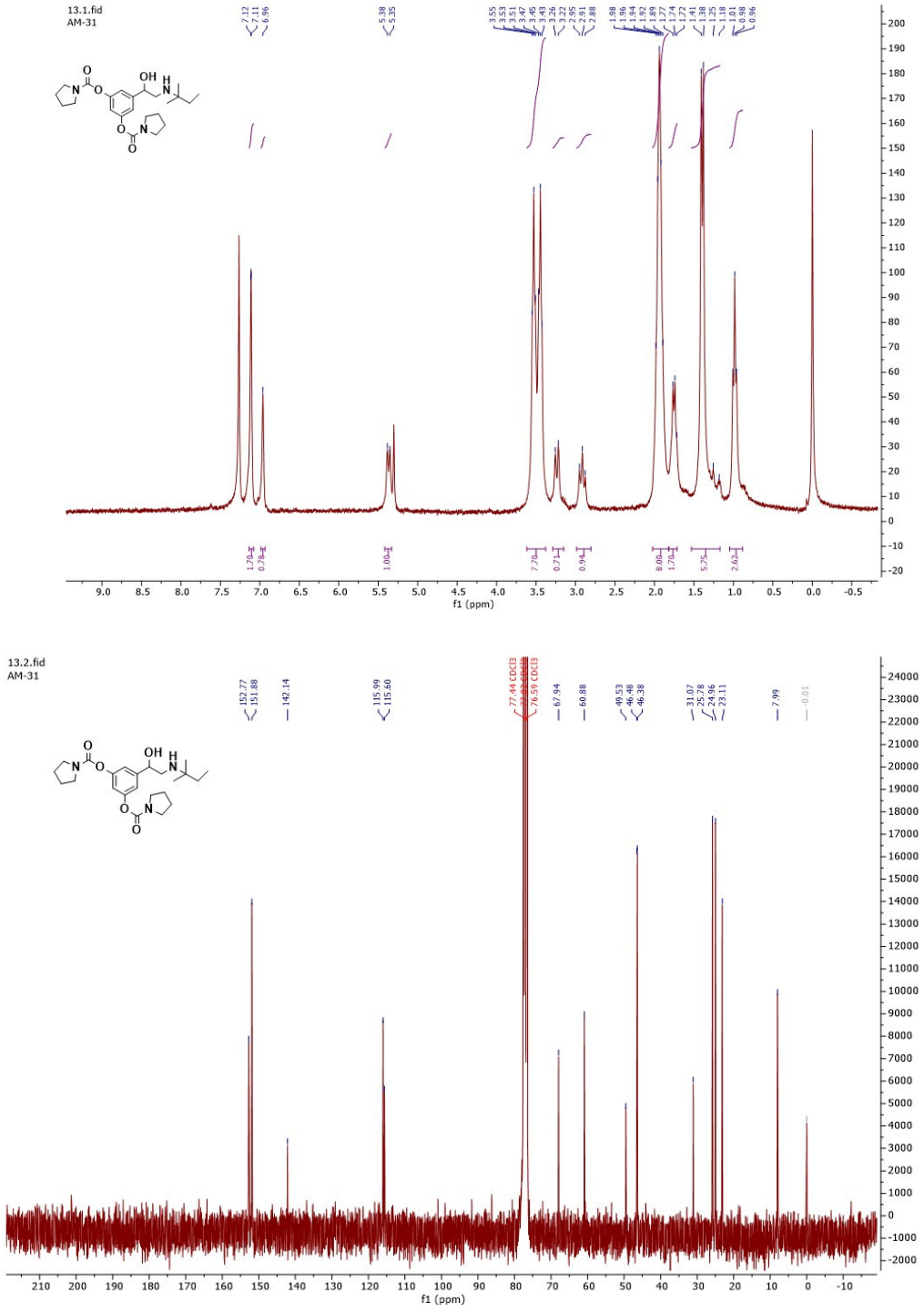


Figure S14. ^{1}H and ^{13}C spectra of the compound **13**

14

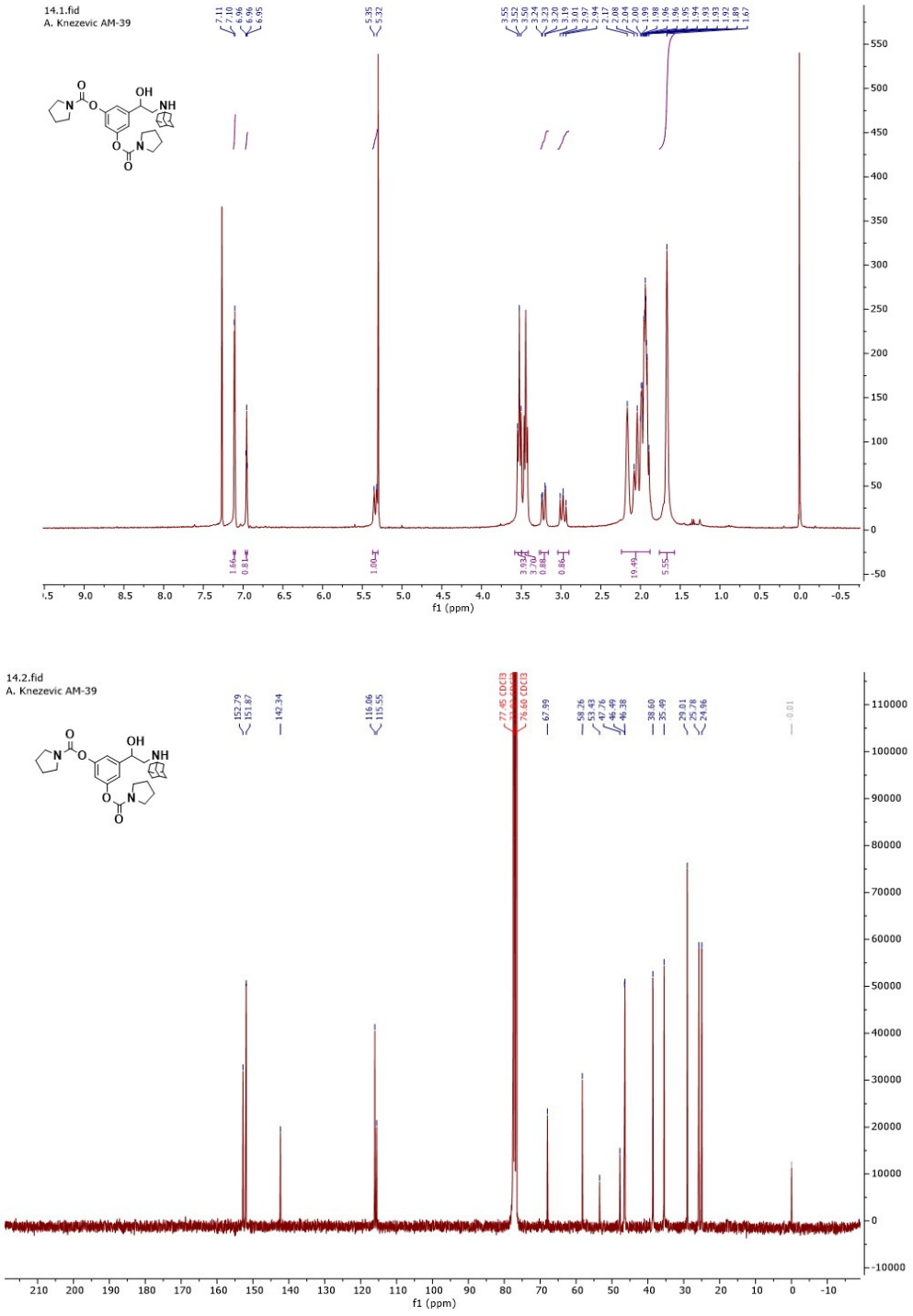


Figure S15. ^{1}H and ^{13}C spectra of the compound **14**

15

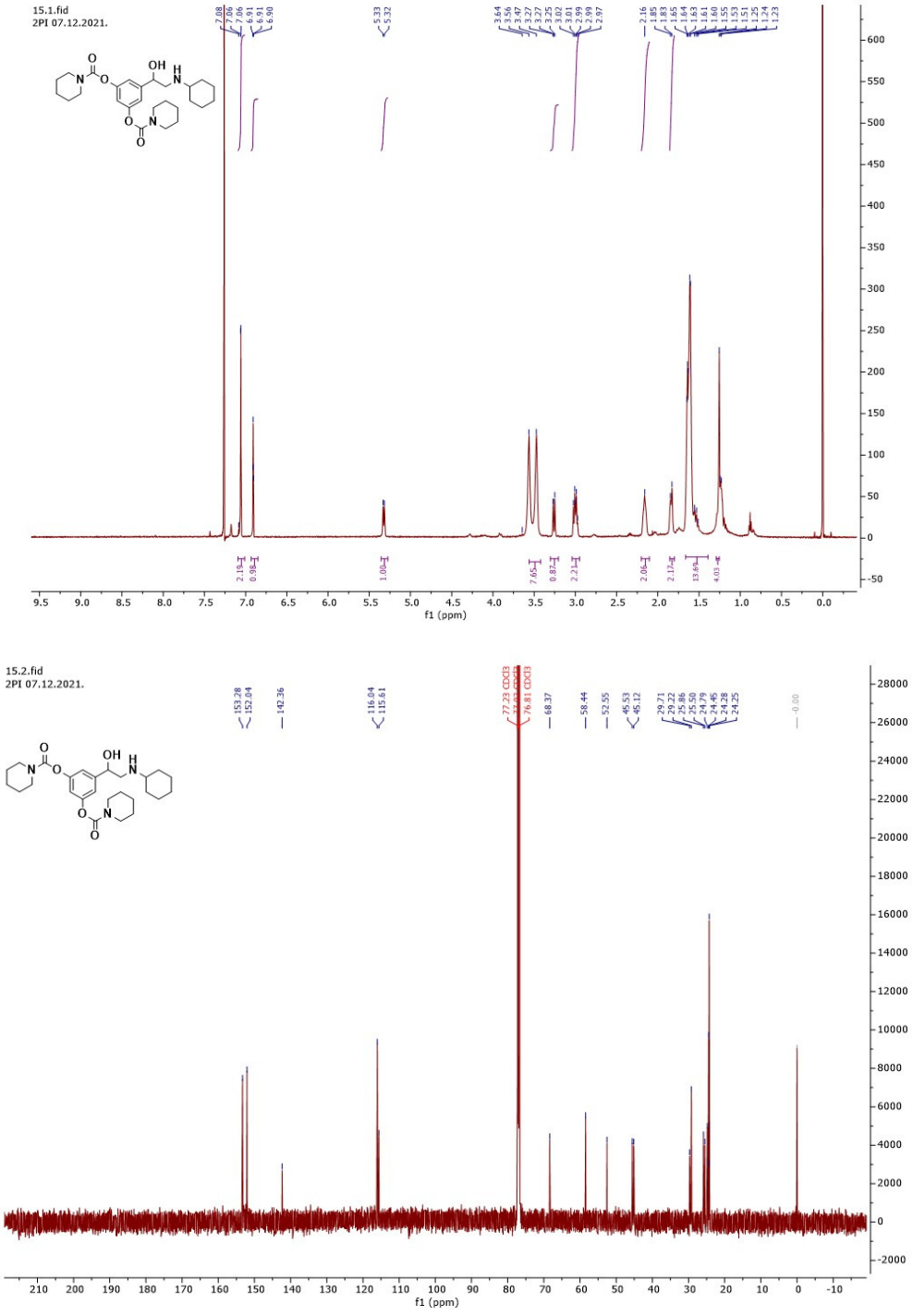


Figure S16. ^{1}H and ^{13}C spectra of the compound **15**

16

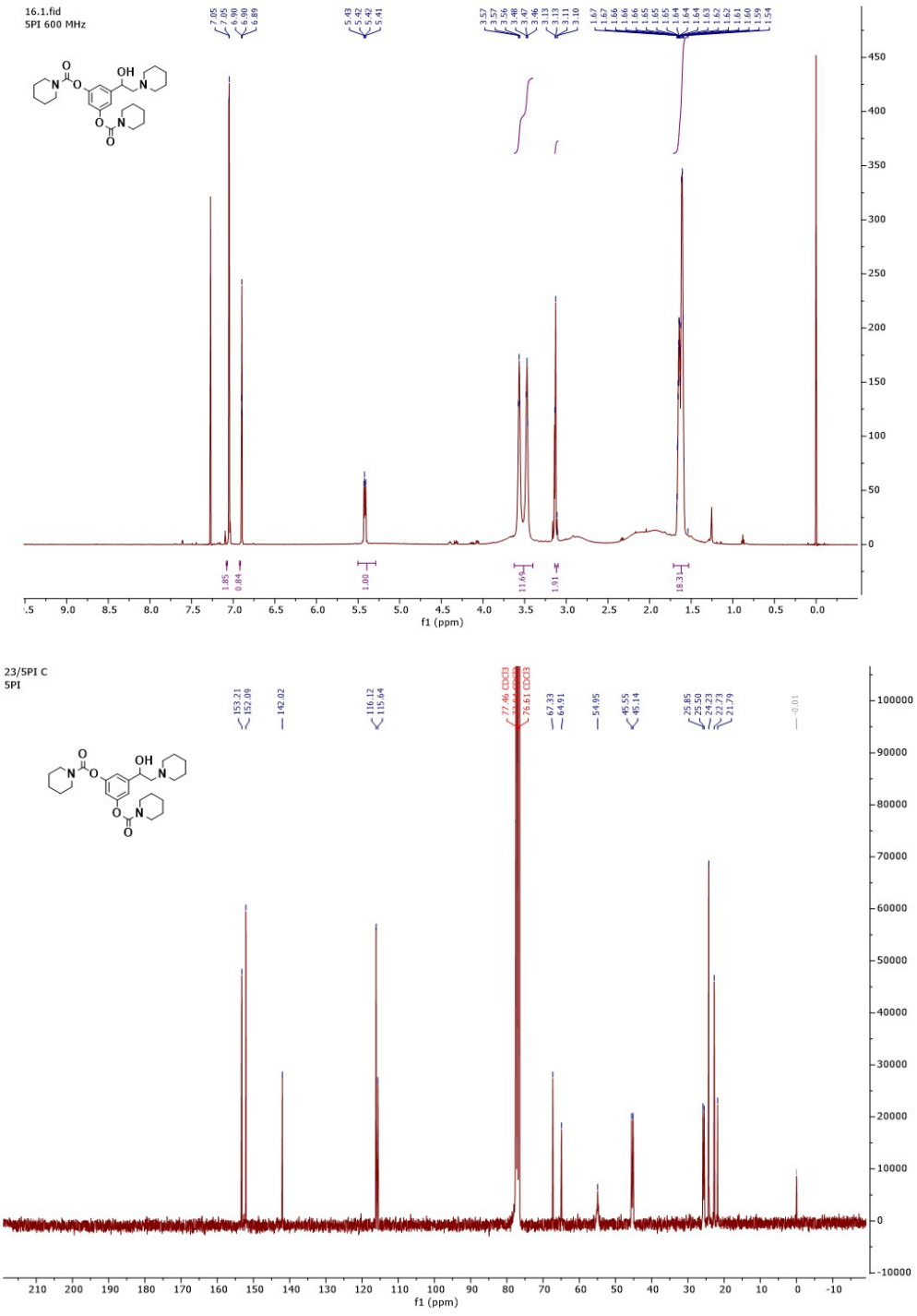


Figure 17. ^{1}H and ^{13}C spectra of the compound **16**

17

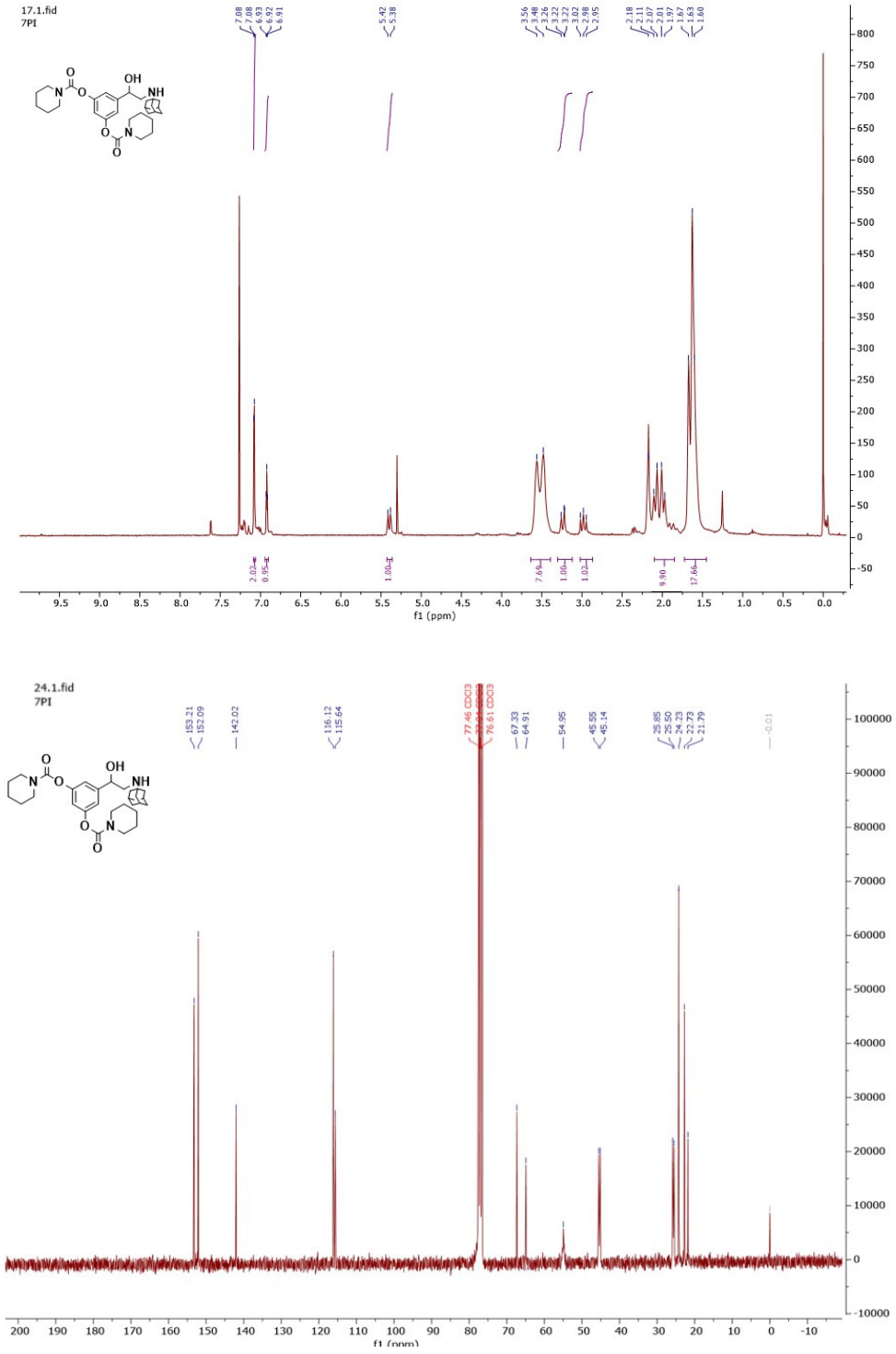


Figure S17. ^{1}H and ^{13}C spectra of the compound **18**

18

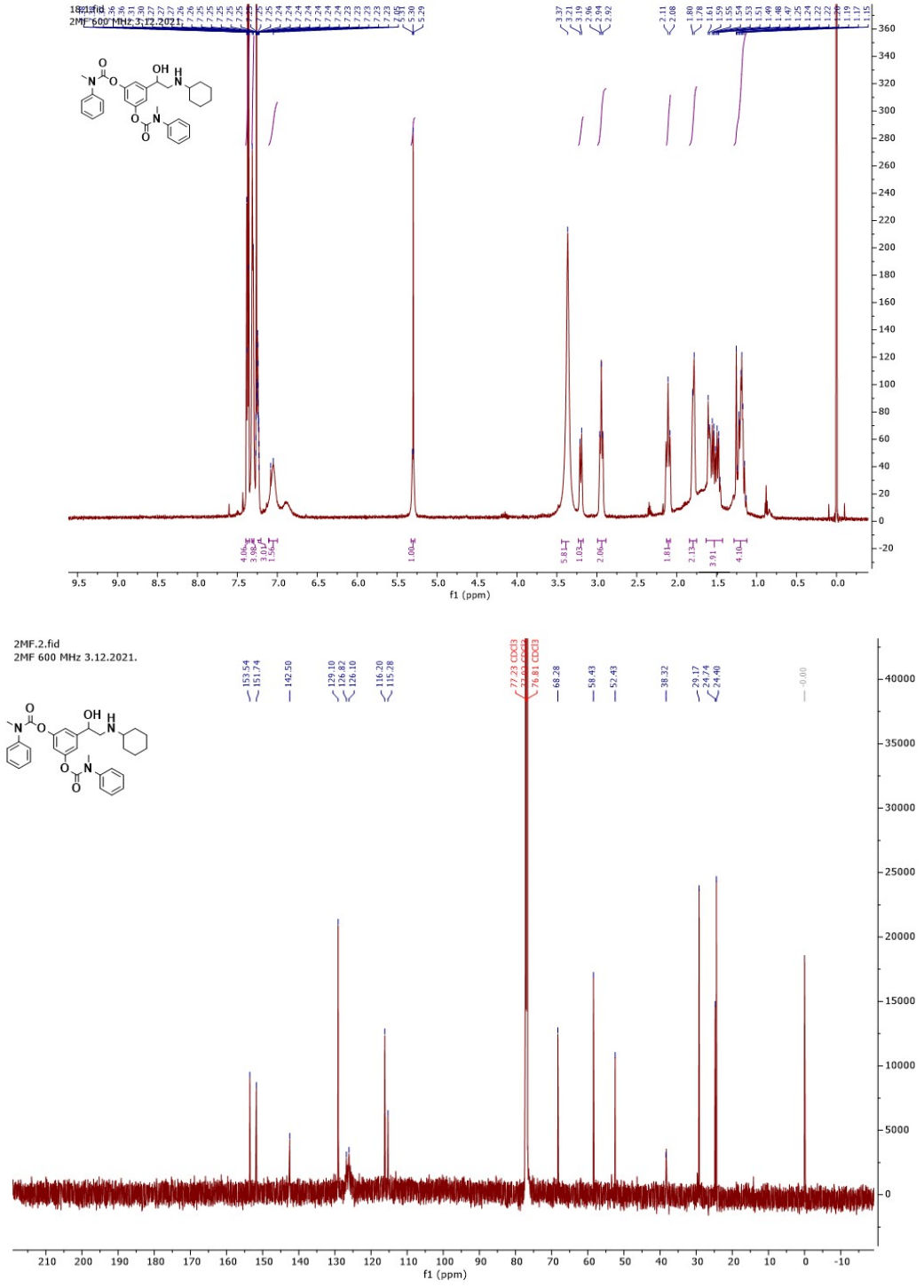


Figure S19. ^{1}H and ^{13}C spectra of the compound **18**

1

Molecular formula: $C_{20}H_{31}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 394.2342

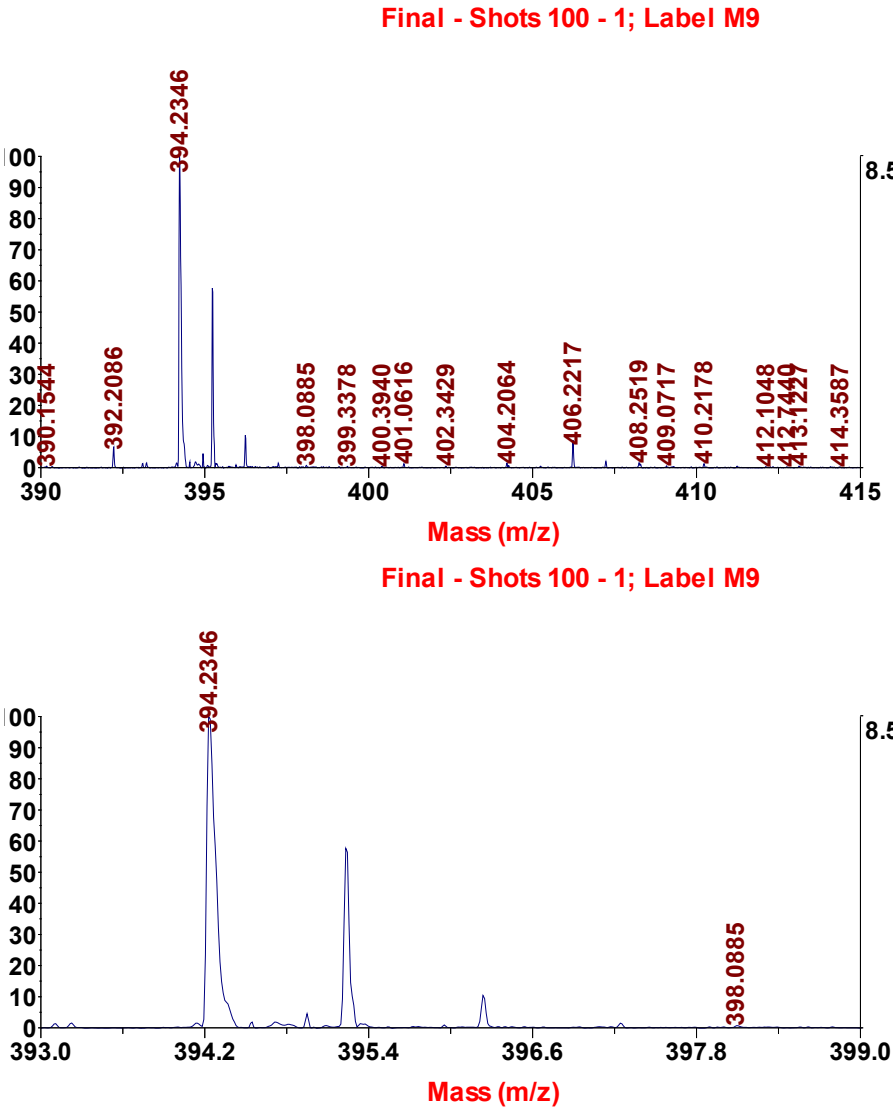


Figure S20. Mass spectar of **1** in the area *m*/*z* 390 – 415 (upper spectrum) and its enlarged view in the area *m*/*z* 393 – 399 (lower spectrum).

2

Molecular formula: $C_{19}H_{29}N_3O_5$

Theoretical monoisotropic mass $[M+Na]^+$: 402.2005

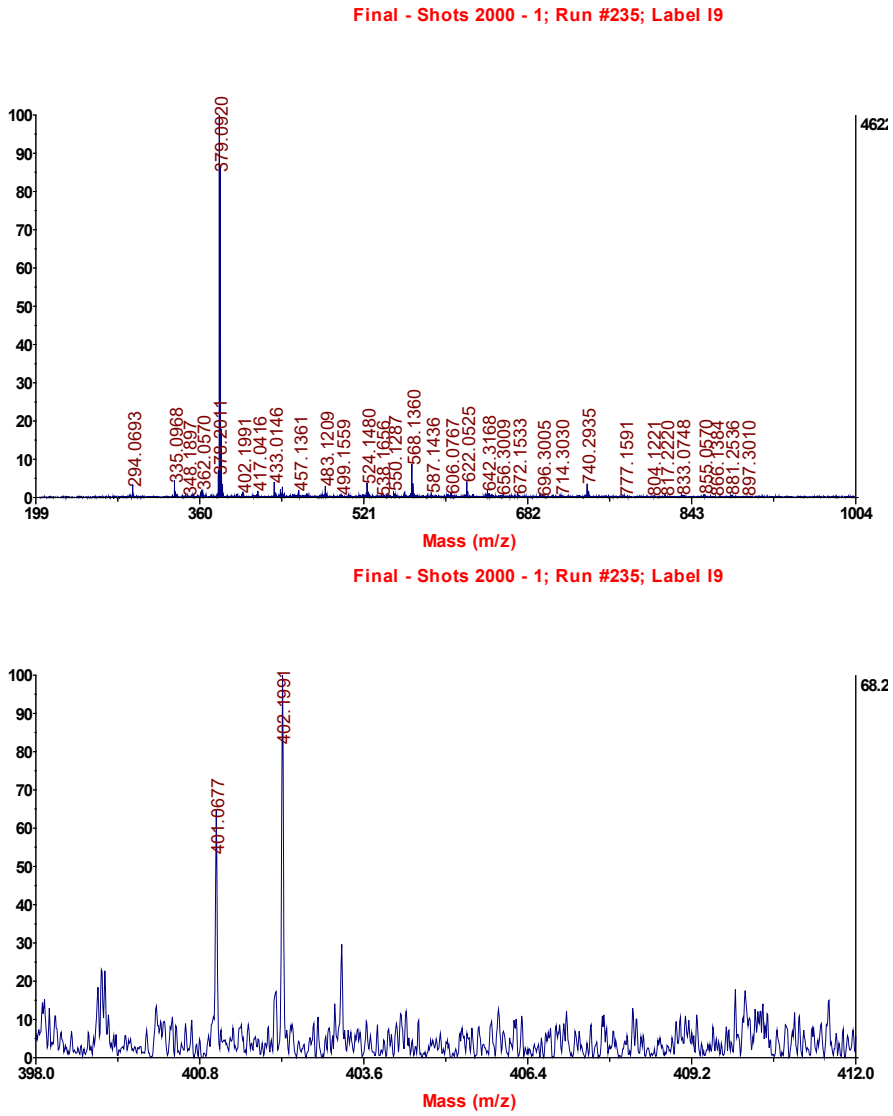


Figure S21. Mass spectar of **2** in the area *m*/*z* 199 – 1004 (upper spectrum) and its enlarged view in the area *m*/*z* 398 – 412 (lower spectrum).

3

Molecular formula: $C_{24}H_{35}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 446.2655

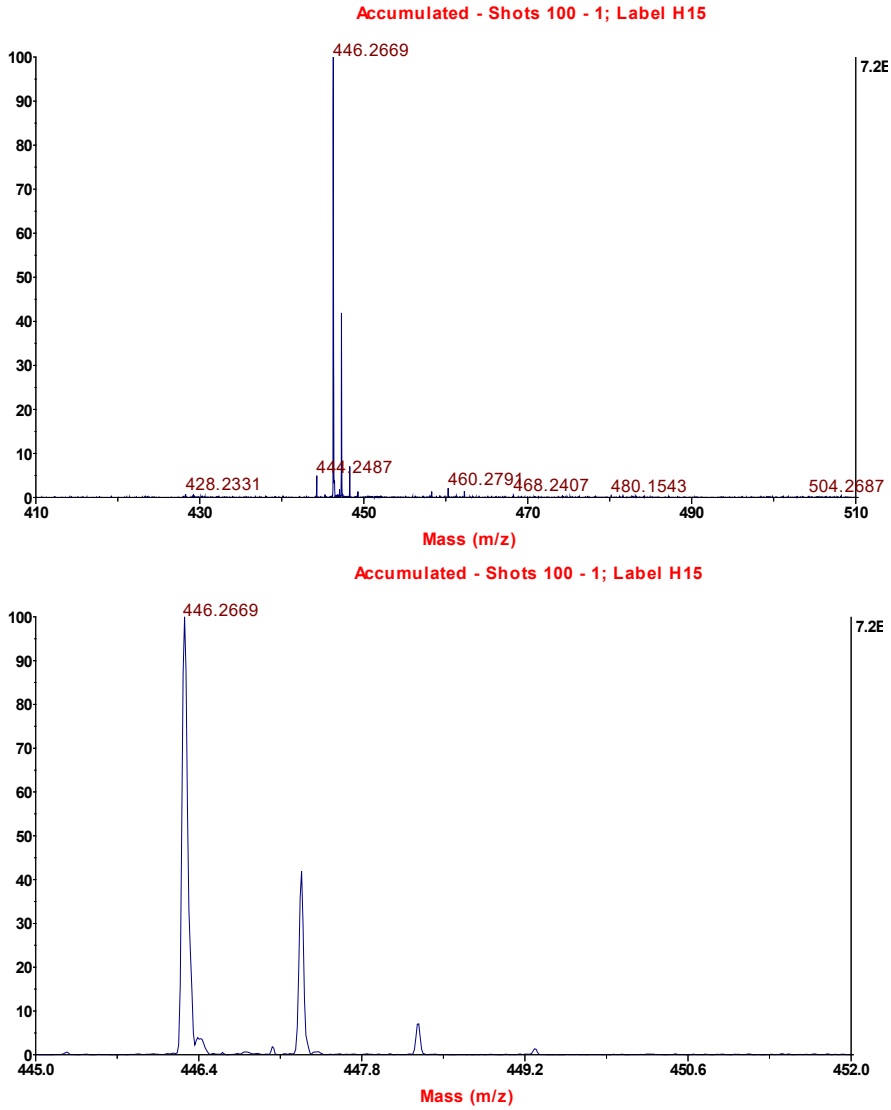


Figure S22. Mass spectar of **3** in the area *m*/*z* 410 – 510 (upper spectrum) and its enlarged view in the area *m*/*z* 445 – 452 (lower spectrum).

4

Molecular formula: $C_{22}H_{35}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 422.2655

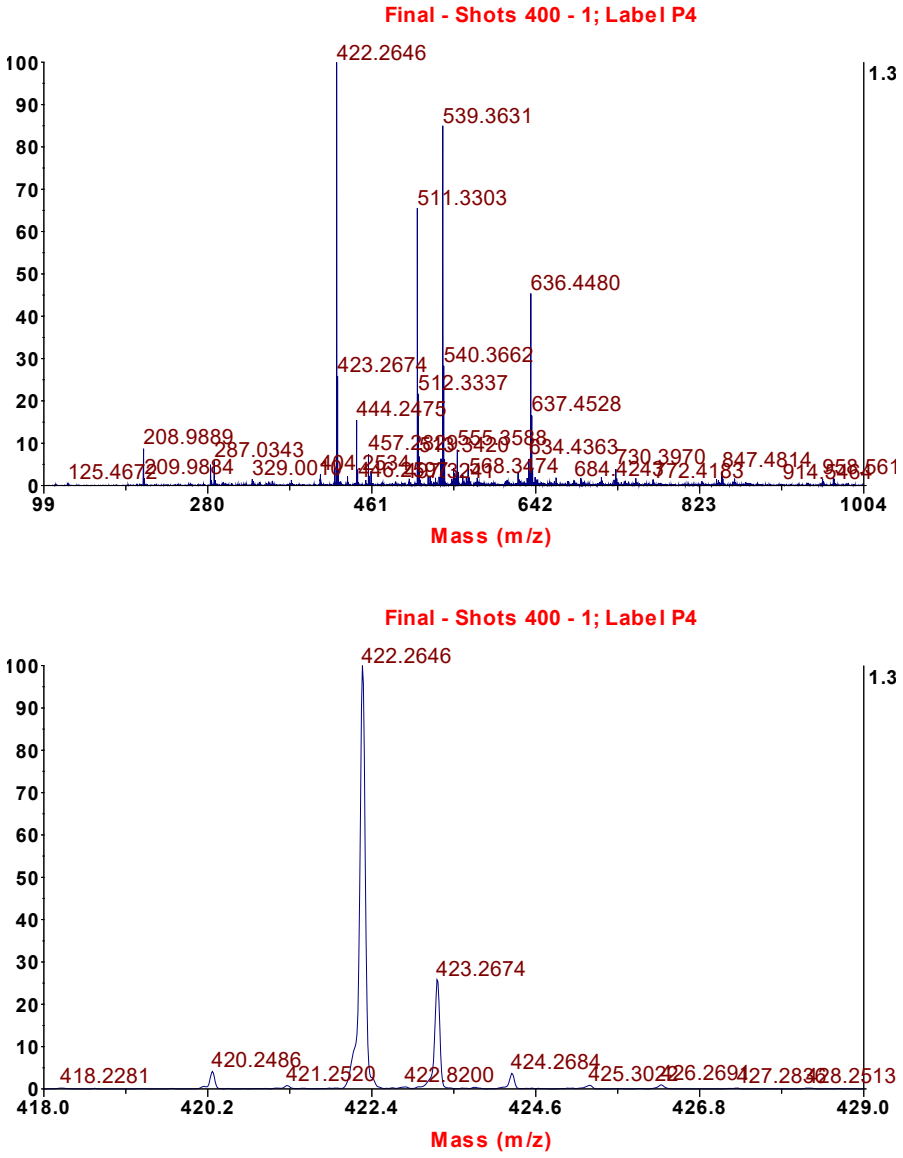


Figure S23. Mass spectar of **4** in the area *m*/*z* 99 – 1004 (upper spectrum) and its enlarged view in the area *m*/*z* 418 – 429 (lower spectrum).

5

Molecular formula: $C_{21}H_{36}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 410.2655

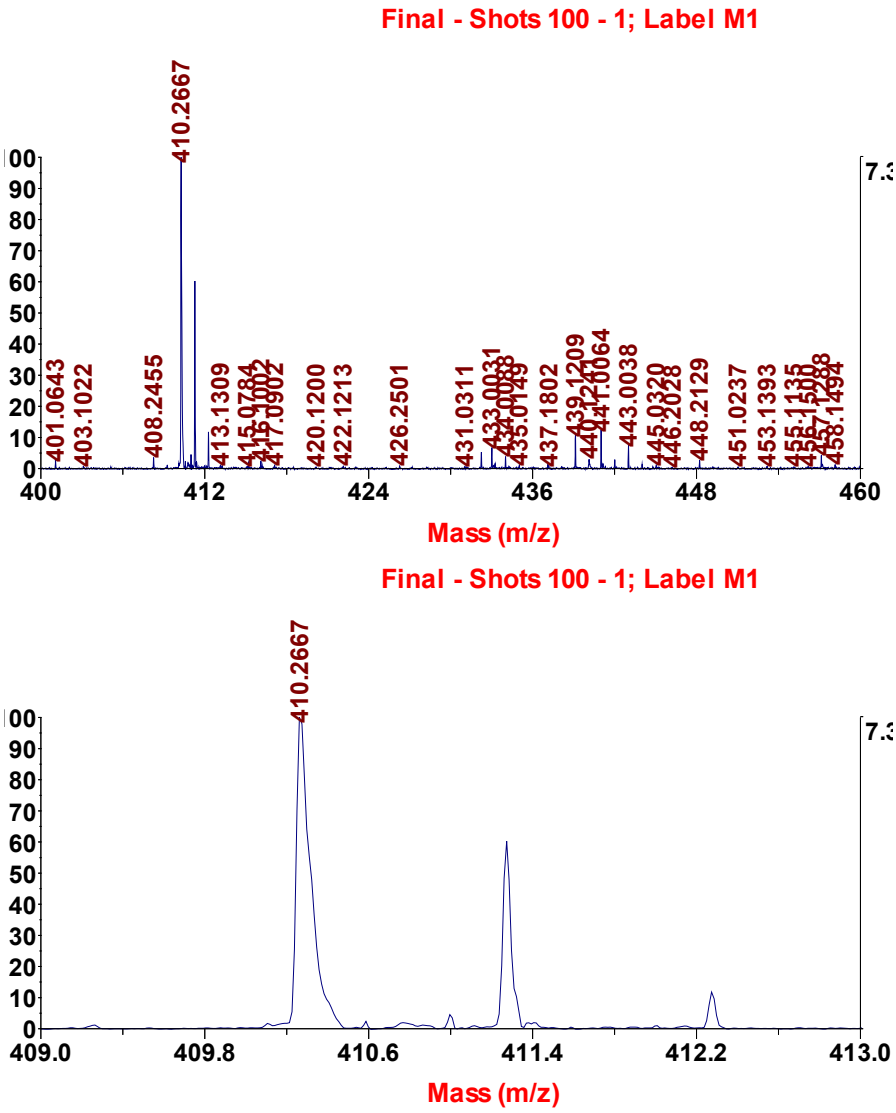


Figure S24. Mass spectar of **5** in the area *m*/*z* 400 – 460 (upper spectrum) and its enlarged view in the area *m*/*z* 409 – 413 (lower spectrum).

6

Molecular formula: $C_{26}H_{39}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 474.2968

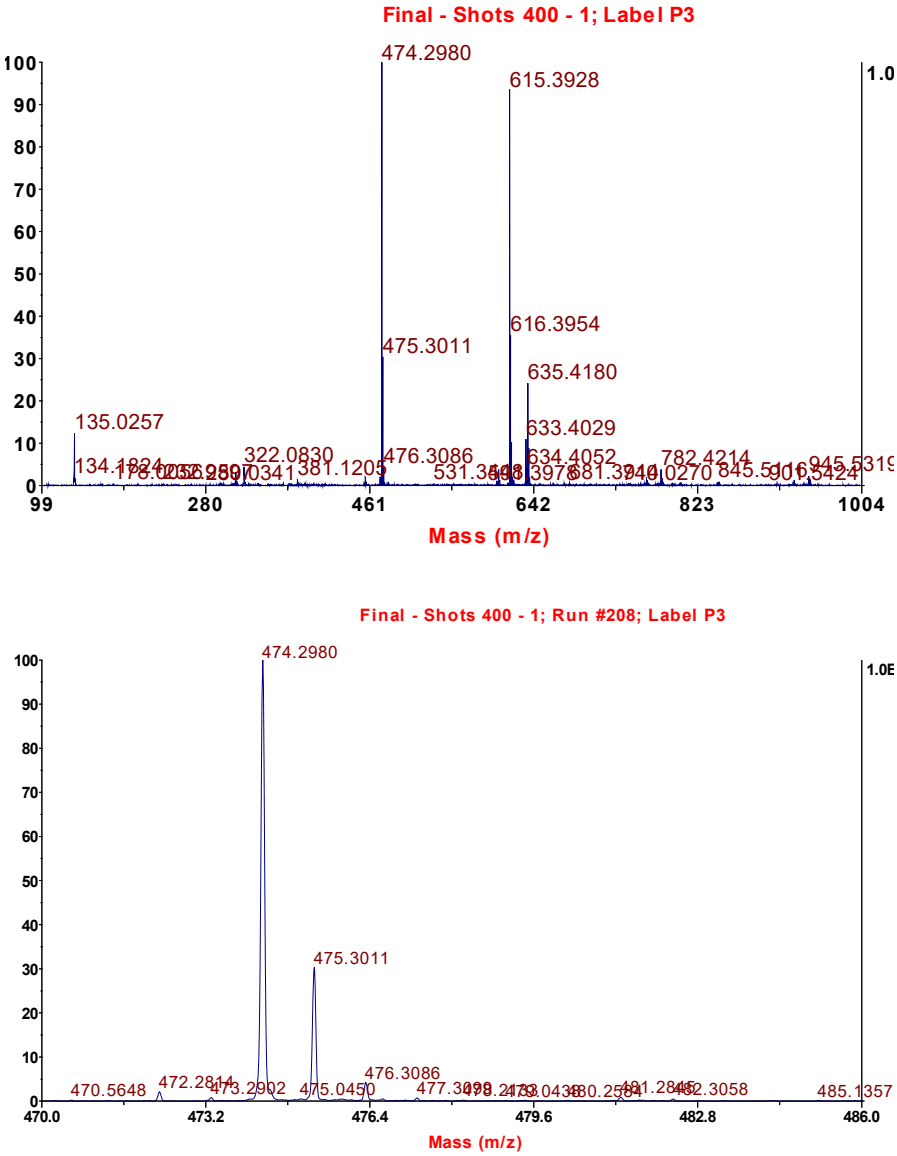


Figure S25. Mass spectar of **6** in the area m/z 99 – 1004 (upper spectrum) and its enlarged view in the area m/z 470 – 486 (lower spectrum).

7

Molecular formula: $C_{24}H_{33}N_3O_5$

Theoretical monoisotropic mass $[M+K]^+$: 482.2057

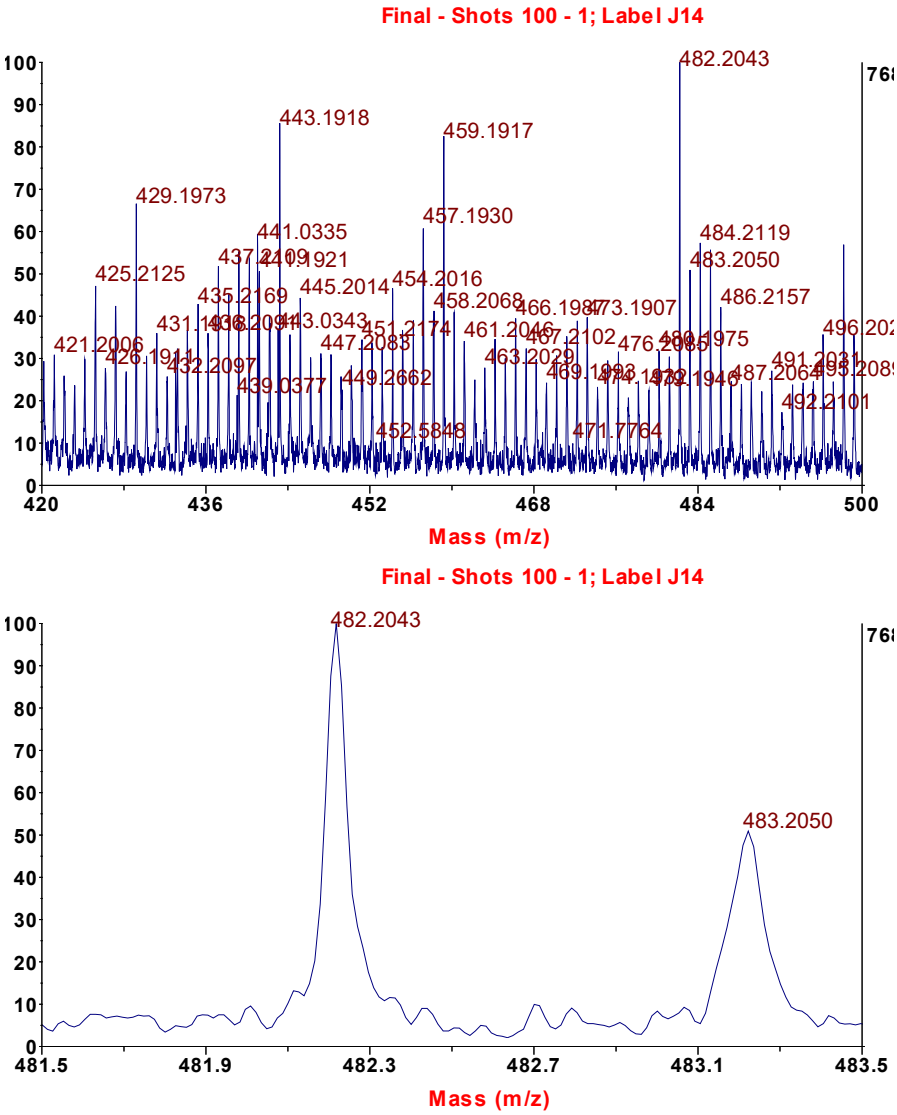


Figure S26. Mass spectar of **7** in the area m/z 420 – 500 (upper spectrum) and its enlarged view in the area m/z 481.5 – 483.5 (lower spectrum).

8

Molecular formula: $C_{23}H_{39}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 438.2968

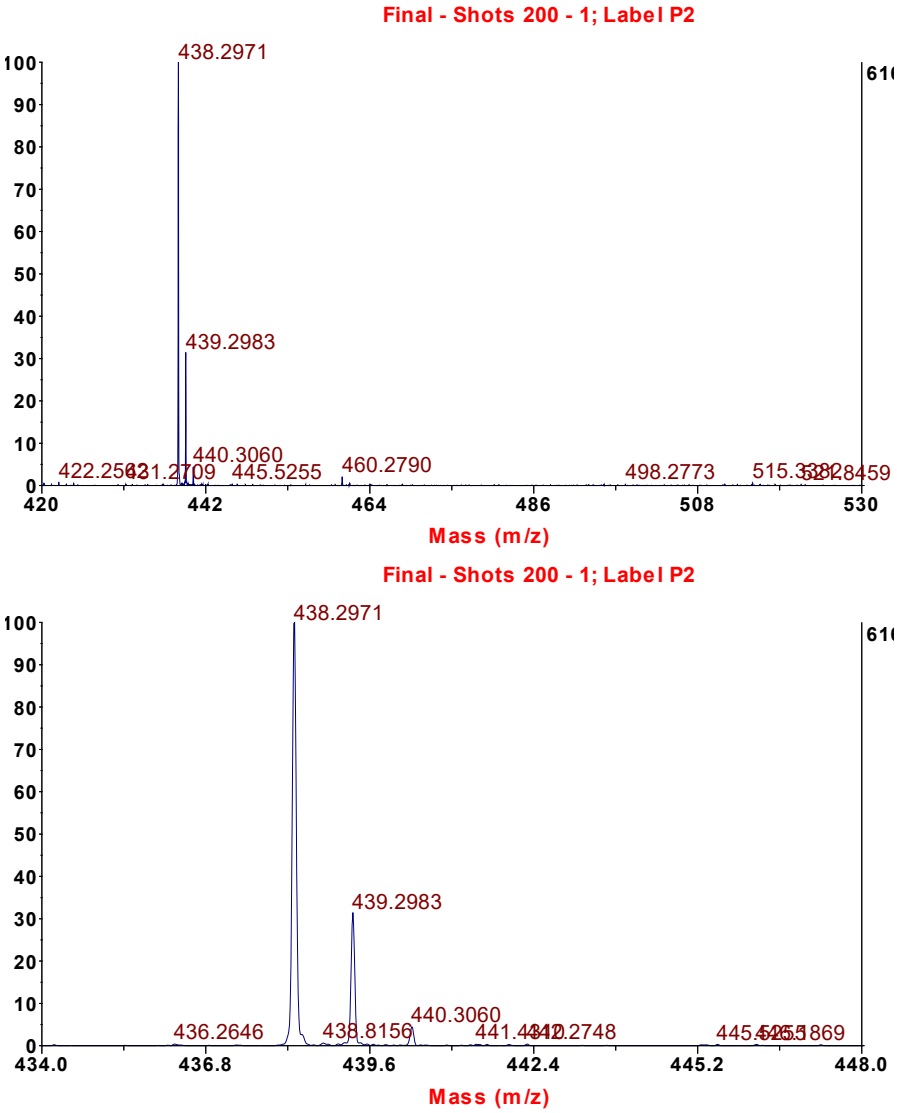


Figure S27. Mass spectar of **8** in the area m/z 420 – 530 (upper spectrum) and its enlarged view in the area m/z 434 – 448 (lower spectrum).

9

Molecular formula: $C_{28}H_{43}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 502.3281

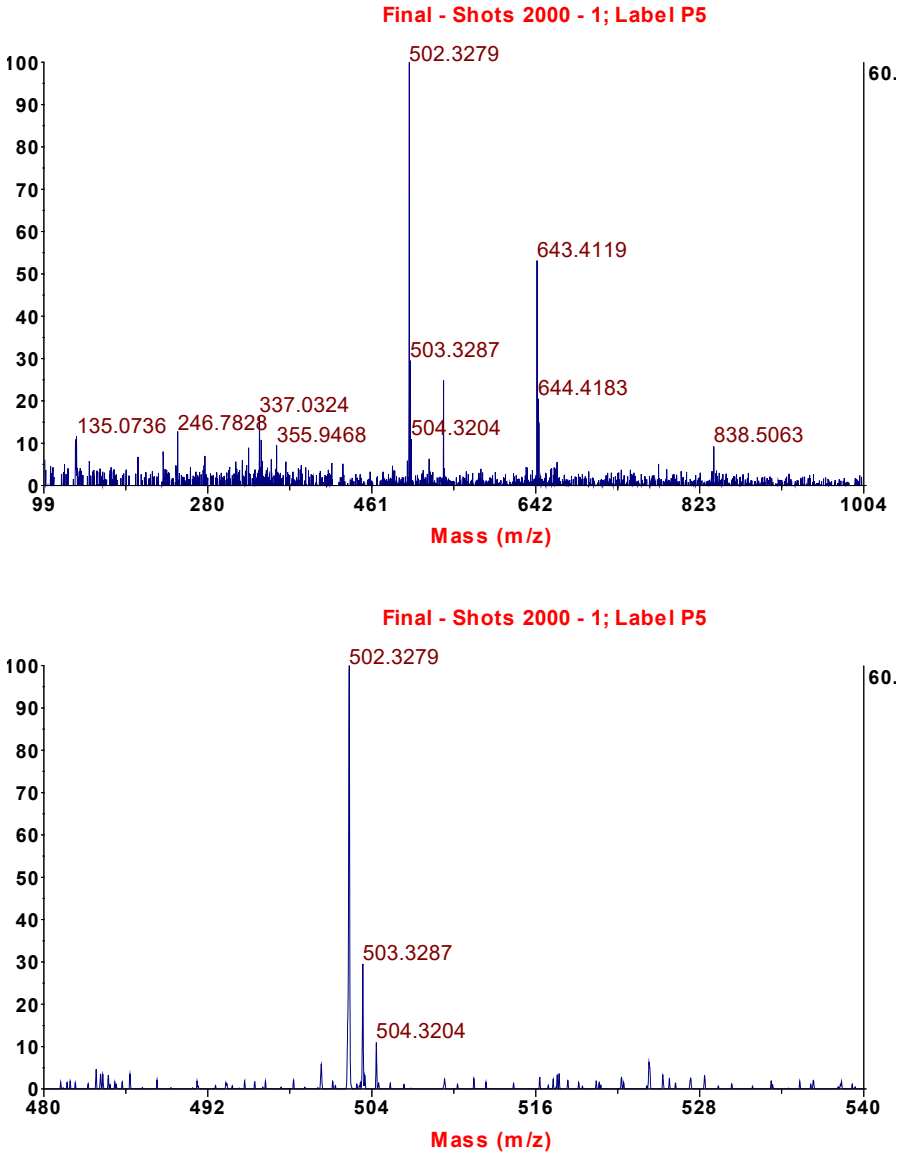


Figure S28. Mass spectar of **9** in the area m/z 99 – 1004 (upper spectrum) and its enlarged view in the area m/z 480 – 540 (lower spectrum).

10

Molecular formula: $C_{26}H_{37}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 472.2811

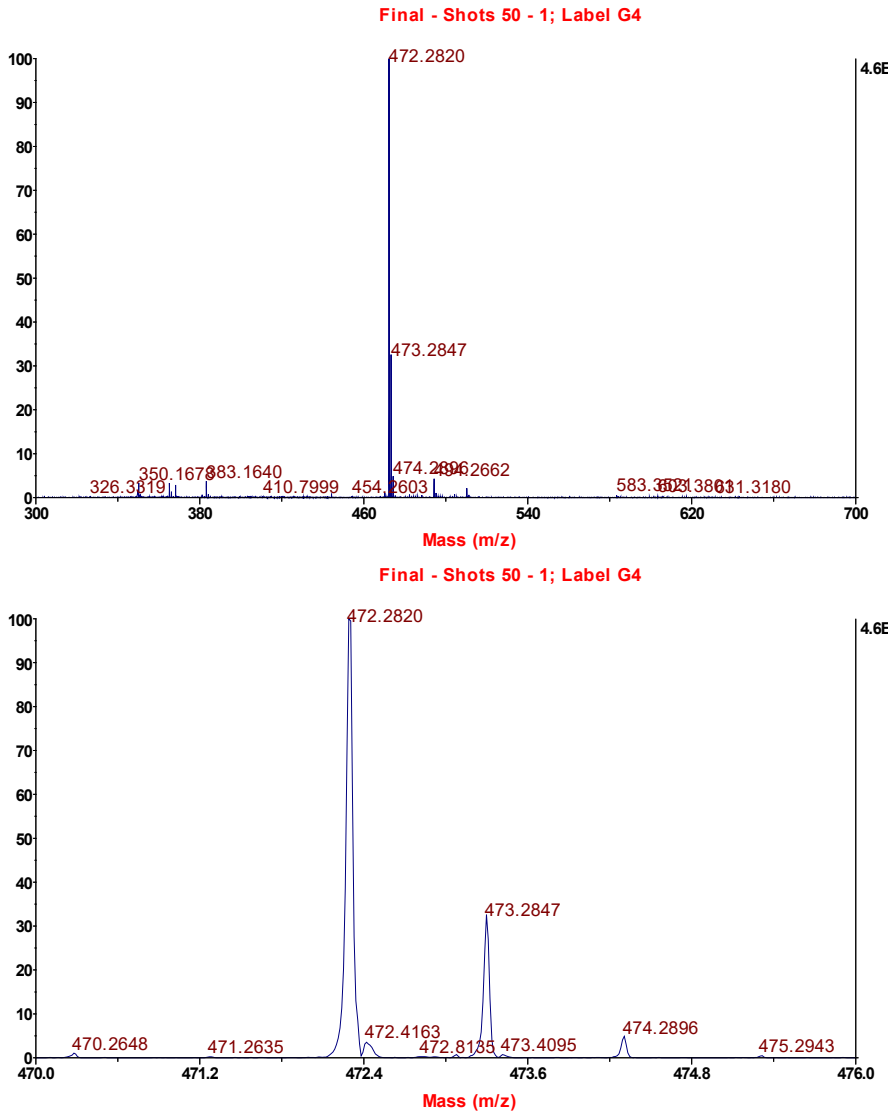


Figure S29. Mass spectar of **10** in the area m/z 300 – 700 (upper spectrum) and its enlarged view in the area m/z 470 – 476 (lower spectrum).

11

Molecular formula: $C_{26}H_{37}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 472.2811

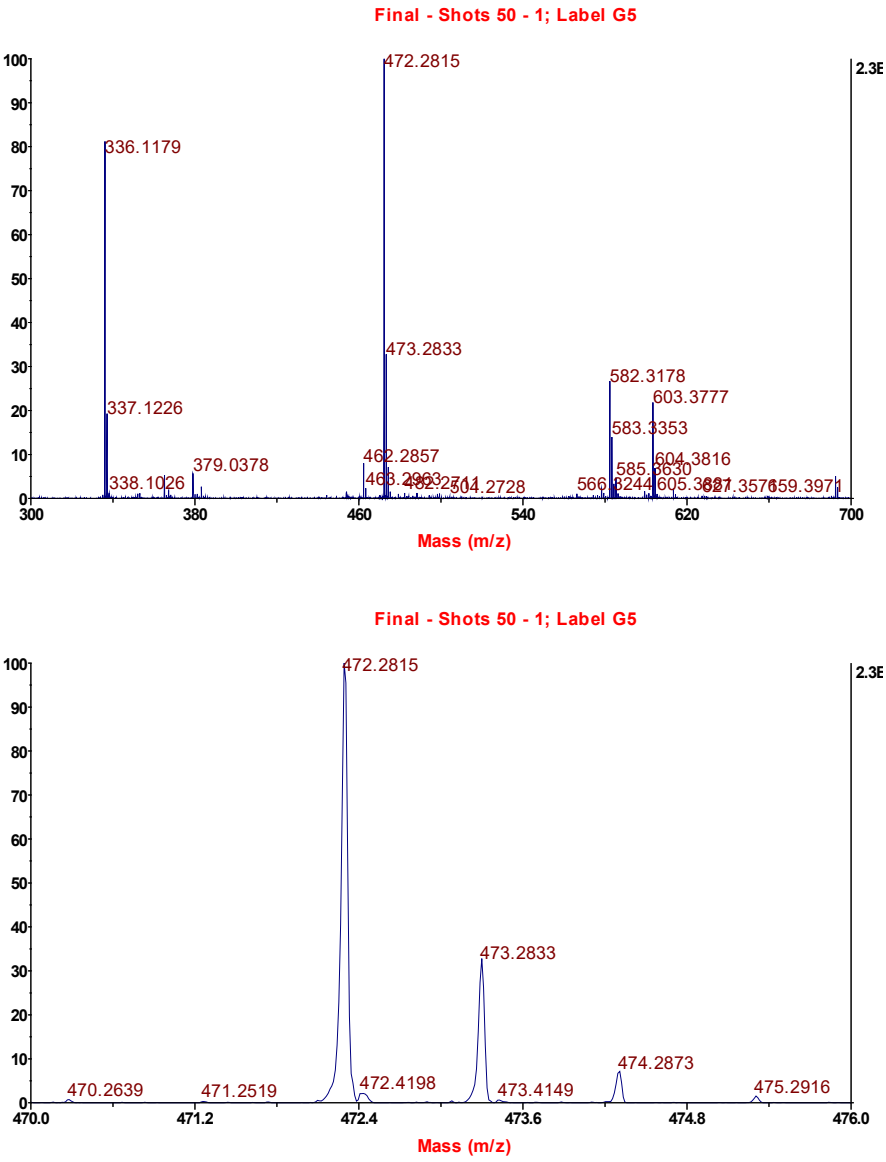


Figure S30. Mass spectar of **11** in the area m/z 300 – 700 (upper spectrum) and its enlarged view in the area m/z 470 – 476 (lower spectrum).

12

Molecular formula: $C_{24}H_{36}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 446.2655

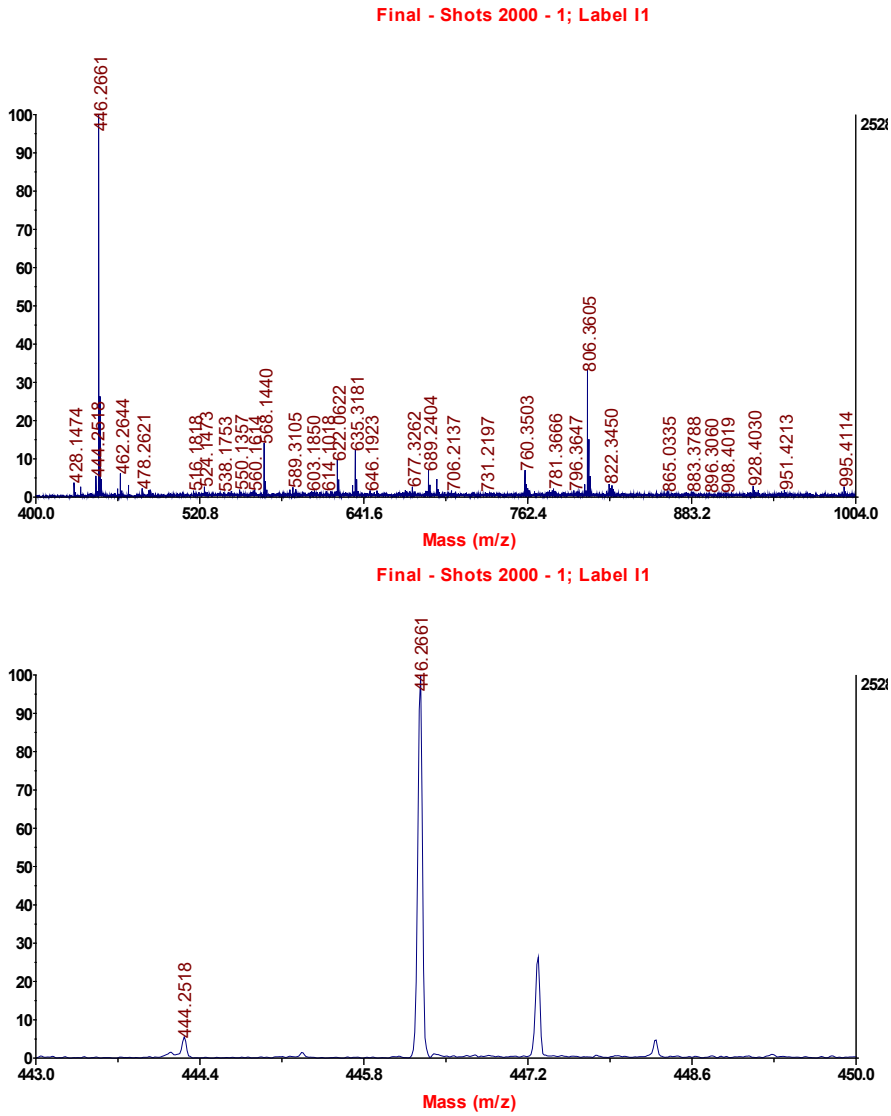


Figure S31. Mass spectar of **12** in the area m/z 400 – 1004 (upper spectrum) and its enlarged view in the area m/z 443 – 450 (lower spectrum).

13

Molecular formula: $C_{23}H_{36}ClN_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 434.2655

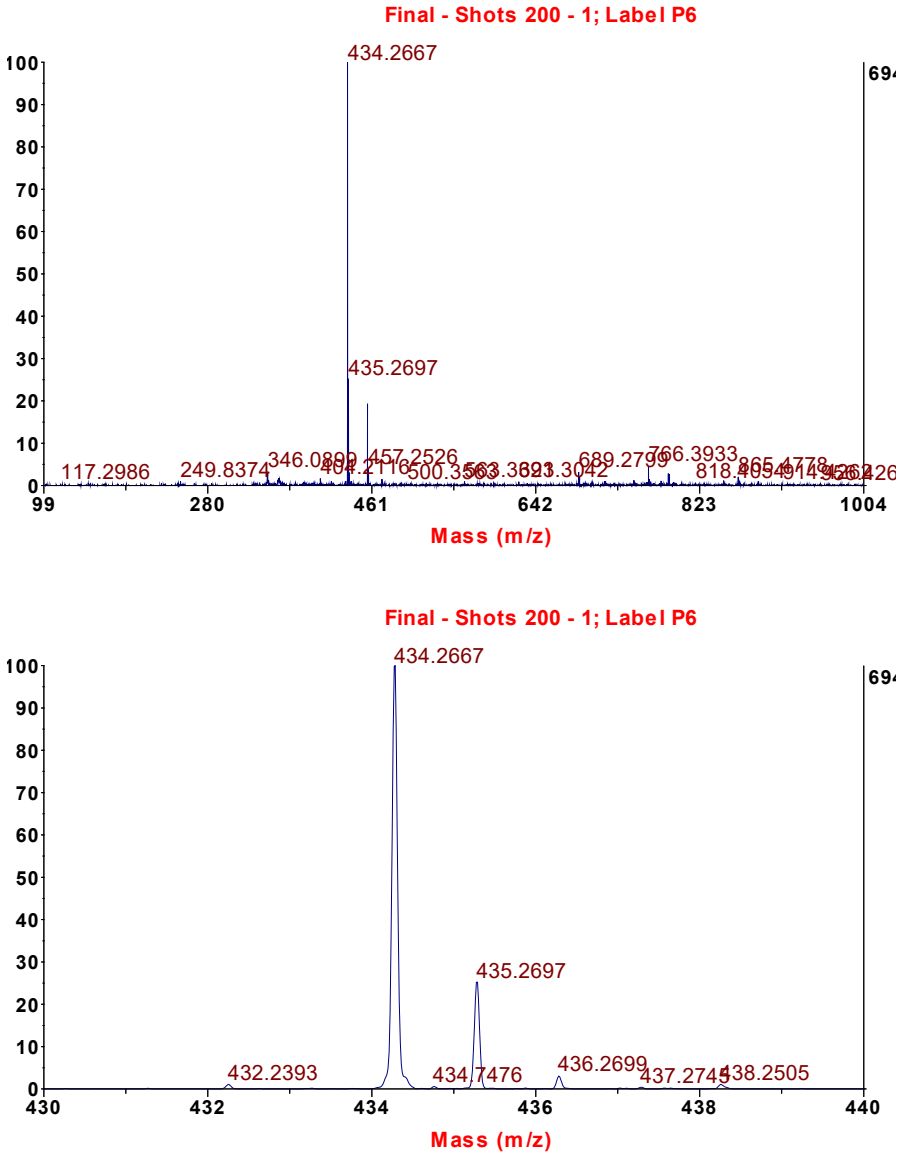


Figure S32. Mass spectar of **13** in the area m/z 99 – 1004 (upper spectrum) and its enlarged view in the area m/z 430– 440 (lower spectrum).

14

Molecular formula: $C_{28}H_{39}ClN_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 498.2968

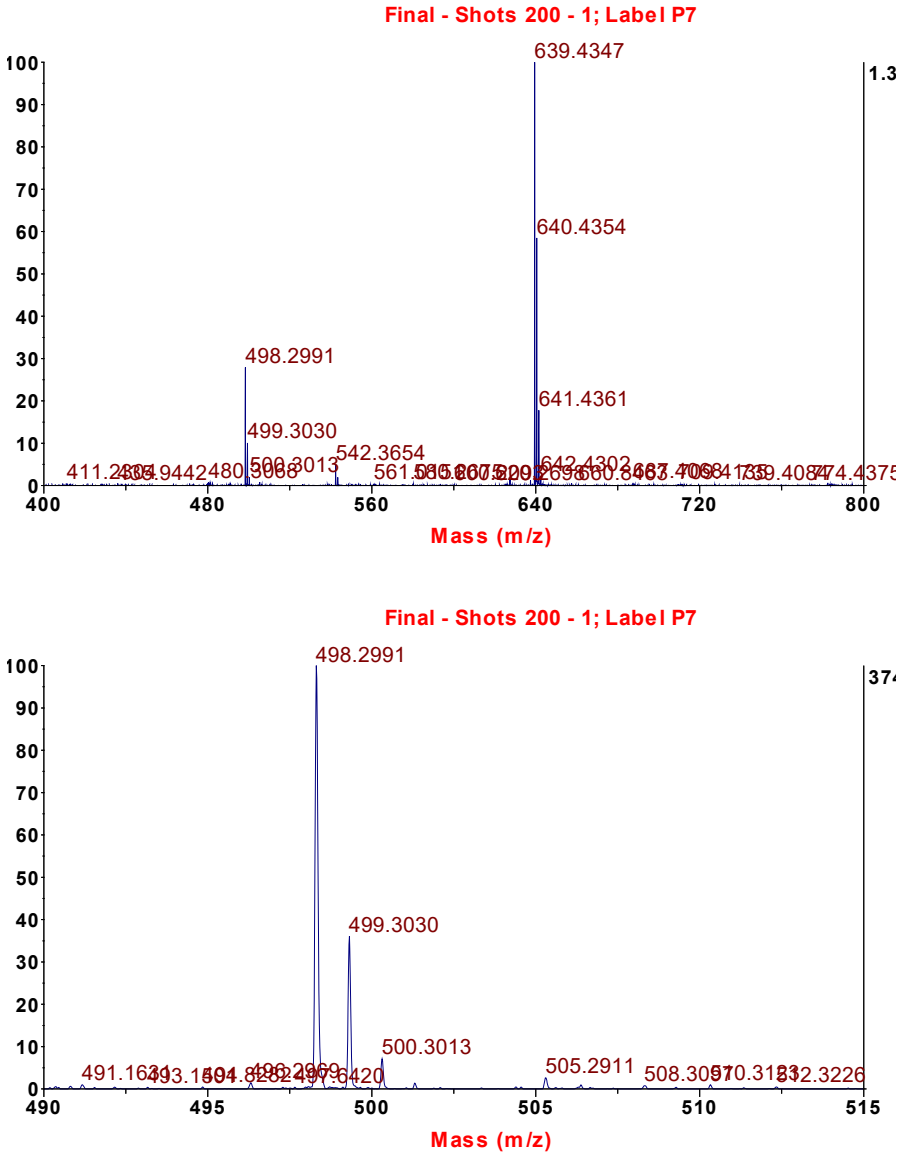


Figure S33. Mass spectar of **14** in the area m/z 400 – 800 (upper spectrum) and its enlarged view in the area m/z 490 – 515 (lower spectrum).

15

Molecular formula: $C_{26}H_{39}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 474.2968

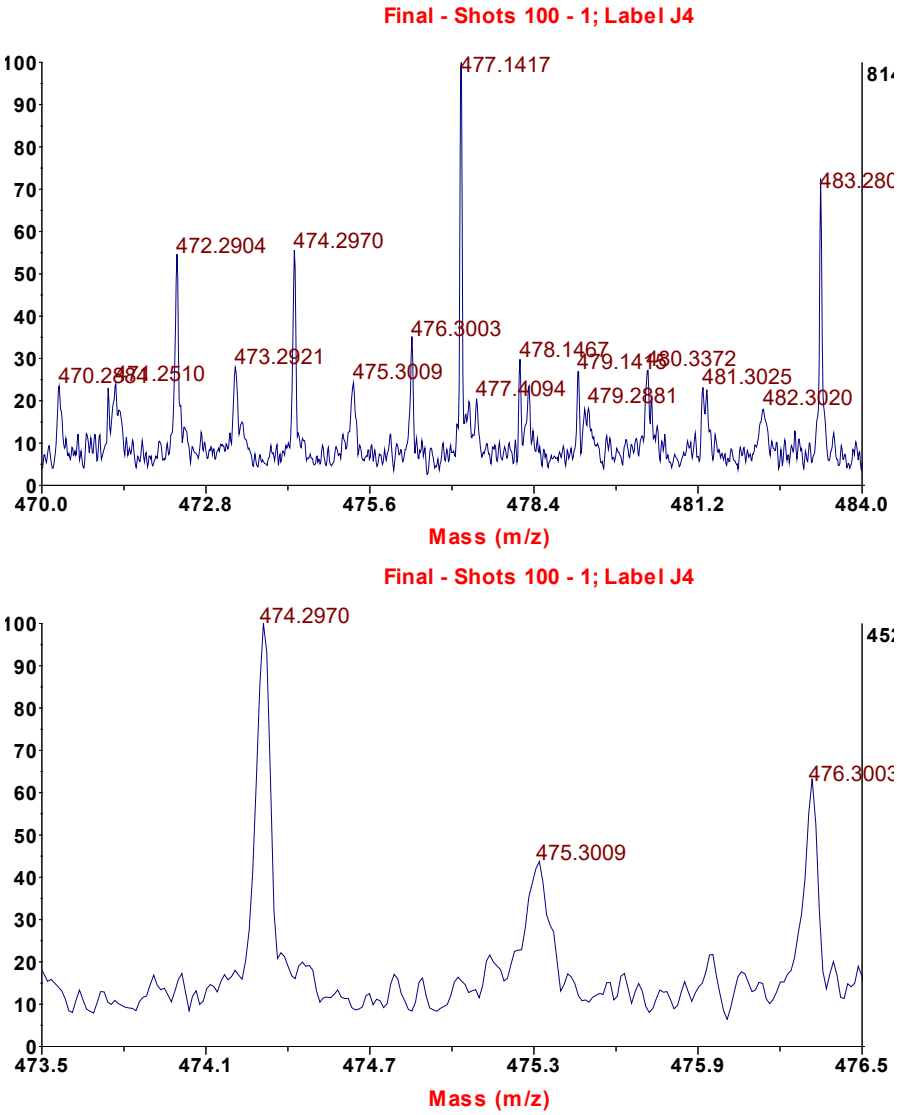


Figure S34. Mass spectar of **15** in the area m/z 470 – 484 (upper spectrum) and its enlarged view in the area m/z 473.5 – 476.5 (lower spectrum).

16

Molecular formula: $C_{25}H_{37}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 460.2811

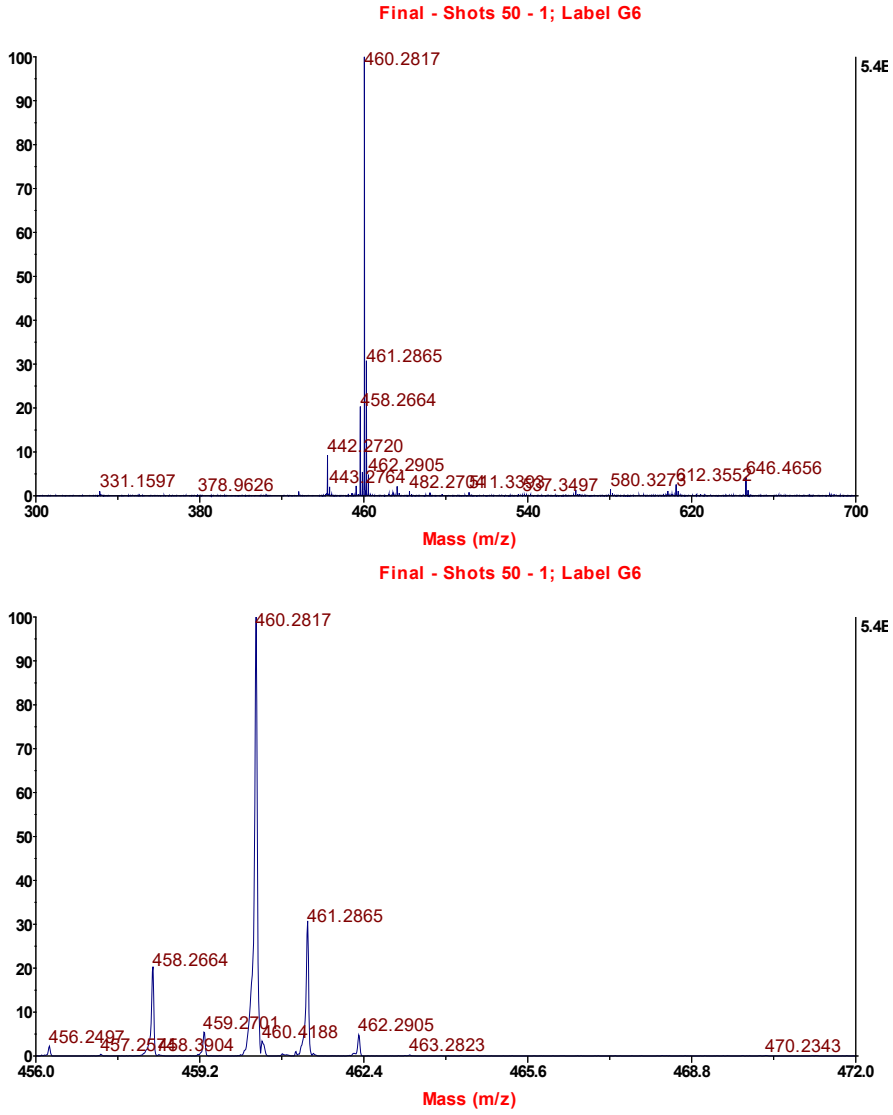


Figure S35. Mass spectar of **16** in the area m/z 300 – 700 (upper spectrum) and its enlarged view in the area m/z 456– 472 (lower spectrum).

17

Molecular formula: $C_{30}H_{43}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 526.3281

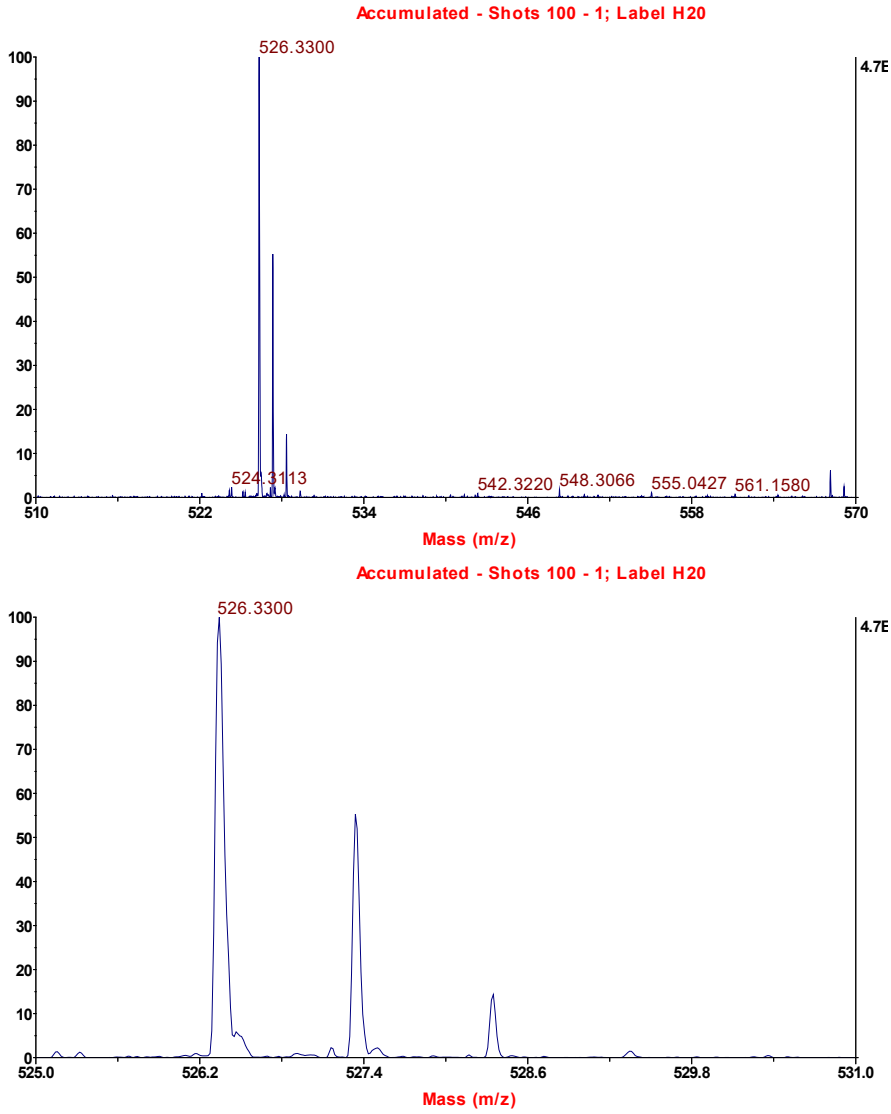


Figure S36. Mass spectar of **17** in the area m/z 510 – 570 (upper spectrum) and its enlarged view in the area m/z 525 – 531 (lower spectrum).

18

Molecular formula: $C_{30}H_{35}N_3O_5$

Theoretical monoisotropic mass $[M+H]^+$: 518.2655

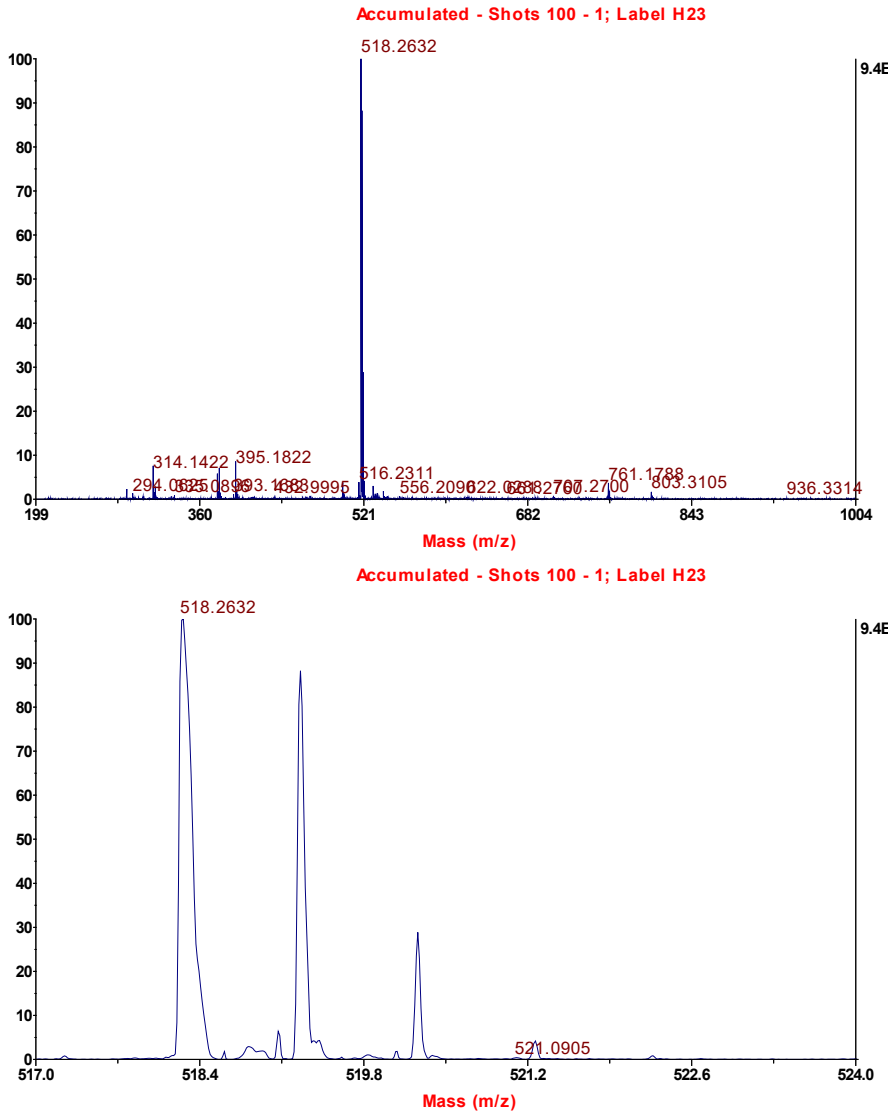


Figure S37. Mass spectar of **18** in the area m/z 199 – 1004 (upper spectrum) and its enlarged view in the area m/z 517 – 524 (lower spectrum).

List of predicted non-bonding interactions between hBChE and biscarbamates

Table S3. Interactions between compound **1** and BChE.

Amino acid	Non-bonding interactions
Ser198	O17, hydrogen bond-conventional hydrogen bond
Pro285	H36, hydrogen bond-conventional hydrogen bond
Gln119	H37, hydrogen bond-conventional hydrogen bond
His438	H48, hydrogen bond-conventional hydrogen bond
Gly117	O8, hydrogen bond-carbon hydrogen bond
His438	O10, hydrogen bond-carbon hydrogen bond
Gln119	H34, hydrogen bond-carbon hydrogen bond
Gln119	H38, hydrogen bond-carbon hydrogen bond
Glu197	H50, hydrogen bond-carbon hydrogen bond
Leu286	H55, hydrogen bond-carbon hydrogen bond
Leu286	H57, hydrogen bond-carbon hydrogen bond
Phe329	2DM, hydrophobic-π-π T-shaped
Leu286	C27, hydrophobic-alkyl
Val288	C27, hydrophobic-alkyl
Leu286	C28, hydrophobic-alkyl
Trp82	C25, hydrophobic-π-alkyl
Trp82	C26, hydrophobic-π-alkyl
Trp82	C25, hydrophobic-π-alkyl
Trp82	C26, hydrophobic-π-alkyl
Trp231	C27, hydrophobic-π-alkyl
Trp231	C28, hydrophobic-π-alkyl
Trp231	C27, hydrophobic-π-alkyl
Trp231	C28, hydrophobic-π-alkyl
Phe398	C28, hydrophobic-π-alkyl
His438	C25, hydrophobic-π-alkyl

Table S4. Interactions between compound **2** and BChE.

Amino acid	Non-bonding interactions
HOH709	O13, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH706	H47, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Gln119	O17, hydrogen bond-conventional hydrogen bond
Gln119	H32, hydrogen bond-conventional hydrogen bond
Gly117	O10, hydrogen bond-carbon hydrogen bond
Ser198	H47, hydrogen bond-carbon hydrogen bond
Trp231	H45, hydrophobic-π-sigma
Leu286	C21, hydrophobic-alkyl
Trp82	C25, hydrophobic-π-alkyl
Trp82	C25, hydrophobic-π-alkyl
Trp231	C22, hydrophobic-π-alkyl
Phe329	C21, hydrophobic-π-alkyl
Phe398	C22, hydrophobic-π-alkyl
His438	C25, hydrophobic-π-alkyl

Table S5. Interactions between compound **3** and BChE.

Amino acid	Non-bonding interactions
HOH709	O13, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Ser287	O17, hydrogen bond-conventional hydrogen bond
Gly117	O7, hydrogen bond-carbon hydrogen bond
Ser198	H59, hydrogen bond-carbon hydrogen bond
Leu286	H61, hydrogen bond-carbon hydrogen bond
Val288	C30, hydrophobic-alkyl
Trp82	7DM, hydrophobic-π-alkyl
Trp82	7DM, hydrophobic-π-alkyl
Trp231	C29, hydrophobic-π-alkyl
Trp231	C30, hydrophobic-π-alkyl
Trp231	C29, hydrophobic-π-alkyl
Trp231	C30, hydrophobic-π-alkyl
Phe398	C29, hydrophobic-π-alkyl
His438	7DM, hydrophobic-π-alkyl

Table S6. Interactions between compound **4** and BChE.

Amino acid	Non-bonding interactions
HOH930	O17, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H38, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH706	H51, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH1031	H66, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Gln119	O8, hydrogen bond-conventional hydrogen bond
Asp70	H35, hydrogen bond-conventional hydrogen bond
Pro285	O17, hydrogen bond-carbon hydrogen bond
Leu286	O7, hydrogen bond-carbon hydrogen bond
Leu286	H56, hydrogen bond-carbon hydrogen bond
Leu286	H57, hydrogen bond-carbon hydrogen bond
Leu286	C27, hydrophobic-alkyl
Val288	C27, hydrophobic-alkyl
Trp82	2EN, hydrophobic-π-alkyl
Trp82	2EN, hydrophobic-π-alkyl
Trp231	C27, hydrophobic-π-alkyl
Trp231	C27, hydrophobic-π-alkyl
Phe329	C26, hydrophobic-π-alkyl
Phe398	C26, hydrophobic-π-alkyl
His438	C26, hydrophobic-π-alkyl

Table S7. Interactions between compound **5** and BChE.

Amino acid	Non-bonding interactions
HOH736	O13, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH910	O10, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H33, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH910	H34, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Gly117	O17, hydrogen bond-carbon hydrogen bond
His438	H40, hydrogen bond-carbon hydrogen bond
Trp82	N15, electrostatic-π-cation
Leu286	C20, hydrophobic-alkyl
Trp82	C29, hydrophobic-π-alkyl
Trp82	C29, hydrophobic-π-alkyl
Trp231	C20, hydrophobic-π-alkyl
Trp231	C20, hydrophobic-π-alkyl
Phe329	C19, hydrophobic-π-alkyl
Phe398	C19, hydrophobic-π-alkyl
His438	C19, hydrophobic-π-alkyl

Table S8. Interactions between compound **6** and BChE.

Amino acid	Non-bonding interactions
HOH786	O17, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH910	O13, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH989	H43, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH706	H64, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Gly116	H39, hydrogen bond-conventional hydrogen bond
Leu286	H59, hydrogen bond-carbon hydrogen bond
Glu197	H69, hydrogen bond-carbon hydrogen bond
Gly116;Gly117	7EN, hydrophobic-amide-π stacked
Leu286	C30, hydrophobic-alkyl
Val288	C30, hydrophobic-alkyl
Trp82	C32, hydrophobic-π-alkyl
Trp82	C32, hydrophobic-π-alkyl
Trp82	C33, hydrophobic-π-alkyl
Trp231	C31, hydrophobic-π-alkyl
Trp231	C31, hydrophobic-π-alkyl
His438	C32, hydrophobic-π-alkyl

Table S9. Interactions between compound **7** and BChE.

Amino acid	Non-bonding interactions
Asp70	H40, hydrogen bond; electrostatic-salt bridge; attractive charge
HOH825	H37, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH806	H40, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH930	H41, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH989	H42, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH708	H59, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Gln119	O17, hydrogen bond-conventional hydrogen bond
Gly116	O7, hydrogen bond-carbon hydrogen bond
Gly117	O17, hydrogen bond-carbon hydrogen bond
His438	O10, hydrogen bond-carbon hydrogen bond
Asp70	H39, hydrogen bond-carbon hydrogen bond
Leu286	H51, hydrogen bond-carbon hydrogen bond
Leu286	H53, hydrogen bond-carbon hydrogen bond
Glu197	H59, hydrogen bond-carbon hydrogen bond
Glu197	H60, hydrogen bond-carbon hydrogen bond
Tyr332	N15, electrostatic-π-cation
Leu286	C27, hydrophobic-alkyl
Val288	C27, hydrophobic-alkyl
Trp82	C31, hydrophobic-π-alkyl
Trp82	C32, hydrophobic-π-alkyl
Trp82	C31, hydrophobic-π-alkyl
Trp82	C32, hydrophobic-π-alkyl
Trp231	C27, hydrophobic-π-alkyl
Trp231	C28, hydrophobic-π-alkyl
Trp231	C27, hydrophobic-π-alkyl
Trp231	C28, hydrophobic-π-alkyl
Phe398	C28, hydrophobic-π-alkyl

Table S10. Interactions between compound **8** and BChE.

Amino acid	Non-bonding interactions
HOH736	O13, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH910	H35, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Gly117	O17, hydrogen bond-carbon hydrogen bond
Ser287	H51, hydrogen bond-carbon hydrogen bond
Trp82	N15, electrostatic-π-cation
Trp82	H68, hydrophobic-π-sigma
Leu286	C20, hydrophobic-alkyl
Val288	C20, hydrophobic-alkyl
Ser287	H66, hydrogen bond-carbon hydrogen bond
Trp82	C31, hydrophobic-π-alkyl
Trp82	C31, hydrophobic-π-alkyl
Trp231	C20, hydrophobic-π-alkyl
Trp231	C20, hydrophobic-π-alkyl
Phe329	C21, hydrophobic-π-alkyl
His438	C21, hydrophobic-π-alkyl

Table S11. Interactions between compound **9** and BChE.

Amino acid	Non-bonding interactions
HOH930	O17, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH709	O13, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH706	H61, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Asp70	H36, hydrogen bond-conventional hydrogen bond
Leu286	H70, hydrogen bond-carbon hydrogen bond
Leu286	C31, hydrophobic-alkyl
Trp82	7DE, hydrophobic-π-alkyl
Trp82	7DE, hydrophobic-π-alkyl
Trp231	C30, hydrophobic-π-alkyl
Trp231	C30, hydrophobic-π-alkyl
Trp231	C31, hydrophobic-π-alkyl
Trp231	C31, hydrophobic-π-alkyl
Phe398	C30, hydrophobic-π-alkyl
His438	7DE, hydrophobic-π-alkyl
His438	C30, hydrophobic-π-alkyl

Table S12. Interactions between compound **10** and BChE.

Amino acid	Non-bonding interactions
HOH825	H39, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH706	H62, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Leu286	C33, hydrophobic-alkyl
Val288	C33, hydrophobic-alkyl
Trp231	C33, hydrophobic-π-alkyl
Trp231	C33, hydrophobic-π-alkyl
Phe329	C32, hydrophobic-π-alkyl
Phe398	C32, hydrophobic-π-alkyl
His438	C32, hydrophobic-π-alkyl

Table S13. Interactions between compound **11** and BChE.

Amino acid	Non-bonding interactions
HOH709	O17, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H61, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH706	H63, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Ser287	O13, hydrogen bond-conventional hydrogen bond
Pro285	H39, hydrogen bond-conventional hydrogen bond
Gln119	H40, hydrogen bond-carbon hydrogen bond
Leu286	H72, hydrogen bond-carbon hydrogen bond
Ala328	C28, hydrophobic-alkyl
Leu286	C33, hydrophobic-alkyl
Val288	C33, hydrophobic-alkyl
Trp231	C32, hydrophobic-π-alkyl
Trp231	C33, hydrophobic-π-alkyl
Phe329	C28, hydrophobic-π-alkyl
Phe329	C29, hydrophobic-π-alkyl
Tyr332	C28, hydrophobic-π-alkyl

Phe398	C32, hydrophobic-π-alkyl
His438	C29, hydrophobic-π-alkyl
His438	C32, hydrophobic-π-alkyl

Table S14. Interactions between compound **12** and BChE.

Amino acid	Non-bonding interactions
Asp70	H41, hydrogen bond; electrostatic-salt bridge; attractive charge
HOH930	O10, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH930	H37, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H42, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH706	H62, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Gln119	O7, hydrogen bond-conventional hydrogen bond
Pro285	O10, hydrogen bond-carbon hydrogen bond
Asp70	H36, hydrogen bond-carbon hydrogen bond
Asp70	H38, hydrogen bond-carbon hydrogen bond
HOH930	2MF, other-π-lone pair
Ala277	2P, hydrophobic-alkyl
Leu286	2P, hydrophobic-alkyl
Trp82	2P, hydrophobic-π-alkyl
Trp82	2P, hydrophobic-π-alkyl
Trp231	2P, hydrophobic-π-alkyl
Trp231	2P, hydrophobic-π-alkyl
His438	2P, hydrophobic-π-alkyl

Table S15. Interactions between compound **13** and BChE.

Amino acid	Non-bonding interactions
Asp70	N15, electrostatic-attractive charge
HOH736	O8, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH786	O17, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH709	6P, hydrogen bond-water hydrogen bond; π-donor hydrogen donor
HOH920	H37, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH989	H38, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH930	H40, hydrogen bond-water hydrogen bond; conventional hydrogen bond
Asp70	H36, hydrogen bond-conventional hydrogen bond
Asp70	H35, hydrogen bond-carbon hydrogen bond
Gln119	H38, hydrogen bond-carbon hydrogen bond
Leu286	6P, hydrophobic-alkyl
Trp82	6P, hydrophobic-π-alkyl
Trp82	6P, hydrophobic-π-alkyl
Trp231	6P, hydrophobic-π-alkyl
Trp231	6P, hydrophobic-π-alkyl

Table S16. Interactions between compound **14** and BChE.

Amino acid	Non-bonding interactions
HOH736	O13, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH930	O17, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH910	H41, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH706	H62, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Ser198	H61, hydrogen bond-carbon hydrogen bond
Leu286	H67, hydrogen bond-carbon hydrogen bond
Trp82	N15, electrostatic-π-cation
Trp82	H50, hydrophobic-π-sigma
Leu286	7P, hydrophobic-alkyl
Trp82	7P, hydrophobic-π-alkyl
Trp231	7P, hydrophobic-π-alkyl
Trp231	7P, hydrophobic-π-alkyl
His438	7P, hydrophobic-π-alkyl

Table S17. Interactions between compound **15** and BChE.

Amino acid	Non-bonding interactions
Asp70	H38, hydrogen bond-carbon hydrogen bond
Gln119	H63, hydrogen bond-carbon hydrogen bond
Leu286	H65, hydrogen bond-carbon hydrogen bond
Leu286	H66, hydrogen bond-carbon hydrogen bond
Trp82	N15, electrostatic-π-cation
Leu286	2PI, hydrophobic-alkyl
Trp82	2PI, hydrophobic-alkyl
Trp231	2PI, hydrophobic-π-alkyl
Trp231	2PI, hydrophobic-π-alkyl

Table S18. Interactions between compound **16** and BChE.

Amino acid	Non-bonding interactions
HOH709	O17, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH1024	H38, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH825	H43, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH825	H50, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH706	H61, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Ala277	C31, hydrophobic-alkyl
Leu286	5PI, hydrophobic-alkyl
Ala328	5PI, hydrophobic-alkyl
Trp231	5PI, hydrophobic-π-alkyl
Trp231	5PI, hydrophobic-π-alkyl
Phe329	5PI, hydrophobic-π-alkyl
Tyr332	5PI, hydrophobic-π-alkyl

Table S19. Interactions between compound **17** and BChE.

Amino acid	Non-bonding interactions
HOH910	O7, hydrogen bond-water hydrogen bond; conventional hydrogen bond
HOH709	O10, hydrogen bond-water hydrogen bond; carbon hydrogen bond
HOH825	H71, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Ser287	H43, hydrogen bond-conventional hydrogen bond
Thr284	H46, hydrogen bond-conventional hydrogen bond
Gly117	O8, hydrogen bond-carbon hydrogen bond
Thr284	H42, hydrogen bond-carbon hydrogen bond
Ser287	H42, hydrogen bond-carbon hydrogen bond
Ser287	H42, hydrogen bond-carbon hydrogen bond
Asp70	H64, hydrogen bond-carbon hydrogen bond
Leu286	H81, hydrogen bond-carbon hydrogen bond
Ala199	7PI, hydrophobic-alkyl
Ala328	7PI, hydrophobic-alkyl
Trp231	7PI, hydrophobic-π-alkyl
Trp231	7PI, hydrophobic-π-alkyl
Phe329	7PI, hydrophobic-π-alkyl
Tyr332	7PI, hydrophobic-π-alkyl

Table S20. Interactions between compound **18** and BChE.

Amino acid	Non-bonding interactions
HOH825	H48, hydrogen bond-water hydrogen bond; carbon hydrogen bond
Leu286	H52, hydrogen bond-carbon hydrogen bond
Ser287	H53, hydrogen bond-carbon hydrogen bond
HOH930	2MF, other-π-lone pair
Tyr332	O10, other-π-lone pair
Trp82	2MF, hydrophobic-π-π T-shaped
Trp231	2MF, hydrophobic-π-π T-shaped
Trp231	2MF, hydrophobic-π-π T-shaped
Tyr332	2MF, hydrophobic-π-π T-shaped
Pro285	2MF, hydrophobic-alkyl
Ala328	C20, hydrophobic-alkyl
Val288	C21, hydrophobic-alkyl
Phe329	C20, hydrophobic-π-alkyl
Tyr332	C20, hydrophobic-π-alkyl
Leu286	2MF, hydrophobic-π-alkyl