Rational Design of Potent α-Conotoxin PeIA Analogues with Non-Natural Amino Acids for the Inhibition of Human $\alpha9\alpha10$ Nicotinic Acetylcholine Receptors

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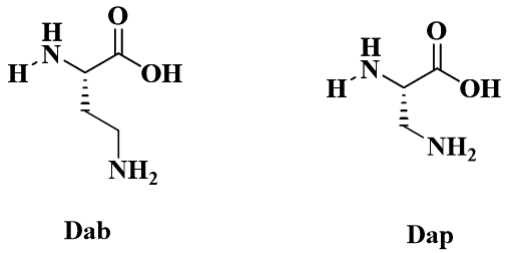
Table S1. Pairwise interactions between PeIA (left) and PeIA[S4Dap, S9Dap] (right) at $\alpha9(+)\alpha9(-)$ binding sites of h$\alpha9\alpha10$ nAChR.

PeIA residue	α9(+)α9(−)		α9(+)α9(−)		PeIA[S4Dap,S9Dap] residue
	α9(+)	α9(−)	α9(+)	α9(−)	
S4		D169		D166, S168, D169	Dap4
P6	W149		W149		P6
S9				Q34	Dap9
N11			N154		N11
H12	Y197		Y197		H12
P13		I59, L115		I59, L115	P13
E14		**R111**		**R111**	E14

Contacts between h$\alpha9\alpha10$ nAChR and PeIA/PeIA[S4Dap, S9Dap] are defined as van der Waals interactions if the distance between heavy atoms of them is between 2 and 4 Å. The electronic interactions are in bold.



Dab **Dap**

Figure S1. The structures of amino acids Dab-OH and Dap-OH. The non-proteinogenic amino acids Dab-OH and Dap-OH contain the same two and one methylene chain, respectively.

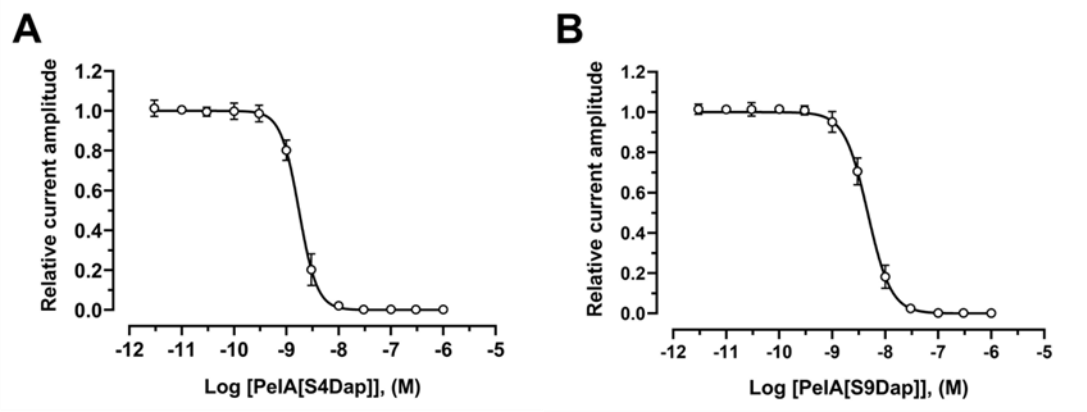


Figure S2. Concentration–response relationships of relative ACh-evoked current amplitude (mean ± SD, n = 7) mediated by hα9α10 nAChRs in the presence of (**A**) PeIA[S4Dap] and (**B**) PeIA[S9Dap] giving IC_{50}'s of 1.74 nM (1.67 – 1.82; 95% CI) and 4.67 nM (4.45 – 4.90; 95% CI), respectively. Whole-cell currents at hα9α10 were activated by 6 μM ACh.

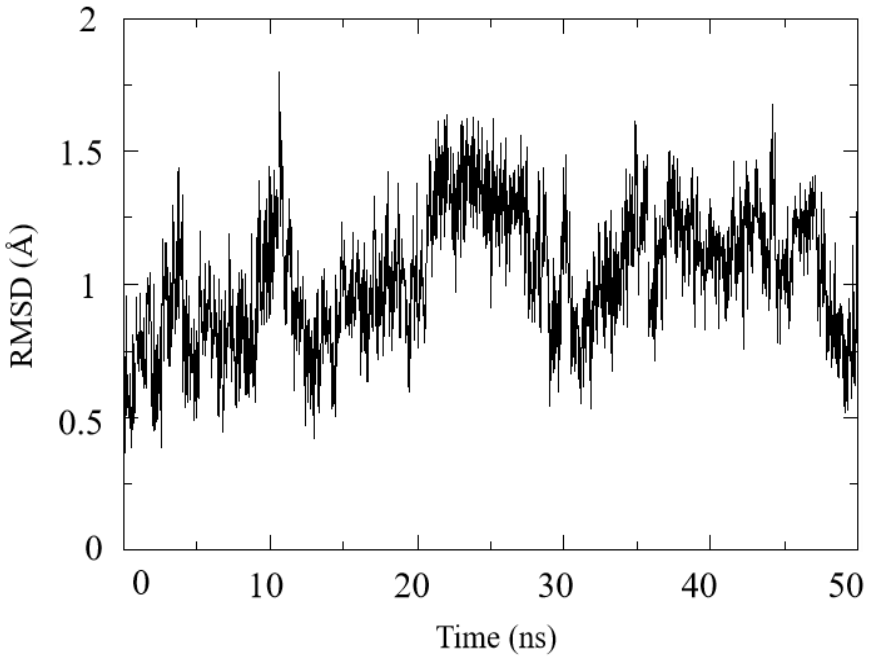


Figure S3. Evolution of root mean square deviation (RMSD) of PeIA.

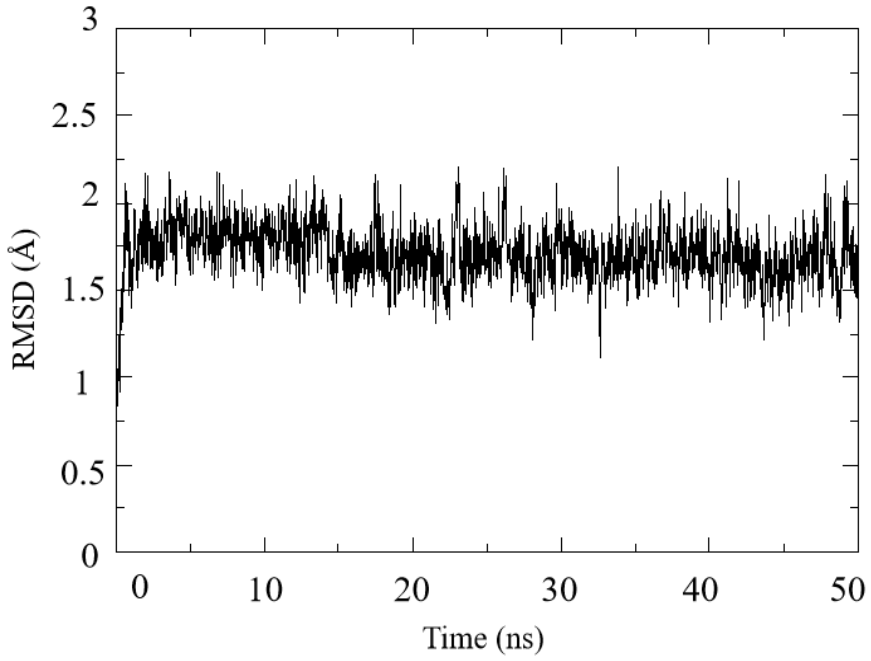


Figure S4. Evolution of root mean square deviation (RMSD) of PeIA[S4Dap, S9Dap].

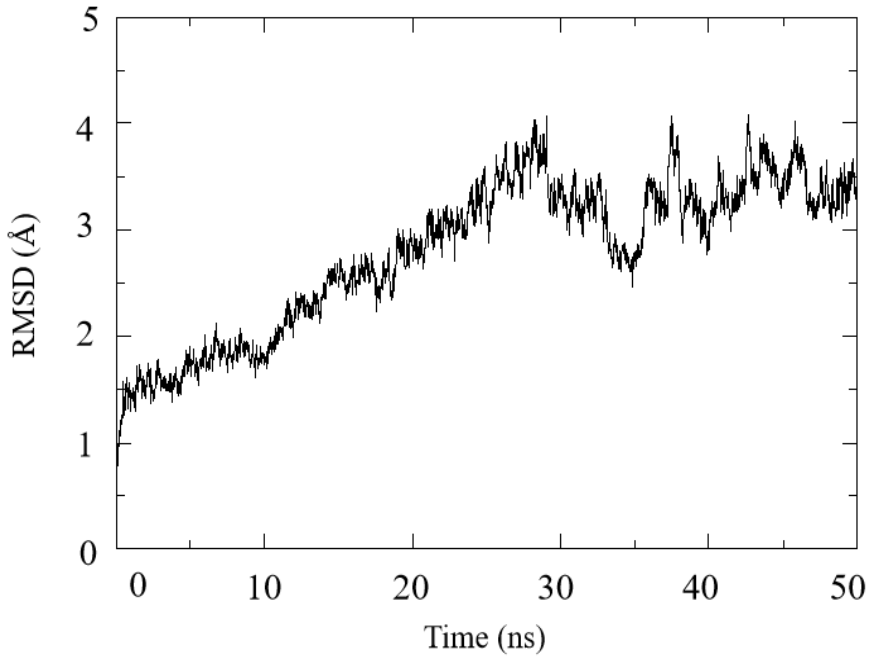


Figure S5. Evolution of root mean square deviation (RMSD) of PeIA bound to hα9α10 nAChR.

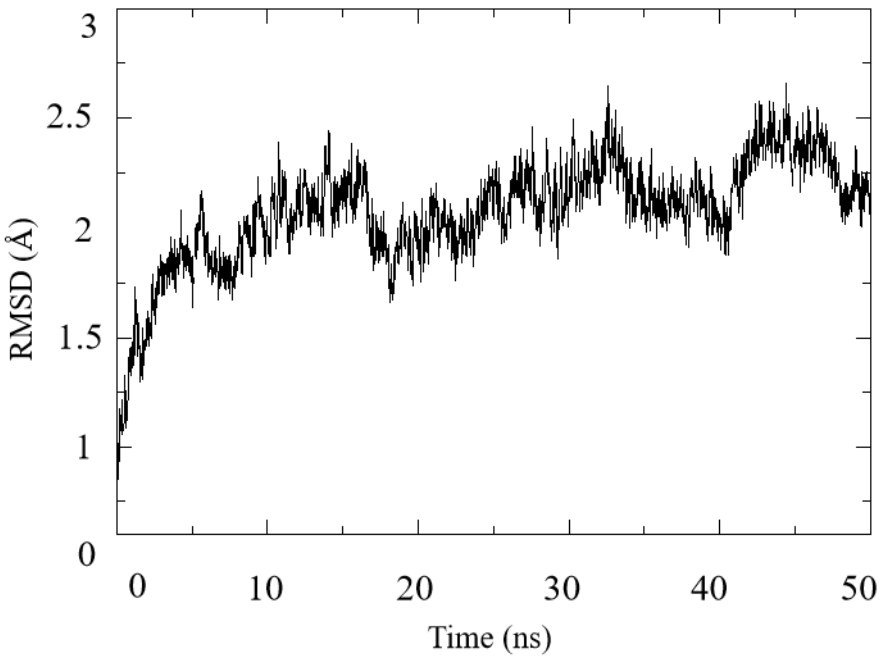
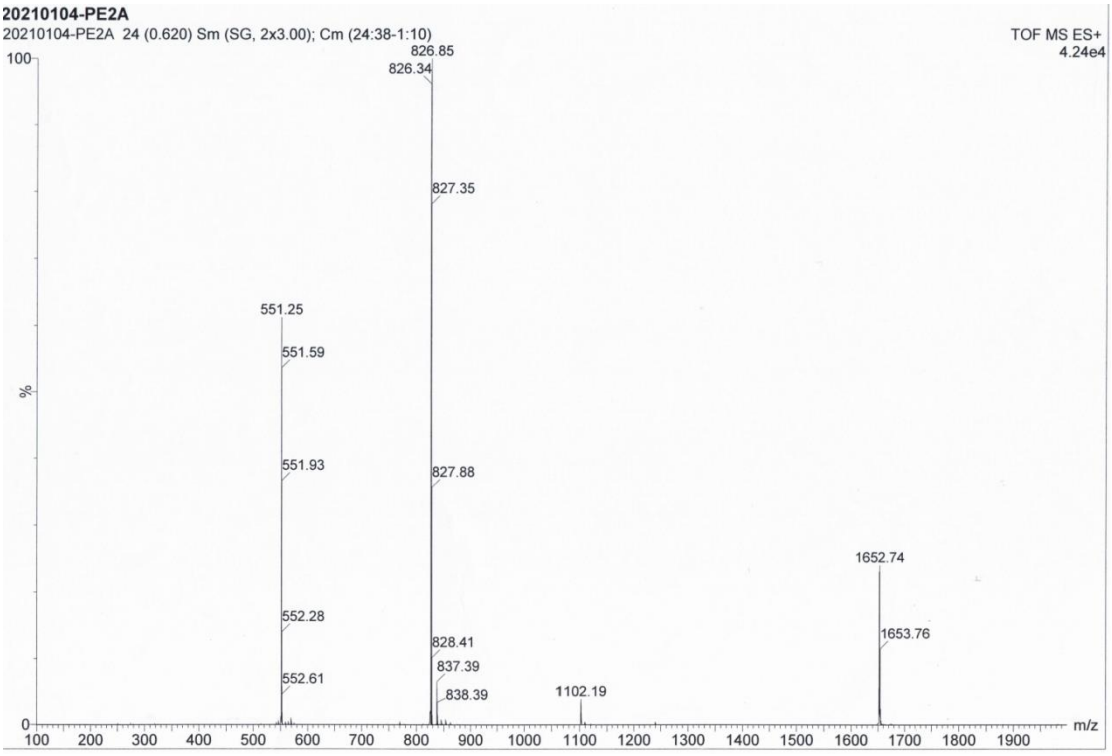


Figure S6. Evolution of root mean square deviation (RMSD) of PeIA[S4Dap, S9Dap] bound to hα9α10 nAChR.



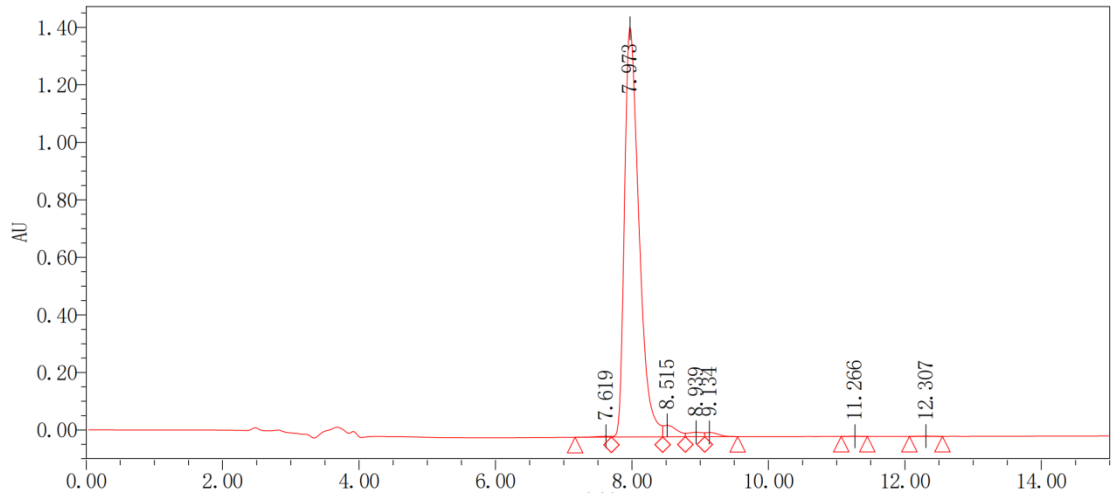
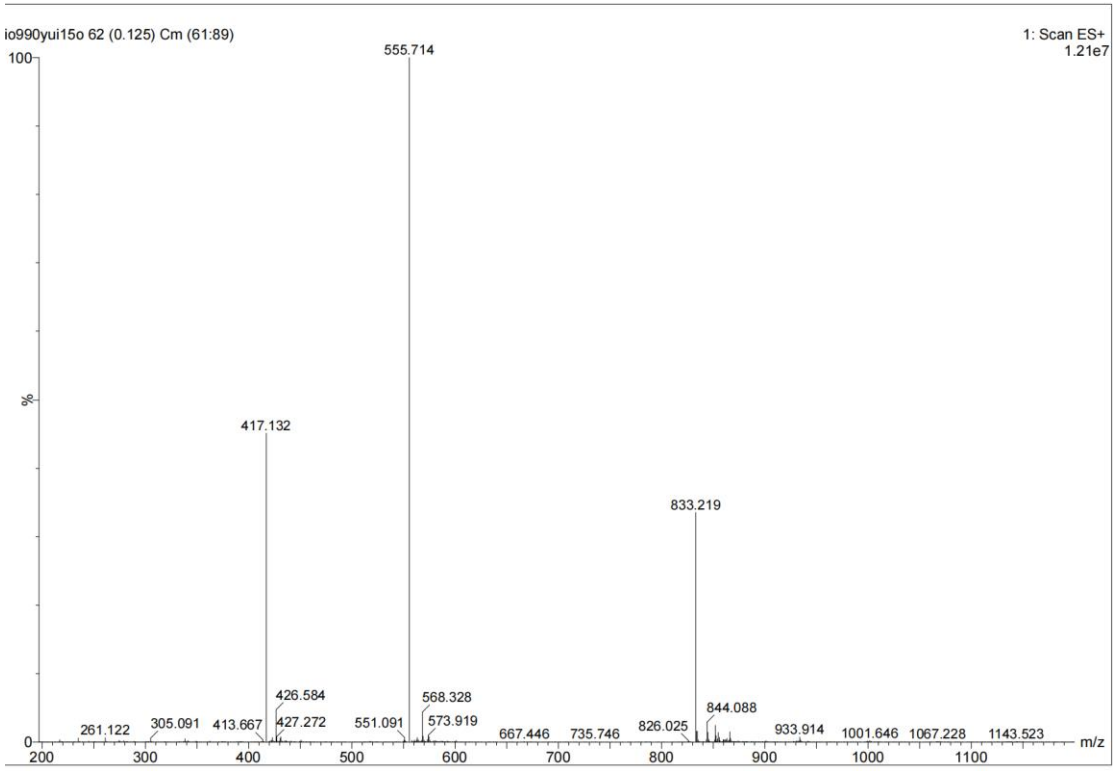


Figure S7. The ESI-MS and RP-HPLC of PeIA with a purity of 95.36%.



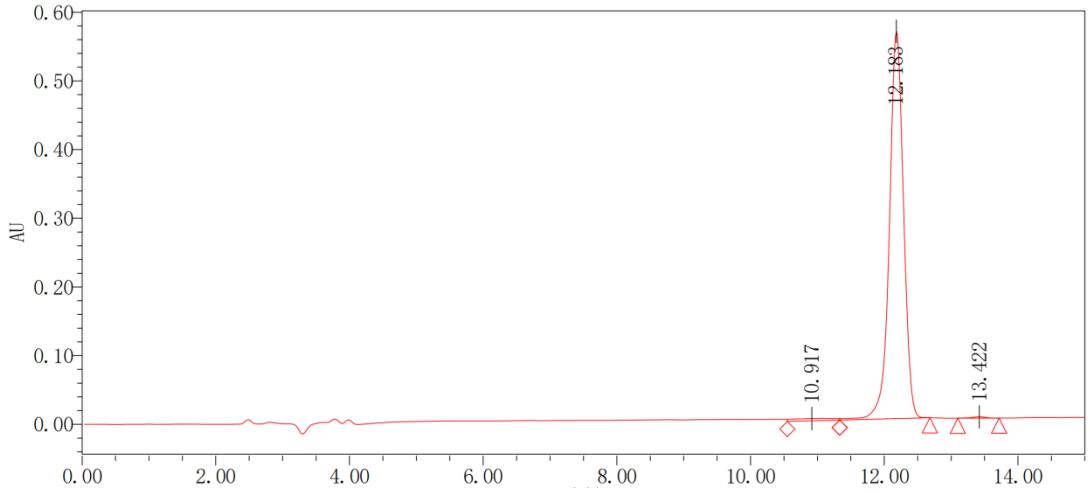
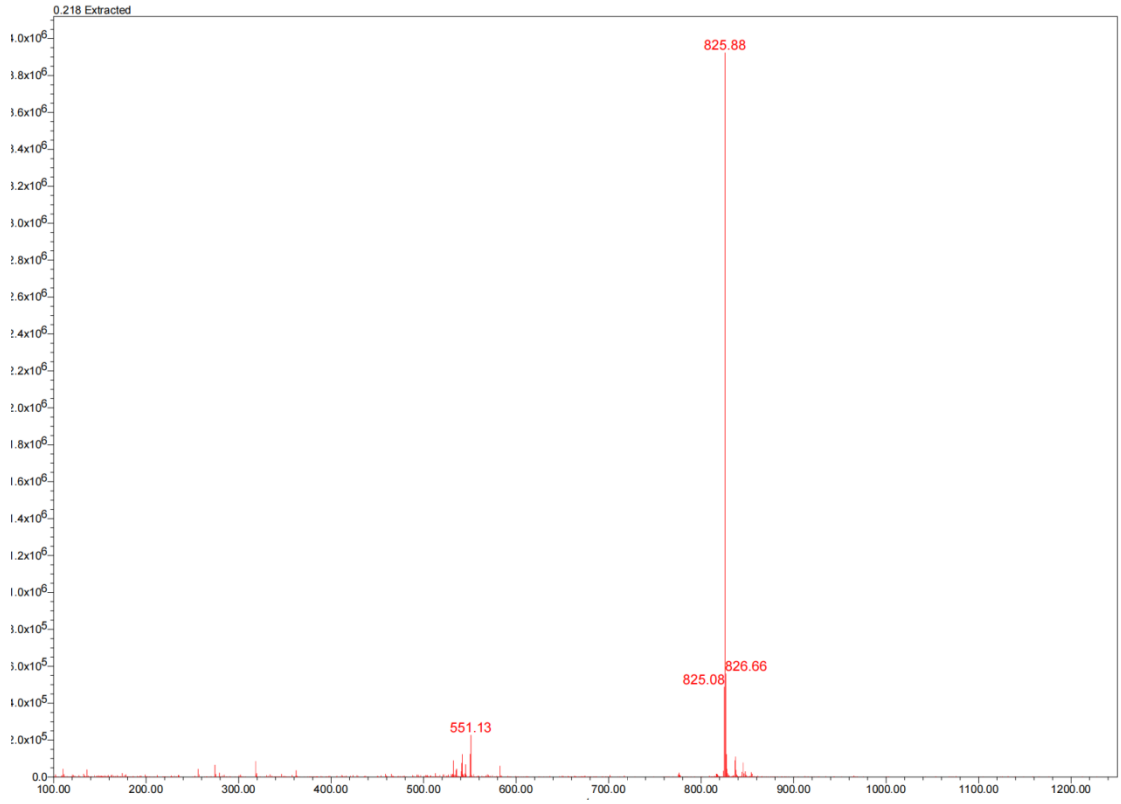


Figure S8. The ESI-MS and RP-HPLC of PeIA[S4Dab] with a purity of 99.67%.



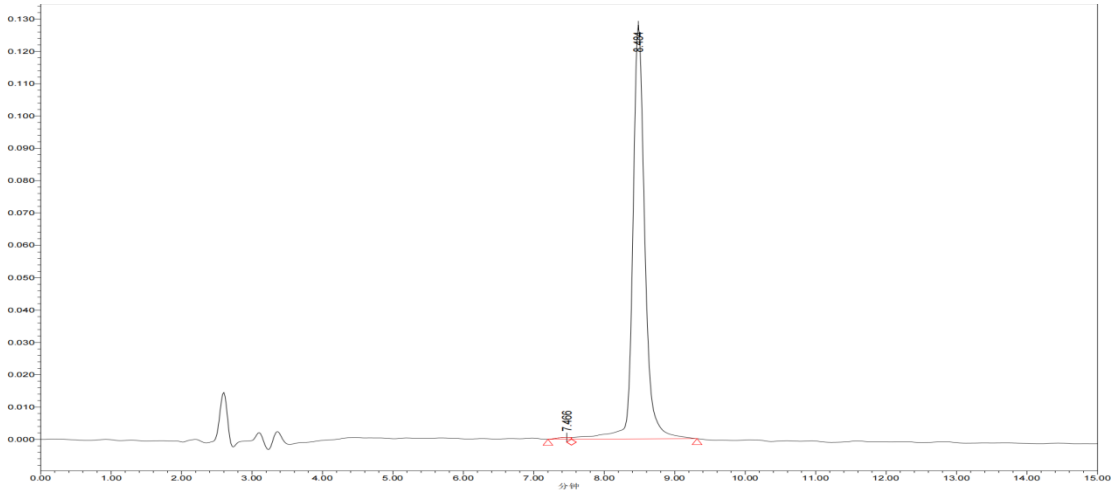
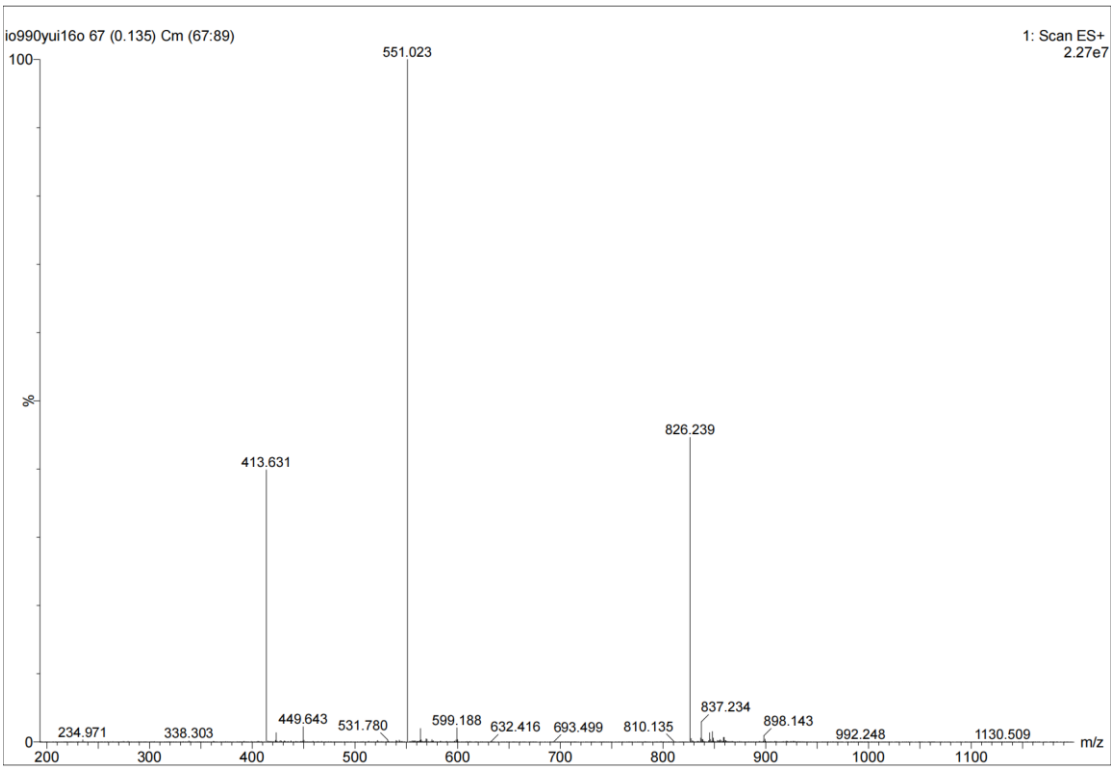


Figure S9. The ESI-MS and RP-HPLC of PeIA[S4Dap] with a purity of 99.53%.



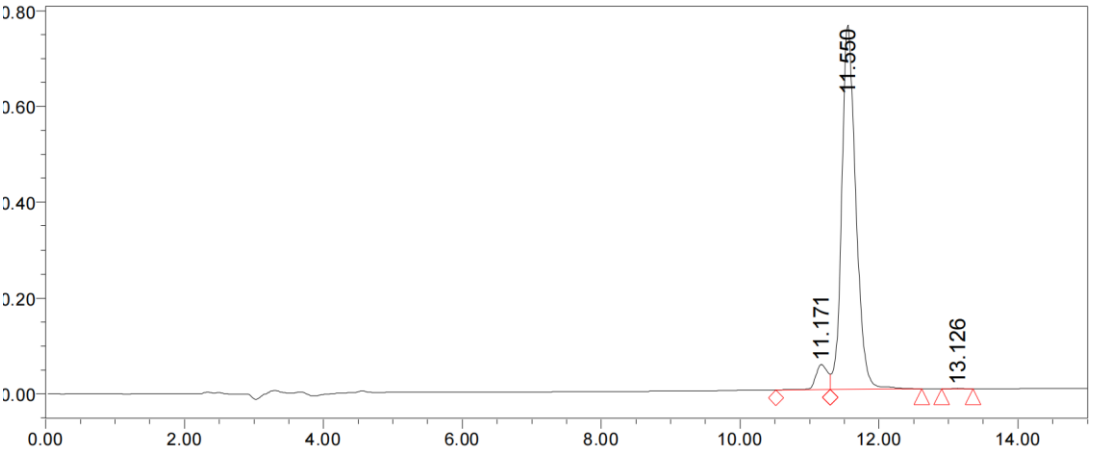


Figure S10. The ESI-MS and RP-HPLC of PeIA[S9Dap] with a purity of 94.68%.

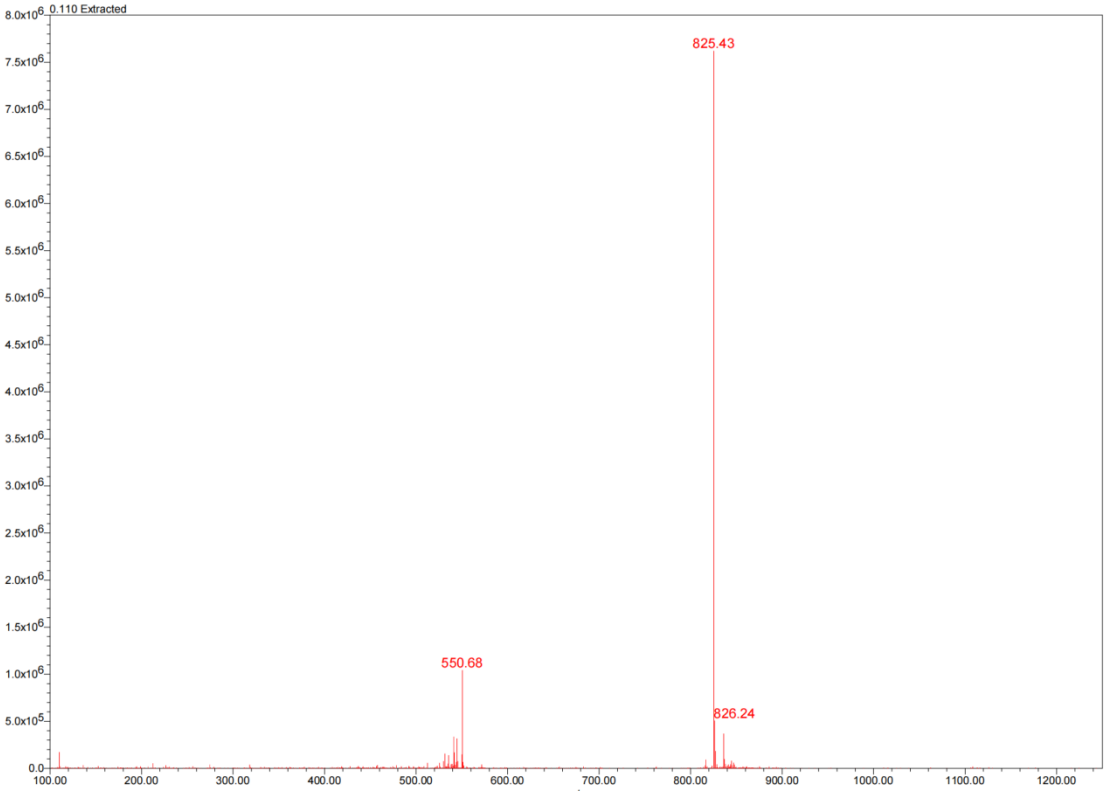


Figure S11. The ESI-MS and RP-HPLC of PeIA[S4Dap, S9Dap] with a purity of 99.28%.