Table S1. Diffusion coefficients of different lipid compositions were calculated in the simulation versus their extrapolation to the infinite box size.

Lipids	Water viscosity η_f (Poise)	Membrane viscosity η_m (Poise cm)	Interleaflet coupling b (Poise/cm)	D^{sim} (cm^2/s)	$D\infty$ (cm2/s)
POPC	0.00311	0.3×10^{-7}	0.1×10^{-7}		5.1×10^{-7}
	0.00311	2.3×10^{-7}	1.0×10^{-7}		1.0×10^{-7}
	0.00311	4.3×10^{-7}	10×10^{-7}	1.5×10^{-07}	0.6×10^{-7}
	0.0089	0.3×10^{-7}	0.1×10^{-7}		4.0×10^{-7}
	0.0089	2.3×10^{-7}	1.0×10^{-7}		0.9×10^{-7}
	0.0089	4.3×10^{-7}	10×10^{-7}		0.5×10^{-7}
POPC:POPG (3:1)	0.00311	0.3×10^{-7}	0.1×10^{-7}		5.2×10^{-7}
	0.00311	2.3×10^{-7}	1.0×10^{-7}		1.0×10^{-7}
	0.00311	4.3×10^{-7}	10×10^{-7}	1.6×10^{-7}	0.6×10^{-7}
	0.0089	0.3×10^{-7}	0.1×10^{-7}		4.0×10^{-7}
	0.0089	2.3×10^{-7}	1.0×10^{-7}		0.9×10^{-7}
	0.0089	4.3×10^{-7}	10×10^{-7}		0.5×10^{-7}
POPC:POPG (1:1)	0.00311	0.3×10^{-7}	0.1×10^{-7}		5.0×10^{-7}
	0.00311	2.3×10^{-7}	1.0×10^{-7}		1.0×10^{-7}
	0.00311	4.3×10^{-7}	10×10^{-7}	1.3×10^{-7}	0.6×10^{-7}
	0.0089	0.3×10^{-7}	0.1×10^{-7}		3.9×10^{-7}
	0.0089	2.3×10^{-7}	1.0×10^{-7}		0.9×10^{-7}
	0.0089	4.3×10^{-7}	10×10^{-7}		0.5×10^{-7}
POPC:POPG (1:3)	0.00311	0.3×10^{-7}	0.1×10^{-7}		5.1×10^{-7}
	0.00311	2.3×10^{-7}	1.0×10^{-7}		1.0×10^{-7}
	0.00311	4.3×10^{-7}	10×10^{-7}	1.5×10^{-7}	0.6×10^{-7}
	0.0089	0.3×10^{-7}	0.1×10^{-7}		4.0×10^{-7}
	0.0089	2.3×10^{-7}	1.0×10^{-7}		0.9×10^{-7}
	0.0089	4.3×10^{-7}	10×10^{-7}		0.5×10^{-7}
POPG	0.00311	0.3×10^{-7}	0.1×10^{-7}		5.1×10^{-7}
	0.00311	2.3×10^{-7}	1.0×10^{-7}		1.0×10^{-7}
	0.00311	4.3×10^{-7}	10×10^{-7}	1.4×10^{-7}	0.6×10^{-7}
	0.0089	0.3×10^{-7}	0.1×10^{-7}		4.0×10^{-7}
	0.0089	2.3×10^{-7}	1.0×10^{-7}		0.9×10^{-7}
	0.0089	4.3×10^{-7}	10×10^{-7}		0.5×10^{-7}

Parameters used in the extrapolation a Water height * H (nm) = 4, System lateral size L (nm) = 12 and Hydrodynamic radius R (nm) = 0.47 [1].

[1]. Venable, R.M.; Ingólfsson, H.I.; Lerner, M.G.; Perrin, B.S.; Camley, B.A.; Marrink, S.J.; Brown, F.L.H.; Pastor, R.W. Lipid and Peptide Diffusion in Bilayers: The Saffman–Delbrück Model and Periodic Boundary Conditions. *J. Phys. Chem. B* **2017**, *121*, 3443–3457, doi:10.1021/acs.jpcb.6b09111.

Table S2. Diffusion coefficients of SNX-482 in POPC: POPG (3:1) membrane calculated by extrapolation to the infinite box size.

toxin-membrane	Water height (nm)	System lateral size (nm)	Water viscosity η_f (Poise)	Membrane viscosity η_m (Poise cm)	Interleaflet coupling b (Poise/cm)	Hydrodynamic radius R (nm)	D^{sim} (cm2/s)	$D\infty$ (cm2/s)
SNX-482 POPC:POPG (3:1)	6	16	0.00311	0.3×10^{-7}	0.1×10^{-7}	1.08	4.1×10^{-8}	2.96×10^{-07}
			0.00311	2.3×10^{-7}	1.0×10^{-7}			1.06×10^{-7}
			0.00311	4.3×10^{-7}	10×10^{-7}			0.66×10^{-7}
			0.0089	0.3×10^{-7}	0.1×10^{-7}			1.87×10^{-7}
			0.0089	2.3×10^{-7}	1.0×10^{-7}			0.89×10^{-7}
			0.0089	4.3×10^{-7}	10×10^{-7}			0.56×10^{-7}

Figure S1. Comparative modeling scheme SNX-482. We randomly selected 3 PDB from Jingzhaotoxin-XI (Id: 2A2V) to perform independent 40 ns all-atom MD simulations. Afterward, we carried out comparative modeling with the central cluster of the simulations to produce 100 comparative models of SNX-482. We randomly selected 3 SNX-482 models and performed 40 ns all-atom MD simulations. The final SNX-482 comparative model corresponds to the central cluster of these simulations.
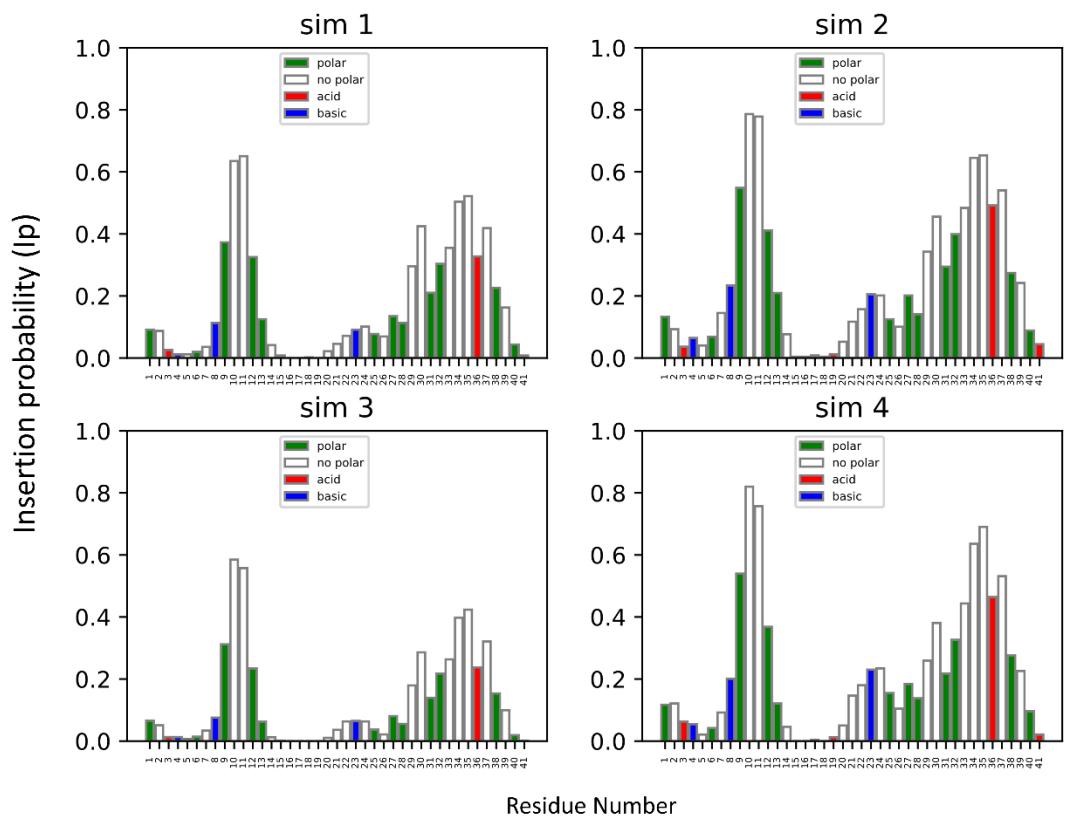
**Figure S2. Insertions probability for each CG simulation of SNX-482 in POPC: POPG (1:1).**
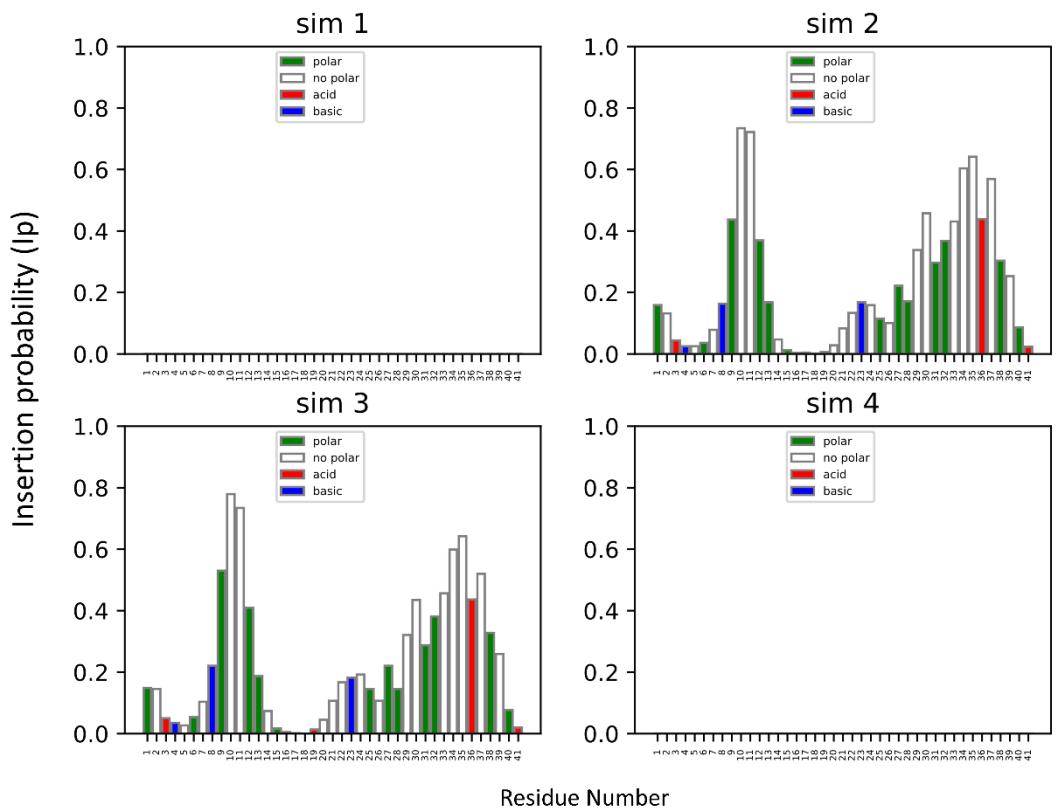
**Figure S3. Insertions probability for each CG simulation of SNX-482 in POPC: POPG (1:3).**
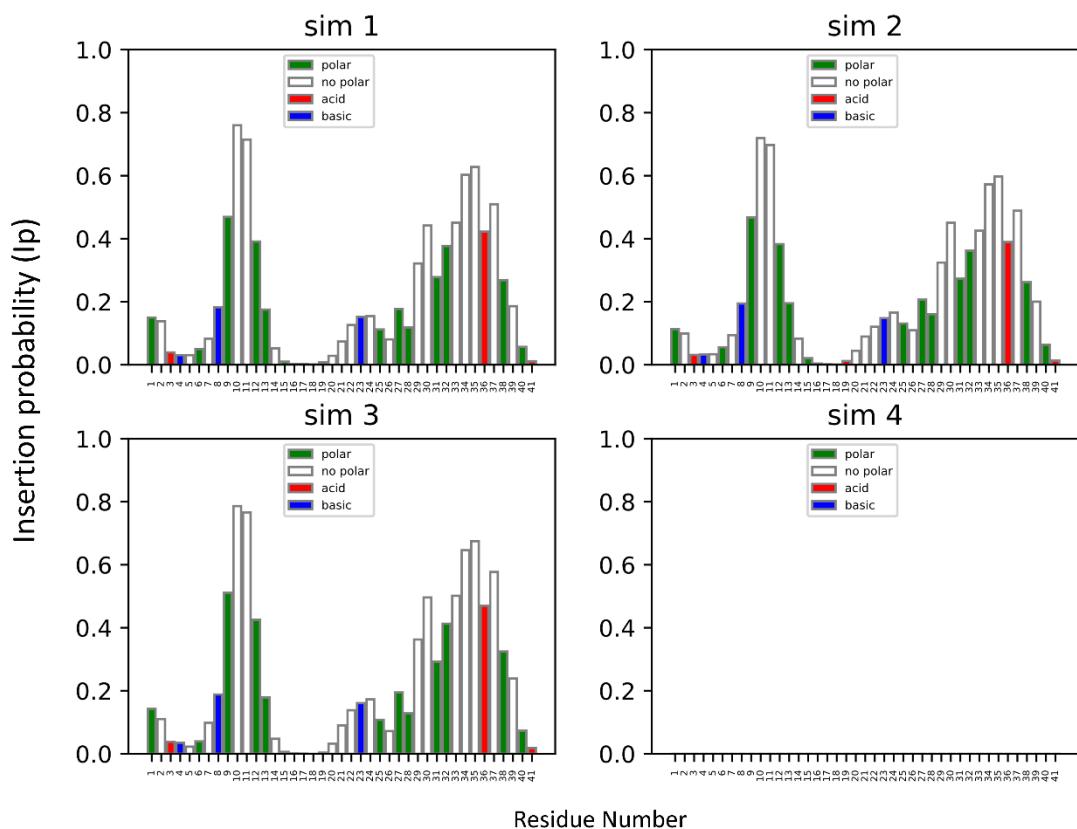
Figure S4. Insertions probability for each CG simulation of SNX-482 in pure POPG
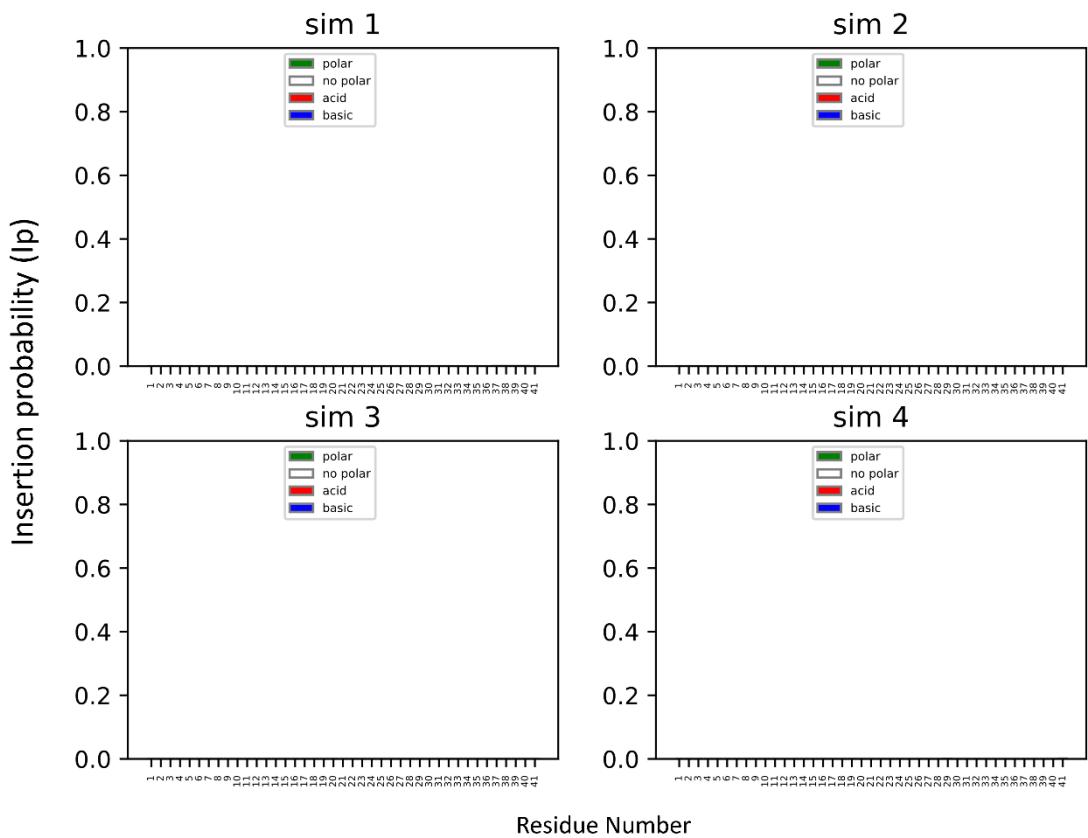
Figure S5. Insertions probability for each CG simulation of SNX-482 in pure POPC
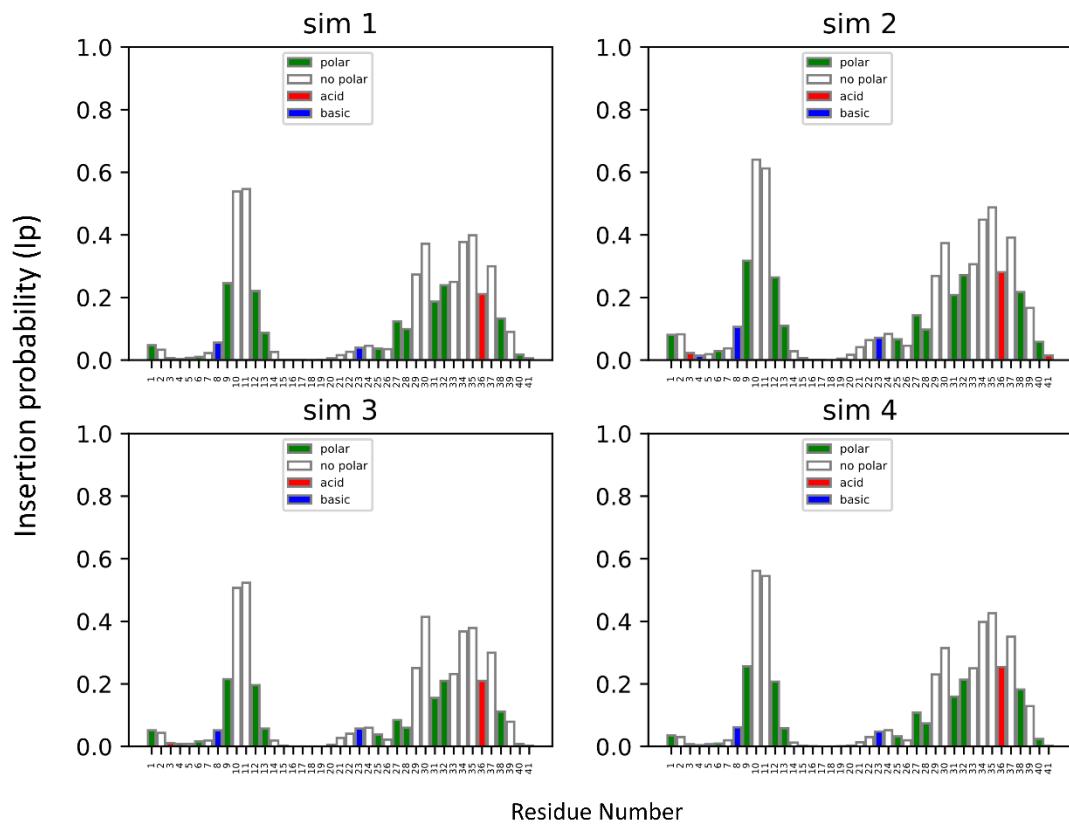
Figure S6. Insertions probability for each CG simulation of SNX-482 in POPC: POPG (3:1).
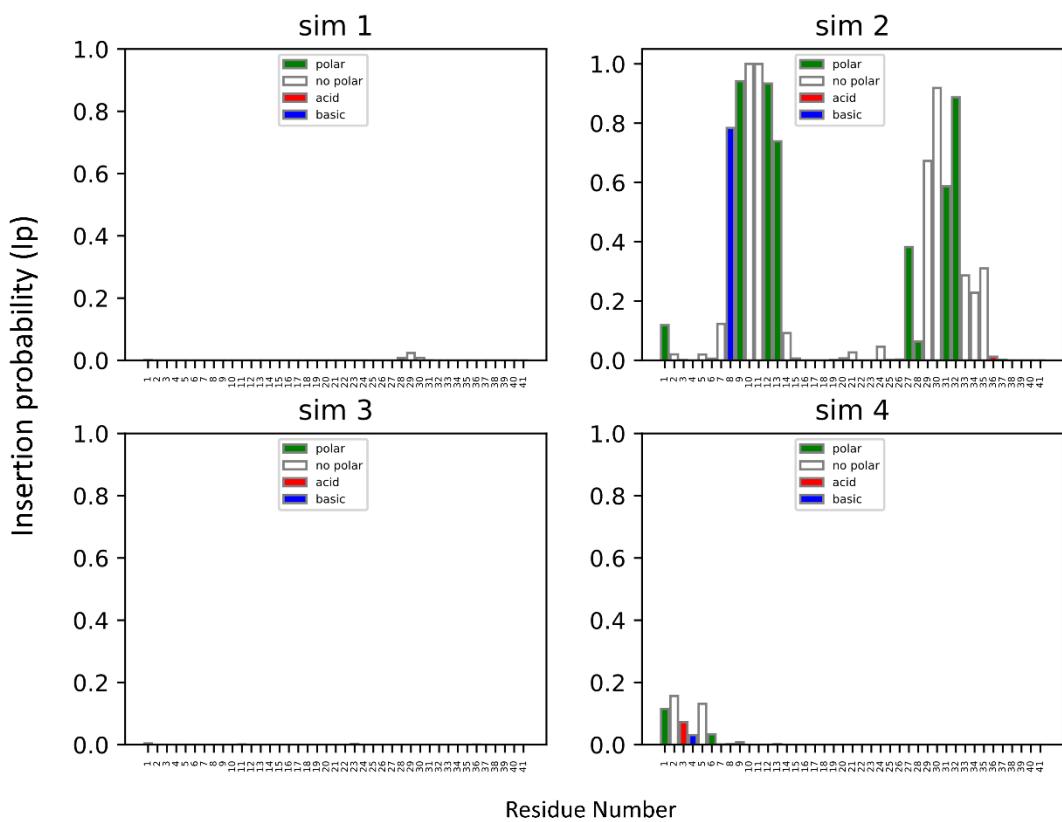
Figure S7. Insertions probability for each all-atom simulation of SNX-482 in pure POPC.
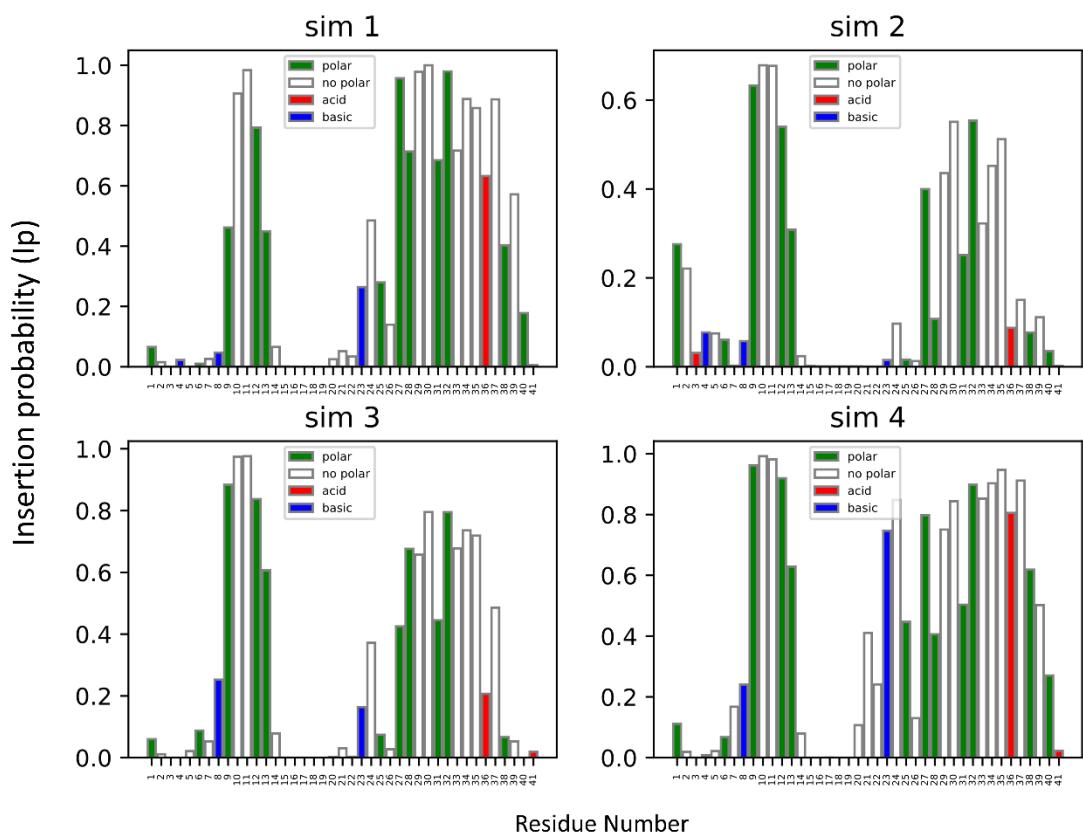
Figure S8. Insertions probability for each all-atom simulation of SNX-482 in POPC: POPG (3:1).
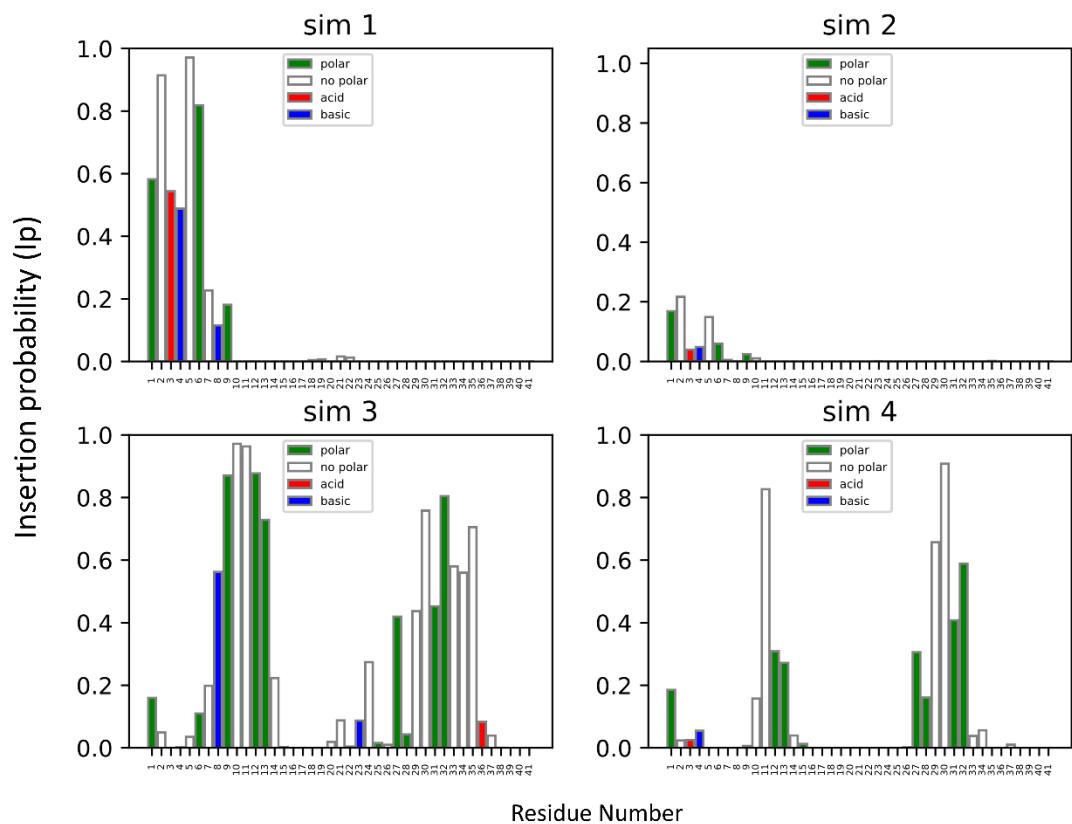
Figure S9. Insertions probability for each all-atom simulation of SNX-482 in POPC: POPG (1:3)
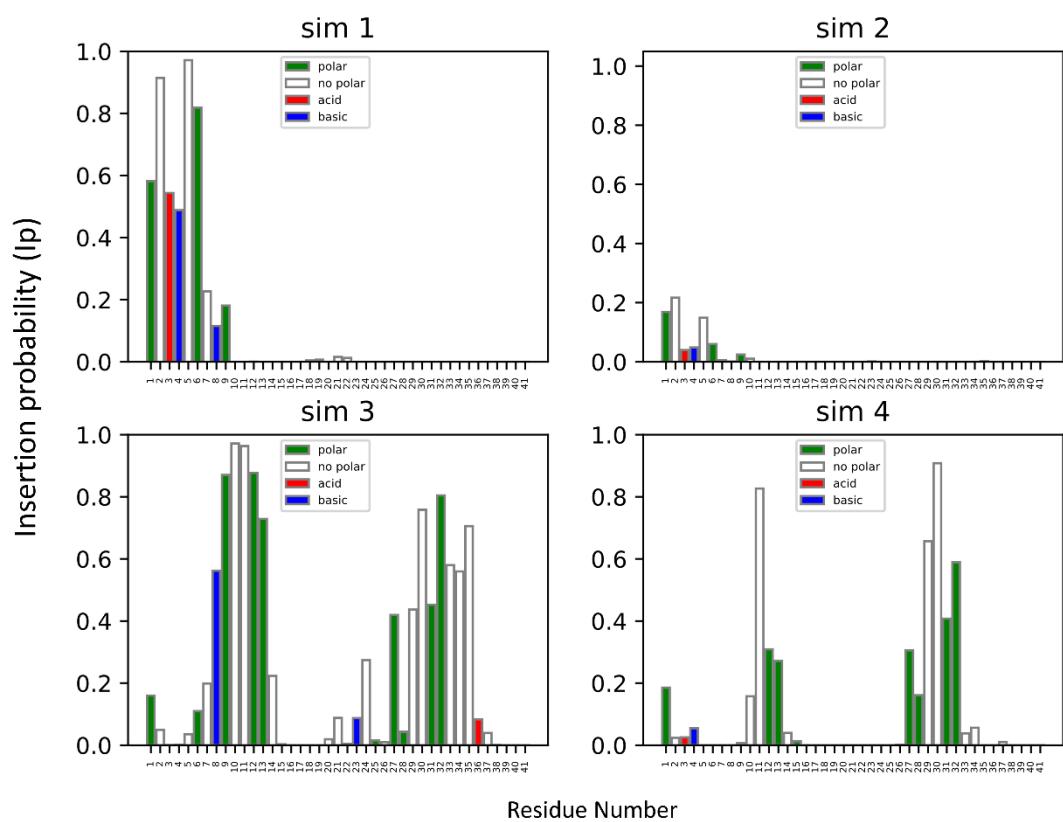
**Figure S10. Insertions probability for each all-atom simulation of SNX-482 in POPC: POPG (1:1)**
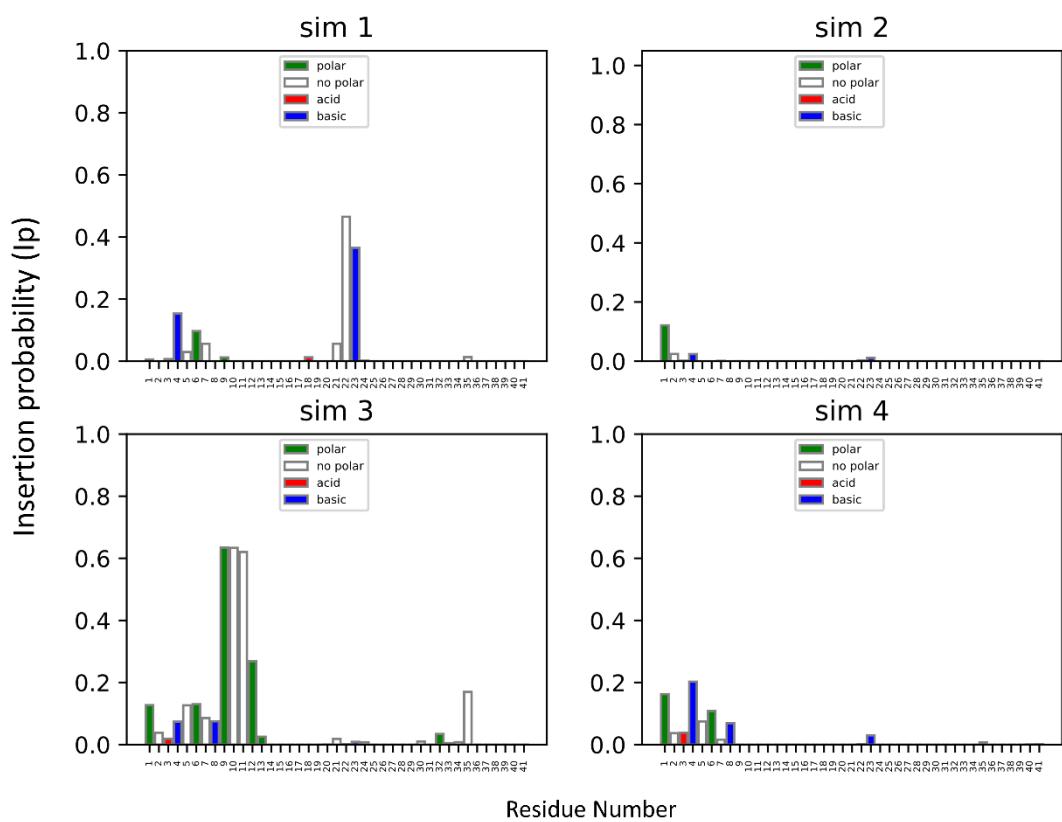
Figure S11. Insertions probability for each all-atom simulation of SNX-482 in POPG
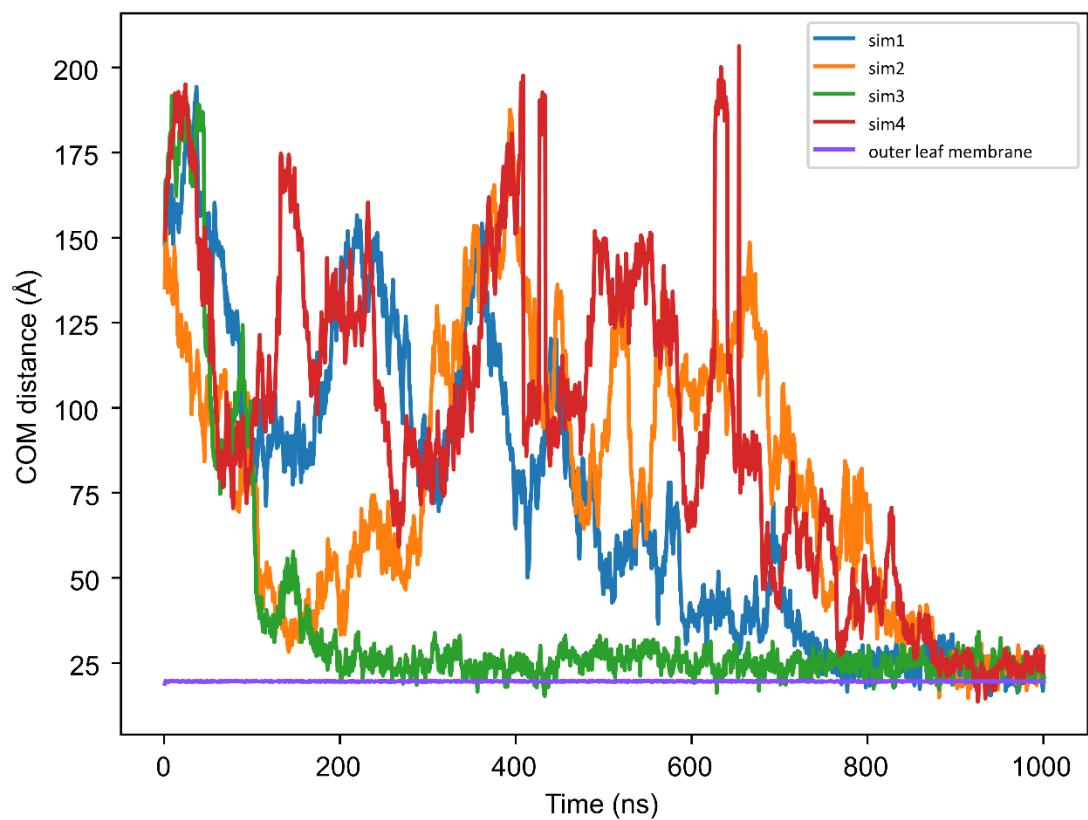
Figure S12. COM distance between toxin and POPC: POPG (1:1) membrane in CG simulations. The purple line is the distance from the center of mass of the membrane to the outer leaf membrane.
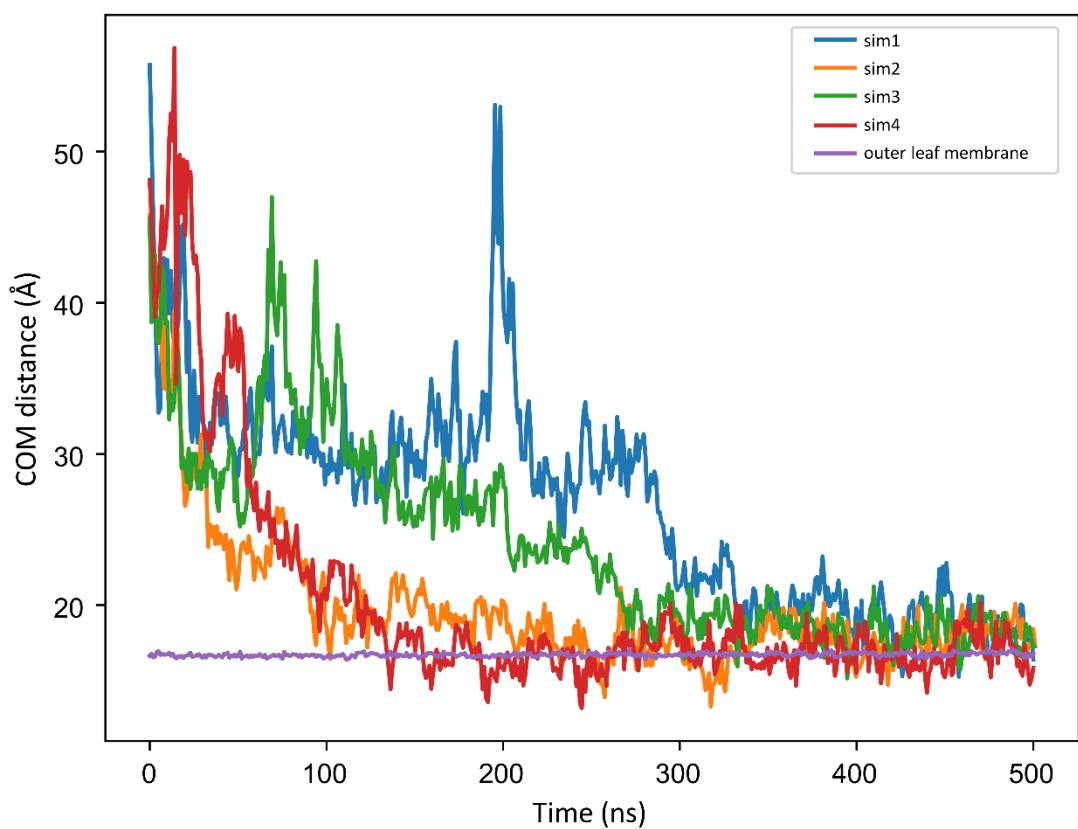
Figure S13. COM distance between toxin and POPC: POPG (3:1) membrane in all-atom simulations. The purple line is the distance from the center of mass of the membrane to the outer leaf membrane.
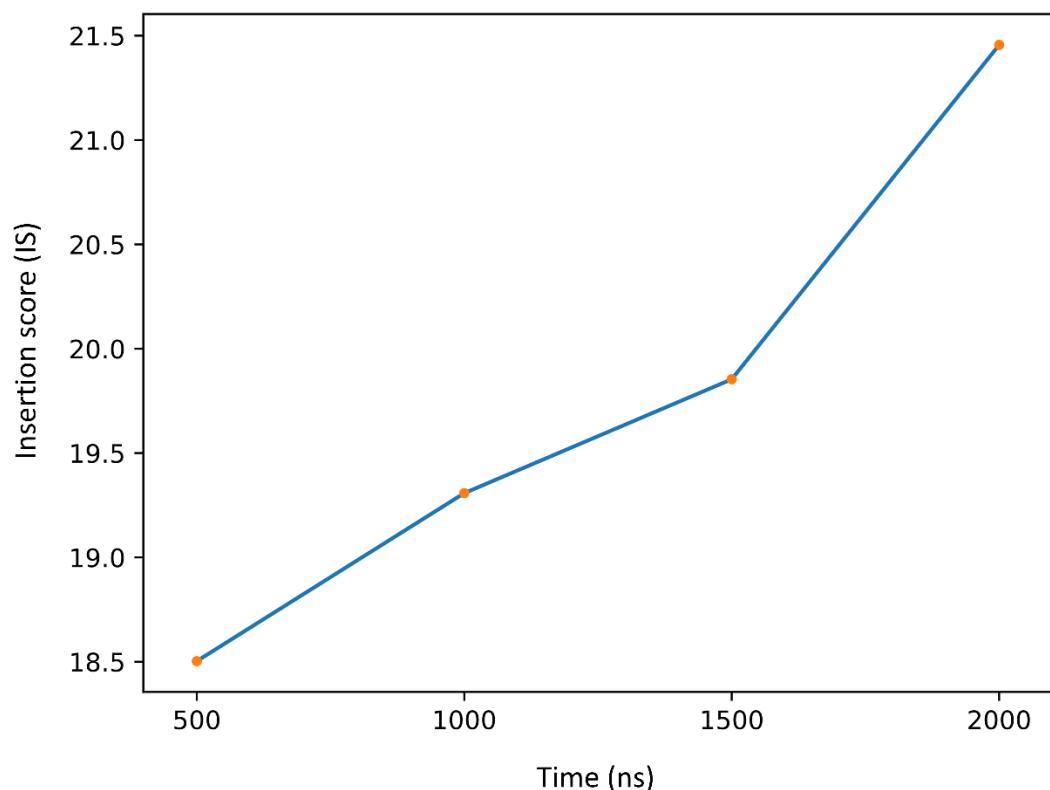
**Figure S14. Insertions score computed for every 0.5 μs of SNX-482 in POPC: POPG (3: 1). during 2 μs.**
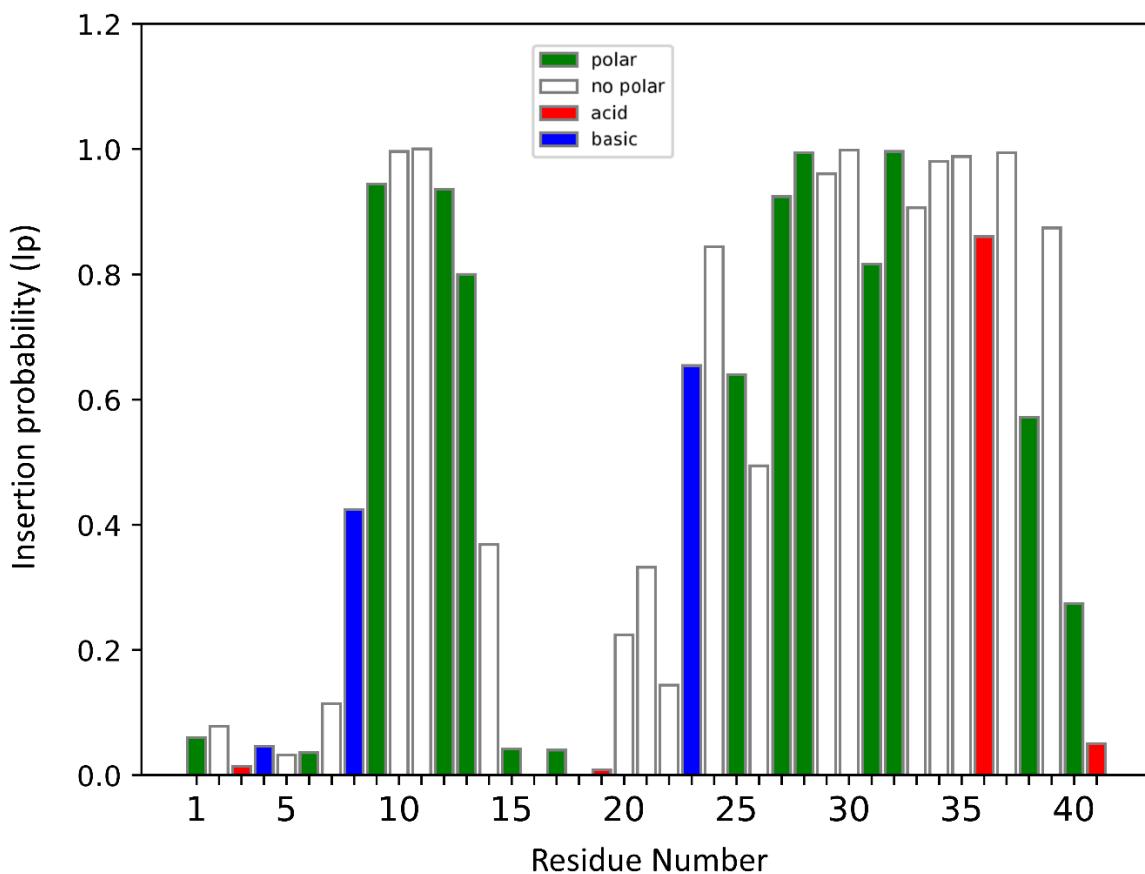
Figure S16. Insertions probability computed in the last 0.5 μs of simulation (1.5 μs -2 μs) of SNX-482 and POPC: POPG (3: 1).