Supplementary Information for

Computational Insight into the Peptide-Based Inhibition of α-Cobratoxin

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Table S1: Structural features and free energy differences between the different conformers of the α-Cbtx dimer in the absence of **Inh**

	Conf-1	**Conf-2**	**Conf-3**	**Conf-4**	**Conf-5**
R_g (Å)	15.06±0.12	15.88±0.18	16.42±0.18	18.67±0.20	16.36±0.14
Contact Area (Å^2)	694.65±68.07	573.42±65.36	462.65±66.70	488.17±65.80	610.05±45.54
$\mathrm{d_{COM}}$ (Å)	17.60±0.39	20.34±0.53	22.31±0.57	26.77±0.58	21.55±0.40
$\mathrm{d_{Loop-II}}$ (Å)	22.26±1.50	25.96±2.20	30.91±2.68	25.99±1.32	36.56±1.58
Angle (θ)	14.53±7.80	80.38±40.15	29.45±11.64	40.38±6.30	106.32±11.18
ΔG (kcal/mol)	0	0.45	0.52	0.59	0.68

Table S2: Structural features and free energy differences between the different conformers of the α-Cbtx dimer in the presence of **Inh**

	Conf-1	**Conf-2**	**Conf-3**	**Conf-4**	**Conf-5**
R_g (Å)	19.05±0.16	16.31±0.18	19.28±0.27	18.93±0.42	16.06±0.18
Contact Area (Å^2)	544.60±80.60	699.42±73.17	354.78±45.92	282.25±28.72	773.69±108.32
$\mathrm{d_{COM}}$ (Å)	28.37±0.48	18.18±0.54	29.41±0.59	28.54±1.03	18.11±0.57
$\mathrm{d_{Loop-II}}$ (Å)	11.23±0.88	25.43±0.72	15.98±1.09	29.23±0.78	25.81±1.01
Angle (θ)	166.84±4.93	169.65±3.87	154.47±6.12	66.55±6.63	157.09±4.01
ΔG (kcal/mol)	0	0.52	0.61	0.70	0.83

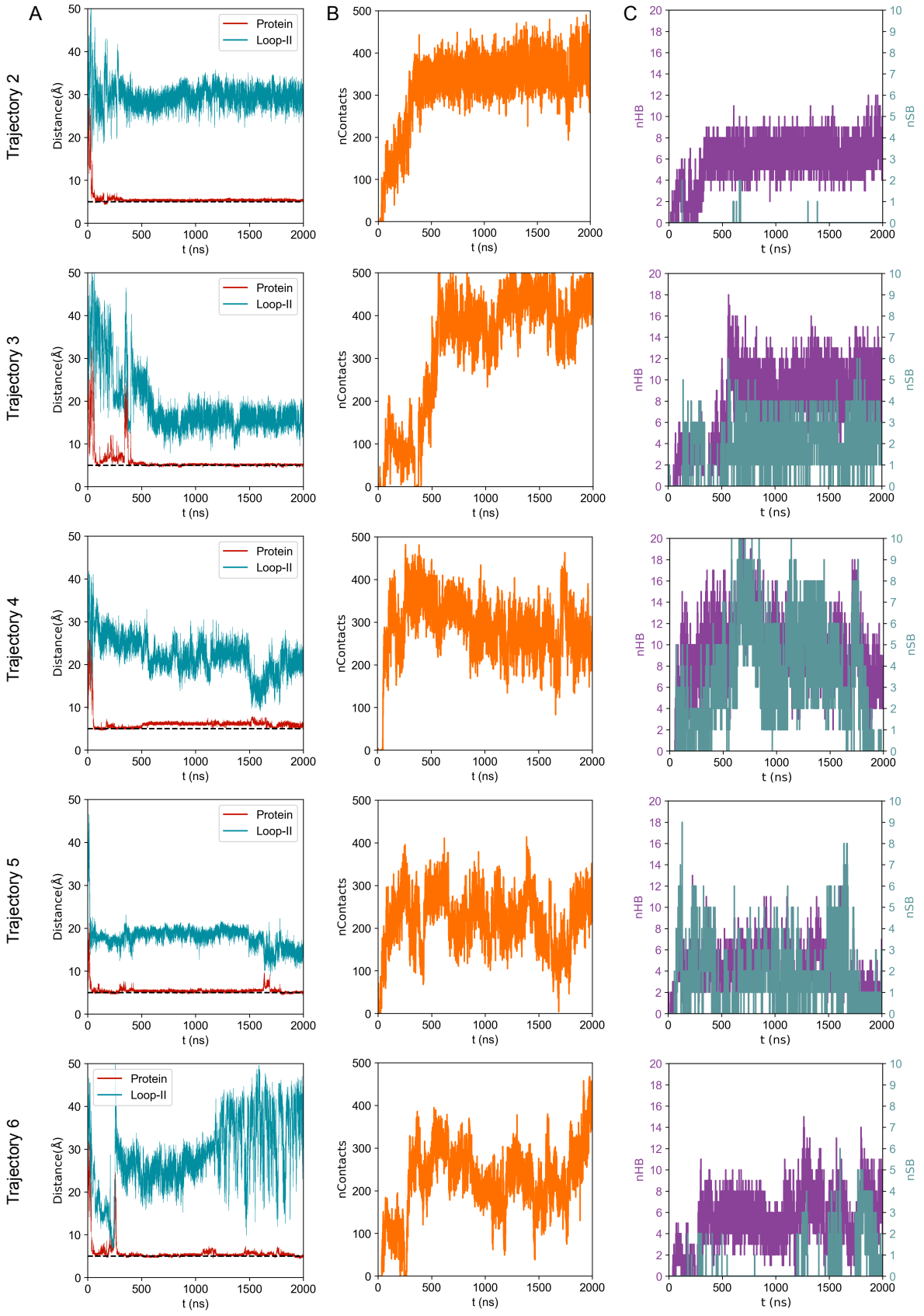

Figure S1: α-Cbtx association dynamics in Trajectory-2 to 6: (A) Distance between non-specific residues on the α-Cbtx surface (red) and the finger region of Loop-II (residues 27 to 36) of the two chains (blue). (B) Number of heavy atom contacts between the two chains. (C) Number of inter-chain hydrogen bonds and salt bridges as a function of time.

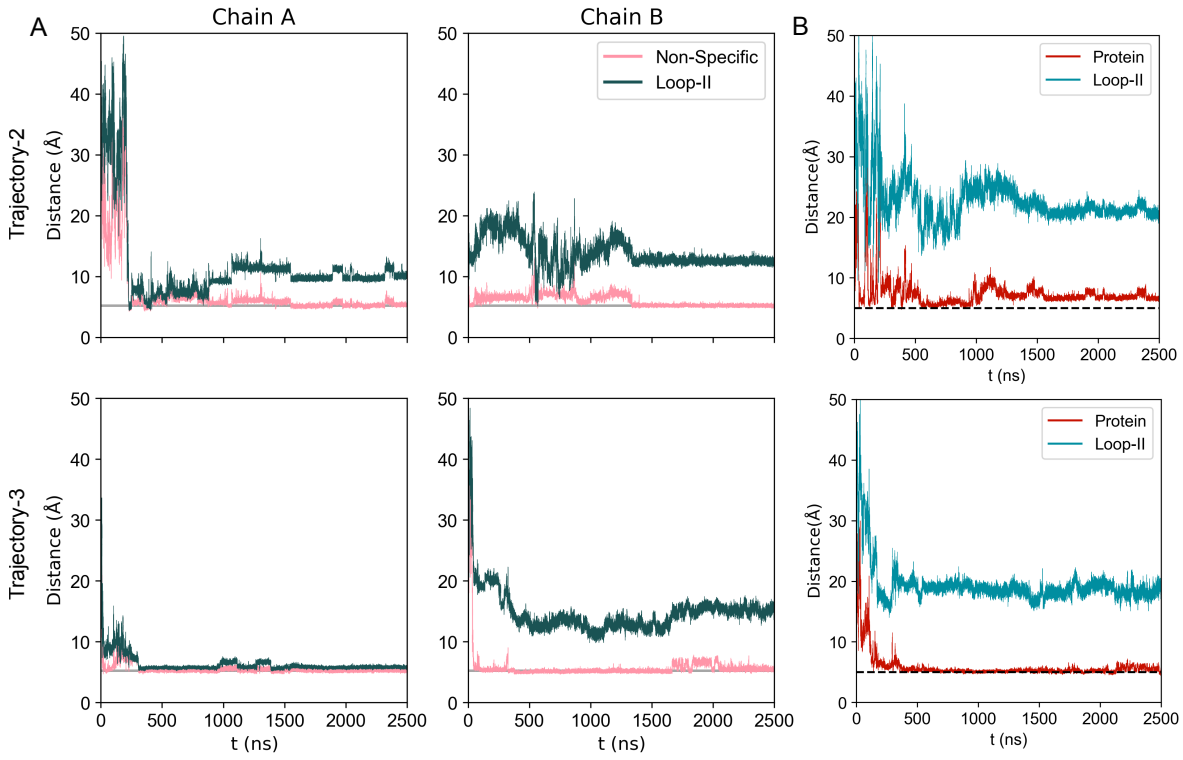

Figure S2: Binding of Inh to α-Cbtx chains in Trajectory-2 and 3: (A) Time evolution of the **Inh** distance to non-specific residues (pink) and Loop-II residues (green) in chain A and chain B. (B) Distance between the α-Cbtx chains (red) and the Loop-II residues of the two chains (blue).

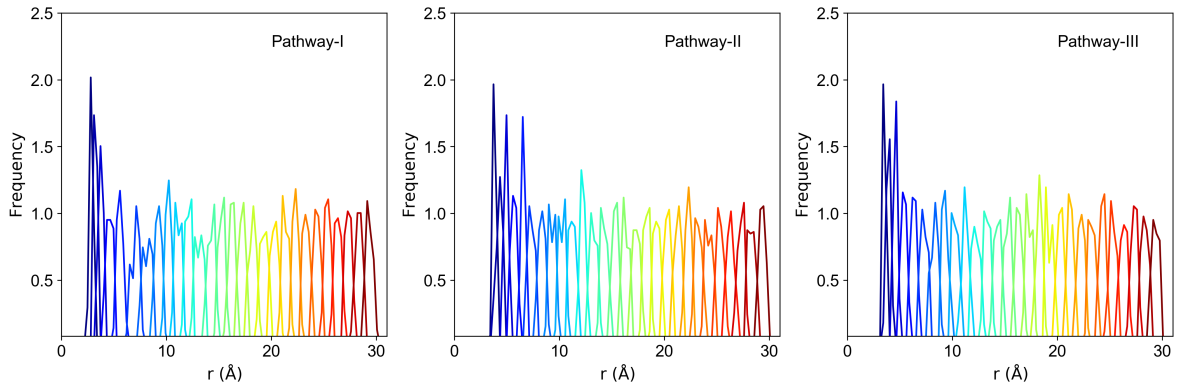

Figure S3: Histograms representing overlap between the consecutive windows in the reaction coordinate of the three proposed pathways of **Inh** unbinding (Pathway-I, Pathway-II and Pathway-III) from the equilibrated crystal structure.