Supporting Information

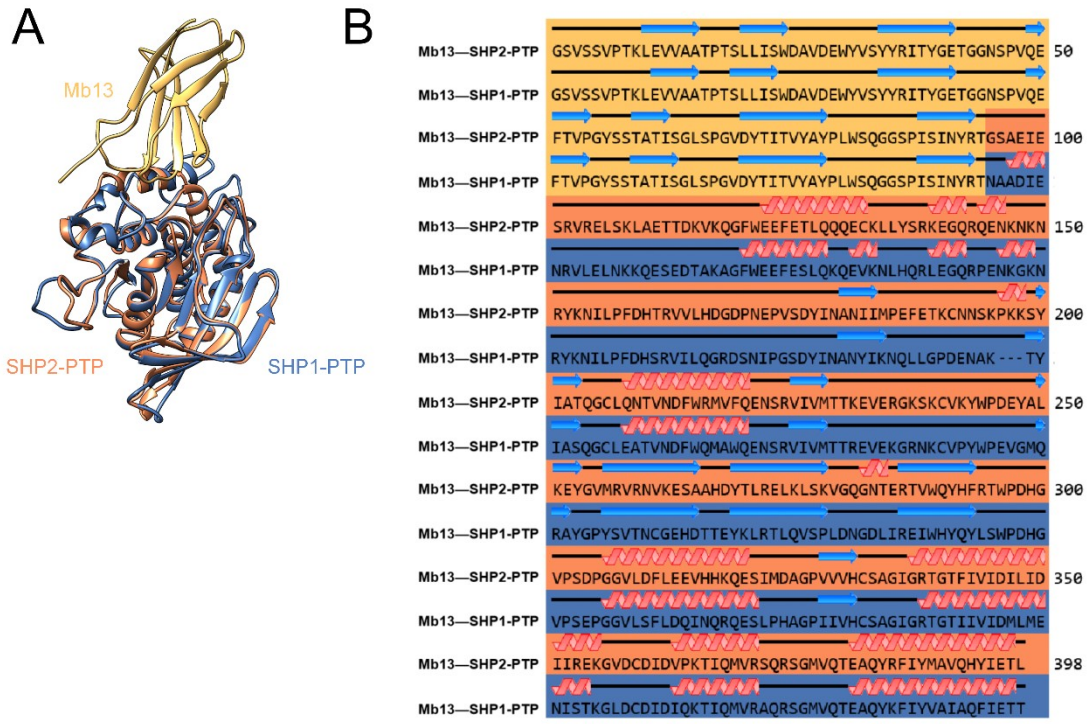

Fig. S1. (A) Structural alignment of the Mb13–SHP2-PTP and Mb13–SHP1-PTP complexes. Mb13 is depicted in light yellow, SHP2-PTP in orange, and SHP1-PTP in blue. (B) Secondary Structure and Residue Sequence Comparison of the Modeled Structures of Mb13–SHP2-PTP and Mb13–SHP1-PTP. β-sheets are represented by blue arrows, and α-helices are represented by red helices. The residue background is shaded light yellow for the Mb13 region, orange for the SHP2-PTP region, and blue for the SHP1-PTP region to distinguish different structural domains.

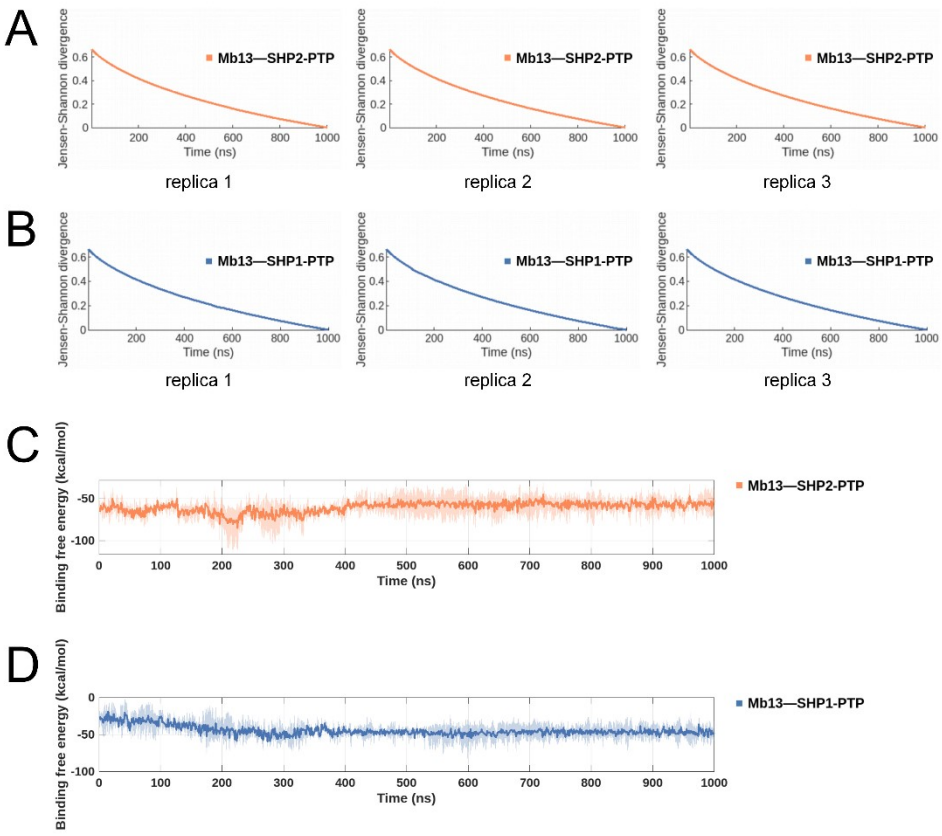

Fig. S2. Convergence assessment of MD simulations for Mb13–SHP2-PTP and Mb13–SHP1-PTP complexes. (A) (B) Time evolution of Jensen-Shannon divergence (JSD) values calculated using the Clustering Ensemble Similarity (CES) method for three independent simulation replicates of both complexes. JSD was computed between adjacent time windows (10 frames per window) based on Cα atom clustering to quantify the similarity of conformational distributions over time. (C) (D) Time-dependent binding free energy profiles obtained from MM/GBSA calculations for both complexes. The thick lines represent the average values from three independent simulation runs. The shade represents the standard deviation for the three replicas of simulations.

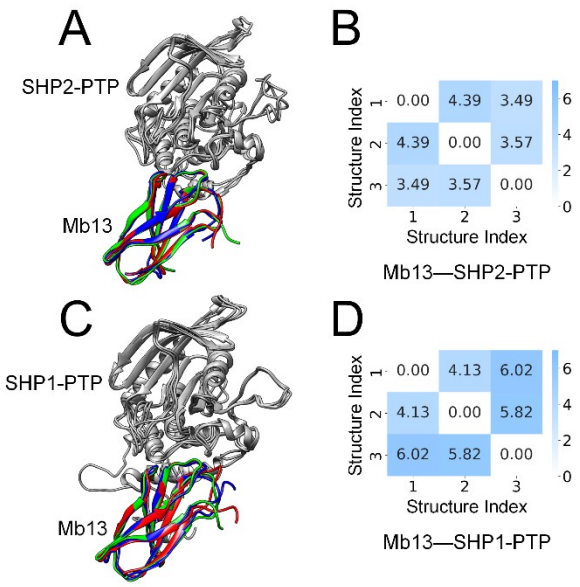

Fig. S3. Cluster analysis of the Mb13–SHP2-PTP and Mb13–SHP1-PTP complexes. Superposition analysis among the three main conformations of Mb13–SHP2-PTP (A) and Mb13–SHP1-PTP (C). Mb13 in the three most important conformations of the Mb13–SHP2-PTP and Mb13–SHP1-PTP are colored in blue, green, and red, respectively. SHP2-PTP and SHP1-PTP are colored in dark gray. The RMSD values among the three main conformations of Mb13–SHP2-PTP (B) and Mb13–SHP1-PTP (D).

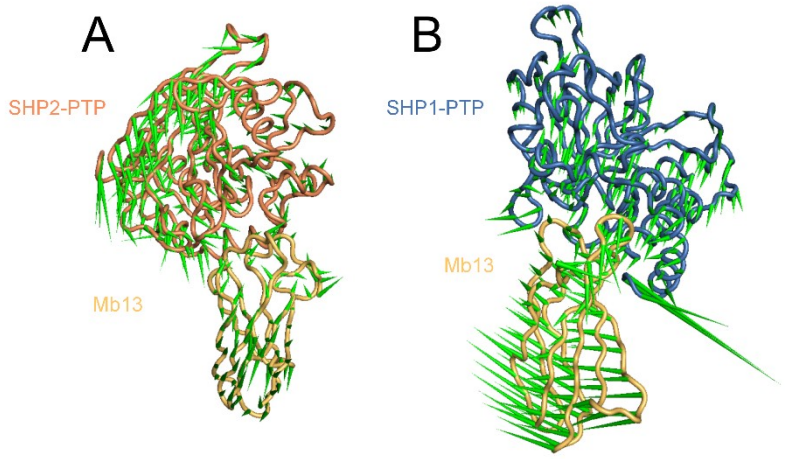

Fig. S4. The porcupine plots of the Mb13−SHP2-PTP (A) and Mb13−SHP1-PTP (B) systems depict the principal pattern of motion along PC1. The sizes and lengths of the green quills are proportional to the amplitude of motions. Mb13 is shown in yellow, SHP2-PTP in orange, and SHP1-PTP in blue.

Table S1. Binding free energies (kcal/mol) of Mb13−SHP2-PTP and Mb13−SHP1-PTP systems computed by the MM/PBSA method, accompanied by independent sample t-test results.

Energy component (kcal/mol)	Mb13–SHP2-PTP	Mb13–SHP1-PTP	t-value	p-value
ΔG_{gas}	-487.21 ± 76.80	-258.88 ± 66.16	/	/
ΔG_{solv}	420.83 ± 68.88	208.12 ± 58.51	/	/
$\Delta G_{binding}$	-66.38 ± 12.24	-50.76 ± 13.03	-21.392	2.9958×10^{-86}

Table S2. Contributions of residues (kcal/mol) involved in hydrogen bonds and salt bridges to $\Delta G_{binding}$.

Residue	Mb13–SHP2	Residue	Mb13–SHP1
E29	-2.52	E29	-1.09
Y31	-6.93	Y31	-5.01
S33	-0.68	S33	-1.93
R36	-3.54	R36	-2.32
W81	-7.83	W81	-5.06
E125	-0.74	E125	-0.34
K153	-3.49	K153	-2.06
N154	-5.94	N154	-2.99
Q379	-0.90	Q376	-0.02