Supporting Information

Molecular Mechanism of Phosphorylation-Mediated Impacts on the Conformation Dynamics of Ligand-Bound BACE1 Probed by Gaussian Accelerated Molecular Dynamics

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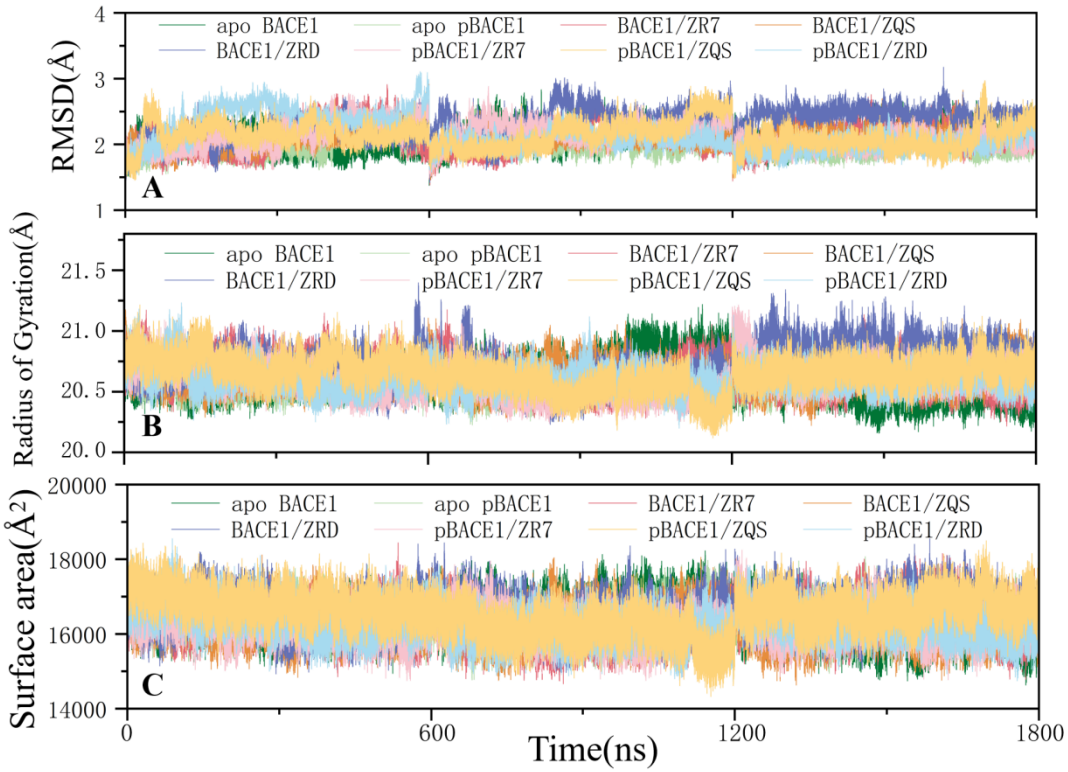

Figure S1. Dynamics information of eight compounds of BACE1. The probability distribution of (A) RMSDs in MR-GaMD; (B) Radius of Gyration and (C) Surface area.

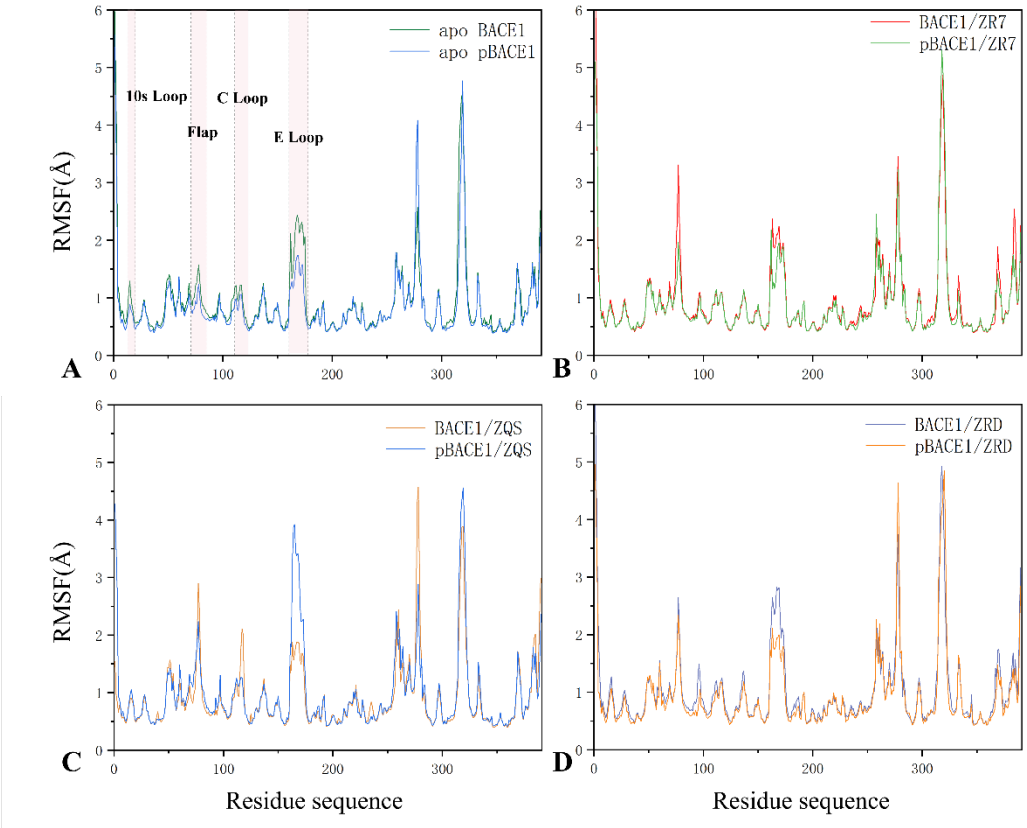

Figure S2. Comparison of RMSF in different systems: (A) *apo* BACE1 with *apo* pBACE1, (B)

BACE1/ZR7 with pBACE1/ZR7, (C) BACE1/ZQS with pBACE1/ZQS and (D) BACE1/ZRD with pBACE1/ZRD.

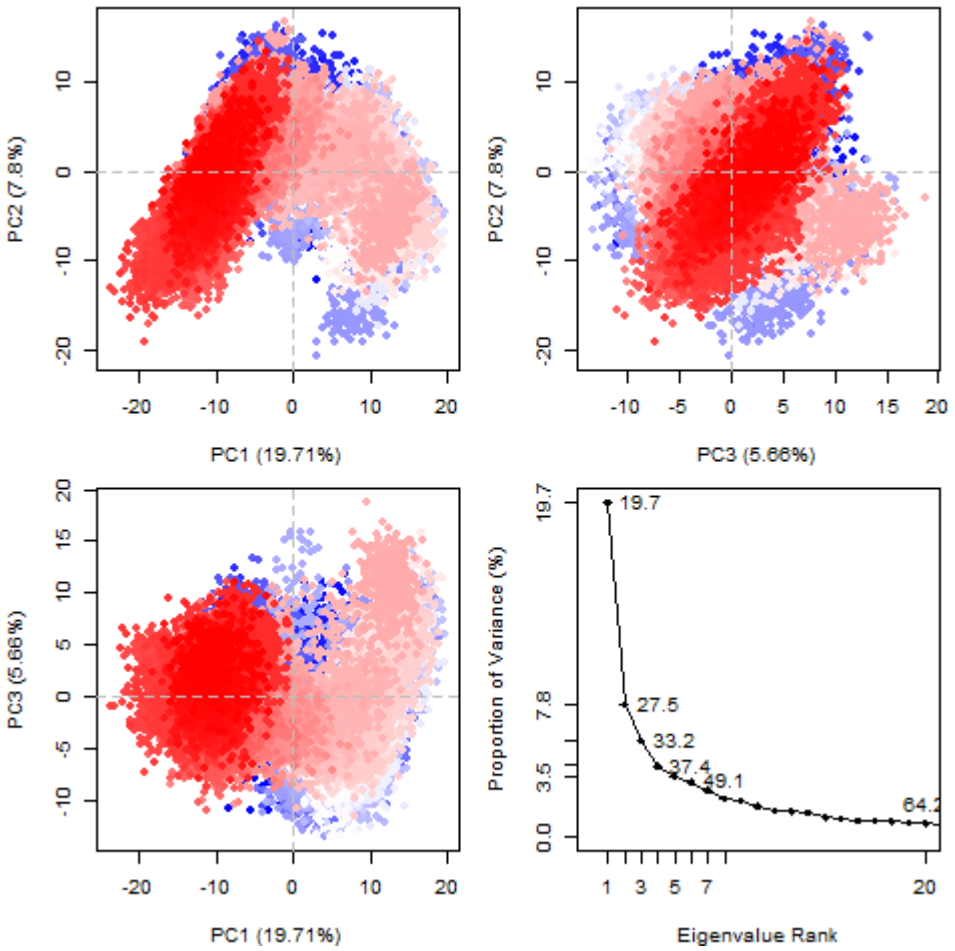

Figure S3. Principal component analysis revealed the conformational changes of *apo* pBACE1. The first three PCs (PC1-PC3) show fluctuating regions with 33.17% of overall fluctuations.

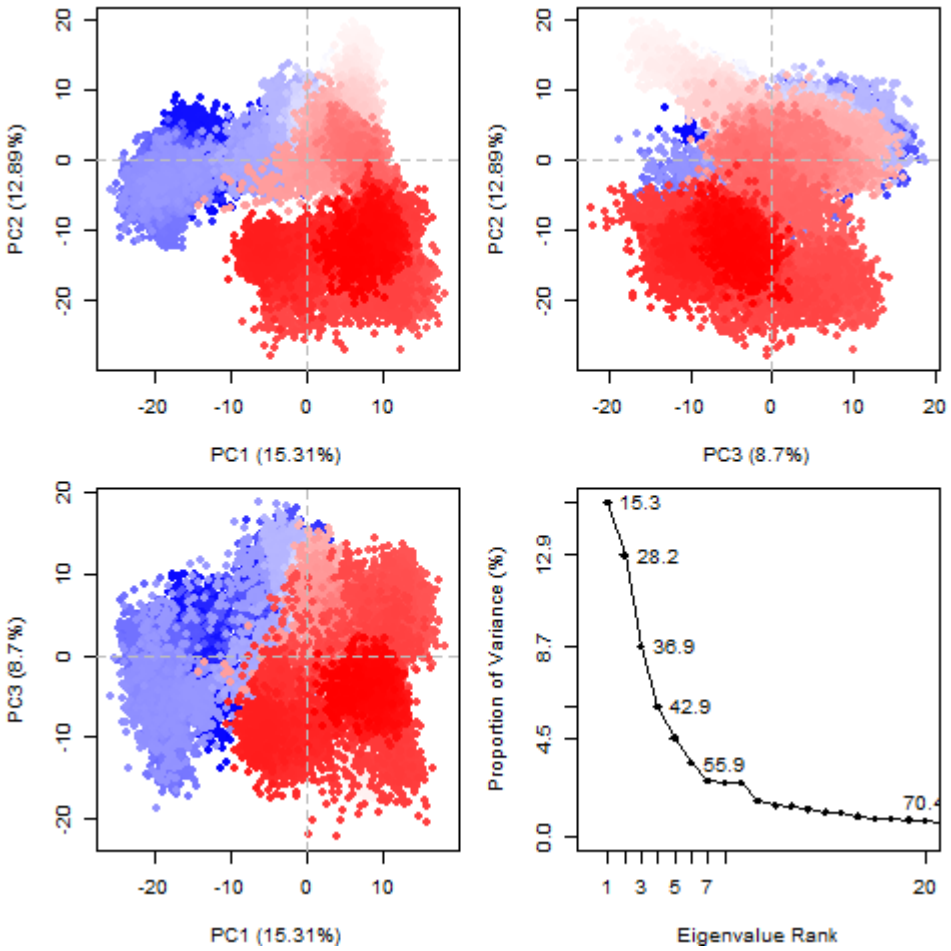

Figure S4. Principal component analysis revealed the conformational changes of BACE1/ZR7. The first three PCs (PC1-PC3) show fluctuating regions with 36.9% of overall fluctuations.

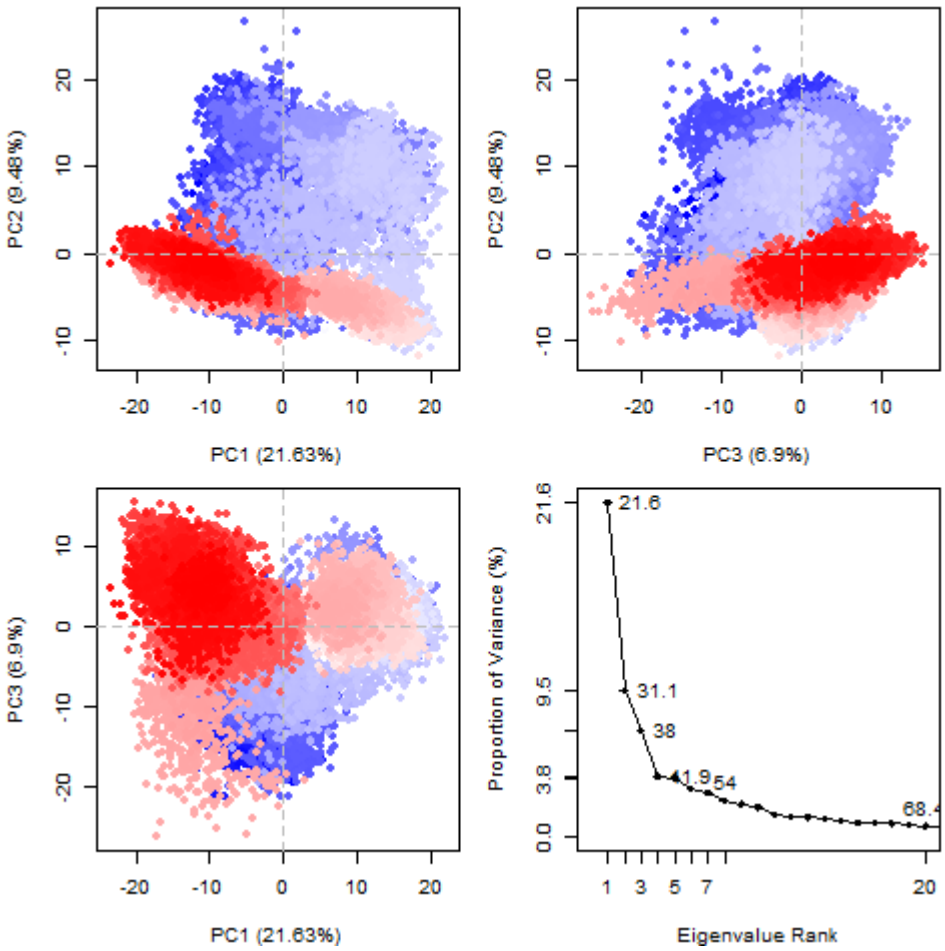

Figure S5. Principal component analysis revealed the conformational changes of pBACE1/ZR7. The first three PCs (PC1-PC3) show fluctuating regions with 38.98% of overall fluctuations.

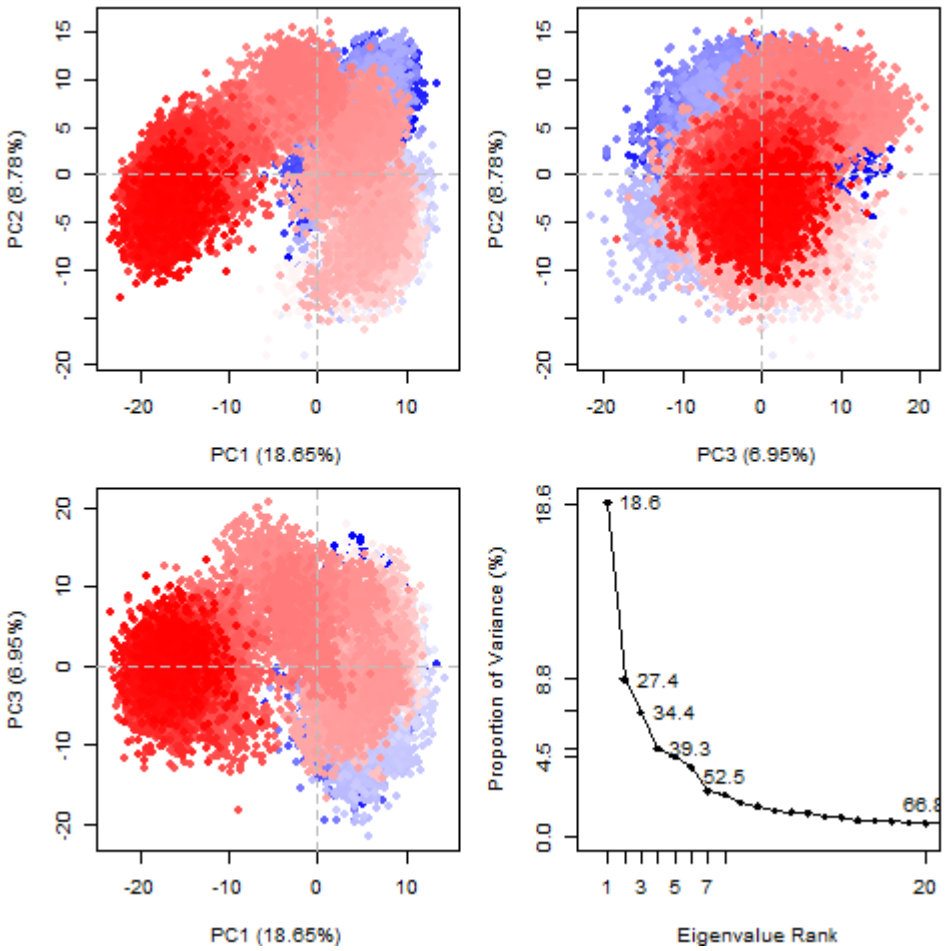

Figure S6. Principal component analysis revealed the conformational changes of BACE1/ZQS. The first three PCs (PC1-PC3) show fluctuating regions with 34.38% of overall fluctuations.

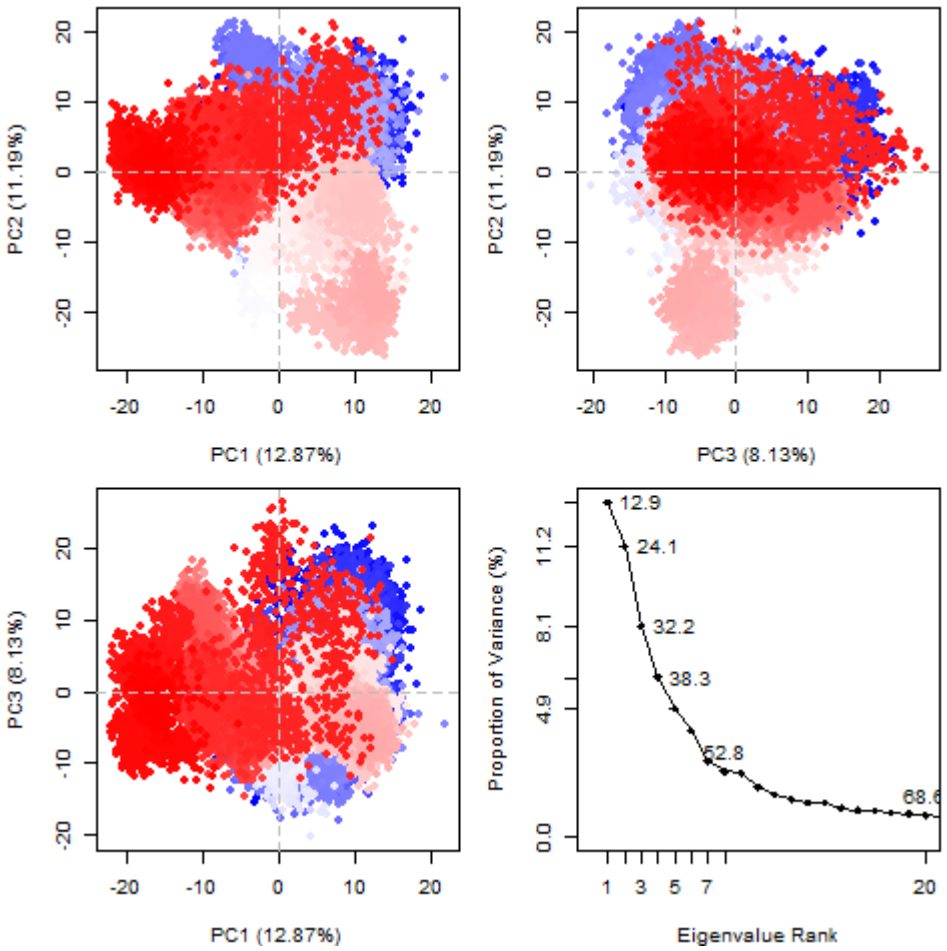

Figure S7. Principal component analysis revealed the conformational changes of pBACE1/ZQS. The first three PCs (PC1-PC3) show fluctuating regions with 32.19% of overall fluctuations.

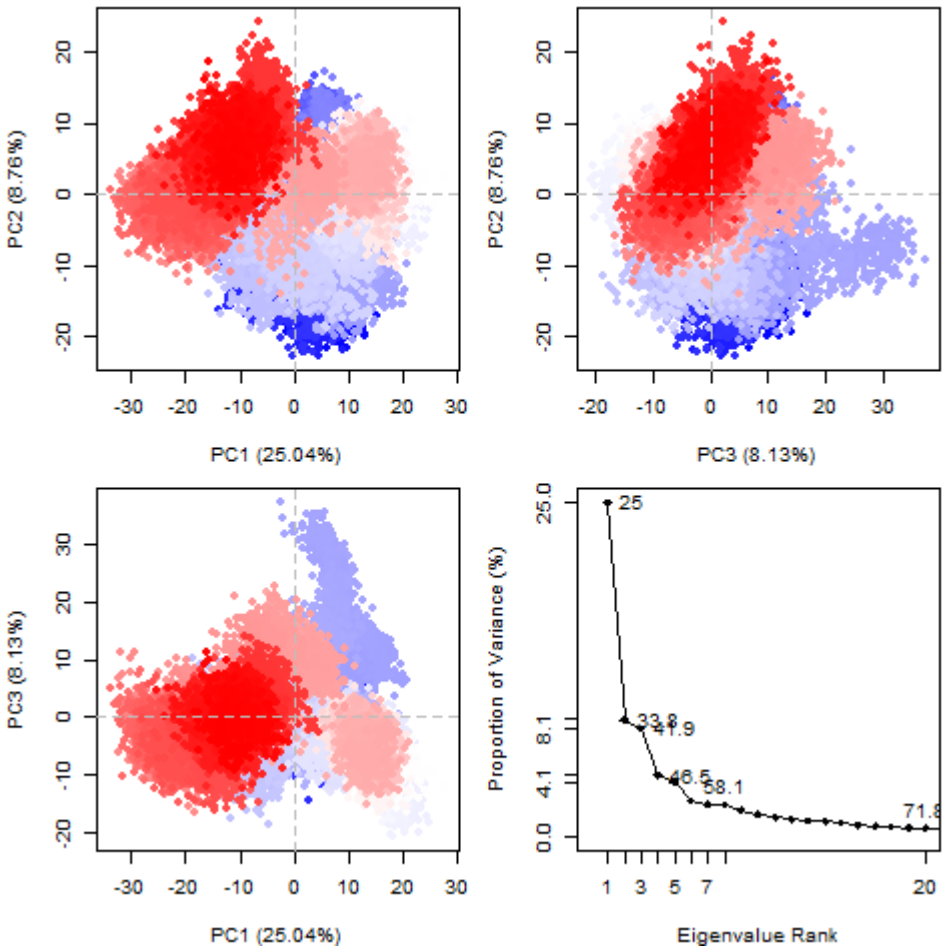

Figure S8. Principal component analysis revealed the conformational changes of BACE1/ZRD. The first three PCs (PC1-PC3) show fluctuating regions with 42.13% of overall fluctuations.

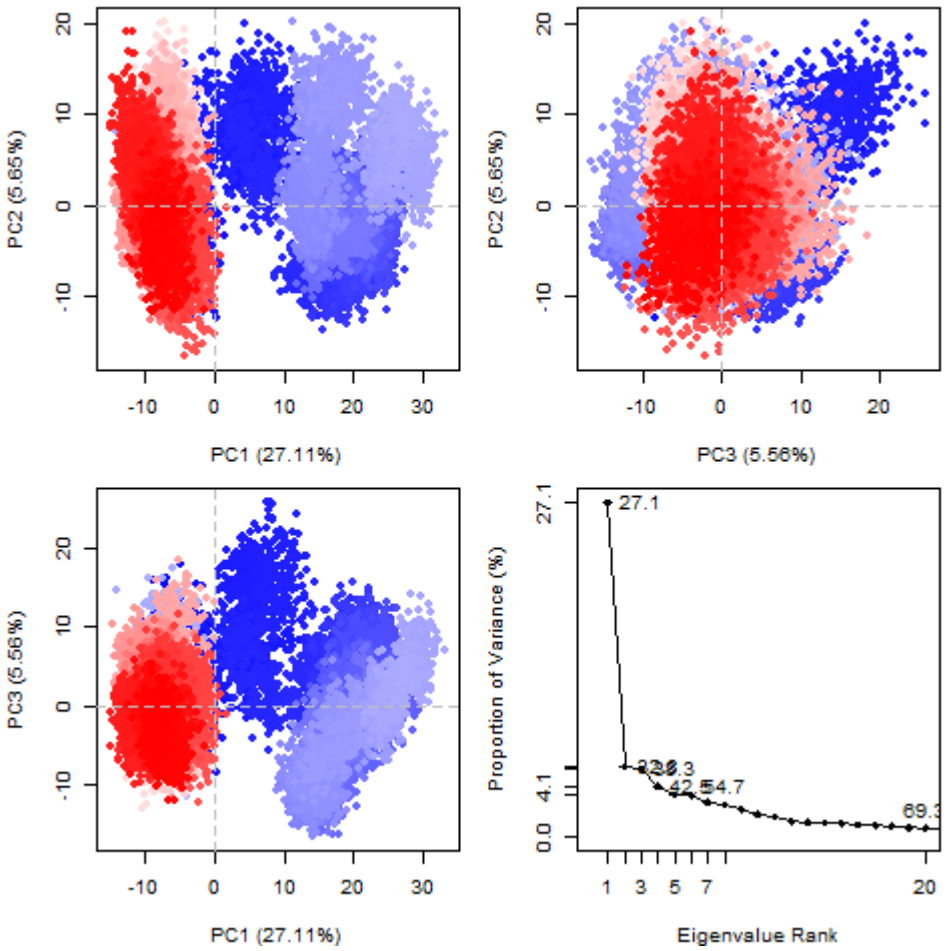

Figure S9. Principal component analysis revealed the conformational changes of pBACE1/ZRD. The first three PCs (PC1-PC3) show fluctuating regions with 38.32% of overall fluctuations.

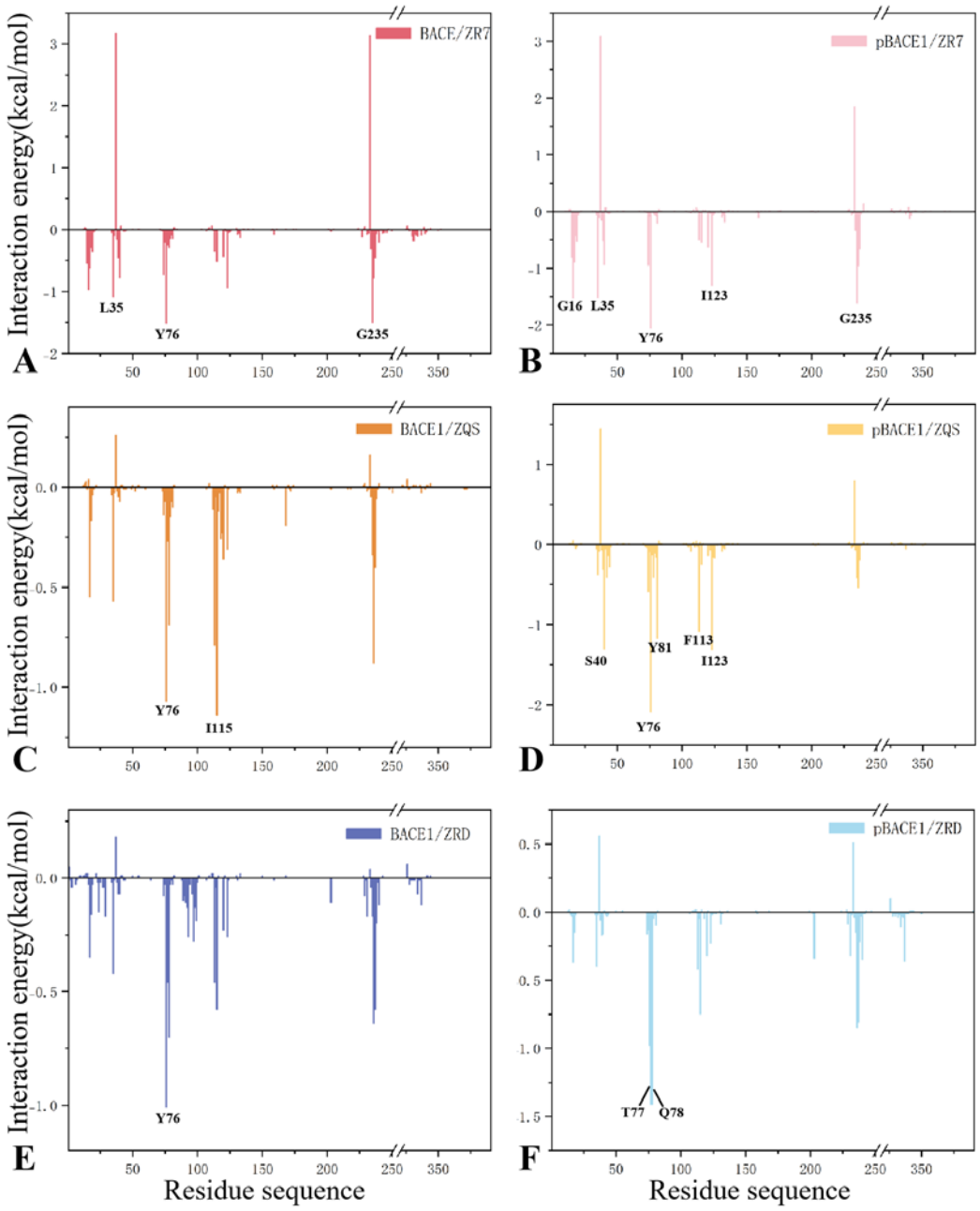

Figure S10. Interaction of BACE1 residues after binding to inhibitors (A) BACE1/ZR7, (B) pBACE1/ZR7, (C) BACE1/ZQS, (D) pBACE1/ZQS, (E) BACE1/ZRD, and (F) pBACE1/ZRD.

Table S1. Hydrogen Bonds Formed between BACE, pBACE1 and Partners Including ZR7 ZQS and ZRD.

Complexes	Hydrogen bonds	Distance(Å)	Angle(deg)	Occupancy(%)
BACE1/ZR7	G16_N-H...ZR7_O1	3.11	146.62	54.29%
	ZR7_N7-H17...T236_OG1	3.04	139.52	48.89%
	ZR7_N4-H12...G235_O	3.15	138.76	34.57%
BACE1/ZQS	N119_N-H...ZQS_N16	3.15	164.57	7.89%
	ZQS_N3-H4...N116_O	2.92	158.81	7.87%
	ZQS_N3-H3...N116_O	2.92	158.81	7.00%
	ZQS_N3-H3...G235_O	2.95	157.49	6.83%
	ZQS_N3-H4...N116_O	2.95	157.49	6.22%
BACE1/ZRD	ZRD_N2-H10...F113_O	2.93	154.73	6.51%
	ZRD_N2-H11...F113_O	2.93	154.89	6.14%
pBACE1/ZR7	G16_N-H...ZR7_O1	3.10	148.00	85.05%
	ZR7_N4-H12...G235_O	3.12	142.68	67.83%
	ZR7_N7-H17...T236_OG1	3.01	137.30	29.09%
	ZR7_N7-H16...T236_OG1	3.02	136.52	28.71%
pBACE1/ZQS	W81_NE1-HE1...ZQS_N16	3.03	145.52	37.73%
	S40_OG-HG...ZQS_N12	2.82	161.70	34.46%
pBACE1/ZRD	T77_OG1-HG1...ZRD_N5	2.96	160.73	18.83%
	ZRD_N2-H11...F113_O	2.91	151.92	11.16%
	ZRD_N2-H10...F113_O	2.91	152.01	11.06%

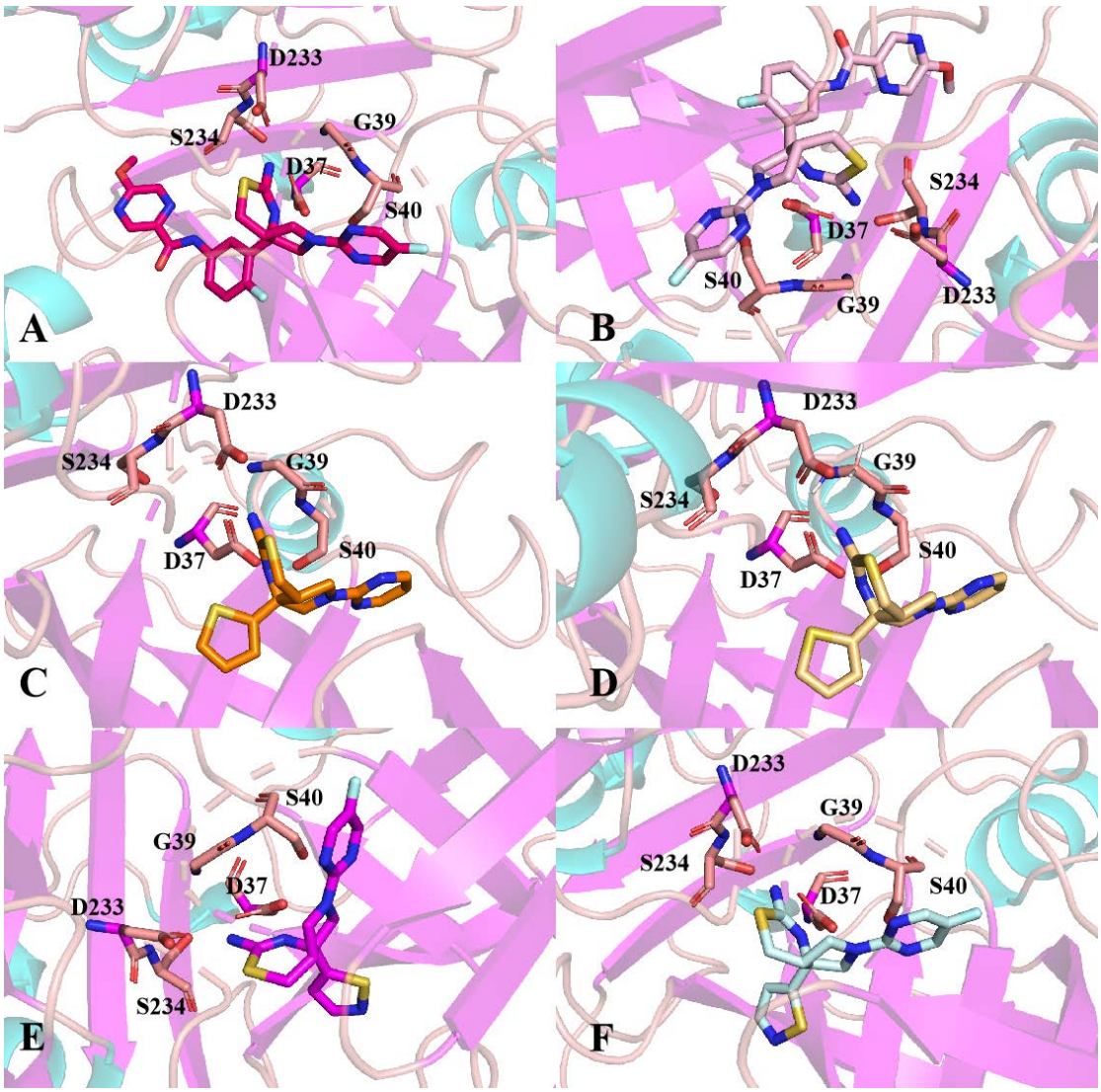

Figure S11. Locations of D37, G39, S40, D233 and S234 in BACE1 Structure: (A) BACE1/ZR7, (B) pBACE1/ZR7, (C) BACE1/ZQS, (D) pBACE1/ZQS, (E) BACE1/ZRD and (F) pBACE1/ZRD.

Table S2. Energy Decomposition Analysis of Residues D37 and D233 in each Systems[a]

Complexes	Residue name	ele	vdW	pol	nonpol	Total
BACE1/ZR7	D37	2.81	-0.71	1.10	-0.03	3.17
	D233	0.58	-0.37	2.96	-0.04	3.14
BACE1/ZQS	D37	-0.30	-0.22	0.79	-0.01	0.26
	D233	-0.17	-0.15	0.49	-0.01	0.16
BACE1/ZRD	D37	-0.00	-0.00	0.01	0.00	0.00
	D233	-0.40	-0.12	0.56	-0.01	0.04
pBACE1/ZR7	D37	3.06	-0.88	0.96	-0.05	3.09
	D233	-3.85	-0.21	5.96	-0.05	1.85
pBACE1/ZQS	D37	1.15	-0.54	0.89	-0.06	1.44
	D233	1.67	-0.18	-0.67	-0.02	0.80
pBACE1/ZRD	D37	0.40	-0.18	0.35	-0.01	0.56
	D233	-0.04	-0.00	0.04	0.00	0.00

[a] All components of free energies are in kcal/mol.