

Supplementary Information

Selective mechanism of inhibitors to two bromodomains of BRD4 revealed by multiple replica molecular dynamics simulations

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TABLE S1 Binding free energies of inhibitors to BD1 and BD2 calculated by MM-GBSA method ^a.

Components	SG3-179/BD1	SG3-179/BD2	GSK778/BD1	GSK778/BD2	GSK620/BD1	GSK620/BD2
ΔE_{ele}	-25.19 \pm 0.35	-20.16 \pm 0.23	-9.22 \pm 0.26	-8.82 \pm 0.19	-18.53 \pm 0.18	-23.84 \pm 0.19
ΔE_{vdW}	-41.63 \pm 0.17	-43.50 \pm 0.15	-45.53 \pm 0.14	-44.04 \pm 0.15	-31.35 \pm 0.12	-36.07 \pm 0.12
ΔG_{pol}	37.13 \pm 0.30	33.01 \pm 0.21	25.27 \pm 0.24	26.12 \pm 0.18	28.83 \pm 0.13	32.75 \pm 0.13
ΔG_{nonpol}	-3.55 \pm 0.01	-3.95 \pm 0.01	-3.59 \pm 0.01	-3.82 \pm 0.01	-3.18 \pm 0.01	-3.72 \pm 0.01
$\Delta G_{ele+pol}^b$	11.94 \pm 0.13	12.84 \pm 0.10	16.05 \pm 0.08	17.31 \pm 0.08	10.30 \pm 0.11	8.91 \pm 0.11
$\Delta G_{vdW+nonpol}^c$	-45.18 \pm 0.12	-47.45 \pm 0.11	-49.12 \pm 0.10	-47.86 \pm 0.11	-34.53 \pm 0.09	-39.79 \pm 0.09
ΔH	-33.23 \pm 0.19	-34.60 \pm 0.14	-33.07 \pm 0.13	-30.55 \pm 0.13	-24.23 \pm 0.13	-30.88 \pm 0.13
$-T\Delta S$	21.75 \pm 0.64	24.14 \pm 0.73	21.85 \pm 0.85	22.73 \pm 0.67	16.75 \pm 0.67	19.85 \pm 0.66
ΔG_{bind}	-11.48	-10.46	-11.22	-7.82	-7.48	-11.03
IC50 (nM)	21	-- ^e	40	6300	15800	79
ΔG_{exp}^d	-10.57		-10.19	-7.16	-6.61	-9.78

^a All values are in kcal/mol.

^b $\Delta G_{ele+pol} = \Delta E_{ele} + \Delta G_{pol}$.

^c $\Delta G_{vdW+nonpol} = \Delta E_{vdW} + \Delta G_{nonpol}$.

^d The experimental values are calculated from the equation: $\Delta G_{exp} = -RT\ln(IC50)$.

^e The IC50 value is not available.

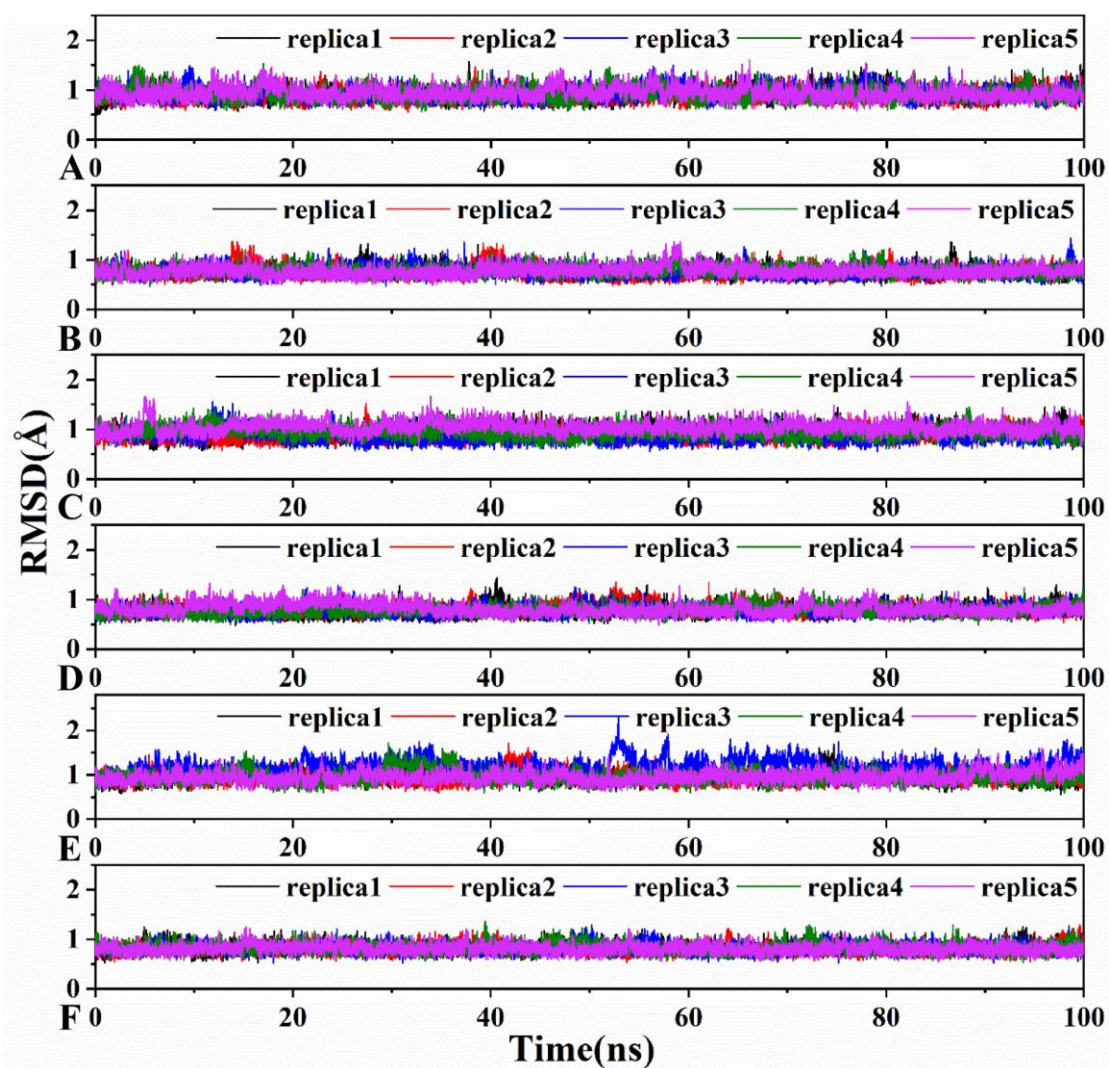


FIG. S1 Root-mean-square deviations (RMSDs) of backbone atoms in BD1 and BD2: (A), (C), and (E) respectively correspond to BD1 complexed with **SG3-179**, **GSK778**, and **GSK620**; and (B), (D) and (F) separately correspond to BD2 complexed with **SG3-179**, **GSK778**, and **GSK620**.

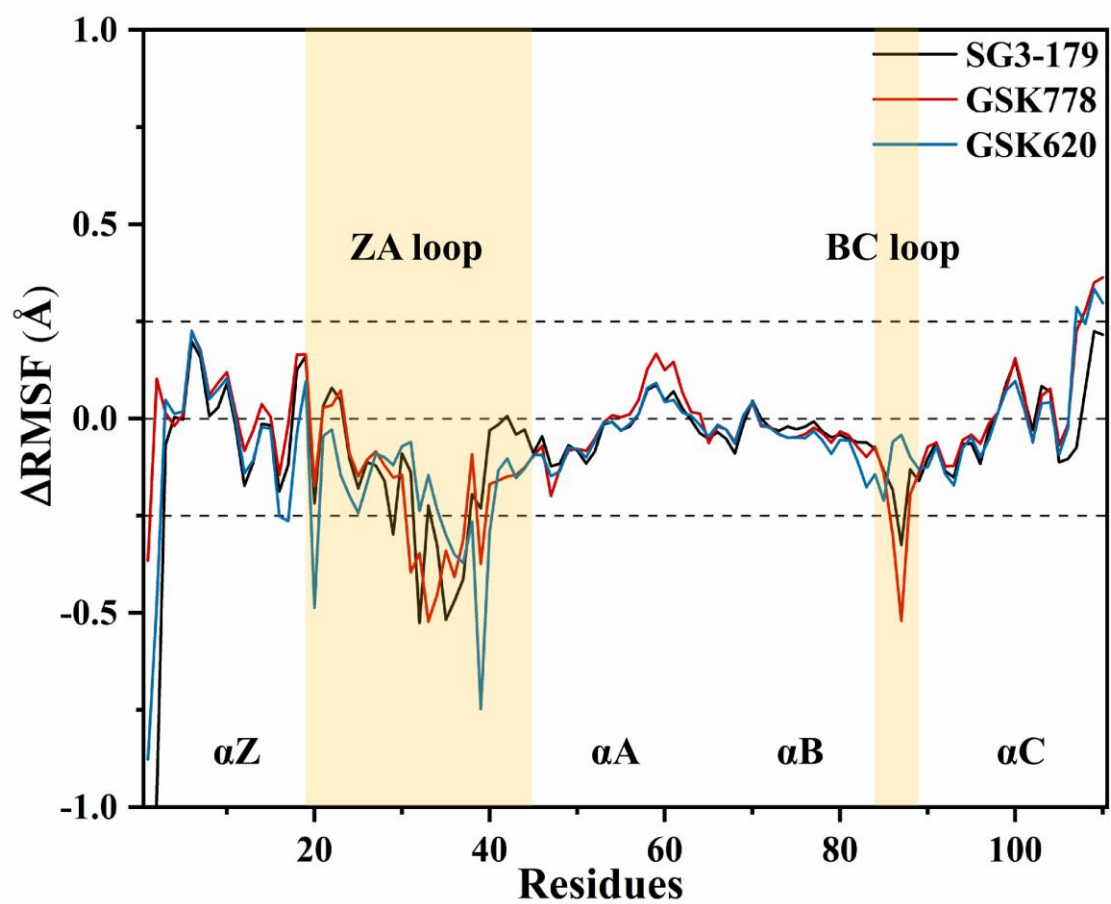


FIG. S2 Difference in root-mean-square fluctuations (ΔRMSF) between BD2 corresponding to the corresponding residues of BD1, $\Delta\text{RMSF} = \text{RMSF}_{\text{BD2}} - \text{RMSF}_{\text{BD1}}$.

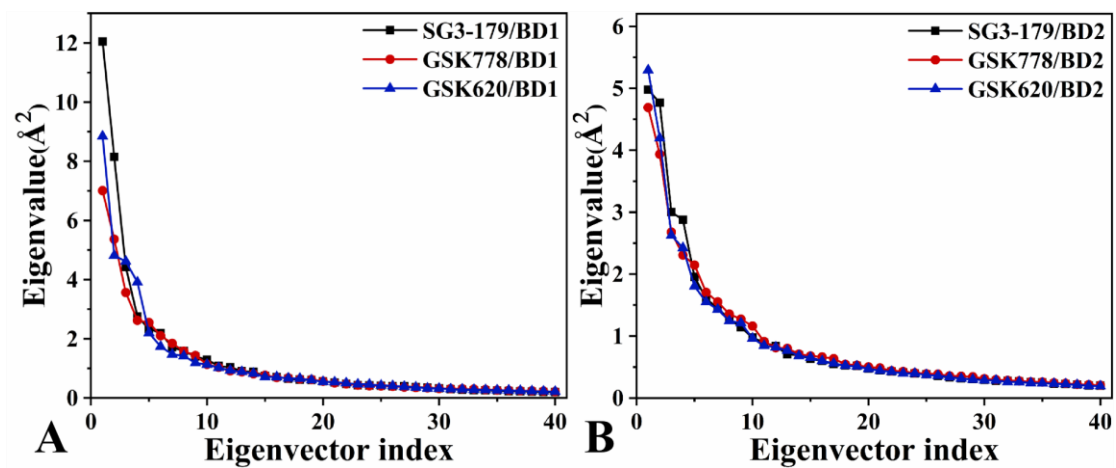


FIG. S3 The function of the eigenvalues VS the eigenvector indices obtained from principal component analysis performed on MRMD trajectories: (A) BD1 and (B) BD2.

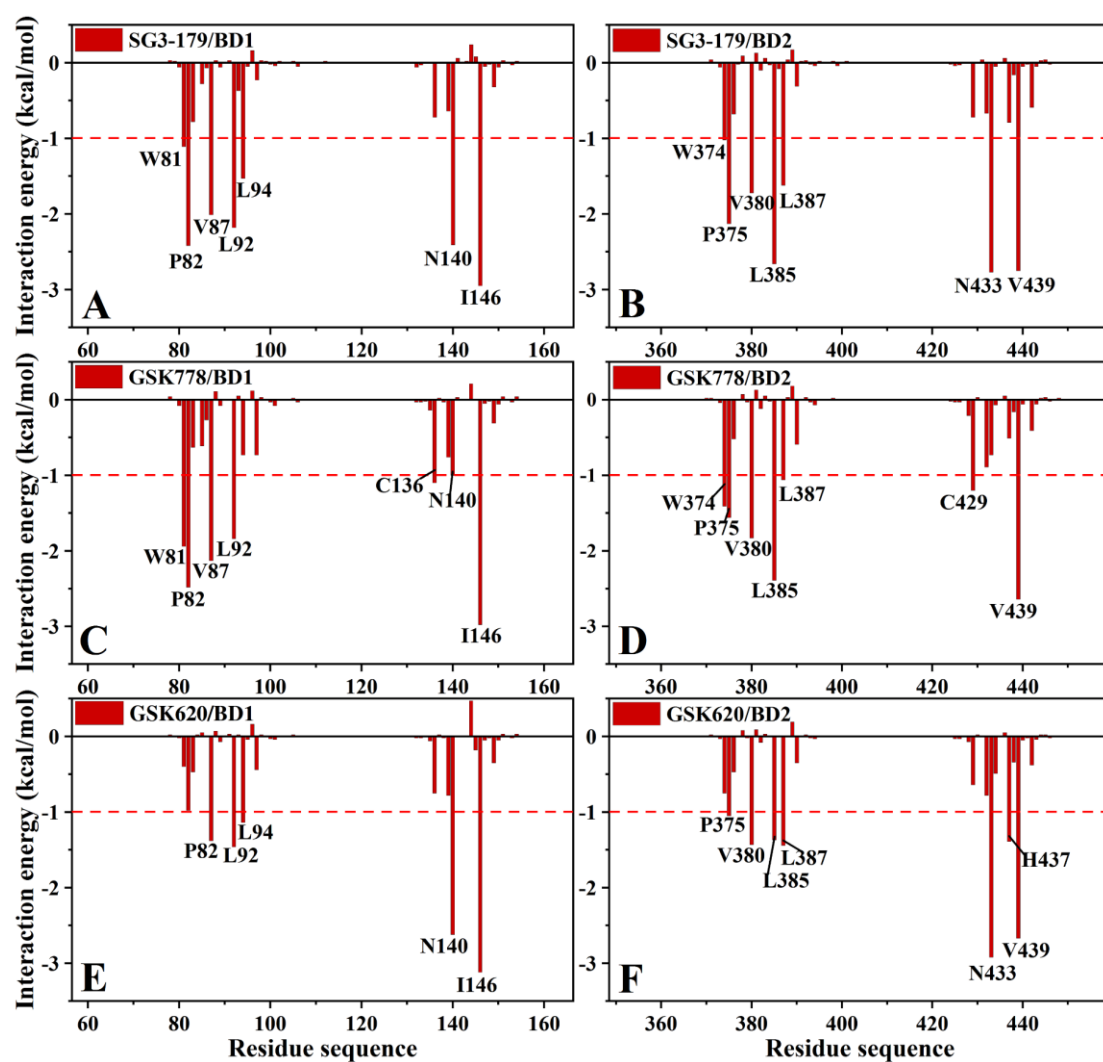


FIG. S4 Interactions of inhibitors with separate residues in BD1 and BD2: (A), (C) and (E) correspond to interactions of inhibitors **SG3-179**, **GSK778** and **GSK620** with residues in BD1, respectively; (B), (D) and (F) correspond to interactions of inhibitors **SG3-179**, **GSK778** and **GSK620** with residues in BD2, respectively.

