Dynamics Revelation of Conformational Changes and Binding Modes of Heat Shock Protein 90 Induced by Inhibitor Associations

Jianzhong Chen*[a,b], Jinan Wang[b], Fengbo Lai[a], Wei Wang[a], Laixue Pang*[a] and Weiliang Zhu*[b]

[a]*School of Science, Shandong Jiaotong University, Jinan, 250014, China,*

[b]*Drug Discovery and Design Center, CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, China,*

***Correspondence to*:** Jianzhong Chen, Laixue Pang and Weiliang Zhu, E-mail:chenjianzhong1970@163.com, jzchen@sdjtu.edu.cn (J.C.), lxpang@sdjtu.edu.cn (L.P.) and wlzhu@simm.ac.cn (W.Z.)

Jianzhong Chen: ORCID: 0000-0003-1558-4398

Jinan Wang: ORCID: 0000-0003-0162-212X

Table S1 Binding free energies of inhibitors to Hsp calculated by MM-GBSA method

[a]Components	YKC-Hsp		YKJ-Hsp		YKI-Hsp	
	Average	[b]STD	Average	STD	Average	STD
ΔE_{ele}	-14.75	3.01	-16.98	4.30	-35.95	4.16
ΔE_{vdW}	-45.10	2.74	-46.09	3.02	-60.70	2.62
ΔG_{pol}	28.55	2.11	26.44	3.11	54.49	2.76
ΔG_{nonpol}	-5.21	0.09	-5.44	0.09	-7.24	0.10
[c]$\Delta G_{ele+pol}$	13.80	1.63	9.46	2.11	18.54	2.95
$-T\Delta S$	18.97	1.98	21.29	1.99	26.90	2.12
ΔG_{bind}	-17.54		-20.78		-22.50	
[d]ΔG^{exp}	-6.96		-8.50		-10.31	

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

[b]Standard errors,

[c]$\Delta G_{ele+pol} = \Delta E_{ele} + \Delta G_{pol}$,

[d]The experimental values were derived from the experimental K_i values in reference using the equation $\Delta G^{exp} = -RTlnK_i$.

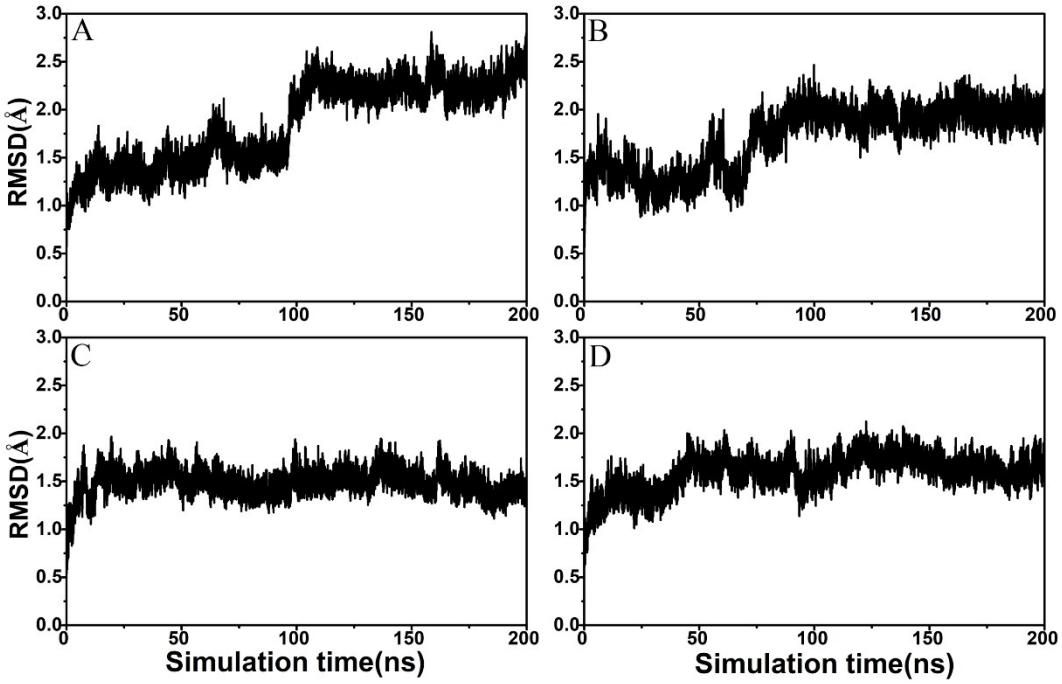

Fig. S1 Root-mean-square deviations of backbone atoms in Hsp90: (A) the apo-Hsp90, (B) the YK9-Hsp90, (C) the YKJ-Hsp90 and (D) the YKI-Hsp90.

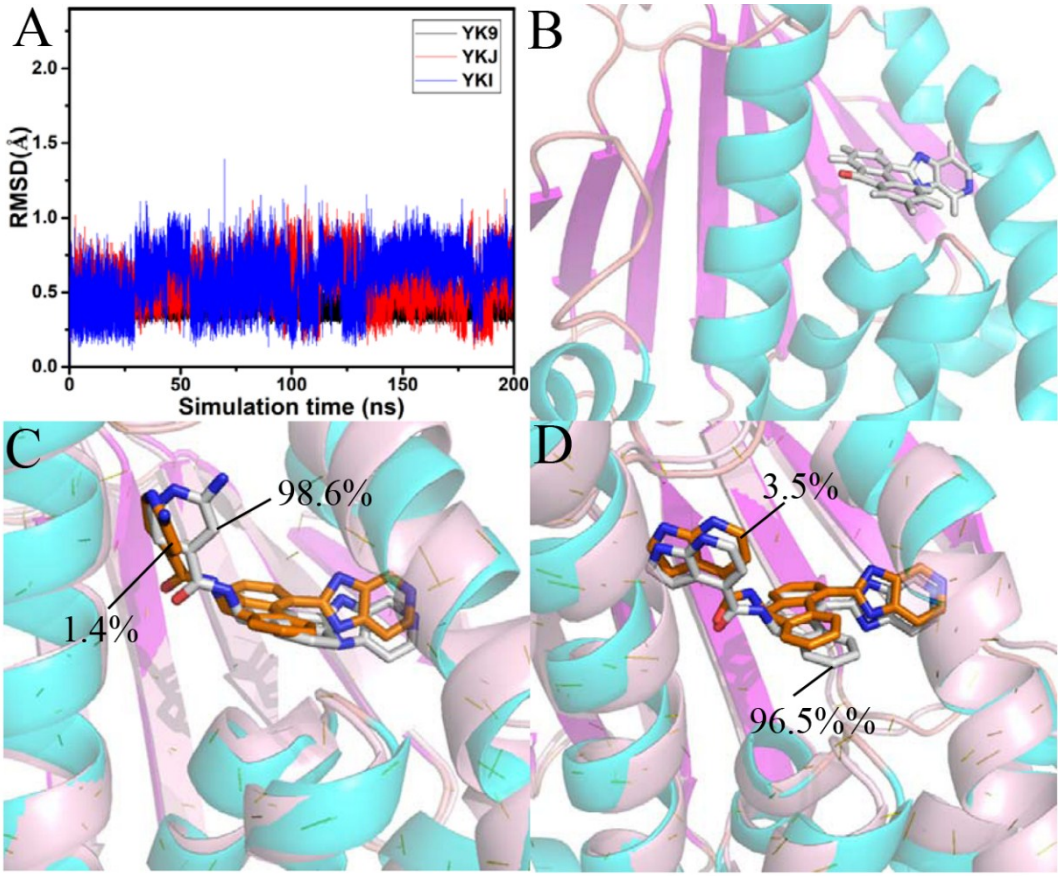

Fig. S2 Root-mean-square deviations (RMSDs) of non-hydrogen atoms in inhibitors and structural cluster analysis: (A) RMSDs, (B), (C) and (D) respectively correspond to structural cluster analysis of inhibitors YK9, YKJ and YKI.

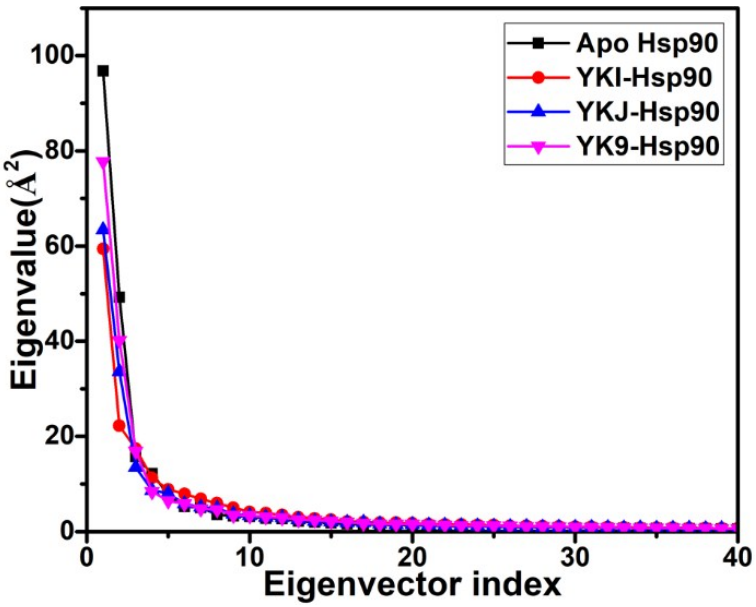

Fig. S3 The function of the eigenvalues VS the eigenvector indices obtained from the C_α covariance matrix constructed from the equilibrated MD trajectories.

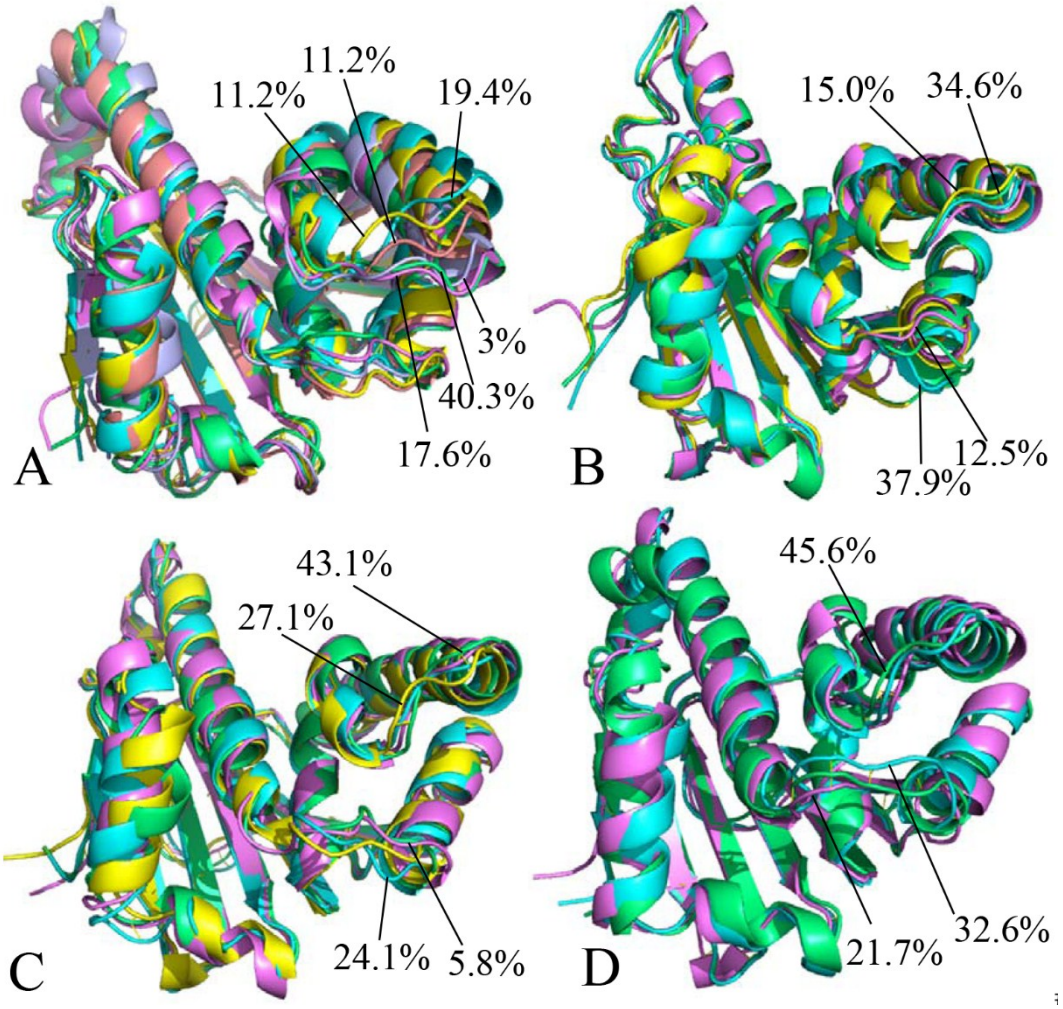

Fig. S4 Cluster analysis performed by using the RMSD values of Cα atoms in Hsp90: (A) the *apo* Hsp90, (B) the YK9-Hsp90, (C) the YKJ-Hsp90 and (D) the YKI-Hsp90.

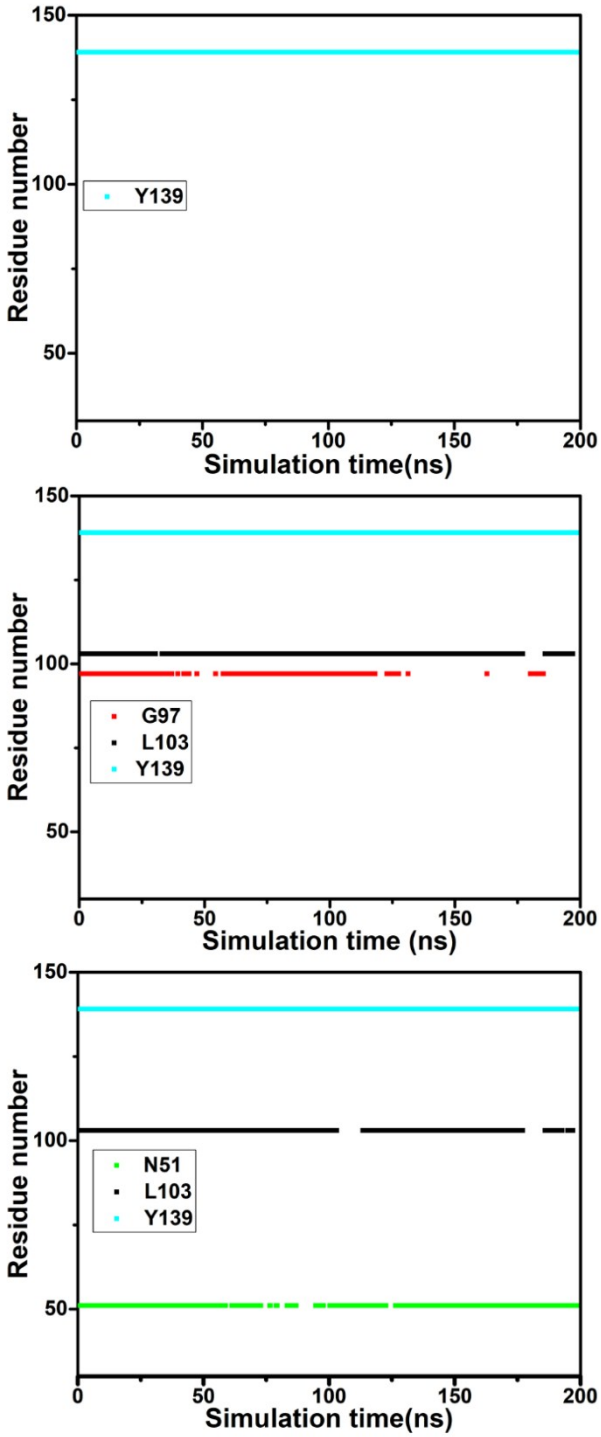

Fig. S5 The hydrogen bond contacts of inhibitors with separate residues of Hsp90 as a function of the simulation time: (A) YK9, (B) YKJ and (C) YKI.

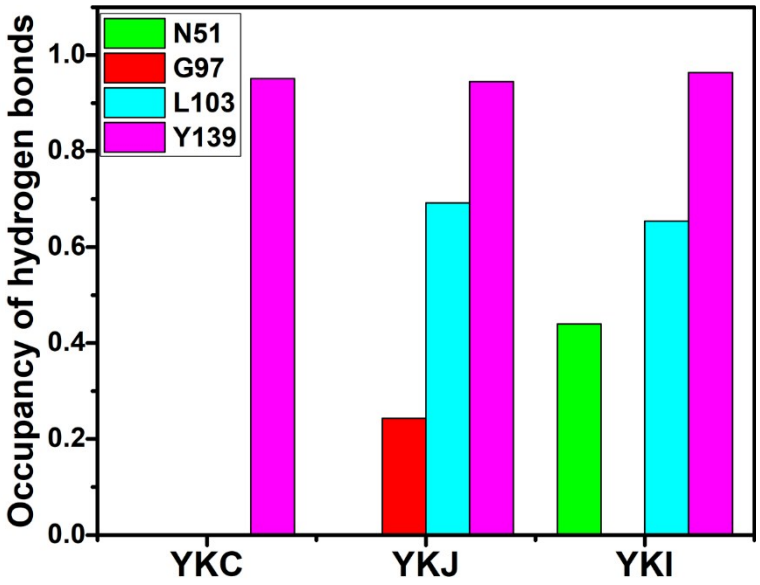

Fig. S6 Statistical analyses of hydrogen bond contacts between inhibitors and separate residues of Hsp90, the occupancy is defined as the number of conformations forming hydrogen bond contacts accounting for the percentage of the total number of conformations recorded in MD trajectories.

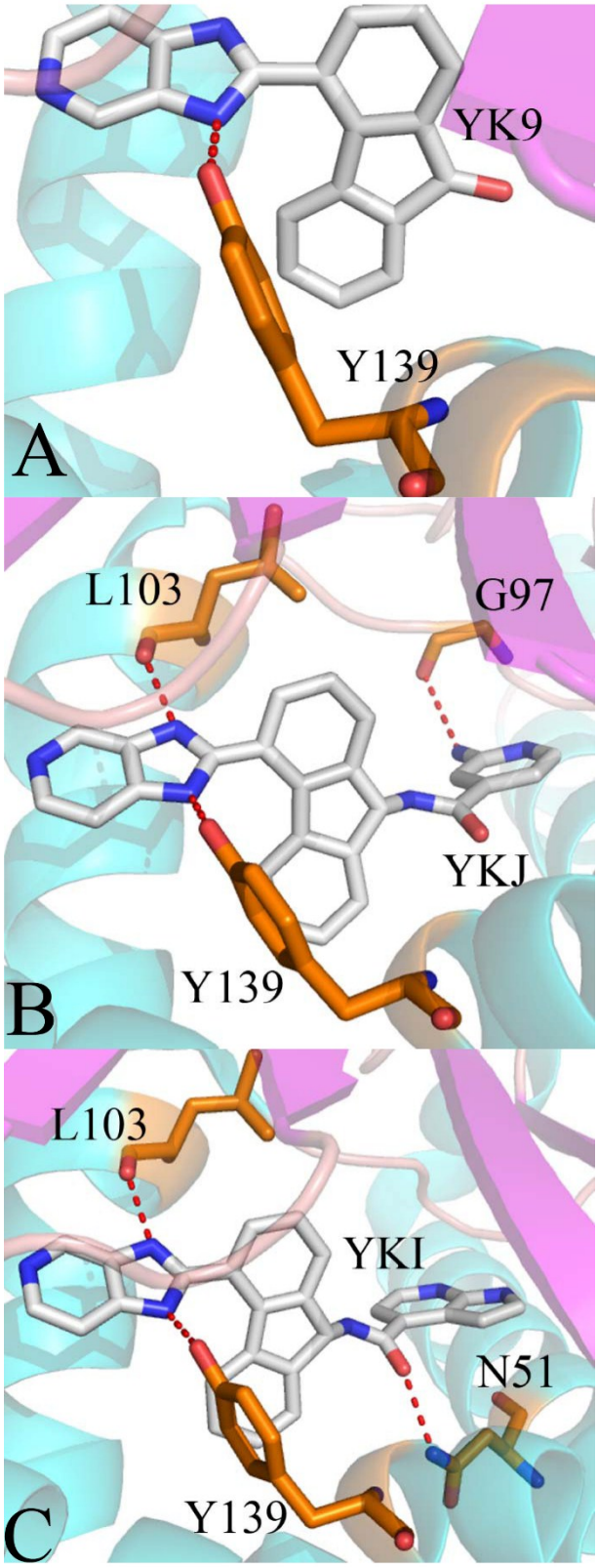

Fig. S7 Hydrogen bonding interactions of inhibitors with Hsp90 detected by hydrogen bond scanning, and key residues and inhibitors are shown in stick modes: (A) YK9, (B) YKJ and (C) YKI.