Mutation L1196M-induced Conformational Changes and Drug Resistant Mechanism of Anaplastic Lymphoma Kinase Studied by Free Energy Perturbation and Umbrella Sampling

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Table S1 Absolute binding free energies of inhibitors to ALK computed by FEP (kcal/mol)

Inhibitors	ALK	[a]ΔG_{vdW}	[b]ΔG_{ele}	[c]ΔG_{bind}
VGH	Wild	-16.61±0.35	3.54±0.27	-13.07±0.35
	L1196M	-15.10±0.27	2.93±0.28	-12.17±0.27
3U9	Wild	-16.56±0.26	2.99±0.16	-13.57±0.43
	L1196M	-14.28±0.14	2.43±0.17	-11.85±0.29
5P8	Wild	-16.96±0.31	2.29±0.19	-14.67±0.51
	L1196M	-16.16±0.27	1.83±0.11	-14.33±0.38
IV7	Wild	-16.69±0.61	2.45±0.51	-14.24±0.65
	L1196M	-18.25±0.52	4.13±0.31	-14.12±0.58

[a]ΔG_{vdW} indicates the changes in the van der Waals interactions decoupling inhibitors from proteins and solvent, respectively.

[b]ΔG_{ele} represents the changes in the electrostatic interactions decoupling inhibitors from proteins and solvent, respectively.

[c]$\Delta G_{bind}=\Delta G_{vdW}+\Delta G_{ele}$.

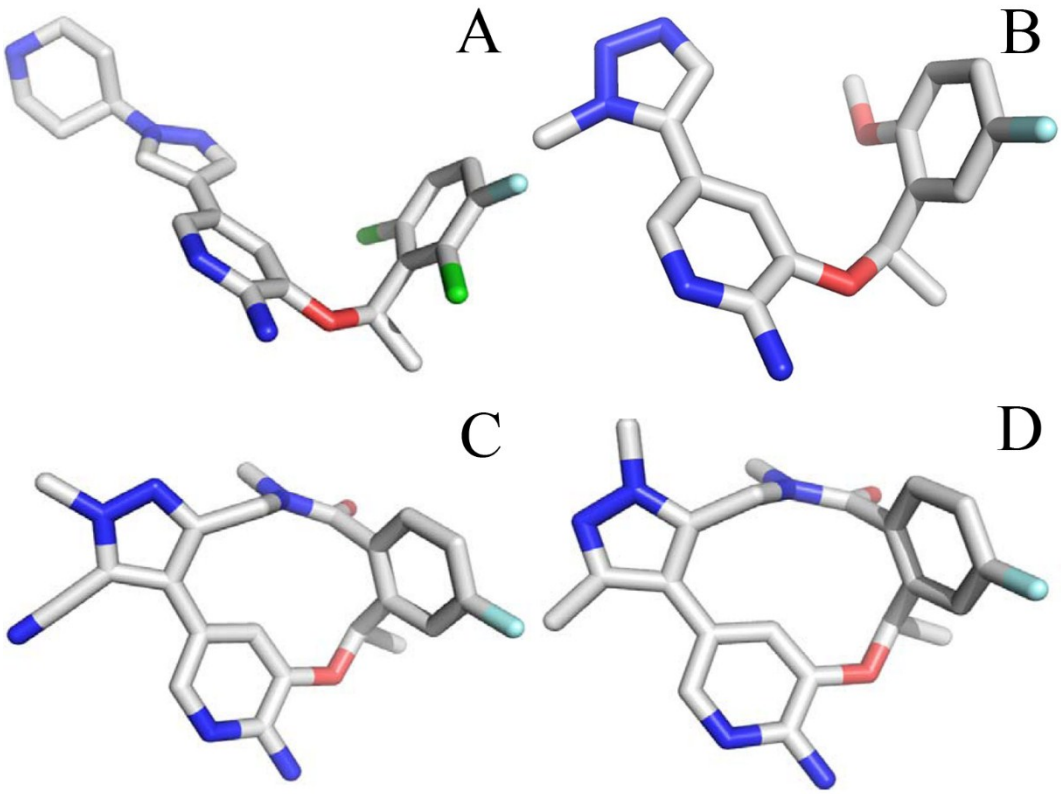

Figure S1 Molecular structures of inhibitors: (A) VGH, (B) 3U9, (C) 5V8 and (D) IV7

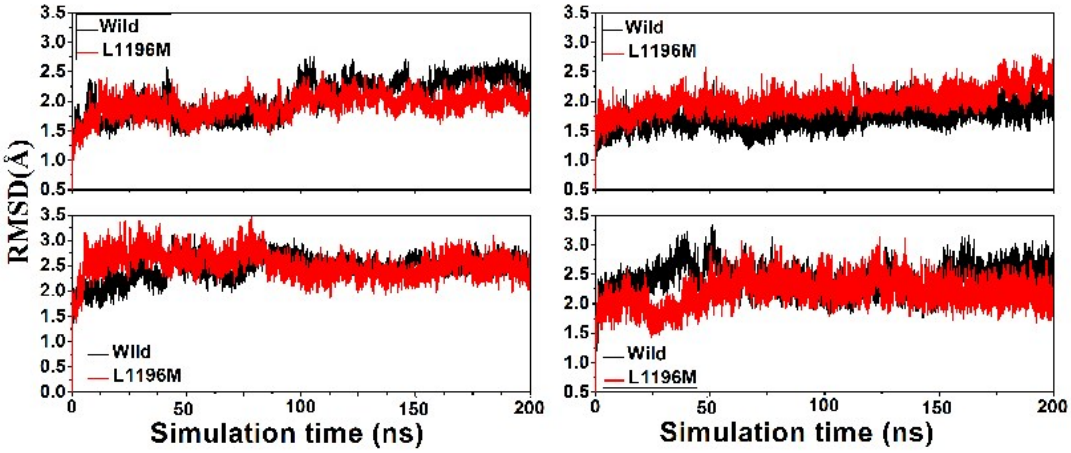

Figure S2 RMSD of backbone atoms in anaplastic lymphoma kinase (ALK): (A) VGH-wild/L1196M complexes, (B) 3U9-wild/L1196M complexes, (C) 5P8-wild/L1196M complexes and (D) IV7-wild/L1196M complexes.

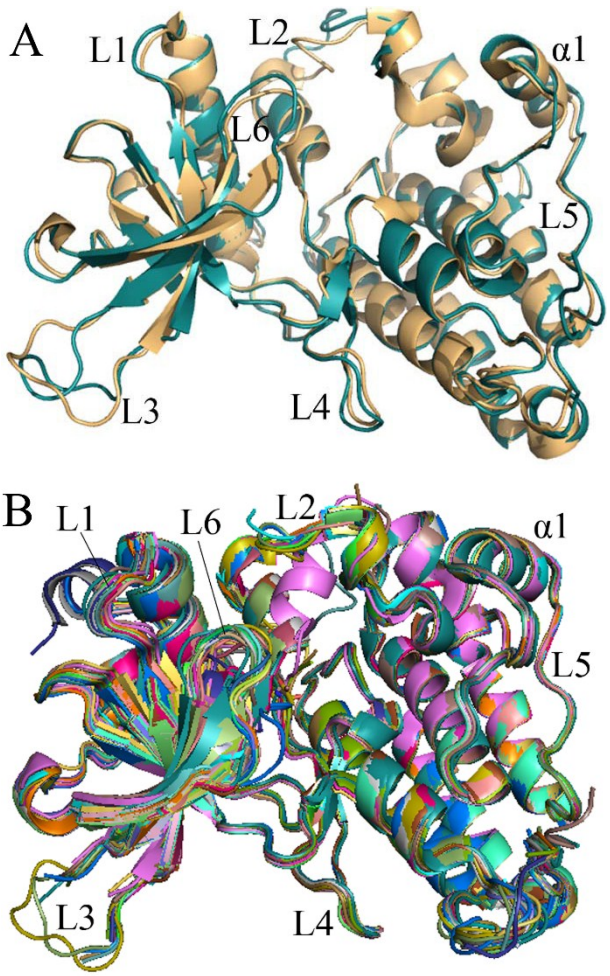

Figure S3 Superimposition of structures: (A) superimposition of the crystal structure of ALK with MD structure of ALK: lightorange for the crystal structure of ALK and deepteal for the structure of ALK extracted from MD trajectory, (B) superimposition of multiple crystal structures.

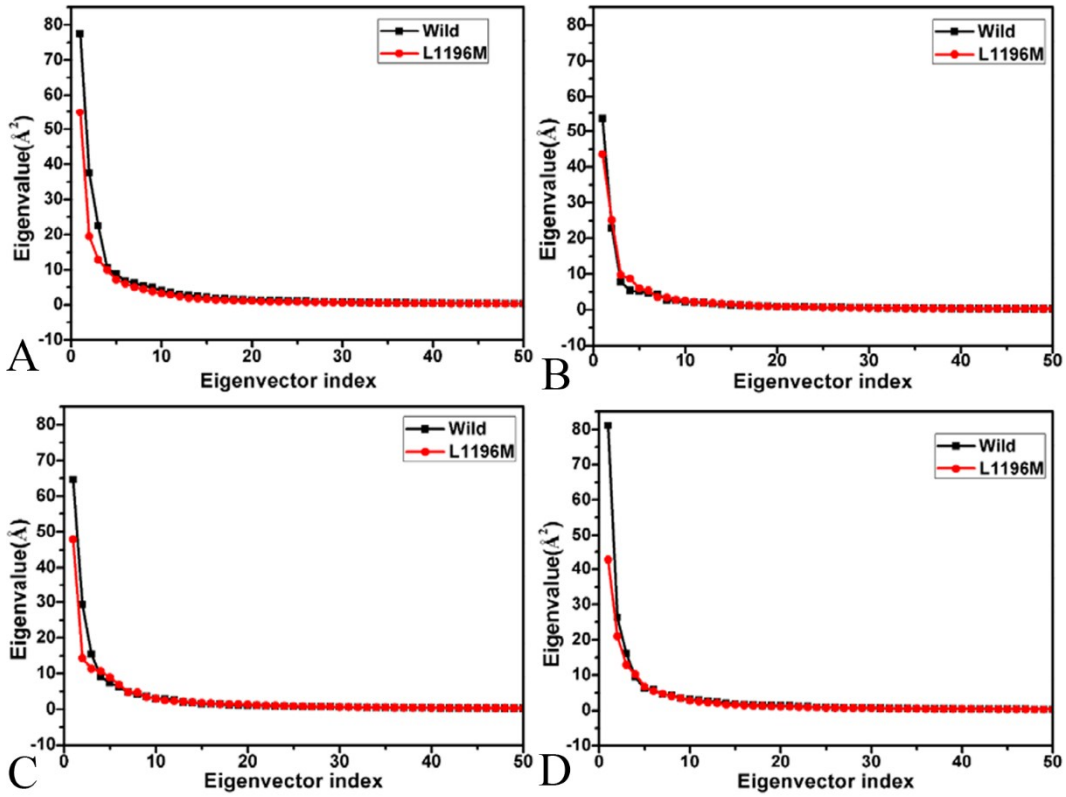

Figure S4 Eigenvalues plotted against the corresponding eigenvector indices obtained from diagonalization of covariance matrix of C_α atoms in anaplastic lymphoma kinase (ALK): (A) VGH-wild/L1196M ALK complexes, (B) 3U9-wild/L1196M ALK complexes, (C) 5P8-wild/L1196M ALK complexes, (D) IV7-wild/L1196M AK complexes.

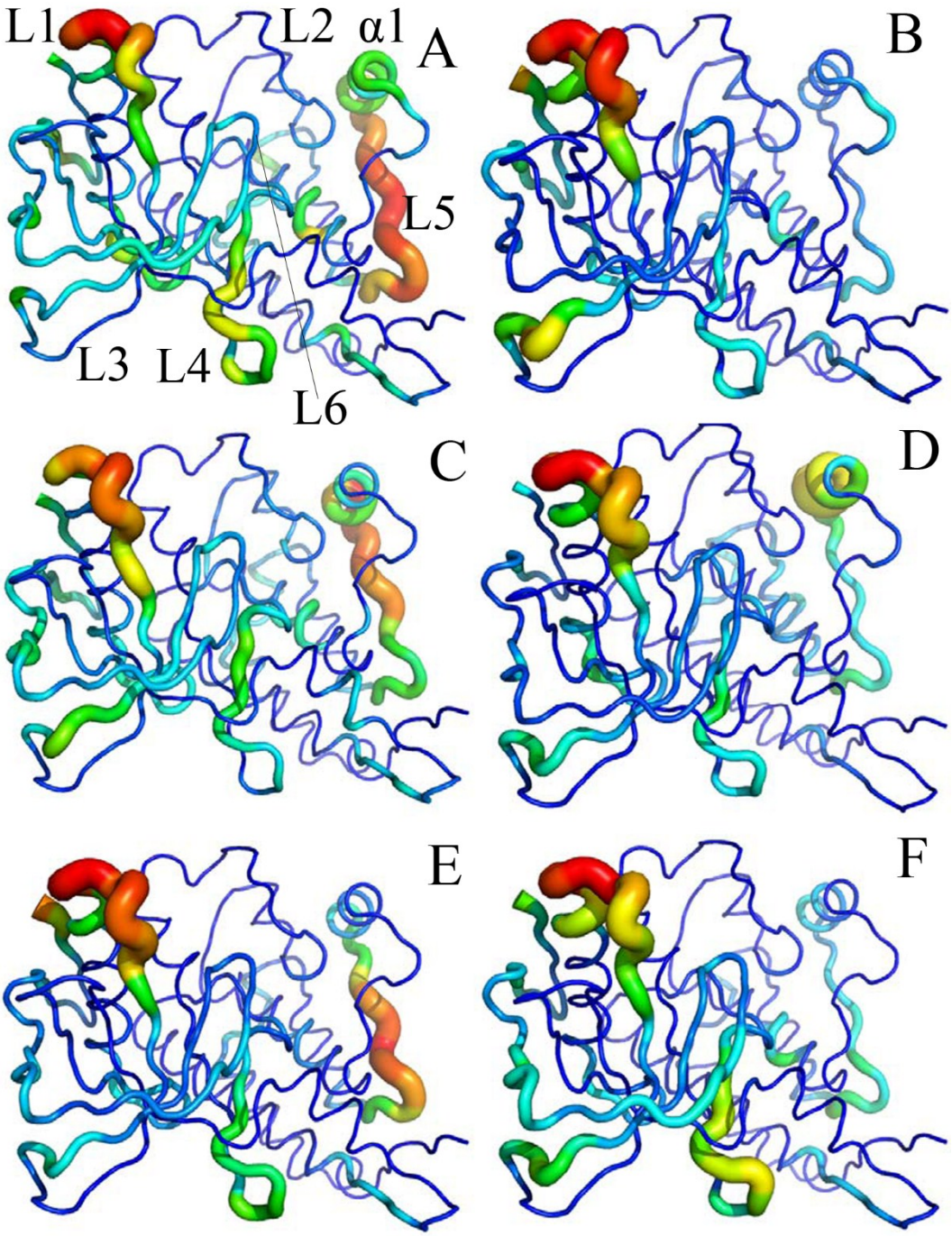

Figure S5 B-factor information from dynamics analysis mapped the structure extracted from principal component analysis. The thickness of the tube corresponds to structural flexibility, with thicker tubes (red and yellow) displaying more flexible regions and thinner tubes (blue) indicating more rigid region: (A) 3U9-wild ALK complex, (B) 3U9-L1196M complex, (C) 5P8-wild ALK complex, (D) 5P8-L1196M complex, (E) IV7-wild ALK complex and (F) IV7-L1196M complex

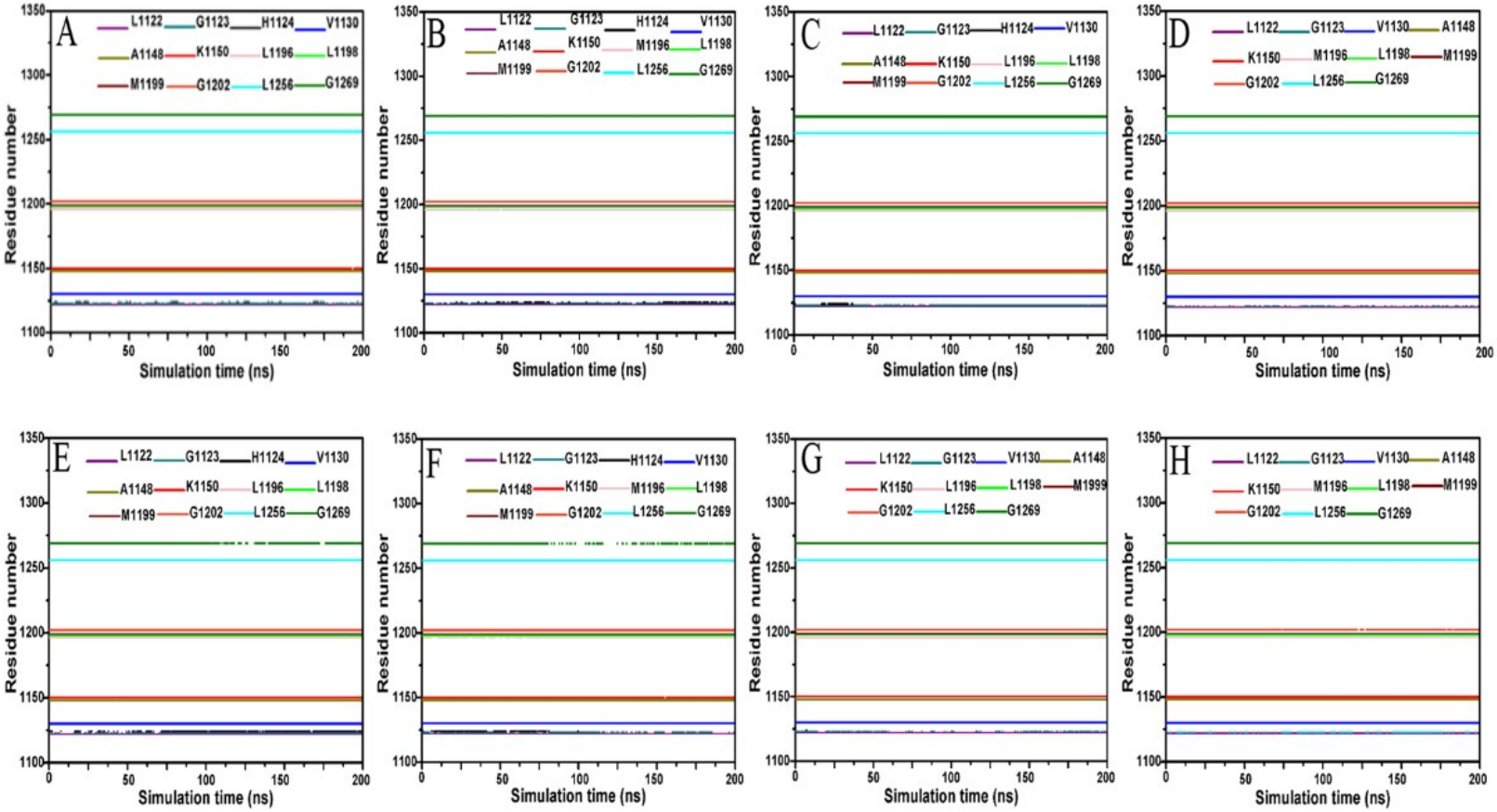

Figure S6 The hydrophobic contacts of inhibitors with separate residues of anaplastic lymphoma kinase (ALK) as a function of the simulation time: (A) VGH-wild ALK, (B) VGH-mutated ALK, (C) 3U9-wild ALK, (D) 3U9-mutated ALK, (E) 5P8-wild ALK, (F) 5P8-mutated ALK, (G) IV7-wild ALK and (H) IV7-mutated ALK.

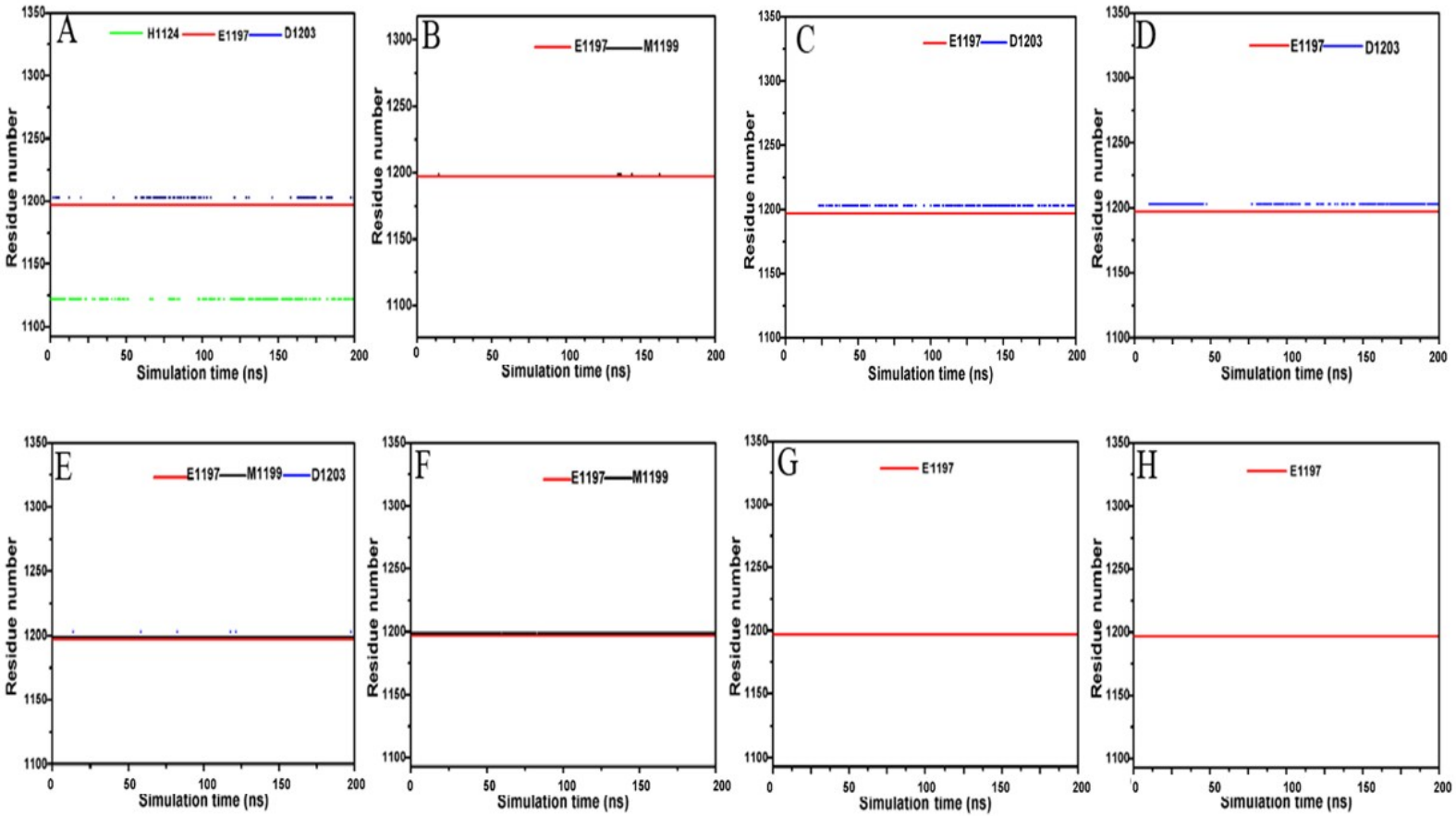

Figure S7 The hydrogen bond contacts of inhibitors with separate residues of anaplastic lymphoma kinase (ALK) as a function of the simulation time, (A) VGH-wild ALK, (B) VGH-mutated ALK, (C) 3U9-wild ALK, (D) 3U9-mutated ALK, (E) 5P8-wild ALK, (F) 5P8-mutated ALK, (G) IV7-wild ALK and (H) IV7-mutated ALK.

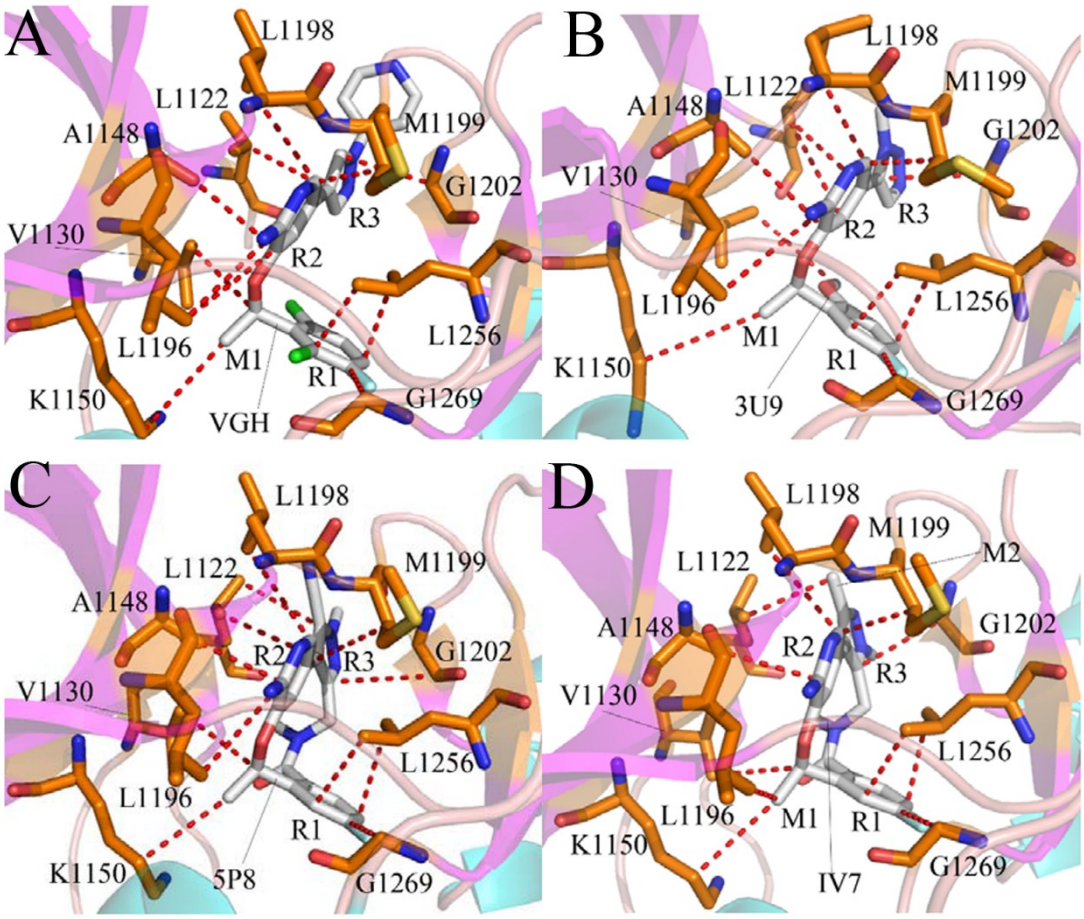

Figure S8 Residues of ALK forming hydrophobic contacts with inhibitors. Key residues and four inhibitors are depicted in stick modes. A pair of carbon atoms lower than 4.2 Å in distances are defined as hydrophobic contacts: (A) VGH-wild ALK, (B) 3U9-wild ALK, (C) 5P8-wild ALK and (D) IV7-wild ALK.

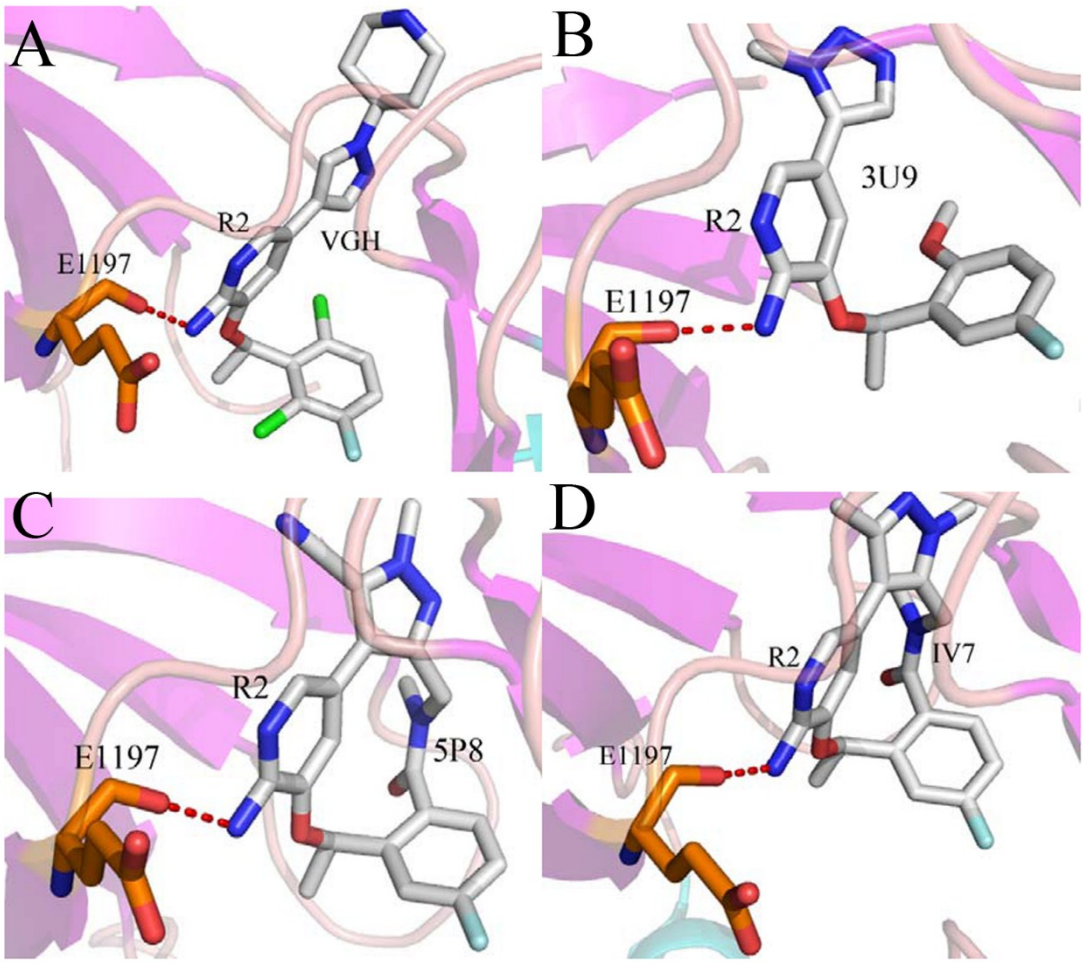

Figure S9 Hydrogen bond detected by hydrogen bond scanning, Key residues and inhibitors are shown in stick modes: (A) VGH-wild ALK, (B) 3U9-wild ALK, (C) 5P8-wild ALK and (D) IV7-wild ALK.