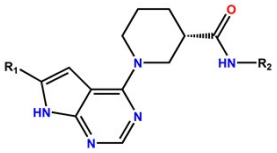
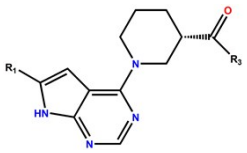
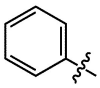
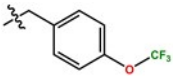
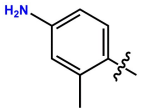
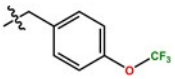
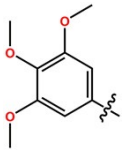
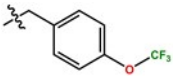
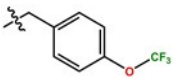
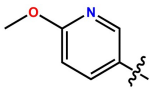
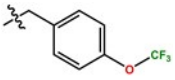
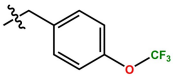
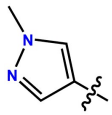
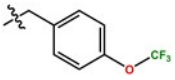
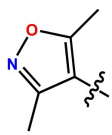
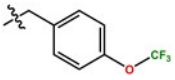
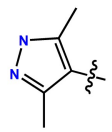
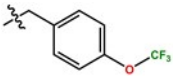
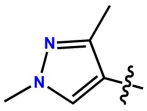
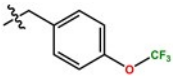
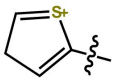
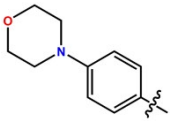
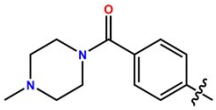
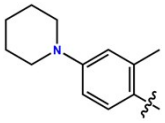
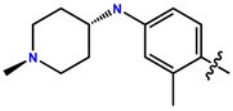
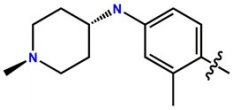
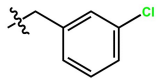
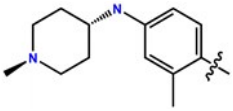
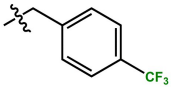
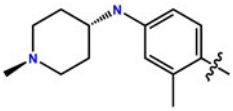
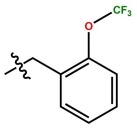
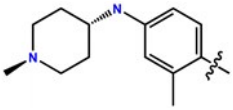
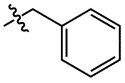
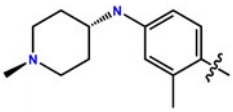
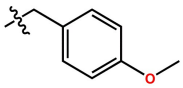
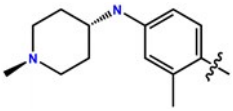
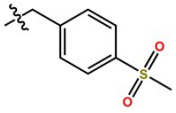
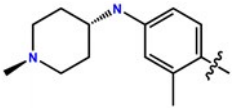
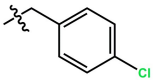
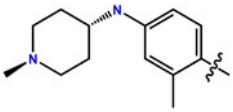
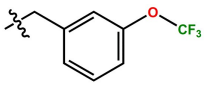
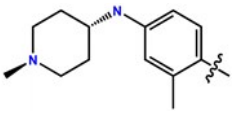
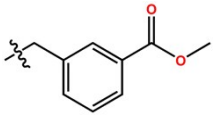
Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information

Table S1. Compound structures and their corresponding biological activities.

Compound Name	R1	R2	R3	IC_{50} (nM)	pIC_{50}
001-001				52.47	7.28
001-002				5.349	8.27
001-003				81.97	7.09
001-006				11.88	7.93
001-007				148.14	6.83
001-008				11.48	7.94
001-009				6.01	8.22
001-010				18.85	7.72
001-011				1.25	8.90
001-012				3.7	8.43

001-013			37.88	7.42
001-014			11.20	7.95
001-015			0.60	9.22
001-016			20.25	7.69
001-017			0.27	9.57
002-001			3.15	8.50
002-002			1.65	8.78
002-003			61.12	7.21
002-004			24.18	7.62
002-005			2.99	8.52
002-006			347.52	6.46
002-007			0.86	9.07
002-008			0.64	9.19
002-009			2.18	8.66

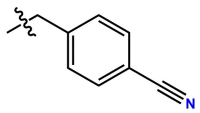
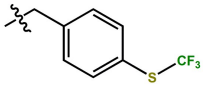
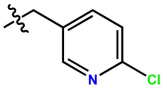
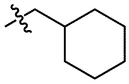
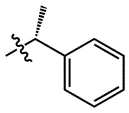
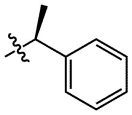
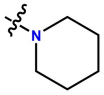
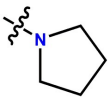
002-010				3.38	8.47
002-011				0.60	9.22
002-012				291.38	6.54
002-013				358.62	6.45
002-014				39.87	7.40
002-015				159.50	6.80
002-016				1921.69	5.72
002-017				1205.98	5.92

Table S2. Binding free energies and their average values of the five representative ALK inhibitors determined by umbrella sampling and MM/GBSA (kcal/mol).

Name	001-007	001-013	001-017	002-012	002-016
PMF_3 ns	11.16[a]±0.30[b]	13.89±0.12	17.40±0.20	12.30±0.14	6.01±0.25
PMF_4 ns	10.96±0.33	13.68±0.13	16.02±0.25	13.76±0.09	6.36±0.26
PMF_5 ns	11.92±0.30	12.95±0.13	16.05±0.36	11.45±0.08	6.27±0.11
PMF_Average	11.35±0.29	13.33±0.12	16.48±0.22	12.51±0.08	6.36±0.26
ΔG_{off}_3ns	9.23[c]	12.92	16.94	8.11	1.90
ΔG_{off}_4ns	9.49	13.60	15.17	10.16	1.95
ΔG_{off}_5ns	9.92	12.55	14.99	8.85	1.97
ΔG_{off}_Average	9.53[d]±0.28[e]	13.01±0.43	15.66±0.87	9.03±0.84	1.95±0.02
pIC_{50}	-6.83	-7.42	-9.57	-6.54	-5.72
ΔG_{bind}[d]	-52.29[f]±0.03[g]	-51.55±1.19	-56.28±0.25	-52.78±0.09	-44.20±0.47

[a]The PMF value was estimated by averaging the bins across 18~20 Å of the RC.

[b]The standard deviation of US simulation (3~5 ns) was estimated based on the bins across 18~20 Å of the RC.

[c]The activation free energy of dissociation determined by US simulation.

[d]The average of the activation free energy.

[e]The standard deviations were estimated from the PMF values of the last 3-5 ns US simulations.

[f]Binding free energy determined by MM/GBSA.

[g]The standard deviations were estimated based on five blocks.

Table S3. Energetic contributions of the key residues to the binding of the representative ALK inhibitors (kcal/mol).

Residue	001-007	001-013	001-017	002-012	002-016
Leu1122	-4.60	-4.76	-5.74	-5.44	-5.68
Gly1123	-0.14	-0.28	-0.30	-0.20	-0.22
Glu1129	0	-0.28	-0.26	-0.30	-0.24
Val1130	-3.56	-3.10	-3.64	-3.78	-3.52
Tyr1131	-0.14	-0.14	-0.18	-0.20	-0.14
Ile1194	-0.36	-0.32	-0.34	-0.36	-0.30
Leu1195	-0.20	-0.14	-0.16	-0.20	-0.18
Leu1196	-3.44	-3.50	-3.56	-3.54	-3.42
Glu1197	0.26	-0.58	-0.30	0.02	0.02
Leu1198	-3.06	-2.92	-3.56	-3.64	-3.54
Met1199	-6.82	-7.00	-6.62	-6.72	-6.42
Ala1200	-0.68	-0.46	-0.80	-0.82	-0.80
Gly1201	-0.62	-0.18	-0.48	-0.60	-0.54
Gly1202	-2.08	-1.32	-2.18	-2.04	-2.30
Asp1203	0.20	-0.50	0.36	0.36	-0.20
Ser1206	-0.04	0.04	-0.20	-0.26	-0.10
Glu1210	0.12	0.24	-0.18	-0.14	-0.14
Asn1254	-0.32	-0.34	-0.24	-0.22	-0.16
Cys1255	-0.10	-0.08	-0.12	-0.14	-0.12
Leu1256	-3.94	-3.78	-4.20	-4.24	-4.10
Ala1148	-2.06	-1.96	-2.04	-2.10	-2.00
Val1149	-0.34	-0.34	-0.32	-0.36	-0.18
Lys1150	-1.86	-1.72	-1.92	-1.96	-3.30
Glu1154	0.02	-0.16	-0.14	-0.14	-0.14
Glu1167	0.54	0.08	0.14	0.72	0.36
Ile1171	-3.20	-3.30	-3.34	-3.06	-1.50
Phe1174	-1.24	-1.08	-1.40	-0.48	-0.02
Ile1179	-2.14	-1.96	-2.04	-1.50	-0.22
Val1180	-2.44	-2.32	-2.38	-2.22	-2.30
Phe1245	-0.22	-0.16	-0.34	0	0.02
His1247	-0.56	-0.50	-0.64	-0.14	0
Ile1268	-1.74	-1.84	-1.74	-1.10	-0.26
Gly1269	-3.68	-3.78	-3.68	-3.90	0.40
Asp1270	-2.28	-2.26	-2.28	-2.54	-1.60

Phe1271	-2.86	-2.44	-2.86	-2.52	-1.28

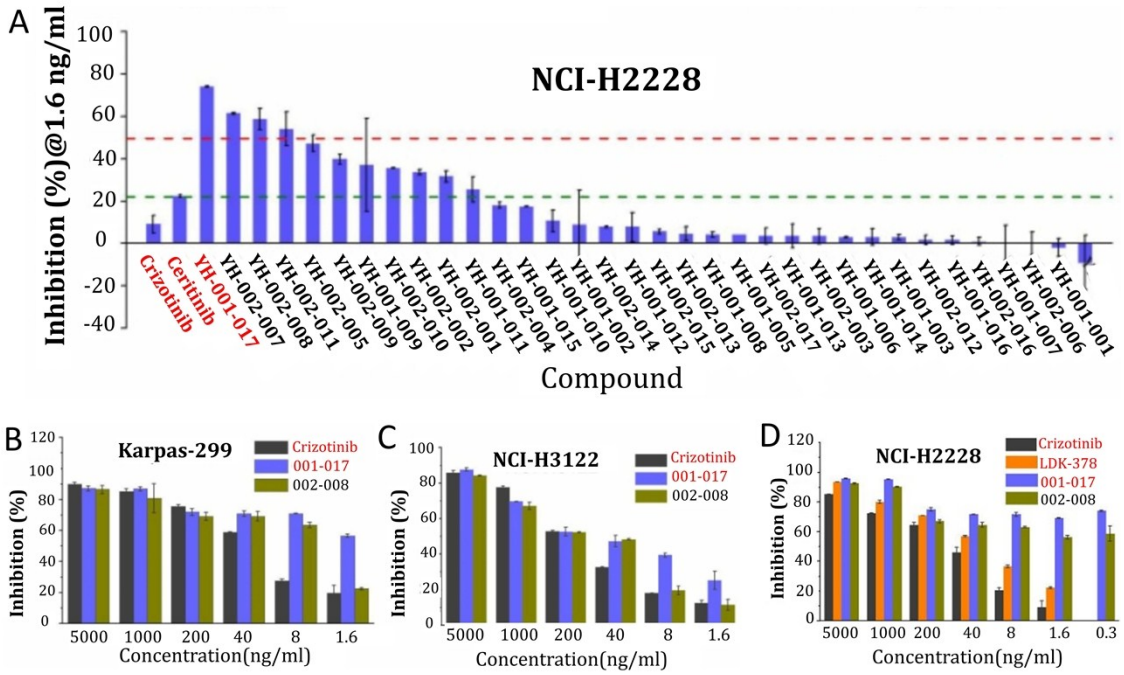


Figure S1. Anti-proliferation activity against NCI-H2228, NCI-H3122, and Karpas-299 cell lines of the studied Type-I$^{1}/_{2}$ inhibitors of ALK.

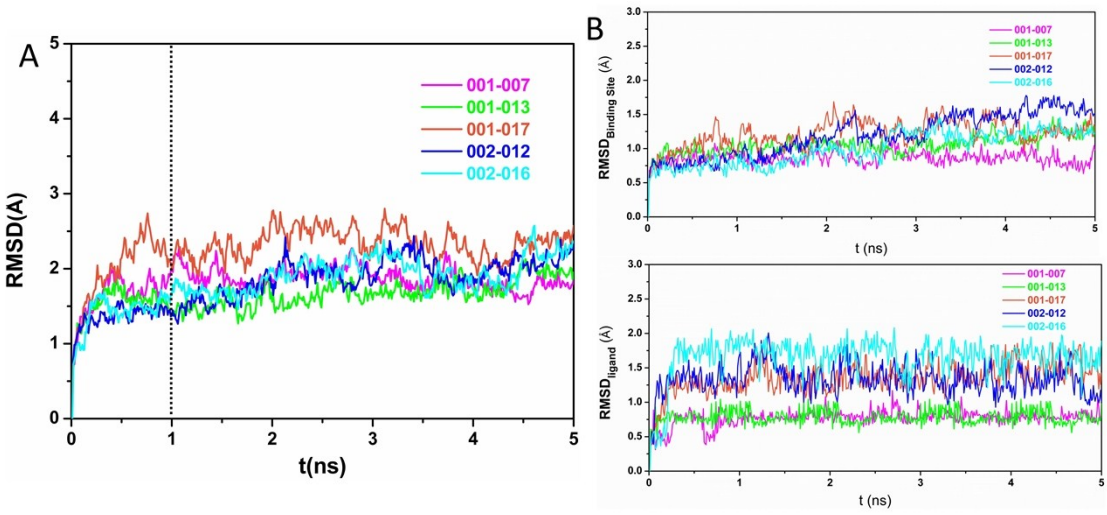


Figure S2. RMSDs (root mean square deviations) of the representative systems.

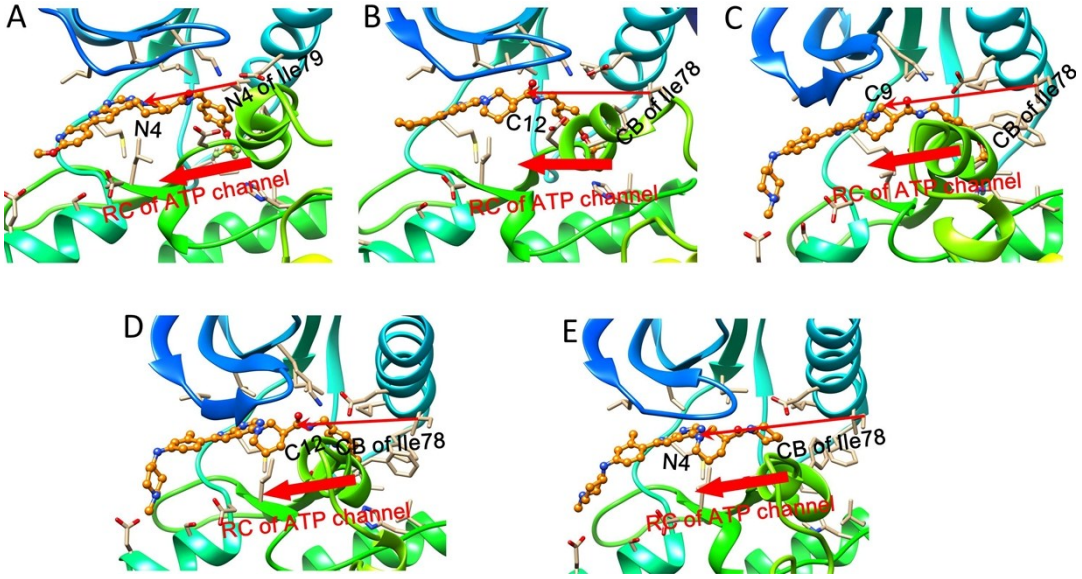


Figure S3. The RCs through ATP channels of the (A) ALK/001-007, (B) ALK/001-013, (C) ALK/001-017, (D) ALK/002-012, and (E) ALK/002-016 systems.

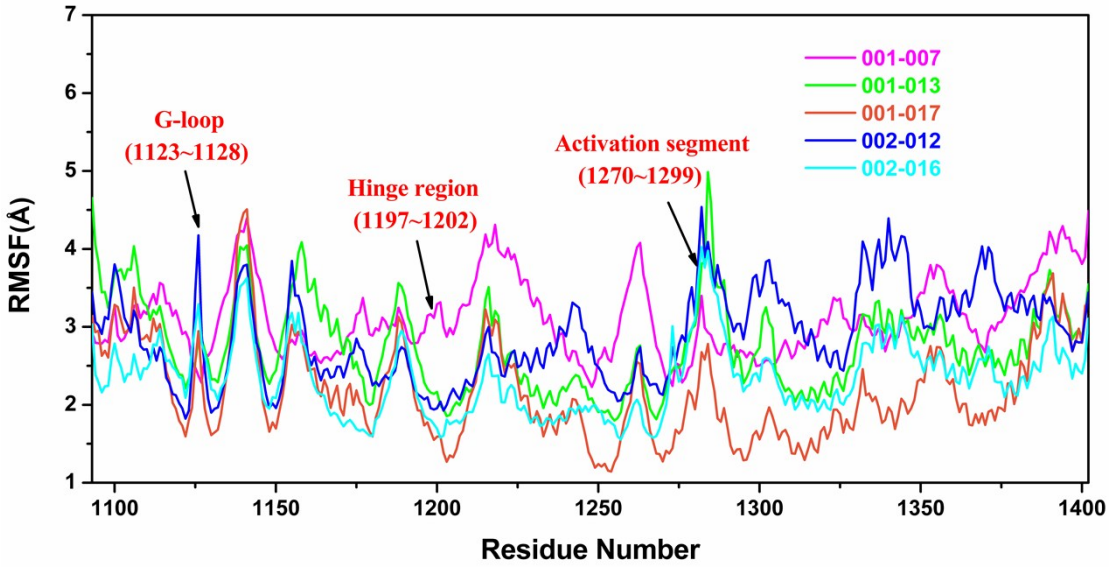


Figure S4. RMSFs (root mean square fluctuations) of the representative systems.

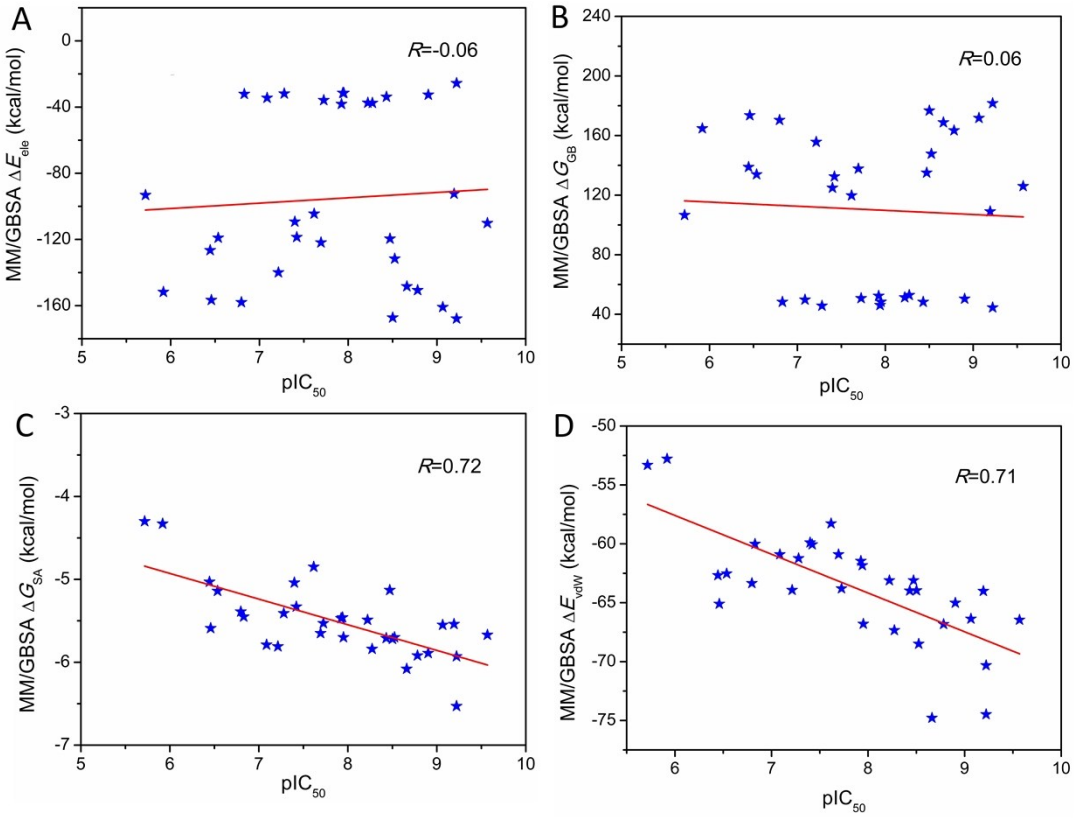


Figure S5. The correlations between the experimental binding affinities and the electrostatic (ΔE_{ele}), van der Waals (ΔE_{vdW}), solvation (ΔG_{GB}), and SASA (ΔG_{SA}) components.

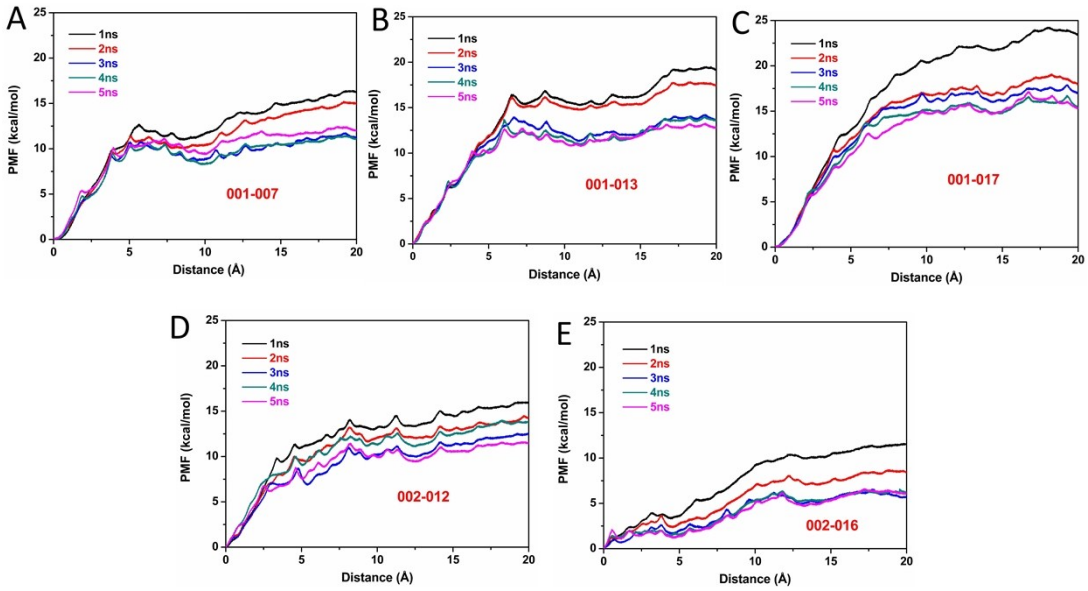


Figure S6. Convergence of the PMFs of the representative systems along the ATP channel in US simulations.