Supporting Information

Discovery of Potential VEGFR-2 Inhibitors from Natural Products by Virtual Screening and Molecular Dynamics Simulation

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Table S1. The docking score of 96 compounds and the calculated binding free energies after 10 ns MD simulations.

Compound code	Docking score	ΔG_{calc} (kcal/mol)
CNP0011393	-11.57	-38.57
CNP0097185	-11.16	-50.69
CNP0037721	-11.13	-32.55
CNP0011062	-10.82	-48.85
CNP0028810	-10.81	-66.71
CNP0011147	-10.77	-40.40
CNP0047340	-10.69	-52.32
CNP0240557	-10.63	-56.24
CNP0069582	-10.42	-52.98
CNP0011435	-10.40	-56.49
CNP0190525	-10.31	-57.87
CNP0065469	-10.25	-49.02
CNP0024354	-10.13	-34.54
CNP0279782	-10.12	-40.39
CNP0047068	-10.06	-54.37
CNP0041068	-10.03	-50.81
CNP0006035	-10.02	-38.04
CNP0036194	-10.01	-54.32
CNP0076764	-9.93	-68.80
CNP0276471	-9.88	-48.39
CNP0006035	-9.75	-28.00

Compound code	Docking score	ΔG_{calc} (kcal/mol)
CNP0171333	-11.48	-31.87
CNP0011148	-11.32	-40.18
CNP0011011	-10.74	-26.62
CNP0048386	-10.68	-65.39
CNP0390700	-10.67	-50.92
CNP0138306	-10.65	-24.80
CNP0027093	-10.58	-40.16
CNP0011430	-10.53	-31.44
CNP0012015	-10.52	-39.27
CNP0033907	-10.45	-64.96
CNP0132005	-10.40	-47.98
CNP0132719	-10.39	-60.33
CNP0362710	-10.36	-52.46
CNP0011149	-10.31	-40.75
CNP0011400	-10.26	-34.41
CNP0097644	-10.16	-50.20
CNP0010948	-10.15	-39.89
CNP0177683	-10.09	-64.32
CNP0069877	-10.07	-53.29
CNP0410951	-10.03	-57.13
CNP0064258	-10.02	-52.48

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CNP0005627	-9.37	-44.27
CNP0161586	-9.06	-27.92
CNP0383938	-9.92	-33.67
CNP0014631	-9.66	-36.64
CNP0152032	-9.36	-33.71
CNP0102334	-9.23	-35.23
CNP0011394	-10.95	-38.52
CNP0010973	-10.46	-35.23
CNP0055793	-10.28	-54.28
CNP0273747	-10.02	-51.73
CNP0198475	-10.82	-42.00
CNP0335080	-10.54	-26.84
CNP0253363	-10.32	-45.31
CNP0025086	-10.20	-53.40
CNP0105843	-10.14	-47.35
CNP0166084	-10.10	-48.05
CNP0251686	-10.72	-47.44
CNP0224199	-10.43	-41.07
CNP0107283	-10.23	-59.18
CNP0027531	-10.06	-32.99
CNP0045431	-10.79	-44.90
CNP0015235	-10.56	-40.91
CNP0194704	-10.22	-57.49
CNP0014757	-11.21	-33.95
CNP0185474	-10.34	-34.50
CNP0347649	-10.66	-34.80
CNP0241425	-10.24	-51.7

CNP0131150	-9.98	-59.59
CNP0066065	-9.97	-47.63
CNP0298946	-9.78	-33.14
CNP0321712	-9.50	-37.21
CNP0101828	-9.24	-37.41
CNP0027272	-11.10	-53.33
CNP0040948	-10.71	-48.17
CNP0006919	-10.42	-47.5
CNP0037934	-10.23	-63.09
CNP0050751	-9.28	-49.7
CNP0011260	-10.82	-34.15
CNP0335080	-10.45	-31.28
CNP0181003	-10.22	-46.50
CNP0117845	-10.18	-56.98
CNP0302585	-10.13	-41.74
CNP0163236	-10.08	-49.99
CNP0297577	-10.58	-57.24
CNP0014499	-10.37	-49.10
CNP0145371	-10.07	-52.95
CNP0117193	-11.49	-56.11
CNP0150175	-10.59	-44.23
CNP0036421	-10.30	-44.52
CNP0037585	-10.14	-50.78
CNP0014646	-11.08	-39.63
CNP0040730	-12.30	-41.97
CNP0048899	-10.31	-49.86

Table S2. Energy contributions of hot residues for the binding inhibitors in VEGFR-2.

	ΔE_{vdw} (kcal/mol)	ΔE_{ele} (kcal/mol)	ΔG_{pol} (kcal/mol)	ΔG_{nopol} (kcal/mol)	ΔG_{calc} (kcal/mol)
Leu840					
CNP0076764	-0.72	0.01	0.14	-0.14	-0.71
CNP0028810	-2.11	-0.27	0.63	-0.33	-2.08
CNP0177683	-2.03	-0.18	0.59	-0.33	-1.95
CNP0132719	-1.90	0.15	0.22	-0.33	-1.86
CNP0107283	-1.32	0.22	-0.10	-0.22	-1.42
sorafenib	-1.34	-0.09	0.29	-0.22	-1.36
Val848					
CNP0076764	-1.05	0.18	-0.14	-0.09	-1.09
CNP0028810	-1.32	-0.12	0.08	-0.13	-1.49
CNP0177683	-1.53	-0.19	0.10	-0.14	-1.76
CNP0132719	-1.27	0.15	-0.05	-0.13	-1.29
CNP0107283	-1.14	0.49	-0.53	-0.13	-1.30
sorafenib	-0.86	0.02	-0.07	-0.08	-0.99
Lys868					
CNP0076764	-1.59	-8.23	3.80	-0.18	-6.20
CNP0028810	-1.57	7.88	-4.88	-0.10	1.32
CNP0177683	-1.42	7.30	-4.97	-0.08	0.81
CNP0132719	-1.85	-0.72	1.98	-0.15	-0.73
CNP0107283	-0.85	34.59	-32.32	-0.09	1.34
sorafenib	-1.71	9.69	-7.09	-0.11	0.78
Glu885					
CNP0076764	-1.49	-1.75	4.42	-0.10	1.08
CNP0028810	0.88	-23.09	14.91	-0.15	-7.45
CNP0177683	0.23	-19.31	14.04	-0.14	-5.18
CNP0132719	-1.29	1.31	0.24	-0.11	0.15
CNP0107283	0.90	-58.53	51.39	-0.11	-6.35
sorafenib	-0.39	-20.08	16.65	-0.15	-3.97
Leu889					
CNP0076764	-1.75	0.03	0.06	-0.18	-1.83
CNP0028810	-1.55	0.36	-0.25	-0.14	-1.58
CNP0177683	-1.33	0.15	-0.05	-0.16	-1.39
CNP0132719	-1.48	-0.15	0.21	-0.18	-1.60
CNP0107283	-1.17	1.40	-1.21	-0.14	-1.12
sorafenib	-1.55	0.63	-0.49	-0.15	-1.56
Val899					
CNP0076764	-1.67	0.14	0.26	-0.10	-1.37
CNP0028810	-1.64	-0.26	0.44	-0.09	-1.55

CNP0177683	-1.41	-0.01	0.27	-0.08	-1.23
CNP0132719	-1.57	0.24	-0.03	-0.07	-1.43
CNP0107283	-1.83	-1.29	2.06	-0.12	-1.19
sorafenib	-1.28	-0.13	0.21	-0.07	-1.26
Val916					
CNP0076764	-1.38	-0.05	0.05	-0.14	-1.52
CNP0028810	-1.28	-0.22	0.18	-0.15	-1.47
CNP0177683	-1.38	0.17	-0.10	-0.14	-1.45
CNP0132719	-1.08	-0.03	0.12	-0.14	-1.13
CNP0107283	-0.80	1.36	-1.16	-0.11	-0.71
sorafenib	-1.20	0.07	-0.03	-0.16	-1.32
Leu1035					
CNP0076764	-1.28	0.01	0.08	-0.15	-1.33
CNP0028810	-1.86	-0.11	0.24	-0.15	-1.89
CNP0177683	-1.65	-0.24	0.22	-0.15	-1.82
CNP0132719	-1.81	0.08	-0.01	-0.15	-1.88
CNP0107283	-1.49	-0.04	0.18	-0.17	-1.53
sorafenib	-1.31	-0.16	0.23	-0.12	-1.37
Cys1045					
CNP0076764	-2.25	0.01	0.87	-0.14	-1.51
CNP0028810	-2.05	-1.68	1.20	-0.09	-2.63
CNP0177683	-1.76	-2.43	1.19	-0.10	-3.10
CNP0132719	-2.41	-0.07	1.26	-0.11	-1.33
CNP0107283	-2.45	3.14	-2.09	-0.19	-1.59
sorafenib	-1.84	-1.74	0.80	-0.11	-2.88
Asp1046					
CNP0076764	-3.03	-2.05	4.64	-0.28	-0.71
CNP0028810	2.56	-2.71	3.38	-0.27	-2.15
CNP0177683	-2.60	-2.26	3.03	-0.25	-2.08
CNP0132719	-2.72	1.05	0.41	-0.22	-1.49
CNP0107283	-0.52	-58.58	53.31	-0.27	-6.06
sorafenib	-2.35	-4.54	4.47	-0.24	-2.65
Phe1047					
CNP0076764	-2.21	-0.25	0.49	-0.11	-2.07
CNP0028810	-2.43	-0.59	1.23	-0.15	-1.94
CNP0177683	-2.31	0.10	1.01	-0.15	-1.35
CNP0132719	-2.91	-0.48	0.47	-0.17	-3.08
CNP0107283	-2.01	-0.35	0.74	-0.15	-1.76
sorafenib	-2.07	-0.80	1.22	-0.18	-1.84

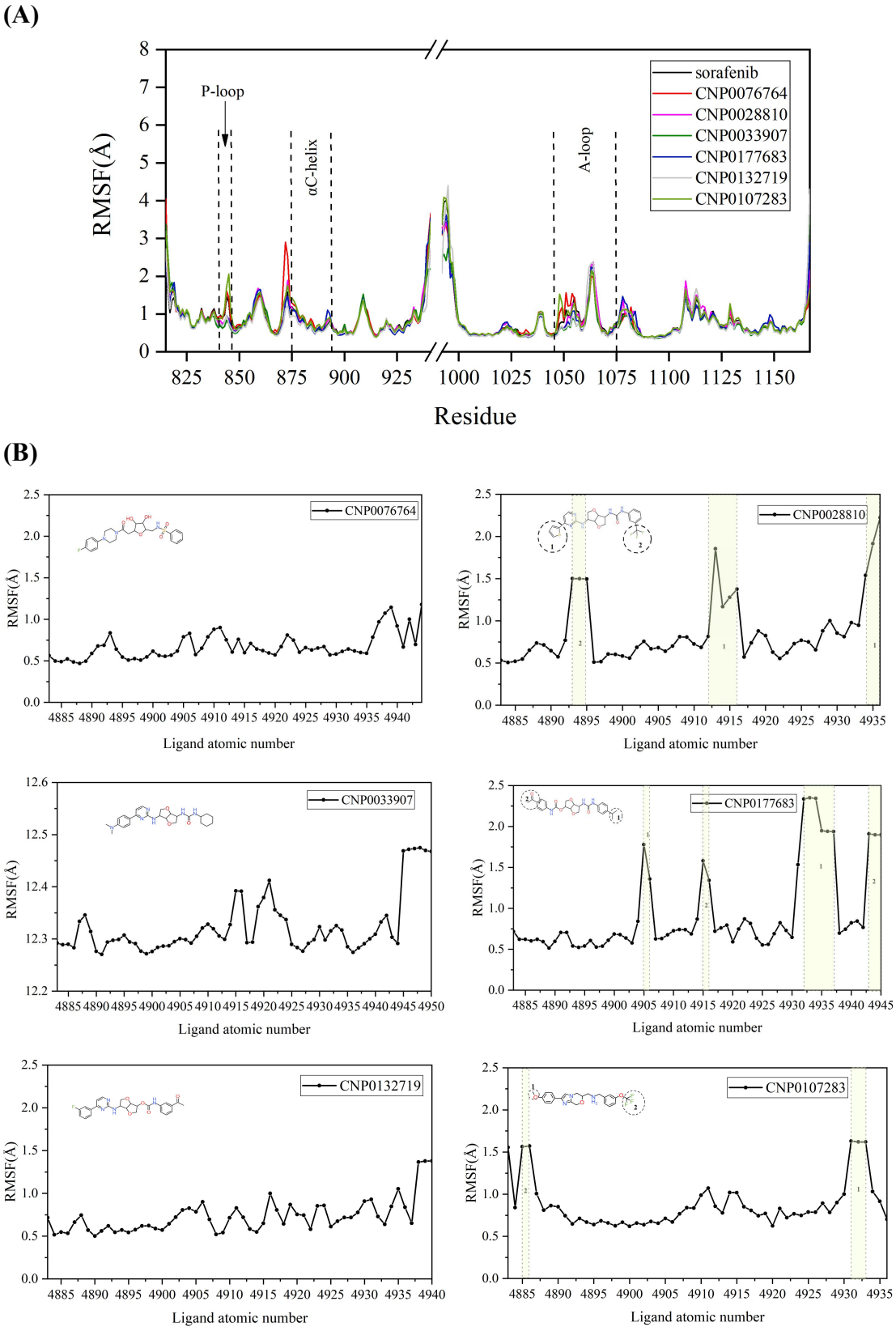


Figure S1. (A) The RMSF of protein Cα atoms for the seven ligand-docking complexes; (B) The RMSF of the individual atoms of the inhibitors

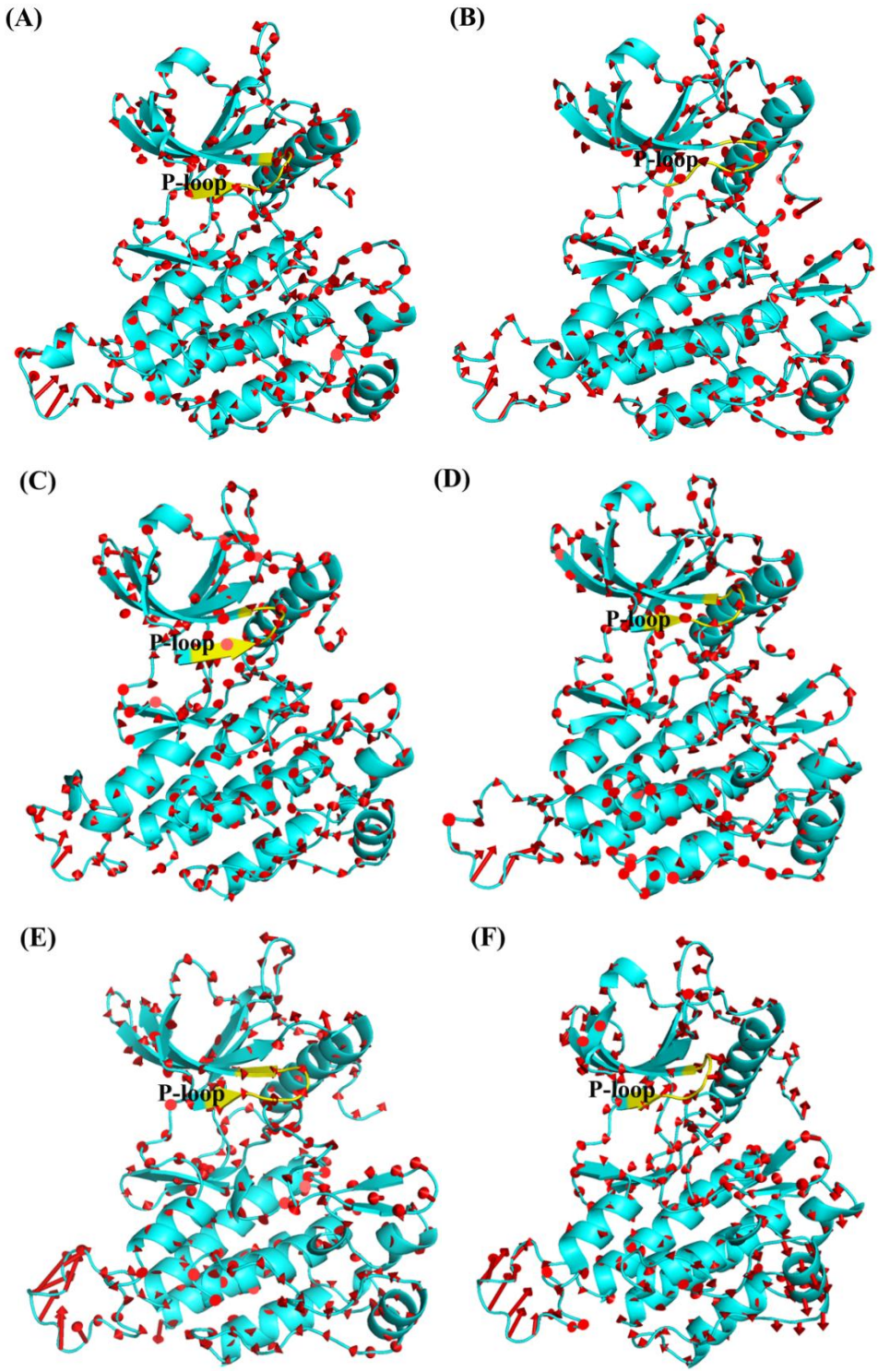
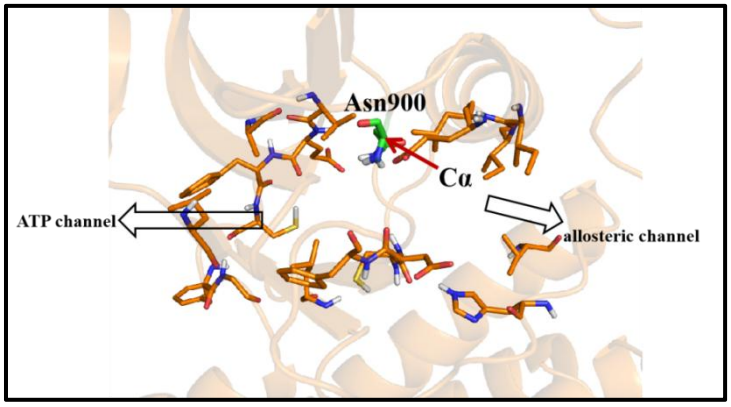


Figure S2. The first eigenvector porcupine plot for (A) sorafenib/VEGFR-2, (B) CNP0076764/VEGFR-2, (C) CNP0028810/VEGFR-2, (D) CNP0177683/VEGFR-2, (E) CNP0132719/VEGFR-2 and (F) CNP0107283/VEGFR-2. The P-loop includes Gly841, Arg842, Gly843, Ala844, Phe845 and Gly846, as depicted as yellow. The length of the arrow denotes the extent of movement of the corresponding part.

(A)



(B)

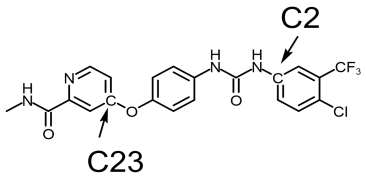
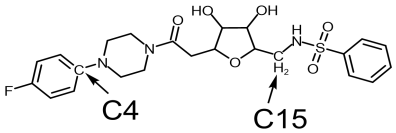
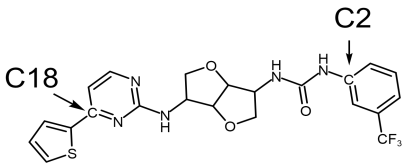
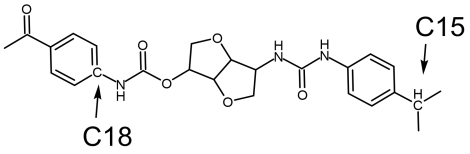
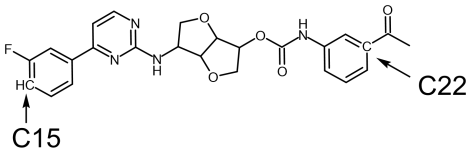
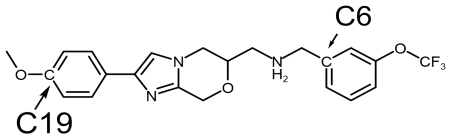
Name	Inhibitor Structure	ATP channel	Allosteric channel
sorafenib		Asn900@Cα →C23	Asn900@Cα →C2
CNP0076764		Asn900@Cα →C4	Asn900@Cα →C15
CNP0028810		Asn900@Cα →C18	Asn900@Cα →C2
CNP0177683		Asn900@Cα →C18	Asn900@Cα →C15
CNP0132719		Asn900@Cα →C15	Asn900@Cα →C22
CNP0107283		Asn900@Cα →C19	Asn900@Cα →C6

Figure S3. (A) Overview of the binding site of VEGFR-2; (B) The direction of inhibitors dissociated from the binding site.

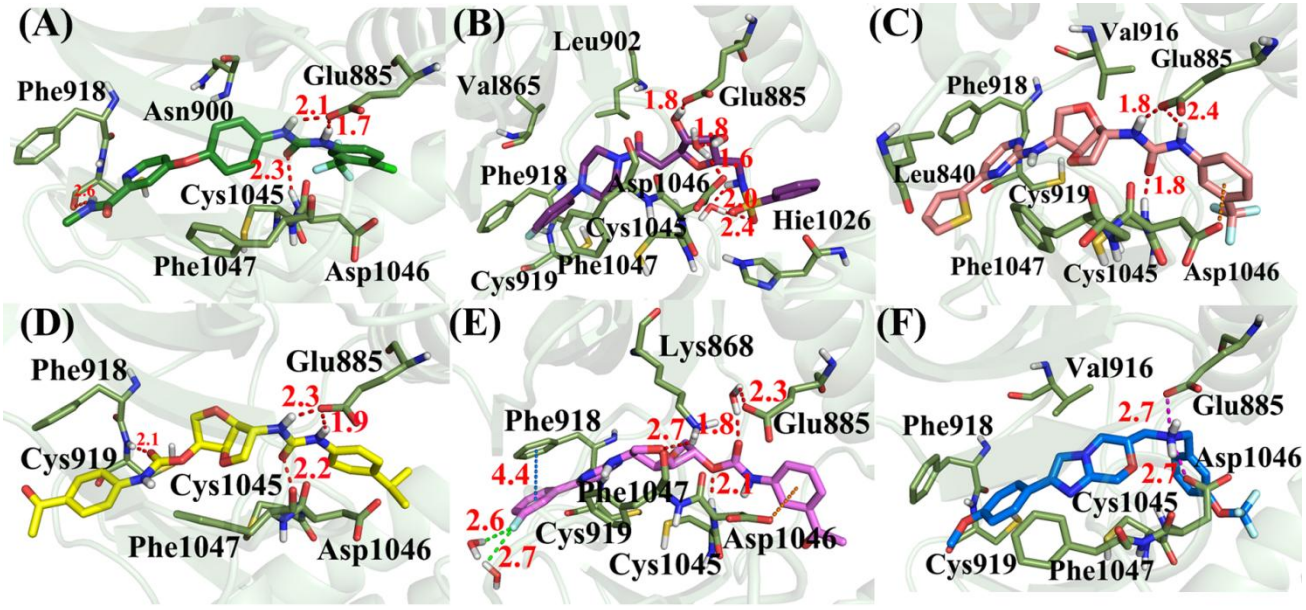


Figure S4. Representative structures of inhibitors binding to the VEGFR-2 from QM/MM MD trajectories. A-F are the binding conformations of sorafenib, CNP0076764, CNP0028810, CNP0177683, CNP0132719 and CNP0107283, respectively. The hydrogen bond interactions are depicted as red dotted lines. The salt bridges are depicted as magenta dotted lines. The π-π interactions are depicted as blue dotted lines, and the anion-π interaction are depicted as orange dotted lines.

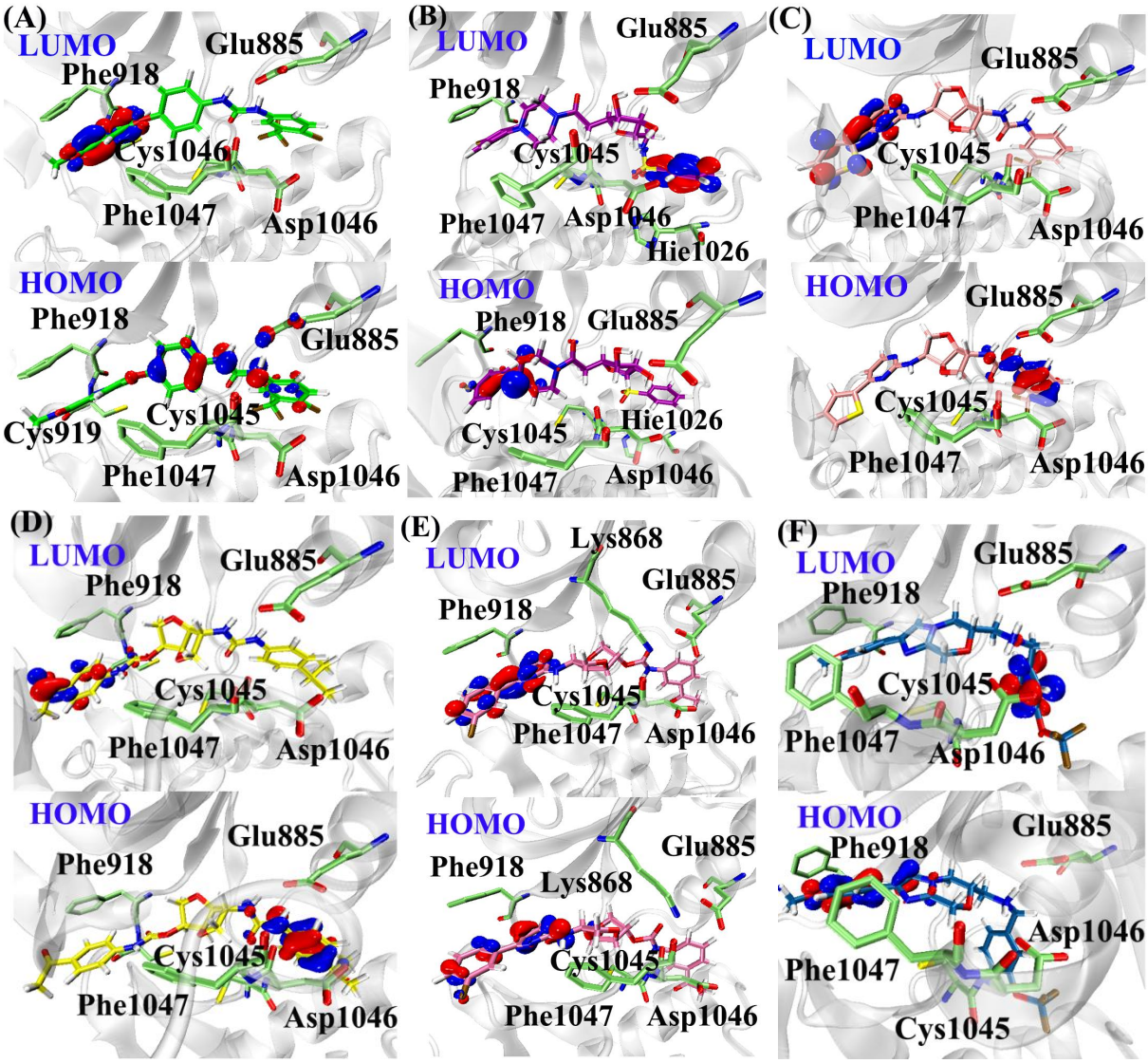


Figure S5. HOMO and LUMO contours imposed on VEGFR-2 ligands. A-F are sorafenib, CNP0076764, CNP0028810, CNP0177683, CNP0132719 and CNP0107283 binding to VEGFR-2, respectively.

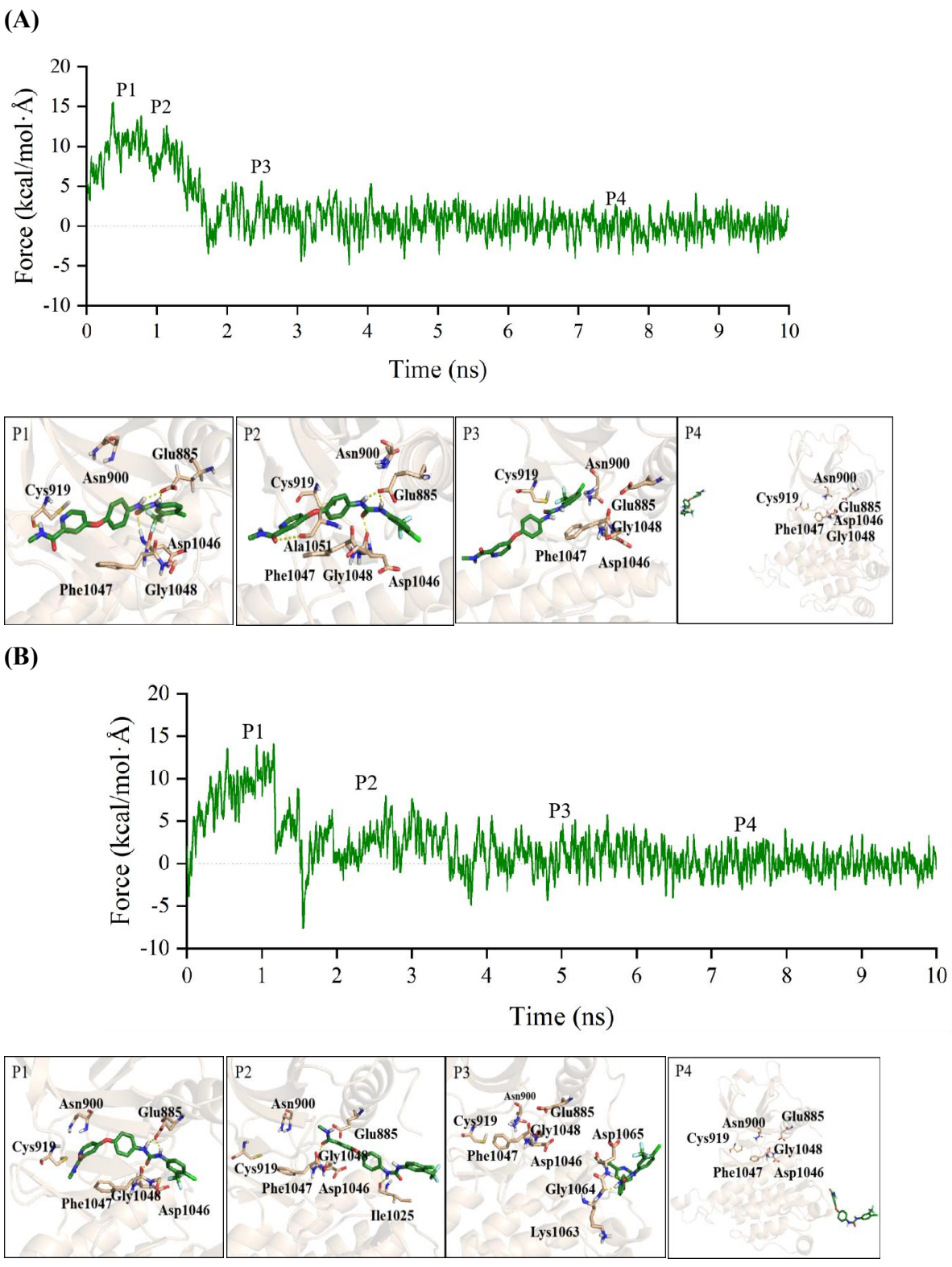
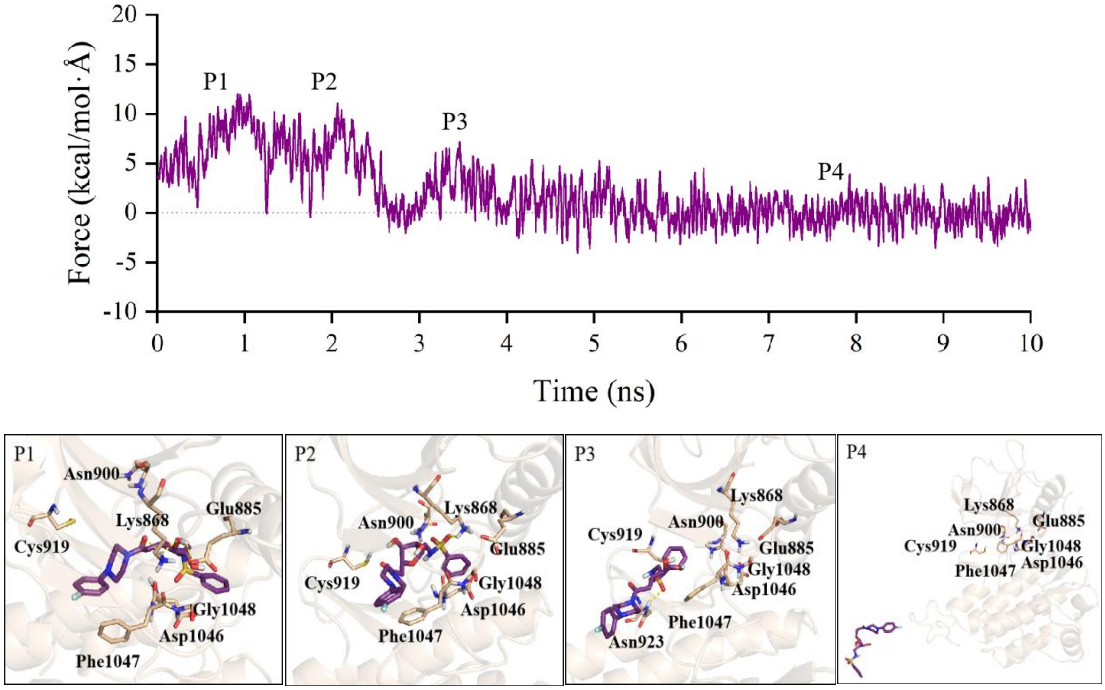


Figure S6. Force vs time of sorafenib dissociated from the binding site of VEGFR-2 and extracted snapshots for the relative positions of sorafenib and VEGFR-2 (A) along ATP channel and (B) along allosteric channel.

(A)



(B)

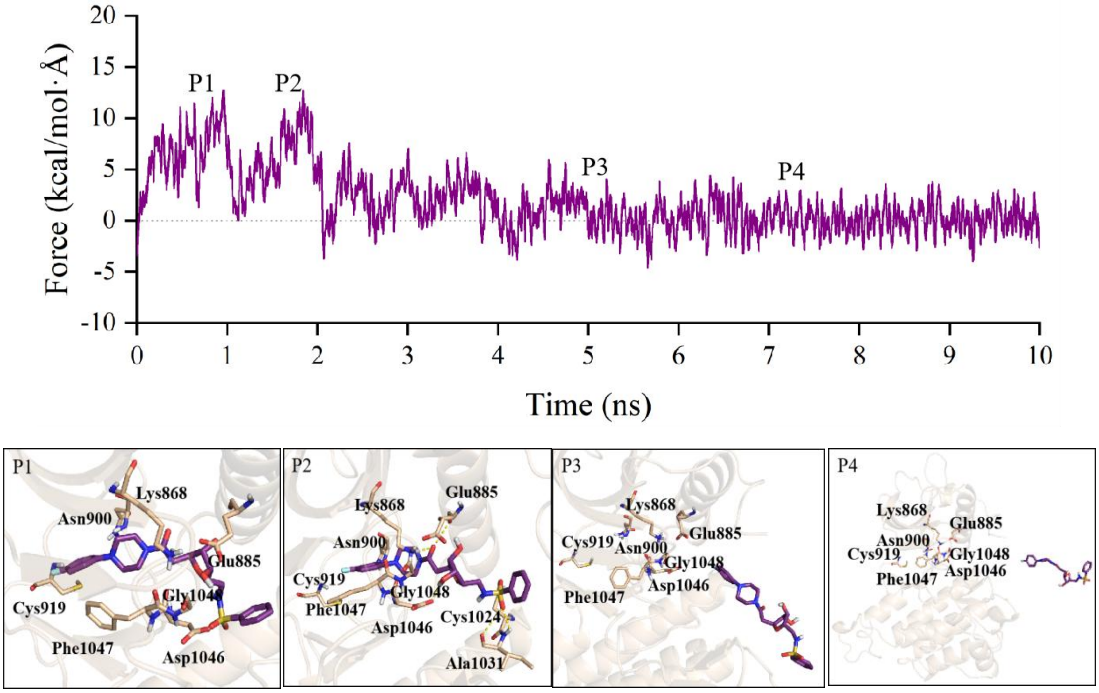
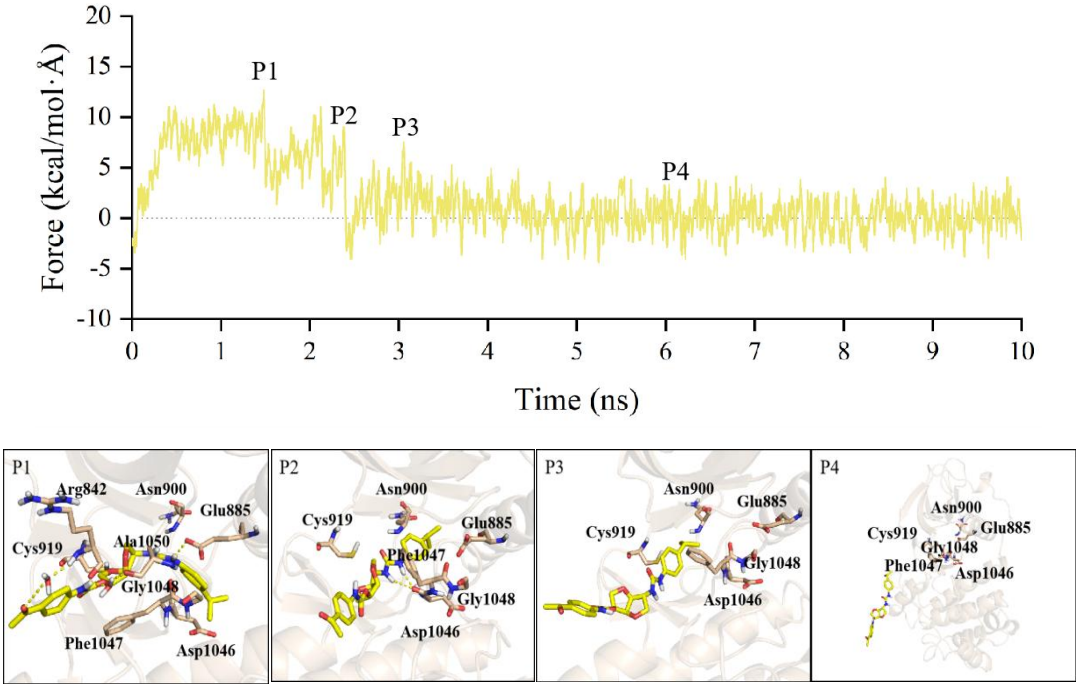


Figure S7. Force vs time of CNP0076764 dissociated from the binding site of VEGFR-2 and extracted snapshots for the relative positions of CNP0076764 and VEGFR-2 (A) along ATP channel and (B) along allosteric channel.

(A)



(B)

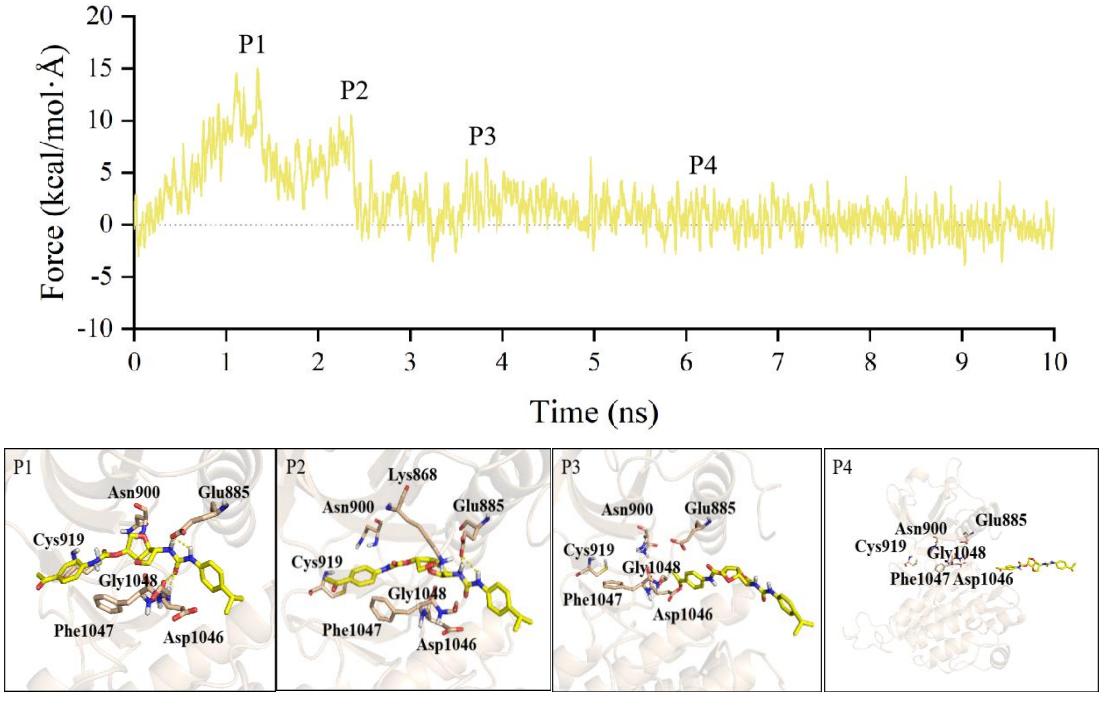
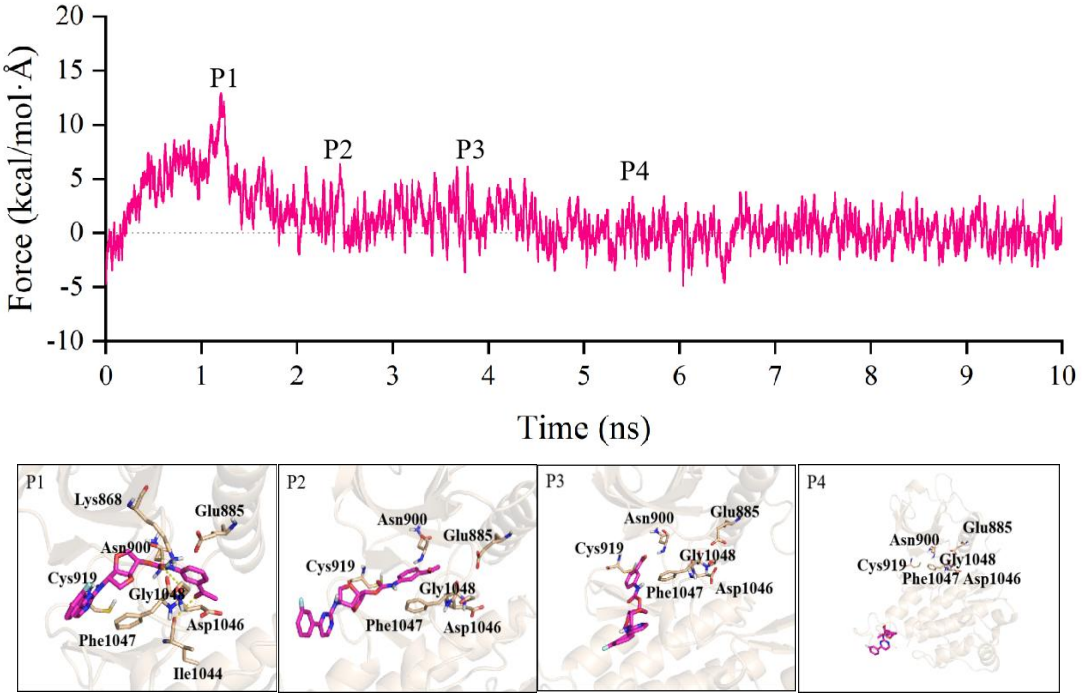


Figure S8. Force vs time of CNP0177683 dissociated from the binding site of VEGFR-2 and extracted snapshots for the relative positions of CNP0177683 and VEGFR-2 (A) along ATP channel and (B) along allosteric channel.

(A)



(B)

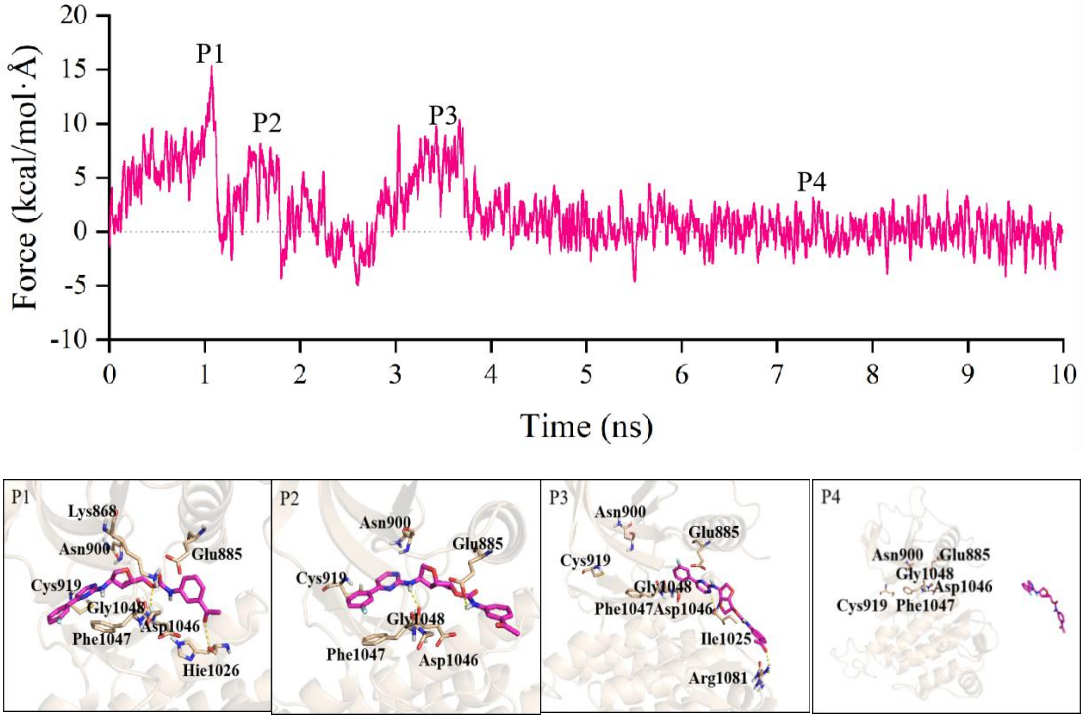
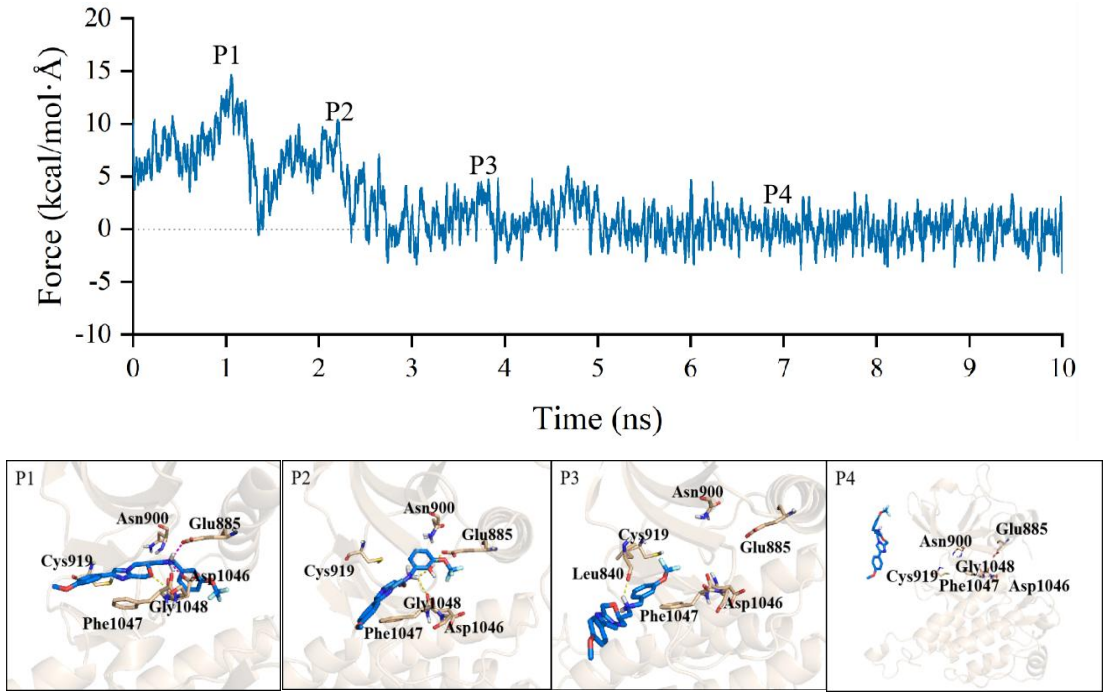


Figure S9. Force vs time of CNP0132719 dissociated from the binding site of VEGFR-2 and extracted snapshots for the relative positions of CNP0132719 and VEGFR-2 (A) along ATP channel and (B) along allosteric channel.

(A)



(B)

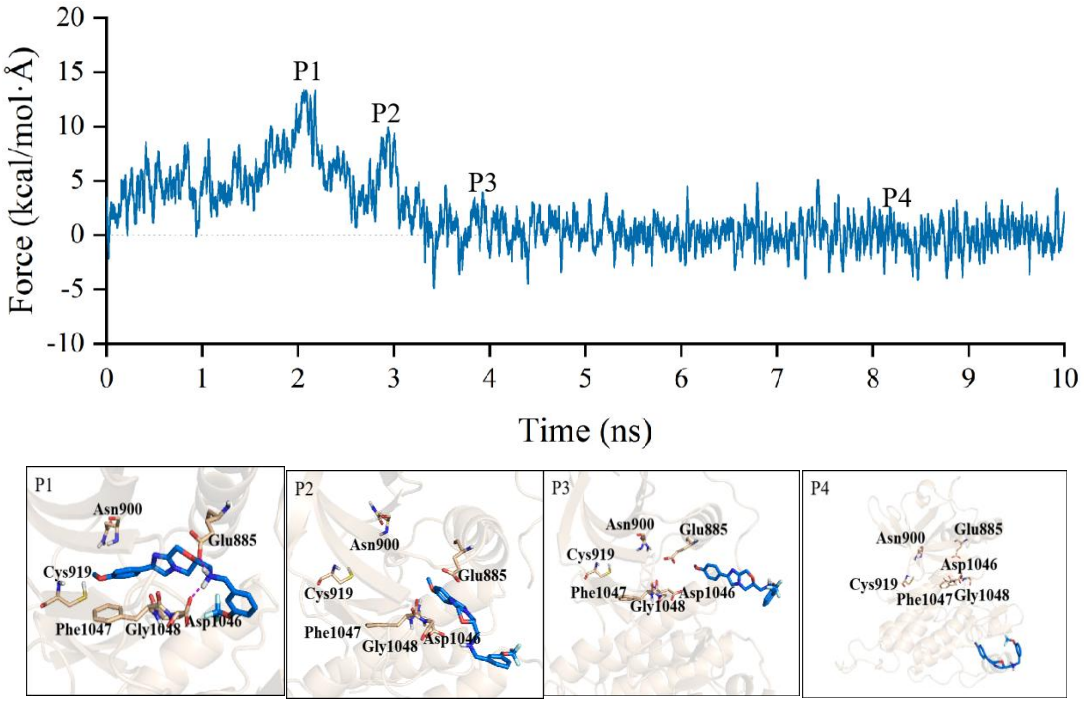


Figure S10. Force vs time of CNP0107283 dissociated from the binding site of VEGFR-2 and extracted snapshots for the relative positions of CNP0107283 and VEGFR-2 (A) along ATP channel and (B) along allosteric channel.