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Supporting Information

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for

Structural Insights into the Flavones as Protein Kinase CK2 Inhibitors Derived from a Combined Computational Study

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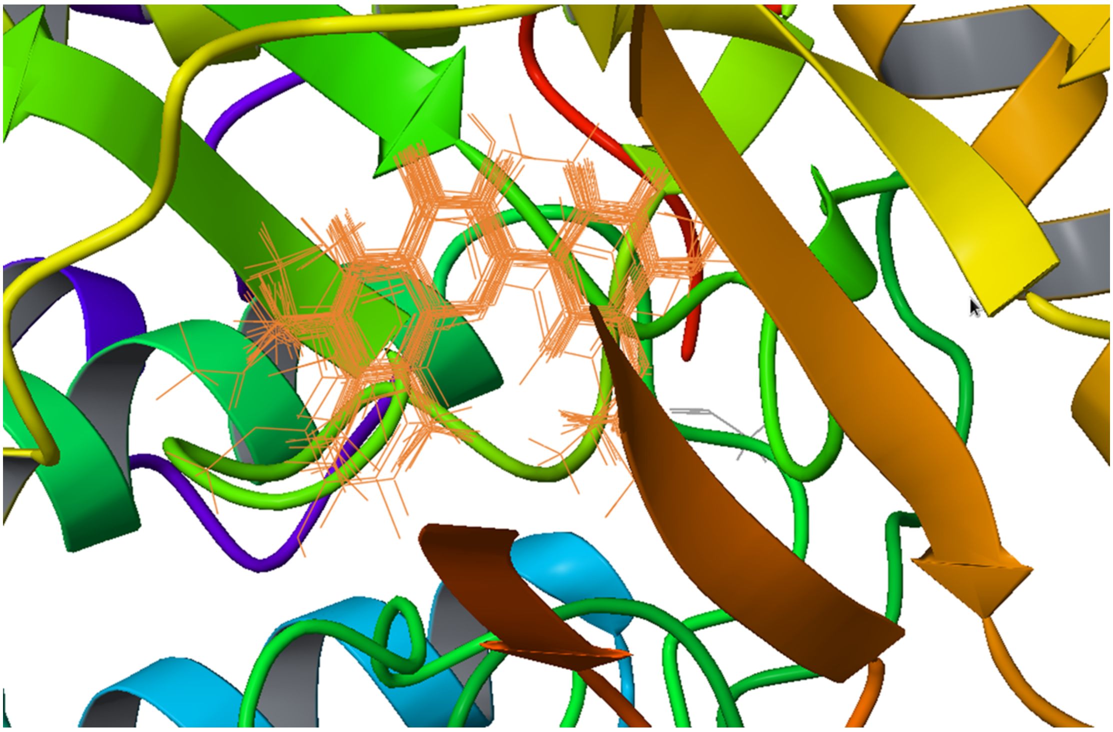


Fig. S1 The alignments of 51 docked structures in the binding site of protein kinase CK2 (the inhibitors are represented as lines and the protein is represented as ribbons).

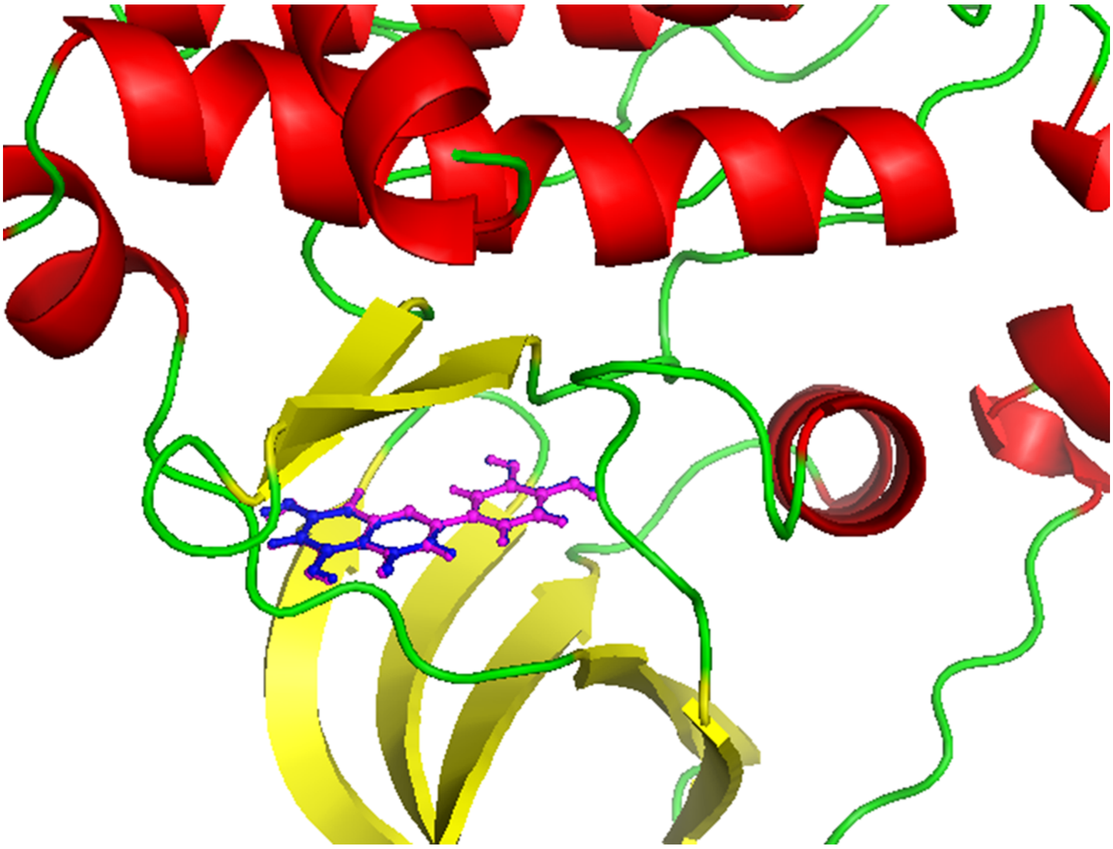
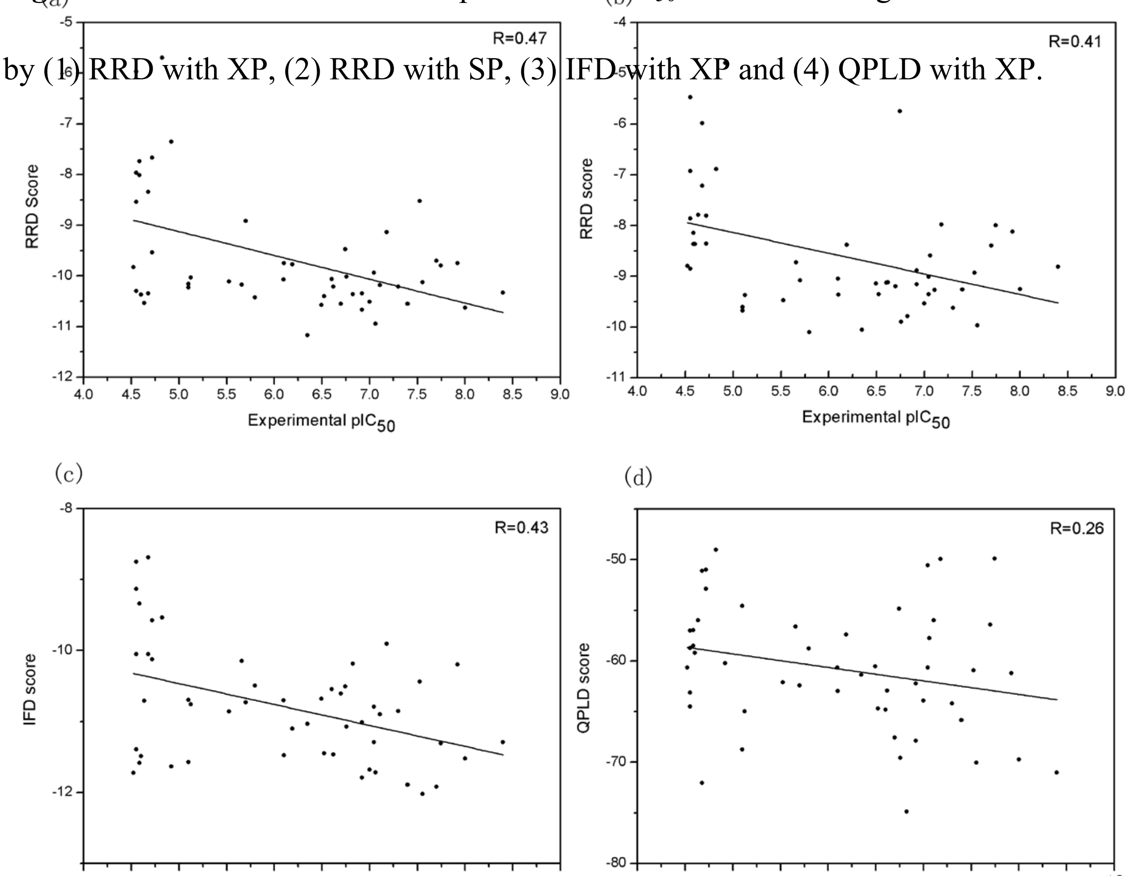


Fig. S2 The superposition of the Glide XP redocked **luteolin** and its original structure in the crystallographic complex. Carbon atoms in the crystal structure and the redocked conformation are colored in blue and magenta, respectively.

Fig. S3 The correlation between experimental PIC$_{50}$ and the docking scores Predicted by (1) RRD with XP, (2) RRD with SP, (3) IFD with XP and (4) QPLD with XP.



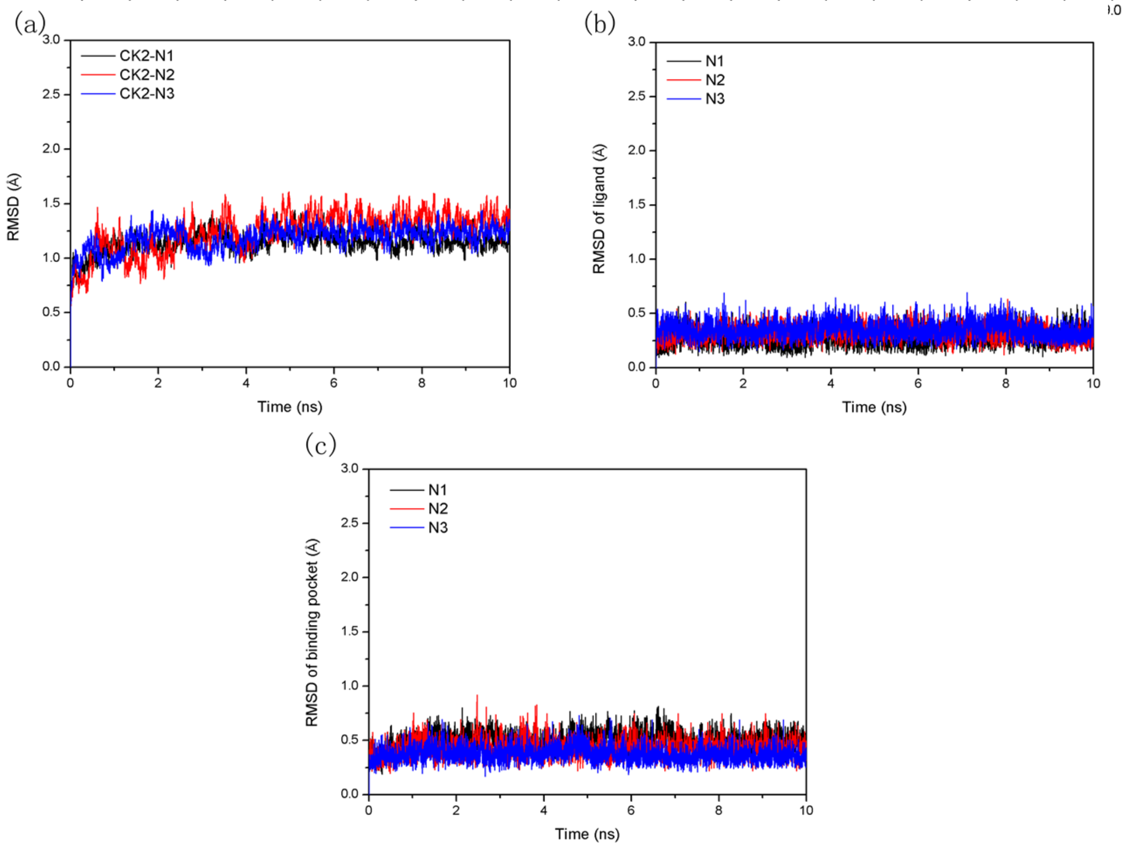
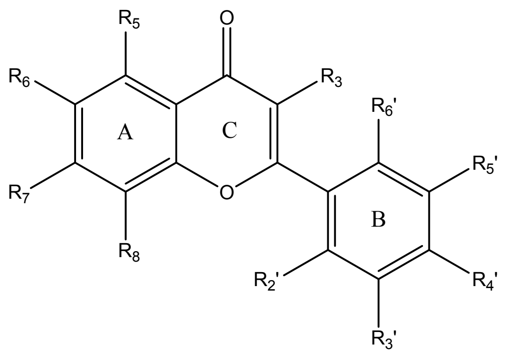


Fig. S4 Plots of the RMSD values relative to the initial structure of the new complexes including CK2-**N1**, CK2-**N2**, and CK2-**N3** during the MD simulations. (a) Time evolution of the RMSD of all protein backbone atoms. (b) Time evolution of the RMSD of heavy atoms for the ligand. (c) Time evolution of the RMSD of the Cα atoms for the residues around 5 Å of the ligand.

Table S1 The structures and corresponding bioactivities of 51 inhibitors



ID	R_2'	R_3'	R_4'	R_5'	R_6'	R_3	R_5	R_6	R_7	R_8	IC_{50}(μM)	PIC_{50}
FNH3	H	H	OMe	H	H	H	H	OH	H	H	30	4.52
FNH12	H	OMe	OH	H	H	H	H	H	H	H	0.8	6.10
FNH13	H	OEt	OH	H	H	H	H	H	H	H	7.5	5.12
FNH16	H	OEt	OH	H	H	H	H	Me	H	H	8	5.10

FNH17	H	H	Cl	H	H	OH	H	Me	H	H	23	4.64
FNH20	H	H	*i*-Pr	H	H	OH	H	Me	H	H	26	4.59
FNH21	OH	H	H	Br	H	OH	H	Me	H	H	28	4.55
FNH22	H	H	OMe	H	H	OH	H	Me	H	H	28	4.55
FNH23	H	OMe	H	H	H	OH	H	Me	H	H	25	4.60
FNH27	H	H	Me	H	H	H	H	Me	H	Me	21	4.68
FNH28	H	OMe	OH	H	H	H	H	Me	H	Me	0.1	7.00
FNH30	H	Br	H	H	H	H	H	OH	H	H	19	4.72
FNH31	H	OMe	OMe	OMe	H	H	H	OH	H	H	26	4.59
FNH36	H	H	Me	H	H	H	H	OH	H	H	19	4.72
FNH39	H	H	Me	H	H	OCH_2CO_2H	H	Me	H	Me	28	4.55
FNH40	H	H	OMe	H	H	OSO_2Me	H	Me	H	Me	28	4.55
FNH41	H	H	OMe	H	H	OCO(1,4-Benzodioxane-2-yl)	Me	H	Me	H	21	4.68
FNH48	H	H	OMe	H	H	H	CH_2N(2-furfuryl)CH_2O		H	H	12	4.92
FNH49	H	H	OMe	H	H	H	CH2N(3-trifluoromethylphenyl)CH2O		H	H	15	4.82

FNH52	H	OH	H	H	H	H	H	Me	H	Me	2.2	5.66
FNH53	H	H	OH	H	H	H	H	Me	H	Me	1.6	5.80
FNH54	H	H	OH	H	H	H	H	Me	H	H	8	5.10
FNH55	H	OH	OH	H	H	H	H	Me	H	Me	0.45	6.35
FNH56	H	OMe	OH	H	H	H	H	OH	H	H	0.25	6.60
FNH57	H	OMe	OH	H	H	H	H	Me	H	H	0.32	6.49
FNH58	H	OMe	OH	H	H	H	H	OMe	H	H	0.2	6.70
FNH59	H	OMe	OH	H	H	H	H	Cl	H	H	0.24	6.62
FNH60	H	OMe	OH	H	H	H	H	Et	H	H	0.12	6.92
FNH61	H	OMe	OH	H	H	H	H	NAc	H	H	0.15	6.82
FNH62	H	OMe	OH	H	H	H	H	Br	H	H	0.12	6.92
FNH63	H	OMe	OH	H	H	H	H	H	Me	H	0.09	7.05
FNH64	H	OMe	OH	Cl	H	H	H	Me	H	Me	0.09	7.05
FNH65	H	OMe	OH	Br	H	H	H	Me	H	Me	0.65	6.19
FNH66	H	OMe	OH	H	H	H	H	Cl	Me	H	0.79	6.10
FNH67	H	OMe	OH	H	H	H	H	Me	Me	H	3	5.52
FNH68	H	OMe	OH	H	H	H	H	Cl	H	Cl	0.01	8.00
FNH69	H	OMe	OH	Cl	H	H	H	Cl	H	Cl	0.02	7.70
FNH70	H	NO2	OH	H	H	H	H	Me	H	Me	0.012	7.92
FNH71	H	OMe	OH	H	H	H	Me	H	Me	H	0.03	7.52
FNH72	H	OMe	OH	NO2	H	H	H	Me	H	Me	0.066	7.18
FNH73	H	Cl	OH	Cl	H	H	H	Me	H	Me	0.078	7.11

FNH74	H	Br	OH	H	H	H	H	Me	H	Me	0.05	7.30
FNH75	H	Br	OH	Br	H	H	H	Me	H	Me	0.18	6.74
FNH76	H	OMe	OH	H	H	H	H	Cl	H	Me	0.04	7.40
FNH77	H	OMe	OH	H	H	H	H	H	C_4H_4		0.028	7.55
FNH78	H	OMe	OH	Cl	H	H	H	Br	H	Br	0.018	7.74
FNH79	H	OMe	OH	H	H	H	H	Br	H	Br	0.004	8.40
FNH80	H	OMe	OH	Cl	H	H	H	H	C_4H_4		0.087	7.06
FNH81	H	OMe	OH	H	H	H	Me	Cl	Me	H	2	5.70
FNH82	H	OMe	OH	H	H	H	H	H	Me	Me	0.3	6.52
FNH83	H	OMe	OH	H	H	H	H	OMe	H	H	0.175	6.76

Table S2 Biological activities of the studied Ck2 inhibitors and corresponding docking scores predicted by four different docking protocols

No.	PIC_{50}	XP	SP	IFD	QPLD
FNH3	4.52	-9.826	-8.800	-11.726	-60.641
FNH12	6.10	-10.074	-9.047	-10.703	-60.652
FNH13	5.12	-10.031	-9.369	-10.757	-64.990
FNH16	5.10	-10.227	-9.607	-11.571	-68.751
FNH17	4.64	-10.534	-7.789	-10.706	-55.975
FNH20	4.59	-7.738	-8.148	-11.586	-58.486
FNH21	4.55	-8.542	-6.926	-8.750	-58.744

FNH22	4.55	-10.298	-8.854	-11.392	-64.514
FNH23	4.60	-10.374	-8.368	-11.488	-59.203
FNH27	4.68	-10.344	-7.214	-10.050	-51.086
FNH28	7.00	-10.516	-9.533	-11.678	-63.928
FNH30	4.72	-9.539	-7.806	-10.121	-50.987
FNH31	4.59	-8.012	-8.362	-9.337	-56.958
FNH36	4.72	-7.666	-8.359	-9.572	-52.861
FNH39	4.55	-7.968	-7.864	-9.128	-63.133
FNH40	4.55	-5.965	-5.473	-10.051	-56.984
FNH41	4.68	-8.342	-5.985	-8.687	-72.054
FNH48	4.92	-7.353	-4.797	-11.636	-60.230
FNH49	4.82	-5.692	-6.883	-9.536	-49.015
FNH52	5.66	-10.176	-8.725	-10.147	-56.592
FNH53	5.80	-10.429	-10.098	-10.496	-58.758
FNH54	5.10	-10.155	-9.676	-10.698	-54.570
FNH55	6.35	-11.173	-10.054	-11.033	-61.346
FNH56	6.60	-10.066	-9.126	-10.543	-64.837
FNH57	6.49	-10.573	-9.143	-10.678	-60.536
FNH58	6.70	-10.554	-9.200	-10.605	-67.577
FNH59	6.62	-10.213	-9.117	-11.464	-62.914
FNH60	6.92	-10.666	-9.161	-11.791	-67.866
FNH61	6.82	-10.365	-9.788	-10.184	-74.890

FNH62	6.92	-10.348	-8.884	-11.012	-62.234
FNH63	7.05	-9.937	-9.359	-10.792	-60.638
FNH64	7.05	-9.938	-9.013	-11.294	-50.543
FNH65	6.19	-9.775	-8.384	-11.100	-57.403
FNH66	6.10	-9.748	-9.365	-11.478	-62.964
FNH67	5.52	-10.111	-9.470	-10.862	-62.089
FNH68	8.00	-10.629	-9.254	-11.521	-69.715
FNH69	7.70	-9.703	-8.399	-11.919	-56.394
FNH70	7.92	-9.749	-8.123	-10.199	-61.217
FNH71	7.52	-8.527	-8.932	-10.436	-60.930
FNH72	7.18	-9.136	-7.977	-9.903	-49.937
FNH73	7.11	-10.184	-9.266	-10.899	-55.984
FNH74	7.30	-10.217	-9.626	-10.855	-64.185
FNH75	6.74	-9.477	-5.746	-10.505	-54.835
FNH76	7.40	-10.552	-9.263	-11.892	-65.856
FNH77	7.55	-10.125	-9.968	-12.019	-70.039
FNH78	7.74	-9.798	-7.995	-11.306	-49.883
FNH79	8.40	-10.331	-8.811	-11.291	-71.034
FNH80	7.06	-10.946	-8.594	-11.716	-57.751
FNH81	5.70	-8.920	-9.077	-10.731	-62.430
FNH82	6.52	-10.399	-9.352	-11.451	-64.702
FNH83	6.76	-10.015	-9.894	-11.073	-69.575