Supplementary Material

Theoretical Studies on the Selectivity Mechanisms of Glycogen Synthase Kinase 3β (GSK3β) with Pyrazine ATP-competitive inhibitors by 3D-QSAR, Molecular Docking, Molecular Dynamics Simulation and Free Energy Calculations

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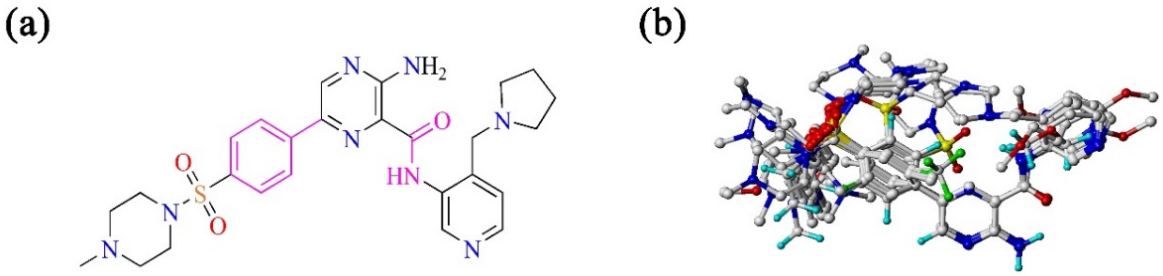

Fig. (S1). (a) the structure of the template molecule Cpd25; **(b)** a molecular overlay of all compounds based on a common backbone using Cpd25 as a template.

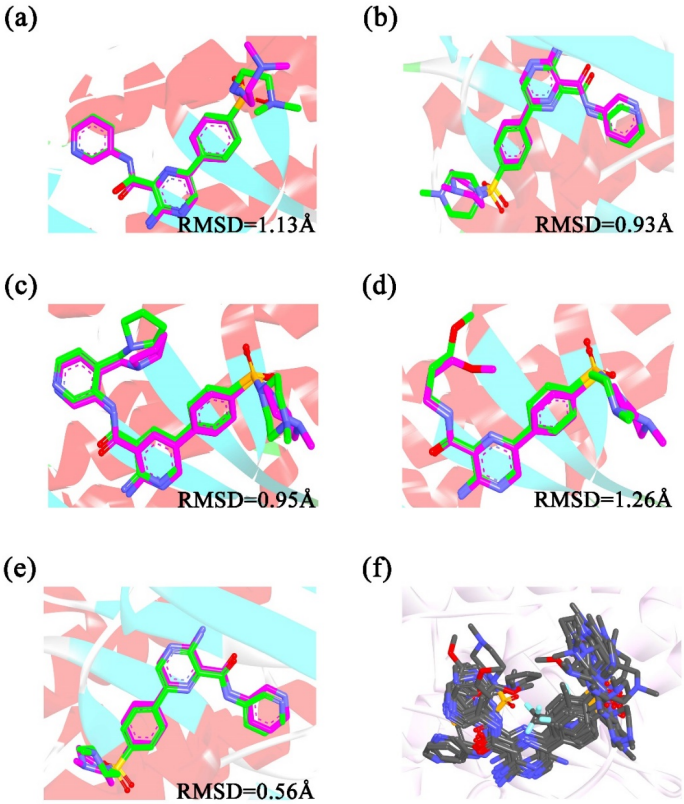

Fig. (S2). The overlap of the best docking results with the original ligands in the experimental crystal structure by CDOCKER **(a)** 4ACC/Cpd23; **(b)** 4ACD/Cpd18; **(c)** 4ACG/Cpd25; **(d)** 4ACH/Cpd51; the overlap of the best docking results with the original ligands in the experimental crystal structure by Flexible docking **(e)** 4ACD/Cpd18; **(f)** the Flexible docking conformational overlay of 31 compounds.

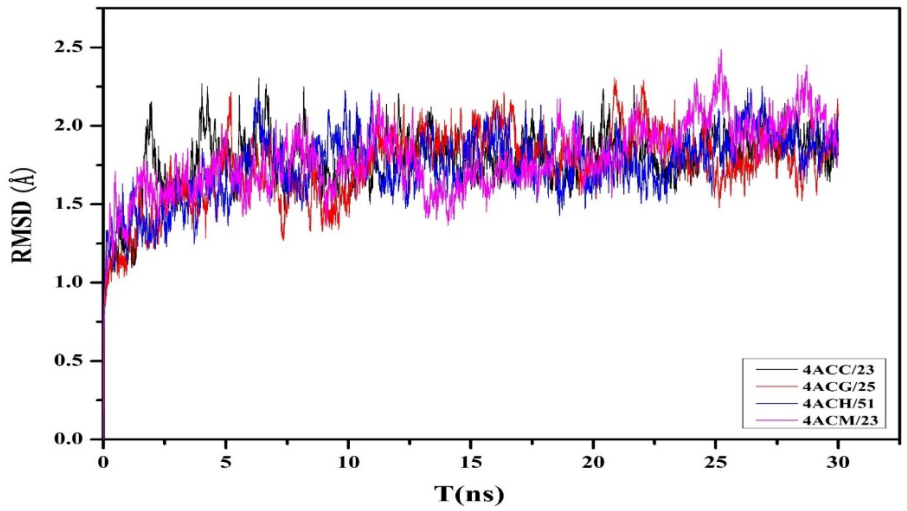

Fig. (S3). The root-mean-square deviations (RMSDs) of the four studied complexes.

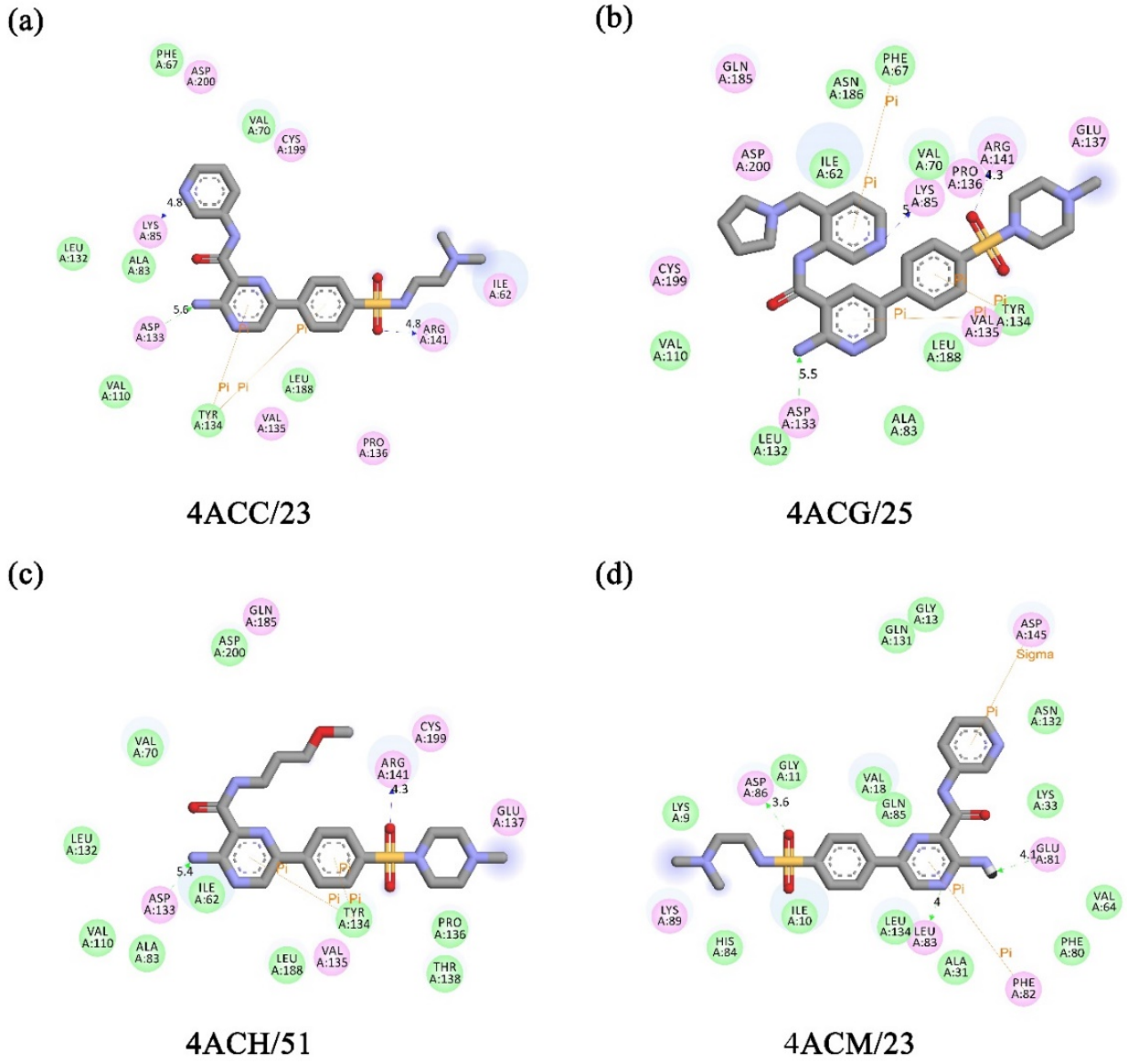

Fig. (S4). 2D presentations of the interactions between GSK3β and **(a)** Cpd23; **(b)** Cpd25; **(c)** Cpd51; **(d)** 2D presentations of the interactions between CDK2 and Cpd23.

Table S1. The predicted activities by CoMFA(1) model and the biological activity of the compounds

No.	Actual pIC_{50}	Pred pIC_{50}	Res
5	7.387	7.457	0.007
8	7.131	7.020	0.111
9	6.523	6.482	0.041
10	9.114	9.151	-0.037
11	9.337	9.324	0.013
12	8.959	8.907	0.052
13	8.824	8.801	0.023
14	8.046	8.334	-0.288
15	8.201	8.203	-0.002
16	8.699	8.651	0.048
*17	7.745	7.729	0.016
*18	8.31	8.465	-0.155
*19	8.357	9.051	-0.694
20	9.398	9.078	0.320
21	7.921	7.967	-0.046
22	9.174	9.456	-0.282
*23	7.699	8.021	0.023
*24	8.076	8.546	0.102
25	9.658	9.539	0.119
26	9.319	9.238	0.081
27	6.921	7.140	-0.219
28	7.194	7.225	-0.031
37	8.509	8.617	-0.108
38	7.796	7.784	0.012
41	6.991	6.782	-0.350
44	7.921	7.899	0.022
45	6.161	6.002	0.159
46	9.004	8.903	0.101
49	7.131	6.799	0.332
*50	7.046	6.300	0.746
*51	7.658	6.311	1.347

Table S2. Structural alignment based on molecular docking statistical results of the CoMFA models.

CoMFA(1)		CoMFA(2)	CoMFA(3)	CoMFA(4)	CoMFA(5)
q^2	0.561	0.433	0.538	0.541	0.556
r^2	0.994	0.997	0.993	0.996	0.997
SEE	0.093	0.067	0.095	0.075	0.061
F	587.493	1146.750	708.881	1136.749	1749.453
Components	5	5	4	4	4
Steric	1			0.271	
Electrostatic	0			0	
Steric (indicator)			1		0.347
Electrostatic (indicator)			0		0
H-bond acceptor		0.671		0.471	0.406
H-bond donor		0.329		0.258	0.247
r_{test}^2	0.188	0.006	0.130	0.007	0.008