

Supplementary materials for Potential Inhibitors of EGFR tyrosine kinase from *Scutellaria baicalensis*: A Chemoinformatics and Molecular Docking Studies

Table S1. High throughput virtual screening of the constituents of *S. baicalensis* against EGFR

Compound	Docking score
5322059	-8.478
5321865	-8.439
15896301	-8.405
21122623	-8.393
5281608	-8.343
141059302	-8.15
3084995	-8.075
64982	-8.028
21722007	-7.991
5280343	-7.87
86311089	-7.771
124211	-7.767
124211	-7.767
124211	-7.767
124211	-7.767
185617	-7.732
5281612	-7.726
5321864	-7.711
71307292	-7.543
5281611	-7.519
124708188	-7.476
5487756	-7.46
159029	-7.348
5320313	-7.33
14655551	-7.27
13889369	-7.124
9818878	-7.121
14655552	-7.11
102445445	-7.104
5322064	-7.07
13889022	-7.066
13889022	-7.066
5271991	-7.057
5271991	-7.057
5271991	-7.057
69717682	-7.001

5321865	-6.998
3082330	-6.948
5281665	-6.919
5281665	-6.919
5280443	-6.903
5315720	-6.887
42608117	-6.887
11609345	-6.859
161271	-6.84
161271	-6.84
141059302	-6.821
44567248	-6.812
44567248	-6.812
5271991	-6.811
5271991	-6.811
5271991	-6.811
9879022	-6.805
440735	-6.802
5281607	-6.774
157633	-6.762
44259518	-6.732
10872445	-6.704
5281616	-6.655
46893290	-6.548
5322076	-6.542
5281703	-6.531
5281703	-6.531
5353588	-6.528
5281618	-6.518
5281605	-6.507
21718608	-6.504
157671	-6.442
157671	-6.442
42607849	-6.442
12004622	-6.416
5321205	-6.412
15223582	-6.386
5281674	-6.378
5281674	-6.378
5281674	-6.378
689043	-6.346
689043	-6.346
3807559	-6.342
12912214	-6.339

54231395	-6.32
5320315	-6.304
5320315	-6.304
5320315	-6.304
5316733	-6.276
177032	-6.276
5316733	-6.276
5320399	-6.229
5320399	-6.229
7476	-6.166
5280343	-6.105
9818878	-6.1
5321864	-6.093
102445447	-6.034
5281612	-6.032
156992	-6.03
28516	-6.02
28516	-6.02
896	-5.993
896	-5.993
156993	-5.986
3084995	-5.967
5487756	-5.929
44259518	-5.928
5322064	-5.902
61361	-5.863
61361	-5.863
13889369	-5.853
443024	-5.848
5319292	-5.835
440735	-5.814
5322060	-5.782
21718608	-5.778
141059302	-5.765
5281611	-5.747
5322078	-5.706
9895632	-5.682
5322075	-5.65
160710	-5.629
160710	-5.629
35755714	-5.617
3084961	-5.617
3084961	-5.617
86311089	-5.611

159278	-5.563
159278	-5.563
159278	-5.563
5281611	-5.561
5352899	-5.535
91895373	-5.509
1203	-5.504
5322076	-5.501
2879	-5.378
5281607	-5.352
44719547	-5.341
6994	-5.324
998	-5.324
998	-5.324
5321865	-5.322
5319022	-5.305
5319022	-5.305
21722008	-5.301
335	-5.286
3308708	-5.277
11609345	-5.251
5321205	-5.246
71307292	-5.243
7338	-5.181
853433	-5.181
853433	-5.181
996	-5.168
996	-5.168
460	-5.124
460	-5.124
5281616	-5.086
5988	-5.083
31244	-5.06
3083857	-5.017
44258718	-5.009
798	-5.009
62368	-5.007
11092	-5.005
11092	-5.005
15511339	-4.994
1183	-4.985
1183	-4.985
5281607	-4.972
5281665	-4.934

5281665	-4.934
11092	-4.93
11092	-4.93
13854	-4.919
10248	-4.912
10248	-4.912
5281800	-4.903
5281800	-4.903
867	-4.898
8369	-4.889
8369	-4.889
14135325	-4.887
14135325	-4.887
5281616	-4.881
5322060	-4.871
5321864	-4.871
6140	-4.852
157671	-4.825
157671	-4.825
42607849	-4.825
3085257	-4.82
3085257	-4.82
157633	-4.818
332	-4.812
91457	-4.81
5281618	-4.791
5322064	-4.759
442027	-4.726
442027	-4.726
21668724	-4.678
5280443	-4.678
1713001	-4.624
5322076	-4.614
5322078	-4.604
440735	-4.592
5281605	-4.581
5281674	-4.56
5281674	-4.56
5281674	-4.56
5487756	-4.526
5320315	-4.493
5320315	-4.493
5320315	-4.493
21722008	-4.492

5281697	-4.454
5281697	-4.454
11230	-4.449
102445445	-4.431
10394343	-4.431
10394343	-4.431
86311089	-4.41
518802	-4.41
71307292	-4.379
5316733	-4.344
177032	-4.344
5316733	-4.344
8346	-4.342
8346	-4.342
6288	-4.325
5281609	-4.305
5281703	-4.292
5281703	-4.292
442359	-4.286
311	-4.239
5315720	-4.167
42608117	-4.167
157633	-4.147
1183	-4.133
1183	-4.133
447315	-4.116
32052	-4.092
5374527	-4.092
13889369	-4.091
5281515	-4.035
5281515	-4.035
9879022	-4.025
19602	-4.016
157671	-3.999

Table S2. Standard Precision Docking scores of the constituents of *S. baicalensis* against EGFR tyrosine

kinase	
Compound	Docking score
5271991	-9.010
5487756	-8.911
124708188	-8.778
159029	-8.649
5281608	-8.482
185617	-8.478
21122623	-8.462
5321865	-8.420
5322059	-8.397
86311089	-8.365
5281612	-8.354
141059302	-8.338
15896301	-8.300
64982	-8.213
5320313	-8.187
14655551	-8.158
124211	-8.139
14655552	-8.126
5321864	-8.087
5281611	-8.010
5281665	-7.968
161271	-7.941
5280443	-7.925
5280343	-7.839
11609345	-7.708
71307292	-7.640
102445445	-7.610
3084995	-7.559
13889022	-7.514
69717682	-7.472
5271991	-7.439
13889369	-7.426
44567248	-7.407
44567248	-7.407
5322064	-7.309
9818878	-7.223
141059302	-7.155
21722007	-7.053
5321865	-6.872
3082330	-6.851
5315720	-6.427

42608117

-6.427

Table S3. Binding free energy calculation of hit compounds with EGFR tyrosine kinase

PubChem ID	Entry name	ΔG _Bind ^a	ΔG Coulomb ^b	ΔG Covalent ^c	ΔG Hbond ^d	ΔG Lipo ^e	ΔG Packing ^f	ΔG Solv GB ^g	ΔG _vdW ^h
5271991	Ganhuangenin	-43.4513	-30.1915	9.835864	-3.37306	-8.87975	0	32.26416	-43.107
5487756	5,7,2',5'-Tetrahydroxyflavone	-39.3022	-28.2353	5.81899	-2.69077	-6.48429	0	30.21668	-37.9274
124708188	(2R)-2-(2,6-dihydroxyphenyl)-3,4-dihydro-2H-chromene-5,7-diol	-39.2002	-31.4269	7.615402	-2.45953	-8.98145	0	27.54883	-31.4965
159029	Tenaxin I	-48.8476	-24.8055	3.371175	-1.14167	-9.14509	0	24.89257	-42.0191
5281608	Chrysosplenetin	-47.3274	-14.3998	5.491525	-1.65793	-13.48	0	24.99788	-48.2791
185617	Scutellarin	-44.9961	-14.8523	2.570812	-4.25227	-9.50361	-3.99E-06	20.98781	-39.9465
	2-(2,5-Dihydroxyphenyl)-5-hydroxy-7,8-dimethoxy-4H-1-benzopyran-4-one								
21122623	benzopyran-4-one	-46.1299	-31.2994	8.691918	-2.91472	-8.89273	0	30.73119	-42.4462
5321865	5,7,2',6'-Tetrahydroxyflavone	-38.5068	-34.9234	4.396579	-2.70863	-2.04719	0	32.56195	-35.7861
5322059	Viscidulin II	-52.6982	-37.7312	-1.93072	-2.26256	-4.32922	0	32.32895	-38.7734
	(2S,3R)-2-(2,6-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one								
86311089	dihydrochromen-4-one	-40.3662	-34.2527	6.493747	-3.05748	-5.54624	0	32.79547	-36.799
5281612	Diosmetin	-42.2557	-20.9691	1.303899	-1.90409	-6.86133	0	22.68601	-36.5111
	2-(2,6-Dihydroxyphenyl)-5,6,7,8-tetrahydroxychromen-4-one								
141059302	2',5-Dihydroxy-3',6,7,8-tetramethoxyflavone	-53.1034	-38.491	0.215452	-2.23954	-5.50258	0	29.91957	-37.0053
15896301	tetramethoxyflavone	-51.8864	-20.1221	-0.68925	-1.38136	-10.8704	0	22.28374	-41.107
64982	Baicalin	-48.3939	-25.4328	-0.98179	-1.38106	-9.83359	0	32.94994	-43.7146
5320313	Oroxin A	-42.689	-33.9468	7.465025	-3.03813	-10.5769	0	39.27628	-41.8685
14655551	Oroxyloside	-49.3517	-25.6646	1.246316	-1.38027	-9.2217	0	32.75997	-47.0915
124211	Skullcapflavone II	-48.4507	-23.7209	2.631647	-2.29617	-10.5429	0	31.09463	-45.617
14655552	Oroxylin A 7-O-beta-D-glucuronide	-37.3309	-14.9838	10.00395	-2.79151	-9.79594	0	29.3297	-49.0933
5321864	5,7,2',3'-Tetrahydroxyflavone	-43.0721	-26.9716	0.762559	-3.1807	-6.3918	0	29.6884	-36.979
5281611	3,7,4'-Trihydroxyflavone	-40.2439	-22.8889	0.917516	-1.73641	-8.72116	0	28.29215	-36.1071
5281665	Isoscutellarein	-38.4011	-20.4467	2.039557	-2.88868	-6.57588	-3.16E-06	23.09482	-33.6241
161271	Salvigenin	-45.4653	-14.6579	0.317833	-1.06995	-9.2249	0	18.91281	-39.7432
5280443	Apigenin	-36.8295	-19.2081	1.315186	-2.63991	-5.55326	-2.97E-06	21.69197	-32.4353
5280343	Quercetin	-40.9999	-18.2092	0.913132	-3.13548	-7.11519	0	27.37618	-40.8294

11609345	5,7-Dihydroxy-6,8-dimethoxyflavone	-46.8905	-18.875	-1.57898	-0.73245	-9.49486	0	18.42495	-34.6341
71307292	2',3,5,6',7-Pentahydroxyflavanone	-35.467	-25.3872	3.56956	-2.32058	-5.4433	0	31.96449	-37.85
102445445	2'-(beta-D-Glucopyranosyloxy)-5,6',7-trihydroxyflavone	-33.8965	-26.0854	6.514125	-3.45502	-7.58237	0	39.15812	-42.446
3084995	Isoschaftoside	-45.634	-48.5735	3.135995	-5.06113	-10.172	0	59.37038	-44.3338
13889022	Rivularin	-43.781	-30.3433	6.025739	-2.37605	-8.00251	0	33.52398	-42.6089
69717682	(2R,3R,4S,5R,6S)-6-(5,6-dihydroxy-4-oxo-2-phenylchromen-7-yl)oxy-3,4,5-trihydroxyoxane-2-carboxylic acid	-56.0158	-22.5807	-1.25295	-1.27788	-9.77465	0	21.71012	-42.8398
13889369	5,7,2'-Trihydroxy-6'-methoxyflavone	-37.1752	-27.2455	3.830154	-2.28827	-5.70407	0	32.83472	-38.6022
44567248	oroxylin A glucuronide	-48.8622	-24.2117	3.097588	-2.27308	-9.66471	0	34.66664	-50.4769
5322064	5,7,2'-Trihydroxyflavone	-39.4607	-26.834	1.058138	-2.23446	-6.25063	0	30.00618	-35.2059
9818878	5,7,2'-Trihydroxy-6,8-dimethoxyflavone	-47.9219	-23.8905	0.543444	-2.02376	-9.97409	0	30.0995	-42.6765
21722007	Chrysin 6-C-glucoside 8-C-arabinoside	-54.5231	-37.6405	4.670753	-5.20742	-15.1549	-0.78293	42.58889	-42.997
3082330	2',3,5,7-Tetrahydroxyflavanone	-33.4951	-20.597	3.673548	-2.89631	-9.66732	0	29.62801	-33.636
5315720	8-Hydroxynaringenin	-35.4315	-25.4402	1.938563	-3.50192	-6.34279	0	28.25334	-30.3386
42608117	Isocarthamidin	-35.4315	-25.4402	1.938563	-3.50192	-6.34279	0	28.25334	-30.3386

^aMM-GBSA free energy (kcal/mol) of binding.

^bContribution to the MM-GBSA free energy of binding (kcal/mol) from the Coulomb energy.

^cContribution to the MM-GBSA free energy of binding (kcal/mol) from hydrogen bonding.

^dContribution to the MM-GBSA free energy of binding (kcal/mol) from lipophilic binding.

^eContribution to the MM-GBSA free energy of binding (kcal/mol) from packing binding.

^fContribution to the MM-GBSA free energy of binding (kcal/mol) from solvent GB binding.

^gContribution to the MMGBSA free energy of binding (kcal/mol) from the van der Waals energy.

Table S4. Induced Fit Docking scores and biological interactions of five top scoring compounds of *S. baicalensis* against EGFR tyrosine kinase

Compound	Conformation	Docking Score	H-Bond Interaction	Hydrophobic Interactions
Ganhuangenin	1	-10.862	GLU 738, ASP 831, THR 830, THR 766 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
	2	-10.426	ASP 831, THR 830, THR 766 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
	3	-9.688	GLU 738, THR 766 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
5,7,2',5'-Tetrahydroxyflavone	1	-9.934	ASP 831, THR 766 and MET 769	MET 742, PHE 832, LEU 764, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
	2	-9.317	GLU 738, ASP 831, THR 766 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
	3	-9.289	GLU 738, ASP 831, THR 766 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
Chrysosplenetin	1	-8.681	LYS 721 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
	2	-8.422	LYS 721, ASP 831 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
	3	-7.5	THR 766, GLU 767 and MET 769	MET 742, LEU 764, CYS 751, LEU 768, LEU 820, PHE 699, MET 769, CYS 773, LEU 694, VAL 702 and ALA 719
Tenaxin I	1	-9.424	THR 766 and MET 769	MET 742, PHE 832, LEU 764, CYS 751, LEU 768, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719

ZINC238777154	2	-8.933	MET 769	MET 742, LEU 764, LEU 768, MET 769, PRO 770, CYS 773, LEU 694, VAL 702, PHE 699, LEU 820 and ALA 719
	3	-8.826	THR 830 and MET 769	MET 742, LEU 764, LEU 768, MET 769, PRO 770, CYS 773, LEU 694, VAL 702, PHE 699, CYS 751, LEU 820 and ALA 719
	1	-9.59	ASP 831, THR 766 and MET 769	MET 742, LEU 764, CYS 751, LEU 768, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719
	2	-10.155	ASP 831, THR 830, ALA 719, MET 769	MET 742, LEU 764, CYS 751, LEU 768, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719, ILE 720 and PHE 832
	3	-9.587	ASP 831, THR 830, ALA 719, MET 769	MET 742, LEU 764, CYS 751, LEU 768, MET 769, PRO 770, CYS 773, LEU 694, VAL 702 and ALA 719, and PHE 832

Table S5. KEGG pathways of identified genes

Pathway ID	Pathway description	Observed gene count	False discovery rate	Matching proteins in network
hsa04012	ErbB signaling pathway	7	3.74e-12	HBEGF, PLCG1, EREG, CBL, EGF, EGFR, TGFA
hsa05200	Pathways in cancer	8	6.55e-09	PLCG1, CDH1, CBL, STAT3, EGF, EGFR
hsa05223	Non-small cell lung cancer	5	3.19e-08	PLCG1, STAT3, EGF, EGFR, TGFA
hsa01521	EGFR tyrosine kinase inhibitor resistance	5	4.61e-08	PLCG1, STAT3, EGF, EGFR, TGFA
hsa05219	Bladder cancer	4	5.34e-07	HBEGF, CDH1, EGF, EGFR
hsa05205	Proteoglycans in cancer	5	2.67e-06	HBEGF, PLCG1, CBL, STAT3, EGFR
hsa05212	Pancreatic cancer	4	3.25e-06	STAT3, EGF, EGFR, TGFA
hsa05214	Glioma	4	3.25e-06	PLCG1, EGF, EGFR, TGFA
hsa04014	Ras signaling pathway	5	3.57e-06	PLCG1, EGF, RASA1, EGFR, TGFA
hsa05210	Colorectal cancer	4	3.76e-06	EREG, EGF, EGFR, TGFA
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	4	4.49e-06	PLCG1, STAT3, EGF, EGFR
hsa05215	Prostate cancer	4	5.76e-06	EGF, EGFR, TGFA, HSP90AA1
hsa04010	MAPK signaling pathway	5	7.81e-06	EREG, EGF, RASA1, EGFR, TGFA
hsa04066	HIF-1 signaling pathway	4	7.81e-06	PLCG1, STAT3, EGF, EGFR
hsa04915	Estrogen signaling pathway	4	1.63e-05	HBEGF, EGFR, TGFA, HSP90AA1
hsa04151	PI3K-Akt signaling pathway	5	1.69e-05	EREG, EGF, EGFR, TGFA, HSP90AA1
hsa04015	Rap1 signaling pathway	4	7.33e-05	PLCG1, CDH1, EGF, EGFR
hsa05213	Endometrial cancer	3	8.28e-05	CDH1, EGF, EGFR
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	3	0.00013	HBEGF, PLCG1, EGFR
hsa05218	Melanoma	3	0.00015	CDH1, EGF, EGFR
hsa05231	Choline metabolism in cancer	3	0.00032	PLCG1, EGF, EGFR
hsa04659	Th17 cell differentiation	3	0.00036	PLCG1, STAT3, HSP90AA1
hsa04068	FoxO signaling pathway	3	0.00066	STAT3, EGF, EGFR
hsa05226	Gastric cancer	3	0.00092	CDH1, EGF, EGFR
hsa04072	Phospholipase D signaling pathway	3	0.00093	PLCG1, EGF, EGFR
hsa04630	JAK-STAT signaling pathway	3	0.0011	STAT3, EGF, EGFR
hsa05160	Hepatitis C	3	0.0011	STAT3, EGF, EGFR
hsa05206	MicroRNAs in cancer	3	0.0011	PLCG1, STAT3, EGFR

hsa05225	Hepatocellular carcinoma	3	0.0011	PLCG1, EGFR, TGFA
hsa04020	Calcium signaling pathway	3	0.0017	PLCG1, EGF, EGFR
hsa04520	Adherens junction	2	0.0072	CDH1, EGFR
hsa05100	Bacterial invasion of epithelial cells	2	0.0075	CDH1, CBL
hsa04540	Gap junction	2	0.0111	EGF, EGFR
hsa04912	GnRH signaling pathway	2	0.0113	HBEGF, EGFR
hsa01522	Endocrine resistance	2	0.0125	HBEGF, EGFR
hsa04933	AGE-RAGE signaling pathway in diabetic complications	2	0.0129	PLCG1, STAT3
hsa04928	Parathyroid hormone synthesis secretion and action	2	0.0138	HBEGF, EGFR
hsa04935	Growth hormone synthesis secretion and action	2	0.0175	PLCG1, STAT3
hsa05224	Breast cancer	2	0.0254	EGF, EGFR
hsa04217	Necroptosis	2	0.0261	STAT3, HSP90AA1
hsa04360	Axon guidance	2	0.0355	PLCG1, RASA1
hsa04062	Chemokine signaling pathway	2	0.0381	PLCG1, STAT3
hsa05167	Kaposi sarcoma-associated herpesvirus infection	2	0.0381	PLCG1, STAT3
hsa04510	Focal adhesion	2	0.0410	EGF, EGFR
hsa04810	Regulation of actin cytoskeleton	2	0.0445	EGF, EGFR
hsa05131	Shigellosis	2	0.0472	PLCG1, EGFR
hsa05163	Human cytomegalovirus infection	2	0.0472	STAT3, EGFR

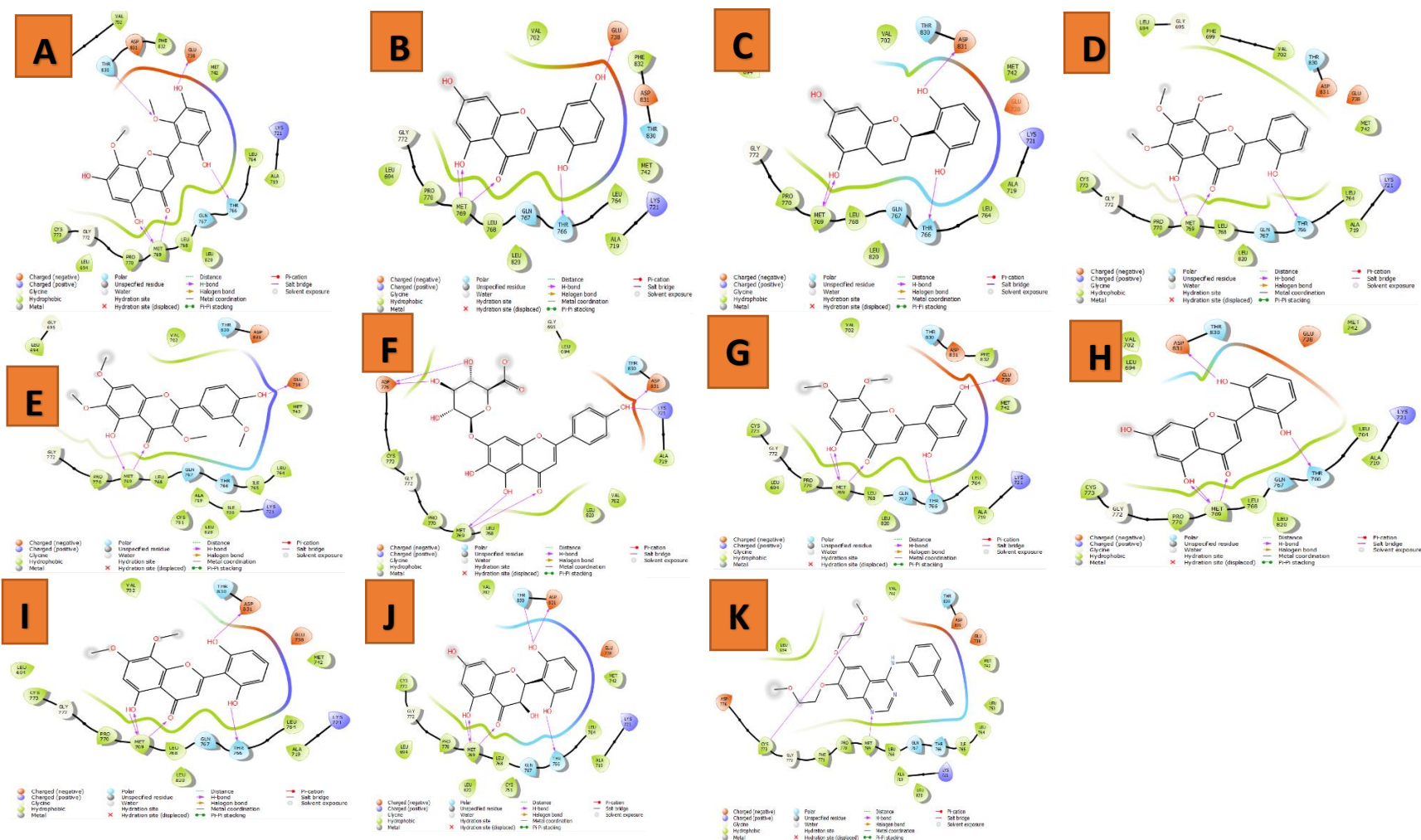


Figure S1. 2D view of the molecular interactions of A=Ganhuangenin, B=5,7,2',5'-Tetrahydroxyflavone, C=(2R)-2-(2,6-dihydroxyphenyl)-3,4-dihydro-2H-chromene-5,7-diol, D=Tenaxin I, E=Chrysosplenetin, F=Scutellarin, G=5,2',5'-trihydroxy-7,8-dimethoxyflavone, H=5,7,2',6'-Tetrahydroxyflavone, I=Viscidulin II, J=(2S,3R)-2-(2,6-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one, K=Erlotinib with EGFR tyrosine kinase

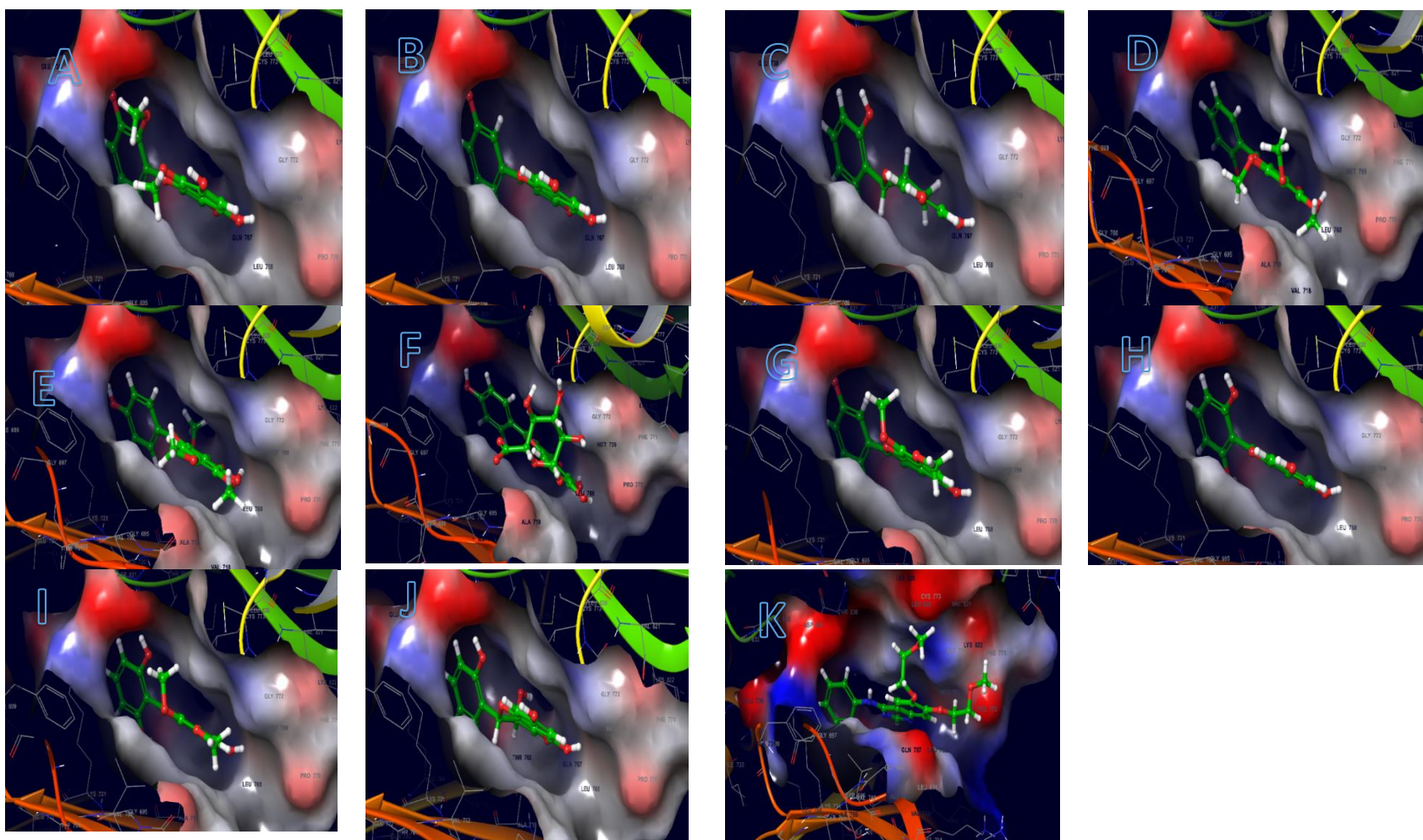


Figure S2. 3D view of the molecular interactions of A=Ganhuangenin, B=5,7,2',5'-Tetrahydroxyflavone, C=(2R)-2-(2,6-dihydroxyphenyl)-3,4-dihydro-2H-chromene-5,7-diol, D=Tenaxin I, E=Chrysosplenetin, F=Scutellarin, G=5,2',5'-trihydroxy-7,8-dimethoxyflavone, H=5,7,2',6'-Tetrahydroxyflavone, I=Viscidulin II, J=(2S,3R)-2-(2,6-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one, K=Erlotinib with EGFR tyrosine kinase