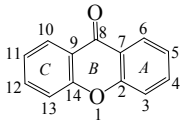
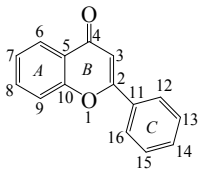
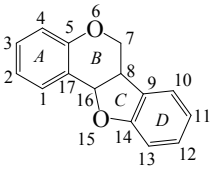
Table S1 Docking scores, experimental and predicted activities of 40 natural compounds



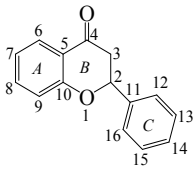
1~7



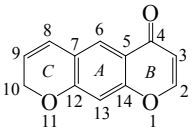
8~21, 35



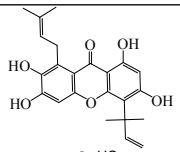
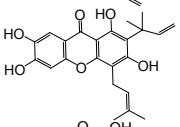
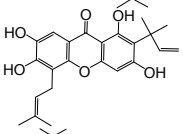
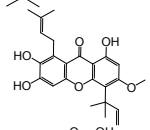
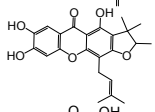
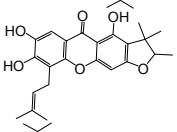
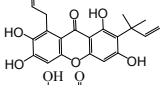
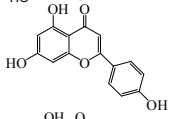
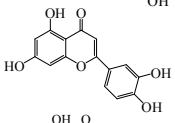
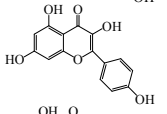
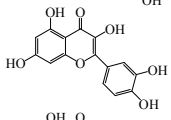
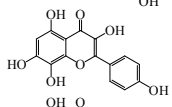
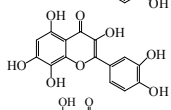
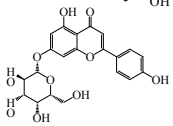
22, 23

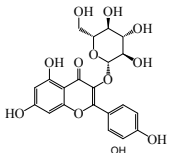
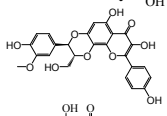
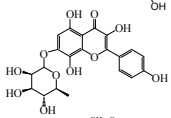
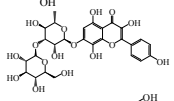
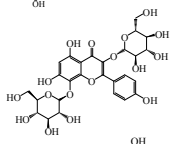
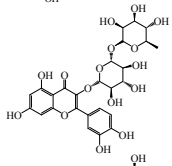
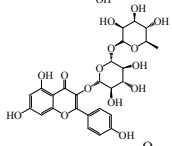
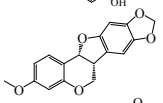
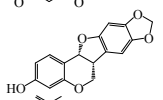
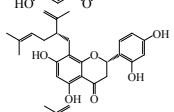
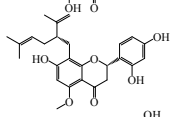
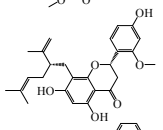
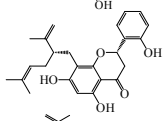
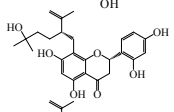
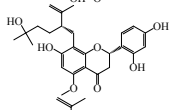
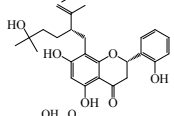
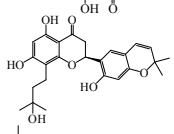
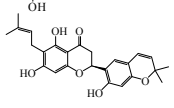


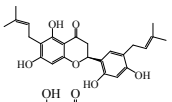
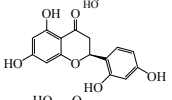
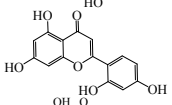
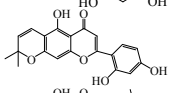
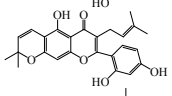
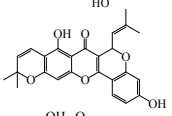
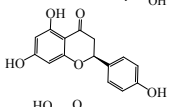
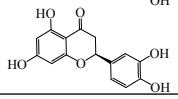
24~34, 39, 40



36~38

No	Ref.	Structures	Exp. pIC_{50}(M)	Pred. pIC_{50}(M)				Total scores	CScore
				SRA	HQSAR	Almond	CoMSIA		
1*	31		6.61	6.17	6.58	6.01	6.19	4.09	3
2	31		6.73	6.69	6.76	6.93	6.70	5.75	3
3	31		6.64	6.51	6.73	6.76	6.63	4.50	2
4	31		5.90	5.88	6.38	6.26	5.81	4.42	4
5*	31		6.56	7.31	6.68	6.43	6.31	6.49	5
6	31		6.73	6.97	6.76	6.46	6.58	7.53	5
7	31		7.10	6.94	6.70	6.51	7.22	6.33	3
8*	32		4.76	4.57	5.45	5.32	5.38	4.26	5
9	32		5.37	5.44	5.62	5.77	5.43	5.42	4
10	32		5.10	5.33	5.43	5.26	5.52	4.65	1
11*	32		5.77	6.36	5.60	5.62	5.56	5.07	1
12	32		5.85	5.52	5.69	5.76	5.82	4.40	2
13	32		6.10	6.16	5.86	5.91	6.03	4.23	2
14	32		4.41	4.16	4.53	4.37	4.37	4.15	5

15*	32		4.53	5.25	4.73	4.85	5.04	4.05	4
16	32		5.21	5.27	5.24	5.26	5.32	5.19	5
17	32		4.39	5.02	4.64	4.54	4.52	3.73	4
18*	32		4.24	4.61	3.95	5.23	4.44	3.09	4
19	32		4.41	4.31	4.38	4.77	4.31	3.11	4
20	32		4.51	4.52	4.47	4.50	4.41	4.77	5
21	32		4.26	4.18	4.29	3.84	4.38	3.68	5
22*	33		5.85	5.15	5.39	5.30	5.80	3.46	5
23	33		5.50	5.25	5.40	5.35	5.56	4.73	5
24	33		4.87	4.97	4.51	4.93	4.54	4.93	4
25*	33		4.82	5.05	4.48	4.58	5.00	4.42	5
26	33		4.70	4.60	4.52	4.60	4.55	4.96	5
27	33		4.83	5.09	4.53	4.86	5.01	4.34	4
28*	33		4.74	4.73	4.85	4.89	4.87	4.71	3
29	33		4.77	4.88	4.82	4.91	4.71	4.68	5
30	33		4.92	4.83	4.86	4.62	4.87	5.21	5
31*	34		6.42	5.74	5.75	5.65	5.17	5.91	3
32	34		5.82	5.72	5.51	5.87	5.54	5.31	2

33	34		4.97	4.92	4.99	4.93	4.87	4.62	5
34*	34		5.09	4.87	4.90	4.88	4.75	6.41	4
35	34		5.95	5.50	5.48	5.46	5.59	4.54	4
36	34		5.22	5.34	5.21	5.19	5.29	5.43	2
37	34		4.99	4.90	5.12	5.04	4.98	5.00	3
38*	34		4.54	5.39	5.31	5.34	5.46	5.25	5
39	34		4.24	4.26	4.85	4.62	4.92	5.01	4
40	34		4.80	5.08	4.99	4.98	4.79	5.07	4

*samples in test set

Table S2 Pred. pIC_{50} of all 40 natural compounds by the other eleven hologram lengths during HQSAR modeling

No	Exp. pIC_{50}	PRED_401	PRED_307	PRED_257	PRED_199	PRED_151	PRED_97	PRED_83	PRED_71	PRED_61	PRED_59	PRED_53
1*	6.6108	6.666	6.622	6.644	6.628	6.580	6.569	6.709	6.572	6.579	6.645	6.694
2	6.7305	6.731	6.763	6.752	6.787	6.758	6.747	6.696	6.543	6.765	6.580	6.782
3	6.6421	6.694	6.718	6.728	6.754	6.790	6.580	6.648	6.733	6.740	6.569	6.623
4	5.8959	6.495	6.475	6.411	6.434	6.407	6.483	6.613	6.446	6.483	6.487	6.530
5*	6.5560	6.637	6.548	6.822	6.622	6.666	6.903	6.590	6.662	6.629	6.682	6.624
6	6.7305	6.730	6.609	6.839	6.693	6.690	6.777	6.616	6.836	6.666	6.927	6.621
7	7.0969	6.743	6.714	6.729	6.773	6.716	6.664	6.731	6.688	6.622	6.693	6.816
8*	4.7595	5.409	5.477	5.355	5.282	5.476	5.410	5.290	5.378	5.126	5.395	5.258
9	5.3665	5.551	5.608	5.585	5.444	5.576	5.550	5.334	5.459	5.263	5.470	5.403
10	5.0969	5.455	5.462	5.327	5.316	5.523	5.416	5.286	5.512	5.112	5.288	5.291
11*	5.7696	5.594	5.594	5.560	5.478	5.616	5.546	5.323	5.595	5.251	5.358	5.433
12	5.8539	5.663	5.632	5.643	5.544	5.587	5.621	5.386	5.650	5.310	5.494	5.430
13	6.0969	5.801	5.764	5.876	5.706	5.681	5.750	5.424	5.732	5.448	5.564	5.572
14	4.4056	4.590	4.584	4.563	4.401	4.481	4.811	4.883	4.811	4.540	4.692	4.754
15*	4.5317	4.812	4.772	4.703	4.737	4.927	4.880	4.861	4.827	4.567	4.617	4.902
16	5.2147	5.068	5.080	5.156	5.073	5.086	4.800	4.994	5.302	4.923	5.213	5.054
17	4.3915	4.737	4.730	4.636	4.573	4.583	4.984	4.814	4.856	4.465	4.779	4.699
18*	4.2449	4.109	4.085	4.086	4.036	4.013	4.452	4.453	4.545	3.912	4.149	4.136
19	4.4078	4.443	4.358	4.354	4.288	4.457	4.332	4.302	4.348	4.275	4.312	4.296
20	4.5100	4.433	4.489	4.526	4.469	4.465	4.391	4.329	4.346	4.451	4.390	4.467
21	4.2557	4.288	4.348	4.296	4.307	4.363	4.268	4.275	4.272	4.318	4.324	4.321
22*	5.8539	5.231	5.208	5.237	5.092	5.216	5.023	5.058	5.190	5.269	5.329	5.342
23	5.4949	5.263	5.204	5.309	5.078	5.253	5.098	5.087	5.181	5.286	5.311	5.318
24	4.8697	4.689	4.603	4.708	4.688	4.667	4.745	4.886	4.627	4.890	4.684	4.826
25*	4.8210	4.631	4.570	4.621	4.682	4.616	4.793	4.809	4.555	4.872	4.704	4.786
26	4.6968	4.706	4.560	4.656	4.707	4.631	4.856	4.910	4.778	4.882	4.845	4.795

27	4.8297	4.665	4.635	4.628	4.747	4.713	4.750	4.935	4.732	4.924	4.697	4.718
28*	4.7375	4.645	4.615	4.742	5.092	4.595	4.551	4.658	4.553	4.888	4.507	4.668
29	4.7696	4.587	4.582	4.656	5.086	4.545	4.598	4.580	4.481	4.870	4.527	4.628
30	4.9172	4.621	4.647	4.663	5.151	4.641	4.555	4.707	4.658	4.922	4.520	4.560
31*	6.4202	5.113	5.211	5.311	6.220	5.245	5.223	5.017	5.327	5.489	5.210	5.093
32	5.8153	5.280	5.431	5.337	5.713	5.483	5.425	5.349	5.440	5.578	5.575	5.224
33	4.9690	5.076	5.168	4.992	4.850	5.082	5.124	5.385	5.015	5.606	5.287	5.071
34*	5.0894	5.019	5.004	4.989	4.856	5.081	5.093	4.999	4.948	4.901	5.000	5.053
35	5.9469	5.454	5.487	5.451	5.216	5.487	5.423	5.300	5.322	5.118	5.338	5.421
36	5.2211	5.267	5.290	5.300	5.393	5.282	5.321	5.309	5.245	5.352	5.241	5.487
37	4.9940	5.186	5.242	5.191	5.284	5.182	5.193	5.378	5.254	5.420	5.201	5.471
38*	4.5375	5.327	5.360	5.335	5.400	5.395	5.404	5.420	5.500	5.618	5.197	5.365
39	4.2372	4.950	4.975	4.855	4.798	5.021	4.955	5.015	4.949	4.949	5.055	4.994
40	4.7967	5.086	5.092	5.086	4.979	5.098	5.036	5.073	5.034	5.064	5.183	5.073

*samples in test set.

Table S3 The individual atomic contribution to activity of all 40 natural compounds

No	Exp. pIC_{50}	Green numbers	Yellow numbers	Orange numbers	Red numbers
1*	6.61	4	2	0	0
2	6.73	3	5	0	0
3	6.64	3	2	0	0
4	5.90	2	2	0	0
5*	6.56	2	0	0	0
6	6.73	2	2	0	0
7	7.10	3	3	0	0
8*	4.76	0	0	0	0
9	5.37	0	0	0	0
10	5.10	0	0	0	0
11*	5.77	0	0	0	0
12	5.85	0	0	0	0
13	6.10	0	0	0	0
14	4.41	0	0	4	6
15*	4.53	0	0	3	6
16	5.21	0	0	0	0
17	4.39	0	0	2	6
18*	4.24	0	0	5	13
19	4.41	0	0	7	10
20	4.51	0	0	4	8
21	4.26	0	0	4	8
22*	5.85	0	0	0	0
23	5.50	0	0	0	0
24	4.87	0	0	6	0
25*	4.82	0	0	6	0
26	4.70	0	0	5	0
27	4.83	0	0	5	0
28*	4.74	0	0	5	1

29	4.77	0	0	6	1
30	4.92	0	0	4	1
31*	6.42	0	0	1	0
32	5.82	0	0	2	0
33	4.97	0	0	4	0
34*	5.09	0	0	2	1
35	5.95	0	0	0	0
36	5.22	0	0	1	1
37	4.99	0	0	1	1
38*	4.54	0	0	1	1
39	4.24	0	0	1	1
40	4.80	0	0	2	1

Colors at the red end of the spectrum (Red: less than –0.241462; Red_orange: –0.241462 to –0.144877; Orange: –0.144877 to –0.0965847; White: –0.0965847 to 0.10176; Yellow: 0.10176 to 0.15264; Green_blue: 0.15264 to 0.254399; Good > Green: 0.254399 and above; Common backbone: cyan). *samples in test set.

Table S4 Statistical results and relative contributions of the constructed QSAR models

Methods	R^2	*SE*	*F*	Q^2	*SEcv*	R^2_{test}	Q^2_{ext}	*A*	Relative contributions				
									Steric	Electrostatic	Hydrophobic	Donor	Acceptor
SRA	0.931	0.248	39.248	0.856	0.362	0.611	0.565						
HQSAR	0.903	0.271		0.767	0.419	0.753	0.750	3					
Almond	0.904	0.249		0.511	0.563	0.612	0.582	4					
CoMSIA	0.936	0.220	116.309	0.654	0.511	0.582	0.571	3	0.136	0.265	0.208	0.251	0.140

R^2: squared multiple correlation coefficients; *SE*: standard error; *F*: Fisher Statistic; Q^2: squared cross-validated correlation coefficient; *SEcv*: cross-validated standard error; R^2_{test} and Q^2_{ext} are R^2 and $Q^2$of test set, respectively; *A*: Components.

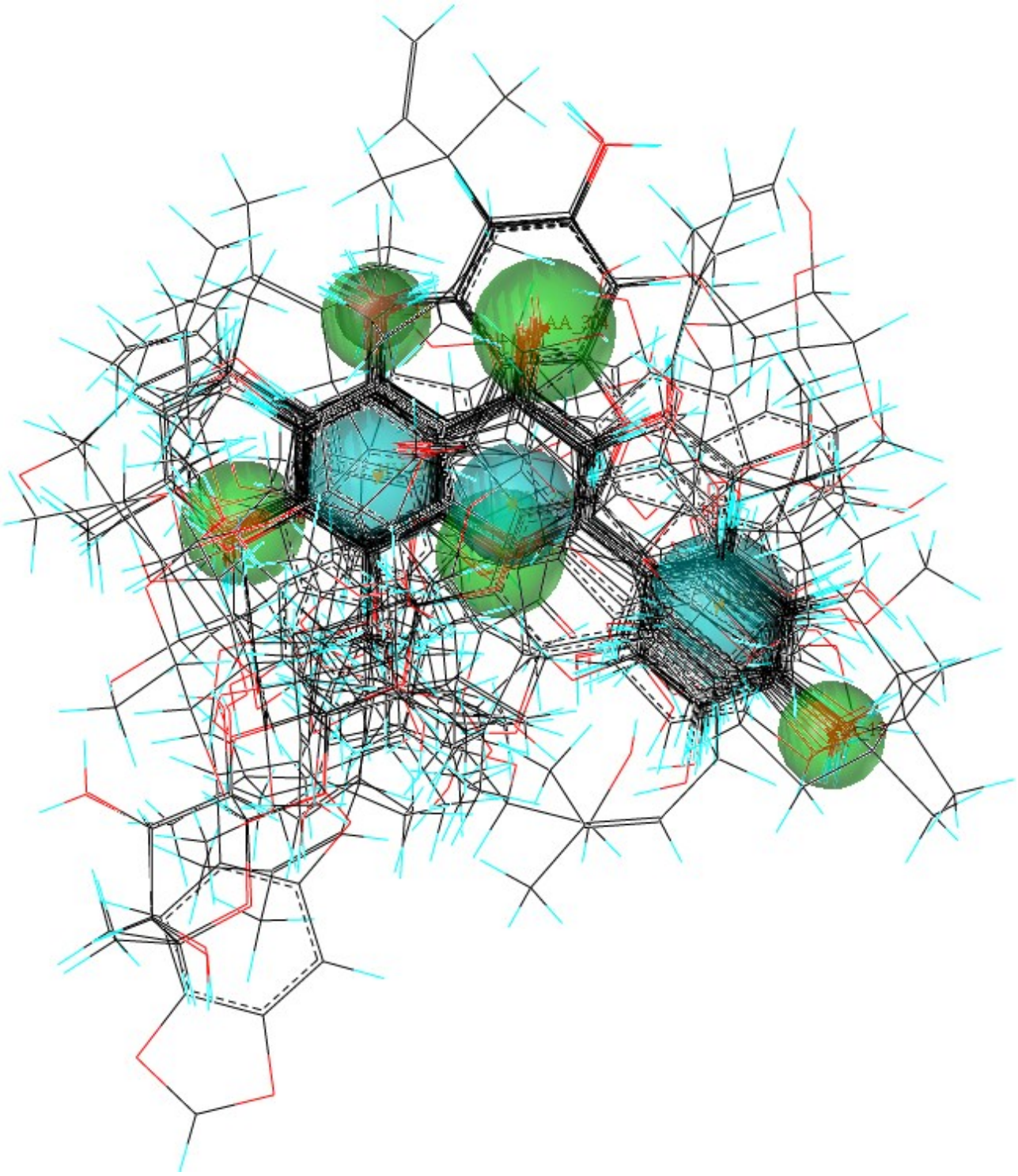


Fig. S1 Pharmacophore models of 40 natural compounds (Donor Atoms (DA), Acceptor Atoms (AA) and Hydrophobes (HY) included DA_1, AA_12, AA_13, AA_24, AA_304, AA_308, HY_28, HY_239 and HY_310. A: references molecules with all samples;)

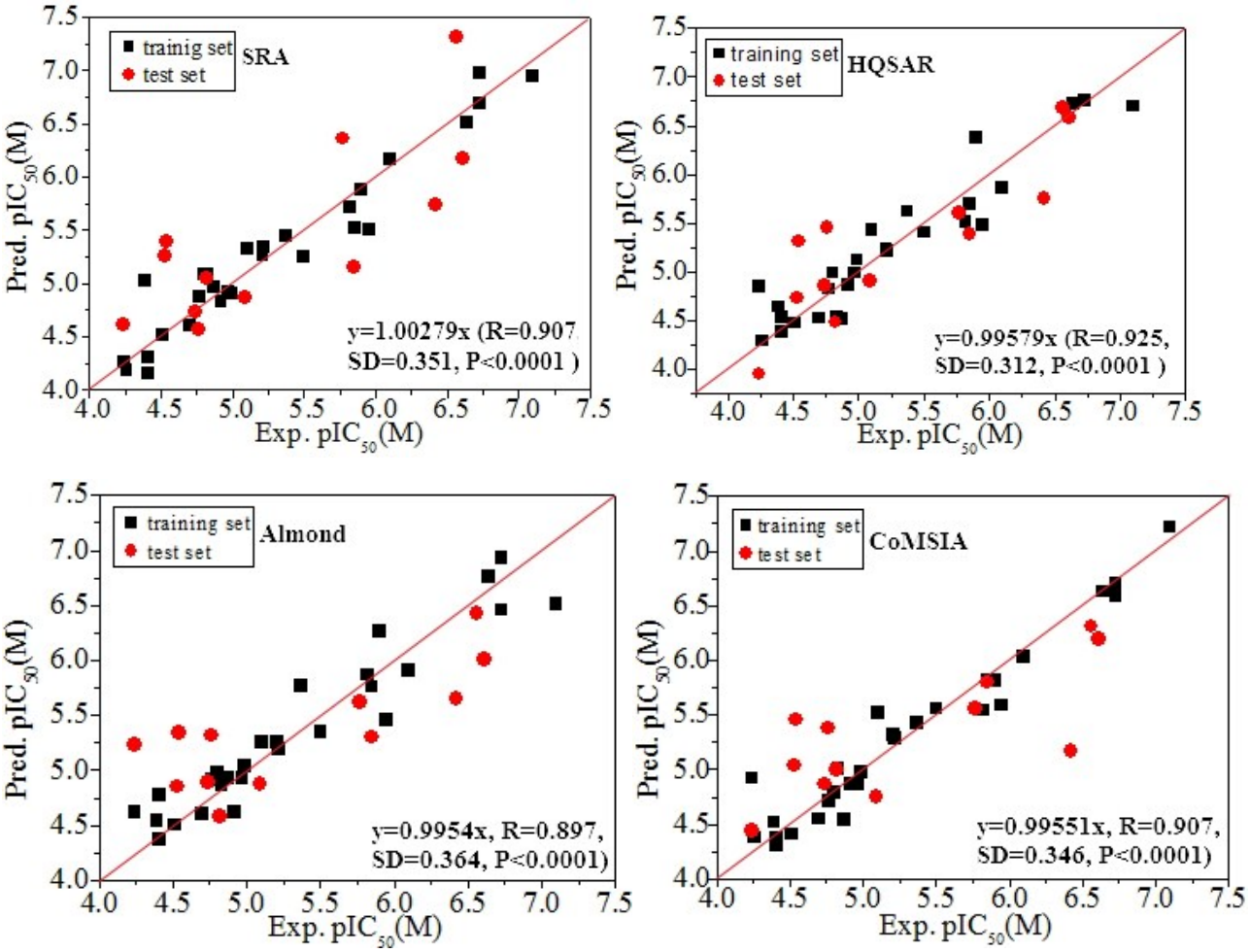


Fig. S2 Relative plot of Exp. vs Pred. activities of all 40 natural compounds through origin

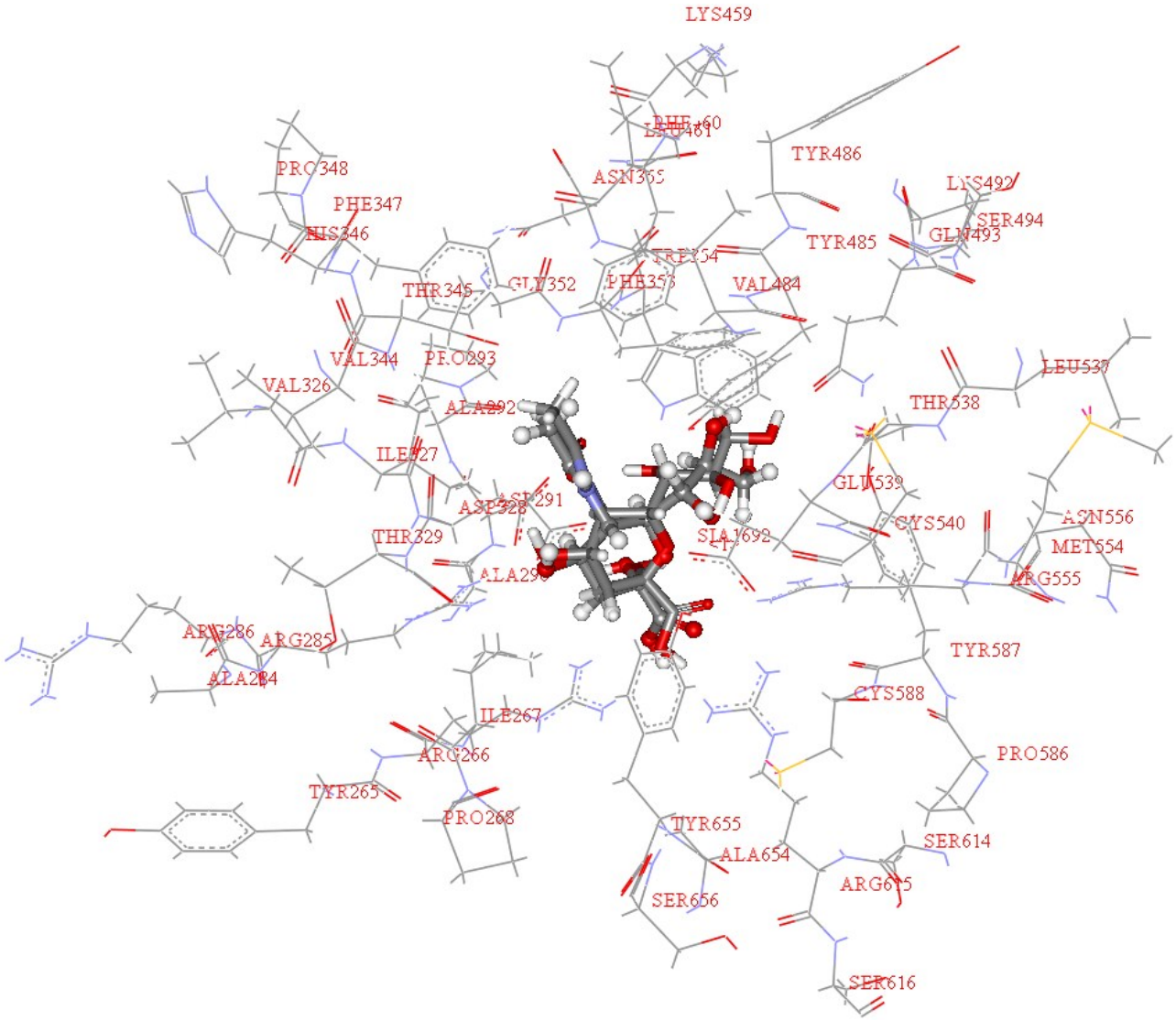


Fig. S3 Comparison between the position calculated of Sia1692 with ball and stick and that observed in the crystal structure with stick

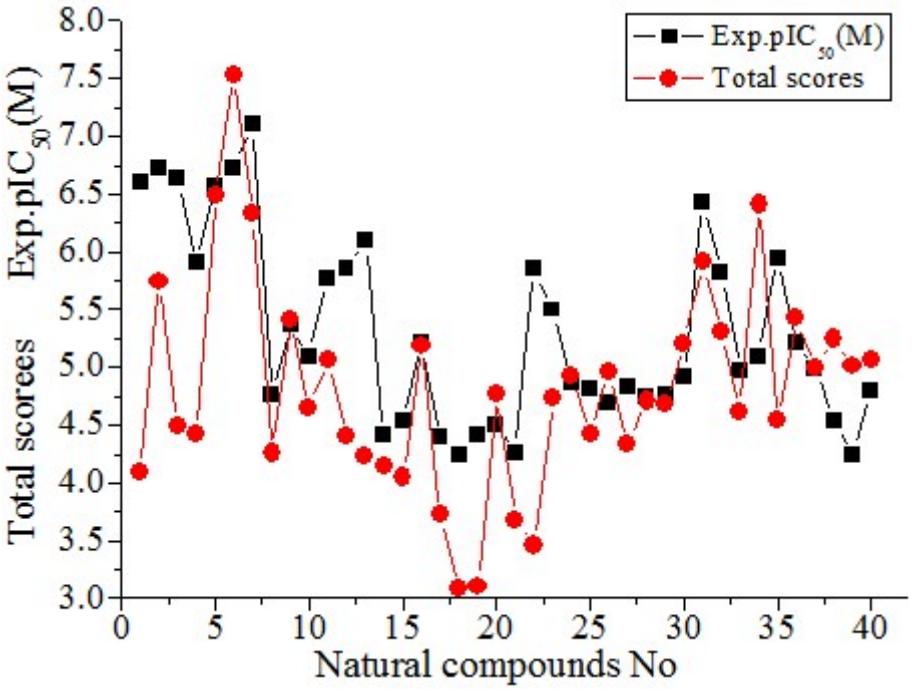


Fig. S4 Scatter plots of compounds No against Exp.IC_{50} and total scores, respectively

Table S5 Total scores, D Score, PMF Score, G Score and CHEM Score and CScore of all 40 natural compounds by docking

No	Total scores	D_SCORE	PMF_SCORE	G_SCORE	CHEMSCORE	CScore
1*	4.09	-83.3382	-131.7836	-130.2180	-23.0371	3
2	5.75	-118.9624	-95.5739	-159.7962	-15.9716	3
3	4.50	-79.6943	-128.2329	-101.9323	-19.1250	2
4	4.42	-95.2721	-146.1366	-130.7881	-23.6543	4
5*	6.49	-120.5729	-155.4849	-185.6666	-23.6158	5
6	7.53	-120.0477	-126.3347	-173.4963	-27.2598	5
7	6.33	-84.1571	-125.6944	-120.8778	-24.0651	3
8*	4.26	-115.2557	-103.4057	-122.6915	-26.6344	5
9	5.42	-99.8512	-64.1845	-128.8416	-31.0606	4
10	4.65	-82.2945	-76.8272	-33.2681	-19.5973	1
11*	5.07	-63.5117	-83.1828	-21.3383	-14.9107	1
12	4.40	-82.7594	-126.1803	-17.0104	-18.6786	2
13	4.23	-85.5622	-120.1079	2.2266	-10.0464	2
14	4.15	-149.3261	-151.7645	-179.3238	-21.1895	5
15*	4.05	-156.9900	-174.6023	-88.4821	-15.2340	4
16	5.19	-147.4066	-184.9815	-132.3911	-27.4204	5
17	3.73	-150.0468	-169.6074	-91.0250	-21.7321	4
18*	3.09	-179.2369	-220.2221	-78.4489	-18.1962	4
19	3.11	-165.6004	-173.4856	-136.8723	-16.9232	4
20	4.77	-190.1011	-231.5389	-137.6082	-15.5093	5
21	3.68	-217.5586	-199.8963	-169.8890	-27.2876	5
22*	3.46	-114.5160	-109.6673	-169.0315	-25.1678	5
23	4.73	-107.6432	-118.7135	-138.8738	-26.4312	5
24	4.93	-178.0596	-119.7367	-234.1309	-30.0116	4

25*	4.42	-156.9080	-123.2411	-256.3464	-28.9414	5
26	4.96	-133.7573	-149.6852	-206.7737	-32.0590	5
27	4.34	-137.6305	-134.2722	-206.7470	-27.7289	4
28*	4.71	-126.4227	-147.6297	-141.1850	-29.3066	3
29	4.68	-144.9420	-131.0761	-198.0954	-30.1156	5
30	5.21	-146.8705	-159.6862	-211.9809	-31.4341	5
31*	5.91	-120.3168	-134.7208	-147.9898	-20.6933	3
32	5.31	-92.4661	-134.2514	-124.1484	-22.5388	2
33	4.62	-133.3988	-131.7382	-182.4661	-25.6405	5
34*	6.41	-92.8379	-118.4574	-96.0152	-22.8506	4
35	4.54	-94.3208	-102.6061	-68.1182	-22.6758	4
36	5.43	-84.3992	-119.0178	-60.7943	-14.4600	2
37	5.00	-126.5704	-111.3110	-129.8324	-18.7761	3
38*	5.25	-129.1892	-122.3137	-182.8948	-29.1835	5
39	5.01	-108.7310	-96.8172	-114.3707	-22.0992	4
40	5.07	-120.8250	-136.4040	-124.1303	-20.0643	4

*samples in test set.

Table S6 hydrogen bond interactions residues of 40 samples in the active pocket of 2bf6

No	hydrogen bond interactions residues in the active pocket of 2bf6
1*	Arg266, Tyr485, Gln493, Arg555, Arg615, Tyr655
2	Arg266, Arg285, Asp328, Arg615
3	Tyr485, Arg555, Arg615, Tyr655
4	Arg266, Tyr485, Gln493, Arg555
5*	Arg266, Arg285, Asp328, Arg615
6	Arg266, Arg285, Asp328, Arg615
7	Arg266, Arg285, Asp328, Arg555
8*	Arg266, Arg285 Asp328, Arg555, Arg615, Tyr655
9	Asp291, Trp354, Tyr485, Gln493, Tyr587
10	Asp291, Trp354, Tyr485, Gln493, Tyr587
11*	Asp291, Ala292, Trp354, Gln493, Tyr485, Tyr587
12	Arg285, Asp291, Asp328, Gln493
13	Arg266, Asp328, Gln493, Arg555, Arg615, Tyr655
14	Asp291, Trp354, Tyr485, Gln493, Arg555, Tyr587
15*	Arg285, Asp291, Asp328, Gln493, Arg555, Arg615, Tyr655
16	Arg266, Arg285, Asp328, Thr345, Arg555, Arg615
17	Asp291, Asp328, Trp354, Arg555, Arg615, Tyr655
18*	Arg266, Arg285, Asp291 Asp328, Trp354, Tyr485, Glu539, Arg555, Arg615
19	Arg266, Asp291, Asp328, Trp354, Gln493, Thr538, Tyr587, Tyr655
20	Arg285, Asp328, Trp354, Tyr485, Gln493, Glu539, Tyr655
21	Arg285, Asp291, Asp328, Trp354, Tyr485, Gln493, Thr538, Tyr587
22*	Tyr485, Arg555, Arg615, Tyr655
23	Arg285, Asp328, Gln493
24	Asp291, Gln493, Tyr587
25*	Arg285, Asp328, Arg555, Arg615, Tyr655
26	Ala292, Phe353, Gln493, Tyr587

27	Tyr485, Gln493, Tyr587
28*	Ala292, Phe353, Trp354, Tyr485, Tyr655
29	Asp291, Asp328, Tyr587
30	Arg266, Asp291, Tyr485, Gln493, Tyr655
31*	Tyr485, Glu539, Tyr587, Arg615, Tyr655,
32	Arg266, Trp354, Arg555, Arg615, Tyr655
33	Arg266, Asp291, Glu539, Arg555, Tyr655
34*	Arg266, Arg285, Asp328, Trp354, Arg555, Arg615, Tyr655
35	Asp291, Trp354, Gln493, Thr538, Glu539, Tyr587, Tyr655
36	Arg266, Gln493, Thr538, Tyr655
37	Trp354, Thr538, Tyr655
38*	Tyr485, Arg555, Arg615, Tyr655
39	Gln493, Thr538, Arg615, Tyr655
40	Gln493, Thr538, Glu539, Tyr587, Arg615, Tyr655

*samples in test set.