

Table S3. Scaffold-hopping candidates for hIKK-2 inhibition predicted by our study.

Cluster 1 hits				Cluster 2 hits				Cluster 3 hits							
	PB	Shape	Combo		PB	Shape	Combo		PB	Shape	Combo				
ZINC12410246	0.699	0.528	1.227	ZINC08298038	0.597	0.349	0.946	ZINC00485744	0.723	0.480	1.203	ZINC00071662	0.536	0.665	1.201
ZINC04222236	0.727	0.498	1.224	ZINC08298000	0.633	0.308	0.941	ZINC03838566	0.704	0.475	1.179	ZINC00138773	0.742	0.438	1.180
ZINC08299593	0.723	0.462	1.185	ZINC04260050	0.609	0.325	0.934	ZINC00346993	0.585	0.586	1.170	ZINC00525792	0.727	0.435	1.162
ZINC08300807	0.606	0.560	1.166	ZINC03851724	0.520	0.414	0.933	ZINC00094845	0.580	0.587	1.167	ZINC03842171	0.424	0.474	0.898
ZINC08300706	0.697	0.460	1.157	ZINC05415683	0.585	0.345	0.929	ZINC00485534	0.651	0.508	1.159	ZINC00126518	0.627	0.444	1.071
ZINC05730981	0.682	0.451	1.134	ZINC08635779	0.579	0.349	0.928	ZINC13424993	0.544	0.613	1.157	ZINC00040813	0.228	0.662	0.890
ZINC08299517	0.645	0.489	1.134	ZINC08299591	0.516	0.412	0.928	ZINC11616540	0.709	0.433	1.141	ZINC05224529	0.511	0.376	0.888
ZINC04235841	0.626	0.498	1.124	ZINC08299896	0.497	0.429	0.926	ZINC00227258	0.660	0.477	1.137	ZINC00517451	0.381	0.504	0.885
ZINC05433728	0.638	0.467	1.105	ZINC08298463	0.580	0.343	0.924	ZINC00485860	0.623	0.510	1.132	ZINC01317724	0.224	0.660	0.884
ZINC08298452	0.716	0.382	1.098	ZINC00058208	0.261	0.661	0.923	ZINC08762138	0.497	0.623	1.120	ZINC02604995	0.600	0.284	0.883
ZINC08635299	0.677	0.414	1.091	ZINC08299131	0.538	0.378	0.917	ZINC00036355	0.626	0.487	1.113	ZINC03786448	0.250	0.633	0.883
ZINC08299522	0.632	0.458	1.091	ZINC08297955	0.444	0.472	0.917	ZINC12657772	0.505	0.607	1.112	ZINC05224397	0.553	0.329	0.881
ZINC12604815	0.542	0.547	1.089	ZINC08300143	0.629	0.287	0.916	ZINC02124459	0.562	0.541	1.104	ZINC00039884	0.342	0.536	0.878
ZINC08623382	0.618	0.457	1.075	ZINC03841142	0.575	0.341	0.915	ZINC04081954	0.524	0.564	1.088	ZINC12604997	0.615	0.261	0.876
ZINC08298456	0.627	0.441	1.068	ZINC00195221	0.491	0.424	0.915	ZINC08738350	0.566	0.521	1.087	ZINC11616541	0.598	0.276	0.875
ZINC05433715	0.601	0.466	1.068	ZINC02023740	0.175	0.739	0.914	ZINC08762259	0.510	0.573	1.082	ZINC02090323	0.423	0.452	0.875
ZINC03841282	0.686	0.380	1.066	ZINC01204686	0.644	0.267	0.911	ZINC00388584	0.665	0.415	1.080	ZINC03852423	0.444	0.430	0.874
ZINC04028468	0.633	0.429	1.062	ZINC08298449	0.588	0.321	0.910	ZINC00130101	0.614	0.464	1.078	ZINC02027203	0.300	0.573	0.874
ZINC08296915	0.695	0.361	1.056	ZINC04082733	0.528	0.381	0.909	ZINC00180655	0.603	0.471	1.074	ZINC03898167	0.461	0.410	0.871
ZINC04222674	0.515	0.540	1.055	ZINC01669260	0.512	0.397	0.909	ZINC01646905	0.584	0.490	1.074	ZINC13424994	0.406	0.463	0.868
ZINC08299611	0.629	0.425	1.054	ZINC04222254	0.483	0.426	0.909	ZINC01102508	0.606	0.459	1.065	ZINC13300696	0.492	0.368	0.868
ZINC04235840	0.629	0.420	1.049	ZINC08299700	0.595	0.313	0.907	ZINC04027790	0.524	0.536	1.060	ZINC01081585	0.400	0.460	0.860
ZINC08300121	0.641	0.407	1.048	ZINC03841141	0.595	0.307	0.902	ZINC12318138	0.590	0.462	1.052	ZINC13306051	0.488	0.371	0.859
ZINC03841201	0.608	0.439	1.048	ZINC08298553	0.563	0.337	0.901	ZINC01854651	0.572	0.475	1.048	ZINC03984208	0.382	0.476	0.858
ZINC08297952	0.648	0.394	1.043	ZINC08296886	0.327	0.573	0.900	ZINC00044054	0.541	0.505	1.046	ZINC01665127	0.337	0.519	0.856
ZINC05433681	0.637	0.403	1.040	ZINC08298004	0.441	0.458	0.899	ZINC00517161	0.582	0.461	1.044	ZINC00369448	0.445	0.410	0.855
ZINC04235837	0.603	0.424	1.027	ZINC05397696	0.467	0.432	0.898	ZINC01321570	0.563	0.478	1.041	ZINC05224220	0.404	0.449	0.853
ZINC08299759	0.530	0.490	1.020	ZINC12604970	0.593	0.303	0.896	ZINC04104779	0.547	0.489	1.036	ZINC01556769	0.245	0.606	0.851
ZINC04260104	0.648	0.370	1.018	ZINC00485710	0.468	0.427	0.896	ZINC01950801	0.631	0.401	1.031				
ZINC08296937	0.696	0.319	1.015	ZINC04235971	0.415	0.481	0.896	ZINC00485558	0.717	0.313	1.029				
ZINC08298035	0.662	0.346	1.009	ZINC04236053	0.519	0.373	0.892	ZINC13425030	0.590	0.436	1.027				
ZINC00460033	0.504	0.500	1.004	ZINC08296889	0.415	0.476	0.891	ZINC12318136	0.585	0.442	1.027				
ZINC04235839	0.618	0.379	0.997	ZINC00058225	0.231	0.660	0.891	ZINC12656099	0.531	0.493	1.024				
ZINC04222682	0.591	0.403	0.993	ZINC05434223	0.476	0.412	0.888	ZINC02124460	0.583	0.438	1.021				
ZINC08254138	0.661	0.331	0.992	ZINC08254330	0.641	0.243	0.883	ZINC04032263	0.531	0.488	1.019				
ZINC00035451	0.679	0.313	0.991	ZINC08299765	0.364	0.518	0.882	ZINC00485559	0.505	0.504	1.009				
ZINC05396170	0.589	0.402	0.991	ZINC08298536	0.519	0.362	0.881	ZINC13425093	0.670	0.336	1.006				
ZINC08254141	0.678	0.312	0.990	ZINC08299629	0.543	0.335	0.878	ZINC01842501	0.545	0.457	1.002				
ZINC03838691	0.598	0.390	0.989	ZINC05433729	0.385	0.492	0.877	ZINC03978029	0.527	0.473	0.999				
ZINC00485569	0.604	0.381	0.986	ZINC05279694	0.487	0.384	0.871	ZINC02372275	0.631	0.366	0.996				
ZINC08299569	0.589	0.396	0.985	ZINC04235956	0.581	0.288	0.869	ZINC13306038	0.456	0.540	0.996				
ZINC00058275	0.329	0.657	0.985	ZINC08296677	0.487	0.382	0.869	ZINC12655829	0.518	0.476	0.994				
ZINC08296946	0.689	0.295	0.984	ZINC04236052	0.495	0.373	0.868	ZINC05224095	0.446	0.543	0.989				
ZINC04236050	0.505	0.479	0.984	ZINC05433716	0.381	0.487	0.868	ZINC13425031	0.593	0.392	0.985				
ZINC04222681	0.591	0.391	0.982	ZINC04236049	0.501	0.365	0.866	ZINC12658812	0.516	0.462	0.979				
ZINC00035452	0.592	0.388	0.979	ZINC08300122	0.496	0.370	0.866	ZINC03683886	0.559	0.419	0.977				
ZINC08300479	0.535	0.443	0.978	ZINC01601221	0.204	0.662	0.866	ZINC00517162	0.533	0.445	0.977				
ZINC08299635	0.641	0.336	0.977	ZINC08298097	0.638	0.227	0.865	ZINC01321569	0.603	0.362	0.965				
ZINC08300733	0.613	0.363	0.976	ZINC04235961	0.592	0.272	0.864	ZINC08552275	0.566	0.398	0.964				
ZINC12604292	0.547	0.424	0.971	ZINC08254273	0.509	0.352	0.861	ZINC04027791	0.414	0.544	0.958				
ZINC03838674	0.578	0.390	0.968	ZINC16946275	0.504	0.357	0.861	ZINC01679223	0.293	0.661	0.954				
ZINC08254375	0.562	0.405	0.966	ZINC04236055	0.517	0.343	0.860	ZINC12657776	0.565	0.387	0.952				
ZINC08298030	0.668	0.296	0.963	ZINC04236051	0.509	0.350	0.859	ZINC12428234	0.655	0.291	0.946				
ZINC00485709	0.396	0.565	0.961	ZINC04235957	0.582	0.274	0.856	ZINC08762235	0.471	0.471	0.942				
ZINC05433719	0.494	0.462	0.957	ZINC08298002	0.555	0.301	0.856	ZINC03838563	0.569	0.369	0.939				
ZINC04260127	0.594	0.360	0.954	ZINC12604752	0.439	0.416	0.855	ZINC08299557	0.429	0.507	0.937				
ZINC08298652	0.570	0.382	0.953	ZINC03841193	0.256	0.598	0.854	ZINC12661595	0.522	0.414	0.936				
ZINC08254451	0.664	0.287	0.951	ZINC04236054	0.503	0.350	0.853	ZINC03898166	0.475	0.457	0.932				
ZINC04260095	0.624	0.327	0.951	ZINC00048191	0.498	0.355	0.853	ZINC12660883	0.664	0.263	0.928				
ZINC08298659	0.619	0.328	0.947	ZINC08299638	0.616	0.235	0.851	ZINC08740325	0.499	0.428	0.927				

The ZINC codes for the 246 hit molecules predicted to inhibit hIKK-2 and belonging to clusters consisting exclusively of natural products. For each hit molecule, the best results of the shape and electrostatic-potential comparisons with 43 poses from 21 known hIKK-2 inhibitors (see Table S1) is shown. Thus, the Tanimoto values for the comparison between the electrostatic potentials of the molecules (using an outer dielectric of 80) are shown in the *PB* columns, whereas the values for the comparison between shapes are shown in the *Shape* columns. The sum of the PB and Shape values is reported in the *Combo* columns. Hits from each cluster are sorted according their decreasing combo value. All of these hit molecules are scaffold-hopping candidates for hIKK-2 inhibition because the Tanimoto similarities between their MOLPRINT 2D fingerprints and those from the hIKK-2 inhibitors in Tables S1 and S2 are quite low. ZINC00058225, ZINC01669260 and ZINC16946275 from Cluster 1, ZINC03683886 from Cluster 2, and ZINC03871389 from Cluster 3 were selected to experimentally test the success rate of our predictions using an *in vitro* assay (in bold in Table S3). The results of this experiment showed that three out of the five molecules (*i.e.*, ZINC01669260 from Cluster 1, ZINC03683886 from Cluster 2 and ZINC03871389 from Cluster 3) inhibited hIKK-2, with IC₅₀ values ranging from 183.8 to 3,325 μM.