

Supporting Information

QM/QM Docking Method Based on the Variational Finite Localized Molecular Orbital Approximation

Victor M. Anisimov,¹ Vladislav L. Bugaenko²

¹FQS Poland Ltd., Starowislna 13, Krakow 31-038, Poland

²Quantum Biochemistry Group, Konstantina Fedina-3/24, 105215 Moscow, Russian

Federation

¹Correspondence to: V. M. Anisimov; (+48 12) 429-4345; fax: (+48 12) 429-6124; e-mail: v.anisimov@fqs.pl

Table S1. ZINC IDs of 1000 ligand structures used in the QM scoring test of different buffer zones and in the first stage QM docking.

Local ID	ZINC ID ^a	Local ID	ZINC ID ^a	Local ID	ZINC ID ^a	Local ID	ZINC ID ^a
3	ZINC00030442	2469	ZINC00030757	4980	ZINC00031079	4980	ZINC00031079
8	ZINC00030443	2495	ZINC00030759	4997	ZINC00031081	4997	ZINC00031081
23	ZINC00030444	2507	ZINC00030760	4998	ZINC00031083	4998	ZINC00031083
33	ZINC00030445	2513	ZINC00030761	5006	ZINC00031085	5006	ZINC00031085
40	ZINC00030446	2527	ZINC00030762	5014	ZINC00031087	5014	ZINC00031087
46	ZINC00030447	2528	ZINC00030763	5023	ZINC00031089	5023	ZINC00031089
60	ZINC00030448	2545	ZINC00030764	5033	ZINC00031091	5033	ZINC00031091
69	ZINC00030449	2548	ZINC00030766	5043	ZINC00031093	5043	ZINC00031093
81	ZINC00030450	2569	ZINC00030768	5053	ZINC00031095	5053	ZINC00031095
84	ZINC00030451	2581	ZINC00030770	5062	ZINC00031097	5062	ZINC00031097
96	ZINC00030452	2591	ZINC00030771	5077	ZINC00031100	5077	ZINC00031100
111	ZINC00030453	2613	ZINC00030773	5083	ZINC00031101	5083	ZINC00031101
116	ZINC00030454	2621	ZINC00030774	5095	ZINC00031103	5095	ZINC00031103
131	ZINC00030455	2623	ZINC00030775	5099	ZINC00031105	5099	ZINC00031105
141	ZINC00030456	2635	ZINC00030776	5109	ZINC00031107	5109	ZINC00031107
149	ZINC00030457	2643	ZINC00030777	5124	ZINC00031109	5124	ZINC00031109
151	ZINC00030458	2658	ZINC00030778	5126	ZINC00031111	5126	ZINC00031111
162	ZINC00030459	2671	ZINC00030779	5135	ZINC00031113	5135	ZINC00031113
177	ZINC00030460	2677	ZINC00030780	5147	ZINC00031115	5147	ZINC00031115
189	ZINC00030461	2685	ZINC00030781	5160	ZINC00031117	5160	ZINC00031117
195	ZINC00030462	2700	ZINC00030783	5172	ZINC00031119	5172	ZINC00031119
207	ZINC00030464	2708	ZINC00030784	5175	ZINC00031121	5175	ZINC00031121
211	ZINC00030475	2716	ZINC00030785	5183	ZINC00031123	5183	ZINC00031123
229	ZINC00030476	2722	ZINC00030786	5186	ZINC00031125	5186	ZINC00031125
238	ZINC00030477	2735	ZINC00030787	5202	ZINC00031127	5202	ZINC00031127
249	ZINC00030478	2746	ZINC00030788	5209	ZINC00031129	5209	ZINC00031129
254	ZINC00030479	2755	ZINC00030789	5214	ZINC00031131	5214	ZINC00031131
269	ZINC00030480	2762	ZINC00030790	5224	ZINC00031134	5224	ZINC00031134
281	ZINC00030482	2771	ZINC00030791	5233	ZINC00031135	5233	ZINC00031135
293	ZINC00030483	2780	ZINC00030792	5247	ZINC00031137	5247	ZINC00031137
302	ZINC00030484	2796	ZINC00030793	5254	ZINC00031139	5254	ZINC00031139
310	ZINC00030485	2805	ZINC00030794	5264	ZINC00031141	5264	ZINC00031141

318	ZINC00030487	2814	ZINC00030795	5273	ZINC00031143	5273	ZINC00031143
329	ZINC00030488	2823	ZINC00030796	5281	ZINC00031145	5281	ZINC00031145
337	ZINC00030489	2833	ZINC00030797	5290	ZINC00031147	5290	ZINC00031147
345	ZINC00030490	2847	ZINC00030798	5298	ZINC00031149	5298	ZINC00031149
358	ZINC00030491	2852	ZINC00030799	5301	ZINC00031153	5301	ZINC00031153
368	ZINC00030492	2865	ZINC00030800	5310	ZINC00031156	5310	ZINC00031156
382	ZINC00030493	2874	ZINC00030801	5324	ZINC00031160	5324	ZINC00031160
385	ZINC00030494	2878	ZINC00030802	5332	ZINC00031167	5332	ZINC00031167
395	ZINC00030496	2894	ZINC00030803	5350	ZINC00031168	5350	ZINC00031168
409	ZINC00030497	2907	ZINC00030804	5367	ZINC00031169	5367	ZINC00031169
412	ZINC00030498	2910	ZINC00030805	5380	ZINC00031170	5380	ZINC00031170
419	ZINC00030499	2922	ZINC00030806	5391	ZINC00031171	5391	ZINC00031171
427	ZINC00030500	2937	ZINC00030807	5396	ZINC00031172	5396	ZINC00031172
438	ZINC00030501	2946	ZINC00030808	5409	ZINC00031173	5409	ZINC00031173
447	ZINC00030502	2957	ZINC00030809	5420	ZINC00031174	5420	ZINC00031174
457	ZINC00030503	2959	ZINC00030810	5429	ZINC00031176	5429	ZINC00031176
465	ZINC00030504	2970	ZINC00030811	5432	ZINC00031177	5432	ZINC00031177
468	ZINC00030505	2973	ZINC00030812	5441	ZINC00031179	5441	ZINC00031179
483	ZINC00030506	2985	ZINC00030813	5454	ZINC00031180	5454	ZINC00031180
490	ZINC00030507	2993	ZINC00030814	5464	ZINC00031181	5464	ZINC00031181
497	ZINC00030508	2997	ZINC00030815	5471	ZINC00031183	5471	ZINC00031183
509	ZINC00030509	3013	ZINC00030816	5484	ZINC00031187	5484	ZINC00031187
518	ZINC00030512	3020	ZINC00030817	5495	ZINC00031203	5495	ZINC00031203
531	ZINC00030513	3033	ZINC00030818	5519	ZINC00031204	5519	ZINC00031204
544	ZINC00030516	3036	ZINC00030819	5525	ZINC00031205	5525	ZINC00031205
555	ZINC00030519	3048	ZINC00030820	5547	ZINC00031206	5547	ZINC00031206
581	ZINC00030521	3056	ZINC00030821	5554	ZINC00031210	5554	ZINC00031210
586	ZINC00030522	3071	ZINC00030823	5576	ZINC00031214	5576	ZINC00031214
599	ZINC00030523	3072	ZINC00030824	5589	ZINC00031232	5589	ZINC00031232
610	ZINC00030524	3078	ZINC00030825	5605	ZINC00031233	5605	ZINC00031233
614	ZINC00030525	3085	ZINC00030826	5612	ZINC00031234	5612	ZINC00031234
629	ZINC00030526	3096	ZINC00030827	5626	ZINC00031236	5626	ZINC00031236
639	ZINC00030527	3104	ZINC00030828	5629	ZINC00031237	5629	ZINC00031237
646	ZINC00030528	3123	ZINC00030829	5634	ZINC00046256	5634	ZINC00046256
652	ZINC00030529	3133	ZINC00030830	5645	ZINC00046257	5645	ZINC00046257
661	ZINC00030530	3142	ZINC00030831	5655	ZINC00046261	5655	ZINC00046261
672	ZINC00030531	3149	ZINC00030832	5662	ZINC00046262	5662	ZINC00046262
677	ZINC00030532	3160	ZINC00030833	5674	ZINC00046266	5674	ZINC00046266
687	ZINC00030533	3166	ZINC00030834	5681	ZINC00046268	5681	ZINC00046268
700	ZINC00030536	3174	ZINC00030835	5695	ZINC00046270	5695	ZINC00046270
709	ZINC00030537	3185	ZINC00030836	5702	ZINC00046272	5702	ZINC00046272
721	ZINC00030538	3190	ZINC00030837	5712	ZINC00046274	5712	ZINC00046274
730	ZINC00030539	3201	ZINC00030838	5721	ZINC00046276	5721	ZINC00046276
740	ZINC00030540	3215	ZINC00030839	5730	ZINC00046278	5730	ZINC00046278
748	ZINC00030541	3224	ZINC00030840	5738	ZINC00046279	5738	ZINC00046279
763	ZINC00030543	3230	ZINC00030841	5748	ZINC00046280	5748	ZINC00046280

775	ZINC00030544	3238	ZINC00030843	5754	ZINC00046282	5754	ZINC00046282
791	ZINC00030545	3240	ZINC00030844	5765	ZINC00046284	5765	ZINC00046284
797	ZINC00030546	3255	ZINC00030846	5779	ZINC00046285	5779	ZINC00046285
809	ZINC00030547	3262	ZINC00030851	5790	ZINC00046287	5790	ZINC00046287
828	ZINC00030549	3278	ZINC00030852	5802	ZINC00046291	5802	ZINC00046291
832	ZINC00030550	3284	ZINC00030854	5813	ZINC00046295	5813	ZINC00046295
851	ZINC00030551	3292	ZINC00030856	5824	ZINC00046297	5824	ZINC00046297
860	ZINC00030552	3302	ZINC00030858	5837	ZINC00046307	5837	ZINC00046307
865	ZINC00030553	3312	ZINC00030859	5855	ZINC00046311	5855	ZINC00046311
876	ZINC00030554	3322	ZINC00030860	5862	ZINC00046313	5862	ZINC00046313
885	ZINC00030555	3331	ZINC00030861	5870	ZINC00046315	5870	ZINC00046315
893	ZINC00030556	3336	ZINC00030862	5871	ZINC00046317	5871	ZINC00046317
910	ZINC00030557	3345	ZINC00030863	5882	ZINC00046319	5882	ZINC00046319
911	ZINC00030558	3353	ZINC00030864	5892	ZINC00046323	5892	ZINC00046323
922	ZINC00030559	3363	ZINC00030865	5898	ZINC00046325	5898	ZINC00046325
940	ZINC00030561	3372	ZINC00030866	5909	ZINC00046330	5909	ZINC00046330
944	ZINC00030562	3374	ZINC00030867	5917	ZINC00046332	5917	ZINC00046332
952	ZINC00030563	3390	ZINC00030869	5928	ZINC00046334	5928	ZINC00046334
963	ZINC00030564	3404	ZINC00030871	5943	ZINC00046336	5943	ZINC00046336
977	ZINC00030565	3421	ZINC00030872	5946	ZINC00046338	5946	ZINC00046338
986	ZINC00030566	3423	ZINC00030873	5948	ZINC00046340	5948	ZINC00046340
992	ZINC00030567	3435	ZINC00030874	5960	ZINC00046342	5960	ZINC00046342
1003	ZINC00030568	3450	ZINC00030875	5967	ZINC00046344	5967	ZINC00046344
1016	ZINC00030569	3459	ZINC00030876	5976	ZINC00046346	5976	ZINC00046346
1026	ZINC00030571	3465	ZINC00030877	5985	ZINC00046348	5985	ZINC00046348
1034	ZINC00030572	3478	ZINC00030878	5992	ZINC00046352	5992	ZINC00046352
1049	ZINC00030577	3482	ZINC00030879	6005	ZINC00046354	6005	ZINC00046354
1050	ZINC00030578	3491	ZINC00030880	6008	ZINC00046355	6008	ZINC00046355
1066	ZINC00030579	3507	ZINC00030881	6013	ZINC00046356	6013	ZINC00046356
1073	ZINC00030580	3513	ZINC00030882	6019	ZINC00046358	6019	ZINC00046358
1085	ZINC00030581	3518	ZINC00030883	6027	ZINC00046359	6027	ZINC00046359
1096	ZINC00030582	3533	ZINC00030884	6037	ZINC00046360	6037	ZINC00046360
1101	ZINC00030583	3538	ZINC00030885	6048	ZINC00046361	6048	ZINC00046361
1118	ZINC00030584	3552	ZINC00030886	6056	ZINC00046362	6056	ZINC00046362
1122	ZINC00030585	3561	ZINC00030887	6060	ZINC00046364	6060	ZINC00046364
1138	ZINC00030586	3568	ZINC00030888	6067	ZINC00046365	6067	ZINC00046365
1141	ZINC00030587	3578	ZINC00030889	6073	ZINC00046367	6073	ZINC00046367
1152	ZINC00030588	3586	ZINC00030890	6085	ZINC00046369	6085	ZINC00046369
1160	ZINC00030589	3599	ZINC00030891	6093	ZINC00046371	6093	ZINC00046371
1169	ZINC00030590	3612	ZINC00030892	6103	ZINC00046373	6103	ZINC00046373
1188	ZINC00030591	3623	ZINC00030893	6111	ZINC00046374	6111	ZINC00046374
1193	ZINC00030592	3629	ZINC00030894	6113	ZINC00046376	6113	ZINC00046376
1199	ZINC00030593	3638	ZINC00030895	6120	ZINC00046378	6120	ZINC00046378
1209	ZINC00030594	3647	ZINC00030896	6131	ZINC00046379	6131	ZINC00046379
1226	ZINC00030595	3659	ZINC00030897	6142	ZINC00046382	6142	ZINC00046382
1234	ZINC00030596	3669	ZINC00030898	6145	ZINC00046383	6145	ZINC00046383

1240	ZINC00030597	3690	ZINC00030900	6160	ZINC00046385	6160	ZINC00046385
1261	ZINC00030599	3696	ZINC00030901	6167	ZINC00046387	6167	ZINC00046387
1273	ZINC00030600	3706	ZINC00030902	6178	ZINC00046391	6178	ZINC00046391
1283	ZINC00030601	3712	ZINC00030903	6187	ZINC00046393	6187	ZINC00046393
1293	ZINC00030602	3723	ZINC00030904	6202	ZINC00046395	6202	ZINC00046395
1304	ZINC00030604	3737	ZINC00030905	6213	ZINC00046397	6213	ZINC00046397
1312	ZINC00030605	3748	ZINC00030906	6230	ZINC00046403	6230	ZINC00046403
1323	ZINC00030606	3754	ZINC00030907	6239	ZINC00046405	6239	ZINC00046405
1324	ZINC00030607	3761	ZINC00030909	6250	ZINC00046407	6250	ZINC00046407
1337	ZINC00030608	3770	ZINC00030910	6256	ZINC00046411	6256	ZINC00046411
1346	ZINC00030610	3784	ZINC00030911	6272	ZINC00046412	6272	ZINC00046412
1362	ZINC00030611	3790	ZINC00030912	6273	ZINC00046413	6273	ZINC00046413
1380	ZINC00030619	3799	ZINC00030913	6286	ZINC00046415	6286	ZINC00046415
1392	ZINC00030620	3816	ZINC00030914	6296	ZINC00046416	6296	ZINC00046416
1408	ZINC00030622	3821	ZINC00030915	6300	ZINC00046417	6300	ZINC00046417
1419	ZINC00030623	3832	ZINC00030916	6310	ZINC00046418	6310	ZINC00046418
1430	ZINC00030630	3840	ZINC00030917	6321	ZINC00046419	6321	ZINC00046419
1434	ZINC00030631	3848	ZINC00030918	6330	ZINC00046420	6330	ZINC00046420
1452	ZINC00030636	3855	ZINC00030919	6338	ZINC00046422	6338	ZINC00046422
1457	ZINC00030637	3865	ZINC00030920	6354	ZINC00046424	6354	ZINC00046424
1468	ZINC00030638	3884	ZINC00030923	6356	ZINC00046425	6356	ZINC00046425
1495	ZINC00030640	3885	ZINC00030925	6369	ZINC00046427	6369	ZINC00046427
1505	ZINC00030641	3902	ZINC00030926	6375	ZINC00046429	6375	ZINC00046429
1513	ZINC00030642	3910	ZINC00030927	6394	ZINC00046433	6394	ZINC00046433
1519	ZINC00030643	3917	ZINC00030928	6415	ZINC00046436	6415	ZINC00046436
1530	ZINC00030644	3928	ZINC00030929	6430	ZINC00046438	6430	ZINC00046438
1543	ZINC00030645	3936	ZINC00030930	6437	ZINC00046440	6437	ZINC00046440
1551	ZINC00030646	3949	ZINC00030931	6447	ZINC00046442	6447	ZINC00046442
1558	ZINC00030647	3950	ZINC00030932	6467	ZINC00046446	6467	ZINC00046446
1575	ZINC00030648	3967	ZINC00030933	6476	ZINC00046447	6476	ZINC00046447
1579	ZINC00030649	3975	ZINC00030935	6477	ZINC00046448	6477	ZINC00046448
1586	ZINC00030650	3986	ZINC00030936	6487	ZINC00046450	6487	ZINC00046450
1592	ZINC00030651	3993	ZINC00030937	6504	ZINC00046452	6504	ZINC00046452
1607	ZINC00030653	4007	ZINC00030938	6513	ZINC00046453	6513	ZINC00046453
1616	ZINC00030654	4013	ZINC00030939	6525	ZINC00046457	6525	ZINC00046457
1619	ZINC00030655	4022	ZINC00030941	6532	ZINC00046459	6532	ZINC00046459
1637	ZINC00030656	4037	ZINC00030942	6542	ZINC00046462	6542	ZINC00046462
1645	ZINC00030657	4046	ZINC00030943	6558	ZINC00046463	6558	ZINC00046463
1657	ZINC00030658	4052	ZINC00030944	6563	ZINC00046464	6563	ZINC00046464
1667	ZINC00030659	4061	ZINC00030945	6566	ZINC00046466	6566	ZINC00046466
1681	ZINC00030661	4078	ZINC00030946	6581	ZINC00046468	6581	ZINC00046468
1694	ZINC00030662	4085	ZINC00030947	6585	ZINC00046469	6585	ZINC00046469
1705	ZINC00030663	4098	ZINC00030948	6601	ZINC00046471	6601	ZINC00046471
1715	ZINC00030664	4105	ZINC00030949	6602	ZINC00046472	6602	ZINC00046472
1724	ZINC00030665	4122	ZINC00030952	6612	ZINC00046474	6612	ZINC00046474
1736	ZINC00030666	4132	ZINC00030953	6633	ZINC00046477	6633	ZINC00046477

1742	ZINC00030667	4157	ZINC00030955	6644	ZINC00046478	6644	ZINC00046478
1756	ZINC00030668	4168	ZINC00030956	6647	ZINC00046479	6647	ZINC00046479
1766	ZINC00030669	4173	ZINC00030957	6660	ZINC00046481	6660	ZINC00046481
1771	ZINC00030670	4181	ZINC00030958	6665	ZINC00046482	6665	ZINC00046482
1786	ZINC00030671	4194	ZINC00030959	6674	ZINC00046484	6674	ZINC00046484
1791	ZINC00030672	4206	ZINC00030960	6689	ZINC00046488	6689	ZINC00046488
1804	ZINC00030673	4213	ZINC00030961	6694	ZINC00046490	6694	ZINC00046490
1813	ZINC00030674	4221	ZINC00030962	6699	ZINC00046492	6699	ZINC00046492
1822	ZINC00030675	4240	ZINC00030964	6708	ZINC00046494	6708	ZINC00046494
1836	ZINC00030676	4244	ZINC00030965	6720	ZINC00046495	6720	ZINC00046495
1841	ZINC00030677	4259	ZINC00030966	6725	ZINC00046497	6725	ZINC00046497
1849	ZINC00030678	4262	ZINC00030967	6737	ZINC00046498	6737	ZINC00046498
1872	ZINC00030680	4272	ZINC00030970	6753	ZINC00046499	6753	ZINC00046499
1883	ZINC00030681	4286	ZINC00030971	6762	ZINC00046500	6762	ZINC00046500
1893	ZINC00030682	4289	ZINC00030974	6765	ZINC00046505	6765	ZINC00046505
1897	ZINC00030683	4325	ZINC00030978	6777	ZINC00046507	6777	ZINC00046507
1906	ZINC00030684	4329	ZINC00030981	6792	ZINC00046508	6792	ZINC00046508
1918	ZINC00030685	4340	ZINC00030982	6794	ZINC00046509	6794	ZINC00046509
1925	ZINC00030686	4349	ZINC00030983	6797	ZINC00046510	6797	ZINC00046510
1934	ZINC00030687	4362	ZINC00030984	6810	ZINC00046511	6810	ZINC00046511
1938	ZINC00030688	4374	ZINC00030985	6820	ZINC00046512	6820	ZINC00046512
1951	ZINC00030689	4383	ZINC00030986	6823	ZINC00046513	6823	ZINC00046513
1958	ZINC00030690	4408	ZINC00030988	6831	ZINC00046515	6831	ZINC00046515
1962	ZINC00030691	4418	ZINC00030989	6839	ZINC00046517	6839	ZINC00046517
1974	ZINC00030692	4424	ZINC00030990	6851	ZINC00046519	6851	ZINC00046519
1985	ZINC00030693	4447	ZINC00030994	6862	ZINC00046520	6862	ZINC00046520
1990	ZINC00030694	4448	ZINC00030995	6865	ZINC00046521	6865	ZINC00046521
1998	ZINC00030695	4465	ZINC00030996	6874	ZINC00046523	6874	ZINC00046523
2006	ZINC00030696	4477	ZINC00030997	6884	ZINC00046524	6884	ZINC00046524
2017	ZINC00030698	4485	ZINC00031001	6892	ZINC00046525	6892	ZINC00046525
2024	ZINC00030699	4490	ZINC00031002	6900	ZINC00046526	6900	ZINC00046526
2033	ZINC00030700	4500	ZINC00031003	6908	ZINC00046528	6908	ZINC00046528
2037	ZINC00030701	4508	ZINC00031004	6911	ZINC00046530	6911	ZINC00046530
2051	ZINC00030702	4536	ZINC00031006	6920	ZINC00046531	6920	ZINC00046531
2056	ZINC00030703	4541	ZINC00031007	6930	ZINC00046533	6930	ZINC00046533
2071	ZINC00030704	4554	ZINC00031008	6933	ZINC00046534	6933	ZINC00046534
2077	ZINC00030705	4558	ZINC00031009	6943	ZINC00046535	6943	ZINC00046535
2092	ZINC00030706	4574	ZINC00031010	6961	ZINC00046537	6961	ZINC00046537
2094	ZINC00030707	4578	ZINC00031011	6965	ZINC00046539	6965	ZINC00046539
2107	ZINC00030708	4589	ZINC00031012	6975	ZINC00046540	6975	ZINC00046540
2116	ZINC00030709	4592	ZINC00031014	6981	ZINC00046541	6981	ZINC00046541
2125	ZINC00030710	4603	ZINC00031015	7001	ZINC00046549	7001	ZINC00046549
2140	ZINC00030711	4612	ZINC00031016	7011	ZINC00046550	7011	ZINC00046550
2149	ZINC00030712	4625	ZINC00031017	7024	ZINC00046551	7024	ZINC00046551
2152	ZINC00030713	4634	ZINC00031018	7027	ZINC00046552	7027	ZINC00046552
2165	ZINC00030714	4648	ZINC00031019	7041	ZINC00046553	7041	ZINC00046553

2176	ZINC00030715	4651	ZINC00031021	7048	ZINC00046554	7048	ZINC00046554
2180	ZINC00030717	4666	ZINC00031022	7058	ZINC00046557	7058	ZINC00046557
2189	ZINC00030718	4670	ZINC00031023	7073	ZINC00046558	7073	ZINC00046558
2197	ZINC00030719	4685	ZINC00031024	7083	ZINC00046559	7083	ZINC00046559
2213	ZINC00030720	4695	ZINC00031025	7090	ZINC00046560	7090	ZINC00046560
2223	ZINC00030721	4708	ZINC00031026	7101	ZINC00046561	7101	ZINC00046561
2225	ZINC00030722	4718	ZINC00031027	7114	ZINC00046563	7114	ZINC00046563
2243	ZINC00030723	4724	ZINC00031028	7119	ZINC00046566	7119	ZINC00046566
2251	ZINC00030724	4730	ZINC00031029	7126	ZINC00046567	7126	ZINC00046567
2257	ZINC00030725	4745	ZINC00031030	7141	ZINC00046569	7141	ZINC00046569
2273	ZINC00030726	4756	ZINC00031031	7145	ZINC00046571	7145	ZINC00046571
2278	ZINC00030727	4762	ZINC00031032	7159	ZINC00046572	7159	ZINC00046572
2289	ZINC00030728	4770	ZINC00031033	7168	ZINC00046573	7168	ZINC00046573
2295	ZINC00030729	4782	ZINC00031035	7175	ZINC00046574	7175	ZINC00046574
2314	ZINC00030730	4795	ZINC00031037	7184	ZINC00046575	7184	ZINC00046575
2319	ZINC00030731	4810	ZINC00031041	7206	ZINC00046578	7206	ZINC00046578
2327	ZINC00030734	4817	ZINC00031043	7215	ZINC00046579	7215	ZINC00046579
2331	ZINC00030735	4824	ZINC00031045	7222	ZINC00046580	7222	ZINC00046580
2332	ZINC00030736	4842	ZINC00031049	7231	ZINC00046581	7231	ZINC00046581
2336	ZINC00030738	4851	ZINC00031051	7233	ZINC00046582	7233	ZINC00046582
2337	ZINC00030739	4854	ZINC00031053	7250	ZINC00046583	7250	ZINC00046583
2341	ZINC00030740	4860	ZINC00031055	7255	ZINC00046584	7255	ZINC00046584
2346	ZINC00030741	4871	ZINC00031057	7258	ZINC00046586	7258	ZINC00046586
2354	ZINC00030742	4886	ZINC00031059	7274	ZINC00046587	7274	ZINC00046587
2362	ZINC00030743	4896	ZINC00031061	7296	ZINC00046589	7296	ZINC00046589
2375	ZINC00030746	4904	ZINC00031063	7299	ZINC00046591	7299	ZINC00046591
2382	ZINC00030747	4911	ZINC00031065	7311	ZINC00046592	7311	ZINC00046592
2393	ZINC00030748	4920	ZINC00031067	7321	ZINC00046593	7321	ZINC00046593
2411	ZINC00030751	4930	ZINC00031069	7331	ZINC00046594	7331	ZINC00046594
2427	ZINC00030752	4945	ZINC00031071	7336	ZINC00046595	7336	ZINC00046595
2430	ZINC00030753	4948	ZINC00031073	7343	ZINC00046596	7343	ZINC00046596
2441	ZINC00030754	4959	ZINC00031075	7360	ZINC00046597	7360	ZINC00046597
2451	ZINC00030755	4967	ZINC00031077	7367	ZINC00046603	7367	ZINC00046603
2458	ZINC00030756	4971	ZINC00031078	7376	ZINC00046604	7376	ZINC00046604

^a <http://zinc.docking.org>

Table S2. ZINC IDs of 100 ligand structures used in the second stage QM docking

Local ID	ZINC ID ^a	Local ID	ZINC ID ^a	Local ID	ZINC ID ^a	Local ID	ZINC ID ^a
468	ZINC00030505	3669	ZINC00030898	5721	ZINC00046276	8357	ZINC00046827
581	ZINC00030521	3723	ZINC00030904	5871	ZINC00046317	8412	ZINC00046835
629	ZINC00030526	3754	ZINC00030907	6430	ZINC00046438	8467	ZINC00046842
809	ZINC00030547	4078	ZINC00030946	6447	ZINC00046442	8651	ZINC00046863

828	ZINC00030549	4173	ZINC00030957	6525	ZINC00046457	8673	ZINC00046867
851	ZINC00030551	4289	ZINC00030974	6725	ZINC00046497	8684	ZINC00046868
1667	ZINC00030659	4349	ZINC00030983	6933	ZINC00046534	8716	ZINC00046871
1724	ZINC00030665	4485	ZINC00031001	7299	ZINC00046591	8754	ZINC00046879
1897	ZINC00030683	4490	ZINC00031002	7311	ZINC00046592	8867	ZINC00046891
2251	ZINC00030724	4708	ZINC00031026	7367	ZINC00046603	8974	ZINC00046918
2469	ZINC00030757	4730	ZINC00031029	7376	ZINC00046604	9193	ZINC00046977
2528	ZINC00030763	4795	ZINC00031037	7466	ZINC00046615	9194	ZINC00046980
2722	ZINC00030786	4896	ZINC00031061	7653	ZINC00046648	9215	ZINC00046983
2874	ZINC00030801	4930	ZINC00031069	7665	ZINC00046652	9248	ZINC00046989
3013	ZINC00030816	5014	ZINC00031087	7691	ZINC00046658	9298	ZINC00046997
3020	ZINC00030817	5043	ZINC00031093	7788	ZINC00046674	9425	ZINC00047020
3240	ZINC00030844	5083	ZINC00031101	7803	ZINC00046676	9591	ZINC00047051
3284	ZINC00030854	5124	ZINC00031109	7916	ZINC00046725	9712	ZINC00047072
3312	ZINC00030859	5135	ZINC00031113	7945	ZINC00046734	9720	ZINC00047073
3331	ZINC00030861	5160	ZINC00031117	7947	ZINC00046736	9740	ZINC00047075
3363	ZINC00030865	5281	ZINC00031145	7992	ZINC00046755	9800	ZINC00047092
3372	ZINC00030866	5324	ZINC00031160	8016	ZINC00046757	9912	ZINC00047111
3459	ZINC00030876	5441	ZINC00031179	8043	ZINC00046763	9932	ZINC00047118
3638	ZINC00030895	5454	ZINC00031180	8107	ZINC00046785	9945	ZINC00047119
3659	ZINC00030897	5464	ZINC00031181	8275	ZINC00046816	9986	ZINC00047123

^a <http://zinc.docking.org>

Table S3. The amino acid sequence of p56 lck protein used in theQM docking studies

ID	Amino Acid	ID	Amino Acid	ID	Amino Acid	ID	Amino Acid
1	(Ammo)(+)	28	His(+)	55	Gly	82	Leu
2	Leu	29	Gly	56	Glu(-)	83	His(+)
3	Glu(-)	30	Ser	57	Val	84	Glu(-)
4	Pro	31	Phe	58	Val	85	Leu
5	Glu(-)	32	Leu	59	Lys(+)	86	Val
6	Pro	33	Ile	60	His	87	Arg(+)
7	Trp	34	Arg(+)	61	Tyr	88	His(+)
8	Phe	35	Glu(-)	62	Lys(+)	89	Tyr
9	Phe	36	Ser	63	Ile	90	Thr
10	Lys(+)	37	Glu(-)	64	Arg(+)	91	Asn
11	Asn	38	Ser	65	Asn	92	Ala
12	Leu	39	Thr	66	Leu	93	Ser
13	Ser	40	Ala	67	Asp(-)	94	Asp(-)
14	Arg(+)	41	Gly	68	Asn	95	Gly
15	Lys(+)	42	Ser	69	Gly	96	Leu
16	Asp(-)	43	Phe	70	Gly	97	Cys
17	Ala	44	Ser	71	Phe	98	Thr
18	Glu(-)	45	Leu	72	Tyr	99	Arg(+)

19	Arg(+)	46	Ser	73	Ile	100	Leu
20	Gln	47	Val	74	Ser	101	Ser
21	Leu	48	Arg(+)	75	Pro	102	Arg(+)
22	Leu	49	Asp(-)	76	Arg(+)	103	Pro
23	Ala	50	Phe	77	Ile	104	Cys
24	Pro	51	Asp(-)	78	Thr	105	Gln
25	Gly	52	Gln	79	Phe	106	Thr
26	Asn	53	Asn	80	Pro	107	Carboxy(-)
27	Thr	54	Gln	81	Gly		

The typical LocalSCF computations and corresponding keywords used in this work.

Protein structure minimization:

```
AM1 MMOK CHARGE=-1 USEFMM GEO-OK OPTFULL CYCLES=50 EPS=78
```

Calculation of the protein density matrix to be reused in the QM/QM calculations:

(the protein structure is imported from a PDB file)

```
AM1 lscf charge=4 pdbinp DEESTOP=0.01 rNeedR=6.0 rExChng=6.0 &
  geo-ok mmok thrDer1=0.01 SijCrt=1.0D-3 4BONDS &
  useFMM FMCCoul=6 FMML1=4 FMML3=3 FMMWS=1 layer=6 save
lkk-cosmo50-protein.out.pdb
```

QM scoring keywords:

(executed as LocalSCF.x 200000_scoring_database.mol2)

```
AM1 lscf DEESTOP=0.01 rNeedR=6.0 rExChng=6.0 &
  geo-ok mmok thrDer1=0.01 SijCrt=1.0D-3 4BONDS dock small noLog &
  useFMM FMCCoul=6 FMML1=4 FMML3=3 FMMWS=1 layer=6
protein/protein
```

The protein density matrix and protein coordinates are imported from the set of “protein.*” files stored in the “protein/” directory.

Docking (ligand relaxation) keywords:

(executed as LocalSCF.x 10000_docking_database.mol2)

```
AM1 DEESTOP=0.01 rNeedR=6.0 rExChng=6.0 optLigand &
  geo-ok mmok thrDer1=0.01 SijCrt=1.0D-3 4BONDS dock small noLog &
  useFMM FMCCoul=6 FMML1=4 FMML3=3 FMMWS=1 layer=6 cycles=10
protein/protein
```

Table S4A. The results of the 4 Å buffer zone second stage QM docking in comparison with full QM calculation.

ID	RMS ^a	Time ^b	Ncyc ^c	Ncyc ^d	E _{bind} ^e	ΔE _{bind} ^f	RMS ^g	E _{complex} ^h	E _{complex} ⁱ
1667	0.35	4548	716	166	-24.41	-8.70	1.54	-4994.84	-4993.97
1724	1.53	2459	387	924	-22.45	-8.09	0.62	-5105.28	-5109.70
1897	0.55	4589	721	368	-31.72	-18.37	2.04	-5024.77	-5027.51
2251	0.00	2524	394	13	-22.08	-7.82	1.01	-4990.62	-4990.94
2469	0.22	5075	1000	239	-21.85	-5.03	1.22	-4906.15	-4905.75
2528	0.40	4357	699	507	-30.08	-13.50	1.52	-4960.29	-4964.72
2722	0.06	1927	278	87	-26.68	-5.14	0.50	-5013.07	-5013.27
2874	0.00	3314	496	8	-20.75	-7.81	0.74	-4968.53	-4970.97
3013	0.44	5442	913	302	-21.31	-1.89	1.17	-4886.02	-4888.57
3020	0.08	4095	629	164	-33.32	-15.79	1.46	-4998.16	-5003.04
3240	0.00	2402	404	6	-23.87	-7.85	0.76	-5005.90	-5006.70
3284	0.10	1394	195	136	-22.26	-12.04	0.68	-4991.02	-4992.09
3312	0.01	1657	209	92	-36.51	-17.02	0.82	-5083.20	-5085.10
3331	0.76	1620	209	675	-30.61	-6.94	0.54	-5035.42	-5037.35
3363	0.14	5421	839	217	-34.55	-19.57	1.93	-5001.79	-5002.69
3372	0.02	1842	257	34	-20.32	-10.44	0.49	-4986.65	-4990.29
3459	0.27	6081	1000	243	-26.34	-11.30	2.41	-5007.91	-5009.03
3638	0.01	1445	220	129	-28.92	-13.20	0.54	-5049.89	-5051.32
3659	0.00	4948	704	12	-31.01	-15.55	1.56	-5017.71	-5018.58
3669	0.00	1468	203	14	-31.54	-9.34	0.62	-5017.32	-5017.36
3723	0.02	4062	674	47	-21.75	-6.35	1.11	-5045.69	-5046.01
3754	0.10	4527	715	82	-26.38	-10.18	1.60	-5007.71	-5009.15
4078	0.15	4704	818	105	-24.73	-8.13	0.95	-5052.52	-5051.69
4173	0.14	1199	195	96	-19.39	-2.88	0.36	-5007.86	-5009.76
4289	0.14	1649	239	123	-21.15	-3.19	0.68	-4950.12	-4950.66
4349	0.06	2200	329	84	-18.66	-3.03	0.75	-4958.13	-4958.83
4485	0.00	2309	288	12	-33.69	-9.40	0.87	-5078.93	-5080.89
4490	0.01	2317	298	29	-36.41	-15.97	0.83	-5078.32	-5078.99
468	0.02	4282	786	49	-22.98	-9.81	0.96	-5001.01	-5002.59
4708	0.06	1249	196	80	-19.91	-4.26	0.44	-5010.19	-5012.44
4730	0.05	4793	803	132	-24.99	-10.52	1.24	-5057.19	-5056.86
4795	0.96	4086	766	799	-24.85	-9.41	0.87	-4822.98	-4826.37
4896	0.00	3614	484	127	-18.71	-2.15	1.12	-4858.12	-4859.45
4930	0.11	5166	643	163	-29.85	-13.60	2.17	-4910.58	-4910.67
5014	0.98	6998	1000	741	-28.13	-12.21	2.24	-4940.84	-4945.74
5043	0.09	4871	688	188	-25.43	-6.87	1.06	-4900.56	-4901.65
5083	0.31	4234	556	268	-26.24	-9.45	1.50	-4935.19	-4938.83
5124	0.02	3592	447	53	-33.58	-17.49	1.24	-4902.42	-4902.80
5135	0.00	3480	427	120	-21.80	-3.74	1.29	-4860.55	-4861.79
5160	0.00	1846	247	6	-25.47	-8.45	0.46	-4879.10	-4880.18
5281	0.00	3059	425	6	-27.76	-11.55	0.77	-4873.32	-4872.74

5324	0.20	3795	505	211	-37.17	-23.55	1.23	-4826.50	-4828.02
5441	0.04	1295	159	44	-50.87	-5.70	0.36	-5053.79	-5055.25
5454	0.34	6205	1000	213	-55.81	-6.50	2.44	-5058.60	-5060.56
5464	0.10	2868	368	148	-50.44	-9.73	0.76	-4989.75	-4990.31
5721	0.14	4410	669	151	-28.25	-15.56	1.60	-4970.20	-4970.61
581	0.06	2676	351	149	-22.28	-8.70	0.86	-4996.66	-4996.50
5871	0.07	2350	368	74	-22.48	-5.78	0.77	-4895.22	-4895.99
629	0.00	2150	332	8	-18.35	-4.17	0.91	-4984.12	-4984.54
6430	0.15	5813	490	221	-23.84	-6.47	0.99	-4900.62	-4900.30
6447	0.12	2252	180	124	-35.02	-16.25	0.54	-4870.08	-4870.54
6525	0.05	5551	507	59	-20.25	-8.75	1.15	-5145.05	-5145.21
6725	0.01	1898	159	24	-19.31	-7.32	0.61	-4987.42	-4989.48
6933	0.00	5880	438	7	-24.32	-7.98	1.46	-5070.75	-5070.85
7299	0.10	4477	615	132	-39.01	-24.33	1.33	-5040.56	-5041.44
7311	0.03	3836	445	58	-28.77	-11.44	1.51	-5032.58	-5032.96
7367	0.70	6828	1000	790	-25.94	-11.75	1.26	-4956.10	-4958.33
7376	0.84	4559	673	1000	-28.31	-12.27	1.08	-4956.70	-4959.72
7466	0.21	2802	436	227	-22.96	-5.33	1.02	-4831.12	-4832.77
7653	0.16	6898	1000	216	-24.72	-6.58	1.51	-4883.70	-4885.78
7665	0.00	2739	342	120	-33.11	-17.76	1.02	-4969.01	-4971.11
7691	0.58	3592	462	399	-20.55	-8.29	0.96	-4878.06	-4880.51
7788	0.33	6201	1000	294	-25.05	-2.68	1.20	-4911.35	-4914.65
7803	0.02	4301	535	134	-36.30	-20.45	1.73	-4902.52	-4902.70
7916	0.65	4423	689	770	-22.92	-9.06	1.07	-4966.48	-4967.73
7945	0.02	3876	578	141	-23.97	-6.02	1.70	-4838.40	-4839.42
7947	0.79	5717	626	478	-30.74	-13.05	1.31	-4965.10	-4968.64
7992	0.75	4834	828	1000	-28.73	-20.21	1.53	-4833.47	-4836.55
8016	0.11	4425	640	146	-31.20	-19.11	1.96	-4858.33	-4859.48
8043	0.15	4697	704	129	-30.27	-11.18	1.59	-4863.41	-4865.51
809	0.00	3441	579	5	-20.06	-7.58	1.15	-4982.22	-4982.09
8107	0.00	3760	579	6	-25.50	-8.66	1.49	-4969.38	-4969.16
8275	0.05	6183	1000	131	-24.36	-9.36	2.28	-4873.75	-4875.15
828	0.57	4640	717	428	-24.96	-11.88	1.39	-5009.04	-5010.14
8357	0.02	6263	853	137	-39.93	-25.54	1.99	-4944.45	-4949.21
8412	1.25	5229	831	1000	-20.40	-5.58	1.30	-4901.01	-4903.63
8467	0.02	4756	633	33	-35.70	-21.09	1.37	-5073.22	-5075.18
851	0.00	2249	364	5	-19.12	-3.28	0.60	-4993.85	-4994.02
8651	0.08	4992	780	93	-23.58	-10.32	1.33	-5048.35	-5049.62
8673	0.00	3280	452	14	-23.82	-11.65	0.92	-5047.07	-5047.67
8684	0.00	4674	701	4	-23.56	-11.73	1.08	-5048.94	-5049.67
8716	1.33	7648	1000	695	-66.39	-7.79	2.37	-5031.66	-5041.61
8754	0.01	2772	479	20	-23.58	-4.57	0.66	-4956.26	-4956.78
8867	0.72	5927	1000	1000	-35.72	-16.00	1.12	-5141.95	-5147.70

8974	0.22	1951	285	154	-28.28	-14.25	0.65	-5072.77	-5074.86
9193	0.14	6461	1000	218	-33.90	-18.28	1.62	-5109.35	-5111.86
9194	0.81	6742	1000	527	-32.97	-19.23	1.81	-5107.67	-5111.92
9215	0.05	6913	976	66	-60.23	-19.65	1.94	-4921.25	-4925.16
9248	0.65	3372	492	311	-26.10	-28.02	1.26	-5002.43	-5006.23
9298	0.07	4258	580	79	-22.13	-8.46	0.94	-5051.99	-5053.24
9425	0.02	4305	395	34	-26.24	-14.04	0.92	-4957.83	-4958.20
9591	0.58	9175	1000	486	-24.31	-8.02	1.95	-4840.35	-4843.02
9712	0.01	3199	248	27	-31.23	-12.81	0.43	-4932.52	-4935.24
9720	0.00	2116	274	18	-31.88	-12.25	0.67	-4932.95	-4935.23
9740	0.01	1329	210	28	-22.81	-6.61	0.24	-4925.41	-4927.67
9800	0.00	4489	412	9	-24.15	-12.20	0.87	-5003.93	-5004.55
9912	0.99	5124	483	875	-23.90	-4.95	1.05	-4876.91	-4879.39
9932	0.02	6487	644	54	-32.07	-10.83	1.11	-5034.46	-5035.24
9945	0.69	8704	1000	501	-25.49	-4.75	1.50	-5027.12	-5028.99
9986	0.02	4169	315	140	-29.26	-14.38	0.84	-4975.40	-4976.00

^a RMS difference in position of ligand non-hydrogen atoms as predicted by QM/QM and full QM calculation of protein-ligand complexes. ^b QM/QM calculation time, seconds. ^c Number of QM/QM ligand geometry optimization cycles where protein atoms were held fixed. ^d Number of full QM ligand geometry optimization cycles; the full QM calculation is initiated from the final QM/QM protein-ligand geometry. ^e Binding energy predicted by the QM/QM method, kcal/mol. ^f Change in binding energy due to ligand relaxation, kcal/mol. ^g RMS difference in position of ligand non-hydrogen atoms due to ligand relaxation. ^h Total energy of protein-ligand complex after QM/QM calculation. ⁱ Total energy of protein-ligand complex after full QM calculation.

Table S4B. The results of the 6 Å buffer zone second stage QM docking in comparison with full QM calculation.

ID	RMS ^a	Time ^b	Ncyc ^c	Ncyc ^d	E _{bind} ^e	ΔE _{bind} ^f	RMS ^g	E _{complex} ^h	E _{complex} ⁱ
1667	0.34	4592	633	292	-23.18	-7.47	1.49	-4993.66	-4993.94
1724	0.10	7072	1000	81	-26.44	-12.08	1.89	-5109.04	-5109.68
1897	0.34	6584	903	468	-37.13	-23.77	2.49	-5028.52	-5028.10
2251	0.00	3070	417	4	-23.20	-8.95	1.05	-4991.67	-4990.94
2469	0.14	5730	995	123	-20.09	-3.28	1.11	-4904.43	-4905.53
2528	0.00	6253	845	5	-34.67	-18.08	1.67	-4964.74	-4964.65
2722	0.00	2393	289	33	-27.52	-5.98	0.48	-5014.02	-5013.22
2874	0.02	3022	353	44	-23.44	-10.50	0.71	-4970.88	-4970.91
3013	0.00	6667	897	9	-23.52	-4.09	1.49	-4888.23	-4888.78
3020	0.00	3489	422	6	-37.50	-19.98	1.31	-5002.12	-5002.10
3240	0.00	3395	472	10	-25.74	-9.72	0.78	-5007.72	-5006.71

3284	0.00	1511	194	7	-23.42	-13.19	0.71	-4992.10	-4992.01
3312	0.01	1793	209	28	-39.20	-19.72	0.86	-5085.98	-5084.93
3331	0.00	6850	1000	6	-30.57	-6.90	0.82	-5037.28	-5037.16
3363	0.20	5689	819	340	-34.51	-19.53	1.88	-5001.64	-5002.66
3372	0.00	1940	226	6	-24.26	-14.38	0.51	-4990.44	-4990.31
3459	0.10	6472	958	162	-27.31	-12.27	2.59	-5009.20	-5009.07
3638	0.04	1715	221	151	-30.14	-14.42	0.55	-5050.98	-5051.46
3659	0.00	6878	1000	13	-29.99	-14.53	1.56	-5016.61	-5018.59
3669	0.00	2330	308	5	-31.96	-9.76	0.60	-5017.80	-5017.42
3723	0.00	5134	802	4	-22.38	-6.98	1.00	-5046.32	-5045.80
3754	0.00	4723	658	5	-25.68	-9.48	1.67	-5006.95	-5009.24
4078	0.00	2884	354	5	-23.48	-6.87	0.85	-5051.42	-5051.18
4173	0.00	1358	194	5	-21.24	-4.72	0.38	-5009.70	-5009.66
4289	0.00	2061	248	4	-21.08	-3.12	0.70	-4949.85	-4950.57
4349	0.00	2497	324	5	-18.99	-3.37	0.76	-4958.44	-4958.88
4485	0.00	2444	286	7	-35.82	-11.52	0.83	-5081.05	-5080.90
4490	0.00	2240	257	5	-36.89	-16.46	0.82	-5078.71	-5078.96
468	0.00	3638	510	4	-25.10	-11.93	0.95	-5002.94	-5002.53
4708	0.00	1480	225	5	-20.85	-5.20	0.46	-5011.18	-5012.41
4730	0.06	4042	515	142	-23.90	-9.44	1.24	-5056.24	-5056.87
4795	0.73	5457	878	525	-27.33	-11.90	1.11	-4825.00	-4826.27
4896	0.00	4028	473	125	-19.86	-3.31	1.09	-4859.23	-4859.49
4930	0.08	5488	664	138	-30.63	-14.38	2.20	-4911.57	-4910.68
5014	0.54	8536	1000	540	-32.64	-16.71	2.57	-4945.24	-4945.69
5043	0.03	6485	754	128	-26.93	-8.36	1.12	-4901.87	-4901.51
5083	0.63	5064	537	277	-31.37	-14.58	2.20	-4940.47	-4942.27
5124	0.00	5136	593	5	-32.96	-16.87	1.23	-4901.87	-4902.77
5135	0.52	4291	542	633	-22.76	-4.70	0.90	-4861.83	-4862.15
5160	0.01	2266	309	26	-25.21	-8.19	0.51	-4878.91	-4880.29
5281	0.00	3584	438	6	-27.24	-11.03	0.75	-4872.80	-4872.73
5324	0.02	4634	532	104	-38.24	-24.62	1.42	-4827.52	-4828.11
5441	0.00	1998	223	6	-51.77	-6.59	0.39	-5054.31	-5055.25
5454	0.89	7214	1000	569	-56.20	-6.89	1.97	-5058.47	-5060.64
5464	0.04	3037	306	72	-52.00	-11.29	0.77	-4991.20	-4990.32
5721	0.00	5771	840	3	-28.30	-15.61	1.66	-4970.20	-4970.35
581	0.01	3836	431	112	-23.16	-9.58	0.89	-4997.54	-4996.48
5871	0.00	2876	380	6	-24.83	-8.14	0.81	-4897.44	-4895.97
629	0.22	4764	830	114	-20.49	-6.30	1.22	-4985.94	-4986.31
6430	0.00	6377	565	4	-24.02	-6.64	0.99	-4900.58	-4900.08
6447	0.00	2431	178	13	-35.15	-16.38	0.57	-4869.67	-4870.52
6525	0.00	7301	500	6	-20.64	-9.14	1.13	-5145.34	-5145.14
6725	0.00	2740	204	5	-20.14	-8.14	0.61	-4988.17	-4989.47
6933	0.00	6162	466	6	-25.24	-8.90	1.47	-5071.64	-5070.85

7299	0.00	4113	402	13	-39.86	-25.17	1.27	-5041.30	-5041.44
7311	0.00	4688	513	14	-28.73	-11.40	1.47	-5032.35	-5033.04
7367	0.81	7975	1000	923	-25.71	-11.52	1.19	-4955.66	-4958.33
7376	0.01	4970	629	36	-27.83	-11.79	0.99	-4956.15	-4957.31
7466	0.04	3321	428	66	-24.74	-7.11	1.10	-4832.77	-4832.72
7653	0.00	7480	879	9	-26.60	-8.46	1.49	-4885.78	-4885.77
7665	0.24	4434	532	176	-36.41	-21.06	1.29	-4972.73	-4973.07
7691	0.07	3490	345	96	-23.21	-10.96	0.93	-4880.10	-4879.94
7788	0.29	7372	1000	260	-27.89	-5.52	1.25	-4914.22	-4914.67
7803	0.16	4896	507	182	-37.06	-21.22	1.66	-4903.05	-4902.46
7916	0.80	4607	547	1000	-24.53	-10.66	1.01	-4967.62	-4967.89
7945	0.10	6461	1000	105	-24.79	-6.85	1.80	-4838.93	-4839.38
7947	1.37	5566	513	590	-26.65	-8.96	0.87	-4961.08	-4968.67
7992	0.00	5240	851	5	-30.35	-21.83	1.50	-4835.16	-4834.89
8016	0.00	5247	709	6	-31.90	-19.82	1.97	-4858.88	-4859.50
8043	0.00	5748	715	7	-31.30	-12.20	1.65	-4864.40	-4865.45
809	0.00	3102	417	7	-20.12	-7.64	1.10	-4982.28	-4982.05
8107	0.00	3875	515	4	-25.47	-8.63	1.36	-4969.28	-4969.03
8275	0.43	6568	1000	293	-24.79	-9.78	2.04	-4873.93	-4876.18
828	0.33	6086	826	264	-25.96	-12.88	1.49	-5010.00	-5010.05
8357	0.00	7829	963	120	-43.35	-28.96	2.05	-4947.70	-4949.31
8412	0.95	7384	1000	786	-21.47	-6.65	1.64	-4902.30	-4903.76
8467	0.00	5592	648	5	-37.66	-23.06	1.35	-5075.25	-5075.14
851	0.02	2137	265	45	-19.37	-3.52	0.49	-4994.08	-4993.97
8651	0.13	7206	1000	204	-23.56	-10.30	1.33	-5048.25	-5049.89
8673	0.00	3821	541	6	-24.47	-12.30	0.92	-5047.63	-5047.69
8684	0.00	4600	637	5	-24.73	-12.89	1.06	-5050.08	-5049.67
8716	1.37	9064	1000	969	-71.07	-12.46	2.28	-5035.37	-5041.54
8754	0.00	3295	506	5	-24.86	-5.85	0.72	-4957.66	-4956.83
8867	0.71	7439	1000	892	-37.47	-17.75	1.09	-5143.88	-5147.78
8974	0.00	2213	304	6	-31.96	-17.94	0.79	-5076.20	-5074.84
9193	0.00	7443	997	3	-35.37	-19.75	1.69	-5110.54	-5111.82
9194	0.61	7833	1000	474	-35.58	-21.84	1.94	-5109.59	-5111.96
9215	0.05	6956	770	81	-64.31	-23.73	1.94	-4924.35	-4925.09
9248	0.45	5213	595	455	-29.78	-31.70	1.54	-5004.73	-5006.70
9298	0.00	5844	655	5	-23.72	-10.06	0.97	-5053.46	-5053.16
9425	0.00	4553	356	5	-26.40	-14.20	0.92	-4957.92	-4958.22
9591	0.27	11221	1000	370	-26.25	-9.96	2.28	-4842.33	-4843.07
9712	0.00	3588	235	16	-33.22	-14.80	0.45	-4934.36	-4935.25
9720	0.00	2530	291	14	-33.49	-13.86	0.67	-4934.46	-4935.27
9740	0.00	2386	366	7	-25.14	-8.95	0.31	-4927.81	-4927.74
9800	0.00	4959	466	5	-26.66	-14.72	0.91	-5006.34	-5004.69
9912	0.00	5270	466	4	-24.08	-5.14	1.12	-4877.41	-4878.19

9932	0.00	5578	409	6	-32.59	-11.35	1.06	-5034.78	-5035.15
9945	0.79	9100	954	505	-26.73	-5.99	1.48	-5028.35	-5029.05
9986	0.01	4669	348	125	-29.43	-14.55	0.81	-4975.50	-4975.90

^a RMS difference in position of ligand non-hydrogen atoms as predicted by QM/QM and full QM calculation of protein-ligand complexes. ^b QM/QM calculation time, seconds. ^c Number of QM/QM ligand geometry optimization cycles where protein atoms were held fixed. ^d Number of full QM ligand geometry optimization cycles; the full QM calculation is initiated from the final QM/QM protein-ligand geometry. ^e Binding energy predicted by the QM/QM method, kcal/mol. ^f Change in binding energy due to ligand relaxation, kcal/mol. ^g RMS difference in position of ligand non-hydrogen atoms due to ligand relaxation. ^h Total energy of protein-ligand complex after QM/QM calculation. ⁱ Total energy of protein-ligand complex after full QM calculation.

Table S4C. The results of the 8 Å buffer zone second stage QM docking in comparison with full QM calculation.

ID	RMS ^a	Time ^b	Ncyc ^c	Ncyc ^d	E _{bind} ^e	ΔE _{bind} ^f	RMS ^g	E _{complex} ^h	E _{complex} ⁱ
1667	0.37	4977	643	346	-23.08	-7.37	1.39	-4994.28	-4994.62
1724	0.45	8332	1000	340	-26.35	-11.98	1.67	-5109.43	-5109.71
1897	0.53	4629	584	306	-34.73	-21.37	2.04	-5027.48	-5027.54
2251	0.00	3395	437	4	-24.45	-10.20	0.98	-4992.91	-4990.90
2469	0.12	6536	1000	136	-22.93	-6.11	1.22	-4907.27	-4905.64
2528	0.29	6472	811	160	-34.45	-17.86	1.61	-4964.38	-4964.71
2722	0.00	2451	305	6	-27.35	-5.80	0.51	-5013.75	-5013.22
2874	0.02	4012	460	42	-22.51	-9.57	0.72	-4970.00	-4970.90
3013	0.00	7986	907	15	-23.82	-4.39	1.53	-4888.58	-4888.88
3020	0.00	4607	592	15	-38.88	-21.36	1.34	-5003.46	-5002.18
3240	0.00	3253	419	15	-25.20	-9.19	0.70	-5006.87	-5006.65
3284	0.00	1673	204	7	-23.31	-13.09	0.71	-4991.97	-4992.02
3312	0.00	2252	269	91	-39.05	-19.56	0.85	-5085.64	-5085.10
3331	0.00	5684	624	6	-30.74	-7.06	0.79	-5037.34	-5037.12
3363	0.27	7515	896	285	-37.19	-22.21	1.89	-5004.35	-5002.80
3372	0.00	2368	229	5	-23.53	-13.65	0.52	-4989.69	-4990.31
3459	0.29	7967	1000	247	-27.95	-12.90	2.41	-5009.37	-5009.05
3638	0.04	1994	226	151	-31.57	-15.86	0.56	-5052.39	-5051.50
3659	0.00	6614	757	5	-32.30	-16.84	1.57	-5018.94	-5018.57
3669	0.00	2020	209	10	-32.76	-10.56	0.60	-5018.51	-5017.30
3723	0.60	4104	517	787	-22.46	-7.06	0.98	-5046.30	-5046.66
3754	0.00	5336	773	3	-28.85	-12.65	1.68	-5010.14	-5009.25
4078	0.00	2488	256	7	-23.95	-7.34	0.84	-5052.17	-5051.06
4173	0.00	1464	170	5	-21.22	-4.71	0.38	-5009.66	-5009.67

4289	0.00	2765	318	16	-21.89	-3.92	0.69	-4950.56	-4950.57
4349	0.00	3147	341	5	-19.84	-4.21	0.81	-4959.29	-4958.92
4485	0.00	2945	343	4	-36.66	-12.36	0.83	-5081.94	-5080.89
4490	0.04	2441	259	49	-37.76	-17.32	0.83	-5079.72	-5078.96
468	0.00	4176	508	13	-25.85	-12.67	0.93	-5003.79	-5002.55
4708	0.00	1355	149	6	-22.50	-6.85	0.48	-5012.76	-5012.41
4730	0.09	7237	971	134	-25.45	-10.98	1.22	-5057.66	-5056.82
4795	1.10	4291	539	841	-27.42	-11.99	0.70	-4825.58	-4826.17
4896	0.20	3614	334	185	-20.05	-3.49	0.93	-4858.91	-4859.55
4930	0.33	5903	515	208	-27.37	-11.12	2.04	-4907.77	-4910.69
5014	0.51	9503	1000	629	-33.02	-17.09	2.58	-4945.72	-4945.60
5043	0.32	4544	406	214	-25.25	-6.68	0.83	-4900.22	-4901.35
5083	0.37	6309	609	255	-30.48	-13.69	1.68	-4938.72	-4939.77
5124	0.28	4433	357	309	-32.82	-16.73	1.11	-4902.04	-4902.79
5135	0.04	4777	442	129	-23.46	-5.40	1.28	-4862.14	-4861.85
5160	0.00	2058	261	7	-27.28	-10.26	0.52	-4881.00	-4880.29
5281	0.00	4198	421	5	-29.49	-13.27	0.75	-4875.08	-4872.74
5324	0.19	5359	514	160	-37.83	-24.21	1.32	-4827.30	-4828.05
5441	0.00	1782	154	4	-54.61	-9.44	0.38	-5057.25	-5055.21
5454	0.00	3959	364	6	-56.08	-6.78	1.02	-5057.50	-5056.12
5464	0.02	4032	360	37	-50.67	-9.96	0.77	-4989.78	-4990.29
5721	0.19	4830	553	173	-27.11	-14.43	1.59	-4968.97	-4970.61
581	0.02	4391	413	109	-23.59	-10.01	0.90	-4997.94	-4996.49
5871	0.02	2787	293	89	-23.01	-6.32	0.68	-4895.58	-4895.94
629	0.00	6042	983	13	-22.49	-8.30	1.44	-4987.47	-4986.57
6430	0.08	6996	480	119	-24.24	-6.87	0.99	-4900.71	-4900.38
6447	0.00	3126	196	6	-36.76	-17.98	0.57	-4871.22	-4870.53
6525	0.00	7022	469	6	-21.05	-9.55	1.09	-5145.73	-5145.10
6725	0.00	2893	181	4	-21.77	-9.77	0.62	-4989.80	-4989.48
6933	0.00	5959	491	5	-24.58	-8.24	1.46	-5070.85	-5070.85
7299	0.00	5285	429	5	-40.77	-26.09	1.26	-5042.23	-5041.43
7311	0.00	6587	574	14	-30.83	-13.50	1.44	-5034.37	-5033.04
7367	0.77	5049	437	652	-26.05	-11.85	1.20	-4955.76	-4958.25
7376	0.84	3422	317	1000	-29.08	-13.04	0.92	-4957.52	-4958.69
7466	0.00	3894	433	6	-25.22	-7.59	1.09	-4833.16	-4832.60
7653	1.06	4279	407	1000	-24.23	-6.08	0.82	-4879.47	-4885.71
7665	0.37	4103	380	268	-36.12	-20.77	1.15	-4972.13	-4972.86
7691	0.00	5619	522	12	-24.26	-12.00	0.98	-4881.16	-4879.95
7788	0.67	6115	635	487	-27.31	-4.94	0.96	-4913.69	-4914.67
7803	0.14	5646	539	164	-37.84	-22.00	1.66	-4903.14	-4902.49
7916	0.72	5633	583	863	-22.65	-8.79	1.00	-4965.87	-4967.78
7945	0.01	7385	1000	29	-27.20	-9.25	1.96	-4841.32	-4839.42
7947	0.79	7636	553	332	-31.44	-13.75	1.35	-4965.67	-4968.64

7992	0.40	4350	638	208	-31.12	-22.60	1.21	-4835.50	-4834.93
8016	0.00	5565	556	3	-33.26	-21.17	2.01	-4860.41	-4859.53
8043	0.00	7768	853	6	-33.85	-14.75	1.63	-4866.95	-4865.44
809	0.15	3417	421	160	-21.82	-9.34	1.05	-4983.96	-4982.10
8107	0.00	4641	539	4	-27.42	-10.58	1.45	-4971.26	-4969.14
8275	0.21	7083	1000	187	-25.62	-10.62	2.16	-4874.91	-4876.34
828	0.22	7325	983	125	-27.71	-14.62	1.62	-5011.91	-5010.11
8357	0.25	7330	692	188	-42.13	-27.74	1.93	-4946.09	-4949.29
8412	1.37	3886	401	1000	-19.24	-4.42	0.83	-4899.00	-4903.08
8467	0.00	6902	813	5	-37.90	-23.30	1.30	-5075.43	-5075.10
851	0.00	3283	369	6	-20.34	-4.49	0.52	-4995.03	-4993.96
8651	0.36	5462	651	211	-24.58	-11.32	1.22	-5049.07	-5049.94
8673	0.00	3473	411	4	-25.09	-12.92	0.95	-5048.21	-5047.70
8684	0.00	5090	576	4	-25.34	-13.51	1.06	-5050.64	-5049.67
8716	0.97	10735	1000	877	-73.75	-15.15	2.48	-5039.26	-5040.67
8754	0.00	3312	429	6	-24.91	-5.90	0.64	-4957.52	-4956.76
8867	0.77	8981	1000	691	-38.79	-19.07	1.18	-5145.74	-5147.90
8974	0.00	2376	292	7	-30.95	-16.92	0.77	-5075.18	-5074.83
9193	0.00	8609	937	15	-36.74	-21.11	1.70	-5111.83	-5111.86
9194	0.40	8271	1000	555	-36.53	-22.79	1.99	-5110.60	-5111.89
9215	0.34	7718	883	212	-64.03	-23.44	1.80	-4923.82	-4925.14
9248	0.87	3508	401	399	-24.86	-26.79	0.73	-5000.26	-5005.45
9298	0.54	4128	367	365	-21.47	-7.80	0.60	-5051.78	-5053.24
9425	0.13	4800	310	106	-27.51	-15.30	0.89	-4958.97	-4958.22
9591	0.26	14061	1000	410	-28.74	-12.44	2.30	-4844.76	-4843.08
9712	0.00	3784	221	6	-34.96	-16.54	0.45	-4936.07	-4935.17
9720	0.00	2753	269	14	-35.21	-15.57	0.67	-4936.18	-4935.27
9740	0.00	1558	174	7	-26.64	-10.44	0.24	-4929.10	-4927.67
9800	0.00	5227	472	4	-26.28	-14.34	0.92	-5005.92	-5004.68
9912	0.00	6647	607	3	-26.97	-8.02	1.13	-4880.33	-4878.20
9932	0.04	7106	464	77	-32.35	-11.11	1.06	-5034.49	-5035.20
9945	0.66	11897	1000	589	-25.61	-4.87	1.56	-5027.13	-5028.79
9986	0.00	4515	323	120	-29.75	-14.87	0.84	-4975.86	-4975.86

^a RMS difference in position of ligand non-hydrogen atoms as predicted by QM/QM and full QM calculation of protein-ligand complexes. ^b QM/QM calculation time, seconds. ^c Number of QM/QM ligand geometry optimization cycles where protein atoms were held fixed. ^d Number of full QM ligand geometry optimization cycles; the full QM calculation is initiated from the final QM/QM protein-ligand geometry. ^e Binding energy predicted by the QM/QM method, kcal/mol. ^f Change in binding energy due to ligand relaxation, kcal/mol. ^g RMS difference in position of ligand non-hydrogen atoms due to ligand relaxation. ^h Total energy of protein-ligand complex after QM/QM calculation. ⁱ Total energy of protein-ligand complex after full QM calculation.

Table S5. pYEEI ligand geometry relaxation in the complex with p56 LCK SH2 domain performed in gas-phase

Conformation	RMSD with crystallographic ligand geometry, Å	Heat of formation of the complex, kcal/mol	Total gradient, kcal/(mol*Å)	Maximum component of gradient, kcal/(mol*Å)
1	1.53	-5223.16	2.26	0.53
32	5.33	-5196.66	13.33	4.00
55	4.44	-5195.27	3.86	0.79
56	3.91	-5193.79	13.18	3.39
28	5.47	-5176.08	13.22	5.86
6	7.09	-5175.80	3.22	0.89
44	7.05	-5175.05	10.39	2.54
17	7.27	-5172.15	4.32	1.04
4	7.41	-5171.91	3.62	0.86
60	4.39	-5171.00	6.46	2.30
12	7.26	-5170.78	4.37	1.11
48	4.65	-5170.52	24.01	12.20
58	7.84	-5169.53	6.86	1.99
52	7.20	-5169.34	3.38	0.84
64	4.53	-5168.96	29.35	10.16
7	6.72	-5168.84	5.27	1.35
22	7.35	-5168.84	5.00	1.52
18	7.05	-5167.93	5.86	1.59
57	8.97	-5167.78	9.74	3.43
2	7.39	-5167.66	7.89	2.58
3	7.37	-5167.46	8.73	2.33
14	6.84	-5167.31	7.31	2.01
8	7.04	-5167.03	3.90	0.90
9	6.87	-5166.92	7.91	2.04
20	7.28	-5166.90	5.45	1.07
11	6.98	-5166.41	6.71	1.88
51	7.01	-5165.82	3.58	0.84
10	6.34	-5165.28	3.56	1.12
13	6.84	-5165.26	3.05	0.72
59	5.33	-5164.95	16.51	5.61
36	6.74	-5164.57	9.15	1.99
16	6.96	-5163.86	3.64	0.92
23	6.96	-5160.92	10.55	2.87

35	6.59	-5160.51	7.09	1.65
43	6.07	-5158.81	5.23	2.24
21	6.61	-5158.23	2.55	0.70
29	5.06	-5157.60	6.22	1.61
42	7.34	-5157.27	6.78	2.13
30	7.55	-5156.96	2.81	0.73
38	7.26	-5156.19	3.32	0.88
24	7.14	-5152.28	2.15	0.49
47	7.06	-5151.98	5.03	1.43
26	7.23	-5151.89	3.56	0.95
5	7.09	-5151.56	9.59	4.08
25	7.94	-5151.41	2.77	1.02
15	7.86	-5151.36	3.07	0.69
19	7.87	-5150.71	1.00	0.24
27	6.87	-5150.46	3.27	1.03
50	7.70	-5150.36	4.79	1.78
37	6.74	-5150.25	3.37	0.90
31	7.49	-5149.58	1.11	0.29
61	6.90	-5149.06	3.72	0.78
34	6.99	-5149.02	4.77	1.06
39	7.13	-5147.61	6.61	2.49
63	6.06	-5145.21	12.28	3.62
33	7.28	-5144.71	1.76	0.47
41	7.18	-5142.27	1.83	0.47
45	7.81	-5140.82	3.11	0.77
53	7.14	-5140.15	3.87	1.11
73	8.67	-5139.51	6.16	1.70
40	8.24	-5139.09	1.99	0.53
69	6.68	-5137.65	9.34	2.05
54	11.27	-5136.61	3.63	0.95
67	5.98	-5135.79	7.33	1.79
46	11.18	-5134.01	7.07	1.93
62	12.44	-5133.43	2.80	0.87
65	7.25	-5129.98	4.37	1.18
49	6.65	-5129.38	11.46	2.82
72	7.72	-5117.25	9.44	3.34
66	5.75	-5116.76	6.84	2.29
70	7.91	-5109.02	16.71	5.88
68	7.08	-5104.46	12.43	4.04
74	10.19	-5095.10	19.99	8.31
71	7.03	-5077.15	9.71	2.28
76	11.68	-5059.34	1.81	0.55
75	12.84	-4860.05	3.50	0.99

Docking (ligand relaxation) keywords pertaining to Table S5:

```
AM1 DEESTOP=0.01 rNeedR=6.0 rExChng=6.0 optLigand &  
  geo-ok mmok thrDer1=0.01 SijCrt=1.0D-3 4BONDS dock small noLog &  
  useFMM FMML1=4 FMML3=3 FMMWS=1 layer=6 cycles=500  
protein/protein
```

Table S6. pYEEI ligand geometry relaxation in the complex with p56 LCK SH2 domain performed in presence of COSMO solvent model

Conformation	RMSD with crystallographic ligand geometry, Å	Heat of formation of the complex, kcal/mol	Total gradient, kcal/(mol*Å)	Maximum component of gradient, kcal/(mol*Å)
1	0.75	-6658.998	14.25	9.79

Docking (ligand relaxation) keywords pertaining to Table S6:

```
AM1 DEESTOP=0.01 rNeedR=6.0 rExChng=6.0 optLigand &  
  geo-ok mmok thrDer1=0.01 SijCrt=1.0D-3 4BONDS dock small noLog &  
  useFMM FMML1=4 FMML3=3 FMMWS=1 layer=6 cycles=500 EPS=78  
protein/protein
```