SUPPORTING INFORMATION FILE

MetaDOCK: A Combinatorial Molecular Docking Approach

Izaz Monir Kamal[1, 2] and Saikat Chakrabarti[1, 2, *]

Figure S1

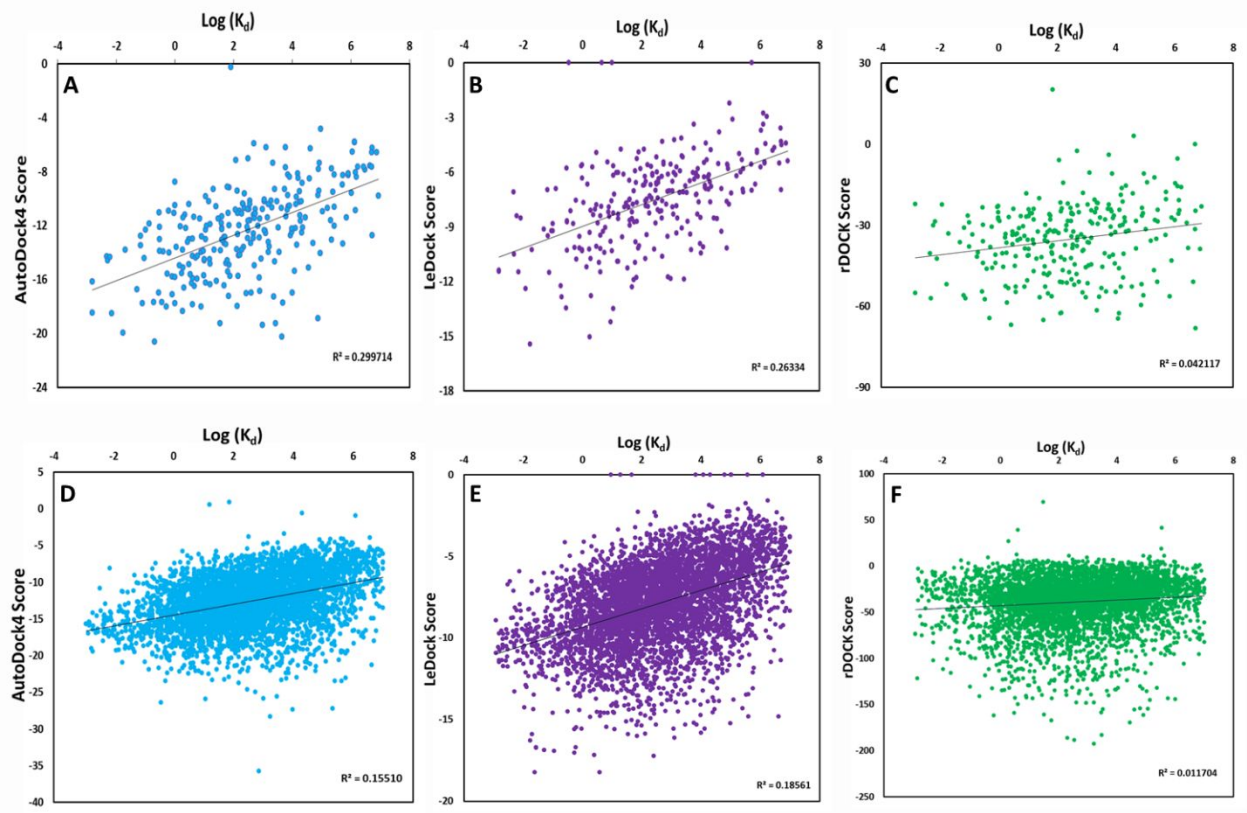

Figure S1: Scoring power analysis and comparison. Scatter plots of the docking scores and the experimental binding free energies (log K_d) for the core (A-C) and refined sets (D-F), respectively. Trend line is colored in black while the correlation coefficients between docking scores and experimental binding free energies are represented by R^2 values. Panels A-D, B-E, and C-F show data for AutoDock4, LeDock, and rDOCK, respectively.

Figure S2

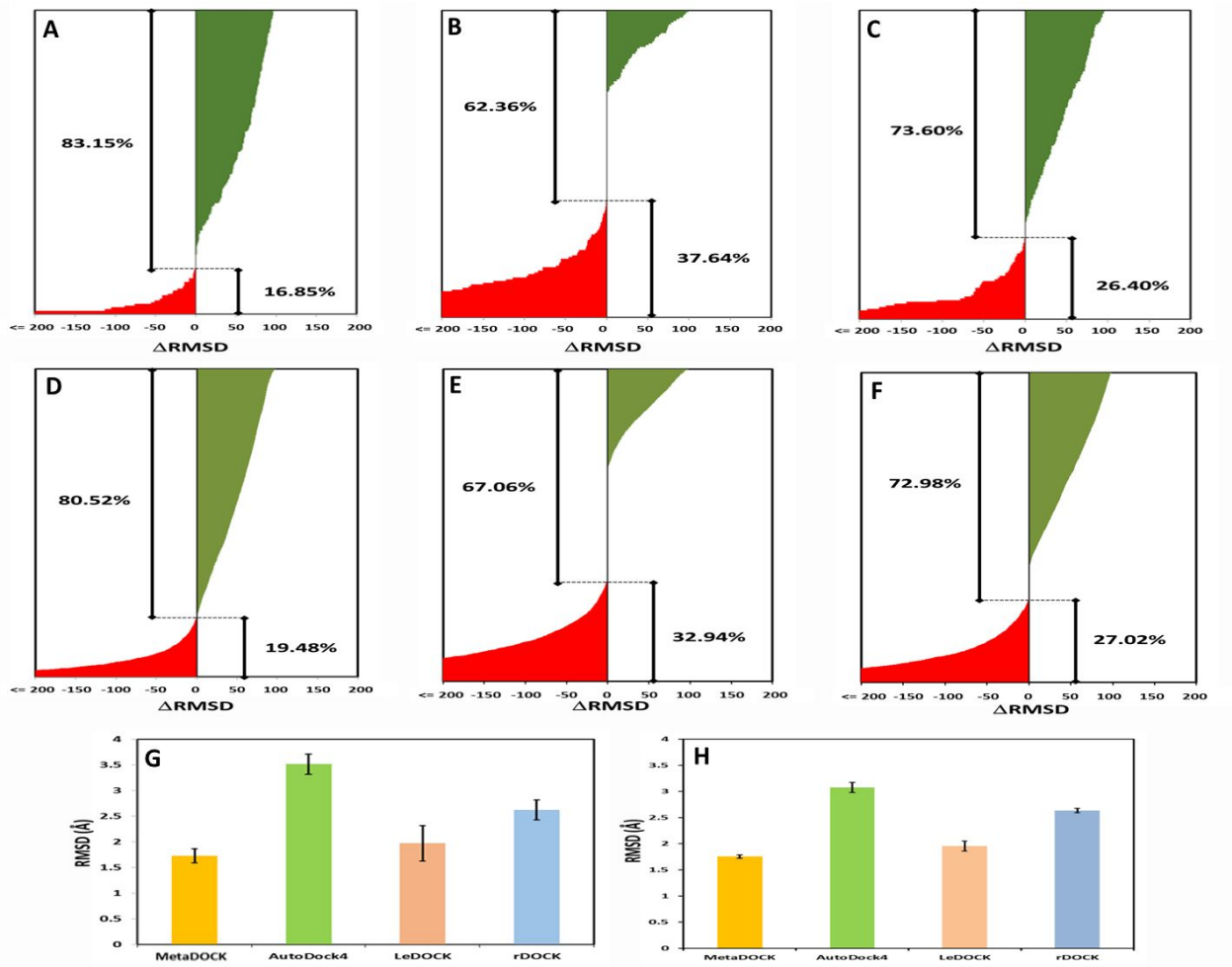

Figure S2: Posing power analysis for the MetaDOCK component programs. Difference of RMSD of the complexes generated by AutoDock4, LeDock, and rDOCK, respectively with respect to the most likely complex derived from the MetaDOCK approach is plotted for core (A-C) and refined (D-F) datasets, respectively. Positive ΔRMSD (green color) indicates better RMSD value of the MetaDOCK complex with respect to the same derived from the individual component programs. Average RMSDs of the docked complexes with respect to their corresponding original complexes are shown in panels G and H for the core and refined datasets, respectively. Error bars indicate standard error.

Figure S3

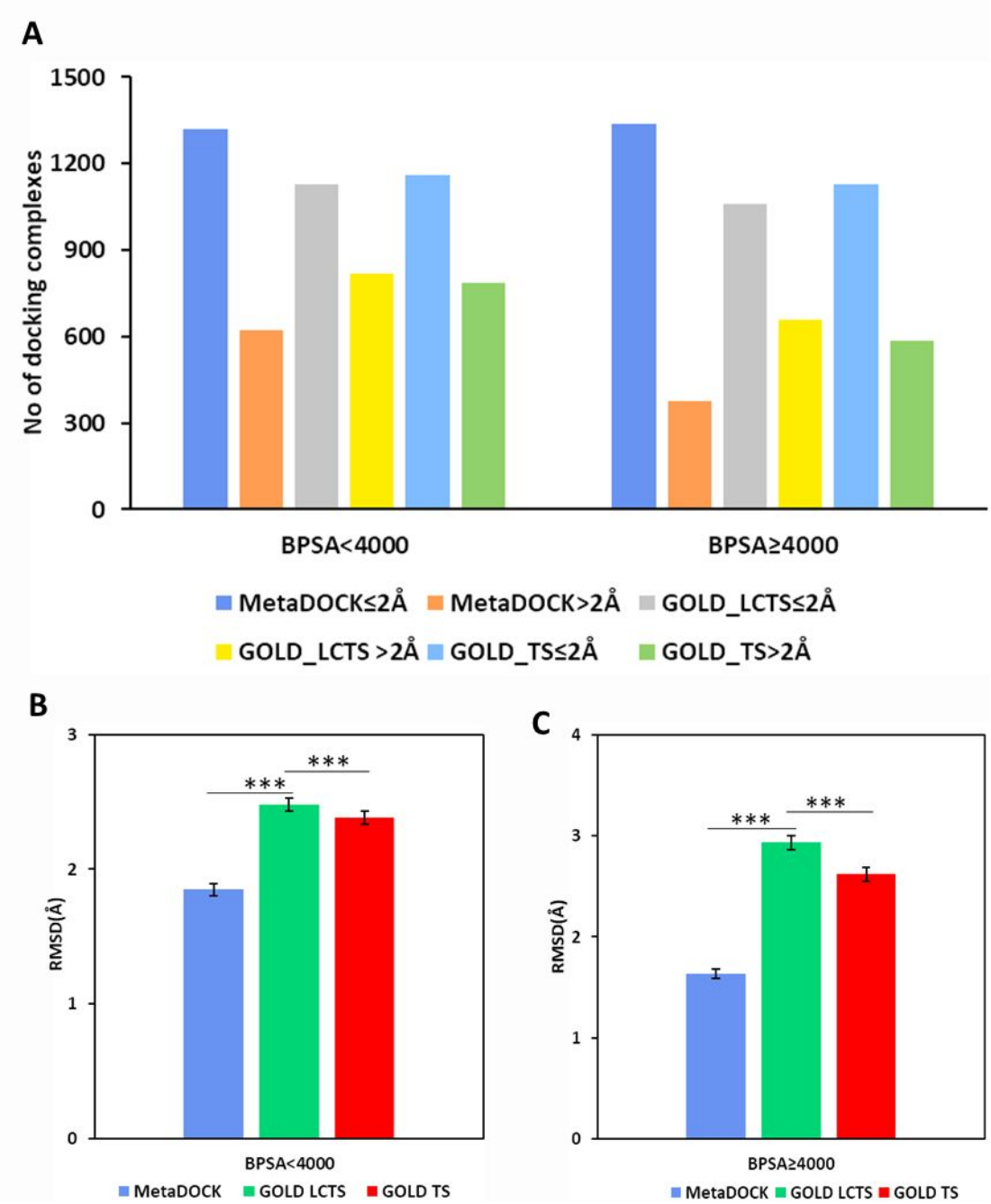

Figure S3: Binding Pocket Surface Area (BPSA) based docking performance analysis and comparison. Panel A plots the number of successful docking complexes (RMSD <=2 Å) and complexes with RMSD > 2 Å for two categories of binding pocket surface area (BPSA) of the ligands, BPSA < 4000 $Å^2$, and BPSA >= 4000 $Å^2$. Panels B-C plot average RMSD of the docked complexes with respect to their corresponding original complexes for the two BPSA categories. *** indicates p-value ≤ 0.001.

Figure S4

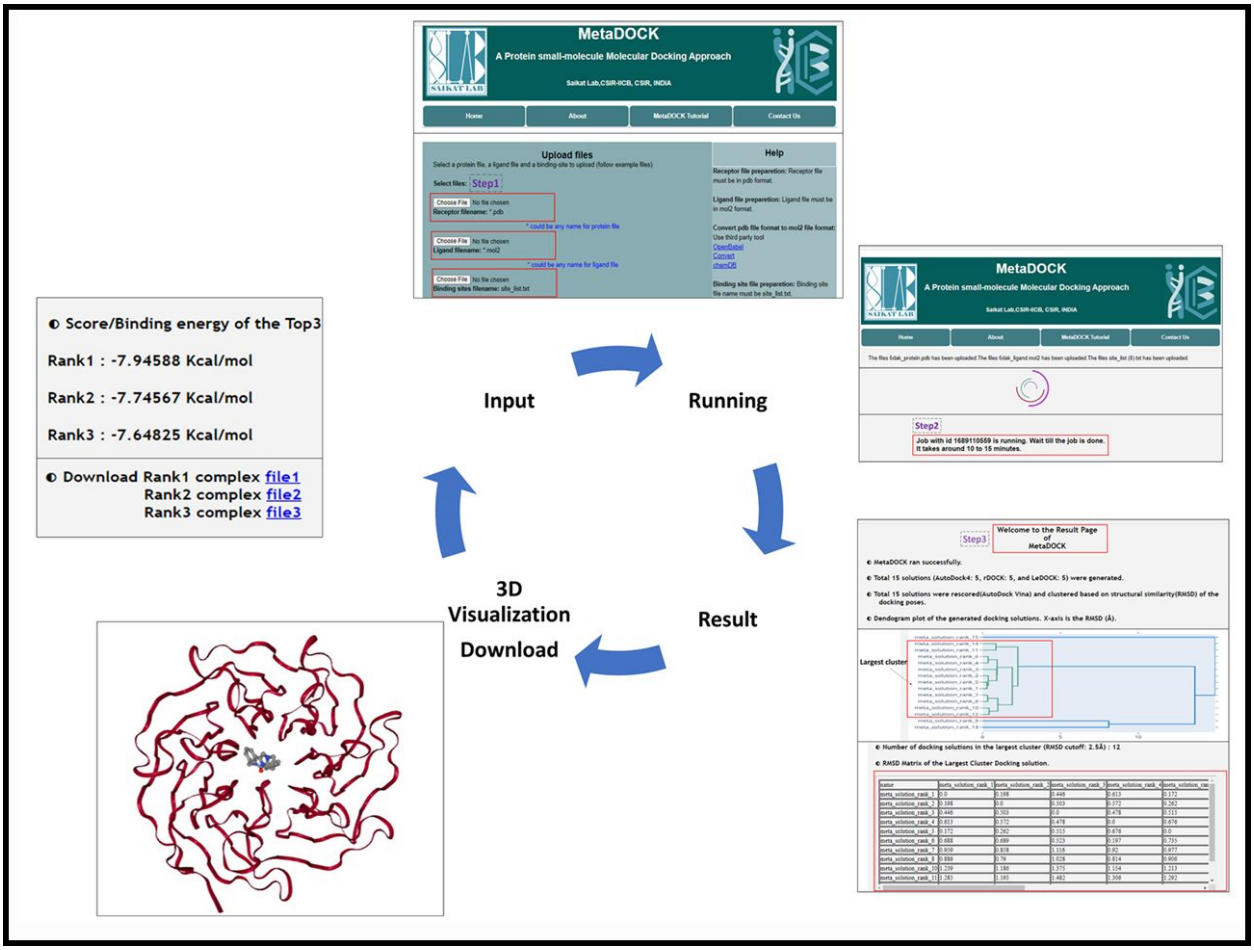

Figure S4: Screenshots of MetaDOCK web server input and output options.

Figure S5

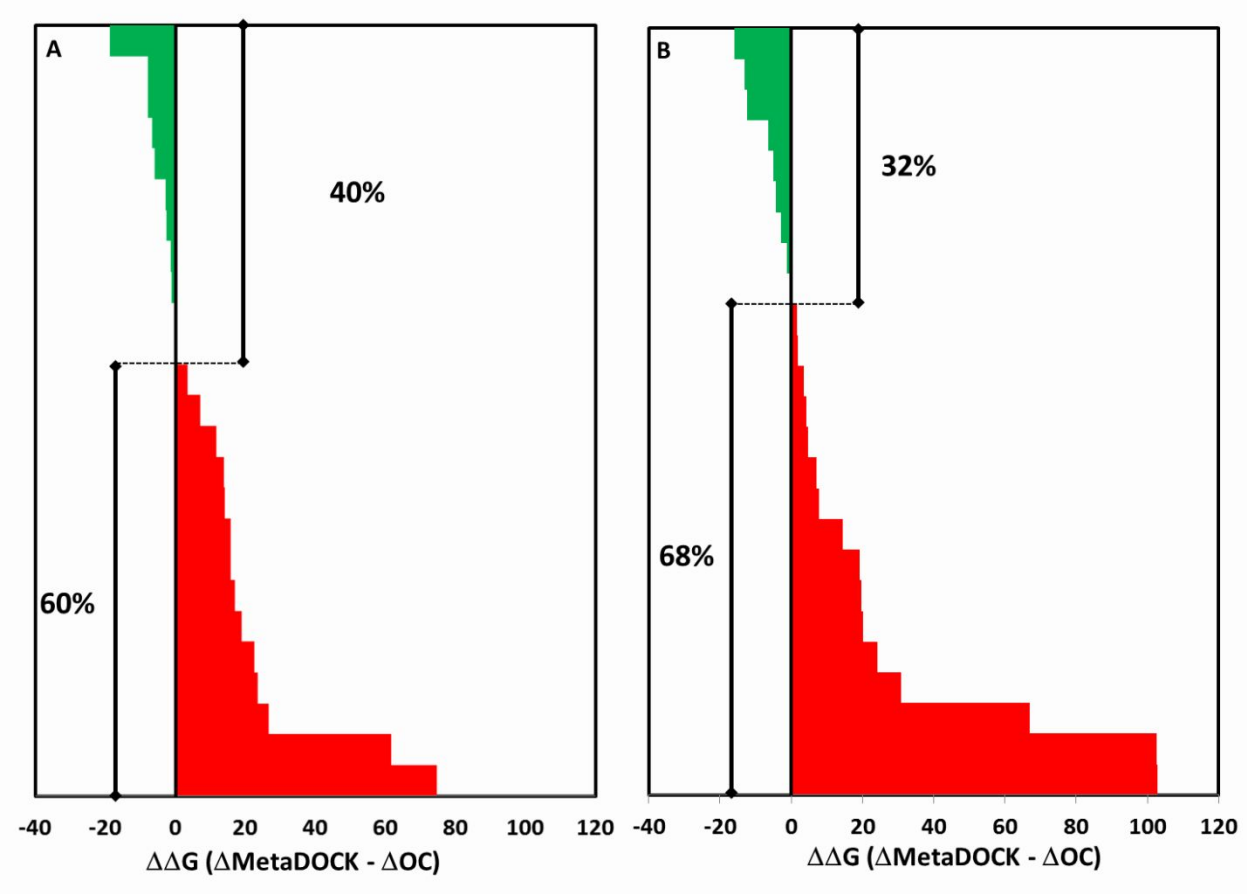

Figure S5: Molecular dynamics (MD) simulation and MM-PBSA analysis based energy estimation of the docked complexes. 25 randomly selected original and docked receptor-ligand complexes from the core dataset were subjected to MD simulations and ensembles of intermediate complexes were utilized to estimate the binding energy of the initial complex using MM-PBSA analysis. Panel A plots the gain/loss of binding free energies (ΔΔG; ΔG of MetaDOCK complex minus ΔG of original complex) of the docked complexes derived by MetaDOCK with respect to the original complexes (OC) obtained via experimental protocols. Panel B plots the gain/loss of binding free energies (ΔΔG; ΔG of GOLD complex - ΔG of original complex) of the docked complexes derived by GOLD with respect to the original complexes. Gain of binding free energy is colored by green while loss is marked in red color.

Table S1

Table S1: List of decoy (ZINC database ID) and active (SMILE) ligands

Decoy ligands						
1njs	**1vso**	**2azr**	**2ojg**	**3bgs**	**3bkl**	**3ccw**
C02771309	C03073566	C05328570	C04114703	C20469550	C04151710	C02344757
C04706417	C16949218	C01870309	C19845630	C20218695	C04221838	C09217291
C04742125	C36300217	C04277632	C18222565	C37572045	C08771640	C09430293
C09083603	C37017697	C19400497	C21531687	C37999690	C12864243	C01159910
C09612395	C37629146	C19797619	C40455146	C20366344	C13202476	C12662478
C09706090	C37802121	C19984013	C42143885	C40998426	C13264303	C13223873
C09706176	C37814579	C20213555	C55176565	C41713968	C08648184	C09613482
C09963312	C37819303	C20257807	C55176654	C41716912	C20228003	C13347106
C12467458	C37835022	C23424096	C50988064	C42455800	C20836302	C13563545
C13148456	C38008018	C26892217	C62870366	C44763553	C20834699	C20831714
C13548749	C38014952	C28225414	C71100313	C49101835	C20835498	C20831732
C14694401	C38717771	C32123984	C72115976	C49239809	C20836053	C20832234
C05732521	C40332304	C12377656	C72133037	C50247829	C20913860	C20833868
C01630966	C40385630	C35154874	C79006545	C51362372	C20914435	C20835411
C20356905	C40601322	C13545780	C79953758	C38042848	C20920855	C20906722
C20889995	C41160028	C37993495	C85330884	C40750410	C20921133	C20909767
C21078577	C42503561	C42521987	C85918152	C61830688	C20904921	C21077817
C21316758	C42807612	C42521333	C86015747	C62451927	C20906681	C21075934
C25262387	C44527145	C42521365	C86016299	C62812477	C20911598	C21076748
C25511754	C44567405	C42522073	C87780168	C63194712	C20921681	C21078869
C31155655	C44931536	C43629422	C87812953	C63195118	C21075486	C21078926
C31164863	C44934218	C45953210	C87813020	C68804406	C21078083	C21079559
C31167925	C45088608	C48652893	C87813376	C69144163	C21083898	C23041698
C31168211	C49265832	C18093757	C87875403	C70174569	C21078740	C24832323
C35454599	C49539317	C57292824	C88044579	C70182625	C21080346	C25262013
C35877936	C49571621	C43630398	C90150369	C70317739	C21080462	C32909866
C36369722	C50421097	C61093782	C91561390	C70316959	C21082069	C09432078
C37246160	C50657232	C62868149	C92137907	C70576916	C21601594	C39914013
C14512219	C59939139	C62922255	C92533517	C70576698	C21839466	C43772313
C38143588	C61809339	C62912888	C92540564	C71139933	C16097287	C09409213
C38143828	C65446854	C62912928	C92550890	C71139934	C09850378	C09409199
C59677403	C70327580	C63009435	C92589705	C80737246	C36500687	C09409279
C08582306	C77968819	C63008918	C93016380	C83590625	C36597643	C08758420
C63426950	C80532042	C45957055	C93915826	C85199360	C37538276	C16682658
C67910476	C80632642	C70118954	C94199074	C85200086	C39737866	C16182373
C67910700	C80749054	C70250545	C94292217	C85368920	C39738035	C32943067
C67911342	C83923985	C71172455	C94353584	C85622716	C43763797	C32943068
C67912156	C50657082	C71606226	C94501163	C87722907	C58994356	C12570131
C67912604	C88467662	C16491505	C94505943	C87868224	C58996998	C13749693
C67912760	C89756337	C17837334	C94606621	C87878329	C59018591	C14897439

C67912918	C90374922	C85632650	C94606647	C88113667	C59040032	C53619553
C67913019	C91301205	C85632711	C94606998	C88668196	C35148266	C46021909
C68604313	C91746441	C86805212	C94731521	C90378817	C20425202	C66200627
C70672689	C92474952	C90536497	C94731522	C90957036	C67913753	C66200669
C72320427	C92746053	C91451689	C94780893	C91275011	C67913756	C16682565
C78999668	C93229560	C91489413	C43536858	C91497034	C70700713	C73836772
C78999672	C95099970	C92917266	C95974048	C93072154	C77293241	C73836732
C85591177	C97248307	C95043887	C40428523	C93231619	C77300830	C13521432
C85866878	C97830879	C95931546	C96466089	C94565329	C85896106	C96507876
C31157904	C97831555	C96485299	C97016339	C94619934	C98231039	C33343435
3d0e	**3hl5**	**3l3m**				
C07344923	C02303660	C04582489				
C09089463	C00873423	C07885935				
C09135472	C08722830	C00402253				
C09257519	C03770019	C20432256				
C09706127	C08853094	C21811903				
C12325445	C09254310	C35611996				
C12644701	C09260573	C36264721				
C13127515	C01288715	C36779274				
C14532697	C09382088	C36961528				
C19219587	C09493253	C37377064				
C02927398	C03428043	C37441779				
C15970091	C09549511	C43095737				
C22911888	C09576385	C43460849				
C27267900	C09611404	C48403173				
C32870922	C10736869	C49122796				
C25174062	C12592951	C59204645				
C35682662	C13005145	C61692179				
C06878694	C13058928	C68585946				
C03670434	C13728643	C76578168				
C06363416	C13936396	C83236425				
C38573992	C16013901	C85685851				
C39218222	C17444844	C86079495				
C39218226	C18063653	C87238630				
C39729643	C20348258	C88126015				
C43472007	C20424330	C90249395				
C49451322	C21080938	C90948411				
C49545405	C24829362	C92774904				
C50120504	C25147238	C92775729				
C54615476	C27308228	C94484465				
C44388890	C35623034	C94668690				
C06213078	C39363028	C94786410				
C15936478	C39920012	C97098058				
C63229078	C36639997	C97411754				
C63303048	C15959258	C97520474				

C63472972	C49467311	C97521185				
C40051793	C09409755	C97582101				
C64481796	C58893421	C97624888				
C67602146	C20290811	C97622886				
C68489525	C15899957	C97645297				
C69040236	C31691335	C97645298				
C72008601	C16440820	C97694119				
C72097076	C72460488	C97737356				
C77971441	C03263279	C97768026				
C95455793	C36357469	C97768365				
C20589094	C64991311	C97768461				
C97111374	C96115566	C97768462				
C97256118	C96579176	C97768472				
C97472935	C96918752	C97768543				
C97938414	C98064929	C97796189				
C20572979	C09420471	C97892153				
Active ligands						
1njs	c1cc(ccc1C(CCCc2c(nc([nH]c2=O)N)N)C(C(F)(F)F)(O)O)C(=O)NC(CCC(=O)[O-])C(=O)[O-]					
1vso	CC(C)(C)c1c(c(no1)OCP(=O)(O)O)CC(C(=O)[O-])[NH3+]					
2azr	c1cc2c(c(sc2nc1)C(=O)[O-])OCC(=O)[O-]					
2ojg	CN(C)C(=O)c1cc(c[nH]1)c2c(cn[nH]2)c3ccccc3					
3bgs	c1c(c2c([nH]1)c(=O)[nH]cn2)C[N@@H+]3CC(C(C3)O)CO					
3bkl	c1ccc(cc1)CC(C(CCC(=O)NC(Cc2c[nH]c3c2cccc3)C(=O)[O-])(O)O)NC(=O)c4ccccc4					
3ccw	CC(C)c1c(nc(n1CCC(CC(CC(=O)[O-])O)O)c2ccc(cc2)F)C(=O)NCc3ccccc3					
3d0e	CCn1c2c(cnc(c2nc1c3c(non3)N)C#CC(C)(C)O)OC[C@@H]4CCC[NH2+]C4					
3hl5	CC1CCN(C1C(=O)Nc2ccccc2c3ncccn3)C(=O)C(C4CCCCC4)NC(=O)C(C)NC					
3l3m	C1CCN=C(C1)C2=C=C(/C(=c\3/[nH]c4=C=C=C=C(c4n3)C(=O)N)/C#C2)F					

Table S2

Table S2: Binding free energy (ΔG) and its enthalpy (ΔH) and entropy (TΔS) components of the docked complexes.

Protein PDB code	ΔH	TΔS	MetaDOCK ΔG	ΔH	TΔS	GOLD LCTS ΔG
1a30	-8.7098	53.9967	45.2869	-10.0125	92.6053	82.5928
1bzc	-72.096	45.4253	-26.6707	-62.5775	57.5267	-5.0508
1e66	-25.991	3.05	-22.9411	-24.9964	5.6946	-19.3018
1g2K	-65.5097	7.8716	-57.6381	-68.4204	6.7683	-61.6521
1gpk	-35.7663	19.6986	-16.0677	-27.5549	20.217	-7.3379
1gpn	-34.0811	12.2894	-21.7917	-29.622	15.2212	-14.4009
1h22	-57.6192	24.6167	-33.0025	-51.6329	38.2703	-13.3626
1h23	-48.594	24.2779	-24.3161	-53.1166	32.8869	-20.2297
1k1i	-13.9784	27.4128	13.4344	-28.8186	10.6166	-18.202
1mq6	-46.4644	6.0818	-40.3826	-38.2197	17.5104	-20.7093
1nc1	-54.4205	6.7144	-47.7061	-50.0992	9.4507	-40.6485
1nc3	-52.5042	13.9924	-38.5118	-47.8489	14.3562	-33.4927
1o0h	-20.6441	98.0475	77.4034	-15.7896	53.6677	37.8781
1o3f	-10.1038	12.9919	2.888	-3.9803	43.2834	39.3032
1p1n	-76.2798	14.9823	-61.2975	-77.3348	13.7743	-63.5605
1p1q	-61.6347	16.2662	-45.3686	-49.2162	6.3635	-42.8527
1pxn	-38.3645	16.8704	-21.4941	-36.8309	8.6973	-28.1336
1q8t	-31.5377	32.0804	0.5427	-26.2386	42.9767	16.7381
1q8u	-32.9547	15.1755	-17.7792	-27.4604	33.5319	6.0714
1qf1	-45.9112	11.2548	-34.6564	-8.1421	5.2777	-2.8644
1u1b	-26.6982	75.3254	48.6272	-15.4971	113.9202	98.4231
1vso	-35.0855	64.2459	29.1604	-32.0921	41.8096	9.7174
1w4o	-30.7797	64.8397	34.0601	-19.5499	81.8837	62.3337
1y6r	-74.6746	17.2623	-57.4123	-70.5982	17.1464	-53.4518
1ydt	-39.5083	23.9727	-15.5356	-42.01	20.0171	-21.993
1z6e	-42.9263	30.6212	-12.3052	-43.8338	39.8768	-3.9569
1z95	-45.0795	3.9549	-41.1247	-33.0145	16.8125	-16.202
2br1	-32.5252	9.7488	-22.7764	-36.397	10.5492	-25.8478
2c3i	-30.0281	22.528	-7.5001	-29.4826	12.2918	-17.1908
2cet	-42.2342	13.0306	-29.2036	-36.6997	26.1526	-10.547
2fvd	-32.8855	12.804	-20.0814	-32.9661	17.1438	-15.8223
2fxs	-38.5532	21.9056	-16.6476	-40.6815	14.0508	-26.6308
2p4y	-66.9097	25.9356	-40.974	-58.3624	41.0921	-17.2702
2pog	-33.7439	42.6209	8.877	-39.0371	3.9894	-35.0477
2qnq	-48.1579	13.6191	-34.5388	-43.8944	36.2002	-7.6942

2r9w	-24.7684	54.156	29.3876	-27.8882	33.3502	5.462
2v00	-12.0351	15.973	3.9387	-9.1484	27.7831	18.6348
2vkm	-85.3358	15.8207	-69.5151	-60.6092	26.1537	-34.4555
2w4x	-36.2395	9.5797	-26.6598	-38.8262	13.0915	-25.7348
2wn9	-19.7543	44.7196	24.9653	-22.0459	22.3735	0.3276
2xbv	-41.3676	27.389	-13.9787	-29.7239	19.0828	-10.6411
2xdl	-27.6593	7.4592	-20.2001	-23.5611	13.8365	-9.7247
2xii	-60.3533	15.3822	-44.9711	-44.8151	33.6093	-11.2058
2xnb	-39.8842	21.2509	-18.6333	-39.1846	26.1401	-13.0445
2y5h	-30.4771	48.2747	17.7976	-40.0084	29.8167	-10.1917
2yfe	-39.2405	25.1145	-14.126	-34.5456	22.1913	-12.3543
2ymd	-31.461	12.2175	-19.2434	-26.0512	19.2683	-6.783
2zb1	-41.8746	11.7449	-30.1296	-34.2215	12.0182	-22.2033
2zcq	-32.6249	17.0938	-15.531	-6.1927	85.9201	79.7274
2zcr	-31.7353	84.1938	52.4585	-34.5783	10.3189	-24.2594
2zy1	-48.3098	33.8874	-14.4224	-19.9591	80.5186	60.5596
3ao4	-23.0445	7.4853	-15.5592	-22.6893	4.691	-17.9983
3arq	-20.62	36.2522	15.6322	-14.1085	86.949	72.8405
3aru	-12.0714	9.6704	-2.4009	-34.2215	12.0182	7.2858
3b65	-51.2795	5.6219	-45.6576	-53.1562	2.8951	-50.2611
3coy	-54.2067	15.0807	-39.126	-48.6586	49.1651	0.5065
3coz	-37.1227	30.0852	-7.0375	-37.7669	14.4145	-23.3524
3d6q	-23.1097	30.1963	7.0866	-20.3191	41.9433	21.6243
3dd0	-19.3596	3.374	-15.9856	-19.2021	10.811	-8.391
3dx2	-35.0055	75.4605	40.455	-50.4108	73.7139	23.3031
3e93	-55.2543	22.4204	-32.8339	-55.0035	32.5704	-22.433
3ebp	-31.8475	30.5596	-1.2879	-25.7526	39.5179	13.7653
3ehy	-13.1721	38.2027	25.0305	28.9525	37.0396	65.9922
3f3a	-21.6678	19.5333	-2.1345	-33.2631	8.0211	-25.242
3f3c	-34.1494	10.5692	-25.238	-34.1625	8.9246	-23.5802
3f3d	-29.7627	4.6396	-25.1231	-31.0775	16.6078	-14.4697
3f3e	-22.7684	14.8827	-7.8857	-28.6417	11.0141	-17.6275
3fv1	-75.1285	10.047	-65.0814	-82.0116	24.0766	-57.935
3g2n	-31.2668	0.1695	-31.0974	-32.7916	2.0745	-30.7171
3g2z	-10.3289	24.0178	13.6889	-3.6007	18.7722	15.1714
3g31	-7.3538	31.8788	24.525	-10.8918	18.0691	7.1773
3gc5	-47.3835	12.645	-34.7385	-39.9409	16.0114	-23.9294
3ge7	-70.0609	23.6541	-46.4068	-70.3986	34.3946	-36.004
3gnw	-42.1173	16.3369	-25.7804	-27.2983	26.2258	-1.0725
3gy4	-24.3089	10.6072	-13.7016	-28.2053	20.634	-7.5713
3ivg	-33.0444	34.3209	1.2765	-35.5339	34.3285	-1.2054

3jvr	-26.407	5.6368	-20.7702	-17.1235	17.7991	0.6755
3jya	-27.4977	9.1229	-18.3748	-19.6081	2.7338	-16.8744
3k5v	-33.1151	15.0098	-18.1053	-29.3655	5.4619	-23.9036
3lka	-14.2824	5.6489	-8.6335	0.0125	42.5043	42.5168
3mss	-34.8436	32.7516	-2.092	-19.6243	24.8391	5.2148
3nw9	-62.8799	6.6802	-56.1996	-53.6621	38.2016	-15.4605
3nx7	-24.9058	6.8814	-18.0244	-40.2958	30.9415	-9.3543
3pww	-31.6892	47.7495	16.0603	-17.2671	76.9598	59.6928
3pxf	-17.7868	28.1985	10.4117	-17.965	27.3847	9.4197
3qqs	-38.4756	57.9534	19.4778	-40.2958	53.2552	12.9594
3rsx	-20.0335	5.8309	-14.2027	-16.0667	5.552	-10.5148
3tsk	-35.5859	18.3935	-17.1925	-47.7953	39.759	-8.0363
3up2	-47.0033	20.9989	-26.0044	-40.1954	49.2852	9.0898
3wz8	-25.7754	22.581	-3.1944	-15.8983	12.4391	-3.4592
3zsx	-25.3945	45.8971	20.5025	-30.8961	13.0592	-17.8369
4abg	-30.4833	22.5583	-7.925	-32.0245	33.1284	1.1039
4cr9	-15.4824	4.1508	-11.3316	-17.6352	7.5807	-10.0544
4crc	-42.0568	19.244	-22.8129	-28.1593	17.6998	-10.4595
4ddk	-16.5801	44.4249	27.8448	-24.0306	35.5363	11.5057
4de1	-35.0006	10.3635	-24.6372	-36.7626	7.3726	-29.39
4e5w	-45.0814	15.2478	-29.8337	-40.0635	19.6261	-20.4374
4ea2	-39.1985	24.798	-14.4005	-36.383	24.624	-11.759
4eky	-49.4172	10.0363	-39.3809	-34.3675	21.8691	-12.4983
4eo8	-32.2379	10.6243	-21.6136	-16.4345	12.4519	-3.9826
4eor	-37.014	10.4703	-26.5437	-33.6511	8.658	-24.993
4f3c	-67.6257	7.6022	-60.0235	-67.2941	18.7661	-48.528
4gid	-98.3348	27.2702	-71.0646	-51.1553	28.5677	-22.5875
4gkm	-42.4938	22.3107	-20.1831	-48.0311	16.2167	-31.8
4ih5	-11.2629	10.7087	-0.5542	-15.9847	8.6628	-7.322
4j28	-44.3898	3.391	-40.9989	-35.8268	6.1062	-29.7206
4j3l	-41.1435	18.6269	-22.5166	-37.7471	10.3096	-27.4375
4jia	-16.7576	48.9493	32.1917	-29.1034	32.4787	3.3753
4jxs	-18.8517	51.2935	32.4418	-23.2746	45.1003	21.8256
4k18	-34.9256	17.8497	-17.0758	-31.5843	11.848	-19.7363
4kz6	-27.831	36.6445	8.8135	-17.8255	30.9468	13.1212
4lzs	-25.353	7.5563	-17.7966	-20.9126	7.5755	-13.3371
4m0y	-28.3416	9.2274	-19.1142	-28.9964	3.8099	-25.1865
4mgd	-36.3738	14.0255	-22.3483	-37.7667	5.633	-32.1337
4ogj	-27.0466	15.8596	-11.187	-40.6935	31.3199	-9.3736
4owm	-14.4868	38.3475	23.8607	-19.4574	25.1726	5.7151
4pcs	-40.7213	24.8413	-15.88	-35.1904	26.926	-8.2644

4qac	-27.8732	11.2577	-16.6156	-33.8292	7.1536	-26.6756
4qd6	-27.1837	16.5212	-10.6624	-25.7229	12.7383	-12.9846
4rfm	-42.444	7.6911	-34.7529	-43.4038	17.8906	-25.5133
4tmn	-18.0458	27.3577	9.3119	0.2235	9.3538	9.5773
4twp	-34.0136	22.3703	-11.6433	-34.7757	24.7268	-10.0489
4ty7	-47.8529	19.6855	-28.1674	-48.4279	17.4008	-31.0271
4w9c	-37.4796	6.7453	-30.7343	-41.4515	7.3453	-34.1063
4w9h	-41.6551	19.223	-22.4322	-45.1633	7.3418	-37.821
4w9i	-39.2278	11.5812	-27.6466	-36.9582	6.8848	-30.0735
4w9l	-42.2234	16.6037	-25.6198	-46.1433	8.5245	-37.6189
5a7b	-45.779	16.785	-28.994	-32.5857	68.8938	36.3081
5c28	-12.2026	4.4592	-7.7434	-11.7765	12.3174	0.5409
5dwr	-36.582	16.4716	-20.1103	-43.5795	25.0369	-18.5426