Molecular Modeling Studies on the Binding Mode of the PD-1/PD-L1 Complex Inhibitors

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Table S1: The glide docking scores (unit, kcal/mol) of **29** ligands against PD-L1 proteins (5NIU and 5N2F).

Title	IC50 (nM)	ΔG(exp)	5NIU_Dock	ΔΔG (5NIU)	5N2F_Dock	ΔΔG (5N2F)
BMS-1001(1, 5NIU)	2.25	-11.80	-11.69	-0.11	-11.60	-0.20
BMS-200 (2, 5N2F)	80	-9.68	-12.06	2.38	-12.18	2.50
BMS-3029 (3)	2350	-7.68	-12.35	4.68	-12.73	5.05
BMS-1166 (4, 5NIX)	1.4	-12.08	-11.08	-1.00	-11.66	-0.42
BMS-114 (5)	43	-10.05	-11.14	1.09	-10.42	0.37
BMS-1197 (6)	1.85	-11.91	-11.15	-0.76	-12.10	0.18
BMS-1205 (7)	2.71	-11.69	-12.14	0.46	-12.14	0.45
BMS-1220 (8)	6.07	-11.21	-14.04	2.83	-10.58	-0.63
BMS-2002 (9)	10	-10.91	-13.04	2.13	-11.63	0.71
BMS-1250 (10)	1.19	-12.17	-12.11	-0.06	-12.64	0.46
BMS-1305 (11)	0.92	-12.33	-11.35	-0.98	-11.34	-0.99
BMS-1239 (12)	148.9	-9.31	-11.10	1.79	-11.19	1.88
BMS-2010 (13)	50	-9.96	-12.00	2.04	-11.93	1.97
BMS-3024 (14)	5.54	-11.26	-12.75	1.49	-11.53	0.27
BMS-16 (15)	1945	-7.79	-9.31	1.52	-8.70	0.91
BMS-82 (16)	3186	-7.50	-9.24	1.74	-9.12	1.62
BMS-39 (17)	4184	-7.34	-8.26	0.92	-8.52	1.18
BMS-172 (18)	107	-9.51	-8.54	-0.97	-9.30	-0.21
BMS-163 (19)	93	-9.59	-10.12	0.53	-10.23	0.63
BMS-202 (20, 5J89)	18	-10.56	-11.22	0.66	-10.34	-0.23
BMS-1043 (21)	239.2	-9.03	-10.51	1.48	-11.33	2.29
BMS-8 (22, 5J8O)	146	-9.32	-11.40	2.08	-10.25	0.92
BMS-107 (23)	329	-8.84	-9.77	0.93	-9.97	1.12
BMS-101 (24)	1076	-8.14	-8.35	0.21	-7.96	-0.19
BMS-1016 (25)	4.55	-11.38	-11.69	0.31	-11.79	0.41
BMS-1057 (26)	985.8	-8.19	-10.31	2.12	-9.66	1.46
BMS-1095 (27)	81.25	-9.67	-9.86	0.18	-11.07	1.40
BMS-1108 (28)	624.2	-8.46	-10.55	2.08	-9.57	1.11
BMS-1082 (29)	828.4	-8.30	-9.66	1.37	-10.68	2.39
Mean Error				1.07		0.91
STDev				1.29		1.22
RMSE				1.66		1.51

Table S2. The pKa values of ligands as predicted by the EPik program.

Title	pK_a	Title	pK_a
BMS-1001(1, 5NIU)	8.28	**BMS-82 (16)**	8.63
BMS-200 (2, 5N2F)	8.76	**BMS-39 (17)**	8.79
BMS-3029 (3)	8.74	**BMS-172 (18)**	8.77
BMS-1166 (4, 5NIX)	8.72	**BMS-163 (19)**	8.2
BMS-114 (5)	8.79	**BMS-202 (20, 5J89)**	7.74
BMS-1197 (6)	8.72	**BMS-1043 (21)**	8.08
BMS-1205 (7)	8.48	**BMS-8 (22, 5J8O)**	8.71
BMS-1220 (8)	10.73	**BMS-107 (23)**	8.72
BMS-2002 (9)	8.19	**BMS-101 (24)**	8.76
BMS-1250 (10)	8.87	**BMS-1016 (25)**	8.27
BMS-1305 (11)	8.11	**BMS-1057 (26)**	8.08
BMS-1239 (12)	8.48	**BMS-1095 (27)**	8.08
BMS-2010 (13)	8.31	**BMS-1108 (28)**	8.08
BMS-3024 (14)	8.34	**BMS-1082 (29)**	8.08
BMS-16 (15)	8.23		

Table S3: The Moveable-Type-based binding free energy (unit, kcal/mol) of **29** ligands against PD-L1 proteins (5NIU and 5N2F), using docked poses from the Glide dock program.

Title	IC50 (nM)	ΔG(exp)	MT_5NIU	ΔΔG (5NIU)	MT_5N2F	ΔΔG (5N2F)
BMS-1001(1, 5NIU)	2.25	-11.80	-10.81	-0.98	-9.72	-2.08
BMS-200 (2, 5N2F)	80	-9.68	-11.75	2.07	-9.00	-0.68
BMS-3029 (3)	2350	-7.68	-9.94	2.26	-8.70	1.02
BMS-1166 (4, 5NIX)	1.4	-12.08	-10.99	-1.09	-10.53	-1.55
BMS-114 (5)	43	-10.05	-10.22	0.17	-8.41	-1.64
BMS-1197 (6)	1.85	-11.91	-12.44	0.53	-10.68	-1.23
BMS-1205 (7)	2.71	-11.69	-11.22	-0.47	-9.82	-1.87
BMS-1220 (8)	6.07	-11.21	-12.14	0.93	-10.58	-0.63
BMS-2002 (9)	10	-10.91	-12.56	1.65	-11.57	0.66
BMS-1250 (10)	1.19	-12.17	-11.99	-0.19	-11.58	-0.59
BMS-1305 (11)	0.92	-12.33	-12.29	-0.04	-9.98	-2.35
BMS-1239 (12)	148.9	-9.31	-11.02	1.71	-9.55	0.24
BMS-2010 (13)	50	-9.96	-11.65	1.69	-11.97	2.01
BMS-3024 (14)	5.54	-11.26	-11.37	0.11	-11.84	0.57
BMS-16 (15)	1945	-7.79	-9.25	1.46	-6.93	-0.86
BMS-82 (16)	3186	-7.50	-8.02	0.52	-6.91	-0.59
BMS-39 (17)	4184	-7.34	-8.59	1.26	-6.19	-1.14
BMS-172 (18)	107	-9.51	-6.57	-2.94	-4.99	-4.52
BMS-163 (19)	93	-9.59	-7.34	-2.25	-5.93	-3.67
BMS-202 (20, 5J89)	18	-10.56	-8.89	-1.68	-9.92	-0.64
BMS-1043 (21)	239.2	-9.03	-11.02	1.99	-9.32	0.29
BMS-8 (22, 5J8O)	146	-9.32	-12.35	3.03	-8.94	-0.39
BMS-107 (23)	329	-8.84	-7.73	-1.11	-7.52	-1.32
BMS-101 (24)	1076	-8.14	-8.29	0.15	-6.98	-1.16
BMS-1016 (25)	4.55	-11.38	-10.11	-1.27	-8.98	-2.40
BMS-1057 (26)	985.8	-8.19	-11.84	3.64	-9.88	1.69
BMS-1095 (27)	81.25	-9.67	-11.76	2.09	-9.97	0.30
BMS-1108 (28)	624.2	-8.46	-10.35	1.89	-9.15	0.68
BMS-1082 (29)	828.4	-8.30	-11.71	3.41	-10.29	2.00
MAE				0.64		-0.68
STDev				1.68		1.54
RMSE				1.77		1.66

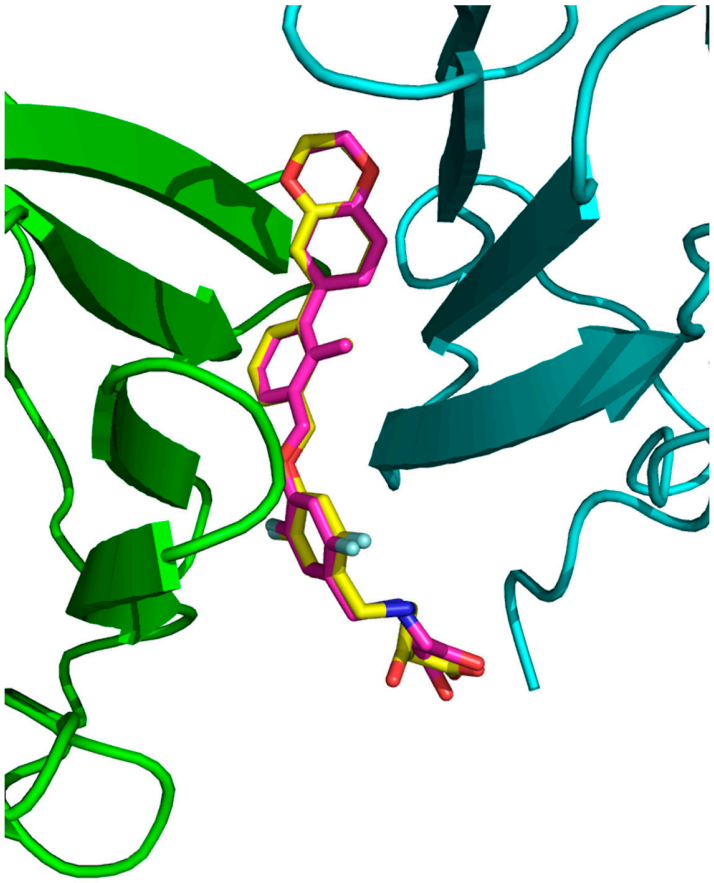

Figure S1: The superposition of the glide-docked generated pose and its native conformation in 5N2F for ligand BMS-200(**2**, 5N2F)**.** The native confirmation is in yellow color, and the docked pose is in magenta color. Chain D is colored with green secondary structure and whereas Chain C in cyan color.

Table S4. Glide docking scores of 261 drug-like molecules obtained from an NCI database against the PD-L1 protein (5NIU).

NCI ID	Docking Scores	NCI ID	Docking Scores	NCI ID	Docking Scores	NCI ID	Docking Scores
66	-1.90	113321	-9.27	221630	-8.50	512107	-7.43
1185	-4.12	113554	-4.04	230200	-4.66	521770	-4.01
1229	-7.67	114380	-9.36	230218	-5.82	602688	-3.37
6594	-5.34	116101	-4.02	230339	-9.58	610172	-5.77
8007	-10.33	116505	-8.66	231593	-5.12	610529	-8.11
8796	-1.82	117598	-1.88	231919	-7.66	614534	-6.53
21357	-7.76	119770	-7.94	237021	-3.00	615401	-2.25
22645	-9.00	121111	-8.85	247507	-6.99	615839	-6.99
24026	-8.48	121426	-5.37	249991	-5.10	618629	-2.94
25686	-8.88	124018	-11.98	251798	-3.25	623064	-6.11
26870	-5.42	125048	-9.71	259678	-6.09	626099	-6.64
26873	-8.85	125658	-7.02	270462	-2.43	627595	-2.62
30850	-3.96	126152	-9.15	275635	-10.75	627988	-4.36
31781	-5.61	132516	-5.20	277563	-5.73	628670	-4.17
34575	-4.94	134098	-6.36	281758	-8.79	628992	-2.58
35739	-8.18	134953	-3.51	285667	-9.00	631580	-7.77
35812	-9.64	135757	-5.57	288368	-3.94	631845	-9.46
37358	-4.86	135906	-3.99	289517	-11.92	631849	-5.17
38206	-5.51	142487	-5.70	291629	-7.21	632252	-9.97
38224	-6.09	142549	-10.46	294195	-9.21	634620	-8.08
40436	-10.72	144471	-3.97	295720	-9.02	639645	-5.23
45231	-1.89	147670	-4.69	295740	-7.00	640635	-4.32
47705	-9.63	149079	-6.85	297359	-9.30	641095	-11.32
47711	-7.88	149802	-10.12	297621	-5.39	641615	-3.96
48191	-5.54	154683	-3.07	300505	-8.40	642066	-5.29
49810	-4.92	155336	-3.17	302647	-7.02	642740	-6.30
50410	-8.57	157443	-8.57	303242	-8.83	645032	-5.16
50920	-3.05	158130	-7.13	311463	-8.73	645548	-8.72
54235	-5.04	161364	-4.00	316070	-11.28	645674	-10.87
54397	-7.35	162378	-8.10	319420	-9.35	647575	-7.13
54700	-8.43	163591	-8.07	319918	-5.66	649829	-7.72
58924	-4.22	164052	-7.08	320301	-2.45	650064	-8.13
60847	-4.01	164132	-9.46	322038	-5.25	650834	-7.93
60855	-6.04	164537	-8.15	323960	-2.36	652204	-9.10
60933	-11.90	166198	-6.60	329103	-7.93	652940	-4.16
61811	-2.87	166781	-8.04	329291	-6.22	653947	-4.61
62543	-6.73	168574	-4.78	331020	-3.27	654629	-9.94

66370	-2.62	169158	-7.59	333476	-10.23	654955	-7.16
69574	-2.05	170950	-5.70	333744	-8.94	655756	-6.58
70127	-5.49	171170	-2.35	333750	-8.84	656909	-5.88
78522	-7.89	174043	-7.51	338398	-6.69	658289	-6.49
78878	-2.55	174941	-7.89	338481	-8.04	658724	-2.58
79594	-9.59	179723	-6.52	338766	-8.42	659848	-8.48
81459	-5.81	180666	-2.97	339623	-10.21	659929	-2.46
81832	-2.76	180705	-8.17	342051	-7.62	671409	-1.92
82444	-1.34	181934	-6.58	343493	-5.11	672969	-5.40
83536	-7.09	184763	-6.09	344021	-3.82	673133	-9.83
84086	-6.32	202113	-6.22	346852	-5.70	676316	-8.93
85530	-9.46	202799	-6.79	351366	-6.29	676960	-0.53
86538	-7.58	203920	-8.18	358301	-3.93	677456	-8.46
90596	-3.14	204278	-7.67	359471	-6.14	677477	-9.87
90610	-2.66	204623	-8.21	366600	-7.43	677542	-2.18
91690	-7.31	205515	-10.88	367308	-4.60	680304	-8.40
91999	-9.26	205608	-7.73	371156	-2.34	685476	-10.01
93327	-7.61	208399	-8.89	380522	-8.88	693118	-5.29
94749	-4.31	209005	-4.13	400283	-5.23	693996	-7.00
102345	-7.03	210472	-8.45	401264	-6.32	694167	-6.93
103877	-1.37	211995	-7.88	402209	-5.52	695179	-6.22
105793	-9.86	216285	-8.03	402672	-4.96	697142	-6.68
106137	-10.34	216342	-8.27	403448	-5.20	697174	-10.56
106151	-8.61	216639	-8.26	403574	-8.37	697412	-5.20
107691	-6.82	216768	-8.82	404384	-7.16	697885	-5.68
108869	-7.46	216958	-8.34	507547	-8.91	697936	-3.18
109830	-5.88	216974	-8.21	508816	-7.76	700418	-4.09
112133	-4.49	220130	-9.53	509389	-7.80	701633	-6.21
112367	-7.44						

Table S5: The ligand-protein interactions between the PD-1/PD-L1 complex inhibitors and the PD-L1 protein of 5N2F.

Title	IC50 (nM)	Chain C	Chain D
BMS-1001(1, 5NIU)	2.25	10	Tyr56, Thr20, Ala18, Asp122, Lys124
BMS-200 (2, 5N2F)	80		Tyr56, Ala18, Phe19, Asp122
BMS-3029 (3)	2350		Tyr56, Thr20, Asp122, Lys124
BMS-1166 (4, 5NIX)	1.4		Tyr56, Thr20, Ala18, Asp122
BMS-114 (5)	43		Tyr56, Thr20, Ala18, Asp122
BMS-1197 (6)	1.85		Tyr56, Phe19, Thr20, Asp122, Lys124
BMS-1205 (7)	2.71		Tyr56, Thr20, Ala18, Asp122, Lys124
BMS-1220 (8)	6.07		Tyr56, Thr20, Ala18, Asp122, Lys124
BMS-2002 (9)	10	Asn63	Tyr56, Phe19, Thr20, Ala121, Asp122, Lys124
BMS-1250 (10)	1.19	Asn63	Tyr56, Ala18, Phe19, Thr20, Asp122
BMS-1305 (11)	0.92		Tyr56, Ala18, Phe19, Asp122
BMS-1239 (12)	148.9		Tyr56, Thr20, Ala18, Asp122, Lys124
BMS-2010 (13)	50		Tyr56, Thr20, Ala18, Asp122, Lys124
BMS-3024 (14)	5.54		Tyr56, Thr20, Asp122, Lys124
BMS-16 (15)	1945		Tyr56, Thr20, Asp122, Lys124
BMS-82 (16)	3186		Tyr56, Asp122, Lys124
BMS-39 (17)	4184	Gln66	Tyr56
BMS-172 (18)	107		Tyr56, Ala18, Asp122
BMS-163 (19)	93	Tyr56	Tyr56, Gly119, Ala121, Asp122, Tyr123
BMS-202 (20, 5J89)	18	Tyr56	Ala121, Asp122
BMS-1043 (21)	239.2	Asn63	Tyr56, Thr20, Ala18, Asp122
BMS-8 (22, 5J8O)	146		Tyr56, Asp122, Lys124
BMS-107 (23)	329		Tyr56, Thr20, Ala18, Asp12
BMS-101 (24)	1076		Tyr56, Asp122
BMS-1016 (25)	4.55		Tyr56, Phe19, Thr20, Asp122, Lys124
BMS-1057 (26)	985.8	Asn63	Tyr56, Thr20, Ala18, Asp122
BMS-1095 (27)	81.25	Asn63	Tyr56, Thr20, Ala18, Asp122
BMS-1108 (28)	624.2		Tyr56, Thr20, Ala18, Asp122
BMS-1082 (29)	828.4		Tyr56, Thr20, Ala18, Asp122

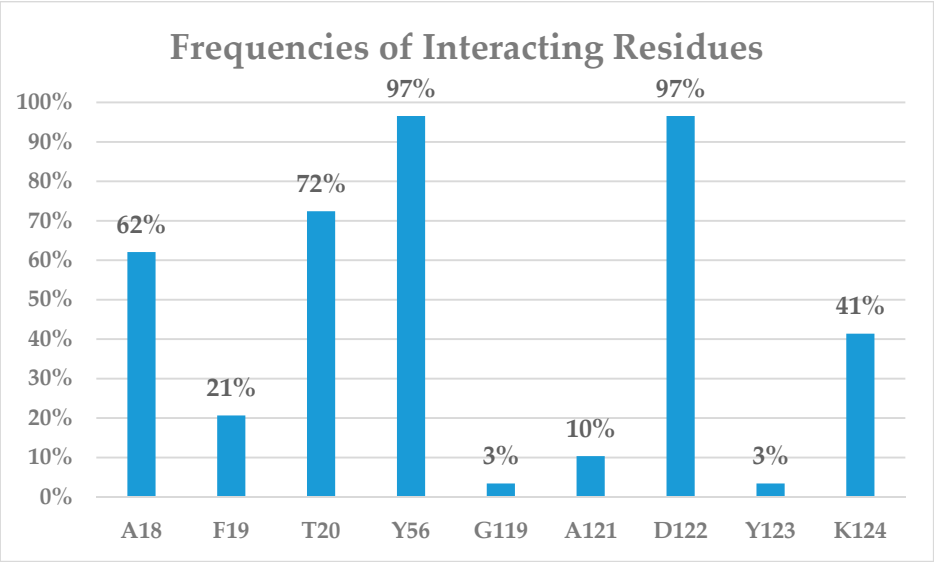

Figure S2: Interacting residues of PD-L1 with all 29 different inhibitors in the 5N2F model.

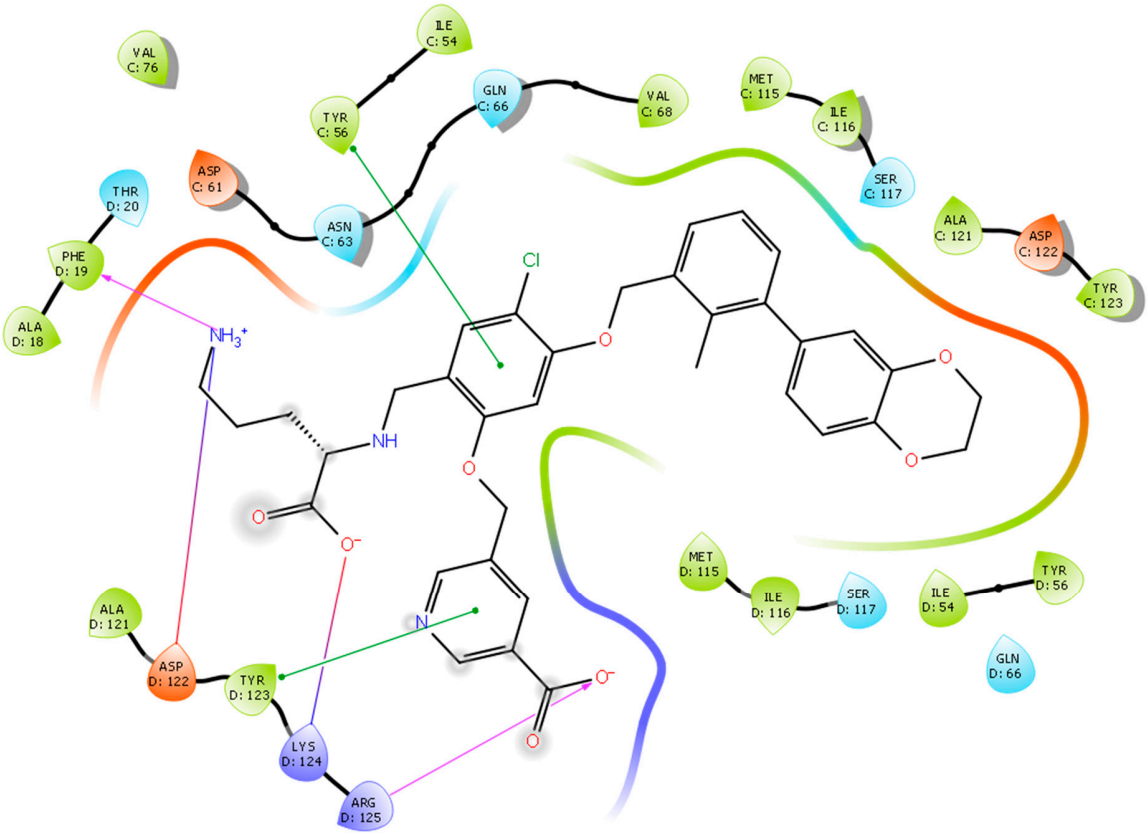

Figure S3: Protein-ligand interactions between 5NIU and BMS-2002 (**9**). It shows that main-chain carbonyl group of Phe19 and the side chain carboxylate of Asp122 form bonds with the amino moiety of ligand and that the Lys124 and Arg125 interact with two carboxylate groups of compound **9**. Tyr56 from chains C and D each forms π-π interactions with two different aromatic rings of **9**.