SUPPLEMENTARY TABLES

Table S1. Difficult cases of the docking benchmark dataset

Case	Molecule 1		Molecule 2		Bound State
1i	3aveA	Ig gamma-1 chain C region	1fnlA	Low affinity immunoglobulin gamma FC region receptor III-B	1e4kA:C
1ii	3aveA	Ig gamma-1 chain C region	1fnlA	Low affinity immunoglobulin gamma FC region receptor III-B	1e4kB:C
2i	2hmiC	FAB fragment of monoclonal antibody 28	1s6pB	POL polyprotein	2hmiC:B
2ii	2hmiD	FAB fragment of monoclonal antibody 28	1s6pB	POL polyprotein	2hmiD:B
3	1cl0A	Thioredoxin reductase	2tirA	Thioredoxin	1f6mA:C
4	1b39A	Cell division protein kinase 2	1fpzF	Cyclin-dependent kinase inhibitor 3	1fq1A:B
5	1x9yA	Cysteine proteinase	1nycA	Cysteine protease inhibitor	1pxvA:C
6	1kwmA	Procarboxypeptidase B	2jtoA	Carboxypeptidase inhibitor	1zliA:B
7	1zm8A	Nuclease	1j57A	Nuclease A inhibitor	2o3bA:B
8	1ijjB	Actin, alpha skeletal muscle	3dniA	Deoxyribonuclease I	1atnA:D
9	1ctqA	Transforming protein P21/H-RAS-1	2ii0A	Son of sevenless homolog 1	1bkdR:S
10	1a6zA	HFE	1cx8A	Transferrin receptor	1de4A:C
11i	1buyA	Erythropoietin	1ernA	Erythropoietin receptor	1eerA:B
11ii	1buyA	Erythropoietin	1ernA	Erythropoietin receptor	1eerA:C

12i	1qfkH	Coagulation factor VIIA heavy chain	1tfhB	Tissue factor	1fakH:T
12ii	1qfkL	Coagulation factor VIIA light chain	1tfhB	Tissue factor	1fakL:T
13	1ijjB	Actin, alpha skeletal muscle	1d0nB	Horse plasma gelsolin	1h1vA:G
14	1qg4A	RAN protein	1f59A	Importin beta-1	1ibrA:B
15	1g0yR	Interleukin-1 receptor, type 1	1ilr1	Interleukin-1 receptor antagonist protein	1iraY:X
16	1qupA	Superoxide dismutase 1 copper chaperone	2jcwA	Cu/Zn superoxide dismutase	1jk9A:B
17	1jmjA	Heparin cofactor II	2cn0H	Prothrombin precursor	1jmoA:H
18i	1jzoA	Thiol:disulfide interchange protein DsbC	1jpeA	DsbD-alpha	1jzdA:C
18ii	1jzoA	Thiol:disulfide interchange protein DsbC	1jpeA	DsbD-alpha	1jzdB:C
19	1hurA	ADP-ribosylation factor 1	1r8mE	Arno	1r8sA:E
20	2fxuA	Actin, alpha skeletal muscle	1ux5A	BNI1 protein	1y64A:B
21	1n0vC	Elongation factor 2	1xk9A	Exotoxin A	1zm4A:B
22	1fchA	Peroxisomal targeting signal 1 receptor	1c44A	Sterol carrier protein 2	2c0lA:B
23	1ywhA	Urokinase plasminogen activator surface receptor	2i9aA	Urokinase-type plasminogen activator	2i9bA:E
24	1j54A	DNA polymerase III, epsilon chain	1se7A	Homologue of the theta subunit of DNA polymerase III	2idoA:B
25	1yzuA	Ras-related protein Rab-21	1txuA	Rab5 GDP/GTP exchange factor	2ot3B:A

Table S2. Other conformations of given molecules in difficult cases of the benchmark dataset, found using 100% sequence homology

Case	Molecule	Other Conformations
1i, 1ii	3aveA	2j6eB, 1h3yB, 1h3tB, 2ig2H, 3agvA, 3ry6B, 1mcoH
1i, 1ii	1fnlA	
2i	2hmiC	
2ii	2hmiD	
2i, 2ii	1s6pB	2i5jA, 1hysA, 1dloA, 3kk3B, 3kk1B, 3kjvB
3	1cl0A	
3	2tirA	
4	1b39A	2uueC, 1jsuA, 1pyeA, 1p2aA, 1jvpP, 2g9xC, 1oiqA, 3ddqC, 3dogC, 3bhvC, 3my5C, 1oiuC, 1h25C, 2wmaC, 1h26C, 2wmbC, 3pxfA
4	1fpzF	1fpzABCDE, 1fq1A
5	1x9yA	1y4hA
5	1nycA	
6	1kwmA	
6	2jtoA	2k2xA, 1zliB
7	1zm8A	
7	1j57A	1ktuA, 2o3bB
8	1ijjB	2yjfBE, 2yjeA, 2vypB, 2y83R, 2q31AB, 3tpqE, 3mfpA, 3g37R
8	3dniA	
9	1ctqA	1nvwR, 1iaqA, 3lo5AE, 2x1vA
9	2ii0A	1xd4AB, 3ksyA, 1xd2C, 1xdvAB, 1bkdS
10	1a6zA	
10	1cx8A	
11i, 11ii	1buyA	1cn4C
11i, 11ii	1ernA	1ebaA
12i	1qfkH	1jbuH
12ii	1qfkL	1danL, 1dvaL, 1f7mA, 1fakL, 1ff7A, 1ffmA, 1jbuL, 1kliL, 1kljL, 1o5dL, 1wqvL, 1wssL, 1wtgL, 1wunL, 1wv7L, 1ygcL, 2a2qL, 2aeiL, 2b7dL, 2f9bL, 2flbL, 2flrL, 2zp0L, 2zwlL, 2zzuL, 3elaL
12i, 12ii	1tfhB	1ahwF, 1fakT, 1jpsT, 1o5dT, 1tfhAB, 1w0yT, 1w2kT, 1wqvT, 1wssT, 1wtgT, 1wunT, 1wv7T, 2b7dT, 2f9bT, 2flbT, 2flrT, 2zp0T, 2zwlT, 2zzuT, 3elaT
13	1ijjB	2yjfBE, 2yjeA, 2vypB, 2y83R, 2q31AB, 3tpqE, 3mfpA, 3g37R
13	1d0nB	1rgiG, 2fh3A, 2fh4AB
14	1qg4A	1k5gJ, 1i2mAC, 3ch5A, 3a6pCH, 1ibrAC, 1a2kC, 1qbkC, 3gj0B, 1rrpC
14	1f59A	1ibrB, 2q5dB, 2qnaA
15	1g0yR	1itbB, 1iraY
15	1ilr1	1irpA
16	1qupA	1jk9B
16	2jcwA	
17	1jmjA	1jmjB, 1jmoA
17	2cn0H	3nxpA, 3k65B, 2hntE

18i, 18ii	1jzoA	1jzoB
18i, 18ii	1jpeA	3pfuA,2hyxC
19	1hurA	1r8qA, 3o47AB, 3o47A, 1r8sA, 1u81A
19	1r8mE	1r8sE
20	2fxuA	2q31AB, 2zwhA, 2y83S, 3tpqE, 3g37P, 2yjfBCE, 2vypB, 2yjeA
20	1ux5A	1y64B
21	1n0vC	2p8wT, 1u2rA, 3b8hE, 1zm3C, 3dnyT, 1s1hT, 2npfB
21	1xk9A	1dmaB, 1ikqA, 1aerB
22	1fchA	1fchB, 2j9qAB, 2c0mC
22	1c44A	1qndA, 2c0lB
23	1ywhA	1ywhCEGIKMO, 3bt1U, 2fd6U, 2i9bEGH
23	2i9aA	2i9aBCD, 2i9bABCD, 3bt2A, 1urkA
24	1j54A	
24	1se7A	2idoB
25	1yzuA	1z0iA, 2ot3B, 1yztAB
25	1txuA	

Table S3. FiberDock energies of the bound forms given in the benchmark dataset

Case	Bound forms	Energy (kJ/mol)	Case	Bound forms	Energy (kJ/mol)
1i	1e4kA:C	-23.42	**12ii**	1fakL:T	-57.60
1ii	1e4kB:C	-27.34	**13**	1h1vA:G	+3.92
2i	2hmiC:B	-0.64	**14**	1ibrA:B	-144.40
2ii	2hmiD:B	-37.85	**15**	1iraY:X	-86.78
3	1f6mA:C	-48.71	**16**	1jk9A:B	-46.51
4	1fq1A:B	-50.90	**17**	1jmoA:H	-170.48
5	1pxvA:C	-110.27	**18i**	1jzdA:C	-21.03
6	1zliA:B	-57.35	**18ii**	1jzdB:C	-49.11
7	2o3bA:B	-21.60	**19**	1r8sA:E	-140.42
8	1atnA:D	-107.31	**20**	1y64A:B	-49.86
9	1bkdR:S	-96.87	**21**	1zm4A:B	-27.33
10	1de4A:C	-74.58	**22**	2c0lA:B	-62.85
11i	1eerA:B	-129.35	**23**	2i9bA:E	-87.64
11ii	1eerA:C	-83.53	**24**	2idoA:B	-124.11
12i	1fakH:T	-21.83	**25**	2ot3B:A	-116.03

Table S4. Alternative structures as the substitute of the bound form

Difficult Case	Query Molecule	Alternative Target Structure
4	1fq1A	-
6	1zliB	1zlhB
9	1bkdS	-
12i	1fakT	1danT
12ii	1fakL	2puqL
14	1ibrB	-
14	1ibrAC	1wa5A
15	1iraY	-
16	1jk9B	1ej8A
17	1jmoA	-
19	1r8sAE	-
20	1y64B	-
22	2c0lB	-
23	2i9bAB	3bt1A
23	2i9bCD	2fd6A
23	2i9bEGH	-
24	2idoB	-
25	2ot3B	-

Table S5. Changes in template organization

Difficult Case	Original Template Representative	Substitute Template Representative
3	1f6mAC	-
4	1fq1AB	-
5	1pxvAC	1y4hAC
11i	1eerAB	1cn4BC
11ii	1eerAC	1cn4AC
14	1ibrAB	-
18i	1jzdAC	-
19	1r8sAE	1re0AB
20	1y64AB	-

Table S6. Energy values of PRISM results obtained using standard template set

Case	Energy Results (kj/mol)		Size of enlarged target set	Case	Energy Results (kj/mol)		Size of enlarged target set
	Standard Target Set	Enlarged Target Set			Standard Target Set	Enlarged Target Set	
1i	-21.85	-21.85	8	**12ii**	none	-102.61	46
1ii	+4.45	-6.66	9	**13**	none	-27.80	13
2i	-16.41	-21.69	8	**14**	+25.97	-144.40	14
2ii	+25.58	-35.96	8	**15**	none	-63.74	5
3	+22.66	+22.66	2	**16**	-27.01	-49.32	3
4	+21.64	-68.75	19	**17**	+5.50	-21.97	6
5	+461.37	-74.40	3	**18i**	-20.13	-20.13	4
6	none	+8.60	4	**18ii**	-43.50	-50.84	4
7	+1.35	-8.22	4	**19**	-13.76	-140.42	7
8	none	-46.33	10	**20**	-2.90	-58.42	11
9	+31.27	-114.68	11	**21**	-1.98	-14.77	12
10	0.00	0.00	2	**22**	+2.29	-40.35	6
11i	-32.28	-63.43	4	**23**	+4.46	-42.70	10
11ii	-37.70	-64.65	4	**24**	none	-43.80	3
12i	-31.70	-57.47	21	**25**	+2.90	+2.90	5

Table S7a. Favorable PRISM predictions of difficult cases using standard template set and standard target set

Difficult Case	Interacting Molecules of the Standard Target Set		Template Interface	Energy (kJ/mol)
1i	3aveAB	1fnl	1t83BC	-21.85
2i	1s6pB	2hmiC	1e8oCD	-16.41
11i	1buy	1ernAB	1eerAB	-32.28
11ii	1buy	1ernAB	1eerAC	-37.70
12i	1qfk	1tfhB	1o5dHT	-31.70
16	1qupAB	2jcw	1pu0CD	-27.01
18i	1jzoA	1jpe	1jzdAC	-20.13
18ii	1jpe	1jzoB	1vrsBE	-43.50
19	1hurAB	1r8m	1r8sAE	-13.76

Table S7b. Favorable PRISM predictions of difficult cases using standard template set and enlarged target set

Difficult Case	Interacting Molecules of the Enlarged Target Set		Template Interface	Energy (kJ/mol)
1i	3aveAB	1fnl	1t83BC	-21.85
2i	1dloA	2hmiC	1qd1AB	-21.69
2ii	2hmiD	3kjvB	1at3AB	-63.70
4	1fpzD	2uueAC	1fq1AB	-68.75
5	1y4hAB	1nyc	1pxvAC	-74.40
8	2y83OPQRT	3dni	2a40DE	-46.33
9	1nvwR	1xd2C	1nvuRS	-114.68
11i	1cn4C	1ebaAB	1eerAB	-63.43
11ii	1cn4C	1ebaAB	1eerAC	-64.65
12i	1jbu	1w0yT	1o5dHT	-57.47
12ii	2zp0L	2zwlT	1wtgLT	-102.61
13	1rgiG	2yjfB	1c0gSA	-27.80
14	1ibrA	1ibrBD	1ibrAB	-144.40
15	1ilr	1iraY	1itbAB	-63.74
16	1jk9BD	2jcw	1pu0CD	-49.32
17	3k65B	1jmjA	2b8nAB	-21.97
18i	1jzoA	1jpe	1jzdAC	-20.13
18ii	3pfu	1jzoB	1vrsBE	-50.84
19	1r8sA	1r8sE	1r8sAE	-140.42
20	2yjfE	1y64B	1y64AB	-58.42
21	1zm3C	1aer	1zm9EF	-14.77
22	1fchB	1c44	1qjcAB	-40.35
23	1ywhG	3bt1A	1pbiAB	-42.70
24	2idoBD	1j54	2b8nAB	-43.80

Table S8. Energies, IS-scores and contact fractions of PRISM predictions obtained using standard template set and standard target set

Difficult Case	Energy (kJ/mol)	IS-score	Rating	Real Contacts	Model Contacts	Common Contacts	f_{nat}	$f_{non\text{-}nat}$
1i	-21.85	0.2366	Near Native	17	27	16	0.94	0.41
2i	-16.41	0.0753	Incorrect	0	70	0	0.00	1.00
11i	-32.28	0.2880	Near Native	34	40	22	0.65	0.45
11ii	-37.70	0.3063	Near Native	28	36	18	0.64	0.50
12i	-31.70	0.3690	Near Native	19	16	15	0.79	0.06
16	-27.01	0.6793	Near Native	45	55	42	0.93	0.24
18i	-20.13	0.4864	Near Native	19	23	18	0.95	0.22
18ii	-43.50	0.3330	Near Native	35	44	25	0.71	0.43
19	-13.76	0.1367	Acceptable	28	33	6	0.21	0.82

Table S9. Energy values of PRISM results obtained using rearranged templates and target sets

Case	Energy Results (kj/mol)		Size of enlarged target set	Case	Energy Results (kj/mol)		Size of enlarged target set
	Standard Target Set	Enlarged Target Set			Standard Target Set	Enlarged Target Set	
1i	-21.85	-21.85	8	**13**	none	-27.80	13
1ii	+4.45	-6.66	9	**14**	+25.97	-36.79	14
3	+22.66	+22.66	2	**15**	none	-27.67	4
4	+75.32	-63.20	18	**16**	-27.01	-45.75	3
5	none	-84.17	3	**17**	+0.50	-21.97	5
6	+8.6	+8.6	4	**18i**	-26.48	-54.15	4
7	+1.35	+1.35	3	**18ii**	-43.50	-50.84	4
8	none	-46.33	10	**19**	none	-13.76	6
9	+31.27	-114.68	10	**20**	-2.90	-52.20	10
10	0.00	0.00	2	**21**	-1.98	-14.77	12
11i	-32.28	-49.87	4	**22**	+2.29	-40.35	5
11ii	-9.53	-57.64	4	**23**	+4.46	-42.70	11
12i	-31.70	-57.47	21	**24**	none	none	2
12ii	none	-102.61	46	**25**	+2.90	+2.90	4

Table S10a. Favorable PRISM predictions of difficult cases using rearranged templates and standard target set

Difficult Case	Interacting Molecules of the Standard Target Set		Template Interface	Energy (kJ/mol)
1i	3aveAB	1fnl	1t83BC	-21.85
11i	1ernAB	1buy	1cn4BC	-27.44
12i	1qfk	1tfhB	1o5dHT	-31.70
16	1qupAB	2jcw	1pu0CD	-27.01
18i	1jpe	1jzoA	1vrsBE	-26.48
18ii	1jpe	1jzoB	1vrsBE	-43.50

Table S10b. Favorable PRISM predictions of difficult cases using rearranged templates and enlarged target set

Difficult Case	Interacting Molecules of the Enlarged Target Set		Template Interface	Energy (kJ/mol)
1i	3aveAB	1fnl	1t83BC	-21.85
4	1fpzF	1pye	1nh0AB	-63.20
5	1y4hAB	1nycAB	1y4hAC	-84.17
8	2y83OPQR	3dni	2a40DE	-46.33
9	1nvwR	1xd2C	1nvuRS	-114.68
11i	1ebaAB	1buy	1cn4BC	-49.87
11ii	1ebaAB	1cn4C	1cn4AC	-57.64
12i	1jbu	1w0yT	1o5dHT	-57.47
12ii	2zp0L	2zwlT	1wtgLT	-102.61
13	1rgiG	2yjfB	1c0gSA	-27.80
14	1f59AB	1i2mC	1l9wCD	-36.79
15	1ilr	1iraY	1itbAB	-27.67
16	1ej8	2jcw	1pu0CD	-45.75
17	3k65B	1jmjA	2b8nAB	-21.97
18i	3pfu	1jzoA	1vrsBE	-54.15
18ii	3pfu	1jzo	1vrsBE	-50.84
19	1r8qAB	1r8m	1re0AB	-90.07
20	2yjfE	1ux5	2btfAP	-52.20
21	1zm3C	1aer	1zm9EF	-14.77
22	1fchB	1c44	1qjcAB	-40.35
23	1ywhG	3bt1A	1pbiAB	-42.70

Table S11a. Energies, IS-scores and contact fractions of PRISM predictions obtained using rearranged templates and standard target set

Difficult Case	Energy (kJ/mol)	IS-score	Rating	Real Contacts	Model Contacts	Common Contacts	f_{nat}	$f_{non\text{-}nat}$
1i	-21.85	0.2366	Near Native	17	27	16	0.94	0.41
11i	-27.44	0.2664	Near Native	26	28	17	0.65	0.39
12i	-31.70	0.3690	Near Native	19	16	15	0.79	0.06
16	-27.01	0.6793	Near Native	45	55	42	0.93	0.24
18i	-26.48	0.4864	Near Native	19	23	18	0.95	0.22
18ii	-43.50	0.3330	Near Native	35	44	25	0.71	0.43

Table S11b. Energies, IS-scores and contact fractions of PRISM predictions obtained using rearranged templates and enlarged target set

Difficult Case	Energy (kJ/mol)	IS-score	Rating	Real Contacts	Model Contacts	Common Contacts	f_{nat}	$f_{non\text{-}nat}$
1i	-21.85	0.2366	Near Native	17	27	16	0.94	0.41
4	-63.20	0.0592	Incorrect	21	31	0	0.00	1.00
5	-84.17	0.6186	Near Native	51	56	42	0.82	0.25
8	-46.33	0.3775	Near Native	38	46	21	0.55	0.54
9	-114.68	0.6956	Near Native	86	113	80	0.93	0.29
11i	-49.87	0.3529	Near Native	34	48	23	0.68	0.52
11ii	-57.64	0.6495	Near Native	38	48	36	0.95	0.25
12i	-57.47	0.4789	Near Native	15	29	15	1.00	0.48
12ii	-102.61	0.5916	Near Native	53	76	47	0.89	0.38
13	-106.01	0.5890	Near Native	46	58	41	0.89	0.29
14	-36.79	0.0696	Incorrect	0	42	0	0.00	1.00
15	-27.67	0.5574	Near Native	56	78	48	0.86	0.38
16	-45.75	0.5497	Near Native	39	46	32	0.82	0.30
17	-21.97	0.0659	Incorrect	0	32	0	0.00	1.00
18i	-54.15	0.0669	Incorrect	0	49	0	0.00	1.00
18ii	-50.84	0.4942	Near Native	35	38	26	0.74	0.32
19	-90.07	0.5517	Near Native	56	57	41	0.73	0.28
20	-52.20	0.0574	Incorrect	0	22	0	0.00	1.00
21	-14.77	0.1770	Near Native	10	21	6	0.60	0.71
22	-40.35	0.0696	Incorrect	0	50	0	0.00	1.00
23	-42.70	0.0679	Incorrect	0	36	0	0.00	1.00

Table S12. Sequence similarity of bound and unbound forms given in the benchmark dataset

Case	Unbound form	Bound from	Sequence Identity (%)	Case	Unbound form	Bound from	Sequence Identity (%)
1i	3aveA	1e4kA	100	**12ii**	1qfkL	1fakL	100
	1fnlA	1e4kC	100		1tfhB	1fakT	100
1ii	3aveA	1e4kB	100	**13**	1ijjB	1h1vA	100
	1fnlA	1e4kC	100		1d0nB	1h1vG	100
2i	2hmiC	2hmiC	100	**14**	1qg4A	1ibrA	100
	1s6pB	2hmiB	100		1f59A	1ibrB	100
2ii	2hmiD	2hmiD	100	**15**	1g0yR	1iraY	100
	1s6pB	2hmiB	100		1ilr1	1iraX	100
3	1cl0A	1f6mA	99.7	**16**	1qupA	1jk9B	99.3
	2tirA	1f6mC	99.1		2jcwA	1jk9A	100
4	1b39A	1fq1B	100	**17**	1jmjA	1jmoA	100
	1fpzF	1fq1A	100		2cn0H	1jmoH	100
5	1x9yA	1pxvA	99.4	**18i**	1jzoA	1jzdA	100
	1nycA	1pxvC	100		1jpeA	1jzdC	99.2
6	1kwmA	1zliA	100	**18ii**	1jzoA	1jzdB	100
	2jtoA	1zliB	100		1jpeA	1jzdC	99.2
7	1zm8A	2o3bA	100	**19**	1hurA	1r8sA	100
	1j57A	2o3bB	100		1r8mE	1r8sE	100
8	1ijjB	1atnA	100	**20**	2fxuA	1y64A	100
	3dniA	1atnD	99.6		1ux5A	1y64B	100
9	1ctqA	1bkdR	100	**21**	1n0vC	1zm4A	100
	2ii0A	1bkdS	100		1xk9A	1zm4B	100
10	1a6zA	1de4A	100	**22**	1fchA	2c0lA	100
	1cx8A	1de4C	100		1c44A	2c0lB	100
11i	1buyA	1eerA	98.8	**23**	1ywhA	2i9bE	100
	1ernA	1eerB	99.5		2i9aA	2i9bA	100
11ii	1buyA	1eerA	98.8	**24**	1j54A	2idoA	100
	1ernA	1eerC	99.5		1se7A	2idoB	100
12i	1qfkH	1fakH	100	**25**	1yzuA	2ot3B	100
	1tfhB	1fakT	100		1txuA	2ot3A	99.3

Table S13. Additional conformations of the query molecules found when the sequence homology is lowered from 100% to 95%

Case	Molecule	Additional Conformations
1ii	3aveA	2rcjLK
1ii	1fnlA	3sgjC, 3sgkC, 3ay4C
2i	2hmiC	-
2ii	2hmiD	-
2i, 2ii	1s6pB	1hmvBDFH, 1eetA, 3nbpB, 3dlgB, 1c0tAB, 1ep4AB, 1rt2B, 1tl1A, 1rtiA, 3ig1A, 3qo9A, 3lp0B, 3hvtB, 1lweA, 1lwfB
3	1cl0A	1f6mA
3	2tirA	-
4	1b39A	2iw9C, 2iw8C
4	1fpzF	-
6	1kwmA	-
6	2jtoA	2k2zA
7	1zm8A	-
7	1j57A	-
10	1a6zA	-
10	1cx8A	-
14	1qg4A	3ea5A, 3gjxFC
14	1f59A	-
17	1jmjA	-
17	2cn0H	1mkxK
18i	1jzoA	-
18i	1jpeA	1jzdCD, 1vrsABC
20	2fxuA	3lueA, 3byhA
20	1ux5A	1ux4B
22	1fchA	-
22	1c44A	-
23	1ywhA	-
23	2i9aA	-
24	1j54A	-
24	1se7A	-
25	1yzuA	-
25	1txuA	2ot3A

Table S14. Favorable PRISM predictions of difficult cases obtained using additional conformations found by 95% sequence homology

Difficult Case	Interacting Molecules		Template Interface	Energy (kJ/mol)
1ii	1t89A	3ay4C	1t83AC	-19.76
2i	3nbpB	2hmiC	1hjrBD	-30.08
2ii	2hmiD	1rt2B	1at3AB	-31.85
3	1f6mABEF	2tir	1f6mAC	-37.07
4	2iw9C	1fqzE	1n4aAB	-41.16
14	3gjfF	1f59AB	2bkuCD	-19.31
17	1jmo	1mkxK	1h1bAB	-41.90
18i	1vrsB	1jzoA	1jd1AB	-63.00
20	3lueABCD	1ux5	2a40DE	-23.95
25	1yzuAB	2ot3A	1ihoAB	-13.21

Table S15. Energies, IS-scores and contact fractions of PRISM predictions obtained using additional conformations found by 95% sequence homology

Difficult case	Energy (kJ/mol)	IS-score	Rating	Real Contacts	Model Contacts	Common Contacts	f_{nat}	$f_{non\text{-}nat}$
1ii	-19.76	0.4319	Near Native	24	38	22	0.92	0.42
2i	-30.08	0.0642	Incorrect	0	35	0	0.00	1.00
2ii	-31.85	0.0692	Incorrect	0	43	0	0.00	1.00
3	-37.07	0.7728	Near Native	41	44	39	0.95	0.11
4	-41.16	0.0669	Incorrect	21	38	0	0.00	1.00
14	-19.31	0.2111	Near Native	13	33	9	0.69	0.73
17	-41.90	0.0592	Incorrect	0	21	0	0.00	1.00
18i	-63.00	0.0669	Incorrect	0	49	0	0.00	1.00
20	-23.95	0.0674	Incorrect	0	45	0	0.00	1.00
25	-13.21	0.0600	Incorrect	0	27	0	0.00	1.00

Table S16. Biological/non-biological interaction test results of predictions with favorable energies but lower IS-scores

Case	Interaction	NOXclass score (%)	NOXclass evaluation	DiMoVo score	DiMoVo evaluation	EPPIC evaluation
2i	1dloA - 2hmiC	2.00	non-biological	-0.15848	non-biological	non-biological
2i	3nbpB - 2hmiC	91.82	biological	0.080515	non-biological	biological
2i	1s6pB - 2hmiC	78.26	biological	0.299148	non-biological	non-biological
2ii	2hmiD - 3kjvB	97.69	biological	0.167662	non-biological	non-biological
2ii	2hmiD - 1rt2B	97.69	biological	0.167662	non-biological	non-biological
4	1fpzF - 1pye	84.81	biological	0.150784	non-biological	non-biological
4	2iw9C - 1fqzE	37.42	non-biological	0.020412	non-biological	non-biological
14	1f59AB - 1i2mC	96.09	biological	0.277509	non-biological	non-biological
17	3k65B - 1jmjA	45.14	non-biological	-0.18798	non-biological	non-biological
17	1jmo - 1mkxK	99.98	biological	0.352058	non-biological	biological
18i	3pfu - 1jzoA	57.26	biological	0.877925	biological	biological
18i	1vrsB - 1jzoA	88.07	biological	0.234299	non-biological	biological
20	2yjfE - 1ux5	27.56	non-biological	0.12399	non-biological	non-biological
20	1ux5 - 3lueABCD	44.02	non-biological	0.002495	non-biological	non-biological
22	1fchB -	69.45	biological	0.143824	non-biological	non-biological

	1c44					
23	1ywhG - 3bt1A	88.67	biological	-0.14501	non-biological	non-biological
24	2idoBD - 1j54	99.97	biological	0.86499	biological	biological
25	1yzuAB - 2ot3A	60.38	biological	0.24899	non-biological	non-biological

Table S17. Different conformations of ERK interacting proteins

Protein name	Query protein	Other conformations
ERK	2ojgA	3i5zA, 3i60A, 2e14A, 2ojjA
MEK1	3eqcA	3dv3A, 3eqiA, 3eqgA, 3eqdA, 3eqfA, 3eqhA, 2p55A, 3eqbA, 3e8nA, 1s9jA, 3dy7A, 3mblA, 3pp1A
MEK2	1s9iA	1s9iB
MP1	3cptA	1skoA, 1tvmA
RSK2	2z7qA	2z7rA, 2z7sA
Mnk1/2	2hw7A	2ac5A

Table S18a. Energetically most favorable PRISM predictions of the query ERK interacting proteins

Protein-1	PDB ID-1	Protein-2	PDB ID-2	Template Interface	Energy (kJ/mol)
MEK2	1s9iA	MEK1	3eqc	1s9iAB	-23.84
ERK	2ojg	MEK1	3eqc	1uaxAB	-10.78
MEK1	3eqc	RSK2	2z7q	1zxeAE	-12.27
MEK2	1s9iA	RSK2	2z7q	1zxeAE	-4.64
Mnk1/2	2hw7	ERK	2ojg	1fvrAB	-10.13

Table S18b. Energetically most favorable PRISM predictions obtained using alternative conformations of the ERK interacting proteins

Protein-1	PDB ID-1	Protein-2	PDB ID-2	Template Interface	Energy (kJ/mol)
MEK2	1s9iA	MEK1	3e8n	1s9iAB	-78.99
MP1	1sko	MEK1	3dv3	1unhAB	-26.50
ERK	2ojg	MEK1	3mbl	1uaxAB	-16.09
MEK1	3eqc	RSK2	2z7s	1zxeAE	-31.40
MEK2	1s9iB	RSK2	2z7r	1zxeAE	-32.18
Mnk1/2	2hw7	ERK	2ojg	1fvrAB	-10.13
RSK2	2z7q	ERK	2ojj	1fvrAB	-30.78