

Table S1: CAPRI Targets analyzed in this study. The decamer peptide at the interface that contributes most to the binding energy is indicated, together with the absolute and relative binding energy contribution (estimated using the Rosetta Energy function, See Methods).

Targets are sorted based on energy funnel towards native and decreasing fraction of interaction energy of peptide.

Target	Complex	Chain I	Chain II	Inhibitory peptide sequence	Peptide interaction energy	Fraction of Total Interaction Energy Contributed by Peptide	Partner from which Peptide is Derived	Funnel in energy landscape towards native	
T32	Protease savinase (1SVN) / bifunctional inhibitor BASI (1AVA_C)	3bx1	A	C	RAYTTCQLQST	-18.37	81.6%	II	yes
T40a	bovine trypsin / protease inhibitor (API-A)	3e8l	A	C	SCEFCKIACP	-20.36	74.8%	II	yes
T17	XIP-1 xylanase inhibitor / xylanase	1te1	A	B	NIRGGPGKPL	-21.64	72.5%	I	yes
T22	U5-15K / U5-52	1sxy	A	B	YNSKRIDFDL	-10.00	63.5%	II	yes
T21	Orc1 / Sir1	1zhi	A	B	EEVSPRFLV	-12.80	62.1%	II	yes
T29	Trm8 / Trm82 tRNA guanine-N(7)-methyltransferase	2vdu	B	E	FIVDKWLFHG	-13.04	61.5%	I	yes
T11	Cohesin / dockerin (Cellulosome)	1ohz	A	B	NSTDVLLLSR	-11.84	54.1%	II	yes
T08	Nidogen-G3 / laminin	1npe	A	B	DNIDPNAVGN	-12.23	53.8%	II	yes
T26	ToIB / Pal	2hqs	A	H	DERGTPEYNI	-13.80	51.0%	II	yes
T20	HemK / eRF1	2b3t	A	B	AGGQHVNTTD	-21.81	47.2%	II	yes
T39	Centaurin-alpha / FHA domain	3fm8	A	C	QPAKIGHPHG	-10.68	45.0%	II	yes
T06	antibody VH domain 3	1kxq	A	H	AIYRRTYGTY	-12.55	43.9%	II	yes
T13	SAG1 / antibody	1ynt	A,B	F	SCTSKAVTSL	-8.27	43.1%	II	yes
T23	GBP1 dimer	2b8w	A	B	DFSLDLEADG	-13.77	23.0%	II	yes
T01 (i)	HPr / Phospho-carrier	1kkl	A,C	H	IMGVMSLGIA	-12.68	70.4%	II	no
T07	T cell receptor beta chain / pyrogenic exotoxin A (SpeA)	110x	A	B	SYGAGSTEKG	-10.18	57.5%	I	no
T16	XIP-1 / xylanase	1ta3	A	B	QWVHPKNVYY	-15.56	56.9%	I	no
T27	E2-25K / Ubc9	2o25	B	C	ENLCAMGFDR	-6.03	56.5%	I	no
T05 (i)	alpha-amylase / camelide antibody VH domain 2	1kxv	A	C	LYRGLPGCPI	-11.63	56.4%	II	no
T03	flu hemagglutinin / Fab HC63	1ken	AC	L,H	FYYDYDFFD	-7.59	56.4%	II	no
T05 (ii)	alpha-amylase / camelide antibody VH domain 2	1kxv	A	C	WPGDIKAVLD	-10.66	51.8%	I	no
T24	Arf1 / ARHGap10	2j59	A	M	VTTIPTIGFN	-11.46	50.6%	I	no
T01 (ii)	HPr / Phospho-carrier	1kkl	A,C	H	LNHLIEHNEE	-9.04	50.2%	I	no
T04	alpha-amylase / camelide antibody VH domain 1	1kxt	A	B	KWSGEKMSYL	-10.43	49.5%	I	no
T18	TAXI / Xylanase	1t6g	A	C	FSRLPHFTGC	-11.46	45.5%	I	no
T37	Arf / Effector	2w83	B	C,D	DLIAKVDELDT	-7.44	44.6%	II	no
T14	phosphatase-1 / myosin phosphatase targeting subunit 1	1s70	A	B	SEKAKYQYG	-22.35	35.2%	I	no
T15	ImmD / ColD	1v74	A	B	LDKKYKHAGD	-9.95	34.9%	I	no
T40b	bovine trypsin / protease inhibitor (API-A)	3e8l	B	C	SMPVPLICDT	-17.14	60.3%	B	no

Table S2: Decamer peptides for Docking Benchmark 3.0 (Hwang et al., Proteins, 2008). See Table S1 for more details.

Targets are sorted based on energy funnel towards native and decreasing fraction of interaction energy of peptide.

PDB	Complex		Inhibitory Peptide Sequence	Peptide interaction energy (best decamer)	Fraction of total interaction energy contributed by peptide	partner from which peptide is derived#
1D6R	Bovine trypsin	Bowman-Birk inhibitor	QCACTKSNNP	-12.85	100.0%	II
1OPH	a-1-Antitrypsin	Trypsinogen	LEAIPRSIPP	-25.29	99.5%	I
2HMI	Fab 28	HIV1 reverse transcriptase	QKEPFLWMG	-6.16	97.0%	I
1AK4	Cyclophilin	HIV capsid	PVHAGPIAPG	-23.54	95.9%	II
1GHQ	Complect C3	Epstein-Barr virus receptor CR2	YKIRGSTPYR	-11.77	93.6%	II
1HIA	Kallikrein	Hirustatin	NEVHCRIRCK	-28.52	92.3%	II
1ACB	Chymotrypsin	Eglin C	PVTLDLRYNR	-31.45	92.1%	II
2UUY	Trypsin	Tryptase inhibitor from tick	GLCKARFTRY	-25.73	91.4%	II
2SNI	Subtilisin	Chymotrypsin inhibitor 2	GTIVTMEYRI	-29.75	89.3%	II
1R0R	Subtilisin Carlsberg	OMTKY	PKPACTLEYR	-30.44	88.0%	II
1PPE	Bovine trypsin	CMTI-1 squash inhibitor	RVCPRIIMEC	-28.12	87.0%	II
2SIC	Subtilisin	Streptomyces subtilisin inhibitor	GEDVMCPMVY	-26.69	86.6%	II
1CGI	Bovine chymotrypsinogen	PSTI	ELNGCTYEYR	-36.02	84.4%	II
1E6J	Fab	HIV-1 capsid protein p24	ALGPAATLEE	-16.81	84.2%	II
1AVX	Porcine trypsin	Soybean trypsin inhibitor	IISSPYRIRF	-23.52	83.9%	II
1BJ1	Fab	vEGF	PHQGQHIGEM	-26.60	82.9%	II
1N80	Chymotrypsin	Ecotin	SPVSTMMACP	-28.46	81.7%	II
2I25	Shark single domain antigen receptor	Lysozyme	ESRYGSYDAV	-21.68	81.3%	I
1GLA	Glycerol kinase	Glucose specific phosphocarrier	GIETTERNYR	-12.64	78.1%	I
1FSK	Fab	Birch pollen antigen Bet V1	NIEGGGPGT	-19.81	76.4%	II
1HE8	Ras GTPase	PIP3 kinase	DPTIEDSYRK	-12.65	75.4%	II
2FD6	Plasminogen receptor antibody	Plasminogen activator receptor	ENLPQNGRQC	-14.74	74.5%	II
1QFW	Fv	Human chorionic gonadotropin	CPRGVNPVVS	-13.38	72.2%	II
1FC2	Staphylococcus Protein A	Human Fc fragment	QQNAFYEILH	-8.61	71.9%	I
1KKL	HPr kinase C-ter domain	HPr	IMGVMSLGIA	-12.62	70.9%	II
1FQ1	CDK2 kinase	CDK inhibitor 3	IQTIKQYNYL	-11.89	70.7%	I
1I9R	Fab	Cd40 liqand	CQHSWEIPPT	-7.37	70.6%	II
2C0L	PTS1 and TRP region of PEX5	SCP2	LQLQPGNAKL	-22.07	69.8%	II
1BVK	Fv Hulys11	HEW lysozyme	KGTDVQAWIR	-12.05	69.6%	II
1AY7	Barnase	Barstar	YGENLDALWD	-14.94	69.5%	II
1EAW	Matriptase	BPTI	TGPCKARIIR	-19.30	68.9%	II
1PXV	Cystein protease	Cystein protease inhibitor	QGITGSRPIV	-29.14	68.5%	II
1E96	Rac GTPase	p67 Phox	TTNAFPGEYI	-11.07	67.9%	I
2O0B	Ubiquitin ligase	Ubiquitin	VDAKIAKLMG	-10.67	67.0%	I
2HLE	Ephrin B4 receptor	Ephrin B2 ectodomain	KFQFSPNLW	-19.52	65.6%	II
1A2K	Ran GTPase	Nuclear transport factor 2	AGQEKFGGLR	-15.62	65.5%	II
1ATN	Actin	Dnase I	PRHQGMVGM	-20.17	65.4%	I
1KTZ	TGF-b	TGF-b receptor	TILYYVGRTP	-12.28	65.1%	I
1K4C	Fab	Potassium Channel Kcsa	RGAPGAQLIT	-22.64	64.5%	II
1Z5Y	N-term of DsbD	E.coli CCMG protein	SADAGFCYPP	-14.94	62.6%	II
1ZHI	BAH domain of Orc1	Sir Orc-interaction domain	EEYVSPRFLV	-12.80	62.1%	II
1MAH	Acetylcholinesterase	Fasciculin	SRRHPPKMVL	-12.00	62.0%	II
1B6C	FKBP binding protein	TGFb receptor	PLLVQRTIAR	-15.38	61.9%	II
2H7V	Rac GTPase	Ypka	FDYDLRPLSY	-12.48	61.5%	II
1NSN	Fab N10	Staphylococcal nuclease	FTKKMVENAK	-6.67	61.4%	II
1VFB	Fv D1.3	HEW lysozyme	KGTDVQAWIR	-13.71	60.5%	II
1S1Q	UEV domain	Ubiquitin	DSYVFNDSGS	-10.12	59.8%	I
1XD3	UCH-L3	Ubiquitin	TLHLVLRLRG	-26.56	59.4%	II
1SBB	T-cell receptor b	Staphylococcus enterotoxin B	YSYGAGSTEK	-10.08	57.8%	I
1BVN	a-Amylase	Tendamistat	VTLYQSWRYS	-17.34	57.6%	II
1KLU	MHC class 2 HLA-DR1	Staphylococcus enterotoxin C3	VDSFFKWDLI	-10.28	57.2%	II
1EFN	HIV-1-NEF protein	SH3 domain	RPQVPLRPMT	-10.15	56.9%	I
2AJF	ACE2	SARS spike protein receptor binding domain	FYTTTGIGYQ	-9.12	56.7%	II
1QA9	CD2	CD58	WKKQKDKVAE	-9.65	56.3%	II
1I4D	Rac GTPase	Arfaptin	TAHLYSLLQT	-8.95	56.3%	I
2MTA	Methylamine dehydrogenase	Amicyanin	YHCTPHPFMR	-9.63	55.6%	II
1EZU	D102N Trypsin	Ecotin	PVSTMMACPD	-27.31	55.2%	II
1F34	Porcine pepsin	Ascaris inhibitor 3	QFLFSMSTGP	-23.13	55.2%	II
2PCC	Cyt C peroxidase	Cytochrome C	GAANNVFTNE	-4.23	54.3%	I
1H1V	Actin	Gelsolin	QDEVAASAIL	-10.74	54.1%	II
2CFH	BET3	TPC6	DEALFLLLHN	-19.11	53.8%	II
1ML0	Viral chemokine binding p. M3	Chemokine Mcp1	TCCYNFTNRK	-20.47	53.3%	II
1AKJ	MHC Class 1 HLA-A2	T-cell CD8 coreceptor	EDQTDQTELV	-11.99	52.9%	I

2HRK	Glutamyl-t-RNA synthetase	GU-4 nucleic binding protein	NLRTFILGGL	-11.20	52.4%	I
11JK	Von Willebrand Factor dom. A1	Botroctetin	QRMSRNFVRY	-10.00	52.2%	II
1GPW	HISF protein	Amidotransferase HISH	RRLPHMGWNE	-11.08	51.0%	II
2HQS	TolB	Pal	DERGTPEYNI	-13.80	51.0%	II
1RLB	Transthyretin	Retinol binding protein	RVRLLNWDV	-6.48	49.8%	II
1MLC	Fab44.1	HEW lysozyme	TNRNTDGSTD	-9.13	49.7%	II
1HE1	Rac GTPase	Pseudomonas toxin GAP dom.	GEYIPTVFDN	-14.77	49.2%	II
1GRN	CDC42 GTPase	CDC42 GAP	QEDYDRLRPL	-13.89	49.1%	I
2JEL	Fab Jel42	HPr	EGEDEQKAVE	-9.84	48.9%	II
2VIS	Fab	Flu virus hemagglutinin	TGVIQNGGSN	-6.54	48.8%	II
1JMO	Heparin cofactor	Thrombin	GFMPPLSTQVR	-27.82	48.3%	I
7CEI	Colicin E7 nuclease	Im7 immunity protein	KVGKAPKTRT	-10.28	48.2%	II
2NZ8	Rac GTPase	DH/PH domain of TRIO	EDYDRLRPLS	-14.98	47.7%	II
112J	Arf1 GTPase	GAT domain of GGA1	LRAANKLIKE	-8.27	47.5%	II
1WEJ	Fab E8	Cytochrome C	IAYLKKATNE	-10.64	46.9%	II
1YVB	Falcipain 2	Cystatin	RLLGAPVPVD	-9.55	46.9%	II
1M10	Von Willebrand Factor dom. A1	Glycoprotein IB-a	DVKAVTSNVA	-13.61	46.4%	II
1AZS	Adenylyl cyclase	AC activator Gs a complex	SIWNNRWLRT	-13.64	45.3%	II
1NW9	Capase-9	Ecotin	GATPFQSSLP	-16.31	44.7%	I
1UDI	Uracyl-DNA glycosylase	Glycosylase inhibitor	QESLMLPEE	-13.90	44.3%	II
1KXQ	Camel VHH	Pancreatic a-amylase	AIYRRGTGYT	-12.55	43.9%	II
1E4K	FC fragment of human IgG 1	Human FCGR III	KDRKYFHHNS	-5.97	43.8%	II
1Z0K	Rab4A GTPase	RAB4 binding domain of Rabenosyn	HTIGVEFGSK	-13.19	43.7%	I
1K74	RXR-a	PPAR-g	FAKLLRLPA	-11.21	43.6%	I
1BUH	CDK2 kinase	Ckshs1	GDSEIDQLFR	-8.96	43.4%	I
1T6B	Anthrax protective antigen	Anthrax toxin receptor	KKYNDKPLLY	-8.49	43.2%	I
1IRA	Interleukin-1 receptor	Interleukin-1 receptor antagonist protein	GYLQGPVNL	-17.06	42.4%	II
1GCQ	GRB2 C-ter SH3 domain	GRB2 N-ter SH3 domain	MFPRNYTPV	-9.14	42.2%	I
1DFJ	Ribonuclease A	Rnase inhibitor	YDTYWTEEEV	-8.84	41.6%	II
11B1	14-3-3 protein	Serotonin N-acteylase	QRRHLPANEF	-14.05	41.3%	II
11PS	Fab D3H44	Tissue factor	SGKKTAKTNT	-13.41	41.2%	II
1R8S	Arf1 GTPase	Sec 7 domain	TIPTIGFNVE	-17.69	40.9%	I
1DQJ	Fab Hyhel63	HEW lysozyme	NCAKKIVSDG	-8.19	40.4%	II
1KAC	Adenovirus fiber knob protein	Adenovirus receptor	SGDKIYDDYY	-7.23	40.4%	II
1E6E	Adrenoxin reductase	Adrenoxin	TDEENDMLDL	-10.36	40.2%	II
1FQJ	Gt-a	RGS9	RVKTTGIIET	-11.68	40.0%	I
1AHW	Fab 5q9	Tissue factor	SGKKTAKTNT	-11.83	39.1%	II
1DE4	b2-microglobulin	Transferrin receptor ectodom.	WDHMFVDFW	-8.15	38.3%	I
2BTF	Actin	Profilin	PIYEGYALPH	-9.89	38.2%	I
2OT3	Rab21 GTPase	Rabex-5 VPS9 domain	EPASADDFLP	-18.73	38.0%	I
1K5D	Ran GTPase	Ran GAP	KKYVATLGE	-10.80	37.8%	I
1GP2	Gi-a	Gi-b,g	SERKKWIHCF	-12.75	37.5%	I
1NCA	Fab	Flu virus neuraminidase N9	EDNFGSLSDY	-9.67	37.2%	I
1BKD	Ras GTPase	Son of Sevenless	GQEEYSAMRD	-16.10	37.1%	II
1Y64	Actin	BNI1 protein	SQQFGINLHM	-5.50	37.0%	I
1IQD	Fab	Factor VIII domain C2	SYFTNMFATW	-10.72	36.7%	II
112M	Ran GTPase	RCC1	SRVTKNVPN	-13.97	36.3%	I
1F51	Sporulation response factor B	Sporulation response factor F	MNKLQLIKGN	-7.26	34.6%	I
2B42	Xylanase	Xylanase inhibitor	FSRLPHFTGC	-9.15	32.9%	I
1FAK	Coagulation factor VIIa	Soluble tissue factor	CFCLPAFEGR	-14.66	31.8%	I
1TMQ	a-Amylase	RAG1 inhibitor	SVGTSCIPGM	-8.51	30.7%	II
1EER	Erythropoietin	EPO receptor	DTSSFVPLEL	-15.34	30.1%	I
1XQS	HspBP1	Hsp70 ATPase domain	TQASLEIDSL	-11.97	29.7%	II
1KXP	Actin	Vitamin D binding protein	SLYASGRITG	-11.85	28.2%	I
11BR	Ran GTPase	Importin b	FHRKKNLQYY	-10.97	27.4%	I
1BGX	Fab	Taq polymerase	YGYWYFDVWG	-6.18	*	I
1EWY	Ferredoxin reductase	Ferredoxin	VGKEMLLPDD	-1.22	*	I
1N2C	Nitrogenase Mo-Fe protein	Nitrogenase Fe protein	GRGVITAINF	-5.92	*	II
1WQ1	Ras GTPase	Ras GAP	EATTLFRATT	-7.06	*	I
2O8V	PAPS reductase	Thioredoxin	APKYGIRGIP	-6.38	*	II
2QFW	Fv	Human chorionic gonadotropin	CTLQENPFFS	-8.09	*	II

‡ First and second partner are as defined in Benchmark 3.0 (Hwang et al., Protein 2008).

* Technical problem with determining total interface interaction energy