SUPPORTING INFORMATION

HADDOCK$_{2P2I}$: A biophysical model for predicting the binding affinity of protein-protein interaction inhibitors

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Table S1. Binding affinity dataset of protein-protein interaction inhibitors

Interaction	Biological role	PDB (complex)	K_d (complex) (*M*)
BclXL/Bak	**Programmed Cell Death**	**1bxl**	**3.40E-7**[1]
Modulator (common name)	Formula	PDB (complex)	K_i ‖ K_d (modulator) *(M)*
N3B	$C_{27}H_{22}FN_3O_5S_2$	1ysi	1.2E-7[2]
ABT-737	$C_{42}H_{45}ClN_6O_5S_2$	2yxj	5.0E-10[2]
4FC (4'-fluoro-1,1'-biphenyl-4-carboxyl acid)	$C_{13}H_9FO_2$	1ysg	3.0E-5[2]
TN1 (5,6,7,8-tetrahydronaphthalen-1-ol)	$C_{10}H_{12}O$	1ysg	4.3E-3[2]
acyl-sulfonamide-based ligand	$C_{30}H_{36}N_4O_5S_2$	2o22	6.7E-8[3]
W1191542	$C_{42}H_{46}N_6O_5S_2$	3inq	1.1E-8[4]
Interaction	Biological role	PDB (complex)	K_d (complex) (*M*)
MDM2/p53	**Transcription regulation**	**1ycr**	**6.00E-7**[5]
Modulator (common name)	Formula	PDB (complex)	K_i ‖ K_d (modulator) *(M)*
HDM2	$C_{23}H_{15}Cl_2IN_2O_4$	1t4e	8.0E-8[6]
WK23	$C_{25}H_{17}Cl_2N_3O_2$	3lbk	9.2E-7[7]
MI-63	$C_{29}H_{35}Cl_2FN_4O_3$	3lbl	3.6E-7[7]
Interaction	Biological role	PDB (complex)	K_d (complex) (*M*)
XIAP-BIR3/CASPASE-9	**Programmed Cell Death**	**1nw9**	**2.0E-8**[8]
Modulator (common name)	Formula	PDB (complex)	K_i ‖ K_d (modulator) *(M)*
998	$C_{25}H_{38}N_4O_3$	1tfq	1.2E-8[9]
997	$C_{31}H_{42}N_4O_4$	1tft	5.0E-9[9]
9JZ	$C_{28}H_{38}N_6O_3$	3hl5	3.4E-5[10]
Interaction	Biological role	PDB (complex)	K_d (complex) (*M*)
XIAP-BIR3/SMAC	**Programmed Cell Death**	**1g73**	**4.2E-7**[8]
Modulator (common name)	Formula	PDB (complex)	K_i ‖ K_d (modulator) *(M)*
BI6	$C_{29}H_{34}N_4O_3$	2jk7	6.7E-8[11]
AoxSPW	$C_{22}H_{25}N_5O_5$	2opy	3.0E-5[12]
Smac005	$C_{28}H_{36}N_4O_4$	3clx	1.2E-7[13]
Smac005	$C_{28}H_{36}N_4O_4$	3cm7	1.2E-7[13]
Smac010	$C_{28}H_{37}N_5O_3$	3cm2	4.2E-7[13]
Smac037	$C_{29}H_{39}N_5O_3$	3eyl	2.2E-7[14]
CZ3	$C_{46}H_{60}N_{14}O_6S_2$	3g76	2.3E-7[15]
Interaction	Biological role	PDB	K_d (complex) (*M*)

			(complex)
ZipA/FtsZ	**Cell Cycle Regulation / Cellular structure**	**1f47**	**2.0E-5[16]**
Modulator (common name)	Formula	PDB (complex)	$K_i \parallel K_d$ (modulator) *(M)*
WAI	$C_{22}H_{26}ClN_7$	1y2f	1.2E-5[17]
CL3	$C_{22}H_{26}ClN_7$	1y2g	8.3E-5[17]
Interaction	Biological role	PDB (complex)	K_d (complex) *(M)*
HPV-E2/E1	**Viral infection**	**1tue**	**n/d**
Modulator (common name)	Formula	PDB (complex)	$K_i \parallel K_d$ (modulator) *(M)*
BILH 434	$C_{29}H_{19}Cl_2N_3O_6S$	1r6n	4.0E-8[18]
Interaction	Biological role	PDB (complex)	K_d (complex) *(M)*
IL-2/IL-2R	**Immune system regulation**	**1z92**	**1.0E-8[19]**
Modulator (common name)	Formula	PDB (complex)	$K_i \parallel K_d$ (modulator) *(M)*
FRG	$C_{26}H_{30}N_4O_3$	1m48	2.2E-5[20]
FRB	$C_{25}H_{33}Cl_2N_7O_2$	1pw6	7.0E-6[21]
SP-1985	$C_{30}H_{35}N_5O_6$	1m49	7.5E-6[22]
FRH	$C_{30}H_{37}Cl_2N_7O_6$	1py2	1.0E-7[23]
SP-4160	$C_{33}H_{42}Cl_2N_8O_4$	1qvn	1.4E-6[21]

Table S2. Different weighting and optimization schemes for binding affinity prediction of PPIs

using the HADDOCK score

REGRESSION COEFFICIENTS[a] FOR MODELS using PRODRG parameters								
MODEL N	HS[b]	VDW[c] (β_1)	ELEC[d] (β_2)	DESOLV[e] (β_3)	BSA[f] (β_4)	CONST[g] (c_i)	TRAINING SET (r^2)	CV-set[h] (4fold) (r^2)
1	-0.05	0	0	0	0	3.72	0.40	0.31
2	0	-0.11	0	0	0	2.82	0.37	0.35
3	0	0	-0.007	0	0	5.6	0.07	0.00
4	0	0	0	-0.05	0	6.22	0.13	0.01
5	0	0	0	0	0.006	2.2	0.50	0.48
6	0	0.047	0	0	0.008	2.3	0.52	0.44
7	0	0	-0.0055	0	0.006	1.74	0.55	0.53
8	0	0	0	-0.01	0.005	2.4	0.52	0.45
9	-0.02	0	0	0	0.004	2.15	0.55	0.50
10	0	0.06	-0.006	0	0.008	1.82	0.58	0.52
11	0	0.04	0	-0.008	0.007	2.4	0.52	0.38
12	**0**	**0**	**-0.006**	**-0.018**	**0.005**	**1.99**	**0.57**	**0.53**
13	0	0.05	-0.006	-0.013	0.007	2	0.58	0.49
14	0	-0.09	-0.006	-0.034	0	2.74	0.46	0.38
15	0	-0.11	-0.005	0	0	2.47	0.41	0.36
16	0	-0.1	0	-0.028	0	3.11	0.42	0.32

REGRESSION COEFFICIENTS[a] FOR MODELS using ACPYPE parameters								
MODEL N	HS[b]	VDW[c] (β_1)	ELEC[d] (β_2)	DESOLV[e] (β_3)	BSA[f] (β_4)	CONST[g] (c_i)	TRAINING SET (r^2)	CV-set[h] (4fold) (r^2)
1	-0.04	0	0	0	0	4.18	0.40	0.37
2	0	-0.09	0	0	0	2.48	0.53	0.50
3	0	0	-0.007	0	0	5.86	0.04	0.00
4	0	0	0	-0.03	0	6.43	0.07	0.00
5	0	0	0	0	0.005	2.17	0.50	0.49
6	0	-0.07	0	0	0.001	2.35	0.53	0.49
7	0	0	0.003	0	0.005	2.15	0.52	0.48
8	0	0	0	-0.004	0.005	2.26	0.52	0.42
9	-0.003	0	0	0	0.005	2.24	0.50	0.50
10	0	-0.074	0.004	0	0.0013	2.34	0.53	0.48
11	0	-0.08	0	-0.01	0.0005	2.59	0.53	0.45
12	0	0	0.003	-0.0006	0.005	2.17	0.52	0.40
13	0	-0.08	0.003	-0.007	0.0008	2.5	0.55	0.40
14	0	-0.1	-0.003	-0.008	0	2.6	0.53	0.45
15	0	-0.1	0.004	0	0	2.47	0.53	0.52
16	0	-0.09	0	-0.01	0	2.65	0.53	0.48

(a) A zero indicates that the respective term was not included in lest-squares fitting. (b) Haddock score. (c) van der Waals component of Haddock score (d) Electrostatic interaction energy (e) Desolvation energy (f) Buried surface area (g) a constant term. Bold entry indicates best performing model overall (HADDOCK$_{2P2I}$). (h) CV-set: Cross-validation set.

Table S3. Small molecule compounds with two or more associated IC50 data, extracted from iPPI-DB.

Compound iPPI-DB AC	Protein A	Protein B	Method 1	pIC50	Method 2	pIC50
1603	BRD2	H4	FP	6.10	FRET	7.49
1605	BRD2	H4	FP	5.00	TR-FRET	5.70
1612	BRD2	H4	FP	5.00	TR-FRET	5.60
1634	BRD2	H4	FP	5.20	TR-FRET	5.80
1606	BRD2	H4	FP	5.30	TR-FRET	5.80
1639	BRD2	H4	FP	4.50	TR-FRET	5.00
1623	BRD2	H4	FP	4.90	TR-FRET	5.30
1607	BRD2	H4	FP	5.40	TR-FRET	5.70
1647	BRD2	H4	FP	5.50	TR-FRET	5.80
1615	BRD2	H4	FP	5.30	TR-FRET	5.60
1603	BRD3	H4	FP	6.40	FRET	7.37
1605	BRD3	H4	FP	5.20	TR-FRET	5.60
1612	BRD3	H4	FP	5.40	TR-FRET	5.70
1615	BRD3	H4	FP	5.40	TR-FRET	5.70
1606	BRD3	H4	FP	5.70	TR-FRET	6.00
1639	BRD3	H4	FP	5.00	TR-FRET	5.20
1634	BRD3	H4	FP	5.80	TR-FRET	6.00
1607	BRD3	H4	FP	5.80	TR-FRET	5.90
1623	BRD3	H4	FP	5.30	TR-FRET	5.40
1647	BRD3	H4	FP	6.00	TR-FRET	5.90
1604[a]	BRD4	H4	FP	6.10	MLL-fusion leukaemic proliferation	7.59
1603[b]	BRD4	H4	LPS-stimulated IL6 production	5.80	FRET	7.44
1602	BRD4	H4	alpha_screen	7.11	cellular viability	8.40
1605	BRD4	H4	LPS-stimulated IL6 production	4.90	TR-FRET	5.70
1606[c]	BRD4	H4	FP	5.70	TR-FRET	6.00
1634[d]	BRD4	H4	FP	5.50	TR-FRET	5.80
1623	BRD4	H4	FP	4.90	TR-FRET	5.20
1639[e]	BRD4	H4	FP	4.70	TR-FRET	5.00
1615	BRD4	H4	FP	5.30	TR-FRET	5.50
1612[f]	BRD4	H4	FP	5.20	TR-FRET	5.30
1647[g]	BRD4	H4	FP	5.50	TR-FRET	5.60
1607[h]	BRD4	H4	FP	5.50	TR-FRET	5.50
20	IL2	IL2R	SPR	6.70	ELISA	6.70
cmpnd5[i]	LFA-1	ICAM	HUVEC	8.60	MLR	7.20
cmpnd2[i]	LFA-1	ICAM	HUVEC	8.00	MLR	6.70
cmpnd1[i]	LFA-1	ICAM	HUVEC	7.70	MLR	6.60
cmpnd4[i]	LFA-1	ICAM	HUVEC	7.90	MLR	6.85
cmpnd3[i]	LFA-1	ICAM	HUVEC	8.00	MLR	7.10
1278[j]	MDM2	P53	FP	4.71	FP	6.72
1449[k]	MDM2	P53	FP	7.55	proliferation assay	4.85
1143	MDM2	P53	ELISA	5.00	proliferation assay	6.8
1282[l]	MDM2	P53	proliferation assay	4.98	proliferation assay	6.11
945[m]	MDM2	P53	FP	6.43	proliferation assay	4.78
595[n]	MDM2	P53	FP	5.69	proliferation assay	4.40
541	MDM2	P53	ELISA	5.00	proliferation assay	6.20

682[o]	MDM2	P53	proliferation assay	4.51	proliferation assay	4.77
392[p]	MDM2	P53	proliferation assay	4.51	proliferation assay	5.13
1091[q]	MDM2	P53	ELISA	7.52	proliferation assay	8.00
1249[r]	MDM2	P53	ELISA	6.00	proliferation assay	6.70
989	MDM2	P53	ELISA	7.00	proliferation assay	8.00
706[s]	MDM2	P53	FP	5.23	proliferation assay	4.76
149	MDM2	P53	ELISA	7.00	proliferation assay	7.70
872	MDM2	P53	ELISA	6.52	proliferation assay	7.20
1548	MDM2	P53	ELISA	6.52	proliferation assay	7.20
1534	MDM2	P53	ELISA	7.00	proliferation assay	7.60
255	MDM2	P53	ELISA	5.52	proliferation assay	6.04
1357	MDM2	P53	ELISA	5.00	proliferation assay	5.49
994	MDM2	P53	ELISA	5.52	proliferation assay	5.15
1465	MDM2	P53	ELISA	6.00	proliferation assay	5.64
1161	MDM2	P53	ELISA	6.52	proliferation assay	6.80
888	MDM2	P53	ELISA	5.00	proliferation assay	5.19
295	MDM2	P53	ELISA	5.52	proliferation assay	5.36
1475	MDM2	P53	ELISA	6.00	proliferation assay	5.85
1539	MDM2	P53	ELISA	5.52	proliferation assay	5.66
433	MDM2	P53	ELISA	5.52	proliferation assay	5.50
1182	MDM2	P53	ELISA	5.52	proliferation assay	5.50
701	MDM2	P53	ELISA	4.84	ELISA	4.85
414	MDM2	P53	ELISA	7.00	proliferation assay	7.00
985	MDM2	P53	ELISA	4.79	ELISA	4.79
1150	MDM2	P53	ELISA	5.28	ELISA	5.28
472	XIAP	SMAC	FP	6.01	proliferation assay	5.22
1179	XIAP	SMAC	FP	6.63	FP	6.48

[a]also: MLL-AF9-fusion leukaemic proliferation;6.24 MLL-ENL-fusion leukaemic proliferation;6.38   MLL-fusion leukaemic proliferation;6.92 MLL-fusion leukaemic proliferation;6.05   MLL-fusion leukaemic proliferation;4.6   LPS-stimulated IL6 production;6.8   MLL-fusion leukaemic proliferation;6   LPS-stimulated IL6 production;5.9 MLL-fusion leukaemic proliferation;7.82 MLL-fusion leukaemic proliferation;6.72   LPS-stimulated IL6 production;5.9.

[b]also: LPS-stimulated IL6 production;6.2   LPS-stimulated IL6 production;6.7

[c]also: LPS-stimulated IL6 production;5.5

[d]also:LPS-stimulated IL6 production;5.6

[e]also:LPS-stimulated IL6 production;4.8

[f]also:LPS-stimulated IL6 production;5.1

[g]also:LPS-stimulated IL6 production;5.5

[h]also:LPS-stimulated IL6 production;5.5

[i]affinity data retrieved from Pubmed id: 20405922

[j]also:TR-FRET;7.82

[k]also:proliferation assay;6.3

[l]also:proliferation assay;5.85   FP;6.66

[m]also:proliferation assay;5.42   proliferation assay;5.76

[n]also:proliferation assay;5.37

[o]also:proliferation assay;5.68

[p]also:proliferation assay;5.54

[q]also:ELISA;7   ELISA;7.52

[r]also:ELISA;7

[s]also:proliferation assay;5.44   proliferation assay;5.49

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