Supplementary Information (SI) for Physical Chemistry Chemical Physics.

Supporting Information

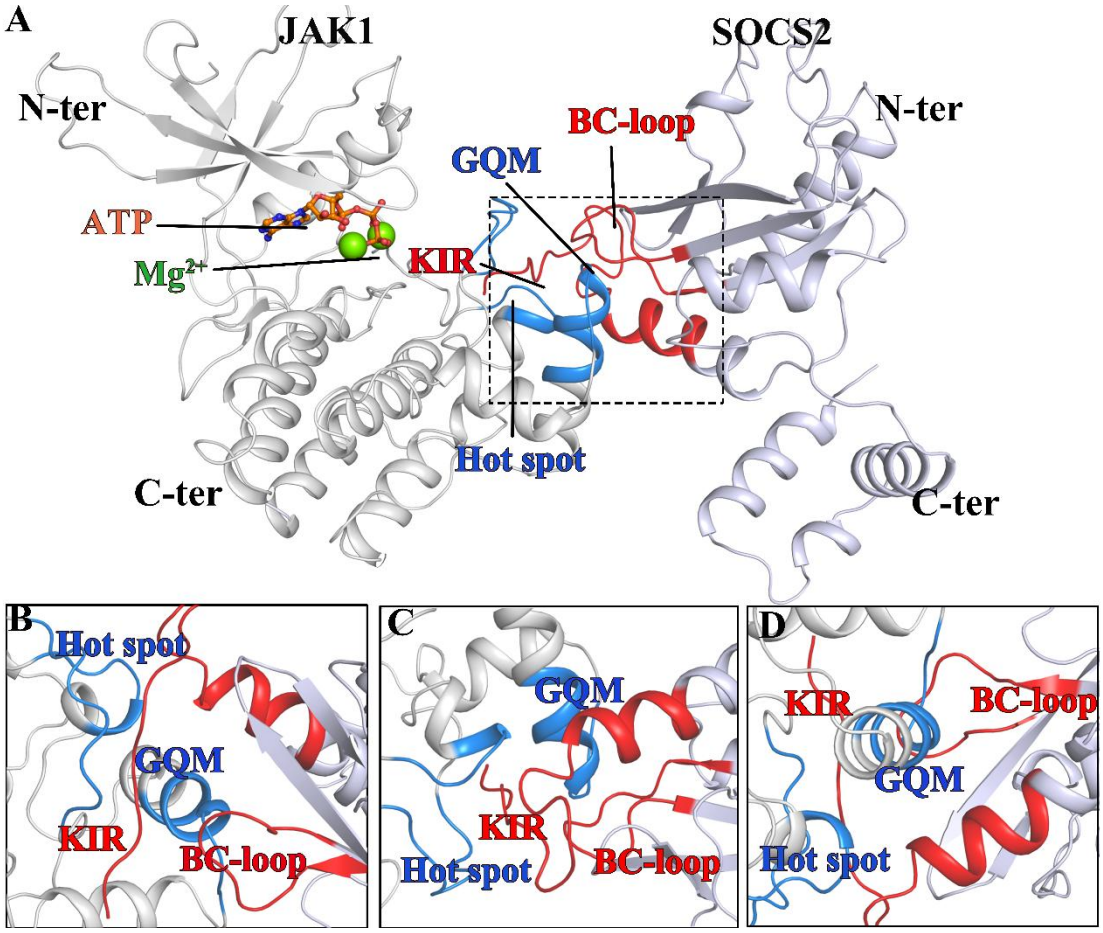

Figure S1. Structural basis of the JAK1/SOCS2 interaction. (A) Ribbon diagram depicting the interaction between JAK1 (blue) and SOCS2 (red). ATP (orange) and a magnesium ion (green) are shown as spheres. The dashed box highlights the primary interaction interface. (B-D) Sequential close-up views of the interaction interface shown in (A), rotated by 90°, 180°, and 270°, respectively, to illustrate the detailed contacts from different angles.

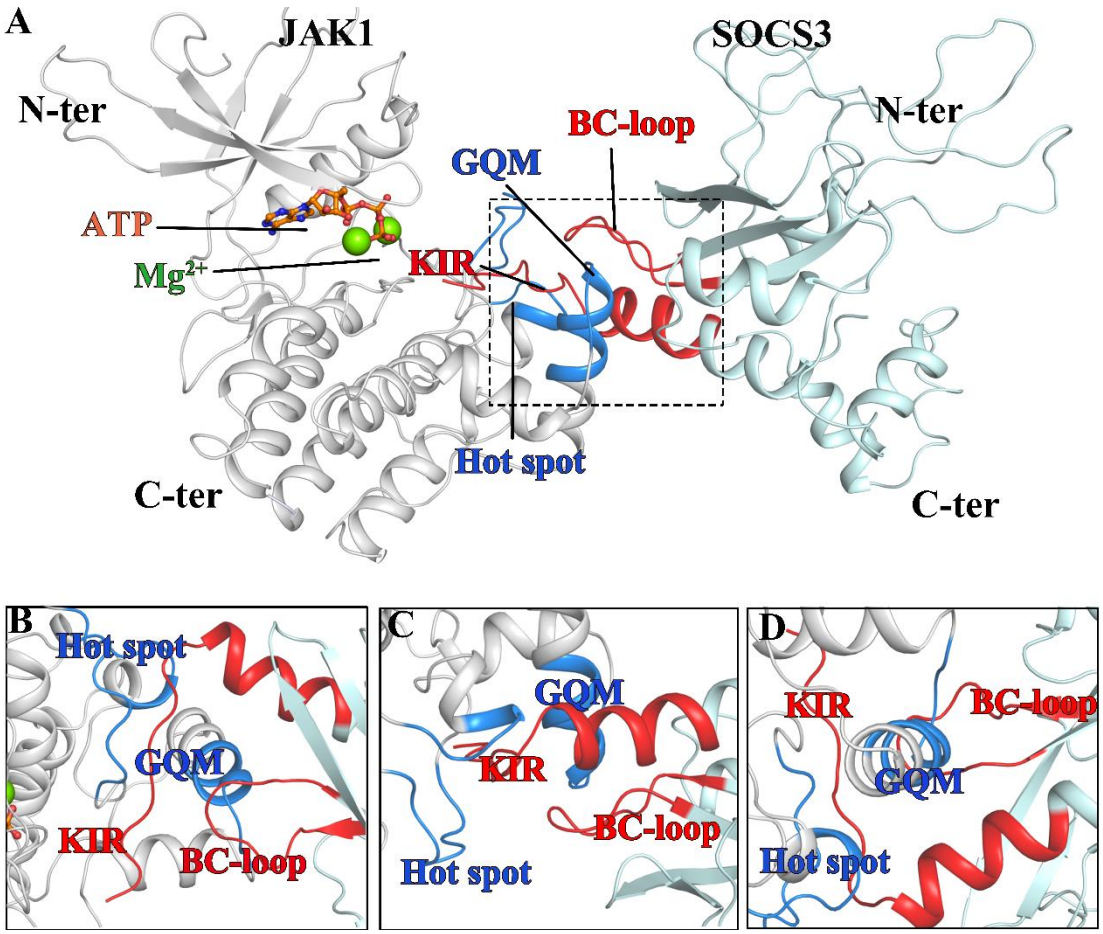

Figure S2. Structural basis of the JAK1/SOCS3 interaction. (A) Ribbon diagram depicting the interaction between JAK1 (blue) and SOCS3 (red). ATP (orange) and a magnesium ion (green) are shown as spheres. The dashed box highlights the primary interaction interface. (B-D) Sequential close-up views of the interaction interface shown in (A), rotated by 90°, 180°, and 270°, respectively, to illustrate the detailed contacts from different angles.

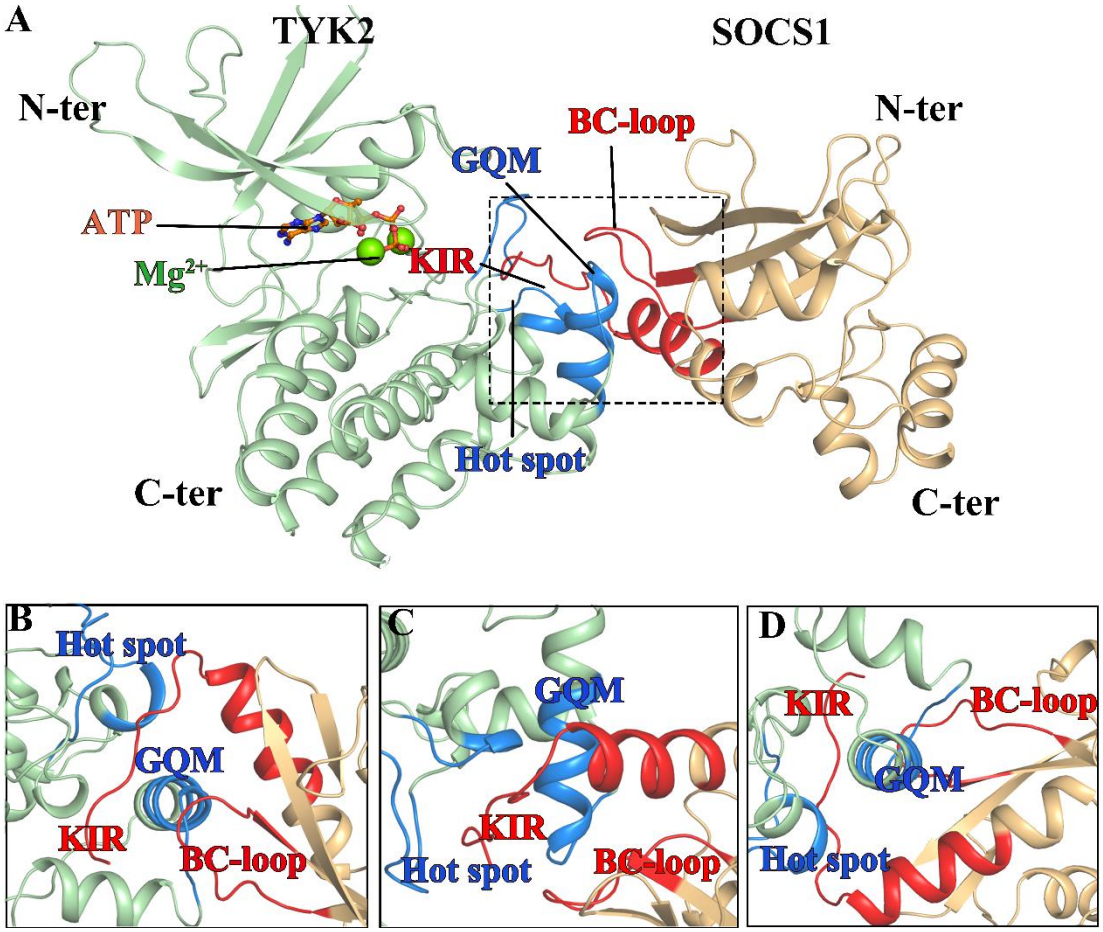

Figure S3. Structural basis of the TYK2/SOCS1 interaction. (A) Ribbon diagram depicting the interaction between TYK2 (blue) and SOCS1 (red). ATP (orange) and a magnesium ion (green) are shown as spheres. The dashed box highlights the primary interaction interface. (B-D) Sequential close-up views of the interaction interface shown in (A), rotated by 90°, 180°, and 270°, respectively, to illustrate the detailed contacts from different angles.

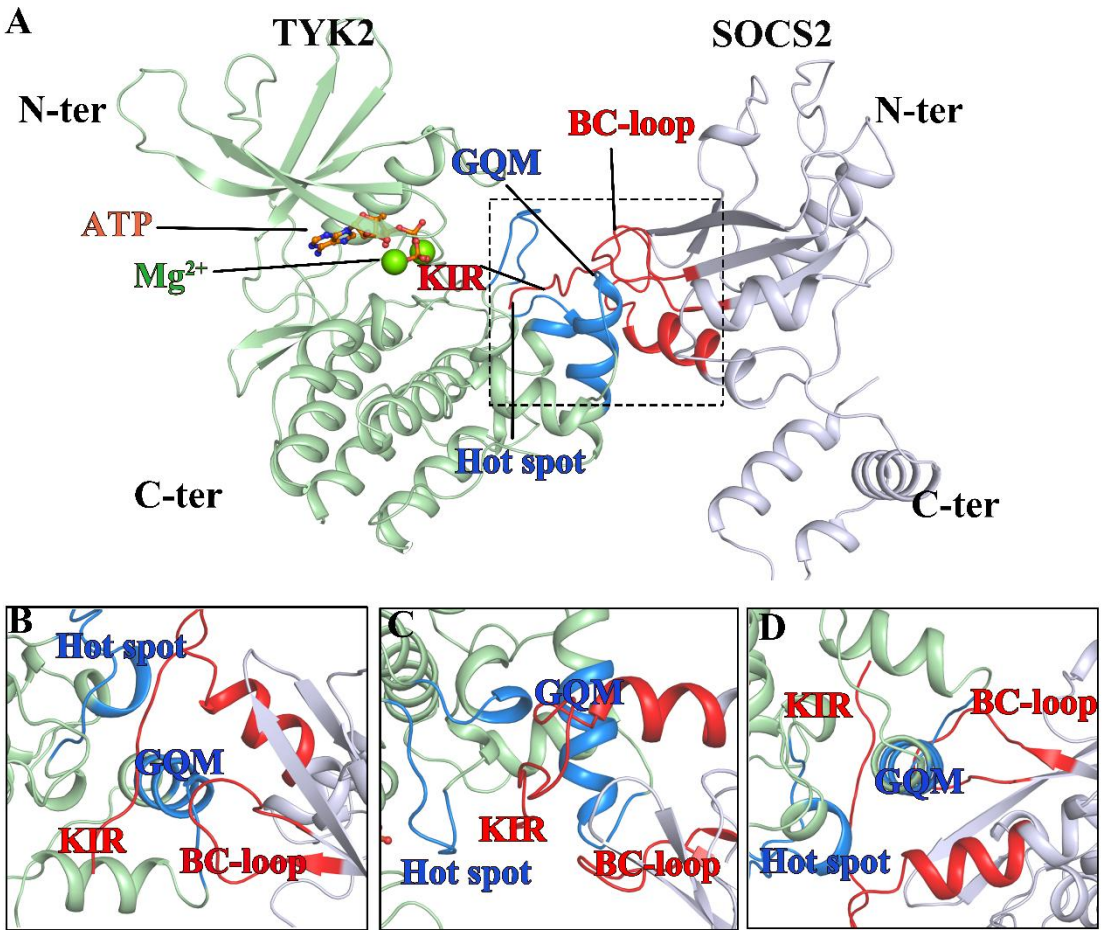

Figure S4. Structural basis of the TYK2/SOCS2 interaction. (A) Ribbon diagram depicting the interaction between TYK2 (blue) and SOCS2 (red). ATP (orange) and a magnesium ion (green) are shown as spheres. The dashed box highlights the primary interaction interface. (B-D) Sequential close-up views of the interaction interface shown in (A), rotated by 90°, 180°, and 270°, respectively, to illustrate the detailed contacts from different angles.

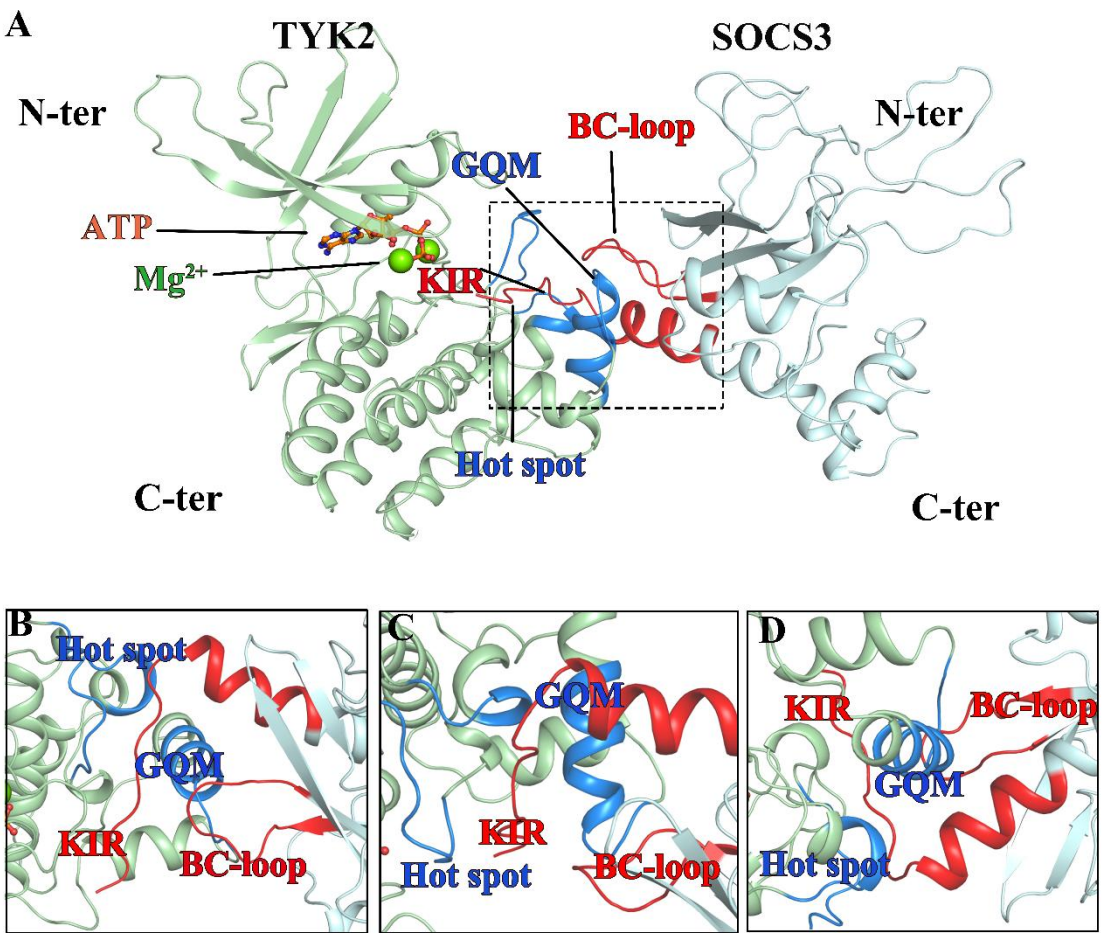

Figure S5. Structural basis of the TYK2/SOCS3 interaction. (A) Ribbon diagram depicting the interaction between TYK2 (blue) and SOCS3 (red). ATP (orange) and a magnesium ion (green) are shown as spheres. The dashed box highlights the primary interaction interface. (B-D) Sequential close-up views of the interaction interface shown in (A), rotated by 90°, 180°, and 270°, respectively, to illustrate the detailed contacts from different angles.

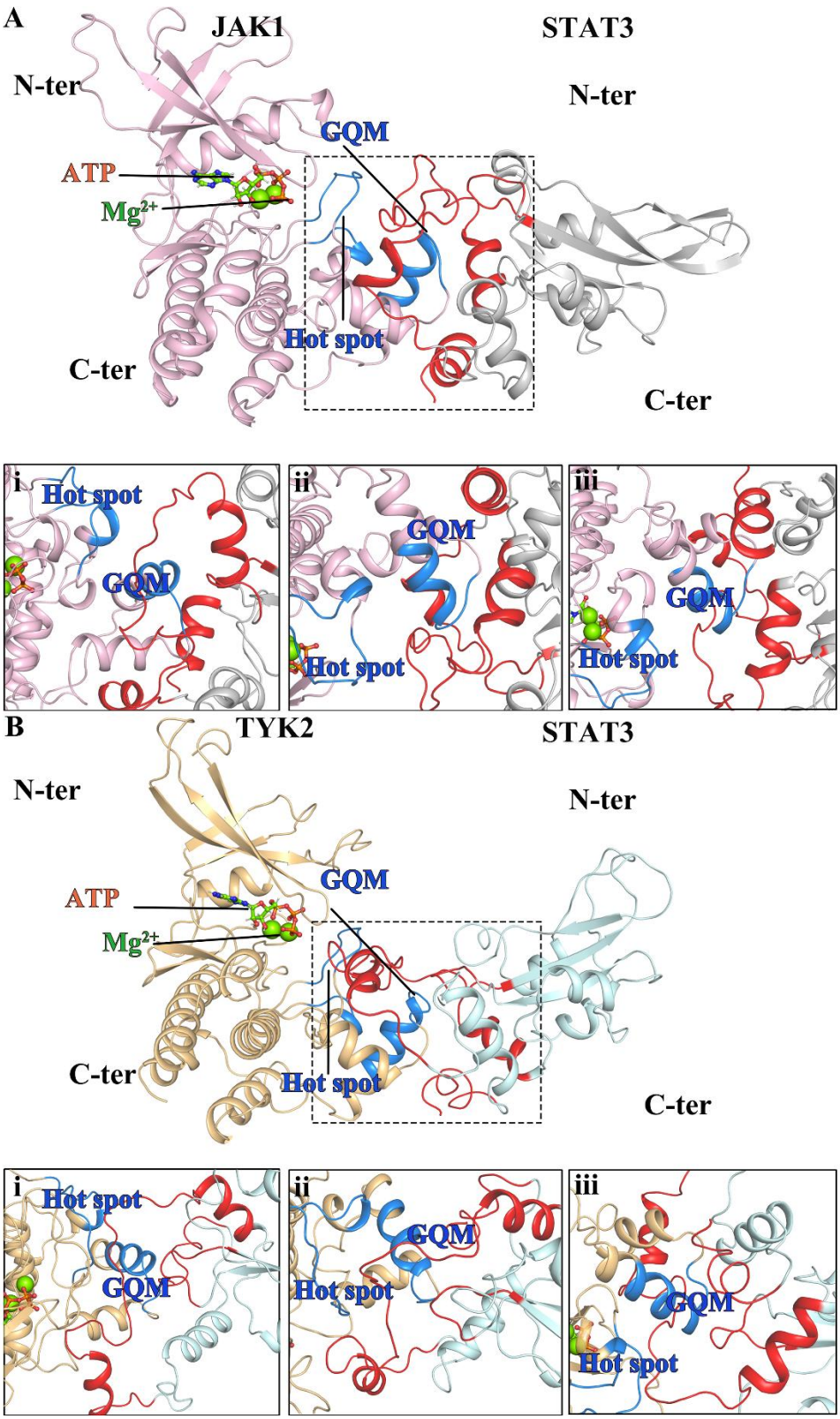

Figure S6. Structures of JAK1/TYK2 in complex with STAT3. (A) JAK1/STAT3 complex, with three subpanels (i, ii, iii) showing different views of the binding interface. (B) TYK2/STAT3 complex, with three subpanels (i, ii, iii) showing different views of the binding interface.

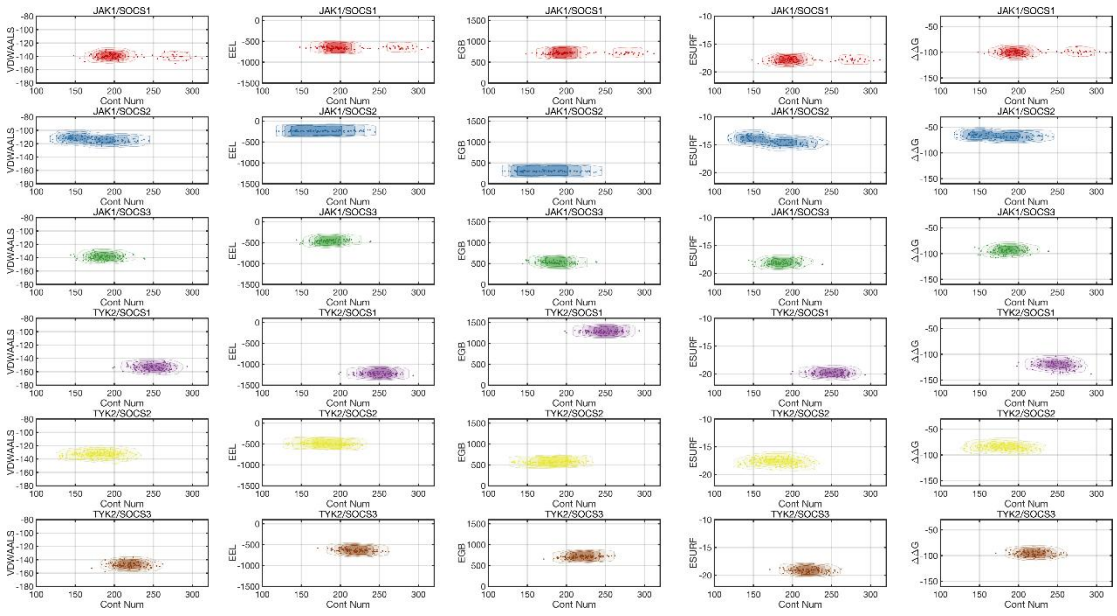

Figure S7. Correlation between total contact numbers and energy components. In both panels, the x-axis represents the contact number, and the y-axis represents the various energy components.

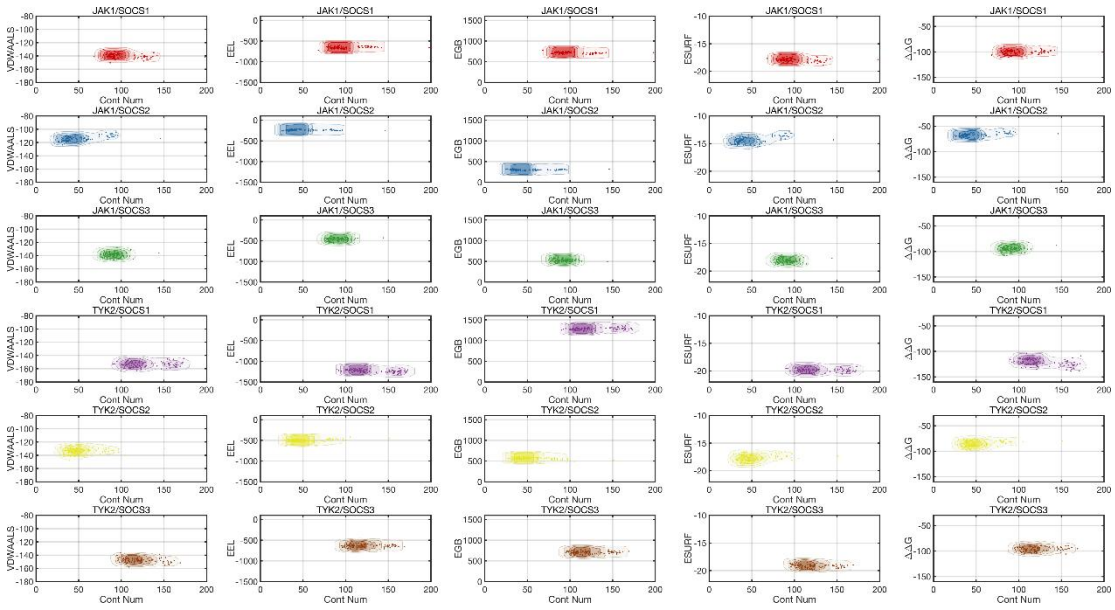

Figure S8. Correlation between native contact numbers and energy components. In both panels, the x-axis represents the contact number, and the y-axis represents the various energy components.

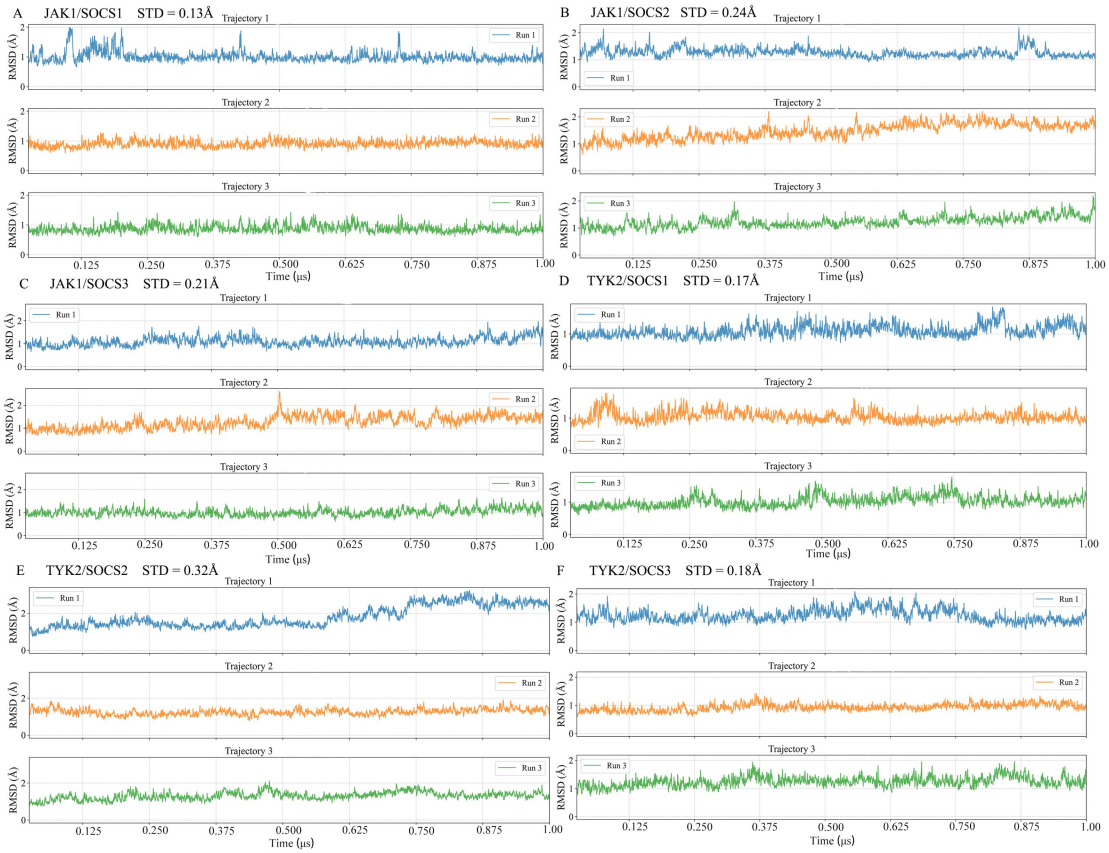

Figure S9. RMSD analyses of JAK1/TYK2 complexes with SOCS1-3. (A-F) Root mean square deviation (RMSD) profiles: (A) JAK1/SOCS1, (B) JAK1/SOCS2, (C) JAK1/SOCS3, (D) TYK2/SOCS1, (E) TYK2/SOCS2, and (F) TYK2/SOCS3.

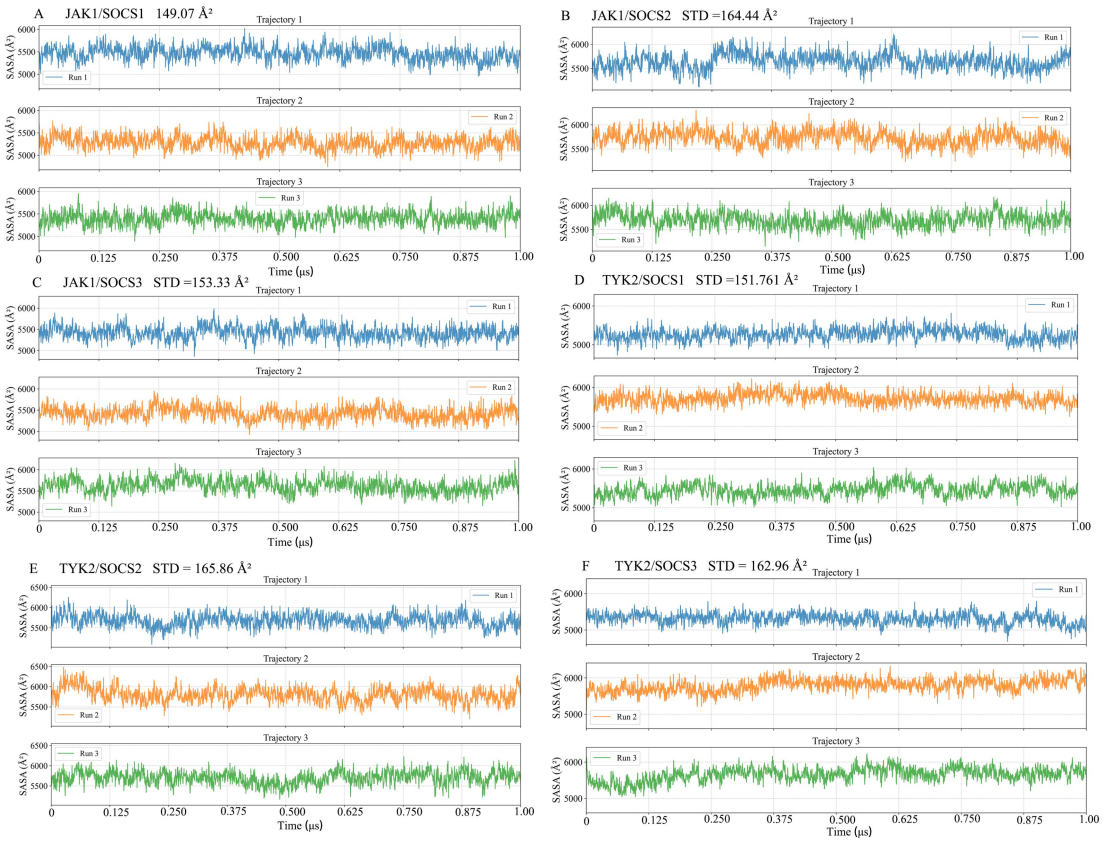

Figure S10. SASA analyses of JAK1/TYK2 complexes with SOCS1-3. (A-F) Solvent-accessible surface area (SASA) profiles: (A) JAK1/SOCS1, (B) JAK1/SOCS2, (C) JAK1/SOCS3, (D) TYK2/SOCS1, (E) TYK2/SOCS2, and (F) TYK2/SOCS3.

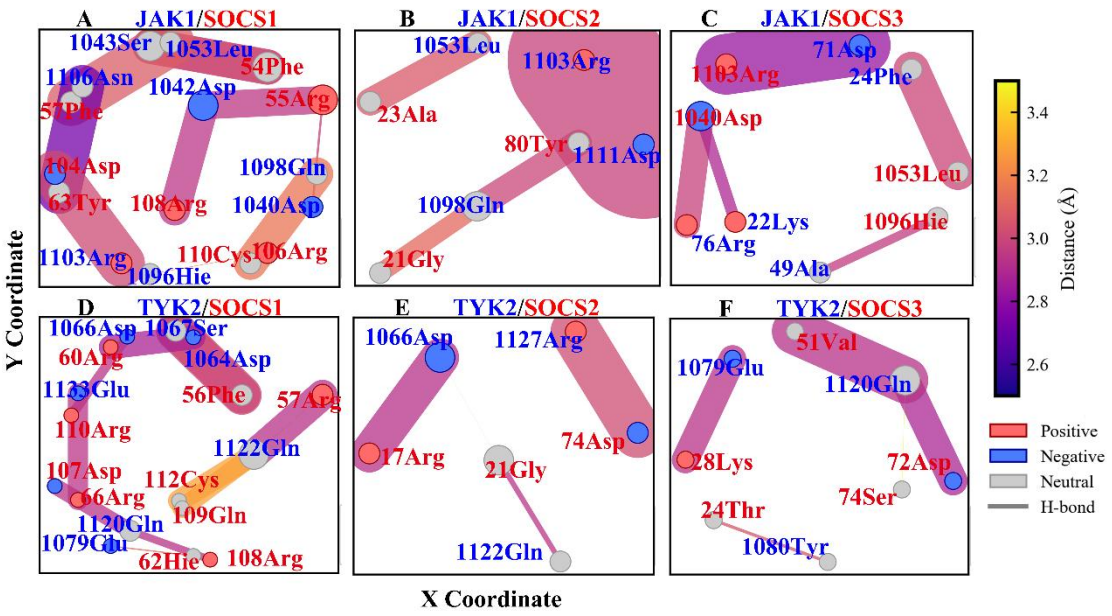

Figure S11. Hydrogen bonding network analysis of JAK/SOCS complexes. (A-C) Hydrogen bonding networks in JAK1/SOCS1 (A), JAK1/SOCS2 (B), and JAK1/SOCS3 (C) complexes. (D-F) Hydrogen bonding networks in TYK2/SOCS1 (D), TYK2/SOCS2 (E), and TYK2/SOCS3 (F) complexes. Nodes represent amino acid residues, with positively charged residues colored red, negatively charged residues blue, and neutral residues white. Lines between residues represent hydrogen bonds, with thickness indicating probability of hydrogen bond formation and color representing hydrogen bond distance. JAK/TYK2 residues are shown in blue, SOCS protein residues in red.

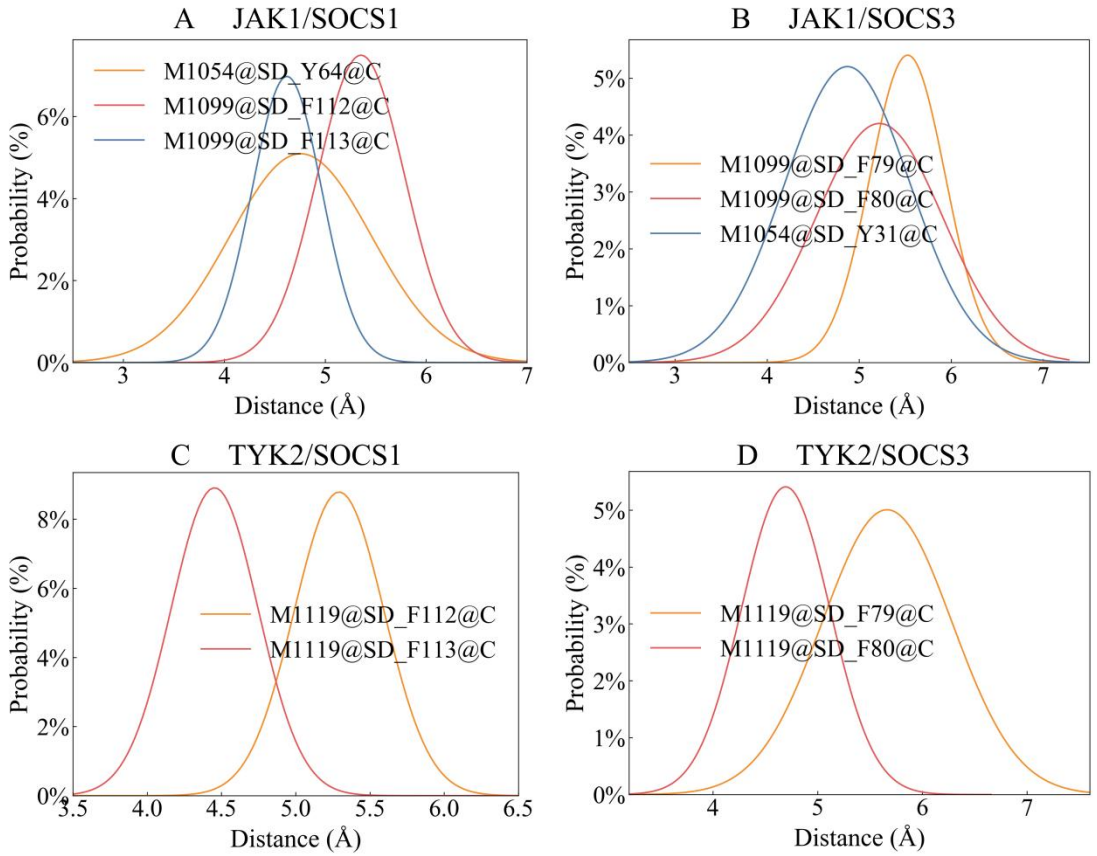

Figure S12. Distance distribution of π-π stacking interactions between residues. (A) Probability distribution of π-π stacking distances for different residue pairs in the JAK1/SOCS1 complex. (B) Distance probability distribution for residue pairs in the JAK1/SOCS3 complex. (C) Distance probability distribution for residue pairs in the TYK2/SOCS1 complex. (D) Distance probability distribution for residue pairs in the TYK2/SOCS3 complex. In all panels, the x-axis represents the distance between residue pairs (Å), while the y-axis indicates the probability of distance occurrence (%). Curves in different colors represent distinct residue pair combinations.

Table S1. Binding free energies of JAK/SOCS complexes and JAK/STAT3 complexes (kcal/mol)

	JAK1/SOCS1	JAK1/SOCS2	JAK1/SOCS3	JAK1/STAT3
Total	-100.13	-67.11	-94.46	-73.59
STD	9.28	3.66	8.30	2.90
	TYK2/SOCS1	TYK2/SOCS2	TYK2/SOCS3	TYK2/STAT3
Total	-121.59	-85.41	-95.86	-85.13
STD	10.73	9.34	8.12	4.00

Table S2. Binding free energies and entropic contributions of JAK/SOCS complexes and JAK/STAT3 complexes (kcal/mol).

	JAK1/SOCS1	JAK1/SOCS2	JAK1/SOCS3	JAK1/STAT3
PBTotal	-112.76	-78.64	-108.03	-88.45
TSTotal	-36.52	-37.75	-38.12	-32.9
Total	-76.24	-40.92	-69.92	-55.50
STD	8.17	9.61	13.18	11.1
	TYK2/SOCS1	TYK2/SOCS2	TYK2/SOCS3	TYK2/STAT3
PBTotal	-120.66	-100.49	-113.25	-103.03
TSTotal	-28.76	-33.67	-31.09	-34.89
Total	-91.86	-66.82	-82.16	-68.14
STD	12.74	15.90	12.41	16.79

Table S3. Binding free energy contributions of key residues in JAK1 complexes with different SOCS proteins (kcal/mol)

	JAK1/SOCS1				JAK1/SOCS2				JAK1/SOCS3		
	Residue 1	Total	STD		Residue 2	Total	STD		Residue 3	Total	STD
	R56	-7.51	1.65		W20	-7.99	0.65		F25	-6.76	0.07
	F55	-6.32	1.24		D74	-5.39	1.71		D72	-5.88	1.09
	F58	-5.54	0.42		L81	-2.39	0.20		L22	-5.67	0.10
	R59	-5.11	0.72		A23	-2.36	0.58		R77	-4.65	3.74
	F112	-3.82	0.14		Q19	-2.10	0.17		F79	-4.29	0.33
	Y64	-3.15	0.07		T22	-1.82	0.15		K23	4.10	0.28
	H54	-2.68	0.29		L40	-1.56	0.65		Y31	-3.37	0.01
SO	D105	-2.16	0.39	SO	L36	-1.46	0.44	SO	T24	-2.52	0.14
CS1	R109	-2.13	1.50	CS	H77	-1.45	0.39	CS	A50	-2.17	0.05
	T57	-2.11	0.39	2	G21	-1.45	0.57	3	H78	-2.15	0.29
	T68	-1.90	0.47		Y80	-1.37	1.63		L20	-1.48	0.21
	P83	-1.65	0.77		A33	-1.11	0.11		F80	-1.07	0.12
	H61	-1.52	0.13						V34	-1.03	0.03
	I67	-1.51	0.15								
	C111	-1.44	0.56								
	R107	-1.16	0.68								
	T53	-1.10	0.41								
	Q1098	-5.74	0.89		R1103	-5.76	0.57		R1103	-7.38	0.68
	R1103	-5.43	0.69		M1099	-5.08	0.63		M1099	-6.02	0.25
	M1099	-4.92	0.64		Q1098	-4.99	0.36		Q1098	-5.07	0.14
	H1096	-2.84	1.32		S1043	-2.70	0.18		H1096	-3.78	0.17
	P1044	-2.82	0.98		P1044	-2.55	0.18		S1043	-2.89	0.08
	D1042	-2.77	1.50		V1045	-2.28	0.15		M1054	-2.73	0.01
	M1054	-2.74	0.07		G1097	-2.21	0.34		V1101	-2.65	0.04
	S1043	-2.63	0.88		H1096	-2.11	0.88		D1042	-2.40	0.59
JA	V1045	-2.48	0.55	JA	Q1055	-1.61	0.76	JA	P1044	-2.38	0.03
K1	Q1055	-2.47	0.09	K1	V1101	-1.46	0.06	K1	Q1055	-2.28	0.09
	G1097	-2.45	0.20		D1042	-1.33	0.26		G1097	-1.98	0.11
	V1101	-2.36	0.17		M1085	-1.17	0.12		L1053	-1.86	0.04
	L1053	-2.02	0.13		F1046	-1.16	0.11		T1102	-1.85	0.05
	T1102	-1.49	0.47		T1100	-1.15	0.17		V1045	-1.76	0.01
	N1106	-1.36	0.22						V1105	-1.43	0.06
	M1085	-1.35	0.37						M1085	-1.31	0.33
	V1105	-1.28	0.10						F1046	-1.18	0.12
	F1046	-1.18	0.16						D1040	-1.14	1.22
	T1100	-1.16	0.12						T1095	-1.09	0.57

Table S4. Binding free energy contributions of key residues in TYK2 complexes with different SOCS proteins (kcal/mol)

	TYK2/SOCS1				TYK2/SOCS2				TYK2/SOCS3		
	Residue 4	Total	STD		Residue 5	Total	STD		Residue 6	Total	STD
	R56	-11.03	1.06		W20	-7.80	0.19		F24	-5.44	0.07
	F55	-6.73	0.52		D74	-5.59	1.16		L21	-5.31	0.22
	F58	-4.96	0.18		L81	-2.80	0.29		F78	-4.91	0.19
	R59	-4.63	2.27		R41	-2.49	2.43		D71	-4.81	0.99
	F112	-4.38	0.11		T22	-2.35	1.14		K22	-4.73	0.57
	Y64	-3.94	0.32		L40	-2.13	0.99		Y30	-4.03	0.09
	R109	-3.33	0.78		A23	-1.70	0.78		H77	-2.46	0.21
	R65	-2.79	1.12		P31	-1.54	0.93		V50	-2.18	0.03
SOCS	T57	-2.47	0.44	SOC	A33	-1.46	0.37	SOC	K27	-2.08	0.33
1	P83	-2.31	0.47	S2	Q19	-1.44	0.30	S3	R76	-2.01	2.23
	H54	-2.26	0.22		Y80	-1.41	1.28		T23	-1.91	0.05
	N110	-2.16	0.55		A37	-1.40	0.79		R20	-1.89	3.08
	D105	-1.75	3.43		R17	-1.24	0.41		A49	-1.83	0.18
	H61	-1.71	0.09		G21	-1.23	0.59		F79	-1.38	0.06
	R107	-1.47	0.40		H77	-1.08	0.35		S73	-1.18	0.06
	S60	-1.31	0.14		M53	-1.04	0.90		S48	-1.11	0.11
	C111	-1.09	0.16		A26	-1.01	0.49		V34	-1.09	0.06
	Q108	-1.08	0.04						V37	-1.07	0.03
	Q1118	-6.57	0.36		M1119	-5.36	0.61		M1119	-6.31	0.25
	R1123	-6.18	0.82		R1123	-4.99	0.85		Q1118	-5.22	0.17
	M1119	-5.86	0.14		Q1118	-4.39	1.14		R1123	-5.09	0.62
	D1062	-4.55	0.54		R1058	-3.58	1.99		Q1116	-3.98	0.18
	L1122	-4.45	0.10		L1122	-3.55	0.97		L1122	-3.89	0.13
	S1063	-3.71	0.23		S1063	-3.41	0.29		E1075	-3.78	0.54
	Y1076	-3.28	0.24		Q1116	-2.90	1.06		V1121	-2.54	0.09
	E1075	-2.56	0.09		P1064	-2.20	0.25		S1063	-2.52	0.06
TYK2	V1121	-2.44	0.05	TYK	Y1076	-2.07	0.47	TYK	P1064	-2.49	0.09
	Q1116	-2.43	1.49	2	V1065	-1.86	0.13	2	D1062	-2.38	1.10
	G1117	-2.37	0.29		V1121	-1.84	0.33		Y1076	-2.08	0.19
	K1074	-2.33	0.10		F1066	-1.73	0.10		G1117	-2.03	0.19
	P1064	-2.30	0.32		G1117	-1.71	0.82		V1065	-1.73	0.07
	V1065	-2.06	0.06		E1126	-1.51	1.80		R1058	-1.65	2.82
	D1060	-1.92	0.46		I1114	-1.50	1.52		L1073	-1.55	0.06

	L1073	-1.67	0.03	D1062	-1.35	0.16	K1074	-1.47	0.06
	T1125	-1.66	0.26	P1105	-1.20	0.13	T1125	-1.43	0.06
	E1129	-1.27	0.48	T1120	-1.04	0.23	F1066	-1.13	0.15
	F1066	-1.24	0.11						

Table S5. Binding free energy contributions of key residues in JAK1 and TYK2 complexes with different STAT3 proteins (kcal/mol)

	JAK1/STAT3				TYK2/STAT3		
	Residue 7	Total	STD		Residue 8	Total	STD
	W564	-5.26	1.15		W564	-4.63	0.93
	W447	-3.75	1.09		L563	-3.17	0.74
	Q512	-3.67	1.44		W546	-3.12	0.89
	L563	-3.42	2.29		L509	-2.27	2.06
	W511	-2.85	0.55		V508	-2.22	1.97
	L503	-2.41	0.54		Q512	-2.16	1.42
	W562	-2.14	1.30		I565	-2.06	1.04
	L569	-2.13	1.26		W511	-2.05	2.00
STAT3	F513	-1.61	0.46	STAT3	W562	-1.77	2.45
	I568	-1.58	1.92		F588	-1.63	0.79
	V508	-1.49	1.30		L529	-1.54	1.06
	I565	-1.39	1.07		R615	-1.27	1.29
	F588	-1.38	1.19		L569	-1.26	1.07
	R548	-1.37	2.64		F549	-1.25	0.94
	T547	-1.28	1.32		F453	-1.12	1.07
	R615	-1.05	1.79		C550	-1.07	0.67
	F549	-1.04	0.95		F559	-1.04	1.10
	P1094	-4.55	0.43		Q1118	-4.56	2.99
	H1096	-4.16	0.92		M1119	-3.92	1.15
	Q1098	-2.52	1.38		G1117	-2.48	0.62
	L1089	-2.56	0.65		L1109	-2.42	0.50
	M1099	-2.48	0.73		Q1116	-2.06	1.71
	T1107	-2.07	0.88		R1130	-2.05	2.33
	M1091	-1.98	1.12		Y1076	-1.77	1.16
	M1085	-1.58	0.56		L1111	-1.63	1.41
JAK1	I1092	-1.31	0.32	TYK2	T1106	-1.62	0.79
	G1097	-1.29	0.81		L1127	-1.53	0.64
	A1086	-1.01	0.47		R987	-1.27	3.48
					L1122	-1.26	0.73
					P1105	-1.25	0.47
					I1112	-1.12	0.53
					V1065	-1.07	0.66
					V1121	-1.04	0.59

Table S6. Donor-acceptor pairs in hydrogen bonding systems and key resultant parameters

JAK1/SOCS1				
Acceptor	Donor	Frac (%)	AvgDist (Å)	AvgAng (°)
D1042(JAK1)@OD1	R56(SOCS1)@NH2	0.28	2.95	151.3
D1042(JAK1)@OD2	R56(SOCS1)@NH2	0.27	2.94	153.51
F55(SOCS1)@O	S1043(JAK1)@N	0.7	2.99	159.79
S1043(JAK1)@O	F55(SOCS1)@N	0.69	3.08	159.75
L1053(JAK1)@O	F58(SOCS1)@N	0.94	3.07	158.23
N1106(JAK1)@OD1	Y64(SOCS1)@OH	0.86	2.72	162.98
D105(SOCS1)@OD2	R1103(JAK1)@NH2	0.57	3.03	152.39
D105(SOCS1)@OD1	R1103(JAK1)@NH1	0.36	2.98	151.39
D1042(JAK1)@OD1	R109(SOCS1)@NH1	0.25	2.86	157.65
C111(SOCS1)@O	Q1098(JAK1)@N	0.65	3.15	149.89

JAK1/SOCS2				
Acceptor	Donor	Frac (%)	AvgDist (Å)	AvgAng (°)
D74(SOCS2)@OD1	R1103(JAK1)@NH1	0.49	2.88	152.12
D74(SOCS2)@OD2	R1103(JAK1)@NH2	0.78	3.10	148.17
D74(SOCS2)@OD1	R1103(JAK1)@NH2	0.79	2.97	152.00
D74(SOCS2)@OD2	R1103(JAK1)@NH1	0.31	2.94	153.22
L1053(JAK1)@O	A23(SOCS2)@N	0.44	3.06	158.49
Q1098(JAK1)@OE1	G21(SOCS2)@N	0.30	3.11	151.27
Y80(SOCS2)@O	Q1098(JAK1)@N	0.41	3.00	162.92

JAK1/SOCS3				
Acceptor	Donor	Frac (%)	AvgDist (Å)	AvgAng (°)
L1053(JAK1)@O	F25(SOCS3)@N	0.94	2.99	157.76
D72(SOCS3)@OD1	R1103(JAK1)@NH1	0.66	2.72	160.77
D72(SOCS3)@OD2	R1103(JAK1)@NH2	0.96	2.85	156.50
D1040(JAK1)@OD2	R77(SOCS3)@NH1	0.25	2.99	152.67
D1040(JAK1)@OD1	R77(SOCS3)@NH1	0.23	3.05	152.12
A50(SOCS3)@O	H1096(JAK1)@NE2	0.24	2.96	147.84

TYK2/SOCS1				
Acceptor	Donor	Frac (%)	AvgDist (Å)	AvgAng (°)
R56(SOCS1)@O	Q1118(TYK2)@NE2	0.79	2.90	155.29
F55(SOCS1)@O	S1063(TYK2)@N	0.93	2.90	159.33
S1063(TYK2)@O	F55(SOCS1)@N	0.98	3.07	157.34

D1060(TYK2)@OD2	R59(SOCS1)@NH2	0.21	2.83	155.30
D1060(TYK2)@OD2	R59(SOCS1)@NH2	0.21	2.82	155.42
E1129(TYK2)@OE1	R64(SOCS1)@NH2	0.25	2.94	154.75
E1129(TYK2)@OE2	R64(SOCS1)@NH1	0.28	2.94	153.17
D105(SOCS1)@O	Q1116(SOCS1)@NE2	0.43	2.94	150.14
C111(SOCS1)@O	Q1118(TYK2)@N	0.58	3.29	146.36
Q108(SOCS1)@O	Q1118(TYK2)@N	0.51	3.28	144.59
D1060(TYK2)@OD1	R56(SOCS1)@NH1	0.27	4.00	141.7
D1060(TYK2)@OD2	R56(SOCS1)@NH1	0.50	3.32	143.26

TYK2/SOCS2

Acceptor	Donor	Frac (%)	AvgDist (Å)	AvgAng (°)
D74(SOCS2)@OD1	R1123(TYK2)@NH2	0.75	3.00	149.65
D1062(TYK2)@OD1	R17(SOCS2)@NH2	0.30	2.96	151.72
D1062(TYK2)@OD2	R17(SOCS2)@NH2	0.30	2.95	152.18

TYK2/SOCS3

Acceptor	Donor	Frac (%)	AvgDist (Å)	AvgAng (°)
D71(SOCS3)@O	Q1116(TYK2)@NE2	0.58	2.89	153.32
V314(SOCS3)@O	Q1116(TYK2)@NE2	0.92	2.97	158.27
E1075(TYK2)@OE1	K27(SOCS3)@NZ	0.28	2.93	153.91
E1075(TYK2)@OE2	K27(SOCS3)@NZ	0.26	2.94	153.74
D71(SOCS3)@OD1	R1123(TYK2)@NH1	0.25	3.21	145.37
D71(SOCS3)@OD2	R1123(TYK2)@NH1	0.59	3.56	140.77
D71(SOCS3)@OD2	R1123(TYK2)@NH2	0.26	3.26	145.90